Chirale, rigide Diamine

–

Von Liganden zu Bispidin-Naturstoffen

DISSERTATION

zur Erlangung des akademischen Grades eines
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vorgelegt von
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Meiner Familie
und
meinen Freunden

« Je suis de ceux qui pensent que la science est d'une grande beauté. Un scientifique dans son laboratoire est non seulement un technicien : il est aussi un enfant placé devant des phénomènes naturels qui l'impressionnent comme des contes de fées. »

„Ich gehöre zu denen, die die besondere Schönheit des wissenschaftlichen Forschens erfasst haben. Ein Gelehrter in einem Laboratorium ist nicht nur ein Techniker, er steht auch vor den Naturvorgängen wie ein Kind vor einer Märchenwelt."

Marie Curie

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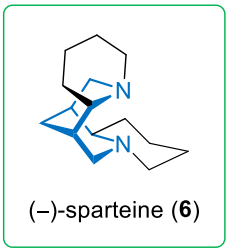
SUMMARY



(–)-sparteine (**6**)

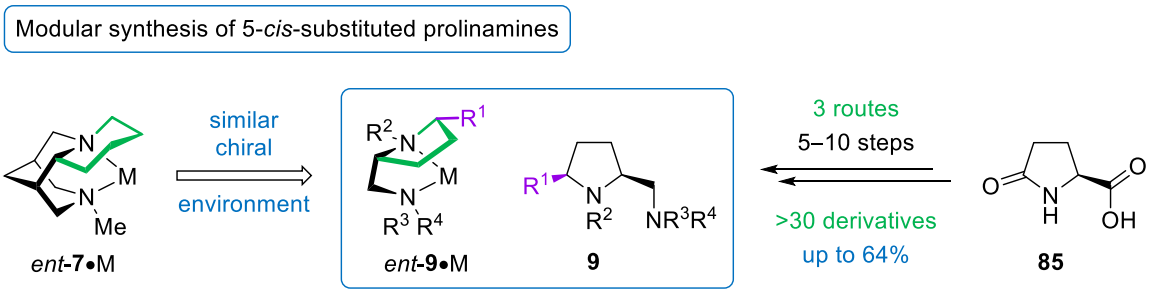
Chiral bispidines, a fascinating class of rigid diamines with a 3,7-diazabicyclo[3.3.1]nonane backbone, were the focus of my work. They form a group of natural products with interesting structures and diverse bioactivities. The most prominent representative, (–)-sparteine (**6**), and artificial derivatives thereof are also potent ligands in enantioselective synthesis and catalysis. A general and flexible route that permits access to this substance class is, however, currently lacking. The search for tailor-made, more efficient ligands as well as the total synthesis of these natural products is thus very laborious.

The motivation for the present dissertation was to solve these problems. The first goal was the development of new ligands – both structurally strongly simplified bispidine surrogates and novel bispidines – for enantioselective catalysis. Secondly, a modular approach enabling the efficient total synthesis of bispidine natural products was to be developed.

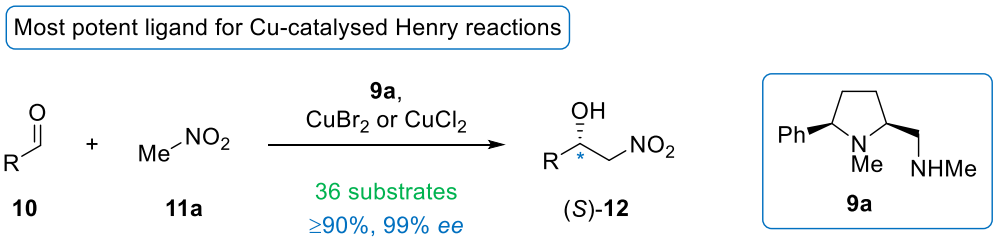
Subproject 1: Search for bispidine surrogates for enantioselective catalysis

Although the structures of a bispidine such as *ent*-**7** and a 5-*cis*-substituted prolinamine *ent*-**9** are quite different, the chiral environments they generate as a ligand in a metal complex should be very similar. The diamines **9** were therefore synthesised and tested as simplified bispidine surrogates in enantioselective transition metal catalysis.

Three modular routes to **9**, which differ in the order of introduction of the substituents R^1 to R^4, were established starting from L-pyroglutamic acid (**85**). These sequences allowed for the preparation of more than 30 different prolinamines **9** in five to ten steps and up to 64% overall yield.

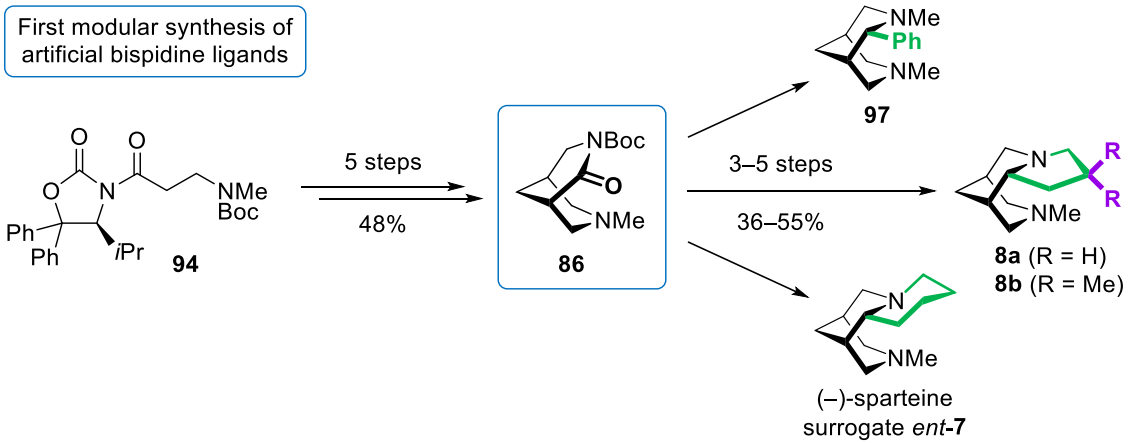


The prolinamines **9** were evaluated as chiral ligands in Cu-catalysed Henry reactions. The 5-*cis*-phenyl-substituted derivative **9a** provided the best results. By optimising the reaction conditions, a catalytic system was developed which enabled unprecedented enantioselectivities in this transformation. The addition of nitromethane (**11a**) to 36 different aromatic, heteroaromatic, vinylic and alkylic aldehydes **10** in the presence of **9a** delivered the corresponding β-nitro alcohols (*S*)-**12** in more than 90% yield with excellent 99% *ee*.



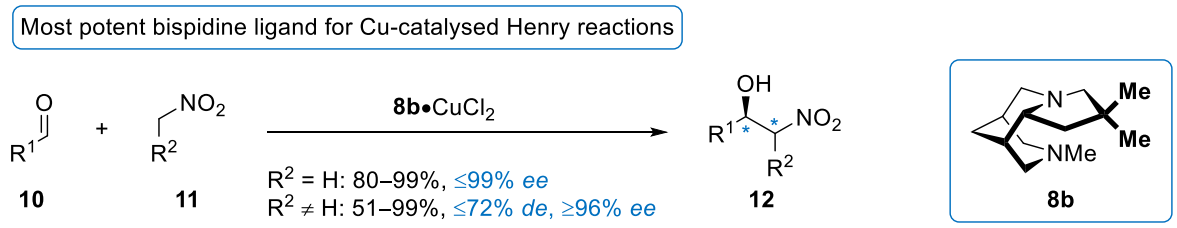
Subproject 2: Development of artificial bispidine ligands for enantioselective synthesis and catalysis

The first modular approach for the efficient preparation of various artificial bispidine ligands was developed. The key intermediate, the chiral bispidine imide **86**, was constructed in 48% yield over five steps from the auxiliary-modified β-amino acid **94**. Stereoselective attachment of different *endo*-annulated rings and substituents (highlighted in green) to **86** delivered the three new ligands **97**, **8a** and **8b** as well as the known (–)-sparteine surrogate *ent*-**7**.



The potential of the two novel ligands **8a** and **8b**, which possess a fused pyrrolidine ring, was compared with that of the prime ligands (–)-sparteine (**6**) and **7** in enantioselective deprotonation reactions. Yet the enantiomeric excesses were low in the presence of **8a** and **8b** (≤52% *ee* vs. **6**/**7**: ≤96% *ee*), confirming that an *endo*-fused piperidine ring as in **6** and **7** is essential for an effective chirality transfer in this kind of reaction.

Bispidine **8b**, however, provided excellent results as the chiral ligand in enantioselective Cu-catalysed Henry reactions. The transformation of various aromatic, heteroaromatic, vinylic and aliphatic aldehydes **10** with nitromethane (**11a**) delivered the products in 80–99% yield with up to 99% *ee*. The catalyst **8b**•$CuCl_2$ also proved to be suited for enantio- and diastereoselective nitroaldol reactions (up to 72% *de*, more than 96% *ee* in both diastereomers). In addition, the performance of ligand **8b** was directly compared to that of (–)-sparteine (**6**) and the surrogate **7** using four substrates. It was found that **8b** (85–98% *ee*) is superior to the established ligands **6** and **7** (45–96% *ee*) and thus the most powerful bispidine ligand for this reaction.

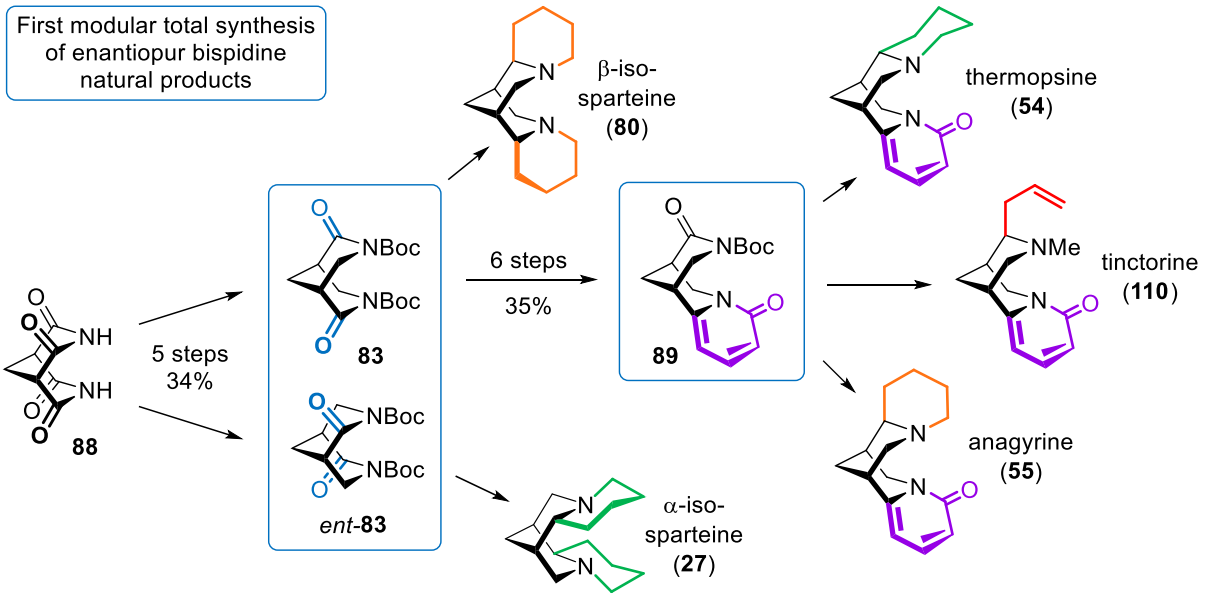


Subproject 3: Total synthesis of bispidine natural products (bisquinolizidine alkaloids)

To extend on the successful preparation of artificial bispidine ligands, an efficient and modular access to bispidine natural products was developed, based on an "inside-out" approach. Within this strategy the chiral backbone is constructed first, followed by the attachment of the characteristic structural elements of each derivative.

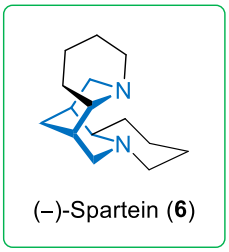
Since both enantiomeric forms of the central bispidine core occur in the natural products, both enantiomers of the diimide **83** were prepared by desymmetrisation of tetraoxobispidine (**88**) over five steps in 34% yield each. The installation of a pyridone ring (highlighted in purple) on **83** provided **89** with 35% yield over six steps.*

Several sequences were established for the synthesis of various natural products, starting from the key intermediates **83** and **89**. They permit the stereoselective attachment of *endo*-fused piperidine rings (green) as in α-isosparteine (**27**) and thermopsine (**54**), of *exo*-annulated piperidine rings (orange) as in β-isosparteine (**80**) and anagyrine (**55**), and of an *exo*-allyl substituent (red) as in tinctorine (**110**). In total 15 bispidine alkaloids – 12 of them in enantiopure form – were prepared via this efficient approach, with only a small selection of them shown below. A notable success was the first enantioselective total synthesis of α-isosparteine (**27**), anagyrine (**55**) and tinctorine (**110**).



* The analoguous preparation of the enantiomer *ent*-**89** from *ent*-**83** was left out within this thesis; the more accessible racemic material was used instead to establish further synthetic routes.

ZUSAMMENFASSUNG



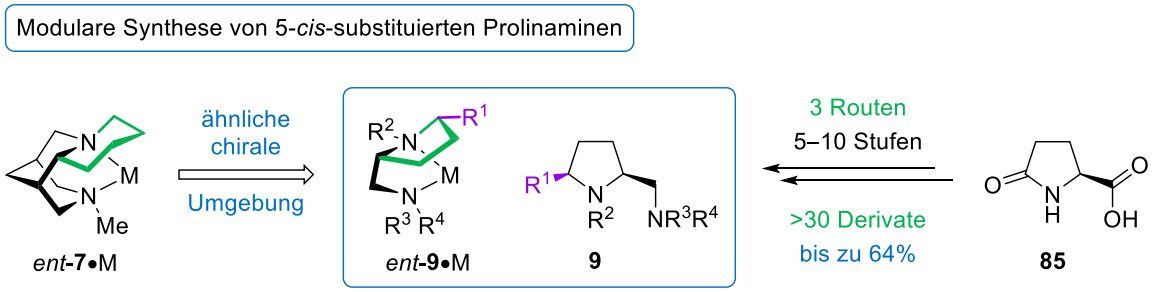
Chirale Bispidine, eine faszinierende Klasse rigider Diamine mit einem 3,7-Diazabicyclo[3.3.1]nonan-Grundgerüst, standen im Fokus dieser Arbeit. Sie bilden nicht nur eine Gruppe von Naturstoffen mit interessanter Struktur und vielfältigen Bioaktivitäten, sondern finden – wie der prominenteste Vertreter, (–)-Spartein (**6**), und davon abgeleitete artifizielle Derivate – auch Anwendung als potente Liganden in der enantioselektiven Synthese und Katalyse. Bislang fehlt jedoch ein allgemeiner und flexibler Zugang zu dieser Substanzklasse, was sowohl die Suche nach maßgeschneiderten, leistungsfähigeren Liganden als auch die Totalsynthese dieser Naturstoffe äußerst erschwert.

Diese Probleme zu lösen war die Motivation der vorliegenden Dissertation. Ein Ziel war die Entwicklung neuer Liganden – sowohl von strukturell stark vereinfachten Bispidin-Ersatzstoffen als auch von neuartigen Bispidinen – für die enantioselektive Katalyse. Darüber hinaus sollte ein modularer Zugang zu Bispidinen-Naturstoffen erarbeitet werden, der eine effiziente Totalsynthese möglichst vieler Vertreter dieser Klasse erlaubt.

Teilprojekt 1: Suche nach Bispidin-Ersatzstoffen für die enantioselektive Katalyse

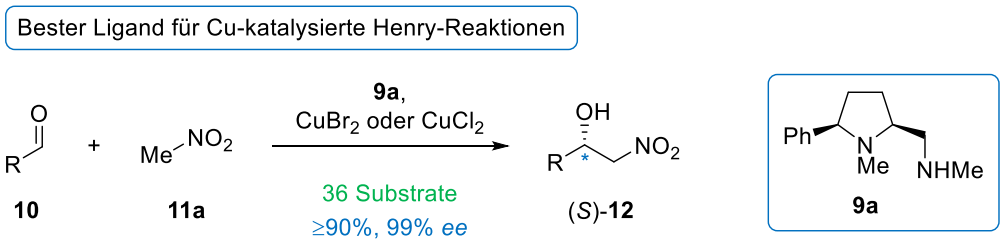
Obwohl ein Bispidin wie *ent*-**7** und ein 5-*cis*-substituiertes Prolinamin *ent*-**9** unterschiedliche Strukturen besitzen, ähneln sich die chiralen Umgebungen, die sie als Ligand in einem Metall-Komplex generieren, stark. Daher war geplant, die Diamine **9** zu synthetisieren und als vereinfachte Bispidin-Ersatzstoffe in der enantioselektiven Übergangsmetall-Katalyse zu testen.

Ausgehend von L-Pyroglutaminsäure (**85**) wurden drei modulare Routen zu **9** etabliert, die sich in der Reihenfolge unterscheiden, mit der die Reste R^1 bis R^4 eingeführt werden. Diese Sequenzen ermöglichten die Darstellung von insgesamt mehr als 30 verschiedenen Prolinaminen **9** über fünf bis zehn Stufen mit bis zu 64% Gesamtausbeute.



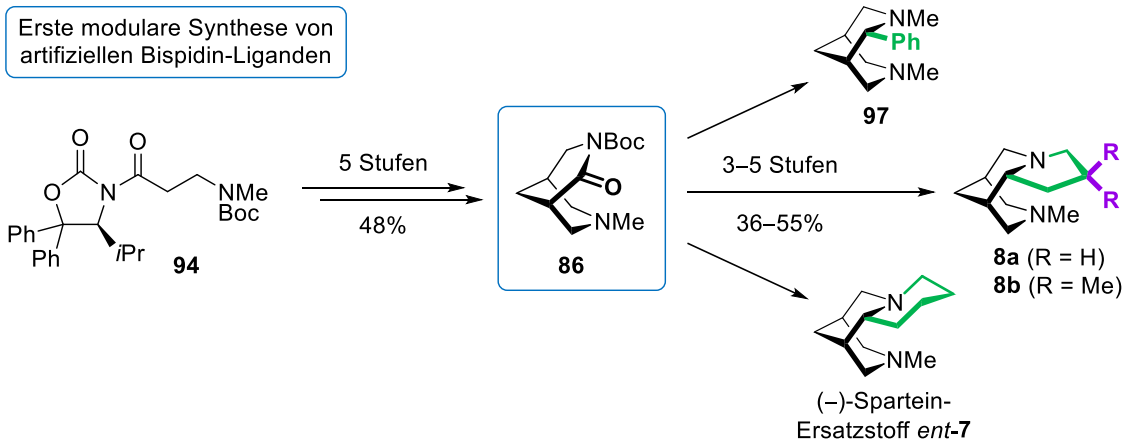
Die Prolinamine **9** wurden als chirale Liganden in Cu-katalysierten Henry-Reaktionen evaluiert. Die besten Ergebnisse lieferte das 5-*cis*-Phenyl-substituierte Derivat **9a**. Durch Optimierung der Reaktionsbedingungen gelang es, ein Katalysatorsystem zu entwickeln, das in dieser Reaktion bisher unerreichte Enantiomerenüberschüsse erzielt. In der Umsetzung von 36 verschiedenen aromatischen, heteroaromatischen, vinylischen und alkylischen Aldehyden **10**

konnten in Gegenwart von **9a** die entsprechenden β-Nitroalkohole (*S*)-**12** in über 90% Ausbeute und mit jeweils ausgezeichneten 99% *ee* erhalten werden.



Teilprojekt 2: Entwicklung von artifiziellen Bispidin-Liganden für die enantioselektive Synthese und Katalyse

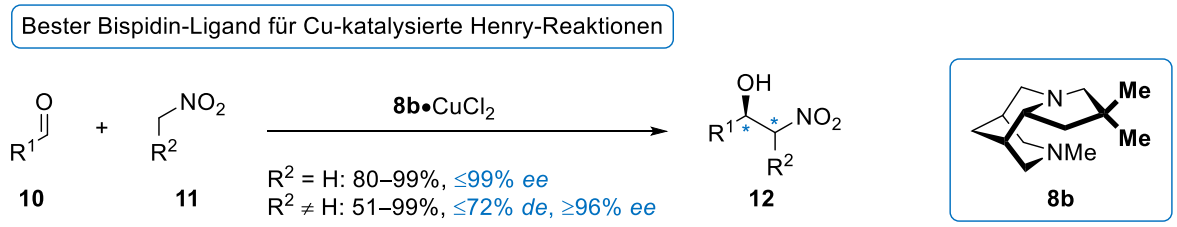
Zur effizienten Darstellung verschiedener artifizieller Bispidin-Liganden wurde erstmals ein modularer Zugang realisiert. Zunächst wurde das Schlüsselintermediat, das chirale Bispidin-Imid **86**, ausgehend von der Auxiliar-verknüpften β-Aminosäure **94** in 48% Gesamtausbeute über fünf Stufen aufgebaut. An **86** ließen sich stereoselektiv unterschiedliche *endo*-ständige Ringe und Substituenten anbringen (grün markiert), was die drei neuen Liganden **97**, **8a** und **8b** sowie den bekannten (–)-Spartein-Ersatzstoff *ent*-**7** lieferte.



Das Potenzial der beiden neuartigen Liganden **8a** und **8b**, die einen anellierten Pyrrolidin-Ring tragen, wurde in enantioselektiven Deprotonierungs-Reaktionen mit dem der Paradeliganden (–)-Spartein (**6**) und **7** verglichen. Die Enantiomerenüberschüsse in Gegenwart von **8a** und **8b** waren allerdings gering (≤52% *ee* vs. **6**/**7**: ≤96% *ee*), was bestätigt, dass ein *endo*-anellierter Piperidin-Ring wie in **6** und **7** in solchen Reaktionen essenziell für einen effektiven Chiralitätstransfer ist.

In enantioselektiven, Cu-katalysierten Henry-Reaktionen hingegen erzielte das Bispidin **8b** als chiraler Ligand ausgezeichnete Ergebnisse. Die Umsetzung verschiedener aromatischer, heteroaromatischer, vinylischer und aliphatischer Aldehyde **10** mit Nitromethan (**11a**) lieferte die Produkte in 80–99% Ausbeute und bis zu 99% *ee*. Auch für enantio- und diastereoselektive Nitroaldol-Reaktionen war **8b**•$CuCl_2$ als Katalysator gut geeignet (bis zu 72% *de*, über

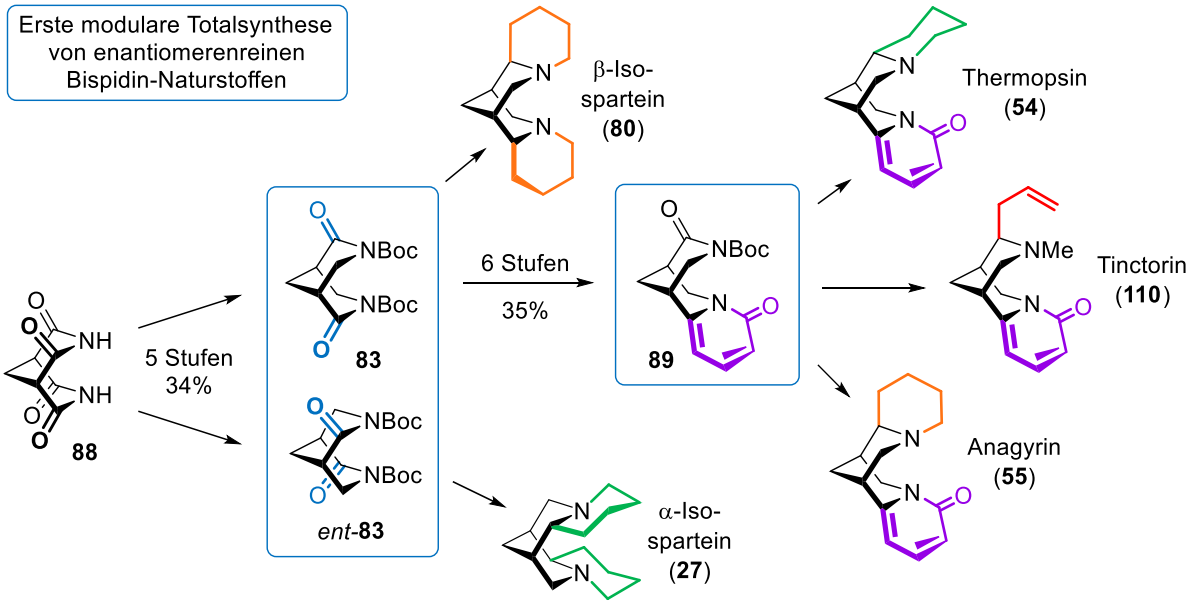
96% *ee* in beiden Diastereomeren). Weiterhin wurde das Potenzial des Liganden **8b** an vier Substraten direkt mit dem von (–)-Spartein (**6**) und dem des Ersatzstoffs **7** verglichen. Dabei zeigte sich, dass **8b** (85–98% *ee*) den etablierten Liganden **6** und **7** (45–96% *ee*) überlegen und damit der leistungsfähigste Bispidin-Ligand in dieser Umsetzung ist.



Teilprojekt 3: Totalsynthese von Bispidin-Naturstoffen (Bischinolizidin-Alkaloiden)

Aufbauend auf den Erfolgen bei der Darstellung der artifiziellen Bispidin-Liganden wurde auch für Bispidin-Naturstoffe ein effizienter und modularer Zugang erarbeitet, der auf einer „Inside-out"-Strategie basiert. Dabei erfolgte zunächst der Aufbau des chiralen Grundgerüsts, an dem die für jedes Derivat charakteristischen Strukturelemente angebracht wurden.

Da in den Naturstoffen beide enantiomere Formen des zentralen Bispidin-Kerns vorkommen, wurden beide Enantiomere des Diimids **83** durch Desymmetrisierung von Tetraoxobispidin (**88**) jeweils über fünf Stufen in 34% Ausbeute dargestellt. An **83** wurde ein Pyridon-Ring (lila markiert) aufgebaut, was in sechs Stufen mit 35% Ausbeute zu **89** führte.*



* Auf die analoge Darstellung des Enantiomers *ent*-**89** aus *ent*-**83** wurde im Rahmen dieser Dissertation verzichtet; stattdessen wurde leichter zugängliches, racemisches Material verwendet, um weiterführende Synthesen zu etablieren.

Aus den Schlüsselintermediaten **83** und **89** konnten verschiedene Naturstoffe synthetisiert werden. Dazu wurden Sequenzen etabliert um stereoselektiv *endo*-anellierte Piperidin-Ringe (grün markiert) wie in α-Isospartein (**27**) und Thermopsin (**54**), *exo*-anellierte Piperidin-Ringe (orange markiert) wie in β-Isospartein (**80**) und Anagyrin (**55**) sowie einen *exo*-ständigen Allyl-Rest (rot markiert) wie in Tinctorin (**110**) anzubringen. Insgesamt konnten über diesen effizienten Zugang 15 Bispidin-Alkaloide dargestellt werden – davon 12 in enantiomeren-reiner Form –, von denen nur eine kleine Auswahl abgebildet ist. Ein besonderer Erfolg war die erstmalige enantioselektive Totalsynthese von α-Isospartein (**27**), Anagyrin (**55**) und Tinctorin (**110**).

ABKÜRZUNGSVERZEICHNIS

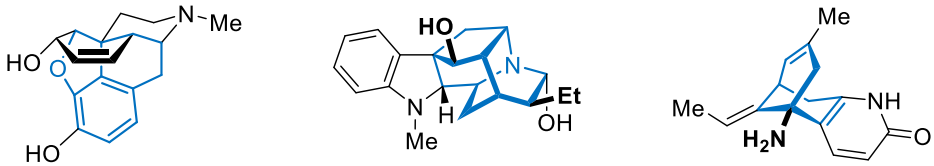
In den Formelbildern und im Text werden folgende Abkürzungen verwendet:

ADDP	1,1'-(Azodicarbonyl)dipiperidin
Äquiv.	Äquivalente
Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-en
de	Diastereomerenüberschuss
DEAD	Diethylazodicarboxylat
DIPEA	*N*,*N*-Diisopropylethylamin
DMAP	4-(Dimethylamino)pyridin
DMF	Dimethylformamid
DPEN	1,2-Diphenylethylendiamin
d.r.	Diastereomerenverhältnis
EDCI	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimid
ee	Enantiomerenüberschuss
Konfig.	Konfiguration
LDA	Lithiumdiisopropylamid
LiHMDS	Lithiumhexamethyldisilazid
Ms	Mesyl
Naph	Naphthyl
Piv	Pivaloyl
Py	Pyridin
RT	Raumtemperatur
TBAF	Tetrabutylammoniumfluorid
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoressigsäure
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylendiamin
TMS	Trimethylsilyl
Ts	*p*-Toluolsulfonyl
Δ	Erhitzen auf Siedetemperatur

1 EINLEITUNG

Selektive Wechselwirkungen spielen in der Biochemie und Pharmazie eine herausragende Rolle. Bereits 1894 postulierte Emil Fischer bei seinen Untersuchungen zur Enzymspezifität das sogenannte Schlüssel-Schloss-Prinzip: Nur wenn Substrat und Enzym wie Schlüssel und Schloss zueinander passen, kann eine Umsetzung stattfinden.[1] Entscheidend für die Selektivität ist hierbei die rigide Umgebung des Enzyms.[2]

Auch bei der spezifischen Erkennung von Wirkstoffen durch Rezeptoren ist die Rigidität, in diesem Fall die der Substrate, von Bedeutung: Zum einen ist die Bindung rigider Liganden entropisch günstiger als die flexibler, da die Beweglichkeit ersterer bereits vor der Anlagerung gering ist, zum anderen sind unspezifische Wechselwirkungen rein geometrisch eingeschränkt.[3] Somit eignen sich Wirkstoffe mit rigider Struktur besonders für pharmazeutische Anwendungen. Einige erfolgreiche Beispiele natürlichen Ursprungs sind in Abbildung 1 gezeigt. Morphin (**1**), das Hauptalkaloid des Schlafmohns,[4] besteht aus einem relativ flachen Molekülteil sowie zwei aus der Ebene herausragenden Ringen.[5] Es wirkt als selektiver Agonist des μ-Opioidrezeptors und wird seit der Antike als Schmerzmittel genutzt. Das Indol-Alkaloid Ajmalin (**2**) mit seiner käfigartigen Struktur wurde aus der Indischen Schlangenwurzel (*Rauwolfia serpentin*) isoliert.[6] Es wird unter dem Namen Gilurytmal® zur Behandlung von Herzrhythmusstörungen vertrieben.[7] Huperzin A (**3**), ein Lycopodium-Alkaloid aus *Huperzia serrata*, besitzt ein äußerst rigides [3.3.1]Nonen-Grundgerüst. Es wirkt als reversibler, sehr selektiver Inhibitor der Acetylcholinesterase, ist in China zur Behandlung von Morbus Alzheimer zugelassen und wird in den USA als Nahrungsergänzungsmittel bei Gedächtnisproblemen angeboten.[8]



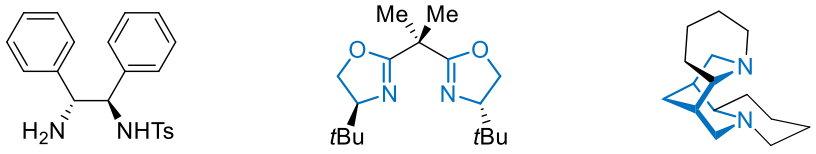
Morphin (**1**) Ajmalin (**2**) Huperzin A (**3**)

Abbildung 1. Morphin (**1**), Ajmalin (**2**) und Huperzin A (**3**) als Beispiele für pharmakologisch bedeutsame, rigide Naturstoffe.

Nicht nur in der Biochemie und Pharmazie, sondern auch in der chemischen Synthese und Katalyse sind selektive Wechselwirkungen von großer Bedeutung. Das ist insbesondere dann der Fall, wenn eine Reaktion nicht nur regio- und diastereoselektiv, sondern auch enantioselektiv ablaufen soll. Um dies zu realisieren, nutzen Chemiker rigide Reagenzien und Auxiliare, die eine definierte chirale Umgebung für die gewünschte Umsetzung erzeugen.

Zu den potentesten Katalysatoren für enantioselektive Reaktionen gehören Übergangsmetall-Komplexe.[9] Die hierfür verwendeten Liganden besitzen neben einem chiralen Rückgrat zwei oder mehr Heteroatome – vor allem Stickstoff, Phosphor oder Sauerstoff –, über die sie mit einem Metall starre Chelat-Komplexe bilden können. Im Vergleich zu phosphorbasierten Liganden besitzen stickstoffbasierte entscheidende Vorteile:[10] Zum einen sind Amine weitgehend luftstabil, was deren Handhabung erheblich erleichtert, und zum anderen sind bereits viele effiziente Syntheserouten zu chiralen Diaminen ausgehend von enantiomerenreinen Naturstoffen oder Grundchemikalien bekannt. Auch finden einige Alkaloide direkt Einsatz als Liganden.

In Abbildung 2 sind drei prominente Diamin-Liganden gezeigt. Ein sehr bekanntes Beispiel ist das Tosylamin (**4**). Obwohl es kein intrinsisch starres Grundgerüst besitzt, bildet **4** äußerst rigide Komplexe, mit denen in Noyoris asymmetrischer Transferhydrierung hervorragende Enantiomerenüberschüsse erzielt werden.[11] Der chirale Box-Ligand **5** besteht aus zwei rigiden, über einen Linker verknüpften Oxazolidin-Ringen. Übergangsmetall-Komplexe von **5** liefern exzellente Resultate in einer Vielzahl enantioselektiver Katalysen, wie beispielsweise in Cyclopropanierungen, (Nitro-)Aldol- und Diels-Alder-Reaktionen.[12] (–)-Spartein (**6**), ein Alkaloid aus dem Besenginster (*Cytisus scoparius*), besitzt ein rigides Bispidin-Grundgerüst, das mit einem *endo*- und einem *exo*-anellierten Ring funktionalisiert ist.[13] Durch die perfekte räumliche Anordnung der beiden Stickstoffatome bildet es stabile Komplexe mit den meisten Metallen.[14] Das Diamin **6** gilt in stöchiometrischer Menge als Ligand der Wahl für enantioselektive Deprotonierungen, findet aber auch in der asymmetrischen Metall-Katalyse viele Anwendungen (s. Kapitel 1.2.1).



(*S*,*S*)-TsDPEN (**4**) | (*S*)-*t*Bu-Box (**5**) | (–)-Spartein (**6**)

Abbildung 2. Erfolgreiche Diamin-Liganden: TsDPEN (**4**), der *t*Bu-Box-Ligand (**5**) und (–)-Spartein (**6**).

Zum Erfolg von (–)-Spartein (**6**) als Ligand trug auch bei, dass es aus natürlichen Quellen verfügbar und vergleichsweise günstig käuflich zu erwerben war. Vor einigen Jahren verschwand es allerdings vom Markt.[15,16] Eine Einschränkung ist zudem, dass der Naturstoff (+)-Spartein (*ent*-**6**), welcher für enantiokomplementäre Umsetzungen benötigt wird, nicht in nennenswerter Ausbeute isoliert werden kann. Zwar existieren mehrere Totalsynthesen von (–)- und (+)-Spartein (**6** und *ent*-**6**; s. Kapitel 1.3.2), diese sind jedoch aufwändig und können nicht die benötigten Mengen liefern.

Eine Möglichkeit, um die genannten Probleme von Spartein (**6**) zu umgehen, ist die Entwicklung neuer, vereinfachter Bispidin-Liganden. O'Brien und Mitarbeitern gelang die Etablierung eines (+)-Spartein-Ersatzstoffs **7**[17,18] (Abbildung 3; aus Gründen der Anschaulichkeit ist das Enantiomer *ent*-**7** gezeigt), der neben dem rigiden Bispidin-Grundgerüst nur noch einen *endo*-anellierten Ring trägt. Der Ligand **7** lässt sich einfacher darstellen und liefert in den meisten Umsetzungen gleichwertige Ergebnisse zu (–)-Spartein (**6**). Daraus lässt sich ableiten, dass vor allem der *endo*-anellierte Ring in **6** und **7** (grün markiert) für die Stereokontrolle verantwortlich ist (für Details s. Kapitel 1.2.1).

Um den Einfluss des *endo*-anellierten Rings auf den Stereotransfer genauer zu untersuchen und leistungsfähigere Liganden zu finden, wäre es denkbar, dieses Strukturelement weiter zu modifizieren. Ein vielversprechender Kandidat könnte der artifizielle Bispidin-Ligand **8**[19] sein, der einen *endo*-anellierten Pyrrolidin-Ring trägt. Damit der sterische Anspruch des Fünfrings im Komplex ausreichend groß ist, wären möglicherweise zusätzliche Substituenten R an **8** notwendig.[20]

Der synthetische Aufwand zur Herstellung Spartein-ähnlicher Liganden könnte zudem verringert werden, indem man auf das Bispidin-Grundgerüst verzichtet. Stattdessen könnte ein Diamin genutzt werden, das erst durch Komplexierung eines Metalls eine ähnliche, rigide Geometrie einnimmt. Ein solcher Ligand wäre beispielsweise ein Prolinamin **9**: Der Pyrrolidin-Ring als Grundstruktur sollte weniger flexibel sein als ein entsprechender Sechsring. Ein zusätzlicher 5-*cis*-Substituent R^1 könnte den sterischen Block oberhalb des Metallzentrums vergrößern; darüber hinaus sollte er eine pseudo-äquatoriale Position am Pyrrolidin-Ring einnehmen und somit als konformativer Anker wirken.

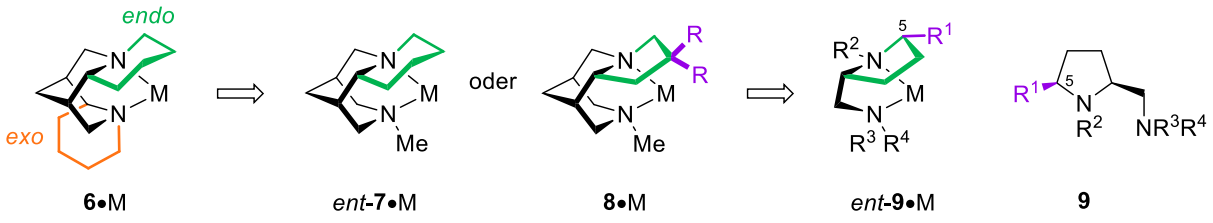


Abbildung 3. Sukzessive Vereinfachung von (–)-Spartein (**6**) als chiralem Liganden[13] über die artifiziellen Bispidin-Liganden **7**[17,18] und **8**[19] hin zu 5-*cis*-substituierten Prolinaminen **9**.

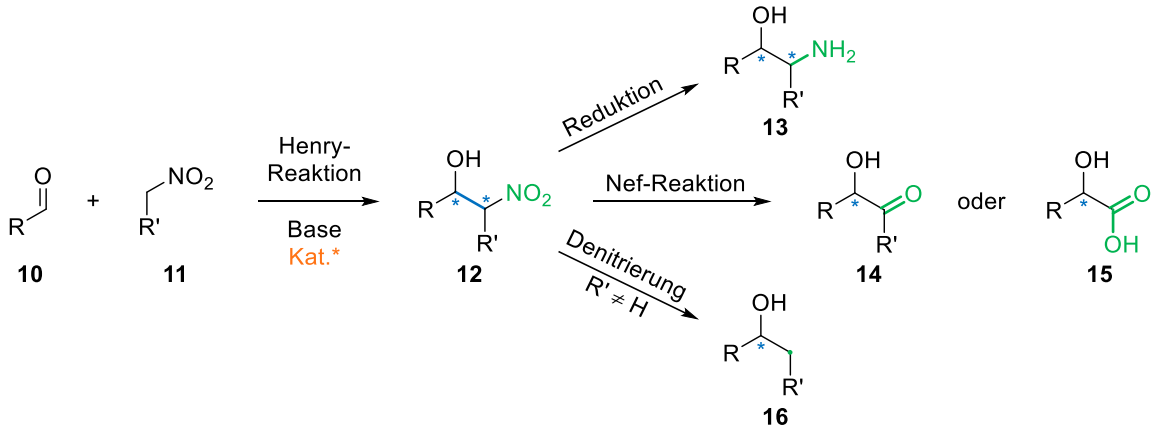
Aus diesen Überlegungen ergeben sich die drei Arten von rigiden, chiralen Diaminen, mit denen sich die vorliegende Dissertation beschäftigt: 5-*cis*-substituierte Prolinamine **9** als stark vereinfachte Bispidin-Ersatzstoffe für die Übergangsmetall-Katalyse, artifizielle Bispidin-Liganden wie **7** und **8** und schließlich die Bispidin-Naturstoffe selbst, mit (–)-Spartein (**6**) als ihrem bekanntesten Vertreter. In den folgenden Kapiteln wird der Stand der Forschung auf diesen Gebieten genauer vorgestellt.

1.1 Prolinamine in der enantioselektiven Übergangsmetall-Katalyse

Während 5-*cis*-substituierte Prolinamine **9** als chirale Liganden bisher keine Beachtung fanden, wurden mit am Pyrrolidin-Grundkörper unsubstituierten Derivaten in der enantioselektiven Übergangsmetall-Katalyse bereits beachtliche Ergebnisse erzielt. So konnten beispielsweise in Sn-katalysierten Mukaiyama-Aldol-Additionen,[21] Diethylzink-Additionen an Aldehyde,[22] oxidativen Biaryl-Kupplungen[23] und insbesondere in Cu-katalysierten Henry-Reaktionen[24,25] die Produkte mit über 90% *ee* isoliert werden. Im Folgenden wird die letztgenannte Umsetzung detaillierter dargestellt.

1.1.1 Cu•Prolinamin-katalysierte enantioselektive Henry-Reaktionen

Die Henry- oder Nitroaldol-Reaktion ist eine wichtige Methode zur C-C-Bindungsknüpfung (Schema 1).[26] Dabei addiert basenkatalysiert ein Nitroalkan **11** an einen Aldehyd **10** und bildet einen β-Nitroalkohol **12**. Durch Verwendung eines chiralen Katalysators – besonders geeignet hierfür erwiesen sich Cu•Diamin-Komplexe[27] – können dabei stereoselektiv ein oder zwei Stereozentren aufgebaut werden. Aus den Produkten **12** lassen sich dann wertvolle Synthese-Bausteine wie beispielsweise Aminoalkohole **13**, Ketone **14**, Carbonsäuren **15** oder Alkohole **16** gewinnen.[28]

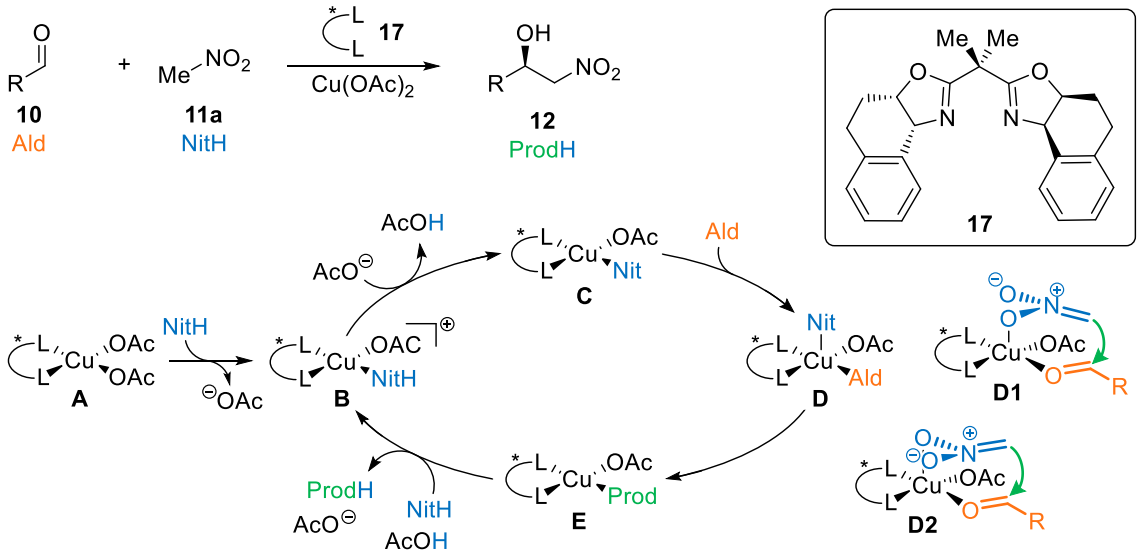


Schema 1. Die Henry-Reaktion[26,27] als Ausgangspunkt für wertvolle Synthese-Bausteine.[28]

1.1.1.1 Mechanismus und Übergangszustand

Zur Erklärung der Stereoselektivität der Henry-Reaktion wurden verschiedene Mechanismen und Übergangszustände postuliert. Ein allgemein akzeptierter, aber nicht experimentell belegter Vorschlag stammt von Evans und Mitarbeitern, die in ihren Untersuchungen $Cu(OAc)_2$ als Kupferquelle und den Box-Liganden **17** als chirales Diamin verwendeten (Schema 2).[29] Zunächst bildet sich der quadratisch-planare Cu•Diamin-Komplex **A**, an dem ein Acetat gegen Nitromethan (**11a**) ausgetauscht wird (→ **B**). Freies Acetat wirkt als Base und deprotoniert **11a** im Komplex **B** zum Nitronat (→ **C**). An **C** kann nun der Aldehyd **10** koordinieren, wobei sich ein quadratisch-pyramidaler Komplex **D** bildet. Im reaktiven Übergangszustand **D** wird der Aldehyd maximal aktiviert, wenn er eine der beiden stärker Lewis-sauren Koordina-

tionsstellen in der Liganden-Ebene einnimmt. Das Nitronat bindet an eine der beiden weniger Lewis-sauren Positionen ober- oder unterhalb dieser Ebene. Die exakte Ausrichtung der Reaktanden zueinander wird dabei von den sterischen und elektronischen Eigenschaften des chiralen Liganden bestimmt. So vorkoordiniert addiert das Nitronat stereoselektiv über einem Sessel- (**D1**) oder Boot-Übergangszustand (**D2**) an den Aldehyd. Das an **E** gebundene Produkt **12** wird durch Austausch gegen Nitromethan freigesetzt; dadurch wird der aktive Katalysator **B** zurückerhalten.

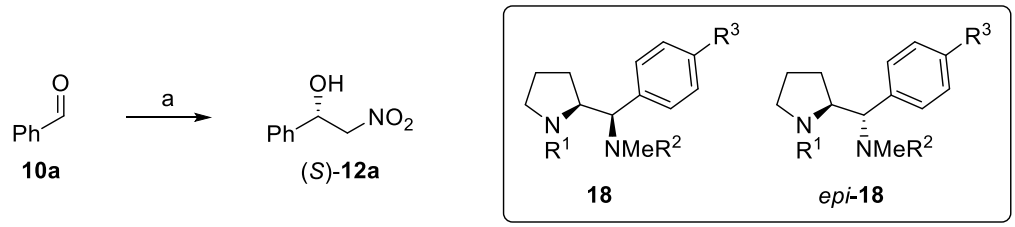


Schema 2. Postulierter Mechanismus der Cu•Diamin-katalysierten Henry-Reaktion nach Evans *et al.*[29]

1.1.1.2 Prolinamine 18 von Kałuża *et al.*

Kałuża und Mitarbeiter evaluierten die Prolin-abgeleiteten Diamine **18** als Liganden in der Cu-katalysierten Henry-Reaktion (Tabelle 1).[24] Charakteristisch an **18** ist der zusätzliche aromatische Substituent an der exocyclischen Methylen-Gruppe, der ein weiteres Stereozentrum erzeugt. Dessen Konfiguration ist entscheidend für einen guten Stereotransfer, wie der Vergleich der beiden Epimere **18a** und *epi*-**18a** zeigte (R^1–R^3 = H, 75% vs. –5% *ee*, Einträge 1 und 2). Während eine weitere Methyl-Gruppe am exocyclischen Amin fast keinen Einfluss auf die Umsetzung hatte (**18b**, R^2 = Me, 72% *ee*, Eintrag 3), sank der *ee* mit einem tertiären Pyrrolidin-Stickstoff deutlich (**18c**, R^1 = Me, 42% *ee*, Eintrag 4). Den besten Chiralitätstransfer lieferte ein 4-Methoxyphenyl-substituiertes Derivat (**18d**, R^3 = OMe, 83% *ee*, Eintrag 5). Nach Optimierung der Reaktionsbedingungen wurden unter Verwendung von $Cu(OAc)_2$•**18d** als Katalysator verschiedene Nitroalkohole **12** mit bis zu 92% *ee* erhalten.

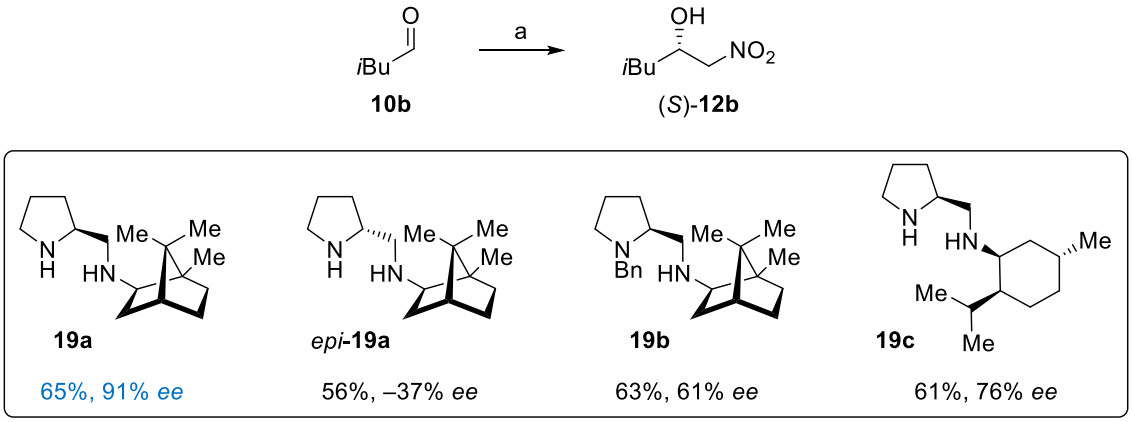
Tabelle 1. Von Kałuża *et al.* entwickelte Prolinamine **18** in der Henry-Reaktion.[24]
Reagenzien und Bedingungen: a) $Cu(OAc)_2$•**18** (10 Mol-%), NEt_3 (5 Mol-%), $MeNO_2$ (**11a**), *i*PrOH, 0 °C.



Eintrag	Prolinamin **18**	R^1	R^2	R^3	Ausbeute [%]	*ee* [%]
1	**18a**	H	H	H	87	75
2	*epi*-**18a**	H	H	H	80	–5
3	**18b**	H	Me	H	83	72
4	**18c**	Me	Me	H	82	42
5	**18d**	H	H	OMe	95	83

1.1.1.3 Prolinamine 19 von Gong *et al.*

Dass bei der Wahl geeigneter Stickstoff-Substituenten auf die exocyclische Phenyl-Gruppe in Kałużas Liganden **18** verzichtet werden kann, zeigen die Arbeiten von Gong und Mitarbeitern.[25] Das von ihnen etablierte Prolinamin **19a** zählt zu den leistungsfähigsten Diaminen für Cu-katalysierte Henry-Reaktionen (Schema 3). Der Ligand **19a** trägt neben dem Stereozentrum am Pyrrolidin-Ring weitere Stereoelemente in Form eines Bornyl-Rests am exocyclischen Amin. Die relative Konfiguration ist hierbei essenziell für eine hervorragende Stereoinduktion: Während im „matched"-Fall mit **19a** der Nitroalkohol (*S*)-**12b** mit guten 91% *ee* gebildet wird, liegt der *ee* von (*R*)-**12b** im „mismatched"-Fall mit *epi*-**19a** bei nur 37%. Eine zusätzliche Benzyl-Gruppe am Pyrrolidin-Stickstoff wie in **19b** wirkt sich negativ auf den Stereotransfer aus (61% *ee*), ebenso der Austausch des Bornyl- gegen einen Menthyl-Rest



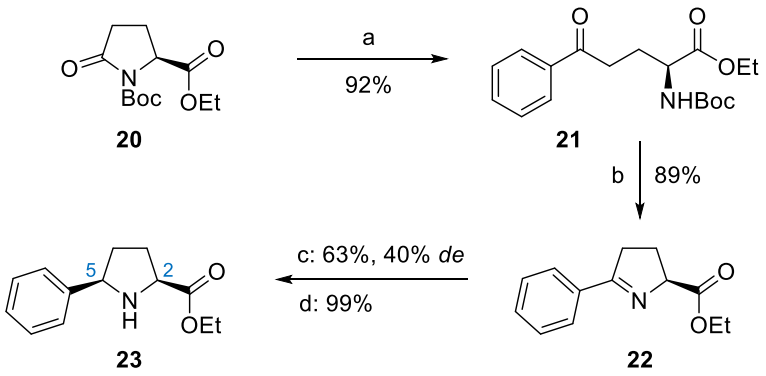
Schema 3. Von Gong *et al.* entwickelte Prolinamine **19** in der Henry-Reaktion.[25a]
Reagenzien und Bedingungen: a) **19** (5 Mol-%), $Cu(OAc)_2$•H_2O (5 Mol-%), DIPEA, $MeNO_2$ (**11a**), EtOH, 4 °C.

(**19c**, 76% *ee*). Unter optimierten Bedingungen lieferte der Kupfer-Komplex von **19a** in enantioselektiven Henry-Reaktionen die Produkte **12** mit ausgezeichneten Enantiomerenüberschüssen von bis zu 99% (an drei Substraten) und in enantio- und diastereoselektiven Reaktionen mit einem d.r. von bis zu 90:10 und bis zu 98% *ee* im Hauptdiastereomer.

Gerade im Hinblick auf die Substratbreite (99% *ee* als Ausnahme) sind die in der enantioselektiven Henry-Reaktion mit Prolinaminen erzielten Ergebnisse durchaus noch optimierbar. Durch Variation der Substituenten an den Stickstoffatomen und an der exocyclischen Methylengruppe – insbesondere durch das Anbringen zusätzlicher Stereoelemente – wurden bereits viele Möglichkeiten zur Optimierung ausgeschöpft. Prolinamine mit einem 5-*cis*-Substituenten wurden bisher jedoch nicht evaluiert, obwohl ein solcher Rest, als zusätzlicher sterischer Block oder konformativer Anker, von Vorteil sein könnte (s. Abbildung 3, S. 13).

1.1.2 Synthese von 5-*cis*-substituierten Prolinestern

Synthesen von 5-*cis*-substituierten Prolin-Derivaten sind in der Literatur bereits bekannt; sie nutzen meist ähnliche Sequenzen ausgehend von einem Derivat der Pyroglutaminsäure. Als Beispiel ist die Darstellung des 5-*cis*-Phenyl-Prolinesters **23** aus dem *N*-Boc-geschützen Ethylester **20** gezeigt (Schema 4).[30] Der anzubringende Rest wurde zunächst als Grignard-Reagenz an **20** addiert, wodurch das offenkettige Keton **21** entstand. Nach *N*-Boc-Entschützung erfolgte die Recyclisierung zum Imin **22**. Während die Reduktion von **22** mit Natriumcyanoborhydrid das Produkt nur mit einem schwachen Diastereomerenverhältnis von 70:30 lieferte,[30b] konnte via Hydrierung das *cis*-2,5-disubstituierte Pyrrolidin **23** diastereomerenrein erhalten werden.[30a]



Schema 4. Synthese des 5-*cis*-Phenyl-substituierten Prolinesters **23** ausgehend vom geschützten Pyroglutaminsäureester **20**.[30]
Reagenzien und Bedingungen: a) PhMgBr, THF, –78 °C → –40 °C; b) TFA, CH_2Cl_2, 0 °C → RT; NEt_3; c) $NaBH_3CN$, konz. HCl, *i*PrOH, RT;[30b] d) H_2 (30 bar), PtO_2, EtOH, RT.[30a]

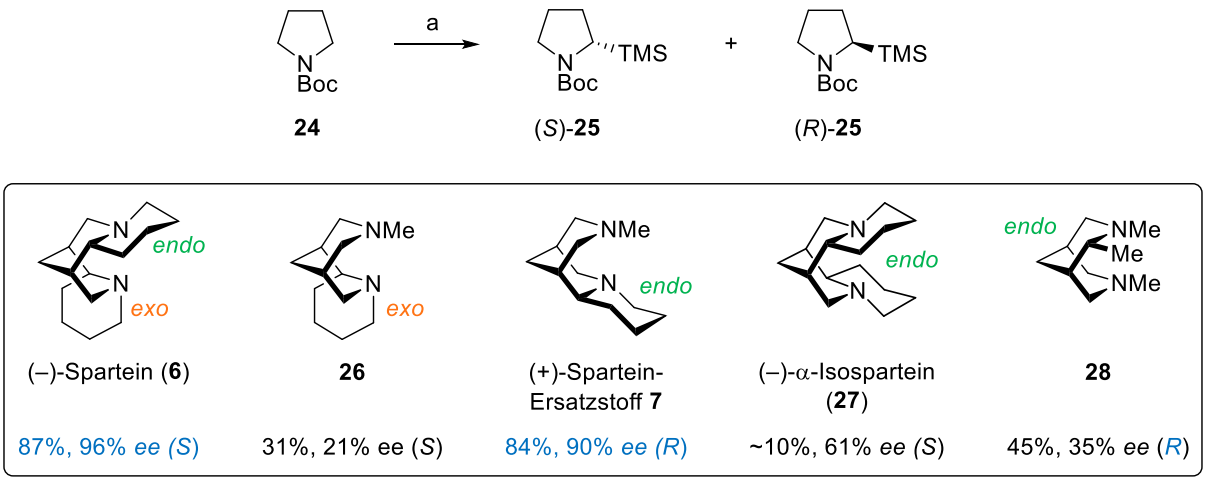
1.2 Chirale Bispidin-Liganden

1.2.1 Anwendungen in der enantioselektiven Synthese und Katalyse

Aufgrund ihrer Rigidität und der guten Chelatisierungseigenschaften[14] eignen sich Bispidine hervorragend als chirale Reagenzien für die asymmetrische Synthese. Insbesondere in enantioselektiven Deprotonierungen[31] gelten der Naturstoff (–)-Spartein (**6**; Abbildung 3, S. 13) und der (+)-Spartein-Ersatzstoff **7** als Liganden der Wahl. Aber auch in der Übergangsmetall-Katalyse konnten mit **6** und **7** sehr gute Ergebnisse erzielt werden, etwa in Cu-katalysierten Henry-Reaktionen,[32,33] in Pd-katalysierten oxidativen kinetischen Racematspaltungen von Alkoholen[34] oder in Desymmetrisierungen von *meso*-Anhydriden durch Grignard-Addition,[35] um nur einige Beispiele zu nennen. Im Folgenden werden Modellreaktionen vorgestellt, anhand derer mit **6**, **7** und weiteren artifiziellen Bispidinen und 9-Oxabispidinen Struktur-Selektivitäts-Untersuchungen durchgeführt wurden.

1.2.1.1 Stöchiometrische Deprotonierungen an Carbamaten

Eine der prominentesten Modellreaktionen mit (–)-Spartein (**6**) als (über)stöchiometrischem[36] Liganden ist die von Beak *et al.* entdeckte, enantioselektive Deprotonierung von *N*-Boc-Pyrrolidin (**24**), die nach elektrophilem Abfang mit TMSCl das Silan **25** liefert (Schema 5).[37] Anhand dieser Umsetzung wurden Struktur-Selektivitäts-Studien mit verschiedenen Bispidin-Liganden durchgeführt, um den Einfluss der Substituenten am Grundgerüst auf den Stereotransfer zu untersuchen. In Gegenwart von (–)-Spartein (**6**), das einen *endo*- und einen *exo*-ständigen anellierten Piperidin-Ring trägt, wurde (*S*)-**25** in exzellenten 87% Ausbeute und 96% *ee* erhalten.[38] Mit dem Bispidin **26**, das ausschließlich den *exo*-anellierten Ring besitzt, wurden nur geringe 21% *ee* erzielt,[39] während der *endo*-substituierte (+)-Spartein-Ersatzstoff **7** (*R*)-**25** in sehr guten 90% *ee* lieferte.[17] Daraus lässt sich schlussfolgern, dass der *endo*-ständige Ring essenziell für einen guten Stereotransfer ist, während der *exo*-anellierte Ring nur einen kleinen Beitrag leistet.[40] Bei Verwendung von α-Isospartein (**27**), dem C_2-symmetrischen, di-*endo*-substituierten Isomer von (–)-Spartein (**6**), wurde (*S*)-**25** in schlechten 10% Ausbeute und mit mäßigen 61% *ee* isoliert.[41] Möglicherweise verhindert hier ein zu großer sterischer Anspruch in der Nähe der Koordinationsstelle eine effiziente Reaktion. Der gleiche Trend wurde auch mit Derivaten von **7** beobachtet, die statt der *N*-Methyl-Gruppe einen größeren Ethyl-, Neopentyl- oder *iso*-Propyl-Rest am Stickstoff tragen.[20] Reduziert man ausgehend vom Ersatzstoff **7** den sterischen Anspruch des *endo*-Substituenten auf ein Minimum – wie mit der Methyl-Gruppe in **28** geschehen – sank der *ee* von **25** enorm (35%).[40a] Warum mit dem zu **7** enantiokomplementären Liganden **28** wider Erwarten ebenfalls das (*R*)-konfigurierte Produkt gebildet wurde, konnte nicht erklärt werden.

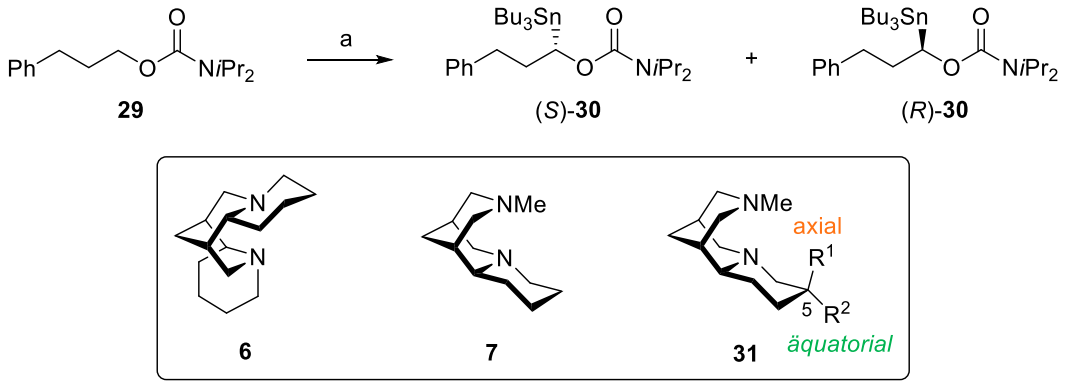


Schema 5. Struktur-Selektivitäts-Untersuchung mit verschiedenen Bispidin-Liganden anhand der enantioselektiven Deprotonierung–Silylierung von *N*-Boc-Pyrrolidin (**24**).[17,38-41]
Reagenzien und Bedingungen: a) Bispidin (1.3 Äquiv.), *s*BuLi (1.3 Äquiv.), Et_2O, –78°C; TMSCl, –78°C → RT.

Um die Leistungsfähigkeit des (+)-Spartein-Ersatzstoffs **7** – auch im Vergleich zu (–)-Spartein (**6**) – zu steigern, wären also Modifikationen am stereochemisch entscheidenden *endo*-anellierten Ring am vielversprechendsten. Diese These untersuchten Breuning und Hein.[42] Sie synthetisierten die Liganden **31**, die am *endo*-anellierten Piperidin-Ring in 5-Position axiale (R^1) oder äquatoriale (R^2) Substituenten tragen, und evaluierten ihr Potenzial anhand einer Variante der von Hoppe *et al.* entwickelten, enantioselektiven Deprotonierung von *O*-Alkylcarbamaten[43] (Tabelle 2). Mit (–)-Spartein (**6**) wurde bei der Umsetzung von **29** mit *s*BuLi und elektrophilem Abfang mit Bu_3SnCl das Stannan (*S*)-**30** in hervorragenden 98% *ee* erhalten (Eintrag 1), mit dem (+)-Spartein-Ersatzstoff **7** entstand (*R*)-**30** in schwächeren 92% *ee* (Eintrag 2).[17] Eine äquatoriale Methyl-Gruppe wie in **31a** änderte, verglichen mit **7**, nichts am Stereotransfer (92% *ee*, R^2 = Me, Eintrag 3), ein sterisch anspruchsvoller *iso*-Propyl-Rest R^2 hingegen ließ den *ee* im Produkt auf 51% sinken (**31b**, Eintrag 4).[42] Auch mit dem axial Methyl-substituierten Derivat **31c** (R^1 = Me, 79% *ee*, Eintrag 5) und dem Dimethyl-substituierten **31d** ($R^{1/2}$ = Me, 34% *ee*, Eintrag 6) war die Stereoinduktion deutlich geringer als mit dem unsubstituierten Liganden **7**. Der große Unterschied im Chiralitätstransfer von **31c** und **31d** – trotz des augenscheinlich vergleichbaren sterischen Anspruchs der Substituenten – wurde mit einer Konformationsänderung erklärt: In **31c** liegt der anellierte Piperidin-Ring nicht als Sessel vor, der Methyl-Rest kann sich von der Koordinationsstelle zwischen den beiden Stickstoffen wegdrehen. Im disubstituierten Derivat **31d** ist dies nicht möglich, und die axiale Methyl-Gruppe verhindert einen effektiven Stereoübertrag. Insgesamt zeigte sich, dass durch eine gezielte Vergrößerung des sterischen Anspruchs des Piperidin-Rings in **7** kein positiver Effekt auf den Stereotransfer erzielt werden kann.

Tabelle 2. Bispidin-Liganden in der enantioselektiven Deprotonierung–Stannylierung des *O*-Alkylcarbamats **29**.[17,42]

Reagenzien und Bedingungen: a) Bispidin (1.3 Äquiv.), *s*BuLi (1.3 Äquiv.), Et_2O, –78°C; Bu_3SnCl, –78°C → RT.

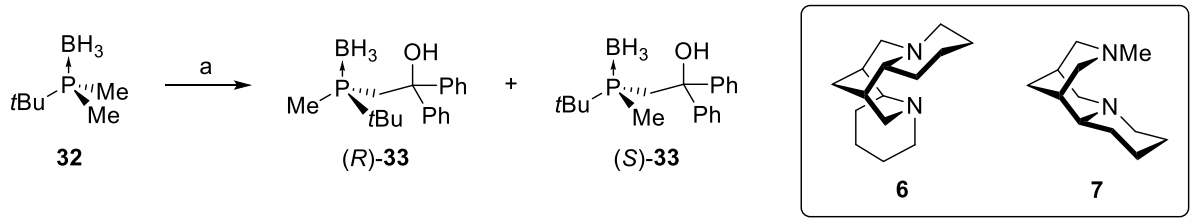


Eintrag	Bispidin	R^1	R^2	Ausbeute [%]	*ee* [%] (Konfig.)
1	**6**	–	–	68	98 (*S*)
2	**7**	–	–	84	92 (*R*)
3	**31a**	H	Me	66	92 (*R*)
4	**31b**	H	*i*Pr	64	51 (*R*)
5	**31c**	Me	H	70	79 (*R*)
6	**31d**	Me	Me	71	34 (*R*)

1.2.1.2 Katalytische Deprotonierungen von Phosphinoboranen

Eine weitere wichtige Modellreaktion zur Evaluierung von Bispidin-Liganden ist die enantioselektive Deprotonierung von Dimethyl-Phosphinoboranen mit anschließendem Benzophenon-Abfang (Tabelle 3).[44] Diese Umsetzung ist unter anderem deshalb interessant, weil neben den üblichen Protokollen mit überstöchiometrischen Mengen des chiralen Diamins[45] auch solche mit katalytischen Mengen[46] bekannt sind. In Gegenwart von 1.2 Äquivalenten (–)-Spartein (**6**) bzw. des (+)-Spartein-Ersatzstoffs **7** konnten die Alkohole (*R*)- oder (*S*)-**30** jeweils in guten 90% *ee* erhalten werden (Einträge 1 und 2).[45] Wurden nur 0.2 Äquivalente **6** oder **7** verwendet, sank der *ee* im Produkt deutlich auf 60% bzw. 72% (Einträge 3 und 4).[46] Interessant ist hier, dass die Umsetzung mit katalytischen Mengen **7** ein deutlich besseres Ergebnis lieferte als mit **6**. Dies liegt wahrscheinlich daran, dass die Deprotonierung mit **6** langsamer abläuft als mit **7** und die unselektive Hintergrundreaktion dadurch relativ gesehen schneller ist. Durch portionsweise Zugabe von *s*BuLi in Gegenwart von nur 0.3 Äquivalenten des chiralen Liganden konnte der *ee* wieder auf akzeptable 72% mit **6** und gute 82% mit **7** gesteigert werden (Einträge 5 und 6).

Tabelle 3. Die enantioselektive Deprotonierung des Phosphinoborans **32** in Gegenwart überstöchiometrischer[45] oder katalytischer Mengen[46] von (–)-Spartein (**6**) oder des (+)-Spartein-Ersatzstoffs **7** mit anschließendem Benzophenon-Abfang.
Reagenzien und Bedingungen: a) Bispidin, *s*BuLi, Et_2O, –78°C; Ph_2CO, –78°C → RT.

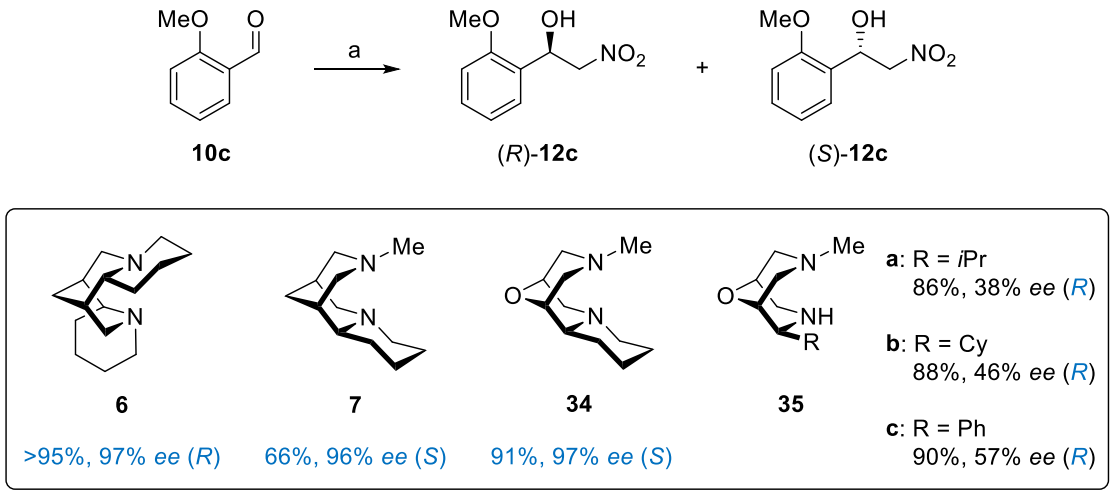


32 (*R*)-**33** (*S*)-**33**

Eintrag	Bispidin	Äquiv. Bispidin	Äquiv. *s*BuLi	Ausbeute [%]	*ee* [%] (Konfig.)
1	**6**	1.2	1.1	88	90 (*S*)
2	**7**	1.2	1.1	89	90 (*R*)
3	**6**	0.2	1.1	64	60 (*S*)
4	**7**	0.2	1.1	63	72 (*R*)
5	**6**	0.3	0.3 + 0.35 + 0.35	89	72 (*S*)
6	**7**	0.3	0.3 + 0.35 + 0.35	83	82 (*R*)

1.2.1.3 Kupfer-katalysierte Henry-Reaktionen

In Cu-katalysierten Henry-Reaktionen (s. Kapitel 1.1.1) konnten, anders als in den vorgestellten Deprotonierungen, mit katalytischen Mengen (–)-Spartein (**6**)[32] oder des (+)-Spartein-Ersatzstoffs **7**[33] hervorragende Ergebnisse erzielt werden (Schema 6). Bei der Umsetzung von 2-Methoxybenzaldehyd (**10c**) mit Nitromethan (**11a**) in Gegenwart von 20 Mol-% **6**•$CuCl_2$ wurde der Nitroalkohol (*R*)-**12c** in exzellenten 97% *ee* erhalten, mit **7**•$CuCl_2$ entstand (*S*)-**12c** in 96% *ee*. Breuning und Mitarbeiter evaluierten in dieser Reaktion auch die 9-Oxabispidine **34** und **35**.[47] Das zu **7** analoge Derivat **34**, das ebenfalls einen *endo*-anellierten Piperidin-Ring trägt, lieferte (*S*)-**12c** in 91% Ausbeute und ausgezeichneten 97% *ee*. Das Potenzial des Katalysators **34**•$CuCl_2$ wurde anschließend durch Umsetzung von 13 aromatischen und aliphatischen Aldehyden **10** zu den entsprechenden Nitroalkoholen (*S*)-**12** in 91–98% *ee* bestätigt. Mit den Liganden **35**, die statt dem anellierten Ring *endo*-ständige Substituenten (R = *i*Pr, Cy oder Ph) tragen, erhielt man wiederum (vgl. Schema 5, **28** als Ligand) das enantiokomplementäre Produkt (*R*)-**12c** in nur mäßigen 38–57% *ee*.



Schema 6. (9-Oxa-)Bispidin-Liganden in der enantioselektiven Henry-Reaktion von 2-Methoxybenzaldehyd (**10c**).[32,33,47]
Reagenzien und Bedingungen: a) $CuCl_2$•(9-Oxa-)Bispidin (20 Mol-%), NEt_3 (3 Mol-%), $MeNO_2$ (**11a**), MeOH, 0 °C oder –10 °C.

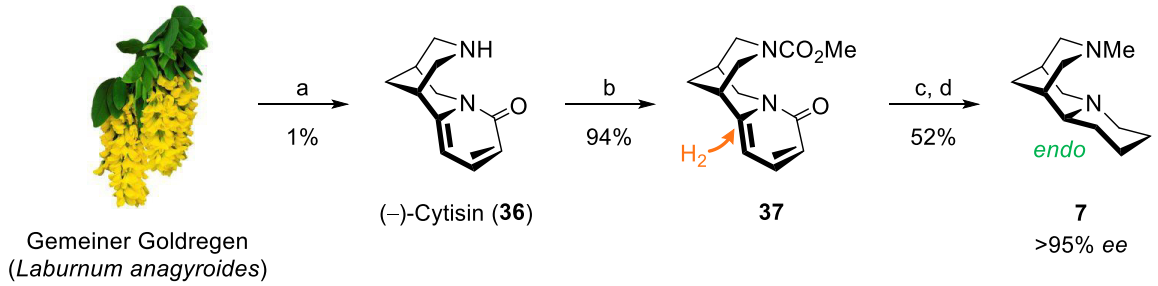
Zusammenfassend lässt sich feststellen, dass ein *endo*-anellierter Piperidin-Ring am Bispidin essenziell für hohe Enantiomerenüberschüsse ist. Erhöht man an dieser Stelle den sterischen Anspruch, führt die zunehmende Hinderung zum *ee*-Verlust im Produkt (s. Tabelle 2). Ersetzt man den anellierten Ring durch einen *endo*-ständigen Substituenten, wird vorzugsweise das enantiokomplementäre Produkt in geringer optischer Reinheit gebildet (s. Schemata 5 und 6). Ob hingegen eine Verkleinerung des *endo*-anellierten Sechsrings hin zu einem Pyrrolidin wie im Bispidin-Liganden **8** (s. Abbildung 3, S. 13) den *ee* positiv beeinflussen könnte, war bisher nicht Gegenstand der Forschung.

1.2.2 Darstellung artifizieller Bispidin-Liganden

Im Folgenden werden ausgewählte Routen zur Synthese einiger, in Kapitel 1.2.1 bereits vorgestellter artifizieller Bispidin-Liganden aufgezeigt.

1.2.2.1 (+)-Spartein-Ersatzstoff 7

Zur Darstellung des (+)-Spartein-Ersatzstoffs **7** und seines Enantiomers *ent*-**7** existieren in der Literatur einige Syntheserouten.[48] Ein äußerst effizientes Protokoll ausgehend von (–)-Cytisin (**36**) entwickelten O'Brien und Mitarbeiter (Schema 7).[17,18a] Der Naturstoff **36** ist das Hauptalkaloid des Gemeinen Goldregens (*Laburnum anagyroides*; gezeigt sind die traubigen Blütenstände) und kann in ein bis zwei Gewichtsprozent aus dessen Samen isoliert werden.[49] Nach Umsetzung von **36** ins Carbamat **37** wurde der Pyridon-Ring in den anellierten Piperidin-Ring überführt: Dabei erfolgte die Hydrierung der beiden Doppelbindungen stereoselektiv von der konvexen Seite des Bispidins, was die *endo*-Stellung festlegte. Im Anschluss wurde die Amid-Carbonyl-Gruppe mit $LiAlH_4$ entfernt und gleichzeitig das Carbamat zur *N*-Methyl-Gruppe reduziert. Über diese dreistufige Sequenz war der (+)-Spartein-Ersatzstoff **7** in 49% Ausbeute mit >95% *ee* im Gramm-Maßstab aus (–)-Cytisin (**36**) zugänglich.

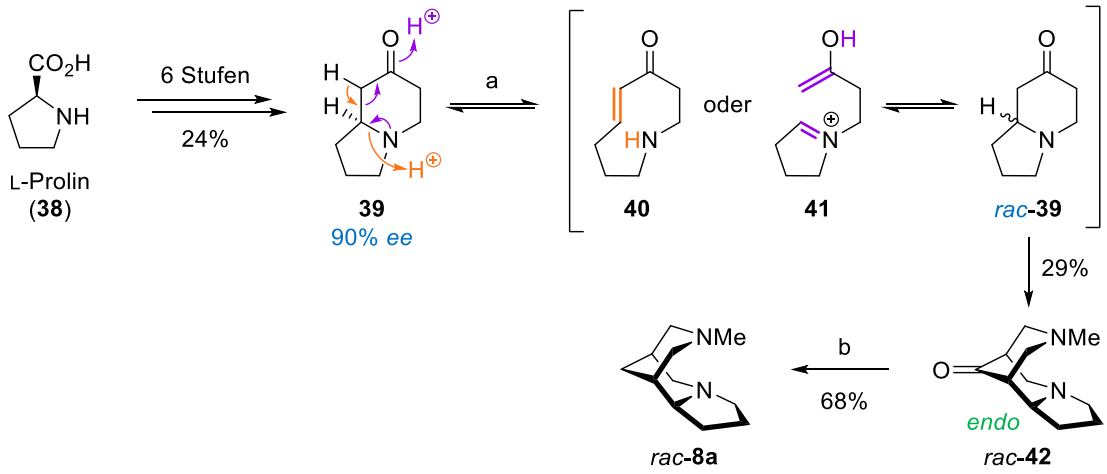


Schema 7. Partialsynthese des (+)-Spartein-Ersatzstoffs **7** aus (–)-Cytisin (**36**).[18a]
Reagenzien und Bedingungen: a) NH_4Cl, MeOH, CH_2Cl_2, RT; b) $ClCO_2Me$, NEt_3, CH_2Cl_2, RT; c) H_2, PtO_2, MeOH, RT; d) $LiAlH_4$, THF, Δ.

Modifikationen der in Schema 7 gezeigten Sequenz erlauben die Variation des Rests am nördlichen Stickstoff[35b] sowie das Einführen von Substituenten in α-Position zur ehemaligen Carbonyl-Gruppe im Piperidin-Ring (vgl. Liganden **31**, Tabelle 2).[42]

1.2.2.2 Bispidin mit anelliertem Fünfring *rac*-8a

Auch der Bispidin-Ligand *ent*-**8a**, der am Grundgerüst einen *endo*-anellierten Pyrrolidin-Ring trägt, war bereits das Ziel synthetischer Untersuchungen von O'Brien *et al.* (Schema 8).[50] Ausgehend von L-Prolin (**38**) konnte zunächst das Keton **39** über sechs Stufen in 24% Ausbeute mit 90% *ee* präpariert werden.[50a] Anschließend sollte durch eine doppelte Mannich-Reaktion das Bispidin-Grundgerüst mit dem *endo*-ständigen Ring aufgebaut werden (→ **42**). Dies gelang diastereoselektiv, allerdings nur in geringen 29% Ausbeute und unter vollständigem Verlust der optischen Reinheit. Vermutlich erfolgte unter den harschen Reaktionsbedingungen eine Racemisierung von **39** via retro-Michael-Reaktion zu **40** oder retro-Mannich-Reaktion zu **41** und Recyclisierung. Trotz dieses Rückschlags wurde die Ketogruppe in *rac*-**42** entfernt, was den Liganden *rac*-**8** in insgesamt acht Stufen und mit 5% Gesamtausbeute lieferte. Der Versuch einer Racematspaltung von *rac*-**8a** durch Kristallisation mit verschiedenen chiralen Alkoholen und Säuren blieb erfolglos.[50b]



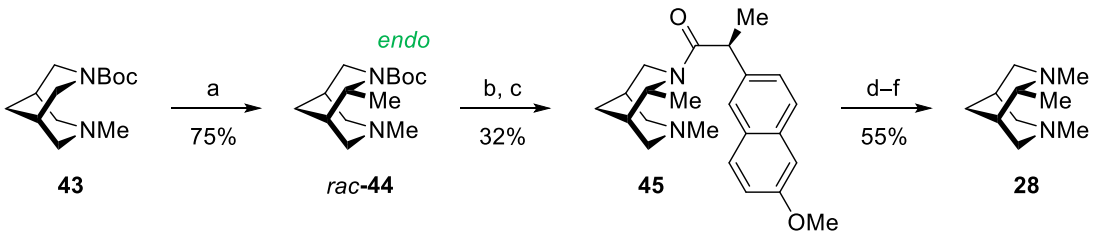
Schema 8. Synthese des Bispidin-Liganden *rac*-**8a**.[50a]
Reagenzien und Bedingungen: a) $MeNH_2$, $(CH_2O)_n$, AcOH, MeOH, Δ; b) $N_2H_4 \bullet H_2O$, KOH, Diethylenglykol, Δ.

Selbst wenn sich eine Auftrennung der Enantiomere realisieren ließe, wäre die in Schema 8 gezeigte Sequenz zu **8a** ungeeignet für Variationen am Pyrrolidin-Ring: Unterschiedliche Substituenten müssten bereits vor Aufbau des Bispidin-Grundgerüsts vorhanden sein, und der synthetische Aufwand wäre damit relativ groß.

1.2.2.3 Methyl-substituiertes Bispidin 28

Der *endo*-Methyl-substituierte Bispidin-Ligand **28** konnte aus racemischen Vorstufen durch Racematspaltung mit Hilfe eines chiralen Auxiliars enantiomerenrein dargestellt werden (Schema 9).[40a] Zunächst wurde am achiralen, unsubstituierten Bispidin **43** durch Lithiierung und Abfang mit Methyliodid stereoselektiv der *endo*-ständige Methyl-Rest angebracht (→ *rac*-**44**).[51] Austausch der *N*-Boc-Gruppe gegen einen chiralen Acyl-Rest lieferte das Amid **45**, das nach Chromatographie diastereomerenrein isoliert werden konnte. Das Auxiliar wurde anschließend im Sauren abgespalten und die *N*-Methyl-Gruppe installiert. Insgesamt lieferte diese Route **28** über sechs Stufen in 13% Ausbeute.

Zur Darstellung von Derivaten mit anderen *endo*-ständigen Substituenten lässt sich die gezeigte Sequenz leider nicht nutzen, da die Abfangreaktion nach der Deprotonierung von **43** nur mit kleinen, reaktiven Elektrophilen gelingt.[51]

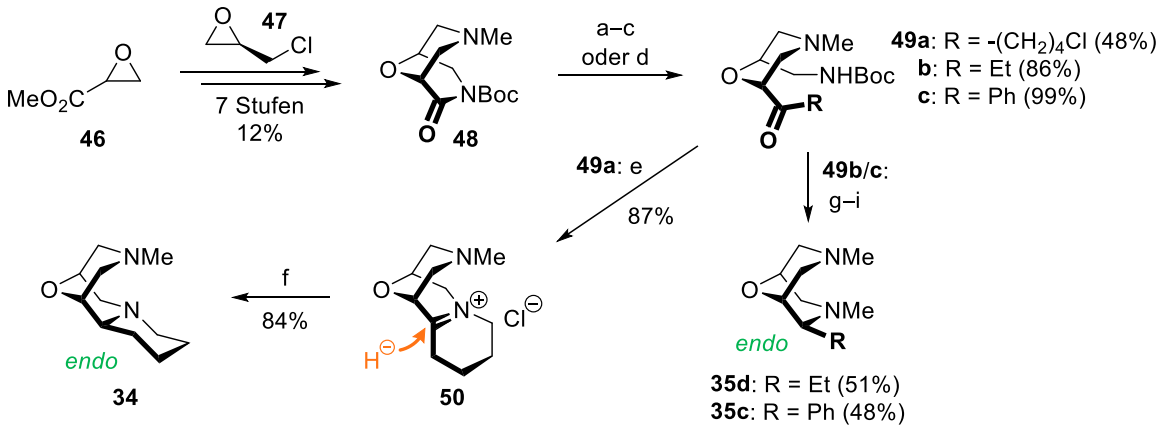


Schema 9. Darstellung des enantiomerenreinen Bispidin-Liganden **28** durch Racematspaltung.[40a] *Reagenzien und Bedingungen*: a) TMEDA, *s*BuLi, Cyclopentan, –78 °C; MeI, –78 °C → RT; b) TFA, CH_2Cl_2, RT; c) (*S*)-2-(6-Methoxy-2-naphthyl)propionsäure, EDCI, CH_2Cl_2, RT; Chromatographie; d) AcOH, konz. HCl, 120 °C; e) Boc_2O, CH_2Cl_2, RT; f) $LiAlH_4$, THF, Δ.

Keine der bisher entwickelten Routen zu artifiziellen Bispidinen eignet sich, wie an den drei vorgestellten Synthesen illustriert, zur effizienten Variation der Strukturelemente. Folglich wäre die Darstellung neuer Derivate für weiterführende Struktur-Selektivitäts-Untersuchungen äußerst aufwändig. Diese Lücke würde ein neuer, modularer Zugang schließen. Als Schlüsselintermediat [52] könnte ein chirales, entsprechend vorfunktionalisiertes Bispidin-Grundgerüst genutzt werden, an dem sich mit geringem synthetischem Aufwand eine Vielzahl unterschiedlicher Substituenten anbringen ließe.

1.2.2.4 Modulare Synthese der 9-Oxabispidine 34 und 35

Die Effizienz einer solchen modularen Synthese demonstrierten Breuning *et al.* anhand der Darstellung der 9-Oxabispidine **34** und **35** (Schema 10).[53] Das chirale Imid **48** als Schlüsselintermediat konnte in sieben Stufen mit 12% Ausbeute aus Glycidsäuremethylester (**46**) und (*R*)-Epichlorhydrin (**47**) synthetisiert werden. An **48** wurde zum Aufbau des anellierten Sechsrings in **34** zunächst der 4-OTBS-substituierte Butyl-Grignard addiert, die TBS-Gruppe anschließend entfernt und via Appel-Reaktion ein Chlorid eingeführt (→ **49a**). Nach *N*-Boc-Entschützung von **49a** erfolgte auf basischem Alox die (Re)cyclisierung des 9-Oxabispidins und des anellierten Rings zu **50**. Die abschließende Reduktion des Iminiumions in **50** mit $NaBH_4$ verlief stereoselektiv von der konvexen Seite des Moleküls und legte die *endo*-Konfiguration des Rings im Liganden **34** fest. In analogen Sequenzen wurden die *endo*-substituierten 9-Oxabispidine **35d** (R = Et) und **35c** (R = Ph) dargestellt. Somit konnten die Liganden **34** und **35** ausgehend vom gemeinsamen Intermediat **48** in vier bis fünf Stufen und 35–48% Ausbeute erhalten werden.[54]



Schema 10. Modulare Synthese der 9-Oxabispidine **34** und **35** über das chirale Imid **48** als Schlüsselintermediat.[53]

Reagenzien und Bedingungen: a) $TBSO(CH_2)_4MgBr$, THF, –78 °C; b) $TBAF{\bullet}H_2O$, THF, RT; c) PPh_3, CCl_4, CH_2Cl_2, RT → Δ; d) EtMgBr bzw. PhMgBr, THF, –78 °C; e) TFA, CH_2Cl_2, –15 °C → RT; bas. Al_2O_3; f) $NaBH_4$, MeOH, –10 °C → 0 °C; g) TFA, 0 °C; NaOH; h) H_2, $Pd(OH)_2/C$, konz. HCl, EtOH, RT; i) MeI, K_2CO_3 oder Cs_2CO_3, CH_2Cl_2, RT.

1.3 Bispidin-Naturstoffe

Die Bispidin-Alkaloide – eigentlich Bischinolizidin-Alkaloide – bilden eine Klasse von pflanzlichen Sekundär-Metaboliten mit etwa 70 Mitgliedern, von denen eine kleine Auswahl in Abbildung 4 gezeigt ist.[55] Die Naturstoffe kommen hauptsächlich in der Familie der Fabaceae (Hülsenfrüchtler) vor, auch in heimischen Gewächsen wie zum Beispiel dem Gewöhnlichen Besenginster (*Cytisus scoparius*), dem Gemeinen Goldregen (*Laburnum anagyroides*) oder der Vielblättrigen Lupine (*Lupinus polyphyllus*).[56]

Bispidin-Alkaloide sind chiral und kommen in zwei enantiomeren Serien vor, die sich in den Anknüpfungspunkten der Substituenten am Grundgerüst unterscheiden (**6**, **51**–**53** vs. **36**, **54**–**56**). Wichtige Strukturelemente sind vor allem *endo*- und *exo*-anellierte Piperidin-Ringe (grün bzw. orange markiert) wie in (–)-Spartein (**6**; Verwendung als Ligand s. Kapitel 1.2.1) und der anellierten 2-Pyridon-Ring (lila) wie in (–)-Cytisin (**36**). Einige Vertreter tragen zudem einen *endo*-anellierten Piperidon-Ring (blau) wie Lupanin (**51**), einen *exo*-Allyl-Substituenten (rot) wie Angustifolin (**52**) oder einen Pyrrolidin-Ring wie Camoensin (**56**). Außerdem existieren verschiedenste Hydroxy-, Oxo- und Dehydro-Derivate wie beispielsweise Multiflorin (**53**). Die große Anzahl an Bispidin-Naturstoffen ergibt sich durch die Kombination aller Strukturmerkmale.

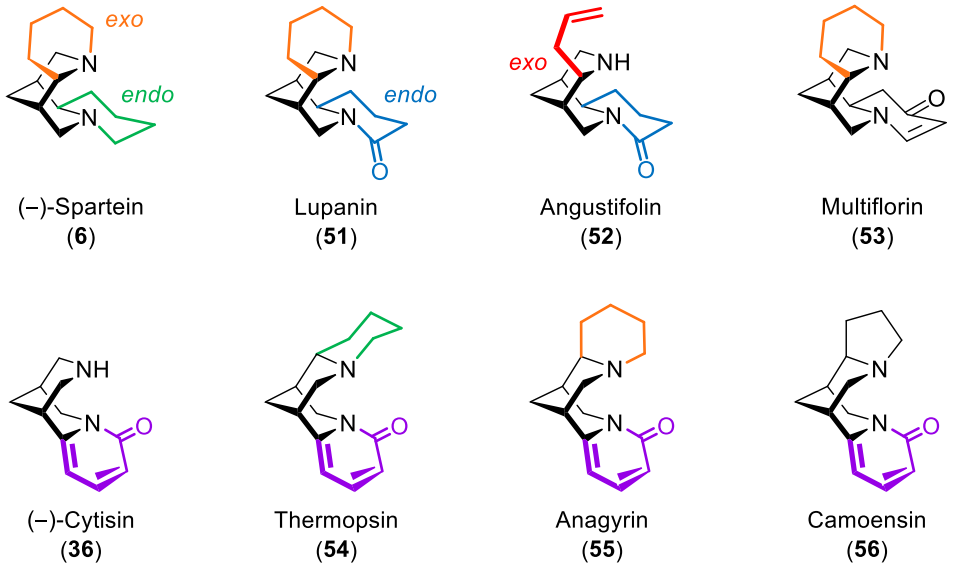


Abbildung 4. Einige ausgewählte Bispidin-Alkaloide mit unterschiedlichen Substitutionsmustern.

1.3.1 Biochemische Aktivitäten

Die biochemischen Eigenschaften der Bispidin-Alkaloide sind äußerst vielfältig. (–)-Spartein (**6**) und Lupanin (**51**), die am weitesten verbreiteten Vertreter dieser Klasse, dienen den Pflanzen zur chemischen Verteidigung:[55b,c] Sie wirken bakteriostatisch und fungistatisch, sind fraßhemmend für Schnecken und toxisch für Insekten; außerdem vermindern sie die Keimfähigkeit und das Wachstum anderer Pflanzen. Zudem ist Anagyrin (**55**) teratogen und verursacht Missbildungen bei neugeborenen Kälbern.

Auch aus pharmakologischer Sicht besitzen Bispidin-Naturstoffe höchst interessante Aktivitäten:[55b,c,e] Zum Beispiel wirkt (–)-Spartein (**6**) antiarrhythmisch und wehenfördernd, Multiflorin (**53**) ist blutzuckersenkend. (–)-Cytisin (**36**), ein selektiver, partieller Agonist des nikotinischen Acetylcholin-Rezeptors (nAChR), wird unter den Handelsnamen Desmoxan® und Tabex® in Mittel- und Osteuropa zur Raucherentwöhnung verkauft.[57]

1.3.2 Enantioselektive Totalsynthesen

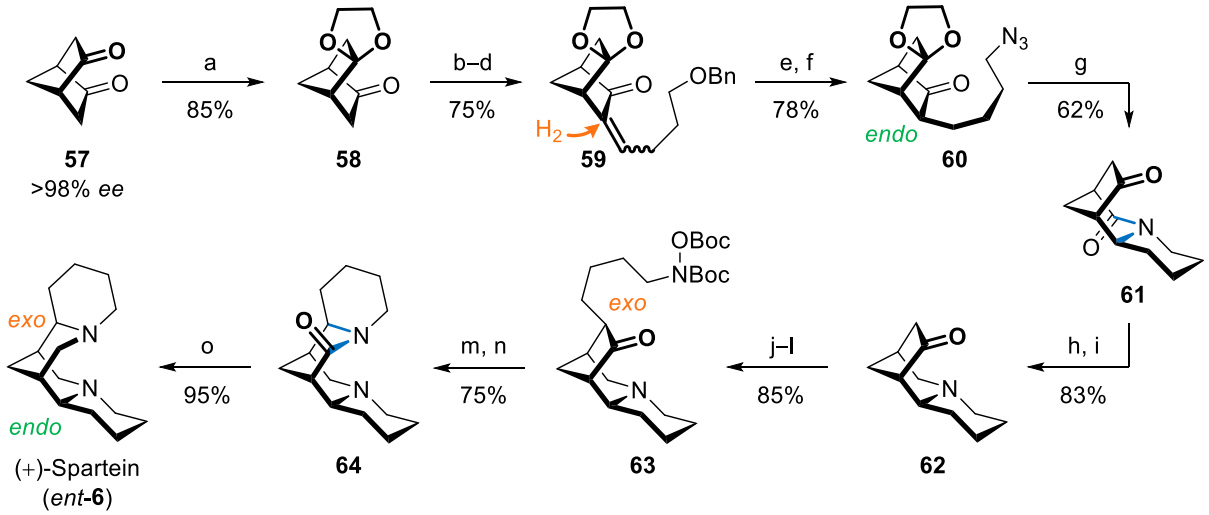
Aufgrund ihrer außergewöhnlichen Struktur und der vielfältigen Eigenschaften sind die Bispidin-Naturstoffe beliebte Ziele der enantioselektiven Totalsynthese. Insbesondere für Spartein (**6**)[58] und Cytisin (**36**),[59] aber auch für einige andere Vertreter,[60] wurden bereits elegante Zugänge entwickelt, von denen einige ausgewählte im Folgenden vorgestellt werden.

1.3.2.1 (+)-Spartein (*ent*-**6**) und (–)-Spartein (**6**)

Die erste enantioselektive Synthese von (+)-Spartein (*ent*-**6**) wurde 2002 von Aubé und Mitarbeitern publiziert (Schema 11).[58a] Ausgangspunkt war das bekannte, chirale Bicyclo[2.2.1]-hepta-2,5-dion (**57**),[61] an dem unter Erweiterung des Grundgerüsts zum Bispidin die anellierten Ringe aufgebaut wurden.

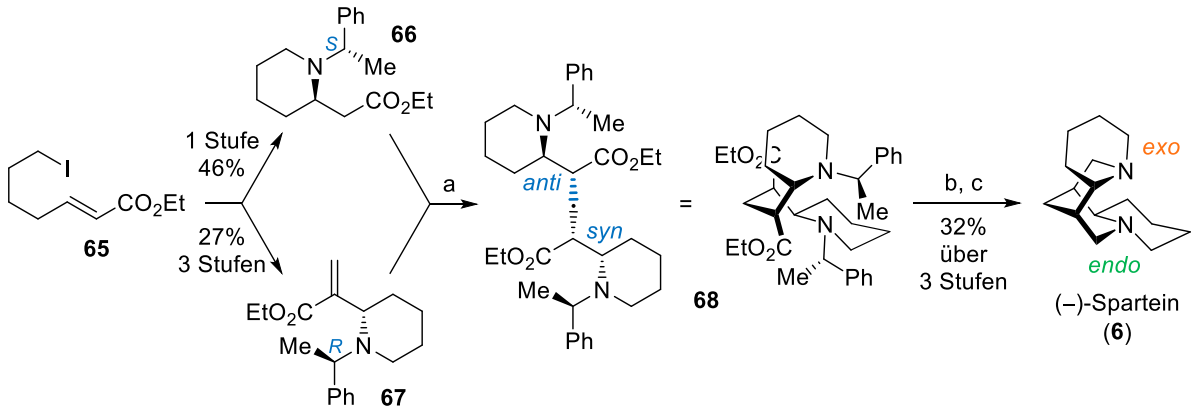
Zunächst sollte der *endo*-Substituent an **57** angebracht werden. Die angestrebte Aldol-Kondensation zum Enon **59** gelang allerdings erst nach Acetalisierung einer der Carbonyl-Gruppen (→ **58**). Hydrierung der Doppelbindung in **59** von der konvexen Seite legte die gewünschte *endo*-Anordnung des Rests fest. Nach Einführung eines Azids (→ **60**) erfolgte in einer Schmidt-Reaktion die Umlagerung zum Lactam **61**. Durch Alkylierung, die erst nach der Reduktion von **61** zum Amin **62** in zufriedenstellender Ausbeute möglich war, wurde der *exo*-ständige Rest installiert. Leider scheiterte der Versuch, auch den zweiten anellierten Ring (→ **64**) analog dem ersten mittels Schmidt-Reaktion aufzubauen. Daher musste auf eine Photo-Beckmann-Umlagerung zurückgegriffen werden: Am *exo*-Substituenten wurde ein Hydroxylamin angebracht (→ **63**), welches nach Boc-Entschützung unter Belichtung ins Keton insertierte und das Lactam **64** lieferte. Finale Reduktion ergab (+)-Spartein (*ent*-**6**) über insgesamt 15 Stufen in 16% Ausbeute.

Diese erste Sequenz zu (+)-Spartein (*ent*-**6**) offenbart, welche Tücken die Synthese von Bispidin-Naturstoffen bereithält: Auf den ersten Blick ist es vollkommen unverständlich, wieso eine Funktionalisierung von **58** und **62**, nicht aber von **57** (Zersetzung) und **61** (<20% Ausbeute), realisiert werden konnte. Eine mögliche Erklärung wäre, dass an diesen rigiden Käfigstrukturen kleinste Konformationsänderungen über den Erfolg oder Misserfolg einer Reaktion entscheiden.



Schema 11. Enantioselektive Synthese von (+)-Spartein (*ent*-**6**) nach Aubé *et al.*[58a]
Reagenzien und Bedingungen: a) Ethylenglykol, TsOH, THF, Δ; b) LDA, THF, –78 °C; BnO-$(CH_2)_3CHO$, –78 °C → 0 °C; c) MsCl, NEt_3, CH_2Cl_2, 0 °C; d) DBU, THF, Δ; e) H_2 (4 bar), Pd/C, $Pd(OH)_2$, Al_2O_3, EtOH, RT; f) PPh_3, $Zn(N_3)$•2Py, DEAD, Benzol, RT; g) $TiCl_4$, CH_2Cl_2, 0 °C → RT; h) Lawessons Reagenz, Benzol, Δ; i) Raney-Ni, EtOH, RT; j) LDA, THF, –78 °C; 1-Chlor-4-Iodbutan, –78 °C → 0 °C; k) NaI, Aceton, Δ; l) NH(OBoc)Boc, K_2CO_3, DMF, RT; m) TFA, Molsieb, CH_2Cl_2, RT; n) hv, Benzol, RT; o) $LiAlH_4$, THF, Δ.

Eine kürzere Sequenz zu (–)-Spartein (**6**), die chirale Auxiliare zum Einbringen der Stereoinformation verwendete, wurde von O'Brien und Mitarbeitern entwickelt (Schema 12).[58b] Ausgehend vom Iodid **65** wurde mit (*S*)-Phenylethylamin der Ester **66** und mit (*R*)-Phenylethylamin der Michael-Akzeptor **67** aufgebaut. Der nachfolgende Schlüsselschritt, die Michael-Addition von **66** an **67**, lieferte diastereoselektiv den Diester **68**. Während der hydrogenolytischen Abspaltung der Auxiliare erfolgte *in situ* die Cyclisierung zum Bispidin-Gerüst, wobei die *anti*-*syn*-Konfiguration in **68** die *endo*- bzw. *exo*-Anordnung der Piperidin-Ringe im Produkt vorgab. Finale Reduktion der gebildeten Amide lieferte schließlich **6** in insgesamt sechs Stufen mit 9% Ausbeute.

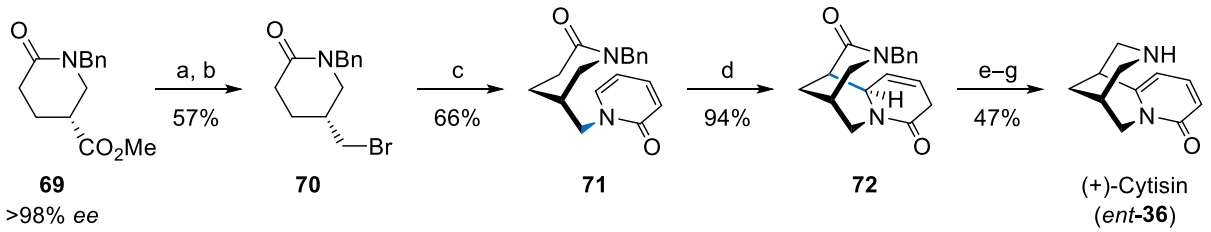


Schema 12. Auxiliar-vermittelte Darstellung von (–)-Spartein (**6**) nach O'Brien *et al.*[58b]
Reagenzien und Bedingungen: a) **66**, LDA, THF, –78 °C; **67**, –78 °C → –30 °C; b) $Pd(OH)_2/C$, NH_4HCO_2, EtOH, Δ; c) $LiAlH_4$, THF, Δ.

1.3.2.2 (+)-Cytisin (*ent*-36)

Gallagher und Gray publizierten eine elegante, enantioselektive Synthese von (+)-Cytisin (*ent*-**36**, Schema 13).[59d] Ausgangspunkt ihrer Route war das chirale Lactam **69**, welches durch enzymatische Racematspaltung in >98% *ee* zugänglich war. Nach Umsetzung zum Bromid **70** wurde zunächst der 2-Pyridon-Ring via S_N2-Reaktion in einem Stück eingebracht (→ **71**). Die Cyclisierung zum Bispidin-Gerüst erfolgte über eine intramolekulare 1,6-Addition (→ **72**). Nach oxidativer Rearomatisierung zum Pyridon-Ring, Reduktion und Entschützung wurde (+)-Cytisin (*ent*-**36**) über diese Sequenz in insgesamt sieben Stufen und mit 17% Ausbeute erhalten.

Über analogen Routen wurden auch racemisches Thermopsin (**54**; s. Abbildung 4) und Anagyrin (**55**) dargestellt,[59d] was für die Flexibilität dieses Ansatzes spricht. Der synthetische Aufwand dabei war jedoch beträchtlich, da die zusätzlichen anellierten Ringe an **54** und **55** bereits in den zu **70** analogen Startmaterialien vorhanden sein mussten und die gezeigte Schlüsselsequenz für jeden Naturstoff neu durchlaufen werden musste.

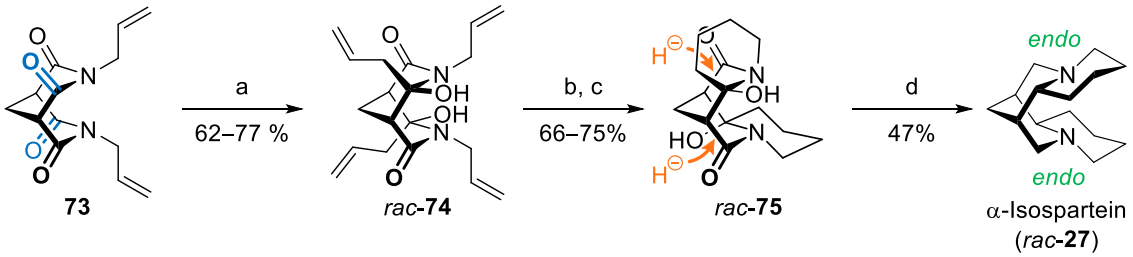


Schema 13. Enantioselektive Synthese von (+)-Cytisin (*ent*-**36**) nach Gallagher *et al.*[59d]
Reagenzien und Bedingungen: a) $LiAlH_4$, THF –10 °C; b) PBr_3, Toluol, Δ; c) 2-Pyridon, K_2CO_3, Bu_4NBr, H_2O, Toluol, Δ; d) LiHMDS, THF, Δ; e) MnO_2, CH_2Cl_2, RT; f) BH_3•THF, THF, 0 °C → RT; g) H_2, $Pd(OAc)_2$, HCl, MeOH, RT.

1.3.2.3 Modulare Synthese von racemischem α-Isospartein (*rac*-27), β-Isospartein (*rac*-80) und Spartein (*rac*-6)

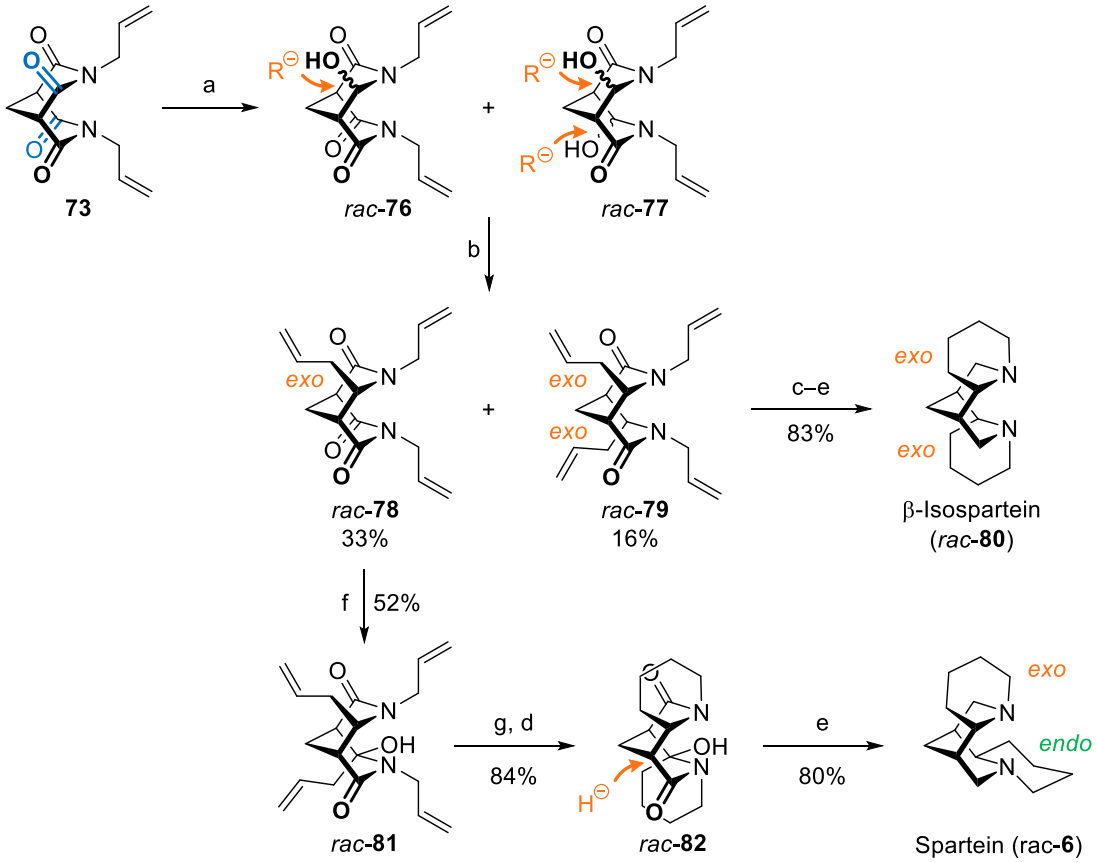
Eine modulare Synthese wurde – zumindest in racemischer Form – von Blakemore und Mitarbeitern für α-Isospartein (*rac*-**27**), β-Isospartein (*rac*-**80**) und Spartein (*rac*-**6**) realisiert (Schemata 14 und 15).[62] Hierbei verwendeten sie das *N*-allylierte Tetraoxobispidin **73** als gemeinsames Edukt.

Zunächst wurde α-Isospartein (*rac*-**27**) dargestellt (Schema 14).[62a,c] Die Umsetzung von **73** mit Allyl-Grignard liefert das Diaminal *rac*-**74**, wobei die Addition selektiv an zwei diagonal gegenüberliegenden Carbonyl-Gruppen erfolgte. Anschließend wurden durch Metathese die Sechsringe aufgebaut und die dabei entstandenen Doppelbindungen hydriert (→ *rac*-**75**). Die stereochemisch entscheidende Reduktion der Aminale und Amide in *rac*-**75** erfolgte von den konvexen Molekülseiten und erzeugte die *endo*-Konfiguration der anellierten Ringe im Produkt. α-Isospartein (*rac*-**27**) konnte so in vier Stufen und bis zu 27% Ausbeute erhalten werden.



Schema 14. Darstellung von α-Isospartein (*rac*-**27**) nach Blakemore *et al.*[62c]
Reagenzien und Bedingungen: a) AllylMgBr, THF, –78 °C; b) Grubbs 1 (4 Mol-%), CH_2Cl_2, RT; c) H_2, Pd/C, MeOH, H_2O, RT; d) BH_3•THF, THF, 0 °C → RT.

Zur Synthese von β-Isospartein (*rac*-**80**, Schema 15) war geplant, zunächst zwei gegenüberliegende Carbonylgruppen von **73** zu reduzieren, was aber nur mäßig gelang;[62b,c] das gewünschte Produkt *rac*-**77** wurde nur als Minderkomponente neben dem monoreduzierten Derivat *rac*-**76** gebildet. Das untrennbare Gemisch aus *rac*-**76** und *rac*-**77** wurde in einer Sakurai-Reaktion, bei der die Addition von den konvexen Seiten erfolgte, zum monosubstituierten Bispidin *rac*-**78** und dem disubstituierten *rac*-**79** umgesetzt. Durch Metathese, Hydrierung und Reduktion konnte β-Isospartein (*rac*-**80**) in insgesamt 13% Ausbeute über fünf Stufen dargestellt werden.



Schema 15. Synthese von β-Isospartein (*rac*-**80**) und Spartein (*rac*-**6**) nach Blakemore *et al.*[62c]
Reagenzien und Bedingungen: a) $NaBH_4$, THF, 0 °C; b) $AllylSiMe_3$, BF_3•OEt_2, CH_2Cl_2, RT; c) Grubbs 1 (2 Mol-%), CH_2Cl_2, RT; d) H_2, Pd/C, MeOH, H_2O, RT; e) $LiAlH_4$, THF, Δ; f) AllylMgBr, THF, –78 °C; g) Grubbs 2 (2 Mol-%), CH_2Cl_2, Δ.

Um zu Spartein (*rac*-**6**) zu gelangen, wurde *rac*-**78** in einer Grignard-Addition zu *rac*-**81** umgesetzt, Metathese und Hydrierung ergaben den Tetracyclus *rac*-**82**.[62c] Durch globale Reduktion (Angriff auf das Aminal auch hier von der konvexen Seite) wurde Spartein (*rac*-**6**) in sechs Stufen und 12% Ausbeute ausgehend von **73** erhalten.

In Blakemores modularer Synthese von α-Isospartein (*rac*-**27**), β-Isospartein (*rac*-**80**) und Spartein (*rac*-**6**) wurde die Konfiguration der anellierten Ringe hoch stereoselektiv durch die Reihenfolge der Reaktionsschritte festgelegt. Genutzt wurde dabei die Tatsache, dass der Angriff am Bispidin-Gerüst generell von der sterisch leichter zugänglichen, konvexen *exo*-Seite erfolgt.[63] Daraus resultiert, dass die Addition eines Nukleophils gefolgt von einer Reduktion einen *endo*-ständigen Substituenten liefert (Schema 14), die umgekehrte Abfolge hingegen einen *exo*-ständigen (Schema 15).

1.3.2.4 Vergleich der Synthesestrategien: „Inside-out“ und „Outside-in“

Die bisher vorgestellten Synthesen von Bispidin-Naturstoffen lassen sich nach der zugrundeliegenden Strategie in zwei Gruppen einteilen, die als „Outside-in“ und „Inside-out“ bezeichnet werden.[64]

Bei Anwendung der „Outside-in“-Strategie geht man von Edukten aus, die bereits die anellierten Ringe tragen, und baut daraus im Folgenden das zentrale Bispidin-Grundgerüst auf. Die Synthese von (–)-Spartein (**6**) nach O’Brien *et al.* (Schema 12)[58b] und von (+)-Cytisin (*ent*-**36**) nach Gallagher *et al.*[59d] (Schema 13) sind klassische Beispiele für diese Vorgehensweise.

Bei der „Inside-out“-Strategie wird hingegen zunächst das Grundgerüst aufgebaut und erst in weiteren Schritten die Peripherie angebracht. Der große Vorteil hierbei ist, dass die Substituenten mit geringerem synthetischem Aufwand variiert werden können, was für eine modulare Synthese essenziell ist. Blakemore *et al.* verfolgten diesen Ansatz bei der Darstellung von α-Isospartein (*rac*-**27**), β-Isospartein (*rac*-**80**) und Spartein (*rac*-**6**, Schemata 14 und 15).[62] Leider konnten über die gezeigten Routen nur racemische[65] Bispidin-Naturstoffe mit anellierten Sechsringen als Substituenten erhalten werden. Auch die Synthese von (+)-Spartein (*ent*-**6**) nach Aubé *et al.* (Schema 11)[58a] wendet im weiteren Sinn diese Strategie an. Aufgrund der aufgetretenen Probleme ist aber fraglich, ob über diese Route Variationen möglich wären. Ein allgemeiner Zugang zu Bispidin-Naturstoffen, der gleichzeitig enantioselektiv und variabel ist, steht also noch aus.

2 ZIELSETZUNG

In den vergangenen Jahrzehnten haben sich viele namhafte Arbeitsgruppen mit der Synthese und Anwendung chiraler Bispidine beschäftigt. Dies führte auf dem Gebiet der asymmetrischen Synthese und Katalyse zur Entwicklung hocheffizienter Verfahren, in denen sich (–)-Spartein (**6**) und der (+)-Spartein-Ersatzstoff **7** als chirale Liganden der Wahl herauskristallisierten. Zudem wurden elegante Routen zu wichtigen Bispidin-Naturstoffen erarbeitet. Trotz dieser Erfolge bleibt ein Hauptproblem: Die Synthese chiraler Bispidine ist noch immer sehr zeit- und arbeitsaufwändig, was die Darstellung maßgeschneiderter Liganden und die Totalsynthese von Naturstoffen stark einschränkt. Es bedarf somit dringend flexibler, breit nutzbarer Zugänge zu Kern-chiralen Bispidinen. Zudem sollte die Suche nach strukturell stark vereinfachten Ersatzstoffen vorangetrieben werden. Genau diese Aspekte – die Entwicklung von Ersatzstoffen und maßgeschneiderten Bispidin-Derivaten für die asymmetrische Synthese sowie die Totalsynthese von Bispidin-Naturstoffen – stehen im Mittelpunkt dieser Arbeit.

Teilprojekt 1: Suche nach Bispidin-Ersatzstoffen für die enantioselektive Katalyse

Aus Struktur-Selektivitäts-Studien ist bekannt, dass der *endo*-anellierte Piperidin-Ring, der weit in die aktive Sphäre reicht, in Bispidin-Metallkomplexen wie *ent*-**7**•M (Abbildung 5) essenziell für einen hohen Stereotransfer ist. Vereinfacht man das Bispidin-Gerüst, indem man einen Teil des Rückgrats entfernt, so verliert der Ligand an Rigidität. Um dies zu kompensieren, könnte der Abstand zwischen den beiden Stickstoffen verringert und statt dem flexibleren Sechsring ein Pyrrolidin-Ring verwendet werden, was zu Komplexen des Typs *ent*-**9**•M führen würde. Um die geringere Größe des Fünfrings auszugleichen, könnte ein zusätzlicher Substituent R^1 neben dem Ringstickstoffatom eingeführt werden. Dieser sollte zudem als konformativer Anker wirken und somit einen effizienten Chiralitätstransfer garantieren. Aus diesem Ansatz ergibt sich das erste Ziel dieser Arbeit, die Entwicklung effizienter und modularer Routen zu den 5-*cis*-substituierten Prolinaminen **9** und deren Evaluierung als chirale Liganden in der enantioselektiven Katalyse. Als Modellreaktion wurde die Cu-katalysierte Henry-Reaktion gewählt, da diese bereits erfolgreich mit Prolin- und Bispidin-Liganden durchgeführt wurde (s. Kapitel 1.1.1 und 1.2.1.3), was einen direkten Vergleich des Potenzials der neuen Liganden erlaubt.

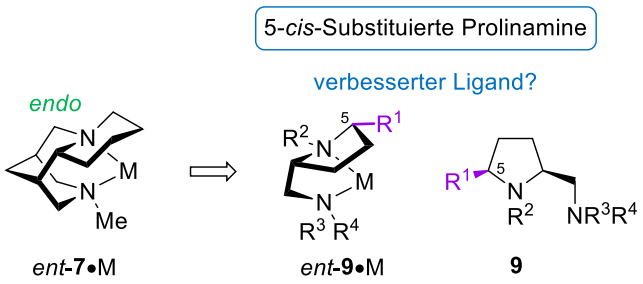


Abbildung 5. Erstes Ziel: Modulare Synthese von 5-*cis*-substituierten Prolinaminen **9** und deren Anwendung in der Cu-katalysierten Henry-Reaktion.

Teilprojekt 2: Entwicklung von artifiziellen Bispidin-Liganden für die enantioselektive Synthese und Katalyse

An Bispidin-Liganden wurden auf der Suche nach verbesserten Derivaten bereits einige Variationen durchgeführt – die Größe des stereochemisch entscheidenden *endo*-anellierten Rings wurde bisher jedoch noch nicht verändert. Durch ähnliche Überlegungen wie bei der Konzipierung der Prolinamine **9** gelangt man zu Bispidin-Liganden wie **8b**, die einen *endo*-anellierten, zusätzlich substituierten Fünfring tragen (Abbildung 6). Vergleicht man die 3D-Struktur von **8b** mit der Kristallstruktur von **7**•$CuCl_2$,[33] so fällt auf, dass eine der Methyl-Gruppen an **8b** (orange markiert) den linken oberen Quadranten am Metall effektiver abschirmen sollte als der Sechsring in **7**, was einen verbesserten Stereotransfer zur Folge haben könnte. Diese These zu überprüfen war das zweite Ziel dieser Dissertation. Hierfür sollte zunächst eine modulare Synthese von artifiziellen Bispidin-Liganden entwickelt werden. Die Leistungsfähigkeit der neuen Liganden wie beispielsweise **8b** könnte dann in enantioselektiven Deprotonierungen und in Cu-katalysierten Henry-Reaktionen untersucht werden (s. Kapitel 1.2.1).

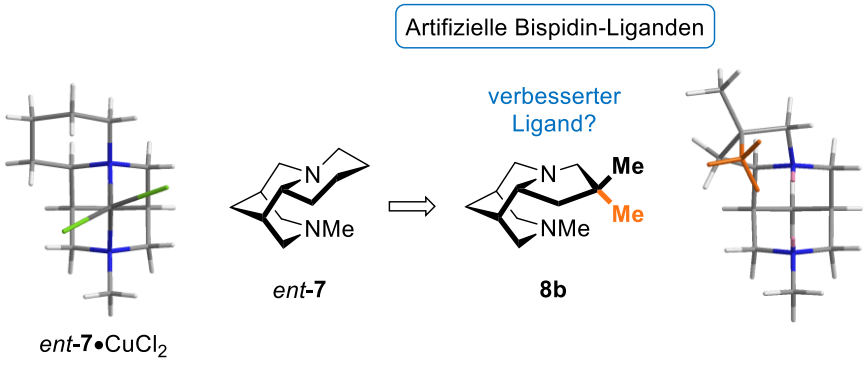


Abbildung 6. Zweites Ziel: Modulare Synthese von artifiziellen Bispidin-Liganden wie beispielsweise **8b** und deren Einsatz in Modellreaktionen.

Teilprojekt 3: Totalsynthese von Bispidin-Naturstoffen (Bischinolizidin-Alkaloiden)

Obwohl bereits einige Routen zur Darstellung enantiomerenreiner Bispidin-Naturstoffe existieren (s. Kapitel 1.3.2), fehlt bislang ein flexibler Zugang zu dieser Naturstoffklasse. Das dritte Ziel der vorliegenden Arbeit war somit, aufbauend auf den Vorarbeiten an artifiziellen Bispidinen, die Entwicklung einer modularen Synthese von Bispidin-Alkaloiden. Gemäß einer „Inside-out"-Strategie war geplant, zunächst das chirale, 2,6-difunktionalisierte Bispidin-Diimid **83** als Schlüsselintermediat darzustellen (Abbildung 7). Daran sollten in weiteren Schritten verschiedene charakteristische Strukturelemente wie *endo*- und *exo*-anellierte Piperidin-Ringe, ein 2-Pyridon-Ring oder ein *endo*-anellierter Piperidon-Ring angebracht werden, um zu Bispidin-Naturstoffen der allgemeinen Struktur **84** zu gelangen.

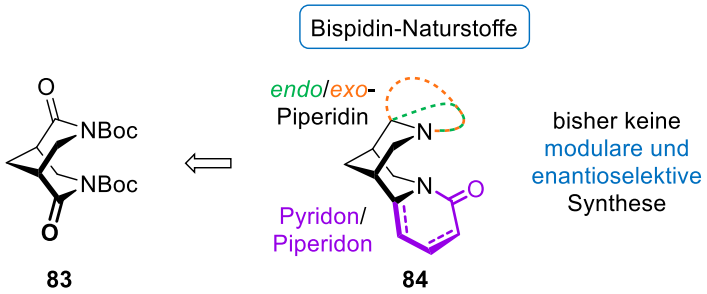


Abbildung 7. Drittes Ziel: Modulare Totalsynthese von Bispidin-Naturstoffen **84** via Schlüsselintermediat **83**.

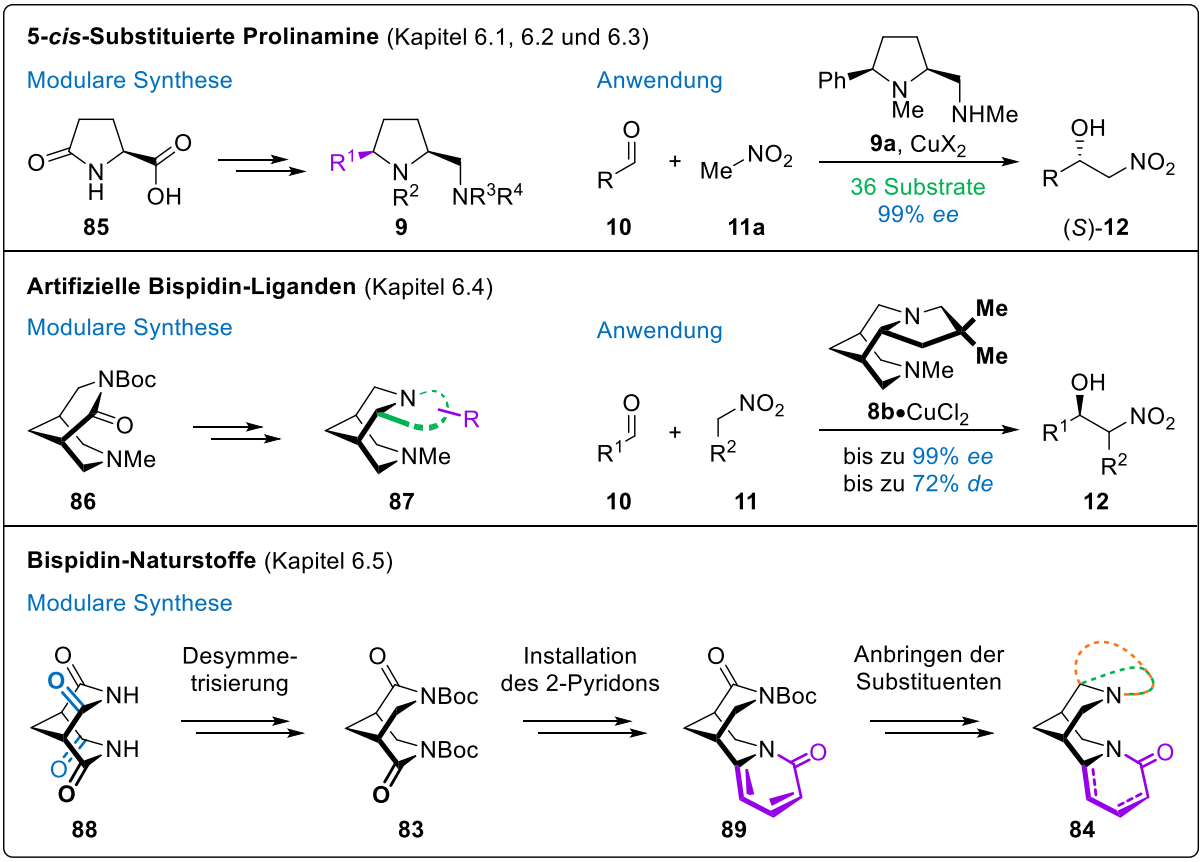
3 SYNOPSIS

Die vorliegende kumulative Dissertation enthält vier Publikationen und ein Manuskript, welche in Kapitel 6 zu finden sind. Diese Arbeiten beschäftigen sich mit der modularen Synthese und Anwendung von chiralen, rigiden Diaminen und lassen sich drei Teilprojekten zuordnen (Schema 16).

Im *ersten Projekt* wurden *5-cis-substituierte Prolinamine* **9** über neu entwickelte, modulare Syntheserouten ausgehend von L-Pyroglutaminsäure (**85**) dargestellt (Kapitel 6.1). Bei deren Evaluierung als chirale Liganden in der Cu-katalysierten Henry-Reaktion wurde mit **9a**•CuX_2 das bisher beste Katalysatorsystem für diese Umsetzung gefunden (Kapitel 6.2 und 6.3).

Im *zweiten Projekt* wurde ein modularer Zugang zu *artifiziellen Bispidin-Liganden* der allgemeinen Struktur **87** über ein funktionalisiertes Bispidin-Grundgerüst **86** als gemeinsames Intermediat etabliert (Kapitel 6.4). Mit dem Diamin **8b** konnten in Cu-katalysierten, enantioselektiven Henry-Reaktionen ebenfalls exzellente Ergebnisse erzielt werden.

Das *dritte Projekt* beschäftigte sich mit der Totalsynthese von *Bispidin-Naturstoffen* des Typs **84** (Kapitel 6.5). Auch hierfür wurde eine modulare Synthese entwickelt, bei der zunächst durch Desymmetrisierung das chirale Schlüsselintermediat **83** dargestellt wurde. Daran wurden sukzessive ein 2-Pyridon-Ring (→ **89**) sowie weitere Substituenten angebracht.



Schema 16. Übersicht über die Teilprojekte dieser Dissertation.

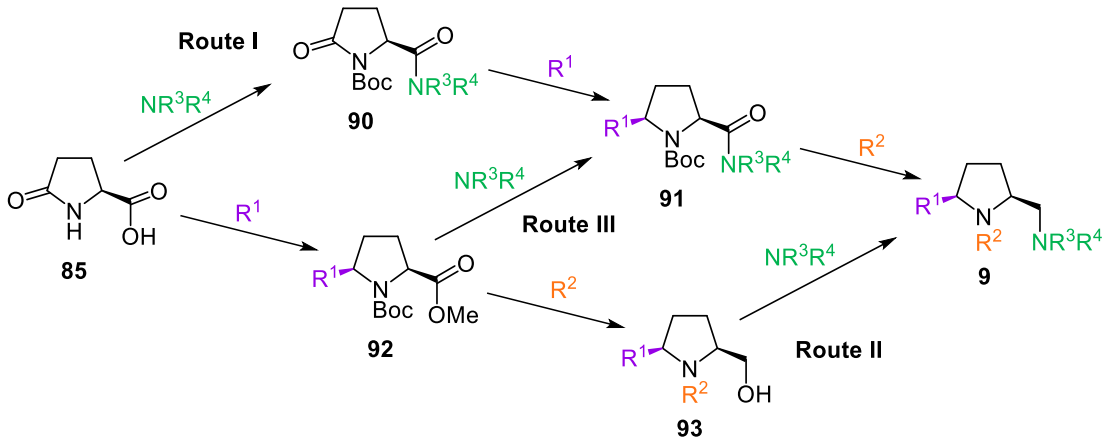
3.1 5-*cis*-Substituierte Prolinamine – Modulare Synthese und Anwendung in enantioselektiven Henry-Reaktionen

3.1.1 Flexible und modulare Synthese der enantiomerenreinen 5-*cis*-substituierten Prolinamine 9 aus L-Pyroglutaminsäure (85)*

Für die geplanten Struktur-Selektivitäts-Untersuchungen an 5-*cis*-substituierten Prolinaminen **9** musste zunächst ein modularer Zugang zu dieser Substanzklasse entwickelt werden, der eine Variation der Substituenten R^1 bis R^4 mit geringem synthetischem Aufwand erlaubt.

Ausgehend von der günstigen L-Pyroglutaminsäure (**85**) konnten drei Routen etabliert werden, in denen die verschiedenen Reste $R^{1–4}$ unabhängig voneinander eingeführt werden (Schema 17). Jeder dieser Wege beinhaltet die folgenden drei Sequenzen: 1) Einführung eines 5-*cis*-Substituenten R^1 durch Grignard-Addition und Recyclisierung; 2) Aufbau von R^2 durch Reduktion der *N*-Boc-Gruppe oder durch Entschützung und reduktive Aminierung; 3) Anbringen von NR^3R^4 durch Amidierung oder S_N2-Reaktion.

In Route I wird R^1 spätestmöglich eingebracht, wodurch sie sich besonders gut zur Variation des 5-*cis*-Restes eignet. Route II erlaubt die Addition des exocyclischen Amins auf der letzten Stufe, sodass NR^3R^4 einfach verändert werden kann. Route III ist eine Kombination der ersten beiden Wege und ermöglicht auch die Darstellung von Derivaten, die über Route II aufgrund von Problemen bei der Isolierung und Aufreinigung oder wegen Inkompatibilität der Reaktionsbedingungen nicht erhalten werden konnten.



Schema 17. Die drei entwickelten modularen Syntheserouten zu 5-*cis*-substituierten Prolinaminen **9**.

Insgesamt wurden über diese drei Routen 25 verschiedene 5-*cis*-substituierte Prolinamine **9** in fünf bis zehn Stufen und bis zu 64% Ausbeute aus L-Pyroglutaminsäure (**85**) synthetisiert. Zusammen mit späteren Publikationen konnten inzwischen über 30 Derivate von **9** dargestellt werden.

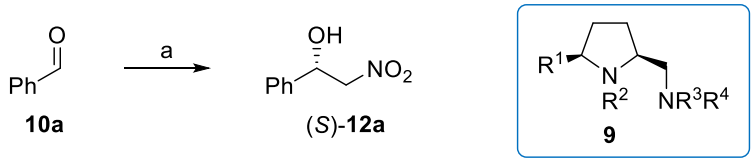
* Dieser Abschnitt der Dissertation wurde in *Synthesis* **2015**, *47*, 575–586 veröffentlicht (siehe Kapitel 6.1).

3.1.2 Evaluierung der 5-*cis*-substituierten Prolinamine 9 als Liganden in enantioselektiven, Kupfer-katalysierten Henry-Reaktionen*

Als Modellreaktion zur Untersuchung der 5-*cis*-substituierten Prolinamine **9** als chirale Liganden wurde die Cu-katalysierte Henry-Reaktion gewählt, da in dieser bereits beachtliche Ergebnisse mit Kupfer-Komplexen von anderen Prolinaminen (s. Kapitel 1.1.1) und Bispidinen (s. Kapitel 1.2.1.3) erzielt wurden.

Struktur-Selektivitäts-Untersuchungen wurden anhand der Umsetzung von Benzaldehyd (**10a**) mit Nitromethan (**11a**) in Gegenwart von 33 verschiedenen Prolinaminen **9** durchgeführt (Tabelle 4). Als erstes wurde der Einfluss des 5-*cis*-Substituenten auf den Stereotransfer untersucht. Während sich mit dem unsubstituierten Derivat **9b** (R^1 = H, $R^{2–4}$ = Me, Eintrag 1) der β-Nitroalkohol (*R*)-**12a** in 71% *ee* bildete, wurde mit den 5-*cis*-substituierten Derivaten das enantiokomplementäre Produkt (*S*)-**12a** erhalten. Mit einer kleinen Methyl-Gruppe R^1 war der erzielte *ee* gering (**9c**, 23% *ee*, Eintrag 2); mit sterisch anspruchsvollen, verzweigten aliphatischen (**9d**, R^1 = *i*Pr; **9e**, R^1 = Cy) oder aromatischen Resten (**9f**, R^1 = Ph; **9g**, R^1 = 3,5-Me_2Ph) konnte der *ee* jedoch auf gute 84–90% gesteigert werden (Einträge 3–6). Dies zeigt, dass der 5-*cis*-Substituent einen positiven Einfluss auf den Chiralitätstransfer ausübt. Anschließend wurden ausgehend von dem am leichtesten zugänglichen Phenyl-Derivat **9f** die Reste R^3 und R^4 am exocyclischen Amin optimiert. Mit einer NHMe-Gruppe wie in **9a** wurden herausragende 98% *ee* erzielt (Eintrag 7). Dieser Wert konnte durch weitere Variation von NR^3R^4 und R^2 nicht verbessert werden.

Tabelle 4. Struktur-Selektivitäts-Untersuchungen von Prolinaminen **9** in der $CuCl_2$-katalysierten Henry-Reaktion (ausgewählte Ergebnisse).
Reagenzien und Bedingungen: a) **9** (4.4 Mol-%), $CuCl_2$ (4.0 Mol-%), NEt_3 (3.0 Mol-%), $MeNO_2$ (**11a**), MeOH, –20 °C.

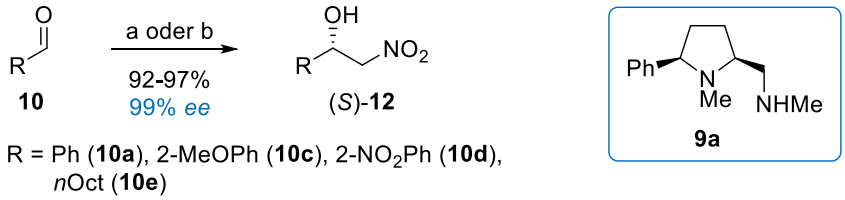


10a (*S*)-**12a** **9**

Eintrag	Prolinamin **9**	R^1	R^2	NR^3R^4	Ausbeute [%]	*ee* [%] (Konfig.)
1	**b**	H	Me	NMe_2	99	71 (*R*)
2	**c**	Me	Me	NMe_2	93	23 (*S*)
3	**d**	*i*Pr	Me	NMe_2	99	84 (*S*)
4	**e**	Cy	Me	NMe_2	93	88 (*S*)
5	**f**	Ph	Me	NMe_2	95	84 (*S*)
6	**g**	3,5-Me_2Ph	Me	NMe_2	92	90 (*S*)
7	**a**	Ph	Me	NHMe	99	98 (*S*)

* Dieser Abschnitt der Dissertation wurde in *ChemCatChem* **2016**, *8*, 1846–1856 veröffentlicht (siehe Kapitel 6.2).

Im Anschluss wurden mit dem leistungsfähigsten Liganden **9a** die Reaktionsparameter wie Kupferquelle, Lösungsmittel, Katalysatorbeladung, Art und Menge der Base und Temperatur an vier verschiedenen Substraten optimiert. Für die aromatischen Aldehyde **10a**,**c**,**d** erwiesen sich 2 Mol-% **9a**•$CuBr_2$ und eine Temperatur von –25 °C als ideal (Schema 18, Bedingungen a), die entsprechenden β-Nitroalkohole (*S*)-**12** konnten mit ausgezeichneten 99% *ee* isoliert werden. In der Umsetzung von Nonanal (**10e**) lieferte $CuCl_2$ bessere Ergebnisse als $CuBr_2$; zudem musste die Katalysatormenge auf 8 Mol-% und die Temperatur auf –20 °C erhöht werden (Bedingungen b), um auch (*S*)-**12e** mit 99% *ee* zu erhalten.



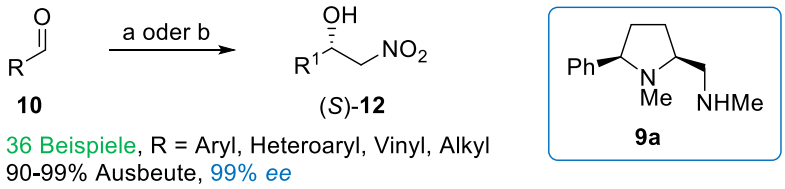
Schema 18. Optimierte Reaktionsbedingungen für aliphatische und aromatische Aldehyde.
Reagenzien und Bedingungen: Für **10a**,**c**,**d**: a) **9a** (2.2 Mol-%), $CuBr_2$ (2.0 Mol-%), NEt_3 (1.5 Mol-%), $MeNO_2$ (**11a**), THF, –25 °C; Für **10e**: b) **9a** (8.8 Mol-%), $CuCl_2$ (8.0 Mol-%), NEt_3 (6.0 Mol-%), $MeNO_2$ (**11a**), THF, –20 °C.

Auch in Reaktionen im Gramm-Maßstab mit nur 1 Mol-% Katalysator (94% Ausbeute, 99% *ee*) und in dia- und enantioselektiven Henry-Reaktionen (*syn*:*anti* bis zu 84:16, bis zu 99% *ee* in beiden Diastereomeren) konnten mit **9a**•$CuBr_2$ die Produkte mit außergewöhnlicher Selektivität erhalten werden.

Durch mechanistische Untersuchungen wurde bewiesen, dass die chirale Information bei der C-C-Bindungsknüpfung übertragen wird. Außerdem konnte in Vergleichsexperimenten gezeigt werden, dass die Reaktionsgeschwindigkeit mit dem sekundären Prolinamin **9a** im Vergleich zum entsprechenden tertiären Derivat **9f** deutlich größer ist.

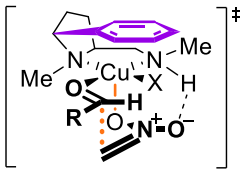
3.1.3 (2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidin (9a), ein chiraler Diamin-Ligand für Kupfer(II)-katalysierte Henry-Reaktionen mit herausragender Enantiokontrolle*

Unter optimierten Reaktionsbedingungen (s. Schema 18) wurde die Substratbreite des Katalysators **9a**•CuX_2 in der enantioselektiven Cu-katalysierten Henry-Reaktion untersucht (Schema 19). Hierbei konnten unter Verwendung von **9a**•$CuBr_2$ 29 verschiedene aromatische, heteroaromatische und vinylische Aldehyde **10** in 90–99% Ausbeute mit jeweils exzellenten 99% *ee* zu den entsprechenden β-Nitroalkoholen (*S*)-**12** umgesetzt werden. Auch die Reaktion von sieben unterschiedlichen aliphatischen Aldehyden **10** in Gegenwart von **9a**•$CuCl_2$ lieferte die Produkte (*S*)-**12** in 95–99% Ausbeute und mit 99% *ee* in jedem Beispiel. Damit ist das 5-*cis*-substituierte Prolinamin **9a** der bisher leistungsfähigste chirale Ligand für Cu-katalysierte Henry-Reaktionen.



Schema 19. Untersuchung der Substratbreite in der CuX_2•**9a**-katalysierten Henry-Reaktion. *Reagenzien und Bedingungen*: R = Aryl, Heteroaryl, Vinyl: a) **9a** (2.2 Mol-%), $CuBr_2$ (2.0 Mol-%), NEt_3 (1.5 Mol-%), $MeNO_2$ (**11a**), THF, –25 °C; R = Alkyl: b) **9a** (8.8 Mol-%), $CuCl_2$ (8.0 Mol-%), NEt_3 (6.0 Mol-%), $MeNO_2$ (**11a**), THF, –20 °C.

Um den ausgezeichneten Stereotransfer mit **9a**•CuX_2 zu erklären, wurde aufbauend auf Evans Arbeiten[29] (s. Kapitel 1.1.1.1) der Übergangszustand **F** vorgeschlagen (Abbildung 8). Im quadratisch-pyramidalen Komplex blockiert der 5-*cis*-Phenyl-Substituent die Oberseite, der Aldehyd nimmt zur größtmöglichen Aktivierung eine äquatoriale Position ein und das Nitronat bindet axial. Die Bindungsknüpfung erfolgt schließlich über den skizzierten sesselartigen Übergangszustand.



F
(X = Br, Cl)

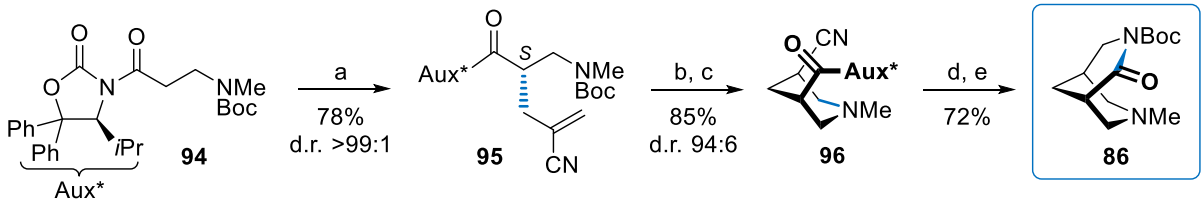
Abbildung 8. Postulierter Übergangszustand **F**.

* Dieser Abschnitt der Dissertation wurde in *Chem. Commun.* **2014**, *50*, 6623–6625 veröffentlicht (siehe Kapitel 6.3).

3.2 Die erste modulare Route zu Kern-chiralen Bispidin-Liganden und deren Anwendung in enantioselektiven Reaktionen*

Zur effizienten Darstellung von artifiziellen Bispidin-Liganden wurde ein modularer Zugang gemäß der „Inside-out"-Strategie (s. Kapitel 1.3.2.4) entwickelt. Die so synthetisierten Liganden wurden in drei Modellreaktionen eingesetzt, um den Einfluss der unterschiedlichen Substituenten auf den Stereotransfer zu untersuchen.

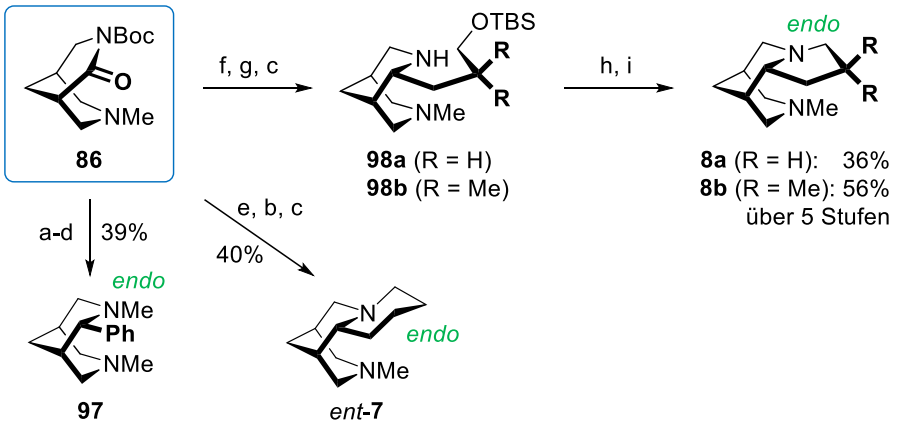
Zunächst wurde das Schlüsselintermediat der Synthese, das chirale Bispidin-Imid **86**, dargestellt (Schema 20). Ausgangspunkt hierfür war die Auxiliar-verknüpfte, geschützte β-Aminosäure **94**, die im ersten Schritt stereoselektiv alkyliert wurde (→ **95**). *N*-Boc-Entschützung und intramolekulare Michael-Addition lieferten das Piperidin **96** mit guter Diastereoselektivität (96:4). Bei der Reduktion des Nitrils in **96** zum Amin erfolgte *in situ* die Cyclisierung zum Bispidin-Gerüst unter Auxiliar-Abspaltung. Nach *N*-Boc-Aktivierung wurde das Imid **86** in insgesamt 48% Ausbeute über fünf Stufen erhalten.



Schema 20. Darstellung des chiralen Bispidin-Imids **86**.
Reagenzien und Bedingungen: a) LiHMDS; 2-(Acetoxymethyl)acrilnitril; b) TFA; c) Δ; d) $NaBH_4$, $NiCl_2$•$6H_2O$; e) *n*BuLi; Boc_2O.

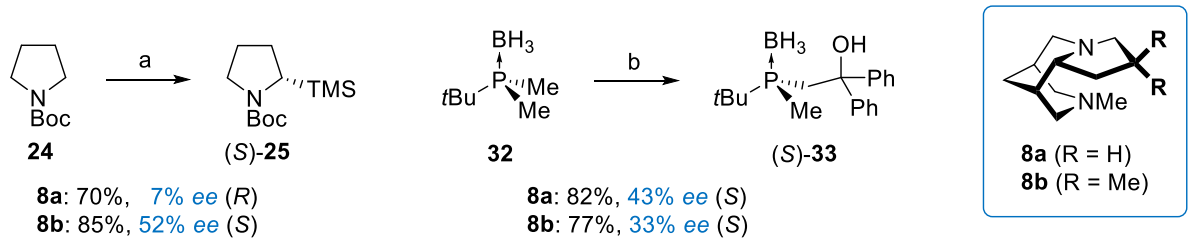
Ausgehend vom Schlüsselintermediat **86** wurden modular die verschiedenen Bispidin-Liganden synthetisiert (Schema 21). Die *endo*-ständigen Substituenten wurden hierbei durch nukleophile Addition, *N*-Boc-Entschützung–Recyclisierung und Reduktion von der konvexen Seite angebracht. Der Ligand **97** wurde über diesen Weg mit Phenyl-Grignard als Nukleophil nach finaler *N*-Methylierung erhalten. In einer ähnlichen Sequenz mit 4-Chlorbutylmagnesiumbromid konnte der Piperidin-Ring in *ent*-**7** aufgebaut werden. Die Synthese der Liganden **8** war etwas aufwändiger: Zunächst wurde wie beschrieben ein unsubstituierter oder dimethylierter *endo*-Propyl-Rest mit terminaler OTBS-Gruppe eingeführt (→ **98**). Nach Entschützung und Überführung ins Chlorid erfolgte die Cyclisierung des anellierten Pyrrolidin-Rings zu **8**. Insgesamt wurden die drei neuen Liganden **97**, **8a** und **8b** sowie der bekannte (–)-Sparteine-Ersatzstoff *ent*-**7** in drei bis fünf Stufen mit guten 36–55% Ausbeute aus **86** gewonnen.

* Dieser Abschnitt der Dissertation wurde in *Chem. Eur. J.* **2015**, *21*, 12488–12500 veröffentlicht (siehe Kapitel 6.4).



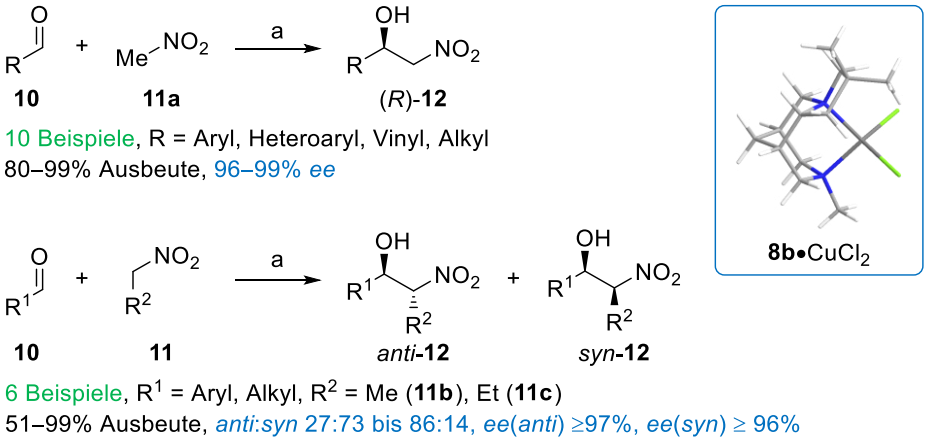
Schema 21. Synthese der Bispidin-Liganden **97**, *ent*-**7** und **8** ausgehend vom Schlüsselintermediat **86**. *Reagenzien und Bedingungen*: a) PhMgBr; b) TFA; NEt_3 oder bas. Al_2O_3; c) $NaBH_4$; d) MeI, K_2CO_3; e) $BrMg(CH_2)_4Cl$; f) $LiCH_2CR_2CH_2OTBS$; g) $ZnBr_2$; Al_2O_3; h) HF; i) CBr_4, PPh_3.

Um den Einfluss des anellierten Pyrrolidin-Rings auf den Stereotransfer zu evaluieren, wurden die neuen Bispidine **8a** und **8b** in zwei Paradereaktionen eingesetzt, der enantioselektiven Lithiierung–Silylierung von *N*-Boc-Pyrrolidin (**24**) und der Deprotonierung des Phosphinoborans **32** mit Benzophenon-Abfang (Schema 22). Leider lieferten weder **8a** noch **8b** die jeweiligen Produkte **25** und **33** mit zufriedenstellender Enantioselektivität (≤52% *ee*) – in Kontrast zu den hervorragenden Resultaten, die mit (–)-Spartein (**6**) oder dem (+)-Sparteinersatzstoff **7** in diesen Modellreaktionen erzielt wurden (s. Kapitel 1.2.1.1 und 1.2.1.2).[17,38,46] Damit bestätigte sich, dass in Deprotonierungen ein *endo*-anellierter Piperidin-Ring am Bispidin-Liganden wie in **6** oder **7** essenziell für eine gute Stereokontrolle ist.



Schema 22. Evaluierung der Bispidin-Liganden **8** in enantioselektiven Deprotonierungen. *Reagenzien und Bedingungen*: a) **8** (1.3 Äquiv.), *s*BuLi (1.3 Äquiv.), Et_2O, –78°C; TMSCl, –78°C → RT; b) **8** (0.3 Äquiv.), *s*BuLi (0.3 + 0.35 + 0.35 Äquiv.), Et_2O, –78°C; Ph_2CO, –78°C → RT.

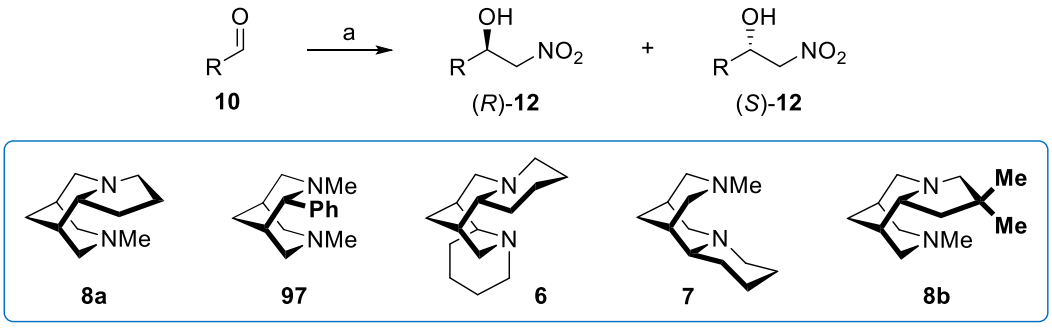
Ausgezeichnete Ergebnisse wurden mit dem Bispidin-Liganden **8b** hingegen in Cu-katalysierten Henry-Reaktionen erzielt. Diese Modellreaktion wurde gewählt, da bereits Resultate mit (–)-Spartein (**6**) und dem Ersatzstoff **7** zum Vergleich vorhanden waren (s. Kapitel 1.2.1.3). Erste Versuche mit **8b** unter Literaturbedingungen[32,33] (20 Mol-% **8b**•$CuCl_2$, MeOH) waren vielversprechend (94% *ee*). Durch Optimierung der Reaktionsparameter konnte die Katalysatorbeladung deutlich auf 2–4 Mol-% gesenkt werden. Unter den neuen Bedingungen wurden zehn verschiedene aromatische, heteroaromatische, vinylische und aliphatische Aldehyde **10** in 80–99% Ausbeute und exzellenten 96–99% *ee* zu den entsprechenden β-Nitroalkoholen (*R*)-**12** umgesetzt (Schema 23). Auch in enantio- und diastereoselektiven Henry-Reaktionen lieferte **8b**•$CuCl_2$ als Katalysator sehr gute Ergebnisse (d.r. bis zu 86:14, ≥96% *ee*).



Schema 23. Enantio- und diastereoselektive $CuCl_2$•**8b**-katalysierte Henry-Reaktionen.
Reagenzien und Bedingungen: a) **8b**•$CuCl_2$ (2–4 Mol-%), NEt_3, THF, –20 °C.

Die neuen Liganden **8a**, **97**, **8b** sowie (–)-Spartein (**6**) und der (+)-Spartein-Ersatzstoff **7** wurden unter optimierten Bedingungen in Cu-katalysierten Henry-Reaktionen an vier verschiedenen Aldehyden **10** getestet, um den Einfluss der unterschiedlichen anellierten Ringe und des Substituenten auf den Chiralitätstransfer direkt vergleichen zu können (Tabelle 5). Hierbei zeigte sich, dass **8b** (bis zu 98% *ee*) den etablierten Liganden **6** und **7** (bis zu 91% bzw. 96% *ee*) überlegen ist. Mit **8a** wurden die β-Nitroalkohole (*R*)-**12** nur mit geringem *ee* erhalten (42–49%). Der Phenyl-substituierte Ligand **97** lieferte, wie schon das analoge 9-Oxabispidin **34** (s. Kapitel 1.2.1.3),[47] die enantiokomplementären Produkte (*S*)-**12** (73–89% *ee*).

Tabelle 5. Vergleich der Bispidin-Liganden in der enantioselektiven Henry-Reaktion.
Reagenzien und Bedingungen: a) Bispidin•$CuCl_2$ (2 Mol-%), NEt_3, $MeNO_2$ (**11a**), THF, –20 °C.

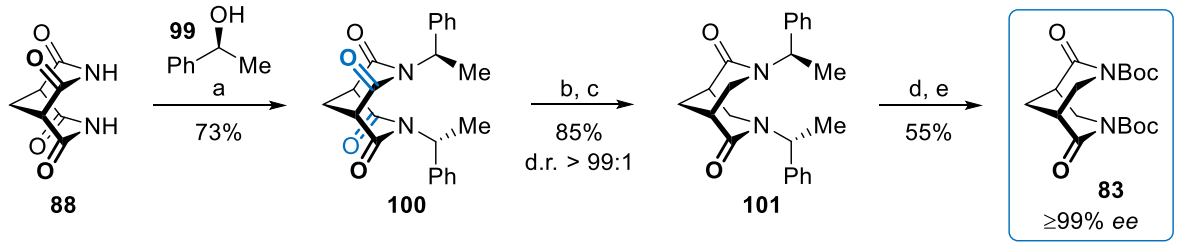


		ee [%] (Konfig.)				
10	R	**8a**	**97**	**6**	**7**	**8b**
a	Ph	49 (*R*)	85 (*S*)	91 (*R*)	96 (*S*)	98 (*R*)
f	3-MeOPh	45 (*R*)	89 (*S*)	89 (*R*)	96 (*S*)	98 (*R*)
g	4-NO_2Ph	42 (*R*)	85 (*S*)	45 (*R*)	81 (*S*)	85 (*R*)
h	Ph$(CH_2)_2$	48 (*R*)	73 (*S*)	83 (*R*)	94 (*S*)	94 (*R*)

3.3 Die enantioselektive Totalsynthese von Bischinolizidin-Alkaloiden: Ein modularer „Inside-out"-Ansatz*

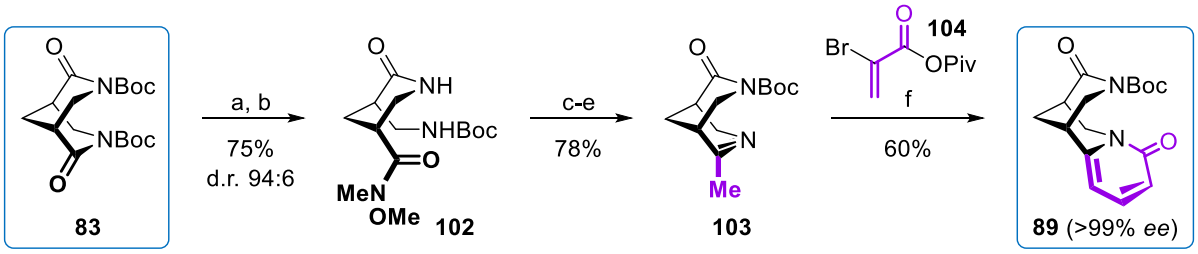
Die Entwicklung eines effizienten Zugangs zu Bispidin-Naturstoffen war, nach den Erfolgen bei der Darstellung von artifiziellen Bispidin-Liganden, das letzte Ziel dieser Dissertation. Gemäß der „Inside-out"-Strategie (s. Kapitel 1.3.2.4) wurde auch für diese Substanzklasse eine modulare Synthese erarbeitet.

Das dafür benötigte Schlüsselintermediat **83** wurde durch Desymmetrisierung aus dem einfach zugänglichen 2,4,6,8-Tetraoxobispidin (**88**)[62a] dargestellt (Schema 24). Dazu wurde an **88** zunächst (*S*)-Phenylethanol (**99**) als chirales Auxiliar angebracht (→**100**). Anschließend erfolgte im stereochemisch entscheidenden Schritt die Reduktion zweier gegenüberliegender Carbonylgruppen, die das Dioxobispidin **101** als einziges Diastereomer lieferte. Schließlich wurde das Diimid **83** nach Entfernen der Auxiliare und *N*-Boc-Aktivierung in insgesamt 34% Ausbeute über fünf Stufen erhalten. Mit (*R*)-Phenylethanol (*ent*-**99**) als Auxiliar konnte analog das enantiokomplementäre Schlüsselintermediat *ent*-**83** dargestellt werden.



Schema 24. Synthese des ersten Schlüsselintermediats **83**.
Reagenzien und Bedingungen: a) ADDP, PBu_3; b) $LiBHEt_3$; c) Et_3SiH, TFA; d) Na, NH_3, *t*BuOH; e) Boc_2O, NEt_3, DMAP.

Da viele der Bispidin-Alkaloide einen 2-Pyridon-Ring tragen, wurde als zweites Schlüsselintermediat die Verbindung **89** gewählt, die dieses Strukturelement bereits enthält (Schema 25). Zur Synthese von **89** wurde das Diimid **83** zunächst zum Weinreb-Amid **102** geöffnet, um selektiv eine der beiden Carbonylgruppen ins Methylimin überführen zu können (→ **103**). An **103** erfolgte der Aufbau des Pyridon-Rings über eine formale [3+3]-Addition mit der aktivierten 2-Bromacrylsäure **104**. Das Bispidin-Imid **89** konnte über diese Sequenz in sechs Stu-

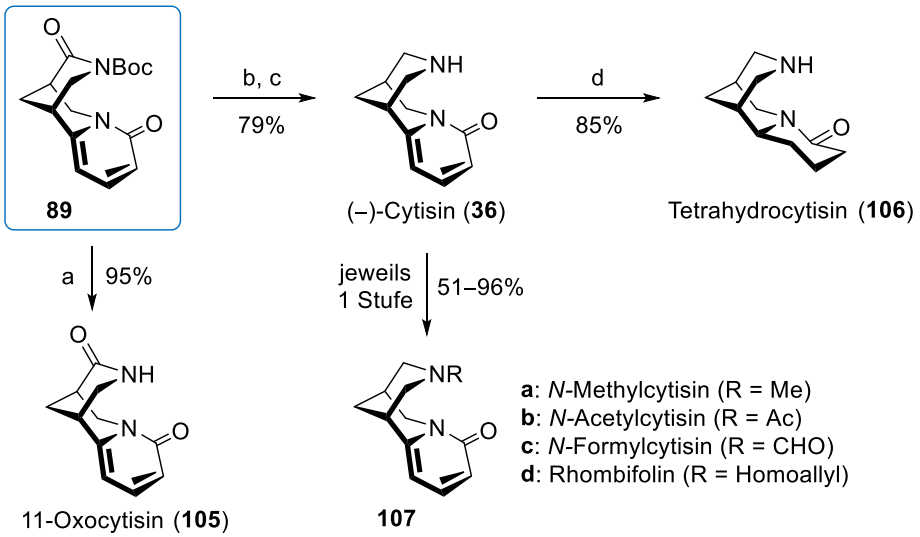


Schema 25. Darstellung des zweiten Schlüsselintermediats **89** durch Anbringen des 2-Pyridon-Rings an **83**.
Reagenzien und Bedingungen: a) HN(Me)OMe•HCl, $AlMe_3$; b) TFA; c) MeMgBr; d) BF_3•Et_2O; NH_3; e) Boc_2O; f) NEt_3.

* Dieser Abschnitt der Dissertation liegt als Manuskript vor (siehe Kapitel 6.5), welches in erweiterter Form in *Angew. Chem. Int. Ed.* **2018**, DOI: 10.1002/anie.201712852 (in Druck) veröffentlicht wurde.

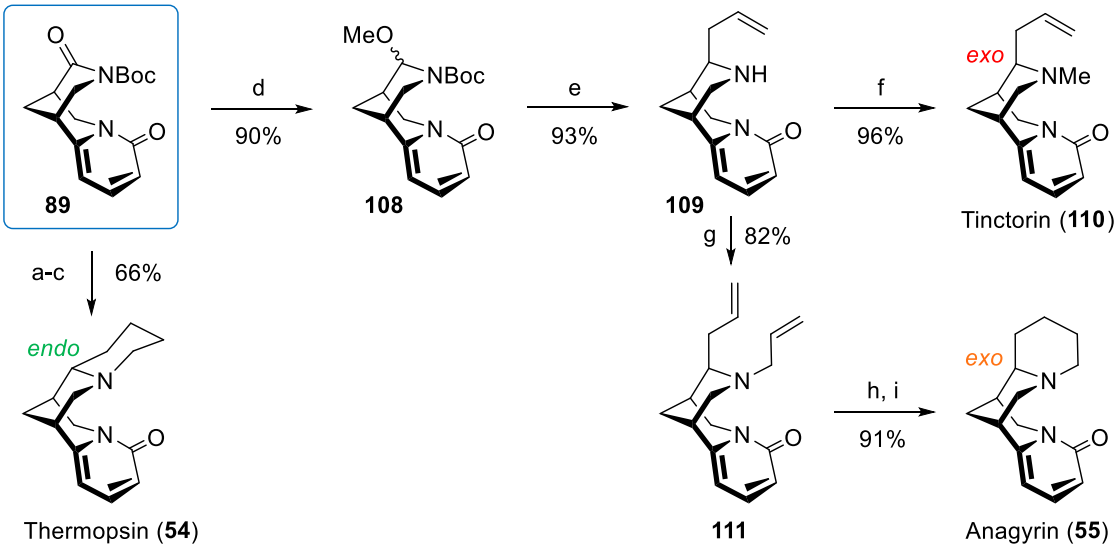
fen mit 35% Gesamtausbeute enantiomerenrein erhalten werden.

Ausgehend von **89** wurden zunächst einige tricyclische Bispidin-Naturstoffe synthetisiert (Schema 26). Die Entschützung von **89** ergab 11-Oxocytisin (**105**), durch Reduktion des Imids war (–)-Cytisin (**36**) zugänglich; Hydrierung (→**106**) oder *N*-Funktionalisierung von **36** (→**107**) lieferten fünf weitere Bispidin-Alkaloide.



Schema 26. Darstellung tricyclischer Bispidin-Naturstoffe aus **89**.
Reagenzien und Bedingungen: a) TFA; b) $NaBH_4$; c) Et_3SiH, BF_3•Et_2O; d) H_2, PtO_2.

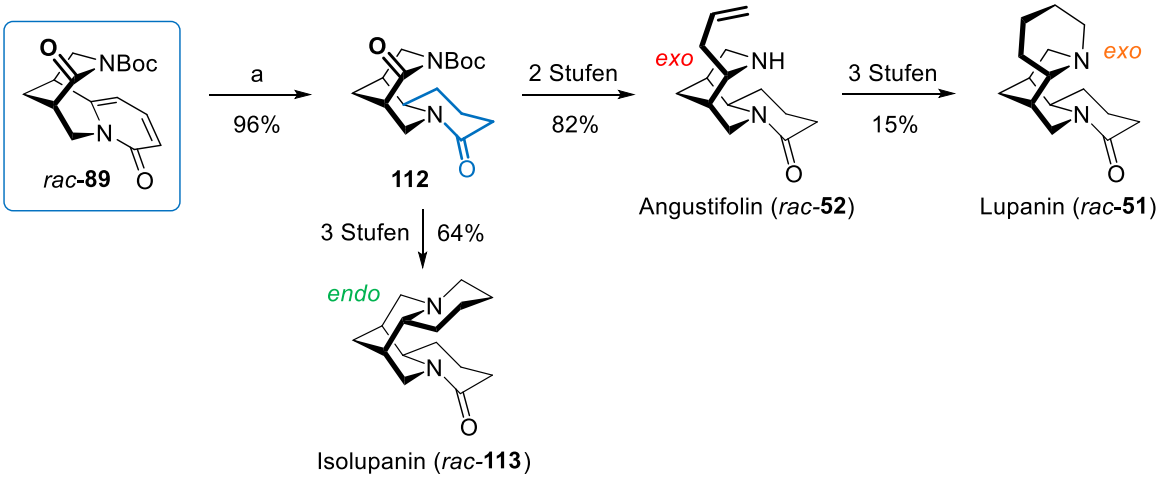
Anschließend wurden Sequenzen entwickelt, um an **89** weitere Substituenten und Ringe stereoselektiv anzubringen (Schema 27). Durch Addition eines Butyl-Grignards mit terminaler Abgangsgruppe, Recyclisierung und Reduktion gelang es, den *endo*-anellierten Piperidin-Ring in Thermopsin (**54**) aufzubauen. Überführung von **89** ins *N*,*O*-Acetal **108** und *exo*-selektive Sakurai-Addition lieferten **109**, das nach *N*-Methylierung Tinctorin (**110**) ergab. Durch *N*-



Schema 27. Synthese tri- und tetracyclischer Bispidin-Naturstoffe aus **89**.
Reagenzien und Bedingungen: a) $Cl(CH_2)_4MgBr$, b) TFA; c) $NaBH_4$; d) $NaBH_4$; HCl, MeOH; e) $AllylSiMe_3$, BF_3•Et_2O; f) CH_2O, $NaBH_3CN$; g) AllylBr, NEt_3; h) Grubbs II; i) H_2, Pd/C.

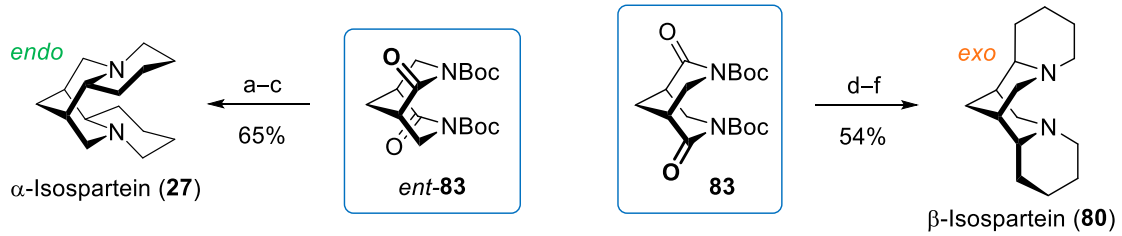
Allylierung von **109** (→**111**), Metathese und Hydrierung wurde der *exo*-anellierte Piperidin-Ring in Anagyrin (**55**) erhalten.

Ein weiteres Ziel waren Naturstoffe, die einen *endo*-anellierten Piperidon-Ring tragen (Schema 28). Deren Synthese wurde an racemischem Material durchgeführt. Zunächst wurde der Pyridon-Ring in *rac*-**89**[66] *exo*-selektiv hydriert (→**112**). Ausgehend von **112** wurden in bekannten Sequenzen (s. Schema 27) der *exo*-ständige Substituent in Angustifolin (*rac*-**52**) und die *endo*- bzw. *exo*-anellierten Ringe in Isolupanin (*rac*-**113**) und Lupanin (*rac*-**51**) angebracht.



Schema 28. Darstellung von Bispidin-Naturstoffen mit anelliertem Piperidon-Ring aus *rac*-**89**. *Reagenzien und Bedingungen*: a) H_2, PtO_2; weitere Sequenzen analog Schema 27.

Abschließend wurden aus *ent*-**83** und **83** die C_2-symmetrischen Alkaloide α- und β-Isospartein (**27** und **80**) synthetisiert (Schema 29). Zur Darstellung von **27** wurde die zuvor etablierte Sequenz zum Aufbau von *endo*-anellierten Piperidin-Ringen verwendet. Die *exo*-anellierten Ringe in **80** konnten via Reduktion und Lewis-Säure-katalysierter *exo*-Addition eines Butyl-Zink-Reagenzes mit terminaler Abgangsgruppe angebracht werden.



Schema 29. Synthese der C_2-symmetrischen Bispidin-Naturstoffe α- und β-Isospartein (**27** und **80**). *Reagenzien und Bedingungen*: a) $Cl(CH_2)_4MgBr$, b) TFA; c) $NaBH_4$; d) Cp_2ZrHCl; MeOH; e) $Cl(CH_2)_4ZnBr$, $BF_3{\bullet}Et_2O$; f) TFA; K_2CO_3.

Insgesamt wurden über diesen modularen Zugang 15 verschiedene Bispidin-Alkaloide dargestellt – davon 12 enantiomerenrein –, was die Effizienz der „Inside-out"-Strategie unterstreicht. Ein besonderer Erfolg war dabei die erstmalige enantioselektive Totalsynthese von Tinctorin (**110**), Anagyrin (**55**) und α-Isospartein (**27**).

4 LITERATURVERZEICHNIS

1 E. Fischer, „Einfluss der Configuration auf die Wirkung der Enzyme“, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2985–2993.

2 Eine Erweiterung dieses Konzepts wird als „Induced Fit“-Theorie bezeichnet, siehe: D. E. Koshland Jr., „The Key-Lock Theory and the Induced Fit Theory“, *Angew. Chem. Int. Ed. Engl*. **1995**, *33*, 2375–2378; *Angew. Chem*. **1994**, *106*, 2468–2472.

3 H. Kubinyi, „Molekulare Ähnlichkeit. 1. Chemische Struktur und biologische Wirkung“, *Pharm. Unserer Zeit* **1998**, *27*, 92–106.

4 E. Breitmaier, *Alkaloide. Betäubungsmittel, Halluzinogene und andere Wirkstoffe, Leitstrukturen aus der Natur*, 3. Aufl., Vieweg + Teubner, Wiesbaden, **2008**.

5 J. Frackenpohl, „Morphin und Opioid-Analgetika“, *Chem. Unserer Zeit* **2000**, *34*, 99–112.

6 S. Siddiqui, R. H. Siddiqui, „Chemical examination of the roots of Rauwolfia serpentina Benth.“, *J. Indian Chem. Soc.* **1931**, *8*, 667–680.

7 C. Köppel, A. Wagemann, F. Martens, „Pharmacokinetics and antiarrhythmic efficacy of intravenous ajmaline in ventricular arrhythmia of acute onset“, *Eur. J. Drug Metab. Pharmacokinet.* **1989**, *14*, 161–167.

8 A. Zangara, „The psychopharmacology of huperzine A: an alkaloid with cognitive enhancing and neuroprotective properties of interest in the treatment of Alzheimer’s disease“, *Pharmacol., Biochem. Behav.* **2003**, *75*, 675–686.

9 H.-U. Blaser, B. Pugin, F. Spindler, „Progress in enantioselective catalysis assessed from an industrial point of view“, *J. Mol. Catal. A: Chem.* **2005**, *231*, 1–20.

10 F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, „Nitrogen-Containing Ligands for Asymmetric Homogeneous and Heterogeneous Catalysis“, *Chem. Rev.* **2000**, *100*, 2159–2231.

11 A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, „Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid–Triethylamine Mixture“, *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522.

12 Übersichtsartikel: a) G. Desimoni, G. Faita, K. A. Jørgensen, „C_2-Symmetric Chiral Bis(Oxazoline) Ligands in Asymmetric Catalysis“, *Chem. Rev.* **2006**, *106*, 3561–3651; b) L. M. Stanley, M. P. Sibi, „Chiral Bisoxazoline Ligands“ in *Privileged Chiral Ligands and Catalysts* (Hrsg.: Q.-L. Zhou), Wiley-VCH, Weinheim, **2011**, S. 171–219.

13 Übersichtsartikel: M. Breuning, M. Steiner, „Chiral Bispidines“, *Synthesis* **2008**, *18*, 2841–2867.

14 P. Comba, M. Kerscher, W. Schiek, „Bispidine Coordination Chemistry“ in *Progress in Inorganic Chemistry*, Vol. 55 (Hrsg.: K. D. Karlin), John Wiley & Sons, New York, **2007**, S. 613-704.

15 S. K. Ritter, „Where has all the sparteine gone?“, *Chem. Eng. News* **2017**, *95*, 18–20.

16 Mittlerweile ist (–)-Spartein (**6**) wieder erhältlich, aber zu deutlich höheren Preisen (>100 €/1 g).

17 M. J. Dearden, C. R. Firkin, J.-P. R. Hermet, P. O’Brien, „A Readily-Accessible (+)-Sparteine Surrogate“, *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871.

18 Übersichtsartikel: a) A. J. Dixon, M. J. McGrath, P. O’Brien, „Synthesis of (+)-(1*R*,2*S*,9*S*)-11-methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane, a (+)-sparteine surrogate“, *Org. Synth.* **2006**, *83*, 141–154; b) P. O’Brien, „Basic instinct: design, synthesis and evaluation of (+)-sparteine surrogates for asymmetric synthesis“, *Chem. Commun.* **2008**, 655–667.

19 Das Bispidin **8a** (R = H) ist literaturbekannt, konnte aber bisher nicht in enantiomerenreiner Form dargestellt werden, s. Kapitel 1.2.2.2, Ref.[50]

20 Rechnungen zur enantioselektiven Deprotonierung–Silylierung von *N*-Boc-Pyrrolidin (**24**; s. Schema 5, S. 19) prognostizieren für **8a** (R = H) eine geringere Stereoinduktion als für den (+)-Spartein-Ersatzstoff **7**, siehe: P. O’Brien, K. B. Wiberg, W. F. Bailey, J.-P. R. Hermet, M. J. McGrath, „An Experimental and

Computational Study of the Enantioselective Lithiation of *N*-Boc-pyrrolidine Using Sparteine-like Chiral Diamines“, *J. Am. Chem. Soc.* **2004**, *126*, 15480–15489.

21 a) T. Mukaiyama, H. Uchiro, S. Kobayashi, „Perfect Stereochemical Control in the Synthesis of syn-α-Methyl-β-hydroxy Thioesters by Asymmetric Aldol Reaction of Silyl Enol Ethers with Aldehydes“, *Chem. Lett.* **1989**, *18*, 1001–1004; b) Übersichtsartikel: I. Shiina, „Asymmetric Mukaiyama Aldol Reactions Using Chiral Diamine–Coordinated Sn(II) Triflate: Development and Application to Natural Product Synthesis“, *Chem. Rec.* **2014**, *14*, 144–183.

22 N. Hosoda, H. Ito, T. Takimoto, M. Asami, „Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by (*S*)-1-Alkyl-2-(arylamino)methylpyrrolidine“, *Bull. Chem. Soc. Jpn*. **2012**, *85*, 1014–1022.

23 Q. Zhang, X. Cui, L. Chen, H. Liu, Y. Wu, „Syntheses of Chiral Ferrocenophanes and Their Application to Asymmetric Catalysis“, *Eur. J. Org. Chem*. **2014**, 7823–7829.

24 P. Niedziejko, M. Szewczyk, P. Kalicki, Z. Kałuża, „L-Proline derived arylmethanamine ligands and their application in the copper-catalyzed asymmetric Henry reaction: a rare example of a Cu-complex with a dicopper tetraacetate core“, *Tetrahedron: Asymmetry* **2015**, *26*, 1083–1094.

25 a) Y. Zhou, J. Dong, F. Zhang, Y. Gong, „Synthesis of C_1-Symmetric Chiral Secondary Diamines and Their Applications in the Asymmetric Copper(II)-Catalyzed Henry (Nitroaldol) Reactions“, *J. Org. Chem*. **2011**, *76*, 588–600; b) Y. Zhou, Y. Zhu, S. Yan, Y. Gong, „Copper-Catalyzed Enantioselective Henry Reaction of Enals and Subsequent Iodocyclization: Stereoselective Construction of Chiral Azatricyclic Frameworks“, *Angew. Chem. Int. Ed.* **2013**, *52*, 10265–10269; *Angew. Chem.* **2013**, *125*, 10455–10459.

26 Übersichtsartikel: a) H. Sasai, „The Henry (Nitroaldol) Reaction“ in *Comprehensive Organic Synthesis (2nd Edition)*, Vol. 2 (Hrsg.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, S. 543–570; b) F. A. Luzzio, „The Henry reaction: recent examples“, *Tetrahedron* **2001**, *57*, 915–945.

27 Übersichtsartikel: a) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, „Catalytic asymmetric Henry reaction“, *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; b) C. Palomo, M. Oiarbide, A. Laso, „Recent Advances in the Catalytic Asymmetric Nitroaldol (Henry) Reaction“, *Eur. J. Org. Chem.* **2007**, 2561–2574; c) N. Ananthi, S. Velmathi, „Asymmetric Henry reaction catalysed by transition metal complexes: A short review“, *Indian J. Chem.* **2013**, *52B*, 87–108; d) G. Murugavel, P. Sadhu, T. Punniyamurthy, „Copper(II)-Catalyzed Nitroaldol (Henry) Reactions: Recent Developments“, *Chem. Rec.* **2016**, *16*, 1906–1917.

28 N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**.

29 D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, „A New Copper Acetate-Bis(oxazoline)-Catalyzed, Enantioselective Henry Reaction“, *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693.

30 a) M.-C. Fournie-Zaluski, P. Coric, V. Thery, W. Gonzalez, H. Meudal, S. Turcaud, J.-B. Michel, B. P. Roques, „Design of Orally Active Dual Inhibitors of Neutral Endopeptidase and Angiotensin-Converting Enzyme with Long Duration of Action“, *J. Med. Chem.* **1996**, *39*, 2594–2608; b) A. Momotake, H. Togo, M. Yokoyama, „Convenient synthesis of *C*-aza-2,3-dideoxynucleosides“, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1193–1200.

31 Übersichtsartikel: a) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, „Regioselective, Diastereoselective, and Enantioselective Lithiation–Substitution Sequences: Reaction Pathways and Synthetic Applications“, *Acc. Chem. Res.* **1996**, *29*, 552–560; b) D. Hoppe, T. Hense, „Enantioselective Synthesis with Lithium/(–)-Sparteine Carbanion Pairs“, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316; *Angew. Chem.* **1997**, *109*, 2376–2410; c) D. Hoppe, G. Christoph, „Asymmetric deprotonation with alkyllithium-(–)-sparteine“ in *The Chemistry of Organolithium Compounds*, Vol. 2 (Hrsg.: Z. Rappoport, I. Marek), John Wiley & Sons, Chichester, **2004**, S. 1055–1164; d) O. Chuzel, O. Riant, „Sparteine as a Chiral Ligand for Asymmetric Catalysis“ in *Topics in Organometallic Chemistry*, *Vol 15*: *Chiral Diazaligands for Asymmetric Synthesis* (Hrsg.: M. Lemaire, P. Mangeney), Springer, Berlin, **2005**,

S. 59–92; e) J.-C. Kizirian, „Mechanism and Stereochemical Features in Asymmetric Deprotonation Using RLi/(–)-Sparteine Bases“, *Top. Stereochem.* **2010**, *26*, 189–251; f) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, „Direct α-Functionalization of Saturated Cyclic Amines“, *Chem. Eur. J.* **2012**, *18*, 10092–10142.

32 H. Maheswaran, K. L. Prasanth, G. G. Krishna, K. Ravikumar, B. Sridhar, M. L. Kantam, „Enantioselective nitroaldol (Henry) reaction using copper(II) complexes of (–)-sparteine“, *Chem. Comm.* **2006**, 4066–4068.

33 S. J. Canipa, A. Stute, P. O'Brien, „Use of copper(II)/diamine catalysts in the desymmetrisation of *meso*-diols and asymmetric Henry reactions: comparison of (–)-sparteine and (+)-sparteine surrogates“, *Tetrahedron* **2014**, *70*, 7395–7403.

34 a) M. S. Sigman, D. R. Jensen, „Ligand-Modulated Palladium-Catalyzed Aerobic Alcohol Oxidations“, *Acc. Chem. Res.* **2006**, *39*, 221–229; b) D. C. Ebner, R. M. Trend, C. Genet, M. J. McGrath, P. O'Brien, B. M. Stoltz, „Palladium-Catalyzed Enantioselective Oxidation of Chiral Secondary Alcohols: Access to Both Enantiomeric Series“, *Angew. Chem. Int. Ed.* **2008**, *47*, 6367–6370; *Angew. Chem.* **2008**, *120*, 6467–6470.

35 a) R. Shintani, G. C. Fu, „Highly Enantioselective Desymmetrization of Anhydrides by Carbon Nucleophiles: Reactions of Grignard Reagents in the Presence of (–)-Sparteine“, *Angew. Chem. Int. Ed.* **2002**, *41*, 1057–1059; *Angew. Chem.* **2002**, *114*, 1099–1101; b) M. J. Dearden, M. J. McGrath, P. O'Brien, „Evaluation of (+)-Sparteine-like Diamines for Asymmetric Synthesis“, *J. Org. Chem.* **2004**, *69*, 5789–5792.

36 Eine Variante der enantioselektiven Deprotonierung, die mit einer katalytischen Menge (–)-Spartein (**6**) oder (+)-Spartein-Ersatzstoff **7** und einer überstöchiometrischen Menge eines achiralen Bispidin-Liganden gute Enantiomerenüberschüsse liefert, wurde vom Arbeitskreis O'Brien entwickelt, siehe: M. J. McGrath, P. O'Brien, „Catalytic Asymmetric Deprotonation Using a Ligand Exchange Approach“, *J. Am. Chem. Soc.* **2005**, *127*, 16378–16379.

37 S. T. Kerrick, P. Beak, „Asymmetric Deprotonations: Enantioselective Syntheses of 2-Substituted (*tert*-Butoxycarbonyl)pyrrolidines“, *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710.

38 P. Beak, S. T. Kerrick, S. Wu, J. Chu, „Complex Induced Proximity Effects: Enantioselective Syntheses Based on Asymmetric Deprotonations of *N*-Boc-pyrrolidines“, *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.

39 B. Danieli, G. Lesma, D. Passarella, P. Piacenti, A. Sacchetti, A. Silvani, A. Virdis, „Synthesis of enantiopure diamine ligands related to sparteine, via scandium triflate-catalyzed imino Diels–Alder reactions“, *Tetrahedron Lett.* **2002**, *43*, 7155–7158.

40 Dies wurde in DFT-Rechnungen bestätigt, siehe: a) P.-W. Phuan, J. C. Ianni, M. C. Kozlowski, „Is the A-Ring of Sparteine Essential for High Enantioselectivity in the Asymmetric Lithiation–Substitution of *N*-Boc-pyrrolidine?“, *J. Am. Chem. Soc.* **2004**, *126*, 15473–15479; b) Ref.[20]

41 D. J. Gallagher, S. Wu, N. A. Nikolic, P. Beak, „Chiral Organolithium Complexes: The Effect of Ligand Structure on the Enantioselective Deprotonation of Boc-Pyrrolidine“, *J. Org. Chem.* **1995**, *60*, 8148–8154.

42 M. Breuning, D. Hein, „5-Substituted Derivatives of the Tricyclic (+)-Sparteine Surrogate in the Enantioselective Lithiation/Stannylation of an *O*-Alkyl Carbamate“, *Eur. J. Org. Chem.* **2013**, 7575–7582.

43 D. Hoppe, F. Hintze, P. Tebben, „Chiral Lithium-1-oxyalkanides by Asymmetric Deprotonation; Enantioselective Synthesis of 2-Hydroxyalkanoic Acids and Secondary Alkanols “, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1422–1424; *Angew. Chem.* **1990**, *102*, 1457–1459.

44 A. R. Muci, K. R. Campos, D. A. Evans, „Enantioselective Deprotonation as a Vehicle for the Asymmetric Synthesis of C_2-Symmetric *P*-Chiral Diphosphines“, *J. Am. Chem. Soc.* **1995**, *117*, 9075–9076.

45 G. Carbone, P. O'Brien, G. Hilmersson, „Asymmetric Deprotonation using *s*-BuLi or *i*-PrLi and Chiral Diamines in THF: The Diamine Matters“, *J. Am. Chem. Soc.* **2010**, *132*, 15445–15450.

46 J. Granander, F. Secci, S. J. Canipa, P. O'Brien, B. Kelly, „One-ligand Catalytic Asymmetric Deprotonation of a Phosphine Borane: Synthesis of *P*-Stereogenic Bisphosphine Ligands", *J. Org. Chem.* **2011**, *76*, 4794–4799.

47 M. Breuning, D. Hein, M. Steiner, V. H. Gessner, C. Strohmann, „Chiral 2-*endo*-Substituted 9-Oxabispidines: Novel Ligands for Enantioselective Copper(II)-Catalyzed Henry Reactions", *Chem. Eur. J.* **2009**, *15*, 12764–12769.

48 Enantioselektive Synthese: a) **7**: B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, A. Silvani, „Chiral diamines for asymmetric synthesis: an efficient RCM construction of the ligand core of (–)- and (+)-sparteine", *Tetrahedron Lett.* **2005**, *46*, 7121–7123; b) *ent*-**7**: J.-P. R. Hermet, A. Viterisi, J. M. Wright, M. J. McGrath, P. O'Brien, A. C. Whitwood, J. Gilday, „Stereocontrolled synthesis and alkylation of cyclic β-amino esters: asymmetric synthesis of a (–)-sparteine surrogate", *Org. Biomol. Chem.* **2007**, *5*, 3614–3622; *ent*-**7** durch Racematspaltung: c) J. D. Firth, P. O'Brien, L. Ferris, „Revisiting the sparteine surrogate: development of a resolution route to the (–)-sparteine surrogate", *Org. Biomol. Chem.* **2014**, *12*, 9357–9365.

49 E. Marrière, J. Rouden, V. Tadino, M.-C. Lasne, „Synthesis of Analogues of (–)-Cytisine for in Vivo Studies of Nicotinic Receptors Using Positron Emission Tomography" *Org. Lett.* **2000**, *2*, 1121–1124.

50 a) J. R. Harrison, P. O'Brien, D. W. Porter, N. M. Smith, „Studies towards the preparation of sparteine-like diamines for asymmetric synthesis", *J. Chem. Soc., Perkin Trans. 1* **1999**, 3623–3631; b) J.-P. R. Hermet, D. W. Porter, M. J. Dearden, J. R. Harrison, T. Koplin, P. O'Brien, J. Parmene, V. Tyurin, A. C. Whitwood, J. Gilday, N. M. Smith, „Synthesis of sparteine-like chiral diamines and evaluation in the enantioselective lithiation–substitution of *N*-(*tert*-butoxycarbonyl)-pyrrolidine", *Org. Biomol. Chem.* **2003**, *1*, 3977–3988.

51 J. R. Harrison, P. O'Brien, „Diastereoselective synthesis of sparteine analogues via lithiation–electrophilic quench of *N*-Boc bispidines", *Tetrahedron Lett.* **2000**, *41*, 6161–6165.

52 Die Darstellung eines enantiomenreinen, funktionalisierten Bispidin-Grundgerüsts, das theroretisch als Schlüsselintermediat zur Synthese von Bispidin-Liganden genutzt werden könnte, wurde von Lesma *et al.* beschrieben, siehe: B. Danieli, G. Lesma, D. Passarella, A. Silvani, N. Viviani, „An Efficient Chemoenzymatic Access to Chiral 3,7-Diazabicyclo[3.3.1]nonane Derivatives", *Tetrahedron* **1999**, *55*, 11871–11878.

53 M. Breuning, M. Steiner, C. Mehler, A. Paasche, D. Hein, „A Flexible Route to Chiral 2-*endo*-Substituted 9-Oxabispidines and Their Application in the Enantioselective Oxidation of Secondary Alcohols", *J. Org. Chem.* **2009**, *74*, 1407–1410.

54 Weitere 9-Oxabispidin-Liganden konnten im Arbeitskreis Breuning über ein *cis*-2,6-disubstituiertes Morpholin als Schlüsselintermediat synthetisiert werden, siehe: Ref.[47]

55 Übersichtsartikel: a) A. D. Kinghorn, M. F. Balandrin, „Quinolizidine alkaloids of the Leguminosae: structural types, analysis, chemotaxonomy, and biological activities" in *Alkaloids: Chemical and Biological Perspectives*, Vol. 2 (Hrsg.: S. W. Pelletier), John Wiley & Sons, New York, **1984**, S. 105–148; b) M. Wink, „Quinolizidine Alkaloids: Biochemistry, Metabolism, and Function in Plants and Cell Suspension Cultures", *Planta med*. **1987**, *53*, 509–514; c) M. Wink, „The Role of Quinolizidine Alkaloids in Plant–Insect Interactions" in *Insect-plant interactions*, Vol. 4 (Hrsg.: E. A. Bernays), CRC Press, Boca Raton, **1992**, S. 131–166; d) S. Ohmiya, K. Saito, I. Murakoshi, „Lupine Alkaloids" in *The Alkaloids*, Vol. 47 (Hrsg.: G. A. Cordell), Academic Press, New York, **1995**, S. 1–114; e) A. M. Lourenço, P. Máximo, L. M. Ferreira, M. M. A. Pereira, „Indolizidine and Quinolizidine Alkaloids Structure and Bioactivity" in *Studies in Natural Products Chemistry: Bioactive Natural Products (Part H)*, Vol. 27 (Hrsg.: Atta-ur-Rahman), Elsevier, Amsterdam, **2002**, S. 233–298.

56 M. Wink, L. Witte, T. Hartmann, C. Theuring, V. Volz, „Accumulation of Quinolizidine Alkaloids in Plants and Cell Suspension Cultures: Genera Lupinus, Cytisus, Baptisia, Genista, Laburnum, and Sophora", *Planta Med.* **1983**, *48*, 253–257.

57 a) P. Tutka, W. Zatoński, „Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy“, *Pharmacol. Rep.* **2006**, *58*, 777–798; b) N. Walker, C. Howe, M. Glover, H. McRobbie, J. Barnes, V. Nosa, V. Parag, B. Bassett, C. Bullen, „Cytisine versus Nicotine for Smoking Cessation“, *N. Engl. J. Med.* **2014**, *371*, 2353–2362.

58 a) B. T. Smith, J. A. Wendt, J. Aubé, „First Asymmetric Total Synthesis of (+)-Sparteine“, *Org. Lett.* **2002**, *4*, 2577–2579; b) J.-P. R. Hermet, M. J. McGrath, P. O'Brien, D. W. Porter, J. Gilday, „Concise asymmetric synthesis of (–)-sparteine“, *Chem. Comm.* **2004**, 1830–1831.

59 a) Übersichtsartikel: D. Stead, P. O'Brien, „Total synthesis of the lupin alkaloid cytisine: comparison of synthetic strategies and routes“, *Tetrahedron* **2007**, *63*, 1885–1897; b) B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, A. Silvani, A. Virdis, „Total Enantioselective Synthesis of (–)-Cytisine“, *Org. Lett.* **2004**, *6*, 493–496; c) T. Honda, R. Takahashi, H. Namiki, „Syntheses of (+)-Cytisine, (–)-Kuraramine, (–)-Isokuraramine, and (–)-Jussiaeiine A“, *J. Org. Chem.* **2005**, *70*, 499–504; d) D. Gray, T. Gallagher, „A Flexible Strategy for the Synthesis of Tri- and Tetracyclic Lupin Alkaloids: Synthesis of (+)-Cytisine, (±)-Anagyrine, and (±)-Thermopsine“, *Angew. Chem. Int. Ed.* **2006**, *45*, 2419–2423; *Angew. Chem.* **2006**, *118*, 2479–2483; e) F. R. Struth, C. Hirschhäuser, „A Modular Approach to the Asymmetric Synthesis of Cytisine“, *Eur. J. Org. Chem.* **2016**, 958–964.

60 a) (+)-Thermopsin (*ent*-**54**): R. Brimioulle, T. Bach, „Enantioselective Lewis Acid Catalysis of Intramolecular Enone [2+2] Photocycloaddition Reactions“, *Science* **2013**, *342*, 840–843; b) (+)-β-Isospartein (*ent*-**80**): F. M. Al-Saffar, R. C. D. Brown, „A Two-Directional Synthesis of (+)-β-Isosparteine“, *Org. Lett.* **2017**, *19*, 3502–3504; c) Virgiboidin: S. Kress, J. Weckesser, S. R. Schulz, S. Blechert, „Concise Total Syntheses of Dipiperidine Alkaloids Virgidivarine and Virgiboidine through Ru-Mediated Ene-Ene-Yne Ring Rearrangement Metathesis (RRM) “, *Eur. J. Org. Chem.* **2013**, 1346–1355.

61 a) T. Hayashi, „Asymmetric Hydrosilylation of Olefins Catalyzed by MOP-Palladium Complexes“, *Acta Chem. Scand.* **1996**, *50*, 259–266; b) A. Weissfloch, R. Azerad, „Chemoenzymatic Access to Enantiomeric Bicyclo[2.2.1]Heptan-2,5-Diones“, *Bioorg. Med. Chem.* **1994**, *2*, 493–500.

62 a) P. R. Blakemore, C. Kilner, N. R. Norcross, P. C. Astles, „A Practical Synthesis of (±)-α-Isosparteine from a Tetraoxobispidine Core“, *Org. Lett.* **2005**, *7*, 4721–4724; b) P. R. Blakemore, N. R. Norcross, S. L. Warriner, P. C. Astles, „A Stereocontrolled Synthesis of (±)-β-Isosparteine“, *Heterocycles* **2006**, *70*, 609–617; c) N. R. Norcross, J. P. Melbardis, M. F. Solera, M. A. Sephton, C. Kilner, L. N. Zakharov, P. C. Astles, S. L. Warriner, P. R. Blakemore, „Total Synthesis of (±)-α-Isosparteine, (±)-β-Isosparteine, and (±)-Sparteine from a Common Tetraoxobispidine Intermediate“, *J. Org. Chem.* **2008**, *73*, 7939–7951.

63 a) J. R. Harrison, P. O'Brien, „Bispidine-derived *N*-acyliminium ions in synthesis: stereocontrolled construction of the BCD rings of sparteine“, *Tetrahedron Lett.* **2000**, *41*, 6167–6170; b) A. Consonni, B. Danieli, G. Lesma, D. Passarella, P. Piacenti, A. Silvani, „An Efficient Enantioselective Entry to the Piperidino-Quinolizidine Ring System of Lupine Alkaloids by Means of *N*-Acyliminium Ion Initiated Cyclization Reactions“, *Eur. J. Org. Chem.* **2001**, 1377–1383; c) Ref.[47,53]

64 Die Begriffe „Outside-in“ und „Inside-out“ zur Beschreibung unterschiedlicher Synthesestrategien wurden erstmal von Blakemore *et al.* verwendet, siehe: Ref.[62c]

65 Der Versuch einer enantioselektiven Reduktion von **73** oder dem entsprechenden *N*-Benzyl-Derivat in Gegenwart des Corey-Bakshi-Shibata-Katalysators – und damit die enantioselektive Synthese von Spartein (**6**) und β-Isospartein (**80**) über diese Route – scheiterte, siehe: Ref.[62c]

66 Das Bispidin-Imid *rac*-**89** wurde analog zu Schema 25 aus racemischem 2,6-Dioxobispidin (Intermediat der Synthese von **83** aus **101**, Schema 24) dargestellt, welches nach Literaturprotokollen synthetisiert wurde, siehe: a) R. G. Kostyanovsky, K. A. Lyssenko, Y. I. El'natanov, O. N. Krutius, I. A. Bronzova, Y. A. Strelenko, V. R. Kostyanovsky, „3,7-Diazabicyclo[3.3.1]nonane-2,6-diones: building of homo- and heterochiral crystals“, *Mendeleev. Commun*. **1999**, *9*, 106–108; b) R. G. Kostyanovsky, I. A. Bronzova, K. A. Lyssenko, „Directed synthesis of compounds capable to spontaneous resolution“, *Mendeleev. Commun.* **2002**, *12*, 4–6.

5 DARSTELLUNG DES EIGENANTEILS

Die in dieser Dissertation präsentierten Publikationen und das Manuskript wurden in Kooperation mit anderen Wissenschaftlern erarbeitet. Der Beitrag aller Koautoren zu den jeweiligen Arbeiten wird im Folgenden detailliert dargestellt.

Kapitel 6.1

Diese Arbeit wurde publiziert in *Synthesis* **2015**, *47*, 575–586 unter dem Titel

„Flexible and Modular Syntheses of Enantiopure 5-*cis*-Substituted Prolinamines from L-Pyroglutamic Acid“

von den Autoren *Felix Prause, Johannes Kaldun, Benjamin Arensmeyer, Benedikt Wennemann, Benjamin Fröhlich, Dagmar Scharnagel und Matthias Breuning*.

Diese Publikation entstand in Kooperation mit Felix Prause und Johannes Kaldun. Felix Prause etablierte mit Hilfe von Johannes Kaldun und mir die Syntheserouten. Die Liganden wurden von Felix Prause und Johannes Kaldun unter meiner Mitarbeit dargestellt. Benjamin Arensmeyer, Benedikt Wennemann und Benjamin Fröhlich haben zu Vorarbeiten beigetragen.

An wissenschaftlichen Diskussionen waren Felix Prause, Johannes Kaldun, Prof. Dr. Matthias Breuning und ich beteiligt. Die Publikation wurde von Felix Prause und Prof. Dr. Matthias Breuning, mit Unterstützung von Johannes Kaldun und mir, verfasst.

Eigenanteil: ca. 10%

Kapitel 6.2

Diese Arbeit wurde publiziert in *ChemCatChem* **2016**, *8*, 1846–1856 unter dem Titel

„Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions“

von den Autoren *Johannes Kaldun, Felix Prause, Dagmar Scharnagel, Frederik Freitag und Matthias Breuning.*

Diese Publikation entstand in Kooperation mit Johannes Kaldun und Felix Prause. Johannes Kaldun und Felix Prause synthetisierten unter Mitarbeit von Frederik Freitag die untersuchten Liganden. Johannes Kaldun führte die Henry-Reaktionen durch. Mein Beitrag war die Entwicklung, Validierung und Durchführung der Enantiomeren- und Diastereomerenanalytik mittels HPLC und NMR sowie die Synthese der dafür benötigten Racemate.

An wissenschaftlichen Diskussionen waren Johannes Kaldun, Felix Prause, Prof. Dr. Matthias Breuning und ich beteiligt. Die Publikation wurde von Prof. Dr. Matthias Breuning und Johannes Kaldun, mit Unterstützung von Felix Prause und mir, verfasst.

Eigenanteil: ca. 10%

Kapitel 6.3

Diese Arbeit wurde publiziert in *Chem. Commun.* **2014**, *50*, 6623–6625 unter dem Titel

„(2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a chiral diamine ligand for copper(II)-catalysed Henry reactions with superb enantiocontrol“

von den Autoren *Dagmar Scharnagel,‡ Felix Prause,‡ Johannes Kaldun,‡ Robert G. Haase und Matthias Breuning.*

‡ Autoren haben gleiche Beiträge geleistet.

Diese Publikation entstand in Kooperation mit Felix Prause und Johannes Kaldun. Felix Prause synthetisierte den verwendeten Liganden und Johannes Kaldun setzte die Katalysen an, die anschließend von ihm, Felix Prause und mir aufgereinigt wurden. Ich entwickelte die Enantiomerenanalytik für alle Produkte, validierte diese und führte sie durch. Die dafür benötigten Racemate wurden ebenfalls von mir dargestellt. Robert Haase hat im Rahmen seiner Masterarbeit Vorarbeiten geleistet.

An wissenschaftlichen Diskussionen waren Felix Prause, Johannes Kaldun, Prof. Dr. Matthias Breuning und ich beteiligt. Die Publikation wurde von Felix Prause, Johannes Kaldun, Prof. Dr. Matthias Breuning und mir verfasst.

Eigenanteil: ca. 30%

Kapitel 6.4

Diese Arbeit wurde publiziert in *Chem. Eur. J.* **2015**, *21*, 12488–12500 unter dem Titel

„The First Modular Route to Core-Chiral Bispidine Ligands and Their Application in Enantioselective Copper(II)-Catalyzed Henry Reactions“

von den Autoren *Dagmar Scharnagel, Andreas Müller, Felix Prause, Martin Eck, Jessica Goller, Wolfgang Milius und Matthias Breuning*.

Der Großteil der synthetischen Arbeiten wurde von mir durchgeführt. Felix Prause und Jessica Goller waren an der Synthese einzelner Verbindungen beteiligt, Andreas Müller und Martin Eck leisteten Vorarbeiten zur Synthese des Schlüsselintermediats. Dr. Wolfgang Milius führte die Röntgenstrukturanalyse durch.

An wissenschaftlichen Diskussionen waren Prof. Dr. Matthias Breuning und ich beteiligt. Die Publikation wurde von Prof. Dr. Matthias Breuning und mir verfasst.

Eigenanteil: ca. 75%

Kapitel 6.5

Diese Arbeit liegt als Manuskript vor, welches in erweiterter Form publiziert wurde in *Angew. Chem. Int. Ed.* **2018**, DOI: 10.1002/anie.201712852 (in Druck) unter dem Titel

„The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular 'Inside-Out' Approach“

von den Autoren *Dagmar Scharnagel,‡ Jessica Goller,‡ Nicklas Deibl, Wolfgang Milius und Matthias Breuning.*

‡ Autoren haben gleiche Beiträge geleistet.

Dieses Manuskript entstand in Kooperation mit Jessica Goller. Die Syntheserouten wurden von mir, unter Mitarbeit von Jessica Goller, entwickelt. Ich synthetisierte und charakterisierte die racemischen und erste enantiomerenreine Alkaloide. Jessica Goller übertrug die an racemischem Material etablierten Synthesen auf die Darstellung weiterer enantiomerenreiner Naturstoffe und charakterisierte diese. Nicklas Deibl leistete im Rahmen seiner Masterarbeit Vorarbeiten. Dr. Wolfgang Milius führte die Röntgenstrukturanalyse durch.

An wissenschaftlichen Diskussionen waren Prof. Dr. Matthias Breuning, Jessica Goller und ich beteiligt. Das Manuskript wurde von Prof. Dr. Matthias Breuning und mir, mit Unterstützung von Jessica Goller, verfasst.

Eigenanteil: ca. 60%

6 PUBLIKATIONEN UND MANUSKRIPTE

6.1 Flexible and Modular Syntheses of Enantiopure 5-*cis*-Substituted Prolinamines from L-Pyroglutamic Acid

Felix Prause,[a] Johannes Kaldun,[a] Benjamin Arensmeyer,[b] Benedikt Wennemann,[c] Benjamin Fröhlich,[b] Dagmar Scharnagel,[a] and Matthias Breuning*[a]

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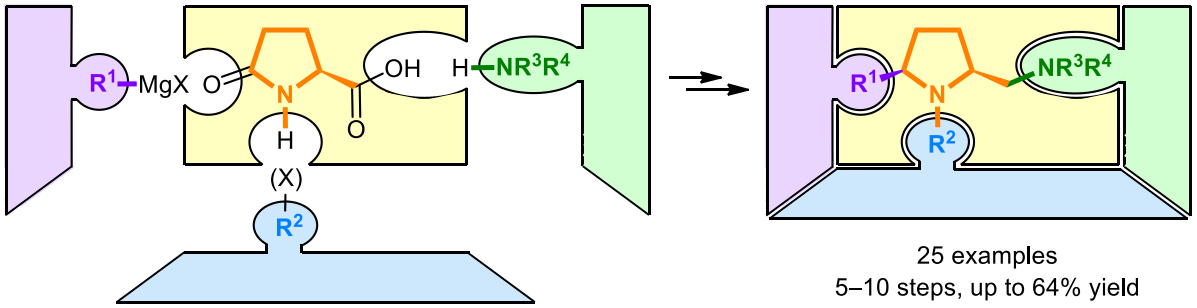

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Flexible and Modular Syntheses of Enantiopure 5-*cis*-Substituted Prolinamines from L-Pyroglutamic Acid

Felix Prause, Johannes Kaldun, Benjamin Arensmeyer,[1] Benedikt Wennemann,[2] Benjamin Fröhlich,[1] Dagmar Scharnagel, Matthias Breuning*

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Abstract: A variety (25 examples) of 5-*cis*-substituted prolinamines was prepared in five to ten steps from cheap L-pyroglutamic acid. Three routes, differing mainly in the order of introduction of the substituents at 5-*cis* position, the pyrrolidine nitrogen atom, and the exocyclic amino function, were successfully developed.

Key words: amines, ligands, stereoselective synthesis, pyrrolidines, prolinamines

Proline-derived amino alcohols and diamines have found manifold applications in asymmetric catalysis. Some prominent examples are Corey's bicyclic CBS-catalyst **1** (Figure 1), nowadays routinely used in enantioselective ketone reductions,[3] Jørgensen's diarylprolinol silyl ether **2**, a standard chiral organocatalyst,[4] Soai's tertiary amino alcohol **3**, one of the first chiral ligands for enantioselective additions of diorgano zinc reagents to aldehydes,[5] and Gong's isoborneol substituted diamine **4**, which permits excellent enantioselectivities in copper-catalyzed Henry reactions.[6] All these compounds gain their high stereodiscriminating abilities from the rigid bi- or oligocyclic nature of the intermediately formed reactive species, which, in return, is defined by the privileged prolinol or prolinamine skeleton. Surprisingly, no attention in asymmetric catalysis has as yet been paid to proline derivatives possessing an additional substituent in 5-*cis* position, although such a substituent might further enhance the level of chirality transfer.

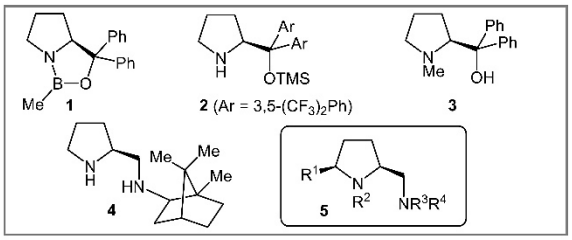
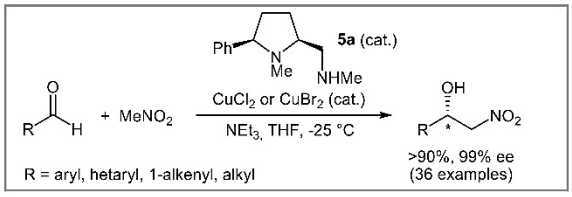


Figure 1 The privileged proline derived ligands **1**–**4**[3–6] and the new 5-*cis*-substituted prolinamines **5**

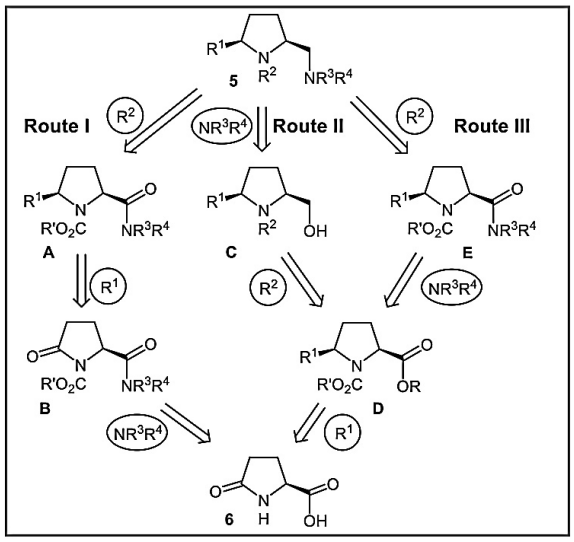
In the course of our studies on conformationally rigid ligands[7] we became interested in prolinamines of general structure **5** and their performance in enantioselective catalysis. Due to their close structural relationship to **4**, we tested these compounds in copper(II)-catalyzed Henry reactions.[8,9] And indeed, the simple diamine **5a**, which carries a 5-*cis*-phenyl group, proved to be an excellent chiral ligand (Scheme 1).[10] Extraordinarily high asymmetric inductions of 99% ee were obtained with a wide variety of aromatic, heteroaromatic, vinylic, and aliphatic aldehydes (36 examples), thus making diamine **5a** superior to all other chiral ligands examined so far in this type of reaction. Encouraged by this success, we decided to study more intensively this interesting, but almost unknown class[11] of diamines **5**, and therefore we had to develop efficient and modular routes for their preparation.



Scheme 1 Enantioselective Henry reactions catalyzed by the prolinamine–copper(II) complexes [CuX_2·**5a**] (X = Cl, Br)[10]

Synthetic Routes

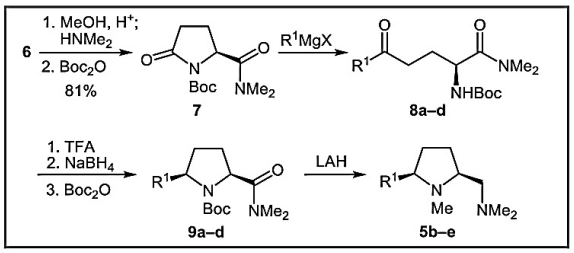
An important precondition for our planned synthesis of various prolinamines **5** was the elaboration of effective strategies (Scheme 2), which permit a flexible screening of the substituent R^1 at 5-*cis* position, R^2 at the pyrrolidine nitrogen atom, and R^3R^4 at the exocyclic amino function. Based on literature protocols on the conversion of carbamate protected pyroglutamic esters to 5-*cis*-substituted proline esters,[12,13] we focused on three major routes (I–III) that all start from cheap L-pyroglutamic acid (**6**), but differ in the order of introduction of R^1–R^4. Route I is characterized by an early-stage installment of the NR^3R^4 group via an amide (**6** → **B**), an intermediate attachment of R^1 (**B** → **A**), and a final incorporation of R^2 (**A** → **5**). In route II, by contrast, R^1 is introduced first (**6** → **D**), then R^2 (**D** → **C**), and NR^3R^4 last by hydroxy–amine exchange (**C** → **5**). Route III also proceeds via the ester **D**, but NR^3R^4 is installed via amidation (**D** → **E**) before R^2 (**E** → **5**). All three routes offer distinct advantages with respect to the substituent to be varied. While the synthetic work is minimized in route I for a screening of R^1 and R^2, route II seems to be well suited for a broad variation of the amino function NR^3R^4 since it can be done in the very last step. Route III provides a welcome alternative to route II, in particular if NR^3R^4 cannot be introduced last for compatibility reasons.



Scheme 2 Envisioned synthetic routes I–III

Route I

Our initial investigations aimed at a fast screening of the 5-*cis* substituent R^1, for which route I is predestinated, and methyl groups were chosen for R^2–R^4 in order to keep the system as simple as possible (Scheme 3 and Table 1). The required precursor, the *N*-Boc-protected dimethyl amide **7**, was prepared in two steps and good 81% yield by esterification of L-pyroglutamic acid (**6**) with methanol, in-situ amidation with $HNMe_2$, and *N*-Boc protection. Four different aryl substituents R^1 were introduced in analogy to known sequences on pyroglutamic esters.[12,13] Treatment of **7** with a slight excess of the respective Grignard reagent R^1MgX afforded the amino ketones **8a–d** in acceptable to good 43–76% yield. The following three-step cyclizations of **8a–d** (*N*-Boc deprotection with concomitant imine formation, reduction of the intermediate Δ^1-pyrrolidine, and renewed *N*-Boc protection) were accomplished in one pot without isolation of the intermediates, giving the prolinamides **9a–c**[14] in good yields (76–90%). The *cis* selectivities in the reductive cyclization step were pleasing (dr ≥ 85:15),[15] even with cheap $NaBH_4$ as the reductant.[16] Solely for the 1-naphthyl derivative **9d**, the *cis* selectivity dropped to 70:30,[15] which explains the low 56% yield isolated. The Boc group at the pyrrolidine nitrogen atom was re-attached for two reasons, because it significantly facilitates the chromatographic purification and because it serves as the precursor for an *N*-methyl group. The final reduction of **9a**,**b**,**d** with LAH at reflux delivered the desired diamines **5b**,**c**,**e** in excellent ≥85% yield. In the case of **9c**, however, partial defluorination of the arylic CF_3-groups occurred, leading to an inseparable mixture.



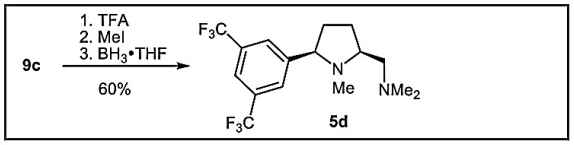
Scheme 3 Route I – three step cyclization

Table 1 Yields of **8**, **9** and **5** prepared according to Scheme 3

Entry	R^1	Yield of **8** (%)	Yield of **9** (%)[a]	Yield of **5** (%)
1	Ph	72 (**8a**)	76 (**9a**)	85 (**5b**)
2	4-$MeOC_6H_4$	55 (**8b**)	90 (**9b**)	97 (**5c**)
3	3,5-$(F_3C)_2C_6H_3$	76 (**8c**)	85 (**9c**)	--[b] (**5d**)
4	1-naphthyl	43 (**8d**)	56 (**9d**)	87 (**5e**)

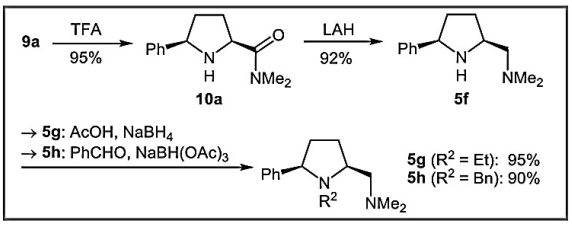
[a] Isolated yield of the pure *cis* diastereomer.
[b] Inseparable mixture of **5d** and partially deflourinated derivatives.

In order to prevent the unwanted fluoride–hydride exchange, we elaborated a milder, stepwise route for the conversion of **9c** to **5d** (Scheme 4). After *N*-deprotection of **9c** with TFA and methylation of the pyrrolidine nitrogen atom, the amide function was reduced with BH_3·THF in refluxing THF. This sequence provided the diamine **5d** in overall 60% yield without the formation of any defluorinated by-products.



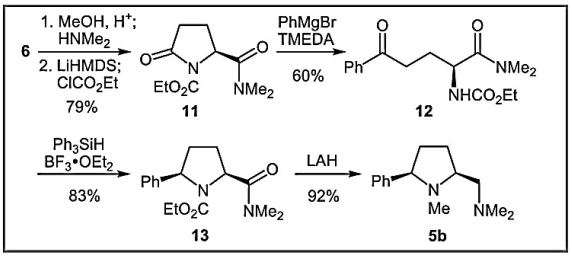
Scheme 4 Preparation of diamine **5d** from **9c**

The possibility of a last-step variation of the substituent R^2 at the pyrrolidine nitrogen was demonstrated on the 5-phenyl derivative **9a** (Scheme 5). *N*-Deprotection with TFA afforded amide **10a**, which was reduced with LAH to give diamine **5f**[14] in 87% yield over two steps. Reductive amination of **5f** with PhCHO–$NaBH(OAc)_3$ provided the *N*-benzyl derivative **5h** in good 90% yield, while the analogous ethylation failed to give sufficient product formation. With the reagent combination AcOH–$NaBH_4$,[17] however, the *N*-ethylated prolinamine **5g** was obtained in high 95% yield.



Scheme 5 Route I – variation of R^2

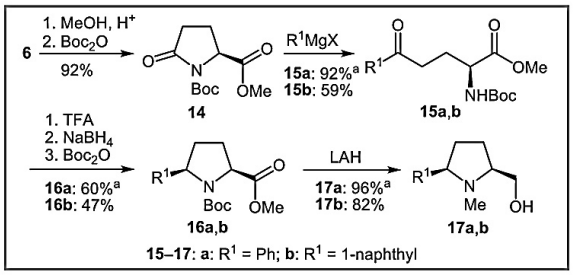
A further shortening of this approach to diamines **5** might be possible by using a variant of Martin's procedure,[18] in which a two-step protocol is described for the introduction of 5-*cis*-substituents to *N*-ethoxycarbonyl protected pyroglutamic esters. We explored this route in the synthesis of diamine **5b** (Scheme 6). The preparation of the required amide **11** was first met with some difficulties. After conversion of L-pyroglutamic acid (**6**) into the corresponding dimethyl amide, all attempts to attach the ethoxycarbonyl group to the lactam function under standard conditions (EtOCOCl, weak base such as NEt_3)[19] failed to give decent yields of **11**, due to fast decomposition of the chloroformate.[19a] This problem was overcome by quantitative deprotonation with LiHMDS and subsequent trapping with EtOCOCl, which delivered **11** in overall 79% yield from **6**. Addition of PhMgBr in the presence of TMEDA,[20] which is required to suppress a competing attack on the carbamate group,[18] afforded the ring-opened ketone **12** in 60% yield. The following reductive one-step cyclization with Ph_3SiH–$BF_3{\cdot}OEt_2$ provided the pyrrolidine amide **13** with excellent *cis* selectivity (initial dr >95:5).[15] Final global reduction with LAH delivered the desired diamine **5b** in overall just five steps and 36% yield from **6**. Compared to the synthesis of **5b** using the three-step cyclization (cf. Scheme 3 and Table 1, entry 1: seven steps, 38% overall yield), this route is shorter by two steps, but the requisite ethoxycarbonyl protective group makes the synthesis more laborious (anhydrous conditions for EtOCOCl attachment, Grignard–TMEDA adducts for addition)[20] and restricts the chemical flexibility (harsher conditions for carbamate cleavage)[21].



Scheme 6 Route I – one-step cyclization

Route II

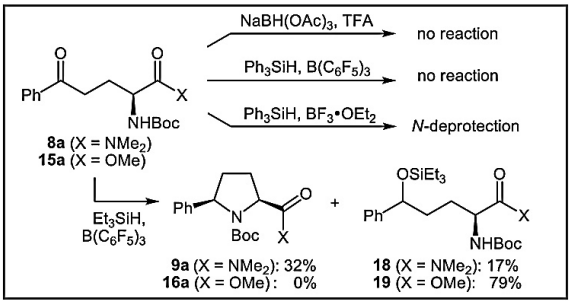
In route II, prolinols of general type **C** (see Scheme 2) are required as the precursors for the last-step variation of the exocyclic amino group NR^3R^4 by hydroxy–amine exchange. The two 5-*cis*-aryl derivatives **17a** and **17b** were prepared as outlined in Scheme 7 starting from L-pyroglutamic acid **6**, which was converted in high 92% yield into the known pyroglutamate **14**[22] by esterification and subsequent *N*-Boc protection. Applying the four-step sequence[12,13,16] that had already been successfully used in route I delivered the prolines **16a**[10] and **16b**[23] in 51% and 26% overall yield, albeit with a lower *cis* preference in the cyclization step (dr = 70:30, 50:50),[15] as compared to the analogous reaction on the corresponding dimethyl amides **7** (dr = 85:15, 70:30, cf. Scheme 3). Interestingly, a partially diastereomer-differentiating *N*-Boc protection was observed for the phenyl substituted intermediate. With just a slight excess of Boc_2O, the *cis/trans* ratio raised from 70:30 to 85:15 in **16a**, presumably since the pyrrolidine nitrogen atom in the *cis* isomer is more freely accessible than in the *trans* one. Global reduction of **16a**,**b** with LAH in refluxing THF afforded the 5-*cis*-aryl substituted prolinols **17a**,**b** in good 82–96% yield and diastereomerically pure form after purification.



Scheme 7 Route II – synthesis of the prolinol precursors **17a**,**b**[23]
[a] Data taken from ref.[10]

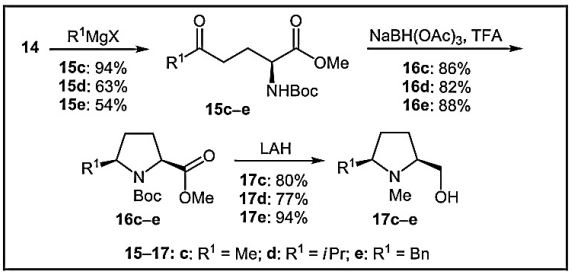
At this point we focused on an omission of the uneconomic *N*-Boc removal and re-attachment, which is a necessary part of the standard three-step cyclizations[12,13] of *N*-Boc-protected α-amino δ-oxo esters. Literature protocols describing more efficient one-step reductive cyclizations are rare; there is just a single report from McDermott et al. about a $NaBH(OAc)_3$–TFA mediated ring closure of an alkynyl derivative of **15**[24] and there are two reports about Ph_3SiH–$B(C_6F_5)_3$ induced cyclizations of alkyl derivatives of **15**.[25] We applied the two conditions to the phenyl substituted model substrates **8a** and **15a** (Scheme 8), but no reaction was observed. The reactivity of the latter phenyl ketones is apparently significantly reduced as compared to those of the alkyl and alkynyl ones. The attempted reductive cyclizations of **8a** and **15a** with Ph_3SiH in the presence of the stronger Lewis acid $BF_3{\cdot}OEt_2$ resulted, as expected, in a quantitative loss of the *N*-Boc group. Some success was achieved with the less bulky silane Et_3SiH. Treatment of the amide

8a with $Et_3SiH–B(C_6F_5)_3$ afforded a 2:1-mixture of the desired prolinamide **9a** (32% yield) and the non-cyclized, silylated alcohol **18** (17% yield).[26] In the case of ester **15a**, however, no product **16a** was detected; only the carbonyl hydrosilylation product **19** was formed in 79% yield.[26]



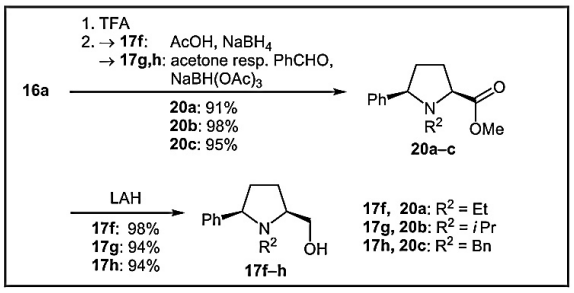
Scheme 8 Studies on the one-step cyclizations of the *N*-Boc-protected γ-amino phenylketones **8a** and **15a**[26]

While all attempts on single-step cyclizations of aryl substituted *N*-Boc α-amino δ-oxo esters and amides failed, we were successful in developing such a procedure for aliphatic derivatives. The amino ketone precursors **15c–e** (R^1 = Me,[27] *i*Pr, Bn), which were prepared in acceptable to high yields by treatment of **14** with the respective Grignard reagents at –40 °C, readily cyclized upon treatment with $NaBH(OAc)_3$–TFA in EtOAc (McDermott conditions)[24]. The resulting *N*-Boc-protected pyrrolidines **16c–e**[23,28,29] were isolated in good 82–88% yield and with pleasing *cis* selectivities (initial dr > 85:15).[15] Thus, this reagent combination permits an efficient synthesis of 5-*cis*-alkyl prolines without the need of any *N*-deprotection–reprotection steps. Final reduction of **16c–e** delivered the prolinols **17c–e** in 77–94% yield.



Scheme 9 Route II – synthesis of the prolinol precursors **17c–e**[23]

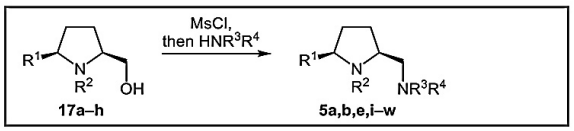
Variations of the substituent R^2 at the pyrrolidine nitrogen atom were done on the 5-phenyl substituted ester **16a** (Table 2). *N*-Deprotection with TFA followed by reductive amination with AcOH–$NaBH_4$, acetone–$NaBH(OAc)_3$, and, respectively, benzaldehyde–$NaBH(OAc)_3$ delivered the *N*-ethyl, *N*-isopopyl and *N*-benzyl pyrrolidine esters **20a–c** in excellent 91–98% yield over two steps. Reduction with LAH provided the prolinols **17f–h** in ≥94% yield.



Scheme 10 Route II – variation of the substituent R^2

The final hydroxy–amine exchange on the prolinols **17a–h** was put into practice by activation of the alcohol function as a mesylate and subsequent treatment of the crude intermediate with an excess of the respective amine (Table 2).[30] A set of 18 5-*cis*-substituted prolinamines **5** was thus prepared by amination with ammonia (→ **5i–m**), methylamine (→ **5a**,[10] **5n–p**), dimethylamine (→ **5b,e,q–s**), and other secondary amines such as diethylamine, pyrrolidine, piperidine, and methyl benzyl amine (→ **5t–w**). The product formation in this two-step sequence was generally high, irrespective of the attached substituents R^1 and R^2, but the high polarity of the products made their purification difficult, which explains the, in part, mediocre isolated yields. In the case of the 5-methyl and 5-isopropyl derivatives **5k,l,q,r**, additional problems arose from their high volatility.

Table 2 Route II – variation of the exocyclic amino group NR^3R^4



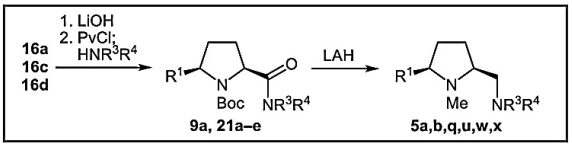
Entry	17	R^1	R^2	5	NR^3R^4	Yield (%)[a]
1	**a**	Ph	Me	**i**	NH_2	85
2	**b**	1-naphthyl	Me	**j**	NH_2	49
3	**c**	Me	Me	**k**	NH_2	24
4	**d**	*i*Pr	Me	**l**	NH_2	48
5	**e**	Bn	Me	**m**	NH_2	32
6	**a**	Ph	Me	**a**	NHMe	75[b]
7	**f**	Ph	Et	**n**	NHMe	84
8	**g**	Ph	*i*Pr	**o**	NHMe	77
9	**h**	Ph	Bn	**p**	NHMe	77
10	**a**	Ph	Me	**b**	NMe_2	65
11	**b**	1-naphthyl	Me	**e**	NMe_2	54
12	**c**	Me	Me	**q**	NMe_2	18
13	**d**	*i*Pr	Me	**r**	NMe_2	23
14	**e**	Bn	Me	**s**	NMe_2	44
15	**a**	Ph	Me	**t**	NEt_2	40
16	**a**	Ph	Me	**u**	pyrrolidinyl	52
17	**a**	Ph	Me	**v**	piperidinyl	51
18	**a**	Ph	Me	**w**	NMeBn	73

[a] Yields not optimized.
[b] Data taken from ref.[10].

Route III

Route III also proceeded via the *N*-Boc-protected methyl esters **16**, but the NR^3R^4 substituents were introduced by amidation and the reductions to the amines were done as the last step (Table 3). After saponification of **16a** (R^1 = Ph), **16c** (R^1 = Me), and **16d** (R^1 = *i*Pr) with LiOH in ethanol, the resulting crude acids were activated with PvCl as unsymmetric anhydrides and in-situ trapped with the respective amines (methylamine, dimethylamine, pyrrolidine, and methyl benzylamine) to give the corresponding amides **9a** and **21a–e**[31] in high 82–95% yield. Reductions with LAH were uneventful and delivered the amines **5a**,**b**,**q**,**u**,**w**,**x** as the major products in 74–98% yield. Smaller amounts of by-products, which were formed in the reductions of the secondary amides **21a**,**b**, were easily removed by column chromatography. This provided a distinctive advantage over route II, where the removal of the excess amine, as required for the hydroxy–amine exchange, from the polar diamines **5** was more laborious. In the cases of the prolinamines **5q** and **5u**, which were also prepared via route II from the esters **16c** and **16a** in low 14% and 50% yield (see Schemes 7 and 9 and Table 2), the overall yields could be significantly raised to 86% and 80%, respectively, by using route III.

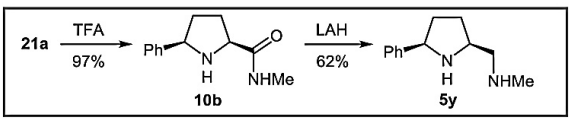
Table 3 Route III – introduction of NR^3R^4 via amides



Entry	16	R^1	NR^3R^4	Yield of 21, 9a (%)	Yield of 5 (%)
1	**a**	Ph	NHMe	86 (**21a**)	82 (**5a**)
2	**d**	*i*Pr	NHMe	82 (**21b**)	74 (**5x**)
3	**a**	Ph	NMe_2	92 (**9a**)	85 (**5b**)[a]
4	**c**	Me	NMe_2	88 (**21c**)	98 (**5q**)
5	**a**	Ph	pyrrolidinyl	82 (**21d**)	98 (**5u**)
6	**a**	Ph	NMeBn	95 (**21e**)	84 (**5w**)

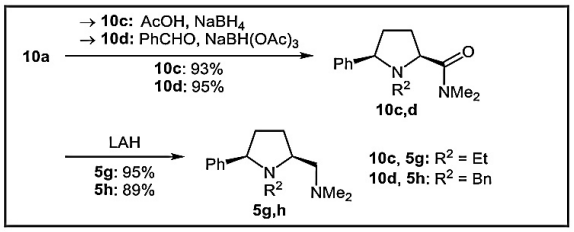
[a] Identically to Table 1, Entry 1.

The preparation of the diamine **5y**, in which the pyrrolidine nitrogen atom is unsubstituted, is shown in Scheme 11. *N*-deprotection of the amide **21a** with TFA and reduction of **10b** with LAH afforded **5y** in 60% yield. It should be noted that this compound will presumably not be accessible via route II since the secondary NH function will prohibit the required selective mesylation of the alcohol (cp. Table 2, R^2 would be H).



Scheme 11 Synthesis of the secondary diamine **5y**

Variations of the substituent R^2 were carried out on the secondary amide **10a** (Scheme 12), which was prepared from **9a** according to Scheme 5. Reductive aminations delivered the amides **10c** and **10d**, which were reduced to give the corresponding amines **5g** and **5h** in 85–88% yield over two steps. This sequence provides a welcome alternative to the one shown in Scheme 5, in which the reduction step precedes the reductive amination.



Scheme 12 Route III – variation of the substituent R^2

Conclusions

Each of the discussed approaches to 5-*cis*-substituted prolinamines of general type **5** includes three key sequences, the installment of the 5-*cis* substituent R^1 via a Grignard addition–recyclization protocol, the introduction of R^2 by direct reduction of the protective group (R^2 = Me) or by *N*-deprotection–reductive amination, and the attachment of the exocyclic NR^3R^4 group, either by amidation or by amination. Major difference is the order of introduction, which directly couples the usefulness of a route with the envisioned substituent pattern.

Route I (order of substituent introduction: NR^3R^4 first, then R^1, and R^2 last) is well suited for a fast screening of R^1 and R^2 under the premise of a given NR^3R^4 group. Moreover, the shortness of this approach (seven to nine steps, by using Martin's one-step cyclization just five steps) in combination with the good diastereoselectivities in the cyclization step makes this route particularly attractive for the larger scale synthesis of a given target prolinamine **5**. Route II (order of substituent introduction: R^1 first, then R^2, and NR^3R^4 last) offers the advantage of a last step variation of NR^3R^4. With the vast number of commercially available amines, this approach provides a facile access to a plethora of derivatives. In route III (order of substituent introduction: R^1 first, then NR^3R^4, and R^2 last), an amide reduction is done as the last step, which normally delivers the diamine **5** with high purity, thus avoiding the need of a time-consuming purification on the stage of the polar final products. Furthermore, due to the introduction of NR^3R^4 as an amide, this approach also permits the synthesis of derivatives that are not accessible by route II without the use of additional protective groups.

In addition, it was shown for the first time that aliphatic, *N*-Boc-protected α-amino δ-oxo esters can be directly cyclized to the corresponding 5-*cis*-alkyl pro-

lines by using $NaBH(OAc)_3$–TFA. This redundantizes an *N*-Boc removal and re-attachment which is required under the standard cyclization conditions.

In summary, we developed three routes to the novel and interesting class of 5-*cis*-substituted prolinamines **5**. Starting from L-pyroglutamic acid (**6**), the diamines **5** were prepared in five to ten steps, depending on the route and the substitution pattern chosen, and up to 64% yield (diamine **5q**). The practicability, applicability and modularity of the approaches were demonstrated in the synthesis of 25 diamines **5**, which carry a broad variety of different substituents R^1–R^4. The now possible, quick access to tailor-made derivatives will permit further investigations on the potential of the diamines **5** as chiral ligands in asymmetric catalysis.

All reactions with moisture-sensitive reagents were carried out under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[32] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey-Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey-Nagel, particle size 40–63 μm) was used for column chromatography. Melting points were measured on a Stuart SMP10 digital or a Büchi M-565 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance 300, a Bruker Avance 400, or a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^1H and ^{13}C NMR data were made on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a Jasco FT-IR-410 or a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra on a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization).

The syntheses of **5b**, **5f**, and **5h** along route I, of **5l** and **5n** along route II, and of **5u** along route III are described here exemplarily. For the preparations of all other compounds, see Supporting Information.

(*S*)-*tert*-Butyl 2-(dimethylcarbamoyl)-5-oxopyrrolidine-1-carboxylate (7)

A solution of (*S*)-pyroglutamic acid (**6**, 15.0 g, 116 mmol) and $TsOH•H_2O$ (663 mg, 3.49 mmol) in anhydrous MeOH (150 mL) was heated under reflux for 24 h. Gaseous $HNMe_2$ was bubbled through the solution at r.t. for 6 h (volume of the solution increased by ca. 25 mL) and the stoppered flask was stirred at r.t. for 48 h. The solvent and excess $HNMe_2$ were carefully removed under reduced pressure to give the crude amide (17.4 g) as yellowish oil that solidifies upon standing. This material was dissolved in anhydrous CH_2Cl_2 (200 mL) and Boc_2O (30.3 g, 139 mmol), NEt_3 (19.3 mL, 15.3 g, 151 mmol), and DMAP (709 mg, 5.80 mmol) were added at r.t. After 24 h of stirring, the reaction mixture was quenched with sat. aq NH_4Cl (200 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and evaporated. Flash chromatography (silica gel, CH_2Cl_2–MeOH, 100:0–95:5) delivered the product **7** (24.0 g, 93.6 mmol, 81%) as a yellowish resin, which crystallized upon standing to give a slightly yellow solid.

Mp 86–89 °C; $[\alpha]_D^{21}$ −35.8 (*c* 1.04, MeOH); R_f = 0.34 (CH_2Cl_2–MeOH, 95:5).

FT-IR (ATR): 2977, 2937, 1771, 1648, 1365, 1305, 1285, 1251, 1146, 1021, 840 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, $C(CH_3)_3$), 1.87 (m, 1 H, 3-*H*H), 2.22 (m, 1 H, 3-H*H*), 2.42 (ddd, *J* = 17.4, 9.5, 3.0 Hz, 1 H, 4-*H*H), 2.70 (ddd, *J* = 17.4, 10.3, 9.8 Hz, 1 H, 4-H*H*), 2.98 (s, 3 H, NCH_3), 3.08 (s, 3 H, NCH_3), 4.92 (dd, *J* = 9.2, 2.4 Hz, 1 H, 2-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (C-3), 28.0 ($C(CH_3)_3$), 31.4 (C-4), 36.0 (NCH_3), 36.8 (NCH_3), 56.4 (C-2), 83.1 ($C(CH_3)_3$), 149.8 (1-CO_2), 170.7 (2-CON), 173.8 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{12}H_{20}N_2O_4$: 279.1315; found: 279.1316.

(*S*)-2-(*tert*-Butoxycarbonylamino)-*N*,*N*-dimethyl-5-oxo-5-phenylpentanamide (8a)

PhMgBr (1.0 M in THF, 12.1 mL, 12.1 mmol) was added at –20 °C to a solution of the 5-oxopyrrolidine **7** (3.00 g, 11.7 mmol) in anhydrous THF (80 mL) and the reaction was allowed to warm to r.t. overnight. Sat. aq NH_4Cl (50 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 1:2–0:1) afforded the amino ketone **8a** (2.82 g, 8.42 mmol, 72%) as a colorless solid.

Mp 74–77 °C; $[\alpha]_D^{22}$ +0.3 (*c* 1.00, MeOH); R_f = 0.31 (Et_2O).

FT-IR (ATR): 3349, 2974, 2931, 1702, 1678, 1645, 1492, 1365, 1163, 1050, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (m, 9 H, $C(CH_3)_3$), 1.82 (m, 1 H, 3-*H*H), 2.22 (m, 1 H, 3-H*H*), 2.95 (s, 3 H, NCH_3), 2.96 (m, 1 H, 4-*H*H), 3.19 (s, 3 H, NCH_3), 3.20 (m, 1 H, 4-H*H*), 4.71 (m, 1 H, 2-H), 5.53 (d, *J* = 8.0 Hz, 1 H, NH), 7.43 (t, *J* = 7.6 Hz, 2 H,

Ph-H), 7.54 (t, J = 7.4 Hz, 1 H, Ph-H), 7.94 (d, J = 7.4 Hz, 2 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.4 (C-3), 28.4 ($C(CH_3)_3$), 33.8 (C-4), 35.8 (NCH_3), 37.2 (NCH_3), 49.7 (C-2), 79.6 ($C(CH_3)_3$), 128.1, 128.6, 133.1 (CH-Ph), 137.1 (C_q-Ph), 155.8 (NCO_2), 172.0 (C-1), 199.4 (C-5).

HRMS–ESI: *m/z* [M + Na]$^+$ calcd for $C_{18}H_{26}N_2O_4$: 357.1785; found: 357.1786.

(2*S*,5*R*)-*tert*-Butyl 2-(dimethylcarbamoyl)-5-phenylpyrrolidine-1-carboxylate (9a)

A solution of the amino ketone **8a** (1.64 g, 4.92 mmol) in anhydrous CH_2Cl_2 (50 mL) was treated at r.t. with TFA (7.50 mL, 11.1 g, 97.4 mmol) and stirred overnight. The solvent was removed under reduced pressure and the resulting orange oil was diluted five times with CH_2Cl_2 (30 mL) and evaporated again, in order to remove excess TFA. $NaBH_4$ (279 mg, 7.38 mmol) was slowly added at 0 °C to a solution of the residue in MeOH (80 mL). The solvent was removed after stirring overnight at r.t. The resulting orange oil was diluted four times with MeOH (35 mL) and evaporated again. The residue was suspended in anhydrous CH_2Cl_2 (100 mL) and NEt_3 (1.03 mL, 747 mg, 7.38 mmol), Boc_2O (1.61 g, 7.38 mmol), and DMAP (30.1 mg, 246 μmol) were added at r.t. Sat. aq NH_4Cl (100 mL) was added after 1 d of stirring and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 2:1–1:2) afforded the pyrrolidine amide **9a**[14] (1.19 g, 3.74 mmol, 76%) as a slightly yellowish oil.

$[\alpha]_D^{21}$ +35.8 (*c* 0.60, CH_2Cl_2); R_f = 0.50 (EtOAc).

FT-IR (ATR): 2974, 1689, 1655, 1389, 1362, 1155, 729, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H-NMR (400 MHz, $CDCl_3$):* δ = 1.10 (s, 6.4 H, $C(CH_3)_3$), 1.39 (s, 2.6 H, $C(CH_3)_3$), 1.97 (m, 1.3 H, 3-*H*H, 4-*H*H), 2.14 (m, 1.7 H, 3-*H*H, 4-H*H*), 2.28 (m, 1 H, 3-H*H*), 3.04 (s, 3 H, NCH_3), 3.12 (s, 0.9 H, NCH_3), 3.15 (s, 2.1 H, NCH_3), 4.68 (m, 1 H, 2-H, 5-H), 4.80 (m, 0.7 H, 2-H), 4.95 (m, 0.3 H, 5-H), 7.19 (t, J = 7.3 Hz, 1 H, Ph-H), 7.31 (t, J = 7.5 Hz, 2 H, Ph-H), 7.74 (d, J = 7.3 Hz, 2 H, Ph-H). * 70:30 mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$):* δ = 28.2, 28.4 ($C(CH_3)_3$), 28.7, 28.9 (C-3), 34.8, 35.9 (C-4), 36.3, 37.2 ($N(CH_3)_2$), 58.0, 62.5 (C-5), 63.6 (C-2), 79.8 ($C(CH_3)_3$), 126.6, 127.0, 128.1, 128.4 (CH-Ph), 144.6 (C_q-Ph), 154.8 (1-CO_2), 172.6 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* [M + H]$^+$ calcd for $C_{18}H_{26}N_2O_3$: 319.2016; found: 319.2018.

(2*S*,5*R*)-2-(Dimethylaminomethyl)-1-methyl-5-phenylpyrrolidine (5b)

LAH (2.0 M in THF, 3.84 mL, 7.69 mmol) was added at 0 °C to a solution of amide **9a** (408 mg, 1.28 mmol) in anhydrous THF (18 mL). After 1 h, the reaction mixture was heated under reflux overnight. The solution was diluted with Et_2O (25 mL) and treated with sat. aq Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was thoroughly washed (CH_2Cl_2–MeOH, 9:1, 300 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH, 90:10) delivered diamine **5b** (238 mg, 1.09 mmol, 85%) as a slightly yellowish oil.

$[\alpha]_D^{29}$ +20.1 (*c* 1.00, MeOH); R_f = 0.26 (CH_2Cl_2–MeOH, 9:1).

FT-IR (ATR): 2943, 2765, 1454, 1155, 1032, 850, 754, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70 (m, 2 H, 3-*H*H, 4-*H*H), 2.04 (m, 2 H, 3-H*H*, 4-H*H*), 2.18 (s, 3 H, 1-CH_3), 2.30 (s, 6 H, $N(CH_3)_2$), 2.37 (dd, J = 12.0, 8.2 Hz, 1 H, 2-H), 2.52 (m, 2 H, 2-CH_2), 3.24 (m, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.30 (m, 2 H, Ph-H), 7.35 (m, 2 H, Ph-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 29.5 (C-3), 34.0 (C-4), 39.7 (1-CH_3), 46.6 ($N(CH_3)_2$), 64.7 (C-2), 65.3 (2-CH_2), 72.7 (C-5), 127.0 , 127.5, 128.4 (CH-Ph), 143.9 (C_q-Ph).

HRMS–ESI: *m/z* [M + H]$^+$ calcd for $C_{14}H_{22}N_2$: 219.1856; found: 219.1858.

(2*S*,5*R*)-*N*,*N*-Dimethyl-5-phenylpyrrolidine-2-carboxamide (10a)

A solution of amide **9a** (1.21 g, 3.80 mmol) in CH_2Cl_2 (38 mL) was treated with TFA (5.86 mL, 8.67 g, 76.0 mmol) and stirred overnight at r.t. The solvent was removed under reduced pressure and the resulting oil was diluted five times with CH_2Cl_2 (20 mL) and evaporated again, in order to remove excess TFA. The residue was filtered through a pad of basic alumina (activity I, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1) to give amide **10a** (790 mg, 3.62 mmol, 95%) as a yellowish solid.

Mp 106−109 °C; $[\alpha]_D^{22}$ –37.7 (*c* 0.50, MeOH); R_f = 0.48 (CH_2Cl_2–MeOH, 9:1).

FT-IR (ATR): 3288, 2952, 2924, 1629, 1397, 1091, 870, 760, 704 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70 (m, 1 H, 4-*H*H), 1.92 (m, 1 H, 3-*H*H), 2.20 (m, 2 H, 3-H*H*, 4-H*H*), 2.89 (br s, 1 H, NH), 3.01 (s, 3 H, NCH_3), 3.05 (s, 3 H, NCH_3), 4.10 (m, 2 H, 2-H, 5-H), 7.25 (m, 1 H, Ph-H), 7.33 (m, 2 H, Ph-H), 7.47 (m, 2 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4 (C-3), 34.8 (C-4), 36.0, 36.6 ($N(CH_3)_2$), 58.6 (C-2), 64.5 (C-5), 127.0, 127.3, 128.6 (CH-Ph), 142.8 (C_q-Ph), 174.1 (2-CON).

HRMS–ESI: *m/z* [M + H]$^+$ calcd for $C_{13}H_{18}N_2O$: 219.1492; found: 219.1493.

(2*S*,5*R*)-2-(Dimethylaminomethyl)-5-phenylpyrrolidine (5f)

Amide **10a** (960 mg, 4.40 mmol) was dissolved in THF (70 mL) and LAH (1.0 M in THF, 13.2 mL, 13.2 mmol) was added at 0 °C. After 1 h, the reaction mixture was heated under reflux overnight. The solution was diluted with Et_2O (30 mL) and treated with sat. aq Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was rinsed with CH_2Cl_2–MeOH (9:1, 300 mL). Evaporation of the solvent and filtration through a pad of basic alumina (activity I, petroleum ether–Et_2O, 1:0–0:1) provided diamine **5f**[14] (825 mg, 4.04 mmol, 92%) as a yellowish oil.

$[\alpha]_D^{21}$ +13.4 (*c* 1.00, MeOH); R_f = 0.21 (CH_2Cl_2–MeOH–NEt_3, 90:10:1.

FT-IR (ATR): 3500–3100, 2942, 2765, 1454, 1263, 1098, 1038, 845, 754, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (m, 1 H, 3-*H*H), 1.73 (m, 1 H, 4-*H*H), 2.02 (m, 1 H, 3-H*H*), 2.17 (m, 1 H, 4-H*H*), 2.32 (s, 6 H, N(CH_3)$_2$), 2.38 (dd, *J* = 12.1, 5.4 Hz, 1 H, 2-C*H*H), 2.47 (dd, *J* = 12.1, 8.3 Hz, 1 H, 2-CH*H*), 3.49 (m, 1 H, 2-H), 3.57 (br s, 1 H, NH), 4.25 (dd, *J* = 8.8, 7.1 Hz, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.30 (m, 2 H, Ph-H), 7.38 (m, 2 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.0 (C-3), 33.5 (C-4), 46.0 (N(CH_3)$_2$), 56.4 (C-2), 62.6 (C-5), 65.7 (2-CH_2), 126.8, 127.1, 128.5 (CH-Ph), 143.9 (C_q-Ph).

HRMS–ESI: *m/z* [M + H]$^+$ calcd for $C_{13}H_{20}N_2$: 205.1699; found: 205.1700.

(2*S*,5*R*)-1-Benzyl-2-(dimethylaminomethyl)-5-phenylpyrrolidine (5h)

Benzaldehyde (39.8 µL, 41.8 mg, 394 µmol) and AcOH (30.0 µL, 31.6 mg, 524 µmol) were added at r.t. to a solution of the amine **5f** (53.6 mg, 262 µmol) in DCE (0.5 mL). $NaBH(OAc)_3$ (88.8 mg, 420 µmol) was added after 10 min and the solution was stirred for 4 h. The reaction mixture was quenched with sat. aq $NaHCO_3$ (4 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 3 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 190:9:1) provided diamine **5h** (69.2 mg, 235 µmol, 90%) as a colorless oil.

$[\alpha]_D^{28}$ +20.3 (*c* 1.00, MeOH); R_f = 0.15 (EtOAc).

FT-IR (ATR): 3030, 2937, 2815, 2769, 1491, 1452, 1033, 754, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67 (m, 1 H, 4-*H*H), 1.78 (m, 1 H, 3-*H*H), 1.98 (m, 3 H, 3-H*H*, 4-H*H*, 2-C*H*H), 2.11 (s, 6 H, N(CH_3)$_2$), 2.24 (t, *J* = 11.1 Hz, 1 H, 2-CH*H*), 2.96 (m, 1 H, 2-H), 3.45 (d, *J* = 13.4 Hz, 1 H, 1-C*H*H), 3.69 (dd, *J* = 9.8, 5.6 Hz, 1 H, 5-H), 3.83 (d, *J* = 13.4 Hz, 1 H, 1-CH*H*), 7.23 (m, 6 H, Ph-H), 7.33 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.46 (d, *J* = 7.3 Hz, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.6 (C-3), 34.9 (C-4), 46.3 (N(CH_3)$_2$), 57.0 (1-CH_2), 60.8 (C-2), 65.9 (2-CH_2), 69.8 (C-5), 126.9, 127.0, 127.6, 128.0, 128.4, 129.8 (CH-Ph), 139.1, 144.4 (C_q-Ph).

HRMS–ESI: *m/z* [M + H]$^+$ calcd for $C_{20}H_{26}N_2$: 295.2169; found: 295.2170.

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-6-methyl-5-oxoheptanoate (15d)

*i*PrMgBr (2.9 M in 2Me-THF, 5.33 mL, 15.5 mmol) was added at –40 °C to a solution of the 5-oxopyrrolidine **14**[22] (2.51 g, 10.3 mmol) in anhydrous THF (30 mL). After 2 h at –40 °C, sat. aq NH_4Cl (100 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 4:1–1:1) delivered **15d** (1.86 g, 6.47 mmol, 63%) as a colorless oil.

$[\alpha]_D^{25}$ +40.4 (*c* 0.48, $CHCl_3$); R_f = 0.52 (petroleum ether–EtOAc, 4:1).

FT-IR (ATR): 3500–3250, 2973, 1744, 1707, 1389, 1364, 1200, 1161, 1025, 1013, 757 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 6.9 Hz, 3 H, CH(C*H*$_3$)$_2$), 1.05 (d, *J* = 6.9 Hz, 3 H, CH(C*H*$_3$)$_2$), 1.39 (s, 9 H, C(CH_3)$_3$), 1.85 (m, 1 H, 3-*H*H), 2.06 (m, 1 H, 3-H*H*), 2.52 (m, 3 H, 4-H_2, 6-H), 3.69 (s, 3 H, OCH_3), 4.22 (m, 1 H, 2-H), 5.09 (d, *J* = 7.4 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.27, 18.29 (C-7, 6-CH_3), 26.5 (C-3), 28.3 (C(*C*H$_3$)$_3$), 36.1 (C-6), 41.0 (C-4), 52.4 (OCH_3), 53.1 (C-2), 80.0 (*C*(CH$_3$)$_3$), 155.5 (NCO_2), 173.0 (C-1), 213.5 (C-5).

HRMS–ESI: *m/z* [M + H]$^+$ calcd for $C_{14}H_{25}NO_5$: 288.1806; found: 288.1803.

(2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-isopropylpyrrolidine-1,2-dicarboxylate (16d)

$NaBH(OAc)_3$ (1.83 g, 8.64 mmol) was added at 0 °C to a solution of the amino ketone **15d** (1.90 g, 6.61 mmol) in EtOAc (35 mL). After 10 min, TFA (2.20 mL, 3.26 g, 28.6 mmol) was added dropwise over a period of 40 min. The reaction mixture was stirred for 2 h at 0 °C and overnight at r.t. Sat. aq $NaHCO_3$ (100 mL) was added and most of the organic solvent was removed under reduced pressure. CH_2Cl_2 (100 mL) was added, the layers were separated and the organic layer was washed with sat. aq $NaHCO_3$ (2 × 100 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chro-

matography (silica gel, petroleum ether–EtOAc, 6:1) provided **16d** (1.47 g, 5.42 mmol, 82%) as a colorless oil.

$[\alpha]_D^{30}$ +40.4 (*c* 1.00, $CHCl_3$); R_f = 0.70 (petroleum ether–EtOAc, 4:1).
FT-IR (ATR): 2959, 2874, 1754, 1692, 1381, 1364, 1194, 1162, 1103, 929, 769 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$):* δ = 0.87 (d, *J* = 6.7 Hz, 3 H, $CH(CH_3)_2$), 0.94 (d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$), 1.37 (br s, 5.4 H, $C(CH_3)_3$), 1.41 (br s, 3.6 H, $C(CH_3)_3$), 1.86 (m, 4 H, 3-*H*H, 4-H_2, $CH(CH_3)_2$), 2.14 (m, 1 H, 3-H*H*), 3.59 (m, 0.4 H, 5-H), 3.67 (m, 0.6 H, 5-H), 3.68 (s, 3 H, OCH_3), 4.17 (m, 0.6 H, 2-H), 4.28 (m, 0.4 H, 2-H). * 60:40 mixture of rotamers.

^{13}C NMR (75 MHz, $CDCl_3$):* δ = 18.2, 18.6 ($CH(CH_3)_2$), 19.9, 20.1 ($CH(CH_3)_2$), 26.5, 27.5 (C-4), 28.3 ($C(CH_3)_3$), 29.2 (C-3), 31.3, 31.4 ($CH(CH_3)_2$), 51.8, 52.0 (OCH_3), 60.0, 60.5 (C-2), 64.1, 64.4 (C-5), 79.8 ($C(CH_3)_3$), 154.6 (1-CO_2), 173.8, 174.0 (2-CO_2). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{14}H_{25}NO_4$: 294.1676; found: 294.1673.

(2*S*,5*S*)-2-(Hydroxymethyl)-5-isopropyl-1-methylpyrrolidine (17d)

LAH (1.23 g, 32.5 mmol) was added at 0 °C to a solution of ester **16d** (1.47 g, 5.42 mmol) in anhydrous THF (30 mL). The reaction mixture was heated under reflux for 16 h. Aq NaOH (10%, 6 mL) was added at 0 °C and the reaction mixture was stirred for 30 min at r.t. The solids formed were removed by filtration through a pad of celite® and the filter cake was rinsed with Et_2O (200 mL). Evaporation of the solvent delivered amino alcohol **17d** (654 mg, 4.16 mmol, 77%) as a slightly yellowish oil.

$[\alpha]_D^{25}$ +47.0 (*c* 2.00, $CHCl_3$); R_f = 0.70 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 80:18:2).

FT-IR (ATR): 3600–3100, 2955, 2871, 2783, 1465, 1385, 1367, 1209, 1032, 963, 755 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$), 0.83 (d, *J* = 6.9 Hz, 3 H, $CH(CH_3)_2$), 1.35–1.85 (m, 5 H, 3-H_2, 4-H_2, $CH(CH_3)_2$), 2.19 (s, 3 H, 1-CH_3), 2.30 (m, 1 H, 5-H), 2.48 (m, 1 H, 2-H), 2.94 (br s, 1 H, OH), 3.31 (dd, *J* = 10.5, 1.9 Hz, 1 H, 2-C*H*H), 3.58 (dd, *J* = 10.6, 3.6 Hz, 1 H, 2-CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 ($CH(CH_3)_2$), 20.2 ($CH(CH_3)_2$), 23.8 (C-4), 26.0 (C-3), 29.0 ($CH(CH_3)_2$), 39.0 (1-CH_3), 61.2 (2-CH_2), 67.1 (C-2), 71.9 (C-5).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_9H_{19}NO$: 158.1539; found: 158.1542.

(2*S*,5*R*)-2-(Aminomethyl)-5-isopropyl-1-methylpyrrolidine (5l)

K_2CO_3 (100 mg, 725 μmol) was added to a solution of the alcohol **17d** (76.0 mg, 483 μmol) in CH_2Cl_2 (3 mL). The resulting suspension was treated with MsCl (46.8 μL, 69.2 mg, 604 μmol) and stirred overnight. Aq NH_3 (25%, 3 mL, 44.0 mmol) and MeOH (3 mL) were added and the reaction mixture was stirred overnight. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1) provided the prolinamine **5l** (36.0 mg, 230 μmol, 48%) as a yellowish oil.

$[\alpha]_D^{25}$ +30.6 (*c* 1.00, $CHCl_3$); R_f = 0.30 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:8:2).

FT-IR (ATR): 3600–2400, 2955, 2871, 2781, 1462, 1320, 1150, 985, 766 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$), 0.84 (d, *J* = 6.9 Hz, 3 H, $CH(CH_3)_2$), 1.48 (m, 3 H, 3-*H*H, 4-H_2), 1.67 (br s, 2 H, NH_2), 1.72 (m, 2 H, 3-H*H*, $CH(CH_3)_2$), 2.19 (s, 3 H, 1-CH_3), 2.22 (m, 1 H, 5-H), 2.34 (m, 1 H, 2-H), 2.61 (dd, *J* = 12.9, 3.1 Hz, 1 H, 2-C*H*H), 2.71 (dd, *J* = 12.9, 5.1 Hz, 1 H, 2-CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 ($CH(CH_3)_2$), 20.3 ($CH(CH_3)_2$), 23.5 (C-4), 26.4 (C-3), 29.1 ($CH(CH_3)_2$), 39.6 (1-CH_3), 43.8 (2-CH_2), 68.2 (C-2), 72.2 (C-5).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_9H_{20}N_2$: 157.1699; found: 157.1702.

(2*S*,5*R*)-Methyl 1-ethyl-5-phenylpyrrolidin-2-carboxylate (20a)

A solution of the ester **16a**[10] (3.20 g, 10.5 mmol) in CH_2Cl_2 (120 mL) was treated with TFA (16.1 mL, 23.9 g, 210 mmol) and stirred overnight at r.t. The solvent was removed under reduced pressure and the resulting oil was diluted five times with CH_2Cl_2 (80 mL) and evaporated again, in order to remove excess TFA. The residue was filtered through a pad of basic alumina (activity I, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5) to give the known[33] ester (2*S*,5*R*)-methyl 5-phenylpyrrolidine-2-carboxylate (2.13 g, 10.4 mmol, 99%) as a colorless oil; R_f = 0.39 (CH_2Cl_2–MeOH, 95:5).

$NaBH_4$ (292 mg, 7.72 mmol) was portionwise added at 0 °C to a solution of the ester prepared above (336 mg, 1.64 mmol) in AcOH (3 mL). After gas evolution had ceased, the solution was heated to 60 °C for 2 h. Sat. aq $NaHCO_3$ (4 mL) was slowly added and the reaction mixture was made basic with solid Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 10:1) afforded the ester **20a** (352 mg, 1.51 mmol, 92%) as a colorless oil.

$[\alpha]_D^{27}$ +53.0 (*c* 1.00, MeOH); R_f = 0.43 (petroleum ether–EtOAc, 9:1).

FT-IR (ATR): 2967, 2951, 1749, 1732, 1192, 1163, 1074, 756, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, 1-CH_2CH_3), 1.85 (m, 1 H, 4-*H*H), 2.01 (m, 1 H, 3-*H*H), 2.12 (m, 2 H, 3-H*H*, 4-H*H*), 2.51 (dq, *J* = 12.9, 7.1 Hz, 1H, 1-C*H*H), 2.69 (dq, *J* = 13.0, 7.3 Hz, 1H, 1-CH*H*), 3.47 (dd, *J* = 9.1, 4.8 Hz, 1 H, 2-H), 3.71 (dd, *J* = 9.4, 5.9 Hz, 1 H, 5-H), 3.76 (s, 3 H, OCH_3), 7.23 (m, 1 H, Ph-H), 7.32 (m, 2 H, Ph-H), 7.48 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.6 (1-CH_2CH_3), 29.4 (C-3), 35.7 (C-4), 47.0 (1-CH_2CH_3), 51.9 (OCH_3), 65.0 (C-2), 69.2 (C-5), 127.1, 127.4, 128.3 (CH-Ph), 144.3 (C_q-Ph), 176.3 (2-CO_2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}NO_2$: 234.1487; found: 234.1489.

(2*S*,5*R*)-1-Ethyl-2-(hydroxymethyl)-5-phenylpyrrolidine (17f)

To a solution of ester **20a** (310 mg, 1.33 mmol) in anhydrous THF (15 mL), LAH (106 mg, 2.79 mmol) was added at 0 °C and the reaction mixture was stirred at r.t. overnight. The solution was diluted with Et_2O (15 mL) and treated with sat. aq Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was rinsed with CH_2Cl_2–MeOH (9:1, 100 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5) provided amino alcohol **17f** (268 mg, 1.31 mmol, 98%) as a colorless oil.

$[\alpha]_D^{28}$ +70.2 (*c* 1.00, MeOH); R_f = 0.36 (CH_2Cl_2–MeOH, 95:5).

FT-IR (ATR): 3500–3100, 2963, 2873, 1452, 1193, 1028, 756, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, 3 H, 1-CH_2CH_3), 1.71 (m, 1 H, 4-*H*H), 1.88 (m, 1 H, 3-*H*H), 1.99 (m, 1 H, 3-H*H*), 2.78 (m, 1 H, 4-H*H*), 2.64 (m, 2 H, 1-CH_2), 3.00 (br s, 1 H, OH), 3.04 (m, 1 H, 2-H), 3.48 (dd, *J* = 10.5, 2.7 Hz, 1 H, 2-C*H*H), 3.70 (dd, *J* = 10.5, 4.1 Hz, 1 H, 2-CH*H*), 3.76 (dd, *J* = 9.7, 6.5 Hz, 1 H, 5-H), 7.24 (m, 1 H, Ph-H), 7.32 (m, 2 H, Ph-H), 7.36 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ =12.3 (1-CH_2CH_3), 27.9 (C-3), 35.4 (C-4), 45.9 (1-CH_2CH_3), 63.1 (C-2), 63.6 (2-CH_2), 69.2 (C-5), 127.2, 128.5 (CH-Ph), 144.3 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{19}NO$: 206.1539; found: 206.1540.

(2*S*,5*R*)-1-Ethyl-2-(methylaminomethyl)-5-phenylpyrrolidine (5n)

NEt_3 (272 µL, 197 mg, 1.95 mmol) and MsCl (102 µL, 152 mg, 1.32 mmol) were added at 0 °C to a solution of the alcohol **17f** (160 mg, 779 µmol) in CH_2Cl_2 (6 mL). After stirring overnight at r.t., aq NH_2Me (40%, 2.12 mL, 23.3 mmol), NEt_3 (108 µL, 78.8 mg, 779 µmol), and MeOH (6 mL) were added and the reaction mixture was stirred overnight. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2) provided the prolinamine **5n** (142 mg, 654 µmol, 84%) as a colorless wax.

$[\alpha]_D^{26}$ +59.7 (*c* 1.00, MeOH); R_f = 0.29 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1).

FT-IR (ATR): 2964, 2790, 1452, 1372, 1190, 1135, 1028, 755, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3 H, 1-CH_2CH_3), 1.67 (m, 1 H, 4-*H*H), 1.79 (m, 1 H, 3-*H*H), 1.95 (m, 1 H, 3-H*H*), 2.05 (m, 1 H, 4-H*H*), 2.52 (s, 3 H, NCH_3), 2.63 (m, 4 H, 1-CH_2, 2-C*H*H, NH), 2.71 (dd, *J* = 11.4, 4.5 Hz, 1 H, 2-CH*H*), 3.00 (m, 1 H, 2-H), 3.69 (dd, *J* = 9.2, 6.6 Hz, 1 H, 5-H), 7.21 (m, 1 H, Ph-H), 7.29 (m, 2 H, Ph-H), 7.37 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.4 (1-CH_2CH_3), 28.9 (C-3), 35.3 (C-4), 37.0 (NCH_3), 46.4 (1-CH_2CH_3), 57.0 (2-CH_2), 62.1 (C-2), 69.0 (C-5), 126.8, 127.2, 128.2 (CH-Ph), 145.3 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{22}N_2$: 219.1856; found: 219.1857.

(2*R*,5*S*)-*tert*-Butyl 2-phenyl-5-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (21d)

LiOH·H_2O (49.7 mg, 1.18 mmol) was added to a solution of the ester **16a**[10] (213 mg, 697 µmol) in EtOH (3 mL). After 16 h of stirring, HCl (1 N, 15 mL) was added and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude acid (200 mg), which was dissolved in anhydrous THF (7 mL). NEt_3 (195 µL, 142 mg, 1.40 mmol) and PvCl (135 µL, 133 mg, 1.10 mmol) were added at r.t. and the resulting suspension was stirred for 2.5 h. Pyrrolidine (165 µL, 147 mg, 2.06 mmol) was added and stirring was continued for 16 h. The reaction mixture was evaporated and sat. aq $NaHCO_3$ (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated. Column chromatography (silica gel, petroleum ether–EtOAc, 3:1–0:1) afforded the amide **21d** (197 mg, 572 µmol, 82%) as a colorless resin.

$[\alpha]_D^{25}$ 32.8 (*c* 1.00, MeOH); R_f = 0.34 (petroleum ether–EtOAc, 1:1).

FT-IR (ATR): 2973, 2873, 1687, 1651, 1389, 1363, 1153, 1118, 760, 733, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$):* δ = 1.08 (s, 6 H, $C(CH_3)_3$), 1.37 (s, 3 H, $C(CH_3)_3$), 1.78–2.21 (m, 7 H, 3-*H*H, 4-H_2, $N(CH_2CH_2)_2$), 2.26 (m, 1 H, 3-H*H*), 3.46 (m, 2 H, $N(CH_2CH_2)_2$), 3.62 (m, 1.34 H, $N(CH_2CH_2)_2$), 3.76 (m, 0.66 H, $N(CH_2CH_2)_2$), 4.45 (m, 0.34 H, 5-H), 4.60 (m, 0.66 H, 5-H), 4.66 (t, *J* =

7.2 Hz, 0.66 H, 2-H), 4.94 (dd, J = 7.9, 2.9 Hz, 0.34 H, 2-H), 7.19 (m, 1 H, Ph-H), 7.29 (m, 2 H, Ph-H), 7.75 (m, 2 H, Ph-H). * 66:34 mixture of rotamers.

^{13}C NMR (125 MHz, $CDCl_3$):* δ = 24.15, 24.24, 26.3, 26.4 ($N(CH_2\mathit{C}H_2)_2$), 28.1, 28.35 ($C(\mathit{C}H_3)_3$), 28.43, 28.7 (C-4), 34.7, 35.8 (C-3), 46.10, 46.16, 46.18, 46.3 ($N(\mathit{C}H_2CH_2)_2$), 59.3, 59.6 (C-5), 62.2, 63.4 (C-2), 79.7, 79.9 ($\mathit{C}(CH_3)_3$), 126.5, 126.6, 126.9, 128.0, 128.3 (CH-Ph), 143.6, 144.6 (C_q-Ph), 153.8, 154.6 (1-CO_2), 171.2 (5-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* [M + 2 H – Boc]$^+$ calcd for $C_{20}H_{28}N_2O_3$: 245.1648; found: 245.1650.

(2*R*,5*S*)-1-Methyl-2-phenyl-5-(pyrrolidin-1-yl)methylpyrrolidine (5u)

LAH (95.8 mg, 2.53 mmol) was added at 0 °C to a solution of ester **21d** (145 mg, 421 μmol) in anhydrous THF (10 mL). After 1 h at 0 °C, the reaction mixture was heated under reflux for 18 h. The solution was diluted with Et_2O (20 mL) and treated with sat. aq Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was rinsed with CH_2Cl_2–MeOH (9:1, 200 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 97:3:0–85:13.5:1.5) provided diamine **5u** (101 mg, 413 μmol, 98%) as a slightly brownish oil.

$[\alpha]_D^{21}$ 2.0 (*c* 0.5, MeOH); R_f = 0.20 (CH_2Cl_2–MeOH, 9:1).

FT-IR (ATR): 2954, 2925, 2777, 1453, 1073, 880, 755, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (m, 6 H, 3-*H*H, 4-*H*H, $N(CH_2C\mathit{H}_2)_2$), 2.05 (m, 2 H, 3-H*H*, 4-H*H*), 2.20 (s, 3 H, 1-CH_3), 2.54 (m, 6 H, 5-H, 5-C*H*H, $N(C\mathit{H}_2CH_2)_2$), 2.73 (dd, J = 11.1, 3.1 Hz, 1 H, 5-CH*H*), 3.24 (m, 1 H, 2-H), 7.22 (m, 1 H, Ph-H), 7.32 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6 ($N(CH_2\mathit{C}H_2)_2$), 29.6 (C-4), 34.0 (C-3), 39.8 (1-CH_3), 55.1 ($N(\mathit{C}H_2CH_2)_2$), 62.0 (5-CH_2), 65.8 (C-5), 72.6 (C-2), 126.9, 127.5, 128.3 (CH-Ph), 144.0 (C_q-Ph).

HRMS–ESI: *m/z* [M + H]$^+$ calcd for $C_{16}H_{24}N_2$: 245.2012; found: 245.2010.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

(1) New address: Institute of Organic Chemistry, University of Würzburg, Am Hubland, 97074 Würzburg, Germany.

(2) New address: Institute of Inorganic Chemistry, University of Würzburg, Am Hubland, 97074 Würzburg, Germany.

(3) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.

(4) (a) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. (c) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

(5) (a) Soai, K.; Ookawa, A.; Ogawa, K.; Kaba, T. *J. Chem. Soc., Chem. Commun.* **1987**, 467. (b) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.

(6) (a) Zhou, Y.; Dong, J.; Zhang, F.; Gong, Y. *J. Org. Chem.* **2011**, *76*, 588. b) Zhou, Y.; Gong, Y. *Eur. J. Org. Chem.* **2011**, 6092. (c) Zhou, Y.; Zhu, Y.; Yan, S.; Gong, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 10265.

(7) (a) Breuning, M.; Steiner, M. *Synthesis* **2008**, 2841. (b) Breuning, M.; Hein, D.; Steiner, M.; Gessner, V. H.; Strohmann, C. *Chem.–Eur. J.* **2009**, *15*, 12764. (c) Breuning, M.; Steiner, M.; Mehler, C.; Paasche, A.; Hein, D. *J. Org. Chem.* **2009**, *74*, 1407. (d) Breuning, M.; Steiner, M.; Hein, D.; Hörl, C.; Maier, P. *Synlett* **2009**, 2749. (e) Breuning, M.; Hein, D. *Eur. J. Org. Chem.* **2013**, 7575.

(8) Reviews: (a) Boruwa, J. ; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315. (b) Palomo, C.; Oiarbide, M.; Laso A. *Eur. J. Org. Chem.* **2007**, 2561. (c) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Synlett* **2011**, 1195. (d) Chelucci, G. *Coord. Chem. Rev.* **2013**, *257*, 1887. (e) Ananthi, N.; Velmathi, S. *Ind. J. Chem.* **2013**, *52B*, 87.

(9) Selected recent examples: (a) Yao, L.; Wei, Y.; Wang, P.; He, W.; Zhang, S. *Tetrahedron* **2012**, *68*, 9119. (b) Qin, D.-D.; Lai, W.-H.; Hu, D.; Chen, Z.; Wu, A.-A.; Ruan, Y.-P.; Zhou, Z.-H.; Chen, H.-B. *Chem.–Eur. J.* **2012**, *18*, 10515. (c) Xu, K.; Lai, G.; Zha, Z.; Pan, S.; Chen, H.; Wang, Z. *Chem.–Eur. J.* **2012**, *18*, 12357. (d) Leighty, M. W.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 15233. (e) White, J. D.; Shaw, S. *Org. Lett.* **2012**, *14*, 6270. (f) Dai, Q.; Rana, N. K.; Zhao, J. C.-G. *Org. Lett.* **2013**, *15*, 2922. (g) Qin, D.-D.; Yu, W.; Zhou, J.-D.; Zhang, Y.-C.; Ruan, Y.-P.; Zhou, Z.-H.; Chen, H.-B. *Chem.–Eur. J.* **2013**, *19*, 16541. (h) Das, A.; Kureshy, R. I.; Prathap, K. J.; Choudhary, M. K.; Rao, G. V. S.; Khan, N. H.; Abdi, S. H. R.; Bajaj, H. C. *Appl. Catal. A* **2013**, *459*, 97. (i) Deng, T.; Cai, C. *J. Fluorine Chem.* **2013**, *156*, 183. (j) Ćwiek, R.; Niedziejko, P.; Kałuża, Z. *J. Org. Chem.* **2014**, *79*, 1222.

(10) Scharnagel, D.; Prause, F.; Kaldun, J.; Haase, R. G.; Breuning, M. *Chem. Commun.* **2014**, *50*, 6623.

(11) Besides **5a**,[10] there are only two further diamines of type **5** known, namely **5f** and a 5-*cis*, *N*′-diaryl derivative: (a) Castro, A. C.; Depew, K. M.; Grogan, M. J.; Holson, E. B.; Hopkins, B. T.; Johannes, C. W.; Keaney, G. F.; Koney, N. O.; Liu, T.; Mann, D. A.; Nevalainen, M.; Peluso, S.; Perez, L. B.; Snyder, D. A.; Tibbitts, T. T. PCT Int. Appl. WO 2008024337 A2, 2008. (b) Hutchison, A.; Peterson, J.; Doller, D.; Gustavson, L. E.; Caldwell, T.; Yoon, T.; Pringle, W.; Bakthavatchalam, R.; Shen, Y.; Steenstra, C.; Yin, H.; De Simone, R.; He, X.-s. PCT Int. Appl. WO 2002094799 A2, 2002.

(12) Selected examples: (a) Fournie-Zaluski, M.-C.; Coric, P.; Thery, V.; Gonzalez, W.; Meudal, H.; Turcaud, S.; Michel, J.-B.; Roques, B. P. *J. Med. Chem.* **1996**, *39*, 2594. (b) Xu, Y.; Choi, J.; Calaza, M. I.; Turner, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069. (c) Baldwin, J. J.; McDonald, E.; Moriarty, K. J.; Sarko, C. R.; Machinaga, N.; Nakayama, A.; Chiba, J.; Shin, I.; Yoneda, Y. PCT Int. Appl. WO 2001000206 A1, 2001. (d) Pei, Z.; Li, X.; Longenecker, K.; von Geldern, T. W.; Wiedeman, P. E.; Lubben, T. H.; Zinker, B. A.; Stewart, K.; Ballaron, S. J.; Stashko, M. A.; Mika, A. K.; Beno, D. W. A.; Long, M.; Wells, H.; Kempf-Grote, A. J.; Madar, D. J.; McDermott, T. S.; Bhagavatula, L.; Fickes, M. G.; Pireh, D.; Solomon, L. R.; Lake, M. R.; Edalji, R.; Fry, E. H.; Sham, H. L.; Trevillyan, J. M.; *J. Med. Chem.* **2006**, *49*, 3520. (e) Kimura, T.; Kawano, K.; Doi, E.; Kitazawa, N.; Takaishi, M.; Ito, K.; Kaneko, T.; Sasaki, T.; Miyagawa, T.; Hagiwara, H.; Yoshida, Y. U.S. Pat. Appl. US 20070117839 A1, 2007. (f) Alvaro, G.; Bergauer, M.; Giovannini, R.; Profeta, R. PCT Int. Appl. WO 2007042239 A1, 2007. (g) Ref. 11b, 13b, 27.

(13) Selected examples: (a) Momotake, A.; Togo, H; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1193. (b) Hoveyda, H.; Schils, D.; Zoute, L.; Parcq, J. PCT Int. Appl. WO 2011073376 A1, 2011.

(14) Amide **9a** and diamine **5f** are known, but not characterized compounds, see ref. 11a.

(15) The *cis/trans* ratios were determined from the ^{1}H NMR spectra of the crude reaction mixtures after reductive cyclization. The determination of the exact values was difficult for the *N*-Boc protected pyrrolidines since both diastereomers exist as mixtures of rotamers.

(16) In most literature protocols, hydrogenations[12] or modified borohydrides[13] are used for the reduction of the intermediate Δ^1-pyrrolidines. Even though these reagents often allow better *cis* selectivities, we choose cheap $NaBH_4$ for the reductions, because this permits to perform the *N*-deprotection, reductive cyclization, and *N*-re-protection sequence as a one-pot three-step procedure with comparable overall yields. To the best of our knowledge, there is just one example in which $NaBH_4$ was used, see. ref. 12e.

(17) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766.

(18) (a) Rudolph, A. C.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895. (b) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301.

(19) Such protocols work well for the corresponding esters, see: (a) Rigo, B.; Lespagnol, C.; Pauly, M. *J. Heterocycl. Chem.* **1988**, *25*, 49. (b) Jain, R. *Org. Prep. Proced. Int.* **2001**, *33*, 405.

(20) In further studies we found that Grignard reagents containing lithium salts, as formed by transmetalation of lithium organyls, are not suited for addition. The reaction of **11** with PhMgBr–LiCl–TMEDA (1.5:1.9:1.5), for example, provided **12** in just 5% yield.

(21) According to ref. 18a, the ethoxycarbonyl group can be removed with TMSI in refluxing MeCN.

(22) Pyroglutamate **14** is also commercially available. For selected procedures on the preparation of **14** from **6** or of *ent*-**14** from *ent*-**6**, see: (a) Coudert, E.; Acher, F.; Azerad, R. *Synthesis* **1997**, 863. (b) Aggarwal, V. K.; Astle, C. J.; Iding, H.; Wirz, B.; Rogers-Evans, M. *Tetrahedron Lett.* **2005**, *46*, 945. (c) Reilly, M. PCT Int. Appl. WO 2007110835 A2, 2007. (d) Vaswani, R. G.; Chamberlin, A. R. *J. Org. Chem.* **2008**, 73, 1661. (e) Anelli, P. L.; Brocchetta, M.; Lattuada, L.; Manfredi, G.; Morosini, P.; Murru, M.; Palano, D.; Sipioni, M.; Visigalli, M. *Org. Process Res. Dev.* **2009**, *13*, 739. (f) Hsu, M.-C.; King, C.-H. R.; Yuan, J.; Chen, W.-C.; Chou, S.-Y.; Shi, B. PCT Int. Appl. WO 2010009014 A2, 2010.

(23) In the cases of **16b** and **16c**, the minor diastereomers could not fully be removed on this stage and the mixtures were carried on to the next step, where separation by column chromatography was successful.

(24) McDermott, T. S.; Bhagavatula, L.; Borchardt, T. B.; Engstrom, K. M.; Gandarilla, J.; Kotecki, B. J.; Kruger, A. W.; Rozema, M. J.; Sheikh, A. Y.; Wagaw, S. H.; Wittenberger, S. J. *Org. Proc. Res. Dev.* **2009**, *13*, 1145.

(25) (a) Lin, G.-J.; Huang, P.-Q. *Org. Biomol. Chem.* **2009**, *7*, 4491. (b) Aebi, J.; Binggeli, A.; Green, L.; Hartmann, G.; Maerki, H. P.; Mattei, P. U.S. Pat. Appl. Publ. US 20110082294 A1, 2011. For related cyclizations of γ-amino ketones, see: (c) Abels, F.; Lindemann, C.; Schneider, C. *Chem.–Eur. J.* **2014**, *20*, 1964.

(26) The silyl ethers **18** and **19** were isolated as single diastereomers with unknown absolute configurations.

(27) Amino ketone **15c** is a known, but not characterized compound: Ayesa, S.; Belda, O.; Björklund, C.; Nilsson, M.; Russo, F.; Sahlberg, C.; Wiktelius, D. PCT Int. Appl. WO 2013095275 A1, 2013.

(28) (a) Mohite, A. R.; Bhat, R. G. *J. Org. Chem.* **2012**, *77*, 5423. (b) Belema, M.; Hewawasam, P. U.S. Pat. Appl. Publ. US 20110237636 A1, 2011.

(29) For other approaches to **16c**, see ref. 28a and: Wei, L.; Lubell, W. D. *Can. J. Chem.* **2001**, *79*, 94.

(30) The structures of the products **5** prepared by hydroxy–amine exchange were unambiguously confirmed by 2D NMR experiments and, for **5a**[10] and **5b**, by comparison with material obtained via route III. Rearrangements of **17** to β-amino piperidines via the sequence mesylation–aziridinium formation–nucleophilic attack at C-2 under ring enlargement were not observed. It had been shown that such rearrangements do not occur under mild mesylation conditions and with amines as the nucleophiles, see: (a) Pargo, D. G.; Cossy, J. *Chem.–Eur. J.* **2014**, *20*, 4516. See also: (b) Reitsema, R. H. *J. Am. Chem. Soc.* **1949**, *71*, 2041. (c) Biel, J. H.; Hoya, W. K.; Leiser, H. A. *J. Am. Chem. Soc.* **1959**, *81*, 2527. (d) Hammer, C. F.; Heller, S. R.; Craig, J. H. *Tetrahedron* **1972**, *28*, 239.

(31) Amide **21c** is a known, but only partially characterized compound: Miyazaki, M.; Naito, H.; Sugimoto, Y.; Yoshida, K.; Kawato, H.; Okayama, T.; Shimizu, H.; Miyazaki, M.; Kitagawa, M.; Seki, T.; Fukutake, S.; Shiose, Y.; Aonuma, M.; Soga, T. *Bioorg. Med. Chem.* **2013**, *21*, 4319.

(32) *Purification of Laboratory Chemicals*, 4th ed., Armarego, W. L. F.; Perrin, D. D., Eds.; Butterworth-Heinemann: Oxford, **2000**.

(33) (a) Haddad, M.; Imogai, H.; Larchevêque, M. *J. Org. Chem.* **1998**, *63*, 5680. (b) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305. (c) van Esseveldt, B. C. J; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791. (d) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.

Flexible and Modular Syntheses of Enantiopure 5-*cis*-Substituted Prolinamines from L-Pyroglutamic Acid

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1. General Information

For general information about apparatus and methods used, see article.

2. General Procedures

2.1. Grignard Addition to Pyroglutamic Esters and Amides (GP–1)[1]

A solution of the Grignard reagent (1.2–3.5 equiv) in anhydrous THF (0.5–3.0 M) was added to a solution of the pyroglutamate **X** (1.0 equiv) in anhydrous THF (5 mL/mmol **X**). For work up, sat. aq NH_4Cl (5 mL/mmol **X**) was added and the organic layer was removed under reduced pressure. The remaining aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL/mmol **X**), and the combined organic layers were washed with brine (5 mL/mmol **X**) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography afforded amino ketone **8** or **15**.

2.2. Three-Step Cyclization to 5-*cis*-substituted Pyroglutamic Esters and Amides (GP–2)[1]

A solution of the amino ketone **X** (1.0 equiv) in anhydrous CH_2Cl_2 (10 mL/mmol **X**) was treated at r.t. with TFA (20 equiv) and stirred overnight. The solvent was removed under reduced pressure and the resulting orange oil was diluted five times with CH_2Cl_2 (6 mL/mmol **X**) and evaporated again, in order to remove excess TFA. $NaBH_4$ (1.5–2.0 equiv) was slowly added at 0 °C to a solution of the residue in MeOH (16 mL/mmol **X**). The solvent was removed after stirring overnight at r.t. The resulting orange oil was diluted three times with MeOH (7 mL/mmol **X**) and evaporated again. The residue was suspended in anhydrous CH_2Cl_2 (25 mL/mmol **X**) and NEt_3 (1.5 equiv), Boc_2O (1.5 equiv), and DMAP (0.05 equiv) were added at r.t. Sat. aq NH_4Cl (20 mL/mmol **X**) was added after 1–3 d of stirring and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL/mmol **X**) and the combined organic layers were extracted with brine (10 mL/mmol **X**) and dried over $MgSO_4$. Removal of the solvent and column chromatography afforded pyrrolidine **9** or **16**.

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(1) Selected examples of related procedures: (a) Fournie-Zaluski, M.-C.; Coric, P.; Thery, V.; Gonzalez, W.; Meudal, H.; Turcaud, S.; Michel, J.-B.; Roques, B. P. *J. Med. Chem.* **1996**, *39*, 2594. (b) Xu, Y.; Choi, J.; Calaza, M. I.; Turner, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069. (c) Momotake, A.; Togo, H; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1193. (d) Baldwin, J. J.; McDonald, E.; Moriarty, K. J.; Sarko, C. R.; Machinaga, N.; Nakayama, A.; Chiba, J.; Shin, I.; Yoneda, Y. PCT Int. Appl. WO 2001000206 A1, **2001**; *Chem. Abstr.* **2001**, *134*, 86149. (e) Hutchison, A.; Peterson, J.; Doller, D.; Gustavson, L. E.; Caldwell, T.; Yoon, T.; Pringle, W.; Bakthavatchalam, R.; Shen, Y.; Steenstra, C.; Yin, H.; De Simone, R.; He, X.-s. PCT Int. Appl. WO 2002094799 A2, **2002**; *Chem. Abstr.* **2002**, *138*, 4617. (f) Pei, Z.; Li, X.; Longenecker, K.; von Geldern, T. W.; Wiedeman, P. E.; Lubben, T. H.; Zinker, B. A.; Stewart, K.; Ballaron, S. J.; Stashko, M. A.; Mika, A. K.; Beno, D. W. A.; Long, M.; Wells, H.; Kempf-Grote, A. J.; Madar, D. J.; McDermott, T. S.; Bhagavatula, L.; Fickes, M. G.; Pireh, D.; Solomon, L. R.; Lake, M. R.; Edalji, R.; Fry, E. H.; Sham, H. L.; Trevillyan, J. M.; *J. Med. Chem.* **2006**, *49*, 3520. (g) Kimura, T.; Kawano, K.; Doi, E.; Kitazawa, N.; Takaishi, M.; Ito, K.; Kaneko, T.; Sasaki, T.; Miyagawa, T.; Hagiwara, H.; Yoshida, Y. U.S. Pat. Appl. US 20070117839 A1, **2007**; *Chem. Abstr.* **2007**, *147*, 31141. (h) Alvaro, G.; Bergauer, M.; Giovannini, R.; Profeta, R. PCT Int. Appl. WO 2007042239 A1, **2007**; *Chem. Abstr.* **2007**, *146*, 422302. (i) McDermott, T. S.; Bhagavatula, L.; Borchardt, T. B.; Engstrom, K. M.; Gandarilla, J.; Kotecki, B. J.; Kruger, A. W.; Rozema, M. J.; Sheikh, A. Y.; Wagaw, S. H.; Wittenberger, S. J. *Org. Proc. Res. Dev.* **2009**, *13*, 1145. (j) Belema, M.; Hewawasam, P. U.S. Pat. Appl. Publ. US 20110237636 A1, **2011**; *Chem. Abstr.* **2011**, *155*, 484481. (k) Mohite, A. R.; Bhat, R. G. *J. Org. Chem.* **2012**, *77*, 5423.

2.3. Reductions with LAH (GP–3)

$LiAlH_4$ (6.0 equiv in the case of the *N*-Boc derivatives, 3.0 equiv in the case of the *N*-alkyl and *N*-H derivatives) was added at 0 °C to a solution of the pyrrolidine amide or ester **X** (1.0 equiv.) in anhydrous THF (15 mL/mmol **X**). The reaction mixture was stirred for 1 h at 0 °C and then refluxed overnight. The resulting suspension was diluted with Et_2O (15 mL/mmol **X**) and treated with sat. aq Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was rinsed with CH_2Cl_2–MeOH (9:1, 200 mL/mmol **X**). Evaporation of the solvent and column chromatography provided diamine **5** or amino alcohol **17**.

2.4. Reductive Amination (GP–4)

AcOH (2.0 equiv) and the aldehyde or ketone (1.5 equiv) were added at r.t. to a solution of the pyrrolidine **X** (1.0 equiv) in anhydrous DCE (2 mL/mmol **X**). After 10 min, $NaBH(OAc)_3$ (1.6 equiv) was added and stirring was continued for 2–3 h. Sat. aq. $NaHCO_3$ (10 mL/mmol **X**) and CH_2Cl_2 (10 mL/mmol **X**) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL/mmol **X**) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent and column chromatography afforded the *N*-alkylated pyrrolidine.

2.5. Mesylation and Amination of Prolinols 17 (GP–5)

MsCl (1.1 equiv) and NEt_3 (1.5 equiv) were added at 0 °C to a solution of the alcohol **17** (1.0 equiv) in anhydrous CH_2Cl_2 (3–11 mL/mmol **17**). After 1 d at r.t., an excess of the amine (10–30 equiv) was added and stirring was continued for 1–4 d. Evaporation of the solvent and column chromatography provided prolinamine **5**.

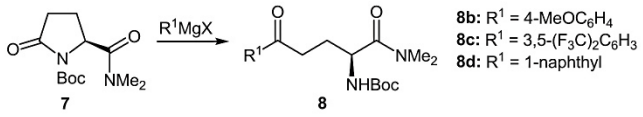
2.6. Saponification and Amidation of Esters 16 (GP–6)

$LiOH•H_2O$ (1.7 equiv) was added at r.t. to a solution of the ester **16** (1.0 equiv) in EtOH (4 mL/mmol **16**). After stirring overnight, aq HCl (1 N, 20 mL/mmol **16**) was added and the aqueous Layer was extracted with EtOAc (4 × 15 mL/mmol **16**). The combined organic layers were dried over $MgSO_4$ and the solvent removed. The resulting crude acid was dissolved in anhydrous CH_2Cl_2 (8 mL/mmol **16**) and NEt_3 (2.0 equiv) and PvCl (1.6 equiv) were added at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and 1.5 h at r.t. The amine or the amine hydrochloride (3.0 equiv) and NEt_3 (4.0 equiv in the case of free amine base, 7.0 equiv in the case of hydrochlorides) were added and stirring was continued overnight. Sat. aq. $NHCO_3$ (10 mL/mmol **16**) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL/mmol **16**) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent and column chromatography afforded pyrrolidine amide **9a** or **21**.

3. Synthesis of Diamines 5 According to Route I

The preparation of compounds **7**, **8a**, **9a**, **10a**, **5b**, **5f**, and **5h** is described in the article.

3.1. Amino Ketones 8b–d



7 8

3.1.1. (*S*)-2-(*tert*-Butoxycarbonylamino)-5-(4-methoxyphenyl)-*N*,*N*-dimethyl-5-oxopentanamide (8b)

Pyroglutamate **7** (1.00 g, 3.90 mmol) was treated with 4-methoxyphenylmagnesium bromide (1.0 M in THF, 4.68 mL, 4.68 mmol) according to GP–1 (addition at –40 °C, then warm up to r.t. overnight) to give, after column chromatography (silica gel, petroleum ether–EtOAc, 2:1–1:1), keto amide **8b** (783 mg, 2.15 mmol, 55%) as a colorless, highly viscous oil.

$[\alpha]_D^{21}$ +4.8 (*c* 1.00, MeOH); R_f = 0.5 (EtOAc).

IR (ATR): 3450–3350, 3350–3200, 2974, 2932, 1639, 1599, 1246, 1166, 1025, 840 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, $C(CH_3)_3$), 1.80 (m, 1 H, 3-*H*H), 2.20 (m, 1 H, 3-H*H*), 2.91 (m, 1 H, 4-*H*H), 2.96 (s, 3 H, NCH_3), 3.15 (m, 1 H, 4-H*H*), 3.18 (s, 3 H, NCH_3), 3.85 (s, 3 H, OCH_3), 4.69 (m, 1 H, 2-H), 5.51 (d, *J* = 7.0 Hz, 1 H, NH), 6.91 (d, *J* = 8.9 Hz, 2 H, Ar-H), 7.92 (d, *J* = 8.9 Hz, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6 (C-3), 28.4 ($C(CH_3)_3$), 33.4 (C-4), 35.8 (NCH_3), 37.2 (NCH_3), 49.8 (C-2), 55.6 (OCH_3), 79.6 ($C(CH_3)_3$), 113.8 (CH-Ar), 130.2 (C_q-Ar), 130.4 (CH-Ar), 155.8 (C_q-Ar), 163.6 (NCO_2), 172.0 (C-1), 197.9 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{19}H_{28}N_2O_5Na$: 387.1890; found: 387.1892.

3.1.2. (*S*)-5-(3,5-Bis(trifluoromethyl)phenyl)-2-(*tert*-butoxycarbonylamino)-*N*,*N*-dimethyl-5-oxopentanamide (8c)

The Grignard reagent (3,5-bis(trifluoromethyl)phenyl)magnesium bromide (1.2 equiv) was prepared by addition of *i*PrMgCl (2 M in THF, 3.80 mL, 7.60 mmol) at –10 °C to a solution of 1-bromo-3,5-bis(trifluoromethyl)benzene (1.31 mL, 2.22 g, 7.60 mmol) in anhydrous THF (4 mL). The resulting brownish solution was stirred at –10 °C for 1 h.

Pyroglutamate **7** (1.60 g, 6.24 mmol) was treated with the Grignard reagent prepared above according to GP–1 (addition at –15 °C, then warm up to r.t. overnight) to give, after column chromatography (silica gel, Et_2O), keto amide **8c** (2.32 g, 4.76 mmol, 76 %) as a colorless, highly viscous oil.

$[\alpha]_D^{21}$ +0.16 (*c* 0.98, MeOH); R_f = 0.40 (CH_2Cl_2–MeOH, 95:5).

IR (ATR): 3450–3370, 3370–3200, 2978, 2933, 1699, 1644, 1490, 1366, 1277, 1171, 1130, 681 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, $C(CH_3)_3$), 1.77 (m, 1 H, 3-*H*H), 2.31 (m, 1 H, 3-H*H*), 2.93 (m, 1 H, 4-*H*H), 2.99 (s, 3 H, NCH_3), 3.24 (s, 3 H, NCH_3), 3.36 (m, 1 H, 4-H*H*), 4.68 (m, 1 H, 2-H), 5.63 (d, *J* = 7.6 Hz, 1 H, NH), 8.05 (s, 1 H, Ar-H), 8.38 (s, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 (C-3), 28.3 ($C(CH_3)_3$), 34.1 (C-4), 35.9 (NCH_3), 37.2 (NCH_3), 49.3 (C-2), 79.9 ($C(CH_3)_3$), 123.1 (q, *J* = 272.7 Hz, CF_3), 126.3 (m, CH-Ar), 128.2 (d, *J* = 3.0 Hz, CH-Ar), 132.4 (q, *J* = 33.7 Hz, CCF_3), 138.7 (C_q-Ar), 156.1 (NCO_2), 171.7 (C-1), 196.8 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{20}H_{24}F_6N_2O_4Na$: 493.1533; found: 493.1531.

3.1.3. (*S*)-2-(*tert*-Butoxycarbonylamino)-*N*,*N*-dimethyl-5-(naphthalen-1-yl)-5-oxopentanamide (8d)

A 0.5 M solution of the Grignard reagent 1-naphthylmagnesium bromide was prepared by reaction of 1-bromonaphthalene (1.75 mL, 2.59 g, 12.5 mmol) with Mg turnings (340 mg, 14.0 mmol, activated by some drops of 1,2-dibromoethane) in anhydrous THF (25 mL). After most of the Mg had been reacted, the reaction mixture was stirred for additional 30 min at r.t. and then heated under reflux for 2 h.

Pyroglutamate **7** (500 mg, 1.95 mmol) was treated with the Grignard reagent prepared above (0.5 M in THF, 4.70 mL, 2.35 mmol) according to GP–1 (addition at –40 °C, then warm up to r.t. overnight) to give, after column chromatography (silica gel, petroleum ether–EtOAc, 2:1–0:1), a mixture of **8d** and the corresponding 4,5-dihydropyrrole. The latter mixture was dissolved in MeOH (2 mL), and water (200 µL) and $TsOH•H_2O$ (10 mg) were added. After 48 h at r.t., the solvent was removed in vacuum and the residue was dissolved in CH_2Cl_2 (10 mL). The organic layer was washed with sat. aq $NaHCO_3$ (2 × 10 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, Et_2O) delivered keto amide **8d** (325 mg, 845 µmol, 43%) as a colorless, highly viscous oil.

$[\alpha]_D^{21}$ –15.1 (*c* 1.00, MeOH); R_f = 0.48 (Et_2O).

IR (ATR): 3450–3375, 3375–3200, 2975, 2931, 1702, 1638, 1490, 1165, 1049, 800, 776 cm^{-1}.

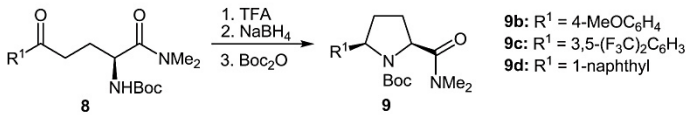
^1H NMR: (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, $C(CH_3)_3$), 1.88 (m, 1 H, 3-*H*H), 2.29 (m, 1 H, 3-H*H*), 2.99 (s, 3 H, NCH_3), 3.05 (m, 1 H, 4-*H*H), 3.24 (s, 3 H, NCH_3), 3.29 (m, 1 H, 4-H*H*), 4.80 (td, *J* = 8.8, 3.0 Hz, 1 H, 2-H), 5.56 (d, *J* = 8.4 Hz, 1 H, NH), 7.53 (m, 3 H, Ar-H), 7.87 (m, 2 H, Ar-H), 7.97 (d, *J* = 8.3 Hz, 1 H, Ar-H), 8.55 (d, *J* = 8.6 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7 (C-3), 28.5 ($C(CH_3)_3$), 35.9 (NCH_3), 37.3 (NCH_3), 37.5 (C-4), 49.7 (C-2), 79.7 ($C(CH_3)_3$), 124.5, 125.9, 126.5, 127.7, 127.9, 128.5 (CH-Ar), 130.2 (C_q-Ar), 132.5 (CH-Ar), 134.1, 136.3 (C_q-Ar), 155.9 (NCO_2), 172.0 (C-1), 203.7 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{22}H_{28}N_2O_4Na$: 407.1941; found: 407.1939.

6

3.2. Pyrrolidine Amides 9b–d



3.2.1 (2*S*,5*R*)-*tert*-Butyl 2-(dimethylcarbamoyl)-5-(4-methoxyphenyl)pyrrolidine-1-carboxylate (9b)

According to GP–2, the keto amide **8b** (1.00 g, 2.74 mmol) was reductively cyclized to give, after column chromatography (silica gel, petroleum ether–EtOAc, 1:1–0:1), pyrrolidine amide **9b** (856 mg, 2.46 mmol, 90%) as a slightly yellowish solid.

Mp 118–121 °C; $[\alpha]_D^{21}$ +28.8 (*c* 1.00, MeOH); R_f = 0.47 (EtOAc).

IR (ATR): 2971, 2932, 1677, 1649, 1513, 1391, 1244, 1154, 1030, 820 cm^{-1}.

^1H NMR: (400 MHz, $CDCl_3$):* δ = 1.13 (s, 6.3 H, $C(CH_3)_3$), 1.38 (s, 2.7 H, $C(CH_3)_3$), 1.95 (m, 1.3 H, 3-*H*H, 4-*H*H), 2.11 (m, 1.7 H, 3-H*H*, 4-*H*H), 2.24 (m, 1 H, 4-H*H*), 3.03 (s, 3 H, NCH_3), 3.11 (s, 0.9 H, NCH_3), 3.14 (s, 2.1 H, NCH_3), 3.77 (s, 0.9 H, OCH_3), 3.79 (s, 2.1 H, OCH_3), 4.66 (m, 1 H, 2-H, 5-H), 4.78 (m, 0.7 H, 2-H), 4.90 (m, 0.3 H, 5-H), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.66 (d, *J* = 8.5 Hz, 2 H, Ar-H). * 70:30 mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$):* δ = 28.2, 28.4 ($C(CH_3)_3$), 28.7 (C-3), 34.9, 35.9 (C-4), 36.3, 37.2 (NCH_3), 55.3, 55.4 (OCH_3), 57.9 (C-2), 61.9, 63.0 (C-5), 79.8, 79.9 ($C(CH_3)_3$), 113.5 113.8, 127.7, 128.1 (CH-Ar), 135.9, 136.9 (C_q-Ar), 153.9, 154.8 (1-CO_2), 158.4 (C_q-Ar), 172.7, 172.8 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{19}H_{28}N_2O_4Na$: 371.1941; found: 371.1943.

3.2.2 (2*R*,5*S*)-*tert*-Butyl 2-(3,5-bis(trifluoromethyl)phenyl)-5-(dimethylcarbamoyl)pyrrolidine-1-carboxylate (9c)

According to GP–2, the keto amide **8c** (2.00 g, 4.25 mmol) was reductively cyclized to give, after column chromatography (silica gel, petroleum ether–EtOAc, 1:1–0:1), pyrrolidine amide **9c** (1.64 g, 3.62 mmol, 85%) as a colorless solid.

Mp 80−84 °C; $[\alpha]_D^{21}$ +19.4 (*c* 1.03, MeOH); R_f = 0.64 (CH_2Cl_2–MeOH, 95:5).

IR (ATR): 3032, 2986, 2938, 1694, 1651, 1376, 1367, 1274, 1163, 1124, 682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$):* δ = 1.10 (s, 6.0 H, $C(CH_3)_3$), 1.39 (s, 3.0 H, $C(CH_3)_3$), 1.98 (m, 1.3 H, 3-*H*H, 4-*H*H), 2.19 (m, 1.7 H, 3-H*H*, 4-*H*H), 2.37 (m, 1 H, 4-H*H*), 3.04 (s, 2.0 H, NCH_3), 3.05 (s, 1.0 H, NCH_3), 3.12 (s, 1.0 H, NCH_3), 3.15 (s, 2.0 H, NCH_3), 4.73 (m, 0.3 H, 5-H), 4.79 (m, 0.7 H, 2-H), 4.87 (dd, *J* = 8.1, 2.7 Hz, 0.7 H, 5-H), 5.01 (m, 0.3 H, 2-H), 7.72 (s, 0.3 H, Ar-H), 7.75 (s, 0.7 H, Ar-H), 8.31 (s, 2 H, Ar-H). * 67:33 mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$):* δ = 28.1, 28.3 ($C(CH_3)_3$), 29.0 (C-4), 34.5, 35.6 (C-3), 36.4, 37.2

(NCH_3), 57.8, 57.9 (C-5), 61.9, 62.9 (C-2), 80.5, 80.8 ($C(CH_3)_3$), 120.7 (m, CH-Ar), 123.7 (q, J = 272.5 Hz, CF_3), 127.2, 127.6 (CH-Ar), 131.5 (q, J = 33.0 Hz, CCF_3), 146.4, 147.6 (C_q-Ar), 153.8, 154.1 (1-CO_2), 172.3, 172.4 (5-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{20}H_{24}F_6N_2O_3Na$: 477.1583; found: 477.1586.

3.2.3 (2*S*,5*R*)-*tert*-Butyl 2-(dimethylcarbamoyl)-5-(naphthalen-1-yl)pyrrolidine-1-carboxylate (9d)

According to GP–2, the keto amide **8d** (500 mg, 1.30 mmol) was reductively cyclized to give, after column chromatography (silica gel, Et_2O), pyrrolidine amide **9d** (270 mg, 733 µmol, 56%) as a colorless solid.

Mp (decomp.) 190 °C; $[\alpha]_D^{21}$ +55.2 (*c* 1.00, MeOH); R_f = 0.24 (Et_2O).

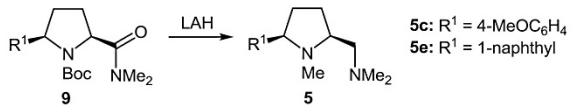
IR (ATR): 3062, 2971, 1692, 1650, 1386, 1159, 1116, 810, 784 cm^{-1}.

^1H NMR: (400 MHz, $CDCl_3$):* δ = 1.04 (s, 5.0 H, $C(CH_3)_3$), 1.43 (s, 4.0 H, $C(CH_3)_3$), 1.94–2.25 (m, 3.0 H, 3-H_2, 4-*H*H), 2.50 (m, 1.0 H, 4-H*H*), 3.07 (s, 3 H, NCH_3), 3.16 (s, 1.4 H, NCH_3), 3.19 (s, 1.6 H, NCH_3), 4.71 (dd, J = 9.6, 6.5 Hz, 0.45 H, 2-H), 4.83 (t, J = 7.1 Hz, 0.55 H, 2-H), 5.64 (dd, J = 7.3, 5.3 Hz, 0.55 H, 5-H), 5.79 (d, J = 8.7 Hz, 0.45 H, 5-H), 7.45 (m, 2 H, Ar-H), 7.55 (m, 1 H, Ar-H), 7.72 (m, 1 H, Ar-H), 7.84 (m, 1 H, Ar-H), 7.97 (dd, J = 15.1, 8.3 Hz, 1 H, Ar-H), 8.68 (m, 1 H, Ar-H). * 55:45 mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$):* δ = 28.1, 28.4 ($C(CH_3)_3$), 28.7 (C-3), 33.3, 34.4 (C-4), 36.37, 36.42, 37.3 (NCH_3), 58.1, 58.3 (C-2), 59.3 (C-5), 79.8, 80.2 ($C(CH_3)_3$), 122.6 123.0, 124.4, 124.6, 125.0, 125.6, 126.3, 126.8, 127.2, 129.0 (CH-Ar), 130.4, 130.6, 133.7, 134.1, 138.2, 139.4 (C_q-Ar), 154.1, 154.9 (1-CO_2), 172.4, 172.6 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{22}H_{28}N_2O_3Na$: 391.1992; found: 391.1991.

3.3. Diamines 5c and 5e



3.3.1. (2*S*,5*R*)-2-(Dimethylaminomethyl)-5-(4-methoxyphenyl)-1-methylpyrrolidine (5c)

According to GP–3, the pyrrolidine **9b** (630 mg, 1.81 mmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1), prolinamine **5c** (436 mg, 1.76 mmol, 97%) as a beige solid.

Mp 25–27 °C; $[\alpha]_D^{21}$ +11.4 (*c* 0.50, MeOH); R_f = 0.15 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 2945, 2815, 1612, 1510, 1457, 1242, 1170, 1034, 827 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.69 (m, 2 H, 3-*H*H, 4-*H*H), 2.03 (m, 2 H, 3-H*H*, 4-H*H*), 2.16 (s,

3 H, 1-CH_3), 2.31 (s, 6 H, $N(CH_3)_2$), 2.38 (dd, *J* = 12.9, 9.1 Hz, 1 H, 2-H), 2.53 (m, 2 H, 2-CH_2), 3.18 (dd, *J* = 9.1, 6.2 Hz, 1 H, 5-H), 3.79 (s, 3 H, OCH_3), 6.84 (m, 2 H, Ar-H), 7.25 (m, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4 (C-3), 33.9 (C-4), 39.6 (1-CH_3), 46.5 ($N(CH_3)_2$), 55.4 (OCH_3), 64.5 (C-2), 65.2 (2-CH_2), 72.2 (C-5), 113.8, 128.6 (CH-Ar), 135.6, 158.8 (C_q-Ar).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{25}N_2O$: 249.1961; found: 249.1960.

3.3.2. (2*S*,5*R*)-2-(Dimethylaminomethyl)-1-methyl-5-(naphthalen-1-yl)pyrrolidine (5e)

According to GP–3, the pyrrolidine **9d** (200 mg, 543 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1), prolinamine **5e** (127 mg, 473 µmol, 87%) as a colorless oil.

$[\alpha]_D^{21}$ +61.2 (*c* 0.50, MeOH); R_f = 0.33 (CH_2Cl_2–MeOH, 9:1).

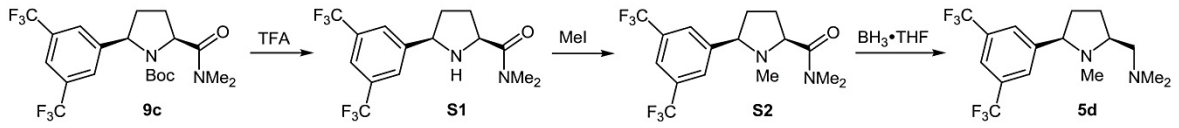
IR (ATR): 2943, 2763, 1595, 1456, 1154, 1032, 931, 853, 797, 776 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (m, 2 H, 3-*H*H, 4-*H*H), 2.18 (m, 1 H, 3-H*H*), 2.30 (s, 3 H, 1-CH_3), 2.36 (m, 1 H, 4-H*H*), 2.39 (s, 6 H, $N(CH_3)_2$), 2.51 (dd, *J* = 12.1, 8.2 Hz, 1 H, 2-C*H*H), 2.67 (dd, *J* = 12.1, 3.7 Hz, 1 H, 2-CH*H*), 2.72 (m, 1 H, 2-H), 4.08 (m, 1 H, 5-H), 7.47 (m, 3 H, Ar-H), 7.75 (m, 2 H, Ar-H), 7.86 (m, 1 H, Ar-H), 8.22 (m, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (C-3), 33.0 (C-4), 40.2 (1-CH_3), 46.5 ($N(CH_3)_2$), 64.6 (C-2), 65.1 (2-C), 68.8 (C-5), 123.6, 123.7, 125.3, 125.6, 126.0, 127.1, 128.9 (CH-Ar), 131.8, 134.1, 139.6 (C_q-Ar).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{18}H_{25}N_2$: 269.2012; found: 269.2013.

3.4. Synthesis of 5d from 9c



3.4.1. (2*S*,5*R*)-5-(3,5-Bis(trifluoromethyl)phenyl)-*N*,*N*-dimethylpyrrolidine-2-carboxamide (S1)

A solution of the amide **9c** (1.20 g, 2.64 mmol) in anhydrous CH_2Cl_2 (30 mL) was treated at r.t. with TFA (4.04 mL, 6.02 g, 52.8 mmol) and stirred overnight. The solvent was removed under reduced pressure and the residue was diluted five times with CH_2Cl_2 (30 mL) and evaporated again, in order to remove excess TFA. Filtration through a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1) afforded the *N*-deprotected pyrrolidine **S1** (874 mg, 2.47 mmol, 93%) as a colorless oil.

$[\alpha]_D^{21}$ –1.2 (*c* 1.00, MeOH); R_f = 0.51 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 3497, 3279, 2941, 1633, 1379, 1275, 1172, 1122, 898, 842, 708, 681 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.67 (m, 1 H, 4-*H*H), 1.96 (m, 1 H, 3-*H*H), 2.22 (m, 2 H, 3-H*H*, 4-H*H*), 2.76 (s, 1 H, NH), 2.98 (s, 3 H, $N(CH_3)_2$), 3.04 (s, 3 H, $N(CH_3)_2$), 4.09 (dd, *J* = 8.8, 4.9 Hz, 1 H, 2-H), 4.21 (dd, *J* = 9.8, 5.5 Hz, 1 H, 5-H), 7.73 (s, 1 H, Ar-H), 7.91 (s, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (C-3), 34.3 (C-4), 36.0, 36.6 ($N(CH_3)_2$), 58.3 (C-2), 63.3 (C-5), 121.2 (sept, *J* = 3.9 Hz, CH-Ar), 123.5 (q, *J* = 272.7 Hz, CF_3), 127.3 (d, *J* = 2.6 Hz, CH-Ar), 131.7 (q, *J* = 33.2 Hz, *C*CF_3), 145.6 (C_q-Ar), 173.5 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}F_6N_2O$: 355.1240; found: 355.1235.

3.4.2. (2*S*,5*R*)-5-(3,5-Bis(trifluoromethyl)phenyl)-*N*,*N*,1-trimethylpyrrolidine-2-carboxamide (S2)

Cs_2CO_3 (1.03 g, 3.16 mmol) and MeI (108 µL, 247 mg, 1.74 mmol) were added at r.t. to a solution of the pyrrolidine **S1** (560 mg, 1.58 mmol) in anhydrous CH_2Cl_2 (25 mL). After vigorous stirring for 4 d, sat. aq $NaHCO_3$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 1:0–0:1) delivered the *N*-methylated pyrrolidine **S2** (500 mg, 1.36 mmol, 86%) as a colorless oil.

$[\alpha]_D^{21}$ +19.3 (*c* 0.50, MeOH); R_f = 0.44 (EtOAc).

IR (ATR): 2948, 2785, 1651, 1276, 1167, 1122, 897, 842, 709, 682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.77 (m, 1 H, 4-*H*H), 1.96 (m, 1 H, 3-*H*H), 2.16 (s, 3 H, 1-CH_3), 2.19 (m, 2 H, 3-H*H*, 4-H*H*), 2.98 (s, 3 H, $N(CH_3)_2$), 3.15 (s, 3 H, $N(CH_3)_2$), 3.44 (m, 2 H, 2-H, 5-H), 7.72 (s, 1 H, Ar-H), 7.88 (s, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 (C-3), 34.7 (C-4), 36.3, 36.8 ($N(CH_3)_2$), 39.6 (1-CH_3), 67.7 (C-2), 70.7 (C-5), 121.3 (sept, *J* = 3.9 Hz, CH-Ar), 123.5 (q, *J* = 272.6 Hz, CF_3), 127.8 (d, *J* = 2.6 Hz, CH-Ar), 131.8 (q, *J* = 33.2 Hz, *C*CF_3), 146.2 (C_q-Ar), 172.2 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{19}F_6N_2O$: 369.1396; found: 369.1397.

3.4.3. (2*R*,5*S*)-2-(3,5-Bis(trifluoromethyl)phenyl)-5-(dimethylaminomethyl)-1-methylpyrrolidine (5d)

BH_3•THF (1.0 M in THF, 8.91 mL, 8.91 mmol) was added at 0 °C to a solution of **S2** (547mg, 1.49 mmol) in anhydrous THF (30 mL). The reaction mixture was stirred for 1 h at 0 °C and then refluxed for 72 h. The solvent was removed under reduced pressure and the residue was diluted five times with MeOH (30 mL) and evaporated again. The residue was dissolved in CH_2Cl_2 (10 mL) and MeOH (5 mL), and TFA (910 µL, 1.35 g, 11.9 mmol) was added. After heating to 40 °C overnight, the solvent was removed and the residue was diluted three times with CH_2Cl_2 (15 mL) and evaporated again. Column chromatography (silica gel, 1. petroleum ether/EtOAc, 1:0–0:1; 2. CH_2Cl_2–

MeOH, 95:5–90:10) afforded diamine **5d** (396 mg, 1.12 mmol, 75%) as a slightly yellowish oil.

$[\alpha]_D^{21}$ +30.1 (*c* 1.00, MeOH); R_f = 0.46 (CH_2Cl_2–MeOH, 9:1).

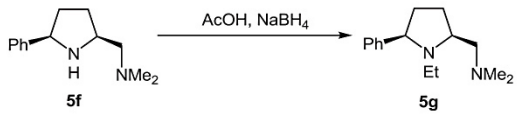
IR (ATR): 2947, 2770, 1459, 1379, 1345, 1276, 1169, 1127, 897, 708, 682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.60 (m, 1 H, 3-*H*H), 1.74 (m, 1 H, 4-*H*H), 2.09 (m, 2 H, 3-H*H*, 4-H*H*), 2.20 (s, 3 H, 1-CH_3), 2.28 (s, 6 H, $N(CH_3)_2$), 2.36 (dd, *J* = 12.2, 8.2 Hz, 1 H, 5-C*H*H), 2.49 (dd, *J* = 12.2, 4.0 Hz, 1 H, 5-CH*H*), 2.63 (m, 1 H, 5-H), 3.42 (dd, *J* = 9.0, 6.9 Hz, 1 H, 2-H), 7.73 (s, 1 H, Ar-H), 7.80 (s, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.5 (C-4), 34.6 (C-3), 39.8 (1-CH_3), 46.6 ($N(CH_3)_2$), 64.6 (C-5), 65.3 (5-C), 71.8 (C-2), 121.1 (sept, *J* = 3.8 Hz, CH-Ar), 123.7 (q, *J* = 272.6 Hz, CF_3), 127.6 (d, *J* = 2.6 Hz, CH-Ar), 131.7 (q, *J* = 33.0 Hz, *C*CF_3), 147.4 (C_q-Ar).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{21}F_6N_2$: 355.1603; found: 355.1602.

3.5. (2*S*,5*R*)-2-(Dimethylaminomethyl)-1-ethyl-5-phenylpyrrolidine (5g)



$NaBH_4$ (35.6 mg, 940 µmol) was portionwise added at 0 °C to a solution of the amine **5f** (40.8 mg, 200 µmol) in AcOH (350 µL). After gas evolution had ceased, the solution was heated to 60 °C for 2 h. Sat. aq $NaHCO_3$ (4 mL) was slowly added and the reaction mixture was made basic with solid Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (4 × 4 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent afforded the analytically pure amine **5g** (44.2 mg, 190 µmol, 95%) as a colorless oil.

$[\alpha]_D^{21}$ +14.1 (*c* 1.00, MeOH); R_f = 0.50 (CH_2Cl_2–MeOH, 8:2).

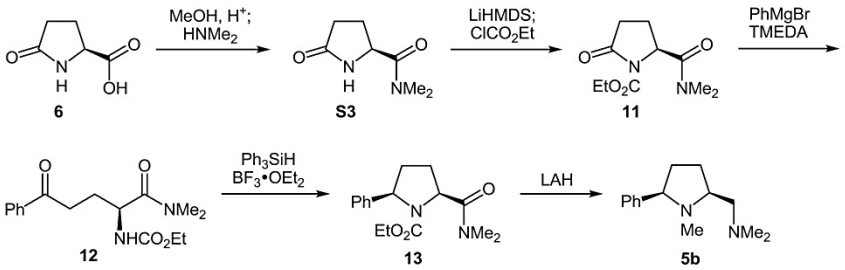
IR (ATR): 2965, 2935, 2815, 2764, 1453, 1153, 1035, 850, 756, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, 1-CH_2CH_3), 1.66 (m, 1 H, 4-*H*H), 1.77 (m, 1 H, 3-*H*H), 2.00 (m, 2 H, 3-H*H*, 4-H*H*), 2.30 (s, 6 H, $N(CH_3)_2$), 2.38 (m, 2 H, 2-CH_2), 2.61 (m, 2 H, 1-CH_2CH_3), 2.92 (m, 1 H, 2-H), 3.66 (dd, *J* = 9.0, 6.3 Hz, 1 H, 5-H), 7.20 (m, 1 H, Ph-H), 7.29 (m, 2 H, Ph-H), 7.38 (m, 2 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9 (1-CH_2CH_3), 29.7 (C-3), 35.1 (C-4), 46.6 ($N(CH_3)_2$), 46.8 (1-CH_2CH_3), 61.1 (C-2), 66.8 (2-CH_2), 69.3 (C-5), 126.8, 127.3, 128.2 (CH-Ph), 145.5 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{25}N_2$: 233.2012; found: 233.2011.

3.6. Synthesis of Diamine 5b via One-Step Cyclisation



3.6.1. Synthesis of 11 from 6

3.6.1.1. (*S*)-*N*,*N*-Dimethyl-5-oxopyrrolidine-2-carboxamide (S3)

A solution of-pyroglutamic acid (**6**, 30.0 g, 232 mmol) and TsOH•H_2O (1.33 g, 6.97 mmol) in anhydrous MeOH (300 mL) was heated under reflux for 24 h. Gaseous $HNMe_2$ was bubbled through the solution at r.t. for 6 h (volume of the solution increased by ca. 50 mL) and the stoppered flask was stirred at 40 °C for 48 h. The solvent and excess $HNMe_2$ were carefully removed under reduced pressure. Purification by flash chromatography (silica gel, CH_2Cl_2–MeOH, 98:2–95:5) and crystallization from CH_2Cl_2–Et_2O delivered the known[2] amide **S3** (33.0 g, 211 mmol, 91%) in analytically pure form as colorless needles, mp 118–120 °C {ref. 2a: Mp 115–117 °C; ref. 2b: Mp 114–115 °C}; $[\alpha]_D^{29}$ –35.6 (*c* 2.00, H_2O) {ref. 2a: $[\alpha]_D^{22}$ –37.2 (*c* 1.16, H_2O); ref. 2b: $[\alpha]_D^{23}$ –33.5 (*c* 2.00, H_2O)}.

The spectroscopic data of **16c** were consistent with those reported in literature.[2b]

3.6.1.2. (*S*)-Ethyl 2-dimethylcarbamoyl-5-oxopyrrolidine-1-carboxylate (11)

The amide **S3** (15.0 g, 96.1 mmol) was dissolved in anhydrous THF (1.1 L) and cooled to –78 °C. LiHMDS (1.0 M in THF, 106 mL, 106 mmol) was added dropwise within 20 min to the resulting beige suspension. After 30 min at –78 °C, $ClCO_2Et$ (11.0 mL, 12.5 g, 115 mmol) in anhydrous THF (100 mL) was added slowly. The reaction was warmed to 0 °C within 2 h and quenched with sat. aq NH_4Cl (800 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 800 mL), and the combined organic layers were washed with brine (800 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and crystallization (CH_2Cl_2–Et_2O–petroleum ether, 1:2:6) delivered imide **11** (19.1 g, 83.7 mmol, 87%) as colorless needles.

Mp 116–120 °C; $[\alpha]_D^{21}$–22.8 (*c* 1.00, MeOH); R_f = 0.27 (CH_2Cl_2–MeOH, 95:5).

IR (ATR): 2979, 2959, 2933, 1746, 1705, 1650, 1294, 1275, 1035, 846, 778, 608 cm^{-1}.

^1H NMR: (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.91 (ddt, *J* = 12.9, 9.7 Hz, 2.5 Hz, 1 H, 3-*H*H), 2.25 (ddt, *J* = 12.8, 10.6 Hz, 9.4 Hz, 1 H, 3-H*H*), 2.45 (ddd, *J* = 17.4, 9.5, 2.7 Hz, 1 H, 4-*H*H), 2.73 (ddd, *J* = 17.4, 10.6, 9.7 Hz, 1 H, 4-H*H*), 2.97 (s, 3 H, NCH_3), 3.09 (s, 3 H,

(2) (a) Angier, R. B.; Smith, V. K. *J. Org. Chem.* **1956**, *21*, 1540. (b) Doyle, M. P.; Winchester, W. R.; Simonsen, S. H.; Ghosh, R. *Inorg. Chim. Acta* **1994**, *220*, 193.

NCH_3), 4.26 (m, 2 H, OCH_2CH_3), 4.98 (dd, J = 9.2, 2.2 Hz, 1 H, 2-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (OCH_2CH_3), 21.7 (C-3), 31.3 (C-4), 36.1 (NCH_3), 36.8 (NCH_3), 56.3 (C-2), 63.0 (OCH_2CH_3), 151.7 (1-CO_2), 170.5 (2-CON), 173.3 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{10}H_{16}N_2O_4Na$: 251.1002; found: 251.1003.

3.6.2. (*S*)-2-(Ethoxycarbonylamino)-*N*,*N*-dimethyl-5-oxo-5-phenylpentanamide (12)

TMEDA (491 μL, 381 mg, 3.28 mmol) was added at r.t. to a solution of PhMgBr (3.0 M in Et_2O, 1.09 mL, 3.28 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred at r.t. for 30 min, cooled to –78 °C, and then added to a solution of amide **11** (500 mg, 2.19 mmol) in anhydrous THF (11 mL). After 90 min at –78 °C, sat. aq NH_4Cl (11 mL) was added and stirring was continued for 1 h at r.t. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, Et_2O) delivered keto amide **12** (400 mg, 1.31 mmol, 60%) as a colorless oil.

$[\alpha]_D^{21}$ +4.9 (*c* 1.00, MeOH); R_f = 0.45 (EtOAc).

IR: 3440–3370, 3770–3290, 2933, 1712, 1683, 1637, 1497, 1229, 1052, 743, 690 cm^{-1}.

^1H NMR: (500 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.85 (m, 1 H, 3-*H*H), 2.23 (m, 1 H, 3-H*H*), 2.97 (s, 3 H, NCH_3), 3.01 (m, 1 H, 4-*H*H), 3.21 (m, 1 H, 4-H*H*), 3.22 (s, 3 H, NCH_3), 4.05 (m, 2 H, OCH_2CH_3), 4.76 (td, J = 8.7, 3.1 Hz, 1 H, 2-H), 5.69 (d, J = 8.2 Hz, 1 H, NH), 7.45 (t, J = 7.7 Hz, 2 H, Ph-H), 7.55 (t, J = 7.3 Hz, 1 H, Ph-H), 7.95 (d, J = 7.7 Hz, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.7 (OCH_2CH_3), 27.3 (C-3), 33.7 (C-4), 35.9 (NCH_3), 37.2 (NCH_3), 50.1 (C-2), 61.1 (OCH_2CH_3), 128.1, 128.7, 133.2 (CH-Ph), 136.9 (C_q-Ph), 156.7 (NCO_2), 171.8 (C-1), 199.4 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{16}H_{22}N_2O_4Na$: 329.1472; found: 329.1270.

3.6.3. (2*S*,5*R*)-Ethyl 2-(dimethylcarbamoyl)-5-phenylpyrrolidine-1-carboxylate (13)

The keto amide **12** (557 mg, 1.82 mmol) and Ph_3SiH (521 mg, 2.00 mmol) were dissolved in CH_2Cl_2 (8 mL). BF_3•Et_2O (250 μL, 2.00 mmol) was added at –78 °C and the reaction mixture was allowed to slowly warm to r.t. overnight. Aq NaOH (1 N, 2 mL) was added and, after 20 min of stirring, CH_2Cl_2 (20 mL) and H_2O (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, 1. petroleum ether; 2. CH_2Cl_2–MeOH, 1:0–9:1) delivered pyrrolidine **13** (439 mg, 1.51 mmol, 83%) as a crystalline colorless solid.

Mp 73–76 °C; $[\alpha]_D^{21}$ +40.2 (*c* 1.02, MeOH); R_f = 0.35 (EtOAc).

IR (ATR): 2979, 2958, 2929, 1693, 1649, 1405, 1334, 1110, 1011, 755, 707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$):* δ = 0.90 (t, *J* = 7.0 Hz, 2.0 H, OCH_2CH_3), 1.18 (m, 1.0 H, OCH_2CH_3), 2.00 (m, 1 H, 3-*H*H), 2.12 (m, 2 H, 3-H*H*, 4-*H*H), 2.31 (m, 1 H, 4-H*H*), 3.03 (s, 3 H, NCH_3), 3.13 (s, 1 H, NCH_3), 3.16 (s, 2 H, NCH_3), 3.93 (q, *J* = 7.0 Hz, 1.3 H, OCH_2CH_3), 4.05 (m, 0.7 H, OCH_2CH_3), 4.79 (m, 1.7 H, 2-H, 5-H), 4.92 (m, 0.3 H, 5-H), 7.19 (m, 1 H, Ph-H), 7.31 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.72 (m, 2 H, Ph-H). * 67:33 mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$):* δ = 14.3, 14.7 (OCH_2CH_3), 28.5, 29.2 (C-4), 34.7, 35.6 (C-3), 36.3, 37.3 (NCH_3), 57.7, 58.3 (C-2), 61.2 (OCH_2CH_3), 62.9, 63.2 (C-5), 126.7, 126.8, 128.2, 128.3 (CH-Ph), 143.2, 143.9 (C_q-Ph), 154.8, 155.7 (1-CO_2), 172.3, 172.6 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{16}H_{22}N_2O_3Na$: 313.1523; found: 313.1521.

3.6.4. (2*S*,5*R*)-2-(Dimethylaminomethyl)-1-methyl-5-phenylpyrrolidine (5b)

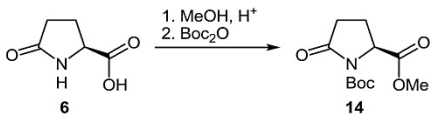
According to GP–3, the pyrrolidine **13** (39.2 mg, 135 μmol) was reduced to give, after filtration through a pad of cotton wool, prolinamine **5b** (27.0 mg, 124 μmol, 92%) as a colorless oil.

For characterization of **5b**, see article.

4. Synthesis of Diamines 5 According to Route II

The preparation of compounds **15a**, **16a**, **17a** and **5a** is described in ref. 3, the preparation of **15d**, **16d**, **17d**, **17f**, **20a**, **5l**, and **5n** is described in the article.

4.1. (*S*)-1-*tert*-Butyl 2-methyl 5-oxopyrrolidine-1,2-dicarboxylate (14)



Note: Pyroglutamate **14** is commercially available, but it can conveniently be prepared in high 92% yield from **6** by the following procedure. For a selection of other procedures for the preparation of **14** from **6** (or *ent*-**14** from *ent*-**6**), see ref. 4.

A solution of L-pyroglutamic acid (**6**, 20.0 g, 155 mmol) and $TsOH•H_2O$ (884 mg, 4.65 mmol) in anhydrous MeOH (250 mL) was heated under reflux for 24 h. The solvent was evaporated and the resulting oil was dissolved in CH_2Cl_2 (200 mL). Boc_2O (37.2 g, 170 mmol), NEt_3 (32.2 mL, 23.5 g, 232 mmol), and DMAP (1.89 g, 15.5 mmol) were added at r.t. and stirring was continued for 24 h.

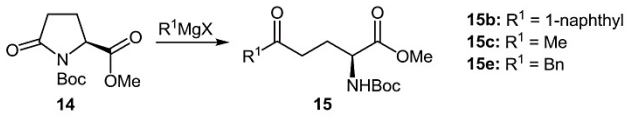
(3) Scharnagel, D.; Prause, F.; Kaldun, J.; Haase, R. G.; Breuning, M. *Chem. Commun.* **2014**, *50*, 6623.

(4) (a) Coudert, E.; Acher, F.; Azerad, R. *Synthesis* **1997**, 863. (b) Aggarwal, V. K.; Astle, C. J.; Iding, H.; Wirz, B.; Rogers-Evans, M. *Tetrahedron Lett.* **2005**, *46*, 945. (c) Reilly, M. PCT Int. Appl. WO 2007110835 A2, **2007**; *Chem. Abstr.* **2007**, *147*, 406709. (d) Vaswani, R. G.; Chamberlin, A. R. *J. Org. Chem.* **2008**, 73, 1661. (e) Anelli, P. L.; Brocchetta, M.; Lattuada, L.; Manfredi, G.; Morosini, P.; Murru, M.; Palano, D.; Sipioni, M.; Visigalli, M. *Org. Process Res. Dev.* **2009**, *13*, 739. (f) Hsu, M.-C.; King, C.-H. R.; Yuan, J.; Chen, W.-C.; Chou, S.-Y.; Shi, B. PCT Int. Appl. WO 2010009014 A2, **2010**; *Chem. Abstr.* **2010**, *152*, 168816.

The reaction mixture was washed with sat. aq NH_4Cl (3 × 200 mL) and the combined aq layers were extracted with CH_2Cl_2 (200 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Flash chromatography (silica gel, petroleum ether–EtOAc, 5:1–1:1) delivered the known[4] pyroglutamate **14** (34.6 g, 142 mmol, 92%) as a colorless solid, $[\alpha]_D^{22}$ –33.7 (*c* 1.00, CH_2Cl_2) {ref. 4b: $[\alpha]_D^{21}$ –32.1 (*c* 1.00, CH_2Cl_2)}.

The spectroscopic data of **14** were consistent with those reported in literature.[4a–d]

4.2. Amino Ketones 15



4.2.1. (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-(naphthalen-1-yl)-5-oxopentanoate (15b)

Pyroglutamate **14** (4.00 g, 16.5 mmol) in anhydrous THF (20 mL) was treated with 1-naphthyl-MgBr (0.5 M in THF, 58.0 mL, 29.0 mmol) according to GP–1 (addition at 0 °C, then warm up to r.t. overnight) to give, after column chromatography (silica gel, petroleum ether–Et_2O, 1:0–1:1), a mixture of **15b** and the corresponding 4,5-dihydropyrrole. The latter mixture was dissolved in MeOH (50 mL), and water (5 mL) and TsOH•H_2O (100 mg) were added. After 5 d at r.t., the solvent was removed in vacuum and the residue was dissolved in CH_2Cl_2 (100 mL). The organic layer was washed with sat. aq $NaHCO_3$ (2 × 75 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–Et_2O, 1:0–1:1) delivered amino ketone **15b** (3.64 g, 9.80 mmol, 59%) as a brownish gum.

$[\alpha]_D^{28}$ –11.5 (*c* 1.00, MeOH); R_f = 0.51 (petroleum ether–Et_2O, 1:2).

IR (ATR): 3470–3230, 2978, 1707, 1683, 1507, 1365, 1160, 1051, 775, 731 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, $C(CH_3)_3$), 2.16 (m, 1 H, 3-*H*H), 2.37 (m, 1 H, 3-H*H*), 3.05–3.31 (m, 2 H, 4-H_2), 3.75 (s, 3 H, OCH_3), 4.43 (m, 1 H, 2-H), 5.22 (m, 1 H, NH), 7.53 (m, 3 H, Ar-H), 7.86 (m, 2 H, Ar-H), 7.97 (d, *J* = 8.3 Hz, 1 H, Ar-H), 8.59 (d, *J* = 8.4 Hz, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3 (C-3), 28.3 ($C(CH_3)_3$), 38.0 (C-4), 52.5 (OCH_3), 53.2 (C-2), 80.1 ($C(CH_3)_3$), 124.4, 125.8, 126.5, 127.7, 128.0, 128.5 (CH-Ar),130.2 (C_q-Ar), 132.9 (CH-Ar), 134.0, 135.7 (C_q-Ar) 155.6 (NCO_2), 173.0 (C-1), 203.0 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{21}H_{25}NO_5Na$: 394.1625; found: 394.1615.

4.2.2. (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-oxohexanoate (15c)

Pyroglutamate **14** (6.08 g, 25.0 mmol) was treated with MeMgBr (3.0 M in THF, 10.4 mL, 31.3 mmol) according to GP–1 (addition at –55 °C, then 2 h at –40 °C) to give, after removal of the solvent under reduced pressure, amino ketone **15c**[5] (6.11 g, 23.6 mmol, 94%) as a colorless oil.

(5) Amino ketone **15c** is a known, but not characterized compound: Ayesa, S.; Belda, O.; Björklund, C.; Nilsson, M.; Russo, F.; Sahlberg, C.; Wiktelius, D. PCT Int. Appl. WO 2013095275 A1, **2013**; *Chem. Abstr.* **2013**, *159*, 166189.

$[\alpha]_D^{30}$ +4.8 (*c* 1.00, $CHCl_3$); R_f = 0.65 (petroleum ether–EtOAc, 1:2).

IR (ATR): 3465–3225, 2973, 2934, 1705, 1511, 1365, 1210, 1162, 1049, 1025, 753, 666 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, $C(CH_3)_3$), 1.83 (m, 1 H, 3-*H*H), 2.06 (m, 1 H, 3-H*H*), 2.10 (s, 3 H, 6-H_3), 2.39 –2.60 (m, 2 H, 4-H_2), 3.69 (s, 3 H, OCH_3), 4.22 (m, 1 H, 2-H), 5.14 (d, *J* = 7.2 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5 (C-3), 28.3 ($C(CH_3)_3$), 30.0 (C-6), 39.3 (C-4), 52.4 (OCH_3), 52.9 (C-2), 80.0 ($C(CH_3)_3$), 155.5 (NCO_2), 172.9 (C-1), 207.5 (C-5).

HRMS–ESI: *m/z* $[M + NH_4]^+$ calcd for $C_{12}H_{25}N_2O_5$: 277.1758; found: 277.1758.

4.2.3. (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-oxo-6-phenylhexanoate (15e)

Pyroglutamate **14** (4.00 g, 16.5 mmol) in anhydrous THF (20 mL) was treated with BnMgBr (1.4 M in THF, 42.3 mL, 59.2 mmol) according to GP–1 (addition at –40 °C, then 4 h at –40 °C) to give, after column chromatography (silica gel, petroleum ether–Et_2O, 1:0–1:2), amino ketone **15e** (2.99 g, 8.91 mmol, 54%) as a colorless oil.

$[\alpha]_D^{25}$ –14.1 (*c* 1.00, MeOH); R_f = 0.38 (petroleum ether–Et_2O, 1:2).

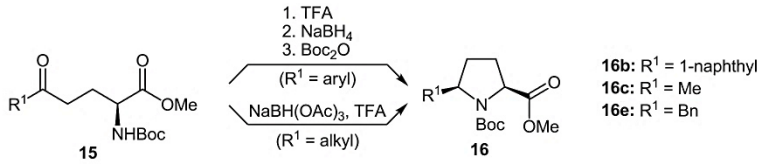
IR (ATR): 3470–3240, 2932, 1708, 1497, 1366, 1160, 1050, 1028, 736, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, $C(CH_3)_3$), 1.87 (m, 1 H, 3-*H*H), 2.11 (m, 1 H, 3-H*H*), 2.46–2.69 (m, 2 H, 4-H_2), 3.69 (m, 2 H, 6-H_2), 3.71 (s, 3 H, OCH_3), 4.26 (m, 1 H, 2-H), 5.13 (d, *J* = 7.7 Hz, 1 H, NH), 7.21 (m, 2 H, Ph-H), 7.31 (m, 3 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6 (C-3), 28.3 ($C(CH_3)_3$), 37.8 (C-4), 50.2 (C-6), 52.4 (OCH_3), 52.9 (C-2), 80.0 ($C(CH_3)_3$), 127.1, 128.8, 129.5 (CH-Ar),134.1 (C_q-Ar), 155.5 (NCO_2), 172.9 (C-1), 207.1 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{18}H_{25}NO_5Na$: 358.1625; found: 358.1624.

4.3. Esters 16



4.3.1. (2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-(naphthalen-1-yl)pyrrolidine-1,2-dicarboxylate (16b)

According to GP–2, the keto ester **15b** (2.85 g, 7.67 mmol) was reductively cyclized to give, after column chromatography (silica gel, petroleum ether–EtOAc, 3:1), a 90:10 mixture of pyrrolidine ester **16b** and its C5-epimer 5-*epi*-**16b**[6] (1.27 g, 3.57 mmol, 47%) as a brownish gum.

$[\alpha]_D^{28}$ +29.4 (*c* 0.5, MeOH); R_f = 0.50 (petroleum ether–EtOAc, 3:1).

(6) 5-*Epi*-**16b** is a known compound: Trost, B. M.; Miege, F. *J. Am. Chem. Soc.* **2014**, *136*, 3016.

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IR (ATR): 3060, 2979, 1743, 1691, 1390, 1365, 1200, 1156, 1128, 911, 781, 728 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$):* δ = 1.10 (s, 4.5 H, $C(CH_3)_3$), 1.14 (s, 0.45 H, $C(CH_3)_3$), 1.45 (m, 4.95 H, $C(CH_3)_3$), 1.91–2.14 (m, 2.20 H, 3-*H*H, 4-*H*H), 2.24 (m, 1.10 H, 3-H*H*), 2.51 (m, 1.10 H, 4-H*H*), 3.81 (s, 0.15 H, OCH_3), 3.82 (s, 0.15 H, OCH_3), 3.85 (s, 3.00 H, OCH_3), 4.41 (dd, *J* = 9.4, 6.9 Hz, 0.50 H, 2-H), 4.52 (t, *J* = 7.2 Hz, 0.50 H, 2-H), 4.65 (d, *J* = 8.6 Hz, 0.05 H, 2-H), 4.75 (m, 0.05 H, 2-H), 5.66 (dd, *J* = 7.5, 3.2 Hz, 0.5 H, 5-H), 5.84 (m, 0.55 H, 5-H), 5.98 (d, *J* = 8.6 Hz, 0.05 H), 7.49 (m, 3.40 H, Ar-H), 7.75 (m, 1.10 H, Ar-H), 7.87 (m, 1.20 H, Ar-H), 7.96 (t, *J* = 7.0 Hz, 1 H, Ar-H), 8.23 (dd, *J* = 11.1, 7.3 Hz, 1 H, Ar-H). * 50:50 mixture of rotamers, 90:10 mixture of diastereomers.[6]

^{13}C NMR (75 MHz, $CDCl_3$):* δ = 28.1, 28.3 ($C(CH_3)_3$), 28.8, 29.2 (C-3), 33.1, 34.1 (C-4), 52.1, 52.3 (OCH_3), 59.2, 59.4 (C-5), 60.5, 61.1 (C-2), 80.2, 80.6 ($C(CH_3)_3$), 122.6, 123.0 123.2, 123.5, 125.2, 125.77, 125.81, 127.1, 127.4, 129.0 (CH-Ar), 130.3, 130.5, 133.7, 134.1, 137.9, 139.0 (C_q-Ar) 154.0, 154.7 (1-CO_2), 173.6, 173.8 (2-CO_2). * Mixture of rotamers; signals of the minor diastereomer[6] are not listed.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{21}H_{25}NO_4Na$: 378.1676; found: 378.1677.

4.3.2. (2*S*,5*S*)-1-*tert*-Butyl 2-methyl 5-methylpyrrolidine-1,2-dicarboxylate (16c)

$NaBH(OAc)_3$ (6.51 g, 30.7 mmol) was added at 0 °C to a solution of the ester **15c** (6.11 g, 23.6 mmol) in EtOAc (120 mL). After 10 min, TFA (7.80 mL, 11.6 g, 102 mmol) was added dropwise. The reaction mixture was allowed to come to r.t. overnight and then quenched with sat. aq $NaHCO_3$ (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic layers were washed with brine (2 × 150 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 6:1–3:1) provided an inseparable 9:1 mixture of the known[7] pyrrolidine **16c** and its C5-epimer (4.96 g, 20.4 mmol, 86%) as a colorless oil, $[\alpha]_D^{30}$ +30.2 (*c* 1.00, $CHCl_3$) {ref. 7: $[\alpha]_D^{25}$ –28.4 (*c* 1.00, MeOH)}.

The spectroscopic data of **16c** were consistent with those reported in literature.[7]

4.3.3. (2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-benzylpyrrolidine-1,2-dicarboxylate (16e)

$NaBH(OAc)_3$ (2.05 g, 9.69 mmol) was added at 0 °C to a solution of the ester **15e** (2.50 g, 7.45 mmol) in EtOAc (25 mL). After 10 min, TFA (2.47 mL, 3.65 g, 32.0 mmol) was added dropwise. The reaction mixture was allowed to come to r.t. within 7 h, EtOAc (25 mL) was added, and then quenched with sat. aq $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 1:0–2:1) provided ester **16e**[8] (2.09 g, 6.54 mmol, 88%) as a colorless oil.

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(7) (a) Mohite, A. R.; Bhat, R. G. *J. Org. Chem.* **2012**, *77*, 5423. (b) Ref. 1j.

(8) Racemic **16e** is a known, but not characterized compound, which was prepared by hydrogenation of the corresponding pyrrole, see: Kaiser, H.-P.; Muchowski, J. M., *J. Org. Chem.* **1984**, *49*, 4203.

$[\alpha]_D^{27}$ –65.5 (*c* 1.0, MeOH); R_f = 0.48 (petroleum ether–Et_2O, 1:1).

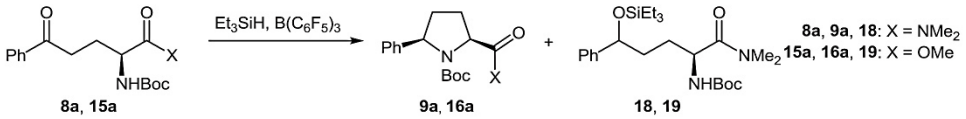
IR (ATR): 2975, 1750, 1693, 1388, 1365, 1199, 1167, 1140, 1113, 740, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$):* δ = 1.45 (m, 9.00 H, $C(CH_3)_3$), 1.67–1.89 (m, 2.00 H, 4-H_2), 2.03 (m, 1.00 H, 3-*H*H), 2.21 (m, 1.00 H, 3-H*H*), 2.60 (m, 1.00 H, 5-C*H*H), 3.28 (dd, *J* = 13.0, 4.0 Hz, 0.45 H, 5-CH*H*), 3.42 (dd, *J* = 13.2, 3.3 Hz, 0.55 H, 5-CH*H*), 3.77 (s, 3.00 H, OCH_3), 4.08 (m, 1.00 H, 5-H), 4.25 (t, *J* = 8.1 Hz, 0.55 H, 2-H), 4.37 (t, *J* = 7.8 Hz, 0.45 H, 2-H), 7.14–7.35 (m, 5 H, Ph-H). * 55:45 mixture of rotamers.

^{13}C NMR (75 MHz, $CDCl_3$):* δ = 28.3 (C-4), 28.4 ($C(CH_3)_3$), 28.8 (C-3), 29.5 (C-4), 39.8, 40.9 (5-CH_2), 52.1, 52.2 (OCH_3), 59.5, 60.0, 60.2, 60.4 (C-2, C-5), 80.1 ($C(CH_3)_3$), 126.2, 128.4, 128.5, 129.4, 129.5(CH-Ph), 139.3 (C_q-Ph) 153.6, 154.3 (1-CO_2), 173.9, 174.0 (2-CO_2). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{18}H_{25}NO_4Na$: 342.1676; found: 342.1673.

4.4. Attempted One-Step Cyclizations of 8a and 15a



4.4.1. Reaction of 8a with Et_3SiH–$B(C_6F_5)_3$

$B(C_6F_5)_3$ (15.3 mg, 29.9 μmol) was slowly added to a solution of Et_3SiH (115 μL, 83.4 mg, 718 μmol) in anhydrous CH_2Cl_2 (2.5 mL). The amide **8a** (200 mg, 598 μmol), dissolved in anhydrous CH_2Cl_2 (7.5 mL), was added at –78 °C. The reaction mixture was allowed to warm to r.t. and stirred for 3 d. Sat. aq $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 1:0–1:1) delivered pyrrolidine **9a** (61.2 mg, 192 μmol, 32%) and diastereomerically pure, silylated amide **18** (46.1 mg, 102 μmol, 17%), both as colorless oils.

For characterization of **9a**, see article.

(2*S*)-2-(*tert*-Butoxycarbonylamino)-*N*,*N*-dimethyl-5-phenyl-5-(triethylsilyloxy)pentanamide (**18**):

$[\alpha]_D^{21}$ –7.8 (*c* 0.93, MeOH); R_f = 0.70 (petroleum ether–EtOAc 1:1).

IR (ATR): 3610–3360, 3360–3180, 2875, 1692, 1634, 1494, 1167, 1048, 1015, 848, 728, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.51 (m, 6 H, $Si(CH_2CH_3)_3$), 0.87 (t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$), 1.42 (s, 9 H, $CH(CH_3)_3$), 1.57 (m, 1 H), 1.72 (m, 3 H), 2.91 (s, 3 H, NCH_3), 2.98 (s, 3 H, NCH_3), 4.57 (m, 1 H), 4.70 (m, 1 H), 5.32 (d, *J* = 8.6 Hz, 1 H), 7.18 (m, 1 H, Ph-H), 7.26 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.81 ($Si(CH_2CH_3)_3$), 6.76 ($Si(CH_2CH_3)_3$), 28.3 ($C(CH_3)_3$), 28.5

(C-3), 35.6 (NCH_3), 35.9 (C-4), 37.0 (NCH_3), 50.1 (C-2), 74.1 (C-5), 79.4 ($C(CH_3)_3$), 125.8, 127.0, 128.0 (CH-Ph), 144.9 (C_q-Ph), 155.5 (NCO_2), 172.1 (C-1).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{24}H_{42}N_2O_4SiNa$: 473.2806; found: 473.2800.

4.4.2. Reaction of 15a with $Et_3SiH–B(C_6F_5)_3$

$B(C_6F_5)_3$ (15.3 mg, 29.9 µmol) was slowly added to a solution of Et_3SiH (115 µL, 83.4 mg, 718 µmol) in anhydrous CH_2Cl_2 (2.5 mL). The ester **15a** (193 mg, 598 µmol), dissolved in anhydrous CH_2Cl_2 (7.5 mL), was added at –78 °C. The reaction mixture was allowed to warm to r.t. and stirred for 3 d. Sat. aq $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–Et_2O, 1:0–3:1) delivered diastereomerically pure, silylated ester **19** (206 mg, 471 µmol, 79%) as a colorless oil.

(2*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-phenyl-5-(triethylsilyloxy)pentanoate (**19**):

$[\alpha]_D^{21}$ –24.2 (*c* 1.01, MeOH); R_f = 0.65 (petroleum ether–Et_2O 1:1).

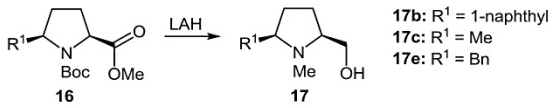
IR (ATR): 3470–3410, 3410–3190, 2953, 2876, 1743, 1714, 1165, 1003, 726, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.52 (m, 6 H, $Si(CH_2CH_3)_3$), 0.87 (t, *J* = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$), 1.43 (s, 9 H, $C(CH_3)_3$), 1.69 (m, 3 H), 1.85 (m, 1 H), 3.70 (s, 3 H, OCH_3), 4.29 (m, 1H), 4.70 (t, *J* = 5.5 Hz, 1 H), 5.05 (d, *J* = 7.6 Hz, 1 H, NH), 7.20 (m, 1 H, Ph-H), 7.28 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.7 ($Si(CH_2CH_3)_3$), 6.7 ($Si(CH_2CH_3)_3$), 28.3 ($C(CH_3)_3$), 28.4 (C-3), 36.2 (C-4), 52.1 (OCH_3), 53.1 (C-2), 73.8 (C-5), 79.7 ($C(CH_3)_3$), 125.7, 127.0, 128.0 (CH-Ph), 144.9 (C_q-Ph), 155.3 (NCO_2), 173.3 (C-1).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{23}H_{39}NO_5SiNa$: 460.2490; found: 460.2486.

4.5. Prolinols 17b, 17c, and 17e



4.5.1. (2*S*,5*R*)-2-(Hydroxymethyl)-1-methyl-5-(napthalen-1-yl)pyrrolidine (17b)

According to GP–3, a 9:1 mixture of the pyrrolidine ester **16b** and its C5-epimer (1.02 g, 2.87 mmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1), prolinol **17b** (567 mg, 2.35 mmol, 82%) as a brownish oil.

$[\alpha]_D^{29}$ +133.7 (*c* 0.50, MeOH); R_f = 0.51 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 3600–3200, 2948, 1596, 1394, 1234, 1087, 1026, 799, 777, 732 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (m, 1 H, 4-*H*H), 2.05 (m, 2.00 H, 3-H_2), 2.30 (s, 3 H, 1-CH_3), 2.41 (m, 1 H, 4-H*H*), 2.78 (br s, 1 H, OH) 2.80 (tdd, *J* = 8.0, 3.4, 1.8 Hz, 1 H, 2-H), 3.61 (dd, *J* = 10.8, 1.7 Hz, 1 H, 2-C*H*H), 3.88 (dd, *J* = 10.8, 3.4 Hz, 1 H, 2-CH*H*), 4.26 (dd, *J* = 9.2, 7.5 Hz, 1 H, 5-H), 7.50 (m, 3 H, Ar-H), 7.76 (m, 2H, Ar-H), 7.89 (m, 1 H, Ar-H), 8.16 (m, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.4 (C-3), 33.4 (C-4), 39.1 (1-CH_3), 61.7 (2-CH_2), 66.7 (C-2), 68.3 (C-5), 123.0, 123.2, 125.4, 125.8, 125.9, 127.3, 129.0 (CH-Ar), 131.8, 134.1, 139.0 (C_q-Ar).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{20}NO$: 242.1539; found: 242.1539.

4.5.2. (2*S*,5*S*)-2-(Hydroxymethyl)-1,5-dimethylpyrrolidine (17c)

According to GP–3, a 9:1 mixture of the pyrrolidine ester **16c** and its C5-epimer (2.25 g, 9.25 mmol) was reduced to give, after column chromatographic (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 80:18:2) removal of the minor diastereomer, prolinol **17c**[9] (956 mg, 7.40 mmol, 80%) as a colorless oil.

$[\alpha]_D^{25}$ +30.2 (*c* 2.00, $CHCl_3$); R_f = 0.26 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:8:2).

IR (ATR): 3600–3000, 2961, 2870, 2786, 1458, 1378, 1204, 1049, 1025, 946, 752 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.0 Hz, 3 H, 5-CH_3), 1.31 (m, 1 H, 4-*H*H), 1.61-1.86 (m, 3 H, 3-H_2, 4-H*H*), 2.23 (s, 3 H, 1-CH_3), 2.36 (m, 1 H, 5-H), 2.45 (m, 1 H, 2-H), 2.95 (br s, 1 H, OH), 3.38 (dd, *J* = 10.8, 2.3 Hz, 1 H, 2-C*H*H), 3.61 (dd, *J* = 10.8, 3.6 Hz, 1 H, 2-CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (5-CH_3), 25.7 (C-3), 32.5 (C-4), 38.4 (1-CH_3), 61.8 (2-CH_2), 62.8 (C-5), 67.3 (C-2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_7H_{16}NO$: 130.1226; found: 130.1227.

4.5.3. (2*R*,5*S*)-2-Benzyl-5-(hydroxymethyl)-1-methylpyrrolidine (17e)

According to GP–3, the pyrrolidine ester **16e** (551 mg, 1.73 mmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1), prolinol **17e** (335 mg, 1.63 mmol, 94%) as a brownish oil.

$[\alpha]_D^{26}$ +50.4 (*c* 0.10, MeOH); R_f = 0.33 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 3500–3100, 2945, 2855, 2789, 1495, 1453, 1092, 1031, 744, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (m, 1 H, 3-*H*H), 1.77–1.98 (m, 3 H, 3-H*H*, 4-H_2), 2.54 (s, 3 H, 1-CH_3), 2.65–2.89 (m, 3 H, 2-H, 5-H, 2-C*H*H), 3.12 (br s, 1 H, OH), 3.14 (dd, *J* = 13.0, 4.0 Hz, 1 H, 2-CH*H*), 3.55 (dd, *J* = 10.8, 2.2 Hz, 1 H, 5-C*H*H), 3.80 (dd, *J* = 10.7, 3.6 Hz, 1 H, 5-CH*H*), 7.35 (m, 3 H, Ph-H), 7.44 (m, 2 H, Ph-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7 (C-4), 29.9 (C-3), 39.1 (1-CH_3), 40.8 (2-CH_2), 61.7 (5-CH_2), 67.3 (C-5), 68.6 (C-2), 126.1, 128.2, 129.4 (CH-Ph), 139.5 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{20}NO$: 206.1539; found: 206.1538.

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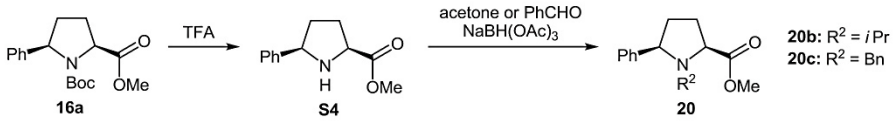
(9) Racemic **17c** is a known, but not characterized compound, which was prepared by reduction of the *N*-ethoxycarbonyl protected ethyl ester, see: Mizoguchi, T.; Iijima, I. *Yakugaku Zasshi* **1965**, *85*, 641.

4.6. Esters 20b and 20c



The preparation of the known[10] compound **S4** is described in the article (intermediate from **16a** to **20a**).

4.6.1. (2*S*,5*R*)-Methyl 1-isopropyl-5-phenylpyrrolidin-2-carboxylate (20b)

According to GP–4, pyrrolidine ester **S4** (650 mg, 3.17 mmol) was *N*-isopropylated with acetone–$NaBH(OAc)_3$ to give, after column chromatography (silica gel, petroleum ether–EtOAc, 9:1–5:1), ester **20b** (774 mg, 3.13 mmol, 99%) as a colorless oil.

$[\alpha]_D^{26}$ +48.3 (*c* 1.00, MeOH); R_f = 0.60 (CH_2Cl_2).

IR (ATR): 2962, 1749, 1730, 1385, 1191, 1164, 1116, 1077, 757, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.4 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 0.97 (d, *J* = 6.8 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 1.85 (m, 1 H, 4-*H*H), 1.97 (m, 1 H, 3-*H*H), 2.03 (m, 1 H, 3-H*H*), 2.09 (m, 1 H, 4-H*H*), 2.91 (sept, *J* = 6.6 Hz, 1 H, 1-C*H*(CH$_3$)$_2$), 3.75 (m, 1 H, 2-H), 3.76 (s, 3 H, OCH_3), 4.01 (dd, *J* = 8.5, 6.2 Hz, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.32 (m, 2 H, Ph-H), 7.55 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0 (1-CH(*C*H$_3$)$_2$), 21.6 (1-CH(*C*H$_3$)$_2$), 30.5 (C-3), 36.3 (C-4), 49.1 (1-*C*H(CH$_3$)$_2$), 51.9 (OCH_3), 59.8 (C-2), 65.9 (C-5), 126.8, 127.3, 128.3 (CH-Ph), 145.8 (C_q-Ph), 177.5 (1-CO_2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_2$: 248.1645; found: 248.1647.

4.6.2. (2*S*,5*R*)-Methyl 1-benzyl-5-phenylpyrrolidin-2-carboxylate (20c)

According to GP–4, pyrrolidine ester **S4** (616 mg, 3.00 mmol) was *N*-benzylated with benzaldehyde–$NaBH(OAc)_3$ to give, after column chromatography (silica gel, petroleum ether–EtOAc, 9:1–5:1), ester **20c** (851 mg, 2.88 mmol, 96%) as a colorless oil.

$[\alpha]_D^{27}$ +7.0 (*c* 1.00, MeOH); R_f = 0.52 (petroleum ether–EtOAc, 9:1).

IR (ATR): 3028, 2950, 1745, 1732, 1454, 1195, 1167, 1130, 1075, 752, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.91 (m, 1 H, 4-*H*H), 2.00 (m, 1 H, 3-*H*H), 2.09 (m, 2 H, 3-H*H*, 4-H*H*), 3.47 (m, 2 H, 1-C*H*H, 2-H), 3.48 (s, 3 H, OCH_3), 3.77 (dd, *J* = 9.4, 5.8 Hz, 1 H, 5-H), 3.91 (d, *J* = 13.7 Hz, 1 H, 1-CH*H*), 7.21 (m, 3 H, Ph-H), 7.27 (m, 3 H, Ph-H), 7.38 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.59 (d, *J* = 7.2 Hz, 2 H, Ph-H).

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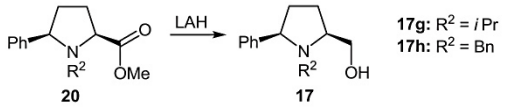
(10) (a) Haddad, M.; Imogai, H.; Larchevêque, M. *J. Org. Chem.* **1998**, *63*, 5680. (b) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305. (c) van Esseveldt, B. C. J; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791. (d) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.1 (C-3), 35.4 (C-4), 51.6 (OCH_3), 56.5 (1-CH_2), 64.8 (C-2), 69.1 (C-5), 127.1, 127.3, 127.8, 128.0, 128.5, 129.7 (CH-Ph), 137.7, 143.4 (C_q-Ph), 175.5 (1-CO_2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{19}H_{22}NO_2$: 296.1645; found: 296.1646.

4.7. Prolinols 17g and 17h



4.7.1. (2*S*,5*R*)-2-(Hydroxymethyl)-1-isopropyl-5-phenylpyrrolidine (17g)

According to GP–3, the pyrrolidine **20b** (620 mg, 2.51 mmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5), prolinol **17g** (519 mg, 2.37 mmol, 94%) as a colorless oil.

$[\alpha]_D^{28}$ +69.6 (*c* 1.00, MeOH); R_f = 0.52 (petroleum ether–EtOAc, 1:1).

IR (ATR): 3500–3160, 2962, 2871, 1451, 1383, 1195, 1066, 1026, 756, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.7 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 1.07 (d, *J* = 6.7 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 1.73 (m, 1 H, 4-*H*H), 1.80 (m, 1 H, 3-*H*H), 1.91 (m, 1 H, 3-H*H*), 2.08 (m, 1 H, 4-H*H*), 2.91 (sept, *J* = 6.7 Hz, 1 H, 1-C*H*(CH$_3$)$_2$), 3.08 (br s, 1 H, OH), 3.27 (m, 1 H, 2-H), 3.44 (dd, *J* = 10.3, 4.1 Hz, 1 H, 2-C*H*H), 3.61 (dd, *J* = 10.4, 5.2 Hz, 1 H, 2-CH*H*), 4.02 (dd, *J* = 9.2, 6.6 Hz, 1 H 5-H), 7.22 (m, 1 H, Ph-H), 7.31 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.37 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.9 (1-CH(*C*H$_3$)$_2$), 20.9 (1-CH(*C*H$_3$)$_2$), 29.4 (C-3), 35.8 (C-4), 49.8 (1-*C*H(CH$_3$)$_2$), 59.1 (C-2), 65.2 (2-CH_2), 65.7 (C-5), 126.9, 128.4 (CH-Ph), 145.8 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{22}NO$: 220.1696; found: 220.1694.

4.7.2. (2*S*,5*R*)-1-Benzyl-2-(hydroxymethyl)-5-phenylpyrrolidine (17h)

According to GP–3, the pyrrolidine **20c** (800 mg, 2.71 mmol) was reduced to give, after column chromatography (silica gel, petroleum ether–EtOAc, 1:1), prolinol **17h** (681 mg, 2.55 mmol, 94%) as a colorless gum.

$[\alpha]_D^{28}$ +65.0 (*c* 1.00, MeOH); R_f = 0.39 (petroleum ether–EtOAc, 4:1).

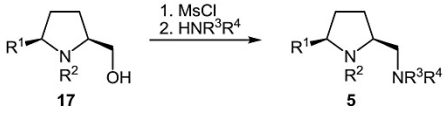
IR (ATR): 3570–3080, 2932, 2868, 1454, 1391, 1283, 1133, 1065, 1026, 746, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73 (m, 1 H, 4-*H*H), 1.89 (m, 1 H, 3-*H*H), 1.96 (m, 1 H, 3-H*H*), 2.04 (m, 1 H, 4-H*H*), 2.45 (s, 1 H, OH), 3.02 (m, 1 H, 2-H), 3.29 (d, *J* = 2.8 Hz, 2 H, 2-CH_2), 3.45 (d, *J* = 13.6 Hz, 1 H, 1-C*H*H), 3.75 (dd, *J* = 10.1, 6.1 Hz, 1 H, 5-H), 3.85 (d, *J* = 13.6 Hz, 1 H, 1-CH*H*), 7.16 (m, 2 H, Ph-H), 7.25 (m, 4 H, Ph-H), 7.36 (m, 2 H, Ph-H), 7.44 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8 (C-3), 35.2 (C-4), 56.2 (1-CH_2), 63.4 (2-CH_2), 63.9 (C-2), 70.0 (C-5), 127.36, 127.43, 127.6, 128.4, 128.7, 129.4 (CH-Ph), 138.4, 143.5 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{18}H_{22}NO$: 268.1696; found: 268.1696.

4.8. Diamines 5



5	R^1	R^2	NR^3R^4
b	Ph	Me	NMe_2
e	Ar[1]	Me	NMe_2
i	Ph	Me	NH_2
j	Ar[1]	Me	NH_2
k	Me	Me	NH_2

5	R^1	R^2	NR^3R^4
m	Bn	Me	NH_2
o	Ph	*i*Pr	NHMe
p	Ph	Bn	NHMe
q	Me	Me	NMe_2
r	*i*Pr	Me	NMe_2

5	R^1	R^2	NR^3R^4
s	Bn	Me	NMe_2
t	Ph	Me	NEt_2
u	Ph	Me	pyrrolidinyl
v	Ph	Me	piperidinyl
w	Ph	Me	NMeBn

[1] Ar = 1-naphthyl

4.8.1. (2*S*,5*R*)-2-(Dimethylaminomethyl)-1-methyl-5-phenylpyrrolidine (5b)

According to GP–5, the alcohol **17a** (790 mg, 4.13 mmol) was mesylated and treated with $HNMe_2$•HCl (3.37 g, 41.3 mmol) and NEt_3 (5.76 mL, 4.18 g, 41.3 mmol) to give, after filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1) and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 98:1.8:0.2–90:9:1), prolinamine **5b** (589 mg, 2.70 mmol, 65%) as a yellowish oil.

For characterization of **5b**, see article.

4.8.2. (2*S*,5*R*)-2-(Dimethylaminomethyl)-1-methyl-5-(naphthalen-1-yl)pyrrolidine (5e)

According to GP–5, the alcohol **17b** (100 mg, 414 μmol) was mesylated and treated with $HNMe_2$•HCl (336 mg, 4.14 mmol) and NEt_3 (578 μL, 419 mg, 4.14 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 99:0.9:0.1–95:4.5:0.5) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1), prolinamine **5e** (60.1 mg, 224 μmol, 54%) as a colorless oil.

For characterization of **5e**, see 3.3.2.

4.8.3. (2*S*,5*S*)-2-(Aminomethyl)-1-methyl-5-phenylpyrrolidine (5i)

According to GP–5, the alcohol **17a** (740 mg, 3.87 mmol) was mesylated and treated with aq ammonia (25%, 29 mL, 387 mmol) and MeOH (40 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5–80:18:2), prolinamine **5i** (624 mg, 3.28 mmol, 85%) as a yellowish oil.

$[\alpha]_D^{22}$ +54.4 (*c* 0.50, MeOH); R_f = 0.35 (CH_2Cl_2–MeOH, 9:1, silica gel deactivated with NH_3).

IR (ATR): 3500–3140, 2945, 2782, 1491, 1451, 1365, 1200, 1119, 1028, 930, 911, 755, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (m, 1 H, 4-*H*H), 1.78 (m, 1 H, 3-*H*H), 1.94 (m, 1 H, 3-H*H*), 2.07 (m, 1 H, 4-H*H*), 2.14 (s, 3 H, 1-CH_3), 2.35 (br s, 2 H, NH), 2.55 (m, 1 H, 2-H), 2.79 (br d, *J* = 12.9 Hz, 1 H, 2-C*H*H), 2.89 (dd, *J* = 12.9, 5.2 Hz, 1 H, 2-CH*H*), 3.31 (dd, *J* = 9.6, 6.7 Hz, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.32 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8 (C-3), 34.5 (C-4), 39.1 (1-CH_3), 43.9 (2-CH_2), 67.2 (C-2), 72.5 (C-5), 127.1, 127.4, 128.4 (CH-Ph), 143.9 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{19}N_2$: 191.1543; found: 191.1542.

4.8.4. (2*S*,5*R*)-2-(Aminomethyl)-1-methyl-5-(naphthalen-1-yl)pyrrolidine (5j)

According to GP–5, the alcohol **17b** (200 mg, 829 µmol) was mesylated and treated with aq ammonia (25%, 1.2 mL, 16.0 mmol) and MeOH (3 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 99:0.9:0.1–90:9:1) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5j** (97.0 mg, 404 µmol, 49%) as a colorless oil.

$[\alpha]_D^{29}$ +137.4 (*c* 0.50, MeOH); R_f = 0.38 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 2945, 2842, 2783, 1595, 1509, 1455, 1203, 1051, 857, 798, 776 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.89 (m, 4 H, 3-*H*H, 4-*H*H, NH_2), 2.01 (m, 1 H, 3-H*H*), 2.26 (s, 3 H, 1-CH_3), 2.38 (m, 1 H, 4-H*H*), 2.65 (m, 1 H, 2-H), 2.87 (d, *J* = 12.6 Hz, 1 H, 2-C*H*H), 2.98 (dd, *J* = 12.9, 5.1 Hz, 1 H, 2-CH*H*), 4.14 (t, *J* = 8.2 Hz, 1 H, 5-H), 7.49 (m, 3 H, Ar-H), 7.75 (d, *J* = 8.1 Hz, 1 H, Ar-H), 7.80 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.88 (m, 1 H, Ar-H), 8.21 (m, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8 (C-3), 33.0 (C-4), 39.4 (1-CH_3), 43.8 (2-CH_2), 67.5 (C-2), 68.5 (C-5), 123.39, 123.43, 125.3, 125.5, 125.9, 127.1, 128.8 (CH-Ar), 131.7, 134.0, 139.6 (C_q-Ar).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{21}N_2$: 241.1699; found: 241.1699.

4.8.5. (2*S*,5*S*)-2-(Aminomethyl)-1,5-dimethylpyrrolidine (5k)

According to GP–5, the alcohol **17c** (243 mg, 1.88 mmol) was mesylated and treated with aq ammonia (25%, 5 mL, 66.7 mmol) and MeOH (5 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5k** (58.0 mg, 452 µmol, 24%) as a yellowish oil.

$[\alpha]_D^{25}$ +5.8 (*c* 1.00, $CHCl_3$); R_f = 0.20 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:8:2).

IR (ATR): 3600–3000, 2961, 2925, 2851, 1459, 1319, 1151, 985, 818, 767 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.1 Hz, 3 H, 5-CH_3), 1.22 (m, 1 H, 4-*H*H), 1.43 (m, 1 H, 3-*H*H), 1.50 (br s, 2 H, NH_2), 1.71 (m, 2 H, 3-H*H*, 4-H*H*), 2.14 (s, 3 H, 1-CH_3), 2.16 (m, 2 H, 2-H, 5-H), 2.58 (dd, *J* = 12.7, 5.9 Hz, 1 H, 2-C*H*H), 2.65 (dd, *J* = 12.7, 3.5 Hz, 1 H, 2-CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (5-CH_3), 26.2 (C-3), 31.8 (C-4), 38.8 (1-CH_3), 44.4 (2-CH_2), 62.7 (C-5), 68.6 (C-2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_7H_{17}N_2$: 129.1386; found: 129.1387.

4.8.6. (2*S*,5*R*)-2-(Aminomethyl)-5-benzyl-1-methylpyrrolidine (5m)

According to GP–5, the alcohol **17e** (200 mg, 974 µmol) was mesylated and treated with aq ammonia (25%, 700 µL, 9.34 mmol) and MeOH (2 mL) to give, after column chromatography (1. silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 100:0:0–90:9:1; 2. silica gel, EtOAc–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5m** (63.1 mg, 309 µmol, 32%) as a colorless oil.

$[\alpha]_D^{29}$ +53.7 (*c* 1.00, MeOH); R_f = 0.17 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1).

IR (ATR): 2944, 2846, 2782, 1603, 1495, 1453, 1356, 1200, 1031, 743, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52–1.75 (m, 4 H, 3-*H*H, 4-*H*H, NH_2), 1.76–1.97 (m, 2 H, 3-H*H*, 4-H*H*), 2.53 (s, 3 H, 1-CH_3), 2.55 (m, 1 H, 2-H), 2.67 (m, 2 H, 5-H, 5-C*H*H), 2.88 (d, *J* = 3.6 Hz, 2 H, 2-CH_2), 3.16 (dd, *J* = 12.0, 2.9 Hz, 1H, 5-CH*H*), 7.35 (m, 3 H, Ph-H), 7.44 (m, 2 H, Ph-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (C-3), 29.6 (C-4), 39.6 (1-CH_3), 41.0 (5-CH_2), 44.4 (2-CH_2), 68.6 (C-2), 69.0 (C-5), 126.0, 128.2, 129.4 (CH-Ph), 139.9 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{21}N_2$: 205.1699; found: 205.1698.

4.8.7. (2*S*,5*R*)-1-Isopropyl-2-(methylaminomethyl)-5-phenylpyrrolidine (5o)

According to GP–5, the alcohol **17g** (160 mg, 750 µmol) was mesylated and treated with aq NH_2Me (40%, 2.05 mL, 22.5 mmol), NEt_3 (105 µL, 75.9 mg, 750 µmol), and MeOH (6 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 97:2.7:0.3–90:9:1), prolinamine **5o** (134 mg, 577 µmol, 77%) as a colorless oil.

$[\alpha]_D^{24}$ +66.7 (*c* 1.00, MeOH); R_f = 0.32 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1).

IR (ATR): 2962, 2932, 2787, 1450, 1382, 1195, 1113, 1027, 753, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 1.04 (d, *J* = 6.8 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 1.67 (m, 1 H, 4-*H*H), 1.76 (m, 1 H, 3-*H*H), 1.86 (m, 1 H, 3-H*H*), 2.07 (m, 1 H, 4-H*H*), 2.54 (s, 3 H, NCH_3), 2.64 (dd, *J* = 11.5, 7.2 Hz, 1 H, 2-C*H*H), 2.69 (dd, *J* = 11.5, 4.9 Hz, 1 H, 2-CH*H*), 2.94 (sept, *J* = 6.7 Hz, 1 H, 1-C*H*(CH$_3$)$_2$), 3.27 (m, 1 H, 2-H), 3.38 (br s, 1 H, NH), 3.98 (dd, *J* = 8.7, 6.7 Hz, 1 H, 5-H), 7.19 (m, 1 H, Ph-H), 7.28 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.37 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3 (1-CH(*C*H$_3$)$_2$), 20.6 (1-CH(*C*H$_3$)$_2$), 29.9 (C-3), 35.9 (C-4), 36.7 (NCH_3), 50.2 (1-*C*H(CH$_3$)$_2$), 58.0 (C-2), 58.4 (2-CH_2), 65.1 (C-5), 126.6, 126.8, 128.2 (CH-Ph), 146.9 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{25}N_2$: 233.2012; found: 233.2011.

4.8.8. (2*S*,5*R*)-1-Benzyl-2-(methylaminomethyl)-5-phenylpyrrolidine (5p)

According to GP–5, the alcohol **17h** (160 mg, 598 µmol) was mesylated and treated with aq NH_2Me (40%, 1.63 mL, 17.9 mmol), NEt_3 (83.5 µL, 60.5 mg, 598 µmol), and MeOH (5 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 99:0.9:0.1–90:9:1),

prolinamine **5p** (129 mg, 460 µmol, 77%) as a colorless oil.

$[\alpha]_D^{27}$ +35.4 (*c* 1.00, MeOH); R_f = 0.23 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5).

IR (ATR): 3028, 2931, 2791, 1493, 1453, 1127, 1105, 1076, 1028, 754, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.72 (m, 1 H, 4-*H*H), 1.90 (m, 2 H, 3-H_2), 2.01 (m, 1 H, 4-H*H*), 2.16 (s, 3 H, NCH_3), 2.24 (dd, *J* = 11.5, 5.6 Hz, 1 H, 2-C*H*H), 2.43 (dd, *J* = 11.5, 2.8 Hz, 1 H, 2-CH*H*), 2.98 (m, 2 H, 2-H, NH), 3.33 (d, *J* = 13.6 Hz, 1 H, 1-C*H*H), 3.64 (d, *J* = 9.9, 6.1 Hz, 1 H, 5-H), 3.83 (d, *J* = 13.5 Hz, 1 H, 1-CH*H*), 7.18 (m, 3 H, Ph-H), 7.23 (m, 3 H, Ph-H), 7.33 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.44 (d, *J* = 7.4 Hz, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.6 (C-3), 34.9 (C-4), 36.4 (NCH_3), 55.4 (2-CH_2), 57.0 (1-CH_2), 63.2 (C-2), 70.3 (C-5), 126.9, 127.1, 127.6, 128.1, 128.4, 129.1 (CH-Ph), 139.4, 144.9 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{19}H_{25}N_2$: 281.2012; found: 281.2014.

4.8.9. (2*S*,5*S*)-2-(Dimethylaminomethyl)-1,5-dimethylpyrrolidine (5q)

According to GP–5, the alcohol **17c** 242 mg, 1.87 mmol) was mesylated and treated with $HNMe_2$•HCl (1.52 g, 18.6 mmol), K_2CO_3 (2.59 g, 18.7 mmol), and CH_2Cl_2 (5 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5q** (54.0 mg, 346 µmol, 18%) as a yellowish oil.

$[\alpha]_D^{25}$–20.9 (*c* 1.00, $CHCl_3$); R_f = 0.15 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:8:2).

IR (ATR): 2960, 2781, 1711, 1674, 1458, 1376, 1157, 1116, 798 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.1 Hz, 3 H, 5-CH_3), 1.35 (m, 1 H, 4-*H*H), 1.50 (m, 1 H, 3-*H*H), 1.80 (m, 1 H, 4-H*H*), 1.91 (m, 1 H, 3-H*H*), 2.21 (m, 2 H, 5-H, 2-C*H*H), 2.22 (s, 6 H, $N(CH_3)_2$), 2.29 (s, 3 H, $N(CH_3)$), 2.31 (m, 1 H, 2-H), 2.42 (dd, *J* = 11.2, 3.4 Hz, 1 H, 2-CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (5-CH_3), 28.9 (C-3), 31.8 (C-4), 39.5 (1-CH_3), 46.5 ($N(CH_3)_2$), 63.0 (C-5), 65.3 (C-2), 65.6 (2-CH_2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_9H_{21}N_2$: 157.1699; found: 157.1701.

4.8.10. (2*S*,5*R*)-2-(Dimethylaminomethyl)-5-isopropyl-1-methylpyrrolidine (5r)

According to GP–5, the alcohol **17d** (60.0 mg, 382 µmol) was mesylated and treated with $HNMe_2$•HCl (311 mg, 3.82 mmol) and K_2CO_3 (528 mg, 3.82 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5r** (16.0 mg, 86.8 µmol, 23%) as a yellowish oil.

$[\alpha]_D^{25}$ –35.6 (*c* 1.00, $CHCl_3$), R_f = 0.27 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:8:2).

IR (ATR): 2956, 2764, 1457, 1385, 1262, 1160, 1104, 1032, 847 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.8 Hz, 3 H, CH(CH_3)$_2$), 0.86 (d, *J* = 6.9 Hz, 3 H, CH(CH_3)$_2$), 1.43 (m, 2 H, 3-*H*H, 4-*H*H), 1.56 (m, 1 H, 4-H*H*), 1.77 (m, 1 H, C*H*(CH_3)$_2$), 1.87 (m, 1

H, 3-H*H*), 2.17 (m, 2 H, 2-H, 5-H), 2.24 (s, 6 H, $N(CH_3)_2$), 2.26 (s, 3 H, 1-CH_3), 2.39 (m, 2 H, 2-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6 ($CH(CH_3)_2$), 20.4 ($CH(CH_3)_2$), 23.3 (C-4), 29.0 ($CH(CH_3)_2$), 29.5 (C-3), 40.4 (1-CH_3), 46.6 ($N(CH_3)_2$), 65.4 (2-CH_2), 65.5 (C-2), 72.6 (C-5).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{11}H_{25}N_2$: 185.2012; found: 185.2011.

4.8.11. (2*R*,5*S*)-2-Benzyl-5-(dimethylaminomethyl)-1-methylpyrrolidine (5s)

According to GP–5, the alcohol **17e** (200 mg, 974 µmol) was mesylated and treated with $HNMe_2$• HCl (794 mg, 9.74 mmol) and NEt_3 (1.36 mL, 986 mg, 9.74 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 100:0:0–90:9:1), prolinamine **5s** (100 mg, 430 µmol, 44%) as a colorless, highly viscous oil.

$[\alpha]_D^{29}$ +7.2 (*c* 0.50, MeOH); R_f = 0.47 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5).

IR (ATR): 2942, 2766, 1453, 1348, 1155, 1030, 850, 742, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (m, 2 H, 3-*H*H, 4-*H*H), 1.66 (m, 1 H, 3-H*H*), 1.88 (m, 1 H, 4-H*H*), 2.26 (m, 1 H, 5-C*H*H), 2.27 (s, 6 H, $N(CH_3)_2$), 2.46 (s, 3 H, 1-CH_3), 2.47 (m, 4 H, 2-H, 5-H, 2-C*H*H, 5-CH*H*), 3.08 (dd, *J* = 17.6, 8.6 Hz, 1 H, 2-CH*H*), 7.20 (m, 3 H, Ph-H), 7.28 (m, 2 H, Ph-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.6 (C-4), 29.5 (C-3), 40.0 (1-CH_3), 41.0 (2-CH_2), 46.4 ($N(CH_3)_2$), 65.2 (C-5), 65.4 (5-CH_2), 69.4 (C-2), 126.0, 128.2, 129.2 (CH-Ph), 140.0 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{25}N_2$: 233.2012; found: 233.2013.

4.8.12. (2*S*,5*R*)-2-(Diethylaminomethyl)-1-methyl-5-phenylpyrrolidine (5t)

According to GP–5, the alcohol **17a** (100 mg, 523 µmol) was mesylated and treated with $HNEt_2$ (1.08 mL, 764 mg, 10.5 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1), prolinamine **5t** (51.0 mg, 207 µmol, 40%) as a brownish oil.

$[\alpha]_D^{22}$ +1.8 (*c* 1.00, MeOH); R_f = 0.18 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 2966, 2791, 1452, 1383, 1291, 1201, 1067, 1039, 754, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.1 Hz, 6 H, $N(CH_2CH_3)_2$), 1.70 (m, 2 H, 3-*H*H, 4-*H*H), 2.04 (m, 2 H, 3-H*H*, 4-H*H*), 2.19 (s, 3 H, 1-CH_3), 2.44 (dd, *J* = 12.4, 8.3 Hz, 1 H, 2-C*H*H), 2.59 (m, 6 H, 2-H, 2-CH*H*, $N(CH_2CH_3)_2$), 3.24 (m, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.33 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0 ($N(CH_2CH_3)_2$), 29.7 (C-3), 34.1 (C-4), 39.8 (1-CH_3), 48.2 ($N(CH_2CH_3)_2$), 58.6 (2-CH_2), 65.3 (C-2), 72.8 (C-5), 127.0, 127.5, 128.4 (CH-Ph), 144.1 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{27}N_2$: 247.2169; found: 247.2168.

4.8.13. (2*R*,5*S*)-1-Methyl-2-phenyl-5-(pyrrolidin-1-ylmethyl)pyrrolidine (5u)

According to GP–5, the alcohol **17a** (180 mg, 941 µmol) was mesylated and treated with pyrrolidine (1.57 mL, 1.34 g, 18.8 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1), prolinamine **5u** (119 mg, 487 µmol, 52%) as a slightly brownish oil.

For characterization of **5u**, see article.

4.8.14. (2*R*,5*S*)-1-Methyl-2-phenyl-5-(piperidin-1-ylmethyl)pyrrolidine (5v)

According to GP–5, the alcohol **17a** (180 mg, 941 µmol) was mesylated and treated with piperidine (1.86 mL, 1.60 g, 18.8 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1), prolinamine **5v** (123 mg, 476 µmol, 51%) as a slightly yellowish oil.

$[\alpha]_D^{22}$ +12.7 (*c* 1.00, MeOH); R_f = 0.28 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 2932, 2772, 1452, 1154, 1119, 1057, 1038, 991, 836, 754, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (m, 2 H, 3'-H_2), 1.60 (m, 4 H, 2× 2'-H_2), 1.71 (m, 2 H, 3-*H*H, 4-*H*H), 2.05 (m, 2 H, 3-H*H*, 4-H*H*), 2.21 (s, 3 H, 1-CH_3), 2.36 (dd, *J* = 13.3, 8.6 Hz, 1 H, 5-C*H*H), 2.46 (m, 4 H, 2× 1'-H_2), 2.60 (m, 2 H, 5-H, 5-CH*H*), 3.23 (m, 1 H, 2-H), 7.23 (m, 1 H, Ph-H), 7.33 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (C-3'), 26.2 (C-2'), 30.0 (C-4), 34.1 (C-3), 39.8 (1-CH_3), 55.6 (C-1'), 64.2 (C-5), 65.1 (5-CH_2), 72.7 (C-2), 127.0, 127.5, 128.4 (CH-Ph), 144.1 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{17}H_{27}N_2$: 259.2169; found: 259.2168.

4.8.15. (2*S*,5*R*)-2-(Benzyl(methyl)aminomethyl)-1-methyl-5-phenylpyrrolidine (5w)

According to GP–5, the alcohol **17a** (100 mg, 523 µmol) was mesylated and treated with HNMeBn (1.35 mL, 1.27 g, 10.5 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5–90:10) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1), prolinamine **5w** (113 mg, 384 µmol, 73%) as a colorless oil.

$[\alpha]_D^{22}$ –3.3 (*c* 0.50, MeOH); R_f = 0.51 (petroleum ether–EtOAc, 3:1).

IR (ATR): 2945, 2837, 2778, 1493, 1452, 1072, 1026, 755, 737, 697 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$): δ = 1.69 (m, 1 H, 4-*H*H), 1.78 (m, 1 H, 3-*H*H), 2.07 (m, 2 H, 3-H*H*, 4-H*H*), 2.23 (s, 3 H, 1-CH_3), 2.30 (s, 3 H, NCH_3), 2.50 (dd, *J* = 13.3, 8.9 Hz, 1 H, 2-C*H*H), 2.65 (m, 2 H, 2-H, 2-CH*H*), 3.27 (dd, *J* = 9.3, 6.5 Hz, 1 H, 5-H), 3.57 (d, *J* = 13.2 Hz, 1 H, NC*H*HPh), 3.63 (d, *J* = 13.2 Hz, 1 H, NCH*H*Ph), 7.23−7.41 (m, 10 H, Ph-H).

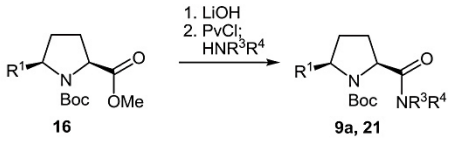
^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3 (C-3,) 34.1 (C-4), 39.8 (1-CH_3), 43.4 (NCH_3), 62.8 (2-CH_2), 63.4 (N*C*H_2Ph), 64.9 (C-2), 72.9 (C-5), 126.96, 127.00, 127.5, 128.3, 128.4, 129.1 (CH-Ph), 139.6, 144.0 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{20}H_{27}N_2$: 295.2169; found: 295.2171.

5. Synthesis of Diamines 5 According to Route III

The preparation of compounds **21d** and **5u** is described in the article. For the reduction of **9a** to **5b**, see Route I.

5.1. Amides 9a and 21



Cmpd	R^1	NR^3R^4
9a	Ph	NMe_2
21a	Ph	NHMe
21b	*i*Pr	NHMe
21c	Me	NMe_2
21e	Ph	NMeBn

5.1.1. (2*S*,5*R*)-*tert*-Butyl 2-dimethylcarbamoyl-5-phenylpyrrolidine-1-carboxylate (9a)

According to GP–6, the ester **16a** (1.36 g, 4.46 mmol) was saponified, activated with PvCl, and treated with $HNMe_2$•HCl to give, after column chromatography (silica gel, petroleum ether–EtOAc, 3:1–0:1), pyrrolidine amide **9a** (1.30 g, 4.09 mmol, 92 %) as a slightly yellowish oil.

For characterization of **9a**, see article.

5.1.2. (2*S*,5*R*)-*tert*-Butyl 2-(methylcarbamoyl)-5-phenylpyrrolidine-1-carboxylate (21a)

According to GP–6, the ester **16a** (1.36 g, 4.46 mmol) was saponified, activated with PvCl in THF (45 mL), and treated with aq H_2NMe (40%) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 99:0.9:0.1–96:3.6:0.4), pyrrolidine amide **21a** (1.17 g, 3.84 mmol, 86%) as a colorless solid.

Mp 136–138 °C; $[\alpha]_D^{26}$ +24.5 (*c* 1.00, MeOH); R_f = 0.41 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5).

IR (ATR): 3358, 2982, 1670, 1552, 1397, 1365, 1150, 1120, 766, 741, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$):* δ = 1.15 (br s, 9 H, $C(CH_3)_3$), 1.83–2.05 (m, 2 H, 3-*H*H, 4-*H*H), 2.27 (m, 1 H, 4-H*H*), 2.51 (br s, 1 H, 3-H*H*), 2.88 (m, 3 H, NCH_3), 4.42 (br s, 1 H, 2-H), 4.63 (br s, 1 H, 5-H), 7.24 (m, 5 H, Ph-H). * Broad signals due to rotamers close to the coalescence temperature.

^{13}C NMR (125 MHz, $CDCl_3$): * δ = 26.4 (NCH_3), 27.1 (br, C-3), 28.1 ($C(CH_3)_3$), 36.1 (br, C-4), 61.5 (br, C-2), 63.8 (br, C-5), 80.8 ($C(CH_3)_3$), 126.3, 126.9, 128.4 (CH-Ph), 144.0 (br, C_q-Ph), 156.3 (br, 1-CO_2), 172.9 (2-CON). * Broad signals due to rotamers close to the coalescence temperature.

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{17}H_{25}N_2O_3$: 305.1860; found: 305.1860.

5.1.3. (2*R*,5*S*)-*tert*-Butyl 2-isopropyl-5-(methylcarbamoyl)pyrrolidine-1-carboxylate (21b)

According to GP–6, the ester **16d** (819 mg, 3.02 mmol) was saponified, activated with PvCl, and treated with aq H_2NMe (40%; MeOH (4 mL) was added as a cosolvent) to give, after column chromatography (silica gel, petroleum ether–EtOAc, 2:1–1:1), pyrrolidine amide **21b** (670 mg, 2.48 mmol, 82%) as a colorless oil.

$[\alpha]_D^{31}$ –38.0 (*c* 1.00, MeOH); R_f = 0.39 (petroleum ether–EtOAc, 1:1).

IR (ATR): 3420–3220, 2962, 1667, 1549, 1384, 1366, 1253, 1166, 1119, 931 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$):* δ = 0.77 (br d, *J* = 3.7 Hz, 3 H, $CH(CH_3)_2$), 0.87 (br d, *J* = 5.4 Hz, 3 H, $CH(CH_3)_2$), 1.45 (s, 9.0 H, $C(CH_3)_3$), 1.77 (q, *J* = 7.0 Hz, 2 H, 3-H_2), 1.89 (br s, 1 H, 4-*H*H), 1.98 (sept, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 2.32 (br s, 1 H, 4-H*H*), 2.79 (d, *J* = 4.9 Hz, 3 H, NCH_3), 3.67 (br d, *J* = 5.4 Hz, 1 H, 2-H), 4.27 (br s, 1 H, 5-H), 6.91 (br s, 1 H, NH). * Broad signals due to rotamers close to the coalescence temperature.

^{13}C NMR (125 MHz, $CDCl_3$):* δ = 17.2 (br, $CH(CH_3)_2$), 20.0 ($CH(CH_3)_2$), 25.7 (br, C-4, NCH_3), 26.2 (C-3), 28.5 ($C(CH_3)_3$), 30.3 (br, $CH(CH_3)_2$), 61.1 (br, C-5), 64.7 (br, C-2), 80.6 ($C(CH_3)_3$), 156.5 (br, 1-CO_2), 173.1 (5-CON). * Broad signals due to rotamers close to the coalescence temperature.

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{27}N_2O_3$: 271.2016; found: 271.2016.

5.1.4. (2*S*,5*S*)-*tert*-Butyl 2-(dimethylcarbamoyl)-5-methylpyrrolidine-1-carboxylate (21c)

According to GP–6, a 9:1 mixture of the pyrrolidine ester **16c** and its C5-epimer (854 mg, 3.51 mmol) was saponified, activated with PvCl, and treated with $HNMe_2$•HCl to give, after column chromatography (silica gel, petroleum ether–Et_2O, 2:1–0:1), the known[11] pyrrolidine amide **21c** (792 mg, 3.09 mmol, 88%) as a colorless oil.

$[\alpha]_D^{29}$ –14.3 (*c* 1.00, MeOH); R_f = 0.24 (Et_2O).

IR (ATR): 2975, 2934, 1694, 1659, 1456, 1392, 1366, 1257, 1174, 1123, 1084 cm^{-1}.

^{1}H NMR: (500 MHz, $CDCl_3$):* δ = 1.34 (d, *J* = 6.2 Hz, 1.65 H, 5-CH_3), 1.35 (d, *J* = 6.4 Hz, 1.35 H, 5-CH_3), 1.39 (s, 4.0 H, $C(CH_3)_3$), 1.45 (s, 5.0 H, $C(CH_3)_3$), 1.70 (m, 1 H, 4-*H*H), 1.82–2.14 (m, 3 H, 3-H_2, 4-H*H*), 2.97 (s, 1.65 H, $N(CH_3)_2$), 2.98 (s, 1.35 H, $N(CH_3)_2$), 3.06 (s, 1.35 H, $N(CH_3)_2$), 3.10 (s, 1.65 H, $N(CH_3)_2$), 3.91 (m, 0.55 H, 5-H), 4.04 (m, 0.45 H, 5-H), 4.55 (t, *J* = 7.5 Hz, 0.45 H, 2-H), 4.69 (dd, *J* = 8.1, 5.5 Hz, 0.55 H, 2-H). * 55:45 mixture of rotamers.

^{13}C NMR (125 MHz, $CDCl_3$):* δ = 19.7, 20.6 (5-CH_3), 28.2 (C-3), 28.5 ($C(CH_3)_3$), 28.7 (C-3, $C(CH_3)_3$), 31.9, 32.6 (C-4), 36.1, 36.2, 37.1, 37.2 ($N(CH_3)_2$), 54.2, 54.4 (C-5), 57.5, 57.7 (C-2), 79.4, 79.5 ($C(CH_3)_3$), 153.5, 154.5 (1-CO_2), 172.6, 173.0 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{25}N_2O_3$: 257.1860; found: 257.1864.

5.1.5. (2*S*,5*R*)-*tert*-Butyl 2-(benzyl(methyl)carbamoyl)-5-phenylpyrrolidine-1-carboxylate (21e)

According to GP–6, the ester **16a** (160 mg, 524 μmol) was saponified, activated with PvCl, and treated with HNMeBn to give, after column chromatography (silica gel, petroleum ether–EtOAc, 9:1–2:1), pyrrolidine amide **21e** (196 mg, 498 μmol, 95%) as a colorless oil.

(11) Amide **21d** is a known, but only partially characterized (^{1}H NMR, MS) compound: Miyazaki, M.; Naito, H.; Sugimoto, Y.; Yoshida, K.; Kawato, H.; Okayama, T.; Shimizu, H.; Miyazaki, M.; Kitagawa, M.; Seki, T.; Fukutake, S.; Shiose, Y.; Aonuma, M.; Soga, T. *Bioorg. Med. Chem.* **2013**, *21*, 4319.

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$[\alpha]_D^{30}$ +25.3 (*c* 1.00, MeOH); R_f = 0.33 (petroleum ether–EtOAc, 1:1).

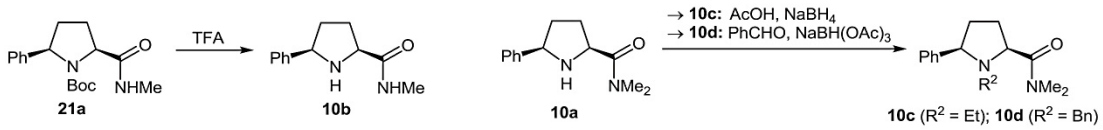
IR (ATR): 2973, 2934, 1691, 1659, 1454, 1391, 1365, 1157, 1125, 701 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ =* 1.12 (s, 6.4 H, $C(CH_3)_3$), 1.37 (s, 1.6 H, $C(CH_3)_3$), 1.43 (s, 1.0 H, $C(CH_3)_3$), 1.83–2.12 (m, 1.7 H, 3-H_2), 2.19 (m, 1.6 H, 3-H*H*, 4-H_2), 2.32 (m, 0.7 H, 4-H*H*), 3.02 (s, 0.6 H, NCH_3), 3.05 (s, 2.4 H, NCH_3), 4.46–4.80 (m, 2.6 H, 2-H, 5-H, NC*H*HPh), 4.92 (m, 1.4 H, 2-H, 5-H, NCH*H*Ph), 7.21 (m, 1 H, Ph-H), 7.30 (m, 6 H, Ph-H), 7.38 (m, 1 H, Ph-H), 7.75 (m, 2 H, Ph-H). * 70:20:10 mixture of rotamers.

^{13}C NMR (125 MHz, $CDCl_3$):* δ = 28.1, 28.2, 28.4, 28.6 ($C(CH_3)_3$), 28.9, 29.1, 29.5, 29.7 (C-3), 34.57 (C-4), 34.64, 34.8 (NCH_3), 34.9 (C-4), 35.0 (NCH_3), 35.8, 35.9 (C-4), 51.4, 51.5, 53.4 (NCH_2Ph), 57.7, 58.0, 58.18, 58.24 (C-2), 62.6, 62.9, 63.5, 63.6 (C-5), 79.8, 79.9, 80.1, 80.4 ($C(CH_3)_3$), 126.4, 126.55, 126.57, 126.61, 126.66, 126.73, 126.9, 127.0, 127.3, 127.6, 127.7, 127.8, 128.0, 128.12, 128.14, 128.3, 128.39, 128.42, 128.8, 129.0, 129.1 (CH-Ph), 136.8, 137.1, 137.3, 143.5, 143.7, 144.5, 144.7 (C_q-Ph), 154.0, 154.75, 154.77 (1-CO_2), 172.9, 173.1, 173.5 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + 2\,H - Boc]^+$ calcd for $C_{19}H_{23}N_2O$: 295.1805; found: 295.1807.

5.2. Amides 10b–d



5.2.1. (2*S*,5*R*)-*N*-Methyl-5-phenylpyrrolidine-2-carboxamide (10b)

A solution of the amide **21a** (660 mg, 2.17 mmol) in anhydrous CH_2Cl_2 (20 mL) was treated at r.t. with TFA (3.34 mL, 4.94 g, 43.4 mmol) and stirred overnight. The solvent was removed under reduced pressure and the residue was diluted five times with CH_2Cl_2 (20 mL) and evaporated again, in order to remove excess TFA. Filtration through a pad of basic alumina (activity I, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1) afforded the *N*-deprotected amide **10b** (432 mg, 2.11 mmol, 97%) as a colorless oil.

$[\alpha]_D^{28}$ –31.0 (*c* 1.00, MeOH); R_f = 0.27 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5).

IR (ATR): 3390–3220, 2944, 1651, 1527, 1493, 1408, 1276, 1246, 1105, 756, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.62 (m, 1 H, 4-*H*H), 2.14 (m, 2 H, 3-*H*H, 4-H*H*), 2.30 (m, 1 H, 3-H*H*), 2.46 (br s, 1 H, NH), 2.87 (d, *J* = 5.1 Hz, 3 H, NCH_3), 3.90 (dd, *J* = 10.1, 3.6 Hz, 1 H, 2-H), 4.33 (dd, *J* = 10.2, 5.8 Hz, 1 H, 5-H), 7.27 (m, 1 H, Ph-H), 7.36 (m, 4 H, Ph-H), 7.70 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0 (NCH_3), 31.1 (C-3), 33.8 (C-4), 60.1 (C-2), 63.1 (C-5), 126.6, 127.3, 128.6 (CH-Ph), 143.9 (C_q-Ph), 176.1 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{17}N_2O$: 205.1335; found: 205.1334.

5.2.2. (2*S*,5*R*)-1-Ethyl-*N*,*N*-dimethyl-5-phenylpyrrolidine-2-carboxamide (10c)

$NaBH_4$ (81.5 mg, 2.15 mmol) was portionwise added at 0 °C to a solution of the amide **10a** (100 mg, 458 μmol) in AcOH (0.8 mL). After the gas evolution had ceased, the solution was heated to 60 °C for 2 h. CH_2Cl_2 (10 mL) and sat. aq $NaHCO_3$ (10 mL) were slowly added and the reaction mixture was made basic with solid Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 98:1.8:0.2–90:9:1) afforded the amide **10c** (105 mg, 426 μmol, 93%) as a colorless oil.

$[\alpha]_D^{29}$ +41.4 (*c* 1.00, MeOH); R_f = 0.40 (CH_2Cl_2–MeOH, 19:1).

IR (ATR): 2965, 2932, 1654, 1636, 1492, 1454, 1397, 1136, 1062, 761, 703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3 H, 1-CH_2CH_3), 1.83 (m, 1 H, 4-*H*H), 1.91 (m, 1 H, 3-*H*H), 2.16 (m, 2 H, 3-H*H*, 4-H*H*), 2.39 (dq, *J* = 13.1, 7.1 Hz, 1 H, 1-C*H*H), 2.64 (dq, *J* = 13.0, 7.4 Hz, 1 H, 1-CH*H*), 2.99 (s, 3 H, NCH_3), 3.31 (s, 3 H, NCH_3), 3.56 (dd, *J* = 9.2, 6.4 Hz, 1 H, 5-H), 3.60 (dd, *J* = 9.0, 6.8 Hz, 1 H, 2-H), 7.24 (t, *J* = 7.3 Hz, 1 H, Ph-H), 7.32 (t, *J* = 7.5 Hz, 2 H, Ph-H), 7.46 (d, *J* = 7.5 Hz, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.3 (1-CH_2CH_3), 28.1 (C-3), 35.1 (C-4), 36.6 (NCH_3), 37.1 (NCH_3), 47.2 (1-CH_2), 66.7 (C-2), 69.5(C-5), 127.1, 127.6, 128.5 (CH-Ph), 144.0 (C_q-Ph), 174.4 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{23}N_2O$: 247.1805; found: 247.1805.

5.2.3. (2*S*,5*R*)-1-Benzyl-*N*,*N*-dimethyl-5-phenylpyrrolidine-2-carboxamide (10d)

According to GP–4, the amide **10a** (100 mg, 458 μmol) was *N*-benzylated with benzaldehyde–$NaBH(OAc)_3$ to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 100:0:0–95:4.5:0.5), pyrrolidine amide **10d** (134 mg, 434 μmol, 95%) as a colorless oil.

$[\alpha]_D^{32}$ +27.6 (*c* 1.00, MeOH); R_f = 0.35 (EtOAc).

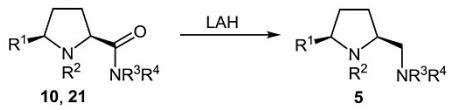
IR (ATR): 3027, 2937, 2798, 1634, 1491, 1452, 1395, 1116, 747, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.88 (m, 1 H, 3-*H*H), 1.95 (m, 1 H, 4-*H*H), 2.11 (m, 2 H, 3-H*H*, 4-H*H*), 2.68 (s, 3 H, NCH_3), 2.91 (s, 3 H, NCH_3), 3.41 (d, *J* = 13.7 Hz, 1 H, 1-C*H*H), 3.61 (m, 2 H, 2-H, 5-H), 3.86 (d, *J* = 13.7 Hz, 1 H, 1-CH*H*), 7.18 (m, 3 H, Ph-H), 7.26 (m, 3 H, Ph-H), 7.37 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.58 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.0 (C-3), 35.0 (C-4), 36.1 (NCH_3), 36.7 (NCH_3), 56.4 (1-CH_2), 65.0 (C-2), 69.1 (C-5), 127.1, 127.3, 127.8, 127.9, 128.6, 129.7 (CH-Ph), 137.3, 143.3 (C_q-Ph), 173.7 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{20}H_{25}N_2O$: 309.1961; found: 309.1967.

5.3. Diamines 5



5	R^1	R^2	NR^3R^4
a	Ph	Me	NHMe
g	Ph	Et	NMe_2
h	Ph	Bn	NMe_2
q	Me	Me	NMe_2

5	R^1	R^2	NR^3R^4
w	Ph	Me	NMeBn
x	*i*Pr	Me	NHMe
y	Ph	H	NHMe

5.3.1. (2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine (5a)

According to GP–3, the amide **21a** (100 mg, 372 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5–85:13.5:1.5), prolinamine **5a** (54.6 mg, 267 µmol, 82%) as a yellowish oil.

For characterization of **5a**, see ref. 3.

5.3.2. (2*S*,5*R*)-2-Dimethylaminomethyl-1-ethyl-5-phenylpyrrolidine (5g)

According to GP–3, the amide **10c** (50.0 mg, 203 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5), prolinamine **5g** (44.8 mg, 193 µmol, 95%) as a colorless oil.

For characterization of **5g**, see 3.5.

5.3.3. (2*S*,5*R*)-1-Benzyl-2-dimethylaminomethyl-5-phenylpyrrolidine (5h)

According to GP–3, the amide **10d** (172 mg, 557 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5h** (146 mg, 495 µmol, 89%) as a colorless oil.

For characterization of **5h**, see article.

5.3.4. (2*S*,5*S*)-2-(Dimethylaminomethyl)-1,5-dimethylpyrrolidine (5q)

According to GP–3, the amide **21c** (250 mg, 975 µmol) was reduced to give, after column chromatography (basic alumina, activity I, CH_2Cl_2–MeOH, 100:0–98:2), prolinamine **5q** (150 mg, 962 µmol, 98%) as a yellowish oil.

For characterization of **5q**, see 4.8.9.

5.3.5. (2*S*,5*R*)-2-Benzyl(methyl)aminomethyl-1-methyl-5-phenylpyrrolidine (5w)

According to GP–3, the amide **21e** (100 mg, 253 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 190:9:1), prolinamine **5w** (62.3 mg, 212 µmol, 84%) as a colorless oil.

For characterization of **5w**, see 4.8.15.

5.3.6. (2*R*,5*S*)-2-Isopropyl-1-methyl-5-(methylaminomethyl)pyrrolidine (5x)

According to GP–3, the amide **21b** (93.0 mg, 344 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 93:6.3:0.7), prolinamine **5x** (43.3 mg, 254 µmol, 74%) as a yellowish oil.

$[\alpha]_D^{20}$ +0.7 (*c* 0.50, MeOH); R_f = 0.23 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1).

IR (ATR): 2958, 2780, 1651, 1593, 1466, 1366, 1293, 1041 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.87 (d, *J* = 6.9 Hz, 3 H, CH(C*H*$_3$)$_2$), 1.47 (m, 1 H, 3-*H*H), 1.58 (m, 2 H, 3-H*H*, 4-*H*H), 1.79 (m, 2 H, 4-H*H*, C*H*(CH$_3$)$_2$), 2.16 (br s, 1 H, NH), 2.23 (m, 1 H, 2-H), 2.24 (s, 3 H, 1-CH_3), 2.47 (s, 3 H, NHC*H*$_3$), 2.49 (m, 1 H, 5-H), 2.56 (dd, *J* = 11.3, 5.6 Hz, 1 H, 5-C*H*H), 2.65 (dd, *J* = 11.4, 3.8 Hz, 1 H, 5-CH*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.6 (CH(*C*H$_3$)$_2$), 20.4 (CH(*C*H$_3$)$_2$), 23.6 (C-3), 27.7 (C-4), 29.1 (*C*H(CH$_3$)$_2$), 37.1 (NHCH$_3$), 40.2 (1-CH_3), 55.0 (5-CH_2), 66.3 (C-5), 72.4 (C-2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{10}H_{23}N_2$: 171.1856; found: 171.1855.

5.3.7. (2*S*,5*R*)-2-Methylaminomethyl-5-phenylpyrrolidine (5y)

According to GP–3, the amide **10b** (250 mg, 1.22 mmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1–85:13.5:1.5), prolinamine **5y** (144 mg, 757 µmol, 62%) as a colorless oil.

$[\alpha]_D^{29}$ +41.2 (*c* 1.00, MeOH); R_f = 0.16 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1).

IR (ATR): 3600–3050, 2934, 1555, 1491, 1451, 1374, 1350, 1065, 1028, 813, 756, 700 cm^{-1}.

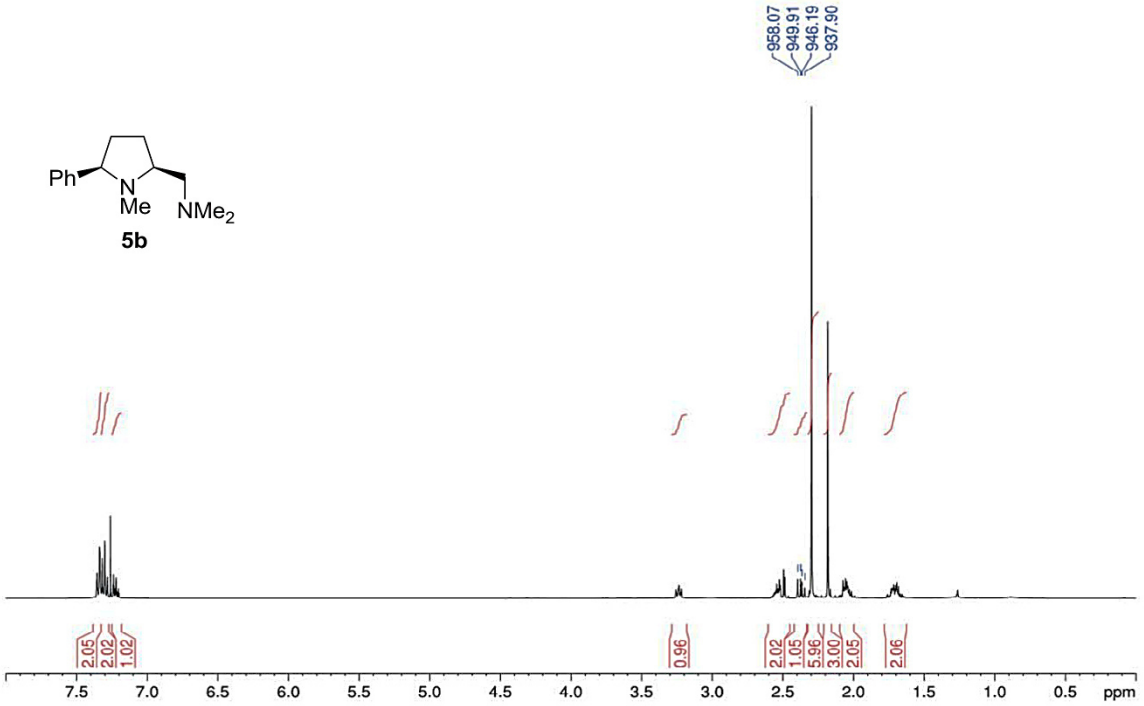
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.61 (m, 1 H, 3-*H*H), 1.68 (m, 1 H, 4-*H*H), 1.97 (m, 1 H, 3-H*H*), 2.03 (br s, 2 H, NH), 2.14 (m, 1 H, 4-H*H*), 2.48 (s, 3 H, NCH_3), 2.62 (dd, *J* = 11.4, 7.7 Hz, 1 H, 2-C*H*H), 2.67 (dd, *J* = 11.4, 4.8 Hz, 1 H, 2-CH*H*), 3.43 (m, 1 H, 2-H), 4.21 (dd, *J* = 8.8, 7.0 Hz, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.31 (m, 2 H, Ph-H), 7.38 (m, 2 H, Ph-H).

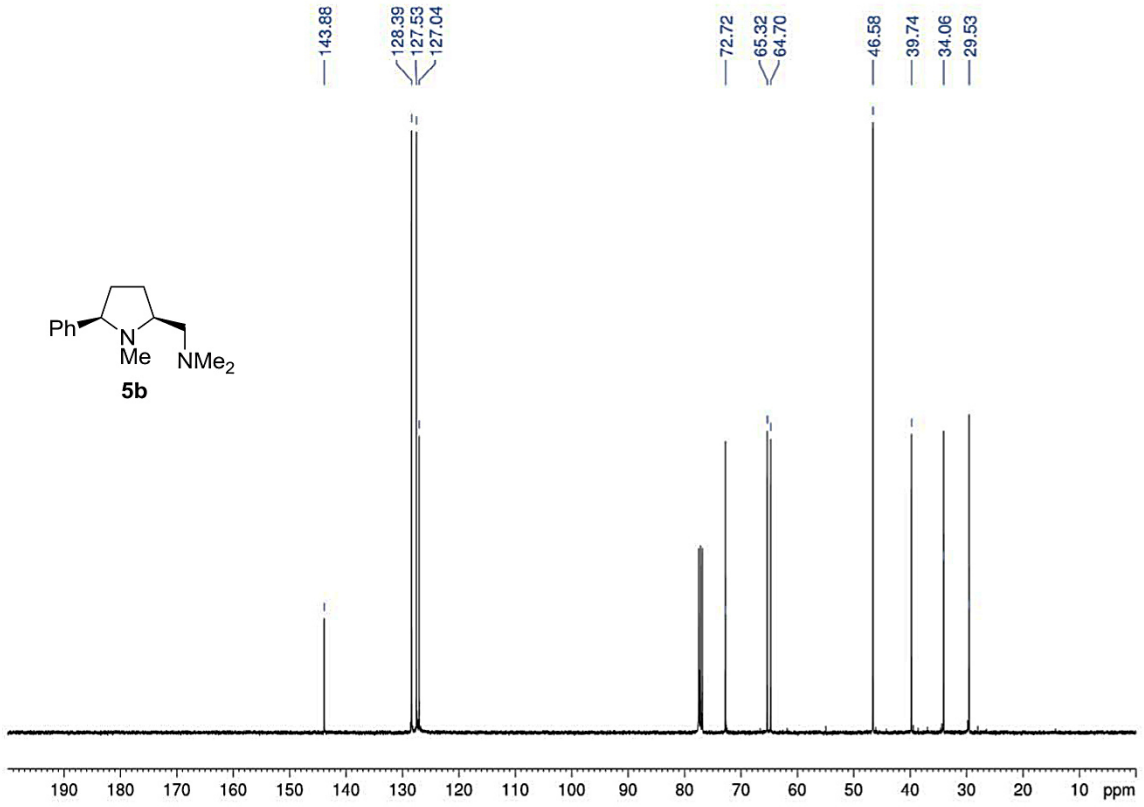
^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.7 (C-3), 34.3 (C-4), 36.9 (NCH_3), 57.9 (C-2), 58.3 (2-CH_2), 62.8 (C-5), 126.7, 126.9, 128.4 (CH-Ph), 145.0 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{19}N_2$: 191.1543; found: 191.1537.

6. Copies of ^{1}H and ^{13}C NMR Spectra

The ^{1}H and ^{13}C NMR spectra of all new compounds are listed in numerical order.





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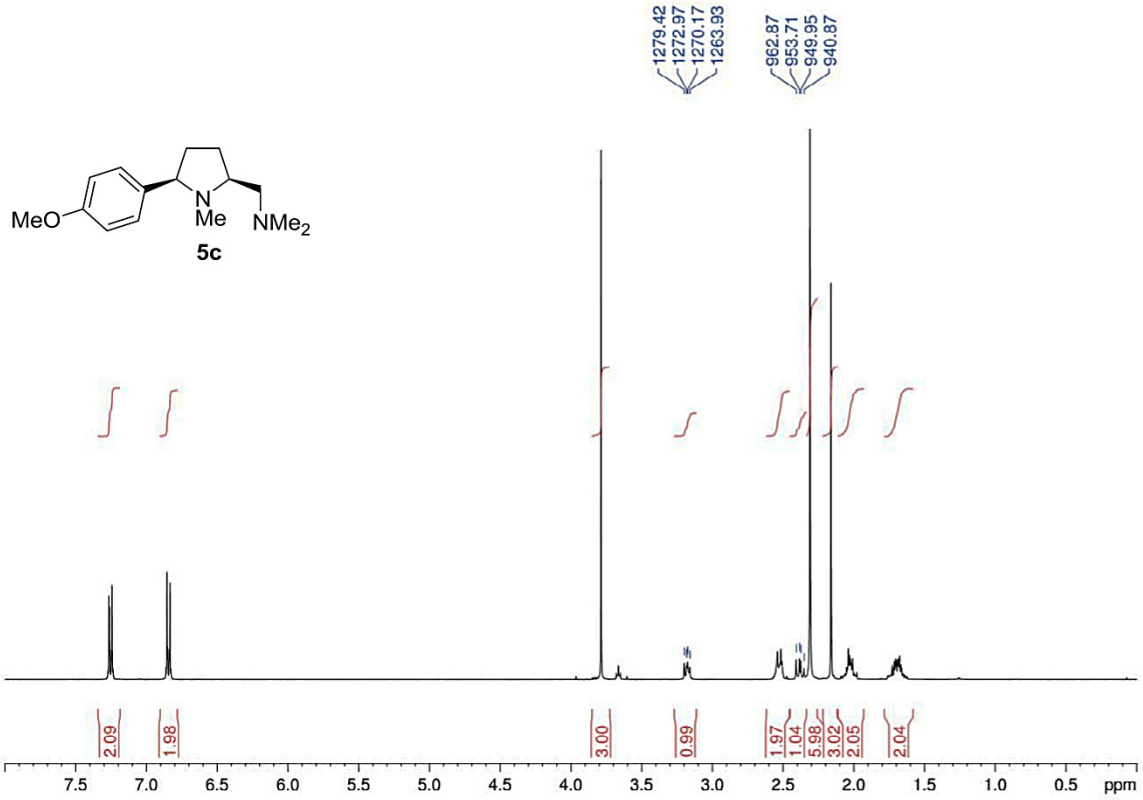
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2.09
1.98
3.00
0.99
1.97
1.04
5.98
3.02
2.05
2.04
7.5
7.0
6.5
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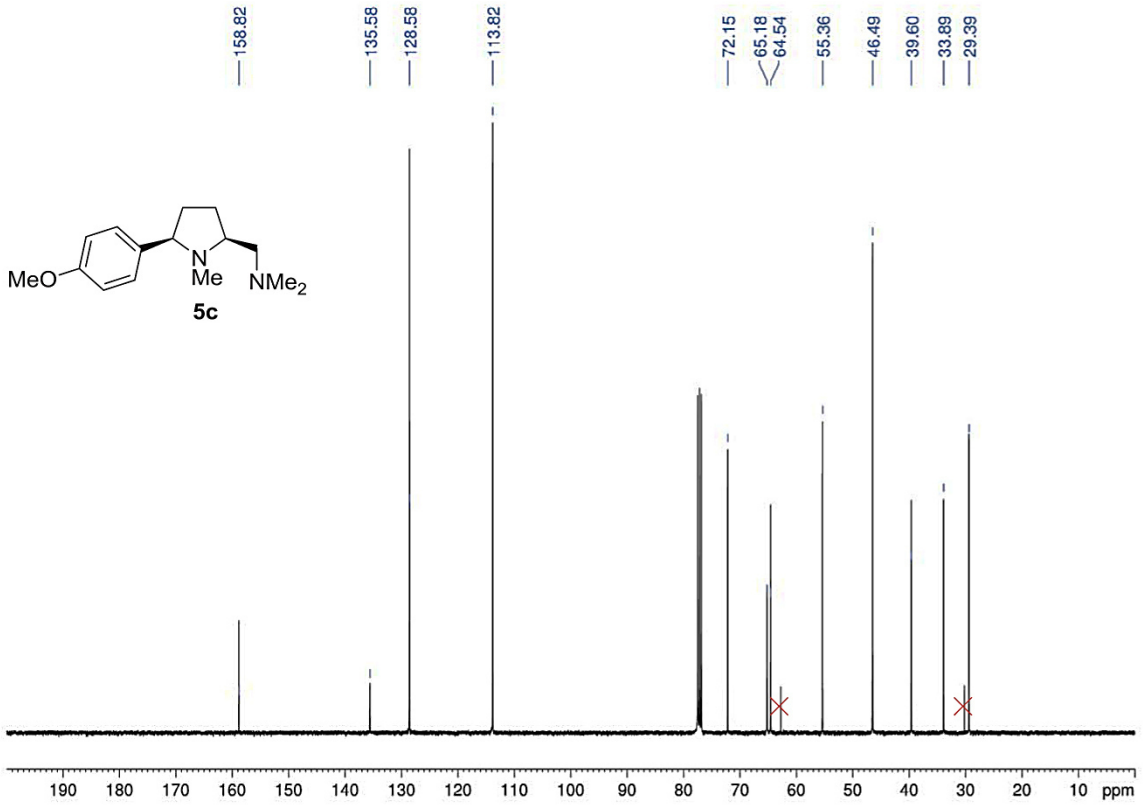
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Me
NMe2
5c
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40
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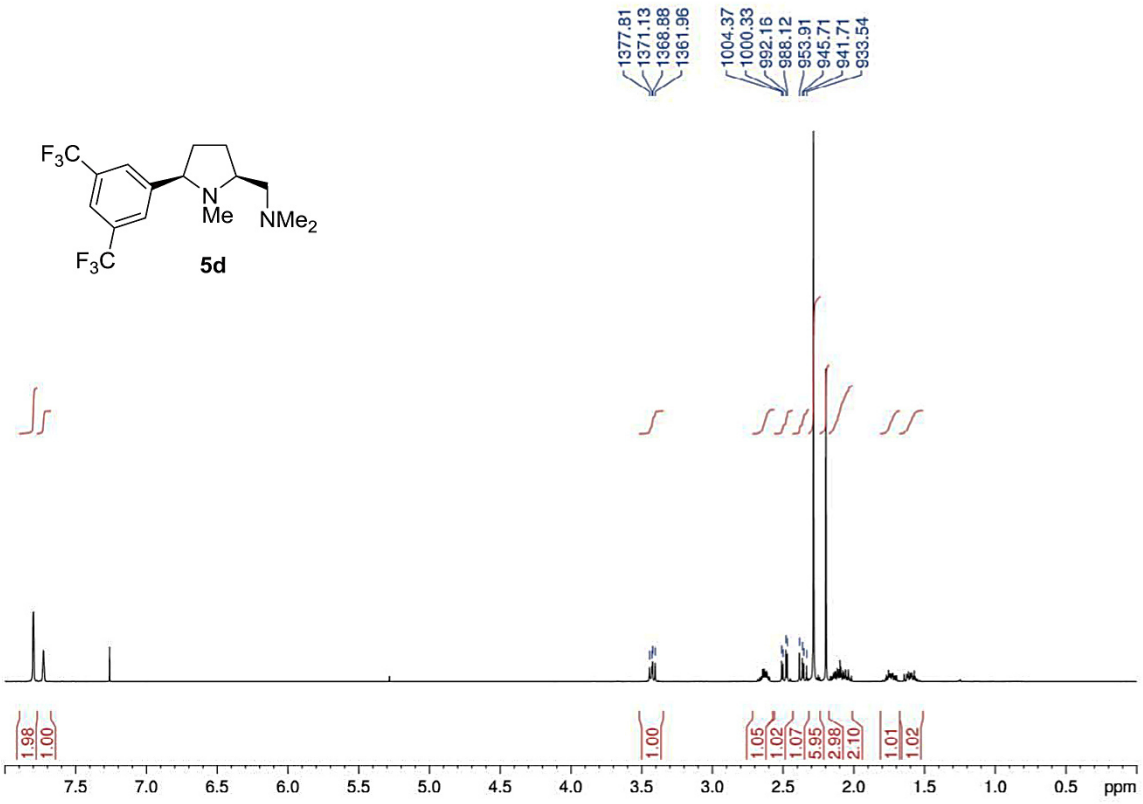
20
10
ppm

36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N
Me
NMe2
F3C
5d
1.98
1.00
1.00
1.05
1.02
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1.01
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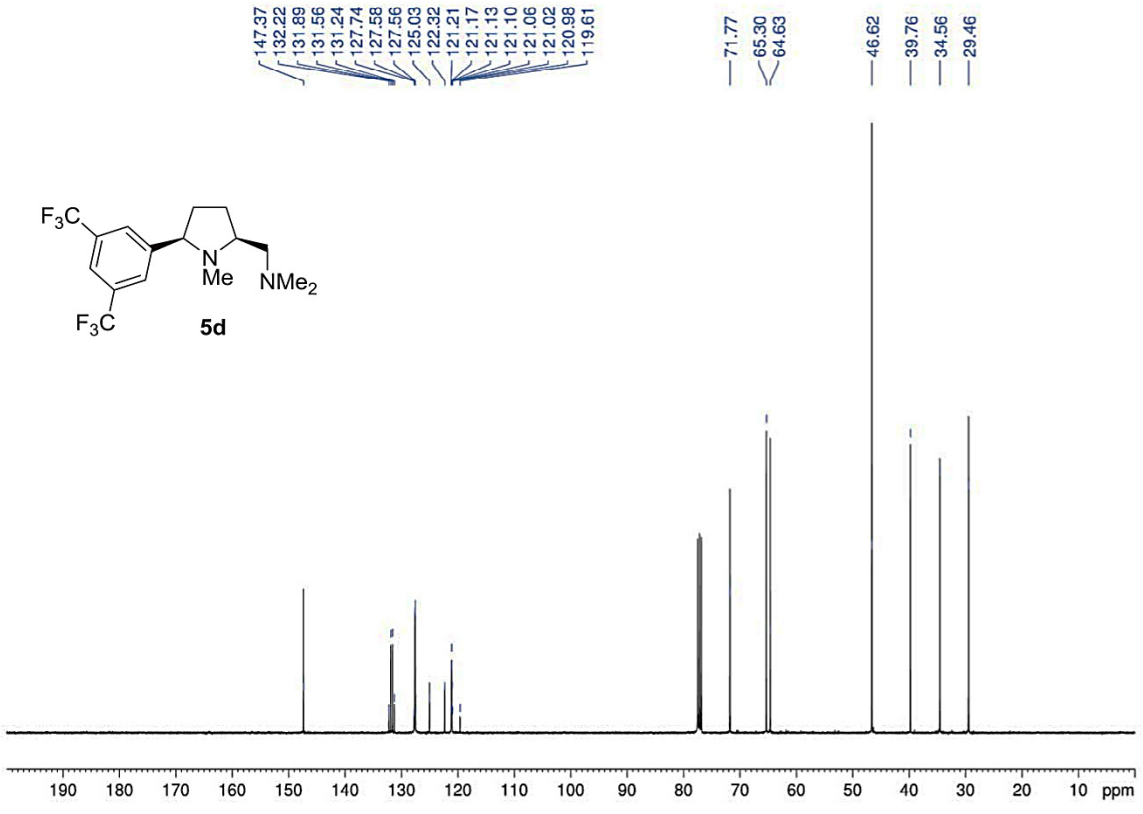
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121.10
121.06
121.02
120.98
119.61
71.77
65.30
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39.76
34.56
29.46
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Me
NMe2
F3C
5d
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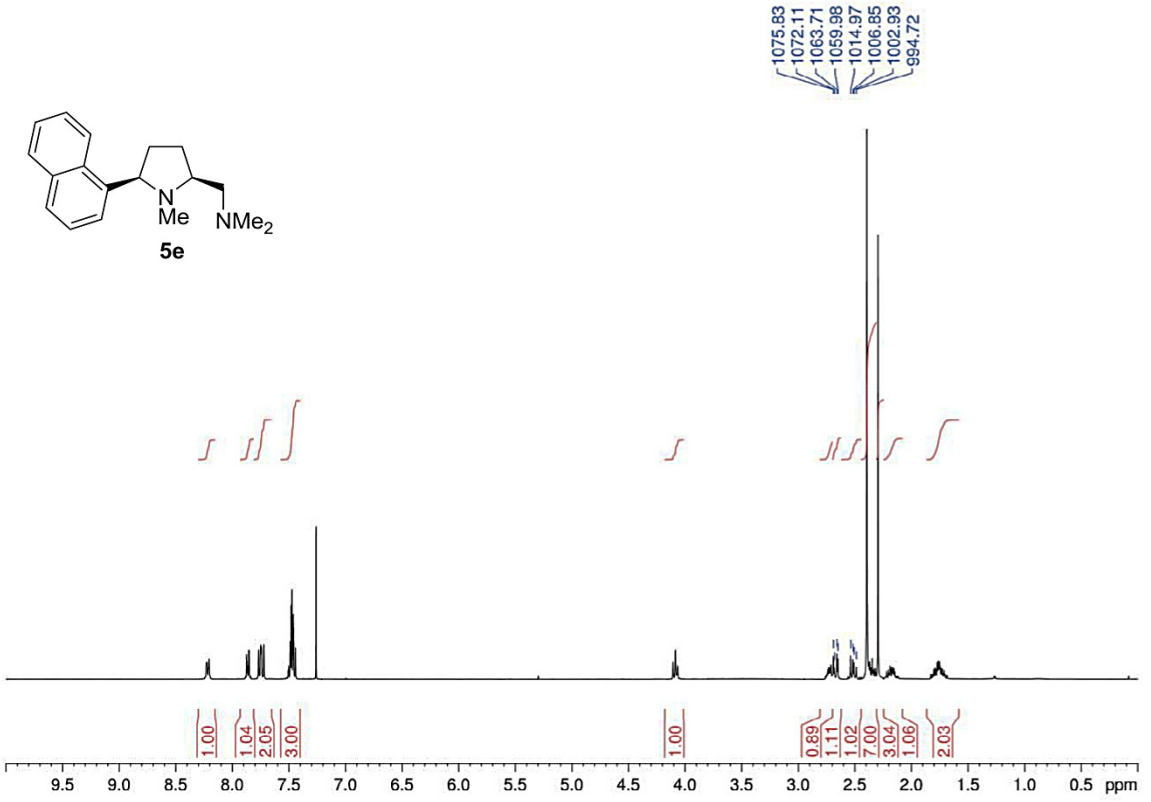
ppm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1014.97
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1002.93
994.72
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NMe2
5e
1.00
1.04
2.05
3.00
1.00
0.89
1.11
1.02
7.00
3.04
1.06
2.03
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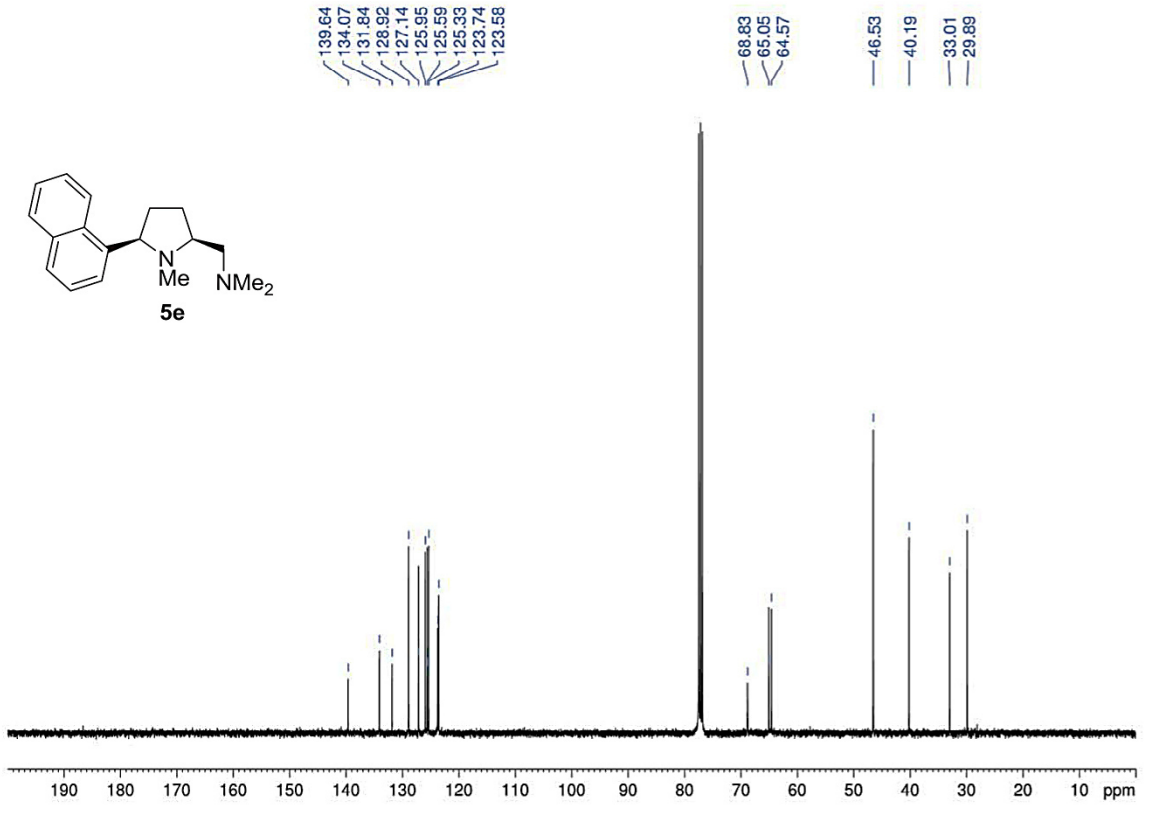
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29.89
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Me
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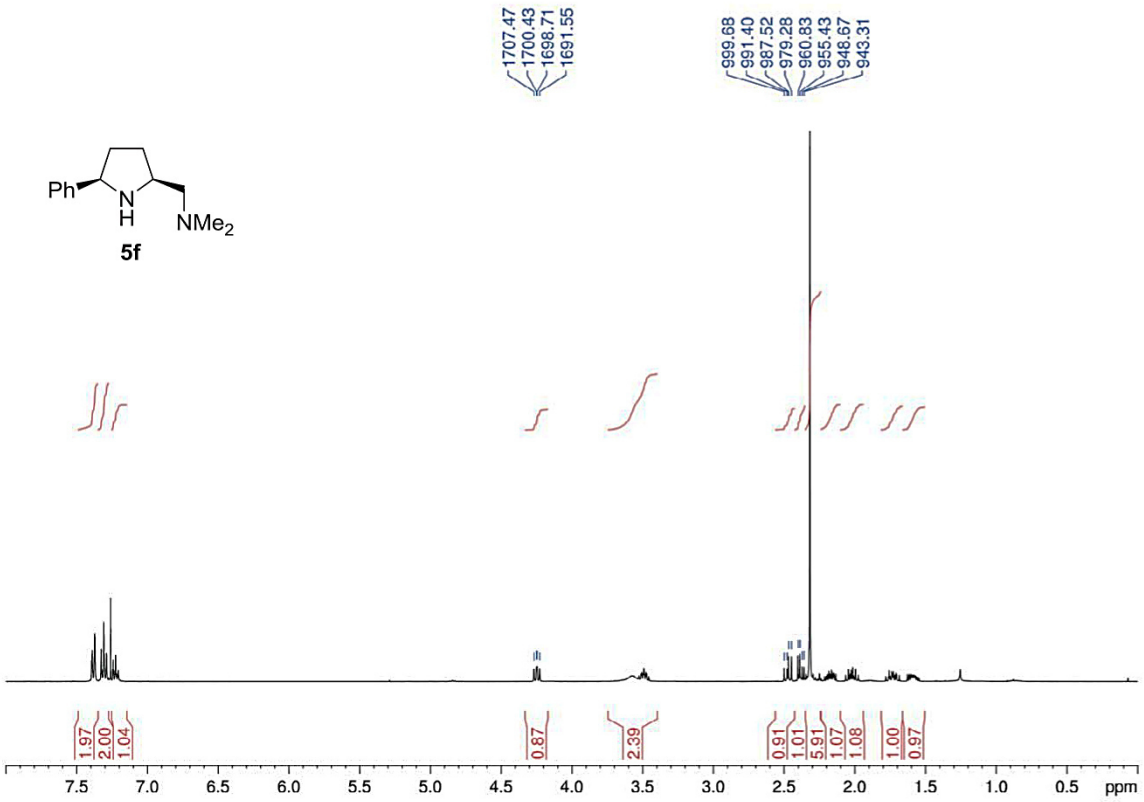
38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H
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5f
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2.00
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0.87
2.39
0.91
1.01
5.91
1.07
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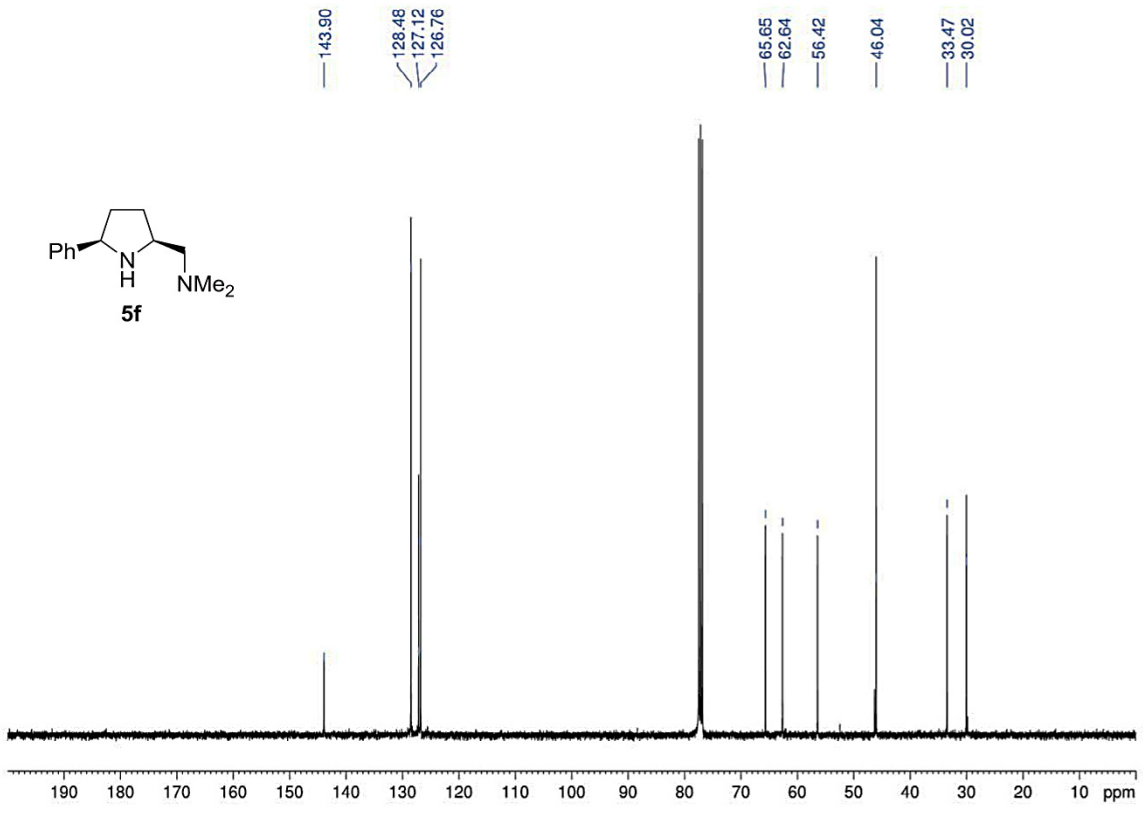
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5f
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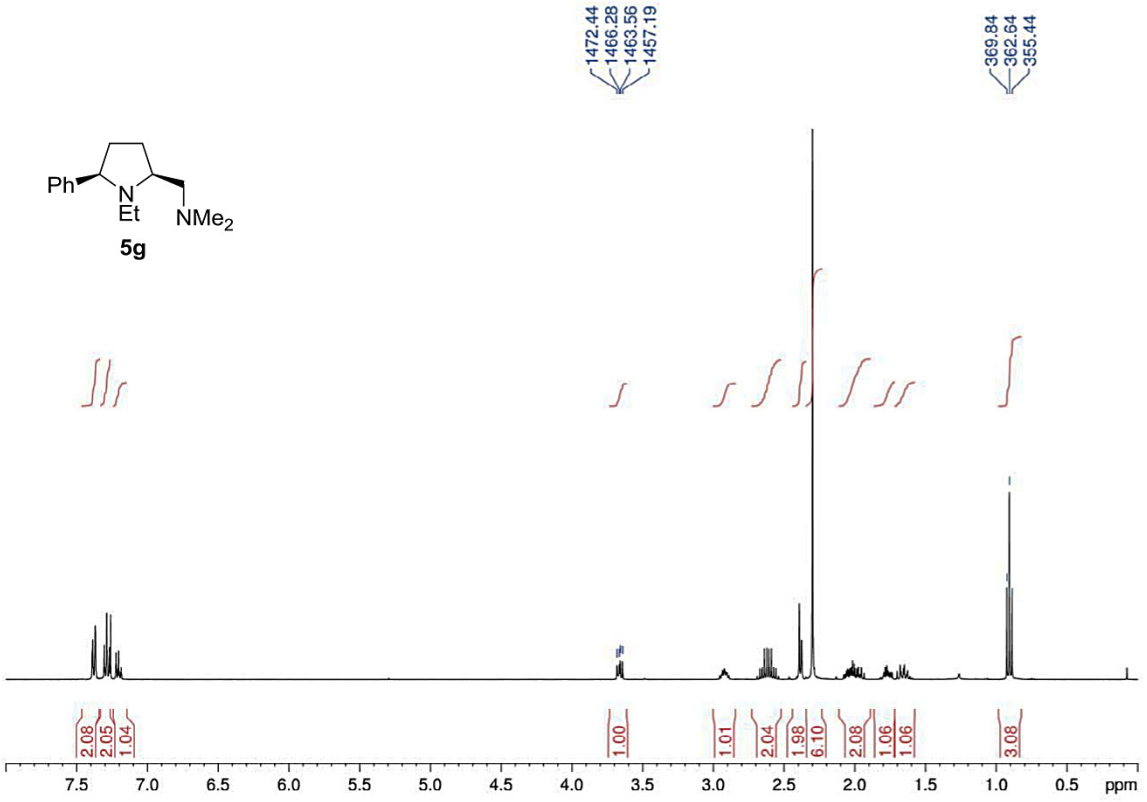
39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2.08
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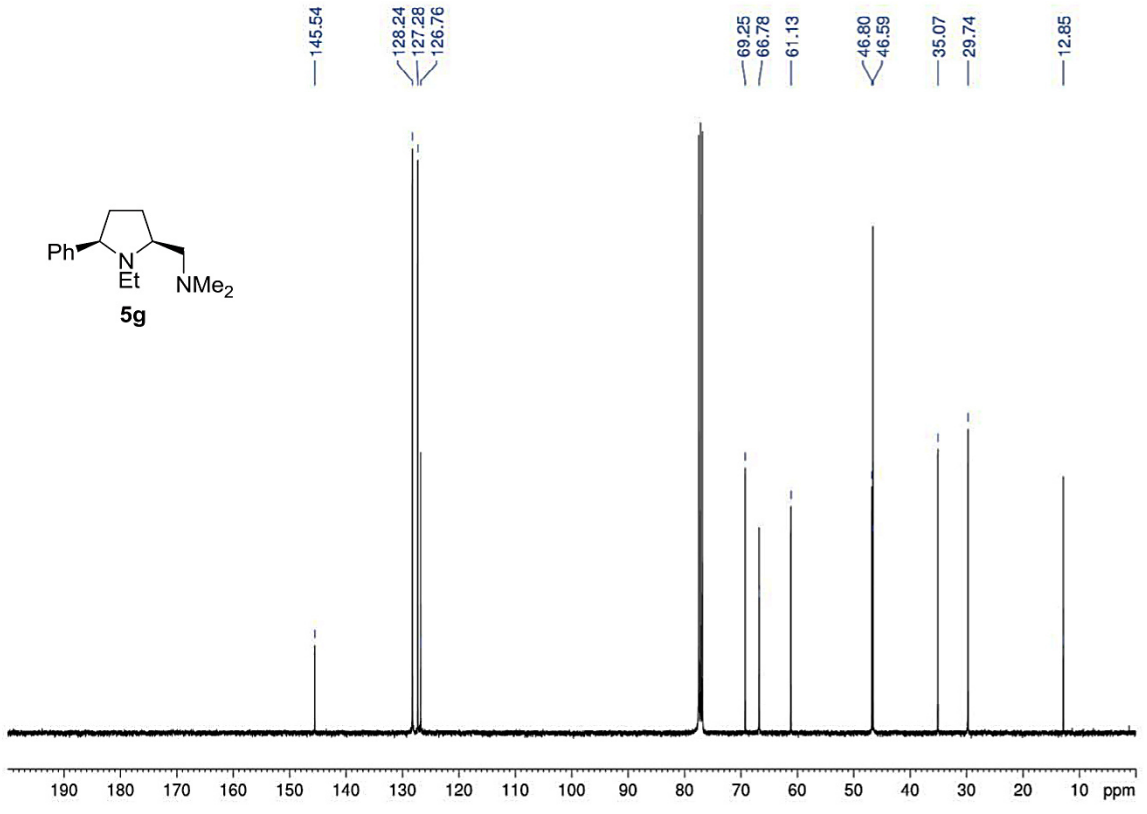
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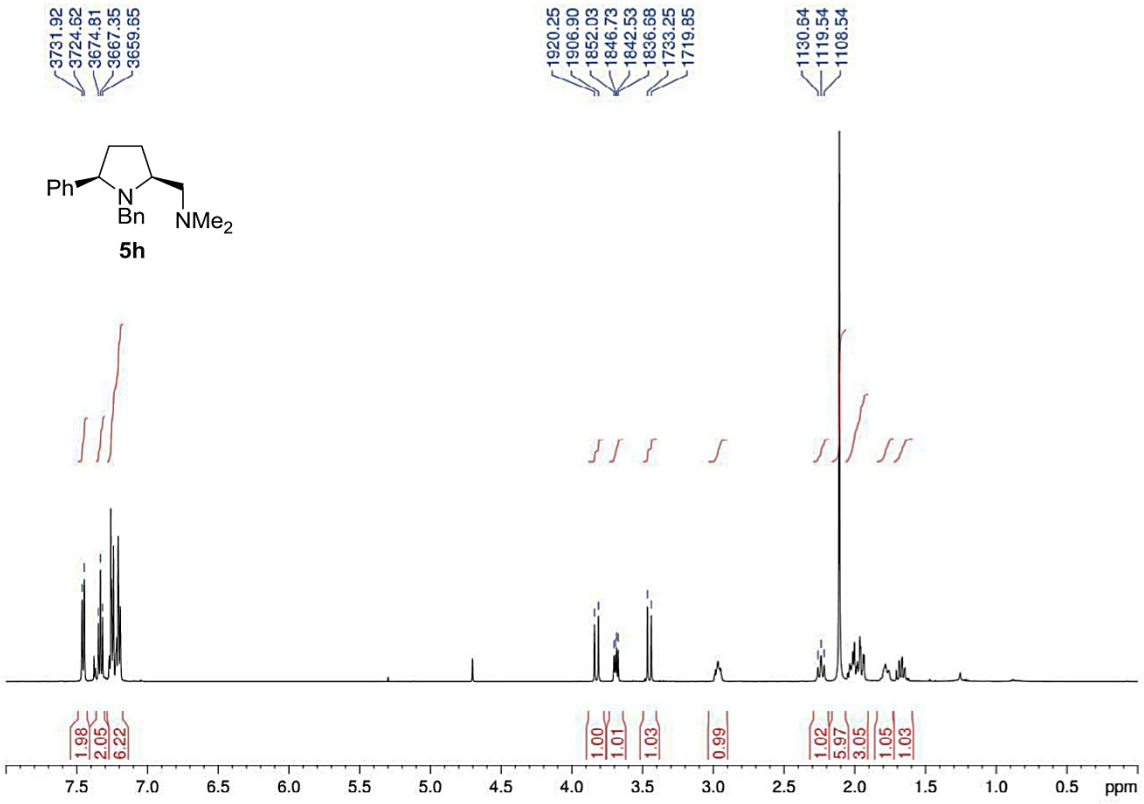
40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1733.25
1719.85
1130.64
1119.54
1108.54
Ph
N
Bn
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5h
1.98
2.05
6.22
1.00
1.01
1.03
0.99
1.02
5.97
3.05
1.05
1.03
7.5
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6.5
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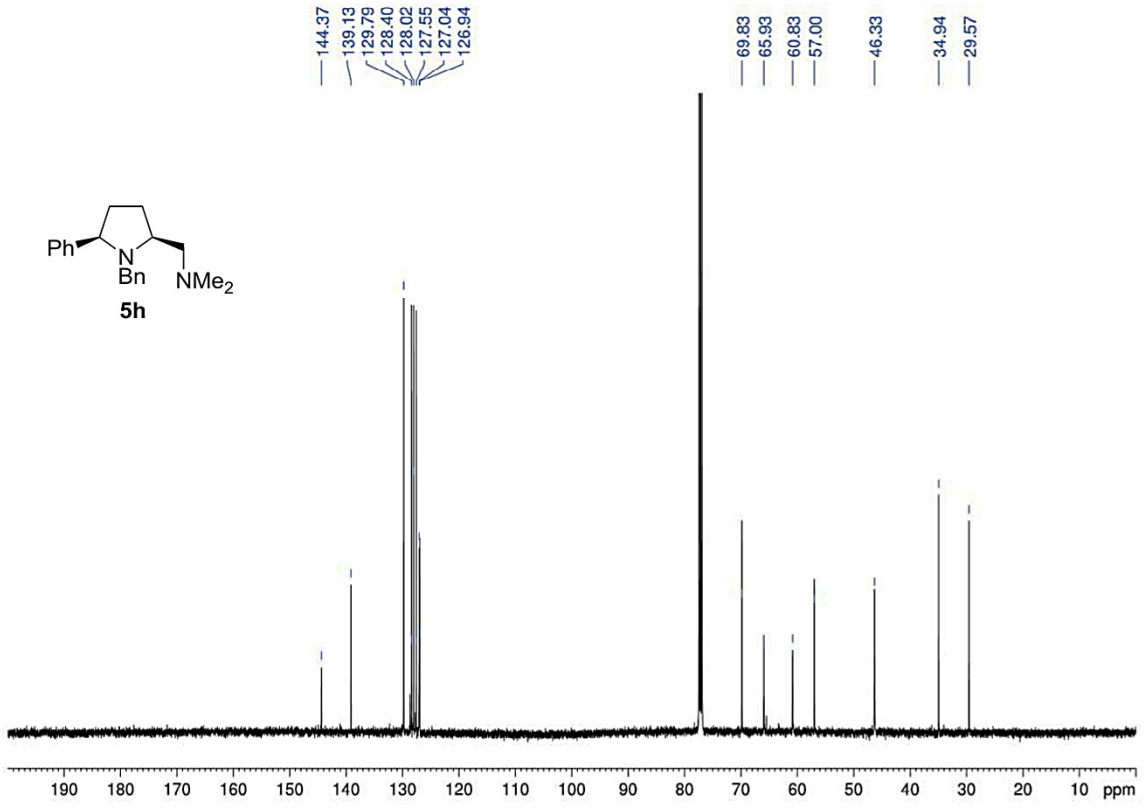
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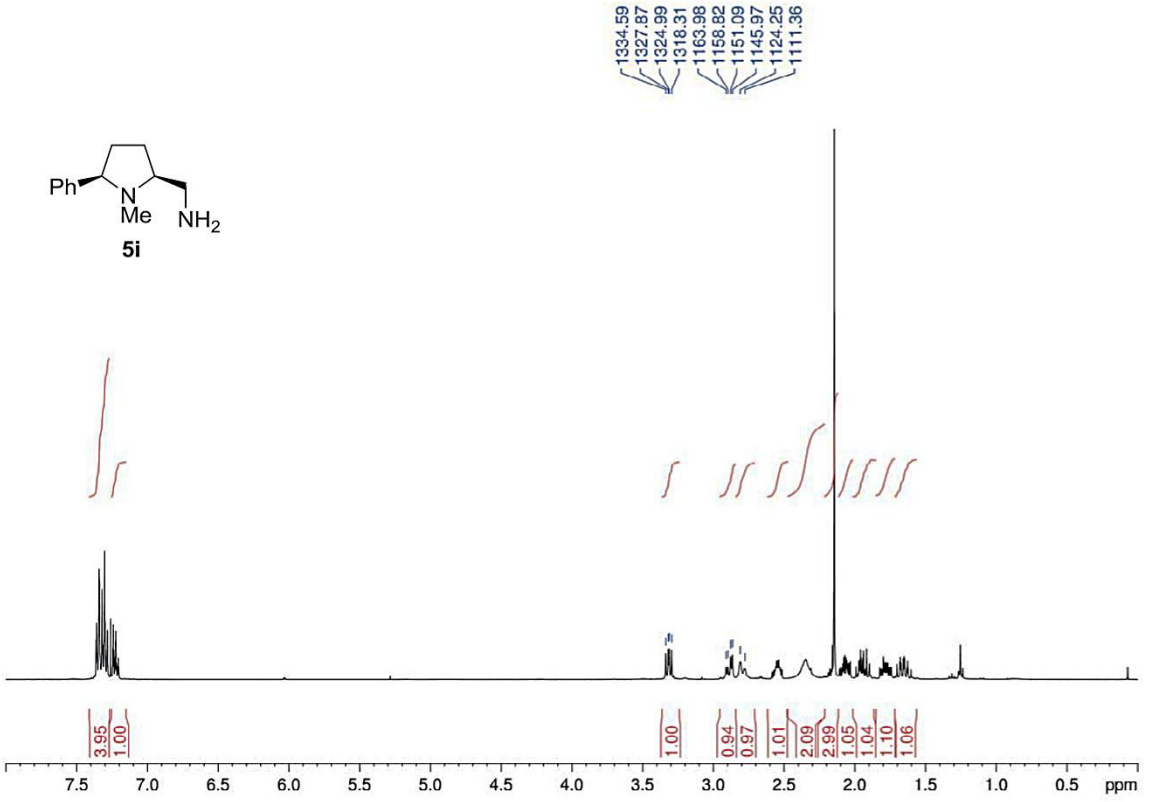
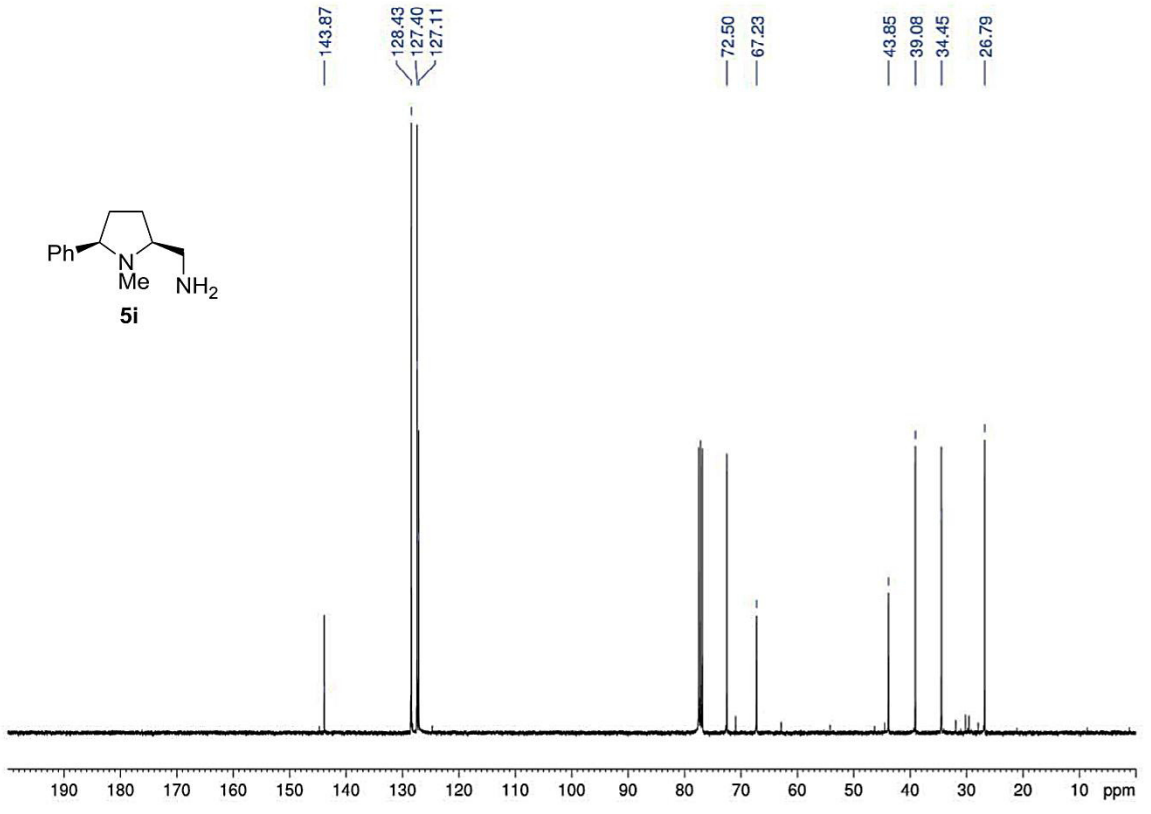
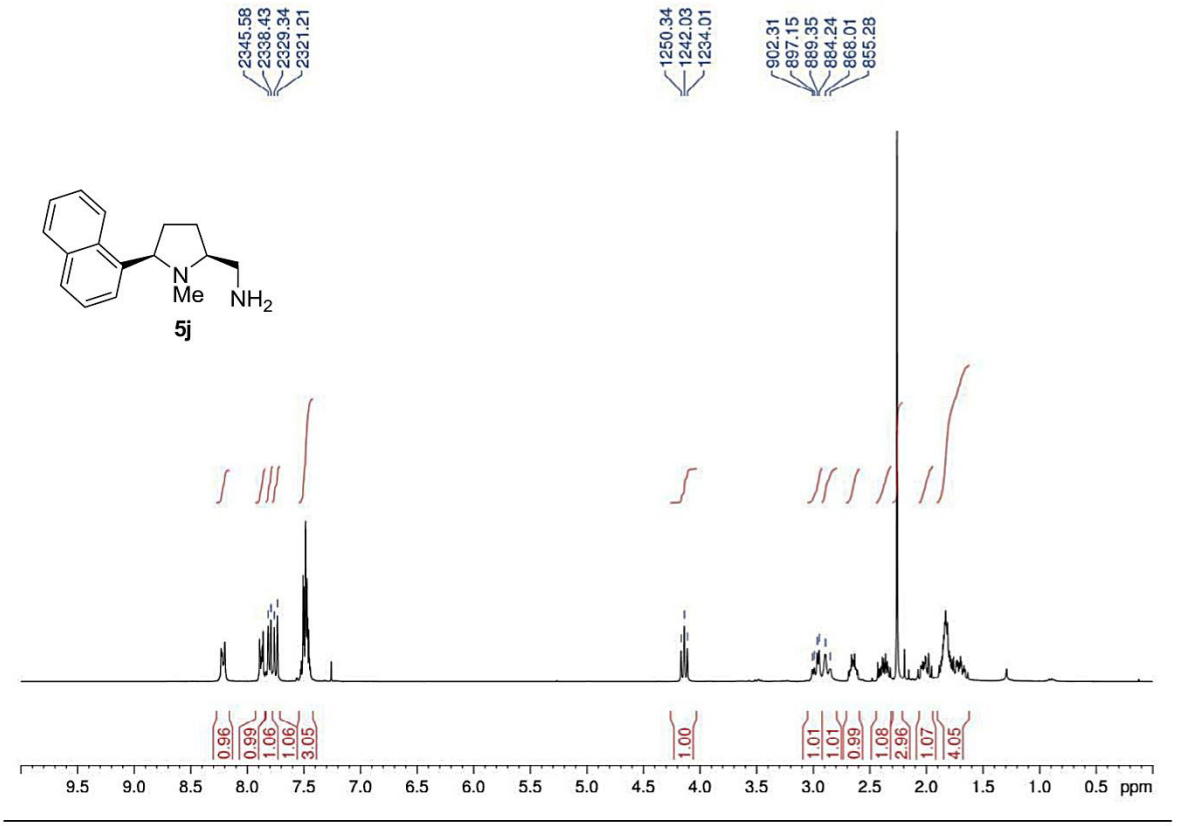
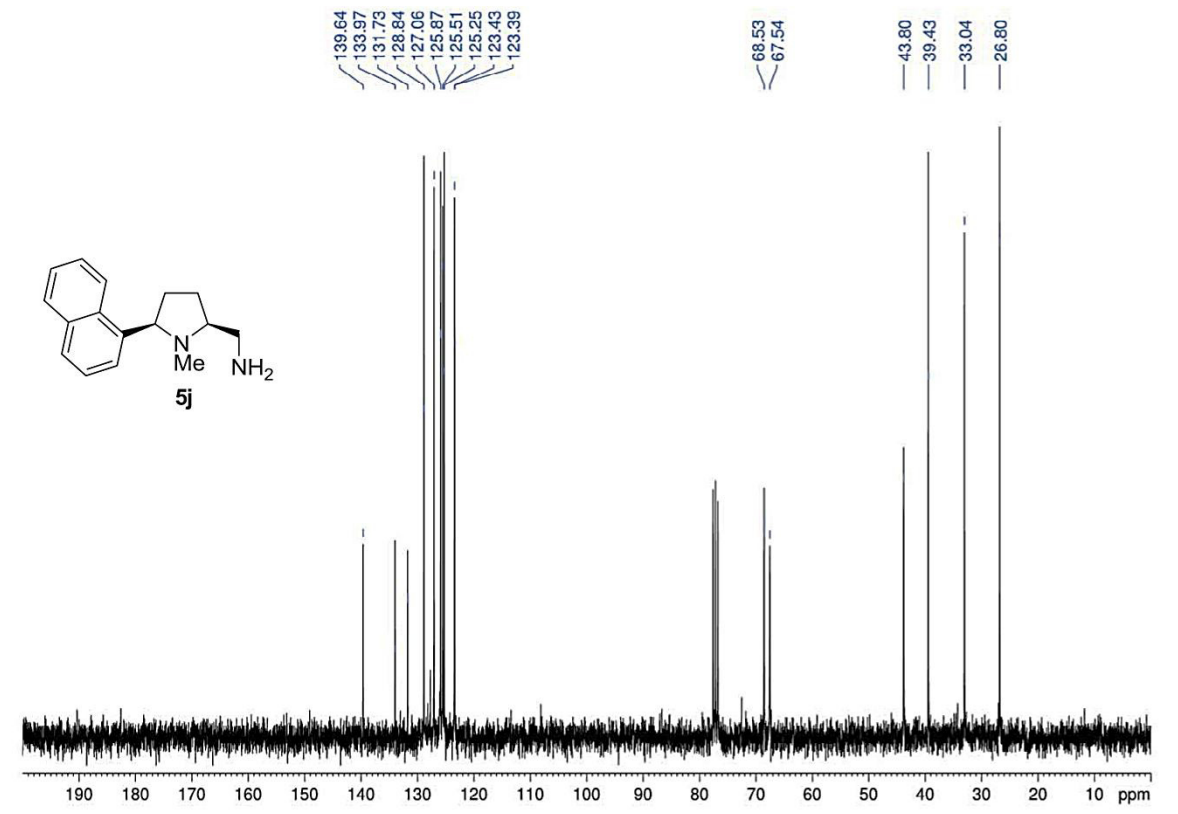
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

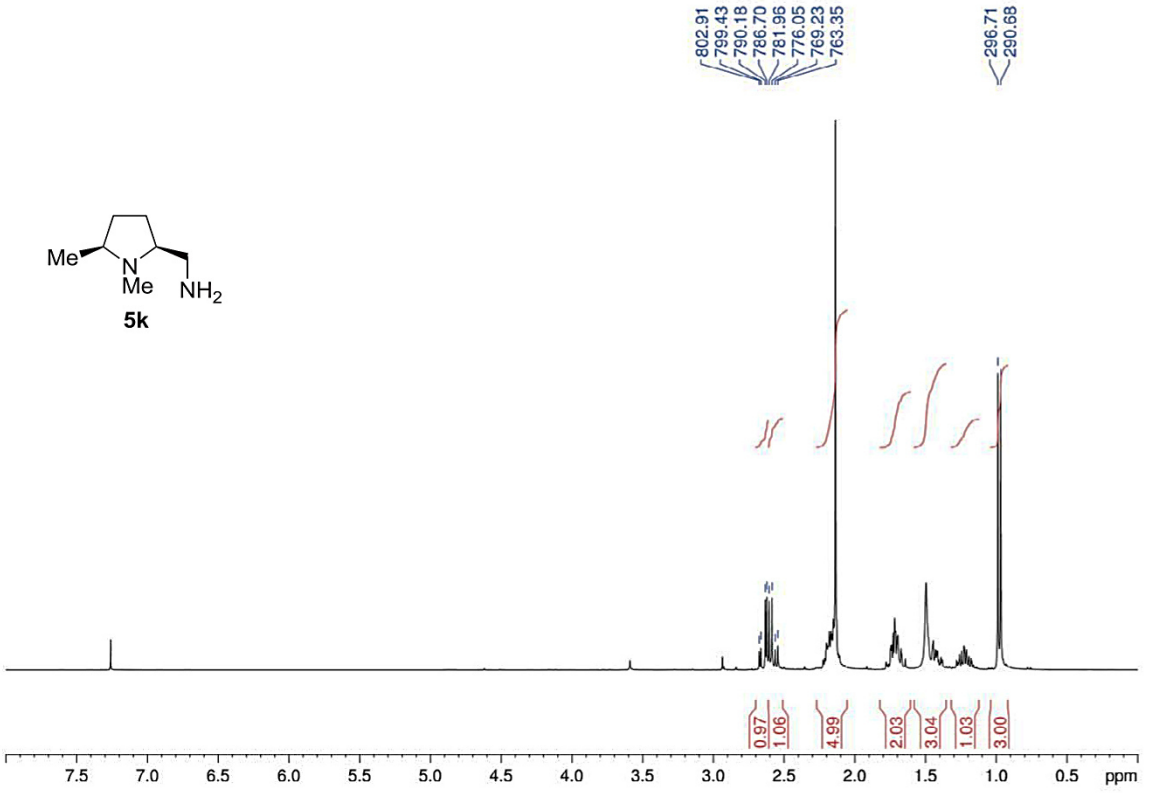

1334.59
1327.87
1324.99
1318.31
1163.98
1158.82
1151.09
1145.97
1124.25
1111.36
Ph
N
Me
NH2
5i
3.95
1.00
1.00
0.94
0.97
1.01
2.09
2.99
1.05
1.04
1.10
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

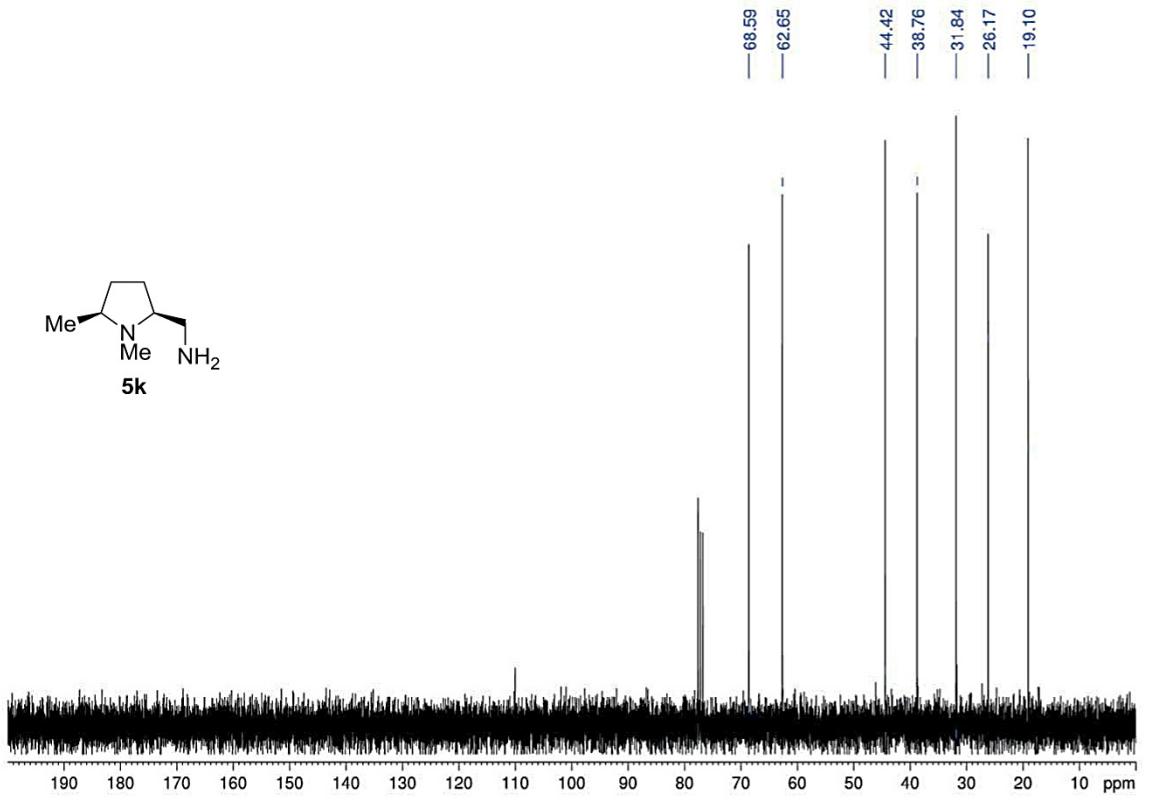

143.87
128.43
127.40
127.11
72.50
67.23
43.85
39.08
34.45
26.79
Ph
N
Me
NH2
5i
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

42

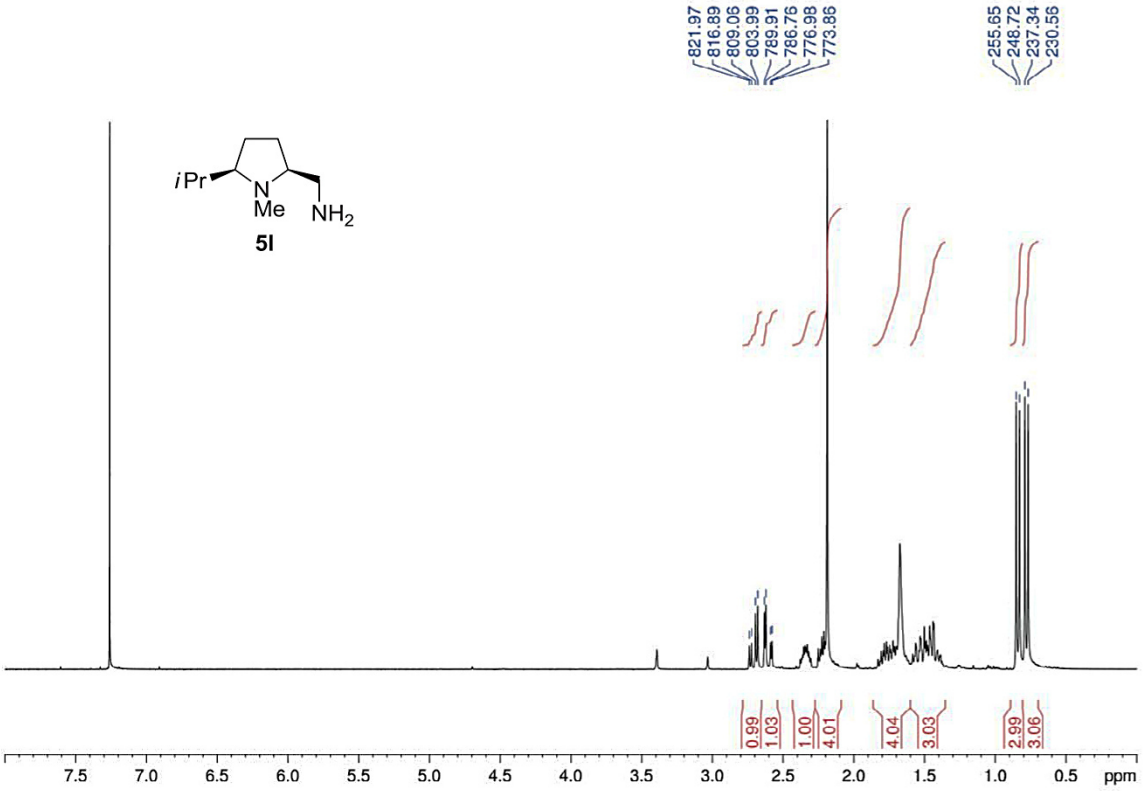

2345.58
2338.43
2329.34
2321.21
1250.34
1242.03
1234.01
902.31
897.15
889.35
884.24
868.01
855.28
N
Me
NH2
5j
0.96
0.99
1.06
1.06
3.05
1.00
1.01
1.01
0.99
1.08
2.96
1.07
4.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

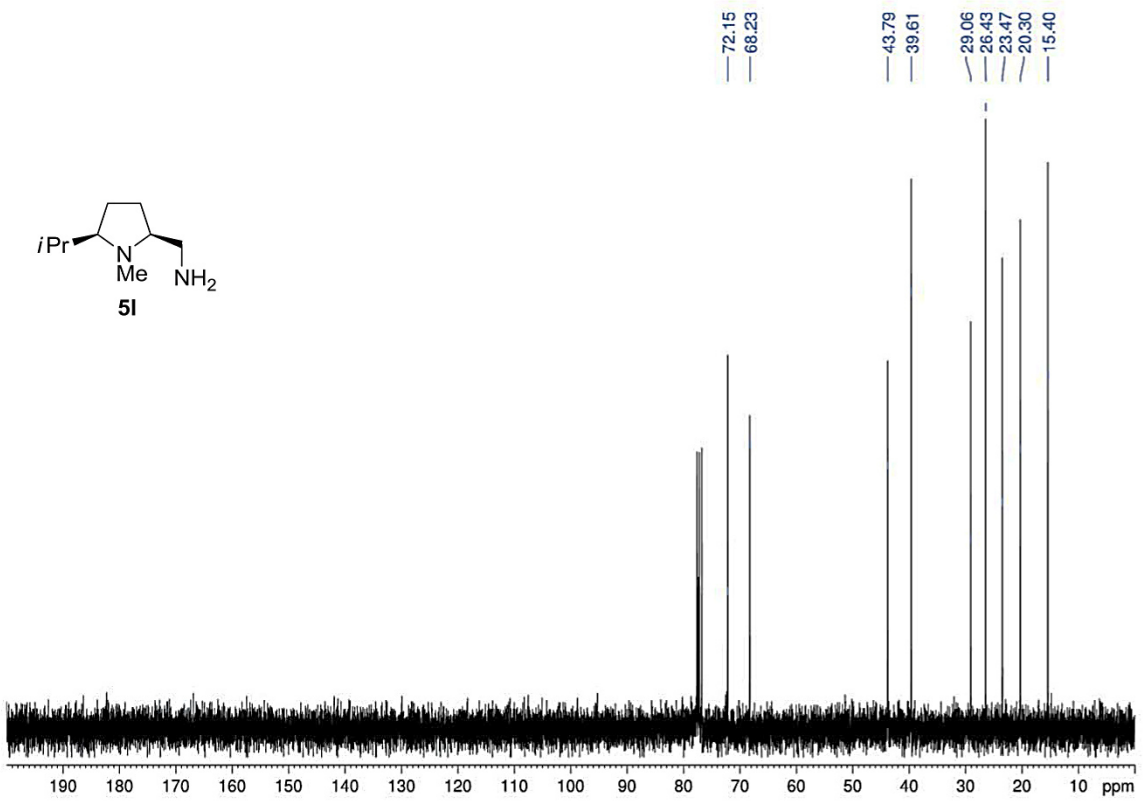

139.64
133.97
131.73
128.84
127.06
125.87
125.51
125.25
123.43
123.39
68.53
67.54
43.80
39.43
33.04
26.80
N
Me
NH2
5j
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

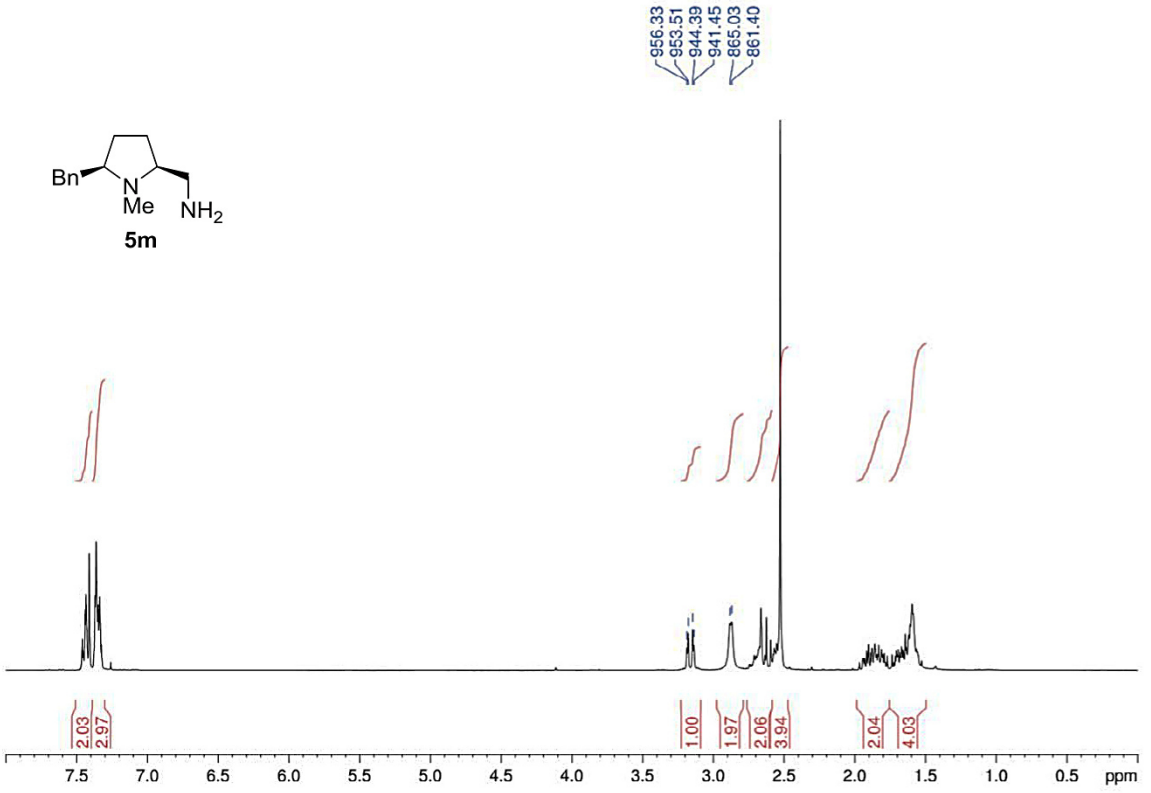

802.91
799.43
790.18
786.70
781.96
776.05
769.23
763.35
296.71
290.68
Me
N
Me
NH2
5k
0.97
1.06
4.99
2.03
3.04
1.03
3.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

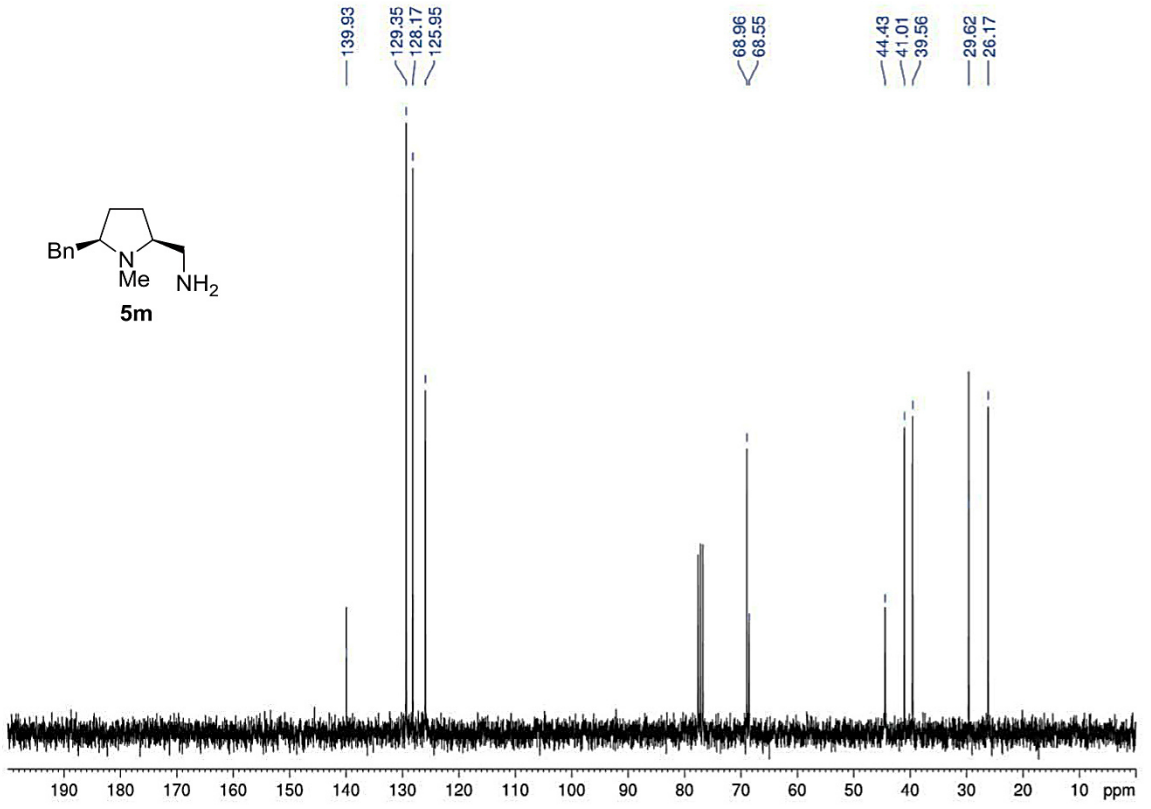

68.59
62.65
44.42
38.76
31.84
26.17
19.10
Me
N
Me
NH2
5k
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

44

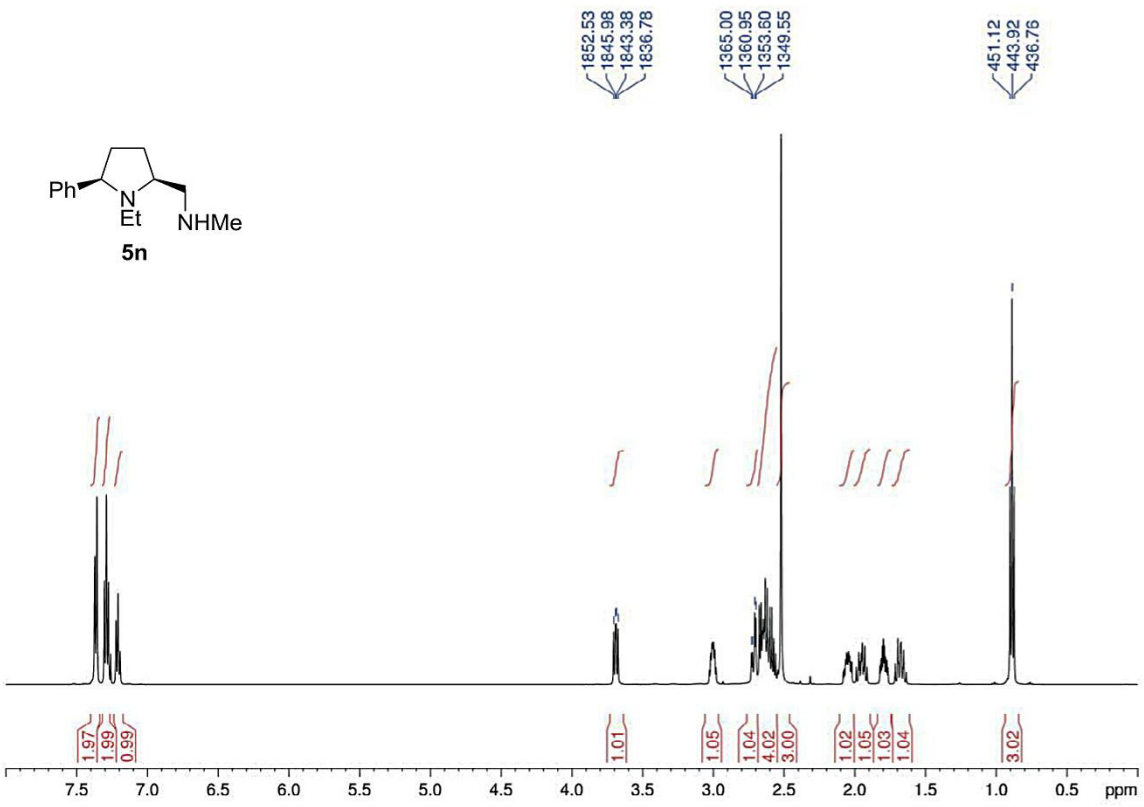

821.97
816.89
809.06
803.99
789.91
786.76
776.98
773.86
255.65
248.72
237.34
230.56
iPr
N
Me
NH2
5l
0.99
1.03
1.00
4.01
4.04
3.03
2.99
3.06
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

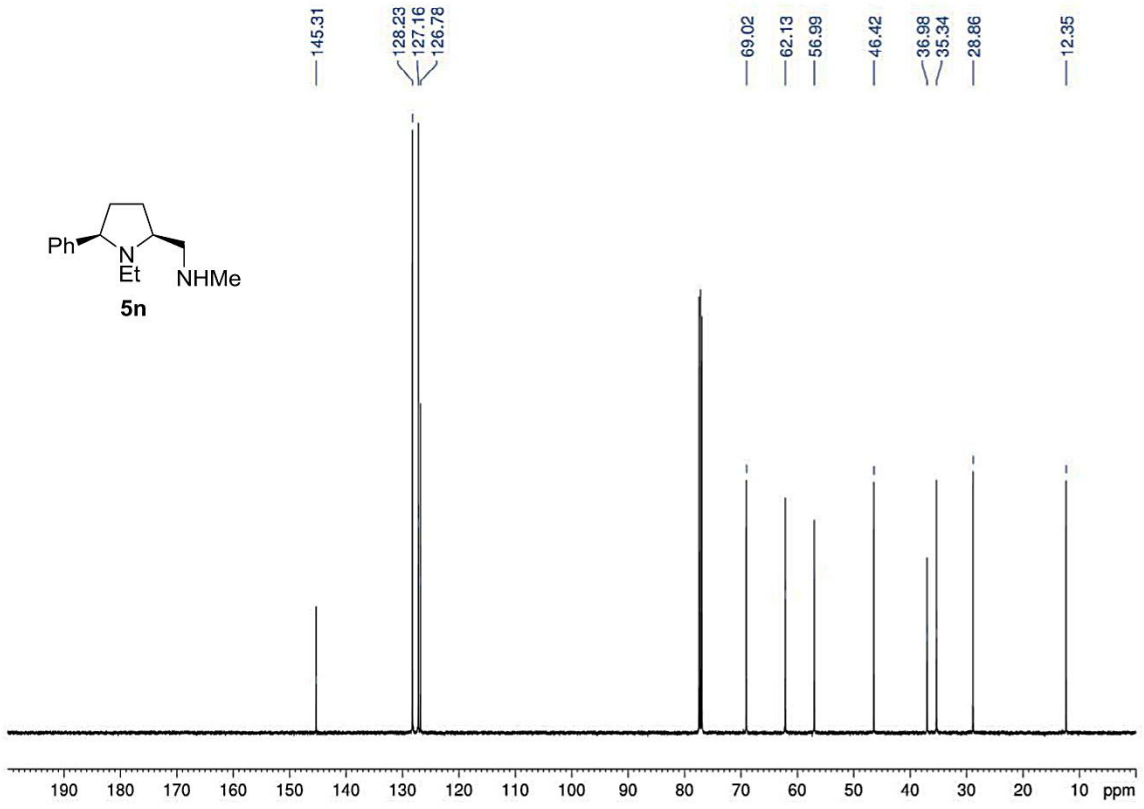

72.15
68.23
43.79
39.61
29.06
26.43
23.47
20.30
15.40
iPr
N
Me
NH2
5l
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


956.33
953.51
944.39
941.45
865.03
861.40
Bn
N
Me
NH2
5m
2.03
2.97
1.00
1.97
2.06
3.94
2.04
4.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

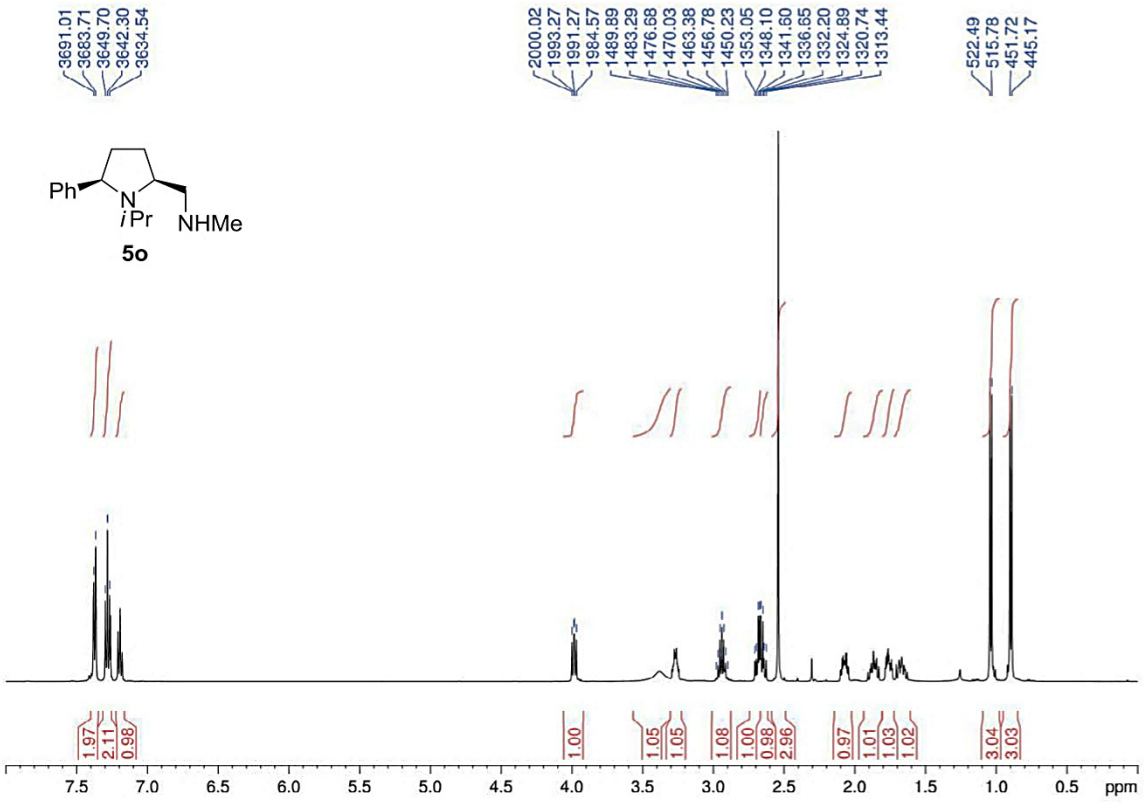

139.93
129.35
128.17
125.95
68.96
68.55
44.43
41.01
39.56
29.62
26.17
Bn
N
Me
NH2
5m
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

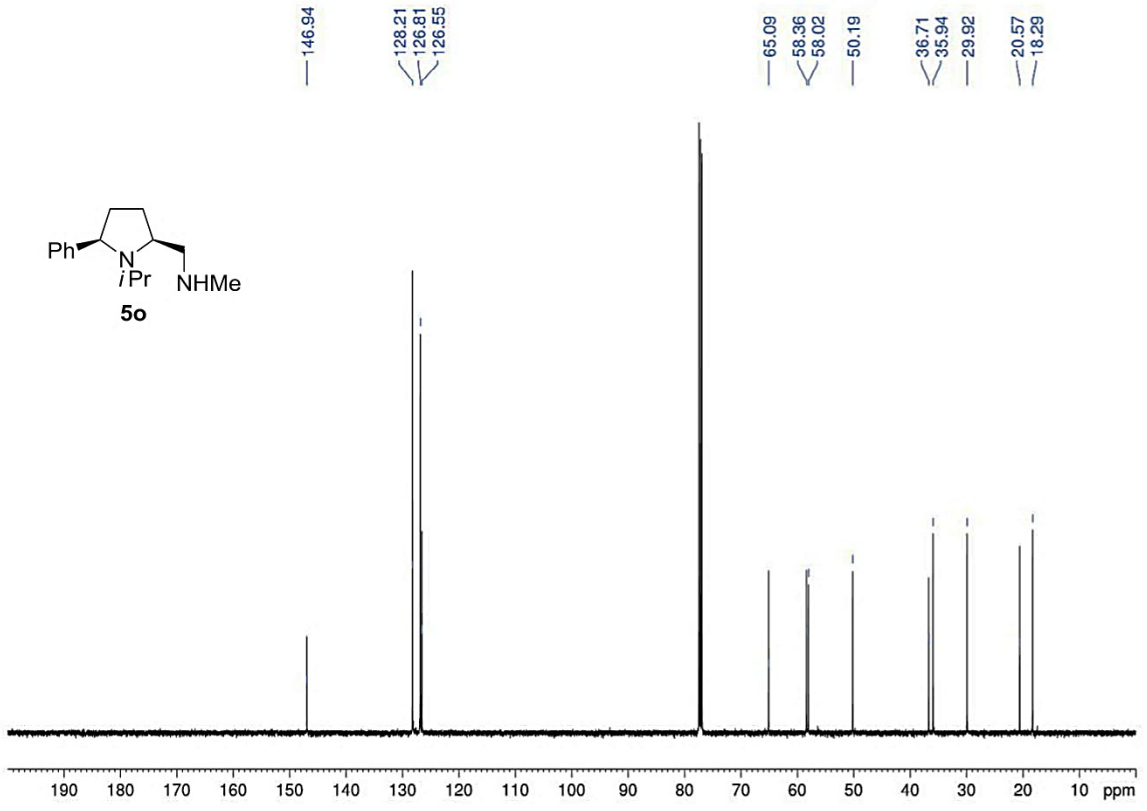
46


1852.53
1845.98
1843.38
1836.78
1365.00
1360.95
1353.60
1349.55
451.12
443.92
436.76
Ph
N
Et
NHMe
5n
1.97
1.99
0.99
1.01
1.05
1.04
4.02
3.00
1.02
1.05
1.03
1.04
3.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

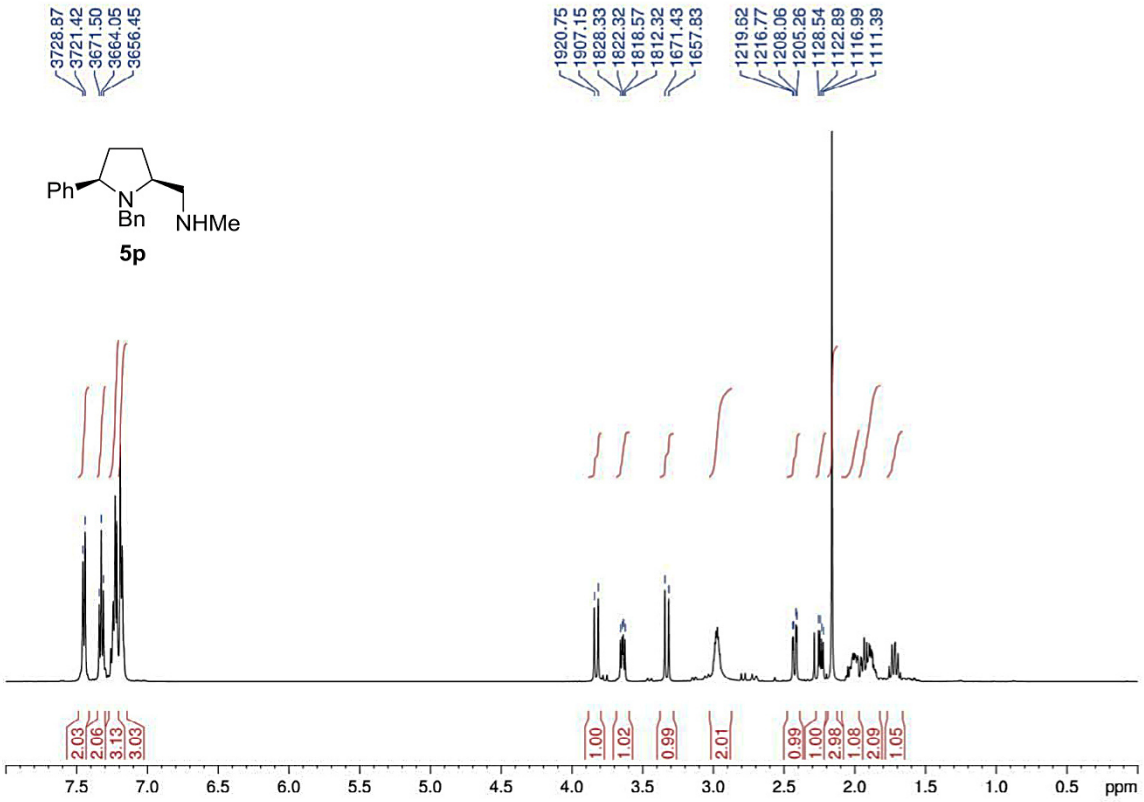

145.31
128.23
127.16
126.78
69.02
62.13
56.99
46.42
36.98
35.34
28.86
12.35
Ph
N
Et
NHMe
5n
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

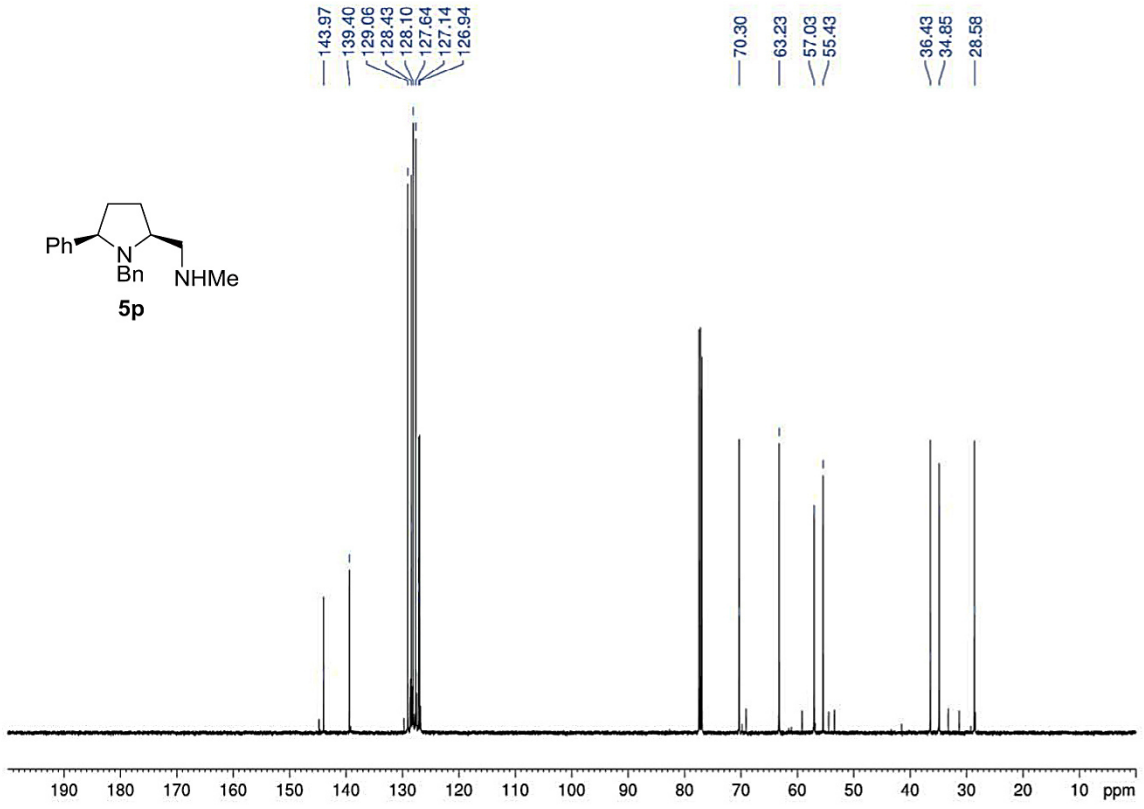
47


3691.01
3683.71
3649.70
3642.30
3634.54
2000.02
1993.27
1991.27
1984.57
1489.89
1483.29
1476.68
1470.03
1463.38
1456.78
1450.23
1353.05
1348.10
1341.60
1336.65
1332.20
1324.89
1320.74
1313.44
522.49
515.78
451.72
445.17
Ph
N
iPr
NHMe
5o
1.97
2.11
0.98
1.00
1.05
1.05
1.08
1.00
0.98
2.96
0.97
1.01
1.03
1.02
3.04
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

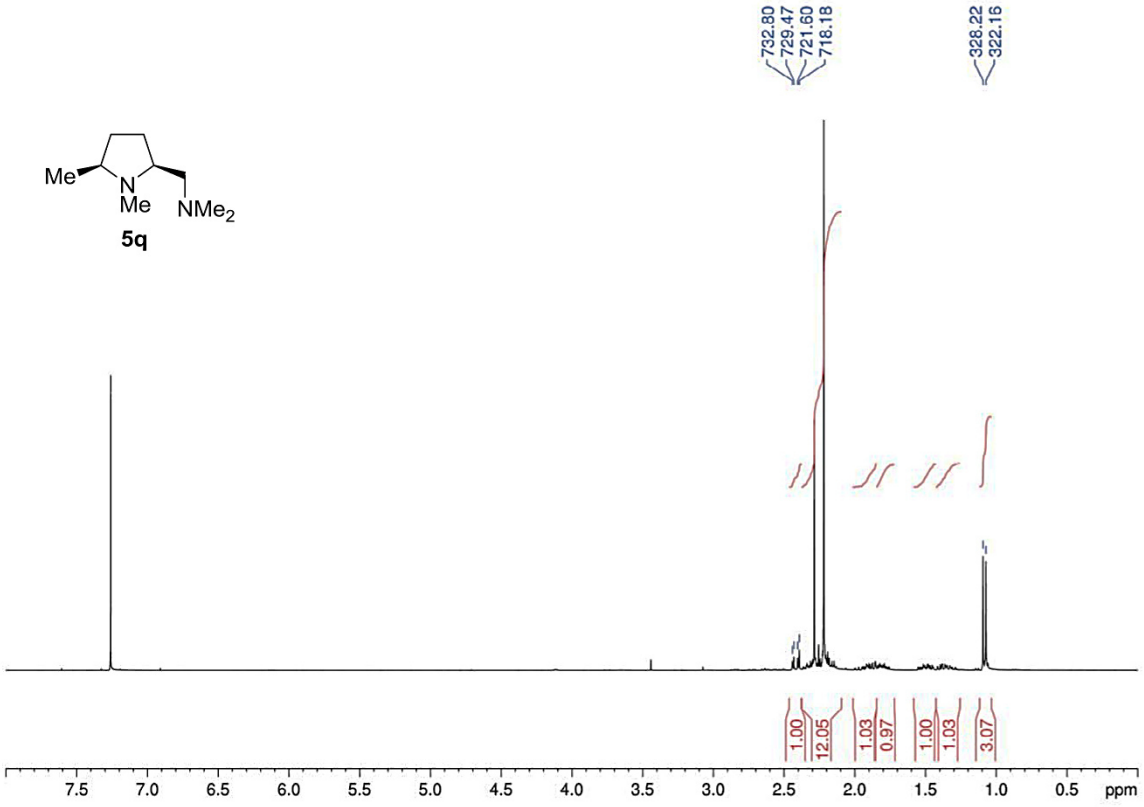

146.94
128.21
126.81
126.55
65.09
58.36
58.02
50.19
36.71
35.94
29.92
20.57
18.29
Ph
N
iPr
NHMe
5o
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

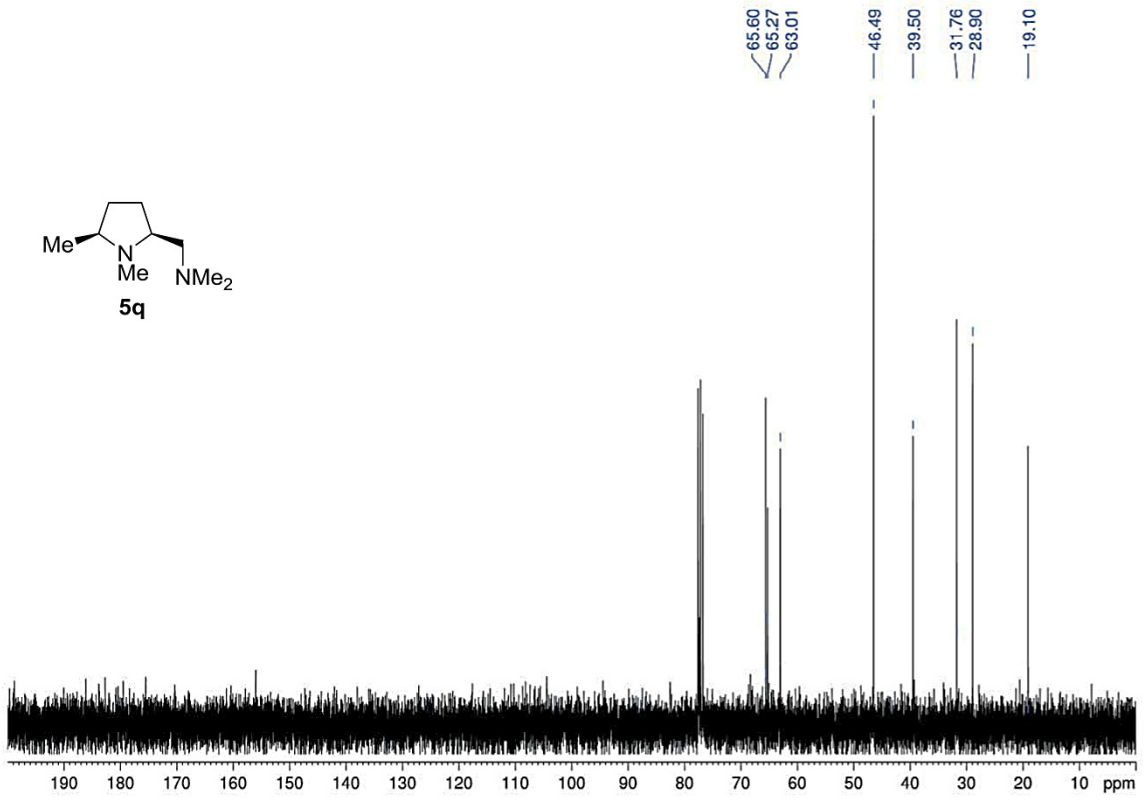
48


3728.87
3721.42
3671.50
3664.05
3656.45
1920.75
1907.15
1828.33
1822.32
1818.57
1812.32
1671.43
1657.83
1219.62
1216.77
1208.06
1205.26
1128.54
1122.89
1116.99
1111.39
Ph
N
Bn
NHMe
5p
2.03
2.06
3.13
3.03
1.00
1.02
0.99
2.01
0.99
1.00
2.98
1.08
2.09
1.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

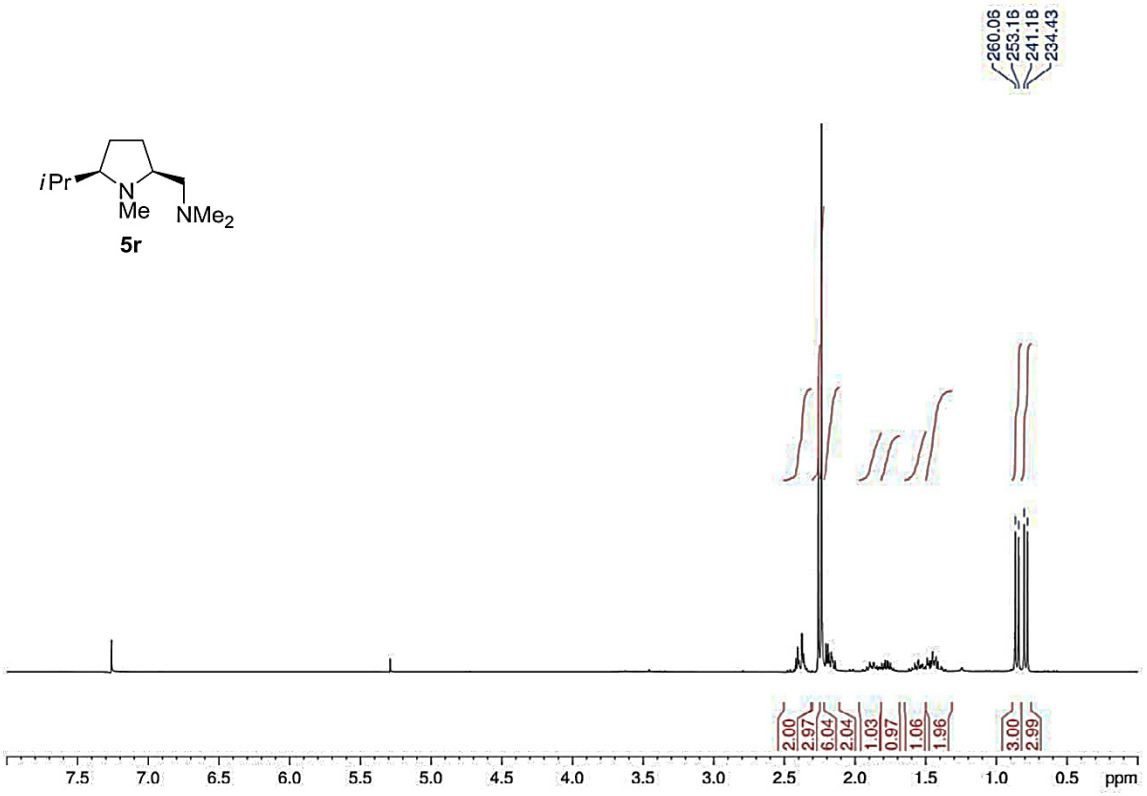

143.97
139.40
129.06
128.43
128.10
127.64
127.14
126.94
70.30
63.23
57.03
55.43
36.43
34.85
28.58
Ph
N
Bn
NHMe
5p
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

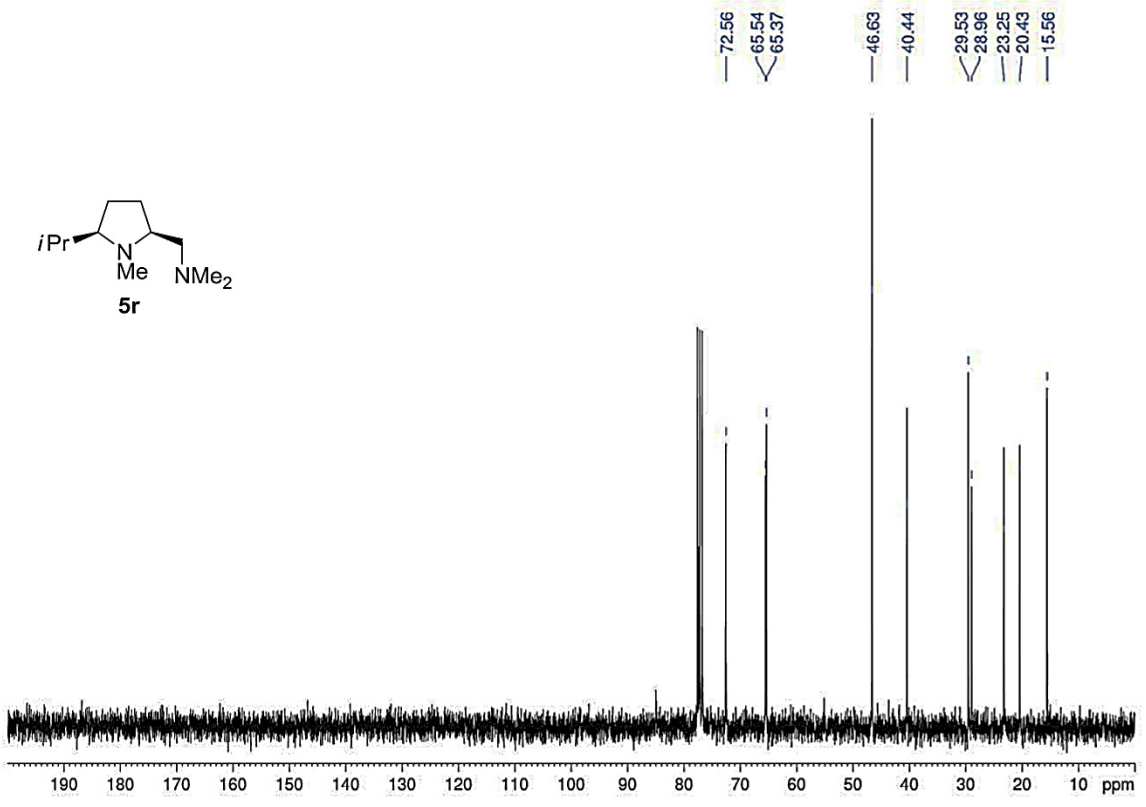
49

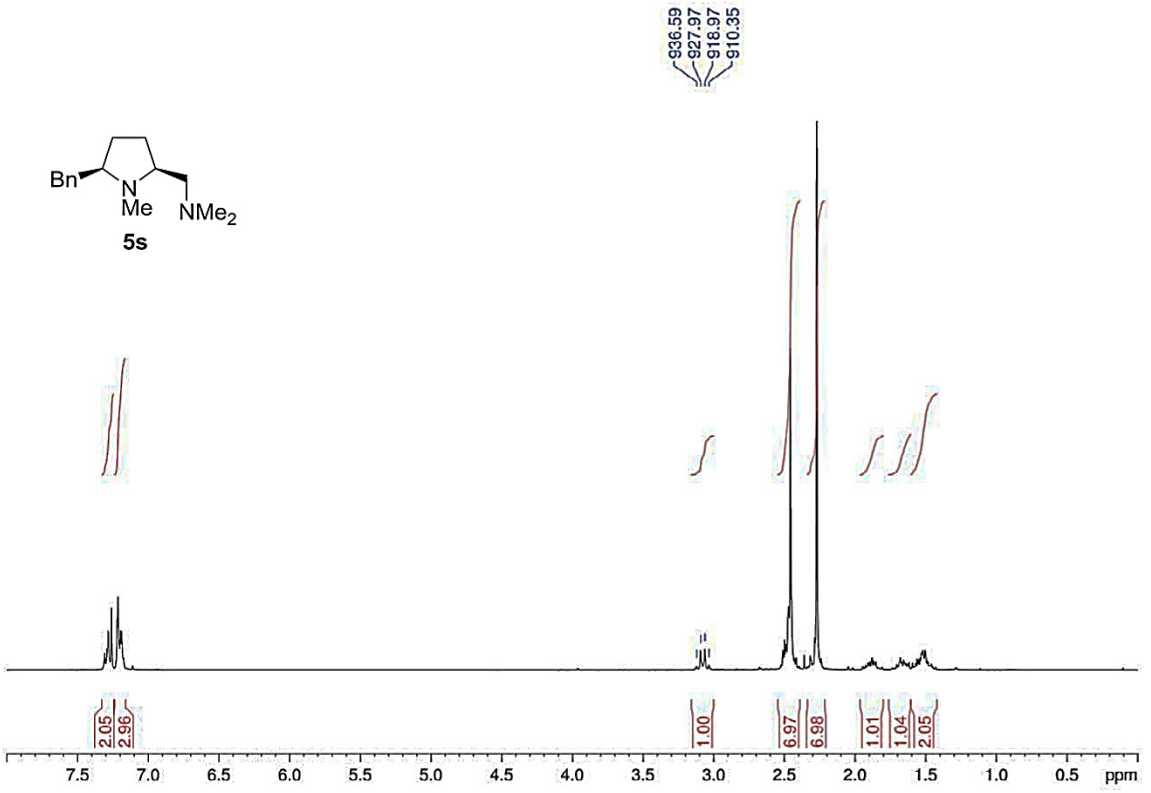

732.80
729.47
721.60
718.18
328.22
322.16
Me
N
Me
NMe2
5q
1.00
12.05
1.03
0.97
1.00
1.03
3.07
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

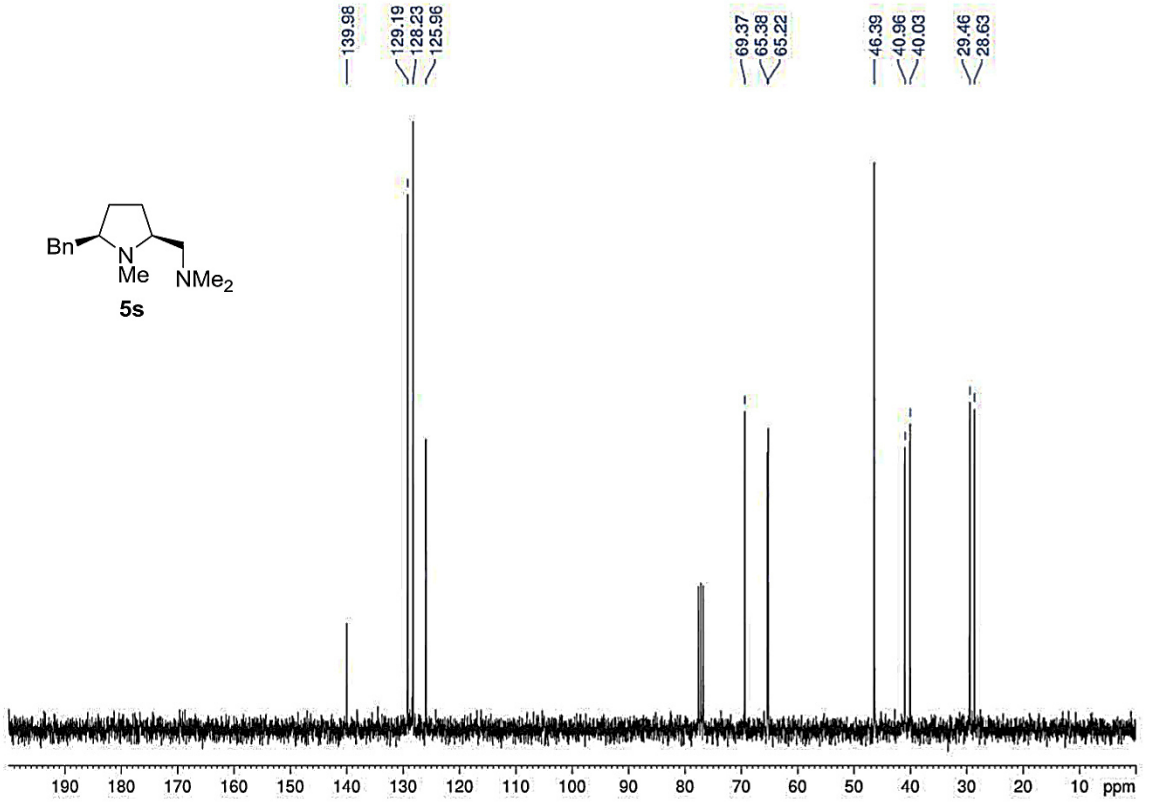

65.60
65.27
63.01
46.49
39.50
31.76
28.90
19.10
Me
N
Me
NMe2
5q
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

50

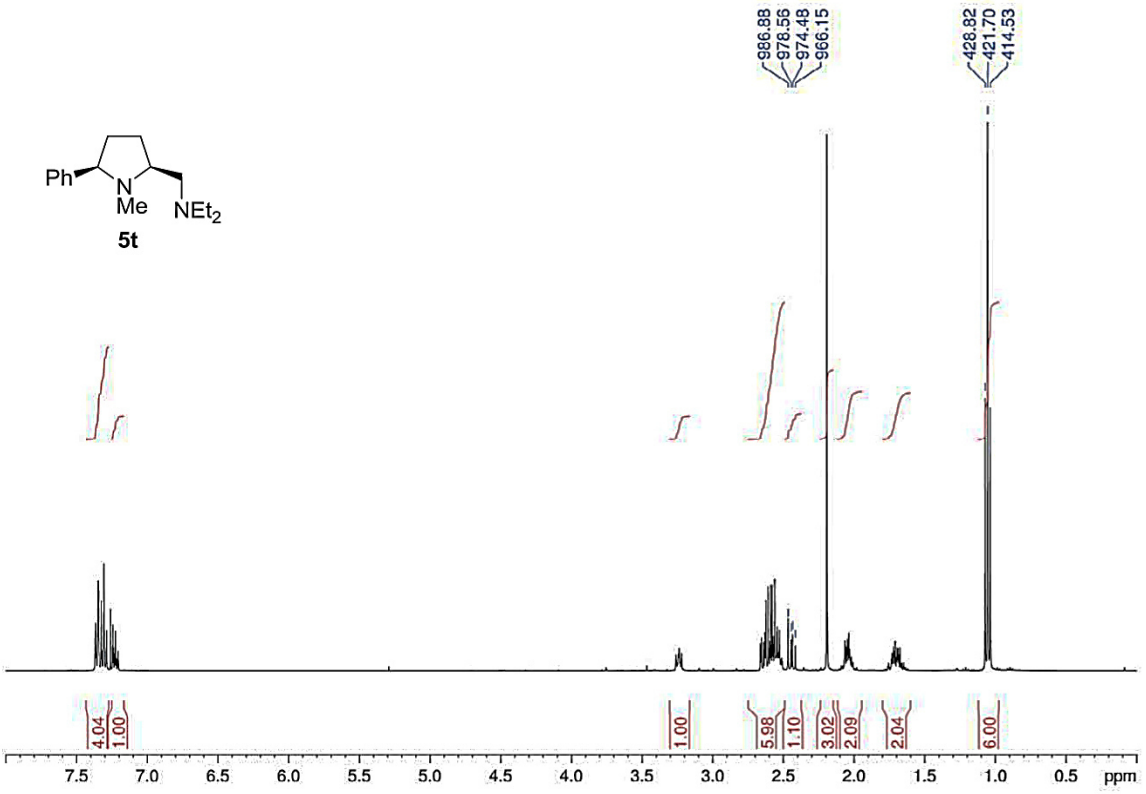

260.06
253.16
241.18
234.43
iPr
N
Me
NMe2
5r
2.00
2.97
6.04
2.04
1.03
0.97
1.06
1.96
3.00
2.99
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

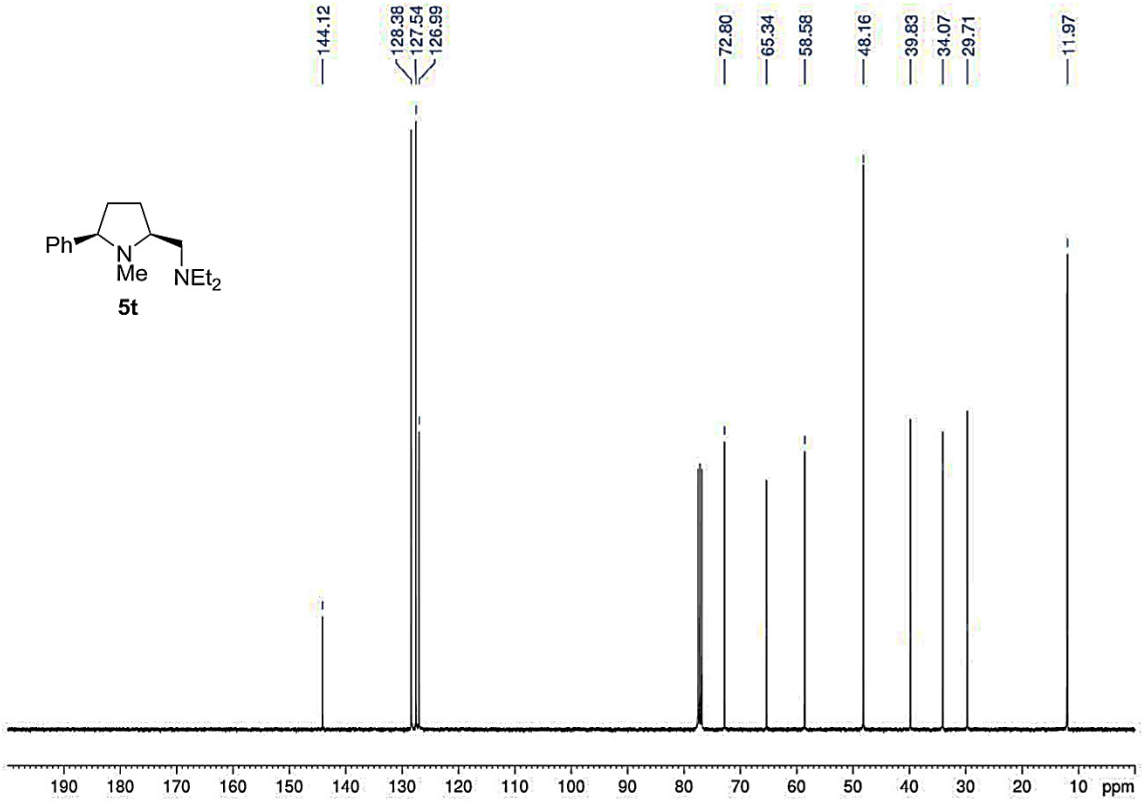

72.56
65.54
65.37
46.63
40.44
29.53
28.96
23.25
20.43
15.56
iPr
N
Me
NMe2
5r
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

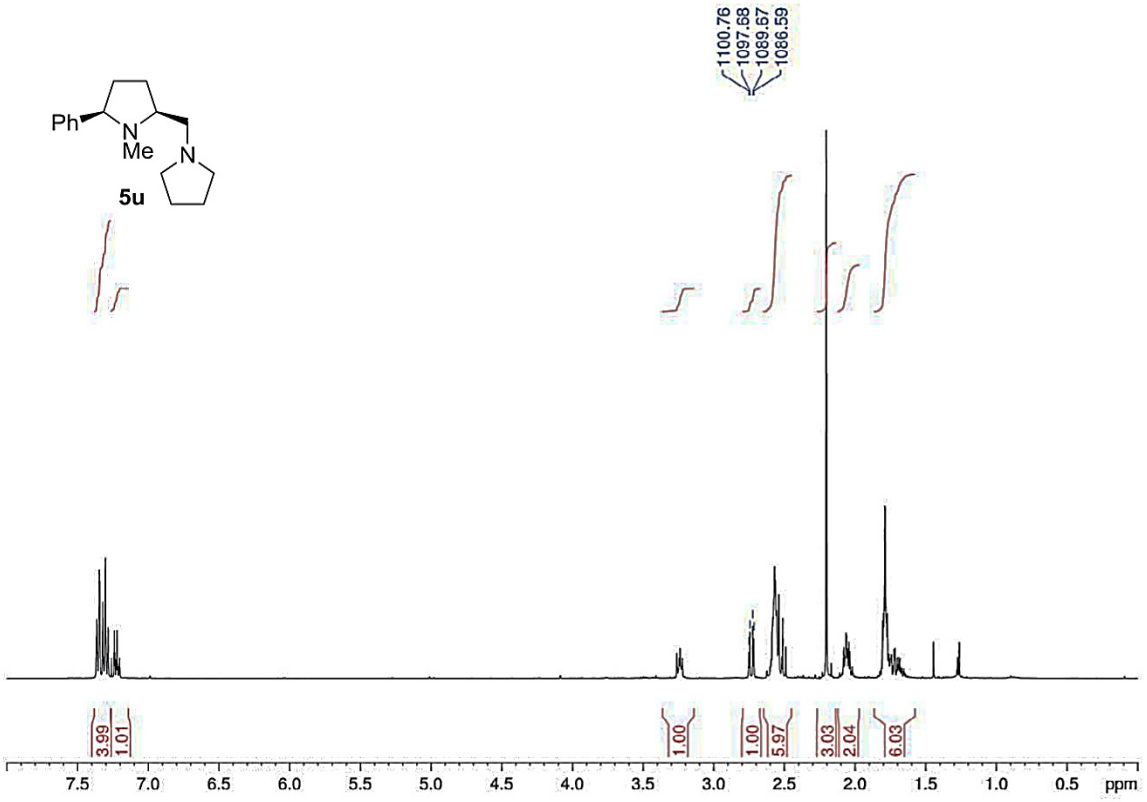

936.59
927.97
918.97
910.35
Bn
N
Me
NMe2
5s
2.05
2.96
1.00
6.97
6.98
1.01
1.04
2.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

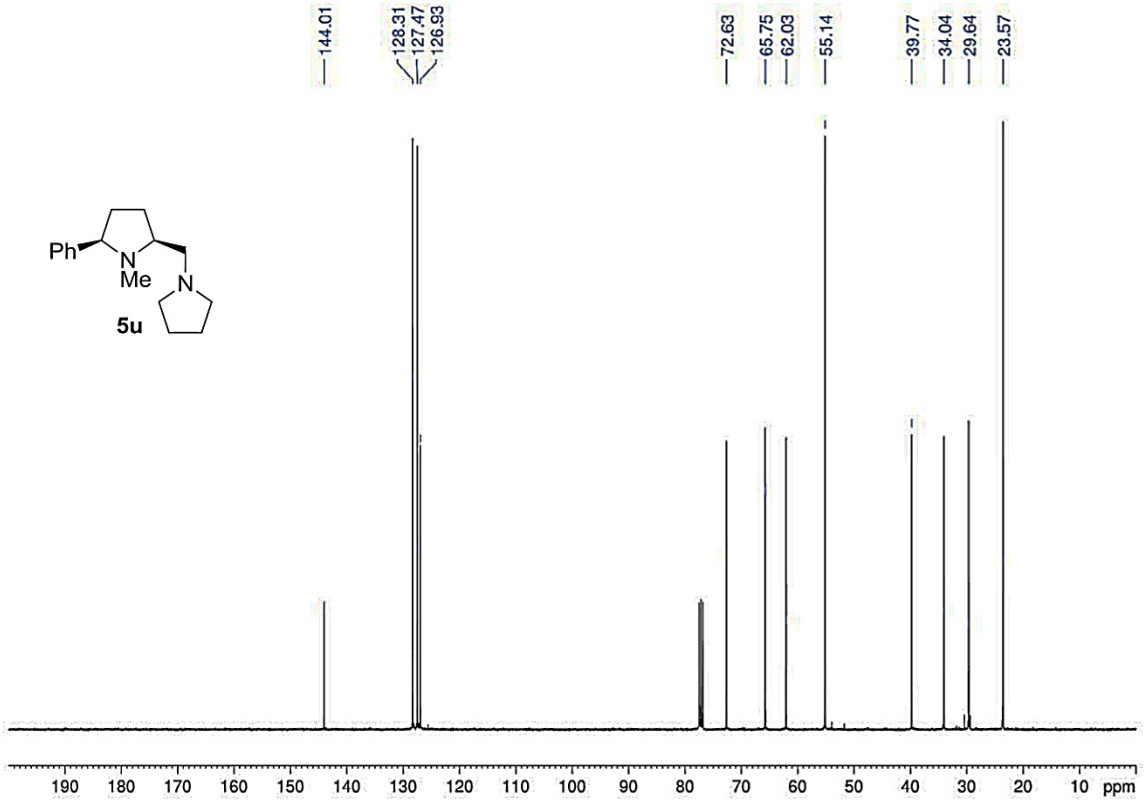

139.98
129.19
128.23
125.96
69.37
65.38
65.22
46.39
40.96
40.03
29.46
28.63
Bn
N
Me
NMe2
5s
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

52

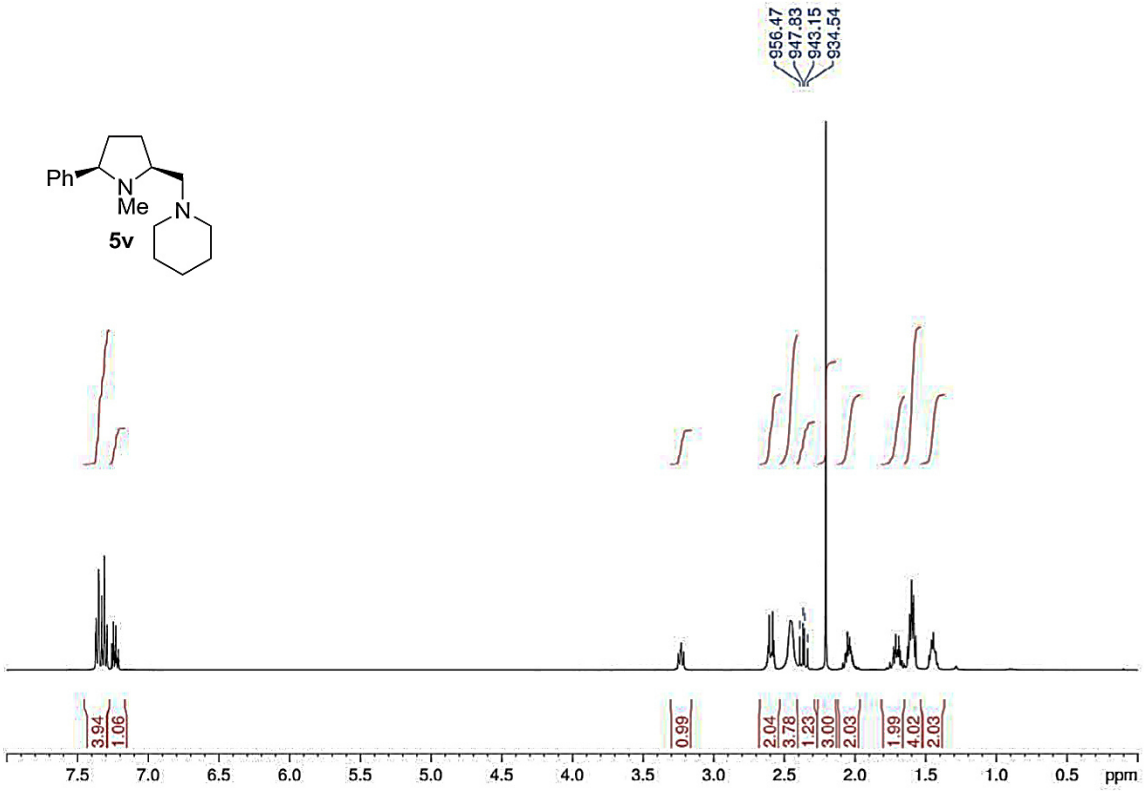

986.88
978.56
974.48
966.15
428.82
421.70
414.53
Ph
N
Me
NEt2
5t
4.04
1.00
1.00
5.98
1.10
3.02
2.09
2.04
6.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

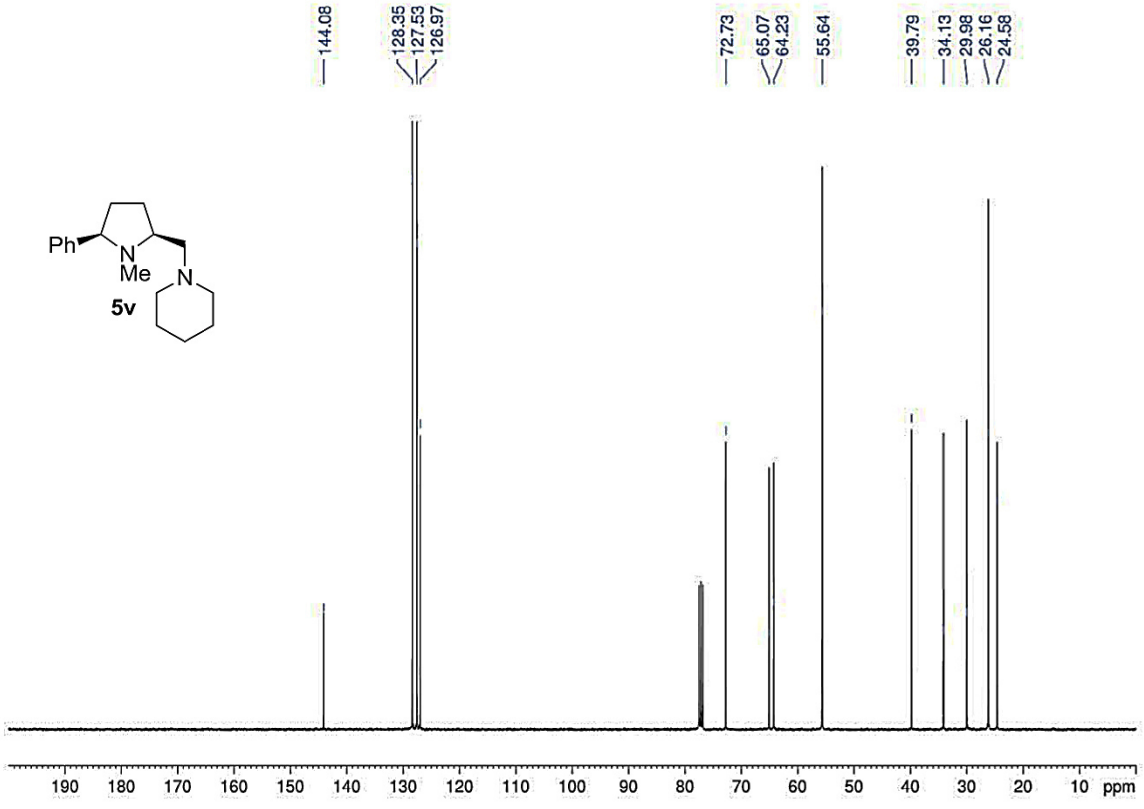

144.12
128.38
127.54
126.99
72.80
65.34
58.58
48.16
39.83
34.07
29.71
11.97
Ph
N
Me
NEt2
5t
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Ph
N
Me
N
5u
1100.76
1097.68
1089.67
1086.59
3.99
1.01
1.00
1.00
5.97
3.03
2.04
6.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

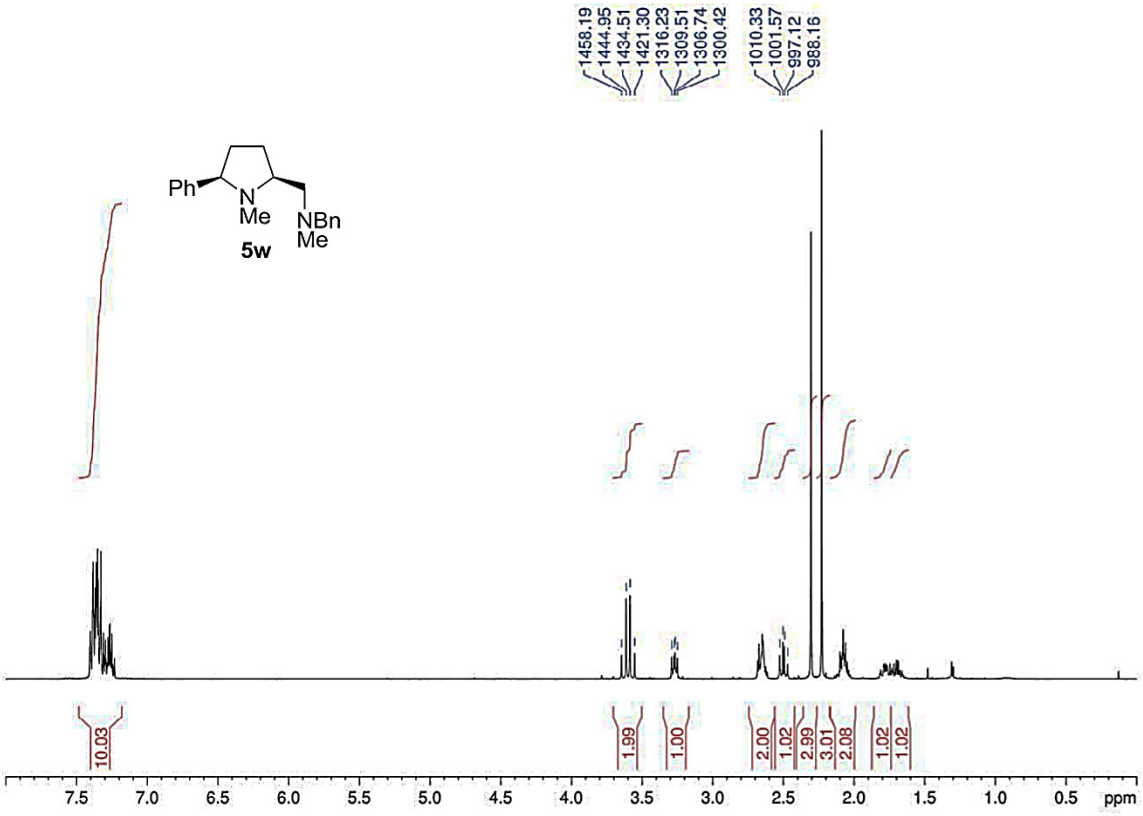

144.01
128.31
127.47
126.93
72.63
65.75
62.03
55.14
39.77
34.04
29.64
23.57
Ph
N
Me
N
5u
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

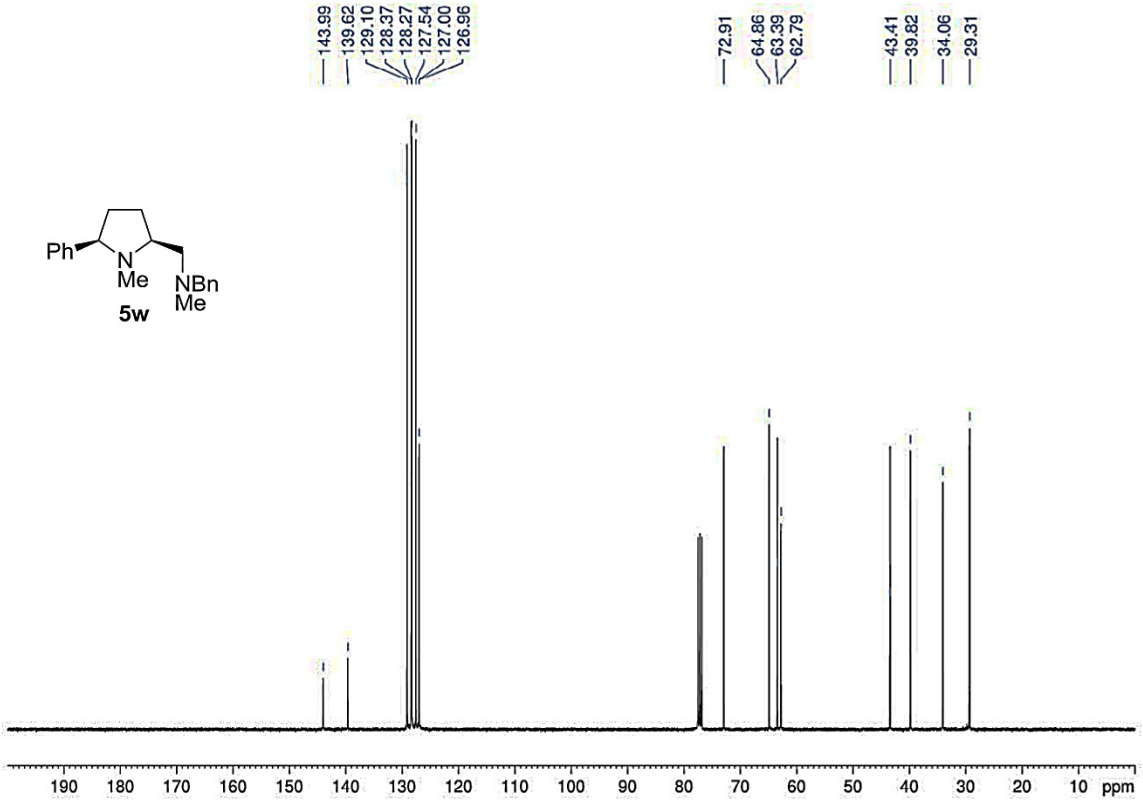
54


956.47
947.83
943.15
934.54
Ph
N
Me
N
5v
3.94
1.06
0.99
2.04
3.78
1.23
3.00
2.03
1.99
4.02
2.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

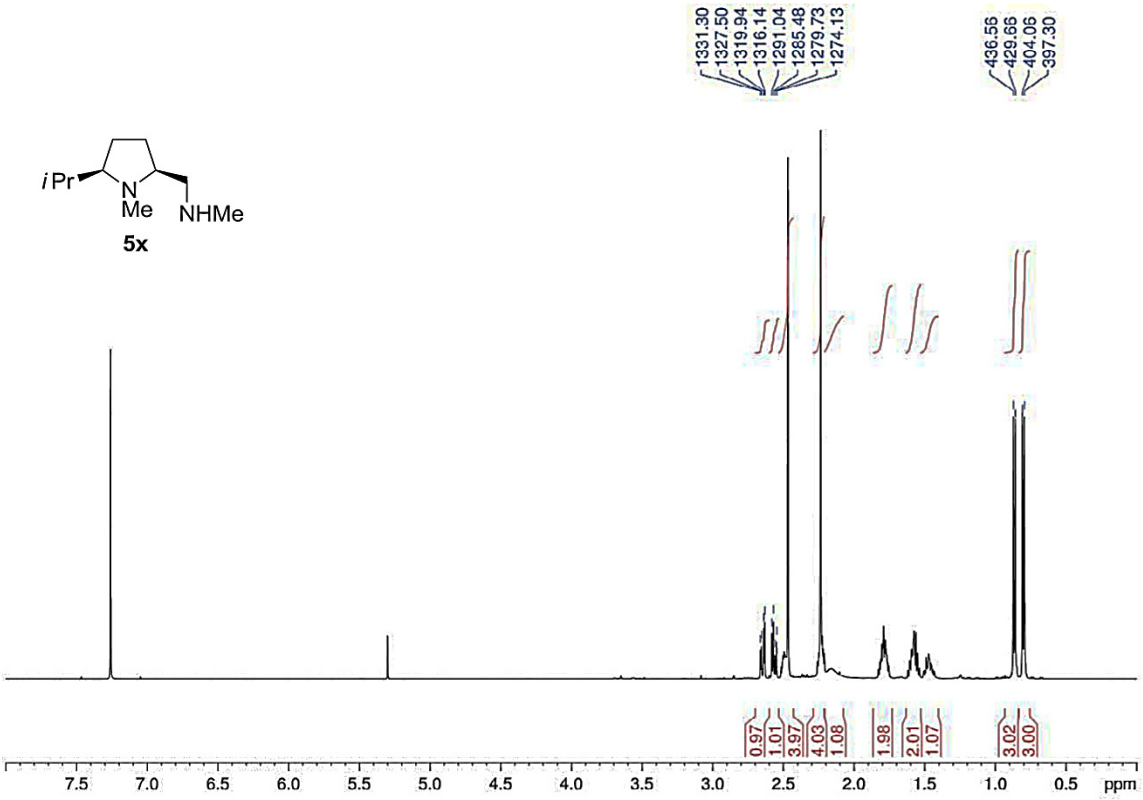

144.08
128.35
127.53
126.97
72.73
65.07
64.23
55.64
39.79
34.13
29.98
26.16
24.58
Ph
N
Me
N
5v
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

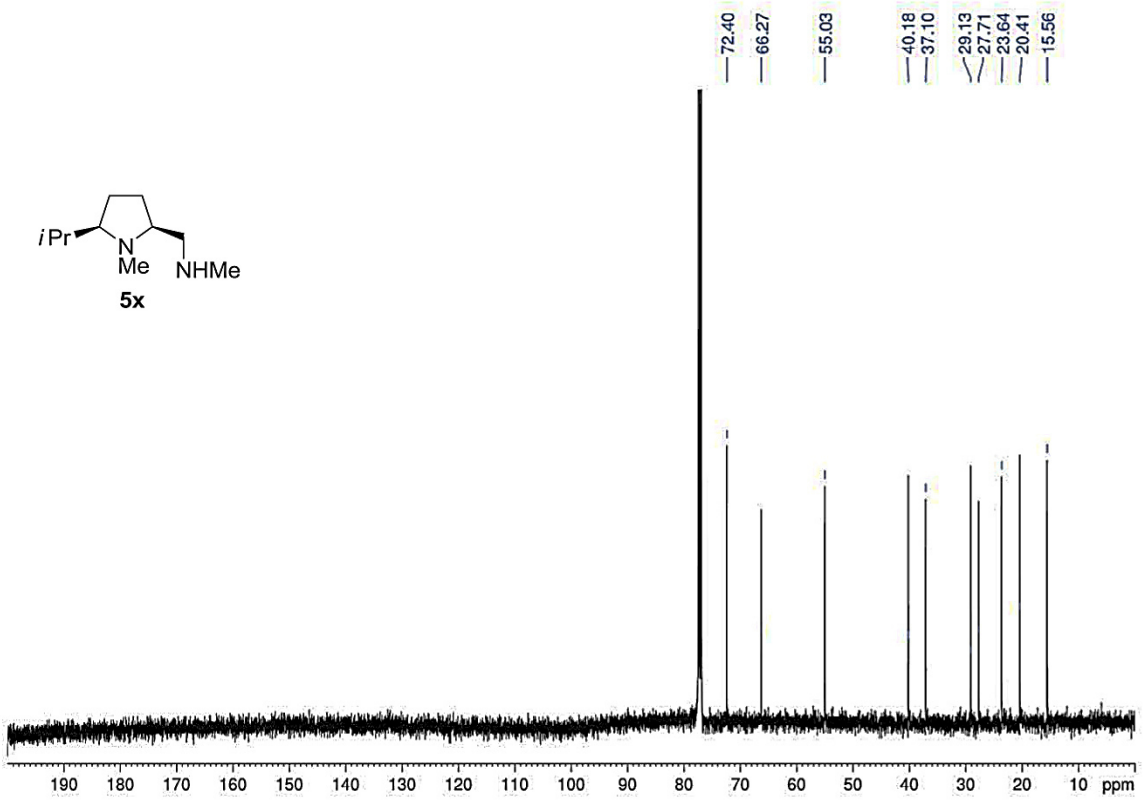
55


1458.19
1444.95
1434.51
1421.30
1316.23
1309.51
1306.74
1300.42
1010.33
1001.57
997.12
988.16
Ph
N
Me
NBn
Me
5w
10.03
1.99
1.00
2.00
1.02
2.99
3.01
2.08
1.02
1.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

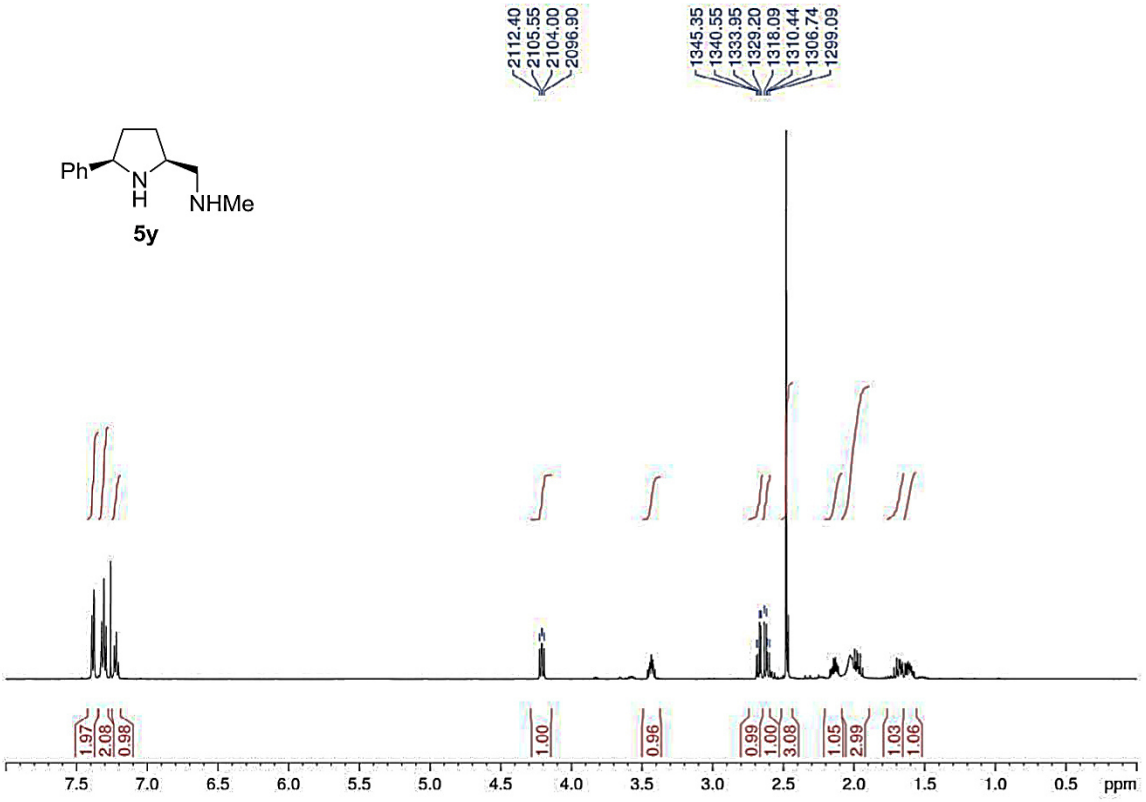

143.99
139.62
129.10
128.37
128.27
127.54
127.00
126.96
72.91
64.86
63.39
62.79
43.41
39.82
34.06
29.31
Ph
N
Me
NBn
Me
5w
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

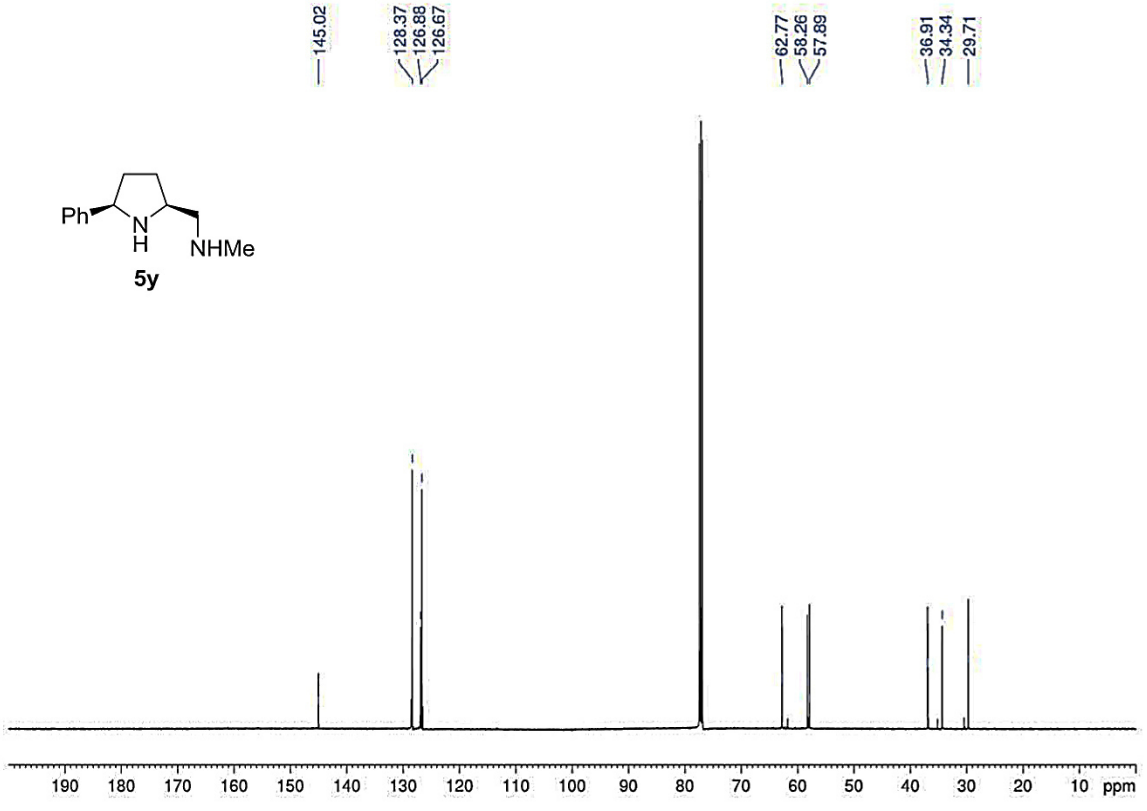
56


1331.30
1327.50
1319.94
1316.14
1291.04
1285.48
1279.73
1274.13
436.56
429.66
404.06
397.30
*i*Pr
N
Me
NHMe
5x
0.97
1.01
3.97
4.03
1.08
1.98
2.01
1.07
3.02
3.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

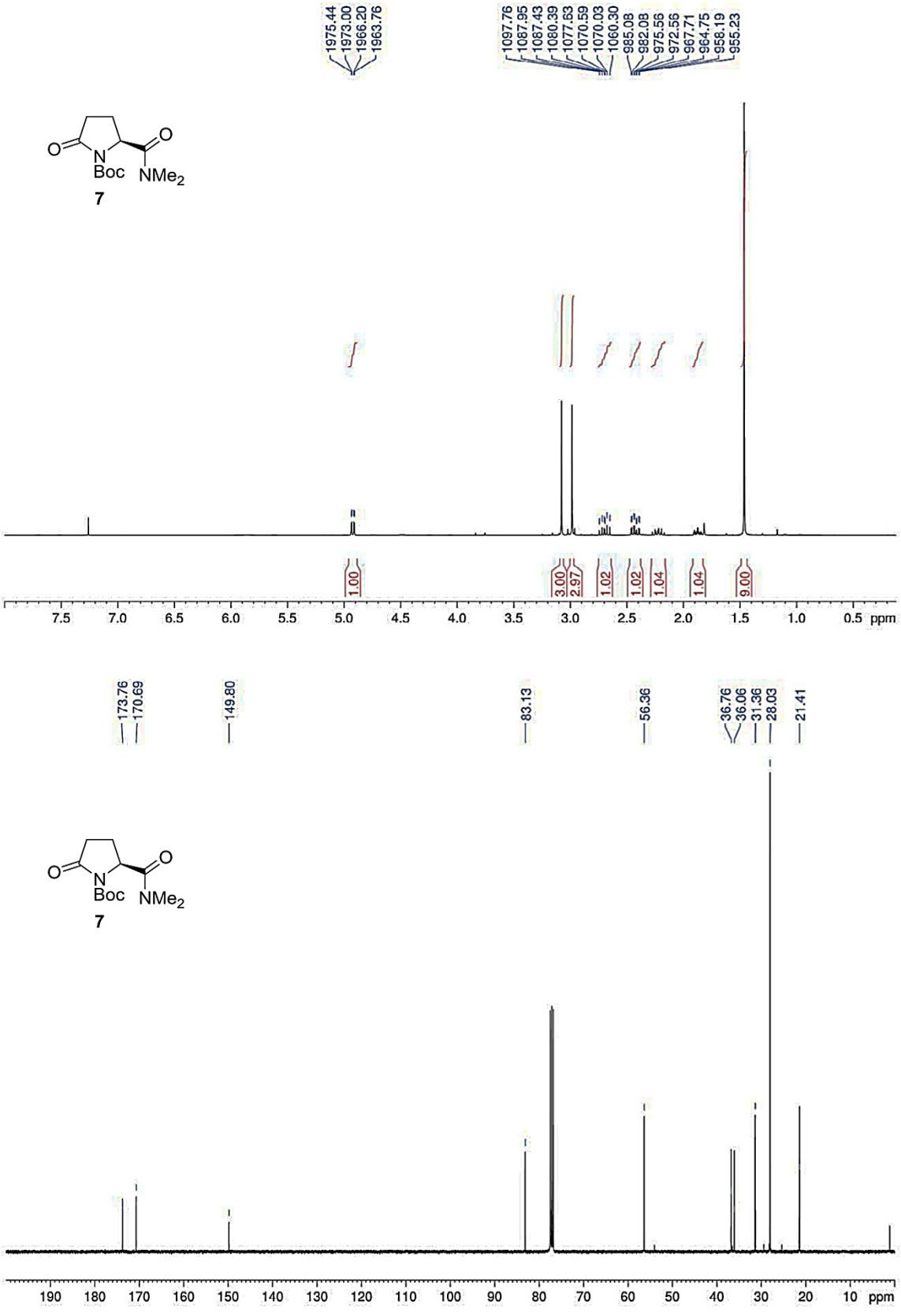

72.40
66.27
55.03
40.18
37.10
29.13
27.71
23.64
20.41
15.56
*i*Pr
N
Me
NHMe
5x
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

57

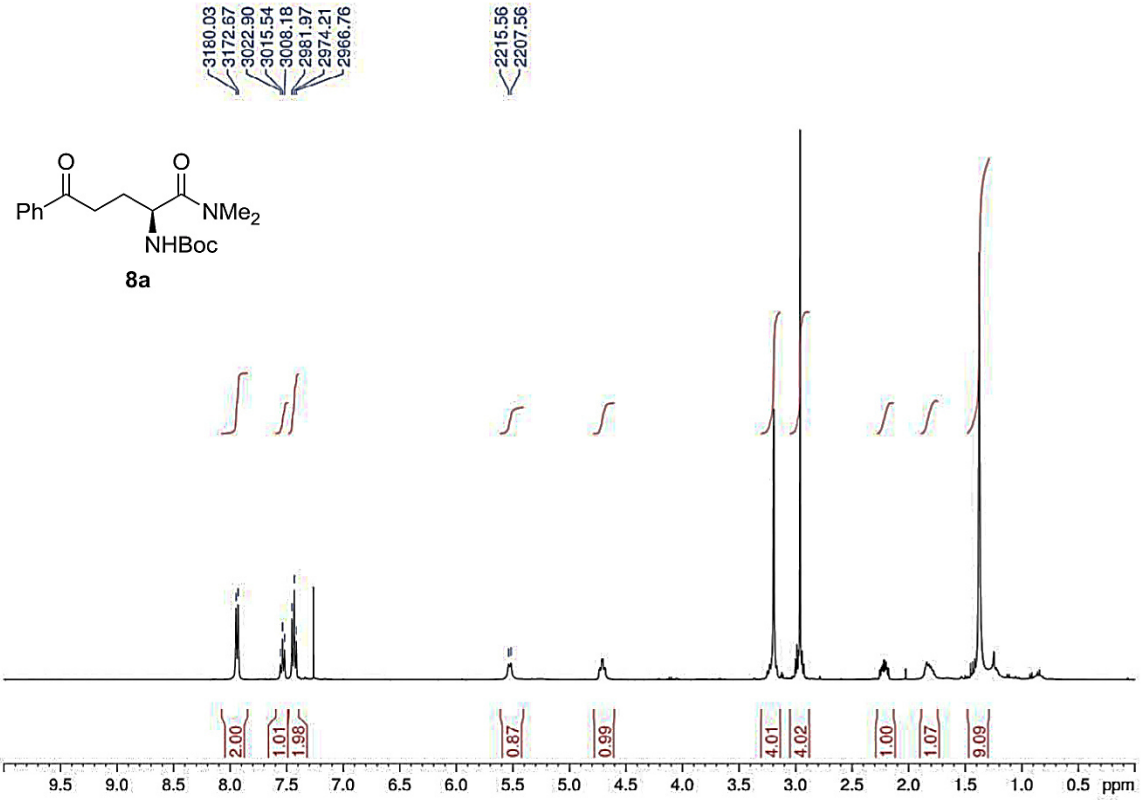

2112.40
2105.55
2104.00
2096.90
1345.35
1340.55
1333.95
1329.20
1318.09
1310.44
1306.74
1299.09
Ph
N
H
NHMe
5y
1.97
2.08
0.98
1.00
0.96
0.99
1.00
3.08
1.05
2.99
1.03
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

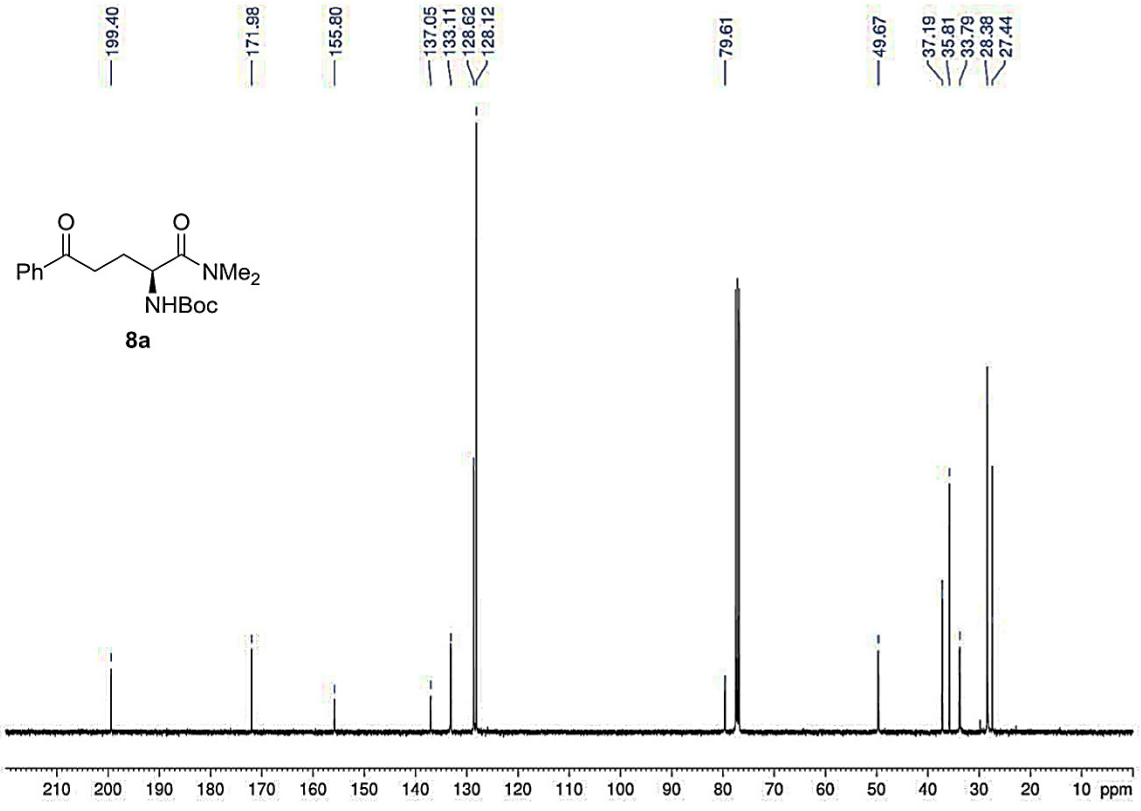

145.02
128.37
126.88
126.67
62.77
58.26
57.89
36.91
34.34
29.71
Ph
N
H
NHMe
5y
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

58

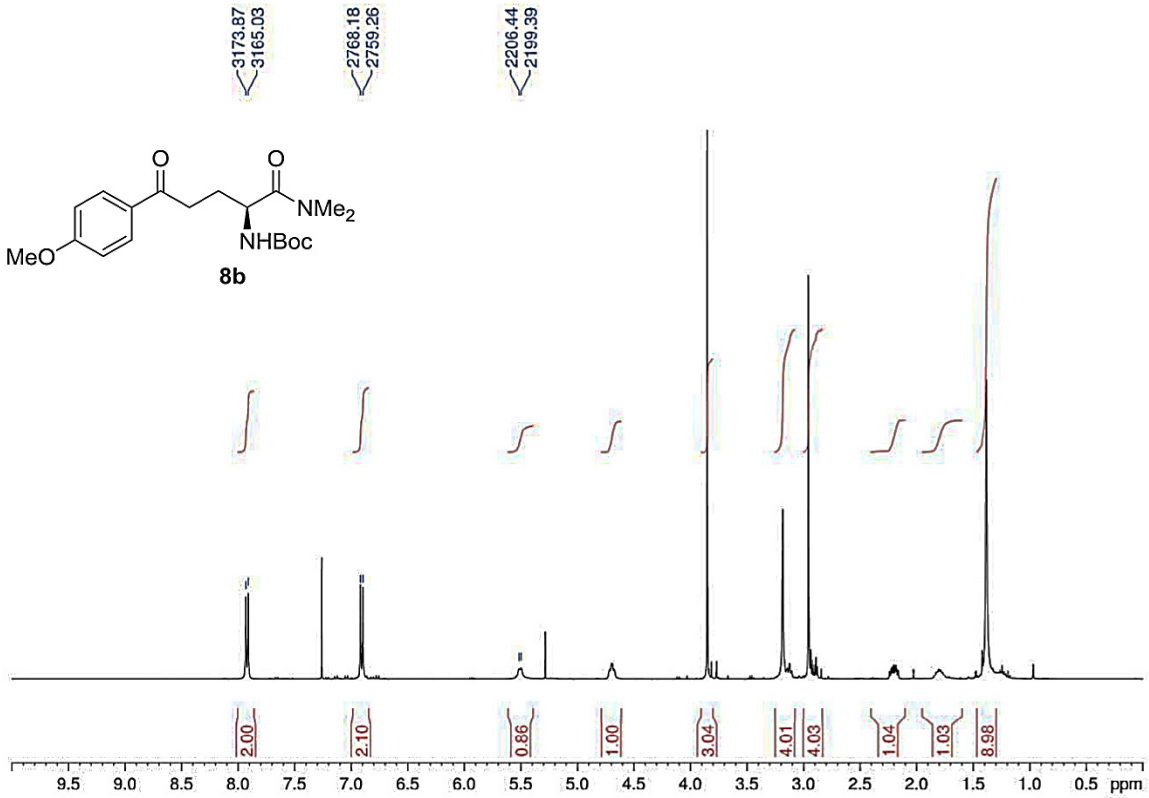

1975.44
1973.00
1966.20
1963.76
1097.76
1087.95
1087.43
1080.39
1077.53
1070.59
1070.03
1060.30
985.08
982.08
975.56
972.56
967.71
964.75
958.19
955.23
O
O
N
Boc
NMe2
7
1.00
3.00
2.97
1.02
1.02
1.04
1.04
9.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
173.76
170.69
149.80
83.13
56.36
36.76
36.06
31.36
28.03
21.41
O
O
N
Boc
NMe2
7
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

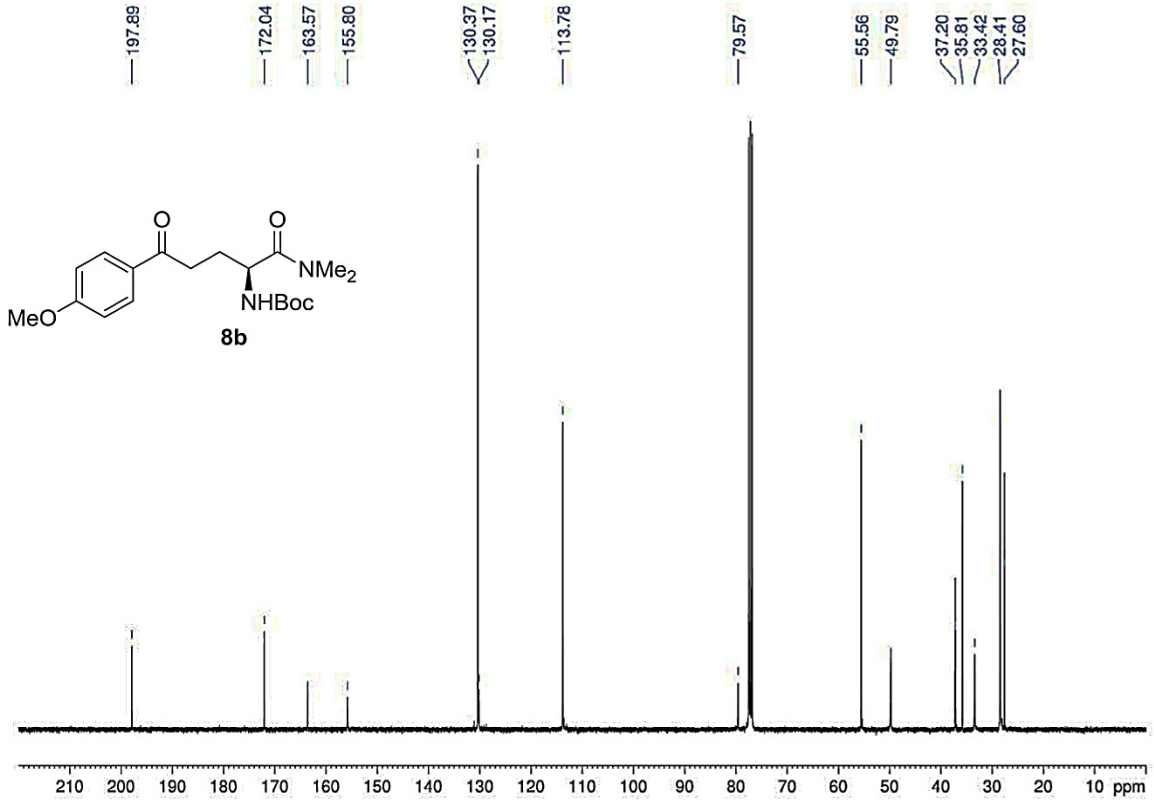
59


3180.03
3172.57
3022.90
3015.54
3008.18
2981.97
2974.21
2966.76
2215.56
2207.56
Ph
O
O
NMe2
NHBoc
8a
2.00
1.01
1.98
0.87
0.99
4.01
4.02
1.00
1.07
9.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

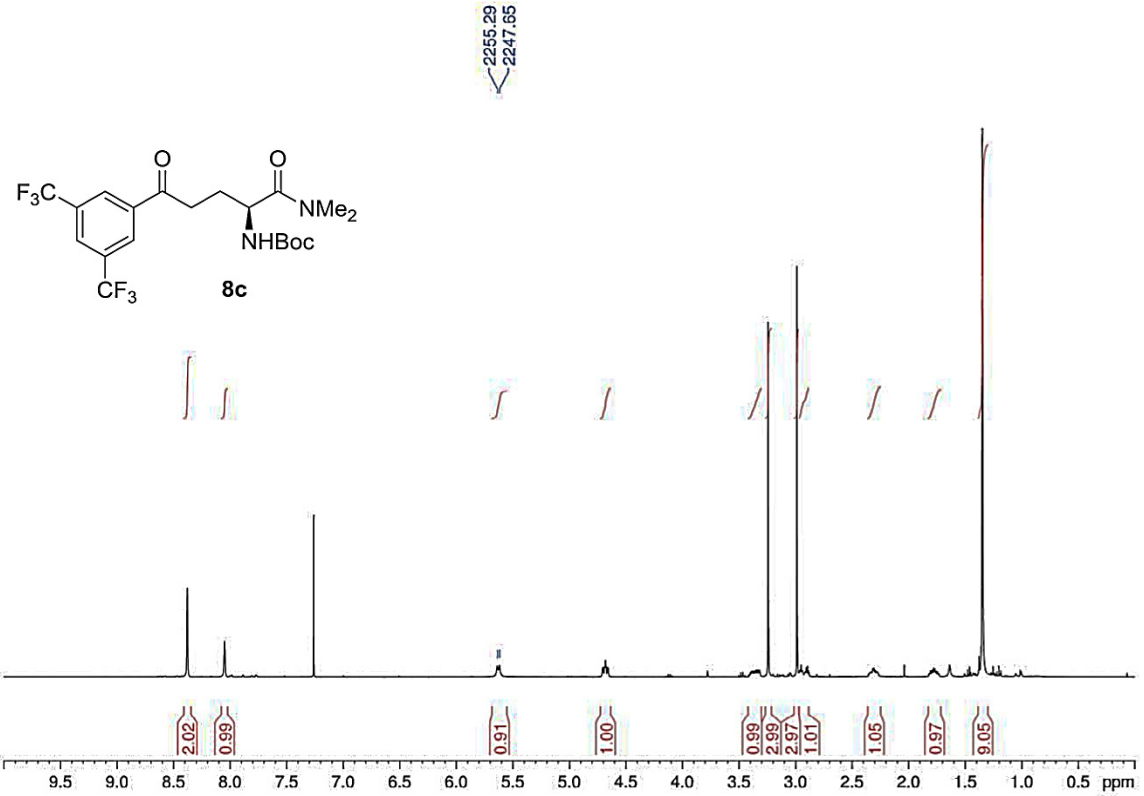

199.40
171.98
155.80
137.05
133.11
128.62
128.12
79.61
49.67
37.19
35.81
33.79
28.38
27.44
Ph
O
O
NMe2
NHBoc
8a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

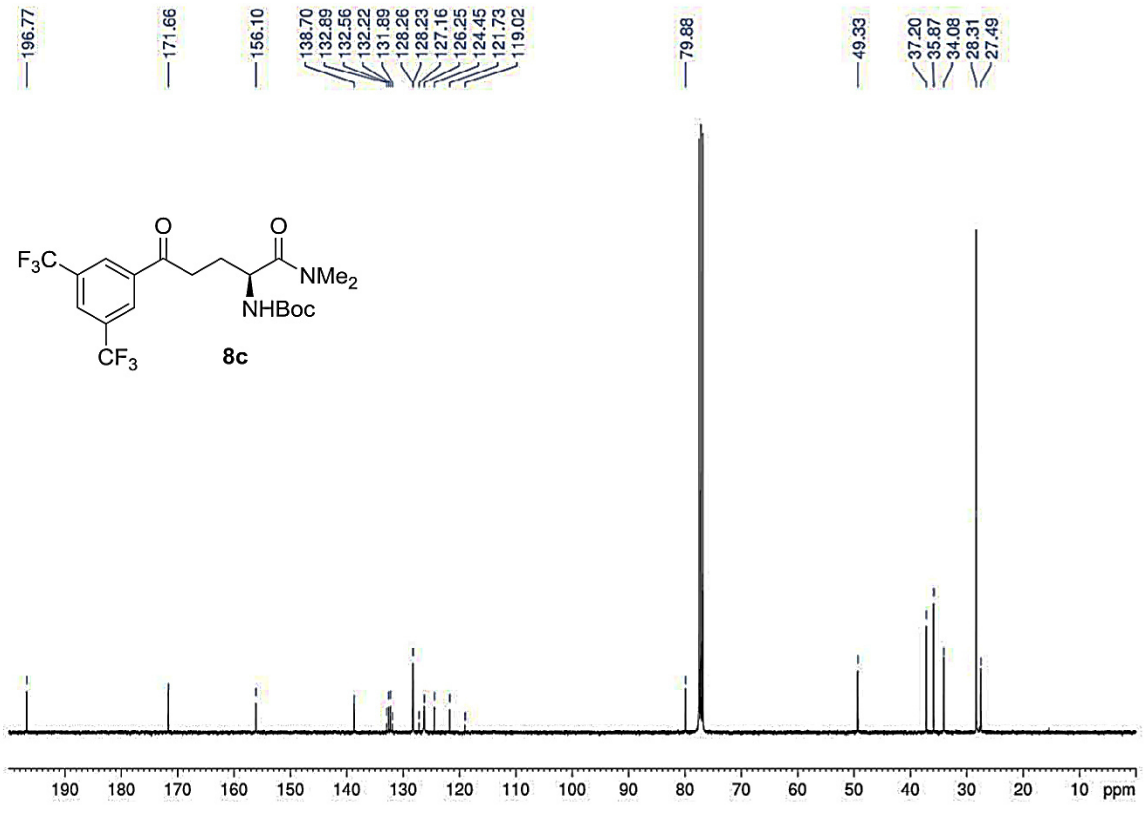
60


3173.87
3165.03
2768.18
2759.26
2206.44
2199.39
O
O
NMe2
NHBoc
MeO
8b
2.00
2.10
0.86
1.00
3.04
4.01
4.03
1.04
1.03
8.98
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

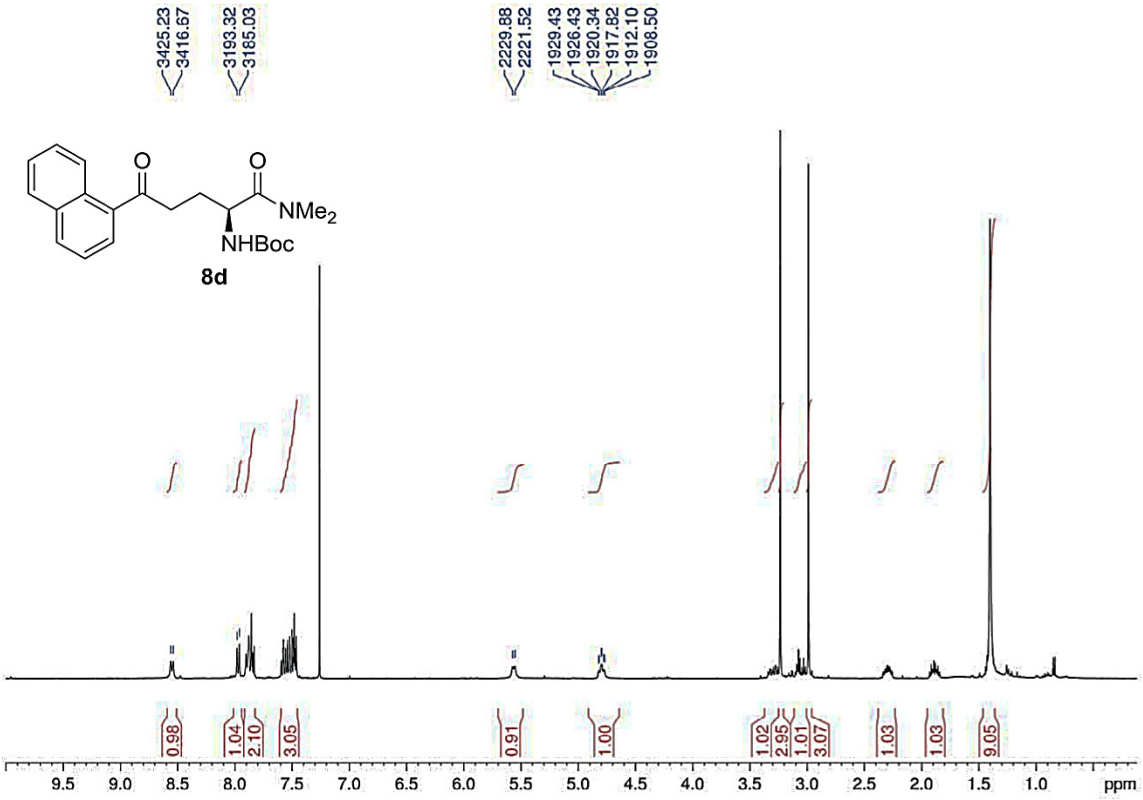

197.89
172.04
163.57
155.80
130.37
130.17
113.78
79.57
55.56
49.79
37.20
35.81
33.42
28.41
27.60
O
O
NMe2
NHBoc
MeO
8b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

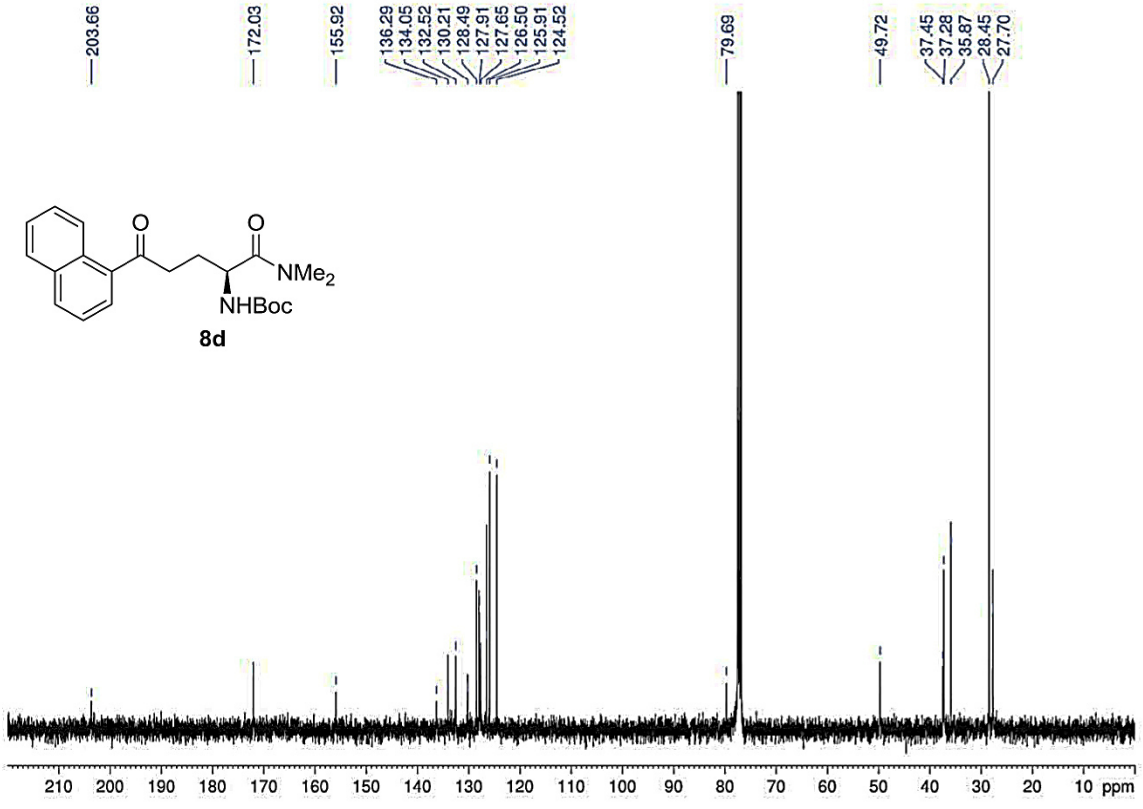
61

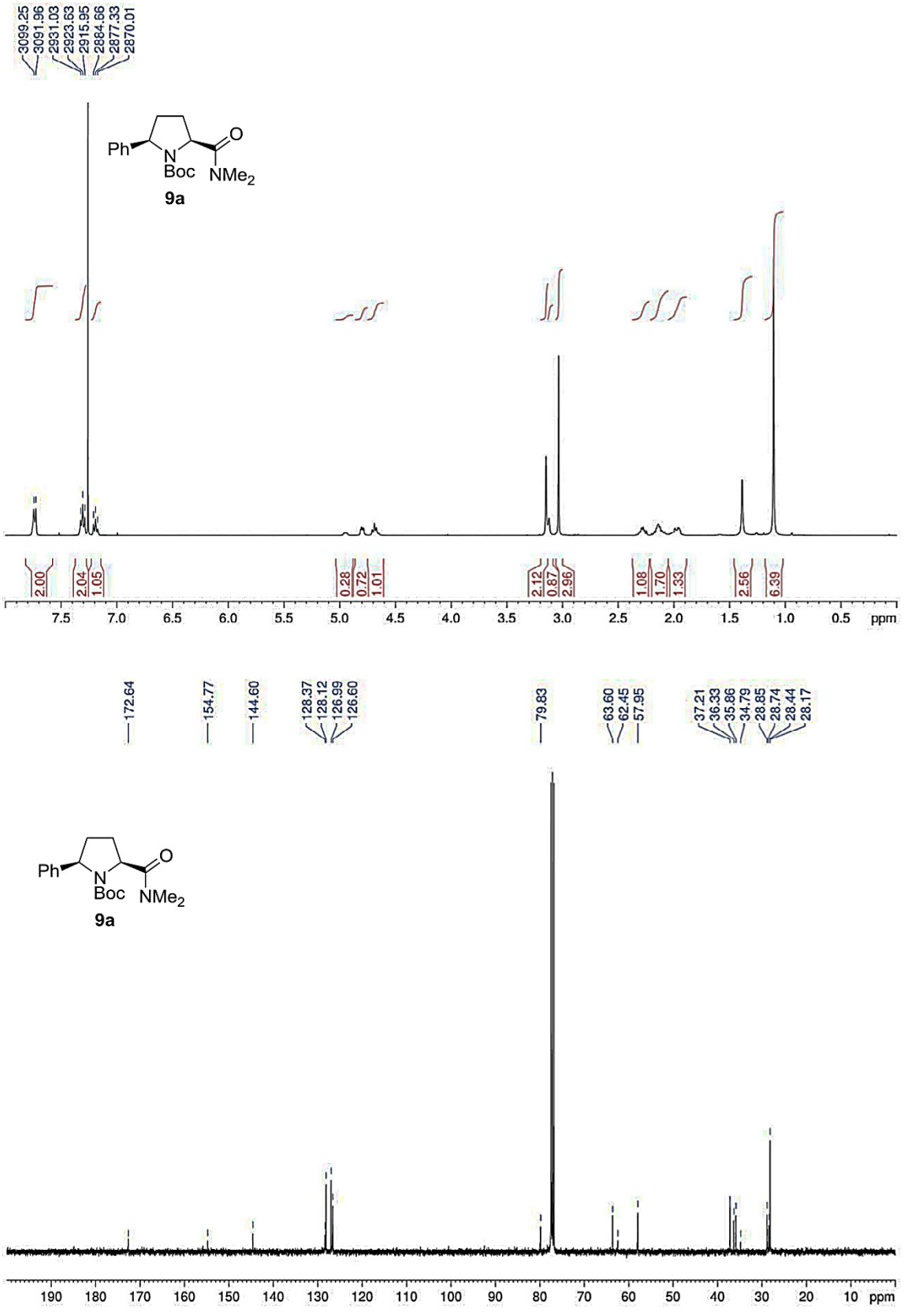

2255.29
2247.65
F3C
O
O
NMe2
NHBoc
CF3
8c
2.02
0.99
0.91
1.00
0.99
2.99
2.97
1.01
1.05
0.97
9.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


196.77
171.66
156.10
138.70
132.89
132.56
132.22
131.89
128.26
128.23
127.16
126.25
124.45
121.73
119.02
79.88
49.33
37.20
35.87
34.08
28.31
27.49
F3C
O
O
NMe2
NHBoc
CF3
8c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

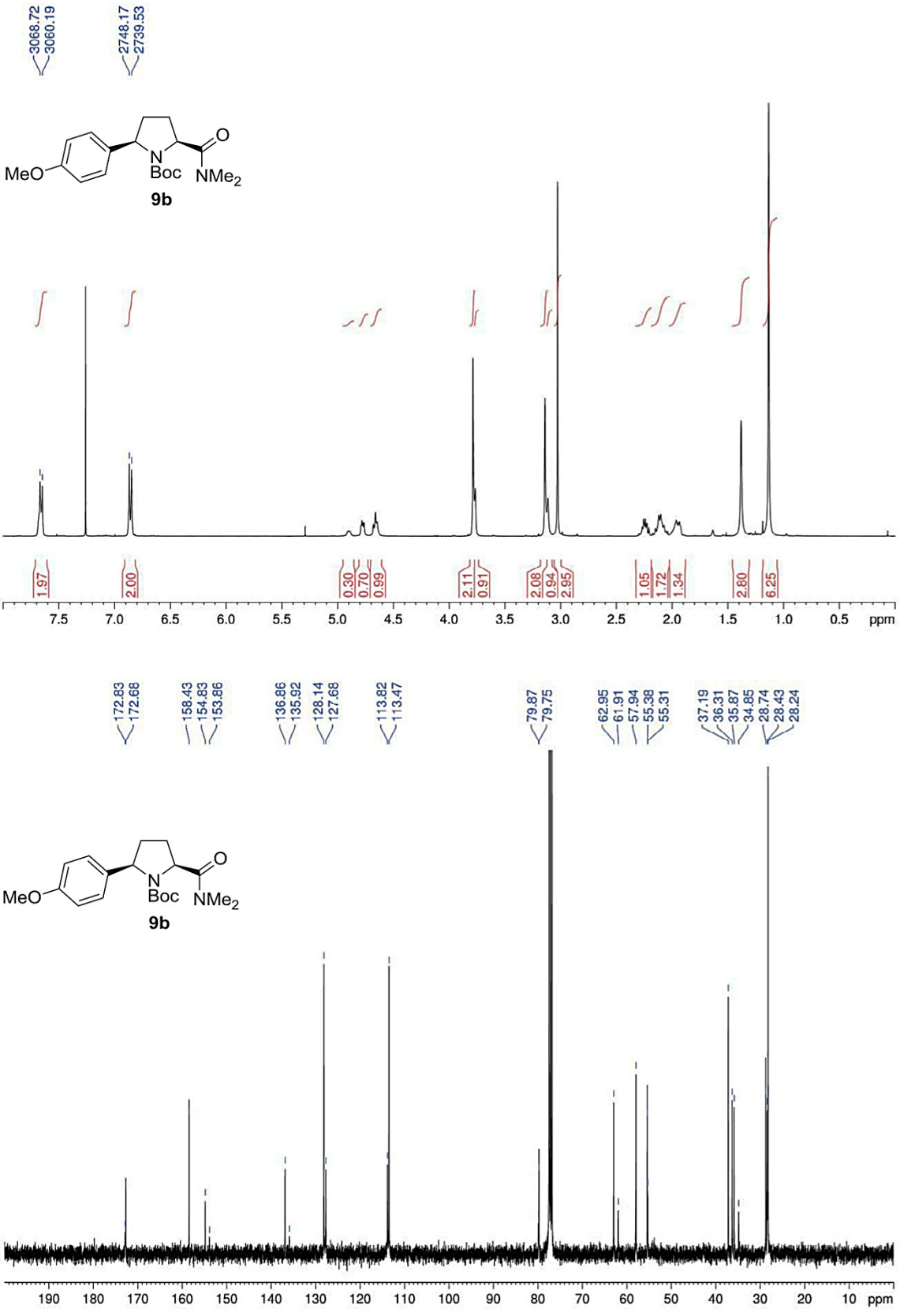
62

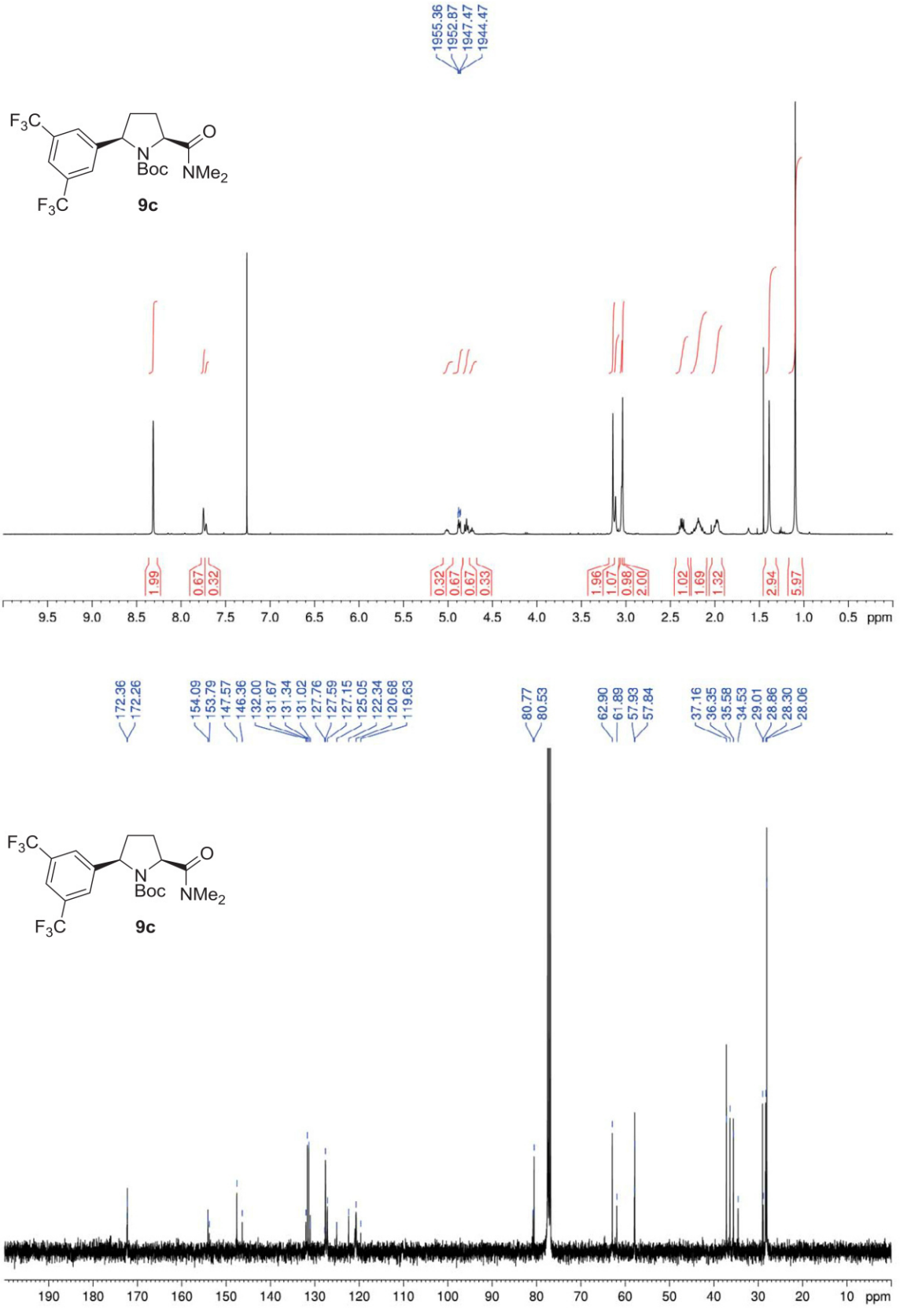

3425.23
3416.67
3193.32
3185.03
2229.88
2221.52
1929.43
1926.43
1920.34
1917.82
1912.10
1908.50
O
O
NMe2
NHBoc
8d
0.98
1.04
2.10
3.05
0.91
1.00
1.02
2.95
1.01
3.07
1.03
1.03
9.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


203.66
172.03
155.92
136.29
134.05
132.52
130.21
128.49
127.91
127.65
126.50
125.91
124.52
79.69
49.72
37.45
37.28
35.87
28.45
27.70
O
O
NMe2
NHBoc
8d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

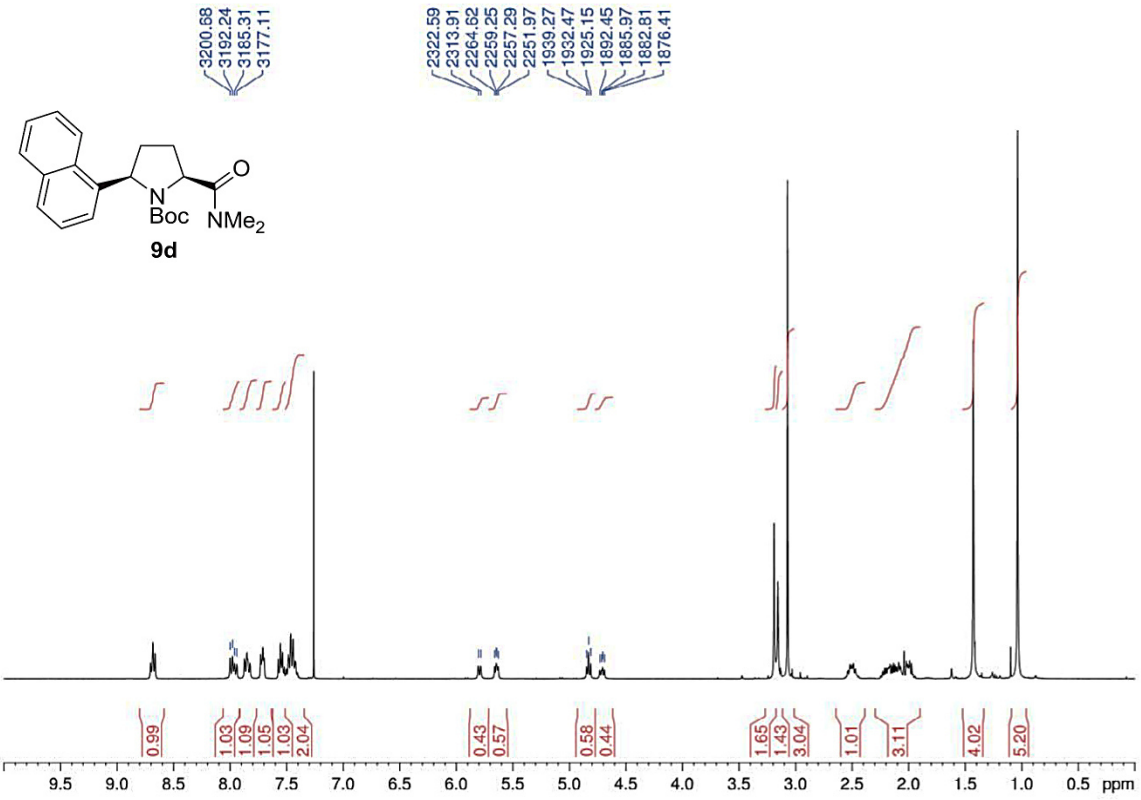

3099.25
3091.96
2931.03
2923.63
2915.95
2884.66
2877.33
2870.01
Ph
N
Boc
O
NMe2
9a
2.00
2.04
1.05
0.28
0.72
1.01
2.12
0.87
2.96
1.08
1.70
1.33
2.56
6.39
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
172.64
154.77
144.60
128.37
128.12
126.99
126.60
79.83
63.60
62.45
57.95
37.21
36.33
35.86
34.79
28.85
28.74
28.44
28.17
Ph
N
Boc
O
NMe2
9a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

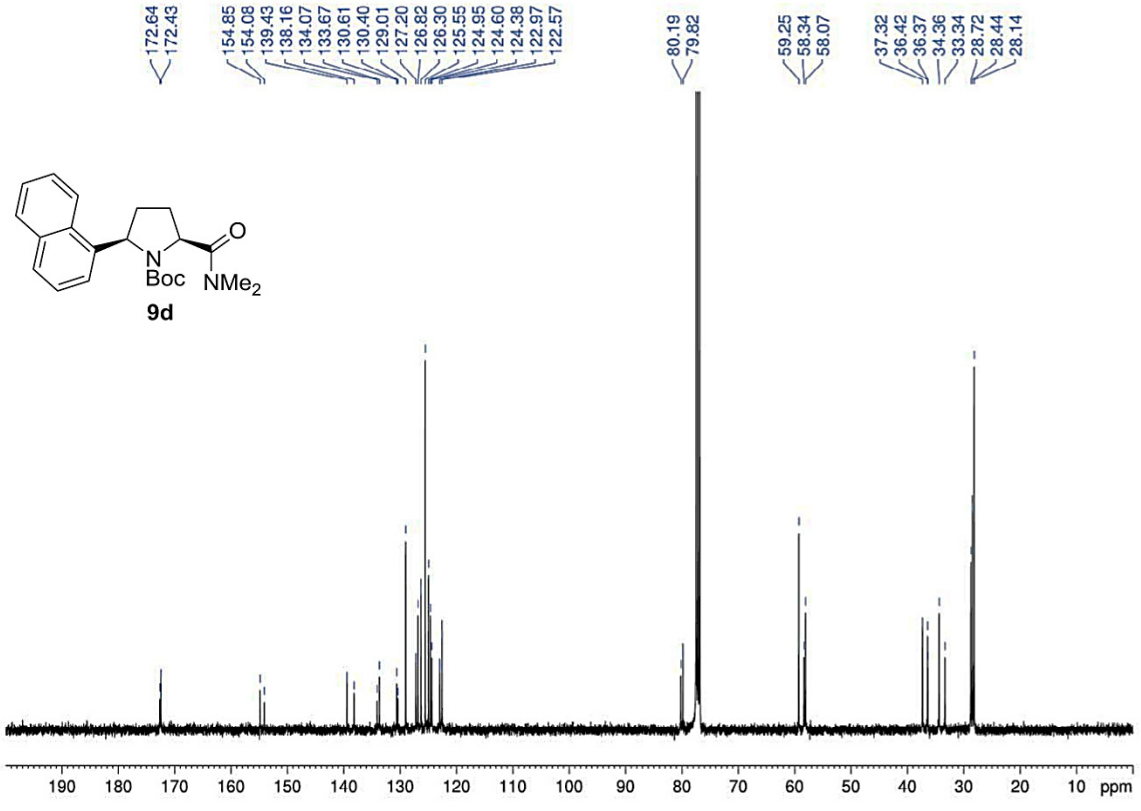
64

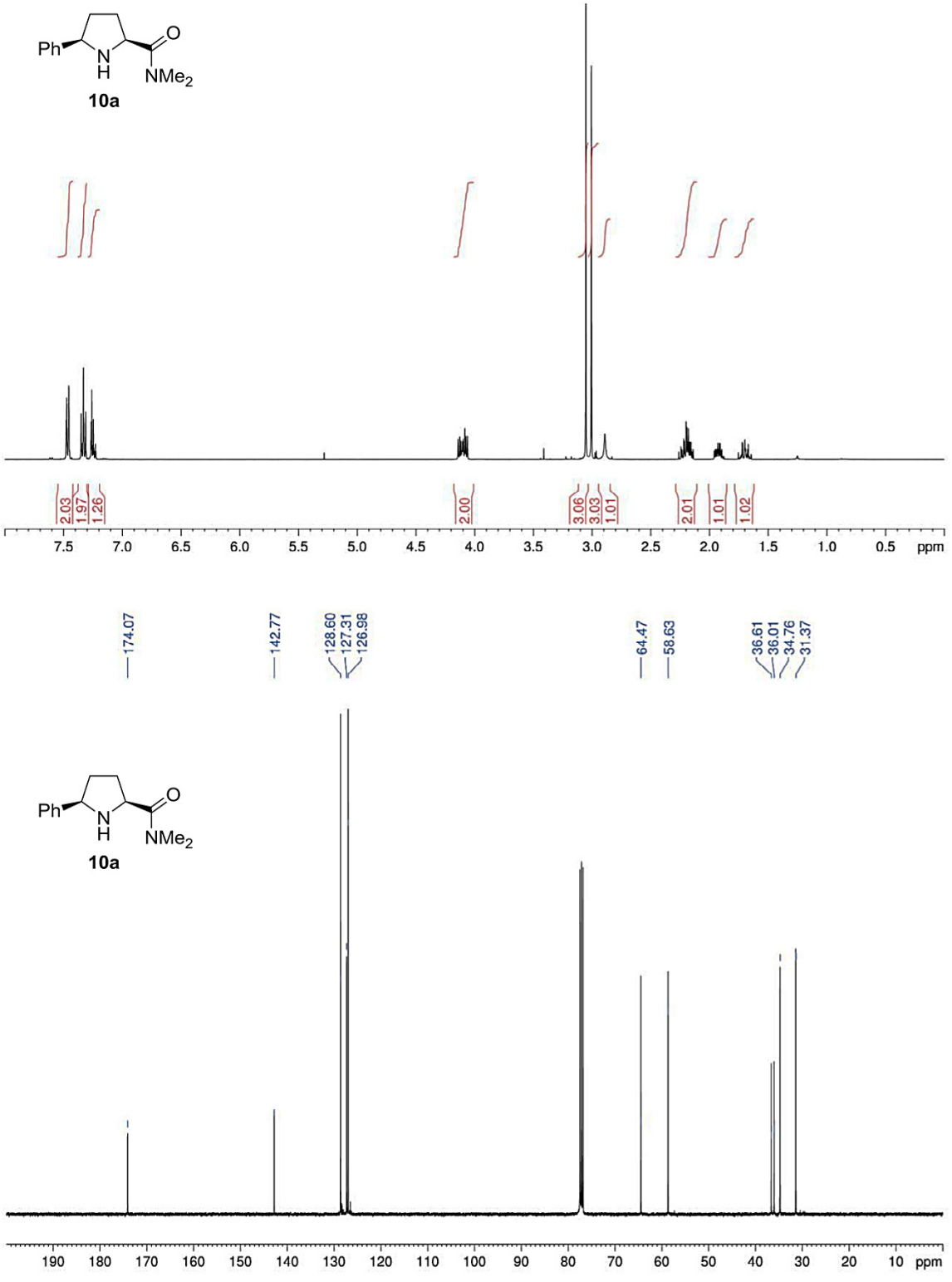

3068.72
3060.19
2748.17
2739.53
MeO
N
Boc
O
NMe2
9b
1.97
2.00
0.30
0.70
0.99
2.11
0.91
2.08
0.94
2.95
1.05
1.72
1.34
2.80
6.25
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
172.83
172.68
158.43
154.83
153.86
136.86
135.92
128.14
127.68
113.82
113.47
79.87
79.75
62.95
61.91
57.94
55.38
55.31
37.19
36.31
35.87
34.85
28.74
28.43
28.24
MeO
N
Boc
O
NMe2
9b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


1955.36
1952.87
1947.47
1944.47
F3C
N
Boc
O
NMe2
F3C
9c
1.99
0.67
0.32
0.32
0.67
0.67
0.33
1.96
1.07
0.98
2.00
1.02
1.69
1.32
2.94
5.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
172.36
172.26
154.09
153.79
147.57
146.36
132.00
131.67
131.34
131.02
127.76
127.59
127.15
125.05
122.34
120.68
119.63
80.77
80.53
62.90
61.89
57.93
57.84
37.16
36.35
35.58
34.53
29.01
28.86
28.30
28.06
F3C
N
Boc
O
NMe2
F3C
9c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

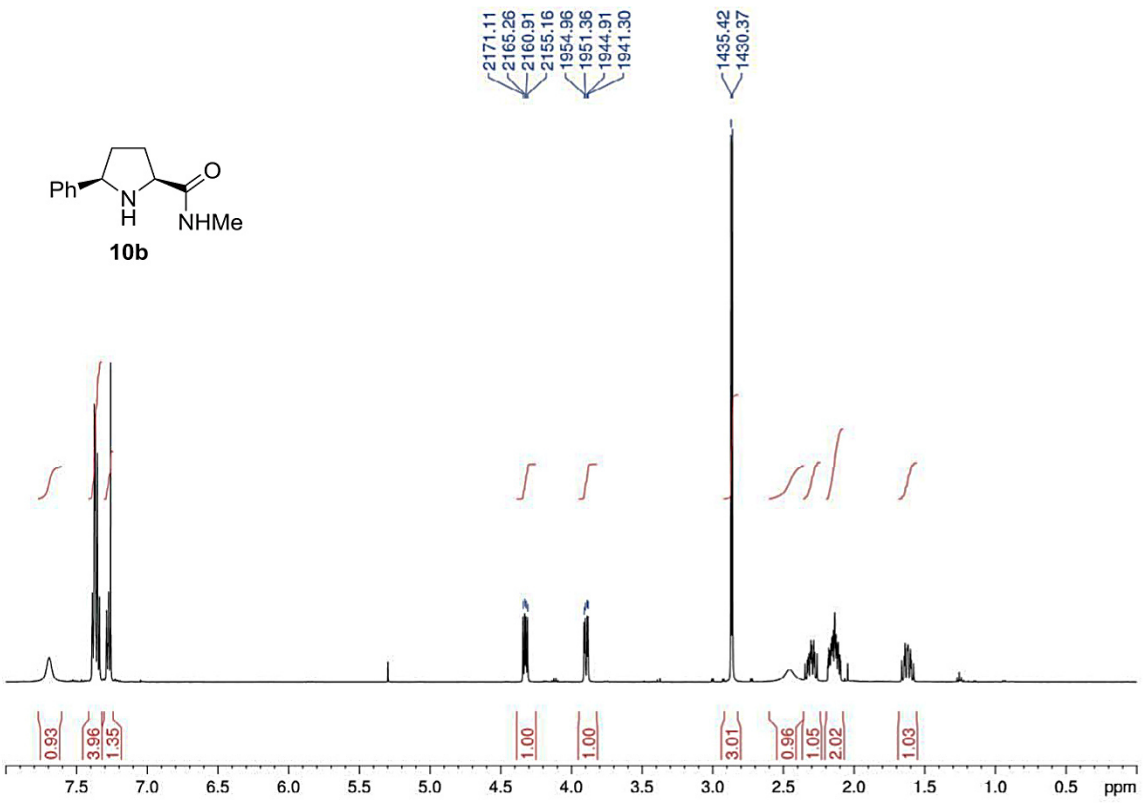
66

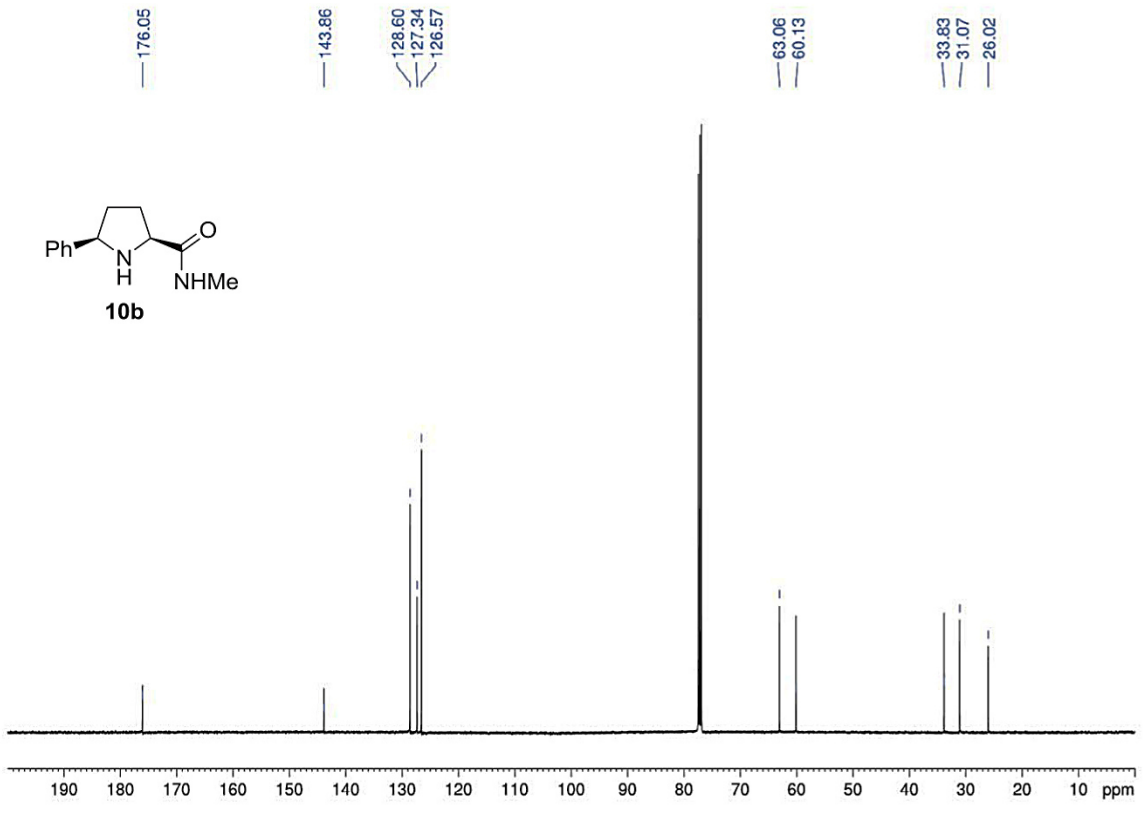

3200.68
3192.24
3185.31
3177.11
2322.59
2313.91
2264.62
2259.25
2257.29
2251.97
1939.27
1932.47
1925.15
1892.45
1885.97
1882.81
1876.41
N
Boc
O
NMe2
9d
0.99
1.03
1.09
1.05
1.03
2.04
0.43
0.57
0.58
0.44
1.65
1.43
3.04
1.01
3.11
4.02
5.20
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

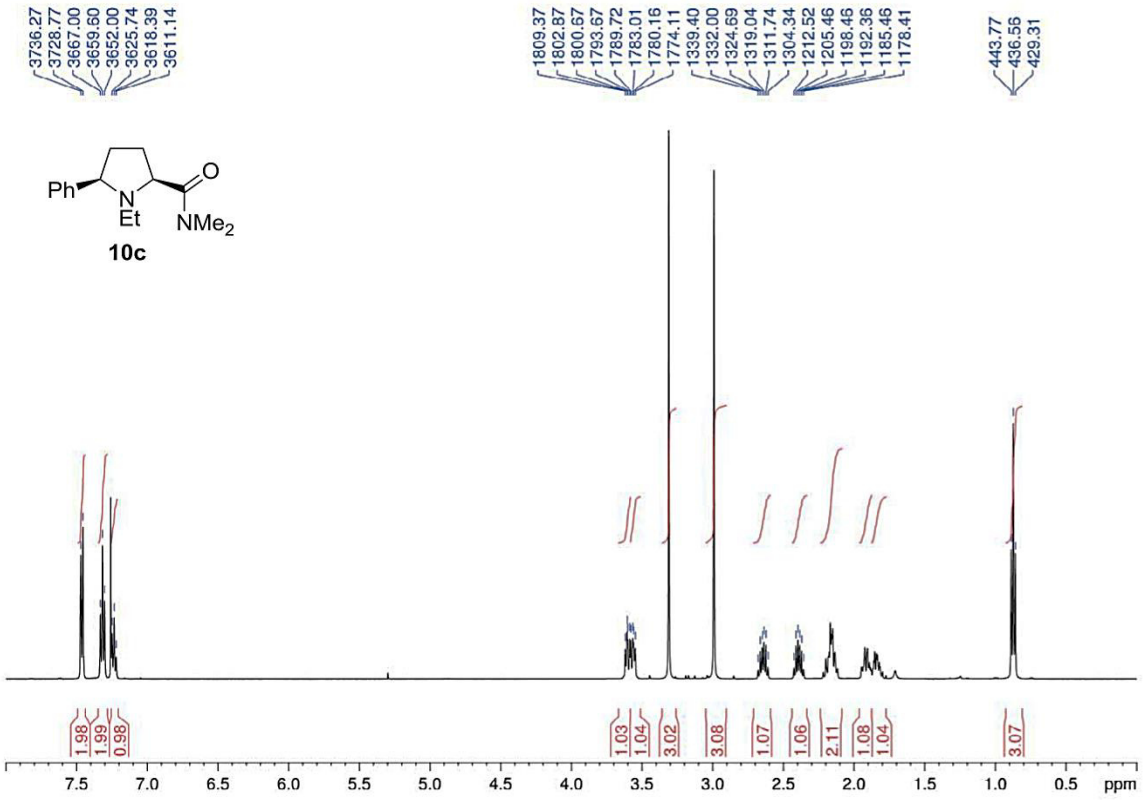

172.64
172.43
154.85
154.08
139.43
138.16
134.07
133.67
130.61
130.40
129.01
127.20
126.82
126.30
125.55
124.95
124.60
124.38
122.97
122.57
80.19
79.82
59.25
58.34
58.07
37.32
36.42
36.37
34.36
33.34
28.72
28.44
28.14
N
Boc
O
NMe2
9d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

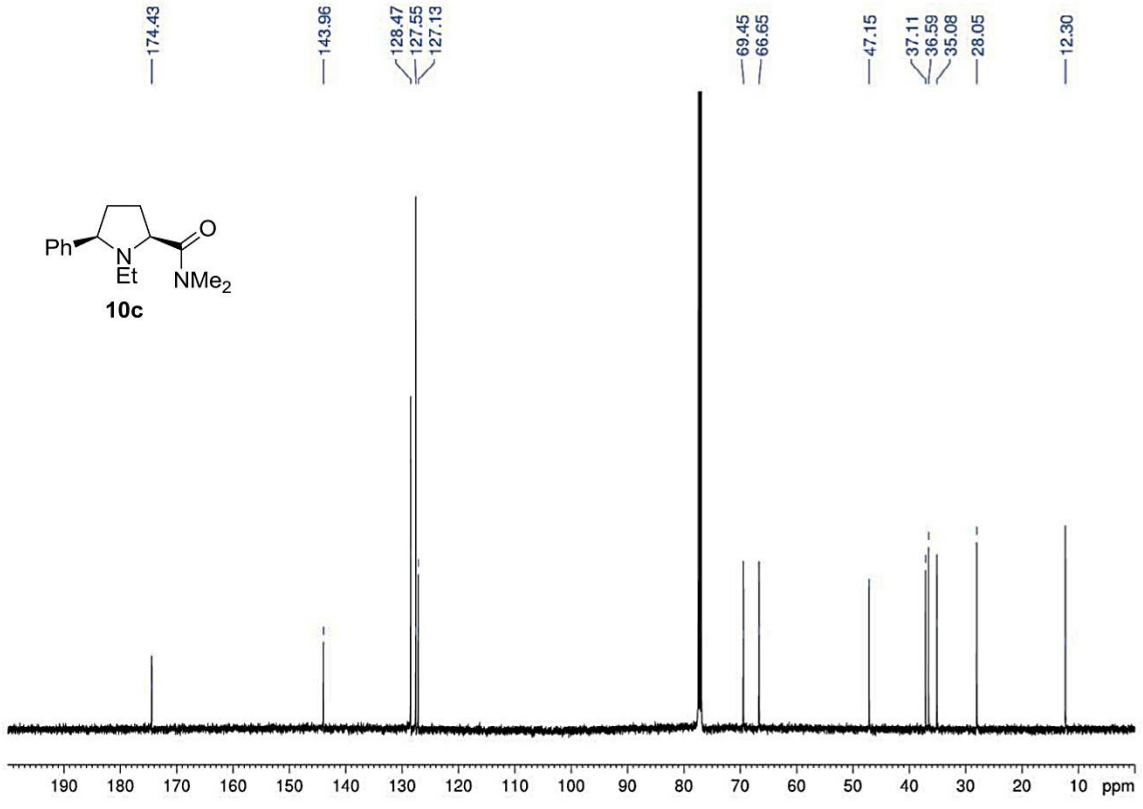

Ph
N
H
O
NMe2
10a
2.03
1.97
1.26
2.00
3.06
3.03
1.01
2.01
1.01
1.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
174.07
142.77
128.60
127.31
126.98
64.47
58.63
36.61
36.01
34.76
31.37
Ph
N
H
O
NMe2
10a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

68

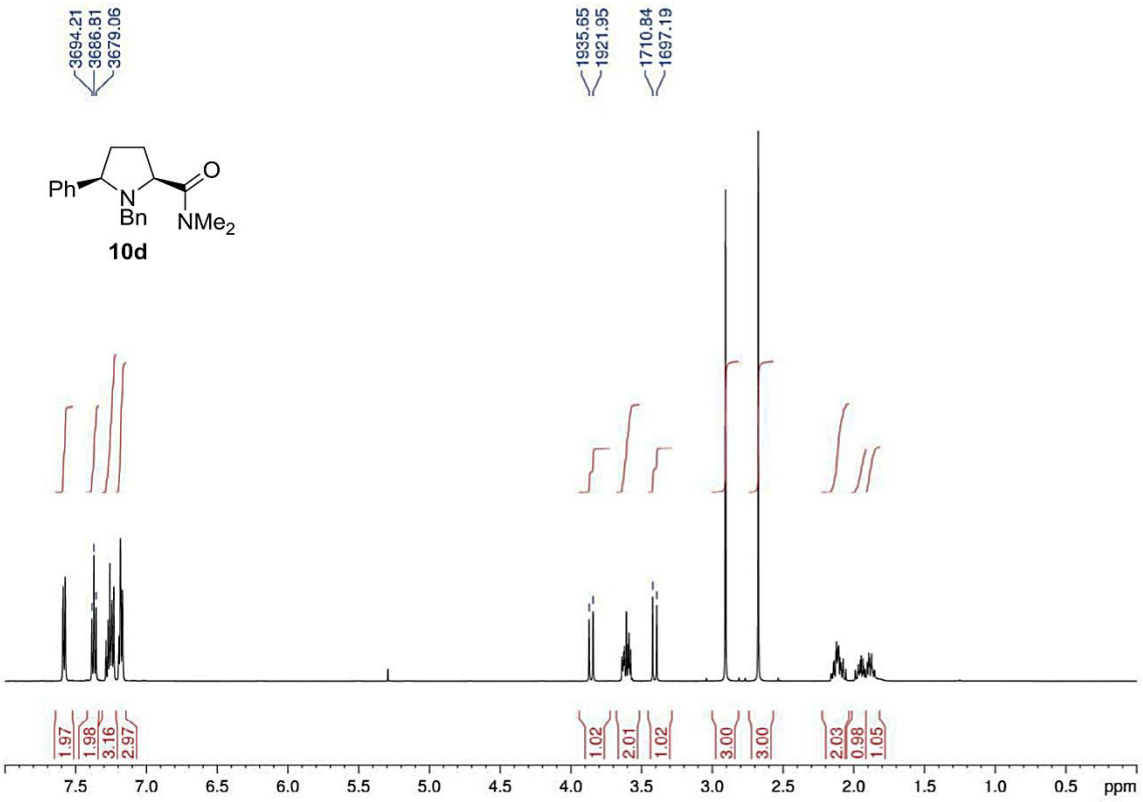

2171.11
2165.26
2160.91
2155.16
1954.96
1951.36
1944.91
1941.30
1435.42
1430.37
Ph
N
H
O
NHMe
10b
0.93
3.96
1.35
1.00
1.00
3.01
0.96
1.05
2.02
1.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

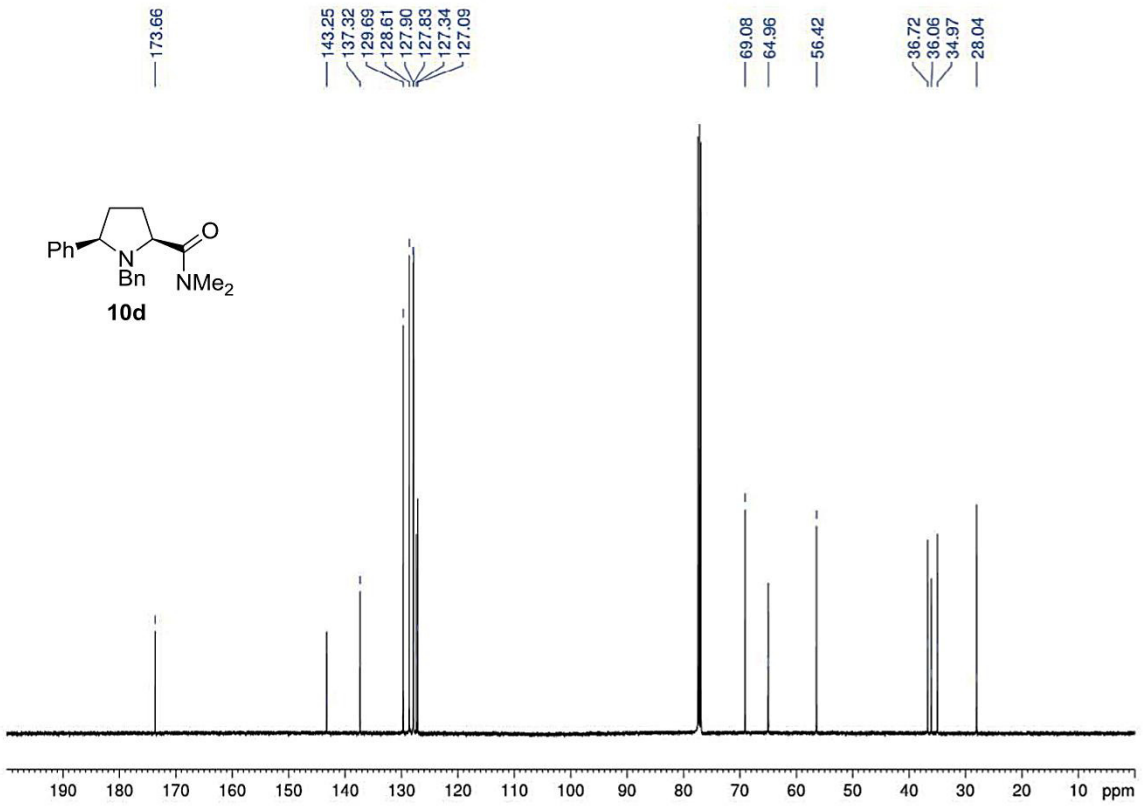

176.05
143.86
128.60
127.34
126.57
63.06
60.13
33.83
31.07
26.02
Ph
N
H
O
NHMe
10b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

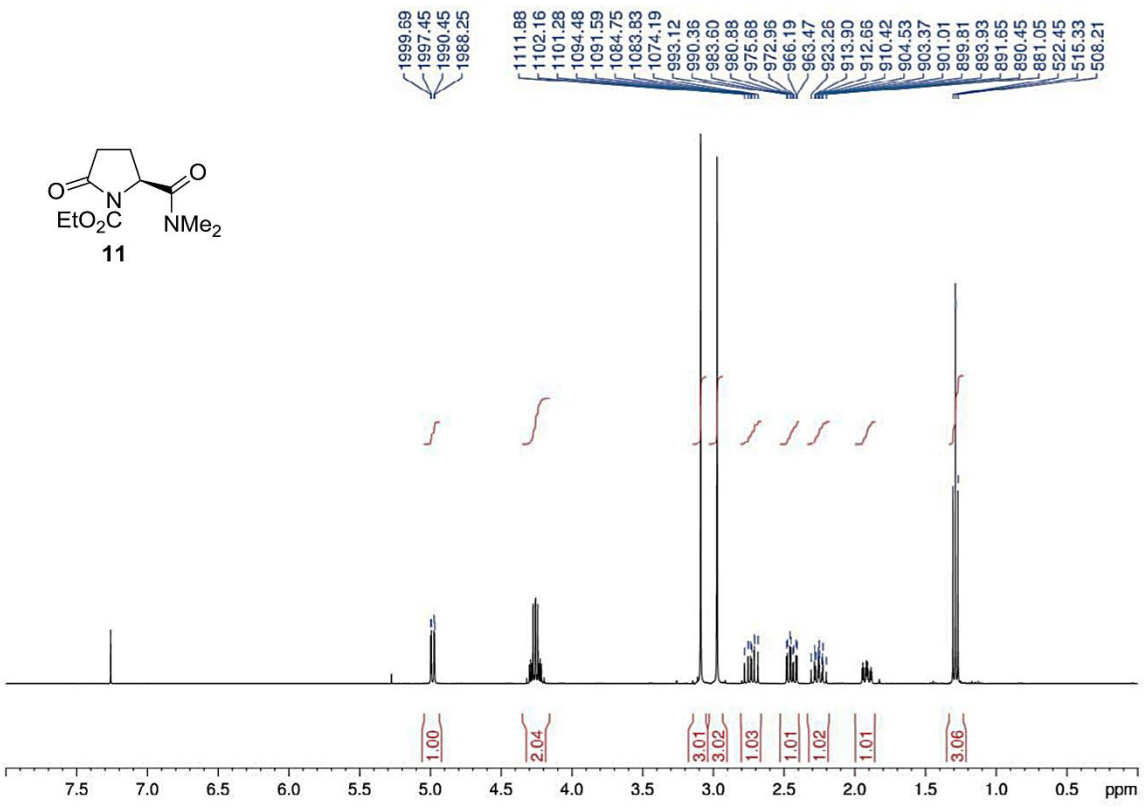

3736.27
3728.77
3667.00
3659.60
3652.00
3625.74
3618.39
3611.14
1809.37
1802.87
1800.67
1793.67
1789.72
1783.01
1780.16
1774.11
1339.40
1332.00
1324.69
1319.04
1311.74
1304.34
1212.52
1205.46
1198.46
1192.36
1185.46
1178.41
443.77
436.56
429.31
Ph
N
Et
O
NMe2
10c
1.98
1.99
0.98
1.03
1.04
3.02
3.08
1.07
1.06
2.11
1.08
1.04
3.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

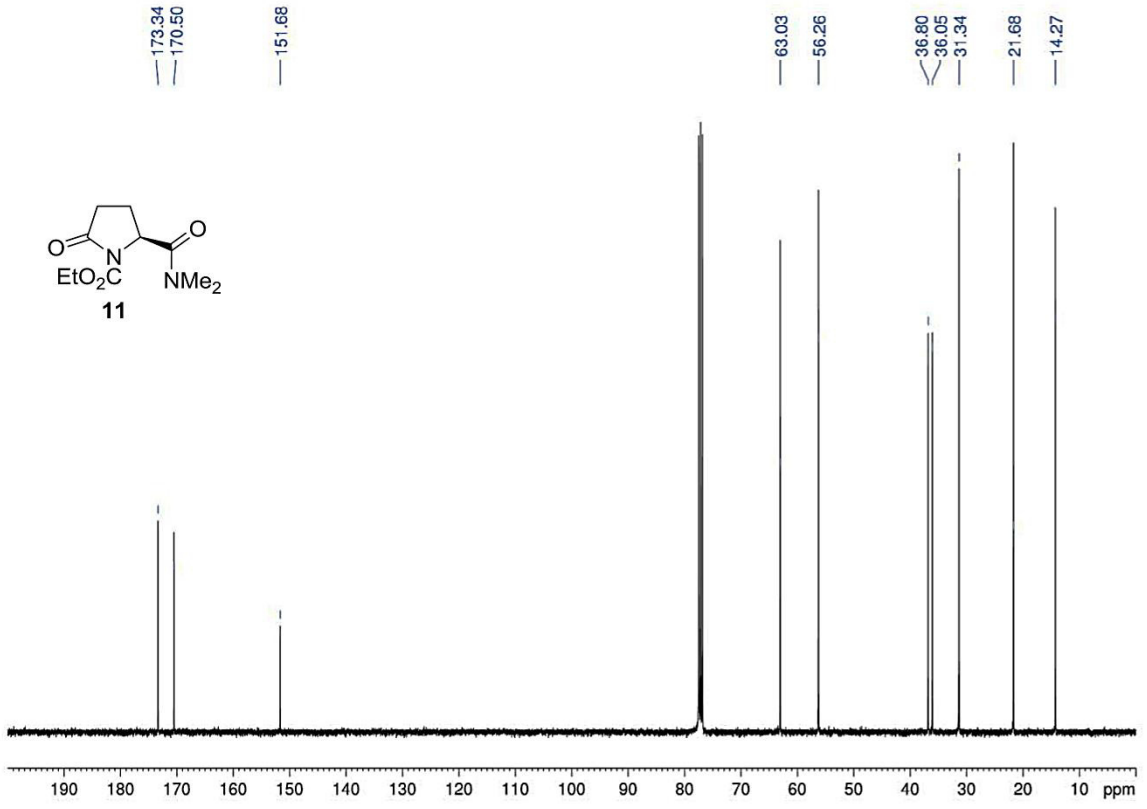

174.43
143.96
128.47
127.55
127.13
69.45
66.65
47.15
37.11
36.59
35.08
28.05
12.30
Ph
N
Et
O
NMe2
10c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

70

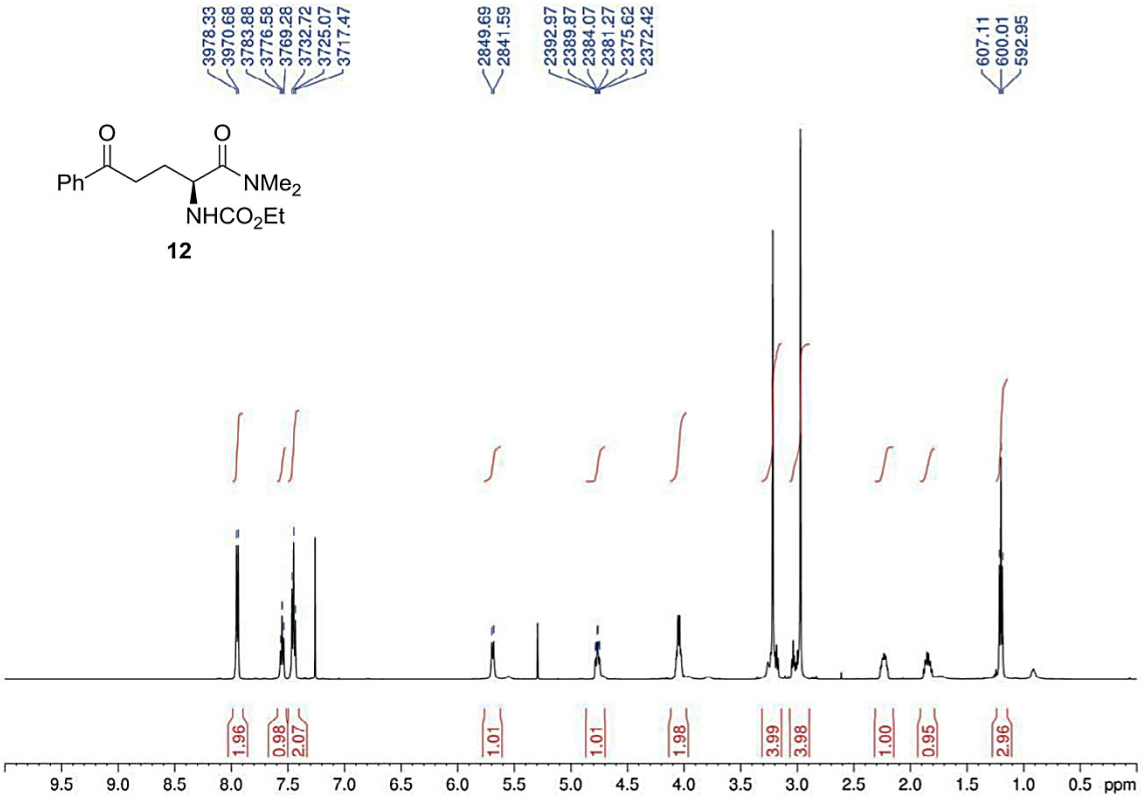

3694.21
3686.81
3679.06
1935.65
1921.95
1710.84
1697.19
Ph
N
Bn
O
NMe2
10d
1.97
1.98
3.16
2.97
1.02
2.01
1.02
3.00
3.00
2.03
0.98
1.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

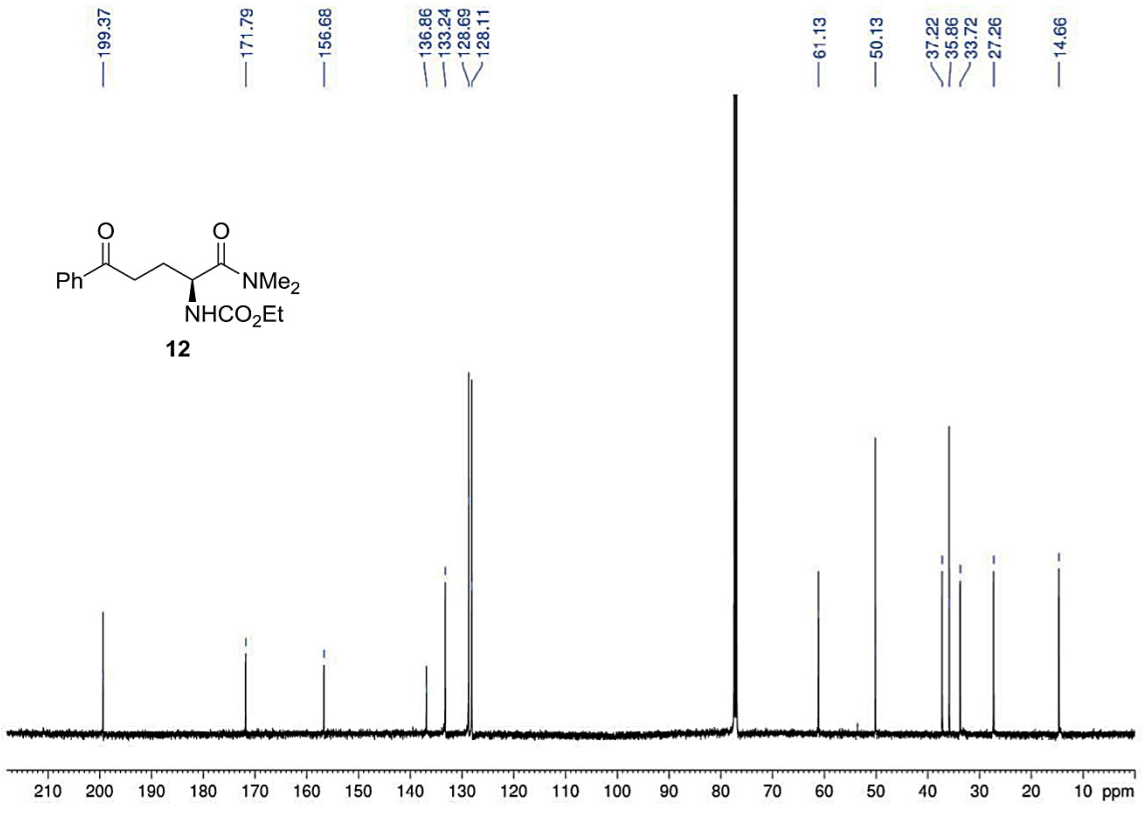

173.66
143.25
137.32
129.69
128.61
127.90
127.83
127.34
127.09
69.08
64.96
56.42
36.72
36.06
34.97
28.04
Ph
N
Bn
O
NMe2
10d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


1999.69
1997.45
1990.45
1988.25
1111.88
1102.16
1101.28
1094.48
1091.59
1084.75
1083.83
1074.19
993.12
990.36
983.60
980.88
975.68
972.96
966.19
963.47
923.26
913.90
912.66
910.42
904.53
903.37
901.01
899.81
893.93
891.65
890.45
881.05
522.45
515.33
508.21
O
O
N
EtO2C
NMe2
11
1.00
2.04
3.01
3.02
1.03
1.01
1.02
1.01
3.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

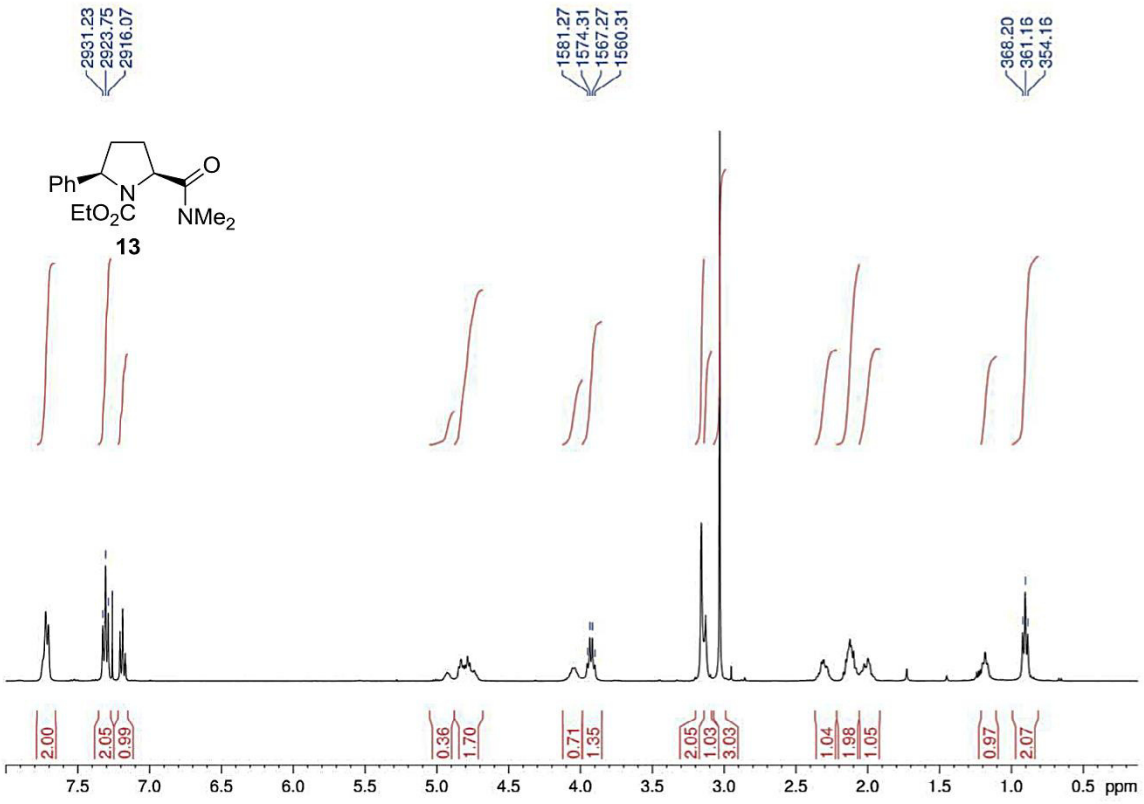

173.34
170.50
151.68
63.03
56.26
36.80
36.05
31.34
21.68
14.27
O
O
N
EtO2C
NMe2
11
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

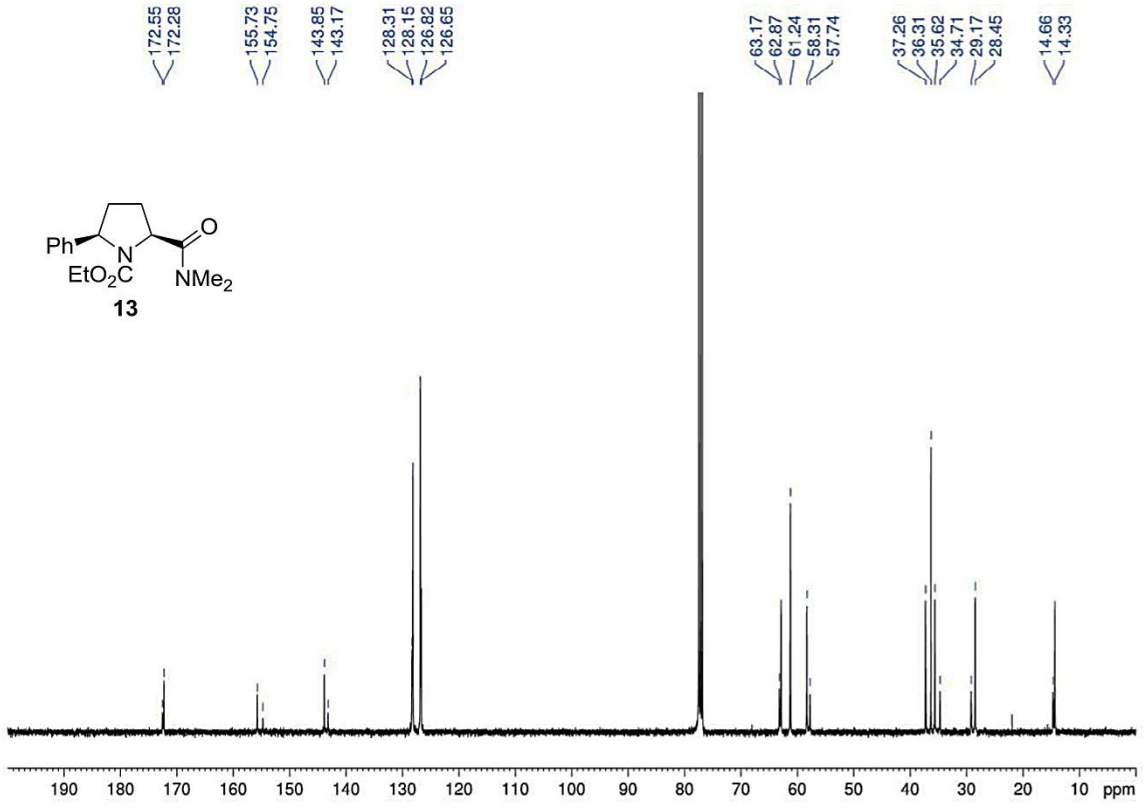
72


3978.33
3970.68
3783.88
3776.58
3769.28
3732.72
3725.07
3717.47
2849.69
2841.59
2392.97
2389.87
2384.07
2381.27
2375.62
2372.42
607.11
600.01
592.95
Ph
O
O
NMe2
NHCO2Et
12
1.96
0.98
2.07
1.01
1.01
1.98
3.99
3.98
1.00
0.95
2.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

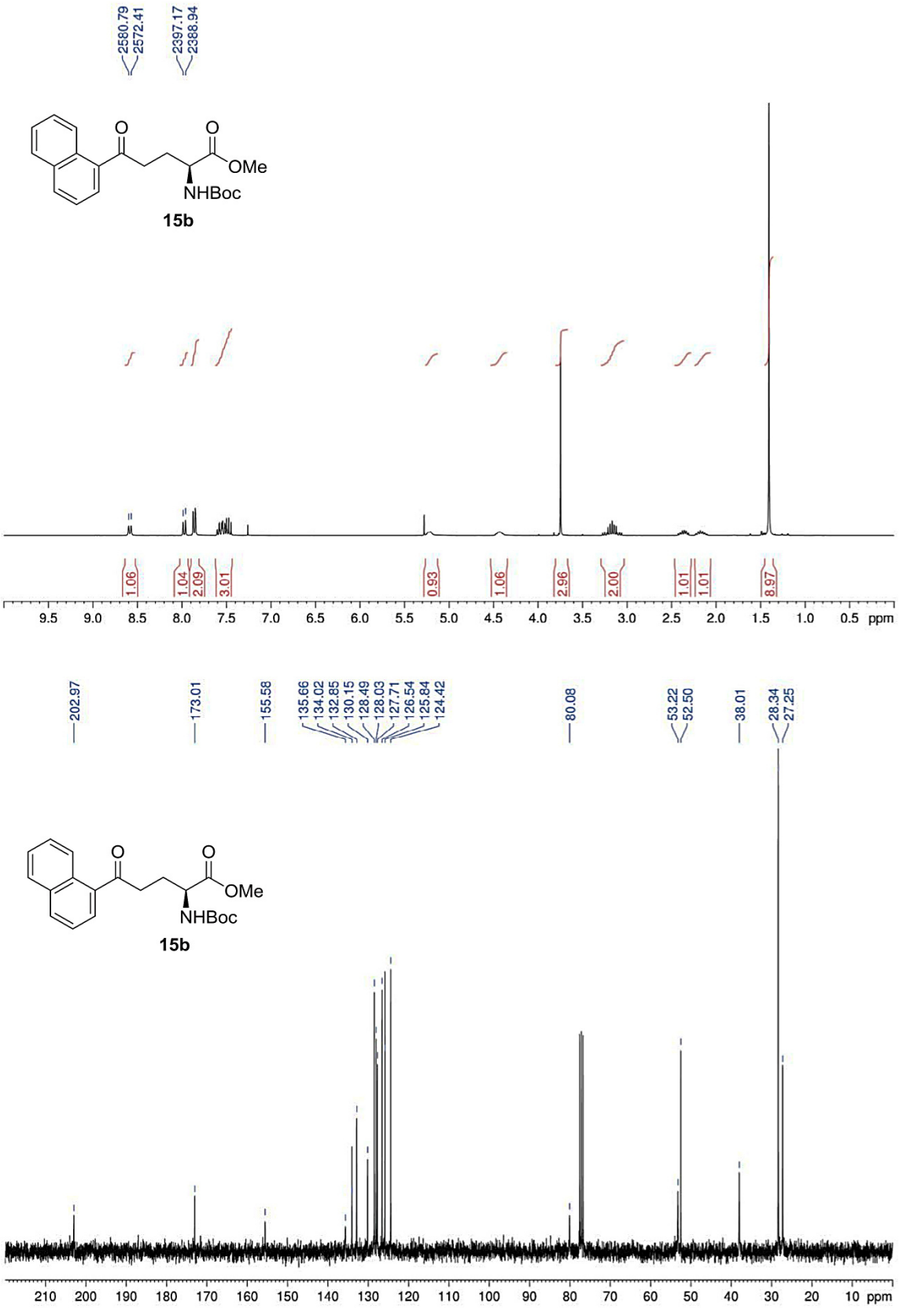

199.37
171.79
156.68
136.86
133.24
128.69
128.11
61.13
50.13
37.22
35.86
33.72
27.26
14.66
Ph
O
O
NMe2
NHCO2Et
12
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

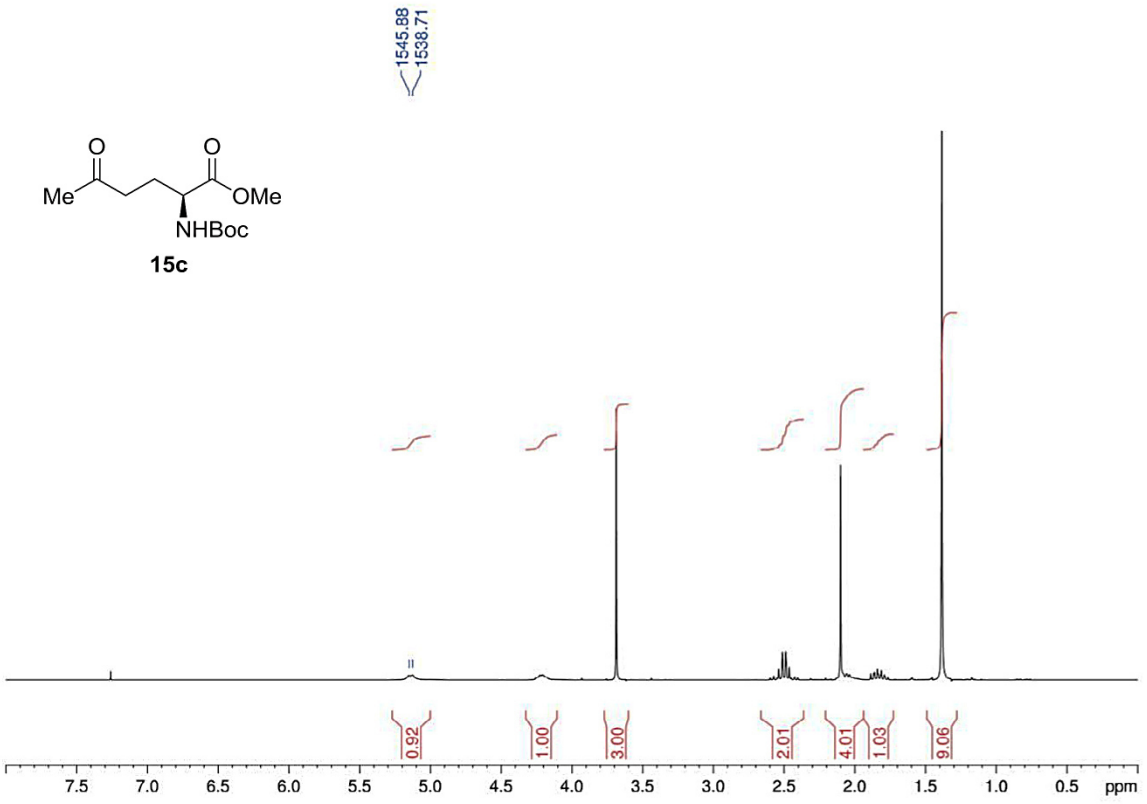
73

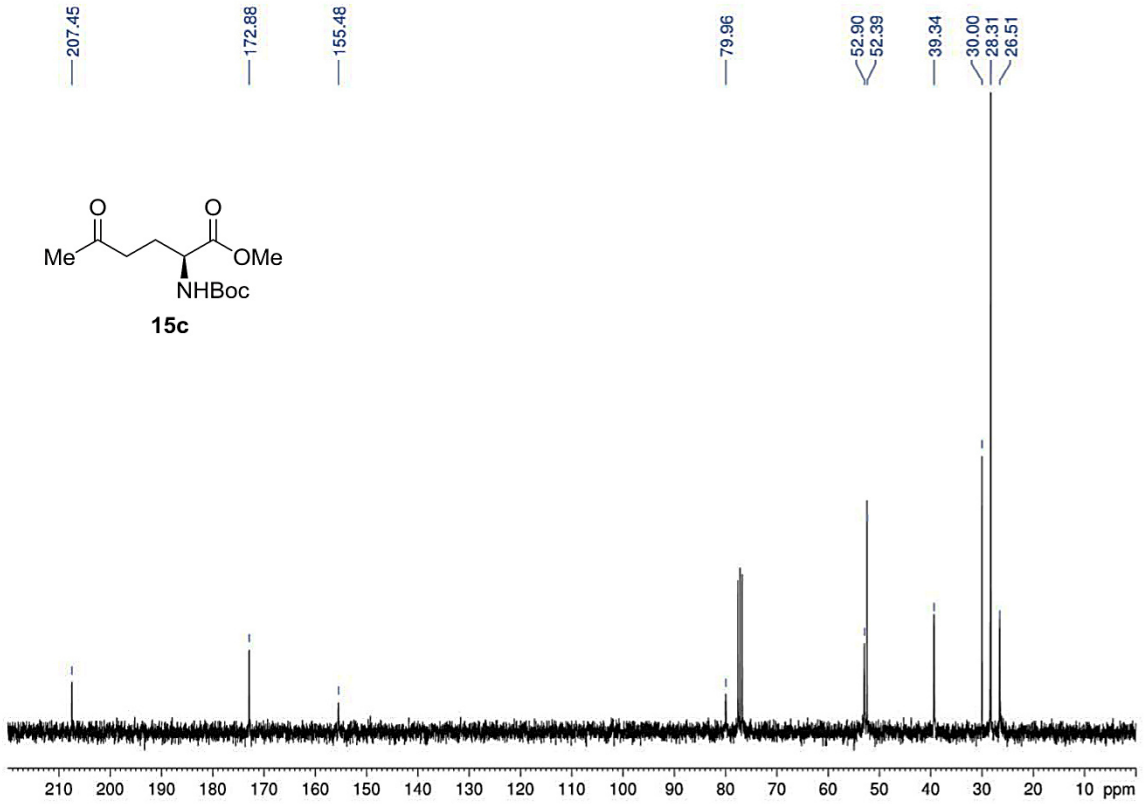

2931.23
2923.75
2916.07
1581.27
1574.31
1567.27
1560.31
368.20
361.16
354.16
Ph
N
EtO2C
O
NMe2
13
2.00
2.05
0.99
0.36
1.70
0.71
1.35
2.05
1.03
3.03
1.04
1.98
1.05
0.97
2.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 ppm


172.55
172.28
155.73
154.75
143.85
143.17
128.31
128.15
126.82
126.65
63.17
62.87
61.24
58.31
57.74
37.26
36.31
35.62
34.71
29.17
28.45
14.66
14.33
Ph
N
EtO2C
O
NMe2
13
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

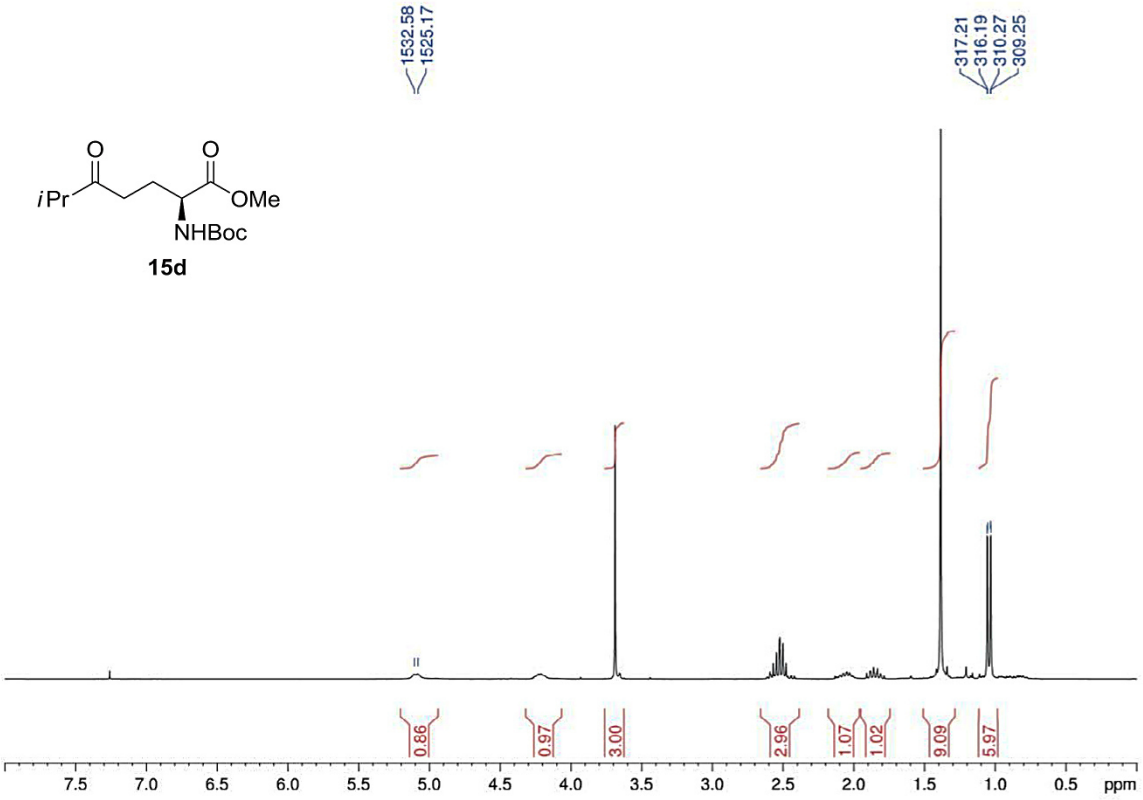
74

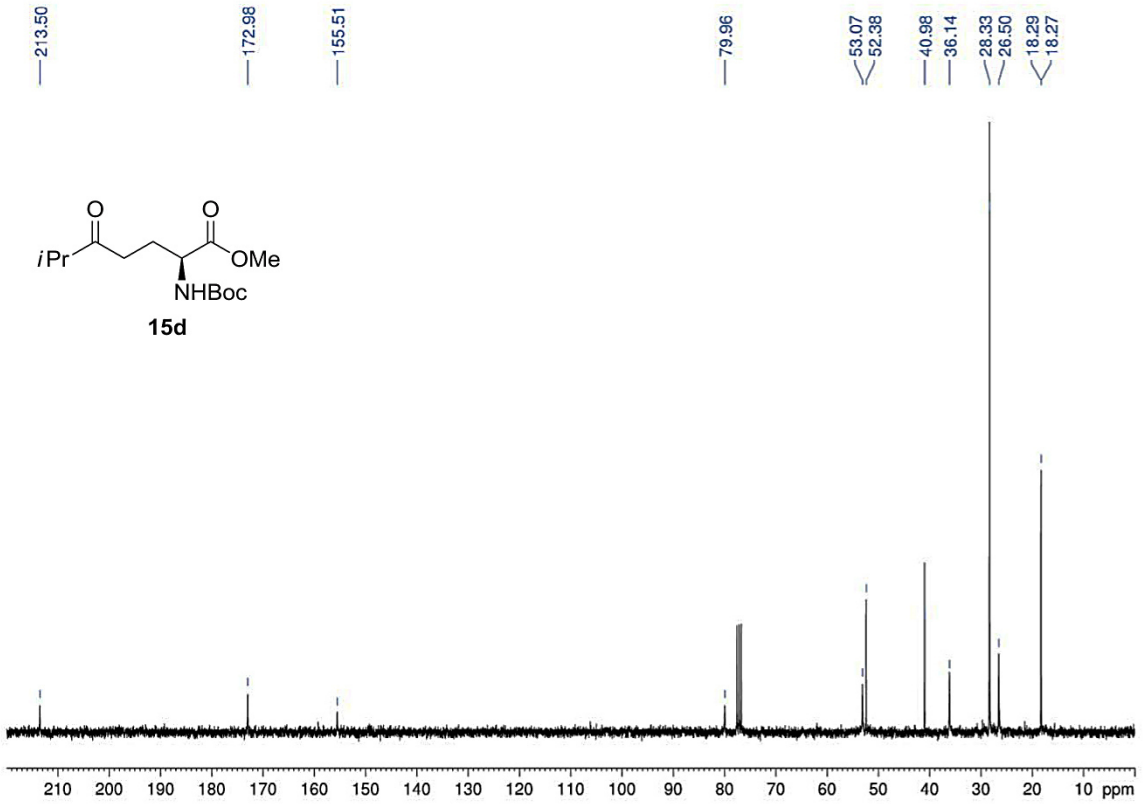

2580.79
2572.41
2397.17
2388.94
O
O
OMe
NHBoc
15b
1.06
1.04
2.09
3.01
0.93
1.06
2.96
2.00
1.01
1.01
8.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
202.97
173.01
155.58
135.66
134.02
132.85
130.15
128.49
128.03
127.71
126.54
125.84
124.42
80.08
53.22
52.50
38.01
28.34
27.25
O
O
OMe
NHBoc
15b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


1545.88
1538.71
Me
OMe
NHBoc
15c
0.92
1.00
3.00
2.01
4.01
1.03
9.06
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

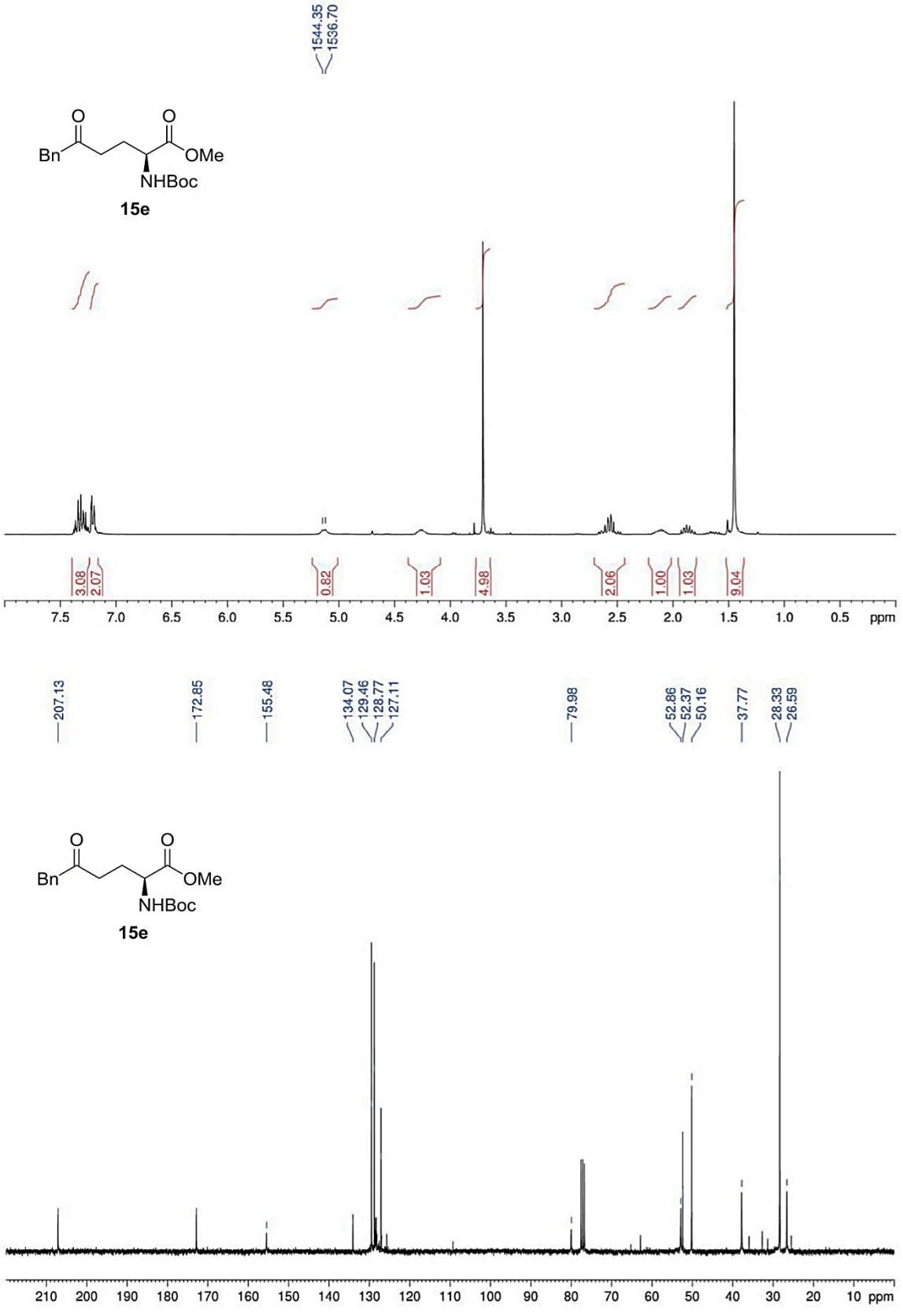

207.45
172.88
155.48
79.96
52.90
52.39
39.34
30.00
28.31
26.51
Me
OMe
NHBoc
15c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

76

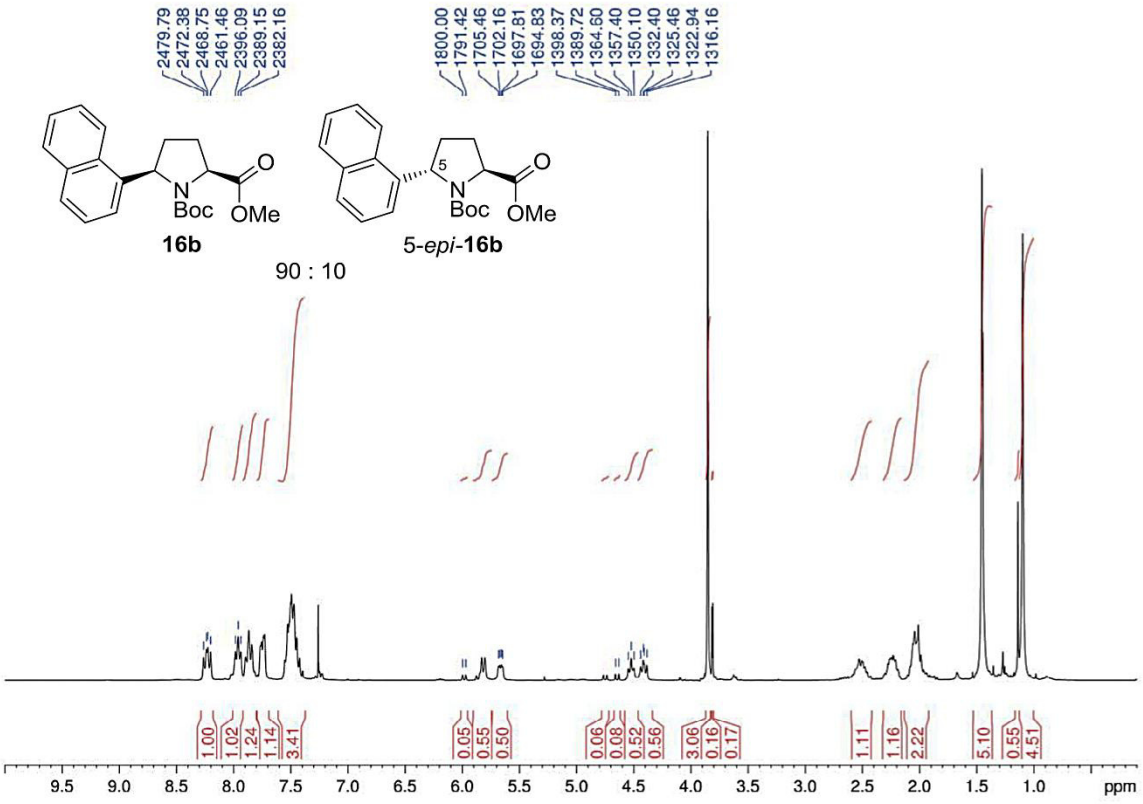

1532.58
1525.17
317.21
316.19
310.27
309.25
O
O
iPr
OMe
NHBoc
15d
0.86
0.97
3.00
2.96
1.07
1.02
9.09
5.97
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

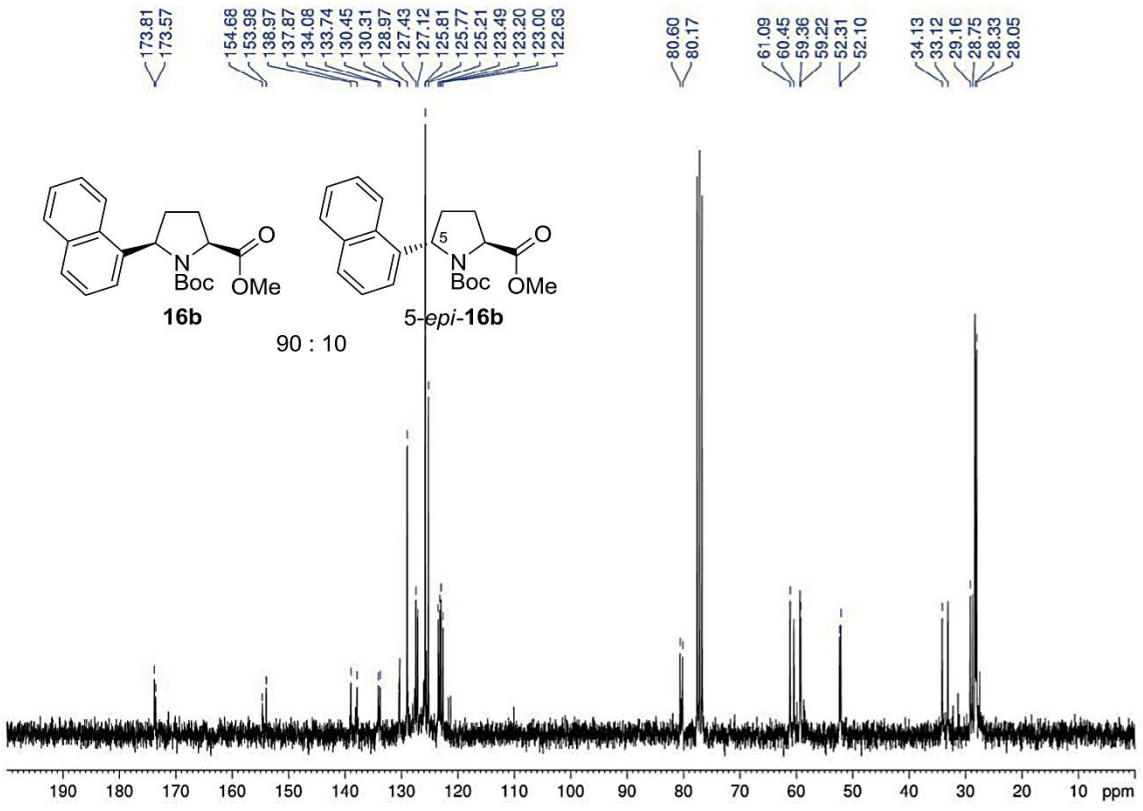

213.50
172.98
155.51
79.96
53.07
52.38
40.98
36.14
28.33
26.50
18.29
18.27
O
O
iPr
OMe
NHBoc
15d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

77

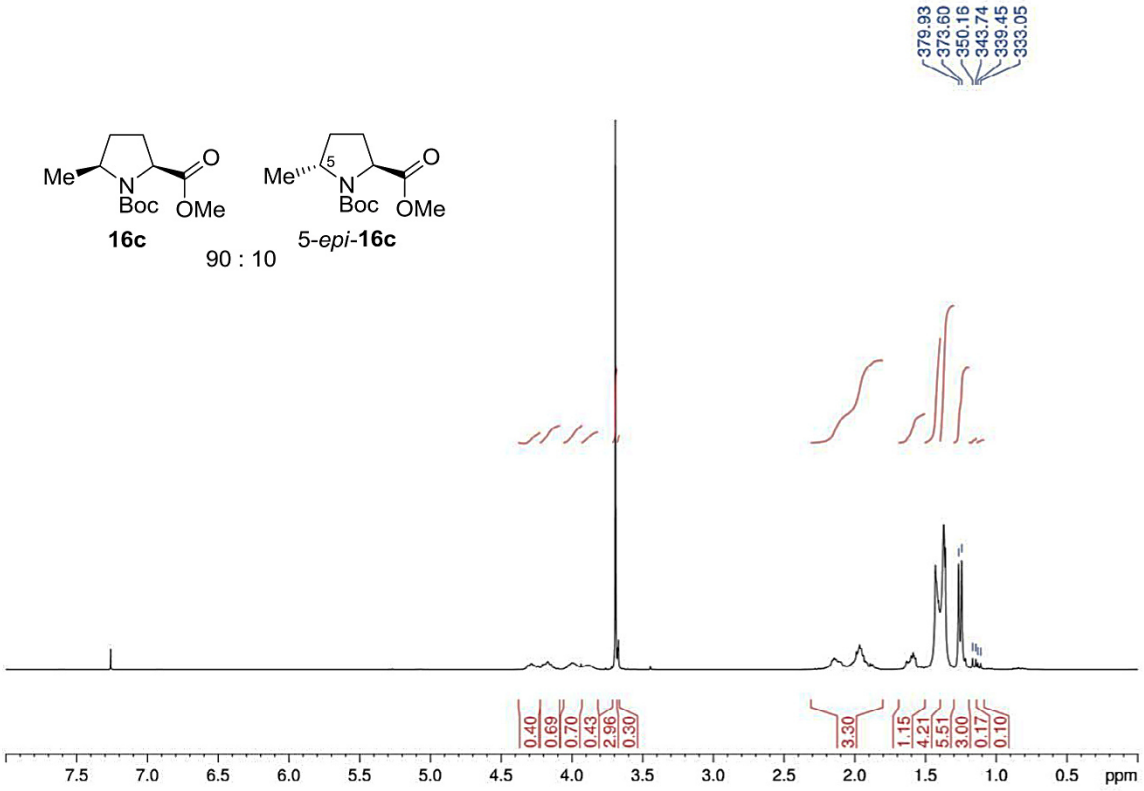

1544.35
1536.70
Bn
OMe
NHBoc
15e
3.08
2.07
0.82
1.03
4.98
2.06
1.00
1.03
9.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
207.13
172.85
155.48
134.07
129.46
128.77
127.11
79.98
52.86
52.37
50.16
37.77
28.33
26.59
Bn
OMe
NHBoc
15e
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

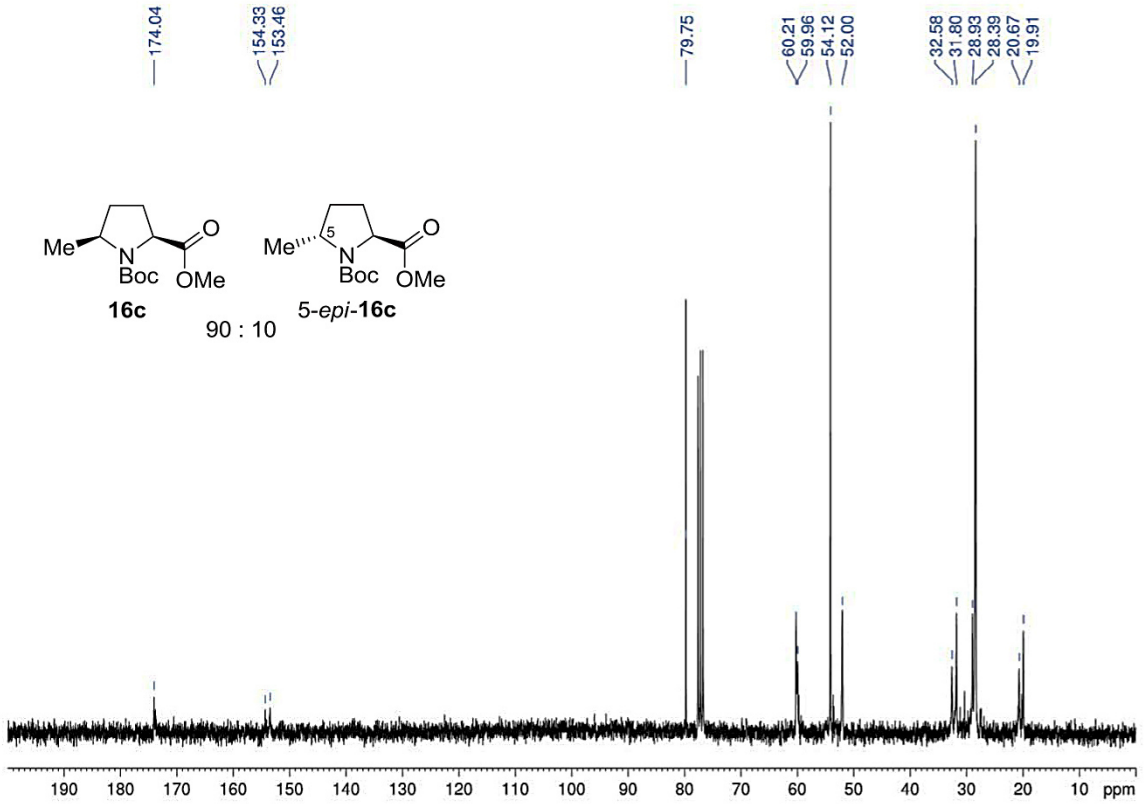
78


2479.79
2472.38
2468.75
2461.46
2396.09
2389.15
2382.16
1800.00
1791.42
1705.46
1702.16
1697.81
1694.83
1398.37
1389.72
1364.60
1357.40
1350.10
1332.40
1325.46
1322.94
1316.16
16b
5-epi-16b
90 : 10
1.00
1.02
1.24
1.14
3.41
0.05
0.55
0.50
0.06
0.08
0.52
0.56
3.06
0.16
0.17
1.11
1.16
2.22
5.10
0.55
4.51
ppm

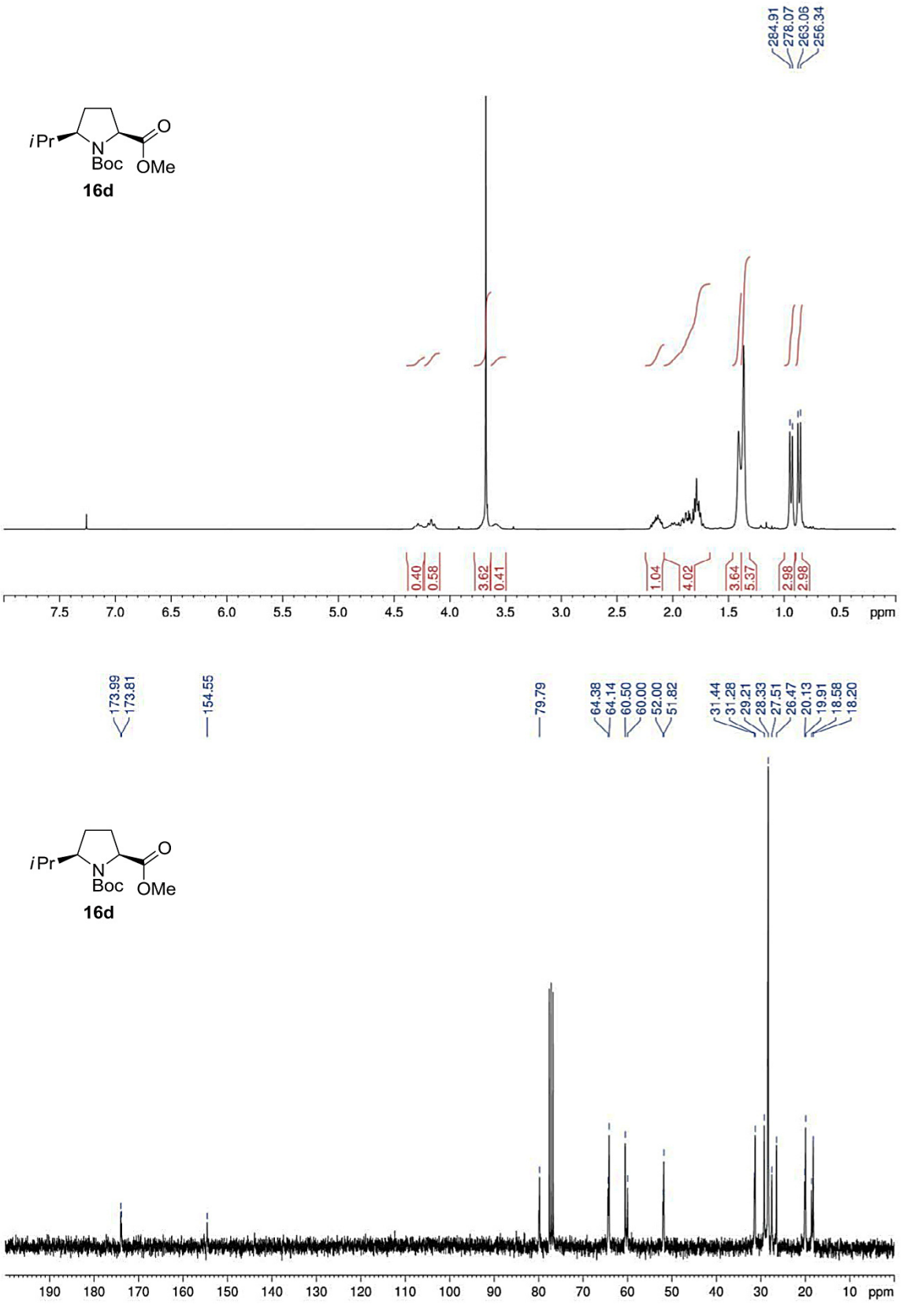

173.81
173.57
154.68
153.98
138.97
137.87
134.08
133.74
130.45
130.31
128.97
127.43
127.12
125.81
125.77
125.21
123.49
123.20
123.00
122.63
80.60
80.17
61.09
60.45
59.36
59.22
52.31
52.10
34.13
33.12
29.16
28.75
28.33
28.05
16b
5-epi-16b
90 : 10
ppm

79

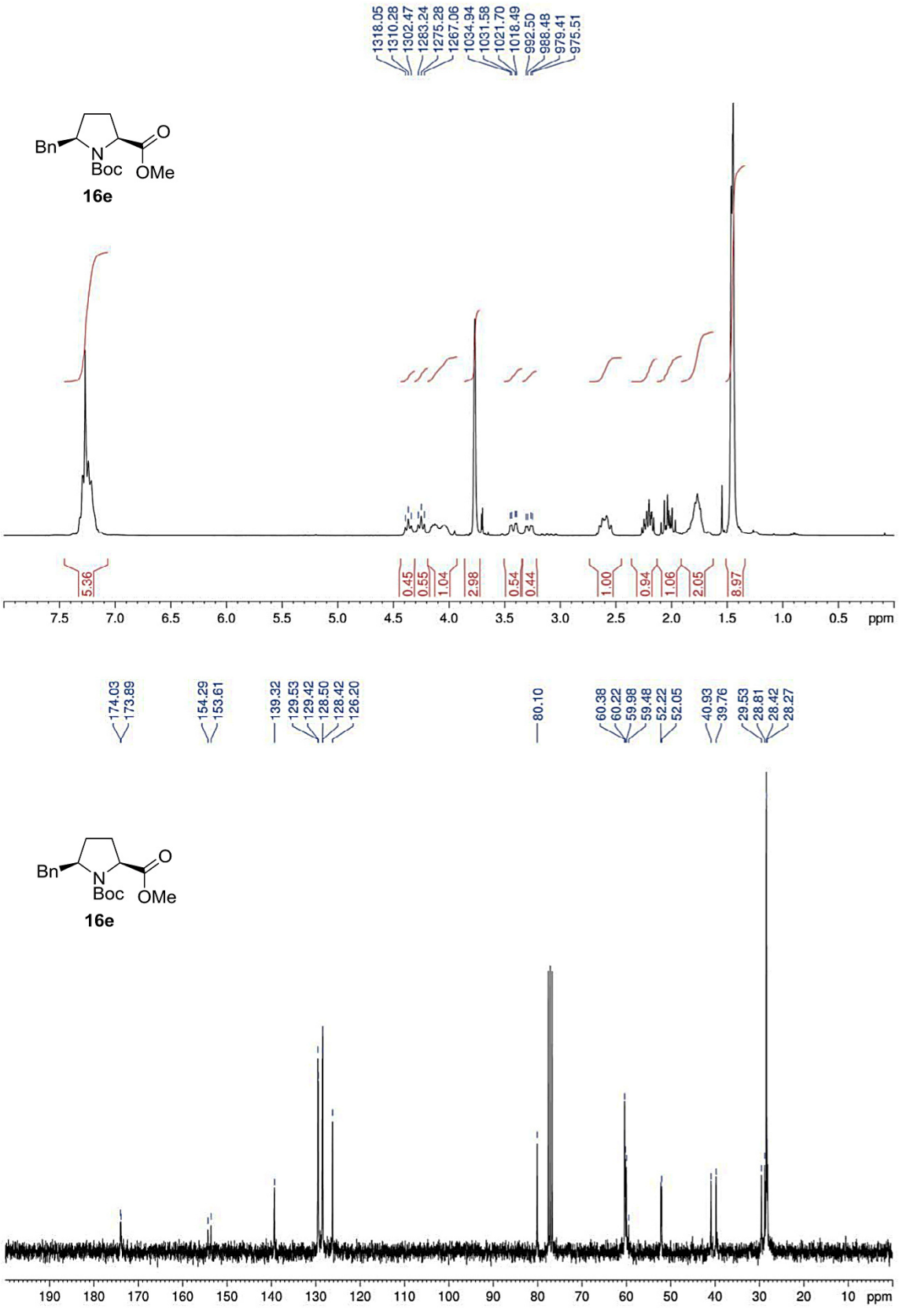

379.93
373.60
350.16
343.74
339.45
333.05
Me
N
Boc
OMe
O
16c
5-epi-16c
90 : 10
0.40
0.69
0.70
0.43
2.96
0.30
3.30
1.15
4.21
5.51
3.00
0.17
0.10
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


174.04
154.33
153.46
79.75
60.21
59.96
54.12
52.00
32.58
31.80
28.93
28.39
20.67
19.91
Me
N
Boc
OMe
O
16c
5-epi-16c
90 : 10
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

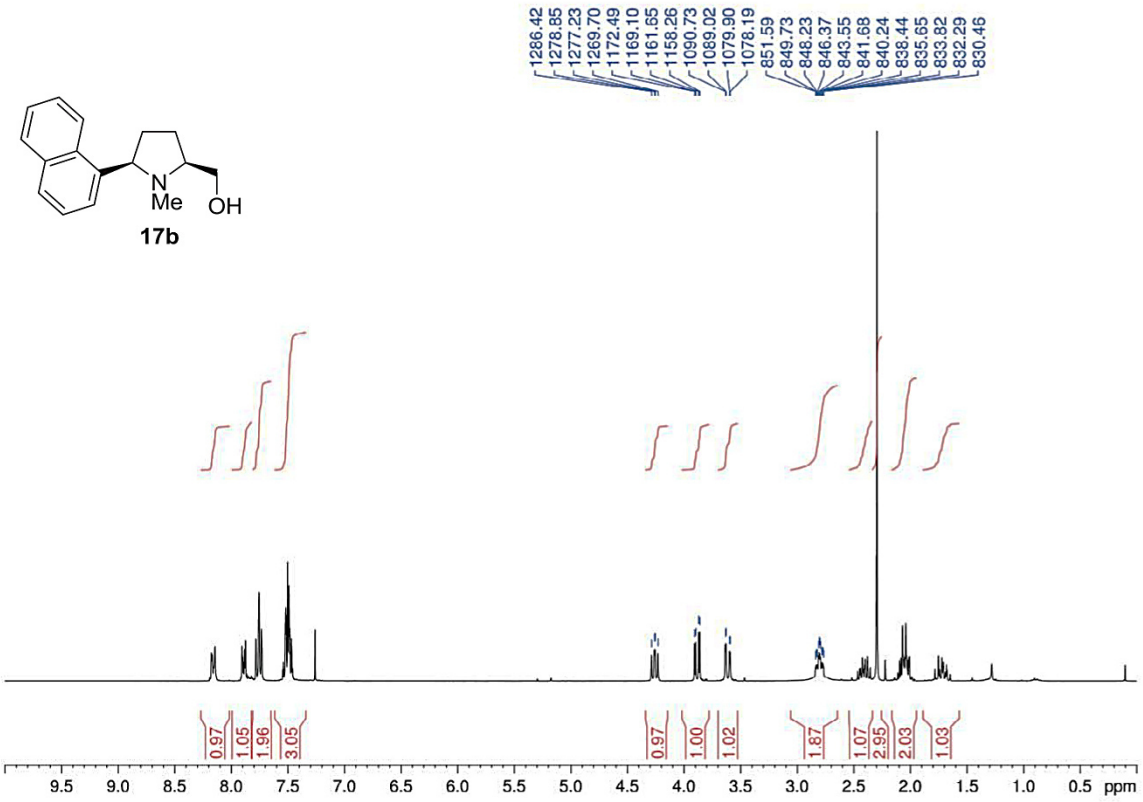
80

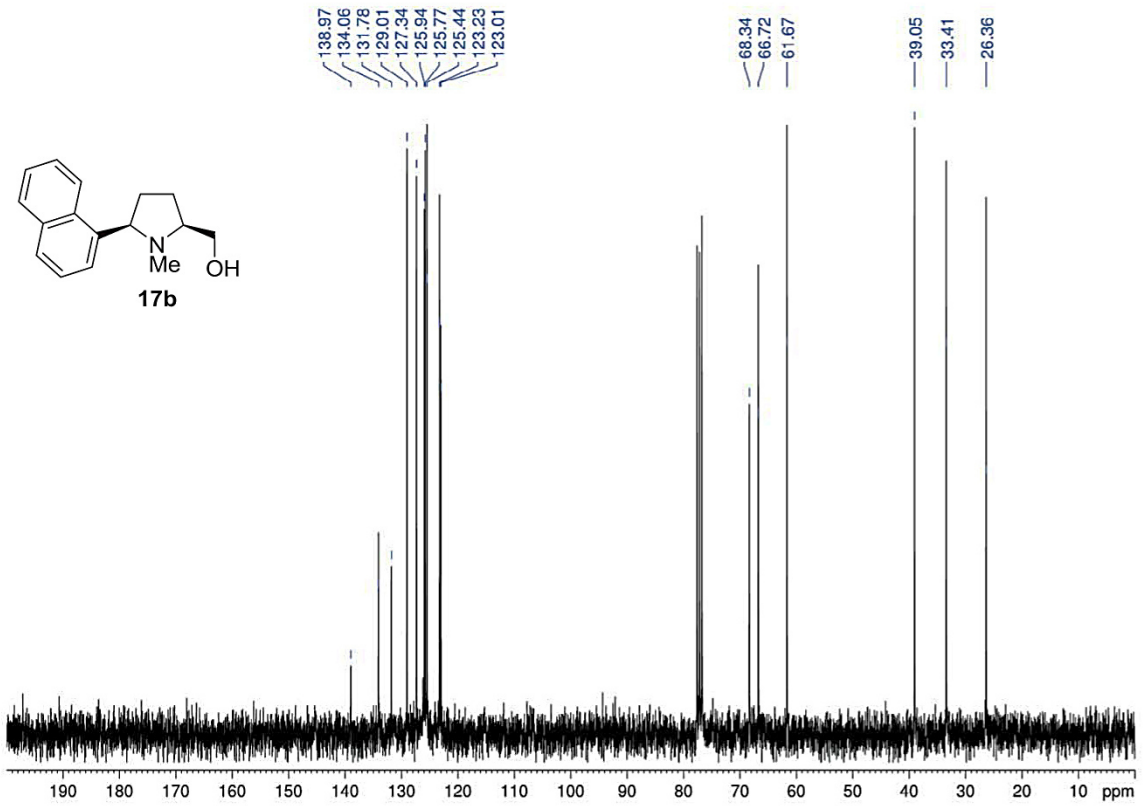

284.91
278.07
263.06
256.34
iPr
N
Boc
OMe
O
16d
0.40
0.58
3.62
0.41
1.04
4.02
3.64
5.37
2.98
2.98
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
173.99
173.81
154.55
79.79
64.38
64.14
60.50
60.00
52.00
51.82
31.44
31.28
29.21
28.33
27.51
26.47
20.13
19.91
18.58
18.20
iPr
N
Boc
OMe
O
16d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

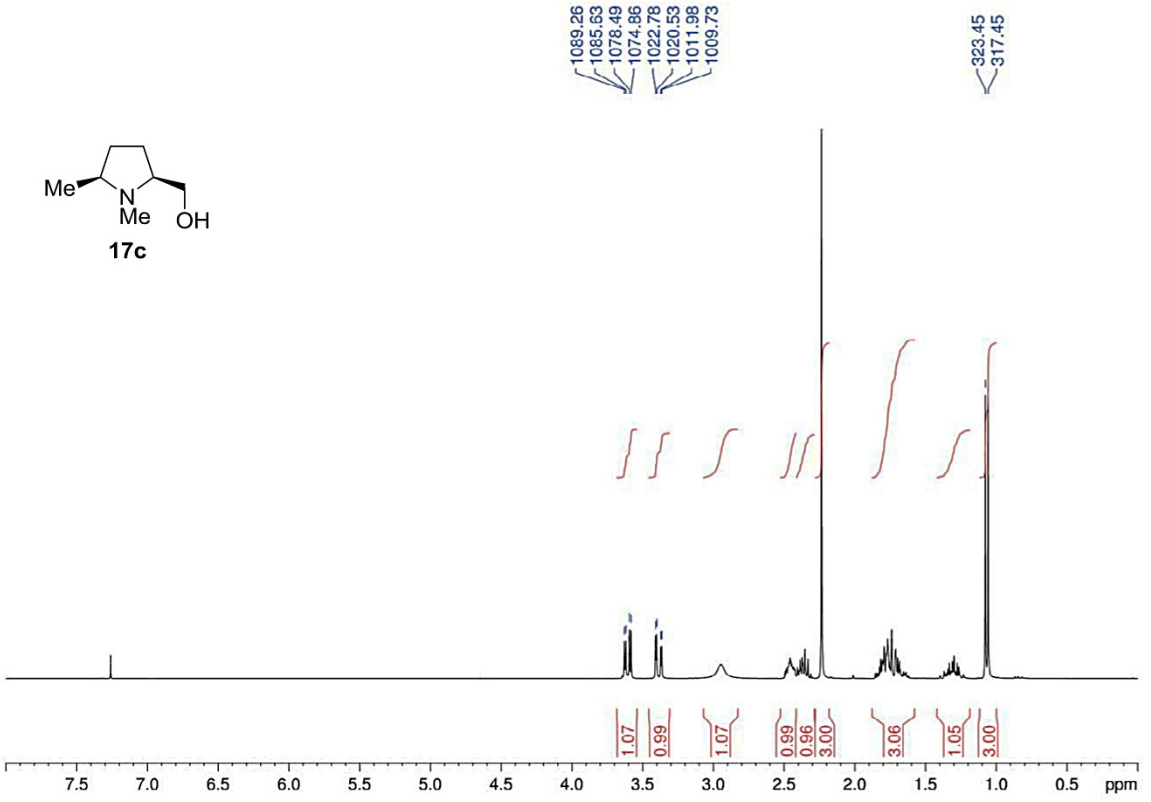
81

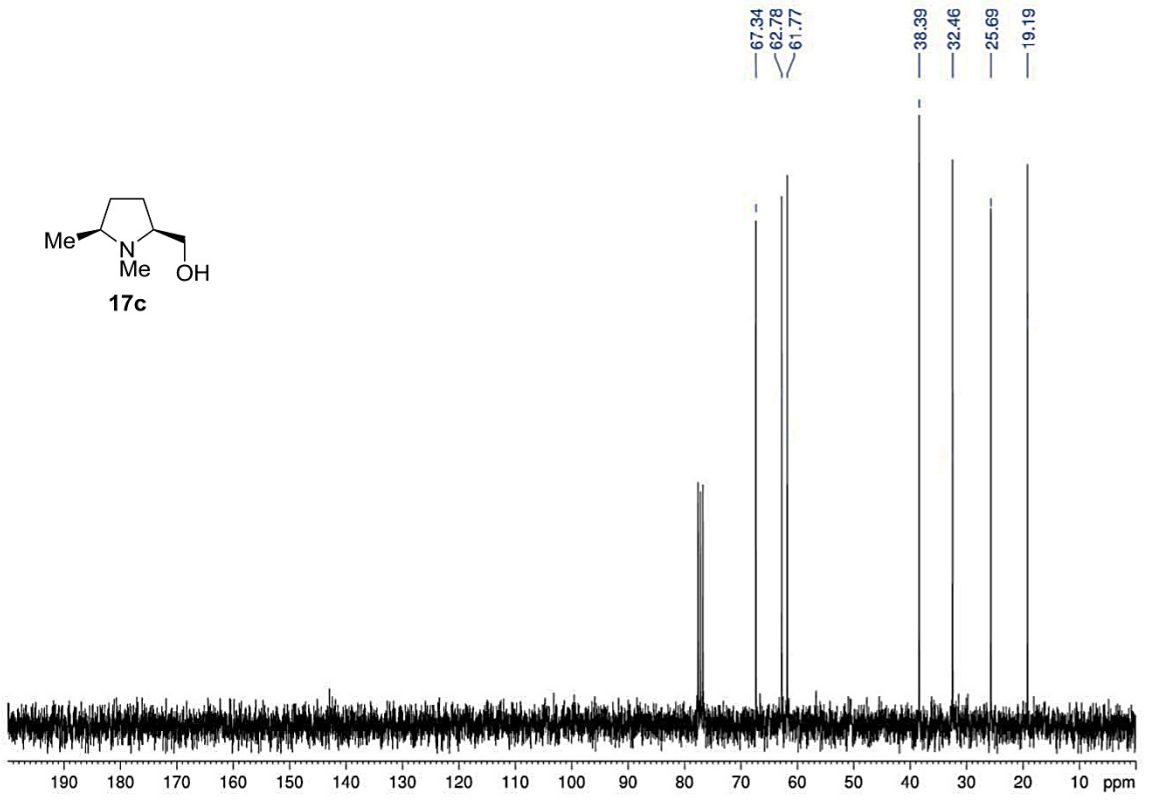

1318.05
1310.28
1302.47
1283.24
1275.28
1267.06
1034.94
1031.58
1021.70
1018.49
992.50
988.48
979.41
975.51
Bn
N
Boc
O
OMe
16e
5.36
0.45
0.55
1.04
2.98
0.54
0.44
1.00
0.94
1.06
2.05
8.97
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
174.03
173.89
154.29
153.61
139.32
129.53
129.42
128.50
128.42
126.20
80.10
60.38
60.22
59.98
59.48
52.22
52.05
40.93
39.76
29.53
28.81
28.42
28.27
Bn
N
Boc
O
OMe
16e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

82

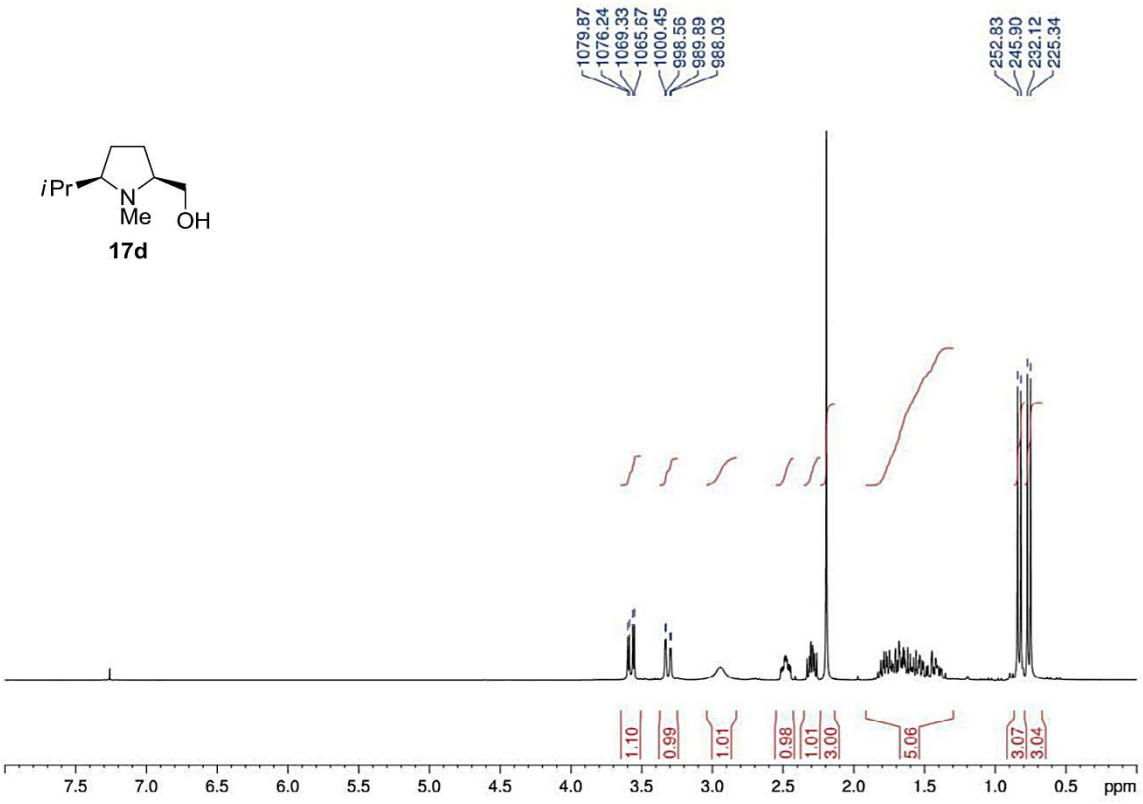

1286.42
1278.85
1277.23
1269.70
1172.49
1169.10
1161.65
1158.26
1090.73
1089.02
1079.90
1078.19
851.59
849.73
848.23
846.37
843.55
841.68
840.24
838.44
835.65
833.82
832.29
830.46
N
Me
OH
17b
0.97
1.05
1.96
3.05
0.97
1.00
1.02
1.87
1.07
2.95
2.03
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

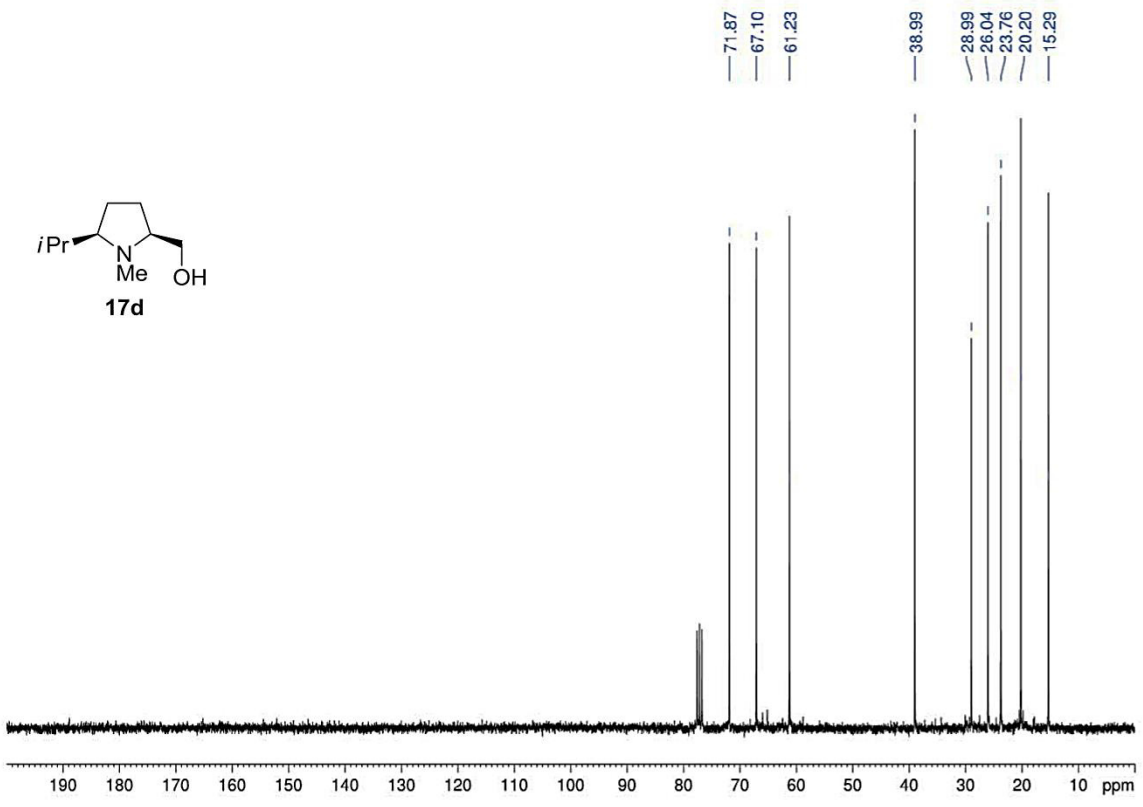

138.97
134.06
131.78
129.01
127.34
125.94
125.77
125.44
123.23
123.01
68.34
66.72
61.67
39.05
33.41
26.36
N
Me
OH
17b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

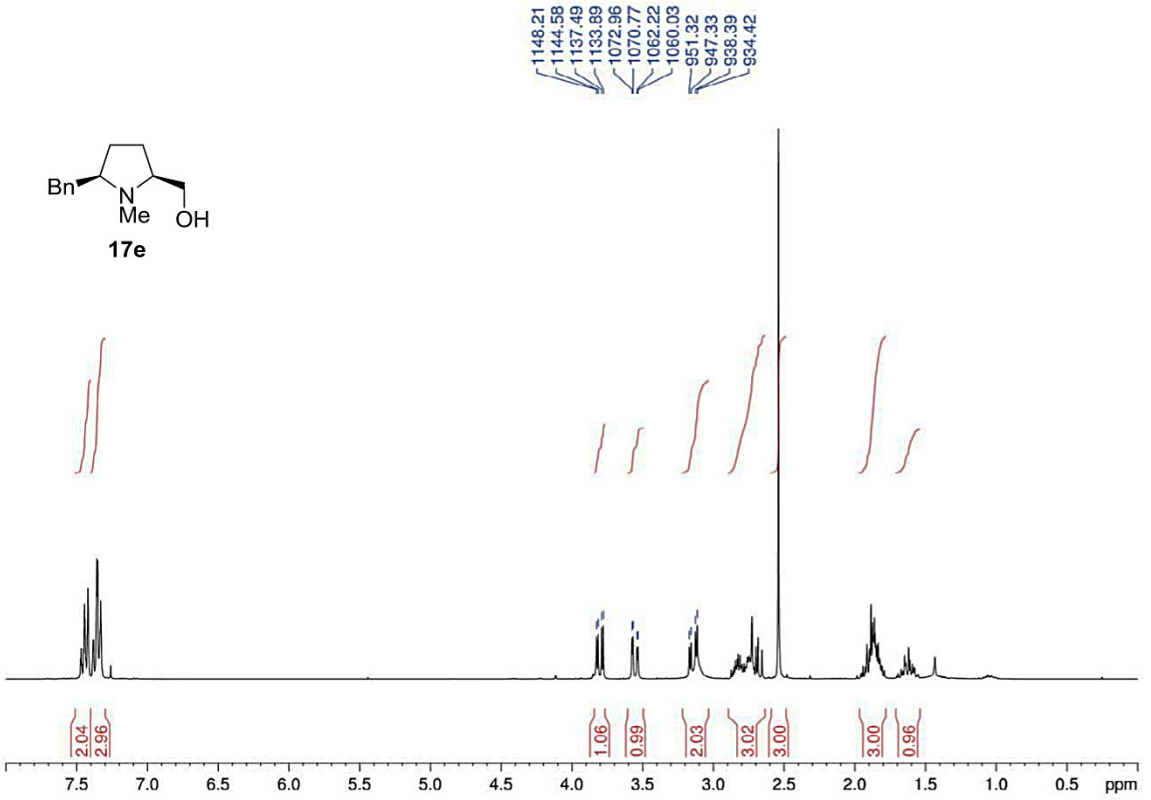

1089.26
1085.63
1078.49
1074.86
1022.78
1020.53
1011.98
1009.73
323.45
317.45
Me
N
Me
OH
17c
1.07
0.99
1.07
0.99
0.96
3.00
3.06
1.05
3.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

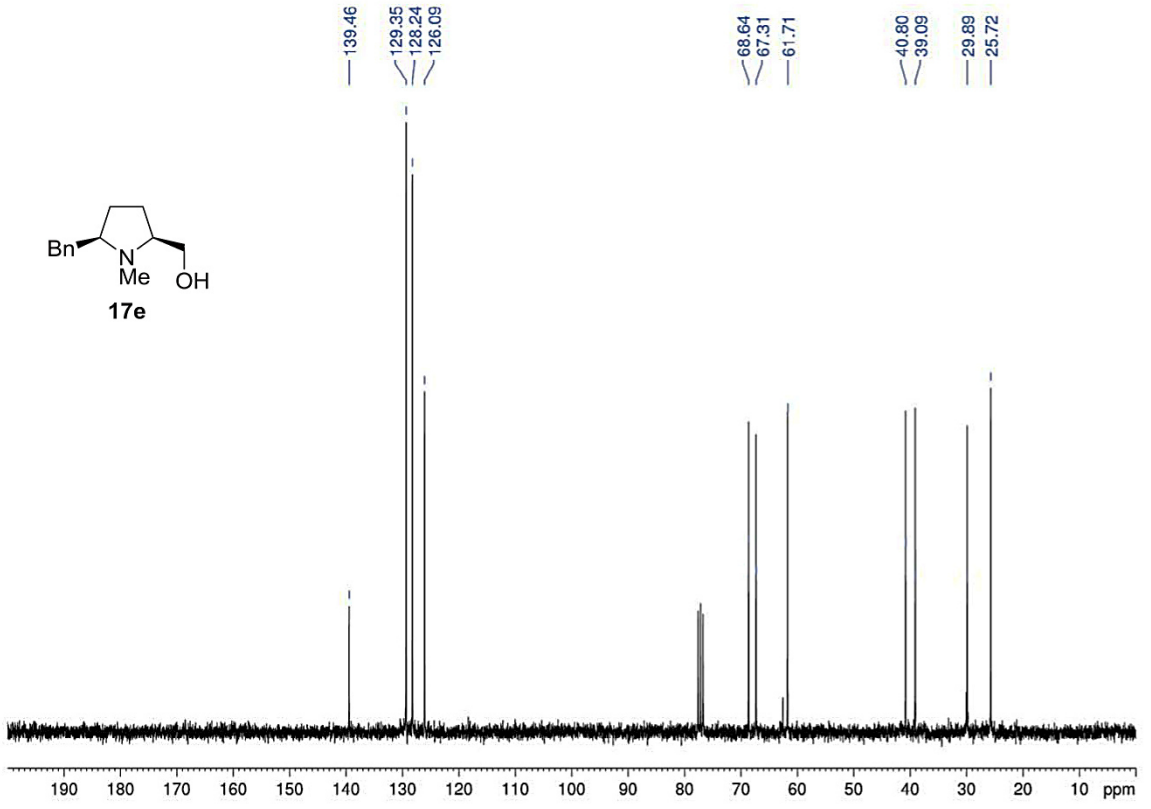

67.34
62.78
61.77
38.39
32.46
25.69
19.19
Me
N
Me
OH
17c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

84

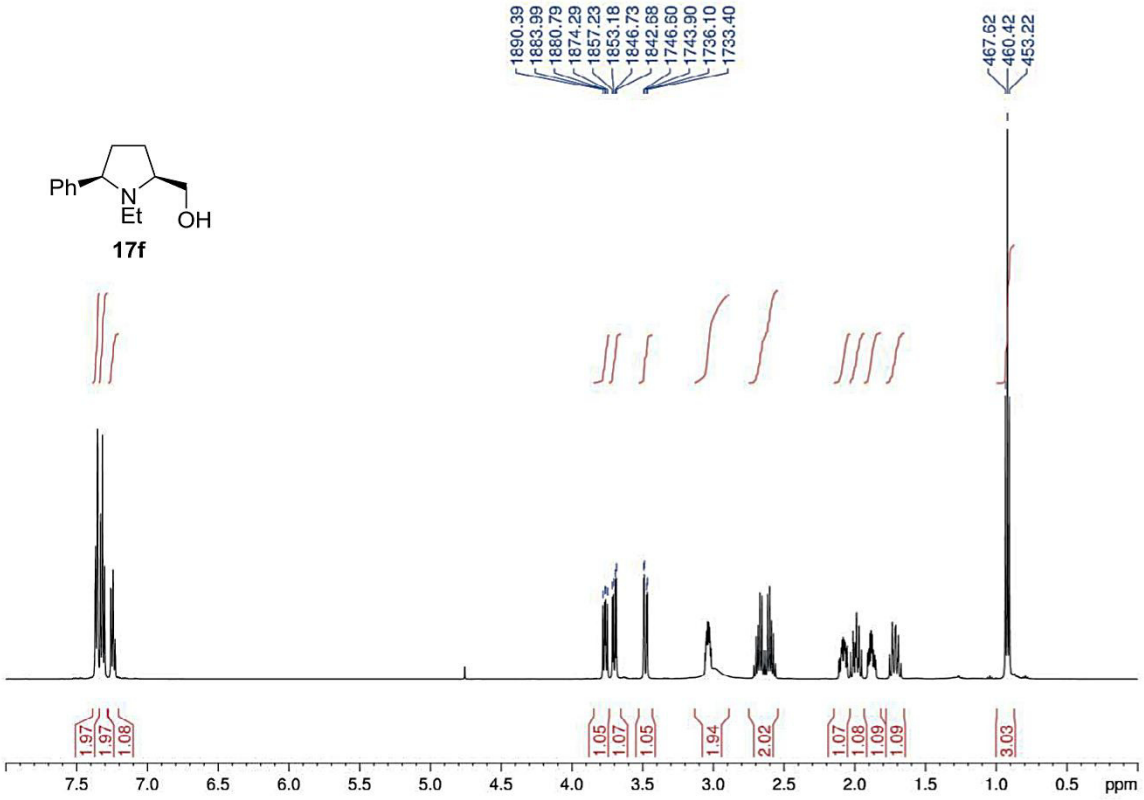

1079.87
1076.24
1069.33
1065.67
1000.45
998.56
989.89
988.03
252.83
245.90
232.12
225.34
iPr
N
Me
OH
17d
1.10
0.99
1.01
0.98
1.01
3.00
5.06
3.07
3.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

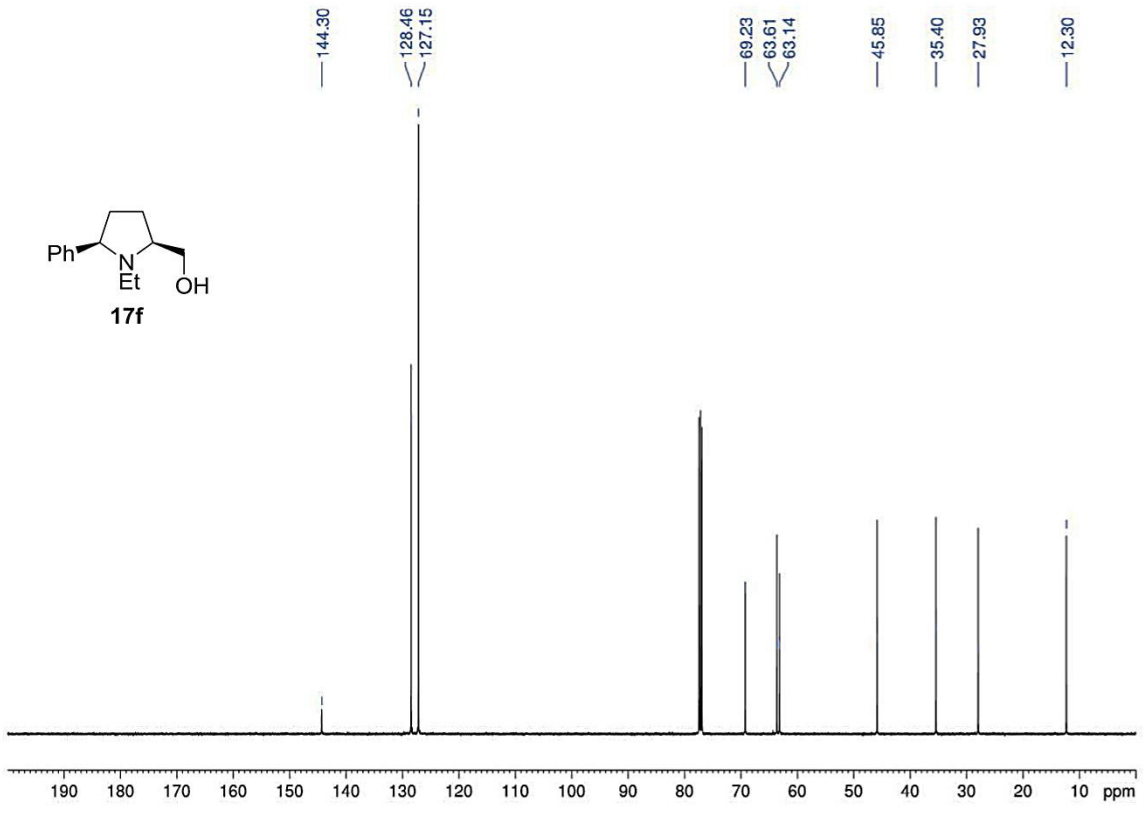

71.87
67.10
61.23
38.99
28.99
26.04
23.76
20.20
15.29
iPr
N
Me
OH
17d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


1148.21
1144.58
1137.49
1133.89
1072.96
1070.77
1062.22
1060.03
951.32
947.33
938.39
934.42
Bn
N
Me
OH
17e
2.04
2.96
1.06
0.99
2.03
3.02
3.00
3.00
0.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

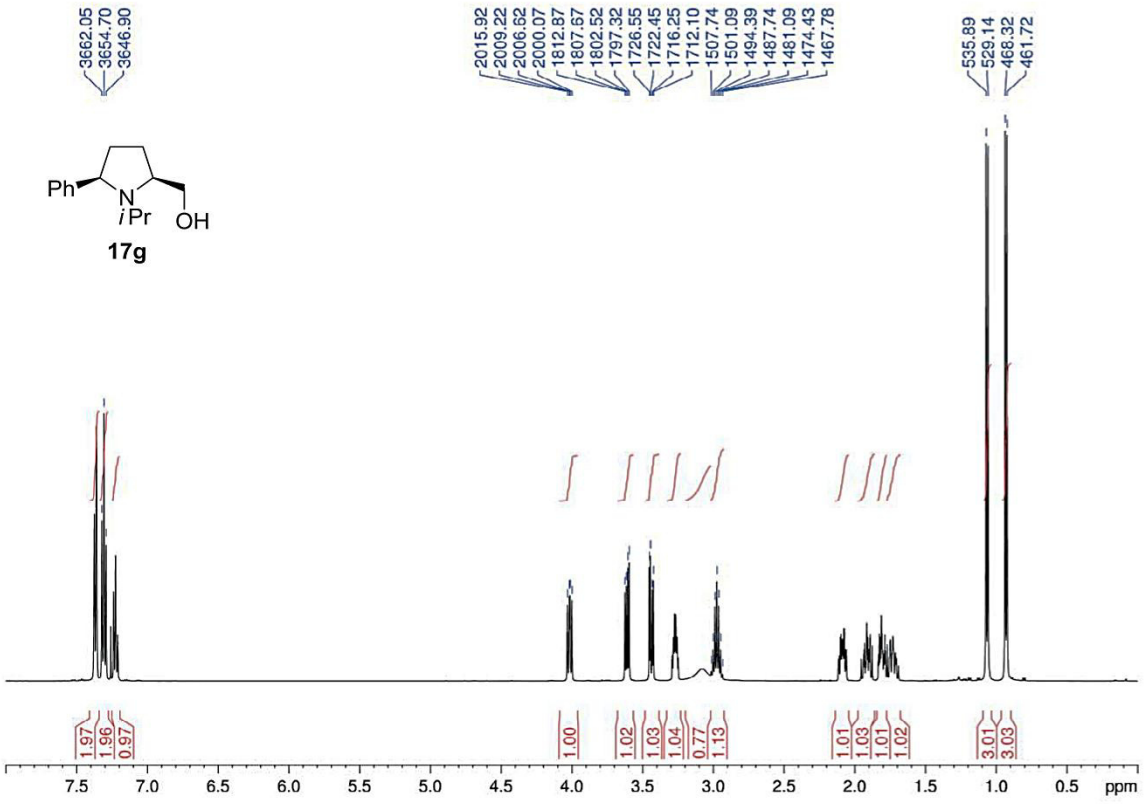

139.46
129.35
128.24
126.09
68.64
67.31
61.71
40.80
39.09
29.89
25.72
Bn
N
Me
OH
17e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

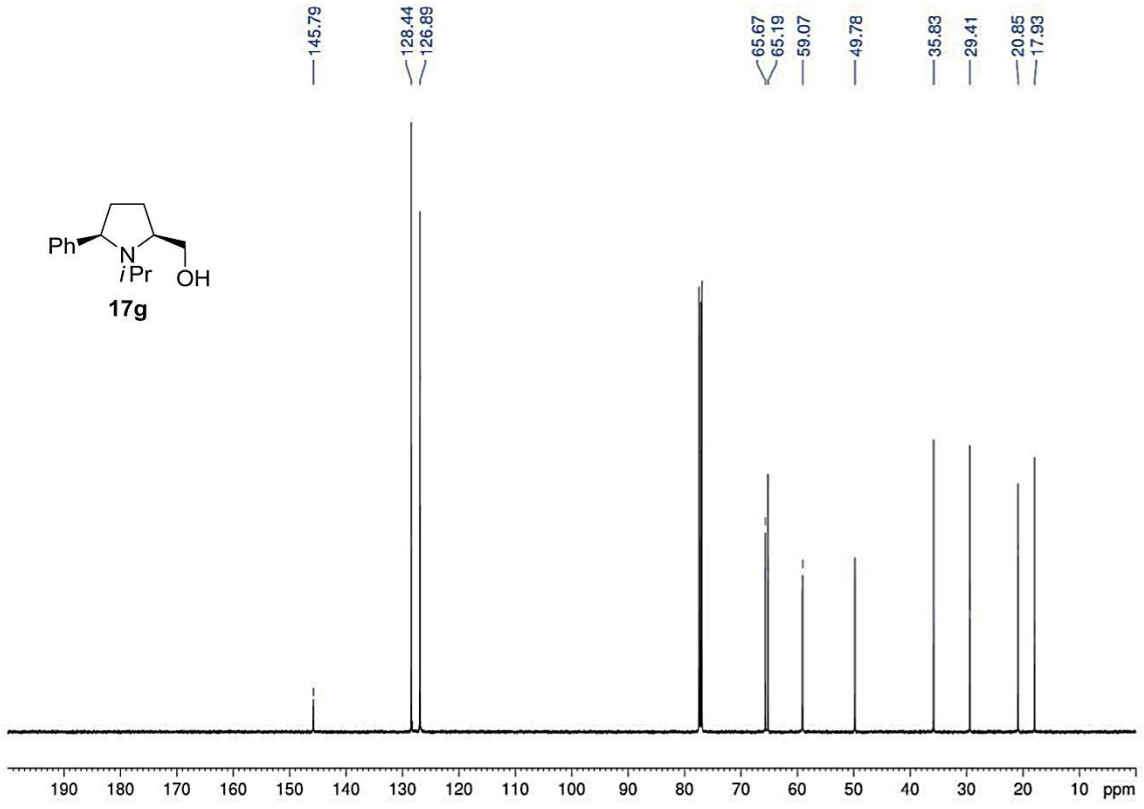
86


1890.39
1883.99
1880.79
1874.29
1857.23
1853.18
1846.73
1842.68
1746.60
1743.90
1736.10
1733.40
467.62
460.42
453.22
Ph
N
Et
OH
17f
1.97
1.97
1.08
1.05
1.07
1.05
1.94
2.02
1.07
1.08
1.09
1.09
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

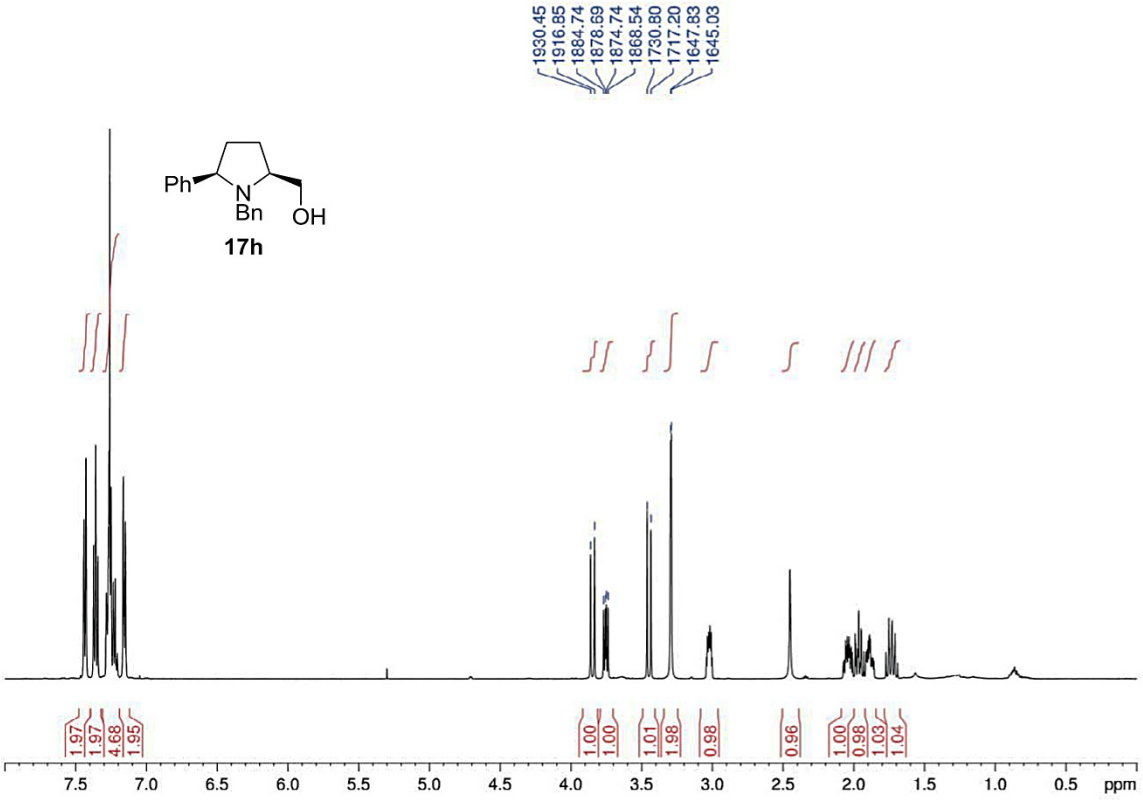

144.30
128.46
127.15
69.23
63.61
63.14
45.85
35.40
27.93
12.30
Ph
N
Et
OH
17f
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

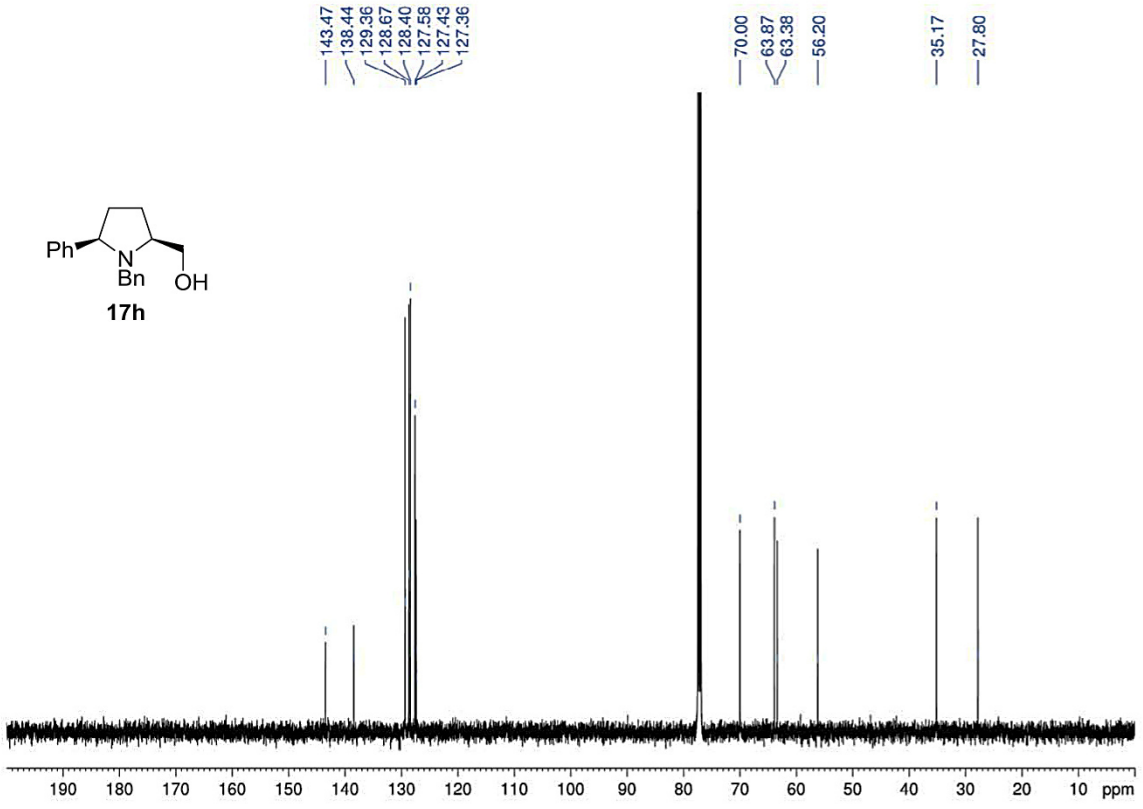
87


3662.05
3654.70
3646.90
2015.92
2009.22
2006.62
2000.07
1812.87
1807.67
1802.52
1797.32
1726.55
1722.45
1716.25
1712.10
1507.74
1501.09
1494.39
1487.74
1481.09
1474.43
1467.78
535.89
529.14
468.32
461.72
Ph
N
iPr
OH
17g
1.97
1.96
0.97
1.00
1.02
1.03
1.04
0.77
1.13
1.01
1.03
1.01
1.02
3.01
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

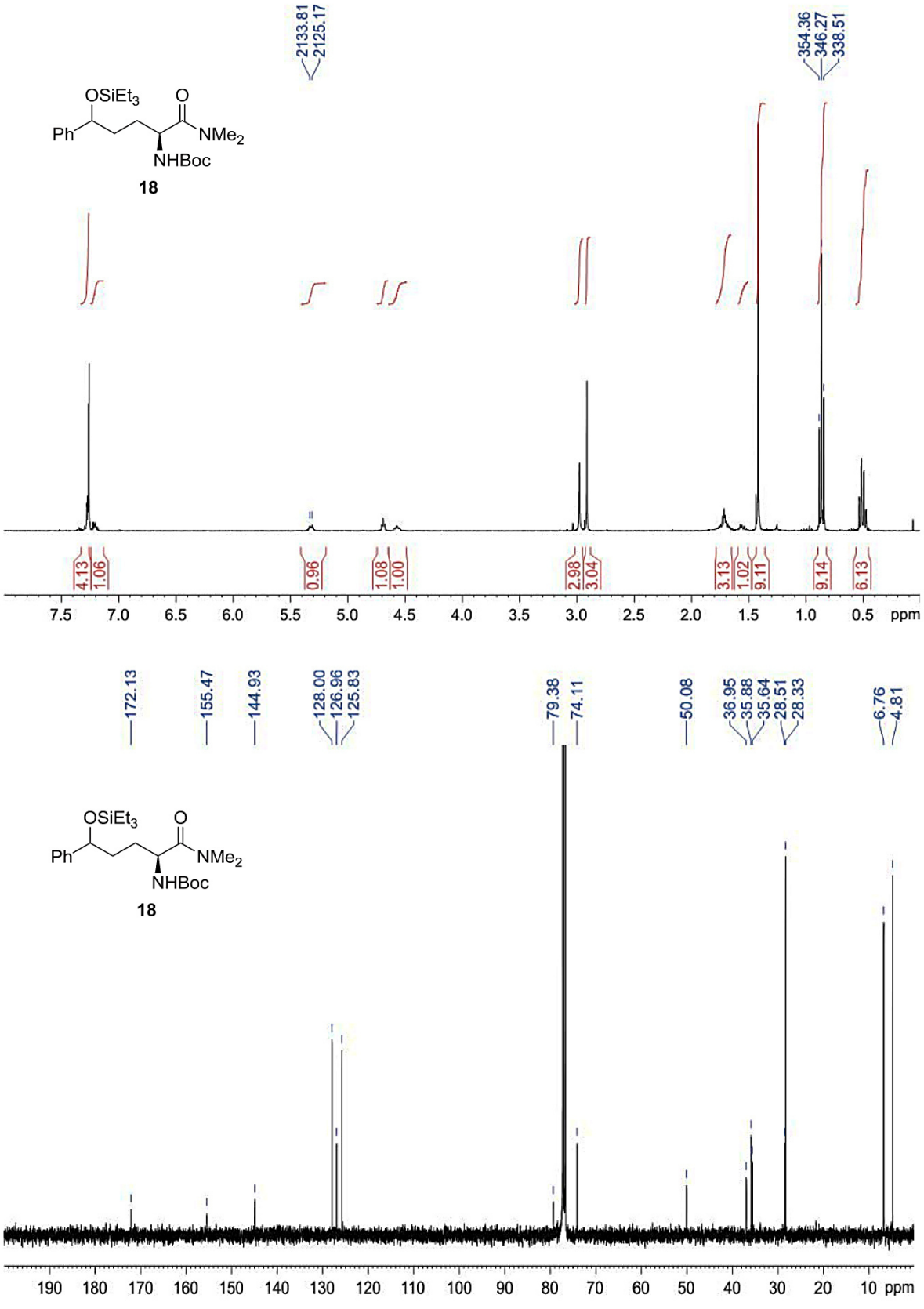

145.79
128.44
126.89
65.67
65.19
59.07
49.78
35.83
29.41
20.85
17.93
Ph
N
iPr
OH
17g
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

88

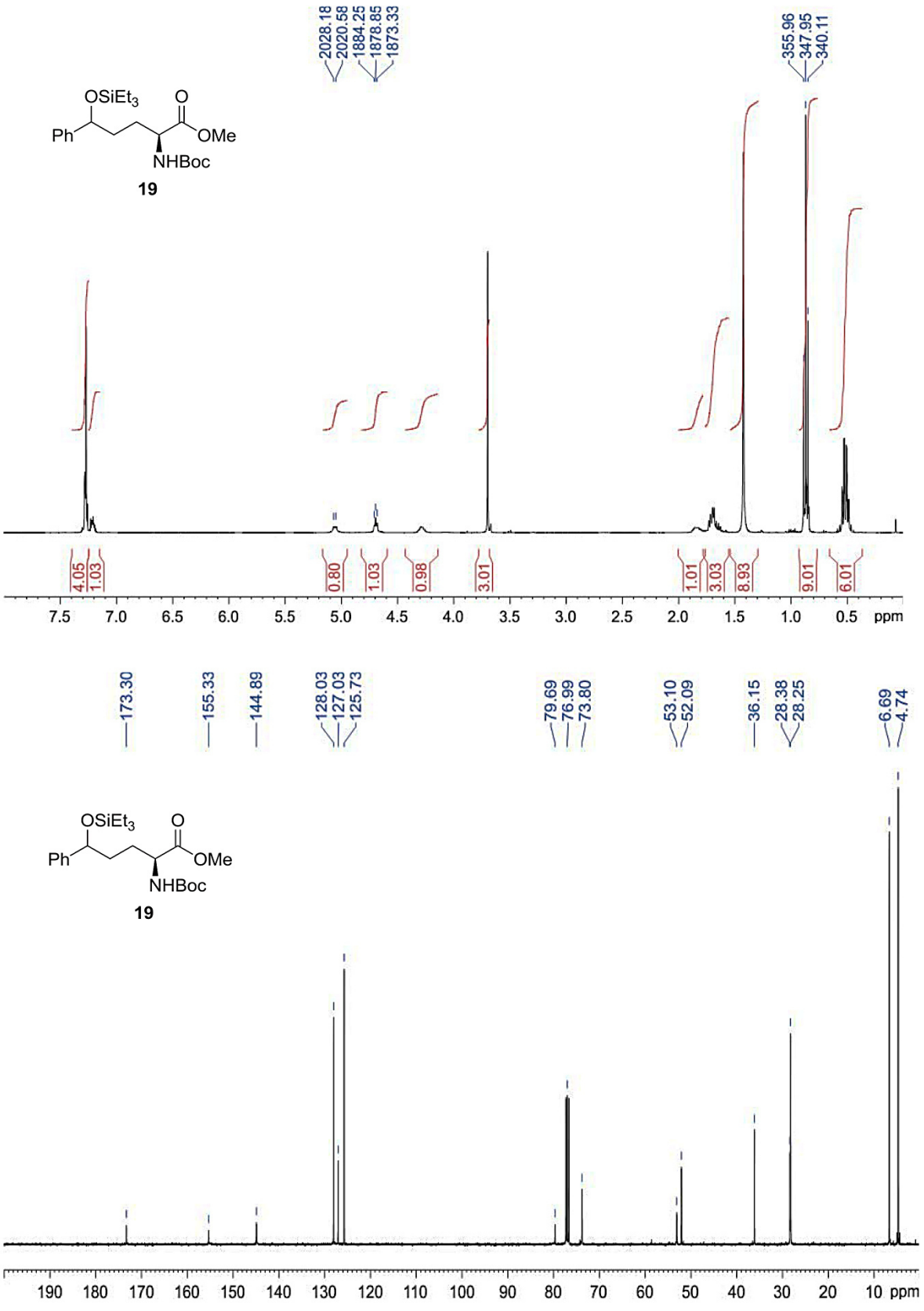

1930.45
1916.85
1884.74
1878.69
1874.74
1868.54
1730.80
1717.20
1647.83
1645.03
Ph
N
Bn
OH
17h
1.97
1.97
4.68
1.95
1.00
1.00
1.01
1.98
0.98
0.96
1.00
0.98
1.03
1.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


143.47
138.44
129.36
128.67
128.40
127.58
127.43
127.36
70.00
63.87
63.38
56.20
35.17
27.80
Ph
N
Bn
OH
17h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

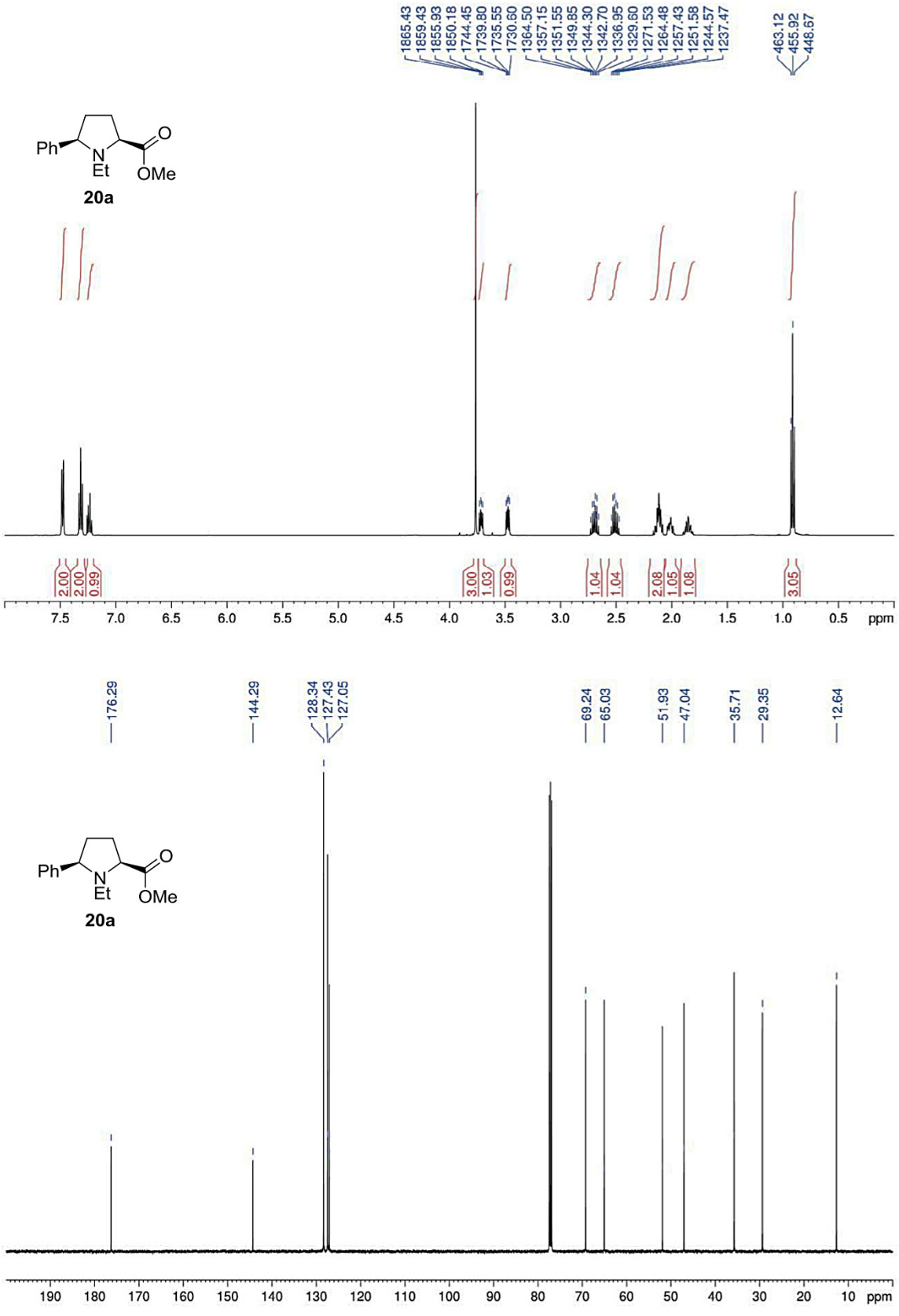
89


OSiEt3
O
Ph
NMe2
NHBoc
18
2133.81
2125.17
354.36
346.27
338.51
4.13
1.06
0.96
1.08
1.00
2.98
3.04
3.13
1.02
9.11
9.14
6.13
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
172.13
155.47
144.93
128.00
126.96
125.83
79.38
74.11
50.08
36.95
35.88
35.64
28.51
28.33
6.76
4.81
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

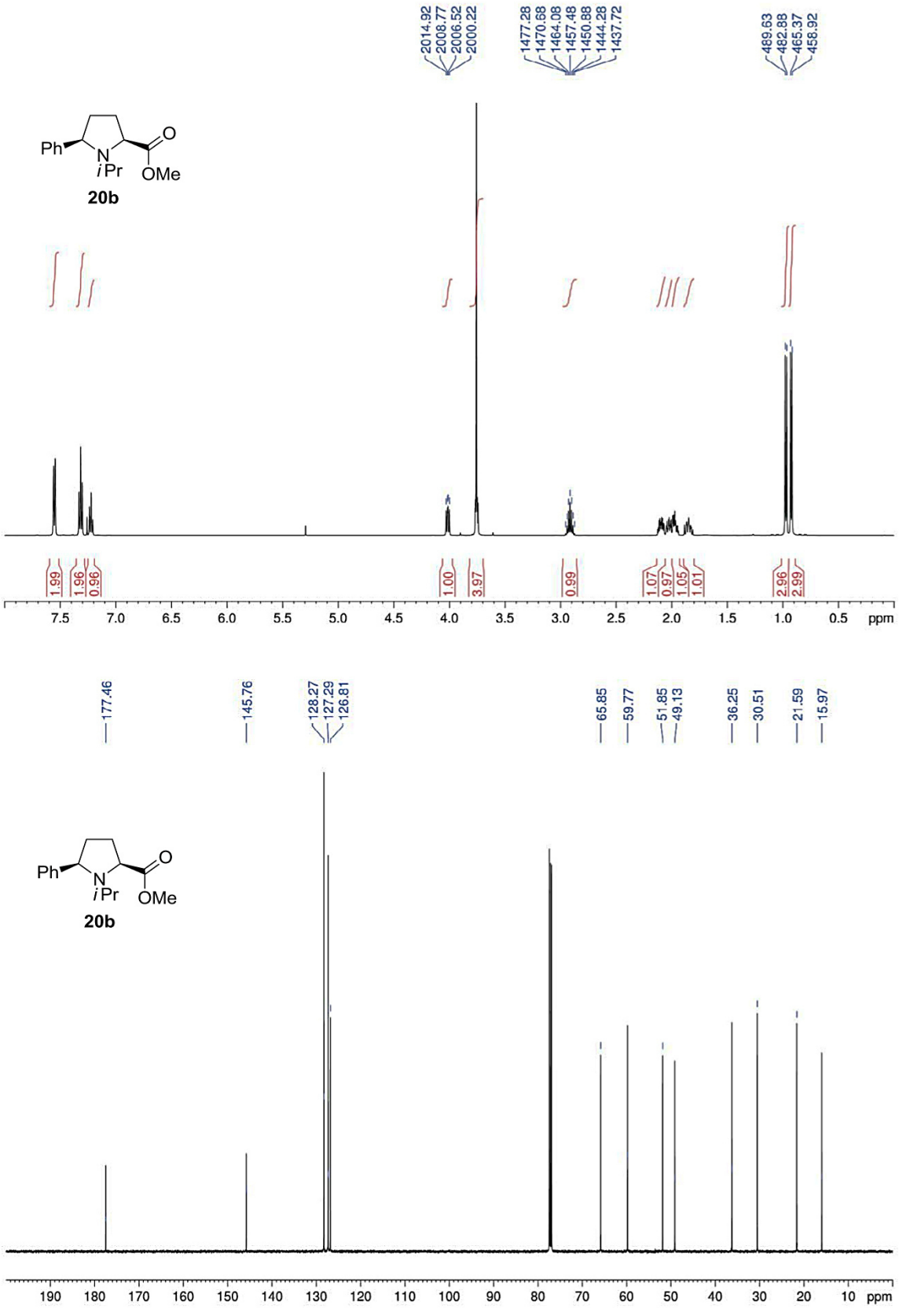
90


OSiEt3
O
Ph
OMe
NHBoc
19
2028.18
2020.58
1884.25
1878.85
1873.33
355.96
347.95
340.11
4.05
1.03
0.80
1.03
0.98
3.01
1.01
3.03
8.93
9.01
6.01
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
173.30
155.33
144.89
128.03
127.03
125.73
79.69
76.99
73.80
53.10
52.09
36.15
28.38
28.25
6.69
4.74
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

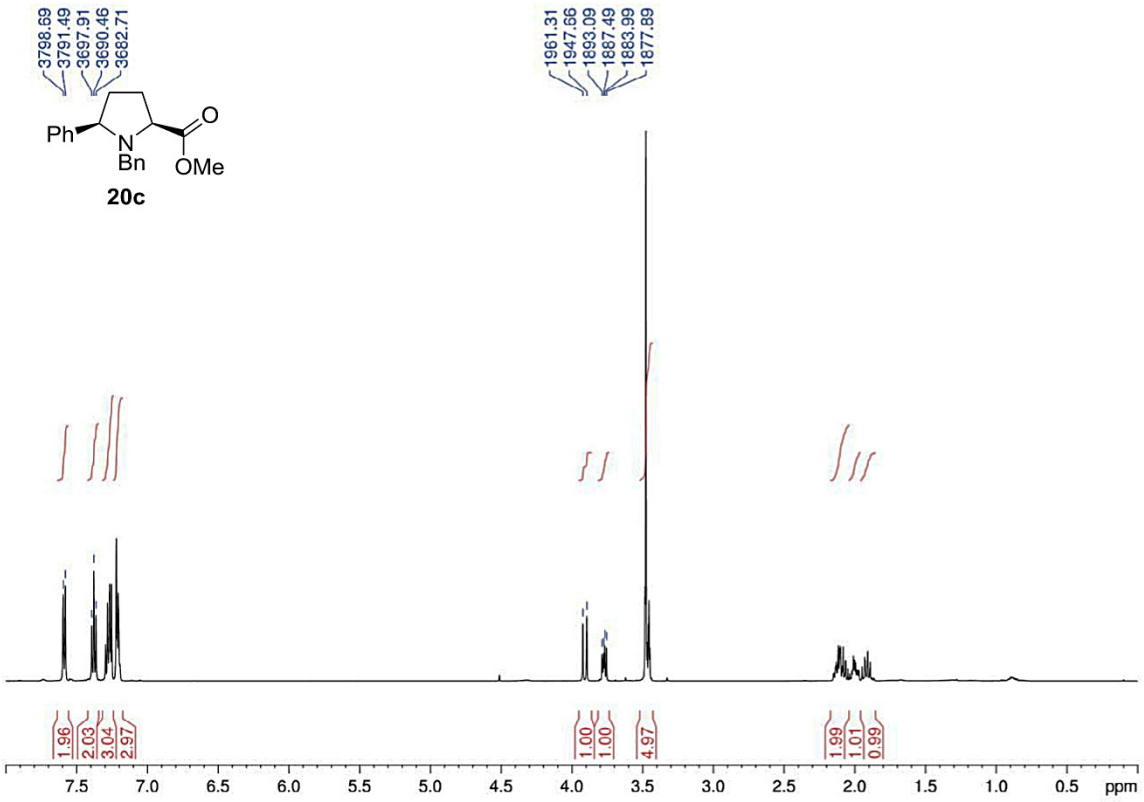
91

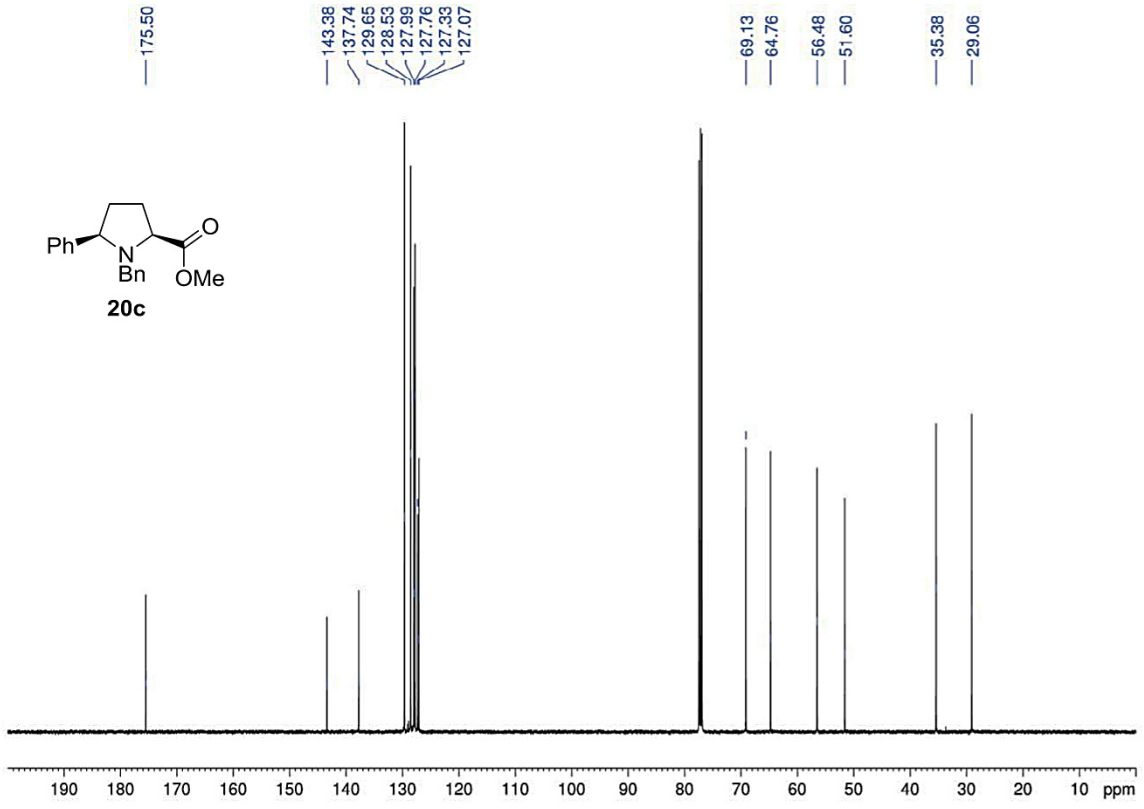

1865.43
1859.43
1855.93
1850.18
1744.45
1739.80
1735.55
1730.60
1364.50
1357.15
1351.55
1349.85
1344.30
1342.70
1336.95
1329.60
1271.53
1264.48
1257.43
1251.58
1244.57
1237.47
463.12
455.92
448.67
Ph
N
Et
O
OMe
20a
2.00
2.00
0.99
3.00
1.03
0.99
1.04
1.04
2.08
1.05
1.08
3.05
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
176.29
144.29
128.34
127.43
127.05
69.24
65.03
51.93
47.04
35.71
29.35
12.64
Ph
N
Et
O
OMe
20a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

92

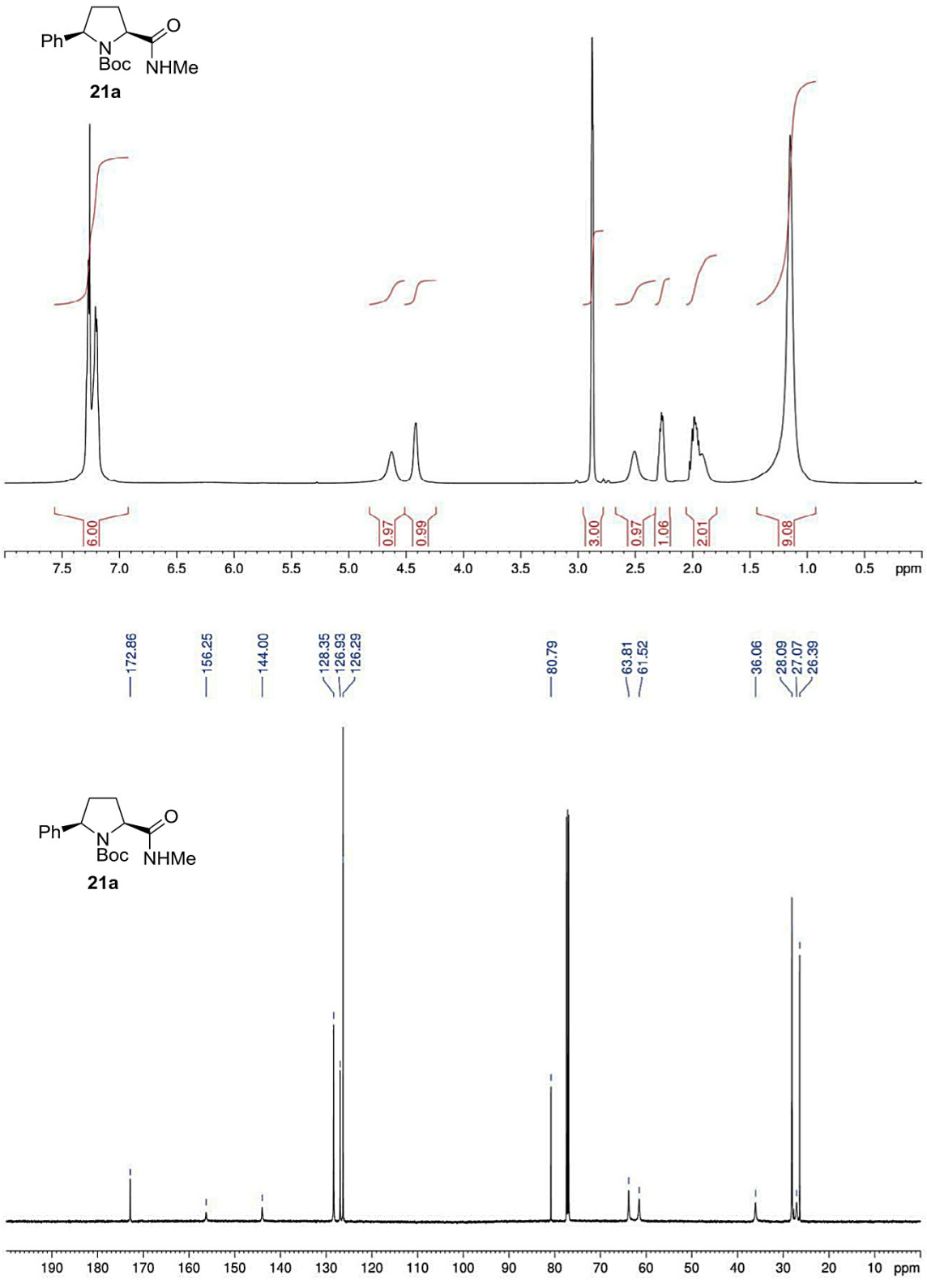

2014.92
2008.77
2006.52
2000.22
1477.28
1470.68
1464.08
1457.48
1450.88
1444.28
1437.72
489.63
482.88
465.37
458.92
Ph
N
iPr
O
OMe
20b
1.99
1.96
0.96
1.00
3.97
0.99
1.07
0.97
1.05
1.01
2.96
2.99
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
177.46
145.76
128.27
127.29
126.81
65.85
59.77
51.85
49.13
36.25
30.51
21.59
15.97
Ph
N
iPr
O
OMe
20b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

93

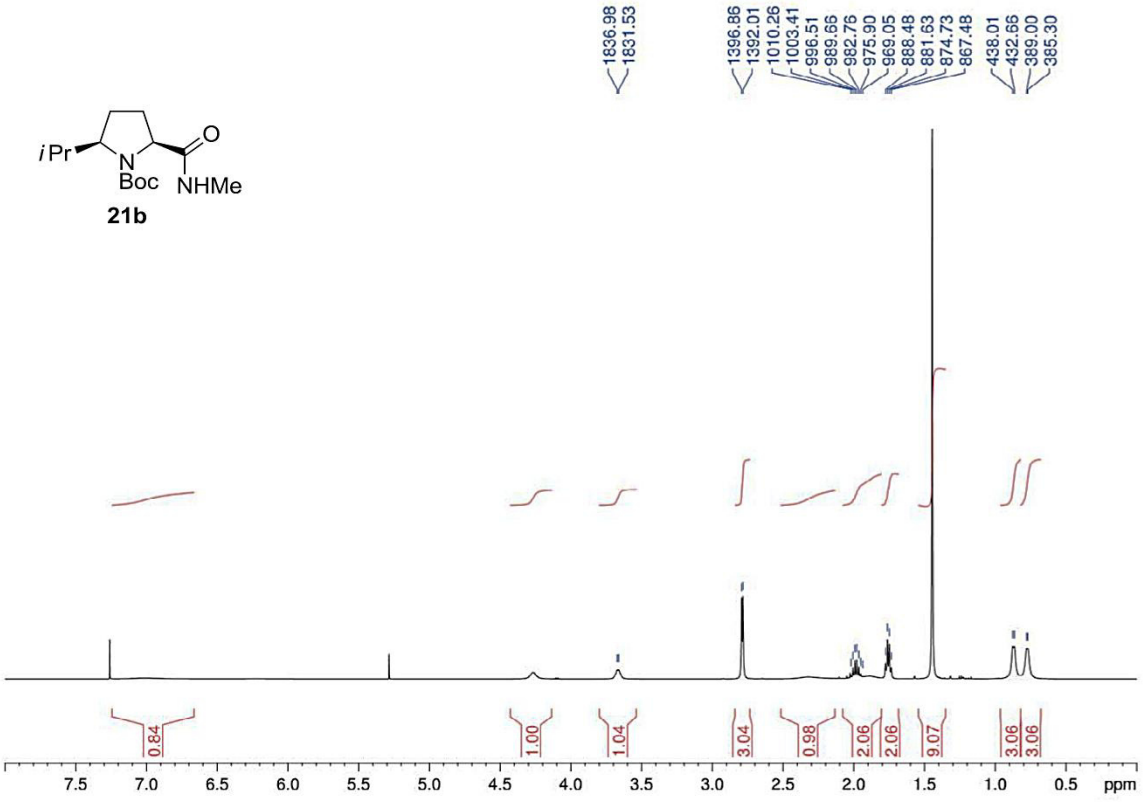

3798.69
3791.49
3697.91
3690.46
3682.71
1961.31
1947.66
1893.09
1887.49
1883.99
1877.89
Ph
N
Bn
O
OMe
20c
1.96
2.03
3.04
2.97
1.00
1.00
4.97
1.99
1.01
0.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

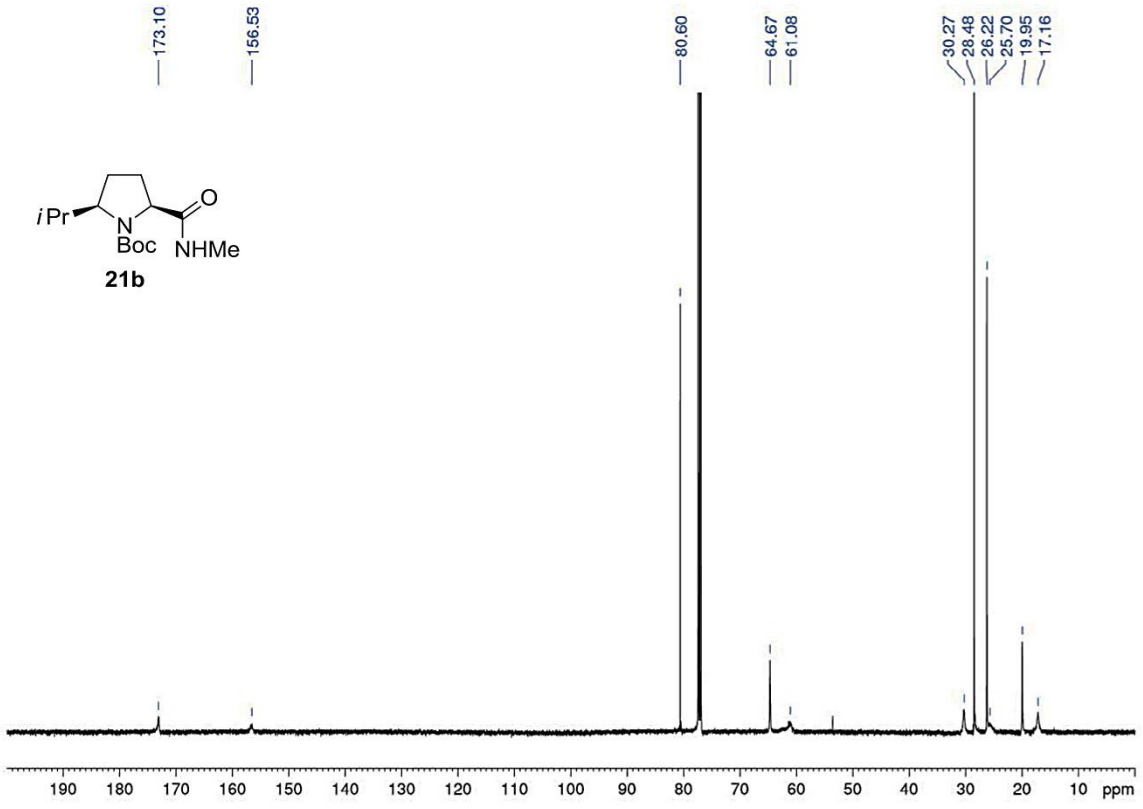

175.50
143.38
137.74
129.65
128.53
127.99
127.76
127.33
127.07
69.13
64.76
56.48
51.60
35.38
29.06
Ph
N
Bn
O
OMe
20c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

94

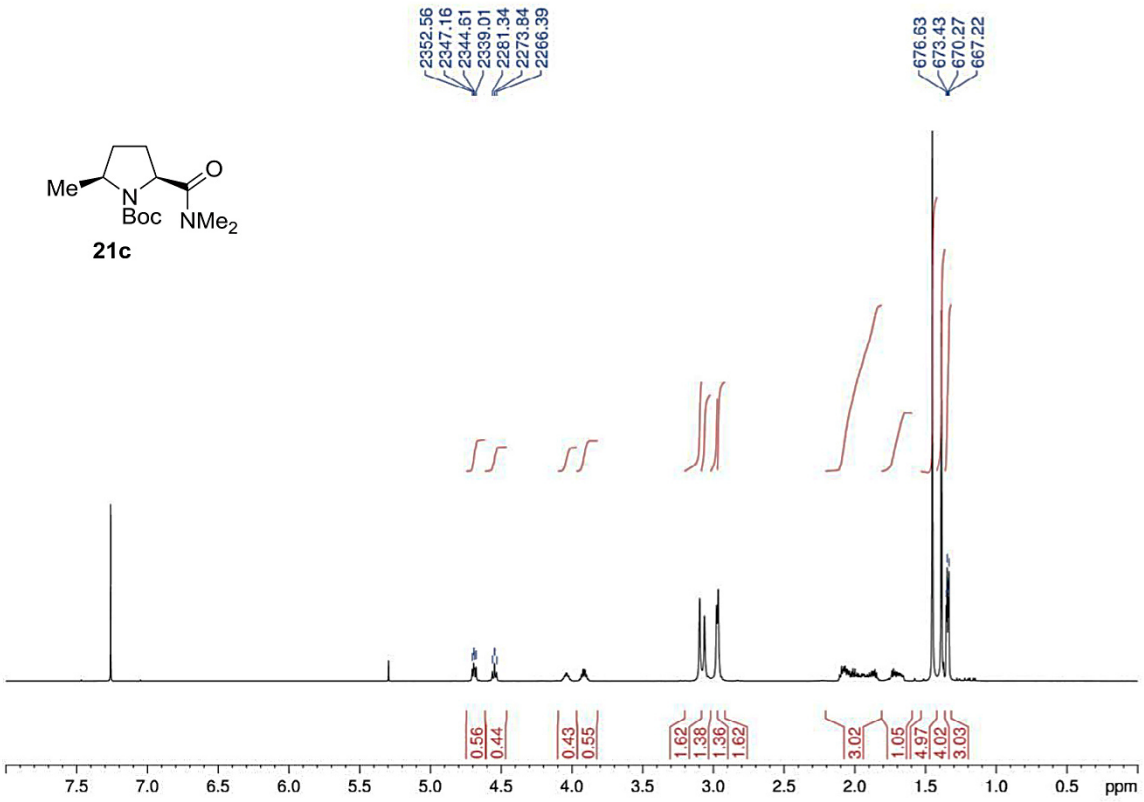

Ph
N
Boc
O
NHMe
21a
6.00
0.97
0.99
3.00
0.97
1.06
2.01
9.08
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
172.86
156.25
144.00
128.35
126.93
126.29
80.79
63.81
61.52
36.06
28.09
27.07
26.39
Ph
N
Boc
O
NHMe
21a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

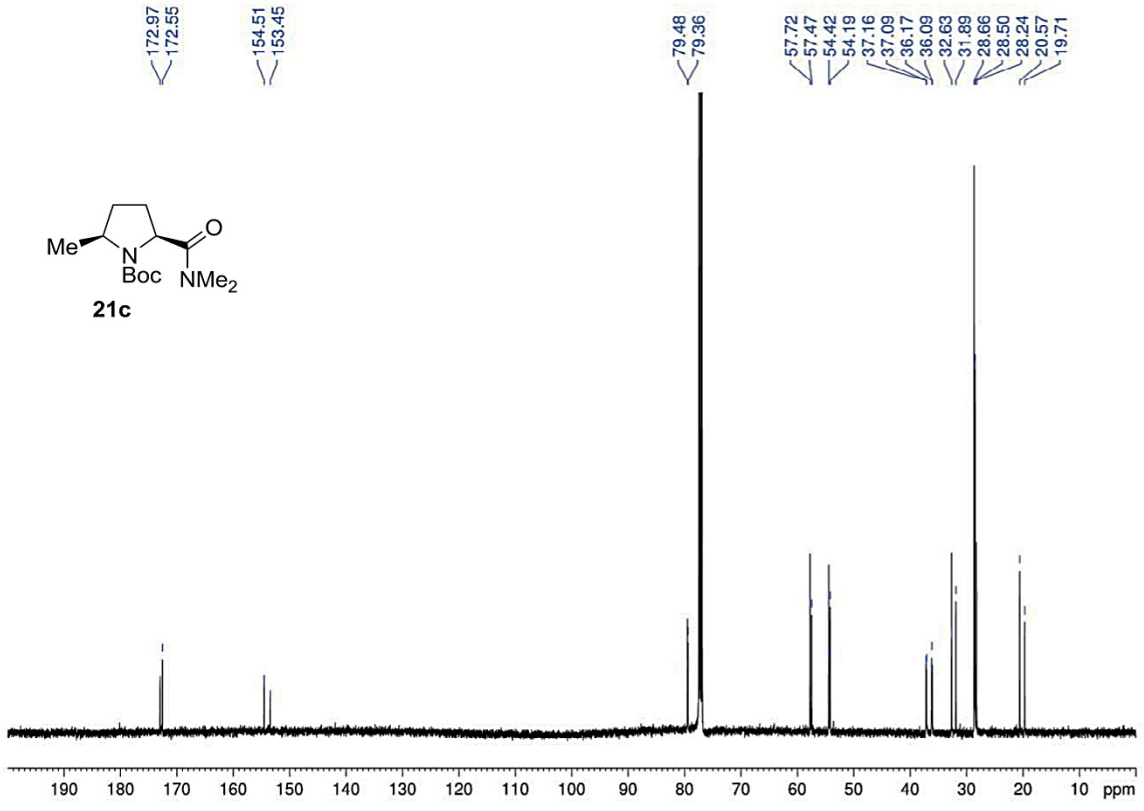
95


1836.98
1831.53
1396.86
1392.01
1010.26
1003.41
996.51
989.66
982.76
975.90
969.05
888.48
881.63
874.73
867.48
438.01
432.66
389.00
385.30
iPr
N
Boc
O
NHMe
21b
0.84
1.00
1.04
3.04
0.98
2.06
2.06
9.07
3.06
3.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

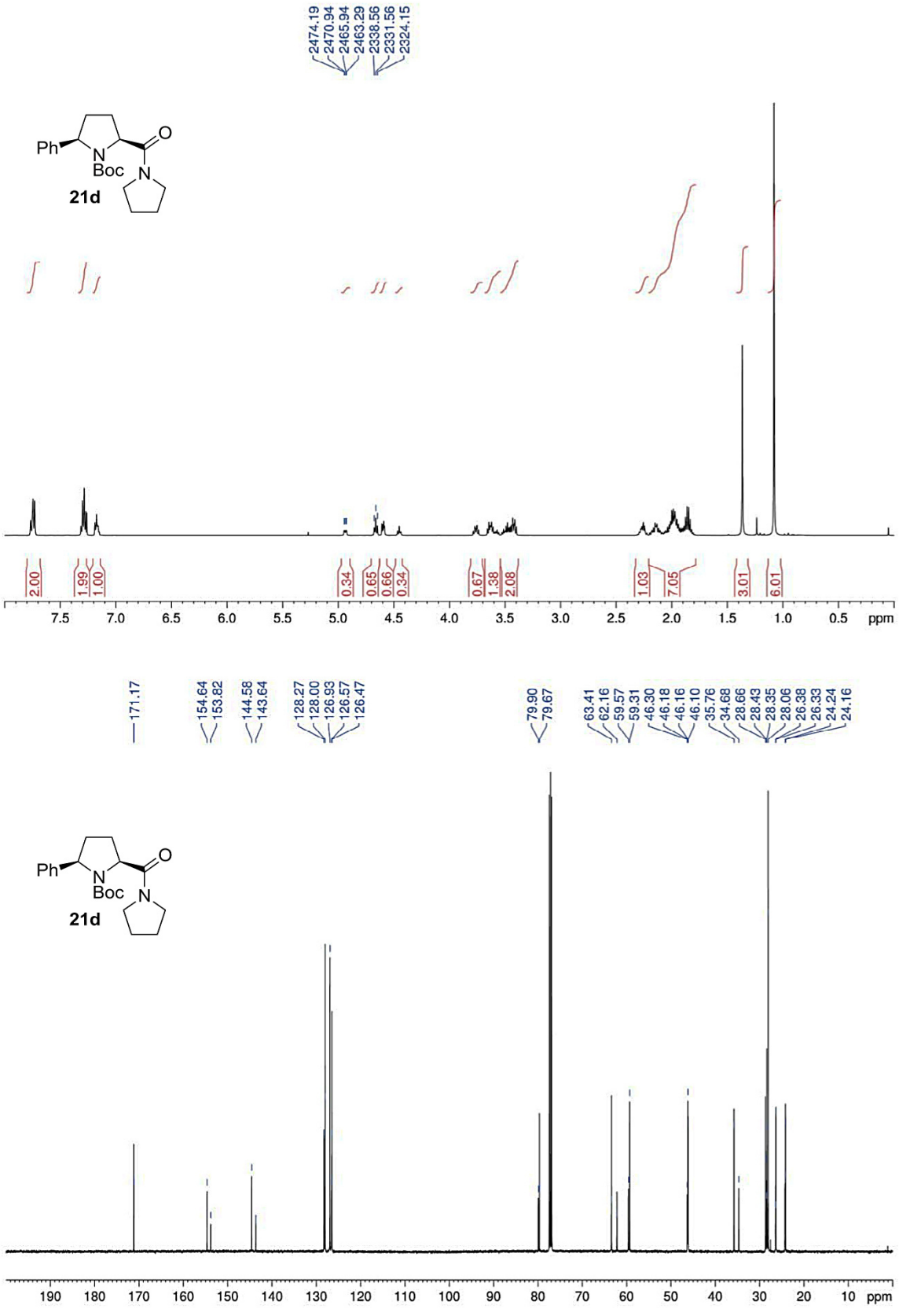

173.10
156.53
80.60
64.67
61.08
30.27
28.48
26.22
25.70
19.95
17.16
iPr
N
Boc
O
NHMe
21b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

96

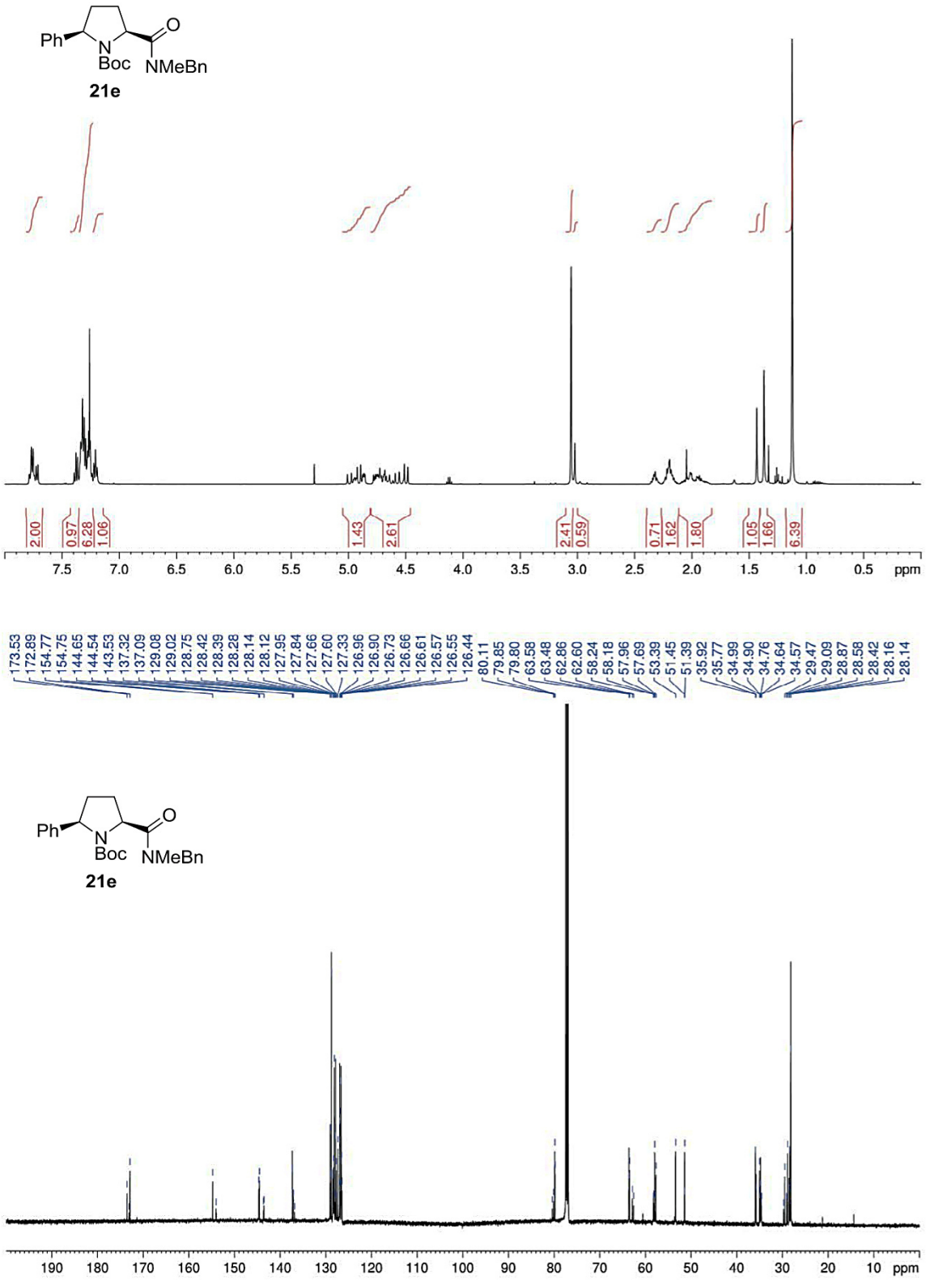

2352.56
2347.16
2344.61
2339.01
2281.34
2273.84
2266.39
676.63
673.43
670.27
667.22
Me
N
Boc
O
NMe2
21c
0.56
0.44
0.43
0.55
1.62
1.38
1.36
1.62
3.02
1.05
4.97
4.02
3.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


172.97
172.55
154.51
153.45
79.48
79.36
57.72
57.47
54.42
54.19
37.16
37.09
36.17
36.09
32.63
31.89
28.66
28.50
28.24
20.57
19.71
Me
N
Boc
O
NMe2
21c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

97


2474.19
2470.94
2465.94
2463.29
2338.56
2331.56
2324.15
Ph
N
Boc
O
N
21d
2.00
1.99
1.00
0.34
0.65
0.66
0.34
0.67
1.38
2.08
1.03
7.05
3.01
6.01
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
171.17
154.64
153.82
144.58
143.64
128.27
128.00
126.93
126.57
126.47
79.90
79.67
63.41
62.16
59.57
59.31
46.30
46.18
46.16
46.10
35.76
34.68
28.66
28.43
28.35
28.06
26.38
26.33
24.24
24.16
Ph
N
Boc
O
N
21d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

98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Boc
O
NMeBn
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1.43
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0.59
0.71
1.62
1.80
1.05
1.66
6.39
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
173.53 172.89 154.77 154.75 144.65 144.54 143.53 137.32 137.09 129.08 129.02 128.75 128.42 128.39 128.28 128.14 128.12 127.95 127.84 127.66 127.60 127.33 126.96 126.90 126.73 126.66 126.61 126.57 126.55 126.44 80.11 79.85 79.80 63.58 63.48 62.86 62.60 58.24 58.18 57.96 57.69 53.39 51.45 51.39 35.92 35.77 34.99 34.90 34.76 34.64 34.57 29.47 29.09 28.87 28.58 28.42 28.16 28.14
Ph
N
Boc
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NMeBn
21e
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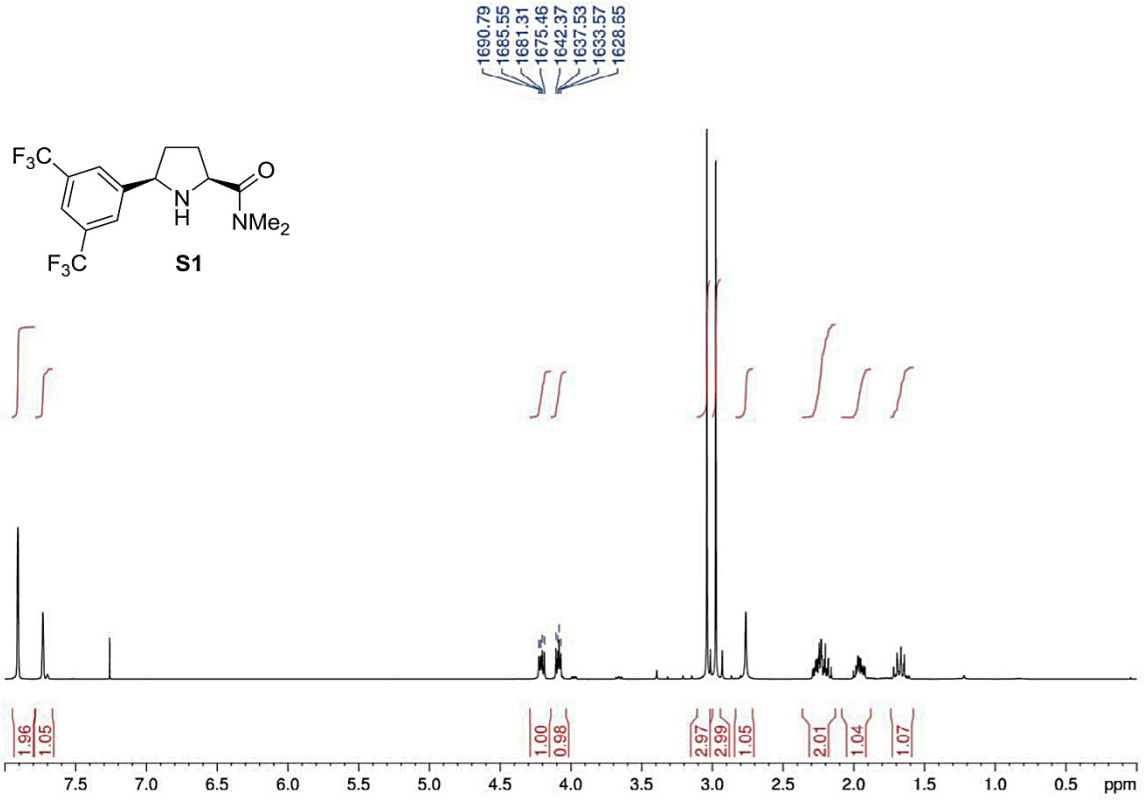
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O
NMe2
F3C
S1
1.96
1.05
1.00
0.98
2.97
2.99
1.05
2.01
1.04
1.07
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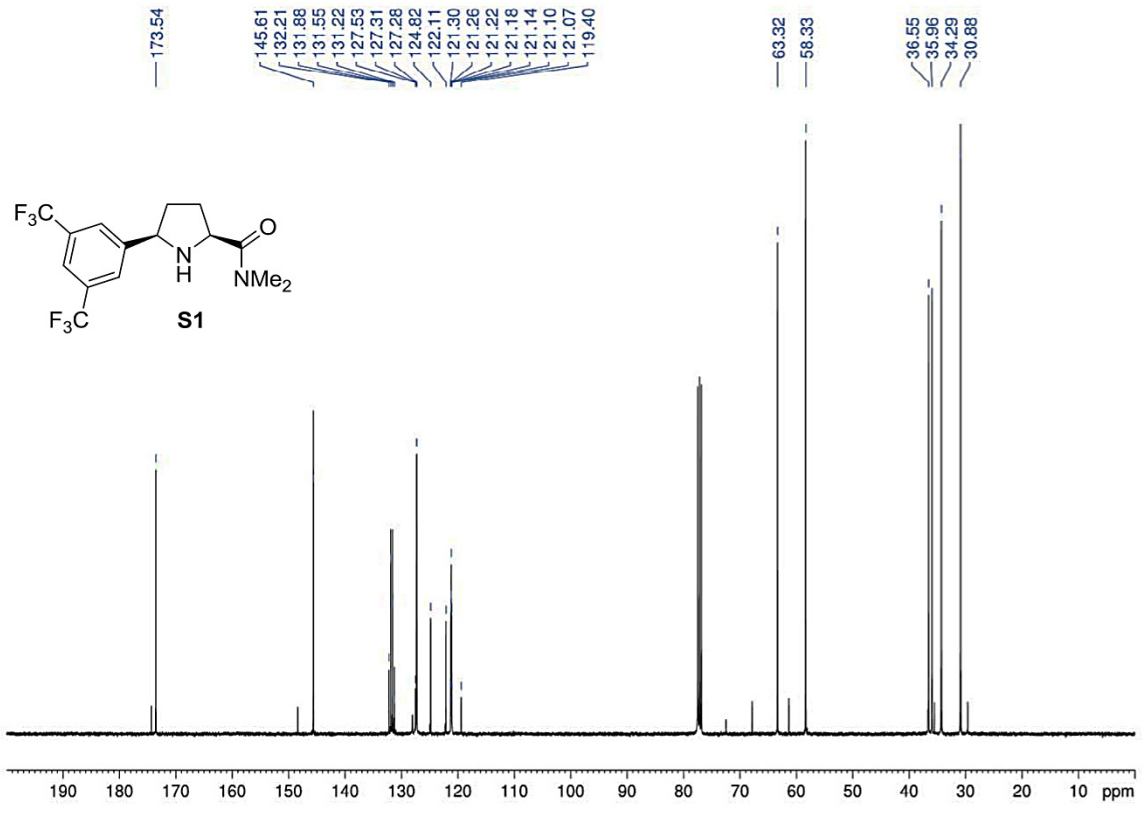
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121.18
121.14
121.10
121.07
119.40
63.32
58.33
36.55
35.96
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NMe2
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S1
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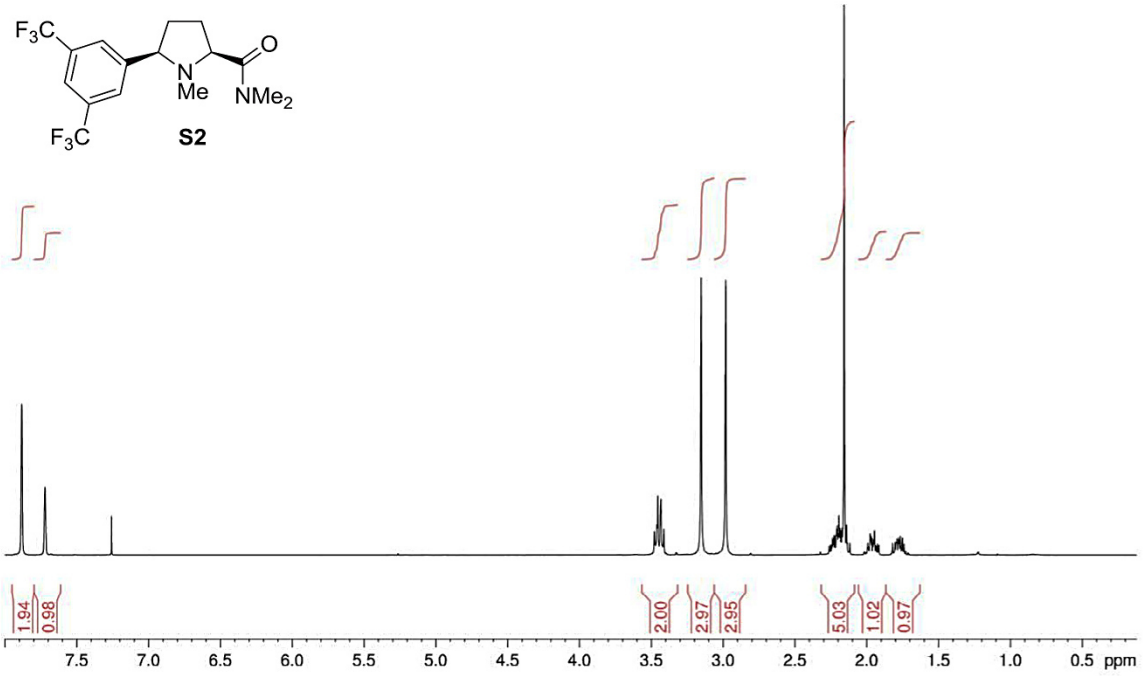
100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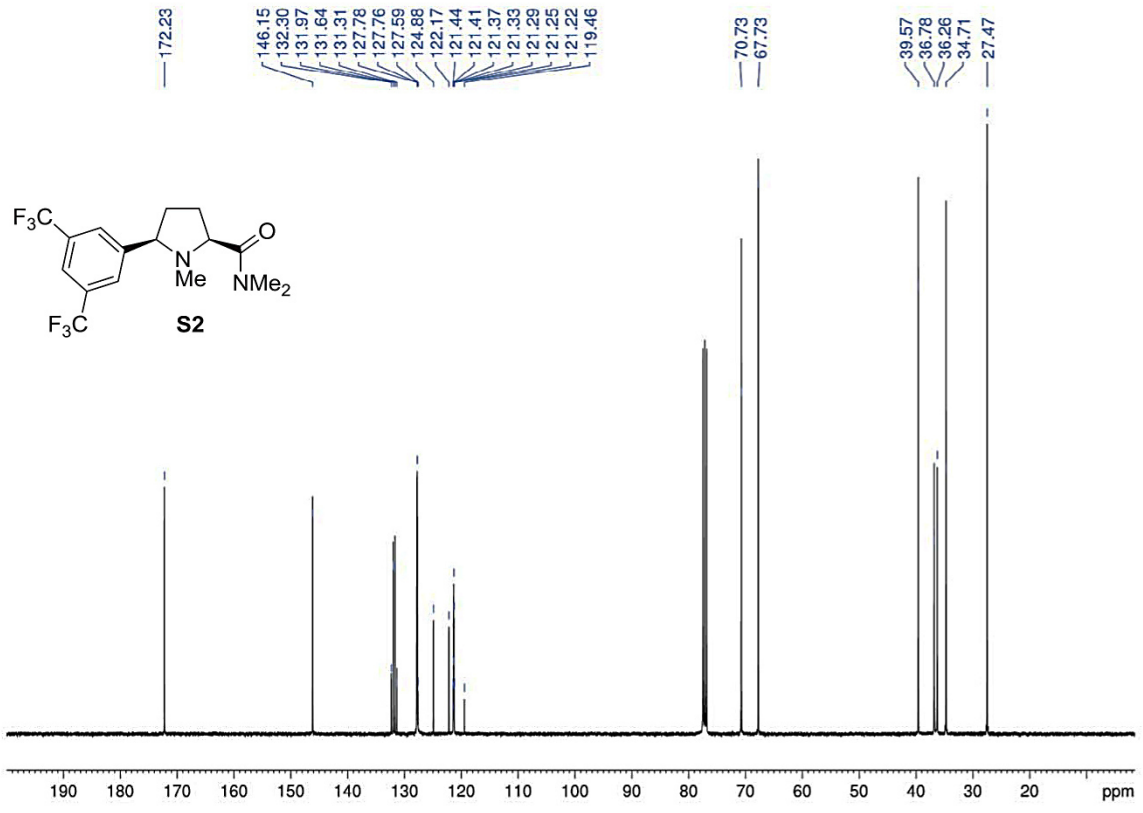
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121.25
121.22
119.46
70.73
67.73
39.57
36.78
36.26
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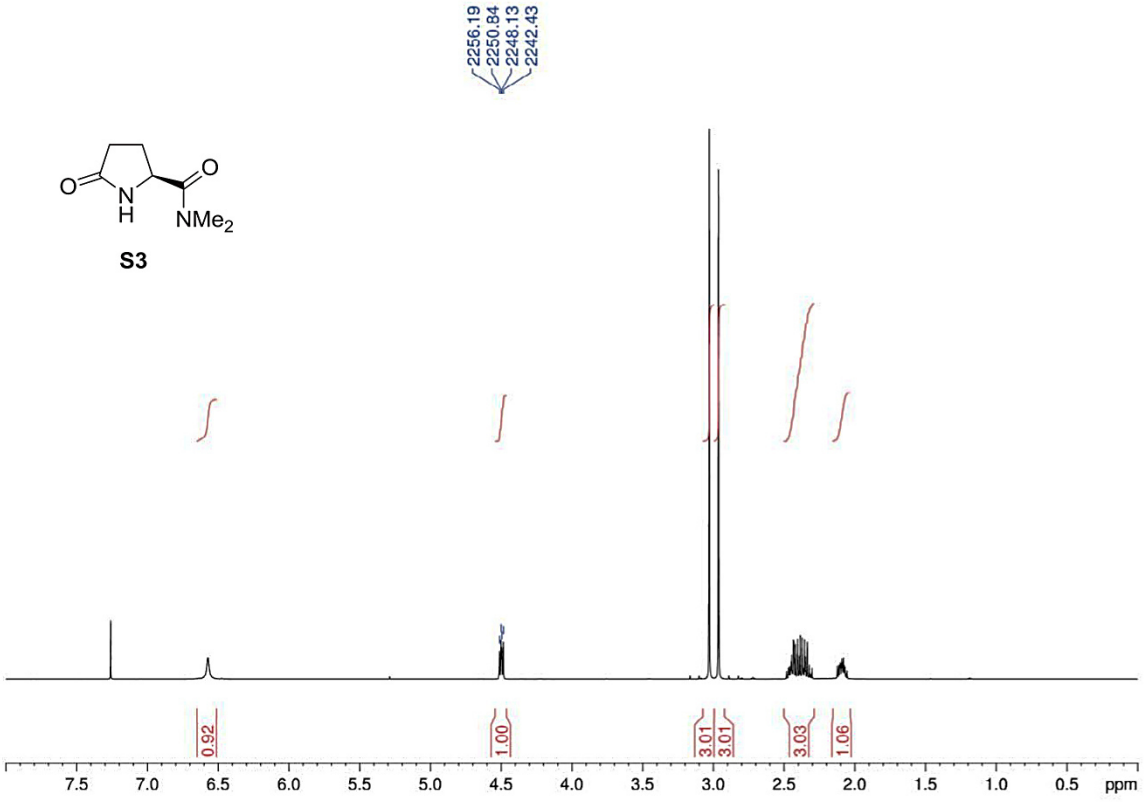
N
Me
O
NMe2
F3C
S2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

101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2248.13
2242.43
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3.03
1.06
7.5
7.0
6.5
6.0
5.5
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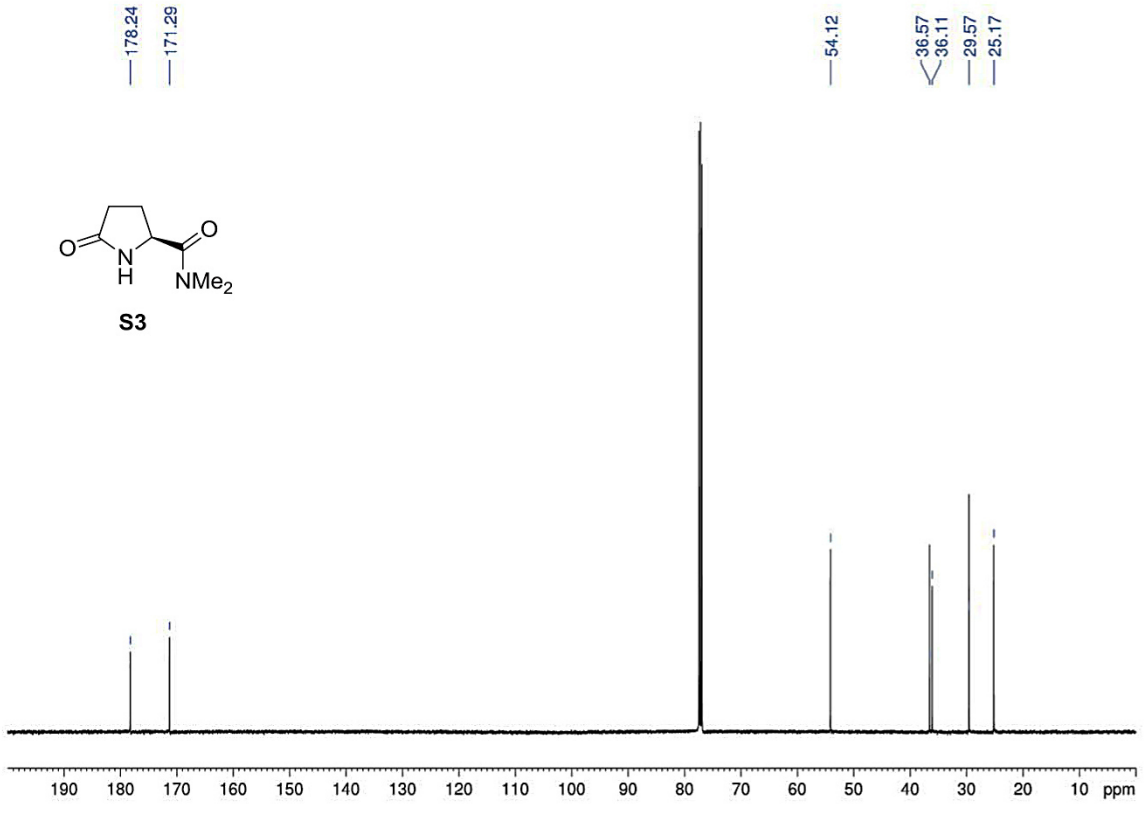
ppm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54.12
36.57
36.11
29.57
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O
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H
NMe2
S3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

6.2 Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions

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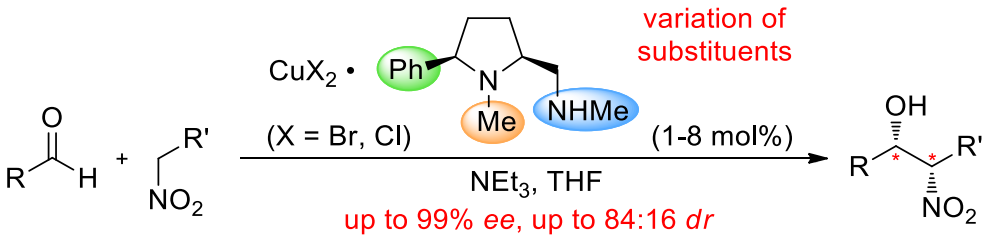

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DOI: 10.1002/cctc.201600240

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Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions

Johannes Kaldun, Felix Prause, Dagmar Scharnagel, Frederik Freitag, and Matthias Breuning*[a]

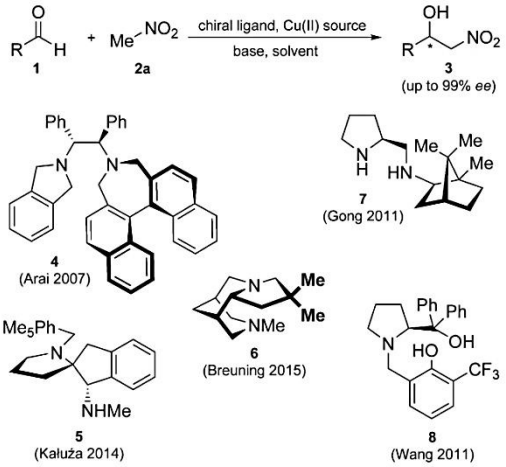
Dedicated to Prof. Dr. Dr. h.c. mult. Gerhard Bringmann on the occasion of his 65th birthday.

The development of a new catalytic system for enantioselective Henry reactions, which permits superb 99% *ee* with a broad variety of aldehydes, is presented. In-depth structure–selectivity investigations with 33 5-*cis*-substituted prolinamines, prepared from methyl Boc-L-pyroglutamate, revealed that an aromatic or sterically demanding aliphatic substituent in 5-*cis* position is crucial for high levels of stereocontrol, while bulkier substituents at the nitrogen atoms diminish both, enantioselectivities and reaction rates. The scope of the prime catalyst was expanded to gram-scale and diastereomeric Henry reactions (up to 84:16 *dr*, 99% *ee*). In the course of mechanistic studies, it was proven that the resulting β-nitro alcohols are configurationally stable under the reaction conditions. In addition, competition experiments were used to determine the relative reaction rates of some of the prolinamine-modified catalysts.

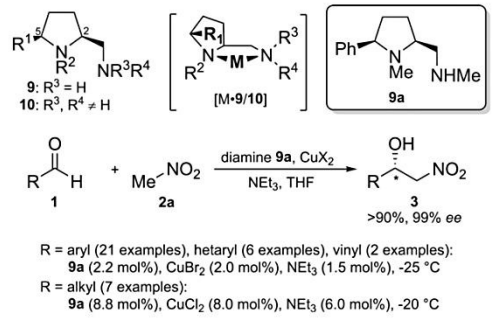
Introduction

The enantioselective Henry (nitro aldol) reaction[1] has drawn much attention as an asymmetric carbon–carbon bond forming reaction,[2] which triggered the development of many efficient catalytic systems based on heterobimetal[3] and transition-metal[4–6] complexes.[7] Chirally modified copper complexes received particular interest because of the wide structural variability of successful ligands, among them diamines, amino alcohols, amino imines, amino pyridines, imino pyridines, Schiff bases, box-type ligands, and salen-type ligands.[5,6,8,9] Examples of diamines (**4**–**7**)[5a,j,p,8a] and ligands containing the proline motif (**7**, **8**)[5j,m] that permit 99% *ee* in the addition of nitromethane (**2a**) to at least one aldehyde substrate **1** are shown in Scheme 1. Notably, Gong's ligand **7**,[5j] which belongs to the most potent ones for this reaction, combines both structural features.

As part of our ongoing work on conformationally rigid diamines[8,10] and encouraged by the stereodiscriminating power of **7**, we became interested in prolinamines of general type **9** and **10** (Scheme 2),[11] which possess, as compared to other proline-derived ligands, an additional substituent R^1 in 5-*cis* position. Upon chelation of a metal M, a bicyclic complex [M·**9**/**10**] will be formed with the substituent R^1 shielding the upper left face, which might permit enhanced levels of stereocontrol in asymmetric transformations. This assumption was recently corroborated by copper-catalyzed, enantioselective Henry reac-



Scheme 1. The enantioselective, copper-catalyzed Henry reaction and a selection of diamine (**4**–**7**)[5a,j,p,8a] and proline-derived (**7**,**8**)[5j,m] ligands that give 99% *ee* with at least one aldehyde substrate.



Scheme 2. The proline-derived diamines **9** and **10**, their metal complexes [M·**9**/**10**], and enantioselective, copper-catalyzed Henry reactions in the presence of the chiral diamine **9a**.[9]

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tions of nitromethane (**2a**) with a series of aromatic, heteroaromatic, vinylic, and aliphatic aldehydes **1**.[9,12] The $CuCl_2$ and $CuBr_2$ complexes of the simple prolinamine **9a** (R^1 = Ph; R^2, R^4 = Me; R^3 = H) provided the corresponding β-nitro alcohols **3** with superb, as yet unrivalled 99% *ee* in all cases (36 examples). Herein we present the development of the catalytic system CuX_2·**9a**, whose optimization included in-depth structure-enantioselectivity investigations with more than 30 diamines of types **9** and **10**. In addition, further studies on the substrate scope, some mechanistic investigations on the origin of the excellent enantioselectivities reached, and the preparation of the new diamines used in this study are described.

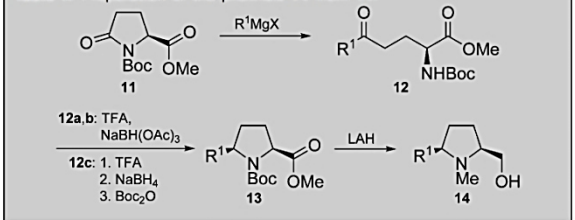
Results and Discussion

Synthesis of the prolinamines

A fast and variable access to prolinamines of type **9** and **10** was essential for the extensive ligand screening planned. We recently developed several routes to this class of diamines that all start from commercially available methyl Boc-L-pyroglutamate (**11**), but differ in the order of introduction of the substituents R^1–R^4, thus permitting a maximum of flexibility.[11] The new prolinamines used in this study were prepared with focus on a late-stage installation of the exocyclic amino function NR^3R^4, which is most easily achieved by hydroxy–amine exchange on the stage of the prolinol precursors **14**.

The substituent R^1 in 5-*cis* position was attached by chemoselective Grignard addition to the pyrrolidine carbonyl group in **11** and reductive cyclization of the resulting β-amino ketones **12** (Table 1). In accordance with earlier results,[11] the yield of the initial addition step strongly depended on the steric hindrance of the Grignard reagent. Good 78% were reached with 3,5-Me_2PhMgBr, whereas just mediocre 37% and 31% were obtained with the more bulky secondary alkyl Grignards *c*PentMgBr and *c*HexMgCl, respectively. The aliphatic β-amino ketones **12a** and **12b** were directly cyclized to the corresponding prolines **13a** and **13b** by using $NaBH(OAc)_3$ as the reductant, whereas ring closure of the aromatic derivative **12c** required a deprotection–reductive cyclization–reprotection sequence.[11] The *cis* diastereoselectivity was high in cyclizations (*dr* > 90:10). Final exhaustive reduction with LAH in refluxing THF afforded the prolinol intermediates **14a–c** in 91–95% yield.

Table 1. Preparation of the prolinols **14** from **11**.

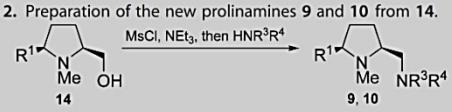


Entry	R^1	Yield of **12**[a] [%]	Yield of **13**[a] [%]	Yield of **14**[a] [%]
1	*c*Pent	37 (**12a**)	90 (**13a**)	92 (**14a**)
2	*c*Hex	31 (**12b**)	70 (**13b**)	95 (**14b**)
3	3,5-Me_2Ph	78 (**12c**)	59 (**13c**)[b]	91 (**14c**)

[a] Isolated yield. [b] 93:7 mixture of **13c** and its C5-epimer.

The alcohols **14a–c** thus prepared and the known derivatives **14d** (R^1 = Me)[11] and **14e** (R^1 = Ph)[9] were converted into the prolinamines **9** and **10** by mesylation of the hydroxy function and subsequent amination with an excess of the respective amine HNR^3R^4 (Table 2). The conversions of these reactions were good,[13] but the high polarity of the resulting diamines led to, in part, significant losses during column chromatographic purification, thus lowering the isolated yields to 50–76%.

Table 2. Preparation of the new prolinamines **9** and **10** from **14**.



Entry	**14**	R^1	**9, 10**	NR^3R^4	Yield [%][a]
1	**a**	*c*Pent	**9b**	NHMe	54
2	**b**	*c*Hex	**9c**	NHMe	56
3	**c**	3,5-Me_2Ph	**9d**	NHMe	76
4[b]	**d**	Me	**9e**	NHMe	52[c]
5[d]	**e**	Ph	**9f**	NHAc	78[c]
6[d]	**e**	Ph	**9g**	NHMs	80[c]
7	**e**	Ph	**9h**	$NH(CH_2)_2OH$	50
8	**e**	Ph	**9i**	$NH(CH_2)_2OMe$	73
9	**a**	*c*Pent	**10a**	NMe_2	57
10	**b**	*c*Hex	**10b**	NMe_2	57
11	**c**	3,5-Me_2Ph	**10c**	NMe_2	73

[a] Isolated yield. [b] Two-step sequence: 1. MsCl, NEt_3, then HN(Me)Bn; 2. H_2, $Pd(OH)_2$/C. [c] Yield over two steps. [d] Two-step sequence: 1. MsCl, NEt_3, then NH_3-MeOH (85%)[11] 2. for **9f**: Ac_2O, NEt_3; for **9g**: MsCl, NEt_3.

Notably, the direct preparation of **9e** (R^1 = Me, NR^3R^4 = NHMe, Table 2 entry 4) from **14d** by using the standard procedure, mesylation and amination with methylamine, failed. The pronounced volatility of the product made a removal of a higher boiling solvent such as MeOH, which was required as co-eluent in the chromatography of **9e**, practically impossible. We circumvented this problem by amination of **14d** with benzylmethylamine, giving the less polar and less volatile *N*-benzyl derivative of **9e**, which could be purified. Hydrogenolytic debenzylation under acidic conditions, basic extraction into Et_2O, and careful evaporation delivered **9e** in high purity and acceptable 52% yield over two steps. Finally, the amides **9f** and **9g** were synthesized by a two-step sequence (entries 5 and 6). Amination of **14e** with ammonia afforded the corresponding primary amine,[11] which was converted into **9f** and **9g** by N-acetylation and N-mesylation, respectively.

Optimization of the catalytic system

All enantioselective Henry reactions were performed under an argon atmosphere in a well-tempered cooling bath. In the case

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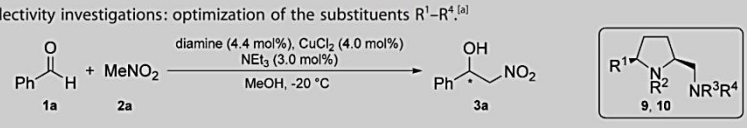
Table 3. First structure–selectivity investigations: optimization of the substituents R^1–R^4.[a]



Entry	Diamine	R^1	R^2	NR^3R^4	*t* [h]	Yield [%][b]	*ee* [%][c]	Configuration[d]
1	**10d**	H	Me	NMe_2	24	99	71	*R*
2	**10e**	Me	Me	NMe_2	18	93	23	*S*
3	**10f**	Bn	Me	NMe_2	24	99	13	*S*
4	**10g**	*i*Pr	Me	NMe_2	40	99	84	*S*
5	**10a**	*c*Pent	Me	NMe_2	18	95	87	*S*
6	**10b**	*c*Hex	Me	NMe_2	18	93	88	*S*
7	**10h**	Ph	Me	NMe_2	20	95	84	*S*
8	**10i**	4-MeOPh	Me	NMe_2	24	99	83	*S*
9	**10j**	3,5-$(CF_3)_2$Ph	Me	NMe_2	24	93	88	*S*
10	**10c**	3,5-Me_2Ph	Me	NMe_2	18	92	90	*S*
11	**10k**	1-naphthyl	Me	NMe_2	24	72	87	*S*
12	**10l**	Ph	Me	N(Me)*t*Bu	48	0	–	–
13	**10m**	Ph	Me	pyrrolidinyl	40	99	94	*S*
14	**9a**	Ph	Me	NHMe	19	99	98	*S*
15	**9j**	Ph	Me	NHEt	48	70	98	*S*
16	**9k**	Ph	Me	NH*i*Pr	48	50	85	*S*
17	**9l**	Ph	Me	NH*t*Bu	48	25	30	*S*
18	**9m**	Ph	Me	NHPh	48	0	–	–
19	**9f**	Ph	Me	NHAc	24	0	–	–
20	**9g**	Ph	Me	NHMs	24	0	–	–
21	**9h**	Ph	Me	$NH(CH_2)_2OH$	40	35	84	*S*
22	**9i**	Ph	Me	$NH(CH_2)_2OMe$	40	34	95	*S*
23	**9n**	Ph	Me	NH_2	48	28	93	*S*
24	**9o**	Ph	H	NHMe	113	23	77	*S*
25	**9p**	Ph	Et	NHMe	40	99	98	*S*
26	**9q**	Ph	Bn	NHMe	40	32	90	*S*
27	**9r**	Ph	*i*Pr	NHMe	24	0	–	–

[a] Performed on a 1 mmol scale in MeOH (600 μL) and $MeNO_2$ (600 μL). [b] Isolated yield. [c] Determined by HPLC on chiral phase and rounded off to whole numbers. [d] Assigned by comparison with literature data.

of an important or unexpected result, the reaction was repeated at least twice. The enantiomeric excess of the products **3** was determined by HPLC on chiral phase with an accuracy of up to ±0.1 percentage points.

Ligand structure (I)

The initial ligand screening was done on the addition of nitromethane (**2a**) to benzaldehyde (**1a**) as the model reaction (Table 3), by using the following protocol: The chiral catalyst (4 mol%), prepared prior to use from $CuCl_2$ (4.0 mol%) and a slight excess of the chiral diamine **9** or **10** (4.4 mol%), and the aldehyde **1a** were dissolved in a 1:1 mixture of $MeNO_2$ (≈11 equivalents with respect to **1a**) and MeOH. After cooling to −20 °C, the reaction was started by addition of the ancillary base NEt_3 (3.0 mol%) and stirred for 18–113 h. Under these conditions, the most simple diamine, the 5-*cis*-unsubstituted prolinamine **10d** (R^1 = H), which furthermore possesses a pyrrolidine *N*-methyl and an exocyclic dimethylamino group (R^{2-4} = Me), provided the *R*-configured β-nitro alcohol (*R*)-**3a** in acceptable 71% *ee* and excellent 99% yield after 24 h (Table 3, entry 1). The level of enantioselection reached was quite remarkable, taking the low steric differentiation around the copper atom in the catalyst into account (see complex [M·**9**/**10**] in Scheme 2, with R^1 = H, R^{2-4} = Me).

In a first set of experiments we kept the methyl groups for R^{2-4} and varied the 5-*cis* substituent R^1 (entries 2–11), which was assumed to exert a strong effect on the chirality transfer. And indeed, its impact is clearly seen on the sense of the asymmetric induction. Compared to the reaction with **10d** (R^1 = H), the enantiomeric product, (*S*)-**3a**, was preferentially formed with all prolinamines carrying such a substituent ($R^1 \neq$ H). The level of stereoinduction rose with an increasing steric demand of R^1. Good enantioselectivities of 83–90% *ee* were reached with all diamines that possess an α-branched aliphatic or an aromatic substituent R^1 as in **10a–c,g–k** (entries 4–11). The good chirality transfers with the aliphatic diamines also exclude a decisive role of a π–π-stacking between R^1 and the aromatic substrate benzaldehyde (**1a**). Among the promising prolinamines, we chose to continue the ligand optimization with derivatives possessing a phenyl group as R^1, since these compounds are most easily accessible (for a reinvestigation on R^1 under optimized conditions, see Table 7).

The influence of the substituents R^3 and R^4 at the exocyclic aminomethyl group was investigated next (Table 3, entries 12–23). Increasing the size of one of these substituents as in **10l** (NR^3R^4 = N(Me)*t*Bu) caused a complete breakdown in reactivity.

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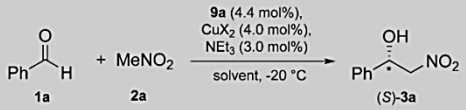
With pyrrolidinyl instead of NMe_2, improved 94% *ee* were reached. Another gain in stereocontrol was observed upon switching to the prolinamines **9**, which carry secondary aminomethyl groups NHR^4 (entries 14–22). Excellent 98% *ee* were reached with the diamines **9a** (NHMe) and **9j** (NHEt), whereas bulkier substituents R^4 as in **9k,l** (NH*i*Pr, NH*t*Bu) resulted in diminished asymmetric inductions. As a general trend, the catalytic activity significantly dropped with increasing steric demand of R^4, which is clear from the falling yields in the row **9a**, **9j**, **9k** to **9l**, even at prolonged reactions times. No product formation was observed with the anilinyl derivative **9m** (NHPh) and the amides **9f** (NHAc) and **9g** (NHMs). The potentially tridendate diamines **9h** ($NH(CH_2)_2OH$) and **9i** ($NH(CH_2)_2OMe$) and the primary diamine **9n** (NH_2) provided (*S*)-**3a** in acceptable 84–95% *ee*, but low 28–35% yield.

After having identified the NHMe group as the optimal NR^3R^4 function, we finally turned our attention to the substituent R^2 at the pyrrolidine nitrogen atom (entries 24–27). The same trend as with the NR^3R^4 group was observed: Excellent asymmetric inductions of 98% *ee* were achieved with small R^2 as in **9a** and **9p** (R^2 = Me, Et), while larger substituents R^2 as in **9q** and **9r** (R^2 = Bn, *i*Pr) or an NH function as in **9o** drastically reduced the activity of the catalyst.

In summary, the best result (98% *ee*, 99% yield) was achieved with the prolinamine **9a** possessing a phenyl substituent in 5-*cis* position, a pyrrolidine *N*-methyl group, and a 2-(methylaminomethyl) side chain. All further experiments were therefore performed with this diamine.

Table 4. Variation of the copper salt, solvent, and the solvent–$MeNO_2$ ratio.[a]



Entry	Cu Salt	Solvent	Solvent:$MeNO_2$	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	$CuCl_2$	MeOH	1:1	19	99	97.7
2	$CuCl_2$	EtOH	1:1	20	99	98.2
3	$CuCl_2$	THF	1:1	18	99	98.3
4	$CuCl_2$	$MeNO_2$	0:2	21	99	98.3
5	$CuBr_2$	MeOH	1:1	22	90	98.7
6	$CuBr_2$	EtOH	1:1	21	99	98.9
7	$CuBr_2$	THF	1:1	18	99	99.0
8	$CuBr_2$	$MeNO_2$	0:2	22	99	98.0
9[e]	$Cu(OAc)_2$[f]	MeOH	1:1	70	7	98.2
10[e]	$Cu(OAc)_2$[f]	EtOH	1:1	70	12	99.0
11[e]	$Cu(OAc)_2$[f]	THF	1:1	70	30	98.7
12[e]	$Cu(OAc)_2$[f]	$MeNO_2$	0:2	70	20	97.8
13	$Cu(OAc)_2$[f]	THF	1:1	17	88	90.8
14	$Cu(OAc)_2$[f]	MeOH	1:1	15	97	91.2
15	$CuBr_2$	THF	3:1	16	99	99.1
16	$CuBr_2$	THF	1:3	16	99	98.6
17[g]	$CuBr_2$	THF	1:1	16	99	99.0
18[h]	$CuBr_2$	THF	1:1	16	99	99.1

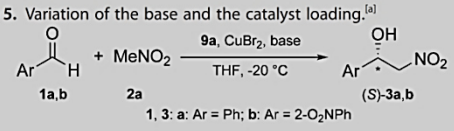
[a] Performed on a 1 mmol scale in the respective solvent–$MeNO_2$ mixture (1200 µL total, *c*(**1a**) = 0.83 M). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 3, entry 14. [e] No NEt_3 added. [f] Dihydrate. [g] Reaction in 600 µL solvent, *c*(**1a**) = 1.66 M. [h] Reaction in 2400 µL solvent, *c*(**1a**) = 0.42 M.

Reaction conditions

The copper source ($CuCl_2$, $CuBr_2$, and $Cu(OAc)_2$) and the solvent (MeOH, EtOH, THF, and $MeNO_2$) were varied first (Table 4, entries 1–12). The influence of both parameters on the chirality transfer was marginal, which is clear from the excellent 97.7–99.0% *ee* obtained in all cases. A distinct difference in reactivity and, thus, in the yields, was observed between the copper halide and the copper acetate complexes. In the latter Henry reactions, no NEt_3 was added since the acetate freed from the catalyst upon coordination of the substrates can act as the base.[14] The low 7–30% yield obtained after 70 h are presumably a consequence of the weaker basicity of acetate, which slows down the deprotonation of nitromethane. Addition of NEt_3 (3 mol%, entries 13 and 14) accelerated the reaction (≥88% yield after 17 h), but resulted in lower stereocontrol (91% *ee*). A closer inspection of the enantioselectivities achieved with the $CuCl_2$ and $CuBr_2$ complexes revealed the latter ones as slightly superior (98.0–99.0% *ee* vs. 97.7–98.3% *ee*). All solvents examined permitted similar levels of chirality transfer, but the reaction with $CuBr_2$ in THF seemed to proceed somewhat faster. Since this will be beneficial for lower-temperature reactions (see Table 6), we decided to continue with this combination. Changes in the solvent–$MeNO_2$ ratio from 1:1 to 3:1 and 1:3 (entries 15 and 16) as well as in the concentration from 0.83 M to 1.66 M and 0.42 M (entries 17 and 18) had no noticeable effect on yield and enantioselectivity.

A short base screening (Table 5, entries 1–3) revealed that the steric demand of the base is not of importance, which is clear from the excellent 99% yield and 99.0% *ee* reached with both, NEt_3 and $EtNiPr_2$. A sufficient basicity, however, was re-

Table 5. Variation of the base and the catalyst loading.[a]



Entry	1, 3	$CuBr_2$:**9a** : Base [mol%/mol%]	Base	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	**a**	4.0:3.0	NEt_3	18	99	99.0
2	**a**	4.0:3.0	$EtNiPr_2$	20	99	99.0
3	**a**	4.0:3.0	pyridine	20	traces	–
4	**a**	4.0:3.0	–	16	0	–
5	**a**	4.0:6.0	NEt_3	21	99	98.9
6	**a**	4.0:1.0	NEt_3	16	13	99.0
7	**a**	2.0:1.5	NEt_3	18	99	99.1
8	**a**	1.0:0.75	NEt_3	17	48	99.2
9	**a**	0.50:0.375	NEt_3	41	7	98.5
10	**b**	4.0:3.0	NEt_3	17	99	99.0
11	**b**	2.0:1.5	NEt_3	17	99	98.9
12	**b**	1.0:0.75	NEt_3	17	64	99.0
13	**b**	0.50:0.375	NEt_3	42	13	94.4

[a] Performed on a 1 mmol scale in THF (600 µL) and $MeNO_2$ (600 µL), **9a** : $CuBr_2$ = 1.1:1. [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 4, entry 7.

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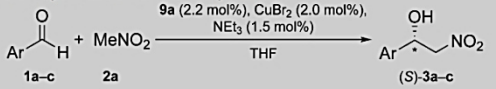
quired, because only traces of product were formed in the presence of pyridine. This observation is in good agreement with the slow reaction rates observed for the $Cu(OAc)_2$ complexes in which acetate served as the base (see Table 4, entries 9–12). As expected, there was no reaction without a base (Table 5, entry 4).

Changing the ratio catalyst–NEt_3 from standard 4:3 to 4:6 or 4:1 had little to no effect on the enantioselectivity (Table 5, entries 5 and 6). The yield, however, dropped to mere 13% if just 1 mol% of NEt_3 was used. The catalyst loading can be reduced to 2 mol% without any loss in yield and stereocontrol, if the catalyst–NEt_3 ratio is kept constant at 4:3 (entry 7). With just 1 mol% of catalyst and 0.75 mol% of base, the hitherto best enantioselection of 99.2% *ee* was achieved (entry 8). Although the 48% yield reached are just mediocre, the level of conversion is quite surprising as compared to the reaction with 4 mol% $CuBr_2$·**9a** and 1 mol% NEt_3 (see entry 6), which provided just 13% product within the same time frame, despite of the higher amounts of base and catalyst. Further lowering of the catalyst loading to 0.5 mol% resulted in a slight loss of asymmetric induction (98.5% *ee*), but a drastically reduced yield (7% after 41 h, entry 9).

At this point we checked that our optimization was not too substrate specific. As electron-deficient aldehydes might more readily undergo the uncatalyzed background reaction (vide infra), and, thus, require higher catalyst loadings, the latter experiments were repeated with 2-nitrobenzaldehyde (**1b**, entries 10–13). In the presence of 2 mol% catalyst, also this substrate provided the corresponding β-nitro alcohol (*S*)-**3b** in excellent 98.9% *ee* and 99% yield. Further reduction of the amount of catalyst to 0.5%, however, led to a significantly stronger depletion in enantioselectivity (94.4% *ee*), as compared to the analogous reaction with benzaldehyde (**1a**, see entry 9).

The last parameter, the temperature, was optimized with benzaldehyde (**1a**), 2-nitrobenzaldehyde (**1b**), and 2-methoxybenzaldehyde (**1c**) as the model substrates (Table 6). As expected, an increase in stereocontrol was observed by lowering the temperature to −30 °C, giving the β-nitro alcohols (*S*)-**3a–c** in excellent 99.1–99.5% *ee*. The reaction rates, however, markedly dropped below −25 °C, which is clear from the prolonged reaction times required and the incomplete conversion of the least reactive aldehyde **1c**. We therefore choose −25 °C as a good compromise between yield and chirality transfer.

Table 6. Optimization of the temperature.[a]



1a–c 2a (*S*)-3a–c

1, 3: **a**: Ar = Ph; **b**: Ar = 2-O_2NPh; **c**: Ar= 2-MeOPh

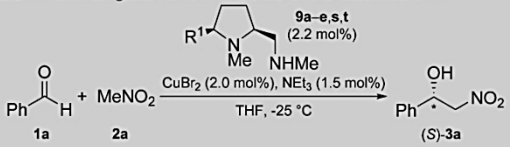
Entry	1, 3	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	**a**	−20	18	99	99.1
2[e]	**a**	−25	24	92	99.3
3	**a**	−30	66	99	99.5
4[f]	**b**	−20	17	99	98.9
5[e]	**b**	−25	20	97	99.0
6	**b**	−30	66	99	99.1
7	**c**	−20	40	99	99.2
8[e]	**c**	−25	42	97	99.5
9	**c**	−30	67	55	99.5

[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 5, entry 7. [e] Data taken from Ref. [9]. [f] See Table 5, entry 11.

Ligand structure (II)

At this final stage we decided to reinvestigate the influence of the 5-*cis* substituent R^1, because there had been no clear preference for a particular group in the initial screening (see Table 3, entries 1–11). The re-evaluation was performed under the optimized reaction conditions with the secondary prolinamines **9b–e,s,t** carrying the better stereo-differentiating exocyclic NHMe group. As seen in Table 7, all derivatives of **9** with an aliphatic or aromatic substituent R^1 provided the β-nitro alcohol (*S*)-**3a** with high stereocontrol (≥96.0% *ee*), even the diamine **9e**, which possesses the small methyl group. The best stereoselection (99.3% *ee*) was achieved with the phenyl-substituted prolinamine **9a** (Table 7, entry 6), maybe as a result of the optimization process done on this compound. The surprising reversal in the sense of enantioselection, as it had been found with the tertiary diamine **10d** missing the substituent R^1 (see Table 3, entry 1), was not observed for the secondary prolinamine **9s**, which also afforded the *S*-configured product (*S*)-**3a**, albeit in low 25% *ee*.

Table 7. Reinvestigation of the influence of the substituent R^1.[a]



1a 2a (*S*)-3a

Entry	9	R^1	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**s**	H	18	95	25.2
2	**e**	Me	18	95	96.0
3	**t**	*i*Pr	18	99	96.9
4	**b**	*c*Pent	19	99	97.0
5	**c**	*c*Hex	18	99	97.7
6[d]	**a**	Ph	24	92	99.3
7	**d**	3,5-Me_2Ph	41	99	98.2

[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 6, entry 2.

Aliphatic aldehydes

When applying the optimized conditions to the Henry reaction of the aliphatic aldehyde nonanal (**1d**), the β-nitro alcohol (*S*)-**3d** was produced in disappointing 53% yield and 94.5% *ee* (Table 8, entry 1). The yield and the level of enantioselection,

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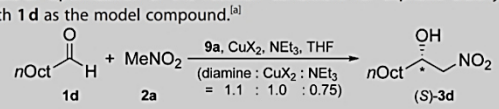
Table 8. Optimization of the reaction conditions for aliphatic aldehydes with **1d** as the model compound.[a]



Entry	Cu Salt ([mol%])	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]
1	$CuBr_2$ (2)	−25	40	53	94.5
2	$CuBr_2$ (4)	−25	60	75	96.2
3	$CuBr_2$ (8)	−25	24	90	97.0
4	$CuCl_2$ (8)	−25	21	87	98.2
5[d]	$CuCl_2$ (8)	−20	60	97	98.6
6	$CuCl_2$ (8)	−10	16	77	97.1

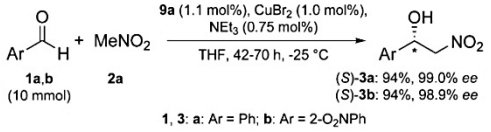
[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] Data taken from ref. [9].

however, were raised by increasing the amount of catalyst to 8 mol% and the temperature to −20 °C, and by changing the copper source to $CuCl_2$. Under these conditions, the product (*S*)-**3d** was obtained in excellent 97% yield and high 98.6% *ee*. One observation made in this context is noteworthy: The enantioselectivity of the reaction at −25 °C with $CuCl_2$·**9a** as the catalyst was slightly lower than the one at −20 °C (entry 4 vs. 5). This unexpected result might have its origin in a beginning aggregation of the catalyst at −25 °C, as judged from the increasing turbidity of the reaction mixture, which would reduce the amount of active catalyst and, thus, favor the non-stereoselective background reaction. A similar effect was not observed for the complex $CuBr_2$·**9a** in the reaction with aromatic aldehydes (see Table 6).

Under the optimized conditions for aromatic aldehydes [$CuBr_2$ (2 mol%), **9a** (2.2 mol%), NEt_3 (1.5 mol%), THF/$MeNO_2$ = 1:1, −25 °C] and aliphatic aldehydes [$CuCl_2$ (8 mol%), **9a** (8.8 mol%), NEt_3 (6.0 mol%), THF/$MeNO_2$ = 1:1, −20 °C], enantioselective Henry reactions with a broad variety of substrates were performed, providing the excellent results reported earlier.[9]

Gram-scale reactions

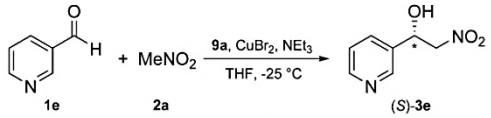
Finally, we decided to prove the practicability of our new catalytic system in gram-scale reactions (10 mmol aldehyde) with benzaldehyde (**1a**) and 2-nitrobenzaldehyde (**1b**) as the model substrates (Scheme 3). To further demonstrate its effectiveness, we cut, compared to the optimized procedure above, the amount of catalyst $CuBr_2$·**9a** in half (1 mol%), which was the minimum amount required to preserve the excellent stereocontrol (see Table 5, entries 8 and 12). Even under these enforced conditions, the Henry products (*S*)-**3a** and (*S*)-**3b** were formed in high 94% yield each. The enantiomeric excess (99.0% and 98.9% *ee*, respectively) was as good as in the small-scale reactions.



Scheme 3. Gram-scale Henry reactions of **1a** and **1b**.

Extending the substrate scope

The good performance of the prolinamine **9a** in Henry reactions prompted us to further study its scope and limitations. A tempting substrate is nicotinaldehyde (**1e**, Scheme 4) because of its basic and nucleophilic pyridine moiety, which might promote the uncatalyzed background reaction[15] and, in addition, might competitively coordinate to the catalyst, thus reducing the amount of catalytically active species. And indeed, the Henry reaction of **1e** in the presence of the catalyst $CuBr_2$·**9a** (2 mol%) proceeded sluggishly and delivered (*S*)-**3e** in unsatisfying 43% yield after 10 d and with low 82% *ee*. To accelerate the catalyzed reaction, we raised the amount of $CuBr_2$·**9a** to 15 mol%. Under these conditions, (*S*)-**3e** was obtained in improved 81% yield and acceptable 90% *ee* after 5 days.



9a (2.2 mol%), $CuBr_2$ (2.0 mol%), NEt_3 (1.5 mol%): 10 d, 43%, 82% *ee*
9a (16.5 mol%), $CuBr_2$ (15 mol%), NEt_3 (12 mol%): 5 d, 81%, 90% *ee*

Scheme 4. Henry reactions with basic nicotinaldehyde (**1e**).

Diastereo- and enantioselective Henry reactions[16] with nitroalkanes **2** (R′ ≠ H) were first studied using benzaldehyde (**1a**) as the substrate (Table 9). Owing to the lower reactivity of the nitroalkanes **2b–d** (R′ = Me, Et, CH_2OTBS), the following reactions were performed at −20 °C and with 8 mol% catalyst $CuBr_2$·**9a**. Whereas the *syn–anti* ratio in the nitroethane (**2b**) derived product **3f** was meager (60:40), acceptable ratios of 78:22 were obtained in **3g** and **3h** prepared from nitropropane (**2c**) and sterically more demanding 2-TBSO-nitroethane (**2d**), respectively. The enantioselectivities were always excellent (≥ 98% *ee*) in the major *syn* products and acceptable to good (82–93% *ee*) in the minor *anti* products. A further gain in selectivity was reached with the combination cyclohexanecarbaldehyde (**1f**)-nitropropane (**2c**), which provided the product **3i** in a good 84:16 *syn-anti* ratio and with 99% *ee* in both diastereomers. Thus, the catalyst $CuBr_2$·**9a** is also well suited for enantio- and diastereoselective Henry reactions.

Mechanistic investigations

Origin of enantioselection

Next we put our focus on the origin of the enantioselection. We wanted to prove that the high levels of stereocontrol solely arise from a kinetic differentiation in the *C,C*-coupling step and that processes involving product species, as, for example, an additional resolution on the stage of the primarily

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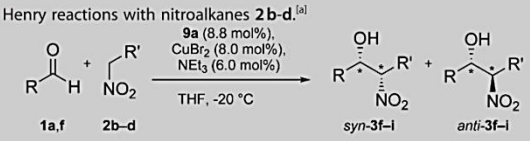
Table 9. Enantio- and diastereoselective Henry reactions with nitroalkanes **2b-d**.[a]

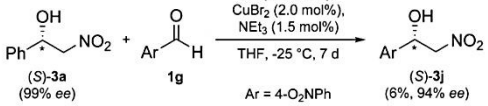


Entry	1	R	2	R′	*t* [d]	3	Yield [%][b]	*syn*:*anti*[c]	ee_{syn} [%][d]	ee_{anti} [%][d]
1	**a**	Ph	**b**	Me	4	**f**	99	60:40	99	93
2	**a**	Ph	**c**	Et	4	**g**	99	78:22	98	82
3	**a**	Ph	**d**	CH_2OTBS	7	**h**	98	78:22	99	93
4	**f**	*c*Hex	**c**	Et	7	**i**	84	84:16	99	99

[a] Performed on a 1 mmol scale in THF (600 μL) and nitroalkane **2** (8 equiv). [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC on chiral phase.

resulting, diastereomeric product–catalyst complexes, do not contribute.

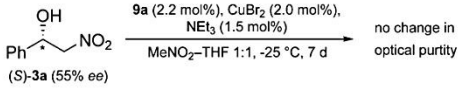
A necessary precondition for any dynamic process that influences the stereochemical outcome on the stage of the products is an equilibrium between the product species and the starting materials. The existence of such an equilibrium, although more or less fully shifted towards the products, was demonstrated by treatment of the β-nitro alcohol (*S*)-**3a** with 4-nitrobenzaldehyde (**1g**) under standard conditions (Scheme 5). The cross product **3j** observed in this reaction



Scheme 5. The formation of the cross product (*S*)-**3j** from (*S*)-**3a** and **1g** proves the reversibility of the Henry reaction under the standard reaction conditions.

must have been formed via a retro-Henry–Henry sequence. The rate of the back reaction, however, is pretty slow, which is clear from the low 6% yield obtained after 7 d. The good 94% *ee* indicates that at least the formation of (*S*)-**3j** must have been catalyzed by $CuBr_2$·**9a**.

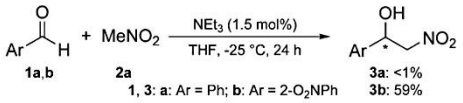
With the existence of the back reaction proven, the question remained whether this process induces any changes in the enantiopurity of the product. This cannot be the case because stirring of the scalemic β-nitro alcohol (*S*)-**3a** (55% *ee*) under standard conditions for 7 d did not noticeably alter its optical purity (Scheme 6). Thus, any scenario that affects the overall stereochemical outcome and involves product species can be safely excluded. The excellent stereodifferentiation observed must have its origin exclusively in the C,C-coupling step.



Scheme 6. The scalemic β-nitro alcohol (*S*)-**3a** (55% *ee*) is configurationally stable under standard Henry conditions.

Uncatalyzed background reaction

From the ≥98.9% *ee* reached with **1a** and **1b** in the presence of just 1 mol% of $CuBr_2$·**9a** (see Scheme 3) it follows that the catalyzed reaction must proceed at least 99 times faster than the non-stereoselective background reaction.[17] This is in good agreement with the observation that the latter one is virtually non-existing for benzaldehyde (**1a**: <1% conversion within 24 h, Scheme 7). In contrast to that, the rate of the background



Scheme 7. Uncatalyzed background reactions of **1a** and **1b**.

reaction is surprisingly high for the more electrophilic 2-nitrobenzaldehyde (**1b**, 59% conversion within 24 h). Although this does not noticeably affect the enantioselectivity of the catalyzed reaction with 1 mol% of $CuBr_2$·**9a**, it is most likely the main reason for the more pronounced loss in stereocontrol in the reaction of **1b** with 0.5 mol% catalyst, as compared to the analogous reaction of **1a** (98.5% vs. 94.4% *ee*, see Table 5, entry 9 vs. 13).

Relative reactivities of the catalysts derived from 9a and 10h

In parallel to the significantly enhanced stereocontrol reached with prolinamines of type **9** (secondary exocyclic amino group), as compared to those of type **10** (tertiary exocyclic amino group), we also observed a gain in reactivity. We therefore decided to measure the relative rates of reactions in the presence of our prime catalyst CuX_2·**9a** in comparison to those with CuX_2·**10h** (**10h**: dimethyl analogue of **9a**) under different conditions. Competition experiments, in which equimolar amounts of two chiral catalysts are used that deliver enantiomeric products, offer an experimentally simple method to do this, without the necessity of extensive kinetic studies. The relative rate constant k_{rel} can be calculated from the enantiomeric ratios of the single-catalyst and competition experiments using Equation (1):[18]

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$$k_{rel} = \frac{k_{cat1}}{k_{cat2}} = \frac{(er_1 + 1)(er_{cp} - er_2)}{(er_2 + 1)(er_1 - er_{cp})} \quad (1)$$

er_1 = *S*/*R* ratio with catalyst 1
er_2 = *S*/*R* ratio with catalyst 2
er_{cp} = *S*/*R* ratio reached in the 1:1-competition experiment

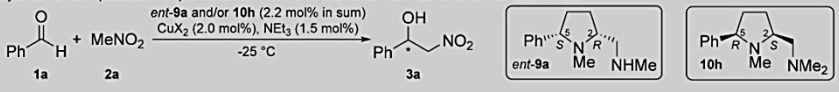
The required pseudo-enantiomeric catalyst *ent*-**9a** was prepared in analogy to **9a**, but starting from methyl Boc-D-pyroglutamate (*ent*-**11**).[9,11] The single-catalyst and competition experiments were done with the $CuBr_2$ and $CuCl_2$ catalysts derived from **10h** (2*S*,5*R*-configuration) and *ent*-**9a** (2*R*,5*S*-configuration) in THF and MeOH at −25 °C (Table 10). In THF and with $CuBr_2$·*ent*-**9a**, the product (*R*)-**3a** was obtained after 18 h in good 92% yield and excellent 99% *ee*, while the analogous reaction with $CuBr_2$·**10h** proceeded more slowly (58% yield after 43 h) and delivered the enantiomer (*S*)-**3a** with significantly lower stereocontrol (84% *ee*). The competition experiment (Table 10, entry 3) with equimolar amounts of both catalysts provided (*R*)-**3a** in 50% *ee*, clearly proving the higher catalytic activity of $CuBr_2$·*ent*-**9a**. By using Equation (1), a relative rate factor k_{rel} ($=k_{ent-9a}k_{10h}^{-1}$) of 2.73 in favor of $CuBr_2$·*ent*-**9a** was calculated. A similar k_{rel} value of 3.54 was observed for the corresponding chloro complexes $CuCl_2$·*ent*-**9a** and $CuCl_2$·**10h** (entries 4–6). MeOH as the solvent (entries 7–9) causes a general decrease in reactivity, which is clear from the prolonged reaction times required, which might be an effect of its better coordination abilities favoring a deactivation of intermediate catalyst species. In addition, the ratio k_{rel} of the reaction rates is higher: The catalytic system $CuCl_2$·*ent*-**9a** reacted 7.32 times faster than $CuCl_2$·**10h**. This furthermore underlines the existence of direct solvent-catalyst interactions—if this were not the case, the same k_{rel} values in THF and MeOH would be expected.

In the transition states of the Henry reactions with the secondary prolinamines **9**, there is the possibility of an additional hydrogen bridge between the NH function of the chiral ligand and the nitronate bound to the copper atom, which would further rigidify the system and, thus, explain the better stereocontrol observed.[9] This interaction should reduce the nucleophilicity of the nitronate and, in consequence, lower the activities of the catalysts CuX_2·**9**, as compared to CuX_2·**10**. Since the opposite effect was observed in the competition experiments, the existence of such a hydrogen bridge seems unlikely.[19] The higher enantioselectivities reached with secondary prolinamines **9** presumably originate from steric and conformational factors.

Conclusions

Several new, 5-*cis*-substituted prolinamines of type **9** and **10** were synthesized in 4–6 steps from methyl Boc-L-pyroglutamate (**11**). Their potential as the chiral ligands in enantioselective, copper-catalyzed Henry reactions was evaluated. In-depth structure–selectivity investigations with more than 30 diamines **9** and **10** revealed that an aromatic or sufficiently bulky aliphatic substituent in 5-*cis* position is crucial for high levels of stereocontrol, while larger groups at the pyrrolidine nitrogen atom or at the exocyclic aminomethyl group cause an, in part, drastic loss in reactivity and enantioselectivity. The prolinamine **9a** (R^1 = Ph; R^2 = Me; NR^3R^4 = NHMe) was found to be the chiral ligand of choice. Optimization of other reaction parameters, such as temperature, solvent, concentration and catalyst loading, led to two highly efficient catalytic systems, $CuBr_2$·**9a** for aromatic aldehydes and $CuCl_2$·**9a** for aliphatic ones. With just 2 mol% of catalyst (8 mol% in the case of aliphatic aldehydes), the superb results reported earlier (99% *ee* with 36 aldehydes) were achieved.[9] In further studies we extended the scope of $CuBr_2$·**9a** to gram-scale and diastereoselective Henry reactions (up to 84:16 *dr*, 99% *ee*). It was also proven that the stereodifferentiation originates solely from the C,C-coupling step and that the product is configurationally stable under the reaction conditions. The uncatalyzed background reaction is virtually non-existing for benzaldehyde (**1a**), but remarkably high for the more electrophilic 2-nitrobenzaldehyde (**1b**). The relative reactivity of the catalysts derived from the prolinamines **9a** and **10h** was studied by competition experiments. The complexes with **9a** reacted up to 7.32 times faster, depending on the reaction conditions. This, however, does not explain the significant increase in enantioselectivity observed

Table 10. Single-catalyst and competition experiments with *ent*-**9a** and **10h** as the chiral diamines.[a]



Entry	Diamine	Cu Salt	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]	Configuration	$k_{rel} = k_{ent-9a}k_{10h}^{-1}$[d]
1	*ent*-**9a**	$CuBr_2$	THF	18	92	99	*R*	
2	**10h**	$CuBr_2$	THF	43	58	84	*S*	
3	*ent*-**9a**/**10h** 1:1[e]	$CuBr_2$	THF	19	87	50	*R*	2.73
4	*ent*-**9a**	$CuCl_2$	THF	18	99	99	*R*	
5	**10h**	$CuCl_2$	THF	39	81	87	*S*	
6	*ent*-**9a**/**10h** 1:1[e]	$CuCl_2$	THF	19	77	58	*R*	3.54
7	*ent*-**9a**	$CuCl_2$	MeOH	40	82	98	*R*	
8	**10h**	$CuCl_2$	MeOH	39	47	85	*S*	
9	*ent*-**9a**/**10h** 1:1[e]	$CuCl_2$	MeOH	41	78	76	*R*	7.32

[a] Performed on a 1 mmol scale in THF (600 µL) and $MeNO_2$ (600 µL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] Calculated using Equation (**1**). [e] The catalysts derived from *ent*-**9a** and **10h** were prepared separately and mixed shortly before use.

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with **9a** (NR^3R^4 = NHMe), as compared to its dimethyl analogue **10h** (NR^3R^4 = NMe_2).

Experimental Section

All reactions with moisture-sensitive reagents were performed under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[20] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey–Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey–Nagel, particle size 40–63 μm) was used for column chromatography. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^{1}H and ^{13}C NMR data were performed on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer, high-resolution mass spectra were recorded on a ThermoFisher Scientific Q-Exactive (Orbitrap) or a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization). The enantiomeric excess and the configuration of the β-nitro alcohols **3** were determined by HPLC analysis on chiral phase; the diastereomeric ratios were measured by ^{1}H NMR (for details see Supporting Information). Prolinols **14d**[11] and **14e**[9] and prolinamines **9a**,[9] **9j–m**,[12] **9n–r,t**,[11] **10e–k,m**[11] and **10l**[12] were prepared according to literature procedures. Diamines **10d** and **9s** are commercially available. The synthesis of the prolinamine **9b** and general procedures for the asymmetric Henry reactions are described here. For the preparation of all other new compounds, see Supporting information.

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-cyclopentyl-5-oxopentanoate (12a)

A solution of the pyroglutamate **11** (10.0 g, 41.1 mmol) in anhydrous THF (120 mL) was treated at −40 °C with *c*PentMgBr, prepared from bromocyclopentane (5.95 mL, 8.27 g, 55.5 mmol) and Mg (1.49 mg, 61.1 mmol) in anhydrous THF (50 mL). The reaction mixture was allowed to warm to RT overnight. Sat. aq. NH_4Cl (20 mL) was added and THF was evaporated in vacuo. The resulting aqueous suspension was partitioned between sat. aq. NH_4Cl (200 mL) and CH_2Cl_2 (200 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×200 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 5:1) afforded amino ketone **12a** (4.75 g, 15.2 mmol, 37%) as a colorless oil. R_f = 0.27 (petroleum ether/EtOAc 6:1); $[\alpha]_D^{31} = -18.6$ (c = 1.00 in MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 3375, 2952, 2871, 1745, 1706, 1513, 1366, 1146 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9H, $C(CH_3)_3$), 1.56 (m, 2H, *c*Pent-H), 1.59–1.75 (m, 4H, *c*Pent-H), 1.79 (m, 2H, *c*Pent-H), 1.89 (m, 1H, 3-*H*H), 2.10 (m, 1H, 3-H*H*), 2.55 (m, 2H, 4-H_2), 2.84 (quint., J = 7.9 Hz, 1H, *c*Pent-H), 3.72 (s, 3H, OCH_3), 4.26 (m, 1H, 2-H), 5.09 ppm (d, J = 8.0 Hz, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.1 (C-*c*Pent), 26.6 (C-3), 28.4 ($C(CH_3)_3$), 29.0, 29.1 (C-*c*Pent), 37.7 (C-4), 51.5 (C-*c*Pent), 52.5 (OCH_3), 53.1 (C-2), 80.1 ($C(CH_3)_3$), 155.6 (NCO_2), 173.1 (C-1), 212.2 ppm (C-5); HRMS (ESI, pos.) m/z calcd for $C_{16}H_{27}NO_5$ $[M+H]^+$ 314.19620, found 314.19637.

(2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-cyclopentylpyrrolidine-1,2-dicarboxylate (13a)

$NaBH(OAc)_3$ (5.53 g, 26.1 mmol) was added at 0 °C to a solution of the amino ketone **12a** (4.20 g, 13.4 mmol) in EtOAc (60 mL). After 10 min, TFA (6.66 mL, 9.85 g, 86.4 mmol) was added dropwise and the reaction mixture was stirred overnight at RT. Sat. aq. $NaHCO_3$ (200 mL) was added and the reaction mixture was extracted with EtOAc (3×200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (silica gel, petroleum ether–EtOAc, 15:1–4:1) provided diastereomerically pure **13a** (3.59 g, 12.1 mmol, 90%) as a colorless oil. R_f = 0.69 (petroleum ether/EtOAc 3:1); $[\alpha]_D^{32} = -26.5$ (c = 1.00 in MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 2948, 2869, 1756, 1694, 1455, 1387, 1365, 1167, 1139, 1108 cm^{-1}; ^{1}H NMR* (500 MHz, $CDCl_3$): δ = 1.12 (m, 1H, *c*Pent-H), 1.36 (s, 5.4H, $C(CH_3)_3$), 1.42 (s, 3.6H, $C(CH_3)_3$), 1.49 (m, 3H, *c*Pent-H), 1.62 (m, 3H, *c*Pent-H), 1.78 (m, 3H, 4-H_2, *c*Pent-H), 1.86–2.13 (m, 2H, 3-*H*H, *c*Pent-H), 2.20 (m, 1H, 3-H*H*), 3.69 (s, 3H, OCH_3), 3.74 (m, 0.4H, 5-H), 3.86 (t, J = 7.9 Hz, 0.6H, 5-H), 4.17 (t, J = 8.6 Hz, 0.6H, 2-H), 4.29 ppm (t, J = 8.3 Hz, 0.4H, 2-H); ^{13}C NMR* (125 MHz, $CDCl_3$): δ = 25.0, 25.1, 25.3, 27.9 (C-*c*Pent), 28.3, 28.5 ($C(CH_3)_3$), 28.8, 28.9 (C-3, C-4), 29.5, 29.7, 30.3, 30.5, 44.6, 44.8 (C-*c*Pent), 51.9, 52.1 (OCH_3), 59.6, 60.1 (C-2), 62.4, 62.7 (C-5), 79.7, 80.0 ($C(CH_3)_3$), 154.4, 155.0 (1-CO_2), 174.1, 174.3 ppm (2-CO_2); HRMS (ESI, pos.) m/z calcd for $C_{16}H_{27}NO_4$ $[M+H]^+$ 298.20128, found 298.20134. * 60:40 mixture of rotamers.

(2*R*,5*S*)-2-Cyclopentyl-5-(hydroxymethyl)-1-methylpyrrolidine (14a)

$LiAlH_4$ (732 mg, 19.3 mmol) was added at 0 °C to a solution of the pyrrolidine ester **13a** (822 mg, 2.76 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred for 1 h at 0 °C and then refluxed for 26 h. The resulting suspension was treated with sat. aq. Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of Celite and the filter cake was rinsed with CH_2Cl_2-MeOH (9:1, 200 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2-MeOH-NH_3 (aq., 25%), 90:9:1) provided amino alcohol **14a** (467 mg, 2.55 mmol, 92%) as a colorless oil. R_f = 0.23 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5); $[\alpha]_D^{31}$ = +22.5 (c = 1.00 in MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 3312, 2948, 2866, 2782, 1771, 1455, 1240, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (m, 2H, *c*Pent-H), 1.43–1.67 (m, 6H, 3-*H*H, 4-*H*H, *c*Pent-H), 1.76 (m, 4H, 3-H*H*, 4-H*H*, *c*Pent-H), 2.02 (m, 1H, *c*Pent-H), 2.32 (s, 3H, 1-CH_3), 2.51 (dd, J = 13.6, 6.6 Hz, 1H, 2-H), 2.58 (m, 1H, 5-H), 2.80–3.25 (br s, 1H, OH), 3.36 (d, J = 10.6 Hz, 1H, 5-C*H*H), 3.63 ppm (dd, J = 10.6, 3.5 Hz, 1H, 5-CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4 (C-*c*Pent), 25.9, 26.3 (C-3, C-4), 26.9, 27.5, 30.7 (C-*c*Pent), 39.9 (1-CH_3), 43.5 (C-*c*Pent), 61.0 (5-CH_2), 67.6 (C-5), 70.7 ppm (C-2); HRMS (ESI, pos.) m/z calcd for $C_{11}H_{21}NO$ $[M + H]^+$ 184.16959, found 184.16908.

(2*R*,5*S*)-2-Cyclopentyl-1-methyl-5-((methylamino)methyl)pyrrolidine (9b)

MsCl (27.8 μL, 41.1 mg, 360 μmol) and NEt_3 (136 μL, 99.4 mg, 982 μmol) were added at 0 °C to a solution of the prolinol **14a** (60.0 mg, 327 μmol) in anhydrous CH_2Cl_2 (4 mL). After 3 d at RT, an excess of methylamine (aq., 40%, 1.30 mL, 1.16 g, 9.81 mmol) and MeOH (4.0 mL) was added and stirring was continued for 3 d. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 97:2.7:0.3–95:4.5:0.5) delivered prolinamine **9b** (34.6 mg, 176 μmol, 54%) as a yellowish oil. R_f = 0.31 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1); $[\alpha]_D^{32}$ = +4.9 (c = 0.20 in

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MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 2951, 2865, 2780, 1450, 1209, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.12–1.30 (m, 2H, *c*Pent-H), 1.41–1.68 (m, 8H, 3-*H*H, 4-*H*H, *c*Pent-H, NH), 1.68–1.87 (m, 3H, 3-H*H*, 4-H*H*, *c*Pent-H), 1.97 (m, 1H, *c*Pent-H), 2.31 (s, 3H, 1-CH_3), 2.33 (m, 1H, 2-H), 2.45 (s, 3H, $NHCH_3$), 2.47 (m, 1H, 5-H), 2.53 (dd, *J* = 11.2, 6.0 Hz, 1H, 5-C*H*H), 2.64 ppm (dd, *J* = 11.2, 3.9 Hz, 1H, 5-CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4, 26.0 (C-*c*Pent), 27.0 (C-3), 27.92 (C-4), 27.93, 30.9 (C-*c*Pent), 37.2 ($NHCH_3$), 40.9 (1-CH_3), 43.8 (C-*c*Pent), 55.7 (5-CH_2), 67.0 (C-5), 71.3 ppm (C-2); HRMS (ESI, pos.) *m/z* calcd for $C_{12}H_{24}N_2$ $[M+H]^+$ 197.20123, found 197.20218.

General procedure for the enantioselective Henry reactions of aromatic aldehydes under optimized conditions

A solution of anhydrous $CuBr_2$ (66.7 mM in MeOH, 300 µL, 4.47 mg, 20.0 µmol, 2.0 mol%) was evaporated to dryness in a Schlenk tube. A solution of diamine **9a** (36.7 mM in anhydrous THF, 600 µL, 4.49 mg, 22.0 µmol, 2.2 mol%), $MeNO_2$ (**2a**, 600 µL, 684 mg, 11.2 mmol, 11.2 equiv), and the aldehyde **1** (1.00 mmol, 1.00 equiv) were added successively at RT. The mixture was ultrasonicated for 10 min to give a clear, brownish solution, which was cooled to −25 °C. NEt_3 (1.50 M in THF, 10.0 µL, 1.52 mg, 15.0 µmol, 1.5 mol%) was added and the resulting blue-green solution was stirred until TLC-control indicated complete consumption of the aldehyde. The crude reaction mixture was purified by column chromatography (silica gel, hexanes–EtOAc 8:1–4:1) providing β-nitro alcohol **3**. The enantiomeric excess of **3** was determined by HPLC on chiral phase.[9] All variations were done on basis of this general procedure and are indicated in the corresponding Tables and Schemes.

General procedure for the enantioselective Henry reactions of aliphatic aldehydes under optimized conditions

A solution of anhydrous $CuCl_2$ (267 mM in MeOH, 300 µL, 10.8 mg, 80.0 µmol, 8.0 mol%) was evaporated to dryness in a Schlenk tube. A solution of diamine **9a** (147 mM in anhydrous THF, 600 µL, 18.0 mg, 88.0 µmol, 8.8 mol%), $MeNO_2$ (**2a**, 600 µL, 684 mg, 11.2 mmol, 11.2 equiv), and the aldehyde **1** (1.00 mmol, 1.00 equiv) were added successively at RT. The mixture was ultrasonicated for 10 min to give a clear, brownish solution and then cooled to −20 °C. NEt_3 (1.50 M in THF, 40 µL, 6.08 mg, 60.0 µmol, 6.0 mol%) was added and the resulting blue-green solution was stirred until TLC-control indicated complete consumption of the aldehyde. The crude reaction mixture was purified by column chromatography (silica gel, pentane–Et_2O 8:1–4:1) providing β-nitro alcohol **3**. The enantiomeric excess of **3** was determined by HPLC on chiral phase.[9] All variations were done on basis of this general procedure and are indicated in the corresponding Tables and Schemes.

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Keywords: aldol reactions · amines · asymmetric catalysis · copper · ligand design

[1] Reviews: a) H. Sasai in *Comprehensive Organic Synthesis Vol. 2, 2nd ed.* (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, chap. 2.13, pp. 543–570; b) F. A. Luzzio, *Tetrahedron* **2001**, *57*, 915–945; c) *The Nitro Group in Organic Synthesis* (Ed.: N. Ono), Wiley-VCH, New York, **2001**.

[2] Reviews: a) P. Drabina, L. Harmand, M. Sedlak, *Curr. Org. Synth.* **2014**, *11*, 879–888; b) R. Ballini, M. Petrini in *Science of Synthesis C-1 Building Blocks in Organic Synthesis* (Ed.: P. W. N. M. Van Leeuwen), Thieme, Stuttgart, **2014**, chap. 1.3.3, pp. 507–524; c) N. Ananthi, S. Velmathi, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2013**, *52*, 87–108; d) G. Chelucci, *Coord. Chem. Rev.* **2013**, *257*, 1887–1932; e) G. Blay, V. Hernández-Olmos, J. R. Pedro, *Synlett* **2011**, 1195–1211; f) Y. Alvarez-Casao, E. Marques-Lopez, R. P. Herrera, *Symmetry* **2011**, *3*, 220–245; g) C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem.* **2007**, 2561–2574; h) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326.

[3] Selected examples: a) K. Hashimoto, N. Kumagai, M. Shibasaki, *Org. Lett.* **2014**, *16*, 3496–3499; b) T. Ogawa, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2013**, *52*, 6196–6201; *Angew. Chem.* **2013**, *125*, 6316–6321; c) D. Sureshkumar, K. Hashimoto, N. Kumagai, M. Shibasaki, *J. Org. Chem.* **2013**, *78*, 11494–11500; d) T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 13860–13869.

[4] Selected examples (except Cu-catalysis): a) J. Dimroth, M. Weck, *RSC Adv.* **2015**, *5*, 29108–29113; b) G.-H. Ouyang, Y.-M. He, Q.-H. Fan, *Chem. Eur. J.* **2014**, *20*, 16454–16457; c) Y.-L. Wei, K.-F. Yang, F. Li, Z.-J. Zheng, Z. Xu, L.-W. Xu, *RSC Adv.* **2014**, *4*, 37859–37867; d) Y. Liu, P. Deng, X. Li, Y. Xiong, H. Zhou, *Synlett* **2014**, *25*, 1735–1738; e) S. Wu, J. Tang, J. Han, D. Mao, X. Liu, X. Gao, J. Yu, L. Wang, *Tetrahedron* **2014**, *70*, 5986–5992; f) K. Lang, J. Park, S. Hong, *Angew. Chem. Int. Ed.* **2012**, *51*, 1620–1624; *Angew. Chem.* **2012**, *124*, 1652–1656; g) S. Liu, C. Wolf, *Org. Lett.* **2008**, *10*, 1831–1834; h) C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884; *Angew. Chem.* **2005**, *117*, 3949–3952.

[5] Cu-catalyzed Henry reactions of nitromethane giving 99% *ee* with at least one aldehyde: a) R. Ćwiek, P. Niedziejko, Z. Kałuża, *J. Org. Chem.* **2014**, *79*, 1222–1234; b) Y. Zhou, Y. Zhu, S. Yan, Y. Gong, *Angew. Chem. Int. Ed.* **2013**, *52*, 10265–10269; *Angew. Chem.* **2013**, *125*, 10455–10459; c) T. Deng, C. Cai, *J. Fluorine Chem.* **2013**, *156*, 183–186; d) A. Das, R. I. Kureshy, K. J. Prathap, M. K. Choudhary, G. V. S. Rao, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *Appl. Catal. A* **2013**, *459*, 97–105; e) D.-D. Qin, W.-H. Lai, D. Hu, Z. Chen, A.-A. Wu, Y.-P. Ruan, Z.-H. Zhou, H.-B. Chen, *Chem. Eur. J.* **2012**, *18*, 10515–10518; f) L. Yao, Y. Wei, P. Wang, W. He, S. Zhang, *Tetrahedron* **2012**, *68*, 9119–9124; g) Y. Wei, L. Yao, B. Zhang, W. He, S. Zhang, *Tetrahedron* **2011**, *67*, 8552–8558; h) R. I. Kureshy, A. Das, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *ACS Catal.* **2011**, *1*, 1529–1535; i) W. Jin, X. Li, B. Wan, *J. Org. Chem.* **2011**, *76*, 484–491; j) Y. Zhou, J. Dong, F. Zhang, Y. Gong, *J. Org. Chem.* **2011**, *76*, 588–600; k) B. V. Subba Reddy, J. George, *Tetrahedron: Asymmetry* **2011**, *22*, 1169–1175; l) A. T. Herrmann, S. R. Martinez, A. Zakarian, *Org. Lett.* **2011**, *13*, 3636–3639; m) G. Lai, F. Guo, Y. Zheng, Y. Fang, H. Song, K. Xu, S. Wang, Z. Zha, Z. Wang, *Chem. Eur. J.* **2011**, *17*, 1114–1117; n) W. Jin, X. Li, Y. Huang, F. Wu, B. Wan, *Chem. Eur. J.* **2010**, *16*, 8259–8261; o) G. Zhang, E. Yashima, W.-D. Woggon, *Adv. Synth. Catal.* **2009**, *351*, 1255–1262; p) T. Arai, M. Watanabe, A. Yanagisawa, *Org. Lett.* **2007**, *9*, 3595–3597; q) M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi, C. Ventrici, *Chem. Commun.* **2007**, 616–618.

[6] Selected recent examples of enantioselective Cu-catalyzed Henry reactions: a) P. Niedziejko, M. Szewczyk, P. Kalicki, Z. Kałuża, *Tetrahedron: Asymmetry* **2015**, *26*, 1083–1094; b) A. Das, M. K. Choudhary, R. I. Kureshy, K. Jana, S. Verma, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, B. Ganguly, *Tetrahedron* **2015**, *71*, 5229–5237; c) Y. Shi, Y. Li, J. Sun, Q. Lai, C. Wei, Z. Gong, Q. Gu, Z. Song, *Appl. Organomet. Chem.* **2015**, *29*, 661–667; d) Q. Song, X. An, T. Xia, X. Zhou, T. Shen, *C. R. Chim.* **2015**, *18*, 215–222; e) J.-L. Li, L. Liu, Y.-N. Pei, H.-J. Zhu, *Tetrahedron* **2014**, *70*, 9077–9083; f) M. Holmquist, G. Blay, M. C. Muñoz, J. R. Pedro, *Org. Lett.* **2014**, *16*, 1204–1207; g) S. J. Canipa, A. Stute, P. O'Brien, *Tetrahedron* **2014**, *70*, 7395–7403; h) X. Wang, W. Zhao, G. Li, J. Wang, G. Liu, L. Liu, R. Zhao, M. Wang, *Appl. Organomet. Chem.* **2014**, *28*, 892–899; i) P. Kiełbasiński, M. Rachwalski, S. Kaczmarczyk, S. Leśniak, *Tetrahedron: Asymmetry* **2013**, *24*, 1417–1420; j) Q. Dai, N. K. Rana, J. C.-G. Zhao, *Org. Lett.* **2013**, *15*, 2922–2925; k) M. W. Leighty, B. Shen, J. N. Johnston, *J. Am. Chem. Soc.* **2012**, *134*, 15233–15236.

[7] Selected recent examples of organocatalyzed and enzymatic Henry reactions: a) M. T. Corbett, J. S. Johnson, *Angew. Chem. Int. Ed.* **2014**, *53*, 255–259; *Angew. Chem.* **2014**, *126*, 259–263; b) K. Matsumoto, S. Asa-

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kura, *Tetrahedron Lett.* **2014**, *55*, 6919 – 6921; c) M. Vlatković, L. Bernardi, E. Otten, B. L. Feringa, *Chem. Commun.* **2014**, *50*, 7773 – 7775; d) P. B. Thorat, S. V. Goswami, W. N. Jadhav, S. R. Bhusare, *Aust. J. Chem.* **2013**, *66*, 661 – 666; e) S. Kitagaki, T. Ueda, C. Mukai, *Chem. Commun.* **2013**, *49*, 4030 – 4032; f) K. Kanagaraj, P. Suresh, K. Pitchumani, *Org. Lett.* **2010**, *12*, 4070 – 4073; g) D. Uraguchi, S. Nakamura, T. Ooi, *Angew. Chem. Int. Ed.* **2010**, *49*, 7562 – 7565; *Angew. Chem.* **2010**, *122*, 7724 – 7727; h) M. Gruber-Khadjawi, T. Purkarthofer, W. Skranc, H. Griengl, *Adv. Synth. Catal.* **2007**, *349*, 1445 – 1450; i) T. Mandal, S. Samanta, C.-G. Zhao, *Org. Lett.* **2007**, *9*, 943 – 945; j) Y. Sohtome, N. Takemura, K. Takada, R. Takagi, T. Iguchi, K. Nagasawa, *Chem. Asian J.* **2007**, *2*, 1150 – 1160.

[8] a) D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, W. Milius, M. Breuning, *Chem. Eur. J.* **2015**, *21*, 12488 – 12500; b) M. Breuning, D. Hein, M. Steiner, V. H. Gessner, C. Strohmann, *Chem. Eur. J.* **2009**, *15*, 12764 – 12769.

[9] D. Scharnagel, F. Prause, J. Kaldun, R. G. Haase, M. Breuning, *Chem. Commun.* **2014**, *50*, 6623 – 6625.

[10] a) M. Breuning, D. Hein, *Eur. J. Org. Chem.* **2013**, 7575 – 7582; b) M. Breuning, A. Paasche, M. Steiner, S. Dilsky, V. H. Gessner, C. Strohmann, B. Engels, *J. Mol. Struct.* **2011**, *1005*, 178 – 185; c) M. Breuning, T. Häuser, C. Mehler, C. Däschlein, C. Strohmann, A. Oechsner, H. Braunschweig, *Beilstein J. Org. Chem.* **2009**, *5*, 81; d) M. Breuning, M. Steiner, C. Mehler, A. Paasche, D. Hein, *J. Org. Chem.* **2009**, *74*, 1407 – 1410.

[11] F. Prause, J. Kaldun, B. Arensmeyer, B. Wennemann, B. Fröhlich, D. Scharnagel, M. Breuning, *Synthesis* **2015**, *47*, 575 – 586.

[12] For a successful application of copper complexes of diamines **9** and **10** in enantioselective, oxidative biaryl coupling reactions, see: F. Prause, B. Arensmeyer, B. Fröhlich, M. Breuning, *Catal. Sci. Technol.* **2015**, *5*, 2215 – 2226.

[13] Rearrangements of **14** to β-amino piperidines (via the sequence mesylation-aziridinium formation-nucleophilic attack at C-2 under ring enlargement) did not occur to a significant degree.

[14] Enantioselective Henry reactions in the presence of chiral, $Cu(OAc)_2$-derived catalysts, a) without an ancillary base: Ref. 5 e,h,k,l,n–q; 6 d,h–k; 16 b,c,e,h; b) with an ancillary base: Ref. 5 a,c,g; 6 a,b; 16 d,i.

[15] Catalytic amounts of pyridine do only weakly promote the Henry reaction (see Table 5, entry 3). In the case of nicotinaldehyde (**1 e**), however, the pyridyl moiety is part of the substrate and, thus, present in a 50-fold excess with respect to the amount of catalyst (2 mol%).

[16] Selected recent examples of diastereo- and enantioselective Cu-catalyzed Henry reactions: a) H. Mei, X. Xiao, X. Zhao, B. Fang, X. Liu, L. Lin, X. Feng, *J. Org. Chem.* **2015**, *80*, 2272 – 2280; b) T. Arai, A. Joko, K. Sato, *Synlett* **2015**, *26*, 209 – 214; c) A. Das, M. K. Choudhary, R. I. Kureshy, T. Roy, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *ChemPlusChem* **2014**, *79*, 1138 – 1146; d) L. Zhang, H. Wu, Z. Yang, X. Xu, H. Zhao, Y. Huang, Y. Wang, *Tetrahedron* **2013**, *69*, 10644 – 10652; e) D.-D. Qin, W. Yu, J.-D. Zhou, Y.-C. Zhang, Y.-P. Ruan, Z.-H. Zhou, H.-B. Chen, *Chem. Eur. J.* **2013**, *19*, 16541 – 16544; f) J. D. White, S. Shaw, *Org. Lett.* **2012**, *14*, 6270 – 6273; g) K. Xu, G. Lai, Z. Zha, S. Pan, H. Chen, Z. Wang, *Chem. Eur. J.* **2012**, *18*, 12357 – 12362; h) R. Boobalan, G.-H. Lee, C. Chen, *Adv. Synth. Catal.* **2012**, *354*, 2511 – 2520; i) A. Chougnet, G. Zhang, K. Liu, D. Häussinger, A. Kägi, T. Allmendinger, W.-D. Woggon, *Adv. Synth. Catal.* **2011**, *353*, 1797 – 1806; j) L. Cheng, J. Dong, J. You, G. Gao, J. Lan, *Chem. Eur. J.* **2010**, *16*, 6761 – 6765; k) T. Arai, Y. Taneda, Y. Endo, *Chem. Commun.* **2010**, *46*, 7936 – 7938; l) Ref. 5 d,f,g,i–k,n,p; 8 a,b.

[17] From $er_{obs} = (S_{cat} + S_{bg})/(R_{cat} + R_{bg}) \geq 99.5:0.5$ and under the assumption of a perfect catalyst ($S_{cat}/R_{cat} = 100:0$) follows $v_{cat}/v_{bg} \geq 99:1$. In the case of a nonperfect catalyst ($S_{cat}/R_{cat} < 100:0$), the ratio v_{cat}/v_{bg} would be even higher. obs = observed, cat = catalyzed reaction, bg = background reaction.

[18] This formula (deduction see Supporting Information) can be used under the following assumptions, which are—most probably—fulfilled by our reactions: (i) the rate laws for the for the two catalytic cycles are identical ($v_{cat1}/v_{cat2} \approx$ constant) and do not change in the course of the reaction, (ii) there is no interaction between the catalysts that unproportionally reduces the concentration of one catalyst (as, for example, the formation of a 2:1 oligomer), and (iii) the uncatalyzed background reaction is slow (here: 1% at maximum because of the excellent 99% *ee* reached) and, thus, does not measurably lower the enantiomeric excess.

[19] The existence of a hydrogen bridge cannot be fully ruled out, because the lower steric hindrance in **9** might induce an acceleration that overcompensates any deceleration induced by the hydrogen bounding.

[20] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals, 4th ed.*, Butterworth-Heinemann, Oxford, **2000**.

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Supporting Information

Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions

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1. Derivation of equation (1)

Definitions:

- Indices 1 and 2 denote to the single-catalyst experiments with catalyst 1 and 2, respectively.
- Index cp denotes to the competition experiment using a 1:1 ratio of catalyst 1 and 2.
- [P], [S], [R] are the concentrations of the product and its *S*- and *R*-enantiomers.
- e.r. is defined as the enantiomeric ratio *S*/*R*.
- k_{rel} gives the relative rate to be calculated.

Preconditions:

- There is no (significant degree of an) enantioselectivity-eroding background reaction.
- The rate laws of the single-catalyst reactions are identical.
- There is no change in the reaction order during the course of the reaction.
- Identical reagent and catalyst concentrations are used in all experiments.
- The parallel reactions occurring in the competition experiment do not interfere. Equimolar amounts of catalyst 1 and 2 are used.

Measured values: $e.r._{.1}$, $e.r._{.2}$, and $e.r._{.cp}$

Primary equations:

(**A**) $k_{rel} = [P_1] / [P_2]$ = constant (Product distribution in non-interfering parallel reactions that obey the same rate law)

(**B**) $[P_1] = [S_1] + [R_1]$ (**C**) $[P_2] = [S_2] + [R_2]$ (**D**) $e.r._{.1} = [S_1] / [R_1]$

(**E**) $e.r._{.2} = [S_2] / [R_2]$ (**F**) $[S_{cp}] = [S_1] + [S_2]$ (**G**) $[R_{cp}] = [R_1] + [R_2]$

(**H**) $e.r._{.cp} = [S_{cp}] / [R_{cp}]$

Derivation:

- From (**A**) and (**B**) – (**E**) follows:

$$k_{rel} = [P_1] / [P_2] = ([S_1] + [R_1]) / ([S_2] + [R_2]) = (e.r._{.1} \bullet [R_1] + [R_1]) / (e.r._{.2} \bullet [R_2] + [R_2])$$
$$= (e.r._{.1} + 1) / (e.r._{.2} + 1) \bullet [R_1] / [R_2] \quad (\mathbf{J})$$

- From (**H**) and (**D**) – (**G**) follows:

$$e.r._{.cp} = [S_{cp}] / [R_{cp}] = ([S_1] + [S_2]) / ([R_1] + [R_2]) = (e.r._{.1} \bullet [R_1] + e.r._{.2} \bullet [R_2]) / ([R_1] + [R_2]) \quad (\mathbf{K})$$

- Solving (**K**) for $[R_1] / [R_2]$ gives:

$$[R_1] / [R_2] = (e.r._{.cp} - e.r._{.2}) / (e.r._{.1} - e.r._{.cp}) \quad (\mathbf{L})$$

- Substitution of $[R_1] / [R_2]$ in (**J**) with (**L**) gives equation (1):

$$k_{rel} = \frac{(e.r._{.1} + 1) \bullet (e.r._{.cp} - e.r._{.2})}{(e.r._{.2} + 1) \bullet (e.r._{.1} - e.r._{.cp})} \quad (1)$$

2. Experimental procedures for the synthesis of the prolinamine ligands 9 and 10

All reactions with moisture-sensitive reagents were carried out under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[1] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey-Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey-Nagel, particle size 40–63 µm) was used for column chromatography. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^{1}H and ^{13}C NMR data were performed on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra were recorded on a ThermoFisher Scientific Q-Exactive (Orbitrap) or a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization). The enantiomeric excess and the configuration of the ß-nitro alcohols **3** were determined by HPLC analysis on chiral phase; the diastereomeric ratios were measured by ^{1}H NMR. Prolinols **14d**[2] and **14e**[3] and prolinamines **9a**,[3] **9j–m**,[4] **9n–r**,**t**,[2] **10e–k,m**[2] and **10l**[4] were prepared according to literature procedures. Diamines **10d** and **9s** are commercially available. The preparations of **9b**, **12a**, **13a**, and **14a** and the general procedures for the enantioselective Henry reactions are given in the main article.

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-cyclohexyl-5-oxopentanoate (12b)

A solution of the pyroglutamate **11** (3.65 g, 15.0 mmol) in anhydrous THF (45 mL) was treated at -40 °C with *c*HexMgCl (1.4 M in THF, 16.1 mL, 22.5 mmol). The reaction mixture was allowed to warm to RT overnight. Sat. aq. NH_4Cl (150 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (150 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 8:1) afforded amino ketone **12b** (1.51 g, 4.61 mmol, 31%) as a colorless oil.

R_f = 0.26 (petroleum ether/EtOAc 6:1). $[\alpha]_D^{31}$ = –17.3 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3362, 2934, 2859, 1748, 1709, 1519, 1450, 1367, 1248, 1167, 1053 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.07-1.34 (m, 5 H, *c*Hex-H), 1.39 (s, 9 H, $C(CH_3)_3$), 1.62 (m, 1 H, *c*Hex-H), 1.76 (m, 4 H, *c*Hex-H), 1.85 (m, 1 H, 3-*H*H), 2.06 (m, 1 H, 3-H*H*), 2.29 (m, 1 H, *c*Hex-H), 2.43-2.59 (m, 2 H, 4-H_2), 3.70 (s, 3 H, OCH_3), 4.22 (m, 1 H, 2-H), 5.09 (d, *J* = 7.9 Hz, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.7, 25.8 (C-*c*Hex), 26.4 (C-3), 28.3 ($C(CH_3)_3$), 28.5 (C-*c*Hex), 36.5 (C-4), 50.9 (C-*c*Hex), 52.5 (OCH_3), 53.1 (C-2), 80.0 ($C(CH_3)_3$), 155.5 (NCO_2), 173.1 (C-1), 213.0 (C-5) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{17}H_{29}NO_5$ $[M + H]^+$ 328.21185, found 328.21179.

[1] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, 4th Ed., Butterworth-Heinemann, Oxford, **2000**.
[2] F. Prause, J. Kaldun, B. Arensmeyer, B. Wennemann, B. Fröhlich, D. Scharnagel, M. Breuning, *Synthesis* **2015**, *47*, 575-586.
[3] D. Scharnagel, F. Prause, J. Kaldun, R. G. Haase and M. Breuning, *Chem. Commun.* **2014**, *50*, 6623-6625.
[4] F. Prause, B. Arensmeyer, B. Fröhlich, M. Breuning, *Catal. Sci. Technol.* **2015**, *5*, 2215-2226.

4

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-(3,5-dimethylphenyl)-5-oxopentanoate (12c)

A solution of the pyroglutamate **11** (3.65 g, 15.0 mmol) in anhydrous THF (40 mL) was treated at -40 °C with 2,5-Me_2PhMgBr (22.5 mL, 1.0 M in THF, 22.5 mmol), prepared from 1-bromo-3,5-dimethylbenzene (6.12 mL, 8.33 g, 45.0 mmol) and Mg (1.31 g, 54.0 mmol) in anhydrous THF (39 mL). The reaction mixture was allowed to warm to RT overnight. Sat. aq. NH_4Cl (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Column chromatography (silica gel, petroleum ether–EtOAc, 5:1–1:1 afforded amino ketone **12c** (4.09 g, 11.7 mmol, 78%) as a colorless oil.

R_f = 0.73 (petroleum ether/EtOAc 2:1). $[\alpha]_D^{31}$ = –9.1 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3376, 2985, 2934, 1748, 1714, 1686, 1520, 1437, 1367, 1247, 1161, 1051 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.41 (s, 9 H, $C(CH_3)_3$), 2.05 (m, 1 H, 3-*H*H), 2.28 (m, 1 H, 3-H*H*), 2.35 (s, 6 H, Ar-CH_3), 3.00 (ddd, *J* = 17.8, 8.3, 6.0 Hz, 1 H, 4-*H*H), 3.10 (ddd, *J* = 17.8, 8.2, 6.6 Hz, 1 H, 4-H*H*), 3.74 (s, 3 H, OCH_3), 4.38 (m, 1 H, 2-H), 5.18 (d, *J* = 8.1 Hz, 1 H, NH), 7.19 (s, 1 H, Ar-H), 7.54 (s, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.3 (Ar-CH_3), 27.1 (C-3), 28.4 ($C(CH_3)_3$), 34.7 (C-4), 52.6 (OCH_3), 53.2 (C-2), 80.1 ($C(CH_3)_3$), 125.9 (CH-Ar), 132.9 (CH-Ar), 136.8, 138.3 (C_q-Ar), 155.6 (NCO_2), 173.1 (C-1), 199.4 (C-5) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{19}H_{27}NO_5$ $[M + H]^+$ 350.19620, found 350.19601.

(2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-cyclohexylpyrrolidine-1,2-dicarboxylate (13b)

$NaBH(OAc)_3$ (615 mg, 2.90 mmol) was added at 0 °C to a solution of the amino ketone **12b** (731 mg, 2.23 mmol) in EtOAc (12 mL). After 10 min, TFA (739 µL, 1.09 g, 9.59 mmol) was added dropwise and the reaction mixture was stirred overnight at RT. Sat. aq. $NaHCO_3$ (50 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (silica gel, petroleum ether–EtOAc, 10:1–5:1) provided diastereomerically pure **3b** (488 mg, 1.57 mmol, 70%) as a colorless oil.

R_f = 0.47 (petroleum ether/EtOAc 6:1). $[\alpha]_D^{31}$ = –9.9 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2924, 2852, 1756, 1695, 1449, 1366, 1253, 1162, 1108 cm^{-1}. ^1H NMR* (500 MHz, $CDCl_3$) δ = 0.86 (m, 1 H, *c*Hex-H), 0.93-1.12 (m, 2 H, *c*Hex-H), 1.17 (m, 2 H, *c*Hex-H), 1.36 (s, 5.7 H, $C(CH_3)_3$), 1.42 (s, 3.3 H, $C(CH_3)_3$), 1.44-1.66 (m, 2 H, 4-*H*H, *c*Hex-H), 1.66-1.92 (m, 7 H, 3-*H*H, 4-H*H*, *c*Hex-H), 2.14 (m, 1 H, 3-H*H*), 3.59 (t, *J* = 7.0 Hz, 0.4 H, 5-H), 3.68 (s, 3 H, OCH_3), 3.69 (m, 0.6 H, 5-H), 4.14 (m, 0.6 H, 2-H), 4.27 (t, *J* = 8.2 Hz, 0.4 H, 2-H) ppm. ^{13}C NMR* (125 MHz, $CDCl_3$) δ = 26.3, 26.4 (C-4), 26.5, 26.6, 26.7, 26.9 (C-*c*Hex), 28.3, 28.5 ($C(CH_3)_3$), 27.7, 29.1 (C-3), 29.30, 29.34, 30.2, 30.5 (C-*c*Hex), 41.3, 41.5 (C-*c*Hex), 51.9, 52.1 (OCH_3), 59.8, 60.3 (C-2), 63.4, 63.5 (C-5), 79.8, 79.9 ($C(CH_3)_3$), 154.6, 155.2 (1-CO_2), 173.9, 174.2 (2-CO_2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{17}H_{29}NO_4$ $[M + H]^+$ 312.21693, found 312.21677. * 60:40 mixture of rotamers.

(2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-(3,5-dimethylphenyl)pyrrolidine-1,2-dicarboxylate (13c)

A solution of the amino ketone **12c** (4.01 g, 11.5 mmol) in abs. CH_2Cl_2 (115 mL) was treated at RT with TFA (17.7 mL, 26.1 g, 229 mmol) and stirred overnight. The solvent was removed under reduced pressure and the resulting orange oil was diluted five times with CH_2Cl_2 (150 mL) and evaporated again, in order to remove excess TFA. $NaBH_4$ (866 mg, 22.9 mmol) was slowly added at 0 °C to a solution of the residue in MeOH (180 mL). After stirring overnight at RT, the solvent was removed. The resulting oil was diluted four times with MeOH (150 mL) and evaporated again. The residue was suspended in anhydrous CH_2Cl_2 (230 mL) and NEt_3 (2.39 mL, 1.74 g, 17.2 mmol), Boc_2O (3.76 g, 17.2 mmol), and DMAP (70.0 mg, 573 µmol) were added at RT. After stirring overnight, sat. aq. NH_4Cl (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL) and the combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, petrol ether–EtOAc, 5:1) afforded a 93:7 mixture of pyrrolidine **13c** and its C5-epimer 5-*epi*-**13c** (2.25 g, 6.79 mmol, 59%) as a colorless oil.

R_f = 0.43 (petroleum ether/EtOAc 5:1). $[\alpha]_D^{32}$ = +21.0 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2974, 2934, 1754, 1694, 1607, 1455, 1390, 1366, 1200, 1160, 1119 cm^{-1}. ^1H NMR* (500 MHz, $CDCl_3$) δ = 1.15 (s, 5 H, $C(CH_3)_3$), 1.41 (s, 4 H, $C(CH_3)_3$), 1.93 (m, 1 H, 4-*H*H), 2.06 (m, 1 H, 3-*H*H), 2.17 (m, 1 H, 3-H*H*), 2.27 (m, 1 H, 4-H*H*), 2.31 (s, 6 H, Ar-CH_3), 3.80 (s, 3 H, OCH_3), 4.34 (m, 0.46 H, 2-H), 4.46 (dd, *J* = 8.2, 4.6 Hz, 0.54 H, 2-H), 4.66 (m, 0.58 H, 5-H), 4.91 (dd, *J* = 7.6, 3.4 Hz, 0.53 H, 5-H), 6.85 (s, 1 H, Ar-H), 7.16 (s, 2 H, Ar-H) ppm. ^{13}C NMR* (125 MHz, $CDCl_3$) δ = 21.4, 21.5 (Ar-CH_3), 28.0, 28.2 ($C(CH_3)_3$), 28.7, 28.9 (C-3), 34.5, 35.4 (C-4), 51.9, 52.1 (OCH_3), 60.2, 60.8 (C-2), 62.1, 62.9 (C-5), 79.9, 80.2 ($C(CH_3)_3$), 123.8, 124.2, 128.2, 128.5 (CH-Ar), 137.4, 137.7, 143.2, 143.9 (C_q-Ar), 153.8, 154.5 (1-CO_2), 173.5, 173.7 (2-CO_2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{19}H_{27}NO_4$ $[M + H]^+$ 334.20128, found 334.20122. * 55:45 mixture of rotamers; signals of the minor diastereomer are not listed.

Reduction of the esters 13 with LAH

General procedure (GP-1): $LiAlH_4$ (7.0 equiv.) was added at 0 °C to a solution of the pyrrolidine ester **13** (1.0 equiv.) in anhydrous THF (5.5 mL/mmol **13**). The reaction mixture was stirred for 1 h at 0 °C and then refluxed for 20–35 h. The resulting suspension was diluted with Et_2O (6 mL/mmol **13**) and treated with sat. aq. Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was rinsed with CH_2Cl_2–MeOH (9:1, 75 mL/mmol **13**). Evaporation of the solvent and column chromatography provided amino alcohol **14**.

(2*R*,5*S*)-2-Cyclohexyl-5-(hydroxymethyl)-1-methylpyrrolidine (14b) According to GP-1, pyrrolidine ester **13b** (1.60 g, 5.12 mmol) was reduced with LAH (1.36 g, 35.8 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1–4:1), prolinol **14b** (956 mg, 4.84 mmol, 95%) as a colorless oil.

R_f = 0.31 (CH_2Cl_2/MeOH 95:5). $[\alpha]_D^{32}$ = +30.5 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3353, 2922, 2851, 2787, 1653, 1448, 1051, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 0.88-1.04 (m, 2 H, *c*Hex-H), 1.05-1.29 (m, 3 H, *c*Hex-H), 1.45-1.81 (m, 10 H, 3-H_2, 4-H_2, *c*Hex-H), 2.30 (s, 3 H, 1-CH_3), 2.38 (m, 1 H, 2-H), 2.59 (m, 1 H, 5-H), 3.00-3.85 (br s, 1 H, OH), 3.38 (dd, *J* = 10.8, 2.1 Hz, 1 H, 5-C*H*H), 3.65 (dd, *J* = 10.8, 3.5 Hz, 1 H, 5-CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.3, 26.2, 26.38 (C-*c*Hex), 26.42 (C-4), 26.9 (C-*c*Hex), 27.0 (C-3), 31.2 (C-*c*Hex), 39.7 (C-*c*Hex), 39.9 (1-CH_3), 61.0 (5-CH_2), 67.6 (C-5), 72.0 (C-2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{12}H_{23}NO$ $[M + H]^+$ 198.18524, found 198.18439.

(2*R*,5*S*)-2-(3,5-Dimethylphenyl)-5-(hydroxymethyl)-1-methylpyrrolidine (14c) According to GP-1, a 93:7 mixture of the pyrrolidine ester **13c** and its C5-epimer (2.25 g, 6.75 mmol) was reduced with LAH (1.79 g, 47.2 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 19:1–9:1), prolinol **14c** (1.35 g, 6.16 mmol, 91%) as a colorless oil.

R_f = 0.43 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5). $[\alpha]_D^{32}$ = +75.9 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3392, 2945, 2863, 2782, 1771, 1606, 1456, 1240, 1151, 1082, 1035 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.67 (m, 1 H, 3-*H*H), 1.95 (m, 2 H, 4-H_2), 2.05 (m, 1 H, 3-H*H*), 2.16 (s, 3 H, 1-CH_3), 2.31 (s, 6 H, Ar-CH_3), 2.65 (m, 1 H, 5-H), 2.75-3.00 (br s, 1 H, OH), 3.34 (t, *J* = 7.7 Hz, 1 H, 2-H), 3.50 (d, *J* = 10.5 Hz, 1H, 5-C*H*H), 3.77 (d, *J* = 9.7 Hz, 1 H, 5-CH*H*), 6.90 (s, 1 H, Ar-H), 6.94 (s, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.0 (Ar-*C*H_3), 26.0 (C-4), 33.9 (C-3), 38.5 (1-CH_3), 61.9 (5-CH_2), 66.5 (C-5), 72.2 (C-2), 124.7, 128.6 (CH-Ar), 137.3, 142.5 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{14}H_{21}NO$ $[M + H]^+$ 220.16959, found 220.16992.

Mesylation and amination of the prolinols 14

General procedure (GP-2): MsCl (1.10–1.50 equiv.) and NEt_3 (3.0 equiv.) were added at 0 °C to a solution of the prolinol **14** (1.0 equiv.) in anhydrous CH_2Cl_2 (12 mL/mmol **14**). After 1–3 d at RT, an excess of the amine (5–30 equiv.) was added and stirring was continued for 3 d. Evaporation of the solvent and column chromatography provided prolinamines **9** and **10**.

(2*R*,5*S*)-2-Cyclohexyl-1-methyl-5-((methylamino)methyl)pyrrolidine (9c) According to GP-2, prolinol **14b** (64.5 mg, 327 µmol) was mesylated and treated with methylamine (aq., 40%, 1.30 mL, 1.16 g, 9.81 mmol) and MeOH (4.0 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 97:2.7:0.3), prolinamine **9c** (38.7 mg, 184 µmol, 56%) as a yellowish oil.

R_f = 0.32 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{32}$ = +13.5 (*c* = 0.50 in MeOH). IR (ATR) ν_{max} = 2925, 2851, 2783, 1769, 1448, 1241, 1130, 1056 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 0.80-1.03 (m, 2 H, 3-*H*H, *c*Hex-H), 1.05-1.30 (m, 3 H, *c*Hex-H), 1.41 (m, 1 H, *c*Hex-H), 1.56 (m, 4 H, 3-H*H*, 4-*H*H, *c*Hex-H), 1.61-1.87 (m, 6 H, 4-H*H*, *c*Hex-H, NH), 2.19 (ddd, *J* = 12.0, 7.5, 4.8 Hz, 1 H, 2-H), 2.22 (s, 3 H, 1-CH_3), 2.43 (s, 3 H, NHCH_3), 2.45 (m, 1 H, 5-H), 2.52 (dd, *J* = 11.2, 5.7 Hz, 1 H, 5-C*H*H), 2.61 (dd, *J* = 11.2, 3.8 Hz, 1 H, 5-CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.0, 26.5,

26.6, 27.1, 27.2 (C-*c*Hex), 27.9 (C-4), 31.3 (C-3), 37.1 ($NHCH_3$), 40.3 (C-*c*Hex), 40.6 (1-CH_3), 55.0 (5-CH_2), 66.2 (C-5), 72.0 (C-2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{13}H_{26}N_2$ $[M + H]^+$ 211.21688, found 211.21688.

(2*R*,5*S*)-2-(3,5-Dimethylphenyl)-1-methyl-5-((methylamino)methyl)pyrrolidine (9d) According to GP-2, prolinol **14c** (71.7 mg, 327 µmol) was mesylated and treated with methylamine (aq., 40%, 1.30 mL, 1.16 g, 9.81 mmol) and MeOH (4.0 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 90:9:1), prolinamine **9d** (58.0 mg, 250 µmol, 76%) as a yellowish oil.

R_f = 0.44 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{32}$ = +52.6 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3320, 2943, 2837, 2779, 1650, 1606, 1466, 1203, 1134, 1046 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.68 (m, 1 H, 3-*H*H), 1.82 (m, 1 H, 4-*H*H), 1.91-2.06 (m, 2 H, 3-H*H*, 4-H*H*), 2.14 (s, 3H, 1-CH_3), 2.30 (s, 6 H, Ar-CH_3), 2.52 (s, 3 H, NHCH_3), 2.56 (m, 1 H, 5-H), 2.68 (dd, *J* = 11.4, 5.8 Hz, 5-C*H*H), 2.76 (m, 1 H, 5-CH*H*), 3.18 (dd, *J* = 9.8, 6.6 Hz, 1 H, 2-H), 6.87 (s, 1 H, Ar-H), 6.95 (s, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.5 (Ar-CH_3), 27.9 (C-4), 34.2 (C-3) 37.1 ($NHCH_3$), 39.5 (1-CH_3), 55.0 (5-CH_2), 65.6 (C-5), 72.7 (C-2), 125.2, 128.9 (CH-Ar), 137.9, 143.6 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{15}H_{24}N_2$ $[M + H]^+$ 233.20123, found 233.20236.

(2*S*,5*S*)-1,2-Dimethyl-5-((methylamino)methyl)pyrrolidine (9e) According to GP-2, prolinol **14d** (100 mg, 774 µmol) was mesylated and treated with *N*-methylbenzylamine (2.00 mL, 1.88 g, 15.5 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 95:4.5:0.5), (2*S*,5*S*)-2-((benzyl(methyl)amino)methyl)-1,5-dimethylpyrrolidine (113 mg, 486 µmol, 63%) as colorless oil.

R_f = 0.35 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{26}$ = –49.1 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2962, 2836, 2778, 1495, 1453, 1372, 1205, 1126, 1022 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.08 (d, *J* = 6.1 Hz, 3 H, 5-CH_3), 1.33 (m, 1 H, 4-*H*H), 1.50 (m, 1 H, 3-*H*H), 1.81 (m, 1 H, 4-H*H*), 1.92 (m, 1 H, 3-H*H*), 2.18 (m, 1 H, 5-H), 2.20 (s, 3 H, 1-CH_3), 2.30 (s, 3 H, NCH_3), 2.35 (dd, *J* = 11.6, 8.3 Hz, 1 H, 2-C*H*H), 2.40 (m, 1 H, 2-H), 2.54 (dd, *J* = 11.6, 3.5 Hz, 1 H, 2-CH*H*), 3.41 (d, *J* = 13.1 Hz, 1 H, NC*H*HPh), 3.57 (d, *J* = 13.1 Hz, 1 H, NCH*H*Ph), 7.23 (m, 1 H, Ph-H), 7.30 (m, 4 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.0 (5-CH_3), 28.7 (C-3), 31.6 (C-4), 39.5 (1-CH_3), 43.2 NCH_3), 63.0 (2-CH_2), 63.2 (C-5), 63.3 (N*C*H_2Ph), 65.3 (C-2), 127.0, 128.3, 129.2 (CH-Ph), 139.3 (C_q-Ph) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{15}H_{24}N_2$ $[M + H]^+$ 233.20123, found 233.20061.

A solution of this prolinamine (58.0 mg, 250 µmol) in MeOH (2 mL) was treated with 10% HCl in MeOH (1 mL) and 20% $Pd(OH)_2$/C (48 mg, 68.4 µmol) was added. After hydrogenation (1 bar) for 2 h at 60 °C the mixture was filtered over a plug of celite® and the solvent was evaporated. The crude product was partitioned between 20% aq. KOH (4 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (5 × 10 mL) and the combined organic

layers were dried over $MgSO_4$. Careful removal of the solvent at 40 °C/100 mbar (note: the product is highly volatile!) provided prolinamine **9e** (23.0 mg, 161 µmol, 83%) as a colorless oil.

R_f = 0.13 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{26}$ = –15.9 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3348, 2959, 2844, 2786, 1682, 1542, 1460, 1377, 1192, 1126, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.09 (d, *J* = 6.1 Hz, 3 H, 2-CH_3), 1.36 (m, 1 H, 3-*H*H), 1.59 (m, 1 H, 4-*H*H), 1.84 (m, 2 H, 3-H*H*, 4-H*H*), 2.00 (s, 1 H, NH), 2.25 (m, 1 H, 2-H), 2.27 (s, 3 H, 1-CH_3), 2.40 (m, 1 H, 5-H), 2.47 (s, 3 H, NHCH_3), 2.55 (dd, *J* = 11.4, 6.7 Hz, 1 H, 5-C*H*H), 2.74 (dd, *J* = 11.4, 3.5 Hz, 1 H, 5-CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.3 (2-CH_3), 27.5 (C-4), 32.0 (C-3), 37.1 (NHCH_3), 39.3 (1-CH_3), 55.7 (5-CH_2), 63.0 (C-2), 66.6 (C-5) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_8H_{19}N_2$ $[M + H]^+$ 143.15428, found 143.15402.

(2*S*,5*R*)-2-((2-Hydroxyethylamino)methyl)-1-methyl-5-phenylpyrrolidine (9h) According to GP-2, prolinol **14e** (180 mg, 941 µmol) was mesylated and treated with 2-aminoethanol (282 µL, 287 mg, 4.71 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 95:4.5:0.5–80:18:2), prolinamine **9h** (110 mg, 469 µmol, 50%) as a colorless oil.

R_f = 0.42 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 85:13.5:1.5). $[\alpha]_D^{29}$ = +52.9 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3299, 2946, 2837, 2784, 1491, 1452, 1078, 1058, 1033, 755, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.69 (m, 1 H, 4-*H*H), 1.86 (m, 1 H, 3-*H*H), 1.98 (m, 1 H, 3-H*H*), 2.06 (m, 1 H, 4-H*H*), 2.15 (s, 3 H, 1-CH_3), 2.63 (m, 1 H, 2-H), 2.74 (dd, *J* = 11.6, 5.5 Hz, 1 H, 2-C*H*H), 2.78-2.95 (m, 5 H, 2-C*H*H, N*H*C$H_2$$CH_2$O*H*), 3.29 (dd, *J* = 9.9, 6.6 Hz, 1 H, 5-H), 3.68 (m, 2 H, CH_2OH), 7.23 (m, 1 H, Ph-H), 7.32 (m, 4 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 27.7 (C-3), 34.3 (C-4), 39.4 (1-CH_3), 51.5 (NH*C*$H_2$$CH_2$OH), 51.8 (2-$CH_2$), 60.5 ($CH_2$OH), 65.8 (C-2), 72.6 (C-5), 127.1, 127.4, 128.4 (CH-Ph), 143.6 (C_q-Ph) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{14}H_{23}N_2O$ $[M + H]^+$ 235.18049, found 235.18063.

(2*S*,5*R*)-2-((2-Methoxyethylamino)methyl)-1-methyl-5-phenylpyrrolidine (9i) According to GP-2, prolinol **14e** (225 mg, 1.18 mmol) was mesylated and treated with 2-methoxyethanamine (3.08 mL, 2.66 g, 35.4 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 98:1.8:0.2–90:9:1), prolinamine **9i** (213 mg, 858 µmol, 73%) as a colorless oil.

R_f = 0.28 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{28}$ = +52.0 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2939, 2875, 2818, 2786, 1452, 1197, 1115, 1073, 756, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.68 (m, 1 H, 4-*H*H), 1.80 (m, 1 H, 3-*H*H), 1.98 (m, 1 H, 3-H*H*), 2.05 (m, 1 H, 4-H*H*), 2.15 (s, 3 H, 1-CH_3), 2.39 (s, 1 H, NH), 2.61 (m, 1 H, 2-H), 2.71 (dd, *J* = 11.3, 6.4 Hz, 1 H, 2-C*H*H), 2.83 (dd, *J* = 11.3, 3.6 Hz, 1 H, 2-CH*H*), 2.87 (m, 2 H, NHC$H_2$$CH_2$O), 3.28 (dd, *J* = 9.7, 6.6 Hz, 1 H, 5-H), 3.38 (s, 3 H, OCH_3), 3.54 (t, *J* = 5.2 Hz, 2 H, CH_2O), 7.21 (m, 1 H, Ph-H), 7.29 (m, 2 H, Ph-H), 7.34 (m, 2 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 28.1 (C-3), 34.3 (C-4), 39.4 (1-CH_3), 49.9 (NH*C*$H_2$$CH_2$O), 53.2 (2-$CH_2$), 58.9 ($OCH_3$), 65.8 (C-2), 71.9 ($CH_2$O), 72.5 (C-5), 127.0, 127.4,

128.3 (CH-Ph), 143.9 (C_q-Ph) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{15}H_{25}N_2O$ $[M + H]^+$ 249.19614, found 249.19605.

(2*R*,5*S*)-2-Cyclopentyl-5-((dimethylamino)methyl)-1-methylpyrrolidine (10a) According to GP-2, prolinol **14a** (60.0 mg, 327 µmol) was mesylated and treated with dimethylamine (aq., 40%, 595 µL, 529 mg 4.91 mmol) and MeOH (4.0 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 95:4.5:0.5), prolinamine **10a** (39.0 mg, 185 µmol, 57%) as a brownish oil.

R_f = 0.35 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{25}$ = –24.4 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2947, 2866, 2764, 1456, 1206, 1155 1032 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.18 (m, 2 H, *c*Pent-H), 1.48 (m, 5 H, 3-*H*H, 4-*H*H, *c*Pent-H), 1.59 (m, 2 H, *c*Pent-H), 1.72 (m, 1 H, 3-H*H*), 1.80 (m, 1 H, *c*Pent-H), 1.85-2.01 (m, 2 H, 4-H*H*, *c*Pent-H), 2.22 (s, 6 H, $N(CH_3)_2$), 2.24 (m, 2 H, 2-H, 5-C*H*H), 2.34 (s, 3 H, 1-CH_3), 2.39 (m, 2 H, 5-H, 5-CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.3, 26.0 (C-*c*Pent), 26.9 (C-3), 28.4 (C-*c*Pent), 29.3 (C-4), 31.2 (C-*c*Pent), 41.1 (1-CH_3), 43.7 (C-*c*Pent), 46.5 ($N(CH_3)_2$), 65.2 (5-CH_2), 65.9 (C-5), 71.8 (C-2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{13}H_{26}N_2$ $[M + H]^+$ 211.21688, found 211.21620.

(2*R*,5*S*)-2-Cyclohexyl-5-((dimethylamino)methyl)-1-methylpyrrolidine (10b) According to GP-2, prolinol **14b** (61.7 mg, 327 µmol) was mesylated and treated with dimethylamine (aq., 40%, 595 µL, 529 mg 4.91 mmol) and MeOH (4.0 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 95:4.5:0.5), prolinamine **10b** (41.4 mg, 185 µmol, 57%) as a yellow oil.

R_f = 0.37 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{25}$ = –9.4 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2923, 2851, 2766, 1449, 1345, 1156, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 0.86-1.02 (m, 2 H, *c*Hex-H), 1.05-1.29 (m, 3 H, *c*Hex-H), 1.44 (m, 2 H, 4-*H*H, *c*Hex-H), 1.57 (m, 3 H, 3-H_2, *c*Hex-H), 1.63-1.79 (m, 4 H, *c*Hex-H), 1.90 (m, 1 H, 4-H*H*), 2.22 (m, 2 H, 2-H, 5-C*H*H), 2.27 (s, 6 H, $N(CH_3)_2$), 2.30 (s, 3 H, 1-CH_3), 2.44 (m, 2 H, 5-H, 5-CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.6 (C-3), 26.5, 26.6, 27.1, 27.2 (C-*c*Hex), 29.7 (C-4), 31.3, 40.0 (C-*c*Hex), 40.8 (1-CH_3), 46.6 ($N(CH_3)_2$), 65.2 (5-CH_2), 65.4 (C-5), 72.3 (C-2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{14}H_{28}N_2$ $[M + H]^+$ 225.23253, found 225.23183.

(2S,5R)-2-((Dimethylamino)methyl)-5-(3,5-dimethylphenyl)-1-methylpyrrolidine (10c) According to GP-2, prolinol **14c** 71.7 mg, 327 µmol) was mesylated and treated with dimethylamine (aq., 40%, 595 µL, 529 mg 4.91 mmol) and MeOH (4.0 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 95:4.5:0.5), prolinamine **10c** (59.0 mg, 239 µmol, 73%) as a yellow oil.

R_f = 0.29 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5). $[\alpha]_D^{32}$ = +27.3 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2945, 2817, 2764, 1606, 1456, 1261, 1201, 1157, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.73 (m, 2 H, 3-*H*H, 4-*H*H), 2.05 (m, 2 H, 3-H*H*, 4-H*H*), 2.19 (s, 3 H, 1-CH_3), 2.30 (s, 6 H, Ar-CH_3), 2.37 (s, 6 H, N(CH_3)$_2$), 2.46 (dd, *J* = 11.5, 7.9 Hz, 1 H, 2-C*H*H), 2.58 (m, 1 H, 2-H), 2.60 (dd, *J* = 11.5, 3.5 Hz, 1 H, 2-CH*H*) 3.17 (dd, *J* = 9.1, 6.6 Hz, 1 H, 5-H), 6.87 (s, 1 H, Ar-H), 6.95 (s, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.5 (Ar-CH_3), 29.5 (C-3), 33.8 (C-4) 39.8 (1-CH_3), 46.5 (N(CH_3)$_2$), 64.6 (C-2), 65.2 (2-CH_2), 72.8 (C-5), 125.3, 128.9 (CH-Ar), 137.9, 143.4 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{16}H_{26}N_2$ $[M + H]^+$ 247.21688, found 247.21634.

(2*S*,5*R*)-2-((Acetylamino)methyl)-1-methyl-5-phenylpyrrolidine (9f)

The primary prolinamine **9n**[2] (110 mg, 578 µmol) was dissolved in anhydrous CH_2Cl_2 (5 mL), and NEt_3 (88.8 µL, 64.3 mg, 636 µmol) and Ac_2O (60.1 µL, 64.9 mg, 636 µmol) were added dropwise. The solvent was evaporated after 3 h at RT and residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 97:2.7:0.3–95:4.5:0.5) to give prolinamine **9f** (123 mg, 529 µmol, 92%) as a colorless oil.

R_f = 0.23 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5). $[\alpha]_D^{28}$ = +10.2 (*c* = 0.50 in MeOH). IR (ATR) ν_{max} = 3289, 2949, 2843, 2782, 1647, 1549, 1452, 1368, 1279, 1193, 1041 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.61 (m, 1 H, 4-*H*H), 1.68 (m, 1 H, 3-*H*H), 1.92 (m, 1 H, 3-H*H*), 2.03 (s, 3 H, $NCOCH_3$), 2.07 (m, 1 H, 4-H*H*), 2.12 (s, 3 H, 1-CH_3), 2.66 (m, 1 H, 2-H), 3.16 (ddd, *J* = 13.7, 4.0, 2.8 Hz, 1 H, 2-C*H*H), 3.30 (dd, *J* = 9.2, 7.0 Hz, 1 H, 5-H), 3.65 (ddd, *J* = 13.7, 7.9, 2.4 Hz, 1 H, 2-CH*H*), 6.2 (s, 1 H, NH), 7.24 (m, 1 H, Ph-H), 7.31 (m, 4 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.4 (NCO*C*H_3), 26.7 (C-3), 34.0 (C-4), 38.5 (1-CH_3), 40.2 (2-CH_2), 64.3 (C-2), 72.0 (C-5), 127.16, 127.22, 128.5 (CH-Ph), 143.2 (C_q-Ph), 170.6 (N*C*OCH$_3$) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{14}H_{21}N_2O$ $[M + H]^+$ 233.16484, found 233.16491.

(2*S*,5*R*)-2-((Methanesulfonylamino)methyl)-1-methyl-5-phenylpyrrolidine (9g)

The primary prolinamine **9n**[2] (100 mg, 526 µmol) was dissolved in anhydrous CH_2Cl_2 (5 mL), and NEt_3 (80.7 µL, 58.5 mg, 578 µmol) and MsCl (44.7 µL, 66.2 mg, 578 µmol) were added dropwise. The solvent was evaporated after 1.5 h at RT and residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 98:1.8:0.3) to give prolinamine **9g** (133 mg, 496 µmol, 94%) as a colorless oil.

R_f = 0.30 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 98:1.8:0.2). $[\alpha]_D^{32}$ = +31.0 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3257, 2958, 2790, 1490, 1397, 1326, 1309, 1163, 1147, 1020, 993 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.68 (m, 1 H, 4-*H*H), 1.90 (m, 1 H, 3-*H*H), 1.98 (m, 1 H, 3-H*H*), 2.08 (m, 1 H, 4-H*H*), 2.13 (s, 3 H, 1-CH_3), 2.72 (m, 1 H, 2-H), 3.01 (s, 3 H, SO_2CH_3), 3.23 (m, 1 H, 2-C*H*H), 3.30 (dd, *J* = 12.0, 3.8 Hz, 1 H, 2-CH*H*), 3.34 (dd, *J* = 9.9, 6.7 Hz, 1 H, C-5), 5.10 (d, *J* = 6.6 Hz, 1 H, NH), 7.25 (m, 1 H, Ph-H), 7.32 (m, 4 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 26.5 (C-3), 34.0 (C-4), 38.4 (1-CH_3), 39.9 (SO_2CH_3), 44.0 (2-CH_2), 64.1 (C-2), 72.1 (C-5), 127.27, 127.34, 128.5 (CH-Ph),

142.8 (C_q-Ph) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{13}H_{21}N_2O_2S$ $[M + H]^+$ 269.13183, found 269.13175.

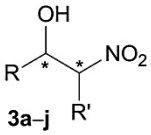
Gram-scale Henry reaction of 2a and b catalyzed by $CuBr_2$·9a

To a solution of diamine **9a** (22.5 mg, 110 µmol) in anhydrous THF (6.0 mL), anhydrous $CuBr_2$ (22.3 mg, 100 µmol), $MeNO_2$ (**2a**, 6.0 mL, 6.84 g, 112 mmol), and the respective aldehyde (**1a**: 1.06 g, 10.0 mmol, 1.01 mL; **1b**: 1.51 g, 10.0 mmol) were added successively at RT. The mixture was ultrasonicated for 10 min to give a clear, brownish solution and then cooled to -25 °C. NEt_3 (10.4 µL, 7.59 mg, 7.50 µmol) was added and the resulting blue-green solution was stirred for 70 h (**1a**) and 42 h (**1b**). The crude reaction mixture was purified by column chromatography (silica gel, hexanes/EtOAc 1:0 → 4:1) to afford the corresponding ß-nitro alcohols (**3a**: 1.57 g, 9.39 mmol, 94%, 99.0% *ee*, colorless oil; **3b**: 1.99 g, 9.39 mmol, 94%, 98.9% *ee*, yellowish solid). The enantiomeric excess of **3a**,**b** was determined by HPLC on chiral phase.[3]

3. HPLC analysis of the ß-nitro alcohols 3

Measurement of the enantiomeric excess (*ee*): The *ee* of each ß-nitro alcohol **3** was determined by HPLC (Knauer HPLC pump type 64.00, Knauer UV/VIS variable wavelength monitor type A0293 or Waters Alliance HPLC, Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase (Daicel Chiralcel OD-3, Daicel Chiralpak AD-H, Daicel Chiralcel OJ-H) with accuracy of integration of up to ± 0.1%. Many of the enantioselective Henry reactions were repeated, always providing the virtually same enantiomeric excesses (Δ*ee* = ± 0.2%).

Determination of the relative and absolute configuration of the major enantiomer: For the ß-nitro alcohols **3a-g,i,j** the absolute configuration was assigned by comparison with literature data.[3,5] In the case of the product **3h**, the major enantiomer was assigned under the assumption that the sense of asymmetric induction was the same as for all other derivatives (*re*-attack on the carbonyl group, see ref. 3). The relative configuration of the diastereomeric ß-nitro alcohols **3f-i** was confirmed by comparison of the NMR spectroscopic data with those given in literature.[5]



3a–j

Table S1. HPLC analysis on chiral phase.

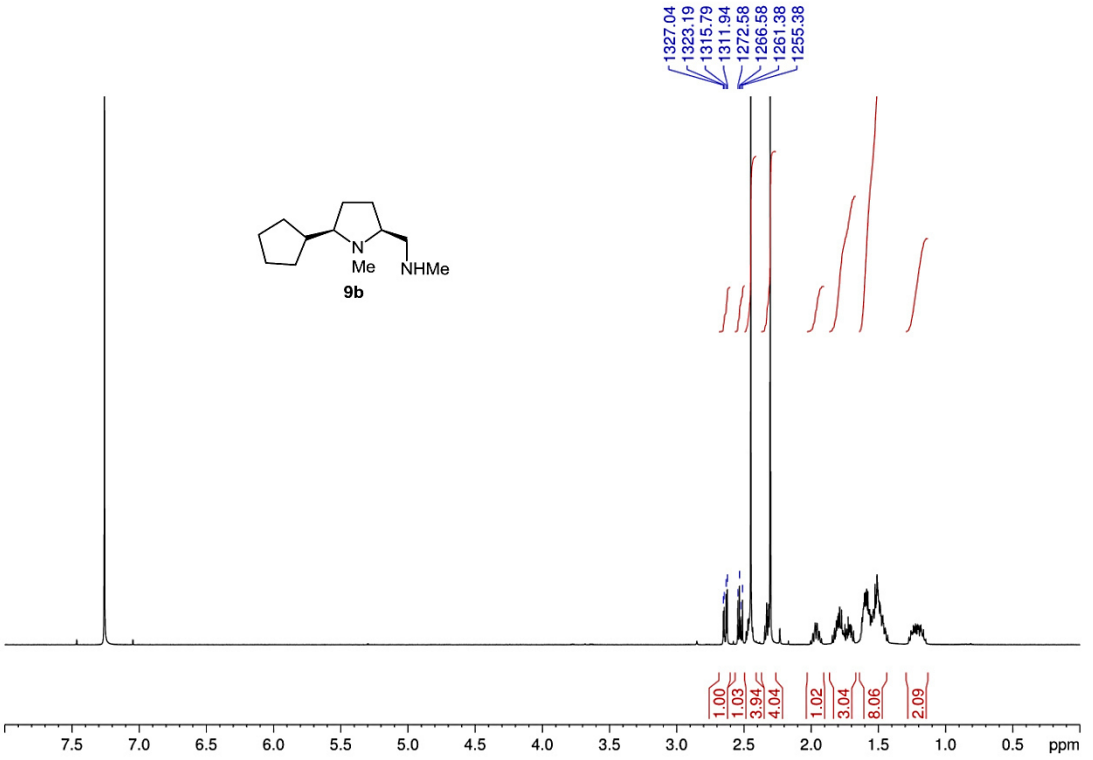
Compound	R	R'	Enantiomer Analysis: HPLC Conditions					
			Column[a]	Solvent System *n*-Hexane/*i*PrOH	Flow [ml/min]	t_r (*R*) [min][b]	t_r (*S*) [min][b]	Ref.[c]
3a	Ph	H	OD-3	85:15	0.8	12.6	14.9	[3]
3b	2-O_2N-Ph	H	OD-3	80:20	0.7	11.5	12.2	[3]
3c	2-MeO-Ph	H	OD-3	90:10	0.9	14.0	16.8	[3]
3d	*n*Oct	H	AD-H	95:5	0.8	14.3	20.2	[3]
3e	3-pyridyl	H	OJ-H	75:25	0.8	15.5	19.5	[5a]
3f	Ph	Me	AD-H	95:5	0.9	17.2 (1*R*,2*S*) 23.6 (1*R*,2*R*)	21.1 (1*S*,2*S*) 15.2 (1*S*,2*R*)	[5b,c]
3g	Ph	Et	OD-3	95:5	0.9	13.9 (1*R*,2*S*) 16.6 (1*R*,2*R*)	20.6 (1*S*,2*S*) 23.3 (1*S*,2*R*)	[5b,c]
3h[d]	Ph	CH_2OTBS	OD-3	95:5	0.9	10.4 (1*R*,2*S*) 12.2 (1*R*,2*R*)	14.2 (1*S*,2*S*) 19.3 (1*S*,2*R*)	[5d]
3i	*c*Hex	Et	AD-H	97:3[e]	0.8	19.7 (1*R*,2*S*) 62.1 (1*R*,2*R*)	20.9 (1*S*,2*S*) 23.7 (1*S*,2*R*)	[5b,c]
3j	4-O_2N-Ph	H	OD-3	85:15	0.8	18.5	23.5	[3]

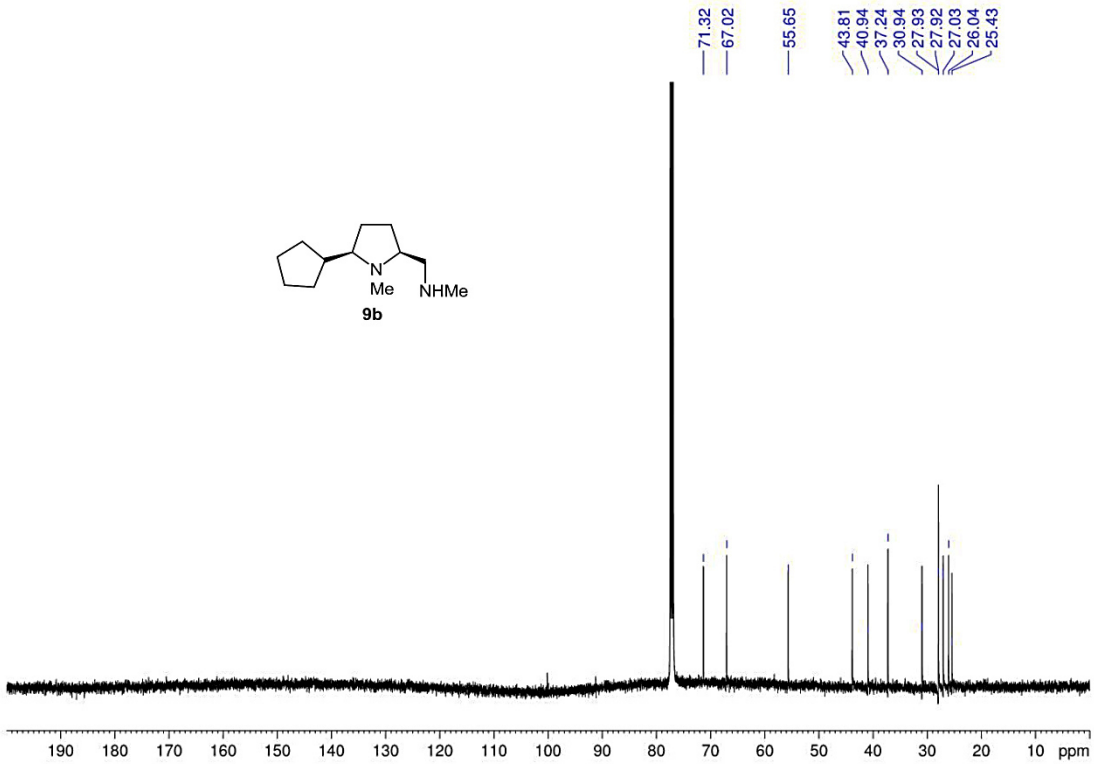
[a] OD-3: Daicel Chiralcel OD-3; AD-H: Daicel Chiralpak AD-H; OJ-H: Daicel Chiralcel OJ-H. [b] Retention time. [c] Reference data for NMR spectra and enantiomer analysis by HPLC on chiral phase.[3,5] [d] The absolute and relative configuration of the major enantiomer was tentatively assigned under the assumption of a *re*-attack on the carbonyl group. [e] As the polar eluent, EtOH was used instead of *i*PrOH.

[5] a) X.-G. Liu, J.-J. Jiang, M. Shi, *Tetrahedron: Asymmetry* **2007**, *18*, 2773-2781; b) D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, W. Milius, M. Breuning, *Chem. Eur. J.* **2015**, *21*, 12488-12500; c) Y. Zhou, J. Dong, F. Zhang, Y. Gong, *J. Org. Chem.* **2011**, *76*, 588-600; d) T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 13860-13869.

4. Copies of ^{1}H and ^{13}C NMR spectra

The ^{1}H and ^{13}C NMR spectra of all new compounds are listed in numerical order.





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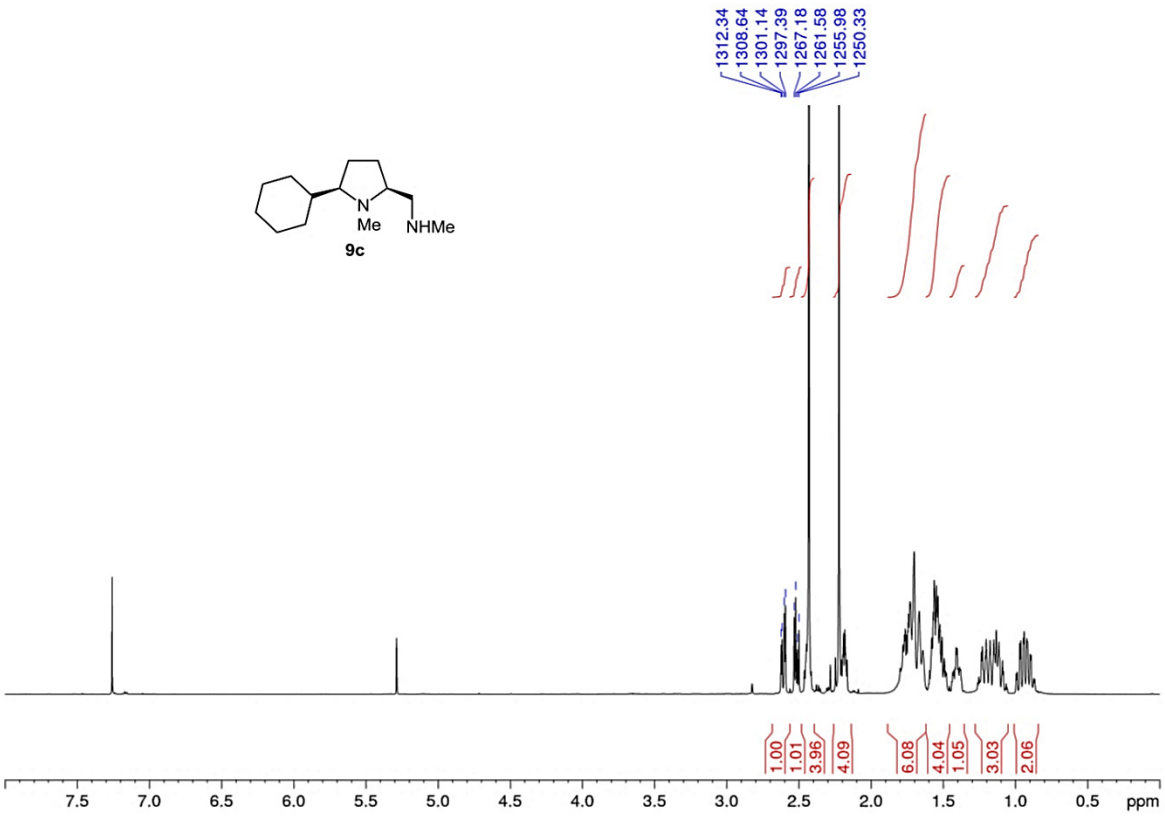
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6.08
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1.05
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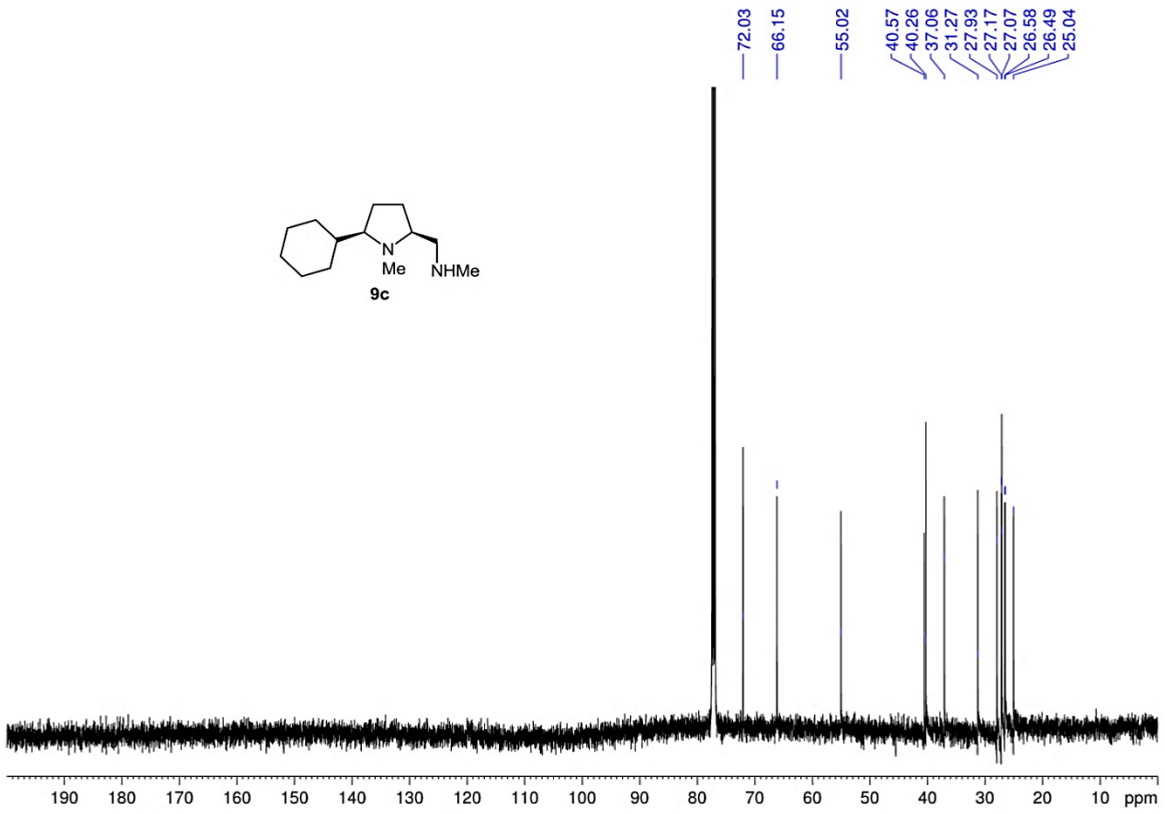
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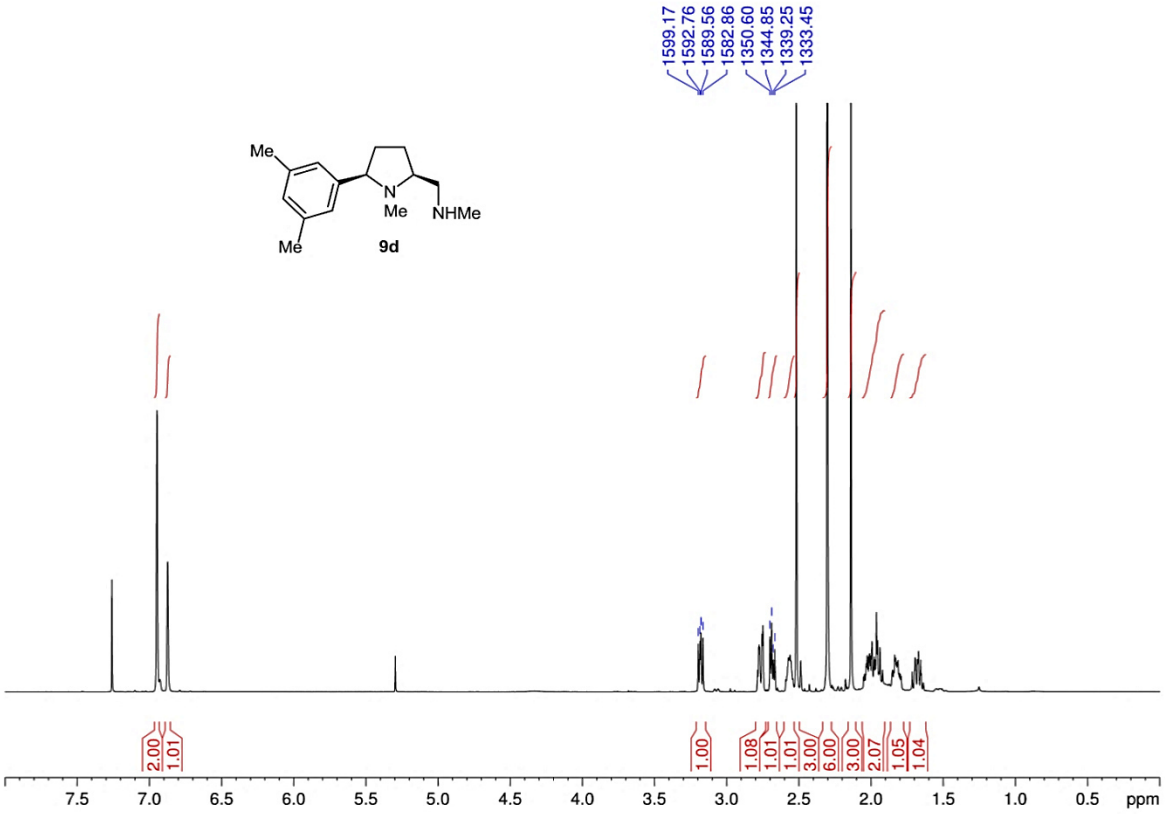
15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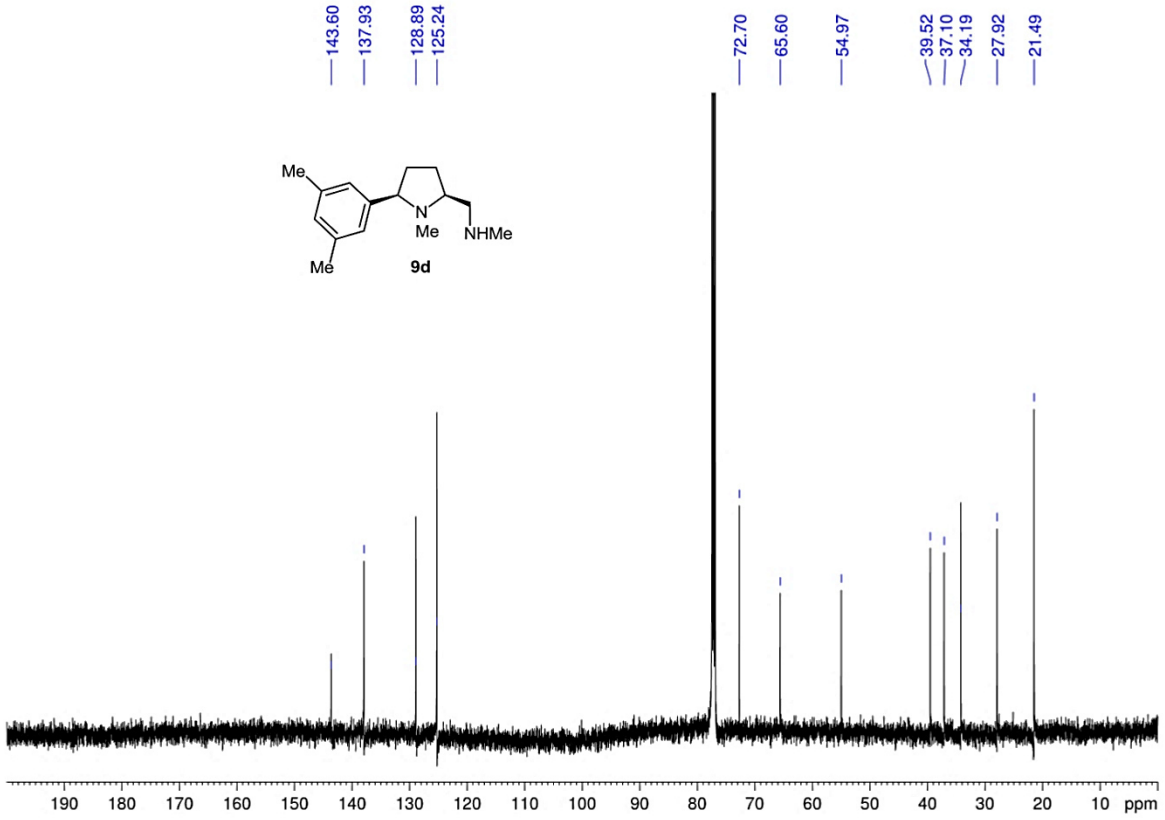
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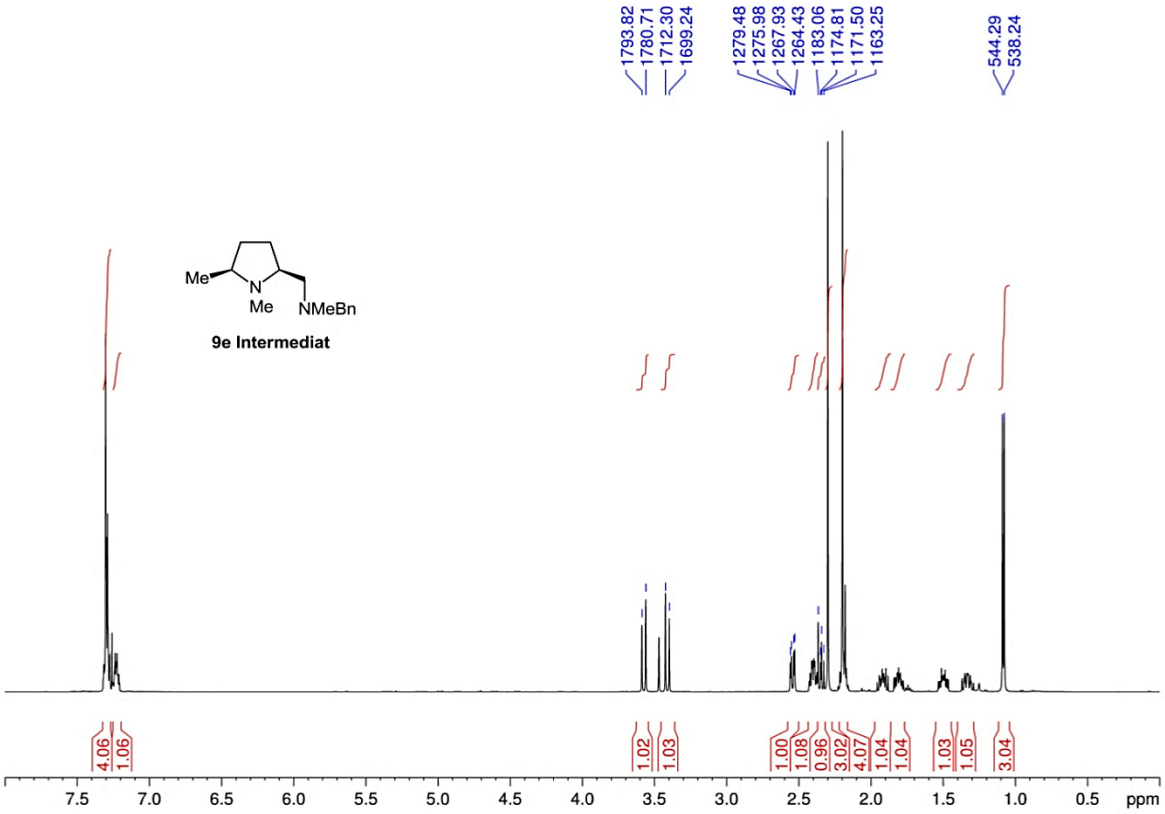
16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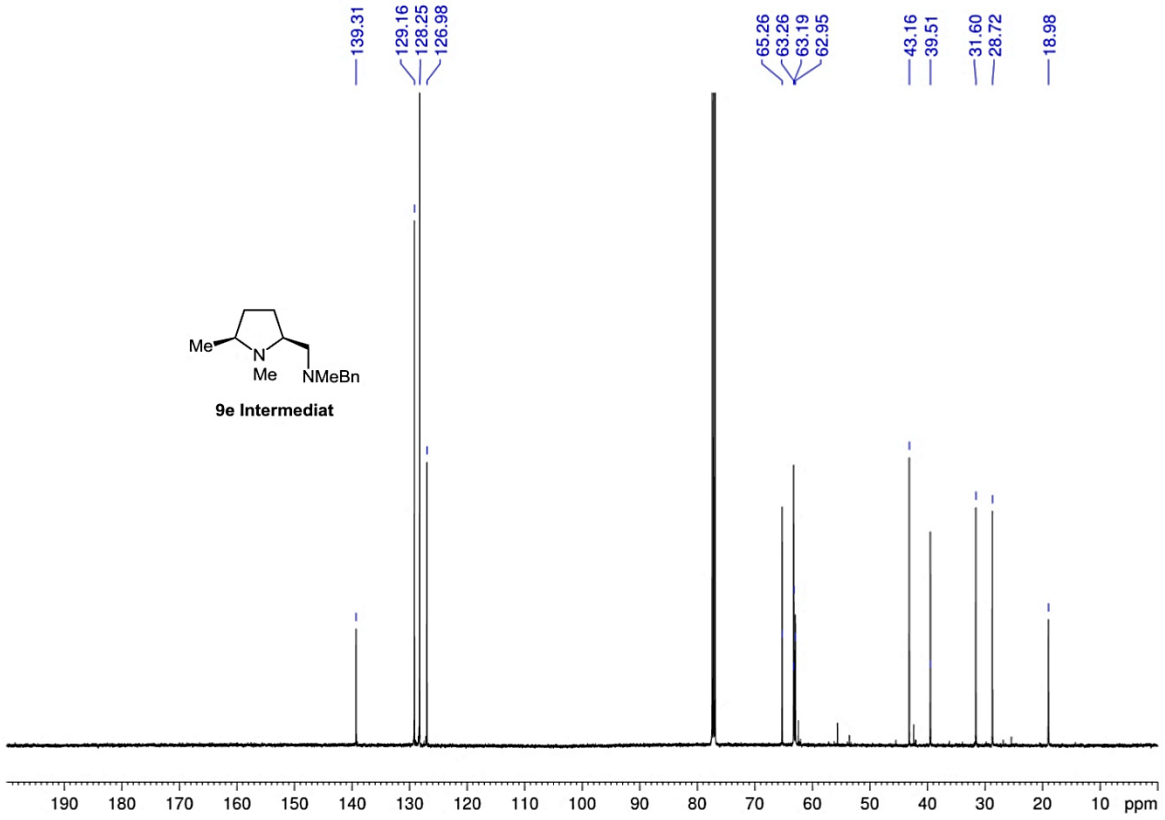
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9e Intermediat
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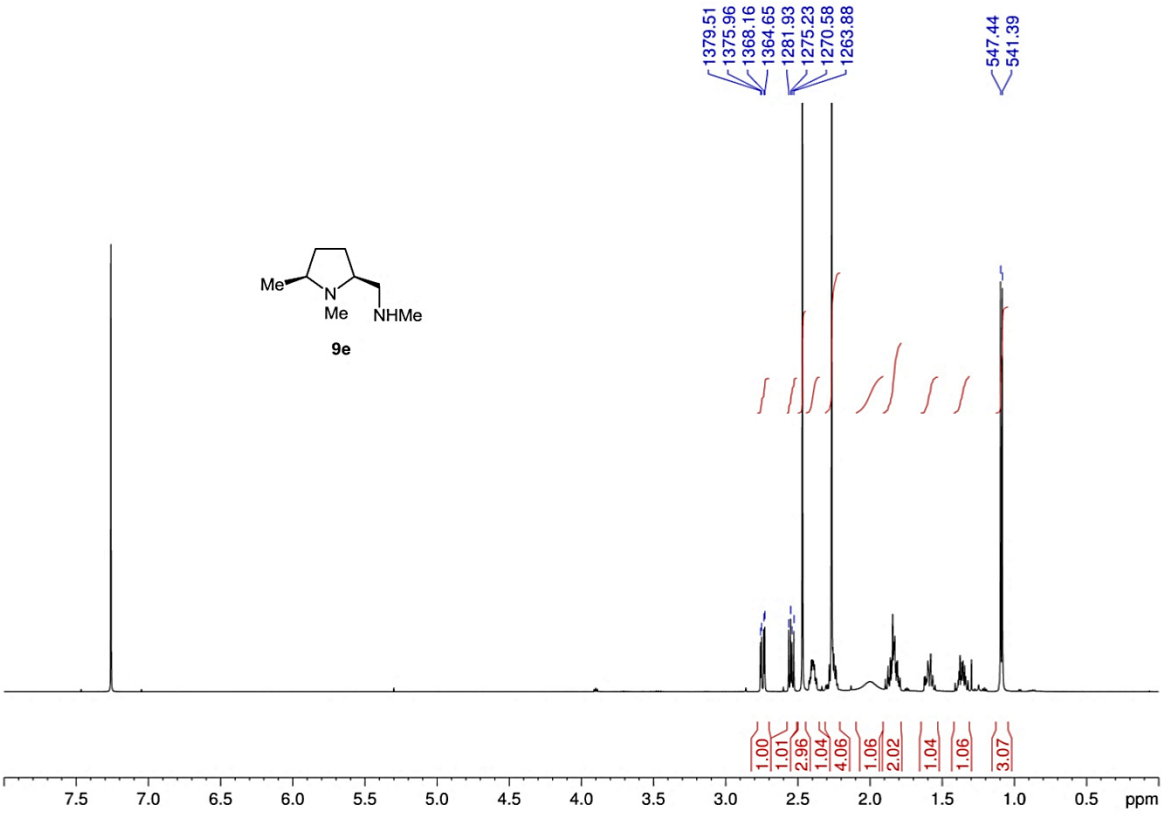
ppm

17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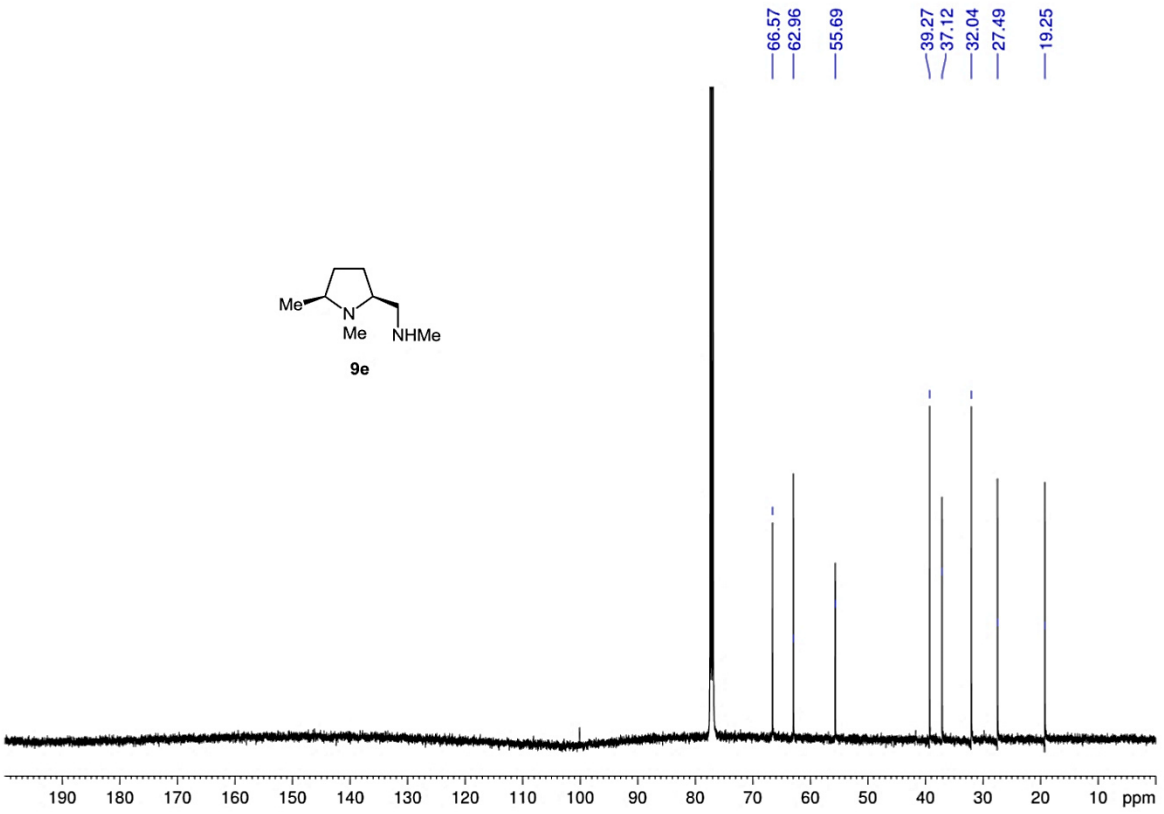
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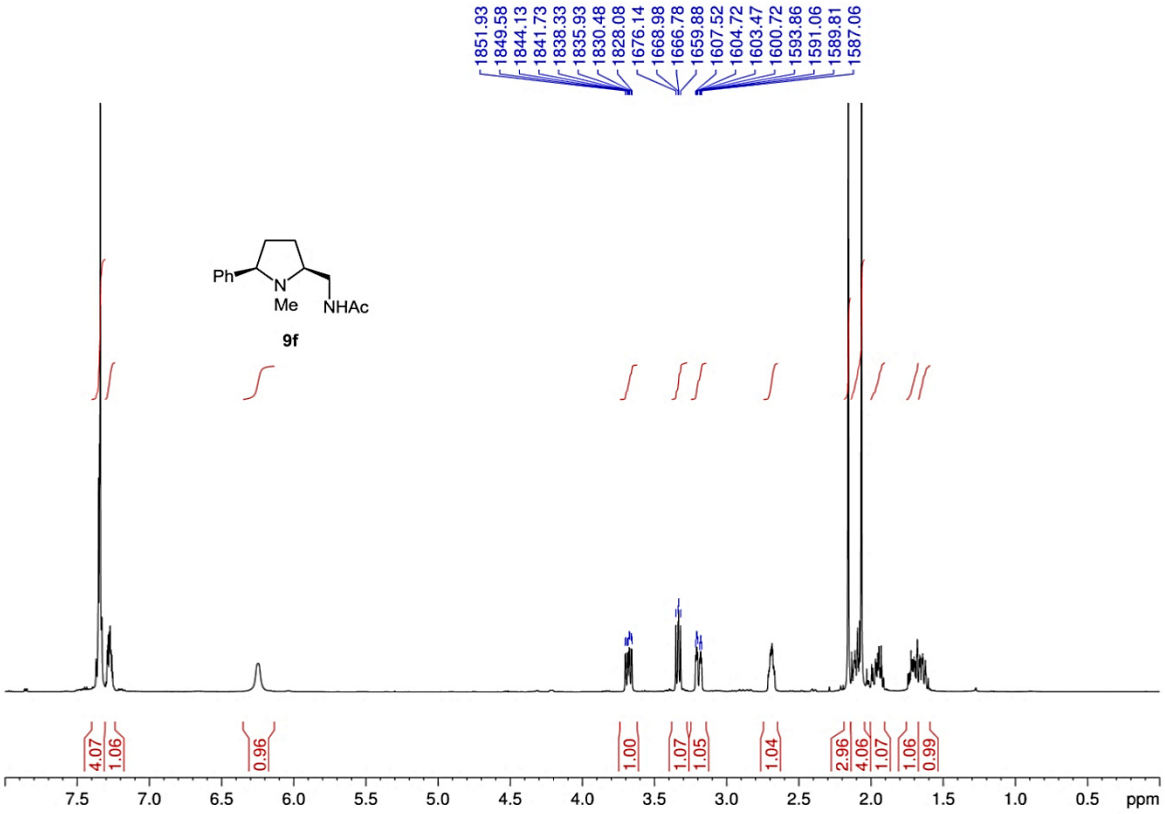
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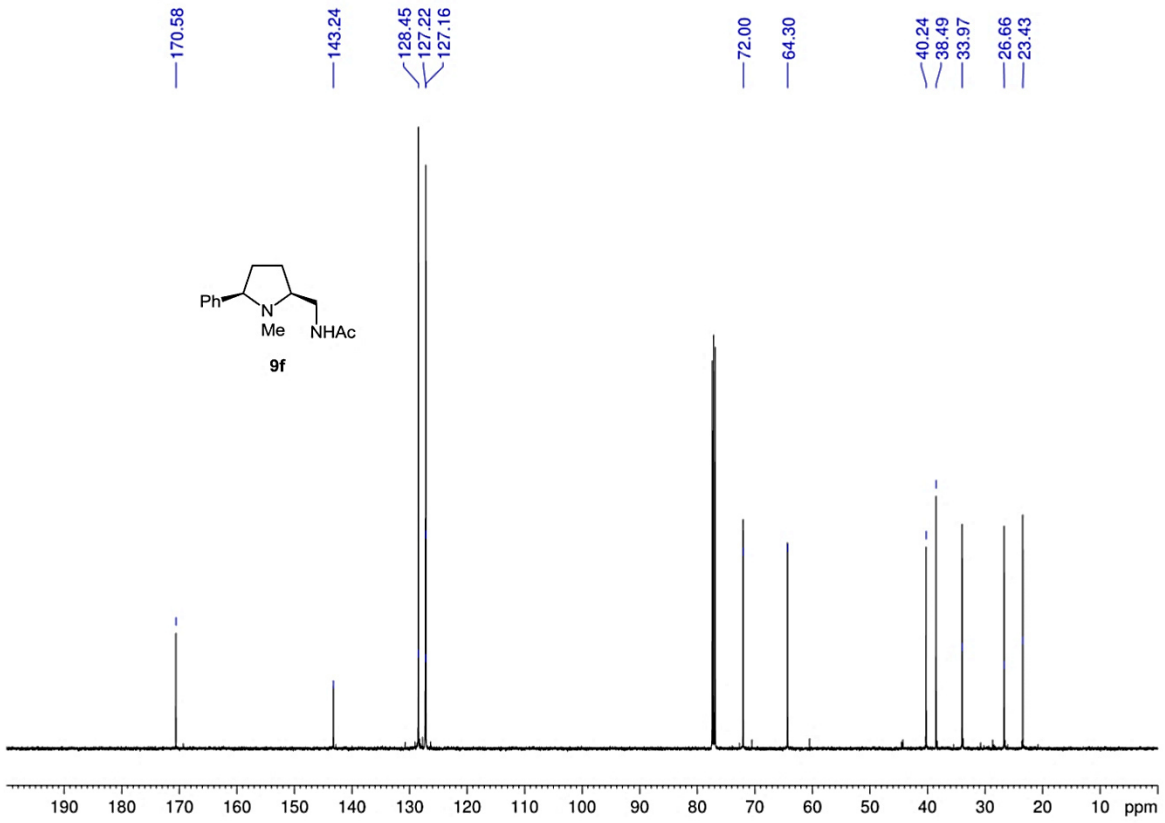
1.06
0.96
1.00
1.07
1.05
1.04
2.96
4.06
1.07
1.06
0.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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143.24
128.45
127.22
127.16
72.00
64.30
40.24
38.49
33.97
26.66
23.43
Ph
N
Me
NHAc
9f
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150
140
130
120
110
100
90
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70
60
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40
30
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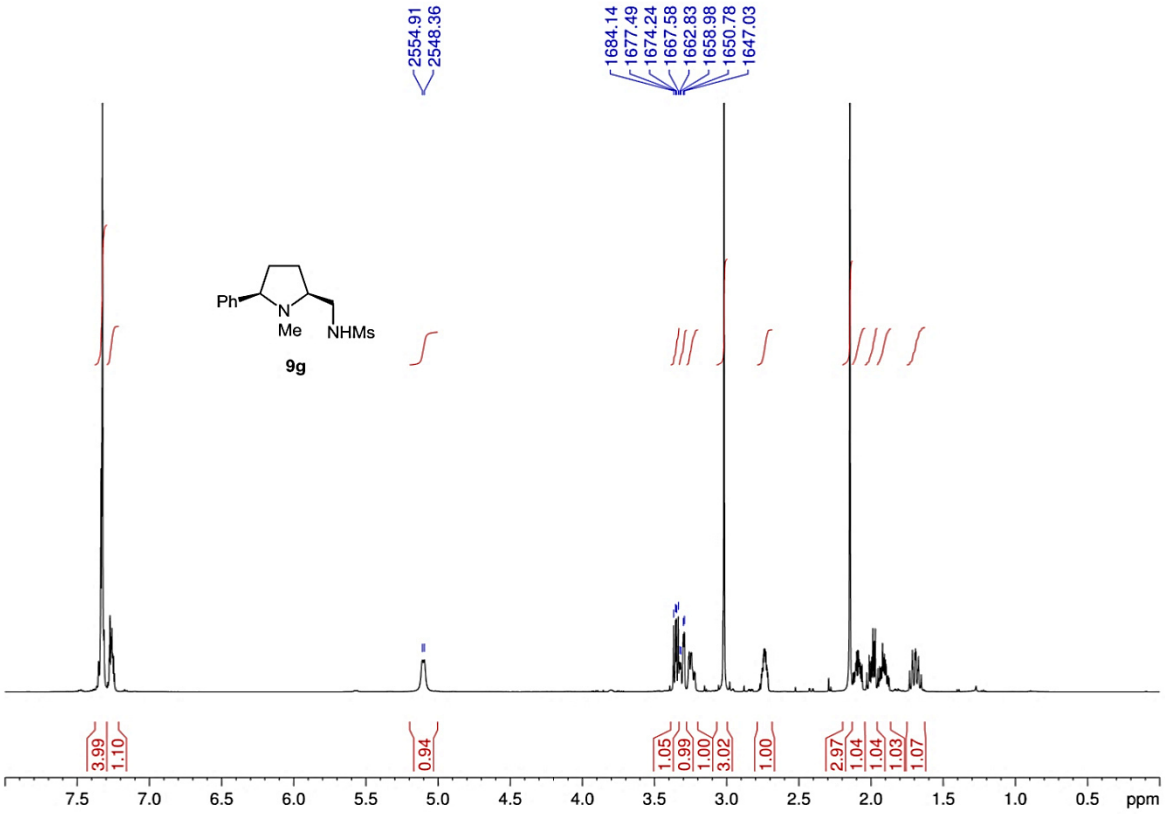
10
ppm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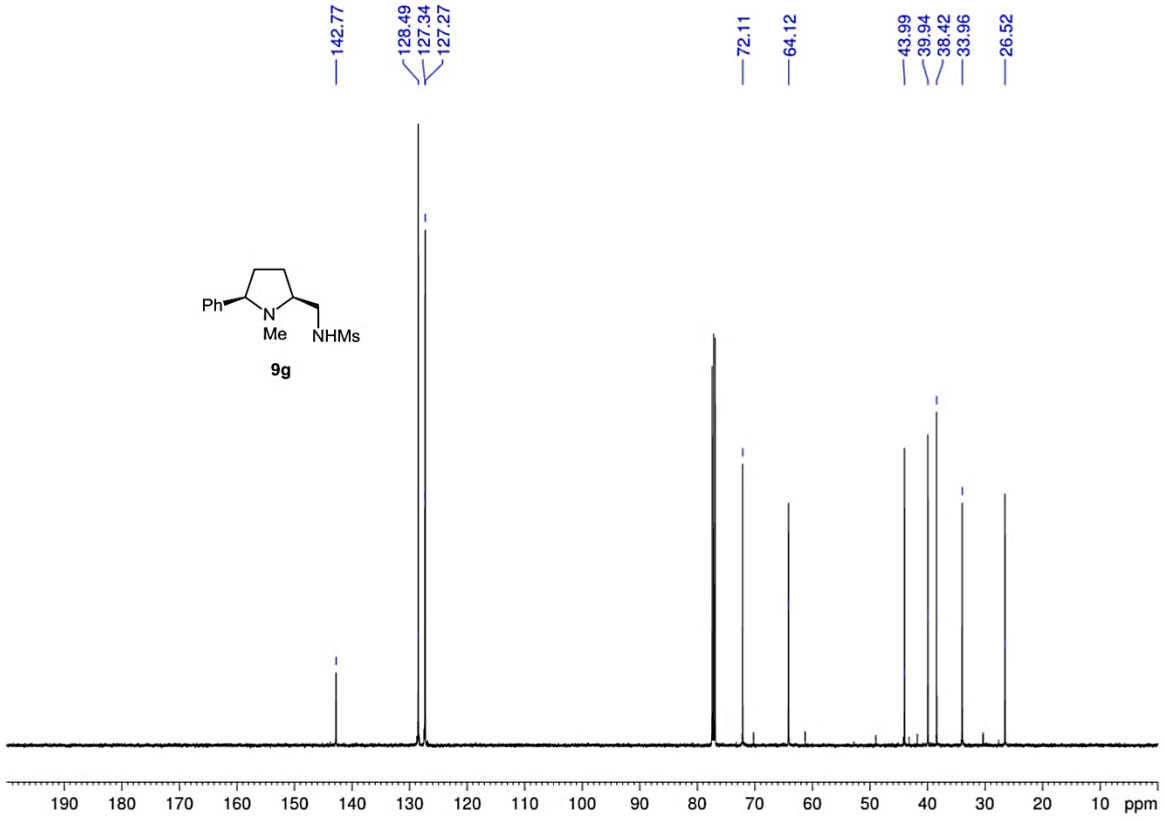
2548.36
1684.14
1677.49
1674.24
1667.58
1662.83
1658.98
1650.78
1647.03
Ph
N
Me
NHMs
9g
3.99
1.10
0.94
1.05
0.99
1.00
3.02
1.00
2.97
1.04
1.04
1.03
1.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


142.77
128.49
127.34
127.27
72.11
64.12
43.99
39.94
38.42
33.96
26.52
Ph
N
Me
NHMs
9g
190
180
170
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140
130
120
110
100
90
80
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60
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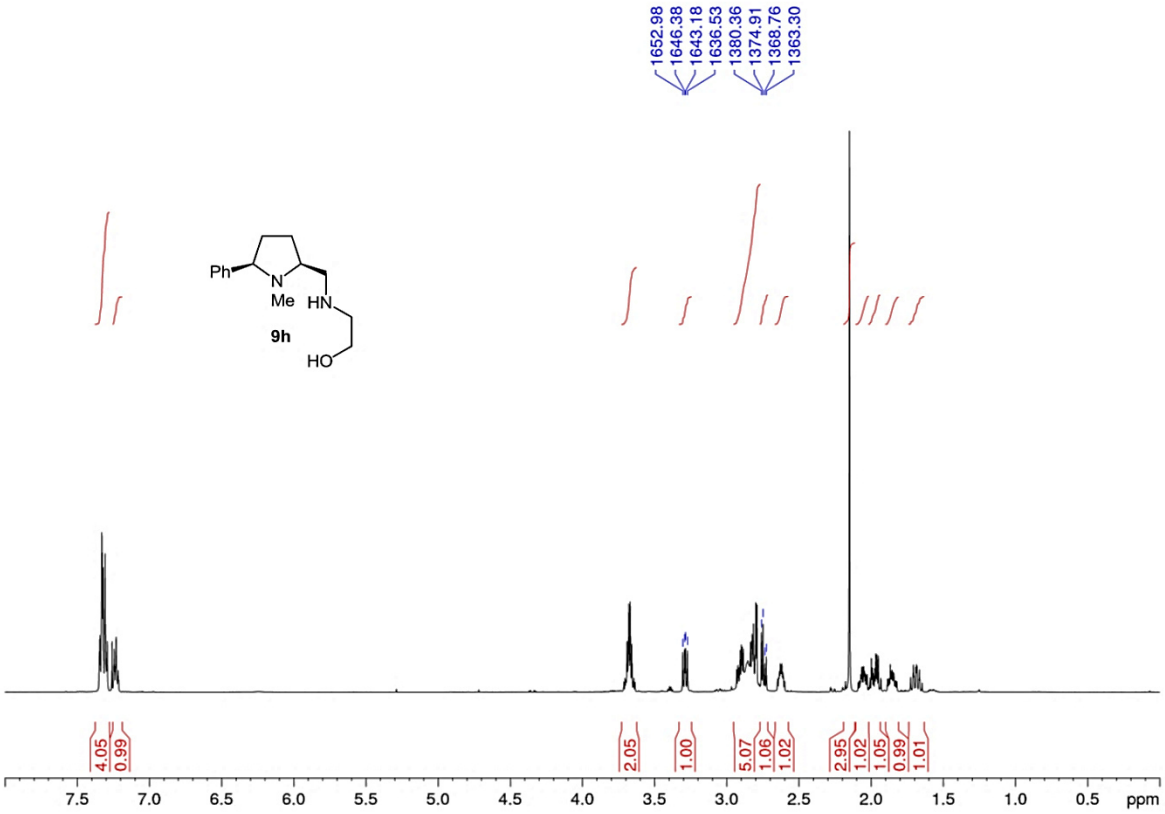
40
30
20
10
ppm

20


1652.98
1646.38
1643.18
1636.53
1380.36
1374.91
1368.76
1363.30
Ph
N
Me
HN
HO
9h
4.05
0.99
2.05
1.00
5.07
1.06
1.02
2.95
1.02
1.05
0.99
1.01
7.5
7.0
6.5
6.0
5.5
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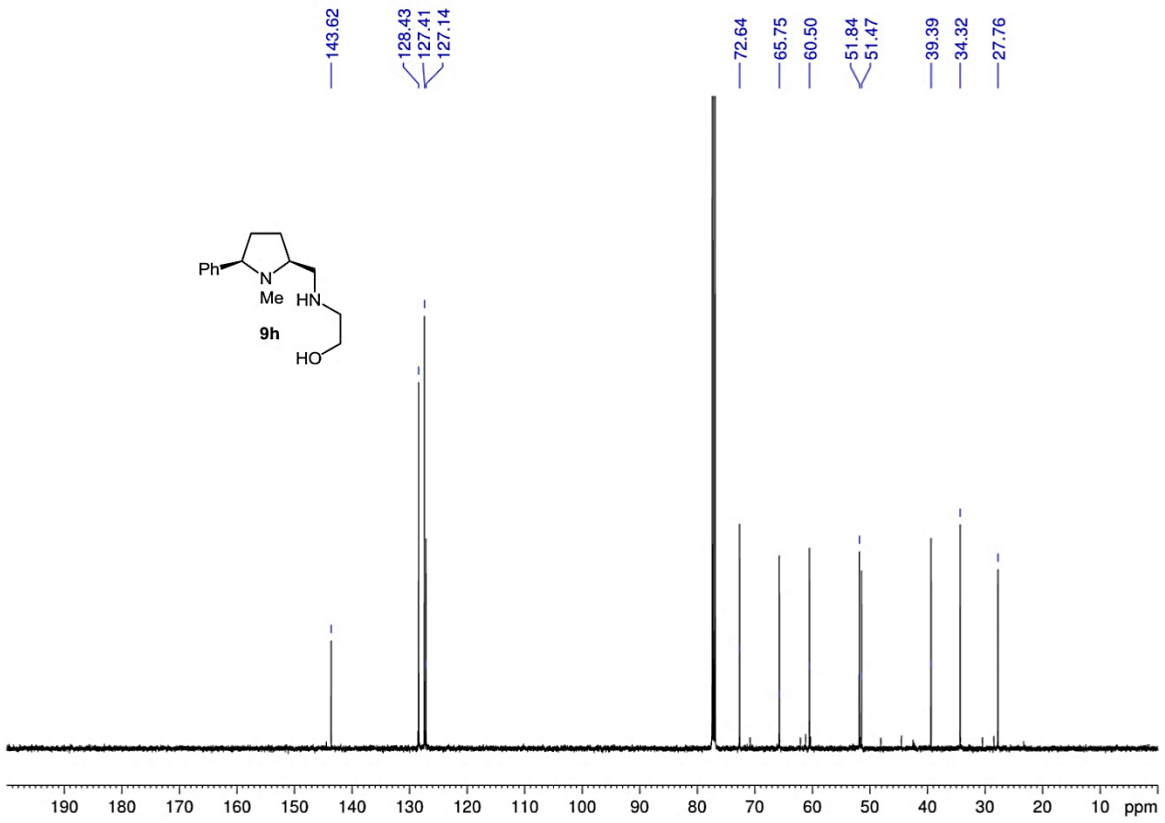
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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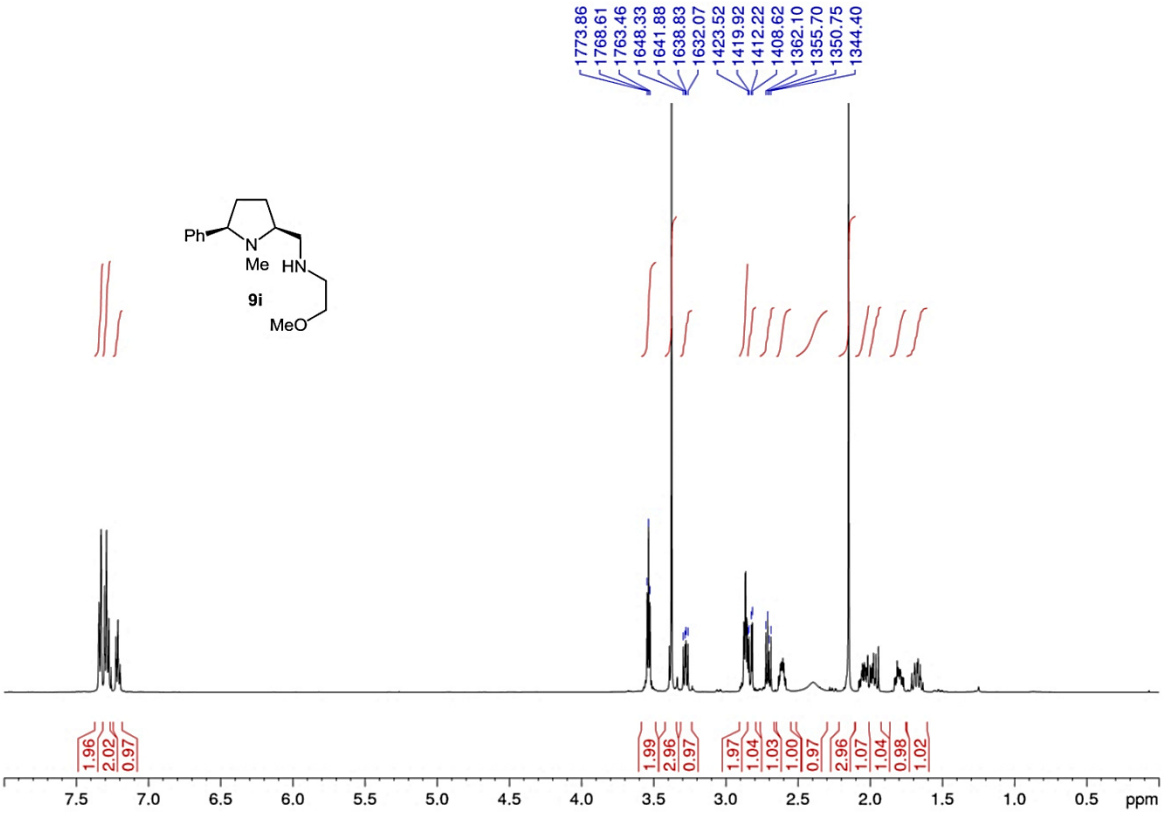
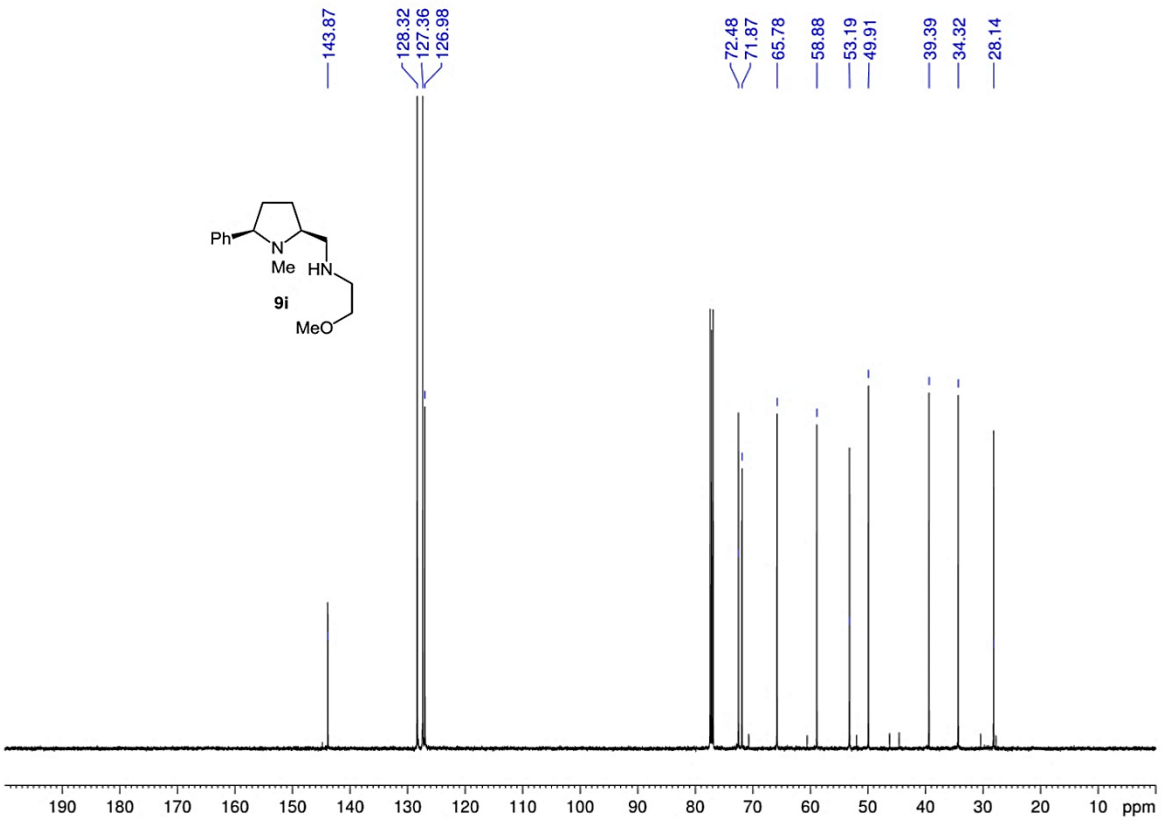
128.43
127.41
127.14
72.64
65.75
60.50
51.84
51.47
39.39
34.32
27.76
Ph
N
Me
HN
HO
9h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


1773.86
1768.61
1763.46
1648.33
1641.88
1638.83
1632.07
1423.52
1419.92
1412.22
1408.62
1362.10
1355.70
1350.75
1344.40
Ph
N
Me
HN
9i
MeO
1.96
2.02
0.97
1.99
2.96
0.97
1.97
1.04
1.03
1.00
0.97
2.96
1.07
1.04
0.98
1.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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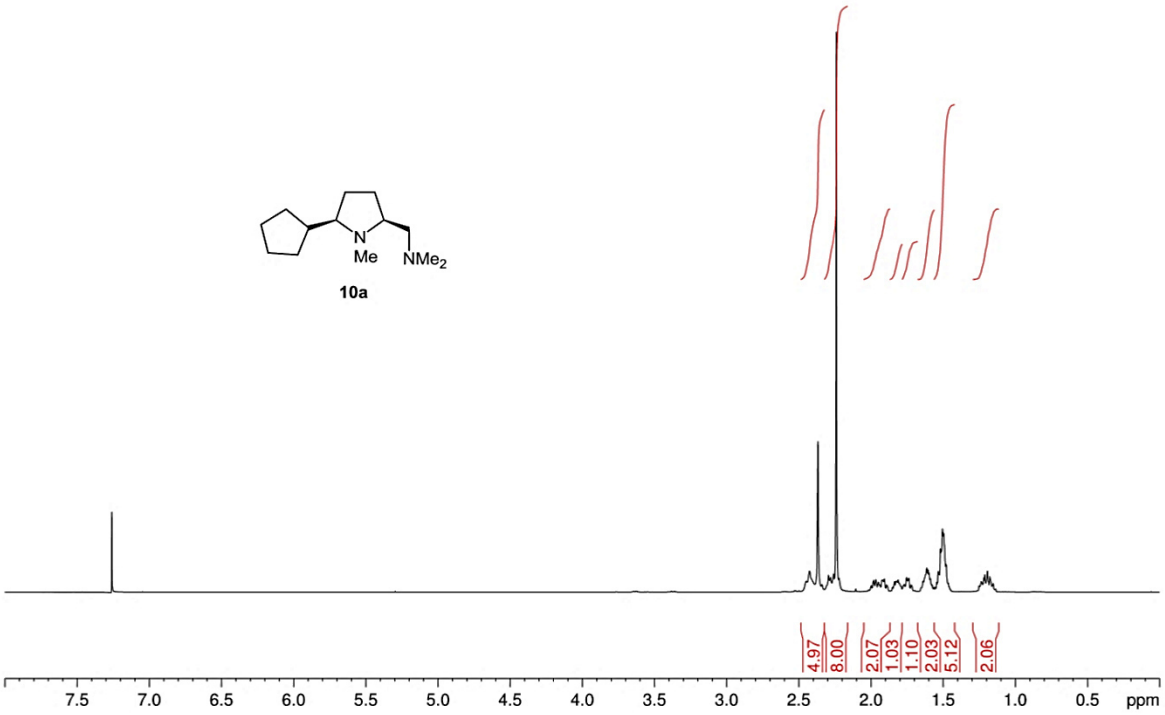
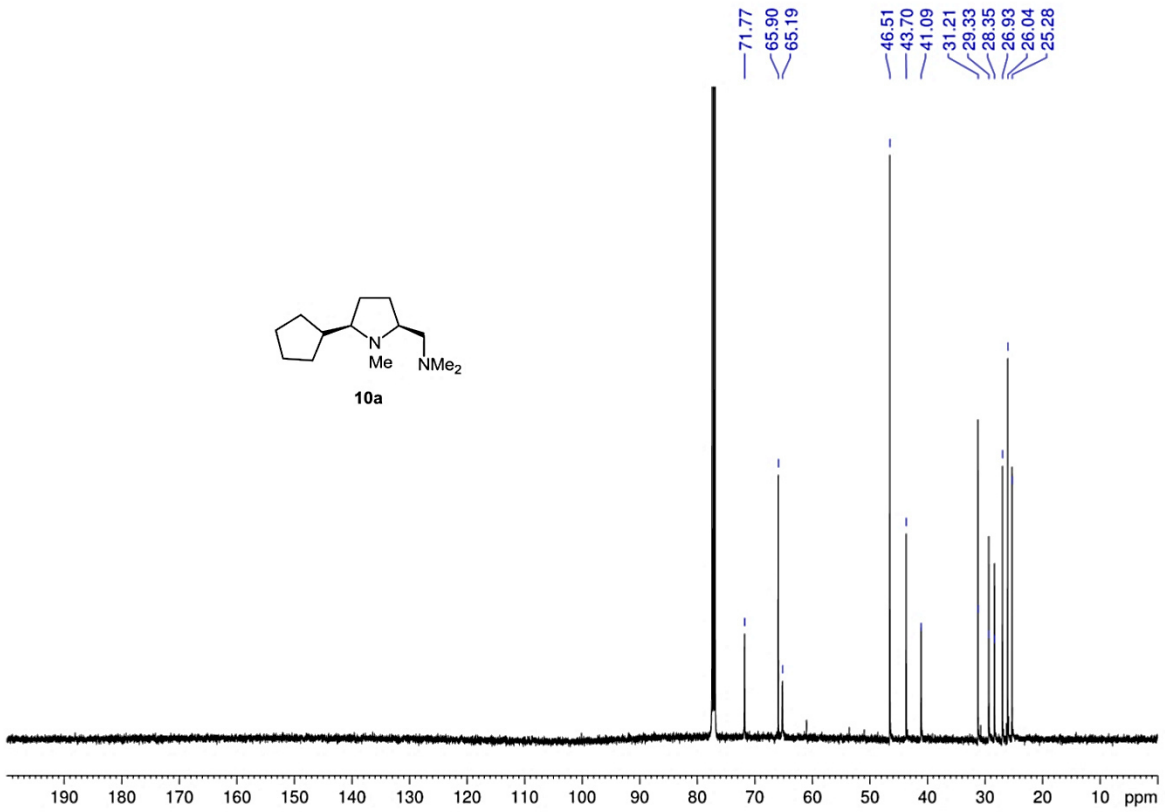
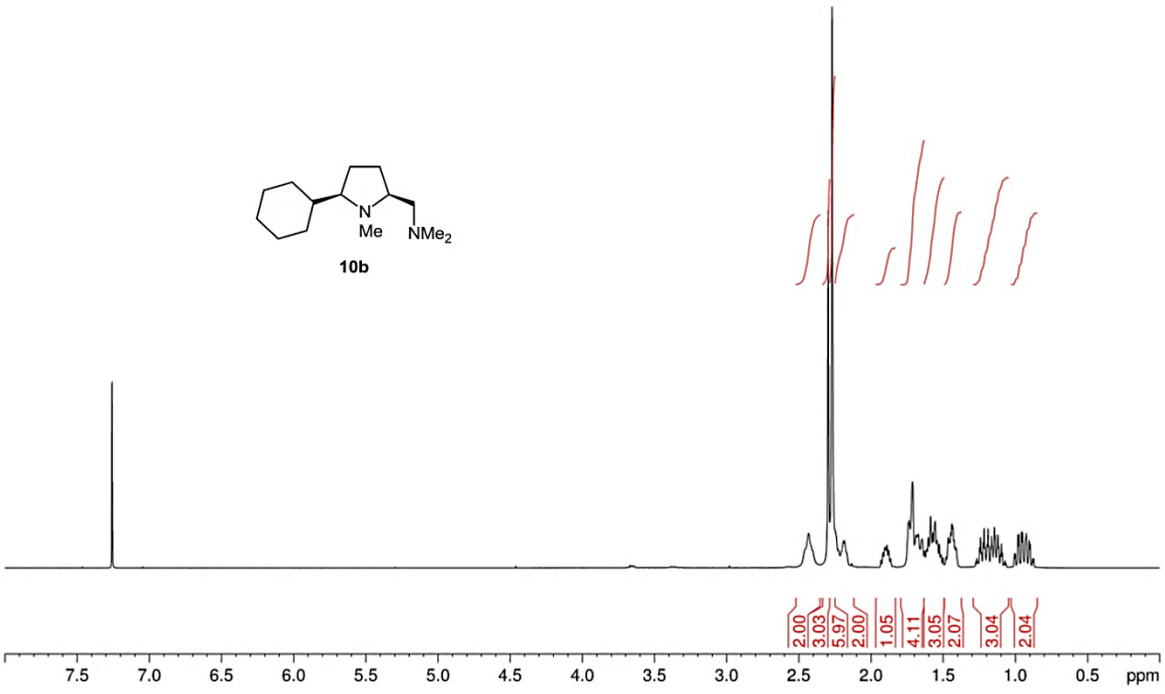
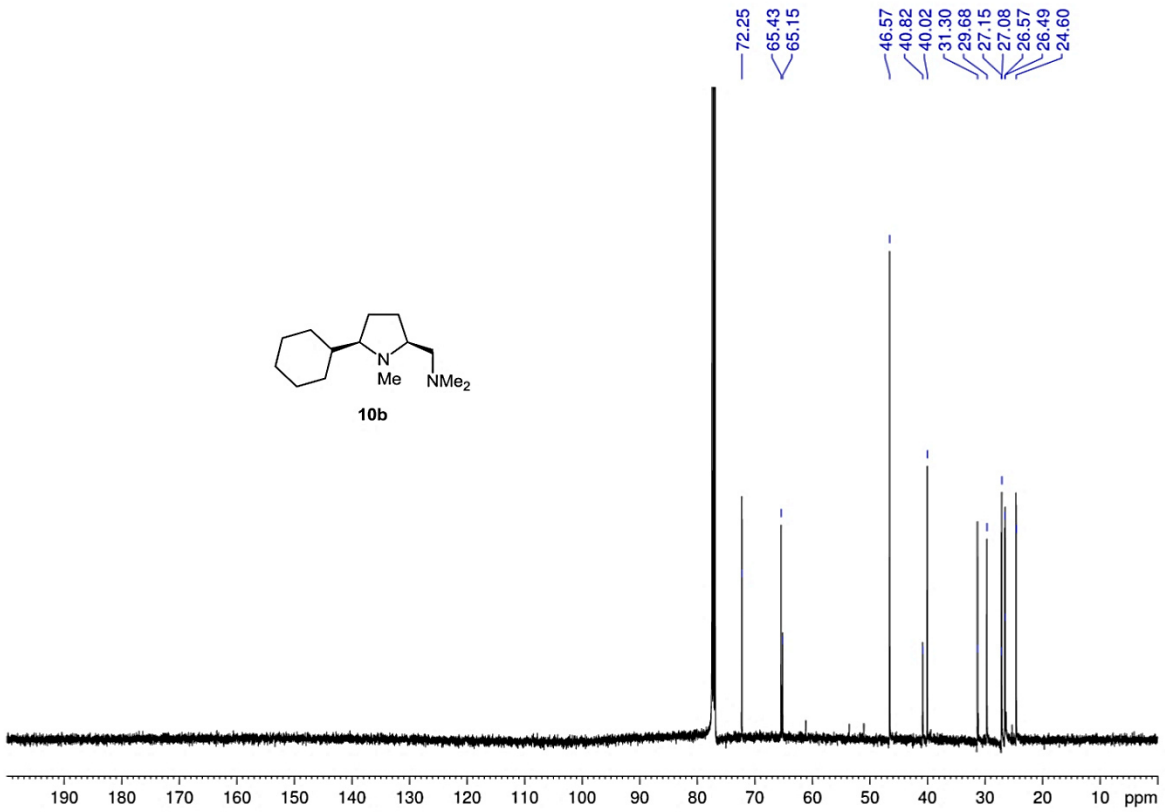
128.32
127.36
126.98
72.48
71.87
65.78
58.88
53.19
49.91
39.39
34.32
28.14
Ph
N
Me
HN
9i
MeO
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

22

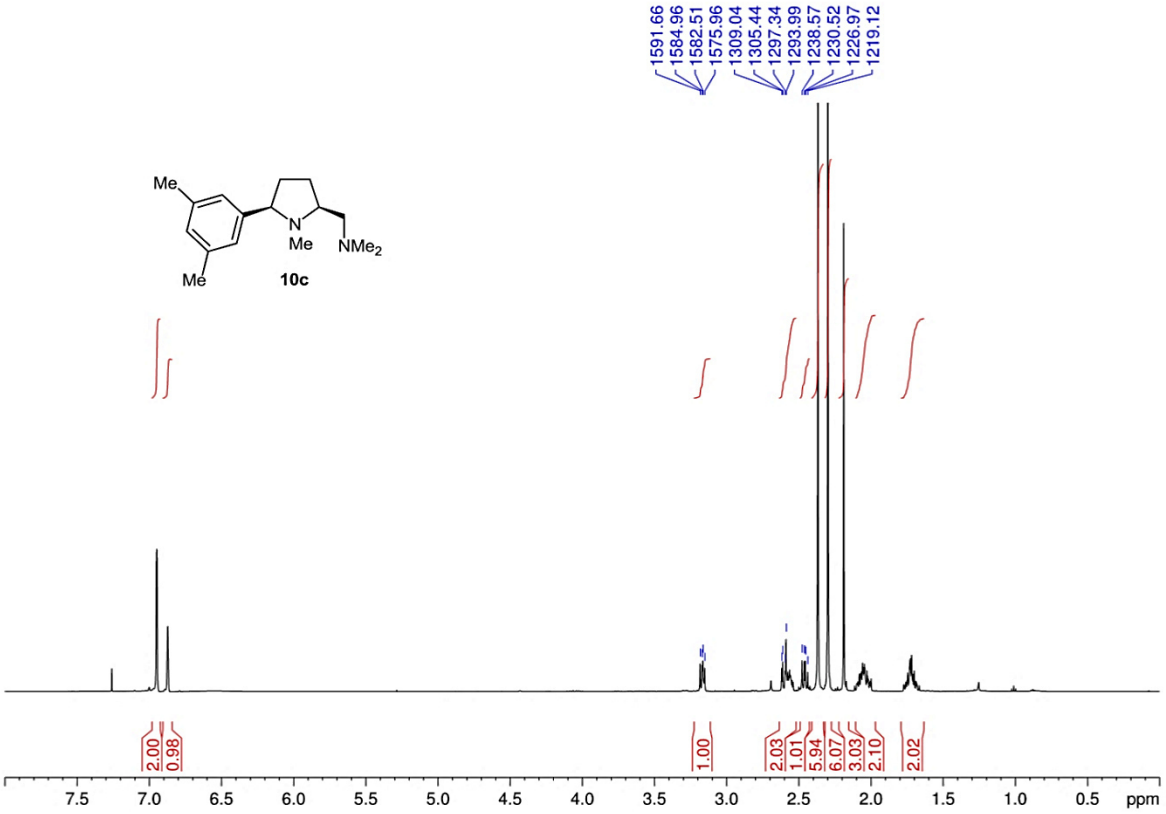

N
Me
NMe2
10a
4.97
8.00
2.07
1.03
1.10
2.03
5.12
2.06
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

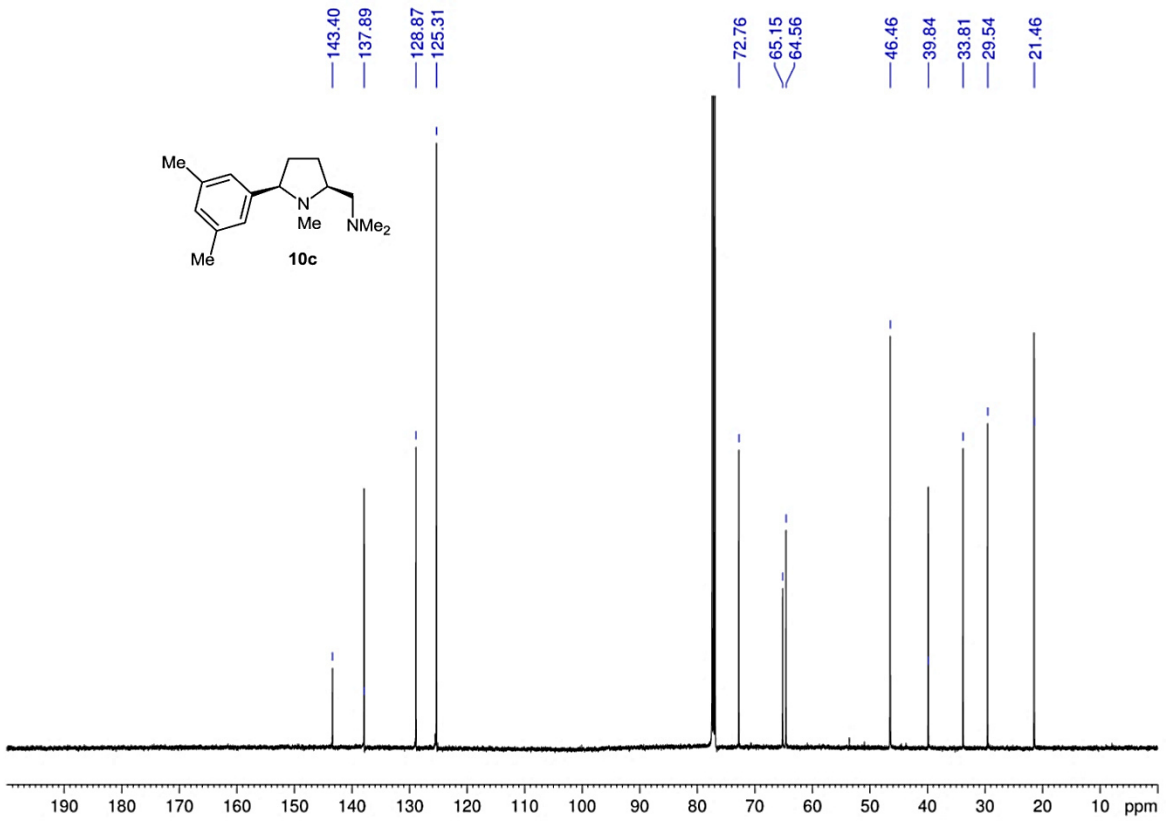

71.77
65.90
65.19
46.51
43.70
41.09
31.21
29.33
28.35
26.93
26.04
25.28
N
Me
NMe2
10a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


N
Me
NMe2
10b
2.00
3.03
5.97
2.00
1.05
4.11
3.05
2.07
3.04
2.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

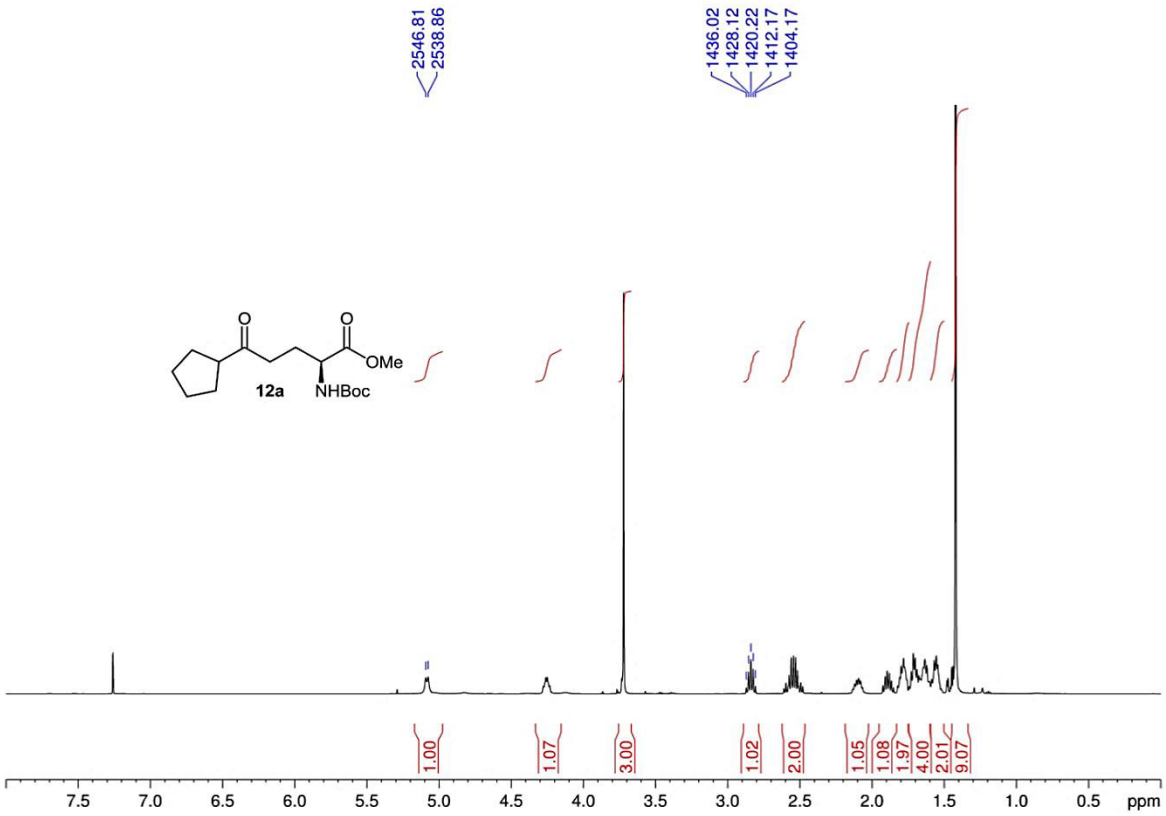

72.25
65.43
65.15
46.57
40.82
40.02
31.30
29.68
27.15
27.08
26.57
26.49
24.60
N
Me
NMe2
10b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

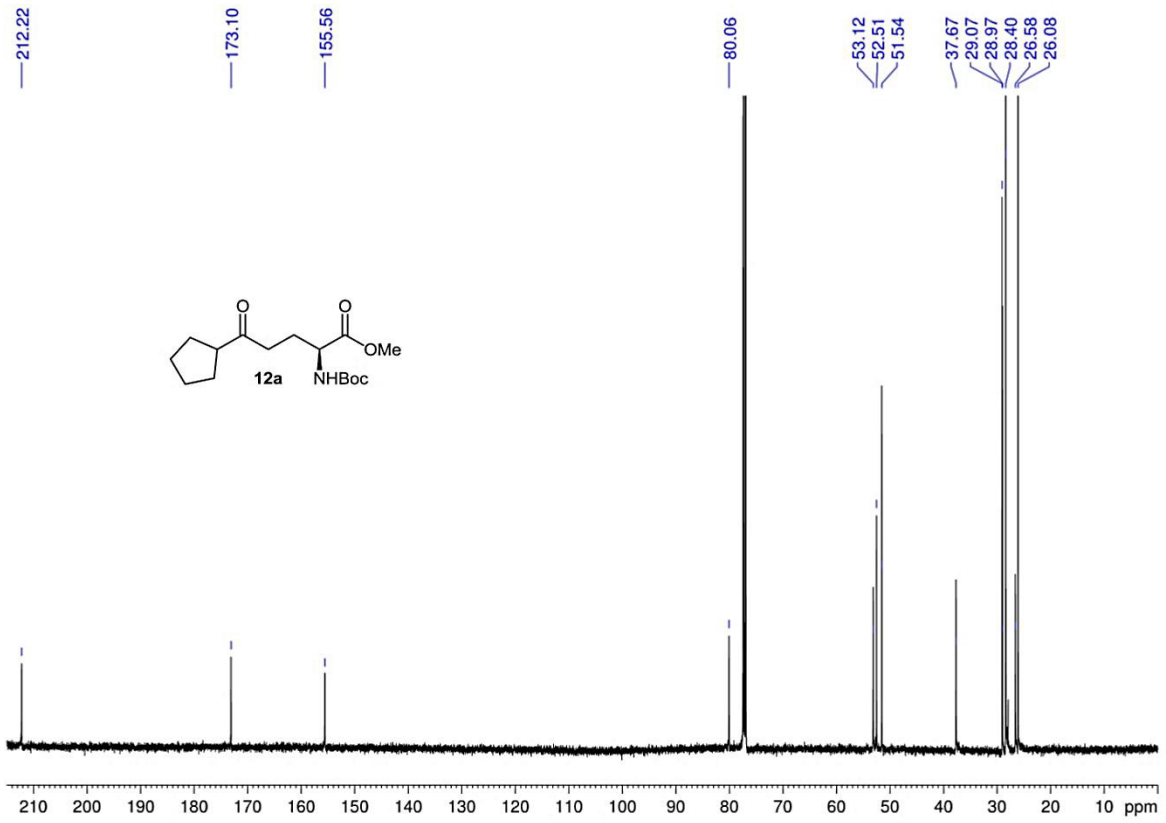
24


1591.66
1584.96
1582.51
1575.96
1309.04
1305.44
1297.34
1293.99
1238.57
1230.52
1226.97
1219.12
Me
N
Me
NMe2
Me
10c
2.00
0.98
1.00
2.03
1.01
5.94
6.07
3.03
2.10
2.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

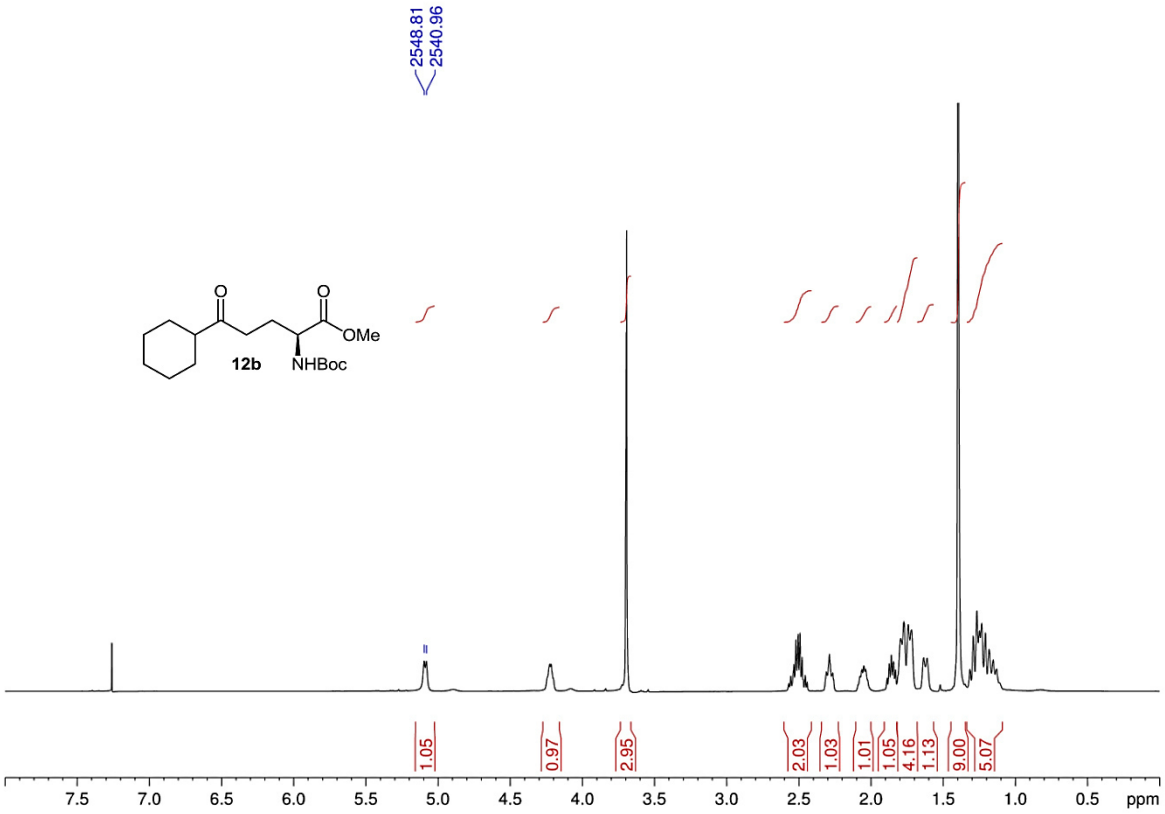

143.40
137.89
128.87
125.31
72.76
65.15
64.56
46.46
39.84
33.81
29.54
21.46
Me
N
Me
NMe2
Me
10c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

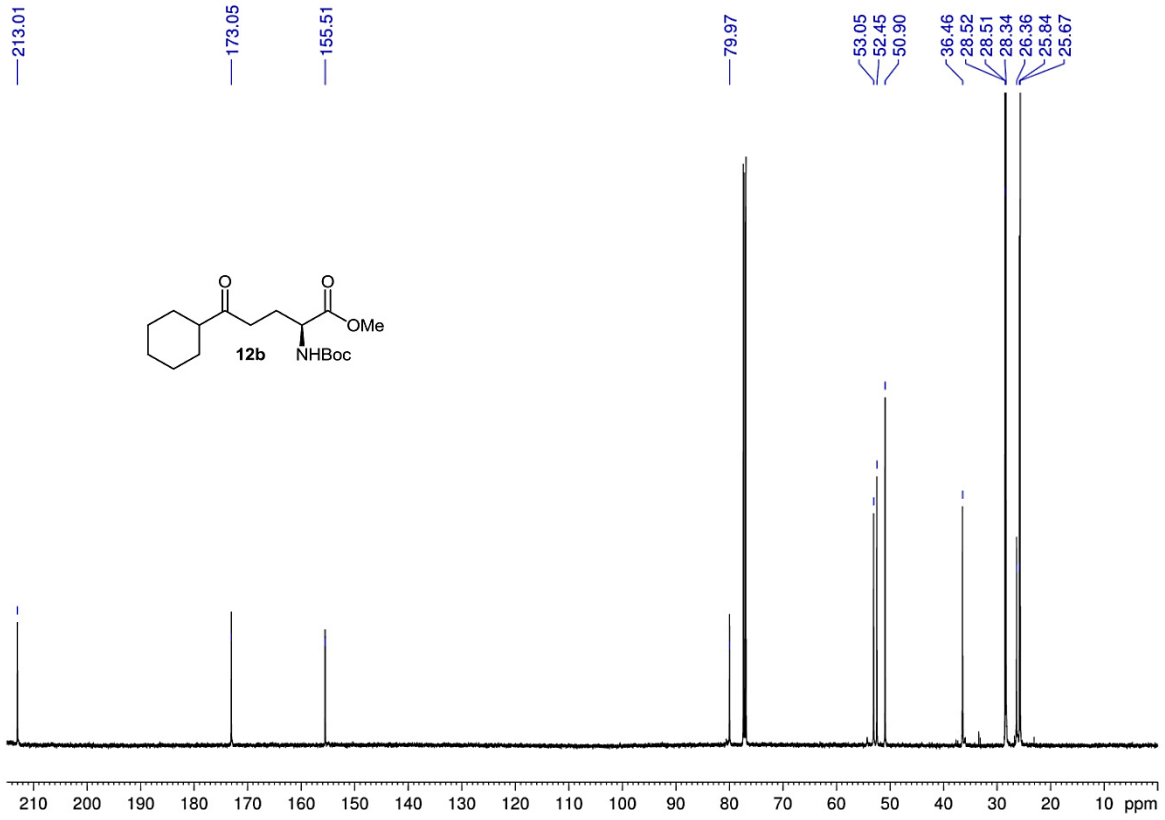
25


2546.81
2538.86
1436.02
1428.12
1420.22
1412.17
1404.17
O
O
OMe
12a
NHBoc
1.00
1.07
3.00
1.02
2.00
1.05
1.08
1.97
4.00
2.01
9.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

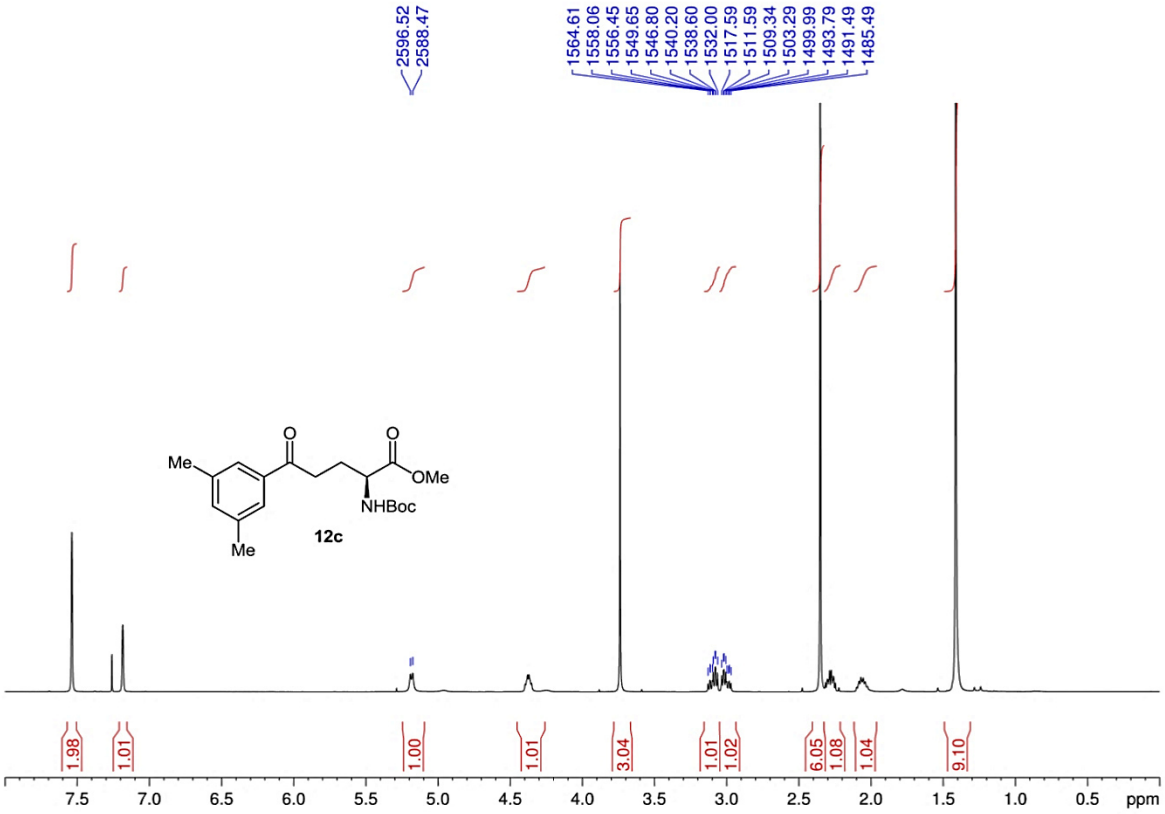

212.22
173.10
155.56
80.06
53.12
52.51
51.54
37.67
29.07
28.97
28.40
26.58
26.08
O
O
OMe
12a
NHBoc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

26


2548.81
2540.96
O
O
OMe
12b
NHBoc
1.05
0.97
2.95
2.03
1.03
1.01
1.05
4.16
1.13
9.00
5.07
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


213.01
173.05
155.51
79.97
53.05
52.45
50.90
36.46
28.52
28.51
28.34
26.36
25.84
25.67
O
O
OMe
12b
NHBoc
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

27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2588.47
1564.61
1558.06
1556.45
1549.65
1546.80
1540.20
1538.60
1532.00
1517.59
1511.59
1509.34
1503.29
1499.99
1493.79
1491.49
1485.49
Me
O
O
OMe
NHBoc
Me
12c
1.98
1.01
1.00
1.01
3.04
1.01
1.02
6.05
1.08
1.04
9.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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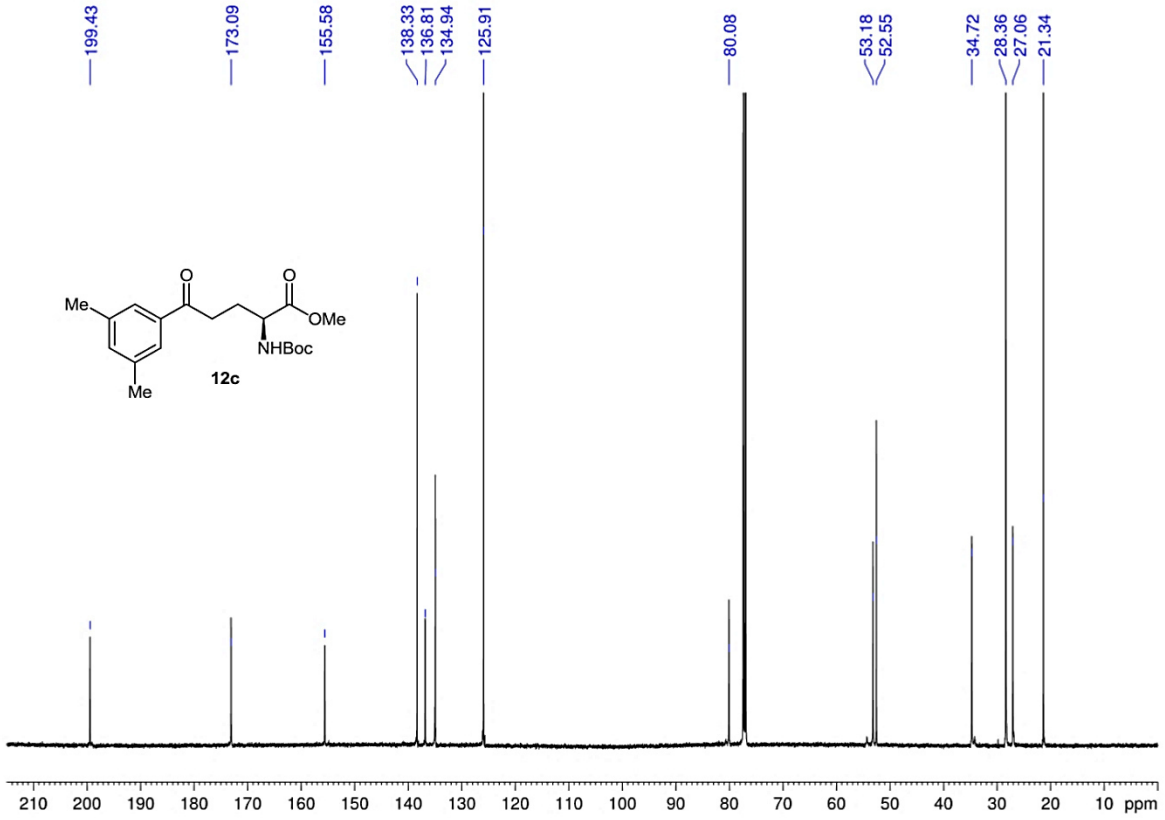
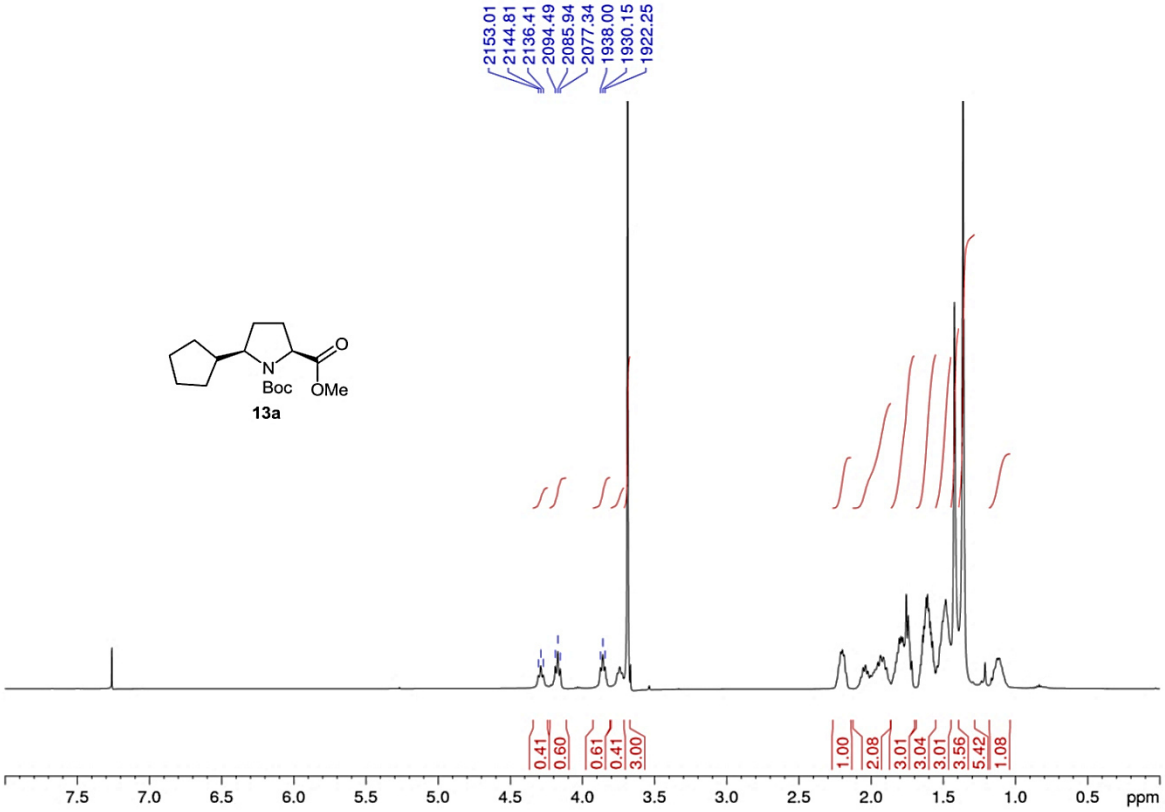
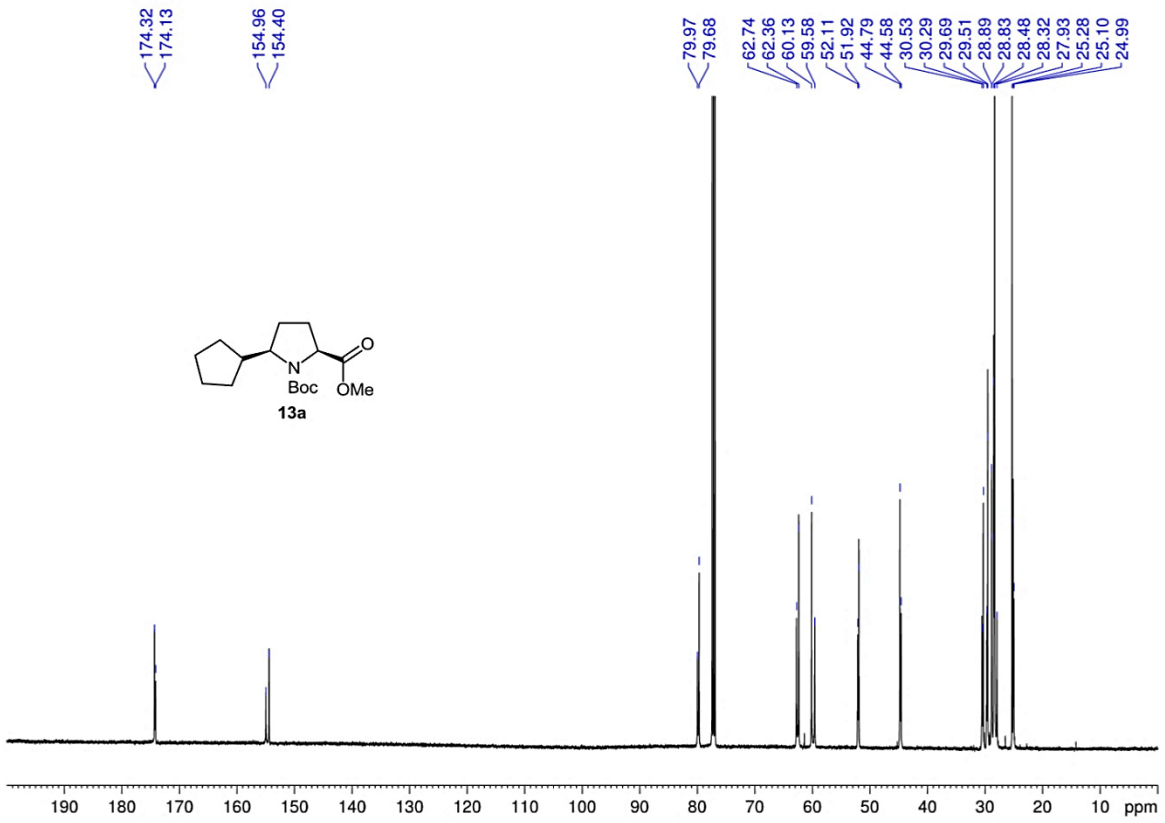
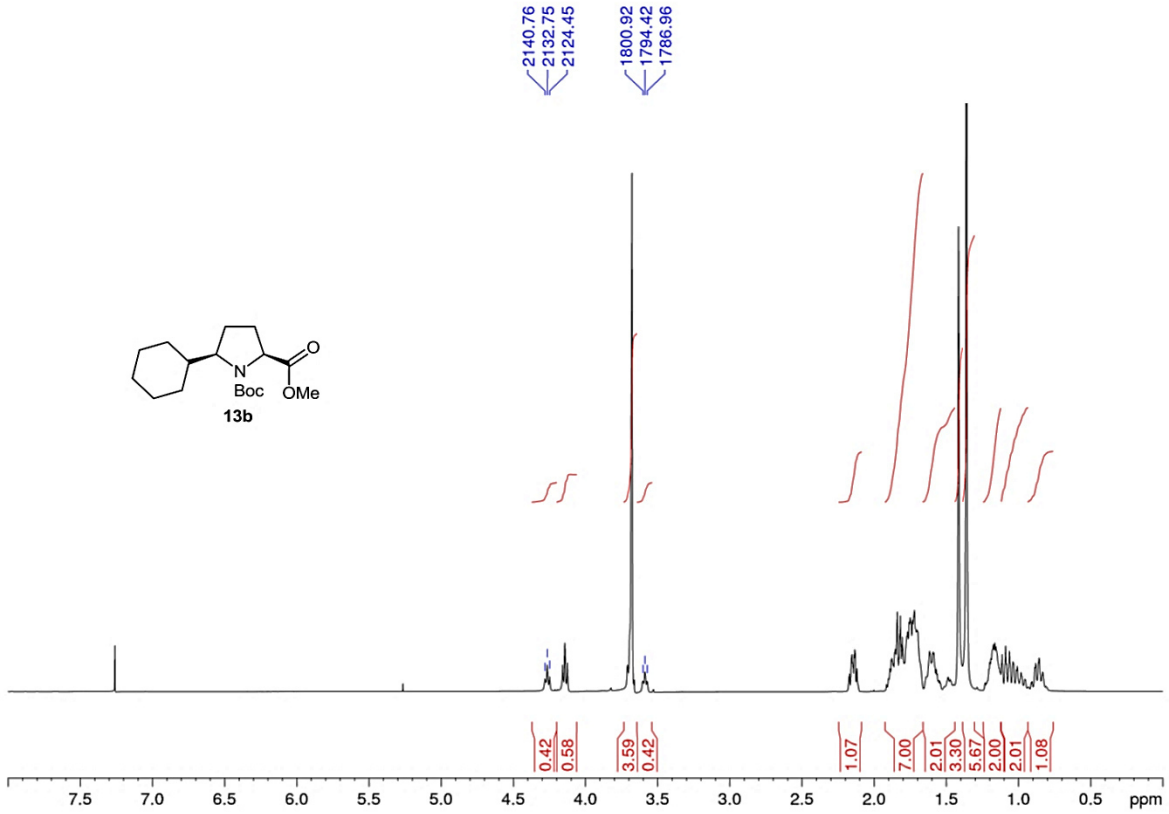
2.0
1.5
1.0
0.5
ppm

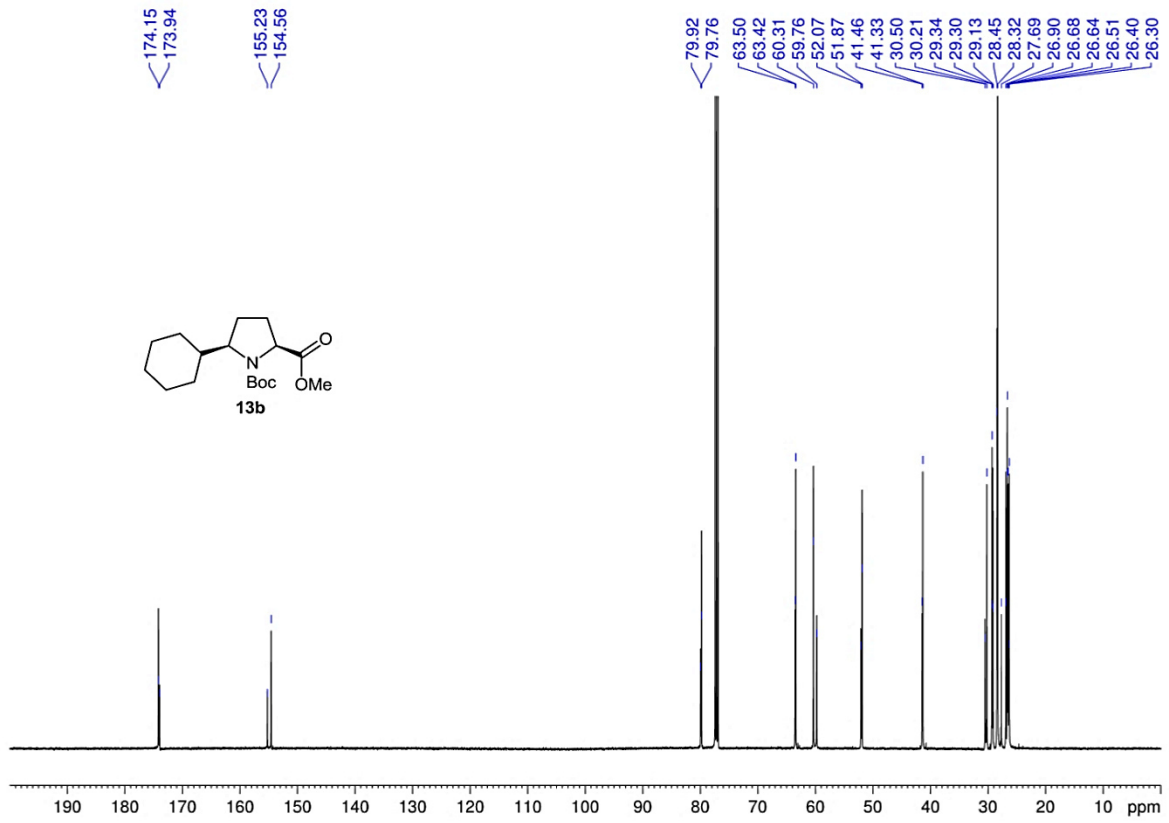

199.43
173.09
155.58
138.33
136.81
134.94
125.91
80.08
53.18
52.55
34.72
28.36
27.06
21.34
Me
O
O
OMe
NHBoc
Me
12c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

28

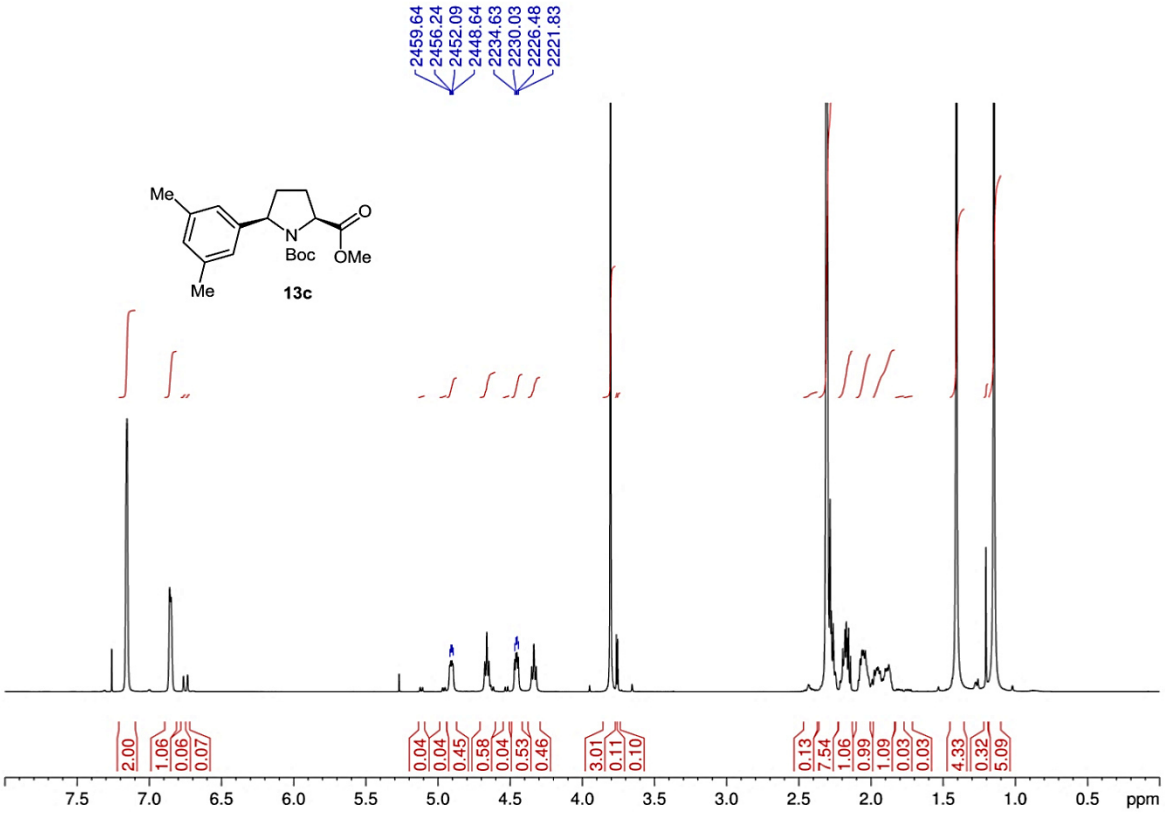

2153.01
2144.81
2136.41
2094.49
2085.94
2077.34
1938.00
1930.15
1922.25
Boc
OMe
13a
0.41
0.60
0.61
0.41
3.00
1.00
2.08
3.01
3.04
3.01
3.56
5.42
1.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


174.32
174.13
154.96
154.40
79.97
79.68
62.74
62.36
60.13
59.58
52.11
51.92
44.79
44.58
30.53
30.29
29.69
29.51
28.89
28.83
28.48
28.32
27.93
25.28
25.10
24.99
Boc
OMe
13a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


2140.76
2132.75
2124.45
1800.92
1794.42
1786.96
N
Boc
OMe
O
13b
0.42
0.58
3.59
0.42
1.07
7.00
2.01
3.30
5.67
2.00
2.01
1.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


174.15
173.94
155.23
154.56
79.92
79.76
63.50
63.42
60.31
59.76
52.07
51.87
41.46
41.33
30.50
30.21
29.34
29.30
29.13
28.45
28.32
27.69
26.90
26.68
26.64
26.51
26.40
26.30
N
Boc
OMe
O
13b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

30


2459.64
2456.24
2452.09
2448.64
2234.63
2230.03
2226.48
2221.83
Me
N
Boc
OMe
O
Me
13c
2.00
1.06
0.06
0.07
0.04
0.04
0.45
0.58
0.04
0.53
0.46
3.01
0.11
0.10
0.13
7.54
1.06
0.99
1.09
0.03
0.03
4.33
0.32
5.09
7.5
7.0
6.5
6.0
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4.5
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3.5
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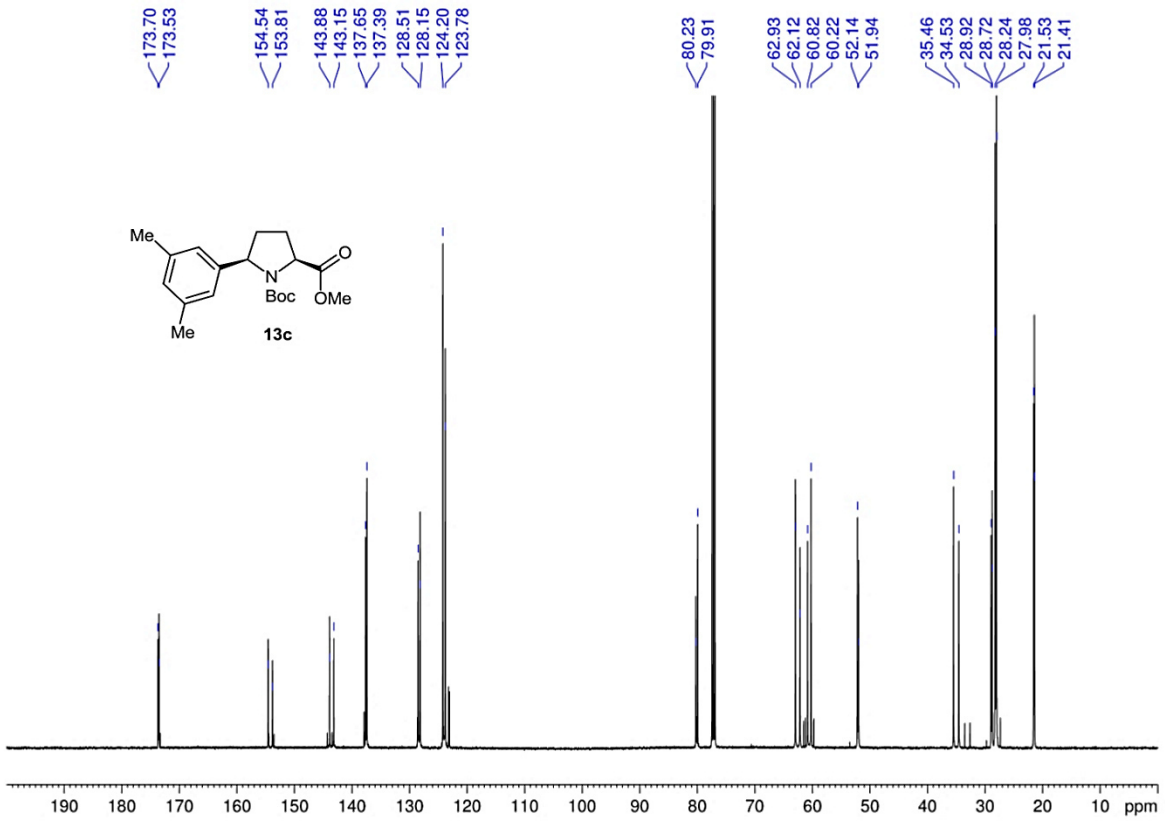
2.0
1.5
1.0
0.5
ppm


173.70
173.53
154.54
153.81
143.88
143.15
137.65
137.39
128.51
128.15
124.20
123.78
80.23
79.91
62.93
62.12
60.82
60.22
52.14
51.94
35.46
34.53
28.92
28.72
28.24
27.98
21.53
21.41
Me
N
Boc
OMe
O
Me
13c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
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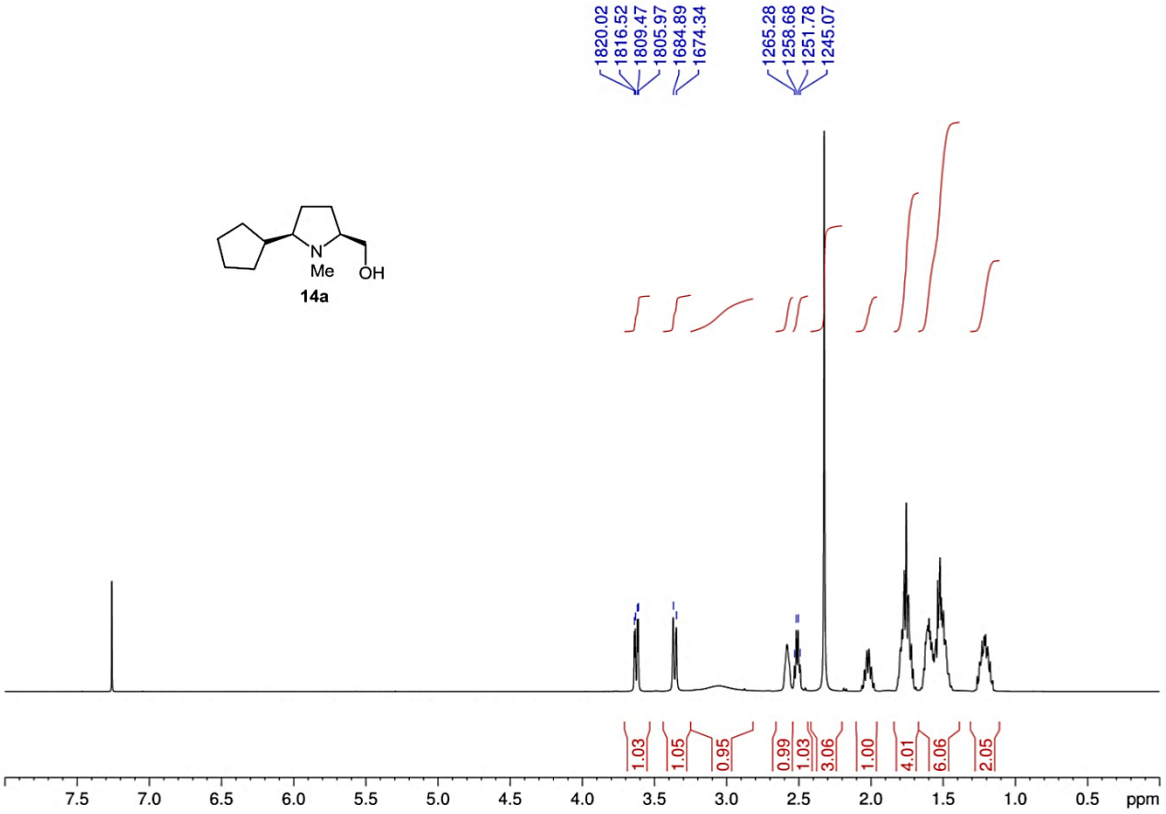
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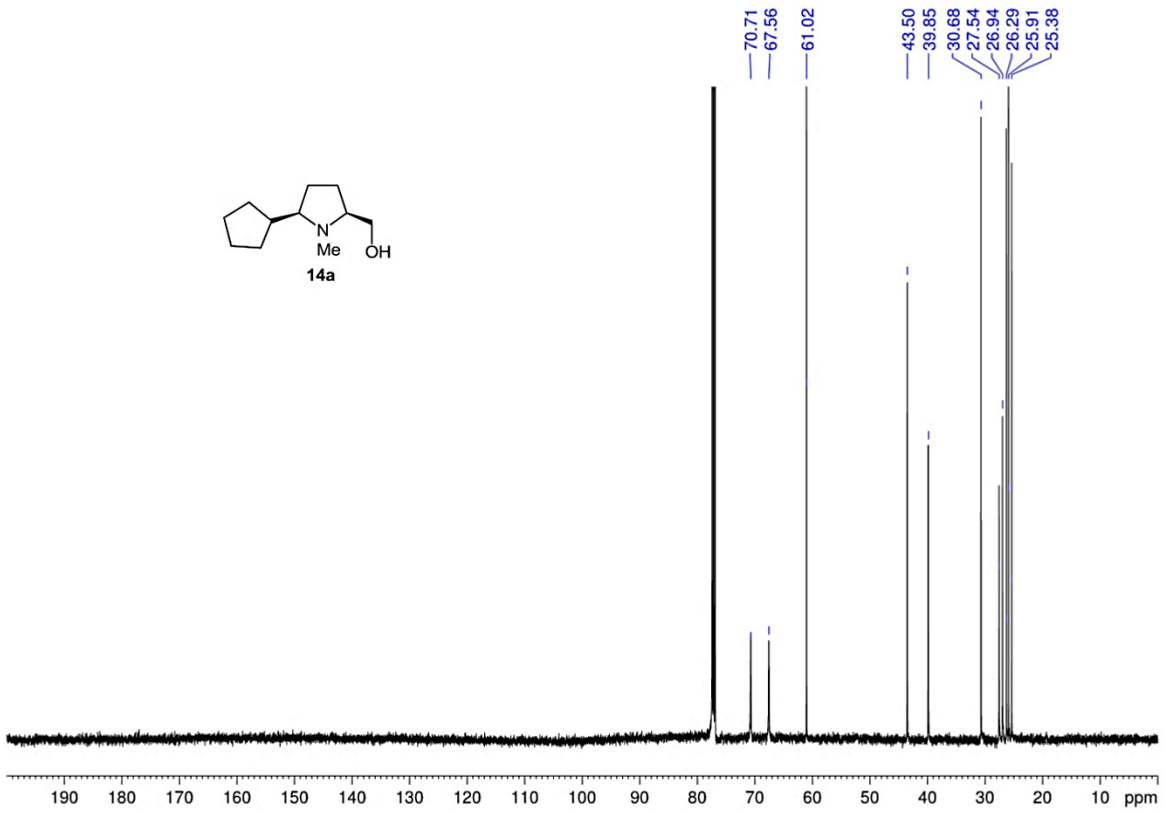
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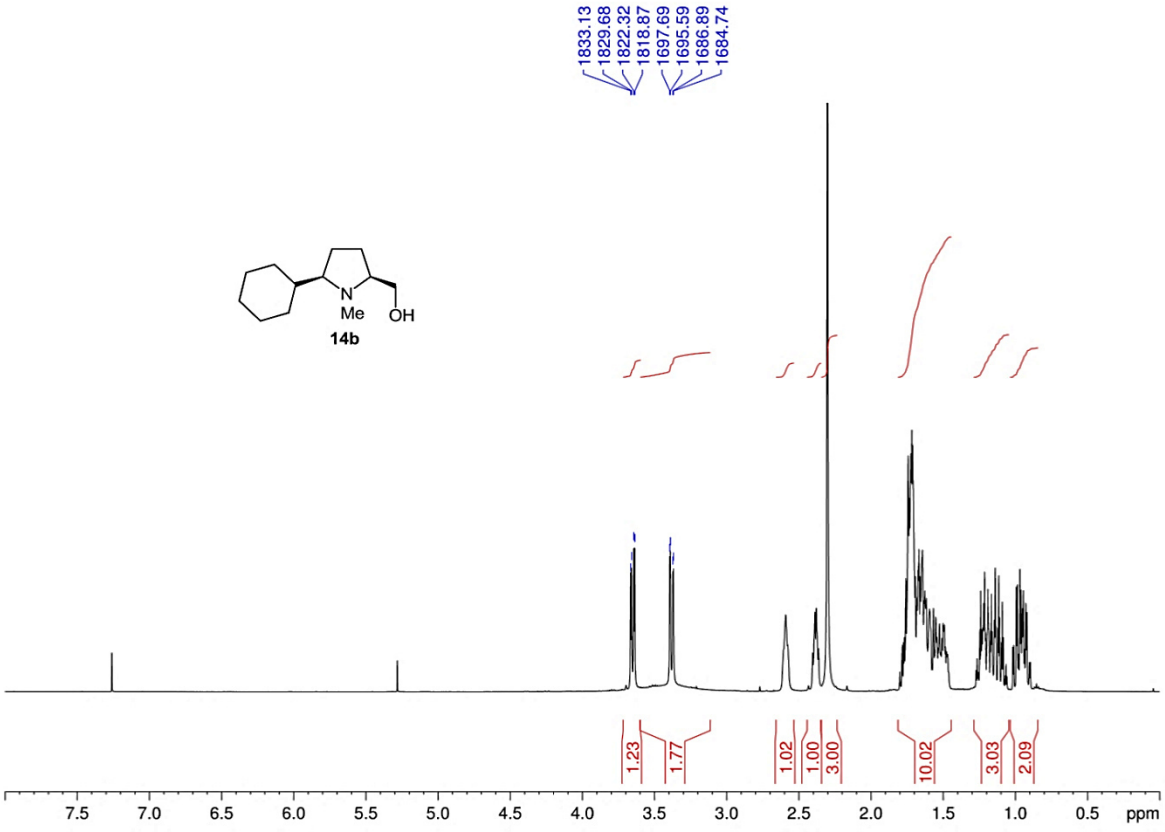
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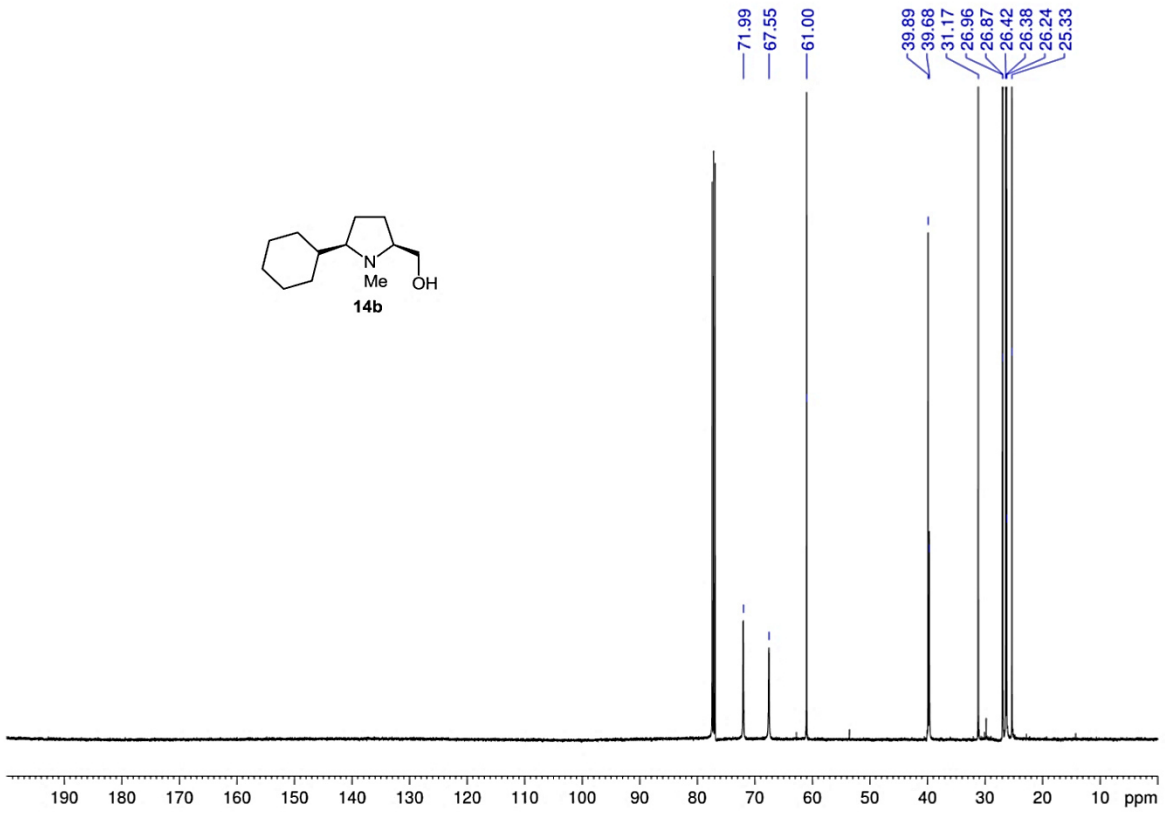
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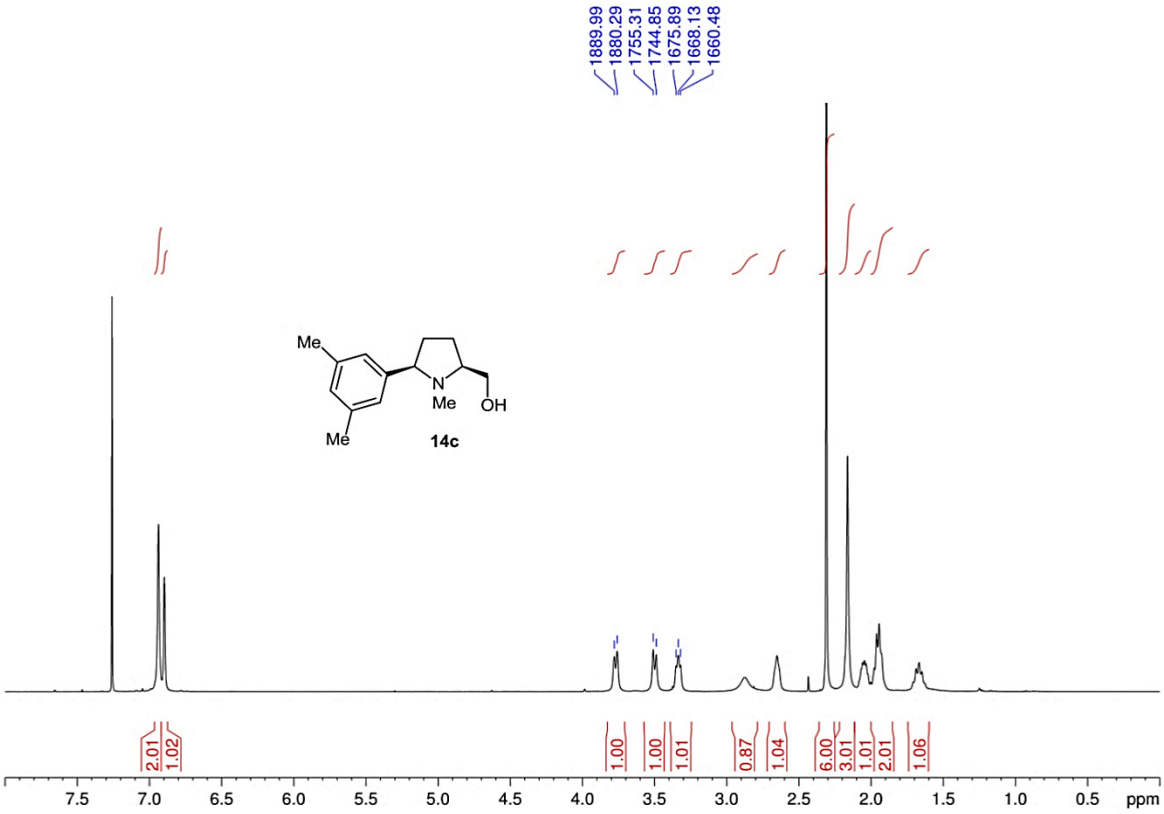
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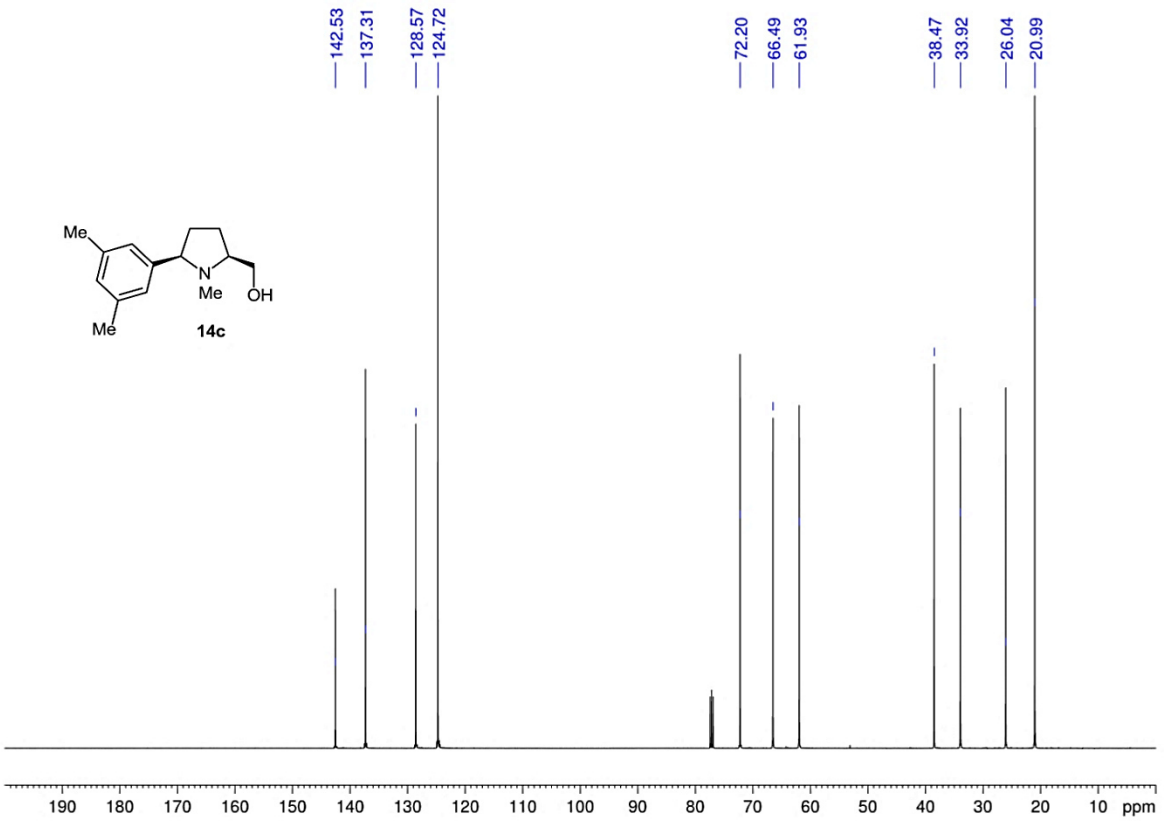
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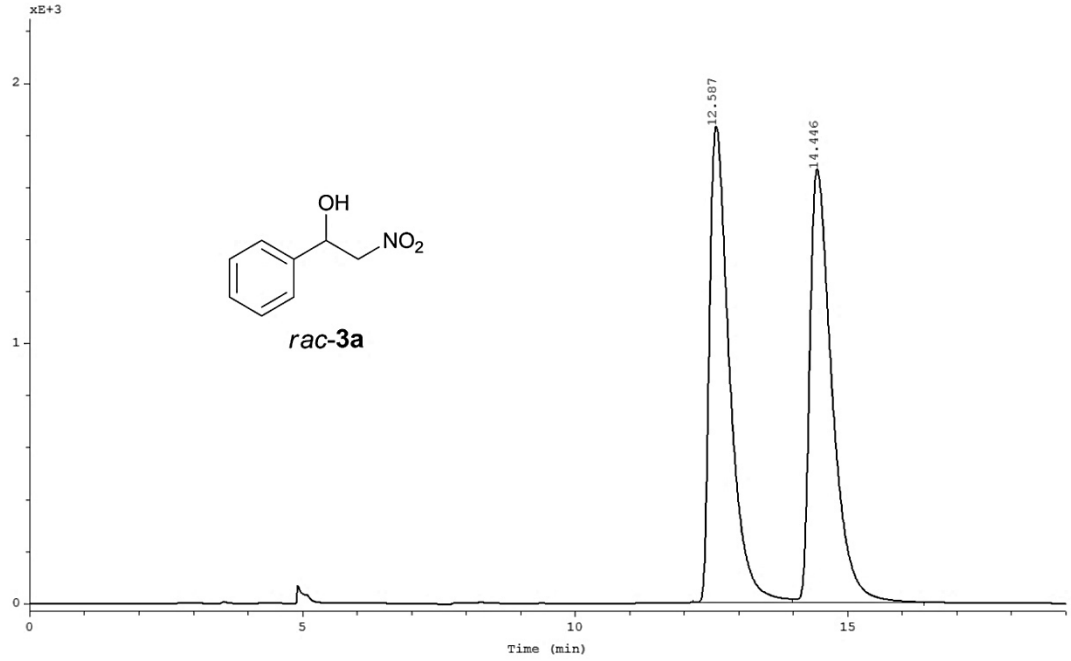
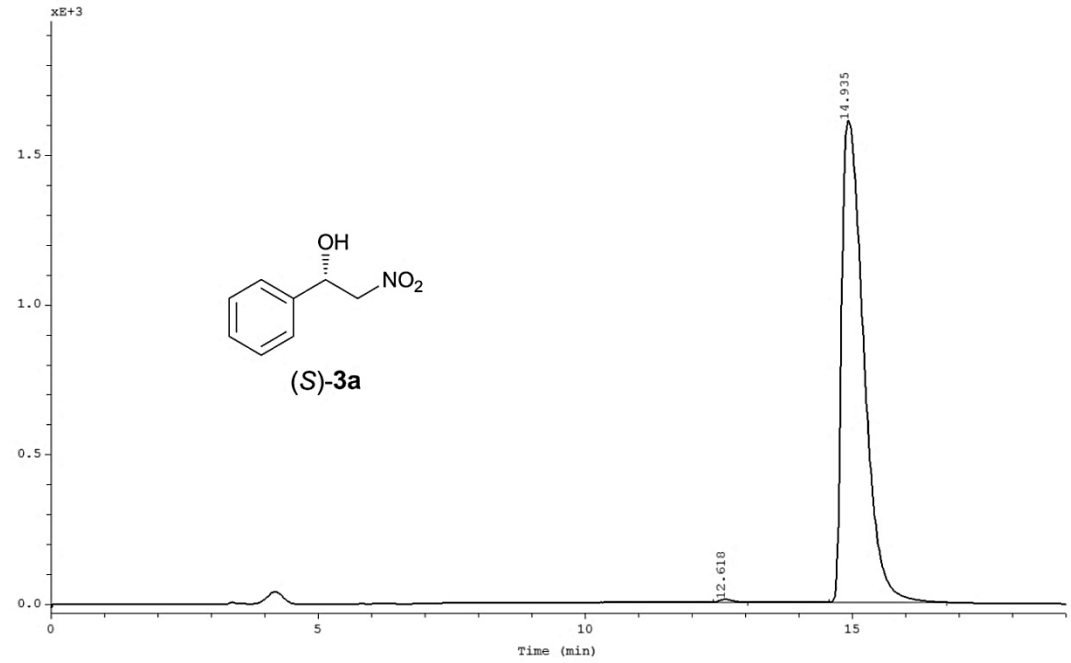
5. Copies of HPLC Spectra

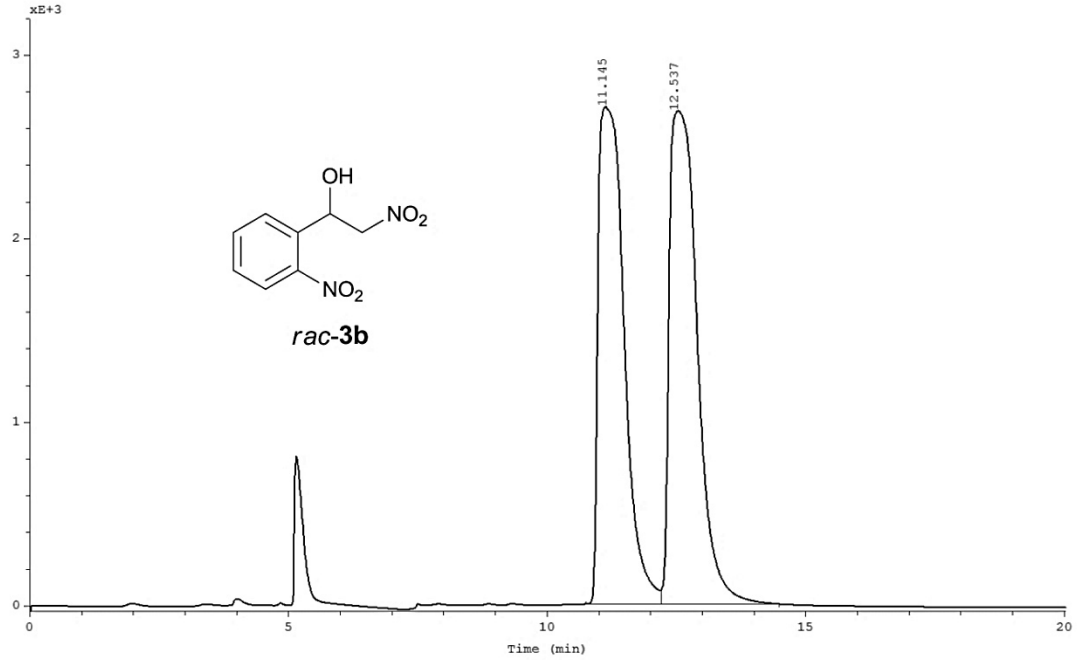


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.59	1831.20	780.62	52.38	49.81
2	14.45	1665.09	786.54	47.62	50.19

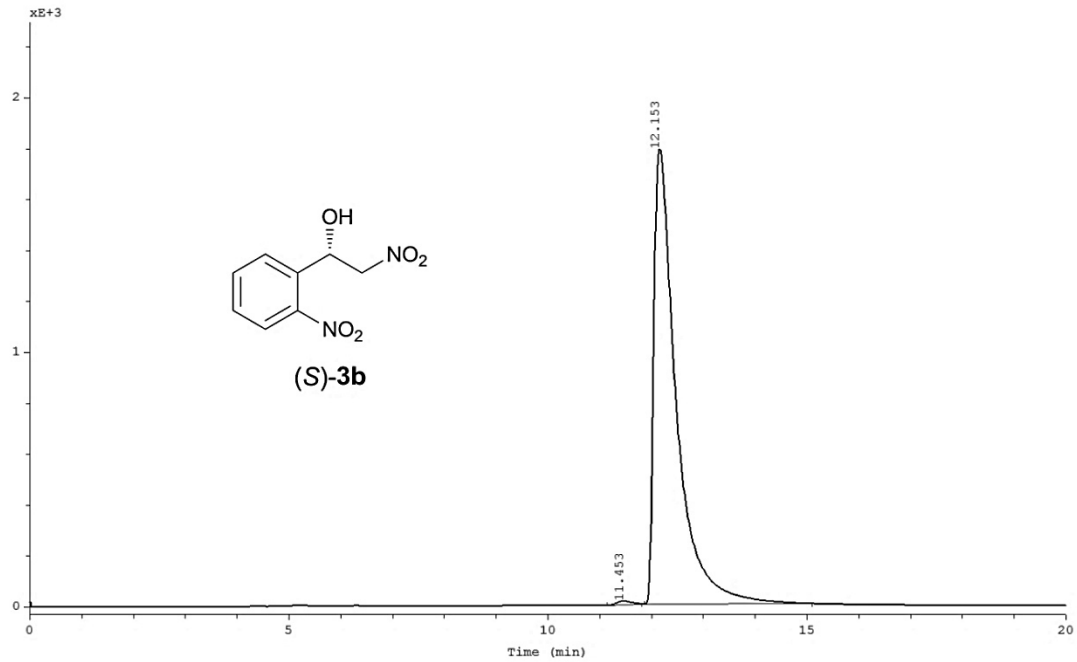


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.62	10.32	2.86	0.64	0.37
2	14.93	1609.83	767.79	99.36	99.63

35

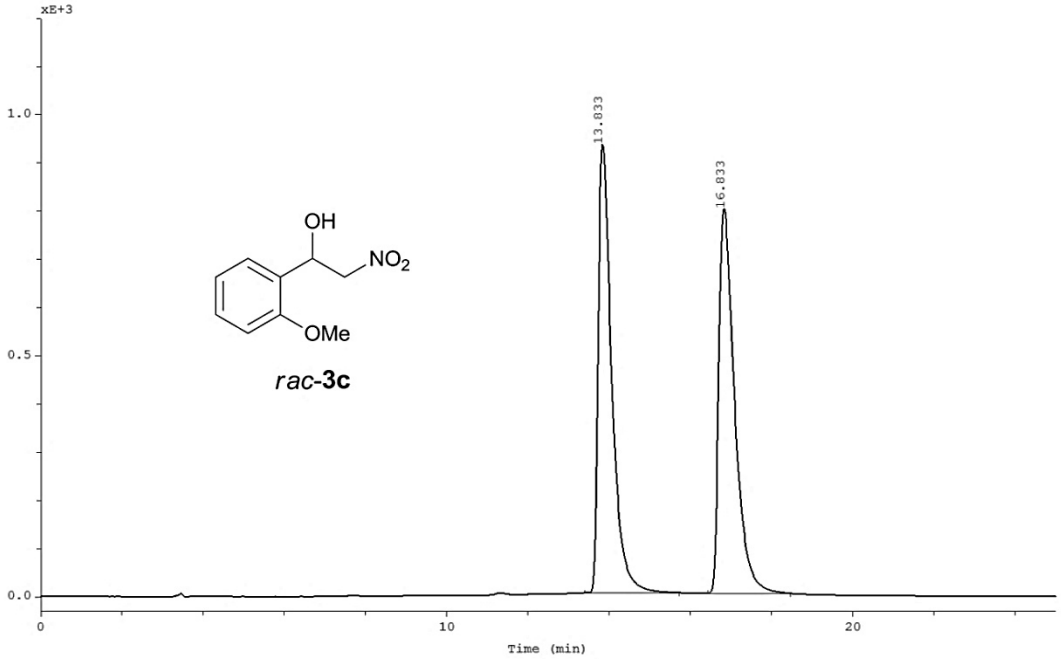


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.14	2710.17	1575.84	50.22	48.33
2	12.54	2686.59	1684.53	49.78	51.67

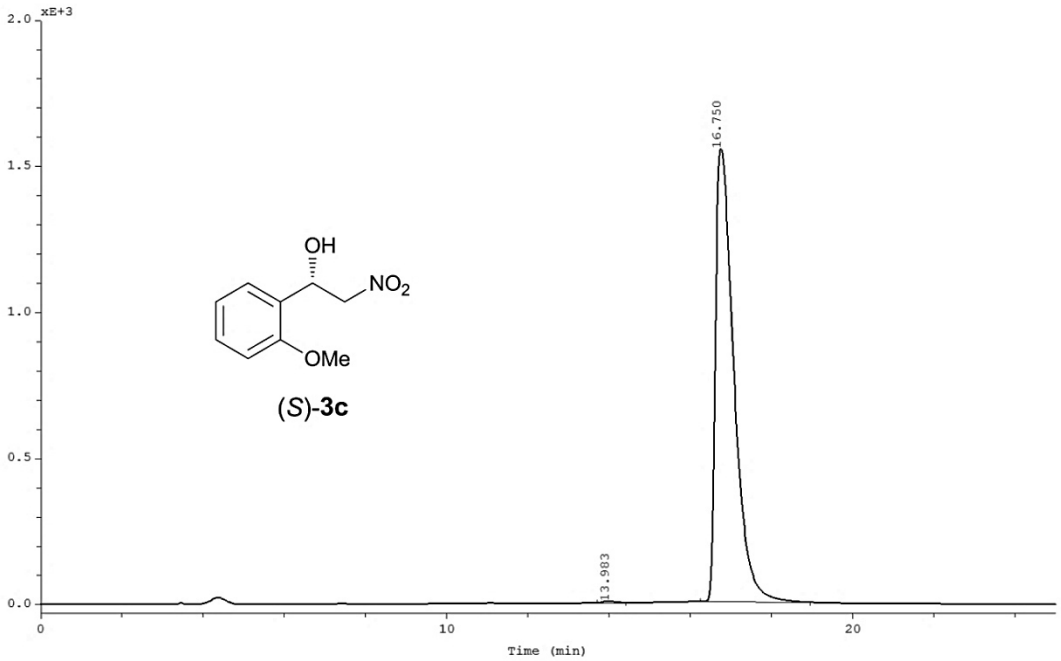


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.45	13.83	4.51	0.77	0.50
2	12.15	1785.65	897.70	99.23	99.50

36

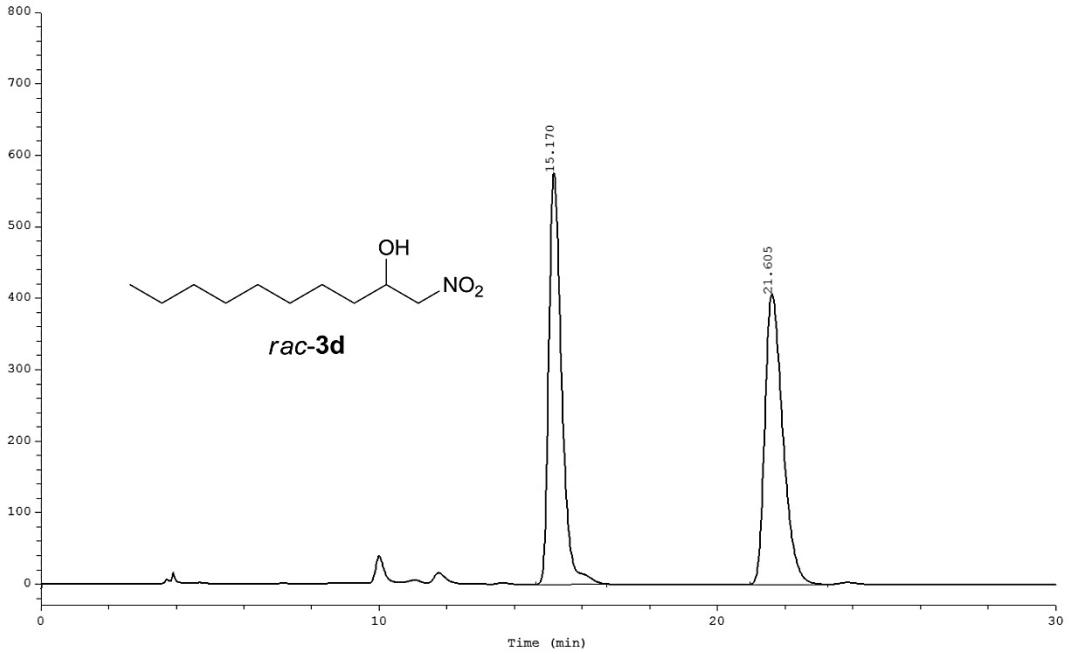


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.83	930.88	359.90	53.83	49.96
2	16.83	798.32	360.49	46.17	50.04

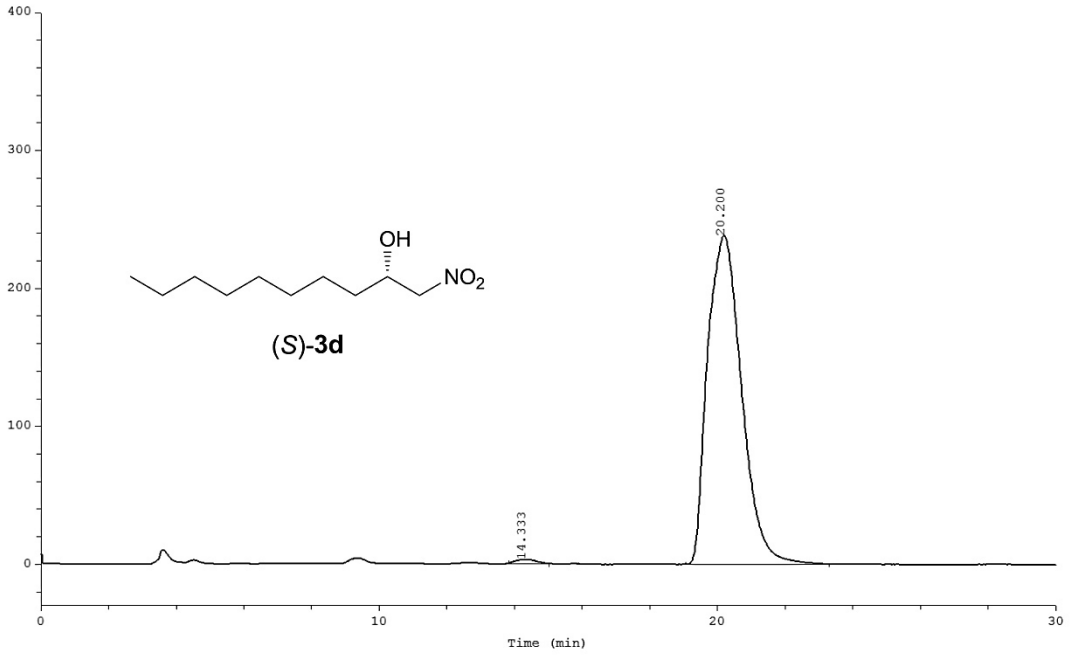


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.98	6.16	1.98	0.40	0.24
2	16.75	1551.47	812.47	99.60	99.76

37

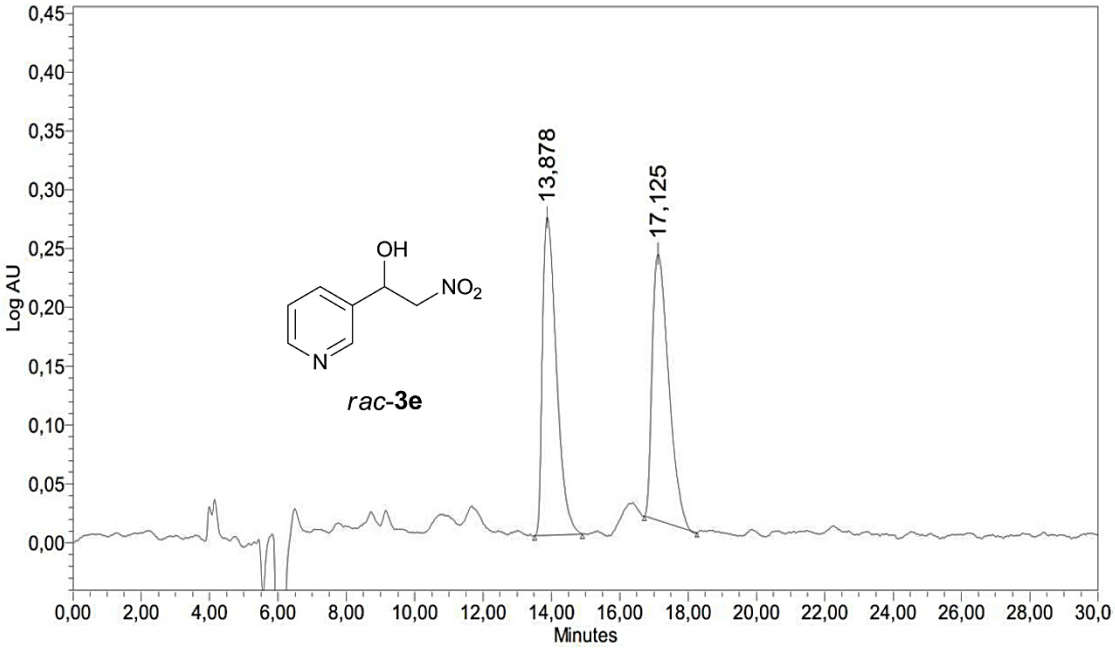


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.17	575.42	253.40	58.61	50.30
2	21.61	406.28	250.38	41.39	49.70

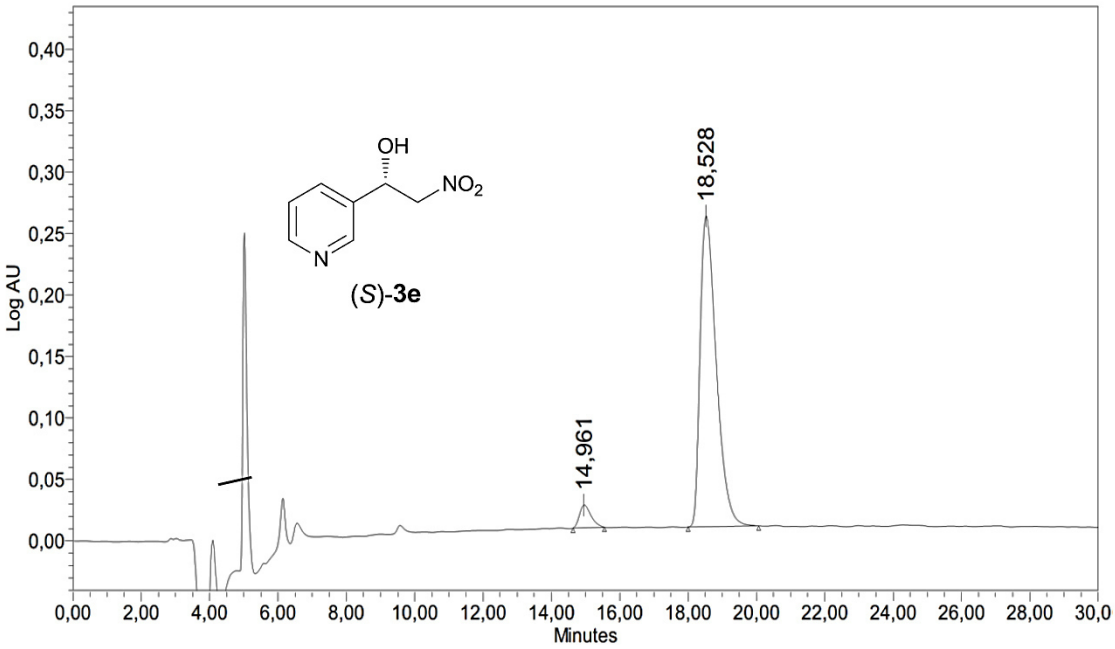


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.33	2.80	1.96	1.16	0.70
2	20.20	238.45	278.10	98.84	99.30

38

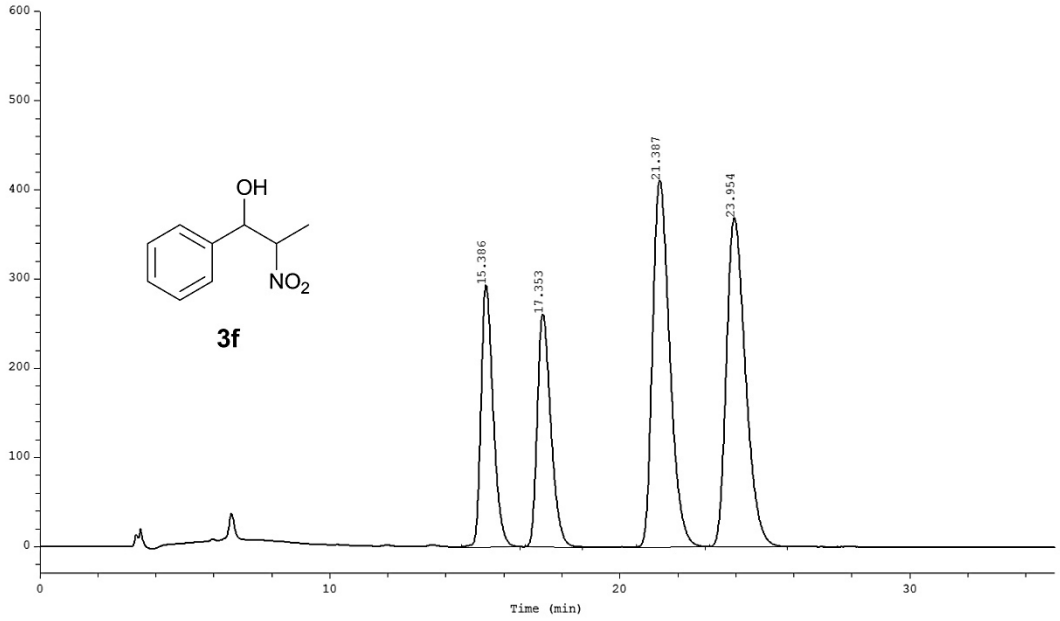


	Ret.time [min]	% Hight	% Area
1	13.88	54.39	50.27
2	17.13	45.61	49.73

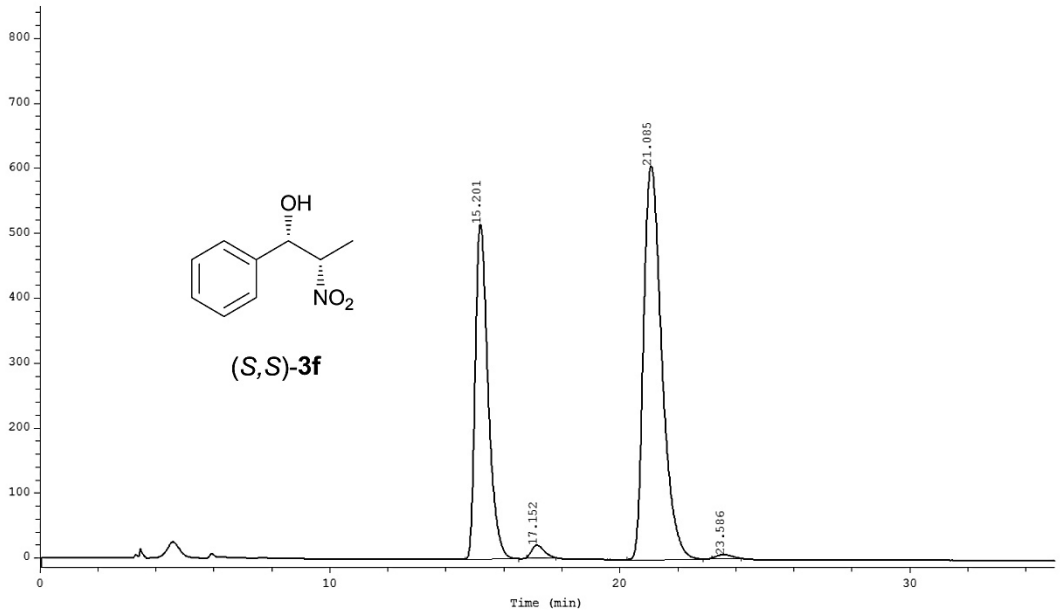


	Ret.time [min]	% Hight	% Area
1	14.96	6.83	4.94
2	18.53	93.17	95.06

39



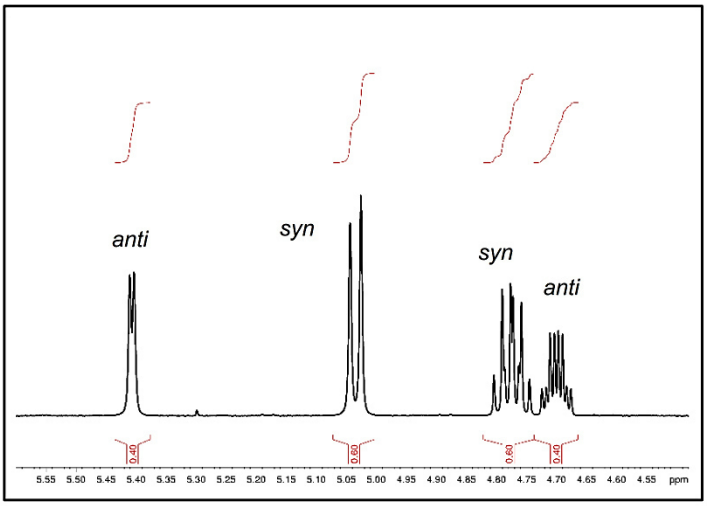
	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.39	293.77	143.47	22.00	16.87
2	17.35	261.40	142.60	19.58	16.77
3	21.39	410.97	281.80	30.78	33.14
4	23.95	369.08	282.38	27.64	33.21

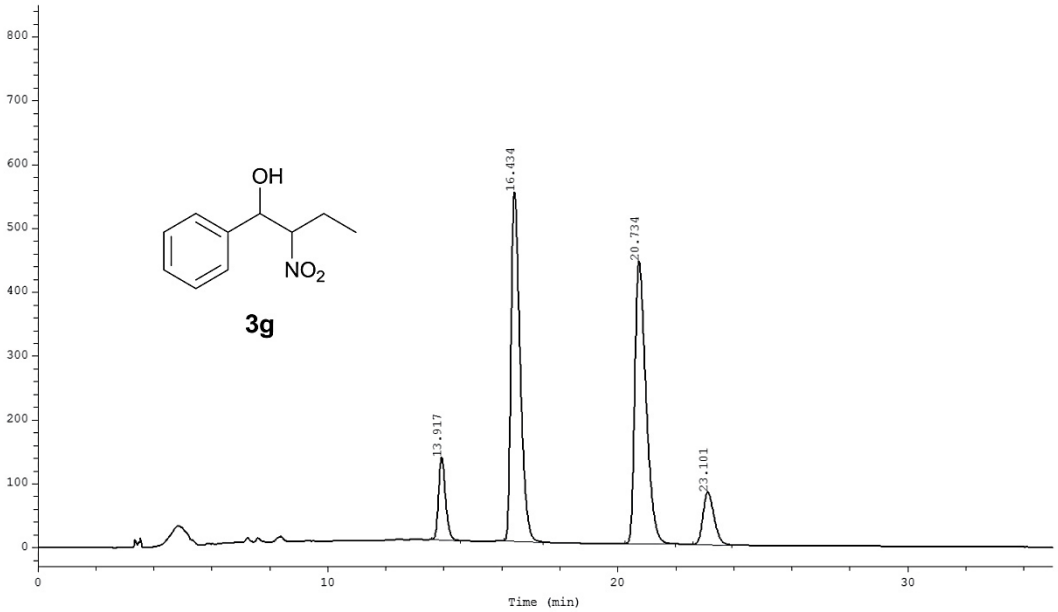


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.20	515.67	266.24	44.97	36.97
2	17.15	19.20	9.53	1.67	1.32
3	21.09	606.17	441.13	52.86	61.25
4	23.59	5.77	3.34	0.50	0.46

40

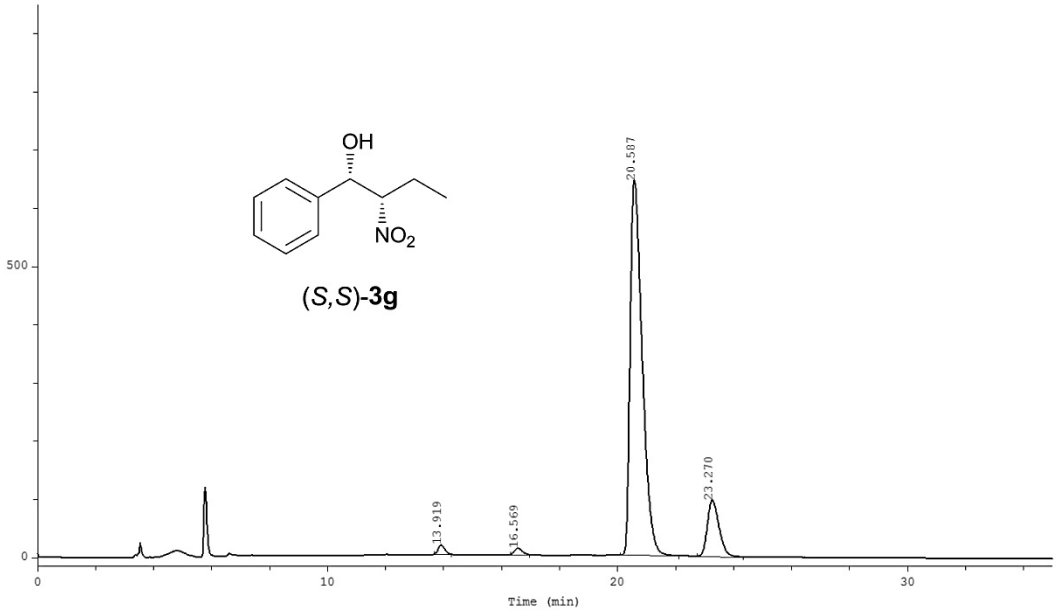
The diastereomeric ratio of **3f** was determined by ^{1}H NMR:





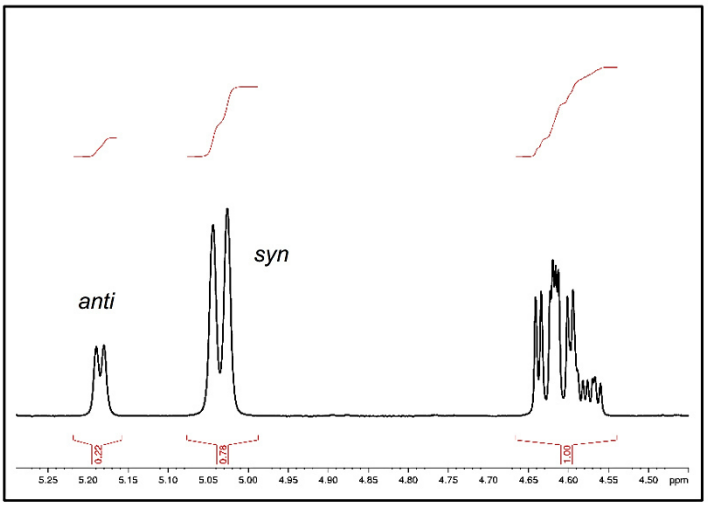
	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.39	293.77	143.47	22.00	16.87
2	17.35	261.40	142.60	19.58	16.77
3	21.39	410.97	281.80	30.78	33.14
4	23.95	369.08	282.38	27.64	33.21

41



	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.92	15.84	4.25	2.06	1.17
2	16.57	10.99	3.48	1.43	0.96
3	20.59	644.44	309.06	83.91	85.44
4	23.27	96.77	44.95	12.60	12.43

The diastereomeric ratio of **3g** was determined by ^{1}H NMR:



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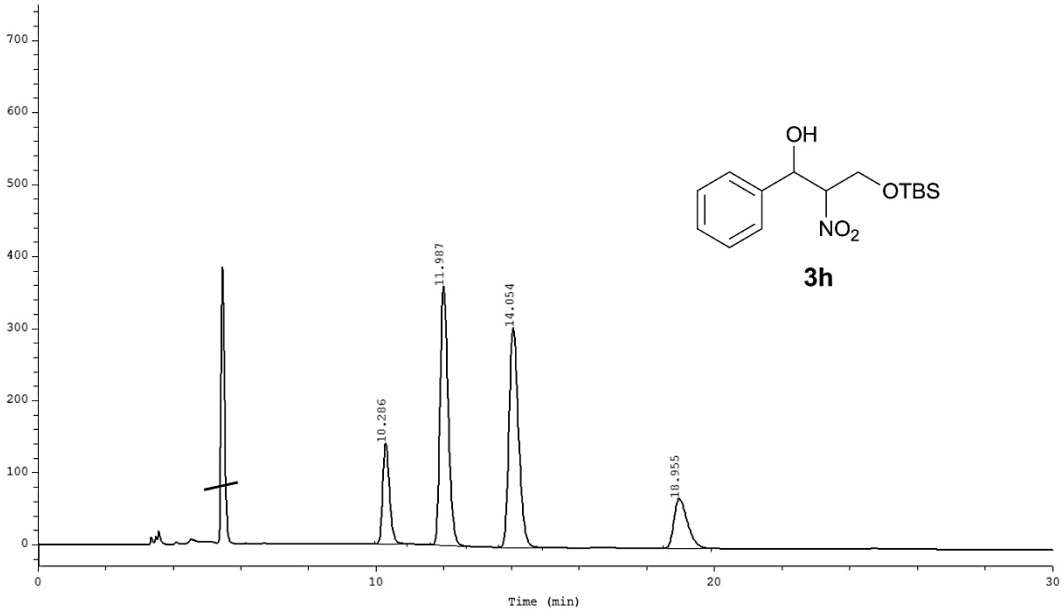
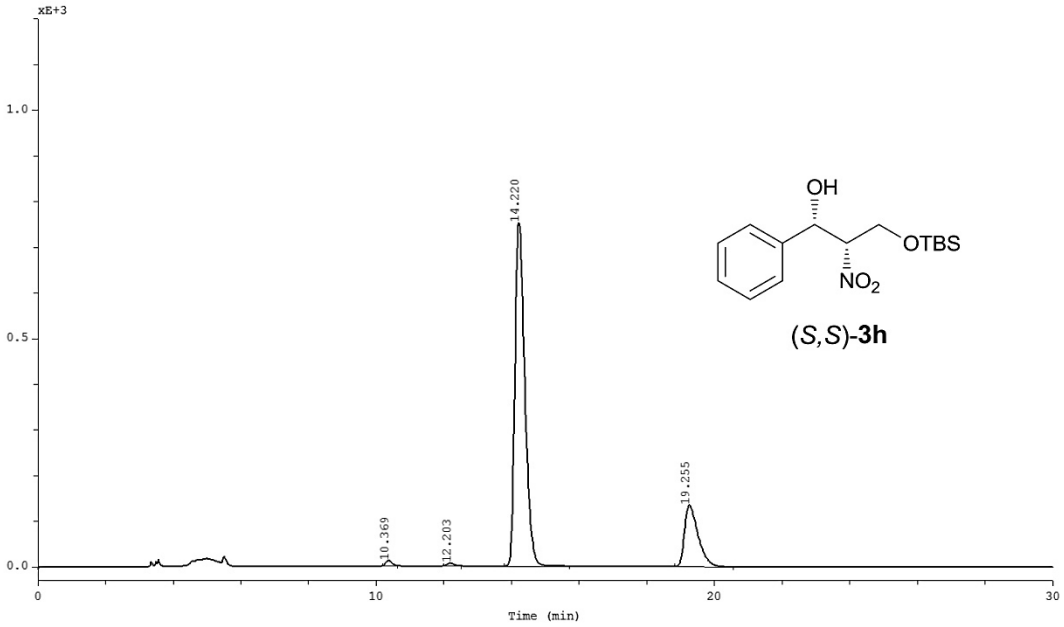
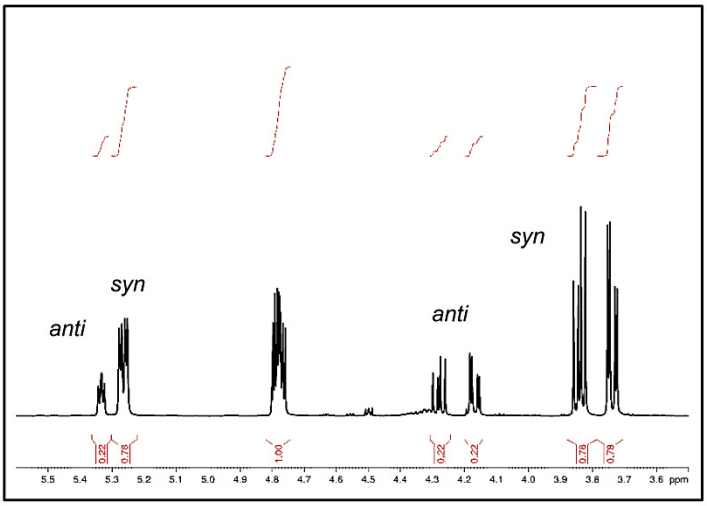


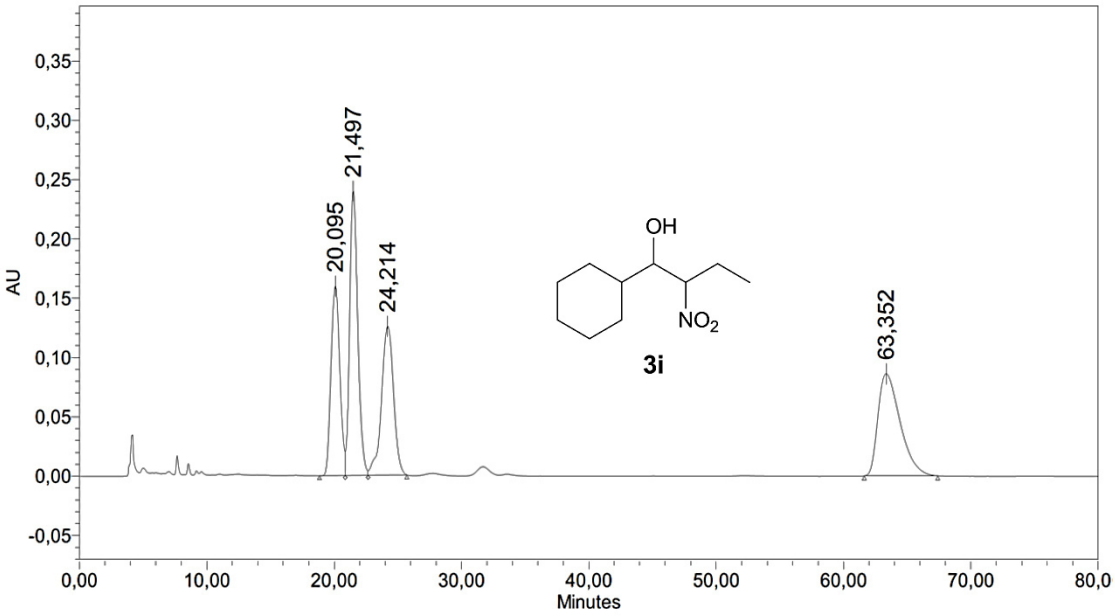
	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.29	139.69	32.53	15.99	12.34
2	11.99	359.72	99.21	41.17	37.62
3	14.05	305.18	99.84	34.92	37.86
4	18.96	69.24	32.11	7.92	12.18



	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.37	11.49	2.40	1.27	0.75
2	12.20	6.19	1.52	0.68	0.47
3	14.22	752.45	255.18	83.18	79.23
4	19.26	134.46	62.99	14.86	19.56

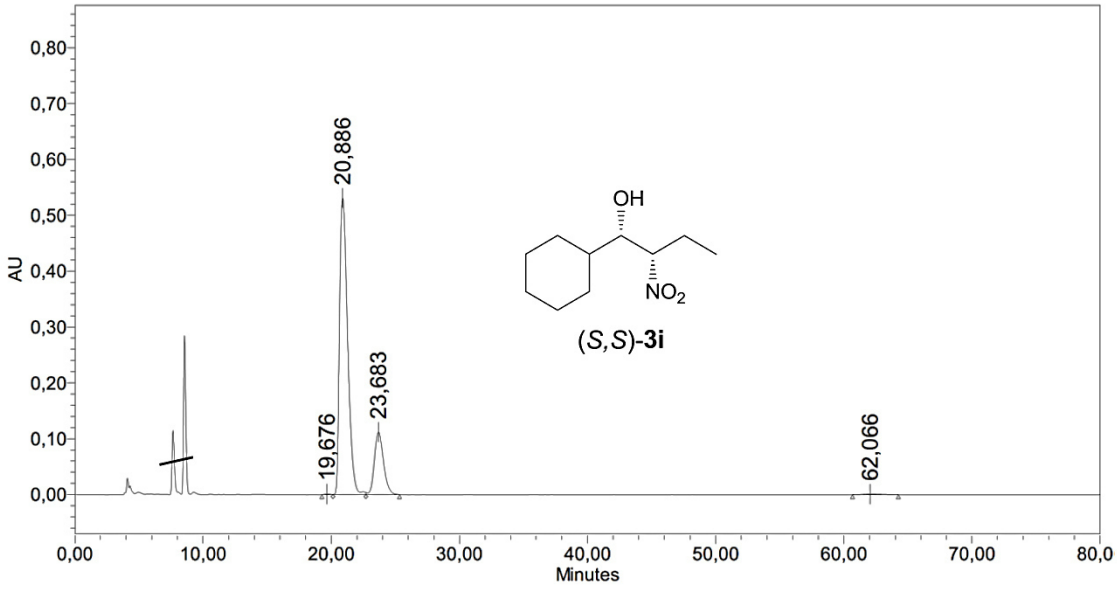
The diastereomeric ratio of **3h** was determined by ^{1}H NMR:





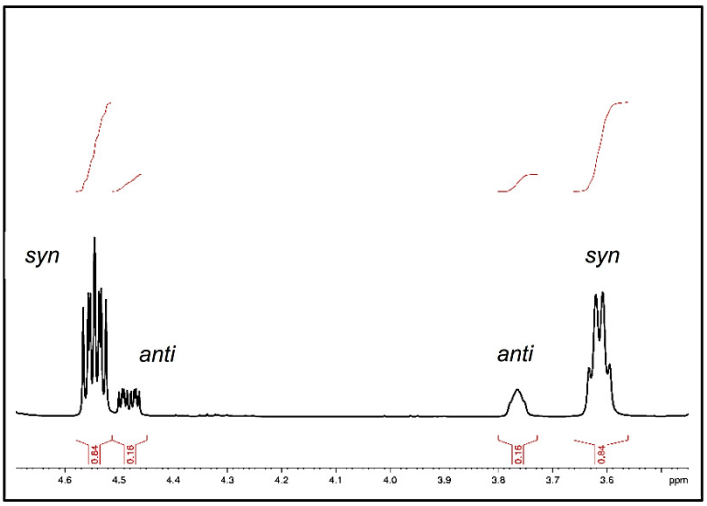
	Ret.time [min]	% Hight	% Area
1	20.09	26.14	20.73
2	21.50	39.24	28.64
3	24.21	20.54	22.47
4	63.35	14.08	28.16

44

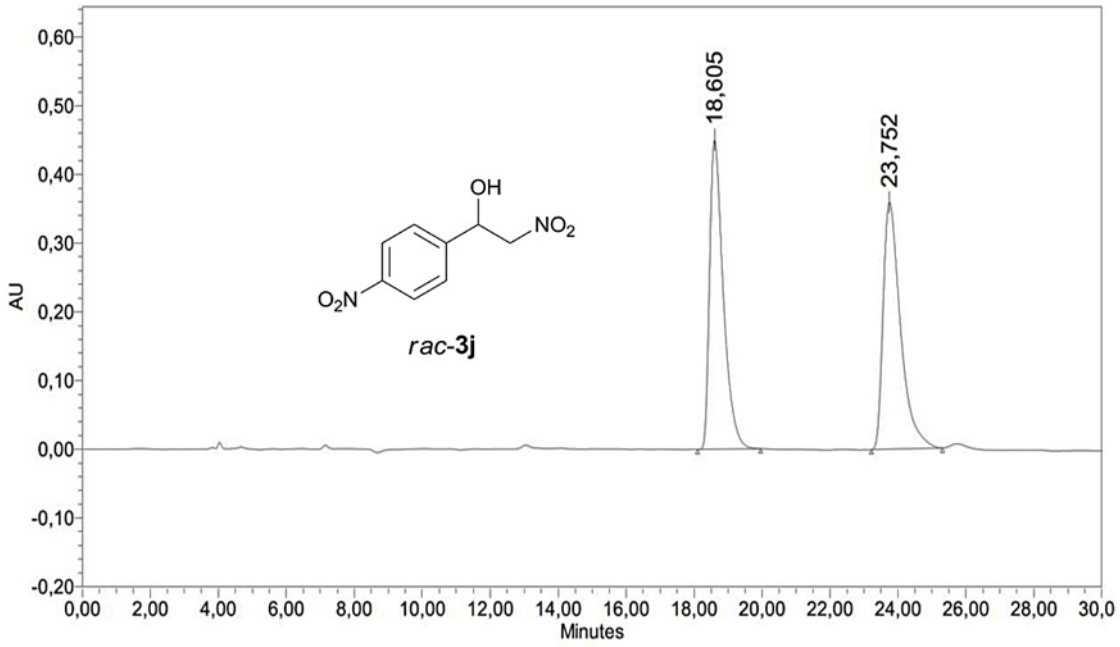


	Ret.time [min]	% Hight	% Area
1	19.68	0.12	0.08
2	20.89	82.40	80.48
3	23.68	17.34	19.13
4	62.07	0.13	0.31

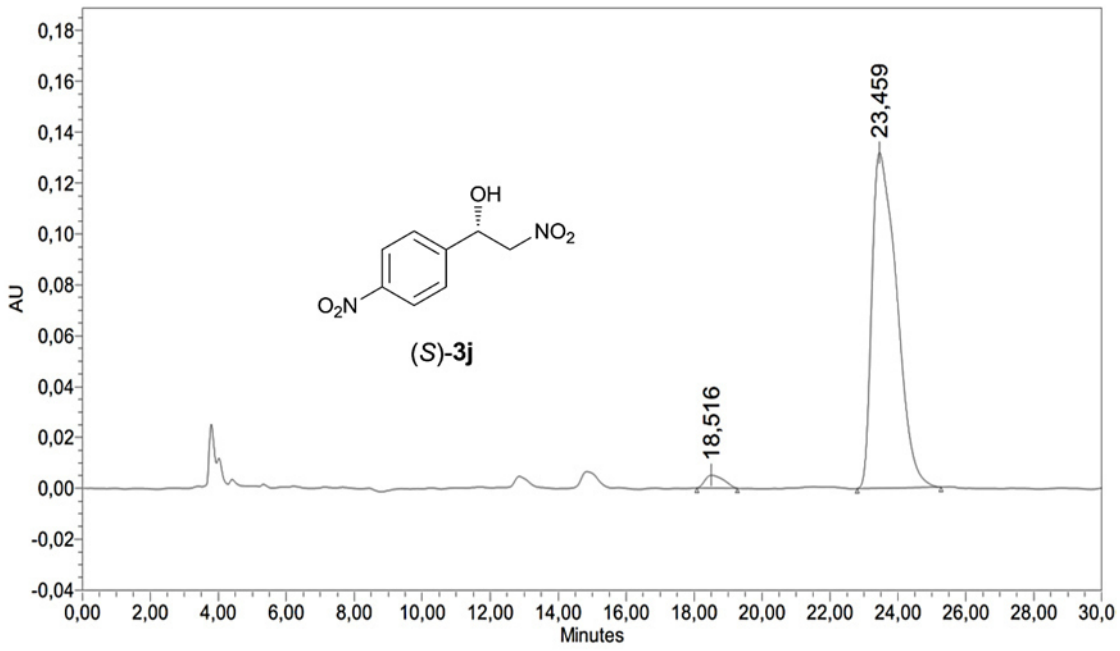
The diastereomeric ratio of **3i** was determined by ^{1}H NMR:



45



	Ret.time [min]	% Hight	% Area
1	18.61	55.61	49.57
2	23.75	44.39	50.43



	Ret.time [min]	% Hight	% Area
1	18.52	3.68	2.80
2	23.46	96.32	97.20

6.3 (2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a chiral diamine ligand for copper(II)-catalysed Henry reactions with superb enantiocontrol

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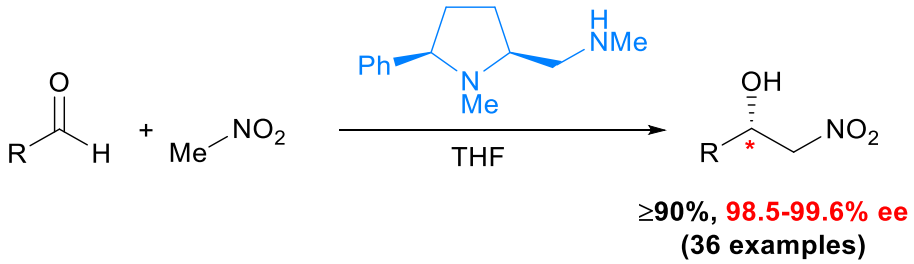

R = aryl: diamine (2.2 mol%), $CuBr_2$ (2 mol%), NEt_3 (1.5 mol%), -25 °C
R = alkyl: diamine (8.8 mol%), $CuCl_2$ (8 mol%), NEt_3 (6 mol%), -20 °C

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(2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a chiral diamine ligand for copper(II)-catalysed Henry reactions with superb enantiocontrol†

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Dagmar Scharnagel,‡ Felix Prause,‡ Johannes Kaldun,‡ Robert G. Haase and Matthias Breuning*

A *cis*-2-aminomethyl-5-phenylpyrrolidine, which is easily available from methyl Boc-L-pyroglutamate, was found to be a highly efficient chiral ligand for Cu(II)-catalysed Henry reactions. Excellent yields (>90%) and superb levels of enantiocontrol (98.5–99.6% ee) were reached with aromatic, heteroaromatic, vinylic, and aliphatic aldehydes (36 examples).

The Henry (or nitroaldol) reaction is a powerful tool for C–C bond formation, because it permits rapid access to valuable synthetic intermediates such as 1,2-amino alcohols and α-hydroxy acids.[1] Tremendous advances have been made over the last two decades in the development of enantioselective versions of this reaction.[2] Among the many highly efficient systems based on heterobimetal,[3] transition metal,[4–6] organo[7] and enzyme[8] catalysis, chirally modified copper complexes have received particular attention due to the wide structural variability of the ligands (diamines, amino alcohols, amino imines, amino pyridines, imino pyridines, Schiff bases, box-type ligands, salen-type ligands, and others),[5,6] the ease of preparation and the, in part, high levels of stereocontrol reached. Several of these catalysts permit 99% ee in the addition of nitromethane to some of the aldehydes tested,[5] but none is capable of providing 99% ee for the majority of substrates. Herein we present the first copper catalyst that fulfils this demand, giving, for the addition of nitromethane to a broad range of aldehydes, the corresponding ß-nitro alcohols in high yield and excellent 99% ee.

In the course of our studies on bicyclic diamines[9] we became interested in 2-aminomethylpyrrolidines of general type **1** (Fig. 1), which carry an additional *cis*-aryl group in 5-position, as compared to proline derived diamines. Chelation of a metal with **1** will lead to a rigid bicyclic system, in which the aryl substituent is forced into an *endo*-position directly on top of the active metal site.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, HPLC- and NMR spectra. See DOI: 10.1039/c4cc02429j

‡ These authors contributed equally to this work.



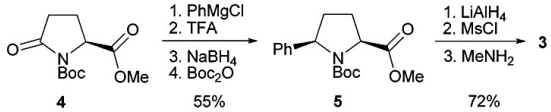
Fig. 1 *cis*-2-Aminomethyl-5-arylpyrrolidines **1** and **3** and a square-pyramidal metal complex of **1**, **2**.

As illustrated by complex **2**, such a shielding might be of particular importance in asymmetric transition metal catalysts preferring Jahn–Teller distorted octahedral geometries, because it selectively blocks one apical position and thereby reduces the number of possible transition states. The equatorial coordination sites L^1_{eq} and L^2_{eq} are still differentiated by the intrinsic steric and electronic properties of the C_1-symmetric diamine **1**, which might offer another advantage over C_2-symmetric ligands.

Copper(II)-catalysed Henry reactions, which are supposed to proceed *via* such a pentacoordinate intermediate,[10] might provide an ideal test system to probe the potential of the diamines **1**.[11] After investigating some derivatives, we quickly identified the simple compound **3** as the ligand of choice for these reactions.[12]

Diamine **3** is easily accessible from commercially available methyl Boc-L-pyroglutamate (**4**, Scheme 1). Treatment of **4** with phenylmagnesium chloride and re-cyclisation of the resulting, ring-opened ketone delivered the diastereomerically pure pyrrolidine **5** after crystallization.[13] Exhaustive reduction followed by OH/NHMe exchange afforded the target molecule **3** in overall seven simple steps and 40% yield.

The enantioselective Henry reactions between the aromatic aldehydes **6a–u** and nitromethane (11 equivalents) were performed on a 1 mmol scale in THF at −25 °C (Table 1, entries 1–21).



Scheme 1 Synthesis of diamine **3** from pyroglutamate **4**.

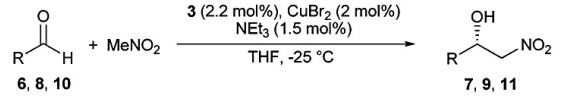
The copper(II) complex [**3**·$CuBr_2$], prepared prior to use by stirring $CuBr_2$ with a slight excess of pyrrolidine **3** in THF, was used as the chiral catalyst and NEt_3 (1.5 mol%) as the base. Under these conditions[12] and in the presence of just 2 mol% [**3**·$CuBr_2$], the Henry products **7a–u** were formed within 18 to 67 h in excellent 92–99% yield. Outstanding 99% ee, in several cases even more than 99.5% ee, were obtained with electronically more or less neutral (**6a–g**), electron-deficient (**6h–o**) and electron-rich (**6p–u**) aromatic aldehydes, carrying substituents in *ortho*-, *meta*-, or *para*-position.

Hetarylic aldehydes **8a–f** were also treated with nitromethane under these conditions (Table 1, entries 22–27). And again, the Henry products **9a–f** were obtained in excellent yields (90–99%) and superb >99.0% ee, irrespective of the heterocycle (furyl, thiophenyl, or NBoc-pyrryl) and the substitution pattern.

The α,β-unsaturated aldehydes **10a** and **10b** solely afforded the 1,2-addition products **11a** and **11b**. The latter one is the only compound tested within this context that delivered less than 99.0% ee, namely 98.7%.

In all cases, the *re*-face of the aldehyde was attacked by the nitronate; the, in part, opposite absolute stereo descriptors in the products are a formal consequence of the CIP-notation.

Table 1 Aromatic, heteroaromatic and vinylic aldehyde scope[a]



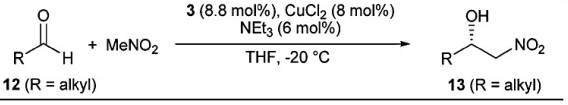
Entry	Compounds	R	Time (h)	Yield[b] (%)	ee[c] (%) (config.)
1	**6a, 7a**	Ph	24	92	99.3 (*S*)
2	**6b, 7b**	2-Me-Ph	18	99	99.2 (*S*)
3	**6c, 7c**	3-Me-Ph	20	99	99.5 (*S*)
4	**6d, 7d**	4-Me-Ph	22	93	99.4 (*S*)
5	**6e, 7e**	4-Ph-Ph	38	99	99.6 (*S*)
6	**6f, 7f**	1-Naphthyl	65	99	99.4 (*S*)
7	**6g, 7g**	2-Naphthyl	42	99	99.0 (*S*)
8	**6h, 7h**	2-O_2N-Ph	20	97	99.0 (*S*)
9	**6i, 7i**	3-O_2N-Ph	22	95	99.4 (*S*)
10	**6j, 7j**	4-O_2N-Ph	21	94	99.4 (*S*)
11	**6k, 7k**	2-Cl-Ph	18	99	99.6 (*S*)
12	**6l, 7l**	3-Cl-Ph	19	96	99.5 (*S*)
13	**6m, 7m**	4-Cl-Ph	42	95	99.5 (*S*)
14	**6n, 7n**	4-F-Ph	20	99	99.6 (*S*)
15	**6o, 7o**	4-NC-Ph	21	94	99.6 (*S*)
16	**6p, 7p**	2-MeO-Ph	42	97	99.5 (*S*)
17	**6q, 7q**	3-MeO-Ph	48	99	99.3 (*S*)
18	**6r, 7r**	4-MeO-Ph	67	99	99.2 (*S*)
19	**6s, 7s**	2,4-$(MeO)_2$-Ph	48	98	99.3 (*S*)
20	**6t, 7t**	2,5-$(MeO)_2$-Ph	39	99	99.6 (*S*)
21	**6u, 7u**	3,4-$(MeO)_2$-Ph	40	93	99.1 (*S*)
22	**8a, 9a**	2-Furyl	40	91	99.6 (*R*)
23	**8b, 9b**	5-Me-2-furyl	112	96	99.5 (*R*)[d]
24	**8c, 9c**	3-Furyl	72	99	99.4 (*S*)
25	**8d, 9d**	2-Thiophenyl	86	95	99.2 (*R*)
26	**8e, 9e**	NBoc-2-pyrryl	21	99	99.5 (*R*)
27	**8f, 9f**	NBoc-3-indolyl	160	90	99.4 (*S*)
28	**10a, 11a**	(*E*)-PhCH=CH	120	90	99.3 (*S*)
29	**10b, 11b**	(*E*)-1-Penten-1-yl	90	97	98.7 (*S*)[d]

[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL ≈ 11 eq.). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral phase; absolute configurations were established by comparison with literature data. [d] Absolute configuration was assigned based on a *re*-face attack on the aldehyde.

Aliphatic aldehydes **12** provided significantly lower enantioselectivities and yields under these conditions. Nonanal (**12b**), for example, delivered the Henry product **13b** in unsatisfying 53% yield and 94.5% ee after 40 h. In order to compensate the lower reactivity, we raised the amount of catalyst to 8 mol% and the temperature to −20 °C, which afforded **13b** in good 86% yield, but low 92.1% ee. Finally, a significant increase in the level of chirality transfer was observed by changing the copper salt from $CuBr_2$ to $CuCl_2$.[14] Under these modified conditions, both, linear (**12a–c**) and α-branched (**12d–g**) aliphatic aldehydes provided the Henry products **13a–g** in excellent 98.5–99.5% ee and >95% yield (Table 2).

The stereochemical outcome of the Henry reactions can be explained *via* the transition state **14** (Fig. 2). As mentioned earlier, the aryl group of the chiral ligand **3** blocks the upper apical position at the Cu(II) ion, thus leaving three open coordination sites, two equatorial ones and one apical one. Based on the known model,[10] the nitronate should bind apically for maximum activation, since its negative charge is less stabilised in this position by the copper ion. Of the two higher Lewis-acidic equatorial sites, the aldehyde should coordinate to the one next to the pyrrolidine moiety for two reasons: (i) this allows the sterically more demanding counter ion X to occupy the less congested position next to the aminomethyl group[9b] and (ii) with the weaker electron donating secondary amine opposite, the electrophilicity of the carbonyl group is increased thus facilitating a nucleophilic attack. Furthermore, the aldehyde must be oriented inwards in order to avoid severe steric repulsions with the chiral backbone. The C–C bond formation will presumably proceed *via* a six-membered,

Table 2 Aliphatic aldehyde scope[a]



Entry	Compounds	R	Time (h)	Yield[b] (%)	ee[c] (%) (config.)
1	**12a, 13a**	*n*Bu	40	95	98.5 (*S*)
2	**12b, 13b**	*n*Oct	60	97	98.6 (*S*)
3	**12c, 13c**	$PhCH_2CH_2$	40	95	99.5 (*S*)
4	**12d, 13d**	iPr	44	96	99.1 (*S*)
5	**12e, 13e**	*c*Pent	44	99	98.9 (*S*)
6	**12f, 13f**	*c*Hex	44	99	99.4 (*S*)
7	**12g, 13g**	*t*Bu	44	99	98.6 (*S*)

[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL ≈ 11 eq.). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral phase; absolute configurations were established by comparison with literature data.

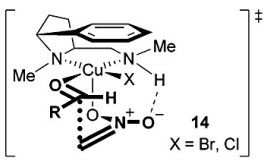


Fig. 2 Proposed transition state **14**.

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chair-shaped transition state, thus obviating repulsions between the nitronate-oxygen and the pyrrolidine *N*-methyl group.[15] It might be possible that this arrangement receives some further stabilisation and rigidness by an intramolecular hydrogen bridge between the nitronate oxygen and the NH-proton of the chiral ligand. Thus, the steric and electronic properties of the diamine ligand apparently create close to perfect preconditions for the experimentally observed, almost exclusive *re*-face attack of the nitronate on the aldehyde carbonyl group.

In summary, the *cis*-5-phenyl substituted 2-aminomethyl-pyrrolidine **3**, which is accessible in just a few steps from methyl Boc-L-pyroglutamate (**4**), was successfully utilized as the chiral ligand in $CuBr_2$- and $CuCl_2$-catalysed Henry reactions. Excellent isolated yields (>90%) and superb enantioselectivities (98.5–99.6% ee) were obtained with a wide variety of aromatic, heteroaromatic, vinylic and aliphatic aldehydes (36 examples). Further studies are ongoing.[16]

Financial support of the German research foundation (DFG) is gratefully acknowledged.

Notes and references

1 Reviews: (*a*) F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915; (*b*) *The Nitro Group in Organic Synthesis*, ed. N. Ono, Wiley-VCH, New York, 2001.

2 Reviews: (*a*) J. Boruwa, N. Gogoi, P. P. Saikia and N. C. Barua, *Tetrahedron: Asymmetry*, 2006, **17**, 3315; (*b*) C. Palomo, M. Oiarbide and A. Laso, *Eur. J. Org. Chem.*, 2007, 2561; (*c*) Y. Alvarez-Casao, E. Marques-Lopez and R. P. Herrera, *Symmetry*, 2011, **3**, 220; (*d*) G. Blay, V. Hernández-Olmos and J. R. Pedro, *Synlett*, 2011, 1195; (*e*) G. Chelucci, *Coord. Chem. Rev.*, 2013, **257**, 1887; (*f*) N. Ananthi and S. Velmathi, *Indian J. Chem., Sect. B*, 2013, **52**, 87.

3 Selected examples: (*a*) H. Sasai, T. Suzuki, S. Arai, T. Arai and M. Shibasaki, *J. Am. Chem. Soc.*, 1992, **114**, 4418; (*b*) T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 13860; (*c*) T. Nitabaru, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2012, **51**, 1644; (*d*) D. Sureshkumar, K. Hashimoto, N. Kumagai and M. Shibasaki, *J. Org. Chem.*, 2013, **78**, 11494.

4 Selected examples (except Cu-catalysis): (*a*) B. M. Trost and V. S. C. Yeh, *Angew. Chem., Int. Ed.*, 2002, **41**, 861; (*b*) C. Palomo, M. Oiarbide and A. Laso, *Angew. Chem., Int. Ed.*, 2005, **44**, 3881; (*c*) J. Park, K. Lang, K. A. Abboud and S. Hong, *J. Am. Chem. Soc.*, 2008, **130**, 16484; (*d*) S. Liu and C. Wolf, *Org. Lett.*, 2008, **10**, 1831; (*e*) R. Kowalczyk, P. Kwiatkowski, J. Skarżewski and J. Jurczak, *J. Org. Chem.*, 2009, **74**, 753; (*f*) K. Lang, J. Park and S. Hong, *Angew. Chem., Int. Ed.*, 2012, **51**, 1620.

5 Cu-catalysed Henry reactions of nitromethane giving 99% ee with at least one aldehyde: (*a*) M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi and C. Ventrici, *Chem. Commun.*, 2007, 616; (*b*) T. Arai, M. Watanabe and A. Yanagisawa, *Org. Lett.*, 2007, **9**, 3595; (*c*) G. Zhang, E. Yashima and W.-D. Woggon, *Adv. Synth. Catal.*, 2009, **351**, 1255; (*d*) W. Jin, X. Li, Y. Huang, F. Wu and B. Wan, *Chem. – Eur. J.*, 2010, **16**, 8259; (*e*) G. Lai, F. Guo, Y. Zheng, Y. Fang, H. Song, K. Xu, S. Wang, Z. Zha and Z. Wang, *Chem. – Eur. J.*, 2011, **17**, 1114; (*f*) A. T. Herrmann, S. R. Martinez and A. Zakarian, *Org. Lett.*, 2011, **13**, 3636; (*g*) B. V. Subba Reddy and J. George, *Tetrahedron: Asymmetry*, 2011, **22**, 1169; (*h*) Y. Zhou, J. Dong, F. Zhang and Y. Gong, *J. Org. Chem.*, 2011, **76**, 588; (*i*) W. Jin, X. Li and B. Wan, *J. Org. Chem.*, 2011, **76**, 484; (*j*) R. I. Kureshy, A. Das, N. H. Khan, S. H. R. Abdi and H. C. Bajaj, *ACS Catal.*, 2011, **1**, 1529; (*k*) Y. Wei, L. Yao, B. Zhang, W. He and S. Zhang, *Tetrahedron*, 2011, **67**, 8552; (*l*) L. Yao, Y. Wei, P. Wang, W. He and S. Zhang, *Tetrahedron*, 2012, **68**, 9119; (*m*) D.-D. Qin, W.-H. Lai, D. Hu, Z. Chen, A.-A. Wu, Y.-P. Ruan, Z.-H. Zhou and H.-B. Chen, *Chem. – Eur. J.*, 2012, **18**, 10515; (*n*) K. Xu, G. Lai, Z. Zha, S. Pan, H. Chen and Z. Wang, *Chem. – Eur. J.*, 2012, **18**, 12357; (*o*) A. Das, R. I. Kureshy, K. J. Prathap, M. K. Choudhary, G. V. S. Rao, N. H. Khan, S. H. R. Abdi and H. C. Bajaj, *Appl. Catal., A*, 2013, **459**, 97; (*p*) T. Deng and C. Cai, *J. Fluorine Chem.*, 2013, **156**, 183; (*q*) R. Ćwiek, P. Niedziejko and Z. Kałuża, *J. Org. Chem.*, 2014, **79**, 1222.

6 Selected recent examples of enantioselective Cu-catalysed Henry reactions: (*a*) G. Blay, V. Hernández-Olmos and J. R. Pedro, *Org. Lett.*, 2010, **12**, 3058; (*b*) T. Arai, Y. Taneda and Y. Endo, *Chem. Commun.*, 2010, **46**, 7936; (*c*) L. Cheng, J. Dong, J. You, G. Gao and J. Lan, *Chem. – Eur. J.*, 2010, **16**, 6761; (*d*) A. Chougnet, G. Zhang, K. Liu, D. Häussinger, A. Kägi, T. Allmendinger and W.-D. Woggon, *Adv. Synth. Catal.*, 2011, **353**, 1797; (*e*) M. W. Leighty, B. Shen and J. N. Johnston, *J. Am. Chem. Soc.*, 2012, **134**, 15233; (*f*) J. D. White and S. Shaw, *Org. Lett.*, 2012, **14**, 6270; (*g*) Q. Dai, N. K. Rana and J. C.-G. Zhao, *Org. Lett.*, 2013, **15**, 2922; (*h*) D.-D. Qin, W. Yu, J.-D. Zhou, Y.-C. Zhang, Y.-P. Ruan, Z.-H. Zhou and H.-B. Chen, *Chem. – Eur. J.*, 2013, **19**, 16541.

7 Selected recent examples: (*a*) D. Uraguchi, S. Nakamura and T. Ooi, *Angew. Chem., Int. Ed.*, 2010, **49**, 7562; (*b*) K. Kanagaraj, P. Suresh and K. Pitchumani, *Org. Lett.*, 2010, **12**, 4070; (*c*) Q. Dai, H. Huang and J. C.-G. Zhao, *J. Org. Chem.*, 2013, **78**, 4153; (*d*) A. Quintavalla, M. Lombardo, S. P. Sanap and C. Trombini, *Adv. Synth. Catal.*, 2013, **355**, 938; (*e*) S. Kitagaki, T. Ueda and C. Mukai, *Chem. Commun.*, 2013, **49**, 4030; (*f*) M. T. Corbett and J. S. Johnson, *Angew. Chem., Int. Ed.*, 2014, **53**, 255.

8 M. Gruber-Khadjawi, T. Purkarthofer, W. Skranc and H. Griengl, *Adv. Synth. Catal.*, 2007, **349**, 1445.

9 (*a*) M. Breuning, D. Hein, M. Steiner, V. H. Gessner and C. Strohmann, *Chem. – Eur. J.*, 2009, **15**, 12764; (*b*) M. Breuning, M. Steiner, C. Mehler, A. Paasche and D. Hein, *J. Org. Chem.*, 2009, **74**, 1407; (*c*) M. Breuning and D. Hein, *Eur. J. Org. Chem.*, 2013, 7575.

10 D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692.

11 Enantioselective, Cu-catalysed Henry reactions using proline-derived ligands: (*a*) B. V. Subba Reddy, S. Madhusudana Reddy, S. Manisha and C. Madan, *Tetrahedron: Asymmetry*, 2011, **22**, 530; (*b*) D. Lu, Y. Zhou, Y. Li, S. Yan and Y. Gong, *J. Org. Chem.*, 2011, **76**, 8869; (*c*) B. Ni and J. He, *Tetrahedron Lett.*, 2013, **54**, 462; (*d*) Y. Zhou, Y. Zhu, S. Yan and Y. Gong, *Angew. Chem., Int. Ed.*, 2013, **52**, 10265; (*e*) H. Yuan, J. Hu and Y. Gong, *Tetrahedron: Asymmetry*, 2013, **24**, 699; (*f*) H. A. Sema, G. Bez and S. Karmakar, *Appl. Organomet. Chem.*, 2014, **28**, 290; (*g*) Ref. 5*e*, *h* and *n*.

12 Details about the diamine screening and the optimization of the reactions conditions as well as further mechanistic investigations will be reported elsewhere.

13 Synthesis of related compounds: (*a*) M.-C. Fournie-Zaluski, P. Coric, V. Thery, W. Gonzalez, H. Meudal, S. Turcaud, J.-B. Michel and B. P. Roques, *J. Med. Chem.*, 1996, **39**, 2594; (*b*) A. Momotake, H. Togo and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1193; (*c*) A. C. Rudolph, R. Machauer and S. F. Martin, *Tetrahedron Lett.*, 2004, **45**, 4895.

14 A similar effect on the ee was not observed with aromatic aldehydes.

15 A boat-type transition state cannot fully be excluded, but seems less likely.

16 Initial studies on Henry reactions with other nitroalkanes revealed acceptable to good diastereoselectivities and excellent enantioselectivities in the major *syn*-diastereomer. The reaction of benzaldehyde (**6a**) with nitropropane, for example, afforded the corresponding ß-nitro alcohol in 99% yield with a *syn*/*anti* ratio of 79 : 21 and 98% ee in the major diastereomer.

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(2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a Chiral Diamine Ligand for Copper(II)-Catalysed Henry Reactions with Superb Enantiocontrol

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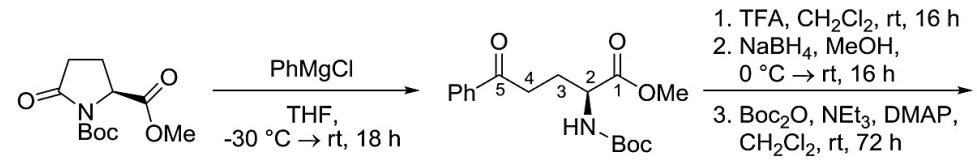
1. General Information

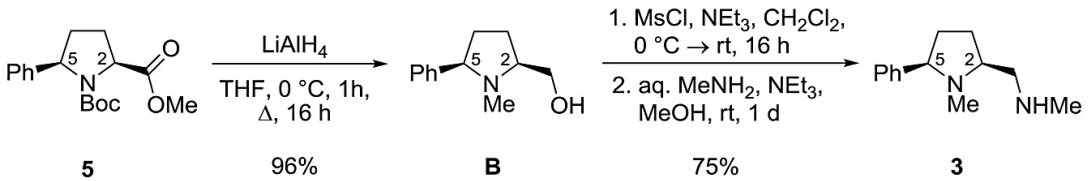
All reactions were carried out under an argon atmosphere with dry solvents. Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), methanol (MeOH), and nitromethane ($MeNO_2$) were prepared using standard procedures.[1]

Commercially available reagents (highest quality available) were used as received. All liquid aldehydes used in enantioselective Henry reactions were distilled prior to use in order to remove any accompanying acid impurities. Reactions were monitored by thin layer chromatography (TLC) on precoated silica gel (Macherey-Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey-Nagel, particle size 40–63 μm) was used for column chromatography.

Melting points (m.p.) were measured on a Stuart SMP10 digital melting point apparatus and are uncorrected. Optical rotations ($[\alpha]_D^T$) were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance 400 or a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^1H and ^{13}C NMR data were made on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared (IR) spectra were recorded on a Jasco FT-IR-410 or a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra (HRMS) on a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization) or on a Finnigan MAT 90 using EI (electron ionisation. 70 eV).

2. Synthesis of the Diamine 3





2.1. (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-oxo-5-phenylpentanoate (A)

PhMgCl (25 wt% in THF, 31.6 mL, 60.0 mmol) was added at -30 °C to a solution of **4** (12.2 g, 50.0 mmol) in abs. THF (150 mL). The reaction mixture was slowly warmed to rt and stirred for 18 h. After addition of sat. aq. NH_4Cl (2 mL), the solvent was removed and the residue was diluted with

1 *Purification of Laboratory Chemicals*, eds. W. L. F. Armarego and D. D. Perrin, 4th ed., Butterworth-Heinemann, Oxford, 2000.

CH_2Cl_2 (200 mL). Sat. aq. NH_4Cl (180 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (180 mL) and the aqueous layer was re-extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (silica gel, petrol ether/ EtOAc 1:0 → 2:1) delivered a mixture of the keto ester **A** and the corresponding 2,3-dihydropyrrole. This mixture was dissolved in MeOH (280 mL) and H_2O (35 mL), treated with TsOH•H_2O (210 mg), and stirred for 1 d at rt. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (250 mL), washed with sat. aq. $NaHCO_3$ (2 × 150 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded keto ester **A** (14.8 g, 46.0 mmol, 92%) as a white solid, $[\alpha]_D^{25}$ = 14.6 (c = 1.13 in $CHCl_3$) [ref[2]: $[\alpha]_D^{20}$ = –14.8 (c = 1.13 in $CHCl_3$) for *ent*-**A**]. The NMR data of **A** were in full agreement with those given in ref.[2]

2.2. (2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-phenylpyrrolidine-1,2-dicarboxylate (5)

A solution of the keto ester **A** (12.1 g, 37.6 mmol) in abs. CH_2Cl_2 (370 mL) was treated at rt with TFA (57.9 mL, 85.7 g, 752 mmol) and stirred overnight. The solvent was removed under reduced pressure and the resulting orange oil was diluted five times with CH_2Cl_2 (300 mL) and evaporated again, in order to remove excess TFA. $NaBH_4$ (2.70 g, 71.4 mmol) was slowly added at 0 °C to a solution of the residue in MeOH (300 mL). After stirring for 16 h at rt, the solvent was removed. The resulting orange oil was diluted four times with MeOH (260 mL) and evaporated again. The residue was suspended in abs. CH_2Cl_2 (1000 mL) and NEt_3 (7.49 mL, 5.71 g, 56.4 mmol), Boc_2O (12.3 g, 56.4 mmol), and DMAP (50.0 mg, 409 µmol) were added at rt. After 3 d of stirring, sat. aq. NH_4Cl (1000 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, petrol ether/EtOAc 1:0 → 0:1) afforded an 86:14 mixture of **5** and its 5-epimer, which was crystallized from CH_2Cl_2/Et_2O/pentane (1:4:14) to give diastereomerically pure **5** (6.90 g, 22.6 mmol, 60%) as colourless needles.

R_f = 0.37 (petrol ether/EtOAc 3:1); m.p. 100–101 °C; $[\alpha]_D^{21}$ = 25.7 (c = 1.00 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$):* δ = 1.14 (s, 5.4H, $C(CH_3)_3$), 1.41 (s, 3.6H, $C(CH_3)_3$), 2.03 (m, 2H, 3-H, 4-H), 2.19 (m, 1H, 3-H), 2.31 (m, 1H, 4-H), 3.81 (s, 3H, OMe), 4.35 (m, 0.4H, 2-H), 4.49 (m, 0.6H, 2-H), 4.74 (m, 0.6H, 5-H), 4.98 (m, 0.4H, 5-H), 7.21 (m, 1H, Ph-H), 7.32 (m, 2H, Ph-H), 7.54 ppm (m, 2H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$):* δ = 28.1, 28.4 ($C(CH_3)_3$), 28.9, 29.1 (C-3), 34.6, 35.7 (C-4), 52.1, 52.3 (OMe), 60.4, 60.9 (C-2), 62.3, 63.2 (C-5), 80.2, 80.4 ($C(CH_3)_3$), 126.1, 126.5, 126.8, 128.2, 128.4 (CH-Ph), 143.2, 144.2 (C_q-Ph), 153.9, 154.6 (NCO_2), 173.8 ppm (CO_2Me); IR (ATR): $\tilde{\nu}$ = 3734 (w), 3628 (w), 2981 (w), 2951 (w), 1747 (m), 1684 (s), 1605 (w), 1398 (s), 1352 (m), 1197 (s), 1155 (s), 1121 (m), 1083 (m), 757 (m), 704 cm^{-1} (m); HRMS (ESI, pos.): *m/z* calcd. for $[C_{17}H_{23}NO_4 + Na]^+$: 328.1519, found: 328.1518. *Mixture of rotamers due to hindered rotation of the carbamate group.

2 J. Ackermann, M. Matthes and C. Tamm, *Helv. Chim. Acta*, 1990, **73**, 122.

2.3. (2*S*,5*R*)-2-Hydroxymethyl-1-methyl-5-phenylpyrrolidine (B)

$LiAlH_4$ (2.46 g, 64.8 mmol) was added at 0 °C to a solution of **5** (3.30 g, 10.8 mmol) in abs. THF (100 mL). After 1 h, the reaction mixture was heated to reflux for 16 h. The solution was diluted with Et_2O (80 mL) and carefully treated with sat. aq. Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was thoroughly washed with CH_2Cl_2/MeOH (9:1, 700 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2/MeOH 95:5) delivered alcohol **B** (1.98 g, 10.4 mmol, 96%) as a colourless oil.

R_f = 0.33 (Et_2O); $[\alpha]_D^{26}$ = 79.6 (c = 0.50 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (m, 1H, 4-H), 1.97 (m, 2H, 3-H), 2.08 (m, 1H, 4-H), 2.18 (s, 3H, NMe), 2.68 (m, 1H, 2-H), 2.80 (br s, 1H, OH), 3.42 (dd, *J* = 10.0, 6.5 Hz, 1H, 5-H), 3.51 (dd, *J* = 10.8, 1.9 Hz, 1H, CH*H*OH), 3.77 (dd, *J* = 10.8, 3.4 Hz, 1H, C*H*HOH), 7.25 (m, 1H, Ph-H), 7.33 ppm (m, 4H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.4 (C-3), 34.6 (C-4), 38.5 (NMe), 61.7 (CH_2OH), 66.6 (C-2), 72.5 (C-5), 127.30, 127.33, 128.5 (CH-Ph), 143.1 ppm (C_q-Ph); IR (ATR): $\tilde{\nu}$ = 3414 (w), 2947 (w), 2871 (w), 2842 (w), 2783 (w), 1603 (w), 1451 (m), 1075 (m), 1027 (s), 755 (s), 699 cm^{-1} (s); HRMS (ESI, pos.): *m/z* calcd. for $[C_{12}H_{17}NO + H]^+$: 192.1383, found: 192.1384.

2.4. (2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine (3)

MsCl (731 µL, 1.08 g, 9.44 mmol) and NEt_3 (1.80 mL, 1.30 g, 12.9 mmol) were added at 0 °C to a solution of the alcohol **B** (1.64 g, 8.58 mmol) in abs. CH_2Cl_2 (20 mL). The reaction was allowed to warm to rt and stirred for further 16 h. Aqeous $MeNH_2$ (11 M in H_2O, 23.0 mL, 257 mmol), NEt_3 (521 mg, 719 µL, 5.15 mmol), and MeOH (30 mL) were added and stirring was continued for 1 d. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2/10% aq. NH_3 in MeOH 95:5 → 85:15) delivered diamine **3** (1.31 g, 6.41 mmol, 75%) as a yellowish oil.

R_f = 0.53 (Et_2O, deact. SiO_2); $[\alpha]_D^{29}$ = 51.2 (c = 1.00 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (m, 1H, 4-H), 1.84 (m, 1H, 3-H), 1.96 (m, 2H, 3-H, NH), 2.05 (m, 1H, 4-H), 2.15 (s, 3H, NMe), 2.52 (s, 3H, HN*Me*), 2.61 (m, 1H, 2-H), 2.69 (dd, *J* = 11.4, 5.6 Hz, 1H, C*H*HN), 2.75 (dd, *J* = 11.4, 3.6 Hz, 1H, C*H*HN), 3.27 (dd, *J* = 9.6, 6.6 Hz, 1H, 5-H), 7.22 (m, 1H, Ph-H), 7.33 ppm (m, 4H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (C-3), 34.4 (C-4), 37.2 (HNMe), 39.4 (NMe), 55.3 (CH_2N), 65.8 (C-2), 72.7 (C-5), 127.1, 127.5, 128.4 (CH-Ph), 144.0 ppm (C_q-Ph); IR (ATR): $\tilde{\nu}$ = 2943 (w), 2872 (w), 2838 (w), 2783 (w), 1603 (w), 1451 (w), 1133 (w), 1073 (w), 1039 (w), 755 (m), 698 cm^{-1} (s); HRMS (ESI, pos.): *m/z* calcd. for $[C_{13}H_{20}N_2 + H]^+$: 205.1699, found: 205.1700.

3. Enantioselective Henry Reactions

3.1. General Remarks

Preparation of the racemic ß-nitro alcohols: These compounds were prepared by treatment of the aldehyde (500 µmol) at rt with nitromethane (300 µL) in the presence of NEt_3 (6.0 µL, 43 µmol) and a $CuCl_2$(tmda) complex, prepared from $CuCl_2$ (1.3 mg, 10 µmol) and TMEDA (1.5 µL, 10 µmol) in MeOH (300 µL). Purification by column chromatography (silica gel, hexanes/EtOAc 8:1 → 4:1) afforded the analytically pure β-nitro alcohols, the NMR spectroscopic data of which were identically with those given in literature.[3]

Solutions used in the enantioselective Henry reactions: In order to ensure maximum accuracy, solutions were prepared for all catalytically used reagents:

- $CuBr_2$ in MeOH (66.7 mM) from anhyd. $CuBr_2$ (44.7 mg, 200 µmol) and abs. MeOH (3.00 mL)
- $CuCl_2$ in MeOH (267 mM) from anhyd. $CuCl_2$ (53.8 mg, 400 µmol) and abs. MeOH (1.50 mL)
- Diamine **3** in THF (36.7 mM) from **3** (22.5 mg, 110.0 µmol) and abs. THF (3.00 mL)
- Diamine **3** in THF (147 mM) from **3** (45.0 mg, 220.0 µmol) and abs. THF (1.50 mL)
- NEt_3 in $MeNO_2$ (1.50 M) from NEt_3 (20.8 µL, 15.2 mg, 150 µmol) and $MeNO_2$ (79 µL)

Measurement of the enantiomeric excess (ee): The ee of each ß-nitro alcohol was determined by HPLC (Knauer HPLC pump type 64.00, Knauer UV/Vis variable wavelength monitor type A0293) on chiral phase (Daicel Chiralcel OD-3, Daicel Chiralpak AD-H, Daicel Chiralcel OJ-H). The accuracy of integration was ± 0.1%. Some of the enantioselective Henry reactions were done up to five times, for example with benzaldehyde (**6a**), 2-nitrobenzaldehyde (**6h**), 2-methoxybenzaldehyde (**6p**), valeraldehyde (**12a**), and 3-phenylpropanal (**12c**). In all cases, virtually the same excellent enantiomeric excesses were measured (Δee = ± 0.2%).

Determination of the absolute configuration of the major enantiomer: For all known ß-nitro alcohols, the absolute configuration of the major enantiomer was assigned by comparison of the order of the measured retention times on HPLC with the literature-known ones, measured under identical conditions (same chiral phase and solvent system).[3] The absolute configuration of the major enantiomer of the new products **9b** and **11b** was tentatively assigned under the assumption that the sense of asymmetric induction was the same as for all other derivatives (*re*-attack on the carbonyl group).

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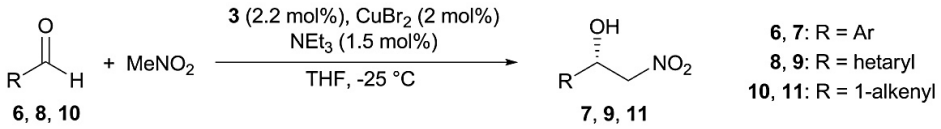
3 (*a*) M. Breuning, D. Hein, M. Steiner, V. H. Gessner and C. Strohmann, *Chem.-Eur. J.*, 2009, **15**, 12764; (*b*) W. Jin, X. Li and B. Wan, *J. Org. Chem.*, 2011, **76**, 484; (*c*) Y. Q. Ji, G. Qi and Z. M. A. Judeh, *Eur. J. Org. Chem.*, 2011, 4892; (*d*) Y. Zhou, J. Dong, F. Zhang and Y. Gong, *J. Org. Chem.*, 2011, **76**, 588; (*e*) L. Yao, Y. Wei, P. Wang, W. He and S. Zhang, *Tetrahedron*, 2012, **68**, 9119; (*f*) R. Kowalczyk, P. Kwiatkowski, J. Skarżewski and J. Jurczak, *J. Org. Chem.*, 2009, **74**, 753; (*g*) L. Zhang, H. Wu, Z. Yang, X. Xu, H. Zhao, Y. Huang and Y. Wang, *Tetrahedron*, 2013, **69**, 10644; (*h*) B. V. S. Reddy and J. George, *Tetrahedron: Asymmetry*, 2011, **22**, 1169; (*i*) Y. Zhou and Y. Gong, *Eur. J. Org. Chem.*, 2011, 6092; (*j*) M. Liu, S. Ma, Z. Tian, H. Wu, L. Wu, X. Xu, Y. Huang and Y. Wang, *Tetrahedron: Asymmetry*, 2013, **24**, 736; (*k*) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen and H. Hiemstra, *Angew. Chem. Int. Ed.*, 2006, **45**, 929; (*l*) A. Gualandi, L. Cerisoli, H. Stoeckli-Evans and D Savoia, *J. Org. Chem.*, 2011, **76**, 3399; (*m*) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.*, 2005, **347**, 1643.

3.2. General Procedure I (Aromatic, Heteroaromatic, and Vinylic Aldehydes)



A solution of anhyd. $CuBr_2$ (66.7 mM in MeOH, 300 µL, 4.47 mg, 20.0 µmol, 2.0 mol%) was evaporated to dryness in a Schlenk tube. A solution of the diamine **3** (36.7 mM in abs. THF, 600 µL, 4.49 mg, 22.0 µmol, 2.2 mol%), $MeNO_2$ (600 µL, 684 mg, 11.2 mmol, 11.2 eq.) and the aldehyde **6**, **8**, or **10** (1.00 mmol, 1.00 eq.) were added successively at rt. The mixture was ultrasonicated for 10 min to give a clear, brownish solution and then cooled to –25 °C. NEt_3 (1.5 M in $MeNO_2$, 10.0 µL, 1.52 mg, 15.0 µmol, 1.5 mol%) was added and the resulting blue-green solution was stirred until TLC-control indicated complete consumption of the aldehyde (18–160 h). The crude reaction mixture was purified by column chromatography (silica gel, hexanes/EtOAc 8:1 → 4:1) delivering β-nitro alcohol **7**, **9**, or **11**.

Table S1. Experimental data and details of HPLC analysis on chiral phase.

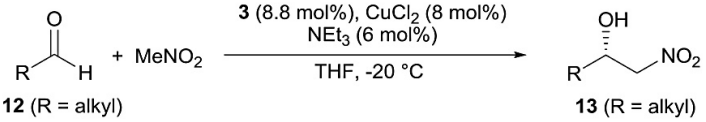
			Reaction Conditions			Enantiomer Analysis: HPLC Conditions					
Entry	Com-pounds	R	t [h]	Yield [%][a]	ee [%][b] (Config.)[c]	Column[d]	Solvent System *n*-Hexane/*i*PrOH	Flow [ml/min]	t_r (*R*) [min][e]	t_r (*S*) [min][e]	Ref.[f]
1	**6a**, **7a**	Ph	24	92	99.3 (*S*)	OD-3	85:15	0.8	12.6	14.9	3a
2	**6b**, **7b**	2-Me-Ph	18	99	99.2 (*S*)	OD-3	85:15	0.9	10.3	16.2	3b
3	**6c**, **7c**	3-Me-Ph	20	99	99.5 (*S*)	OD-3	90:10	0.9	14.4	16.7	3c
4	**6d**, **7d**	4-Me-Ph	22	93	99.4 (*S*)	OD-3	90:10	0.9	17.7	22.5	3c
5	**6e**, **7e**	4-Ph-Ph	38	99	99.6 (*S*)	OD-3	85:15	0.9	16.1	18.5	3c
6	**6f**, **7f**	1-naphthyl	65	99	99.4 (*S*)	OD-3	85:15	0.9	14.8	22.3	3b
7	**6g**, **7g**	2-naphthyl	42	99	99.0 (*S*)	OD-3	80:20	0.9	24.5	36.5	3b
8	**6h**, **7h**	2-O_2N-Ph	20	97	99.0 (*S*)	OD-3	80:20	0.7	11.5	12.2	3a
9	**6i**, **7i**	3-O_2N-Ph	22	95	99.4 (*S*)	OD-3	85:15	0.9	18.2	20.6	3d
10	**6j**, **7j**	4-O_2N-Ph	21	94	99.4 (*S*)	OD-3	85:15	0.9	18.6	22.7	3a
11	**6k**, **7k**	2-Cl-Ph	18	99	99.6 (*S*)	OD-3	97: 3	0.9	25.9	27.0	3a
12	**6l**, **7l**	3-Cl-Ph	19	96	99.5 (*S*)	OD-3	90:10	0.9	17.1	22.0	3c
13	**6m**, **7m**	4-Cl-Ph	42	95	99.5 (*S*)	OD-3	85:15	0.9	11.5	14.1	3a
14	**6n**, **7n**	4-F-Ph	20	99	99.6 (*S*)	OD-3	90:10	0.9	13.7	16.2	3e
15	**6o**, **7o**	4-NC-Ph	21	94	99.6 (*S*)	OD-3	80:20	0.9	12.9	14.6	3f
16	**6p**, **7p**	2-MeO-Ph	42	97	99.5 (*S*)	OD-3	90:10	0.9	14.0	16.8	3a
17	**6q**, **7q**	3-MeO-Ph	48	99	99.3 (*S*)	OD-3	85:15	0.9	19.3	25.6	3b

Table S1. (Continued).

Entry	Com-pounds	R	Reaction Conditions			Enantiomer Analysis: HPLC Conditions					
			t [h]	Yield [%][a]	ee [%][b] (Config.)[c]	Column[d]	Solvent System *n*-Hexane/*i*PrOH	Flow [ml/min]	t_r (*R*) [min][e]	t_r (*S*) [min][e]	Ref.[f]
18	**6r**, **7r**	4-MeO-Ph	67	99	99.2 (*S*)	OD-3	85:15	0.9	15.9	19.7	3a
19	**6s**, **7s**	2,4-$(MeO)_2$-Ph	48	98	99.3 (*S*)	OD-3	80:20	0.9	10.0	15.2	3g
20	**6t**, **7t**	2,5-$(MeO)_2$-Ph	39	99	99.6 (*S*)	OD-3	85:15	0.9	11.0	11.8	3h
21	**6u**, **7u**	3,4-$(MeO)_2$-Ph	40	93	99.1 (*S*)	OD-3	80:20	0.9	16.8	21.3	3i
22	**8a**, **9a**	2-furyl	40	91	99.6 (*R*)	AD-H	95:5	0.6	39.6	37.8	3d
23	**8b**, **9b**	5-Me-2-furyl	112	96	99.5 (*R*)	AD-H	95:5	0.6	30.4	33.0	–[g]
24	**8c**, **9c**	3-furyl	72	99	99.4 (*S*)	AD-H	90:10	0.9	15.8	21.7	3j
25	**8d**, **9d**	2-thiophenyl	86	95	99.2 (*R*)	OJ-H	85:15	0.9	30.6	26.0	3h
26	**8e**, **9e**	*N*Boc-2-pyrryl	21	99	99.5 (*R*)	OD-3	90:10	0.9	7.7	7.0	3k
27	**8f**, **9f**	*N*Boc-3-indolyl	160	90	99.4 (*S*)	OD-3	90:10	0.9	14.2	12.1	3l
28	**10a**, **11a**	(*E*)-PhCH=CH	120	90	99.3 (*S*)	OD-3	85:15	0.9	36.0	31.5	3h
29	**10b**, **11b**	(*E*)-1-pen-ten-1-yl	90	97	98.7 (*S*)	OJ-H	97:3	0.9	22.5	25.5	–[g]

[a] Isolated yield. [b] Determined by HPLC analysis on a chiral phase. [c] The absolute configuration of the major enantiomer was determined by comparison of the order of the measured retention times on HPLC with the literature-known ones, measured under identical conditions.[3] [d] OD-3: Daicel Chiralcel OD-3; AD-H: Daicel Chiralpak AD-H; OJ-H: Daicel Chiralcel OJ-H. [e] Retention time. [f] References, in which data for the HPLC analysis on chiral phase are given. [g] The absolute configuration of the major enantiomer was tentatively assigned under the assumption of a *re*-attack on the carbonyl group.

3.3. General Procedure II (Aliphatic Aldehydes)



12 (R = alkyl) **13** (R = alkyl)

A solution of anhyd. $CuCl_2$ (267 mM in MeOH, 300 µL, 10.8 mg, 80.0 µmol, 8.0 mol%) was evaporated to dryness in a Schlenk tube. A solution of the diamine **3** (147 mM in abs. THF, 600 µL, 18.0 mg, 88.0 µmol, 8.8 mol%), $MeNO_2$ (600 µL, 684 mg, 11.2 mmol, 11.2 eq.) and aldehyde **12** (1.00 mmol, 1.00 eq.) were successively added at rt. The mixture was ultra-sonicated for 10 min to give a clear, greenish solution and then cooled to –20 °C. NEt_3 (1.5 M in $MeNO_2$, 40 µL, 6.08 mg, 60.0 µmol, 6.0 mol%) was added and the resulting blue solution was stirred until TLC-control indicated complete consumption of the aldehyde (40–60 h). The crude reaction mixture was purified by column chromatography (silica gel, pentane/Et_2O 8:1 → 4:1) delivering β-nitro alcohol **13**.

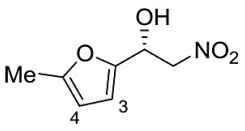
Table S2. Experimental data and details of HPLC analysis on chiral phase.

			Reaction Conditions			Enantiomer Analysis: HPLC Conditions					
Entry	Com-pounds	R	t [h]	Yield [%][a]	ee [%][b] (Config.)[c]	Column[d]	Solvent System *n*-Hexane/*i*PrOH	Flow [ml/min]	t_r (*R*) [min][e]	t_r (*S*) [min][e]	Ref.[f]
1	**12a**, **13a**	*n*Bu	40	95	98.5 (*S*)	OJ-H	97:3	0.8	21.9	22.9	3b
2	**12b**, **13b**	*n*Oct	60	97	98.6 (*S*)	AD-H	95:5	0.8	14.3	20.2	3h
3	**12c**, **13c**	$PhCH_2CH_2$	40	95	99.5 (*S*)	AD-H	90:10	0.9	13.1	16.3	3b
4	**12d**, **13d**	*i*Pr	44	96	99.1 (*S*)	OD-3	97:3	0.9	15.8	17.5	3m
5	**12e**, **13e**	*c*Pent	44	99	98.9 (*S*)	OD-3	98:2	0.9	23.8	24.9	3b
6	**12f**, **13f**	*c*Hex	44	99	99.4 (*S*)	AD-H	95:5 (EtOH)	0.9	34.3	31.1	–[g]
7	**12g**, **13g**	*t*Bu	44	99	98.6 (*S*)	OD-3	97:3	0.9	12.8	15.0	3m

[a] Isolated yield. [b] Determined by HPLC analysis on a chiral phase. [c] The absolute configuration of the major enantiomer was determined by comparison of the order of the measured retention times on HPLC with the literature-known ones, measured under identical conditions.[3] [d] OD-3: Daicel Chiralcel OD-3; AD-H: Daicel Chiralpak AD-H; OJ-H: Daicel Chiralcel OJ-H. [e] Retention time. [f] References, in which the data for the HPLC analysis on chiral phase are given. [g] The absolute configuration of the major enantiomer was assigned by comparison of the measured sign of the optical rotation with the literature-known one.[3b]

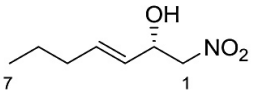
3.4. Characterization of New ß-Nitro Alcohols

3.4.1. (*R*)-1-(5-Methylfuran-2-yl)-2-nitroethanol (9b)



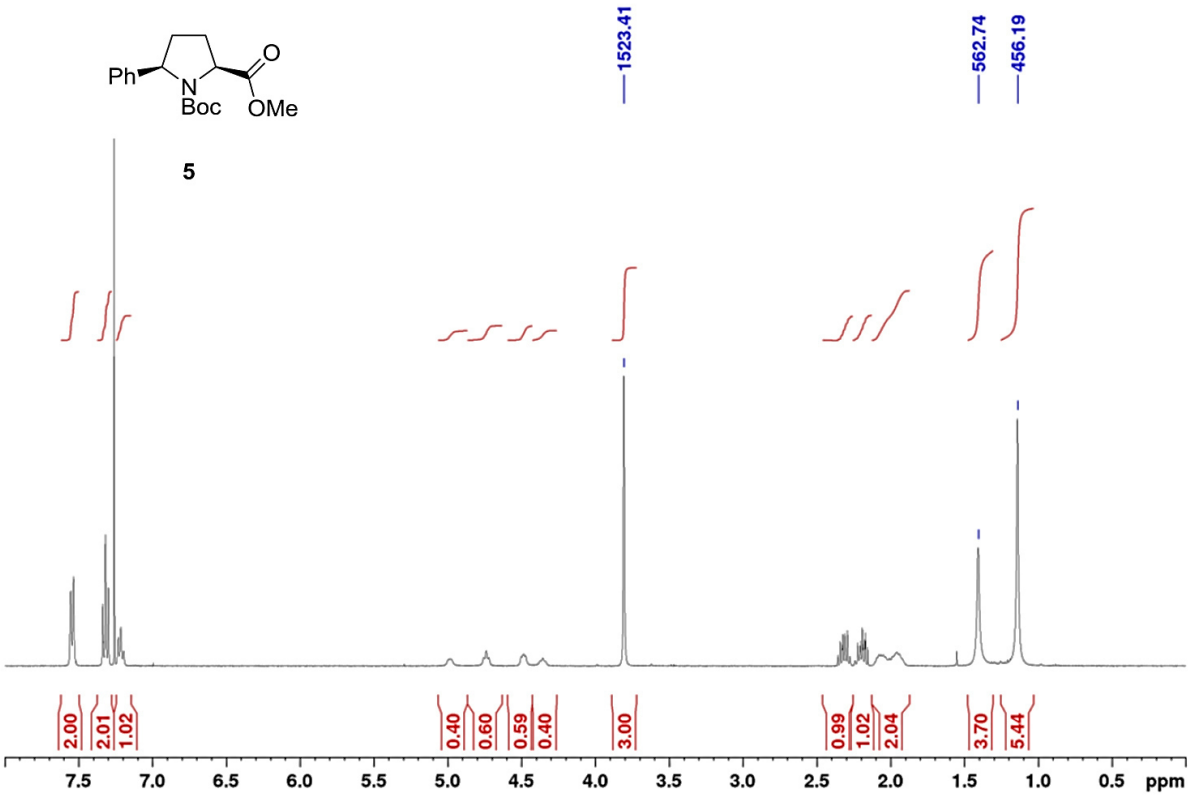
Ee = 99.5%; R_f = 0.32 (petrol ether/EtOAc 4:1); $[\alpha]_D^{28}$ = 50.1 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (s, 3H, CH_3), 2.78 (br s, 1H, OH), 4.64 (dd, *J* = 13.5, 3.4 Hz, 1H, C*H*H), 4.78 (dd, *J* = 13.5, 9.3 Hz, 1H, C*H*H), 5.40 (dd, *J* = 9.3, 3.3 Hz, 1H, C*H*OH), 5.95 (m, 1H, 4-H), 6.26 ppm (d, *J* = 3.1 Hz, 1H, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6 (CH_3), 65.0 (COH), 78.6 (CH_2), 106.7 (C-4), 109.3 (C-3), 148.9 (C-2), 153.3 ppm (C-5); IR (ATR): $\tilde{\nu}$ = 3409 (w), 2925 (w), 1698 (w), 1550 (s), 1421 (w), 1379 (m), 1019 (m), 788 (m), 705 (m), 631 cm^{-1} (m); HRMS (EI, 70 eV, peak match): *m/z* calcd. for $[C_7H_9NO_4]^{\bullet+}$: 171.0526, found: 171.0526.

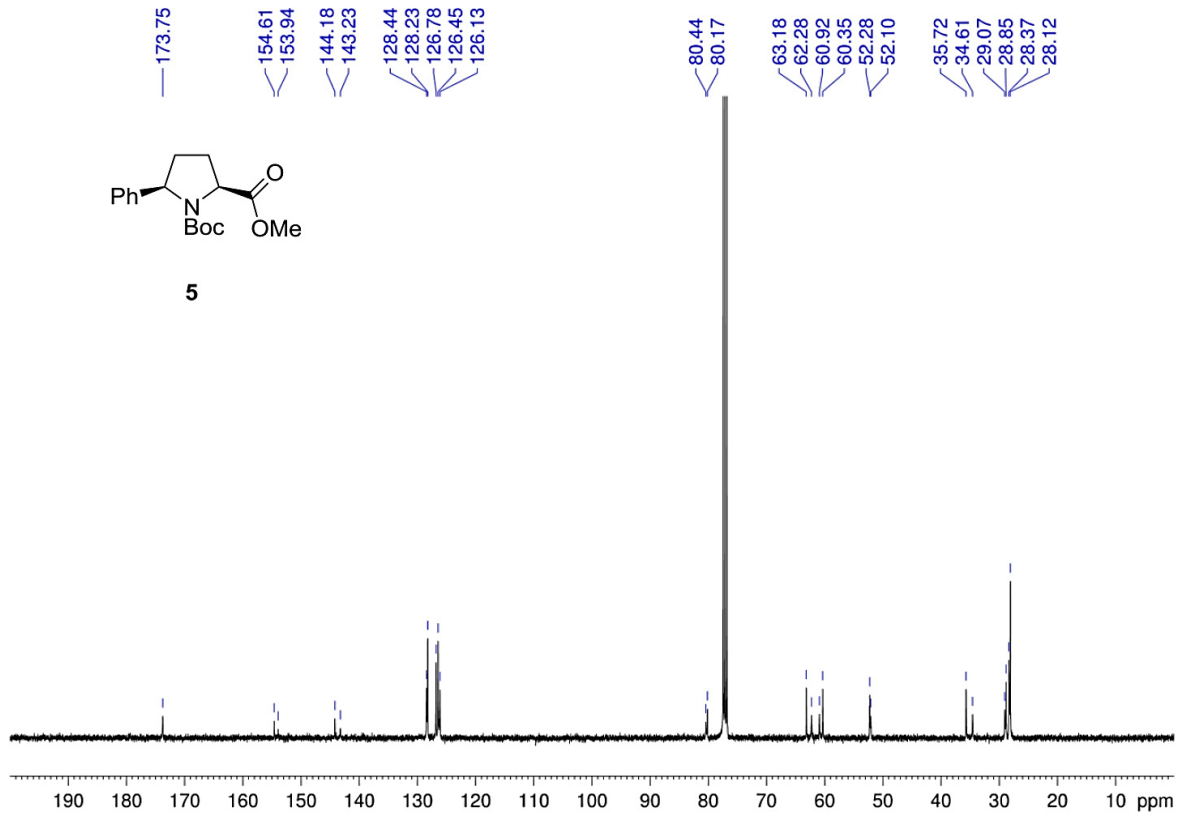
3.4.2. (*S*,*E*)-1-Nitrohept-3-en-2-ol (11b)



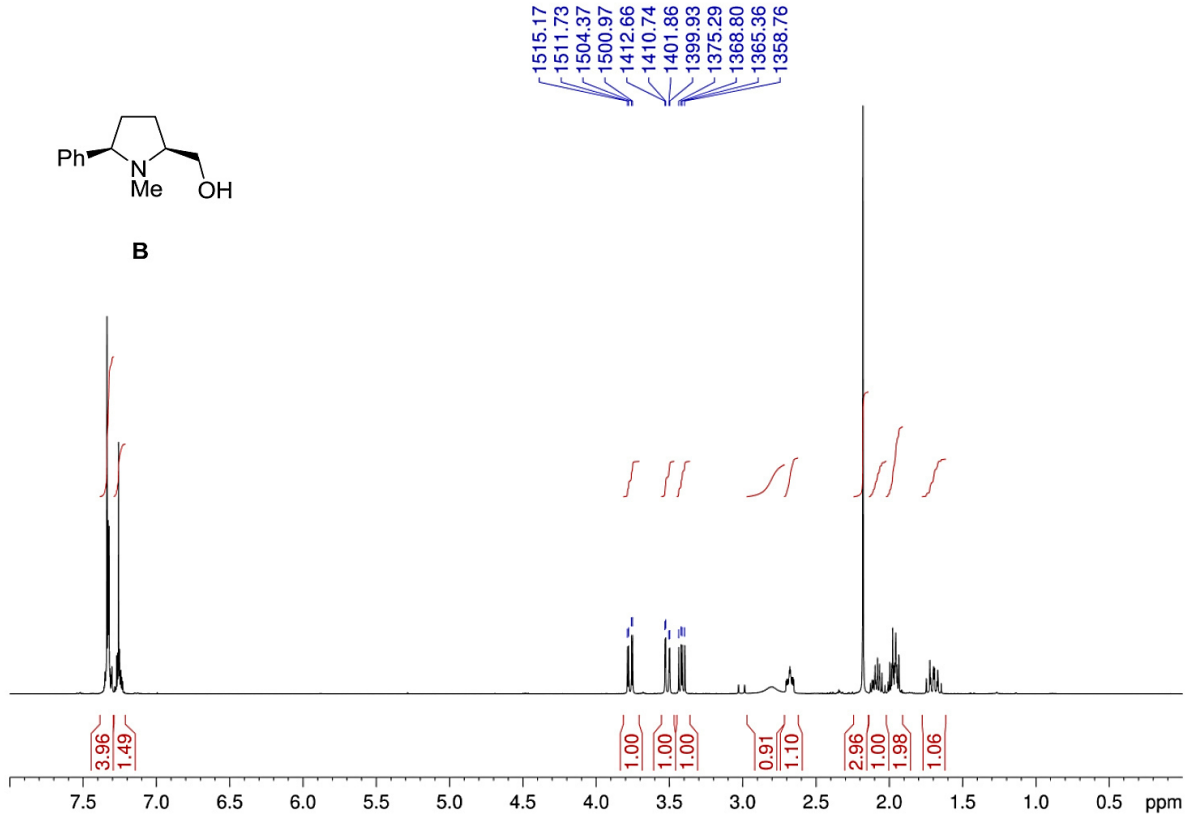
Ee = 98.7%; R_f = 0.21 (petrol ether/EtOAc 8:1); $[\alpha]_D^{28}$ = –1.4 (c = 1.00 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3H, 7-H), 1.41 (sext, *J* = 7.4 Hz, 2H, 6-H), 2.04 (q, *J* = 7.2 Hz, 2H, 5-H), 2.42 (d, *J* = 4.4 Hz, 1H, OH), 4.42 (m, 2H, CH_2NO_2), 4.82 (m, 1H, C*H*OH), 5.44 (ddt, *J* = 15.4, 6.7, 1.5 Hz, 1H, 3-H), 5.88 ppm (dtd, *J* = 15.4, 6.8, 1.0 Hz, 1H, 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7 (C-7), 22.1 (C-6), 34.4 (C-5), 69.8 (C-2), 80.2 (C-1), 126.3 (C-3), 136.1 ppm (C-4); IR (ATR): $\tilde{\nu}$ = 3415 (w), 2960 (w), 2932 (w), 2874 (w), 1671 (w), 1549 (s), 1379 (m), 1057 (w), 969 (m), 887 (w), 737 cm^{-1} (w); HRMS (EI, 70 eV, peak match): *m/z* calcd. for $[C_7H_{13}NO_3 - HNO_2]^{\bullet+}$: 112.0885, found: 112.0883.

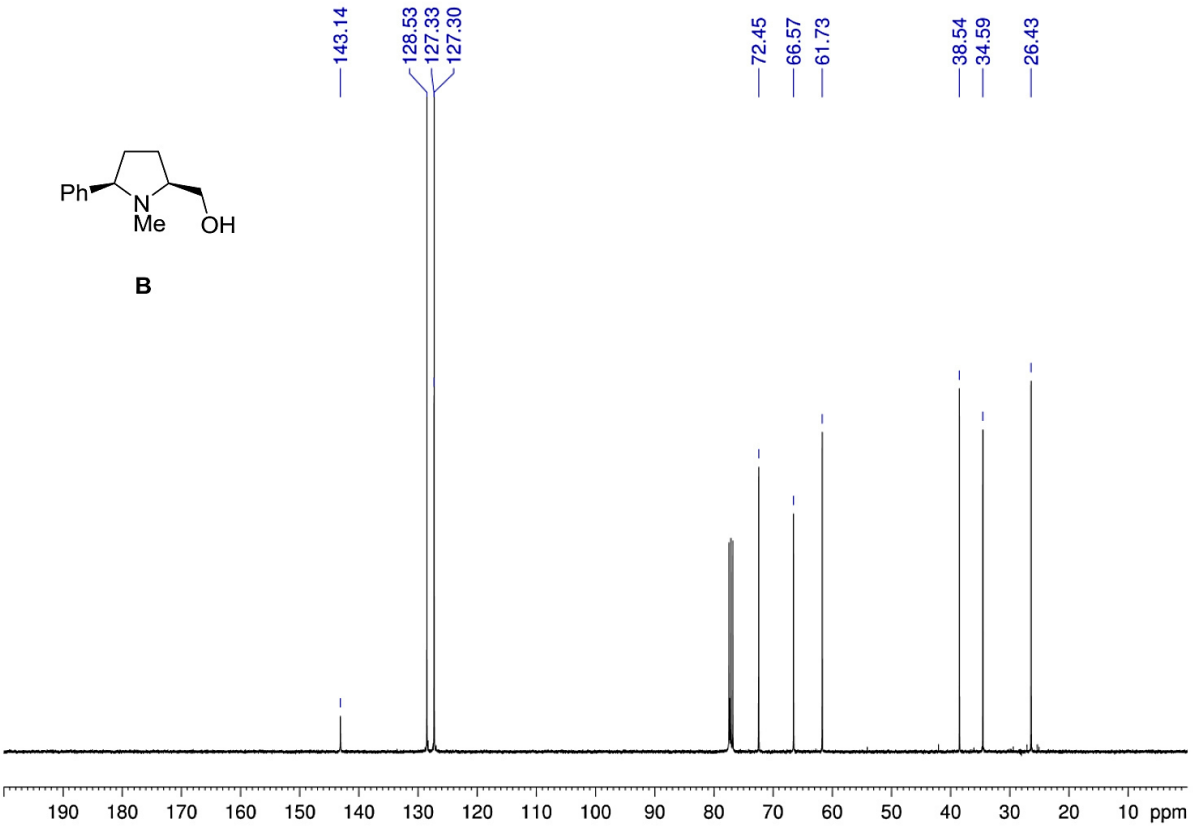
4. Copies of ^{1}H and ^{13}C NMR Spectra





11


1515.17
1511.73
1504.37
1500.97
1412.66
1410.74
1401.86
1399.93
1375.29
1368.80
1365.36
1358.76
Ph
N
Me
OH
B
3.96
1.49
1.00
1.00
1.00
0.91
1.10
2.96
1.00
1.98
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


143.14
128.53
127.33
127.30
72.45
66.57
61.73
38.54
34.59
26.43
Ph
N
Me
OH
B
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140
130
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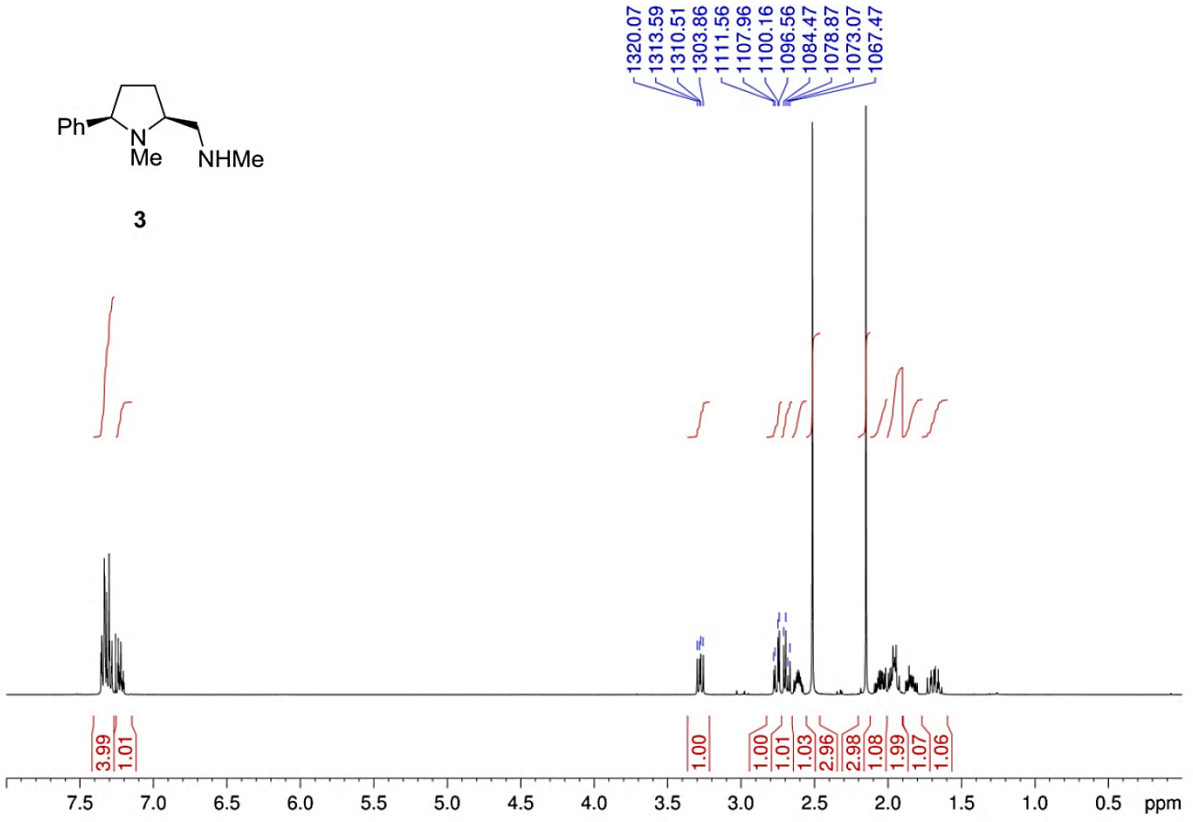
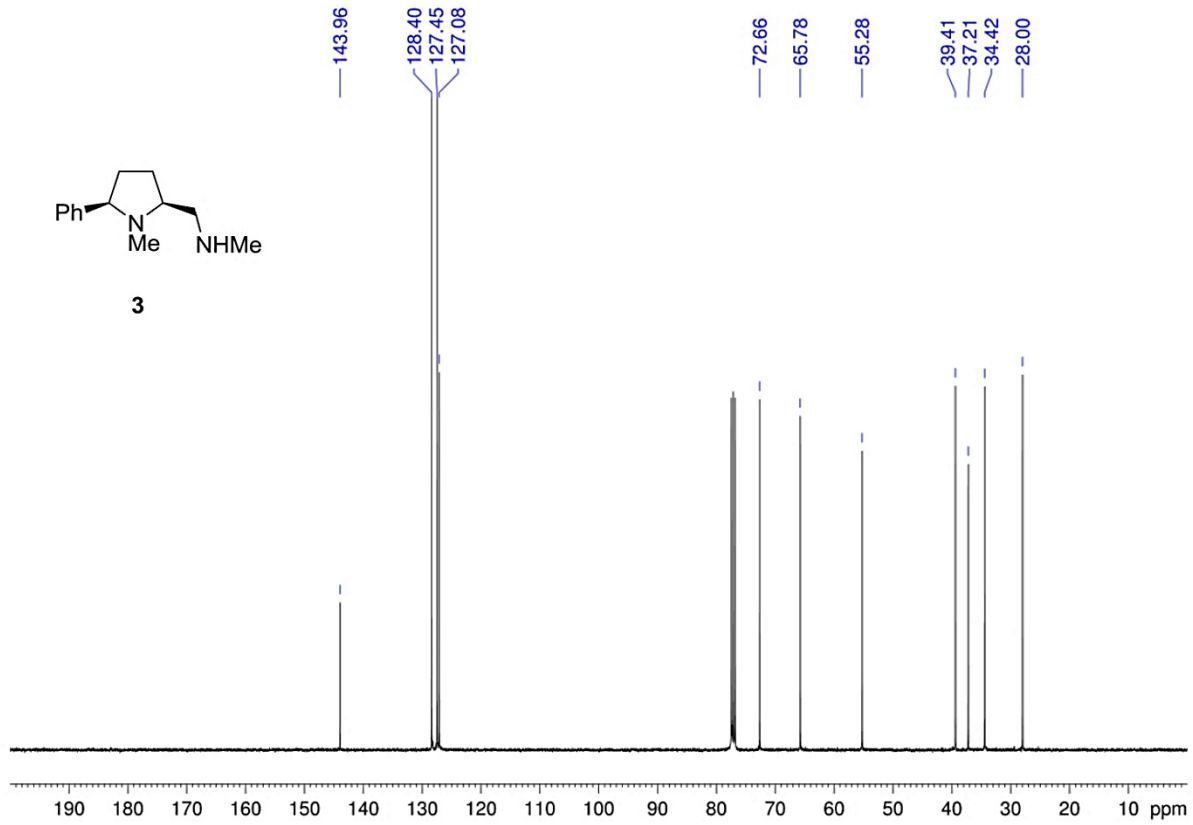
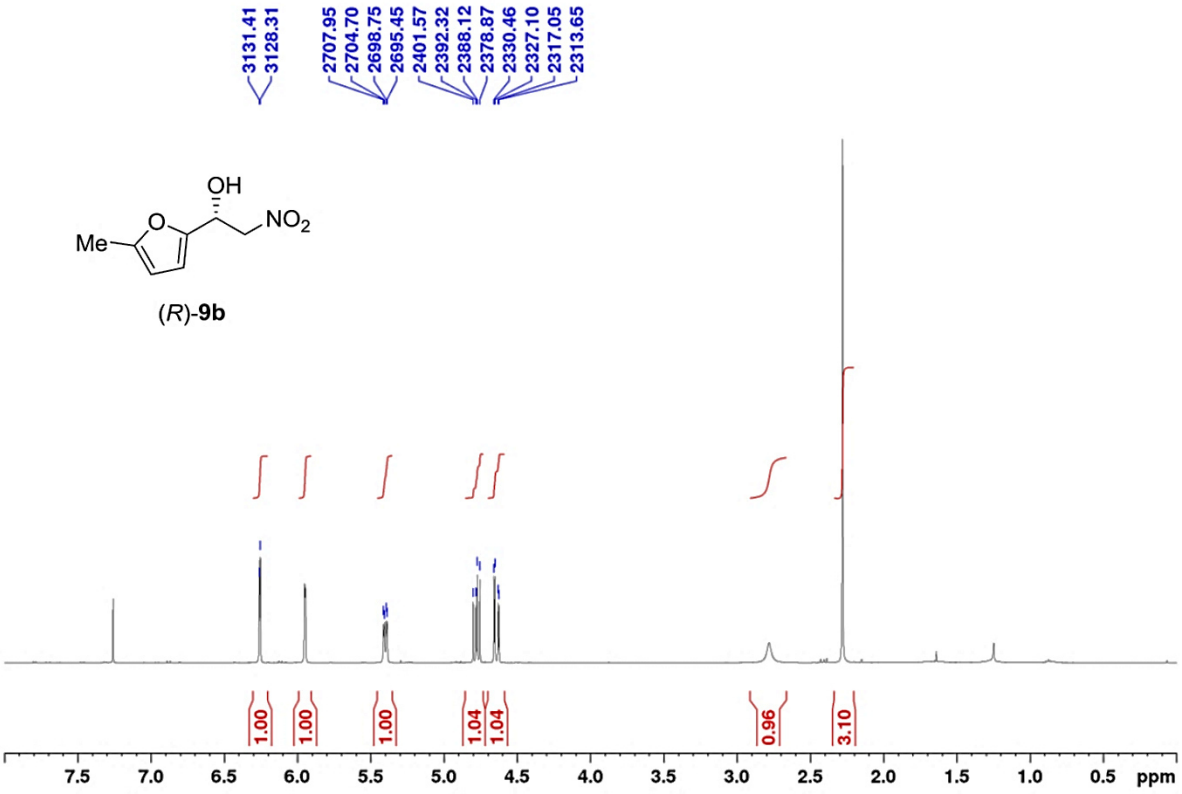
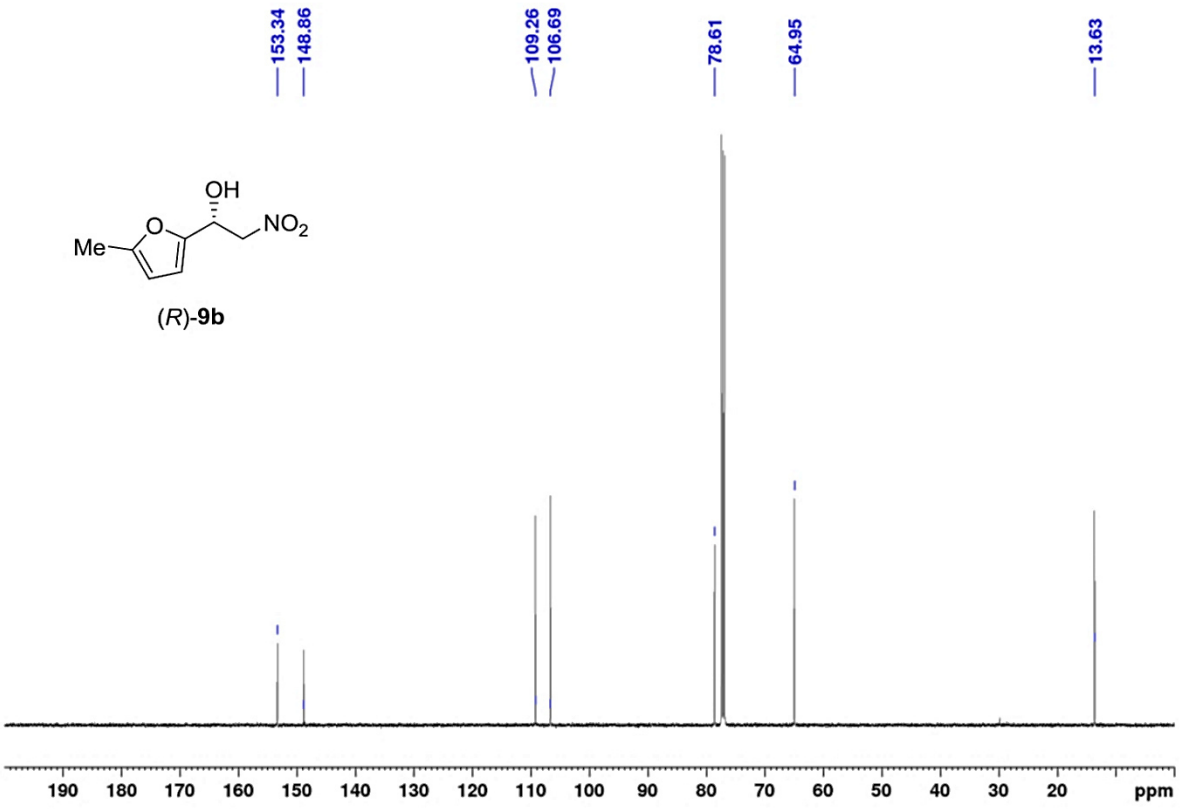
90
80
70
60
50
40
30
20
10
ppm

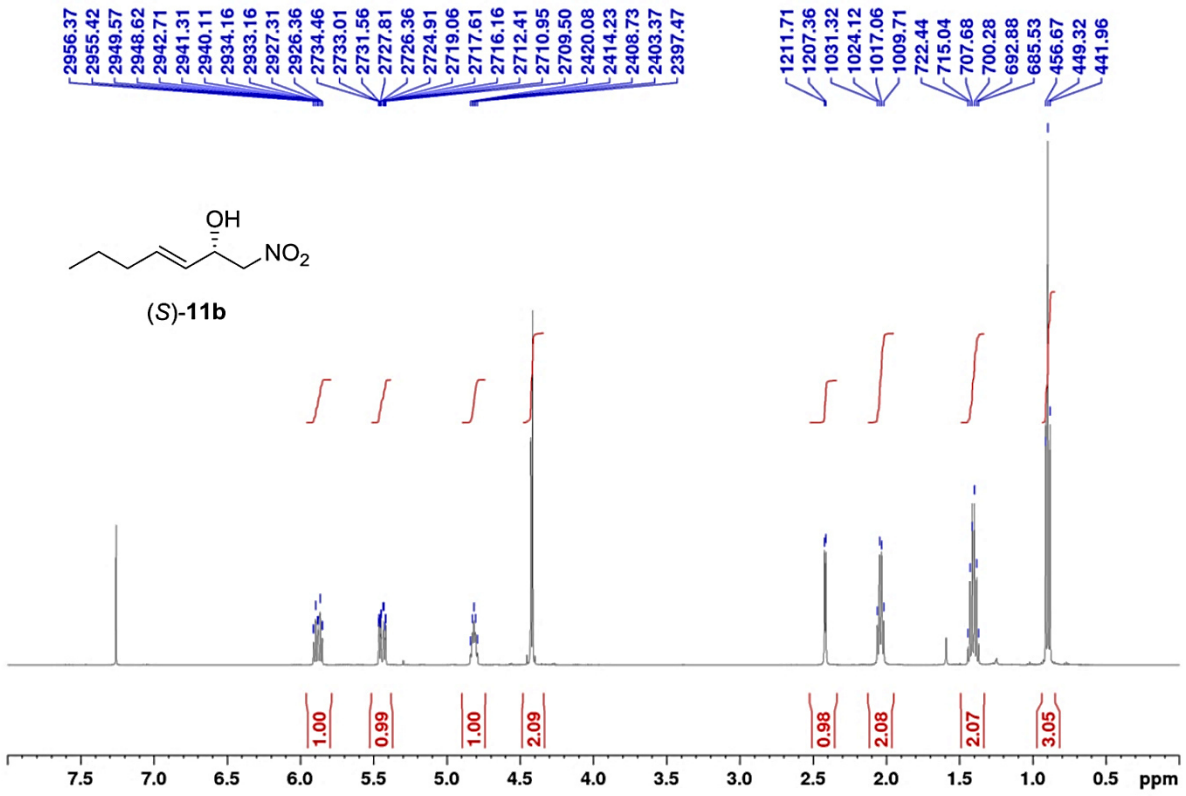

1320.07
1313.59
1310.51
1303.86
1111.56
1107.96
1100.16
1096.56
1084.47
1078.87
1073.07
1067.47
Ph
N
Me
NHMe
3
3.99
1.01
1.00
1.00
1.01
1.03
2.96
2.98
1.08
1.99
1.07
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

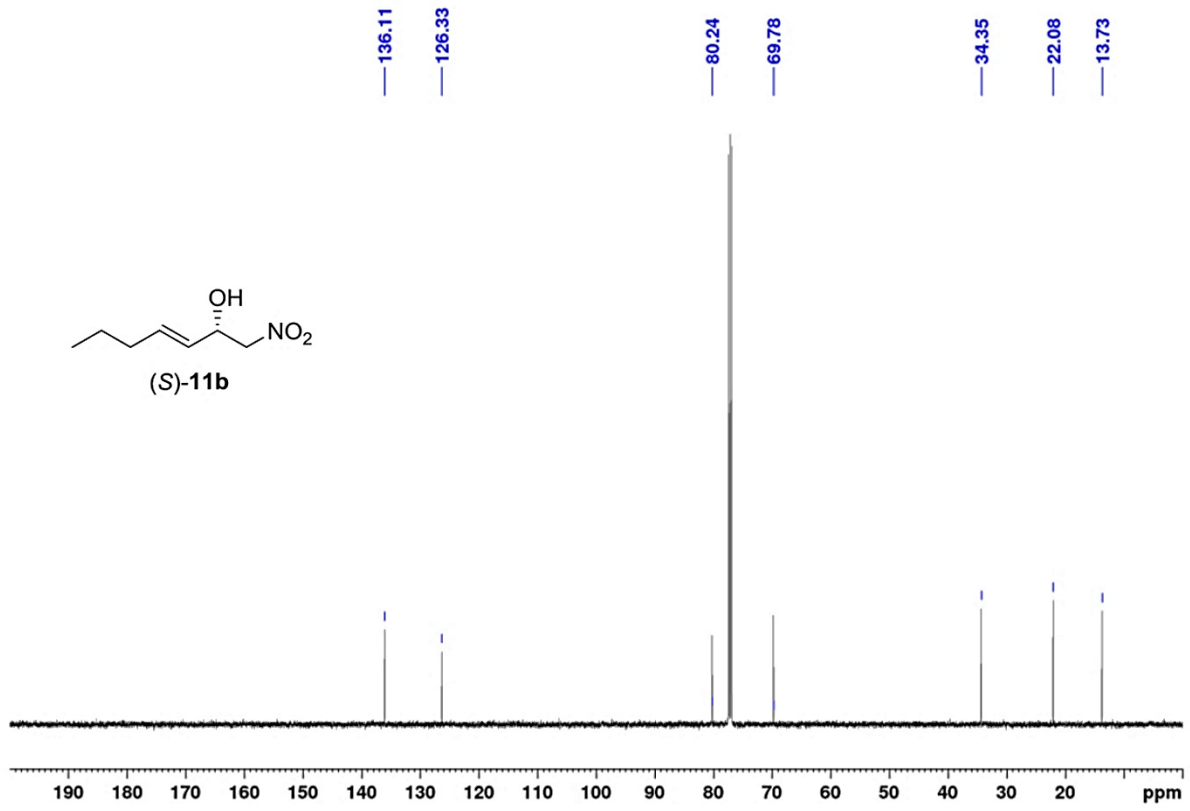

143.96
128.40
127.45
127.08
72.66
65.78
55.28
39.41
37.21
34.42
28.00
Ph
N
Me
NHMe
3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

13


3131.41
3128.31
2707.95
2704.70
2698.75
2695.45
2401.57
2392.32
2388.12
2378.87
2330.46
2327.10
2317.05
2313.65
OH
O
NO2
Me
(R)-9b
1.00
1.00
1.00
1.04
1.04
0.96
3.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

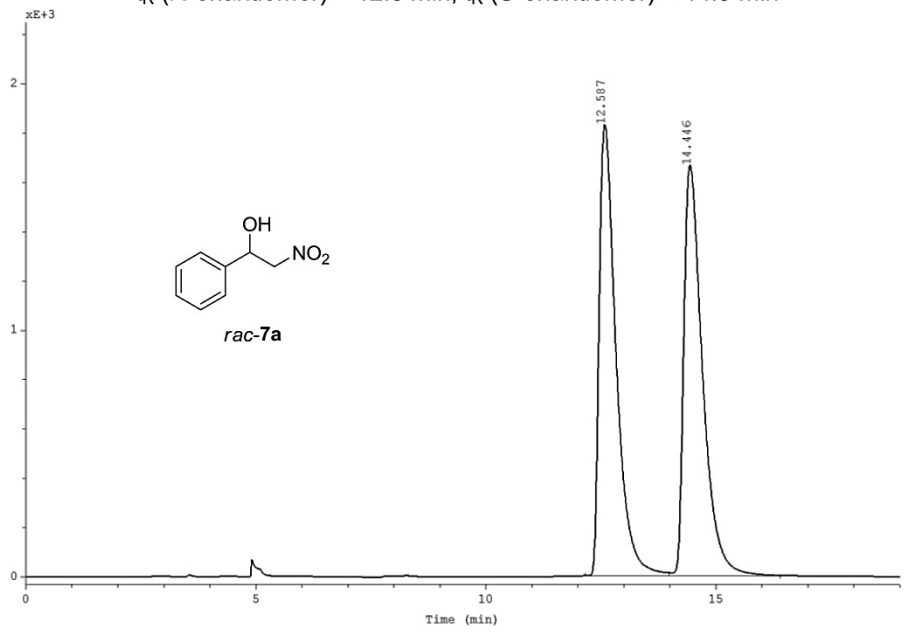

153.34
148.86
109.26
106.69
78.61
64.95
13.63
OH
O
NO2
Me
(R)-9b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


2956.37
2955.42
2949.57
2948.62
2942.71
2941.31
2940.11
2934.16
2933.16
2927.31
2926.36
2734.46
2733.01
2731.56
2727.81
2726.36
2724.91
2719.06
2717.61
2716.16
2712.41
2710.95
2709.50
2420.08
2414.23
2408.73
2403.37
2397.47
1211.71
1207.36
1031.32
1024.12
1017.06
1009.71
722.44
715.04
707.68
700.28
692.88
685.53
456.67
449.32
441.96
OH
NO2
(S)-11b
1.00
0.99
1.00
2.09
0.98
2.08
2.07
3.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

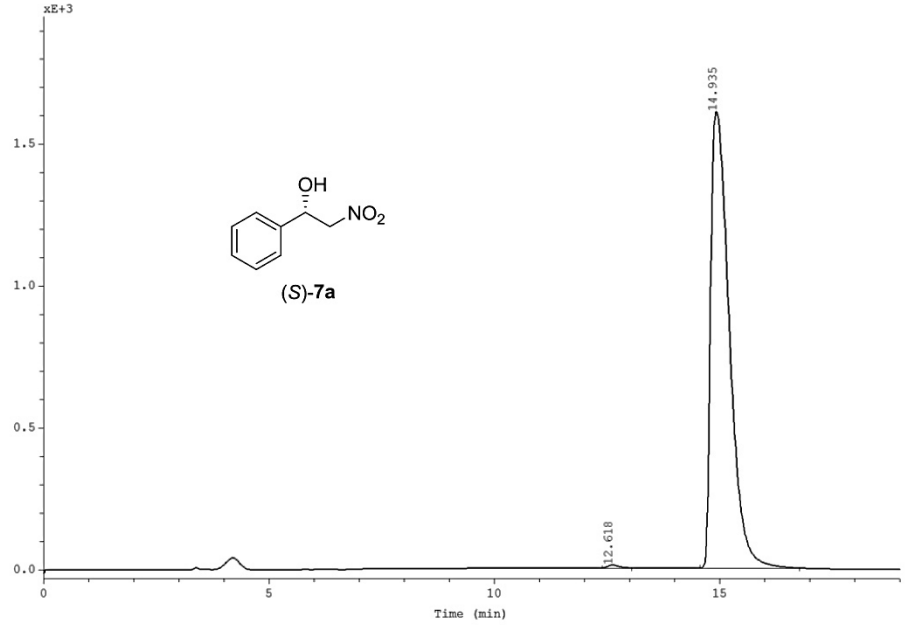

136.11
126.33
80.24
69.78
34.35
22.08
13.73
OH
NO2
(S)-11b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

5. Copies of HPLC Spectra

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.8 mL/min, 215 nm:
t_R (*R*-enantiomer) = 12.6 min; t_R (*S*-enantiomer) = 14.9 min

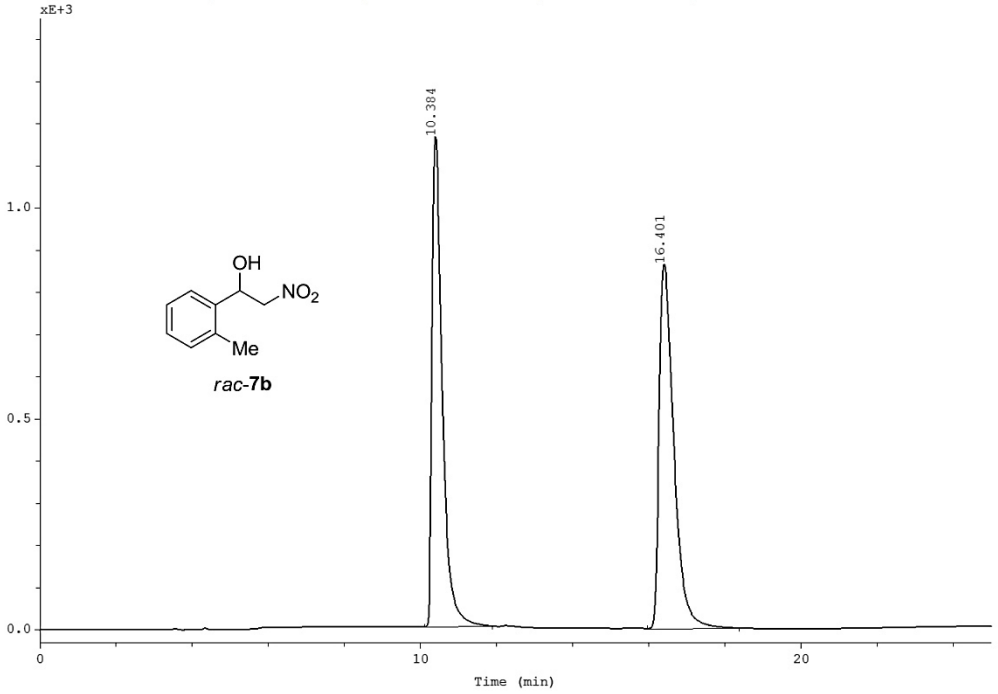


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.59	12.16	13.98	1831.20	780.62	52.38	49.81
2	14.45	13.98	16.40	1665.09	786.54	47.62	50.19

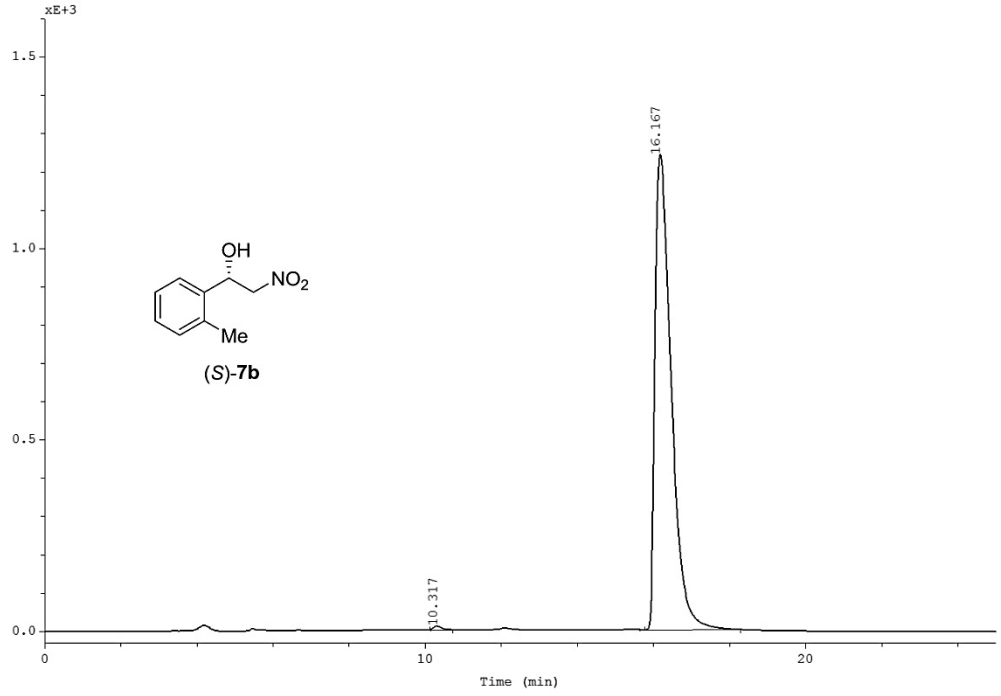


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.62	12.39	13.05	10.32	2.86	0.64	0.37
2	14.93	14.56	16.77	1609.83	767.79	99.36	99.63

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 10.3 min; t_R (*S*-enantiomer) = 16.2 min



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.38	10.10	11.88	1162.30	364.12	57.35	48.51
2	16.40	15.96	18.37	864.51	386.44	42.65	51.49



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.32	10.12	10.72	9.85	2.43	0.79	0.40
2	16.17	15.76	18.29	1240.90	613.36	99.21	99.60

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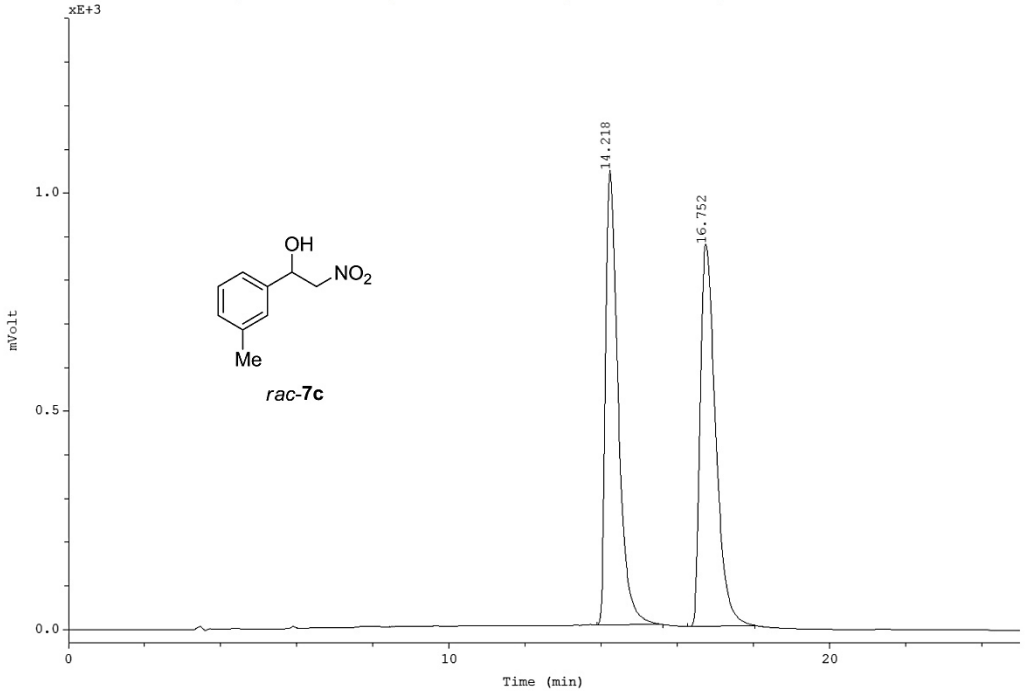
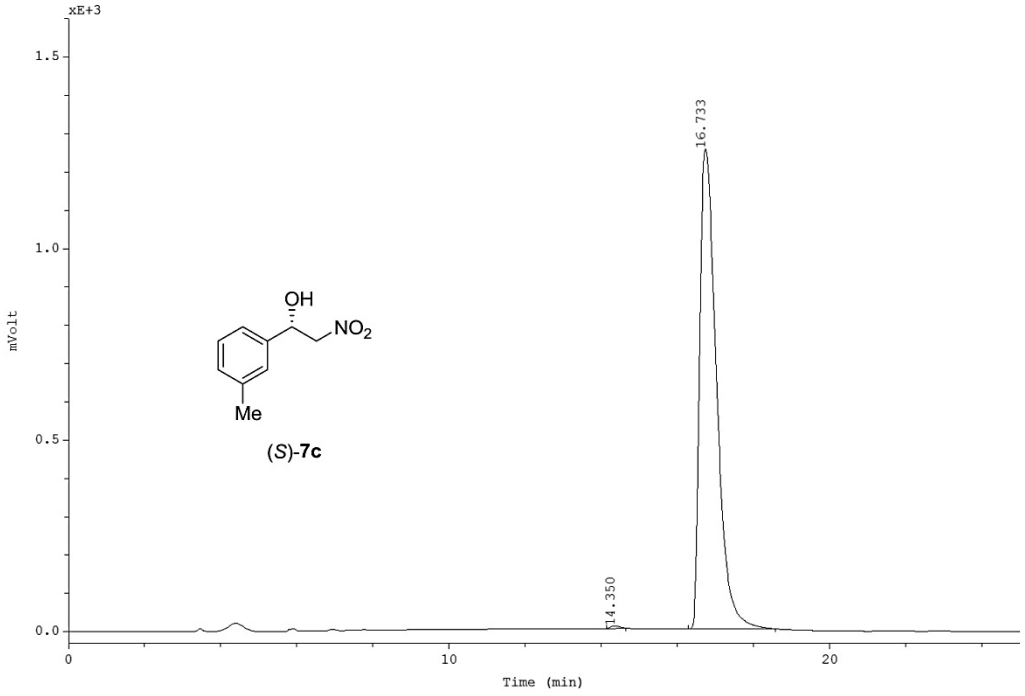
Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 14.4 min; t_R (*S*-enantiomer) = 16.7 min



rac-**7c**

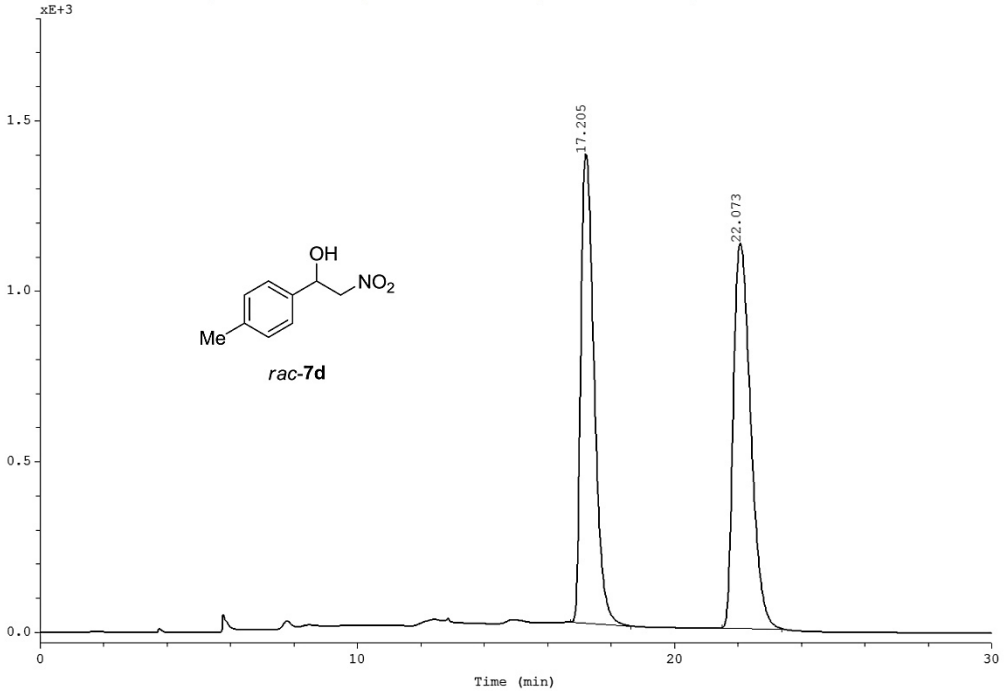
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.22	13.88	15.62	1040.79	401.61	54.35	49.45
2	16.75	16.26	18.03	874.27	410.58	45.65	50.55



(*S*)-**7c**

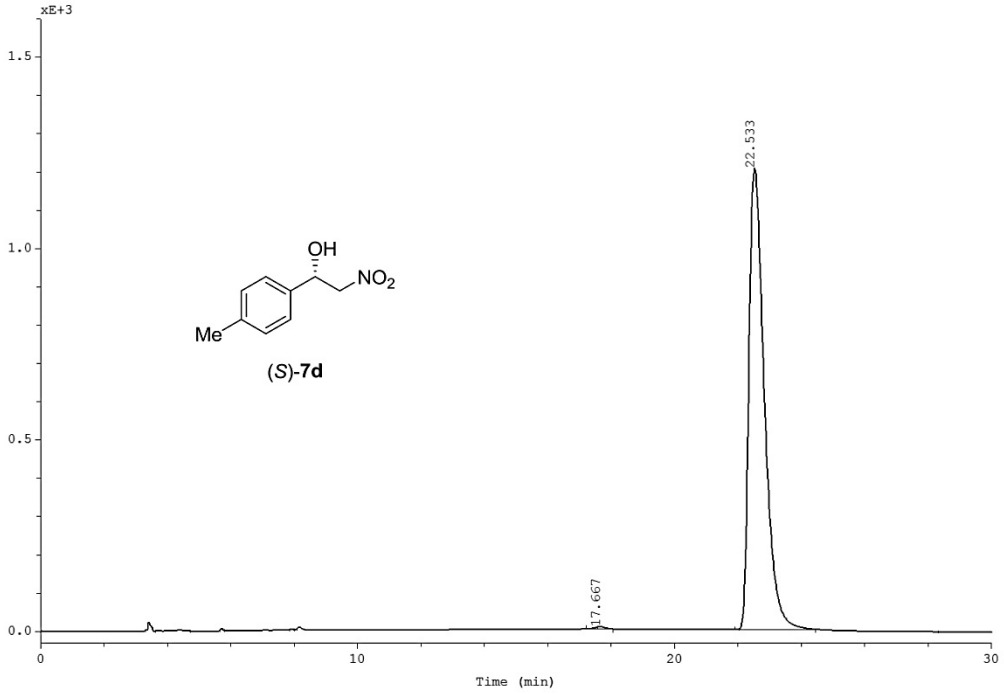
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.35	14.14	14.63	6.58	1.75	0.52	0.27
2	16.73	16.28	18.57	1253.18	640.34	99.48	99.73

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 17.7 min; t_R (*S*-enantiomer) = 22.5 min



rac-**7d**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	17.20	16.73	18.62	1376.24	672.41	54.93	48.51
2	22.07	21.49	23.38	1129.06	713.66	45.07	51.49



(*S*)-**7d**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	17.67	17.22	18.05	5.47	1.93	0.45	0.28
2	22.53	21.91	24.46	1205.63	679.96	99.55	99.72

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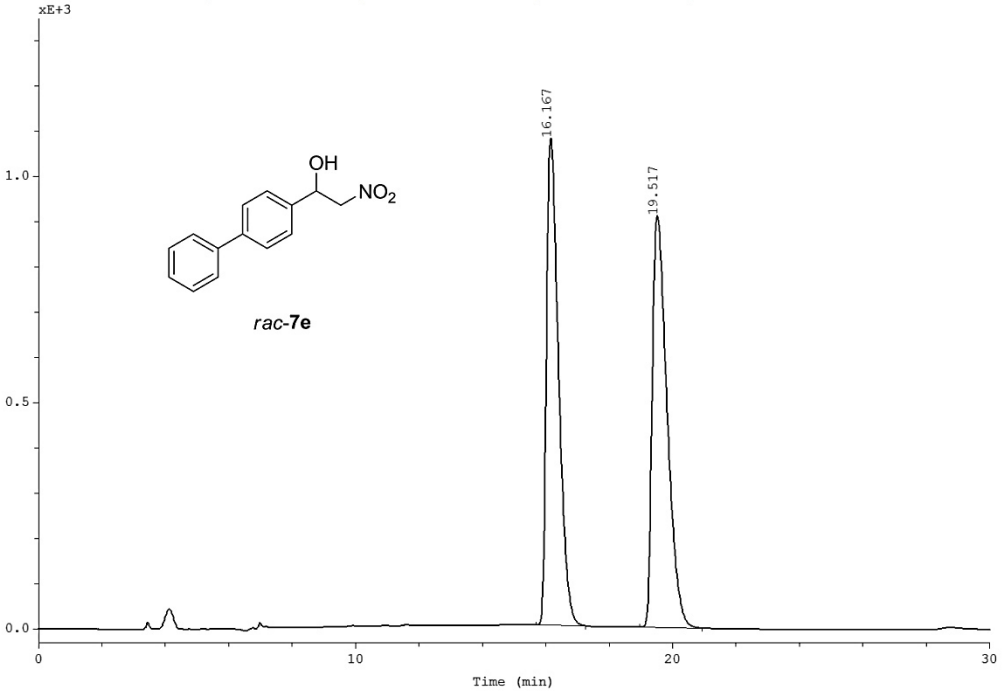
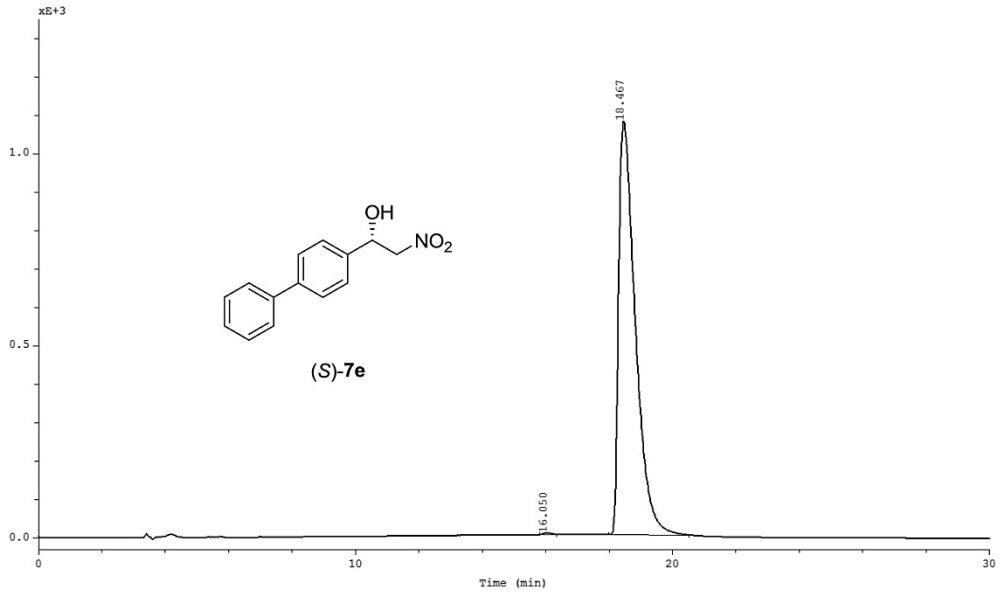
Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 16.1 min; t_R (*S*-enantiomer) = 18.5 min

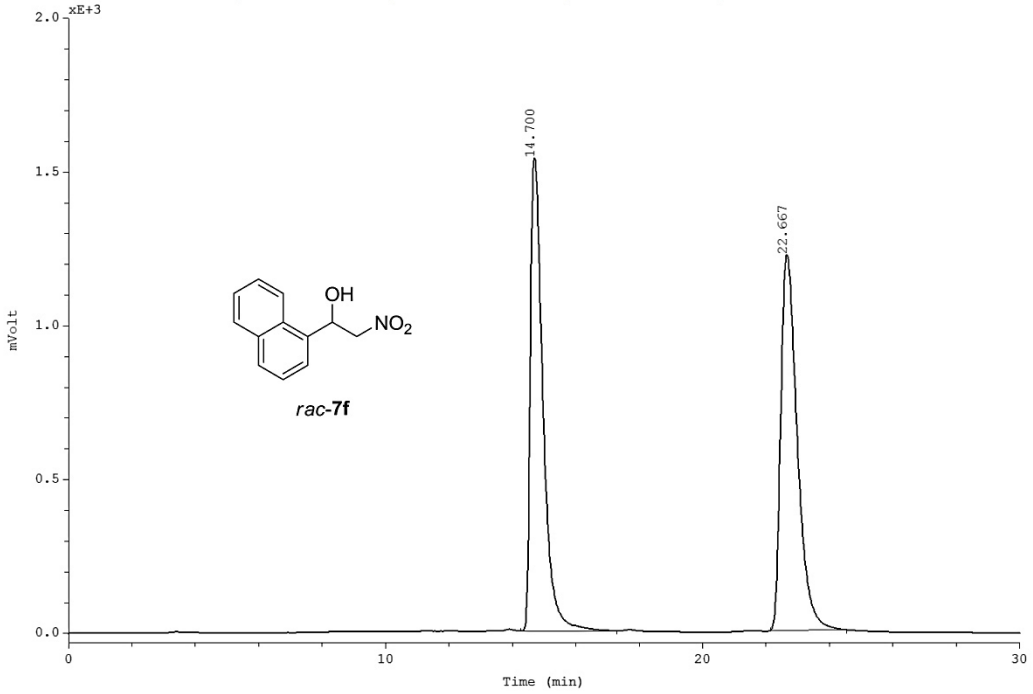


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	16.17	15.69	17.25	1076.49	474.73	54.17	48.99
2	19.52	18.96	20.93	910.74	494.41	45.83	51.01



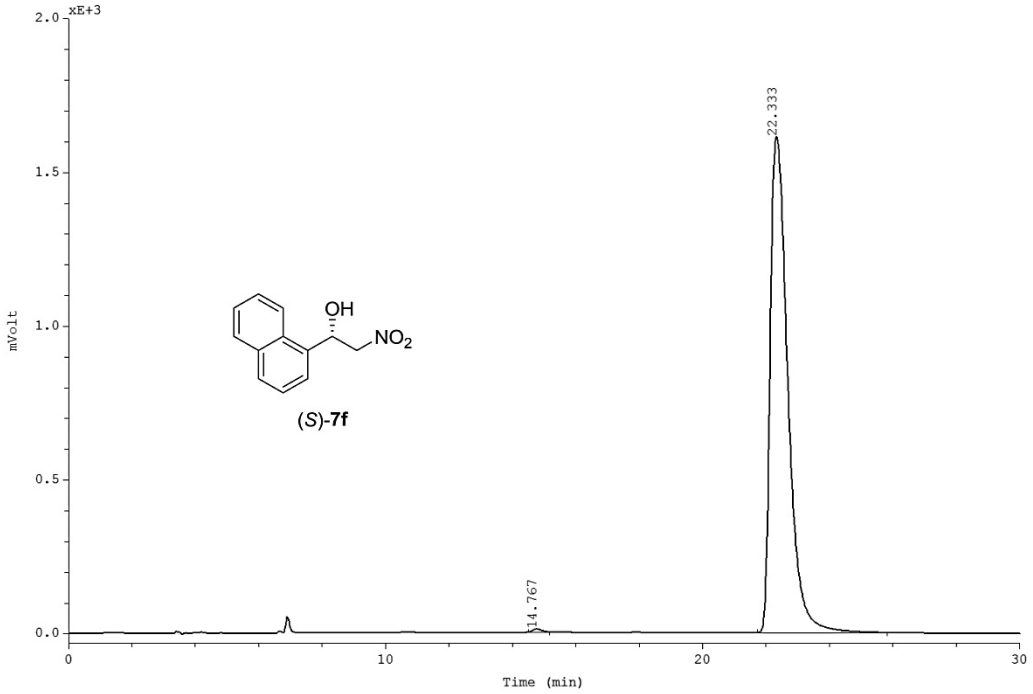
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	16.05	15.80	16.34	4.32	1.28	0.40	0.19
2	18.47	17.98	20.53	1076.75	655.12	99.60	99.81

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 14.8 min; t_R (*S*-enantiomer) = 22.3 min



rac-**7f**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.70	14.27	17.29	1538.67	714.07	55.73	49.21
2	22.67	22.15	24.54	1222.22	737.10	44.27	50.79

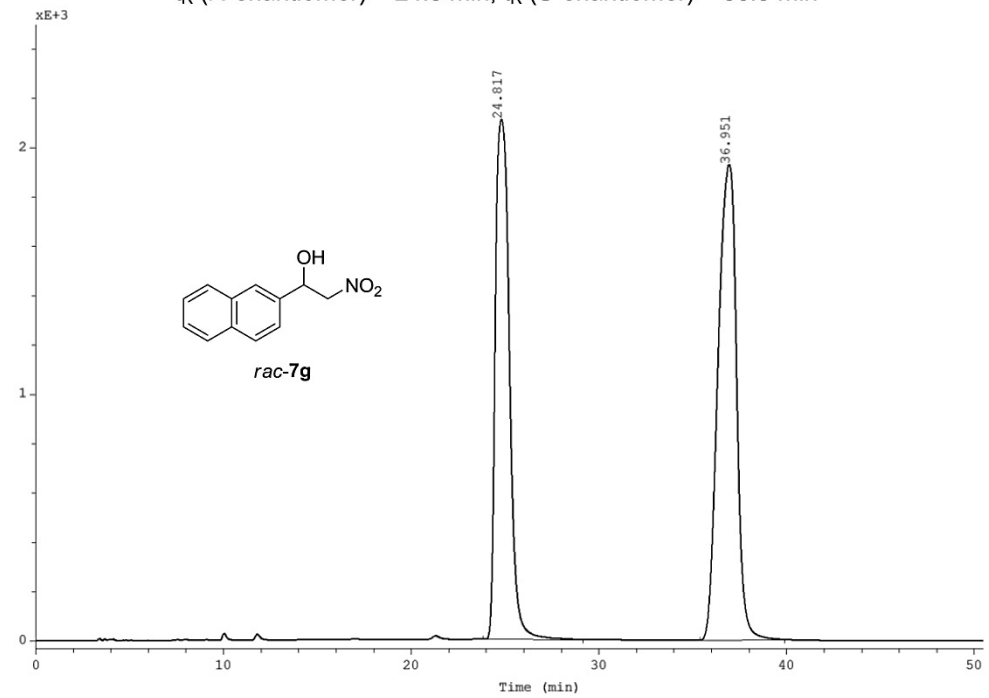


(*S*)-**7f**

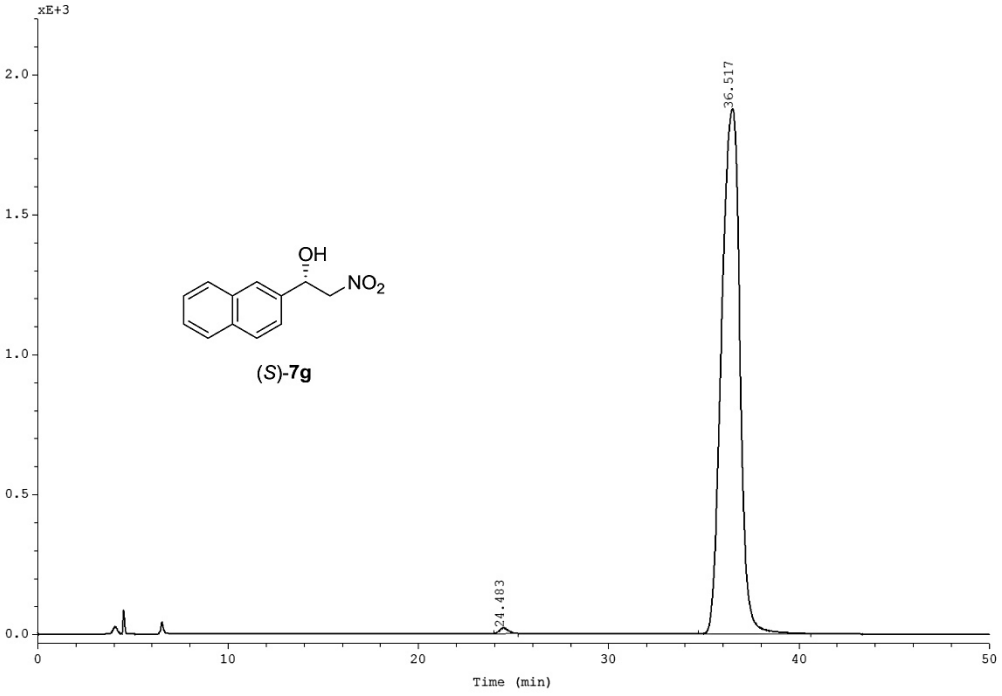
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.77	14.51	15.17	9.96	3.19	0.61	0.31
2	22.33	21.74	25.83	1613.72	1040.01	99.39	99.69

21

Chiralcel OD-3, *n*-hexane/*i*PrOH 80:20, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 24.5 min; t_R (*S*-enantiomer) = 36.5 min

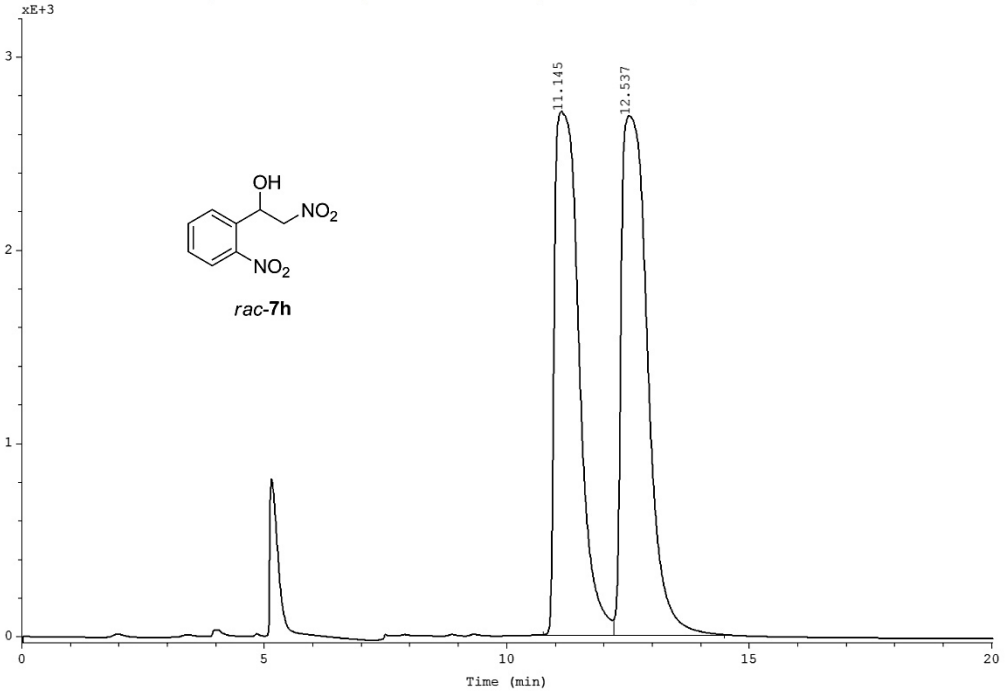


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	24.82	23.83	29.16	2108.09	1822.63	52.23	45.19
2	36.95	35.41	39.89	1928.16	2210.96	47.77	54.81

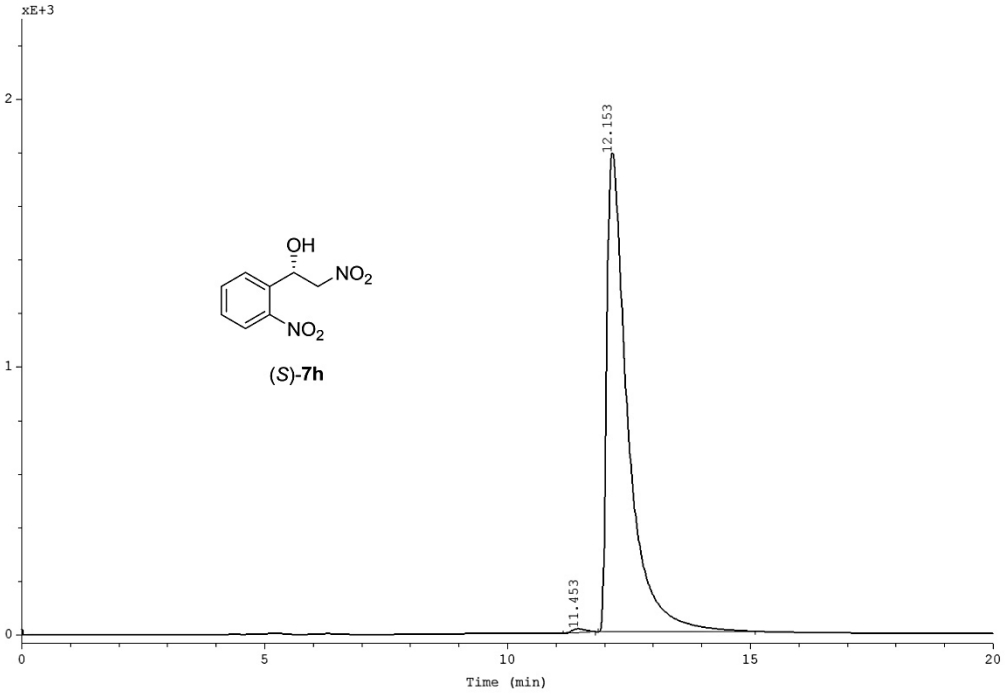


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	24.48	23.96	25.23	19.78	10.91	1.04	0.52
2	36.52	34.72	40.61	1874.37	2081.89	98.96	99.48

Chiralcel OD-3, *n*-hexane/*i*PrOH 80:20, 0.7 mL/min, 215 nm:
t_R (*R*-enantiomer) = 11.5 min; t_R (*S*-enantiomer) = 12.2 min



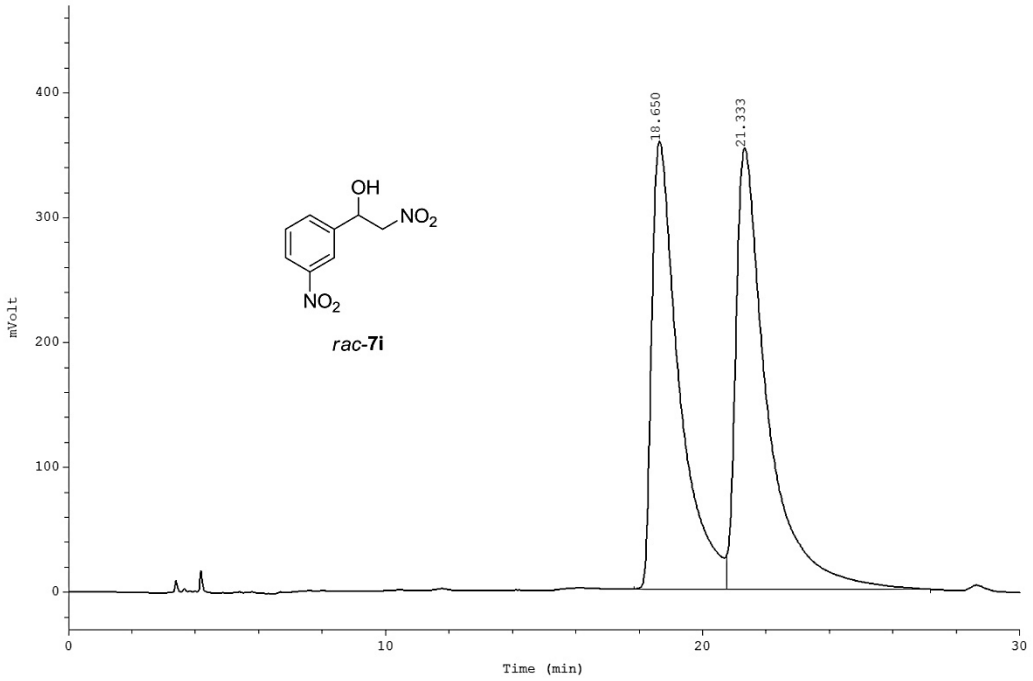
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.14	10.76	12.21	2710.17	1575.84	50.22	48.33
2	12.54	12.21	14.49	2686.59	1684.53	49.78	51.67



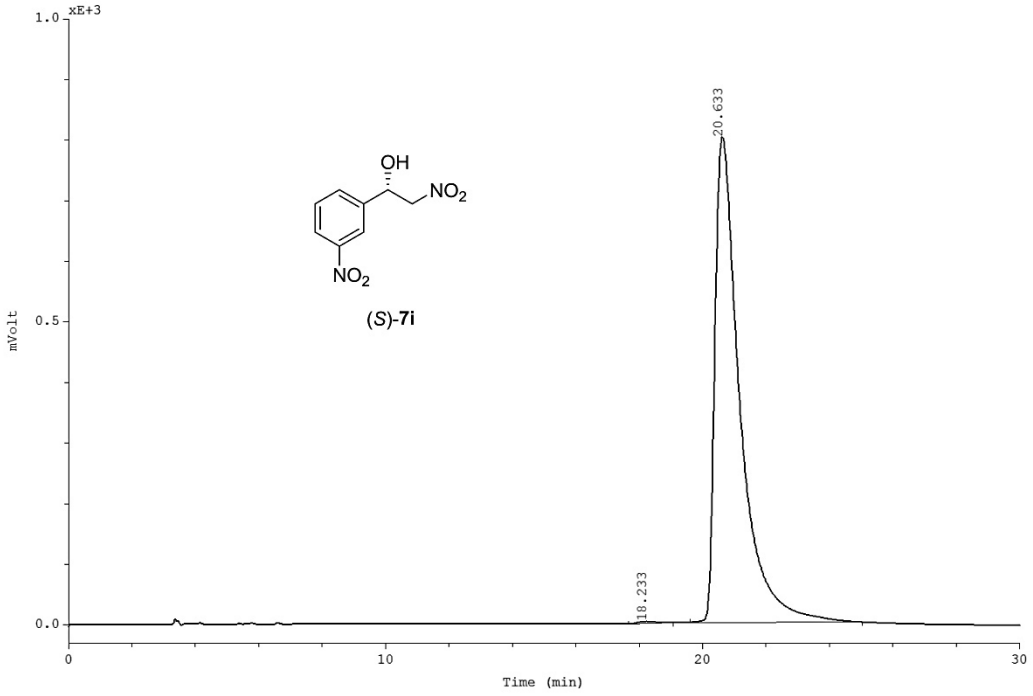
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.45	11.14	11.81	13.83	4.51	0.77	0.50
2	12.15	11.87	15.10	1785.65	897.70	99.23	99.50

23

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 18.2 min; t_R (*S*-enantiomer) = 20.6 min

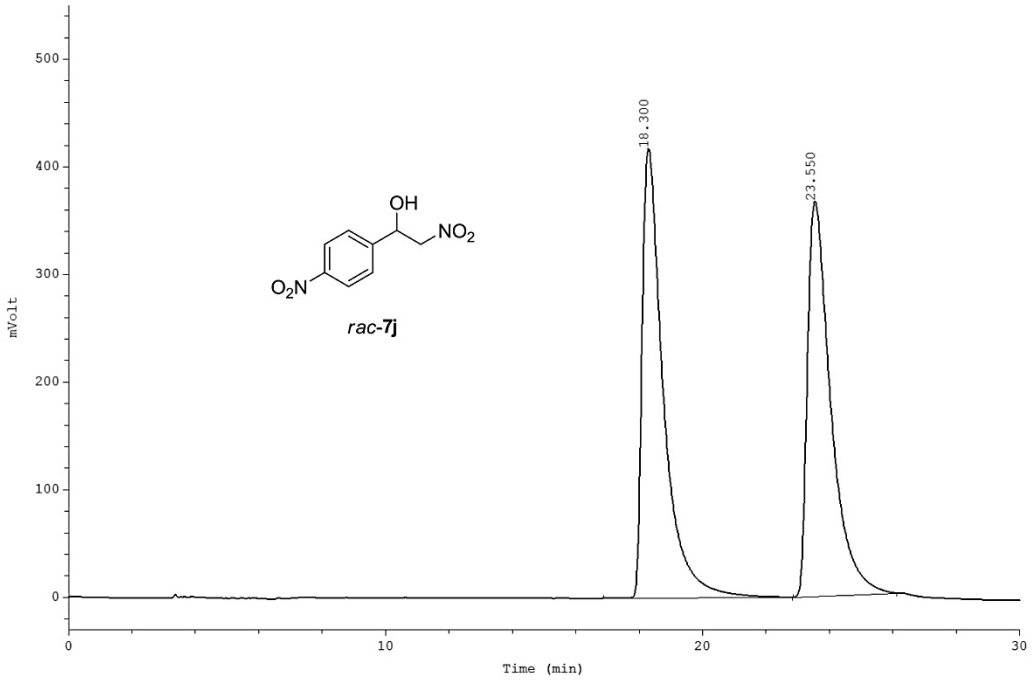


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	18.65	17.84	20.75	358.87	360.39	50.38	47.07
2	21.33	20.75	27.19	353.53	405.22	49.63	52.93

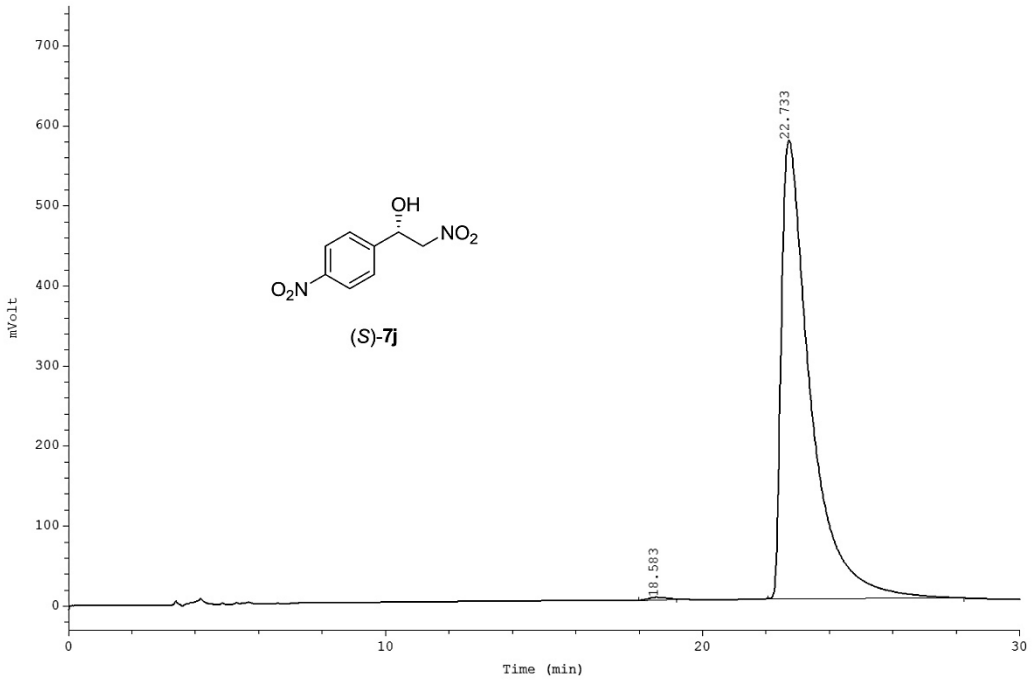


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	18.23	17.65	19.07	3.39	2.19	0.42	0.30
2	20.63	19.62	25.04	800.89	729.32	99.58	99.70

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 18.6 min; t_R (*S*-enantiomer) = 22.7 min



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	18.30	16.88	22.83	418.14	325.02	53.25	50.94
2	23.55	22.87	26.12	367.11	313.04	46.75	49.06



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	18.58	17.98	19.18	2.84	1.78	0.49	0.29
2	22.73	22.06	28.24	573.10	607.04	99.51	99.71

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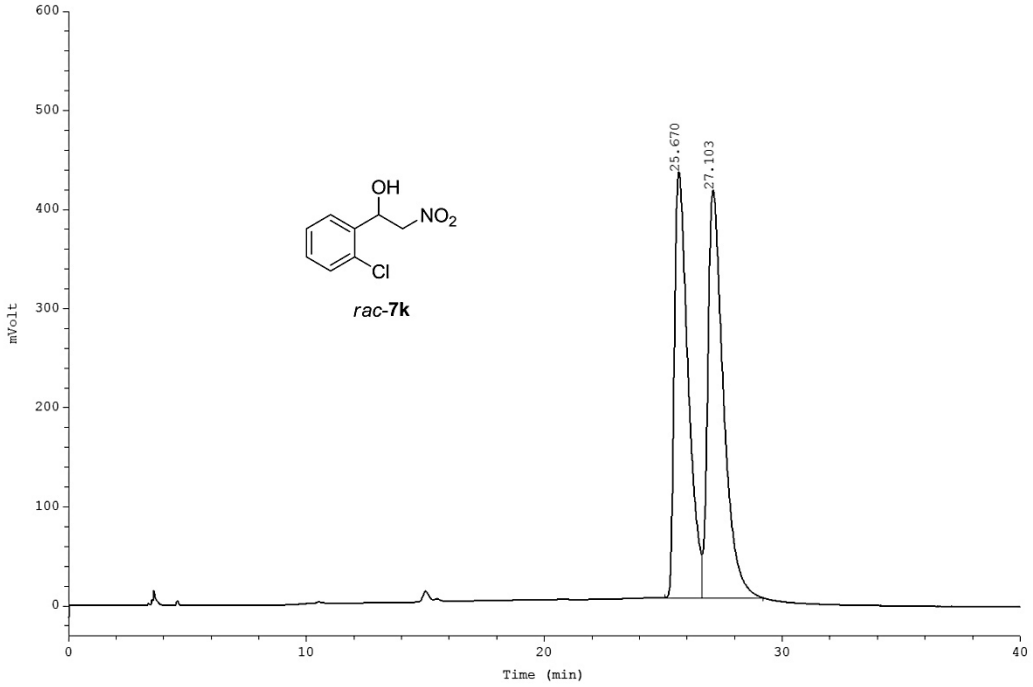
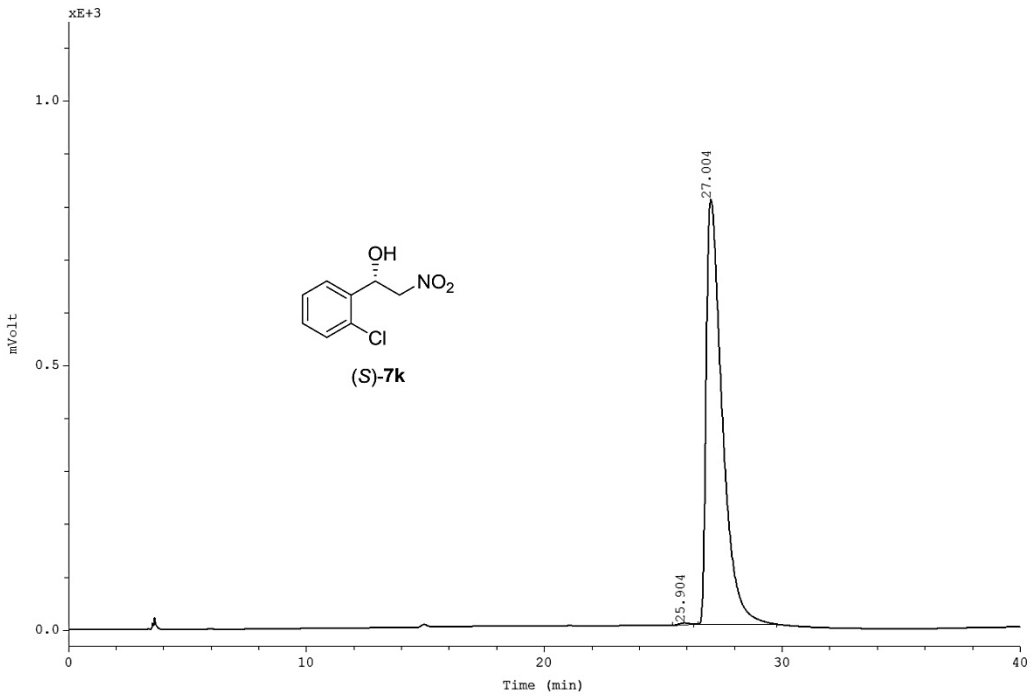
Chiralcel OD-3, *n*-hexane/*i*PrOH 97:3, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 25.9 min; t_R (*S*-enantiomer) = 27.0 min

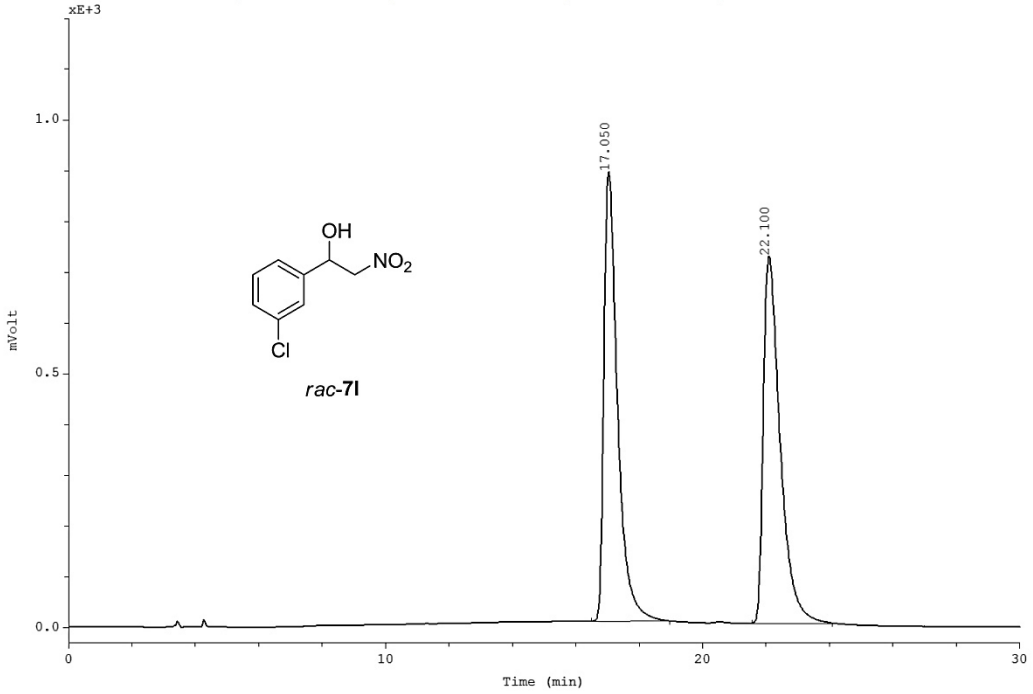


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	25.67	25.06	26.63	429.59	287.24	51.07	47.77
2	27.10	26.63	29.20	411.57	314.01	48.93	52.23



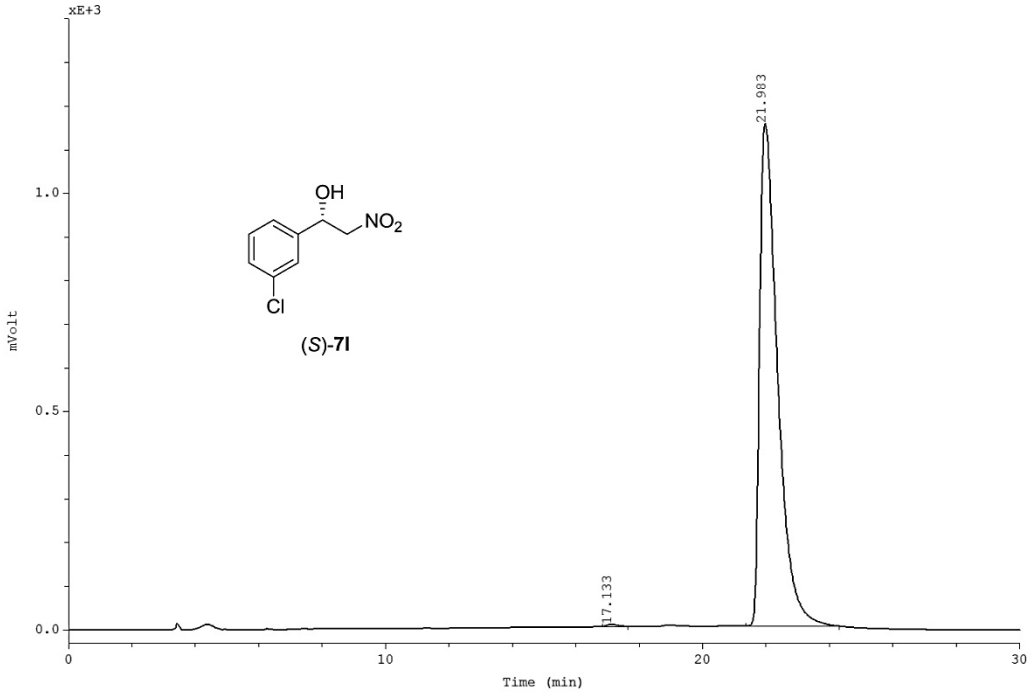
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	25.90	25.39	26.29	3.15	1.40	0.39	0.22
2	27.00	26.44	29.77	803.87	625.77	99.61	99.78

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 17.1 min; t_R (*S*-enantiomer) = 22.0 min



rac-**7l**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	17.05	16.49	18.96	885.84	441.20	55.04	49.73
2	22.10	21.55	24.10	723.73	445.92	44.96	50.27

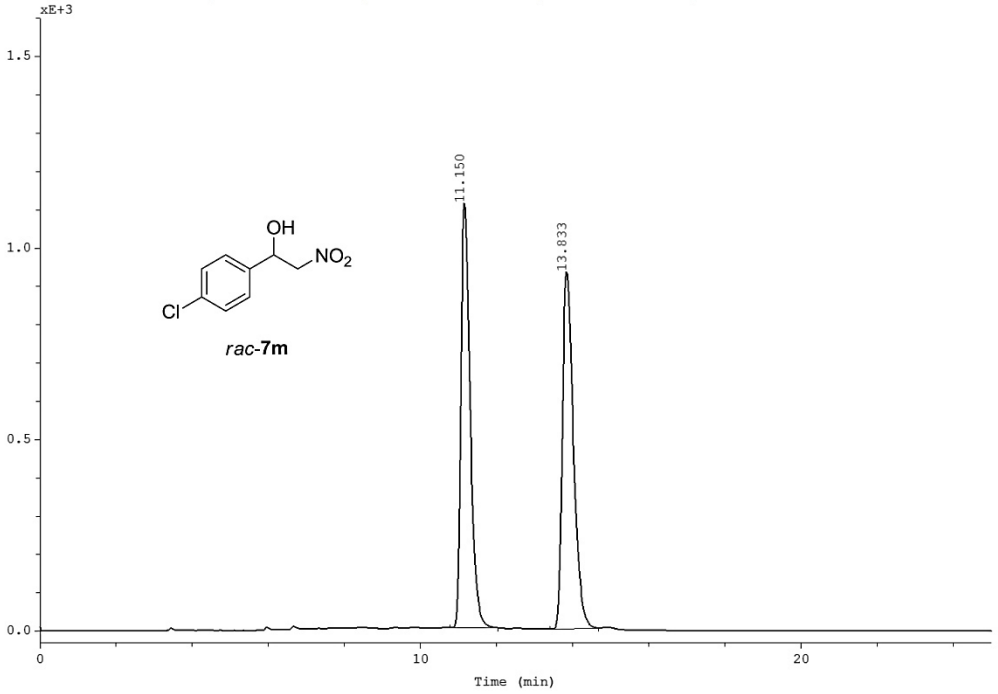


(*S*)-**7l**

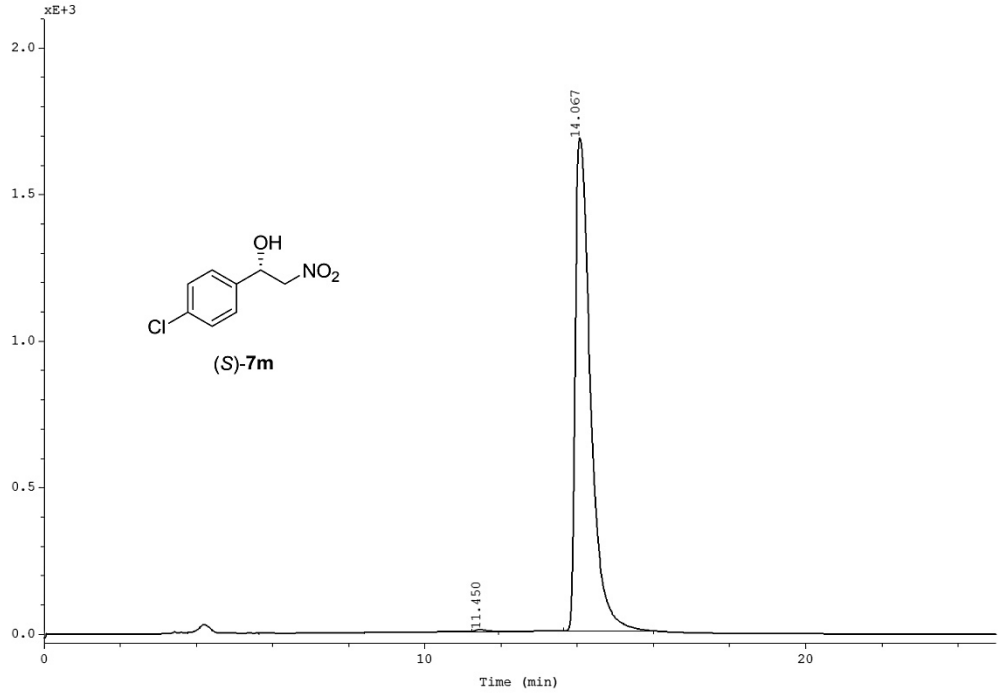
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	17.13	16.85	17.65	4.84	1.90	0.42	0.25
2	21.98	21.37	24.31	1150.93	758.59	99.58	99.75

27

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 11.5 min; t_R (*S*-enantiomer) = 14.1 min

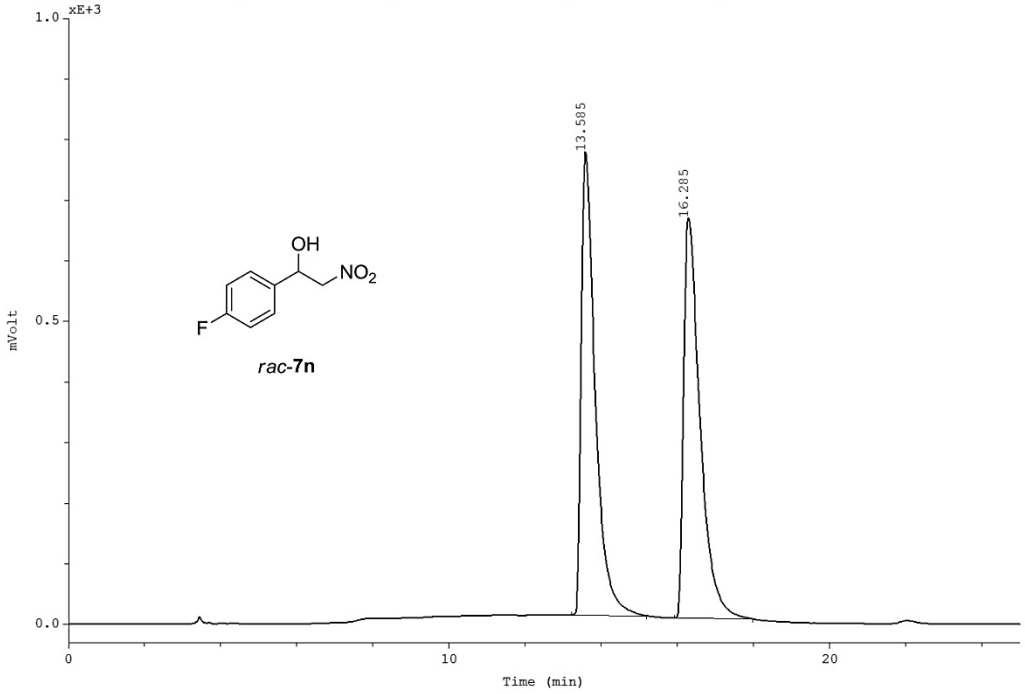


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.15	10.76	12.04	1108.84	312.44	54.33	49.86
2	13.83	13.40	14.67	932.05	314.24	45.67	50.14

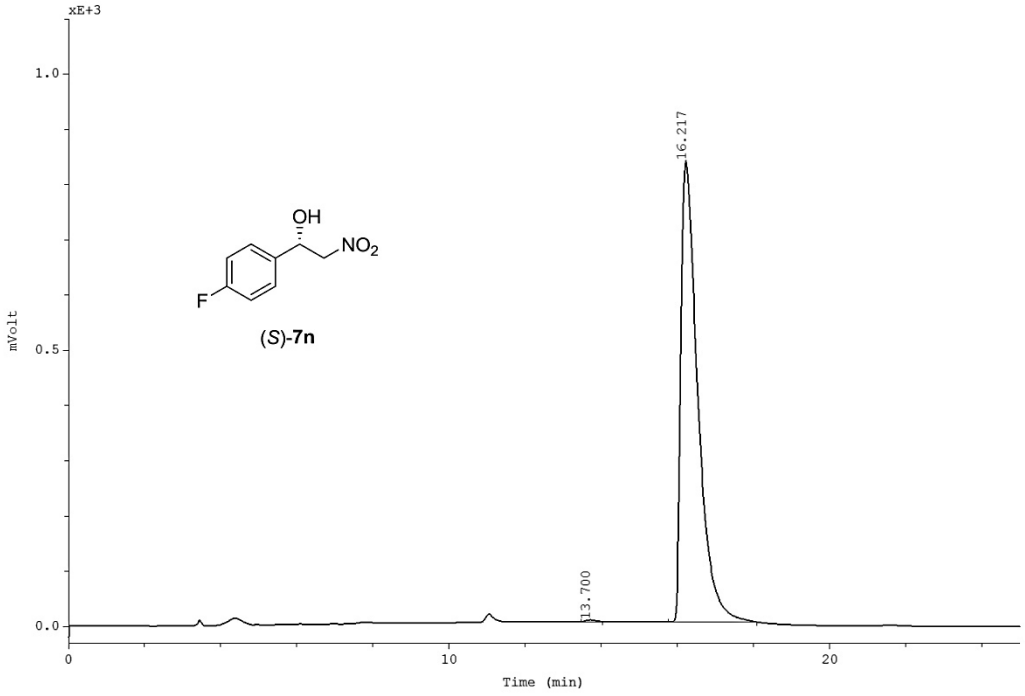


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.45	11.22	11.94	7.00	2.13	0.41	0.27
2	14.07	13.64	16.01	1681.56	784.33	99.59	99.73

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 13.7 min; t_R (*S*-enantiomer) = 16.2 min



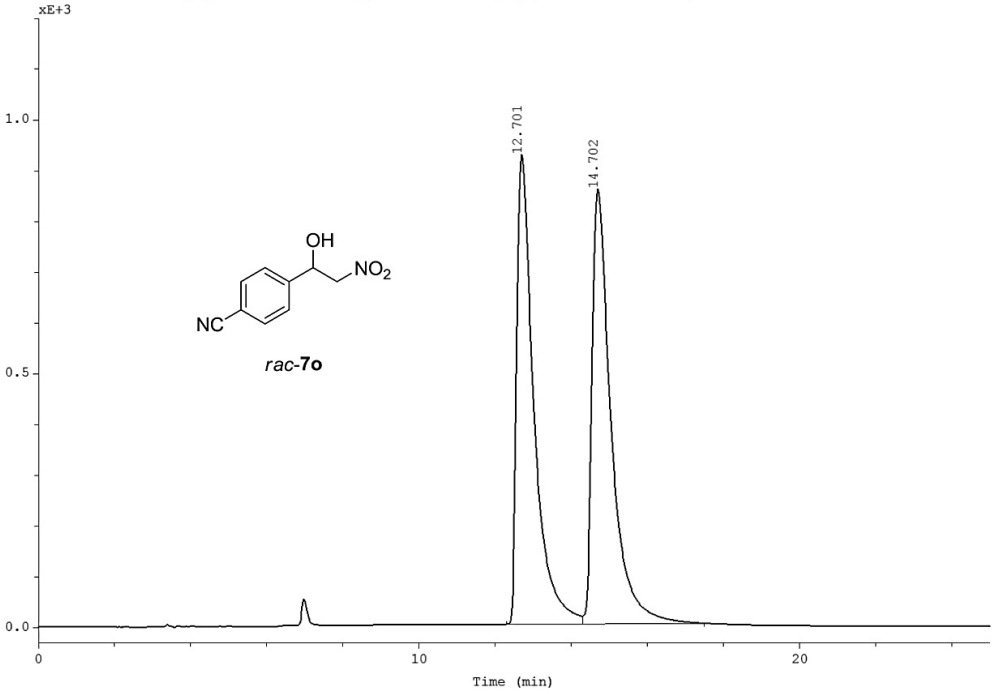
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.58	13.22	15.19	765.06	327.09	53.66	49.66
2	16.28	15.92	17.98	660.77	331.63	46.34	50.34



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.70	13.47	14.02	2.98	0.86	0.36	0.20
2	16.22	15.75	18.08	835.16	430.87	99.64	99.80

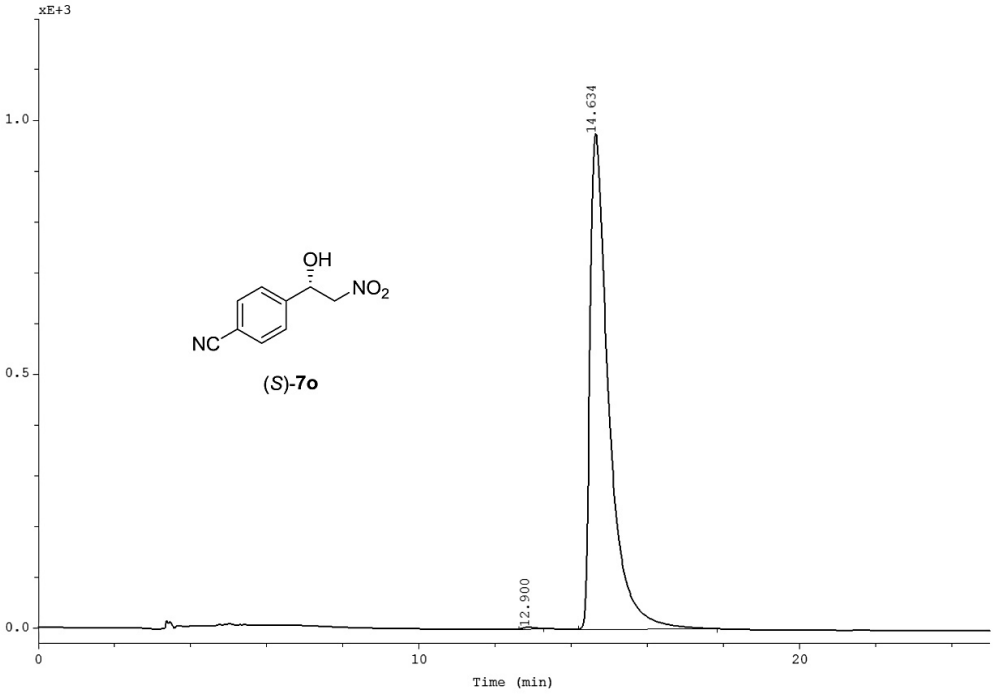
29

Chiralcel OD-3, *n*-hexane/*i*PrOH 80:20, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 12.9 min; t_R (*S*-enantiomer) = 14.6 min



rac-**7o**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.70	12.29	14.30	926.32	488.62	51.93	49.44
2	14.70	14.30	17.49	857.36	499.75	48.07	50.56

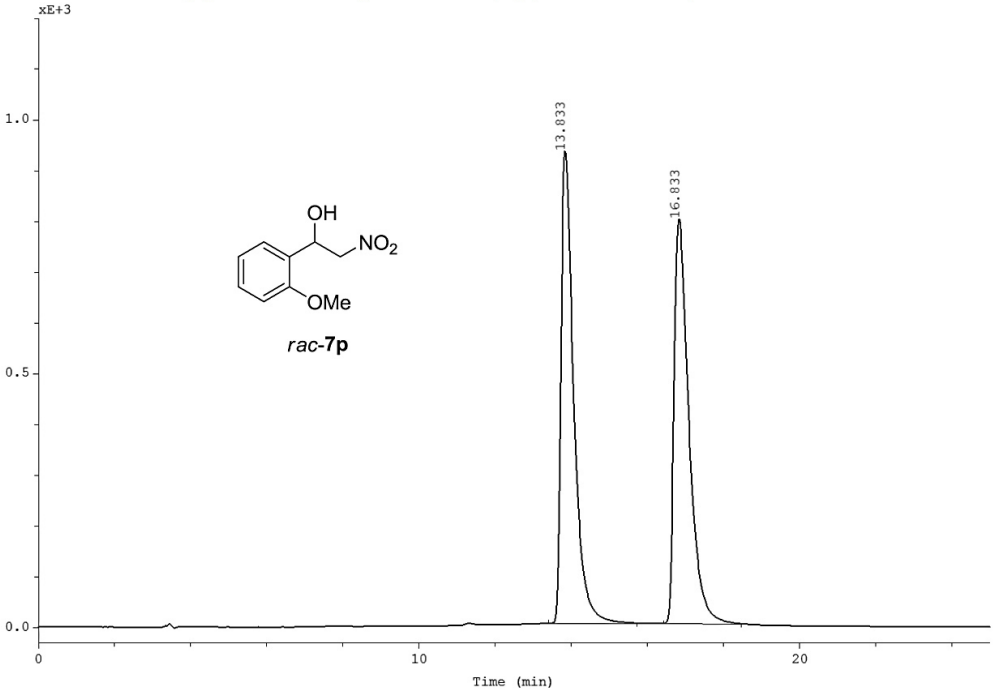


(*S*)-**7o**

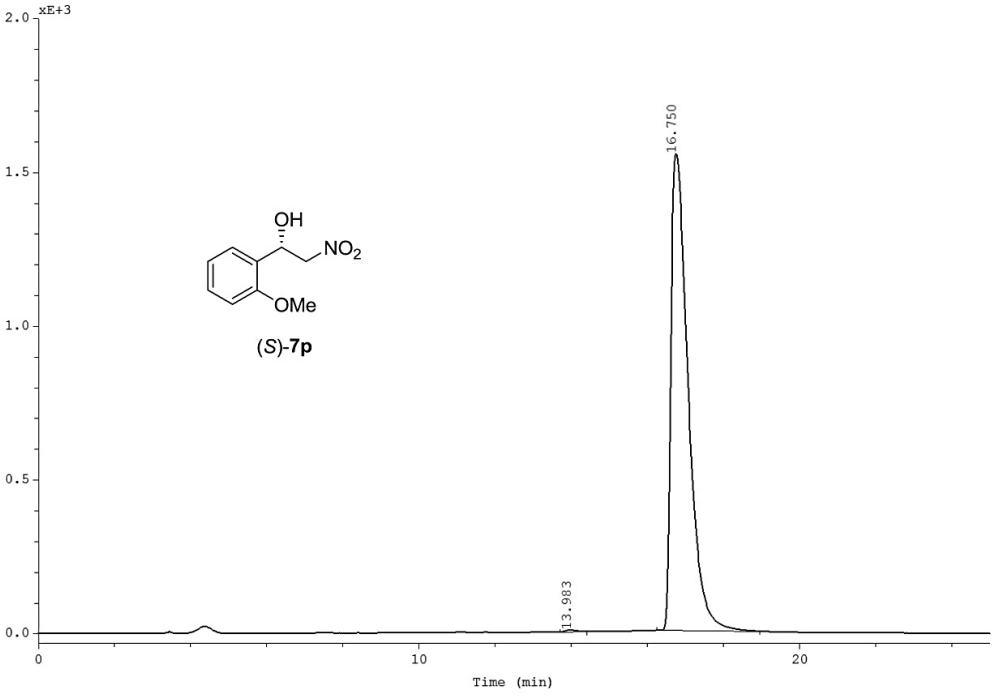
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.90	12.61	13.27	3.26	1.16	0.33	0.21
2	14.63	14.19	17.83	976.92	560.04	99.67	99.79

30

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 14.0 min; t_R (*S*-enantiomer) = 16.8 min



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.83	13.40	15.72	930.88	359.90	53.83	49.96
2	16.83	16.42	18.45	798.32	360.49	46.17	50.04



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.98	13.70	14.40	6.16	1.98	0.40	0.24
2	16.75	16.25	18.95	1551.47	812.47	99.60	99.76

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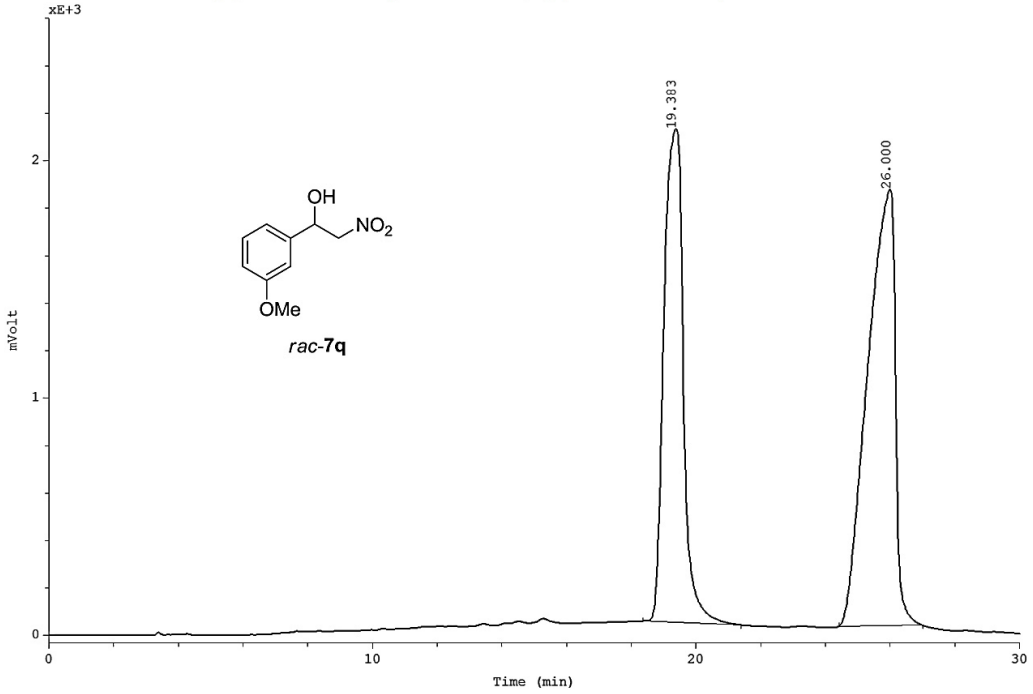
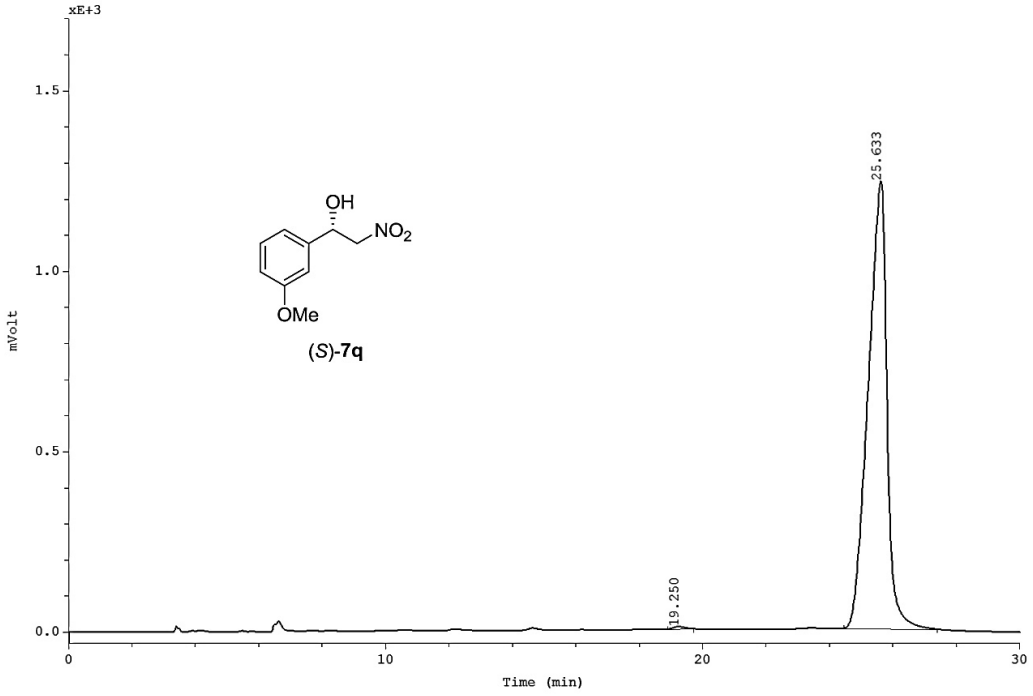
Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 19.3 min; t_R (*S*-enantiomer) = 25.6 min

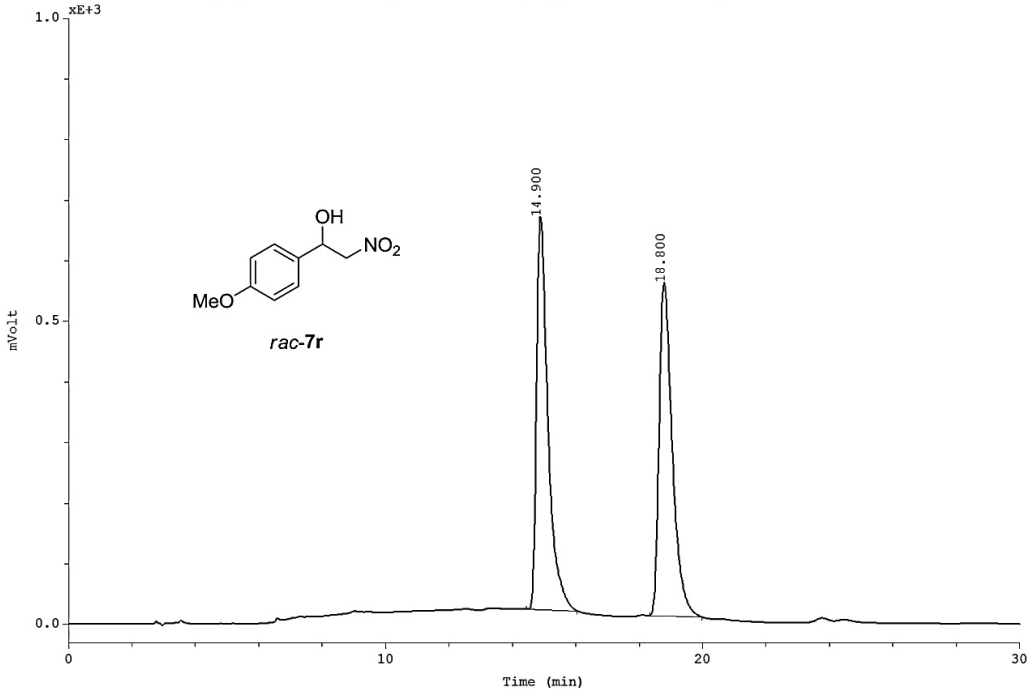


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	19.38	18.37	21.40	2079.65	1442.60	53.08	44.33
2	26.00	24.43	27.00	1838.34	1811.85	46.92	55.67

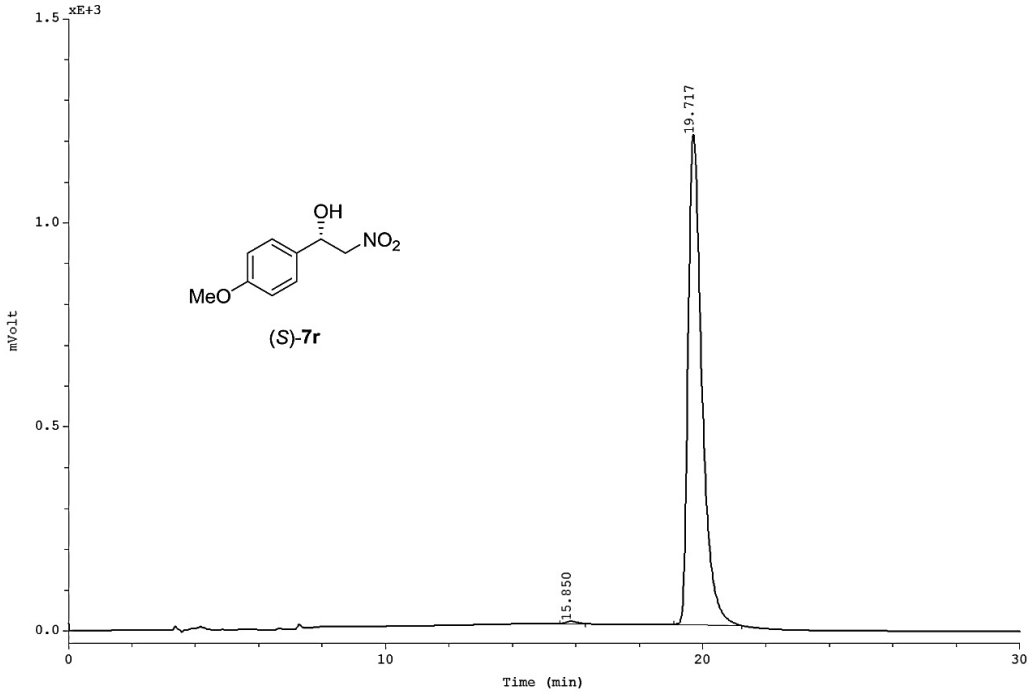


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	19.25	18.89	19.73	6.90	2.83	0.55	0.33
2	25.63	24.46	27.41	1240.99	848.65	99.45	99.67

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 15.9 min; t_R (*S*-enantiomer) = 19.7 min



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.90	14.45	16.05	647.93	270.08	54.07	50.51
2	18.80	18.35	19.98	550.39	264.57	45.93	49.49



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.85	15.50	16.29	6.18	2.31	0.51	0.38
2	19.72	19.10	21.24	1201.58	607.87	99.49	99.62

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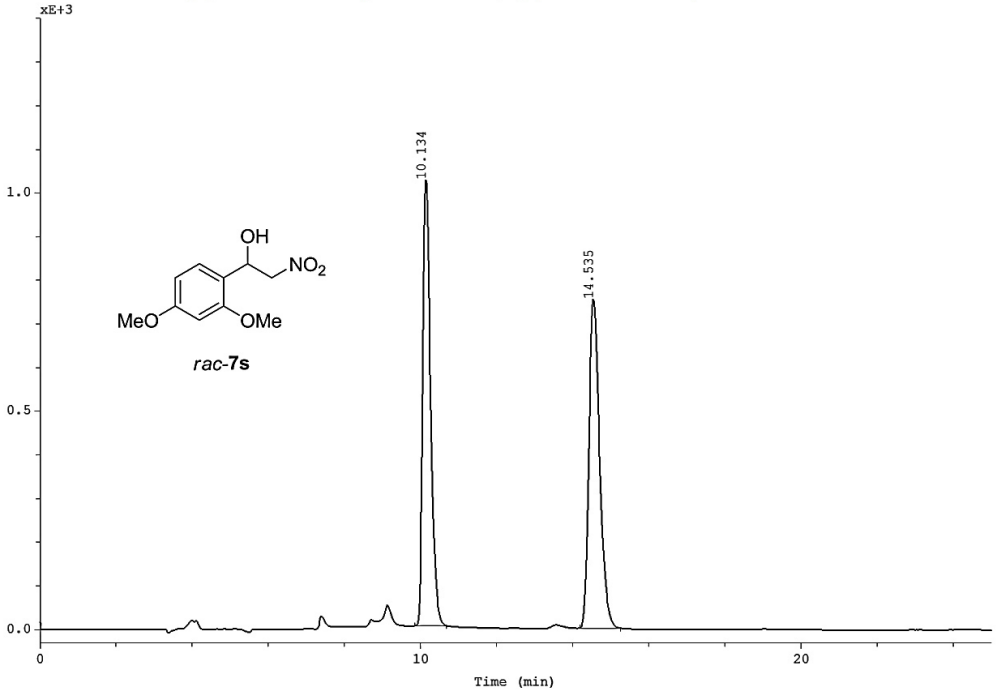
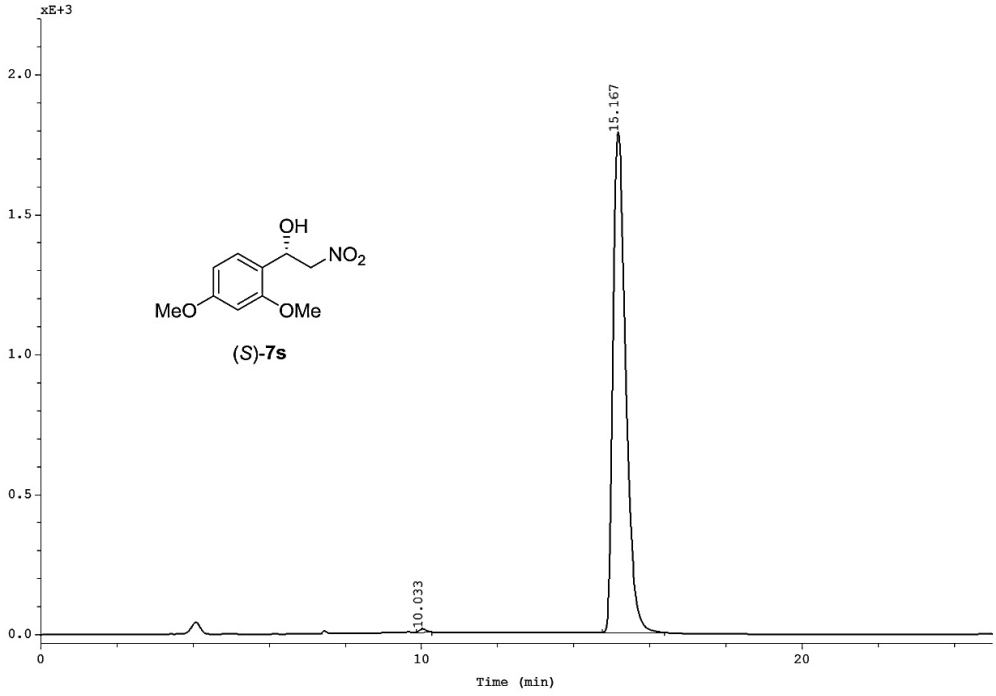
Chiralcel OD-3, *n*-hexane/*i*PrOH 80:20, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 10.0 min; t_R (*S*-enantiomer) = 15.2 min

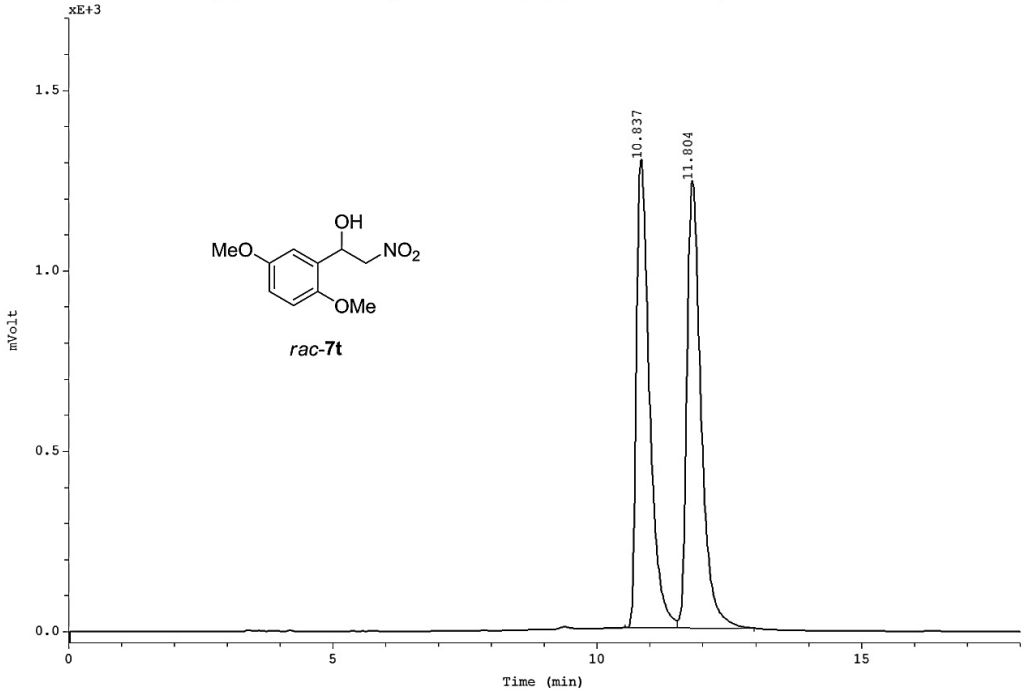


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.13	9.85	10.67	1021.08	241.17	57.55	49.55
2	14.53	14.19	15.25	753.08	245.51	42.45	50.45

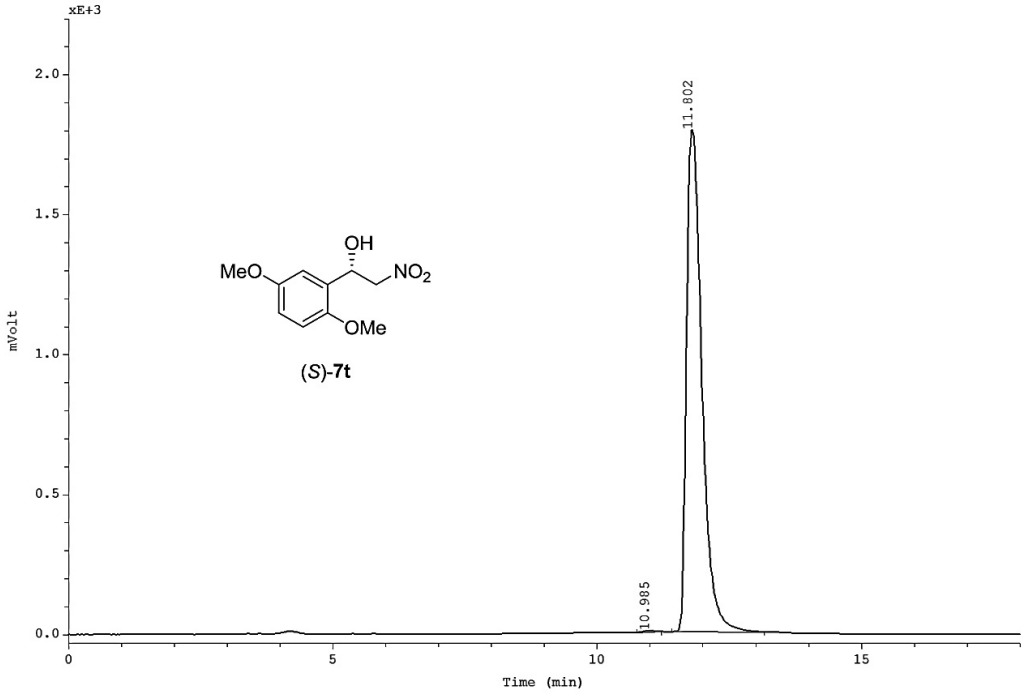


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.03	9.87	10.27	12.70	2.55	0.71	0.37
2	15.17	14.75	16.39	1787.89	693.02	99.29	99.63

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 11.0 min; t_R (*S*-enantiomer) = 11.8 min



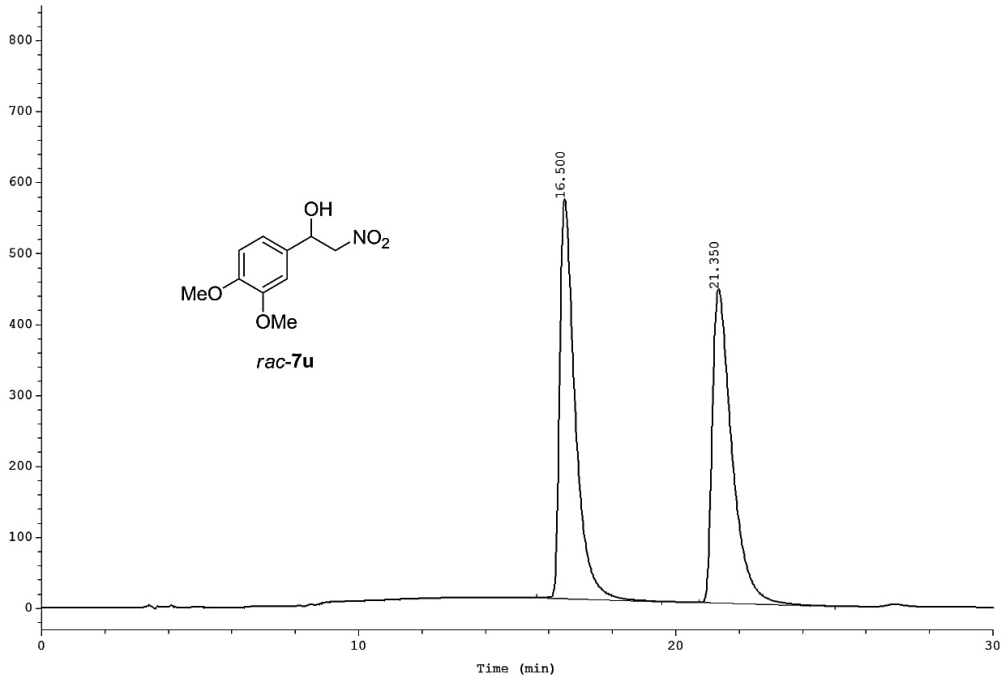
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.84	10.52	11.51	1298.70	376.34	51.14	49.35
2	11.80	11.51	12.97	1240.72	386.27	48.86	50.65



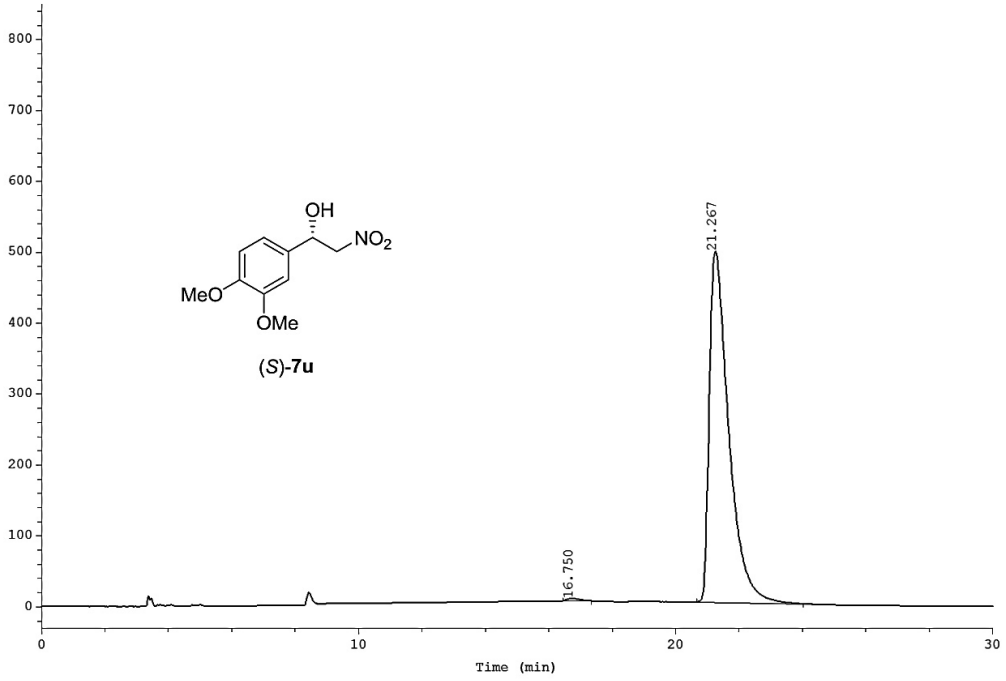
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.99	10.75	11.22	4.93	1.15	0.27	0.19
2	11.80	11.41	13.16	1795.31	604.90	99.73	99.81

35

Chiralcel OD-3, *n*-hexane/*i*PrOH 80:20, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 16.8 min; t_R (*S*-enantiomer) = 21.3 min



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	16.50	15.62	19.57	562.53	317.77	55.98	50.06
2	21.35	20.75	25.02	442.42	317.03	44.02	49.94



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	16.75	16.44	17.35	3.40	1.51	0.68	0.43
2	21.27	20.67	24.03	494.65	350.63	99.32	99.57

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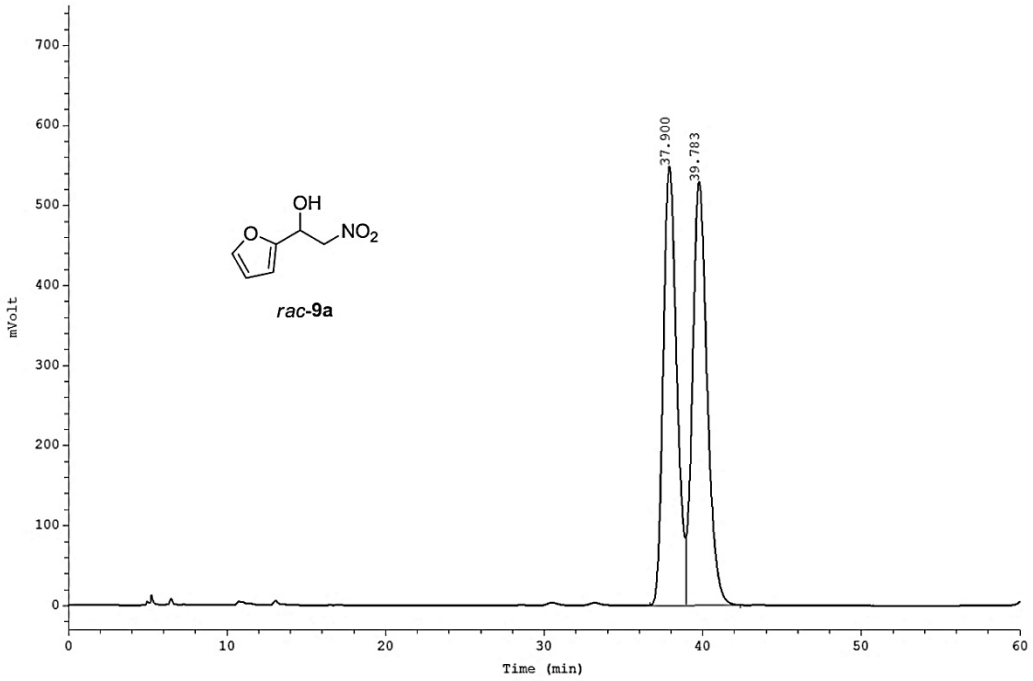
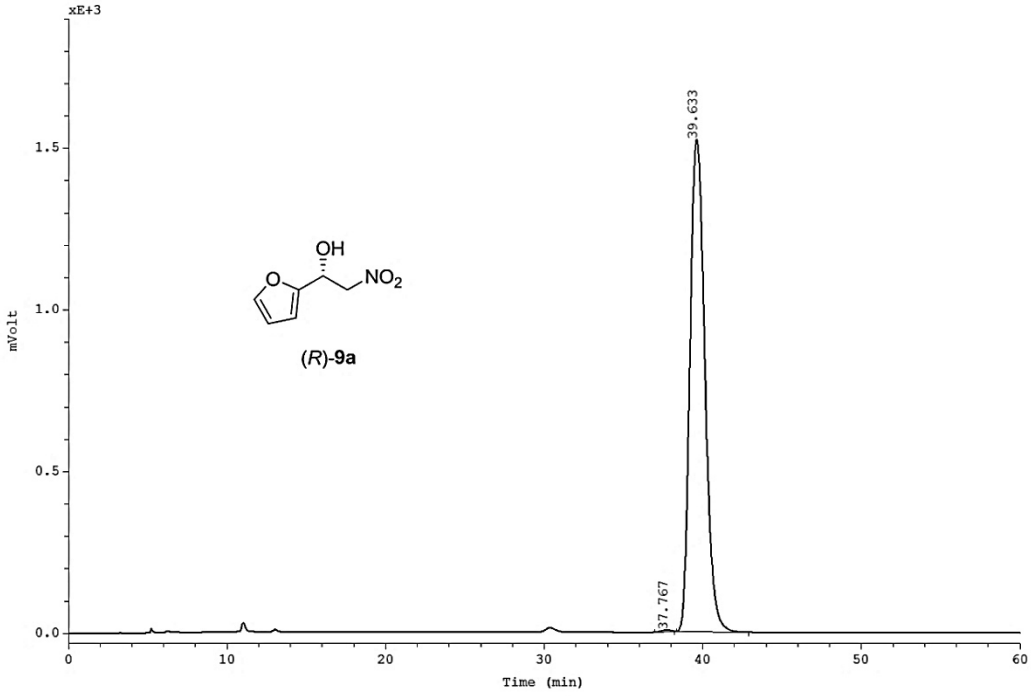
Chiralpak AD-H, *n*-hexane/*i*PrOH 95:5, 0.6 mL/min, 215 nm:
t_R (*R*-enantiomer) = 39.6 min; t_R (*S*-enantiomer) = 37.8 min



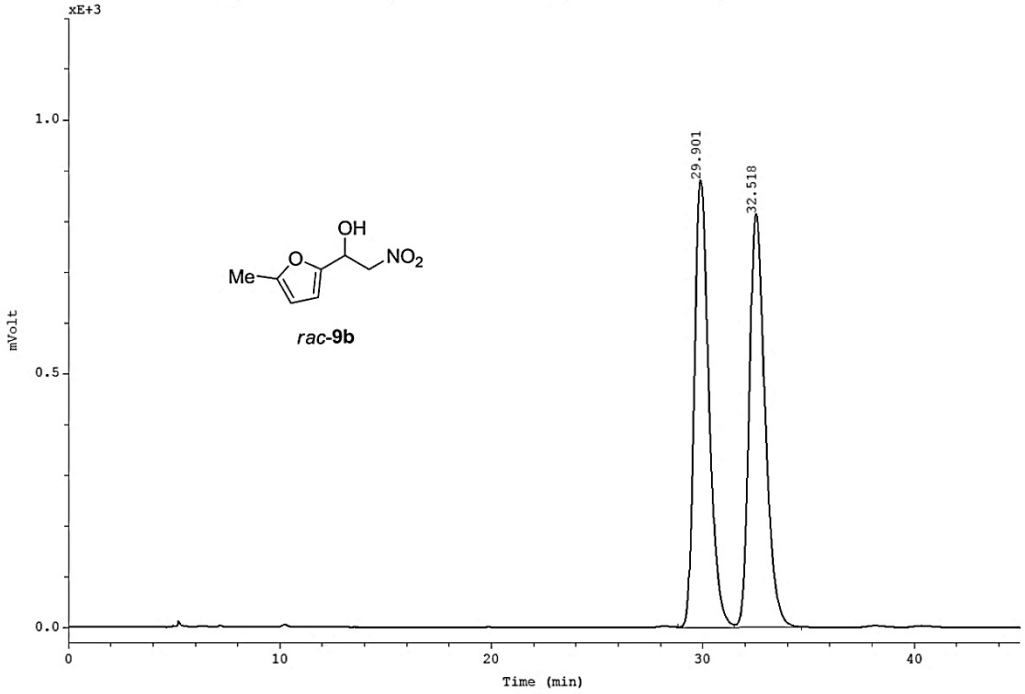
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	37.90	36.68	38.94	549.10	537.37	50.93	48.66
2	39.78	38.94	42.36	529.03	567.03	49.07	51.34



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	37.77	36.95	38.24	5.00	3.40	0.33	0.20
2	39.63	38.35	42.90	1521.85	1658.92	99.67	99.80

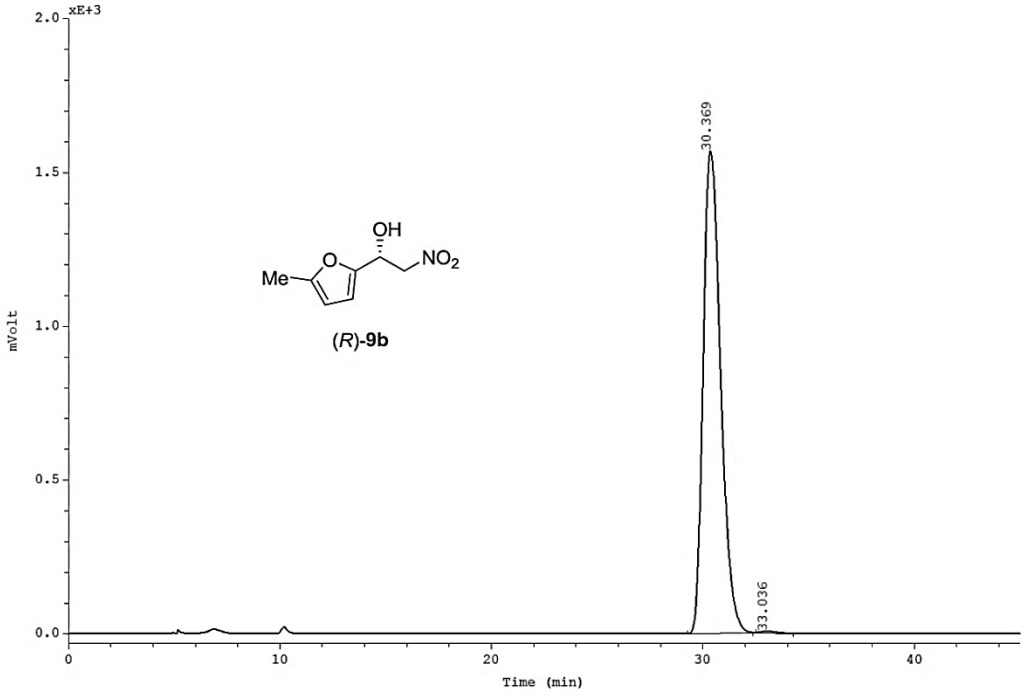
37

Chiralpak AD-H, *n*-hexane/*i*PrOH 95:5, 0.6 mL/min, 215 nm:
t_R (*R*-enantiomer) = 33.0 min; t_R (*S*-enantiomer) = 30.4 min



rac-**9b**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	29.90	28.81	31.49	881.34	704.76	51.98	49.91
2	32.52	31.49	34.67	814.19	707.39	48.02	50.09

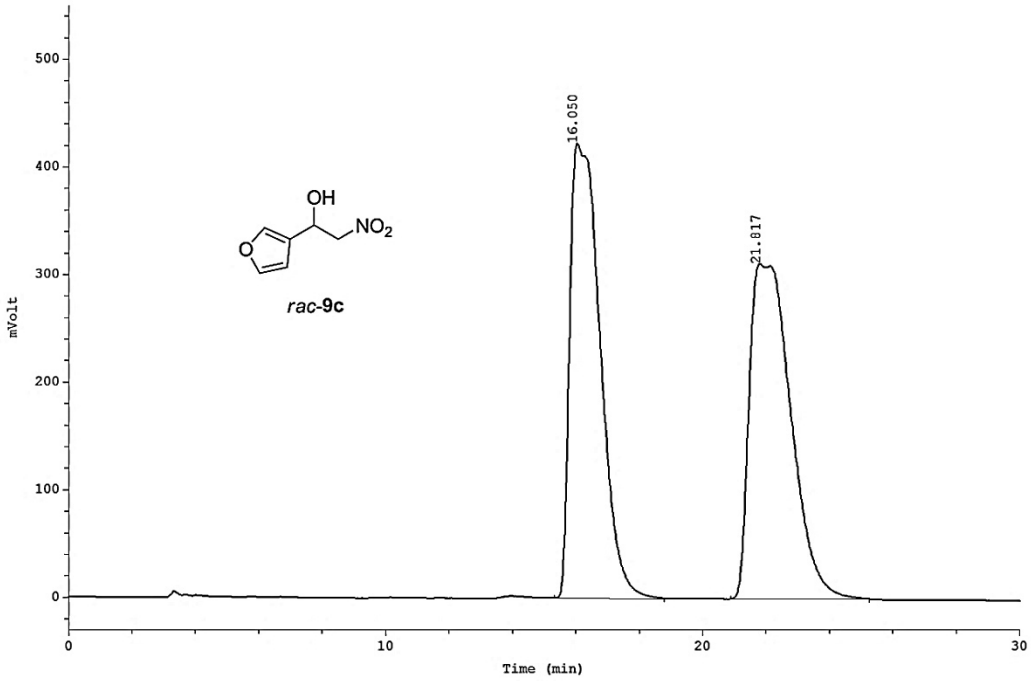


(*R*)-**9b**

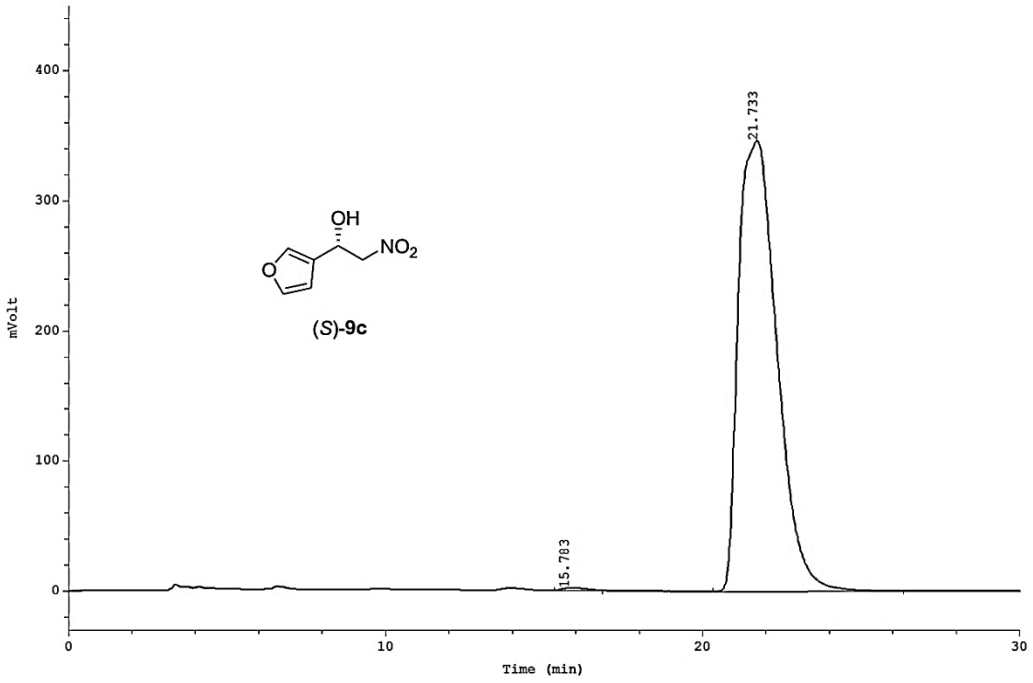
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	30.37	29.26	32.36	1567.98	1501.65	99.68	99.74
2	33.04	32.50	34.28	4.96	3.95	0.32	0.26

38

Chiralpak AD-H, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 15.8 min; t_R (*S*-enantiomer) = 21.7 min



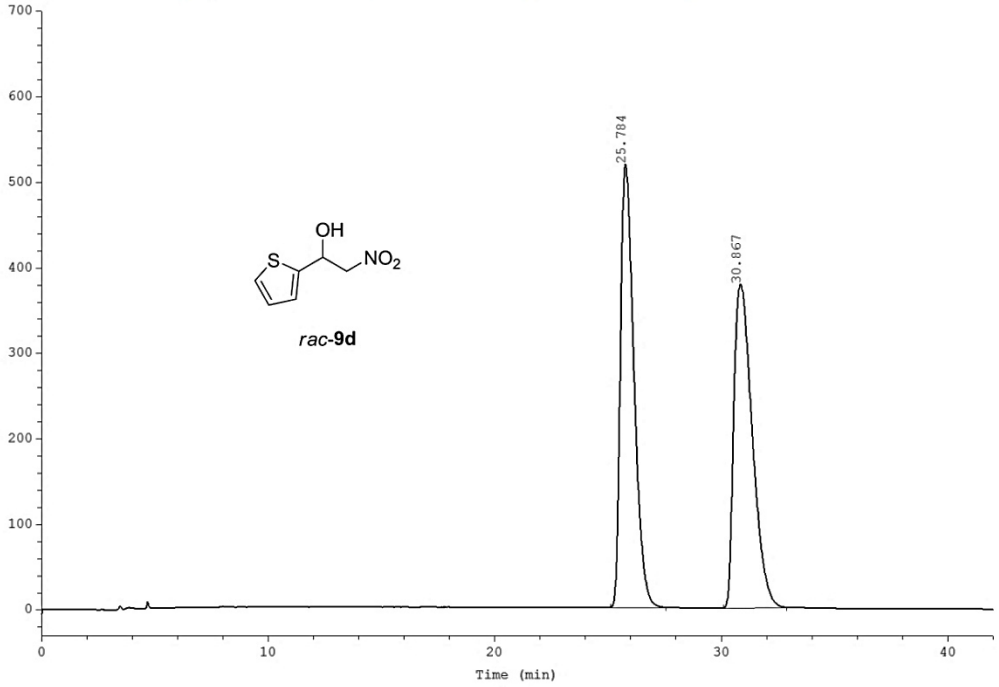
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	16.05	15.32	18.78	422.76	467.62	57.58	49.86
2	21.82	20.89	25.26	311.45	470.22	42.42	50.14



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.78	15.33	16.85	1.63	1.49	0.47	0.30
2	21.73	20.32	26.35	346.55	486.01	99.53	99.70

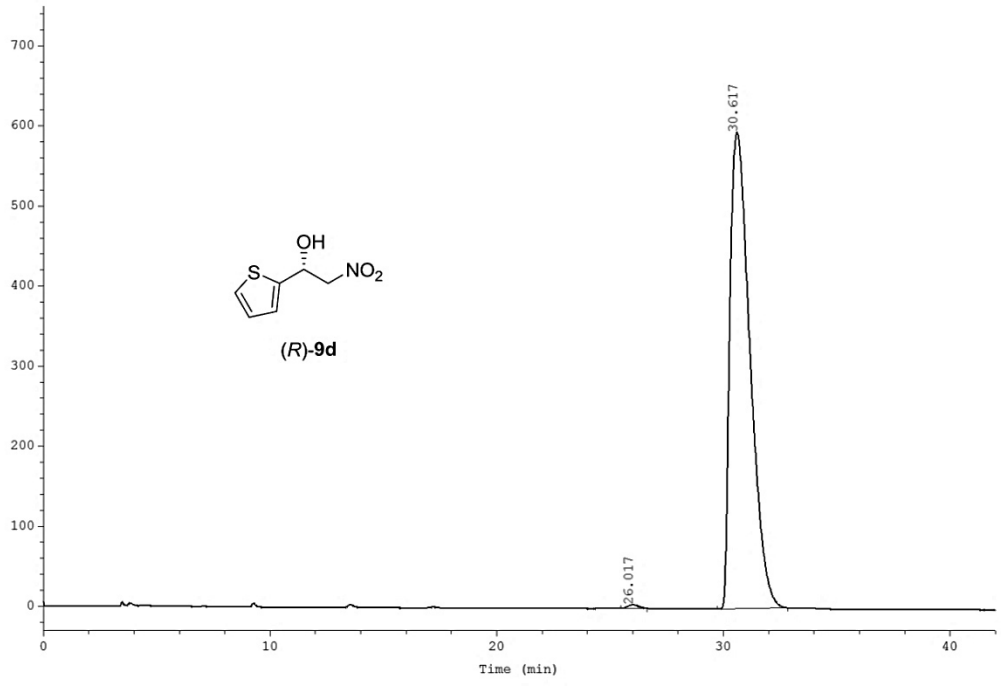
39

Chiralcel OJ-H, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 30.6 min; t_R (*S*-enantiomer) = 26.0 min



rac-**9d**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	25.78	25.11	27.55	518.41	358.24	57.78	50.07
2	30.87	30.10	32.90	378.74	357.22	42.22	49.93

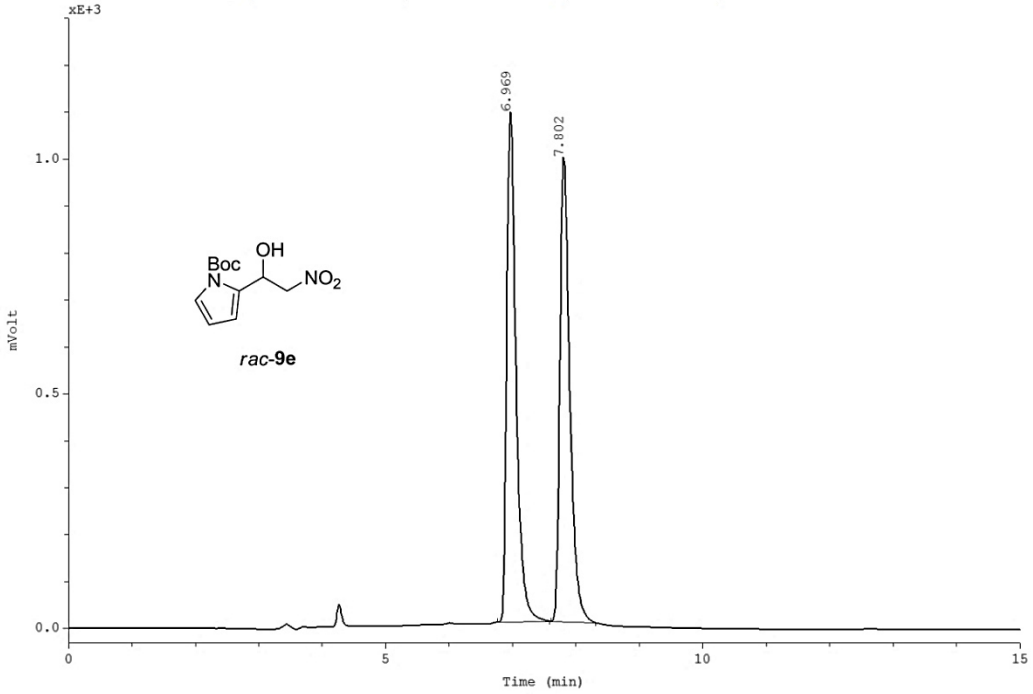


(*R*)-**9d**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	26.02	25.47	26.63	4.47	2.43	0.75	0.40
2	30.62	29.74	32.85	595.05	609.21	99.25	99.60

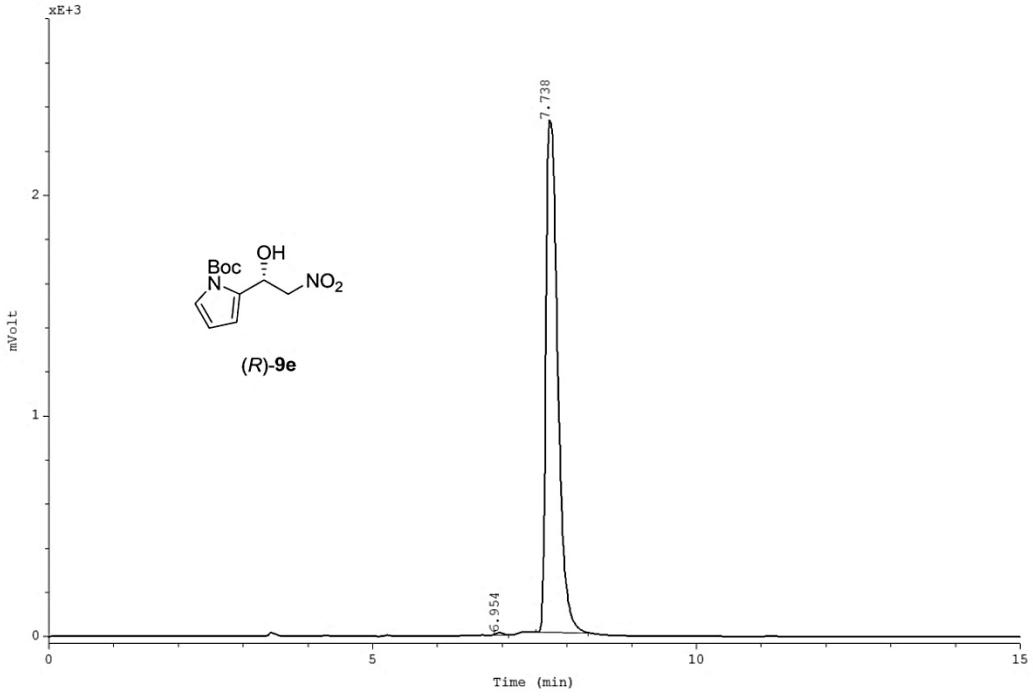
40

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 7.0 min; t_R (*S*-enantiomer) = 7.7 min



rac-**9e**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	6.97	6.77	7.58	1086.31	183.21	52.32	50.30
2	7.80	7.60	8.31	990.06	181.02	47.68	49.70

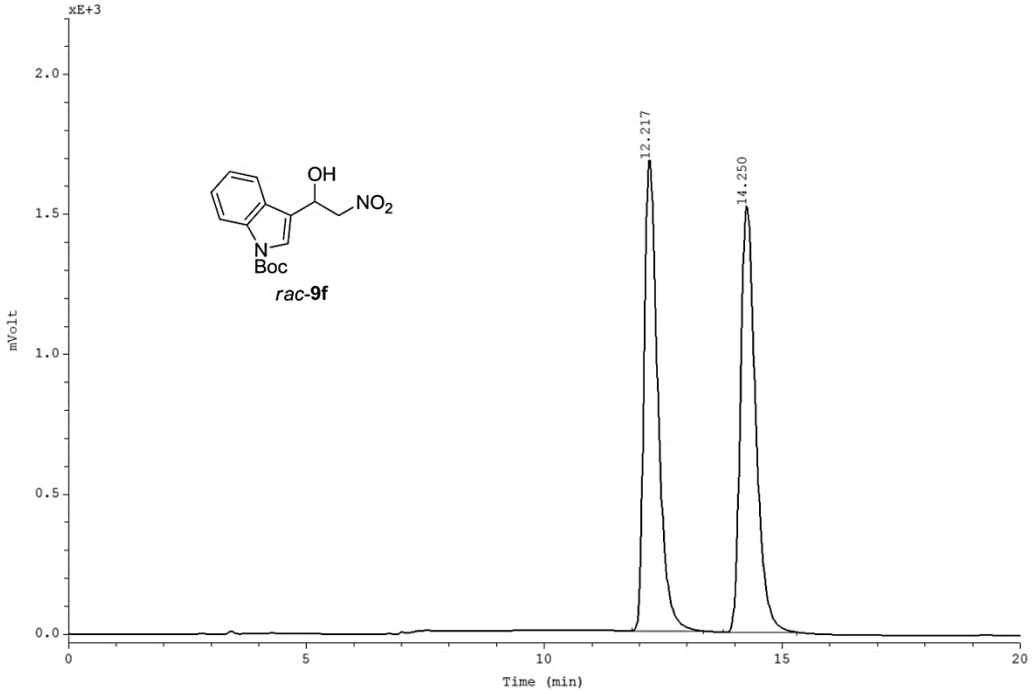


(*R*)-**9e**

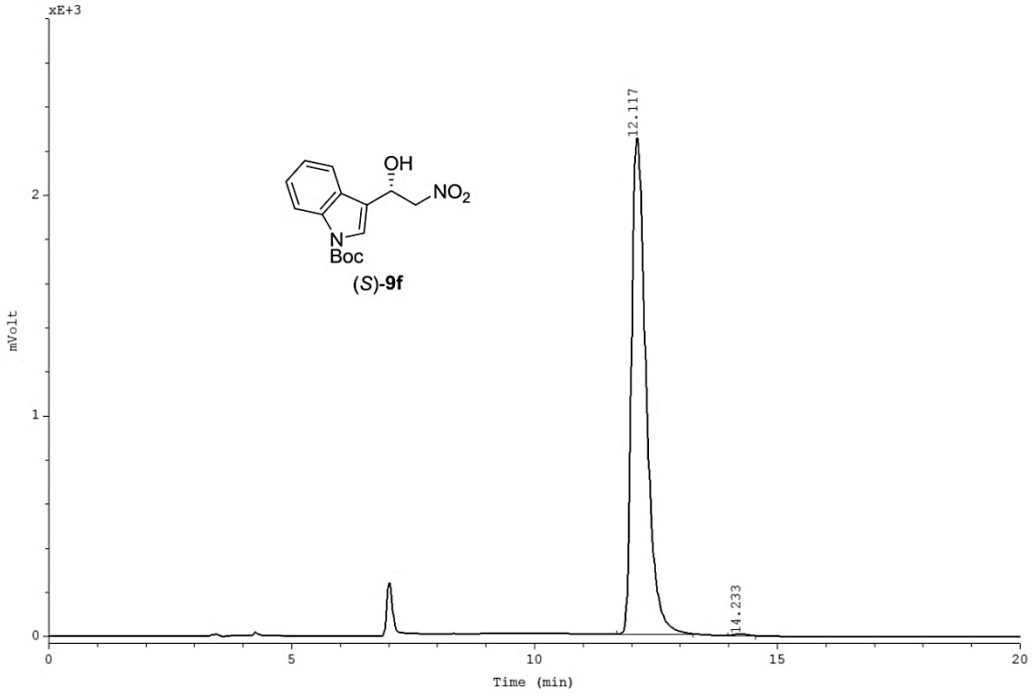
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	6.95	6.87	7.10	9.41	1.17	0.40	0.24
2	7.74	7.52	8.33	2321.72	495.29	99.60	99.76

41

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 14.2 min; t_R (*S*-enantiomer) = 12.1 min



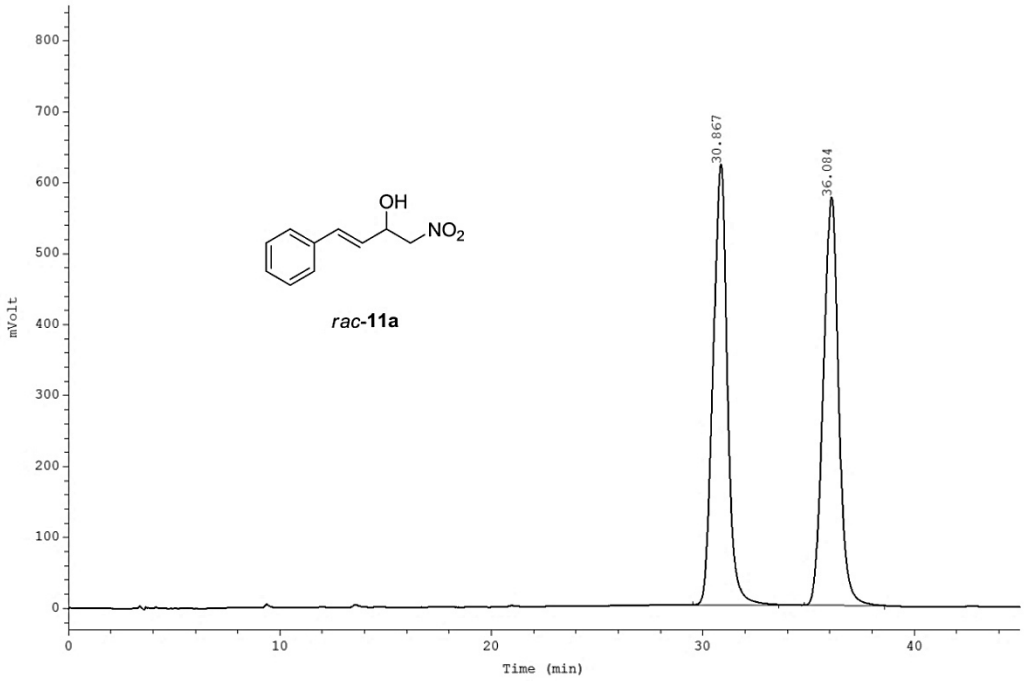
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.22	11.84	13.34	1682.54	565.18	52.47	49.94
2	14.25	13.77	15.30	1524.37	566.65	47.53	50.06



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.12	11.70	13.27	2250.06	783.35	99.63	99.68
2	14.23	13.98	14.55	8.47	2.51	0.37	0.32

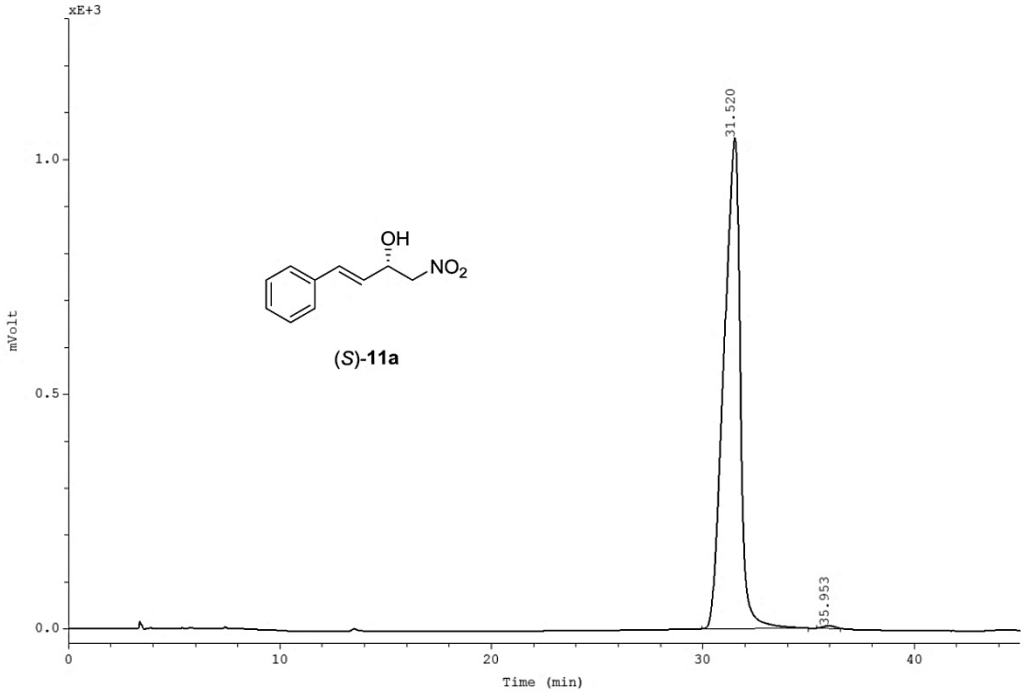
42

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 36.0 min; t_R (*S*-enantiomer) = 31.5 min



rac-**11a**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	30.87	29.52	33.58	621.43	485.83	51.91	49.96
2	36.08	34.78	38.58	575.59	486.64	48.09	50.04

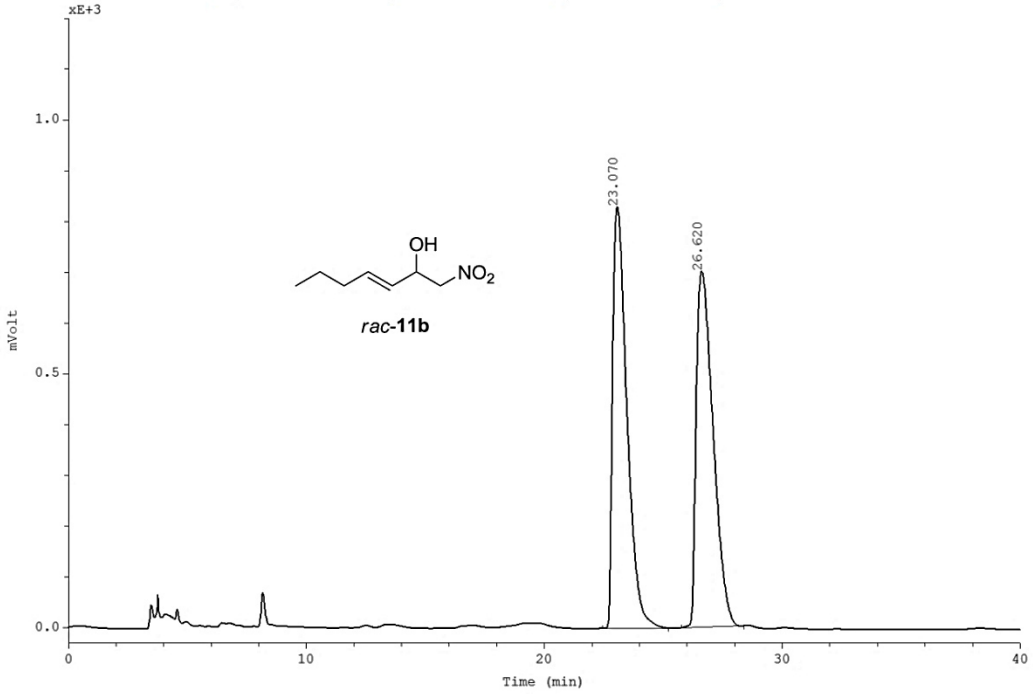


(*S*)-**11a**

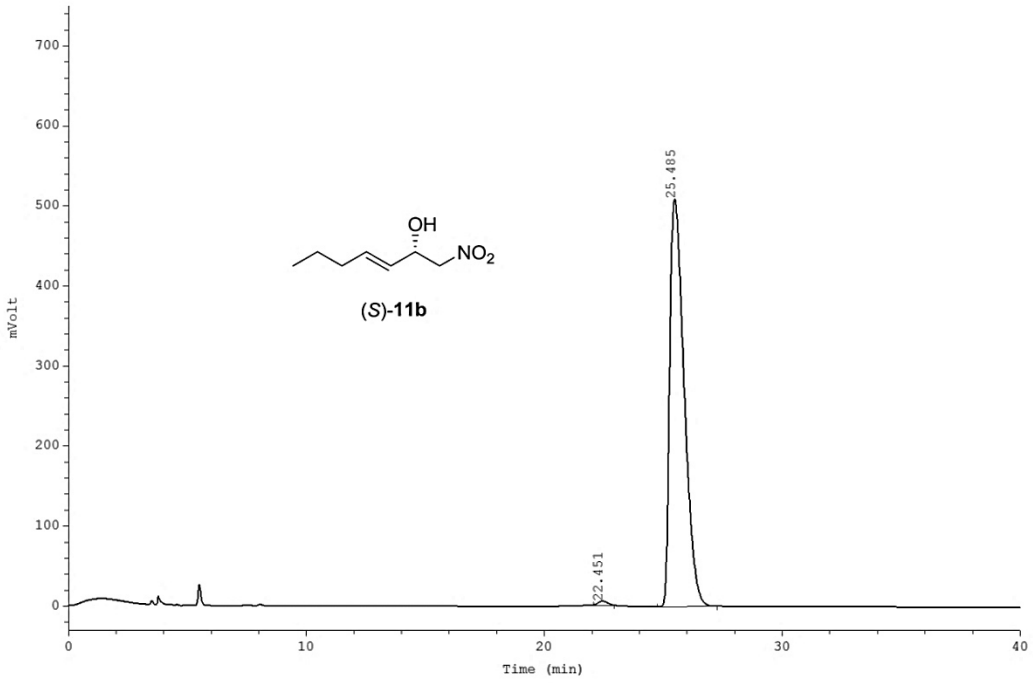
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	31.52	29.94	34.99	1045.52	934.68	99.48	99.65
2	35.95	35.38	36.52	5.44	3.33	0.52	0.35

43

Chiralcel OJ-H, *n*-hexane/*i*PrOH 97:3, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 22.5 min; t_R (*S*-enantiomer) = 25.5 min

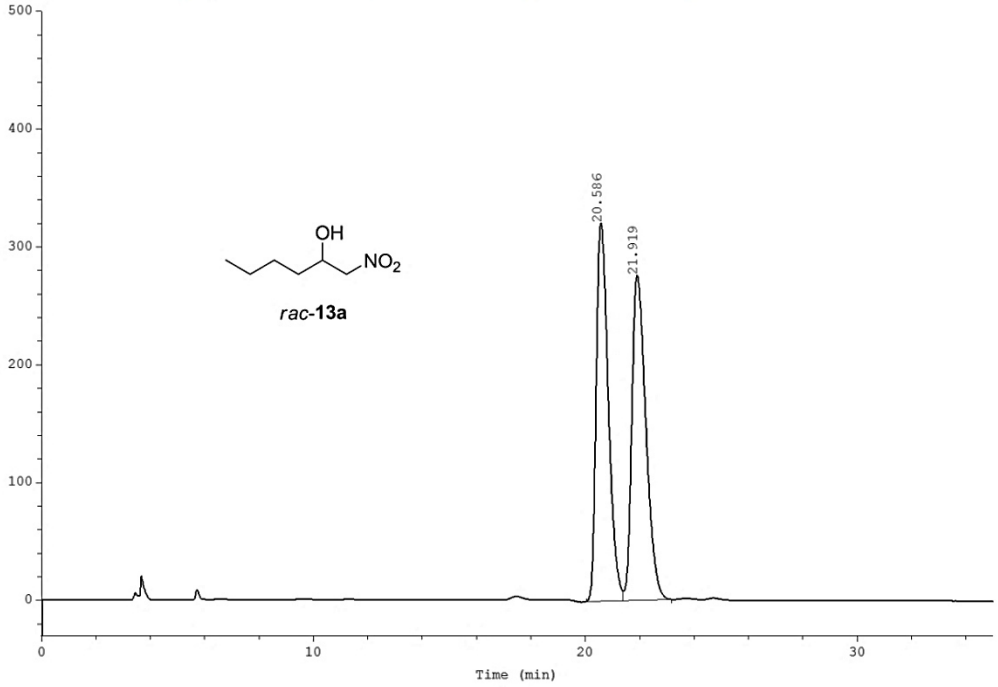


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	23.07	22.46	25.22	830.90	580.25	54.23	50.12
2	26.62	25.76	28.38	701.41	577.57	45.77	49.88

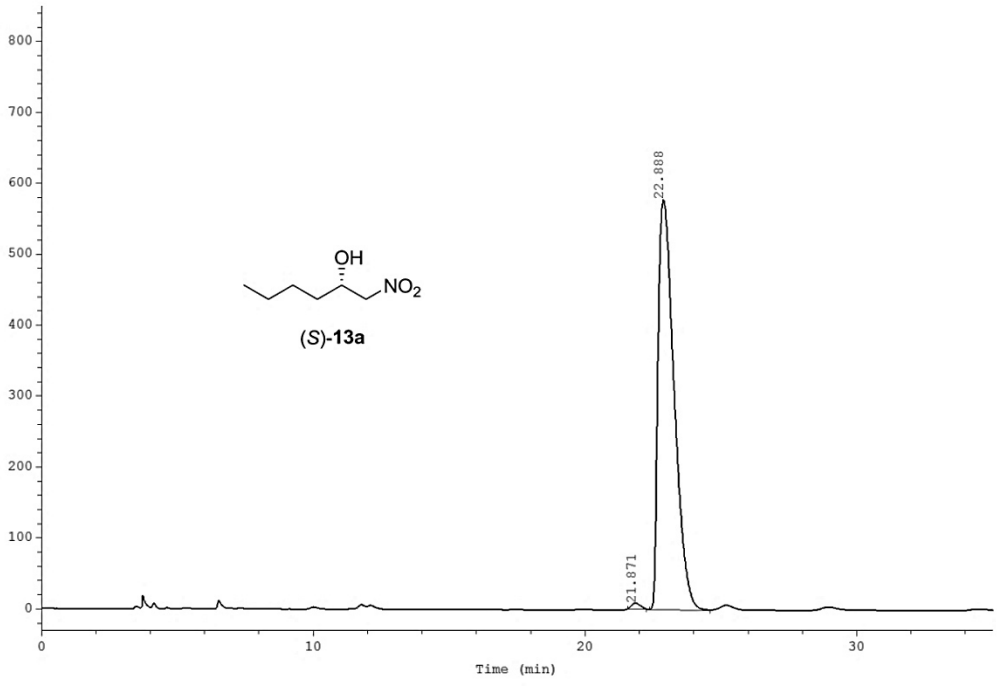


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	22.45	22.07	22.93	4.99	2.26	0.97	0.63
2	25.49	24.74	27.26	509.37	358.45	99.03	99.37

Chiralcel OJ-H, *n*-hexane/*i*PrOH 97:3, 0.8 mL/min, 215 nm:
t_R (*R*-enantiomer) = 21.9 min; t_R (*S*-enantiomer) = 22.9 min



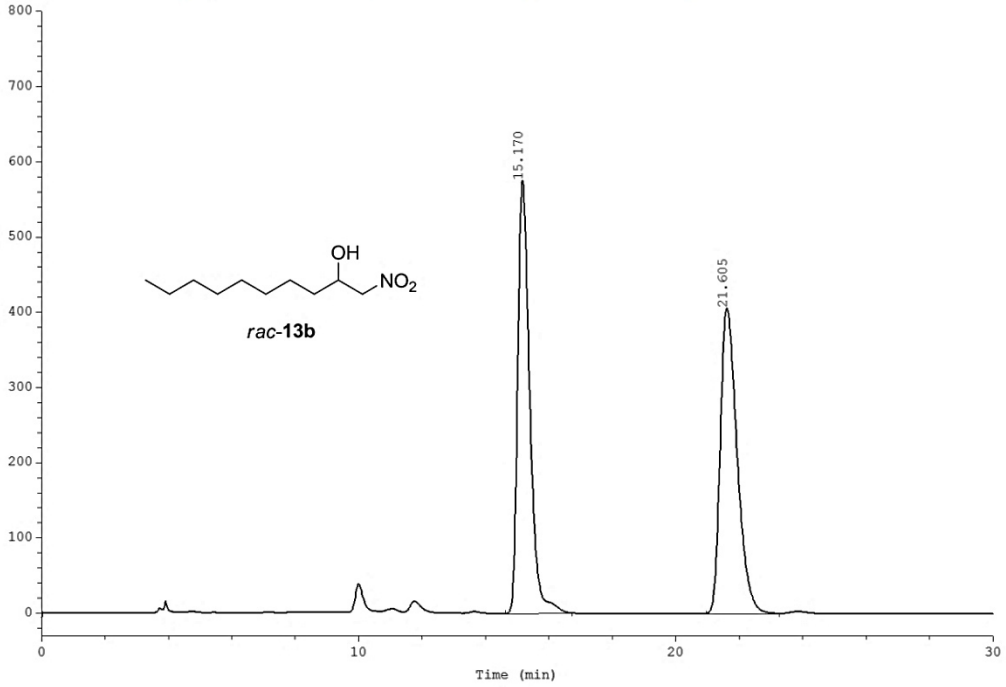
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	20.59	20.03	21.39	321.23	165.68	53.77	49.84
2	21.92	21.39	23.17	276.19	166.73	46.23	50.16



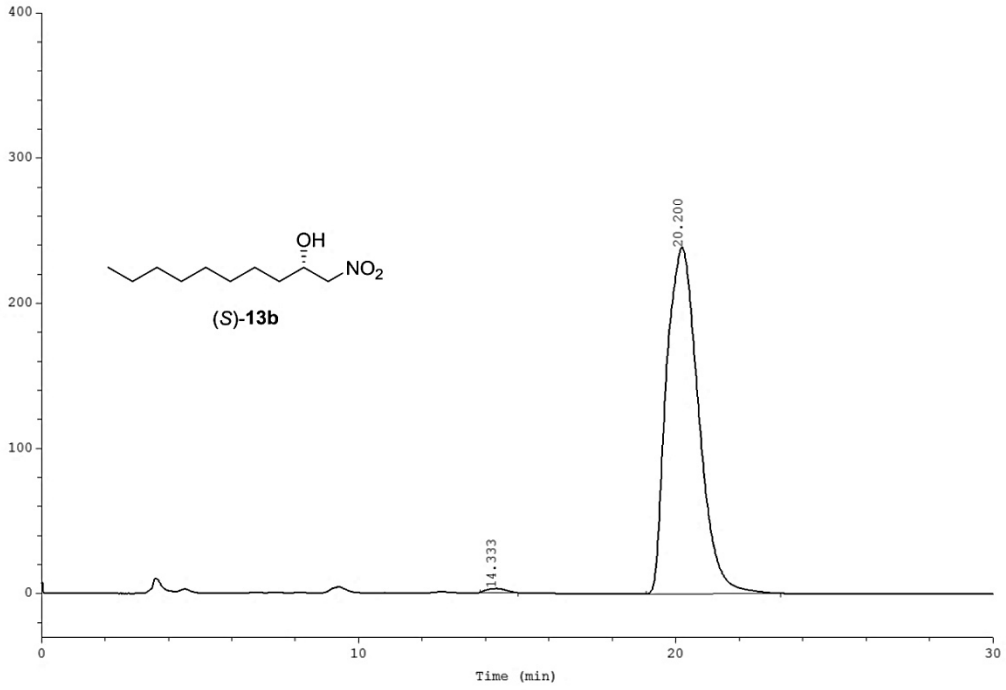
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	21.87	21.57	22.26	8.10	2.99	1.38	0.75
2	22.89	22.38	24.59	577.72	395.15	98.62	99.25

45

Chiralpak AD-H, *n*-hexane/*i*PrOH 95:5, 0.8 mL/min, 215 nm:
t_R (*R*-enantiomer) = 14.3 min; t_R (*S*-enantiomer) = 20.2 min

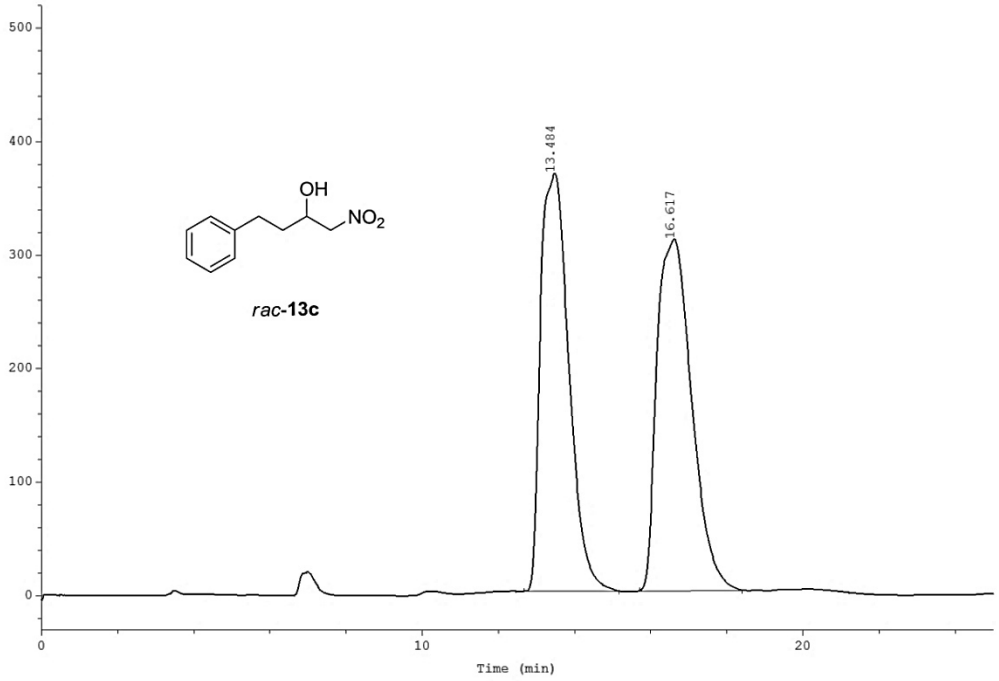


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.17	14.63	16.73	575.42	253.40	58.61	50.30
2	21.61	20.95	23.25	406.28	250.38	41.39	49.70

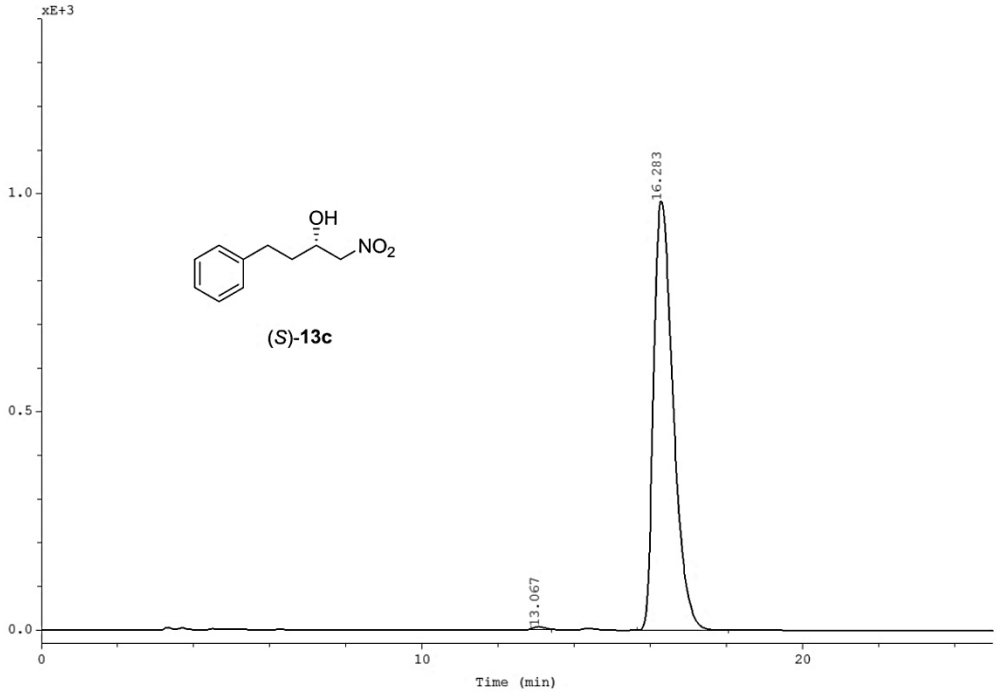


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.33	13.82	15.03	2.80	1.96	1.16	0.70
2	20.20	19.06	23.30	238.45	278.10	98.84	99.30

Chiralpak AD-H, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 13.1 min; t_R (*S*-enantiomer) = 16.3 min



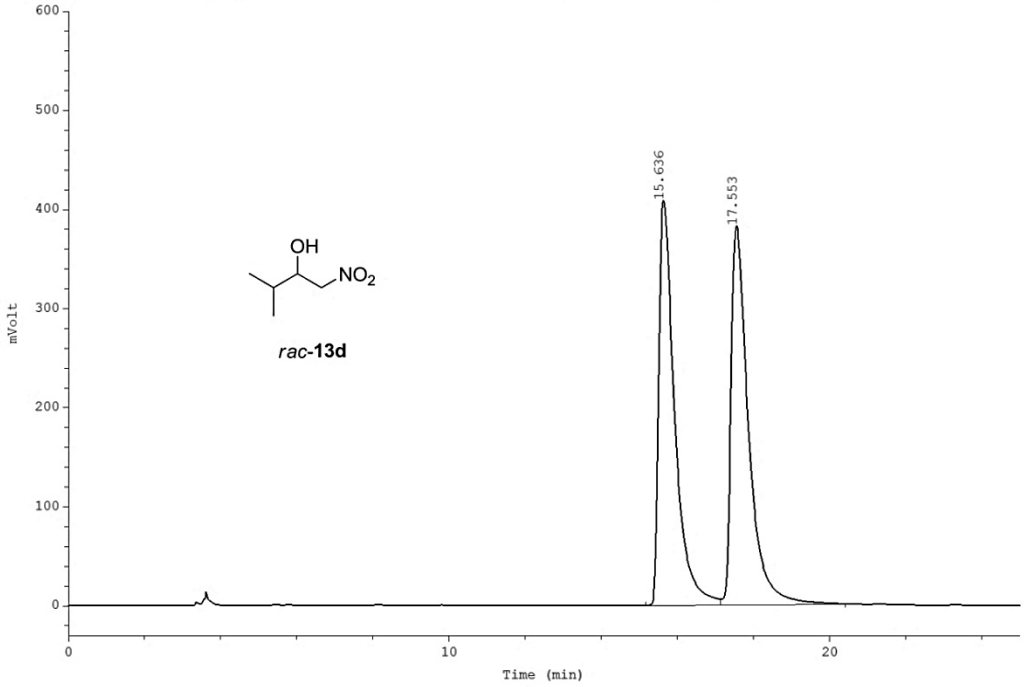
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.48	12.67	15.16	368.44	316.71	54.32	49.22
2	16.62	15.70	18.40	309.79	326.70	45.68	50.78



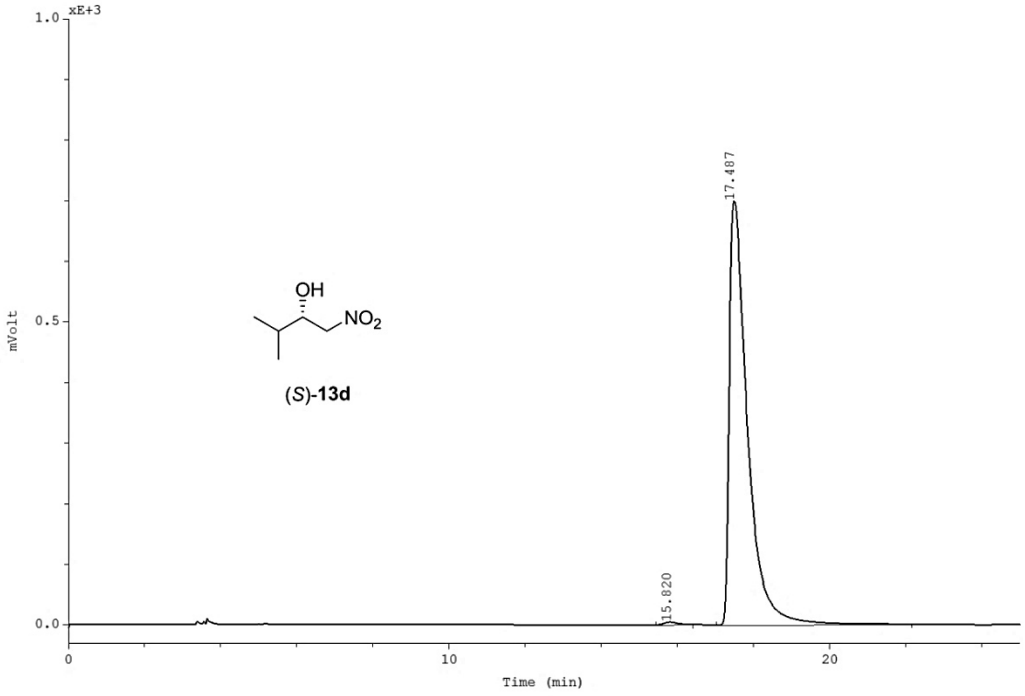
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.07	12.85	13.40	5.26	1.60	0.53	0.27
2	16.28	15.66	18.04	983.87	584.21	99.47	99.73

47

Chiralcel OD-3, *n*-hexane/*i*PrOH 97:3, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 15.8 min; t_R (*S*-enantiomer) = 17.5 min



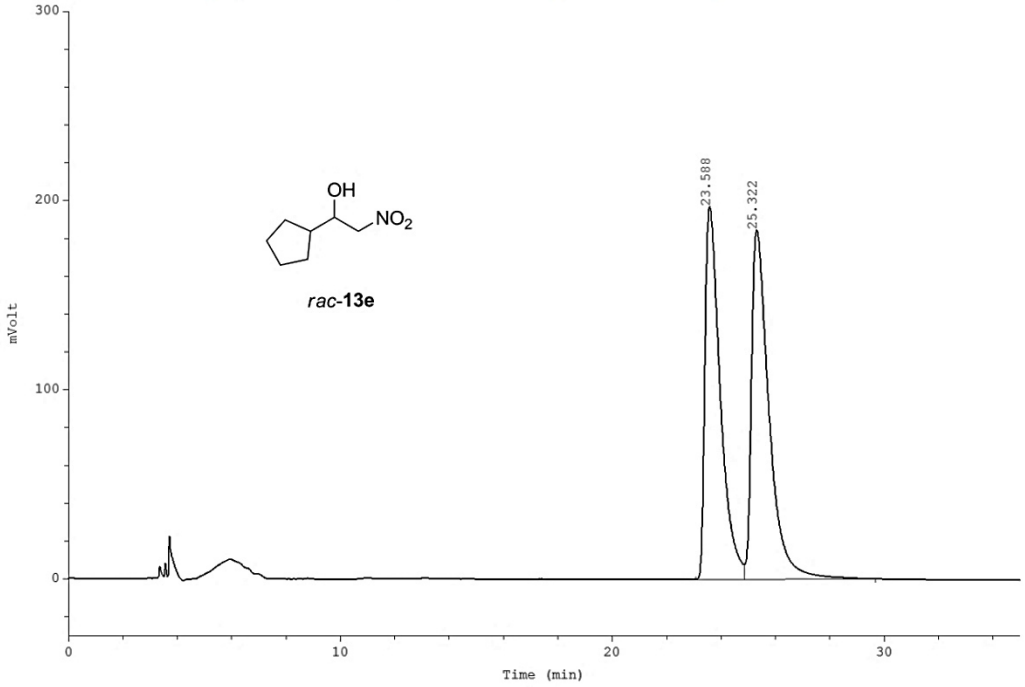
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.64	15.16	17.13	408.93	198.55	51.68	49.29
2	17.55	17.13	20.40	382.40	204.27	48.32	50.71



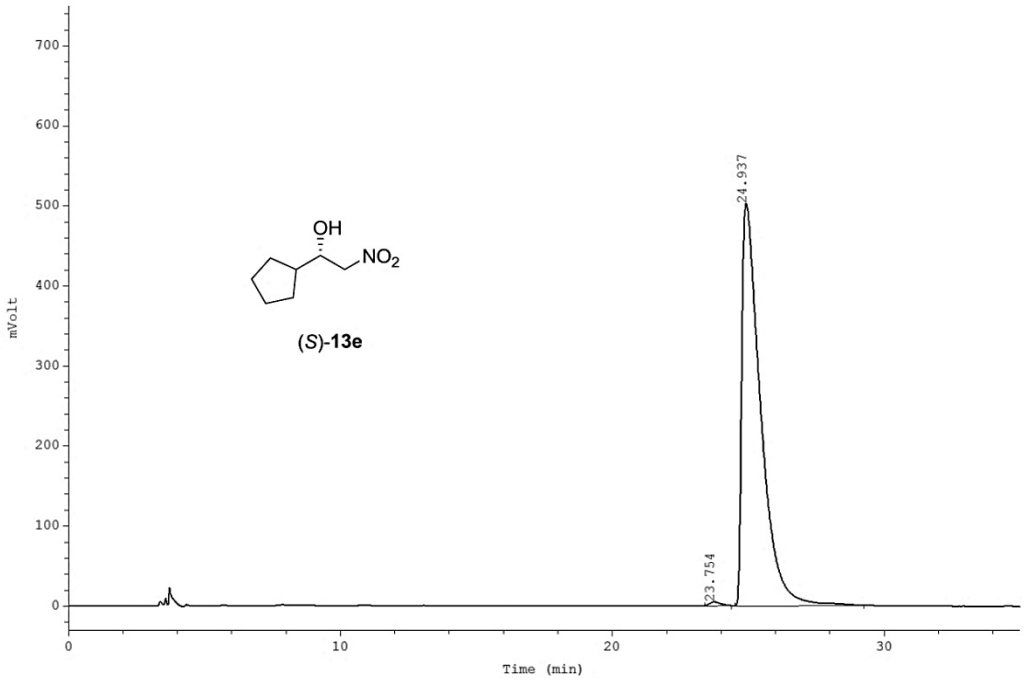
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.82	15.42	16.41	4.62	1.80	0.66	0.46
2	17.49	17.03	22.15	700.05	387.99	99.34	99.54

48

Chiralcel OD-3, *n*-hexane/*i*PrOH 98:2, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 23.8 min; t_R (*S*-enantiomer) = 24.9 min



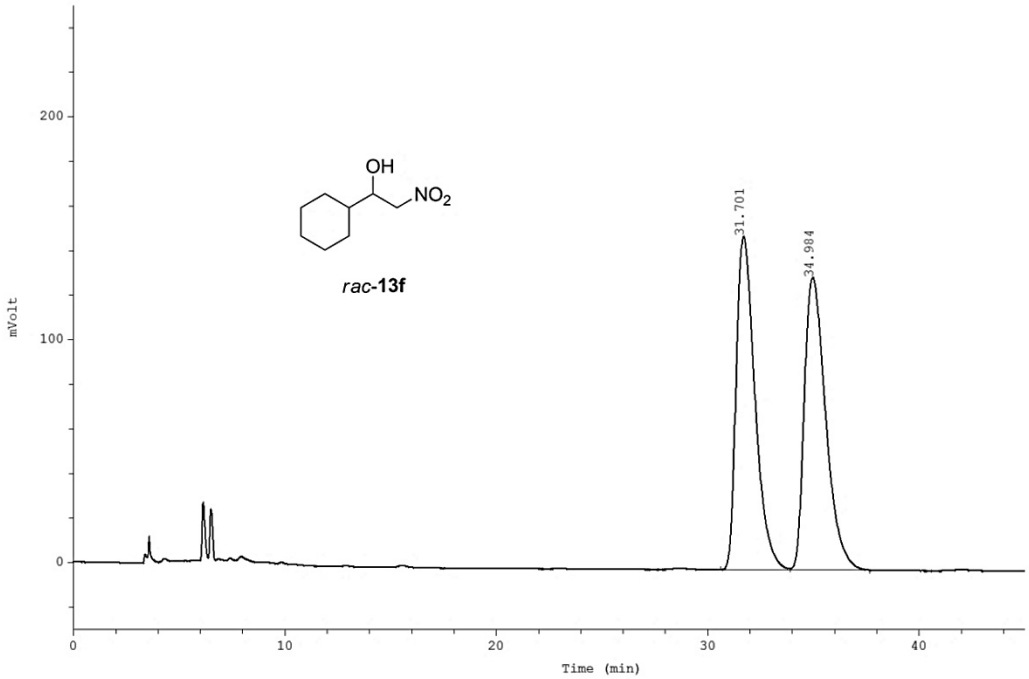
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	23.59	23.07	24.85	197.21	128.56	51.64	48.22
2	25.32	24.85	29.67	184.70	138.07	48.36	51.78



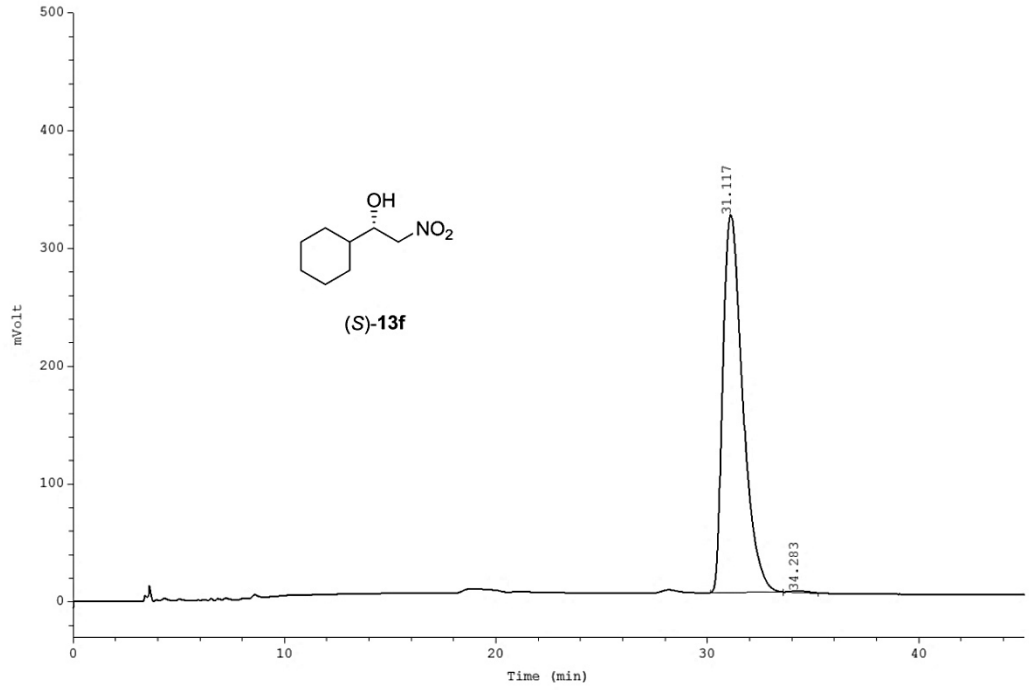
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	23.75	23.39	24.38	4.75	2.26	0.94	0.56
2	24.94	24.49	29.25	502.62	402.83	99.06	99.44

49

Chiralpak AD-H, *n*-hexane/EtOH 95:5, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 34.3 min; t_R (*S*-enantiomer) = 31.1 min

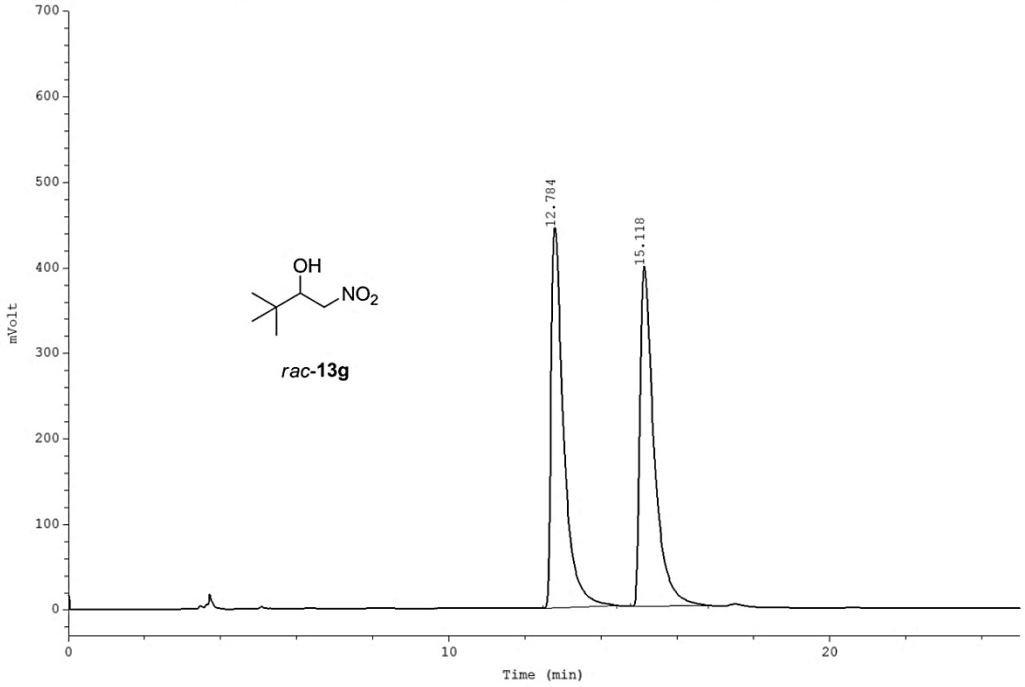


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	31.70	30.62	33.89	149.54	154.21	53.28	50.01
2	34.98	33.89	37.65	131.14	154.14	46.72	49.99

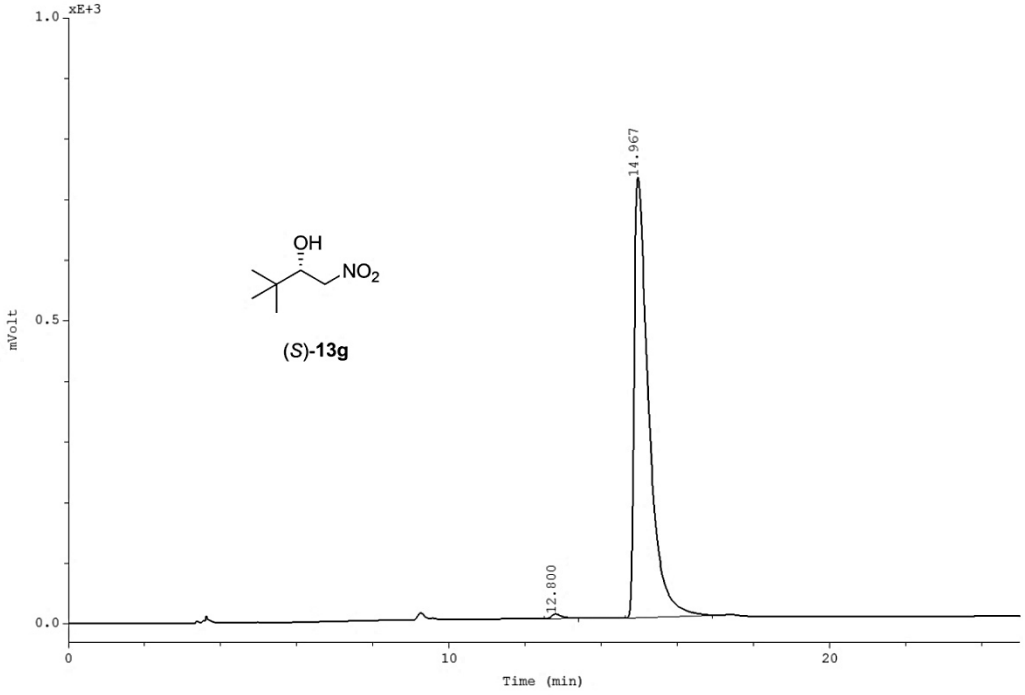


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	31.12	30.13	33.59	320.98	349.59	99.62	99.70
2	34.28	33.59	35.23	1.23	1.05	0.38	0.30

Chiralcel OD-3, *n*-hexane/*i*PrOH 97:3, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 12.8 min; t_R (*S*-enantiomer) = 15.0 min



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.78	12.46	14.40	444.95	169.74	52.80	49.77
2	15.12	14.76	16.80	397.69	171.30	47.20	50.23



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.80	12.49	13.40	7.22	2.22	0.98	0.68
2	14.97	14.61	16.92	726.51	322.98	99.02	99.32

6.4 The First Modular Route to Core-Chiral Bispidine Ligands and Their Application in Enantioselective Copper(II)-Catalyzed Henry Reactions

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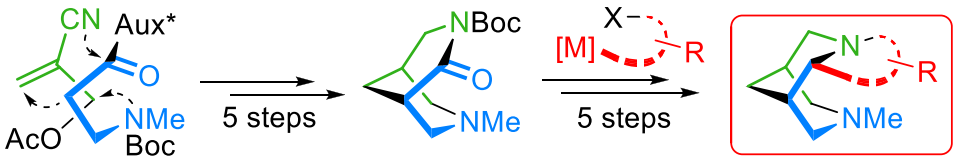

application: up to 99% *ee* in enantioselective Henry reactions

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CHEMISTRY A European Journal Full Paper

Asymmetric Synthesis

The First Modular Route to Core-Chiral Bispidine Ligands and Their Application in Enantioselective Copper(II)-Catalyzed Henry Reactions

Dagmar Scharnagel,[a] Andreas Müller,[b] Felix Prause,[a] Martin Eck,[c] Jessica Goller,[a] Wolfgang Milius,[d] and Matthias Breuning*[a]

Abstract: The first modular and flexible synthesis of core-chiral bispidines was achieved by using an "inside-out" strategy. The key intermediate, a NBoc-activated bispidine lactam, was constructed in enantiomerically pure form from a chirally modified β-amino acid and 2-(acetoxymethyl)acrylonitrile in just five steps and good 48% yield. A simple addition–reduction protocol permitted a highly *endo*-selective introduction of substituents and, thus, a fast and variable access to 2-*endo*-substituted and 2-*endo*,*N*-fused bi- and tricyclic bispidines. The new diamines were evaluated as the chiral ligands in asymmetric Henry reactions. Excellent enantioselectivities of up to 99% *ee* and good diastereomeric ratios of up to 86:14 were reached with a copper(II) complex modified by a 2-*endo*,*N*-(3,3-dimethylpyrrolidine)-annelated bispidine. Its performance is superior to that of the well-known bispidines (−)-sparteine and the (+)-sparteine surrogate.

Introduction

Among chiral diamine ligands, the natural bisquinolizidine alkaloid[1] (−)-sparteine (**1**) and the synthetic[2] (+)-sparteine surrogate **2** (Figure 1) have received particular attention because of their unique effectiveness in many asymmetric transformations.[3–5] In combination with the strong base *s*BuLi, they are the ligands of choice[6] in all kind of enantioselective deprotonation–electrophilic trapping reactions of weakly C–H acidic compounds.[7] Since the pioneering work of Hoppe[8] and Beak[9] on the (−)-sparteine mediated lithiation of α-methylene groups in *O*-alkyl and *N*-alkyl carbamates, this new principle has been extended to many other substrates, including allylic,[10] benzylic,[11] and aromatic[12] protons, and prochiral methyl groups in phosphine boranes.[13] New recent applications include Aggarwal's enantioselective homologation of boronic esters[14] and McGlacken's α-alkylation of *N*,*N*-dimethylhydrazones.[15] High enantioselectivities were also reached with **1** and **2** in the addition of organolithium reagents to alkenes (carbolithiation).[16] The excellent coordination abilities of **1** and **2** to other metals were successfully used in the desymmetrization of *meso*-anhydrides with Grignard reagents[17] and in Reformatzky reactions.[18] In addition to these applications, which require (over)stoichiometric amounts of **1** and **2**, the number of catalytic enantioselective reactions with **1** and **2** as the chiral ligands is steadily growing.[19] Excellent selectivity factors were reached in the Pd-catalyzed, oxidative kinetic resolution of secondary alcohols developed by Sigman[20] and Stoltz.[21] With copper complexes of **1** and **2**, good to excellent enantioselectivities were achieved in the dynamic thermodynamic resolution of binol derivatives[22] and in Henry reactions.[23,24]

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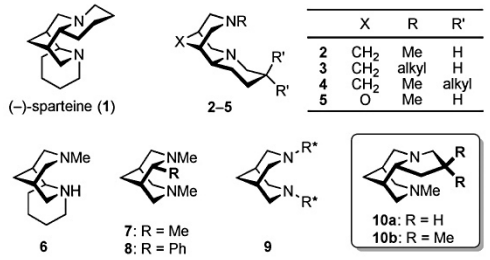

Figure 1. A selection of known bispidine ligands and the primary target structures **8** and **10**.

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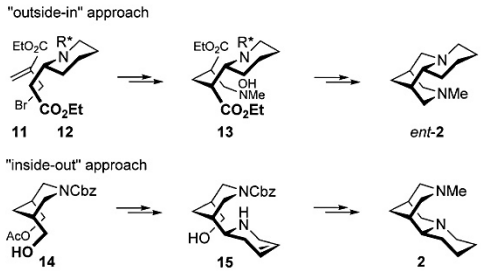
The high stereodiscrimination abilities of these diamines have their origin in the rigid bispidine (3,7-diazabicyclo[3.3.1]-nonane) core that is flanked by an *endo*-fused piperidine and, in the case of **1**, also by an *exo*-annelated one. Structure–selectivity studies on deprotonation–trapping reactions[25] revealed that the *exo*-ring in **1** is only of minor importance for the chirality transfer, as obvious from the high degree of stereocontrol reached with **2** and the low one observed with **6**.[26] Modifications of the structure of **2**, for example, variation of the *N*-alkyl group as in **3**,[27] addition of substituents on the *endo*-fused piperidine as in **4**,[28] or replacement of this ring by an *endo*-oriented methyl group as in **7**,[29] usually resulted in significantly lower levels of chirality transfer. Formal exchange of the methylene bridge in **2** by an ether function lead to the structurally closely related 9-oxabispidine **5**,[30,31] which, however, underwent rearrangement in the strong basic milieu required for deprotonation reactions.[32] Finally, bispidines of type **9**, carrying the chiral information in the side chains at the nitrogen atoms, could also not compete with **1** and **2** in terms of yield and stereocontrol.[33] Thus, the core-chiral, *N*-methyl bispidine **2** with the *endo*-fused piperidine seems to meet best the minimum requirements for a high chirality transfer. It should be noted that the bispidines **5** and **9**, although they gave insufficient results in deprotonation reactions, induced promising enantioselectivities in several other asymmetric transformations.[30,31,34]

The enantioselective total synthesis of core-chiral bispidine ligands and natural products is still a considerable task.[35,36] The existing approaches can loosely be categorized in "outside-in" and "inside-out" according to the strategy used.[37] In the former ones,[35c–e,g–k] the bispidine core is assembled in the final stages from individual precursors that already possess the later-on outer rings or substituents. These routes are characterized by a high degree of convergence, but do not permit late-stage variations of the substituents at the core. An instructive example for such an approach is O'Brien's concise synthesis of *ent*-**2** (Scheme 1), in which the bispidine skeleton is successively constructed using a diastereoselective Michael addition between the chiral homopipecolate **12** and the α-bromomethyl acrylate **11** as the key step.[35c] "Inside-out" approaches,[35a,b,f] by contrast, start with the stereoselective construction of a bispidine core precursor, to which the outer rings or substituents are attached. This strategy usually requires more steps, but will allow a maximum of flexibility and modularity, although this advantage has not yet been exploited in bispidine chemistry.[38] Lesma applied the "inside-out" principle in his synthesis of the (+)-sparteine surrogate **2**, in which the chiral, mono-acetylated piperidine-3,5-dimethanol **14** containing all carbon atoms of the central bispidine framework served as the key intermediate.[35b]

In the course of our investigations on rigid diamines,[39] we intended to develop a more generally applicable route to enantiopure, core-chiral bispidines. Herein we present a multigram approach that fulfills the demand of high flexibility. We demonstrate its modularity on the synthesis of the new 2-*endo*-phenyl-substituted bicyclic bispidine **8** (see Figure 1), the known derivative *ent*-**2**, and the novel tricyclic bispidines **10a**[36a,40] and **10b**, both carrying a 2-*endo*,*N*-fused pyrrolidine.



Scheme 1. Key steps of O'Brien's[35c] and Lesma's[35b] enantioselective syntheses of the tricyclic bispidines *ent*-**2** and **2**, illustrating the basic strategy of the "outside-in" and "inside-out" approaches.

The latter compounds are of particular interest since they allow, for the first time, a study of the influence of the ring size on the chirality transfer in bispidine-mediated asymmetric reactions. We found that diamine **10b** gives excellent enantioselectivities in copper-catalyzed Henry reactions, superior to those reached with the standard bispidines **1** and **2**.

Results and Discussion

Retrosynthetic analysis

Main focus was put on a route that permits a maximum of modularity and flexibility with respect to a late-stage introduction of 2-*endo* substituents and 2-*endo*,*N*-fused rings. We anticipated that this demand will be fulfilled best by using the "inside-out" strategy (vide supra) in combination with the NBoc-activated bispidine lactam **16** as the chiral key intermediate (Scheme 2). In analogy to reactions on related bicyclic systems,[30] the direct nucleophilic attack on the carbonyl group in **16** as well as the second one on the resulting imine or iminium species should selectively occur from the sterically less hindered, convex *exo*-face. The envisioned introduction of *endo*-substituents will thus be possible by a simple addition–*exo*-reduction sequence. For the construction of **16**, we choose the chirally modified β-amino acid **18** and the acryl nitrile **17** for the following reasons: i) the stereotransfer in the decisive addition of **18** to **17** should be high since well-established auxiliary-based methods can be used; ii) all carbon and nitrogen atoms of the bispidine to be synthesized are already in place in **17** and **18**; iii) both educts serve as trifunctional building blocks, with **17**, possessing two electrophilic positions in 3 and 3′ position and a nucleophilic nitrogen atom masked as a cyanide, and **18**, carrying an electrophilic carbonyl group and two nucleophilic positions, the α-carbon atom and the amino function; iv) similar disconnections had been successfully used in O'Brien's syntheses of *ent*-**2**[35c] (see Scheme 1) and **1**.[35e] Thus, diastereoselective addition of **18** to **17** will join the two building blocks and, after elimination of HX, create a new Michael system, to which the amino function of **18** can add after deprotection. Reduction of the nitrile in the resulting piperidine frees the second nitrogen atom that will attack the carbonyl

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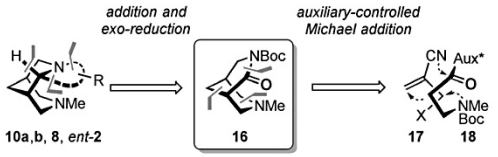
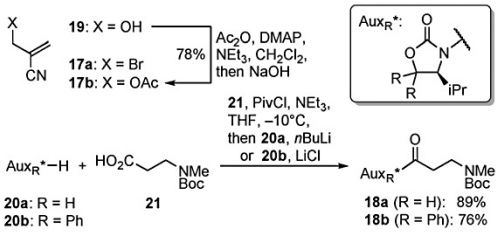


Scheme 2. Retrosynthetic analysis of *ent*-**2**, **8** and **10a,b** via the chiral NBoc bispidine lactam **16** as the key intermediate.

group, thereby generating the desired bispidine system **16** under loss of the chiral auxiliary.

Synthesis of the key intermediate 16

The preparation of **16** required suited starting materials of the general formulae **17** and **18** (Scheme 3). The known bromide **17a**[41] and the acetate **17b** were chosen as the Michael acceptors. The latter compound, **17b**,[42] was prepared using a protocol that took care of its high volatility and reliably afforded good yields: The alcohol **19** was acetylated with Ac_2O/NEt_3 in CH_2Cl_2 to quantitatively give crude **17b** after fast flash chromatography. The residual impurities, Ac_2O and AcOH, were removed by short treatment of the mixture with an equimolar amount of NaOH in CH_2Cl_2. This provided, after careful evaporation of most of the solvent, a concentrated solution of analytically pure **17b** in good 78% yield.[43] As the chiral auxiliaries in **18**, the two L-valine derived oxazolidinones **20a**[44] and **20b**[45] were selected. Activation of the known[46] NBoc-protected[47] β-amino acid **21** with pivaloyl chloride and treatment with lithiated **20a** or **20b**/LiCl delivered **18a** and **18b** in good 89 and 76% yield, respectively.

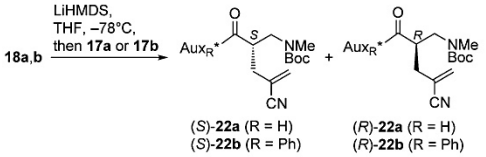


Scheme 3. Preparation of the building blocks **17a,b** and **18a,b**.

The results of the Michael additions of **17** to **18** are shown in Table 1. Deprotonation of **18a** with LiHMDS in THF at −78 °C and trapping of the enolate with **17a** furnished, under elimination of HBr, the acrylonitrile (*S*)-**22a** with acceptable 89:11 d.r. All attempts to remove the minor isomer by column chromatography provided an insufficient 95:5 mixture in 59% yield at best. α-Alkylation of the Superquad-modified β-amino acid **18b** afforded (*S*)-**22b** with comparable 90:10 d.r., irrespective whether **17a** or **17b** were used as the Michael acceptors. In this case, chromatographic separation of the major diastereomer was successful, delivering 59% of analytically pure (*S*)-**22b**. Advantageously for larger scale preparations, unwanted (*R*)-**22b** could also be removed by simple trituration of the primarily resulting semi-solid with Et_2O/*n*-pentane under ultra-sonification. This afforded diastereomerically pure (*S*)-**22b** in good 78% yield, which was used further on.

After TFA-mediated deprotection of the NBoc group in (*S*)-**22b**, a ring closure to the 3,5-*cis*-disubstituted piperidine (*R*,*S*)-**23** was examined (Scheme 4). A fast cyclization occurred in the presence of the Lewis acid $LiClO_4$, giving a 70:30 mixture of (*R*,*S*)-**23** and the unwanted *trans*-diastereomer (*S*,*S*)-**23**. Under thermal conditions (CH_2Cl_2, reflux), the ring closure proceeded more slowly, but with a significantly improved 91:9 initial diastereomeric ratio. Although purification by flash chromatography resulted in a slight diastereomeric enrichment (94:6, 85% yield), full separation of the isomers was tedious. Luckily, this is not necessary since (*S*,*S*)-**23** cannot cyclize to a bispidine due to the *trans*-orientation of the substituents.[48] Moreover, experiments with the pure isomers revealed that (*S*,*S*)-**23** and (*R*,*S*)-**23** react differently when treated with $NaBH_4/NiCl_2{\cdot}6H_2O$ (Table 2).[49] The nitrile function is selectively reduced in the *cis*-diastereomer (*R*,*S*)-**23**, giving the desired bispidine amide **24** in high 92% yield after in-situ cyclization under loss of the chiral auxiliary, while transesterification to (*S*,*S*)-**25** occurred in the *trans*-diastereomer (*S*,*S*)-**23** under the very same conditions. Application of the reduction-cyclization protocol to mixtures of

Table 1. Michael additions of **18** to **17**.



Amino Acid	Acrylate	Product	Initial d.r.[a]	Purification[b]	Yield [%][c]	Final d.r.[d]
18a	**17a**	**22a**	89:11	**A**	59	95:5
18b	**17a**	**22b**	90:10	**A**	59	>99:1[e]
18b	**17b**	**22b**	90:10	**B**	78	>99:1[e]

[a] Ratio (*S*)-**22**/(*R*)-**22**, determined by ^{1}H NMR of the crude reaction mixture. [b] Purification and diastereomer separation by chromatography (**A**) or trituration (**B**). [c] Isolated yield. [d] Ratio (*S*)-**22**/(*R*)-**22**, determined by ^{1}H NMR of the purified product. [e] Minor diastereomer no more detectable by ^{1}H NMR.

Table 2. Reduction and cyclization of (*R*,*S*)-**23**/(*S*,*S*)-**23** mixtures.

(*R*,*S*)-**23**/(*S*,*S*)-**23**	Yield **24** [%][a]	Yield (*S*,*S*)-**25** [%][a]
100:0	92	0
94:6	88 (94)[b]	n.d.[c]
60:40	59 (98)[b]	n.d.[c]
0:100	0	95

[a] Isolated yield. [b] % of the maximum theoretical yield. [c] n.d.: not determined.

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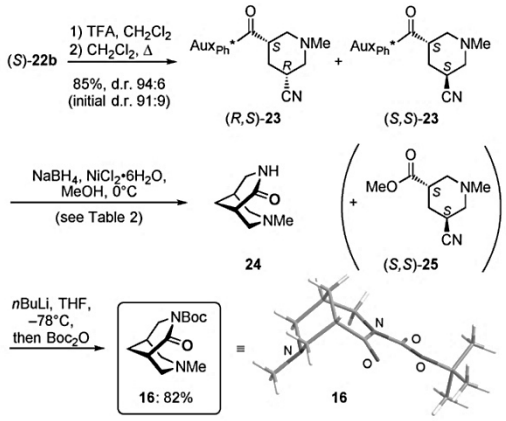
(*R*,*S*)-**23** and (*S*,*S*)-**23** afforded the readily separable products **24** and (*S*,*S*)-**25** exactly in the ratio of the starting materials. Thus, bispidine **24** was accessible from (*R*,*S*)-**23** (d.r. 94:6) in 88% yield, which corresponds to 94% of the maximum theoretical yield. Final attachment of the NBoc group required deprotonation of the amide[50] and provided **16** in 82% yield. In sum, the key intermediate **16**, the crystal structure of which is shown in Scheme 4,[51] was accessed from the chirally modified β-amino acid **18a** in just five steps and good 48% overall yield.

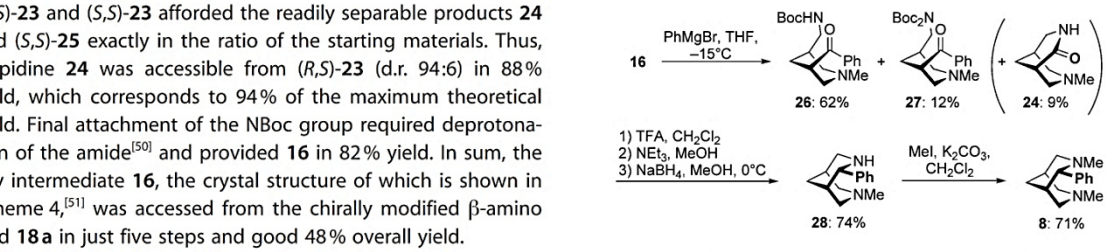


Scheme 4. Synthesis of the chiral key intermediate **16** from (*S*)-**22b** and the crystal structure of **16**.[51]

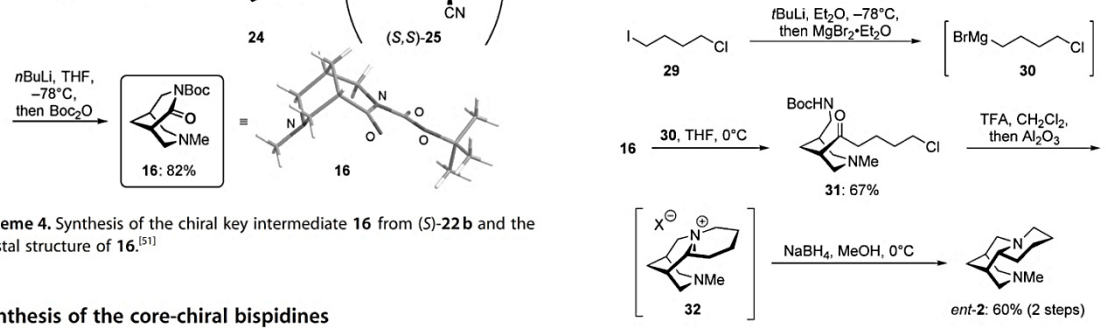
Synthesis of the core-chiral bispidines

Key to the *endo*-selective introduction of substituents at the NBoc-activated bispidine lactam **16** was the addition–*exo*-reduction strategy mentioned earlier. The synthesis of the first target molecule, the bicyclic, 2-*endo*-phenyl bispidine **8**, was straightforward (Scheme 5). Addition of PhMgBr to **16** delivered the expected ring-opened amino ketone **26** in 62% yield, along with the $NBoc_2$ derivative **27** (12%) and the *N*-deprotected bispidine lactam **24** (9%). The latter two products are apparently the result of an intermolecular Boc transfer between the imide **16** and the initially formed anion of **26**. The ketones **26** and **27** were subjected to a three-step deprotection–cyclization–reduction sequence. NBoc removal with TFA, imine formation under slightly basic conditions, and *exo*-selective reduction with $NaBH_4$ provided exclusively the 2-*endo*-phenyl bispidine **28** in 74% yield. Final methylation with MeI/K_2CO_3 delivered the desired product **8** in overall five steps and 39% yield from **16**.

The tricyclic bispidine *ent*-**2** with the 2-*endo*,*N*-fused piperidine was accessed in just three steps and good 40% overall yield following the same route (Scheme 6). The Grignard reagent **30**, which already carries the leaving group required for the construction of the outer piperidine ring, was prepared from 1-chloro-4-iodobutane (**29**) by lithiation with *t*BuLi and subsequent transmetalation with $MgBr_2{\cdot}OEt_2$. Its addition to **16** furnished the chloroketone **31**, which was deprotected and reductively cyclized to give enantiopure *ent*-**2** in 60% yield over two steps. It should be noted that the substitution of the chloride by the nitrogen atom occurred on the stage of the imine, leading to the iminium salt **32** as an intermediate. The existence of **32** was confirmed by NMR spectroscopy.



Scheme 5. Preparation of the bicyclic bispidine **8** from the key intermediate **16**.



Scheme 6. Three-step sequence to the tricyclic bispidine *ent*-**2** from **16**.

Since Grignard reagents and lithium organyls of 1,3-dihalogenated propanes are not stable,[52] the synthesis of the 2-*endo*,*N*-pyrrolidine-fused bispidines **10a**[36a,40] (R = H) and **10b** (R = Me) had to be slightly modified (Scheme 7). The organolithium compounds **34**, which are conveniently prepared from lithium wire and ethereal solutions of the OTBS-protected 3-bromopropanols **33**,[53] were added to the bispidine **16** in good to excellent yields (72 and 96%, respectively). Desilylation of the resulting ketones **35** furnished complex product mixtures, dominated by the hydroxy ketones **36** and the diastereomeric, cyclic hemiacetals **37**. Treatment of **36a**/**37a** with PPh_3/CCl_4 provided the desired chloroketone **38** (84% yield over two steps), which was *N*-deprotected and reductively cyclized to give the target bispidine **10a** in overall five steps and low 19% yield from **16**. In the case of **36b**/**37b**, no Appel product was observed, but the enol ether **39**. This reaction pathway is probably a consequence of the strong Thorpe–Ingold effect of the geminal methyl groups,[54] which stabilize the cyclic hemiacetal that dehydrates upon activation of the hydroxy group. All attempts to convert **39** into **10b** failed.

The unwanted hemiacetal formation was avoided by changing the strategy and constructing the bispidine core first

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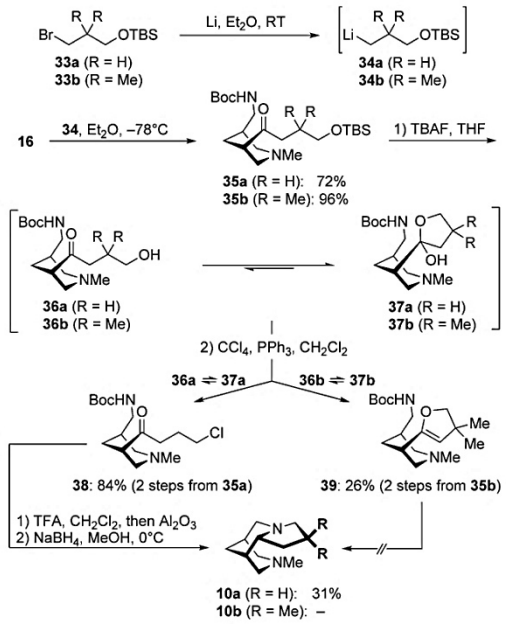
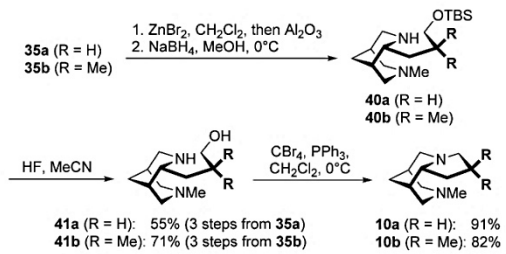


Scheme 7. Synthesis of the tricyclic bispidine **10a** under simultaneous bispidine and pyrrolidine formation.

(Scheme 8). Selective NBoc deprotection in **35** with $ZnBr_2$[55] followed by reductive cyclization provided the bispidines **40a** and **40b**, which were *O*-desilylated to give the amino alcohols **41a** and **41b** in 55 and 71% yield over three steps. The final pyrrolidine ring closure was initiated by hydroxy-bromide exchange and delivered the target bispidines **10a** and **10b** in overall five steps and good 36 and 56% yield from **16**.

In sum, the practicability and flexibility of our "inside-out" approach via the chiral key intermediate **16** was demonstrated by the successful synthesis of the enantiomerically pure bi- and tricyclic bispidines *ent*-**2**, **8**, and **10a**,**b**.

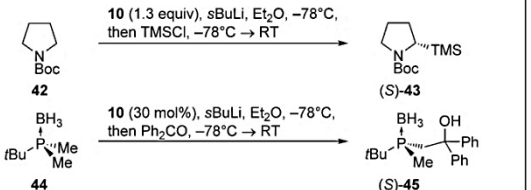


Scheme 8. Successful preparation of the pyrrolidine-fused bispidines **10a** and **10b** by using a bispidine formation–annelation sequence.

Evaluation of the new bispidines in asymmetric synthesis

The chirality transfer abilities of the tricyclic, pyrrolidine fused bispidines **10a** and **10b** were first studied in asymmetric deprotonation–electrophilic trapping reactions. As model reactions served the lithiation–silylation of NBoc pyrrolidine (**42**),[4,5,25] which requires an (over)stoichiometric amount of the chiral diamine, and the enantiotopos-selective lithiation–benzophenone trapping of the dimethylphosphine borane **44**,[13e] for which a catalytic amount of the chiral diamine can be used (Table 3). Acceptable to good yields were achieved in these reactions with the two bispidines **10a** and **10b** as the chiral ligands, but the enantioselectivities (<52% *ee*) were mediocre as compared to the excellent values (up to 98% *ee* for **43** and up to 82% *ee* for **45**) reached with sparteine (**1**) and the (+)-sparteine surrogate **2**.[13e,25] This result is not surprising for the unsubstituted derivative **10a** since quantum chemical calculations by O'Brien, Wiberg and Bailey had predicted a low stereoinduction with this diamine.[25] A high chirality transfer, however, had been expected for the bispidine **10b**, because of the comparable spatial arrangements of **10b** and *ent*-**2**: The 4-*endo*-methyl group in **10b** occupies almost the same space as the outermost methylene group in *ent*-**2**, which should create a very similar chiral environment. There was another surprising observation within this context. From the sense of stereoinduction reached with **1** and **2**,[4,5,25] a preference for the *S*-configured product (*S*)-**43** was expected in the lithiation–silylation of **42**. This product enantiomer was indeed obtained in 52% *ee* with **10b** as the chiral ligand, while the formation of (*R*)-**43** (7% *ee*) was slightly favored in the presence of **10a**,[56] although the very same quadrant is blocked in both diamines by the chirality-transferring pyrrolidine moiety. These results clearly demonstrate the high susceptibility of enantioselective deprotonation reactions to even small geometric changes in the bispidine and, for the first time, prove the eminent importance of the 2-*endo*,*N*-fused pyrrolidine ring in **1** and **2**.

Table 3. Bispidines **10a** and **10b** as the chiral ligands in enantioselective deprotonation–electrophilic trapping reactions.



Entry	Reaction	Bispidine	Yield [%][a]	*ee* [%][b] (config.)
1	**42**→**43**	**10a**	70	7 (*R*)
2	**42**→**43**	**10b**	85	52 (*S*)
3	**44**→**45**	**10a**	82	43 (*S*)
4	**44**→**45**	**10b**	77	33 (*S*)

[a] Isolated yield. [b] Determined by HPLC on chiral phase.

Research by Maheswaran,[23] O'Brien,[24] and our group[31] had shown that $CuCl_2$ complexes of the chiral bispidines **1** and **2** and of the tricyclic 9-oxabispidine **5** are effective catalysts for asymmetric Henry (nitroaldol) reactions.[57,58] The β-nitro alcohols were formed in acceptable to excellent 73–98% *ee*, although the catalyst loadings required (20 mol%) were relative-

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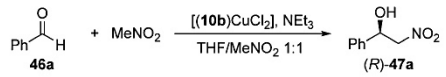
ly high. These promising results prompted us to evaluate our new bispidines **8** and **10** in these *C,C*-bond forming reactions.

Optimization of the reaction conditions was done on the addition of $MeNO_2$ to benzaldehyde (**46a**) in the presence of NEt_3 as the ancillary base and the catalyst [(**10b**)$CuCl_2$], which was obtained as a greenish solid after treatment of **10b** with $CuCl_2$ in MeOH and filtration (Table 4). Under literature conditions,[23,24] the β-nitro alcohol (*R*)-**47a** was accessed in 73% yield and good 94% *ee* (entry 1). The amount of catalyst could be reduced to pleasing 2 mol% if THF/$MeNO_2$ was used as the solvent mixture (entries 2–4). The more than tenfold higher turnover frequency and the gain in enantiocontrol (97% *ee*) have most probably their origin in the better solubility of the catalyst. Lowering the temperature to −20 °C resulted in a further slight increase in asymmetric induction. A significantly prolonged reaction time was required at −25 °C, but without any beneficial effect on the *ee*. Thus, under the optimized conditions requiring just 2 mol% of catalyst, the product (*R*)-**47a** was formed after 42 h in virtually quantitative yield and excellent 98% *ee* (entry 6).

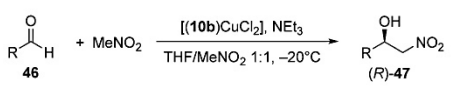
Table 4. Enantioselective Henry reactions catalyzed by [(**10b**)$CuCl_2$]: Optimization of the reaction conditions.



Entry	Cat. [mol%]	NEt_3 [mol%]	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1[c]	20	3	0	48	73	94
2	20	3	0	46	97	95
3	5	5	0	21	99	96
4	2	2	0	45	96	97
5	2	2	−10	47	99	97
6	2	2	−20	42	99	98
7	2	2	−25	66	89	98

[a] Isolated yield. [b] Determined by HPLC on chiral phase. [c] Conditions: $MeNO_2$ (2 equiv), MeOH, 0 °C, see refs. [23, 24].

Table 5. Substrate scope of the enantioselective Henry reactions catalyzed by [(**10b**)$CuCl_2$].



Entry	46, 47	R	Cat./NEt_3 [mol%]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**a**	Ph	2/2	42	99	98
2	**b**	1-naphthyl	2/2	70	94	97
3	**c**	2-MeO-C_6H_4	2/2	41	98	99
4	**d**	3-MeO-C_6H_4	2/2	48	92	98
5	**e**	4-MeO-C_6H_4	2/2	72	80	99
6	**f**	2-O_2N-C_6H_4	2/2	21	94	83
7	**g**	4-O_2N-C_6H_4	2/2	23	81	85
8	**f**	2-O_2N-C_6H_4	10/2	18	98	92
9	**g**	4-O_2N-C_6H_4	10/2	18	76	94
10	**h**	3-furyl	2/2	68	82	97
11	**i**	PhCH=CH	4/4	71	99	96
12	**j**	$PhCH_2CH_2$	4/4	42	88	97
13	**k**	cyclohexyl	4/4	45	99	98
14	**l**	*n*Oct	4/4	49	98	96

[a] Isolated yield. [b] Determined by HPLC on chiral phase.

The substrate scope was investigated next (Table 5). Superb 96–99% *ee* were obtained with electronically more or less neutral (**46a**,**b**) and electron-rich (**46c**–**e**) aromatic aldehydes, carrying substituents in *ortho*-, *meta*-, or *para*-position, and with hetarylic (**46h**), vinylic (**46i**), and aliphatic (**46j**–**l**) aldehydes. For the latter four compounds, the catalyst loading was raised to 4 mol%, in order to counterbalance their lower reactivity. Mediocre levels of stereocontrol (83 and 85% *ee*) were only observed with the electron-poor aromatic aldehydes **46f** and **46g** (entries 6 and 7). This is presumably a consequence of their higher reactivity, which makes the uncatalyzed background reaction competitive. To compensate this effect, the amount of catalyst was increased to 10 mol%, which raised the enantiomeric excess in the β-nitro alcohols **47f** and **47g** to good 92 and 94% (entries 8 and 9).

A critical direct comparison of the efficiency of the chiral bispidines **1**, **2**, **8**, and **10** was done with benzaldehyde (**46a**), 3-methoxybenzaldehyde (**46d**), 4-nitrobenzaldehyde (**46g**), and hydrocinnamaldehyde (**48j**) as the model substrates (Table 6). In these enantioselective Henry reactions, which were all performed under the new conditions with 2 mol% of the respective catalyst [(bispidine)$CuCl_2$], some interesting trends were observed: Firstly, the enantioselectivities increased in the row **10a** ≪ **8** < **1** < **2** < **10b**. Thus, the unsubstituted *endo*-pyrrolidine in **10a** was significantly less stereo-directing than the *endo*-piperidine in **1** and **2**. With the additional methyl groups in **10b**, however, the situation changed. The excellent asymmetric inductions reached with [(**10b**)$CuCl_2$] make this complex the best bispidine-derived catalyst currently known for this type of reactions and impressively show the huge impact of the methyl groups on the chirality transfer. The additional *exo*-annelated piperidine in (−)-sparteine (**1**) appearenty exerts a slight negative effect on the asymmetric induction, as obvious from the somewhat higher *ee* values reached with **2** as compared to **1**. Secondly, the loss of selectivity in the reaction of the nitro derivative **46g** is by far more pronounced with **1** than with **2**, **10a**, and **10b**. This is in good agreement with the observation that Henry reactions catalyzed by [(**1**)$CuCl_2$] proceeded significantly slower, which enhanced the stereo-deterioration by the uncatalyzed background reaction. And thirdly, the bicyclic 2-*endo*-phenyl bispidine **8**, which permits acceptable 73–88% *ee*, again preferentially afforded the enantiocomplementary *S*-configured β-nitro alcohols (*S*)-**47**, although its spatial arrangement is analogous to that of **1**, **10a** and **10b** (all *R*-selective) and opposite to that of **2** (*S*-selective). A good explanation for this surprising reversal in the sense of asymmetric induction is still missing.[59]

Finally, we explored the scope of our new catalyst [(**10b**)$CuCl_2$] in enantio- and diastereoselective Henry reactions (Table 7). Combinations of benzaldehyde (**46a**) or 2-methoxybenzaldehyde (**46c**) with nitroethane (**48a**) or nitropropane (**48b**) delivered the corresponding β-nitro alcohols **49aa**–**cb** with good *anti*/*syn* ratios of up to 86:14 and excellent enantio-

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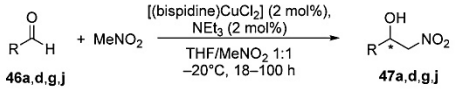
Table 6. Comparison of enantioselectivities reached in Henry reactions catalyzed by [(bispidine)$CuCl_2$] complexes.[a]



46a,**d**,**g**,**j** **47a**,**d**,**g**,**j**

a: R = Ph; **d**: R = 3-MeO-C_6H_4; **g**: R = 4-O_2N-C_6H_4; **j**: R = $PhCH_2CH_2$

	ee [%][b] (configuration) reached with the chiral bispidine				
46	**10a**	**8**	**1**	**2**	**10b**
a	49 (*R*)	85 (*S*)	91 (*R*)	96 (*S*)	98 (*R*)[c]
d	45 (*R*)	89 (*S*)	89 (*R*)	96 (*S*)	98 (*R*)[c]
g	42 (*R*)	85 (*S*)	45 (*R*)	81 (*S*)	85 (*R*)[c]
j	48 (*R*)	73 (*S*)	83 (*R*)	94 (*S*)	94 (*R*)

[a] Yields: 22–78% with **1** and **2**, 77–95% with **8** and **10a**,**b**. [b] Determined by HPLC on chiral phase. [c] Data taken from Table 5.

Table 7. Enantio- and diastereoselective Henry reactions catalyzed by [(**10b**)$CuCl_2$].



46a,**c**,**k** **48a**,**b**

46a: R = Ph; **46c**: R = 2-MeO-C_6H_4; **46k**: R = cyclohexyl
48a: R' = Me; **48b**: R' = Et

Entry	**46**	**48**	**49**	Cat./NEt_3 [mol%]	Yield [%][a]	*anti*-**49**/*syn*-**49**[b]	ee_{anti} [%][c]	ee_{syn} [%][c]
1	**a**	**a**	**aa**	2	90	86:14	97	99
2	**a**	**b**	**ab**	2	93	80:20	97	97
3	**c**	**a**	**ca**	2	89	85:15	99	99
4	**c**	**b**	**cb**	2	99	76:24	98	97
5	**k**	**a**	**ka**	4	82	31:69	97	96
6	**k**	**b**	**kb**	4	51	27:73	98	96

[a] Isolated yield. [b] Determined by ^1H NMR of the product mixture; the relative configurations were assigned based on literature data. [c] Determined by HPLC on chiral phase.

selectivities (≥97% *ee*) in both diastereomers (entries 1–4). The *syn*-diastereomers, by contrast, were preferentially formed with up to 73:27 d.r. in the reactions of the aliphatic cyclohexanecarboxaldehyde (**46k**, entries 5 and 6). Such a reversal in diastereoselectivity is rarely observed.[60]

In the crystal structure of the catalyst [(**10b**)$CuCl_2$] (Figure 2),[61] the highly distorted geometry at the central copper atom is striking. The coordination sphere is neither square planar nor tetrahedral, but an intermediate arrangement with an angle of ca. 60° between the $CuCl_2$ and the CuN_2 plane. This distortion, which is caused by the dimethylpyrrolidine moiety of the chiral bispidine **10b**, clearly shows the strong interactions of the annelated ring with the coordination sites at the copper atom and, in consequence, its stereo-directing effect. Similar tiltings were observed in the crystal structures of [(**2**)$CuCl_2$][24] and [(**5**)$CuCl_2$][31] and appear to be characteristic for copper(II) complexes chirally modified by tricyclic bispidines.

The stereochemical outcome of the Henry reactions with **10** as the chiral ligands can be rationalized by the transition states **50** (Figure 3). In agreement with the commonly accepted

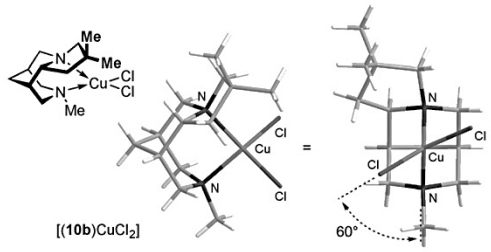
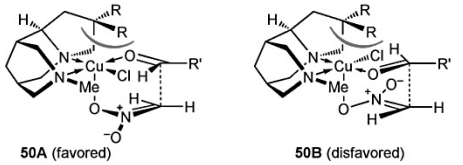


Figure 2. Crystal structure of [(**10b**)$CuCl_2$].[61]

model,[62] we propose a neutral, pentavalent copper species, in which, for maximum activation, the nitronate should bind apically and the aldehyde equatorially. With the northern hemisphere being blocked by the pyrrolidine moiety of the chiral bispidine **10**, the nitronate must coordinate to the southern apical position. Of the two equatorial binding sites, the larger chloride occupies the less hindered and forces the aldehyde into the more congested one in proximity to the pyrrolidine. The orientation of the aldehyde is again determined by steric factors leading to the arrangement shown in **50A**, in which the substituent R′ points into the free space. As a consequence, the nitronate will attack the activated carbonyl group from the *Si* face, leading to the experimentally observed *R*-configured product.[63] The opposite arrangement of chloride and aldehyde, shown in transition state **50B**, is less favored and would lead to the enantio-complementary, *S*-configured product. The energetic difference between **50A** and **50B** strongly depends on the substituents R at the pyrrolidine. While transition state **50B** is still partially accessible with **10a** (R = H) as the chiral ligand, the higher steric pressure of **10b** (R = Me), in particular on the neighboring equatorial binding site, virtually excludes a noticeable population of **50B**. The diastereoselectivities of the Henry reactions cannot be safely predicted by the transition state **50A**, since both, the *E*- and the *Z*-nitronate, show destabilizing interactions, either with the substituent R′ of the aldehyde or the bispidine backbone.[63]



50A (favored) **50B** (disfavored)

Figure 3. Proposed transition states **50A** and **50B**.

Conclusion

Although several conceptually diverse syntheses of core-chiral bispidines are known, a flexible and modular approach to this important class of chiral diamines was still missing. We devel-

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oped an "inside-out" approach that fulfills this demand. The chiral key intermediate, the NBoc-activated bispidine lactam **16**, was constructed from 2-(acetoxymethyl)acrylonitrile **17b** and the β-amino acid **18b**, chirally modified by the Superquad auxiliary. The preparation includes two diastereoselective Michael additions and a nitrile reduction with in-situ amidation, and permits a convenient access to **16** in good 48% overall yield and just five steps. Additions of Grignard reagents or organolithium compounds to **16** furnished ring-opened amino ketones, which were reductively re-cyclized to give highly stereoselectively bicyclic 2-*endo*-substituted bispidines such as **8** or, after further ring closure, 2-*endo*,*N*-fused tricyclic bispidines such as *ent*-**2** or **10**. The new diamines were evaluated on their efficacy in asymmetric transformations. While mediocre enantioselectivities were reached with **10a** and **10b** in lithiation–electrophilic trapping reactions, excellent results were achieved in copper(II)-catalyzed Henry reactions. The addition of nitromethane to diverse aldehydes **46**, comprising aromatic, hetarylic, vinylic, and aliphatic ones, provided, in the presence of just 2–4 mol% of the chiral complex [(**10b**)$CuCl_2$], the corresponding β-nitro alcohols (*R*)-**47** with good yields and in up to superb 99% *ee*. Direct comparison of the catalysts derived from **1**, **2**, **8**, **10a** and **10b** revealed that the geminal methyl groups at the annelated pyrrolidine in **10b** are essential for an efficient chirality transfer and that **10b** is superior to all other bispidine ligands tested so far in this type of reaction. Surprisingly, the enantio-complementary products (*S*)-**47** were obtained with the bicyclic bispidine **8**, although it possesses the same spatial arrangement as **1**, **2**, and **10**. Good diastereoselectivities of up to 86:14 were found in Henry reactions with nitroethane (**48a**) and nitropropane (**48b**). A transition state, **50 A**, that satisfactorily explains the excellent levels of stereocontrol reached with the catalyst [(**10b**)$CuCl_2$] and the sense of the asymmetric induction was proposed.

Experimental Section

All reactions with moisture-sensitive reagents were carried out under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[64] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey-Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey-Nagel, particle size 40–63 μm) was used for column chromatography. Melting points were measured on a Stuart SMP10 digital or a Büchi M-565 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance 400 or a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^1H and ^{13}C NMR data were made on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a Jasco FT-IR-410 or a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra on a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electrospray ionization). The enantiomeric excess of the β-nitro alcohols **47** and **49** and of the phosphine borane **45** was determined by HPLC analysis (Waters Alliance HPLC; Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase. The enantiomeric excess of the pyrrolidine **43** was measured by GC (Trace ThermoQuest) on chiral phase.

The synthesis of the key intermediate **16**, which had been done several times in similar scales and with comparable yields, the preparation of the tricyclic bispidine **10b**, and a general procedure for the enantioselective Henry reactions are given below. For all other experimental procedures, see Supporting Information. The acrylonitrile **17a**,[41] the β-amino acid **21**,[46] the oxazolidinone **20b**,[45] and the TBS-protected 3-bromopropanol **33b**[53] were prepared according to literature protocols.

2-(Acetoxymethyl)acrylonitrile (17b): A solution of 2-(hydroxymethyl)acrylonitrile (**19**; 7.40 g, 89.1 mmol) in dry CH_2Cl_2 (150 mL) was treated at RT with Ac_2O (25.5 mL, 270 mmol), NEt_3 (14.8 mL, 106 mmol), and DMAP (360 mg, 2.95 mmol). Sat. aq. $NaHCO_3$ (50 mL) was added after 3 d and stirring was continued for 10 min. The organic layer was separated and washed with sat. aq. $NaHCO_3$ (2×150 mL). The aqueous layers were re-extracted with CH_2Cl_2 (2× 150 mL) and the combined organic layers were dried over $MgSO_4$. Most of the solvent was evaporated (850 mbar, 40 °C) and the crude product was subjected to flash chromatography (silica gel, Et_2O/*n*-pentane 1:2), delivering **17b** contaminated with Ac_2O and AcOH in a 100:98:60 ratio. This mixture was dissolved in CH_2Cl_2 (50 mL) and 1N NaOH (183 mL; 2.05 equiv NaOH per equiv Ac_2O and 1.05 equiv NaOH per equiv AcOH) was added at 0 °C. After 10 min, the layers were separated and the organic layer was washed with brine (20 mL) and dried over $MgSO_4$. Mild evaporation of most of the solvent (500 mbar, 40 °C) provided a colorless solution (60 w/w%, 14.5 g) of pure **17b** (8.70 g, 69.5 mmol, 78%) in CH_2Cl_2. Note: Special attention was paid to the evaporation of the solvents because of the high volatility of **17b**. Evaporation to dryness results in a significantly lower yield. R_f=0.63 (EtOAc/petroleum ether 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ=6.07 (s, 1H; C=C*H*H), 6.01 (t, J=1.4 Hz, 1H; C=CH*H*), 4.64 (s, 2H; OCH_2), 2.11 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.0 (CO_2), 133.3 (C=CH_2), 118.6 (*C*=CH_2), 116.5 (CN), 63.1 (OCH_2), 20.6 ppm (CH_3); IR (ATR): $\tilde{\nu}$= 2961, 2229, 1743, 1373, 1214, 1038, 956, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_6H_7N_1NaO_2$ [*M*+Na^+]: 148.0369; found: 148.0368.

(*S*)-3-(3-(*tert*-Butoxycarbonyl(methyl)amino)propanoyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one (18b): The β-amino acid **21** (20.0 g, 98.4 mmol) was dissolved in THF (1.5 L), cooled to −35 °C, and treated successively with NEt_3 (34.3 mL, 246 mmol) and PivCl (13.3 mL, 108 mmol). The resulting suspension was stirred for 4 h at −25 °C. LiCl (4.58 g, 108 mmol) and the oxazolidinone **20b** (24.9 g, 88.6 mmol) were added and stirring was continued for 20 h at RT. Et_2O (300 mL) was added and the turbid reaction mixture was washed with sat. aq. NH_4Cl (600 mL), sat. aq. $NaHCO_3$ (2× 600 mL), and brine (400 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography (silica gel, EtOAc/petroleum ether 0:1 → 1:2) and trituration of the resulting white solid in Et_2O/hexane (1:10) under ultra-sonification provided **18b** (31.4 g, 67.3 mmol, 76%) as a white solid. R_f= 0.51 (Et_2O/*n*-pentane 1:1); m.p. 113 °C; $[\alpha]_D^{21}$=−156.8 (c=0.1 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=7.46 (m, 2H; Ph), 7.38 (m, 2H; Ph), 7.34–7.21 (m, 6H; Ph), 5.36 (d, J=3.3 Hz, 1H; 4-H), 3.56–3.31 (m, 2H; NCH_2), 3.15 (ddd, J=16.7, 7.3, 7.1 Hz, 1H; COC*H*H), 3.03–2.89 (m, 1H; COCH*H*), 2.74 (s, 3H; NCH_3), 2.02–1.90 (m, 1H; 4-CH), 1.39 (s, 9H; $C(CH_3)_3$), 0.86 (d, J=7.0 Hz, 3H; 4-CHC*H*$_3$), 0.74 ppm (d, J=6.8 Hz, 3H; 4-CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.1 (3-C), 155.3 (CO_2N), 152.9 (C-2), 142.3, 138.0, 128.9, 128.6, 128.3, 127.9, 125.8, 125.5 (Ph), 89.4 (C-5), 79.5 (*C*(CH_3)$_3$), 64.5 (C-4), 44.7, 44.3 (NCH_2), 34.6 (NCH_3), 34.1, 33.7 ($COCH_2$), 29.8 (4-CH), 28.3

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($C(CH_3)_3$), 21.7, 16.3 ppm (4-$CH(CH_3)_2$); IR (ATR): $\tilde{\nu}$ = 2970, 1781, 1692, 1450, 1364, 1209, 1141, 760, 736, 699 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{34}N_2NaO_5$ [*M*+Na^+]: 489.2360; found: 489.2360.

(*S*)-4-((*tert*-Butoxycarbonyl(methyl)amino)methyl)-5-((*S*)-4-isopropyl-2-oxo-5,5-diphenyloxazolidin-3-yl)-2-methylene-5-oxopentanenitrile [(*S*)-22b]: The chirally modified β-amino acid **18b** (20.6 g, 44.2 mmol), dissolved in dry THF (500 mL), was deprotonated with LiHMDS (1.0 M in *n*-hexane, 48.6 mL, 48.6 mmol) at −78 °C for 3 h. 2-(Acetoxymethyl)acrylonitrile **17b** (60 w/w% in CH_2Cl_2, 12.0 g, 57.6 mmol) was added dropwise and the resulting dark mixture was slowly warmed to RT and stirred overnight. The reaction mixture was quenched with sat. aq. NH_4Cl (300 mL) and extracted with Et_2O (5×100 mL). The combined organic layers were washed with brine (300 mL) and dried over $MgSO_4$ giving, after removal of the solvent under reduced pressure, a 90:10 mixture of the diastereomers (*S*)-**22b** and (*R*)-**22b** in 86% yield. Trituration with Et_2O/*n*-pentane under ultra-sonification provided diastereomerically pure (*S*)-**22b** (18.4 g, 34.6 mmol, 78%) as a colorless solid. R_f = 0.59 (Et_2O/*n*-pentane 3:1); m.p. 144–145 °C; $[\alpha]_D^{21}$ = −129.4 (*c* = 0.1 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (m, 2H; Ph), 7.43–7.26 (m, 8H; Ph), 5.90 (m, 2H; 2-CH_2), 5.35 (d, *J* = 2.7 Hz, 1H; C*H*CH(CH_3)$_2$), 4.48–4.29 (m, 1H; 4-H), 3.57–3.27 (br m, 1H; 4-C*H*H), 2.96–2.62 (br m, 2H; 4-CH*H*, 3-*H*H), 2.46 (s, 3H; NCH_3), 2.37 (dd, *J* = 14.5, 4.8 Hz, 1H; 3-H*H*), 2.07–1.93 (m, 1H; C*H*(CH_3)$_2$), 1.39 (s, 9H; $C(CH_3)_3$), 0.85 (d, *J* = 6.8 Hz, 3H; CHCH_3), 0.75 ppm (d, *J* = 6.8 Hz, 3H; CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$):* δ = 172.8, 172.4 (C-5), 156.0, 155.2 ($CO_2C(CH_3)_3$), 152.7 (CO_2N), 142.3, 142.1, 137.7 (Ph), 132.7 (2-CH_2), 129.1, 128.9, 128.6, 128.3, 128.2, 127.8, 126.4, 125.8, 125.7, 125.5, 125.3, 125.1 (Ph), 120.3 (C-2), 118.3 (C-1), 89.6 (CPh_2), 80.3, 79.9 ($C(CH_3)_3$), 65.5, 65.3 (*C*HCH(CH_3)$_2$), 50.1, 49.4 (4-CH_2), 41.7, 41.4 (C-4), 34.8, 34.6 (NCH_3), 34.3, 33.9 (C-3), 29.7 (*C*H(CH_3)$_2$), 28.44, 28.37 ($C(CH_3)_3$), 21.8, 16.5 ppm (CH(*C*H$_3$)$_2$); IR (ATR): $\tilde{\nu}$ = 2972, 1781, 1693, 1450, 1364, 1173, 1143, 735, 702 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{30}N_3O_3$ [*M*−Boc+2H$^+$]: 432.2282; found: 432.2282. *Mixture of rotamers due to hindered rotation.

The analogous reaction between **18b** (7.02 g, 15.0 mmol) and 2-(bromomethyl)acrylonitrile (**17a**, 2.22 g, 15.2 mmol) gave crude (*S*)-**22b** in 90:10 d.r. as a brown oil. Column chromatography (silica gel, Et_2O/petroleum ether 1:3→1:1) delivered diastereomerically pure (*S*)-**22b** (4.69 g, 8.82 mmol, 59%) as a colorless solid.

(3*R*,5*S*)- and (3*S*,5*S*)-5-((*S*)-4-Isopropyl-2-oxo-5,5-diphenyloxazolidine-3-carbonyl)-1-methylpiperidine-3-carbonitrile [(*R*,*S*)-23 and (*S*,*S*)-23]: A solution of (*S*)-**22b** (20.5 g, 38.6 mmol) in CH_2Cl_2 (600 mL) was treated with TFA (29.8 mL, 389 mmol) and stirred for 20 h at RT. The solvent was removed under reduced pressure and the resulting oil was diluted four times with CH_2Cl_2 (150 mL) and evaporated again. The residue was dissolved in CH_2Cl_2 (60 mL) and NaOH (1 N, 100 mL) was added. After 10 min, the reaction mixture was extracted with CH_2Cl_2 (4×150 mL), and the combined organic layers were washed with brine (300 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue, dissolved in CH_2Cl_2 (300 mL), was heated at 40 °C for 6 d. Removal of the solvent provided a 91:9 mixture of (*R*,*S*)-**23** and (*S*,*S*)-**23**, which was purified by flash chromatography (silica gel, petroleum ether/EtOAc 1:0 → 1:1) to give a 94:6 mixture of (*R*,*S*)-**23** and (*S*,*S*)-**23** (14.1 g, 32.7 mmol, 85%), which was directly used in the next step.

Slow column chromatography (silica gel, CH_2Cl_2/MeOH 100:0 → 95:5) provided, in addition to large batches of mixtures, analytically pure samples of (*S*,*S*)-**23** (d.r. 100:0) and (*R*,*S*)-**23** (d.r. 100:0), which were characterized.

(*R*,*S*)-**23**: Colorless solid; R_f = 0.46 (Et_2O/*n*-pentane 2:1); m.p. 63–65 °C; $[\alpha]_D^{21}$ = −101.8 (*c* = 0.2 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (m, 2H; Ph), 7.41–7.26 (m, 8H; Ph), 5.34 (d, *J* = 3.5 Hz, 1H; C*H*CH(CH_3)$_2$), 3.62 (dddd, *J* = 12.1, 11.0, 3.6, 3.6 Hz, 1H; 5-H), 3.06 (m, 1H; 2-*H*H), 2.86 (dddd, *J* = 12.5, 11.6, 3.9, 3.9 Hz, 1H; 3-H), 2.50 (dm, *J* = 12.1 Hz, 2H; 4-*H*H, 6-*H*H), 2.21 (s, 3H; NCH_3), 2.09 (dd, *J* = 11.4, 11.4 Hz, 1H; 2-H*H*), 2.03–1.91 (m, 2H; 6-H*H*, *CH*(CH_3)$_2$), 1.69–1.57 (m, 1H; 4-H*H*), 0.85 (d, *J* = 7.0 Hz, 3H; CHCH_3), 0.76 ppm (d, *J* = 6.8 Hz, 3H; CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (5-C), 152.6 (CO_2N), 142.3, 137.9, 129.1, 128.8, 128.6, 128.2, 125.9, 125.7 (Ph), 120.2 (3-C), 89.9 (CPh_2), 64.7 (CHCH(CH_3)$_2$), 56.8 (C-2), 55.7 (C-6), 45.7 (1-CH_3), 39.9 (C-5), 30.7 (C-4), 29.9 (*C*H(CH_3)$_2$), 27.0 (C-3), 21.8, 16.5 ppm (CH(CH_3)$_2$); IR (ATR): $\tilde{\nu}$ = 2965, 2800, 1777, 1698, 1362, 1208, 1173, 1051, 734, 702 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{30}N_3O_3$ [*M*+H$^+$]: 432.2282; found: 432.2282.

(*S*,*S*)-**23**: Colorless solid; R_f = 0.56 (Et_2O/*n*-pentane 2:1); m.p. 166–168 °C; $[\alpha]_D^{21}$ = −104.5 (*c* = 0.1 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (m, 2H; Ph), 7.41–7.26 (m, 8H; Ph), 5.26 (d, *J* = 3.4 Hz, 1H; C*H*CH(CH_3)$_2$), 3.95 (m, 1H; 5-H), 3.31 (m, 1H; 3-H), 2.52 (dd, *J* = 10.9, 3.1 Hz, 1H; 2-*H*H), 2.43 (m, 1H; 2-H*H*), 2.25 (dd, *J* = 12.0, 4.0 Hz, 1H; 6-*H*H), 2.08–1.95 (m, 4H; 4-H_2, 6-H*H*, *CH*(CH_3)$_2$), 1.93 (s, 3H; NCH_3), 0.89 (d, *J* = 7.0 Hz, 3H; CHCH_3), 0.77 ppm (d, *J* = 6.8 Hz, 3H; CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3 (5-C), 152.9 (CO_2N), 142.5, 138.0, 129.1, 128.7, 128.6, 128.2, 126.0, 125.7 (Ph), 120.9 (3-C), 89.8 (CPh_2), 65.5 (CHCH(CH_3)$_2$), 56.8 (C-2), 56.3 (C-6), 46.0 (1-CH_3), 37.7 (C-5), 29.8 (CH(CH_3)$_2$), 28.6 (C-4), 26.0 (C-3), 22.0, 16.7 ppm (CH(CH_3)$_2$); IR (ATR): $\tilde{\nu}$ = 2966, 2798, 1781, 1703, 1657, 1449, 1361, 1207, 1177, 741, 697 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{26}H_{30}N_3O_3$ [*M*+H$^+$]: 432.2282; found: 432.2282.

(1*S*,5*S*)-7-Methyl-3,7-diazabicyclo[3.3.1]nonan-2-one (24): $NiCl_2$·$6H_2O$ (5.51 g, 23.2 mmol) was added at 0 °C to a solution of diastereomerically enriched (*R*,*S*)-**23** (d.r. 94:6, 10.0 g, 23.2 mmol) in MeOH (400 mL). $NaBH_4$ (6.14 g, 162 mmol) was added portionwise and the resulting black reaction mixture was stirred for 17 h at RT. The solvent was removed under vacuum and the residue was suspended in EtOAc (500 mL) and filtered through a pad of Celite (5 cm). The filter cake was thoroughly washed with EtOAc (3000 mL) and the combined filtrate and washings were evaporated. Column chromatography (silica gel, CH_2Cl_2/MeOH 9:1→7:3) provided **24** (3.14 g, 20.4 mmol, 88%, 94% of the maximum theoretical yield) as a slightly yellowish solid. R_f = 0.27 (CH_2Cl_2/MeOH4:1); m.p. 93–95 °C; $[\alpha]_D^{21}$ = +20.8 (*c* = 0.3 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (br s, 1H; 3-H), 3.51 (dd, *J* = 11.8, 6.6 Hz, 1H; 4-*H*H), 3.31 (dm, *J* = 11.8 Hz, 1H; 4-H*H*), 3.09 (dm, *J* = 10.9 Hz, 1H; 8-*H*H), 2.84 (dm, *J* = 11.0 Hz, 1H; 6-*H*H), 2.52 (m, 1H; 1-H), 2.22 (s, 3H; 7-CH_3), 2.19 (m, 1H; 6-H*H*), 2.13 (m, 1H; 5-H), 2.07 (dd, *J* = 10.9, 2.5 Hz, 1H; 8-H*H*), 1.95 (dm, *J* = 12.7 Hz, 1H; 9-*H*H), 1.66 ppm (dm, *J* = 12.8 Hz, 1H; 9-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9 (C-2), 62.5 (C-6), 58.4 (C-8), 46.9 (C-4), 46.4 (7-CH_3), 38.7 (C-1), 27.3 (C-9), 27.2 ppm (C-5); IR (ATR): $\tilde{\nu}$ = 3248, 2932, 2779, 1643, 1497, 1315, 1268, 1142, 1045, 729 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_8H_{15}N_2O$ [*M*+H$^+$]: 155.1179; found: 155.1180.

(1*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-7-methyl-3,7-diazabicyclo[3.3.1]-nonan-2-one (16): The bispidine **24** (2.86 g, 18.5 mmol) was suspended in dry THF (220 mL) and *n*BuLi (1.6 M in hexanes, 13.4 mL, 21.4 mmol) was added at −78 °C. After 30 min, Boc_2O (6.08 g, 27.9 mmol) was introduced and the reaction mixture was warmed to RT overnight. Sat. aq. NH_4Cl (200 mL) was added and the aqueous layer was extracted with EtOAc (4×300 mL). The combined organic layers were washed with brine (300 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2/MeOH 1:0 → 9:1) delivered **16** (3.83 g, 15.1 mmol, 82%) as an off-white solid. R_f = 0.39 (CH_2Cl_2/MeOH 95:5); m.p. 99–101 °C; $[\alpha]_D^{21}$ = +29.2 (*c* = 0.1 in CH_2Cl_2); ^{1}H NMR (400 MHz,$CDCl_3$): δ = 3.73 (ddd, *J* = 12.6, 7.4 Hz, 1.0 Hz, 1H; 4-*H*H), 3.61 (dm, *J* = 12.7 Hz, 1H; 4-H*H*), 3.10 (dm, *J* = 10.7 Hz, 1H; 8-*H*H),

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2.79 (dm, J=11.1 Hz, 1H; 6-*H*H), 2.65 (m, 1H; 1-H), 2.24 (m, 1H; 5-H), 2.17 (s, 3H; 7-CH_3), 2.16 (m, 1H; 6-H*H*), 2.07 (dd, J=10.7, 2.3 Hz, 1H; 8-H*H*), 1.94 (dm, J=12.9 Hz, 1H; 9-*H*H), 1.62 (dm, J=13.0 Hz, 1H; 9-H*H*), 1.53 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.6 (C-2), 152.7 (3-C), 82.7 ($C(CH_3)_3$), 62.2 (C-6), 59.6 (C-8), 51.5 (C-4), 46.3 (7-CH_3), 41.4 (C-1), 28.2 ($C(CH_3)_3$), 27.9 (C-5), 26.3 ppm (C-9); IR (ATR): $\tilde{\nu}$=2937, 2785, 1765, 1708, 1469, 1367, 1272, 1247, 1145, 1026 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{23}N_2O_3$ [M+H$^+$]: 255.1703; found: 255.1703.

(3*S*,5*S*)-3-((*tert*-Butoxycarbonylamino)methyl)-5-(4-(*tert*-butyldimethylsilyloxy)-3,3-dimethylbutanoyl)-1-methylpiperidine (35b): Lithium wire (1.39 g, 201 mmol) was added to a solution of the bromide **33b** (11.3 g, 40.1 mmol) in dry Et_2O (80 mL) and the reaction mixture was stirred for 1 h at RT. A portion of this solution (68.0 mL, 30.7 mmol) was added at −78 °C to a solution of the bispidine lactam **16** (6.00 g, 23.6 mmol) in dry Et_2O (300 mL). After 1 h, the reaction mixture was quenched at −78 °C with sat. aq. NH_4Cl (100 mL) and warmed to RT. The aqueous layer was extracted with EtOAc (4×150 mL), and the combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, and evaporated. Column chromatography (silica gel, CH_2Cl_2/MeOH 1:0→9:1) delivered ketone **35b** (10.4 g, 22.7 mol, 96%) as a colorless oil. R_f=0.45 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{30}$=−6.1 (c=1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.60 (br m, 1H; NH), 3.31 (s, 2H; OCH_2), 3.08–2.92 (m, 3H; 3-C*H*$_2$, 6-*H*H), 2.89 (dm, J=10.5 Hz, 1H; 2-*H*H), 2.70 (t, J=11.4 Hz, 1H; 5-H), 2.39 (s, 2H; $COCH_2$), 2.31 (s, 3H; 1-CH_3), 1.91–1.77 (m, 3H; 3-H, 4-*H*H, 6-H*H*), 1.58 (t, J=11.0 Hz, 1H; 2-H*H*), 1.41 (s, 9H; $OC(CH_3)_3$), 0.93 (m, 1H, 4-H*H*), 0.91 (s, 6H; $C(CH_3)_2$), 0.86 (s, 9H, $SiC(CH_3)_3$), −0.01 ppm (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ=211.6 (5-C), 156.1 (CO_2N), 79.5 ($OC(CH_3)_3$), 71.0 (OCH_2), 59.3 (C-2), 56.9 (C-6), 50.1 (C-5), 48.1 ($COCH_2$), 46.3 (1-CH_3), 44.3 (3-CH_2), 36.7 (C-3), 35.9 ($C(CH_3)_2$), 30.2 (C-4), 28.5 ($OC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 24.6, 24.5 ($C(CH_3)_2$), 18.4 ($SiC(CH_3)_3$), −5.4 ppm ($Si(CH_3)_2$); IR (ATR): $\tilde{\nu}$=3359, 2929, 2856, 1703, 1250, 1171, 1092, 836, 774 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{49}N_2O_4Si$ [M+H$^+$]: 457.3456; found: 457.3453.

(1*S*,2*R*,5*S*)-2-(3-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylpropyl)-7-methyl-3,7-diazabicyclo[3.3.1]nonane (40b): A solution of **35b** (10.4 g, 22.7 mmol) in dry CH_2Cl_2 (100 mL) was treated with dry $ZnBr_2$ (10.3 g, 45.6 mmol) and stirred for 2 d. Filtration (basic alumina, activity V, $CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1) and removal of the solvent delivered an oily residue, which was dissolved in MeOH (380 mL). After portionwise addition of $NaBH_4$ (2.58 g, 68.3 mmol) at −15 °C, the reaction mixture was warmed to RT overnight. Removal of the solvent and chromatography (silica gel, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 96:3.6:0.4→80:18:2) provided a mixture of the bispidine **40b** and its protonated form **40b**·HX (7.50 g), which was directly used in the next step.

Basic extraction of **40b**/**40b**·HX afforded analytically pure **40b** as a yellowish oil, which was characterized. R_f=0.48 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{26}$=−11.1 (c=1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.29 (d, J=9.7 Hz, 1H; OC*H*H), 3.24 (m, 1H; 4-*H*H), 3.21 (d, J=9.7 Hz, 1H; OCH*H*), 3.13 (dm, J=11.6 Hz, 1H; 8-*H*H), 3.06 (m, 2H; 2-H, 4-H*H*), 2.93 (dm, J=11.0 Hz, 1H; 6-*H*H), 2.27 (dm, J=11.1 Hz, 1H; 6-H*H*), 2.14 (dm, J=11.6 Hz, 1H; 8-H*H*), 2.11 (s, 3H; 7-CH_3), 1.79–1.64 (m, 4H; 1-H, 5-H, 9-H$_2$), 1.60 (dd, J=14.2, 6.4 Hz, 1H; 2-C*H*H), 1.44 (dd, J=14.2, 4.9 Hz, 1H; 2-CH*H*), 0.91 (s, 3H; $C(CH_3)(CH_3)$), 0.89 (s, 3H; $C(CH_3)(CH_3)$), 0.86 (s, 9H; $C(CH_3)_3$), 0.00 (s, 3H; $Si(CH_3)(CH_3)$), −0.01 ppm (s, 3H; $Si(CH_3)(CH_3)$); ^{13}C NMR (125 MHz, $CDCl_3$): δ=71.8 (OCH_2), 61.4 (C-6), 57.3 (C-2), 56.9 (C-8), 51.9 (C-4), 46.7 (7-CH_3), 41.9 (2-CH_2), 35.4 ($C(CH_3)_2$), 33.5 (C-9), 33.3 (C-1), 28.3 (C-5), 26.0 $C(CH_3)_3$), 25.6, 24.4 ($C(CH_3)_2$), 18.3 ($C(CH_3)_3$), −5.40, −5.43 ppm ($Si(CH_3)_2$); IR (ATR): $\tilde{\nu}$=2927, 2894, 2855, 2773, 1471, 1256, 1088, 850, 833, 772 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{41}N_2OSi$ [M+H$^+$]: 341.2983; found: 341.2984.

(1*S*,2*R*,5*S*)-2-(3-Hydroxy-2,2-dimethylpropyl)-7-methyl-3,7-diazabicyclo[3.3.1]nonane (41b): The mixture of **40b** and **40b**·HX (7.50 g) was dissolved in acetonitrile (75 mL) and treated with HF (38 w/w% in H_2O, 3.75 mL). After 1 h, K_2CO_3 (10 g) and H_2O (10 mL) were added and stirring was continued for 10 min. Evaporation of the solvent and addition of H_2O (50 mL) resulted in a suspension, which was extracted with EtOAc (4×100 mL). Removal of the solvent under vacuum and column chromatography (silica gel, $CHCl_3$/MeOH/NH_3 (aq., 25%) 95:4.5:0.5→90:9:1) delivered the amino alcohol **41b** (3.65 g, 16.1 mmol, 71% from **35b**) as a yellow oil, which solidified upon standing. R_f=0.40 ($CHCl_3$/MeOH/NH_3 (aq., 25%) 80:18:2); m.p. 53 °C; $[\alpha]_D^{25}$=26.5 (c=1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.24 (br s, 1H, NH or OH), 3.30 (d, J=11.5 Hz, 1H; OC*H*H), 3.26 (m, 1H; NH or OH), 3.13 (dd, J=11.4, 1.7 Hz, 1H, OCH*H*), 2.99 (dm, J=11.5 Hz, 2H; 4-*H*H, 8-*H*H), 2.91–2.79 (m, 3H; 2-H, 4-H*H*, 6-*H*H), 2.24 (ddd, J=10.9, 2.7, 2.6 Hz, 1H; 6-H*H*), 2.10 (dm, J=12.0 Hz, 1H; 8-H*H*), 2.08 (s, 3H; 7-CH_3), 1.76 (dm, J=12.3 Hz, 1H, 9-*H*H), 1.66 (dddd, J=12.3, 3.4, 3.3, 2.6 Hz, 1H; 9-H*H*), 1.59 (m, 1H; 5-H), 1.38 (m, 2H; 1-H, 2-*H*H), 1.20 (dm, J=14.4 Hz, 1H; 2-H*H*), 0.97 (s, 3H; $C(CH_3)(CH_3)$), 0.81 ppm (s, 3H, $C(CH_3)(CH_3)$); ^{13}C NMR (125 MHz, $CDCl_3$): δ=71.7 (OCH_2), 61.7 (C-6), 57.0 (C-8), 55.7 (C-2), 51.4 (C-4), 49.4 (2-CH_2), 47.1 (7-CH_3), 35.7 ($C(CH_3)_2$), 35.3 (C-1), 34.6 (C-9), 28.95, 28.92 (C-5, $C(CH_3)(CH_3)$), 22.8 ppm ($C(CH_3)(CH_3)$); IR (ATR): $\tilde{\nu}$=3129, 2901, 2774, 1470, 1444, 1263, 1151, 1066, 1043, 955, 873, 746 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{27}N_2O$ [M+H$^+$]: 227.2118; found 227.2121.

(1*S*,2*R*,8*R*)-4,4,10-Trimethyl-6,10-diazatricyclo[6.3.1.0^{2,6}]dodecane (10b): CBr_4 (6.07 g, 18.3 mmol) and PPh_3 (6.00 g, 22.9 mmol) were added successively at 0 °C to a solution of the amino alcohol **41b** (3.45 g, 15.2 mmol) in dry CH_2Cl_2 (170 mL). After stirring for 1 h, the solvent was evaporated. Flash chromatography (silica gel, deactivated with 7.5% aq. NH_3 (25%), CH_2Cl_2/MeOH/NH_3 95:4.5:0.5→80:18:2) delivered protonated **10b** (4.03 g) as a pale-brown solid, which was dissolved in 2N NaOH (150 mL). Extraction with Et_2O (5×350 mL), drying of the combined organic layers over $MgSO_4$, and evaporation of the solvent provided the bispidine **10b** (2.58 g, 12.4 mmol, 82%) as a slightly reddish oil. R_f=0.21 ($CHCl_3$/MeOH/NH_3 (aq., 25%) 80:18:2); $[\alpha]_D^{21}$=9.2 (c=1.0 in MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ=2.97 (d, J=10.8 Hz, 1H; 7-*H*H), 2.92 (d, J=11.5 Hz, 1H; 11-*H*H), 2.81 (m, 2H; 5-*H*H, 9-*H*H), 2.37 (dd, J=11.0, 3.8 Hz, 1H; 9-H*H*), 2.33–2.18 (m, 3H; 2-H, 7-H*H*, 11-H*H*), 2.16 (s, 3H; 10-CH_3), 1.90 (br s, 1H; 8-H), 1.81 (br s, 1H; 1-H), 1.77 (d, J=8.5 Hz, 1H; 5-H*H*), 1.73 (m, 1H; 12-*H*H), 1.47 (m, 2H; 3-*H*H, 12-H*H*), 1.38 (dd, J=11.4, 5.5 Hz, 1H; 3-H*H*), 1.17 (s, 3H; 4-CH_3), 1.03 ppm (s, 3H; 4-CH_3); ^{13}C NMR (125 MHz, CD_3OD): δ=70.0 (C-5), 68.4 (C-2), 61.1 (C-9), 58.4 (C-7), 55.6 (C-11), 47.2 (10-CH_3), 44.7 (C-3), 36.1 (C-4), 33.5 (C-12), 32.3 (C-1), 31.1, 30.9 (C-8, 4-CH_3), 30.3 ppm (4-CH_3); IR (ATR): $\tilde{\nu}$=2949, 2922, 2767, 1460, 1445, 1371, 1266, 1152, 1106, 779, 732 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{25}N_2$ [M+H$^+$]: 209.2012; found: 209.2013.

General procedure for the asymmetric Henry reactions: The catalysts [(bispidine)$CuCl_2$] were prepared by stirring equimolar amounts of the bispidine **1**, **2**, **8** or **10** and $CuCl_2$ in methanol for 5 h and filtration of the resulting green solid. The aldehyde **46** (300 μmol) was added to a solution of the respective catalyst (6.00 μmol, 2 mol%) in THF (200 μL) and $MeNO_2$ (200 μL, 3.69 mmol), $EtNO_2$ (267 μL, 3.69 mmol), or nPrNO$_2$ (333 μL, 3.69 mmol). The reaction mixture was cooled to −20 °C and NEt_3 (0.5 M in $MeNO_2$, 12.0 μL, 6.00 μmol, 2 mol%) was added. The resulting green solution was stirred until TLC control indicated complete consumption of the aldehyde (18–167 h). Purification by

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column chromatography (silica gel, petroleum ether/EtOAc) delivered β-nitro alcohol **47** or **49**. The enantiomeric excess of the product was determined by HPLC on chiral phase and the *syn/anti* ratios in **49** by ^{1}H NMR of the product mixture. The spectral data of the products were fully consistent with those previously reported. For details, see Supporting Information.

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[1] M. Wink, *Planta Med.* **1987**, *53*, 509 – 514.
[2] A. J. Dixon, M. J. McGrath, P. O'Brien, *Org. Synth.* **2006**, *83*, 141 – 154.
[3] Reviews: a) D. Hoppe, F. Hintze, P. Tebben, M. Paetow, H. Ahrens, J. Schwerdtfeger, P. Sommerfeld, J. Haller, W. Guarnieri, S. Kolczewski, T. Hense, I. Hoppe, *Pure Appl. Chem.* **1994**, *66*, 1479 – 1486; b) D. Hoppe, T. Hense, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282 – 2316; *Angew. Chem.* **1997**, *109*, 2376 – 2410; c) I. Marek, *J. Chem. Soc. Perkin Trans. 1* **1999**, 535 – 544; d) J. Clayden, *Organolithiums: Selectivity for Synthesis* Pergamon Press, New York, **2002**; e) D. M. Hodgson, *Topics in Organometallic Chemistry, Vol 5: Organolithiums in Enantioselective Synthesis* Springer, Berlin, **2003**; f) R. E. Gawley, I. Coldham in *The Chemistry of Organolithium Compounds*, Vol 2 (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**, pp. 997 – 1053; g) D. Hoppe, G. Christoph in *The Chemistry of Organolithium Compounds, Vol. 2* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**, pp. 1055 – 1164; h) O. Chuzel, O. Riant in *Topics in Organometallic Chemistry, Vol 15: Chiral Diazaligands for Asymmetric Synthesis* (Eds.: M. Lemaire, P. Mangeney), Springer, Berlin, **2005**, pp. 59 – 92; i) D. Hoppe, *Synthesis* **2009**, 43 – 55; j) S. P. Thomas, R. M. French, V. Jheengut, V. K. Aggarwal, *Chem. Rec.* **2009**, *9*, 24 – 39; k) J.-C. Kizirian, *Top. Stereochem.* **2010**, *26*, 189 – 251; l) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092 – 10142; m) A. Gómez-SanJuan, N. Sotomayor, E. Lete, *Beilstein J. Org. Chem.* **2013**, *9*, 313 – 322.
[4] M. Breuning, M. Steiner, *Synthesis* **2008**, 2841 – 2867.
[5] P. O'Brien, *Chem. Commun.* **2008**, 655 – 667.
[6] There is just one exception: High 90% *ee* were also reached in the lithiation–silylation of NBoc pyrrolidine (**42**) with (*R*,*R*)-*N*,*N*′-dimethyl-*N*,*N*′-bis(3,3-dimethylbutyl)cyclohexane-1,2-diamine as the chiral ligand, see: a) D. Stead, P. O'Brien, A. Sanderson, *Org. Lett.* **2008**, *10*, 1409 – 1412; b) G. Barker, J. L. McGrath, A. Klapars, D. Stead, G. Zhou, K. R. Campos, P. O'Brien, *J. Org. Chem.* **2011**, *76*, 5936 – 5953; c) P. J. Rayner, P. O'Brien, R. A. J. Horan, *J. Am. Chem. Soc.* **2013**, *135*, 8071 – 8077.
[7] For selected recent work on enantioselective deprotonations in the presence of **1** or **2**, see: a) X. Wu, P. O'Brien, S. Ellwood, F. Secci, B. Kelly, *Org. Lett.* **2013**, *15*, 192 – 195; b) K. B. Wiberg, W. F. Bailey, *J. Org. Chem.* **2013**, *78*, 1742 – 1746; c) G. Gelardi, G. Barker, P. O'Brien, D. C. Blakemore, *Org. Lett.* **2013**, *15*, 5424 – 5427; d) R. Mansueto, F. M. Perna, A. Salomone, S. Florio, V. Capriati, *Chem. Commun.* **2013**, *49*, 4911 – 4913; e) M. Blangetti, H. Müller-Bunz, D. F. O'Shea, *Chem. Commun.* **2013**, *49*, 6125 – 6127; f) Y. K. Ko, C. Im, J. Do, Y. S. Park, *Eur. J. Org. Chem.* **2014**, 3460 – 3467; g) G. J. Tanoury, M. Chen, Y. Dong, R. Forslund, V. Jurkauskas, A. D. Jones, D. Belmont, *Org. Process Res. Dev.* **2014**, *18*, 1234 – 1244; h) E. J. Cochrane, D. Leonori, L. A. Hassall, I. Coldham, *Chem. Commun.* **2014**, *50*, 9910 – 9913; i) J. L.-Y. Chen, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, *53*, 10992 – 10996; *Angew. Chem.* **2014**, *126*, 11172 – 11176; j) J. Fässler, J. A. McCubbin, A. Roglans, T. Kimachi, J. W. Hollett, R. W. Kunz, M. Tinkl, Y. Zhang, R. Wang, M. Campbell, V. Snieckus, *J. Org. Chem.* **2015**, *80*, 3368 – 3386; k) Ref. [6c].
[8] D. Hoppe, F. Hintze, P. Tebben, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*,1422 – 1424; *Angew. Chem.* **1990**, *102*, 1457 – 1459.
[9] S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708 – 9710.
[10] a) D. Hoppe, O. Zschage, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 69 – 71; *Angew. Chem.* **1989**, *101*, 67 – 69; b) M. C. Whisler, L. Vaillancourt, P. Beak, *Org. Lett.* **2000**, *2*, 2655 – 2658.
[11] a) S. Thayumanavan, S. Lee, C. Liu, P. Beak, *J. Am. Chem. Soc.* **1994**, *116*, 9755 – 9756; b) S. Thayumanavan, A. Basu, P. Beak, *J. Am. Chem. Soc.* **1997**, *119*, 8209 – 8216.
[12] a) M. Tsukazaki, M. Tinkl, A. Roglans, B. J. Chapell, N. J. Taylor, V. Snieckus, *J. Am. Chem. Soc.* **1996**, *118*, 685 – 686; b) R. S. Laufer, U. Veith, N. J. Taylor, V. Snieckus, *Org. Lett.* **2000**, *2*, 629 – 631; c) K. Kanda, K. Endo, T. Shibata, *Org. Lett.* **2010**, *12*, 1980 – 1983.
[13] a) A. R. Muci, K. R. Campos, D. A. Evans, *J. Am. Chem. Soc.* **1995**, *117*, 9075 – 9076; b) T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa, K. Yamaguchi, *J. Am. Chem. Soc.* **1998**, *120*, 1635 – 1636; c) M. J. Johansson, L. Schwartz, M. Amedjkouh, N. Kann, *Tetrahedron: Asymmetry* **2004**, *15*, 3531 – 3538; d) M. J. Johansson, K. H. O. Andersson, N. Kann, *J. Org. Chem.* **2008**, *73*, 4458 – 4463; e) J. Granander, F. Secci, S. J. Canipa, P. O'Brien, B. Kelly, *J. Org. Chem.* **2011**, *76*, 4794 – 4799.
[14] a) J. L. Stymiest, G. Dutheuil, A. Mahmood, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2007**, *46*, 7491 – 7494; *Angew. Chem.* **2007**, *119*, 7635 – 7638; b) M. Althaus, A. Mahmood, J. R. Suárez, S. P. Thomas, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 4025 – 4028; c) M. Binanzer, G. Y. Fang, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2010**, *49*, 4264 – 4268; *Angew. Chem.* **2010**, *122*, 4360 – 4364; d) R. Larouche-Gauthier, C. J. Fletcher, I. Couto, V. K. Aggarwal, *Chem. Commun.* **2011**, *47*, 12592 – 12594; e) A. Bonet, M. Odachowski, D. Leonori, S. Essafi, V. K. Aggarwal, *Nat. Chem.* **2014**, *6*, 584 – 589; f) S. Balieu, G. E. Hallett, M. Burns, T. Bootwicha, J. Studley, V. K. Aggarwal, *J. Am. Chem. Soc.* **2015**, *137*, 4398 – 4403.
[15] C. M. McSweeney, V. M. Foley, G. P. McGlacken, *Chem. Commun.* **2014**, *50*, 14817 – 14819.
[16] a) S. Klein, I. Marek, J.-F. Poisson, J.-F. Normant, *J. Am. Chem. Soc.* **1995**, *117*, 8853 – 8854; b) A.-M. L. Hogan, D. F. O'Shea, *Chem. Commun.* **2008**, 3839 – 3851; c) D. Castagnolo, L. Degennaro, R. Luisi, J. Clayden, *Org. Biomol. Chem.* **2015**, *13*, 2330 – 2340.
[17] a) R. Shintani, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 1057 – 1059; *Angew. Chem.* **2002**, *114*, 1099 – 1101; b) M. J. Dearden, M. J. McGrath, P. O'Brien, *J. Org. Chem.* **2004**, *69*, 5789 – 5792.
[18] a) M. Guetté, J. Capillon, J.-P. Guetté, *Tetrahedron* **1973**, *29*, 3659 – 3667; b) M. M. Hansen, P. A. Bartlett, C. H. Heathcock, *Organometallics* **1987**, *6*, 2069 – 2074; c) K. Sorger, H. Petersen, J. Stohrer (Consortium fuer Elektrochemische Industrie GmbH), EP 1394140, **2004** [*Chem. Abstr.* **2004**, *140*, 217387].
[19] a) M. J. McGrath, P. O'Brien, *J. Am. Chem. Soc.* **2005**, *127*, 16378 – 16379; b) M. J. McGrath, J. L. Bilke, P. O'Brien, *Chem. Commun.* **2006**, 2607 – 2609; c) C. Genet, S. J. Canipa, P. O'Brien, S. Taylor, *J. Am. Chem. Soc.* **2006**, *128*, 9336 – 9337; d) P. O'Brien, J. L. Bilke, *Angew. Chem. Int. Ed.* **2008**, *47*, 2734 – 2736; *Angew. Chem.* **2008**, *120*, 2774 – 2776; e) Ref. [13e].
[20] Selected exampes: a) D. R. Jensen, J. S. Pugsley, M. S. Sigman, *J. Am. Chem. Soc.* **2001**, *123*, 7475 – 7476; b) M. S. Sigman, D. R. Jensen, *Acc. Chem. Res.* **2006**, *39*, 221 – 229.
[21] Selected examples: a) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2001**, *123*, 7725 – 7726; b) D. C. Ebner, R. M. Trend, C. Genet, M. J. McGrath, P. O'Brien, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2008**, *47*, 6367 – 6370; *Angew. Chem.* **2008**, *120*, 6467 – 6470.
[22] a) Y. Zhang, S.-M. Yeung, H. Wu, D. P. Heller, C. Wu, W. D. Wulff, *Org. Lett.* **2003**, *5*, 1813 – 1816; b) G. Hu, D. Holmes, B. F. Gendhar, W. D. Wulff, *J. Am. Chem. Soc.* **2009**, *131*, 14355 – 14364.
[23] H. Maheswaran, K. L. Prasanth, G. G. Krishna, K. Ravikumar, B. Sridhar, M. L. Kantam, *Chem. Commun.* **2006**, 4066 – 4068.
[24] J. Canipa, A. Stute, P. O'Brien, *Tetrahedron* **2014**, *70*, 7395 – 7403.
[25] P. O'Brien, K. B. Wiberg, W. F. Bailey, J.-P. R. Hermet, M. J. McGrath, *J. Am. Chem. Soc.* **2004**, *126*, 15480 – 15489.
[26] B. Danieli, G. Lesma, D. Passarella, P. Piacenti, A. Sacchetti, A. Silvani, A. Virdis, *Tetrahedron Lett.* **2002**, *43*, 7155 – 7158.
[27] a) M. J. Johansson, L. O. Schwartz, M. Amedjkouh, N. C. Kann, *Eur. J. Org. Chem.* **2004**, 1894 – 1896; b) C. Genet, M. J. McGrath, P. O'Brien, *Org. Biomol. Chem.* **2006**, *4*, 1376 – 1382; c) A. R. Germain, D. M. Bruggemey-

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er, J. Zhu, C. Genet, P. O'Brien, J. A. Porco Jr., *J. Org. Chem.* **2011**, *76*, 2577 – 2584; d) Refs. [5], [7g], [13c], [17b], [25].

[28] M. Breuning, D. Hein, *Eur. J. Org. Chem.* **2013**, 7575 – 7582.

[29] P.-W. Phuan, J. C. Ianni, M. C. Kozlowski, *J. Am. Chem. Soc.* **2004**, *126*, 15473 – 15479.

[30] M. Breuning, M. Steiner, C. Mehler, A. Paasche, D. Hein, *J. Org. Chem.* **2009**, *74*, 1407 – 1410.

[31] M. Breuning, D. Hein, M. Steiner, V. H. Gessner, C. Strohmann, *Chem. Eur. J.* **2009**, *15*, 12764 – 12769.

[32] M. Breuning, M. Steiner, D. Hein, C. Hörl, P. Maier, *Synlett* **2009**, 2749 – 2754.

[33] a) D. J. Gallagher, S. Wu, N. A. Nikolic, P. Beak, *J. Org. Chem.* **1995**, *60*, 8148 – 8154; b) M. Karikomi, M. Toda, Y. Sasaki, M. Shibuya, K. Yamada, T. Kimura, M. Minabe, K. Hiratani, *Tetrahedron Lett.* **2014**, *55*, 7099 – 7101.

[34] For a selection of successful applications of **9** in enantioselective catalysis, see: a) J. Spieler, O. Huttenloch, H. Waldmann, *Eur. J. Org. Chem.* **2000**, 391 – 399; b) O. Huttenloch, E. Laxman, H. Waldmann, *Chem. Commun.* **2002**, 673 – 675; c) G. Lesma, B. Danieli, D. Passarella, A. Sacchetti, A. Silvani, *Tetrahedron: Asymmetry* **2003**, *14*, 2453 – 2458; d) J. Liu, Z. Yang, Z. Wang, F. Wang, X. Chen, X. Liu, X. Feng, Z. Su, C. Hu, *J. Am. Chem. Soc.* **2008**, *130*, 5654 – 5655; e) Z. Yang, J. Liu, X. Liu, Z. Wang, X. Feng, Z. Su, C. Hu, *Adv. Synth. Catal.* **2008**, *350*, 2001 – 2006; f) J. Liu, Z. Yang, X. Liu, Z. Wang, Y. Liu, S. Bai, L. Lin, X. Feng, *Org. Biomol. Chem.* **2009**, *7*, 4120 – 4127.

[35] For the enantioselective synthesis of bispidines, see: a) (−)-sparteine surrogates *ent*-**2** and **6**: Ref. [26]; b) (+)-sparteine surrogate **2**: B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, A. Silvani, *Tetrahedron Lett.* **2005**, *46*, 7121 – 7123; c) (−)-sparteine surrogate *ent*-**2**: J.-P. R. Hermet, A. Viterisi, J. M. Wright, M. J. McGrath, P. O'Brien, A. C. Whitwood, J. Gilday, *Org. Biomol. Chem.* **2007**, *5*, 3614 – 3622; d) (+)-sparteine (*ent*-**1**): B. T. Smith, J. A. Wendt, J. Aubé, *Org. Lett.* **2002**, *4*, 2577 – 2579; e) (−)-sparteine (**1**): J.-P. R. Hermet, M. J. McGrath, P. O'Brien, D. W. Porter, J. Gilday, *Chem. Commun.* **2004**, *16*, 1830 – 1831; f) (−)-cytisine: B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, A. Silvani, A. Virdis, *Org. Lett.* **2004**, *6*, 493 – 496; g) (+)-cytisine: T. Honda, R. Takahashi, H. Namiki, *J. Org. Chem.* **2005**, *70*, 499 – 504; h) D. Gray, T. Gallagher, *Angew. Chem. Int. Ed.* **2006**, *45*, 2419 – 2423; *Angew. Chem.* **2006**, *118*, 2479 – 2483; i) (+)-thermopsine: R. Brimioulle, T. Bach, *Science* **2013**, *342*, 840 – 843; j) virgiboidine: S. Kress, J. Weckesser, S. R. Schulz, S. Blechert, *Eur. J. Org. Chem.* **2013**, 1346 – 1355; k) *N,N'*-diakyl 2,6-diphenylbispidine: M. Breuning, D. Hein, *Tetrahedron: Asymmetry* **2007**, *18*, 1410 – 1418.

[36] For the total synthesis of core-chiral bispidines via resolution, see: a) J.-P. R. Hermet, D. W. Porter, M. J. Dearden, J. R. Harrison, T. Koplin, P. O'Brien, J. Parmene, V. Tyurin, A. C. Whitwood, J. Gilday, N. M. Smith, *Org. Biomol. Chem.* **2003**, *1*, 3977 – 3988; b) F. H. V. Chau, E. J. Corey, *Tetrahedron Lett.* **2006**, *47*, 2581 – 2583; c) J. D. Firth, P. O'Brien, L. Ferris, *Org. Biomol. Chem.* **2014**, *12*, 9357 – 9365; d) Ref. [29].

[37] The expressions "outside-in" and "inside-out" in the context of bispidine syntheses were introduced by Blakemore: N. R. Norcross, J. P. Melbardis, M. F. Solera, M. A. Sephton, C. Kilner, L. N. Zakharov, P. C. Astles, S. L. Warriner, P. R. Blakemore, *J. Org. Chem.* **2008**, *73*, 7939 – 7951.

[38] The flexibility of "inside-out" approaches has been demonstrated in the enantioselective synthesis of 9-oxabispidines[30,31] and in the non-enantioselective preparation of all three diastereomers of sparteine from a common achiral tetraoxobispidine.[37]

[39] a) M. Breuning, M. Steiner, *Synthesis* **2007**, 1702 – 1706; b) M. Breuning, M. Steiner, *Tetrahedron: Asymmetry* **2008**, *19*, 1978 – 1983; c) D. Scharnagel, F. Prause, J. Kaldun, R. G. Haase, M. Breuning, *Chem. Commun.* **2014**, *50*, 6623 – 6625; d) F. Prause, J. Kaldun, B. Arensmeyer, B. Wennemann, B. Fröhlich, D. Scharnagel, M. Breuning, *Synthesis* **2015**, 575 – 586; e) F. Prause, B. Arensmeyer, B. Fröhlich, M. Breuning, *Catal. Sci. Technol.* **2015**, *5*, 2215 – 2226.

[40] J. R. Harrison, P. O'Brien, D. W. Porter, N. M. Smith, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3623 – 3631.

[41] C. Madelaine, V. Valerio, N. Maulide, *Angew. Chem. Int. Ed.* **2010**, *49*, 1583 – 1586; *Angew. Chem.* **2010**, *122*, 1628 – 1631.

[42] Acrylonitrile **17b** is commercially available and was used in several reactions, but no protocol for its preparation was found.

[43] Evaporation to dryness is not recommended because of significant product loss, even under mild conditions (800 mbar, 40 °C).

[44] C.-D. Lu, A. Zakarian, *Org. Synth.* **2008**, *85*, 158 – 171.

[45] M. Brenner, L. La Vecchia, T. Leutert, D. Seebach, *Org. Synth.* **2003**, *80*, 57 – 65.

[46] I. Kauffmann-Hefner, N. Hauel, R. Walter, H. Ebel, H. Doods, A. Ceci, A. Schuler-Metz, (Boehringer Ingelheim Pharma Gmbh & Co. KG), DE 102006039003, **2008** [*Chem. Abstr.* **2008**, *148*, 284899].

[47] Initial experiments showed that an NBoc-protected β-amino acid derivative had to be used to prevent an in-situ cyclization to the piperidine **23**, which occurred with just low stereocontrol.

[48] An isomerization at the stereogenic center next to the carbonyl group in (*S,S*)-**23** might lead to (*S,R*)-**23** and, after reduction and cyclization, to *ent*-**24**, which would erode the enantiopurity of **24**. This can be excluded since all attempts to isomerize (*S,S*)-**23** under basic conditions failed and since the optical rotations measured for **24**, prepared from batches with varying (*S,S*)-**23**/(*R,S*)-**23** ratios, were virtually identically.

[49] S. Caddick, A. K. de K. Haynes, D. B. Judd, M. R. V. Williams, *Tetrahedron Lett.* **2000**, *41*, 3513 – 3516.

[50] NBoc protection of **24** under standard conditions (Boc_2O, DMAP, NEt_3) provided **16** in just low 50% yield.

[51] Suitable crystals were obtained from DMF. CCDC-1402975 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data%5Frequest/cif.

[52] Grignard reagents or lithium organyls derived from 1,3-dihalogenated propanes rapidly decompose by intramolecular ring closure to cyclopropanes.

[53] a) **33a**: C. Trapella, C. Fischetti, M. Pela', I. Lazzari, R. Guerrini, G. Calo', A. Rizzi, V. Camarda, D. G. Lambert, J. McDonald, D. Regoli, S. Salvadori, *Bioorg. Med. Chem.* **2009**, *17*, 5080 – 5095; b) **33b**: D. H. Hua, S. Venkataraman, R. A. Ostrande, G.-Z. Sinai, P. J. McCann, M. J. Coulter, M. R. Xu, *J. Org. Chem.* **1988**, *53*, 507 – 515.

[54] R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc. Trans.* **1915**, *107*, 1080 – 1106.

[55] S. C. Nigama, A. Mann, M. Taddei, C.-G. Wermuth, *Synth. Commun.* **1989**, *19*, 3139 – 3142.

[56] It should be noted that the unexpected enantiomer was also preferentially formed in the presence of **7** as the chiral ligand, see ref. [29].

[57] General reviews about enantioselective Henry reactions: a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187 – 2209; b) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymmetry* **2006**, *17*, 3315 – 3326; c) C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem.* **2007**, 2561 – 2574; d) Y. Alvarez-Casao, E. Marques-Lopez, R. P. Herrera, *Symmetry* **2011**, *3*, 220 – 245; e) N. Ananthi, S. Velmathi, *Ind. J. Chem.* **2013**, *52*, 87 – 108.

[58] Selected recent examples of enantioselective Cu-catalyzed Henry reactions: a) G. Blay, V. Hernández-Olmos, J. R. Pedro, *Org. Lett.* **2010**, *12*, 3058 – 3061; b) T. Arai, Y. Taneda, Y. Endo, *Chem. Commun.* **2010**, *46*, 7936 – 7938; c) L. Cheng, J. Dong, J. You, G. Gao, J. Lan, *Chem. Eur. J.* **2010**, *16*, 6761 – 6765; d) A. Chougnet, G. Zhang, K. Liu, D. Häussinger, A. Kägi, T. Allmendinger, W.-D. Woggon, *Adv. Synth. Catal.* **2011**, *353*, 1797 – 1806; e) B. V. Subba Reddy, J. George, *Tetrahedron: Asymmetry* **2011**, *22*, 1169 – 1175; f) Y. Zhou, J. Dong, F. Zhang, Y. Gong, *J. Org. Chem.* **2011**, *76*, 588 – 600; g) W. Jin, X. Li, B. Wan, *J. Org. Chem.* **2011**, *76*, 484 – 491; h) R. I. Kureshy, A. Das, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *ACS Catal.* **2011**, *1*, 1529 – 1535; i) L. Yao, Y. Wei, P. Wang, W. He, S. Zhang, *Tetrahedron* **2012**, *68*, 9119 – 9124; j) K. Xu, G. Lai, Z. Zha, S. Pan, H. Chen, Z. Wang, *Chem. Eur. J.* **2012**, *18*, 12357 – 12362; k) J. D. White, S. Shaw, *Org. Lett.* **2012**, *14*, 6270 – 6273; l) D.-D. Qin, W. Yu, J.-D. Zhou, Y.-C. Zhang, Y.-P. Ruan, Z.-H. Zhou, H.-B. Chen, *Chem. Eur. J.* **2013**, *19*, 16541 – 16544; m) R. Ćwiek, P. Niedziejko, Z. Kałuża, *J. Org. Chem.* **2014**, *79*, 1222 – 1234; n) H. Mei, X. Xiao, X. Zhao, B. Fang, X. Liu, L. Lin, X. Feng, *J. Org. Chem.* **2015**, *80*, 2272 – 2280; o) T. Arai, A. Joko, K. Sato, *Synlett* **2015**, *26*, 209 – 214; p) Ref. [39c].

[59] A similar reversal in the sense of asymmetric induction was observed earlier in copper-catalyzed Henry reactions with 9-oxabispidines, see ref. [31].

[60] a) F. Liu, S. Gou, L. Li, *Appl. Organomet. Chem.* **2014**, *28*, 186 – 193; b) Ref. [58a].

[61] Suitable crystals were obtained from $CHCl_3$/EtOAc. CCDC-1402974 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data%5Frequest/cif.

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[62] D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692 – 12693.

[63] A boat transition state cannot fully be excluded. It would provide the same configuration at the alcoholic carbon atom, but the reversed configuration at the nitro-substituted one.

[64] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, 4th ed., Butterworth-Heinemann, Oxford, UK, **2000**.

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Supporting Information

The First Modular Route to Core-Chiral Bispidine Ligands and Their Application in Enantioselective Copper(II)-Catalyzed Henry Reactions

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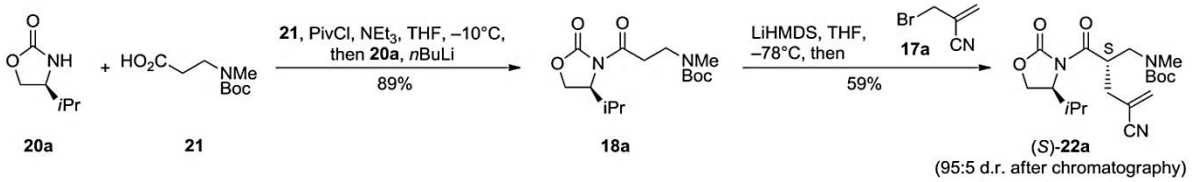
1. Synthetic procedures

For general information about apparatus and methods used, the syntheses of **16** and **10b**, and the general procedure for the Henry reactions, see article.

The acrylonitrile **17a**,[1] the ß-amino acid **21**,[2] the oxazolidinone **20a**,[3] and the TBS-protected 3-bromopropanol **33a**[4] were prepared according to literature protocols.

1.1 Additional investigations on the synthesis of the key intermediate 16

1.1.1 Synthesis and α-alkylation of the chirally modified β-amino acid 18a



1.1.1.1 (*S*)-3-(3-(*tert*-Butoxycarbonyl(methyl)amino)propanoyl)-4-isopropyloxazolidin-2-one (18a)

NEt_3 (43.3 mL, 311 mmol) and PivCl (18.0 mL, 146 mmol) were added at –10°C to a solution of the ß-amino acid **21** (27.0 g, 133 mmol) in anhyd. THF (500 mL), giving an off-white suspension that was stirred for 2 h. The lithiated oxazolidinone, prepared by deprotonation of a solution of **20a** (21.2 g, 164 mmol) in anhyd. THF (200 mL) with *n*BuLi (1.6M in hexanes, 108 mL, 173 mmol) at –20°C for 1 h, was added. After 24 h at RT, the solvent was removed under reduced pressure and the crude product was dissolved in CH_2Cl_2 (500 mL). The reaction mixture was washed with sat. aq. NH_4Cl (200 mL) and brine (200 ml). The aqueous layers were re-extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic layers were washed with brine (200 mL) and dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (silica gel, Et_2O/petroleum ether 0:1 → 3:1) afforded **18a** (37.1 g, 118 mmol, 89%) as a yellowish oil.

R_f = 0.37 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{22}$ = 55.0 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.38 (br s, 1 H; 4-H), 4.26 (dd, *J* = 9.0, 8.3 Hz, 1 H; 5-*H*H), 4.19 (dd, *J* = 9.0, 2.8 Hz, 1 H; 5-H*H*), 3.70–3.44 (m, 2 H; NCH_2), 3.23–3.04 (m, 2 H; $COCH_2$), 2.86 (s, 3 H; NCH_3), 2.41–2.27 (m, 1 H; 4-CH), 1.43 (s, 9 H; $C(CH_3)_3$), 0.89 (d, *J* = 7.0 Hz, 3 H; 4-CHCH_3), 0.86 ppm (d, *J* = 6.9 Hz, 3 H; 4-CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (3-C), 155.7 (CO_2N), 154.2 (C-2), 79.7 ($C(CH_3)_3$), 63.6 (C-5), 58.6 (C-4), 44.7 (NCH_2), 34.8 (NCH_3), 34.4 (br, $COCH_2$), 28.5 ($C(CH_3)_3$, 4-CH), 18.1, 14.8 ppm (4-CH(CH_3)$_2$); IR (ATR): $\tilde{\nu}$ = 2966, 1777, 1687, 1387, 1364, 1203, 1141, 1061, 772 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{26}N_2NaO_5$ [*M* + Na^+]: 337.1734; found: 337.1733.

1.1.1.2 (*S*)-4-((*tert*-Butoxycarbonyl(methyl)amino)methyl)-5-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-2-methylene-5-oxopentanenitrile [(*S*)-22a, d.r. 95:5]

Compound **18a** (8.08 g, 25.7 mmol), dissolved in anhyd. THF (250 mL), was deprotonated with LiHMDS (1.0M in *n*-hexane, 28.3 mL, 28.3 mmol) at –78°C for 1 h. 2-(Bromomethyl)acrylonitrile (**17a**, 7.0 w/w% in Et_2O, 64.2 g, 30.8 mmol) was added dropwise and the resulting dark mixture was slowly warmed to RT and stirred overnight. The reaction mixture was quenched with sat. aq. NH_4Cl (200 mL) and extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$ giving, after removal of the solvent under reduced pressure, an 89:11 mixture of the diastereomers (*S*)-**22a** and (*R*)-**22a** in 86% yield. Column chromatography (silica gel, Et_2O/petroleum ether 1:4 → 1:1) delivered, in addition to several batches of (*S*)-**22a** with different diastereomeric ratios, a lager fraction of (*S*)-**22a** with 95:5 d.r. (5.79 g, 15.3 mmol, 59%) as a colorless oil, which was characterized.

---

[1] Acrylonitrile **17a** is commercially available or can be prepared from **19** using PBr_3, see, for example: a) C. Madeleine, V. Valerio, N. Maulide, *Angew. Chem.* **2010**, *122*, 1628-1631; *Angew. Chem. Int. Ed.* **2010**, *49*, 1583-1586; b) S. Patil, L. Chen, J. M. Tanko, *Eur. J. Org. Chem.* **2014**, 502-505.

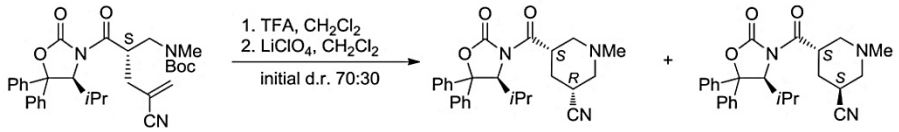
[2] I. Kauffmann-Hefner, N. Hauel, R. Walter, H. Ebel, H. Doods, A. Ceci, A. Schuler-Metz, (Boehringer Ingelheim Pharma Gmbh & Co. KG), DE 102006039003, **2008** [*Chem. Abstr.* **2008**, *148*, 284899].

[3] C.-D. Lu, A. Zakarian, *Org. Synth.* **2008**, *85*, 158-171.

[4] C. Trapella, C. Fischetti, M. Pela', I. Lazzari, R. Guerrini, G. Calo', A. Rizzi, V. Camarda, D. G. Lambert, J. McDonald, D. Regoli, S. Salvadori, *Bioorg. Med. Chem.* **2009**, *17*, 5080-5095.

R_f = 0.40 (petroleum ether/Et_2O 2:1); $[\alpha]_D^{21}$ = –60.0 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89 (s, 1 H; 2-C*H*H), 5.83 (s, 1 H; 2-CH*H*), 4.60–4.36 (m, 2 H; 4-H, C*H*CH(CH_3)$_2$), 4.26 (dd, *J* = 9.0, 8.3 Hz, 1 H; OC*H*H), 4.19 (m, 1 H; OCH*H*), 3.72–3.49 (br m, 1 H; 4-C*H*H), 3.42–3.23 (br m, 1 H; 4-CH*H*), 2.89 (s, 0.15 H; NCH_3 minor diastereomer), 2.88 (s, 2.85 H; NCH_3 major diastereomer), 2.85–2.65 (br m, 1 H; 3-*H*H), 2.37 (dd, *J* = 14.7, 5.0 Hz, 1 H; 3-H*H*), 2.32 (m, 1 H; C*H*(CH_3)$_2$), 1.43 (s, 9 H; C(CH_3)$_3$), 0.89 (d, *J* = 7.0 Hz, 3 H; CHC*H*$_3$), 0.85 ppm (d, *J* = 6.9 Hz, 3 H; CHC*H*$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.7 (C-5), 156.2 (*C*O_2C(CH_3)$_3$), 153.9 (*C*O_2N), 132.6 (2-CH_2), 120.4 (C-2), 118.2 (C-1), 79.9 (*C*(CH_3)$_3$), 63.5 (OCH_2), 59.1 (*C*HCH(CH_3)$_2$), 50.7 (4-CH_2), 41.5 (C-4), 35.5 (NCH_3), 34.7 (C-3), 28.5, 28.4 (C(*C*H$_3$)$_3$, *C*H(CH_3)$_2$), 18.1, 14.8 ppm (CH(*C*H$_3$)$_2$); IR (ATR): $\tilde{\nu}$ = 2967, 1775, 1689, 1385, 1364, 1301, 1201, 1142, 772 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{29}N_3NaO_5$ [*M* + Na$^+$]: 402.1999; found: 402.2005.

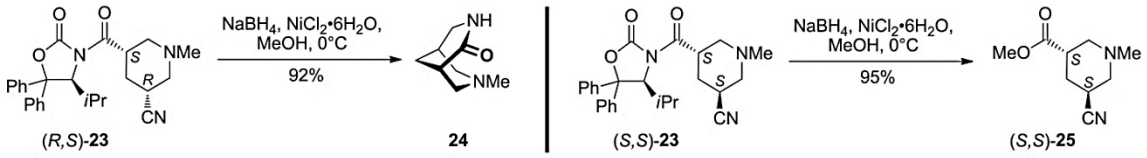
1.1.2 Cyclization of (*S*)-22b in the presence of $LiClO_4$



A solution of (*S*)-**22b** (4.54 g, 8.54 mmol) in CH_2Cl_2 (300 mL) was treated with TFA (6.57 mL, 85.4 mmol) and stirred for 44 h at RT. The solvent was removed under reduced pressure and the resulting oil was diluted three times with CH_2Cl_2 (50 mL) and evaporated again. The residue was dissolved in CH_2Cl_2 (100 mL) and NaOH (0.25N, 90 mL) was added. After 10 min, the reaction mixture was extracted with CH_2Cl_2 (5 × 100 mL), and the combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated and $LiClO_4$ (1.78 g, 16.8 mmol) was added to the residue dissolved in MeCN (150 mL). After 5 h at RT, H_2O (150 mL) was added and the aqueous layer was extracted with Et_2O (4 × 150 mL). The combined organic layers were washed with brine (150 mL) and dried over $MgSO_4$. Removal of the solvent provided a 70:30 mixture of (*R*,*S*)-**23** and (*S*,*S*)-**23**, which was separated by flash chromatography (silica gel, petroleum ether/EtOAc 3:1 → 2:1) to give, in the order of elution, (*S*,*S*)-**23** (1.17 g, 2.71 mmol, 32%) and (*R*,*S*)-**23** (1.60 g, 3.71 mmol, 43%) as colorless solids.

For characterization data of (*S*,*S*)-**23** and (*R*,*S*)-**23**, see article.

1.1.3 (Attempted) reduction and cyclization of (*R*,*S*)-23 and (*S*,*S*)-23



1.1.3.1 (1*S*,5*S*)-7-Methyl-3,7-diazabicyclo[3.3.1]nonan-2-one (24) from (*R*,*S*)-23 [100:0 d.r.]

$NiCl_2$•$6H_2O$ (692 mg, 2.92 mmol) was added at 0°C to a solution of diastereomerically pure (*R*,*S*)-**23** (1.26 g, 2.92 mmol) in MeOH (50 mL). $NaBH_4$ (773 mg, 20.4 mmol) was added portionwise and the resulting black reaction mixture was stirred for 16 h at RT. The solvent was removed under vacuum and the residue was suspended in EtOAc (250 mL) and filtered through a pad of Celite (3 cm). The filter cake was thoroughly washed with EtOAc (1000 mL) and the combined filtrate and washings were evaporated. Column chromatography (silica gel, CH_2Cl_2/MeOH 9:1 → 7:3) provided **24** (413 mg, 2.68 mmol, 92%) as a slightly yellowish solid.

For characterization data of **24**, see article.

1.1.3.2 (1*S*,5*S*)-7-Methyl-3,7-diazabicyclo[3.3.1]nonan-2-one (24) from (*R*,*S*)-23 [60:40 d.r.]

In analogy to the procedure described above, a 60:40 mixture of (*R*,*S*)-**23** and (*S*,*S*)-**23** (2.10 g, 4.87 mmol) was reductively cyclized, delivering **24** (440 mg, 2.85 mmol, 59%) in 98% of the maximum theoretical yield.

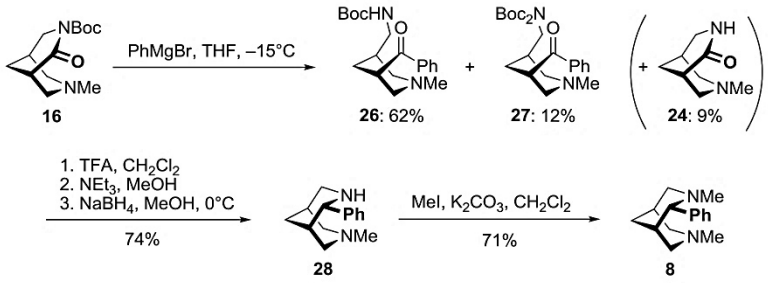
For characterization data of **24**, see article.

1.1.3.3 Methyl (3*S*,5*S*)-5-cyano-1-methylpiperidine-3-carboxylate [(*S*,*S*)-25] from (*S*,*S*)-23 [100:0 d.r.]

The *trans* diastereomer (*S*,*S*)-**23** (52.6 mg, 112 µmol) was treated with $NiCl_2$•$6H_2O$ (29.0 mg, 122 µmol) and $NaBH_4$ (32.3 mg, 854 µmol) in analogy to the procedure above. Column chromatography (silica gel, *n*-pentane/ EtOAc 4:1 → 2:1) provided (*S*,*S*)-**25** (21.1 mg, 116 µmol, 95%) as a colorless oil.

R_f = 0.32 (EtOAc/*n*-pentane 1:1); $[\alpha]_D^{21}$ = –4.9 (*c* = 0.2 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71 (s, 3 H; OCH_3), 3.05 (ddd, *J* = 11.2, 5.7, 3.6 Hz, 1 H; 5-H), 2.88 (m, 1 H; 3-H), 2.76 (m, 1 H; 2-*H*H), 2.64 (m, 1 H; 2-H*H*), 2.54–2.40 (m, 2 H; 6-H_2), 2.31 (s, 3 H; NCH_3), 2.07–1.91 ppm (m, 2 H; 4-H_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2 (3-C), 120.9 (5-C), 56.73, 56.67 (C-2, C-6), 52.2 (OCH_3), 46.2 (NCH_3), 38.9 (C-3), 28.4 (C-4), 26.4 ppm (C-5); IR (ATR): $\tilde{\nu}$ = 2923, 2853, 2791, 1733, 1625, 1447, 1283, 1199, 1153, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_9H_{15}N_2O_2$ [*M* + H$^+$]: 183.1128; found: 183.1130.

1.2 Synthesis of the bicyclic bispidine 8 from 16



1.2.1 (3*S*,5*S*)-3-Benzoyl-5-((*tert*-butoxycarbonylamino)methyl)-1-methylpiperidine (26) and (3*S*,5*R*)-3-benzoyl-5-((di(*tert*-butoxycarbonyl)amino)methyl)-1-methylpiperidine (27)

PhMgBr (1.0M in THF, 3.30 mL, 3.30 mmol) was added at –15°C to a solution of the bispidine lactam **16** (700 mg, 2.75 mmol) in anhyd. THF (50 mL). The reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) and water (5 mL) after 1 h. The aqueous layer was extracted with EtOAc (4 × 50 mL), and the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (basic alumina activity V, Et_2O/MeOH 1:0 → 1:1) afforded the bispidine amide **24** (36.6 mg, 237 µmol, 9%) and a 5:1 mixture of the ketones **26** (565 mg, 1.70 mmol, 62%) and **27** (146 mg, 338 µmol, 12%), which was directly used in the next step.

For characterization data of **24**, see article.

A portion (100 mg) of the mixture of **26** and **27** was subjected to column chromatography (silica gel, Et_2O/MeOH 1:0 → 4:1), providing the analytically pure compounds **26** and **27** as beige resins, which were characterized.

26: R_f = 0.22 (Et_2O/MeOH 9:1); $[\alpha]_D^{21}$ = +6.3 (*c* = 1.0 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (m, 2 H; Ph), 7.54 (m, 1 H; Ph), 7.45 (m, 2 H; Ph), 4.66 (br s, 1 H; NH), 3.69–3.57 (m, 1 H; 3-H), 3.12–2.89 (m, 4 H; 2-*H*H, 6-*H*H, 5-CH_2), 2.31 (s, 3 H; 1-CH_3), 2.08–1.88 (m, 3 H; 2-H*H*, 4-*H*H, 5-H), 1.63 (t, *J* = 11.0 Hz, 1 H; 6-H*H*), 1.41 (s, 9H, C(CH_3)$_3$), 1.16 ppm (ddd, *J* = 12.4, 12.4, 12.3 Hz, 1 H; 4-H*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 201.6 (3-C); 156.1 (CO_2N), 136.0, 133.3, 128.9, 128.4 (Ph), 79.4 (*C*(CH_3)$_3$), 59.6 (C-6), 58.0 (C-2), 46.4 (1-CH_3), 44.4 (5-CH_2), 44.2 (C-3), 36.9 (C-5), 31.3 (C-4), 28.5 ppm (C(*C*H_3)$_3$); IR (ATR): $\tilde{\nu}$ = 3370, 2933, 2791, 1678, 1509, 1447, 1365, 1251, 1166, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{29}N_2O_3$ [*M* + H$^+$]: 333.2173; found: 333.2172.

27: R_f = 0.84 (Et_2O/MeOH 9:1); $[\alpha]_D^{21}$ = –8.5 (*c* = 0.9 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (m, 2 H; Ph), 7.55 (m, 1 H; Ph), 7.46 (m, 2 H; Ph), 3.73–3.48 (m, 3 H; 3-H, 5-CH_2), 3.01 (m, 1 H; 2-*H*H), 2.89 (m, 1 H; 6-*H*H), 2.31 (s, 3 H; 1-CH_3), 2.21–2.08 (m, 1 H; 5-H), 2.02 (t, *J* = 11.3 Hz, 1 H; 2-H*H*), 1.92 (dm, *J* = 13.0 Hz, 1 H; 4-*H*H), 1.67 (t, *J* = 11.3 Hz, 1 H; 6-H*H*), 1.48 (s, 18 H; C(CH_3)$_3$), 1.19 ppm (ddd, *J* = 12.7, 12.5, 12.5 Hz, 1 H; 4-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6 (3-C), 152.9 (CO_2N), 136.2, 133.3, 128.9, 128.4 (Ph), 82.6 (*C*(CH_3)$_3$), 59.9 (C-6), 58.0 (C-2), 49.8 (5-CH_2), 46.5 (1-CH_3), 44.4 (C-3), 36.7 (C-5), 31.6 (C-4), 28.2 ppm (C(*C*H_3)$_3$): IR (ATR): $\tilde{\nu}$ = 2977, 2935, 2790, 1739, 1683, 1366, 1344, 1222, 1163, 1133, 1117, 701 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{37}N_2O_5$ [*M* + H$^+$]: 433.2697; found: 433.2695.

1.2.2 (1*S*,2*S*,5*S*)-7-Methyl-2-phenyl-3,7-diazabicyclo[3.3.1]nonane (28)

TFA (1.57 mL, 20.4 mmol) was added to a 5:1 mixture of the ketones **26** and **27** (in sum 711 mg, 2.04 mmol) in anhyd. CH_2Cl_2 (50 mL). After 24 h, the solvent was removed under reduced pressure and the resulting oil was diluted two times with CH_2Cl_2 (50 mL) and evaporated again. The residue was dissolved in MeOH (100 mL) and NEt_3 (572 µL, 4.08 mmol) was added. The reaction mixture was stirred for 22 h, cooled to 0°C, and $NaBH_4$ (232 mg, 6.12 mmol) was added portionwise. After 2 h, the solvent was removed and the resulting oil was diluted two times with MeOH (80 mL) and evaporated again. Column chromatography (basic alumina activity V, Et_2O) delivered the bispidine **28** (326 mg, 1.51 mmol, 74%) as a brownish resin.

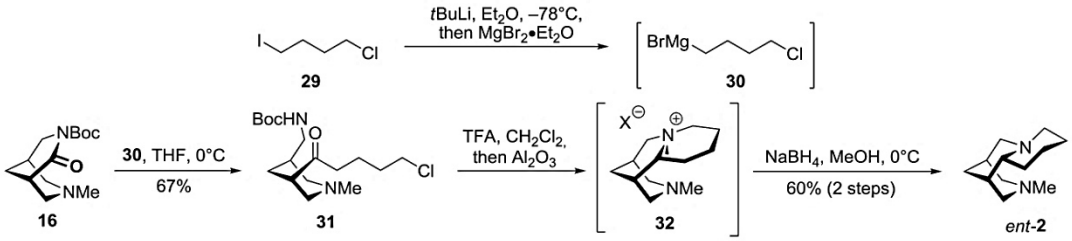
R_f = 0.21 (MeOH + 1% NEt_3); $[\alpha]_D^{21}$ = –52.3 (*c* = 0.9 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 2 H; Ph), 7.27 (m, 2 H; Ph), 7.22 (m, 1 H; Ph), 4.07 (s, 1 H; 2-H), 3.58 (br s, 1 H; 3-H), 3.32 (dm, *J* = 13.5 Hz, 1 H; 4-*H*H), 3.13 (dt, *J* = 13.5, 2.7 Hz, 1 H; 4-H*H*); 3.02 (dm, *J* = 10.9 Hz, 1 H; 6-*H*H), 2.70 (dm, *J* = 11.7 Hz, 1 H; 8-*H*H), 2.33 (dt, *J* = 10.9, 2.7 Hz, 1 H; 6-H*H*), 2.07 (s, 3 H; 7-CH_3), 2.00 (m, 2 H; 8-H*H*, 9-*H*H), 1.84 (m, 2 H; 1-H, 9-H*H*), 1.70 ppm (m, 1 H; 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.9, 128.4, 126.7, 126.3 (Ph), 63.9 (C-2), 61.8 (C-6), 56.7 (C-8), 52.7 (C-4), 46.9 (7-CH_3), 35.4 (C-1), 34.3 (C-9), 29.1 ppm (C-5); IR (ATR): $\tilde{\nu}$ = 2918, 2849, 2773, 1589, 1468, 1264, 1114, 757, 699 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{21}N_2$ [*M* + H$^+$]: 217.1699; found: 217.1700.

1.2.3 (1*S*,2*S*,5*R*)-3,7-Dimethyl-2-phenyl-3,7-diazabicyclo[3.3.1]nonane (8)

Bispidine **28** (138 mg, 638 µmol), dissolved in CH_2Cl_2 (25 mL), was treated with K_2CO_3 (177 mg, 1.28 mmol) and a solution of MeI in CH_2Cl_2 (0.185M, 4.90 mL, 902 µmol) and stirred overnight. 1N NaOH (15 mL) and brine (15 mL) were added, and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Column chromatography (basic alumina activity V, petroleum ether/Et_2O 1:0 → 0:1) provided the bispidine **8** (105 mg, 456 µmol, 71%) as a beige oil.

R_f = 0.06 (MeOH + 1% NEt_3); $[\alpha]_D^{21}$ = –99.8 (*c* = 1.0 in MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.68–7.04 (m, 5 H; Ph), 3.25 (d, *J* = 2.2 Hz, 1 H; 2-H), 3.16 (dm, *J* = 11.5 Hz, 1 H; 4-*H*H), 3.05 (dm, *J* = 11.0 Hz, 1 H; 6-*H*H), 2.74 (dm, *J* = 11.4 Hz, 1 H; 8-*H*H), 2.45 (dm, *J* = 11.4 Hz, 1 H; 4-H*H*), 2.27 (dm, *J* = 11.0 Hz, 1 H; 6-H*H*), 2.14 (s, 3 H; 7-CH_3), 2.00 (s, 3 H; 3-CH_3), 1.96 (m, 1 H; 5-H), 1.86 (dm, *J* = 11.9 Hz, 1 H; 8-H*H*), 1.81–1.67 ppm (m, 3 H; 1-H, 9-H_2); ^{13}C NMR (100 MHz, CD_3OD): δ = 144.5, 129.2, 129.0, 127.9 (Ph), 74.9 (C-2), 62.4 (C-4), 61.5 (C-6), 56.8 (C-8), 47.3 (7-CH_3), 46.0 (3-CH_3), 38.6 (C-1), 34.6 (C-9), 32.2 ppm (C-5); IR (ATR): $\tilde{\nu}$ = 2978, 1780, 1750, 1709, 1365, 1300, 1250, 1149, 1017, 778 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{23}N_2$ [*M* + H$^+$]: 231.1856; found: 231.1857.

1.3 Synthesis of the tricyclic bispidine *ent*-2 from 16



1.3.1 (3*S*,5*S*)-3-((*tert*-Butoxycarbonylamino)methyl)-5-(5-chloropentanoyl)-1-methylpiperidine (31)

*t*BuLi (1.7M in pentane, 8.33 mL, 14.2 mmol) was slowly added at –78°C to a solution of 1-chloro-4-iodobutane (**29**; 800 µL, 6.54 mmol) in anhyd. Et_2O (8 mL). After 2 h, $MgBr_2$•OEt_2 (1.77 g, 6.87 mmol) was introduced and the reaction mixture was stirred for 1 h at –78°C and 1 h at 0°C. A portion of this Grignard solution (6.18 mL, 2.36 mmol) was added at 0°C to a solution of the bispidine lactam **16** (200 mg, 786 µmol) in anhyd. THF (15 mL). After 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl (25 mL) and the aqueous layer was extracted with EtOAc (5 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and evaporated. Column chromatography (silica gel, CH_2Cl_2/MeOH 1:0 → 9:1) delivered the chloroketone **31** (184 mg, 530 µmol, 67%) as a yellowish oil.

R_f = 0.48 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{21}$ = –9.3 (*c* = 1.0 in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.61 (br s, 1 H; NH), 3.52 (t, *J* = 6.2 Hz, 2 H; CH_2Cl), 3.11–2.94 (m, 4 H; 2-*H*H, 6-*H*H, 3-CH_2), 2.86 (m, 1 H; 5-H), 2.56–2.45 (m,

2 H; $COCH_2$), 2.39 (s, 3 H; 1-CH_3), 2.10–1.91 (m, 3 H; 3-H, 4-*H*H, 6-H*H*), 1.80–1.66 (m, 5 H; 2-H*H*, C*H*$_2$C*H*$_2$CH$_2$Cl), 1.43 (s, 9 H; C(CH_3)$_3$), 1.01 ppm (ddd, *J* = 12.7, 12.6, 12.5 Hz, 1 H; 4-H*H*). ^{13}C NMR (125 MHz,$CDCl_3$): *δ* = 210.5 (5-C), 156.1 (CO_2N), 79.7 (*C*(CH_3)$_3$), 59.1 (C-2), 56.6 (C-6), 48.3 (C-5), 46.1 (1-CH_3), 44.7 (CH_2Cl), 44.1 (3-CH_2), 40.3 ($COCH_2$), 36.6 (C-3), 32.0 (*C*H$_2$CH$_2$Cl), 30.3 (C-4), 28.5 (C(*C*H$_3$)$_3$), 20.9 ppm (*C*H$_2$CH$_2$CH$_2$Cl); IR (ATR): $\tilde{\nu}$ = 3369, 2934, 2790, 1700, 1266, 1166, 733, 702 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{31}ClN_2NaO_3$ [*M* + Na$^+$]: 369.1915; found: 369.1917.

1.3.2 (1*S*,2*R*,9*R*)-11-Methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane (*ent*-2)

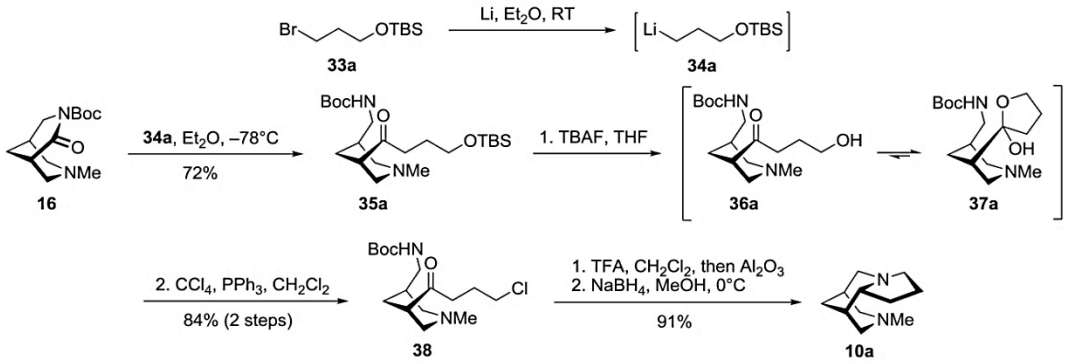
TFA (402 µL, 5.22 mmol) was added at 0°C to a solution of the chloroketone **31** (90.5 mg, 261 µmol) in anhyd. CH_2Cl_2 (5 mL). The reaction mixture was stirred overnight at RT and the solvent was removed under reduced pressure. The resulting oil was diluted three times with CH_2Cl_2 (5 mL) and evaporated again. Column chromatography (basic alumina, activity V, EtOAc/MeOH/NH_3 (aq., 25%) 1:0:0 → 0:9:1) provided the iminium salt **32** (77.1 mg) as a violet resin, which was characterized by its ^{1}H and ^{13}C NMR data.

R_f = 0.44 ($CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1); ^{1}H NMR (500 MHz, CD_3OD): *δ* = 3.97 (dd, *J* = 16.0, 6.0 Hz, 1 H; 8-*H*H), 3.84–3.66 (m, 3 H; 6-H$_2$, 8-H*H*), 3.09 (dm, *J* = 11.0 Hz, 1 H; 12-*H*H), 3.04 (br m, 0.70 H; 3-*H*H)*, 2.96 (m, 2 H; 1-H, 10-*H*H), 2.89–2.78 (m, 0.6 H; 3-H*H*)*, 2.38 (m, 1 H; 9-H), 2.34 (dd, *J* = 11.8, 2.6 Hz, 1 H; 12-H*H*), 2.27 (m, 1 H; 10-H*H*), 2.25 (s, 3 H; 11-CH_3), 2.06–1.88 (m, 4 H; 4-*H*H, 5-H$_2$, 13-*H*H), 1.75 ppm (m, 2 H; 4-H*H*, 13-H*H*); ^{13}C NMR (125 MHz, CD_3OD): δ = 190.6 (C-2), 62.3 (C-10), 60.9 (C-8), 58.3 (d, *J* = 6.3 Hz, C-12), 54.5 (C-6), 45.8 (11-CH_3), 39.3 (d, *J* = 3.9 Hz, C-1), 32.4 (quin., *J* = 20.9 Hz, C-3)*, 29.0 (C-9), 24.7 (C-13), 21.6 (C-5), 17.7 ppm (t, *J* = 13.0 Hz, C-4). *Note: The protons at C3 undergo fast H/D-exchange in CD_3OD and are only detectable by prompt measurement; the carbon atom C3 appears therefore as a quintet.

The iminium salt **32** (77.1 mg) was dissolved in MeOH (10 mL), cooled to 0°C, and $NaBH_4$ (39.5 mg, 1.04 mmol) was added portionwise. The reaction mixture was stirred overnight at RT and the solvent was removed in vacuum. The residue was suspended three times with MeOH (10 mL) and evaporated again. Column chromatography (basic alumina, activity V, Et_2O/MeOH 100:0 → 95:5) afforded the known[5] tricyclic bispidine *ent*-**2** (30.6 mg, 157 µmol, 60%) as a slightly yellowish oil.

R_f = 0.08 ($CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1); $[\alpha]_D^{24}$ = –29.9 (*c* = 0.9 in EtOH) {ref. [5]: $[\alpha]_D$ = –29.6 (c = 1.00 in EtOH), ref. [6]: $[\alpha]_D^{20}$ = +29.7 (c = 1.10 in EtOH) for **2**}. The further spectral data are fully consistent with those previously reported for *ent*-**2**.[5]

1.4 Synthesis of the tricyclic bispidine 10a from 16 via 36a ⇆ 37a



[5] J.-P. R. Hermet, A. Viterisi, J. M. Wright, M. J. McGrath, P. O'Brien, A. C. Whitwood, J. Gilday, *Org. Biomol. Chem.* **2007**, *5*, 3614-3622.

[6] A. J. Dixon, M. J. McGrath, P. O'Brien, *Org. Synth.* **2006**, *83*, 141-154.

1.4.1 (3*S*,5*S*)-3-((*tert*-Butoxycarbonylamino)methyl)-5-(4-(*tert*-butyldimethylsilyloxy)-butanoyl)-1-methylpiperidine (35a)

Lithium wire (973 mg, 140 mmol) was added to a solution of the bromide **33a** (6.51 mL, 28.1 mol) in anhyd. Et_2O (55 mL) and the reaction mixture was stirred for 1 h at RT. A portion of this solution (52.0 mL, 24.0 mmol) was added at –78°C to a solution of the bispidine lactam **16** (4.20 g, 16.5 mmol) in anhyd. Et_2O (210 mL). After 2 h, the reaction mixture was quenched at –78°C with sat. aq. NH_4Cl (70 mL) and warmed to RT. The aqueous layer was extracted with EtOAc (4 × 100 mL), and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and evaporated. Column chromatography (silica gel, CH_2Cl_2/MeOH 1:0 → 4:1) delivered ketone **35a** (5.09 g, 11.9 mol, 72%) as a colorless oil.

R_f = 0.24 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$ = –5.5 (*c* = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.59 (br m, 1 H; NH), 3.56 (t, *J* = 6.1 Hz, 2 H, OCH_2), 3.08–2.92 (m, 3 H; 6-*H*H, 3-CH_2), 2.87 (dm, *J* = 10.2 Hz, 1 H; 2-*H*H), 2.71 (tm, *J* = 11.6 Hz, 1 H; 5-H), 2.51 (t, *J* = 7.2 Hz, 2 H, $COCH_2$), 2.30 (s, 3 H; 1-CH_3), 1.94–1.78 (m, 3 H; 3-H, 4-*H*H, 6-H*H*), 1.73 (quin., *J* = 6.6 Hz, 2 H; OCH_2CH_2), 1.56 (t, *J* = 11.0 Hz, 1 H, 2-H*H*), 1.40 (s, 9 H, $OC(CH_3)_3$), 0.95 (ddd, *J* = 12.4, 12.4, 12.4 Hz, 1 H; 4-H*H*), 0.85 (s, 9 H; $SiC(CH_3)_3$), 0.00 ppm (s, 6 H; $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.6 (5-C), 156.1 (CO_2N), 79.5 ($OC(CH_3)_3$), 62.1 (OCH_2), 59.4 (C-2), 57.0 (C-6), 48.9 (C-5), 46.4 (1-CH_3), 44.3 (3-CH_2), 37.6 ($COCH_2$), 36.8 (C-3), 30.4 (C-4), 28.5 ($OC(CH_3)_3$), 26.6 (OCH_2CH_2), 26.1 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), –5.2 ppm ($Si(CH_3)_2$); IR (ATR): $\tilde{\nu}$ = 3373, 2928, 2856, 1704, 1250, 1171, 1093, 834, 775 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{45}N_2O_4Si$ [*M* + H$^+$]: 429.3143; found: 429.3141.

1.4.2 (3*S*,5*S*)-3-((*tert*-Butoxycarbonylamino)methyl)-5-(4-chlorobutanoyl)-1-methylpiperidine (38)

A solution of **35a** (50.6 mg, 118 µmol) in anhyd. THF (2.5 mL) was treated with TBAF·3H_2O (74.5 mg, 236 µmol) and stirred for 19 h. Removal of the solvent under reduced pressure and column chromatography (silica gel, deactivated with 7.5 w/w% NH_3, acetone/MeOH 1:0 → 4:1) delivered a complex product mixture of **36a**/**37a**, which was dissolved in anhyd. CH_2Cl_2 (4 mL). CCl_4 (74.7 µL, 767 µmol) and PPh_3 (77.4 mg, 295 µmol) were added and the mixture was stirred for 30 min at RT and heated under reflux for 5 h. Evaporation of the solvent and column chromatography (silica gel, acetone) provided the chloroketone **38** (33.0 mg, 99.1 µmol, 84%) as a colorless resin.

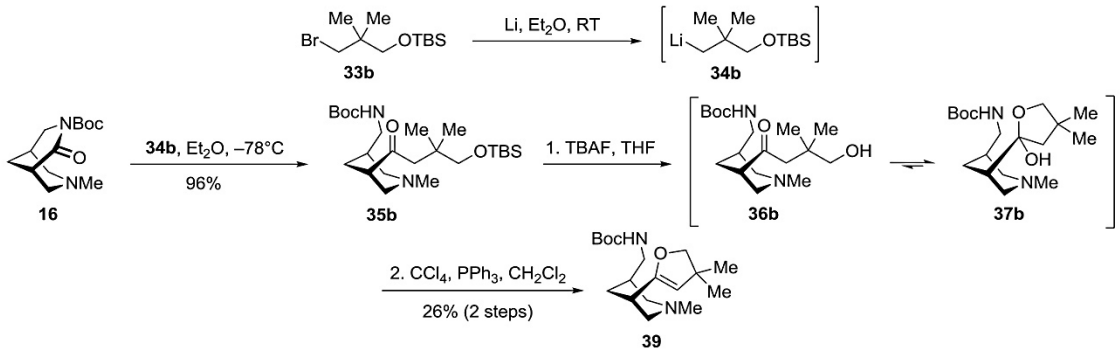
R_f = 0.31 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{17}$ = –4.8 (*c* = 0.8 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.58 (br s, 1 H; NH), 3.54 (t, *J* = 6.2 Hz, 2 H; CH_2Cl), 3.13–2.88 (m, 4 H; 2-*H*H, 3-CH_2, 6-*H*H), 2.86–2.74 (m, 1 H; 5-H), 2.71–2.60 (m, 2 H; $COCH_2$), 2.35 (s, 3 H; 1-CH_3), 2.02 (quin., *J* = 6.6 Hz, 2 H; CH_2CH_2Cl), 2.04–1.83 (m, 3 H; 3-H, 4-*H*H, 6-H*H*), 1.66 (tm, *J* = 10.7 Hz, 1 H; 2-H*H*), 1.42 (s, 9 H; $C(CH_3)_3$), 0.98 ppm (ddd, *J* = 12.5, 12.2, 12.1 Hz, 1 H; 4-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.1 (5-C), 156.1 (CO_2N), 79.6 ($C(CH_3)_3$), 59.2 (C-2), 56.8 (C-6), 48.8 (C-5), 46.2 (1-CH_3), 44.5 (CH_2Cl), 44.2 (3-CH_2), 37.9 ($COCH_2$), 36.8 (C-3), 30.3 (C-4), 28.5 ($C(CH_3)_3$), 26.2 ppm (CH_2CH_2Cl); IR (ATR): $\tilde{\nu}$ = 3353, 2930, 2788, 1702, 1364, 1250, 1168 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{30}ClN_2O_3$ [*M* + H$^+$]: 333.1940; found: 333.1941.

1.4.3 (1*S*,2*R*,8*R*)-10-Methyl-6,10-diazatricyclo[6.3.1.0^{2,6}]dodecane (10a)

A solution of the chloroketone **38** (31.0 mg, 93.1 µmol) in anhyd. CH_2Cl_2 (3 mL) was treated at 0°C with TFA (179 µL, 2.33 mmol). After stirring for 21 h at RT, the solvent was removed under reduced pressure, and the resulting oil was diluted three times with CH_2Cl_2 (**3** mL) and evaporated again. The residue was dissolved in EtOAc/MeOH 4:1 (100 mL) and filtered through a pad of basic alumina (activity V). The resulting brown resin was dissolved in anhyd. MeOH (7 mL) and $NaBH_4$ (12.3 mg, 325 µmol) was added at 0°C. The solvent was removed under reduced pressure after 1 h at 0°C and 23 h at RT. The resulting oil was diluted four times with MeOH (**3** mL) and evaporated again. Column chromatography (basic alumina, activity V, $CHCl_3$/MeOH/NH_3 (aq., 25%) 95:4.5:0.5 → 90:9:1) provided the crude product, which was dissolved in 1N HCl (1 mL). After extraction with CH_2Cl_2 (2 × 0.5 mL), adjustment of the pH to 10 by addition of 4N NaOH, and renewed extraction with EtOAc (3 × 1 mL) and $CHCl_3$ (2 × 1 mL), the aqueous layer was evaporated to dryness. Filtration of the residue through a pad of basic alumina (activity V) delivered the bispidine **10a** (5.20 mg, 28.9 µmol, 31%) as an orange-brown resin.

For characterization data of **10a**, see its preparation from **41a** (section 1.6.3).

1.5 Attempted synthesis of the tricyclic bispidine 10b from 35b via 36b ⇆ 37b



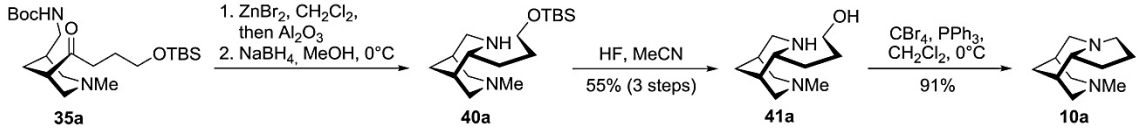
For the preparation of **35b** from **16**, see article.

(3*S*,5*S*)-3-((*tert*-Butoxycarbonylamino)methyl)-5-(4,4-dimethyl-4,5-dihydrofuran-2-yl)-1-methylpiperidine (39)

A solution of **35b** (66.1 mg, 145 µmol) in anhyd. THF (2.5 mL) was treated with TBAF·3H_2O (91.3 mg, 289 µmol) and stirred for 15 h. Removal of the solvent under reduced pressure and column chromatography (silica gel, deactivated with 7.5 w/w% NH_3, acetone) delivered a complex product mixture of **36b**/**37b**, which was dissolved in anhyd. CH_2Cl_2 (4 mL). CCl_4 (92.4 µL, 949 µmol) and PPh_3 (95.7 mg, 365 µmol) were added and the mixture was stirred for 30 min at RT and heated under reflux for 5 h. Evaporation of the solvent and column chromatography (silica gel, acetone) provided the enol ether **39** (12.3 mg, 37.9 µmol, 26%) as a colorless resin.

R_f = 0.29 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{17}$ = –4.6 (*c* = 1.3 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.54 (br s, 1 H; NH), 4.49 (d, *J* = 1.0 Hz, 1 H; C=CH), 3.91 (s, 2 H; OCH_2), 3.01 (m, 3 H; 3-CH_2, 6-*H*H), 2.88 (dm, *J* = 10.9 Hz, 1 H; 2-*H*H), 2.41 (tm, *J* = 11.6 Hz, 1 H; 5-H), 2.29 (s, 3 H; 1-CH_3), 1.92 (dm, *J* = 12.7 Hz, 1 H; 4-*H*H), 1.87–1.70 (m, 2 H; 3-H, 6-H*H*), 1.57 (tm, *J* = 10.8 Hz, 1 H; 2-H*H*), 1.43 (s, 9 H; $C(CH_3)_3$), 1.08 (s, 6 H; $C(CH_3)_2$), 0.88 ppm (ddd, *J* = 12.9, 12.3, 12.3 Hz, 1 H; 4-H*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (5-C), 156.1 (CO_2N), 105.5 (C=*C*H), 82.6 (OCH_2), 79.4 (*C*(CH_3)$_3$), 59.8 (C-2), 59.4 (C-6), 46.4 (1-CH_3), 44.5 (3-CH_2), 42.9 (*C*(CH_3)$_2$), 37.1 (C-3), 35.8 (C-5), 32.3 (C-4), 28.5 (C(*C*H_3)$_3$), 28.2, 28.1 ppm (C(*C*H_3)$_2$); IR (ATR): $\tilde{\nu}$ = 3348, 2929, 2786, 1695, 1250, 1169, 994, 730 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{33}N_2O_3$ [*M* + H^+]: 325.2486; found: 325.2489.

1.6 Synthesis of the tricyclic bispidine 10a from 16 via the bispidine 41a



1.6.1 (1*S*,2*R*,5*S*)-2-(3-(*tert*-Butyldimethylsilyloxy)propyl)-7-methyl-3,7-diazabicyclo[3.3.1]nonane (40a)

A solution of **35a** (5.06 g, 11.8 mmol) in anhyd. CH_2Cl_2 (50 mL) was treated with anhyd. $ZnBr_2$ (5.32 g, 23.6 mmol) and stirred for 2 d. Filtration (basic alumina, activity V, $CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1) and removal of the solvent delivered an oily residue, which was dissolved in MeOH (200 ml). After portionwise addition of $NaBH_4$ (1.34 g, 35.4 mmol) at –15°C, the reaction mixture was warmed to RT overnight. Removal of the solvent and chromatography (silica gel, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 96:3.6:0.4 → 80:18:2) provided a mixture of the bispidine **40a** and its protonated form **40a**•HX (3.38 g), which was directly used in the next step.

Basic extraction of **40a**/**40a**•HX afforded analytically pure **40a** as a yellowish oil, which was characterized.

R_f = 0.36 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{26}$ = –8.3 (*c* = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.89 (br s, 1 H; NH), 3.57 (m, 1 H; OC*H*H), 3.51 (m, 1 H; OCH*H*), 3.10 (dm, *J* = 13.4 Hz, 1 H; 4-*H*H), 2.93 (dm, *J* = 13.2 Hz, 2 H; 4-H*H*, 8-*H*H), 2.85 (dm, *J* = 11.2 Hz, 1 H; 6-*H*H), 2.79 (ddm, *J* = 6.3, 5.2 Hz, 1 H; 2-H), 2.18 (dm, *J* = 11.0 Hz, 1 H; 6-H*H*), 2.04 (m, 1 H; 8-H*H*), 2.02 (s, 3 H; 7-CH_3), 1.64 (m, 3 H; 5-H, 9-H_2), 1.59–1.38 (m, 5 H; 1-H, 2-CH_2CH_2), 0.79 (s, 9 H; $C(CH_3)_3$), –0.05 ppm (s, 6 H; $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 62.9 (OCH_2), 61.2 (C-6), 59.7 (C-2), 56.5 (C-8), 51.5 (C-4), 46.7 (7-CH_3), 33.1 (C-9), 31.0 (C-1), 29.7 (OCH_2CH_2), 29.1 (2-CH_2), 28.5 (C-5), 26.0 (C(*C*H_3)$_3$), 18.4 (*C*(CH_3)$_3$), –5.2, –5.3 ppm ($Si(CH_3)_2$); IR (ATR): $\tilde{\nu}$ = 2927, 2855, 2777, 1472, 1253, 1091, 832, 772 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{37}N_2OSi$ [*M* + H^+]: 313.2670; found: 313.2667.

1.6.2 (1*S*,2*R*,5*S*)-2-(3-Hydroxypropyl)-7-methyl-3,7-diazabicyclo[3.3.1]nonane (41a)

The mixture of **40a** and **40a**•HX (3.35 g) was dissolved in acetonitrile (35 mL) and treated with HF (38w/w-% in H_2O, 1.75 mL). After 1 h, K_2CO_3 (5 g) and H_2O (5 mL) were added and stirring was continued for 10 min. Evaporation of the solvent and addition of H_2O (25 mL) resulted in a suspension, which was extracted with EtOAc (4 × 50 mL) and CH_2Cl_2 (5 × 50 mL). Removal of the solvent under vacuum and column chromatography (silica gel, $CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1 → 80:18:2) delivered the amino alcohol **41a** (1.28 g, 6.47 mmol, 55% from **35a**) as a yellowish oil.

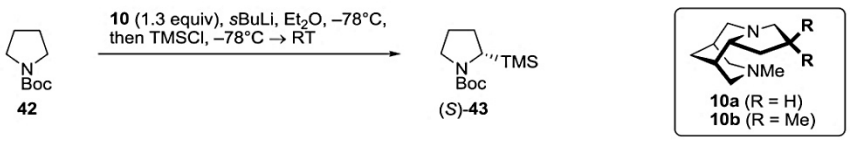
R_f = 0.15 ($CHCl_3$/MeOH/NH_3 (aq., 25%) 80:18:2); $[\alpha]_D^{24}$ = –6.6 (*c* = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* = 3.67 (m, 1 H; OC*H*H), 3.50 (m, 1 H; (OCH*H*), 3.14 (dm *J* = 13.5 Hz, 1 H; 4-*H*H), 3.02 (dm, *J* = 11.5 Hz, 1 H; 8-*H*H), 2.96 (dt, *J* = 13.5, 2.6 Hz, 1 H; 4-H*H*), 2.92 (dm, *J* = 11.1 Hz, 1 H; 6-*H*H), 2.86 (dm, *J* = 9.6 Hz, 1 H; 2-H), 2.28 (dm, *J* = 11.2 Hz, 1 H; 6-H*H*), 2.16 (dm, *J* = 11.5 Hz, 1 H; 8-H*H*), 2.11 (s, 3 H; 7-CH_3), 1.85–1.48 ppm (m, 8 H; 1-H, 2-CH_2CH_2, 5-H, 9-H_2); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* = 62.7 (OCH_2), 61.5 (C-6), 60.7 (C-2), 56.9 (C-8), 51.4 (C-4), 46.9 (7-CH_3), 35.4 (2-CH_2), 34.2 (C-1), 34.1 (C-9), 32.3 (OCH_2CH_2), 28.8 ppm (C-5); IR (ATR): $\tilde{\nu}$ = 3218, 2907, 2855, 2772, 1445, 1263, 1043, 963, 848, 757, 730 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{23}N_2O$ [*M* + H$^+$]: 199.1805; found: 199.1808.

1.6.3 (1*S*,2*R*,8*R*)-10-Methyl-6,10-diazatricyclo[6.3.1.0^{2,6}]dodecane (10a)

CBr_4 (2.53 g, 7.62 mmol) and PPh_3 (2.50 g, 9.53 mmol) were added successively at 0°C to a solution of the amino alcohol **41a** (1.26 g, 6.35 mmol) in anhyd. CH_2Cl_2 (70 mL). After stirring for 1 h, the solvent was evaporated. Flash chromatography (silica gel, deactivated with 7.5% aq. NH_3 (25%), CH_2Cl_2/MeOH/NH_3 95:4.5:0.5 → 80:18:2) delivered protonated **10a** (2.23 g) as a pale-brown solid, which was dissolved in 2N NaOH (70 mL). Extraction with Et_2O (5 × 150 mL), drying of the combined organic layers over $MgSO_4$, and evaporation of the solvent provided the bispidine **10a** (1.04 g, 5.77 mmol, 91%) as a yellowish oil.

R_f = 0.17 ($CHCl_3$/MeOH/NH_3 (25 %) 80:18:2); $[\alpha]_D^{22}$ = –36.9 (*c* = 1.0 in MeOH); ^{1}H NMR (500 MHz, CD_3OD): *δ* = 3.09 (dm, *J* = 10.7 Hz, 1 H; 7-*H*H), 3.01 (m, 2 H; 5-*H*H, 11-*H*H), 2.88 (dm, *J* = 11.1 Hz, 1 H; 9-*H*H), 2.30 (m, 2 H; 7-H*H*, 9-H*H*), 2.20 (dd, *J* = 11.6, 3.6 Hz, 1 H; 11-H*H*), 2.15 (s, 3 H; 10-CH_3), 2.12 (m, 1 H; 2-H), 1.93–1.74 (m, 4 H; 1-H, 8-H, 5-H*H*, 4-*H*H), 1.73–1.57 (m, 4 H; 3-H_2, 4-H*H*, 12-*H*H), 1.52 ppm (dm, *J* = 12.4 Hz, 1 H; 12-H*H*); ^{13}C NMR (125 MHz, CD_3OD): *δ* = 68.2 (C-2), 61.4 (C-9), 58.1 (C-7), 55.8 (C-11), 54.9 (C-5), 47.2 (10-CH_3), 34.2 (C-12), 32.5 (C-1), 31.4 (C-8), 27.8 (C-3), 21.6 ppm (C-4). The NMR Spectra in $CDCl_3$ and further spectral data are fully consistent with those previously reported for **10a**.[7]

1.7 Lithiation–silylation of NBoc pyrrolidine (42)



In analogy to a literature protocol,[8] *s*BuLi (1.3M in cyclohexane, 1.00 mL, 1.30 mmol) was added to a solution of freshly distilled bispidine **10a** or **10b** (234 resp. 271 mg,1.30 mmol) in Et_2O (10 mL) at –78°C. After stirring for 10 min, a solution of NBoc pyrrolidine (**42**; 175 µL, 1.00 mmol) in Et_2O (1 mL) was added dropwise over 10 min. The resulting mixture was stirred for 5 h and TMSCl (191 µL, 1.50 mmol) was added. The reaction was slowly warmed to RT overnight. H_3PO_4 (5 v/v% in H_2O, 3 mL) was added and stirring was continued for 20 min. The organic layer was washed with H_3PO_4 (5 v/v% in H_2O, 3 × 3 mL) and the combined aqueous layers were re-extracted with Et_2O (4 × 5 mL), dried over $MgSO_4$ and evaporated. Flash chromatography (silica gel, petroleum ether/EtOAc 95:5) delivered the product **43** as a colorless oil. The enantiomeric excess of **43** was determined by GC on chiral phase. The spectral data of **43** were fully consistent with those previously reported.[9]

GC conditions: BGB-176SE, 30 m x 0.25 mm ID, 0.25µm film, T = 100°C isothermal, injector temperature 240°C, detector temperature 240°C, H_2 carrier gas at 83 kPa constant pressure, t_R = 39.8 min (*S*), 40.5 min (*R*).

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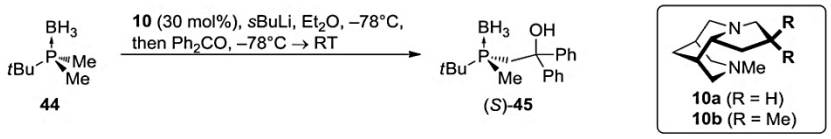
[7] J. R. Harrison, P. O'Brien, D. W. Porter, N. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 3623-3631.

[8] P. O'Brien, K. B. Wiberg, W. F. Bailey, J.-P. R. Hermet, M. J. McGrath, *J. Am. Chem. Soc* **2004**, *126*, 15480-15489.

[9] P. Beak, S. T. Kerrick, S. Wu, J. Chu, *J. Am. Chem. Soc.* **1994**, *116*, 3231-3239.

10

1.8 Lithiation–benzophenone trapping of *tert*-butyldimethylphosphine borane (44)



According to literature procedure,[10] *s*BuLi (1.3M in cyclohexane, 231 µL, 300 µmol) was added to a solution of freshly distilled bispidine **10a** or **10b** (54.1 resp. 62.5 mg, 300 µmol) in Et_2O (3 mL) at –78°C. After stirring for 15 min, a solution of *tert*-butyldimethylphosphine borane (**44**; 132 mg, 1.00 mmol) in Et_2O (2 mL) was added over 30 min using a syringe pump. After 35 and 70 min, two further portions of *s*BuLi (269 µL, 350 µmol each) were added. Stirring was continued for 70 min and a solution of benzophenone (219 mg, 1.20 mmol) in Et_2O (2 mL) was added dropwise. The reaction was slowly warmed to RT overnight and quenched with HCl (5 w/w% in H_2O, 10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and evaporated. Flash chromatography (silica gel, petroleum ether/EtOAc 19:1 → 9:1) delivered the product **45** as white solid. The enantiomeric excess of **45** was determined by HPLC on chiral phase. The spectral data of **45** were fully consistent with those previously reported.[10]

HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 95:5, 0.8 mL/min, 215 nm, t_R = 6.9 (*R*), 8.1 (*S*).

2. Enantioselective Henry reactions

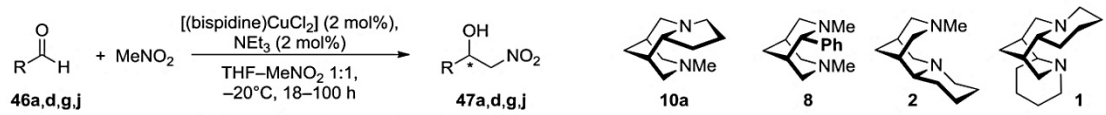
Preparation of the racemic ß-nitro alcohols: The racemic β-nitro alcohols **47** and **49** were prepared according to literature protocols.[11] The NMR spectroscopic data were identically with those given in literature.[12,13]

Measurement of the enantiomeric excess (ee): The enantiomeric excess of the β-nitro alcohols **47** and **49** was determined by HPLC analysis (Waters Alliance HPLC; Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase (Daicel Chiralcel OD-3, Daicel Chiralpak AD-H). The accuracy of integration was ± 0.1%. Some of the enantioselective Henry reactions were done up to five times, for example with benzaldehyde (**47a**). In all cases, virtually the same excellent enantiomeric excesses were measured (Δee = ± 0.2%).

Determination of the relative and absolute configuration of the major isomer: For all known ß-nitro alcohols **47** and **49**, the absolute configuration of the major enantiomer was assigned by comparison of the measured retention times on HPLC with the literature-known ones, measured under identical conditions (same chiral phase and solvent system).[12,13] The relative configuration of the diastereomeric ß-nitro alcohols **49** was confirmed by comparison of the NMR spectroscopic data with those given in literature.[13]

2.1 Evaluation of the bispidine ligands in enantioselective Henry reactions (46 → 47)

For the general reaction procedure, see article.



a: R = Ph; **d**: R = 3-MeOPh; **g**: R = 4-O_2NPh; **j**: R = $PhCH_2CH_2$

Table S1. Comparison of the ligands **1**,**2**,**8** and **10a** in enantioselective Henry reactions.

			Reaction time, yield and *ee* (configuration) reached with the ligand											
			10a			**8**			**1**			**2**		
Entry	Compound	R	t [h]	Yield [%]	*ee* [%]	t [h]	Yield [%]	*ee* [%]	t [h]	Yield [%]	*ee* [%]	t [h]	Yield [%]	*ee* [%]
1	**47a**	Ph	25	85	49 (*R*)	40	93	85 (*S*)	69	39	91 (*R*)	43	78	96 (*R*)
2	**47d**	3-MeO-C_6H_4	50	88	45 (*R*)	40	92	89 (*S*)	70	33	89 (*R*)	46	68	96 (*R*)
3	**47g**	4-O_2N-C_6H_4	24	85	42 (*R*)	18	86	85 (*S*)	26	70	45 (*R*)	18	77	81 (*R*)
4	**47j**	$PhCH_2CH_2$	46	87	48 (*R*)	42	77	73 (*S*)	95	22	83 (*R*)	47	48	94 (*R*)

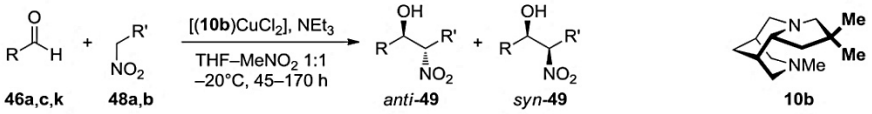
[10] J. Granander, F. Secci, S. J. Canipa, P. O'Brien, B. Kelly, *J. Org. Chem.* **2011**, *76*, 4794-4799.
[11] D. Scharnagel, F. Prause, J. Kaldun, R. G. Haase, M. Breuning, *Chem. Commun.* **2014** ,*50*, 6623-6625.

Table S2. Enantiomer analysis of the β-nitro alcohols **47** by HPLC on chiral phase.

Entry	Compound	R	Column[a]	Solvent System *n*-hexane/*i*PrOH	Flow [ml/min]	t_R (*R*) [min][b]	t_R (*S*) [min][b]	Ref.[c]
1	**47a**	Ph	OD-3	85:15	0.8	12.3	14.9	12a
2	**47b**	1-naphthyl	OD-3	85:15	0.8	15.2	23.9	12b
3	**47c**	2-MeO-C_6H_4	OD-3	90:10	0.8	14.3	17.6	12a
4	**47d**	3-MeO-C_6H_4	OD-3	85:15	0.8	19.3	24.8	12b
5	**47e**	4-MeO-C_6H_4	OD-3	85:15	0.8	16.3	20.6	12a
6	**47f**	2-O_2N-C_6H_4	OD-3	80:20	0.8	9.3	10.1	12a
7	**47g**	4-O_2N-C_6H_4	OD-3	85:15	0.8	18.6	23.8	12a
8	**47h**	3-furyl	AD-H	90:10	0.8	18.0	24.3	12c
9	**47i**	(*E*)-PhCH=CH	OD-3	85:15	0.8	37.5	32.1	12d
10	**47j**	$PhCH_2CH_2$	AD-H	90:10	0.8	14.4	17.9	12b
11	**47k**	*c*Hex	AD-H	95:5[d]	0.8	37.2	34.0	12e
12	**47l**	*n*Oct	AD-H	95:5	0.8	15.7	22.4	12d

[a] OD-3: Daicel Chiralcel OD-3; AD-H: Daicel Chiralpak AD-H. [b] Retention time. [c] Reference data for enantiomer analysis by HPLC on chiral phase.[12] [d] Solvent system *n*-hexane/EtOH.

2.2 Evaluation of the bispidine ligand 10b in enantio- and diastereoselective Henry reactions (48 → 49)



46a: R = Ph; **46c**: R = 2-MeOPh; **46k**: R = cyclohexyl
48a: R = Me; **48b**: R = Et

Table S3. Enantiomer analysis of the β-nitro alcohols **49** by HPLC on chiral phase.

Entry	Com-pound	R	R	Column[a]	Solvent System *n*-hexane/*i*PrOH	Flow [ml/min]	t_R (*R*,*S*) [min][b]	t_R (*S*,*R*) [min][b]	t_R (*R*,*R*) [min][b]	t_R (*S*,*S*) [min][b]	Ref.[c]
1	**49aa**	Ph	Me	AD-H	95:5	0.9	17.4	15.6	24.1	21.7	13a
2	**49ab**	Ph	Et	OD-3	95:5	0.9	13.7	22.6	16.3	20.6	13b,c
3	**49ca**	2-MeO-C_6H_4	Me	AD-H	95:5	1.0	20.9	15.7	30.0	28.8	13d
4	**49cb**	2-MeO-C_6H_4	Et	AD-H	97:3	1.0	24.7	20.3	42.0	43.8	13c,d
5	**49ka**	*c*Hex	Me	AD-H	96:4[d]	0.8	27.0	37.0	65.0	24.8	13a,e
6	**49kb**	*c*Hex	Et	AD-H	97:3[d]	0.8	20.6	25.1	65.8	22.2	13a,f

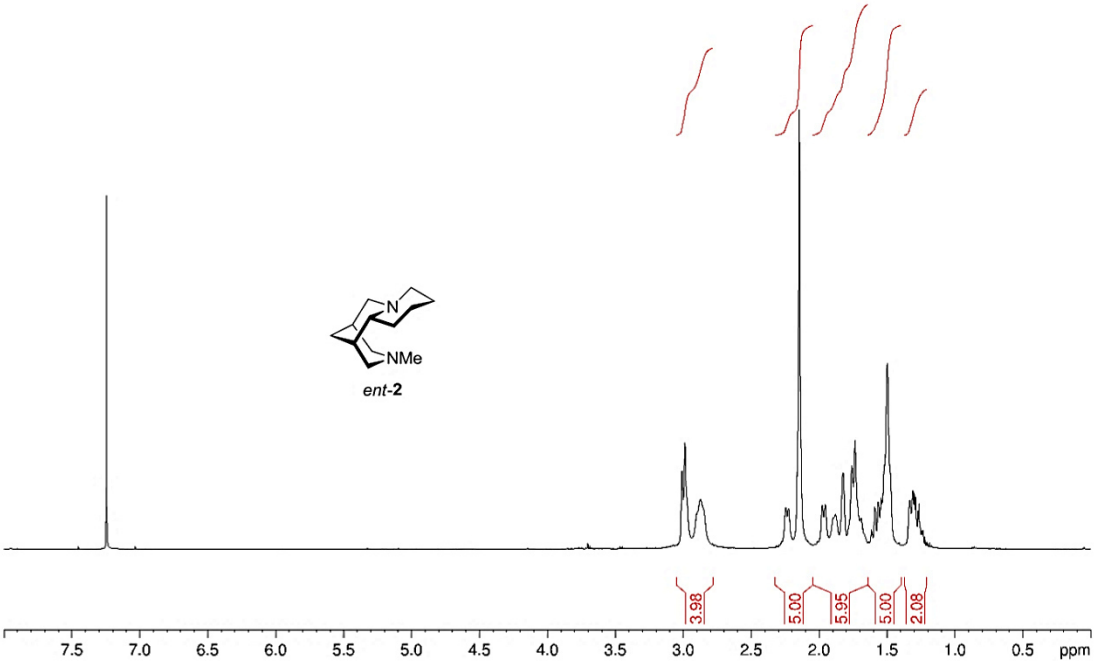
[a] OD-3: Daicel Chiralcel OD-3; AD-H: Daicel Chiralpak AD-H. [b] Retention time. [c] Reference data for NMR spectra and enantiomer analysis by HPLC on chiral phase.[13] [d] Solvent system *n*-hexane/EtOH.

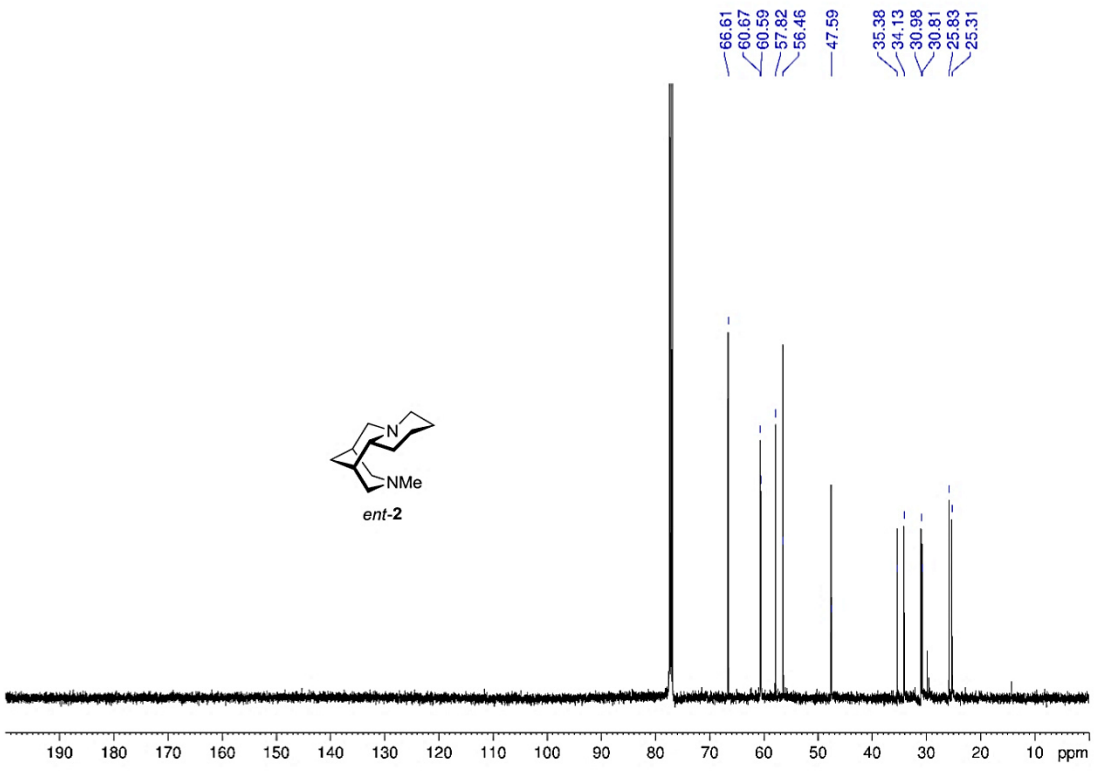
[12] (*a*) M. Breuning, D.Hein, M. Steiner, V. H. Gessner, C. Strohmann, *Chem.-Eur. J.* **2009**, *15*, 12764-12769; (*b*) W. Jin, X. Li, B. Wan, *J. Org. Chem.* **2011**, *76*, 484-491; (*c*) M. Liu, S. Ma, Z. Tian, H. Wu, L. Wu, X. Xu, Y. Huang, Y. Wang, *Tetrahedron: Asymmetry* **2013**, *24*, 736-743; (d) B. V. S. Reddy, J. George, *Tetrahedron: Asymmetry* **2011**, *22*, 1169-1175; (e) see ref.11.

[13] (*a*) Y. Zhou, J. Dong, F. Zhang, Y. Gong, *J. Org. Chem.* **2011**, *76*, 588-600; (b) D. Uraguchi, S. Sakaki, T. Ooi, *J. Am. Chem. Soc.* **2007**, *129*, 12392-12393; (c) W. Jin, X. Li, B. Wan, *J. Org. Chem.* **2011**, *76*, 484-491; (d) G. Blay, L. R. Domingo, V. Hernández-Olmos, J. R. Pedro, *Chem. Eur. J.* **2008**, *14*, 4725-4730; e) D.-D. Qin, W. Yu, J.-D. Zhou, Y.-C. Zhang, Y.-P. Ruan, Z.-H. Zhou, H.-B. Chen, *Chem. Eur. J.* **2013**, *19*, 16541-16544; (f) A. Toussaint, A. Pfalz, *Eur. J. Org. Chem.* **2008**, 4591-4597.

3. Copies of ^{1}H and ^{13}C NMR spectra

The ^{1}H and ^{13}C NMR spectra of all new compounds are listed in numerical order.





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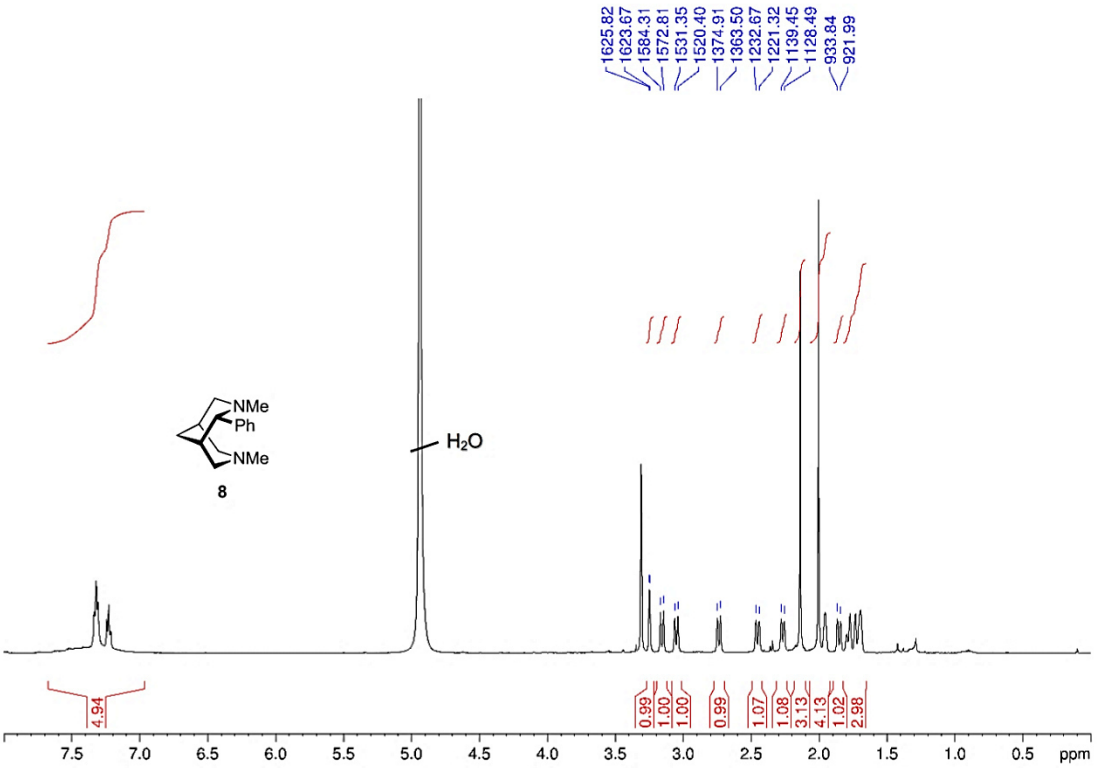
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1531.35
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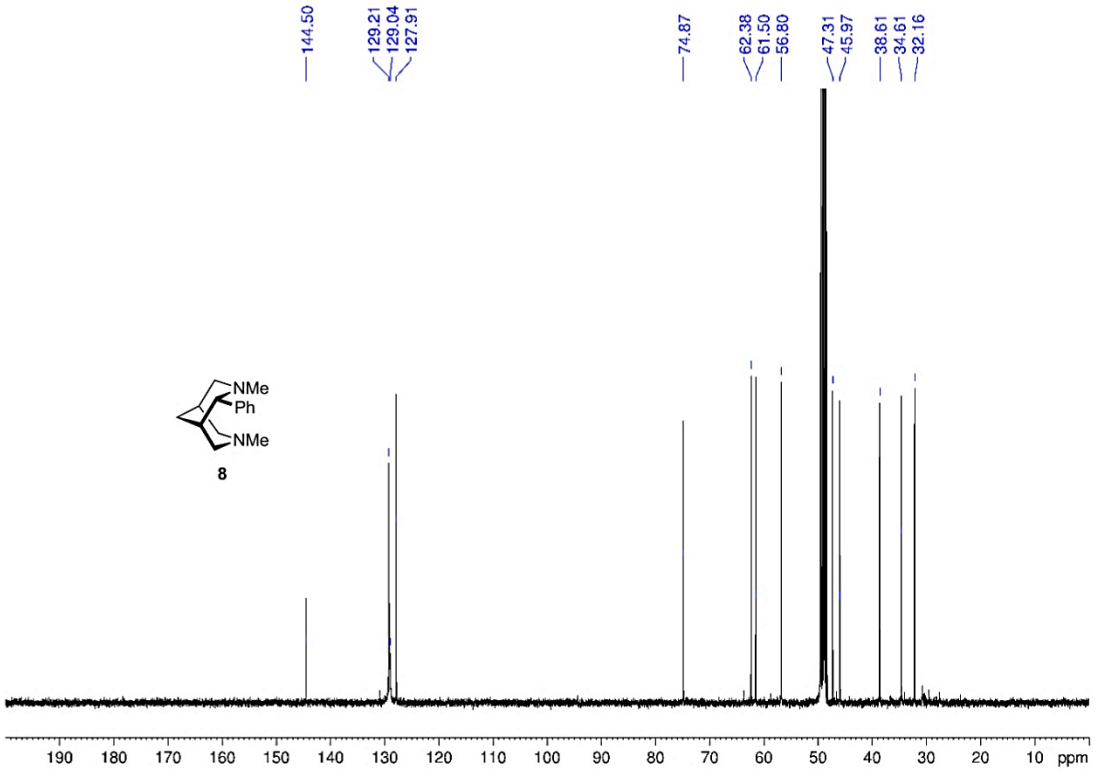
1221.32
1139.45
1128.49
933.84
921.99
NMe
Ph
NMe
8
H2O
4.94
0.99
1.00
1.00
0.99
1.07
1.08
3.13
4.13
1.02
2.98
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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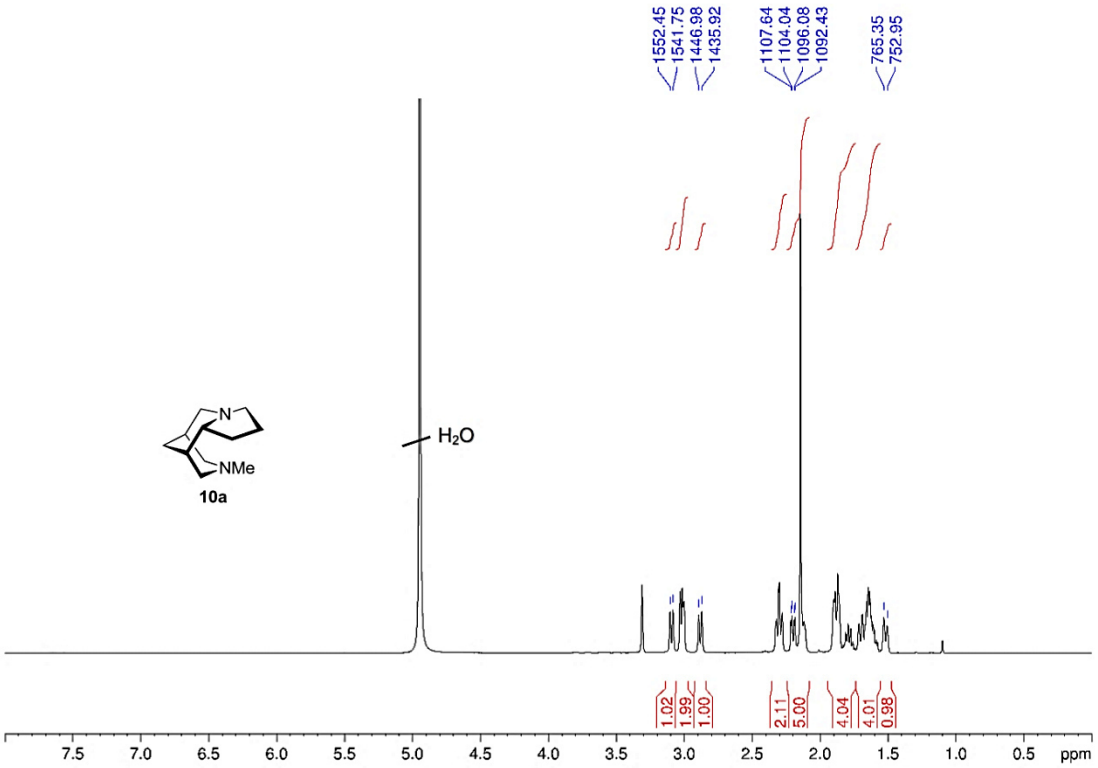
129.21
129.04
127.91
74.87
62.38
61.50
56.80
47.31
45.97
38.61
34.61
32.16
NMe
Ph
NMe
8
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

14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1541.75
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N
NMe
10a
H2O
1.02
1.99
1.00
2.11
5.00
4.04
4.01
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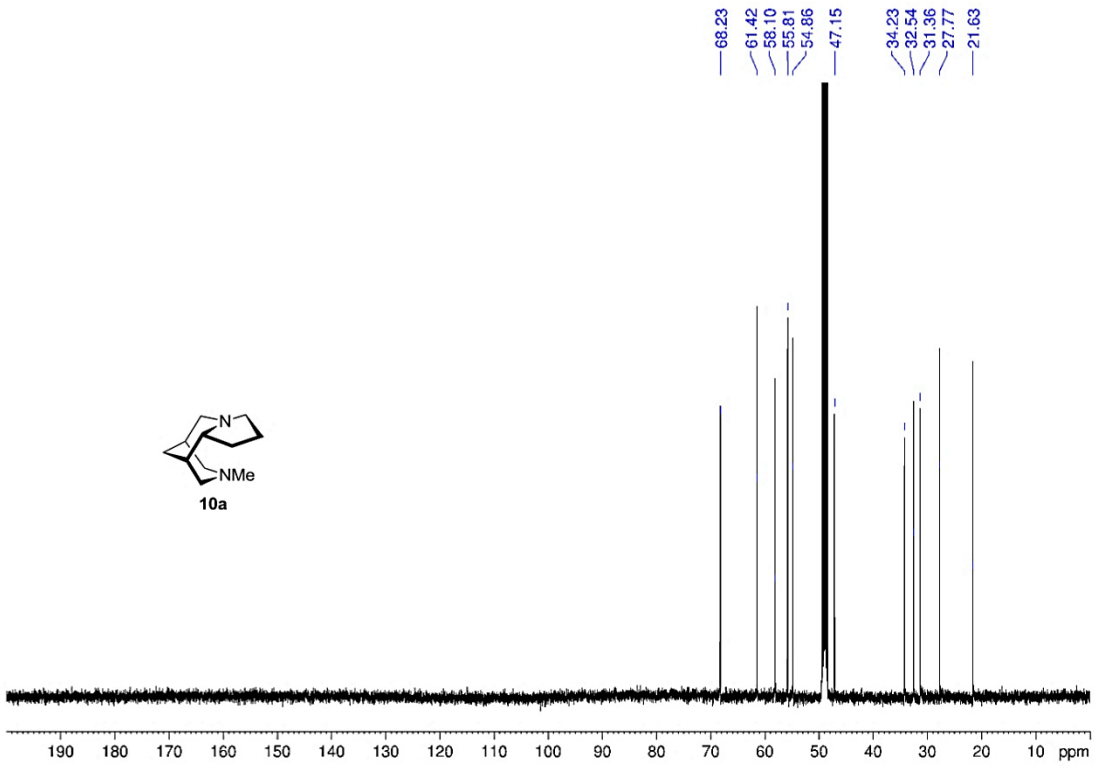
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61.42
58.10
55.81
54.86
47.15
34.23
32.54
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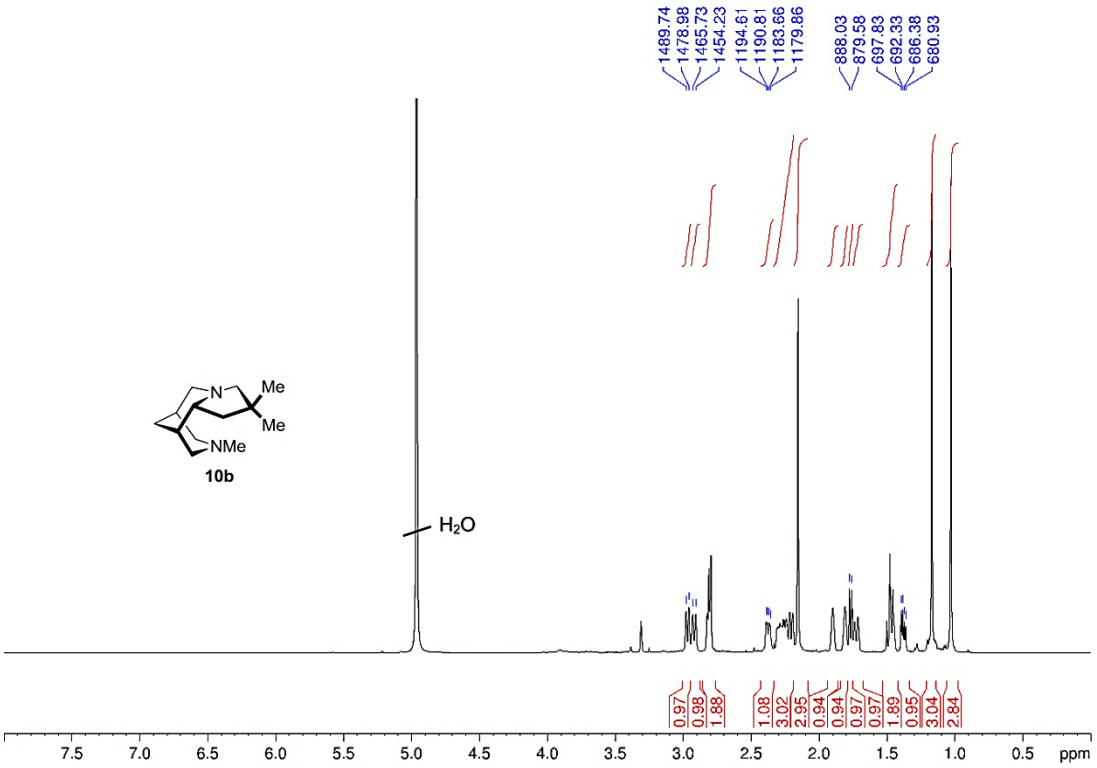
27.77
21.63
N
NMe
10a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

15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1478.98
1465.73
1454.23
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879.58
697.83
692.33
686.38
680.93
Me
Me
N
NMe
10b
H2O
0.97
0.98
1.88
1.08
3.02
2.95
0.94
0.94
0.97
0.97
1.89
0.95
3.04
2.84
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
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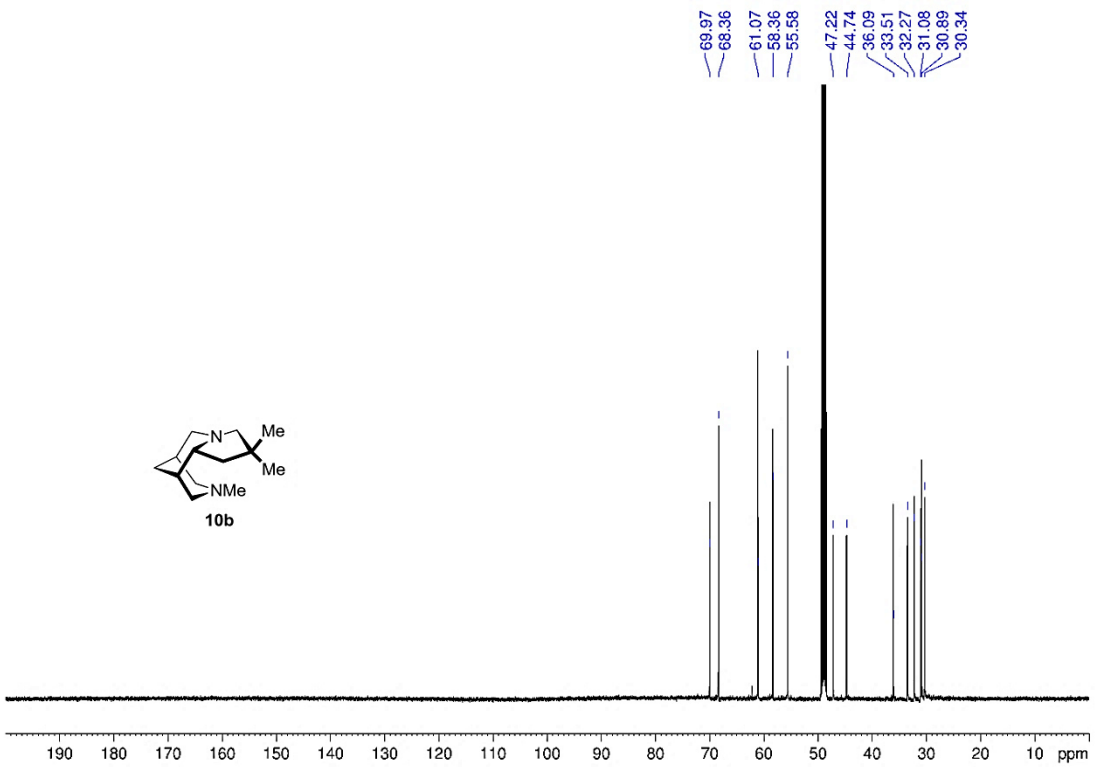
2.0
1.5
1.0
0.5
ppm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68.36
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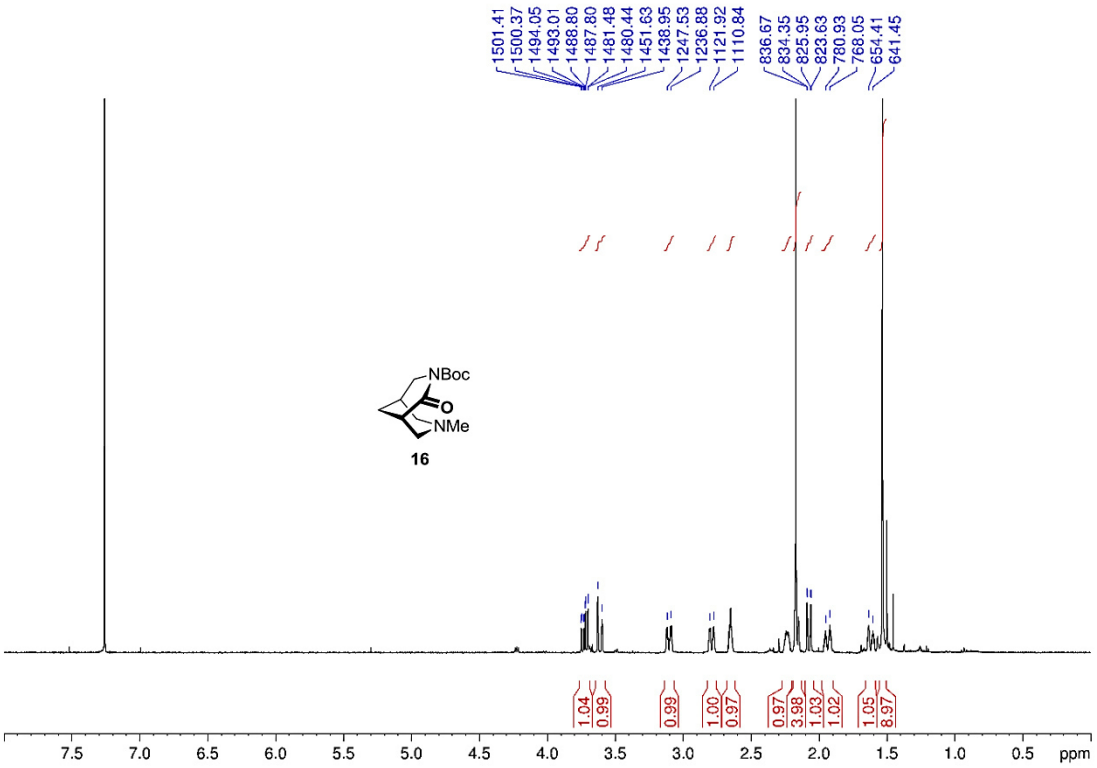
58.36
55.58
47.22
44.74
36.09
33.51
32.27
31.08
30.89
30.34
Me
Me
N
NMe
10b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

16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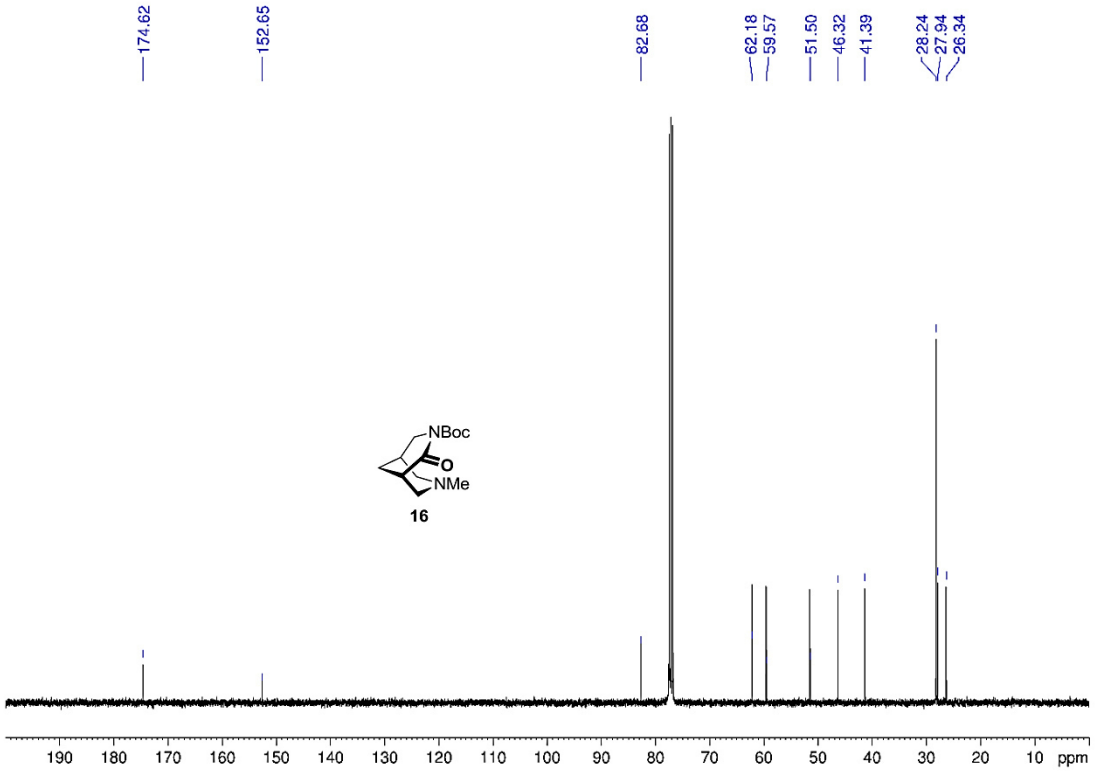
1493.01
1488.80
1487.80
1481.48
1480.44
1451.63
1438.95
1247.53
1236.88
1121.92
1110.84
836.67
834.35
825.95
823.63
780.93
768.05
654.41
641.45
NBoc
O
NMe
16
1.04
0.99
0.99
1.00
0.97
0.97
3.98
1.03
1.02
1.05
8.97
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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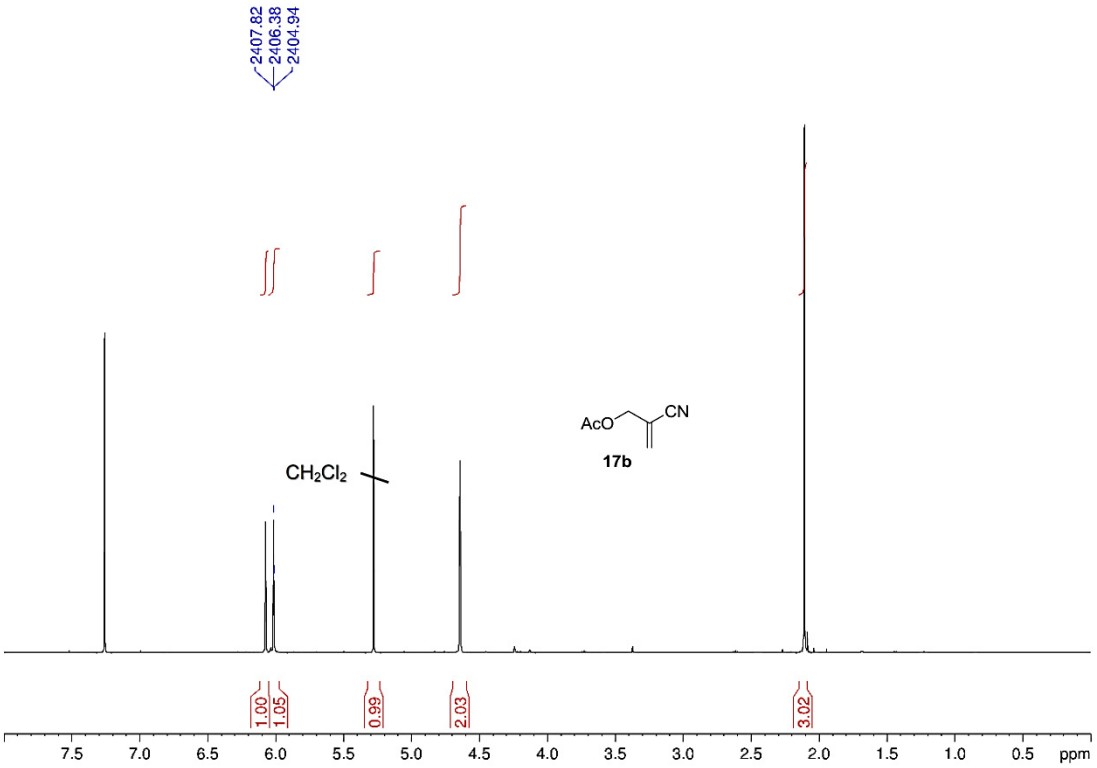
152.65
82.68
62.18
59.57
51.50
46.32
41.39
28.24
27.94
26.34
NBoc
O
NMe
16
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

17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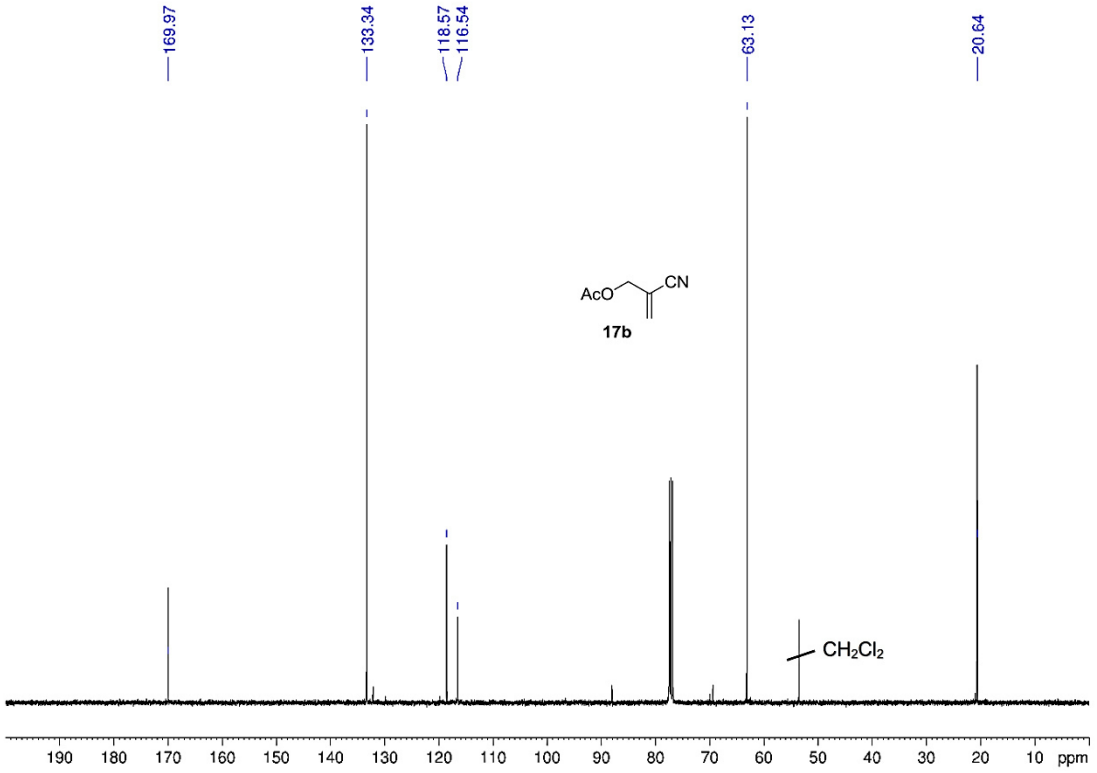
2406.38
2404.94
AcO
CN
17b
CH_2Cl_2
1.00
1.05
0.99
2.03
3.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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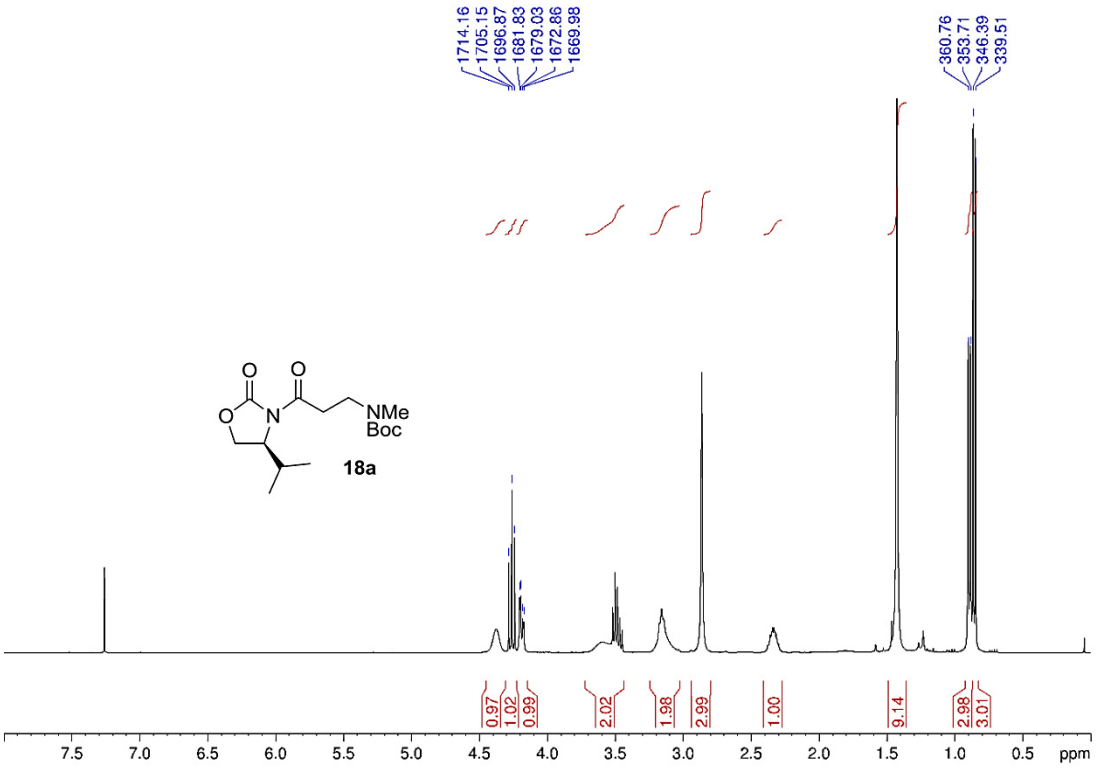
133.34
118.57
116.54
63.13
20.64
AcO
CN
17b
CH_2Cl_2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

18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1679.03
1672.86
1669.98
360.76
353.71
346.39
339.51
NMe
Boc
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1.98
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1.00
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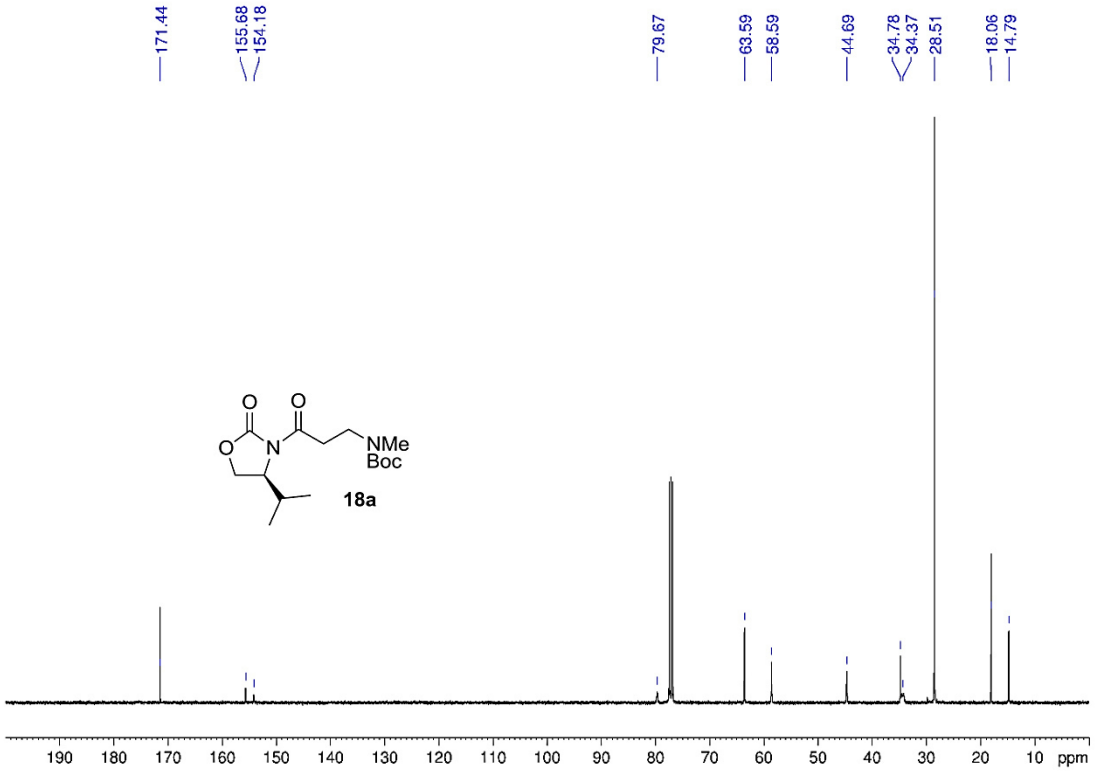
2.98
3.01
ppm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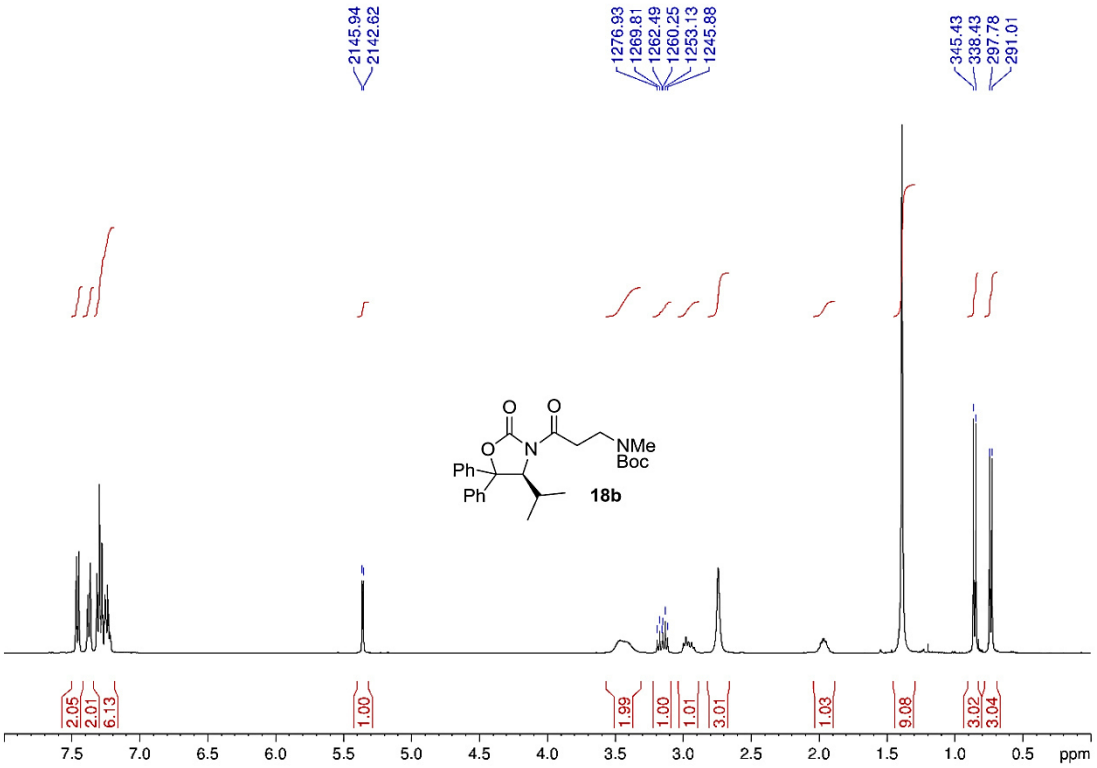
154.18
79.67
63.59
58.59
44.69
34.78
34.37
28.51
18.06
14.79
NMe
Boc
18a
ppm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1269.81
1262.49
1260.25
1253.13
1245.88
345.43
338.43
297.78
291.01
NMe
Boc
Ph
Ph
18b
2.05
2.01
6.13
1.00
1.99
1.00
1.01
3.01
1.03
9.08
3.02
3.04
7.5
7.0
6.5
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4.5
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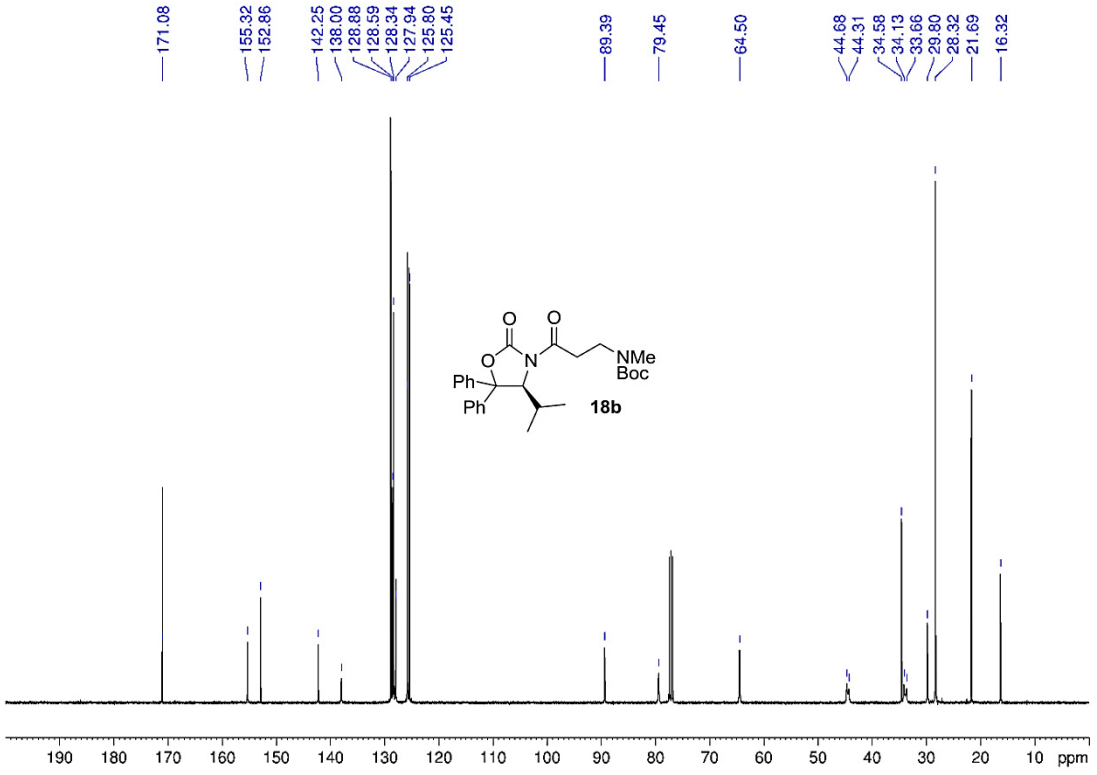
2.0
1.5
1.0
0.5
ppm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128.34
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125.80
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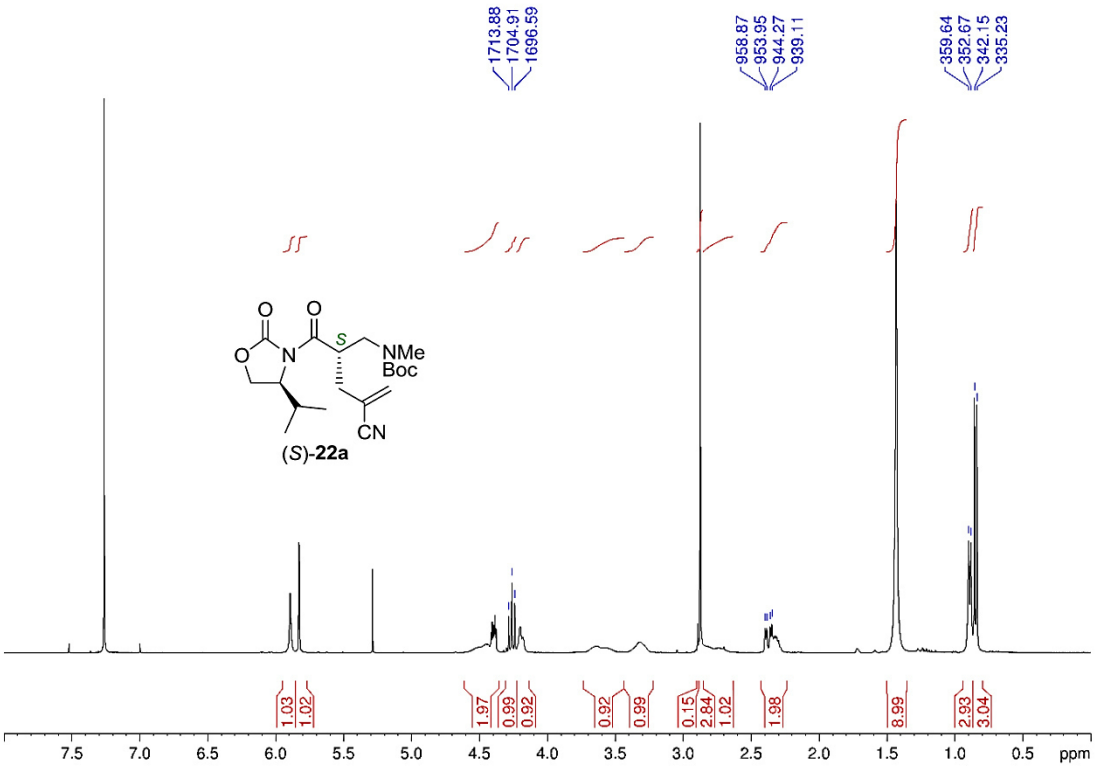
79.45
64.50
44.68
44.31
34.58
34.13
33.66
29.80
28.32
21.69
16.32
NMe
Boc
Ph
Ph
18b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

20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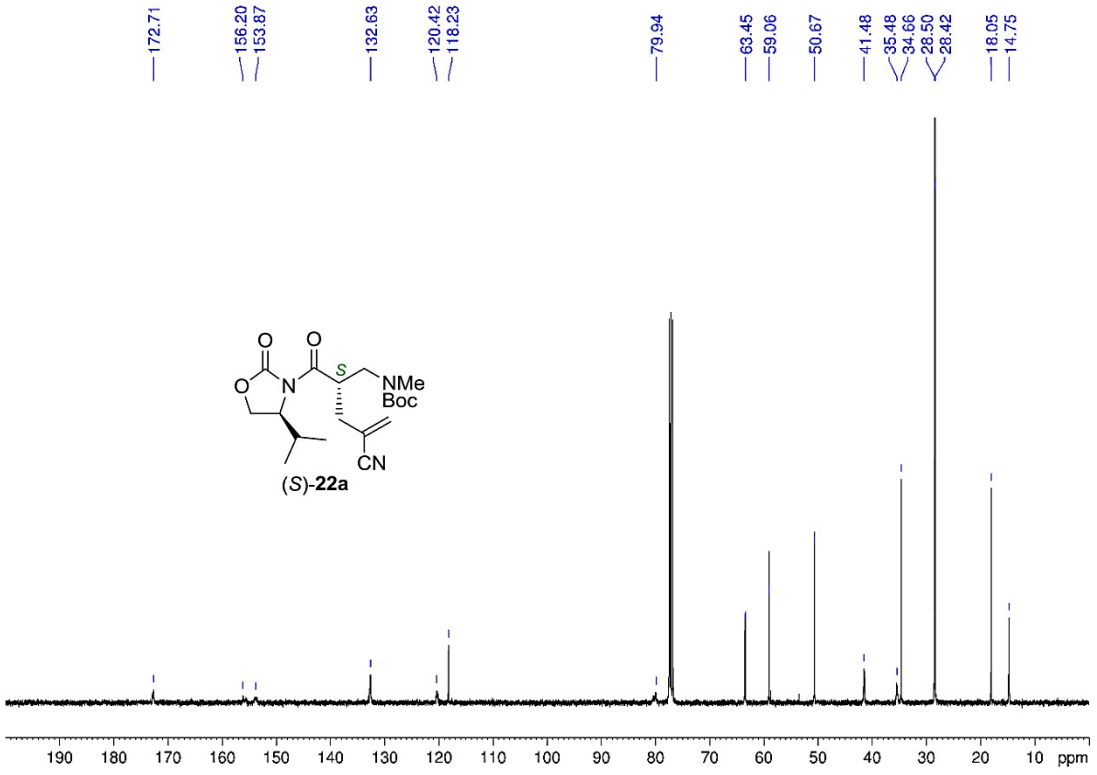
NMe
Boc
CN
(S)-22a
1.03
1.02
1.97
0.99
0.92
0.92
0.99
0.15
2.84
1.02
1.98
8.99
2.93
3.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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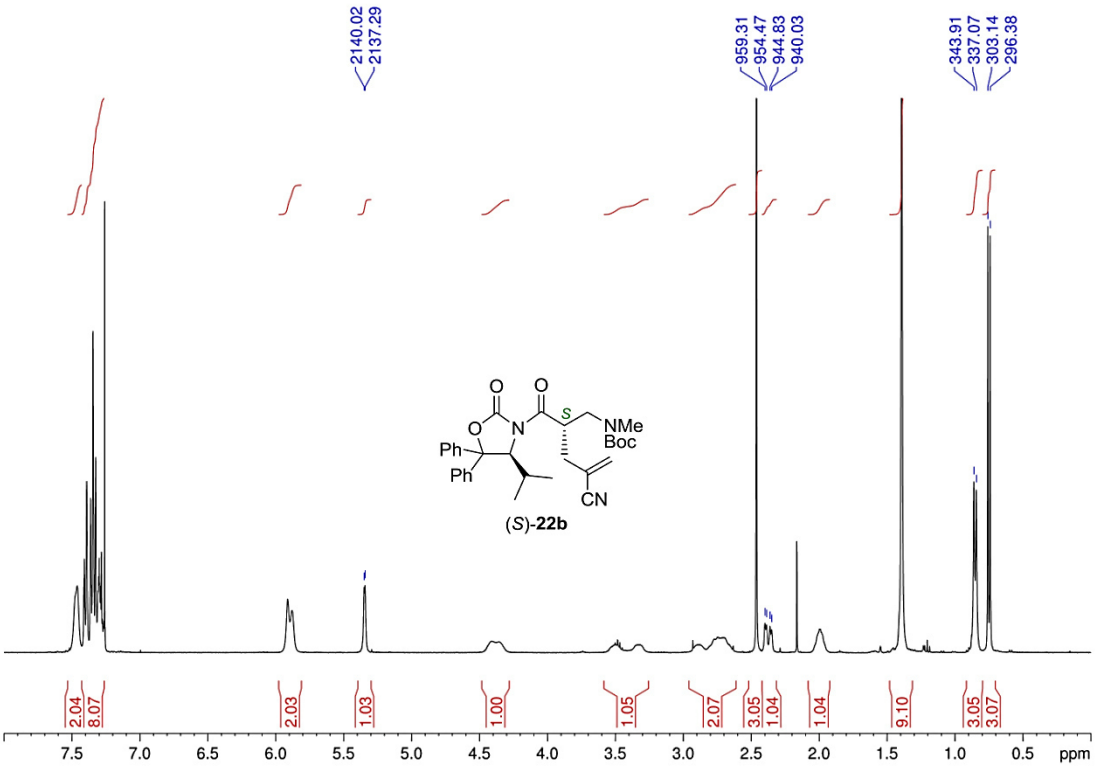
63.45
59.06
50.67
41.48
35.48
34.66
28.50
28.42
18.05
14.75
NMe
Boc
CN
(S)-22a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

21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303.14
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O
O
N
S
NMe
Boc
Ph
Ph
CN
(S)-22b
2.04
8.07
2.03
1.03
1.00
1.05
2.07
3.05
1.04
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3.0
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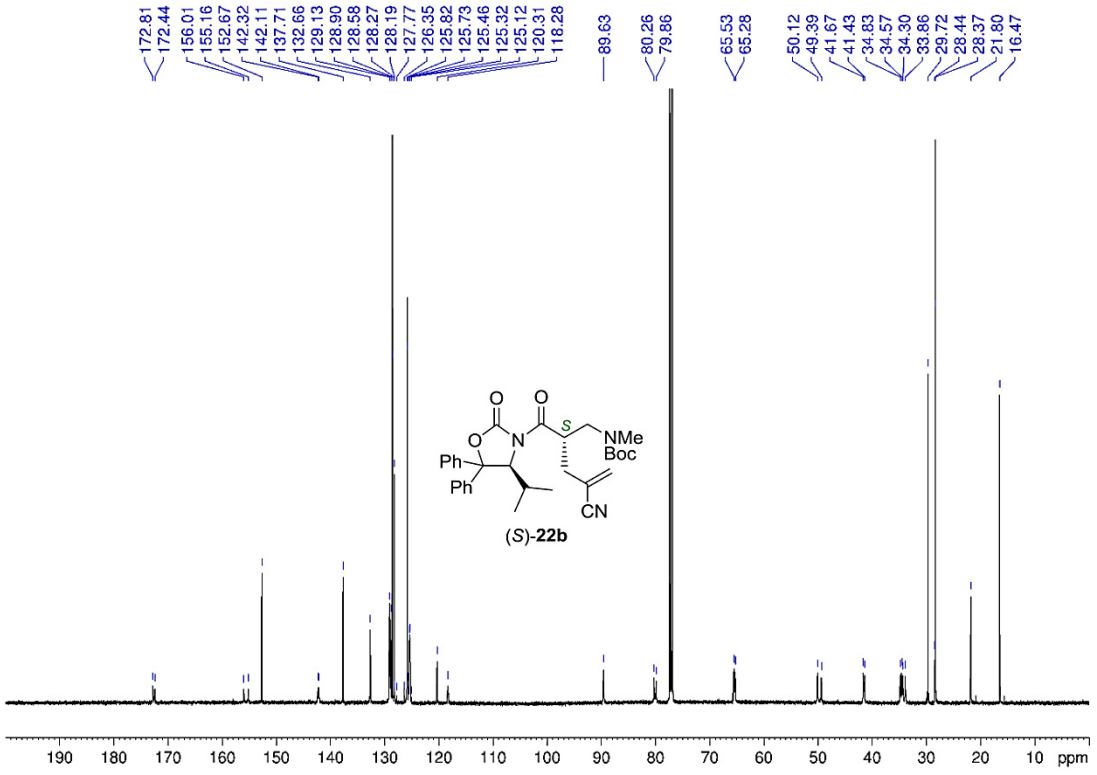
ppm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127.77
126.35
125.82
125.73
125.46
125.32
125.12
120.31
118.28
89.63
80.26
79.86
65.53
65.28
50.12
49.39
41.67
41.43
34.83
34.57
34.30
33.86
29.72
28.44
28.37
21.80
16.47
O
O
O
N
S
NMe
Boc
Ph
Ph
CN
(S)-22b
190
180
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160
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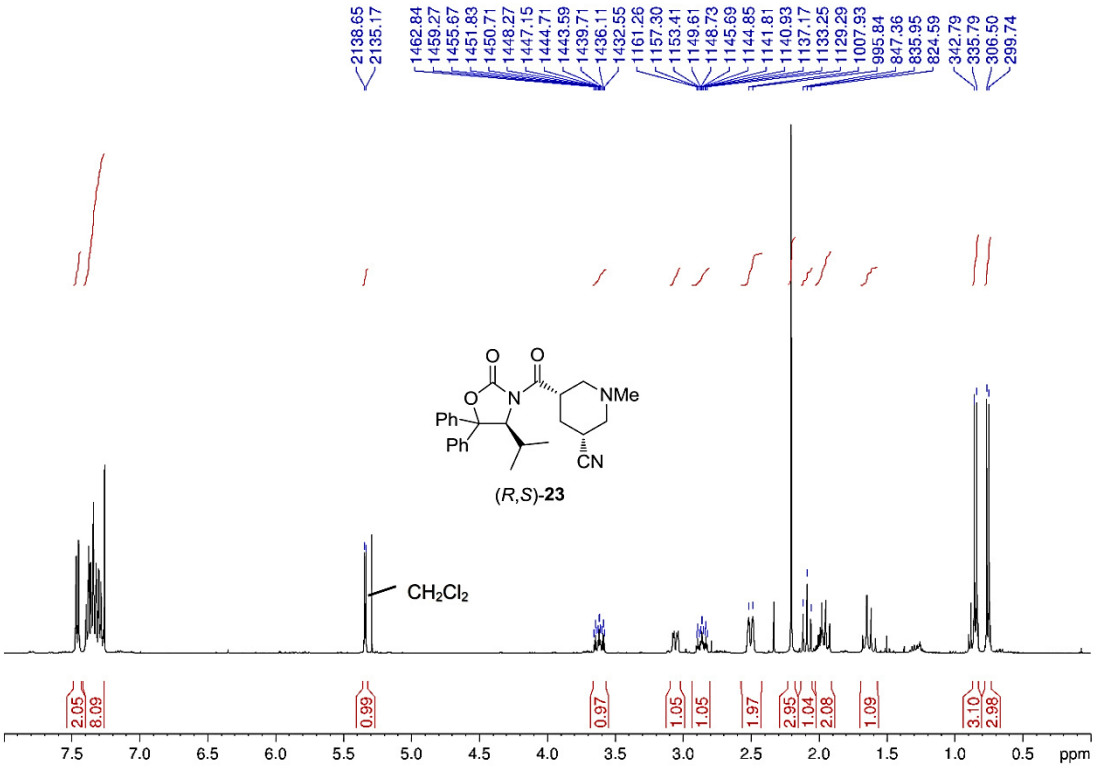
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

22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1439.71
1436.11
1432.55
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1157.30
1153.41
1149.61
1148.73
1145.69
1144.85
1141.81
1140.93
1137.17
1133.25
1129.29
1007.93
995.84
847.36
835.95
824.59
342.79
335.79
306.50
299.74
O
O
O
N
NMe
Ph
Ph
CN
(R,S)-23
CH2Cl2
2.05
8.09
0.99
0.97
1.05
1.05
1.97
2.95
1.04
2.08
1.09
3.10
2.98
7.5
7.0
6.5
6.0
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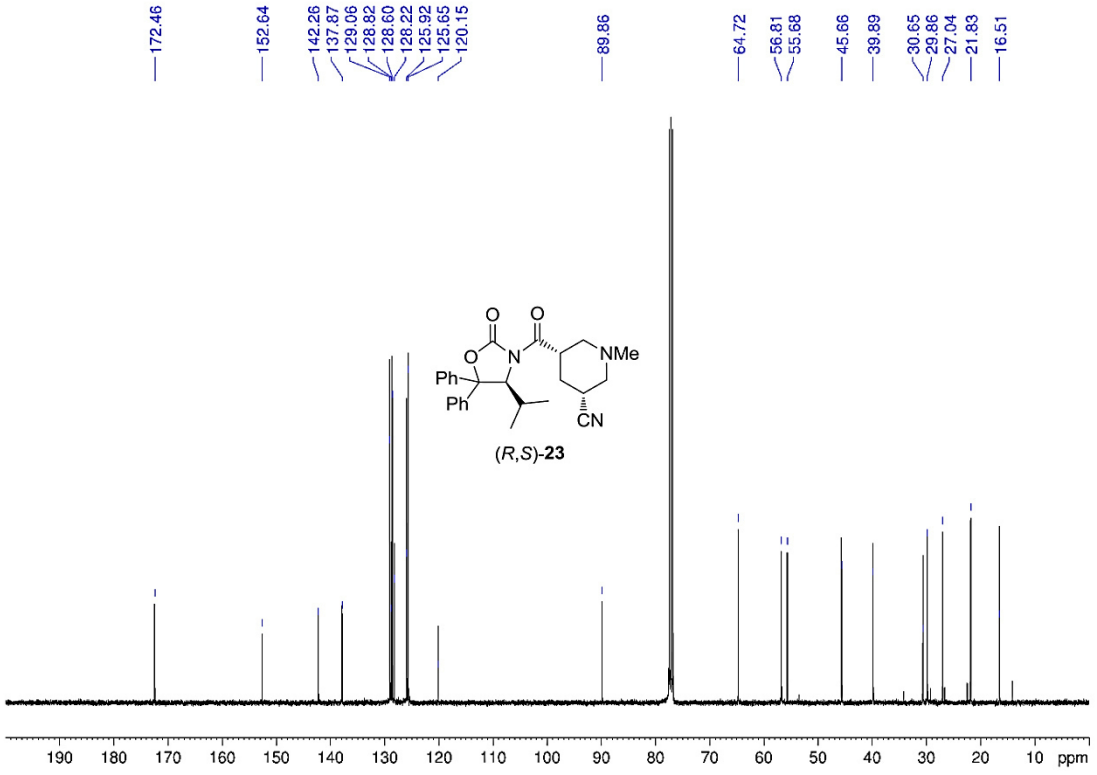
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56.81
55.68
45.66
39.89
30.65
29.86
27.04
21.83
16.51
O
O
O
N
NMe
Ph
Ph
CN
(R,S)-23
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180
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140
130
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60
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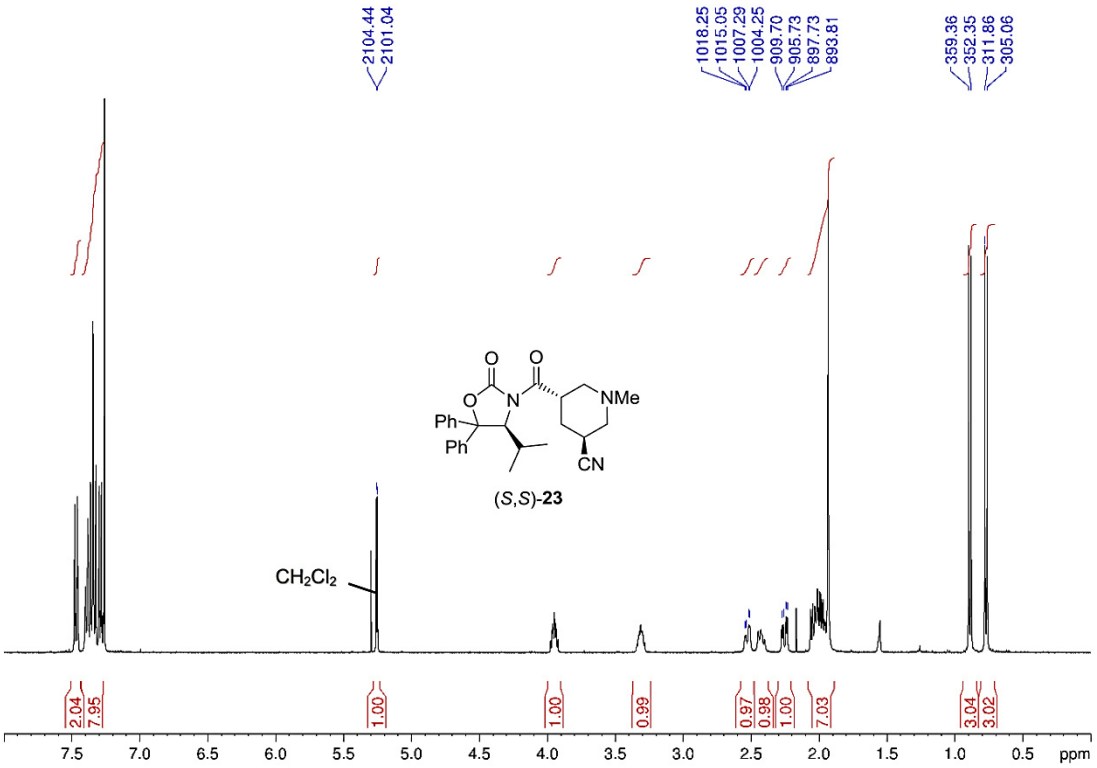
20
10
ppm

23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1007.29
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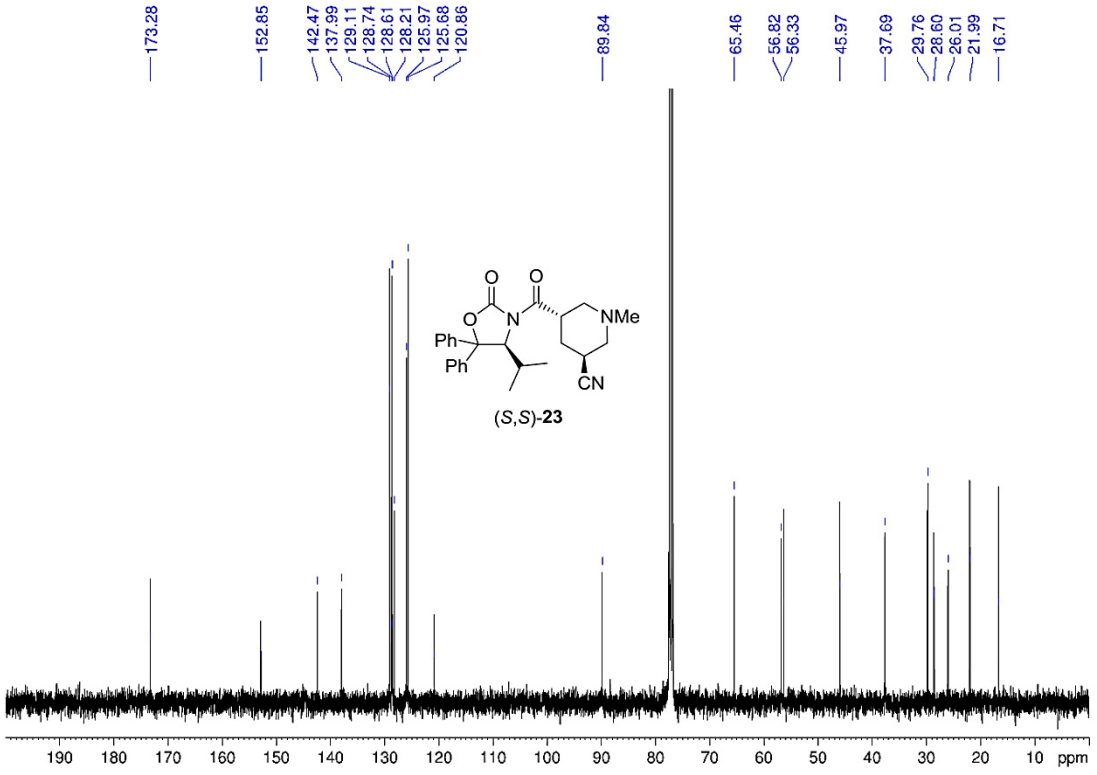
352.35
311.86
305.06
CH2Cl2
2.04
7.95
1.00
1.00
0.99
0.97
0.98
1.00
7.03
3.04
3.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
O
O
O
N
NMe
Ph
Ph
CN
(S,S)-23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128.21
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120.86
89.84
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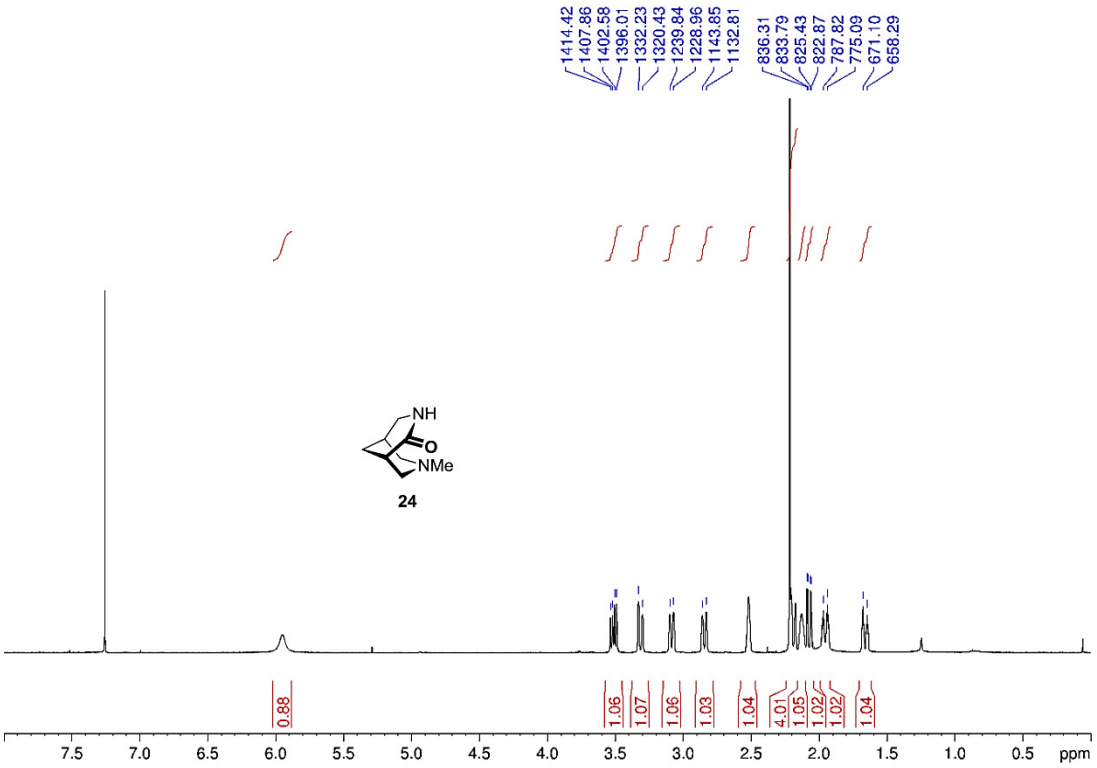
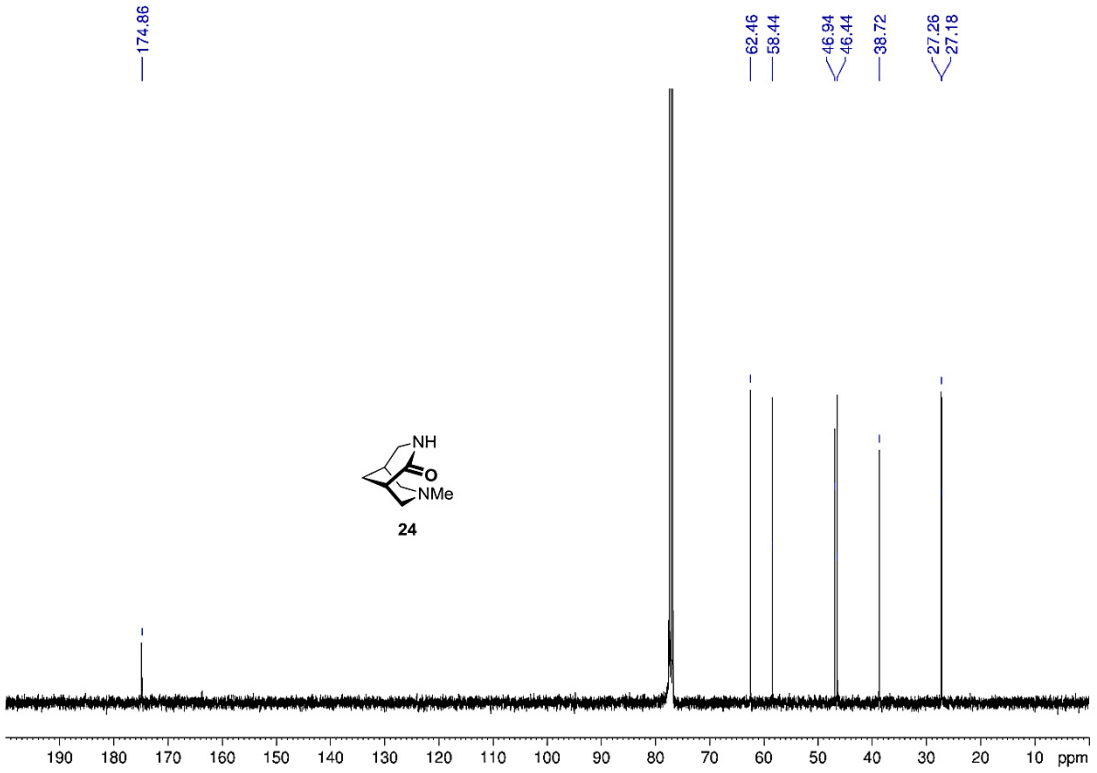
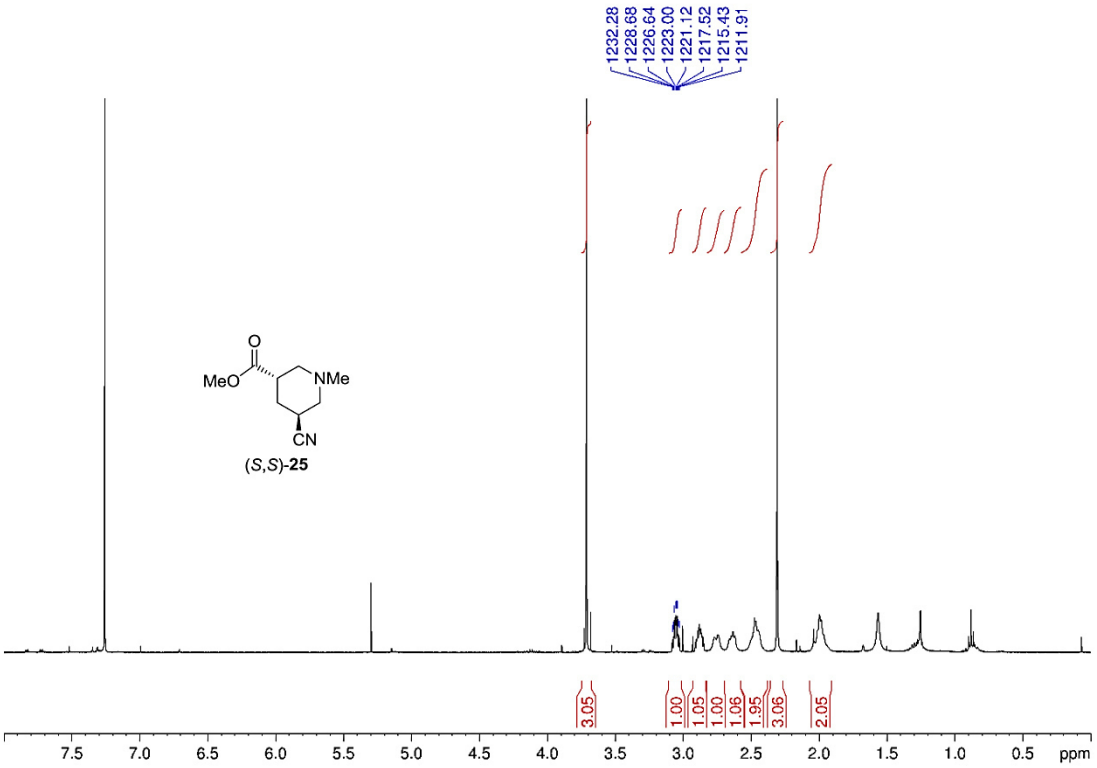
56.82
56.33
45.97
37.69
29.76
28.60
26.01
21.99
16.71
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
O
O
O
N
NMe
Ph
Ph
CN
(S,S)-23

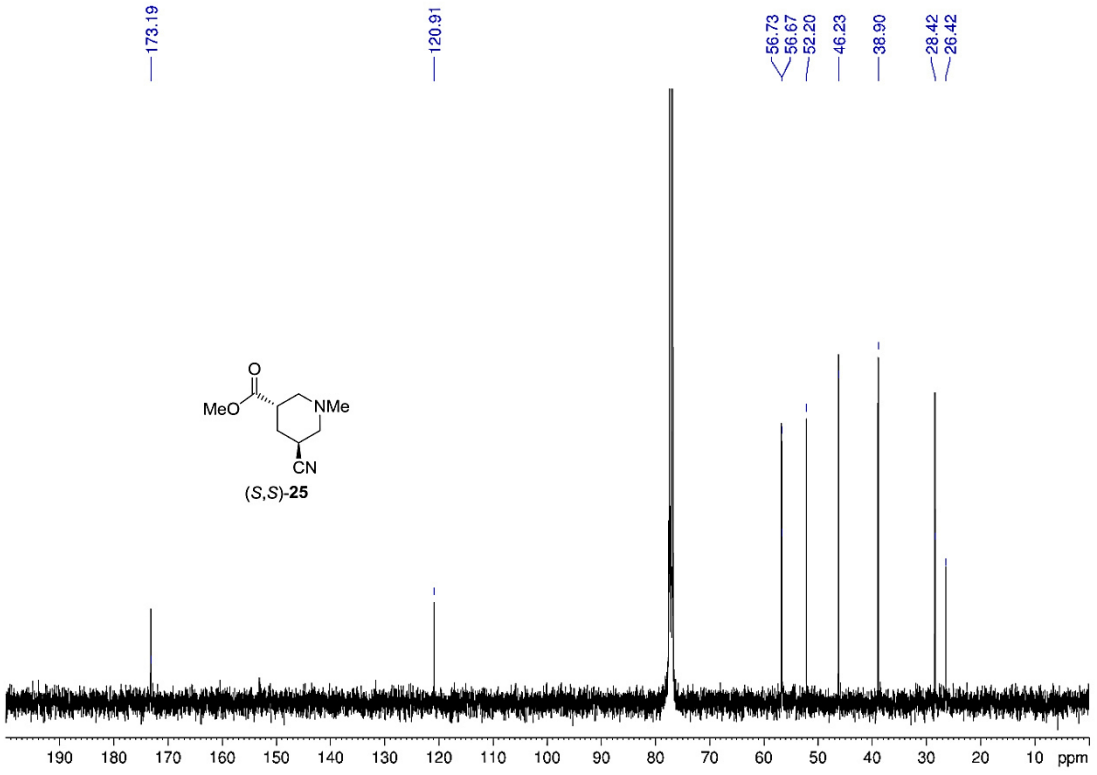
24


1414.42
1407.86
1402.58
1396.01
1332.23
1320.43
1239.84
1228.96
1143.85
1132.81
836.31
833.79
825.43
822.87
787.82
775.09
671.10
658.29
NH
O
NMe
24
0.88
1.06
1.07
1.06
1.03
1.04
4.01
1.05
1.02
1.02
1.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

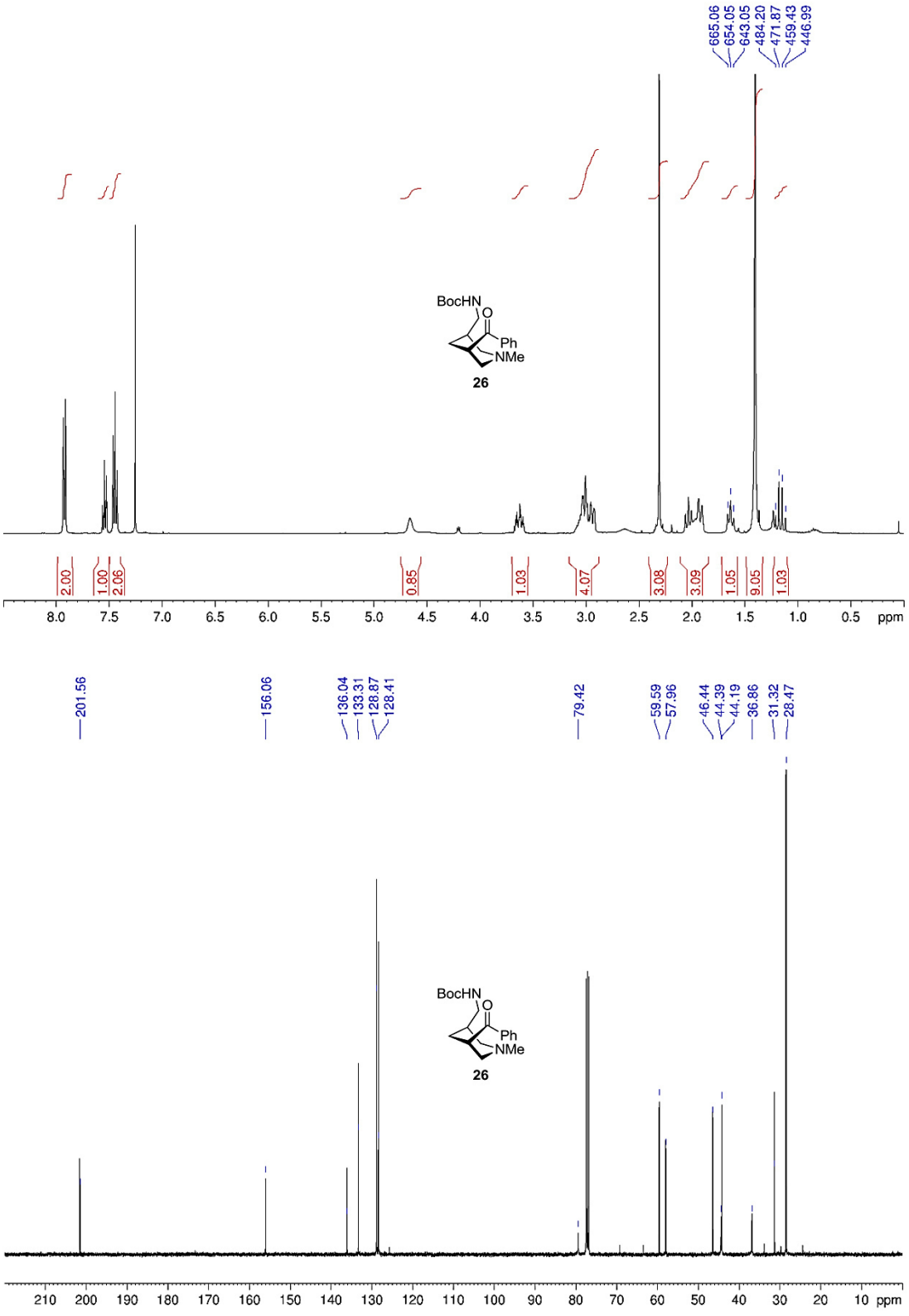

174.86
62.46
58.44
46.94
46.44
38.72
27.26
27.18
NH
O
NMe
24
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

25

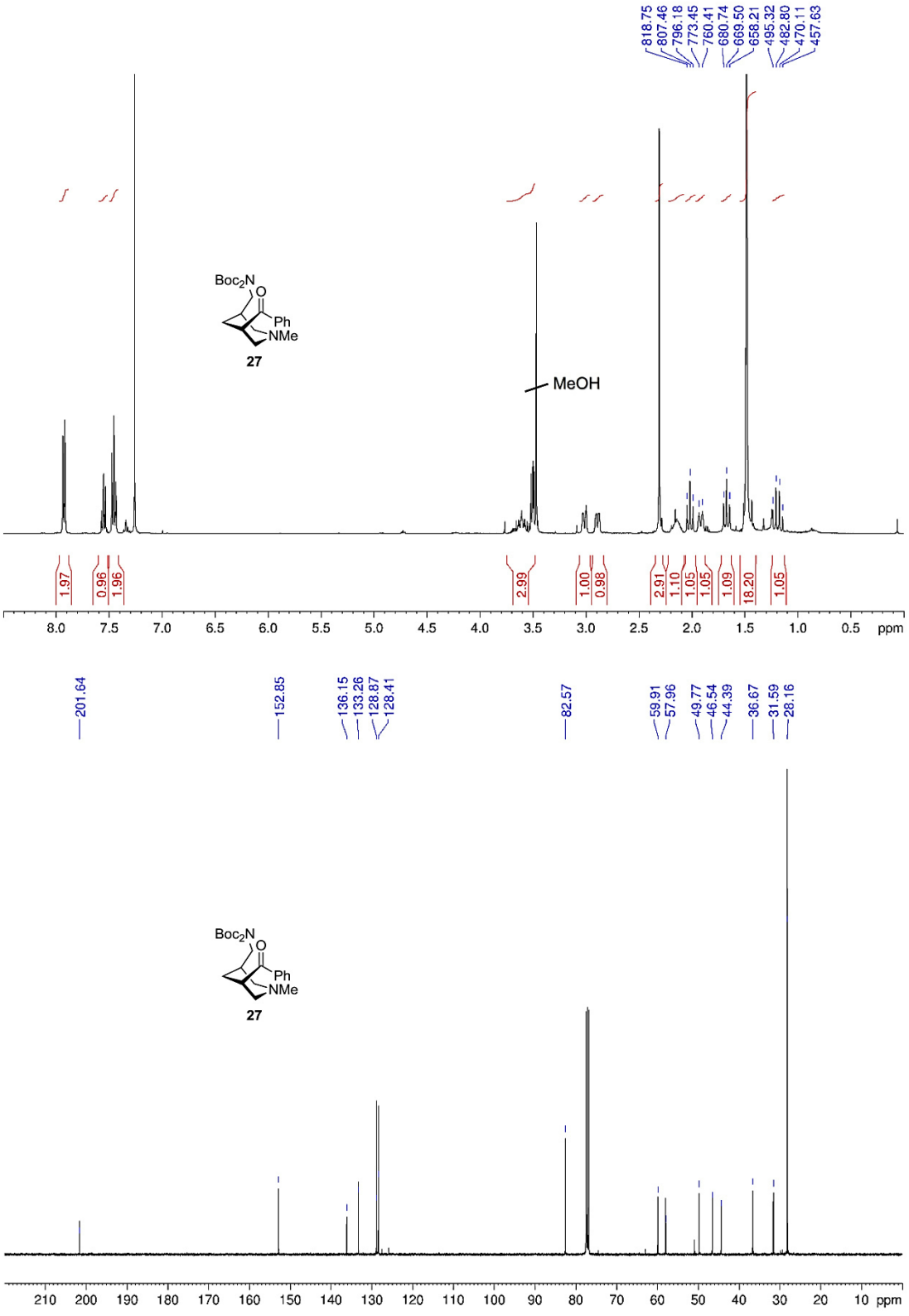

1232.28
1228.68
1226.64
1223.00
1221.12
1217.52
1215.43
1211.91
MeO
O
NMe
CN
(S,S)-25
3.05
1.00
1.05
1.00
1.06
1.95
3.06
2.05
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


173.19
120.91
56.73
56.67
52.20
46.23
38.90
28.42
26.42
MeO
O
NMe
CN
(S,S)-25
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

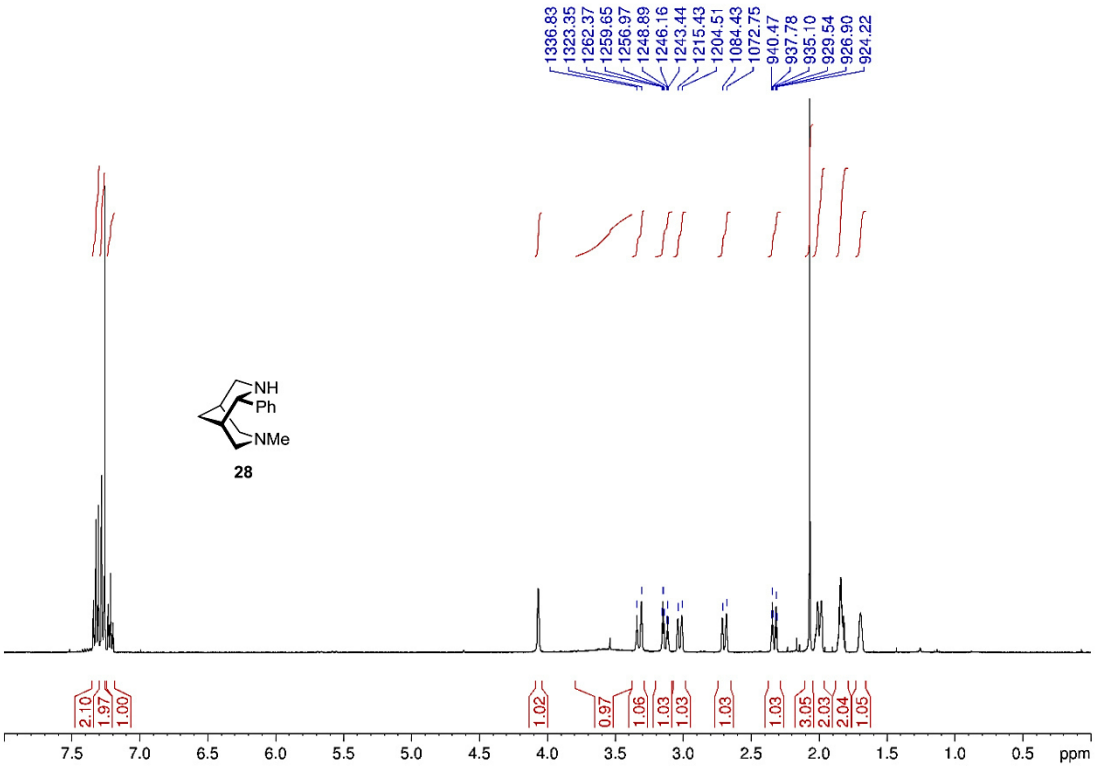
26

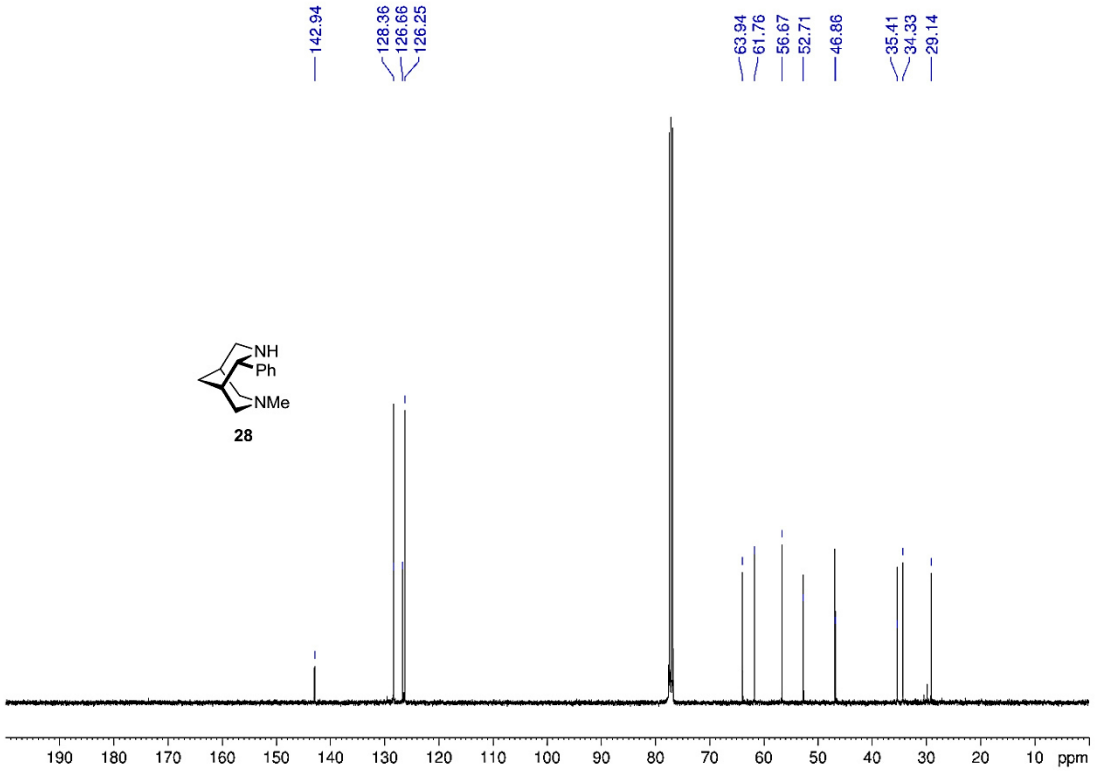

665.06
654.05
643.05
484.20
471.87
459.43
446.99
BocHN
O
Ph
NMe
26
2.00
1.00
2.06
0.85
1.03
4.07
3.08
3.09
1.05
9.05
1.03
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
201.56
156.06
136.04
133.31
128.87
128.41
79.42
59.59
57.96
46.44
44.39
44.19
36.86
31.32
28.47
BocHN
O
Ph
NMe
26
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

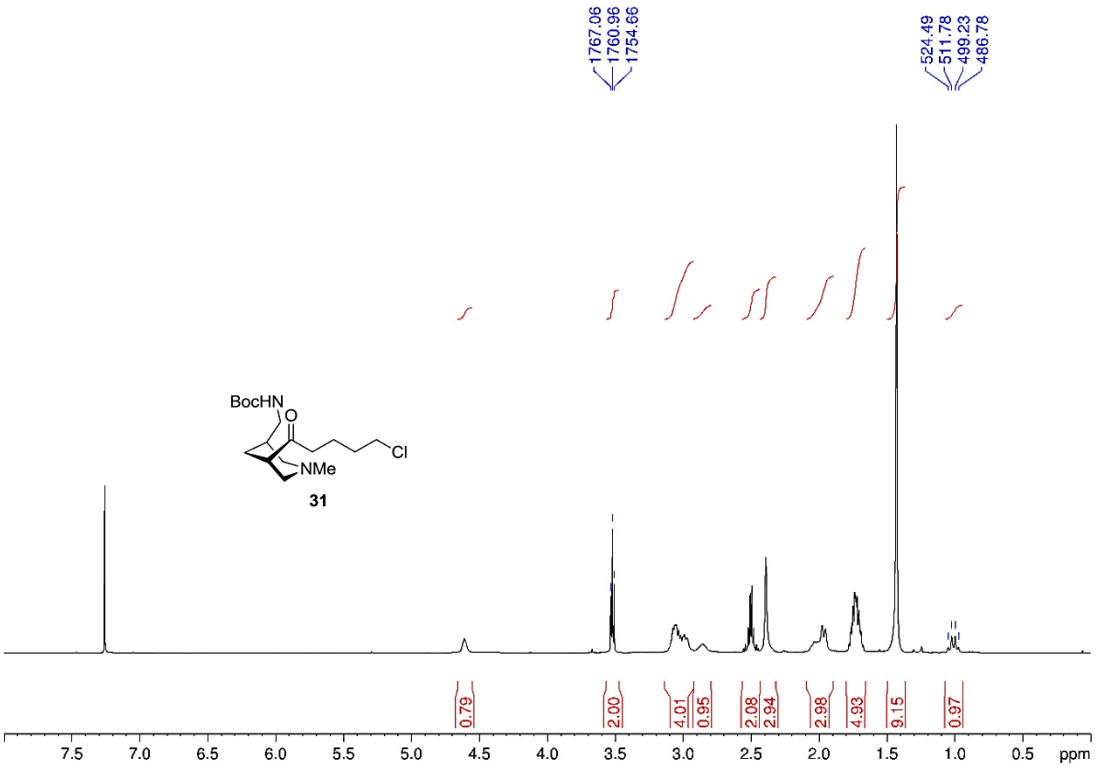
27

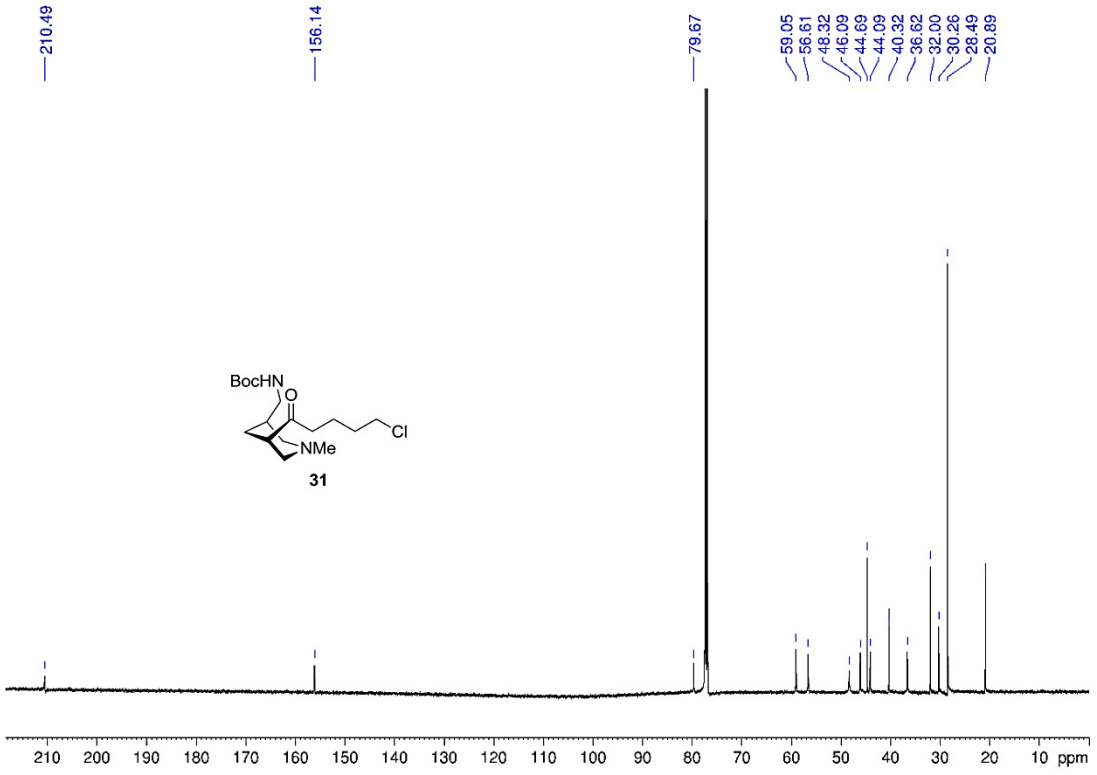

818.75
807.46
796.18
773.45
760.41
680.74
669.50
658.21
495.32
482.80
470.11
457.63
Boc2N
O
Ph
NMe
27
MeOH
1.97
0.96
1.96
2.99
1.00
0.98
2.91
1.10
1.05
1.05
1.09
18.20
1.05
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
201.64
152.85
136.15
133.26
128.87
128.41
82.57
59.91
57.96
49.77
46.54
44.39
36.67
31.59
28.16
Boc2N
O
Ph
NMe
27
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

28

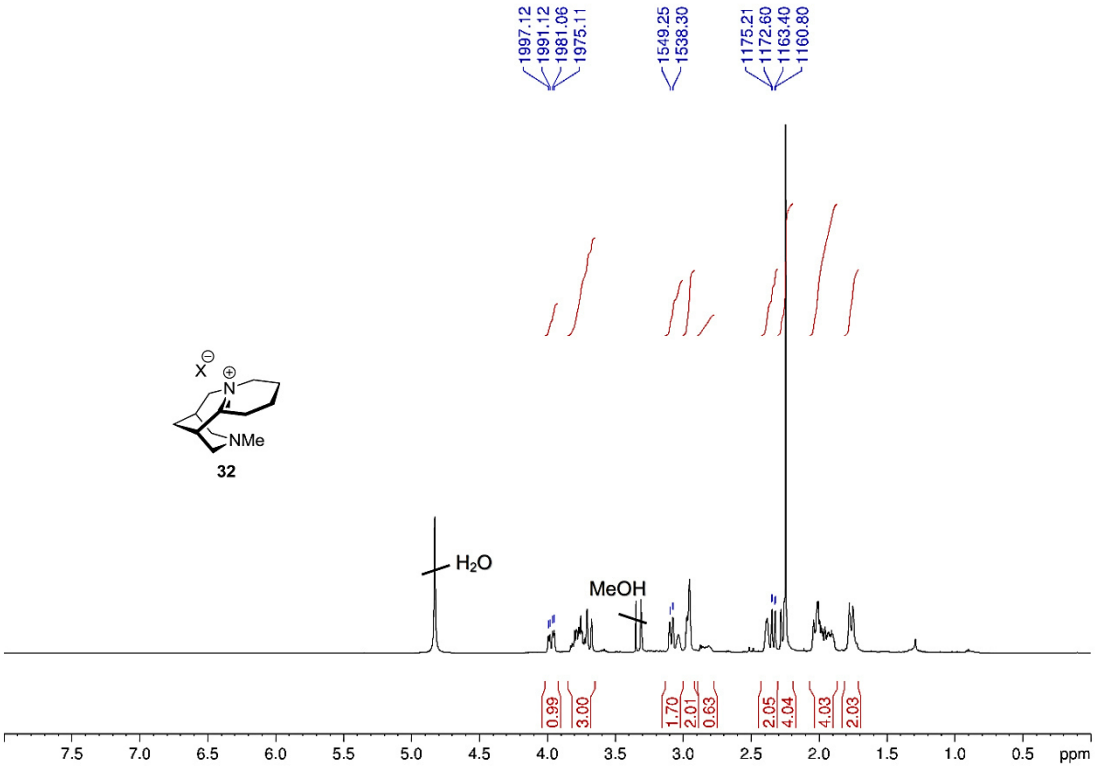

1336.83
1323.35
1262.37
1259.65
1256.97
1248.89
1246.16
1243.44
1215.43
1204.51
1084.43
1072.75
940.47
937.78
935.10
929.54
926.90
924.22
NH
Ph
NMe
28
2.10
1.97
1.00
1.02
0.97
1.06
1.03
1.03
1.03
1.03
3.05
2.03
2.04
1.05
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

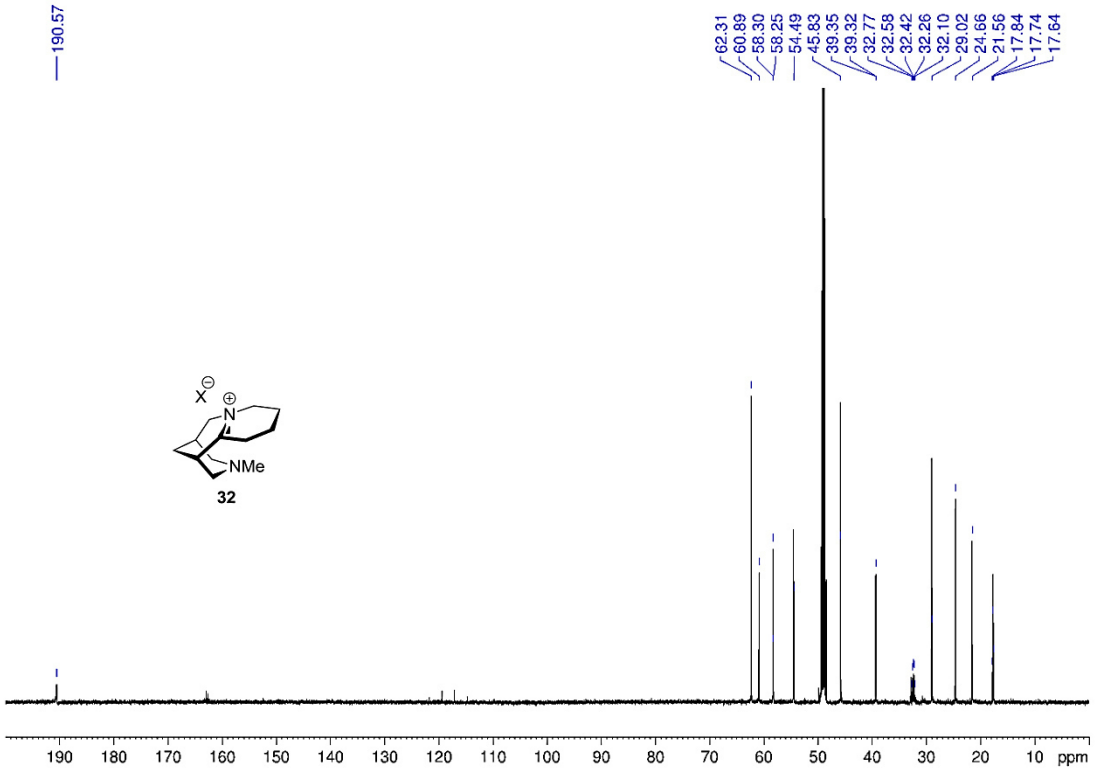

142.94
128.36
126.66
126.25
63.94
61.76
56.67
52.71
46.86
35.41
34.33
29.14
NH
Ph
NMe
28
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


1767.06
1760.96
1754.66
524.49
511.78
499.23
486.78
BocHN
O
Cl
NMe
31
0.79
2.00
4.01
0.95
2.08
2.94
2.98
4.93
9.15
0.97
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

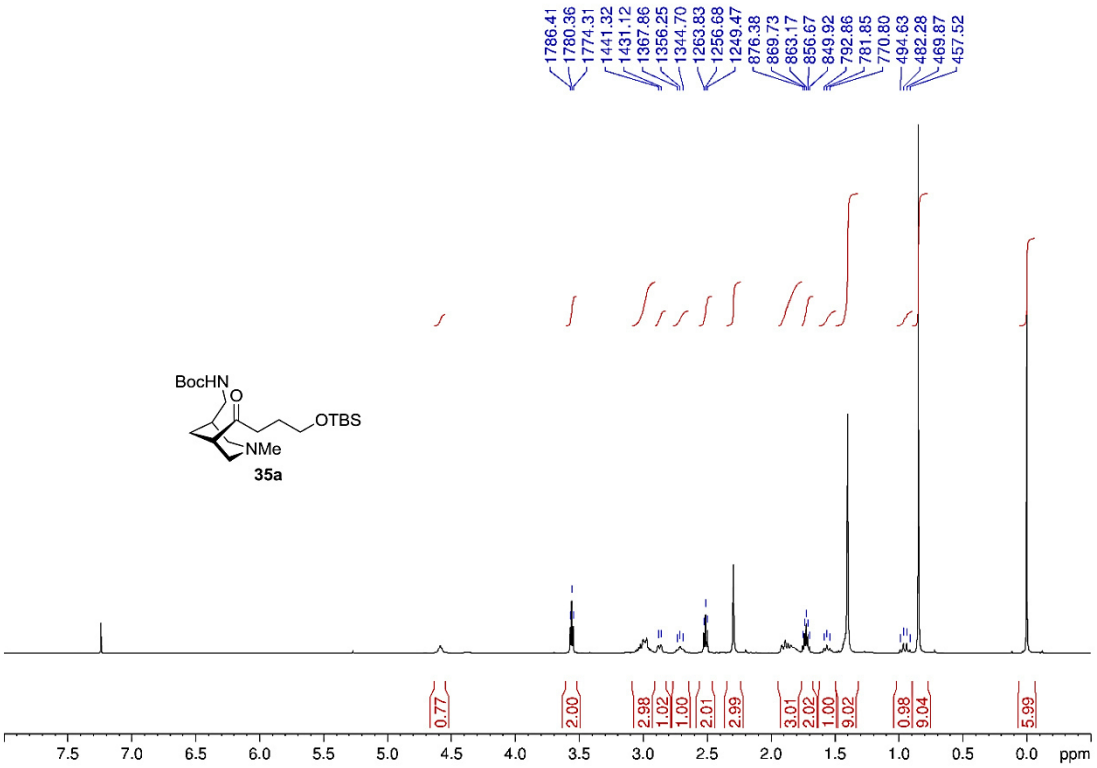

210.49
156.14
79.67
59.05
56.61
48.32
46.09
44.69
44.09
40.32
36.62
32.00
30.26
28.49
20.89
BocHN
O
Cl
NMe
31
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

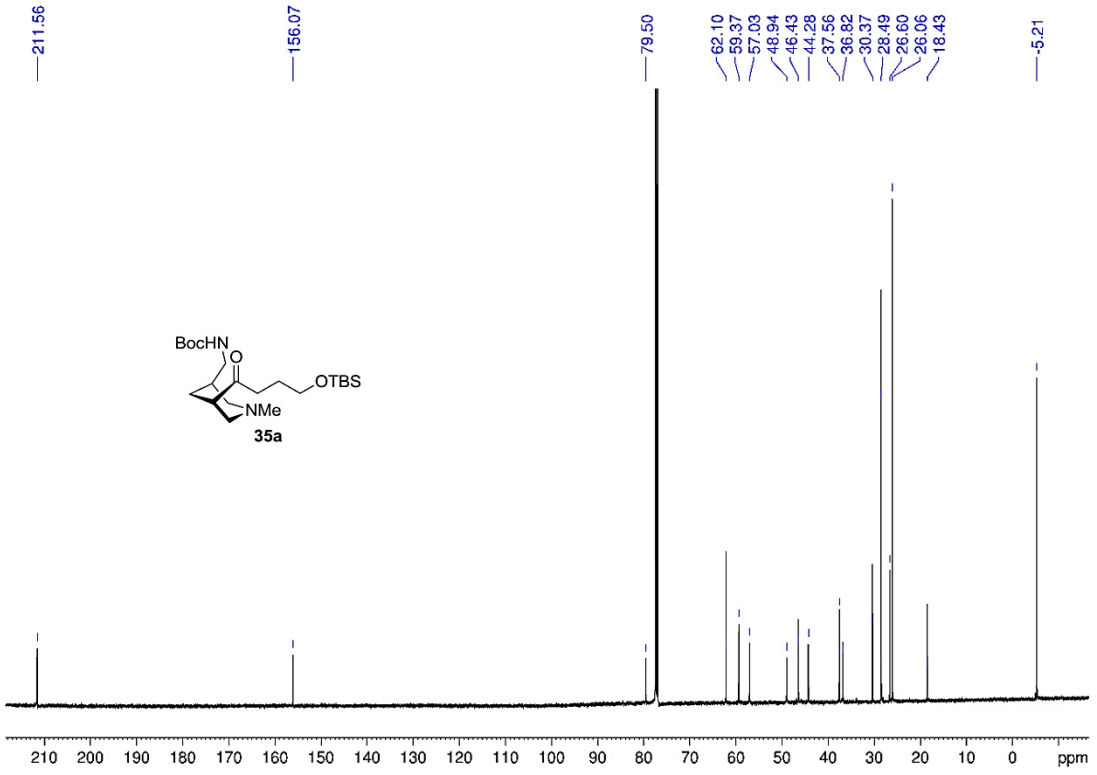
30


1997.12
1991.12
1981.06
1975.11
1549.25
1538.30
1175.21
1172.60
1163.40
1160.80
X
N
NMe
32
H2O
MeOH
0.99
3.00
1.70
2.01
0.63
2.05
4.04
4.03
2.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

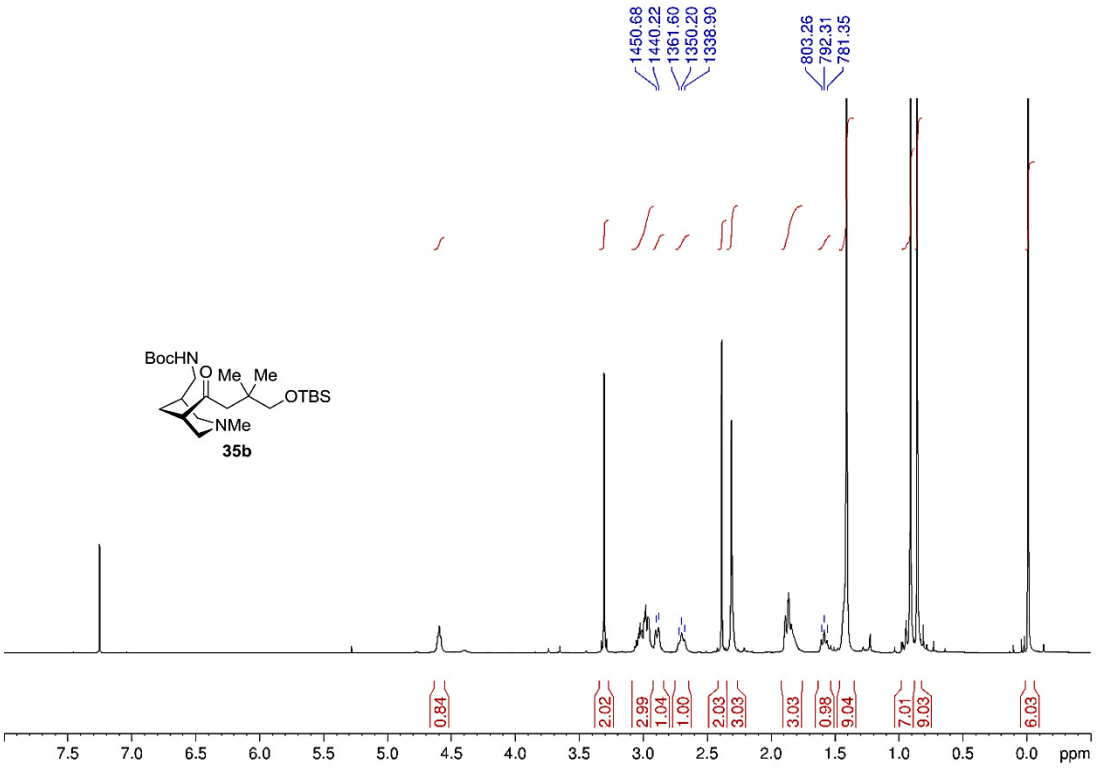

190.57
62.31
60.89
58.30
58.25
54.49
45.83
39.35
39.32
32.77
32.58
32.42
32.26
32.10
29.02
24.66
21.56
17.84
17.74
17.64
X
N
NMe
32
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

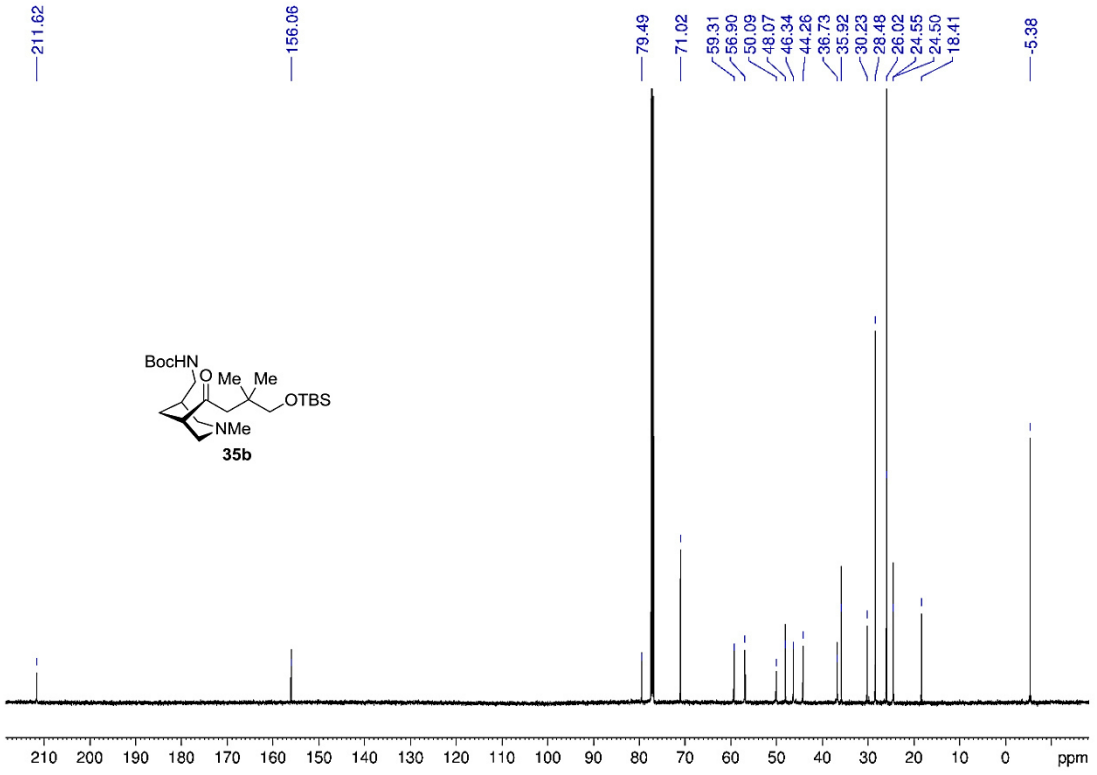
31

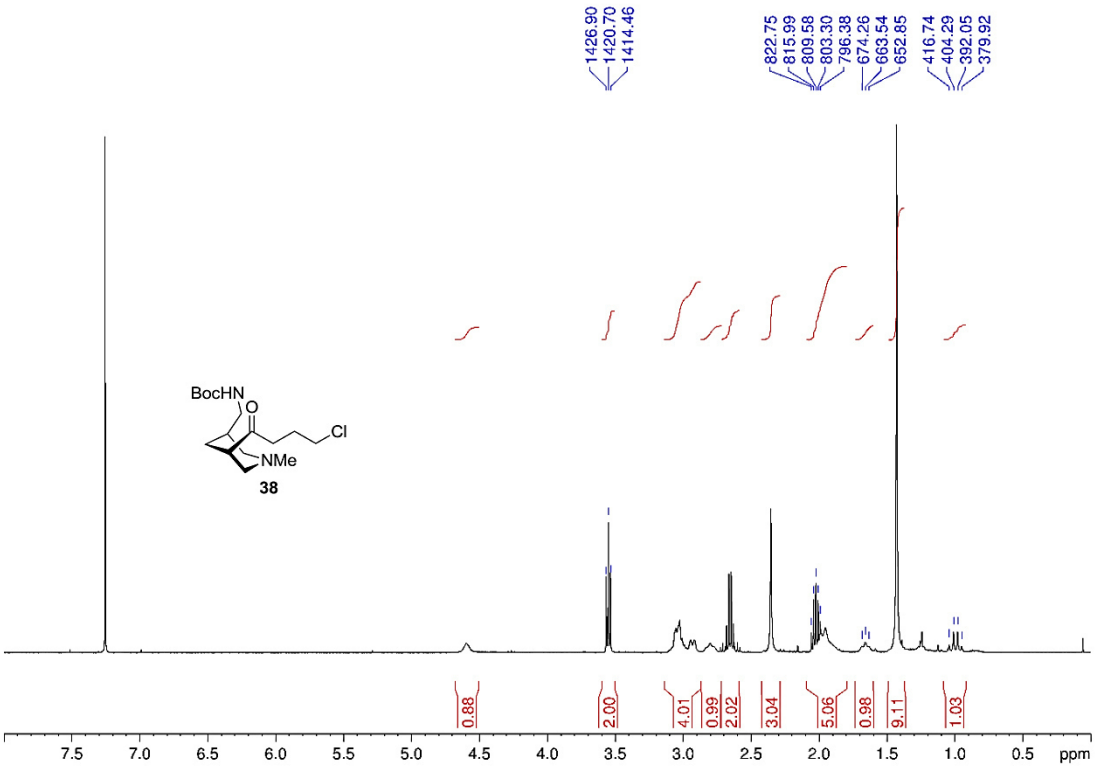

1786.41
1780.36
1774.31
1441.32
1431.12
1367.86
1356.25
1344.70
1263.83
1256.68
1249.47
876.38
869.73
863.17
856.67
849.92
792.86
781.85
770.80
494.63
482.28
469.87
457.52
BocHN
O
OTBS
NMe
35a
0.77
2.00
2.98
1.02
1.00
2.01
2.99
3.01
2.02
1.00
9.02
0.98
9.04
5.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

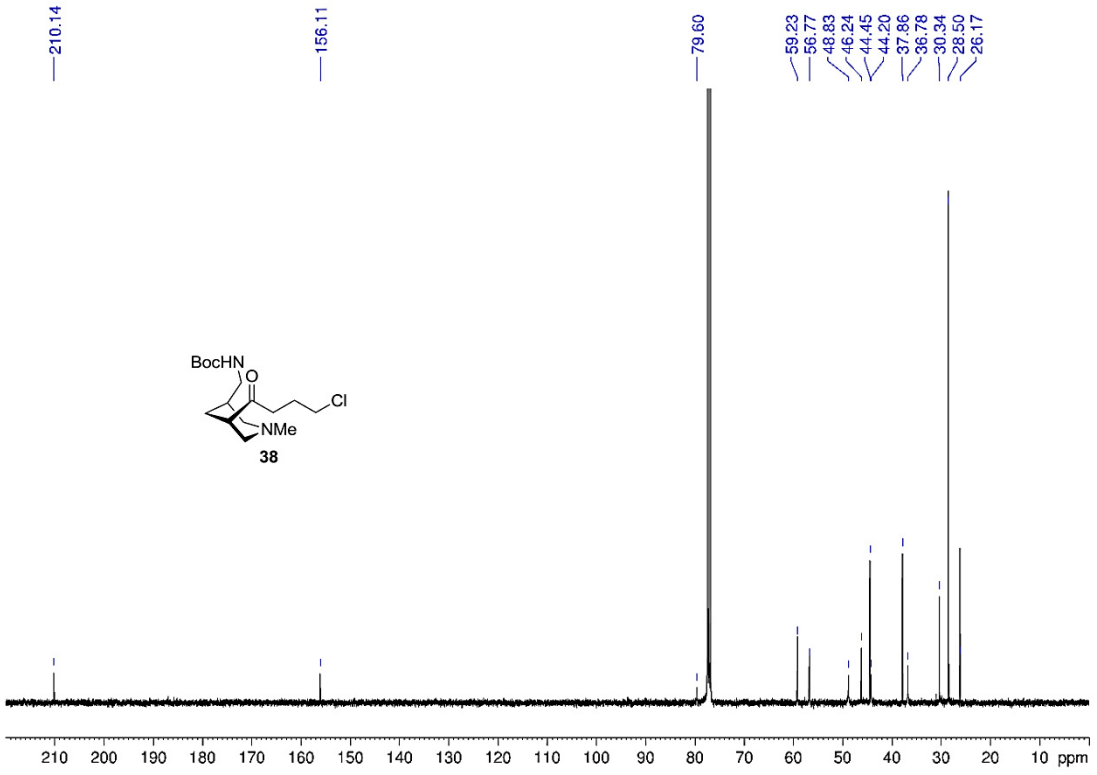

211.56
156.07
79.50
62.10
59.37
57.03
48.94
46.43
44.28
37.56
36.82
30.37
28.49
26.60
26.06
18.43
-5.21
BocHN
O
OTBS
NMe
35a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

32

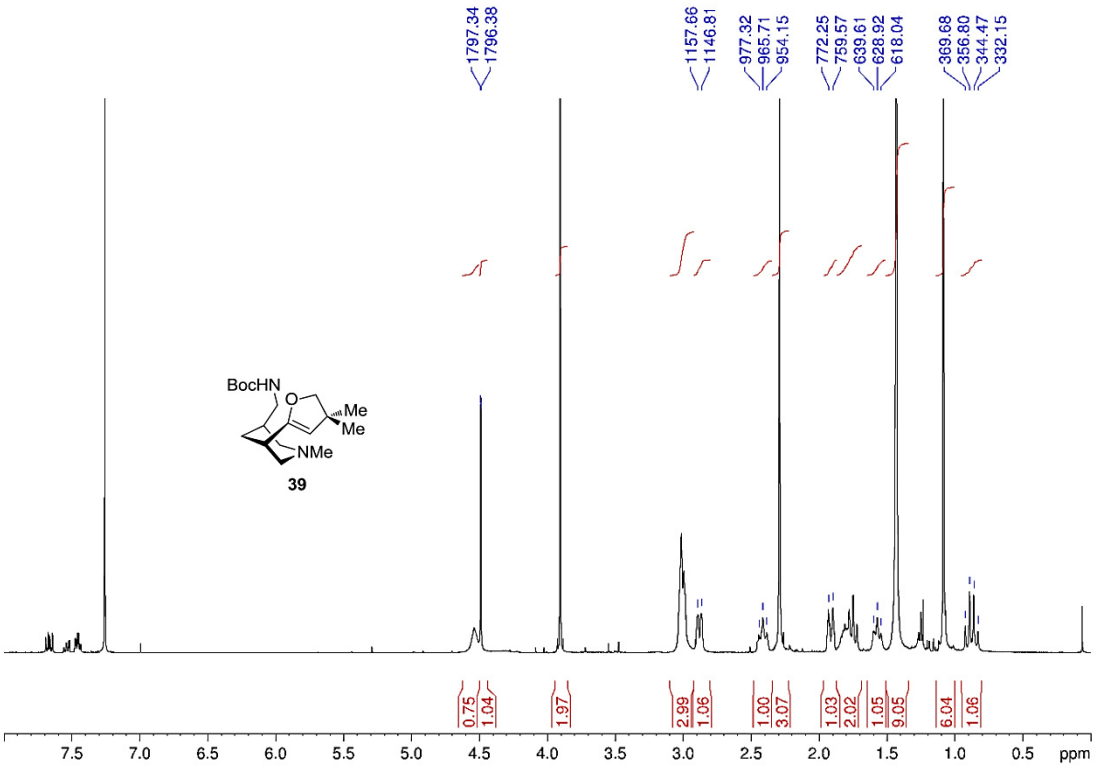

1450.68
1440.22
1361.60
1350.20
1338.90
803.26
792.31
781.35
BocHN
O
Me
Me
OTBS
NMe
35b
0.84
2.02
2.99
1.04
1.00
2.03
3.03
3.03
0.98
9.04
7.01
9.03
6.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

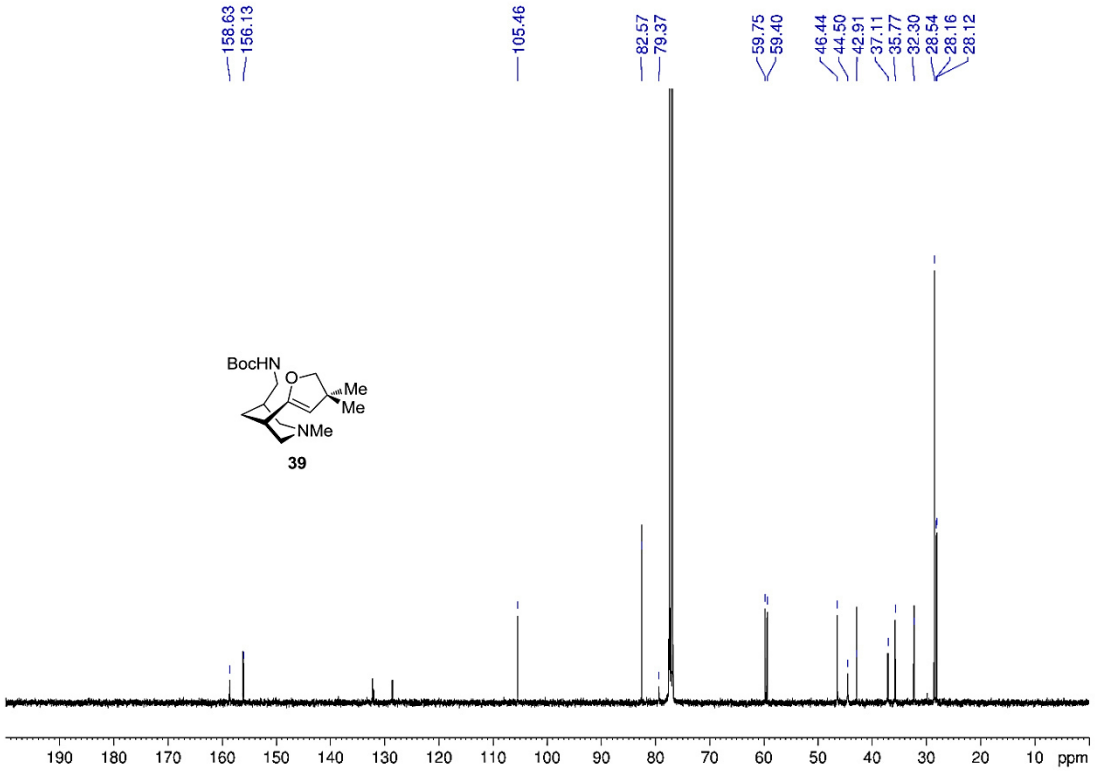

211.62
156.06
79.49
71.02
59.31
56.90
50.09
48.07
46.34
44.26
36.73
35.92
30.23
28.48
26.02
24.55
24.50
18.41
-5.38
BocHN
O
Me
Me
OTBS
NMe
35b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

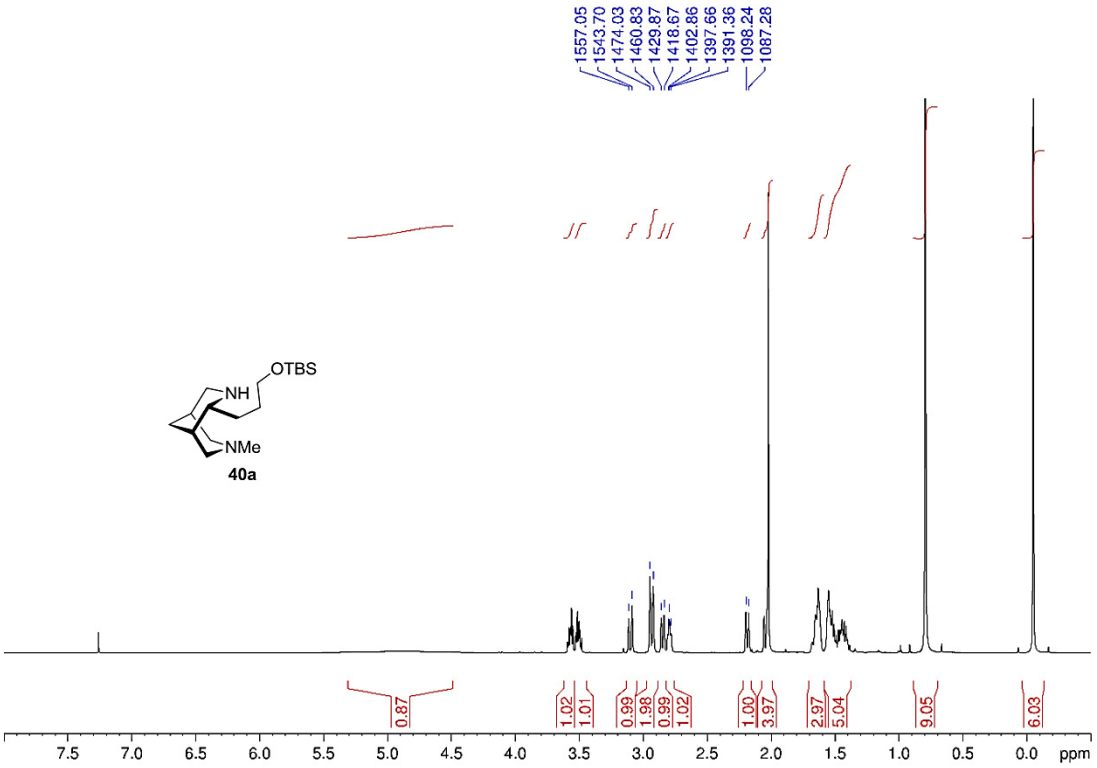

1426.90
1420.70
1414.46
822.75
815.99
809.58
803.30
796.38
674.26
663.54
652.85
416.74
404.29
392.05
379.92
BocHN
O
Cl
NMe
38
0.88
2.00
4.01
0.99
2.02
3.04
5.06
0.98
9.11
1.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

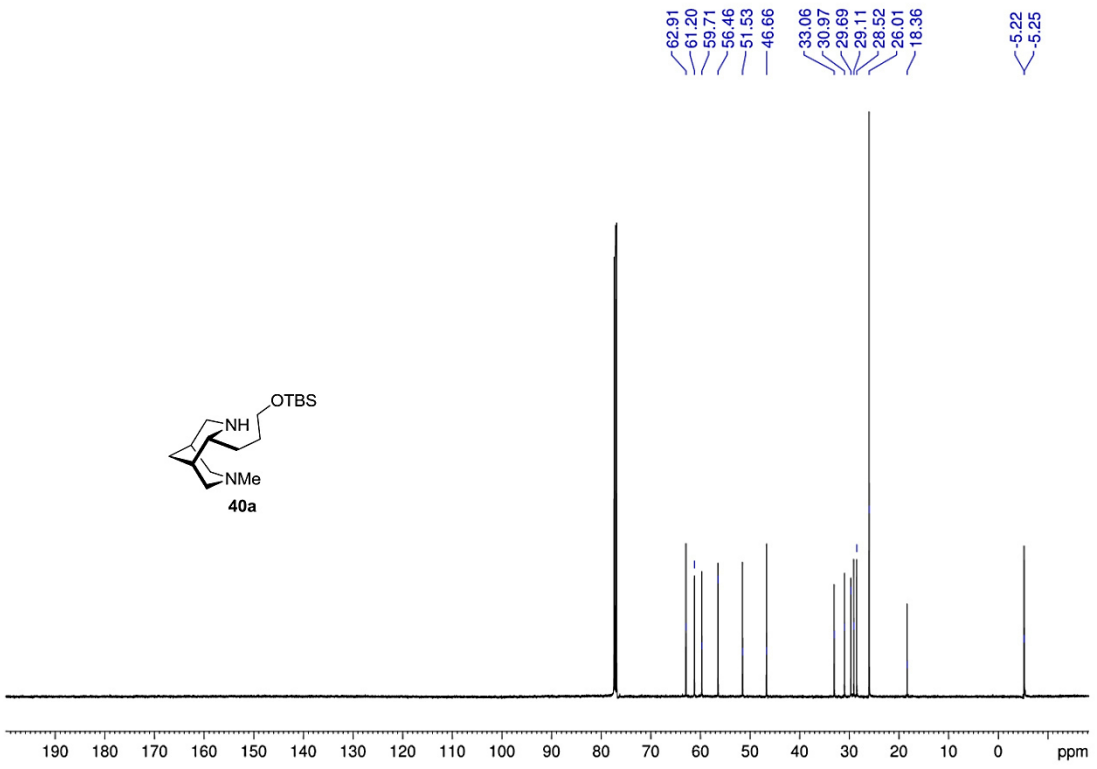

210.14
156.11
79.60
59.23
56.77
48.83
46.24
44.45
44.20
37.86
36.78
30.34
28.50
26.17
BocHN
O
Cl
NMe
38
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

34

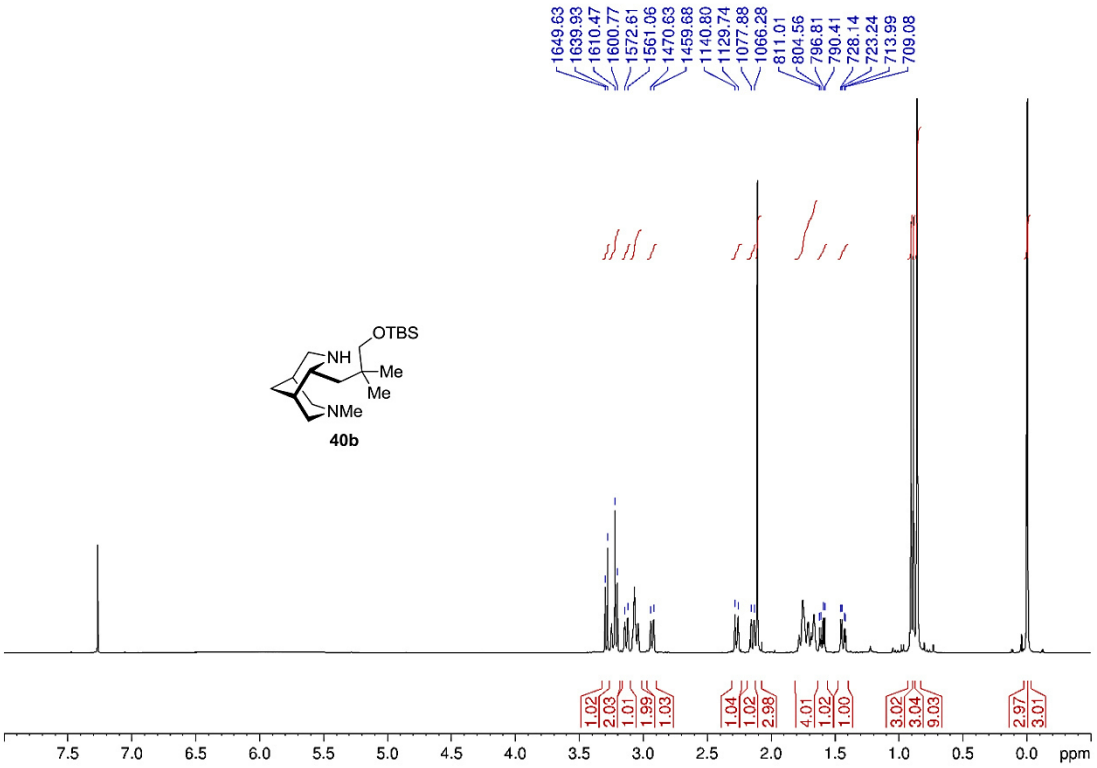

1797.34
1796.38
1157.66
1146.81
977.32
965.71
954.15
772.25
759.57
639.61
628.92
618.04
369.68
356.80
344.47
332.15
BocHN
O
Me
Me
NMe
39
0.75
1.04
1.97
2.99
1.06
1.00
3.07
1.03
2.02
1.05
9.05
6.04
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

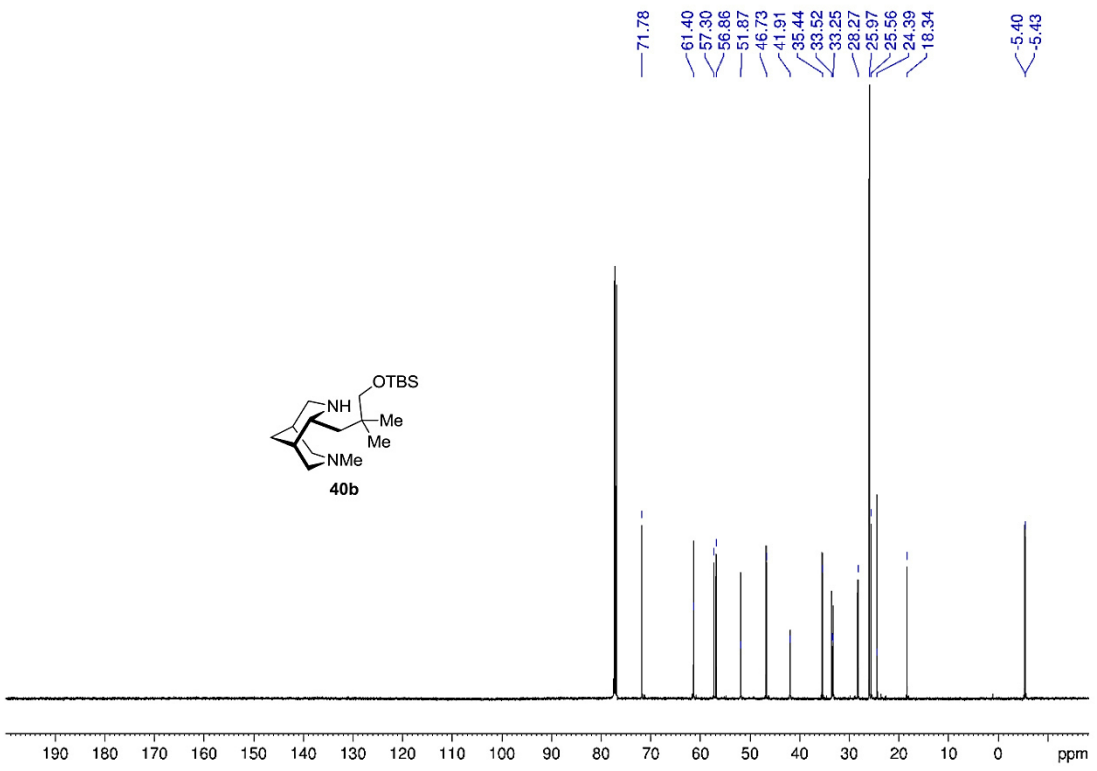

158.63
156.13
105.46
82.57
79.37
59.75
59.40
46.44
44.50
42.91
37.11
35.77
32.30
28.54
28.16
28.12
BocHN
O
Me
Me
NMe
39
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


1557.05
1543.70
1474.03
1460.83
1429.87
1418.67
1402.86
1397.66
1391.36
1098.24
1087.28
OTBS
NH
NMe
40a
0.87
1.02
1.01
0.99
1.98
0.99
1.02
1.00
3.97
2.97
5.04
9.05
6.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

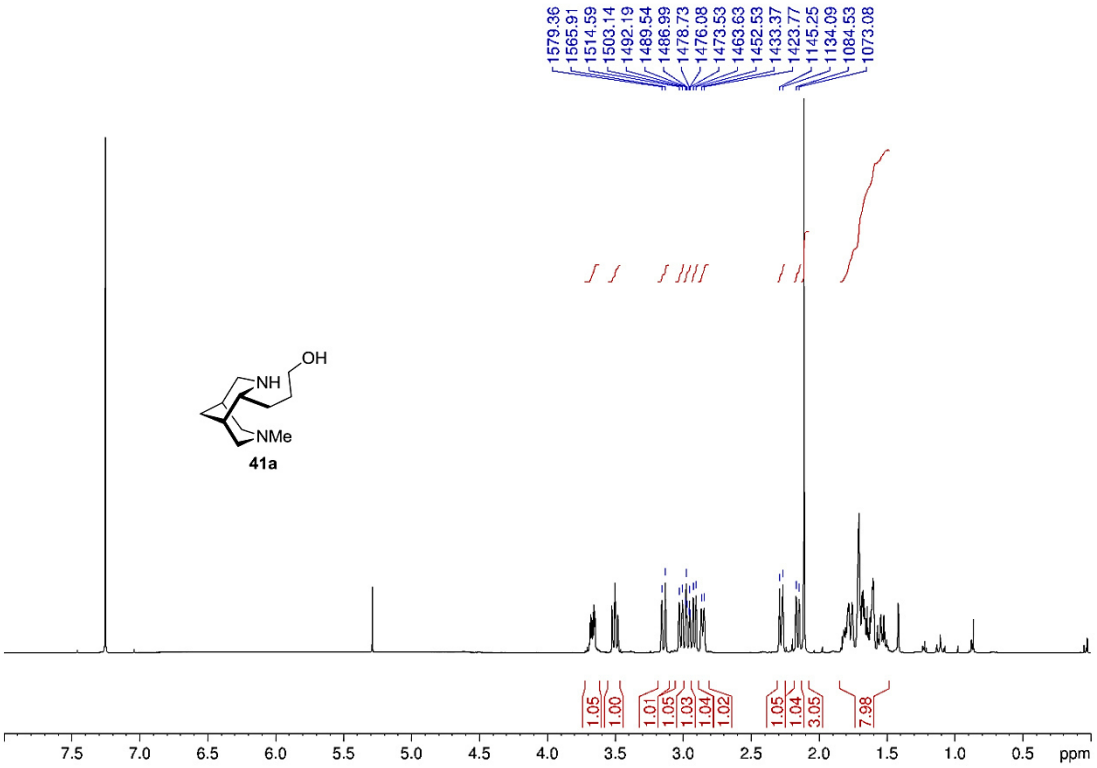

62.91
61.20
59.71
56.46
51.53
46.66
33.06
30.97
29.69
29.11
28.52
26.01
18.36
-5.22
-5.25
OTBS
NH
NMe
40a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

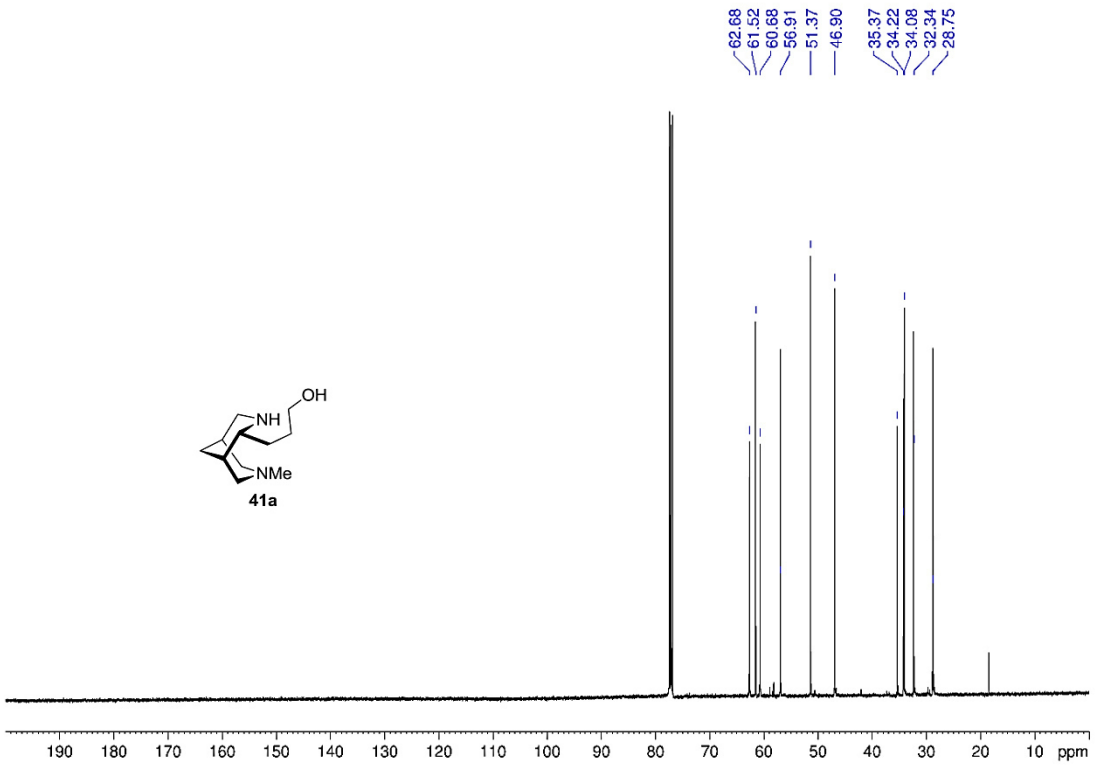
36


1649.63
1639.93
1610.47
1600.77
1572.61
1561.06
1470.63
1459.68
1140.80
1129.74
1077.88
1066.28
811.01
804.56
796.81
790.41
728.14
723.24
713.99
709.08
OTBS
NH
Me
Me
NMe
40b
1.02
2.03
1.01
1.99
1.03
1.04
1.02
2.98
4.01
1.02
1.00
3.02
3.04
9.03
2.97
3.01
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

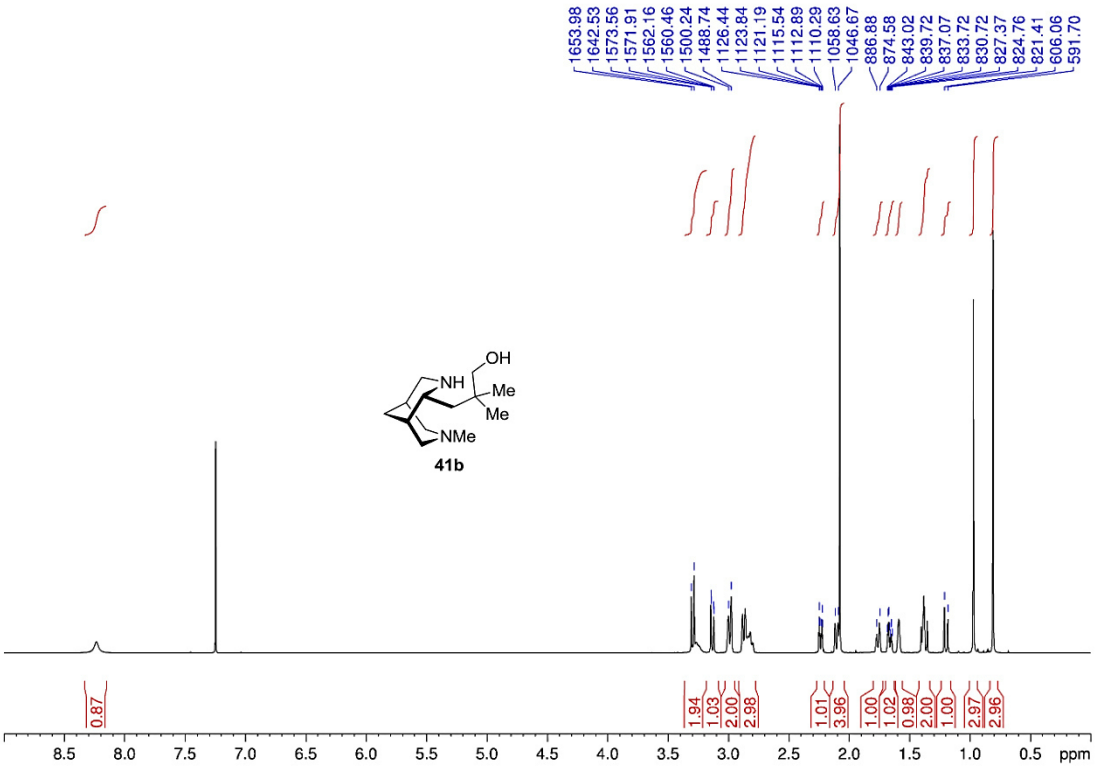

71.78
61.40
57.30
56.86
51.87
46.73
41.91
35.44
33.52
33.25
28.27
25.97
25.56
24.39
18.34
-5.40
-5.43
OTBS
NH
Me
Me
NMe
40b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

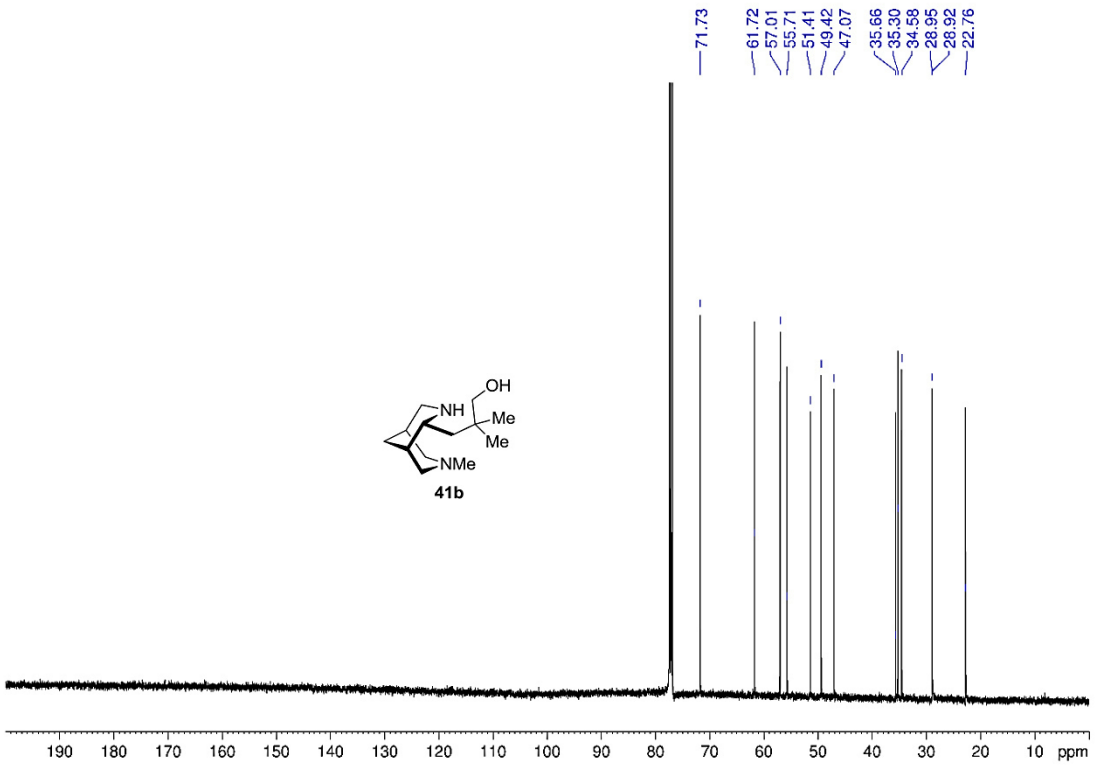
37


1579.36
1565.91
1514.59
1503.14
1492.19
1489.54
1486.99
1478.73
1476.08
1473.53
1463.63
1452.53
1433.37
1423.77
1145.25
1134.09
1084.53
1073.08
OH
NH
NMe
41a
1.05
1.00
1.01
1.05
1.03
1.04
1.02
1.05
1.04
3.05
7.98
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


62.68
61.52
60.68
56.91
51.37
46.90
35.37
34.22
34.08
32.34
28.75
OH
NH
NMe
41a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

38


1653.98
1642.53
1573.56
1571.91
1562.16
1560.46
1500.24
1488.74
1126.44
1123.84
1121.19
1115.54
1112.89
1110.29
1058.63
1046.67
886.88
874.58
843.02
839.72
837.07
833.72
830.72
827.37
824.76
821.41
606.06
591.70
OH
NH
Me
Me
NMe
41b
0.87
1.94
1.03
2.00
2.98
1.01
3.96
1.00
1.02
0.98
2.00
1.00
2.97
2.96
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

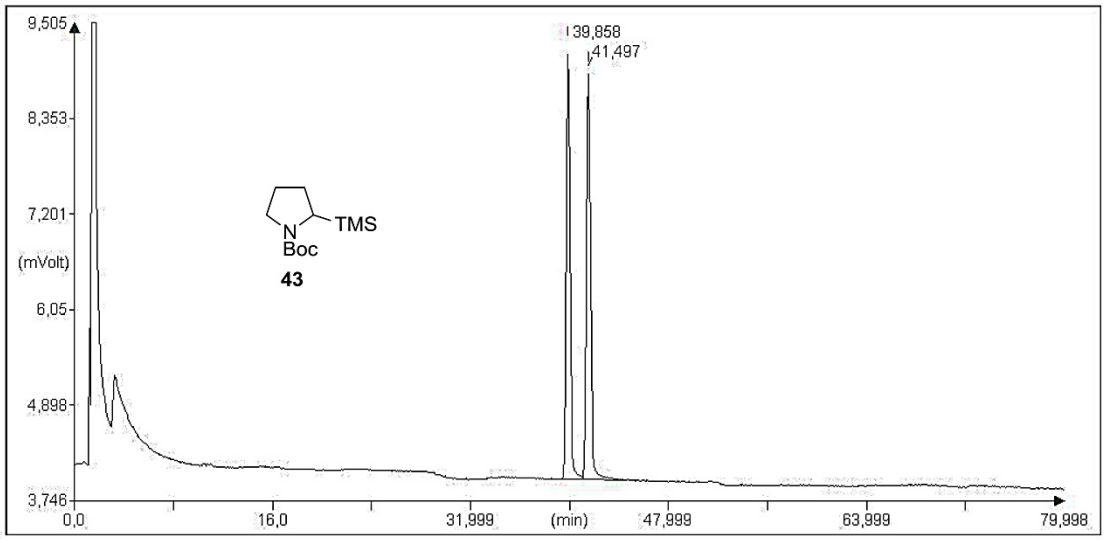

71.73
61.72
57.01
55.71
51.41
49.42
47.07
35.66
35.30
34.58
28.95
28.92
22.76
OH
NH
Me
Me
NMe
41b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

4. Copies of GC and HPLC spectra

4.1 Enantiomer analysis of 43 by GC on chiral phase

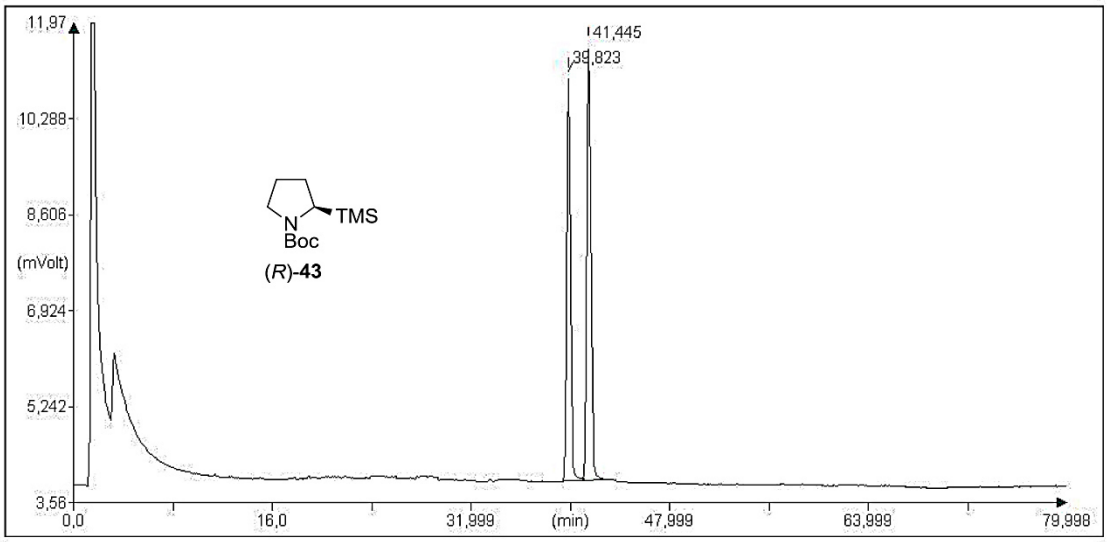
GC conditions: chiral column BGB-176SE, 30 m x 0.25 mm ID, 0.25 µm film, T = 100°C isothermal, injector temperature 240°C, detector temperature 240°C, H_2 carrier gas at 83 kPa constant pressure, t_R = 39.8 min (*S*), 41.5 min (*R*).

43 (racemic)



Peak Number (#)	Retention Time (min)	Peak Height (uV)	Peak Height % (%)	Area (.1*uV*sec)	Area % (%)
1	39.858	5236	51.511	1056193	49.212
2	41.497	4929	48.489	1090009	50.788
		10164		2146201	

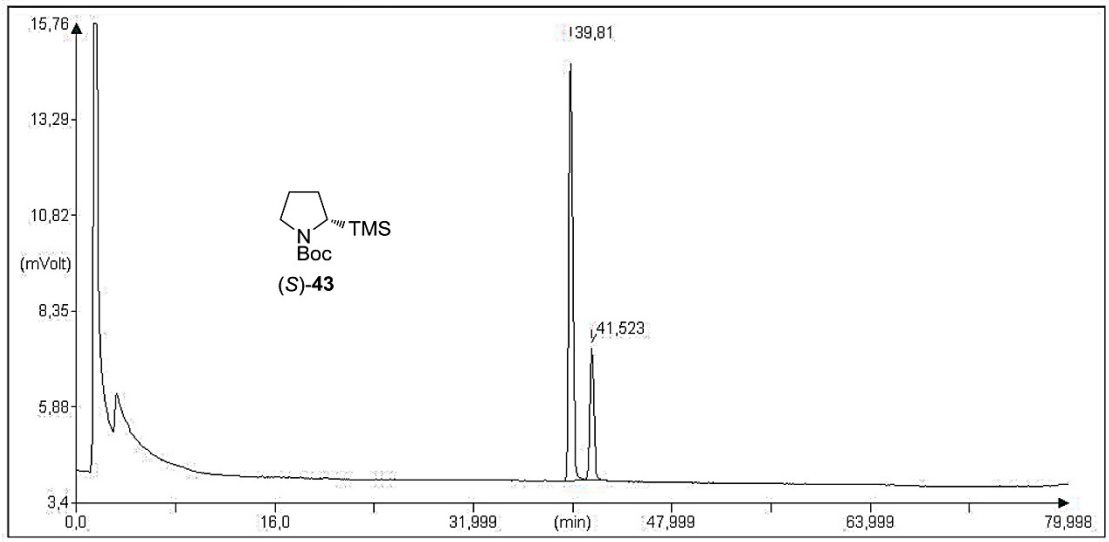
(*R*)-**43** (7% *ee*, see Table 3, entry 1)



Peak Number (#)	Retention Time (min)	Peak Height (uV)	Peak Height % (%)	Area (.1*uV*sec)	Area % (%)
1	39.823	7098	48.191	1409617	46.417
2	41.445	7631	51.809	1627214	53.583
		14729		3036831	

40

(*S*)-**43** (52% *ee*, see Table 3, entry 2)

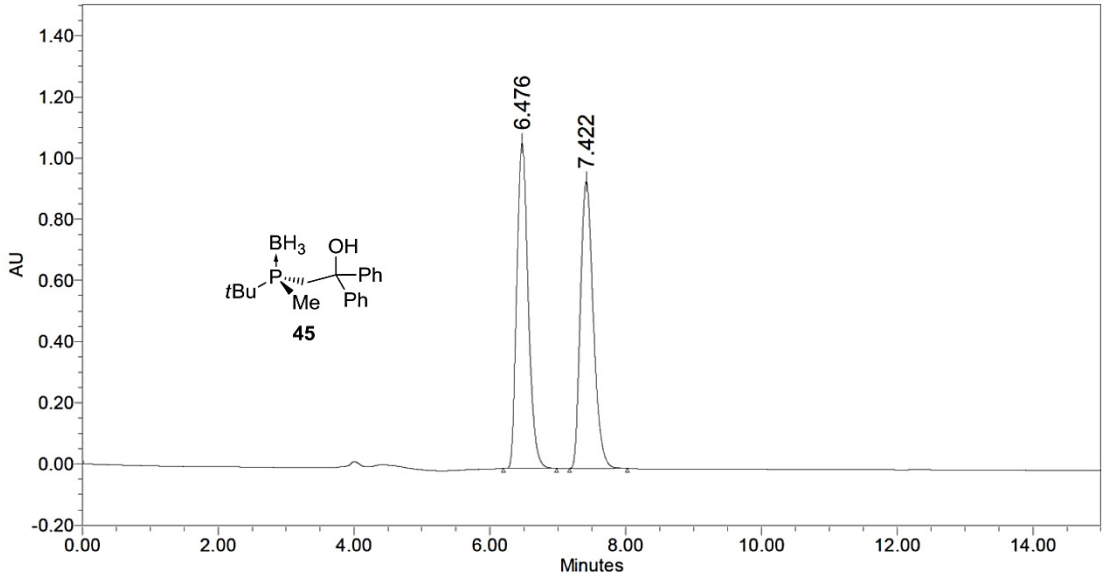


Peak Number (#)	Retention Time (min)	Peak Height (uV)	Peak Height % (%)	Area (.1*uV*sec)	Area % (%)
1	39.810	11227	76.668	2270846	75.841
2	41.523	3417	23.333	723359	24.159
		14644		2994205	

4.2 Enantiomer analysis of 45 by HPLC on chiral phase

HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 95:5, 0.8 mL/min, 215 nm, t_R = 6.9 min (*R*), 8.1 min (*S*).

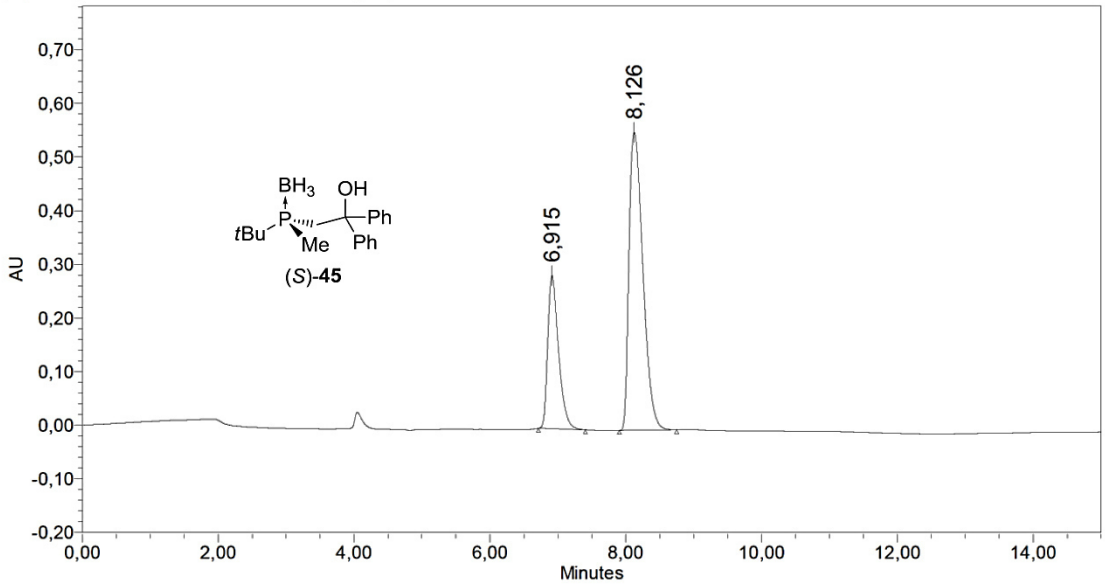
45 (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	6.48	6.20	6.98	1064008	53.12	12353584	49.96
2	7.42	7.18	8.03	939103	46.88	12374380	50.04

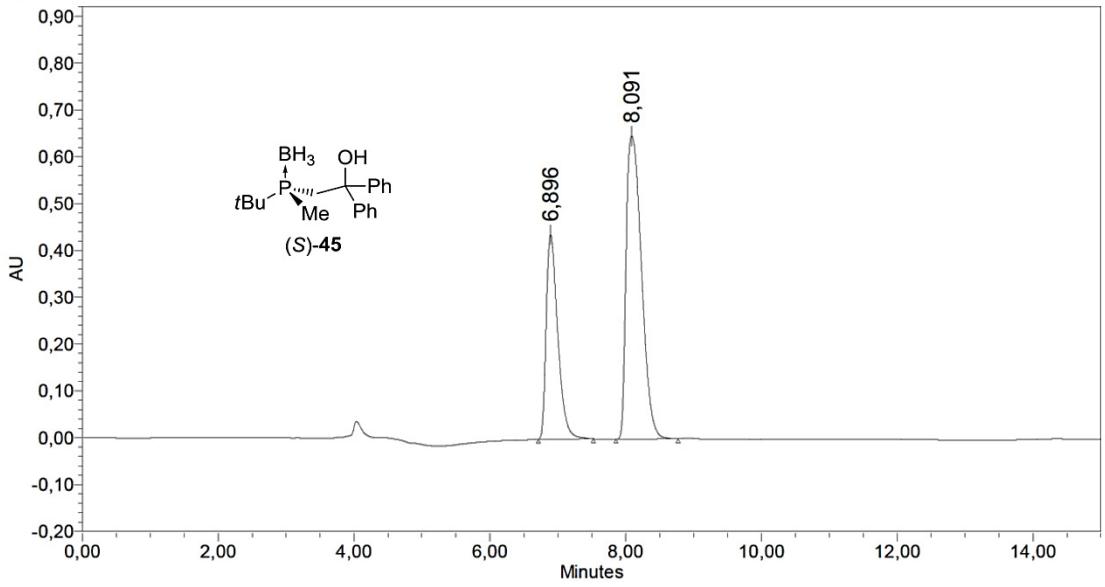
41

(*S*)-**45** (43% *ee*, see Table 3, entry 3)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	6,92	6,72	7,41	285707	33,96	3124280	28,47
2	8,13	7,91	8,75	555662	66,04	7848763	71,53

(*S*)-**45** (33% *ee*, see Table 3, entry 4)

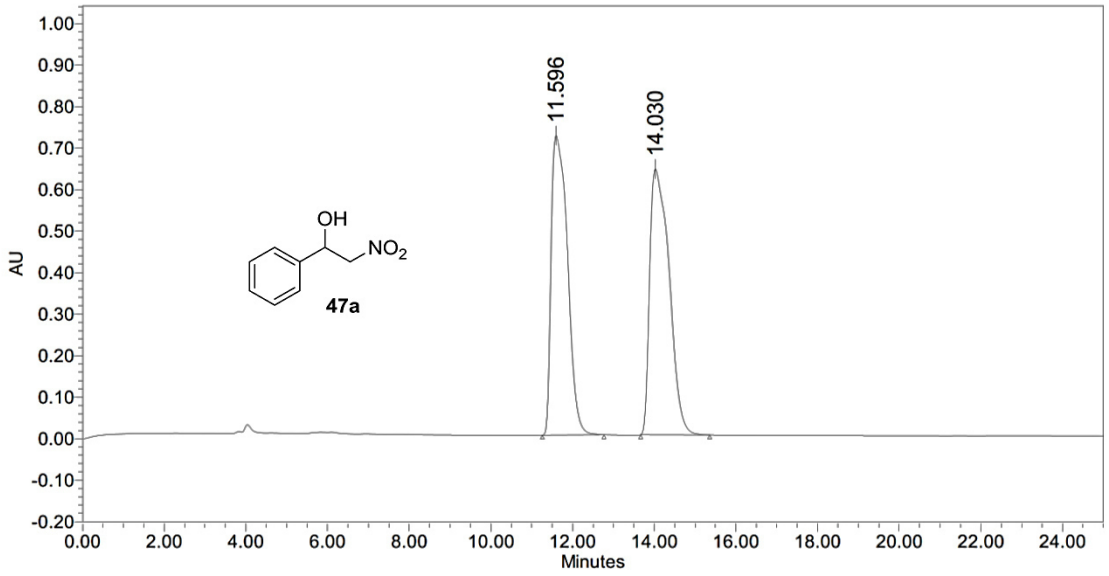


	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	6,90	6,72	7,53	437334	40,33	5125298	33,64
2	8,09	7,86	8,78	646941	59,67	10111230	66,36

4.3 Enantiomer analysis of the β-nitro alcohols 47 by HPLC on chiral phase

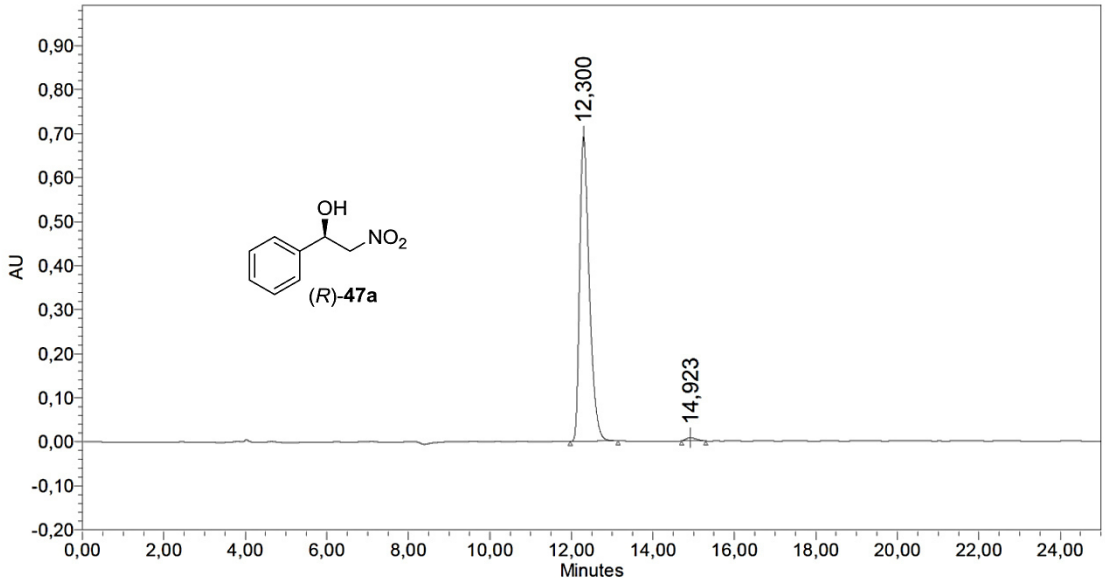
Compound **47a**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 12.3 min (*R*), 14.9 min (*S*).

47a (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	11.60	11.26	12.77	720902	52.98	19983241	48.59
2	14.03	13.67	15.36	639804	47.02	21145124	51.41

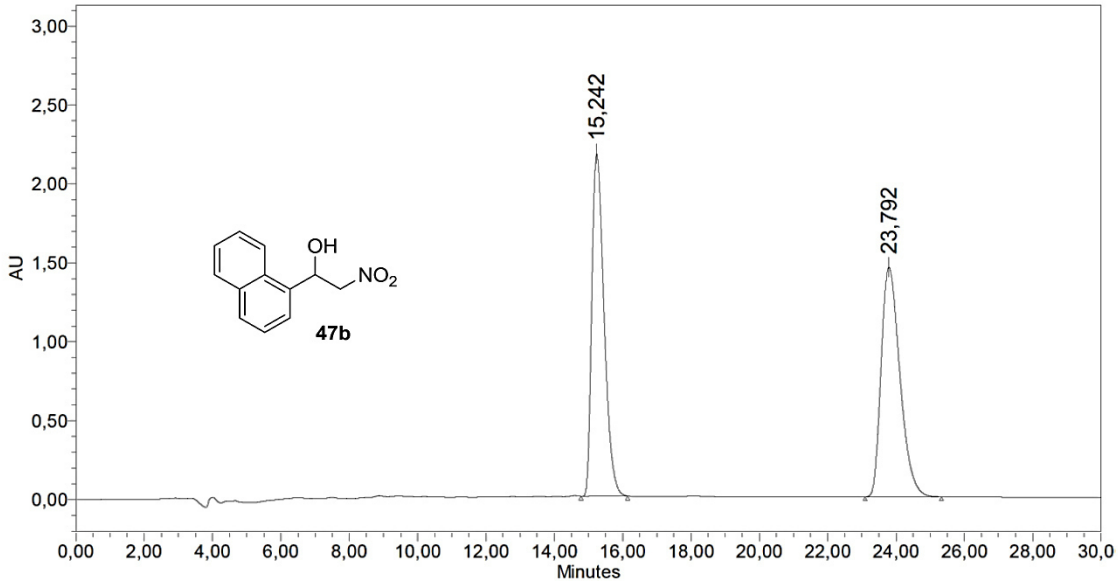
(*R*)-**47a** (98% *ee*, see Table 5, entry 1)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	12,30	11,98	13,15	692857	98,93	11375379	98,90
2	14,92	14,71	15,30	7463	1,07	126661	1,10

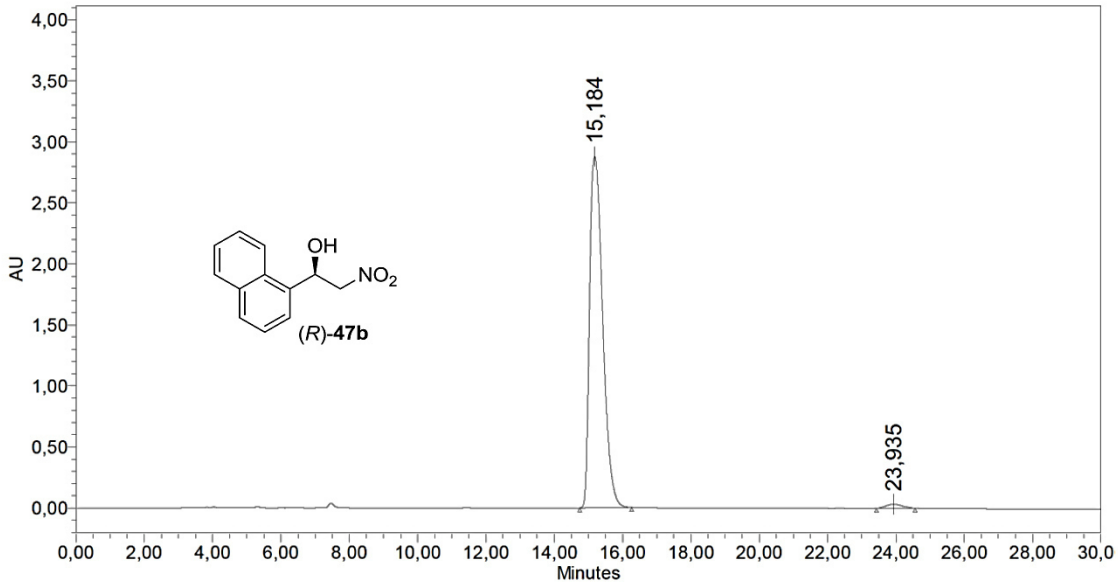
Compound **47b**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 15.2 min (*R*), 23.9 min (*S*).

47b (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	15,24	14,78	16,15	2170061	59,86	53771687	49,31
2	23,79	23,10	25,33	1455469	40,14	55274937	50,69

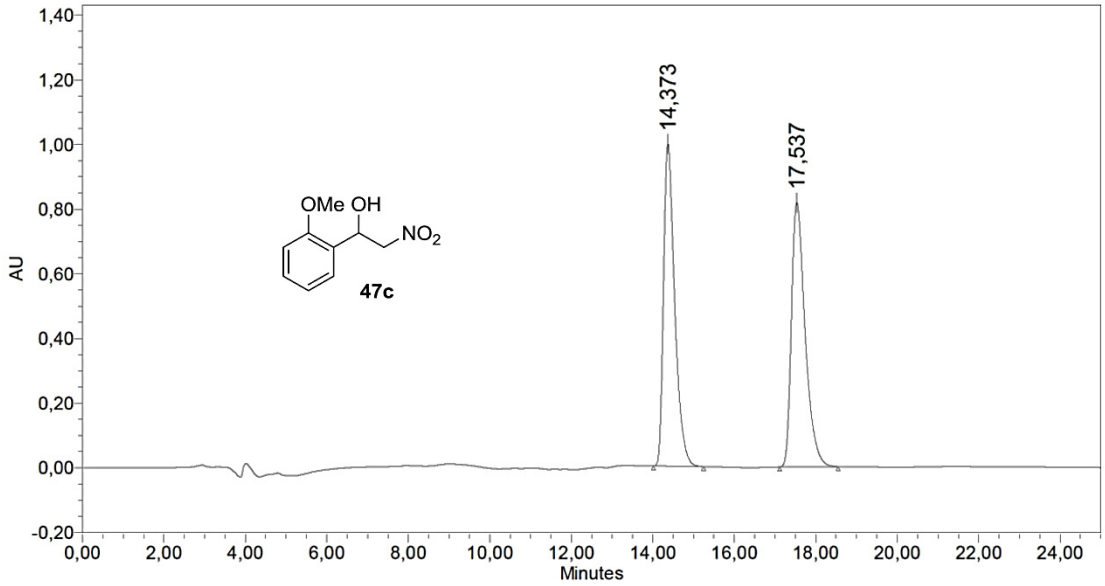
(*R*)-**47b** (97% *ee*, see Table 5, entry 2)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	15,18	14,75	16,27	2877578	98,88	76321526	98,60
2	23,94	23,43	24,57	32608	1,12	1082811	1,40

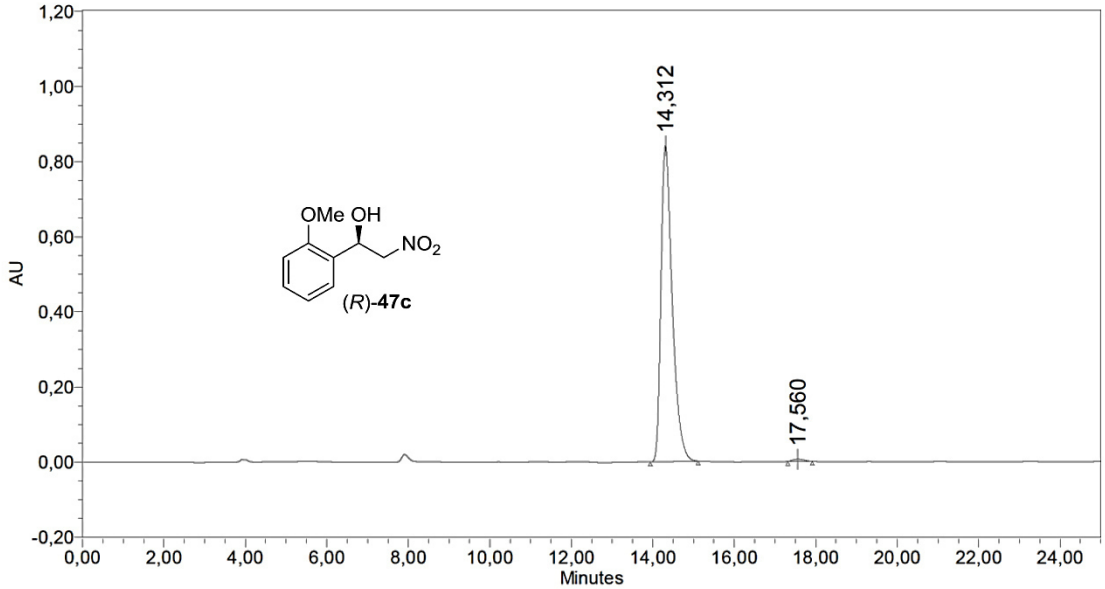
Compound **47c**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 90:10, 0.8 mL/min, 215 nm, t_R = 14.3 min (*R*), 17.6 min (*S*).

47c (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	14,37	14,02	15,25	996740	54,95	18951121	49,89
2	17,54	17,12	18,55	817301	45,05	19031363	50,11

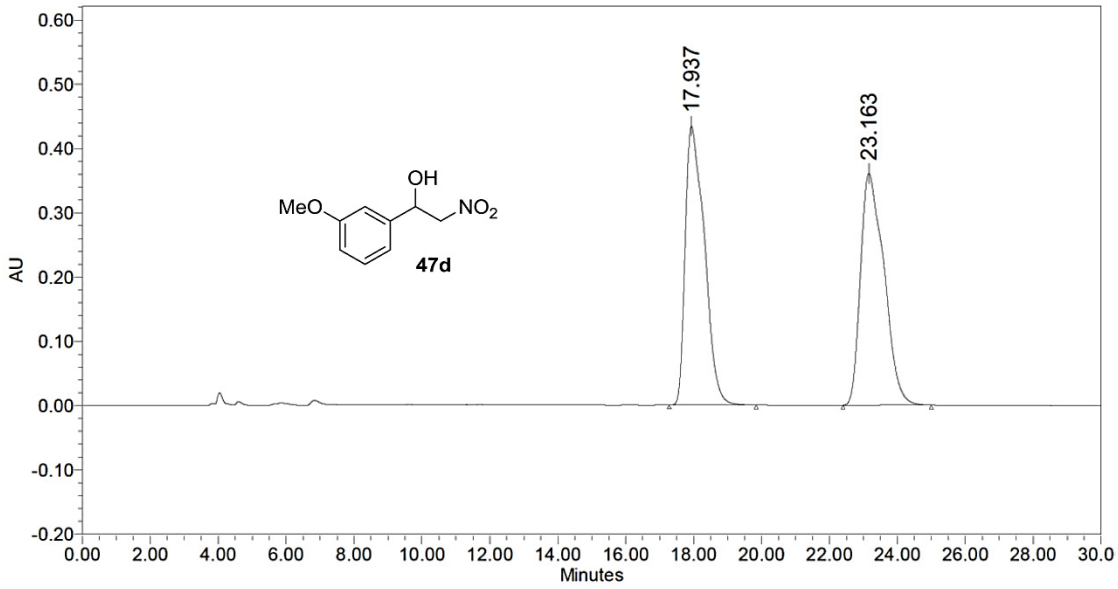
(*R*)-**47c** (99% *ee*, see Table 5, entry 3)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	14,31	13,94	15,12	841378	99,31	16181540	99,33
2	17,56	17,32	17,92	5845	0,69	108785	0,67

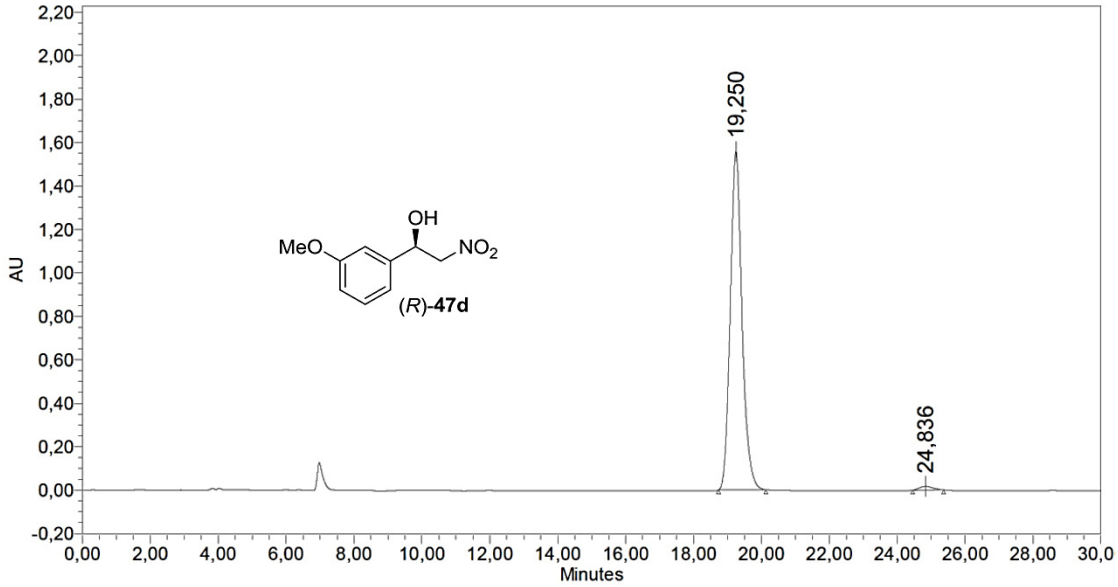
Compound **47d**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 19.3 min (*R*), 24.8 min (*S*).

47d (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	17.94	17.28	19.84	433825	54.62	16991485	49.53
2	23.16	22.40	25.00	360487	45.38	17312065	50.47

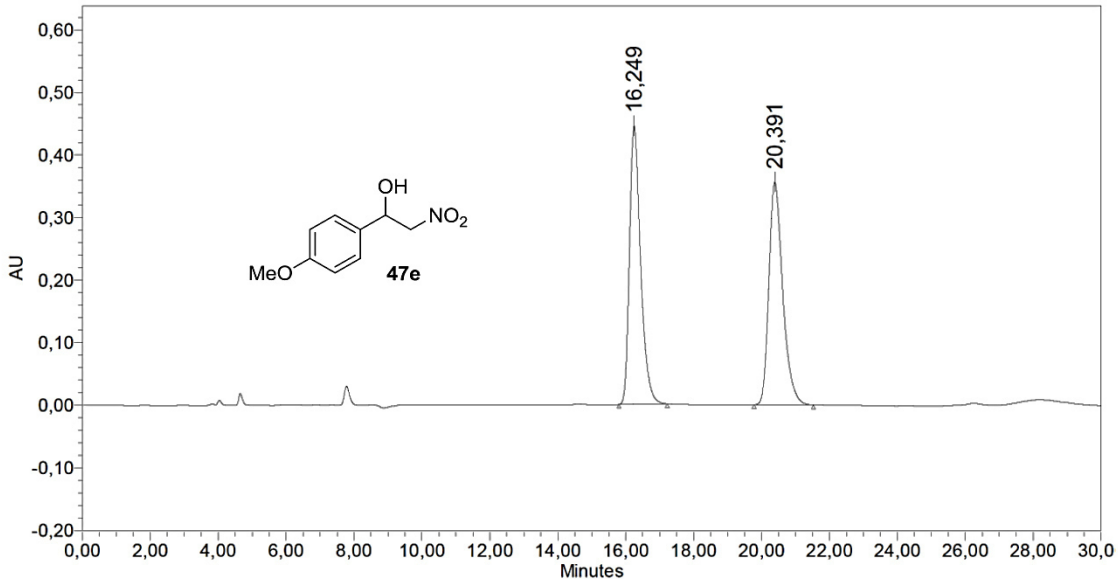
(*R*)-**47d** (98% *ee*, see Table 5, entry 4)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	19,25	18,74	20,13	1557892	98,91	37421963	98,78
2	24,84	24,46	25,37	17240	1,09	462366	1,22

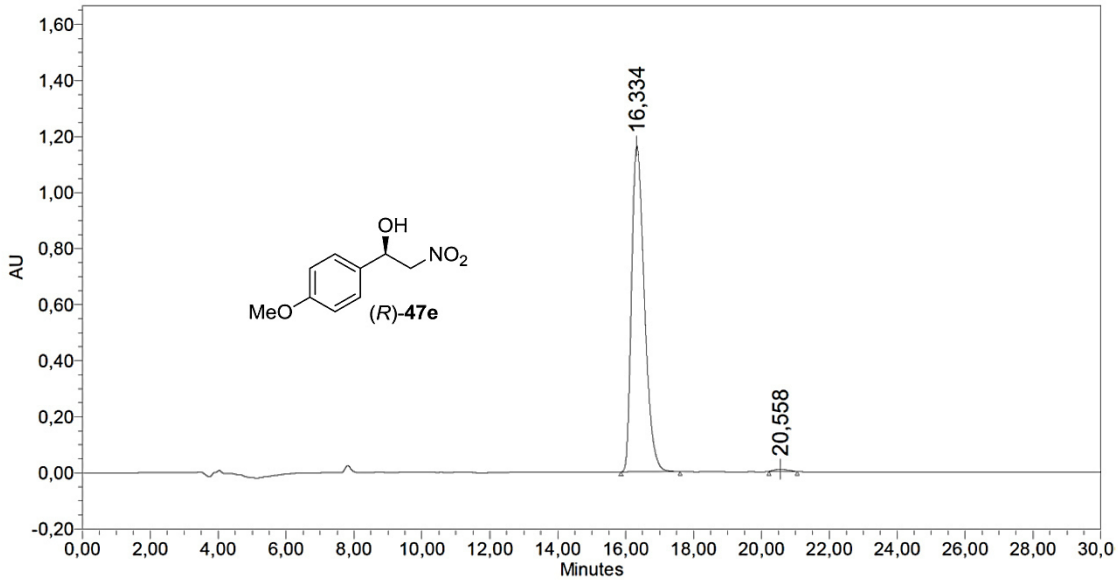
Compound **47e**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 16.3 min (*R*), 20.6 min (*S*).

47e (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	16,25	15,81	17,23	444926	55,55	10057754	50,05
2	20,39	19,78	21,53	355963	44,45	10037948	49,95

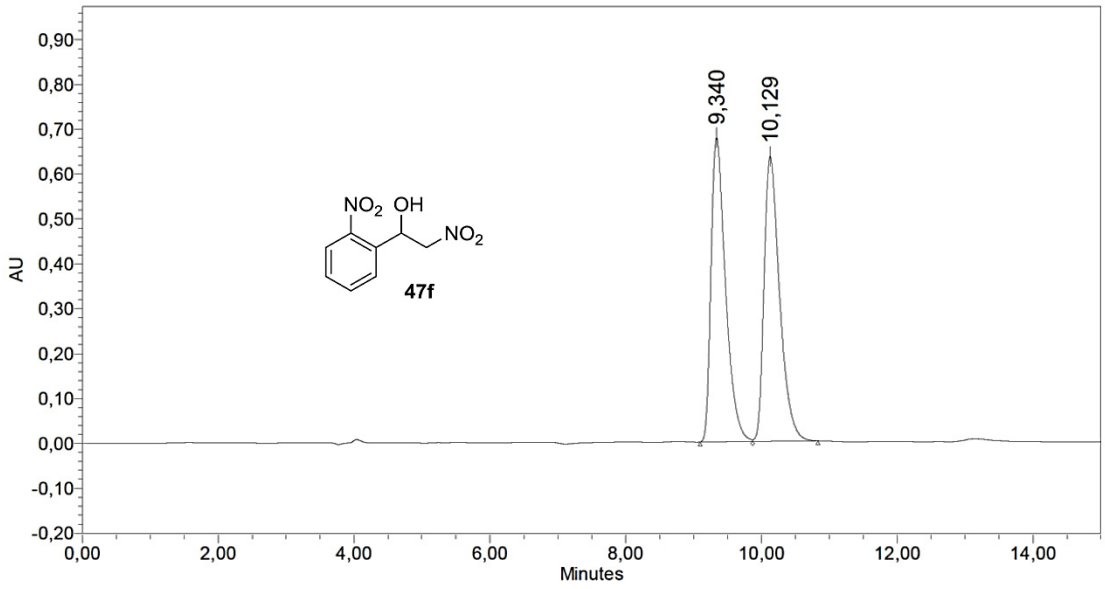
(*R*)-**47e** (99% *ee*, see Table 5, entry 5)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	16,33	15,87	17,61	1162666	99,27	30439392	99,26
2	20,56	20,23	21,06	8493	0,73	228164	0,74

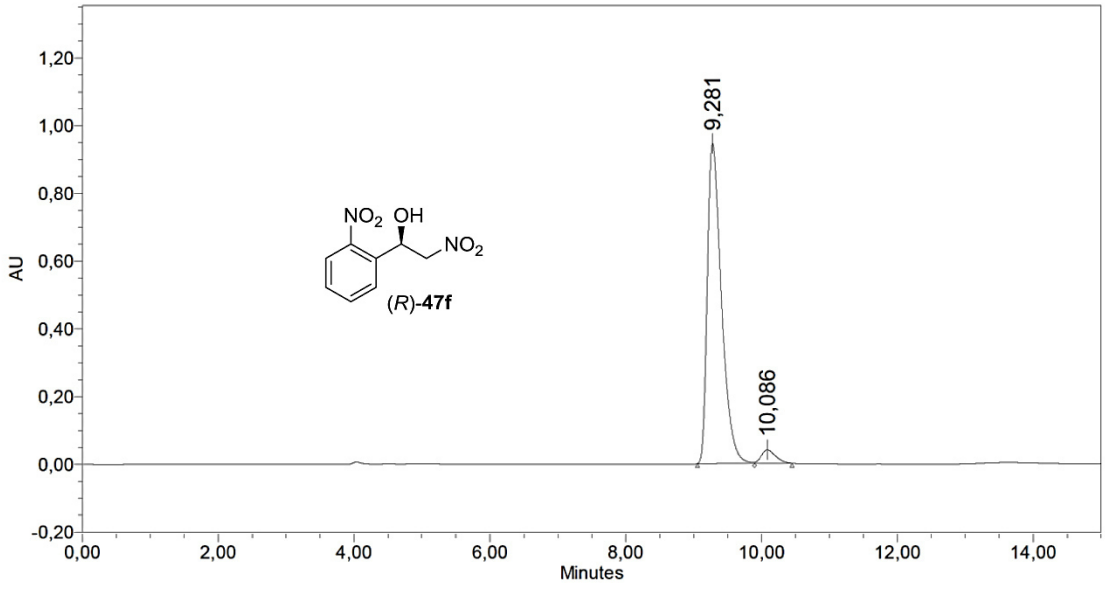
Compound **47f**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 80:20, 0.8 mL/min, 215 nm, t_R = 9.3 min (*R*), 10.1 min (*S*).

47f (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,34	9,10	10,83	677930	51,60	10028168	49,92
2	10,13	9,10	10,83	635862	48,40	10061132	50,08

(*R*)-**47f** (92% *ee*, see Table 5, entry 8)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,28	9,06	10,45	945636	95,94	13582595	95,92
2	10,09	9,06	10,45	40012	4,06	577604	4,08

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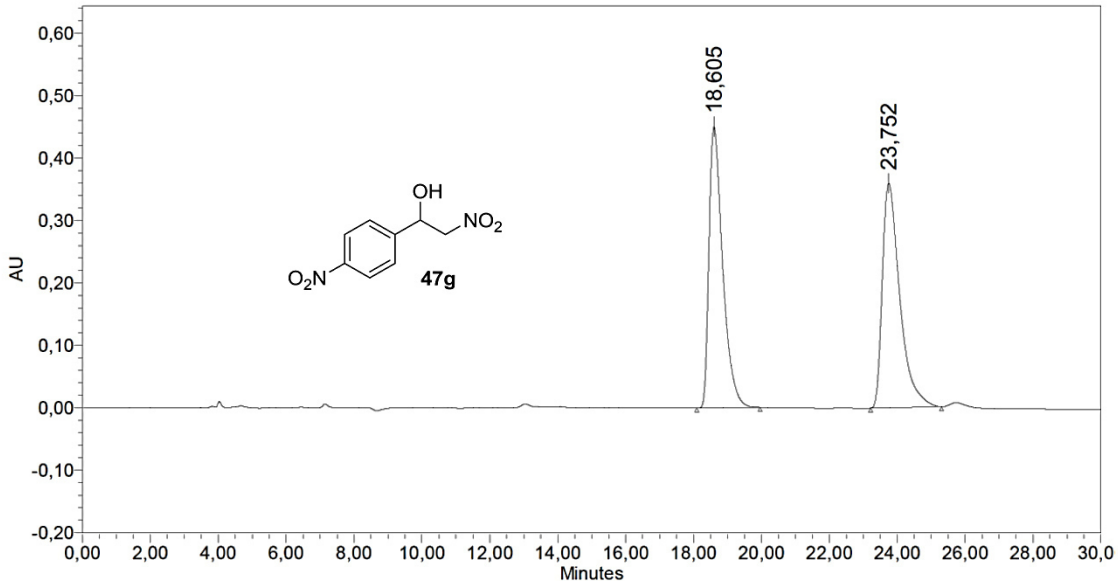
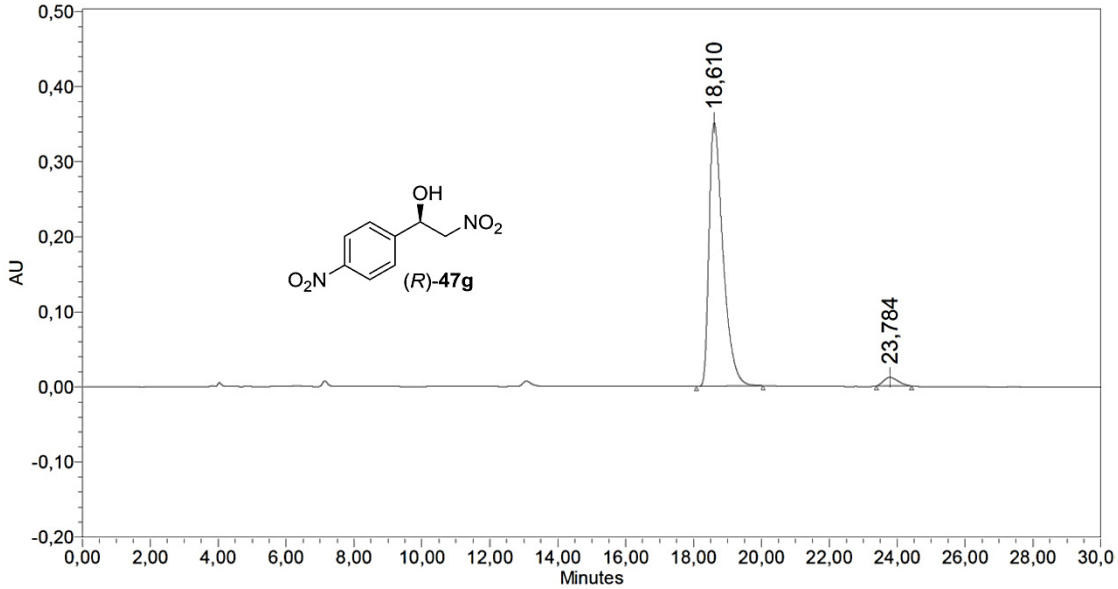
Compound **47g**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 18.6 min (*R*), 23.8 min (*S*).

47g (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	18,60	18,10	19,96	450487	55,61	12583719	49,57
2	23,75	23,22	25,31	359631	44,39	12799757	50,43

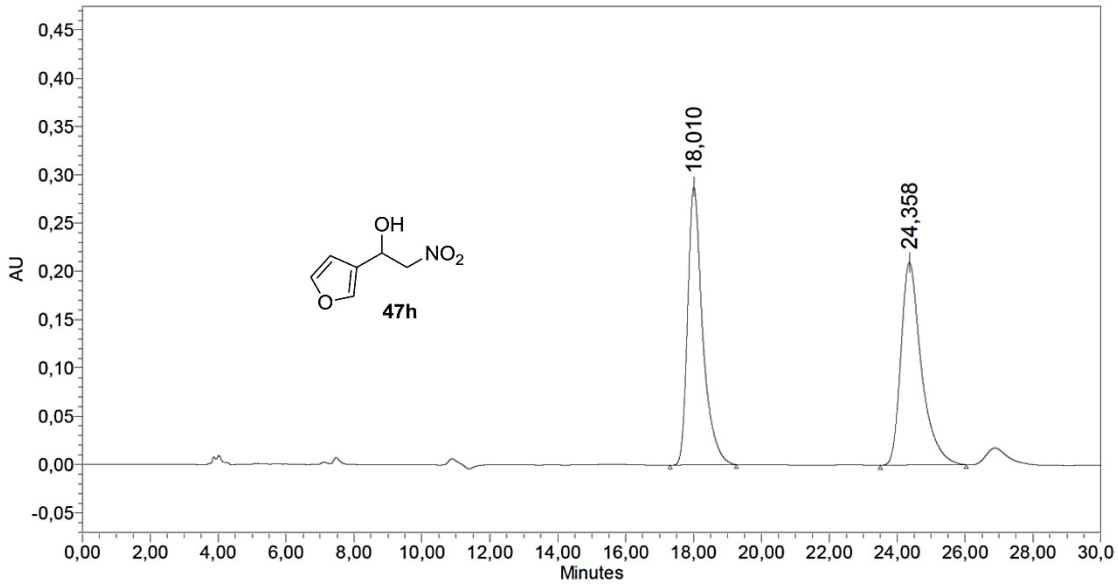
(*R*)-**47g** (94% *ee*, see Table 5, entry 9)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	18,61	18,09	20,05	351343	96,87	9995078	96,75
2	23,78	23,39	24,43	11361	3,13	335391	3,25

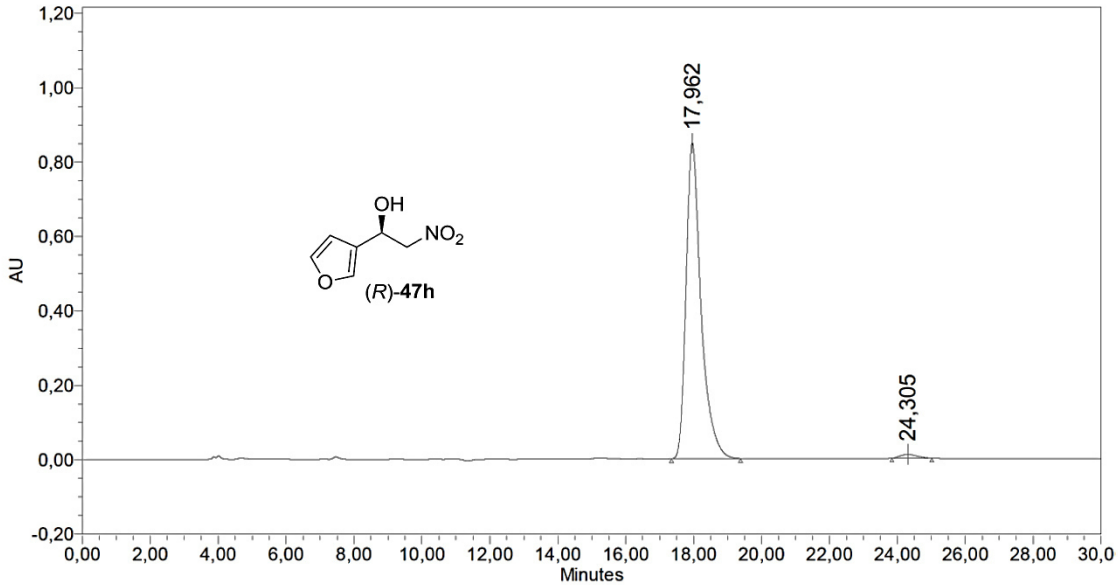
Compound **47h**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 90:10, 0.8 mL/min, 215 nm, t_R = 18.0 min (*R*), 24.3 min (*S*).

47h (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	18,01	17,32	19,27	288015	57,85	8815013	50,06
2	24,36	23,51	26,03	209849	42,15	8794862	49,94

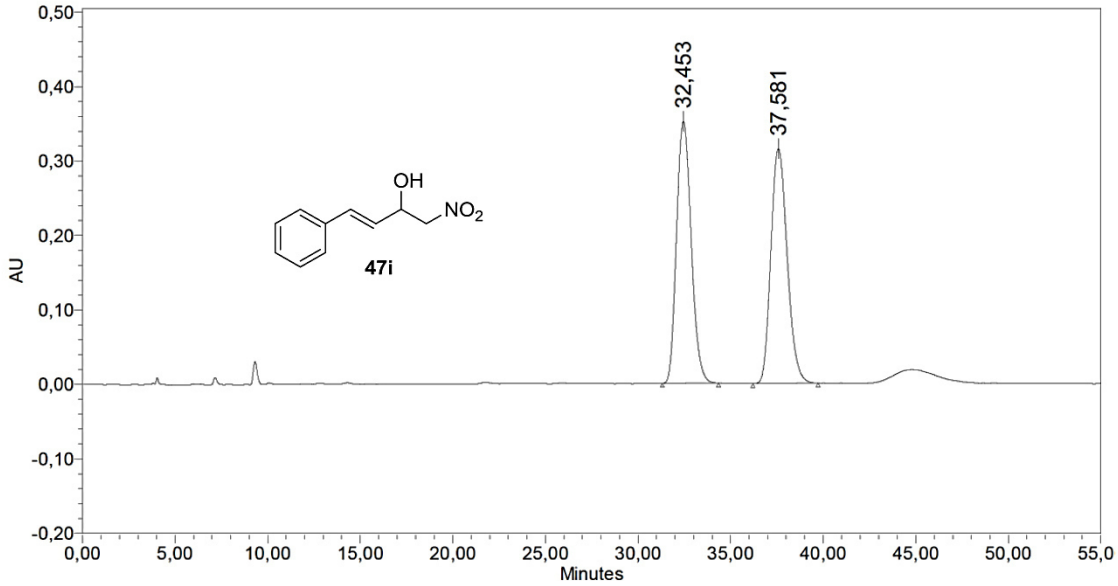
(*R*)-**47h** (97% *ee*, see Table 5, entry 10)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	17,96	17,35	19,38	848669	98,81	26053894	98,70
2	24,31	23,84	25,02	10191	1,19	344325	1,30

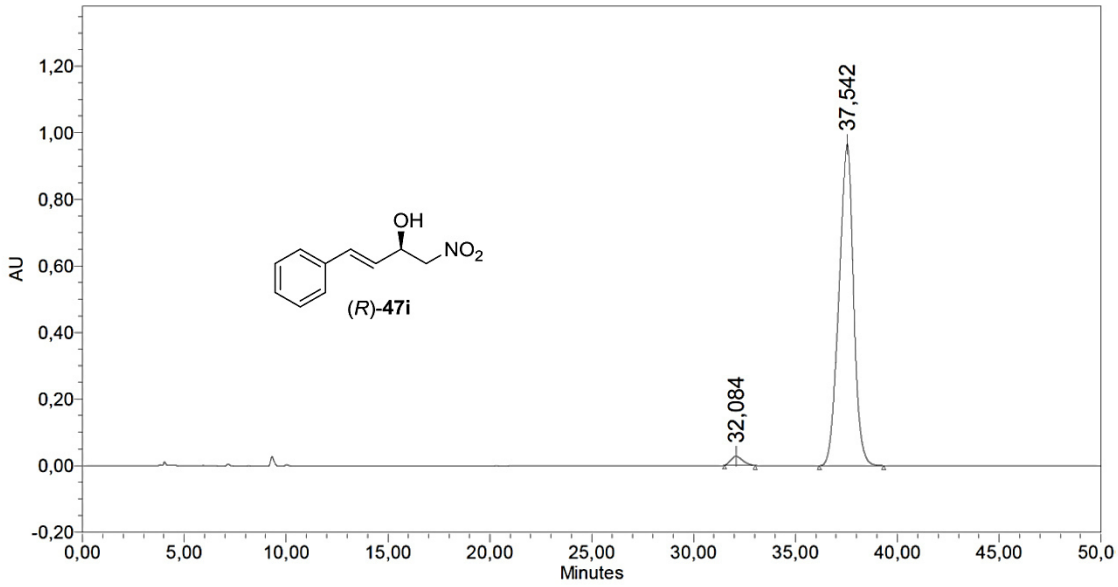
Compound **47i**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 37.5 min (*R*), 32.1 min (*S*).

47i (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	32,45	31,32	34,36	351923	52,76	19250648	49,97
2	37,58	36,22	39,73	315067	47,24	19276735	50,03

(*R*)-**47i** (96% *ee*, see Table 5, entry 11)

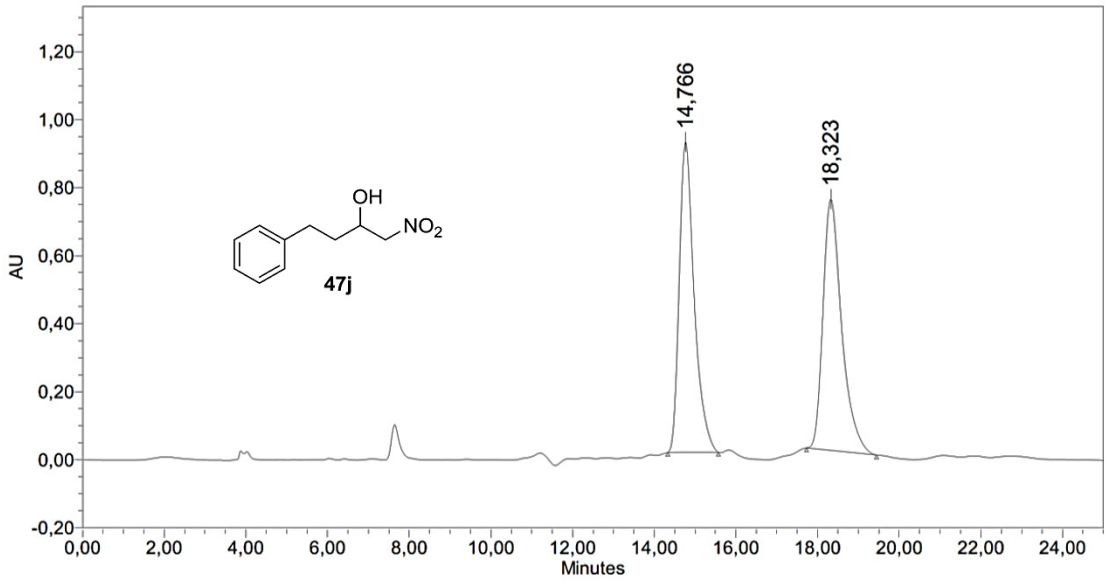


	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	32,08	31,53	33,03	26511	2,67	1064617	2,18
2	37,54	36,18	39,33	965540	97,33	47802182	97,82

51

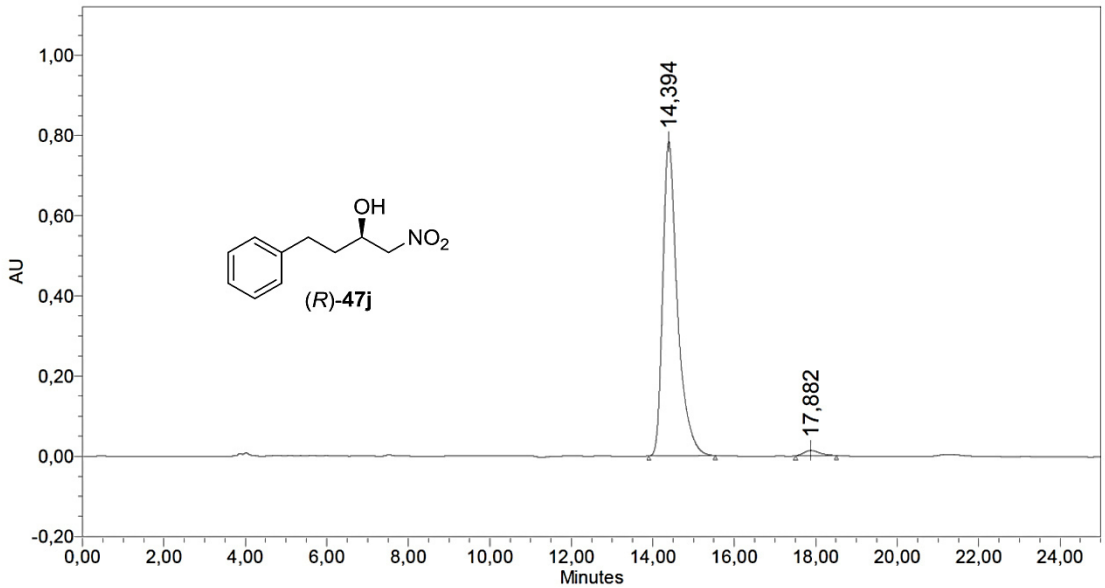
Compound **47j**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 90:10, 0.8 mL/min, 215 nm, t_R = 14.4 min (*R*), 17.9 min (*S*).

47j (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	14,77	14,33	15,57	911807	55,26	23154380	49,64
2	18,32	17,73	19,44	738240	44,74	23489794	50,36

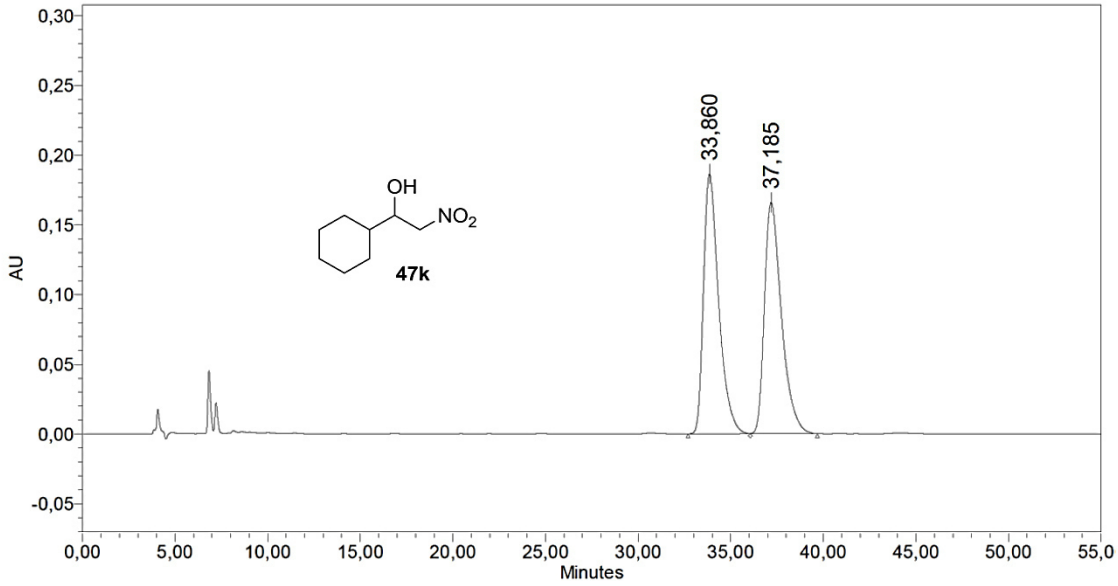
(*R*)-**47j** (97% *ee*, see Table 5, entry 12)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	14,39	13,91	15,53	783732	98,36	19582620	98,24
2	17,88	17,51	18,51	13105	1,64	351072	1,76

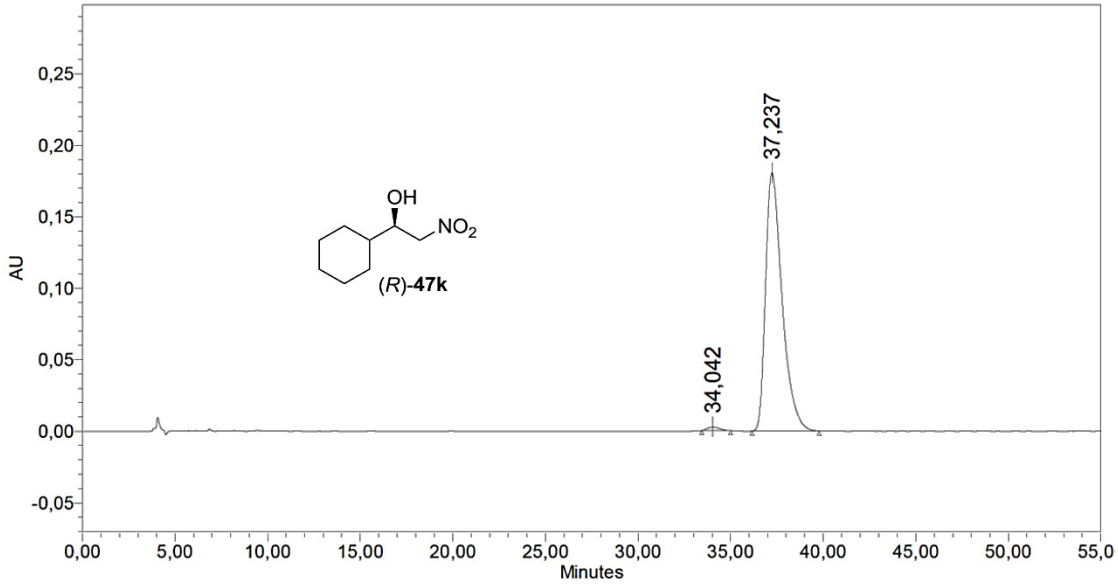
Compound **47k**: HPLC conditions: Chiralpak AD-H, *n*-hexane/EtOH 95:5, 0.8 mL/min, 215 nm, t_R = 37.2 min (*R*), 34.0 min (*S*).

47k (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	33,86	32,71	39,68	186409	52,92	10590651	50,02
2	37,19	32,71	39,68	165858	47,08	10583623	49,98

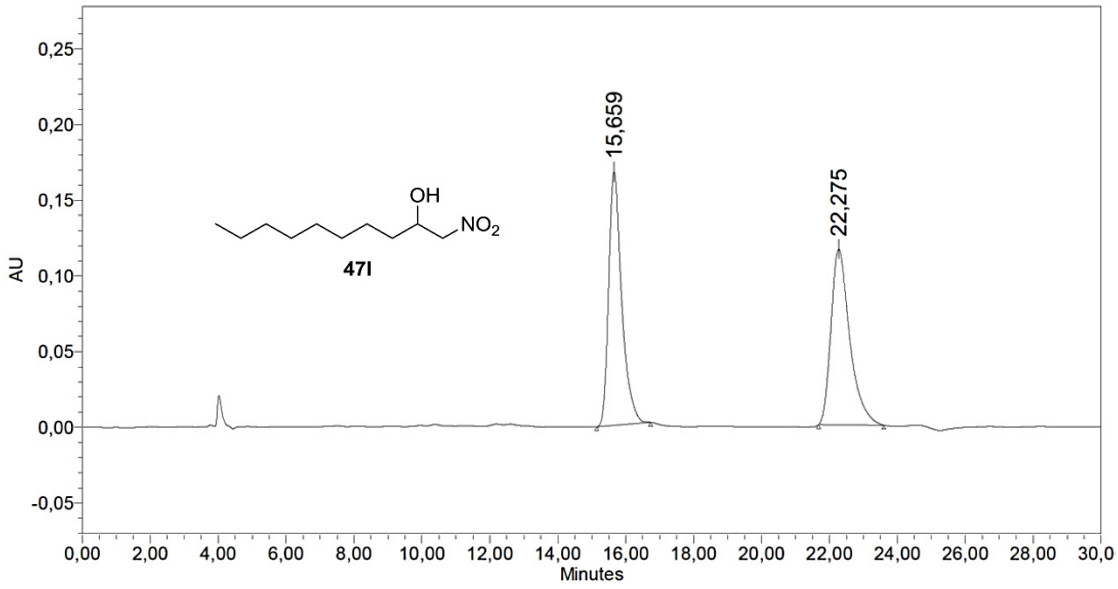
(*R*)-**47k** (98% *ee*, see Table 5, entry 13)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	34,04	33,45	35,01	2598	1,42	115977	1,03
2	37,24	36,17	39,79	180497	98,58	11182213	98,97

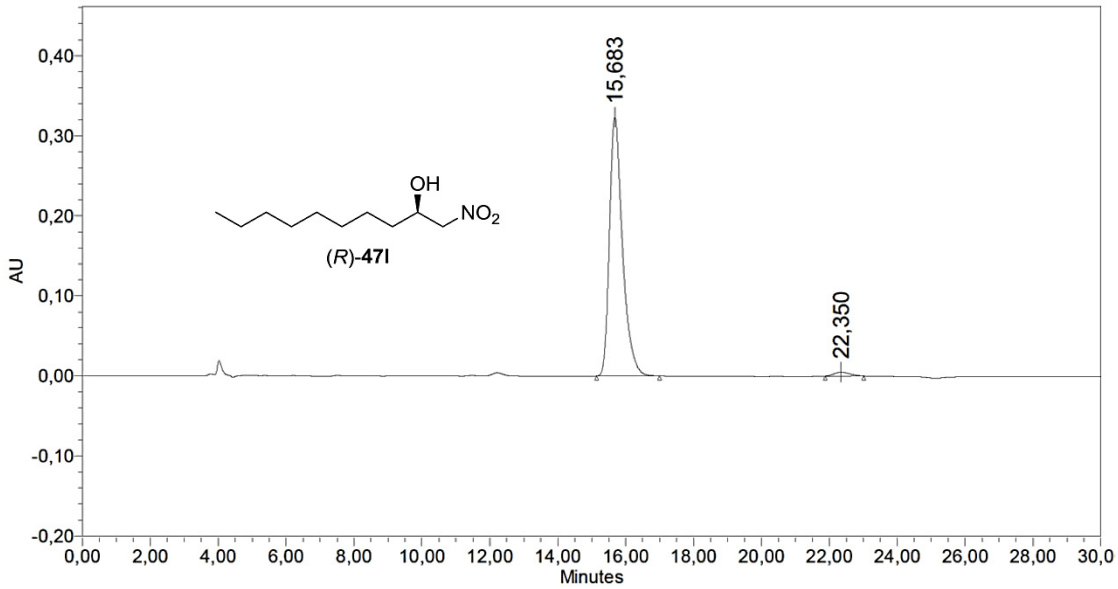
Compound **47l**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 95:5, 0.8 mL/min, 215 nm, t_R = 15.7 min (*R*), 22.4 min (*S*).

47l (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	15,66	15,15	16,73	167480	59,09	4453063	50,09
2	22,28	21,68	23,60	115953	40,91	4437624	49,91

(*R*)-**47l** (96% *ee*, see Table 5, entry 14)

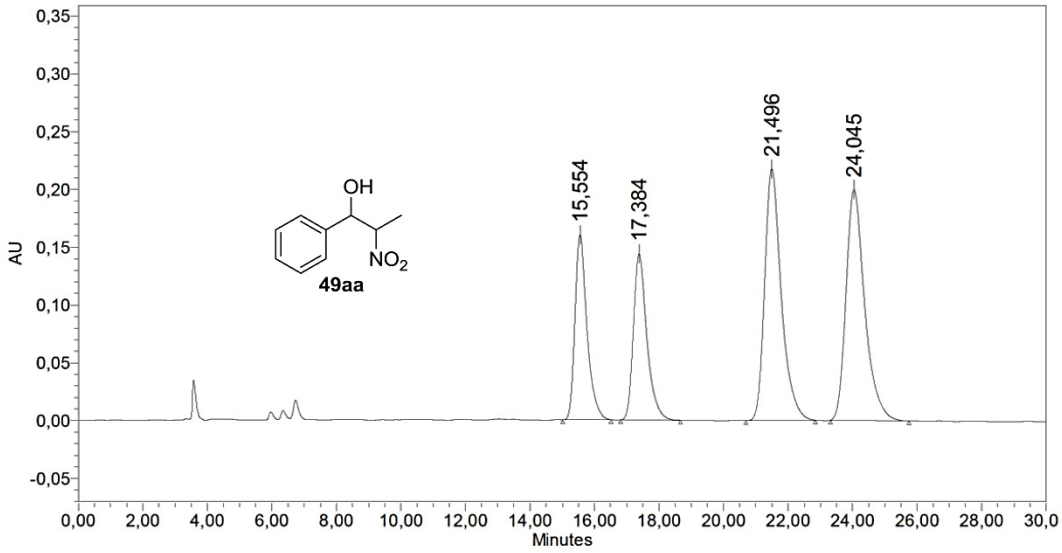


	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	15,68	15,15	17,00	323203	98,49	8625212	98,16
2	22,35	21,88	23,02	4961	1,51	161631	1,84

4.4 Enantiomer analysis of the β-nitro alcohols 49 by HPLC on chiral phase and diastereomer analysis by ^{1}H NMR

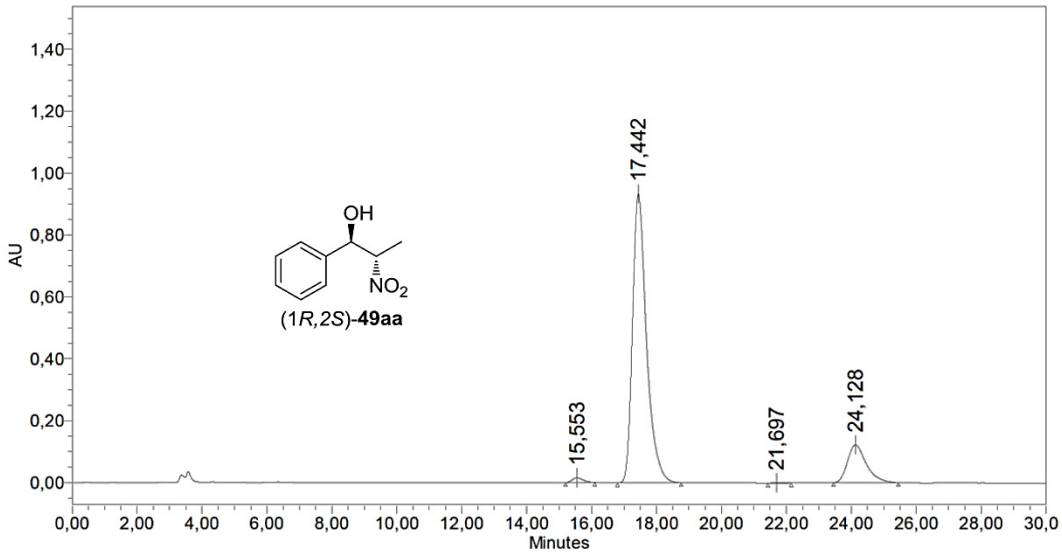
Compound **49aa**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 95:5, 0.9 mL/min, 215 nm, t_R = 15.6 min (1*S*,2*R*), 17.4 min (1*R*,2*S*), 21.7 min (1*S*,2*S*), 24.1 min (1*R*,2*R*).

49aa (racemic)



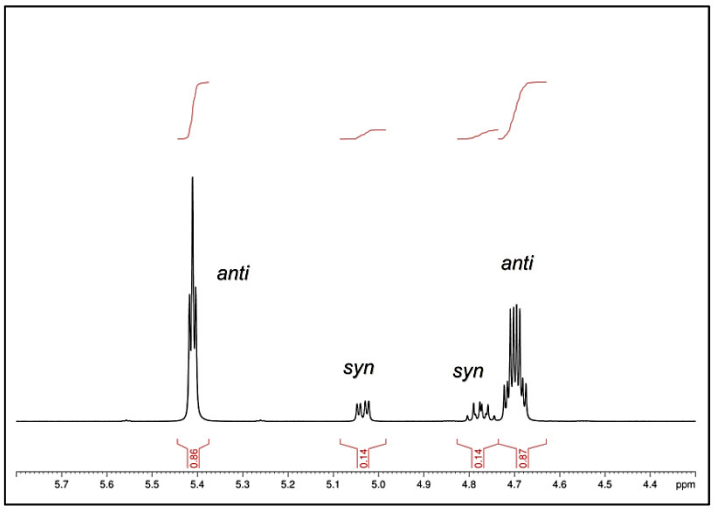
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	15,55	15,02	16,52	160102	22,19	4127461	17,12
2	17,38	16,82	18,67	143875	19,94	4150843	17,22
3	21,50	20,70	22,85	217633	30,16	7788097	32,31
4	24,04	23,32	25,75	199888	27,70	8036958	33,34

(1*R*,2*S*)-**49aa** (*anti*:*syn* 86:14, 97% ee_{anti}, 99% ee_{syn}, see Table 7, entry 1)



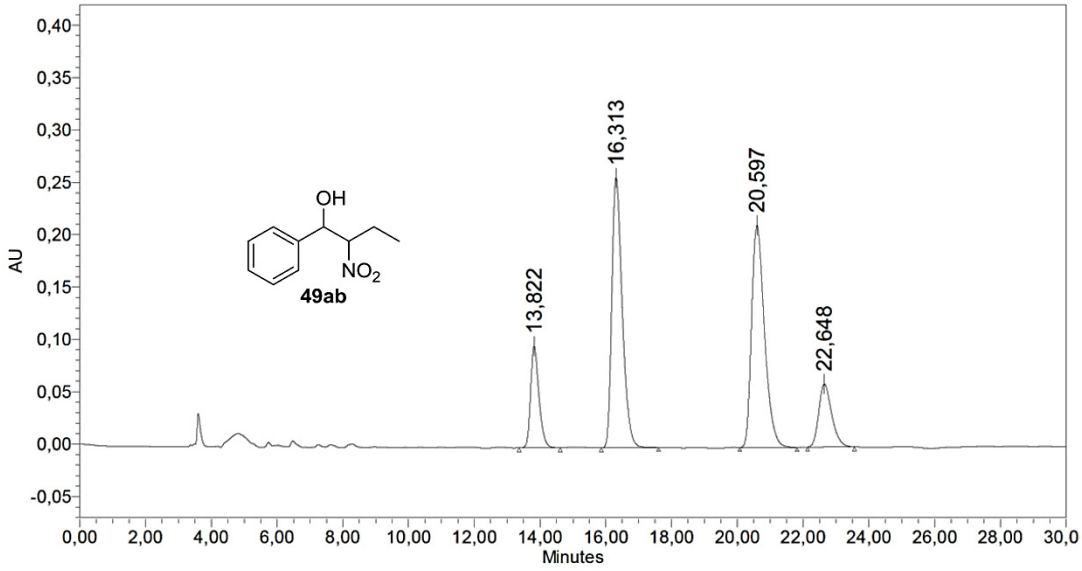
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	15,55	15,20	16,10	15887	1,48	372503	1,13
2	17,44	16,80	18,77	934546	87,03	27752063	83,92
3	21,70	21,43	22,15	1207	0,11	27863	0,08
4	24,13	23,45	25,45	122170	11,38	4917854	14,87

Excerpt of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **49aa**



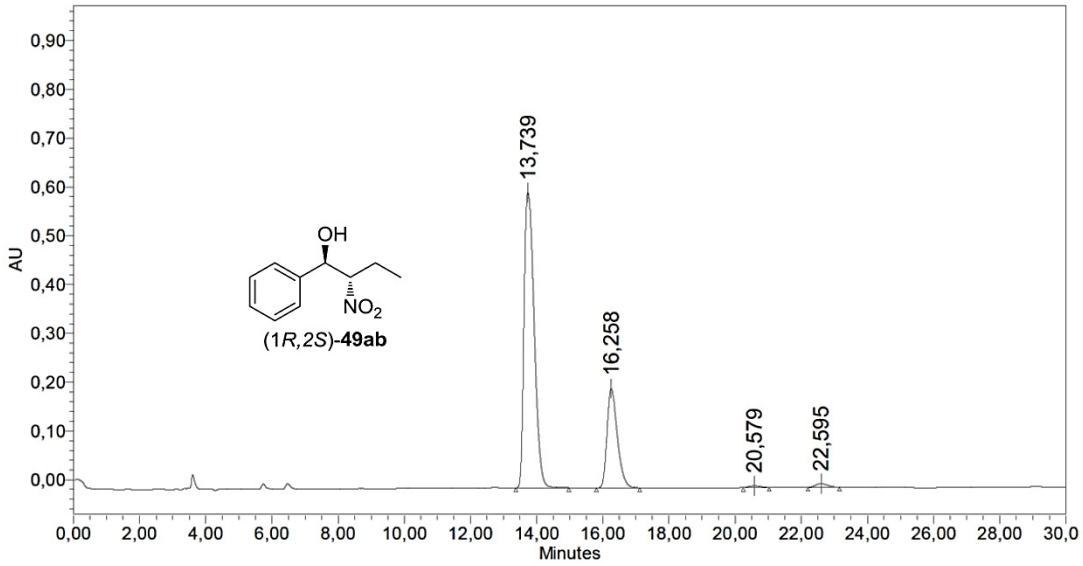
Compound **49ab**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 95:5, 0.9 mL/min, 215 nm, t_R = 13.7 min (1*R*,2*S*), 16.3 min (1*R*,2*R*), 20.6 min (1*S*,2*S*), 22.6 min (1*S*,2*R*).

49ab (racemic)



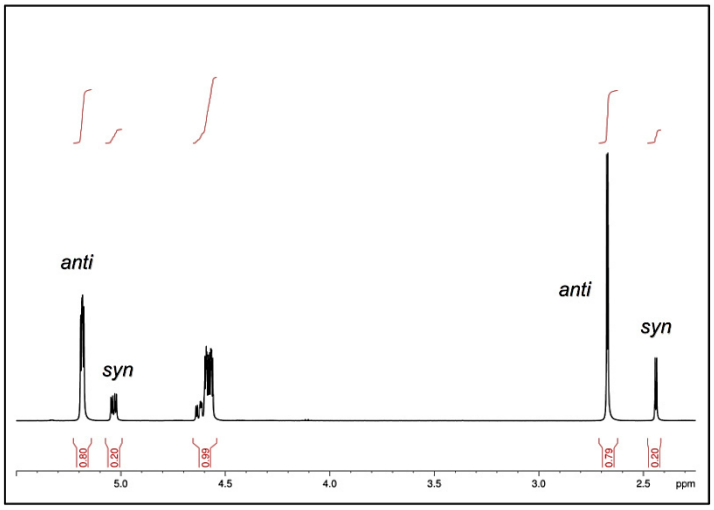
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	13,82	13,37	14,62	96960	15,46	1702461	11,51
2	16,31	15,87	17,61	257735	41,10	5673738	38,36
3	20,60	20,08	21,82	212179	33,83	5769590	39,00
4	22,65	22,14	23,57	60244	9,61	1646258	11,13

(1*R*,2*S*)-**49ab** (*anti*:*syn* 80:20, 97% ee_{anti}, 97% ee_{syn}, see Table 7, entry 2)



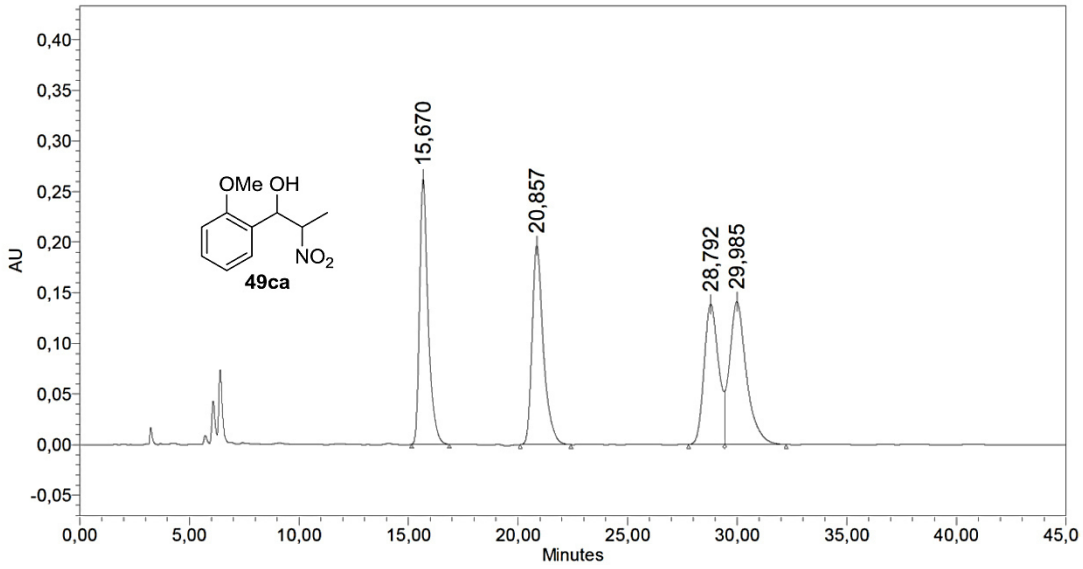
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	13,74	13,38	14,98	604679	73,81	12891749	73,41
2	16,26	15,81	17,12	203426	24,83	4394322	25,02
3	20,58	20,25	21,03	3481	0,42	79188	0,45
4	22,60	22,20	23,16	7646	0,93	195817	1,12

Excerpt of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **49ab**



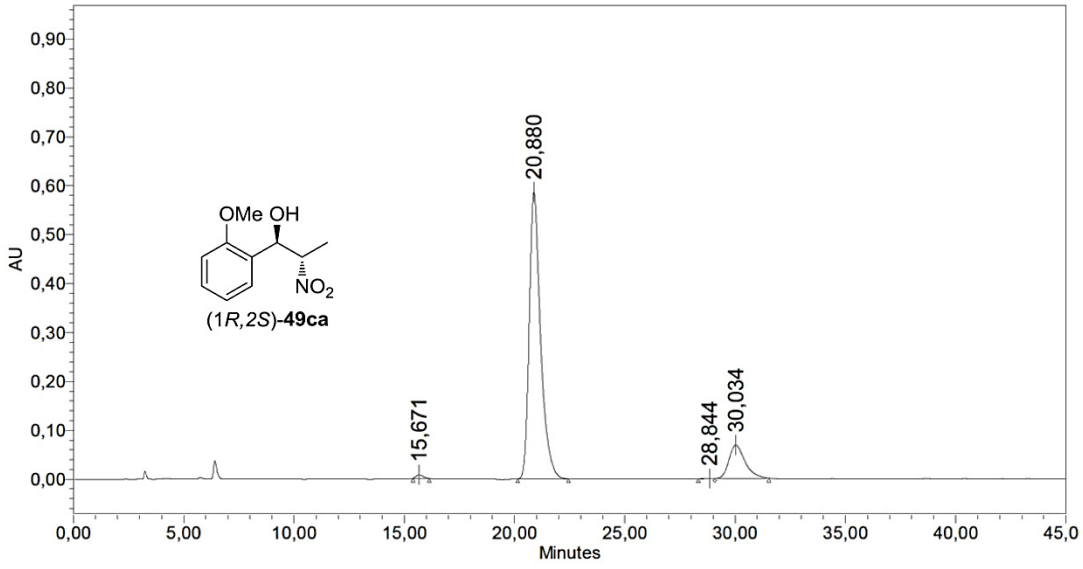
Compound **49ca**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 95:5, 1.0 mL/min, 215 nm, t_R = 15.7 min (1*S*,2*R*), 20.9 min (1*R*,2*S*), 28.8 min (1*S*,2*S*), 30.0 min (1*R*,2*R*).

49ca (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	15,67	15,15	16,87	262570	35,54	7055087	25,16
2	20,86	20,10	22,42	196593	26,61	7030539	25,07
3	28,79	27,78	32,23	138524	18,75	6388838	22,78
4	29,99	27,78	32,23	141152	19,10	7568811	26,99

(1*R*,2*S*)-**49ca** (*anti*:*syn* 85:15, 99% ee_{anti}, 99% ee_{syn}, see Table 7, entry 3)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	15,67	15,40	16,13	7316	1,10	155778	0,63
2	20,88	20,15	22,45	586653	88,52	20945785	85,21
3	28,84	28,33	31,53	584	0,09	18721	0,08
4	30,03	28,33	31,53	68163	10,29	3460916	14,08

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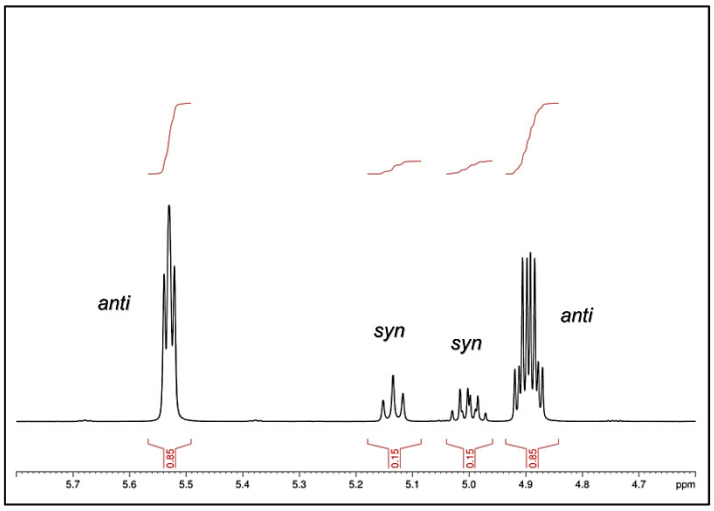
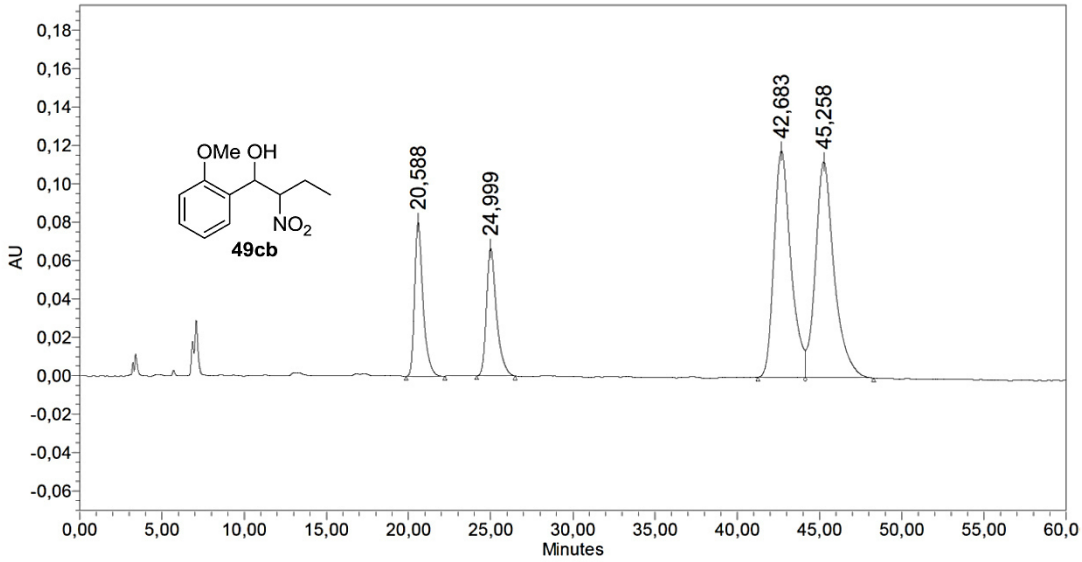
Excerpt of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **49ca**



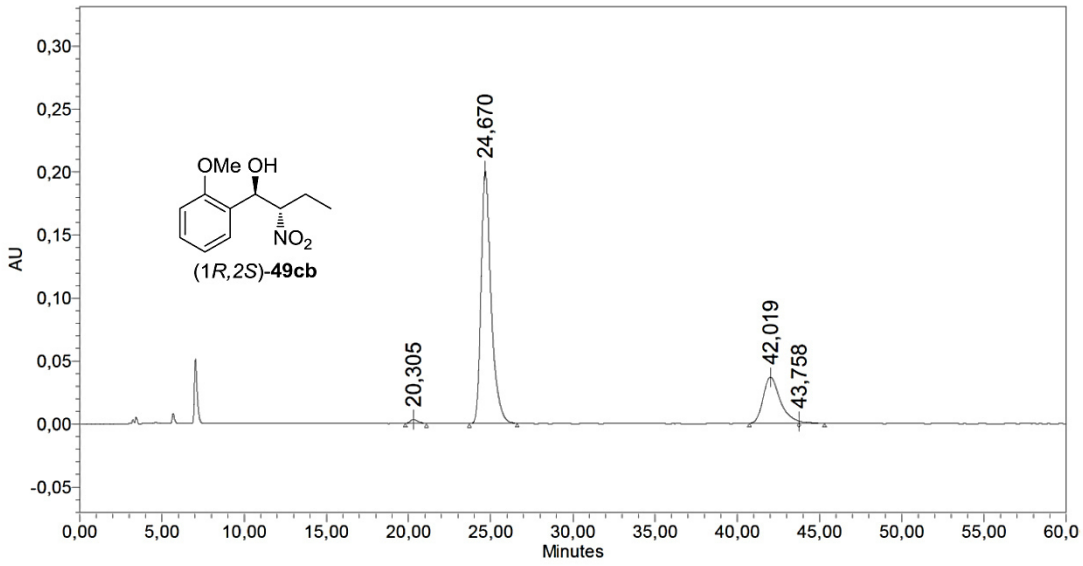
Compound **49cb**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 97:3, 1.0 mL/min, 215 nm, t_R = 20.3 min (1*S*,2*R*), 24.7 min (1*R*,2*S*), 24.0 min (1*S*,2*S*), 43.1 min (1*R*,2*R*).

49cb (racemic)



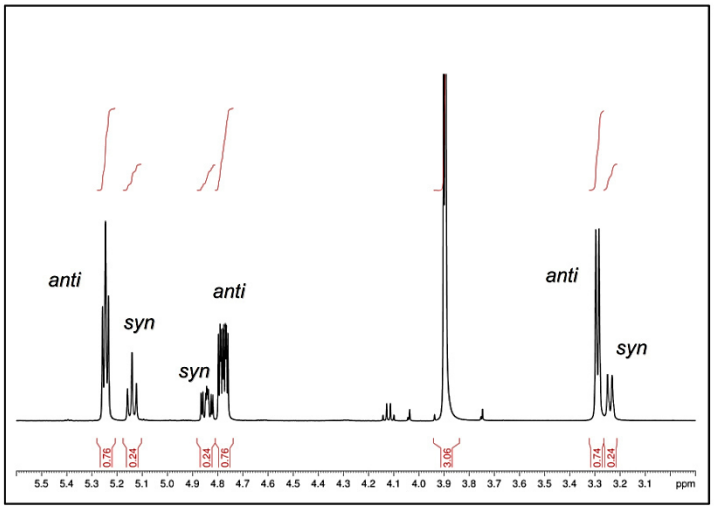
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	20,59	19,86	22,22	80131	21,27	2854757	12,39
2	25,00	24,16	26,48	66365	17,62	2812600	12,21
3	42,68	41,26	48,30	117837	31,28	8453866	36,69
4	45,26	41,26	48,30	112359	29,83	8922637	38,72

(1*R*,2*S*)-**49cb** (*anti*:*syn* 76:24, 98% ee_{anti}, 97% ee_{syn}, see Table 7, entry 4)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	20,31	19,81	21,09	3043	1,26	100182	0,89
2	24,67	23,70	26,61	200509	82,96	8499640	75,50
3	42,02	40,73	45,31	36517	15,11	2612817	23,21
4	43,76	40,73	45,31	1615	0,67	45454	0,40

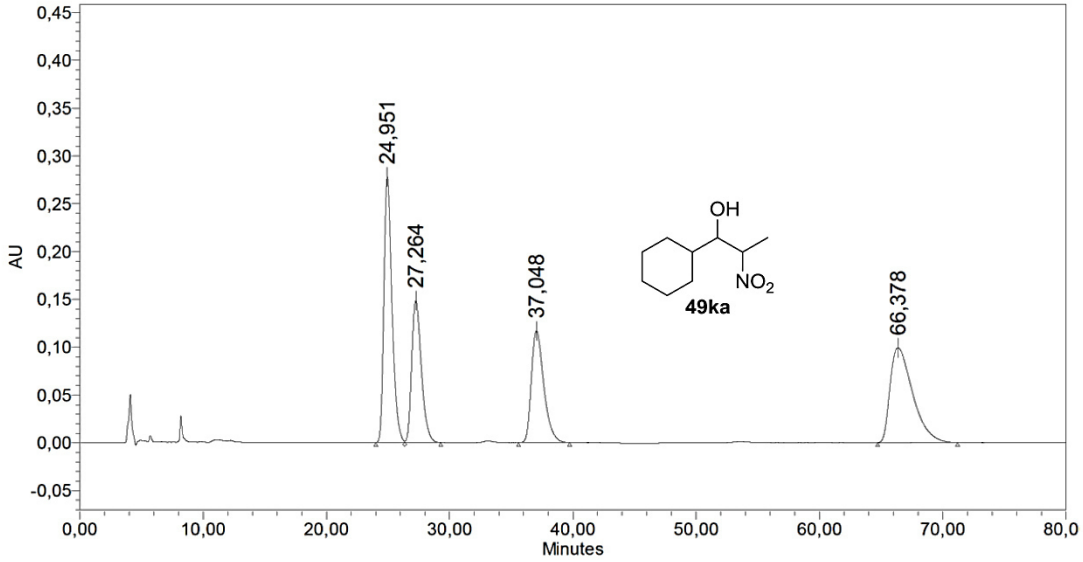
Excerpt of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **49cb**



60

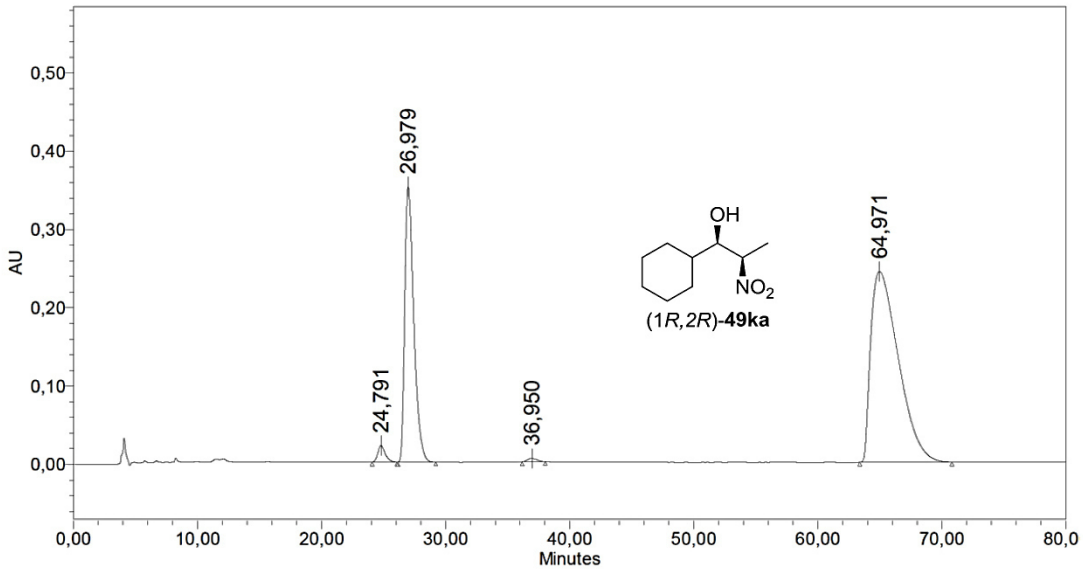
Compound **49ka**: HPLC conditions: Chiralpak AD-H, *n*-hexane/EtOH 96:4, 0.8 mL/min, 215 nm, t_R = 24.8 min (1*S*,2*S*), 27.0 min (1*R*,2*S*), 37.0 min (1*S*,2*R*), 65.0 min (1*R*,2*R*).

49ka (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	24,95	24,03	29,29	277645	43,24	12590274	30,36
2	27,26	24,03	29,29	148432	23,12	8119522	19,58
3	37,05	35,60	39,74	116800	18,19	8192691	19,75
4	66,38	64,73	71,21	99214	15,45	12571613	30,31

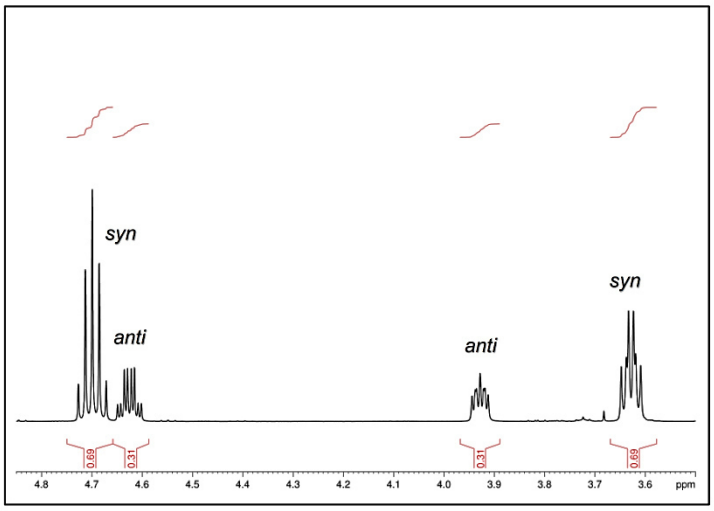
(1*R*,2*R*)-**49ka** (*anti*:*syn* 31:69, 97% ee_{anti}, 96% ee_{syn}, see Table 7, entry 5)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	24,79	24,08	26,08	21174	3,41	872489	1,54
2	26,98	26,16	29,21	351861	56,65	17868730	31,56
3	36,95	36,18	38,03	4390	0,71	235319	0,42
4	64,97	63,39	70,82	243725	39,24	37646094	66,49

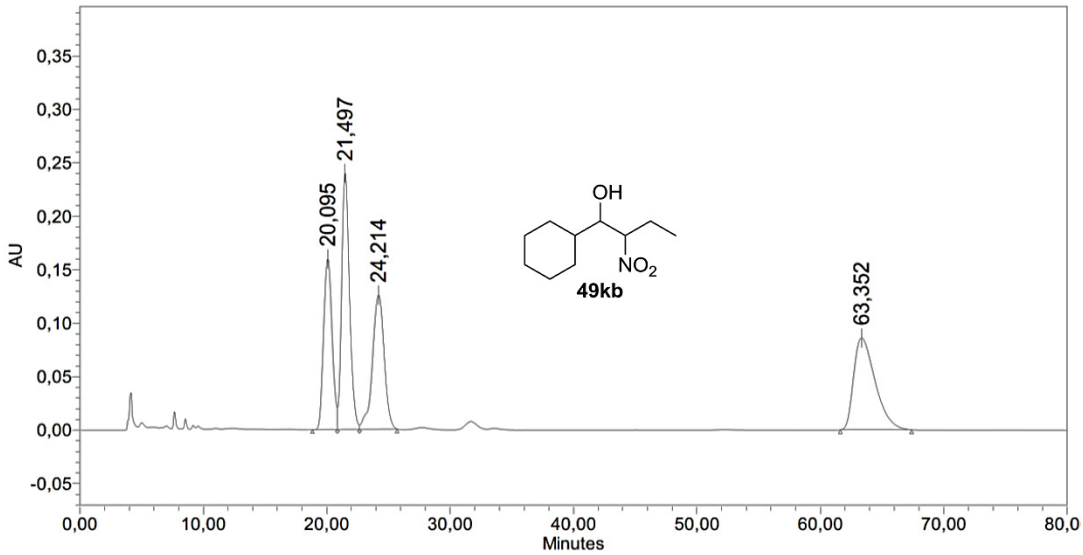
61

Excerpt of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **49ka**



Compound **49kb**: HPLC conditions: Chiralpak AD-H, *n*-hexane/EtOH 97:3, 0.8 mL/min, 215 nm, t_R = 20.6 min (1*R*,2*S*), 22.2 min (1*S*,2*S*), 25.1 min (1*S*,2*R*), 65.8 min (1*R*,2*R*).

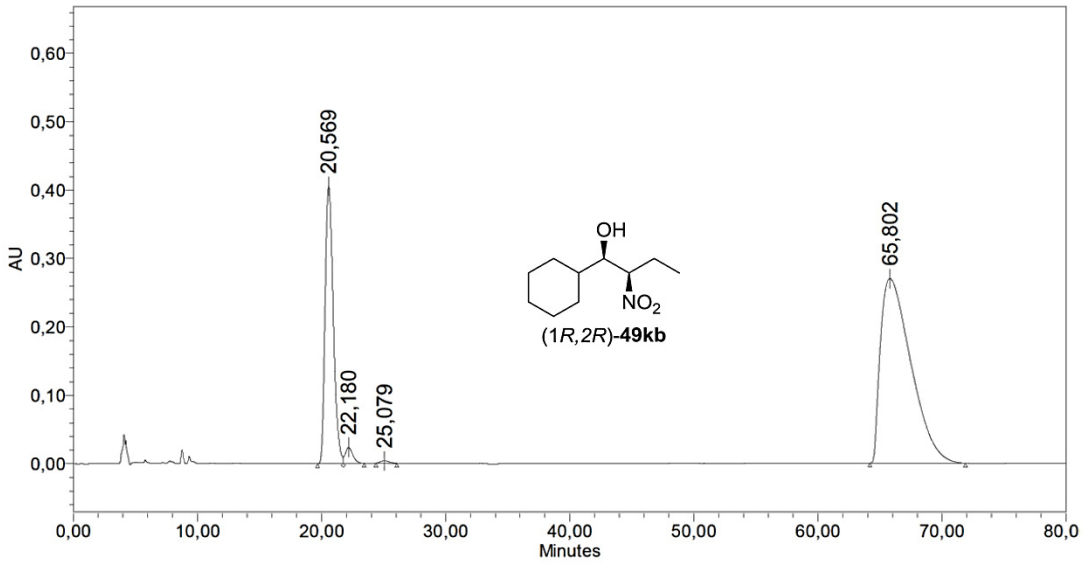
49kb (racemic)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	20,09	18,84	25,71	159626	26,14	7657748	20,73
2	21,50	18,84	25,71	239678	39,24	10576912	28,64
3	24,21	18,84	25,71	125443	20,54	8298222	22,47
4	63,35	61,63	67,40	85989	14,08	10401842	28,16

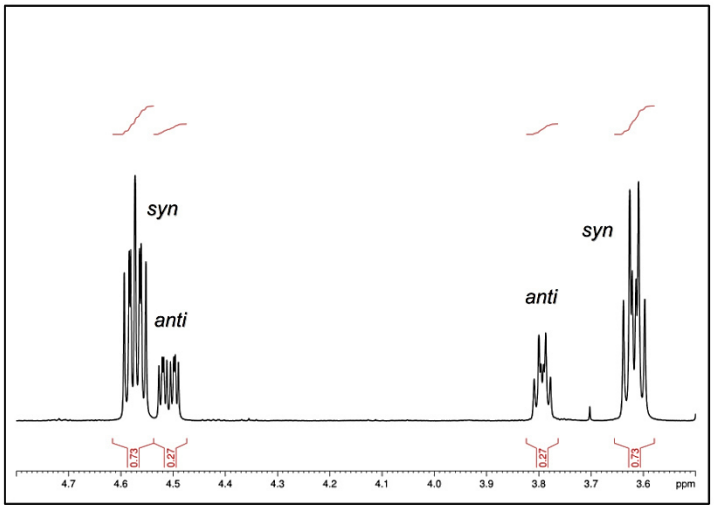
62

(1*R*,2*R*)-**49kb** (*anti*:*syn* 27:73, 98% ee_{anti}, 96% ee_{syn}, see Table 7, entry 6)



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	20,57	19,68	23,43	404964	57,70	18523231	28,23
2	22,18	19,68	23,43	23560	3,36	987533	1,50
3	25,08	24,39	26,07	3624	0,52	179978	0,27
4	65,80	64,19	71,88	269720	38,43	45926895	69,99

Excerpt of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **49kb**



6.5 The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular 'Inside-Out' Approach

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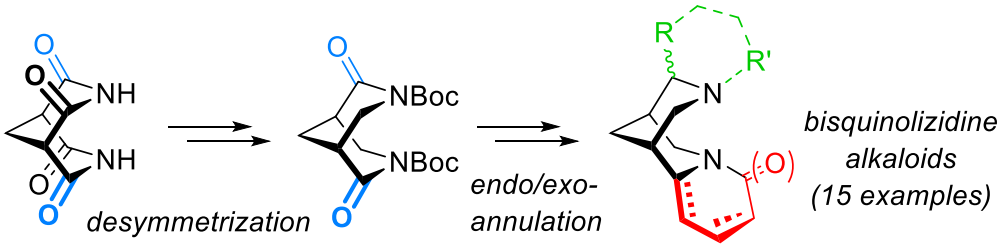

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The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular 'Inside-Out' Approach

Dagmar Scharnagel[+], Jessica Goller[+], Nicklas Deibl, Wolfgang Milius, and Matthias Breuning

Abstract: Bisquinolizidine alkaloids are characterized by a chiral bispidine core (3,7-diazabicyclo[3.3.1]nonane) to which combinations of an α,*N*-fused 2-pyridone, an *endo*- or *exo*-α,*N*-annulated piperidin(on)e, and an *exo*-allyl substituent are attached. We developed a modular 'inside-out' approach that permits access to most members of this class. Its applicability was proven in the enantioselective total synthesis of 15 natural bisquinolizidine alkaloids. Key steps are the first successful synthesis of both enantiomers of C_2-symmetric 2,6-dioxobispidine by desymmetrization of a 2,4,6,8-tetraoxo precursor, the construction of the α,*N*-fused 2-pyridone by using an enamine–bromoacrylic acid strategy, and the installation of *endo*- or, optionally, *exo*-annulated piperidin(on)es.

(–)-Sparteine (**1**), lupanine (**2**), α-isosparteine (**3**), anagyrine (**4**), and cytisine (**5**) are the most prominent bisquinolizidine alkaloids, a class of secondary metabolites with about 50 members (Figure 1).[1] These natural products are produced by plants of the Faboideae subfamily, which includes the genera *Cytisus*, *Laburnum*, *Thermopsis*, and *Anagyris*. The biological activities of these diamines are widespread: (–)-Sparteine (**1**) possesses antiarrhythmic and oxytoxic properties, lupanine (**2**) is moderately toxic and hypoglycemic, and anagyrine (**4**) teratogenic.[1] Cytisine (**5**), a partial agonist of the nicotinic acetylcholine receptor, is pharmaceutically marketed under the brand names Tabex® and Desmoxan® in Poland and Bulgaria for smoking cessation.[2] In asymmetric synthesis, (–)-sparteine (**1**) and O'Brien's artificial (+)-sparteine surrogate **6**,[3] prepared in a few steps from **5**,[4] received particular attention as the chiral ligands of choice in the deprotonation of weakly CH-acidic compounds,[5] the homologation of boronic acids,[6] and the Pd-catalyzed, oxidative kinetic resolution of secondary alcohols.[7,8]

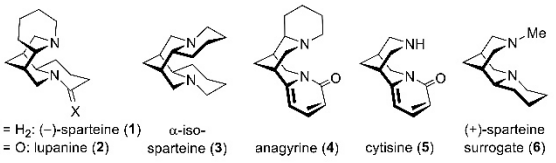

Figure 1. The most prominent bisquinolizidine alkaloids (**1**–**5**) and the artificial (+)-sparteine surrogate **6**.

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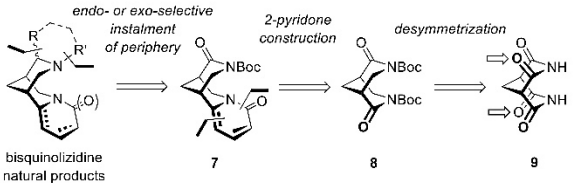
Supporting information for this article is available.

Common structural feature of the bisquinolizidine alkaloids is a chiral bispidine core (3,7-diazabicyclo[3.3.1]nonane), which occurs in nature in both enantiomeric forms (**1**–**3** vs. **4**,**5**). Typically, combinations of an α,*N*-fused 2-pyridone, an *endo*- or *exo*-α,*N*-annulated piperidin(on)e, and an *exo*-allyl substituent are attached to the central core on opposite sites.

Several elegant, enantioselective syntheses of bisquinolizidine alkaloids have been reported so far,[9] but these approaches are mostly limited to a particular target, mainly because 'outside-in' strategies were used that start with the periphery, which, however, is diverse in nature. A flexible route that permits access to a broad range is still missing. We developed such an approach and proved its applicability in the enantioselective total synthesis of 15 natural bisquinolizidine alkaloids. Key sequences are a desymmetrization permitting access to chiral, C_2-symmetric 2,6-dioxobispidine in both enantiomeric forms, a novel procedure for the annulation of an α,*N*-fused 2-pyridone, and robust methods for the *endo*- or, optionally, *exo*-selective attachment of fused piperidin(on)es and *exo*-allyl substituents to the bispidine core.

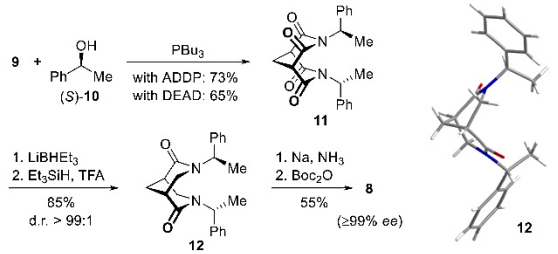
Our diversity-driven approach to bisquinolizidine alkaloids is based on a modular 'inside-out' strategy, in which the peripheral rings and substituents are installed on an adequately functionalized, chiral bispidine core (Scheme 1). With many of the alkaloids possessing a fused 2-pyridone or a reduced form thereof, the tricyclic imide **7** was chosen as a late stage key intermediate. Further disconnection of the annulated pyridone led to the C_2-symmetric 2,6-dioxobispidine **8** as the second key intermediate, which we intended to prepare in either enantiomeric form by desymmetrization of achiral 2,4,6,8-tetraoxobispidine **9**.[10]



Scheme 1. Retrosynthetic analysis of the natural bisquinolizidine alkaloids. Only one of the two enantiomeric bispidine cores is shown.

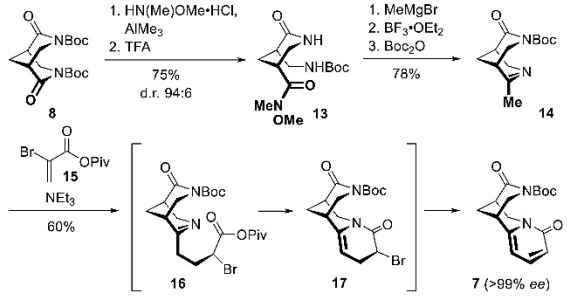
The synthesis of the chiral 2,6-dioxobispidine **8** commenced with achiral 2,4,6,8-tetraoxobispidine **9** (Scheme 2), which is available from cheap malonic ester in just two steps.[11] For desymmetrization, one of the two enantiotopic pairs of carbonyl groups had to be desoxygenated. This was achieved by chiral modification of both nitrogen atoms in **9** with (*S*)-phenylethanol [(*S*)-**10**] under Mitsunobu conditions, followed by two-step diastereoselective reduction of resulting **11**. Pleasingly, the diamide **12** was obtained with virtually complete regio- and stereocontrol (d.r. >99:1). Its absolute configuration was established by X-ray crystallography.[12] Reductive removal of the chiral auxiliary under Birch conditions and activation of the amide groups as *N*-Boc

imides furnished the chiral key intermediate **8** in overall five steps, 30–34% yield, and ≥99% *ee* from **9**. The enantiomer, *ent*-**8**, was prepared analogously using (*R*)-**10**.



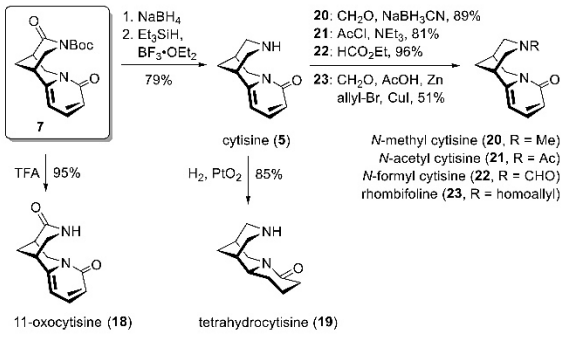
Scheme 2. Synthesis of the chiral key intermediate **8** and X-ray structure of **12**.[12] DEAD = diethylazodicarboxylate, ADDP = 1,1'-(azodicarbonyl)dipiperidine, TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl.

Conversion of C_2-symmetric **8** into the tricyclic bispidine **7** required the α,*N*-annulation of a 2-pyridone (Scheme 3). Selective modification of just one of the two imide groups was achieved by Lewis acid-catalyzed ring opening with HN(OMe)Me·HCl/$AlMe_3$,[13] which provided, after *N*-Boc removal from the imide function, Weinreb amide **13** in 75% yield and with 94:6 dr. It is important to keep the temperature below –30 °C in the first step, in order to suppress isomerization at the former bridgehead carbon atoms. Annulation of the pyridone moiety was accomplished by using an enamine–Michael addition strategy.[14] Reaction of **13** with MeMgBr, *N*-Boc removal under Lewis-acidic conditions with concomitant imine formation, and *N*-Boc protection of the amide furnished bispidine **14**, which was treated with in-situ prepared α-bromoacrylic pivalic anhydride (**15**) and NEt_3 to give the desired pyridone fused bispidine **7** in >99% *ee* after crystallization.[15] For the latter sequence, we propose that the enamine tautomer of **14** undergoes Michael addition to the anhydride **15** generating intermediate **16**, which, after renewed enamine formation and lactamization to **17**, finally eliminates HBr.



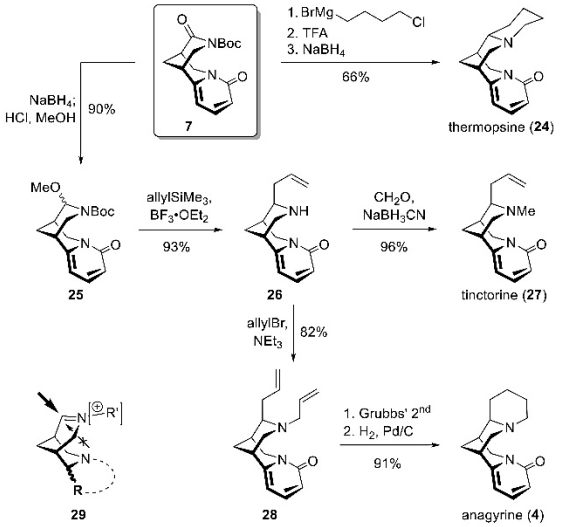
Scheme 3. Annulation of **8** to the tricyclic key intermediate **7**. Piv = pivaloyl.

With key intermediate **7** in hand we synthesized a first set of natural tricyclic bisquinolizidine alkaloids (Scheme 4). Simple deprotection afforded 11-oxocytisine (**18**), reduction and *N*-Boc removal cytisine (**5**). The latter compound was hydrogenated or *N*-functionalized following literature protocols[16] to give tetrahydrocytisine (**19**), *N*-methyl cytisine (**20**), *N*-acetyl cytisine (**21**), *N*-formyl cytisine (**22**), and rhombifoline (**23**), respectively.



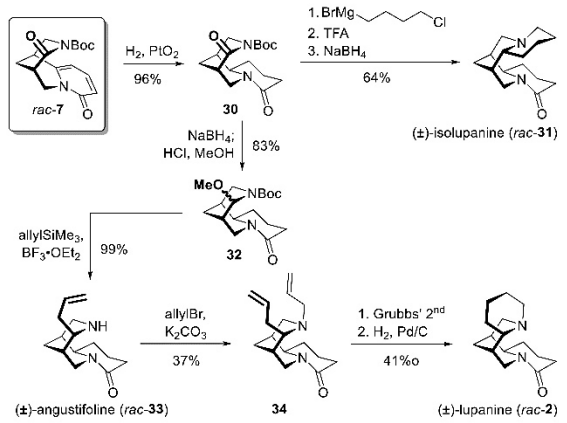
Scheme 4. Natural tricyclic bisquinolizidine alkaloids prepared from **7**.

The instalment of an *endo*-[17] or *exo*-fused ring or substituent at the imide carbonyl group of **7** involves a hydride and an alkyl addition. Earlier investigations by us[18] and others[19] on related systems revealed that an attack of a nucleophile on a bispidine imine or iminium salt of type **29** occurs with high selectivity from the sterically less hindered *exo*-face (Scheme 5). Thus, reduction followed by addition will establish *exo*-orientation, whereas the reversed addition–reduction sequence will provide access to the *endo*-epimer. And indeed, treatment of **7** with 4-chlorobutyl magnesium bromide, *N*-deprotection, and reductive amination with concomitant nucleophilic substitution afforded the *endo*-piperidine fused alkaloid thermopsine (**24**) in just three steps and good 66% yield. *Exo*-substituents were introduced after reduction of **7** to the *N*,*O*-acetal **25**.[20] Sakurai allylation under loss of the *N*-Boc group and reductive *N*-methylation delivered tinctorine (**27**) in good 89% yield, while *N*-allylation of **26** followed by ring closing metathesis and hydrogenation gave access to the tetracyclic bispidine anagyrine (**4**).



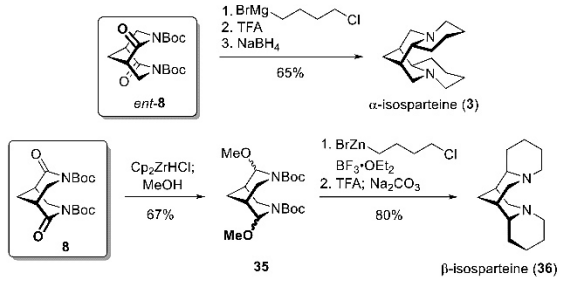
Scheme 5. Natural, core-disubstituted bisquinolizidine alkaloids prepared from **7**.

The following bisquinolizidine alkaloids possessing the enantiomeric bispidine core were synthesized from racemic **7** (Scheme 6), which was prepared from racemic **8**[21] according to Scheme 3. Hydrogenation of *rac*-**7** provided the piperidone **30**, which was subjected to the *endo*-piperidine annulation procedure described above to give isolupanine (*rac*-**31**). Reduction of imide **30** to the *N,O*-acetal **32**[20] set the stage for *exo*-functionalization (*vide supra*), permitting access to racemic angustifoline (*rac*-**33**) and lupanine (*rac*-**2**).



Scheme 6. Racemic tri- and tetracyclic bisquinolizidine alkaloids prepared from *rac*-**7**.

Applying the *exo*- and *endo*-annulation procedures to both imide groups on the key intermediates *ent*-**8** and **8** permits a concise access to C_2-symmetric alkaloids (Scheme 7). Natural α-isosparteine (**3**) was thus available from *ent*-**8** in in just three steps and good 65% overall yield. The *exo*-fused piperidine moieties in β-isosparteine (**36**) were constructed via the bis-*N,O*-acetal **35**,[20] which is available by reduction of **8** with the Schwartz reagent[22] and acetalization. Twofold Lewis acid assisted addition of 4-chlorobutylzinc bromide,[23] *N*-deprotection, and ring closure under basic conditions delivered **36** in 54% yield.



Scheme 7. Synthesis of the C_2-symmetric bisquinolizidine alkaloids α- and β–isosparteine (**3**, **36**) from *ent*-**8** and **8**.

In conclusion, we have developed a flexible route to bisquinolizidine alkaloids. It permits access to the majority of all natural derivatives, which was proven in the enantioselective total synthesis of 15 alkaloids. Key was an 'inside-out' strategy based on the chiral 2,6-dioxobispidines **8** and *ent*-**8**, both available in enantiopure form by desymmetrization of the achiral tetraoxobispidine **9**. The α,*N*-fused 2-pyridone moiety in **7** was constructed by using a new enamine–Michael addition strategy. High diversity was reached by applying the *endo*- and *exo*-annulation protocols to the key intermediates **7**, *rac*-**7**, **8**, and *ent*-**8**.

Acknowledgements

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Keywords: total synthesis • natural products • bispidine • alkaloids • enantioselectivity

[1] a) M. Wink, *Planta Med.* **1987**, *53*, 509-514; b) M. Wink in *Insect-plant interactions, Vol. 4* (Ed.: E. A. Bernays), CRC Press, **1992**, pp. 131-166; c) A. M. Lourenço, P. Maximo, L. M. Ferreira, M. M. A. Pereira in *Studies in Natural Products Chemistry: Bioactive Natural Products, Part H, Vol. 27* (Ed.: Atta-ur-Rahman), Elsevier, **2002**, pp. 233-298.

[2] a) P. Tutka, W. Zatoński, *Pharmacol. Rep.* **2006**, *58*, 777-798; b) N. Walker, C. Howe, M. Glover, H. McRobbie, J. Barnes, V. Nosa, V. Parag, B. Bassett, C. Bullen, *N. Engl. J. Med.* **2014**, *371*, 2353-2362.

[3] P. O'Brien, *Chem. Commun.* **2008**, 655-667.

[4] A. J. Dixon, M. J. McGrath, P. O'Brien, *Org. Synth.* **2006**, *83*, 141-154.

[5] a) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552-560; b) D. Hoppe, T. Hense, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282-2316; *Angew. Chem.* **1997**, *109*, 2376-2410; c) D. Hoppe, G. Christoph in *The Chemistry of Organolithium Compounds, Vol. 2* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**, pp. 1055-1164; d) O. Chuzel, O. Riant in *Topics in Organometallic Chemistry, Vol 15: Chiral Diazaligands for Asymmetric Synthesis* (Eds.: M. Lemaire, P. Mangeney), Springer, Berlin, **2005**, pp. 59-92; e) J.-C. Kizirian, *Top. Stereochem.* **2010**, *26*, 189-251; f) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092-10142.

[6] S. P. Thomas, R. M. French, V. Jheengut, V. K. Aggarwal, *Chem. Rec.* **2009**, *9*, 24-39.

[7] a) M. S. Sigman, D. R. Jensen, *Acc. Chem. Res.* **2006**, *39*, 221-229; b) D. C. Ebner, R. M. Trend, C. Genet, M. J. McGrath, P. O'Brien, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2008**, *47*, 6367-6370; *Angew. Chem.* **2008**, *120*, 6467-6470.

[8] For bispidine derivatives in enantioselective, copper-catalyzed Henry reactions, see: a) H. Maheswaran, K. L. Prasanth, G. G. Krishna, K. Ravikumar, B. Sridhar, M. L. Kantam, *Chem. Commun.* **2006**, 4066-4068; b) J. Canipa, A. Stute, P. O'Brien, *Tetrahedron* **2014**, *70*, 7395-7403; c) D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, W. Milius, M. Breuning, *Chem. Eur. J.* **2015**, *21*, 12488-12500.

[9] For the enantioselective total synthesis of bispidine natural products, see: a) (+)-sparteine (*ent*-**1**): B. T. Smith, J. A. Wendt, J. Aubé, *Org. Lett.* **2002**, *4*, 2577-2579; b) (–)-sparteine (**1**): J.-P. R. Hermet, M. J. McGrath, P. O'Brien, D. W. Porter, J. Gilday, *Chem. Commun.* **2004**, *16*, 1830-1831; c) (–)-cytisine (**5**): B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, A. Silvani, A. Virdis, *Org. Lett.* **2004**, *6*, 493-496; d) (+)-cytisine (*ent*-**5**): T. Honda, R. Takahashi, H. Namiki, *J. Org. Chem.* **2005**, *70*, 499-504; e) D. Gray, T. Gallagher, *Angew. Chem. Int. Ed.* **2006**, *45*, 2419-2423; *Angew. Chem.* **2006**, *118*, 2479–2483; f) (+)- and (–)-cytisine (**5** and *ent*-**5**): F. R. Struth, C. Hirschhäuser, *Eur. J. Org. Chem.* **2016**, 958-964; g) (+)-thermopsine (*ent*-**24**): R. Brimioulle, T. Bach, *Science* **2013**, *342*, 840-843; h) (+)-β-Isosparteine (*ent*-**36**): F. M. Al-Saffar, R. C. D. Brown, *Org. Lett.* **2017**, *19*, 3502-3504; i) virgiboidine: S. Kress, J. Weckesser, S. R. Schulz, S. Blechert, *Eur. J. Org. Chem.* **2013**, 1346-1355.

[10] An earlier attempt to desymmetrize the *N,N'*-dibenzyl or *N,N'*-diallyl derivative of **9** by CBS reduction had little success, see: N. R. Norcross, J. P. Melbardis, M. F. Solera, M. A. Sephton, C. Kilner, L. N. Zakharov, P. C. Astles, S. L. Warriner, P. R. Blakemore, *J. Org. Chem.* **2008**, *73*, 7939-7951.

[11] P. R. Blakemore, C. Kilner, N. R. Norcross, P. C. Astles, *Org. Lett.* **2005**, *7*, 4721-4724.

[12] Crystals were obtained from Et_2O/CH_2Cl_2/pentane. CCDC 1565771 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures.

[13] All attempts to selectively modify just one carbonyl group in **8**, while keeping the bicyclic system intact (e.g., *N*-Boc deprotection or carbonyl reduction), mainly provided the undesired product of an attack on both imides. Ring opening reactions, by contrast, occurred with high monoselectivity, presumably due to the release of conformational strain.

[14] For the construction of dihydropyridones from imines and acrylic acid derivatives see, for example: a) P. W. Hickmott, G. Sheppard, *J. Chem. Soc. C* **1971**, 1358-1362; b) B. Danieli, G. Lesma, G. Palmisano, S. Tollari, *Synthesis* **1984**, *4*, 353-356; c) K. Paulvannan, J. R. Stille, *J. Org. Chem.* **1992**, *57*, 5319-5328.

[15] Crude **7** had just 94% *ee*. The loss of enantiopurity is most likely caused by the minor *trans*-diastereomer of **13**, which could not be removed. It had to be carried through the following steps, providing a mixture of **7** and *ent*-**7**. The enantiopurity of **7** was re-raised to >99% by simple fractional crystallization.

[16] a) Tetrahydrocytisine (**19**): M. J. Johansson, L. Schwartz, M. Amedjkouh, N. Kann, *Tetrahedron: Asymmetry* **2004**, *15*, 3531-3538; b) *N*-methyl cytisine (**20**): F. Frigerio, C. A. Haseler, T. Gallagher, *Synlett* **2010**, *5*, 729-730; c) *N*-acetyl cytisine (**21**): J. Rouden, A. Ragot, S. Gouault, D. Cahard, J.-C. Plaquevent, M.-C. Lasne, *Tetrahedron: Asymmetry* **2002**, *13*, 1299-1305; d) *N*-formyl cytisine (**22**): S. Ohmiya, H. Otomasu, I. Murakoshi, J. Haginiwa, *Phytochemistry* **1974**, *13*, 643-644.

[17] a) M. Breuning, D. Hein, M. Steiner, V. H. Gessner, C. Strohmann, *Chem. Eur. J.* **2009**, *15*, 12764-12769; b) Ref. [8c].

[18] a) M. Breuning, M. Steiner, C. Mehler, A. Paasche, D. Hein, *J. Org. Chem.* **2009**, *74*, 1407-1410; c) Refs. [8c], [17a].

[19] a) H. Kubo, S. Ohmiya, I. Murakoshi, *Can. J. Chem.* **1994**, *72*, 214-217; b) J. R. Harrison, P. O'Brien, *Tetrahedron Lett.* **2000**, *41*, 6167-6170; c) A. Consonni, B. Danieli, G. Lesma, D. Passarella, P. Piacenti, A. Silvani, *Eur. J. Org. Chem.* **2001**, 1377-1383; d) J. Kurek, B. Jasiewicz, E. Wyrzykiewicz, W. Boczoń, *J. Mol. Struct.* **2011**, *1003*, 10-20; e) P. R. Blakemore, N. R. Norcross, S. L. Warriner, P. C. Astles, *Heterocycles* **2006**, *70*, 609-617; f) Refs. [10], [11].

[20] The ^1H and ^{13}C NMR spectra of **25** and **32** display two sets of signals, those of **35** three sets of signals. They probably result from *N*-Boc rotamers of the *exo*-configured diastereomer, but the existence of *endo*-diastereomers cannot be fully excluded.

[21] Racemic **8** was obtained by *N*-Boc-activation of racemic 2,6-dioxobispidin, which was prepared according to literature protocols, see: a) R. G. Kostyanovsky, K. A. Lyssenko, Y. I. El'natanov, O. N. Krutius, I. A. Bronzova, Y. A. Strelenko, V. R. Kostyanovsky, *Mendeleev. Commun.* **1999**, *9*, 106-108; b) R. G. Kostyanovsky, I. A. Bronzova, K. A. Lyssenko, *Mendeleev. Commun.* **2002**, *12*, 4-6

[22] Twofold reduction of **8** with Cp_2ZrHCl was found to give higher yields, as compared to $NaBH_4$, $LiBHEt_3$, or iBu_2AlH.

[23] The Lewis acid assisted addition of 4-chlorobutylzinc bromide worked well on the bis-*N,O*-acetal **35** (Scheme 7), but failed for unknown reasons on **25** (Scheme 5) and **32** (Scheme 6).

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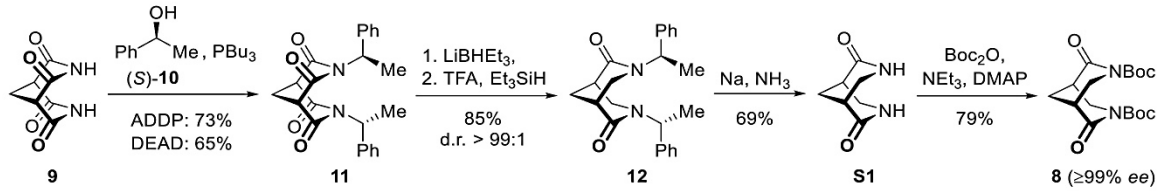
1. Synthetic Procedures

All reactions with moisture-sensitive reagents were carried out under argon atmosphere in anhydrous solvents, prepared using standard procedures.[1] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey-Nagel Alugram SIL G/UV254 or Merck TLC Silica gel 60 F_{254}). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$ or vanillin. Silica gel (Macherey-Nagel, particle size 40–63 µm) was used for column chromatography. Melting points were measured on a Thermo Scientific 9300 melting point apparatus or by differential scanning calorimetry (DSC) on a Mettler Toledo 821 DSC system. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell) and are given in units of $deg cm^3 g^{-1} dm^{-1}$. NMR spectra were taken on a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. All signal assignments in the ^1H and ^{13}C NMR data were made on basis of 2D NMR spectra (COSY, HSQC, HMBC). Infrared spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra on a ThermoFisher Scientific Q-Exactive (Orbitrap) mass spectrometer using ESI (electrospray ionization). The enantiomeric ratios of **7** and **8** were determined by HPLC analysis (Waters Alliance HPLC; Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase (Daicel Chiralcel OD-3). 2,4,6,8-Tetraoxobispidine (**9**)[2] and racemic 2,6-dioxobispidin (*rac*-**S1**)[3] were prepared according to literature protocols.

[1] *Purification of Laboratory Chemicals*, Eds.: W. L. F. Armarego, D. D. Perrin, 4th ed., Butterworth-Heinemann, Oxford, **2000**.
[2] P. R. Blakemore, C. Kilner, N. R. Norcross, P. C. Astles, *Org. Lett.* **2005**, *7*, 4721-4724.
[3] a) R. G. Kostyanovsky, K. A. Lyssenko, Y. I. El'natanov, O. N. Krutius, I. A. Bronzova, Y. A. Strelenko, V. R. Kostyanovsky, *Mendeleev. Commun*. **1999**, *9*, 106-108; b) R. G. Kostyanovsky, I. A. Bronzova, K. A. Lyssenko, *Mendeleev. Commun.* **2002**, *12*, 4-6.

1.1 Enantioselective Synthesis of Key Intermediate 8



Note: The enantiomeric compounds (*ent*-**11**, *ent*-**12**, *ent*-**S1**, and *ent*-**8**) were prepared using the same sequence, but with (*R*)-**10** instead of (*S*)-**10**.

1.1.1 3,7-Bis((*R*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane-2,4,6,8-tetraone (11)

PBu_3 (14.4 mL, 57.6 mmol) was added to a solution of ADDP [1,1'-(azodicarbonyl)dipiperidine; 14.5 g, 57.6 mmol] in anhydr. benzene/toluene (1:1, 170 mL) at −15 °C. After 15 min, 2,4,6,8-tetraoxo-bispidine (**9**; 3.50 g, 19.2 mmol) and (*S*)-1-phenylethanol [(*S*)-**10**; 6.97 mL, 57.6 mmol] were added. The reaction mixture was allowed to reach rt and stirring was continued for 26 h. Evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2; hexane/EtOAc 80:20 → 50:50) delivered diimide **11** (5.49 g, 14.1 mmol, 73%) as a white solid.

The analogous reaction with DEAD (7.77 mL, 49.5 mmol) instead of ADDP, PBu_3 (12.2 mL, 49.5 mmol), **9** (3.00 g, 16.5 mmol), and (*S*)-**10** (5.98 mL, 49.5 mmol) in anhydr. THF (150 mL) at 0 °C delivered **11** (4.20 g, 10.8 mmol) in 65% yield.

R_f = 0.22 (hexane/EtOAc 2:1); m.p. 179 °C; $[\alpha]_D^{29}$ = +140.4 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (m, 10 H, H_{Ar}), 5.98 (q, *J*=7.1 Hz, 2H, 3-CH, 7-CH), 3.96 (t, *J*=2.8 Hz, 2H, 1-H, 5-H), 2.49 (t, *J*=2.9 Hz, 9-H_2), 1.70 (d, *J*=7.2 Hz, CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.1 (C-2, C-4, C-6, C-8), 139.2, 128.4, 127.7, 127.1 (C_{Ar}), 50.9 (3-CH, 7-CH), 49.8 (C-1, C-5), 22.3 (C-9), 16.2 (CH_3) ppm; IR (ATR): $\tilde{\nu}$ = 2950 (w), 1699 (s), 1379 (m), 1320 (s), 1258 (s), 1190 (s), 1063 (s), 758 (s), 706 (s), 696 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{23}N_2O_4$ [*M* + H^+]: 391.16523; found: 391.16495.

1.1.2 (1*R*,5*R*)-3,7-Bis((*R*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane-2,6-dione (12)

A solution of diimide **11** (9.14 g, 23.4 mmol) in anhydr. CH_2Cl_2 (195 mL) was cooled to −78 °C and $LiBHEt_3$ (1.7 M in THF; 55.1 mL, 93.6 mmol) was added over a period of 30 min using a syringe pump. The mixture was stirred for 2 h, treated with MeOH (240 mL), and stirred for further 30 min. Sat. aq. $NaHCO_3$ (480 mL) was added and the mixture was allowed to warm to rt. The resulting suspension was extracted with $CHCl_3$ (4 × 550 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the resulting yellowish resin was suspended in CH_2Cl_2 (480 mL) and cooled to 0 °C. Et_3SiH (22.4 mL, 140 mmol) and TFA (30.7 mL, 398 mmol) were added and the solution was allowed to warm to rt and stirred for 14 h. The solvent was removed under

reduced pressure and the resulting oil was diluted two times with CH_2Cl_2 (250 mL) and evaporated again. The residue was dissolved in $CHCl_3$ (370 mL) and washed with sat. aq. $NaHCO_3$ (370 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 370 mL) and the combined organic layers were dried over $MgSO_4$. Column chromatography (SiO_2, hexane/*i*PrOH 90:10) delivered dilactam **12** (7.20 g, 19.9 mmol, 85%) as a white solid and in virtually diastereomerically pure form (d.r. > 99:1).

R_f = 0.44 (hexane/*i*PrOH 90:10); m.p. 154 °C; $[\alpha]_D^{29}$ = +138.5 (*c*=0.5 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (m, 4H, H_{Ar}), 7.28 (m, 6H, H_{Ar}), 6.04 (q, *J*=7.0 Hz, 2H, 3-CH, 7-CH), 3.33 (d, *J*=12.3 Hz, 2H, 4-*H*H, 8-*H*H), 2.84 (m, 2H, 1-H, 5-H), 2.80 (dd, *J*=12.3 Hz, 4.2 Hz, 2H, 4-H*H*, 8-H*H*) 1.96 (m, 2H, 9-H_2), 1.45 (d, *J*=7.1 Hz, 6H, CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7 (C-2, C-6), 139.1, 128.7, 128.0, 127.8 (C_{Ar}), 50.3 (3-CH, 7-CH), 47.0 (C-4, C-8), 37.5 (C-1, C-5), 25.4 (C-9), 15.1 (CH_3) ppm; IR (ATR): $\tilde{\nu}$ = 2981 (w), 2939 (w), 1637 (s), 1625 (s), 1487 (m), 1422 (s), 1168 (s), 701 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{27}N_2O_2$ [*M* + H$^+$]: 363.20670; found: 363.20605.

1.1.3 (1*R*,5*R*)-3,7-Diazabicyclo[3.3.1]nonane-2,6-dione (S1)

Sodium slices (1.83 g, 79.5 mmol) were added at –78 °C to a solution of liquid NH_3 (approx. 250 mL), *t*BuOH (3.80 mL, 39.7 mmol), and anhydr. THF (5 mL). After 5 min, the dilactam **12** (7.20 g, 19.9 mmol), dissolved in anhydr. THF (45 mL), was added and the cooling bath was removed. After 10 min, additional sodium slices (457 mg, 19.9 mmol) were added. The reaction was stirred for further 10 min, quenched with sat. aq. NH_4Cl (15 mL), and NH_3 was allowed to evaporate overnight at rt. Column chromatography (1. SiO_2, CH_2Cl_2/MeOH 90:10 → 70:30; 2. C18-SiO_2: H_2O) delivered diamide **S1** (2.11 g, 13.7 mmol, 69%) as a white powder.

R_f = 0.32 (CH_2Cl_2/MeOH 80:20); m.p. 382 °C (decomposition); $[\alpha]_D^{30}$ = +63.1 (*c*=1.0 in H_2O); ^{1}H NMR (500 MHz, D_2O): δ = 3.59 (dd, *J*=13.0 Hz, 4.8 Hz, 2H, 4-*H*H, 8-*H*H), 3.39 (d, *J*=13.1 Hz, 2H, 4-H*H*, 8-H*H*), 2.84 (m, 2H, 1-H, 5-H), 2.17 (t, *J*=2.9 Hz, 2H, 9-H_2) ppm; ^{13}C NMR (125 MHz, D_2O): δ = 175.2 (C-2, C-6), 45.3 (C-4, C-8), 34.4 (C-1, C-5), 23.4 (C-9) ppm; IR (ATR): $\tilde{\nu}$ = 3233 (m), 2957 (w), 2886 (w), 1645 (s),1622 (s), 1496 (s), 1356 (s), 1318 (s), 1198 (m), 1030 (m), 1022 (m), 811 (s), 780 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_7H_{11}N_2O_2$ [*M* + H$^+$]: 155.08150; found: 155.08141.

The spectroscopic data are in accordance with those reported in literature for racemic and scalemic **S1**.[3]

1.1.4 (1*R*,5*R*)-3,7-Di-*tert*-butoxycarbonyl-3,7-diazabicyclo[3.3.1]nonane-2,6-dione (8)

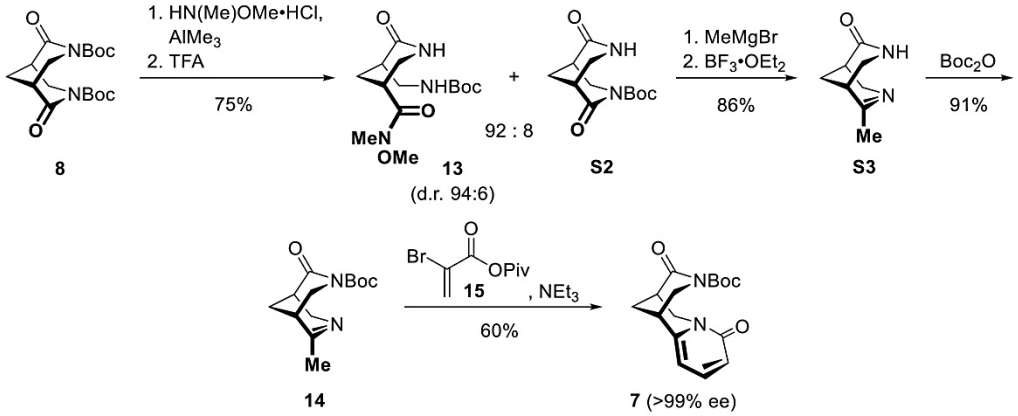
Diamide **S1** (2.07 g, 13.4 mmol) was suspended in MeCN (47 mL) and treated with NEt_3 (7.44 mL, 53.7 mmol), Boc_2O (8.80 g, 40.3 mmol), and DMAP (820 mg, 6.71 mmol). After 19 h, additional NEt_3 (3.71 mL, 26.8 mmol) and Boc_2O (4.39 g, 20.1 mmol) were added and the mixture was stirred for further 22 h. The solvent was removed under reduced pressure and aq. HCl (1%; 35 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 80 mL) and the combined organic layers were dried over

$MgSO_4$. Column chromatography (SiO_2, pentane/Et_2O/CH_2Cl_2 50:40:10 → 0:15:85) delivered diimide **8** (3.77 g, 10.6 mmol, 79%) as a beige solid.

The enantiomeric excess was determined to be 99% by HPLC on chiral phase [Chiralcel OD-3, *n*-hexane/*i*PrOH 75:25, 0.8 mL/min, 215 nm, t_R = 9.4 min (*S*,*S*), 12.9 min (*R*,*R*)].

R_f = 0.33 (Et_2O/CH_2Cl_2 80:20); m.p. 209 °C; $[\alpha]_D^{30}$ = +37.0 (*c*=1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.07 (d, *J*=13.0 Hz, 2H, 4-*H*H, 8-*H*H), 3.67 (dd, *J*=12.9 Hz, 4.8 Hz, 2H, 4-H*H*, 8-H*H*), 3.07 (m, 2H, 1-H, 5-H), 2.13 (s, 2H, 9-H_2), 1.50 (s, 18H, C(CH_3)$_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8 (C-2, C-6), 151.0 (CO_2N), 84.1 (*C*(CH_3)$_3$), 51.3 (C-4, C-8), 39.3 (C-1, C-5), 28.0 (C-9), 24.2 (C(*C*H_3)$_3$) ppm; IR (ATR): $\tilde{\nu}$ = 2981 (w), 2939 (w), 1759 (s), 1677 (m), 1289 (s), 1242 (s), 1137 (s), 955 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{26}N_2O_6Na$ [*M* + Na^+]: 377.16831; found: 377.16766.

1.2 Synthesis of Key Intermediate 7



1.2.1 (3*R*,5*R*)-5-((*tert*-Butoxycarbonylamino)methyl)-*N*-methoxy-*N*-methyl-6-oxopiperidine-3-carboxamide (13) and (1*R*,5*R*)-3-*tert*-Butoxycarbonyl-3,7-diazabicyclo[3.3.1]nonane-2,6-dione (S2)

Weinreb salt (HNMe(OMe)·HCl; 727 mg, 7.45 mmol) was suspended three times in benzene (5 mL) and evaporated again. The residue was dissolved in anhydr. CH_2Cl_2 (24 mL), cooled to 0 °C and treated with $AlMe_3$ (2.0 M in toluene; 3.73 mL, 7.45 mmol). The reaction mixture was stirred for 10 min at 0 °C and for 20 min at rt. At –35 °C, a solution of diimide **8** (2.40 g, 6.77 mmol) in anhydr. CH_2Cl_2 (24 mL) was added and the mixture was stirred for 18 h at this temperature.[4] Sat. aq. potassium sodium tartrate (33 mL) was introduced and the mixture was stirred for 1 h at rt. After extraction with CH_2Cl_2 (3 × 65 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuum. The residue was dissolved in anhydr. CH_2Cl_2 (60 mL) and treated

[4] Note: Higher temperatures lead to increased epimerization.

with TFA (1.04 mL, 13.5 mmol) at 0 °C. After 19 h at rt, sat. aq. $NaHCO_3$ (35 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 65 mL) and the combined organic layers were dried over Na_2SO_4. Column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2 → 95:5) delivered an inseparable mixture of the Weinreb amide **13** (d.r. 94:6, 1.47 g, 4.66 mmol, 69 %) and the imide **S2** (110 mg, 433 µmol, 6%) as an off-white resin.

R_f = 0.19 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{29}$ = –19.2 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): **13** (94:6 mixture of diastereomers): δ = 6.52 (br s, 0.06H, 1-H), 6.39 (br s, 0.94H, 1-H), 5.56 (br s, 0.94H, 5-CH_2NH), 5.42 (br s, 0.06H, 5-CH_2NH), 3.70 (s, 3H, OCH_3), 3.48 (m, 2H, 2-*H*H, 5-C*H*H), 3.34 (m, 1H, 2-H*H*), 3.29-3.10 (m, 5H, 3-H, 5-CH*H*, NCH_3), 2.56 (m, 0.06H, 5-H), 2.46 (m, 0.94H, 5-H), 2.08 (m, 1H, 4-*H*H), 1.86 (m, 0.06H, 4-H*H*), 1.75 (q, *J*=12.7 Hz, 0.94H, 4-H*H*), 1.40 (s, 9H, $(C(CH_3)_3)$ ppm; **S2**: δ = 6.74 (br s, 1H, NH), 4.02 (d, *J*=12.9 Hz, 1H, 4-*H*H), 3.66 (m, 1H, 4-H*H*), 3.61 (dm, *J*=12.2 Hz, 1H, 8-*H*H), 3.55 (m, 1H, 8-H*H*), 2.99 (m, 1H, 1-H), 2.87 (m, 1H, 5-H), 2.14 (m, 2H, 9-H_2), 1.49 (s, 9H, $(C(CH_3)_3)$ ppm; ^{13}C NMR (125 MHz, $CDCl_3$): **13** (major diastereomer): δ = 173.7 (C-6), 172.9 (3-CON), 156.3 (CO_2N), 79.2 ($C(CH_3)_3$), 61.8 (OCH_3), 43.6 (C-2), 41.7 (5-CH_2), 41.4 (C-5), 36.1 (C-3), 32.3 (NCH_3), 28.5 ($C(CH_3)_3$), 28.3 (C-4) ppm; **S2**: δ = 171.9, 171.5 (C-2, C-6), 151.4 (CO_2N), 83.9 ($C(CH_3)_3$), 51.1 (C-4), 46.8 (C-8), 38.7 (C-1), 36.3 (C-5), 28.0 ($C(CH_3)_3$), 24.7 (C-9) ppm; IR (ATR): $\tilde{\nu}$ = 3312 (br), 2976 (w), 2939 (w), 1698 (m), 1651 (s), 1496 (m), 1392 (m), 1365 (m), 1269 (m), 1251 (m), 1168 (s), 994 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{25}N_3O_5Na$ [*M* + Na^+]: 338.16864 ; found: 338.16770.

1.2.2 (1*R*,5*R*)-6-Methyl-3,7-diazabicyclo[3.3.1]non-6-en-2-one (S3)

A mixture of Weinreb amide **13** (1.45 g, 4.60 mmol, d.r. = 94:6) and imide **S2** (109 mg, 429 µmol) was dissolved in anhydr. THF (50 mL). It was treated at –40 °C with MeMgBr (3.0 M in Et_2O; 8.40 mL, 25.2 mmol) and allowed to warm to rt over 17 h. Sat. aq. NH_4Cl (25 mL) was added and the aqueous layer was extracted with EtOAc (3 × 70 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in anhydr. CH_2Cl_2 (45 mL) and $BF_3{\cdot}Et_2O$ (1.91 mL, 15.1 mmol) was added. After 19 h of stirring, the reaction was quenched by addition of MeOH/NH_3 [(aq., 25%) 90:10, 5 mL] and directly subjected to fast column chromatography[5] [SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1] to give imine **S3** (655 mg, 4.30 mmol, 86 %) as an off-white solid.

R_f = 0.50 [$CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1]; m.p. 238-251 °C (DSC); $[\alpha]_D^{26}$ = –2.3 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.48 (br d, *J*=18.5 Hz, 1H, NH), 3.94 (dm, *J*=18.2 Hz, 1H, 8-*H*H), 3.77 (dm, *J*=18.3 Hz, 1H, 8-H*H*), 3.49 (dd, *J*=12.2, 4.9 Hz, 1H, 4-*H*H), 3.33 (dm, *J*=12.2 Hz, 1H, 4-H*H*), 2.65 (s, 1H, 1-H), 2.55 (s, 1H, 5-H), 2.04 (t, *J*=1.8 Hz, 3H, 6-CH_3), 1.98 (dm, *J*=12.7 Hz, 1H, 9-*H*H), 1.91 (dm, *J*=12.7 Hz, 1H, 9-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.6 (C-2), 167.7

[5] Note: The intermediate ketone is somewhat configurationally unstable at the carbon atoms next to the carbonyl groups and has to be handled with care. Addition of MeOH/NH_3 [(aq., 25%) 90:10] prior to column chromatography is requisite for an excellent *ee* and yield of the product and, thus, of key intermediate **7**.

(C-6), 54.4 (C-8), 44.8 (C-4), 36.3 (C-1), 32.9 (C-5), 26.0 (6-CH_3), 23.8 (C-9) ppm; IR (ATR): $\tilde{\nu}$ = 3247 (br), 2930 (w), 2882 (w), 1661 (s), 1633 (s), 1490 (m), 1434 (m), 1314 (m), 1180 (m), 797 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_8H_{13}N_2O$ [*M* + H^+]: 153.10224; found: 153.10191.

1.2.3 (1*R*,5*R*)-3-*tert*-Butoxycarbonyl-6-methyl-3,7-diazabicyclo[3.3.1]non-6-en-2-one (14)

Imine **S3** (638 mg, 4.19 mmol) was dissolved in anhydr. CH_2Cl_2 (16.5 mL) and treated with NEt_3 (1.16 mL, 8.38 mmol), Boc_2O (1.37 g, 6.29 mmol), and DMAP (25.6 mg, 210 µmol). After 20 h, the solvent was removed under reduced pressure. Column chromatography (SiO_2, CH_2Cl_2/MeOH 97:3 → 93:7) delivered imide **14** (967 mg, 3.83 mmol, 91%) as a yellowish solid.

R_f = 0.51 (CH_2Cl_2/MeOH 90:10); m.p. 94-95 °C; $[\alpha]_D^{31}$ = +1.9 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.97 (d, *J*=18.2 Hz, 1H, 8-*H*H), 3.82 (dm, *J*=12.9 Hz, 1H, 4-*H*H), 3.76 (dm, *J*=18.2 Hz, 1H, 8-H*H*), 3.58 (dd, *J*=12.9 Hz, 5.1 Hz, 1H, 4-H*H*), 2.80 (m, 1H, 1-H), 2.60 (m, 1H, 5-H), 2.04 (m, 3H, 6-CH_3), 2.00 (dm, *J*=12.8 Hz, 1H, 9-*H*H), 1.91 (dm, *J*=12.7 Hz, 1H, 9-H*H*), 1.50 (s, 9H, C(CH_3)$_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6 (C-2), 167.7 (C-6), 152.4 (CO_2N), 83.4 (*C*(CH_3)$_3$), 55.0 (C-8), 49.7 (C-4), 39.3 (C-1), 33.5 (C-5), 28.0 (C(*C*H_3)$_3$), 26.0 (6-CH_3), 23.6 (C-9) ppm; IR (ATR): $\tilde{\nu}$ = 2982 (w), 2934 (w), 1767 (m), 1712 (s), 1663 (m), 1248 (s), 1153 (s), 1134 (s), 728 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{21}N_2O_3$ [*M* + H^+]: 253.15467; found: 253.15410.

1.2.4 (1*R*,9*R*)-11-*tert*-Butoxycarbonyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridec-2,4-dien-6,10-dione (7)

NEt_3 (1.04 mL, 7.50 mmol) and pivaloyl chloride (923 µL, 7.50 mmol) were added at 0 °C to a solution of 2-bromoacrylic acid (1.13 g, 7.50 mmol) in anhydr. THF (55 mL). The reaction mixture was stirred at 0 °C for 15 min and at rt for 1.75 h. Imine **14** (947 mg, 3.75 mmol), dissolved in anhydr. THF (11 mL), and, after 3 h, NEt_3 (1.04 mL, 7.50 mmol) were added and stirring was continued for further 2 h. The crude mixture was filtered through a pad of basic alumina (act. V, THF) and column chromatographed (SiO_2, CH_2Cl_2/MeOH 100:0 → 95:5) to give pyridone **7** (855 mg, 2.81 mmol, 75%, 94% *ee*) as an off-white solid. Fractional crystallization at –20 °C from CH_2Cl_2/Et_2O (1:3) overlaid with *n*-pentane (approx. 15 mL) provided highly enantiomerically enriched **7** (685 mg, 2.25 mmol, 60%, >99% *ee*, off-white foam after evaporation)[6] in the mother liquor.

The enantiomeric excess of **7** was determined by HPLC on chiral phase [Chiralcel OD-3, *n*-hexane/*i*PrOH 75:25, 0.8 mL/min, 215 nm, t_R = 20.6 min (*S*,*S*), 29.1 min (*R*,*R*)].

R_f = 0.30 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{26}$ = –101.3 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (dd, *J*=9.1 Hz, 6.9 Hz, 1H, 4-H), 6.50 (dd, *J*=9.1 Hz, 1.0 Hz, 1H, 5-H), 6.11 (dm, *J*=6.6 Hz, 1H, 3-H), 4.56 (dm, *J*=15.4 Hz, 1H, 8-*H*H), 3.86 (dt, *J*=12.7 Hz, 2.0 Hz, 1H, 12-*H*H), 3.81 (dd, *J*=12.7 Hz,

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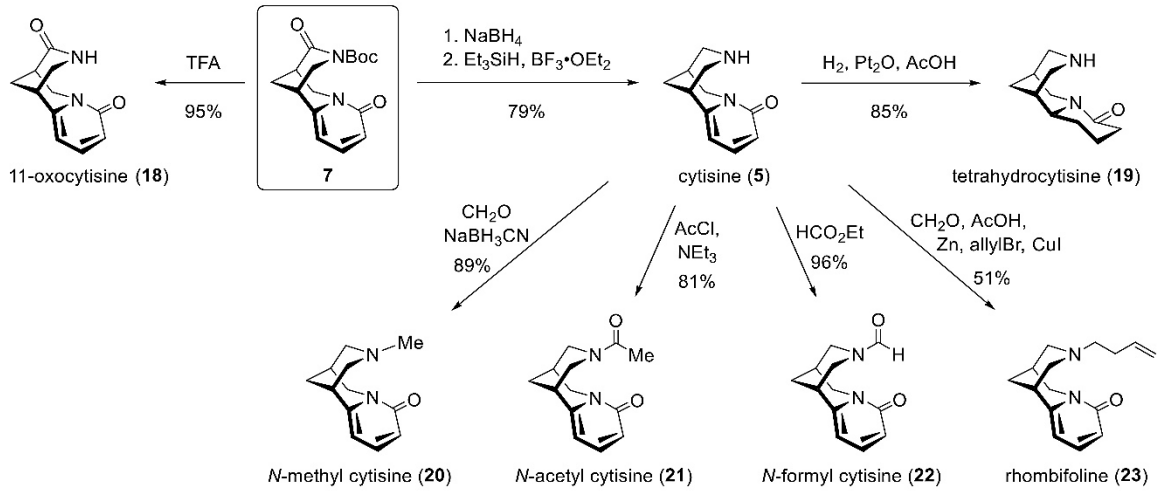
[6] Note: If the enantiomeric excess of **7** in the mother liquor was <99% or if too much material had crystallized, the corresponding fraction was subjected to renewed crystallization.

4.3 Hz, 1H, 12-H*H*), 3.75 (dd, *J*=15.4 Hz, 5.7 Hz, 1H, 8-H*H*), 3.38 (m, 1H, 1-H), 3.27 (m, 1H, 9-H), 2.24 (dm, *J*=13.2 Hz, 1H, 13-*H*H), 2.10 (dm, *J*=13.2 Hz, 1H, 13-H*H*), 1.50 (s, 9H, C(CH_3)$_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4 (C-10), 163.1 (C-6), 152.1 (CO_2N), 147.7 (C-2), 139.1 (C-4), 118.7 (C-5), 106.2 (C-3), 84.1 (*C*(CH_3)$_3$), 54.9 (C-12), 48.7 (C-8), 39.0 (C-9), 33.0 (C-1), 28.1 (C(*C*H_3)$_3$), 23.3 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 2981 (w), 1768 (m), 1724 (s), 1690 (s), 1657 (s), 1581 (s), 1542 (s), 1269 (s), 1251 (s), 1137 (s), 805 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{21}N_2O_4$ [*M* + H^+]: 305.14958; found: 305.14903.

1.3 Core-Monosubstituted, Tricyclic Alkaloids Derived from Pyridone 7



1.3.1 11-Oxocytisine (18)

A solution of imide **7** (48.9 mg,161 µmol) in anhydr. CH_2Cl_2 (2.5 mL) was treated at 0 °C with TFA (61.9 µL, 803 µmol) and stirred for 16 h at rt. The solvent was removed under reduced pressure and the resulting oil was diluted two times with CH_2Cl_2 (5 mL) and evaporated again. Column chromatography [SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1] delivered 11-oxocytisine (**18**; 31.3 mg, 153 µmol, 95%) as a white solid.

R_f = 0.24 (CH_2Cl_2/MeOH 95:5); m.p. 291-294 °C (DSC; lit.[7] 272-275 °C); $[\alpha]_D^{27}$ = +0.2 (*c*=0.5 in EtOH) [lit.[7] $[\alpha]_D^{12}$ = +6.7 (*c*=0.5 in EtOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (dd, *J*=9.1 Hz, 6.9 Hz, 1H, 4-H), 6.73 (br s, 1H, NH), 6.47 (dd, *J*=9.1 Hz, 1.2 Hz, 1H, 5-H), 6.09 (d, *J*=6.5 Hz, 1H, 3-H), 4.54 (dm, *J*=15.2 Hz, 1H, 8-*H*H), 3.73 (dd, *J*=7.0 Hz, 4.3 Hz, 1H, 12-*H*H), 3.70 (dd, *J*=11.7 Hz, 5.6 Hz, 1H, 8-H*H*), 3.39 (dm, *J*=11.9 Hz, 1H, 12-H*H*), 3.29 (m, 1H, 1-H), 3.08 (m, 1H 9-H), 2.21 (dm, *J*=13.1 Hz, 1H, 13-*H*H), 2.10 (dm, *J*=13.2 Hz, 1H, 13-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (C-10), 163.2 (C-6), 148.4 (C-2), 139.1 (C-4), 118.5 (C-5), 106.2 (C-3), 50.8 (C-12), 48.4 (C-

[7] I. Murakoshi, H. Kubo, M. Ikram, M. Israr, N. Shafi, S. Ohmiya, H. Otomasu, *Phytochemistry* **1986**, *25*, 2000-2002.

8), 36.0 (C-9), 32.4 (C-1), 23.5 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 3210 (m), 2942 (w), 2872 (w), 1647 (s), 1575 (m), 1537 (s), 1173 (m), 1145 (m), 1089 (m), 1055 (m), 798 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{13}N_2O_2$ [*M* + H^+]: 205.09715; found: 205.09659.

The spectroscopic data are in accordance with those reported in literature.[7]

1.3.2 Cytisine (5)

A solution of imide **7** (400 mg, 1.31 mmol) in MeOH (24 mL) was treated with $NaBH_4$ (149 mg, 3.94 mmol) at 0°C and stirred for 2 h at rt. Sat. aq. $NaHCO_3$ (40 mL) was added and the solvent was evaporated. The aqueous layer was extracted with CH_2Cl_2 (4 × 80 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was removed in vacuum. The residue was dissolved in anhydr. CH_2Cl_2 (12 mL) and the mixture was cooled to –78 °C. Et_3SiH (629 µL, 3.94 mmol) and $BF_3{\cdot}Et_2O$ (582 µL, 4.59 mmol) were added and the reaction was allowed to reach rt over 15 h. After addition of MeOH/NH_3 [(aq., 25%) 90:10, 360 µL], the resulting suspension was directly subjected to column chromatography [SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 97:2.7.0.3 → 90:9:1] to give cytisine (**7**; 198 mg, 1.04 mmol, 79%) as a white solid.

R_f = 0.26 [$CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1]; m.p. 148-154 °C (DSC; lit.[8] 153-154 °C); $[\alpha]_D^{34}$ = –60.8 (*c*=1.0 in $CHCl_3$) [lit.[8] $[\alpha]_D^{20}$ = –59.3 (*c*=0.84 in $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (dd, *J*=9.0 Hz, 6.9 Hz, 1H, 4-H), 6.45 (dd, *J*=9.1 Hz, 1.2 Hz, 1H, 5-H), 5.99 (dm, *J*=6.9 Hz, 1H, 3-H), 4.12 (d, *J*=15.6 Hz, 1H, 8-*H*H), 3.89 (dd, *J*=15.6 Hz, 6.7 Hz, 1H, 8-H*H*), 3.09 (d, *J*=12.2 Hz, 1H, 10-*H*H), 3.05 (dd, *J*=12.0 Hz, 2.2 Hz, 1H, 12-*H*H), 3.00 (d, *J*=12.5 Hz, 2H, 10-H*H*, 12-H*H*), 2.90 (m, 1H, 1-H), 2.32 (m, 1H, 9-H), 1.96 (m, 2H, 13-H_2), 1.42 (br s, 1H, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.8 (C-6), 151.1 (C-2), 138.9 (C-4), 116.9 (C-5), 105.1 (C-3), 54.0 (C-12), 53.0 (C-10), 49.8 (C-8), 35.6 (C-1), 27.8 (C-9), 26.4 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 3315 (w), 3280 (w), 2933 (w), 2803 (w), 1643 (s), 1561 (m), 1538 (s), 1139 (m), 788 (s), 735 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{15}N_2O$ [*M* + H^+]: 191.11789; found: 191.11730.

The spectroscopic data are in accordance with those reported in literature.[8]

1.3.3 Tetrahydrocytisine (19)

According to a literature procedure,[9] a solution of cytisine (**5**; 40.0 mg, 210 µmol) in AcOH (2 mL) and Pt_2O (4.8 mg, 21.0 µmol) were stirred under an H_2 atmosphere (1 atm.) at rt for 22 h. The reaction mixture was filtered through a pad of celite® and the filter cake was thoroughly washed (CH_2Cl_2/MeOH 90:10, 20 mL). The solvent was removed in vacuum and the residue was partitioned between CH_2Cl_2 (5 mL) and aq. NaOH (2.0 M; 1 mL). The aqueous layer was extracted with CH_2Cl_2

[8] A. J. Dixon, M. J. McGrath, P. O'Brien, *Org. Synth.* **2006**, *83*, 141-154.
[9] M. J. Johansson, L. Schwartz, M. Amedjkouh, N. Kann, *Tetrahedron: Asymmetry* **2004**, *15*, 3531-3538.

(5 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent delivered tetrahydrocytisine (**19**; 34.5 mg, 178 µmol, 85%; lit.[9] 69%) as a white crystalline solid.

R_f = 0.19 [$CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1]; m.p. 101-109 °C (DSC; lit.[10] 113 °C); $[\alpha]_D^{25}$ = –36.3 (*c*=1.0 in $CHCl_3$) [lit.[9] $[\alpha]_D^{20}$ = –32.8 (*c*=1.0 in $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.67 (dt, *J*=13.7 Hz, 2.0 Hz, 1H, 8-*H*H), 3.54 (m, 1H, 2-H), 3.34 (d, *J*=14.2 Hz, 1H, 12-*H*H), 3.10 (d, *J*=13.5 Hz, 1H, 10-*H*H), 2.99 (dt, *J*=13.4 Hz, 2.6 Hz, 1H, 10-H*H*), 2.94 (dm, *J*=14.2 Hz, 1H, 8-H*H*), 2.86 (ddm, *J*=14.2 Hz, 2.1 Hz, 1H, 12-H*H*), 2.49 (dm, *J*=17.3 Hz, 1H, 5-*H*H), 2.34 (ddd, *J*=17.4 Hz, 12.8 Hz, 6.1 Hz, 1H, 5-H*H*), 2.02 (dm, *J*=12.7 Hz, 1H, 13-*H*H), 1.93 (m, 1H, 4-*H*H), 1.84 (m, 3H, 3-H_2, 13-H*H*), 1.77 (m, 1H, 9-H), 1.70 (m, 1H, 4-H*H*), 1.62 (br s, 1H, NH), 1.46 (m, 1H, 1-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0 (C-6), 60.1 (C-2), 52.0 (C-10), 47.1 (C-8), 46.9 (C-12), 33.6, 33.3 (C-5, C-13), 33.2 (C-1), 28.6 (C-9), 28.3 (C-3), 20.4 (C-4) ppm; IR (ATR): $\tilde{\nu}$ = 3351 (br), 2944 (m), 2910 (m), 2881 (m), 2855 (m), 1613 (s), 1442 (m), 1417 (m), 1344 (m), 1162 (m), 922 (m), 807 (m), 735 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{19}N_2O$ [*M* + H^+]: 195.14919; found: 195.14854.

The spectroscopic data are in accordance with those reported in literature.[9]

1.3.4 *N*-Methyl cytisine (20)

According to a literature procedure,[11] a solution of cytisine (**5**; 50.0 mg, 263 µmol) in MeOH/THF (1:1, 3 mL) was treated with formaldehyde (37% in H_2O; 124 µL, 1.58 mmol) and $NaBH_3CN$ (57.9 mg, 921 µmol) After 2.5 h, the solvent was evaporated and sat. aq. NH_4Cl (1.5 mL) was added (caution: release of HCN!). The mixture was stirred for 30 min and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuum. Column chromatography (SiO_2, CH_2Cl_2/MeOH 95:5 → 90:10) delivered *N*-methyl cytisine (**20**; 47.8 mg, 234 µmol, 89%; lit.[11] 99%) as a white crystalline solid.

R_f = 0.44 (CH_2Cl_2/MeOH 90:10); m.p. 135-138 °C (DSC; lit.[12] 130-132 °C); $[\alpha]_D^{30}$ = –200.1 (*c*=1.0 in MeOH) [lit.[12] $[\alpha]_D^{25}$ = –194.7 (*c*=5 in MeOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (m, 1H, 4-H), 6.42 (d, *J*=9.0 Hz, 1H, 5-H), 5.96 (d, *J*=6.8 Hz, 1H, 3-H), 4.03 (d, *J*=15.4 Hz, 1H, 8-*H*H), 3.89 (dd, *J*=15.4 Hz, 6.9 Hz, 1H, 8-H*H*), 2.92 (m, 1H, 1-H), 2.87 (d, *J*=11.1 Hz, 1H 10-*H*H), 2.82 (d, *J*=10.7 Hz, 1H, 12-*H*H), 2.41 (m, 1H, 9-H), 2.23 (dd, *J*=10.7 Hz, 2.1 Hz, 1H, 12-H*H*), 2.20 (d *J*=11.1 Hz, 1H, 10-H*H*), 2.11 (s, 3H, 11-CH_3), 1.84 (dm, *J*=12.7 Hz, 1H, 13-*H*H), 1.71 (dm, *J*=12.7 Hz,1H, 13-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7 (C-6), 151.6 (C-2), 138.7 (C-4), 116.7 (C-5), 104.7 (C-3), 62.6 (C-12), 62.2 (C-10), 50.0 (C-8), 46.3 (11-CH_3), 35.5 (C-1), 28.0 (C-9), 25.5 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 3034 (w), 2932 (m), 2833 (w), 2776 (m), 2734 (w), 1646 (s), 1569 (s), 1547 (s), 1143 (s), 808 (s), 743 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{17}N_2O$ [*M* + H^+]: 205.13354; found: 205.13296.

The spectroscopic data are in accordance with those reported in literature.[11,12]

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[10] F. Bohlmann, E. Winterfeldt, H. Overwien, H. Pagel, *Chem. Ber.* **1962**, *95*, 944-948.
[11] F. Frigerio, C. A. Haseler, T. Gallagher, *Synlett* **2010**, *5*, 729-730.
[12] M. M. Al-Azizi, M. S. Al-Said, M. M. El-Olemy, E. Abdel Sattar, A. S. Khalifa, *Arch. Pharm. Res.* **1994**, *17*, 393-397.

1.3.5 *N*-Acetyl cytisine (21)

According to a literature procedure,[13] a solution of cytisine (**5**; 50.0 mg, 263 µmol) in anhydr. CH_2Cl_2 (1 mL) was treated at 0°C with NEt_3 (72.9 µl, 526 µmol) and AcCl (28.2 µl, 395 µmol) and stirred for 18 h at rt. The solvent was removed in vacuum, the residue filtered through a pad of celite®, and the filter cake was thoroughly washed with EtOAc (20 mL). Evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 99:1→95:5) delivered *N*-acetyl cytisine (**21**; 49.3 mg, 212 µmol, 81%; lit.[13] 86%) as a white solid.

R_f = 0.21 (CH_2Cl_2/MeOH 95:5); m.p. 208-210 (DSC; lit.[13] 212 °C); $[\alpha]_D^{30}$ = –219.3 (*c*=0.5 in EtOH) [lit.[14] $[\alpha]_D^{26}$ = –208 (*c*=0.2 in EtOH)]; ^{1}H NMR (500 MHz, CDCl3; 51:49 mixture of rotamers): δ = 7.26 (m, 1H, 4-H), 6.43 (m, 1H, 5-H), 6.05 (m, 1H, 3-H), 4.78 (d, *J*=13.3 Hz, 0.49H, 12-*H*H), 4.66 (d, *J*=12.9 Hz, 0.51H, 12-*H*H), 4.10 (m, 1H, 8-*H*H), 3.95-3.79 (m, 2H, 8-H*H*, 10-*H*H), 3.38 (m, 1H, 10-H*H*), 3.07 (s, 1H, 1-H), 2.83 (d, *J*=13.0 Hz, 0.51H, 12-H*H*), 2.78 (d, *J*=13.4 Hz, 0.49H, 12-H*H*), 2.51 (br s, 1H, 9-H), 2.01 (m, 3.53H, 13-H_2, 11-$COCH_3$), 1.73 (s, 1.47H, 11-$COCH_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$; mixture of rotamers): δ = 169.8, 169.7 (11-CO), 163.5, 163.3 (C-6), 148.6, 148.5 (C-2), 139.2, 138.5 (C-4), 118.0, 117.5 (C-5), 106.0, 104.9 (C-3), 53.8, 52.6 (C-10), 48.99, 48.96, 48.5, 47.6 (C-8, C-12), 35.1, 34.4 (C-1), 27.7, 27.4 (C-9), 26.2, 26.1 (C-13), 21.5, 20.9 (11-CO*C*H_3) ppm; IR (ATR): $\tilde{\nu}$ = 2931 (w), 1653 (s), 1631 (s), 1615 (s), 1542 (s), 1450 (m), 1424 (s), 1362 (m), 1240 (m), 1108 (m), 814 (m), 797 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{17}N_2O_2$ [*M* + H$^+$]: 233.12845; found: 233.12770.

The spectroscopic data are in accordance with those reported in literature.[13]

1.3.6 *N*-Formyl cytisine (22)

According to a literature procedure,[15] a solution of cytisine (**5**; 30.0 mg, 158 µmol) in ethyl formiate (500 µL) was refluxed for 19 h. Evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 95:5) delivered *N*-formyl cytisine (**22**; 33.1 mg, 152 µmol, 96%; lit.[15] 95%) as a white solid.

R_f = 0.21 (CH_2Cl_2/MeOH 95:5); m.p. 164-167 °C (DSC; lit.[16] 164-166 °C); $[\alpha]_D^{30}$ = –231.9 (*c*=0.5 in EtOH) [lit.[15] $[\alpha]_D^{20}$ = –233 (*c*=0.4 in EtOH)]; ^{1}H NMR (500 MHz, $CDCl_3$; 56:44 mixture of rotamers): δ = 7.88 (s, 0.56H, 11-CHO), 7.65 (s, 0.44H, 11-CHO),7.26 (m, 1H, 4-H), 6.42 (d, *J*=9.1 Hz, 1H, 5-H), 6.05 (d, *J*=6.8 Hz, 0.56H, 3-H), 5.99 (d, *J*=6.8 Hz, 0.44H, 3-H), 4.52 (d, *J*=13.4 Hz, 0.44H, 12-*H*H), 4.42 (d, *J*=12.9 Hz, 0.56H, 12-*H*H), 4.08 (d, *J*=5.0 Hz, 0.44H, 8-*H*H), 4.05 (d, *J*=4.9 Hz, 0.56H, 8-*H*H), 3.86 (m, 1H, 8-H*H*), 3.64 (d, *J*=13.2 Hz, 0.56H, 10-*H*H), 3.53 (d, *J*=12.2 Hz, 0.44H, 10-*H*H), 3.42 (m, 1H, 10-H*H*), 3.08 (s, 1H, 1-H), 2.91 (m, 1H, 12-H*H*), 2.53 (s, 1H, 9-H), 2.07 (m, 2H, 13-H_2)

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[13] J. Rouden, A. Ragot, S. Gouault, D. Cahard, J.-C. Plaquevent, M.-C. Lasne, *Tetrahedron: Asymmetry* **2002**, *13*, 1299-1305.
[14] S. Ohmiya, H. Otomasu, I. Murakoshi, J. Haginiwa, *Phytochemistry* **1974**, *13*, 1016.
[15] S. Ohmiya, H. Otomasu, I. Murakoshi, J. Haginiwa, *Phytochemistry* **1974**, *13*, 643-644.
[16] J. Doulcet, G. R. Stephenson, *Chem. Eur. J.* **2015**, *21*, 13431-13436.

ppm; ^{13}C NMR (125 MHz, $CDCl_3$; mixture of rotamers): δ = 163.5, 163.3 (C-6), 161.3, 161.2 (11-CHO), 148.1 ,148.0 (C-2), 139.1, 138.7 (C-4), 118.1, 117.8 (C-5), 105.9, 105.1 (C-3), 53.5, 52.2 (C-10), 48.9, 48.7 (C-8), 47.2, 46.2 (C-12), 34.7, 34.0 (C-1), 27.2, 26.8 (C-9), 26.51, 26.46 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 2943 (w), 2868 (w), 1645 (s), 1543 (s), 1438 (m), 1262 (m), 1065 (m), 802 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}N_2O_2$ [*M* + H$^+$]: 219.11280; found: 219.11220.

The spectroscopic data are in accordance with those reported in literature.[16]

1.3.7 Rhombifoline (23)

A mixture of cytisine (**5**; 40.0 mg, 210 µmol), formaldehyde (37% aq.; 20.5 µL, 252 µmol), allyl bromide (36.3 µL, 420 µmol), CuI (40.0 mg, 210 µmol), granulated Zn (34.3 mg, 525 µmol), and AcOH (24.0 µL, 420 µmol) in H_2O (210 µL) was stirred vigorously for 22 h at rt.[17] Aq. NaOH (2.0 M; 3 mL) was added, the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2 → 95:5) delivered rhombifoline (**23**; 26.1 mg, 107 µmol, 51%) as yellowish oil.

R_f = 0.38 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{31}$ = –231.6 (*c*=1.0 in EtOH) [lit.[12] $[\alpha]_D^{25}$ = –232.4 (*c*=2.1 in EtOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (m, 1H, 4-H), 6.41 (dd, *J*=9.0 Hz, 1.3 Hz, 1H, 5-H), 5.94 (dd, *J*=6.8 Hz, 1.1 Hz, 1H, 3-H), 5.56 (m, 1H, 11-CH_2CH_2CH=CH_2), 4.85 (m, 2H, 11-CH_2CH_2CH=CH_2), 4.00 (d, *J*=15.3 Hz, 1H, 8-*H*H), 3.86 (dd, *J*=15.3 Hz, 6.7 Hz, 1H, 8-H*H*), 2.90 (m, 3H, 1-H, 10-*H*H, 12-*H*H), 2.40 (m, 1H, 9-H), 2.28 (m, 4H, 10-H*H*, 12-H*H*, 11-CH_2), 2.02 (m, 2H, 11-CH_2CH_2), 1.86 (dm, *J*=12.7 Hz, 1H, 13-*H*H), 1.75 (dm, *J*=12.7 Hz, 1H, 13-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7 (C-6), 151.7 (C-2), 138.7 (C-4), 136.4 (11-CH_2CH_2CH=CH_2), 116.6 (C-5), 115.5 (11-CH_2CH_2CH=CH_2), 104.6 (C-3), 60.4, 60.1 (C-10, C-12), 57.1 (11-CH_2), 50.1 (C-8), 35.7 (C-1), 31.2 (11-CH_2CH_2), 28.2 (C-9), 26.1 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 3075 (w), 2937 (w), 2792 (w), 1646 (s), 1566 (m), 1543 (s), 1139 (m), 795 (m), 735 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{21}N_2O$ [*M* + H$^+$]: 245.16484; found: 245.16400.

The spectroscopic data are in accordance with those reported in literature.[12]

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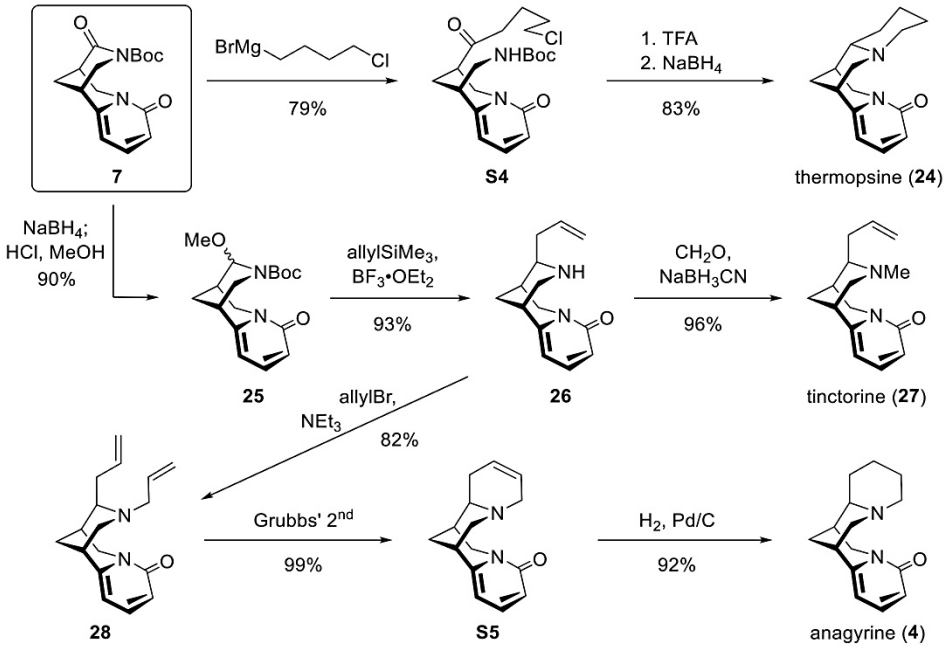
[17] For a general procedure for such Barbier-type reactions, see: I. H. S. Estevam, L. W. Bieber, *Tetrahedron Lett.* **2003**, *44*, 667-670.

1.4 Core-Disubstituted, Tri- and Tetracyclic Alkaloids Derived from Pyridone 7



1.4.1 Synthesis of Thermopsine (24)

1.4.1.1 (7*R*,9*R*)-9-((*tert*-Butoxycarbonylamino)methyl)-7-(5-chloropentanoyl)-6,7,8,9-tetrahydro-4*H*-quinolizin-4-one (S4)

Preparation of 4-chlorobutylmagnesium bromide: According to a literature procedure,[18] a small amount of 1-bromo-4-chlorobutane (approx. 12 µL) was added to Mg (82.4 mg, 3.39 mmol) and a catalytic amount of I_2 in anhydr. THF (6 mL). The Grignard reaction was started by ultrasonication for 10 min. Remaining 1-bromo-4-chlorobutane (in total: 390 µL, 3.39 mmol) was added at 0 °C and the reaction mixture was stirred for 3 h at this temperature, giving a 0.53 M solution of the Grignard reagent.

4-Chlorobutylmagnesium bromide (0.53 M; 744 µL, 394 µmol) was added at –78 °C to a solution of imide **7** (60.0 mg, 197 µmol) in anhydr. THF (3 mL). After 3 h, additional 4-chlorobutylmagnesium bromide (0.53 M, 372 µL, 197 µmol) was added and stirring was continued for 2 h. The reaction was quenched with sat. aq. NH_4Cl (3 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (SiO_2, CH_2Cl_2/MeOH 99.5:0.5 → 98:2) delivered ketone **S4** (61.4 mg, 155 µmol, 79%) as a colorless oil.

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[18] F. F. Flemming, B. C. Shook, T. Jiang, O. W. Steward, *Tetrahedron* **2003**, *59*, 737-745.

R_f = 0.42 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{28}$ = –96.0 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (m, 1H, 2-H), 6.43 (d, *J*=9.0 Hz, 1H, 3-H), 6.08 (d, *J*=6.8 Hz, 1H, 1-H), 4.90 (br s, 1H, NH), 4.35 (dd, *J*=14.2 Hz, 4.4 Hz, 1H, 6-*H*H), 4.10 (dd, *J*=14.2 Hz, 8.2 Hz, 1H, 6-H*H*), 3.52 (m, 3H, 9-C*H*H, CH_2Cl), 3.29 (m, 1H, 9-CH*H*), 3.05 (m, 1H, 9-H), 2.98 (m, 1H, 7-H), 2.63 (m, 1H, 7-COC*H*H), 2.55 (m, 1H, 7-COCH*H*), 2.15 (m, 1H, 8-*H*H), 1.90-1.66 (m, 5H, 8-H*H*, 7-$COCH_2CH_2CH_2$), 1.41 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.9 (7-CO), 163.1 (C-4), 156.0 (CO_2N), 147.7 (C-10), 138.9 (C-2), 117.6 (C-3), 104.2 (C-1), 80.0 ($C(CH_3)_3$), 45.3 (C-7), 44.7 (CH_2Cl), 43.8 (9-CH_2), 41.0 (C-6), 40.4 (7-$COCH_2$), 38.0 (C-9), 31.8 (7-$COCH_2CH_2$), 28.5 ($C(CH_3)_3$), 25.1 (C-8), 20.9 (7-$COCH_2CH_2CH_2$) ppm; IR (ATR): $\tilde{\nu}$ = 3304 (br), 2959 (w), 2931 (w), 1706 (s), 1653 (s), 1572 (s), 1546 (s), 1366 (m), 1274 (m), 1252 (m), 1167 (s), 798 (w) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{30}N_2O_4Cl$ [*M* + H^+]: 397.18886 ; found:397.18872.

1.4.1.2 Thermopsine (24)

A solution of ketone **S4** (49.8 mg,125 µmol) in anhydr. CH_2Cl_2 (2.5 mL) at 0 °C was treated with TFA (145 µL, 1.89 mmol) and stirred for 17 h at rt. The solvent was removed under reduced pressure and the resulting oil was diluted three times with CH_2Cl_2 (5 mL) and evaporated again. After column chromatography [bas. Al_2O_3, act. V, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1], the intermediate was dissolved in MeOH (2 mL), treated with $NaBH_4$ (14.3 mg, 378 µmol) at 0 °C and stirred for 3 h. The solvent was removed and the resulting residue was diluted three times with MeOH (5 mL) and evaporated again. Column chromatography (SiO_2, CH_2Cl_2/MeOH 97:3 → 90:10) delivered thermopsine (**24**; 25.5 mg, 104 µmol, 83%) as a white solid.

R_f = 0.48 (CH_2Cl_2/MeOH 90:10); m.p. 198-203 °C (DSC; lit.[19] 205-206 °C); $[\alpha]_D^{29}$ = –151.4 (*c*=1.0 in EtOH) [lit.[19] $[\alpha]_D^{20}$ = –159.6 (*c*= 10 in EtOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (m, 1H, 4-H), 6.43 (d, *J*=9.0 Hz, 5-H), 5.95 (d, *J*=6.8 Hz, 1H, 3-H), 4.25 (d, *J*=15.8 Hz, 1H, 8-*H*H), 3.66 (dd, *J*=15.8 Hz, 6.8 Hz, 1H, 8-H*H*), 2.91 (m, 1H, 1-H), 2.77 (d, *J*=10.9 Hz, 1H, 16-*H*H), 2.58 (d, *J*=11.2 Hz, 1H, 14-*H*H), 2.32 (dd, *J*=10.9 Hz, 2.4 Hz, 1H, 16-H*H*), 2.08 (m, 1H, 9-H), 1.99 (d, *J*=11.4 Hz, 1H, 10-H), 1.95 (dm, *J*=12.2 Hz, 1H, 17-*H*H), 1.85 (m, 2H, 14-H*H*, 17-H*H*), 1.74 (dm, *J*=12.8 Hz, 1H, 12-*H*H), 1.57 (m, 1H, 11-*H*H), 1.49 (m, 1H, 13-*H*H), 1.41 (m, 2H, 11-H*H*, 13-H*H*), 1.24 (m, 1H, 12-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.8 (C-6), 151.8 (C-2), 138.7 (C-4), 116.6 (C-5), 104.6 (C-3), 66.1 (C-10), 63.5 (C-16), 56.2 (C-14), 45.0 (C-8), 35.4 (C-1), 33.0 (C-9), 29.9 (C-11), 27.7 (C-17), 25.4 (C-13), 24.5 (C-12) ppm; IR (ATR): $\tilde{\nu}$ = 2927 (m), 2917 (m), 2808 (w), 2784 (w), 2763 (w), 1642 (s), 1569 (s), 1542 (s), 1348 (m), 1279 (m), 1137 (m), 1127 (m), 1114 (m), 804 (s), 748 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{21}N_2O$ [*M* + H^+]: 245.16484 ; found: 245.16455.

The spectroscopic data are in accordance with those reported in literature.[20]

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[19] A. Orechoff, S. Norkina, H. Gurewitch, *Ber. Dtsch. Chem. Ges. B* **1933**, *66B*, 625-630.
[20] Z. Liu, L. Yang, Z. Jia, J. Chen, *Magn. Reson. Chem.* **1992**, *30*, 511-514.

1.4.2 Synthesis of Tinctorine (27)

1.4.2.1 (1*R*,9*R*)-11-*tert*-Butoxycarbonyl-10-methoxy-7,11-diazatricyclo[7.3.1.0^{2,7}]tridec-2,4-dien-6-one (25)

A solution of imide **7** (600 mg, 1.97 mmol) in MeOH (36 mL) was treated with $NaBH_4$ (224 mg, 5.91 mmol) at 0°C and stirred for 1.5 h at this temperature. Methanolic HCl (2.0 M; 5.5 mL) was added and the reaction mixture was allowed to reach rt over 4.5 h. Aq. $NaHCO_3$ (18 mL) was added and the solvent was removed in vacuum. The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL) and the combined organic layers were dried over Na_2SO_4. Column chromatography (SiO_2, CH_2Cl_2/MeOH 95:5 → 90:10) delivered *N*,*O*-acetal **25** (571 mg, 1.78 mmol, 90%) as a colorless resin, which solidified upon standing.

The ^1H and ^{13}C NMR spectra of **25** display two sets of signals. These probably result from the *N*-Boc rotamers of the *exo*-diastereomer, but the existence of the *endo*-diastereomer cannot be fully excluded.

R_f = 0.44 (CH_2Cl_2/MeOH 95:5); m.p. 185-217 °C (DSC); $[\alpha]_D^{25}$ = –179.0 (*c*=1.0 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, 60:40 mixture of isomers): δ = 7.26 (m, 1H, 4-H), 6.42 (m, 1H, 5-H), 6.04 (d, *J*=6.8 Hz, 0.60H, 3-H), 6.00 (d, *J*=6.8 Hz, 0.40H, 3-H), 5.39 (s, 0.40H, 10-H), 5.21 (s, 0.60H, 10-H), 4.07 (m, 1H, 8-*H*H), 3.96 (d, *J*=12.8 Hz, 0.60H, 12-*H*H), 3.83 (d, *J*=12.9 Hz, 0.40H, 12-*H*H), 3.79 (d, *J*=6.9 Hz, 0.60H, 8-H*H*), 3.76 (d, *J*=6.9 Hz, 0.40H, 8-H*H*), 3.31 (dd, *J*=12.9 Hz, 2.0 Hz, 0.40H, 12-H*H*), 3.28 (s, 1.2H, OCH_3), 3.26 (s, 1.8H, OCH_3), 3.22 (dd, *J*=12.8 Hz, 2.2 Hz, 0.60H, 12-H*H*), 2.94 (s, 0.60H, 1-H), 2.87 (s, 0.40H, 1-H), 2.54 (m, 1H, 9-H), 2.33 (m, 1H, 13-*H*H), 1.72 (m, 1H, 13-H*H*), 1.33 (s, 5.4H, $C(CH_3)_3$), 1.21 (s, 3.6H, $C(CH_3)_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, mixture of isomers): δ = 163.6, 163.5 (C-6), 154.6, 154.5 (CO_2N), 149.5, 149.0 (C-2), 139.2, 138.6 (C-4), 117.5, 117.3 (C-5), 105.6, 104.9 (C-3), 86.3, 84.9 (C-10), 81.2, 80.5 ($C(CH_3)_3$), 54.8, 54.7 (OCH_3), 46.82, 46.76, 46.5, 45.1 (C-8, C-12), 34.5, 34.4 (C-1), 31.7, 31.6 (C-9), 28.2, 28.1 ($C(CH_3)_3$), 20.7, 20.6 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 3002 (w), 2972 (w), 2931 (w), 2830 (w), 1679 (s), 1655 (s), 1577 (m), 1543 (s), 1413 (s), 1366 (m), 1162 (s), 1137 (s), 1125 (m), 1077 (s), 794 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{25}N_2O_4$ [*M* + H^+]: 321.18088; found: 321.18052.

1.4.2.2 (1*R*,9*R*,10*R*)-10-Allyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridec-2,4-dien-6-one (26)

Allyltrimethylsilane (1.33 mL, 8.40 mmol) and $BF_3{\cdot}Et_2O$ (532 µL, 4.20 mmol) were added at 0 °C to a solution of the *N*,*O*-acetal **25** (450 mg, 1.40 mmol) in anhydr. CH_2Cl_2 (20 mL). After 16 h at rt, the crude mixture was filtered through a pad of basic alumina (act. I, CH_2Cl_2/MeOH 90:10) and column chromatographed [SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 98:1.8:0.2 → 95:4.5:0.5] to give amine **26** (300 mg, 1.30 mmol, 93%) as a white solid.

R_f = 0.37 [CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5]; m.p. 99-102 °C (DSC); $[\alpha]_D^{28}$ = –50.6 (*c*=1.0 in EtOH) [lit.[21] $[\alpha]_D^{20}$ = –94.7 (*c*=1.0 in EtOH)][22]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (dd, *J*=9.0 Hz, 6.9 Hz, 1H, 4-H), 6.43 (dd, *J*=9.0 Hz, 1.2 Hz, 1H, 5-H), 5.97 (d, *J*=6.9 Hz, 1H, 3-H), 5.75 (m, 1H, 10-CH_2CH=CH_2), 5.10 (m, 2H, 11-CH_2CH=CH_2), 4.10 (d, *J*=15.6 Hz, 1H, 8-*H*H), 3.92 (dd, *J*=15.6 Hz, 6.6 Hz, 1H, 8-H*H*), 3.21 (dd, *J*=12.0 Hz, 2.3 Hz, 1H, 12-*H*H), 2.98 (t, *J*=7.2 Hz, 1H, 10-H), 2.85 (s, 1H, 1-H), 2.71 (dt, *J*=12.0 Hz, 2.3 Hz, 1H, 12-H*H*), 2.52 (m, 1H, 10-C*H*H), 2.29 (m, 1H, 10-CH*H*), 2.23 (s, 1H, 9-H), 2.10 (d, *J*=13.2 Hz, 1H, 13-*H*H), 1.75 (dd, *J*=13.2 Hz, 2.5 Hz, 1H, 13-H*H*), 1.96-1.36 (br s, 1H, 11-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6 (C-6), 151.3 (C-2), 138.8 (C-4), 135.7 (10-CH_2CH=CH_2), 117.4 (10-CH_2CH=CH_2), 116.7 (C-5), 104.8 (C-3), 58.2 (C-10), 51.4 (C-8), 47.5 (C-12), 35.2 (C-1), 35.0 (10-CH_2), 30.3 (C-9), 21.2 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 3308 (w), 2935 (w), 2797 (w), 1641 (s), 1569 (s), 1541 (s), 1469 (m), 1150 (s), 928 (m), 804 (s), 728 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{19}N_2O$ [*M* + H^+]: 231.14919 ; found: 231.14861.

The spectroscopic data are in accordance with those reported in literature.[21]

1.4.2.3 Tinctorine (27)

A solution of amine **26** (40.0 mg, 174 µmol) in MeOH/THF (1:1, 2 mL) was treated with aq. formaldehyde (37%; 81.9 µL, 1.04 mmol) and $NaBH_3CN$ (38.3 mg, 609 µmol). After 2.5 h, the solvent was evaporated and sat. aq. NH_4Cl (2 mL) was added (caution: release of HCN!). The mixture was stirred for 10 min and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuum. Column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2 → 95:5) delivered tinctorine (**27**; 40.8 mg, 167 µmol, 96%) as a white crystalline solid.

R_f = 0.57 [$CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1]; m.p. 108-113 °C (DSC; lit.[23] 112-113 °C); $[\alpha]_D^{29}$ = –58.4 (*c*=0.1 in EtOH) [lit.[24] $[\alpha]_D^{23}$ = –59 (*c*=0.1 in EtOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (m, 1H, 4-H), 6.42 (dd, *J*=9.0 Hz, 1.2 Hz, 1H, 5-H), 5.95 (d, *J*=6.9 Hz, 1H, 3-H), 5.73 (m, 1H, 10-CH_2CH=CH_2), 5.08 (m, 2H, 11-CH_2CH=CH_2), 3.94 (m, 2H, 8-H_2), 2.84 (m, 3H, 1-H, 10-H, 12-*H*H), 2.47 (d, *J*=11.2 Hz, 1H, 12-H*H*), 2.39 (m, 2H, 9-H, 10-C*H*H), 2.24 (m, 1H, 10-CH*H*), 2.19 (s, 3H, 11-CH_3), 1.95 (dt, *J*=13.2 Hz, 2.9 Hz, 1H, 13-*H*H), 1.65 (dm, *J*=13.2 Hz, 1H, 13-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7 (C-6), 152.0 (C-2), 138.7 (C-4), 136.2 (10-CH_2CH=CH_2), 117.0 (10-CH_2CH=CH_2), 116.6 (C-5), 104.4 (C-3), 65.4 (C-10), 55.1 (C-12), 51.4 (C-8), 42.6 (11-CH_3), 35.3 (C-1), 29.0 (C-9), 25.7 (10-CH_2), 19.7 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 3069 (w), 2922 (w), 2784 (w), 1661 (s), 1644 (s), 1576 (s), 1548 (s), 1355 (m), 1136 (s), 920 (s), 785 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{21}N_2O$ [*M* + H^+]: 245.16484; found: 245.16403.

The spectroscopic data are in accordance with those reported in literature.[23,24]

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[21] H. Kubo, S. Ohmiya, I. Murakoshi, *Can. J. Chem.* **1994**, *72*, 214-217.
[22] We found that analytically pure **26** is a white solid. In ref.[21], however, **26** is described as a colorless oil, which might explain the difference in optical rotation.
[23] D. Knöfel, H. R. Schütte, *J. Prakt. Chem.* **1970**, *312*, 887-895.
[24] A.-L. Sagen, J. Gertsch, R. Becker, J. Heilmann, O. Sticher, *Phytochemistry* **2002**, *61*, 975-978.

1.4.3 Synthesis of Anagyrine (4)

1.4.3.1 (1*R*,9*R*,10*R*)-10,11-Diallyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridec-2,4-dien-6-one (28)

A solution of amine **26** (150 mg, 651 µmol) in anhydr. CH_2Cl_2 (6 mL) was successively treated with three portions of allyl bromide (0 h: 112 µL, 1.30 mmol; 20 h: 336 µL, 3.90 mmol; 48 h: 112 µL, 1.30 mmol) and NEt_3 (0 h: 270 µL, 1.95 µmol; 20 h: 270 µL, 1.95 µmol; 48 h: 270 µL, 1.95 µmol). After 96 h, sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuum. Column chromatography (SiO_2, CH_2Cl_2/MeOH 99:1 → 98:2) delivered diene **28** (145 mg, 536 µmol, 82%) as a colorless oil.

R_f = 0.57 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{26}$ = –74.1 (*c*=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (m, 1H, 4-H), 6.43 (dd, *J*=9.0 Hz, 1.2 Hz, 1H, 5-H), 5.93 (d, *J*=6.9 Hz, 1H, 3-H), 5.71 (m, 1H, 10-CH_2CH=CH_2), 5.45 (m, 1H, 11-CH_2CH=CH_2), 5.06 (m, 2H, 10-CH_2CH=CH_2), 4.90 (m, 2H, 11-CH_2CH=CH_2), 3.99 (d, *J*=15.5 Hz, 1H, 8-*H*H), 3.92 (dd, *J*=15.5 Hz, 6.7 Hz, 1H, 8-H*H*), 3.05 (dd, *J*=14.2 Hz, 5.6 Hz, 1H, 11-C*H*HCH=CH_2), 2.92 (m, 2H, 10-H, 11-CH*H*CH=CH_2), 2.87 (s, 1H, 1-H), 2.74 (dd, *J*=11.3 Hz, 2.2 Hz, 1H, 12-*H*H), 2.58 (d, *J*=11.3 Hz, 1H, 12-H*H*), 2.39 (s, 1H, 9-H), 2.30 (m, 2H, 10-CH_2CH=CH_2), 1.99 (d, *J*=13.2 Hz, 1H, 13-*H*H), 1.69 (dd, *J*=13.2 Hz, 1.2 Hz, 1H, 13-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6 (C-6), 151.9 (C-2), 138.6 (C-4), 135.9 (10-CH_2CH=CH_2), 135.7 (11-CH_2CH=CH_2), 117.0 (10-CH_2CH=CH_2), 116.6 (C-5), 116.5 (11-CH_2CH=CH_2), 104.3 (C-3), 64.0 (C-10), 57.0 (11-CH_2), 52.6 (C-12), 51.3 (C-8), 35.4 (C-1), 29.0 (C-9), 26.5 (10-CH_2), 20.3 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 2924 (w), 2800 (w), 1649 (s), 1564 (m), 1544 (s), 1424 (w), 1356 (m), 1140 (m), 996 (w), 912 (m), 801 (m), 734 (w) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{23}N_2O$ [*M* + H^+]: 271.18049; found: 271.17949.

1.4.3.2 (1*R*,9*R*,10*R*)-7,15-diazatetracyclo[7.7.1.$0^{2,7}$.$0^{10,15}$]heptadec-2,4,12-trien-6-one (S5)

A solution of diene **28** (130 mg, 481 µmol) in anhydr. CH_2Cl_2 (48 mL) was thoroughly degassed and treated with 2nd generation Grubbs' catalyst (20.5 mg, 24.1 µmol). After heating under reflux for 1 h, the solvent was removed in vacuum. Column chromatography (SiO_2, with a pad of Florisil® on top, CH_2Cl_2/MeOH 99:1 → 95:5) delivered alkene **S5** (116 mg, 479 µmol, 99%) as a brownish oil.

R_f = 0.31 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{25}$ = –100.8 (*c*=0.5 in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (m, 1H, 4-H), 6.41 (d, *J*=9.0 Hz, 1H, 5-H), 5.95 (*J*=6.9 Hz, 1H, 3-H), 5.74 (m, 1H, 12-H), 5.57 (m, 1H, 13-H), 4.02 (d, *J*=15.4 Hz, 1H, 8-*H*H), 3.93 (dd, *J*=15.4 Hz, 6.7 Hz, 1H, 8-H*H*), 3.45 (d, *J*=18.3 Hz, 1H, 14-*H*H), 3.15 (m, 2H, 10-H, 16-*H*H), 2.91 (s, 1H, 1-H), 2.67 (d, *J*=18.2 Hz, 1H, 14-H*H*), 2.45 (m, 2H, 11-*H*H, 16-H*H*), 2.20 (s, 1H, 9-H), 2.05 (d, *J*=13.2 Hz, 1H, 17-*H*H), 1.70 (m, 2H, 11-H*H*, 17-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7 (C-6), 152.2 (C-2), 138.7 (C-4), 125.3 (C-13), 124.1 (C-12), 116.7 (C-5), 104.6 (C-3), 58.3 (C-10), 54.3 (C-16), 53.2 (C-14), 51.5 (C-8), 35.9 (C-1), 31.4 (C-9), 21.5 (C-11), 21.0 (C-17) ppm; IR (ATR): $\tilde{\nu}$ = 2919 (w), 2838 (w), 1647 (s), 1562 (m), 1545 (s),

1356 (m), 1159 (m), 1143 (m), 1134 (m), 797 (m), 745 (s), 729 (s), 650 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{19}N_2O$ [*M* + H^+]: 243.14919; found: 243.14837.

1.4.3.3 Anagyrine (4)

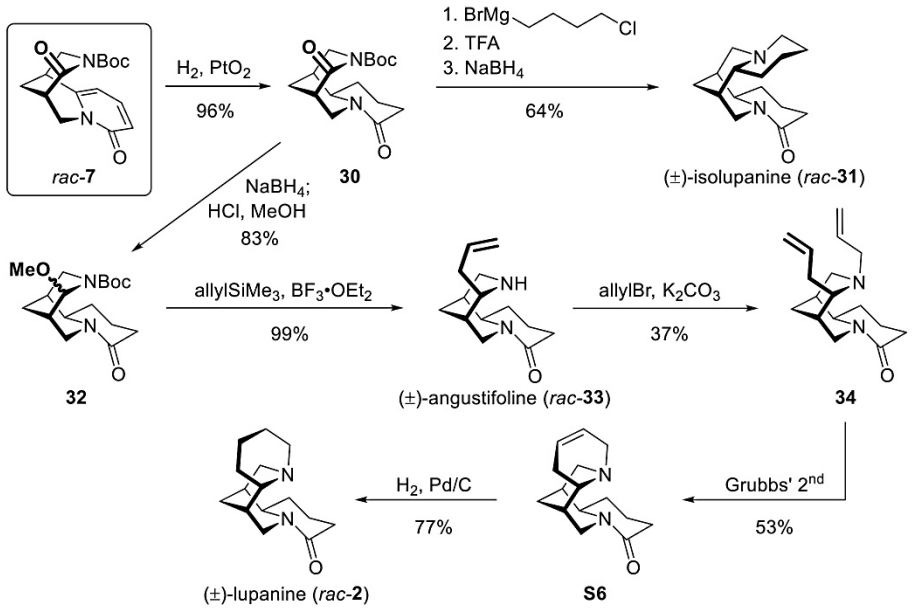
Alkene **S5** (80.9 mg, 334 µmol), dissolved in MeOH (4 mL), and Pd on carbon (10 wt% Pd; 35.5 mg, 33.4 µmol) were stirred under a H_2 atmosphere (1 atm.) at rt for 2.5 h. The reaction mixture was filtered through a pad of celite® and the filter cake was thoroughly washed with CH_2Cl_2/MeOH (80:20, 100 mL). Column chromatography (bas. Al_2O_3, act. I, CH_2Cl_2/MeOH 95:5) delivered anagyrine monohydrate (**4**·H_2O; 80.8 mg, 308 µmol, 92%) as a colorless oil.

R_f = 0.26 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{24}$ = –167.7 (*c*=0.5 in EtOH) [lit.[25] $[\alpha]_D$ = –166 (in EtOH, concentration not given)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (m, 1H, 4-H), 6.42 (d, *J*=9.0 Hz, 1H, 5-H), 5.95 (d, *J*=6.9 Hz, 1H, 3-H), 4.05 (d, *J*=15.4 Hz, 1H, 8-*H*H), 3.88 (dd, *J*=15.4 Hz, 6.7 Hz, 1H, 8-H*H*), 3.36 (dd, *J*=10.8 Hz, 2.5 Hz, 1H, 16-*H*H), 2.94 (s, 1H, 1-H), 2.87 (d, *J*=12.0 Hz, 1H, 10-H), 2.76-2.60 (m, 2H, 14-H_2), 2.44 (d, *J*=10.9 Hz, 1H, 16-H*H*), 2.14 (s, 1H, 9-H), 1.99 (d, *J*=12.8 Hz, 1H, 17-*H*H), 1.87 (d, *J*=10.6 Hz, 2H, 11-*H*H, 13-*H*H), 1.72 (br s, 2H, H_2O), 1.69-1.54 (m, 2H, 12-*H*H, 17-H*H*), 1.48 (m, 1H, 13-H*H*), 1.14 (d, *J*=13.0 Hz, 2H, 11-H*H*; 12-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7 (C-6), 152.1 (C-2), 138.8 (C-4), 116.7 (C-5), 104.6 (C-3), 63.2 (C-10), 54.5 (C-14), 53.0 (C-16), 51.6 (C-8), 35.6 (C-1), 32.7 (C-9), 25.7 (C-13), 22.6 (C-11), 20.9 (C-17), 19.2 (C-12) ppm; IR (ATR): $\tilde{\nu}$ = 3447 (br), 2925 (m), 2852 (w), 1645 (s), 1567 (m), 1543 (s), 1444 (w), 1355 (w), 1220 (w), 1139 (m), 796 (m), 728 (w) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{21}N_2O$ [*M* + H^+]: 245.16484; found: 245.16414.

The spectroscopic data are in accordance with those reported in literature.[25,26]

[25] S. Okuda, I. Murakoshi, H. Kamata, Y. Kashida, J. Haginiwa, K. Tsuda, *Chem. Pharm. Bull.* **1965**, *13*, 482-487.
[26] D. S. Rycroft, D. J. Robins, I. H. Sadler, *Magn. Reson. Chem.***1991**, *29*, 936-940.

1.5 Tri- and Tetracyclic Alkaloids Derived from Pyridone *rac*-7



Note: The racemic compound *rac*-**7** was prepared using the same sequence as for **7** (see par. 1.1 and 1.2), starting from *rac*-**S1**.[3]

1.5.1 Synthesis of (±)-Isolupanine (*rac*-31)

1.5.1.1 (1*SR*,2*RS*,9*SR*)-11-*tert*-Butoxycarbonyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane-6,10-dione (30)

Imide *rac*-**7** (60.0 mg, 197 µmol), dissolved in MeOH (1 mL), and Pt_2O (4.48 mg, 19.7 µmol) were stirred under an H_2 atmosphere (1 atm.) at rt for 2 h. The reaction mixture was filtered through a pad of celite® and the filter cake was thoroughly washed with CH_2Cl_2/MeOH (90:10, 15 mL). Evaporation of the solvent delivered imide **30** (58.6 mg, 190 µmol, 96%) as a white crystalline solid.

R_f = 0.31 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.88 (d, *J*=13.4 Hz, 1H, 8-*H*H), 3.91 (d, *J*=13.7 Hz, 1H, 12-*H*H), 3.52 (dd, *J*=13.7 Hz, 6.5 Hz, 1H, 12-H*H*), 3.44 (m, 1H, 2-H), 2.77 (s, 1H, 9-H), 2.73 (dd, *J*=13.5 Hz, 3.0 Hz, 1H, 8-H*H*), 2.43 (dm, *J*=16.9 Hz, 1H, 5-*H*H), 2.28 (m, 1H, 5-*H*H), 2.21 (dm, *J*=13.0 Hz, 1H, 13-*H*H), 2.07 (s, 1H, 1-H), 1.89 (m, 3H, 3-*H*H, 4-*H*H, 13-H*H*), 1.78 (m, 1H, 3-H*H*), 1.68 (m, 1H, 4-H*H*), 1.50 (s, 9H, ($C(CH_3)_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.8 (C-10), 170.5 (C-6), 152.8 (CO_2N), 83.4 ($C(CH_3)_3$), 59.8 (C-2), 45.7 (C-8), 45.4 (C-12), 40.1 (C-9), 33.0 (C-5), 32.2 (C-1), 28.9 (C-13), 28.1 ($C(CH_3)_3$), 27.6 (C-3), 19.9 (C-4) ppm.

1.5.1.2 (±)-Isolupanine (*rac*-31)

A solution of **30** (56.7 mg, 184 µmol) in anhydr. THF (2.5 mL) was cooled to −78 °C and 4-chlorobutylmagnesium bromide (0.55 M; 1.00 mL, 552 µmol, prepared according to 1.4.1.1) was added. After 1 h, sat. aq. NH_4Cl (3 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuum. Column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2) delivered a colorless oil, which solidified upon standing. The intermediate was dissolved in anhydr. CH_2Cl_2 (3 mL) at 0 °C, treated with TFA (155 µL, 2.03 mmol) and stirred for 20 h at rt. The solvent was removed under reduced pressure and the resulting oil was diluted two times with CH_2Cl_2 (5 mL) and evaporated again. After column chromatography [bas. Al_2O_3, act. V, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1], the intermediate was dissolved in MeOH (2.5 mL), treated at 0 °C with $NaBH_4$ (15.3 mg, 405 µmol) and stirred for 2 h. The solvent was removed and the residue was diluted two times with MeOH (5 mL) and evaporated again. Column chromatography [SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5] delivered (±)-isolupanine (*rac*-**31**, 29.2 mg, 118 µmol, 64%) as a colorless oil.

R_f = 0.30 (CH_2Cl_2/MeOH 90:10); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.91 (d, *J*=13.8 Hz, 1H, 8-*H*H), 3.48 (m, 1H, 2-H), 2.96 (d, *J*=11.6 Hz, 1H, 16-*H*H), 2.60 (dm, *J*=11.2 Hz, 1H, 14-*H*H), 2.54 (dd, *J*=13.7 Hz, 2.8 Hz, 1H, 8-H*H*), 2.38 (dm, *J*=17.0 Hz, 1H, 5-*H*H), 2.22 (m, 1H, 5-H*H*), 2.12 (dd, *J*=11.7 Hz, 2.4 Hz, 1H, 16-H*H*), 1.92 (dm, *J*=11.1 Hz, 1H, 10-H), 1.79 (m, 5H, 3-H_2, 4-*H*H, 17-H_2), 1.65 (m, 5H, 1-H, 4-H*H*, 11-*H*H, 12-*H*H, 14-H*H*), 1.56 (m, 1H, 9-H), 1.46 (m, 2H, 13-H_2), 1.32 (m, 1H, 11-H*H*), 1.18 (m, 1H, 12-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9 (C-6), 65.9 (C-10), 58.8 (C-2), 57.5 (C-14), 57.0 (C-16), 42.4 (C-8), 35.7 (C-17), 34.6 (C-1), 34.5 (C-9), 33.3 (C-5), 30.6 (C-11), 27.9 (C-3), 25.9 (C-13), 25.0 (C-12), 20.1 (C-4) ppm.

The spectroscopic data are in accordance with those reported in literature.[27]

1.5.2 Synthesis of (±)-Angustifoline (*rac*-33)

1.5.2.1 (1*SR*,2*RS*,9*SR*)-11-*tert*-Butoxycarbonyl-10-methoxy-7,11-diazatricyclo[7.3.1.0^{2,7}]-tridecane-6-one (32)

A solution of imide **30** (81.2 mg, 263 µmol) in MeOH (5 mL) was treated at 0°C with $NaBH_4$ (29.9 mg, 790 µmol) and stirred for 2.5 h at this temperature. Methanolic HCl (2.0 M; 1 mL) was added and the reaction mixture was allowed to reach rt over 4 h. Sat aq. $NaHCO_3$ (2.5 mL) was added and the solvent was removed in vacuum. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. Column chromatography (SiO_2, CH_2Cl_2/MeOH 97:3) delivered *N*,*O*-acetal **32** (70.9 mg, 219 µmol, 83%) as a colorless resin.

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[27] T. H. Al-Tel, S. S. Sabri, M. H. Abu Zarga, A. Pervin, Z. Shah, Atta-ur-Rahman, D. S. Rycroft, *Phytochemistry* **1991**, *30*, 2393-2395.

The ^{1}H and ^{13}C NMR spectra of **32** display two sets of signals. These probably result from the *N*-Boc rotamers of the *exo*-diastereomer, but the existence of the *endo*-diastereomer cannot be fully excluded.

R_f = 0.67 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (500 MHz, $CDCl_3$, 89:11 mixture of isomers): δ = 5.33 (s, 0.11H, 10-H), 5.16 (s, 0.89H, 10-H), 4.65 (m, 1H, 8-*H*H), 4.37 (d, *J*=13.8 Hz, 0.89H, 12-*H*H), 4.13 (d, *J*=13.9 Hz, 0.11H, 12-*H*H), 3.38 (dm, *J*=9.6 Hz, 1H, 2-H), 3.24 (s, 0.33H, OCH_3), 3.21 (s, 2.67H, OCH_3), 3.07 (dd, *J*=13.8 Hz, 2.5 Hz, 0.11H, 12-*H*H), 2.96 (dd, *J*=13.8 Hz, 1.6 Hz, 0.89H, 12-*H*H), 2.76 (m, 1H, 8-H*H*), 2.30 (m, 3H, 5-H_2, 13-*H*H), 2.13-1.97 (m, 2H, 3-*H*H, 9-H), 1.87 (m, 1H, 4-*H*H), 1.76 (m, 1H, 3-H*H*), 1.66-1.50 (m, 3H, 1-H, 4-H*H*, 13-H*H*), 1.44 (s, 0.99H, $C(CH_3)_3$), 1.41 (s, 8.01H, $C(CH_3)_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, mixture of isomers): δ = 169.9, 169.5 (C-6), 154.41, 154.36 (CO_2N), 85.7, 84.3 (C-10), 80.5, 80.0 ($C(CH_3)_3$), 59.7, 59.6 (C-2), 54.6, 54.1 (OCH_3), 44.1 (C-8), 39.8, 38.7 (C-12), 33.1, 33.0 (C-5), 32.7, 32.6 (C-1), 32.2, 32.0 (C-9), 28.5, 28.2 ($C(CH_3)_3$), 27.9 (C-3), 27.5, 27.1 (C-13), 20.31, 20.25 (C-4) ppm.

1.5.2.2 (±)-Angustifoline (*rac*-33)

Allyltrimethylsilane (88.2 µL, 555 µmol) and $BF_3{\cdot}Et_2O$ (35.1 µL, 277 µmol) were added at 0 °C to a solution of *N*,*O*-acetal **32** (30.0 mg, 92.5 µmol) in anhydr. CH_2Cl_2 (1.5 mL). After 17 h at rt, the crude mixture was filtered through a pad of basic alumina (act. V, pentane/$CHCl_3$ 100:0 → 0:100) and column chromatographed [SiO_2, $CHCl_3$/MeOH/NH_3 (aq., 25%) 98:1.8:0.2 → 95:4.5:0.5] to give (±)-angustifoline (*rac*-**33**; 21.5 mg, 91.7 µmol, 99%) as a colorless resin.

R_f = 0.46 (CH_2Cl_2/MeOH 90:10); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76 (m, 1H, 10-CH_2CH=CH_2), 5.06 (m, 2H, 10-CH_2CH=CH_2), 4.62 (d, *J*=13.6 Hz, 1H, 8-*H*H), 3.46 (m, 1H, 2-H), 3.00 (d, *J*=3.3 Hz, 2H, 12-H_2), 2.87 (m, 2H, 8-H*H*,10-H), 2.50-2.19 (m, 5H, 5-H_2, 10-CH_2, NH), 2.12 (dm, *J*=12.9 Hz, 1H, 13-*H*H), 1.89 (m, 1H, 4-*H*H), 1.83-1.61 (m, 4H, 3-H_2, 4-H*H*, 9-H), 1.58 (d, *J*=13.0 Hz, 1H, 13-H*H*), 1.53 (m, 1H, 1-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9 (C-6), 135.7 (10-CH_2CH=CH_2), 117.3 (10-CH_2CH=CH_2), 60.5 (C-2), 57.1 (C-10), 48.0 (C-8), 41.8 (C-12), 37.2 (10-CH_2), 33.2 (C-5), 32.5 (C-1), 30.8 (C-9), 28.0, 27.6 (C-3, C-13), 20.2 (C-4) ppm.

The spectroscopic data are in accordance with those reported in literature.[28]

[28] W. Wysocka, A. Przybył, T. Brukwicki, *Monatsh. Chem.* **1994**, *125*, 1267-1272.

1.5.3 Synthesis of (±)-Lupanine (*rac*-2)

1.5.3.1 (1*SR*,2*RS*,9*SR*,10*SR*)-10,11-Diallyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane-6-one (34)

A solution of (±)-angustifoline (*rac*-**33**; 21.5 mg, 91.7 µmol) in MeCN (1 mL) was treated with allyl bromide (16.0 µL, 185 µmol) and K_2CO_3 (38.4 mg, 278 µmol) at 0 °C. After 19 h, additional allyl bromide (16.0 µL, 185 µmol) was added and the reaction mixture was stirred for 4 h. Removal of the solvent in vacuum and column chromatography (SiO_2, CH_2Cl_2/MeOH 97:3) delivered diene **34** (9.2 mg, 33.5 µmol, 37%) as a colorless resin.

R_f = 0.55 (CH_2Cl_2/MeOH 90:10); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.67 (m, 2H, 10-CH_2CH=CH_2, 11-CH_2CH=CH_2), 5.15-4.95 (m, 4H, 10-CH_2CH=CH_2, 11-CH_2CH=CH_2), 4.66 (d, *J*=13.6 Hz, 1H, 8-*H*H), 3.44 (m, 1H, 2-H), 3.06 (dd, *J*=13.3 Hz, 5.3 Hz, 1H, 11-C*H*H), 2.96 (dm, *J*=8.5 Hz, 1H, 10-H), 2.83 (m, 3H, 8-H*H*, 12-*H*H, 11-CH*H*), 2.45 (m, 2H, 5-*H*H, 12-H*H*), 2.23 (m, 3H, 5-H*H*, 10-CH_2), 2.00 (dm, *J*=12.7 Hz, 1H, 13-*H*H), 1.85 (m, 2H, 4-*H*H, 9-H), 1.77-1.48 (m, 5H, 1-H, 3-H_2, 4-H*H*, 13-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (C-6), 137.3, 136.7 (10-CH_2CH=CH_2, 11-CH_2CH=CH_2), 116.8, 116.5 (10-CH_2CH=CH_2, 11-CH_2CH=CH_2), 63.2 (C-10), 59.6 (C-2), 57.8 (11-CH_2), 47.7 (C-8), 46.5 (C-12), 34.0 (C-1), 33.3 (C-5), 30.2 (C-9), 28.0, 27.8, 27.7 (C-3, C-13, 10-CH_2), 20.2 (C-4) ppm.

1.5.3.2 (1*SR*,2*RS*,9*SR*,10*SR*)-7,15-Diazatetracyclo[7.7.1.$0^{2,7}$.$0^{10,15}$]heptadec-12-en-6-one (S6)

A solution of diene **34** (9.2 mg, 33.5 µmol) in anhydr. CH_2Cl_2 (3.5 mL) was thoroughly degassed and treated with 2nd generation Grubbs' catalyst (1.4 mg, 1.68 µmol). After heating under reflux for 2 h, the solvent was removed in vacuum. Column chromatography (SiO_2, CH_2Cl_2/MeOH 95:5 → 90:10) delivered alkene **S6** (4.4 mg, 17.9 µmol, 53%) as a brownish resin.

R_f = 0.41 (CH_2Cl_2/MeOH 90:10); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.70 (m, 1H, 12-H), 5.62 (m, 1H, 13-H), 4.57 (dt, *J*=13.4 Hz, 2.2 Hz, 1H, 8-*H*H), 3.31 (m, 1H, 2-H), 3.20 (d, *J*=15.8 Hz, 1H, 14-*H*H), 3.04 (t, *J*=10.1 Hz, 1H, 16-*H*H), 2.76 (d, *J*=16.7 Hz, 1H, 14-H*H*), 2.59 (dd, *J*=13.4 Hz, 3.0 Hz, 1H, 8-H*H*), 2.47 (dm, *J*=17.2 Hz, 1H, 5-*H*H), 2.32 (m, 1H, 5-H*H*), 2.27-2.00 (m, 6H, 1-H, 10-H, 11-H_2, 16-H*H*, 17-*H*H), 1.82 (m, 2H, 3-*H*H, 4-*H*H), 1.70 (s, 1H, 9-H), 1.68-1.49 (m, 2H, 3-H*H*, 4-H*H*), 1.34 (d, *J*=12.6 Hz, 1H, 17-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3 (C-6), 125.2 (C-12), 124.8 (C-13), 61.0 (C-2), 59.2 (C-10), 54.4 (C-14), 51.7 (C-16), 46.9 (C-8), 34.4 (C-9), 33.3 (C-11), 33.0 (C-5), 32.1 (C-1), 27.5 (C-3), 25.8 (C-17), 19.6 (C-4) ppm.

1.5.3.3 (±)-Lupanine (*rac*-2)

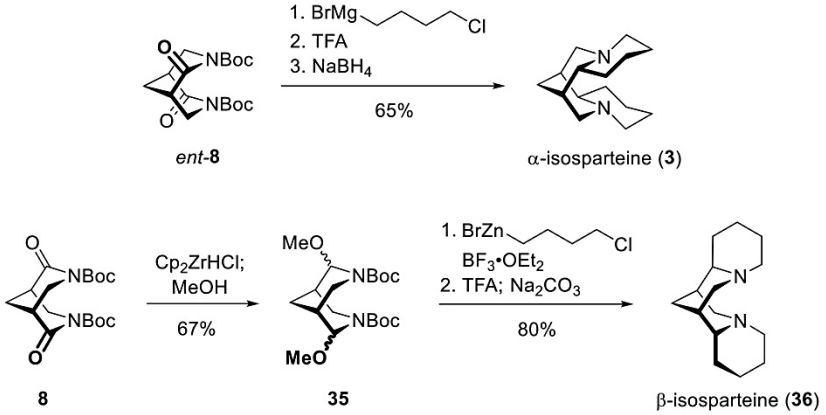
Alkene **S6** (4.0 mg, 16.3 µmol), dissolved in MeOH (0.2 mL), and Pd on carbon (10 wt% Pd; 1.7 mg, 1.63 µmol) were stirred under a H_2 atmosphere (1 atm.) at rt for 2.5 h. The reaction mixture was filtered through a pad of celite® and the filter cake was thoroughly washed with CH_2Cl_2/MeOH (90:10,

10 mL). Column chromatography (SiO_2, CH_2Cl_2/MeOH 90:10) delivered (±)-lupanine (*rac*-**2**; 3.1 mg, 12.5 µmol, 77%) as a brownish resin.

R_f = 0.29 (CH_2Cl_2/MeOH 90:10); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.50 (d, *J*=13.3 Hz, 1H, 8-*H*H), 3.29 (dd, *J*=10.6 Hz, 4.9 Hz, 1H, 2-H), 3.04-2.71 (m, 2H, 14-*H*H, 16-*H*H), 2.48 (m, 2H, 5-*H*H, 8-H*H*), 2.40-2.16 (m, 2H, 5-*H*H, 17-H*H*), 2.10 (m, 1H, 1-H), 1.97 (m, 2H, 14-H*H*, 16-H*H*), 1.88-1.36 (m, 11H, 3-H_2, 4-H_2, 9-H, 10-H, 11-H_2, 12-*H*H, 13-H_2), 1.28 (m, 2H, 12-H*H*, 17-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6 (C-6), 64.4 (C-10), 61.0 (C-2), 55.6 (C-14), 52.9 (C-16), 46.8 (C-8), 34.8 (C-9), 33.6 (C-11), 33.2 (C-5), 32.3 (C-1), 27.5 (C-3), 26.8 (C-17), 25.2 (C-13), 24.4 (C-12), 19.7 (C-4) ppm.

The spectroscopic data are in accordance with those reported in literature.[29,30]

1.6 C_2-Symmetric Isosparteines Derived from 2,6-Dioxobispidines *ent*-8 and 8



1.6.1 α-Isosparteine (3)

4-Chlorobutylmagnesium bromide (0.53 M; 6.38 mL, 3.38 mmol, prepared according to 1.4.1.1) was added at –78 °C to a solution of diimide *ent*-**8** (150 mg, 423 µmol) in anhydr. THF (5.5 mL). After 1.5 h, the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and the aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (15 mL), dried over Na_2SO_4 and the solvent was evaporated. The residue was dissolved in anhydr. CH_2Cl_2 (6.5 mL) and treated at 0 °C with TFA (486 µL, 6.35 mmol). After 19 h at rt, the solvent was removed under reduced pressure and the resulting oil was diluted four times with CH_2Cl_2 (10 mL) and evaporated again. After column chromatography [bas. Al_2O_3, act. V, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1], the intermediate was dissolved in MeOH (8 mL), treated with $NaBH_4$ (70.4 mg, 1.86 mmol) at 0 °C, and stirred for 17 h at rt. The mixture was heated to reflux for 1 h. The solvent was removed in vacuum and the residue was partitioned between Et_2O (10 mL) and aq. NaOH (6.0 M; 2 mL). The

[29] F. Bohlmann, R. Zeisberg, *Chem. Ber.* **1975**, *108*, 1043-1051.
[30] R. Kolanoś, W. Wysocka, T. Brukwicki, *Tetrahedron* **2003**, *59*, 5531-5537.

aqueous layer was extracted with Et_2O (4 × 10 mL) and the combined organic layers were dried over K_2CO_3. Evaporation of the solvent delivered a residue which was dissolved in CH_2Cl_2 (2.5 mL) and extracted with aq. HCl (4.0 M; 2 × 1.9 mL). The combined aqueous layers were basified (pH = 14) with aq. NaOH (12.5 M; 2 mL) and cooled to 4 °C overnight. The precipitate formed was isolated by centrifugation and washed with H_2O (2 × 15 mL). Drying under high vaccum delivered α-isosparteine partial hydrate[31] (**3**·0.9H_2O; 69.2 mg, 274 µmol, 65%) as an off-white solid.

R_f = 0.23 [$CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1]; m.p. 62-65 (DSC; lit.[32] 61-117 °C; lit.[33] 98-115 °C)[34]; $[\alpha]_D^{25}$ = –57.9 (*c*=0.5 in MeOH) [lit.[33] $[\alpha]_D^{30}$ = –55.8 (*c*=7.22 in MeOH)]; ^{1}H NMR (500 MHz, MeOD): δ = 4.89 (s, 1.8H, H_2O), 2.98 (d, *J*=11.7 Hz, 2H, 8-*H*H, 16-*H*H), 2.79 (d, *J*=7.2 Hz, 2H, 6-*H*H, 14-*H*H), 2.13 (dd, *J*=11.7 Hz, 2.6 Hz, 2H, 8-H*H*, 16-H*H*), 2.02 (d, *J*=11.4 Hz, 2H, 2-H, 10-H), 1.80 (m, 6H, 4-*H*H, 5-*H*H, 6-*H*H, 12-*H*H, 13-*H*H, 14-*H*H), 1.70 (s, 2H, 17-H_2), 1.63 (m, 2H, 3-*H*H, 11-*H*H), 1.53 (m, 4H, 1-H, 4-H*H* or 5-H*H*, 9-H, 12-H*H* or 13-H*H*), 1.36 (m, 4H, 3-H*H*, 4-H*H* or 5-H*H*, 11-H*H*, 12-H*H* or 13-H*H*) ppm; ^{13}C NMR (125 MHz, MeOD): δ = 68.0 (C-2, C-10), 58.7 (C-6, C-14), 57.4 (C-8, C-16), 37.3 (C-17), 36.8 (C-1, C-9), 31.2 (C-3, C-11), 25.9, 25.8 (C-4, C-5, C-12, C-13) ppm; IR (ATR): $\tilde{\nu}$ = 3379 (br), 2925 (s), 2854 (m), 2760 (w), 2736 (w), 1641 (w), 1443 (m), 1351 (m), 1291 (s), 1271 (m), 1104 (s), 1056 (s), 729 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{27}N_2$ [M + H^+]: 235.21688; found: 235.21640.

The spectroscopic data are in accordance with those reported in literature.[2,35]

1.6.2 Synthesis of β-Isosparteine (36)

1.6.2.1 (1*R*,5*R*)-2,6-Dimethoxy-3,7-diazabicyclo[3.3.1]nonane (35)

A solution of zirconocene hydrochloride (873 mg, 3.39 mmol) in anhydr. THF (6 mL) was treated at 0°C with a solution of diimide **8** (300 mg, 847 µmol) in anhydr. THF (6 mL) and stirred for 2 h at this temperature. Methanol (6 mL) was added and the reaction mixture was allowed to reach rt over 1.5 h. SiO_2 (0.9 g) was added and the solvent was removed in vacuum. Column chromatography (SiO_2, hexane/Et_2O/CH_2Cl_2 50:40:10 → 0:80:20) delivered di-*N*,*O*-acetal **35** (219 mg, 567 µmol, 67%) as a as a colorless oil.

The ^{1}H and ^{13}C NMR spectra of **35** display three sets of signals. These probably result from the *N*-Boc rotamers of the *exo*-diastereomer, but the existence of *endo*-diastereomers cannot be fully excluded.

R_f = 0.40 (hexane/Et_2O/CH_2Cl_2 50:40:10); $[\alpha]_D^{26}$ = +3.3 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, 53:27:20 mixture of isomers): δ = 5.33 (d, *J*=2.0 Hz, 0.54H, 2-H, 6-H), 5.31 (d, *J*=2.3 Hz, 0.20H, 2-

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[31] α-Isosparteine was isolated as a hydrate as described in ref.[2] because the free base tends to decompose.
[32] D. Kettelhack, M. Rink, K. Winterfeld, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1954**, *287*, 1-11.
[33] N. J. Leonard, R. E. Beyler, *J. Am. Chem. Soc.* **1950**, *72*, 1316-1323.
[34] The melting point strongly depends on the degree of hydration and the sample heating rate.[2,32,33]
[35] V. Galasso, F. Asaro, F. Berti, B. Kovač, I. Habuš, A. Sacchetti, *Chem. Phys.* **2003**, *294*, 155-169.

H, 6-H), 5.19 (d, *J*=2.4 Hz, 1.06 H, 2-H, 6-H), 5.14 (d, *J*=2.4 Hz, 0.20H, 2-H, 6-H), 3.96 (m, 1.26H, 4-*H*H, 8-*H*H), 3.88 (d, *J*=13.7 Hz, 0.54H, 4-*H*H, 8-*H*H), 3.81 (d, *J*=13.5 Hz, 0.20H, 4-*H*H, 8-*H*H), 3.26 (m, 6H, OCH_3), 3.22-3.07 (m, 2H, 4-H*H*, 8-H*H*), 2.02-1.86 (m, 4H, 1-H, 5-H, 9-H_2), 1.44 (m, 18H, $C(CH_3)_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, mixture of isomers): δ = 155.6, 155.5, 155.1, 154.9 (CO_2N), 85.8, 85.6, 84.6, 84.3 (C-2, C-6), 80.3, 80.2, 80.1, 79.9 ($C(CH_3)_3$), 55.2, 54.8, 54.7, 54.6 (OCH_3), 43.04, 43.02, 41.9, 41.5 (C-4, C-8), 31.61, 31.58, 31.5, 31.4 (C-1, C-5), 28.7, 28.6, 28.5, 28.4 ($C(CH_3)_3$), 19.4, 18.62, 18.61, 18.4 (C-9) ppm; IR (ATR): $\tilde{\nu}$ = 2974 (w), 2927 (w), 1684 (s), 1412 (s), 1239 (m),1159 (s), 1124 (s), 1073 (s), 994 (s), 916 (s), 767 (m), 675 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{34}N_2O_6Na$ [*M* + Na^+]: 409.23091; found: 409.23012.

1.6.2.2 β-Isosparteine (36)

4-Chlorobutylzinc bromide (0.5 M in THF; 5.93 mL, 2.97 mmol) and $BF_3{\cdot}Et_2O$ (376 µL, 2.97 mmol) were added at 0 °C to a solution of di-*N*,*O*-acetal **35** (191 mg, 494 µmol) in anhydr. THF (2.5 mL) and the reaction mixture was allowed to reach rt over 2 h. Sat. aq. $NaHCO_3$ (18 mL) was added and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in anhydr. CH_2Cl_2 (13 mL) and treated at 0 °C with TFA (567 µL, 7.41 mmol). After 17 h at rt, the mixture was diluted with anhydr. CH_2Cl_2 (13 mL). K_2CO_3 (1.37 g, 9.88 mmol) and MeOH (4.5 mL) were added. After 25 h, H_2O (15 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was partitioned between Et_2O (30 mL) and aq. HCl (3.0 M; 18 mL), and the aqueous layer was washed with Et_2O (2 × 30 mL). The aqueous layer was basified (pH = 10) with aq. NaOH (6.0 M; 16 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum, providing β-isosparteine (**36**; 92.2 mg, 393 µmol, 80%) as a yellowish oil.

R_f = 0.23 [$CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1]; $[\alpha]_D^{26}$ = –17.2 (*c*=1.0 in EtOH) [lit.[36] $[\alpha]_D^{32}$ = –15.3 (*c*=2.3 in EtOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.97 (dd, *J*=10.8 Hz, 6.7 Hz, 2H, 8-*H*H, 16-*H*H), 2.75 (dm, *J*=12.7 Hz, 2H, 6-*H*H, 14-*H*H), 2.40 (td, *J*=12.7 Hz, 2.6 Hz, 2H, 6-H*H*, 14-H*H*), 2.21 (dm, *J*=11.8 Hz, 2H, 2-H, 10-H), 2.12 (dd, *J*=10.9 Hz, 2.8 Hz, 2H, 8-H*H*, 16-H*H*), 1.73 (m, 2H, 4-*H*H or 5-*H*H, 12-*H*H or 13-*H*H), 1.62 (m, 2H, 1-H, 9-H), 1.54 (m, 4H, 3-*H*H, 4-*H*H or 5-*H*H, 11-*H*H, 12-*H*H or 13-*H*H), 1.46 (t, *J*=3.3 Hz, 2H, 17-H_2), 1.32 (m, 4H, 4-H*H*, 5-H*H*, 12-H*H*, 13-H*H*), 1.20 (d, *J*=12.6 Hz, 2H, 3-H*H*, 11-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 62.8 (C-2, C-10), 55.1 (C-6, C-14), 55.0 (C-8, C-16), 34.4 (C-1, C-9), 28.7 (C-3, C-11), 25.5, 22.7 (C-4, C-5, C-12, C-13), 19.8 (C-17) ppm; IR (ATR): $\tilde{\nu}$ = 2927 (s), 2853 (m), 1652 (br m), 1444 (m), 1301 (m), 1222 (w), 1129 (m), 1107 (m), 729 (s), 568 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{27}N_2$ [*M* + H^+]: 235.21688; found: 235.21644.

The spectroscopic data are in accordance with those reported in literature.[37,38]

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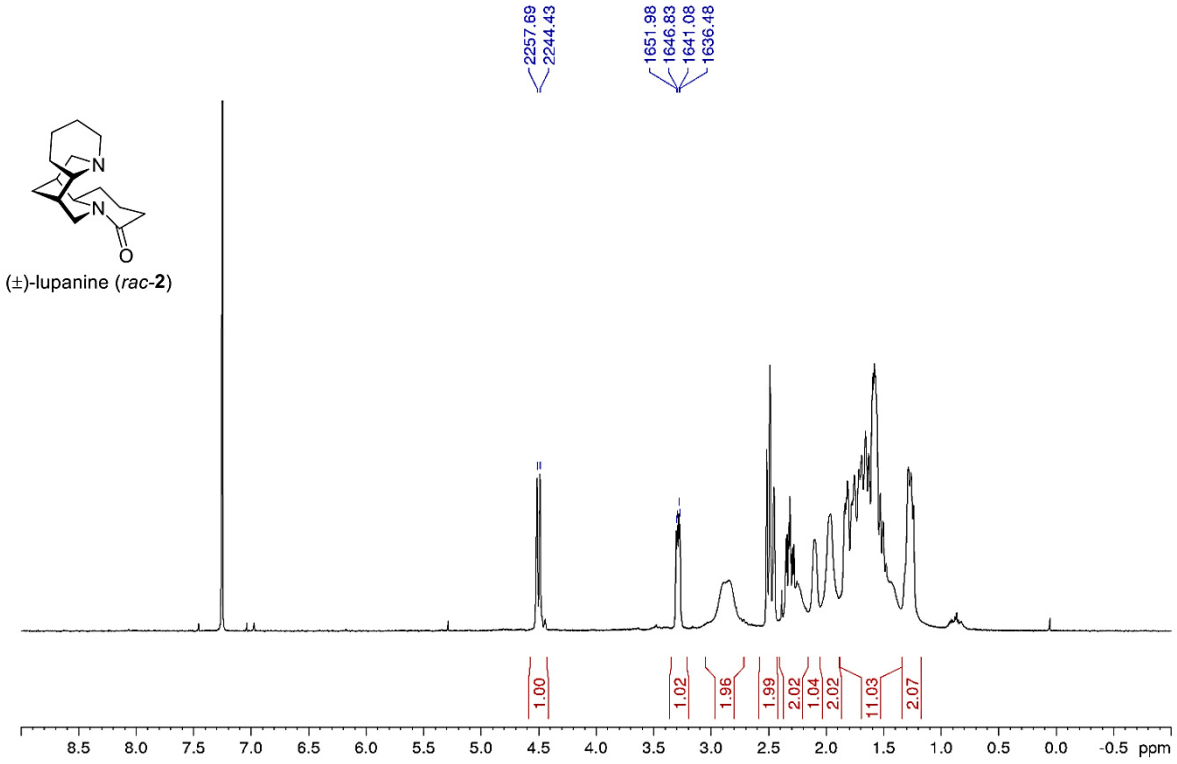
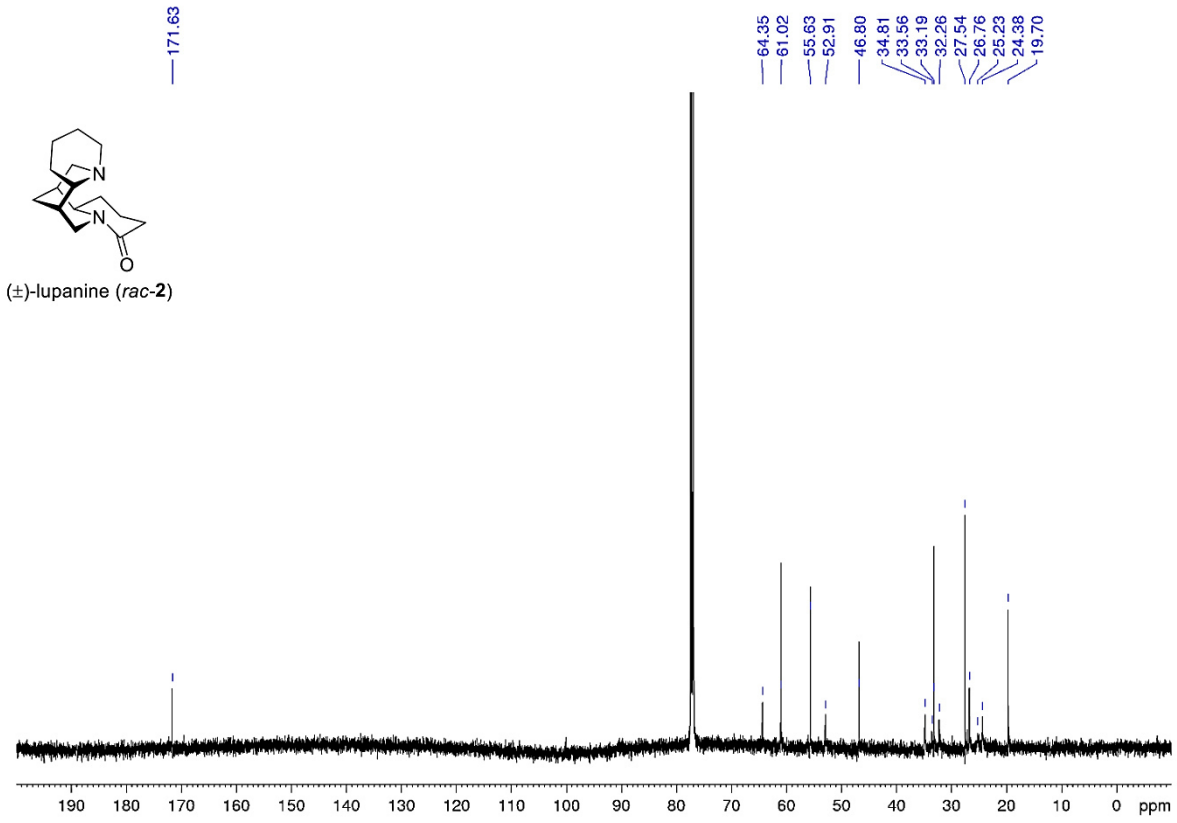
[36] R. Greenhalgh, L. Marion, *Can. J. Chem* **1956**, *34*, 456-458.
[37] P. R. Blakemore, N. R. Norcross, S. L. Warriner, P. C. Astles, *Heterocycles* **2006**, *70*, 609-617.
[38] F. M. Al-Saffar, R. C. D. Brown, *Org. Lett.* **2017**, *19*, 3502-3504.

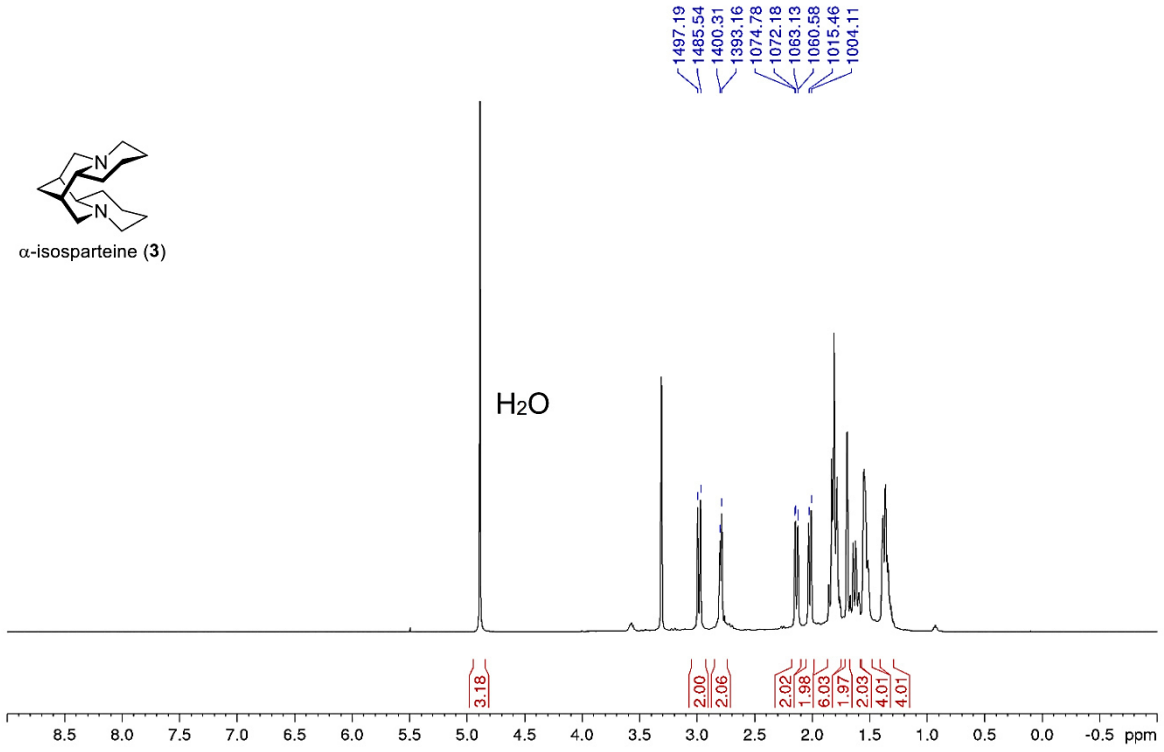
2. Copies of ^{1}H and ^{13}C NMR Spectra

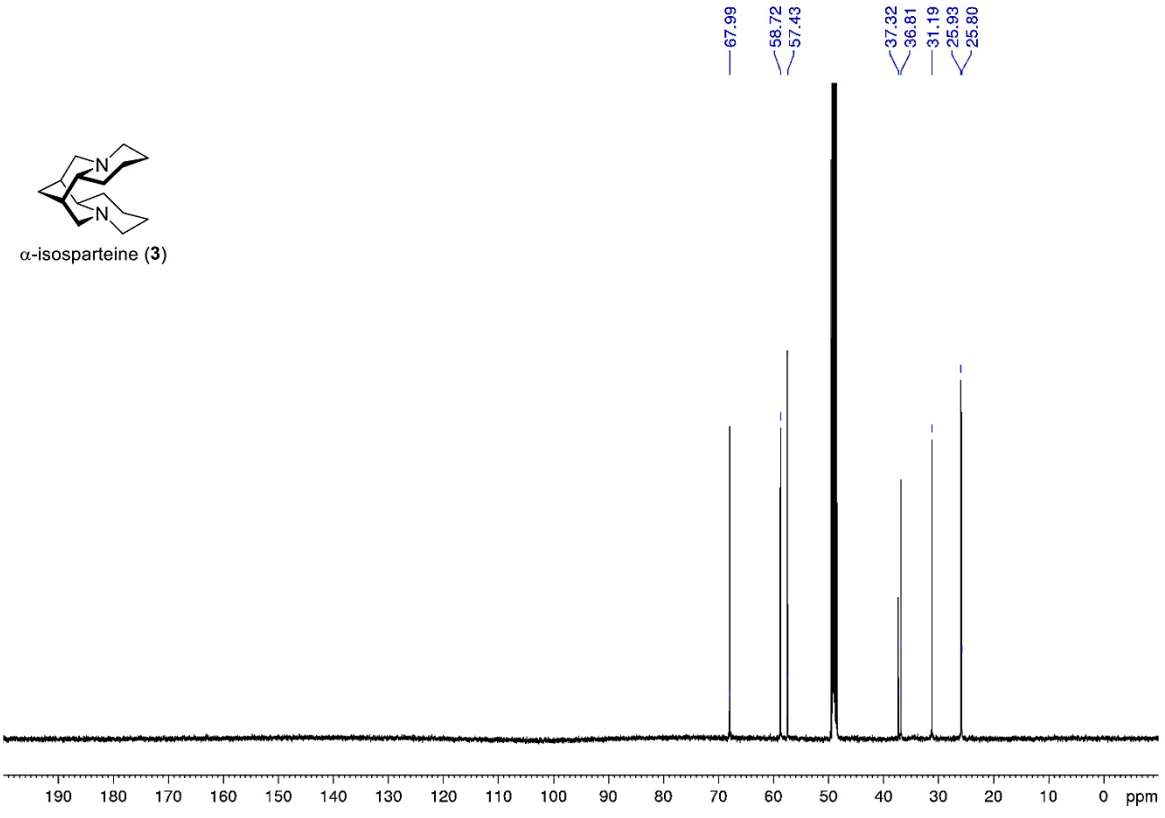
The ^{1}H and ^{13}C NMR spectra of all new compounds are listed in numerical order.



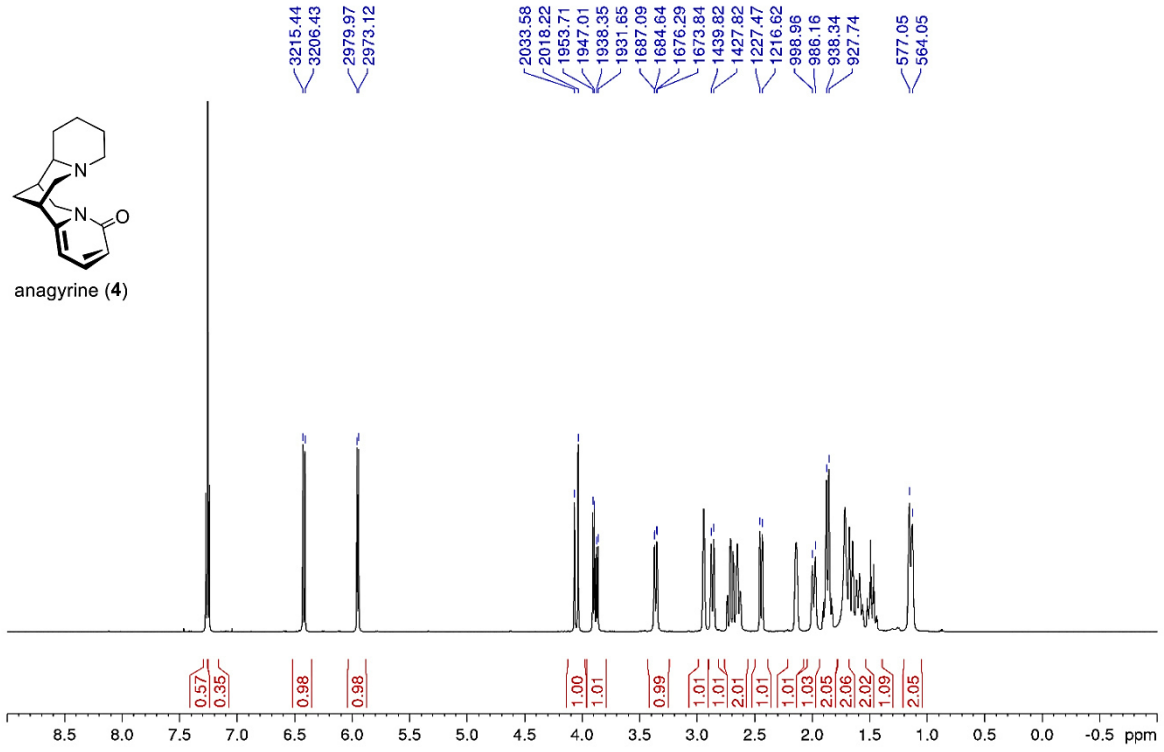


27


1497.19
1485.54
1400.31
1393.16
1074.78
1072.18
1063.13
1060.58
1015.46
1004.11
α-isosparteine (3)
H2O
3.18
2.00
2.06
2.02
1.98
6.03
1.97
2.03
4.01
4.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm


67.99
58.72
57.43
37.32
36.81
31.19
25.93
25.80
α-isosparteine (3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

28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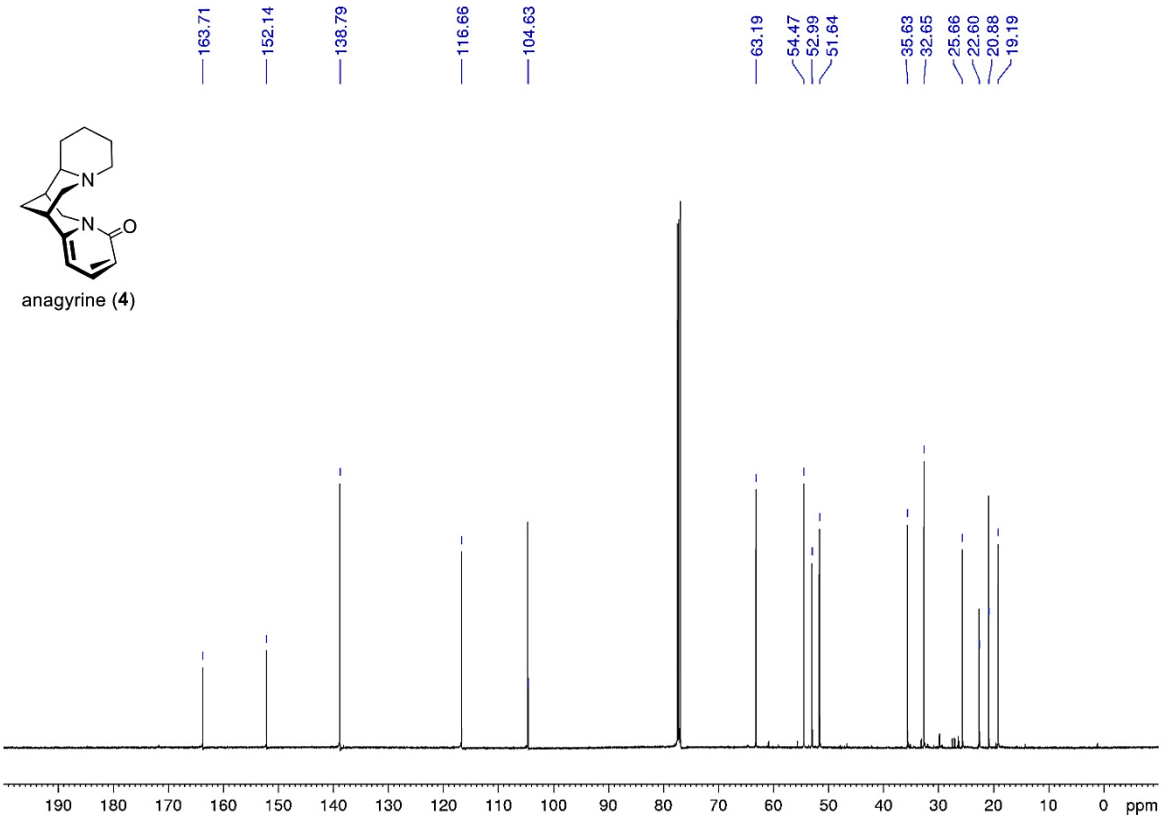
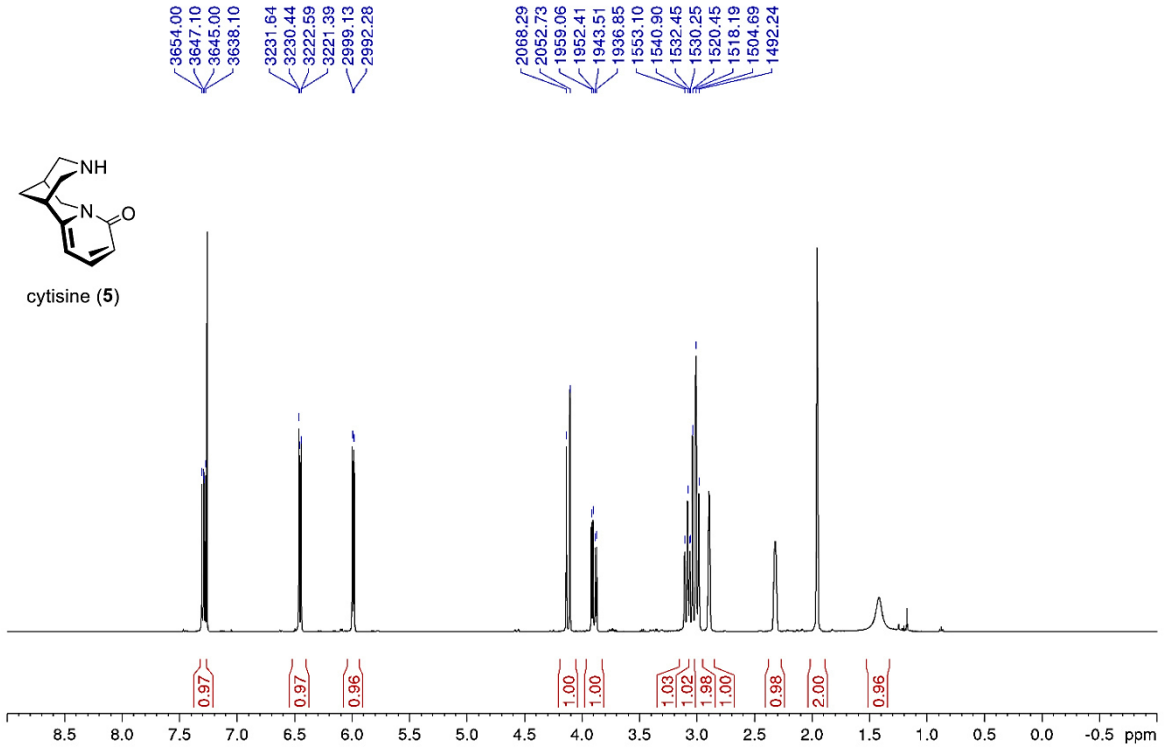
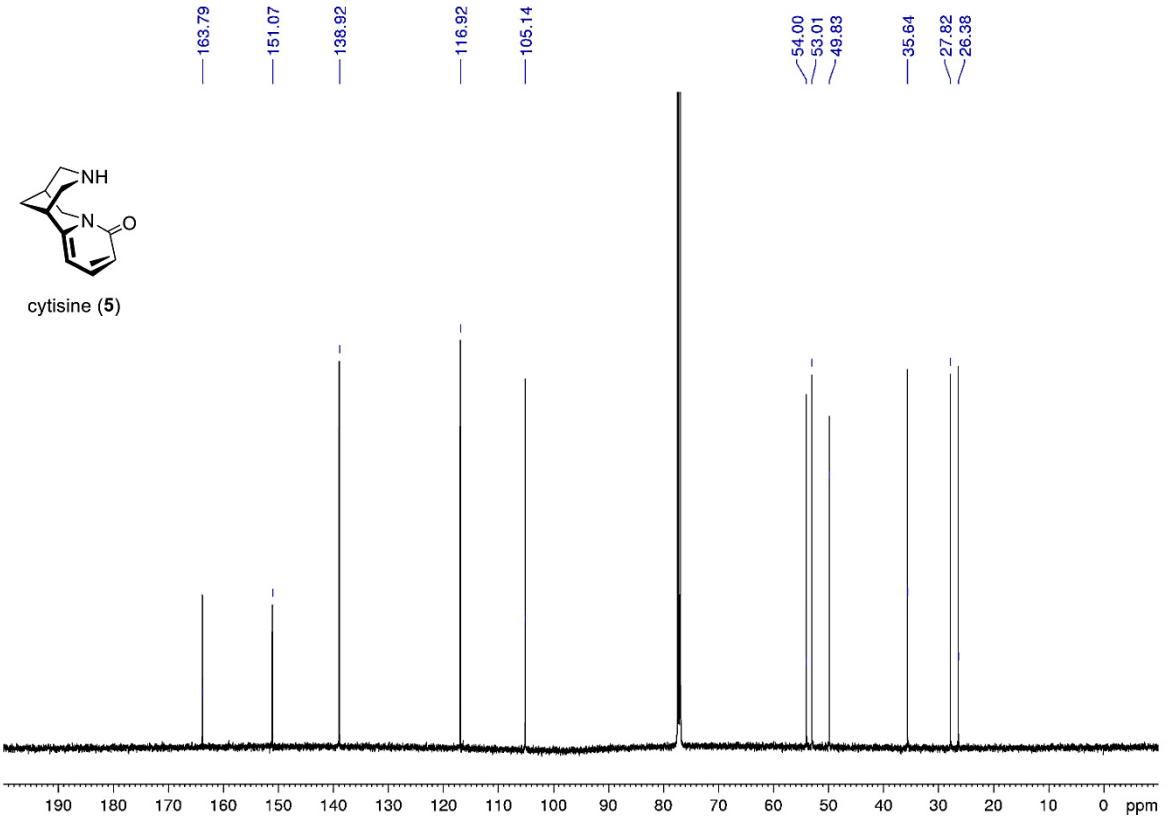
3206.43
2979.97
2973.12
2033.58
2018.22
1953.71
1947.01
1938.35
1931.65
1687.09
1684.64
1676.29
1673.84
1439.82
1427.82
1227.47
1216.62
998.96
986.16
938.34
927.74
577.05
564.05
anagyrine (4)
0.57
0.35
0.98
0.98
1.00
1.01
0.99
1.01
1.01
2.01
1.01
1.01
1.03
2.05
2.06
2.02
1.09
2.05
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

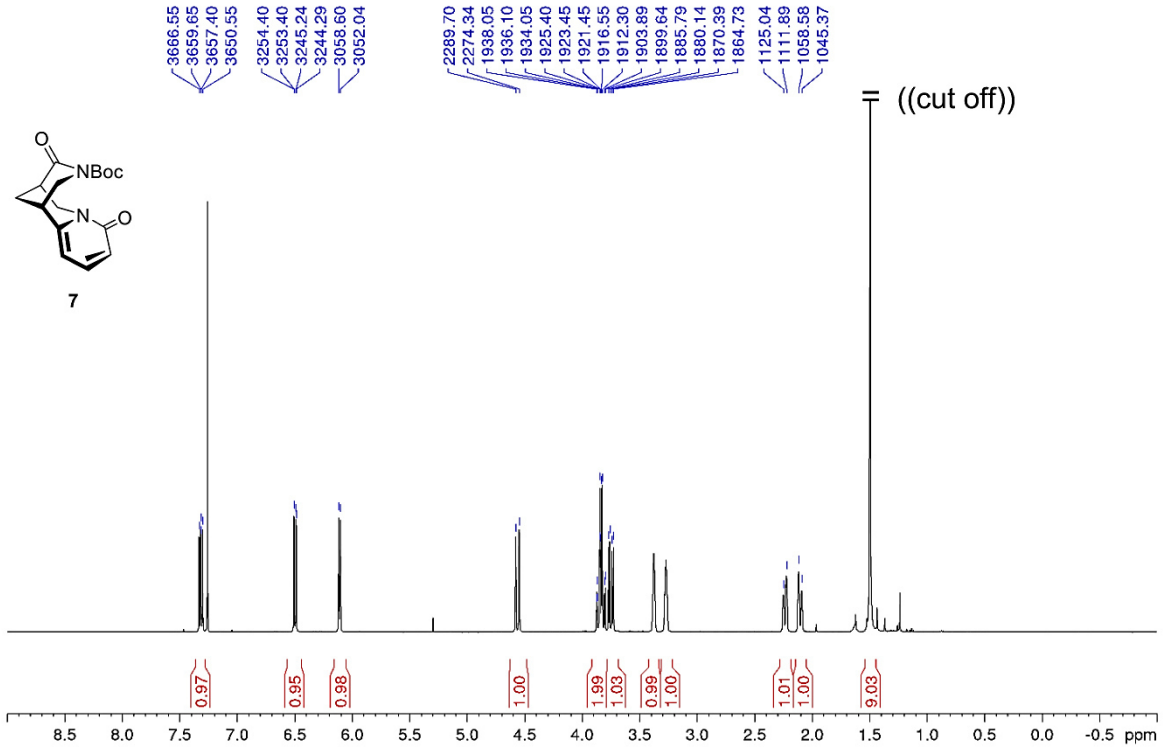

163.71
152.14
138.79
116.66
104.63
63.19
54.47
52.99
51.64
35.63
32.65
25.66
22.60
20.88
19.19
anagyrine (4)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

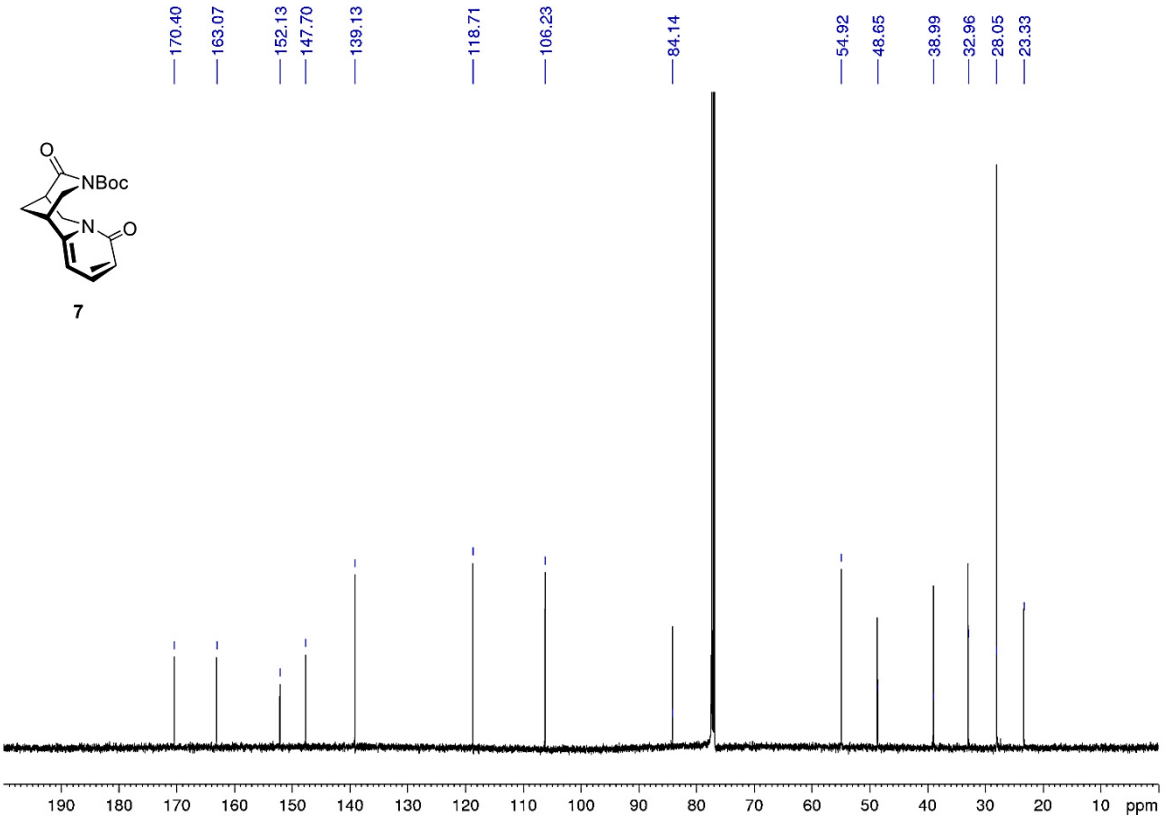
29


3654.00
3647.10
3645.00
3638.10
3231.64
3230.44
3222.59
3221.39
2999.13
2992.28
2068.29
2052.73
1959.06
1952.41
1943.51
1936.85
1553.10
1540.90
1532.45
1530.25
1520.45
1518.19
1504.69
1492.24
NH
N
O
cytisine (5)
0.97
0.97
0.96
1.00
1.00
1.03
1.02
1.98
1.00
0.98
2.00
0.96
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

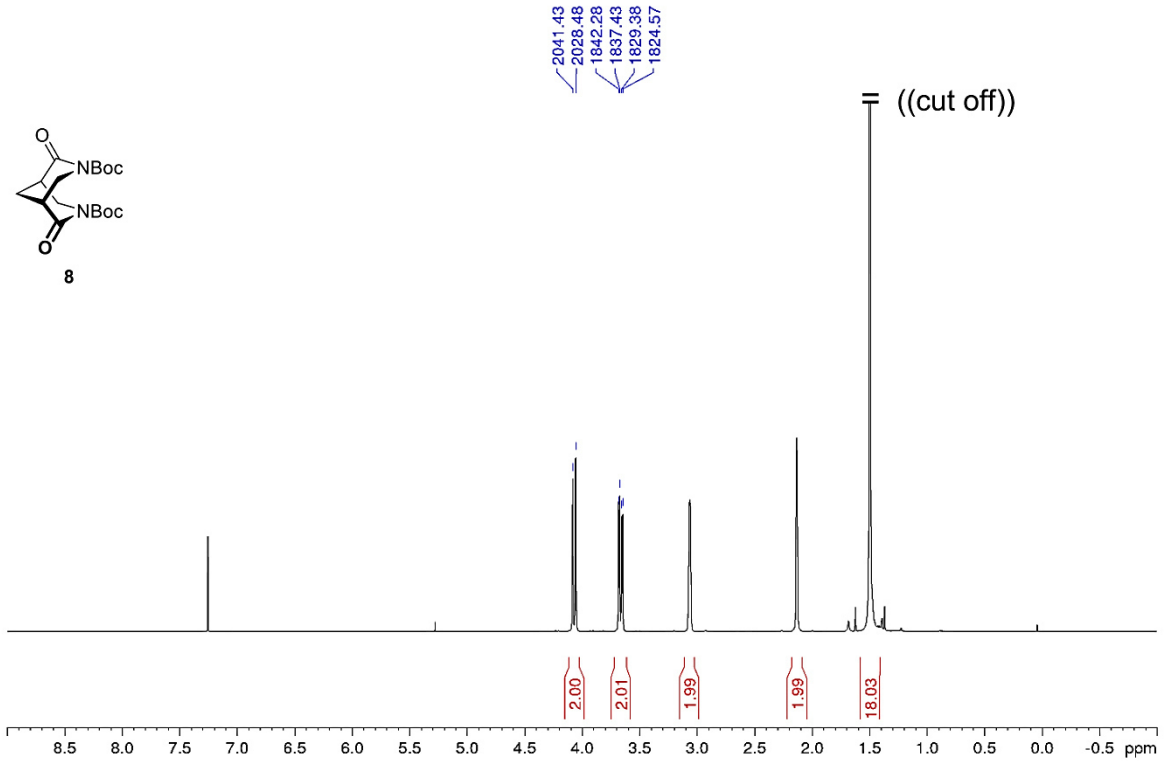

163.79
151.07
138.92
116.92
105.14
54.00
53.01
49.83
35.64
27.82
26.38
NH
N
O
cytisine (5)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

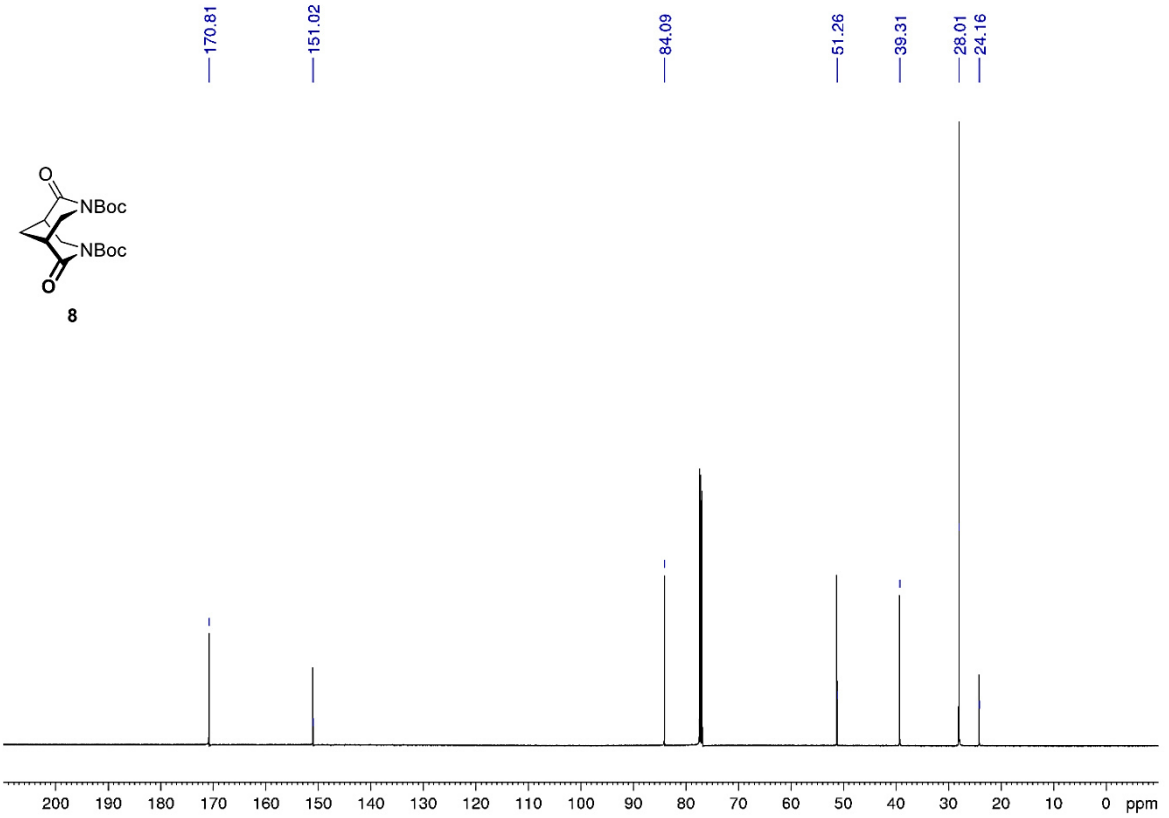
30


3666.55
3659.65
3657.40
3650.55
3254.40
3253.40
3245.24
3244.29
3058.60
3052.04
2289.70
2274.34
1938.05
1936.10
1934.05
1925.40
1923.45
1921.45
1916.55
1912.30
1903.89
1899.64
1885.79
1880.14
1870.39
1864.73
1125.04
1111.89
1058.58
1045.37
= ((cut off))
NBoc
N
O
7
0.97
0.95
0.98
1.00
1.99
1.03
0.99
1.00
1.01
1.00
9.03
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

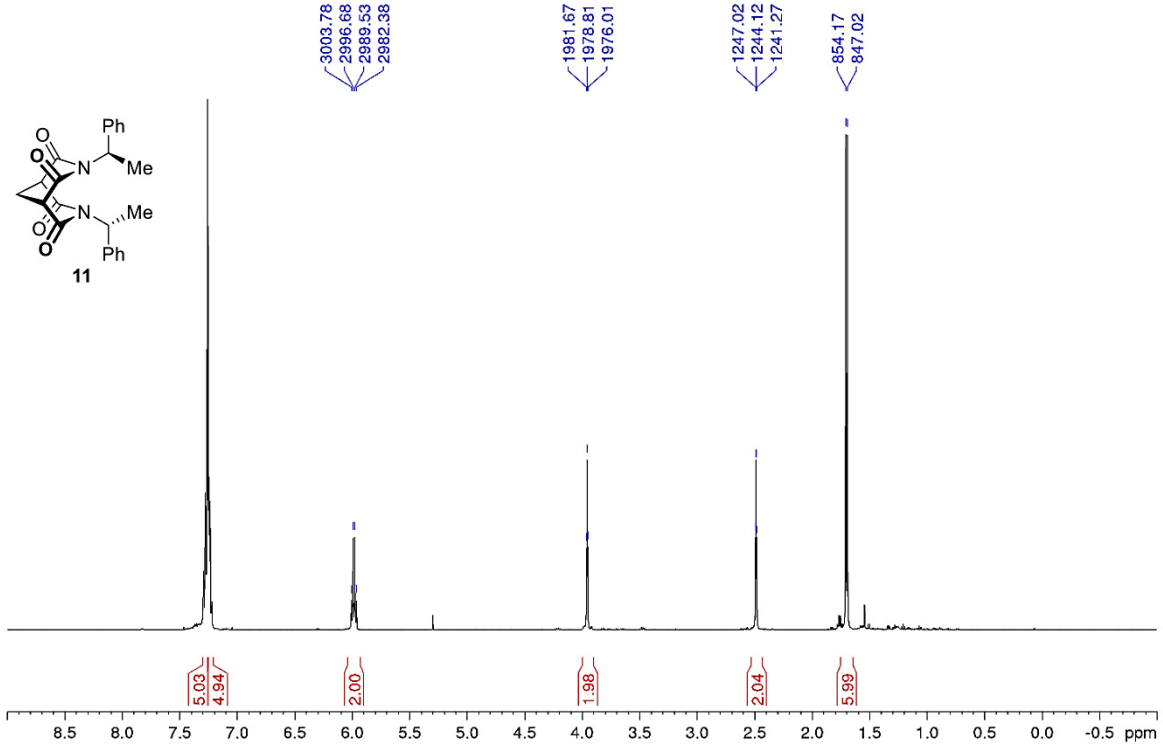

170.40
163.07
152.13
147.70
139.13
118.71
106.23
84.14
54.92
48.65
38.99
32.96
28.05
23.33
NBoc
N
O
7
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

31


2041.43
2028.48
1842.28
1837.43
1829.38
1824.57
= ((cut off))
NBoc
NBoc
O
O
8
2.00
2.01
1.99
1.99
18.03
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm


170.81
151.02
84.09
51.26
39.31
28.01
24.16
NBoc
NBoc
O
O
8
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

32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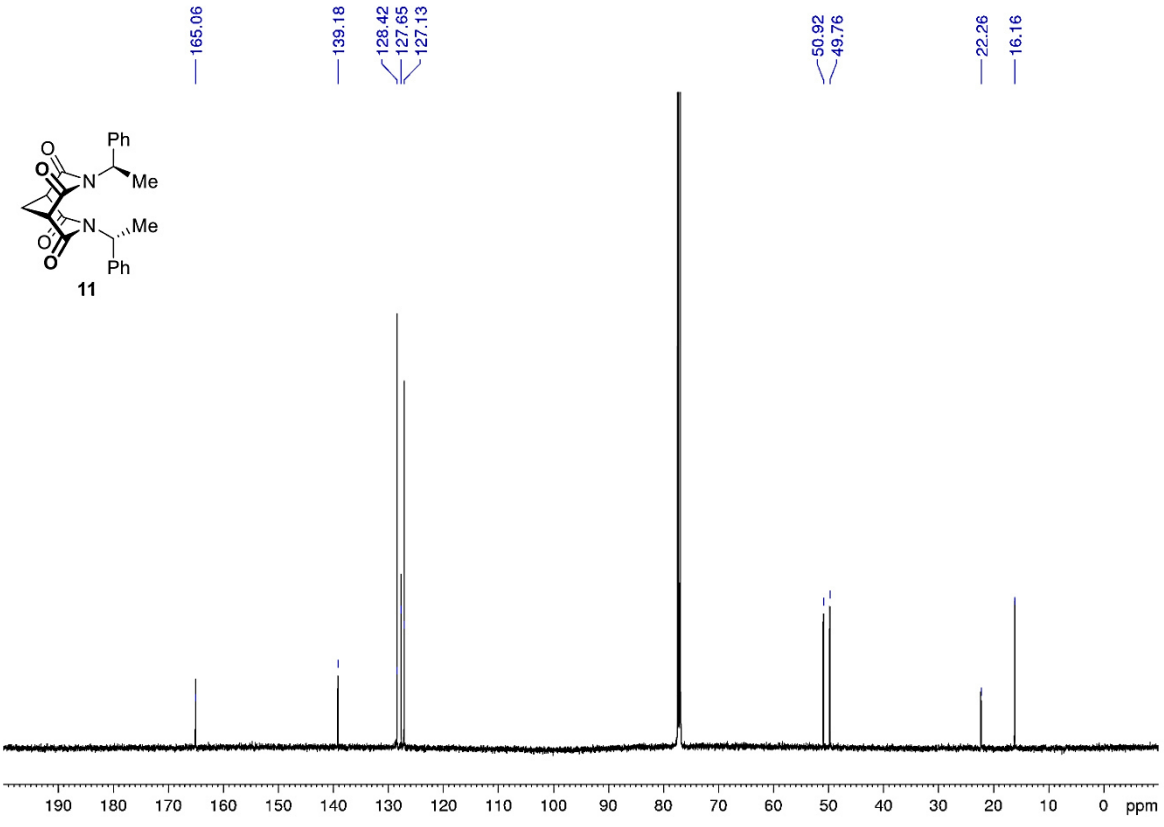
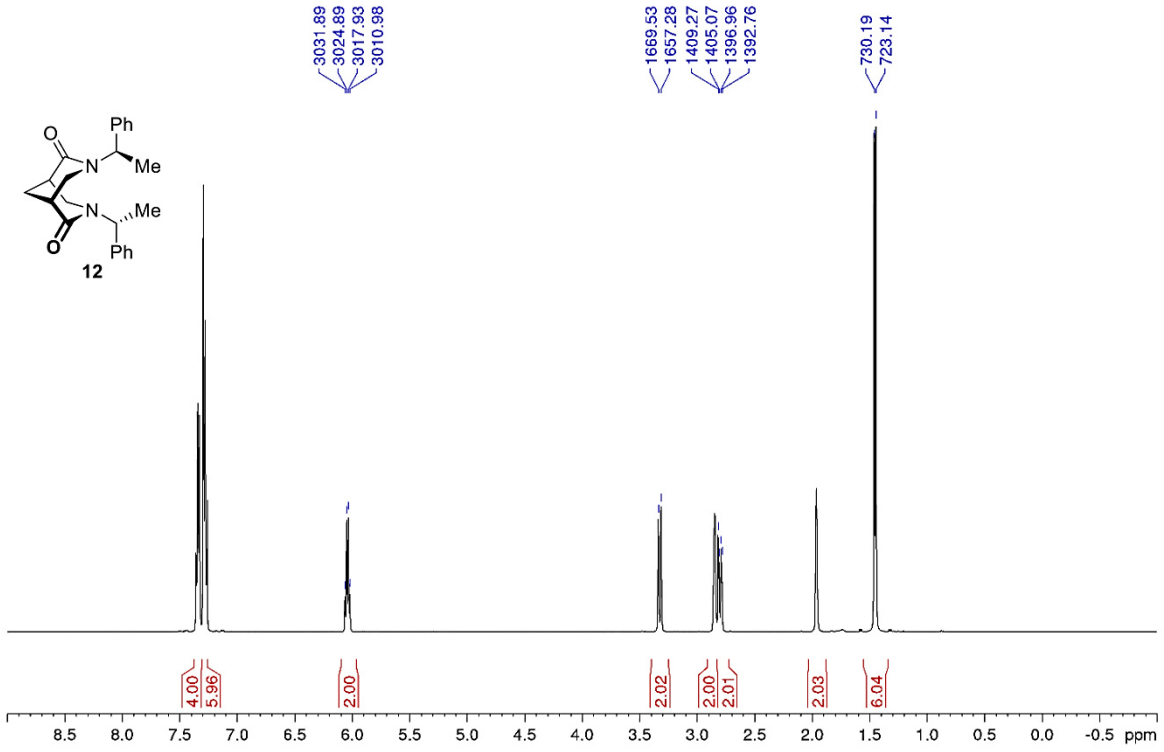
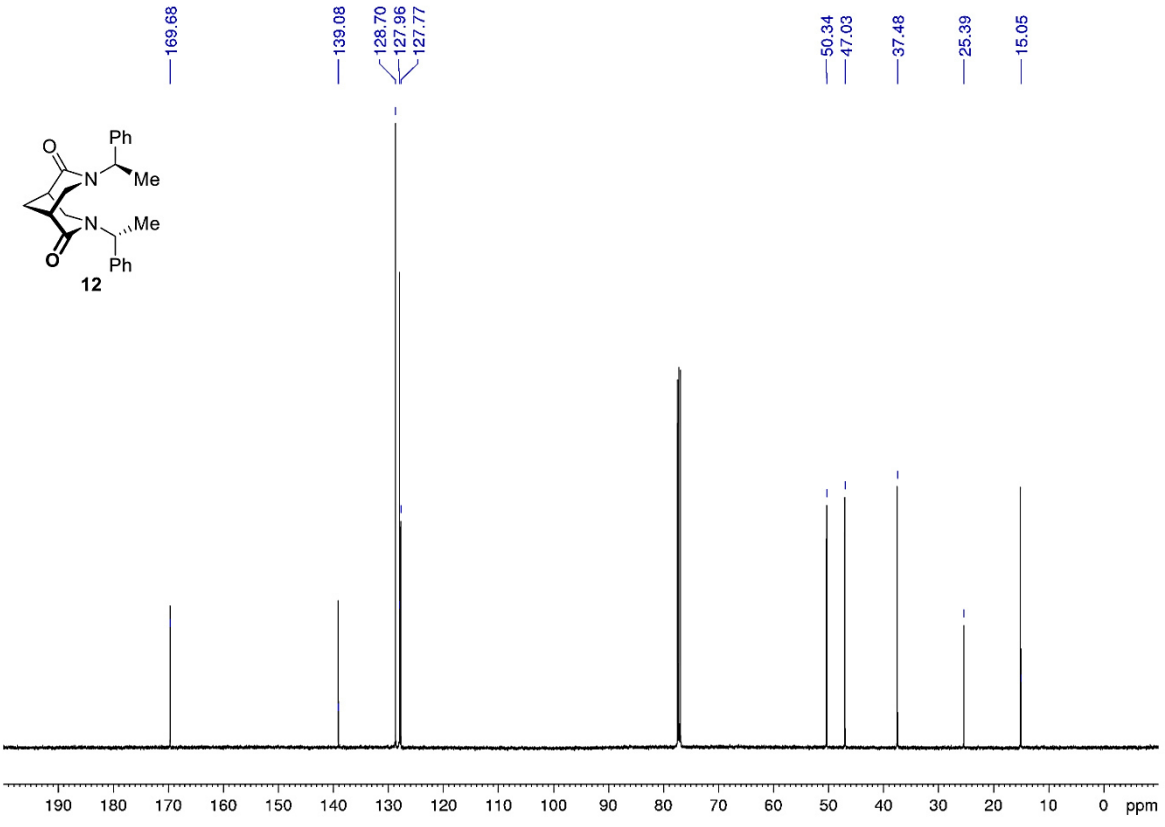
2996.68
2989.53
2982.38
1981.67
1978.81
1976.01
1247.02
1244.12
1241.27
854.17
847.02
Ph
N
Me
O
Me
N
Ph
11
5.03
4.94
2.00
1.98
2.04
5.99
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

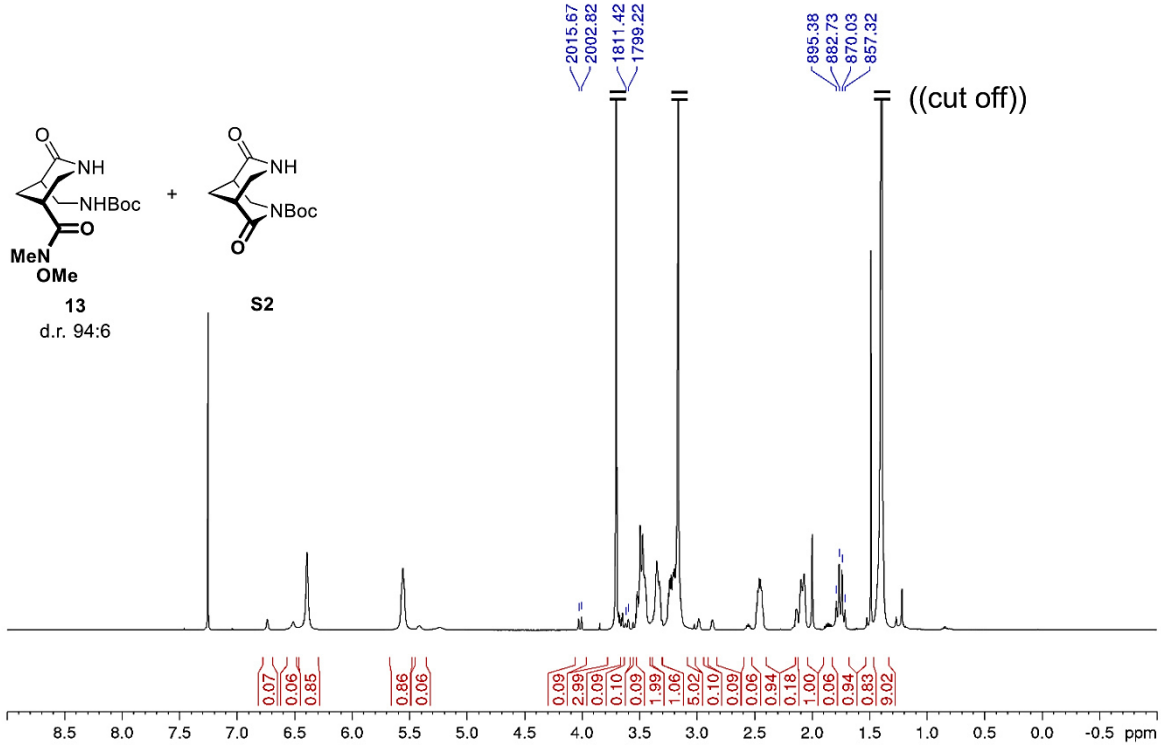

165.06
139.18
128.42
127.65
127.13
50.92
49.76
22.26
16.16
Ph
N
Me
O
Me
N
Ph
11
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

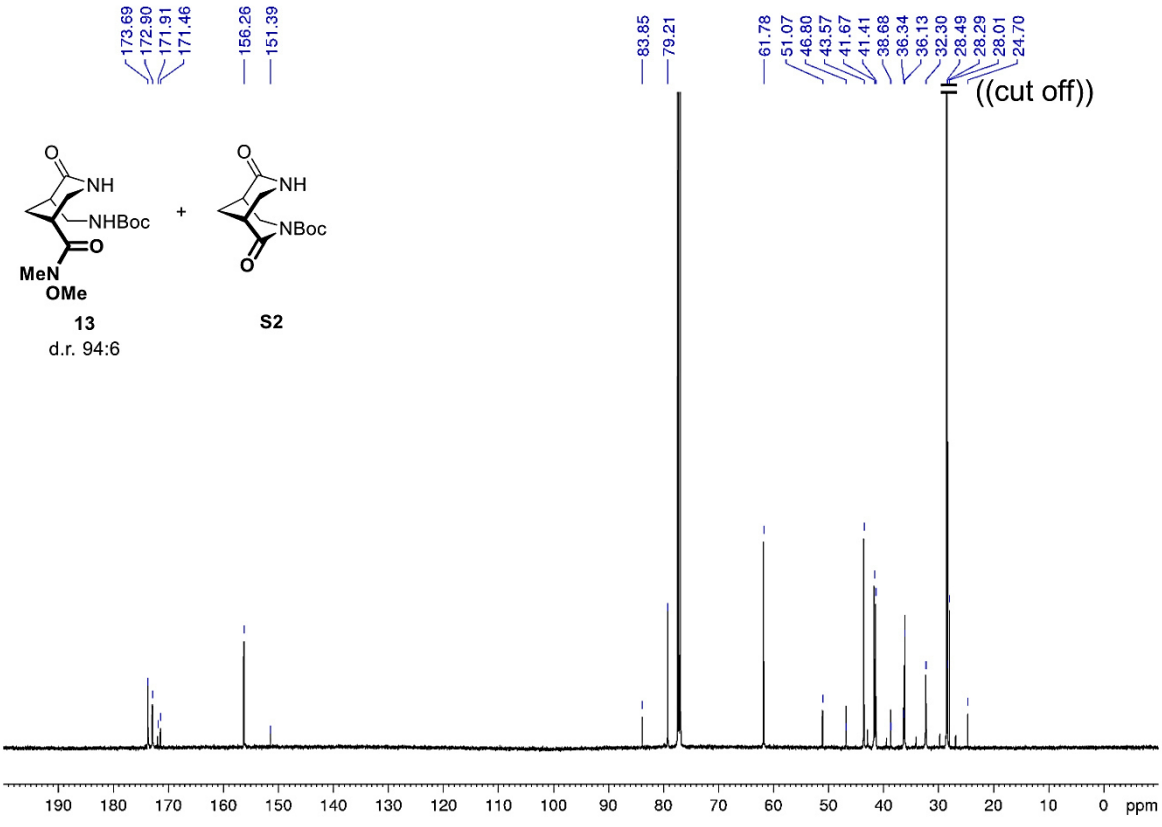
33


3031.89
3024.89
3017.93
3010.98
1669.53
1657.28
1409.27
1405.07
1396.96
1392.76
730.19
723.14
Ph
Me
N
Me
N
Ph
O
O
12
4.00
5.96
2.00
2.02
2.00
2.01
2.03
6.04
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

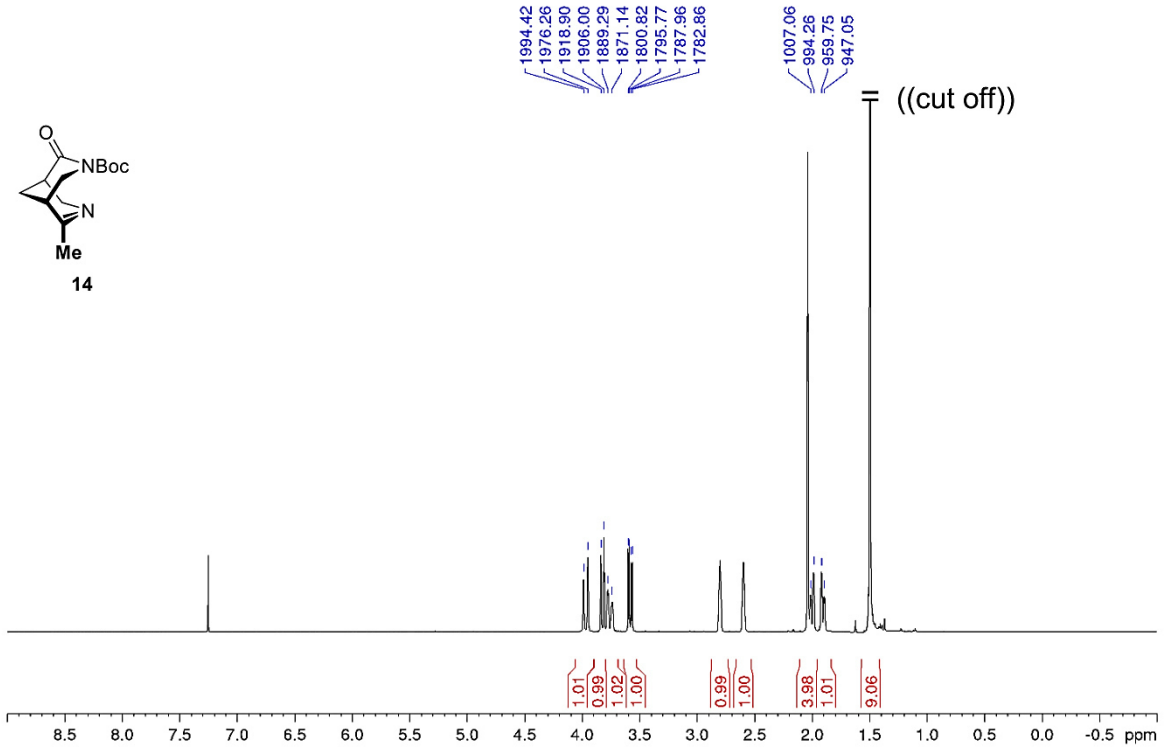

169.68
139.08
128.70
127.96
127.77
50.34
47.03
37.48
25.39
15.05
Ph
Me
N
Me
N
Ph
O
O
12
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

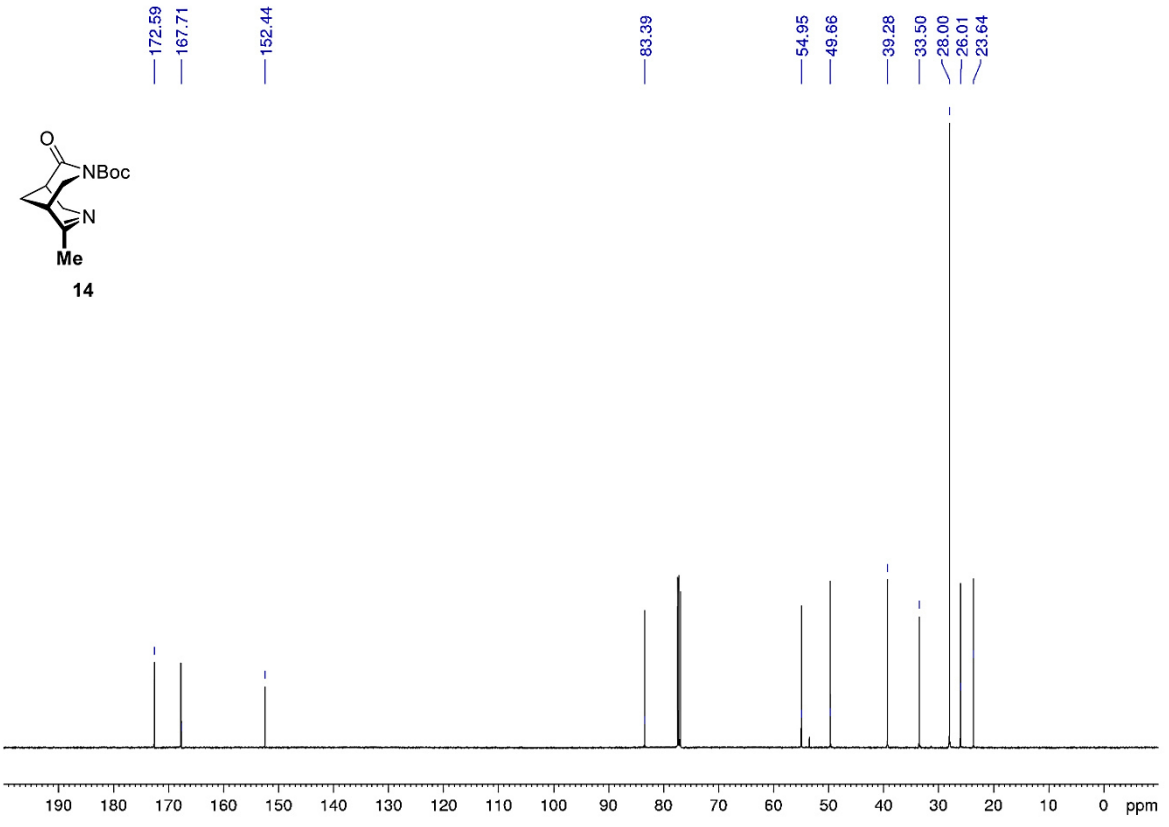
34


2015.67
2002.82
1811.42
1799.22
895.38
882.73
870.03
857.32
((cut off))
NH
NHBoc
O
MeN
OMe
13
d.r. 94:6
+
NH
NBoc
O
S2
0.07
0.06
0.85
0.86
0.06
0.09
2.99
0.09
0.10
0.09
1.99
1.06
5.02
0.10
0.09
0.06
0.94
0.18
1.00
0.06
0.94
0.83
9.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

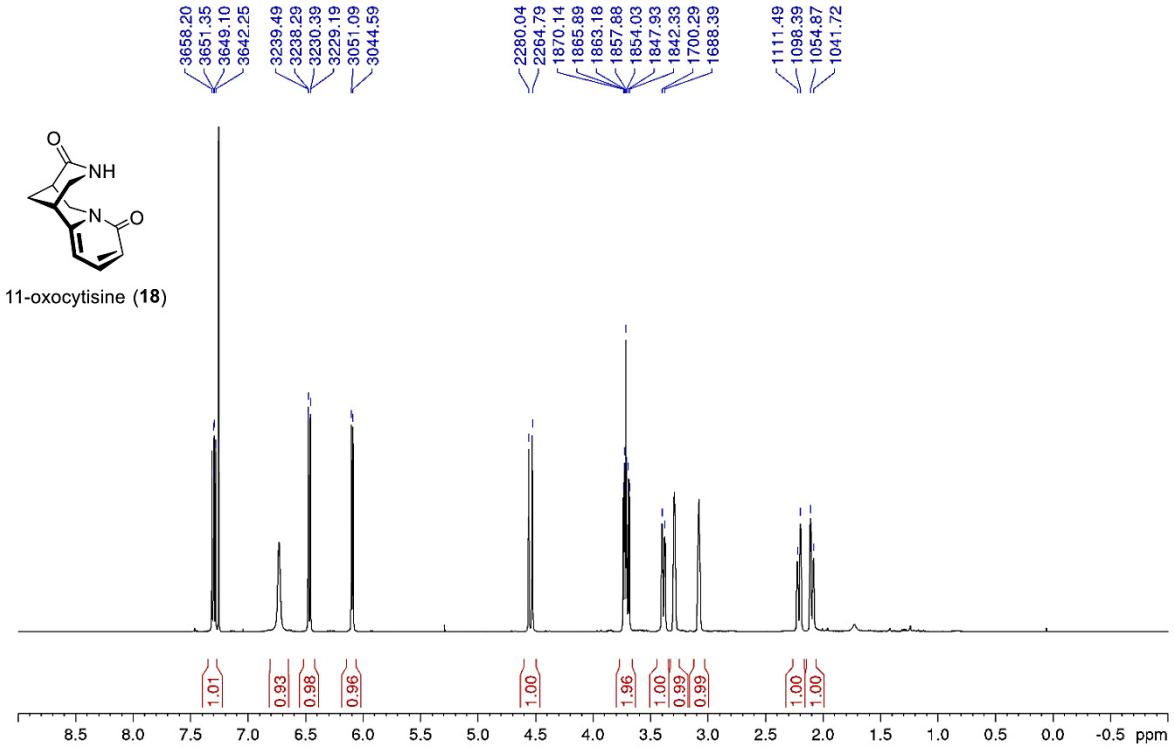

173.69
172.90
171.91
171.46
156.26
151.39
83.85
79.21
61.78
51.07
46.80
43.57
41.67
41.41
38.68
36.34
36.13
32.30
28.49
28.29
28.01
24.70
((cut off))
NH
NHBoc
O
MeN
OMe
13
d.r. 94:6
+
NH
NBoc
O
S2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

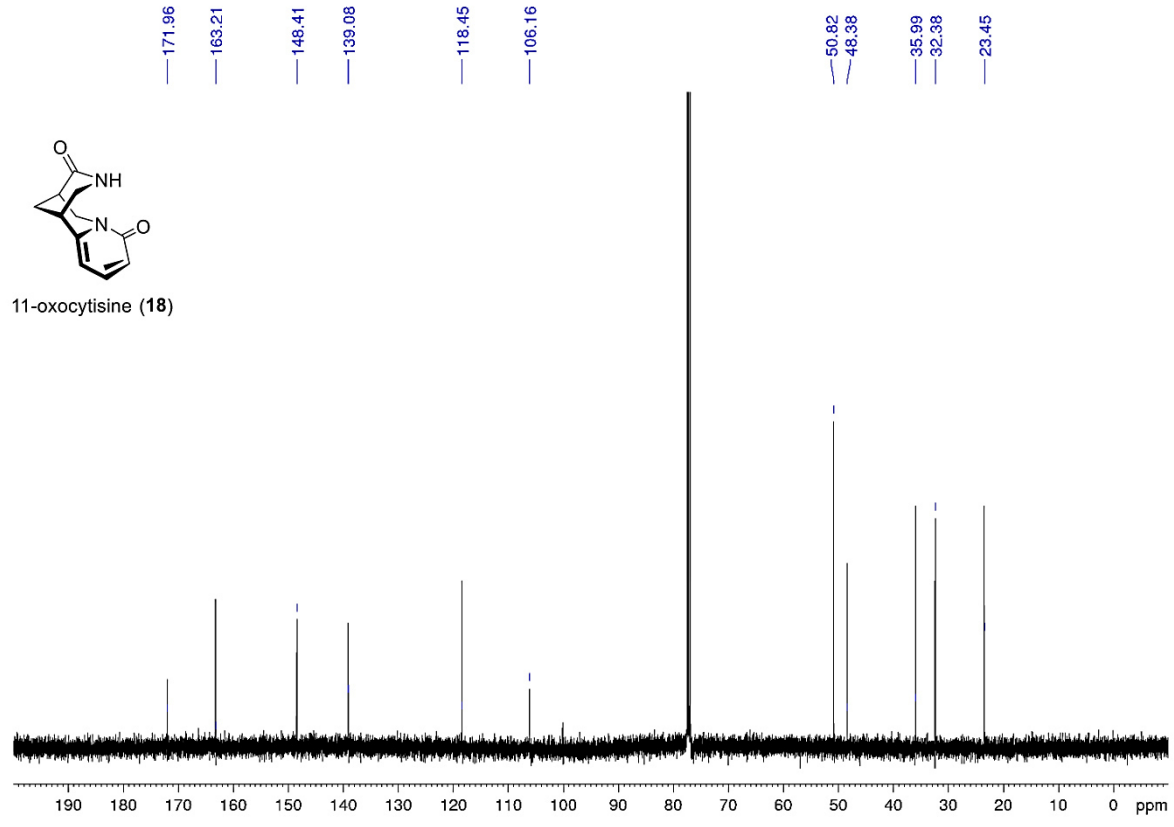
35


1994.42
1976.26
1918.90
1906.00
1889.29
1871.14
1800.82
1795.77
1787.96
1782.86
1007.06
994.26
959.75
947.05
= ((cut off))
O
NBoc
N
Me
14
1.01
0.99
1.02
1.00
0.99
1.00
3.98
1.01
9.06
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

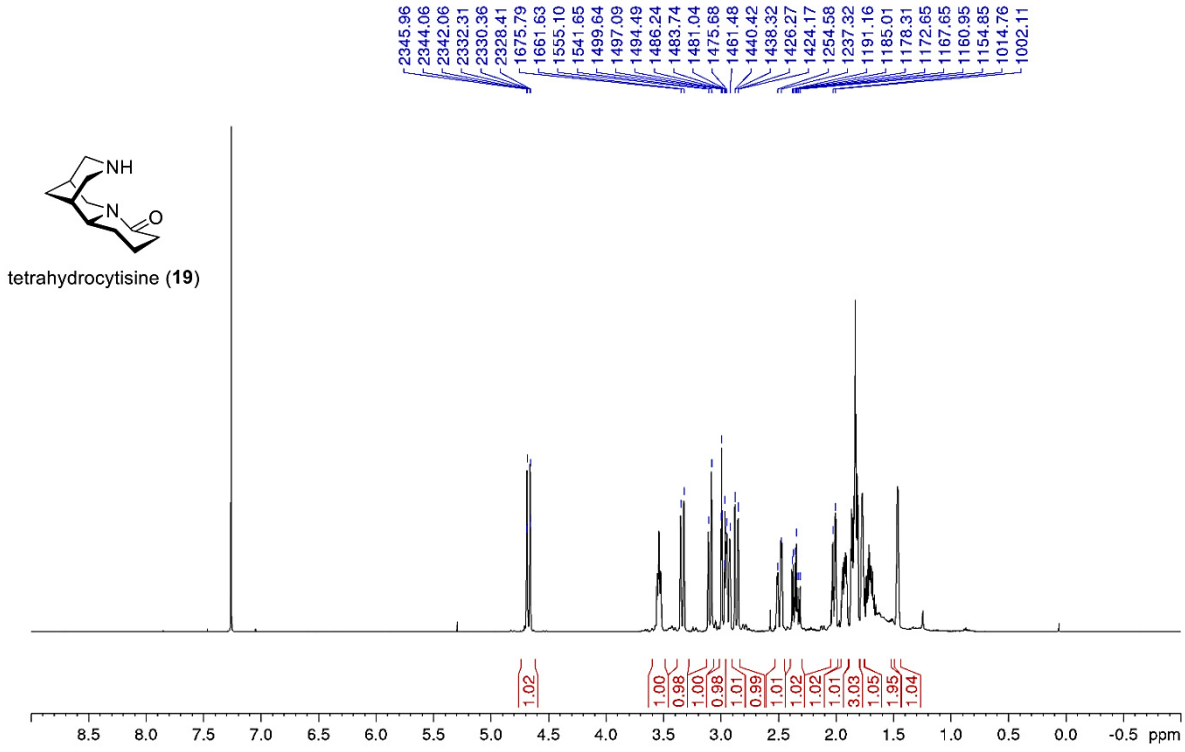

172.59
167.71
152.44
83.39
54.95
49.66
39.28
33.50
28.00
26.01
23.64
O
NBoc
N
Me
14
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

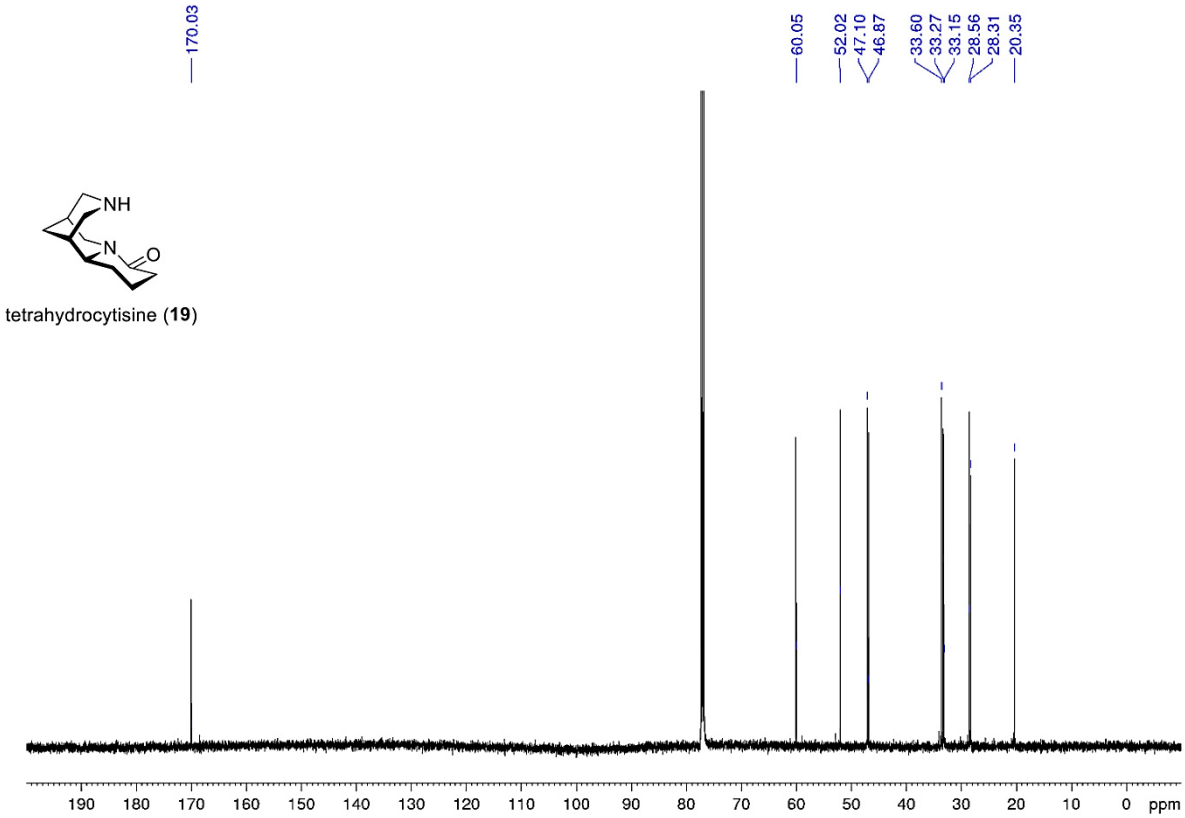
36


3658.20
3651.35
3649.10
3642.25
3239.49
3238.29
3230.39
3229.19
3051.09
3044.59
2280.04
2264.79
1870.14
1865.89
1863.18
1857.88
1854.03
1847.93
1842.33
1700.29
1688.39
1111.49
1098.39
1054.87
1041.72
NH
N
O
O
11-oxocytisine (18)
1.01
0.93
0.98
0.96
1.00
1.96
1.00
0.99
0.99
1.00
1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

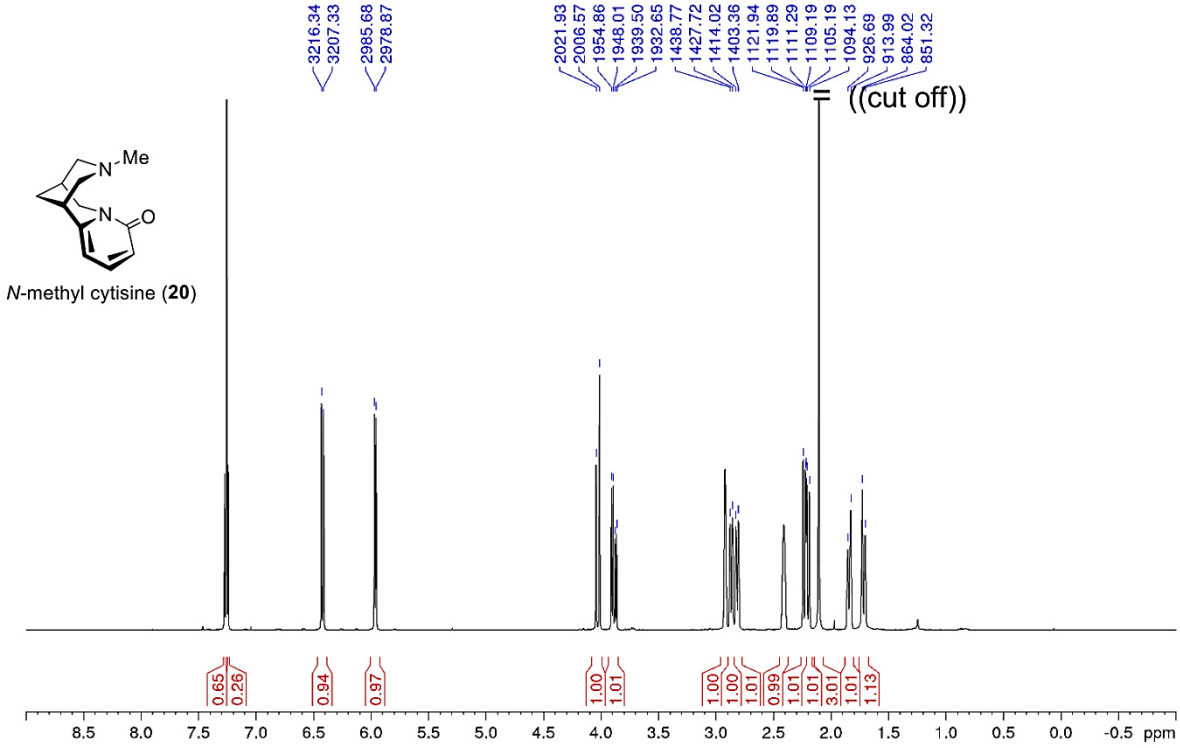

171.96
163.21
148.41
139.08
118.45
106.16
50.82
48.38
35.99
32.38
23.45
NH
N
O
O
11-oxocytisine (18)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

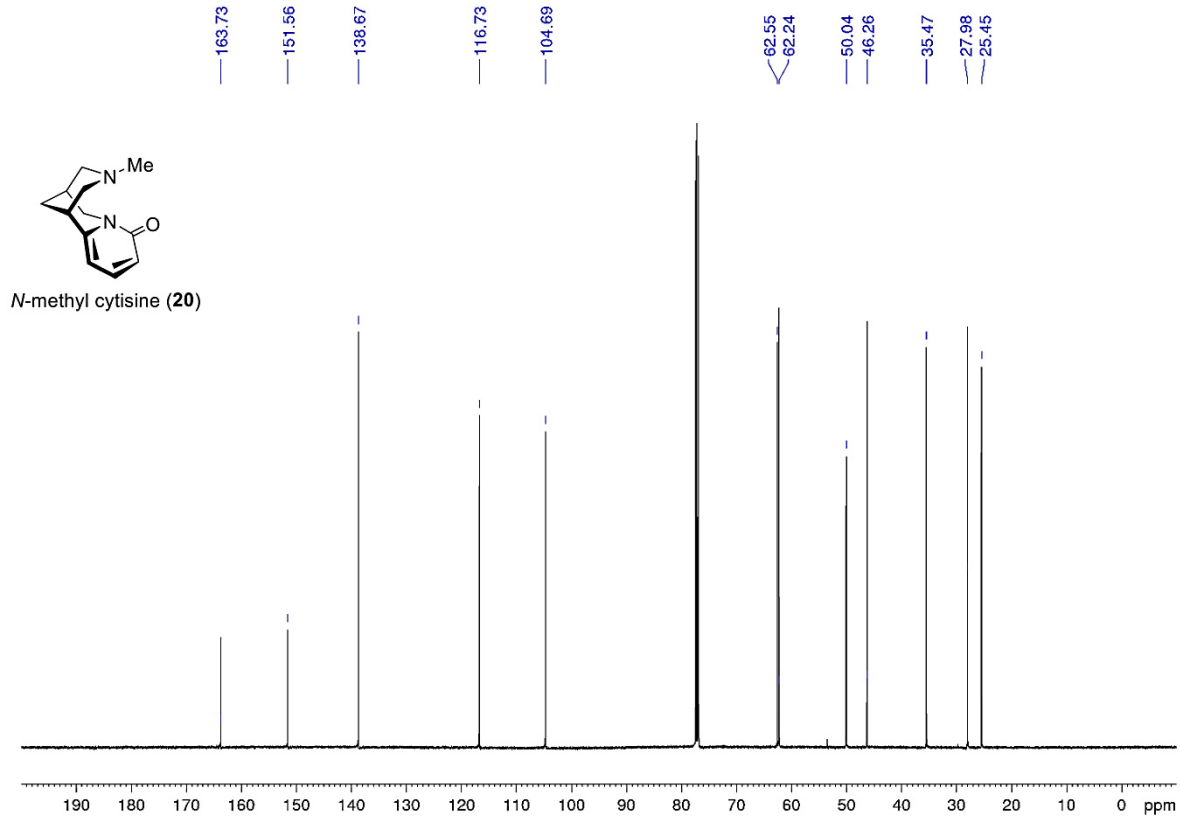
37


2345.96
2344.06
2342.06
2332.31
2330.36
2328.41
1675.79
1661.63
1555.10
1541.65
1499.64
1497.09
1494.49
1486.24
1483.74
1481.04
1475.68
1461.48
1440.42
1438.32
1426.27
1424.17
1254.58
1237.32
1191.16
1185.01
1178.31
1172.65
1167.65
1160.95
1154.85
1014.76
1002.11
NH
N
O
tetrahydrocytisine (19)
1.02
1.00
0.98
1.00
0.98
1.01
0.99
1.01
1.02
1.02
1.01
3.03
1.05
1.95
1.04
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

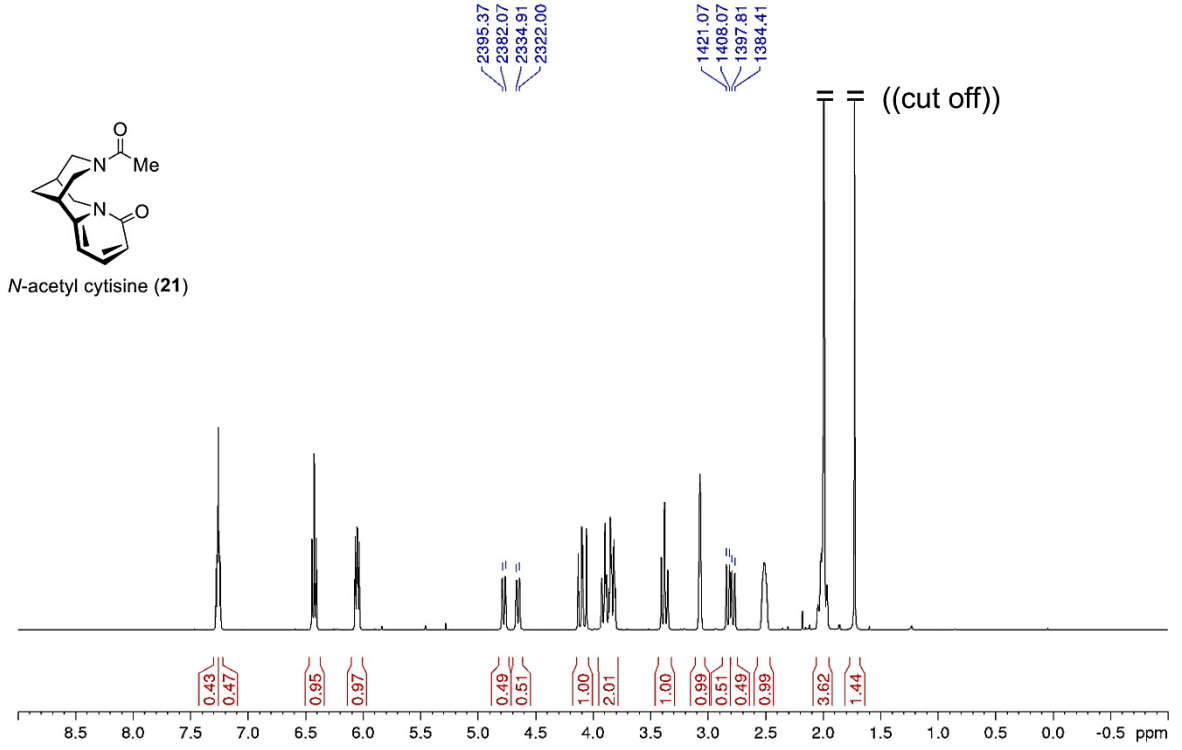

170.03
60.05
52.02
47.10
46.87
33.60
33.27
33.15
28.56
28.31
20.35
NH
N
O
tetrahydrocytisine (19)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

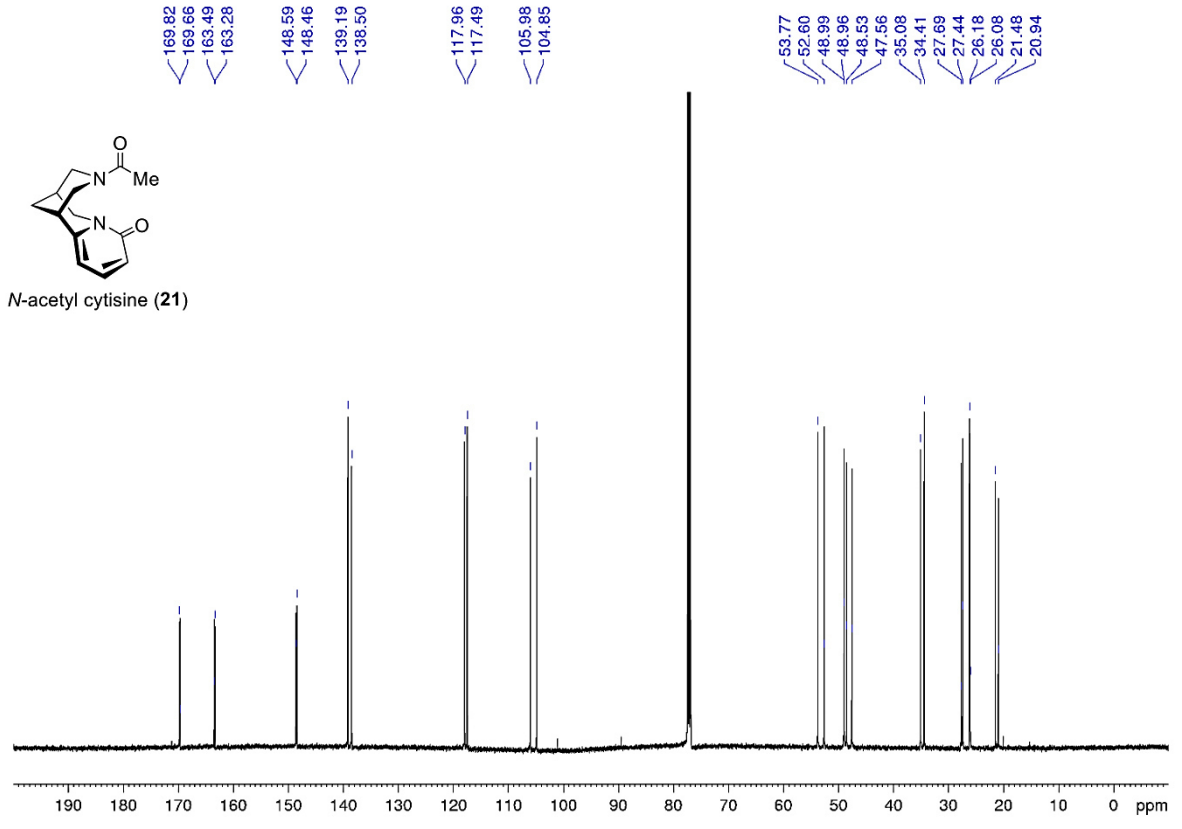
38


3216.34
3207.33
2985.68
2978.87
2021.93
2006.57
1954.86
1948.01
1939.50
1932.65
1438.77
1427.72
1414.02
1403.36
1121.94
1119.89
1111.29
1109.19
1105.19
1094.13
926.69
913.99
864.02
851.32
((cut off))
N
Me
N
O
N-methyl cytisine (20)
0.65
0.26
0.94
0.97
1.00
1.01
1.00
1.00
1.01
0.99
1.01
1.01
3.01
1.01
1.13
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

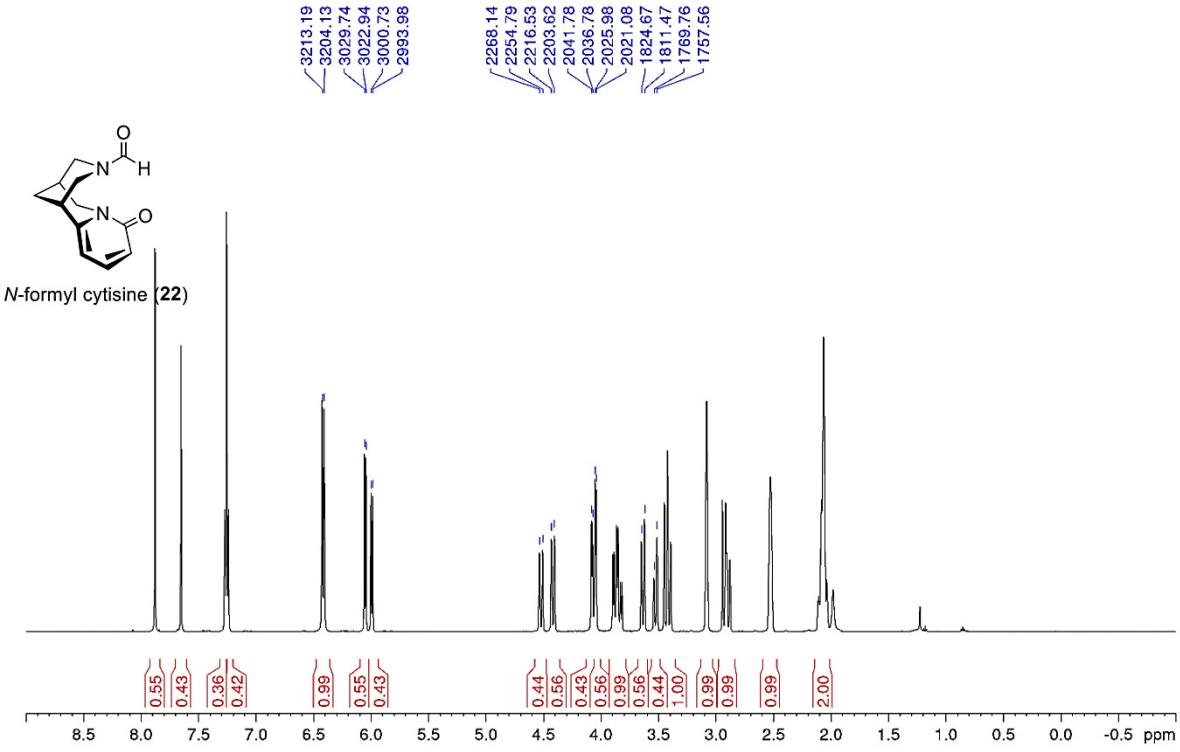

163.73
151.56
138.67
116.73
104.69
62.55
62.24
50.04
46.26
35.47
27.98
25.45
N
Me
N
O
N-methyl cytisine (20)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

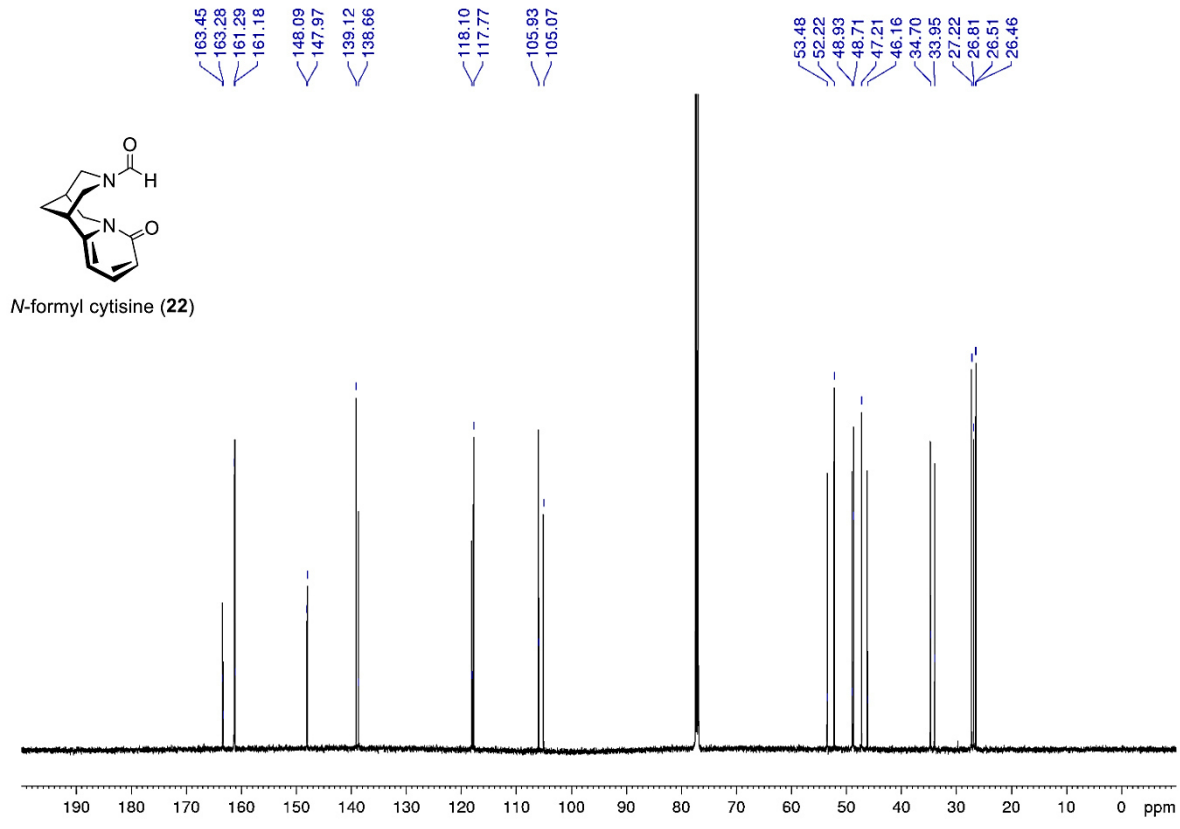
39


2395.37
2382.07
2334.91
2322.00
1421.07
1408.07
1397.81
1384.41
= = ((cut off))
N
Me
O
N
O
N-acetyl cytisine (21)
0.43
0.47
0.95
0.97
0.49
0.51
1.00
2.01
1.00
0.99
0.51
0.49
0.99
3.62
1.44
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

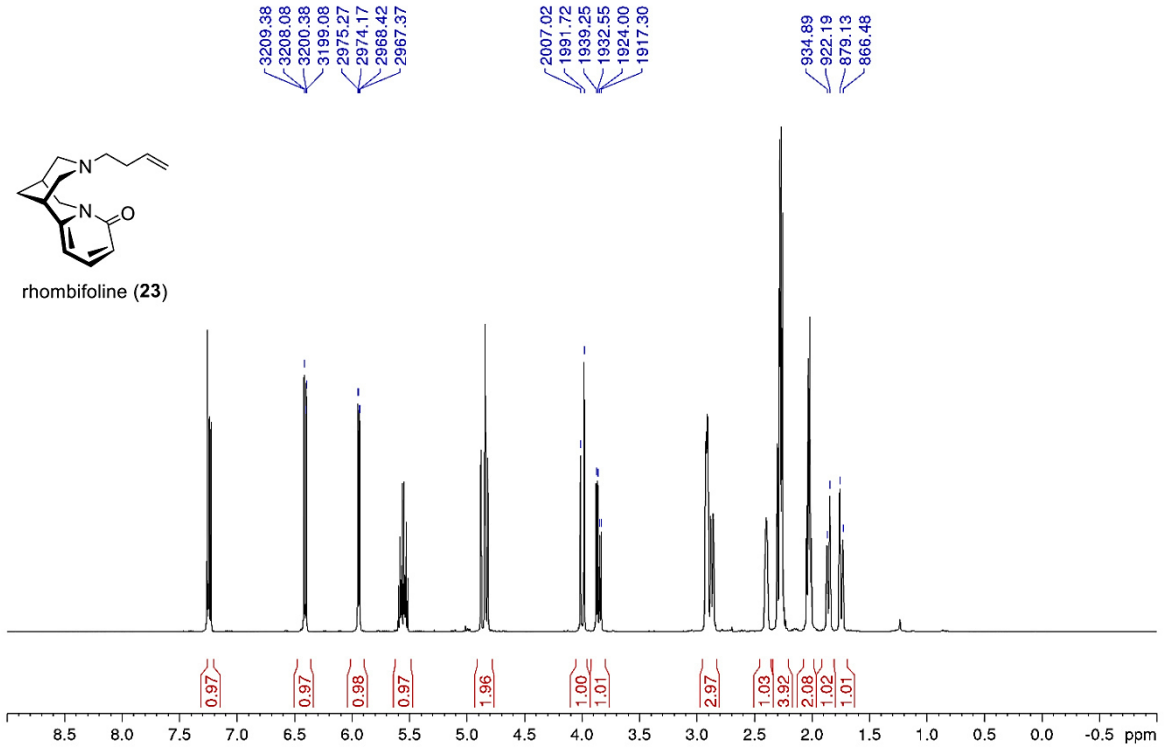

169.82
169.66
163.49
163.28
148.59
148.46
139.19
138.50
117.96
117.49
105.98
104.85
53.77
52.60
48.99
48.96
48.53
47.56
35.08
34.41
27.69
27.44
26.18
26.08
21.48
20.94
N
Me
O
N
O
N-acetyl cytisine (21)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

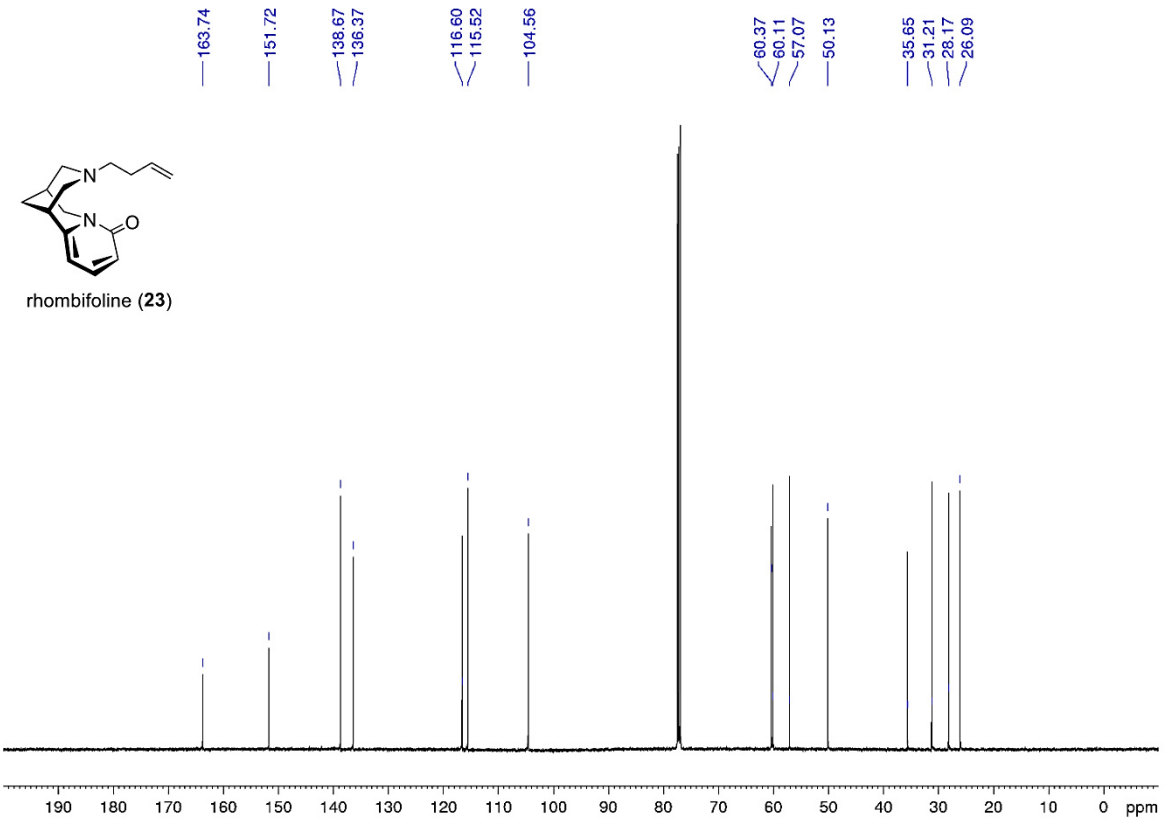
40


3213.19
3204.13
3029.74
3022.94
3000.73
2993.98
2268.14
2254.79
2216.53
2203.62
2041.78
2036.78
2025.98
2021.08
1824.67
1811.47
1769.76
1757.56
O
N
H
N
O
N-formyl cytisine (22)
0.55
0.43
0.36
0.42
0.99
0.55
0.43
0.44
0.56
0.43
0.56
0.99
0.56
0.44
1.00
0.99
0.99
0.99
2.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

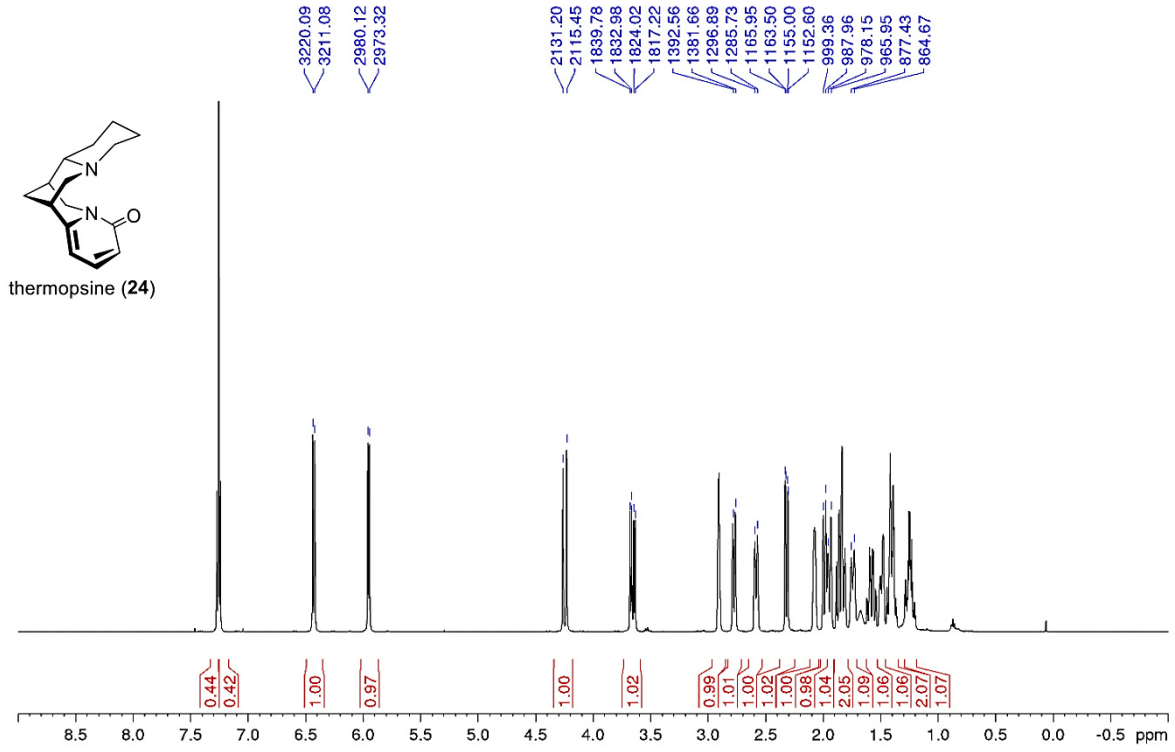

163.45
163.28
161.29
161.18
148.09
147.97
139.12
138.66
118.10
117.77
105.93
105.07
53.48
52.22
48.93
48.71
47.21
46.16
34.70
33.95
27.22
26.81
26.51
26.46
O
N
H
N
O
N-formyl cytisine (22)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

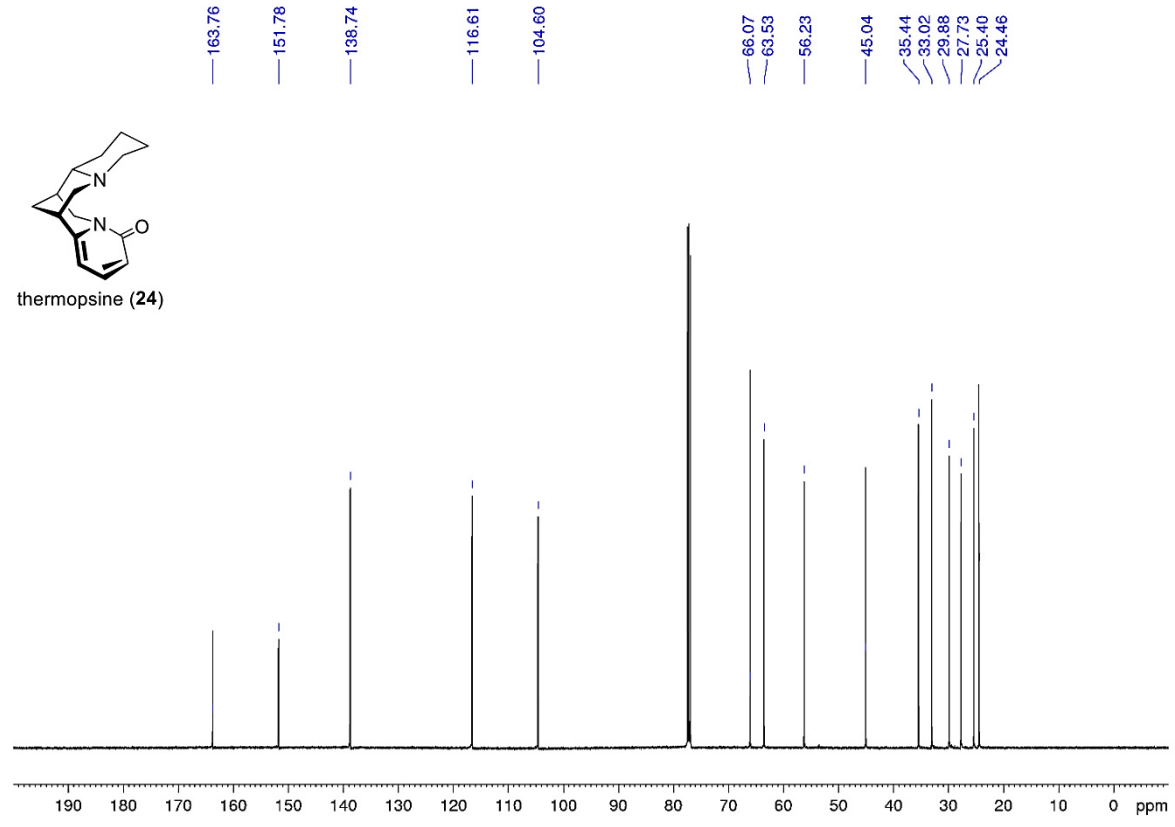
41


3209.38
3208.08
3200.38
3199.08
2975.27
2974.17
2968.42
2967.37
2007.02
1991.72
1939.25
1932.55
1924.00
1917.30
934.89
922.19
879.13
866.48
rhombifoline (23)
0.97
0.97
0.98
0.97
1.96
1.00
1.01
2.97
1.03
3.92
2.08
1.02
1.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

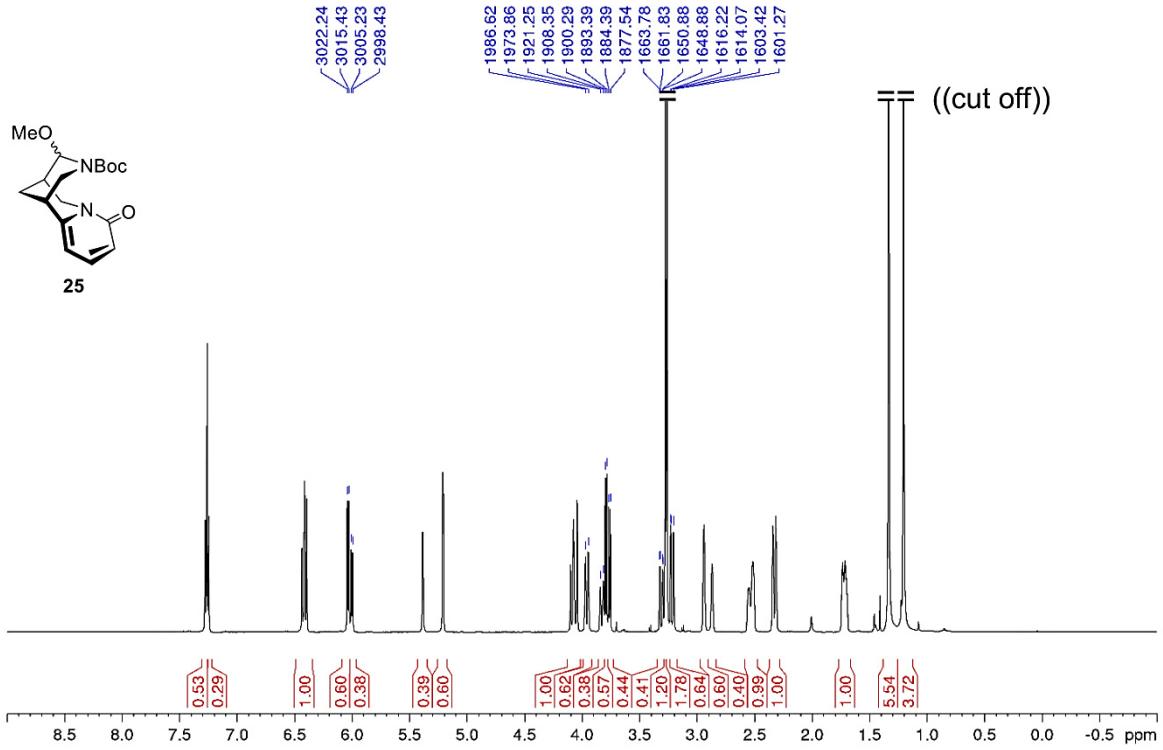

163.74
151.72
138.67
136.37
116.60
115.52
104.56
60.37
60.11
57.07
50.13
35.65
31.21
28.17
26.09
rhombifoline (23)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

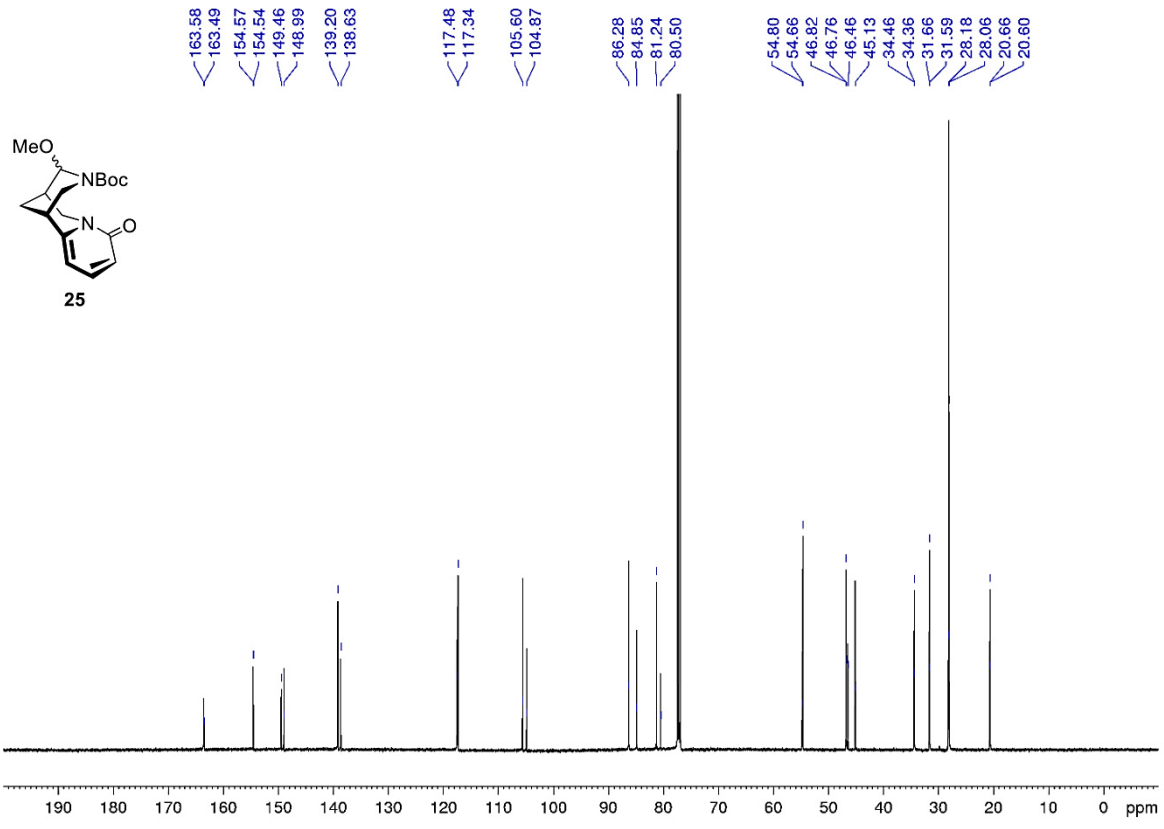
42


3220.09
3211.08
2980.12
2973.32
2131.20
2115.45
1839.78
1832.98
1824.02
1817.22
1392.56
1381.66
1296.89
1285.73
1165.95
1163.50
1155.00
1152.60
999.36
987.96
978.15
965.95
877.43
864.67
thermopsine (24)
0.44
0.42
1.00
0.97
1.00
1.02
0.99
1.01
1.00
1.02
1.00
0.98
1.04
2.05
1.09
1.06
1.06
2.07
1.07
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

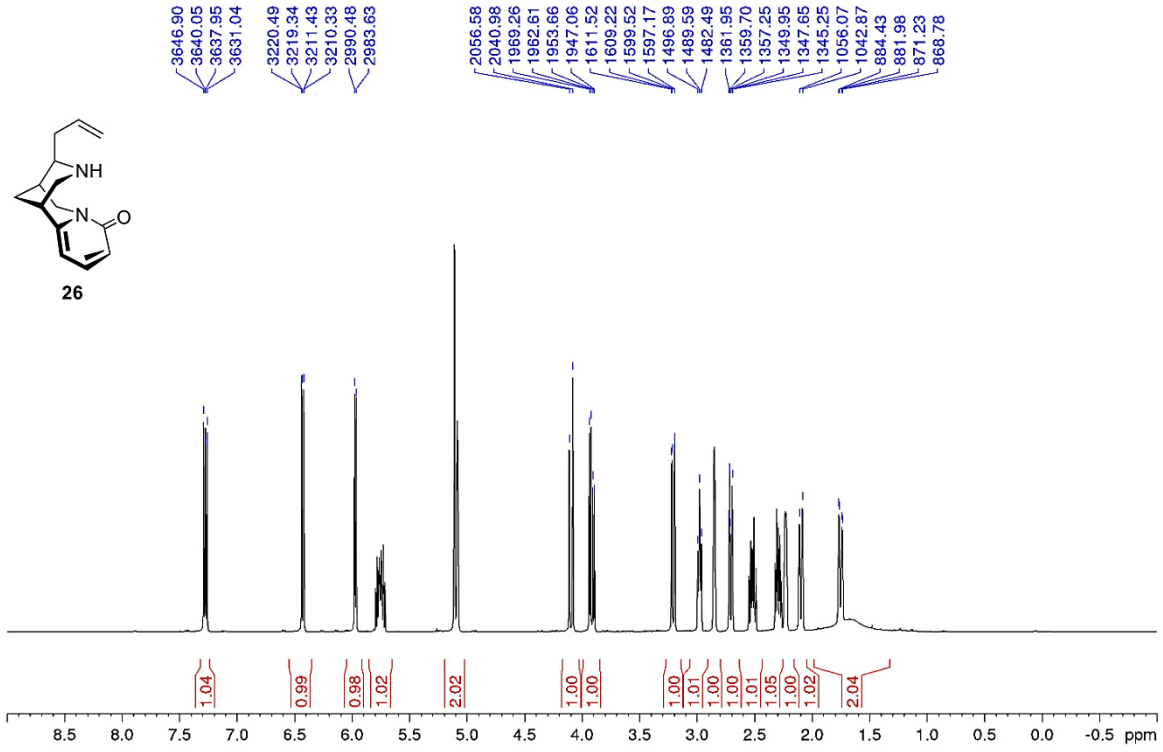

163.76
151.78
138.74
116.61
104.60
66.07
63.53
56.23
45.04
35.44
33.02
29.88
27.73
25.40
24.46
thermopsine (24)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

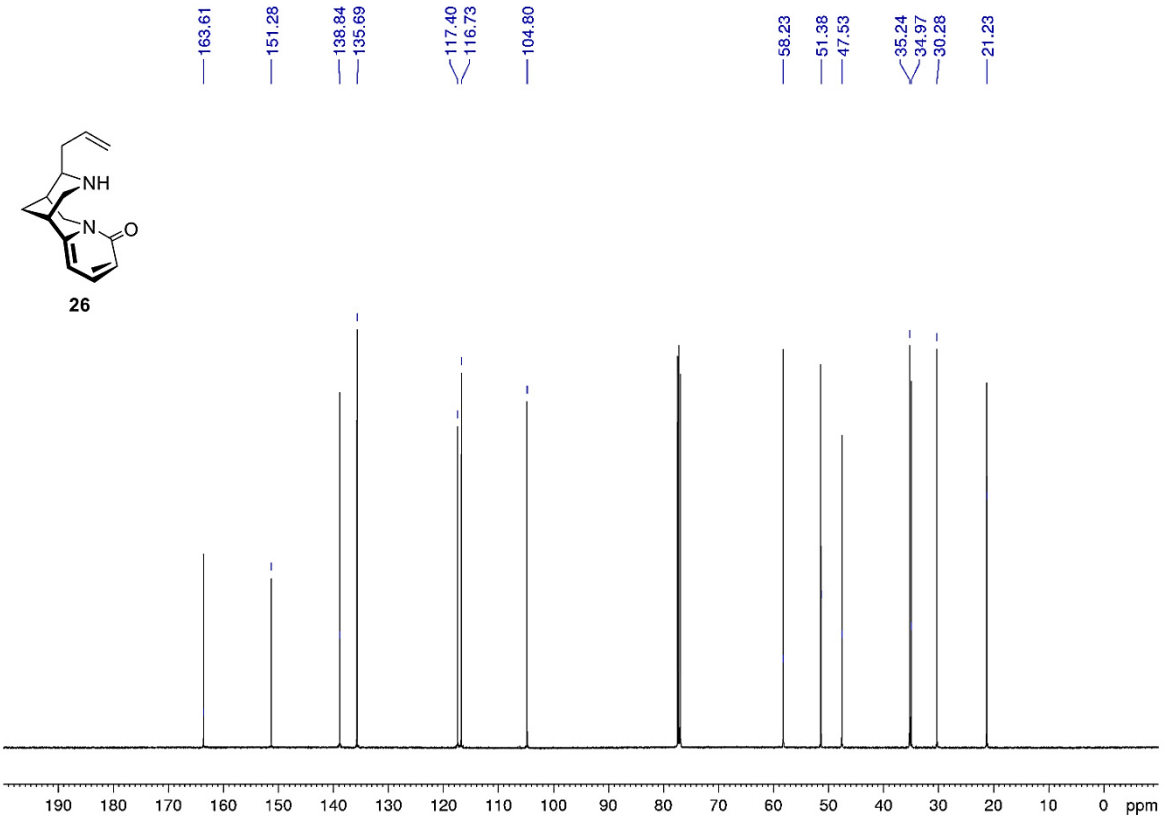
43


3022.24
3015.43
3005.23
2998.43
1986.62
1973.86
1921.25
1908.35
1900.29
1893.39
1884.39
1877.54
1663.78
1661.83
1650.88
1648.88
1616.22
1614.07
1603.42
1601.27
((cut off))
MeO
NBoc
N
O
25
0.53
0.29
1.00
0.60
0.38
0.39
0.60
1.00
0.62
0.38
0.57
0.44
0.41
1.20
1.78
0.64
0.60
0.40
0.99
1.00
1.00
5.54
3.72
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

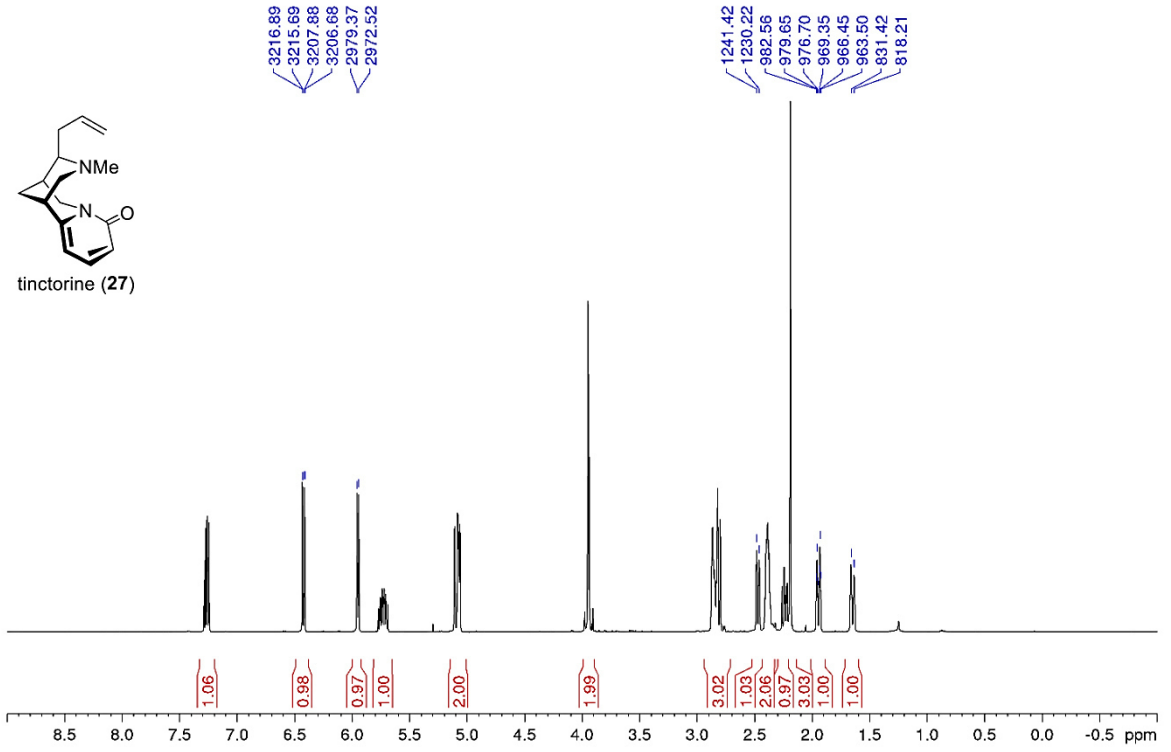

163.58
163.49
154.57
154.54
149.46
148.99
139.20
138.63
117.48
117.34
105.60
104.87
86.28
84.85
81.24
80.50
54.80
54.66
46.82
46.76
46.46
45.13
34.46
34.36
31.66
31.59
28.18
28.06
20.66
20.60
MeO
NBoc
N
O
25
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

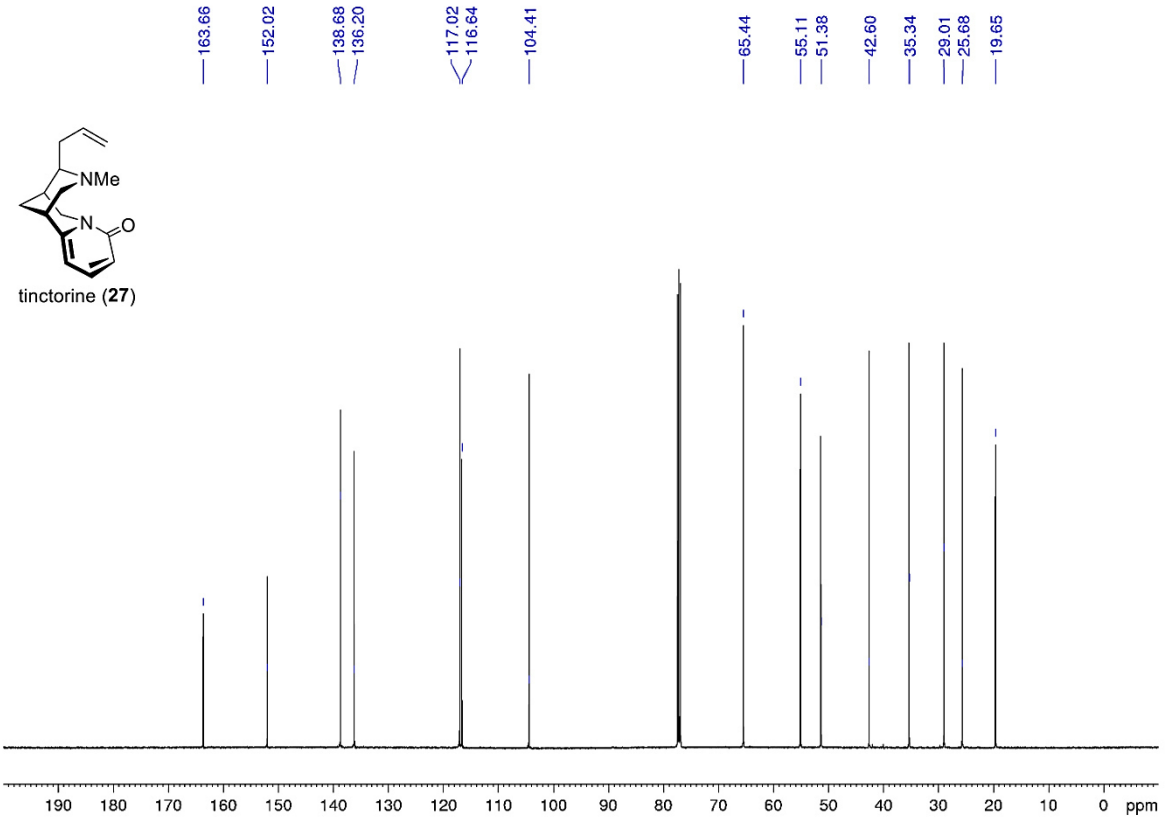
44


3646.90
3640.05
3637.95
3631.04
3220.49
3219.34
3211.43
3210.33
2990.48
2983.63
2056.58
2040.98
1969.26
1962.61
1953.66
1947.06
1611.52
1609.22
1599.52
1597.17
1496.89
1489.59
1482.49
1361.95
1359.70
1357.25
1349.95
1347.65
1345.25
1056.07
1042.87
884.43
881.98
871.23
868.78
NH
N
O
26
1.04
0.99
0.98
1.02
2.02
1.00
1.00
1.00
1.01
1.00
1.00
1.01
1.05
1.00
1.02
2.04
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

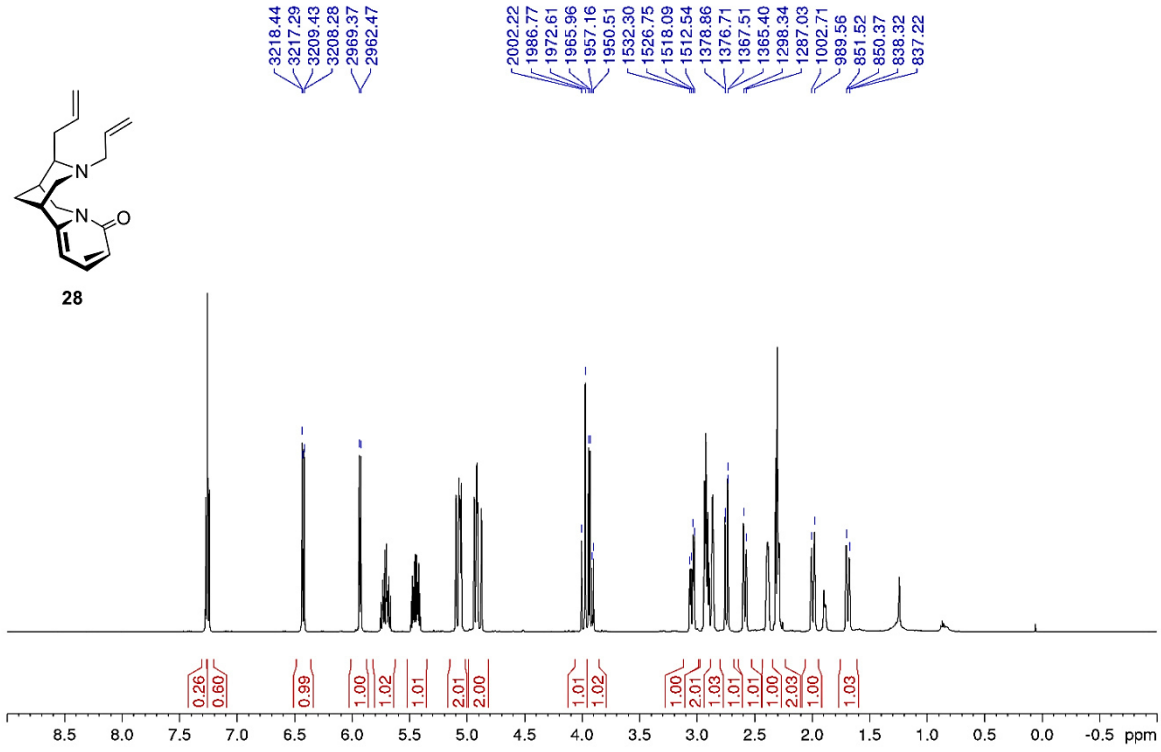

163.61
151.28
138.84
135.69
117.40
116.73
104.80
58.23
51.38
47.53
35.24
34.97
30.28
21.23
NH
N
O
26
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

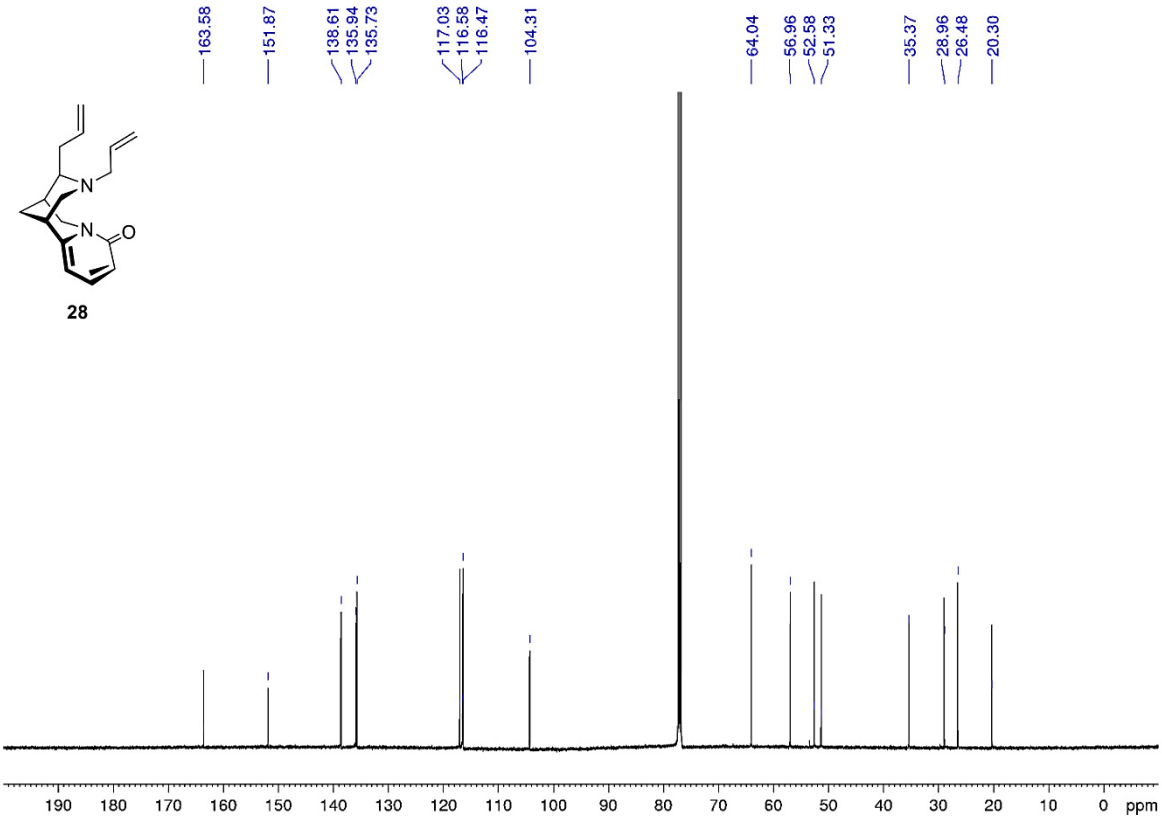
45


3216.89
3215.69
3207.88
3206.68
2979.37
2972.52
1241.42
1230.22
982.56
979.65
976.70
969.35
966.45
963.50
831.42
818.21
NMe
N
O
tinctorine (27)
1.06
0.98
0.97
1.00
2.00
1.99
3.02
1.03
2.06
0.97
3.03
1.00
1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

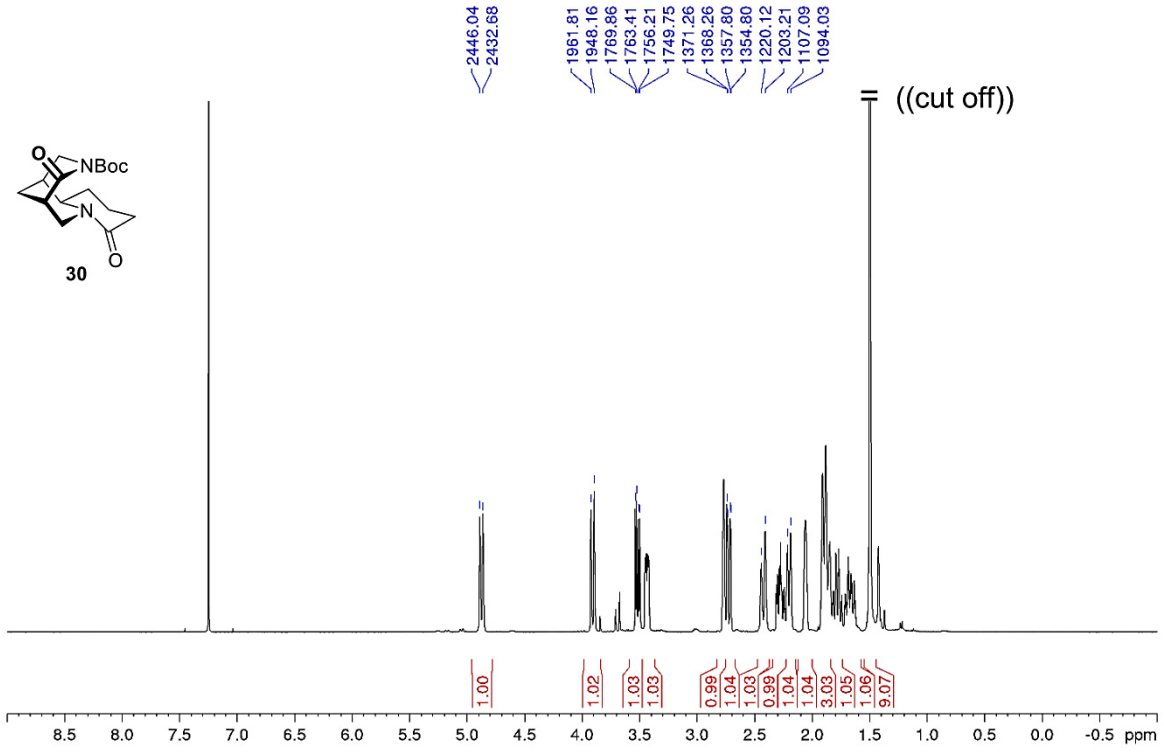

163.66
152.02
138.68
136.20
117.02
116.64
104.41
65.44
55.11
51.38
42.60
35.34
29.01
25.68
19.65
NMe
N
O
tinctorine (27)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

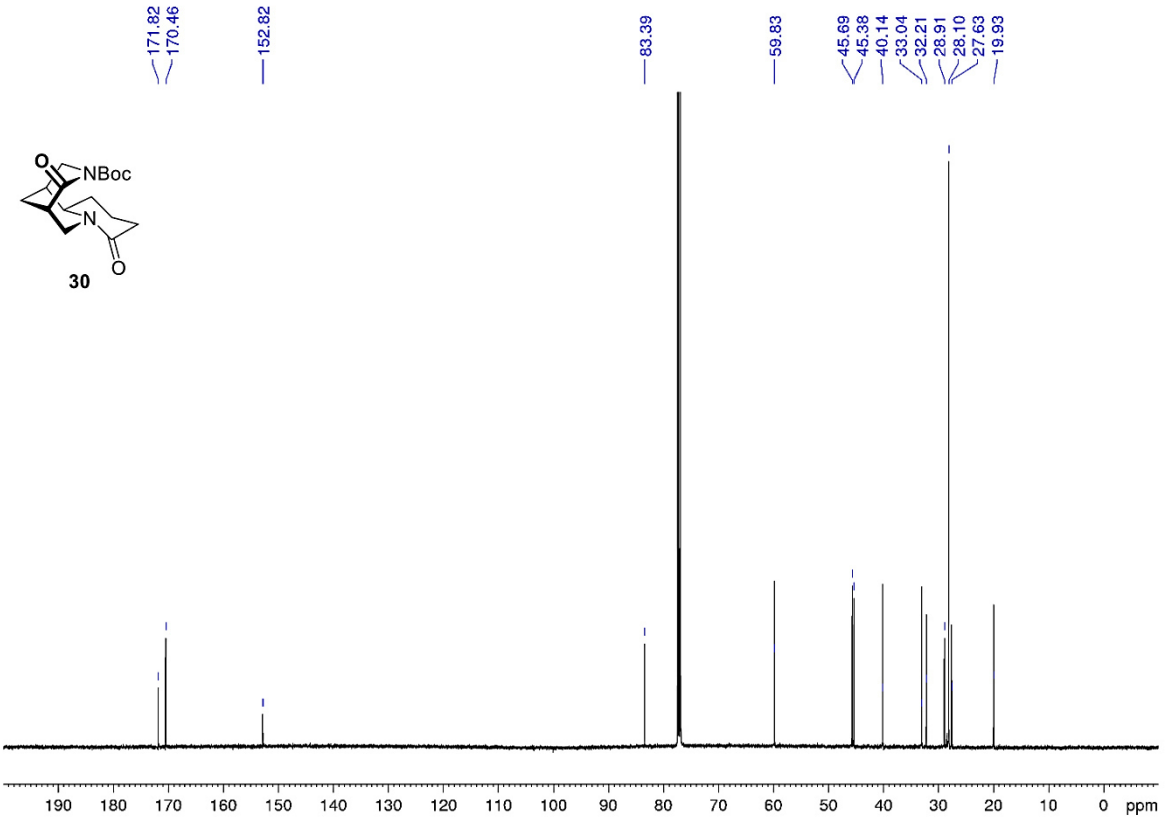
46


3218.44
3217.29
3209.43
3208.28
2969.37
2962.47
2002.22
1986.77
1972.61
1965.96
1957.16
1950.51
1532.30
1526.75
1518.09
1512.54
1378.86
1376.71
1367.51
1365.40
1298.34
1287.03
1002.71
989.56
851.52
850.37
838.32
837.22
28
0.26
0.60
0.99
1.00
1.02
1.01
2.01
2.00
1.01
1.02
1.00
2.01
1.03
1.01
1.01
1.00
2.03
1.00
1.03
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

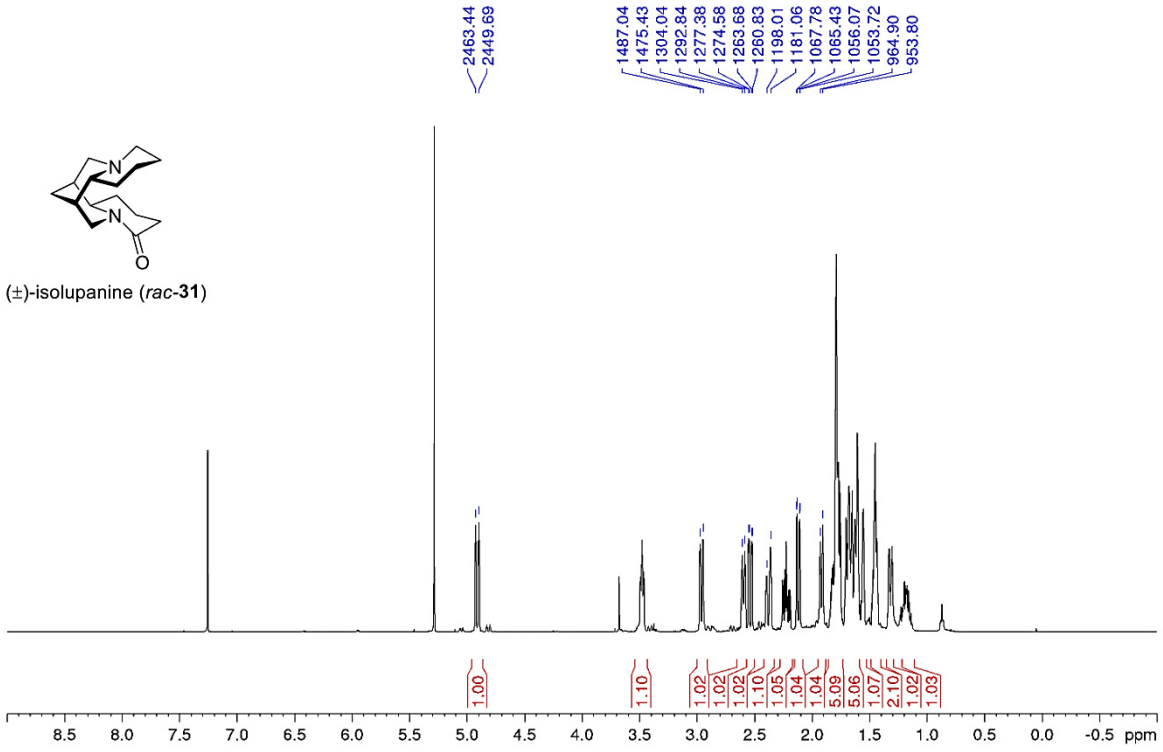

163.58
151.87
138.61
135.94
135.73
117.03
116.58
116.47
104.31
64.04
56.96
52.58
51.33
35.37
28.96
26.48
20.30
28
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

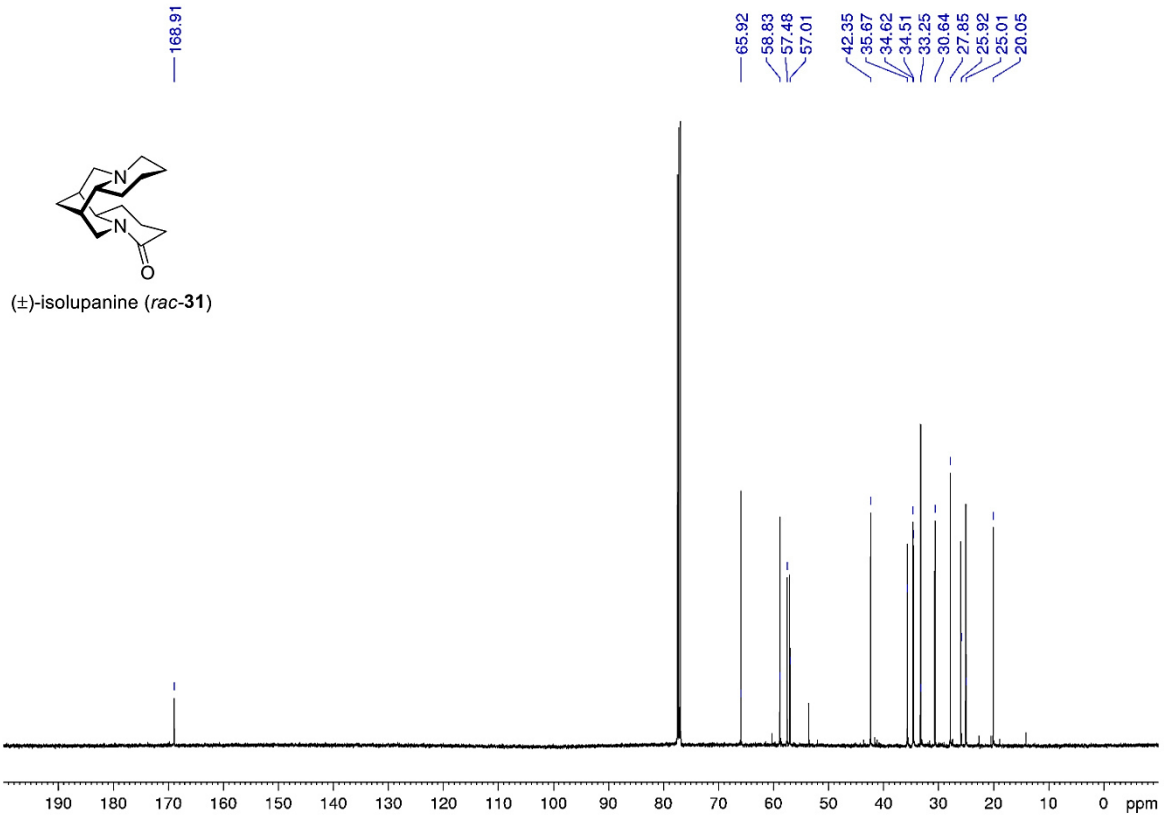
47


2446.04
2432.68
1961.81
1948.16
1769.86
1763.41
1756.21
1749.75
1371.26
1368.26
1357.80
1354.80
1220.12
1203.21
1107.09
1094.03
= ((cut off))
NBoc
N
O
O
30
1.00
1.02
1.03
1.03
0.99
1.04
1.03
0.99
1.04
1.04
3.03
1.05
1.06
9.07
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

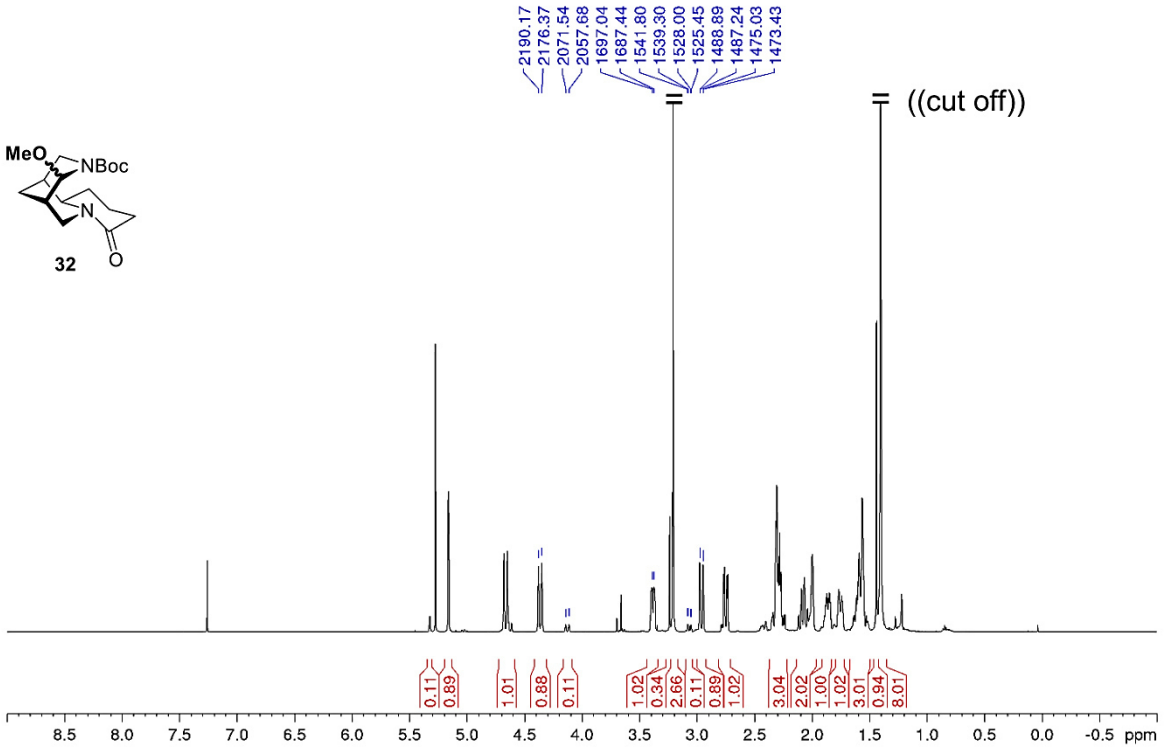

171.82
170.46
152.82
83.39
59.83
45.69
45.38
40.14
33.04
32.21
28.91
28.10
27.63
19.93
NBoc
N
O
O
30
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

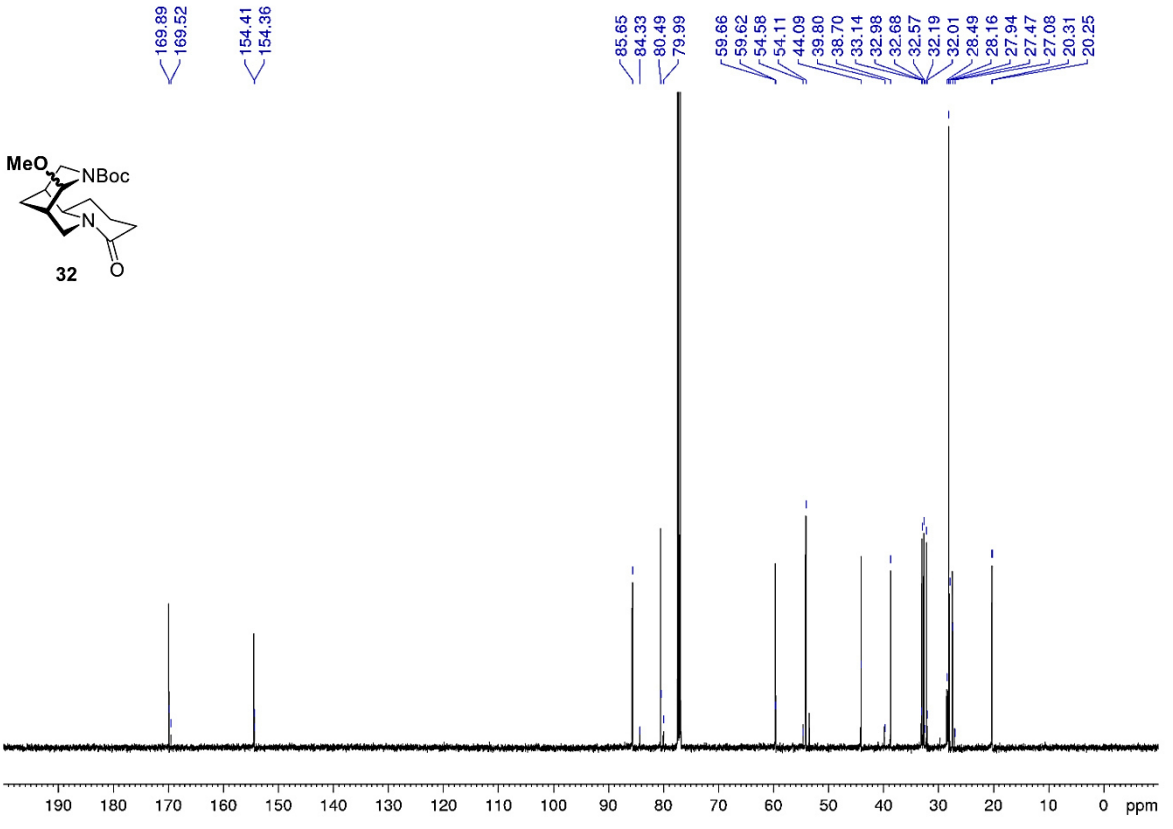
48


2463.44
2449.69
1487.04
1475.43
1304.04
1292.84
1277.38
1274.58
1263.68
1260.83
1198.01
1181.06
1067.78
1065.43
1056.07
1053.72
964.90
953.80
(±)-isolupanine (rac-31)
1.00
1.10
1.02
1.02
1.02
1.10
1.05
1.04
1.04
5.09
5.06
1.07
2.10
1.02
1.03
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

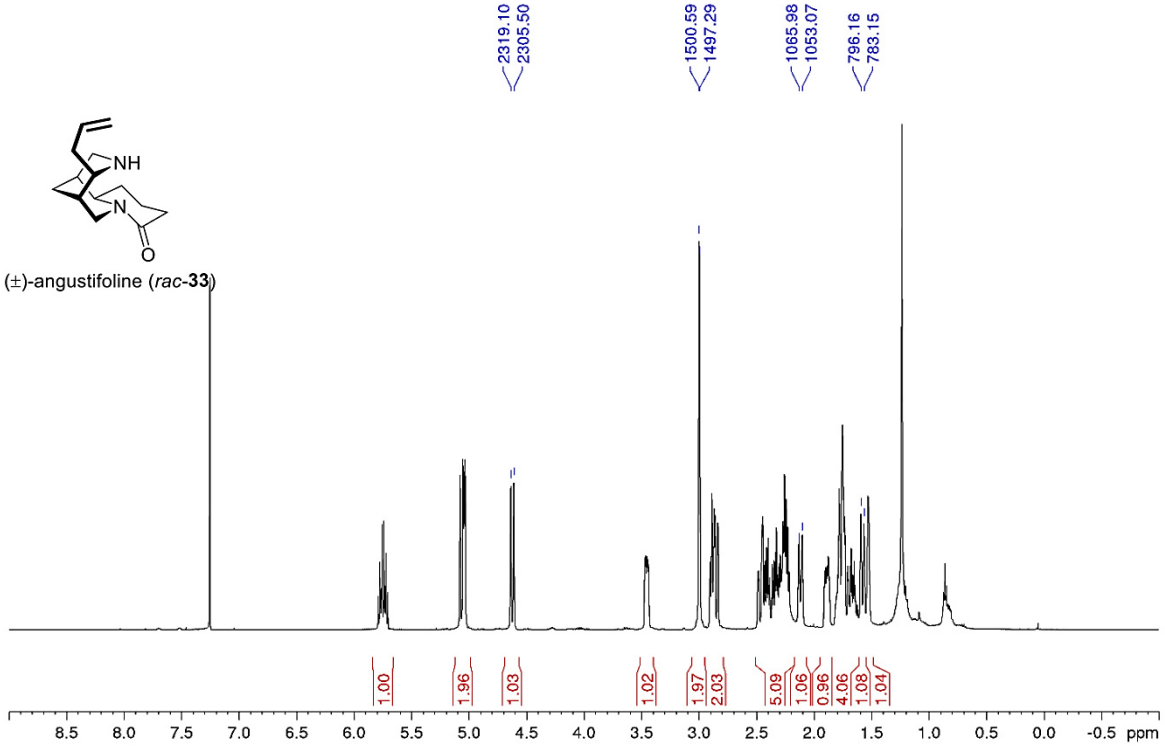

168.91
65.92
58.83
57.48
57.01
42.35
35.67
34.62
34.51
33.25
30.64
27.85
25.92
25.01
20.05
(±)-isolupanine (rac-31)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

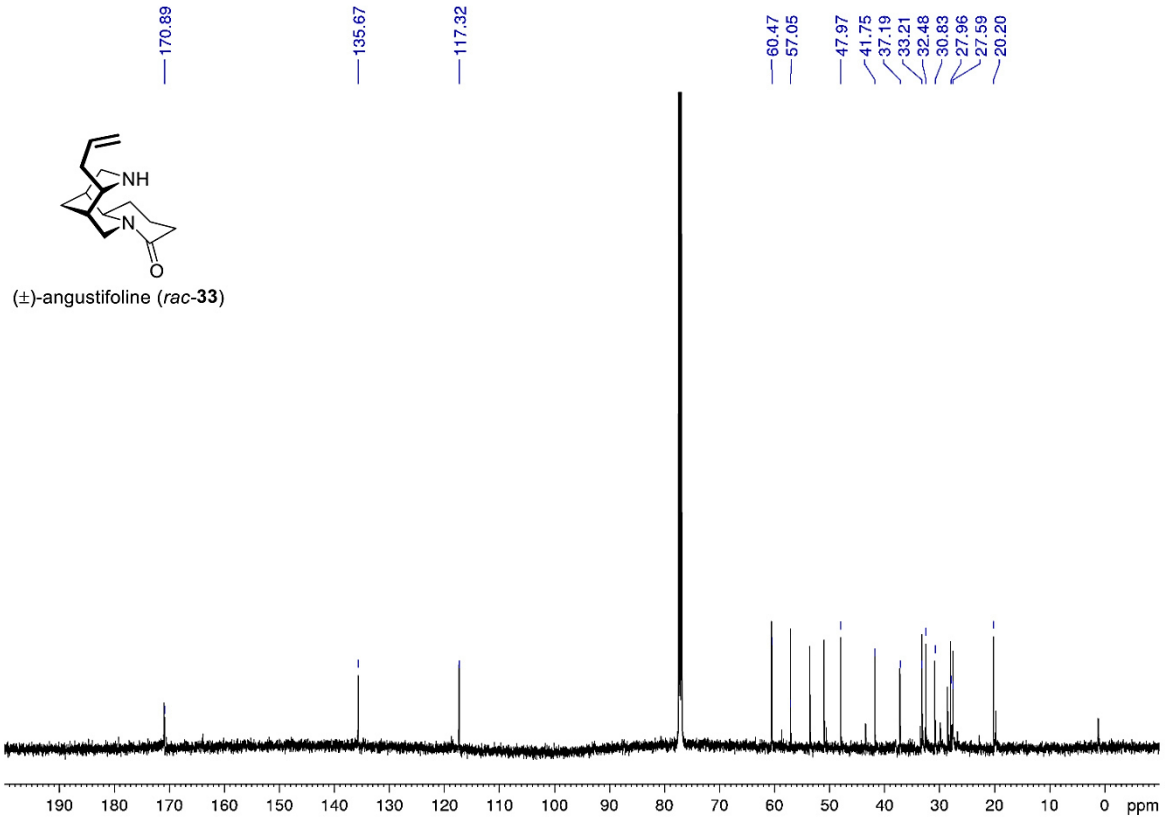
49


2190.17
2176.37
2071.54
2057.68
1697.04
1687.44
1541.80
1539.30
1528.00
1525.45
1488.89
1487.24
1475.03
1473.43
= ((cut off))
MeO
NBoc
N
O
32
0.11
0.89
1.01
0.68
0.11
1.02
0.34
2.66
0.11
0.89
1.02
3.04
2.02
1.00
1.02
3.01
0.94
8.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

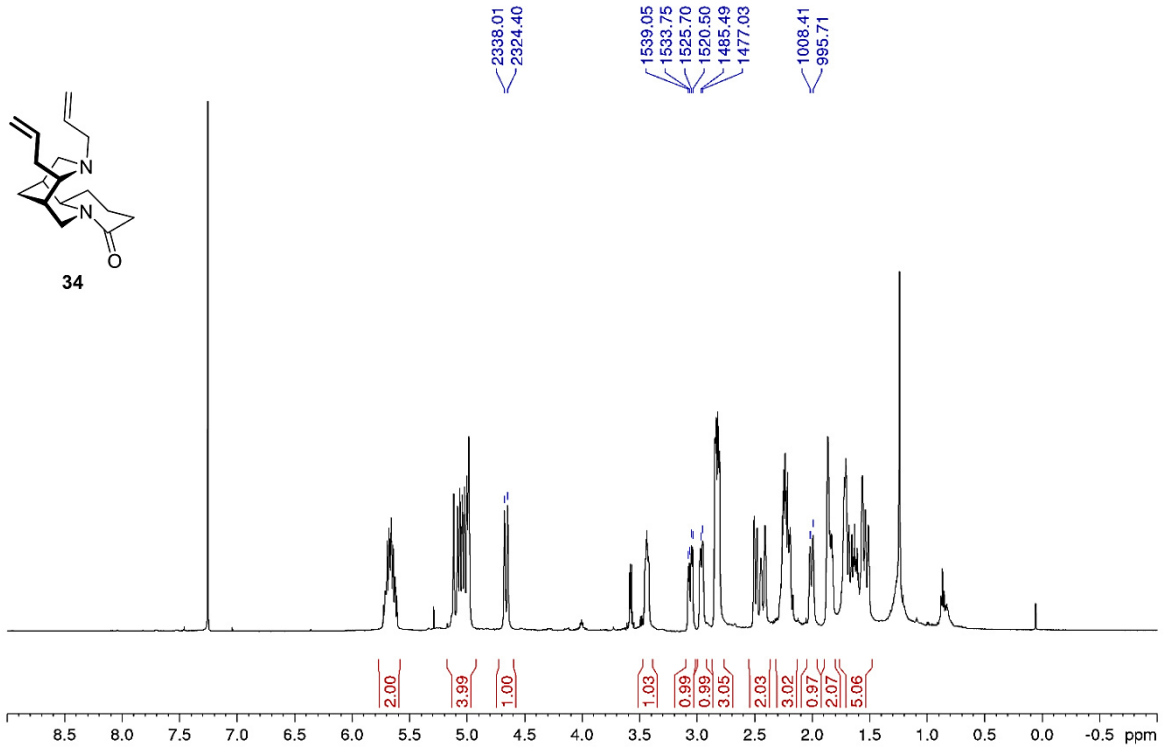

169.89
169.52
154.41
154.36
85.65
84.33
80.49
79.99
59.66
59.62
54.58
54.11
44.09
39.80
38.70
33.14
32.98
32.68
32.57
32.19
32.01
28.49
28.16
27.94
27.47
27.08
20.31
20.25
MeO
NBoc
N
O
32
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

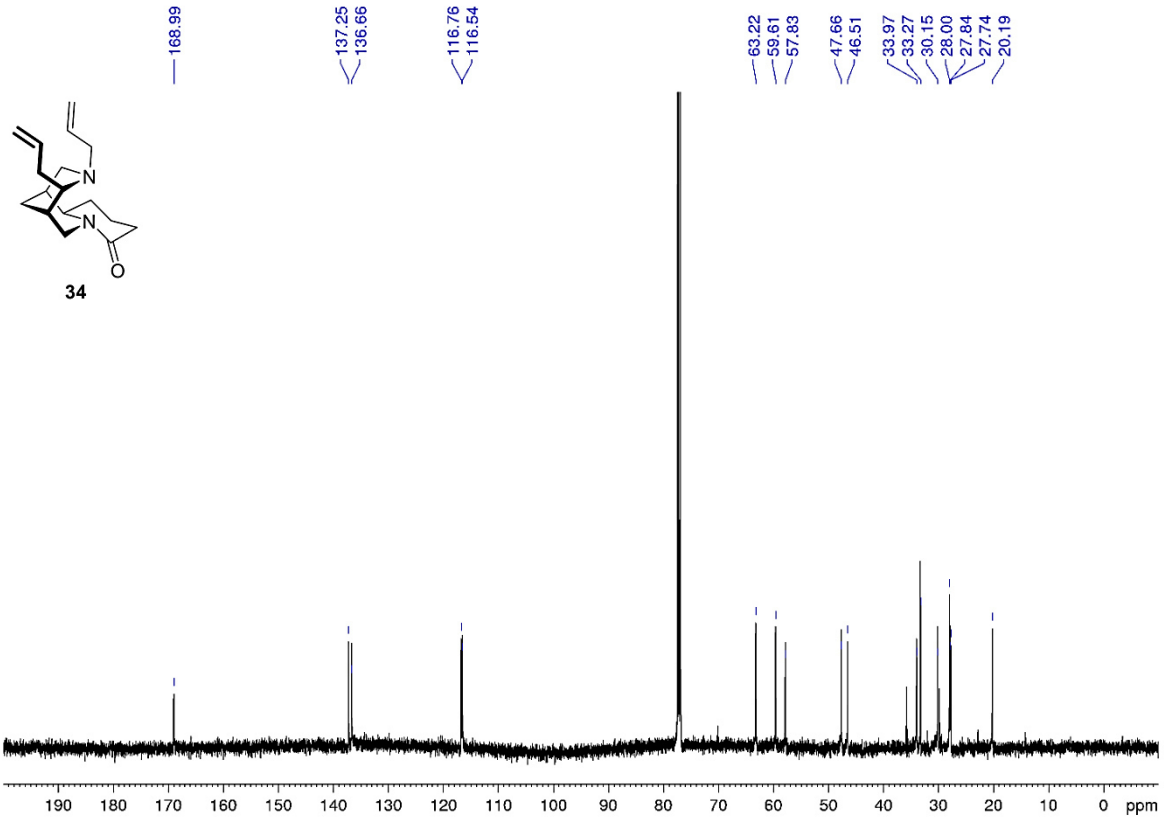
50


2319.10
2305.50
1500.59
1497.29
1065.98
1053.07
796.16
783.15
NH
N
O
(±)-angustifoline (rac-33)
1.00
1.96
1.03
1.02
1.97
2.03
5.09
1.06
0.96
4.06
1.08
1.04
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

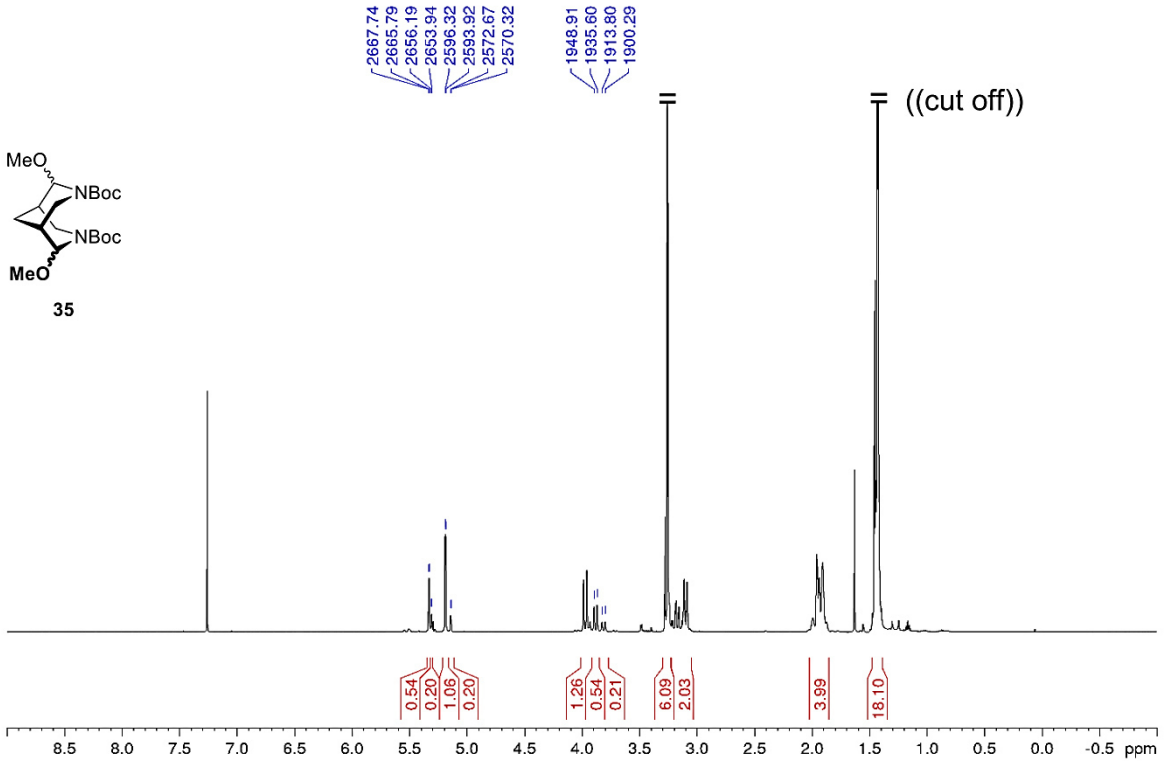

170.89
135.67
117.32
60.47
57.05
47.97
41.75
37.19
33.21
32.48
30.83
27.96
27.59
20.20
NH
N
O
(±)-angustifoline (rac-33)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

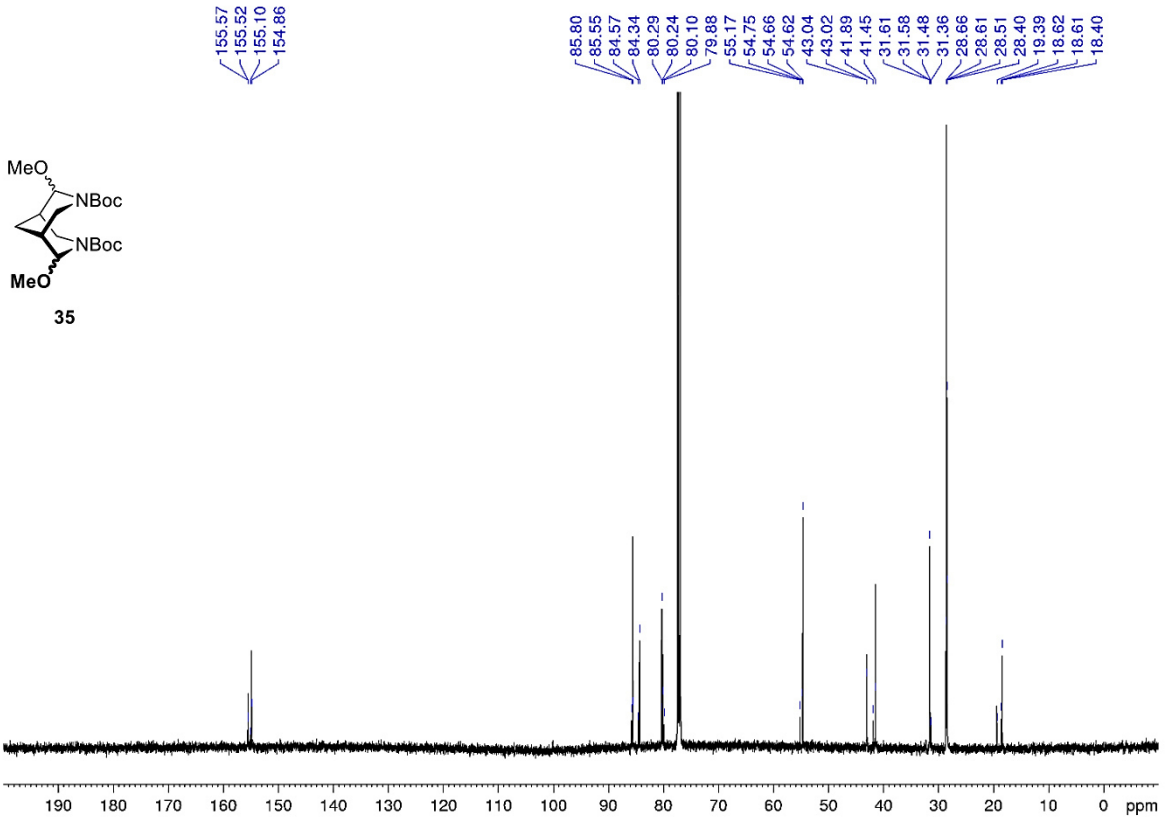
51


2338.01
2324.40
1539.05
1533.75
1525.70
1520.50
1485.49
1477.03
1008.41
995.71
34
2.00
3.99
1.00
1.03
0.99
0.99
3.05
2.03
3.02
0.97
2.07
5.06
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

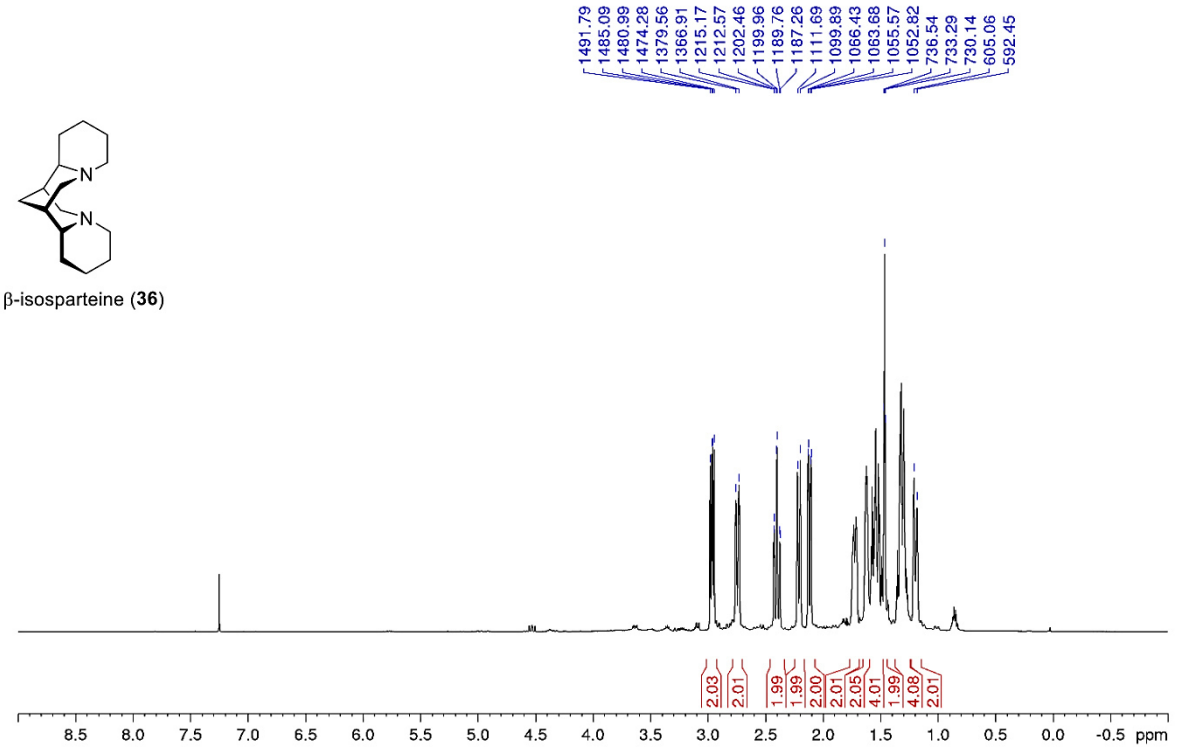

168.99
137.25
136.66
116.76
116.54
63.22
59.61
57.83
47.66
46.51
33.97
33.27
30.15
28.00
27.84
27.74
20.19
34
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

52

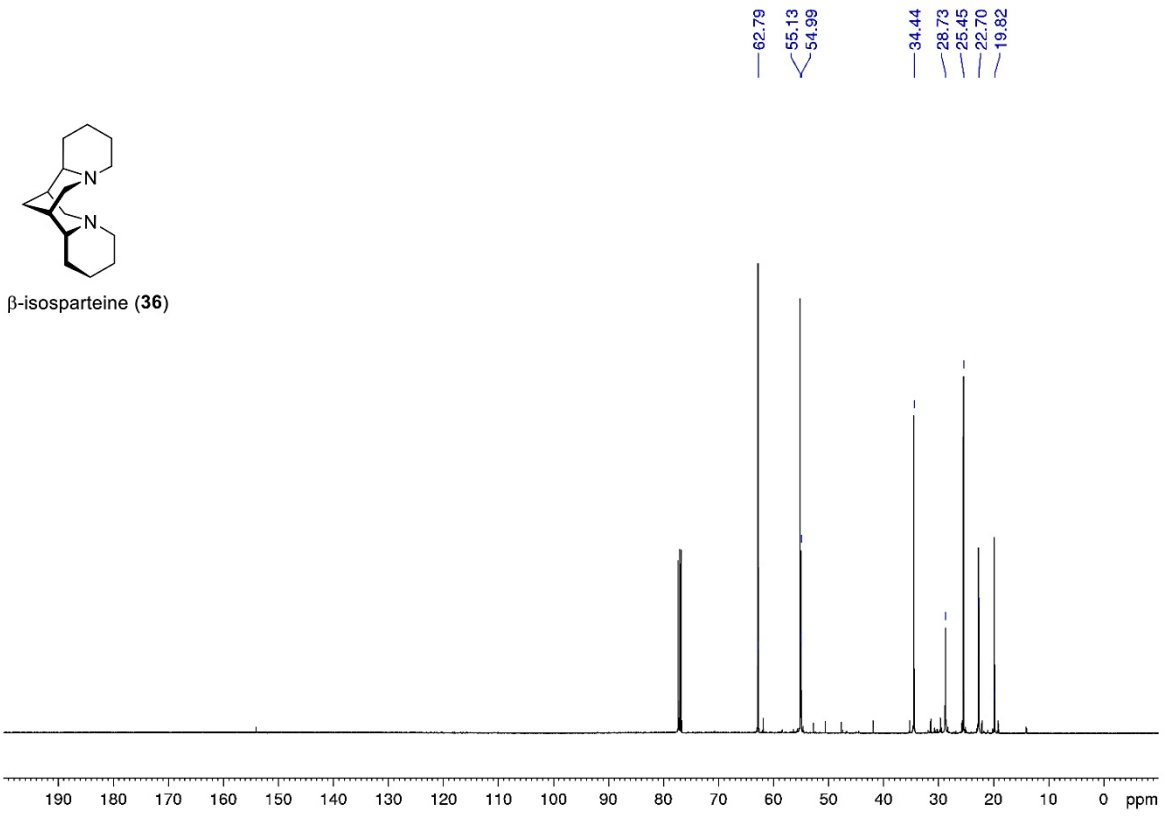

2667.74
2665.79
2656.19
2653.94
2596.32
2593.92
2572.67
2570.32
1948.91
1935.60
1913.80
1900.29
((cut off))
MeO
NBoc
NBoc
MeO
35
0.54
0.20
1.06
0.20
1.26
0.54
0.21
6.09
2.03
3.99
18.10
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm


155.57
155.52
155.10
154.86
85.80
85.55
84.57
84.34
80.29
80.24
80.10
79.88
55.17
54.75
54.66
54.62
43.04
43.02
41.89
41.45
31.61
31.58
31.48
31.36
28.66
28.61
28.51
28.40
19.39
18.62
18.61
18.40
MeO
NBoc
NBoc
MeO
35
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

53

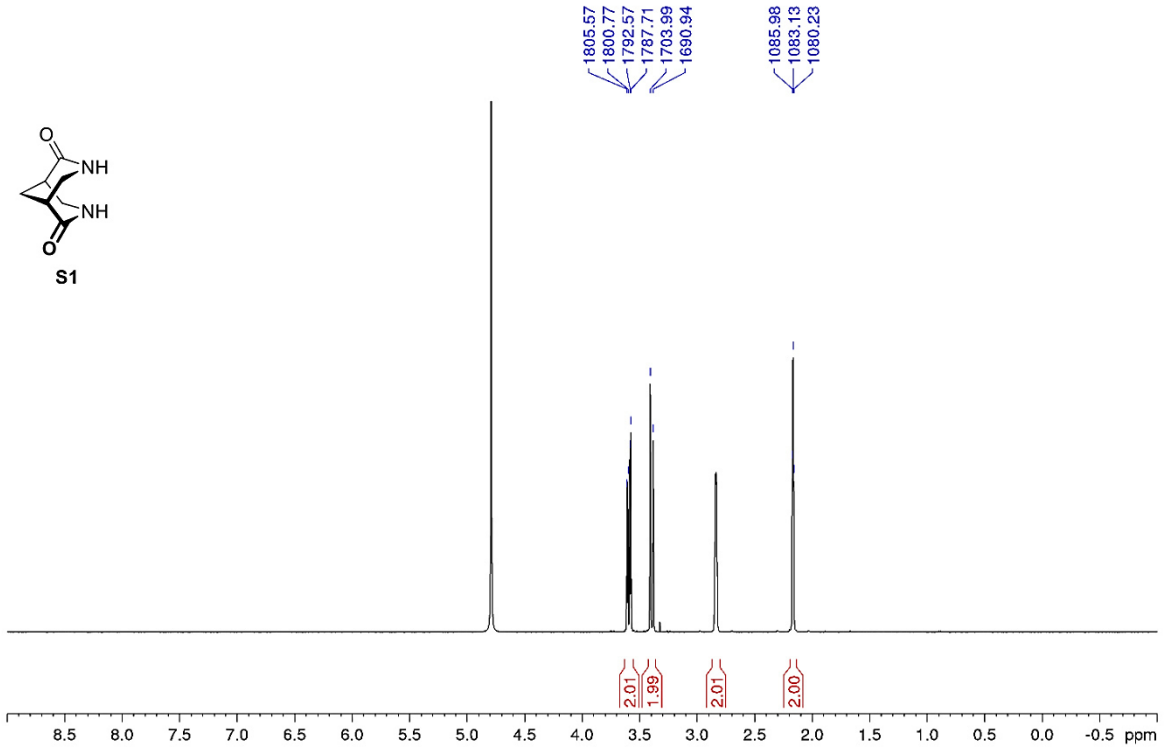


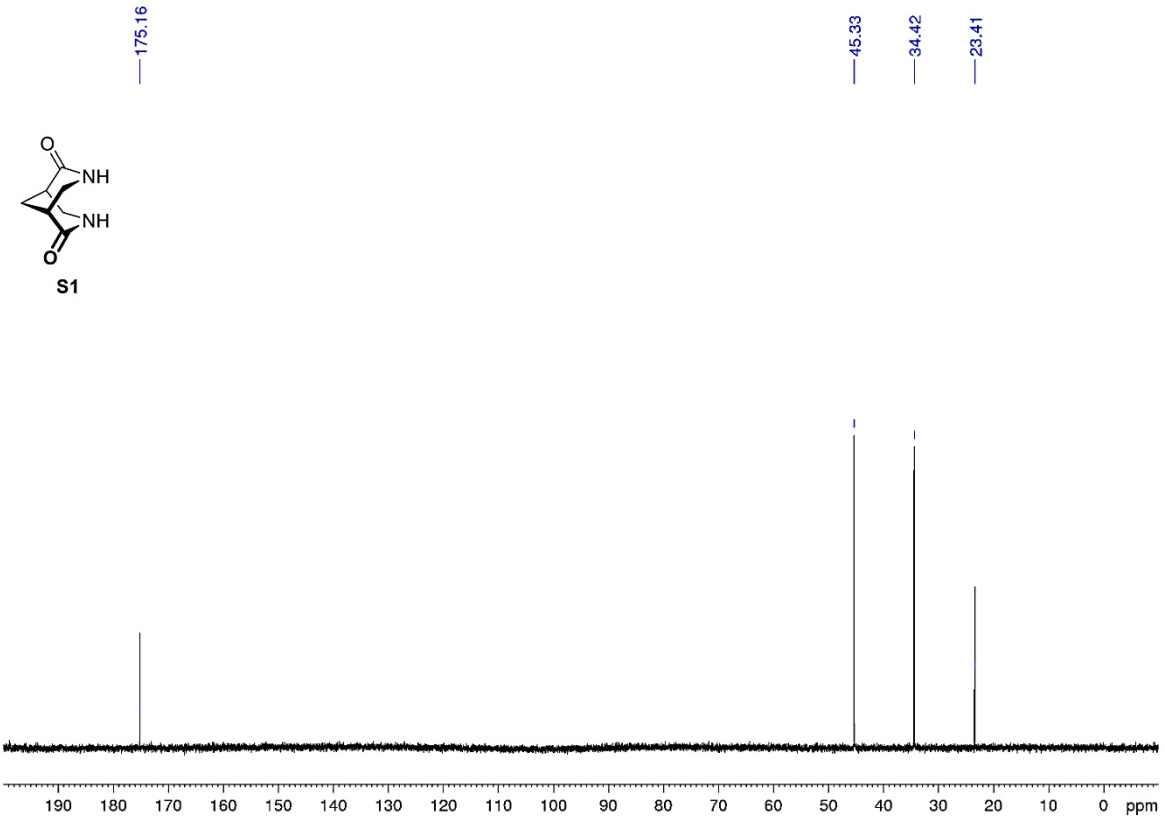
β-isosparteine (**36**)



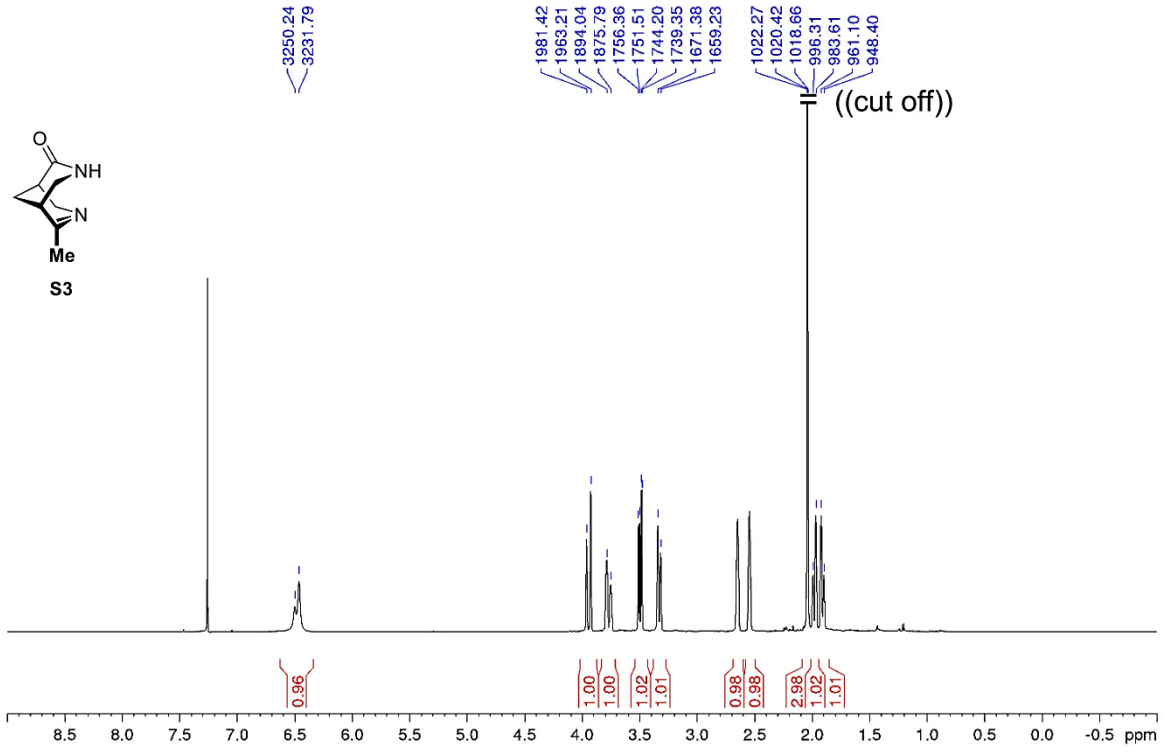
β-isosparteine (**36**)

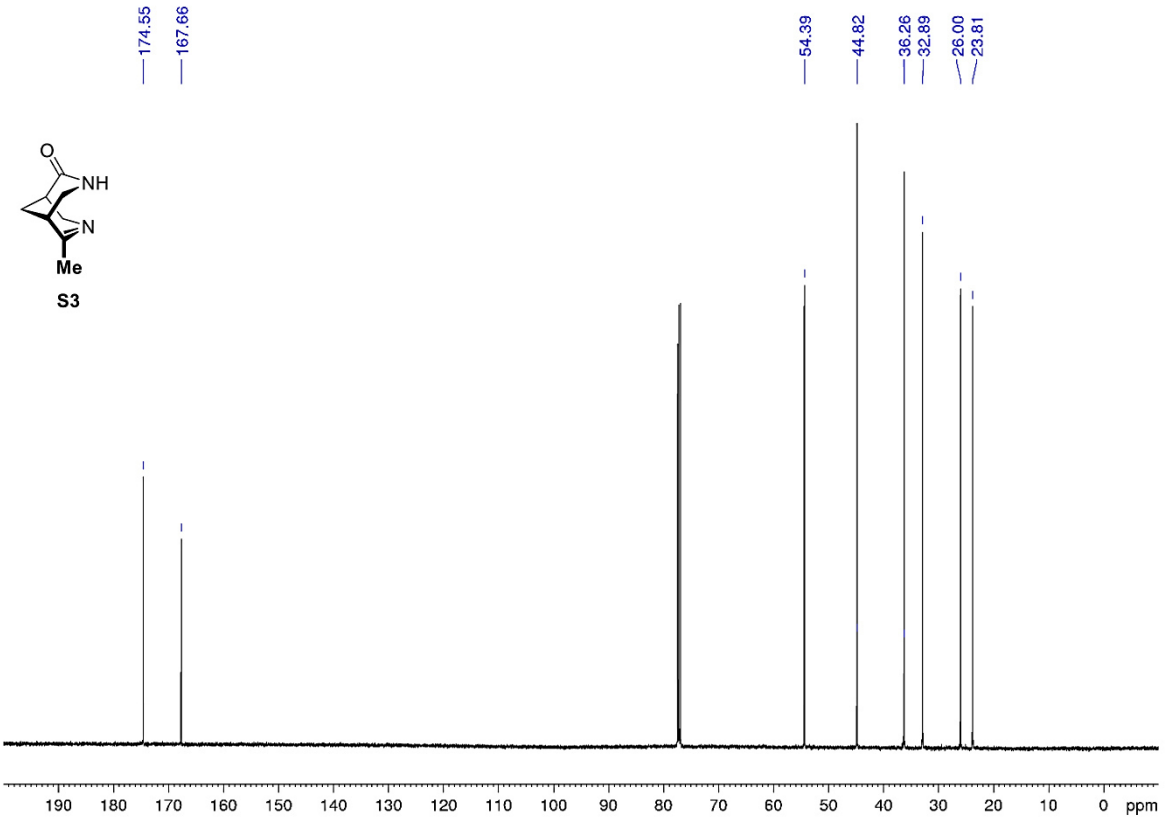
54


1805.57
1800.77
1792.57
1787.71
1703.99
1690.94
1085.98
1083.13
1080.23
NH
NH
O
O
S1
2.01
1.99
2.01
2.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

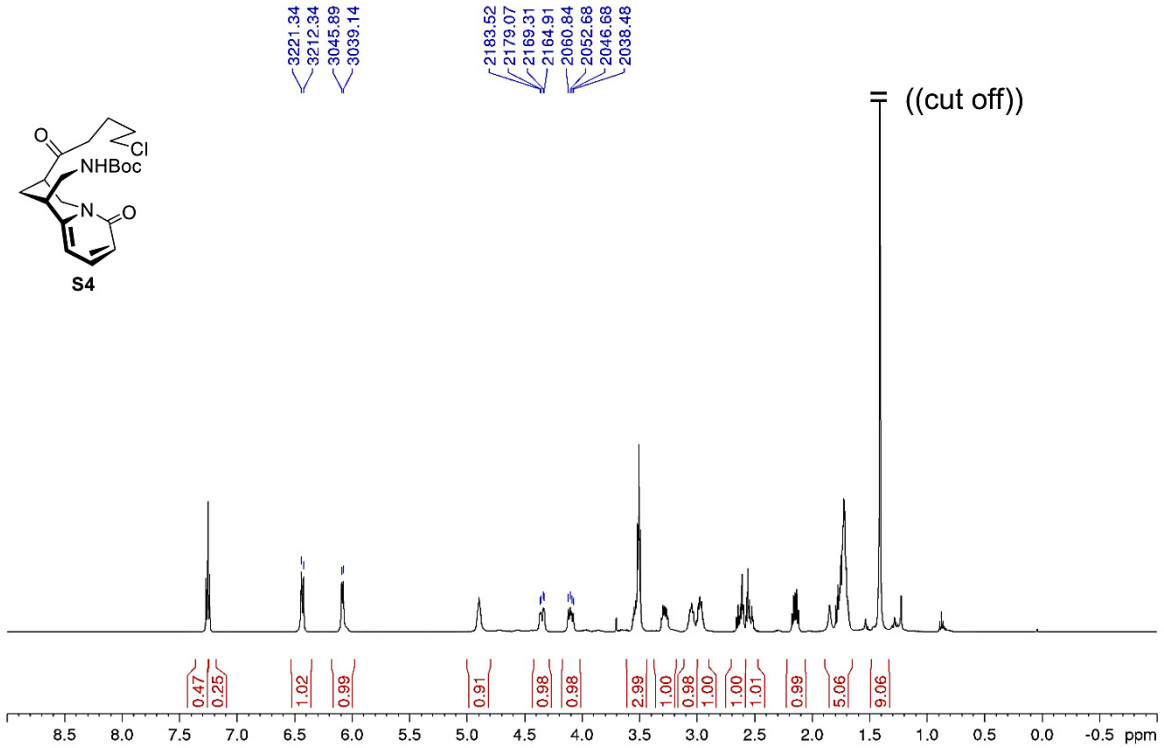

175.16
45.33
34.42
23.41
NH
NH
O
O
S1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

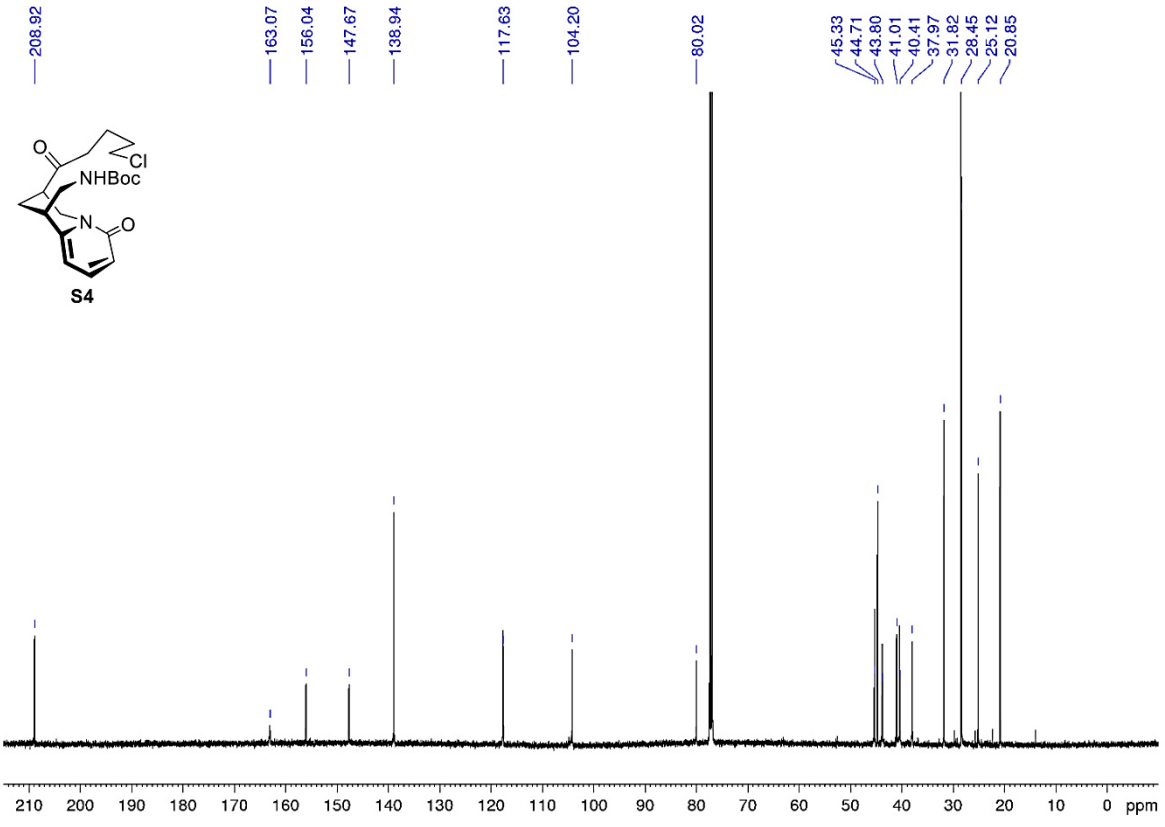
55


3250.24
3231.79
1981.42
1963.21
1894.04
1875.79
1756.36
1751.51
1744.20
1739.35
1671.38
1659.23
1022.27
1020.42
1018.66
996.31
983.61
961.10
948.40
((cut off))
O
NH
N
Me
S3
0.96
1.00
1.00
1.02
1.01
0.98
0.98
2.98
1.02
1.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

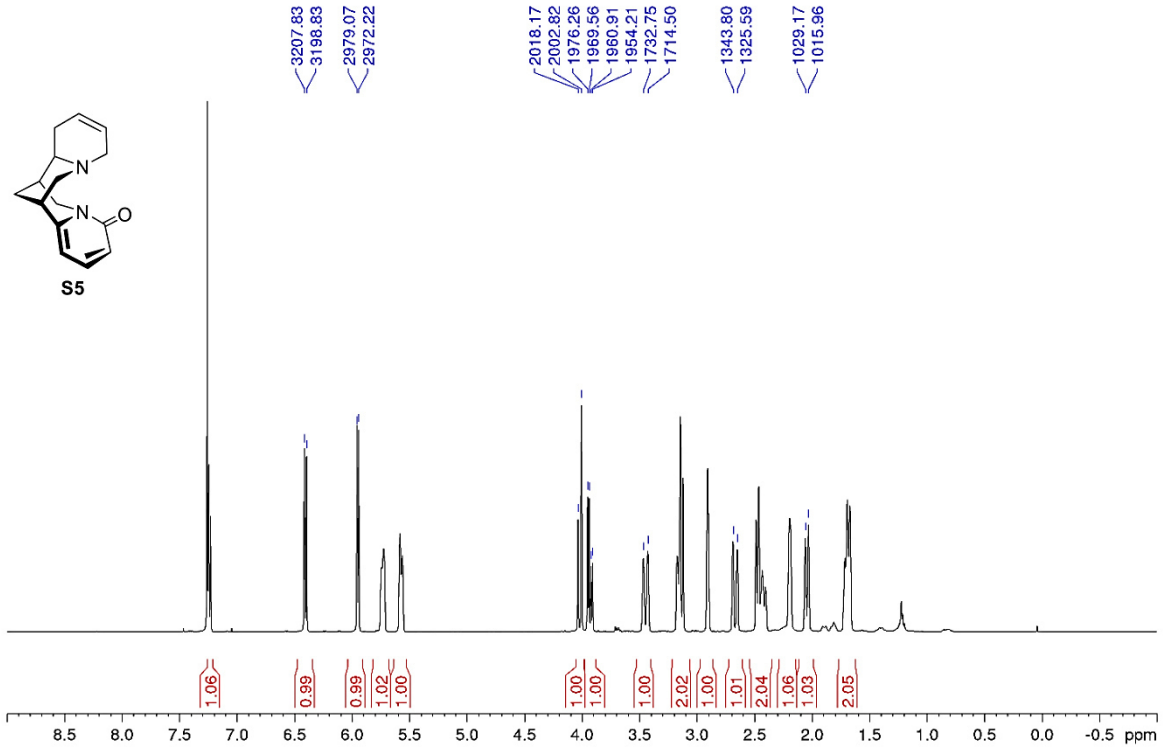

174.55
167.66
54.39
44.82
36.26
32.89
26.00
23.81
O
NH
N
Me
S3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

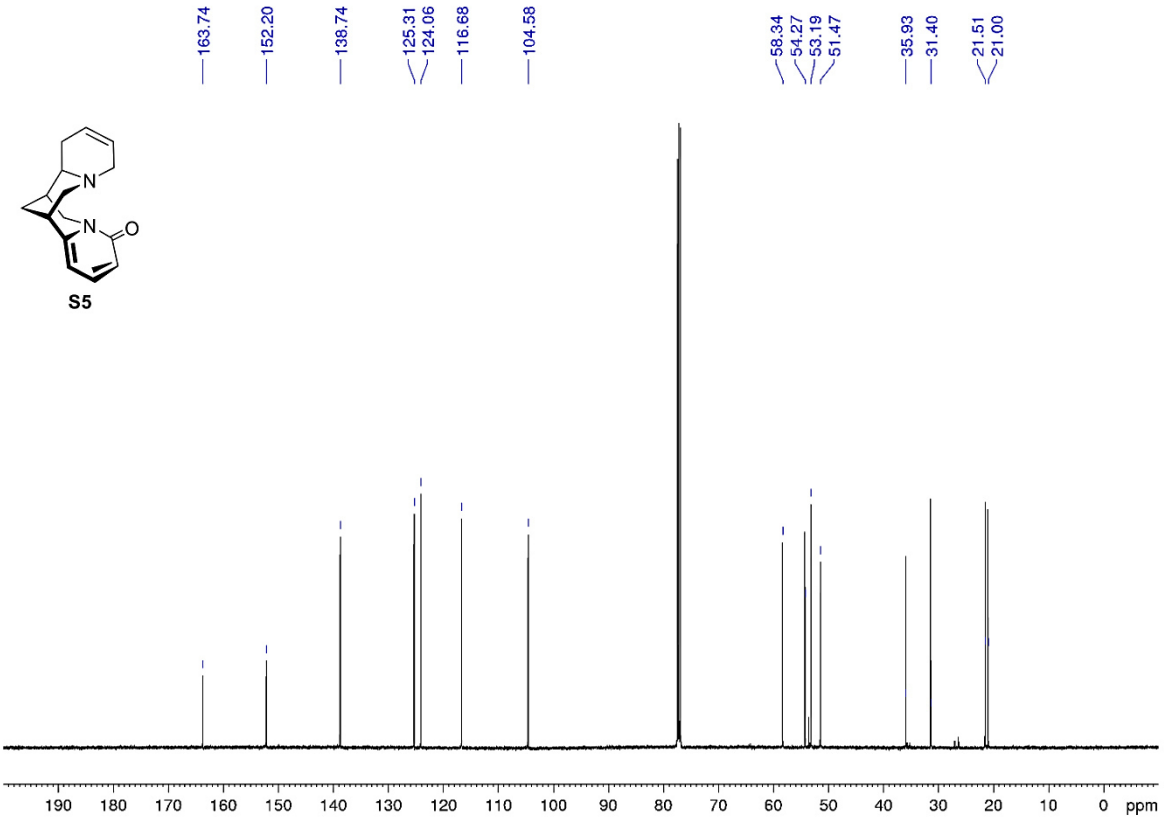
56


3221.34
3212.34
3045.89
3039.14
2183.52
2179.07
2169.31
2164.91
2060.84
2052.68
2046.68
2038.48
= ((cut off))
Cl
NHBoc
N
O
O
S4
0.47
0.25
1.02
0.99
0.91
0.98
0.98
2.99
1.00
0.98
1.00
1.00
1.01
0.99
5.06
9.06
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

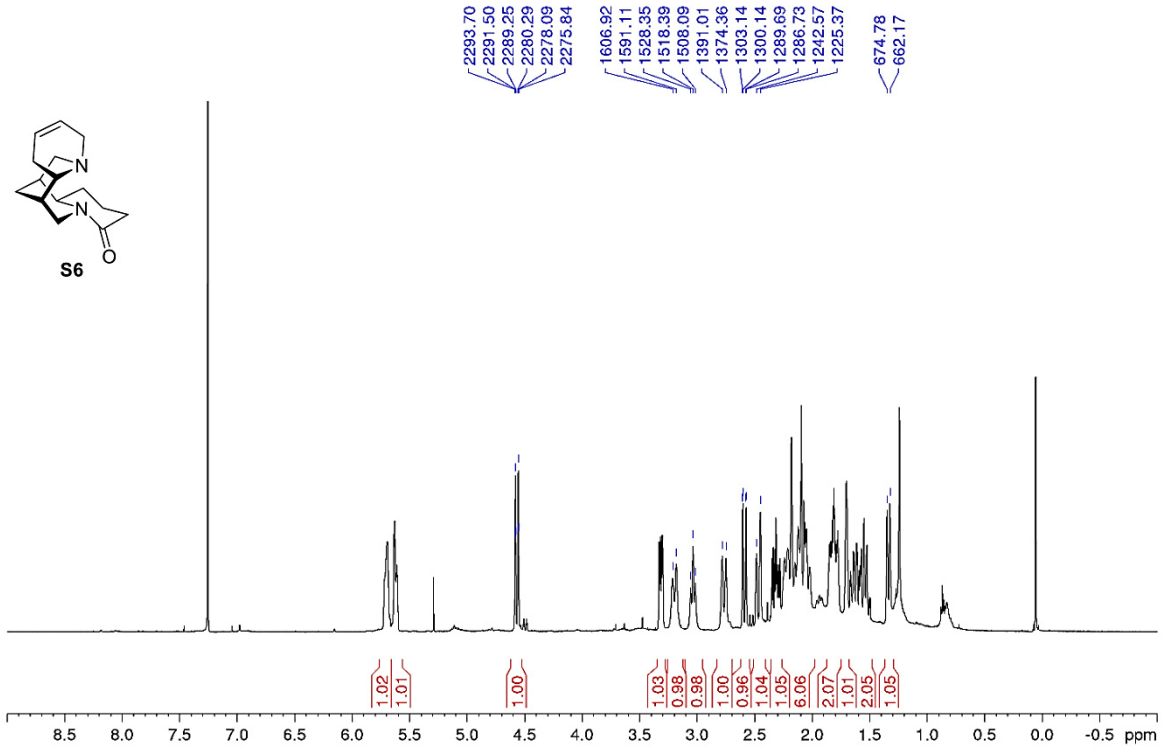

208.92
163.07
156.04
147.67
138.94
117.63
104.20
80.02
45.33
44.71
43.80
41.01
40.41
37.97
31.82
28.45
25.12
20.85
Cl
NHBoc
N
O
O
S4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

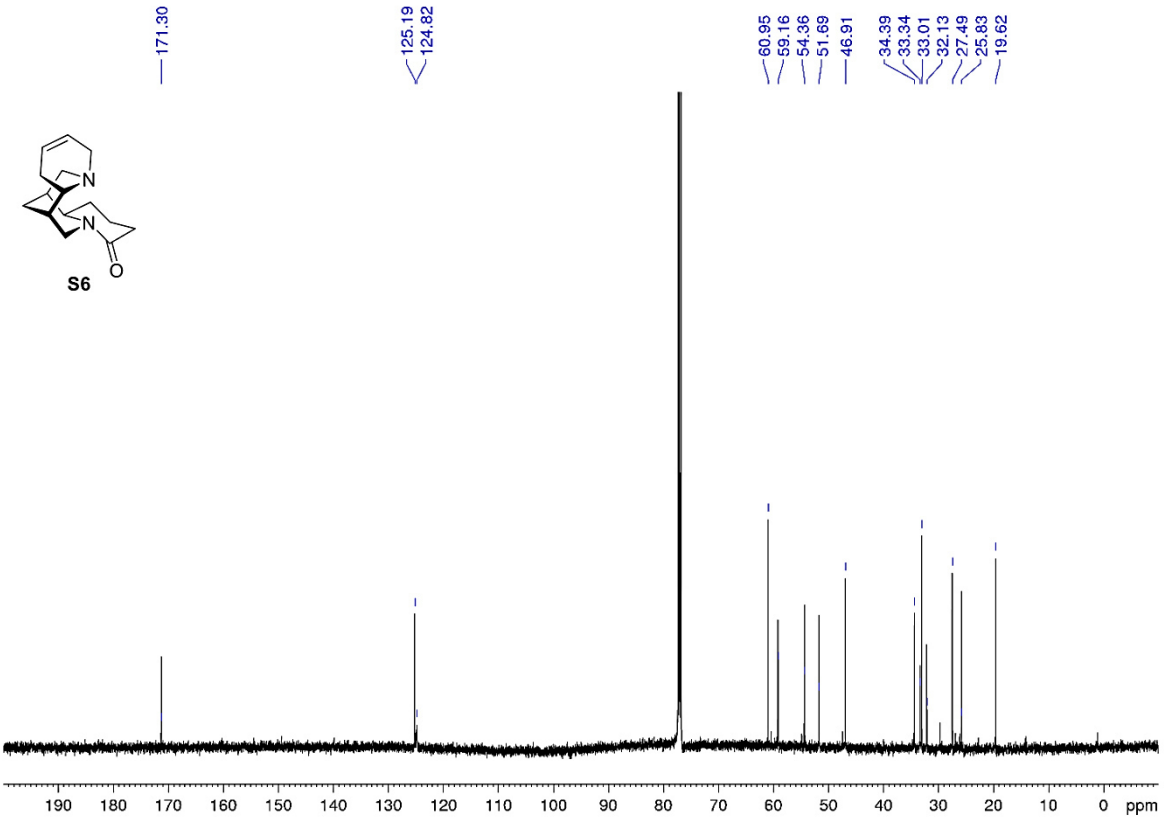
57


3207.83
3198.83
2979.07
2972.22
2018.17
2002.82
1976.26
1969.56
1960.91
1954.21
1732.75
1714.50
1343.80
1325.59
1029.17
1015.96
S5
1.06
0.99
0.99
1.02
1.00
1.00
1.00
1.00
2.02
1.00
1.01
2.04
1.06
1.03
2.05
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm


163.74
152.20
138.74
125.31
124.06
116.68
104.58
58.34
54.27
53.19
51.47
35.93
31.40
21.51
21.00
S5
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

58


2293.70
2291.50
2289.25
2280.29
2278.09
2275.84
1606.92
1591.11
1528.35
1518.39
1508.09
1391.01
1374.36
1303.14
1300.14
1289.69
1286.73
1242.57
1225.37
674.78
662.17
S6
1.02
1.01
1.00
1.03
0.98
0.98
1.00
0.96
1.04
1.05
6.06
2.07
1.01
2.05
1.05
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

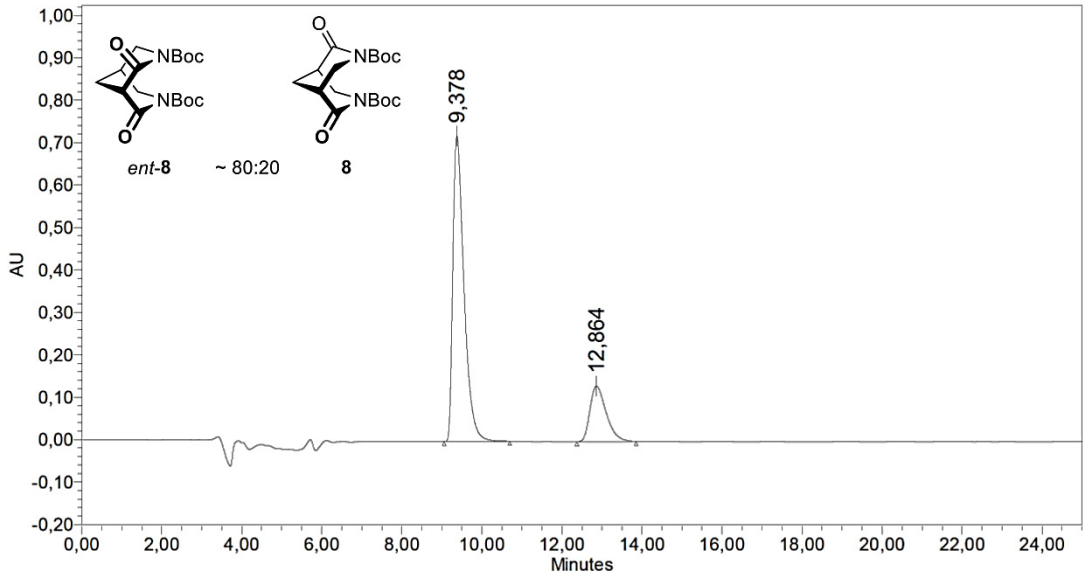

171.30
125.19
124.82
60.95
59.16
54.36
51.69
46.91
34.39
33.34
33.01
32.13
27.49
25.83
19.62
S6
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

3. Copies of HPLC Spectra

3.1 Enantiomer Analysis of the Key Intermediate 8

HPLC conditions:
Chiralcel OD-3, *n*-hexane/*i*PrOH 75:25, 0.8 mL/min, 215 nm, t_R = 9.4 min (*S,S*), 12.9 min (*R,R*).

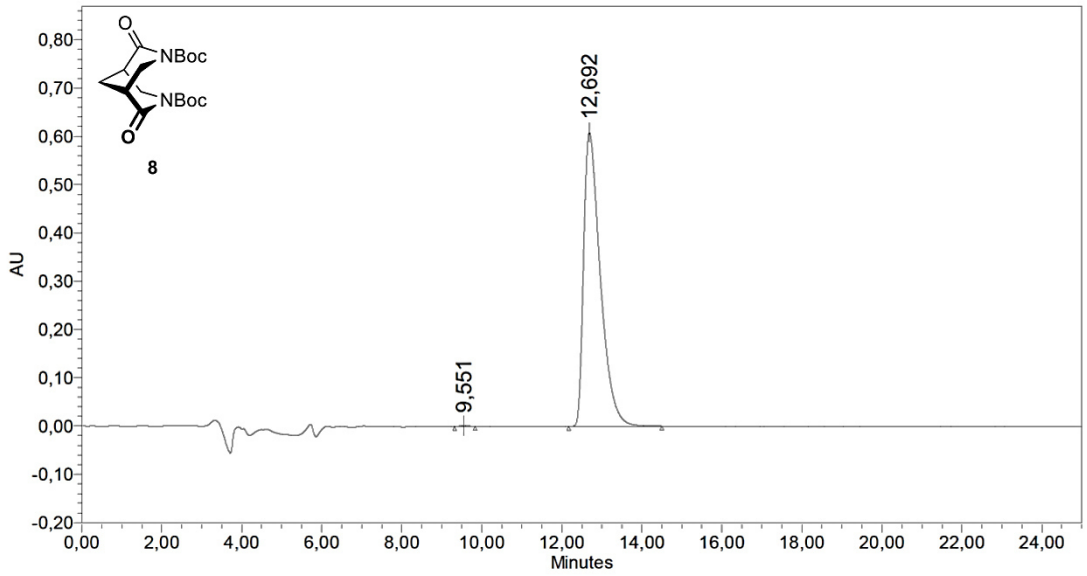
Mixture of *ent*-**8** and **8**



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,38	9,06	10,70	720452	84,61	13907016	78,98
2	12,86	12,38	13,86	131076	15,39	3701352	21,02

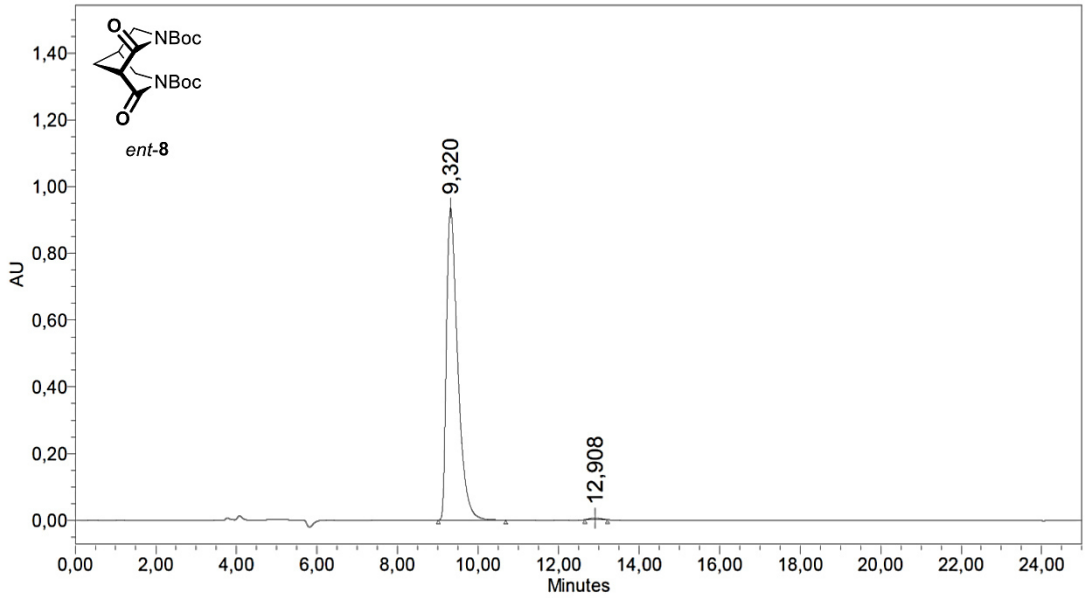
60

8: 99% *ee*



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,55	9,33	9,83	1617	0,27	24762	0,14
2	12,69	12,18	14,50	608512	99,73	17563114	99,86

ent-**8**: 99% *ee*

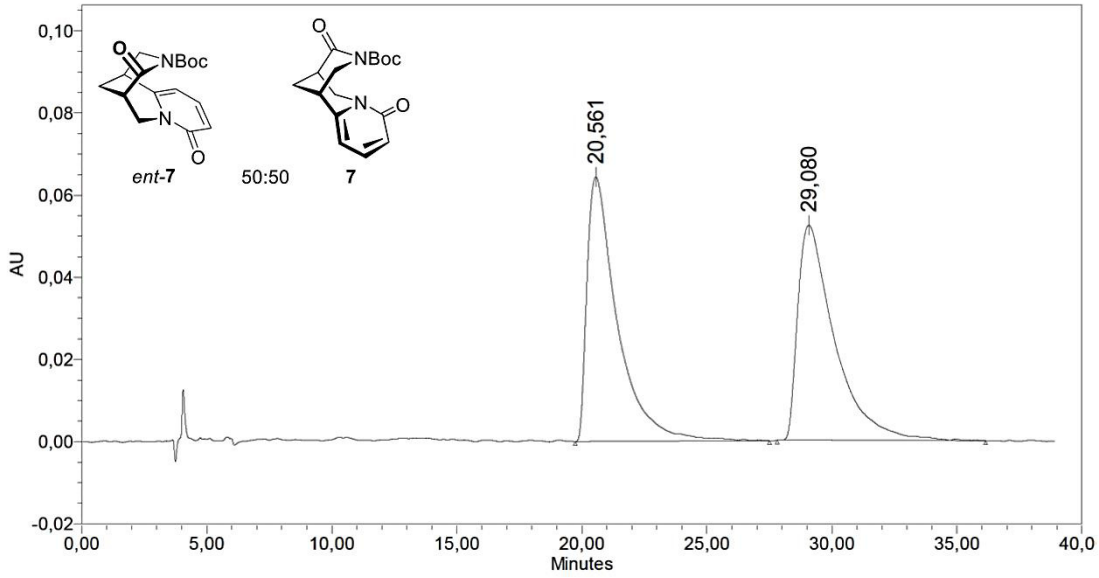


	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,32	9,02	10,69	934879	99,53	18038860	99,52
2	12,91	12,66	13,22	4423	0,47	87205	0,48

3.2 Enantiomer Analysis of the Key Intermediate 7

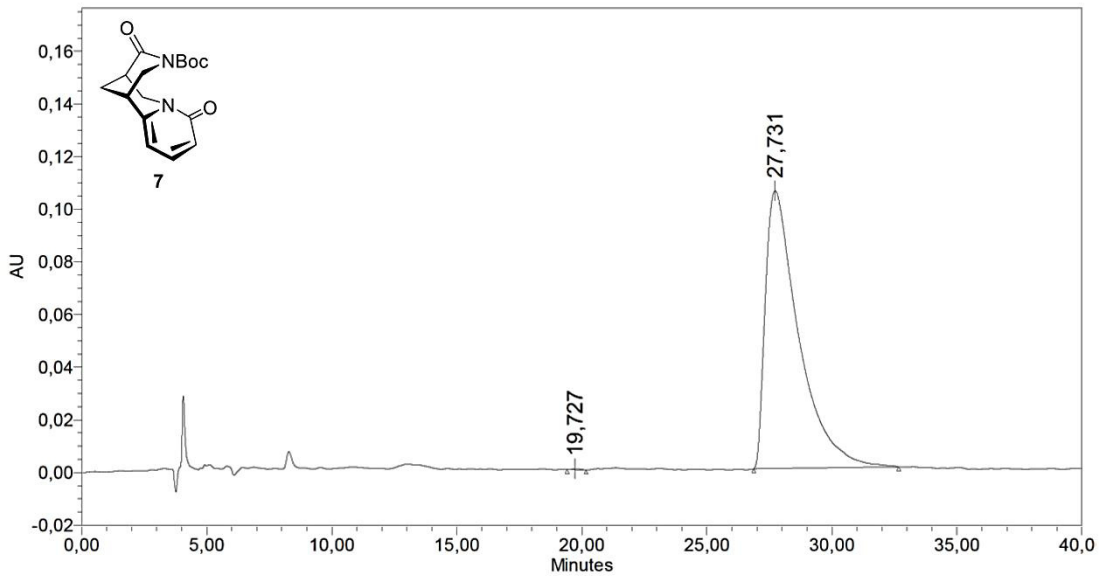
HPLC conditions:
Chiralcel OD-3, *n*-hexane/*i*PrOH 75:25, 0.8 mL/min, 215 nm, t_R = 20.6 min (*S*,*S*), 29.1 min (*R*,*R*).

Mixture of *ent*-**7** and **7**



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	20,56	19,74	27,51	64396	55,18	5432253	50,32
2	29,08	27,82	36,15	52315	44,82	5363052	49,68

7: 99% *ee*



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	19,73	19,42	20,18	322	0,30	8214	0,08
2	27,73	26,88	32,68	105534	99,70	9775918	99,92

AUFLISTUNG ALLER PUBLIKATIONEN

[5] D. Scharnagel,‡ J. Goller,‡ N. Deibl, W. Milius, M. Breuning, „The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular 'Inside-Out' Approach“, *Angew. Chem. Int. Ed.* **2018**, DOI: 10.1002/anie.201712852 (in Druck).
‡ Autoren haben gleiche Beiträge geleistet.

[4] J. Kaldun, F. Prause, D. Scharnagel, F. Freitag, M. Breuning, „Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions“, *ChemCatChem* **2016**, *8*, 1846–1856.

[3] D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, W. Milius, M. Breuning, „The First Modular Route to Core-Chiral Bispidine Ligands and Their Application in Enantioselective Copper(II)-Catalyzed Henry Reactions“, *Chem. Eur. J.* **2015**, *21*, 12488–12500.

[2] F. Prause, J. Kaldun, B. Arensmeyer, B. Wennemann, B. Fröhlich, D. Scharnagel, M. Breuning, „Flexible and Modular Syntheses of Enantiopure 5-*cis*-Substituted Prolinamines from L-Pyroglutamic Acid“, *Synthesis* **2015**, *47*, 575–586.

[1] D. Scharnagel,‡ F. Prause,‡ J. Kaldun,‡ R. G. Haase, M. Breuning, „(2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a chiral diamine ligand for copper(II)-catalysed Henry reactions with superb enantiocontrol“, *Chem. Commun.* **2014**, *50*, 6623–6625.
‡ Autoren haben gleiche Beiträge geleistet.

AUFLISTUNG ALLER TAGUNGSBEITRÄGE

Poster

[5] D. Scharnagel, J. Goller, M. Breuning, „A Modular Approach to Chiral Bispidines: Application to the Synthesis of Natural Products and Ligands“, EuCheMS Chemistry Congress, Sevilla, **2016**.

[4] D. Scharnagel, J. Goller, F. Prause, A. Müller, M. Eck, M. Breuning, „Modular Synthesis of Core-Chiral Bispidine Ligands and their Application in Asymmetric Henry Reactions“, GDCh-Wissenschaftsforum Chemie, Dresden, **2015**.

[3] F. Prause, J. Kaldun, D. Scharnagel, M. Breuning, „5-*cis*-Substituted Prolinamines: Modular Synthesis and Application in Enantioselective Catalysis“, GDCh-Wissenschaftsforum Chemie, Dresden, **2015**.*
* IUPAC Poster Preis

[2] D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, M. Breuning, „The First Modular Route to Core-Chiral Bispidine Ligands and their Application in Copper(II)-Catalyzed Asymmetric Henry Reactions“, JCF-Frühjahrssymposium, Münster, **2015**.

[1] F. Prause,‡ J. Kaldun,‡ D. Scharnagel,‡ M. Breuning, „5-*cis*-Substituted Prolinamines – Privileged Ligands for Asymmetric Henry Reactions“, Lecture Conference ORCHEM, Weimar, **2014**.
‡ Autoren haben gleiche Beiträge geleistet.

Vorträge

[3] D. Scharnagel, „Enantioselective, modular synthesis of bispidine natural products“, 52. Doktorandenworkshop Naturstoffe: Chemie, Biologie und Ökologie, München, **2017**.

[2] D. Scharnagel, „Chiralität oder warum ich maulige Moleküle mag“, 1. Science Slam der Physik & Chemie, Bayreuth, **2017**.

[1] D. Scharnagel, J. Goller, „Enantioselective Synthesis of Core-Chiral Bispidines – From Ligands to Natural Products“, 49. Doktorandenworkshop Naturstoffe: Chemie, Biologie und Ökologie, Jena, **2015**.

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