UNIVERSITÄT BAYREUTH

Bispidine:

Faszinierende Naturstoffe

und effiziente Liganden

DISSERTATION

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Meiner Familie

“Leicht ist das Leben für keinen von uns.
Doch was nützt das, man muss Ausdauer
haben und vor allem Zutrauen zu sich selbst.
Man muss daran glauben, für eine bestimmte
Sache begabt zu sein,
und diese Sache muss man erreichen,
koste es, was es wolle.”

MARIE CURIE

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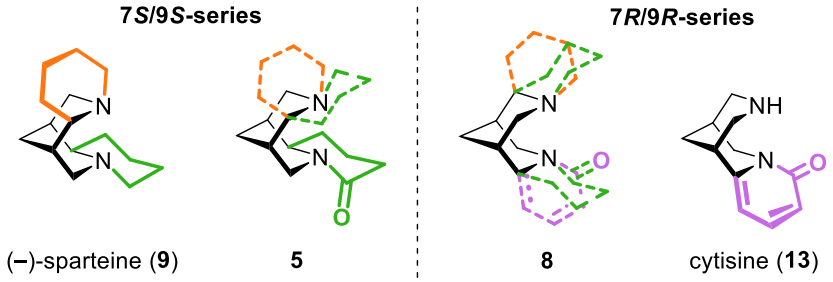
SUMMARY

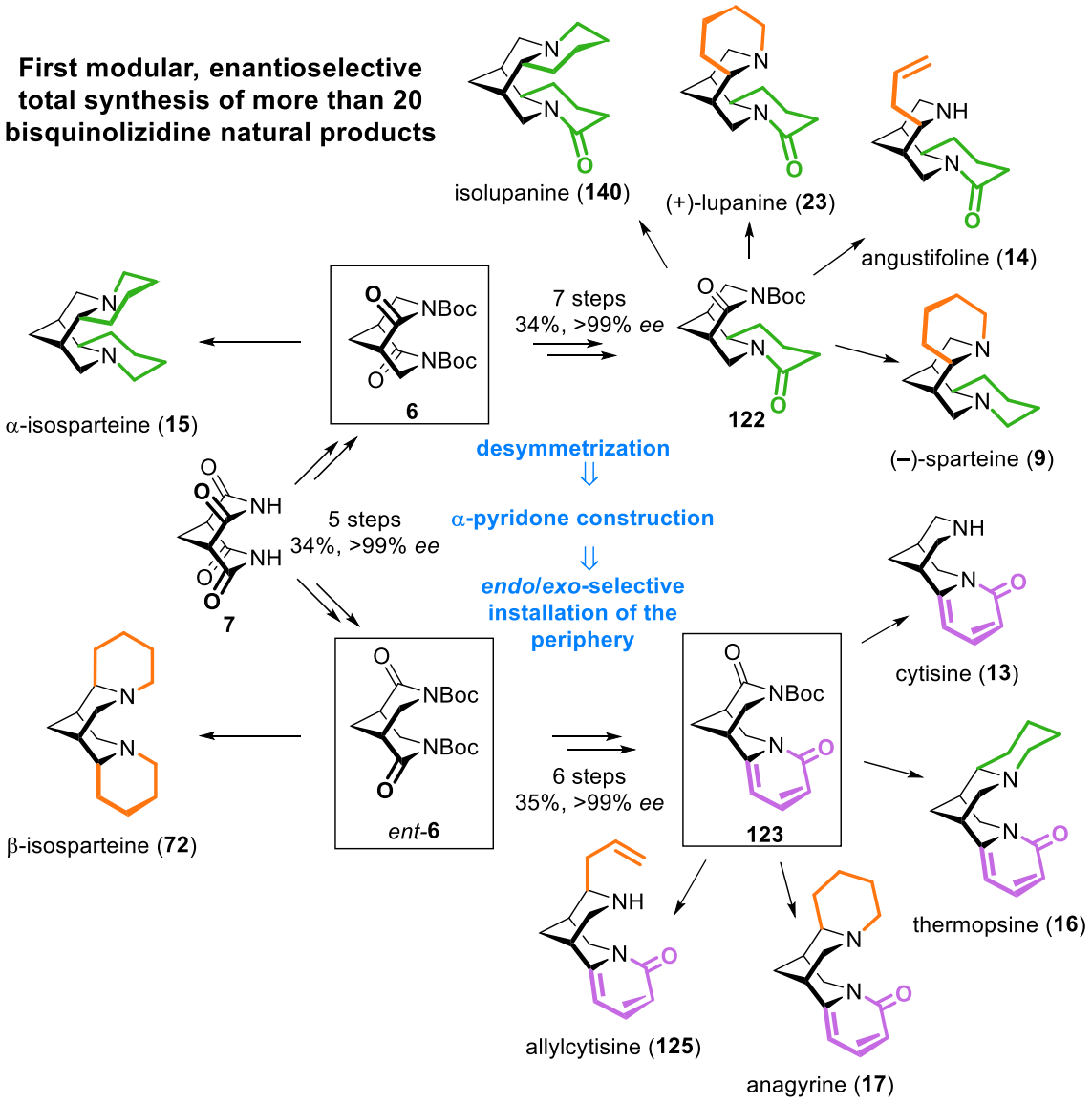
Bisquinolizidine alkaloids are a fascinating natural product class of secondary metabolites with about 50 members. The most prominent ones are (−)-sparteine (**9**), which can be isolated from scotch broom and serves as the ligand of choice in several asymmetric reactions, but also has antiarrhythmic and oxytocic properties, and cytisine (**13**), which is a partial agonist of the nicotinic acetylcholine receptor and pharmaceutically marketed for smoking cessation.



Common structural element of all bisquinolizidine natural products is a 3,7-diazabicyclo[3.3.1]-nonane skeleton, which builds the chiral core and appears in nature in both enantiomeric forms (7*S*/9*S* and 7*R*/9*R* series). Combinations of an α,*N*-fused pyridone, *endo*- or *exo*-α,*N*-annulated piperidin(on)es, and an *exo*-allyl substituent can be attached to it. To date, several elegant, enantioselective total syntheses are described, but these are all based on an "*outside-in*" strategy. The periphery, in which the natural products are differing, is constructed first and the common bispidine core is closed in a later stage. This usually limits the applicability of the approach to particular target molecules. A flexible route, as required for the efficient total synthesis of bisquinolizidine natural products and for the synthesis of new bispidine ligands, is still missing.

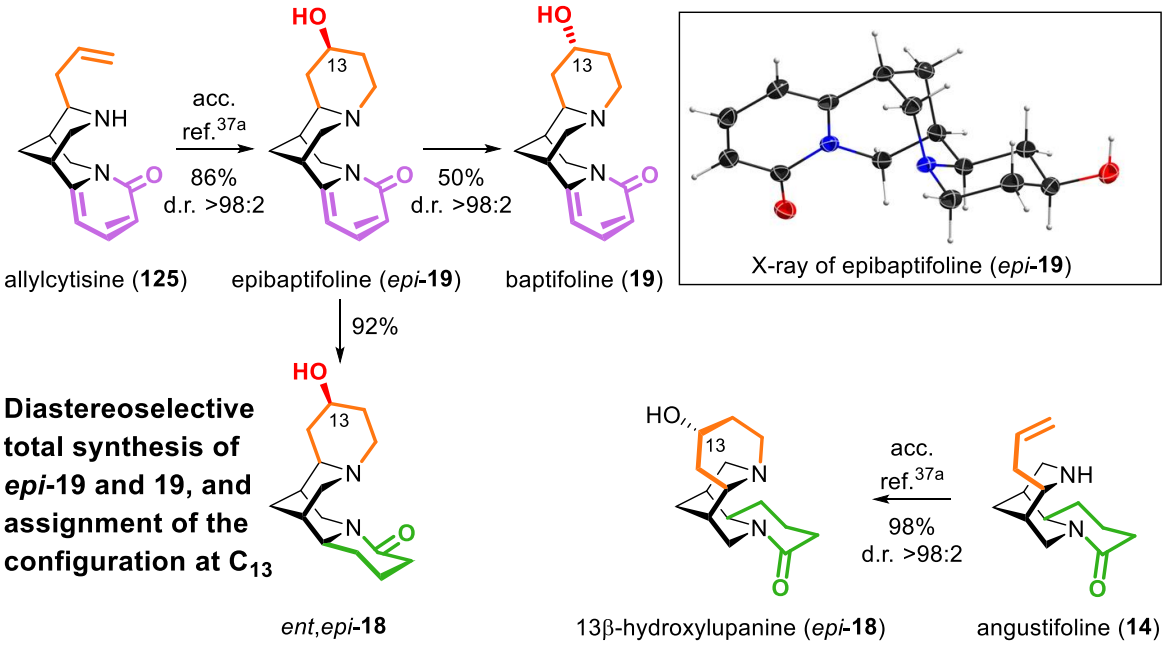
Main goal of this work was the development of a modular, enantioselective "*inside-out*"-strategy for the synthesis of tri- and tetracyclic bisquinolizidine alkaloids. The achiral tetraoxobispidine **7** was desymmetrized in the first key step, which delivered the dioxobispidine **6** or, optionally, its enatiomer *ent*-**6** in 34% yield and >99% *ee* over five steps. The installation of the α,*N*-fused pyridone **123**, which exclusively occurs in the 7*R*/9*R*-series, was the second key step and achieved, after selective modification of only one of the two imide groups, via an enamine-bromoacrylic acid strategy. Six steps were needed for that, giving the pyridone **123** in an overall yield of 35% and >99% *ee*. The enantiomeric pyridone was hydrogenated to provide the key intermediate **122** of the 7*S*/9*S*-series. By choice of the reaction sequence *endo*-

substituents were attached via addition and subsequent reduction, while *exo*-substituents were installed via reduction and following addition.



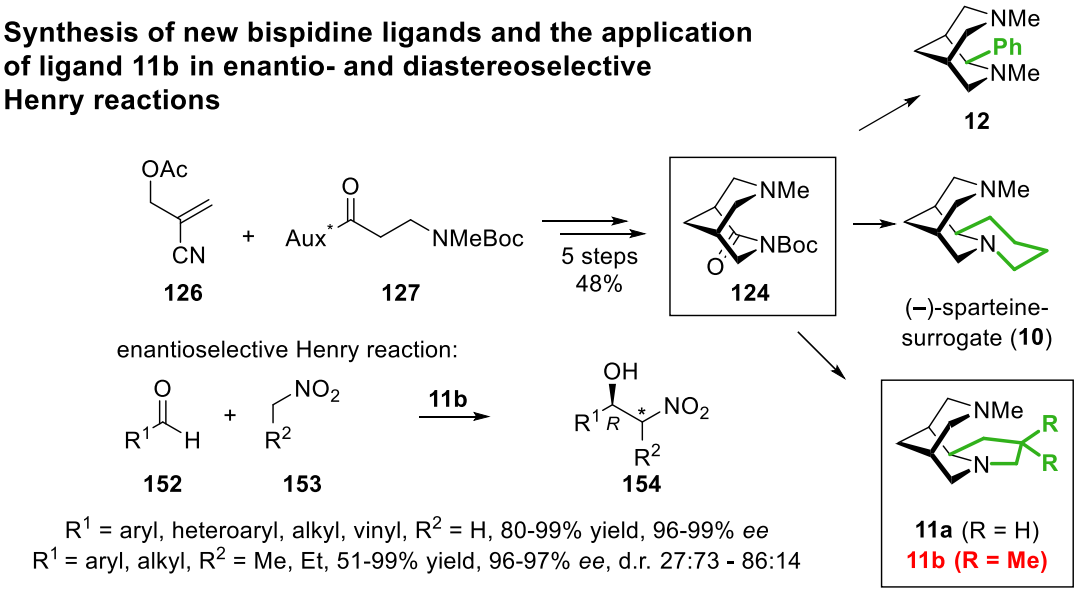
In conclusion, a modular and broadly applicable route to bisquinolizidine alkaloids was developed. The versatility was proven in the asymmetric synthesis of 21 natural products, including the first enantioselective total syntheses of angustifoline (**14**), α-isosparteine (**15**), thermospsine (**16**), anagyrine (**17**), (+)- and (−)-lupanine (**23** and *ent*-**23**), tetrahydrorhombifoline (**37**), 11-allylcytisine (**125**), 11-oxocytisine (**133**), tinctorine (**135**), isolupanine (**140**), and *N*-methylangustifoline (**142**).

The second project was the synthesis of baptifoline (**19**) and epibaptifoline (*epi*-**19**) and the unambiguous elucidation of their configuration at C_{13}. The configuration suggested by CAS/scifinder is based on a 50-year-old assignment, which was done on basis of IR spectroscopy, by using the wavenumber of the OH vibration. In other literature, however, the opposite configuration is given. To unambiguously determine the correct stereochemistry, epi-baptifoline (*epi*-**19**) was synthesized from allylcytisine (**125**) in 86% yield (>98:2 dr) and converted via an oxidation/reduction-sequence into baptifoline (**19**, 50% yield, dr >98:2). By hydration to *ent*,*epi*-**18**, the enantiomer of 13β-hydroxylupanine (*epi*-**18**), NMR spectroscopic studies, and X-ray analysis, the configuration at C_{13} bearing the alcohol function was unequivocally determined: it is equatorial in epibaptifoline (*epi*-**19**) and axial in baptifoline (**19**).



A side project dealt with the modular, stereoselective synthesis of new bispidine ligands derived from key intermediate **124**, which was synthesized in five steps and 48% yield. *Endo*-substituents were introduced via addition followed by reduction. By doing so, the three new ligands **11a**,**b** and **12** as well as the known (−)-sparteine surrogate (**10**) were synthesized. Under optimized conditions, ligand **11b** delivered the β-nitroalcohols **154** in enantioselective, Cu-catalyzed Henry reactions with 2-4 mol% catalyst in 80-99% yield and 96-99% *ee* (ten examples). Enantioselective and diastereoselective Henry reactions of **152** with nitroethane or nitropropane were done on six examples, giving 51-99% yield, 96-99% *ee*, and up to 86:14 d.r. Thus, diamine **11b** is the most efficient bispidine derived ligand for this reaction.

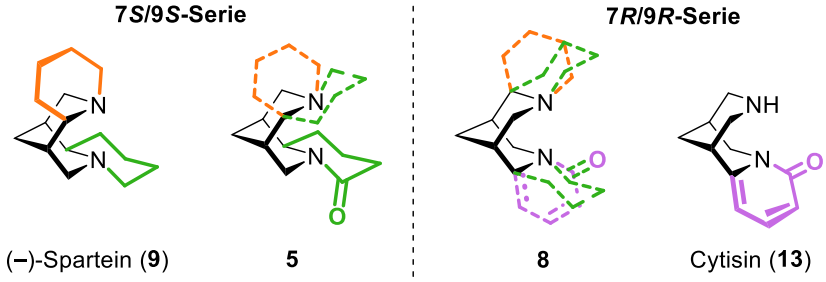
Synthesis of new bispidine ligands and the application of ligand 11b in enantio- and diastereoselective Henry reactions



R^1 = aryl, heteroaryl, alkyl, vinyl, R^2 = H, 80-99% yield, 96-99% *ee*
R^1 = aryl, alkyl, R^2 = Me, Et, 51-99% yield, 96-97% *ee*, d.r. 27:73 - 86:14

ZUSAMMENFASSUNG

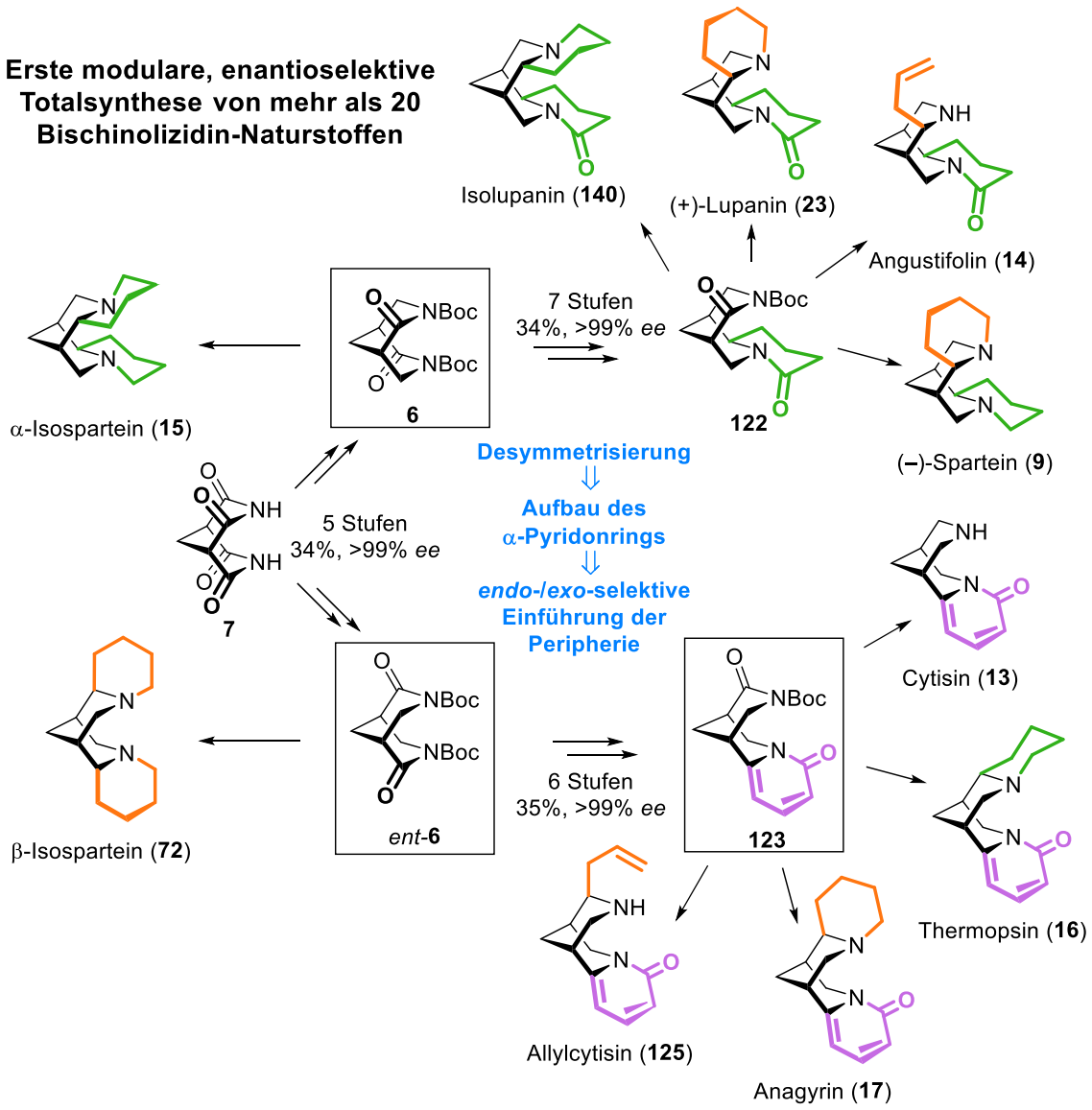
Die Bischinolizidin-Alkaloide bilden eine faszinierende Naturstoffklasse von Sekundärmetaboliten mit über 50 Vertretern. Die Bekanntesten unter ihnen sind (−)-Spartein (**9**), das unter anderem aus Besenginster gewonnen werden kann und als Ligand für diverse asymmetrische Reaktionen eingesetzt wird, aber auch wehenfördernde und antiarrhythmische Wirkungen aufweist, und Cytisin (**13**), das ein partieller Agonist des nikotinischen Acetylcholinrezeptors ist und als Wirkstoff in Medikamenten zur Rauchentwöhnung vertrieben wird.



Gemeinsames Strukturelement aller Bischinolizidin-Alkaloide ist das 3,7-Diazabicyclo[3.3.1]-nonan-Grundgerüst (Bispidin), das den chiralen Kern bildet und in der Natur in beiden enantiomeren Formen (7*S*/9*S*- und 7*R*/9*R*-Serie) vorkommt. Daran können Kombinationen aus einem α,*N*-anellierten Pyridon, *endo*- oder *exo*-α,*N*-anellierten Piperidin(on)en und einem *exo*-Allylsubstituenten angebracht sein. Zwar gibt es einige elegante enantioselektive Totalsynthesen, aber diese basieren zumeist auf einer „*Outside-In*"-Strategie. Hier wird zunächst die Peripherie, anhand derer sich die Naturstoffe unterscheiden, aufgebaut und erst auf später Stufe der gemeinsame Bispidin-Kern geschlossen, was normalerweise nur die Synthese eines konkreten Zielmoleküls erlaubt. Eine flexible Route, wie sie für eine effiziente Totalsynthese von Bischinolizidin-Naturstoffen und für die Synthese neuer Bispidin-Liganden benötigt wird, fehlt noch.

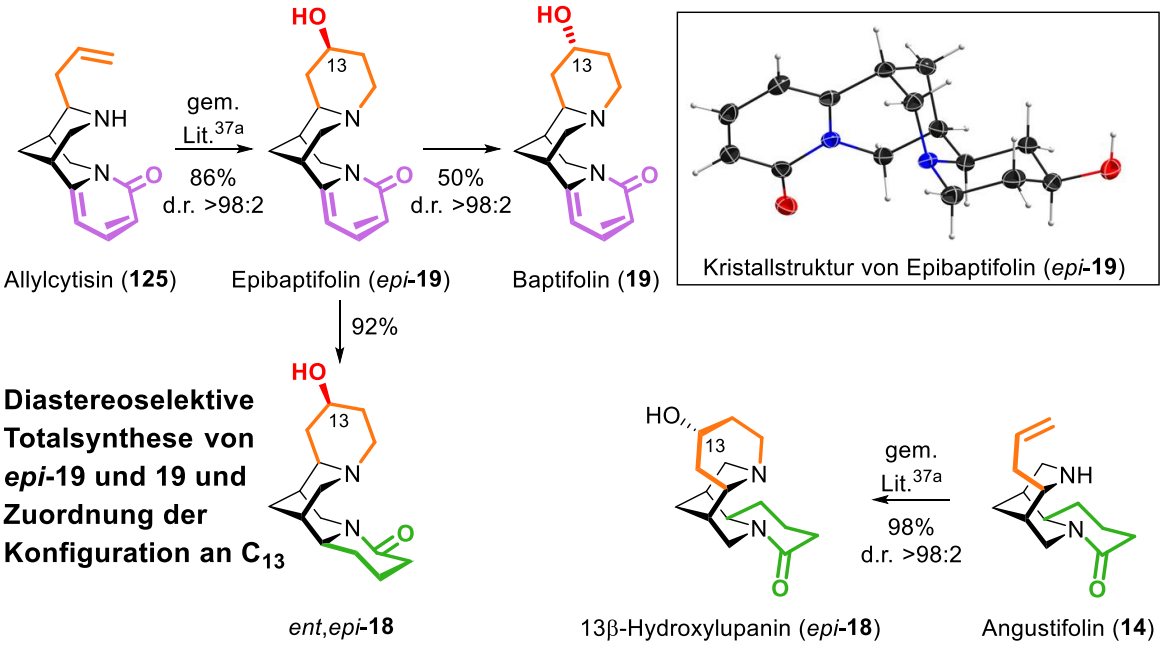
Hauptziel dieser Arbeit war die Entwicklung einer modularen, enantioselektiven „*Inside-Out*"-Strategie zur Synthese tri- und tetracyclischer Bischinolizidin-Alkaloide ausgehend vom achiralen Tetraoxobispidin **7**. Dieses wurde im ersten Schlüsselschritt desymmetrisiert, was das Dioxobispidin **6** oder, optional, dessen Enantiomer *ent*-**6** in 34% Ausbeute und >99% *ee* über fünf Stufen lieferte. Der Aufbau des α-Pyridonrings **123**, welcher ausschließlich in der 7*R*/9*R*-Serie vorkommt, bildete den zweiten Schlüsselschritt und erfolgte nach selektiver Modifikation nur einer der beiden Imidgruppen über eine Enamin-Bromacrylsäure-Strategie. Dafür wurden

sechs Stufen benötigt, welche in einer Gesamtausbeute von 35% und einem Enantiomeren-überschuss von >99% das Pyridon **123** lieferten. Für das Schlüsselintermediat **122** der 7*S*/9*S*-Serie wurde das enantiomere Pyridon hydriert. Durch die Wahl der Reaktionssequenz wurden an **123** und **122** entweder via Addition und anschließender Reduktion *endo*-Reste oder via Reduktion und anschließender Addition *exo*-Reste angebracht.



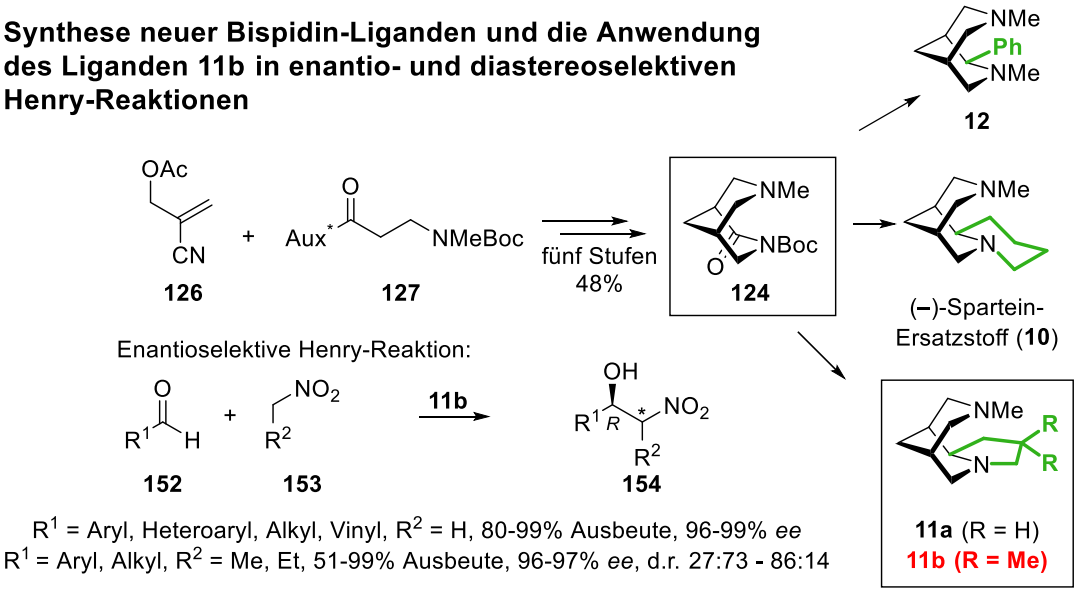
Insgesamt wurde eine modulare und breit anwendbare Route zu Bischinolizidin-Alkaloiden entwickelt, deren Potenzial anhand der asymmetrischen Synthese von 21 Naturstoffen belegt wurde. Darunter befinden sich zwölf enantioselektive Erstsynthesen, namentlich von Angustifolin (**14**), α-Isospartein (**15**), Thermopsin (**16**), Anagyrin (**17**), (+)- und (−)-Lupanin (**23** und *ent*-**23**), Tetrahydrorhombifolin (**37**), 11-Allylcytisin (**125**), 11-Oxocytisin (**133**), Tinctorin (**135**), Isolupanin (**140**) und *N*-Methylangustifolin (**142**).

Das zweite Hauptprojekt war die Synthese und eindeutige Klärung der Konfiguration an C_{13} von Baptifolin (**19**) und Epibaptifolin (*epi*-**19**). Die in CAS/Scifinder vorgeschlagene Konfiguration beruht auf einer 50 Jahre alten Zuordnung, die über die Verschiebung der OH-Schwingung im IR-Spektrum erfolgte. In anderen Literaturquellen hingegen wird die umgekehrte Konfiguration angegeben. Um die korrekte Stereochemie zweifelsfrei bestimmen zu können, wurde Epibaptifolin (*epi*-**19**) ausgehend von Allylcytisin (**125**) in 86% Ausbeute (d.r. >98:2) synthetisiert und via einer Oxidations-/Reduktionssequenz in Baptifolin (**19**, 50% Ausbeute, d.r. >98:2) überführt. Mittels Hydrierung zum enantiomeren 13β-Hydroxylupanin (*ent*,*epi*-**18**), NMR-spektroskopischen Untersuchungen sowie Röntgenkristallstrukturanalyse ließ sich die Orientierung der OH-Gruppe eindeutig bestimmen: äquatorial in Epibaptifolin (*epi*-**19**) und axial in Baptifolin (**19**).



Ein Nebenprojekt befasste sich mit der modularen, stereoselektiven Synthese neuer Bispidin-Liganden über das Schlüsselintermediat **124**, das über fünf Stufen in 48% Ausbeute dargestellt wurde. *Endo*-ständige Reste wurden über Addition und anschließender Reduktion eingeführt. So konnten die drei neuen Liganden **11a**,**b** und **12** sowie der bekannte (−)-Spartein-Ersatzstoff (**10**) synthetisiert werden. Unter optimierten Bedingungen lieferte der Ligand **11b** in enantioselektiven Cu-katalysierten Henry-Reaktionen bei nur 2-4 Mol-% Katalysatorbeladung die β-Nitroalkohole **154** in 80-99% Ausbeute und 96-99% *ee* (zehn Beispiele). Die enantio- und diastereoselektiven Henry-Reaktionen von **152** mit Nitroethan oder Nitropropan ergaben an sechs Beispielen 51-99% Ausbeute, 96-99% *ee* und bis zu 86:14 d.r. Mit **11b** wurde der effizienteste, von Bispidinen abgeleitete Ligand für diese Reaktion gefunden.

Synthese neuer Bispidin-Liganden und die Anwendung des Liganden 11b in enantio- und diastereoselektiven Henry-Reaktionen



R^1 = Aryl, Heteroaryl, Alkyl, Vinyl, R^2 = H, 80-99% Ausbeute, 96-99% *ee*
R^1 = Aryl, Alkyl, R^2 = Me, Et, 51-99% Ausbeute, 96-97% *ee*, d.r. 27:73 - 86:14

ABKÜRZUNGSVERZEICHNIS

Ac	Acetyl
ADDP	1,1′-(Azodicarbonyl)dipiperidin
Alox B	basisches Aluminiumoxid
äq	äquatorial
aq.	wässrig (*aqua*)
Äquiv.	Äquivalente
Aux.*	chirales Auxiliar
ax	axial
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
Cb	*N*,*N*-Diisopropylcarbamoyl
Cbz	Benzyloxycarbonyl
CIP	Cahn-Ingold-Prelog
Cy	Cyclohexyl
d.r.	Diastereomerenverhältnis (*diastereomeric ratio*)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-en
DCC	*N*,*N*′-Dicyclohexylcarbodiimid
DDQ	2,3-Dichlor-5,6-dicyano-1,4-benzochinon
de	Diastereomerenüberschuss (*diastereomeric excess*)
DEAD	Azodicarbonsäurediethylester
DIAD	Azodicarbonsäurediisopropylester
DIBAL-H	Diisobutylaluminiumhydrid
DMAP	4-(Dimethylamino)-pyridin
DMF	Dimethylformamid
DMSO	Dimethylsulfoxid
ee	Enantiomerenüberschuss (*enantiomeric excess*)
ent	enantiomer
epi	epimer
Et	Ethyl
et al.	und andere (*et alii*)
fl.	flüssig
HMDS	Hexamethyldisilazan
Hz	Hertz
i	*iso*
IUPAC	International Union of Pure and Applied Chemistry
LDA	Lithiumdiisopropylamid
mAChR	muskarinischer Acetylcholinrezeptor
Me	Methyl

MOP	2-(Diphenylphosphin)-2′-methoxy-1,1′-binaphthyl
Ms	Mesyl
n	*normal*
nAChR	nikotinischer Acetylcholinrezeptor
NMR	Kernspinresonanz (*nuclear magnetic resonance*)
NOESY	Kern-Overhauser-Effekt Spektroskopie (*nuclear overhauser enhancement and exchange spectroscopy*)
p	*para*
PDI	Polydispersitätsindex
Ph	Phenyl
Pin	Pinakoyl
Piv	Pivaloyl
P_m	Wahrscheinlichkeit für Einbau von *meso*-Verbindungen
PMP	*para*-Methoxyphenyl
ppm	*parts per million*
Pr	Propyl
Pyr	Pyridin
RCM	Ringschlussmetathese (*ring closing metathesis*)
RT	Raumtemperatur
s	*sekundär*
t	*tertiär*
TBAB	Tetrabutylammoniumbromid
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoressigsäure
TFAA	Trifluoressigsäureanhydrid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	Tosyl
ü.N.	über Nacht
X-Ray	Röntgenkristallstrukturanalyse

1 EINLEITUNG

Eine der ältesten und heute noch angewandten Heilkundeverfahren der Welt ist die Pflanzenheilkunde.[1] Diese Art von Medizin, bei der Pflanzen oder deren Extrakte zur Behandlung diverser Krankheiten verwendet werden, kann in Ägypten bis ins Jahr 2900 v. Chr. zurückverfolgt werden. Der älteste noch erhaltene Text dazu ist der „Papyrus Ebers“ aus dem Jahr 1500 v. Chr., der über 700 Heilmittel dokumentiert.[2] Dank der Entwicklung moderner Analytikverfahren ab dem 19. Jahrhundert ist es möglich, die verschiedenen Inhaltsstoffe dieser traditionellen Heilpflanzen zu charakterisieren und deren biologische Wirksamkeit zu studieren.[1]

Ein interessantes Beispiel dafür bietet Chinin (**1**), ein Alkaloid, welches aus der Rinde des Chinarindenbaums, einem Gewächs der Subfamilie *Cinchonoideae*, isoliert werden kann (Abbildung 1). Diese Rinde wurde schon lange von der Bevölkerung der Anden zur Bekämpfung von Schüttelfrost eingesetzt.[3] Im 17. Jahrhundert wurde die Chinabaumrinde von Peru nach Europa gebracht, nachdem die Gräfin von Chinchón dort mit einem daraus gewonnenen Heilmittel der Ureinwohner von Malaria kuriert wurde.[4] Der eigentliche Wirkstoff Chinin (**1**) wurde erstmals im Jahr 1820 von Pelletier und Caventou erfolgreich isoliert.[5] Die erste formale Totalsynthese wurde 1945 von Woodward veröffentlicht,[6] die erste tatsächliche Totalsynthese 1970 von Uskokovic.[7]

Abbildung 1. Chinin (**1**) und dessen Diastereomer Chinidin (*epi*-**1**), welche aus dem Chinarindenbaum (*Cinchona pubescens*) isoliert werden.[8]

Chinin (**1**) und weitere Cinchona Alkaloide werden heute noch kommerziell in Mengen von 700 t pro Jahr aus der Rinde der Cinchona-Bäume, welche in Zentralafrika, Indien und Indonesien kultiviert werden,[9] isoliert.[10] Chinin (**1**) war lange das einzige Mittel gegen Malaria,

bevor synthetische Chinin-Analoga, wie Mepacrin (**2**, 1930), Chloroquin (**3**, 1934) und Mefloquin (**4**, 1978), als Antimalariamittel auf den Markt kamen.[11]

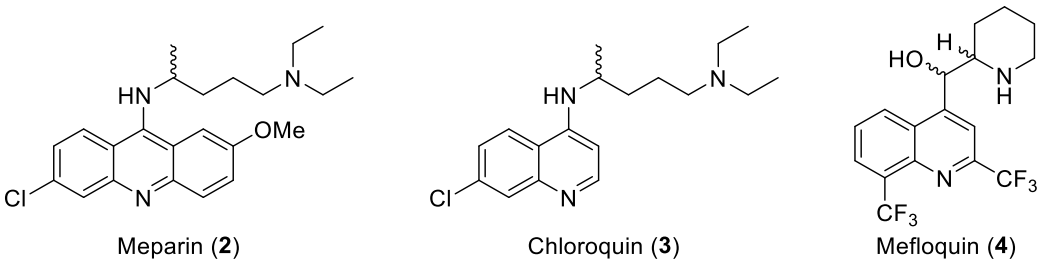


Abbildung 2. Synthetische Arzneistoffe zur Prophylaxe und Therapie von Malaria.

Dieses Beispiel zeigt, wie wichtig die Isolierung und Strukturaufklärung von Naturstoffen ist, welche von Pflanzen, Tieren und Mikroorganismen gebildet werden.[1] Vor allem aber ermöglicht die Synthese die Herstellung ausreichender Mengen von Naturstoffen, um diese in biologischen Studien zu testen und durch Derivatisierung auch Wirkstoffe mit verbesserten pharmakologischen Eigenschaften erhalten zu können.[12] Besonders wichtig ist die diastereo- und enantioselektive Synthese der Naturstoffe, da in vielen Fällen bereits die Veränderung eines einzigen Stereozentrums zu einer stark veränderten pharmakologischen Aktivität führt. So wird z. B. Chinin (**1**) als Antimalariamittel und dessen Diastereomer Chinidin (*epi*-**1**) als Antiarrhythmikum eingesetzt (s. Abbildung 1).[13] Im schlimmsten Fall kann die Verabreichung von Medikamenten mit stereoisomeren Gemischen sogar schwere Nebenwirkungen aufweisen.[14]

Betrachtet man Chinin (**1**) nun genauer, so fällt auf, dass es ein chirales Gerüst besitzt, welches vielfältig einsetzbar und auch modifizierbar ist (Abbildung 3).[15] Unter anderem nutzte Pasteur Chinin (**1**) zur ersten Racematspaltung von Weinsäure, einem Meilenstein in der organischen Chemie.[10] Aber auch als chirale Liganden in stereoselektiven, metallkatalysierten Synthesen, wie enantioselektive C-C- und C-Heteroatom-Bindungsknüpfungen, oder als Organokatalysatoren in enantioselektiven Reduktionen und Oxidationen wurden Chinin (**1**) und dessen Derivate über die letzten Jahrzehnte etabliert.[15] Der Höhepunkt in der Forschung mit chiralen Cinchona-Liganden war mit der Verleihung des Nobelpreises an Sharpless für die asymmetrische Dihydroxylierung, in welcher diese als chirale Liganden eingesetzt wurden, erreicht.[16]

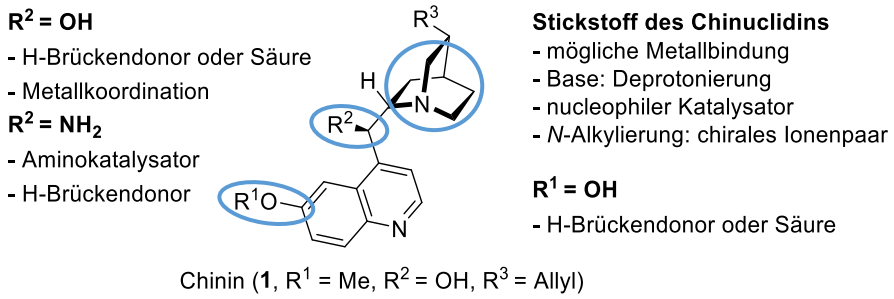
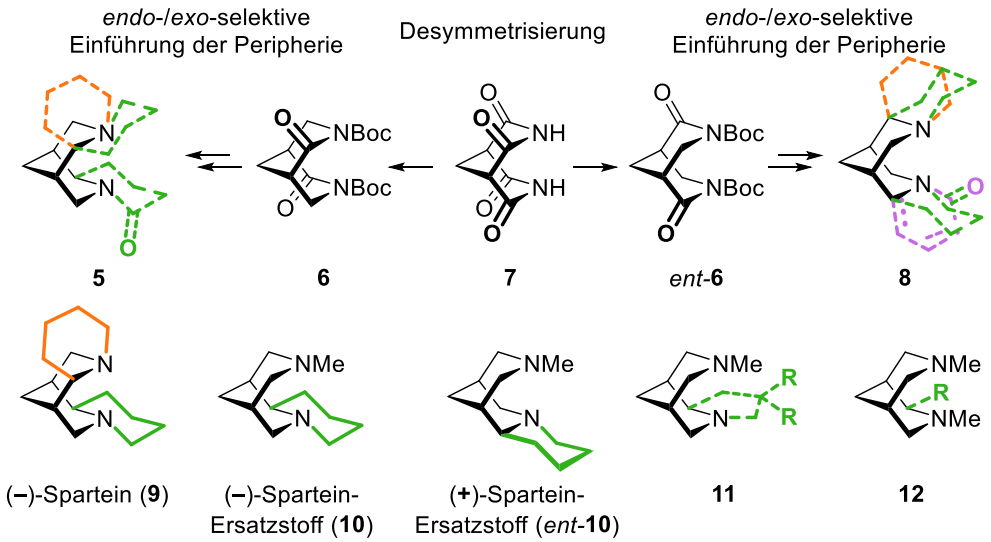


Abbildung 3. Chinin (**1**) und dessen Derivate als potentielle Liganden für die stereoselektive Synthese.[15]

Ein ebenso vielseitig einsetzbarer Naturstoff ist (−)-Spartein (**9**), welcher unter anderem aus Besenginster gewonnen wird und wehenfördernde sowie antiarrhythmische Wirkung aufweist (Schema 1).[17] (−)-Spartein (**9**) gehört zu den Bischinolizidin-Alkaloiden, deren modulare, enantioselektive Totalsynthese den Hauptteil dieser Dissertation bildet. Hierzu wurde eine neuartige „*Inside-Out*"-Strategie ausgehend von dem Kernbaustein, dem Tetraoxobispidin **7**, entwickelt. Da einige dieser Alkaloide auch großes Potenzial als Liganden in der stereoselektiven Synthese besitzen, ist deren Synthese von besonderer Bedeutung, zumal der wichtigste Ligand, (−)-Spartein (**9**), aktuell käuflich nur noch schwer zu erwerben ist.[18,19] Bisher offenbarten nur die von O'Brien synthetisierten Spartein-Ersatzstoffe (**10** und *ent*-**10**) ein ähnliches Potenzial wie (−)-Spartein (**9**). Die Synthese von neuen, Bispidin-abgeleiteten Liganden des Typs **11** und **12** bildet ein Nebenprojekt meiner Doktorarbeit.



Schema 1. Übersicht über die modulare Totalsynthese von Bischinolizidin-Naturstoffen der Typen **5** und **8**, ausgehend von dem achiralen Tetraoxobispidin **7**, und die Bispidin-abgeleiteten Liganden **11** und **12**. *Exo*-anellierte Reste sind zur besseren Übersicht in orange dargestellt, *endo*-anellierte Reste in grün. Anellierte Pyridonringe, die ausschließlich in Bischinolizidin-Alkaloiden des Typs **8** vorkommen, sind lila gekennzeichnet.

1.1 Bischinolizidin-Naturstoffe

Die Bischinolizidin-Alkaloide, die als Kern ein Bispidinsystem besitzen, bilden eine Klasse von Sekundärmetaboliten mit über 50 Vertretern.[20,21] Ihre besonderen strukturellen Merkmale sowie ihre interessanten Bioaktivitäten werden in den folgenden Kapiteln vorgestellt.

1.1.1 Isolierung

Bischinolizidin-Naturstoffe finden sich vor allem in Pflanzen der *Faboideae*-Unterfamilie (Schmetterlingsblütler, auch *Papilionoideae* genannt; Abbildung 4).[21,22] Diese gehören zur Familie der *Fabaceae* (Hülsenfrüchtler) und Ordnung der *Fabales* (Schmetterlingsblütenartige). Die *Faboideae* werden in 28 Tribus gegliedert, wobei Bischinolizidin-Alkaloide in *Genisteae*, *Thermopsideae*, *Euchresteae* und *Sophoreae* vorkommen. Die Tribus können in weitere Gattungen unterteilt werden, z. B. *Laburnum* (Goldregen) oder *Lupinus* (Lupinen).

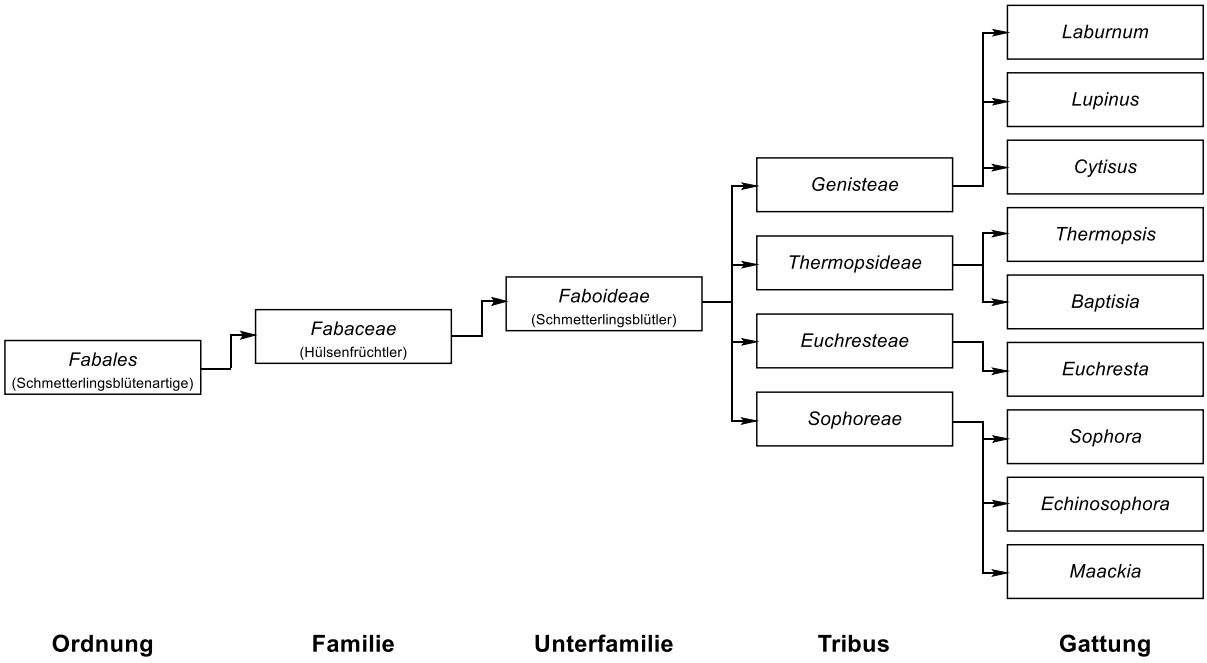


Abbildung 4. Taxonomie der *Fabales* (Schmetterlingsblütenartige).[21,22]

Unterteilt man die Bischinolizidin-Naturstoffe in zwei Gruppen, erhält man eine Spartein/Lupanin-Gruppe und eine α-Pyridon-Gruppe.[21] Saito *et al.* untersuchten verschiedene Arten der oben gezeigten Gattungen auf Vorkommen dieser Lupin-Alkaloide. Tabelle 1 zeigt die relativen Mengen der beiden Bischinolizidin-Typen bezogen auf die gesamte Alkaloidfraktion, wobei zum Teil auch beide Gruppen in nur einer Pflanzenart vorkommen, jedoch nie in gleichen Mengen. Zum Beispiel kommt in *Sophora secundiflora* (Meskalbohne) weniger als 5% des Spartein/Lupanin-Typs vor, während der α-Pyridon-Typ mehr als 30%

ausmacht. In den hier gezeigten *Euchresta*-Arten ist ausschließlich der α-Pyridon-Typ zu finden, wohingegen aus den aufgeführten *Lupinus*-Arten ausschließlich der Spartein/Lupanin-Typ isoliert werden kann.

Tabelle 1. Verteilung von Lupin-Alkaloiden in *Fabaceae/ Leguminosae* (Hülsenfrüchtlern).[21]

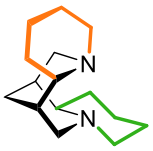
Gattung/Art	**Spartein/Lupanin-Typ**	**α-Pyridon-Typ**
***Genisteae*:**		
Lupinus luteus	++	
L. hirsutus	+++	
L. termis	+++	
Cytisus scoparius	+++	
***Thermopsideae*:**		
Thermopsis lupinoides	+	+++
T. chinensis	+	+++
Baptisia australis	+	+++
***Euchresteae*:**		
Euchresta japonica		+
E. formosana		++
***Sophoreae*:**		
Sophora flavescens	+	++
S. tomentosa		++
S. chrysophylla	+++	+
S. franchetiana		+++
S. mollis	++	+++
S. secundiflora	+	+++
S. exigua	+	+++
Echinosophora koreensis		
Maackia amurensis	+	++
M. tashiroi		+++
M. pubescens		++
M. floribunda	+	+++

+++: >30%, ++: <30% und +: <5% bezogen auf die gesamte Alkaloidfraktion.

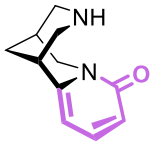
Einer der bekanntesten Bischinolizidin-Naturstoffe des Spartein/Lupanin-Typs ist (−)-Spartein (**9**), welches unter anderem aus dem Gewöhnlichen Besenginster (*Cytisus scoparius*) und Schöllkraut (*Chelidonium majus*) gewonnen werden kann (Abbildung 5).[23,24] Der α-Pyridon-Typ wird von Cytisin (**13**) vertreten und kommt beispielsweise im Gemeinen Goldregen (*Laburnum anagyroides*) vor.[25]

Gewöhnlicher Besenginster
(*Cytisus scoparius*)

Schöllkraut
(*Chelidonium majus*)[26]



(–)-Spartein (**9**)



Cytisin (**13**)

Gemeiner Goldregen
(*Laburnum anagyroides*)

Abbildung 5. (−)-Spartein (**9**) aus Gewöhnlichem Besenginster (*Cytisus scoparius*) und Schöllkraut (*Chelidonium majus*),[26] sowie Cytisin (**13**) aus Gemeinem Goldregen (*Laburnum anagyroides*).

1.1.2 Chemischer Aufbau

Die Bischinolizidin-Naturstoffe leiten sich vom gemeinsamen Kernmotiv, einem Bispidin (3,7-Diazabicyclo[3.3.1]nonan), ab (Abbildung 6).[18] Dieses tritt in beiden enantiomeren Formen auf, wobei der Spartein/Lupanin-Typ sowohl *S*- (7*S*/9*S*) als auch *R*-konfiguriert (7*R*/9*R*) sein kann.[21] Der α-Pyridon-Typ kommt ausschließlich in den *R*-konfigurierten Enantiomeren (7*R*/9*R*) vor. An das Bispidin-Gerüst können Kombinationen aus einem *α,N*-anellierten 2-Pyridon (lila), *endo*- (grün) oder *exo*- (orange) *α,N*-anellierten Piperidin(on)en sowie einem *exo*-Allyl-substituenten angebracht sein.

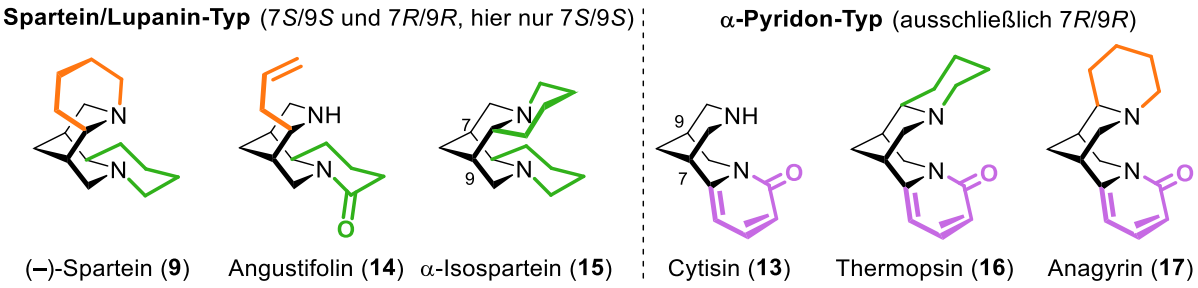


Abbildung 6. Bekannte Vertreter der Bischinolizidin-Naturstoffe (**9**, **13**-**17**), geordnet nach Spartein/Lupanin- und α-Pyridon-Typ. Der 3,7-Diazabicyclo[3.3.1]nonan-Kern (Bispidin) ist in schwarz dargestellt.

Die Konformation von (−)-Spartein (**9**) wurde von mehreren Gruppen untersucht. Bohlmann *et al*. zeigten schon 1958 und 1965 via IR- und ^{1}H-NMR-Experimenten, dass (−)-Spartein (**9**) in

einer Boot/Sessel-Konformation vorliegen muss (Abbildung 7).[27,28] Über Vergleiche der ^{13}C-NMR-Spektren von (−)-Spartein (**9**) mit dem symmetrischen α-Isospartein (**15**) im Jahr 1975 wurde diese Annahme untermauert.[29] Durch den γ-Effekt[30] kann ein Hochfeld-Shift von C_8 in (−)-Spartein (**9**) beobachtet werden (27.6 ppm; −9.1 ppm im Vergleich zu α-Isospartein (**15**)), der durch die Nähe von C_8 zu dem freien Elektronenpaar in N_{16} hervorgerufen wird.

Gołębiewski konnte 1986 diese Konformation in Ring C und D mit weiteren NMR-Experimenten bestätigen.[31,32] Zu dieser Strukturannahme kamen sie unter anderem über die Tieffeld-Shifts von $H_{17äq}$ (2.67 ppm), $H_{15äq}$ (2.76 ppm) und $H_{8äq}$ (2.34 ppm), da diese durch das freie Elektronenpaar vom benachbarten N_{16} stark entschirmt sind. $H_{17äq}$ zeigt eine große vicinale Kopplung zu H_7 (10.8 Hz), wohingegen H_{17ax} eine kleine vicinale Kopplung (3.9 Hz) aufweist. Dies ist nur bei einer Boot-Konformation möglich, in welcher der Diederwinkel zwischen dem „pseudo-äquatorialen“ $H_{17äq}$ und H_7 (6°) klein und zwischen dem „pseudo-axialen“ H_{17ax} und H_7 aufgrund des Karplus-Effekts groß (100°) ist. Die kleine Kopplung zwischen H_9 und H_{11} (2.1 Hz), sowie die große diaxiale Kopplung zwischen H_{11} und H_{12ax} (10.7 Hz) zeigen, dass H_{11} nicht äquatorial stehen kann. Die Kopplungen zwischen H_6, H_{5ax} (13.2 Hz) und $H_{5äq}$ (5.4 Hz), beweisen, dass H_6 in beiden Ringen A und B axial angebracht sein muss.

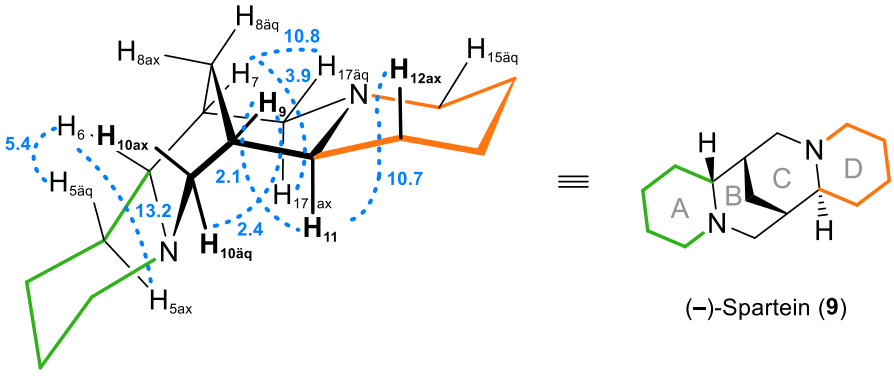


Abbildung 7. Konformation von (−)-Spartein (**9**), wobei der *exo*-Ring in der Boot/Sessel-Konformation eine *endo*-Position einnimmt. Zur besseren Übersicht ist dieser dennoch in orange dargestellt.[31,32]

Im Gegensatz zu (−)-Spartein (**9**) liegt Anagyrin (**17**), trotz *exo*-Konfiguration des Piperidin-Rings, nicht in der Boot/Sessel-, sondern in der Sessel/Sessel-Konformation (Ringe C und D) vor (Abbildung 8).[33,34] Dies kann zum einen durch die Kopplungen zwischen H_7, $H_{17äq}$ (3.1 Hz) und H_{17ax} (3.0 Hz), zum anderen durch die Kopplungen im NOESY zwischen H_{8ax}, H_{12ax} und H_{17ax} belegt werden. H_{11} muss aufgrund der großen diaxialen Kopplung zu H_{12ax} (12.0 Hz) und der kleinen Kopplung zu H_9 (2.5 Hz) axial in den Sesseln angeordnet sein.

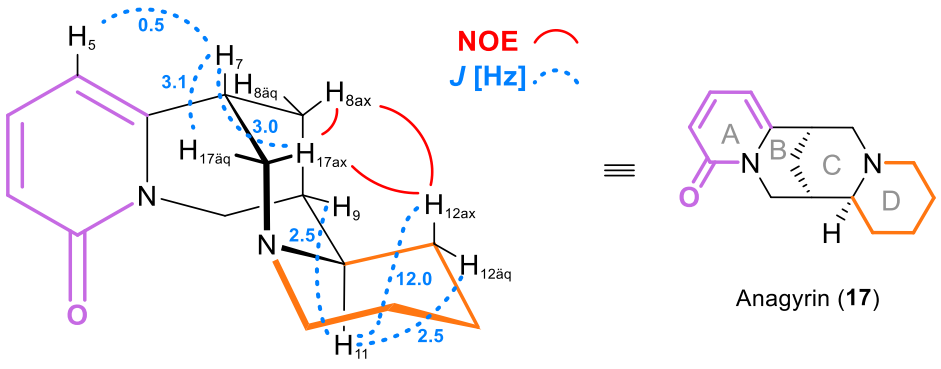


Abbildung 8. Konformation von Anagyrin (**17**).[33,34]

Häufig wird bei Hydroxy-Bischinolizidinen **18** die α,β-Nomenklatur nach IUPAC verwendet (Abbildung 9).[35] Diese wird in diesem Fall nicht von Steroiden oder Zuckern, sondern von cyclischen Molekülen mit mehreren Stereozentren abgeleitet. Man geht dabei vom Stereozentrum mit der niedrigsten Atomnummer aus (Spartein/Lupanin-Typ C_6, α-Pyridon-Typ C_7). Die α-Seite ist diejenige, in welche der Rest mit der höchsten CIP-Priorität an diesem Stereozentrum zeigt (bei **18**: N_1), die β-Seite ist dieser entgegengesetzt.

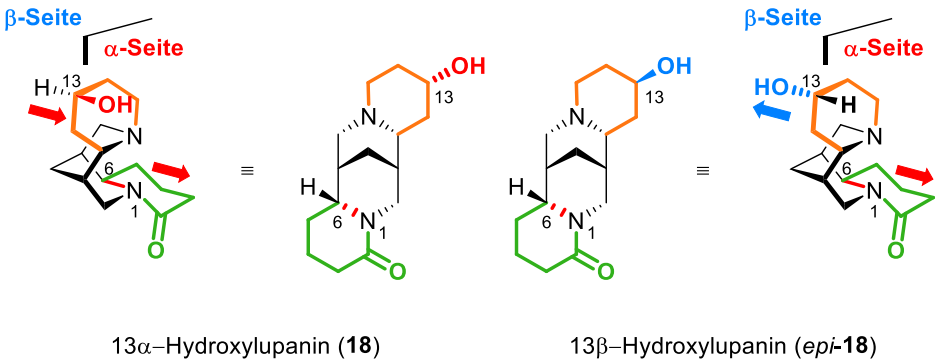
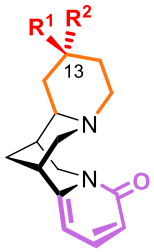


Abbildung 9. 13α-Hydroxylupanin (**18**) und 13β-Hydroxylupanin (*epi*-**18**) mit hervorgehobener CIP-Priorität am Stereozentrum in C_6 (rote Bindung) und Betrachtung des Stereozentrums in C_{13}.

Wie 13α-Hydroxylupanin (**18**) und 13β-Hydroxylupanin (*epi*-**18**) gibt es auch im α-Pyridon-Typ in 13-Position hydroxylierte Bischinolizidin-Naturstoffe, welche von Anagyrin (**17**) abgeleitet sind (Abbildung 10).[36] Jedoch zeigt die Literatur Uneinigkeiten bezüglich der richtigen Konfiguration an C_{13}. Die CAS/Scifinder-Zuordnung basiert auf einer 50 Jahre alten Publikation, in der aufgrund der Verschiebungen der OH-Schwingung im IR um 1000 cm^{-1} Epibaptifolin (*epi*-**19**, 13*R*) eine axiale OH-Gruppe zugeordnet wurde und folglich dem Diastereomer Baptifolin (**19**, 13*S*) eine äquatoriale.[36c] In anderen Publikationen sind **19** und *epi*-**19** ohne Stereochemie an C_{13}, mit inverser Konfiguration an C_{13} oder stereochemisch völlig falscher Anordnung, z. B. mit *endo*-Ring an C_{11}, abgebildet.[37]



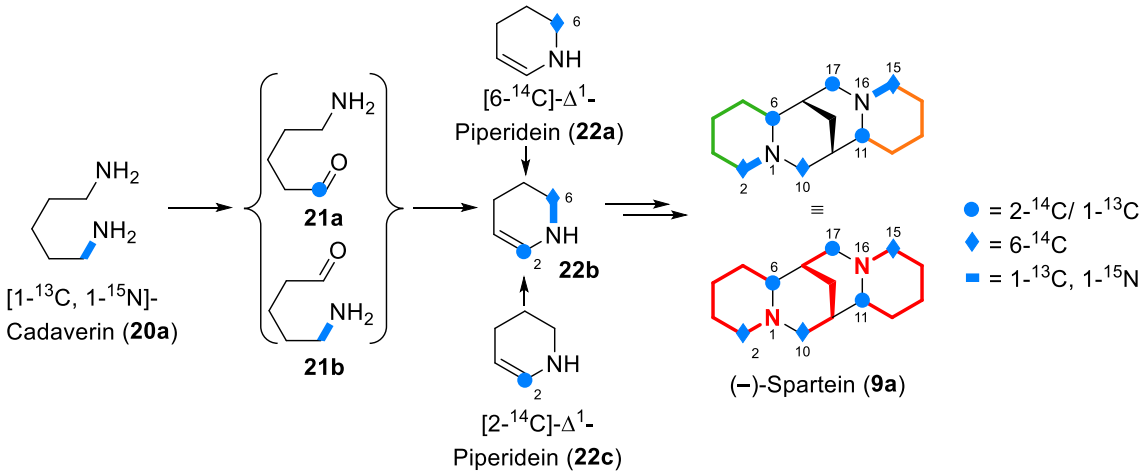
Epibaptifolin (*epi*-**19**) { R^1 = OH, R^2 = H (13*S*)
Baptifolin (**19**) { R^1 = H, R^2 = OH (13*R*)

Abbildung 10. Epibaptifolin (*epi*-**19**) und Baptifolin (**19**) mit nicht eindeutig zugeordneter Stereochemie an Position 13.

Eine eindeutige, unzweifelhafte Zuordnung der Konfiguration an C_{13} wurde bis heute noch nicht vorgenommen.

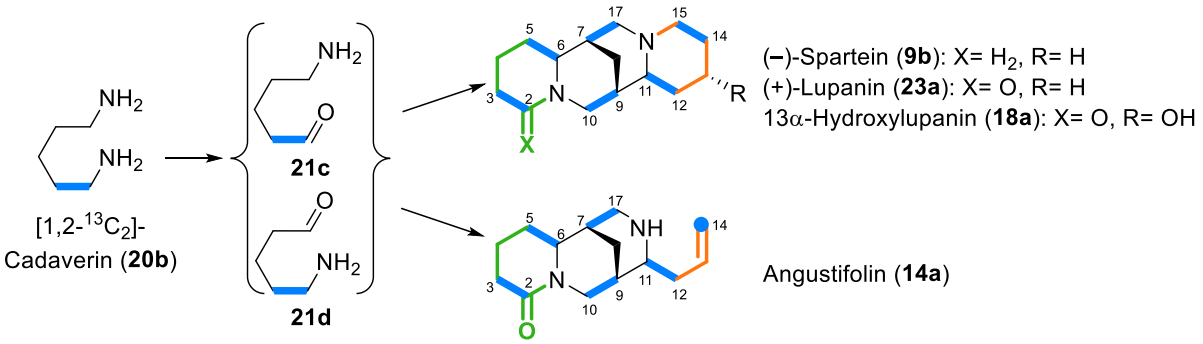
1.1.3 Biosynthese

Bei den Bischinolizidin-Alkaloiden handelt es sich um stickstoffhaltige Sekundärmetabolite, die aus drei Molekülen L-Lysin aufgebaut werden.[38] Um den genauen Biosynthesemechanismus zu erklären, wurden verschiedene Markierungsexperimente durchgeführt. Schema 2 zeigt drei solcher Experimente zusammengefasst, wobei zum einen [1-^{13}C, 1-^{15}N]-Cadaverin (**20a**) und zum anderen [2-^{14}C]- bzw. [6-^{14}C]-Δ^1-Piperidein (**22a** und **22c**) eingesetzt wurden.[39] Bei Applikation von **20a** konnten in (−)-Spartein (**9**) sechs ^{13}C-angereicherte Signale im NMR beobachtet werden, was auf den Einbau von drei Einheiten Cadaverin schließen lässt. Da C_2 und C_{15} als Dubletts aufspalten, müssen die intakten ^{13}C-^{15}N-Bindungen zwischen C_2 und N_1 sowie C_{15} und N_{16} liegen. C_6 und C_{11} sind nur Singuletts im NMR. Dies belegt, dass die Ringe A und D jeweils aus einer Cadaverin-Einheit stammen, da C_6 nicht ^{13}C-angereichert sein kann, wenn N_1 ^{15}N-angereichert ist. Das gleiche gilt für C_{11} und N_{16}. Das Bispidin-Gerüst ($C_{10,9,8,7,17}$) wird aus der dritten Cadaverin-Einheit gebildet, wobei beide Stickstoffe eliminiert wurden. Setzte man [2-^{14}C]-Δ^1-Piperidein (**22c**) ein, waren C_6, C_{11} und C_{17} ^{14}C-markiert, bei [6-^{14}C]-Δ^1-Piperidein (**22a**) C_2, C_{10} und C_{15}, wodurch jeweils der Anfang und das Ende jeder Cadaverin-Einheit bestimmt werden konnten.



Schema 2. (−)-Spartein (**9a**), wenn [1-^{13}C, 1-^{15}N]-Cadaverin (**20a**), [2-^{14}C]- oder [6-^{14}C]-Δ^1-Piperidein (**22a** bzw. **22c**) verfüttert wurde (alles in einem Schema zusammengefasst). Die drei Cadaverin-Einheiten sind in Rot hervorgehoben.[39]

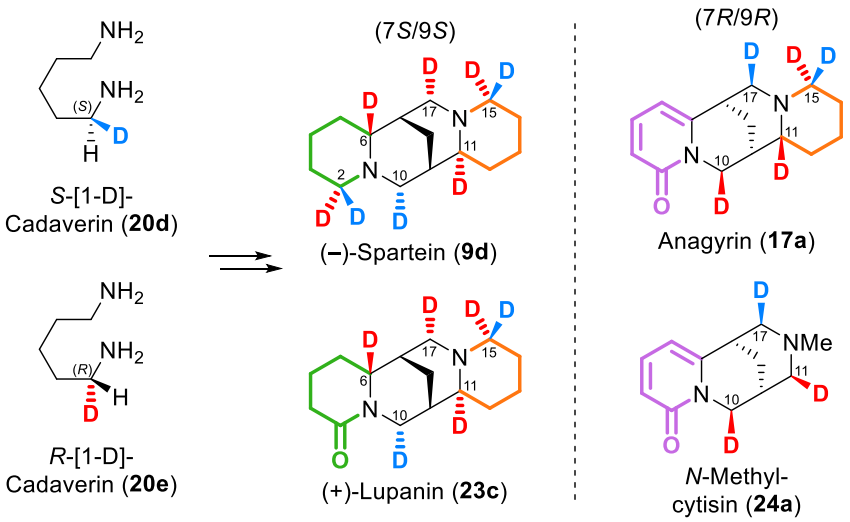
Im nächsten Markierungsexperiment wurde [1,2-$^{13}C_2$]-Cadaverin (**20b**) an zwei *Lupinus*-Arten verfüttert (Schema 3).[40] Deren Einbau bestätigte, dass die tetracyclischen Bischinolizidin-Naturstoffe (−)-Spartein (**9b**), (+)-Lupanin (**23a**) und 13α-Hydroxylupanin (**18a**) ebenfalls aus drei Cadaverin-Einheiten gebildet wurden. Die Tricyclen entstehen durch Abbau der Tetracyclen, was die ^{13}C-markierte Allylgruppe in Angustifolin (**14a**) beweist.



Schema 3. Einbau von [1,2-$^{13}C_2$]-Cadaverin (**20b**) in (−)-Spartein (**9b**), (+)-Lupanin (**23a**), 13α-Hydroxylupanin (**18a**) und Angustifolin (**14a**).[40]

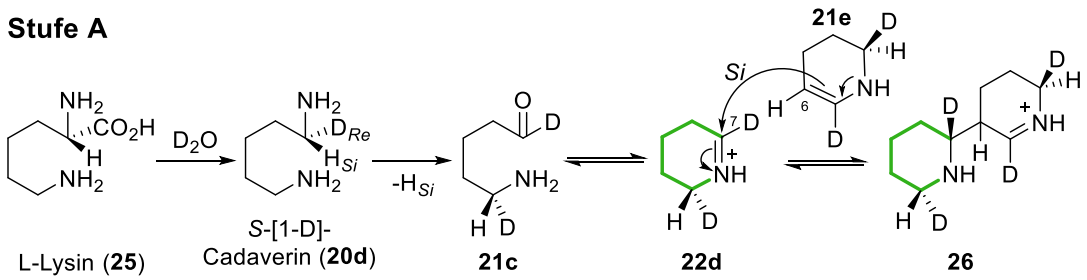
Sowohl Spenser *et al.* als auch Robins *et al.* führten Markierungsuntersuchungen mit *S*-[1- D]- und *R*-[1-D]-Cadaverin (**20d** und **20e**) durch (Schema 4).[40,41,42] Diese zeigten, dass in (−)-Spartein (**9d**) sowohl an C_2 als auch an C_{15} beide deuterierten Wasserstoffe verbleiben, weshalb an diesen Positionen keine Oxidation oder Reduktion stattgefunden haben kann. Somit kann (+)-Lupanin (**23c**) als Vorstufe von (−)-Spartein (**9d**) ausgeschlossen werden. In der 7*S*/9*S*-Serie verbleiben an C_6, C_{11} und C_{17} nur das durch *R*-[1-D]-Cadaverin (**20e**) eingebrachte Deuterium, während an C_{10} nur das aus *S*-[1-D]-Cadaverin (**20d**) stammende Deuterium zu finden ist. In der enantiomeren 7*R*/9*R*-Serie ist genau das Gegenteil der Fall. Dies deutet darauf

hin, dass die stereoselektiven Oxidationen enzymatisch verlaufen. Da in *N*-Methylcytisin (**24a**) die Methylgruppe nicht Deuterium-markiert ist, muss diese erst nach Abbau des D-Rings eingebracht worden sein. Der Erhalt des Deuteriums an C_{11} weist darauf hin, dass der Tricyclus **24a** aus dem tetracyclischen Anagyrin (**17a**) durch Abbau entstanden sein könnte.



Schema 4. Einbau von *S*-[1-D]- und *R*-[1-D]-Cadaverin (**20d** und **20e**) in (−)-Spartein (**9b**), (+)-Lupanin (**23c**), Anagyrin (**17a**) und *N*-Methylcytisin (**24a**) in einem Schema aufgezeigt.[40,41,42]

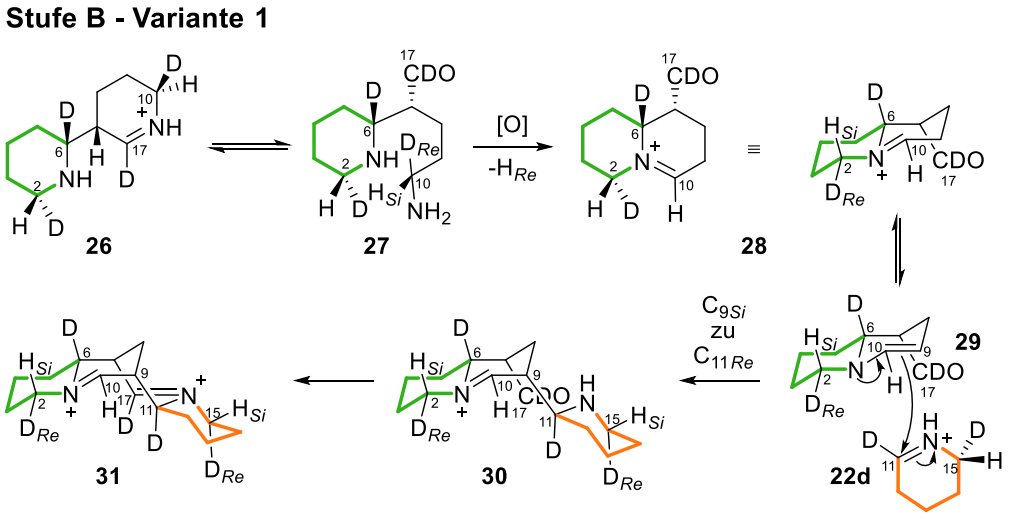
Aufbauend auf den gezeigten Markierungsexperimenten wurde von Spenser und Gołębiewski ein in drei Abschnitte gegliederter Mechanismus für die Biosynthese von (−)-Spartein (**9f**) aufgestellt (Schema 5-8).[39] In Stufe A wird L-Lysin (**25**) decarboxyliert und im Experiment mit D_2O abgefangen, wodurch ein Deuterium von der *Re*-Seite eingeführt wird (Schema 5). Bei der Oxidation einer der NH_2-Gruppen zum Aldehyd **21c** wird das Si-Proton entfernt. Ringschluss zum Δ^1-Piperidein (**22d**) und Angriff eines zweiten Δ^1-Piperidein (**22e**) führen zum protonierten Tetrahydroanabasin (**26**).



Schema 5. Stufe A der Biosynthese von (−)-Spartein (**9f**).[39]

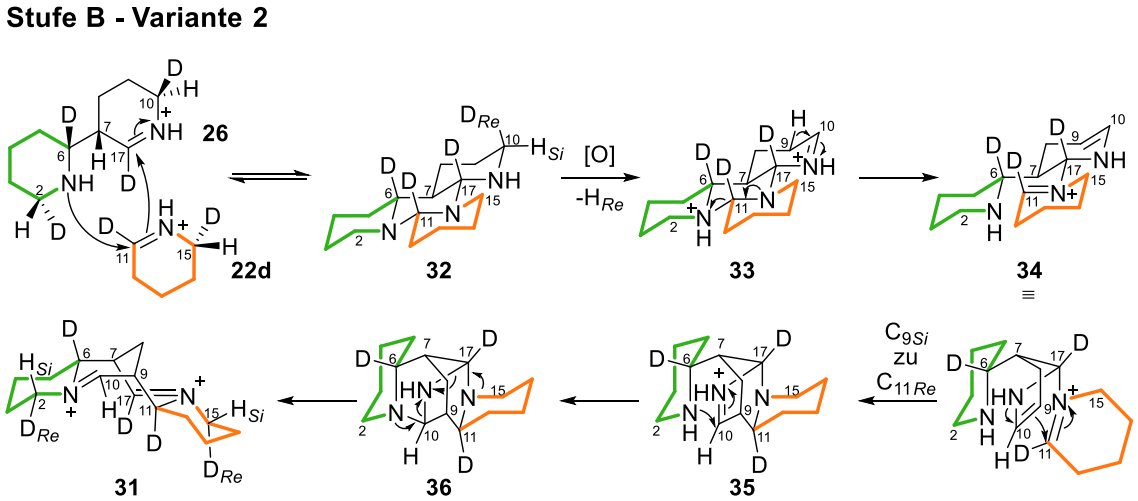
Für Stufe B gibt es zwei verschiedene Möglichkeiten. In Variante 1 wird zuerst in **27** das primäre Amin zu einem Aldehyd oxidiert, an das, nach Ringschluss zu **28** und

Doppelbindungsshift zu **29**, ein drittes Δ^1-Piperidein (**22d**) von der C_9-*Si*-Seite an die C_{11}-*Re*-Seite addiert (→ **30**, Schema 6). Finaler Ringschluss unter Iminumbildung führt zum Didehydrosparteinium-Dikation (**31**).



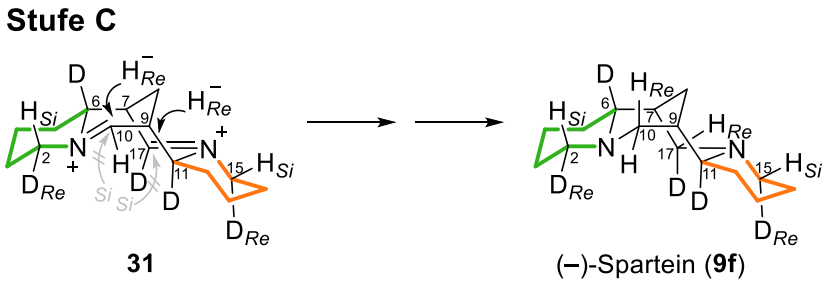
Schema 6. Variante 1 der Stufe B des Biosynthesemechanismus von (−)-Spartein (**9f**).[39]

Variante 2 baut auf einen Angriff des Tetrahydroanabasins (**26**) an ein drittes Δ^1-Piperidein (**22d**) auf (→ **32**, Schema 7). Nach Oxidation an C_{10}, bei der das Deuterium auf der *Si*-Seite entfernt wird (→ **33**), Ringöffnung (→ **34**) und Angriff des C_9 von der *Si*-Seite an die *Re*-Seite von C_{11} ergibt sich das Iminiumsalz **35**. Ringschluss (→ **36**) und Eliminerung des Stickstoffs führen ebenso wie Variante 1 zum Didehydrosparteinium-Dikation (**31**).



Schema 7. 2. Variante der Stufe B in der Biosynthese von (−)-Spartein (**9f**).[39]

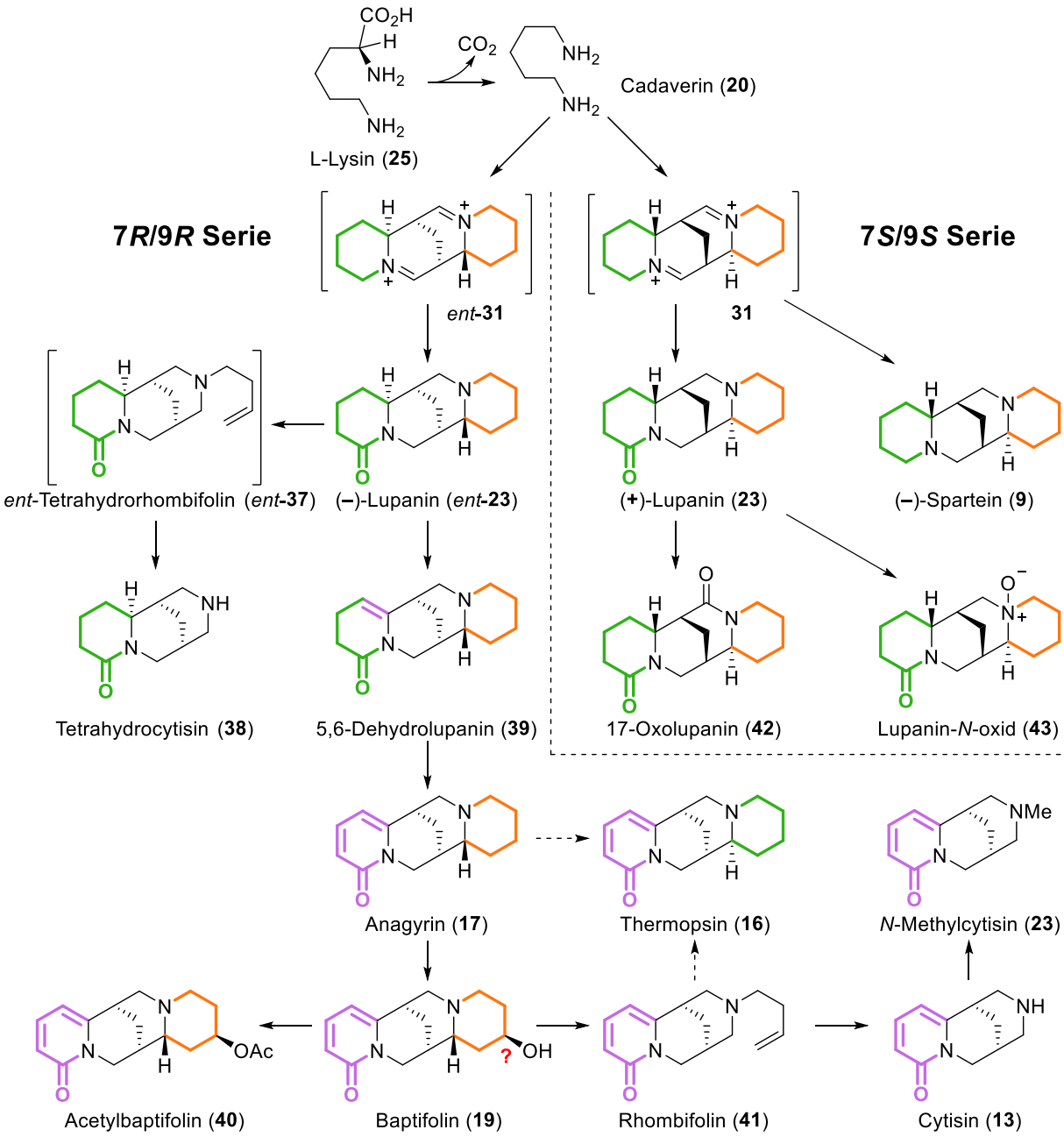
In der finalen Stufe C wird jeweils ein Hydrid an die *Re*-Seite von C_{10} und C_{17} in **31** addiert, was (−)-Spartein (**9f**) liefert (Schema 8).



Schema 8. Finale Stufe C zur Biosynthese von (−)-Spartein (**9f**).[39]

Weitere Transformationen zu den verschiedenen Bischinolizidin-Naturstoffen erfolgen ausgehend von **31** auf zellulärer Ebene durch Enzyme über Dehydrierung, Oxygenierung, Hydroxylierung, Glykosylierung und Veresterung.[43]

Cho *et al.* und Saito *et al*. untersuchten die Biosynthese von Bischinolizidinen in *Thermopsis*-Pflanzen, in denen beide Enantiomere der Bischinolizidin-Alkaloide produziert werden (Schema 9).[21,44,45] Die 7*S*,9*S*-Serie kann durch die in Schema 5 gezeigten C_6-*Si*- auf C_7-*Si*-Seiten-Angriffe und in Schema 6 bzw. 7 gezeigten C_9-*Si*- an C_{11}-*Re*-Seiten-Angriffe erhalten werden, die 7*R*,9*R*-Serie über die gespiegelten Angriffe. Cho *et al.* verfütterten ^{14}C-markiertes CO_2 in verschiedenen Versuchsreihen an *T. rhombifolia*, wodurch über die Abnahme des ^{14}C-Gehalts die Reihenfolge der bei der Biosynthese entstandenen Bischinolizidine bestimmt werden konnte.[44] Aus der 7*S*,9*S*-Serie können durch Folgereaktionen (−)-Spartein (**9**) oder (+)-Lupanin (**23**) sowie die Oxidationsprodukte **42** und **43** gebildet werden. Auf der 7*R*,9*R*-Seite wird (−)-Lupanin (*ent*-**23**) gefunden, das über *ent*-Tetrahydrorhombifolin (*ent*-**37**) zu Tetrahydrocytisin (**38**) führt.[44,45] Sukzessive Oxidation des Piperidonrings zum Pyridonring (→ 5,6-Dehydrolupanin (**39**), Anagyrin (**17**)) und Oxidation an C_{13} liefern Baptifolin (**19**), das über Acetylierung in Acetylbaptifolin (**40**), über Ringöffnung in Rhombifolin (**41**) und Abbau des vierten Rings in Cytisin (**13**), sowie nach Methylierung in *N*-Methylcytisin (**24**) umgebaut wird. Thermopsin (**16**) könnte aufgrund der ^{14}C-Markierungsexperimente sowohl aus Anagyrin (**17**) als auch aus Rhombifolin (**41**) entstanden sein. Dass in der 7*S*,9*S*-Serie kein α-Pyridon-Typ auftritt, liefert den Hinweis, dass in dieser Serie das für den Aufbau des Pyridon-Rings benötigte Enzym fehlt.



Schema 9. Vermuteter Biosyntheseweg der Bischinolizidin-Alkaloide in Pflanzen der Gattung *Thermopsis*.[21,44,45]

Durch die Versuchsreihen von Cho *et al.* wurde ebenfalls gezeigt, dass Spartein (**9**) keine Rolle bei der Biosynthese der meisten Bischinolizidin-Naturstoffe spielt und auch nicht biosynthetisch aus Lupanin (**23**) gebildet wird.[44]

Die Biosynthese erfolgt lichtabhängig in den Chloroplasten.[46] Von dort werden die Bischinolizidine über das Phloem in die restlichen Pflanzenteile transportiert.[47] Die Alkaloide akkumulieren dort bis zu einer Konzentration von 30 bis 200 mmol pro kg Zelle.[48] Sie sind keine inerten Endprodukte, sondern unterliegen metabolischen Prozessen, wodurch die Pflanze den gebundenen Stickstoff bei Bedarf wieder nutzbar machen kann.[47]

1.1.4 Bioaktivität

Die verschiedenen Lupin-Alkaloide besitzen einige interessante pharmakologischen Eigenschaften, wobei Bischinolizidin-Naturstoffe mit Pyridonring, wie Cytisin (**13**) und Anagyrin (**17**), toxischer sind als die gesättigten Verbindungen (−)-Spartein (**9**) oder Lupanin (**23** und *ent*-**23**).[22a,49] Alkaloide dienen den Pflanzen als Schutz vor Herbivoren. So ist der bittere Geschmack charakteristisch für Lupinen, welche viele toxische Alkaloide besitzen. Alkaloidarme Süßlupinen hingegen werden von Fraßfeinden nicht gemieden.

Über die Krankheit „crooked calf disease" wurde erstmals in den späten 50er, frühen 60er Jahren berichtet.[50] Dabei kommt es bei neugeborenen Kälbern zu Missbildungen, wie Fehlstellungen der Wirbelsäule, des Halses und der Vordergliedmaßen, oder in seltenen Fällen zu einer Gaumenspalte, wodurch Milch oder Pansenflüßigkeit in die Lunge aspiriert wird, was zu einer Lungenentzündung führt. Der Auslöser dieser Krankheit ist die Aufnahme bestimmter Lupinenarten durch das Muttertier während der ersten 100 Tage der Trächtigkeit. Durch Ultraschalluntersuchungen wurde herausgefunden, dass teratogene Alkaloide die Bewegungen des Fötus in der kritischen Phase der Schwangerschaft verlangsamen, was zu den oben genannten Fehlstellungen führt. Um herauszufinden, welche Alkaloide der Lupinenarten die teratogene Wirkung hervorrufen, führte Keeler Untersuchungen an trächtigen Rindern durch (Tabelle 2).[51] Die Muttertiere wurden zwischen dem 40. und 75. Tag der Trächtigkeit während einer Dauer von 15 bis 31 Tagen mit alkaloidreichen Präparaten gefüttert. Spartein (**9**), Lupinenextrakte mit geringem Anteil an Anagyrin (**17**) sowie ein Präparat aus 5,6-Dehydrolupanin (**39**) und Lupanin (**23**) führten selbst in hohen Dosen nicht zu Missbildungen der Kälber, auch wenn die Muttertiere Toxizitätserscheinungen wie Depressionen, Gleichgewichtsprobleme, gestelzten Gang oder anhaltende Muskelzuckungen zeigten. Je höher aber der Anagyrin-Gehalt in den gefütterten Präparaten und je länger die Dauer des Versuchs war, desto stärkere Fehlbildungen konnten am neugeborenen Kälbchen festgestellt werden. Mehr als 100 Kontrollkühe, welche keine dieser Präparate erhielten, gebaren normale Jungtiere. Frühere Versuche mit Verfüttern von 1 kg Pflanzen pro Tag, welche 1.5 bis 10.5 g Anagyrin (**17**) pro kg getrocknetes Pflanzenmaterial enthielten, zeigten ähnliche Ergebnisse.[52] Aufgrund dieser Untersuchungen wurde deutlich, dass in Lupinen hauptsächlich Anagyrin (**17**) teratogene Wirkung aufweist.

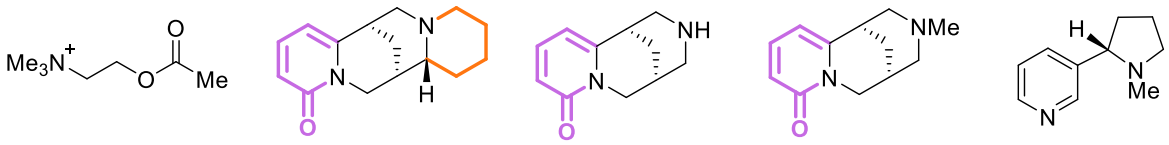
Tabelle 2. Verabreichung von Lupinenextrakten, Präparaten und Spartein an trächtigen Kühen.[51]

Jahr	Kuh-Nr.	Verfüttertes Material (Alkaloidgehalt)	Tägl. Alkaloid-dosis (mg/kg)	Tägl. Anagyrin-dosis (mg/kg)	Trächtigkeits-phase (d)	Toxizitäts-erscheinung am Muttertier	Ergebnis
1965 - 1966	1	Lupinenextrakt (23%)	1.8	0.67	40-60	unerheblich	1 Kalb normal
	2	Lupinenextrakt	1.8	0.67	40-60	unerheblich	1 Kalb normal
	3	Spartein (100%)	8.1	-	22-70	keine	1 Kalb normal
	4	Spartein	8.1	-	22-70	keine	1 Kalb normal
1966 - 1967	5	Lupinenextrakt (5%)	2.2	0.48	50-65	unerheblich	2 Kälber zweifelhaft deformiert
	6	Lupinenextrakt	1.8	0.39	50-65	unerheblich	1 Kalb normal
1971 - 1972	7	Alkaloidpräparat mit Anagyrin (35%)	3.9	1.5	60-75	leicht	1 Kalb leicht deformiert
	8	Alkaloidpräparat mit Anagyrin	3.1	1.2	60-75	leicht	1 Kalb zweifelhaft deformiert
	9	Alkaloidpräparat	4.6	1.8	60-75	leicht	1 Kalb normal
1972 - 1973	13	Spartein	34.6	-	50-75	moderat	1 Kalb normal
	14	Spartein	46.0	-	50-75	stark	1 Kalb normal
	17	Alkaloidpräparat mit Anagyrin (95%)	27.4	6.5	45-70	moderat	1 Kalb moderat deformiert
	18	Alkaloidpräparat mit Anagyrin	50.3	11.9	50-75	moderat	1 Kalb moderat deformiert
1973 - 1974	24	Präparat mit 5,6-Dehydrolupanin, Lupanin (95%)	32.2	-	50-75	leicht-moderat	1 Kalb normal
	25	Alkaloidpräparat mit Anagyrin (95%)	117.0	31.4	50-75	stark	1 Kalb stark deformiert

Da Anagyrin (**17**) nur bei Rindern zu Missbildungen führt, Schafe und Ziegen jedoch nicht von der teratogenen Wirkung betroffen sind, wird vermutet, dass der Metabolismus oder die Absorption bei Rindern und kleinen Wiederkäuern unterschiedlich ist.[49] Möglich wäre, dass Kühe Anagyrin (**17**) zu komplexen Piperidinen metabolisieren können und diese dann die

eigentlichen teratogenen Stoffe sind. Dies ist allerdings nicht bewiesen und widerspricht zum Teil der Absorption und dem Ausscheidungsmuster von Chinolizidin-Alkaloiden in Rindern, Schafen und Ziegen.

Anagyrin (**17**) weist neben der teratogenen Wirkung auch eine schwache Bindung an den muskarinischen Acetylcholinrezeptor (mAChR) auf.[49,53] Agonisten des mAChR besitzen unter physiologischen Bedingungen ein quartäres Stickstoffatom und einen Sauerstoff im gleichen räumlichen Abstand wie die Estergruppe in Acetylcholin (**44**, Abbildung 11), wohingegen Agonisten des nikotinischen Acetylcholinrezeptors (nAChR) sekundäre und tertiäre Stickstoffatome in Pyrrolidin- oder Piperidinringen besitzen, welche unter physiologischen Bedingungen protoniert werden. Sehr starke Agonisten des nAChR sind unter anderem einige Chinolizidin-Alkaloide wie Cytisin (**13**) und *N*-Methylcytisin (**24**).



Acetylcholin (**44**) Anagyrin (**17**) Cytisin (**13**) *N*-Methylcytisin (**24**) Nicotin (**45**)

Abbildung 11. Acetylcholin (**44**), Bischinolizidin-Alkaloide und Nicotin (**45**) als Agonisten des AChR.

Seit 1912 sind die Nicotin-ähnlichen Eigenschaften von Cytisin (**13**) bekannt.[54] Beide Naturstoffe **13** und **45** weisen eine sehr ähnliche 3D-Struktur auf, was von Barlow *et al*. via Röntgenkristallstrukturanalyse näher untersucht wurde.[55] Aufgrund dieser strukturellen und wirkungsspezifischen Eigenschaften geriet Cytisin (**13**) als Rauchentwöhnungsmittel in den Fokus. In Deutschland wurde schon im Jahr 1965 vom Minister des Gesundheitswesens auf „die zunehmenden Zahlen der Tabakschädigungen, besonders die in den letzten Jahren ständig ansteigenden Ziffern der Todesfälle an Bronchialkrebs und Herzinfarkt" hingewiesen.[56] Raucher sollten daher psychologisch und medikamentös unterstützt werden, um das Rauchen einzustellen. In einem Sonderdruck aus „Das Deutsche Gesundheitswesen“ von 1968 wurden Versuchsreihen mit dem Cytisin-haltigen Medikament Tabex® veröffentlicht, worin dieses Präparat im internationalen Vergleich am besten abschnitt. Auch in neueren Veröffentlichungen wird Cytisin immer noch als sehr effektives Raucherentwöhnungsmittel gesehen.[57] Durch die günstigen Kosten ist es vor allem in einkommensschwachen Ländern eine gute Option zur Behandlung von Rauchern.

(−)-Spartein (**9**) weist zwar auch eine Bindungsaffinität an den mAChR auf,[53] jedoch war dessen antiarrhythmische Wirkung von größerer Bedeutung, so dass es einige Zeit unter dem Markennamen Depasan® als Arzneimittel vertrieben wurde. Im Jahr 1979 fanden jedoch Eichelbaum *et al*. heraus, dass bei einer Versuchsreihe 18 von 360 Testpersonen (5%) (−)-Spartein (**9**) nicht metabolisieren können und die verabreichte Dosis zu 100% über den Urin wieder ausschieden.[58] Dieser defekte Metabolismus ist auf genetische Ebene zurückzuführen. Die Anlage zur N_1-Oxidation, welche notwendig ist um (−)-Spartein (**9**) zu metabolisieren, findet sich auf zwei allelischen Genen. Nichtmetabolisierer sind homozygot für ein autosomal rezessives Gen. Später im Jahr 1991 wurden zusätzlich Anwendungseinschränkungen für Antiarrhythmika wie Depasan® herausgegeben, da für die Medikamente keine Lebensverlängerung bei der Behandlung von Herzrhythmusstörungen nachgewiesen werden konnte.[59]

Weitere Bischinolizidin-Naturstoffe weisen ebenfalls interessante Bioaktivitäten auf. Lupanin (**23**) und 13α-Hydroxylupanin (**18**) erhöhen unter anderem die Insulinausschüttung.[60] Extrakte aus Bischinolizidin-haltigen Pflanzen zeigten Wirkung gegen verschiedene Bakterienstämme,[61] Larven[62] und Nematoden.[63] Bispidinkomplexe lassen sich möglicherweise auch als Radiopharmazeutika,[64] zur Behandlung von Schlaganfallpatienten[65] oder als Analoga für Cis- oder Carboplatin einsetzen.[66]

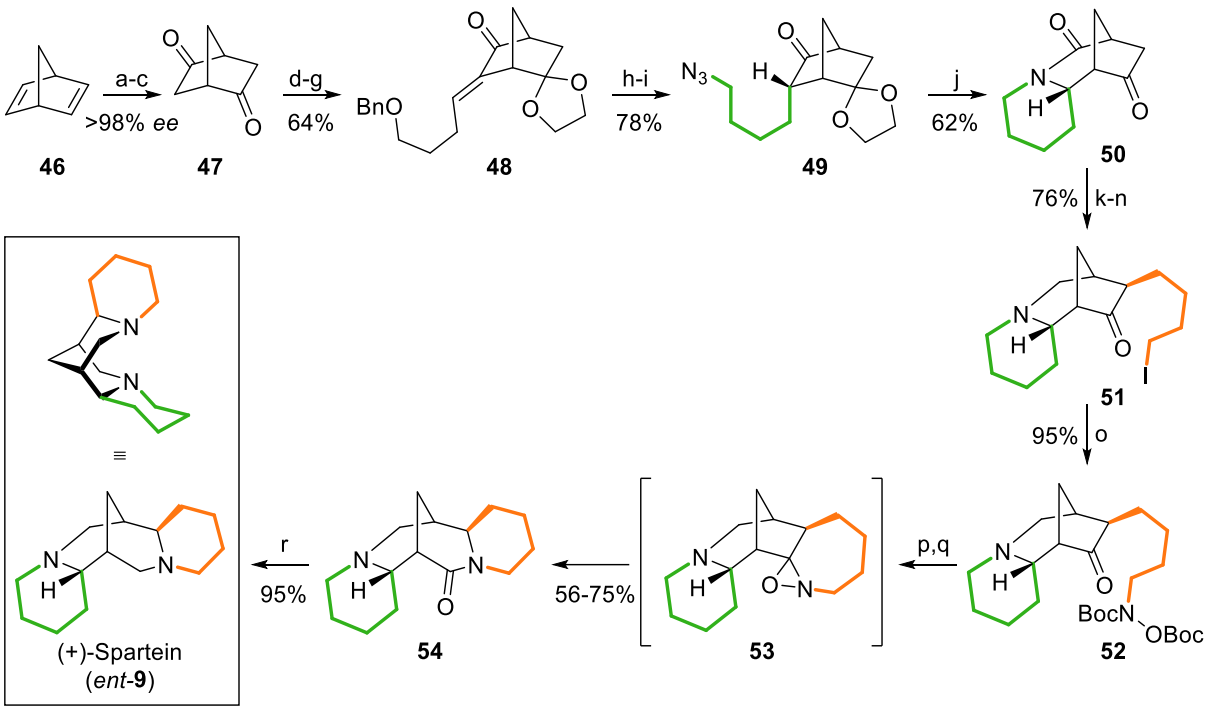
1.1.5 Enantioselektive Totalsynthesen

Da Bischinolizidine, wie (−)-Spartein (**9**) und Cytisin (**13**), eine chemisch anspruchsvolle Struktur und interessante Wirk- und Anwendungsweisen aufweisen, beschäftigten sich in den letzten Jahren einige Arbeitsgruppen mit deren enantioselektiven Totalsynthesen. Im Folgenden werden die ersten enantioselektiven Totalsynthesen von (+)-Spartein (*ent*-**9**), (−)-Spartein (**9**), Cytisin (**13**) und (+)-β-Isospartein (**72**) beschrieben.

1.1.5.1 (+)-Spartein (*ent*-9) nach Aubé

Aubé *et al.* arbeiteten über einen langen Zeitraum an der Synthese von Spartein (**9**) ausgehend von Norbornandion (**47**). Erste Vorarbeiten wurden 1996 publiziert.[67] Die finale, erste enantioselektive Totalsynthese von (+)-Spartein (*ent*-**9**) folgte 2002 (Schema 10).[68] Schlüsselschritte dabei waren zwei Ringexpansionen, wobei eine intramolekulare Schmidt-Reaktion zum Aufbau des *endo*- und eine neuartige Photo-Beckmann-Umlagerung zum Aufbau des *exo*-anellierten Piperidinrings genutzt wurde.

Norbornadien (**46**) wurde zunächst einer zweifachen, asymmetrischen Hayashi-Hydrosilylierung[69] und einer zweifachen Oxidation unterzogen, was (*S*,*S*)-Norbornandion (**47**) nach Umkristallisation in >98% *ee* ergab. Zum Aufbau des ersten Piperidinrings musste zunächst eine Ketogruppe als Acetal geschützt werden, damit eine Aldoladdition und Eliminierung zum Enon **48** möglich war. Hydrierung von der weniger gehinderten *exo*-Seite und Einbringen eines Azids via modifizierter Mitsunobu-Azidierung lieferten Verbindung **49**, welche in einer intramolekularen Schmidt-Reaktion zum Lactam **50** mit *endo*-anellierten Piperidin umlagerte. Direkte Alkylierung des Ketolactams **50** war wenig erfolgreich, weshalb zunächst zum Amin reduziert und anschließend zu **51** alkyliert wurde. An dieser Stelle sollte eine weitere intramolekulare Schmidt-Reaktion erfolgen, welche jedoch unter allen versuchten Bedingungen scheiterte. Vermutlich koordinierten die jeweils verwendeten Lewis- oder Brønsted-Säuren an das Amin anstelle des Ketons, was jedoch für die Reaktion mit dem schwach nucleophilen Azid nötig wäre. Letztendlich erfolgreich war eine Photo-Beckmann-Umlagerung. Nach Austausch des Iodids gegen eine BocNOBoc-Gruppe (→ **52**) und deren Entschützung gelang die Umlagerung via des Oxaziridins **53** und lieferte das Lactam **54** mit *exo*-anellierten Piperidin. Finale Reduktion führte zu (+)-Spartein (*ent*-**9**) in 15 Stufen mit 16% Gesamtausbeute.



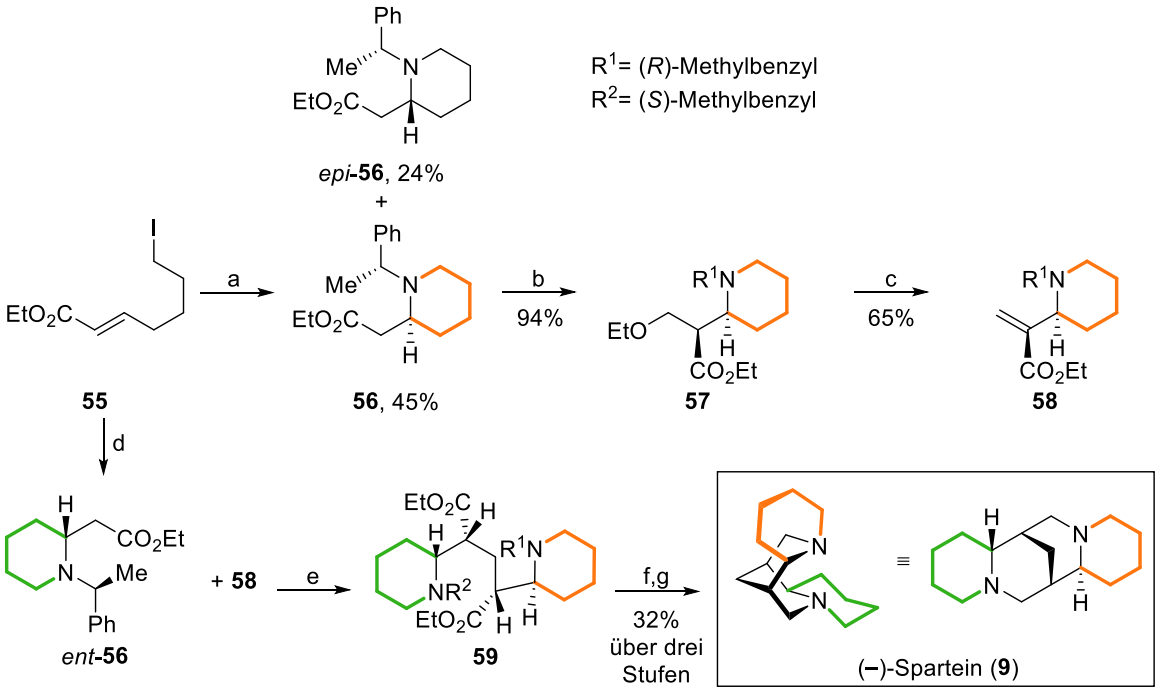
Schema 10. Erste enantioselektivte Totalsynthese von (+)-Spartein (*ent*-**9**) nach Aubé *et al.*[68]
Reagenzien und Bedingungen: a) $HSiCl_3$, $[(Allyl)PdCl]_2$, (−)-*S*-MOP; b) H_2O_2, KI, $KHCO_3$, MeOH, THF; c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; d) Ethylenglykol, *p*TsOH, THF, Δ, 24 h; e) LDA, THF, −78 °C, 1 h; $BnO(CH_2)_3CHO$, −78 → 0°C, 2 h; f) MsCl, NEt_3, CH_2Cl_2, 0 °C, 1 h; g) DBU, THF, Δ, 24 h; h) H_2 (4 bar), Pd/C, $Pd(OH)_2$, Alox B, EtOH, RT, 24 h; i) $Zn(N_3)_2$·2pyr, DEAD, PPh_3, Benzol, RT, 24 h; j) $TiCl_4$, CH_2Cl_2, RT, 24 h; k) Lawesson-Reagenz, Benzol, Δ, 2 h; l) Raney-Nickel, EtOH, RT, 24 h; m) LDA, 1-Chlor-4-iodbutan, THF, −78 → 0 °C; n) NaI, Aceton, Δ, 24 h; o) BocNHOBoc, K_2CO_3, DMF, RT, 24 h; p) TFA, 4Å Molsieb, CH_2Cl_2, RT, 24 h, dann $NaHCO_3$; q) hν (254 nm), Benzol, RT, 2 h; r) $LiAlH_4$, THF, Δ, 2 h.

1.1.5.2 (−)-Spartein (9) nach O'Brien

O`Brien *et al.* synthetisierten erstmals (−)-Spartein (**9**) enantioselektiv in nur sechs Stufen (Schema 11).[70] Schlüsselschritt dabei war die Michael-Addition eines Aminoesterenolats an einen α,β-ungesättigten Aminoester. Eine neuere, optimierte Synthese für (−)-Spartein (**9**) von O`Brien *et al.* ist in Kapitel 1.3 gezeigt.[71]

Aus dem Iodid **55** wurde durch Umsetzung mit (*R*)-α-Methylbenzylamin der β-Aminoester **56** und dessen Epimer *epi*-**56** im Verhältnis 2:1 erhalten, welche durch Säulenchromatographie aufgetrennt wurden. α-Alkylierung (→**57**) und Eliminierung lieferten den Michael-Akzeptor **58**. Diastereoselektive Michael-Addition des β-Aminoesters *ent*-**56**, welcher ausgehend von **55** und (*S*)-α-Methylbenzylamin synthetisiert wurde, an **58** führte zu Verbindung **59**. Der Ringschluss erfolgte *in situ* bei der Abspaltung der Auxiliare, wobei der *endo*-anellierte

Piperidinring aus *ent*-**56** und der *exo*-anellierte Piperidinring aus **58** hervorgingen. Nach Reduktion wurde (−)-Spartein (**9**) in insgesamt 9% Ausbeute über sechs Stufen erhalten.

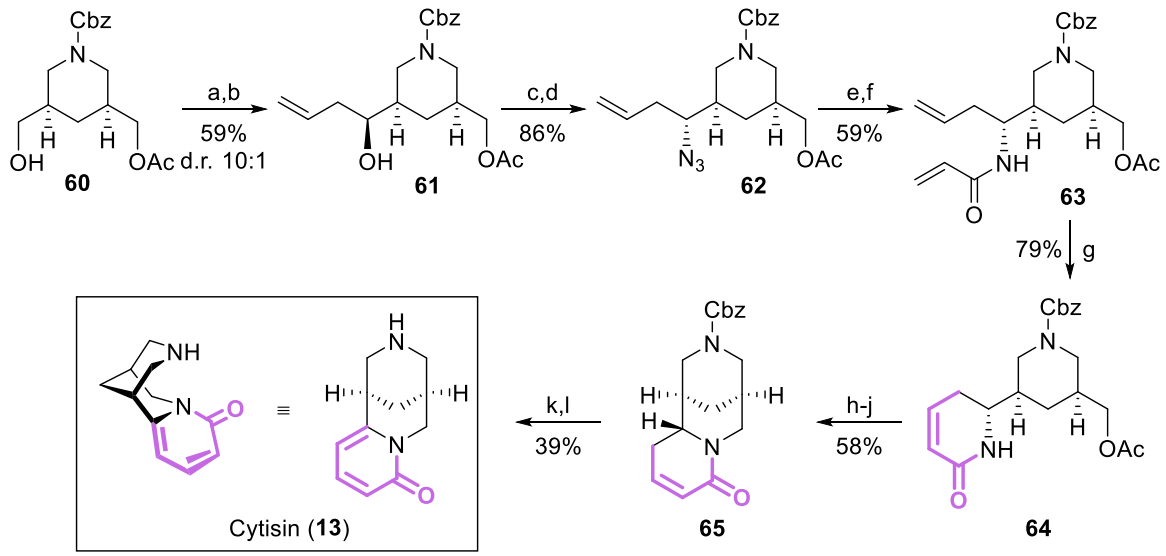


Schema 11. Erste enantioselektive Totalsynthese von (−)-Spartein (**9**) nach O'Brien *et al.*[70]
Reagenzien und Bedingungen: a) (*R*)-α-Methylbenzylamin, NEt_3, EtOH, Δ, 16 h; b) LHMDS, THF, −78 °C, 1 h, dann $EtOCH_2Cl$, −78 °C → RT über 4 h, RT, 12 h; c) KO*t*Bu, THF; −78 °C, 8.5 h; d) (*S*)-α-Methylbenzylamin, NEt_3, EtOH, Δ, 16 h; e) LDA, THF, −78 °C, dann **58**, −78 → −30 °C über 5.5 h, −30 °C, 3 h, dann 1 M aq. HCl; f) $Pd(OH)_2$/C, NH_4HCO_3, EtOH, Δ, 14 h, dann Umkristallisation; g) $LiAlH_4$, THF, Δ, 16 h.

1.1.5.3 (−)-Cytisin (13) nach Lesma

Die erste enantioselektive Totalsynthese von (−)-Cytisin (**13**) wurde von Lesma *et al.* im Jahr 2004 publiziert (Schema 12).[72,73] *Cis*-Piperidin-3,5-dimethanolmonoacetat (**60**) bildet den chiralen Kernbaustein, welcher in beiden enantiomeren Formen käuflich erwerblich ist. Schlüsselschritt der Synthese ist eine Ruthenium-katalysierte Ringschlussmetathese.

Oxidation und Allylierung von **60** mit Allyldiisopinocampheylboran und AllylMgBr führten zum Homoallylalkohol **61** mit einem guten d.r. von 10:1. Anschließend wurde die Alkoholfunktion in **61** über das Azid **62** in das Amid **63** überführt. Die Ringschlussmetathese erfolgte mit einem Grubbs Katalysator der ersten Generation, die das Lactam **64**, welches den späteren Pyridonring bilden wird, in 79% Ausbeute lieferte. Entschützung der Acetatgruppe und Mesylierung ergaben den Tricyclus **65**, aus dem nach Dehydrogenierung und Cbz-Entschützung Cytisin (**13**) in zwölf Stufen und einer Gesamtausbeute von 9% erhalten wurde.

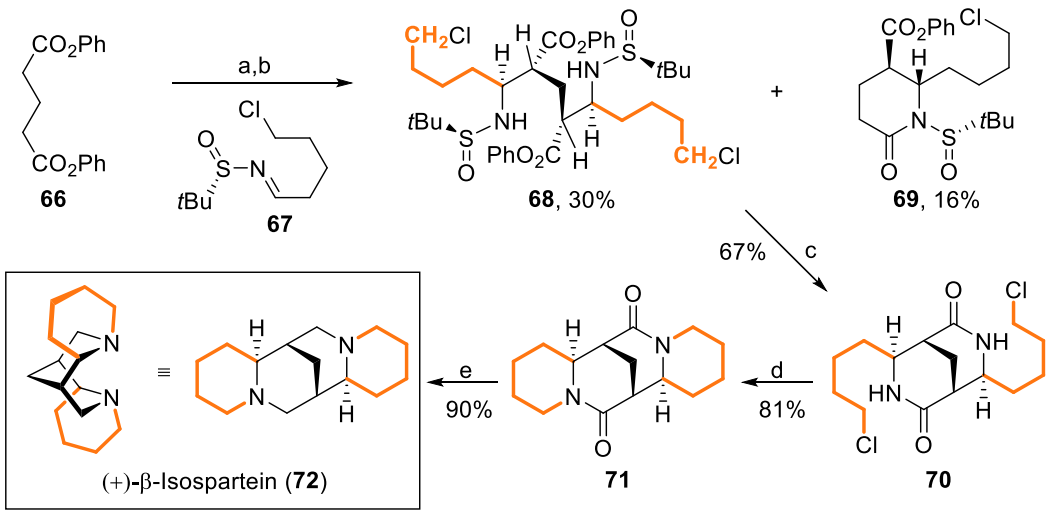


Schema 12. Erste enantioselektive Totalsynthese von (−)-Cytisin (**13**) nach Lesma *et al.*[72]
Reagenzien und Bedingungen: a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; b) (−)-*B*-Methoxydiisopinocampheylboran, AllylMgBr, Et_2O, −78 °C, 1 h, RT, 1 h, dann Edukt, −78 °C, 2 h, RT, 2 h; c) MsCl, NEt_3, DMAP, CH_2Cl_2, RT, 1.5 h; d) NaN_3, DMF, 80 °C, 2 h; e) PPh_3, THF, dann H_2O; f) Acryloylchlorid, NEt_3, DMAP, CH_2Cl_2 , 0 °C, 30 min, RT, 4 h; g) Grubbs I, CH_2Cl_2, Δ, 12 h; h) 0.5 M aq. NaOH, THF, RT, 2 h; i) MsCl, NEt_3, DMAP, CH_2Cl_2, RT, 1.5 h; j) NaH, THF; 0 °C, 2 h; k) DDQ, Dioxan, 110 °C, 4 h; l) 6 N aq. HCl, THF, Δ, 3 h.

1.1.5.4 (+)-β-Isospartein (72) nach Brown

Brown *et al.* beschäftigten sich in ihrer Arbeitsgruppe mit Imino-Aldolreaktionen von *tert*-Butylsulfiniminen (**67**).[74] Aufbauend hierauf wurde ein Zugang zu (+)-β-Isospartein (**72**) realisiert (Schema 13).[75]

Diphenylglutarsäure (**66**) wurde mit LDA deprotoniert und durch Umsetzung mit *tert*-Butylsulfinimin (**67**) in das Doppel-Imino-Aldolprodukt **68** überführt. Verbindung **68**, welche bereits das gesamte Gerüst von (+)-β-Isospartein (**72**) mit der richtigen relativen und absoluten Stereochemie aufweist, wurde diastereomerenrein in 30% Ausbeute erhalten. Als Nebenprodukte entstanden unter anderem das mono-cyclisierte *syn*-Iminoaldolprodukt **69**, das Edukt **67** sowie eine Mischung aus weiteren cyclisierten und uncyclisierten Doppel-Imino-Aldol-Stereoisomeren. Entfernen der *tert*-Butylsulfinylgruppen in **68** führte zur Cyclisierung und Ausbildung des Bispidin-Kerns in **70**. Die Ringschlüsse zu den *exo*-ständigen Piperidinringen erfolgten unter basischen Bedingungen (→**71**). Finale Reduktion lieferte (+)-β-Isospartein (**72**) in fünf Stufen mit 15% Ausbeute.

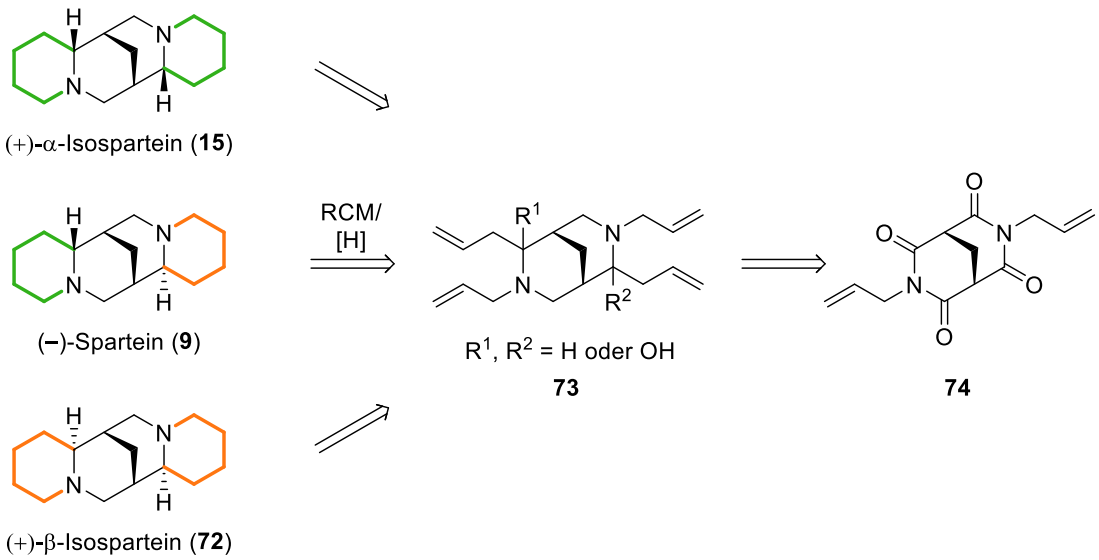


Schema 13. Erste enantioselektive Totalsynthese von (+)-β-Isospartein (**72**) nach Brown *et al.*[75]
Reagenzien und Bedingungen: a) LDA, THF, −78 °C, 1 h; b) **67**, THF, −78 °C, 1 h; c) I_2, THF/ H_2O, 50 °C, 1 h, dann Na_2CO_3, 1 h; d) K_2CO_3, KOH, TBAB, DMSO, 60 °C, 4 h; e) $LiAlH_4$, THF, Δ, 4 h.

1.1.6 Modulare Synthese aller Spartein-Diastereomere nach Blakemore

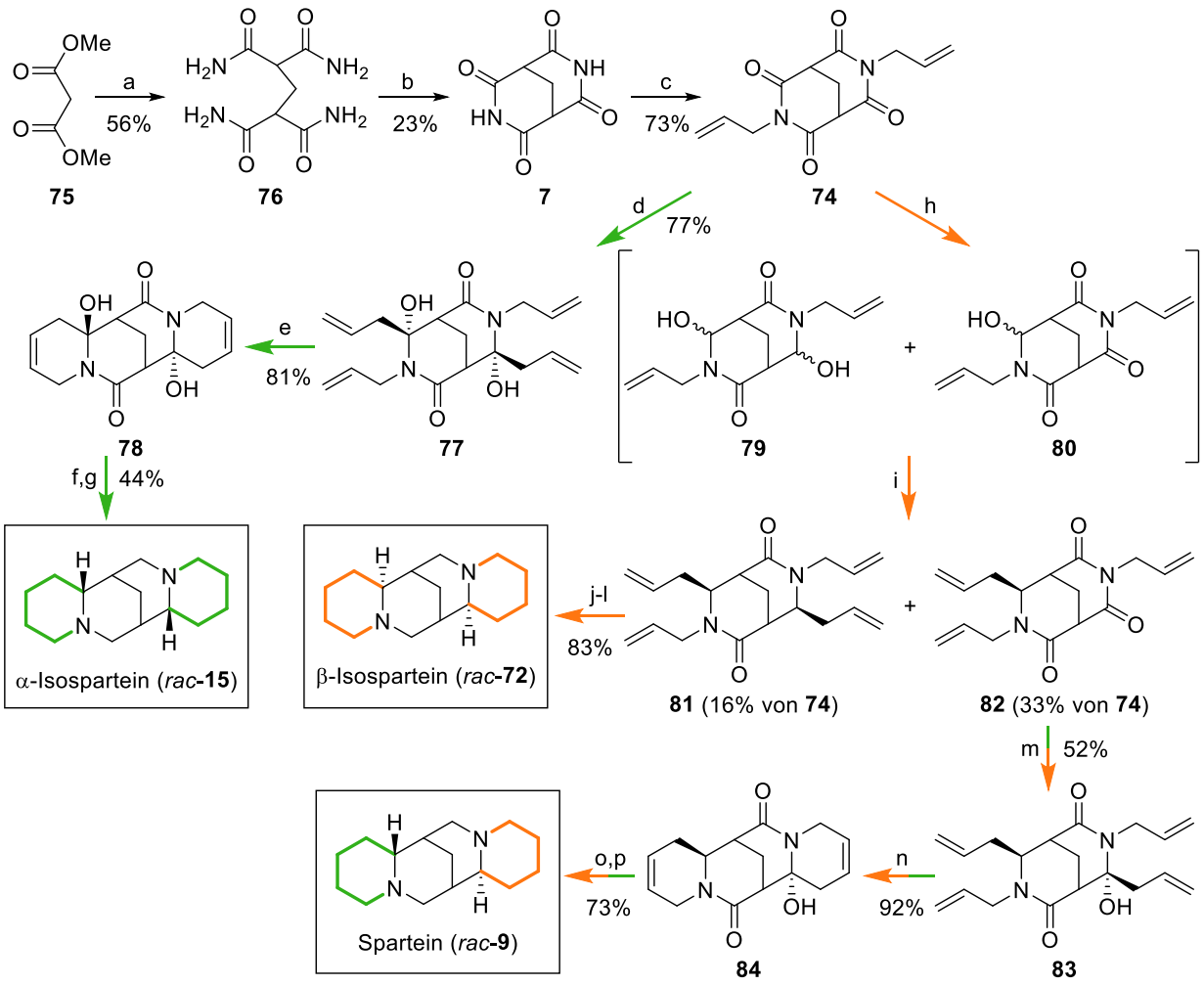
Blakemore und Mitarbeiter beschäftigten sich mit einem modularen Zugang zu den stereoisomeren Bischinolizidin-Naturstoffen Spartein (*rac*-**9**), α-Isospartein (*rac*-**15**) und β-Isospartein (*rac*-**72**).[76]

Da alle Bischinolizidine ein 3,7-Diazabicyclo[3.3.1]nonan-Gründgerüst besitzen, bietet ein Zugang via einer „*Inside-Out*"-Strategie, bei der zunächst der Bispidin-Kern **74** aufgebaut wird und erst danach die Peripherie (→**73**), eine gute Möglichkeit, um mehrere Naturstoffe dieser Substanzklasse aus einer gemeinsamen Vorstufe zu synthetisieren (Schema 14).[76c] Die bisher vorgestellten enantioselektiven Synthesen zeigten genau das Gegenteil. Hier wurden zuerst die anellierten Ringe aufgebaut und in späteren Stufen das zentrale Bispidin-Grundgerüst geschlossen, was wenig flexibel ist und letztendlich nur die Synthese eines Zielmoleküls zulässt.



Schema 14. Retrosynthetische Zerlegung zum modularen Aufbau der stereoisomeren Bischinolizidin-Naturstoffe Spartein (*rac*-**9**), α-Isospartein (*rac*-**15**) und β-Isospartein (*rac*-**72**) nach Blakemore *et al.*[76c]

Der Aufbau des Tetraoxobispidins **7** erfolgte über eine Knoevenagel-Kondensation von Dimethylmalonat (**75**) mit Paraformaldehyd, Überführen der Estergruppen in Amide (→**76**) und anschließender Guthzeit-Cyclisierung (Schema 15).[76a] Nach *N*-Allylierung wurde das gemeinsame Schlüsselintermediat **74** erhalten. Die Synthese zu α-Isospartein (*rac*-**15**) erfolgte über Allyl-Grignard-Addition (→**77**), Ringschlussmetathese (→**78**), Hydrierung und finaler Reduktion in einer Ausbeute von 27% (grüne Pfeile).[76a,c] Die Grignard-Addition erfolgte selektiv an zwei sich diagonal gegenüberliegenden Carbonylgruppen, die finale Reduktion lief hoch stereoselektiv von der weniger gehinderten *exo*-Seite ab, wodurch die *endo*-Stellung der Piperidinringe erreicht wurde. Um *exo*-ständige Reste anbringen zu können, sollte **74** zunächst an zwei diagonal gegenüberliegenden Carbonylgruppen reduziert werden, wobei aber sowohl das gewünschte direduzierte Produkt **79** als auch das monoreduzierte Produkt **80** als untrennbares Gemisch im Verhältnis 1:2 erhalten wurden.[76b,c] Die Allylierung der Hemiamidale erfolgte über eine Sakurai-Reaktion, die ebenfalls ausschließlich von der weniger gehinderten *exo*-Seite stattfand, was zu *exo*-ständigen Resten führte (→ **81**, **82**). Nach Auftrennung der Mischung wurde **81** via Ringschlussmetathese, Hydrierung und Reduktion in einer Gesamtausbeute von 12% in β-Isospartein (*rac*-**72**) überführt (orange Pfeile). Verbindung **82** ist ein gutes Edukt für Spartein (*rac*-**9**), welches sowohl einen *endo*- als auch *exo*-ständigen Piperidinrest besitzt. Selektive Grignard-Addition an die dem Allylrest gegenüberliegende Carbonylgruppe (→ **83**), Ringschlussmetathese (→ **84**), Hydrierung und finale Reduktion von der weniger gehinderten *exo*-Seite lieferten Spartein (*rac*-**9**) in 11% Gesamtausbeute (grün-orange Pfeile).

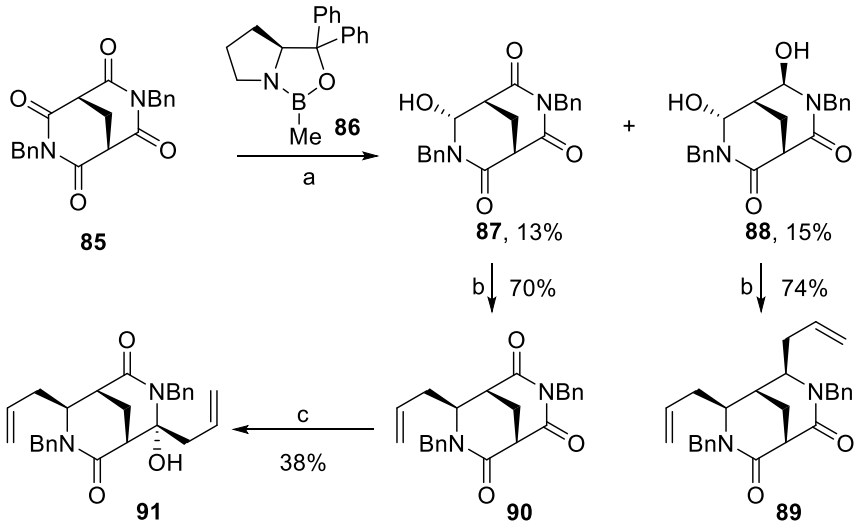


Schema 15. Modulare Synthese der stereoisomeren Bischinolizidine Spartein (*rac*-**9**), α-Isospartein (*rac*-**15**) und β-Isospartein (*rac*-**72**) nach Blakemore *et al.*[76]
Reagenzien und Bedingungen: a) $[CH_2O]_n$, kat. KOH, MeOH, 80 °C, 22 h, dann aq. NH_3, RT, 24 h; b) MsOH, Δ; c) AllylBr, NaH, DMF, 0 °C → RT, 1.5 h; d) AllylMgBr, Et_2O, THF, −78 °C, 10 min; e) Grubbs I, CH_2Cl_2, RT, 31 h; f) H_2 (1 bar), Pd/C, MeOH, H_2O, RT, 22 h; g) BH_3·THF, THF, 0 °C → RT, 20 h; h) $NaBH_4$, THF, 0 °C, 4.5 h; i) $AllylSiMe_3$, BF_3·Et_2O, RT, 40 h; j) Grubbs I, CH_2Cl_2, RT, 29 h; k) H_2 (1 bar), Pd/C, MeOH, H_2O, RT, 25 h; l) $LiAlH_4$, THF, Δ, 16 h; m) AllylMgBr, THF, −78 °C, 25 min; n) Grubbs II, CH_2Cl_2, Δ, 7 h; o) H_2 (1 bar), Pd/C, MeOH, H_2O, RT, 8 h; p) $LiAlH_4$, THF, Δ, 16 h.

Die Ergebnisse von Blakemore *et al.* zeigen, dass das Einbringen der *endo*- bzw. *exo*-ständigen Reste gesteuert werden kann, da Angriffe auf das Bispidin stets von der weniger gehinderten *exo*-Seite erfolgen, was auch durch andere Arbeiten bestätigt wurde.[77] Um *endo*-ständige Reste zu erhalten, muss zuerst eine Addition und anschließend eine Reduktion erfolgen, für *exo*-ständige Reste muss die Reaktionssequenz umgedreht werden.

Blakemore *et al.* untersuchten auch die enantioselektive Reduktion des Tetraoxobispidins **85** (Schema 16), aufbauend auf den Vorarbeiten an cyclischen *meso*-Imiden von Hiemstra *et al.*[78]

Hierfür sollte **85** in Gegenwart des CBS-Katalysators **86** enantioselektiv mit Boran reduziert werden.[76c] Dies gelang jedoch nur in schlechter Ausbeute (13%) und führte neben dem monoreduzierten Produkt **87** auch zum ungewünschten Nebenprodukt **88** (15% Ausbeute). Bei der Bestimmung der Enantiomerenreinheit auf Stufe der Verbindung **90** ergab sich ein mittelmäßiger *ee* von 71%. Erfolgreiche Grignard-Addition an **90** zeigte, dass diese Methode für die Synthese von (−)-Spartein (**9**) genutzt werden könnte, jedoch wurde die Synthese aufgrund der nur mittelmäßigen Enantioselektivität auf dieser Stufe abgebrochen.

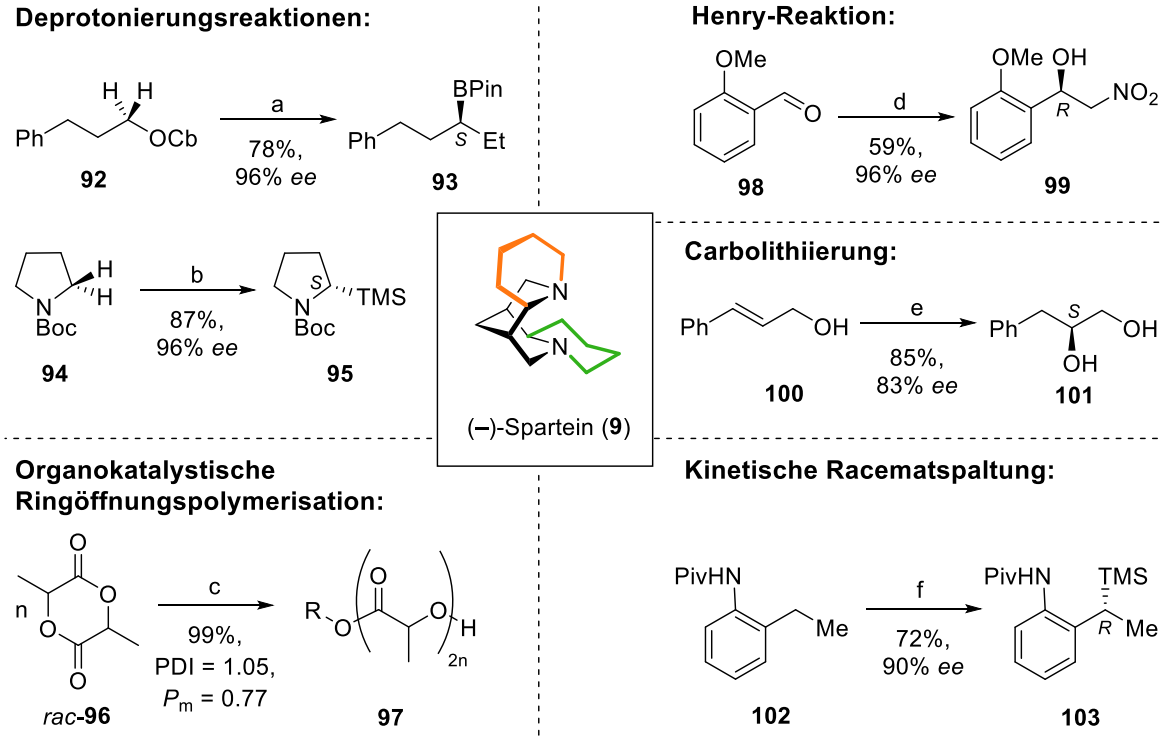


Schema 16. Versuchte enantioselektive Reduktion des Tetraoxobispidins **85** mit dem CBS-Katalysator **86** und Folgechemie.
Reagenzien und Bedingungen: a) **86**, THF, BH_3·THF, 0 °C, 2.5 h; b) $AllylSiMe_3$, BF_3·Et_2O, RT, 24 h; c) AllylMgBr, THF, −78 °C, 2 h.

Zur enantioselektiven Synthese von Bischinolizidin-Naturstoffen über einen modularen Zugang wurden seit Blakemore im Jahr 2008 keine neuen Versuche unternommen, was die Schwierigkeit dieses Vorhabens erahnen lässt.

1.2 Bischinolizidin-Naturstoffe in der Synthesechemie

Neben seiner Bioaktivität weist (−)-Spartein (**9**) auch hervorragende Eigenschaften als Stereoinduktor in der asymmetrischen Synthesechemie auf (Schema 17).[18] So findet es unter anderem Anwendung in enantioselektiven Deprotonierungsreaktionen,[79] Henry-Reaktionen,[80] Carbolithierungen,[81] kinetischen Racematspaltungen[82] und Ringsöffnungspolymerisationen.[83] In den gezeigten enantioselektiven Synthesen liefert (−)-Spartein (**9**) gute bis sehr gute Ausbeuten und Enantiomerenüberschüsse. In der organokatalytischen Ringöffnungspolymerisation weist es neben der nahezu quantitativen Ausbeute auch einen sehr guten Polydispersitätsindex (PDI) und eine sehr hohe Wahrscheinlichkeit für den Einbau von *meso*-Verbindungen (P_m) auf.



Schema 17. Beispiele für Reaktionen mit (−)-Spartein (**9**) als Stereoinduktor.[18,79-83]
Reagenzien und Bedingungen: a) **9** (> 1.0 Äquiv.), *s*BuLi, Et_2O, –78 °C, dann EtBPin; b) **9** (1.3 Äquiv.), *s*BuLi, Et_2O, –78 °C, dann TMSCl, –78 °C → RT; c) Thioharnstoff, **9** (5 Mol-%), 4-Pyren-1-butanol, $CDCl_3$; d) $CuCl_2$·[**9**] (20 Mol-%), NEt_3 (3 Mol-%), $MeNO_2$, MeOH, 0 °C; e) **9** (1.0 Äquiv.), *n*BuLi, Cumol, 0 °C; f) *s*BuLi, Et_2O, –25 °C, dann **9** (2.9 Äquiv.), dann –78 °C, TMSCl.

Da (+)-Spartein (*ent*-**9**) in der Natur selten vorkommt, lassen sich die enantiomeren Produkte der gezeigten Reaktionen nicht ohne Weiteres darstellen.[84] Ein weiteres großes Problem ist, dass (−)-Spartein (**9**) käuflich nur noch schwer zu erwerben ist.[18] Eine Lösung dieser beiden Probleme liefern synthetische Bischinolizidin-Naturstoffe oder Derivate davon, die in der enantioselektiven Synthese ähnliches Potenzial erbringen wie (−)-Spartein (**9**).

1.3 Synthese von Bispidin-Derivaten

Beak *et al.* untersuchten 1995 neben (−)-Spartein (**9**) weitere chirale Diaminliganden für die Deprotonierungsreaktion von Boc-Pyrrolidin **94** (siehe Schema 17).[85] Keiner der verwendeten Liganden erzielte jedoch so gute Ausbeuten und Enantiomerenüberschüsse wie (−)-Spartein (**9**). Aufgrund dieser Ergebnisse und der Tatsache, dass (+)-Spartein (*ent*-**9**) nur schwer zu erwerben war, wurde O'Brien auf das „(+)-Spartein-Problem" aufmerksam, wie er in seiner Publikation „Basic instinct: design, synthesis and evaluation of (+)-sparteine surrogates for asymmetric synthesis" aus dem Jahr 2008 schilderte.[84] Er suchte also nach einem Liganden mit dem die schlechte Verfügbarkeit von (+)-Spartein (*ent*-**9**) kompensiert werden konnte. Der Veröffentlichung von Beak *et al.* waren Chem3D®-Strukturen der Lithium-Komplexe von (−)-Spartein (**9**) und dessen Stereoisomer α-Isospartein (**15**) angefügt, um die Ergebnisse der Deprotonierungsreaktionen zu veranschaulichen (Abbildung 12).[85] Bei (−)-Spartein (**9**) ist der *exo*-D-Ring vom aktiven Zentrum weg orientiert, während bei α-Isospartein der *endo*-D-Ring zum aktiven Zentrum hin zeigt, was eine geringere Reaktivität des *s*BuLi/α-Isospartein-Komplexes bedingt und die „unkatalysierte" Reaktionen fördert. O'Brien schloss aufgrund dieser 3D-Strukturen, dass der D-Ring in (−)-Spartein (**9**) entfernt werden könnte ohne die Stereoselektivität zu beeinflussen.[84] Am Stickstoff sollte eine *N*-Me-Gruppe angebracht werden, da diese der *N*-CH_2-Gruppe des D-Rings in (−)-Spartein (**9**) am ähnlichsten wäre (Abbildung 12, rechts). Dieser Ansatz führte zur Entwicklung des (+)-Spartein-Ersatzstoffs (*ent*-**10**).

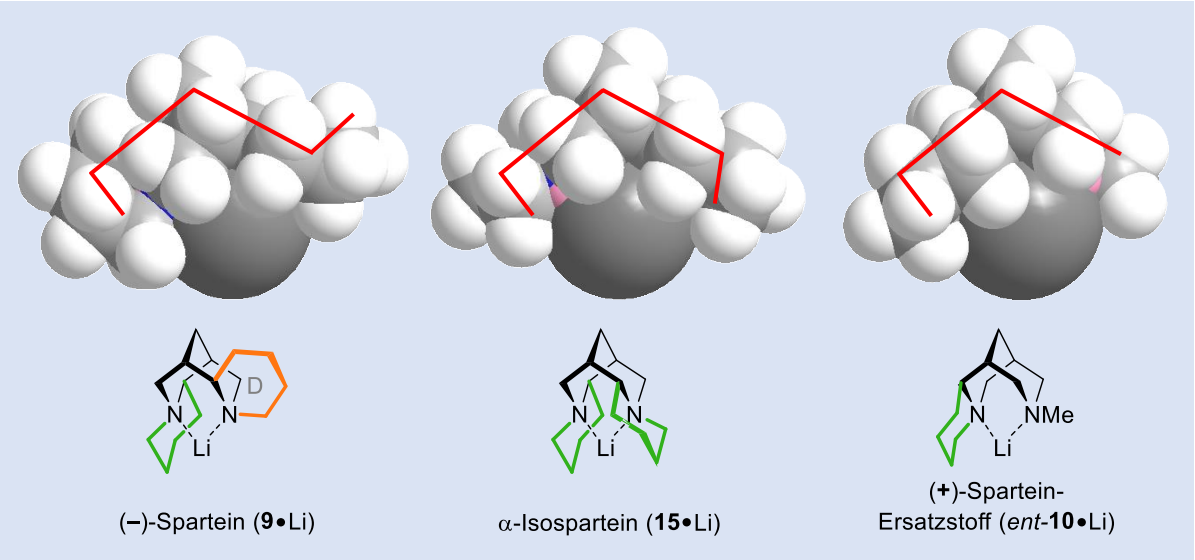
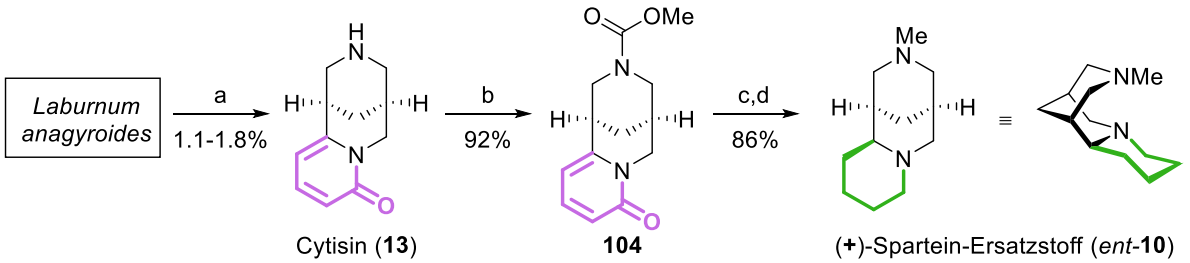


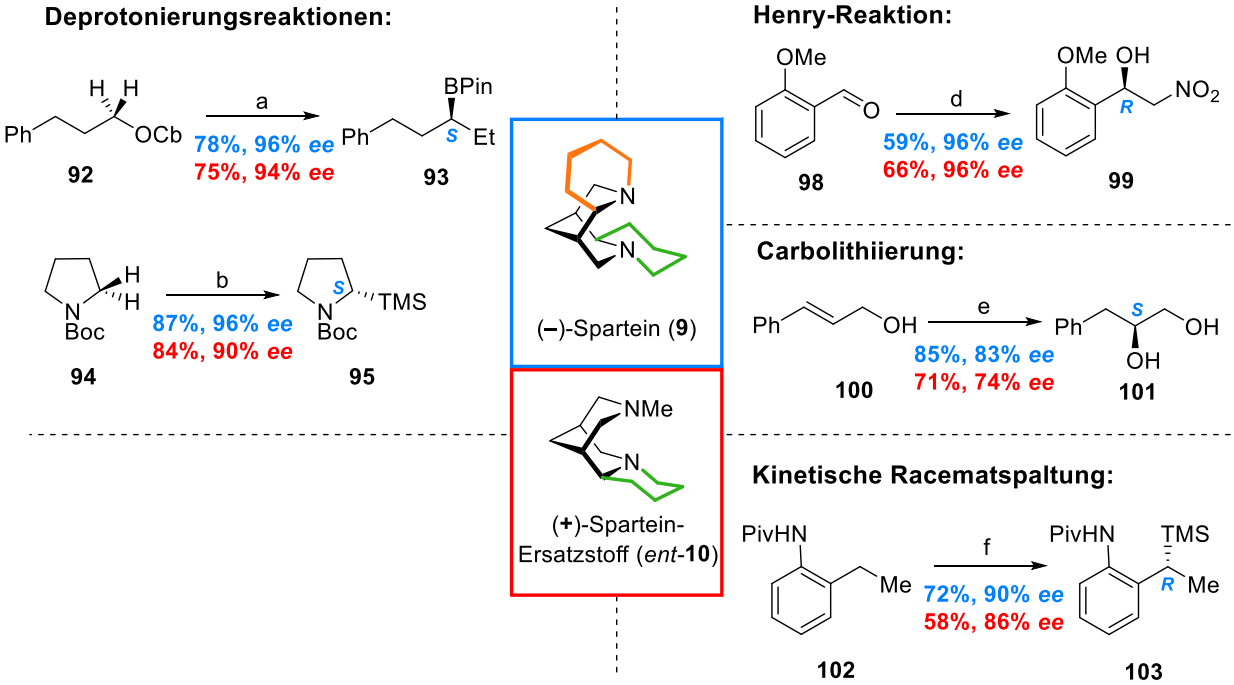
Abbildung 12. 3D-Strukturen der Li-Komplexe von (−)-Spartein (**9**·Li), α-Isospartein (**15**·Li) und dem synthetischen (+)-Spartein-Ersatzstoff (*ent*-**10**·Li). Die Abbildung wurde in Analogie zu Beak *et al.* und O'Brien erstellt. Liganden am Metall wurden übersichtshalber weggelassen.[84,85]

Ausgangsmaterial für den (+)-Spartein-Ersatzstoff (*ent*-**10**) ist natürliches Cytisin (**13**), das aus *Laburnum anagyroides* in 1.1-1.8% Ausbeute isolierbar ist (Schema 18).[86] MeOC-Schützung, Hydrierung und Reduktion liefern den (+)-Spartein-Ersatzstoff (*ent*-**10**) in nur drei Stufen mit >99% *ee* und einer Gesamtausbeute von 79% erhalten.



Schema 18. Synthese des (+)-Spartein-Ersatzstoffs (*ent*-**10**) ausgehend von Cytisin (**13**) nach O'Brien *et al.*[84,86] *Reagenzien und Bedingungen*: a) aq. NH_4OH, MeOH-CH_2Cl_2, RT, 69 h; aq. HCl; aq. NH_4OH, Extraktion mit CH_2Cl_2; b) MeO_2CCl, NEt_3, CH_2Cl_2, 0 °C → RT, 4 h; c) H_2 (1 bar), PtO_2, MeOH, RT, 5 h; d) $LiAlH_4$, THF, Δ, 16 h.

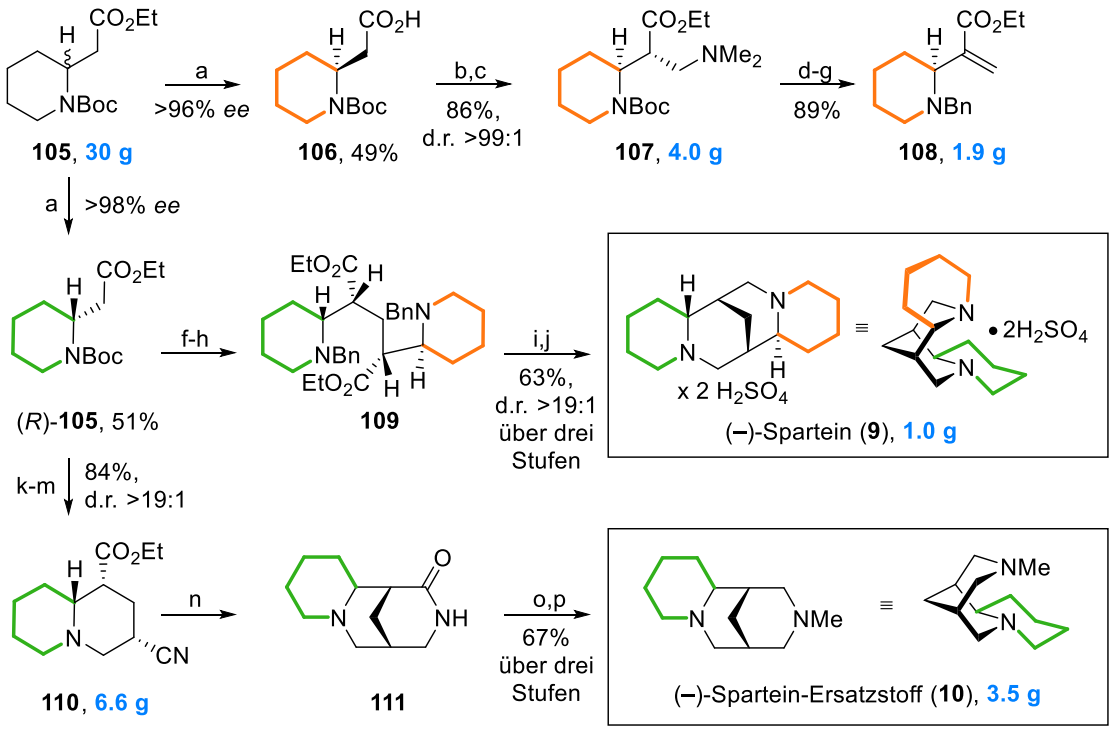
Schema 19 zeigt eine Gegenüberstellung der Ergebnisse von (−)-Spartein (**9**, in Blau dargestellt) und dem synthetischen (+)-Spartein-Ersatzstoff (*ent*-**10**, in Rot dargestellt) in verschiedenen asymmetrischen Reaktionen.



Schema 19. Beispiele für Reaktionen mit (−)-Spartein (**9**) und (+)-Spartein-Ersatzstoff (*ent*-**10**) als Stereoinduktor. Mit (+)-Spartein-Ersatzstoff (*ent*-**10**) wird das enantiomere Produkt erhalten.[18,79-83] *Reagenzien und Bedingungen*: a) **9** oder *ent*-**10** (> 1.0 Äquiv.), *s*BuLi, Et_2O, –78 °C, dann EtBPin; b) **9** oder *ent*-**10** (1.3 Äquiv.), *s*BuLi, Et_2O, –78 °C, dann TMSCl, –78 °C → RT; d) $CuCl_2$·[**9**] oder $CuCl_2$·[*ent*-**10**] (20 Mol-%), NEt_3 (3 Mol-%), $MeNO_2$, MeOH, 0 °C; e) **9** oder *ent*-**10** (1.0 Äquiv.), *n*BuLi, Cumol, 0 °C; f) *s*BuLi, Et_2O, –25 °C, dann **9** oder *ent*-**10** (2.9 Äquiv.), dann –78 °C, TMSCl.

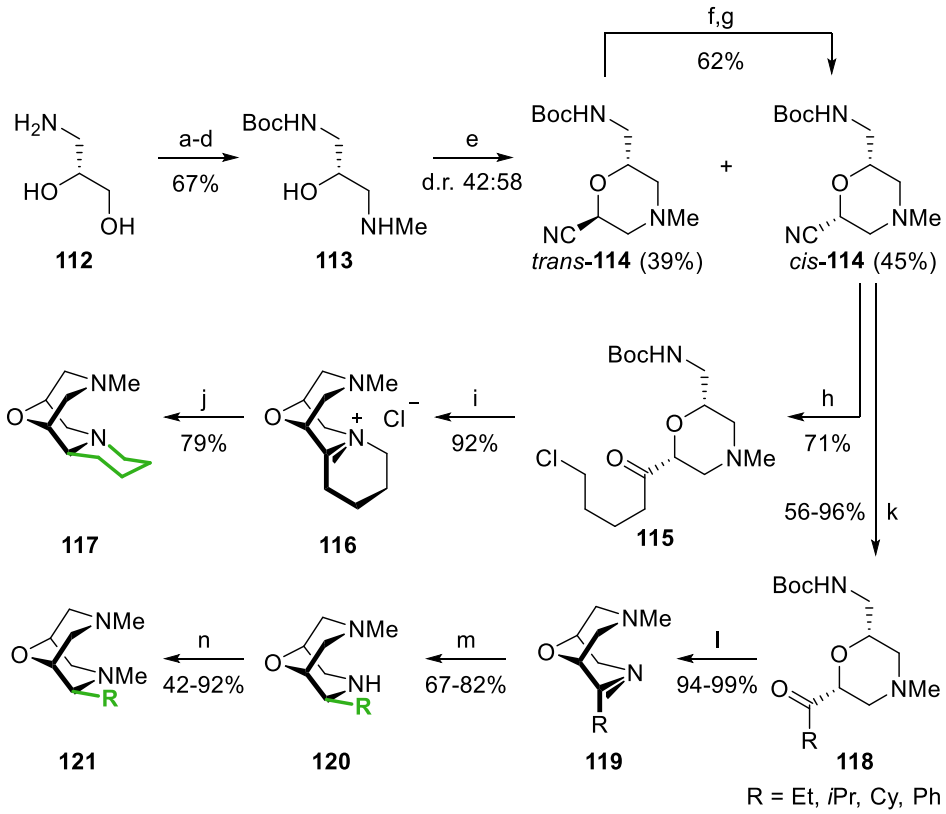
Sowohl Ausbeuten als auch Enantiomerenüberschüsse mit dem (+)-Spartein-Ersatzstoff (*ent*-**10**) sind nahezu gleich denen mit (−)-Spartein (**9**). So erreichte **9** bei der enantioselektiven Henry-Reaktion von 2-Methoxybenzaldehyd (**98**) 59% Ausbeute und 96% *ee*, *ent*-**10** eine vergleichbare Ausbeute von 66%, bei identischer Stereoinduktion.

Da es für (−)-Spartein (**9**) Lieferengpässe gab und es nicht mehr in ausreichender Menge zur Verfügung stand, verbesserte O'Brien im Jahr 2018 seine bisherige Syntheseroute (Kapitel 1.1.5.2) und zeigte so eine Möglichkeit, in zehn Stufen (−)-Spartein (**9**) im Grammmaßstab und guten 31% Gesamtausbeute zu synthetisieren (Schema 20).[71] Ebenfalls präsentierte er eine Route über acht Stufen und einer Gesamtausbeute von 22% für die Synthese des (−)-Spartein-Ersatzstoffs (**10**). Schlüsselschritt dabei ist die enantioselektive Esterspaltung von **105** mit einer Lipase aus *B. Cepacia*, die hohe Enantioselektivitäten und eine Trennung der Enantiomere ermöglichte. Für die Synthese von (−)-Spartein (**9**) wurden der Ester (*R*)-**105** und die enantiomere Säure **106** benötigt, wobei letztere verestert und in den α,β-ungesättigten Ester **108** überführt wurde. Die weiteren Schritte erfolgten dann wie bei der ersten enantioselektiven Totalsynthese von (−)-Spartein (**9**, siehe Schema 11). Dabei stammt der *endo*-anellierte Ring aus dem Ester (*R*)-**105** und der *exo*-anellierte Ring aus dem Michael-System **108**. Die Synthese des (−)-Spartein-Ersatzstoffs (**10**) erfolgte ausgehend von (*R*)-**105**. In drei Stufen wurde der Tricyclus **111** erhalten, welcher nach Methylierung und Reduktion **10** lieferte.



Schema 20. Optimierte enantioselektive Synthese von (−)-Spartein (**9**) und des (−)-Spartein-Ersatzstoffs (**10**) nach O'Brien *et al.*[71]
Reagenzien und Bedingungen: a) Lipase von *B. Cepacia*, pH = 7, H_2O, THF, 35 °C, 39 h; b) EtOH, DCC, DMAP, MeCN, RT, 2 h; c) LiHMDS, THF, −78 °C, dann Eschenmoser-Salz, −78 °C → RT, 16 h; d) MeI, THF, RT, 1.5 h; e) DBU, Toluol, Δ, 16 h; f) TFA, CH_2Cl_2, RT, 1 h; g) BnBr, Na_2CO_3, CH_2Cl_2/H_2O, RT, 16 h; h) LDA, −78 °C, 2 h, dann **108**, −78 °C → RT, 16 h; i) $Pd(OH)_2/C$, $NH_4^+HCO_2^-$, EtOH, Δ, 4 h, dann K_2CO_3, Δ, 16 h; j) $LiAlH_4$, THF, Δ, 16 h, dann H_2SO_4; k) LiHMDS, THF, −78 °C, 1 h, dann 2-Brommethylacrylnitril, 16 h; l) TFA, CH_2Cl_2, RT, 10 h; m) K_2CO_3, EtOH, RT, 16 h; n) kat. $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, 0 °C → RT, 16 h; o) NaH, MeI, THF, 0 °C → RT, 16 h; p) DIBAL-H, THF, 0 °C → RT, 1 h.

Weitere Alternativen als Liganden bieten die von Breuning *et al*. entwickelten 9-Oxabispidine, welche über eine modulare Synthese zugänglich sind (Schema 21).[87] Ausgehend vom käuflich erwerblichen Aminodiol **112** wird über fünf Stufen das *cis*-konfigurierte Cyanomorpholin *cis*-**114** aufgebaut. Ebenfalls entstehendes *trans*-**114** kann zu *cis*-**114** isomerisiert werden. Verbindung *cis*-**114** bildet das Schlüsselintermediat, von dem aus über drei Stufen das *endo*-konfigurierte, tricyclische 9-Oxabispidin **117** synthetisiert wurde. Um den sterischen Einfluss des Rests in 2-Position zu untersuchen, wurden via Grignard-Reaktion Reste unterschiedlicher Größe (→ **118**: R = Et, *i*Pr, Cy, Ph) angebracht. Nach Entschützung (→ **119**), Reduktion (→ **120**) und reduktiver Aminierung (→ **121**) konnten so vier weitere Liganden **121** erhalten werden. Der Ringschluss zum Bispidin-Kerngerüst erfolgt bei der Entschützung und anschließenden Filtration über basischem Alox *in situ*. Das Hydrid greift bei der Reduktion stets von der weniger gehinderten *exo*-Seite an.



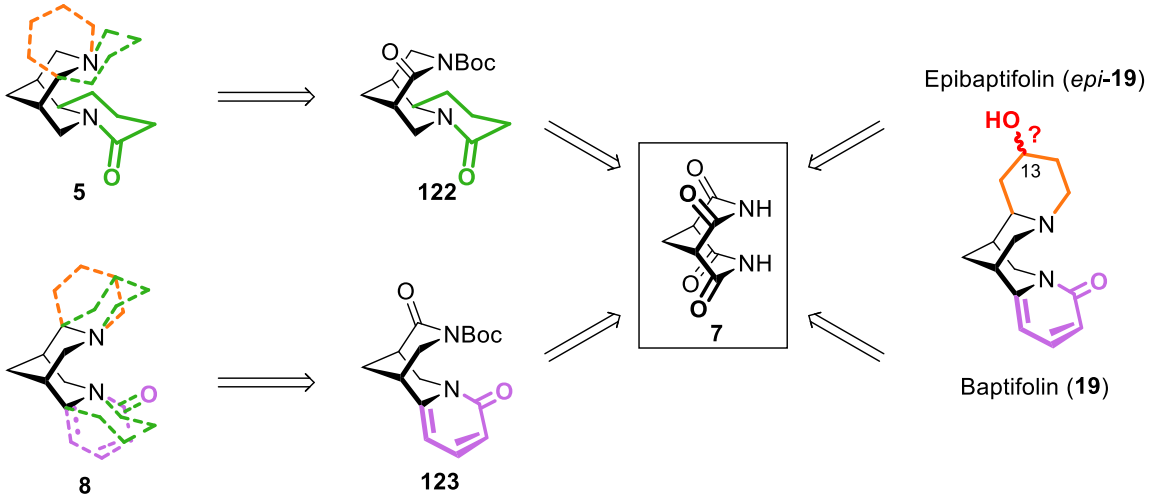
Schema 21. Synthese von 9-Oxabispidinen nach Breuning *et al.*[87]
Reagenzien und Bedingungen: a) Boc_2O, NEt_3, MeOH, CH_2Cl_2, RT; b) TsCl, Pyridin, RT; c) NaH, THF, RT; d) aq. $MeNH_2$, EtOH, RT; e) 2-Chloracrylnitril, THF, KO*t*Bu, RT, 16 h; f) KO*t*Bu, *t*BuOH, 55 °C, 16 h; g) TFAA, NEt_3, THF, −20 °C → RT, ü.N.; h) $Cl(CH_2)_4MgBr$, THF, 0 °C, 7 h; i) TFA, RT, dann Alox B, 16 h; j) $NaBH_4$, MeOH, −10 °C, 4 h; k) RMgX, THF, 0 °C; l) TFA, RT, dann Alox B; m) $NaBH_4$, MeOH, 0 °C; n) Für R= Et/Ph: MeI, K_2CO_3, CH_2Cl_2, RT; für R= *i*Pr/Cy: 1. $ClCO_2Me$, NEt_3, CH_2Cl_2, 2. $LiAlH_4$, THF, Δ.

Diese Liganden wurden in enantioselektiven Henry-Reaktionen getestet, wobei **110** in der in Schema 17 und 19 gezeigten Reaktion mit 2-Methoxybenzaldehyd **98** eine Ausbeute von 91% und einen *ee* von 97% (*S*) lieferte.[87d] Damit liegen diese Liganden mit (−)-Spartein (**9**) und (+)-Spartein-Ersatzstoff (*ent*-**10**) gleichauf.

Da es bisher nur wenige mit (−)-Spartein (**9**) vergleichbare Liganden gibt, ist die Suche nach weiteren Liganden, die genauso gute oder bessere Enantiomerenüberschüsse und Ausbeuten erzielen, ein attraktives Forschungsfeld.

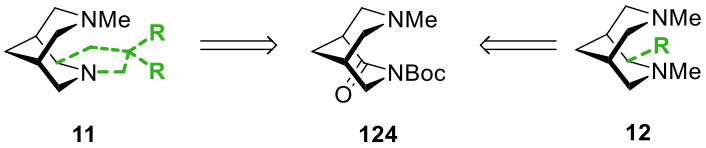
2 ZIELSETZUNG

Trotz einiger eleganter Totalsynthesen existiert noch kein modularer Zugang zu Bischinolizidin-Alkaloiden. Hauptziel dieser Arbeit war daher die Entwicklung einer diversitätsorientierten, enantioselektiven Route zu einer Vielzahl an Vertretern dieser interessanten Naturstoffklasse. Anvisiert war dabei eine Strategie, die von achiralem Tetraoxobispidin **7** ausgeht und über die enantiomeren, tricyclischen Bispidine **123** und **122** zu den Alkaloiden **5** und **8** führt (Schema 22). Ein darauf aufbauendes Projekt bestand in der Synthese der C_{13}-hydroxylierten, epimeren Alkaloide Baptifolin (**19**) und Epibaptifolin (*epi*-**19**), um deren Konfiguration an C_{13}, über die in der Literatur widersprüchliche Angaben vorliegen, zweifelsfrei zu bestimmen.



Schema 22. Hauptprojekte 1 und 2: Modulare, enantioselektive Synthese von Bischinolizidin-Naturstoffen der Typen **5**, **8** und (Epi)Baptifolin (**19** bzw. *epi*-**19**), sowie Aufklärung der Konfiguration letzterer an C_{13}.

Als Nebenprojekt war die enantioselektive Synthese von artifiziellen Bispidinen der Strukturen **11** und **12** geplant (Schema 23). Deren Potential als Ersatzstoffe für (+)- bzw. (−)-Spartein (*ent*-**9** bzw. **9**) sollte anhand verschiedener asymmetrischer Transformationen und als chirale Liganden in der enantioselektiven Katalyse evaluiert werden.

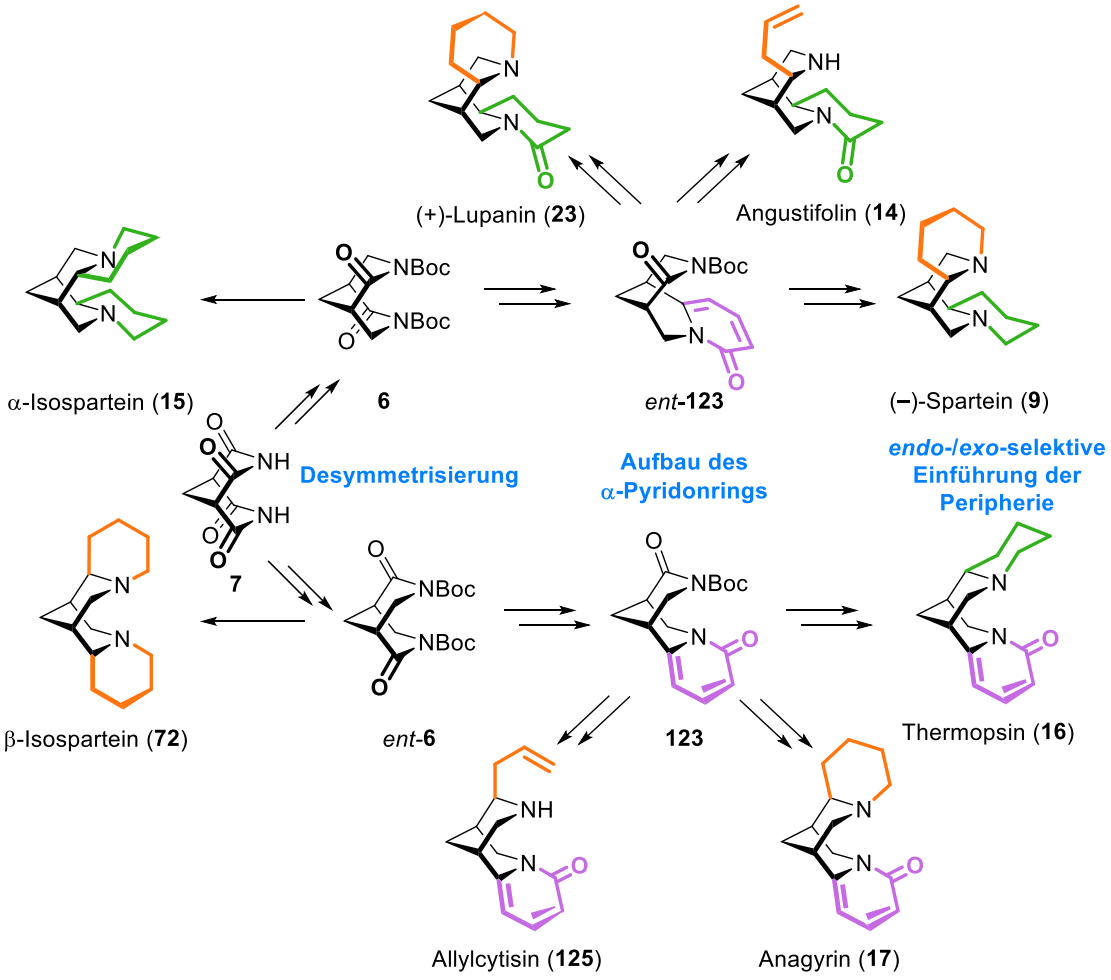


Schema 23. Projekt 3: Neue Bispidin-Liganden **11** und **12** für die Anwendung in der enantioselektiven Katalyse.

3 SYNOPSIS

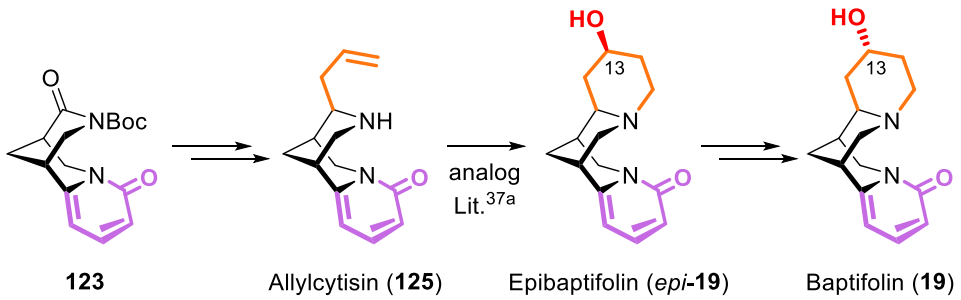
Die vorliegende kumulative Dissertation beinhaltet drei Publikationen, welche in Kapitel 6 zu finden sind.

Hauptziel dieser Arbeit war die Entwicklung eines modularen, enantioselektiven Zugangs zu tri- und tetracyclischen Bischinolizidinen (über 20 Naturstoffe synthetisiert) ausgehend vom achiralen Tetraoxobispidin **7** (Schema 24). Dieses wurde im ersten Schlüsselschritt desymmetrisiert, was zu den beiden enantiomeren Dioxobispidinen **6** und *ent*-**6** führte. Der Aufbau des α-Pyridonrings in **123** bzw. *ent*-**123** bildete den zweiten Schlüsselschritt. Durch die Wahl der Reaktionssequenz wurden daran via Addition und anschließender Reduktion *endo*-Reste angebracht, oder via Reduktion und anschließender Addition *exo*-Reste, was zu verschiedenen Bischinolizidin-Naturstoffen führte. Diese Ergebnisse wurden 2018 in der Zeitschrift *Angewandte Chemie* (*Int. Ed.*) veröffentlicht (Kapitel 6.1.1, 6.1.2) und im gleichen Jahr von Carreira und Wolleb in *Synfacts* gewürdigt (Kapitel 6.1.3).



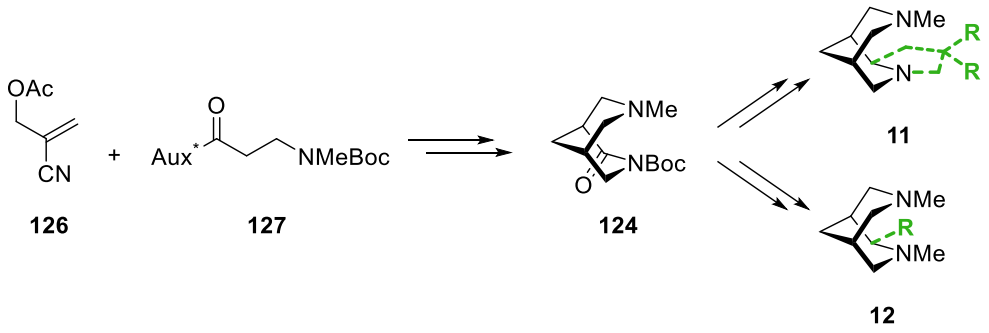
Schema 24. Hauptprojekt 1: Modulare, enantioselektive Totalsynthese von Bischinolizidin-Naturstoffen.

Ausgehend von Allylcytisin (**125**), das über den modularen Zugang in ausreichender Menge zur Verfügung stand, wurden im zweiten Projekt die beiden epimeren Bischinolizidin-Naturstoffe Epibaptifolin (*epi*-**19**) und Baptifolin (**19**) synthetisiert (Schema 25). Deren umstrittene Konfiguration an C_{13} wurde mittels Röntgenkristallstrukturanalyse, NMR-Analytik und Derivatisierung eindeutig bestimmt. Die Synthese und Strukturklärung wurde 2019 in der Zeitschrift *European Journal of Organic Chemistry* veröffentlicht (Kapitel 6.2).



Schema 25. Hauptprojekt 2: Enantioselektive Synthese von Baptifolin (**19**) und Epibaptifolin (*epi*-**19**) und Bestimmung deren Konfiguration an C_{13}.

Die modulare Synthese neuer Bispidin-Liganden ausgehend vom Schlüsselintermediat **124**, welches über fünf Stufen aus **126** und **127** synthetisiert wurde, war das dritte Projekt dieser Dissertation (Schema 26). Die chiralen Liganden des Typs **11** und **12** lieferten in Cu-katalysierten, enantioselektiven Henry-Reaktionen exzellente Enantiomerenüberschüsse und sehr gute Ausbeuten bei nur geringer Katalysatorbeladung (2 Mol-%). Diese Ergebnisse wurden 2015 in der Zeitschrift *Chemistry – A European Journal* publiziert (Kapitel 6.3).

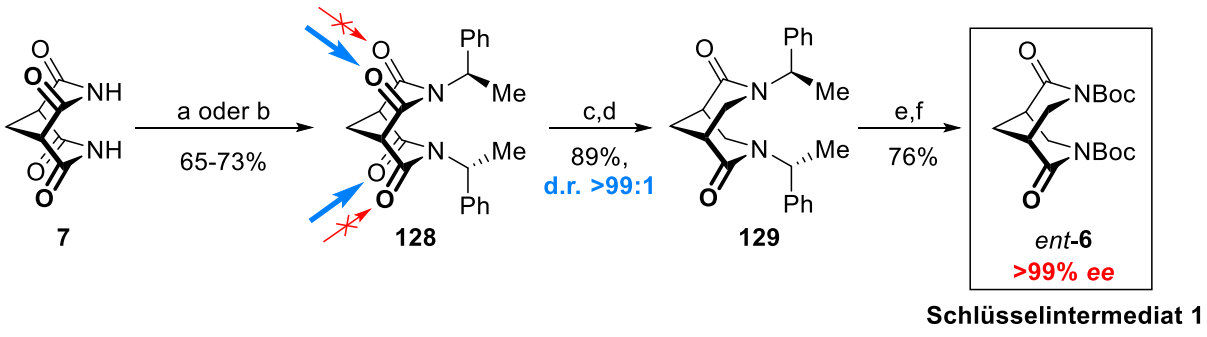


Schema 26. Nebenprojekt 3: Modulare Synthese der Liganden **11** und **12** und deren Anwendung in enantioselektiven, Cu-katalysierten Henry-Reaktionen.

3.1 Die enantioselektive Totalsynthese von Bischinolizidin-Alkaloiden: Ein modularer „Inside-Out"-Zugang

Da bis dato kein modularer Zugang zu Bischinolizidin-Alkaloiden existierte, war es das Hauptziel dieser Dissertation einen modularen Zugang zu einer Vielzahl an enantiomerenreinen Naturstoffen dieser Klasse zu entwickeln. Dabei sollte eine neue „*Inside-Out*"-Strategie genutzt werden, gemäß der zuerst der Bispidin-Kern und anschließend die Peripherie aufgebaut wird. In der Literatur wurden die meisten Bischinolizidine über einen sogenannten „*Outside-In*"-Zugang synthetisiert, bei dem zuerst die Peripherie aufgebaut und anschließend der Bispidin-Kern geschlossen wurde. Dies erlaubt zumeist nur die Synthese einzelner Zielmoleküle.

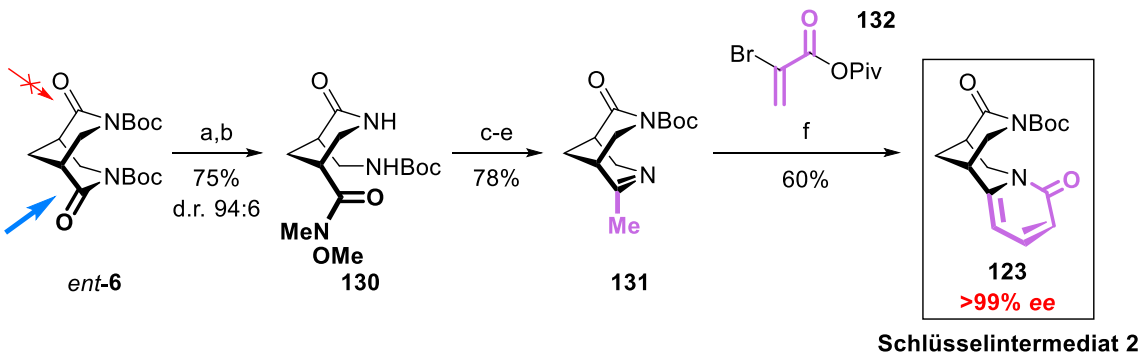
Die eigene Synthese erfolgte ausgehend vom achiralen Tetraoxobispidin **7**, welches nach Einführen eines chiralen Auxiliars ((*S*)-1-Phenylethanol) via Mitsunobu-Reaktion (→ **128**) durch die Reduktion zweier gegenüberliegender Carbonylgruppen (blaue Pfeile) in das Dioxobispidin **129** mit einem d.r. >99:1 überführt wurde (Schema 27). Entfernen des Auxiliars und Anbringen aktivierender Boc-Gruppen lieferte das erste Schlüsselintermediat (*ent*-**6**) in einer Gesamtausbeute von 30-34% über fünf Stufen und einem Enantiomerenüberschuss von >99%. Für die Synthese des enantiomeren Dioxobispidins **6** wurde anstelle von (*S*)-1-Phenylethanol (*R*)-1-Phenylethanol als chirales Auxiliar verwendet.



Schema 27. Stereoselektive Synthese des ersten, chiralen Schlüsselintermediats, des Dioxobispidins *ent*-**6**. *Reagenzien und Bedingungen*: a) (*S*)-1-Phenylethanol, PBu_3, ADDP, −15 °C → RT, 26 h; b) (*S*)-1-Phenylethanol, PBu_3, DEAD, 0 °C, 26 h; c) $LiBHEt_3$, CH_2Cl_2, −78 °C, 2 h, dann MeOH, RT, 30 min; d) Et_3SiH, TFA, 0 °C → RT, 14 h; e) Na, fl. NH_3, *t*BuOH, THF, −78 °C, 10 min; f) Boc_2O, NEt_3, DMAP, MeCN, RT, 22 h.

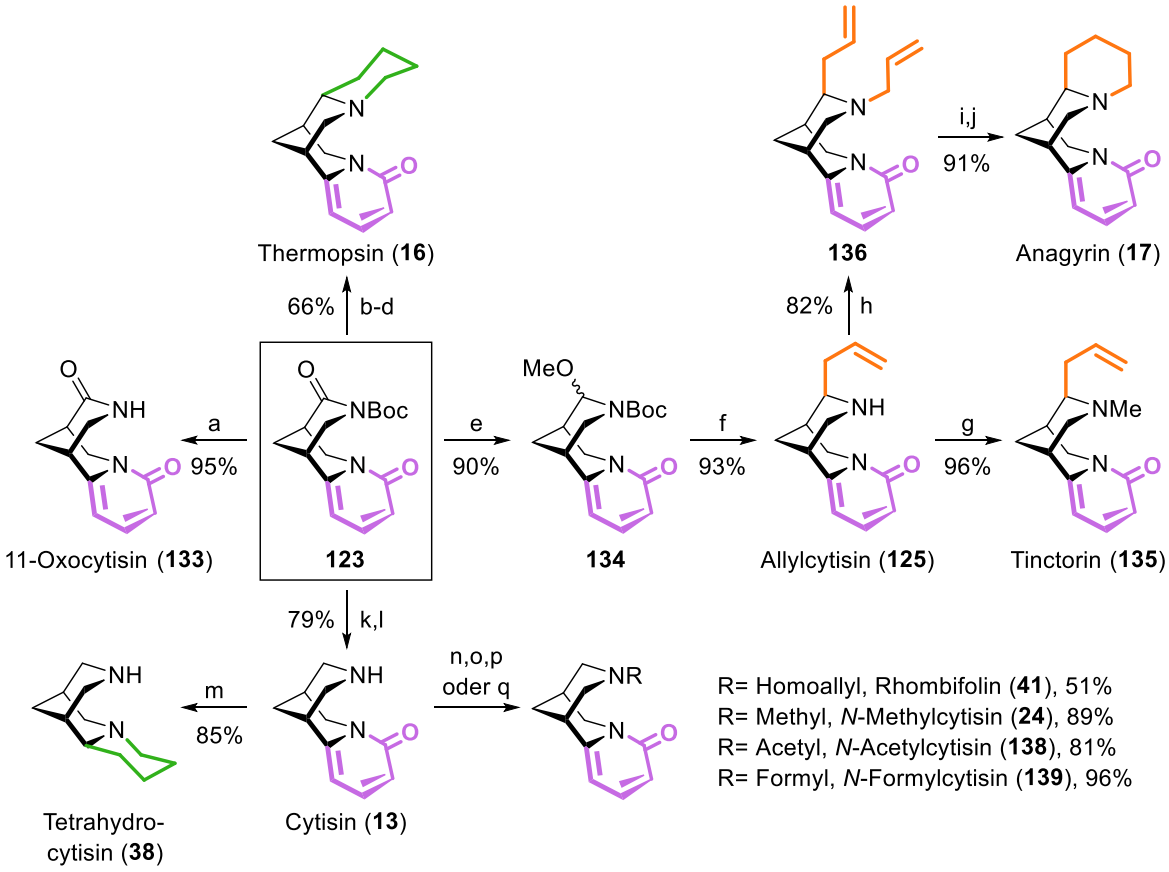
Zum Aufbau des Pyridonrings in **123** musste eine der beiden Imidgruppen selektiv modifiziert werden (Schema 28). Dies gelang durch Lewis-Säure-katalysierte Ringöffnung mit HNMe(OMe)·HCl/$AlMe_3$ bei −35 °C. Selektive Boc-Entschützung des cyclischen Imids lieferte das Weinreb-Amid **130** in 75% Ausbeute und einem d.r. von 94:6. Bei höheren Temperaturen

kann es zu einer Isomerisierung an den ehemaligen Brückenköpfen kommen, was den *ee* des Pyridons **123** beeinträchtigen würde. Grignard-Addition an das Keton, Boc-Entschützung des Amins und Boc-Schützung des Amids nach erfolgtem Ringschluss lieferten das Iminimid **131** in 78% Ausbeute über drei Stufen. Eine anschließende Enamin-Michael-Addition mit **132** führte zum zweiten Schlüsselintermediat, dem Pyridon **123**, nach Umkristallisation in >99% *ee*.



Schema 28. Stereoselektive Anellierung von *ent*-**6** zum tricyclischen Schlüsselintermediat **123**.
Reagenzien und Bedingungen: a) HNMe(OMe)·HCl, $AlMe_3$, CH_2Cl_2, −35 °C, 18 h; b) TFA, CH_2Cl_2, 0 °C → RT, 19 h; c) MeMgBr, THF, −40 °C → RT, 17 h; d) BF_3·Et_2O, CH_2Cl_2, RT, 19 h; e) Boc_2O, NEt_3, DMAP, MeCN, RT, 20 h; f) **132**, THF, 3 h, dann NEt_3, 2 h.

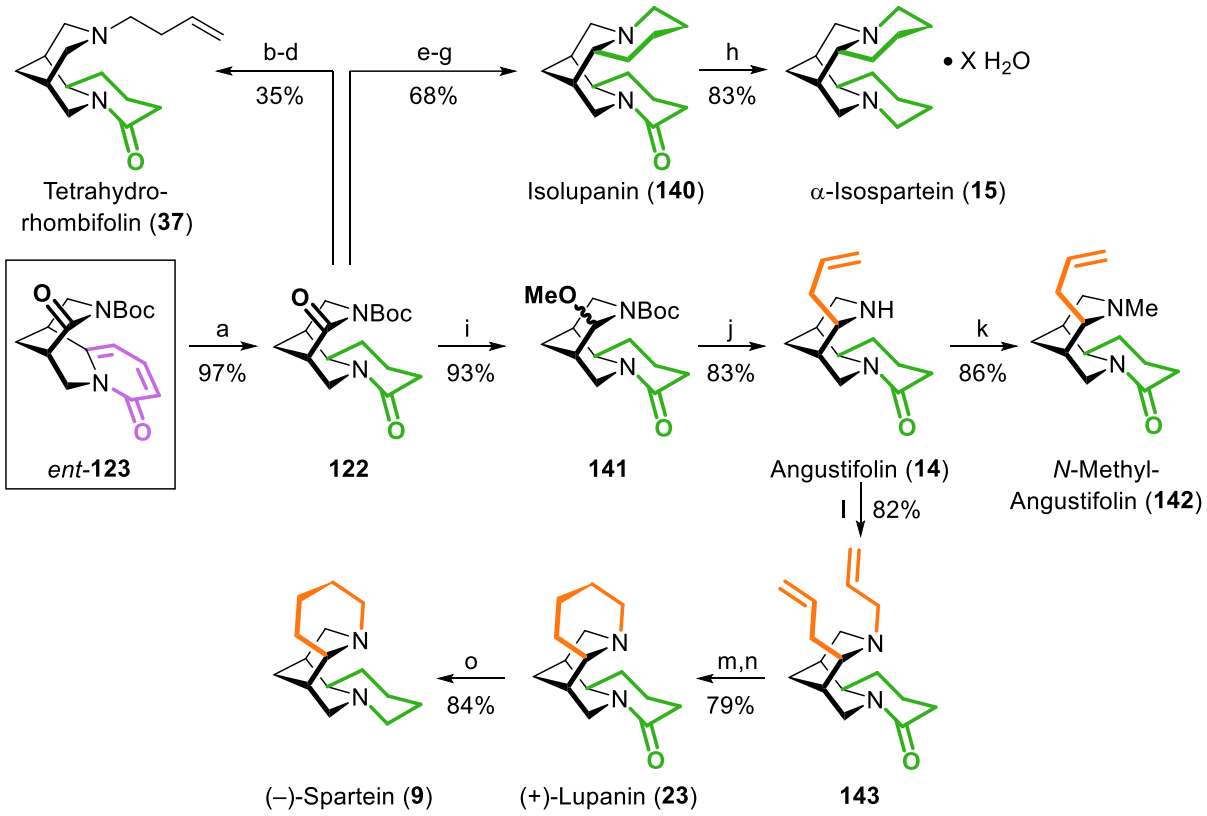
Mit dem chiralen Schlüsselintermediat **123** wurden die ersten enantiomerenreinen Naturstoffe der 7*R*/9*R*-Serie synthetisiert (Schema 29). Einfache Entschützung lieferte 11-Oxocytisin (**133**) in 96% Ausbeute. Der *endo*-ständige Piperidinring in Thermopsin (**16**) wurde über eine Grignard-Addition-/Reduktion-Sequenz über drei Stufen in 66% Ausbeute aufgebaut. Die umgekehrte Sequenz − erst Reduktion, dann Sakurai-Reaktion – führte zu 11-Allylcytisin (**125**) mit *exo*-ständigem Allylrest über zwei Stufen in guten 84% Ausbeute. Ausgehend von **125** wurde über reduktive Aminierung Tinctorin (**135**, 96% Ausbeute) synthetisiert, über *N*-Allylierung (→ **136**), Grubbs Ringschlussmetathese und Hydrierung Anagyrin (**17**, drei Stufen, 75% Ausbeute). Cytisin (**13**) wurde durch Reduktion und Entschützung aus dem Schlüsselintermediat **123** in 79% Ausbeute erhalten. Anschließende Hydrierung lieferte Tetrahydrocytisin (**38**). Der Homoallyl-Rest in Rhombifolin (**41**) wurde über eine Barbier-ähnliche Reaktion an **13** eingeführt. Reduktive Aminierung von Cytisin (**13**) lieferte *N*-Methylcytisin (**24**) in 89% Ausbeute. Acetylierung bzw. Formylierung von **13** führten zu den beiden Naturstoffen *N*-Acetylcytisin (**138**) und *N*-Formylcytisin (**139**) in sehr guten Ausbeuten.



Schema 29. Synthese von zehn enantiomerenreinen Naturstoffen der 7*R*/9*R*-Serie ausgehend vom Pyridon **123**. *Reagenzien und Bedingungen*: a) TFA, CH_2Cl_2, 0 °C → RT, 16 h; b) 4-Cl-$(CH_2)_4$MgBr, THF, −78 °C, 5 h; c) TFA, CH_2Cl_2, 0 °C → RT, 17 h; d) $NaBH_4$, MeOH, 0 °C, 3 h; e) $NaBH_4$, MeOH, 0 °C, 1.5 h, dann MeOH/HCl, RT, 4 h; f) $AllylSiMe_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C → RT, 16 h; g) CH_2O, MeOH/THF; $NaBH_3CN$, RT, 2.5 h; h) AllylBr, NEt_3, CH_2Cl_2, 96 h; i) Grubbs II, CH_2Cl_2, Δ, 1 h; j) H_2 (1 bar), Pd/C, MeOH, RT, 2.5 h; k) $NaBH_4$, MeOH, 0 °C → RT, 2 h; l) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C → RT 15 h; m) H_2 (1 bar), PtO_2, AcOH, RT, 22 h; n) CH_2O, AllylBr, Zn, AcOH, H_2O, RT, 22 h; o) CH_2O, $NaBH_3CN$, MeOH/THF, RT, 2.5 h; p) AcCl, NEt_3, CH_2Cl_2, 0 °C → RT, 18 h; q) Ethylformiat, Δ, 19 h.

Das enantiomere Schlüsselintermediat *ent*-**123** wurde ebenfalls über die in Schema 28 gezeigte Route synthetisiert. Für die 7*S*/9*S*-Serie wurde *ent*-**123** zum Piperidon **122** hydriert, da es in dieser Serie keine Bischinolizidin-Naturstoffe mit Pyridon-Ring gibt (Schema 30). Um zu Tetrahydrorhombifolin (**37**) zu gelangen, wurde **122** reduziert, entschützt und via Barbier-ähnlicher Reaktion *N*-homoallyliert. Grignard-Addition, Entschützung und Reduktion lieferten den *endo*-Piperidinring in Isolupanin (**140**, 68% Ausbeute), welches durch Reduktion mit $LiAlH_4$ in α-Isospartein (**15**, 83% Ausbeute) überführt wurde. Der Aufbau des *exo*-ständigen Rests in Angustifolin (**14**) erfolgte wieder via der umgekehrten Reduktions-/Additions-Sequenz in einer Ausbeute von 77% über zwei Stufen. Die Methylierung zu *N*-Methylangustifolin (**142**) wurde mit MeI und K_2CO_3 durchgeführt, da reduktive Aminierung mit CH_2O und $NaBH_3CN$

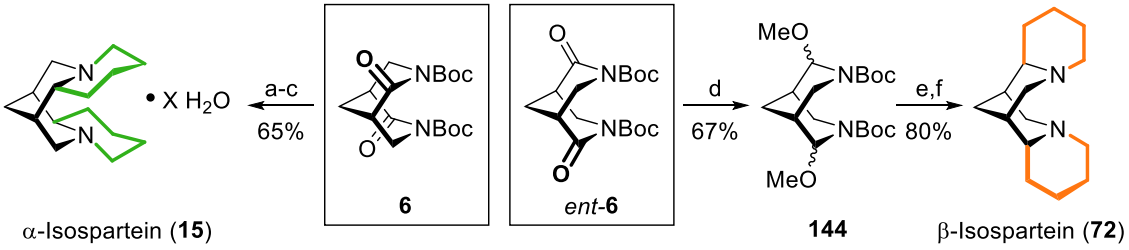
eine Mischung aus *N*-Methylangustifolin (**142**) und Tetrahydrorhombifolin (**37**) lieferte. Angustifolin (**14**) wurde anschließend mit AllylBr *N*-allyliert (→ **143**), via Grubbs cyclisiert und anschließend hydriert, um (+)-Lupanin (**23**) über drei Stufen in 66% Ausbeute zu erhalten. (+)-Lupanin (**23**) wurde im finalen Schritt mit $LiAlH_4$ zu (−)-Spartein (**9**) in 84% Ausbeute reduziert.



Schema 30. Darstellung von sieben enantiomerenreinen Naturstoffen der 7*S*/9*S*-Serie.
Reagenzien und Bedingungen: a) H_2 (1 bar), PtO_2, MeOH, 4 h; b) $NaBH_4$, MeOH, 0 °C, 2 h; c) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C → RT, 17 h; d) CH_2O, AllylBr, Zn, AcOH, H_2O, RT, 22 h; e) 4-Cl-$(CH_2)_4MgBr$, THF, −78 °C, 1 h; f) TFA, CH_2Cl_2, 0 °C → RT, 20 h; g) $NaBH_4$, MeOH, 0 °C, 2 h; h) $LiAlH_4$, THF, Δ, 17 h; i) $NaBH_4$, MeOH, 0 °C, 2.5 h, dann MeOH/HCl, RT, 4 h; j) $AllylSiMe_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C → RT, 17 h; k) MeI; K_2CO_3, Cs_2CO_3, CH_2Cl_2, RT, 24 h; l) AllylBr, NEt_3, CH_2Cl_2, 5 d; m) Grubbs II, CH_2Cl_2, Δ, 1 h; n) H_2 (1 bar), Pd/C, MeOH, RT, 2.5 h; o) $LiAlH_4$, THF, Δ, 18 h.

Die beiden C_2-symmetrischen Naturstoffe α-Isospartein (**15**) und β-Isospartein (**72**) wurden aus den beiden enantiomeren Dioxobispidinen **6** und *ent*-**6** dargestellt (Schema 31). Die Einführung der *endo*-Ringe in α-Isospartein (**15**) erfolgte über Grignard-Addition, Entschützung und Reduktion in 65% Ausbeute über drei Stufen. Um die *exo*-Ringe in β-Isospartein (**72**) zu erhalten, wurde *ent*-**6** zuerst mit dem Schwartz-Reagenz reduziert und ins Bis-*N*,*O*-Acetal **144**

überführt. Anschließende Lewis-Säure-vermittelte Addition von 4-Cl-ButylZnBr, Entschützung und Ringschluss führten in insgesamt drei Stufen und 80% Ausbeute zu β-Isospartein (**72**).



Schema 31. Synthese der C_2-symmetrischen Bischinolizidin-Naturstoffe α-Isospartein (**15**) und β-Isospartein (**72**). *Reagenzien und Bedingungen*: a) 4-Cl-ButylMgBr, THF, −78 °C, 1.5 h; b) TFA, CH_2Cl_2, 0 °C → RT, 19 h; c) $NaBH_4$, MeOH, 0 °C, 17 h, dann Δ, 1 h; d) Schwartz-Reagenz, THF, 0 °C, 2 h, dann MeOH RT, 1.5 h; e) 4-Cl-$(CH_2)_4$ZnBr, $BF_3{\cdot}Et_2O$, THF, 0 °C → RT, 2 h; f) TFA, CH_2Cl_2, 0 °C → RT, 17 h; dann K_2CO_3, MeOH, 25 h.

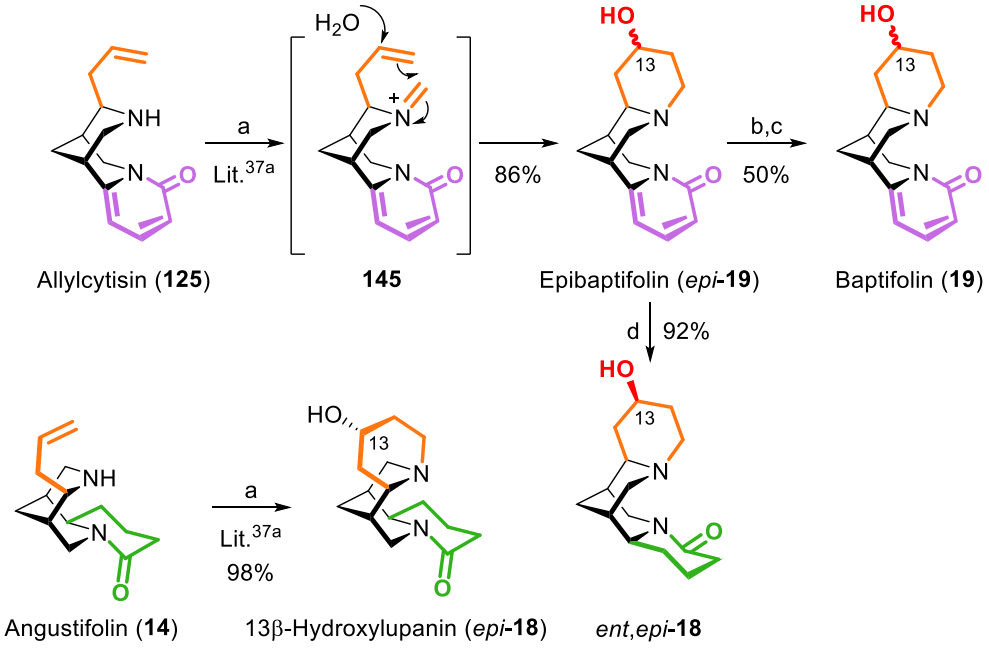
Letztendlich wurde erstmalig eine flexible und modulare Route für die asymmetrische Synthese von 21 Bischinolizidin-Naturstoffen entwickelt, worunter sich zwölf enantioselektive Erstsynthesen (Angustifolin (**14**), α-Isospartein (**15**), Thermopsin (**16**), Anagyrin (**17**), (+)- und (−)-Lupanin (**23** und *ent*-**23**), Tetrahydrorhombifolin (**37**), 11-Allylcytisin (**124**), 11-Oxocytisin (**133**), Tinctorin (**135**), Isolupanin (**140**), und *N*-Methylangustifolin (**142**)) befanden.

3.2 Die hydroxylierten, tetracyclischen Bischinolizidin-Alkaloide Baptifolin und Epibaptifolin: Enantioselektive Synthese und eindeutige Zuordnung ihrer Konfiguration an C_{13}

Bisher gibt es in der Literatur keine eindeutige Zuordnung der Konfiguration an C_{13} in Baptifolin (**19**) und Epibaptifolin (*epi*-**19**). Aktuell (gemäß Scifinder) gilt eine 50 Jahre alte Zuordnung, die von Vasquez *et al*. basierend auf der Verschiebung der OH-Gruppe im IR-Spektrum vorgenommen wurde.[36c] Im Gegensatz dazu verwenden Saito *et al*. stets die umgekehrte Zuordnung, begründen dies jedoch nicht.[21,37h] Daher war das Ziel dieses Projekts die beiden Bischinolizidin-Naturstoffe Baptifolin (**19**) und Epibaptifolin (*epi*-**19**) zu synthetisieren und deren Konfiguration an C_{13} eindeutig zu bestimmen.

Da Allylcytisin (**125**) und Angustifolin (**14**) bereits von uns enantioselektiv synthetisiert wurden (Kapitel 3.1 und 6.1.1, 6.1.2), sollte darauf aufbauend Epibaptifolin (*epi*-**19**), Baptifolin (**19**) und 13β-Hydroxylupanin (*epi*-**18**) dargestellt werden (Schema 32). Gemäß Bohlmann *et*

al.[37a] wurde **125** mit wässrigem Formaldehyd in Phosphatpuffer (pH = 5) in das tetracyclische Bischinolizidin Epibaptifolin (*epi*-**19**) in 86% Ausbeute und einem d.r. >98:2 überführt. Erste Versuche, das Stereozentrum an C_{13} über Mitsunobu-Reaktion (DIAD, PPh_3, HOAc) oder Tosylierung (TsCl, HOAc) zu invertieren, scheiterten. Erst eine Oxidations-/Reduktions-sequenz mit Swern-Oxidation und L-Selektrid-Reduktion führten zum gewünschten Baptifolin (**19**) in 50% Ausbeute und einem d.r. >98:2. Alle Charakterisierungsdaten (NMR, IR, Drehwert und Schmelzpunkt) zwischen synthetischem und natürlichem Baptifolin (**19**) bzw. Epibapti-folin (*epi*-**19**) stimmten überein. Zur Bestimmung der absoluten Konfiguration an C_{13} wurde Epibaptifolin (*epi*-**19**) zu *ent*,*epi*-**18** hydriert. Das Enantiomer dieser Verbindung, 13β-Hydroxylupanin (*epi*-**18**), wurde zudem aus Angustifolin (**14**) synthetisiert. Da die absolute Konfiguration von *epi*-**18** bekannt ist – sie wurde unter anderem durch Wysocka *et al.*[88] mittels Röntgenkristallstrukturanalyse bestimmt – und die NMR-Daten von *epi*-**18** und *ent*,*epi*-**18** identisch, aber die Drehwerte entgegengesetzt waren, konnte somit auf die absolute Konfiguration von *epi*-**19** und damit auf die Stellung der Hydroxygruppe rückgeschlossen werden.



Schema 32. Synthese der beiden epimeren Bischinolizidin-Naturstoffe Baptifolin (**19**) und Epibaptifolin (*epi*-**19**), die Überführung von *epi*-**19** in *ent*,*epi*-**18** und die Synthese von 13β-Hydroxylupanin (*epi*-**18**) aus Angustifolin (**14**).
Reagenzien und Bedingungen: a) CH_2O, Phosphatpuffer (pH= 5), 45 °C, 19 h; b) DMSO, $(COCl)_2$, CH_2Cl_2, 3 h, dann NEt_3; c) L-Selektrid, THF, 0 °C, 10 min; d) H_2 (1 bar), PtO_2, AcOH, MeOH, RT, 22 h.

Den letzendlichen Beweis der exakten Konfigurationen an C_{13} lieferten NMR-Experimente und die Kristallstruktur von Epibaptifolin (*epi*-**19**, Abbildung 13). Beide Bischinolizidin-

Naturstoffe liegen wie Anagyrin (**17**) in der Sessel-Sessel-Konformation vor, was die kleine Kopplungskonstante zwischen H_{17exo} und H_7 (2.6 Hz) bewies. Die ^{1}H-NMR-Experimente deuteten auf eine axiale Hydroxygruppe in Baptifolin (**19**) und eine äquatoriale OH-Gruppe in Epibaptifolin (*epi*-**19**) hin: Zum einen ist H_{13} in **19** um 0.5 ppm ins Tieffeld verschoben, was auf den Anisotropie-Effekt der übernächsten C,C-Bindungen zurückzuführen ist. Dies ist typisch für äquatoriale Protonen in Sechsringen. In **19** zeigen H_{12ax} und H_{14ax} jeweils ein Triplett mit großen Kopplungskonstanten, darunter eine geminale Kopplung zu den jeweils äquatorialen Protonen und eine vicinale, 1,2-diaxiale Koppung zu H_{11ax} und H_{15ax}. Eine weitere, 1,2-diaxiale Kopplung zu einem axialen Proton an H_{13} ist jedoch nicht vorhanden. Diese ist aber in *epi*-**19** im Quartett von H_{12ax} zu finden. Da H_{13} sowohl in **19** als auch in *epi*-**19** als Multiplett höherer Ordnung aufspaltet, konnte keine Kopplungskonstante ermittelt werden; dass in **19** keine zwei großen 1,2-diaxialen Kopplungen vorliegen, ergab sich aus der Signalbreite (<15 Hz). Im Gegensatz dazu kann dies aber in *epi*-**19** (>35 Hz) der Fall sein. Bei einer axialen OH-Gruppe ist ein γ-Effekt an C_{11} und C_{15} zu erwarten, wodurch die Signale im ^{13}C ins Hochfeld verschoben sein müssten. Dies tritt in Baptifolin (**19**), aber nicht in Epibaptifolin (*epi*-**19**) auf. Im NOE-Spektrum waren in *epi*-**19** Wechselwirkungen zwischen H_{11ax}, H_{13ax} und H_{15ax} erkennbar, in **19** nur zwischen H_{11ax} und H_{15ax}. Final wurden letzte Zweifel anhand der Röntgenkristallstruktur von Epibaptifolin ausgeräumt. Diese beweist eindeutig, dass die OH-Gruppe in Epibaptifolin (*epi*-**19**) äquatorial angeordnet ist. Demnach muss im Epimer Baptifolin (**19**) die Hydroxygruppe axial stehen.

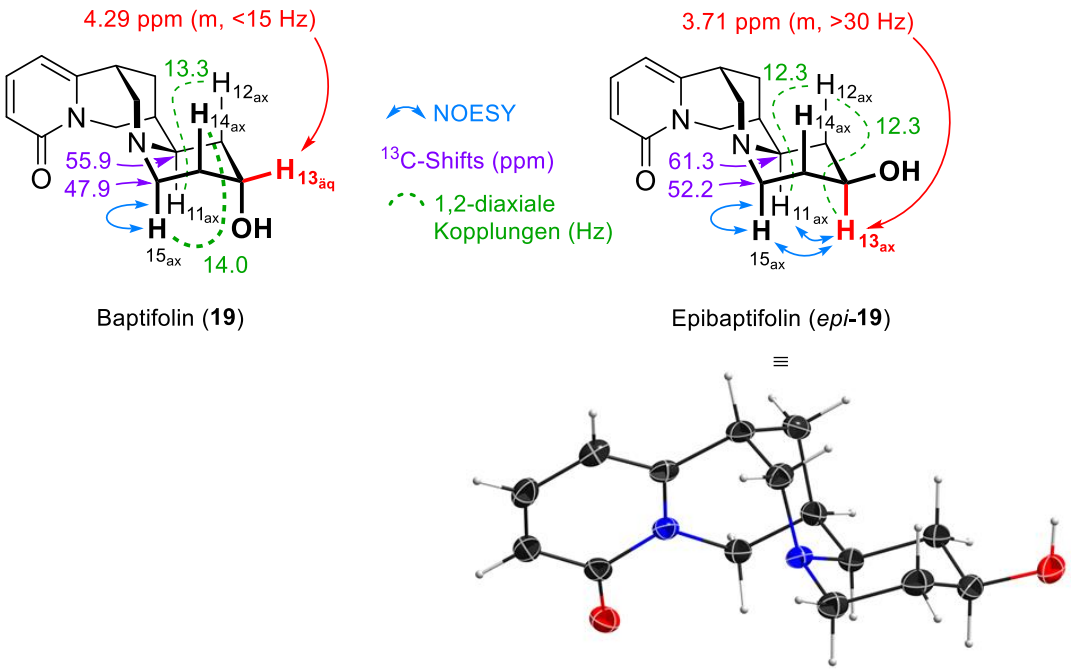


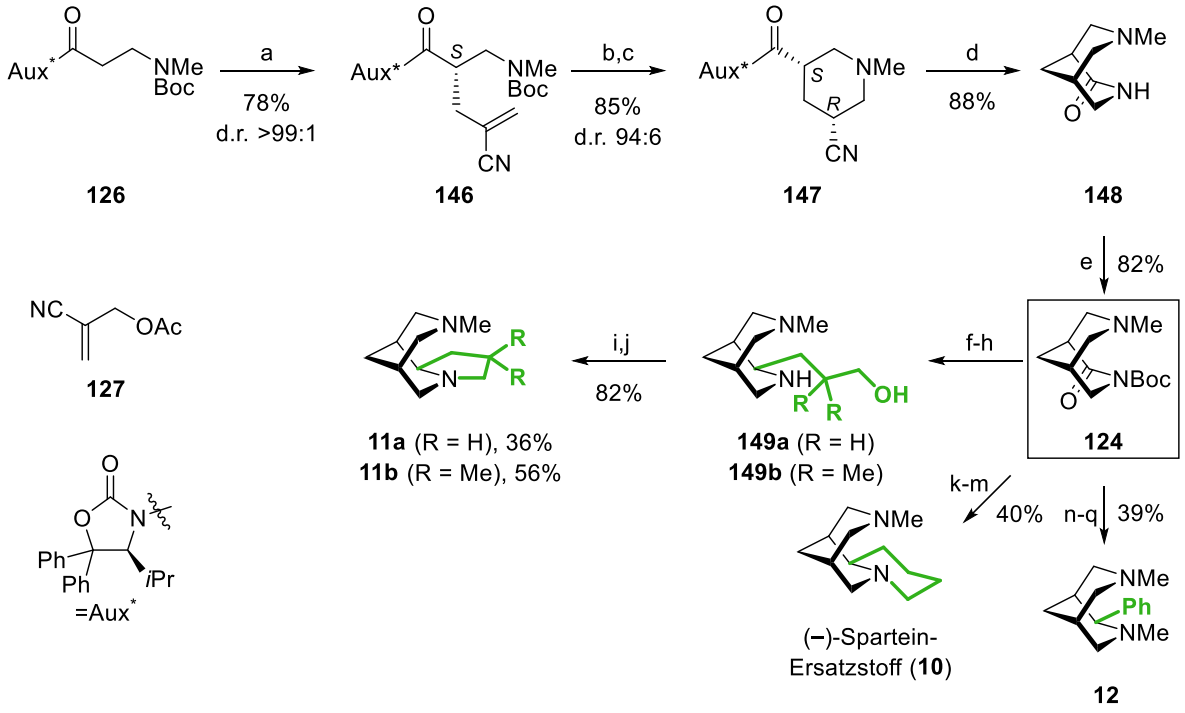
Abbildung 13. Eindeutige Zuordnung der Konfiguration an C_{13} in Baptifolin (**19**) und Epibaptifolin (*epi*-**19**) durch NMR-Experimente und Röntgenkristallstrukturanalyse.

Im zweiten Hauptprojekt dieser Dissertation wurden Baptifolin (**19**) und Epibaptifolin (*epi*-**19**) enantioselektiv synthetisiert und via Derivatisierung, NMR-Experimente und Röntgenkristallstrukturanalyse die Konfiguration an C_{13} eindeutig bestimmt.

3.3 Erste modulare Route zu kernchiralen Bispidin-Liganden und ihre Anwendung in enantioselektiven Cu(II)-katalysierten Henry-Reaktionen

Ein Nebenprojekt dieser Dissertation befasste sich mit der modularen Synthese neuer Bispidin-Liganden, die als Alternativen zu (−)-Spartein (**9**) und den (+)-Sparteinersatzstoff (*ent*-**10**) in der enantioselektiven Katalyse bzw. Synthesechemie eingesetzt werden sollten.

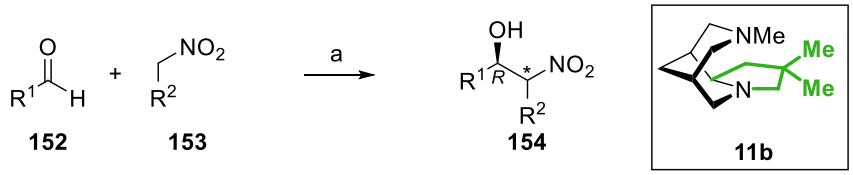
Zur Darstellung dieser Diamine wurde die Auxiliar-verknüpfte, geschützte β-Aminosäure **126** stereoselektiv mit **127** zum Acrylnitril **146** alkyliert (Schema 33). Nach Boc-Entschützung und intramolekularer Michael-Addition erfolgte der Ringschluss zu **147** mit einem d.r. von 94:6. Reduktion des Nitrils und *in situ*-Cyclisierung lieferten das Aminimid **148**, welches mit einer aktivierenden Boc-Gruppe (→ **124**) versehen wurde.



Schema 33. Modulare Synthese der Bispidin-Liganden **11**, **10** und **12**.
Reagenzien und Bedingungen: a) LiHMDS, THF, −78 °C, 3 h, dann **127**, −78 °C → RT, ü. N.; b) TFA, CH_2Cl_2, RT, 20 h; c) CH_2Cl_2, Δ, 6 h; d) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, 0 °C → RT, 17 h; e) *n*BuLi, THF, −78 °C, dann Boc_2O, −78 °C → RT, ü.N.; f) $LiCH_2CR_2CH_2OTBS$, Et_2O, RT, 1 h; g) $ZnBr_2$, CH_2Cl_2, RT, 2 d, dann bas. Alox; h) $NaBH_4$, MeOH, − 15 °C → RT, ü.N.; i) HF, MeCN, RT, 1 h; j) CBr_4, PPh_3, CH_2Cl_2, 1 h; k) 4-Cl-$(CH_2)_4$MgBr, THF, −78 °C, 2 h; l) TFA, CH_2Cl_2, RT, ü.N., dann bas. Alox; m) $NaBH_4$, MeOH, 0 °C → RT, ü.N.; n) PhMgBr, THF, − 15 °C, 1 h; o) TFA, CH_2Cl_2, RT, 24 h, dann NEt_3, 22 h; p) $NaBH_4$, CH_2Cl_2, 0 °C, 2 h; q) MeI, K_2CO_3, CH_2Cl_2, RT, ü.N.

Verbindung **124** bildet das Schlüsselintermediat zur Synthese der Bispidin-Liganden **11** und **12**. Hierbei erfolgte die Einführung der *endo*-ständigen Reste wie bei den Naturstoffen via Additions-/Reduktionssequenz (siehe Kapitel 3.1). So wurden die tricyclischen Liganden **11a** und **11b** über fünf Stufen in 36-56% Ausbeute erhalten. Der (−)-Spartein-Ersatzstoff (**10**) und der in *endo*-Position phenylierte Ligand **12** wurden jeweils über drei weitere Stufen ausgehend vom Schlüsselintermediat **124** in 40% bzw. 39% Ausbeute synthetisiert.

Diese Liganden wurden in verschiedenen asymmetrischen Transformationen getestet, lieferten jedoch nur in Kupfer(II)-katalysierten, enantioselektiven Henry-Reaktionen sehr gute Ausbeuten, exzellente Enantiomerenüberschüsse und gute Diastereomerenverhältnisse. Vor allem der tricyclische Ligand **11b** stach hier hervor (Schema 34). Durch Optimierung der Reaktionsparameter konnte die Katalysatorbeladung auf 2-4 Mol-% gesenkt werden. So wurden zehn verschiedene aromatische, heteroaromatische, aliphatische und vinylische Aldehyde **152** mit Nitromethan in die entsprechenden, *R*-konfigurierten β-Nitroalkohole **154** in 80-99% Ausbeute und 96-99% *ee* überführt. In enantio- und diastereoselektiven Henry-Reaktionen von **152** mit Nitroethan oder Nitropropan wurden an sechs Beispielen 51-99% Ausbeute, 96-99% *ee* und Diastereomerenverhältnisse bis zu 86:14 erreicht.



152 **153** **154** **11b**

R^1 = Aryl, Heteroary, Alkyl, Vinyl, R^2 = H, 80-99% Ausbeute, 96-99% *ee*
R^1 = Aryl, Alkyl, R^2 = Me, Et, 51-99% Ausbeute, 96-97% *ee*, d.r. 27:73 - 86:14

Schema 34. Enantio- und diastereoselektive Henry-Reaktion mit dem neuen Bispidin-Liganden **11b**. Reagenzien und Bedingungen: a) $CuCl_2$·[**11b**] (2−4 Mol-%), NEt_3, THF, −20 °C.

Die synthetisierten Liganden **10**, **11a**, **11b** und **12** zeigten unterschiedlich starke Stereoinduktionen. Während **11a** mit anelliertem *endo*-Pyrrolidin schlechtere Stereoselektivitäten als die *endo*-Piperidine (−)-Spartein (**9**) und (−)-Spartein-Ersatzstoff (**10**) aufwies, lieferte **11b** mit dimethyliertem *endo*-Pyrrolidinrest bessere Ergebnisse. Der *endo*-Phenylrest in **12** erlaubte akzeptable 73-88% *ee*, wobei die β-Nitroalkohole **154** *S*-konfiguriert waren. Somit wurde mit **11b** der effizienteste, von Bispidinen abgeleitete Ligand in dieser Reaktion gefunden.

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5 DARSTELLUNG DES EIGENANTEILS

Diese Dissertation beinhaltet drei Publikationen, welche in Zusammenarbeit mit anderen Wissenschaftlern erarbeitet wurden. Im Folgenden werden die Beiträge aller Kooperationspartner zu den jeweiligen Veröffentlichungen detailliert dargestellt.

Kapitel 6.1

Diese Arbeit wurde in der Zeitschrift *Angewandte Chemie* (*Angew. Chem. Int. Ed.* **2018**, *57*, 2432-2435 sowie *Angew. Chem.* **2018**, *130*, 2456-2460) 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*[*] veröffentlicht.

[+] gleichberechtigte Autorenschaft

Hauptautoren dieser Publikation waren Dr. Dagmar Scharnagel und ich. Nicklas Deibl führte im Rahmen seiner Masterarbeit Vorarbeiten zur Desymmetrisierung durch, Dr. Wolfgang Milius fertigte Röntgenkristallstrukturanalysen zweier Zwischenstufen an. Die globalen Syntheserouten zu den Bischinolizidin-Alkaloiden wurden in gleichberechtigter Kooperation zwischen Dr. Dagmar Scharnagel und mir entwickelt. Dr. Dagmar Scharnagel erarbeitete und optimierte überwiegend die primären Reaktionssequenzen, zumeist an racemischem Material, synthetisierte aber nur wenige dieser Alkaloide in enantiomerenreiner Form. Mein Schwerpunkt lag auf dem weiteren Ausbau der Reaktionssequenzen hin zu den verschiedenen Naturstoffen und der enantioselektiven Synthese dieser Alkaloide.

An wissenschaftlichen Diskussionen waren Prof. Dr. Matthias Breuning, Dr. Dagmar Scharnagel und ich beteiligt. Die Publikation und das Titelbild wurden von Prof. Dr. Matthias Breuning und mir, mit Unterstützung von Dr. Dagmar Scharnagel, verfasst und erstellt.

Kapitel 6.2

Diese Arbeit wurde in der Zeitschrift *European Journal of Organic Chemistry* (*Eur. J. Org. Chem.* **2019**, *895-899*) unter dem Titel

„The Hydroxylated, Tetracyclic Bisquinolizidine Alkaloids Baptifoline and Epibaptifoline: Enantioselective Synthesis and Unambiguous Assignment of their Configuration at C-13"

von den Autoren *Jessica Goller, Christian Hübschle und Matthias Breuning*[*] veröffentlicht.

Ich synthetisierte und charakterisierte die C_{13}-hydroxylierten Bischinolizidin-Naturstoffe Baptifolin, Epibaptifolin und 13β-Hydroxylupanin. Dr. Christian Hübschle führte die Röntgenkristallstrukturanalyse durch. Nach Synthese, Derivatisierung, NMR-Analytik und Röntgenkristallstrukturanalyse wurden von mir die Konfigurationen von Baptifolin und Epibaptifolin an C_{13} eindeutig zugeordnet.

An wissenschaftlichen Diskussionen waren Prof. Dr. Matthias Breuning und ich beteiligt. Die Publikation wurde von Prof. Dr. Matthias Breuning und mir verfasst. Das Titelbild wurde von mir, mit Unterstützung von Prof. Dr. Matthias Breuning, erstellt.

Kapitel 6.3

Diese Arbeit wurde in der Zeitschrift *Chemistry – A European Journal* (*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*[*] veröffentlicht.

Andreas Müller und Martin Eck führten Vorarbeiten zur Synthese des Schlüsselintermediats durch. Dr. Felix Prause synthetisierte einzelne Verbindungen. Ich bearbeitete die Grignard-Additions-/Reduktionssequenzen am zentralen Bispidinimid, aus welchen der *ent*-Sparteinersatzstoff und der phenylsubstituierte Ligand hervorgingen. Den Großteil der synthetischen Arbeiten und Charakterisierungen leistete Dr. Dagmar Scharnagel. Dr. Wolfgang Milius führte die Röntgenkristallstrukturanalyse durch.

An wissenschaftlichen Diskussionen waren Prof. Dr. Matthias Breuning und vor allem Dr. Dagmar Scharnagel beteiligt. Die Publikation wurde von Prof. Dr. Matthias Breuning und Dr. Dagmar Scharnagel verfasst.

6 PUBLIKATIONEN

6.1 Bischinolizidin-Alkaloide

Die englische Version und Supporting Information dieser Publikation ist in Kap. 6.1.1 zu finden, die deutsche Version in Kap. 6.1.2. Eine Würdigung dieser Arbeit als Highlight erfolgte in Synfacts durch E. M. Carreira und H. Wolleb (Kap. 6.1.3).

6.1.1 The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular "Inside-Out" Approach

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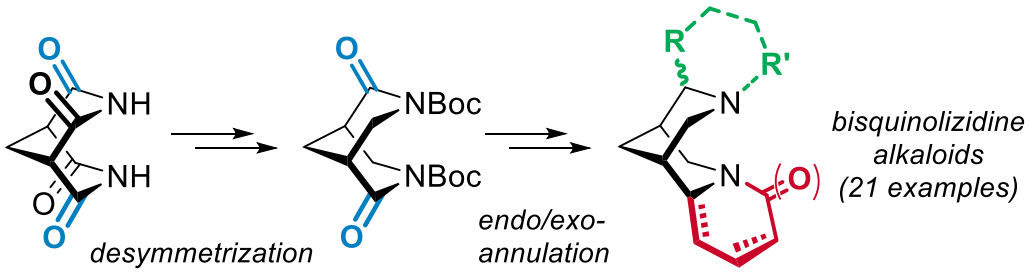

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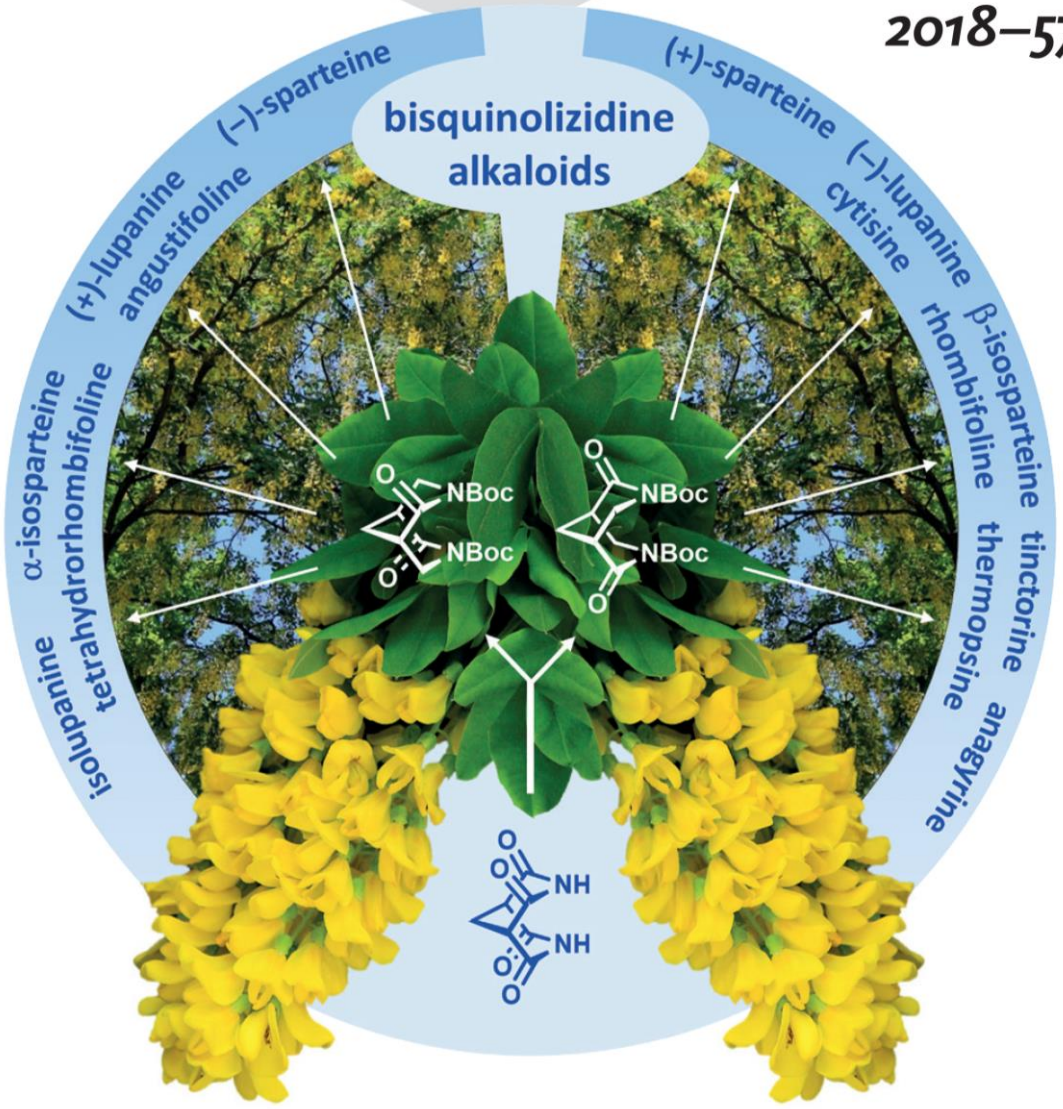

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The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular "Inside-Out" Approach

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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 asymmetric synthesis of 21 natural bisquinolizidine alkaloids, among them more than ten first enantioselective total syntheses. Key steps are the first successful preparation 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.*

The compounds (−)-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 oxytocic properties, (+)-lupanine (**2**) is moderately toxic, and anagyrine (**4**) is teratogenic.[1] Cytisine (**5**), a partial agonist of the nicotinic acetylcholine receptor, is pharmaceutically marketed for smoking cessation under the brand names Tabex and Desmoxan in Poland and Bulgaria.[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 esters,[6] and the Pd-catalyzed, oxidative kinetic resolution of secondary alcohols.[7,8]

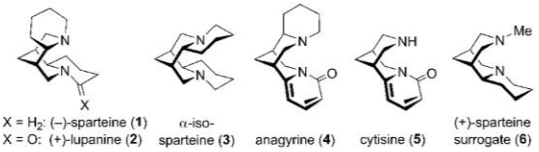
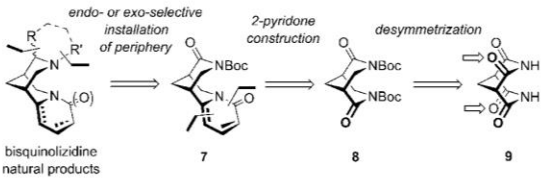


Figure 1. The most prominent bisquinolizidine alkaloids (**1**–**5**) and the artificial (+)-sparteine surrogate (**6**).

Common structural feature of all 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] However, 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 confirmed its applicability in the enantioselective total synthesis of 21 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 bisquinolizidines 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.

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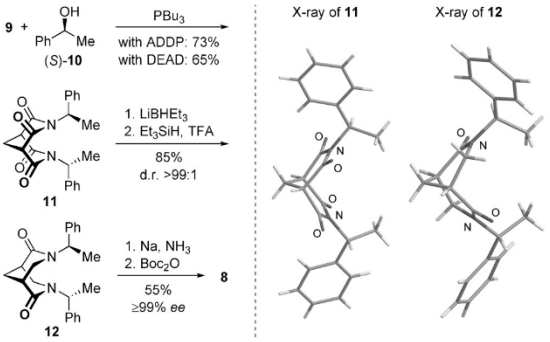
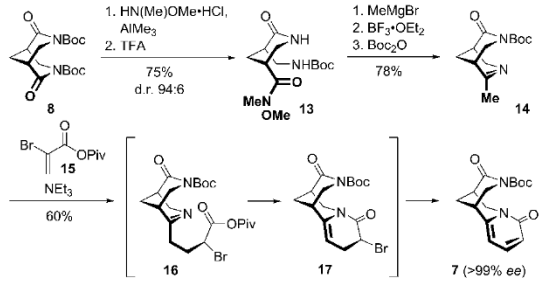
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201712852.



Scheme 2. Synthesis of the chiral key intermediate **8** and X-ray structures of **11** and **12**.[13] DEAD = diethylazodicarboxylate, ADDP = 1,1′-(azodicarbonyl)dipiperidine, TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl.

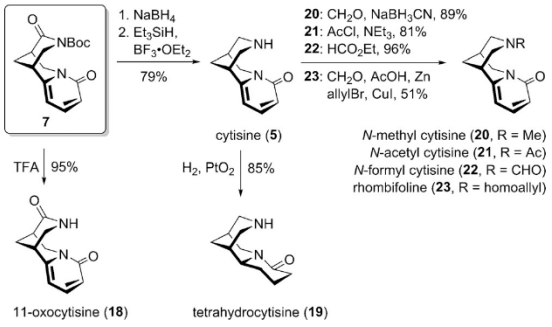
The synthesis of the chiral 2,6-dioxobispidine **8** commenced with achiral 2,4,6,8-tetraoxobispidine **9** (Scheme 2), which is available from cheap malonic ester in just two steps.[11] For desymmetrization, one of the two enantiotopic pairs of carbonyl groups had to be deoxygenated. This was achieved 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).[12] Its absolute configuration was established by X-ray crystallography.[13] 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**.

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/$AlMe_3$,[14] which provided, after *N*-Boc removal from the imide function, Weinreb amide **13** in 75 % yield and with 94:6 d.r. It is important to keep the temperature below −30 °C in the first step to suppress isomerization at the former bridgehead carbon atoms. Annulation of the pyridone moiety was accomplished by using an enamine-Michael addition strategy.[15] 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.[16] 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.

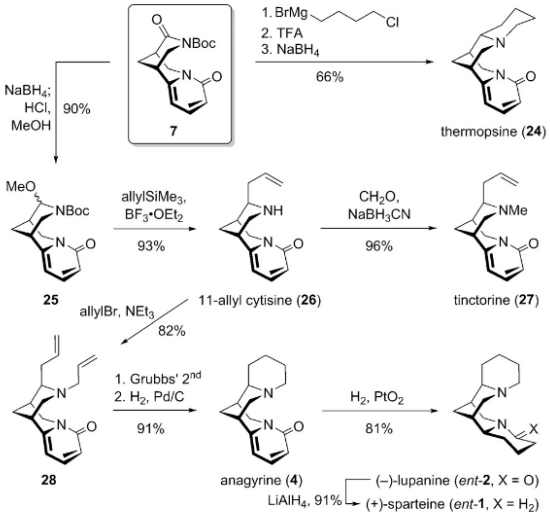
With key intermediate **7** in hand, we synthesized a first set of natural tricyclic bisquinolizidine alkaloids (Scheme 4). Simple deprotection afforded 11-oxocytisine (**18**), reduction and *N*-Boc removal cytisine (**5**). The latter compound was hydrogenated or *N*-functionalized following previously reported methods[17] to give tetrahydrocytisine (**19**), *N*-methyl cytisine (**20**), *N*-acetyl cytisine (**21**), *N*-formyl cytisine (**22**), and rhombifoline (**23**), respectively.



Scheme 4. Tricyclic bisquinolizidine alkaloids **18**–**23** prepared from **7**.

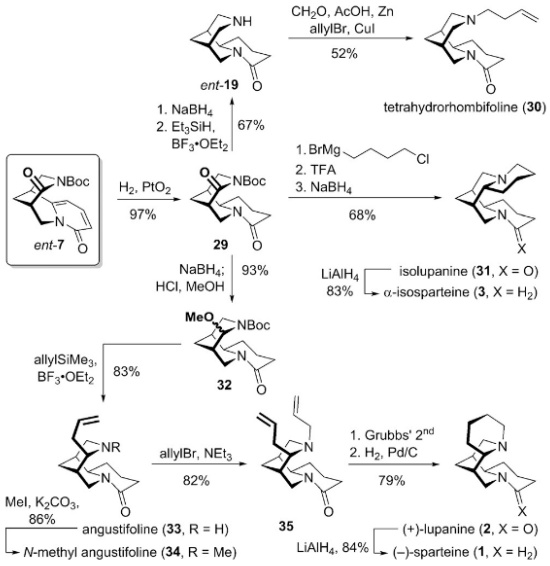
The installation of an *endo*-[8c,18] or *exo*-fused ring or substituent at the imide carbonyl group of **7** involves a hydride and an alkyl addition. Earlier investigations by us[8c,18,19] and others[10,11,20] on related systems revealed that an attack of a nucleophile on a bispidine imine or iminium salt 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. 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 yield (66 %). *Exo*-substituents were introduced after reduction of **7** to the *N*,*O*-acetal **25**.[21] Sakurai allylation under loss of the *N*-Boc group delivered 11-allyl cytisine (**26**) and, after reductive *N*-methylation, tinctorine (**27**) in good 89 % yield. *N*-Allylation of **26** followed by ring closing metathesis and hydrogenation gave access to the tetracyclic bispidine anagyrine (**4**), which was converted into (−)-lupanine (*ent*-**2**) by hydrogenation of the pyridone and, after reduction of the amide group, into (+)-sparteine (*ent*-**1**).

Bisquinolizidine alkaloids possessing the enantiomeric bispidine core were synthesized from *ent*-**7** (Scheme 6), which



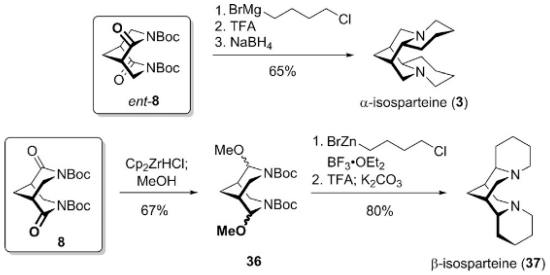
Scheme 5. Core-disubstituted bisquinolizidine alkaloids from **7**.

was prepared from *ent*-**8** according to Scheme 3. Hydrogenation of *ent*-**7** provided the piperidone **29**, which was reduced and deprotected to give amine *ent*-**19** and, after Barbier-type *N*-homoallylation, tetrahydrorhombifoline (**30**).[22] Isolupanine (**31**) and its deoxygenated analog, α-isosparteine (**3**), were obtained by using the *endo*-piperidine annulation procedure described above. Reduction of imide **29** to the *N,O*-acetal **32**[21] set the stage for *exo*-functionalization (see above), finally leading to angustifoline (**33**), *N*-methyl angustifoline (**34**), (+)-lupanine (**2**), and (−)-sparteine (**1**).



Scheme 6. Tri- and tetracyclic bisquinolizidine alkaloids from *ent*-**7**.

The application of the *exo*- and *endo*-annulation procedures to both imide groups in the key intermediates *ent*-**8** and **8** also permitted a concise access to C_2-symmetric alkaloids (Scheme 7). Natural α-isosparteine (**3**) was thus available from *ent*-**8** in just three steps and good overall yield (65%). The *exo*-fused piperidine moieties in β-isosparteine (**37**) were constructed via the bis-*N,O*-acetal **36**,[21] which was available by reduction of **8** with the Schwartz reagent[23] and acetalization. Twofold Lewis acid assisted addition of 4-chlorobutylzinc bromide,[24] *N*-deprotection, and ring closure under basic conditions delivered **37** in 54% yield.



Scheme 7. Synthesis of the C_2-symmetric bisquinolizidine alkaloids α- and β-isosparteine (**3**, **37**) from *ent*-**8** and **8**.

In conclusion, we have developed a flexible and broadly applicable route to natural bisquinolizidines, the versatility of which was proven in the asymmetric synthesis of 21 alkaloids, including the first enantioselective total syntheses of (+)- and (−)-lupanine (**2** and *ent*-**2**), α-isosparteine (**3**), anagyrine (**4**), 11-oxocytisine (**18**), thermopsine (**24**), 11-allyl cytisine (**26**), tinctorine (**27**), isolupanine (**31**), tetrahydrorhombifoline (**30**), angustifoline (**33**), and *N*-methyl angustifoline (**34**). 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 procedures to the key intermediates **7**, *ent*-**7**, **8**, and *ent*-**8**.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · bispidine · enantioselectivity · natural products · total synthesis

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[14] All attempts to selectively modify just one carbonyl group in **8**, while keeping the bicyclic system intact (for example, *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 mono-selectivity, which is presumably due to the release of conformational strain.

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[16] 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-increased to > 99% by simple fractional crystallization.

[17] 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**, 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.

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[21] The ^1H and ^{13}C NMR spectra of **25** and **32** display two sets of signals, those of **36** 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.

[22] Note that tetrahydrorhombifoline (**30**) and rhombifoline (**23**) possess "enantiomeric" bispidine cores.

[23] Twofold reduction of **8** with Cp_2ZrHCl was found to give higher yields, as compared to $NaBH_4$, $LiBHEt_3$, or iBu_2AlH.

[24] The Lewis acid assisted addition of 4-chlorobutylzinc bromide worked well on the bis-*N*,*O*-acetal **36** (Scheme 7), but failed for unknown reasons on **25** (Scheme 5) and **32** (Scheme 6).

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Supporting Information

The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular "Inside-Out" Approach

*Dagmar Scharnagel[+], Jessica Goller[+], Nicklas Deibl, Wolfgang Milius, and Matthias Breuning**

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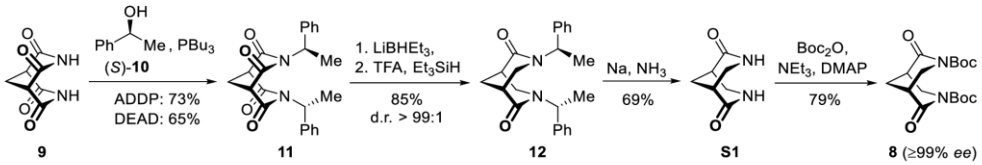
1. Synthetic Procedures

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 chromategraphy on precoated silica gel (Macherey-Nagel Alugram SIL G/UV_{254} 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 messured 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 (electronspray 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**) was prepared according to a literature protocol.[2]

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-tetraoxobispidine (**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

[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.

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.

Crystals were obtained from Et_2O/CH_2Cl_2/pentane. CCDC 1815735 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.

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.

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.

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. RP C_{18} silica: 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 (dec.); $[\alpha]_D^{30}$ = +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 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, $CDCl_3$):

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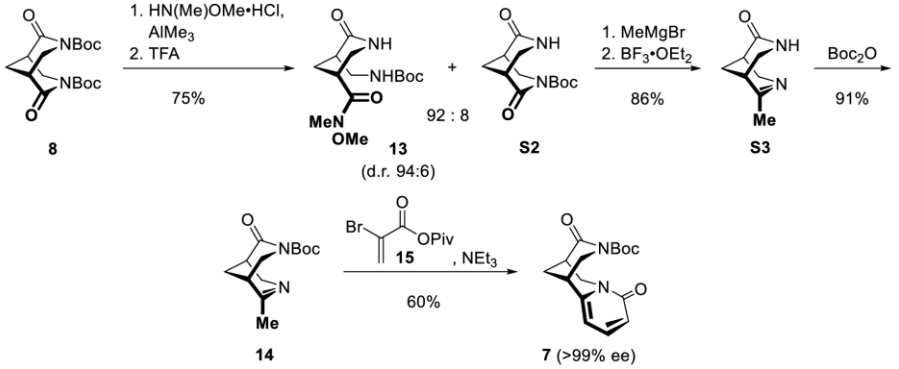
[3] a) R. G. Kostyanovsky, K. A. Lyssenko, Y. I. El'natanov, O. N. Krutius, I. A. Bronzova, Y. A. Strelenko, V. R. Kostyanovsky, *Mendeleev. Commun.* **1999**, *9*, 106-108; b) R. G. Kostyanovsky, I. A. Bronzova, K. A. Lyssenko, *Mendeleev. Commun.* **2002**, *12*, 4-6.

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 ($C(CH_3)_3$) 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 the Key Intermediate 7



Note: The enantiomeric compounds (*ent*-**13**, *ent*-**S2**, *ent*-**S3**, *ent*-**14**, and *ent*-**7**) were prepared using the same sequence, but starting from *ent*-**8** instead of **8**.

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 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.

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[4] Note: Higher temperatures lead to increased epimerization.

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(*C*$H_3)_3$), 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(*C*$H_3)_3$), 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, **13**): *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 (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.

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[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**.

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.

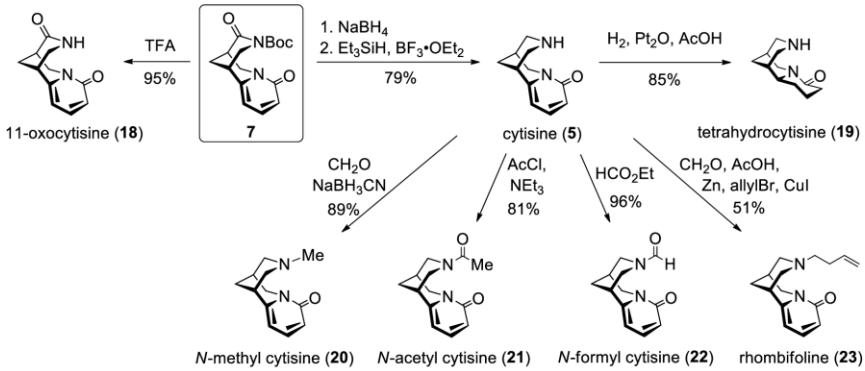
The enantiomeric excess of **7** was determined by HPLC on chiral phase [Chiralcel OD-3, *n*-hexane/*i*PrOH 75:25, 0.8 mL/min, 215 nm, t_R = 20.6 min (*S*,*S*), 29.1 min (*R*,*R*)].

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, 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

[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.

($C(CH_3)_3$), 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-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]

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[7] I. Murakoshi, H. Kubo, M. Ikram, M. Israr, N. Shafi, S. Ohmiya, H. Otomasu, *Phytochemistry* **1986**, *25*, 2000-2002.

Table S1. Comparison of synthetic and natural 11-oxocytisine (**18**).

Pos.	^{1}H NMR (δ in ppm, J in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 7) (270 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 7) (25 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	3.29 (m)	3.30 (m)	0.01	32.4[a]	35.9[b]	3.5
2				148.4	148.3	0.1
3	6.09 (d, J=6.5)	6.10 (d, J=7)	0.01	106.2	106.3	0.1
4	7.30 (dd, J=9.1, 6.9)	7.31 (dd, J=9, 7)	0.01	139.1	139.0	0.1
5	6.47 (dd, J=9.1, 1.2)	6.48 (d, J=9)	0.01	118.5	118.2	0.3
6				163.2	163.0	0.2
8a	4.54 (dm, J=15.2)	4.56 (d, J=15.5)	0.02	48.4	48.3	0.1
8b	3.70 (dd, J=11.7, 5.6)	3.72 (dd, J=15.5, 5.5)	0.02			
9	3.08 (m)	3.10 (m)	0.02	36.0[a]	32.3[b]	3.7
10				172.0	172.0	0.0
11	6.73 (br s, NH)	6.39 (br, NH)	0.34			
12a	3.73 (dd, J=7.0, 4.3)	3.77 (dd, J=12, 4.5)	0.04	50.8	50.6	0.2
12b	3.39 (dm, J=11.9)	3.40 (dm, J=12)	0.01			
13a	2.21 (dm, J=13.1)	2.23 (dm, J=13)	0.02	23.5	23.4	0.1
13b	2.10 (dm, J=13.2)	2.11 (dm, J=13)	0.01			

[a] Assigned by HSQC and HMBC measurements. [b] The bridgehead carbon atoms are probably wrongly assigned.

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 (**5**; 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, $CDCl_3$):

[8] A. J. Dixon, M. J. McGrath, P. O'Brien, *Org. Synth.* **2006**, *83*, 141-154.

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]

Table S2. Comparison of synthetic and natural cytisine (**5**).

Pos.	^{1}H NMR (δ in ppm, J in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 8)[a] (300 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 8)[a] (75 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	2.90 (m)	2.89 (br s)	0.01	35.6	35.3	0.2
2				151.1	150.7	0.4
3	5.99 (dm, *J*=6.9)	5.98 (dd, *J*=6.8, 1.4)	0.01	105.1	105.1	0.0
4	7.29 (dd, *J*=9.0, 6.9)	7.27 (dd, *J*=9.1, 6.9)	0.02	138.9	138.8	0.1
5	6.45 (dd, *J*=9.1, 1.2)	6.42 (dd, *J*=9.1, 1.4)	0.03	116.9	116.8	0.1
6				163.8	163.6	0.2
8a 8b	4.12 (d, *J*=15.6) 3.89 (dd, *J*=15.6, 6.7)	4.10 (d, *J*=15.5) 3.90 (dd, *J*=15.5, 6.5)	0.02 0.01	49.8	49.6	0.2
9	2.32 (m)	2.32 (br s)	0.00	27.8	27.6	2.5
10a 10b	3.09 (d, *J*=12.2) 3.00 (d, *J*=12.5)	2.97–3.13 (m) 2.97–3.13 (m)	0.00 0.00	53.0	52.6	0.4
11	1.42 (br s, NH)	2.24 (br s, NH)	0.82	---	---	---
12a 12b	3.05 (dd, *J*=12.0, 2.2) 3.00 (d, *J*=12.5)	2.97–3.13 (m) 2.97–3.13 (m)	0.00 0.00	54.0	53.6	0.4
13a,b	1.96 (m)	1.94 (br s)	0.02	26.4	26.1	0.3

[a] There were no assignments in the original literature.

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 (4.77 mg, 21.0 µmol) were stirred under 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 (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,

[9] M. J. Johansson, L. Schwartz, M. Amedjkouh, N. Kann, *Tetrahedron: Asymmetry* **2004**, *15*, 3531-3538.
[10] F. Bohlmann, E. Winterfeldt, H. Overwien, H. Pagel, *Chem. Ber.* **1962**, *95*, 944-948.

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 (C-13), 33.3 (C-5), 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]

Table S3. Comparison of synthetic and partial synthetic tetrahydrocytisine (**19**).

Pos.	^{1}H NMR (δ in ppm, J in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Partial Synthetic (ref. 9) (400 MHz, $CDCl_3$)[a]	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Partial Synthetic (ref. 9) (100 MHz, $CDCl_3$)[a]	$\lvert\Delta\delta\rvert$
1	1.46 (m)	1.48 (s)	0.02	33.2	33.2	0.0
2	3.54 (m)	3.55 (t, *J*=6.4)	0.01	60.1	60.2	0.1
3a/b	1.84 (m)	2.06-1.67 (m)	0.00	28.3	28.4	0.1
4a 4b	1.93 (m) 1.70 (m)	2.06-1.67 (m) 2.06-1.67 (m)	0.00 0.00	20.4	20.5	0.1
5a 5b	2.49 (dm, *J*=17.3) 2.34 (ddd, *J*=17.4, 12.8, 6.1)	2.50 (dd, *J*=17.2, 5.2) 2.40-2.31 (m)	0.01 0.00	33.3	33.4	0.1
6				170.0	170.2	0.2
8a 8b	4.67 (dt, *J*=13.7, 2.0) 2.94 (dm, *J*=14.2)	4.68 (d, *J*=12.0) 3.00-2.85 (m)	0.01 0.00	47.1	47.2	0.1
9	1.77 (m)	2.06-1.67 (m)	0.00	28.6	28.7	0.1
10a 10b	3.10 (d, *J*=13.5) 2.99 (dt, *J*=13.4, 2.6)	3.01 (d, *J*=13.6) 3.00-2.85 (m)	0.09 0.00	52.0	[b]	---
11	1.62 (br s, NH)	2.06-1.67 (m)	0.00			
12a 12b	3.34 (d, *J*=14.2) 2.86 (ddm, *J*=14.2, 2.1)	3.35 (d, *J*=14.4) 3.00-2.85 (m)	0.01 0.00	46.9	47.0	0.1
13a 13b	2.02 (dm, *J*=12.7) 1.84 (m)	2.06-1.67 (m) 2.06-1.67 (m)	0.00 0.00	33.6	33.7	0.1

[a] There were no assignments in the original literature. [b] This signal is missing. There is another signal at δ = 30.4 ppm given which, however, cannot belong to the natural product.

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% aq.; 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

[11] F. Frigerio, C. A. Haseler, T. Gallagher, *Synlett* **2010**, *5*, 729-730.

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]

Table S4. Comparison of synthetic and natural *N*-methyl cytisine (**20**).

Pos.	**^{1}H NMR (δ in ppm, *J* in Hz)**			**^{13}C NMR (δ in ppm)**		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 12) (200 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 12) (50 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	2.92 (m)	[a]		35.5	35.3	0.2
2				151.6	151.4	0.2
3	5.96 (d, *J*=6.8)	5.99 (dd, *J*=7.1, 1.3)	0.03	104.7	104.5	0.2
4	7.26 (m)	7.26 (dd, *J*=8.8, 7.1)	0.00	138.7	138.5	0.2
5	6.42 (d, *J*=9.0)	6.4 (dd, *J*=8.8, 1.3)	0.02	116.7	116.6	0.1
6				163.7	163.5	0.2
8a 8b	4.03 (d, *J*=15.4) 3.89 (dd, *J*=15.4, 6.9)	4.1 (d, *J*=14.2) 3.88 (dd, *J*=14.2, 6.2)	0.07 0.01	50.0	49.9	0.1
9	2.41 (m)	[a]		28.0	27.8	0.2
10a 10b	2.87 (d, *J*=11.1) 2.20 (d, *J*=11.1)	[a]		62.2	62.1	0.1
11-Me	2.11 (s)	[a]		46.3	46.1	0.2
12a 12b	2.82 (d, *J*=10.7) 2.23 (dd, *J*=10.7, 2.1)	[a] [a]		62.6	62.4	0.2
13a 13b	1.84 (dm, *J*=12.7) 1.71 (dm, *J*=12.7)	[a] [a]		25.5	25.3	0.2

[a] There are no signals given for the natural product. For a complete set of ^{1}H NMR signals, see ref. 11.

[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, $CDCl_3$; 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]

Table S5. Comparison of synthetic and partial synthetic *N*-acetyl cytisine (**21**).

Pos.	**^{1}H NMR (δ in ppm, *J* in Hz)**			**^{13}C NMR (δ in ppm)**		
	Synthetic (500 MHz, $CDCl_3$)	Partial Synthetic (ref. 13)[a] (250 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Partial Synthetic (ref. 13)[a] (63 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	3.07 (s)	3.03 (s)	0.04	35.1, 34.4	33.7, 33.0	1.4
2				148.6, 148.5	147.2, 147.0	1.4
3	6.05 (m)	6.00 (d, *J*=6.6)	0.05	106.0, 104.9	104.6, 103.5	1.4
4	7.26 (m)	7.24 (m)	0.02	139.2, 138.5	137.8, 137.1	1.4
5	6.43 (m)	6.46 (m)	0.03	118.0, 117.5	116.5, 116.0	1.5
6				163.5, 163.3	162.1, 161.9	1.4
8a 8b	4.10 (m) 3.95-3.79 (m)	4.01, 4.07 (d, *J*=10.1) 3.89-3.72 (m)	0.05 0.06	48.99, 48.96, 48.5, 47.6[b]	47.5, 47.1, 46.2[c]	1.4
9	2.51 (br s)	2.46 (br s)	0.05	27.7, 27.4	26.3, 26.0	1.4
10a 10b	3.95-3.79 (m) 3.38 (m)	3.89-3.72 (m) 3.34 (m)	0.06 0.04	53.8, 52.6	52.4, 51.2	1.4

[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.

11-Ac	2.01 (s, 1.53H) 1.73 (s, 1.47H)	1.98 (br s, 1H) 1.67 (s, 2H)	0.03 0.06	169.8, 169.7 (CO) 21.5, 20.9 (CH_3)	168.4, 168.3 (CO) 20.0, 19.4 (CH_3)	1.4 1.5
12a	4.78 (d, *J*=13.3, 0.49H) 4.66 (d, *J*=12.9, 0.51H)	4.72 (d, *J*=13.1) 4.60 (d, *J*=13.1)	0.06 0.06	48.99,48.96, 48.5, 47.6[b]	47.5, 47.1, 46.2[c]	1.4
12b	2.83 (d, *J*=13.0, 0.51H) 2.78 (d, *J*=13.4, 0.49H)	2.76 (m)	0.04			
13a,b	2.01 (m)	1.98 (br s)	0.03	26.2, 26.1	24.8, 24.7	1.4

[a] There were only a few assignments in the original literature. [b] Two signals belong to C-8, two to C-12. [c] One or two signals belong to C-8, one or two to C-12.

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) 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]

Table S6. Comparison of synthetic and partial synthetic *N*-formyl cytisine (**22**).

Pos.	**^{1}H NMR (δ in ppm, *J* in Hz)**			**^{13}C NMR (δ in ppm)**		
	Synthetic (500 MHz, $CDCl_3$)	Partial Synthetic (ref. 16)[a] (500 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Partial Synthetic (ref. 16) (125 MHz, $CDCl_3$)[a]	$\lvert\Delta\delta\rvert$
1	3.08 (s)	3.11 (s)	0.03	34.7, 34.0	34.6, 33.9	0.1
2				148.1, 148.0	148.0, 147.8	0.1
3	6.05 (d, *J*=6.8, 0.56H) 5.99 (d, *J*=6.8, 0.44H)	6.08 (dd, *J*=6.9, 1.0 0.57H) 6.02 (dd, *J*=6.9, 1.0, 0.43H)	0.03 0.03	105.9, 105.1	105.9, 105.0	0.1

[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.

4	7.26 (m)	7.29 (dd, *J*=6.9, 1.0, 0.57H) 7.28 (dd, *J*=6.9, 1.0, 0.43H)	0.03 0.02	139.1, 138.7	139.0, 138.6	0.1
5	6.42 (d, *J*=9.1)	6.46 (t, *J*=6.6, 0.57H) 6.44 (t, *J*=6.9, 0.43H)	0.03	118.1, 117.8	118.1, 117.7	0.1
6				163.5, 163.3	163.4, 163.2	0.1
8a	4.08 (d, *J*=5.0, 0.44H) 4.05 (d, *J*=4.9, 0.56H)	4.11 (d, *J*=6.0, 0.43H) 4.08 (d, *J*=6.0, 0.57H)	0.03 0.03			
8b	3.86 (m)	3.90 (ddd, *J*=17.0, 6.6, 1.3, 0.57H) 3.87 (ddd, *J*=17.0, 6.6, 1.3, 0.43H)	0.04 0.01	48.9, 48.7	48.8, 48.6	0.1
9	2.53 (s)	2.55 (br s)	0.02	27.2, 26.8	27.1, 26.7	0.1
10a	3.64 (d, *J*=13.2, 0.56H) 3.53 (d, *J*=12.2, 0.44H)	3.69-3.64 (m, 0.57H) 3.57-3.53 (m, 0.43H)	0.03 0.03			
10b	3.42 (m)	3.46 (dd, *J*=12.9, 2.2, 0.57H) 3.45-3.41 (m, 0.43H)	0.04 0.00	53.5, 52.2	53.4, 52.1	0.1
11-CHO	7.88 (s, 0.56H) 7.65 (s, 0.44H)	7.91 (s, 0.57H) 7.68 (s, 0.43H)	0.03 0.03	161.3, 161.2	161.2, 161.1	0.1
12a	4.52 (d, *J*=13.4, 0.44H) 4.42 (d, *J*=12.9, 0.56H)	4.55 (m, 0.43H) 4.45 (m, 0.57H)	0.03 0.03			
12b	2.91 (m)	2.95 (dd, *J*=12.9, 2.5, 0.57H) 2.93-2.89 (m, 0.43H)	0.04 0.00	47.2, 46.2	47.1, 46.1	0.1
13a 13b	2.07 (m)	2.15-2.11 (m, 0.86H) 2.11-2.07 (m, 1.14H)	0.06 0.02	26.51, 26.46	26.4	0.1

[a] There were no assignments in the original literature.

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 (C-12), 60.1 (C-10), 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),

[17] For a general procedure for such Barbier-type reactions, see: I. H. S. Estevam, L. W. Bieber, *Tetrahedron Lett.* **2003**, *44*, 667-670.

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.

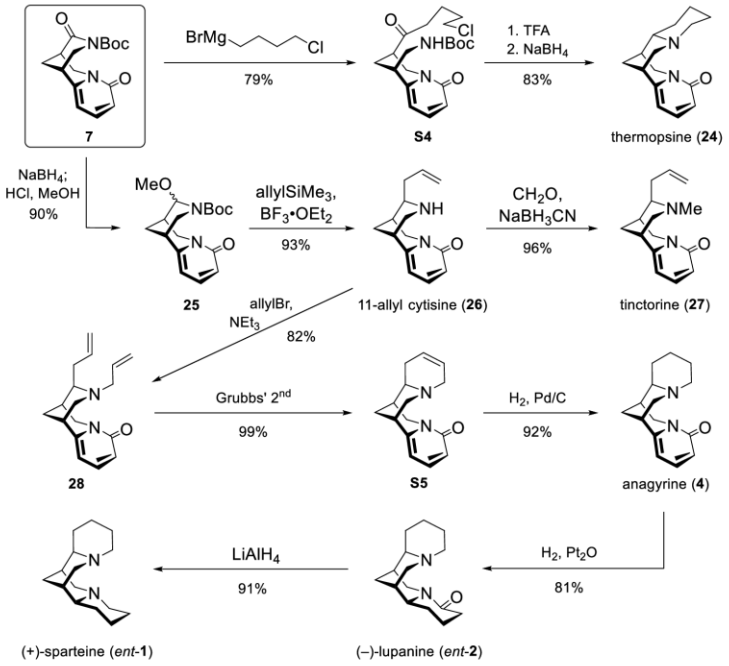
The spectroscopic data are in accordance with those reported in literature.[12]

Table S7. Comparison of synthetic and natural rhombifoline (**23**).

Pos.	^{1}H NMR (*δ* in ppm, *J* in Hz)			^{13}C NMR (*δ* in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 12) (200 MHz, $CDCl_3$)	$\|\Delta\delta\|$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 12) (50 MHz, $CDCl_3$)	$\|\Delta\delta\|$
1	2.90 (m)	[a]		35.7	35.5	0.2
2				151.7	151.6	0.1
3	5.94 (dd, *J*=6.8, 1.1)	6.02 (dd, *J*=7.1, 1.2)	0.08	104.6	104.6	0.0
4	7.24 (m)	7.27 (dd, *J*=8.8, 7.1)	0.03	138.7	138.7	0.0
5	6.41 (dd, *J*=9.0, 1.3)	6.45 (dd, *J*=8.8, 1.2)	0.04	116.6	116.4	0.2
6				163.7	163.6	0.1
8a	4.00 (d, *J*=15.3)	4.01 (d, *J*=14.2)	0.01	50.1	50.0	0.1
8b	3.86 (dd, *J*=15.3, 6.7)	3.86 (dd, *J*=14.2, 6.2)	0.00			
9	2.40 (m)	[a]		28.2	28.0	0.2
10a	2.90 (m)	[a]		60.1	59.9	0.2
10b	2.28 (m)	[a]				
11-R	5.56 (m, CH_2CH_2CH=CH_2)	5.8 (m)	0.24	136.4 (CH_2CH_2CH=CH_2)	136.2	0.2
	4.85 (m, CH_2CH_2CH=CH_2)	4.9 (m)	0.05	115.5 (CH_2CH_2CH=CH_2)	115.4	0.1
	2.28 (m, CH_2CH_2CH=CH_2)	[a]		57.1 (CH_2CH_2CH=CH_2)	56.9	0.2
	2.02 (m, CH_2CH_2CH=CH_2)	[a]		31.2 (CH_2CH_2CH=CH_2)	31.1	0.1
12a	2.90 (m)	[a]		60.4	60.2	0.2
12b	2.28 (m)	[a]				
13a	1.86 (dm, *J*=12.7)	[a]		26.1	25.9	0.2
13b	1.75 (dm, *J*=12.7)	[a]				

[a] There are no signals given for the natural product.

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.

Table S8. Comparison of synthetic and natural thermopsine (**24**).

Pos.	^{1}H NMR (δ in ppm, J in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 20) (400 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 20) (100 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	2.91 (m)	2.93 (s)	0.02	35.4	35.2	0.2
2				151.8	151.6	0.2
3	5.95 (d, *J*=6.8)	5.98 (dd, *J*=6.9, 1.2)	0.03	104.6	104.4	0.2
4	7.26 (m)	7.25 (dd, *J*=9.0, 6.9)	0.01	138.7	138.6	0.1
5	6.43 (d, *J*=9.0)	6.40 (dd, *J*=9.0, 1.4)	0.03	116.6	116.4	0.2
6				163.8	163.4	0.4
8	4.25 (d, *J*=15.8) 3.66 (dd, J=15.8, 6.8)	4.24 (d, *J*=15.8) 3.64 (dd, *J*=15.8, 6.8)	0.01 0.02	45.0	44.8	0.2
9	2.08 (m)	2.09 (br s)	0.01	33.0	32.8	0.2
10	1.99 (d, *J*=11.4)	2.00 (d, *J*=10.7)	0.01	66.1	65.8	0.3
11a 11b	1.57 (m) 1.41 (m)	1.59 (m) 1.43 (m)	0.02 0.02	29.9	29.7	0.2
12a 12b	1.74 (dm, *J*=12.8) 1.24 (m)	1.74 (d) 1.25 (m)	0.00 0.01	24.5	24.3	0.2
13a 13b	1.49 (m) 1.41 (m)	1.54 (m)	0.06 0.13	25.4	25.2	0.2
14a 14b	2.58 (d, *J*=11.2) 1.85 (m)	2.58 (d, *J*=10.9) 1.86 (br s)	0.00 0.01	56.2	56.0	0.2
16a 16b	2.77 (d, *J*=10.9) 2.32 (dd, *J*=10.9, 2.4)	2.78 (d, *J*=10.7) 2.33 (d, *J*=10.0)	0.01 0.01	63.5	63.3	0.2
17a 17b	1.95 (dm, *J*=12.2) 1.85 (m)	1.93 (m)	0.02 0.08	27.7	27.5	0.2

1.4.2 Synthesis of 11-Allyl Cytisine (26) and 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. Sat. 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 ^{1}H 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); ^{1}H 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 11-Allyl Cytisine (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 11-allyl cytisine (**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, 10-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]

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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.

Table S9. Comparison of synthetic and natural 11-allyl cytisine (**26**).

Pos.	^{1}H NMR (δ in ppm, J in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 21) (270 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 21) (68 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	2.85 (s)	2.87 (m)	0.02	35.2	35.2	0.0
2				151.3	151.1	0.2
3	5.97 (d, J=6.9)	5.98 (dd, J=6.7, 1.2)	0.01	104.8	104.8	0.0
4	7.28 (dd, J=9.0, 6.9)	7.30 (dd, J=8.5, 6.7)	0.02	138.8	138.8	0.0
5	6.43 (dd, J=9.0, 1.2)	6.45 (dd, J=8.5, 1.2)	0.02	116.7	117.2	0.5
6				163.6	163.6	0.0
8a	4.10 (d, J=15.6)	4.13 (d, J=15.9)	0.03	51.4[a]	47.6[b]	3.8
8b	3.92 (dd, J=15.6, 6.6)	3.94 (dd, J=15.9, 6.7)	0.02			
9	2.23 (s)	2.26 (m)	0.03	30.3	30.1	0.2
10	2.98 (t, J=7.2)	3.03 (t, J=6.7)	0.05	58.2	58.3	0.1
10-R	5.75 (m, CH_2CH=CH_2)	5.76 (ddd, J=17.1, 10.4, 5.5)	0.01	135.7 (CH_2CH=CH_2)	135.6	0.1
	5.10 (m, CH_2CH=CH_2)	5.09 (m)	0.01	117.4 (CH_2CH=CH_2)	107.0[c]	10.4
	2.52 (m, $CHHCH$=CH_2)	2.54 (m)	0.02	35.0 (CH_2CH=CH_2)	35.0	0.0
	2.29 (m, $CHHCH$=CH_2)	2.33 (m)	0.04			
11	1.96-1.36 (br s, NH)	---				
12a	3.21 (dd, J=12.0, 2.3)	3.24 (dd, J=12.2, 2.4)	0.03	47.5[a]	51.3[b]	3.8
12b	2.71 (dt, J=12.0, 2.3)	2.75 (dt, J=12.2, 2.4)	0.04			
13a	2.10 (d, J=13.2)	2.12 (dm, J=11.6)	0.02	21.2	21.2	0.0
13b	1.75 (dd, J=13.2, 2.5)	1.78 (dm, J=11.6)	0.03			

[a] Assigned by HSQC and HMBC measurements. [b] These carbon atoms are probably wrongly assigned. [c] Probably a typing error.

1.4.2.3 Tinctorine (27)

A solution of 11-allyl cytisine **26** (40.0 mg, 174 µmol) in MeOH/THF (1:1, 2 mL) was treated with formaldehyde (37% aq.; 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, 10-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-

[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.

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_2*C*H=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]

Table S10. Comparison of synthetic and natural tinctorine (**27**).

Pos.	^{1}H NMR (δ in ppm, *J* in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 24) (500 MHz, MeOD)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 24) (75 MHz, MeOD)	$\lvert\Delta\delta\rvert$
1	2.84 (m)	3.02 (br d, *J*=2.2)	0.18	35.3	36.6	1.3
2				152.0	154.2	2.2
3	5.95 (d, *J*=6.9)	6.26 (dd, *J*=7.0, 1.1)	0.31	104.4	107.6	3.2
4	7.26 (m)	7.46 (dd, *J*=8.9, 7.0)	0.20	138.7	141.3	2.6
5	6.42 (dd, *J*=9.0, 1.2)	6.41 (dd, *J*=8.9, 1.3)	0.01	116.6	116.5	0.1
6				163.7	165.6	1.9
8a,b	3.94 (m)	3.93 (m)	0.01	51.4	53.0	1.6
9	2.39 (m)	2.45 (m)	0.06	29.0	30.4	1.4
10	2.84 (m)	2.91 (m)	0.07	65.4	66.9	1.5
10-R	5.73 (m, CH_2CH=CH_2)	5.81 (m)	0.08	136.2 (CH_2*C*H=CH_2)	137.6	1.4
	5.08 (m, CH_2CH=CH_2)	5.14 (m, *J*=17.0) 5.08 (td, *J*=10.1, 1.3)	0.06 0.00	117.0 (CH_2CH=*C*H_2)	117.3	0.3
	2.39 (m, C*H*HCH=CH_2) 2.24 (m, CH*H*CH=CH_2)	2.45 (m) 2.33 (m)	0.06 0.09	25.7 (*C*H_2CH=CH_2)	26.8	1.1
11-Me	2.19 (s)	2.23 (s)	0.04	42.6[a]	56.2[b]	13.6
12a 12b	2.84 (m) 2.47 (d, *J*=11.2)	2.91 (m) 2.51 (m, *J*=11.4)	0.07 0.04	55.1[a]	42.8[b]	12.3
13a 13b	1.95 (dt, *J*=13.2, 2.9) 1.65 (dm, *J*=13.2 Hz	2.07 (td, *J*=13.4, 2.8) 1.70 (dd, *J*=13.3, 1.3)	0.12 0.05	19.7	20.1	0.4

[a] Assigned by HSQC and HMBC measurements. [b] These carbon atoms are probably wrongly assigned.

1.4.3 Synthesis of Anagyrine (4), (–)-Lupanine (*ent*-2) and (+)-Sparteine (*ent*-1)

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 11-allyl cytisine (**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), 124.0 (C-12), 116.6 (C-5), 104.5 (C-3), 58.3 (C-10), 54.2 (C-16), 53.2 (C-14), 51.4 (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)

A solution of the alkene **S5** (80.9 mg, 334 µmol) in MeOH (4 mL) and Pd on carbon (10 wt% Pd; 35.5 mg, 33.4 µmol) were stirred under 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, 12-*H*H), 1.72 (br s, 2H, H_2O), 1.69-1.54 (m, 2H, 13-*H*H, 17-H*H*), 1.48 (m, 1H, 12-H*H*), 1.14 (d, *J*=13.0 Hz, 2H, 11-H*H*; 13-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-12), 22.6 (C-11), 20.9 (C-17), 19.2 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 3447 (br, w), 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]

Table S11. Comparison of synthetic and natural anagyrine (**4**).

Pos.	**^{1}H NMR (δ in ppm, *J* in Hz)**			**^{13}C NMR (δ in ppm)**		
	Synthetic[a] (500 MHz, $CDCl_3$)	Natural (ref. 26) (600 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic[a] (125 MHz, $CDCl_3$)	Natural (ref. 26) (150 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	2.94 (s)	2.88 (dq, *J*=3, 2)	0.06	35.6	35.2	0.4
2				152.1	151.7	0.4
3	5.95 (d, *J*=6.9)	5.89 (ddd, *J*=6.9, 1.4, 0.5)	0.06	104.6	104.5	0.1
4	7.26 (m)	7.18 (dd, *J*=9.0, 6.9)	0.06	138.8	138.5	0.3
5	6.42 (d, *J*=9.0)	6.32 (dd, *J*=9.0, 1.4)	0.10	116.7	116.3	0.4
6				163.7	163.4	0.3
8a	4.05 (d, *J*=15.4)	3.96 (dt, *J*=15.3, 1.3)	0.09	51.6	51.3	0.3
8b	3.88 (dd, *J*=15.4, 6.7)	3.79 (dd, *J*=15.3, 6.7)	0.09			
9	2.14 (s)	2.07 (br s)	0.07	32.7	32.4	0.3
10	2.87 (d, *J*=12.0)	2.79 (br dt, *J*=12.0, 2.5)	0.08	63.2	62.9	0.7
11a	1.87 (d, *J*=10.6)	1.795 (qd, *J*=14, 12, 13, 4)	0.07	22.6	22.5	0.1
11b	1.14 (d, *J*=13.0)	1.09 (br d, *J*=14)	0.05			
12a	1.87 (d, *J*=10.6)	1.79 (br d, *J*=13.0)	0.08	25.7	25.3	0.4
12b	1.48 (m)	1.39 (qt, *J*=13, 4)	0.09			
13a	1.69-1.54 (m)	1.53 (br qt, *J*=13, 4)	0.01	19.2	19.0	0.2
13b	1.14 (d, *J*=13.0)	1.08 (br d, *J*=13)	0.06			
14a	2.76-2.60 (m)	2.63 (ddd, *J*=14.0, 13.0, 3.0)	0.00	54.5	54.2	0.3
14b	2.76-2.60 (m)	2.57 (br d, *J*=14)	0.03			

[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.

16a 16b	3.36 (dd, *J*=10.8, 2.5) 2.44 (d, *J*=10.9)	3.30 (dd, *J*=10.9, 3.0) 2.37 (ddd, *J*=10.9, 3.1, 1.7)	0.04 0.07	53.0	52.8	0.2
17a 17b	1.99 (d, *J*=12.8) 1.69-1.54 (m)	1.93 (br d, *J*=13) 1.58 (dtdd, *J*=13.1, 3.0, 1.7, 0.7)	0.06 0.00	20.9	20.5	0.4

[a] The synthetic compound was isolated as the monohydrate [signal of the bound water: 1.72 (br s)].

1.4.3.4 (–)-Lupanine (*ent*-2)

A solution of anagyrine (**4**; 40.0 mg, 164 µmol) in MeOH (1 mL) and Pt_2O (11.3 mg, 49.2 µmol) were stirred under H_2 atmosphere (1 atm.) at rt. After 9 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, 50 mL). Evaporation of the solvent and column chromatography (RP C_{18} silica, MeOH/H_2O 2:1) delivered (–)-lupanine (*ent*-**2**; 33.1 mg, 133 µmol, 81%) as a colorless resin.

R_f = 0.29 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{23}$ = –80.7 (*c*=1.0 in EtOH) [lit.[27] $[\alpha]_D$ = –81.8 (*c*=1.0 in EtOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.47 (dt, *J*=13.2 Hz, 2.3 Hz, 1H, 8-*H*H), 3.26 (m, 1H, 2-H), 2.80 (m, 1H, 16-*H*H), 2.73 (m, 1H, 14-*H*H), 2.45 (m, 2H, 5-*H*H, 8-H*H*), 2.30 (m, 1H, 5-H*H*), 2.15 (m, 1H, 17-*H*H), 2.04 (m, 1H, 1-H), 1.89 (m, 2H, 14-H*H*, 16-H*H*), 1.80 (m, 1H, 4-*H*H), 1.74 (m, 1H, 3-*H*H), 1.66 (m, 1H, 12-*H*H), 1.62-1.45 (m, 7H, 3-H*H*, 4-H*H*, 9-H, 10-H, 11-*H*H, 13-H_2), 1.34 (m, 1H, 11-H*H*), 1.23 (m, 2H, 12-H*H*, 17-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5 (C-6), 64.2 (C-10), 61.0 (C-2), 55.5 (C-14), 53.0 (C-16), 46.8 (C-8), 34.9 (C-9), 33.8 (C-11), 33.1 (C-5), 32.4 (C-1), 27.5 (C-3), 26.8 (C-17), 25.5 (C-13), 24.5 (C-12), 19.7 (C-4) ppm; IR (ATR): $\tilde{\nu}$ = 2923 (m), 2853 (w), 2805 (w), 1635 (s), 1439 (m), 1333 (m), 1247 (m), 1117 (m), 786 (w), 657 (w) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}N_2O$ [*M* + H^+]: 249.19614; found: 249.19562.

The spectroscopic data are in accordance with those reported in literature.[28,29]

Table S12. Comparison of synthetic (–)-lupanine (*ent*-**2**) and natural (+)-lupanine (**2**).

Pos.	^{1}H NMR (δ in ppm, *J* in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 29) (300 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 28) (20 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	2.04 (m)	2.06	0.02	32.4[a]	34.9[b]	2.5
2	3.26 (m)	3.29	0.03	61.0	61.7	0.7
3a 3b	1.74 (m) 1.62-1.45 (m)	1.76 1.55	0.02 0.00	27.5	26.7	0.8
4a 4b	1.80 (m) 1.62-1.45 (m)	1.83 1.62	0.03 0.00	19.7	19.6	0.1
5a 5b	2.45 (m) 2.30 (m)	2.47 2.33	0.02 0.03	33.1	33.0	0.1
6				171.5	[c]	

[27] A. K. Przybyl, M. Kubicki, *Tetrahedron* **2011**, *67*, 7787-7797.
[28] F. Bohlmann, R. Zeisberg, *Chem. Ber.* **1975**, *108*, 1043-1051.
[29] R. Kolanoś, W. Wysocka, T. Brukwicki, *Tetrahedron* **2003**, *59*, 5531-5537.

8a 8b	4.47 (dt, *J*=13.2, 2.3) 2.45 (m)	4.50 2.51	0.03 0.06	46.8	46.6	0.2
9	1.62-1.45 (m)	1.62	0.00	34.9[a]	32.4[b]	2.5
10	1.62-1.45 (m)	1.62	0.00	64.2	63.8	0.4
11a 11b	1.62-1.45 (m) 1.34 (m)	1.54 1.35	0.00 0.01	33.8	33.5	0.3
12a 12b	1.66 (m) 1.23 (m)	1.69 1.26	0.03 0.03	24.5	24.5	0.0
13a 13b	1.62-1.45 (m) 1.62-1.45 (m)	1.56 1.53	0.00 0.00	25.5	25.3	0.2
14a 14b	2.73 (m) 1.89 (m)	2.75 1.90	0.02 0.01	55.5	55.3	0.2
16a 16b	2.80 (m) 1.89 (m)	2.82 1.93	0.02 0.04	53.0	52.8	0.2
17a 17b	2.15 (m) 1.23 (m)	2.16 1.24	0.01 0.01	26.8	27.3	0.5

[a] Assigned by HSQC and HMBC measurements. [b] The bridgehead carbon atoms are probably wrongly assigned. [c] There is no signal given for the natural product.

1.4.3.5 (+)-Sparteine (*ent*-1)

According to a literature procedure,[27] (–)-lupanine (*ent*-**2**; 20.0 mg, 80.5 µmol) was dissolved in anhydr. THF (1.5 mL) and cooled to 0 °C. $LiAlH_4$ (24.4 mg, 644 µmol) was added and the reaction mixture was refluxed for 18 h. At rt, sat. aq. Na_2SO_4 (5 mL) was added dropwise until gas evolution ceased. The aqueous layer was extracted with $CHCl_3$ (5 × 5 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was partitioned between Et_2O (5 mL) and aq. H_2SO_4 (2.0 M; 5 mL), and the aqueous layer was washed with Et_2O (2 × 5 mL). The aqueous layer was basified (pH = 10) with aq. NaOH (6.0 M; 8 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum. (+)-Sparteine (*ent*-**1**;17.2 mg, 73.3 µmol, 91%; lit.[27] 84%) was obtained as a colorless oil.

R_f = 0.56 [$CHCl_3$/MeOH/NH_3 (aq., 25%) 80:18:2]; $[\alpha]_D^{24}$ = +19.2 (*c*=0.5 in EtOH) [lit.[27] $[\alpha]_D$ = +21.2 (*c*=1.6 in EtOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.80 (d, *J*=11.0 Hz, 1H, 14-*H*H), 2.69 (m, 2H, 6-*H*H, 16-*H*H), 2.52 (d, *J*=10.6 Hz, 1H, 8-*H*H), 2.35 (d, *J*=9.8 Hz, 1H, 16-H*H*), 2.17-1.89 (m, 5H, 6-H*H*, 8-H*H*, 10-H, 14-H*H*, 17-*H*H), 1.84 (m, 1H, 1-H), 1.70 (m, 3H, 2-H, 4-*H*H, 12-*H*H), 1.64-1.43 (m, 6H, 5-H_2, 9-H, 13-H_2, 11-*H*H), 1.43-1.12 (m, 5H, 3-H_2, 4-H*H*, 11-H*H*, 12-H*H*), 1.05 (d, *J*=11.8 Hz, 1H, 17-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 66.6 (C-2), 64.6 (C-10), 62.1 (C-8), 56.4 (C-6), 55.5 (C-14), 53.7 (C-16), 36.1 (C-9), 34.7 (C-11), 33.1 (C-1), 29.5 (C-3), 27.7 (C-17), 26.0 (C-5, C-13), 24.9 (C-4), 24.8 (C-12) ppm; IR (ATR): $\tilde{\nu}$ = 2928 (s), 2854 (m), 2759 (m), 1648 (br w), 1442 (m), 1350 (m), 1289 (m), 1125 (m), 1113 (m), 1014 (w), 785 (w) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{27}N_2O$ [$M + H^+$]: 235.21688; found: 235.21638.

The spectroscopic data are in accordance with those reported in literature.[27,28,30,31]

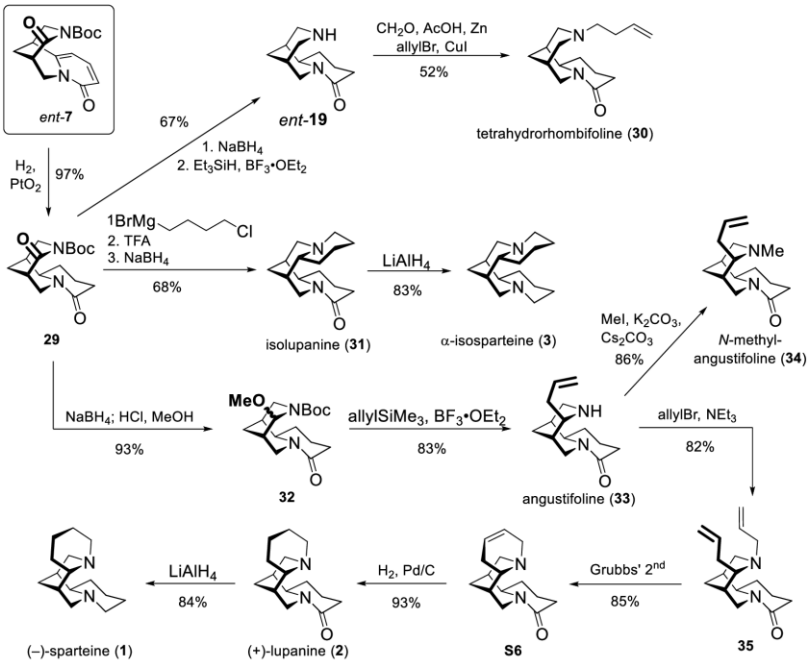
Table S13. Comparison of synthetic (+)-sparteine (*ent*-**1**) with partial synthetic *ent*-**1** and natural (–)-sparteine (**1**).[28]

	^{1}H NMR (δ in ppm, J in Hz)			**^{13}C NMR (δ in ppm)**		
Pos.	Synthetic (500 MHz, $CDCl_3$)	Partial Synthetic (ref. 27)[a] (400 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 28) (20 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	1.84 (m)	1.84	0.00	33.1[b]	36.2[c]	
2	1.70 (m)	1.67	0.03	66.6	66.5	0.1
3a,b	1.43-1.12 (m)	1.35 1.20	0.00 0.00	29.5	29.4	0.1
4a 4b	1.70 (m) 1.43-1.12 (m)	1.67 1.30	0.03 0.00	24.9	24.9	0.0
5a,b	1.64-1.43 (m)	2.01	0.37	26.0	25.9	0.1
6a 6b	2.69 (m) 2.17-1.89 (m)	2.64 1.89	0.05 0.00	56.4	56.2	0.2
8a 8b	2.52 (d, J=10.6) 2.17-1.89 (m)	2.48 1.96	0.04 0.00	62.1	62.0	0.1
9	1.64-1.43 (m)	1.42	0.01	36.1[b]	33.0[c]	
10	2.17-1.89 (m)	1.90	0.00	64.6	64.4	0.2
11a 11b	1.64-1.43 (m) 1.43-1.12 (m)	1.45 1.34	0.00 0.00	34.7	34.7	0.0
12a 12b	1.70 (m) 1.43-1.12 (m)	1.67 1.67	0.03 0.24	24.8	24.7	0.1
13a,b	1.64-1.43 (m)	1.51	0.00	26.0	25.9	0.1
14a 14b	2.80 (d, J=11.0) 2.17-1.89 (m)	2.64 1.89	0.16 0.00	55.5	55.4	0.1
16a 16b	2.69 (m) 2.35 (d, J=9.8)	2.65 2.30	0.04 0.05	53.7	53.6	0.1
17a 17b	2.17-1.89 (m) 1.05 (d, J=11.8)	2.01 1.00	0.00 0.05	27.7	27.6	0.1

[a] There are no multiplicities and coupling constants given in ref. 27 [b] Assigned by HSQC and HMBC measurements. [c] These bridgehead carbon atoms are probably wrongly assigned. In ref. 27 (partial synthetic *ent*-**1**), the bridgehead carbon atoms assigned in analogy to our synthetic compound.

[30] J.-P. R. Hermet, M. J. McGrath, P. O'Brien, D. W. Porter, J. Gilday, *Chem. Commun.* **2004**, 1830-1831.
[31] B. T. Smith, J. A. Wendt, J. Aubé, *Org. Lett.* **2002**, *4*, 2577-2579.

1.5 Tri- and Tetracyclic Alkaloids Derived from Pyridone *ent*-7



1.5.1 Synthesis of Tetrahydrorhombifoline (30)

1.5.1.1 (1*S*,2*R*,9*S*)-11-*tert*-Butoxycarbonyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane-6,10-dione (29)

A solution of the imide *ent*-**7** (620 mg, 2.04 mmol) in MeOH (11.5 mL) and Pt_2O (46.3 mg, 204 µmol) were stirred under H_2 atmosphere (1 atm.) at rt for 4 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). Evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 99:1 → 95:5), delivered imide **29** (608 mg, 1.97 mmol, 97%) as a white crystalline solid.

R_f = 0.31 (CH_2Cl_2/MeOH 95:5); m.p. 147-153 °C (DSC); $[\alpha]_D^{25}$ = +25.6 (*c*=1.0 in CH_2Cl_2); ^{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(*C*H$_3$)$_3$), 27.6 (C-3), 19.9 (C-4) ppm; IR (ATR): $\tilde{\nu}$ = 2984 (w), 2858 (w), 1760 (s), 1671 (w), 1633 (s), 1447 (m), 1346 (m), 1271 (s), 1241 (s), 1147 (s), 1137 (s), 1025 (m), 851 (w), 718 (w) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{24}N_2O_4Na$ [*M* + Na$^+$]: 331.16283; found: 331.16334.

1.5.1.2 *ent*-Tetrahydrocytisine (*ent*-19)

A solution of imide **29** (90 mg, 292 µmol) in MeOH (6 mL) was treated with $NaBH_4$ (31.1 mg, 876 µmol) at 0°C and stirred for 2 h at rt. Sat. aq. $NaHCO_3$ (10 mL) was added and the solvent was evaporated. The aqueous layer was extracted with CH_2Cl_2 (4 × 15 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 (3 mL) and the mixture was cooled to –78 °C. Et_3SiH (140 µL, 876 µmol) and $BF_3{\cdot}Et_2O$ (129 µL, 1.02 mmol) were added and the reaction mixture was allowed to reach rt over 17 h. After addition of MeOH/NH_3 [(aq., 25%) 90:10, 100 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 *ent*-tetrahydrocytisine (*ent*-**19**; 37.9 mg, 195 µmol, 67%) as a colorless oil.

R_f = 0.19 [$CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1]; $[\alpha]_D^{27}$ = +31.6 (*c*=1.0 in $CHCl_3$) [lit.[9] $[\alpha]_D^{20}$ = –32.8 (*c*=1.0 in $CHCl_3$) for the enantiomer].

The spectroscopic data of *ent*-**19** are identical to those reported for **19** in section 1.3.3.

1.5.1.3 Tetrahydrorhombifoline (30)

A mixture of *ent*-tetrahydrocytisine (*ent*-**19**; 33.0 mg, 170 µmol), formaldehyde (37% aq.; 16.6 µL, 204 µmol), allyl bromide (29.4 µL, 340 µmol), CuI (32.4 mg, 170 µmol), granulated Zn (27.8 mg, 425 µmol), and AcOH (19.4 µL, 340 µmol) in H_2O (170 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 × 5 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 99:1) delivered tetrahydrorhombifoline (**30**; 22.1 mg, 89.0 µmol, 52%) as colorless oil.

R_f = 0.48 [DCM:MeOH 90:10]; $[\alpha]_D^{28}$ = +72.1 (*c*=1.0 in CH_2Cl_2) [lit.[32] $[\alpha]_D^{23}$ = +70 (*c*=0.03 in EtOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76 (m, 1H, 11-CH_2CH_2CH=CH_2), 4.97 (m, 2H, 11-CH_2CH_2CH=CH_2), 4.66 (d, *J*=13.6 Hz, 1H, 8-*H*H), 3.45 (m, 1H, 2-H), 3.14 (d, *J*=9.4 Hz, 1H, 12-*H*H), 2.93 (d, *J*=10.7 Hz, 1H, 10-*H*H), 2.79 (d, *J*=13.5 Hz, 1H, 8-H*H*), 2.41 (m, 1H, 5-*H*H), 2.26 (m, 2H, 5-H*H*, 11-C*H*H), 2.21-2.07 (m, 4H, 10-H*H*, 11-C*H*H, 11-CH_2CH_2), 2.00 (d, *J*=11.5 Hz, 1H, 12-H*H*), 1.90 (s, 1H, 9-H), 1.83 (m, 1H, 4-*H*H), 1.75 (m, 2H, 3-H_2), 1.71 (m, 2H, 13-H_2), 1.64 (m, 2H, 1-H, 4-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1 (C-6), 137.2 (11-CH_2CH_2CH=CH_2), 115.3 (11-CH_2CH_2CH=CH_2), 59.4 (C-10), 59.0 (C-2), 58.3 (11-CH_2), 54.1 (C-12), 46.5 (C-8), 34.1 (C-1), 33.6

[32] M. F. Balandrin, A. D. Kinghorn, *J. Nat. Prod.* **1981**, *44*, 495-497.

(C-13), 33.2 (C-5), 31.6 (11-CH_2CH_2), 29.4 (C-9), 28.1 (C-3), 20.3 (C-4) ppm; IR (ATR): $\tilde{\nu}$ = 2923 (m), 2859 (w), 1615 (s), 1443 (m), 1348 (m), 1259 (m), 1160 (m), 1062 (w), 913 (m), 765 (w), 639 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}N_2O$ [$M + H^+$]: 249.19614; found: 249.19529.

The spectroscopic data are in accordance with those reported in literature.[32,33]

Table S14. Comparison of synthetic and natural tetrahydrorhombifoline (**30**).

Pos.	^{1}H NMR (δ in ppm, J in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 33) (400 MHz, $CDCl_3$)[a]	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 33) (100 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	1.64 (m)	1.66	0.02	34.1	33.98	0.1
2	3.45 (m)	3.47	0.02	59.0	58.79	0.2
3a,b	1.75 (m)	ca. 1.9-1.7	0.00	28.1	27.94	0.2
4a 4b	1.83 (m) 1.64 (m)	1.84 ca. 1.66	0.01 0.02	20.3	20.7	0.4
5a 5b	2.41 (m) 2.26 (m)	2.43 2.27	0.02 0.01	33.2	32.99	0.2
6				169.1	168.86	0.2
8a 8b	4.66 (d, J=13.6) 2.79 (d, J=13.5)	4.68 2.81	0.02 0.02	46.5	46.33	0.2
9	1.90 (s)	1.92	0.02	29.4	29.21	0.2
10a 10b	2.93 (d, J=10.7) 2.21-2.07 (m)	2.95 ca. 2.2	0.02 0.00	59.4	59.23	0.2
11-R	5.76 (m, CH_2CH_2CH=CH_2) 4.97 (m, CH_2CH_2CH=CH_2) 2.26 (m, $CH$$HCH_2CH$=$CH_2$) 2.21-2.07 (m, $CH$$HCH_2CH$=$CH_2$)	5.79 5.02, 4.95 2.3-2.1 2.15	0.03 0.00 0.00 0.00	137.2 (CH_2CH_2CH=CH_2) 115.3 (CH_2CH_2CH=CH_2) 58.3 (CH_2CH_2CH=CH_2), 31.6 (CH_2CH_2CH=CH_2)	137.02 115.08 58.15 31.40	0.2 0.2 0.1 0.2
12a 12b	3.14 (d, J=9.4) 2.00 (d, J=11.5)	3.17 2.02	0.03 0.02	54.1	53.98	0.1
13a,b	1.71 (m)	ca. 1.8 ca. 1.7	0.00	33.6	33.43	0.2

[a] There are no multiplicities and coupling constants given in ref. 33.

1.5.2 Synthesis of Isolupanine (31) and α-Isosparteine (3)

1.5.2.1 Isolupanine (31)

A solution of imide **29** (80.0 mg, 259 µmol) in anhydr. THF (3.5 mL) was cooled to −78 °C and 4-chlorobutylmagnesium bromide (0.55 M; 1.41 mL, 777 µmol, prepared according to 1.4.1.1) was added. After 1 h, sat. aq. NH_4Cl (5 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 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 99:1) delivered the addition product as a colorless oil (74.3 mg) that solidified upon standing. This intermediate was dissolved in anhydr. CH_2Cl_2 (4.5 mL), treated with TFA (215 µL, 2.81 mmol) at 0 °C, and stirred for 20 h at rt. The solvent

[33] T. Brukwicki, A. Przybyl, W. Wysocka, J. Sośnicki, *Tetrahedron* **1999**, *55*, 14501-14512.

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 (4.0 mL), treated at 0 °C with $NaBH_4$ (21.2 mg, 561 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%) 98:1.8:0.2 → 95:4.5:5] delivered isolupanine (**31**; 43.7 mg, 177 µmol, 68%) as an off-white solid.

R_f = 0.30 (CH_2Cl_2/MeOH 90:10); m.p. 112 °C (lit.[34] 113 °C); $[\alpha]_D^{25}$ = +43.8 (*c*=0.5 in MeOH) [lit.[35] $[\alpha]_D$ = +41.0 (*c*=7.9 in MeOH)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.91 (d, *J*=13.8 Hz, 1H, 8-*H*H), 3.47 (m, 1H, 2-H), 2.96 (d, *J*=11.4 Hz, 1H, 16-*H*H), 2.60 (d, *J*=10.3 Hz, 1H, 14-*H*H), 2.54 (dd, *J*=13.8 Hz, 2.3 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 (d, *J*=11.4 Hz, 1H, 16-H*H*), 1.92 (d, *J*=10.6 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 = 168.8 (C-6), 65.9 (C-10), 58.8 (C-2), 57.4 (C-14), 57.0 (C-16), 42.3 (C-8), 35.7 (C-17), 34.6 (C-1), 34.5 (C-9), 33.2 (C-5), 30.6 (C-11), 27.8 (C-3), 25.9 (C-13), 25.0 (C-12), 20.0 (C-4) ppm; IR (ATR): $\tilde{\nu}$ = 2925 (m), 2854 (m), 2758 (w), 2733 (w), 1601 (s), 1475 (m), 1441 (m), 1360 (m), 1279 (m), 1111 (m), 1097 (m), 1027 (m), 876 (w), 751 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}N_2O$ [$M + H^+$]: 249.19614; found: 249.19548.

The spectroscopic data are in accordance with those reported in literature.[35,36]

Table S15. Comparison of synthetic and natural isolupanine (**31**).

Pos.	^{1}H NMR (δ in ppm, *J* in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref.36) (400 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref.36) (100 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	1.65 (m)	1.60 (m)	0.05	34.6	34.4	0.2
2	3.47 (m)	3.45 (d)	0.02	58.8	58.7	0.1
3a,b	1.79 (m)	1.76 (m)	0.03	27.8	27.6	0.2
4a 4b	1.79 (m) 1.65 (m)	1.80 (m) 1.59 (m)	0.01 0.06	20.0	19.8	0.2
5a 5b	2.38 (dm, *J*=17.0) 2.22 (m)	2.36 (m) 2.23 (m)	0.02 0.01	33.2	32.9	0.3
6				168.8	169.0	0.2
8a 8b	4.91 (d, *J*=13.8) 2.54 (dd, *J*=13.8, 2.3)	4.86 (br d) 2.54 (m)	0.05 0.00	42.3	42.2	0.1
9	1.56 (m)	1.56 (m)	0.00	34.5	34.2	0.3
10	1.92 (d, *J*=10.6)	1.93 (m)	0.01	65.9	65.8	0.1
11a 11b	1.65 (m) 1.32 (m)	1.62 (m) 1.30 (m)	0.03 0.01	30.6	30.4	0.2

[34] G. R. Clemo, G. C. Leitch, *J. Chem. Soc.* **1928**, 1811-1820.
[35] 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.
[36] E. J. Kennelly, T. J. Flynn, E. P. Mazzola, J. A. Roach, T. G. McCloud, D. E. Danford, J. M. Betz, *J. Nat. Prod.* **1999**, *62*, 1385-1389.

12a 12b	1.65 (m) 1.18 (m)	1.68 (m) 1.17 (m)	0.03 0.01	25.0	24.8	0.2
13a,b	1.46 (m)	1.45 (m)	0.01	25.9	25.6	0.3
14a 14b	2.60 (d, *J*=10.3) 1.65 (m)	2.67 (m) 1.68 (m)	0.07 0.03	57.4	57.3	0.1
16a 16b	2.96 (d, *J*=11.4) 2.12 (d, *J*=11.4)	2.97 (m) 2.13 (m)	0.01 0.01	57.0	56.7	0.4
17a,b	1.79 (m)	1.78 (m)	0.01	35.7	35.4	0.3

1.5.2.2 α-Isosparteine (3)

Isolupanine[37] (**31**; 20.0 mg, 80.9 µmol) was dissolved in anhydr. THF (2 mL) and cooled to 0 °C. $LiAlH_4$ (24.6 mg, 647 µmol) was added and the reaction mixture was refluxed for 17 h. At rt, sat. aq. Na_2SO_4 (5 mL) was added dropwise until gas evolution ceased. The aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL), the combined organic layers were dried over K_2CO_3 and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.5 mL) and extracted with aq. HCl (4.0 M; 2 × 1.5 mL). The combined aqueous layers were basified (pH = 14) with aq. NaOH (12.5 M; 1.6 mL) and cooled to 4 °C for 4 h. The formed precipitate was isolated by centrifugation and washed with H_2O (2 × 10 mL). Drying under high vacuum delivered α-isosparteine partial hydrate[38] (**3**·1.2H_2O; 17.2 mg, 67.2 µmol, 83%) as an off-white solid.

R_f = 0.23 [$CHCl_3$/MeOH/NH_3 (aq., 25%) 90:9:1]; m.p. 70-72 °C (DSC; lit.[39] 61-117 °C; lit.[40] 98-115 °C)[41]; $[\alpha]_D^{25}$ = –57.0 (*c*=0.5 in MeOH) [lit.[40] $[\alpha]_D^{30}$ = –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, w), 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.[2,42]

[37] The procedure is related to that one used for the reduction of lupanine, see ref.[27] and section 1.4.3.5.
[38] α-Isosparteine was isolated as a hydrate as described in ref.[2] because the free base tends to decompose.
[39] D. Kettelhack, M. Rink, K. Winterfeld, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1954**, *287*, 1-11.
[40] N. J. Leonard, R. E. Beyler, *J. Am. Chem. Soc.* **1950**, *72*, 1316-1323.
[41] The melting point strongly depends on the degree of hydration and the sample heating rate.[2,39,40]
[42] V. Galasso, F. Asaro, F. Berti, B. Kovač, I. Habuš, A. Sacchetti, *Chem. Phys.* **2003**, *294*, 155–169.

Table S16. Comparison of synthetic and natural α-isosparteine (**3**).

Pos.	^{1}H NMR (δ in ppm, J in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic[a] (500 MHz, MeOD)	Natural[b]	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, MeOD)	Natural (ref. 42) (150 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1/9	1.53 (m)			36.8	35.6	1.2
2/10	2.02 (d, J=11.4)			68.0	66.4	1.6
3a/11a 3b/11b	1.63 (m) 1.36 (m)			31.2	30.2	1.0
4/12, 5/13	1.80 (m) 1.53 (m) 1.36 (m)			25.9, 25.8	25.4, 25.0	0.5, 0.8
6a/14a 6b/14b	2.79 (d, J=7.2) 1.80 (m)			58.7	57.4	1.3
8a/16a 8b/16b	2.98 (d, J=11.7) 2.13 (dd, J=11.7, 2.6)			57.4	56.1	1.3
17a,b	1.70 (s)			37.3	36.4	1.1

[a] The synthetic compound was isolated as a partial hydrate [signal of the bound water: 4.89 (br s)]. [b] There are no ^{1}H data available for the natural product. For a complete set of ^{1}H NMR signals, see ref. 2.

1.5.3 Synthesis of Angustifoline (33) and *N*-Methyl Angustifoline (34)

1.5.3.1 (1*S*,2*R*,9*S*)- 11-*tert*-Butoxycarbonyl-10-methoxy-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane-6-one (32)

A solution of imide **29** (390 mg, 1.27 mmol) in MeOH (20 mL) was treated at 0°C with $NaBH_4$ (144 mg, 3.81 mmol) and stirred for 2.5 h at this temperature. Methanolic HCl (2.0 M; 5 mL) was added and the reaction mixture was allowed to reach rt over 4 h. Sat aq. $NaHCO_3$ (10 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. Evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 99:1 → 98:2) delivered *N,O*-acetal **32** (383 mg, 1.18 mmol, 93%) as a colorless oil.

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); $[\alpha]_D^{23}$ = +108.3 (c=1.0 in CH_2Cl_2); ^{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=10.7 Hz, 1H, 2-H), 3.24 (s, 0.33H, OCH_3), 3.21 (s, 2.67H, OCH_3), 3.07 (dm, J=13.9 Hz, 0.11H, 12-*H*H), 2.96 (dm, J=13.9 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*), 1.64-1.50 (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), 154.4, 154.3 (CO_2N), 85.6, 84.3 (C-10), 80.5, 80.0 (*C*$(CH_3)_3$), 59.7, 59.6 (C-2), 54.6, 54.1 (OCH_3),

44.2 (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, 28.4 ($C(CH_3)_3$), 27.9 (C-3), 27.5, 27.1 (C-13), 20.32, 20.25 (C-4) ppm. IR (ATR): $\tilde{\nu}$ = 2934 (br w), 1688 (s), 1635 (s), 1442 (m), 1413 (s), 1383 (m), 1233 (m), 1167 (s), 1134 (s), 1070 (s), 1012 (m), 977 (m), 914 (m),767 (w), 576 (w) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{28}N_2O_4Na$ [$M + Na^+$]: 347.19413; found: 247.19326.

1.5.3.2 Angustifoline (33)

Allyltrimethylsilane (1.09 mL, 6.84 mmol) and $BF_3{\cdot}Et_2O$ (433 µL, 3.42 mmol) were added at 0 °C to a solution of *N,O*-acetal **32** (370 mg, 1.14 mmol) in anhydr. CH_2Cl_2 (18 mL). After 17 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, $CHCl_3$/MeOH/NH_3 (aq., 25%) 98:1.8:0.2 → 95:4.5:0.5] to give angustifoline (**33**; 221 mg, 943 µmol, 83%) as a white crystalline solid.

R_f = 0.46 (CH_2Cl_2/MeOH 90:10); m.p. 79 °C (lit.[43] 80 °C); $[\alpha]_D^{24}$ = +7.9 (*c*=1.0 in EtOH) [lit.[43] $[\alpha]_D^{20}$ = –8.0 (*c*=1.2 in EtOH), lit.[44] $[\alpha]_D^{25}$ = +5.2 (concentration not given, in EtOH)][45]; ^{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 (m, 2H, 12-H_2), 2.87 (m, 2H, 8-H*H*,10-H), 2.47 (m, 1H, 5-*H*H), 2.44-2.27 (m, 2H, 10-C*H*H, 5-H*H*), 2.23 (m, 1H, 10-CH*H*), 2.11 (m, 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 (m, 2H, 13-H*H*, NH), 1.49 (m, 1H, 1-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4 (C-6), 136.4 (10-CH_2CH=CH_2), 116.7 (10-CH_2CH=CH_2), 60.4 (C-2), 57.1 (C-10), 48.1 (C-8), 42.0 (C-12), 37.6 (10-CH_2), 33.3 (C-5), 32.8 (C-1), 31.3 (C-9), 28.1, 28.0 (C-3, C-13), 20.4 (C-4); IR (ATR): $\tilde{\nu}$ = 2907 (m), 2870 (m), 1634 (s), 1618 (s), 1440 (m), 1416 (m), 1308 (m), 1237 (m), 1183 (m), 1076 (m), 1002 (m), 908 (s), 749 (s), 643 (m), 595 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{23}N_2O$ [$M + H^+$]: 235.18049; found: 235.17962.

The spectroscopic data are in accordance with those reported in literature.[43,47]

Table S17. Comparison of synthetic and natural angustifoline (**33**).

Pos.	^{1}H NMR (δ in ppm, *J* in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 47) (600 MHz, $CDCl_3$)[a]	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 47) (150 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	1.49 (m)	1.52	0.03	32.8	32.79	0.0
2	3.46 (m)	3.49	0.03	60.4	60.29	0.1
3a,b	1.83-1.61 (m)	1.82, 1.80	0.00	28.1 or 28.0	27.97 or 28.07	0.1

[43] F. Bohlmann, E. Winterfeldt, *Chem. Ber.* **1960**, *93*, 1956-1960.
[44] H. A. Lloyd, E. C. Horning, *J. Org. Chem.* **1960**, *25*, 1959-1962.
[45] The negative sign of the optical rotation of isolated angustifoline (**33**), as given in ref. 43, seems to be incorrect. Our sample of synthetic **33** was analytically pure and its absolute configuration was confirmed by conversion into the known natural alkaloids **34**, **2**, and (**–**)-**1**. Furthermore, the sign of the optical rotation of natural 'jamaicensine', which was later found to be identical to angustifoline (**33**),[46] is also positive.[44]
[46] H. A. Lloyd, *J. Org. Chem.* **1961**, *26*, 2143-2145.
[47] W. Wysocka, A. Przybyl, T. Brukwicki, *Monatsh. Chem.* **1994**, *125*, 1267-1272.

4a 4b	1.89 (m) 1.83-1.61 (m)	1.92 1.70	0.03 0.00	20.4	20.20	0.2
5a 5b	2.47 (m) 2.44-2.27 (m)	2.50 2.35	0.03 0.00	33.3	33.24	0.1
6				170.4	170.04	0.3
8a 8b	4.62 (d, *J*=13.6) 2.87 (m)	4.67 2.89	0.04 0.02	48.1	48.09	0.0
9	1.83-1.61 (m)	1.76	0.00	31.3	31.25	0.0
10	2.87 (m)	2.90	0.03	57.1	57.02	0.1
10-R	5.76 (m, CH_2CH=CH_2) 5.06 (m, CH_2CH=CH_2) 2.44-2.27 (m, CHHCH=CH_2) 2.23 (m, CHHCH=CH_2)	5.79 5.08, 5.06 2.42 2.26	0.03 0.00 0.00 0.03	136.4 (CH_2CH=CH_2) 116.7 (CH_2CH=CH_2) 37.6 (CH_2CH=CH_2)	136.14 116.47 37.58	0.3 0.2 0.0
11	1.58 (m, NH)	1.63 (NH)	0.05			
12a,b	3.00 (m)	3.02, 3.01	0.02	42.0	41.92	0.1
13a 13b	2.11 (m) 1.58 (m)	2.14 1.61	0.03 0.03	28.1 or 28.0	27.97 or 28.07	0.1

[a] There are no multiplicities and coupling constants given in ref. 47.

1.5.3.3 *N*-Methyl Angustifoline (34)

A solution of angustifoline (**33**; 20.0 mg, 85.4 µmol), K_2CO_3 (23.6 mg, 171 µmol), and Cs_2CO_3 (2.78 mg, 8.54 µmol) in anhydr. CH_2Cl_2 (3 mL) was successively treated with MeI in anhydr. CH_2Cl_2 (0.2 M; 0 h: 515 µL, 103 µmol; 19 h: 128 µL, 25.6 µmol; 22 h: 214 µL, 42.7 µmol). After 24 h, the reaction mixture was diluted with NaOH (1.0 M; 3 mL). The aqueous layer was extracted with $CHCl_3$ (4 × 5 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and column chromatography (SiO_2, hexane/$CHCl_3$/MeOH 100:0:0 → 0:98:2) delivered *N*-methyl angustifoline (**34**; 18.3 mg, 73.7 µmol, 86%) as a white crystalline solid.

R_f = 0.42 (CH_2Cl_2/MeOH 90:10); m.p. 85 °C (lit.[48] 85-86 °C); $[\alpha]_D^{27}$ = +12.9 (*c*=1.0 in MeOH) [lit.[48] $[\alpha]_D^{20}$ = +12.3 (in MeOH, concentration not given)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.71 (m, 1H, 10-CH_2CH=CH_2), 5.04 (m, 2H, 10-CH_2CH=CH_2), 4.56 (d, *J*=13.6 Hz, 1H, 8-*H*H), 3.39 (m, 1H, 2-H), 2.73 (dd, *J*=13.6 Hz, 3.5 Hz, 1H, 8-H*H*), 2.68 (dd, *J*=12.0 Hz, 5.1 Hz, 1H, 12-*H*H), 2.53 (m, 1H, 10-H), 2.45 (m, 2H, 5-*H*H, 12-H*H*), 2.29 (m, 2H, 5-H*H*, 10-C*H*H), 2.20 (s, 3H, 11-CH_3), 2.16 (m, 1H, 10-CH*H*), 2.00 (m, 1H, 13-*H*H), 1.88 (s, 1H, 9-H), 1.83 (m, 1H, 4-*H*H), 1.80-1.58 (m, 4H, 1-H, 3-H_2, 4-H*H*), 1.43 (m, 1H; 13-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0 (C-6), 136.1 (10-CH_2CH=CH_2), 116.8 (10-CH_2CH=CH_2), 64.2 (C-10), 60.0 (C-2), 51.1 (C-12), 47.6 (C-8), 42.6 (11-CH_3), 33.7 (C-1), 33.1 (C-5), 30.9 (10-CH_2), 30.7 (C-9), 28.0 (C-3), 27.2 (C-13), 20.1 (C-4) ppm; IR (ATR): $\tilde{\nu}$ = 2925 (m), 2856 (m), 1625 (s), 1615 (s); 1442 (m), 1418 (m), 1325 (m), 1261 (m), 1158 (m), 1014 (m), 915 (s), 795 (w), 640 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}N_2O$ [*M* + H$^+$]: 249.19614; found: 249.19553.

The spectroscopic data are in accordance with those reported in literature.[33]

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[48] M. D. Bratek-Wiewiórowska, *J. Mol. Struct.* **1979**, *55*, 69-87.

Table S18. Comparison of synthetic and natural *N*-methyl angustifoline (**34**).

Pos.	^{1}H NMR (δ in ppm, J in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural (ref. 33) (400 MHz, $CDCl_3$)[a]	$\lvert\Delta\delta\rvert$	Synthetic (125 MHz, $CDCl_3$)	Natural (ref. 33) (100 MHz, $CDCl_3$)	$\lvert\Delta\delta\rvert$
1	1.80-1.58 (m)	1.72	0.00	33.7	33.43	0.3
2	3.39 (m)	3.40	0.01	60.0	59.65	0.3
3a,b	1.80-1.58 (m)	ca. 1.8-1.7	0.00 0.00	28.0	27.75	0.2
4a 4b	1.83 (m) 1.80-1.58 (m)	ca. 1.8 1.66	0.03 0.00	20.1	19.83	0.3
5a 5b	2.45 (m) 2.29 (m)	2.43 2.30	0.02 0.01	33.1	32.88	0.2
6				170.0	169.62	0.4
8a 8b	4.56 (d, J=13.6) 2.73 (dd, J=13.6, 3.5)	4.57 2.74	0.01 0.01	47.6	47.32	0.3
9	1.88 (s)	1.88	0.00	30.7	30.29	0.4
10	2.53 (m)	2.54	0.01	64.2	63.90	0.3
10-R	5.71 (m, CH_2CH=CH_2) 5.04 (m, CH_2CH=CH_2) 2.29 (m, CHHCH=CH_2) 2.16 (m, CHHCH=CH_2)	5.72 5.03, 4.96 ca. 2.31 2.17	0.01 0.09 0.02 0.01	136.1 (CH_2CH=CH_2) 116.8 (CH_2CH=CH_2) 30.9 (CH_2CH=CH_2)	135.90 116.50 30.59	0.2 0.3 0.3
11-Me	2.20 (s)	2.21	0.01	42.6	42.32	0.3
12a,b	2.68 (dd, J=12.0, 5.1) 2.45 (m)	2.69 2.49	0.01 0.04	51.1	50.81	0.3
13a 13b	2.00 (m) 1.43 (m)	2.00 1.44	0.00 0.01	27.2	26.90	0.3

[a] There are no multiplicities and coupling constants given in ref. 33.

1.5.4 Synthesis of Lupanine (2) and (–)-Sparteine (1)

1.5.4.1 (1*S*,2*R*,9*S*,10*S*)- 10,11-Diallyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane-6-one (35)

A solution of angustifoline (**33**; 60.0 mg, 256 µmol) in anhydr. CH_2Cl_2 (2 mL) was successively treated with three portions of allyl bromide (0 h: 111 µL, 1.28 mmol; 23 h: 44.3 µL, 512 µmol; 65 h: 44.3 µL, 512 µmol) and NEt_3 (0 h: 213 µL, 1.54 mmol, 23 h: 106 µL, 768 µmol). After 5 d, sat. aq. $NaHCO_3$ (3 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 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 **35** (145 mg, 536 µmol, 82%) as a colorless oil.[49]

R_f = 0.55 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{25}$ = +51.6 (c=1.0 in $CHCl_3$); ^{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), 4.64 (d, J=13.7 Hz, 1H, 8-HH), 3.42 (m, 1H, 2-H), 3.04 (dd, J=13.4 Hz, 5.4 Hz, 1H, 11-CHH), 2.96 (m,

[49] Note: Compound **35** easily decomposes upon storage or exposure to air and light. It should immediately be converted into **S6**.

1H, 10-H), 2.81 (m, 3H, 8-H*H*, 12-*H*H, 11-CH*H*), 2.47 (dd, *J*=12.2 Hz, 2.2 Hz, 1H, 12-H*H*), 2.41 (m, 1H, 5-*H*H), 2.28-2.13 (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), 1.77-1.53 (m, 4H, 1-H, 3-H_2, 4-H*H*), 1.50 (dm, *J*=12.9 Hz, 1H, 13-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9 (C-6), 137.2, 136.6 (10-CH_2*C*H=CH_2, 11-CH_2*C*H=CH_2), 116.7, 116.5 (10-CH_2CH=*C*H_2, 11-CH_2CH=*C*H_2), 63.2 (C-10), 59.5 (C-2), 57.8 (11-CH_2), 47.6 (C-8), 46.5 (C-12), 33.9 (C-1), 33.2 (C-5), 30.1 (C-9), 27.9, 27.8, 27.7 (C-3, C-13, 10-CH_2), 20.1 (C-4) ppm; IR (ATR): $\tilde{\nu}$ = 2921 (m), 2866 (m), 1627 (s), 1445 (m), 1418 (m), 1345 (m), 1256 (m), 1156 (m), 997 (m), 914 (m), 642 (w), 570 (w) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{27}N_2O$ [*M* + H^+]: 275.21179; found: 275.21150.

1.5.4.2 (1*S*,2*R*,9*S*,10*S*)-7,15-Diazatetracyclo[7.7.1.0^{2,7}.0^{10,15}]heptadec-12-en-6-one (S6)

A solution of diene **35** (64.1 mg, 234 µmol) in anhydr. CH_2Cl_2 (23 mL) was thoroughly degassed and treated with 2nd generation Grubbs' catalyst (9.93 mg,11.7 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 100:0 → 95:5) delivered alkene **S6** (49.0 mg, 199 µmol, 85%) as a brownish oil.

R_f = 0.41 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{25}$ = +5.4 (*c*=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.70 (m, 1H, 12-H), 5.62 (m, 1H, 13-H), 4.56 (dt, *J*=13.4 Hz, 2.1 Hz, 1H, 8-*H*H), 3.31 (m, 1H, 2-H), 3.14 (m, 1H, 14-*H*H), 2.98 (dd, *J*=11.0 Hz, 9.7 Hz, 1H, 16-*H*H), 2.73 (d, *J*=16.8 Hz, 1H, 14-H*H*), 2.59 (dd, *J*=13.4 Hz, 3.0 Hz, 1H, 8-H*H*), 2.47 (m, 1H, 5-*H*H), 2.32 (m, 1H, 5-H*H*), 2.23-1.97 (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), 1.67 (m, 1H, 9-H), 1.65-1.49 (m, 2H, 3-H*H*, 4-H*H*), 1.31 (dm, *J*=12.4 Hz, 1H, 17-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3 (C-6), 125.3 (C-12), 125.2 (C-13), 61.1 (C-2), 59.2 (C-10), 54.5 (C-14), 51.9 (C-16), 47.1 (C-8), 34.6 (C-9), 33.6 (C-11), 33.1 (C-5), 32.3 (C-1), 27.6 (C-3), 26.0 (C-17), 19.8 (C-4) ppm; IR (ATR): $\tilde{\nu}$ = 2901 (m), 2864 (m), 1634 (s), 1441 (m), 1333 (m), 1249 (m), 1165 (m), 1124 (m), 993 (w), 917 (w), 790 (w), 661 (m) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{23}N_2O$ [*M* + H^+]: 247.19049; found: 247.18033.

1.5.4.3 (+)-Lupanine (2)

A solution of alkene **S6** (30.0 mg, 122 µmol) in MeOH (1.5 mL) and Pd on carbon (10 wt% Pd; 13.0 mg, 12.2 µmol) were stirred under 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, $CHCl_3$/MeOH/NH_3 (aq., 25%) 98:1.8:0.2] delivered (+)-lupanine (**2**; 28.1 mg, 113 µmol, 93%) as a yellowish oil.

R_f = 0.29 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{22}$ = +81.0 (*c*=1.0 in EtOH) [lit.[27] $[\alpha]_D^{20}$ = +80.9 (*c*=1.0 in EtOH); lit.[50] $[\alpha]_D^{20}$ = +80 (*c*=0.92 in EtOH)]

The spectroscopic data of **2** are identical to those reported for *ent*-**2** in section 1.4.3.4.

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[50] M. Rink, H. Schäfer, *Arch. Pharm.* **1954**, *287*, 290-302.

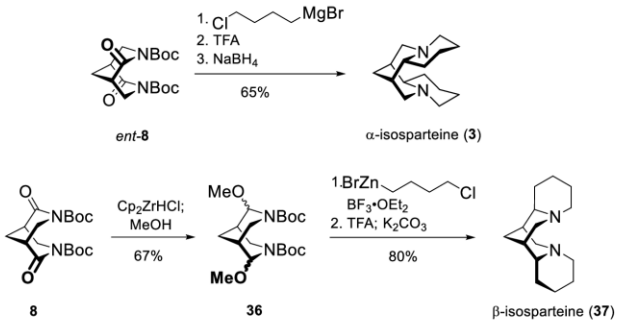
1.5.4.4 (–)-Sparteine (1)

According to a literature procedure,[27] (+)-lupanine (**2**; 20.0 mg, 80.5 µmol) was dissolved in anhydr. THF (1.5 mL) and cooled to 0 °C. $LiAlH_4$ (24.4 mg, 644 µmol) was added and the reaction mixture was refluxed for 18 h. At rt, sat. aq. Na_2SO_4 (5 mL) was added dropwise until gas evolution ceased. The aqueous layer was extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was partitioned between Et_2O (5 mL) and aq. HCl (4.0 M; 5 mL), and the aqueous layer was washed with Et_2O (2 × 5 mL). The aqueous layer was basified (pH = 10) with aq. NaOH (6.0 M; 8 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum, providing (–)-sparteine (**1**; 15.8 mg, 67.6 µmol, 84%, lit.[27] 84%) as a colorless oil.

R_f = 0.56 [$CHCl_3$/MeOH/NH_3 (aq., 25%) 80:18:2]; $[\alpha]_D^{23}$ = –18.9 (*c*=0.5 in EtOH) [lit.[27] $[\alpha]_D^{20}$ = –20.7 (*c*=1.8 in EtOH); lit.[30] $[\alpha]_D$ = –18.0 (*c*=1.3 in EtOH)]

The spectroscopic data of **1** are identical to those reported for *ent*-**1** in section 1.4.3.5.

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 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 vacuum delivered α-isosparteine partial hydrate[38] (**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 °C (DSC; lit.[39] 61-117 °C; lit.[40] 98-115 °C)[41]; $[\alpha]_D^{25}$ = –57.9 (*c*=0.5 in MeOH) [lit.[40] $[\alpha]_D^{30}$ = –55.8 (*c*=7.22 in MeOH)].

The spectroscopic data of **3** are given in section 1.5.2.3.

1.6.2 Synthesis of β-Isosparteine (37)

1.6.2.1 (1*R*,5*R*)-2,6-Dimethoxy-3,7-diazabicyclo[3.3.1]nonane (36)

A solution of zirconocene hydrochloride (Schwartz reagent; 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 **36** (219 mg, 567 µmol, 67%) as a colorless oil.

The ^1H and ^{13}C NMR spectra of **36** 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); ^1H 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-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 (37)

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 **36** (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 (**37**; 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.[51] $[\alpha]_D^{32}$ = –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.[42,52,53]

Table S19. Comparison of synthetic and natural β-isosparteine (**37**).

Pos.	^{1}H NMR (δ in ppm, *J* in Hz)			^{13}C NMR (δ in ppm)		
	Synthetic (500 MHz, $CDCl_3$)	Natural[a]	|Δδ|	Synthetic (125 MHz, $CDCl_3$)	Natural (ref.42) (75 MHz, $CDCl_3$)	|Δδ|
1/9	1.62 (m)			34.4	34.4	0.0
2/10	2.21 (dm, *J*=11.8)			62.8	62.8	0.0
3a/11a 3b/11b	1.54 (m) 1.20 (d, *J*=12.6)			28.7	28.7	0.0
4/12, 5/13	1.73 (m) 1.54 (m) 1.32 (m)			25.5, 22.7	25.4, 22.7	0.1

[51] R. Greenhalgh, L. Marion, *Can. J. Chem* **1956**, *34*, 456-458.
[52] P. R. Blakemore, N. R. Norcross, S. L. Warriner, P. C. Astles, *Heterocycles* **2006**, *70*, 609-617.
[53] F. M. Al-Saffar, R. C. D. Brown, *Org. Lett.* **2017**, *19*, 3502-3504.

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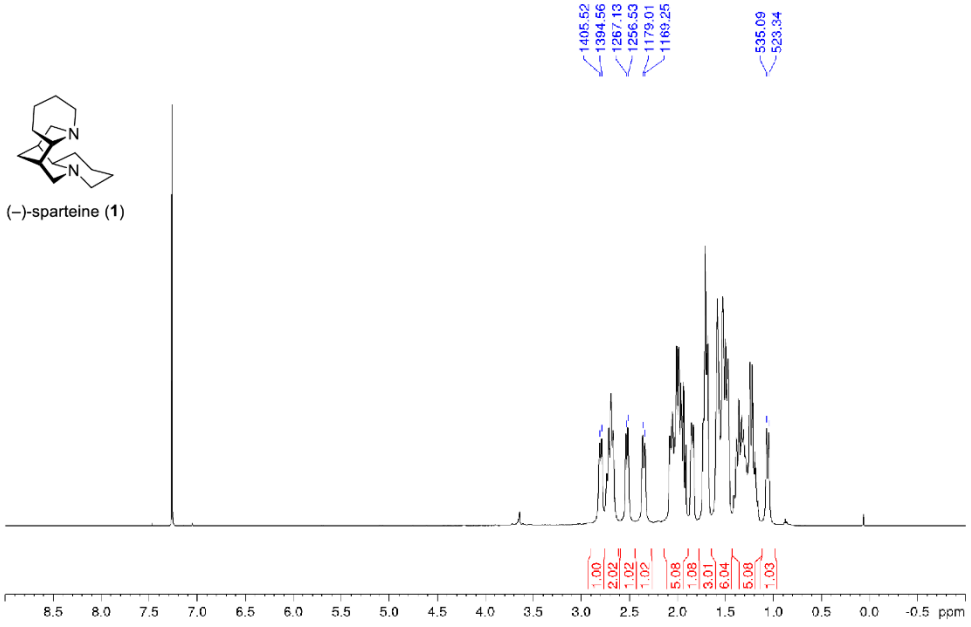
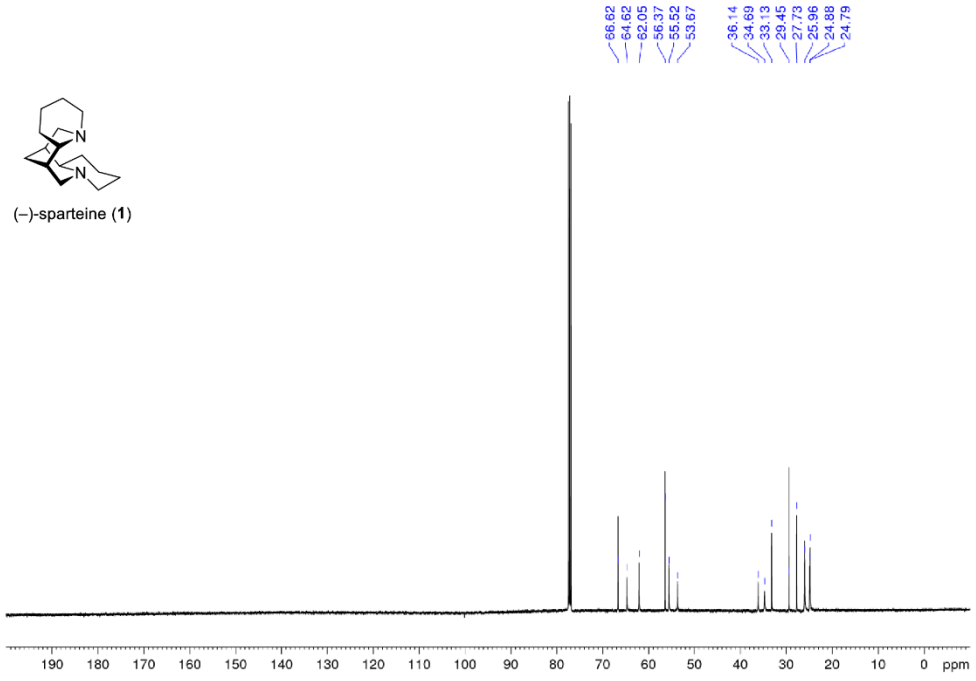
6a/14a 6b/14b	2.75 (dm, *J*=12.7) 2.40 (td, *J*=12.7, 2.6)	55.1	55.1	0.0
8a/16a 8b/16b	2.97 (dd, *J*=10.8, 6.7) 2.12 (dd, *J*=10.9, 2.8)	55.0	54.9	0.1
17a,b	1.46 (t, *J*=3.3)	19.8	19.8	0.0

[a] There are no ^{1}H data available for the natural product. For a complete set of ^{1}H NMR signals (synthetic **37**), see refs. 52 and 53.

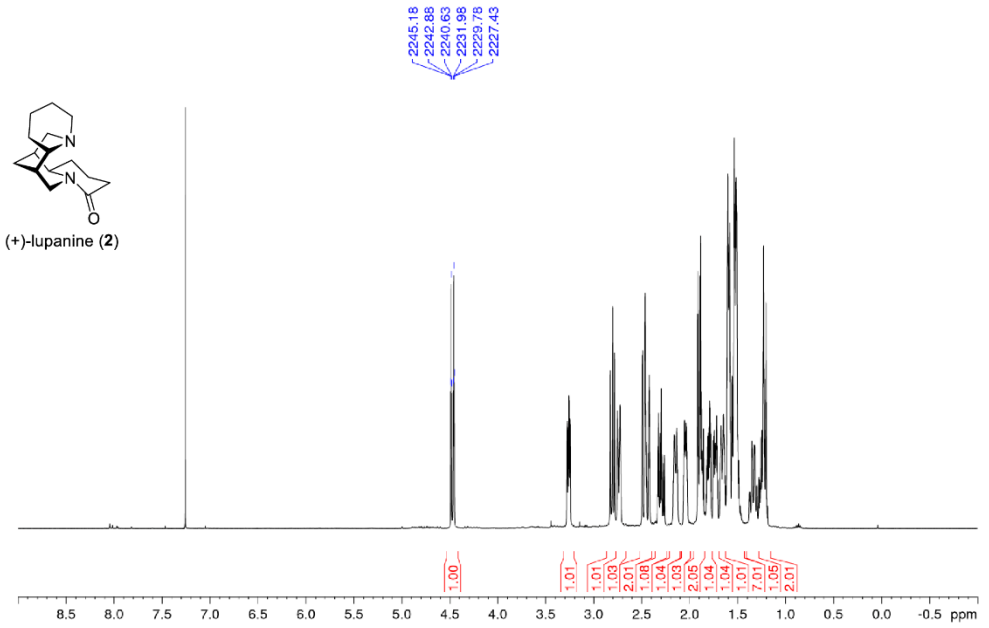
2. Copies of ^{1}H and ^{13}C NMR Spectra

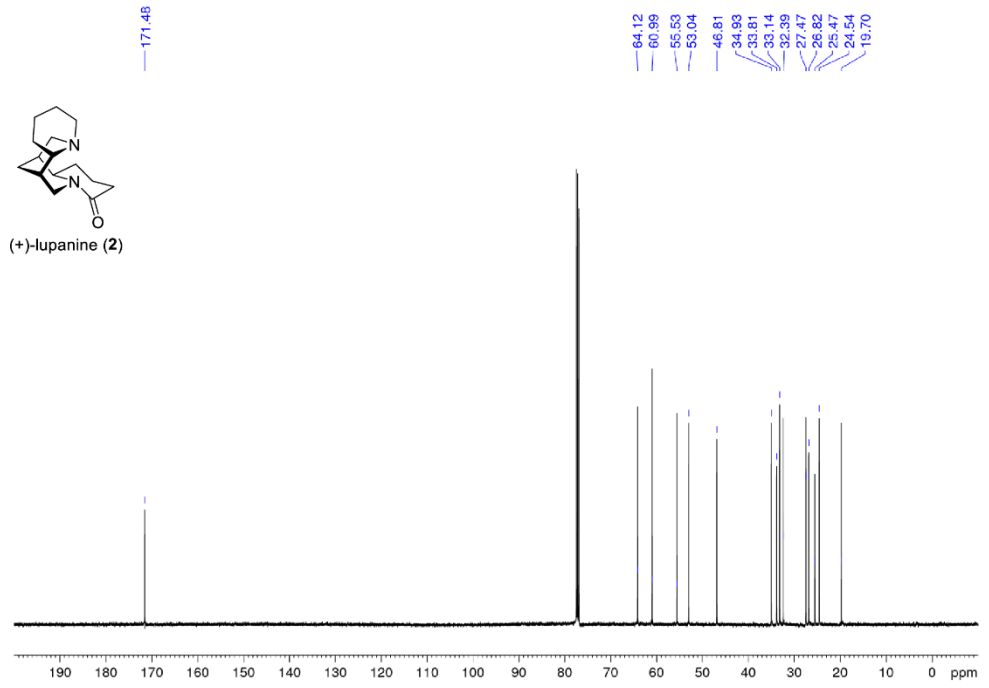
The ^{1}H and ^{13}C NMR spectra of all new compounds are listed in numerical order.



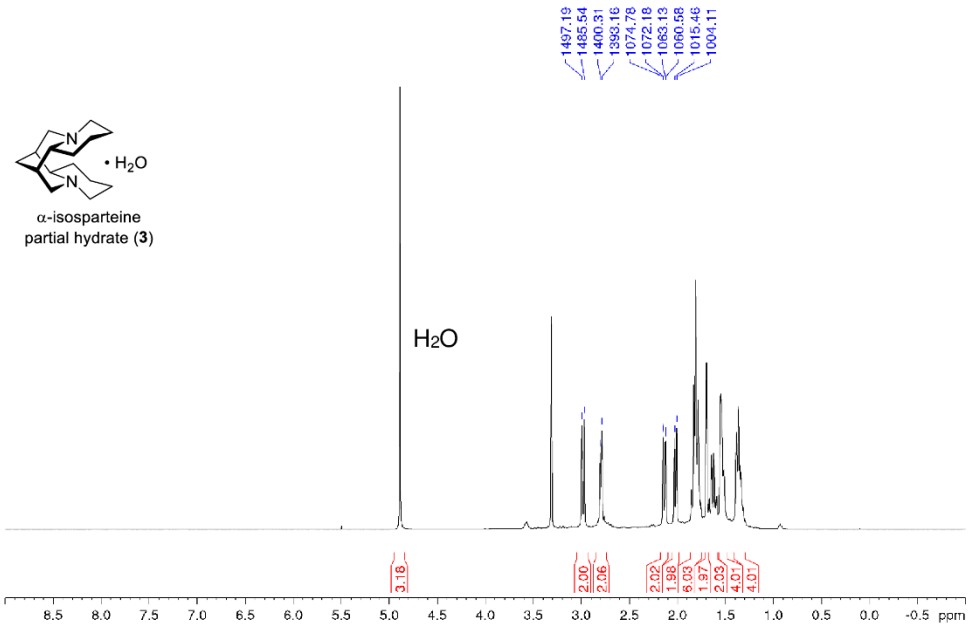


43


2245.18
2242.88
2240.63
2231.98
2229.78
2227.43
(+)-lupanine (2)
1.00
1.01
1.01
1.03
2.01
1.08
1.04
1.03
2.05
1.04
1.04
1.01
7.01
1.05
2.01
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


171.48
64.12
60.99
55.53
53.04
46.81
34.93
33.81
33.14
32.39
27.47
26.82
25.47
24.54
19.70
(+)-lupanine (2)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

44


1497.19
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1393.16
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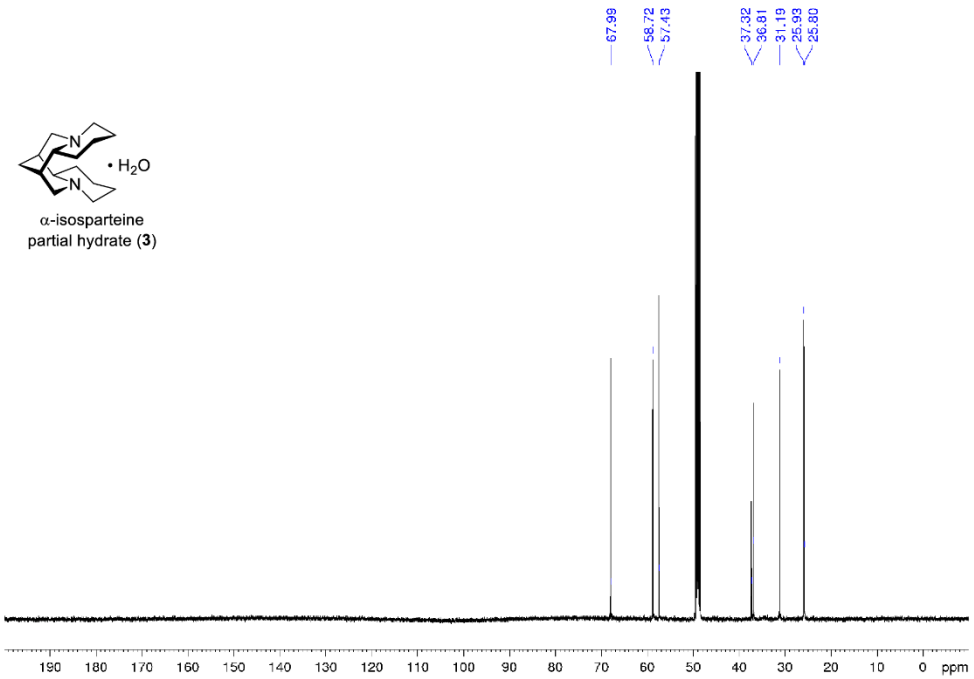
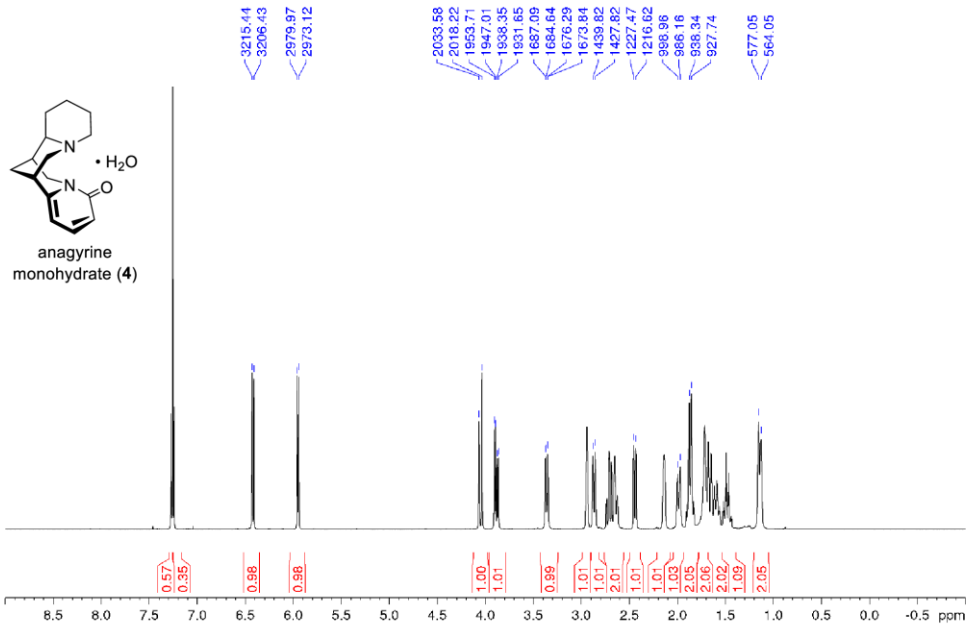
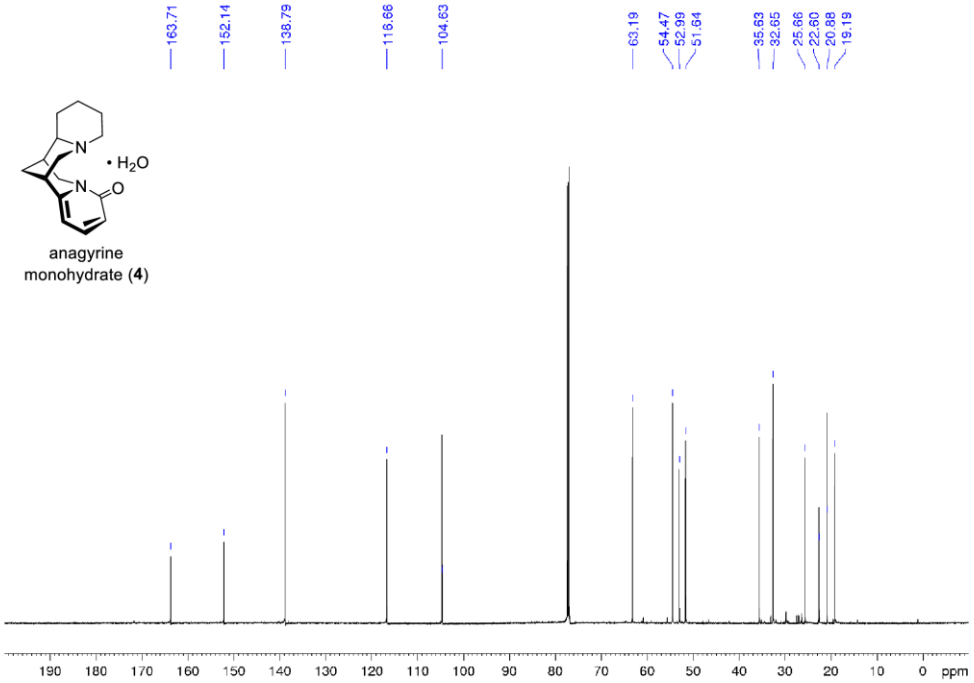
1063.13
1060.58
1015.46
1004.11
• H2O
α-isosparteine
partial hydrate (3)
H2O
3.16
2.00
2.06
2.02
1.98
6.03
1.97
2.03
4.01
4.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

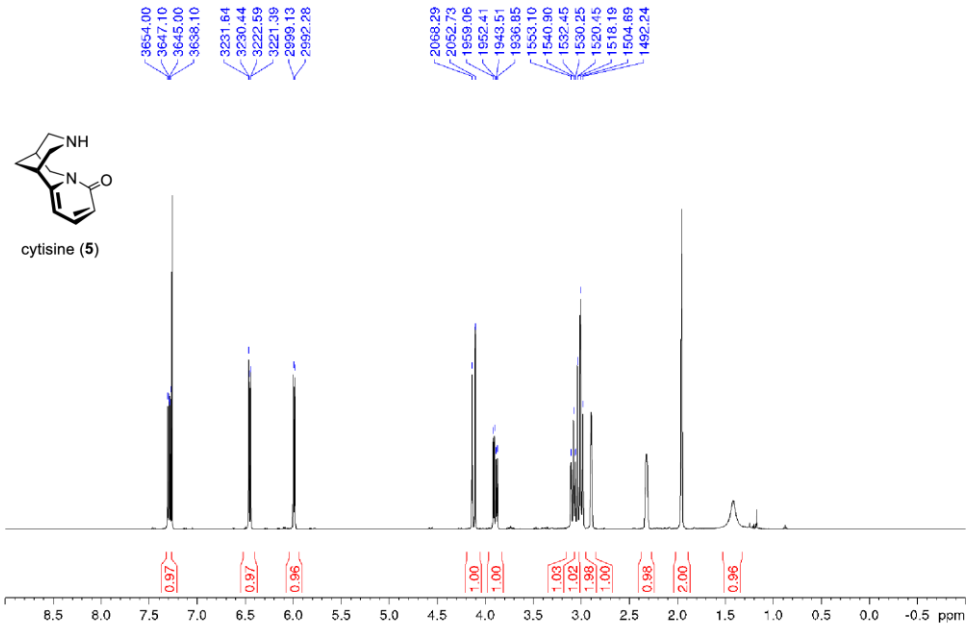

67.99
58.72
57.43
37.32
36.81
31.19
25.93
25.80
• H2O
α-isosparteine
partial hydrate (3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

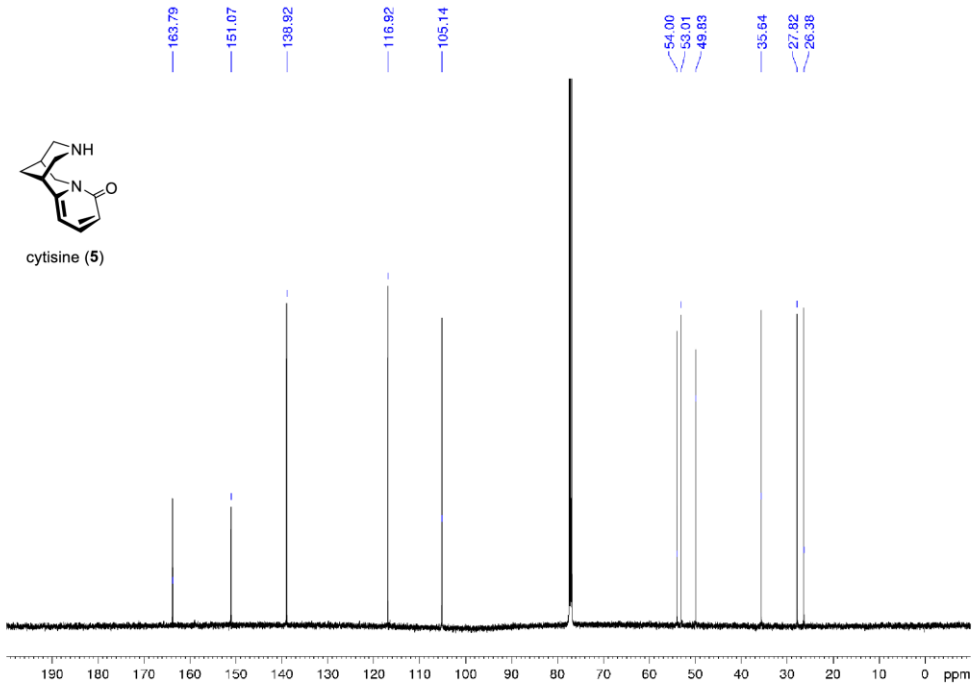
45


3215.44
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
• H2O
anagyrine
monohydrate (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

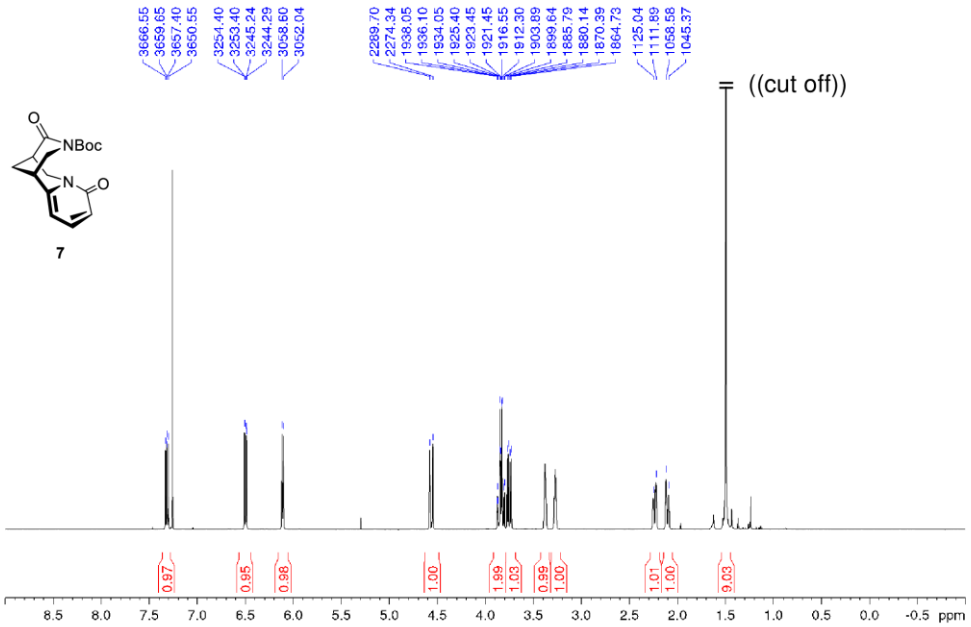

163.71
152.14
138.79
116.66
104.63
63.19
54.47
52.99
51.64
35.63
32.65
25.66
22.60
20.88
19.19
• H2O
anagyrine
monohydrate (4)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

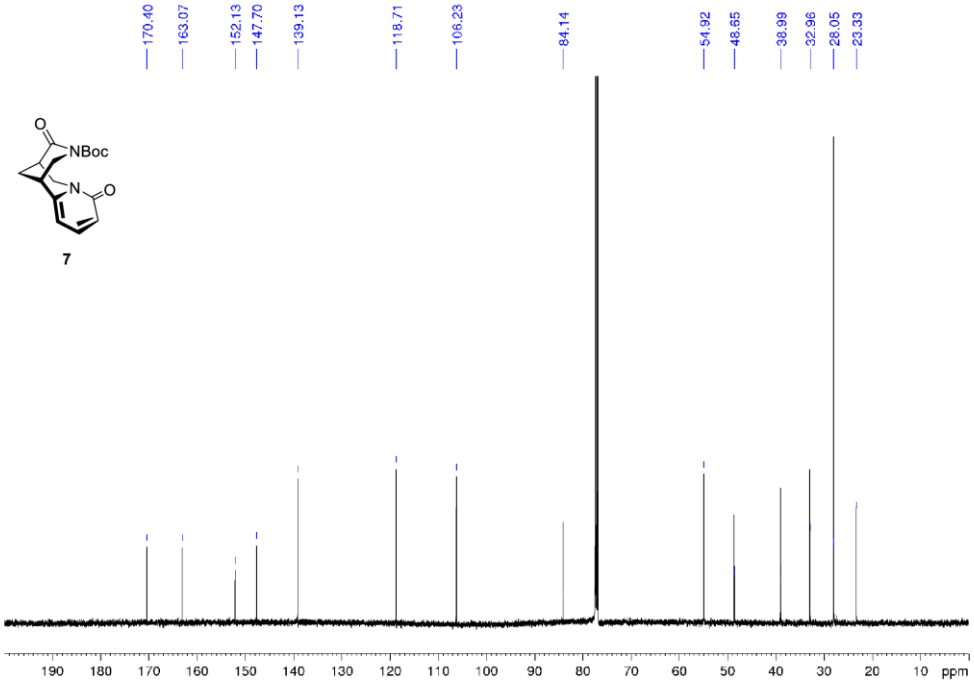
46


3654.00
3647.10
3645.00
3638.10
3231.84
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
1504.89
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

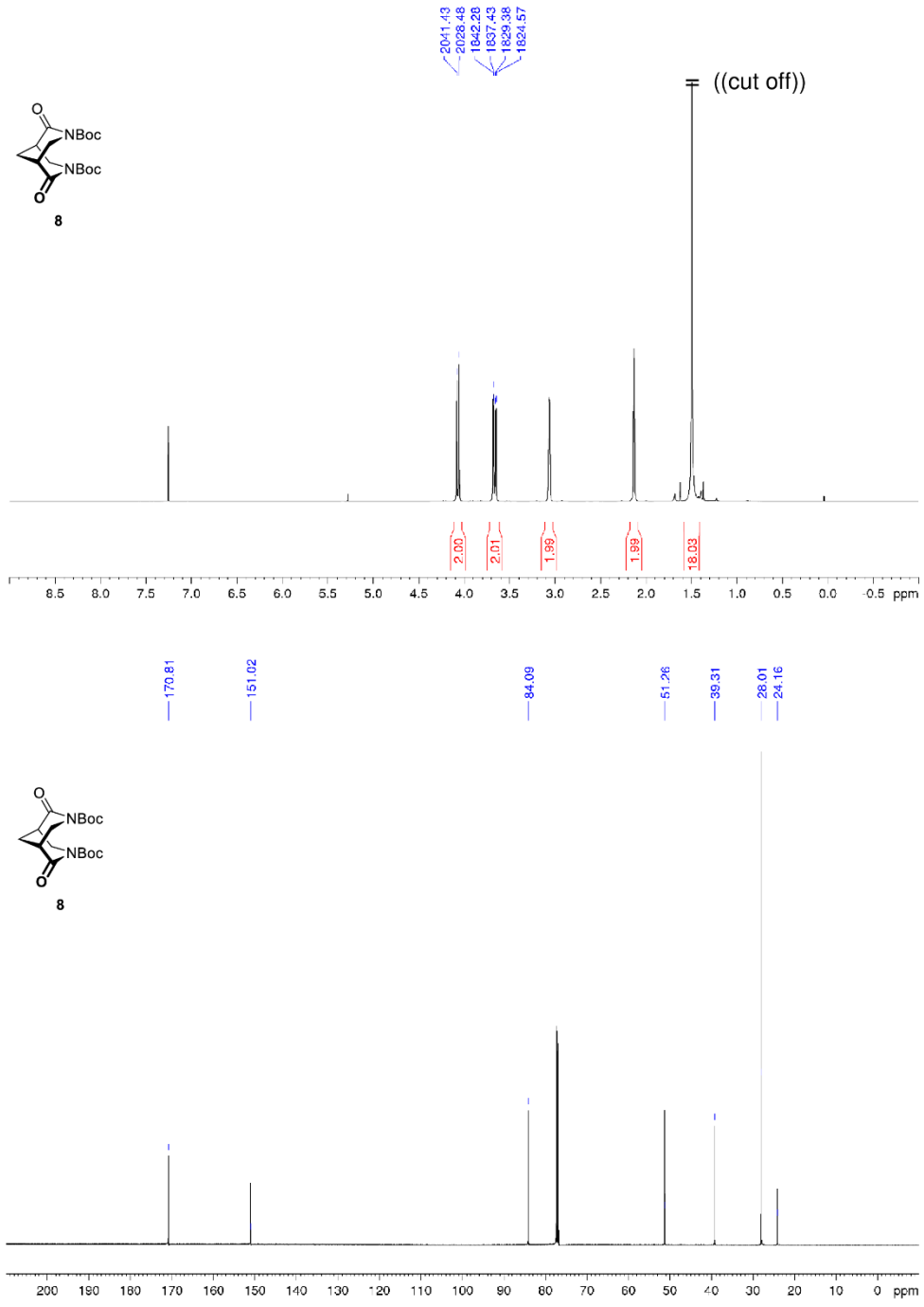

163.79
151.07
138.92
116.92
105.14
54.00
53.01
49.83
35.64
27.82
26.38
NH
N
O
cytisine (5)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

47

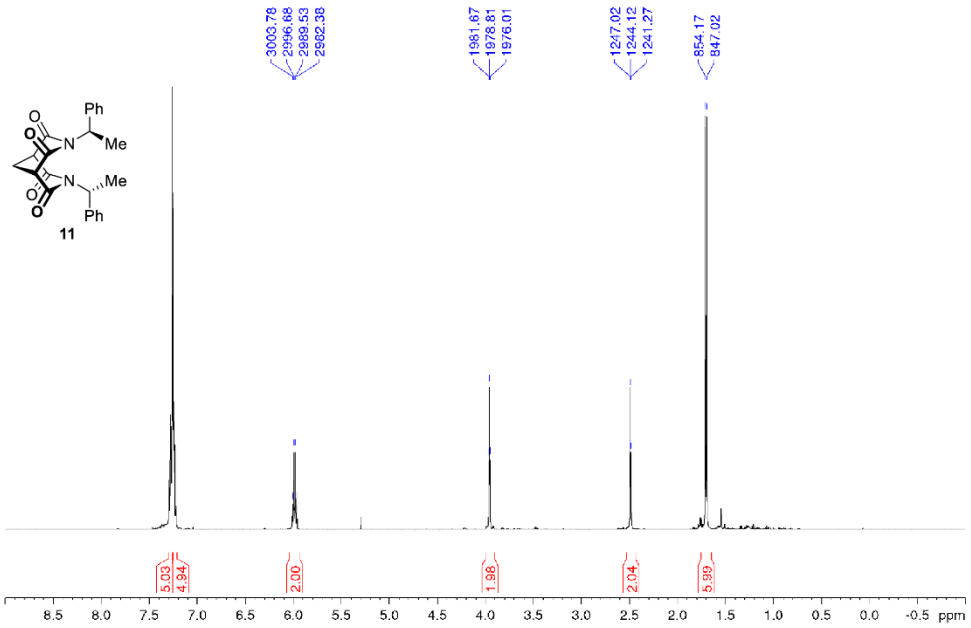

3666.55
3659.65
3657.40
3650.55
3254.40
3253.40
3245.24
3244.29
3058.60
3052.04
2289.70
2274.34
1938.05
1936.10
1934.05
1925.40
1923.45
1921.45
1916.55
1912.30
1903.89
1899.64
1885.79
1880.14
1870.39
1864.73
1125.04
1111.89
1058.58
1045.37
((cut off))
NBoc
O
N
O
7
0.97
0.95
0.98
1.00
1.99
1.03
0.99
1.00
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

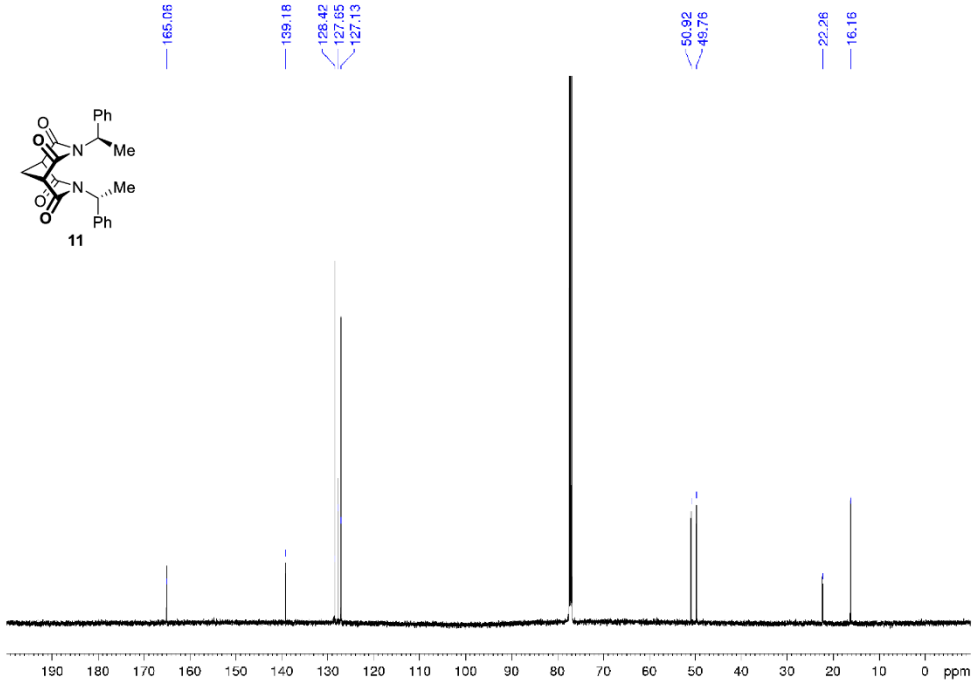

170.40
163.07
152.13
147.70
139.13
118.71
106.23
84.14
54.92
48.65
38.99
32.96
28.05
23.33
NBoc
O
N
O
7
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

48

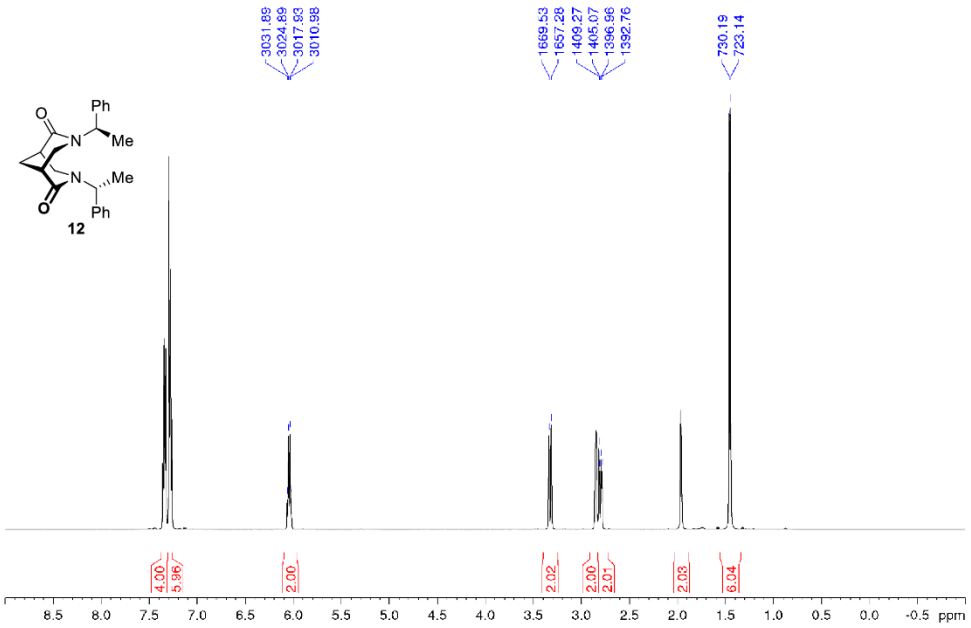

2041.43
2026.48
1842.26
1837.43
1829.38
1824.57
((cut off))
NBoc
NBoc
O
O
8
2.00
2.01
1.99
1.99
18.03
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
170.81
151.02
84.09
51.26
39.31
28.01
24.16
NBoc
NBoc
O
O
8
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

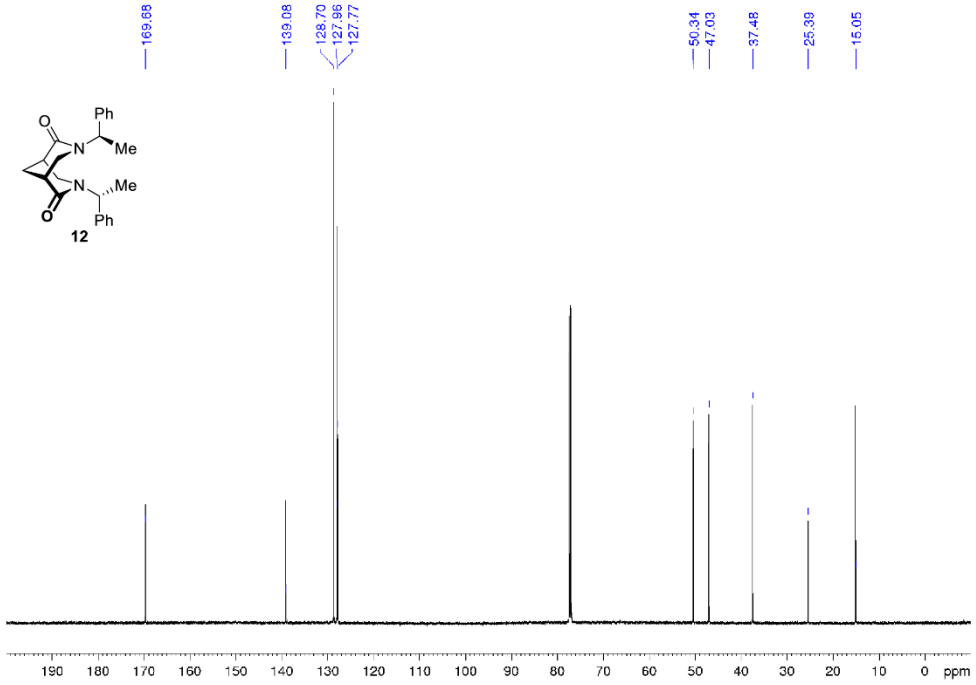
49


3003.78
2996.68
2889.53
2862.38
1981.67
1878.81
1876.01
1247.02
1244.12
1241.27
854.17
847.02
Ph
Me
Me
Ph
11
5.03
4.94
2.00
1.98
2.04
5.89
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

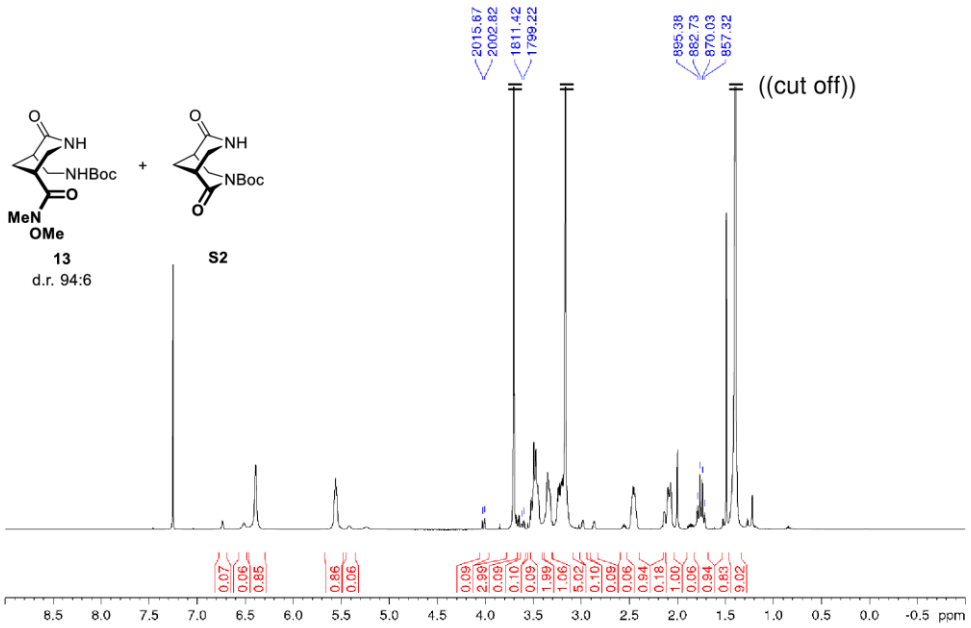

165.06
139.18
128.42
127.65
127.13
50.92
49.76
22.26
16.16
Ph
Me
Me
Ph
11
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

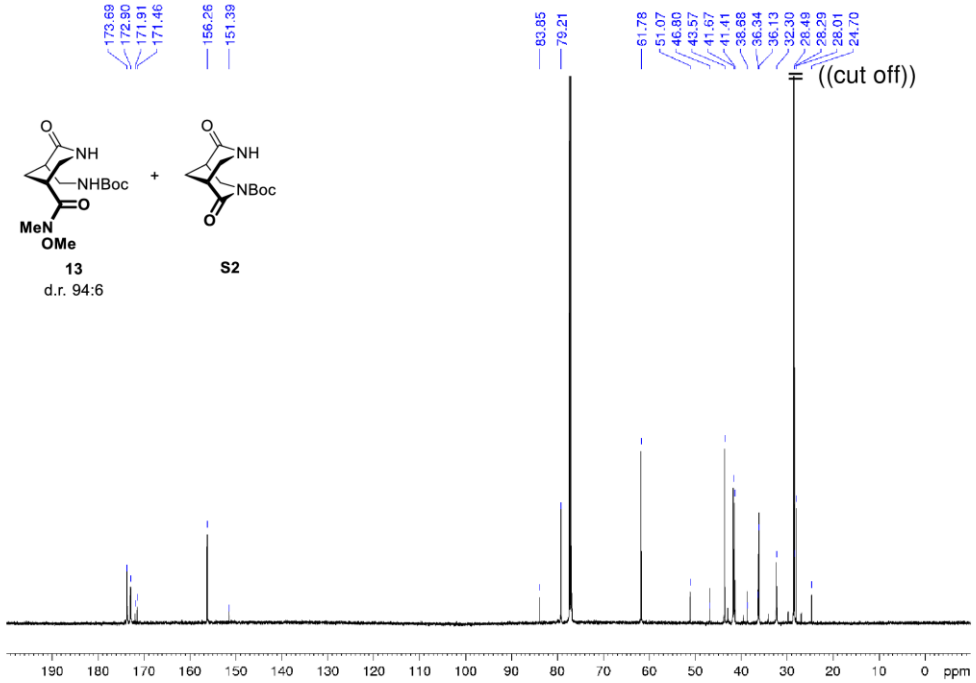
50


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
O
Me
Ph
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

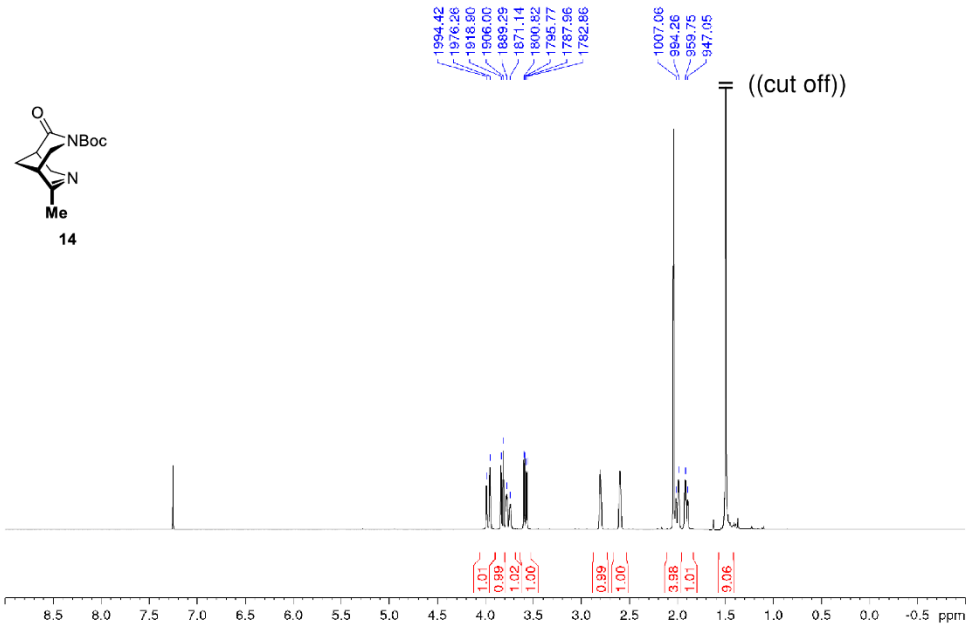

169.68
139.08
128.70
127.86
127.77
50.34
47.03
37.48
25.39
15.05
Ph
Me
N
O
Me
Ph
12
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

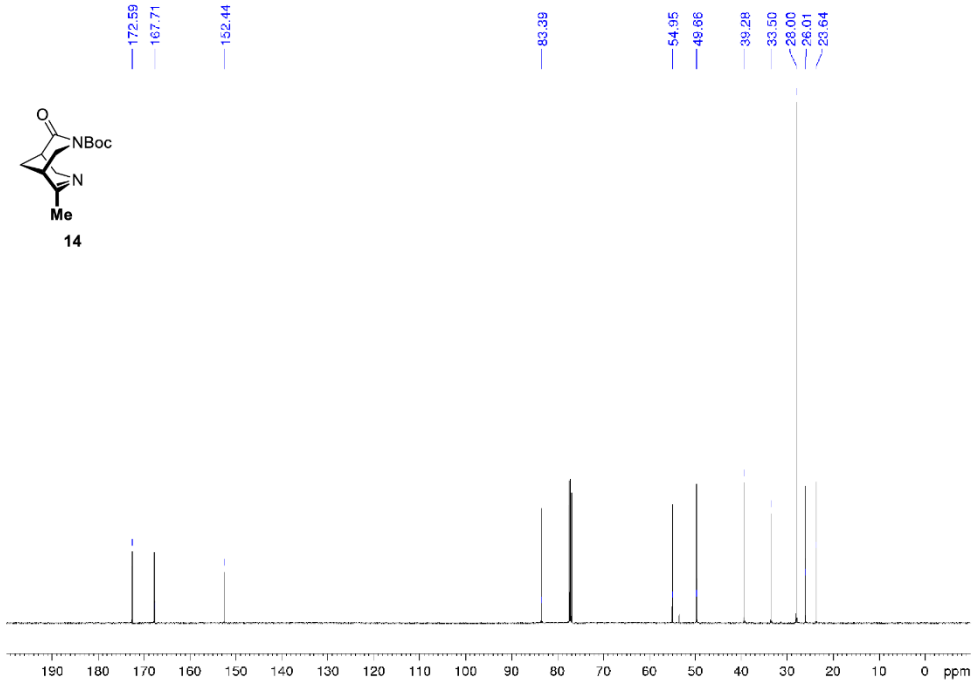
51


2015.67
2002.82
1811.42
1799.22
895.38
882.73
870.03
857.32
((cut off))
NH
NHBoc
MeN
OMe
13
d.r. 94:6
+
NH
NBoc
S2
0.07
0.06
0.85
0.66
0.06
0.09
2.99
0.09
0.10
0.09
1.89
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

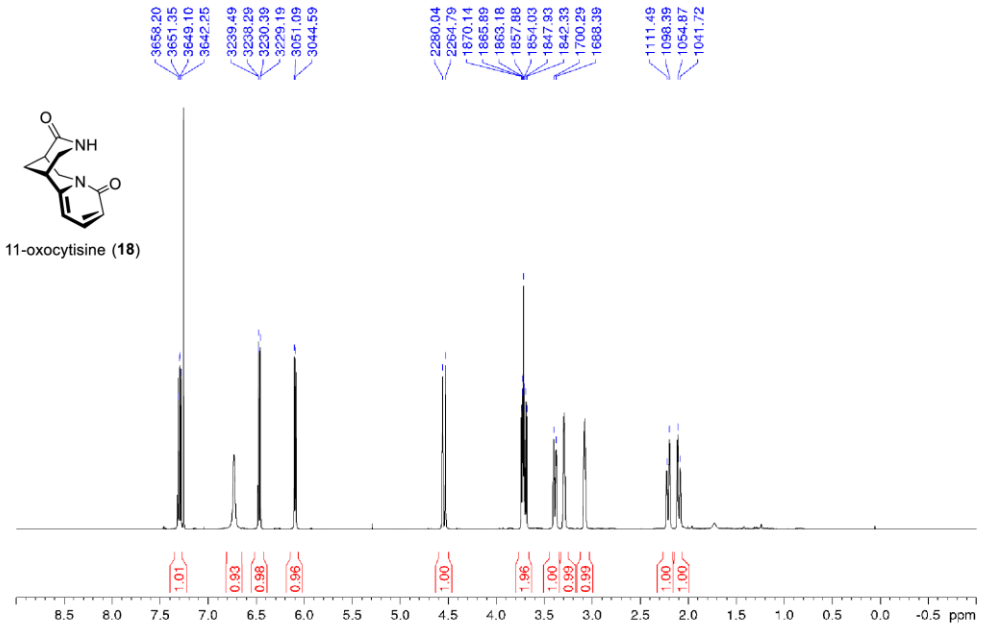

173.69
172.90
171.91
171.46
156.26
151.39
83.85
79.21
61.78
51.07
46.80
43.57
41.67
41.41
38.68
36.34
36.13
32.30
28.49
28.29
28.01
24.70
((cut off))
NH
NHBoc
MeN
OMe
13
d.r. 94:6
+
NH
NBoc
S2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

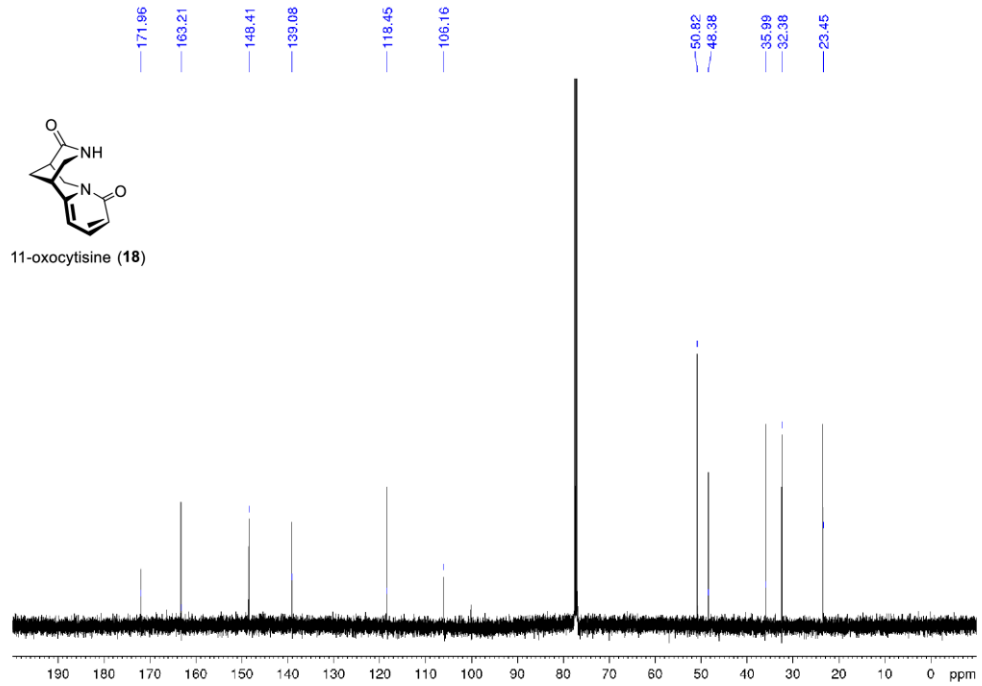
52


1994.42
1976.26
1918.80
1906.00
1889.29
1871.14
1800.82
1795.77
1787.96
1782.86
1007.06
994.26
959.75
947.05
((cut off))
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

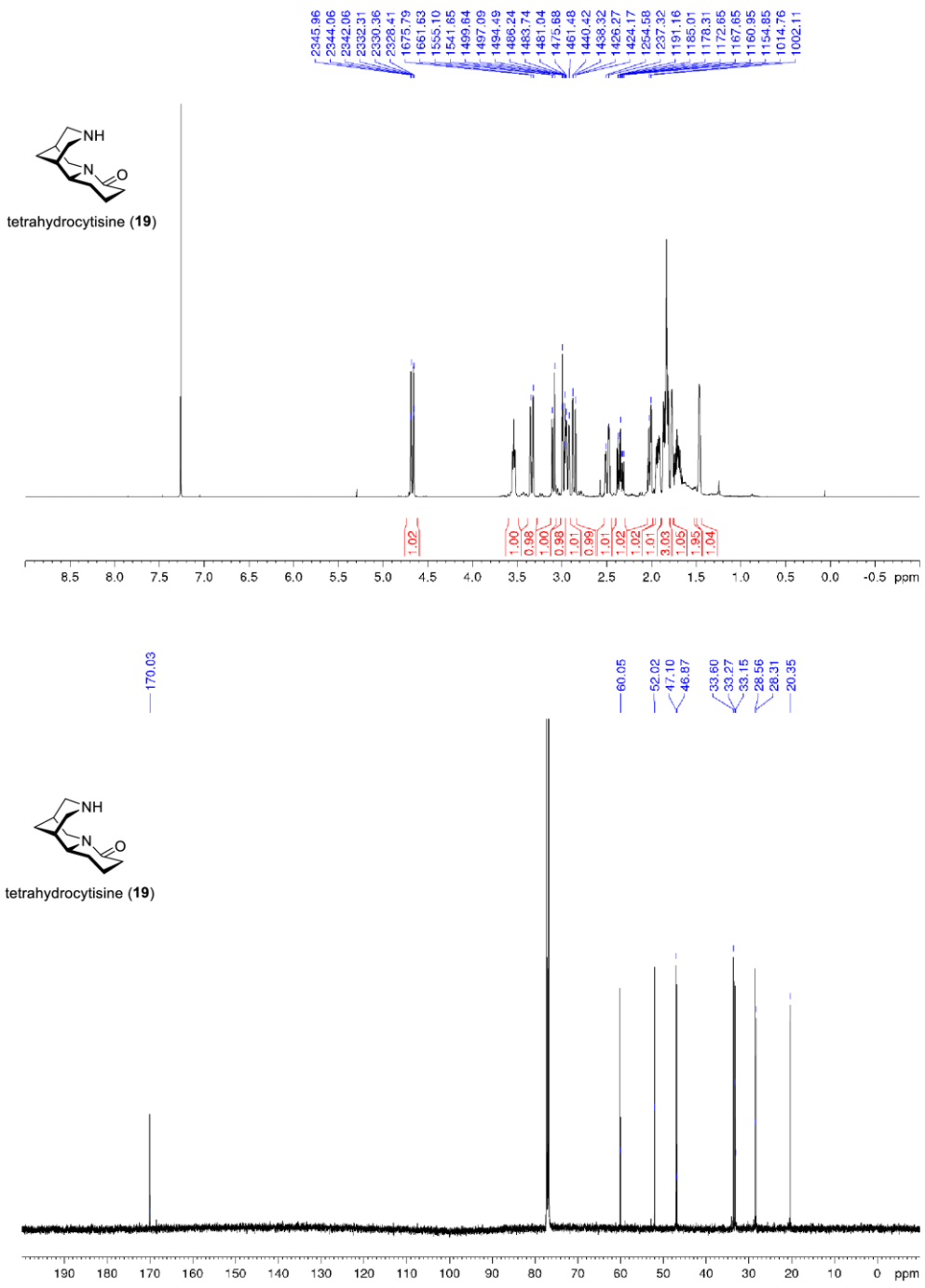

172.59
167.71
152.44
83.39
54.95
49.66
39.28
33.50
28.00
26.01
23.64
NBoc
N
Me
14
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

53

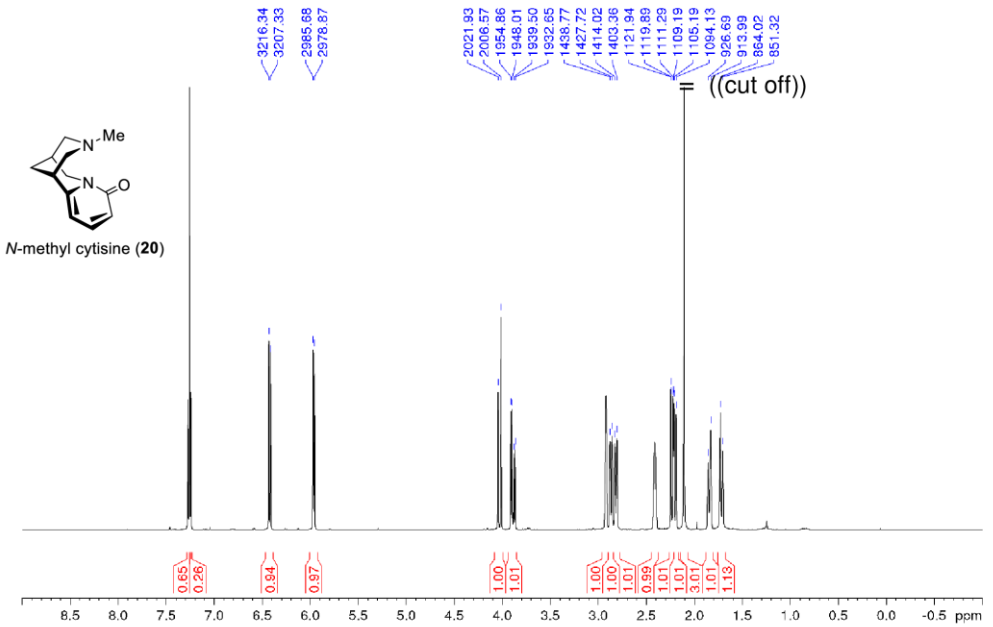

3658.20
3651.35
3649.10
3642.25
3239.49
3238.29
3230.39
3229.19
3051.09
3044.59
2280.04
2264.79
1870.14
1865.89
1863.18
1857.88
1854.03
1847.93
1842.33
1700.29
1688.39
1111.49
1098.39
1054.87
1041.72
NH
O
N
O
11-oxocytisine (18)
1.01
0.93
0.98
0.96
1.00
1.96
1.00
0.99
0.99
1.00
1.00
8.5 8.0 7.5 7.0 6.5 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

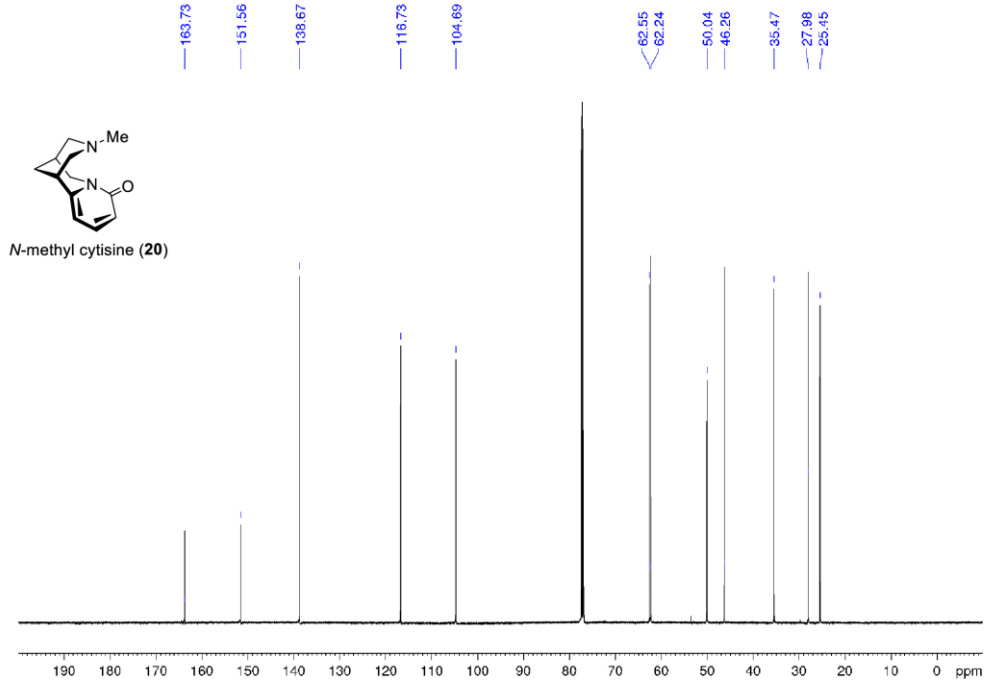

171.96
163.21
148.41
139.08
118.45
106.16
50.82
48.38
35.99
32.38
23.45
NH
O
N
O
11-oxocytisine (18)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

54

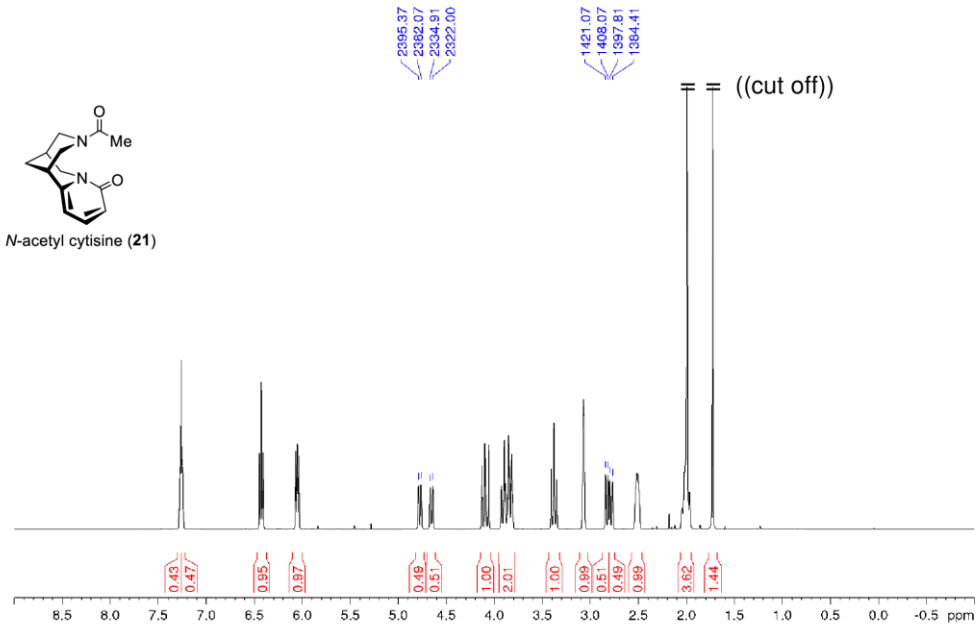

2345.96
2344.06
2342.06
2332.31
2330.36
2328.41
1675.79
1661.63
1555.10
1541.65
1499.64
1497.09
1494.49
1486.24
1483.74
1481.04
1475.88
1461.48
1440.42
1438.32
1426.27
1424.17
1254.58
1237.32
1191.16
1185.01
1178.31
1172.65
1167.65
1160.95
1154.85
1014.76
1002.11
NH
N
O
tetrahydrocytisine (19)
1.02
1.00
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

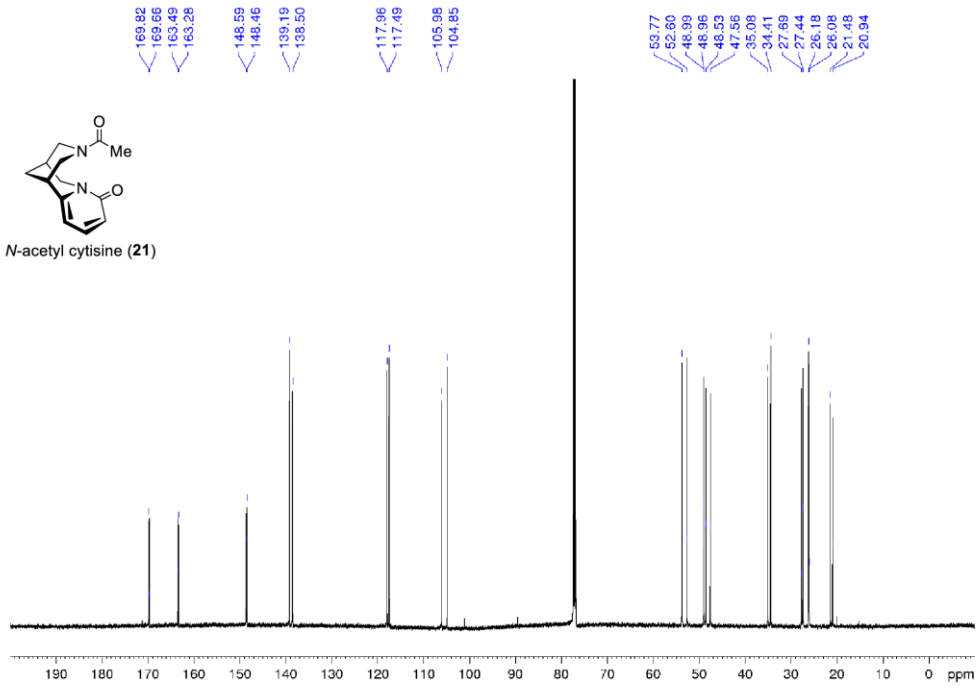
55


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))
Me
N
N
O
N-methyl cytisine (20)
0.65
0.26
0.64
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

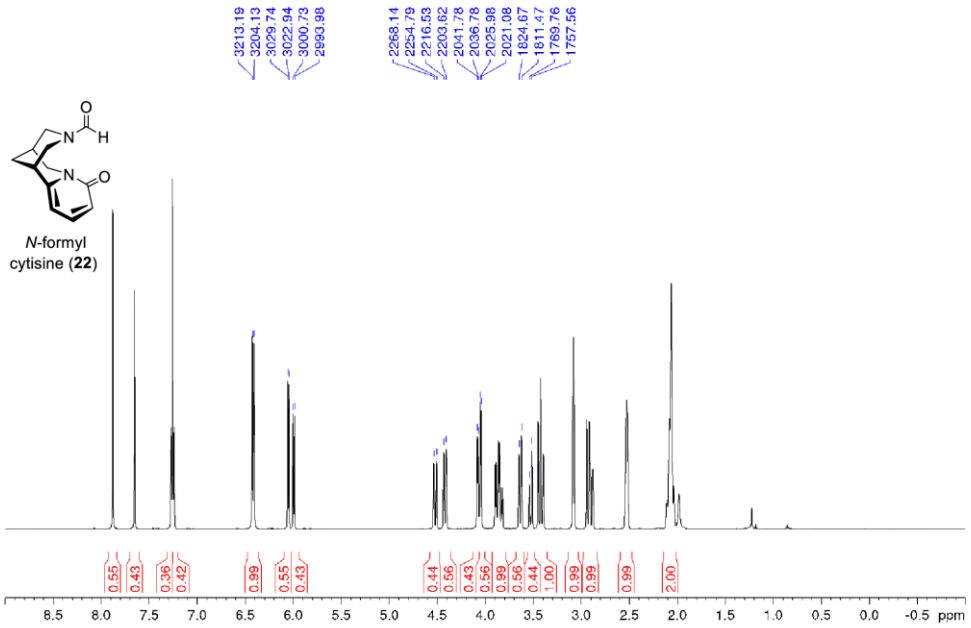

163.73
151.56
138.67
116.73
104.69
62.55
62.24
50.04
46.26
35.47
27.98
25.45
Me
N
N
O
N-methyl cytisine (20)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

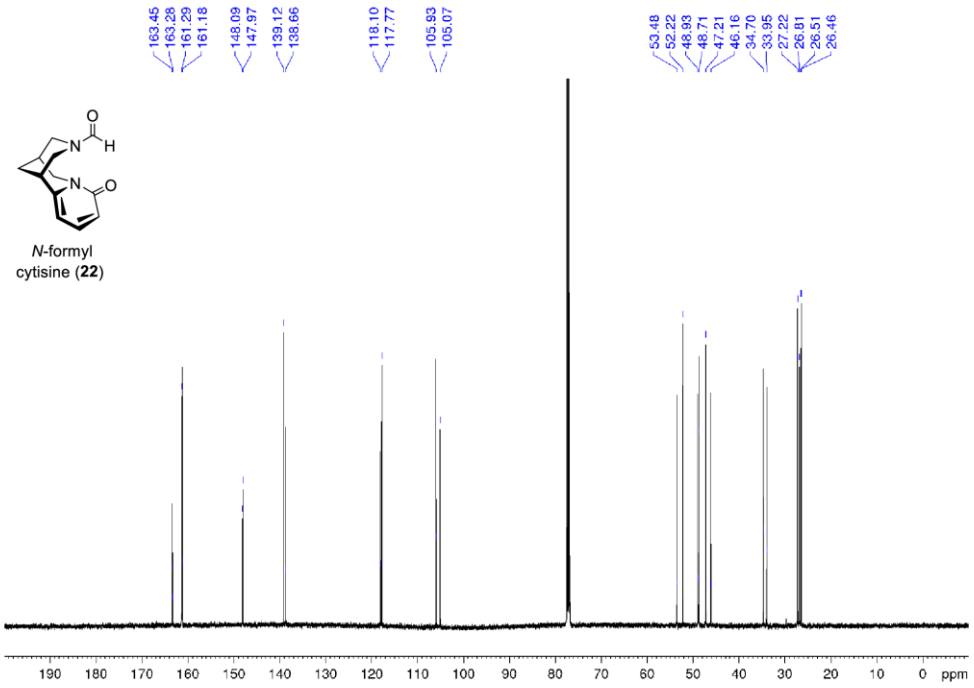
56


2395.37
2382.07
2334.91
2322.00
1421.07
1408.07
1397.81
1384.41
((cut off))
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
0.89
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

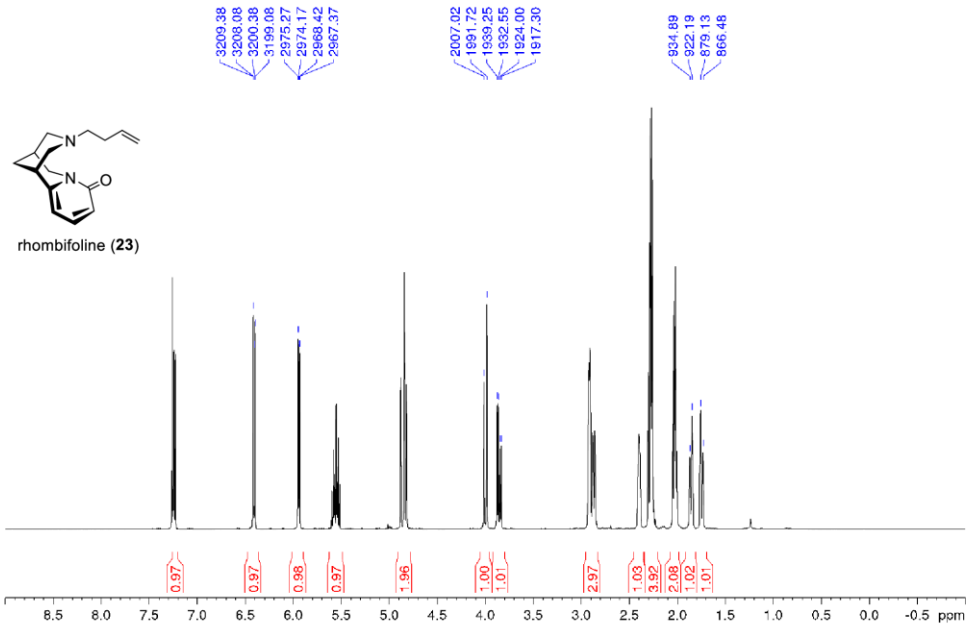

169.82
169.66
163.49
163.28
148.59
148.46
139.19
138.50
117.96
117.49
105.98
104.85
53.77
52.60
48.99
48.96
48.53
47.56
35.08
34.41
27.69
27.44
26.18
26.08
21.48
20.94
N-acetyl cytisine (21)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

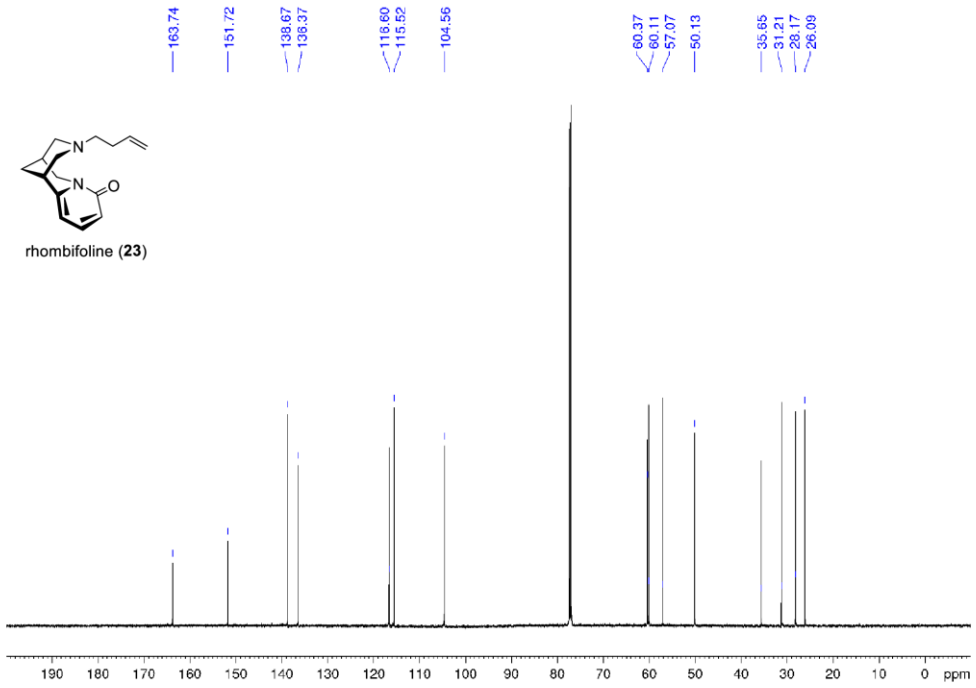
57


3213.19
3204.13
3099.74
3022.94
3000.73
2893.98
2268.14
2254.79
2216.53
2203.62
2041.78
2036.78
2025.98
2021.08
1824.67
1811.47
1769.76
1757.56
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

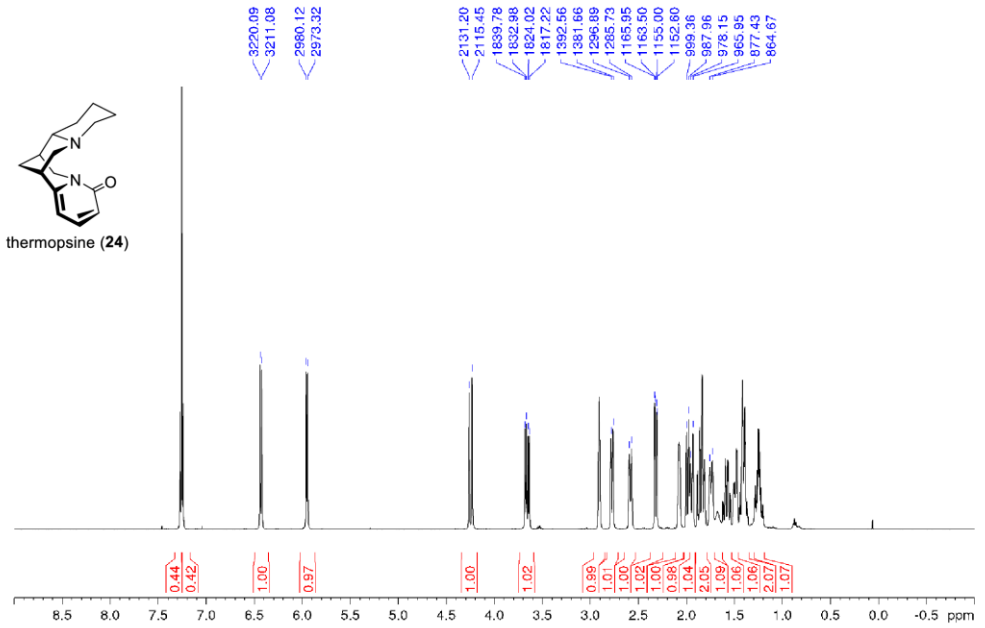

163.45
163.28
161.29
161.18
148.09
147.97
139.12
138.66
118.10
117.77
105.93
105.07
53.48
52.22
48.93
48.71
47.21
46.16
34.70
33.95
27.22
26.81
26.51
26.46
N-formyl
cytisine (22)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

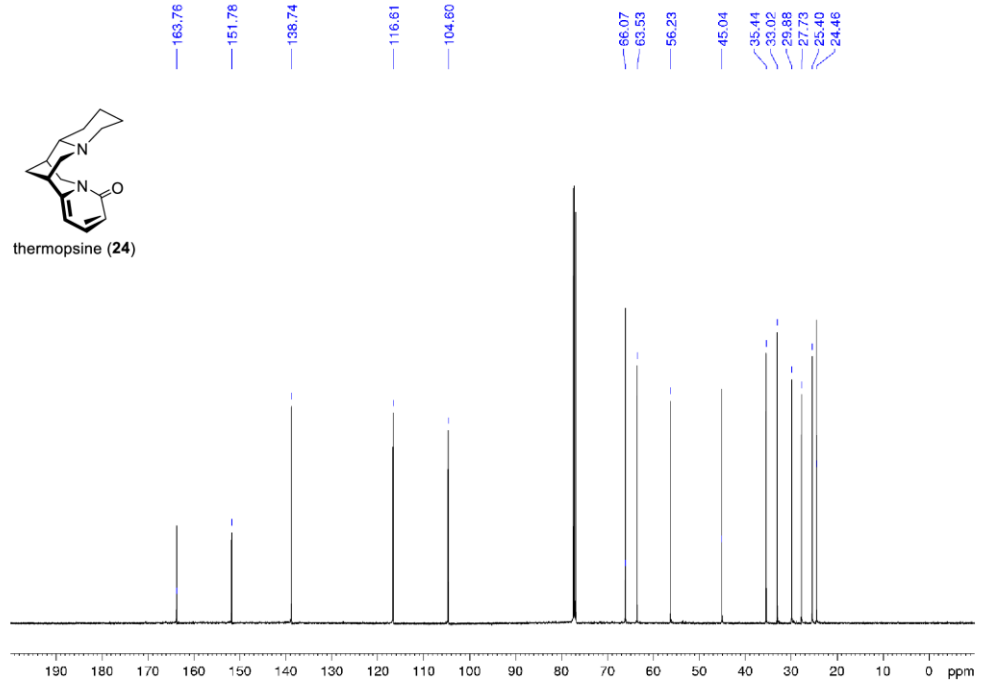
58


3209.38
3208.08
3200.38
3199.08
2975.27
2974.17
2868.42
2867.37
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

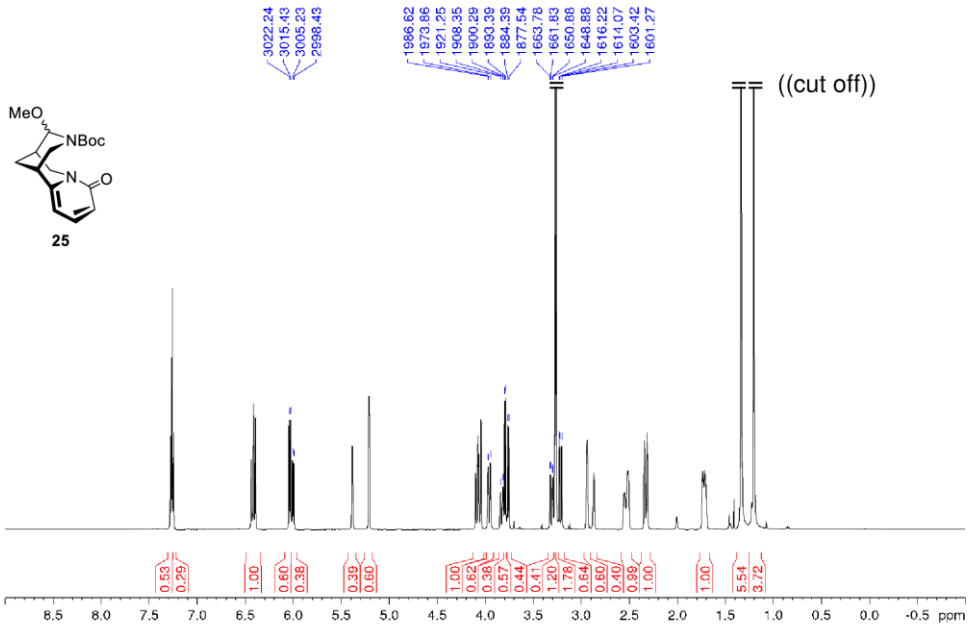

163.74
151.72
138.67
138.37
116.60
115.52
104.56
60.37
60.11
57.07
50.13
35.65
31.21
28.17
26.09
rhombifoline (23)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

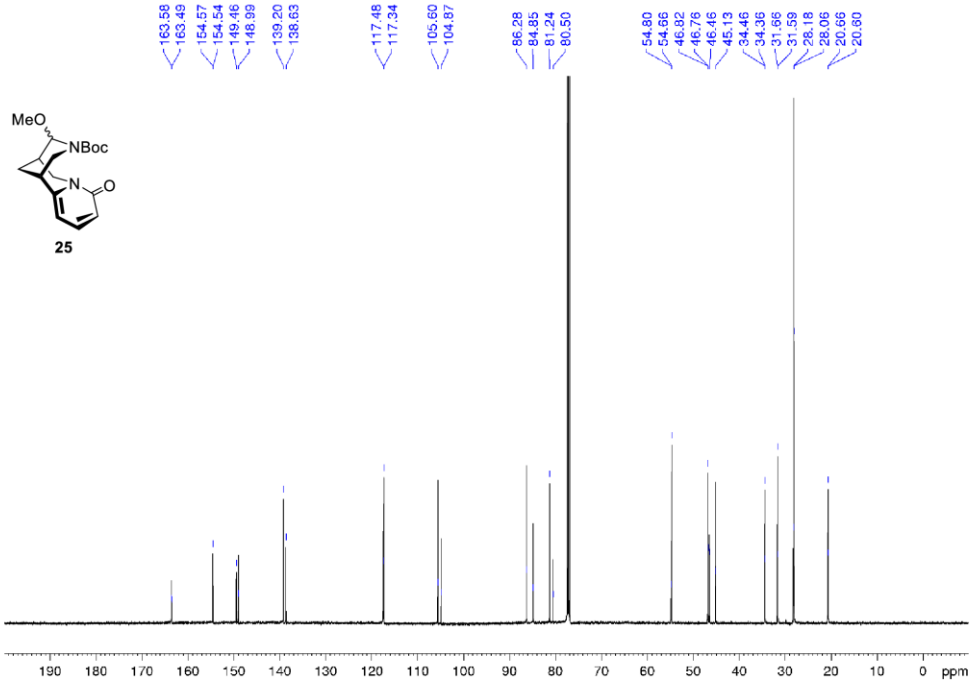
59


3220.09
3211.08
2980.12
2973.32
2131.20
2115.45
1839.78
1632.98
1624.02
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
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

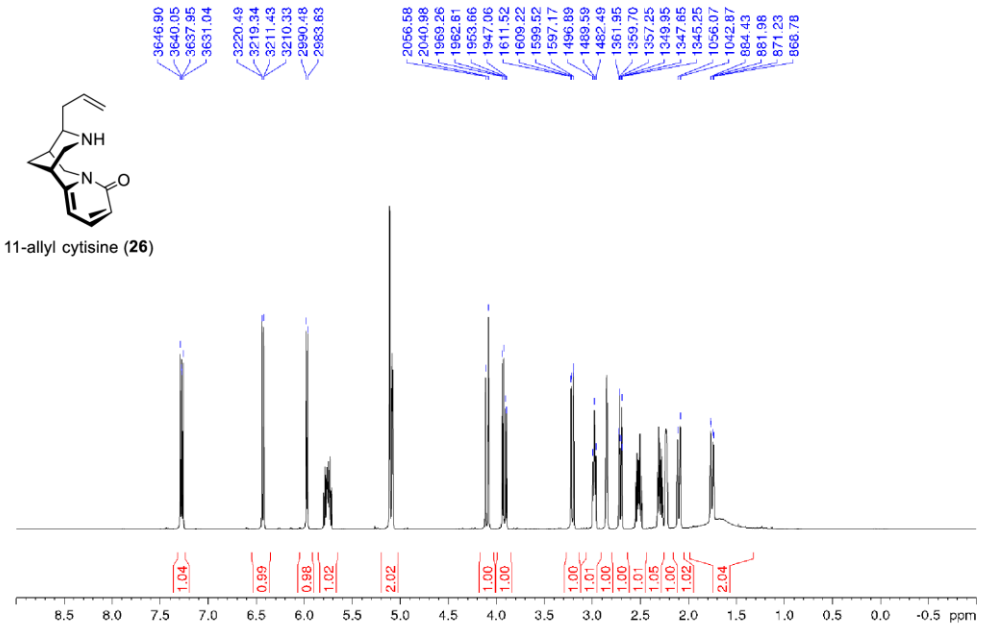

163.76
151.78
138.74
116.61
104.60
66.07
63.53
56.23
45.04
35.44
33.02
29.88
27.73
25.40
24.46
thermopsine (24)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

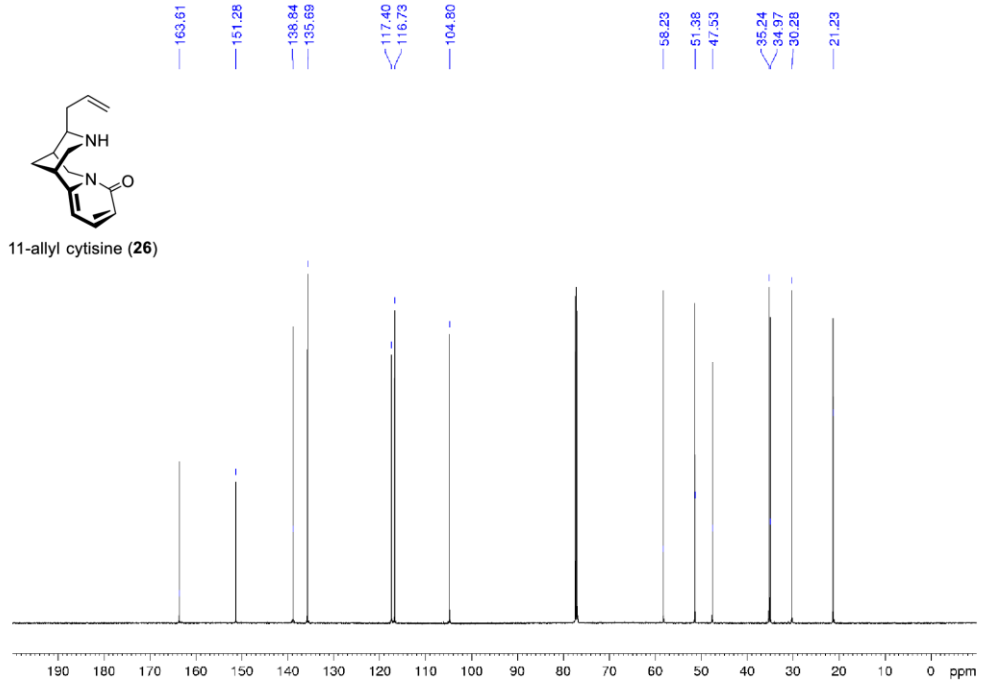
60


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
0.39
0.57
0.44
0.41
1.20
1.78
0.64
0.59
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

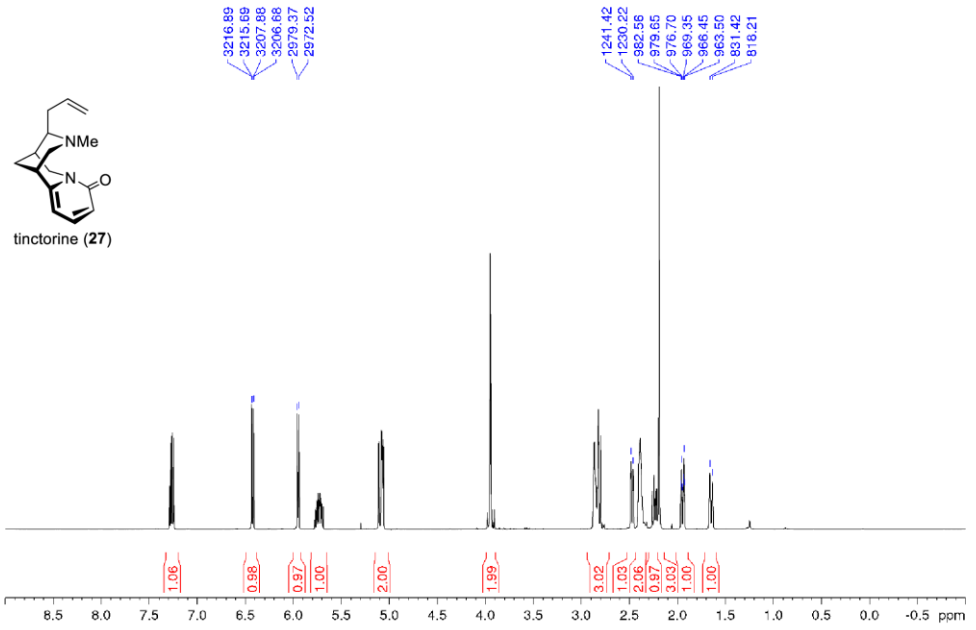

163.58
163.49
154.57
154.54
149.46
148.99
139.20
138.63
117.48
117.34
105.60
104.87
86.28
84.85
81.24
80.50
54.80
54.66
46.82
46.76
46.46
45.13
34.46
34.36
31.66
31.59
28.18
28.06
20.66
20.60
MeO
NBoc
N
O
25
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

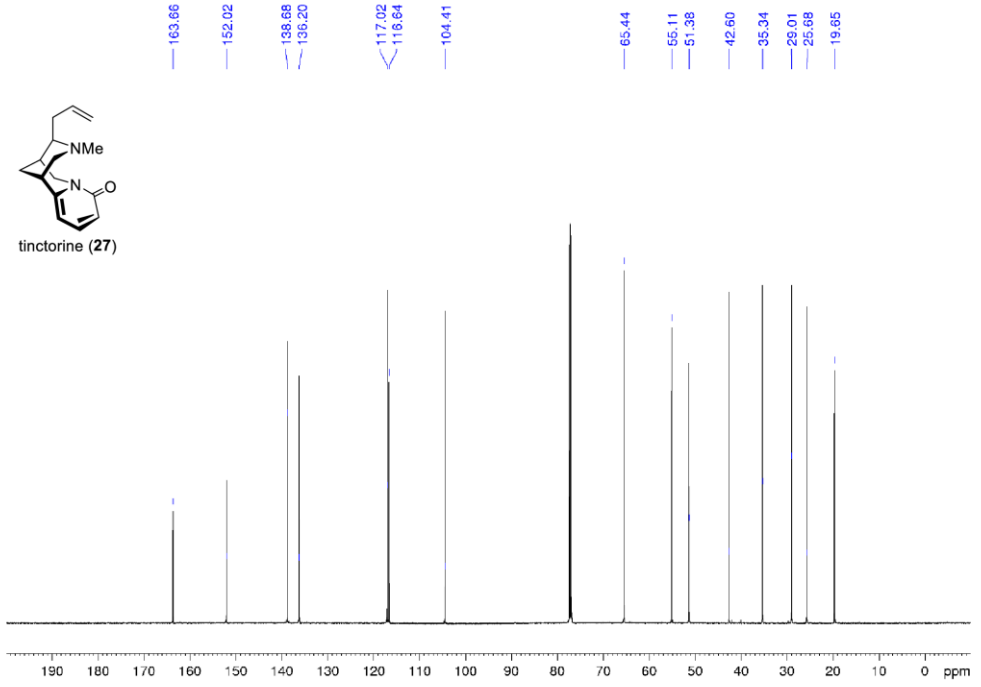
61


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
11-allyl cytisine (26)
1.04
0.99
0.98
1.02
2.02
1.00
1.00
1.00
1.01
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

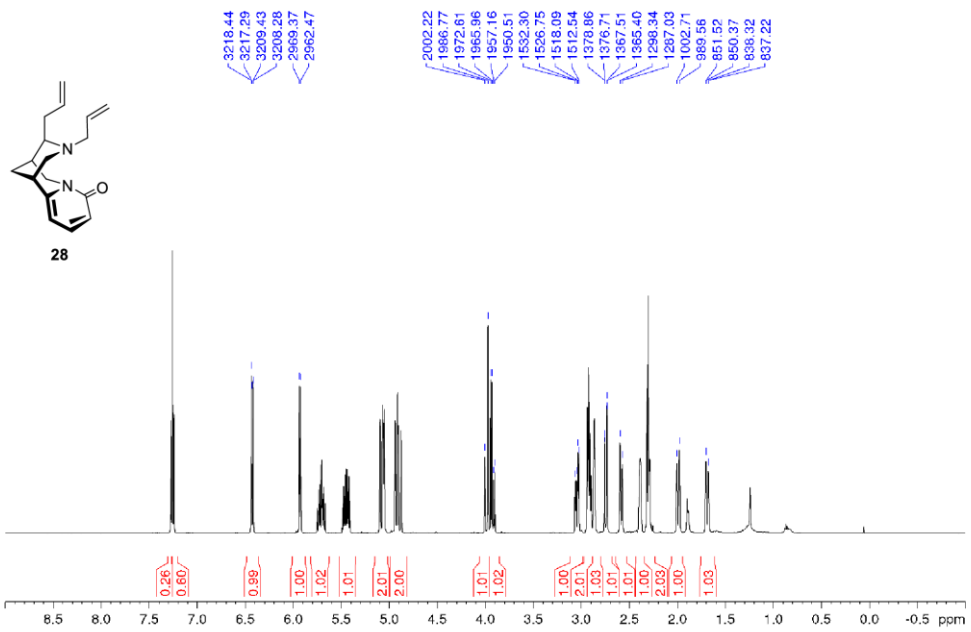

163.61
151.28
138.84
135.69
117.40
116.73
104.80
58.23
51.38
47.53
35.24
34.97
30.28
21.23
NH
N
O
11-allyl cytisine (26)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

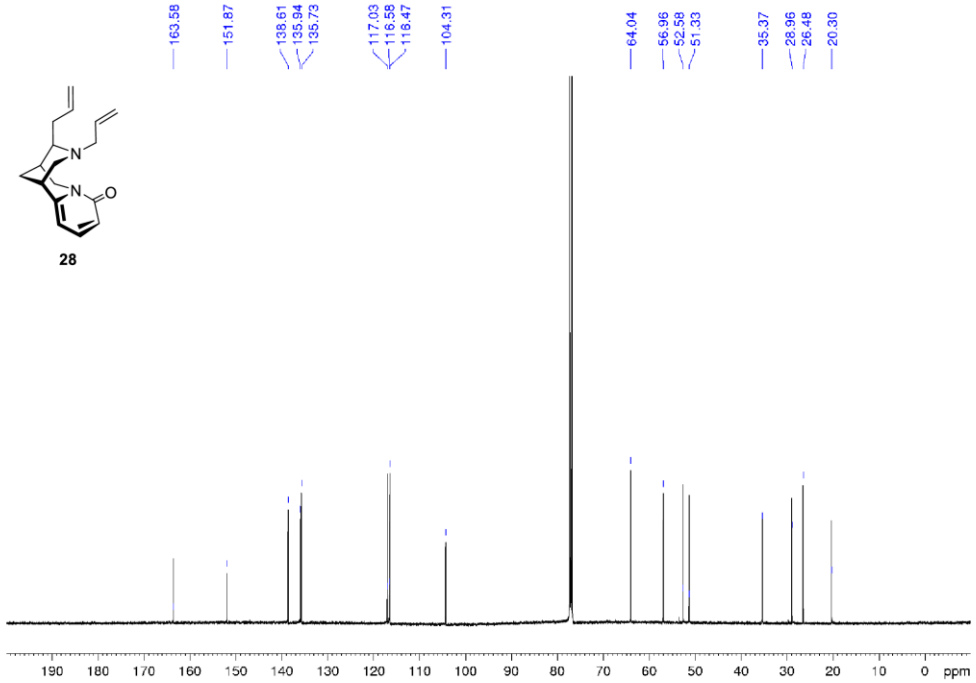
62


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

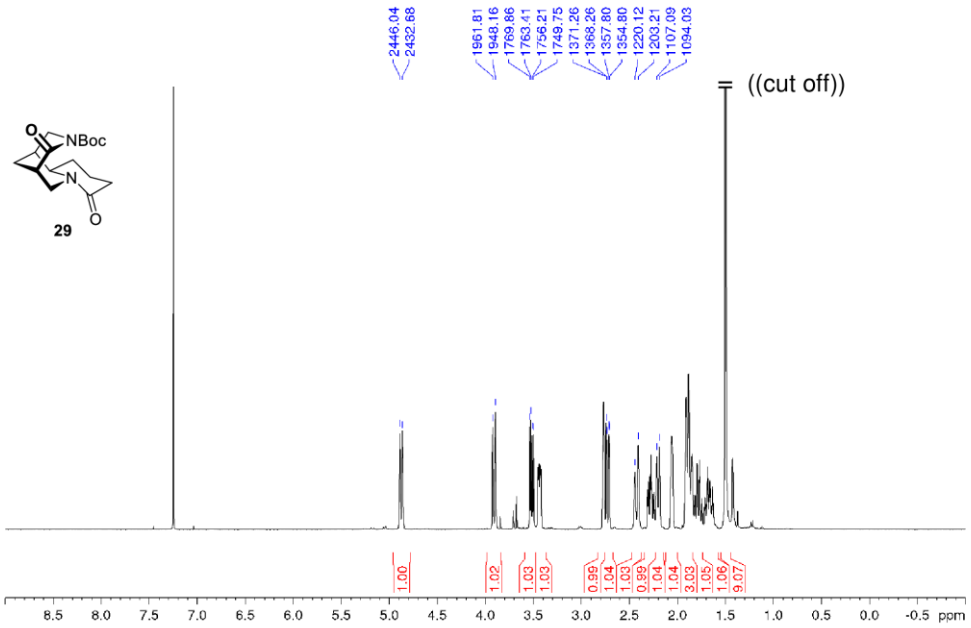

163.66
152.02
138.68
136.20
117.02
118.64
104.41
65.44
55.11
51.38
42.60
35.34
29.01
25.68
19.65
NMe
N
O
tinctorine (27)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

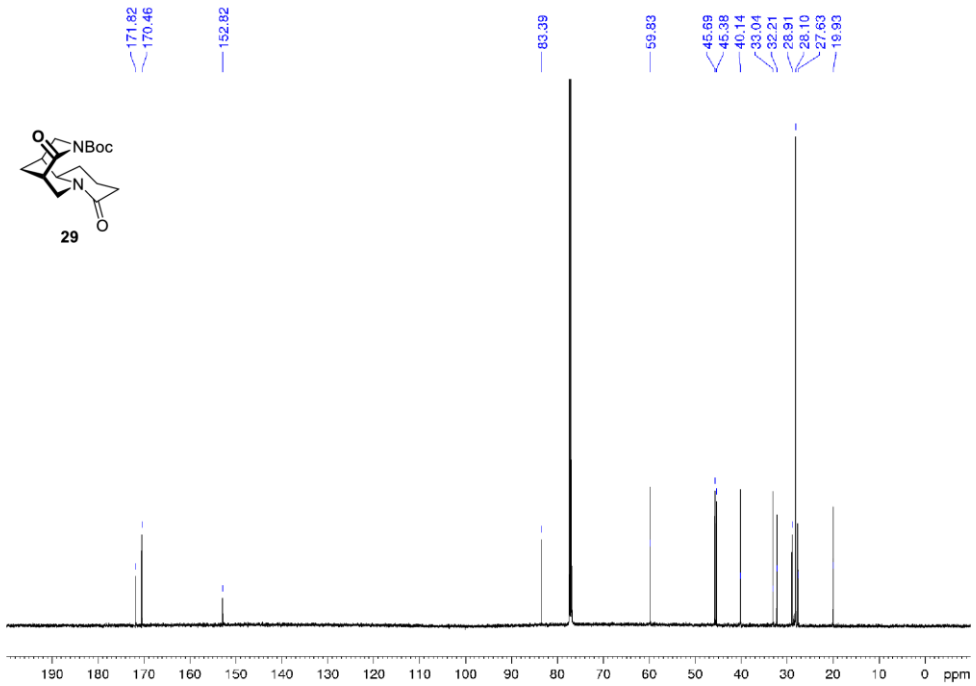
63


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

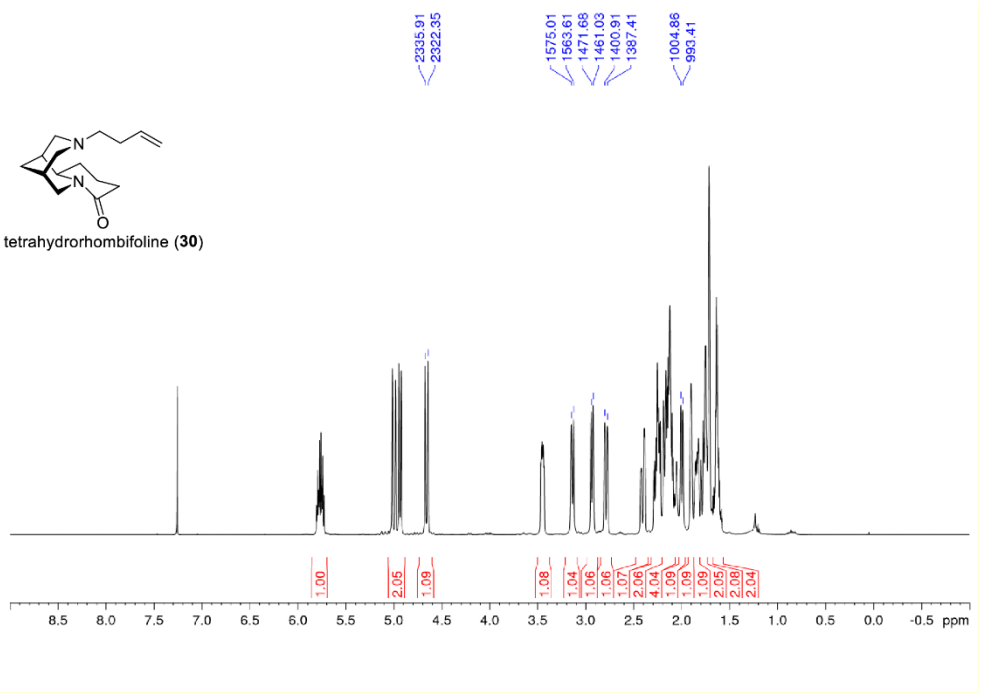

163.58
151.87
138.61
135.94
135.73
117.03
116.58
118.47
104.31
64.04
56.96
52.58
51.33
35.37
28.96
26.48
20.30
28
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

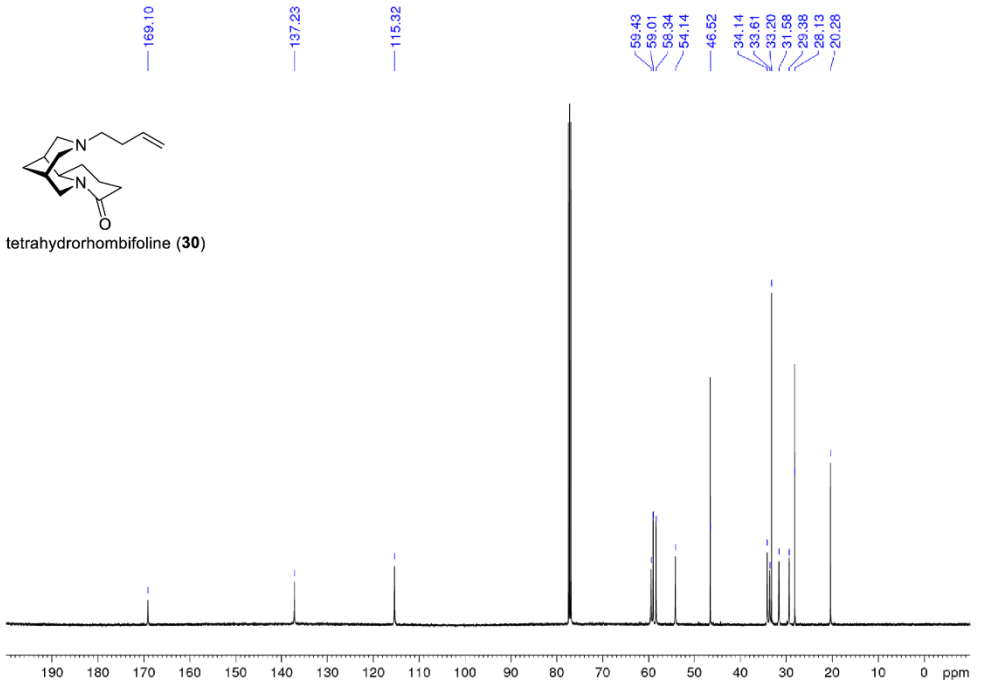
64


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
29
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

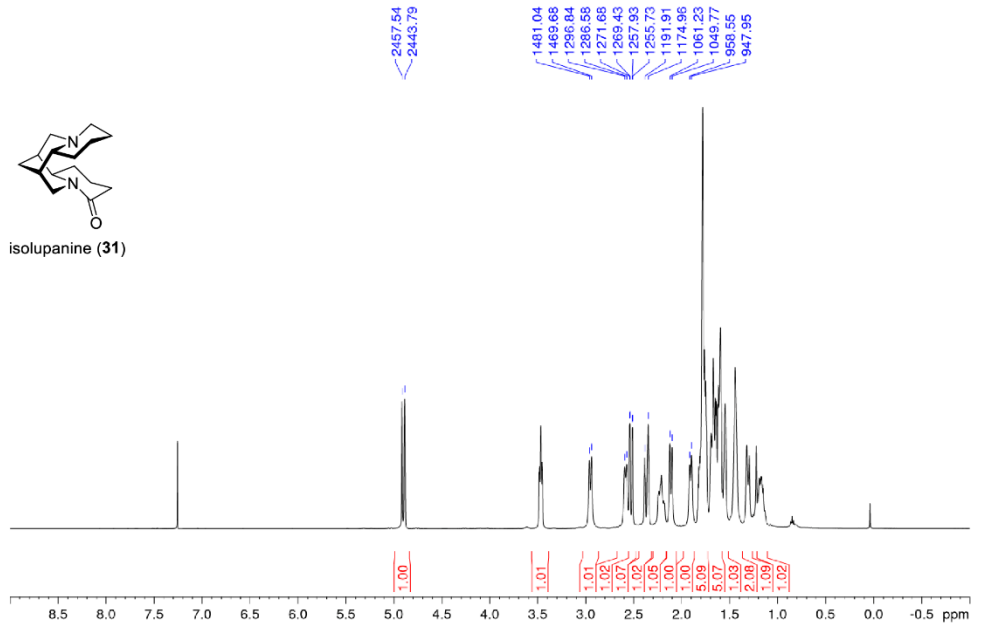

171.82
170.46
152.82
83.39
59.83
45.69
45.38
40.14
33.04
32.21
28.91
28.10
27.63
19.93
NBoc
N
O
29
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

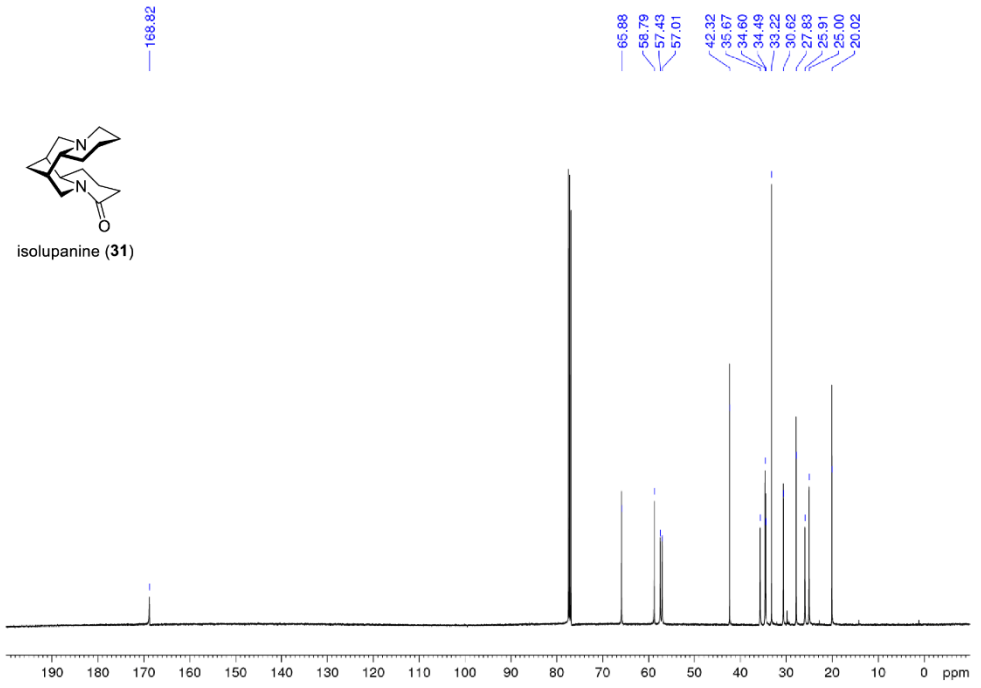
65


2335.91
2322.35
1575.01
1563.61
1471.68
1461.03
1400.91
1387.41
1004.86
993.41
tetrahydrorhombifoline (30)
1.00
2.05
1.09
1.08
1.04
1.06
1.06
1.07
2.06
4.04
1.09
1.09
1.09
2.05
2.08
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

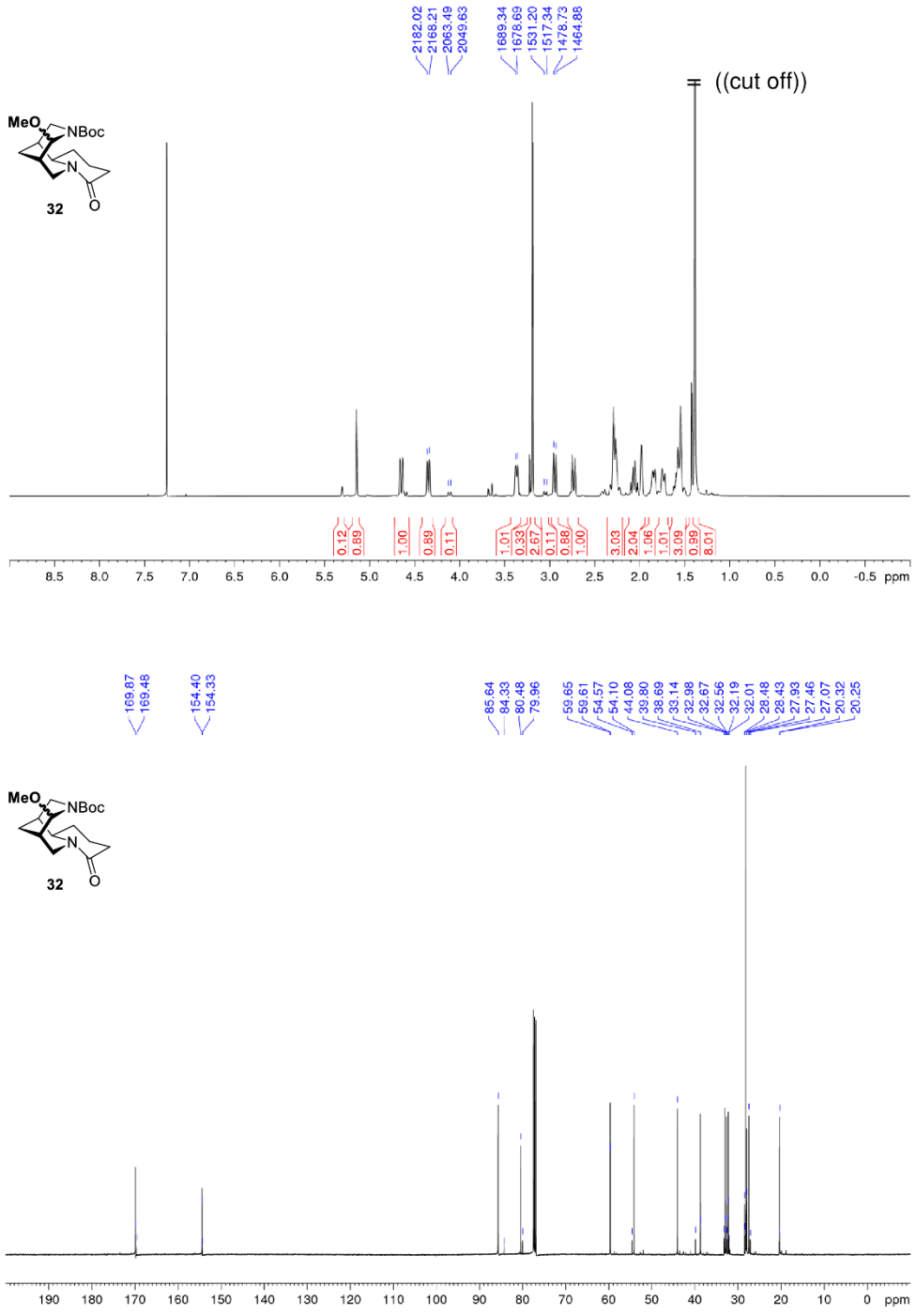

169.10
137.23
115.32
59.43
59.01
58.34
54.14
46.52
34.14
33.61
33.20
31.58
29.38
28.13
20.28
tetrahydrorhombifoline (30)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

66

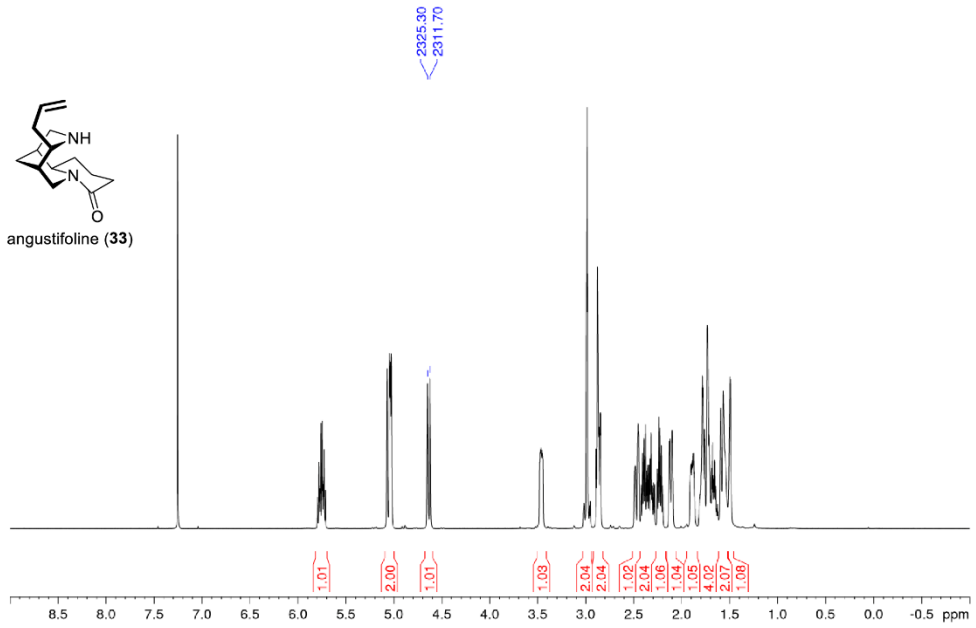

2457.54
2443.79
1481.04
1469.68
1296.84
1286.58
1271.68
1263.43
1257.93
1255.73
1191.91
1174.96
1061.23
1049.77
958.55
947.95
isolupanine (31)
1.00
1.01
1.01
1.02
1.07
1.02
1.05
1.00
1.00
5.09
5.07
1.03
2.06
1.09
1.02
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

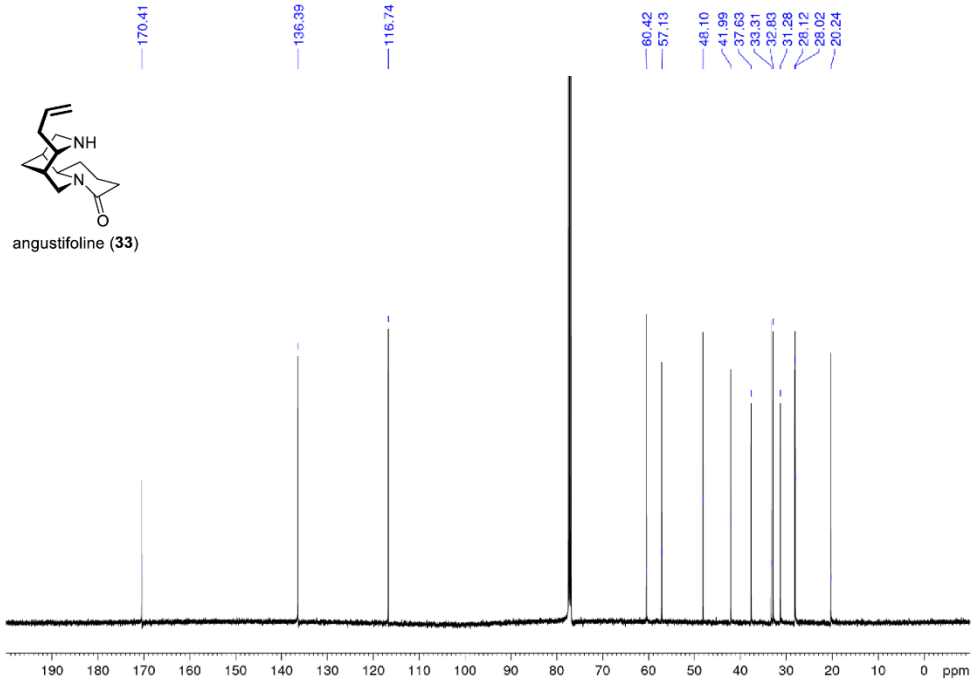

168.82
65.88
58.79
57.43
57.01
42.32
35.67
34.60
34.49
33.22
30.62
27.83
25.91
25.00
20.02
isolupanine (31)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

67

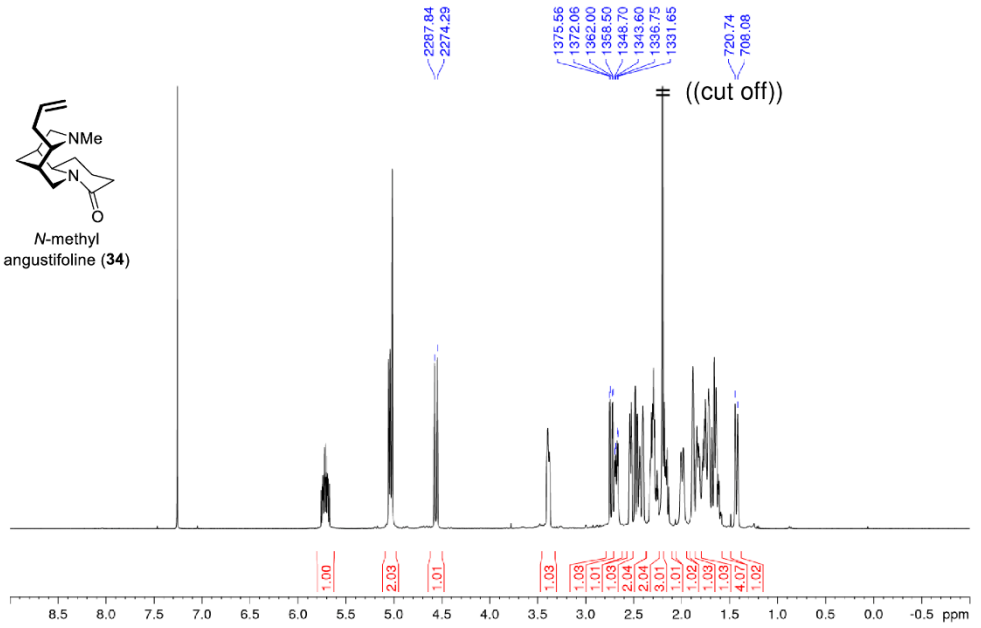

2182.02
2168.21
2063.49
2049.63
1689.34
1678.69
1531.20
1517.34
1478.73
1464.88
= ((cut off))
MeO
NBoc
N
O
32
0.12
0.89
1.00
0.89
0.11
1.01
0.33
2.67
0.11
0.88
1.00
3.03
2.04
1.06
1.01
3.09
0.99
8.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
169.87
169.48
154.40
154.33
85.64
84.33
80.48
79.96
59.65
59.61
54.57
54.10
44.08
39.80
38.69
33.14
32.98
32.67
32.56
32.19
32.01
28.48
28.43
27.93
27.46
27.07
20.32
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

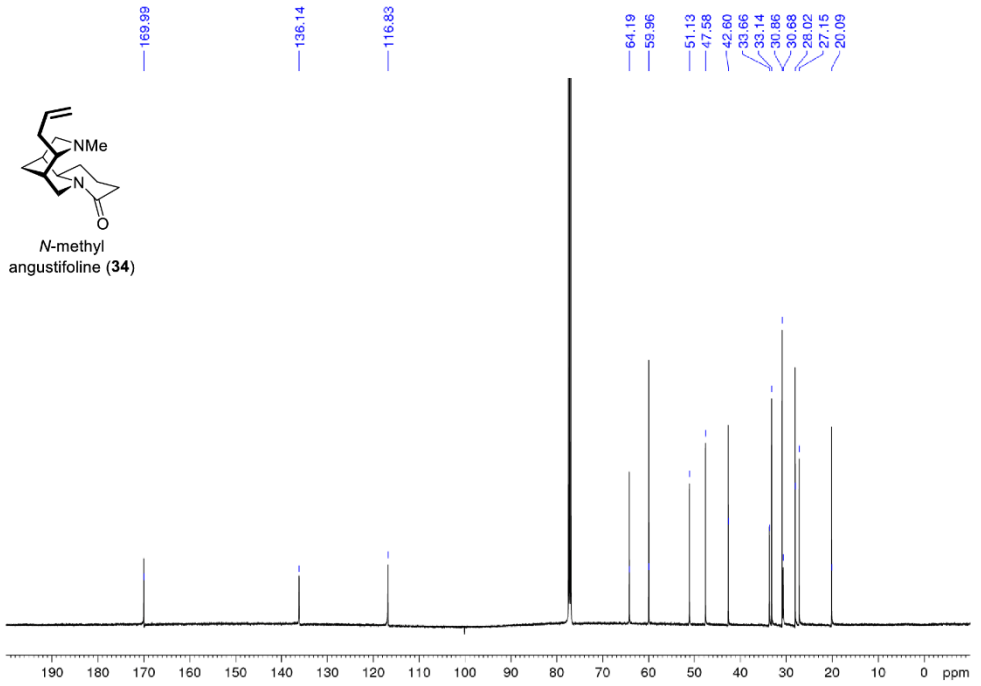
68


2325.30
2311.70
NH
N
O
angustifoline (33)
1.01
2.00
1.01
1.03
2.04
2.04
1.02
2.04
1.06
1.04
1.05
4.02
2.07
1.08
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

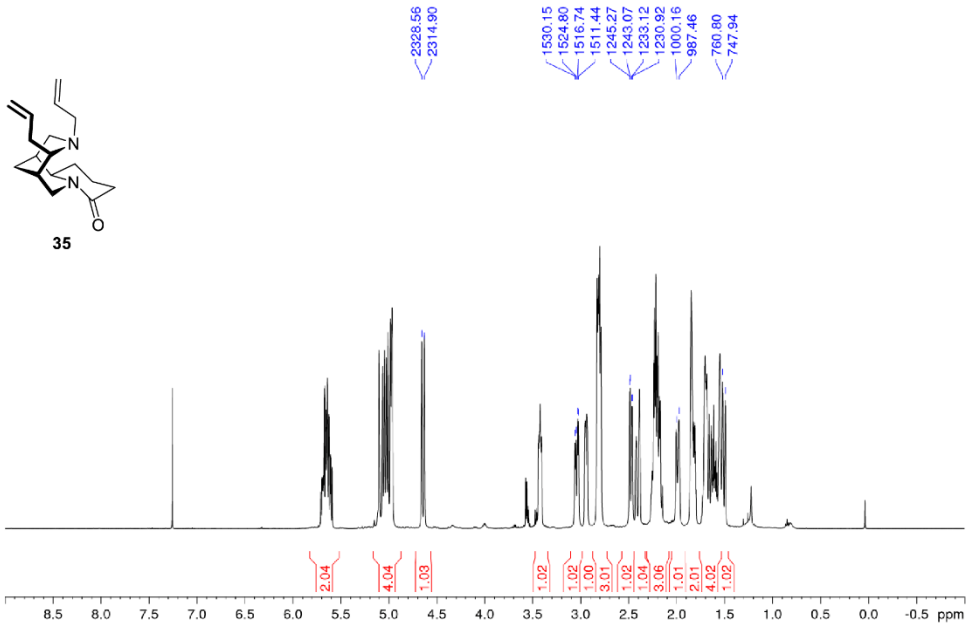

170.41
136.39
116.74
60.42
57.13
48.10
41.99
37.63
33.31
32.83
31.28
28.12
28.02
20.24
NH
N
O
angustifoline (33)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

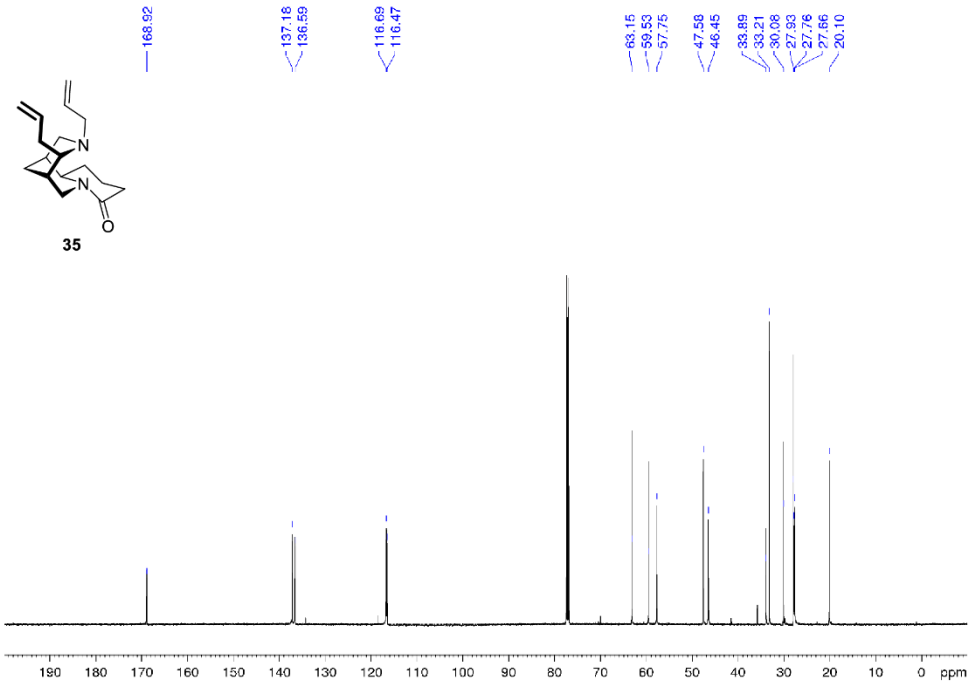
69


2287.84
2274.29
1375.56
1372.06
1362.00
1358.50
1348.70
1343.60
1336.75
1331.65
720.74
708.08
((cut off))
NMe
N
O
N-methyl
angustifoline (**34**)
1.00
2.03
1.01
1.03
1.03
1.01
1.03
2.04
2.04
3.01
1.01
1.02
1.03
1.03
4.07
1.02
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

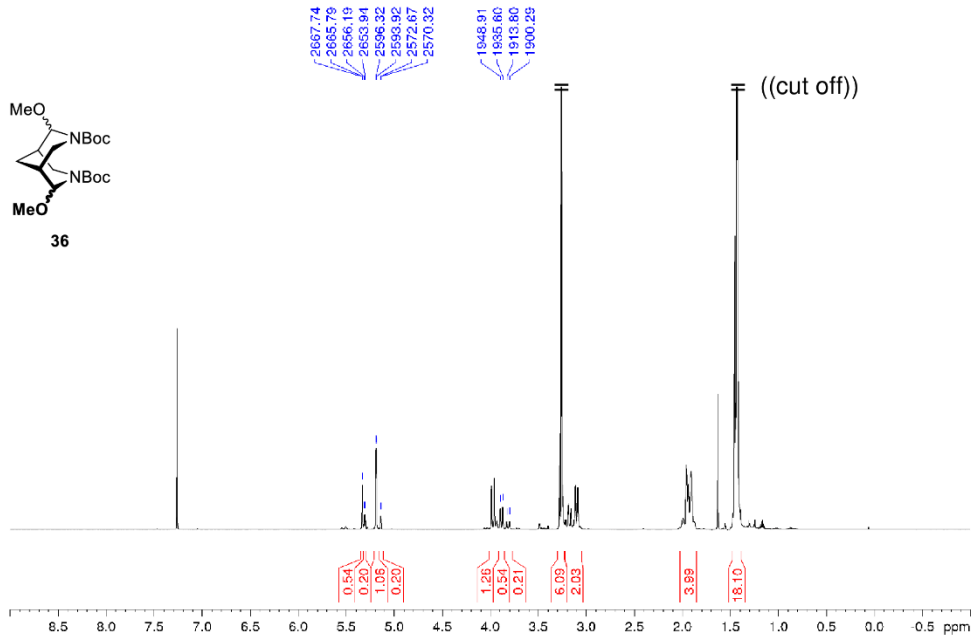

169.99
136.14
116.83
64.19
59.96
51.13
47.58
42.60
33.66
33.14
30.86
30.68
28.02
27.15
20.09
NMe
N
O
N-methyl
angustifoline (**34**)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

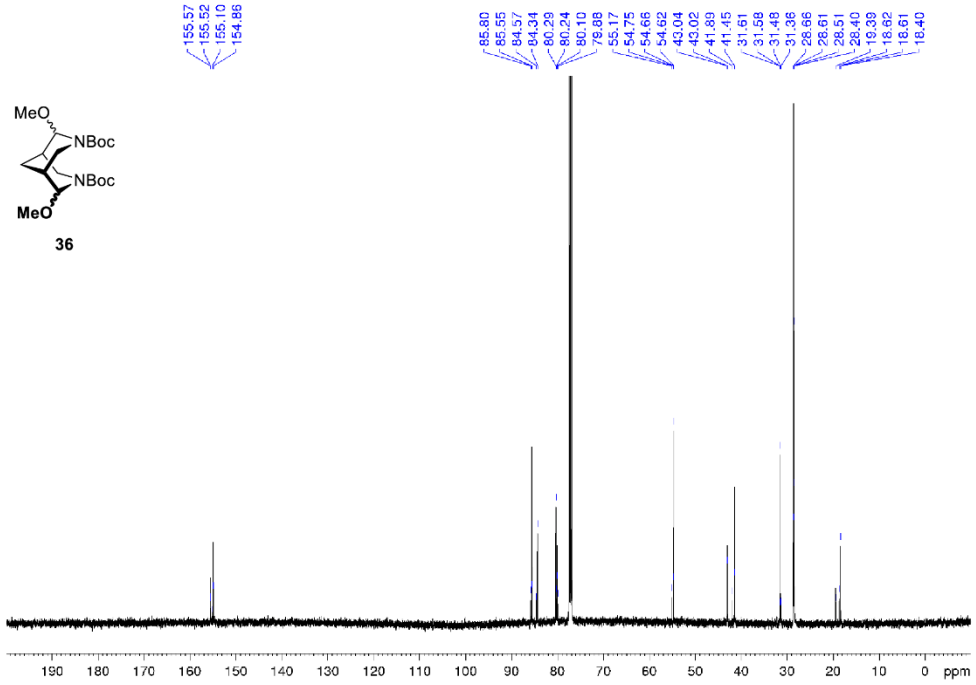
70


2328.56
2314.90
1530.15
1524.80
1516.74
1511.44
1245.27
1243.07
1233.12
1230.92
1000.16
987.46
760.80
747.94
35
2.04
4.04
1.03
1.02
1.02
1.00
3.01
1.02
1.04
3.06
1.01
2.01
4.02
1.02
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

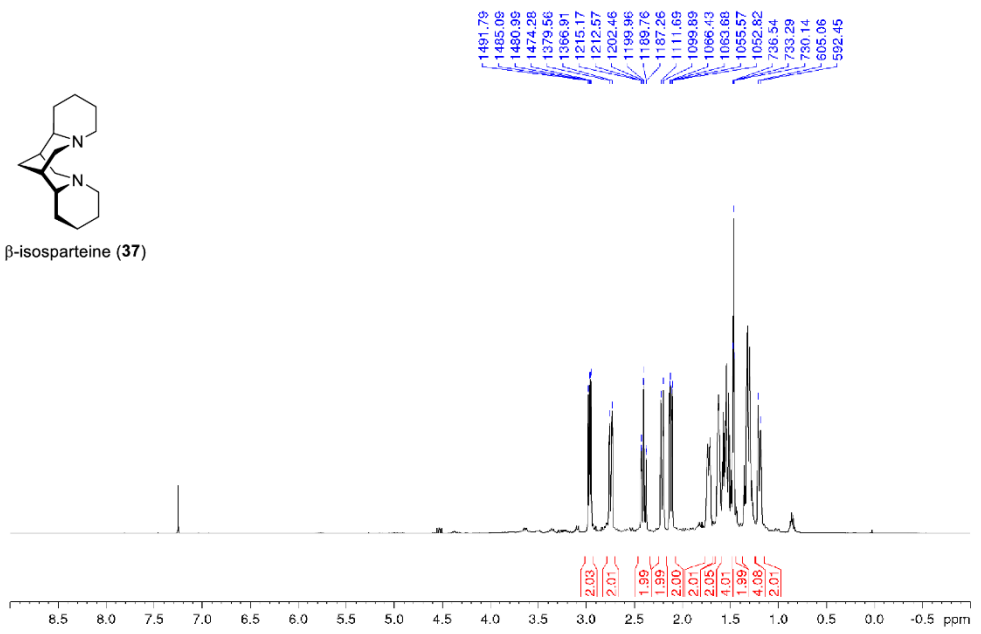

168.92
137.18
136.59
116.69
116.47
63.15
59.53
57.75
47.58
46.45
33.89
33.21
30.08
27.93
27.76
27.66
20.10
35
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

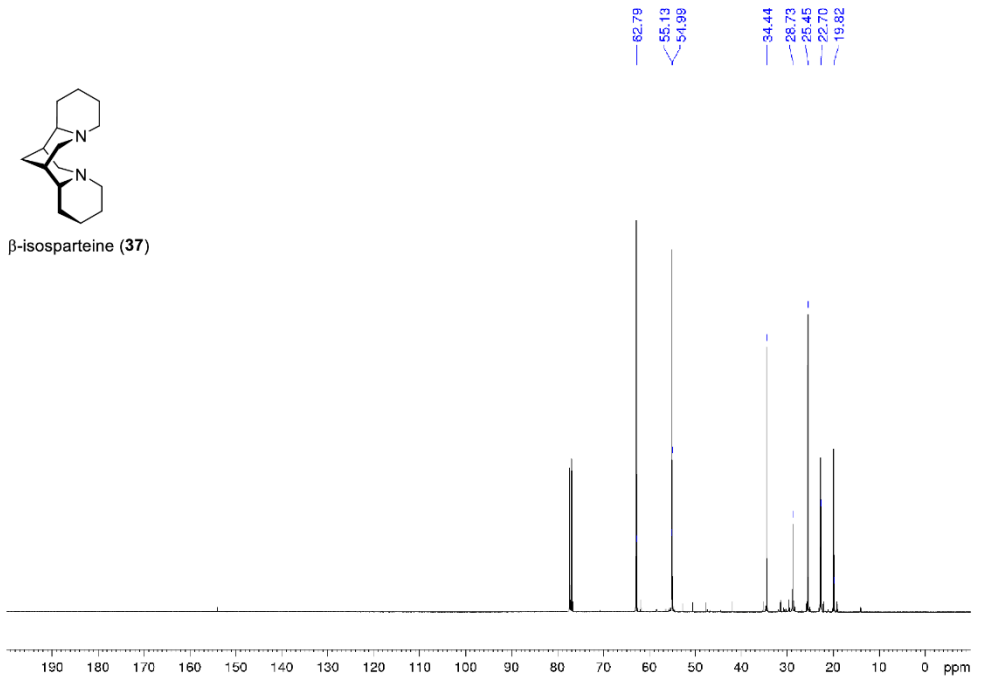
71


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
36
0.54
0.20
1.06
0.20
1.26
0.54
0.21
6.09
2.03
3.89
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

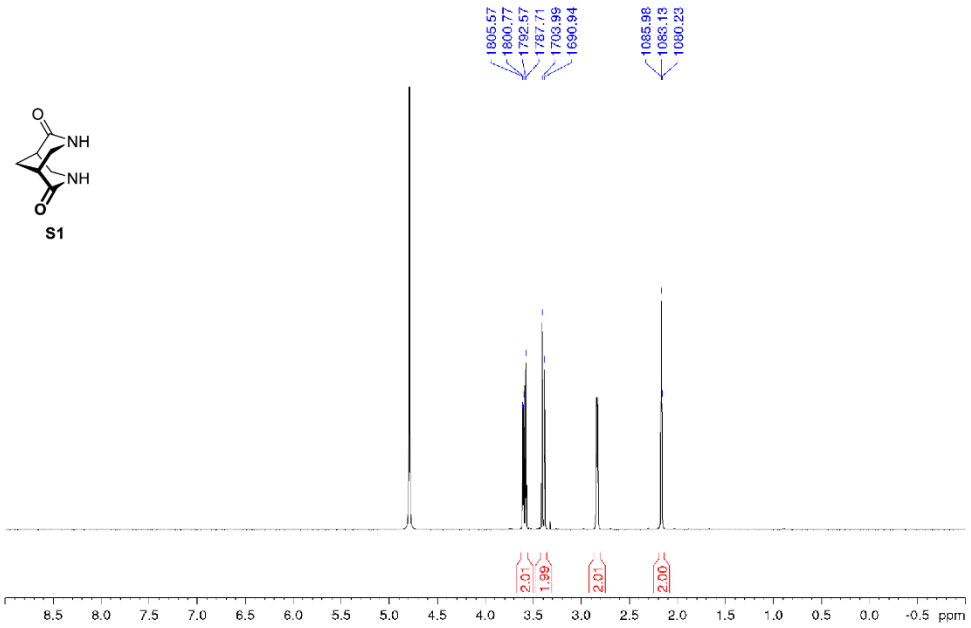

155.57
155.52
155.10
154.86
85.80
85.55
84.57
84.34
80.29
80.24
80.10
78.88
55.17
54.75
54.66
54.62
43.04
43.02
41.89
41.45
31.61
31.58
31.48
31.38
28.66
28.61
28.51
28.40
19.39
18.62
18.61
18.40
MeO
NBoc
NBoc
MeO
36
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

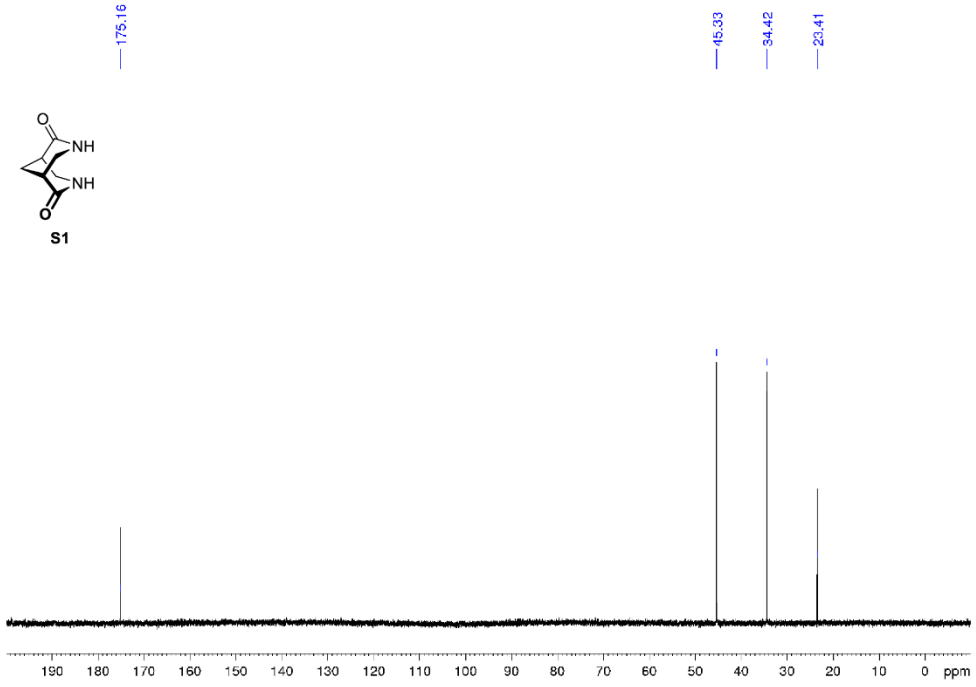
72


1491.79
1485.09
1480.99
1474.28
1379.56
1366.91
1215.17
1212.57
1202.46
1199.96
1189.76
1187.26
1111.69
1099.89
1066.43
1063.68
1055.57
1052.82
736.54
733.29
730.14
605.06
592.45
N
N
β-isosparteine (**37**)
2.03
2.01
1.99
1.99
2.00
2.01
2.05
4.01
1.99
4.08
2.01
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

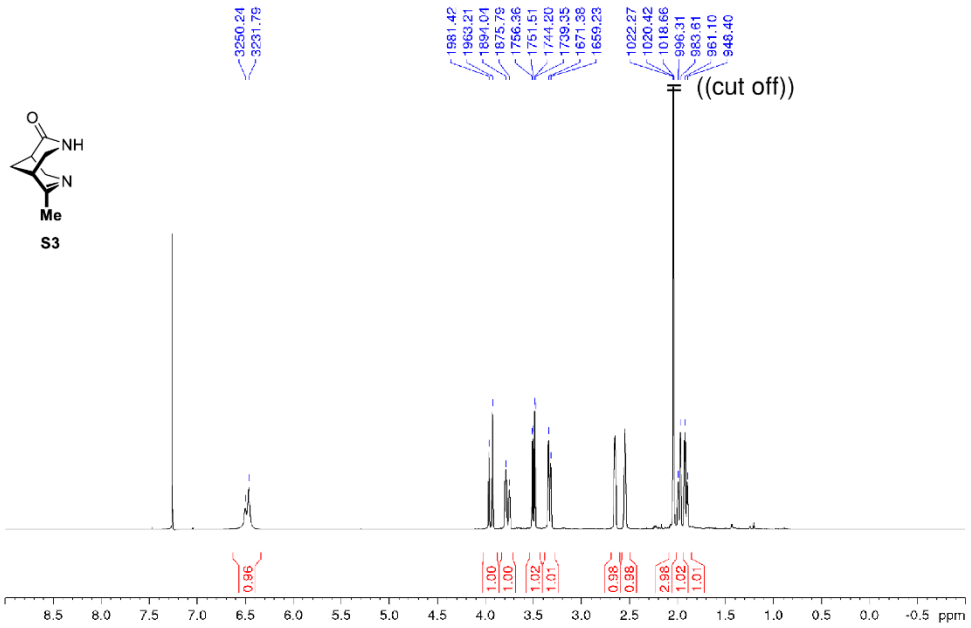

82.79
55.13
54.99
34.44
28.73
25.45
22.70
19.82
N
N
β-isosparteine (**37**)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

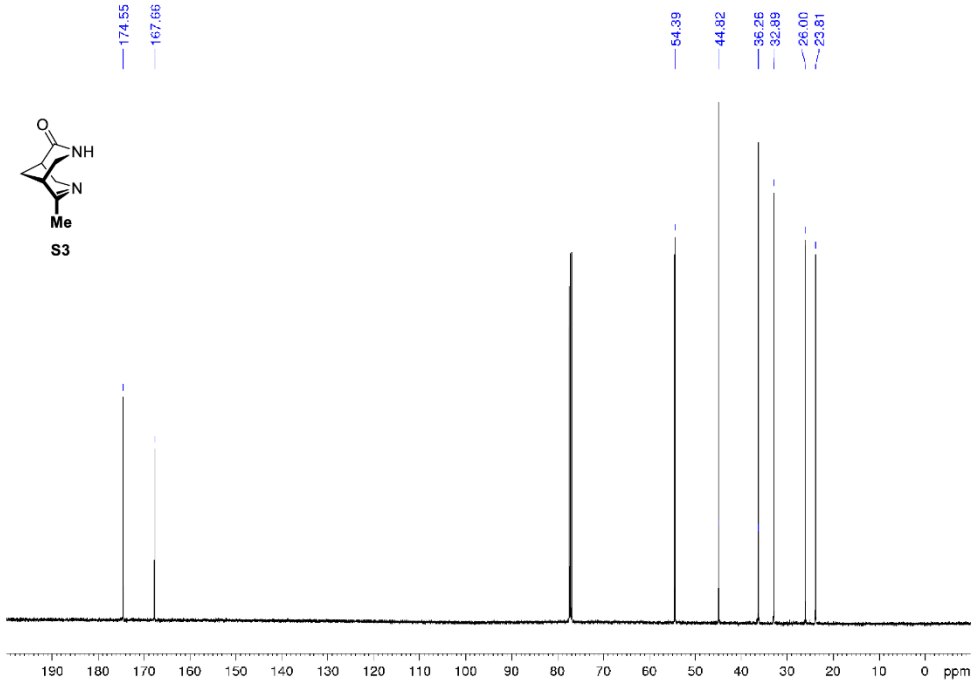
73


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

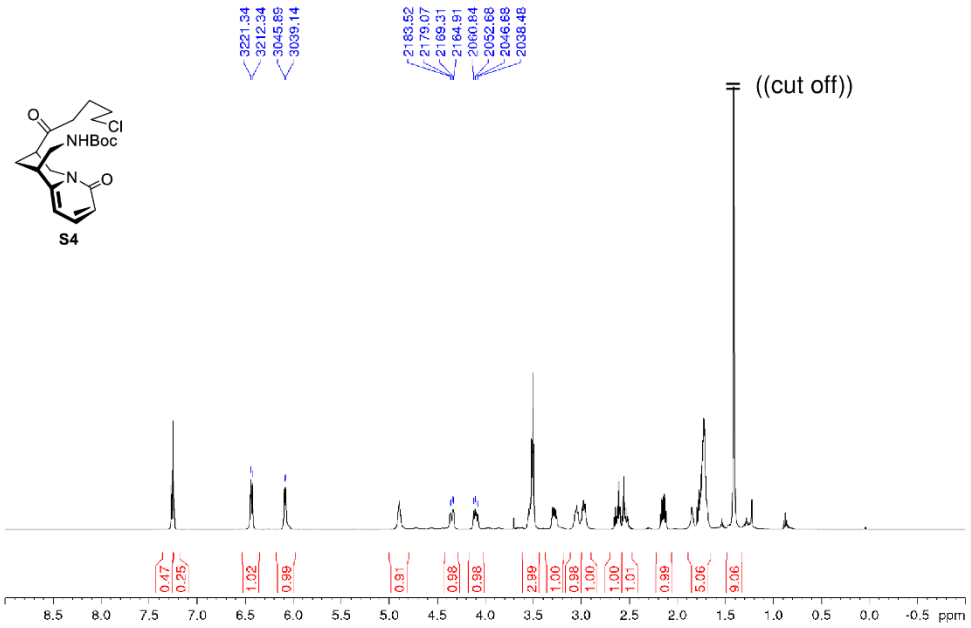

175.16
45.33
34.42
23.41
NH
NH
O
O
S1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

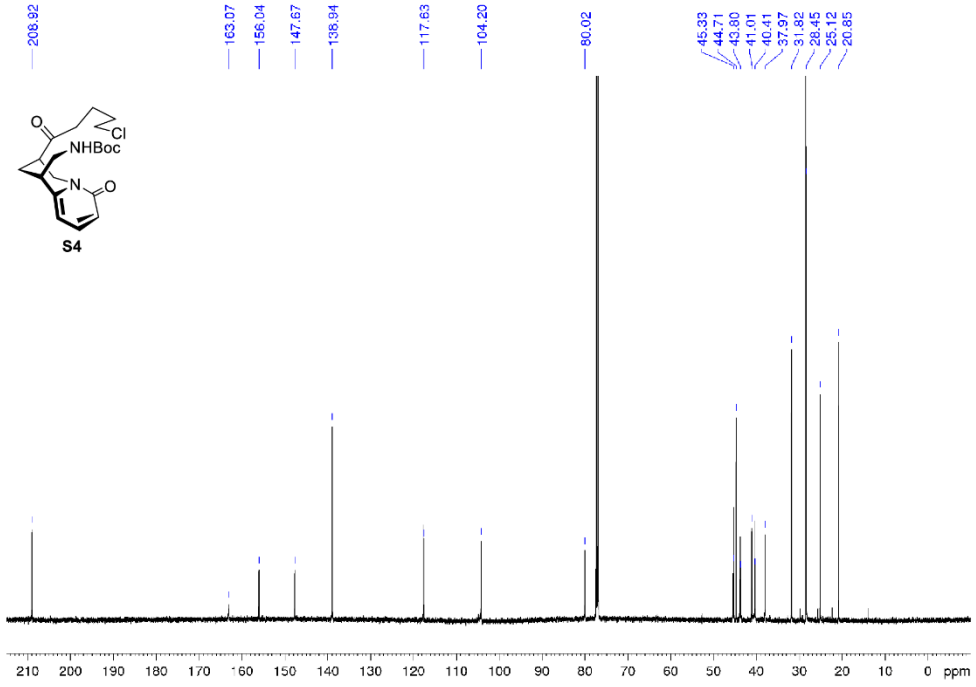
74


3250.24
3231.79
1981.42
1963.21
1894.01
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))
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

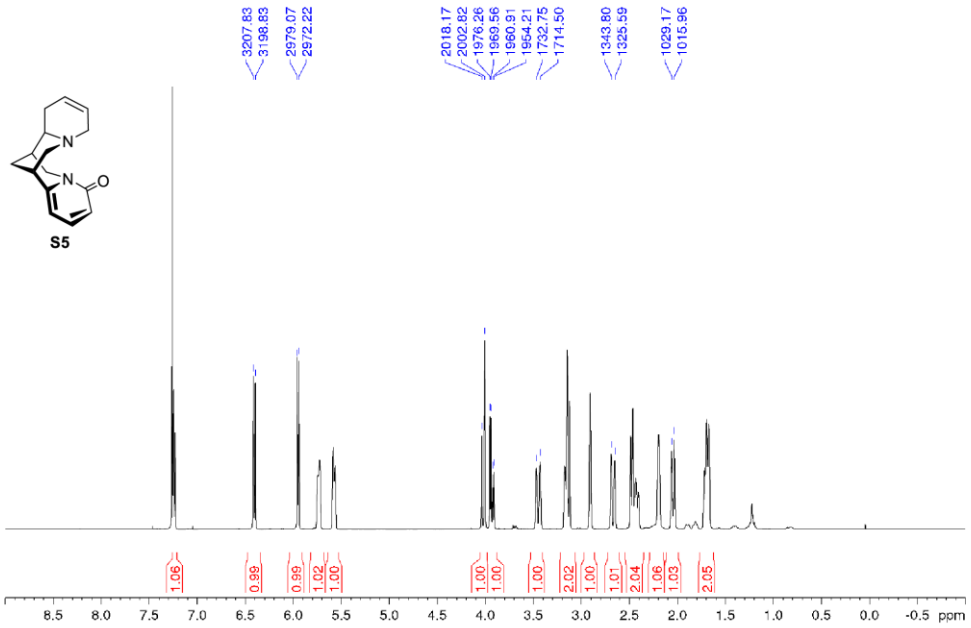

174.55
167.66
54.39
44.82
36.26
32.89
26.00
23.81
NH
N
Me
S3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

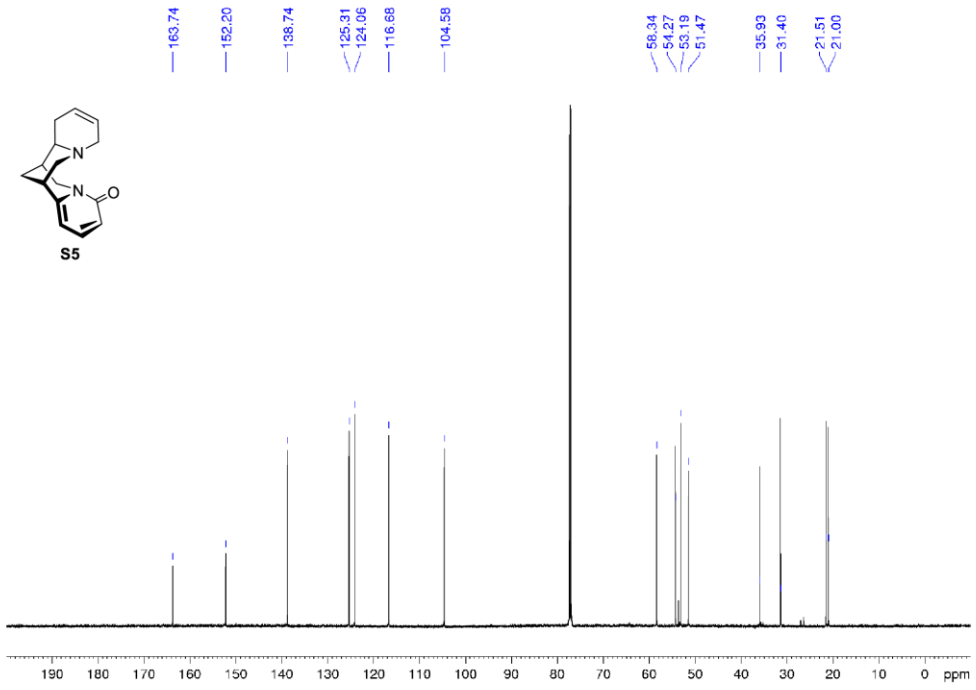
75


3221.34
3212.34
3045.86
3039.14
2183.52
2179.07
2169.31
2164.91
2060.84
2052.68
2046.88
2038.48
((cut off))
NHBoc
Cl
O
N
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

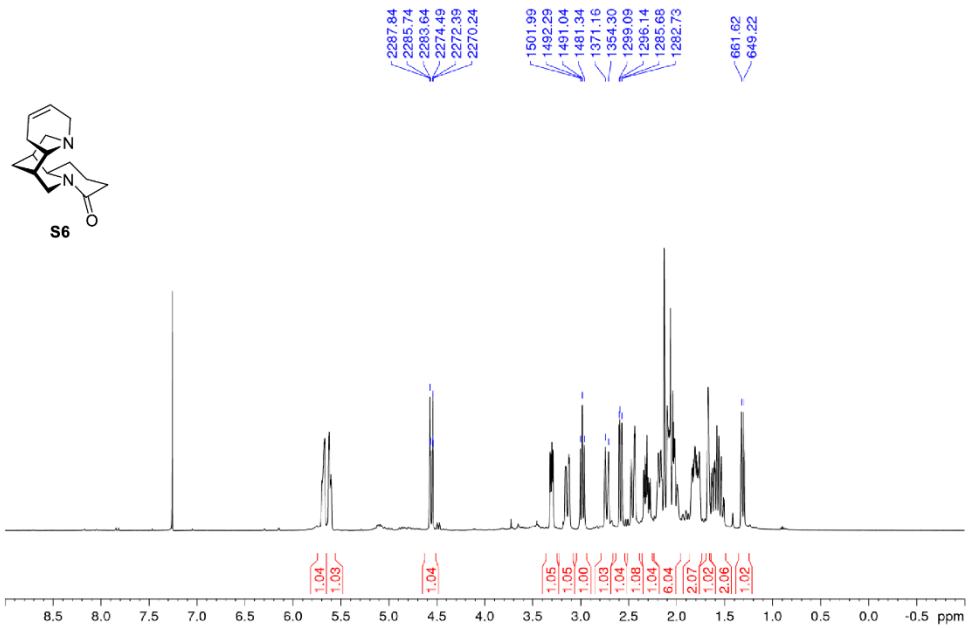

206.92
163.07
156.04
147.67
138.94
117.63
104.20
80.02
45.33
44.71
43.80
41.01
40.41
37.97
31.82
28.45
25.12
20.85
NHBoc
Cl
O
N
O
S4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

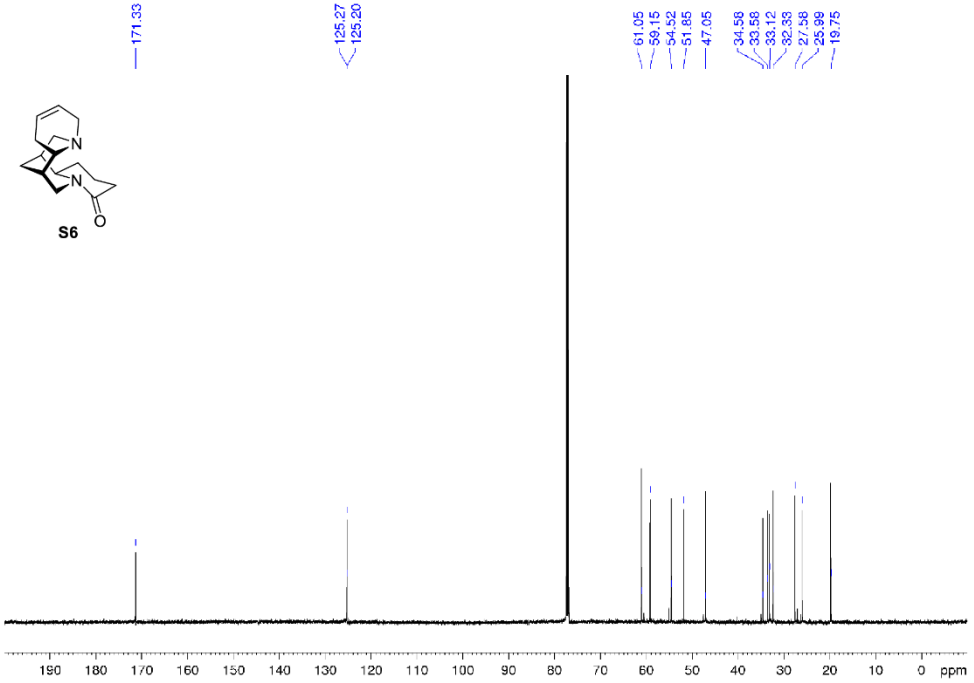
76


3207.83
3196.83
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
1015.86
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

77


2287.84
2285.74
2283.64
2274.49
2272.39
2270.24
1501.99
1492.29
1491.04
1481.34
1371.16
1354.30
1299.09
1296.14
1285.68
1282.73
661.62
649.22
S6
1.04
1.03
1.04
1.05
1.05
1.00
1.03
1.04
1.08
1.04
6.04
2.07
1.02
2.06
1.02
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

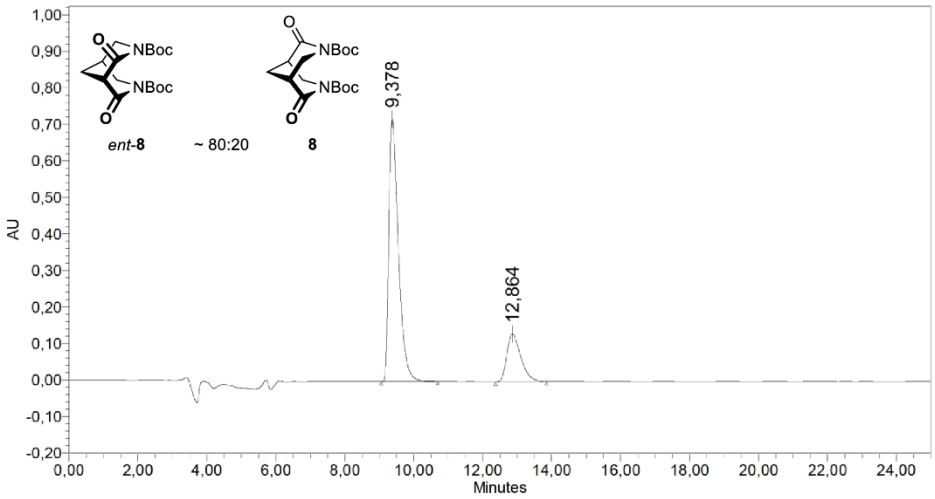

171.33
125.27
125.20
61.05
59.15
54.52
51.85
47.05
34.58
33.58
33.12
32.33
27.58
25.99
19.75
S6
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

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*)

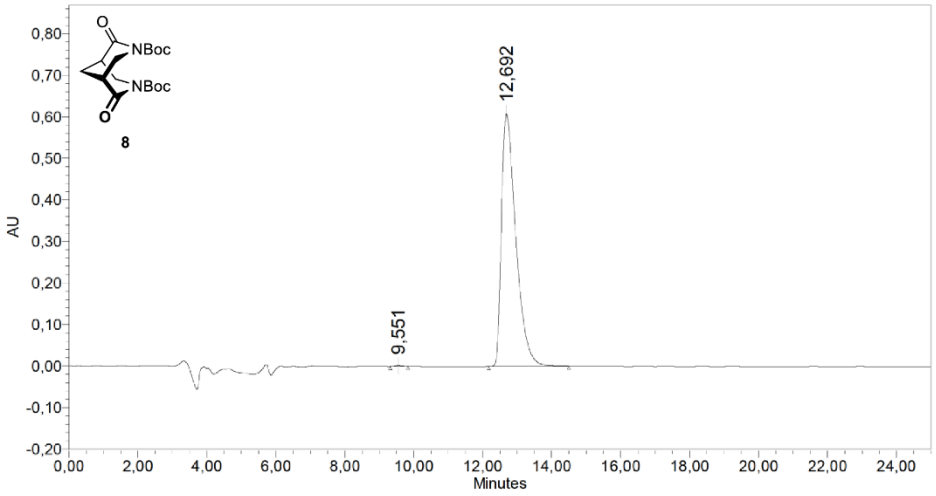
Mixture of *ent*-**8** and **8**



	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

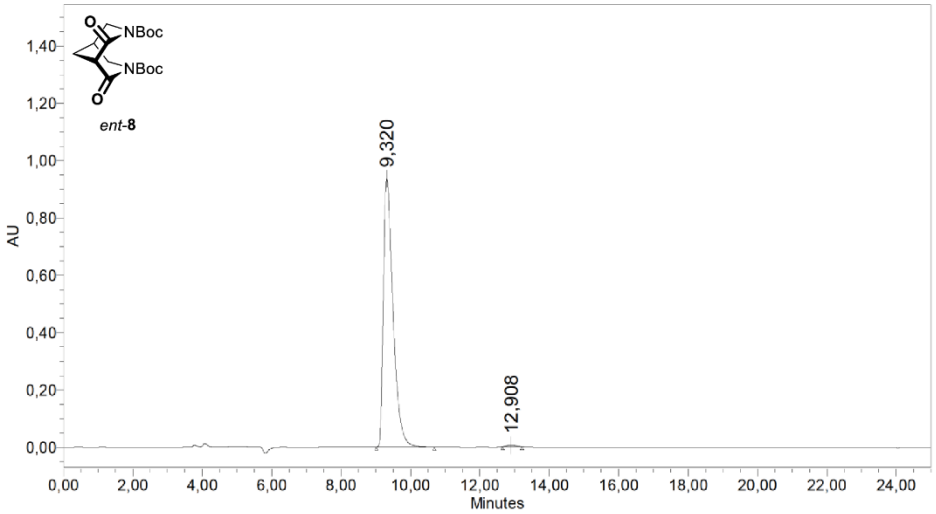
79

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*

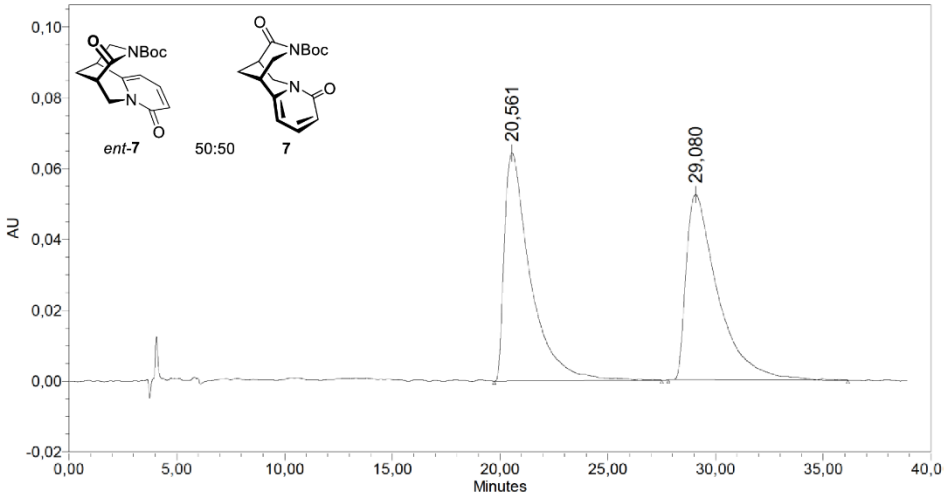


	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,32	9,02	10,69	934879	99,53	18038860	99,52
2	12,91	12,66	13,22	4423	0,47	87205	0,48

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*)

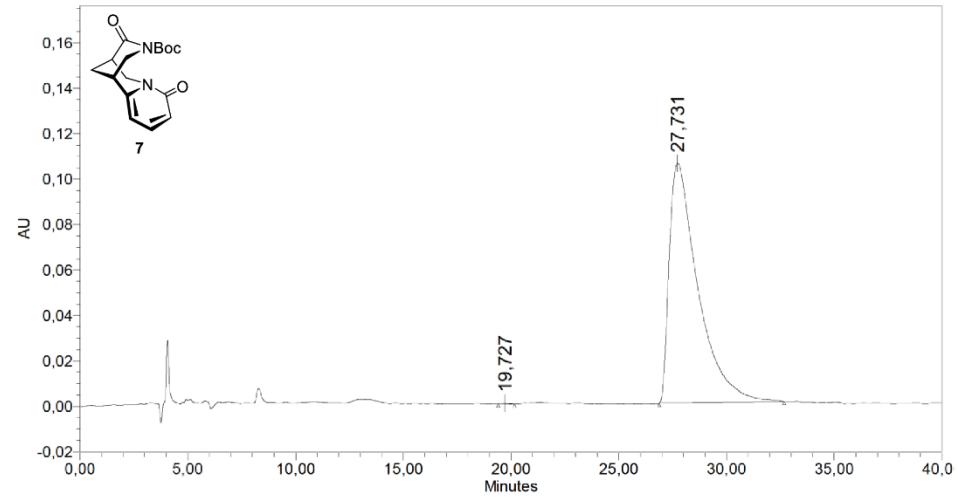
Mixture of *ent*-**7** and **7**



	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

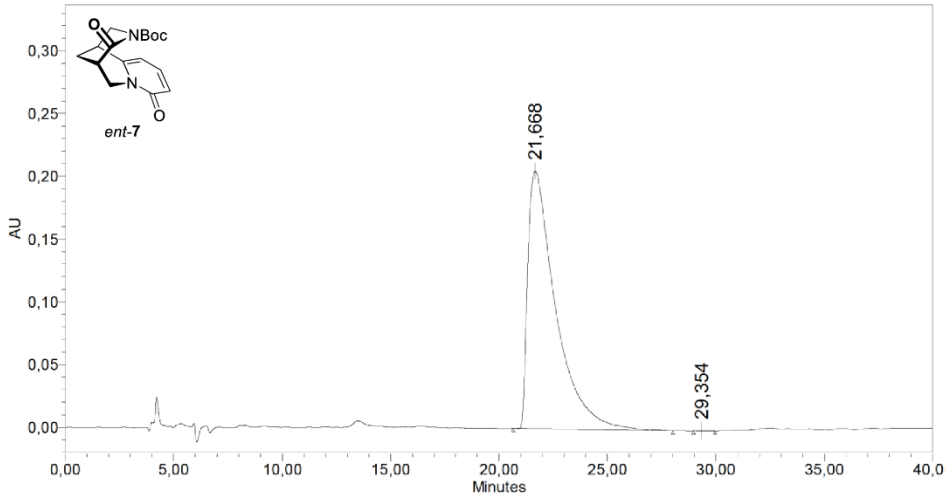
81

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

ent-**7**: 99% *ee*



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	21,67	20,66	28,03	205159	99,87	18302387	99,95
2	29,35	28,98	29,97	272	0,13	8283	0,05

6.1.2 Die enantioselektive Totalsynthese von Bischinolizidin-Alkaloiden: Ein modularer „Inside-Out“-Zugang

Dagmar Scharnagel,[‡a] Jessica Goller,[‡a] Nicklas Deibl,[b] Wolfgang Milius,[b] Matthias Breuning[*a]

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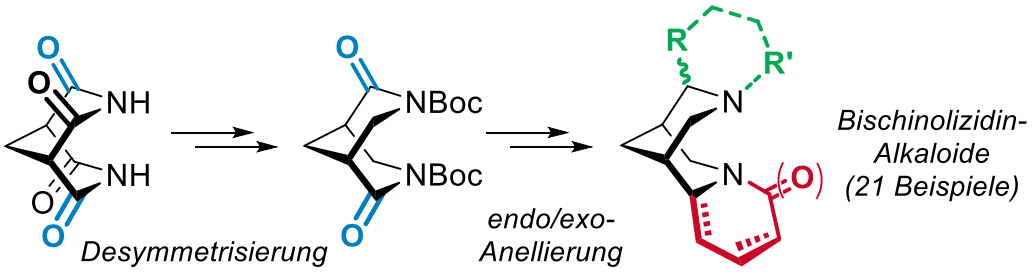
[‡] Diese Autoren haben zu gleichen Teilen zu der Arbeit beigetragen.

[*] Matthias.Breuning@uni-bayreuth.de



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DOI: 10.1002/ange.201712852

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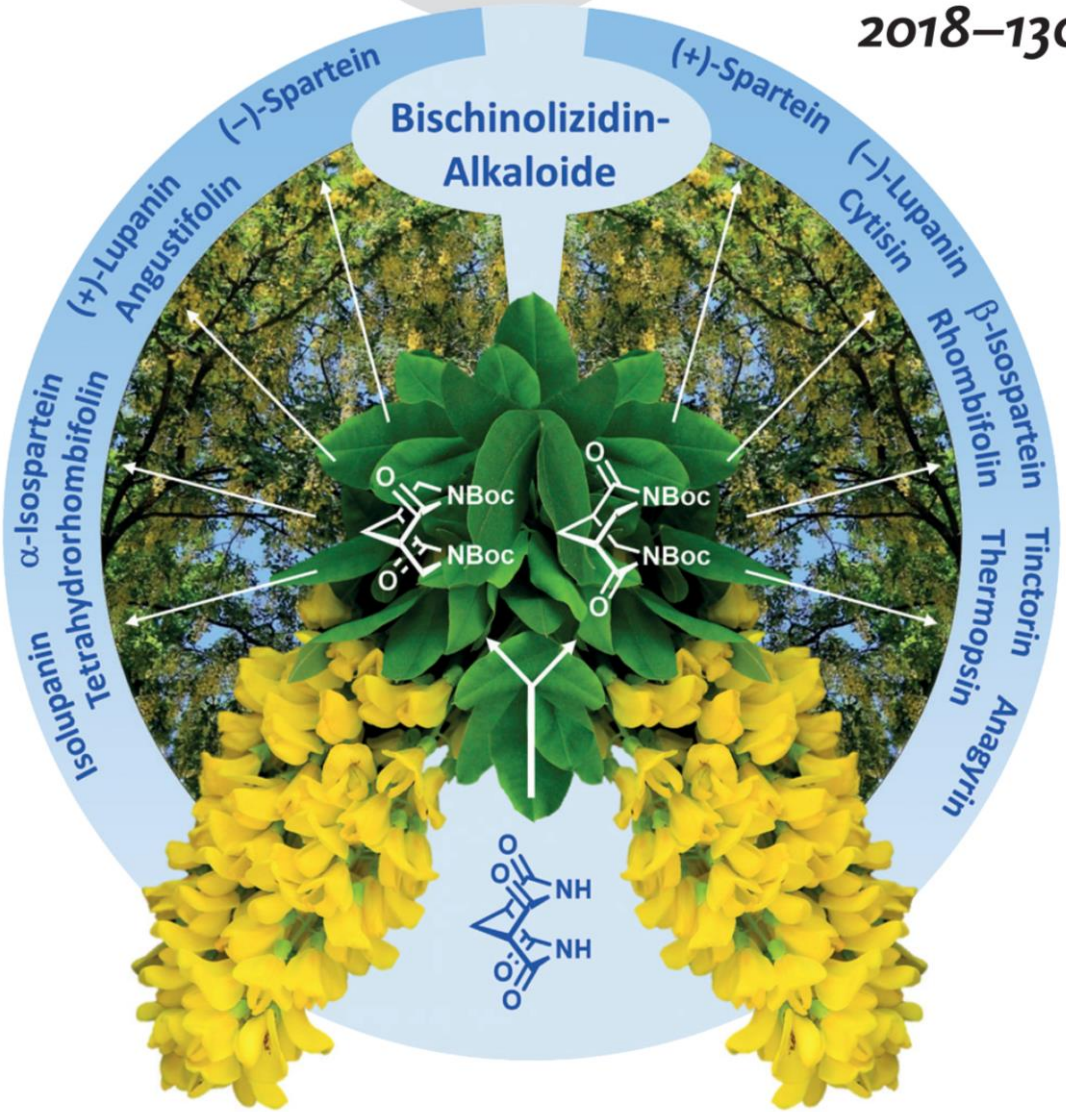
2018–130/9



Titelbild

M. Breuning et al.

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Die enantioselektive Totalsynthese von Bischinolizidin-Alkaloiden: Ein modularer „Inside-Out"-Zugang

*Dagmar Scharnagel[+], Jessica Goller[+], Nicklas Deibl, Wolfgang Milius und Matthias Breuning**

Abstract: *Charakteristisch für Bischinolizidin-Alkaloide ist ein chirales Bispidin-Kerngerüst (3,7-Diazabicylo[3.3.1]-nonan), an das Kombinationen aus einem α,N-anellierten 2-Pyridon, endo- oder exo-α,N-anellierten Piperidin(on)en und einem exo-Allylsubstituenten angebracht sind. Wir entwickelten eine modulare „Inside-Out"-Strategie, die einen Zugang zu den meisten Vertretern dieser Naturstoffklasse erlaubt. Ihr Anwendungspotential wurde anhand der asymmetrischen Synthese von 21 Bischinolizidin-Naturstoffen demonstriert, darunter mehr als zehn enantioselektive Erstsynthesen. Schlüsselschritte sind die erste erfolgreiche Herstellung beider Enantiomere von C_2-symmetrischem 2,6-Dioxobispidin durch Desymmetrisierung einer 2,4,6,8-Tetraoxo-Vorstufe, der Aufbau des α,N-anellierten 2-Pyridons über eine Enamin-Bromacrylsäure-Strategie und die Einführung von endo- oder, wahlweise, exo-anellierten Piperidin(on)en.*

Die Verbindungen (−)-Spartein (**1**), (+)-Lupanin (**2**), α-Isospartein (**3**), Anagyrin (**4**) und Cytisin (**5**) sind die bekanntesten Bischinolizidin-Alkaloide, einer Klasse von Sekundärmetaboliten mit etwa 50 Vertretern (Abbildung 1).[1]

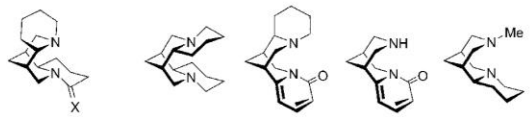

Abbildung 1. Die bekanntesten Vertreter der Bischinolizidin-Naturstoffe (**1**–**5**) und der synthetische (+)-Spartein-Ersatzstoff (**6**).

Diese Naturstoffe werden von Pflanzen der Faboideae-Unterfamilie produziert, welche die Gattungen *Cytisus*, *Laburnum*, *Thermopsis* und *Anagyris* einschließt. Die biologischen Aktivitäten dieser Diamine sind breit gefächert: (−)-Spartein (**1**) besitzt antiarrhythmische und wehenfördernde Eigenschaften, (+)-Lupanin (**2**) wirkt moderat toxisch und Anagyrin (**4**) weist teratogene Wirkung auf.[1] Cytisin (**5**), ein partieller Agonist des nikotinischen Acetylcholinrezeptors, wird als Wirkstoff in Medikamenten zur Rauchentwöhnung unter den Markennamen Tabex und Desmoxan in Polen und Bulgarien vertrieben.[2] In der asymmetrischen Synthese wird (−)-Spartein (**1**) und O'Briens (+)-Spartein-Ersatzstoff (**6**),[3] der in wenigen Stufen aus **5** hergestellt werden kann,[4] besondere Aufmerksamkeit zuteil, denn sie sind die chiralen Liganden der Wahl in Deprotonierungsreaktionen schwach CH-acider Verbindungen,[5] Homologisierungen von Boronsäureestern[6] und Pd-katalysierten, oxidativen kinetischen Racematspaltungen sekundärer Alkohole.[7,8]

Gemeinsames Strukturelement aller Bischinolizidin-Alkaloide bildet ein chirales Bispidin-Kerngerüst (3,7-Diazabicyclo[3.3.1]nonan), das in der Natur in beiden enantiomeren Formen auftritt (**1**–**3** vs. **4**,**5**). Typischerweise finden sich Kombinationen aus einem α,*N*-anellierten 2-Pyridon, einem *endo*- oder *exo*-α,*N*-anellierten Piperidin(on) oder einem *exo*-Allylsubstituenten an den gegenüberliegenden Seiten des zentralen Kerngerüsts.

Bisher existieren einige elegante, enantioselektive Synthesen von Bischinolizidin-Alkaloiden.[9] Die meisten dieser Routen sind allerdings nur zur Herstellung eines einzelnen Zielmoleküls geeignet, denn häufig werden „Outside-In"-Strategien verfolgt, in denen zuerst die Peripherie aufgebaut wird, anhand derer sich die Naturstoffe unterscheiden. Es gibt jedoch noch keine flexible Route, die einen Zugang zu einem breiten Spektrum an Bischinolizidin-Alkaloiden erlaubt. Ein solcher wurde nun von uns entwickelt und seine Anwendbarkeit anhand der enantioselektiven Totalsynthese von 21 Bischinolizidin-Naturstoffen belegt. Schlüsselsequenzen sind eine Desymmetrisierung, über die sich beide enantiomeren Formen des chiralen C_2-symmetrischen 2,6-Dioxobispidins herstellen lassen, ein neues Verfahren zum Aufbau eines α,*N*-anellierten 2-Pyridons und verlässliche Methoden zur wahlweise *endo*- oder *exo*-selektiven Einführung von Piperidin(on)en und *exo*-Allylsubstituenten am Bispidin-Kerngerüst.

Unser diversitätsorientierter Zugang zu Bischinolizidin-Alkaloiden basiert auf einer modularen „Inside-Out"-Strategie, in der die peripheren Ringe und Substituenten an ein geeignet funktionalisiertes, chirales Bispidin-Kerngerüst angebracht werden (Schema 1). Da viele Bischinolizidine ein α,*N*-anelliertes 2-Pyridon oder eine reduzierte Form davon aufweisen, wurde das tricyclische Imid **7** als fortgeschrittenes Schlüsselintermediat gewählt. Weitere Zerlegung des Pyridons führt zum C_2-symmetrischen 2,6-Dioxobispidin **8** als zweites Schlüsselintermediat, das wir in beiden enantiomeren Formen ausgehend vom achiralen 2,4,6,8-Tetraoxobispidin **9** präparieren wollten.[10]

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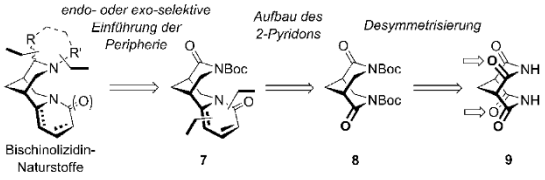
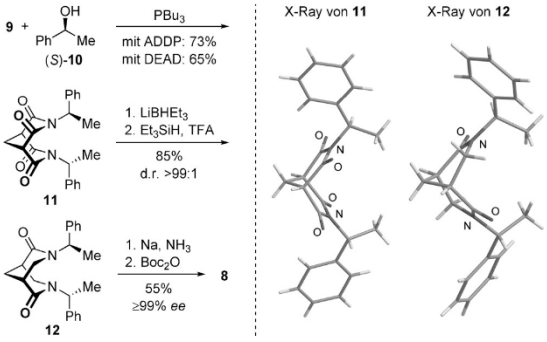


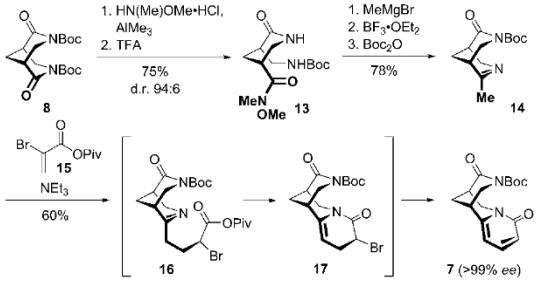
Schema 1. Retrosynthese der Bischinolizidin-Naturstoffe. Nur eines der beiden enantiomeren Bispidin-Kerngerüste ist abgebildet.

Die Synthese des 2,6-Dioxobispidins **8** erfolgte aus dem achiralen 2,4,6,8-Tetraoxobispidin **9** (Schema 2), das in nur zwei Stufen aus günstigem Malonsäureester zugänglich ist.[11] Für die Desymmetrisierung muss eines der beiden enantiotopen Paare der Carbonylgruppen desoxygeniert werden. Dazu wurde **9** an beiden Stickstoffatomen mit (*S*)-Phenylethanol [(*S*)-**10**] unter Mitsunobu-Bedingungen chiral modifiziert und das resultierende Imid **11** in zwei Stufen diastereoselektiv reduziert. Das Diamid **12** wurde nahezu vollständig regio- und stereoselektiv erhalten (dr > 99:1)[12] und seine absolute Konfiguration anhand der Röntgenkristallstruktur bestimmt.[13] Reduktive Abspaltung der chiralen Auxiliare unter Birch-Bedingungen und Aktivierung der Amidgruppen als *N*-Boc-Imide lieferte das chirale Schlüsselintermediat **8** in 30–34 % Ausbeute und ≥ 99 % *ee* über fünf Stufen ausgehend von **9**. Das Enantiomer *ent*-**8** wurde analog mit (*R*)-**10** synthetisiert.



Schema 2. Synthese des chiralen Schlüsselintermediats **8** und die Röntgenkristallstrukturen von **11** und **12**.[13] DEAD = Diethylazodiacarboxylat, ADDP = 1,1′-(Azodicarbonyl)dipiperidin, TFA = Trifluoressigsäure, Boc = *tert*-Butoxycarbonyl.

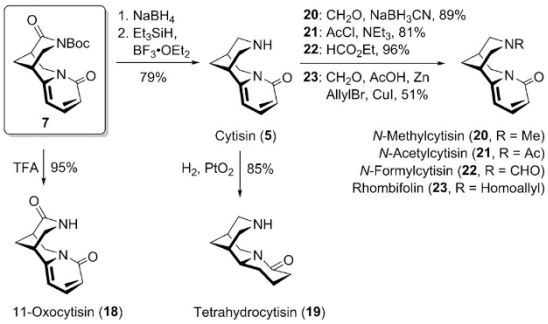
Die Umsetzung des C_2-symmetrischen 2,6-Dioxobispidins **8** in das tricyclische Bispidin **7** erforderte eine α,*N*-Anellierung eines 2-Pyridons (Schema 3). Die selektive Modifikation nur einer der beiden Imidgruppen wurde durch Lewis-Säure-katalysierte Ringöffnung mit HN(OMe)Me·HCl/$AlMe_3$ erreicht.[14] Boc-Entschützung des Imids ergab das Weinreb-Amid **13** in 75 % Ausbeute und einem dr von 94:6. Dabei ist es wichtig die Temperatur im ersten Reaktionsschritt unter −30 °C zu halten, um Isomerisierungen an den ehemaligen Brückenkopfkohlenstoffen zu unterdrücken. Die Anellierung des Pyridons wurde über eine Enamin-Michael-Additions-



Schema 3. Anellierung von **8** zum tricyclischen Schlüsselintermediat **7**. Piv = Pivaloyl.

Strategie vervollständigt.[15] Reaktion von **13** mit MeMgBr, *N*-Boc-Entschützung unter Lewis-sauren Bedingungen mit nachfolgender Iminbildung und *N*-Boc-Schützung des Amids lieferten das Bispidin **14**. Umsetzung mit in situ präpariertem α-Bromacrylsäurepivaloylanhydrid (**15**) und NEt_3 ergab das gewünschte Pyridon **7** nach Kristallisation in > 99 % *ee*.[16] In der letzten Sequenz unterlief vermutlich das Enamin-Tautomer von **14** mit dem Anhydrid **15** eine Michael-Addition zum Intermediat **16**. Erneute Enaminbildung und Lactamisierung führten zu **17**, das schließlich HBr eliminierte.

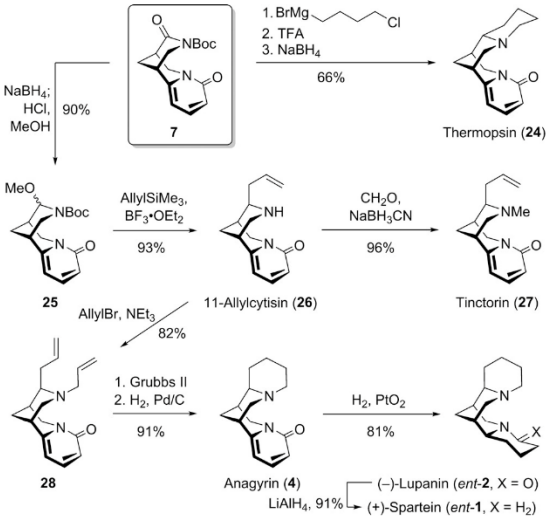
Mit dem Schlüsselintermediat **7** synthetisierten wir nun die ersten tricyclischen Bischinolizidin-Alkaloide (Schema 4).



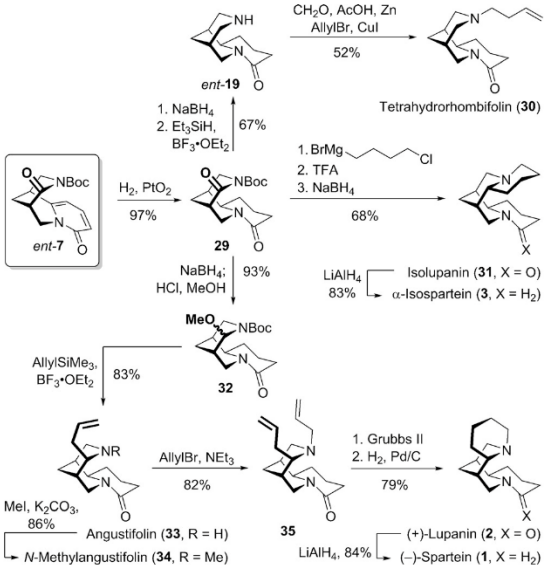
Schema 4. Tricyclische Bischinolizidin-Naturstoffe **18**–**23** aus **7**.

Simple Entschützung von **7** führte zu 11-Oxocytisin (**18**), Reduktion und *N*-Boc-Entschützung zu Cytisin (**5**). Letztere Verbindung wurde gemäß Literaturprotokollen[17] hydriert oder *N*-funktionalisiert, was Tetrahydrocytisin (**19**), *N*-Methylcytisin (**20**), *N*-Acetylcytisin (**21**), *N*-Formylcytisin (**22**) und Rhombifolin (**23**) lieferte.

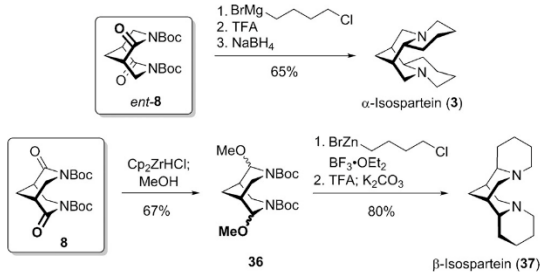
Das Anbringen eines *endo*-[8c,18] bzw. *exo*-anellierten Rings oder Substituenten am Imidcarbonylkohlenstoff in **7** schließt eine Hydrid- und Alkyladdition ein. Frühere Untersuchungen von uns[8c,18,19] und anderen Gruppen[10,11,20] an ähnlichen Systemen zeigten, dass ein Angriff durch ein Nukleophil auf ein Bispidinimin oder Bispidiniminiumsalz mit hoher Selektivität von der sterisch weniger gehinderten *exo*-Seite erfolgt (Schema 5). Demnach führt eine Reduktion gefolgt von einer Addition zur *exo*-Ausrichtung, während die umgekehrte Additions-Reduktions-Sequenz Zugang zum



Schema 5. Kern-disubstitutierte Bischinolizidin-Naturstoffe aus **7**.



Schema 6. Tri- und tetracyclische Bischinolizidin-Naturstoffe aus *ent*-**7**.



Schema 7. Synthese der C_2-symmetrischen Bischinolizidin-Alkaloide α- und β-Isospartein (**3**, **37**) aus *ent*-**8** und **8**.

endo-Epimer erlaubt. In der Tat lieferten die Umsetzung von **7** mit 4-Chlorbutyl-MgBr, *N*-Boc-Entschützung und reduktive Aminierung, bei der gleichzeitig nukleophile Substitution eintrat, das *endo*-Piperidinalkaloid Thermopsin (**24**) in nur drei Stufen und guten 66% Ausbeute. *Exo*-Substituenten wurden nach Reduktion von **7** zum *N,O*-Acetal **25** eingeführt.[21] Sakurai-Allylierung unter Verlust der *N*-Boc-Gruppe ergab 11-Allylcytisin (**26**) und, nach reduktiver *N*-Methylierung, Tinctorin (**27**) in guten 89% Ausbeute. *N*-Allylierung von **26** gefolgt von Ringschlussmetathese und Hydrierung lieferte das tetracyclische Bispidin Anagyrin (**4**), das durch Hydrierung des Pyridons in (−)-Lupanin (*ent*-**2**) und, nach Reduktion der Amidgruppe, in (+)-Spartein (*ent*-**1**) überführt wurde.

Bischinolizidin-Alkaloide mit dem enantiomeren Bispidin-Kerngerüst wurden aus dem Imid *ent*-**7** synthetisiert (Schema 6), das aus *ent*-**8** gemäß Schema 3 hergestellt wurde. Hydrierung von *ent*-**7** ergab das Piperidon **29**, das zum Amin *ent*-**19** reduziert und entschützt wurde. Anschließende Barbier-artige *N*-Homoallylierung lieferte Tetrahydrorhombifolin (**30**).[22] Isolupanin (**31**) und dessen desoxygeniertes Analogon α-Isospartein (**3**) wurden gemäß der zuvor beschriebenen *endo*-Piperidin-Anellierungssequenz erhalten. Reduktion des Imids **29** zum *N,O*-Acetal **32**[21] bildete den Ausgangspunkt für die *exo*-Funktionalisierung (siehe oben), aus der letztendlich Angustifolin (**33**), *N*-Methylangustifolin (**34**), (+)-Lupanin (**2**) und (−)-Spartein (**1**) hervorgingen.

Die Anwendung der *exo*- und *endo*-Anellierungssequenzen an beiden Imidgruppen der Schlüsselintermediate *ent*-**8** und **8** erlaubte auch einen effizienten Zugang zu C_2-symmetrischen Alkaloiden (Schema 7). Natürliches α-Isospartein (**3**) wurde auf diese Weise aus *ent*-**8** in nur drei Stufen und guten 65% Ausbeute erhalten. Die *exo*-anellierten Piperidine in β-Isospartein (**37**) wurden über das Bis-*N,O*-Acetal **36** aufgebaut,[21] das durch Reduktion von **8** mit dem Schwartz-Reagenz[23] und Acetalisierung erhalten wurde. Zweifache Lewis-Säure-vermittelte Addition von 4-Chlorbutylzinkbromid,[24] *N*-Boc-Entschützung und Ringschluss unter basischen Bedingungen lieferten **37** in 54% Ausbeute.

Zusammenfassend entwickelten wir eine flexible und breit anwendbare Route zu Bischinolizidin-Alkaloiden, deren Potential anhand der asymmetrischen Synthese von 21 Naturstoffen belegt wurde. Darunter befinden sich die enantioselektiven Erstsynthesen von (+)- und (−)-Lupanin (**2** und *ent*-**2**), α-Isospartein (**3**), Anagyrin (**4**), 11-Oxocytisin (**18**), Thermopsin (**24**), 11-Allylcytisin (**26**), Tinctorin (**27**), Isolupanin (**31**), Tetrahydrorhombifolin (**30**), Angustifolin (**33**) und *N*-Methylangustifolin (**34**). Schlüssel zum Erfolg war eine „Inside-Out"-Strategie basierend auf den chiralen 2,6-Dioxobispidinen **8** und *ent*-**8**, die beide in enantiomerenreiner Form durch Desymmetrisierung von achiralem Tetraoxobispidin **9** erhalten wurden. Das α,*N*-anellierte 2-Pyridon in **7** wurde über eine neuartige Enamin-Michael-Additions-Strategie aufgebaut. Hohe Diversität wurde durch Verwendung der *endo*- und *exo*-Anellierungssequenzen an den Schlüsselintermediaten **7**, *ent*-**7**, **8**, und *ent*-**8** erzielt.

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Die Autoren erklären, dass keine Interessenkonflikte vorliegen.

Stichwörter: Alkaloide · Bispidin · Enantioselektivität · Naturstoffe · Totalsynthese

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[14] Alle Versuche, selektiv nur eine der beiden Carbonylgruppen in **8** zu modifizieren und dabei das bicyclische System intakt zu lassen (z. B. *N*-Boc-Entschützung oder Carbonylreduktion), lieferten hauptsächlich das ungewünschte Produkt eines Angriffs auf beide Imide. Im Gegensatz dazu verlaufen Ringöffnungsreaktionen äußerst mono-selektiv, vermutlich aufgrund des Abbaus von Ringspannung.

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[21] Die ^{1}H- und ^{13}C-NMR-Spektren von **25** und **32** zeigen zwei Signalsätze, das von **36** drei. Diese werden vermutlich von *N*-Boc-Rotameren des *exo*-konfigurierten Diastereomers verursacht, allerdings kann die Anwesenheit von *endo*-Diastereomeren nicht völlig ausgeschlossen werden.

[22] Hinweis: Tetrahydrorhombifolin (**30**) und Rhombifolin (**23**) besitzen zueinander „enantiomere" Bispidin-Kerngerüste.

[23] Zweifache Reduktion von **8** mit Cp_2ZrHCl ergab im Vergleich zu $NaBH_4$, $LiBHEt_3$ oder iBu_2AlH höhere Ausbeuten.

[24] Die Lewis-Säure-vermittelte Addition von 4-Chlorbutylzinkbromid funktionierte gut am Bis-*N,O*-Acetal **36** (Schema 7), schlug jedoch aus unbekannten Gründen an **25** (Schema 5) und **32** (Schema 6) fehl.

Manuskript erhalten: 14. Dezember 2017
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6.1.3 Modular Synthesis of Bisquinolizidine Alkaloids

Würdigung der Publikation 6.1.1 und 6.1.2 in Synfacts.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

bisquinolizidine alkaloids

(–)-cytisine

(–)-thermopsine

(–)-anagyrine

(+)-sparteine

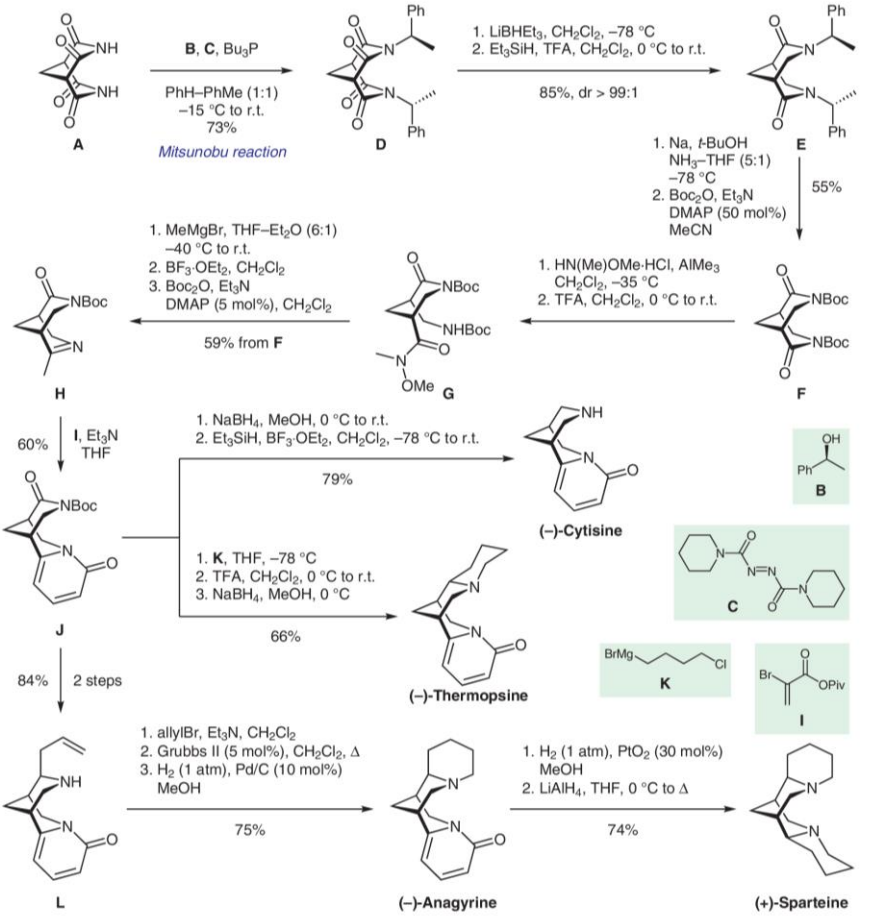
bispidine

desymmetrization

D. SCHARNAGEL, J. GOLLER, N. DEIBL, W. MILIUS, M. BREUNING* (UNIVERSITY OF BAYREUTH, GERMANY)

The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular "Inside-Out" Approach
Angew. Chem. Int. Ed. **2018**, *57*, 2432–2435.

Modular Synthesis of Bisquinolizidine Alkaloids



Significance: Breuning and co-workers report a modular approach to the bisquinolizidine class of alkaloids. Their synthesis of 21 natural diamines relies on the efficient construction of α,*N*-fused 2-pyridone **J** as a common intermediate.

Comment: Tetraoxobispidine **A** is desymmetrized reductively employing a chiral auxiliary. Michael addition of the enamine of **H** to acrylate **I** followed by lactamization and elimination affords pyridone **J**. This intermediate allows facile access to *endo*- or *exo*-annulated derivatives.

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6.2 The Hydroxylated, Tetracyclic Bisquinolizidine Alkaloids Baptifoline and Epibaptifoline: Enantioselective Synthesis and Unambiguous Assignment of their Configuration at C-13

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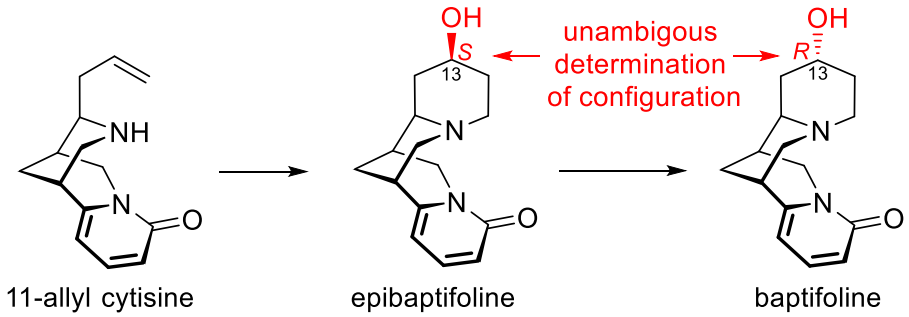

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Matthias Breuning et al.
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Natural Product Synthesis

The Hydroxylated, Tetracyclic Bisquinolizidine Alkaloids Baptifoline and Epibaptifoline: Enantioselective Synthesis and Unambiguous Assignment of their Configuration at C-13

Jessica Goller,[a] Christian B. Hübschle,[b] and Matthias Breuning*[a]

Dedicated to Professor Dietmar Stalke on the occasion of his 60th birthday.

Abstract: The epimeric bisquinolizidines baptifoline and epibaptifoline are C-13 hydroxylated derivatives of the well-known lupine alkaloid anagyrine. We synthesized both compounds from 11-allylcytisine and determined their uncertain configuration at the C-13 stereocenter by NMR, chemical transformation, and X-ray. The alcohol function was found to be in *endo* (α) position in baptifoline (configuration: 7*R*, 9*R*, 11*R*, 13*R*) and in *exo* (β) position in epibaptifoline (configuration: 7*R*, 9*R*, 11*R*, 13*S*).

Introduction

Common structural motif of bisquinolizidine alkaloids is a chiral bispidine core[1] (3,7-diazabicyclo[3.3.1]nonane), surrounded on opposite sides by α,*N*-fused 2-pyridones, piperidin(on)es, pyrrolidines, or α-allyl substituents.[2,3] Famous representatives of this natural product class are (–)-sparteine (**1**), (+)-lupanine (**2**), anagyrine (**4**), and (–)-cytisine (**6**, Figure 1). Several hydroxylated derivatives are also known, including the epimeric pairs 13α-/13β-hydroxylupanine (**3a**/**3b**, derived from **2**),[4–6] and baptifoline/epibaptifoline (**A**/**B**, derived from **4**). Baptifoline (**A**) was isolated in 1948 by Marion et al. as a minor ingredient of *Baptisia perfoliata* and *Baptisia minor* Lehm.[7,8] Epibaptifoline (**B**) was first synthesized in 1962 by Bohlmann et al.[9] and later recognized by Vasquez et al. as a natural product occurring in *Retama sphaerocarpa*.[10] Meanwhile, both alkaloids were found in more than a dozen genera of the Fabaceae family.[11]

The identical configurations of the bridgehead carbon atoms in **A** and **B** (7*R*, 9*R*, 11*R*) were firmly established by partial synthesis[9] and degradation,[8,10] whereas the differing stereochemistry at C-13 was originally just proposed on basis of IR spectroscopy, using the wavenumber of the OH vibration around 1000 cm^{-1}.[10,12,13] This 50-year-old stereochemical assignment – structure **5b** (13*S*, OH: *exo* = β) for baptifoline (**A**) and structure **5a** (13*R*, OH: *endo* = α) for epibaptifoline (**B**) – is still the official one according to CAS/SciFinder, although its correctness has never been approved by modern techniques.

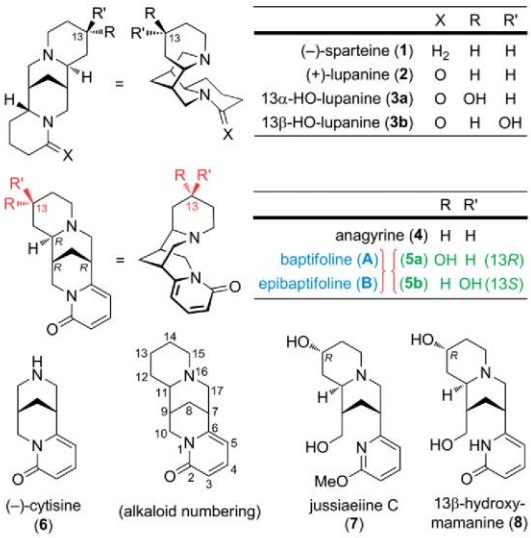

Figure 1. The prominent bisquinolizidine alkaloids **1**, **2**, **4**, and **6**, the C-13-oxidized derivatives of **2** and **4**, **3a**/**3b** and **A**/**B**, and the natural degradation products of **A**, **7** and **8**.

In several more recent publications, the opposite configuration at C-13, thus **5a** for **A** and **5b** for **B**, is purposely drawn,[3,14,15] but this change was neither mentioned nor explained. The latter stereochemistry is supported by the fact that the natural products jussiaeiine C (**7**)[16] and 13β-hydroxymamanine (**8**),[14] which are both supposed to be oxidative cleavage products of natural baptifoline (**A**), are known to possess *R* configuration at the alcohol function. To dissolve the confusion about the C-13

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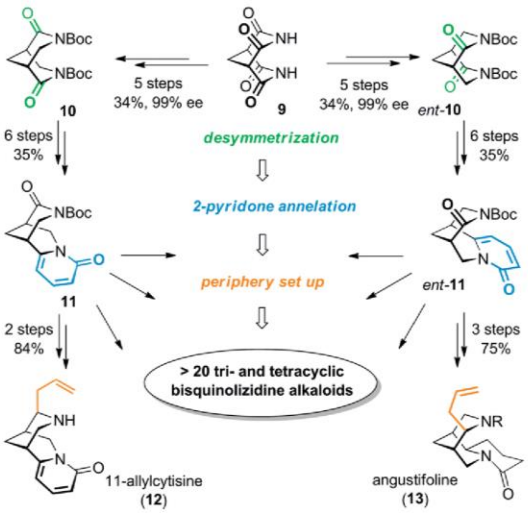
stereocenter in **A** and **B**, their configurations have to be re-determined unequivocally.

We recently developed a modular "inside-out" route to bisquinolizidine alkaloids that permits enantioselective access to a variety of members of this class (> 20 synthesized, Scheme 1).[17,18] Desymmetrization of achiral tetraoxobispidine (**9**) provided the *N*-Boc activated bispidine lactam **10** or, optionally, *ent*-**10** in 99 % *ee*. α,*N*-Annulation of a 2-pyridone afforded **11** and *ent*-**11**, which were transformed into tetracyclic bisquinolizidine alkaloids by *endo*- or *exo*-selective introduction of a piperidine. Tricyclic derivatives such as 11-allylcytisine (**12**) and angustifoline (**13**) were also successfully prepared by using this approach.

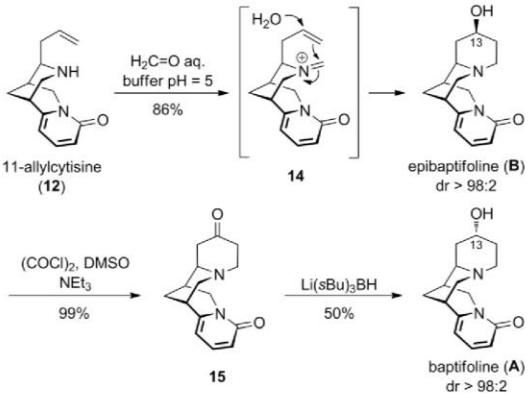


Scheme 1. Modular synthesis of bisquinolizidine alkaloids.[17]

Since **12** is a known precursor to baptifoline (**A**) and epibaptifoline (**B**), we decided to synthesize both alkaloids and to firmly establish the debated configuration at C-13 by NMR studies, chemical transformation, and X-ray analysis.

Results and Discussion

The synthesis of epibaptifoline (**B**) and baptifoline (**A**) started with 11-allylcytisine (**12**, Scheme 2), prepared according to Scheme 1.[17,19] Following Bohlmann's original procedure,[9] the tricyclic alkaloid **12** was simply treated with aqueous formaldehyde in a phosphate buffer (pH = 5), which delivered synthetic epibaptifoline (**B**) in high 86 % yield as a single diastereomer (*dr* > 98:2,[20] structure **5b**, assignment see below). The reaction presumably proceeds via the intermediate **14** and involves an attack of the double bond on the electrophilic iminium function.[9] To convert **B** into baptifoline (**A**), we initially intended to invert the stereocenter at C-13 via an S_N2 reaction.[21] All attempts (e.g. PPh_3, DIAD, HOAc or 1. TsCl or MsCl; 2. HOAc), however, failed to give decent amounts of *O*-acetylated **A**. We therefore switched to an oxidation–reduction sequence: Swern oxidation of **B** quantitatively provided the ketone **15**, which was reduced with L-selectride, giving baptifoline (**A**) in 50 % yield as the only product (*dr* > 98:2,[20] structure **5a**, assignment see below). All characterization data (IR, ^1H and ^{13}C NMR, optical rotation, and melting point) of synthetic baptifoline (**A**) and epibaptifoline (**B**) excellently matched the data published for the natural products,[22–25] and, thus, prove their identity. The central bispidine core of both alkaloids **A** and **B** adopts the expected chair-chair conformation, as evident from the small coupling constants ($J \leq 2.6$ Hz) between 17-H_{exo} and the bridgehead proton 7-H (synclinal arrangement).[26–28]



Scheme 2. Synthesis of epibaptifoline (**B**) and baptifoline (**A**) from **12**. See below for the assignment of the configuration of **A** and **B** at C-13.

The NMR spectra[28] of **A** and **B** provide several clues on the configuration of the stereocenter at C-13, all indicating that the attached hydroxy group is located equatorially in epibaptifoline (**B**) and axially in baptifoline (**A**, Figure 2): (i) In the ^1H NMR of **A**, the signals of 12-H_{ax} and 14-H_{ax} each accommodate a triplet with a large coupling constant (J = 13.3 Hz and J = 14.0 Hz) that originates from the geminal coupling with the corresponding equatorial protons and the vicinal, 1,2-diaxial coupling with 11-H_{ax} and 15-H_{ax}, respectively, as obvious from their coupling constants. A further large 1,2-diaxial coupling, as expected if 13-H occupies the axial position, is not present. In contrast to that, the quartet ($J \approx$ 13.3 Hz) observed for 12-H_{ax} in the ^1H NMR spectrum of epibaptifoline (**B**) clearly indicates a 1,2-diaxial arrangement between 12-H_{ax} and 13-H.[29] The overall widths of the 13-H multiplets are in good agreement with that, too. The signal in **A** is too small (<15 Hz) to harbor two large 1,2-diaxial couplings (with 12-H_{ax} and 14-H_{ax}), whereas the width of that in **B** is more than sufficient (> 35 Hz). (ii) The chemical shift of 13-H is 3.71 ppm in **B** and 4.29 ppm in **A**. The downfield shift of the latter one, caused by the magnetic anisotropy of the over-next, collinear C,C-bond, is typical for equatorial protons in six-membered rings adopting a chair conformation, as known, for example, from the α/β-anomers of carbohydrates.[30] (iii) An axial hydroxyl group at C-13 will exert a γ-effect[30a] on the resonances of C-11 and C-15. The expected upfield shift is found in baptifoline (**A**, $\Delta\delta_{C-11}$ = −5.4 ppm and $\Delta\delta_{C-15}$ = −3.3 ppm). (iv) NOESY interactions of 11-H_{ax} and 15-

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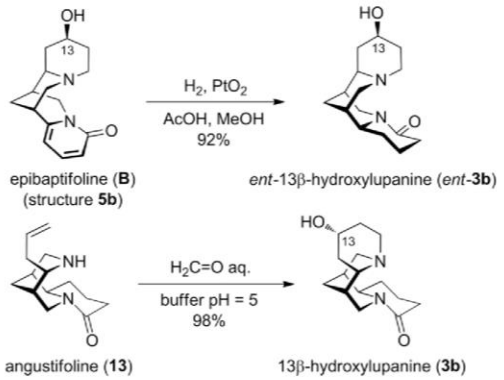
H_{ax} with 13-H, which prove an axial orientation of 13-H, are observed in epibaptifoline (**B**), but not in baptifoline (**A**). All these findings point out that the annulated piperidine adopts chair conformation in both alkaloids,[29] and that the alcohol function is axial (*endo*, α) in baptifoline (**A**), hinting at structure **5a** with 13*R* configuration, and equatorial (*exo*, β) in epibaptifoline (**B**), as depicted in structure **5b** with 13*S* configuration.

Figure 2. Selected 1,2-diaxial couplings, NOESY interactions, and ^{13}C shifts in the *exo*-fused piperidine of baptifoline (**A**) and epibaptifoline (**B**).

The NMR spectroscopically derived orientation of the alcohol functions in **A** and **B** is also in good agreement with stereochemistry observed in the synthesis of both compounds (see Scheme 2). The cyclization of **12** occurs under thermodynamic conditions, which will provide the energetically favored diastereomer **5b** with the equatorial hydroxy group and that is epibaptifoline (**B**). Furthermore, the sterically demanding hydride transfer reagent L-selectride will preferentially attack the ketone **15** in an equatorial fashion from the less hindered *exo*-side, thus leading to the epimer **5a** with the axial hydroxy group, which is baptifoline (**A**).

To further corroborate the configuration at C-13, epibaptifoline (**B**) was partially hydrogenated over PtO_2, which provided a 13-hydroxylupanine in good 92 % yield (Scheme 3). All spectroscopic data of this compound were fully identical with those reported for natural 13β-hydroxylupanine (**3b**)[4] and those of synthetic **3b**, prepared in 98 % yield by treatment of angustifoline (**13**) with aqueous formaldehyde. Since the equatorial (*exo*, β) orientation of the alcohol function in natural **3b** is firmly established,[5,31] the hydrogenation product must be *ent*-**3b** (the core of **B** is enantiomeric to that of **3** and **13**), and, thus, epibaptifoline (**B**) must carry an equatorial hydroxy group as in structure **5b**.



Scheme 3. Hydrogenation of epibaptifoline (**B**) to *ent*-13β-hydroxylupanine (*ent*-**3b**) and synthesis of 13β-hydroxylupanine (**3b**) from angustifoline (**13**).

Finally, we were able to get crystals of epibaptifoline (**B**) suitable for X-ray analysis (Figure 3).[32,33] In agreement with the preceding findings, the crystal structure confirms the chair-chair conformation of the central bispidine core, the axial orientation and chair-form of the *exo*-α,*N*-annulated piperidine, and the equatorial (*exo*, β) position of the alcohol function at C-13.

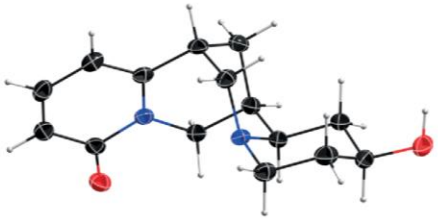


Figure 3. Crystal structure of epibaptifoline (**B**).[32,33]

Conclusions

Epibaptifoline (**B**) was synthesized from 11-allylcytisine (**12**) and converted into baptifoline (**A**) via an oxidation-reduction sequence. The configuration at C-13 bearing the alcohol function was unequivocally determined by ^1H NMR studies, chemical transformation, and X-ray analysis. The currently used stereostructures have to be revised at C-13: The correct stereostructure of baptifoline (**A**) is given by **5a** (configuration: 7*R*, 9*R*, 11*R*, 13*R*), with the hydroxyl group in axial (*endo*, α) position. Accordingly, its C-13 epimer, epibaptifoline (**B**), carries an equatorial (*exo*, β) hydroxy group as shown in structure **5b** (configuration: 7*R*, 9*R*, 11*R*, 13*S*).

Experimental Section

Reactions were monitored by thin layer chromatography on precoated silica gel (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. 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. 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).

Epibaptifoline (B, Structure 5b): According to a literature procedure,[9] a solution of 11-allylcytisine[17] (**12**, 110 mg, 478 μmol) and formaldehyde (37 % aq.; 680 μL, 8.37 mmol) in phosphate buffer (0.1 M, 12 mL, pH = 5) was stirred for 19 h at 45 °C. The reaction mixture was basified with aq. NaOH (2.0 M, 4 mL) and the aqueous layer was extracted with $CHCl_3$ (5 × 15 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed under vacuum. Column chromatography (SiO_2, $CHCl_3$/MeOH, 95:5 →

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90:10) delivered epibaptifoline (**B**, 107 mg, 411 µmol, 86 %) as a white crystalline solid. R_f = 0.24 ($CHCl_3$/MeOH, 90:10). Mp. 214 °C {ref.[3,10] m.p. 215 °C}. $[\alpha]_D^{24}$ = –139.0 (*c* = 1.0, EtOH) {ref.[3,10] $[\alpha]_D$ = –138.9 (no further data given)}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (m, 1 H, H-4), 6.42 (dd, *J* = 9.0, 1.2 Hz, 1 H, H-3), 5.98 (dd, *J* = 6.9, 0.9 Hz, 1 H, H-5), 4.06 (d, *J* = 15.5 Hz, 1 H, H-10), 3.90 (dd, *J* = 15.5, 6.7 Hz, 1 H, H-10), 3.71 (m, 1 H, H-13_{ax}), 3.23 (dd, *J* = 10.7, 2.5 Hz, 1 H, H-17), 2.94 (d, *J* = 1.7 Hz, 1 H, H-7), 2.87 (d, *J* = 12.4 Hz, 1 H, H-11_{ax}), 2.69 (m, 2 H, 2 × H-15), 2.44 (ddd, *J* = 10.7, 2.6, 1.5 Hz, 1 H, H-17), 2.24 (br. s, 1 H, OH), 2.20 (m, 1 H, H-9), 1.96 (d, *J* = 13.1 Hz, 1 H, H-8), 1.77 (q, *J* = 12.3 Hz, 1 H, H-12_{ax}), 1.70 (dd, *J* = 13.1, 1.2 Hz, 1 H, H-8), 1.53 (m, 3 H, 2 × H-14, H-12_{eq}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.68 (C-2), 151.69 (C-6), 138.84 (C-4), 116.90 (C-3), 104.64 (C-5), 70.27 (C-13), 61.32 (C-11), 52.60 (C-17), 52.23 (C-15), 51.65 (C-10), 35.56 (C-7), 32.33 (C-9), 31.97 (C-12), 28.72 (C-14), 20.88 (C-8) ppm. IR (ATR): $\tilde{\nu}$ = 3332, 2934, 2856, 1647, 1546, 1361, 1137, 1033, 980, 800, 729 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{21}N_2O_2$ [M + H]$^+$: 261.15975, found 261.15912. All NMR spectroscopic data of synthetic **B** were in excellent agreement with those reported for the natural product.[23–25]

Baptifoline (A, Structure 5a): Under an argon atmosphere, a solution of DMSO (59.0 µL, 690 µmol) in anhydr. CH_2Cl_2 (2 mL) was slowly treated with $(COCl)_2$ (0.55 M in CH_2Cl_2, 630 µL, 347 µmol) at –78 °C and stirred for 20 min. A solution of epibaptifoline (**B**, 30.0 mg, 115 µmol) in CH_2Cl_2 (1 mL) was added. After 3 h, the reaction mixture was treated with NEt_3 (159 µL, 1.15 mmol) and allowed to reach room temp. within 1 h. H_2O (3 mL) was added and the aqueous layer was extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. Column chromatography (SiO_2, $CHCl_3$/MeOH, 99:1 → 95:5) delivered the ketone **15** (29.4 mg, 114 µmol, 99 %), which was dissolved in anhydr. THF (1 mL) and cooled to 0 °C. L-Selectride (0.1 M in THF, 1.20 mL, 120 µmol) was added and the reaction mixture was stirred for 10 min. Sat. aq. $NaHCO_3$ (4 mL) was added and the aqueous layer was extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. Column chromatography (SiO_2, $CHCl_3$/MeOH, 95:5 → 85:15) delivered baptifoline (**A**, 14.8 mg, 56.9 µmol, 50 %) as a white solid. R_f = 0.20 ($CHCl_3$/MeOH, 90:10). Mp. 208 °C {ref.[3] 208 °C; ref.[34] 210 °C}. $[\alpha]_D^{23}$ = –134.7 (*c* = 0.5, EtOH) {ref.[3,34] $[\alpha]_D$ = –135 (EtOH, concentration not given)}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (m, 1 H, H-4), 6.42 (dd, *J* = 9.0, 1.2 Hz, 1 H, H-3), 5.96 (dd, *J* = 6.9, 0.9 Hz, 1 H, H-5), 4.29 (m, 1 H, H-13_{eq}), 4.08 (d, *J* = 15.4 Hz, 1 H, H-10), 3.91 (dd, *J* = 15.4, 6.7 Hz, 1 H, H-10), 3.44 (d, *J* = 12.8 Hz, 1 H, H-11_{ax}), 3.32 (dd, *J* = 10.8, 2.6 Hz, 1 H, H-17), 3.20 (td, *J* = 14.0, 2.9 Hz, 1 H, H-15_{ax}), 2.95 (s, 1 H, H-7), 2.46 (d, *J* = 10.0 Hz, 1 H, H-17), 2.40 (dd, *J* = 14.1, 4.0 Hz, 1 H, H-15_{eq}), 2.12 (td, *J* = 13.3, 2.5 Hz, 1 H, H-12_{ax}), 2.09 (m, 1 H, H-9), 2.00–1.90 (m, 2 H, OH, H-8), 1.88 (tdd, *J* = 14.0, 4.3, 2.8 Hz, 1 H, H-14_{ax}), 1.69 (d, *J* = 13.1 Hz, 1 H, H-8), 1.32–1.20 (m, 2 H, H-12_{eq}, H-14_{eq}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.71 (C-2), 151.98 (C-6), 138.83 (C-4), 116.78 (C-3), 104.74 (C-5), 65.87 (C-13), 55.87 (C-11), 52.14 (C-17), 51.74 (C-10), 47.86 (C-15), 35.51 (C-7), 32.06 (C-9), 29.04 (C-12), 25.91 (C-14), 20.70 (C-8) ppm. IR (ATR): $\tilde{\nu}$ = 3342, 2927, 1645, 1544, 1425, 1142, 1037, 961, 798, 749, 663 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{21}N_2O_2$ [M + H]$^+$: 261.15975, found 261.15921. All NMR spectroscopic data of synthetic **A** were in excellent agreement with those reported for the natural product.[22,24,25]

***Ent*-13β-Hydroxylupanine (*ent*-3b):** A mixture of epibaptifoline (**B**, 19.8 mg, 76.0 µmol), AcOH (4.5 µL, 78.7 µmol) and PtO_2 (3.45 mg, 15.2 µmol) in MeOH (0.5 mL) were stirred at room temp. under an H_2 atmosphere (1 atm.) for 22 h. The reaction mixture was filtered through a pad of SiO_2 and the filter cake was thoroughly washed ($CHCl_3$/MeOH/NH_3, 85:13.5:1.5, 20 mL). Removal of the solvent in vacuo delivered *ent*-13β-hydroxylupanine (*ent*-**3b**; 18.4 mg, 69.9 µmol, 92 %) as a colorless oil. R_f = 0.30 ($CHCl_3$/MeOH/NH_3, 90:9:1). $[\alpha]_D^{26}$ = –63.0 (*c* = 1.0, EtOH) {ref.[3,4a] $[\alpha]_D$ = +63.7 (EtOH, concentration not given) for the enantiomer}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.53 (d, *J* = 13.3 Hz, 1 H, H-10), 3.60 (m, 1 H, H-13), 3.32 (m, 1 H, H-6), 2.88 (m, 1 H, 17-H), 2.78 (d, *J* = 11.8 Hz, 1 H, H-15), 2.55 (d, *J* = 13.3 Hz, 1 H, H-10), 2.46 (d, *J* = 17.2 Hz,1 H, H-3), 2.30 (m, 1 H, H-3), 2.16 (d, *J* = 11.9 Hz, 1 H, H-8), 2.10–1.96 (m, 3 H, H-7, H-15, H-17), 1.73–1.88 (m, 5 H, H-4, H-5, H-11, H-12, H-14), 1.68 (s, 1 H, H-9), 1.65–1.47 (m, 4 H, OH, H-4, H-5, H-14), 1.41 (m, 1 H, H-12), 1.29 (d, *J* = 12.4 Hz, H-8) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.38 (C-2), 69.10 (C-13), 61.32 (C-11), 60.79 (C-6), 52.92 (C-15), 51.67 (C-17), 46.89 (C-10), 41.79 (C-12), 34.57 (C-9), 34.10 (C-14), 33.19 (C-3), 32.63 (C-7), 27.55 (C-5), 26.84 (C-8), 19.76 (C-4) ppm. IR (ATR): $\tilde{\nu}$ = 3399, 2928, 2862, 1615, 1444, 1257, 1081, 1026, 1001, 729 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{25}N_2O_2$ [M + H]$^+$: 265.19105, found 261.19034. All NMR spectroscopic data of *ent*-**3b** were in excellent agreement with those reported for the enantiomeric natural product.[5,35]

13β-Hydroxylupanine (3b): A solution of angustifoline[17] (**13**, 20.0 mg, 85.3 µmol) and formaldehyde (37 % aq.; 85.4 µL, 1.05 mmol) in phosphate buffer (0.1 M, 2 mL, pH = 5) was stirred for 19 h at 45 °C. The reaction mixture was basified with aq. NaOH (2.0 M, 2 mL). The aqueous layer was extracted with $CHCl_3$ (5 × 5 mL), the organic layer was dried with Na_2SO_4, and the solvent was removed under vacuum. Column chromatography (SiO_2, $CHCl_3$/MeOH/NH_3, 99:0.9:0.1 → 95:4.5:0.5) delivered 13β-hydroxylupanine (**3b**, 22.2 mg, 84.0 µmol, 98 %) as a colorless oil. R_f = 0.30 ($CHCl_3$/MeOH/NH_3, 90:9:1). $[\alpha]_D^{24}$ = +62.7 (*c* = 1.0, EtOH) {ref.[3,4a] $[\alpha]_D$ = +63.7 (EtOH, concentration not given)}. All NMR spectroscopic data of **3b** were in excellent agreement with those reported above for *ent*-**3b** and with those reported for the natural product.[5,35]

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Keywords: Alkaloids · Asymmetric synthesis · Configuration determination · Quinolizidine · Bispidine

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[25] For a tabular comparison of all NMR spectroscopic data, see Supporting Information.

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[29] In the ^{1}H NMR spectrum of epibaptifoline (**B**), the signals of 15-H_{ax}/15-H_{eq} (δ = 2.69 ppm) and 14-H_{ax}/14-H_{eq} (δ = 1.53 ppm) are isochronous. The widths of these multiplets (<15 Hz) are too small to harbor large 1,2-diaxial coupling constants, which hints at a distorted chair conformation in this region.

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Supporting Information

The Hydroxylated, Tetracyclic Bisquinolizidine Alkaloids Baptifol-ine and Epibaptifoline: Enantioselective Synthesis and Unambiguous Assignment of their Configuration at C-13

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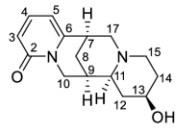

1. Tabular Comparison of NMR Data

Table S1. Epibaptifoline (**B**, structure **5b**).

Pos.	^{1}H NMR (δ in ppm, J in Hz)[a]			^{13}C NMR (δ in ppm)[a]		
	Synthetic[b]	Natural[c] (ref. [1])	$\lvert\Delta\delta\rvert$	Synthetic[b]	Natural[c] (ref. [1,2])	$\lvert\Delta\delta\rvert$
2				163.68	163.67	0.01
3	6.42 dd (9.0, 1.2)	6.44 dd (9.0, 1.5)	0.02	116.90	116.78	0.12
4	7.26 m	7.29 dd (9.0, 6.8)	0.03	138.84	138.81	0.03
5	5.98 dd (6.9, 0.9)	6.00 dd (6.8, 1.5)	0.02	104.64	104.67	0.03
6				151.69	151.70	0.01
7	2.94 d (1.7)	2.97 m	0.03	35.56	35.57	0.01
8	1.70 dd (13.1, 1.2) 1.96 d (13.1)	1.77 m 1.99 m	0.07 0.03	20.88	20.84	0.04
9	2.20 m	2.21 m	0.01	32.33	32.34	0.01
10	3.90 dd (15.5, 6.7) 4.06 d (15.5)	3.92 dd (15.4, 7.6) 4.07 d (15.4)	0.02 0.01	51.65	51.62	0.03
11	2.87 d (12.4) [ax]	2.90 d[d]	0.03	61.32	61.34	0.02
12	1.53 m [eq] 1.77 q (12.3) [ax]	1.55 m 1.77 m	0.02 0.00	31.97	32.09	0.12
13	3.71 m [ax] 2.24 br s (OH)	3.73 m 2.21 m (OH)	0.02 0.03	70.27	70.09	0.18
14	1.53 m 1.53 m	1.55 m 1.55 m	0.02 0.02	28.72	28.74	0.02
15	2.69 m 2.69 m	2.71 m 2.71 m	0.02 0.02	52.23	52.22	0.01
17	2.44 ddd (10.7, 2.6, 1.5) 3.23 dd (10.7, 2.5)	2.46 dq[d] 3.25 q[d]	0.02 0.02	52.60	52.65	0.05

[a] Synthetic material was measured at 500 MHz (^{1}H) and 125 MHz (^{13}C) in $CDCl_3$; natural material was measured at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$.[1] [b] The positions of all protons and carbon atoms were assigned on basis of COSY, HSQC and HMBC measurements. The orientations (axial vs. equatorial) of the protons were assigned on basis of NOESY measurements and the (non)existence of 1,2-diaxial couplings. [c] There were no assignments in the original literature except for the OH group. [d] No coupling constants given.

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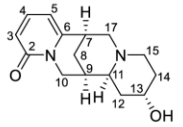


Table S2. Baptifoline (**A**, structure **5a**).

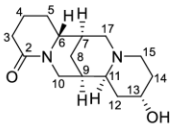
Pos.	^{1}H NMR (δ in ppm, J in Hz)[a]			^{13}C NMR (δ in ppm)[a]		
	Synthetic[b]	Natural (ref. [3])	$\lvert\Delta\delta\rvert$	Synthetic[b]	Natural (ref. [2,3])	$\lvert\Delta\delta\rvert$
2				163.71	163.6	0.1
3	6.42 dd (9.0, 1.2)	6.40 dd (9.0, 1.0)	0.02	116.78	116.5	0.3
4	7.26 m	7.26 dd (9.0, 7.0)	0.00	138.83	138.9	0.1
5	5.96 dd (6.9, 0.9)	5.97 dd (7.0, 1.3)	0.01	104.74	105.0	0.3
6				151.98	151.8	0.2
7	2.95 s	2.95 m	0.00	35.51	35.2	0.3
8	1.69 d (13.1) 1.90-2.00 m	1.67 br d (13.0) 1.97 br d (13.0)	0.02 0.00	20.70	20.4	0.3
9	2.09 m	2.08 m	0.01	32.06	31.8	0.3
10	3.91 dd (15.4, 6.7) 4.08 d (15.4)	3.88 dd (15.4, 6.6) 4.06 br d (15.4)	0.03 0.02	51.74	51.5	0.2
11	3.44 d (12.8) [ax]	3.44 br dt (13.0, 2.0)	0.00	55.87	55.8[c]	0.1
12	1.20-1.32 m [eq] 2.12 td (13.3, 2.5) [ax]	1.25 br d (14.0) 2.10 br dt (14.0, 2.5)	0.00 0.02	29.04	29.0	0.0
13	4.29 m [eq] 1.90-2.00 m (OH)	4.26 m ---	0.03 ---	65.87	65.3[c]	0.6
14	1.20-1.32 m [eq] 1.88 tdd (14.0, 4.3, 2.8) [ax]	1.31 br d (13.5) 1.85 td (13.5, 2.0)	0.00 0.03	25.91	25.7	0.2
15	2.40 dd (14.1, 4.0) [eq] 3.20 td (14.0, 2.9) [ax]	2.37 br d (14.0) 3.19 td (14.0, 2.8)	0.03 0.01	47.86	47.8	0.1
17	2.46 d (10.0) 3.32 dd (10.8, 2.6)	2.45 br d (10.7) 3.33 br d (10.7)	0.01 0.01	52.14	52.1	0.0

[a] Synthetic material was measured at 500 MHz (^{1}H) and 125 MHz (^{13}C) in $CDCl_3$; natural material was measured at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$.[3] [b] The positions of all protons and carbon atoms were assigned on basis of COSY, HSQC and HMBC measurements. The orientations (axial vs. equatorial) of the protons were assigned on basis of NOESY measurements and the (non)existence of 1,2-diaxial couplings. [c] C-11 and C-13 were incorrectly assigned in the original literature.[3]

[3] E. J. Kennelly, T. J. Flynn, E. P. Mazzola, J. A. Roach, T. G. McCloud, D. E: Danford, J. M. Betz, *J. Nat. Prod.* **1999**, *62*, 1385-1389.

4

Table S3. Synthetic *ent*-13β-hydroxylupanine (*ent*-**3b**, from epibaptifoline (**B**)), synthetic 13β-hydroxylupanine (**3b**, from angustifoline (**13**)), and natural 13β-hydroxylupanine (**3b**).



Pos.	^{1}H NMR (δ in ppm, J in Hz)[a]			^{13}C NMR (δ in ppm)[a]		
	Synthetic[b] (*ent*-**3b**, **3b**)	Natural (ref. [4])	$\lvert\Delta\delta\rvert$	Synthetic[b] (*ent*-**3b**, **3b**)	Natural (ref. [4])	$\lvert\Delta\delta\rvert$[c]
2				171.38	171.25	0.13
3	2.30 m 2.46 d (17.2)	2.30 ddd (17.5, 12.4, 5.4) 2.46 ddt (17.4, 4.4, 2.3)	0.00 0.00	33.19	32.42	0.77
4	1.47-1.65 m 1.73-1.88 m	1.62 qdd (13.1, 4.1, 2.5) 1.82 m	0.00 0.00	19.76	19.50	0.26
5	1.47-1.65 m 1.73-1.88 m	1.56 m 1.77 dddd (12.9, 5.8, 2.7, 2.3)	0.00 0.00	27.55	27.31	0.24
6	3.32 m	3.32 ddd (11.2, 5.6, 1.8)	0.00	60.79	60.57	0.22
7	1.96-2.10 m	2.02 m	0.00	32.63	32.24	0.39
8	1.29 d (12.4) 2.16 d (11.9)	1.30 dt (12.3, 2.3) 2.15 dtd (12.3, 4.0, 2.1)	0.01 0.01	26.84	26.62	0.22
9	1.68 s	1.68 m	0.00	34.57	34.35	0.22
10	2.55 d (13.3) 4.53 d (13.3)	2.55 dd (13.3, 2.8) 4.53 dt (13.3, 2.4)	0.00 0.00	46.89	46.71	0.18
11	1.73-1.88 m	1.82 m	0.00	61.32	61.17	0.15
12	1.41 m 1.73-1.88 m	1.43 td (12.0, 11.4) 1.82 m	0.02 0.00	41.79	41.56	0.23
13	1.47-1.65 m (OH) 3.60 m	2.21 (OH) 3.59 tt (10.9, 4.4)	0.01	69.10	68.97	0.13
14	1.47-1.65 m 1.73-1.88 m	1.52 dtd (12.4, 11.4, 4.3) 1.82 m	0.00 0.00	34.10	33.84	0.26
15	1.96-2.10 m 2.78 d (11.8)	2.05 td (12.4, 2.5) 2.77 ddd (12.2, 4.3, 2.5)	0.00 0.01	52.92	52.78	0.14
17	1.96-2.10 m 2.88 m	2.00 d (3.6) 2.87 dd (11.1, 8.9)	0.00 0.01	51.67	51.49	0.18

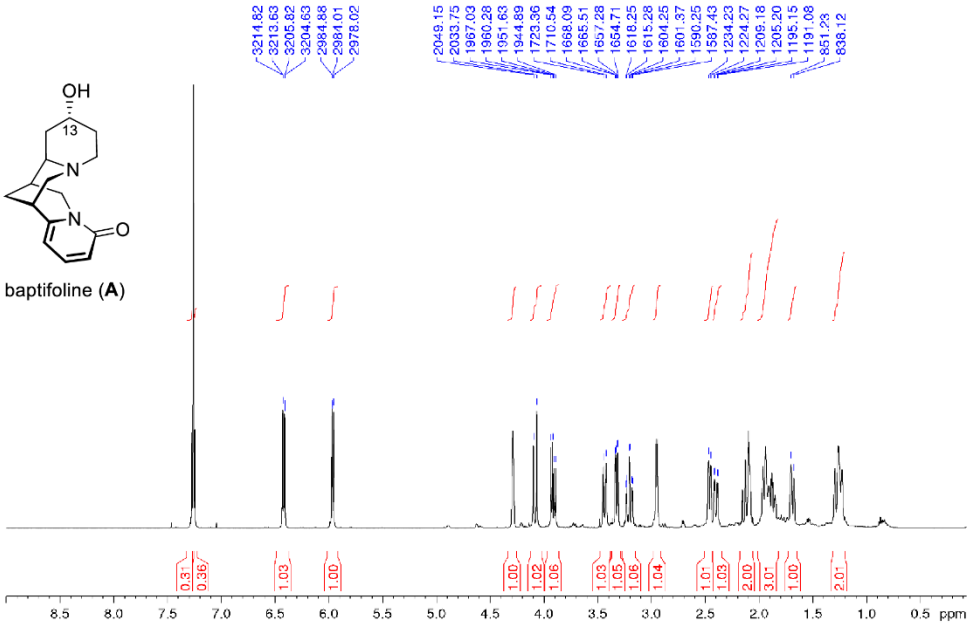
[a] Synthetic material was measured at 500 MHz (^{1}H) and 125 MHz (^{13}C) in $CDCl_3$; natural material was measured at 600 MHz (^{1}H) and 150 MHz (^{13}C) in $CDCl_3$.[4] [b] The positions of all protons and carbon atoms were assigned on basis of COSY, HSQC and HMBC measurements. The orientations (axial vs. equatorial) of the protons were assigned on basis of NOESY measurements and the (non)existence of 1,2-diaxial couplings. [c] Compared to the data reported for natural **3b**, all signals of synthetic *ent*-**3b** and **3b** are shifted downfield by 0.1–0.2 ppm, probably due to a slightly different calibration.

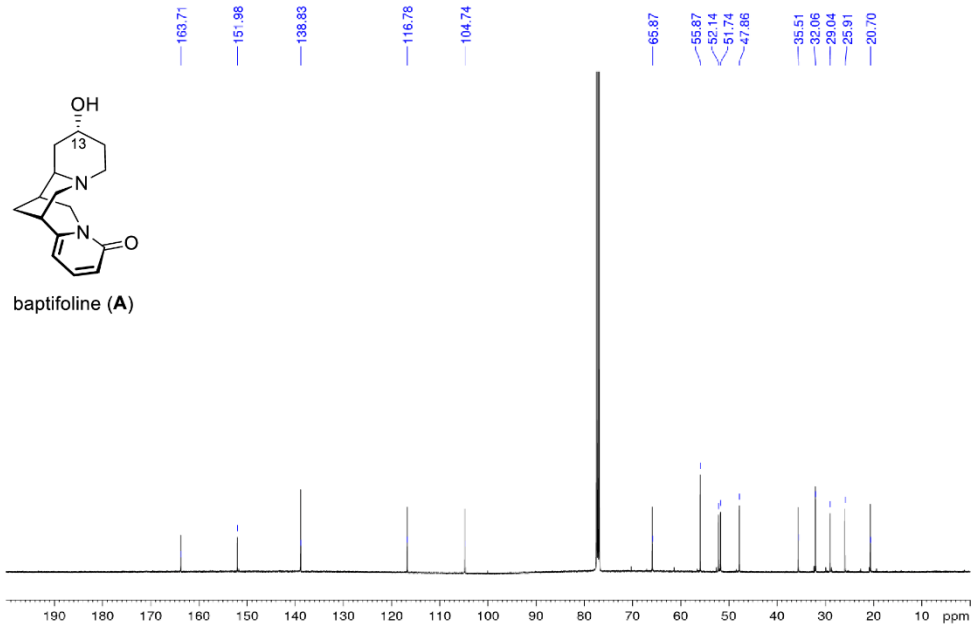
The NMR data of **3b** and *ent*-**3b** match with that of ref.[4], but they differ in some cases from those published in ref.[5].

[4] T. Borowiak, I. Wolska, W. Wysocka, T. Brukwicki, *J. Mol. Struct.* **2005**, *753*, 27-34.
[5] a) F. Bohlmann, R. Zeisberg, *Chem. Ber.* **1975**, *108*, 1043-1051; b) K. Asres, W. A. Gibbons, J. D. Phillipson, P. Mascagni, *Phytochemistry* **1986**, *25*, 1443-1447; c) G. Veen, C. Schmidt, L. Witte, V. Wray, F.-C. Czygan, *Phytochemistry* **1992**, *31*,4343-4345; d) I. van Rensen, V. Wray, L. Witte, P. Canto, R. Greinwald, G. Veen, M. Veit, F.-C. Czygan, *Phytochemistry* **1994**, *35*, 421-424.

2. Copies of ^{1}H and ^{13}C NMR Spectra

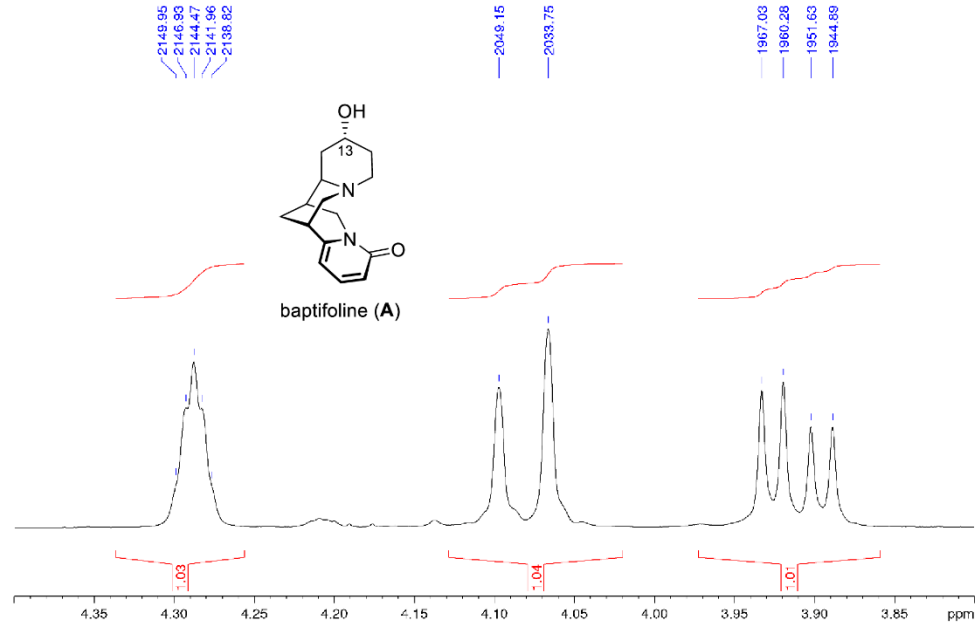
Baptifoline (A, structure 5a):

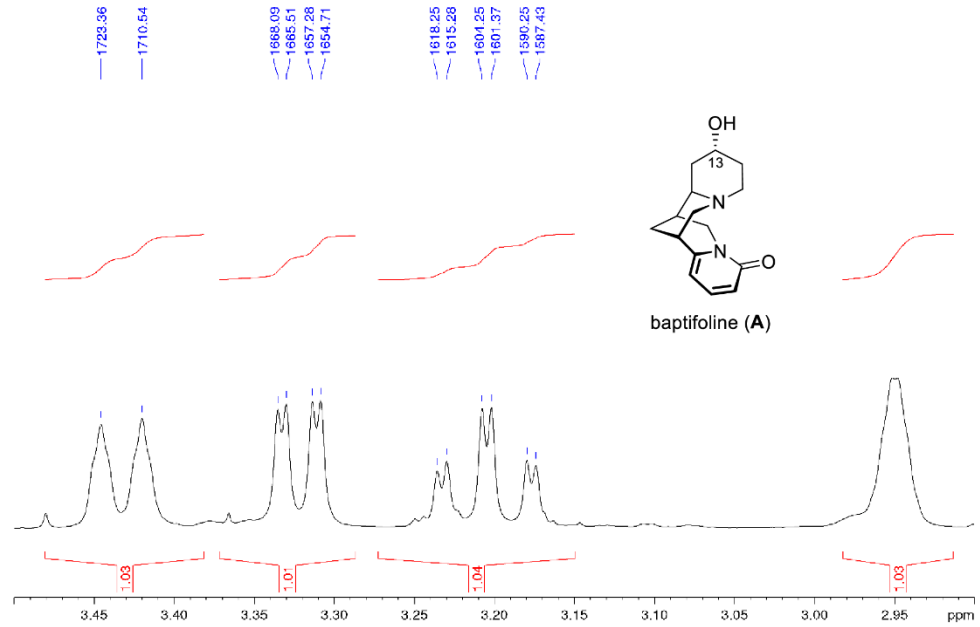




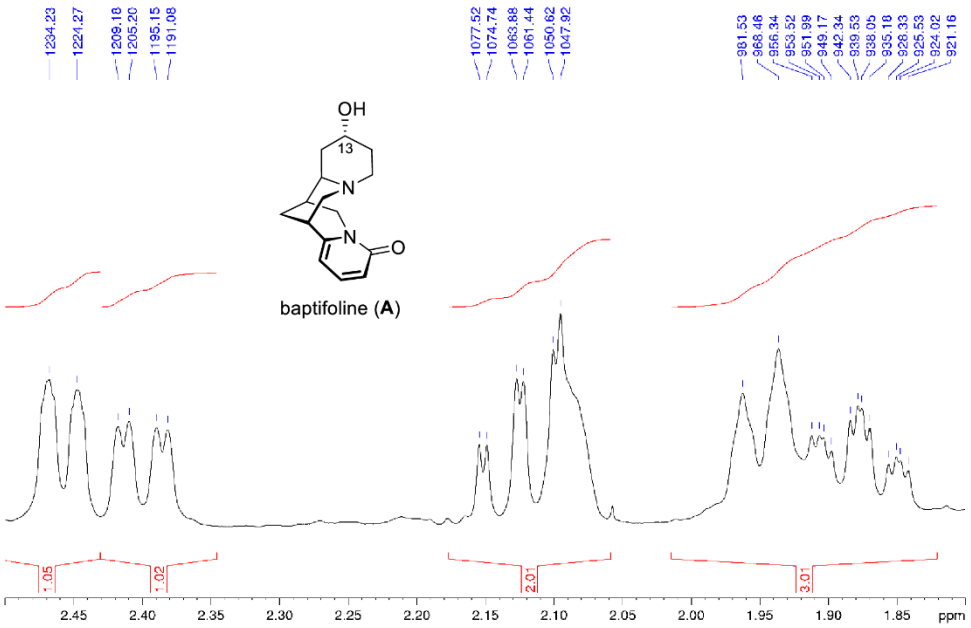
6

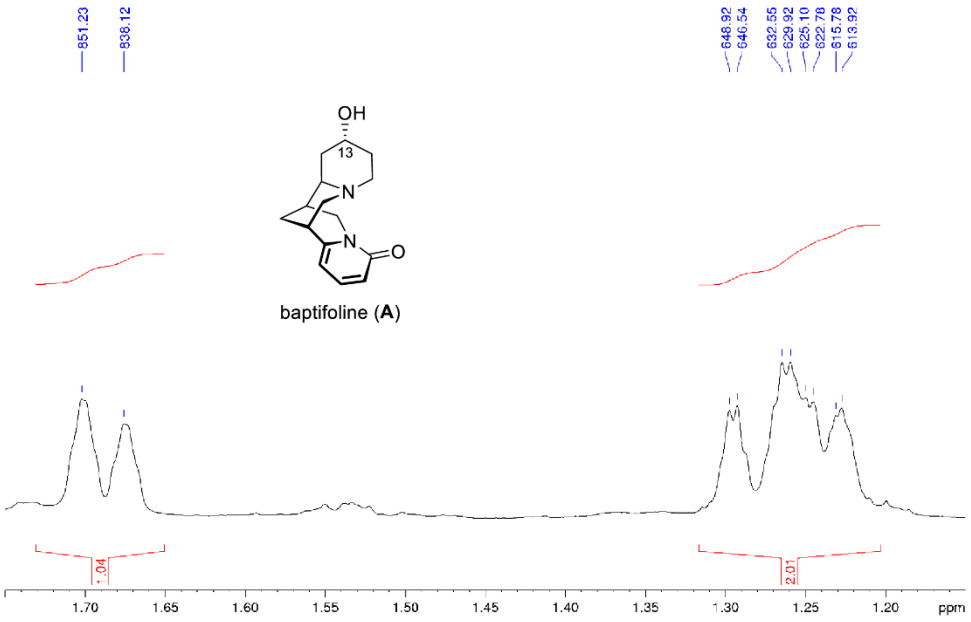
Excerpts of the ^{1}H NMR spectrum of baptifoline (**A**):



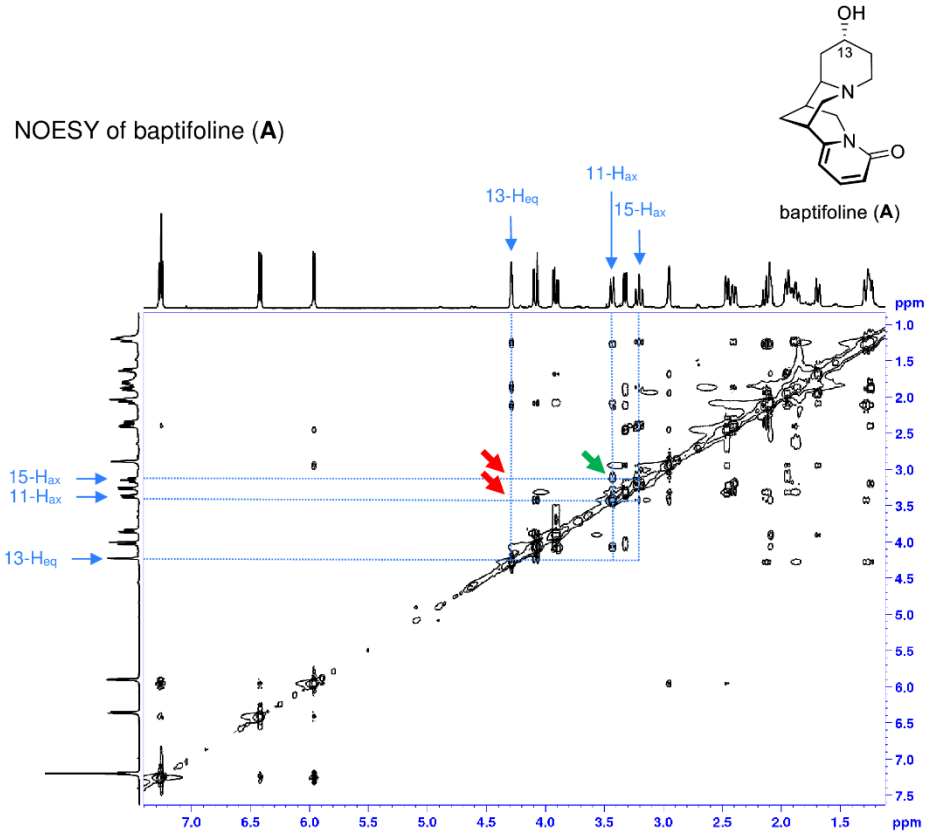


7


1234.23
1224.27
1209.18
1205.20
1195.15
1191.08
1077.52
1074.74
1063.88
1061.44
1050.62
1047.92
981.53
968.46
956.34
953.52
951.99
949.17
942.34
939.53
938.05
935.18
928.33
925.53
924.02
921.16
OH
13
N
N
O
baptifoline (A)
1.05
1.02
2.01
3.01
2.45
2.40
2.35
2.30
2.25
2.20
2.15
2.10
2.05
2.00
1.95
1.90
1.85
ppm

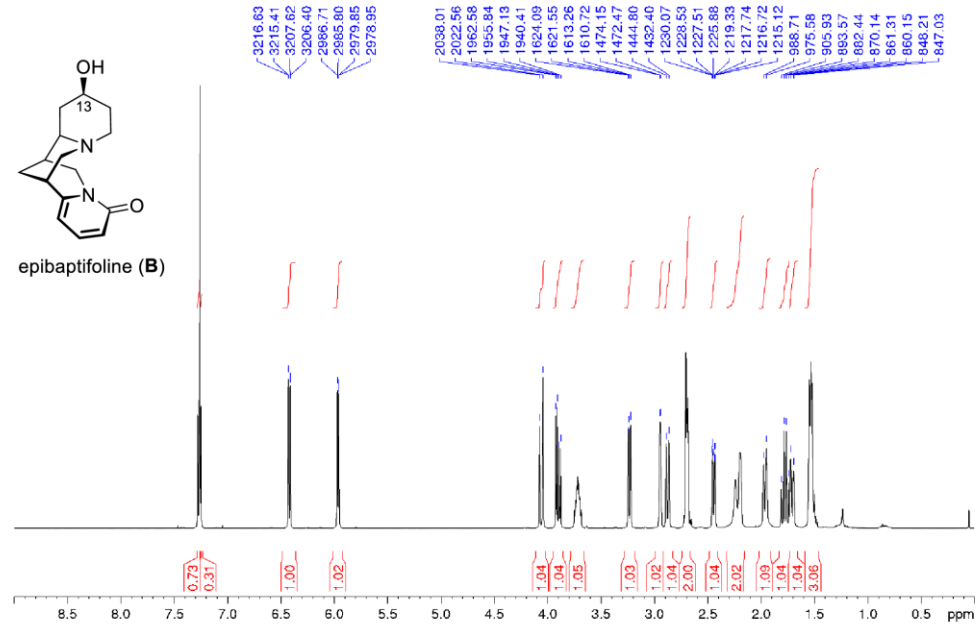

851.23
838.12
648.92
646.54
632.55
629.92
625.10
622.78
615.78
613.92
OH
13
N
N
O
baptifoline (A)
1.04
2.01
1.70
1.65
1.60
1.55
1.50
1.45
1.40
1.35
1.30
1.25
1.20
ppm

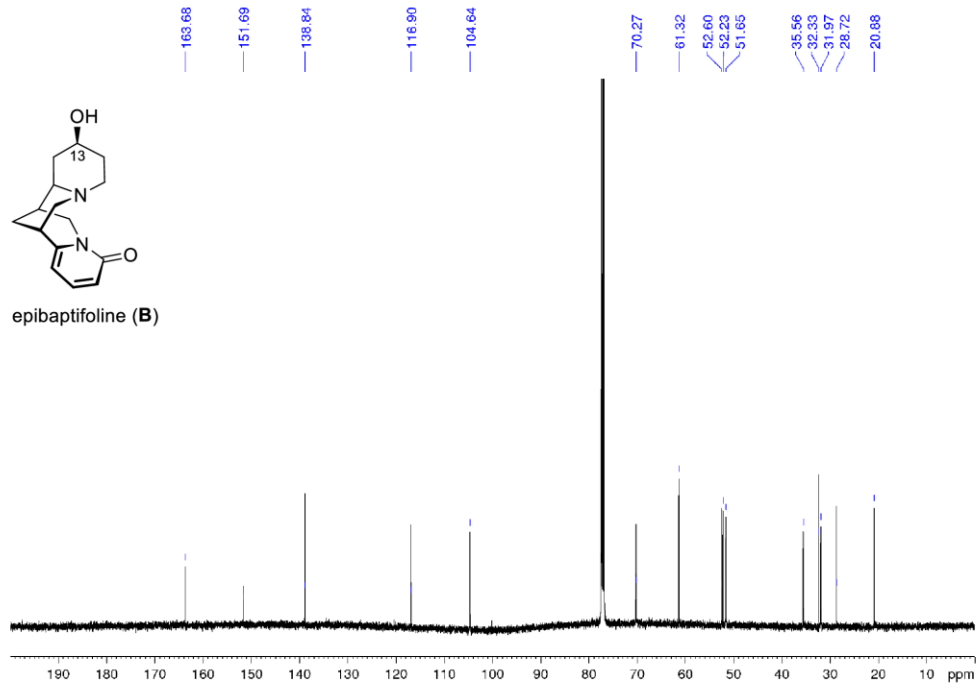
8


NOESY of baptifoline (**A**)
OH
13
N
N
O
baptifoline (**A**)
13-Heq
11-Hax
15-Hax
15-Hax
11-Hax
13-Heq
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
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
ppm

9

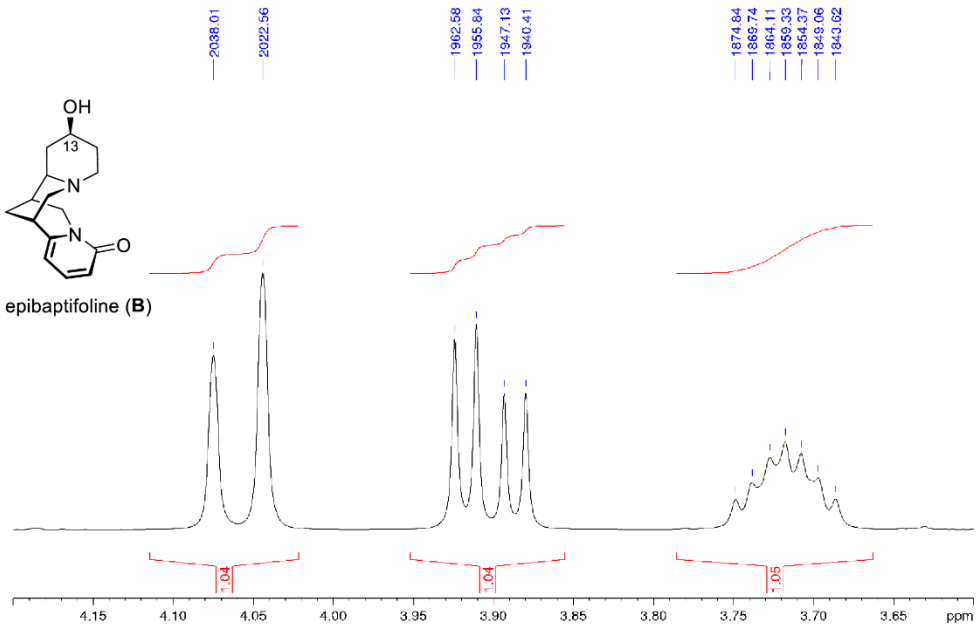
Epibaptifoline (B, structure 5b):

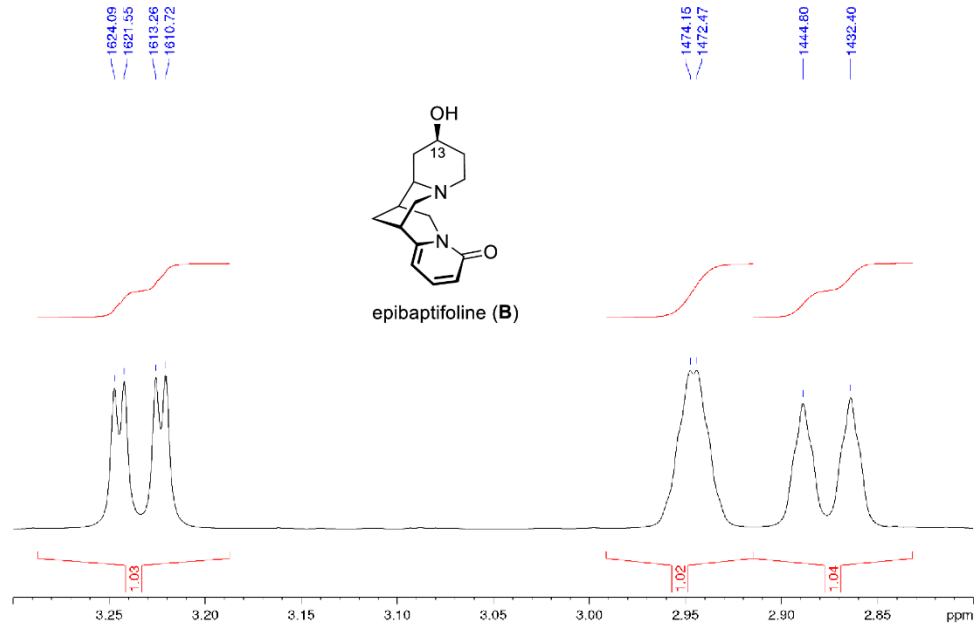




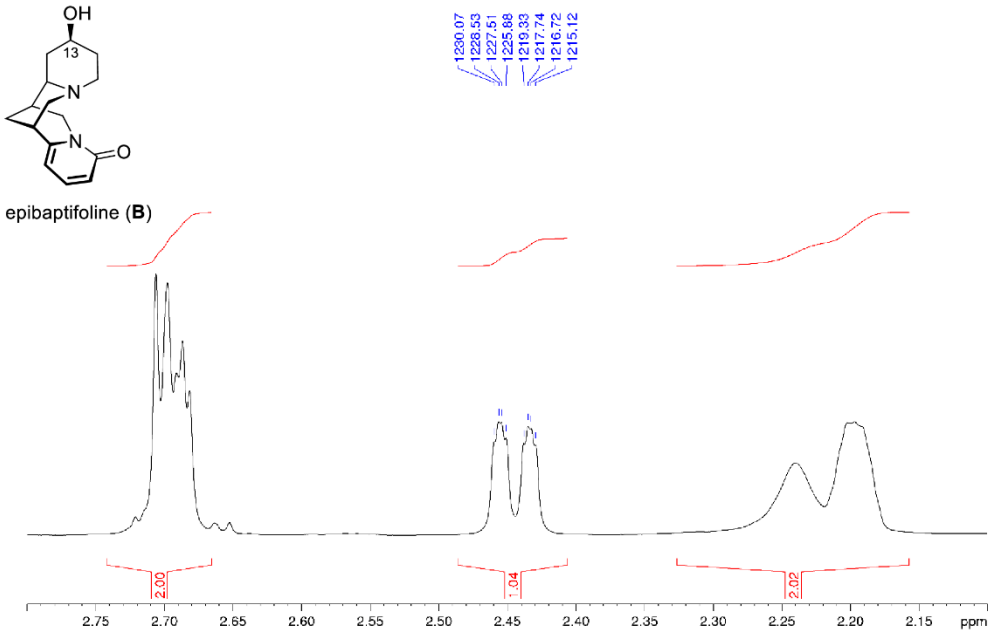
10

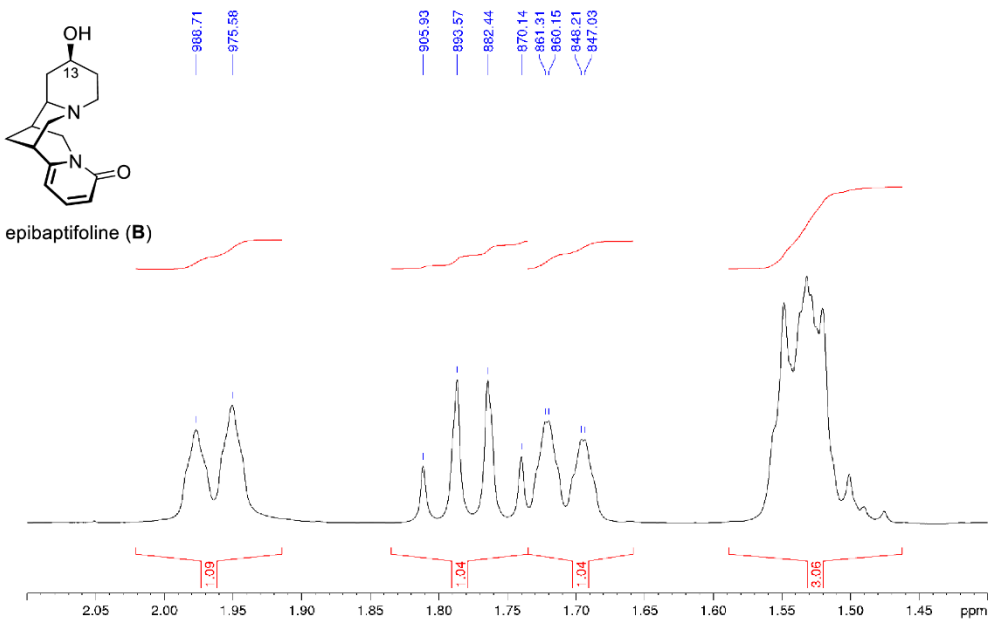
Excerpts of the ^{1}H NMR spectrum of epibaptifoline (**B**):





11


OH
13
N
N
O
epibaptifoline (B)
1230.07
1228.53
1227.51
1225.88
1219.33
1217.74
1216.72
1215.12
2.00
1.04
2.02
2.75
2.70
2.65
2.60
2.55
2.50
2.45
2.40
2.35
2.30
2.25
2.20
2.15
ppm


OH
13
N
N
O
epibaptifoline (B)
988.71
975.58
905.93
893.57
882.44
870.14
861.31
860.15
848.21
847.03
1.09
1.04
1.04
3.06
2.05
2.00
1.95
1.90
1.85
1.80
1.75
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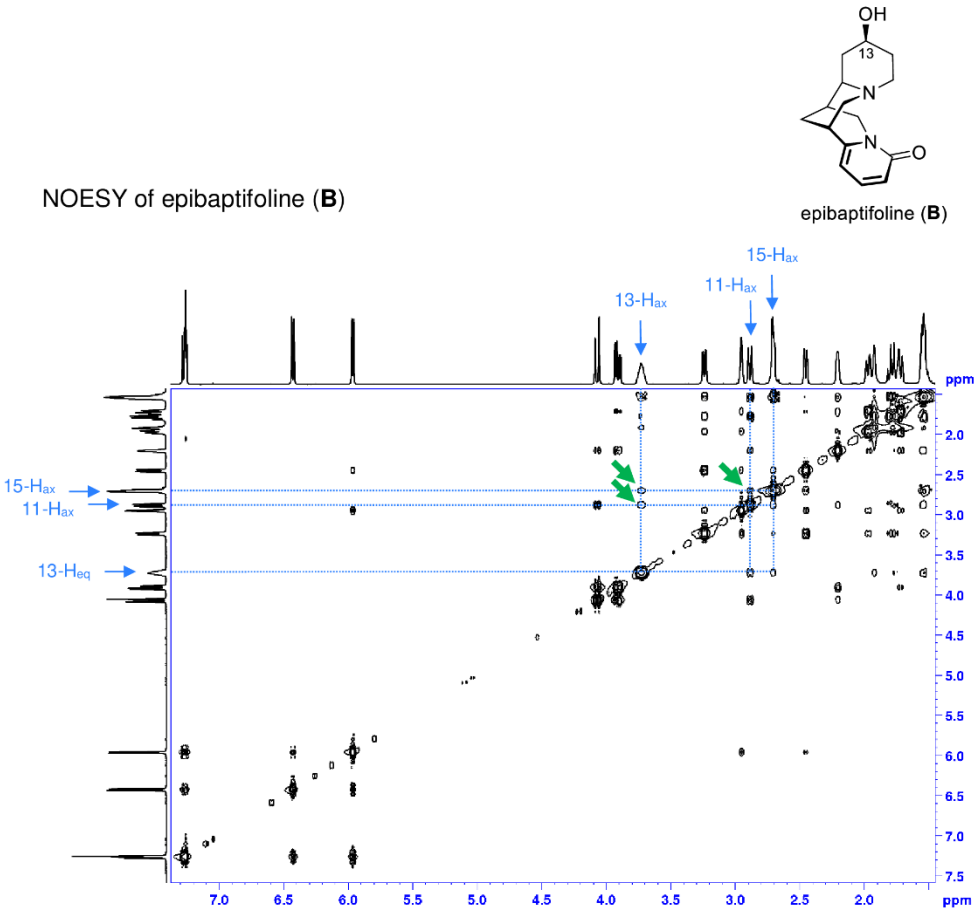
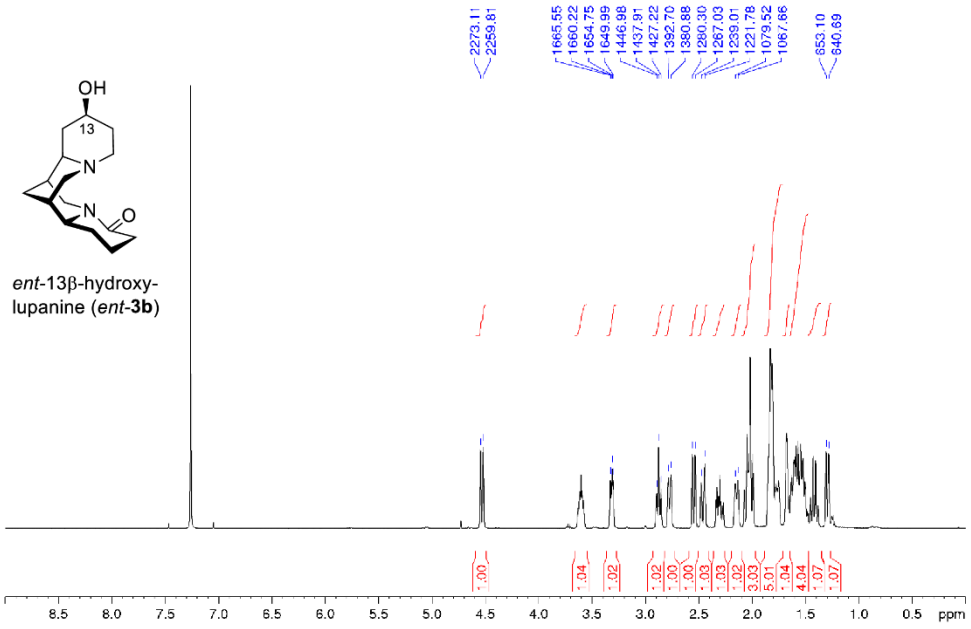
1.60
1.55
1.50
1.45
ppm

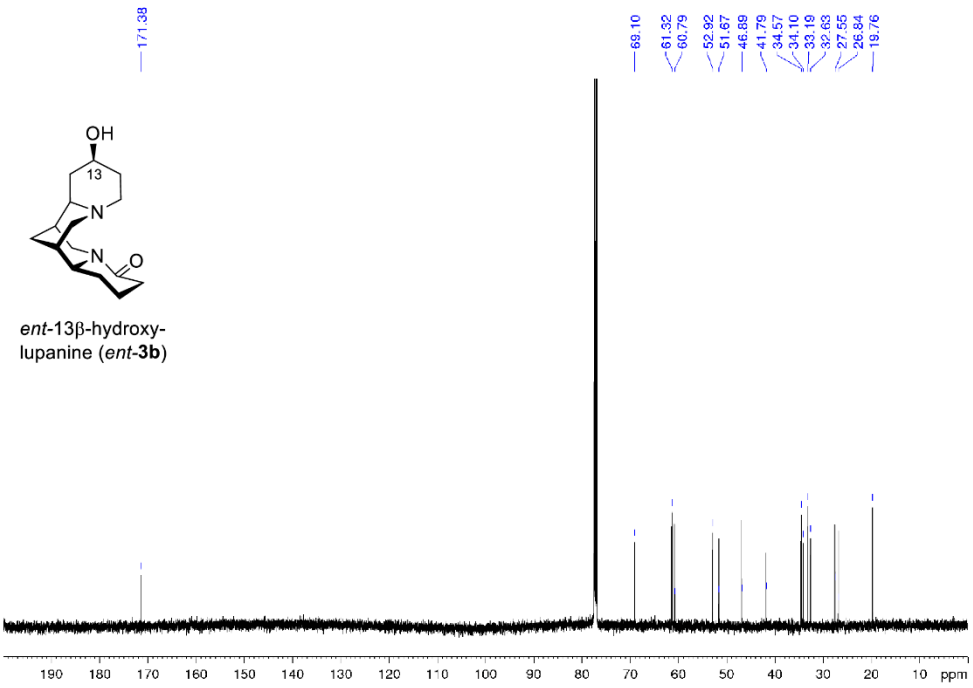
12


OH
13
N
N
O
epibaptifoline (**B**)
NOESY of epibaptifoline (**B**)
15-Hax
13-Hax
11-Hax
15-Hax
11-Hax
13-Heq
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

13

***ent*-13β-Hydroxylupanine (*ent*-3b):**





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

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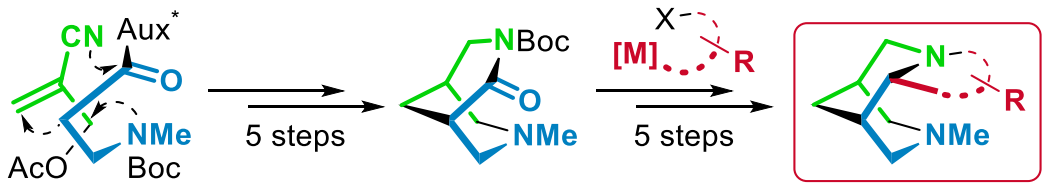

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DOI: 10.1002/chem.201502090

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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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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201502090.

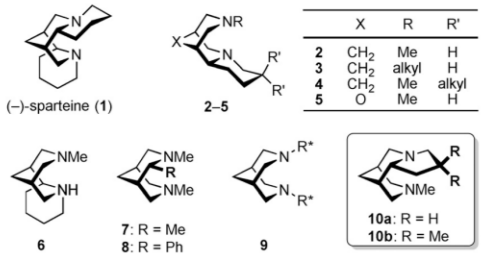

Figure 1. A selection of known bispidine ligands and the primary target structures **8** and **10**.

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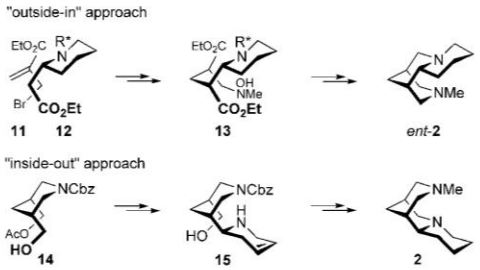
The high stereodiscrimination abilities of these diamines have their origin in the rigid bispidine (3,7-diazabicyclo[3.3.1]-nonane) core that is flanked by an *endo*-fused piperidine and, in the case of **1**, also by an *exo*-annelated one. Structure–selectivity studies on deprotonation–trapping reactions[25] 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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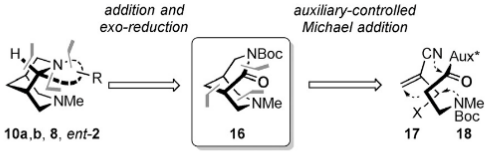
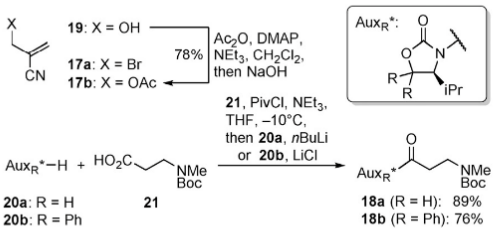


Scheme 2. Retrosynthetic analysis of *ent*-**2**, **8** and **10a,b** via the chiral NBoc bispidine lactam **16** as the key intermediate.

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.

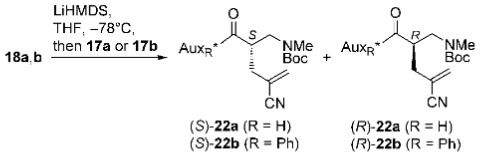


Scheme 3. Preparation of the building blocks **17a,b** and **18a,b**.

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

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.

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*-

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.

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

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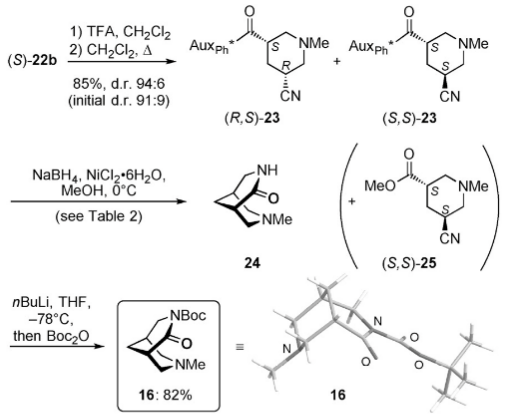
(*R*,*S*)-**23** and (*S*,*S*)-**23** afforded the readily separable products **24** and (*S*,*S*)-**25** exactly in the ratio of the starting materials. Thus, bispidine **24** was accessible from (*R*,*S*)-**23** (d.r. 94:6) in 88% yield, which corresponds to 94% of the maximum theoretical yield. Final 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.

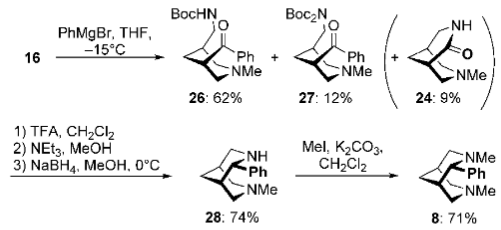


Scheme 4. Synthesis of the chiral key intermediate **16** from (*S*)-**22b** and the crystal structure of **16**.[51]

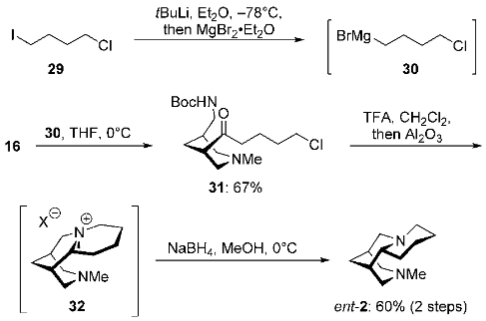
Synthesis of the core-chiral bispidines

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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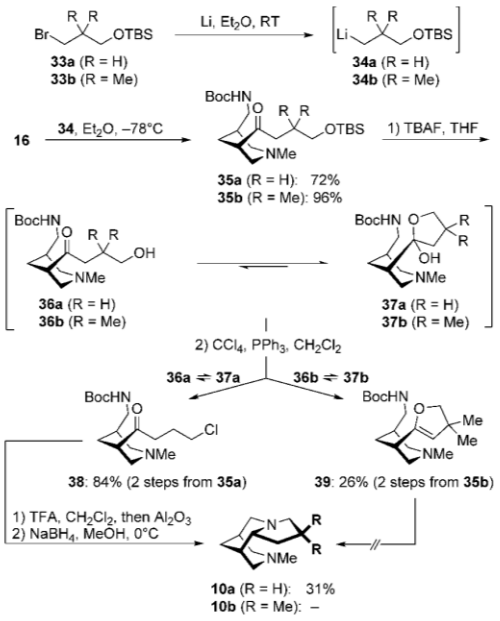
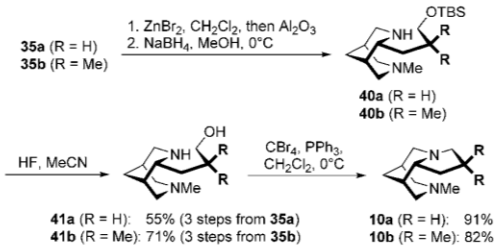


Scheme 7. Synthesis of the tricyclic bispidine **10a** under simultaneous bispidine and pyrrolidine formation.

(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**.

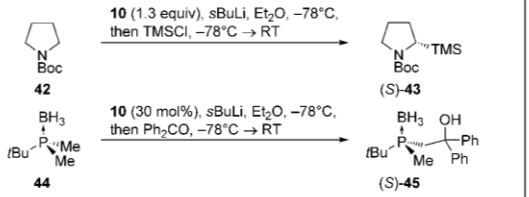


Scheme 8. Successful preparation of the pyrrolidine-fused bispidines **10a** and **10b** by using a bispidine formation–annelation sequence.

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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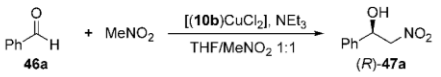
ly high. These promising results prompted us to evaluate our new bispidines **8** and **10** in these *C*,*C*-bond forming reactions.

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.



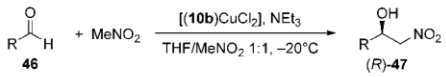
Entry	Cat. [mol%]	NEt_3 [mol%]	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1[c]	20	3	0	48	73	94
2	20	3	0	46	97	95
3	5	5	0	21	99	96
4	2	2	0	45	96	97
5	2	2	−10	47	99	97
6	2	2	−20	42	99	98
7	2	2	−25	66	89	98

[a] Isolated yield. [b] Determined by HPLC on chiral phase. [c] Conditions: $MeNO_2$ (2 equiv), MeOH, 0 °C, see refs. [23, 24].

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

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.

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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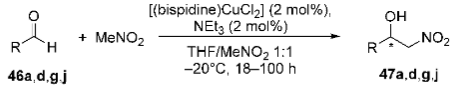
Table 6. Comparison of enantioselectivities reached in Henry reactions catalyzed by [(bispidine)$CuCl_2$] complexes.[a]

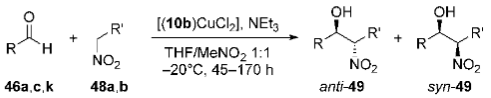


a: R = Ph; **d**: R = 3-MeO-C_6H_4; **g**: R = 4-O_2N-C_6H_4; **j**: R = $PhCH_2CH_2$

	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: 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

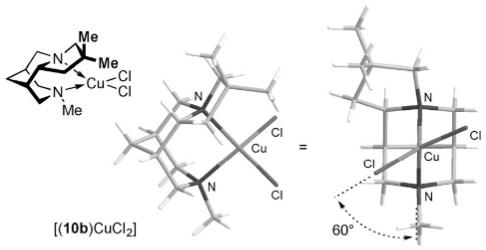


Figure 2. Crystal structure of [(**10b**)$CuCl_2$].[61]

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]

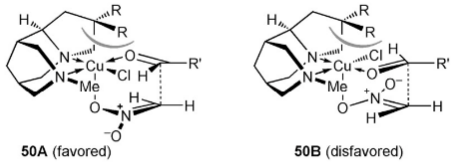


Figure 3. Proposed transition states **50A** and **50B**.

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=*C*H$_2$), 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-CH*C*H_3), 0.74 ppm (d, J = 6.8 Hz, 3H; 4-CH*C*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 (CHCH(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(CH_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 (*C*H(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 (35 b): Lithium wire (1.39 g, 201 mmol) was added to a solution of the bromide **33 b** (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 **35 b** (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-CH_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 (40 b): A solution of **35 b** (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 **40 b** and its protonated form **40 b**·HX (7.50 g), which was directly used in the next step.

Basic extraction of **40 b**/**40 b**·HX afforded analytically pure **40 b** 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 (41 b): The mixture of **40 b** and **40 b**·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 **41 b** (3.65 g, 16.1 mmol, 71% from **35 b**) 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 (10 b): 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 **41 b** (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 **10 b** (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 **10 b** (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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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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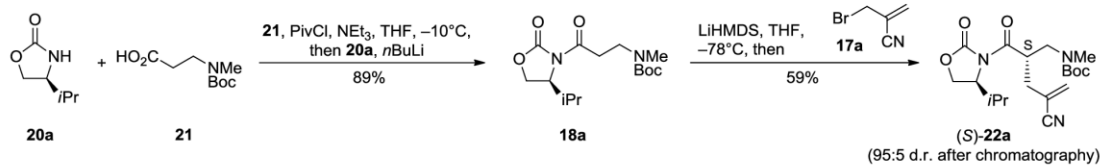
1. Synthetic procedures

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-CHC*H*$_3$), 0.86 ppm (d, *J* = 6.9 Hz, 3 H; 4-CHC*H*$_3$); ^{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, CO*C*H_2), 28.5 (C(*C*$H_3)_3$, 4-CH), 18.1, 14.8 ppm (4-CH(*C*$H_3)_2$); 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.

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[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.

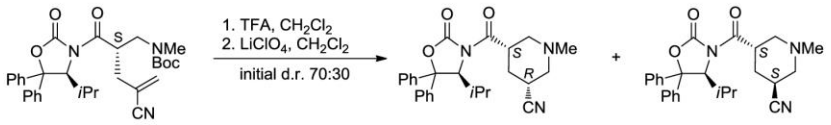
[2] I. Kauffmann-Hefner, N. Hauel, R. Walter, H. Ebel, H. Doods, A. Ceci, A. Schuler-Metz, (Boehringer Ingelheim Pharma Gmbh & Co. KG), DE 102006039003, **2008** [*Chem. Abstr.* **2008**, *148*, 284899].

[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); ^1H 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 $LiClO_4$

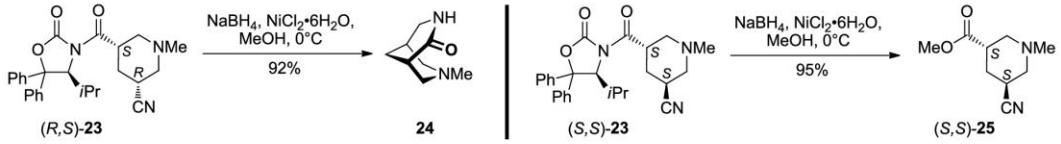


(*S*)-**22b** (*R*,*S*)-**23**: 43% (*S*,*S*)-**23**: 32%

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



(*R*,*S*)-**23** **24** (*S*,*S*)-**23** (*S*,*S*)-**25**

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.

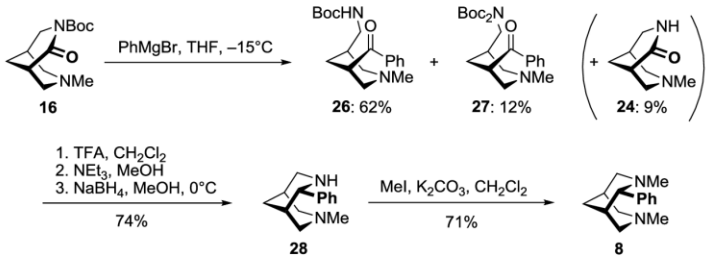
For characterization data of **24**, see article.

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.

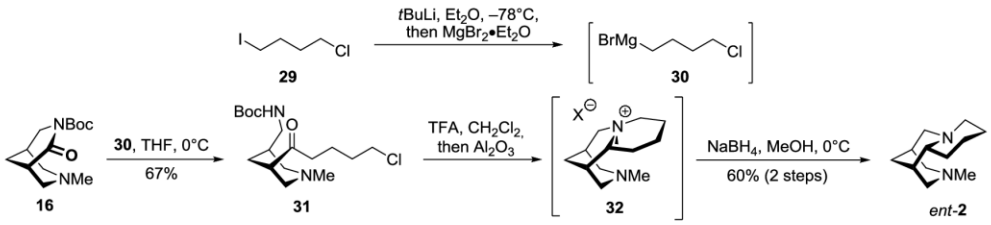
R_f = 0.21 (MeOH + 1% NEt_3); $[\alpha]_D^{21}$ = –52.3 (*c* = 0.9 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 2 H; Ph), 7.27 (m, 2 H; Ph), 7.22 (m, 1 H; Ph), 4.07 (s, 1 H; 2-H), 3.58 (br s, 1 H; 3-H), 3.32 (dm, *J* = 13.5 Hz, 1 H; 4-*H*H), 3.13 (dt, *J* = 13.5, 2.7 Hz, 1 H; 4-H*H*); 3.02 (dm, *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*, $CH_2CH_2CH_2Cl$), 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 (CH_2CH_2Cl), 30.3 (C-4), 28.5 ($C(CH_3)_3$), 20.9 ppm ($CH_2CH_2CH_2Cl$); 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)

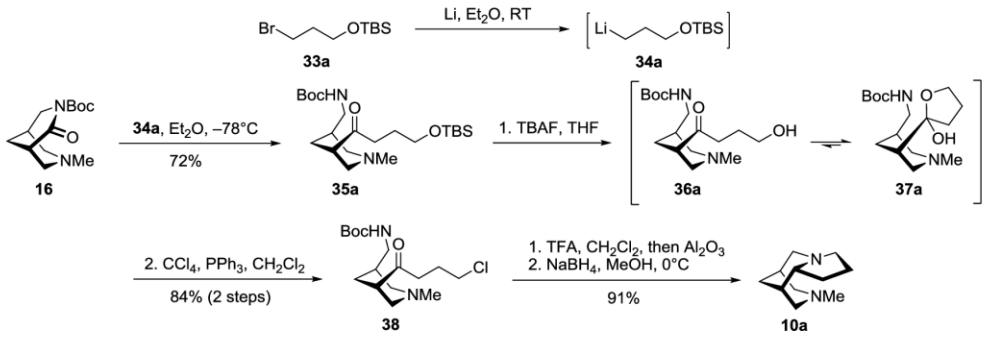
TFA (402 µL, 5.22 mmol) was added at 0°C to a solution of the chloroketone **31** (90.5 mg, 261 µmol) in anhyd. CH_2Cl_2 (5 mL). The reaction mixture was stirred overnight at RT and the solvent was removed under reduced pressure. The resulting oil was diluted three times with CH_2Cl_2 (5 mL) and evaporated 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-methyl-piperidine (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.

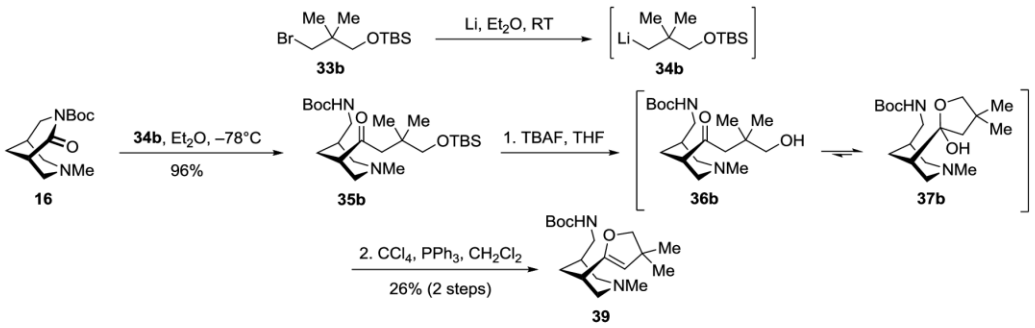
R_f = 0.31 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{17}$ = –4.8 (*c* = 0.8 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.58 (br s, 1 H; NH), 3.54 (t, *J* = 6.2 Hz, 2 H; CH_2Cl), 3.13–2.88 (m, 4 H; 2-*H*H, 3-CH_2, 6-*H*H), 2.86–2.74 (m, 1 H; 5-H), 2.71–2.60 (m, 2 H; $COCH_2$), 2.35 (s, 3 H; 1-CH_3), 2.02 (quin., *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



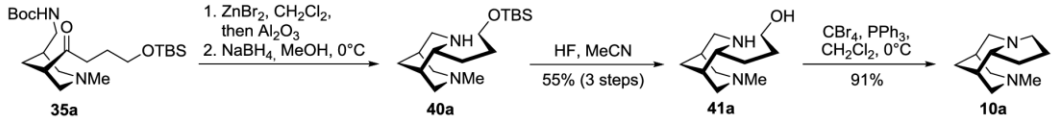
For the preparation of **35b** from **16**, see article.

(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.

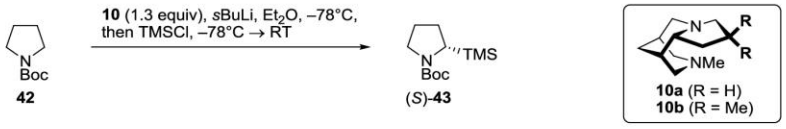
R_f = 0.15 ($CHCl_3$/MeOH/NH_3 (aq., 25%) 80:18:2); $[\alpha]_D^{24}$ = –6.6 (*c* = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.67 (m, 1 H; OC*H*H), 3.50 (m, 1 H; (OCH*H*), 3.14 (dm *J* = 13.5 Hz, 1 H; 4-*H*H), 3.02 (dm, *J* = 11.5 Hz, 1 H; 8-*H*H), 2.96 (dt, *J* = 13.5, 2.6 Hz, 1 H; 4-H*H*), 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]

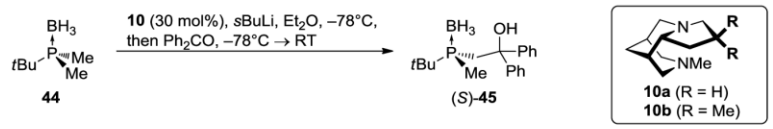
GC conditions: BGB-176SE, 30 m x 0.25 mm ID, 0.25µm film, T = 100°C isothermal, injector temperature 240°C, detector temperature 240°C, H_2 carrier gas at 83 kPa constant pressure, t_R = 39.8 min (*S*), 40.5 min (*R*).

[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.

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.

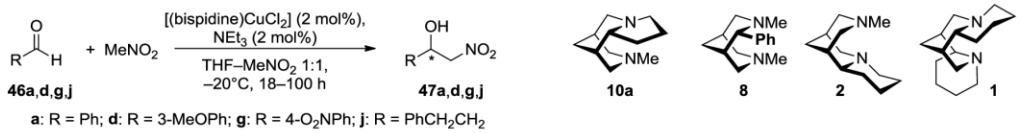


Table S1. Comparison of the ligands **1**,**2**,**8** and **10a** in enantioselective Henry reactions.

			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.

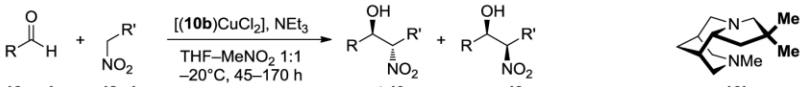
[11] D. Scharnagel, F. Prause, J. Kaldun, R. G. Haase, M. Breuning, *Chem. Commun.* **2014** ,*50*, 6623-6625.

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,**c**,**k** **48a**,**b** *anti*-**49** *syn*-**49** **10b**

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

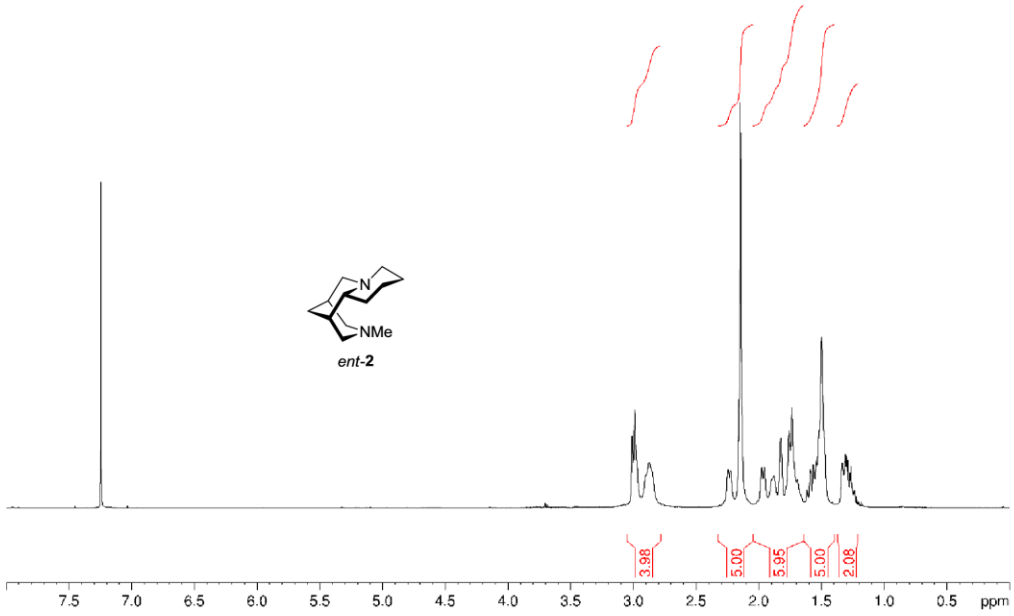
[a] OD-3: Daicel Chiralcel OD-3; AD-H: Daicel Chiralpak AD-H. [b] Retention time. [c] Reference data for NMR spectra and enantiomer analysis by HPLC on chiral phase.[13] [d] Solvent system *n*-hexane/EtOH.

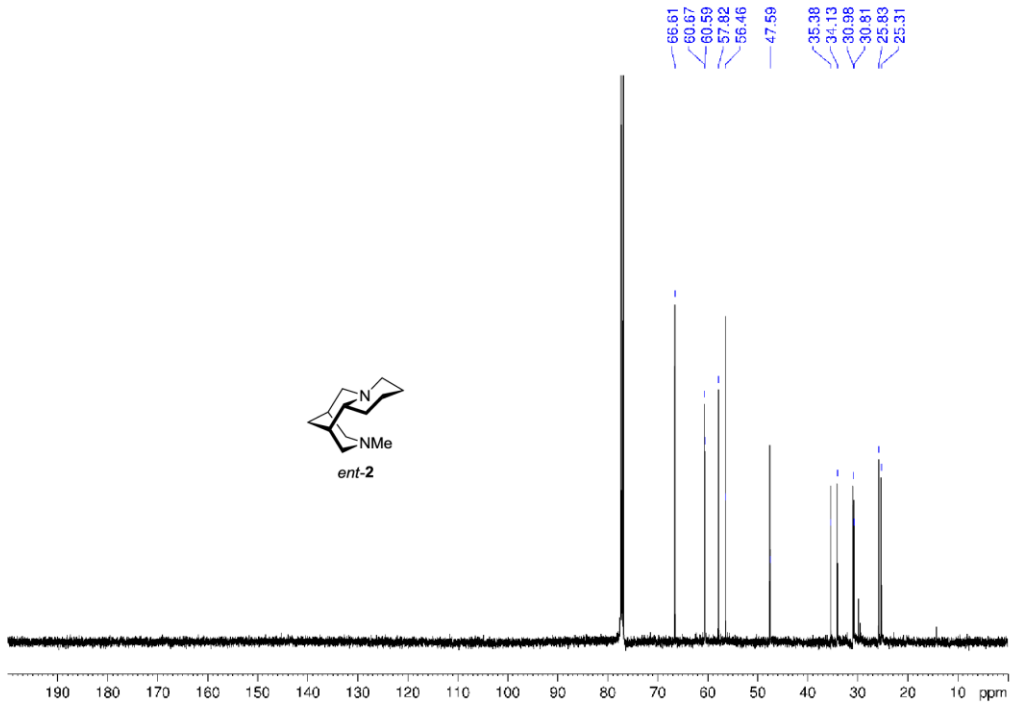
[12] (*a*) M. Breuning, D.Hein, M. Steiner, V. H. Gessner, C. Strohmann, *Chem.-Eur. J.* **2009**, *15*, 12764-12769; (*b*) W. Jin, X. Li, B. Wan, *J. Org. Chem.* **2011**, *76*, 484-491; (*c*) M. Liu, S. Ma, Z. Tian, H. Wu, L. Wu, X. Xu, Y. Huang, Y. Wang, *Tetrahedron: Asymmetry* **2013**, *24*, 736-743; (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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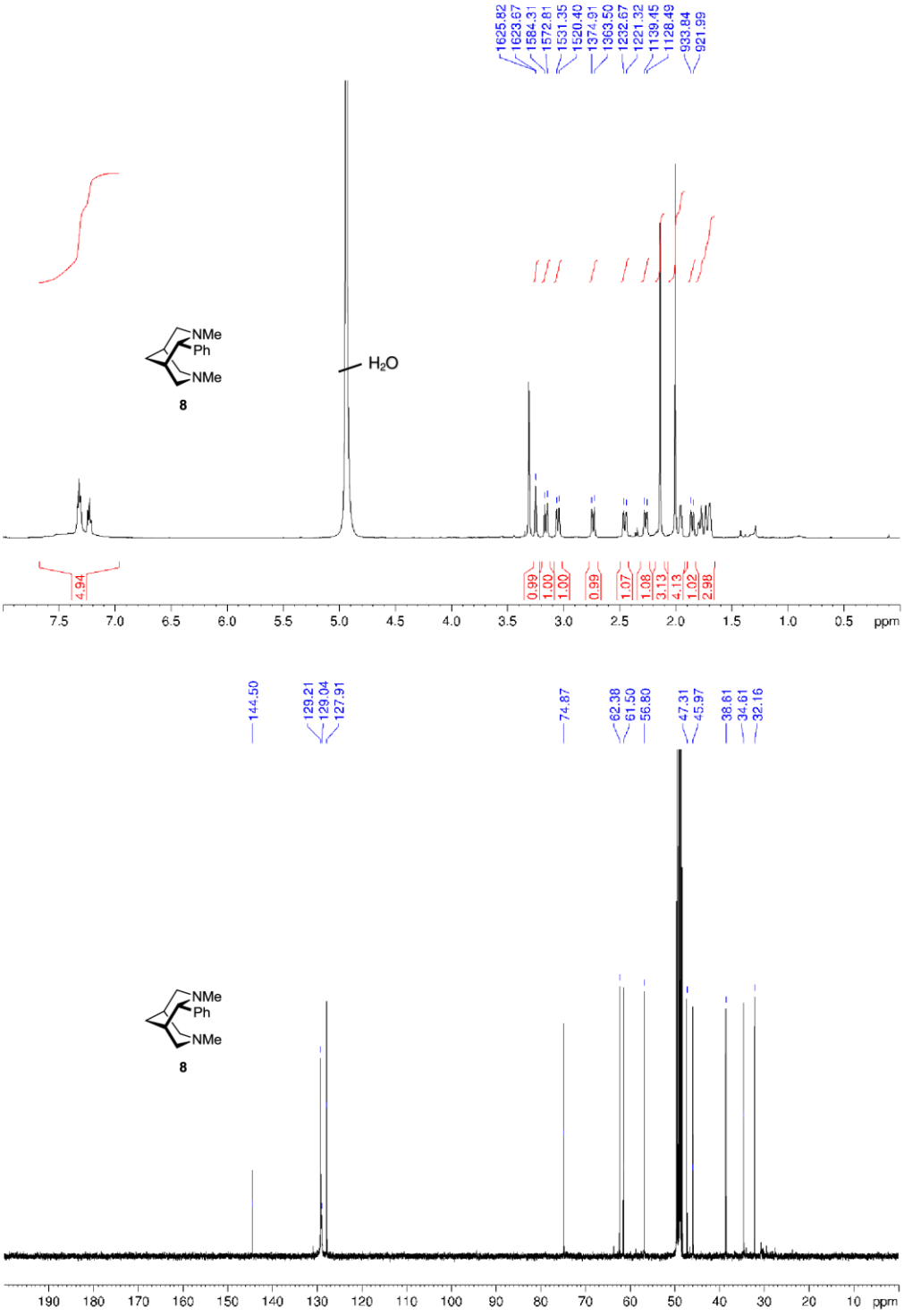
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1139.45
1128.49
933.84
921.99
NMe
Ph
NMe
8
H2O
4.94
0.99
1.00
1.00
0.99
1.07
1.08
3.13
4.13
1.02
2.98
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
144.50
129.21
129.04
127.91
74.87
62.38
61.50
56.80
47.31
45.97
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34.61
32.16
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Ph
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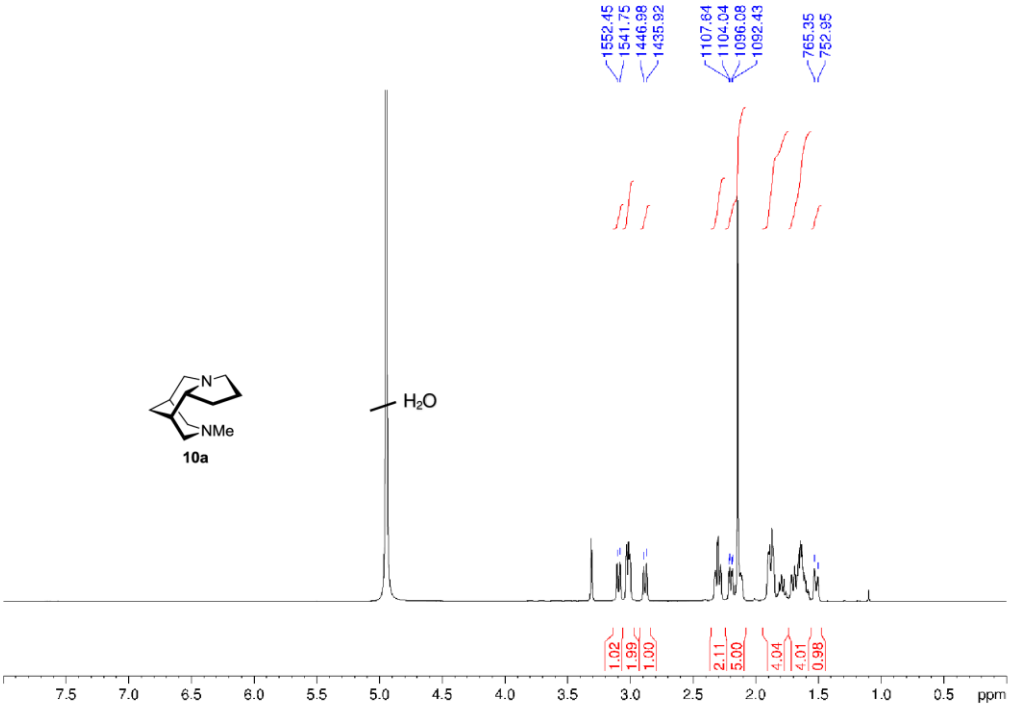
14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10a
H2O
1.02
1.99
1.00
2.11
5.00
4.04
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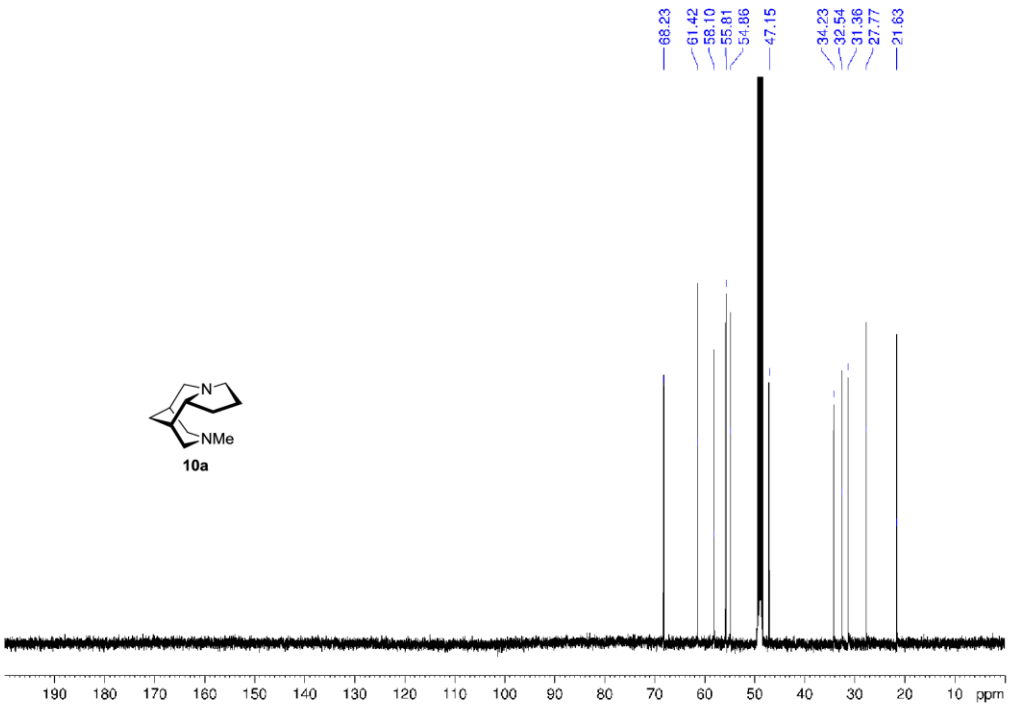
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55.81
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NMe
10a
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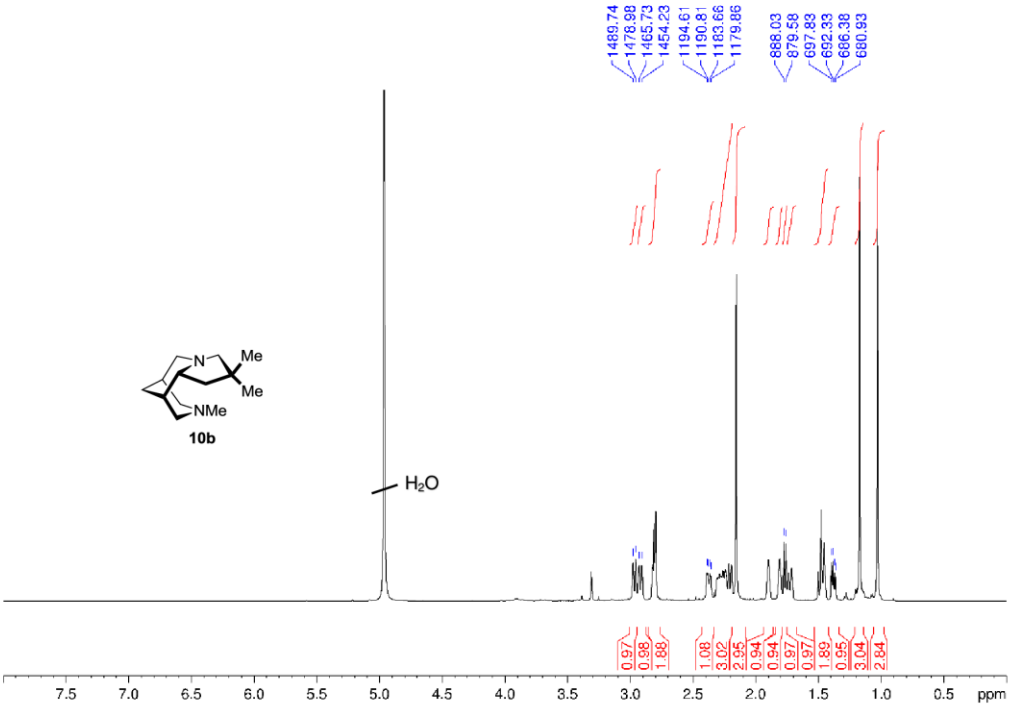
15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692.33
686.38
680.93
Me
Me
NMe
10b
H2O
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0.98
1.88
1.08
3.02
2.95
0.94
0.94
0.97
0.97
1.89
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7.0
6.5
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4.0
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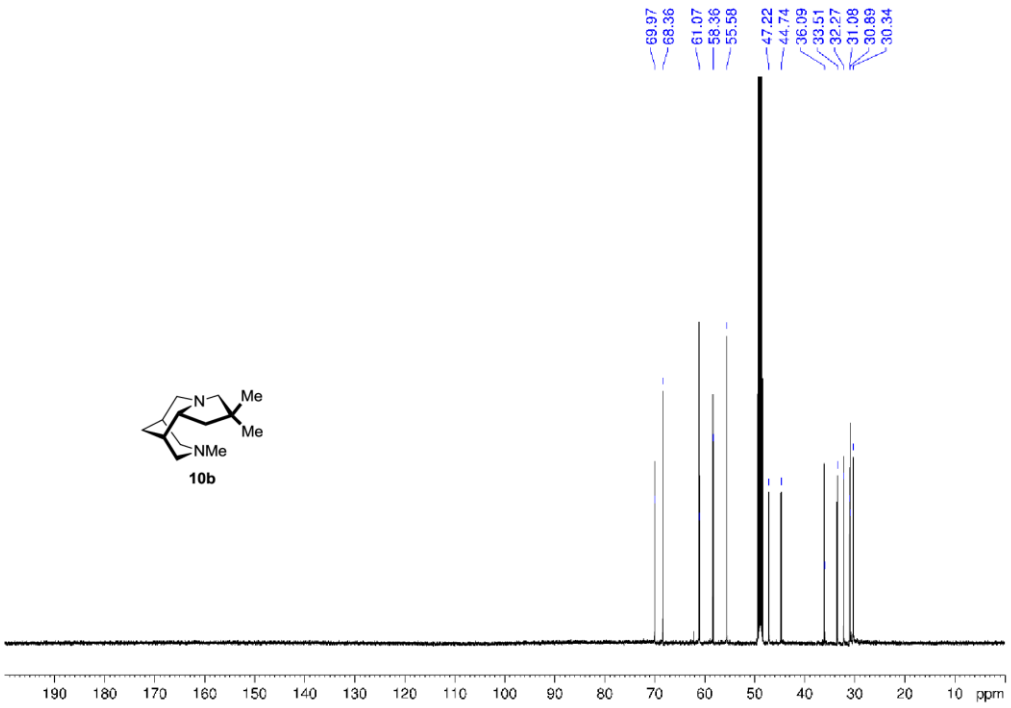
2.0
1.5
1.0
0.5
ppm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33.51
32.27
31.08
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Me
Me
NMe
10b
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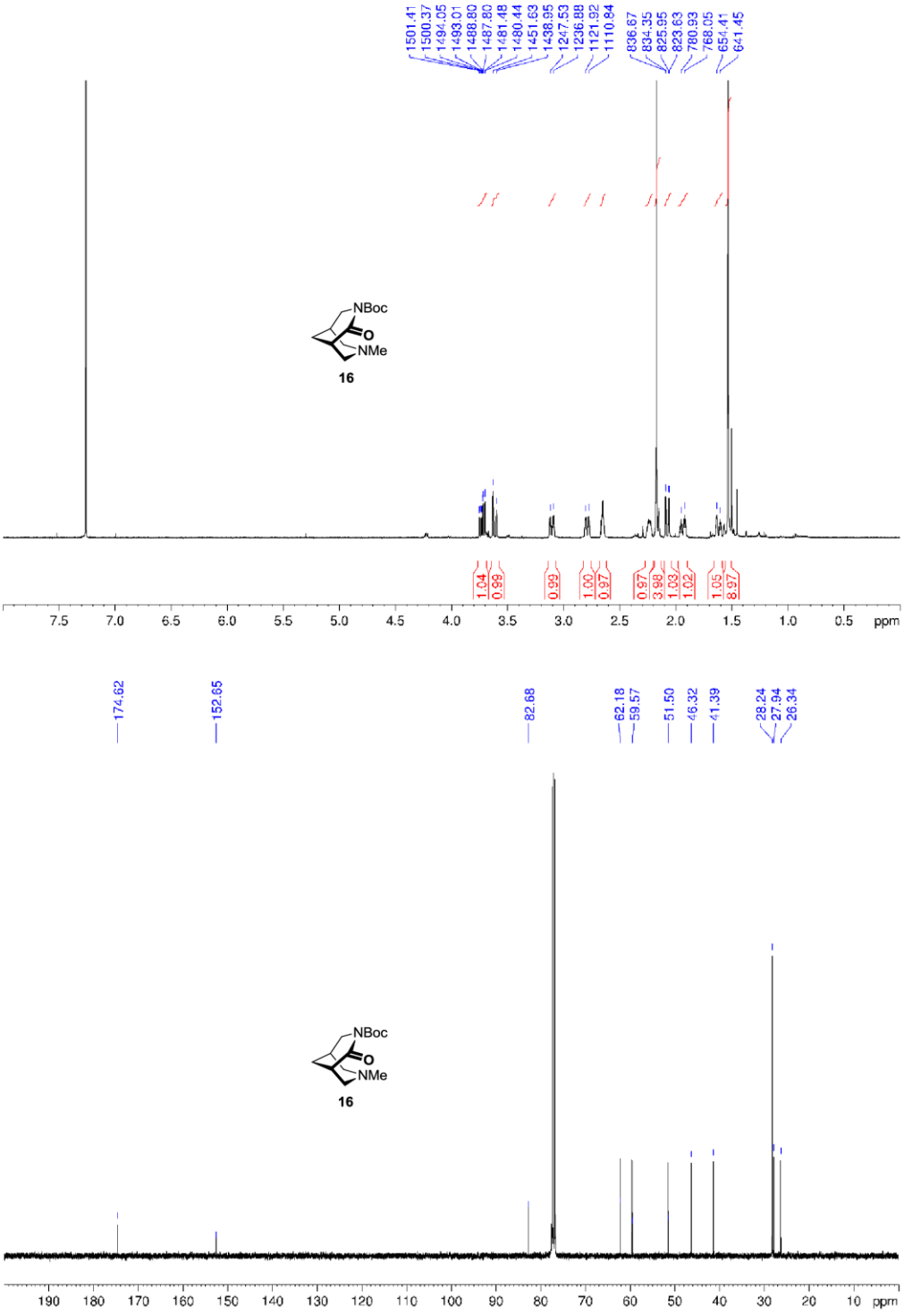
20
10
ppm

16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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
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26.34
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O
NMe
16
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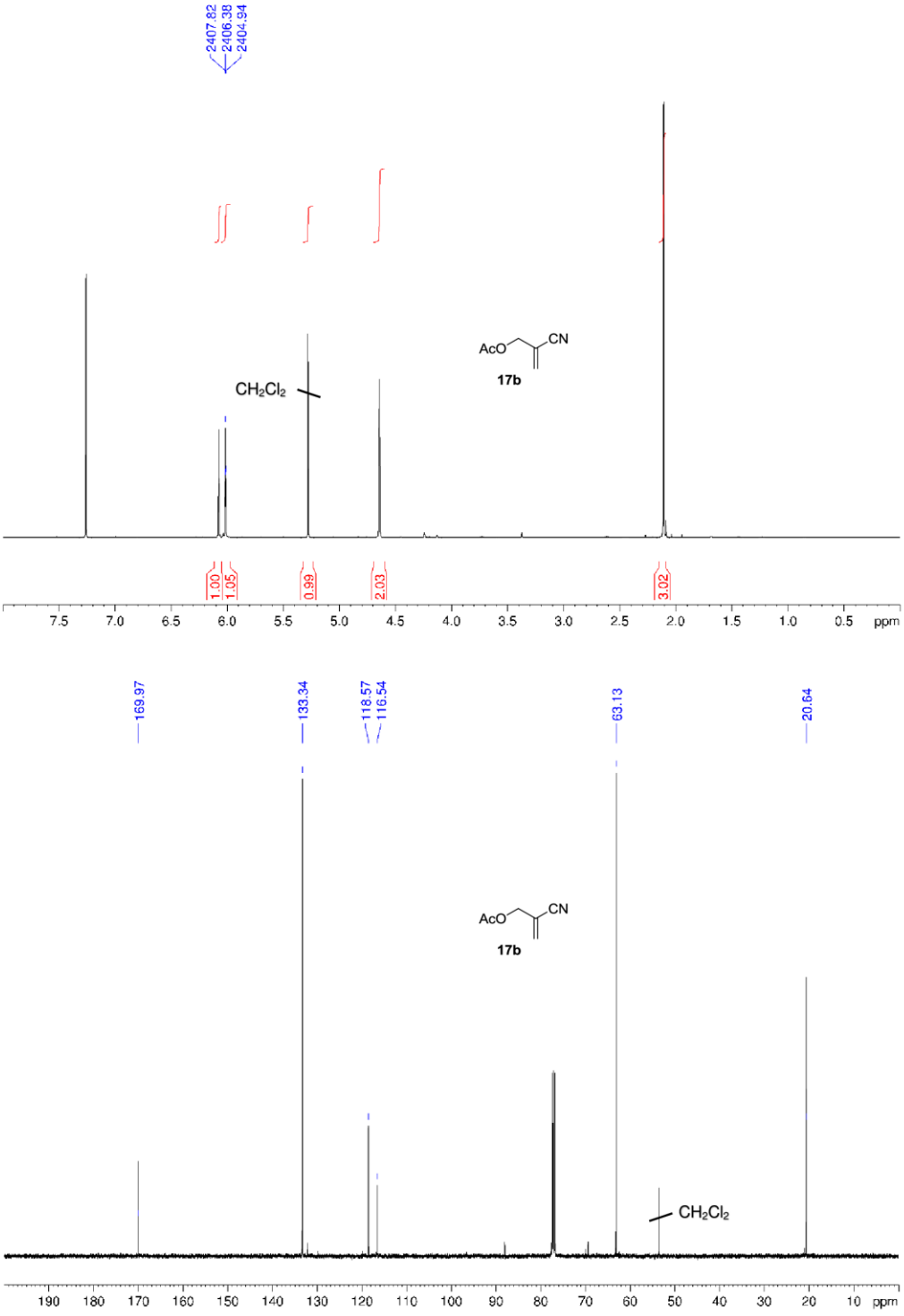
17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0.99
2.03
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133.34
118.57
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AcO
CN
17b
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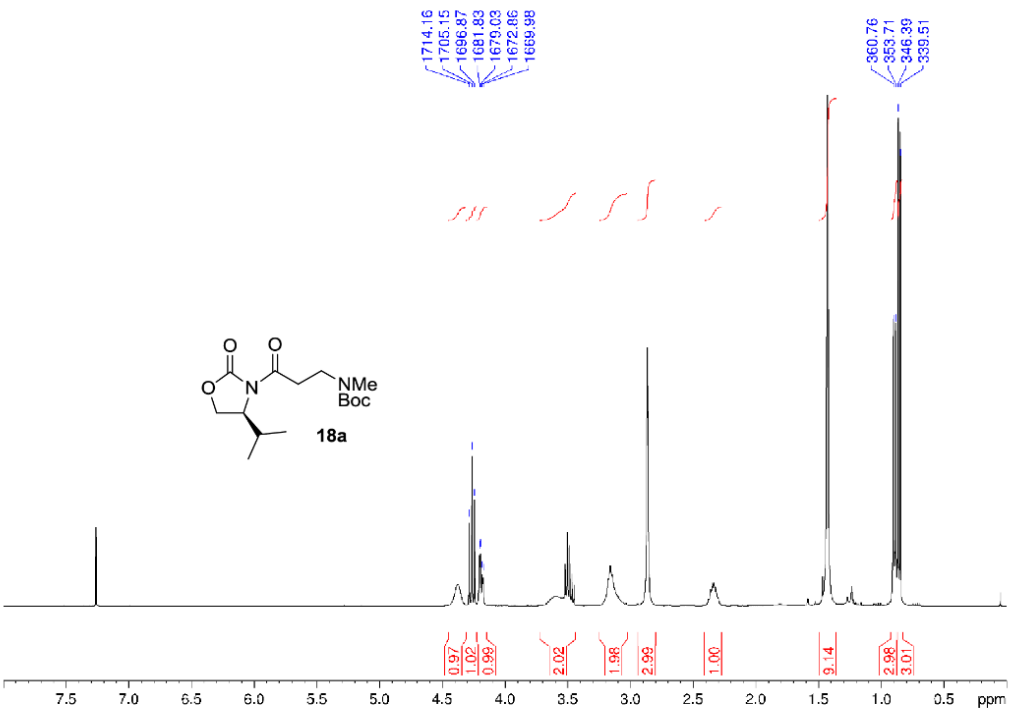
18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Boc
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1.02
0.99
2.02
1.98
2.99
1.00
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2.98
3.01
7.5
7.0
6.5
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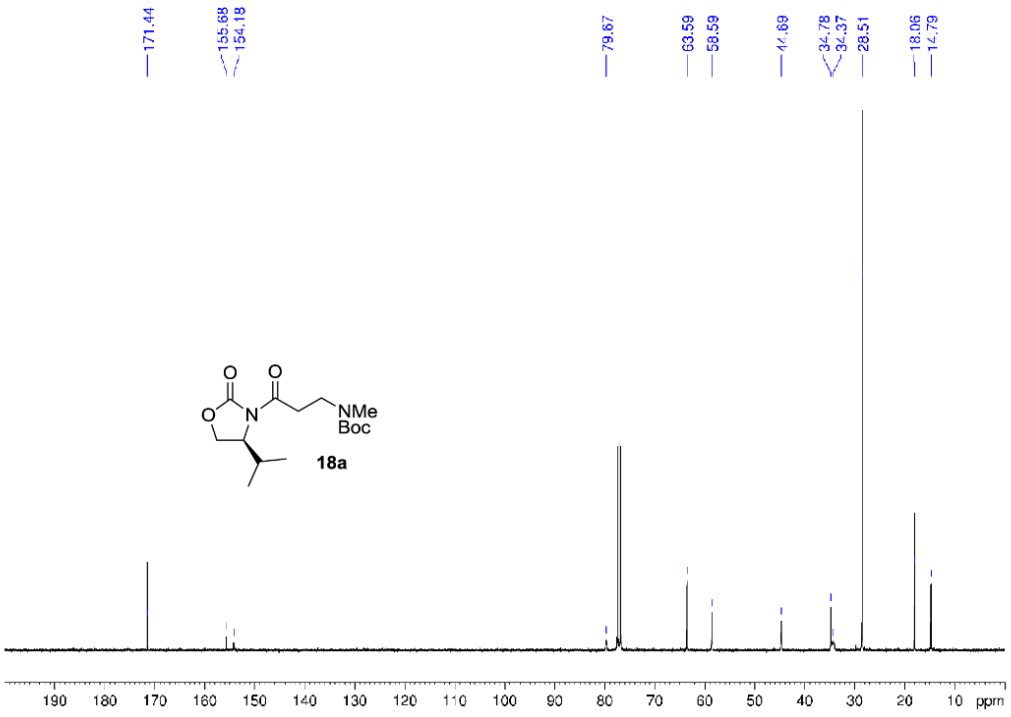
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Boc
18a
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140
130
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100
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70
60
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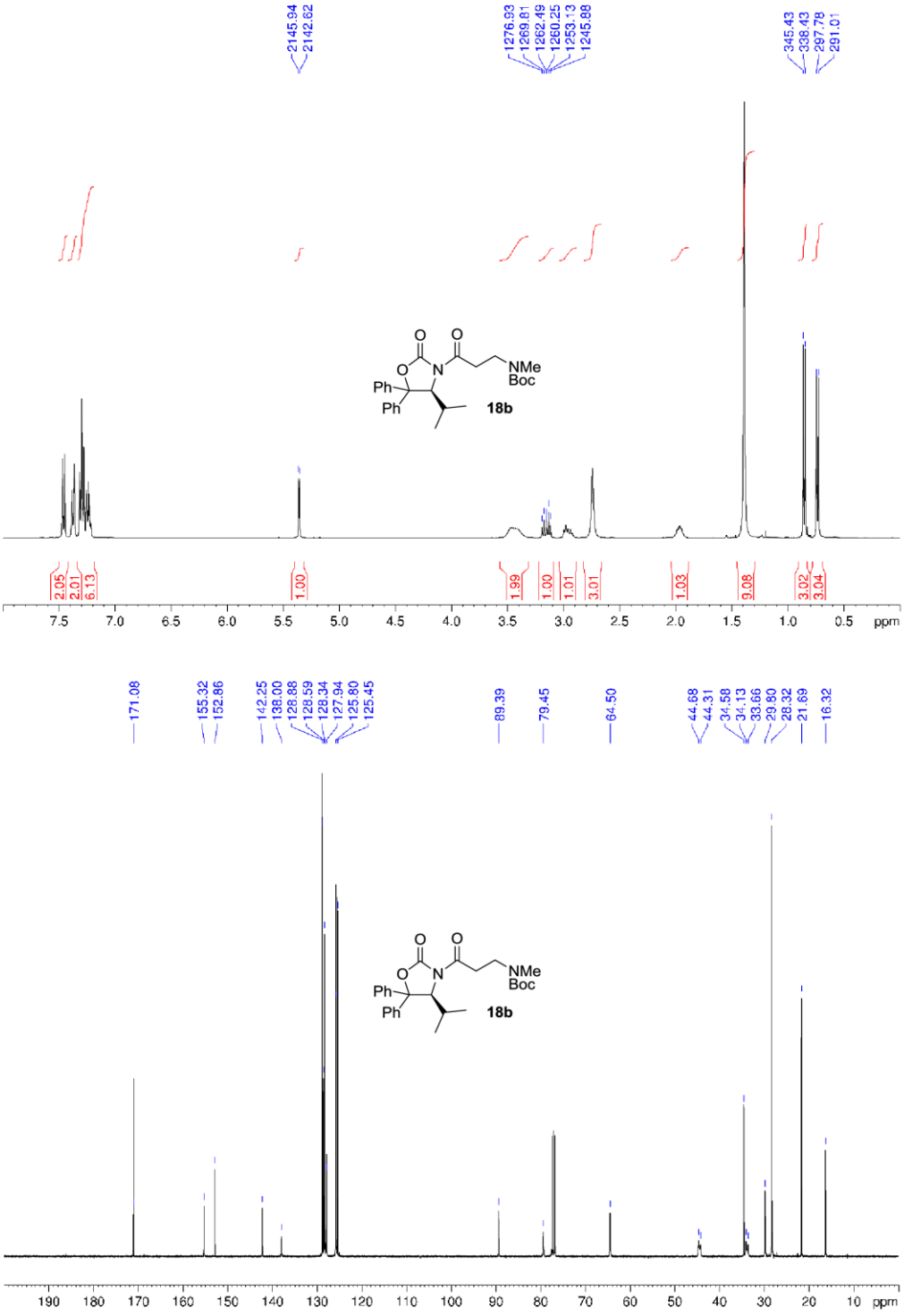
40
30
20
10
ppm

19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291.01
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Boc
Ph
Ph
18b
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2.01
6.13
1.00
1.99
1.00
1.01
3.01
1.03
9.08
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6.5
6.0
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Boc
Ph
Ph
18b
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60
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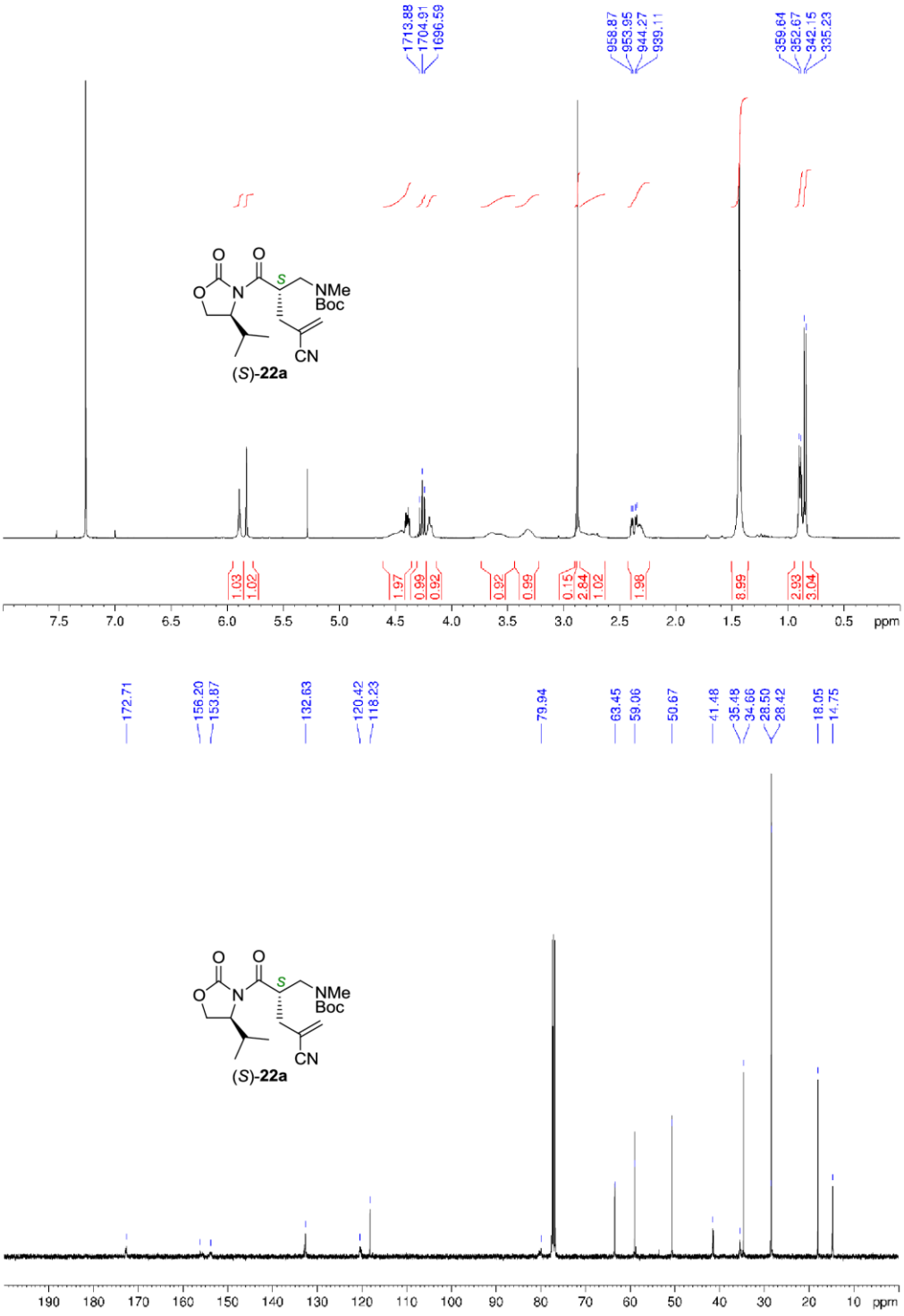
10
ppm

20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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
NMe
Boc
CN
(S)-22a
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156.20
153.87
132.63
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79.94
63.45
59.06
50.67
41.48
35.48
34.66
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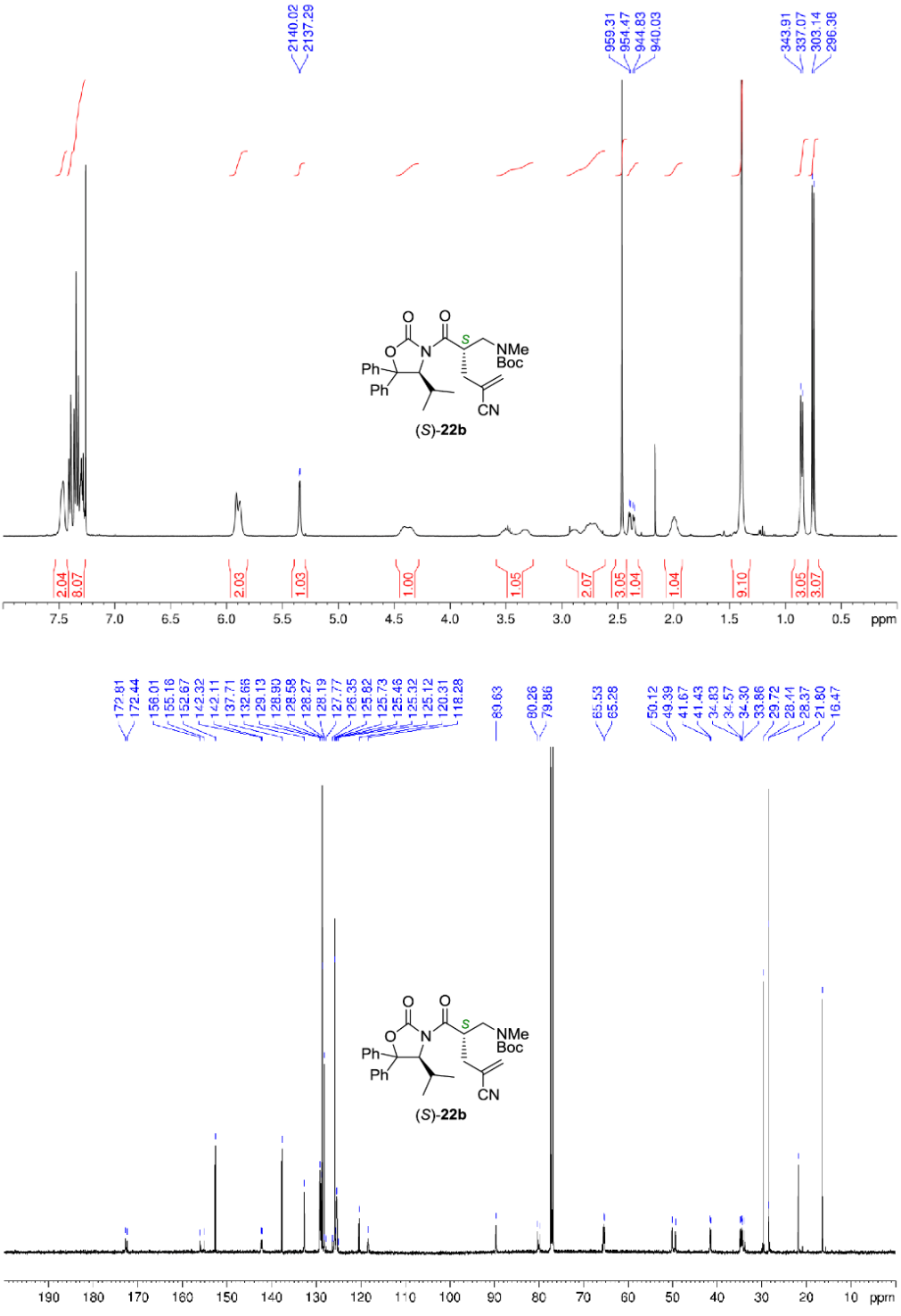
Boc
CN
(S)-22a

21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303.14
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3.05
3.07
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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
Ph
Ph
NMe
Boc
CN
(S)-22b
172.81
172.44
156.01
155.16
152.67
142.32
142.11
137.71
132.66
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128.90
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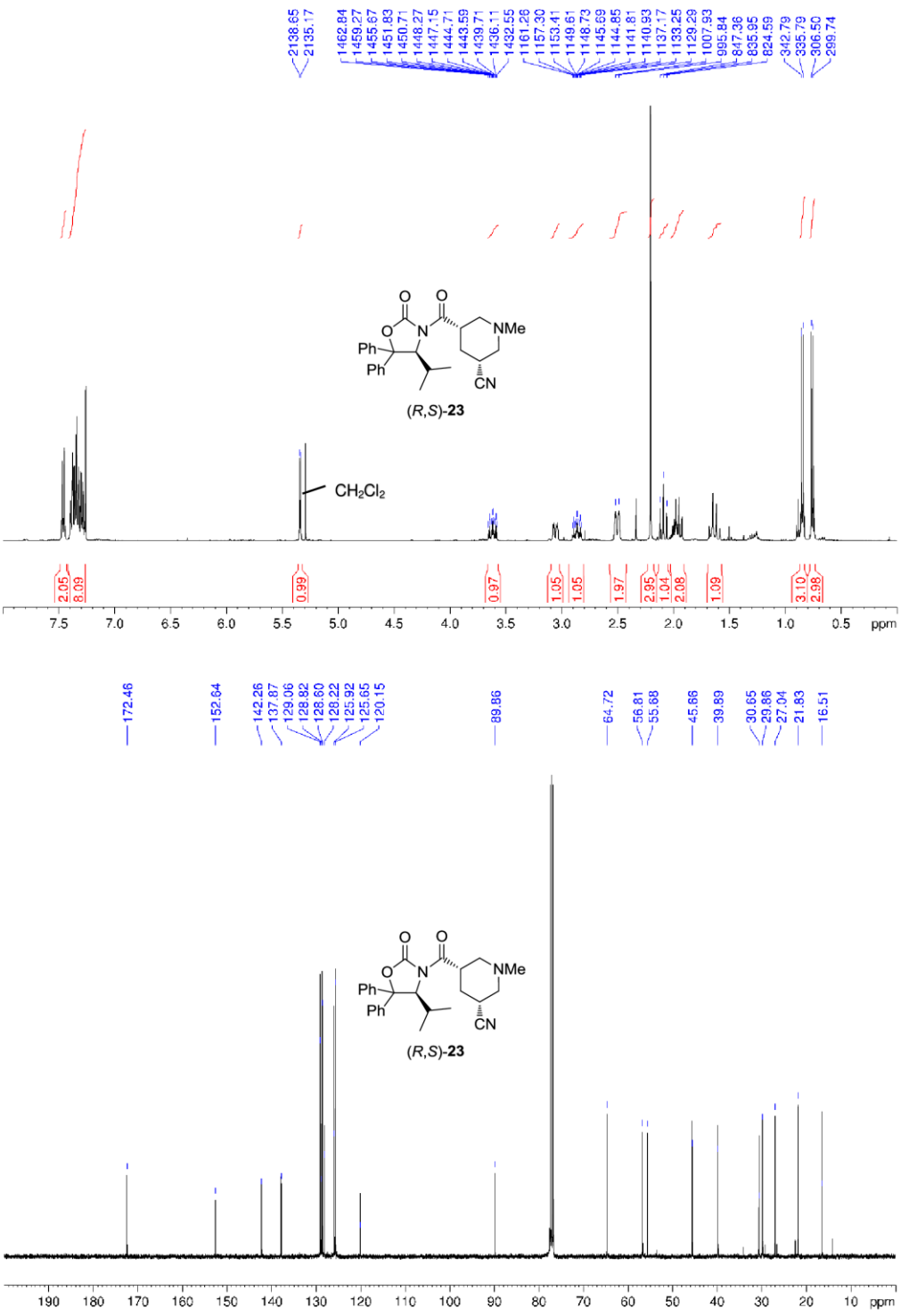
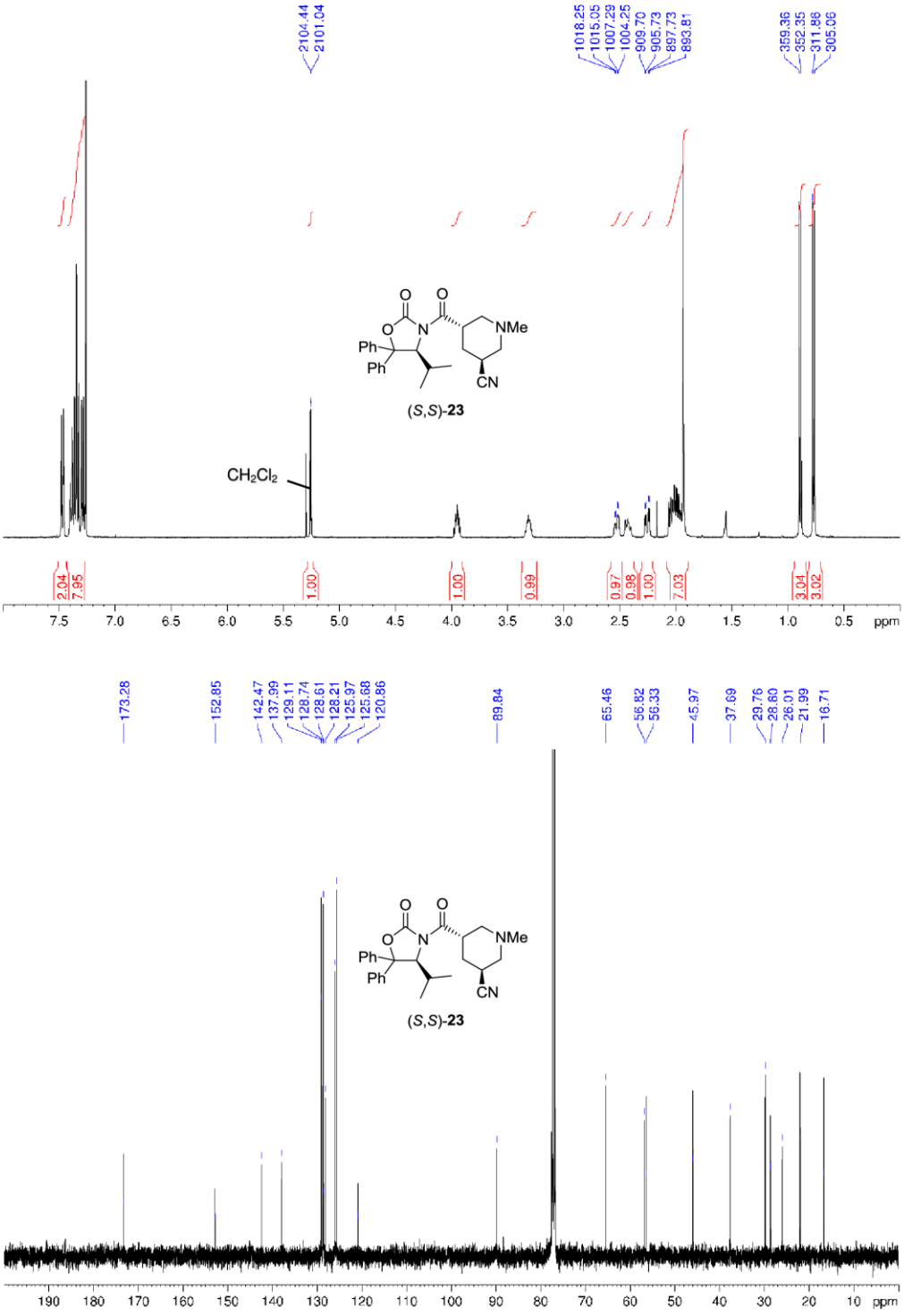
128.27
128.19
127.77
126.35
125.82
125.73
125.46
125.32
125.12
120.31
118.28
83.63
80.26
79.86
65.53
65.28
50.12
49.39
41.67
41.43
38.83
37.57
34.30
33.86
29.72
28.41
28.37
21.80
16.47
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

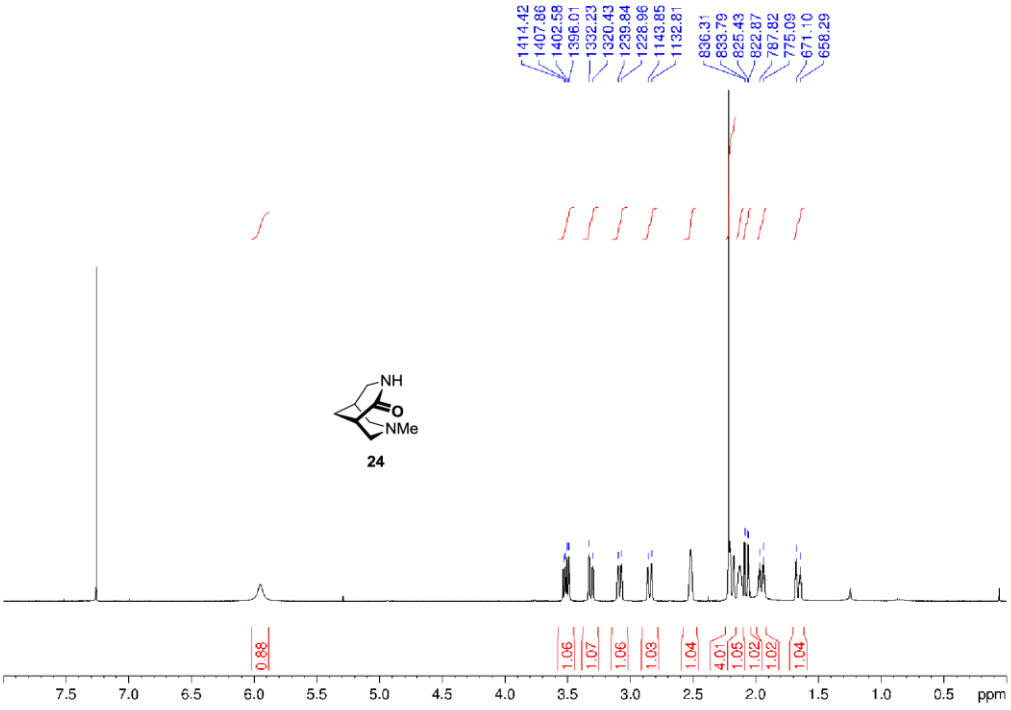
22

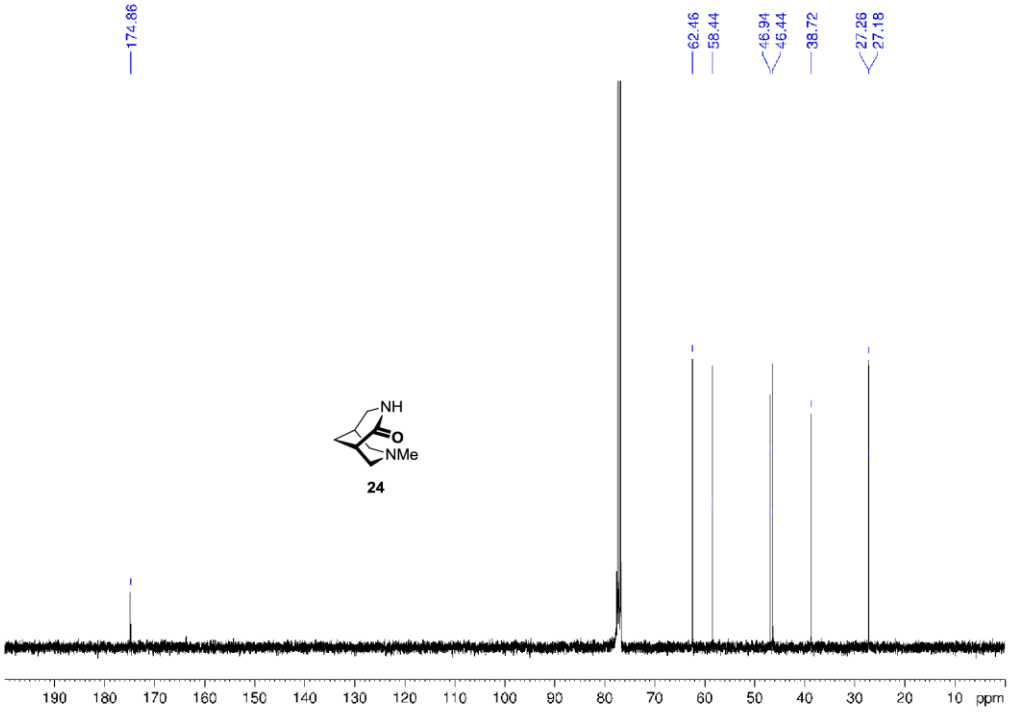

2138.65
2135.17
1462.84
1459.27
1455.67
1451.83
1450.71
1448.27
1447.15
1444.71
1443.59
1439.71
1436.11
1432.55
1161.26
1157.30
1153.41
1149.61
1148.73
1145.69
1144.85
1141.81
1140.93
1137.17
1133.25
1129.29
1007.93
995.84
847.36
835.95
824.59
342.79
335.79
306.50
299.74
O
O
O
N
Ph
Ph
NMe
CN
(R,S)-23
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
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
172.46
152.64
142.26
137.87
129.06
128.82
128.60
128.22
125.92
125.65
120.15
89.86
64.72
56.81
55.68
45.66
39.89
30.65
29.86
27.04
21.83
16.51
O
O
O
N
Ph
Ph
NMe
CN
(R,S)-23
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

23

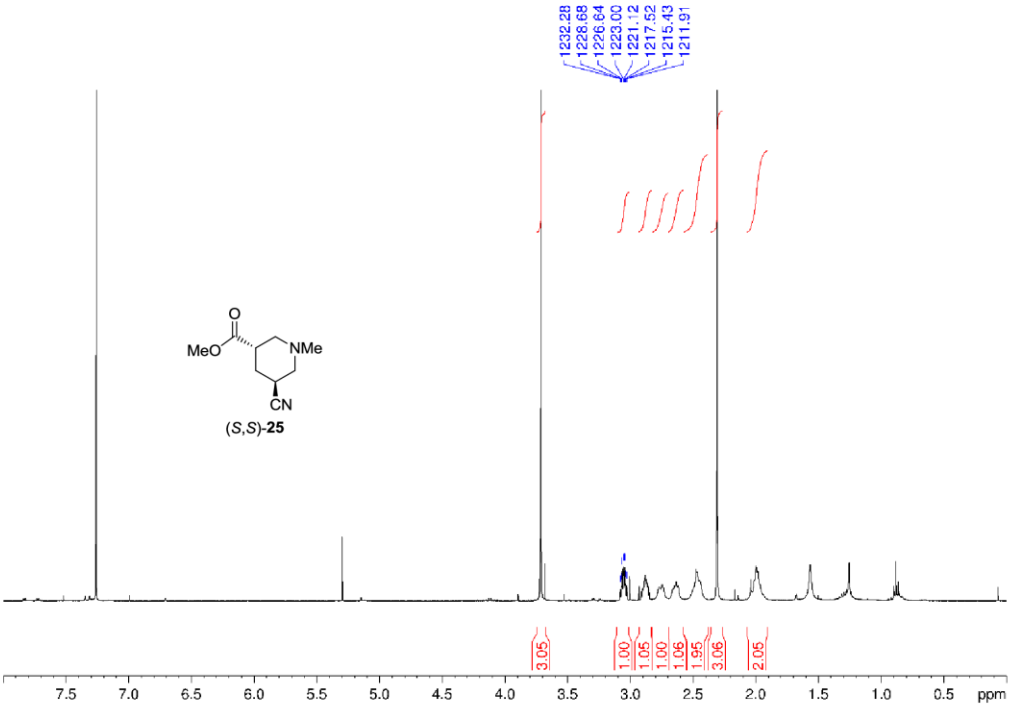

2104.44
2101.04
1018.25
1015.05
1007.29
1004.25
909.70
905.73
897.73
893.81
359.36
352.35
311.86
305.06
Ph
Ph
NMe
CN
(S,S)-23
CH2Cl2
2.04
7.95
1.00
1.00
0.99
0.97
0.98
1.00
7.03
3.04
3.02
ppm
173.28
152.85
142.47
137.99
129.11
128.74
128.61
128.21
125.97
125.68
120.86
89.84
65.46
56.82
56.33
45.97
37.69
29.76
28.80
26.01
21.99
16.71
ppm

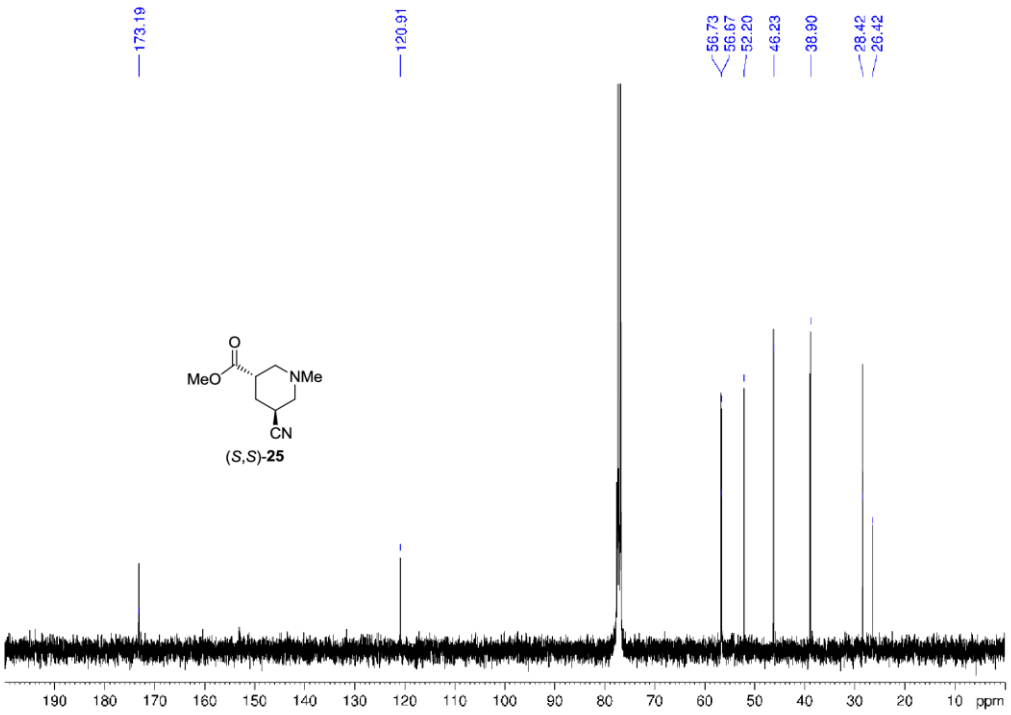
24


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

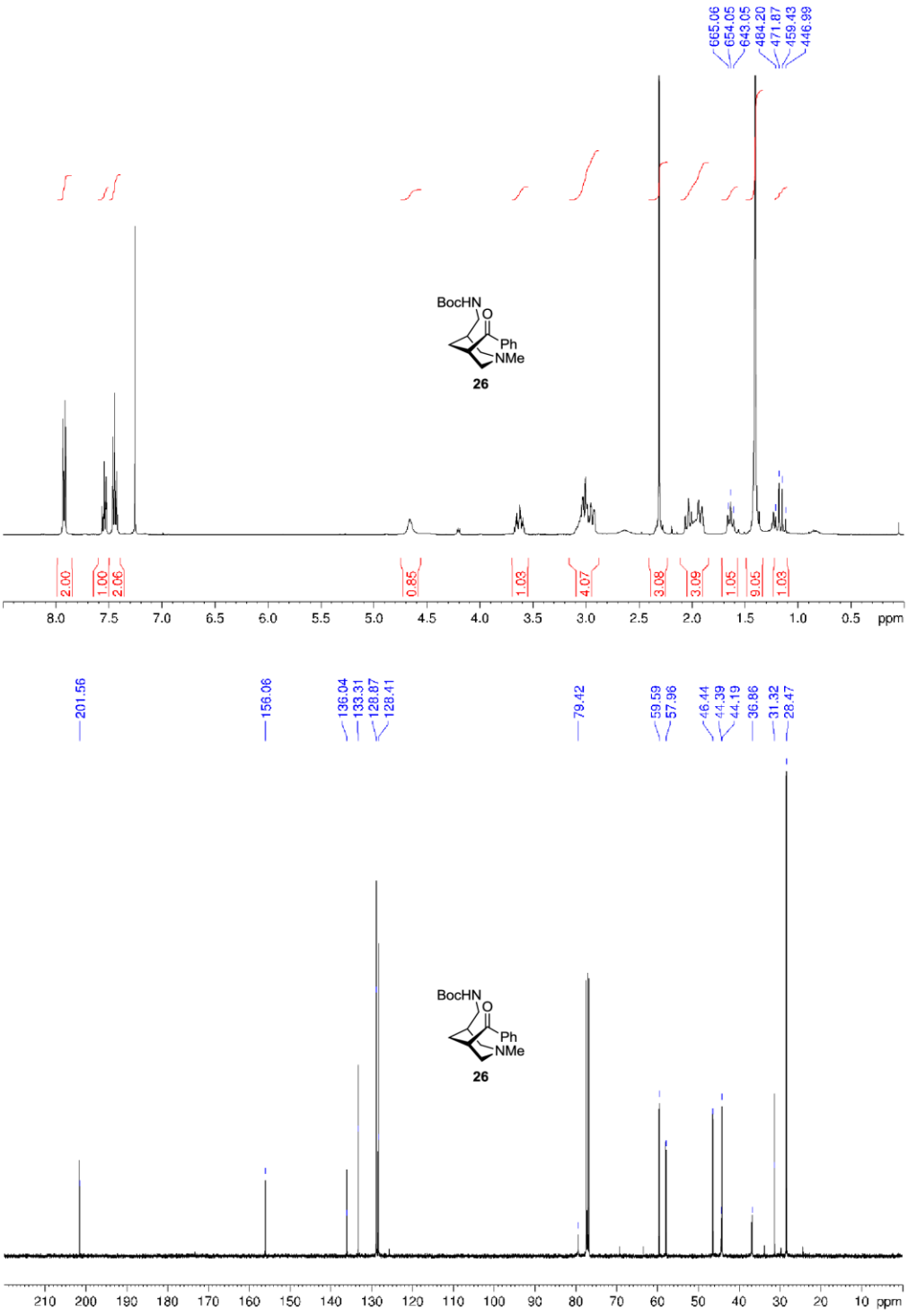

174.86
62.46
58.44
46.94
46.44
38.72
27.26
27.18
NH
O
NMe
24
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

25

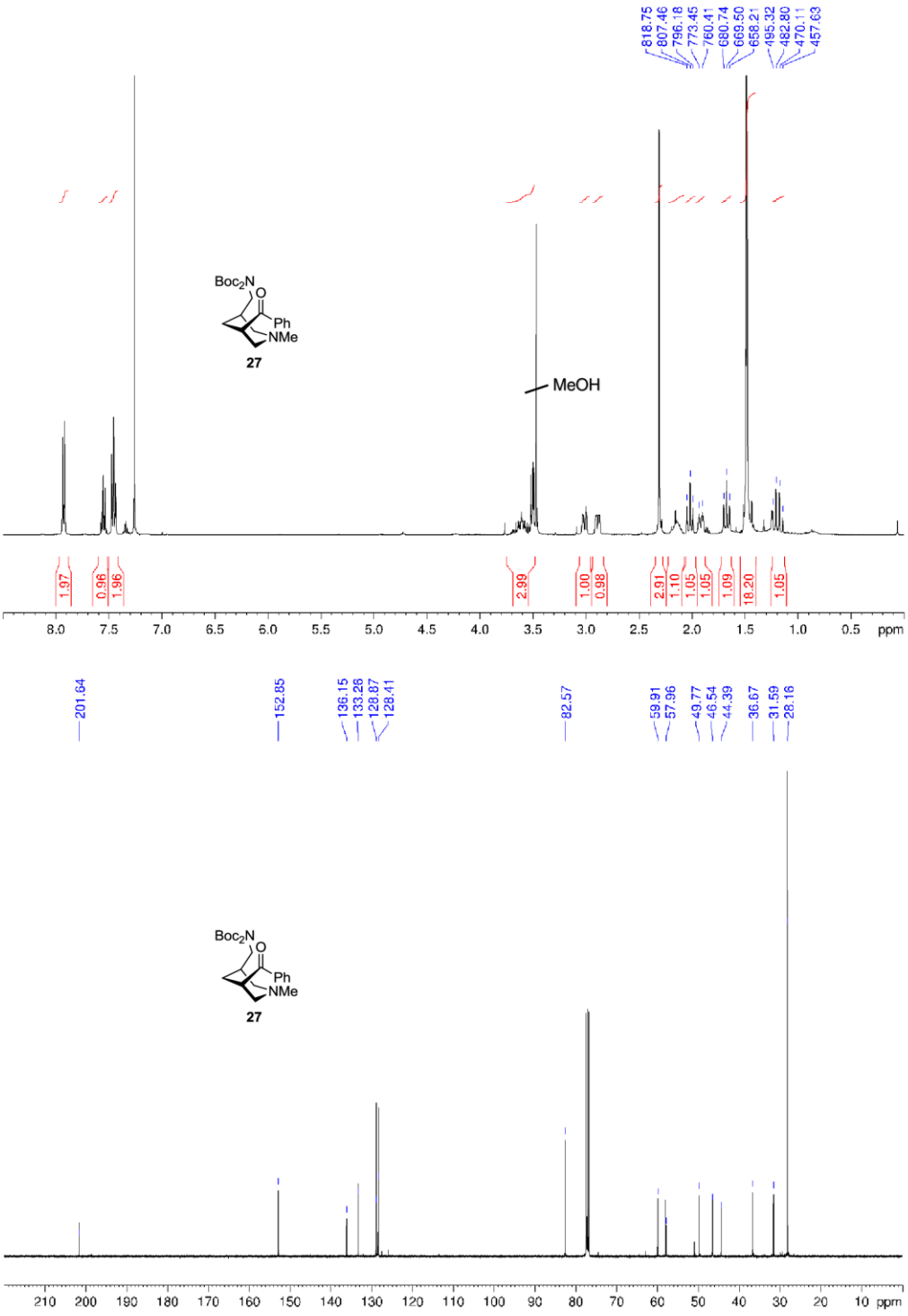

1232.28
1228.68
1226.64
1223.00
1221.12
1217.52
1215.43
1211.91
MeO
NMe
CN
(S,S)-25
3.05
1.00
1.05
1.00
1.06
1.95
3.06
2.05
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


173.19
120.91
56.73
56.67
52.20
46.23
38.90
28.42
26.42
MeO
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

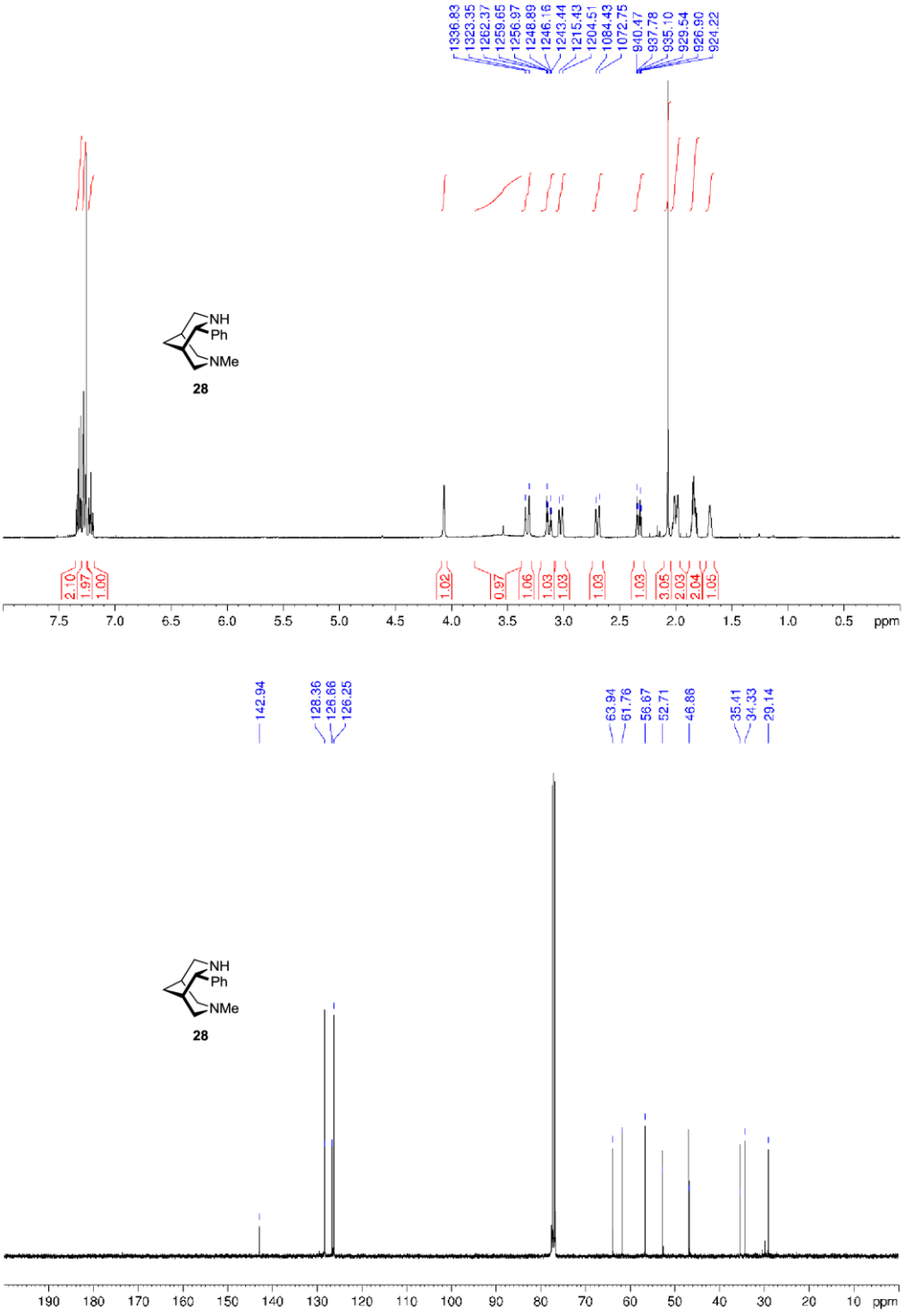
26


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

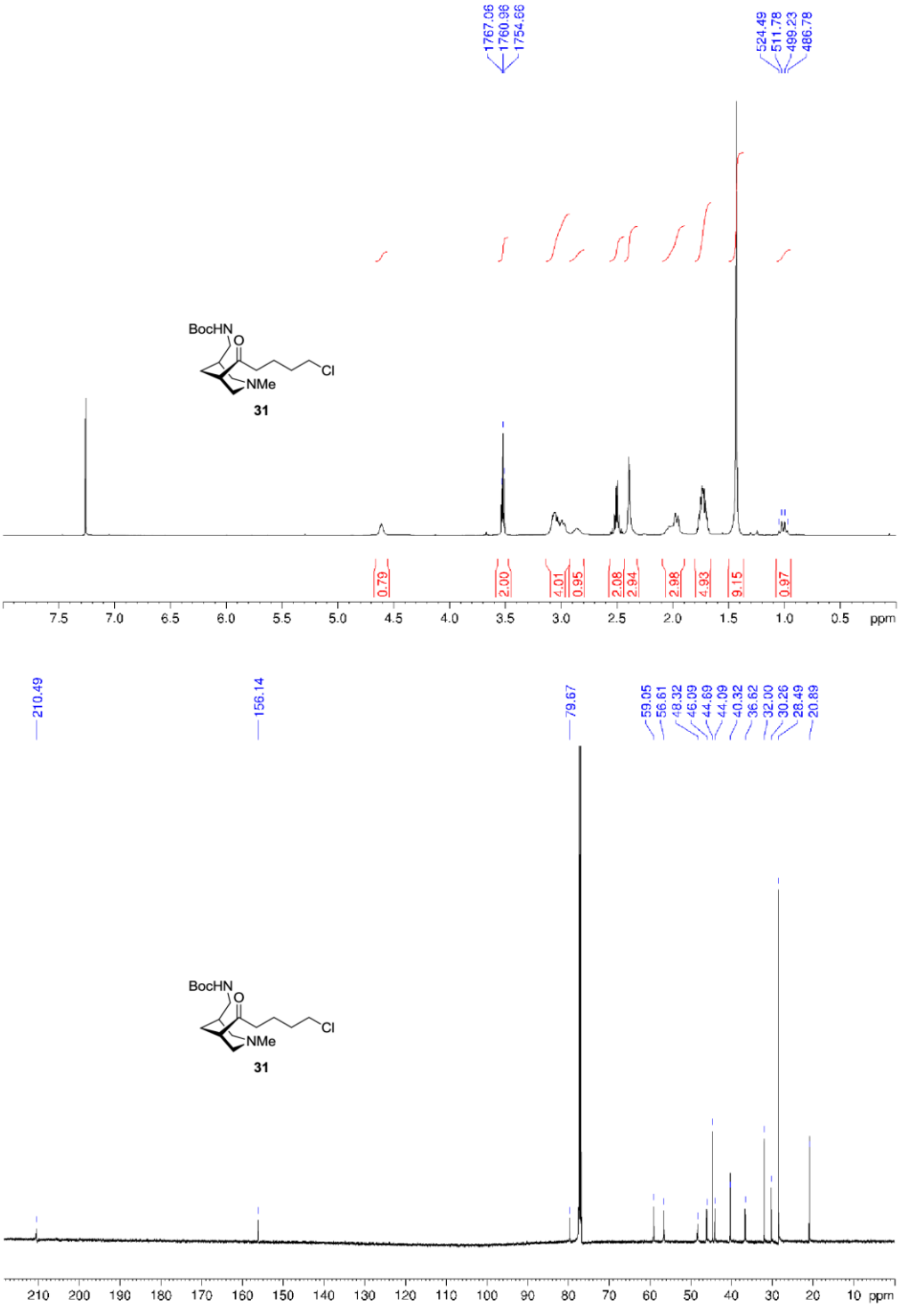
27


818.75
807.46
796.18
773.45
760.41
680.74
665.50
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

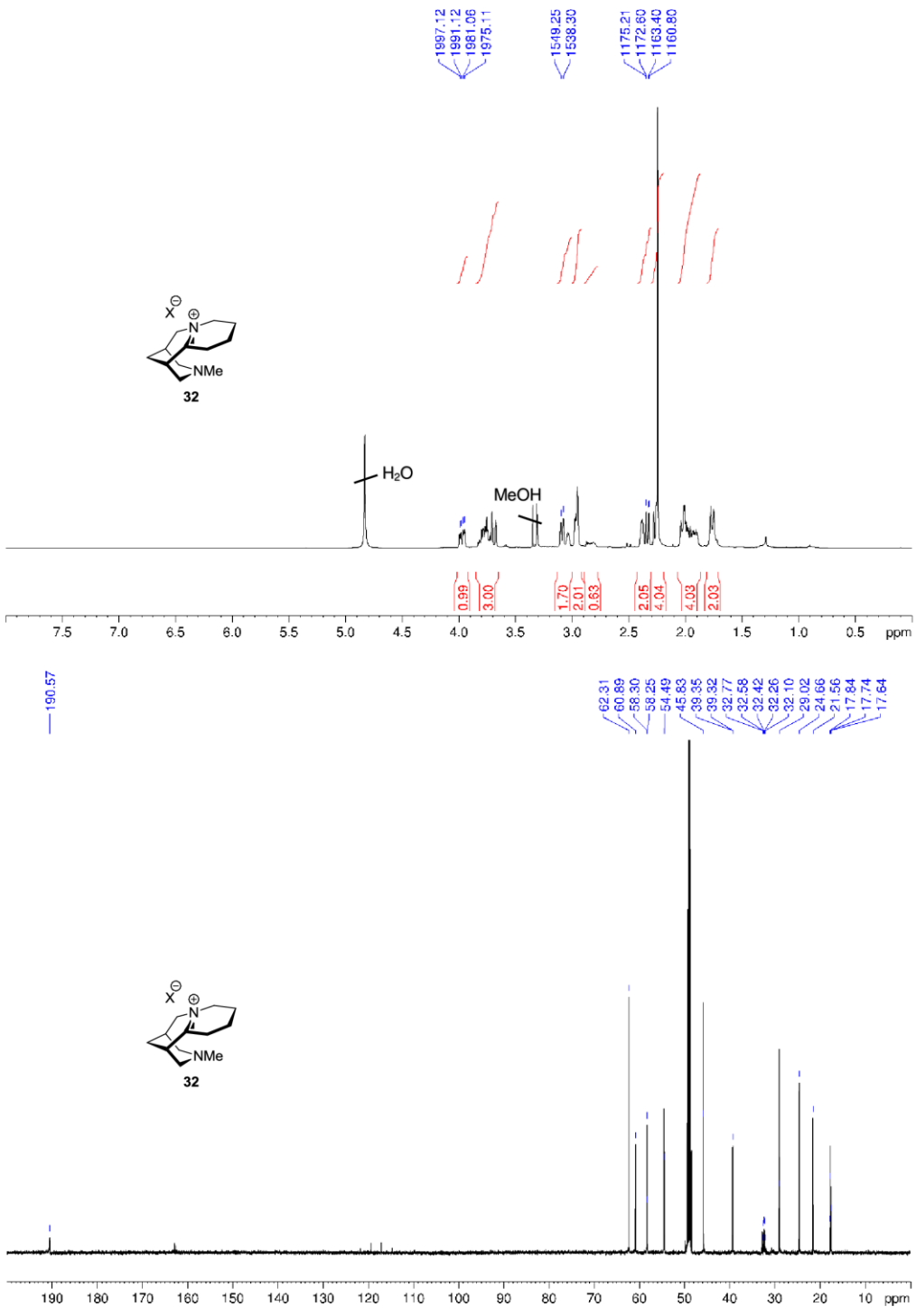
28


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
928.54
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

29


1767.06
1760.96
1754.66
524.49
511.78
499.23
486.78
BocHN
O
NMe
Cl
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
NMe
Cl
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
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
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

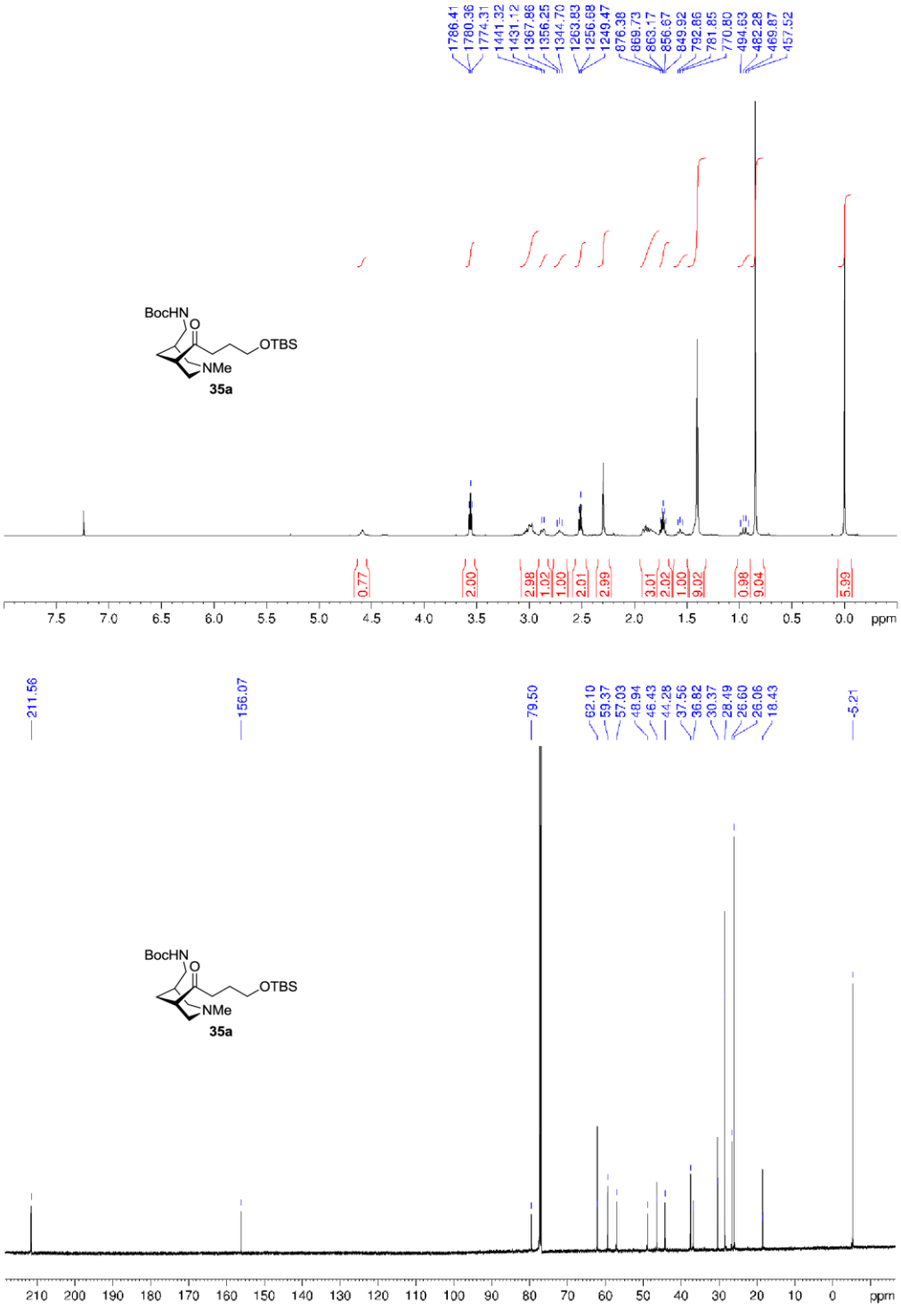
NMe

32

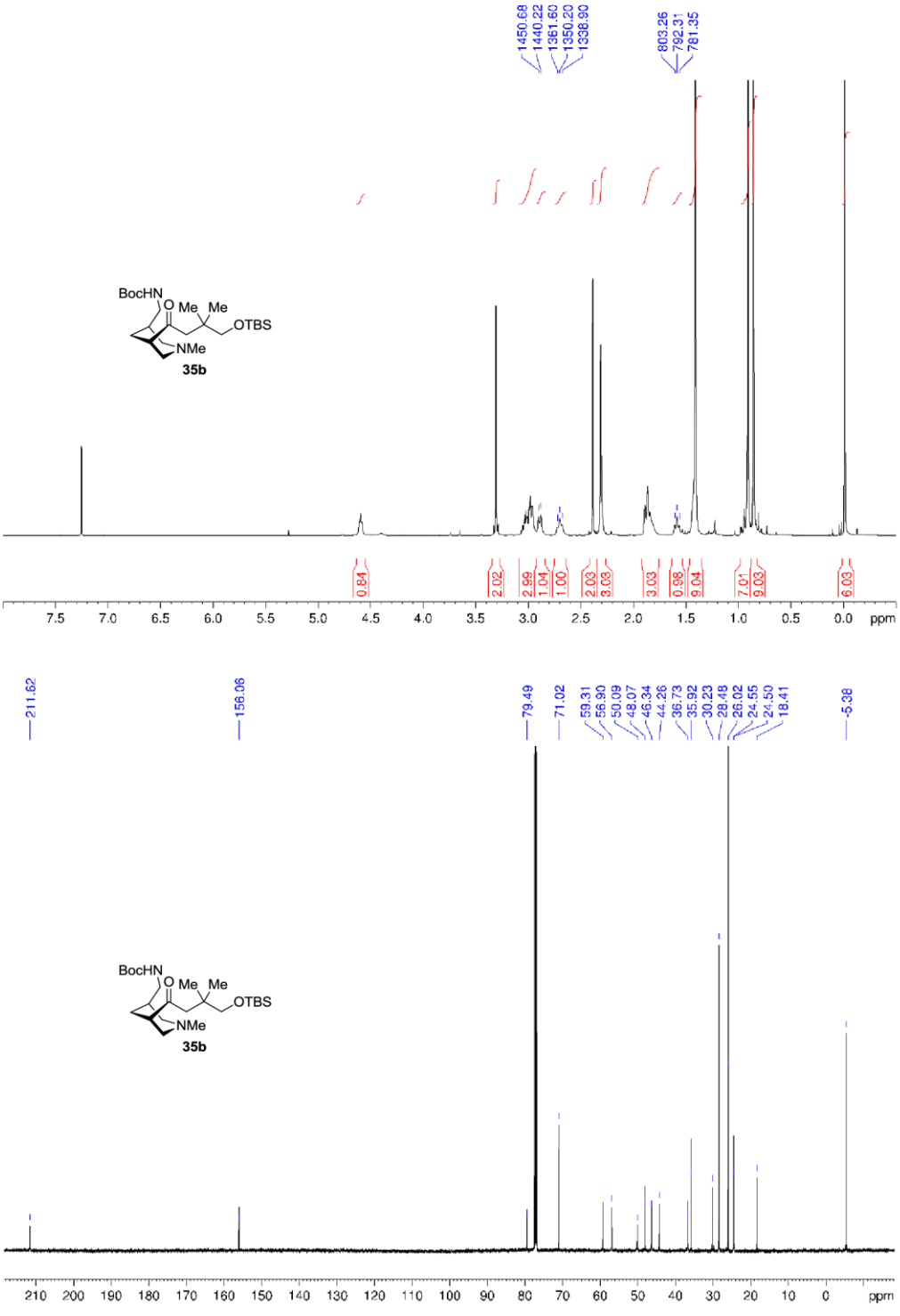
NMe

32

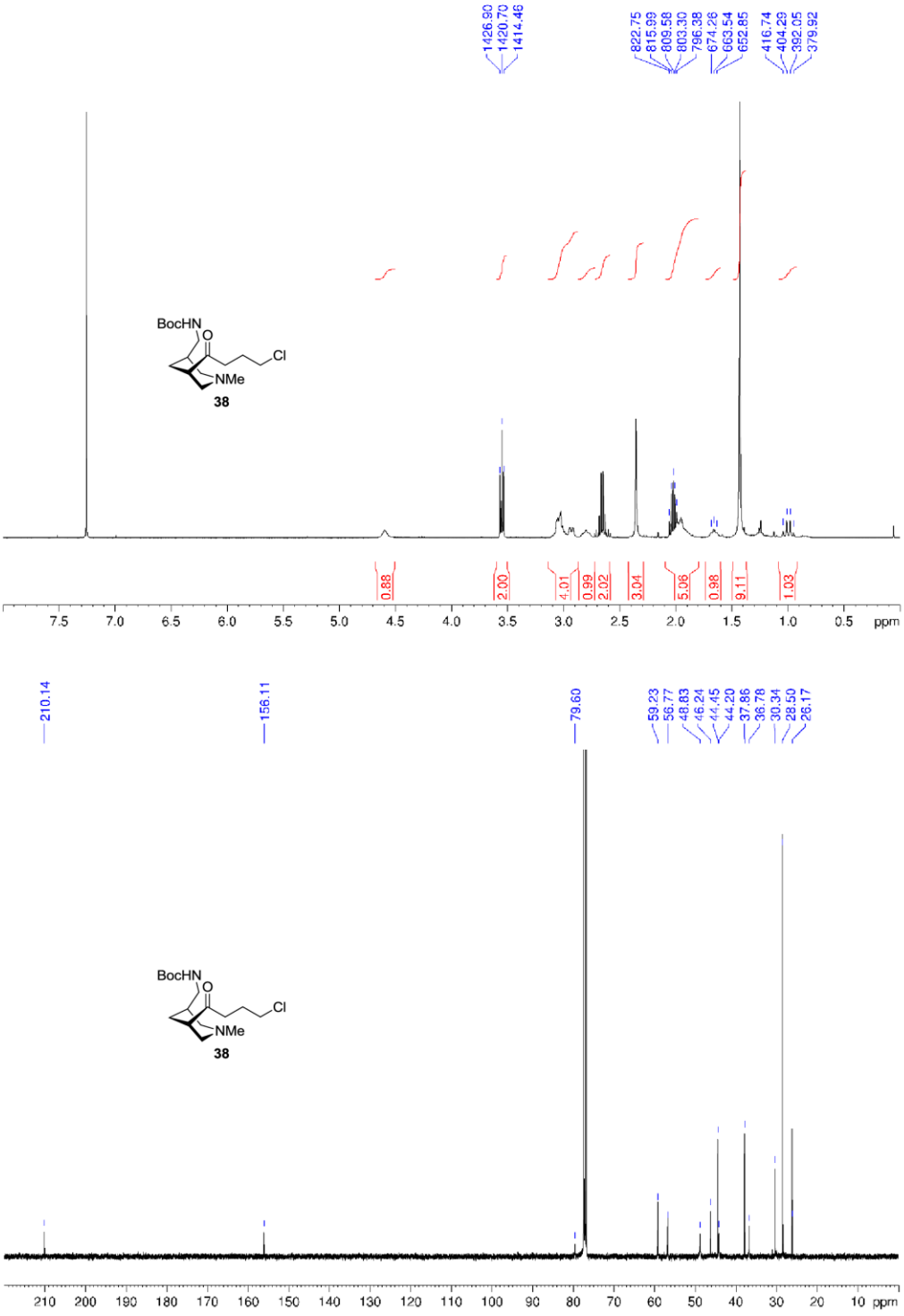
31


1786.41
1760.36
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

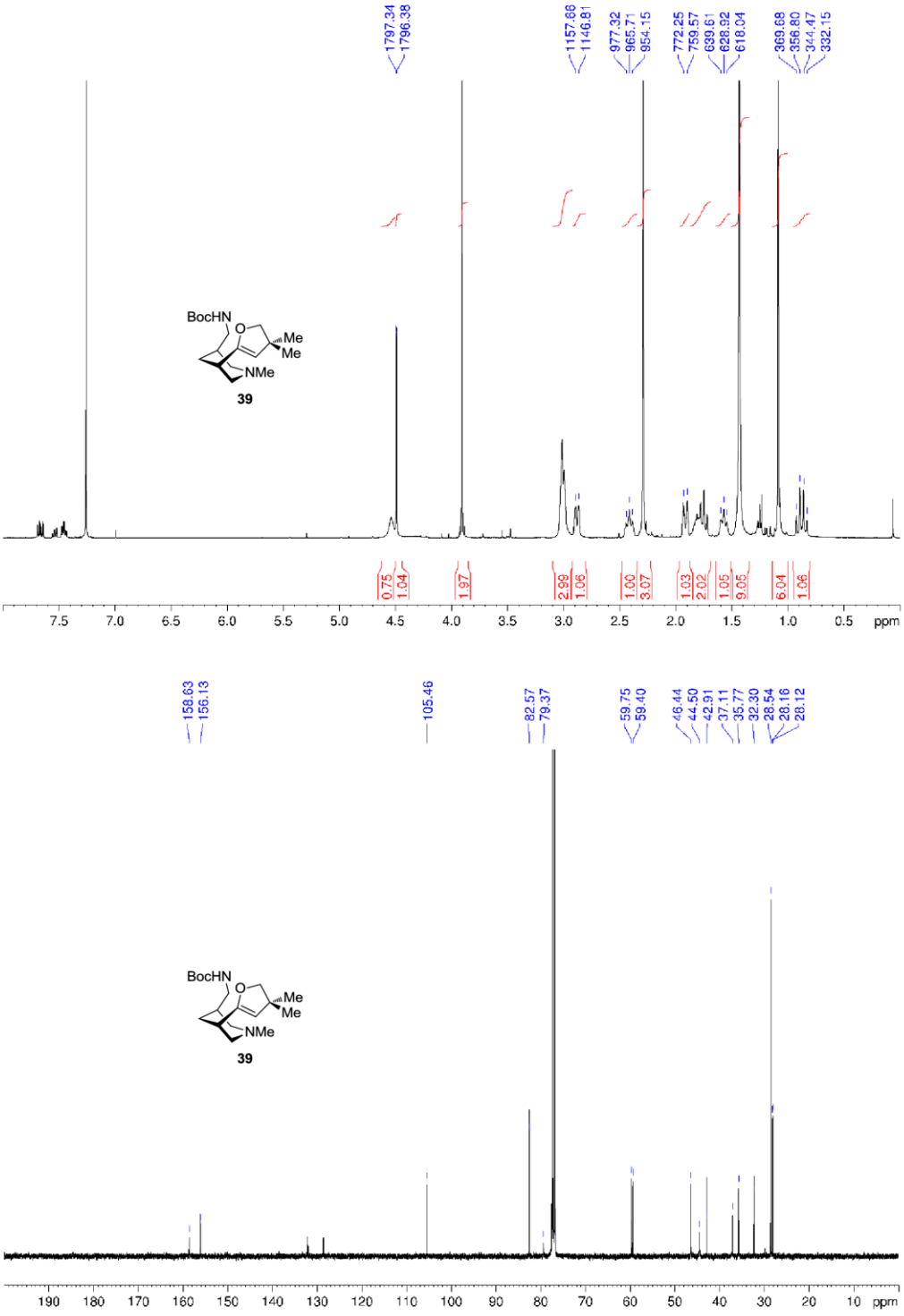
32


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
58.90
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

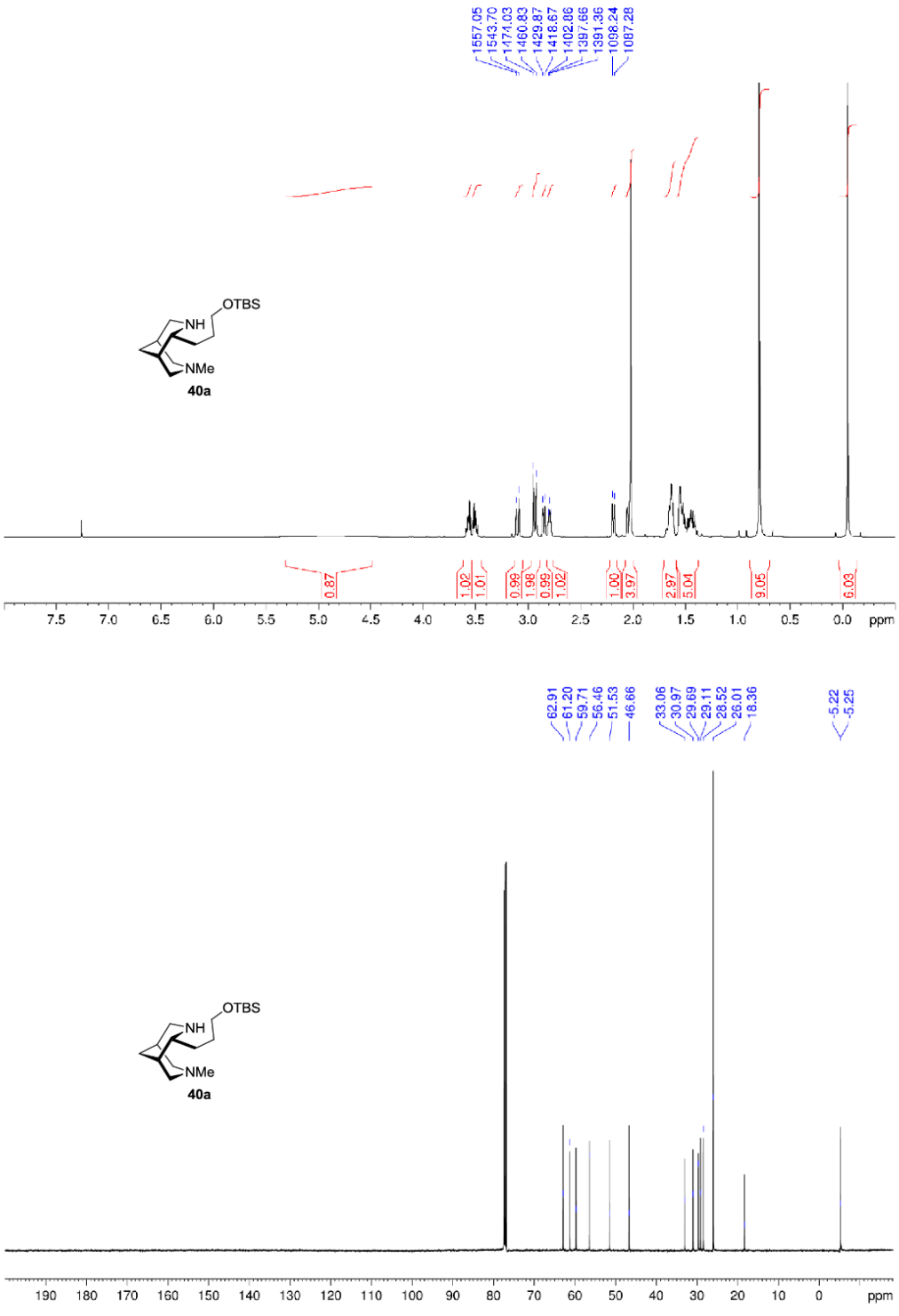
33


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

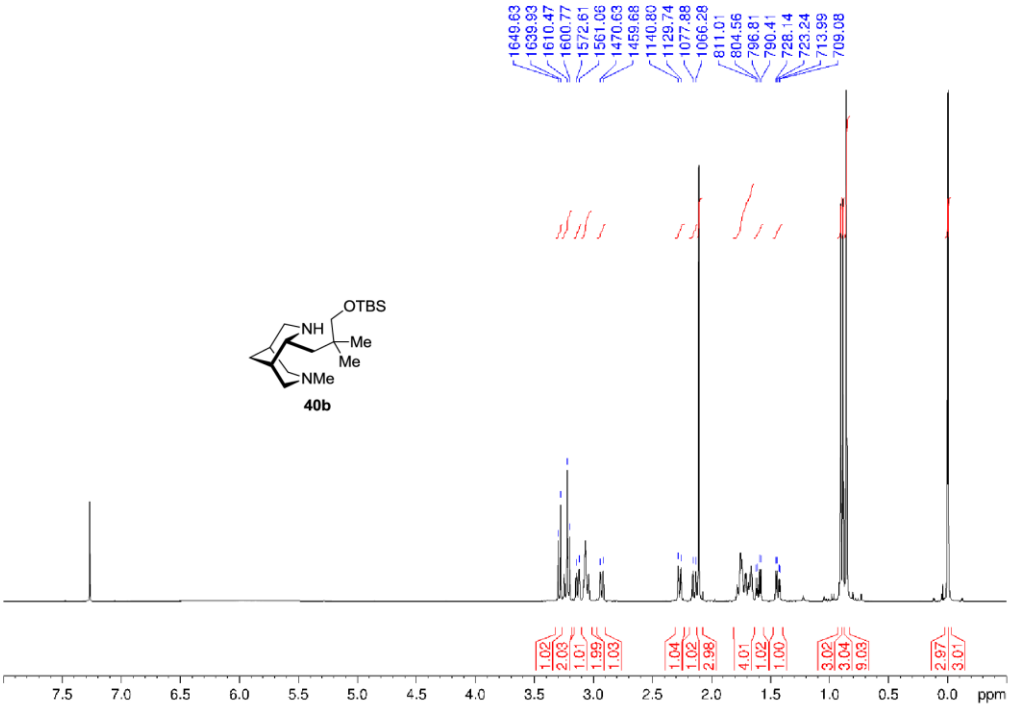
34

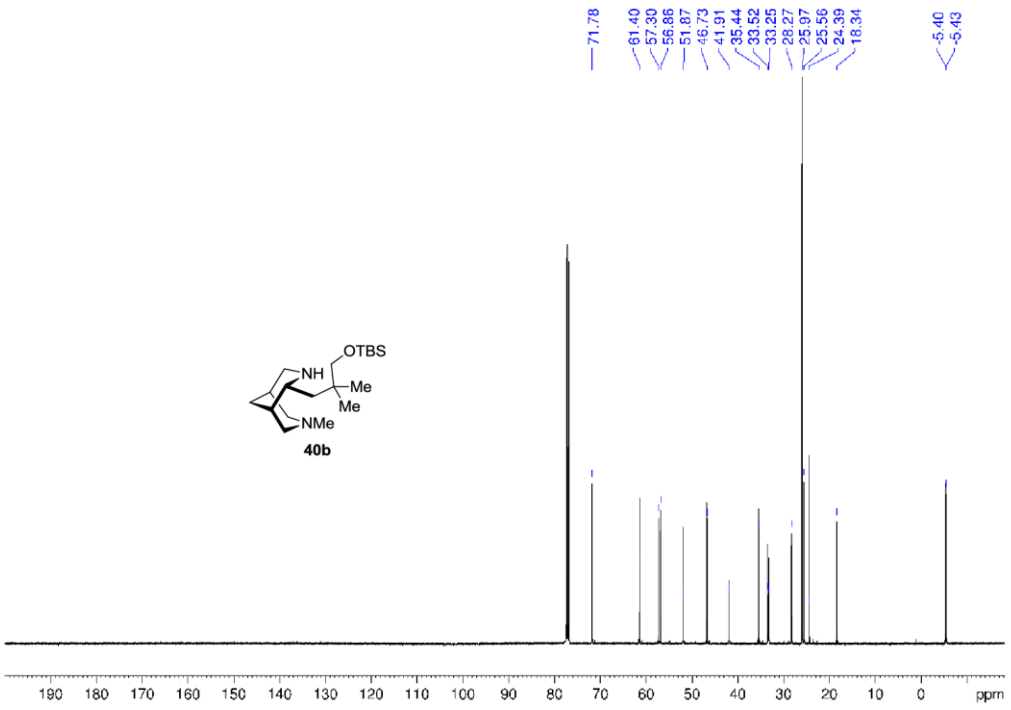

1797.34
1796.38
1157.66
1146.81
977.32
965.71
954.15
772.25
759.57
639.61
628.92
618.04
369.68
356.80
344.47
332.15
BocHN
O
Me
Me
NMe
39
0.75
1.04
1.97
2.99
1.06
1.00
3.07
1.03
2.02
1.05
9.05
6.04
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
158.63
156.13
105.46
82.57
79.37
59.75
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

35

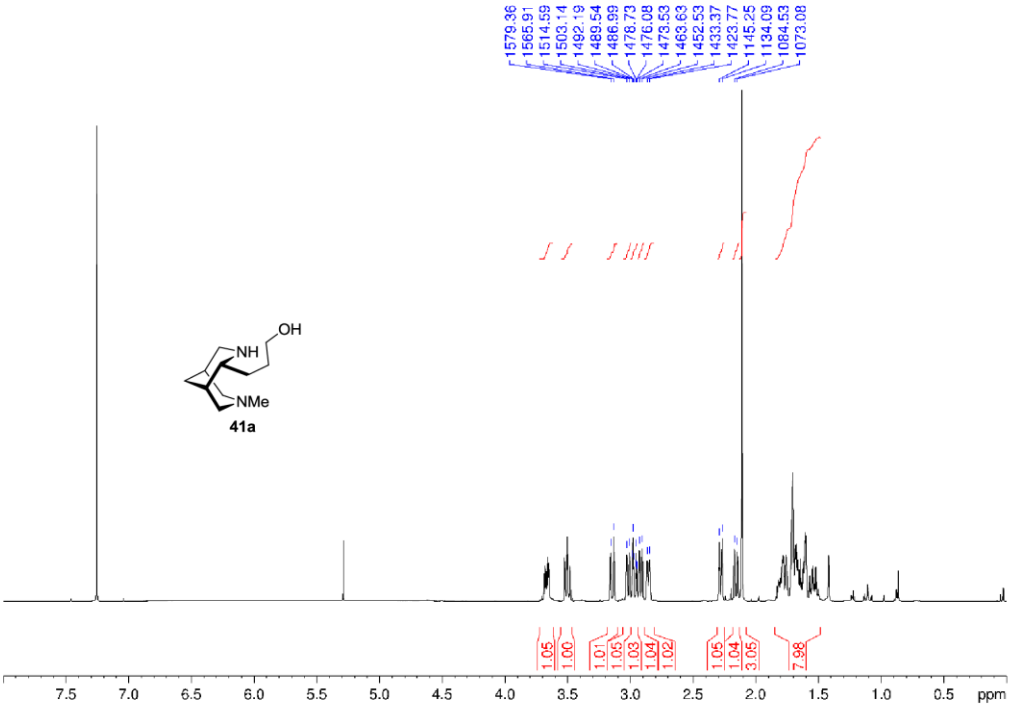

1557.05
1543.70
1471.03
1460.83
1429.87
1418.67
1402.86
1397.66
1391.36
1098.24
1087.28
OTBS
NH
NMe
40a
0.87
1.02
1.01
0.99
1.98
0.99
1.02
1.00
3.97
2.97
5.04
9.05
6.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
62.91
61.20
59.71
56.46
51.53
46.66
33.06
30.97
29.69
29.11
28.52
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

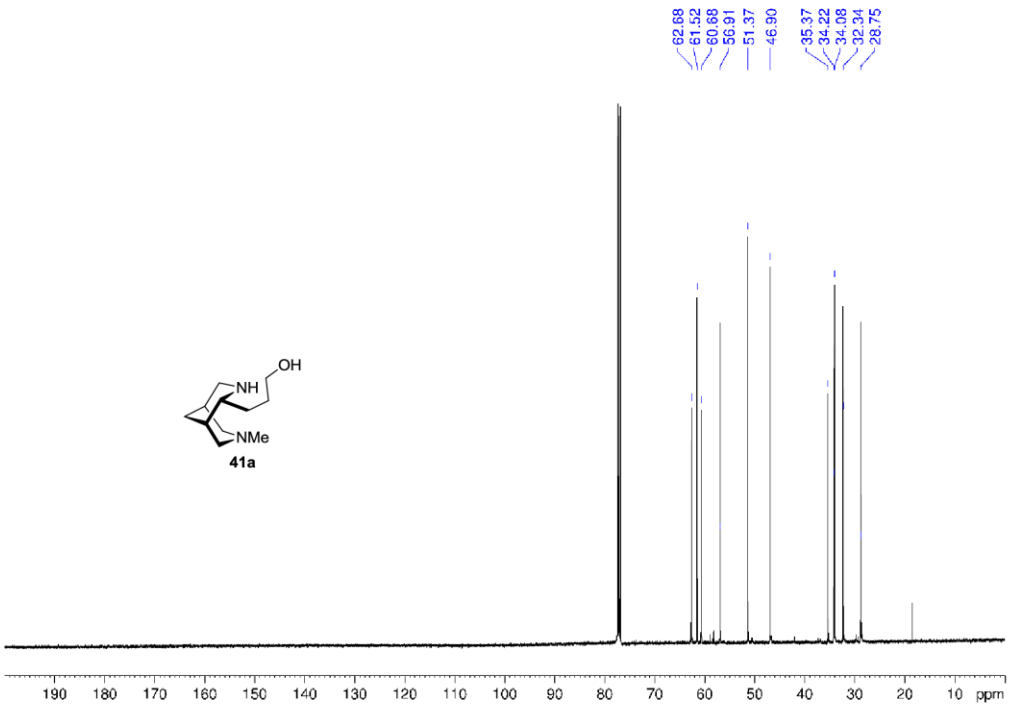
36


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

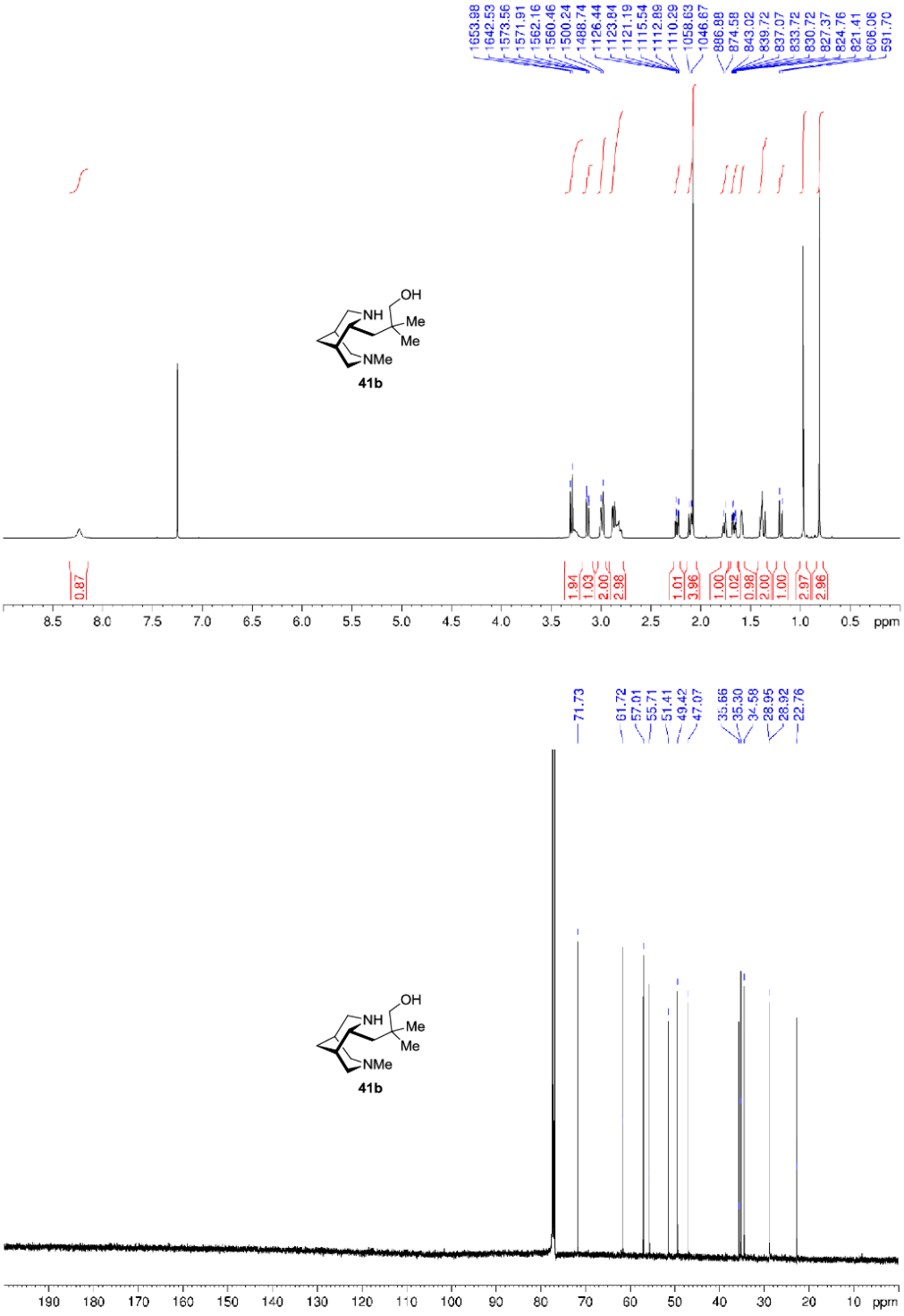

71.78
61.40
57.30
56.86
51.87
46.73
41.91
35.44
33.52
33.25
28.27
25.97
25.56
24.39
18.34
-5.40
-5.43
OTBS
NH
Me
Me
NMe
40b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

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

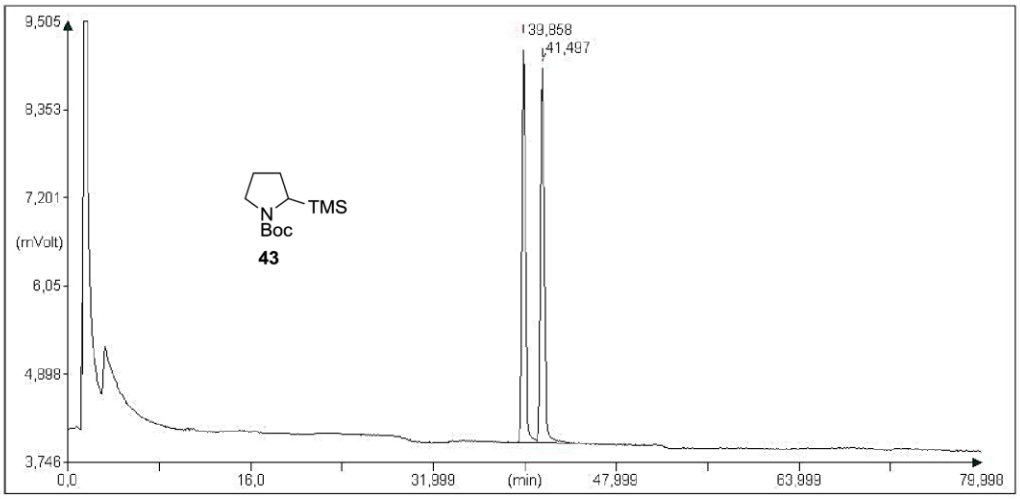

1653.98
1642.53
1573.56
1571.91
1562.16
1560.46
1500.24
1488.74
1126.44
1123.84
1121.19
1115.54
1112.89
1110.29
1058.63
1046.67
886.88
874.58
843.02
839.72
837.07
833.72
830.72
827.37
824.76
821.41
606.06
591.70
OH
NH
Me
Me
NMe
41b
0.87
1.94
1.03
2.00
2.98
1.01
3.96
1.00
1.02
0.98
2.00
1.00
2.97
2.96
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

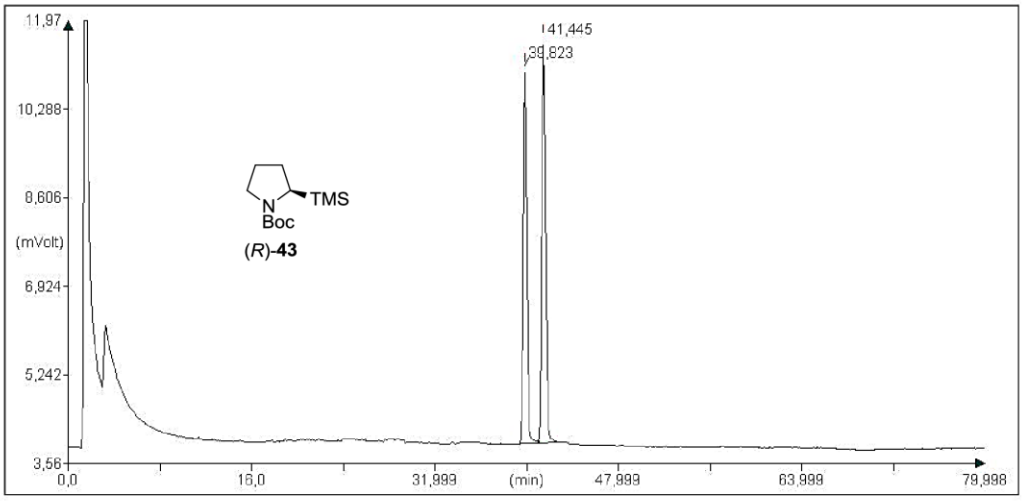
GC conditions: chiral column BGB-176SE, 30 m x 0.25 mm ID, 0.25 µm film, T = 100°C isothermal, injector temperature 240°C, detector temperature 240°C, H_2 carrier gas at 83 kPa constant pressure, t_R = 39.8 min (*S*), 41.5 min (*R*).

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	

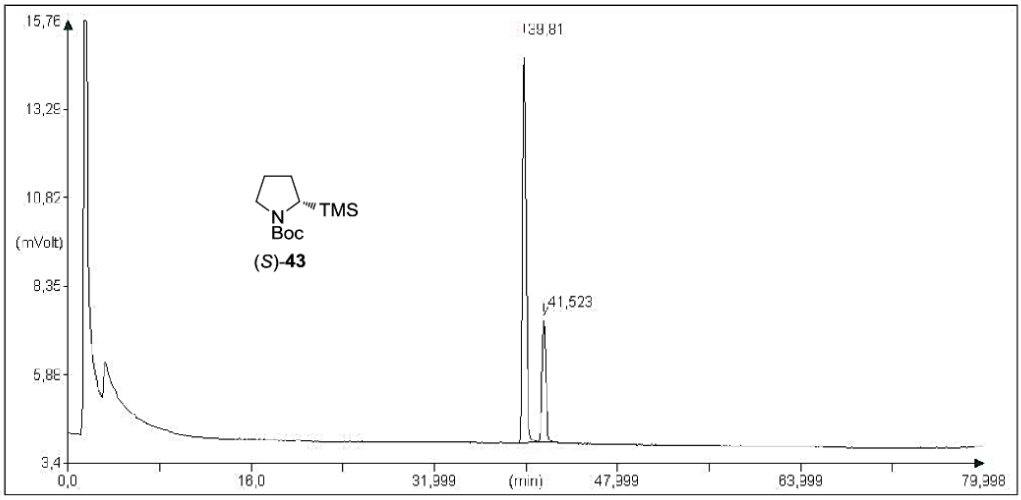
(*R*)-**43** (7% *ee*, see Table 3, entry 1)



Peak Number (#)	Retention Time (min)	Peak Height (uV)	Peak Height % (%)	Area (.1*uV*sec)	Area % (%)
1	39.823	7099	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)

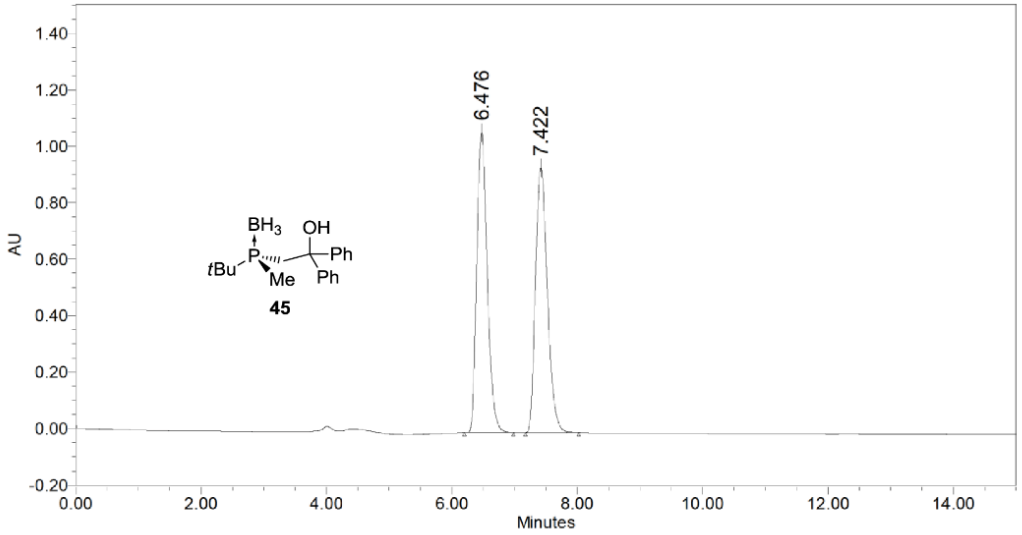


Peak Number (#)	Retention Time (min)	Peak Height (uV)	Peak Height % (%)	Area (.1*uV*sec)	Area % (%)
1	39.810	11227	76.668	2270848	75.841
2	41.523	3417	23.333	723359	24.159
		14644		2994205	

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*).

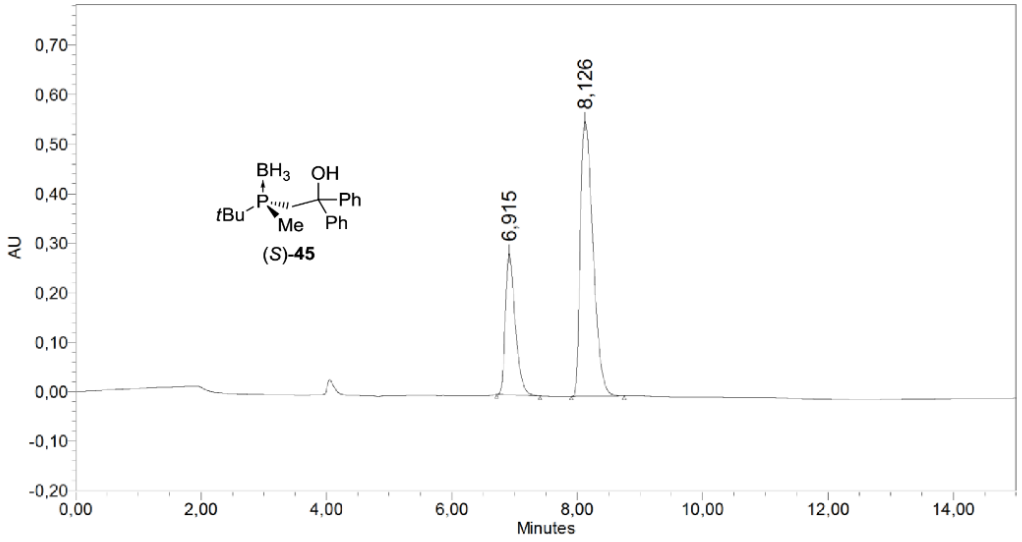
45 (racemic)



	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

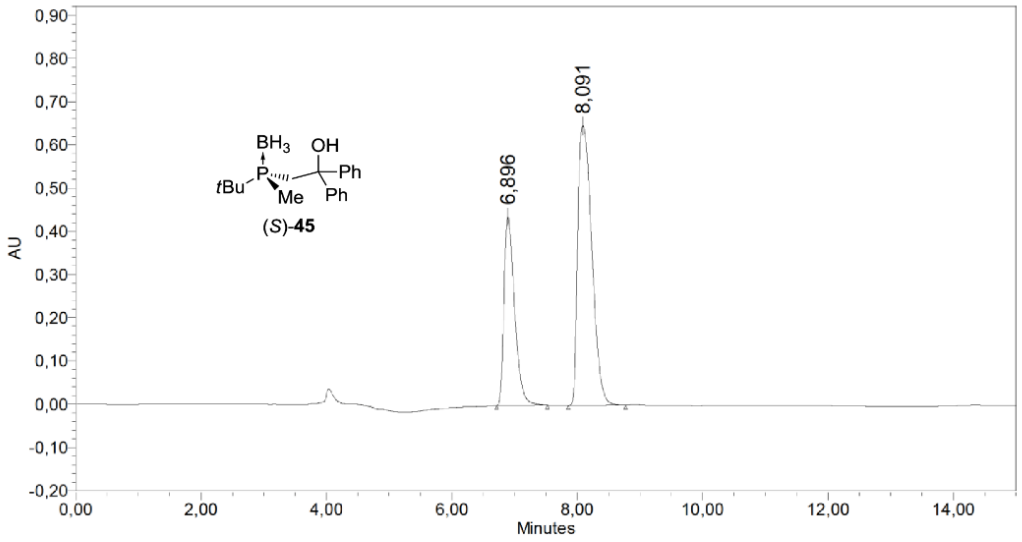
41

(*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)

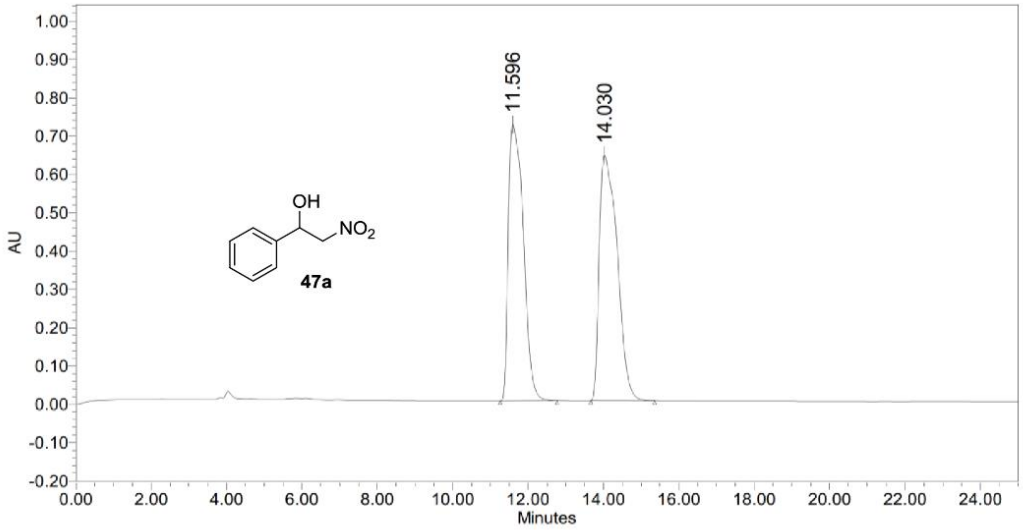


	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	6,90	6,72	7,53	437334	40,33	5125298	33,64
2	8,09	7,86	8,78	646941	59,67	10111230	66,36

4.3 Enantiomer analysis of the β-nitro alcohols 47 by HPLC on chiral phase

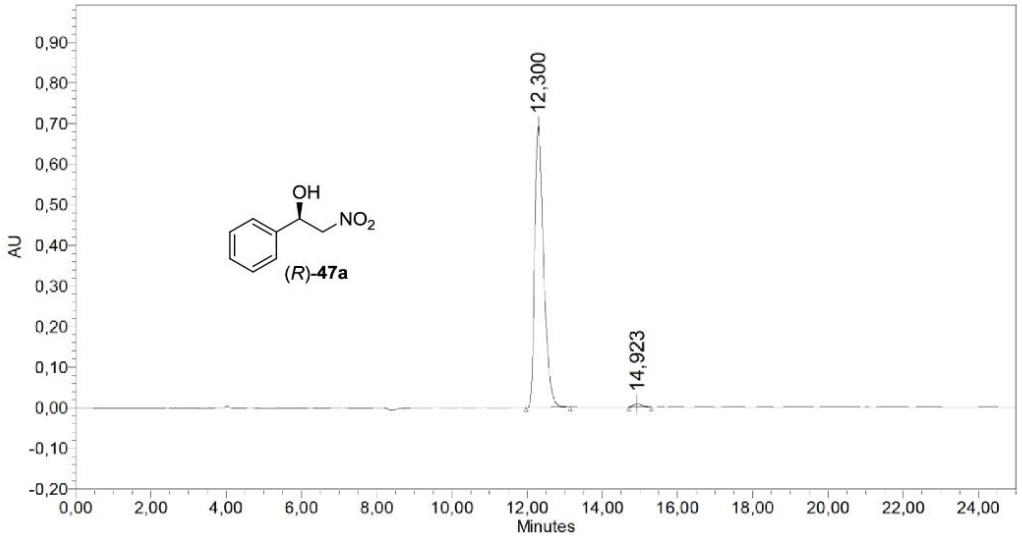
Compound **47a**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 12.3 min (*R*), 14.9 min (*S*).

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

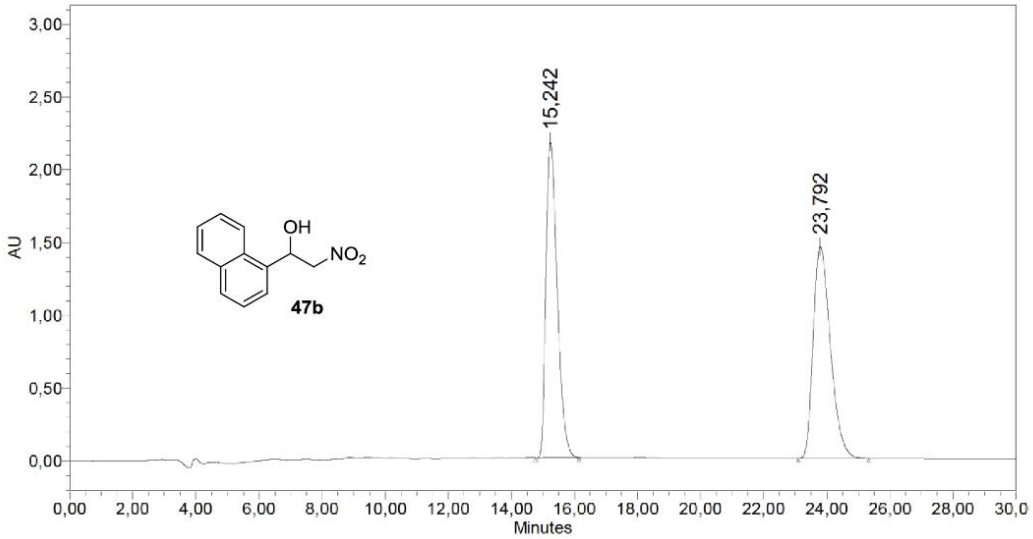
(*R*)-**47a** (98% *ee*, see Table 5, entry 1)



	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

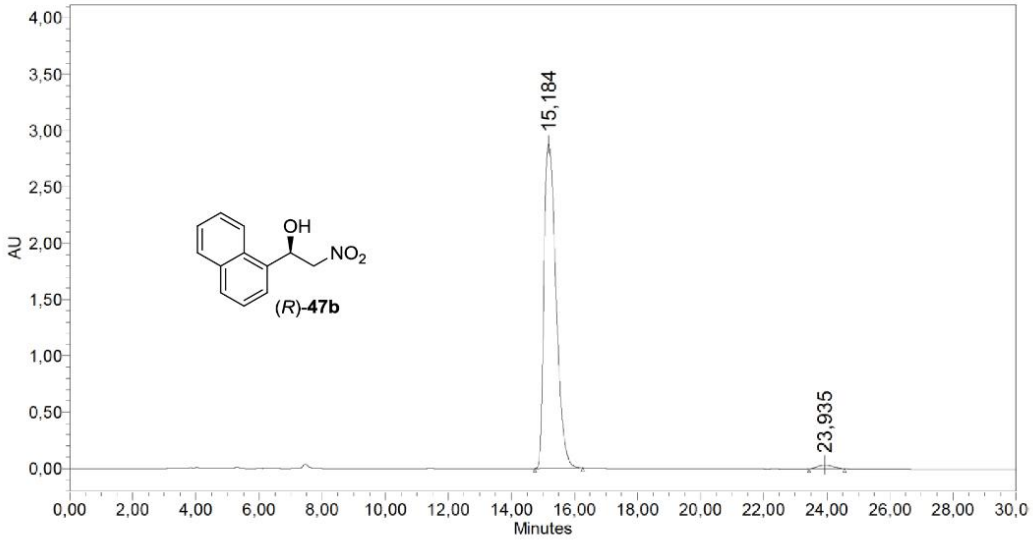
Compound **47b**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 15.2 min (*R*), 23.9 min (*S*).

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

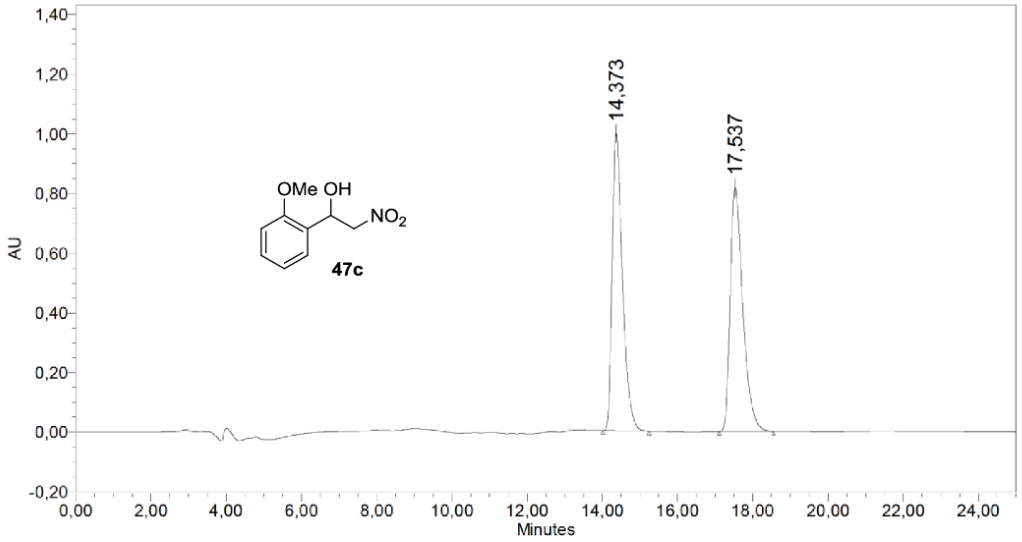
(*R*)-**47b** (97% *ee*, see Table 5, entry 2)



	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

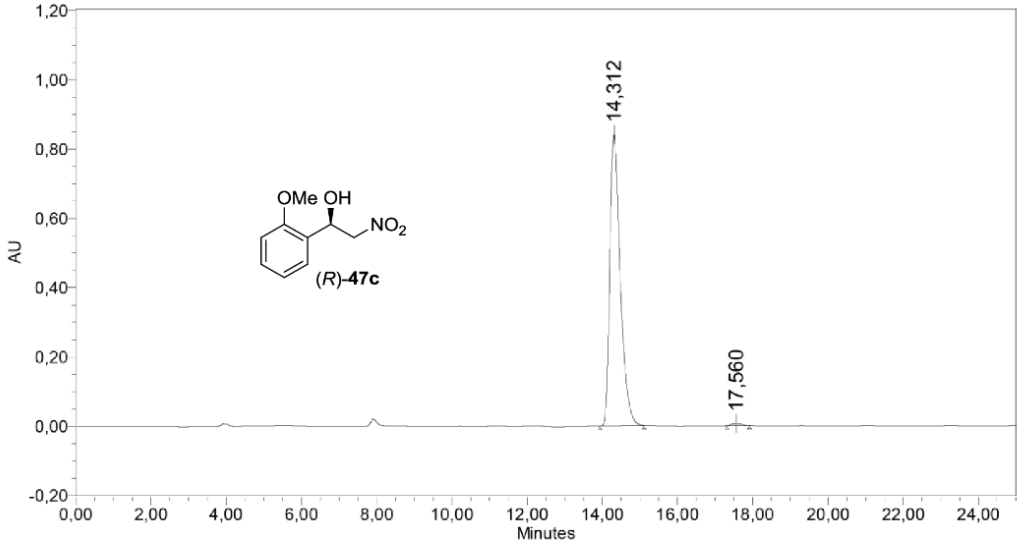
Compound **47c**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 90:10, 0.8 mL/min, 215 nm, t_R = 14.3 min (*R*), 17.6 min (*S*).

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

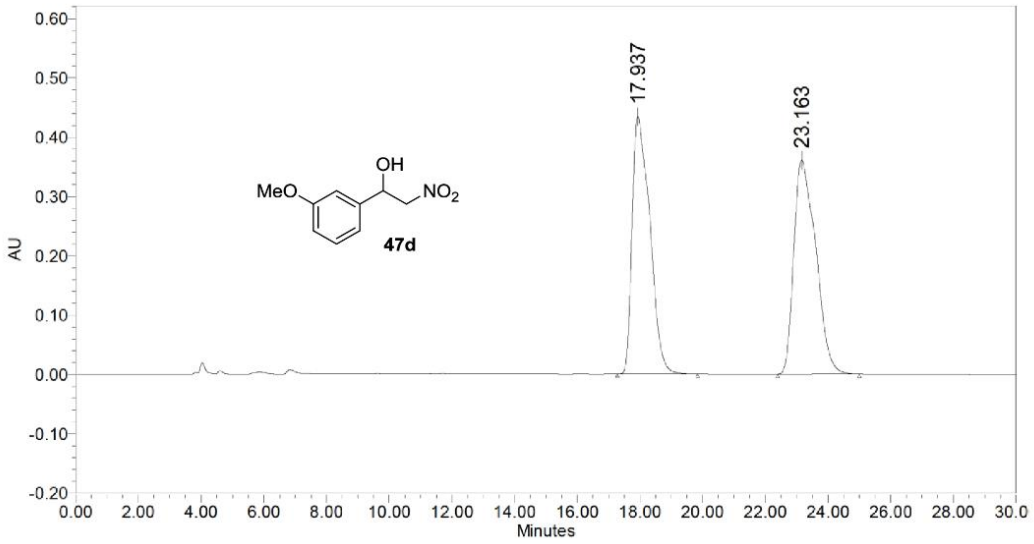
(*R*)-**47c** (99% *ee*, see Table 5, entry 3)



	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

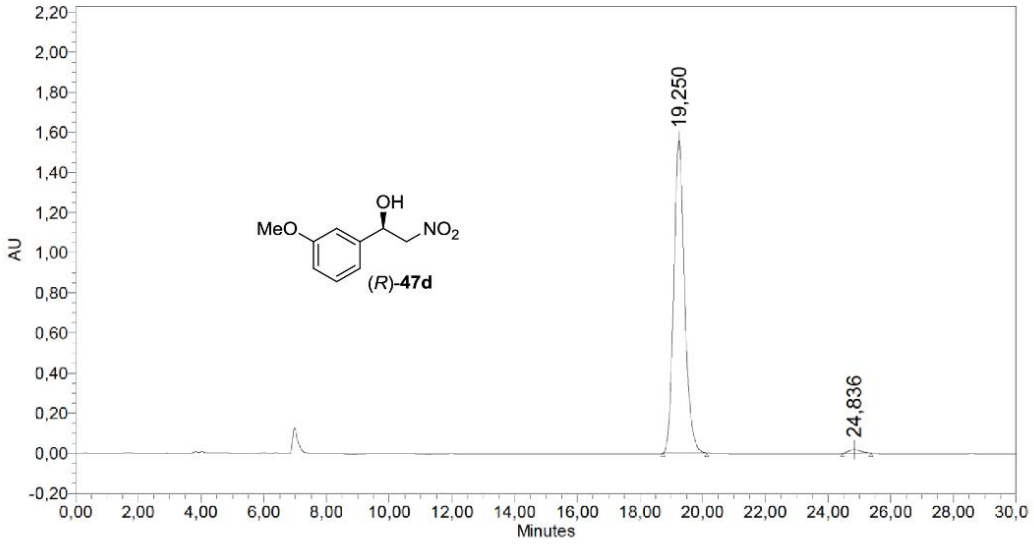
Compound **47d**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 19.3 min (*R*), 24.8 min (*S*).

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

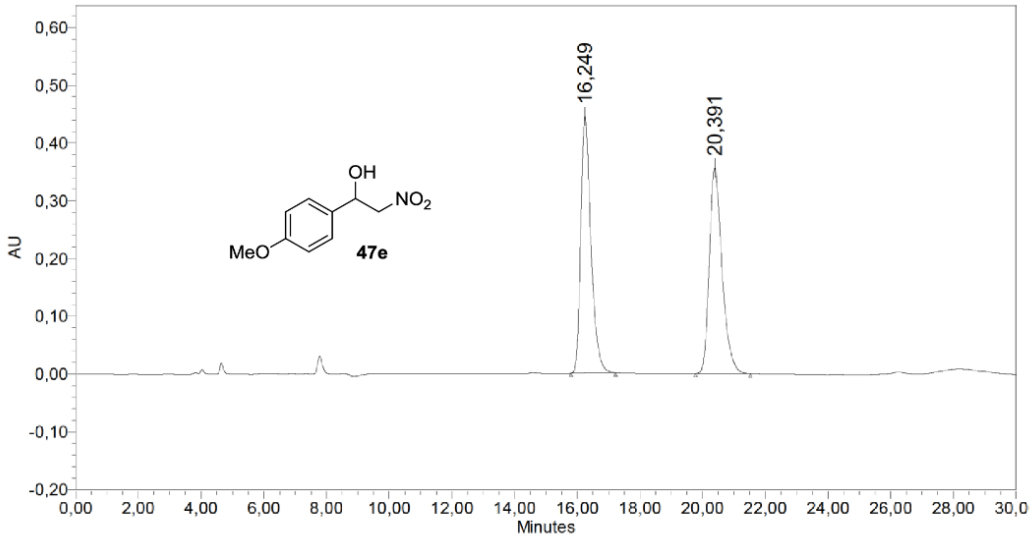
(*R*)-**47d** (98% *ee*, see Table 5, entry 4)



	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

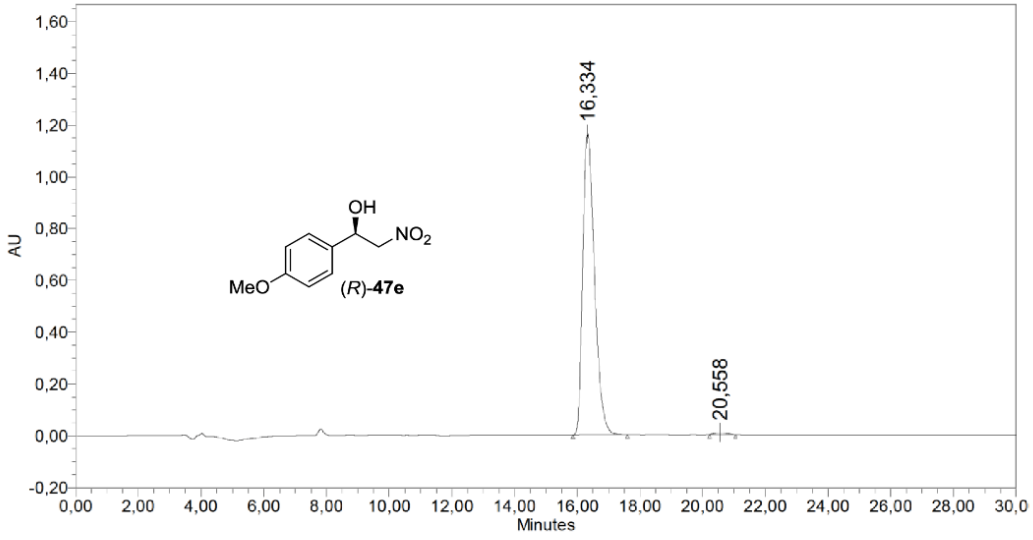
Compound **47e**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 16.3 min (*R*), 20.6 min (*S*).

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

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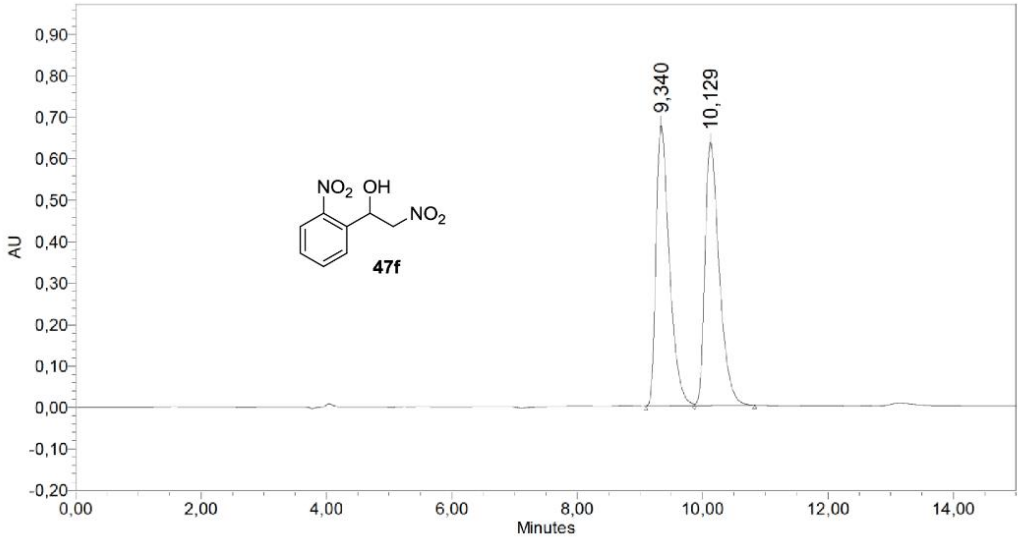
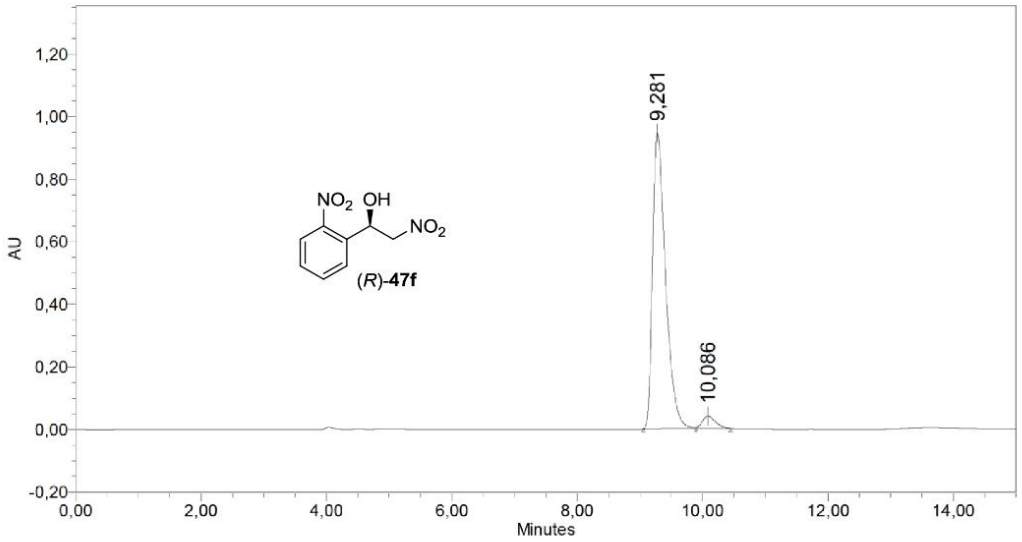
Compound **47f**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 80:20, 0.8 mL/min, 215 nm, t_R = 9.3 min (*R*), 10.1 min (*S*).

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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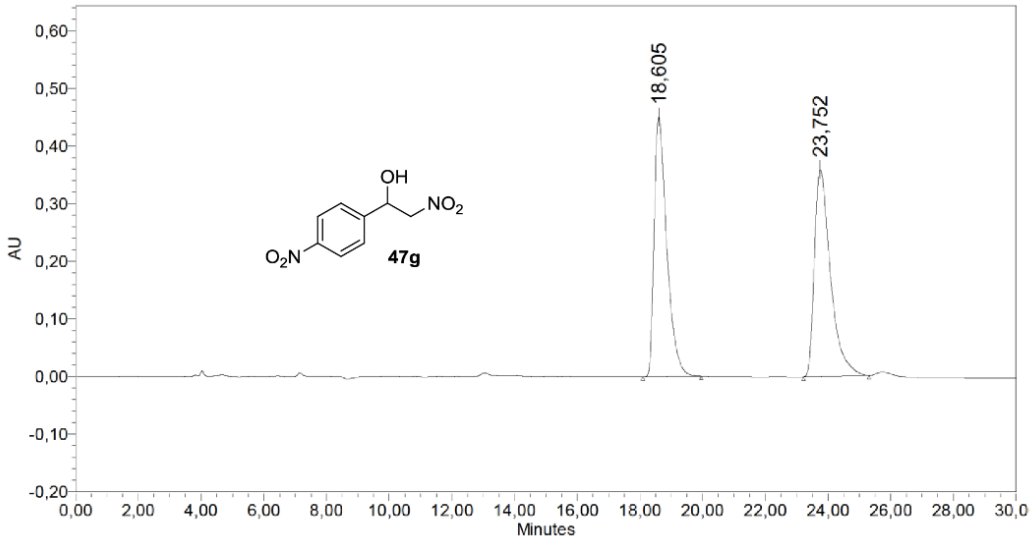
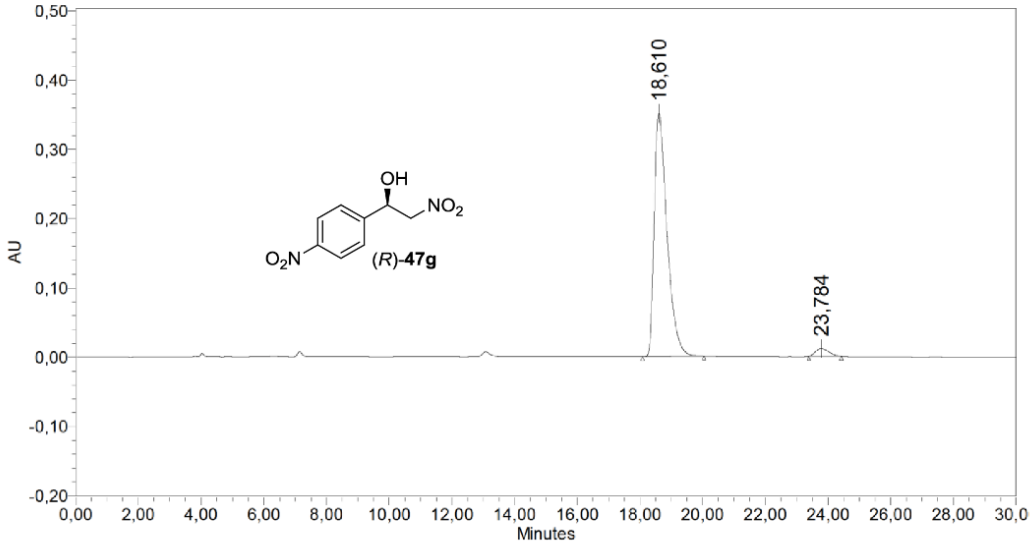
Compound **47g**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 18.6 min (*R*), 23.8 min (*S*).

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

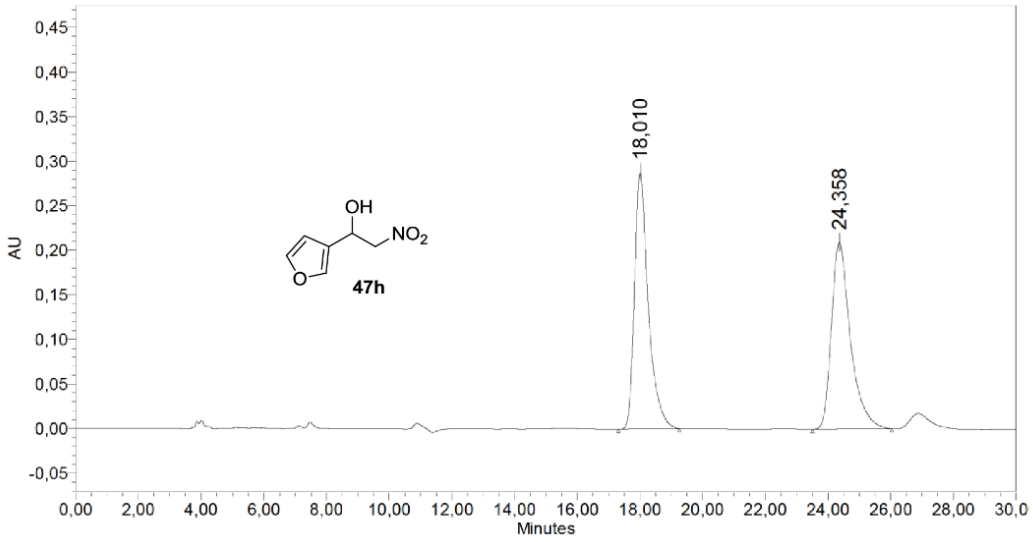
(*R*)-**47g** (94% *ee*, see Table 5, entry 9)



	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

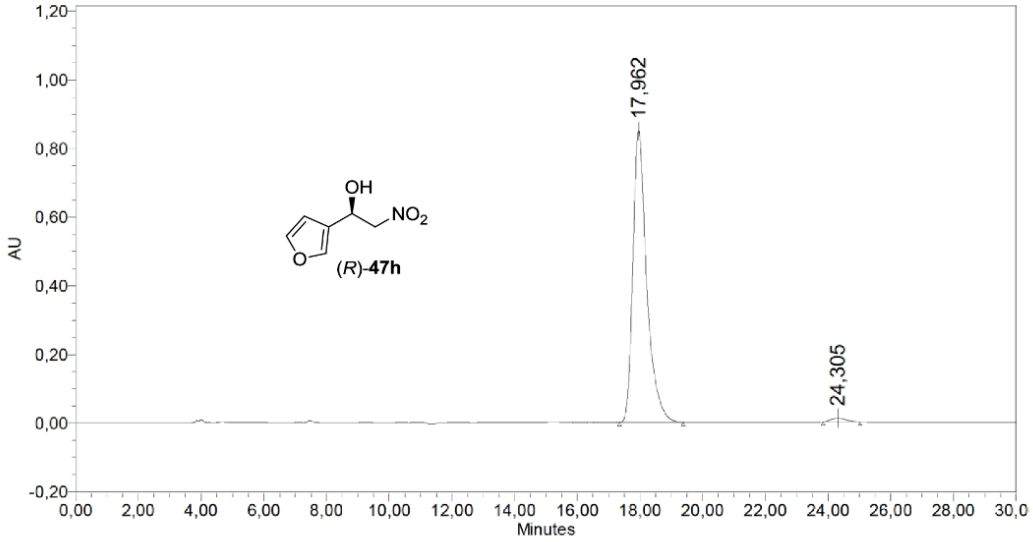
Compound **47h**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 90:10, 0.8 mL/min, 215 nm, t_R = 18.0 min (*R*), 24.3 min (*S*).

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

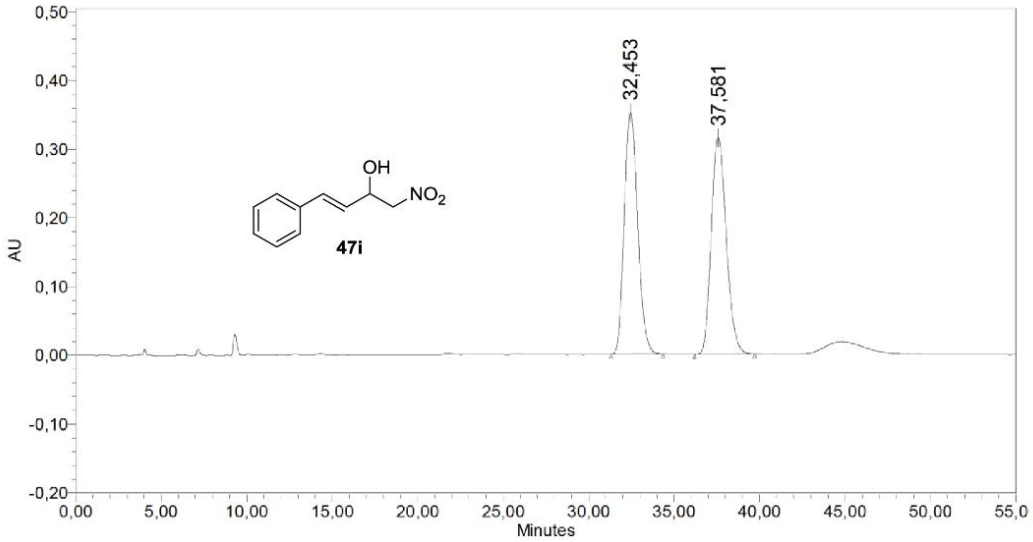
(*R*)-**47h** (97% *ee*, see Table 5, entry 10)



	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

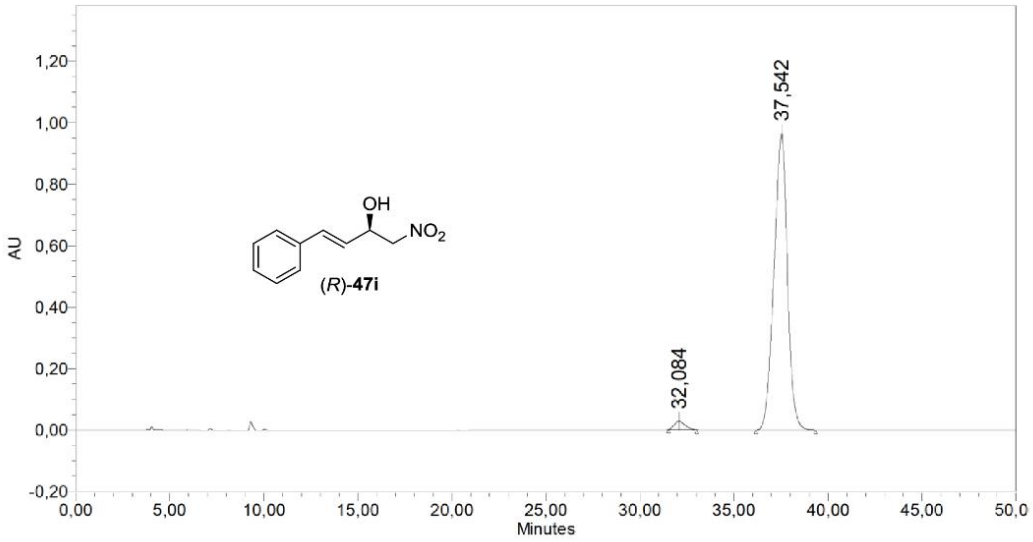
Compound **47i**: HPLC conditions: Chiralcel OD-3, *n*-hexane/iPrOH 85:15, 0.8 mL/min, 215 nm, t_R = 37.5 min (*R*), 32.1 min (*S*).

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

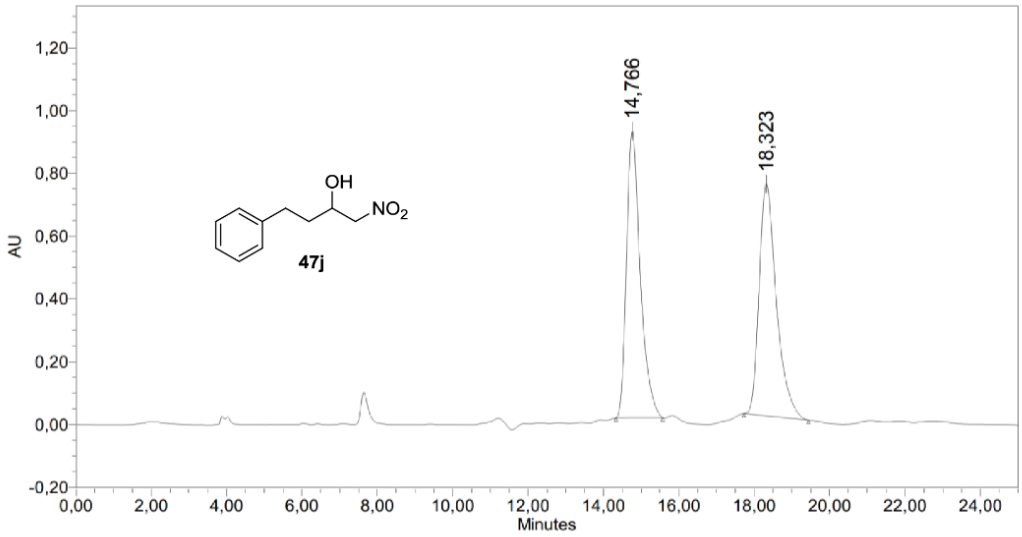
(*R*)-**47i** (96% *ee*, see Table 5, entry 11)



	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

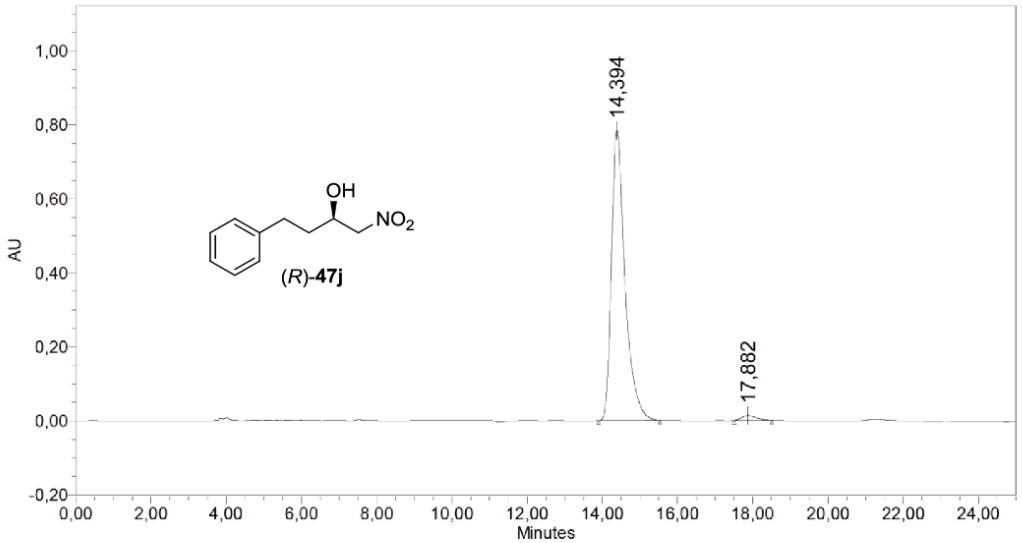
Compound **47j**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 90:10, 0.8 mL/min, 215 nm, t_R = 14.4 min (*R*), 17.9 min (*S*).

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

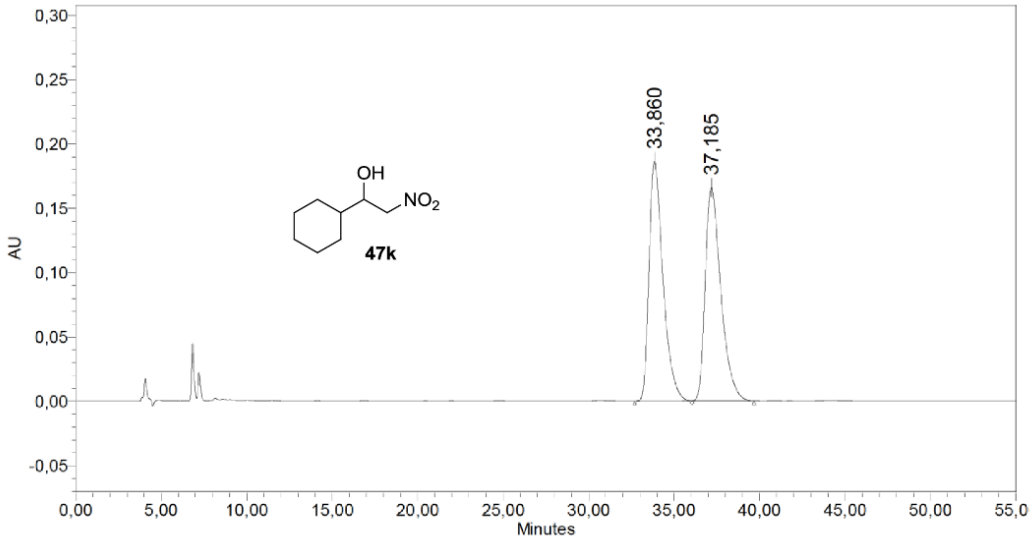
(*R*)-**47j** (97% *ee*, see Table 5, entry 12)



	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

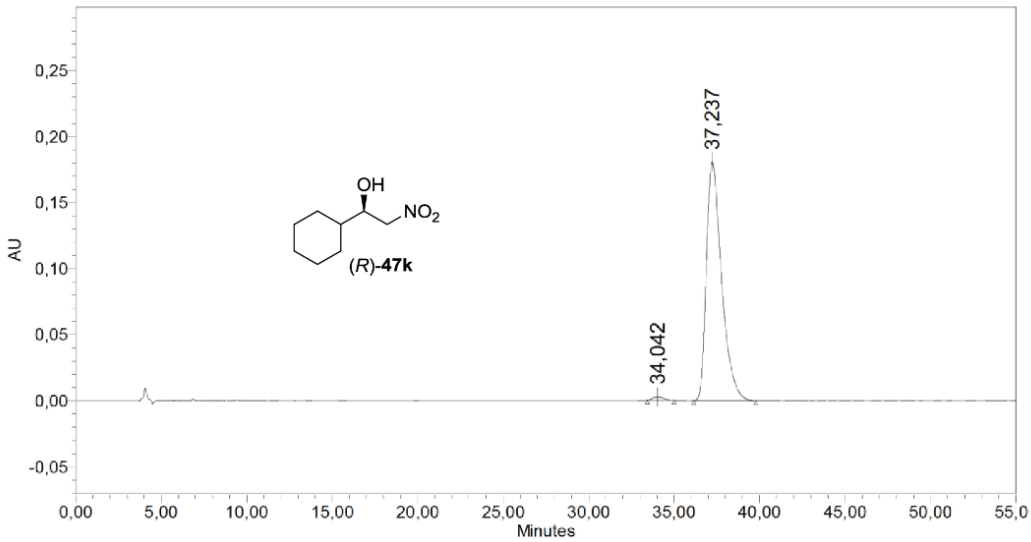
Compound **47k**: HPLC conditions: Chiralpak AD-H, *n*-hexane/EtOH 95:5, 0.8 mL/min, 215 nm, t_R = 37.2 min (*R*), 34.0 min (*S*).

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

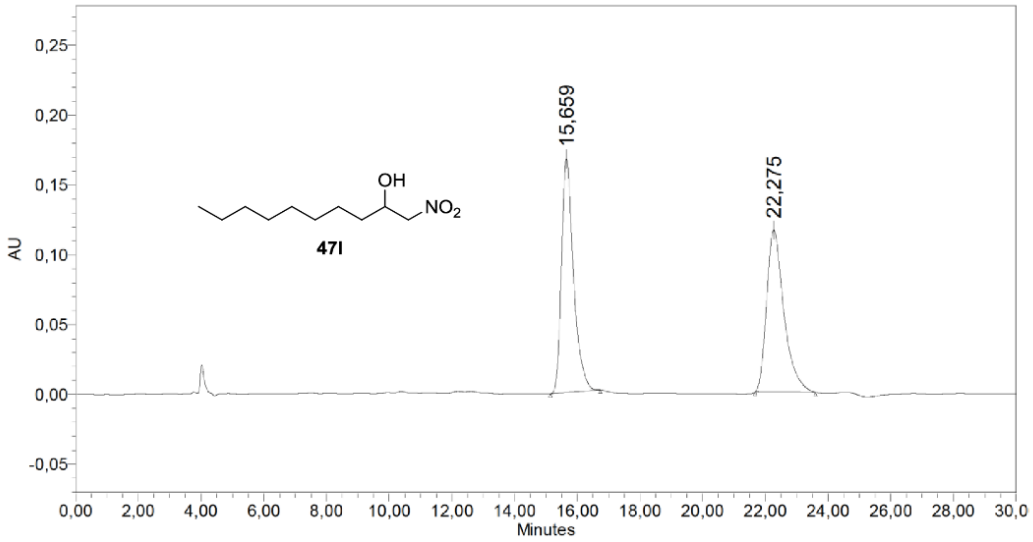
(*R*)-**47k** (98% *ee*, see Table 5, entry 13)



	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

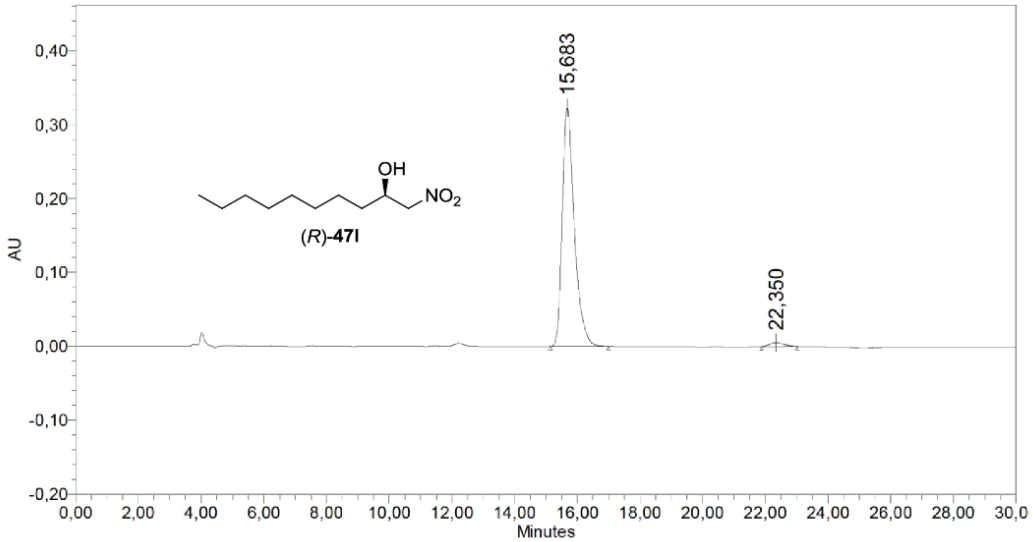
Compound **47l**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 95:5, 0.8 mL/min, 215 nm, t_R = 15.7 min (*R*), 22.4 min (*S*).

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)

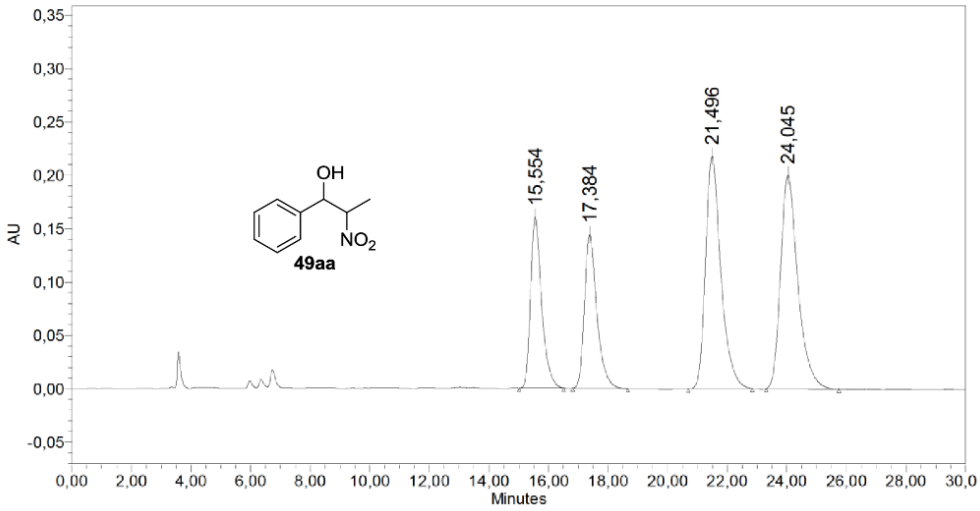


	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	15,68	15,15	17,00	323203	98,49	8625212	98,16
2	22,35	21,88	23,02	4961	1,51	161631	1,84

4.4 Enantiomer analysis of the β-nitro alcohols 49 by HPLC on chiral phase and diastereomer analysis by ^{1}H NMR

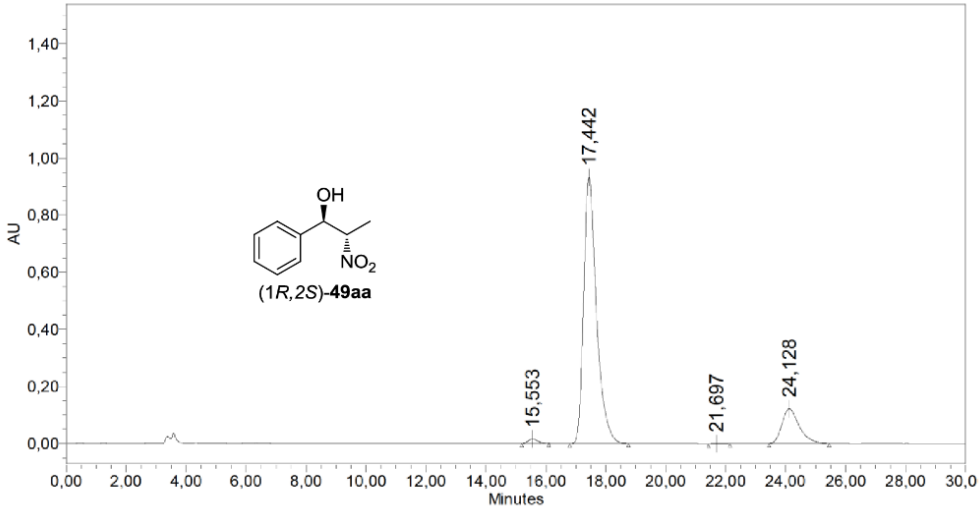
Compound **49aa**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 95:5, 0.9 mL/min, 215 nm, t_R = 15.6 min (1*S*,2*R*), 17.4 min (1*R*,2*S*), 21.7 min (1*S*,2*S*), 24.1 min (1*R*,2*R*).

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

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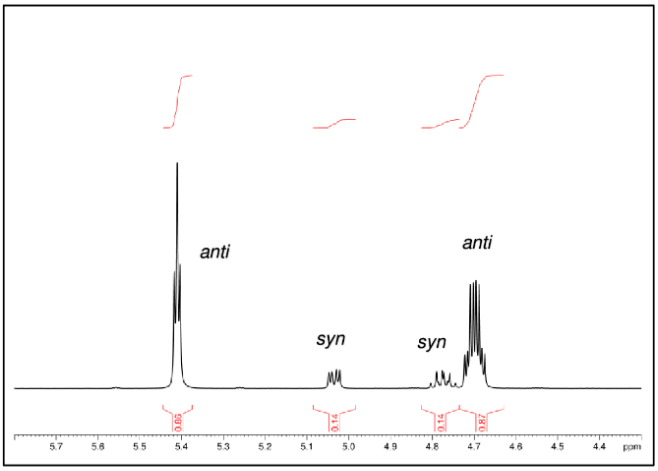
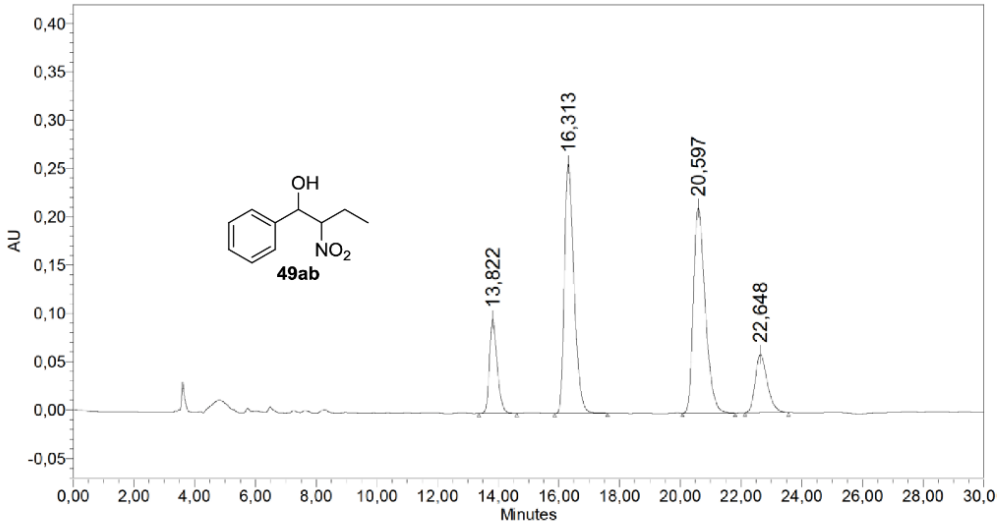
Excerpt of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **49aa**



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

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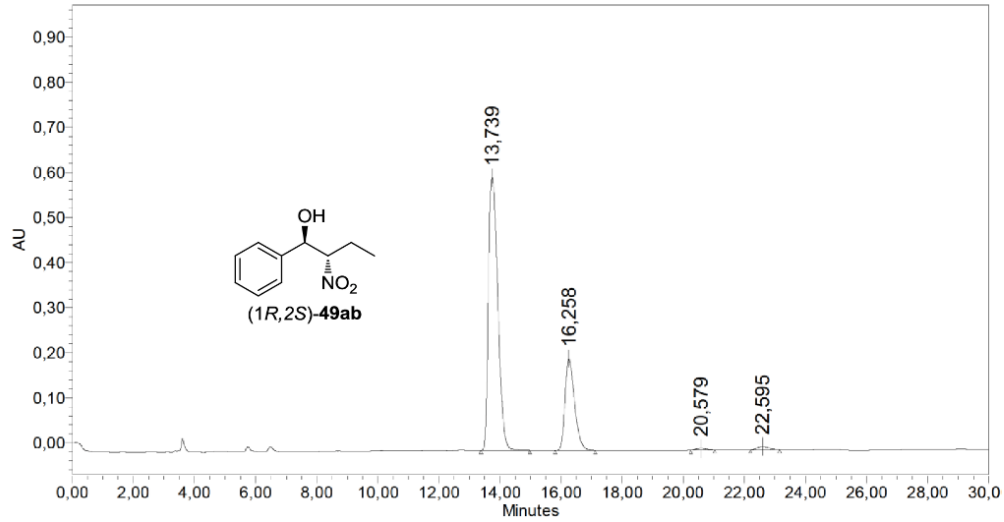
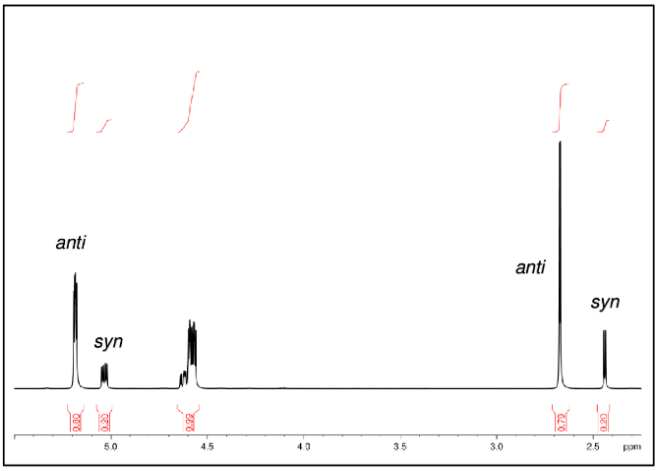
(1*R*,2*S*)-**49ab** (*anti*:*syn* 80:20, 97% ee_{anti}, 97% ee_{syn}, see Table 7, entry 2)



	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**



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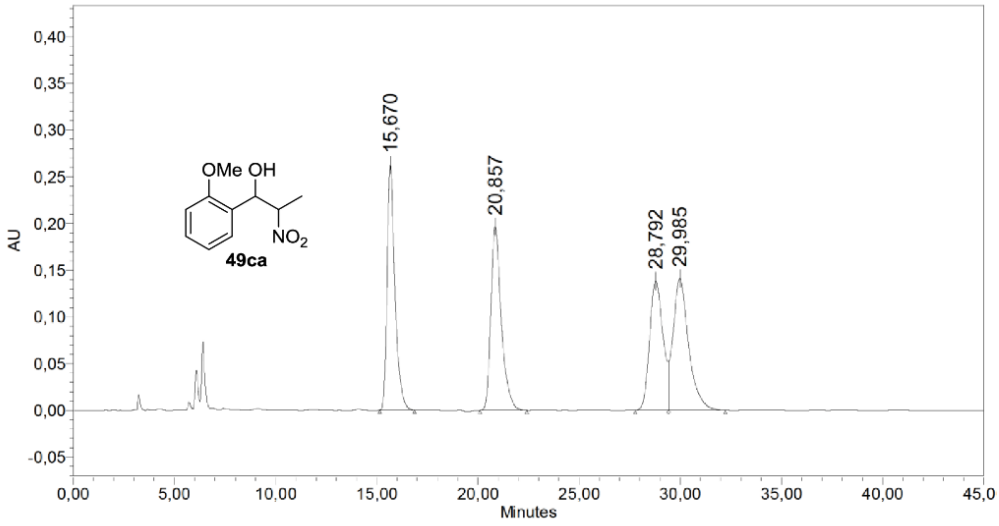
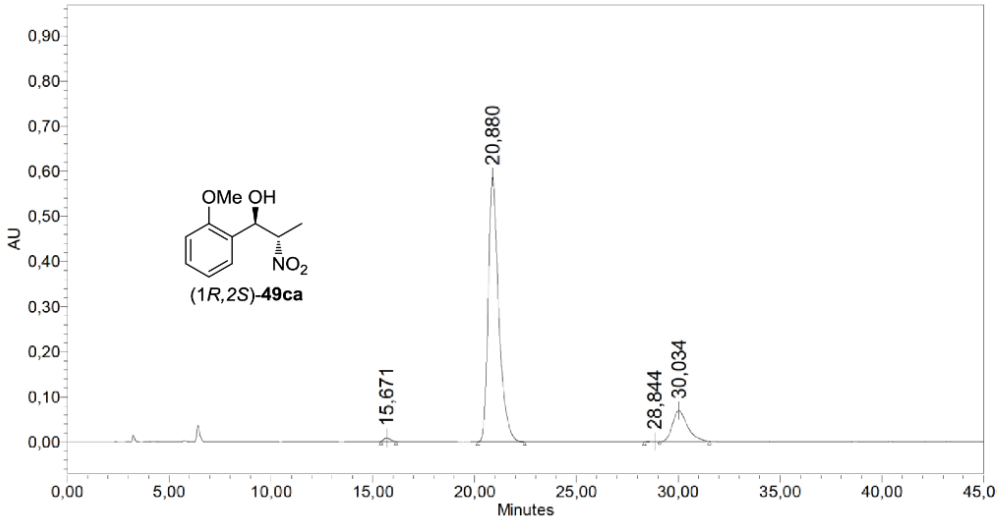
Compound **49ca**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 95:5, 1.0 mL/min, 215 nm, t_R = 15.7 min (1*S*,2*R*), 20.9 min (1*R*,2*S*), 28.8 min (1*S*,2*S*), 30.0 min (1*R*,2*R*).

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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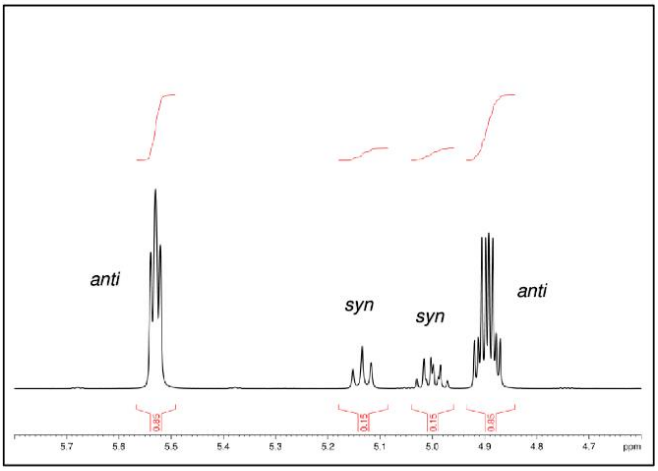
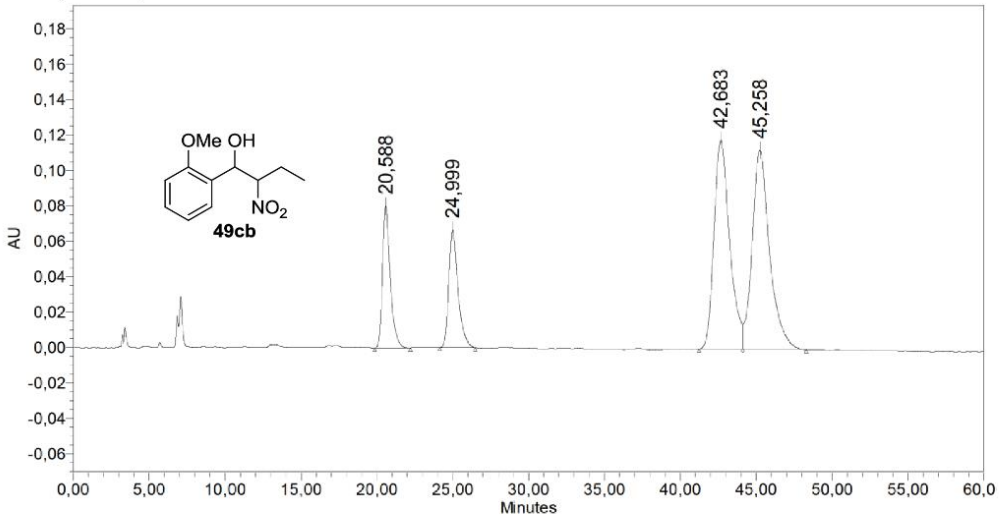
Excerpt of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **49ca**



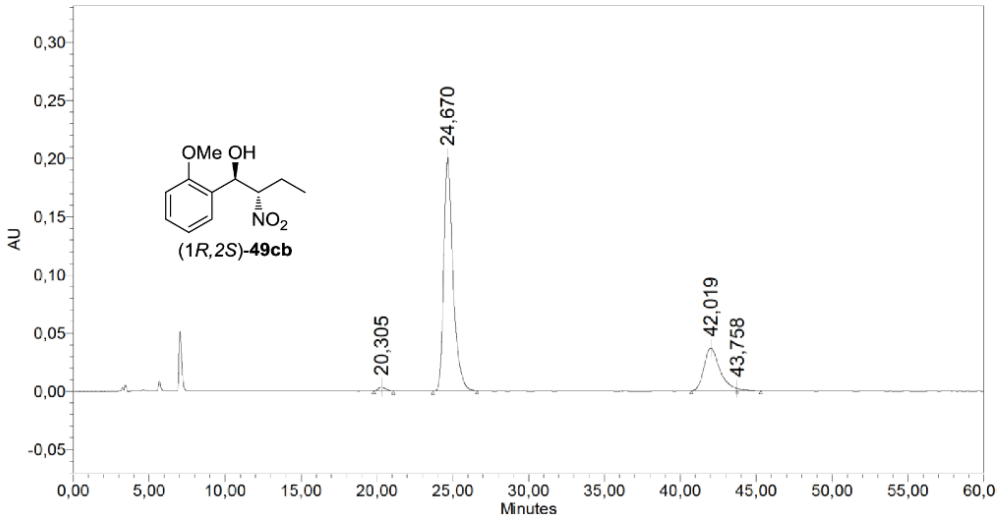
Compound **49cb**: HPLC conditions: Chiralpak AD-H, *n*-hexane/iPrOH 97:3, 1.0 mL/min, 215 nm, t_R = 20.3 min (1*S*,2*R*), 24.7 min (1*R*,2*S*), 24.0 min (1*S*,2*S*), 43.1 min (1*R*,2*R*).

49cb (racemic)



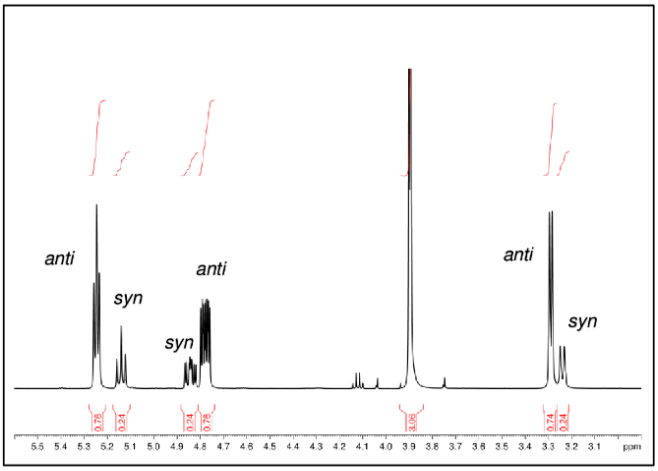
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	20,59	19,86	22,22	80131	21,27	2854757	12,39
2	25,00	24,16	26,48	66365	17,62	2812600	12,21
3	42,68	41,26	48,30	117837	31,28	8453866	36,69
4	45,26	41,26	48,30	112359	29,83	8922637	38,72

(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**



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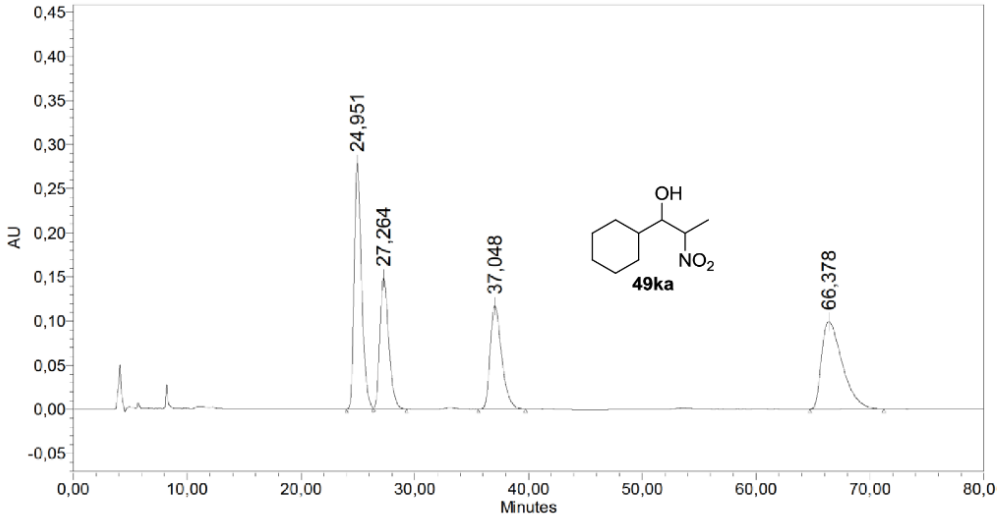
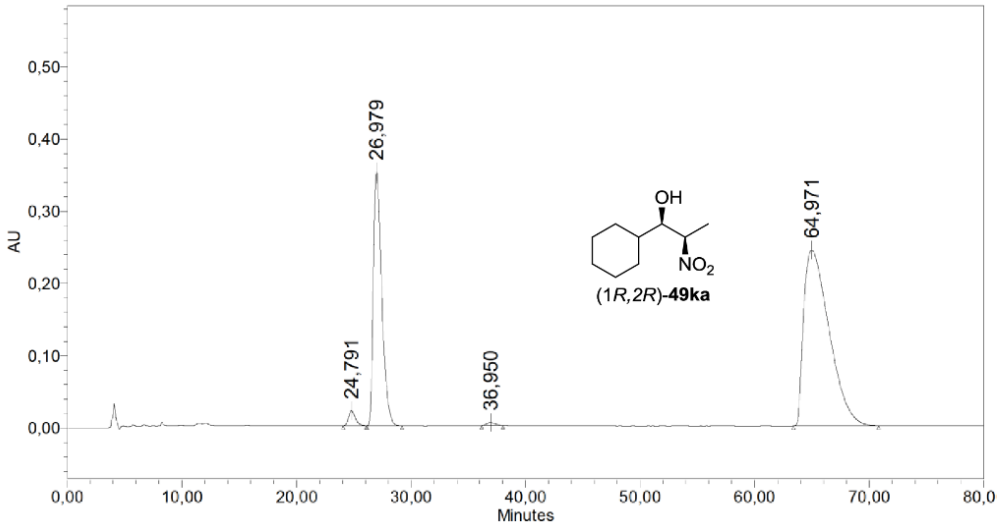
Compound **49ka**: HPLC conditions: Chiralpak AD-H, *n*-hexane/EtOH 96:4, 0.8 mL/min, 215 nm, t_R = 24.8 min (1*S*,2*S*), 27.0 min (1*R*,2*S*), 37.0 min (1*S*,2*R*), 65.0 min (1*R*,2*R*).

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

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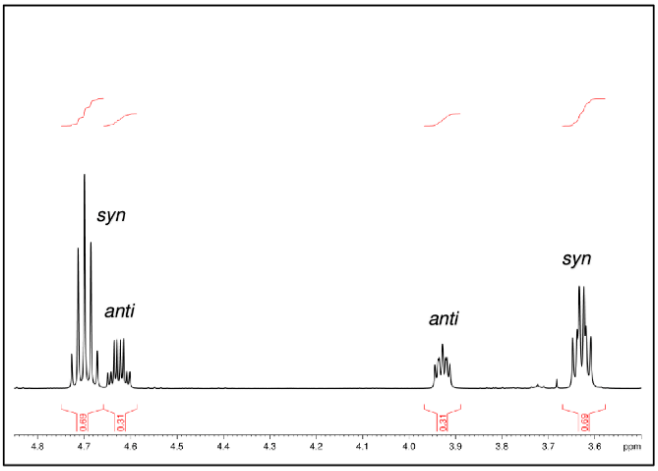
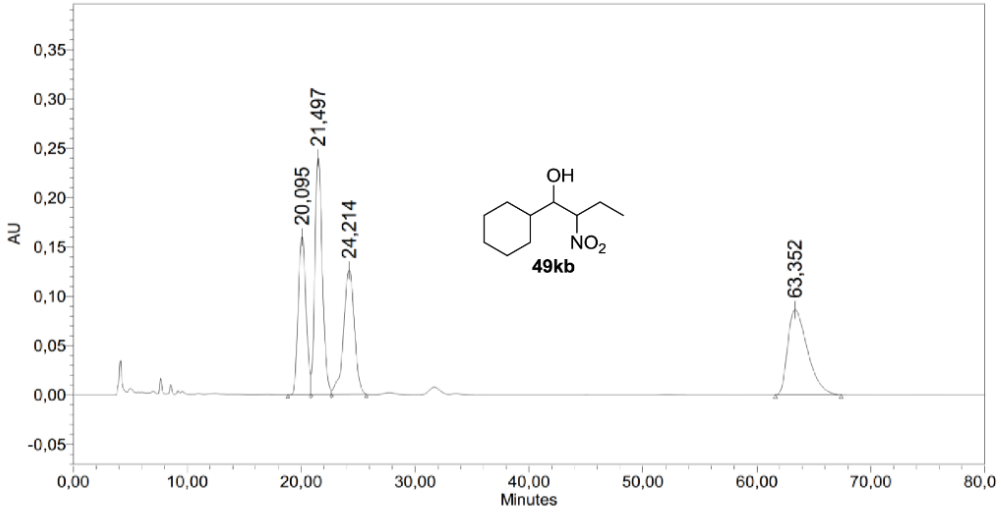
Excerpt of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **49ka**



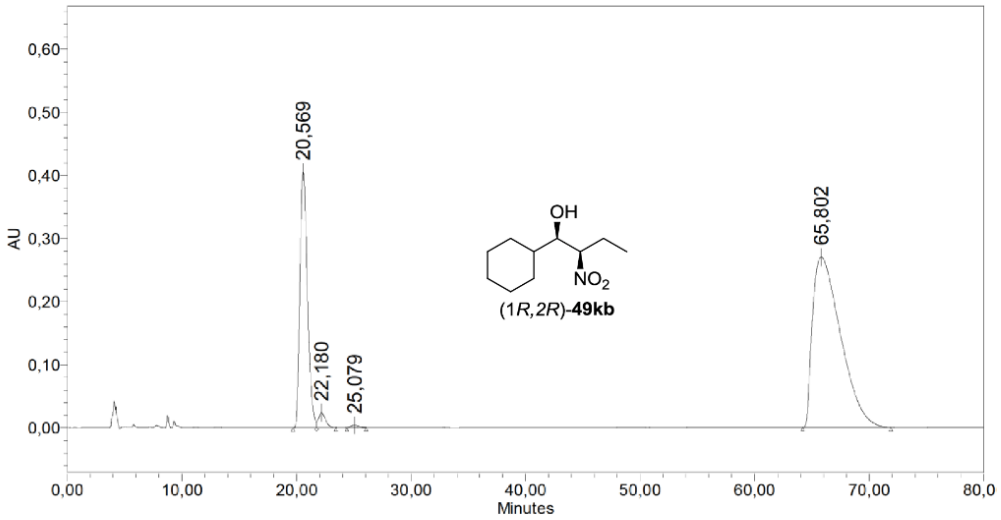
Compound **49kb**: HPLC conditions: Chiralpak AD-H, *n*-hexane/EtOH 97:3, 0.8 mL/min, 215 nm, t_R = 20.6 min (1*R*,2*S*), 22.2 min (1*S*,2*S*), 25.1 min (1*S*,2*R*), 65.8 min (1*R*,2*R*).

49kb (racemic)



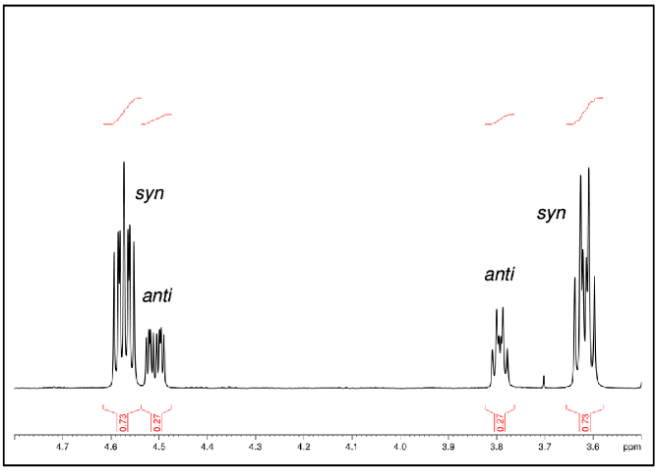
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	20,09	18,84	25,71	159626	26,14	7657748	20,73
2	21,50	18,84	25,71	239678	39,24	10576912	28,64
3	24,21	18,84	25,71	125443	20,54	8298222	22,47
4	63,35	61,63	67,40	85989	14,08	10401842	28,16

(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**



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Zum Abschluss meiner Dissertation möchte ich mich bei allen bedanken, die mich während des Studiums und der Promotion unterstützt haben und immer an mich geglaubt haben.

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Zuletzt danke ich ganz besonders dir, Johannes, für dein Verständnis, deine liebevolle Unterstützung und dass du mich immer wieder ermutigt hast nicht aufzugeben, wenn mal wieder nichts funktionierte. Danke!

(EIDESSTATTLICHE) VERSICHERUNGEN UND ERKLÄRUNGEN

(§ 8 Satz 2 Nr. 3 PromO Fakultät)

Hiermit versichere ich eidesstattlich, dass ich die Arbeit selbständig verfasst und keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt habe (vgl. Art. 64 Abs. 1 Satz 6 BayHSchG).

(§ 8 Satz 2 Nr. 3 PromO Fakultät)

Hiermit erkläre ich, dass ich die Dissertation nicht bereits zur Erlangung eines akademischen Grades eingereicht habe und dass ich nicht bereits diese oder eine gleichartige Doktorprüfung endgültig nicht bestanden habe.

(§ 8 Satz 2 Nr. 4 PromO Fakultät)

Hiermit erkläre ich, dass ich Hilfe von gewerblichen Promotionsberatern bzw. –vermittlern oder ähnlichen Dienstleistern weder bisher in Anspruch genommen habe noch künftig in Anspruch nehmen werde.

(§ 8 Satz 2 Nr. 7 PromO Fakultät)

Hiermit erkläre ich mein Einverständnis, dass die elektronische Fassung der Dissertation unter Wahrung meiner Urheberrechte und des Datenschutzes einer gesonderten Überprüfung unterzogen werden kann.

(§ 8 Satz 2 Nr. 8 PromO Fakultät)

Hiermit erkläre ich mein Einverständnis, dass bei Verdacht wissenschaftlichen Fehlverhaltens Ermittlungen durch universitätsinterne Organe der wissenschaftlichen Selbstkontrolle stattfinden können.

_____

Ort, Datum, Unterschrift (Jessica Goller)