UNIVERSITÄT BAYREUTH

ENTWICKLUNG FLEXIBLER SYNTHESESTRATEGIEN ZUR DARSTELLUNG NATÜRLICHER, TYROSIN-ABGELEITETER 3-ACYLTETRAMSÄUREN

–

DIE SYNTHESEN VON TORRUBIELLON D, F-14329, MILITARINON C UND FUMOSORINON A

DISSERTATION

zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften (Dr. rer. nat.)

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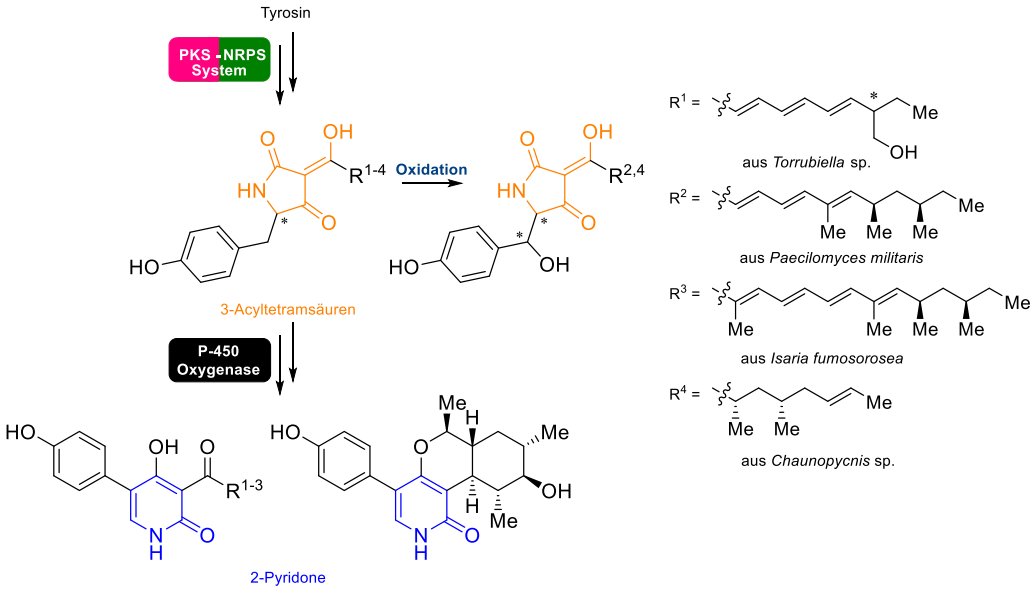
INHALTSVERZEICHNIS

ZUSAMMENFASSUNG

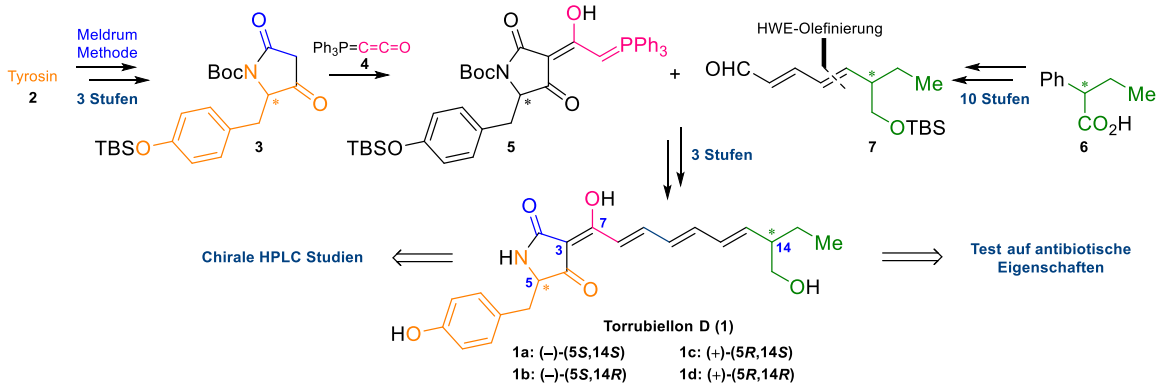
Ziel dieser Dissertation war die Entwicklung flexibler, enantioselektiver Syntheserouten zu Tyrosin-abgeleiteten 3-Acyltetramsäuren. Bei den Zielverbindungen handelte es sich dabei um Zischenmetaboliten der 2-Pyridonbiosynthese verschiedener Pilzkulturen (vgl. Schema **1**). Nach erfolgreicher Etablierung der jeweiligen Syntheseroute wurden dann etwaige, nicht aufgeklärte Konfigurationen asymmetrischer Zentren im jeweiligen Molekül vorläufig definiert.



Schema 1. Die Rolle Tyrosin-abgeleiteter Tetramsäuren für die 2-Pyridonbiosynthese.

Das erste Teilprojekt befasste sich mit der Synthese des Spinnenpathogenen Pilzmetaboliten Torrubiellon D (**1**), welcher im Biotest schwach cytotoxische Aktivität gegen KB Zellen (IC_{50} 44 µM) zeigte (vgl. Schema **2**). Jedoch waren zum Zeitpunkt dieser Arbeit die Konfigurationen der Stereozentren an C-5 und C-14 noch nicht aufgeklärt, weswegen die Konfigurationszuordnung des aktiven Stereosiomers bis dato noch nicht erfolgt ist.

Deswegen wurden im Zuge der Totalsynthese alle vier Torrubiellon D Stereoisomere **1a-d** über 13 Stufen in einer Maximalausbeute von 16% (für **1b**) hergestellt. Deren Enantiomerenreinheit wurde anschließend mittels chiraler HPLC-Analyse überprüft und die antibiotischen Eigenschaften der einzelnen Stereoisomere ermittelt.

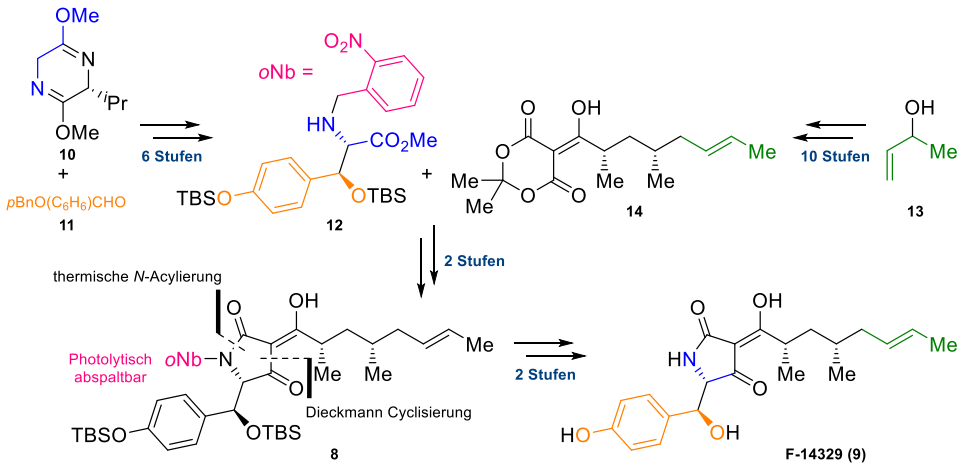


Schema 2. Überblick der Torrubiellon D (**1**) Synthese. Detaillierter in Kapitel **3.1** und **6.1**.

Im zweiten Teilprojekt wurde eine Synthesestratgie entwickelt die es ermöglicht β-Hydroxytyrosin-abgeleitete 3-Acyltetramsäuren darzustellen (vgl. Schema **3**). Damit ist es erstmalig möglich diese Stoffklasse totalsynthetisch im Labor herzustellen.

Über eine thermisch induzierte *N*-Acylierungsreaktion wurde β-Ketoamid **8** dargestellt, für dessen Dieckmann-Cyclisierung ein Stickstoffsubstituent essentiell ist. Standardmäßig verwendete, hydrogenolytisch abnehmbare Schutzgruppen kamen dabei im Fall von F-14329 (**9**) auf Grund der im Molekül enthaltenen Doppelbindung nicht in Betracht. Hier war die Einführung der photolytisch abspaltbaren *ortho*-Nitrobenzyl Schutzgruppe entscheidend für den Erfolg der Synthese. Diese wurde dabei erstmalig in der Tetramsäurechemie eingesetzt und stellt somit eine neue Alternative zu den bisher verwendeten Tetramsäure-Amidschutzgruppen dar.

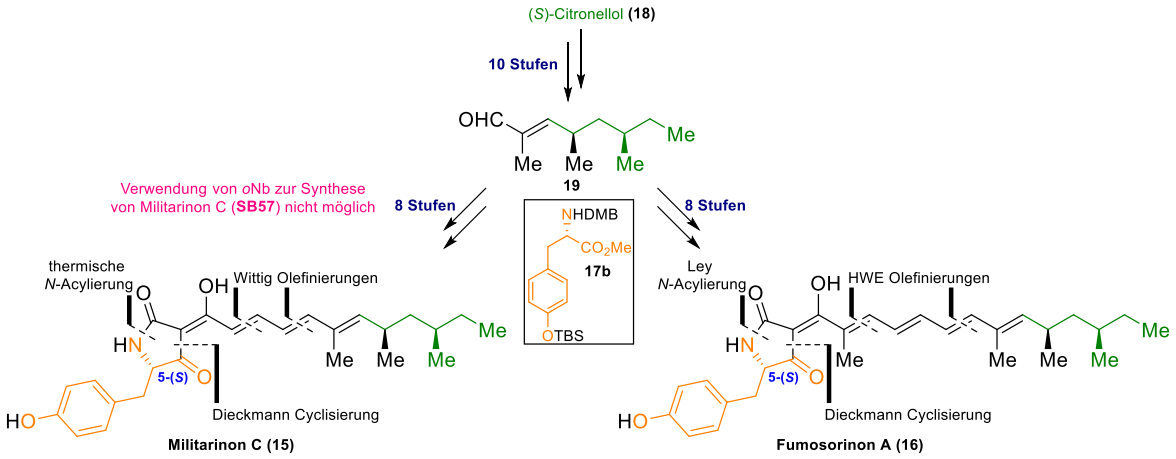
Auf diese Weise gelang es, die β-Hydroxytyrosin-abgeleitete 3-Acyltetramsäure F-14329 (**9**) über 14 Stufen in einer Gesamtausbeute von 3.9% darzustellen.



Schema 3. Überblick über die Synthese von F-14329 (**9**). Detaillierter in Kapitel **3.2** und **6.2**.

Im dritten Teilprojekt wurde eine Synthese zur Darstellung der entomopathogenen Pilzmetaboliten Militarinon C (**15**) und Fumosorinon A (**16**) entwickelt (vgl. Schema **4**). Analog zum ersten Teilprojekt war auch hier die Stereokonfiguration an C-5 beider Verbindungen zum Zeitpunkt dieser Arbeit noch nicht geklärt. Mit Blick auf die PTP1B-inhibitorischen Eigenschaften (IC_{50} 3.59 µM) von Fumosorinon A (**16**), welche das aktive Stereoisomer als potentielle Leitstruktur zur Behandlung von Typ II Diabetes interessant machen, stand die Aufklärung dessen Stereokonfiguration an C-5 mittels Totalsynthese im Fokus dieses Teilprojekts. Zusätzlich wurde am Beispiel von Militarinon C (**15**) die Verwendung der in Teilprojekt zwei eingeführten *ortho*-Nitrobenzyl Schutzgruppe an einer Polyenoyltetramsäure untersucht. Dabei zeigte sich jedoch, dass deren Verwendung auf Grund von *cis-trans*-Isomerisierung der Polyenkette nicht zielführend ist.

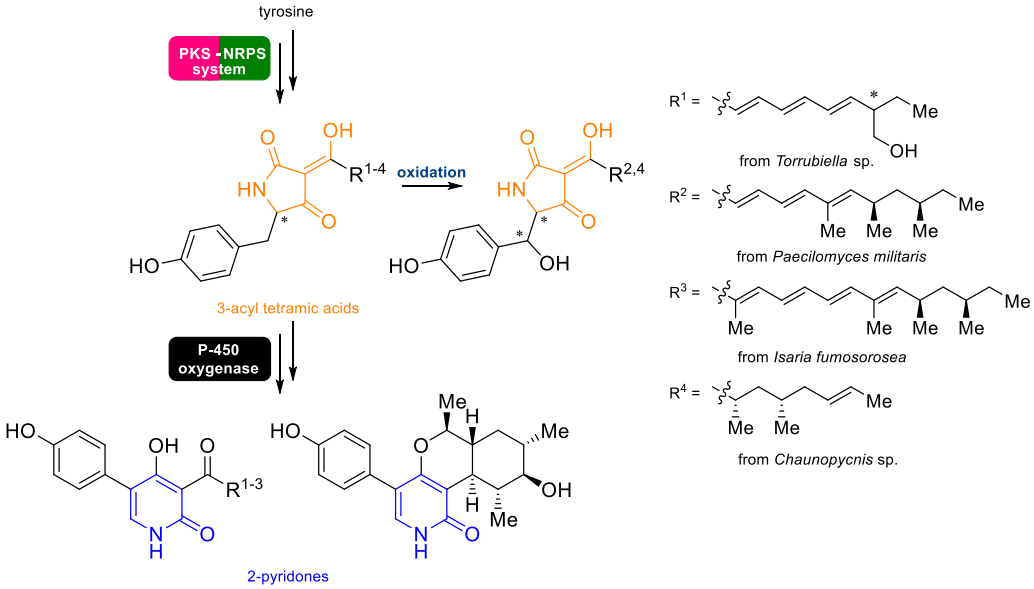
Deshalb wurde in der Synthese der beiden Naturstoffe der 2,4-Dimethoxybenzyl geschützte Tyrosinester **17b** verwendet. Damit war es möglich, sowohl Militarinon C (**15**) als auch Fumosorinon A (**16**) über jeweils 18 Stufen in einer Gesamtausbeute von 2.5% bzw. 2.0% darzustellen und die Konfiguration von C-5 für beide Moleküle als (*S*) vorzuschlagen.



Schema 4. Überblick der Synthesen von Militarinon C (**15**) und Fumosorinon A (**16**). Detaillierter in Kapitel **3.3** und **6.3**.

SUMMARY

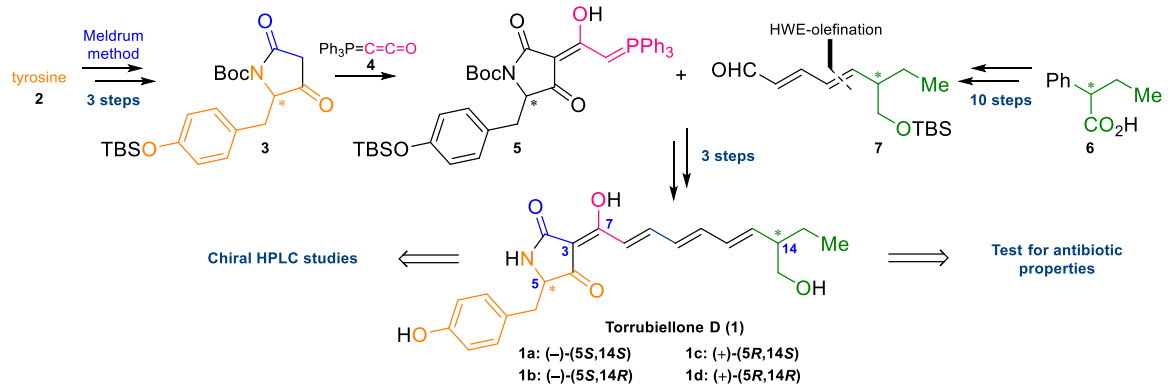
Focus of this thesis was the development of flexible, enantioselective synthetic routes towards tyrosine-derived 3-acyl tetramic acids. All target compounds were intermediary metabolites of the 2-pyridone biosynthesis of different fungal cultures (see scheme **1**). After successful establishment of the respective synthetic route, unresolved configurations of asymmetric centres in the respective molecules have been provisionally assigned.



Scheme 1. The role of tyrosine-derived tetramic acids for the 2-pyridone biosynthesis.

The first sub-project dealt with the synthesis of the spider-pathogenic fungus metabolite torrubiellone D (**1**), which showed weak cytotoxic activity against KB cells (IC_{50} 44 µM). However, at the time of this work the configuration of the stereogenic centres at C-5 and C-14 had yet to be resolved, which is why a configurational assignment of the active stereoisomer could not be accomplished to date.

For this reason, all four torrubiellone D stereoisomers **1a-d** had been synthesised over 13 steps in a maximum yield of 16% (for **1b**). Their enantiopurity was confirmed using chiral HPLC-analysis and the antibiotic properties of each isomer had been determined.

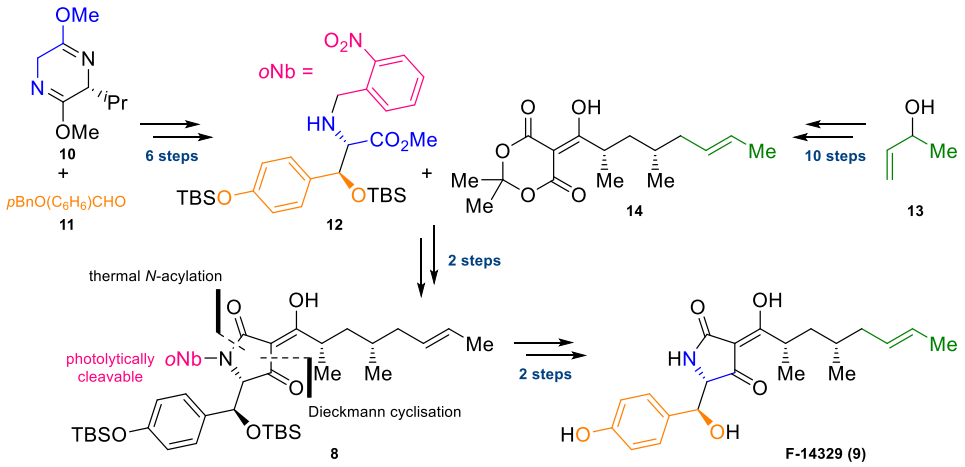


Scheme 2. Overview of the torrubiellone D (**1**) synthesis. For more details see chapters **3.1** and **6.1**.

In the second sub-project, a synthetic strategy which enables the synthesis of β-hydroxytyrosine-derived 3-acyl tetramic acids had been developed. With this, it is possible to synthesise this class of compounds in the laboratory for the first time.

The β-keto amide **8** was prepared by a thermically induced *N*-acylation reaction. For the Dieckmann-cyclisation of this amide, a *N*-substituent is essential. Default protection groups, that are removed hydrogenolytically could not be used in the case of F-14329 (**9**) because of the double bond present in the molecule. Therefore, the introduction of the photolytically removable *ortho*-nitrobenzyl protection group was crucial for the success of the synthesis. This group was used for the first time in tetramic acid chemistry and poses a new alternative to the standard tetramic acid amide protection groups.

Hence, it was possible to synthesise the β-hydroxytyrosine-derived 3-acyl tetramic acid F-14329 (**9**) for the first time in 14 steps and an overall yield of 3.9%.

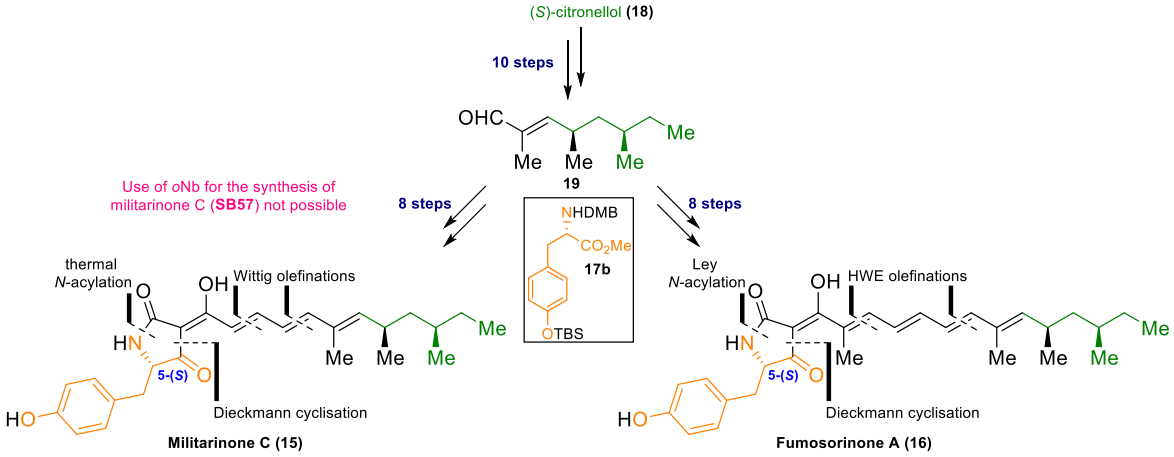


Scheme 3. Overview of the synthesis of F-14329 (**9**). For more details see chapters **3.2** and **6.2**.

The third sub-project dealt with the development of a synthesis for the entomopathogenic fungus metabolites militarinone C (**15**) and fumosorinone A (**16**). Analogously to the first sub-project, the stereochemistry at C-5 for both compounds had not been assigned at the time of this work. In view of the PTP1B-inhibitory properties (IC_{50} 3.59 µM) of fumosorinone A (**16**), which makes the active stereoisomer a potential lead for the treatment of typ II diabetes the assignment of the stereoconfiguration at C-5 using totalsynthesis was the main focus of this sub-project.

Furthermore, using militarinone C (**15**) as a model system, the usability of the in sub-project two introduced *ortho*-nitrobenzyl protection group for the synthesis of polyenoyl tetramic acids had been evaluated. However, due to *cis-trans* isomerisation of the polyene side chain, its use proved to be not productive.

Hence, 2,4-dimethoxybenzyl protected tyrosine ester **17b** was used for the final syntheses of both natural products. With this it was possible to synthesise both militarinone C (**15**) and fumosorinone A (**16**) in 18 steps and an overall yield of 2.5% and 2.0 respectively and suggest the configuration at C-5 as (*S*) for both molecules.



Scheme 4. Overview of the synthesis of militarinone C (**15**) and fumosorinone A (**16**). For more details see chapters **3.3** and **6.3**.

ABKÜRZUNGSVERZEICHNIS

In den Formelbildern und im Text werden folgende Abkürzungen verwendet:

Ac	Acetyl
Acetyl CoA	Acetyl Coenzym A
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
bzw.	beziehungsweise
DCC	Dicyclohexylcarbodiimid
de	Diastereomerenüberschuss
DIBAL-H	Diisobutylaluminiumhydrid
DMAP	4-(Dimethylamino)-pyridin
DMB	2,4-Dimethoxybenzyl
DMF	*N,N*-Dimethylformamid
DMSO	Dimethylsulfoxid
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimid
Et	Ethyl
FDA	U.S. Food and Drug Administration
h	Stunden
HMDS	1,1,1,3,3,3-Hexamethyldisilazan
HPLC	Hochleistungsflüssigkeitschromatographie
HWE	Horner-Wadsworth-Emmons
IPCF	Chlorameisensäureisopropylester
kat.	katalytisch
KB Zellen	Orale, menschliche Epidermoidtumor Zellen
LDA	Lithiumdiisopropylamid
LNKS	Lovastatin Nonaketidsynthase
Me	Methyl
min	Minuten
Ms	Methansulfonyl
MS	Molekularsieb

NMR	Nuclear Magnetic Resonance
NRPS	nichtribosomale Peptidsynthetase
*o*Nb	*ortho*-Nitrobenzyl
Piv	Pivaloyl
PKS	Polyketidsynthase
Pr	Propyl
PTP1B	Protein-Tyrosin-Phosphatase 1B
quant.	quantitativ
rflx	unter Rückfluss
RT	Raumtemperatur
SAM	*S*-Adenosylmethionin
TBAF	Tetrabutylammoniumfluorid
TBS	*tert*-Butyldimethylsilyl
Tf	Trifluormethansulfonyl
TFA	Trifluoressigsäure
THF	Tetrahydrofuran
TMS	Trimethylsilyl
vgl.	vergleiche
üNa	über Nacht

1 EINLEITUNG

1.1 Naturstoffsynthese

Die Verwendung von natürlichen Heilmitteln lässt sich bis auf 2900 vor Christus durch die Ägypter zurückdatieren.[1] Neben diesen entwickelten aber auch andere Kulturen traditionell überlieferte Formulierungen natürlicher Wirkstoffe, ohne die dabei wirksamen Bestandteile genauer zu kennen. Erst zu Beginn des 19. Jhd. wurden verschiedene wirksame Naturstoffe (Acetylsalicylsäure, Morphin) bewusst isoliert und gegen diverse Beschwerden verwendet.[2] Dies war der Beginn einer gezielten Wirkstofffindung auf Basis natürlicher Ressourcen,[3] die bis heute andauert. Obwohl kurzzeitig der Trend weg von klassischen auf Naturstoffen basierenden, hin zu rein synthetischen Wirkstoffen bestand, welche unter Einsatz kombinatorischer Chemie erhalten werden sollten,[4] so führte die geringe Trefferquote dieser Methodik schnell zu einem neuen Ansatz. In diesem wurden durch Modifikation natürlicher Strukturen unter Verwendung kombinatorischer Chemie die Erfolgschancen auf den Erhalt neuer Wirkstoffe signifikant gesteigert.[5] Die Relevanz natürlich inspirierter Pharmakophore zeigt sich besonders auch dadurch, dass von den zwischen 1981 und 2014 von der FDA zugelassenen niedermolekularen Wirkstoffen 32% direkt von Naturstoffen abgeleitet sind. Diese Zahl erhöht sich weiter auf 64%, sobald die Wirkstoffe addiert werden, die ein natürliches Pharmakophor aufweisen oder kompetitive Inhibitoren natürlicher Substrate sind.[6] Auch unter Betrachtung der neueren FDA Zulassungen spielen Naturstoffe weiterhin eine wichtige Rolle im Rahmen der Wirkstofffindung[7] und stellen somit noch immer eine wichtige Quelle zur Entwicklung neuer pharmakologisch aktiver Leitstrukturen dar.

1.2 Tetramsäuren als biologisch aktive Naturstoffe

Eine Stoffklasse, die seit den 1960er Jahren auf Grund ihrer vielfältigen biologischen Eigenschaften besondere Beachtung fand, sind die Tetramsäuren.[8] Der 1909 von Anschütz[9] vorgeschlagene Begriff der Tetramsäure beschreibt dabei allgemein Verbindungen, die ein Pyrrolidin-2,4-dion System aufweisen (vgl. Abbildung **1**). Diese Verbindungsklasse zeigt ein breites Reaktionsspektrum und liegt in wässriger Lösung, pH-abhängig, vorwiegend in ihrer deprotonierten Enolat-Form **20** vor.[8] Die Hauptzahl der natürlich vorkommenden Tetramsäuren

sind in Position-3 acyliert, was sich vor allem in einem stark verminderten pKa-Wert (~6.4 für **21**, ~3.4 für unkomplexierte **22**[10]) zeigt. Zusätzlich ergibt sich auf Grund der Acylierung in Position-3 ein komplexes System von Tautomeren. Die interne Tautomerisierung zwischen den *endo*- und *exo*-enol Paaren **23a**/**23b** und **23c**/**23d** ist in unpolaren Solventien dabei so schnell, dass eine Beobachtung dieses Prozesses mittels NMR-Spektroskopie nicht möglich ist. Allerdings gelang es Steyn[11] und Nolte[12] den langsameren externen Tautomerisierungsprozess per NMR nachzuweisen. Dieser verläuft intermediär über die Triketoform **24** und ist bedingt durch die Bindungsrotation der dabei vorhandenen C-C σ-Bindung an C-3. An Hand dieser Daten konnte für R^5 = *i*Pr das Tautomerenverhältnis **23a**:**23b**:**23c**:**23d** zu 5:15:0:80 bestimmt und damit gezeigt werden, dass *exo*-enol Form **23d** für diese Verbindung das Haupttautomer darstellt. Dies wurde ebenfalls durch Röntgenkristallstrukturen belegt. Spätere Untersuchungen von Moloney et al.[13] zeigten jedoch, dass diese Tautomerenverhältnisse zusätzlich vom Stickstoffsubstituenten sowie der 3-Acyleinheit abhängig sind.

Durch die im NMR beobachtbaren Tautomeren, deren Verhältnisse molekülspezifisch variieren, ist die Strukturbestimmung neu isolierter 3-Acyltetramsäuren auf Grund von überlappenden Signalen eine Herausforderung.[14,15] Durch lösemittelspezifische Signalverbreiterung[13,16] sowie durch die charakteristische Eigenschaft des 3-Acyltetramsäuresystems der Metallkomplexierung wird diese zusätzlich erschwert. Da 3-Acyltetramsäuren unter physiologischen Bedingungen auf Grund des geringen pKa-Wertes in ihrer deprotonierten Form vorliegen, sind sie hervorragende Liganden für Metallkationen.[17] Dies wurde am Beispiel der Tenuazonsäure erschöpfend durch die Synthese diverser Tetramsäure-Metallkomplexe (**22**) gezeigt.[18,19,20] Tatsächlich wurden einige Tetramsäuren als Metallsalz aus natürlichen Quellen isoliert, da ihre protonierte Form instabil ist.[21,22] Ein weiterer Effekt, der mit der Metallkomplexierung einhergeht, ist eine erhöhte Lipophilie und eine damit verbundene erhöhte Zellmembrangängigkeit,[23] was teilweise die vielfältigen biologischen Aktivitäten begründen könnte. Bei Harziansäure zum Beispiel geht die biologische Aktivität mit Verlust des Zn^{2+} Kations sogar verloren.[24]

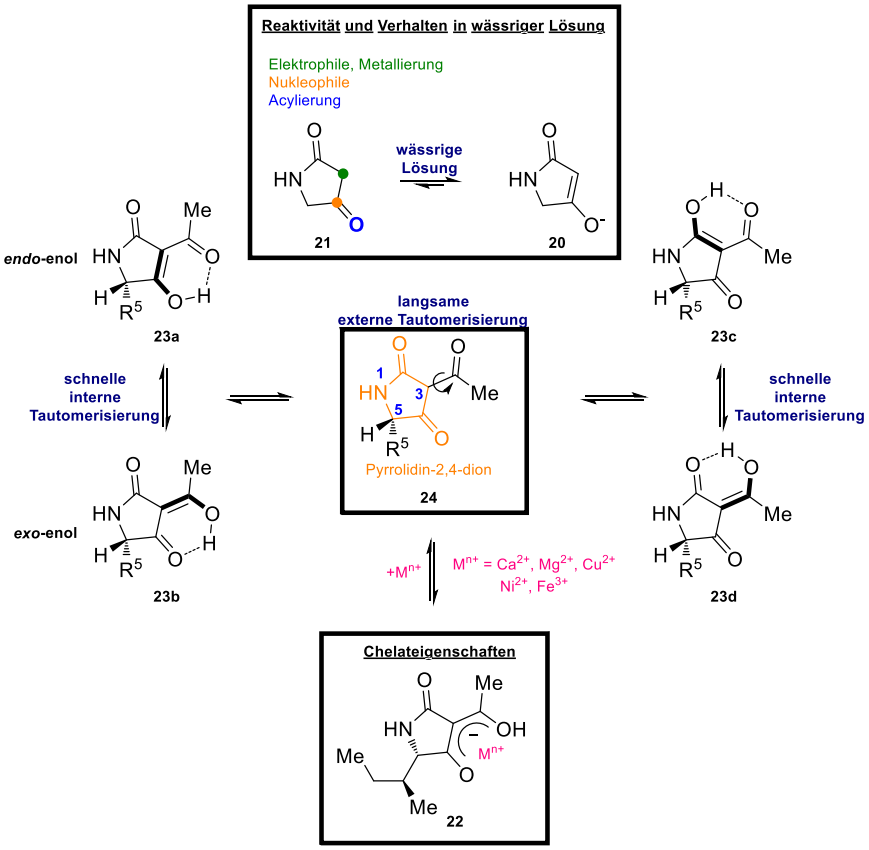


Abbildung 1. Reaktivität und Tautomerie einfacher Tetramsäuren sowie Tautomerie und Chelateigenschaften von 3-Acyltetramsäuren.

In Abbildung **2** sind einige Vertreter natürlicher, biologisch aktiver 3-Acyltetramsäuren dargestellt. Im Folgenden soll eine allgemeine strukturelle Klassifizierung unter Berücksichtigung nur der am häufigsten vorkommenden Tetramsäurevertreter getroffen werden. Eine ausführlichere Auflistung verschiedener biologisch aktiver Tetramsäuren sowie deren struktureller Eigenschaften kann in diversen Literaturzusammenfassungen gefunden werden.[8,25,26]

Das 2008 aus dem Pilz *Penicillium* sp. GQ-7 isolierte cytotoxisch aktive (IC_{50} 0.76 µM gegen HL-60 Zellen) Penicillenol A_1 (**25**)[27] wird den einfacheren Tetramsäuren zugeordnet. Charakteristisch für diese Untergruppe ist das wie bei allen weiteren auch vorhandene Pyrrolidin-2,4-dion Motiv, an welches in 3-Position eine gesättigte Carbonsäureseitenkette variablen Substitutionsmusters kondensiert ist.

Die nächste häufiger vorkommende Klasse sind die 3-Dienoyltetramsäuren, hier repräsentiert durch das 1956 aus *Streptomyces lydicus* isolierte antibiotisch aktive Streptolydigin (**26**).[28] Bei dieser Klasse sind zwei Doppelbindungen in Konjugation mit der *exo*-enol Form des 3-acylierten Pyrrolidin-2,4-dion Systems.

Bei mehrfach ungesättigten Seitenketten an diesem Motiv spricht man von Polyenoyltetramsäuren. Diesen zugehörig ist das antibiotisch wirkende Pigment des Pilzes *Penicillium islandicum* L.S.H.T.M. no. BB233, Erythroskyrin (**27**).[29]

Die nächste Gruppe sind die makrocyclischen 3-Acyltetramsäuren. Diese zeichnen sich dadurch aus, dass das Tetramsäuremotiv in einem größeren Ringsystem integriert ist. Auch deren Vertreter zeigen vielfältige biologische Aktivitäten, wie die hier dargestellten antifungalen und cytotoxischen Verbindungen Lysobacteramid B (**28**) und HSAF (**29**), welche aus dem Bakterium *Lysobacter enzymogenes* C3 isoliert werden können,[30] oder das herbizide Macrocidin A (**30**), ein aktiver Metabolit aus *Phoma macrostoma*.[31]

Die letzte hier erwähnte Klasse sind die Decalinoyltetramsäuren, bei denen eine Decalinsäure an das Tetramsäuresystem acyliert ist. Ein Beispiel ist der HIV-1 Integrase Inhibitor Equisetin (**31**), 1997 erstmalig isoliert aus *Fusarium heterosporum*.[32]

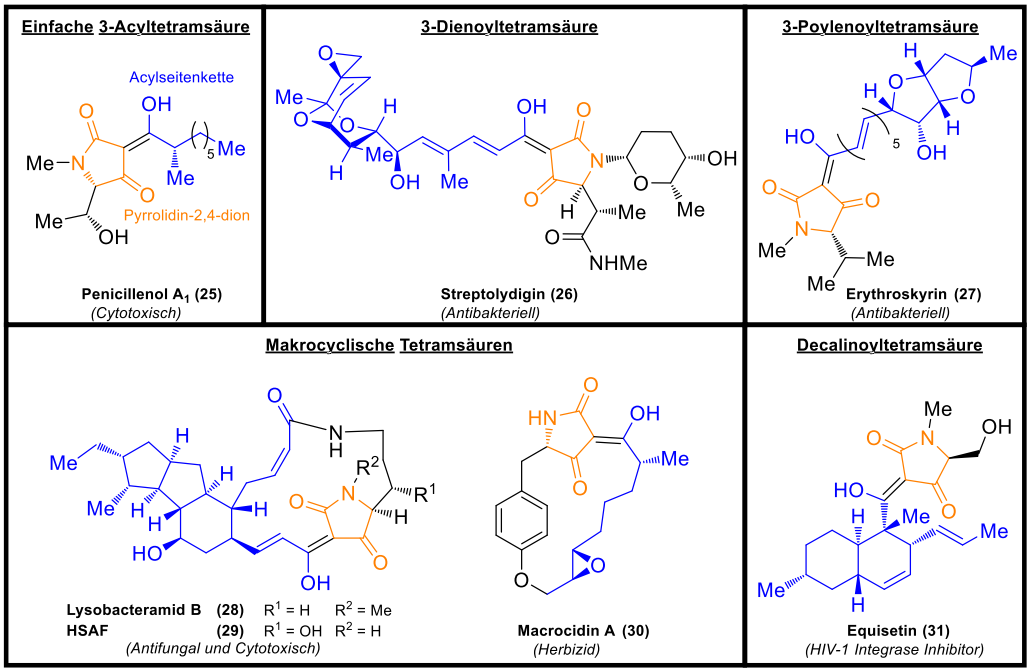


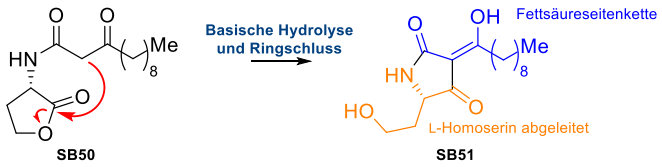
Abbildung 2. Vertreter strukturell unterschiedlicher, biologisch aktiver 3-Acyltetramsäuren.

1.2.1 Biosynthese von 3-Acyltetramsäuren

Das natürliche Auftreten von 3-Acyltetramsäuren wird generell über zwei Biosynthesewege erklärt.

Der erste beschreibt das Auftreten von 3-Acyltetramsäuren in biologischen Systemen als Folge der Quorum-sensing Aktivität von Bakterien.[33] Diese Zell-zu-Zell Kommunikation koordiniert kollektive Aktivitäten von Bakterien, wie z.B. von *Pseudomonas aeruginosa* oder

Staphylococcus aureus unter Verwendung bestimmter Signalmoleküle wie 3-Oxo-Acetylhomoserinlacton **32**.[34] Durch Produktion solcher Signalmoleküle werden gezielt bakterielle Signalwege aktiviert bzw. deaktiviert, was diverse biochemische Effekte zur Folge hat.[34,35] Neben Lacton **32** konnten Kaufmann et al. auch die 3-Acyltetramsäure **33** aus *Pseudomonas aeruginosa* isolieren. Dabei postulierten sie, dass diese nonenzymatisch in einer Claisen-artigen Kondensationsreaktion unter Lactonöffnung von *Pseudomonas* selbst synthetisiert wird (vgl. Schema **5**) und durch ihre schwach antibiotische Wirkung, den Bakterien einen evolutionären Vorteil gegenüber anderen Stämmen liefert.[33] Diese Art der Biosynthese beschränkt sich jedoch ausschließlich auf Homoserin-abgeleitete Tetramsäuren und kann somit nicht auf strukturell anspruchsvollere Vertreter dieser Stoffklasse angewandt werden.



Schema 5. Nonenzymatische 3-Acyltetramsäurebiosynthese in *Pseudomonas aeruginosa*.

Der zweite Biosyntheseweg erklärt die Biosynthese von 3-Acyltetramsäuren über Hybride von Polyketidsynthase und nichtribosomalen Peptidsynthetase (PKS-NRPS) Einheiten und wird sowohl in Pilzen als auch Bakterien gefunden.[15] Erste Untersuchungen dazu wurden 2005 von Sims et al.[36] am Beispiel von Equisetin (**31**) durchgeführt. Auf Grund der strukturellen Ähnlichkeit zwischen Equisetin und dem anti-hypercholesterinämischen Lovastatin (**34**), welches über eine iterative PKS, die Lovastatin Nonaketidsynthase (LNKS), aufgebaut wird, vermutete Sims, dass dies für Equisetin ebenfalls der Fall sein könnte. Über Genknockoutexperimente und Exprimierungsanalysen an *Fusarium heterosporum* ATCC 74349 postulierte er, dass innerhalb des *eqi* Genklusters *eqiS* für die Equisetin Biosynthese verantwortlich ist. Spätere Untersuchungen von Kakule et al.[37] zeigten jedoch, dass dieses Gen die Synthese einer zuvor unbekannten, zusätzlich in 3-Position methylierten Tetramsäure, Fusaridion A (**35**), kodiert, welche zu spontaner Retro-Dieckmann Kondensation neigt und daher zuvor noch nicht nachgewiesen werden konnte (vgl. Abbildung **3**).

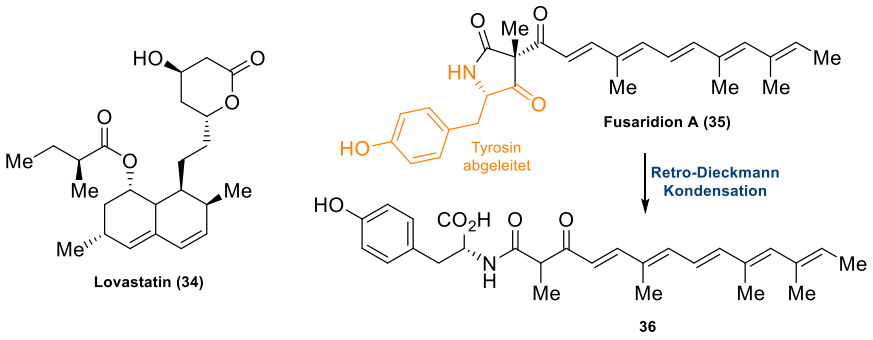
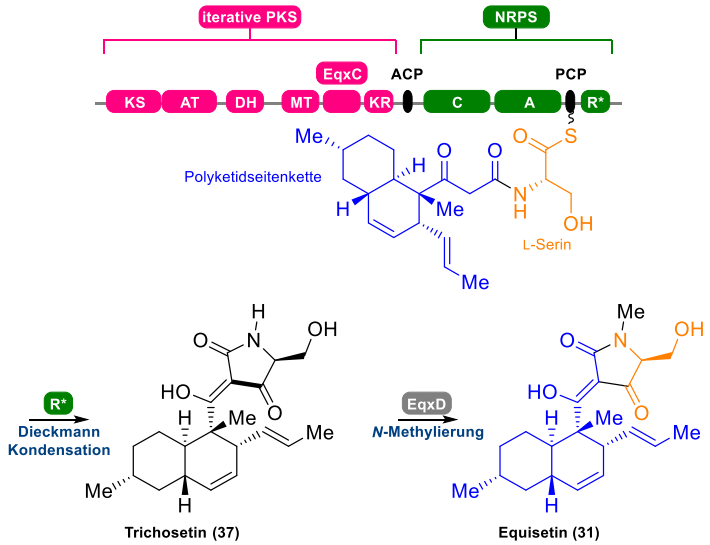


Abbildung 3. Strukturen von Lovastatin (**34**), Fusaridion A (**35**) sowie dessen Retro-Dieckmann Produkts **36**.

Als den für die Biosynthese von Equisetin verantwortlichen Genkluster konnte Kakule schließlich *eqx* identifizieren. Dabei führt die daraus expremierte PKS Domäne den iterativen Aufbau der Polyketidseitenkette aus. In der NRPS Domäne wird anschließend ligiertes L-Serin an die Acylkette kondensiert und nach Überführung an die Dieckmann-Cyclase Einheit Trichosetin (**37**) cyclisiert. Anschließende *N*-Methylierung durch EqxD liefert daraufhin Equisetin (**31**) (vgl. Schema **6**). Diese Art der Biosynthese ermöglicht es, die vielfältigen Strukturen der natürlich vorkommenden 3-Acyltetramsäuren zu erklären, und stellt somit vermutlich den Hauptbiosyntheseweg dieser Stoffklasse dar.



Schema 6. Schematisches Modell der Biosynthese von Equisetin (**31**) nach Kakule et al.[37] KS:Beta-ketoacylsynthase; AT: Acyltransferase; DH: Dehydratase; MT: Methyltransferase; EqxC: Enoylreduktasen Domäne; KR: Beta-ketoacylreduktase; ACP: Acylcarrierprotein; C: Kondensation; A: Adenylierung; PCP: Peptidylcarrierprotein; R*: Dieckmann-Cyclase; EqxD: *N*-methylierungsdomäne.

1.2.2 Die Rolle von Tyrosin- und Phenylalanin-abgeleiteten 3-Acyltetramsäuren als essentielle Metaboliten der 2-Pyridonbiosynthese

Im Rahmen der Aufklärung der 2-Pyridonbiosynthese wurden seit 2003 vermehrt verschiedenste 3-Acyltetramsäuren isoliert. Eine kleine Auswahl davon ist in Abbildung **4** dargestellt. Dabei handelt es sich um aus dem jeweils gleichen Pilzisolat gewonnene Vertreter der jeweiligen Substanzklassen. Auf Grund der vielfältigen biologischen Aktivitäten wurden in den letzten Jahrzehnten verstärkte Bemühungen zur Aufklärung dieses Biosyntheseweges unternommen.

Die ersten Untersuchungen bezüglich der Biosynthese von 2-Pyridonen wurden dabei von McInnes et al.[38] an Tenellin (**38**) durchgeführt. An Hand von Verfütterungsexperimenten mit ^{13}C-markiertem Phenylalanin, Tyrosin, Acetat und Methionin konnten sie zeigen, dass zuerst die Polyketidkette mittels Acetat Einheiten aufgebaut wird und die dabei von der Kette abzweigenden Methylgruppen von *S*-Adenosylmethionin (SAM) übertragen werden (vgl. Schema **7**). Außerdem gelang es ihnen, alle Aminosäurekohlenstoffe im finalen Naturstoff nachzuweisen und auf Grund deren Positionen festzustellen, dass auf dem Weg zum 2-Pyridon Ring eine Umlagerungsreaktion stattfinden muss. Einen ersten mechanistischen Vorschlag für diese Umlagerung gab McInnes in Zusammenarbeit mit Wright[39] 1977 ab. Dabei postulierten sie, dass intermediär eine 3-Acyltetramsäure, ähnlich zu Pretenellin A (**39**), gebildet werden muss, welche anschließend unter oxidativer Ringerweiterung in das 2-Pyridon Tenellin (**38**) umlagert.

Es dauerte jedoch bis 1991, bevor durch die Gruppe um Cox weitere Nachforschungen auf diesem Gebiet angestellt wurden.[40] Analog zu Sims et al.[36] konnten sie 2007 den für die Synthese von Tenellin (**38**) verantwortlichen Gencluster identifizieren[41] und, basierend auf dieser Arbeit, weitere Erkenntnisse über dessen Biosynthese gewinnen. So zeigten sie später, dass bei fungalen PKS-NRPS Systemen, in der Adenylierungsdomäne, bevorzugt Tyrosin metabolisiert wird, wohingegen bei bakteriellen Adenylierungsdomänen Phenylalanin bevorzugt wird.[15] Zudem wurde von ihnen 2008 ein plausibler Umlagerungsmechanismus, ausgehend von 3-Acyltetramsäuren, postuliert.[42] Dieser widerlegte die zuvor bestehende Vermutung, dass β-Hydroxytyrosin-abgeleitete Tetramsäuren, welche ebenfalls in verschiedenen Pilzisolaten gefunden wurden (vgl. Abbildung **4**), essentielle Zwischenstufen der 2-Pyridonbiosynthese sind. Deswegen stellten sie die These auf, dass es sich bei diesen Verbindungen um Metaboliten eines alternativen Biosyntheseweges ungeklärter Art handeln

muss. Weitere Untersuchungen zu möglichen biologischen Funktionen dieser Verbindungsklasse wurden von ihnen jedoch nicht durchgeführt.

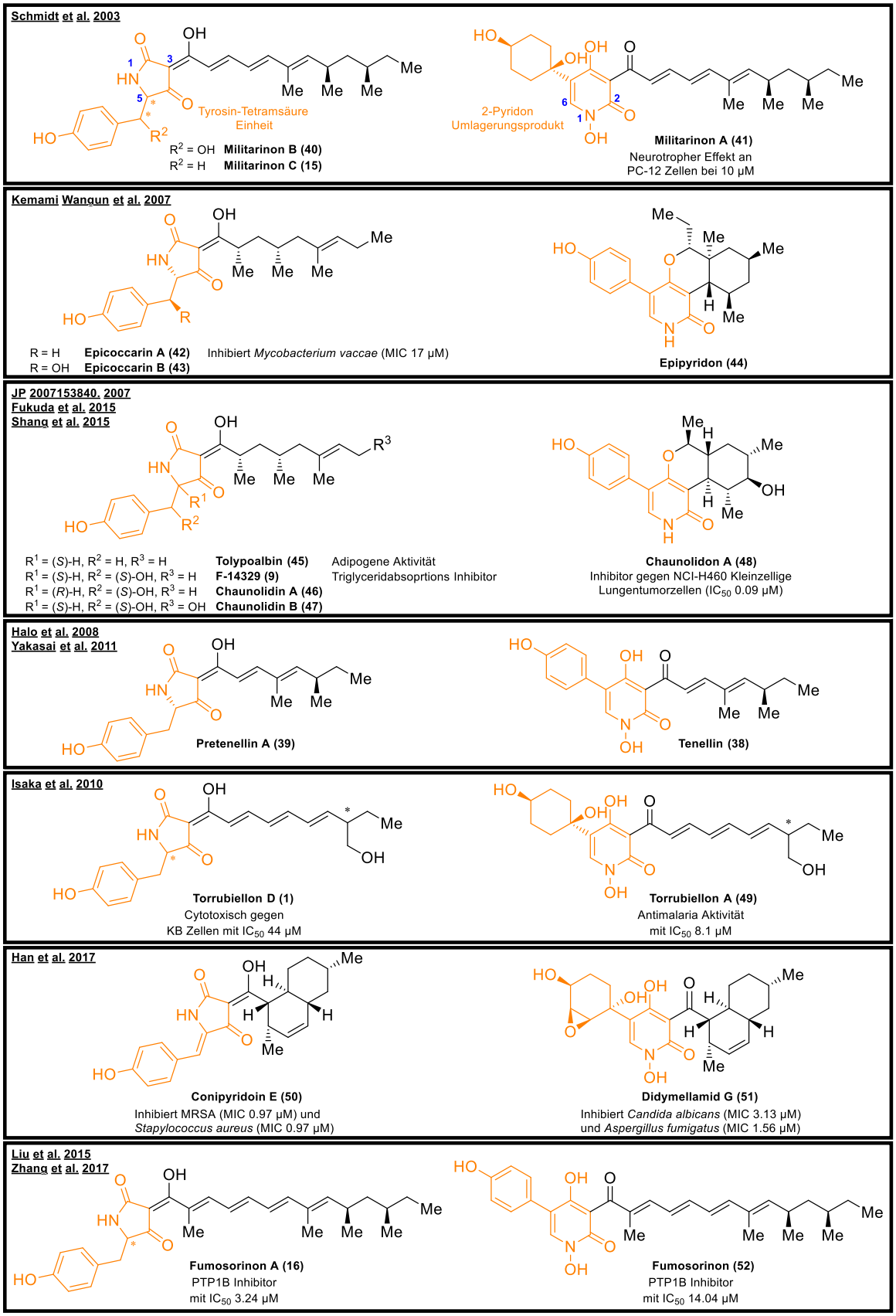
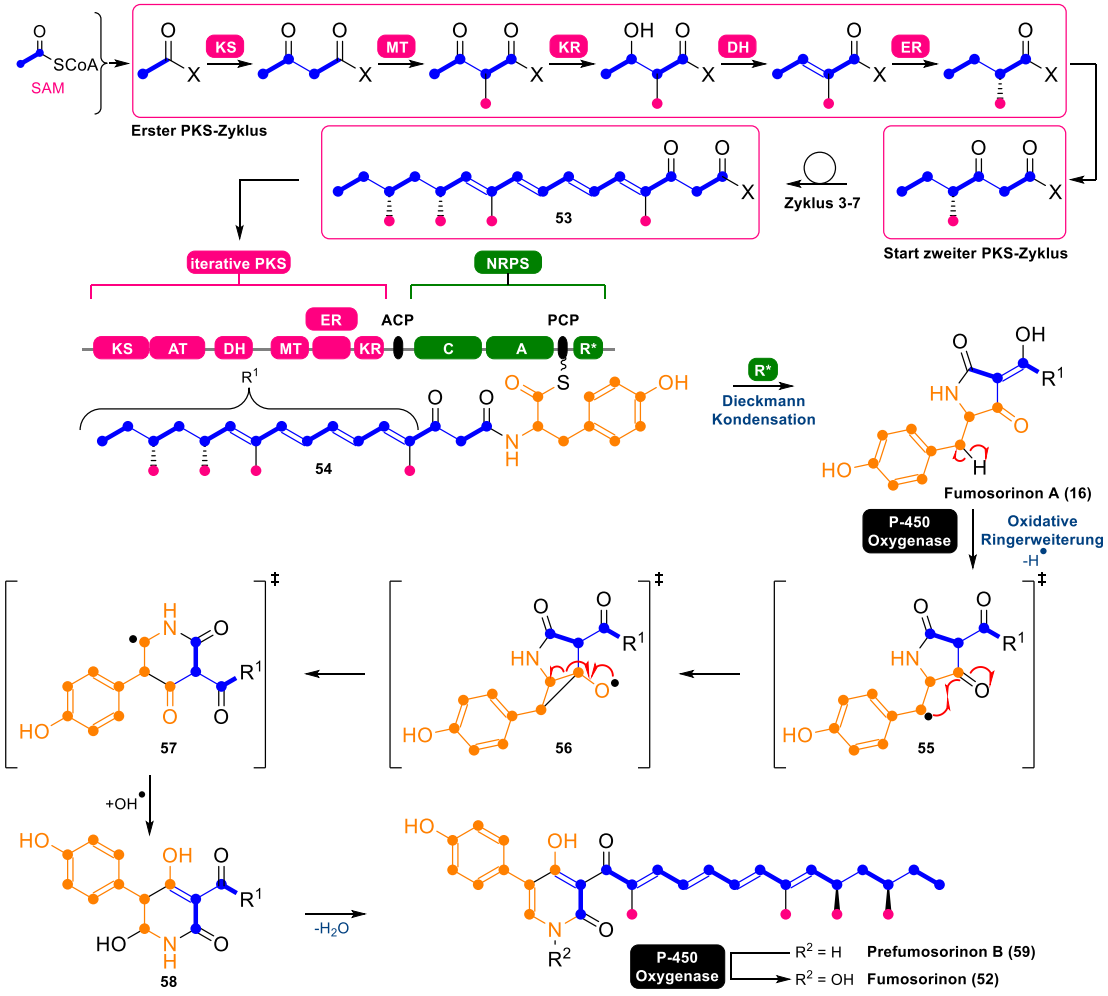


Abbildung 4. Eine Auswahl natürlicher, fungaler 3-Acyltetramsäuren und ihrer gleichzeitig mit isolierten 2-Pyridon-Nachfolgemetaboliten.[16,43,44,45,46,42,47,48,49,50,51]

Basierend auf diesen Ergebnissen und der Arbeit von Liu et al.[50] soll nachfolgend ein möglicher Biosyntheseweg für Fumosorinon (**52**) gezeigt werden (vgl. Schema **7**). Die Polyketidkette **53** wird dabei, ähnlich zu Equisetin (**31**), iterativ von der PKS-Domäne des Proteins, aus Acetyl CoA und SAM, aufgebaut (vgl. Schema **7**). Anschließend wird die Seitenkette an zuvor ligiertes Tyrosin kondensiert und das so gebildete β-Ketoamid **54**, in der Dieckmann-Cyclase Domäne R*, zu Fumosorinon A (**16**) cyclisiert. Cytochrom P-450 vermittelt wird dann das benzylische Radikal **55** erzeugt, von dem ausgehend das Cyclpropyloxyradikals **56** gebildet wird. Dieses initiiert die radikalische Ringerweiterung zu Intermediat **57**, welches durch Rekombination mit einem Hydroxylradikal 6-Hydroxy-2-Pyridon **58** bildet. Durch Dehydratisierung wird anschließend Prefumosorinon B (**59**) erzeugt, welches, nachfolgend Cytochrom P-450 vermittelt, in *N*-hydroxiliertes Fumosorinon (**52**) überführt wird.

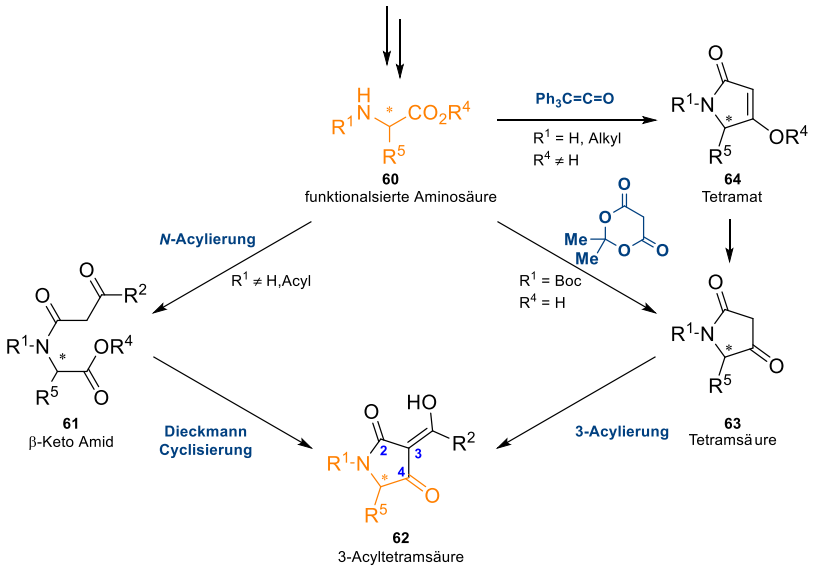


Schema 7. Mögliche Biosynthese von Fumosorinon (**52**) basierend auf den Arbeiten von Halo[42] und Liu.[50] KS:Beta-ketoacylsynthase; AT: Acyltransferase; DH: Dehydratase; MT: Methyltransferase; ER: Enoylreduktasen Domäne; KR: Beta-ketoacylreduktase; ACP: Acylcarrierprotein; C: Kondensation; A: Adenylierung; PCP: Peptidylcarrierprotein; R*: Dieckmann-Cyclase.

1.3 Strategien zur Darstellung von 3-Acyltetramsäuren

Um die große Anzahl strukturell diverser Tetramsäuren darstellen zu können, sind im Laufe der Jahre verschiedene Synthesestrategien entwickelt worden. Nachfolgend werden die für diese Arbeit relevanten Methoden vorgestellt. Detailliertere Zusammenstellungen der verschiedenen Strategien können der Literatur entnommen werden.[8,13,52,53]

Schema **8** gibt einen generellen Überblick über die Synthesestrategien und Methoden, die nachfolgend noch genauer erläutert werden. Allen gemein ist jedoch, dass die stereochemische Information in Form einer funktionalisierten Aminosäure **60** aus dem chiralen Pool bezogen wird. Anschließend wird entweder ein β-Ketoamid **61** generiert das mittels Dieckmann Cyclisierung, angelehnt an die Tetramsäurebiosynthese (vgl. Kapitel **1.2.1**), in die gewünschte 3-Acyltetramsäure **62** überführt wird. Oder alternativ kann auch, mittels verschiedener Methoden, zuerst die 3*H*-Tetramsäure **63** aufgebaut werden, welche nachträglich durch direkte 3-Acylierung in die 3-Acyltetramsäure **62** umgewandelt wird.



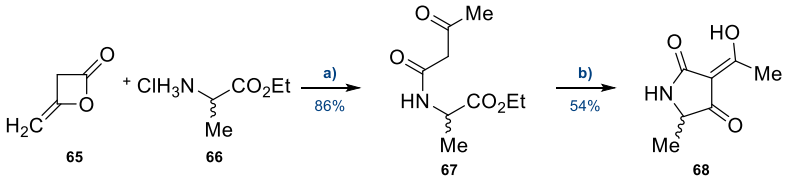
Schema 8. Überblick über verschiedene Zugänge zu 3-Acyltetramsäuren.

1.3.1 3-Acyltetramsäuren über β-Ketoamide

Die Synthese von 3-Acyltetramsäuren über β-Ketoamide ist eine der meist verwendeten Synthesestrategien zur Darstellung dieser Substanzklasse. Zum einen kann ein breites Substitutionsmuster sowohl für den Aminosäureester als auch die β-Ketoacylseitenkette bedient werden, wobei hier die einzige Einschränkung die Stabilität gegenüber den für die

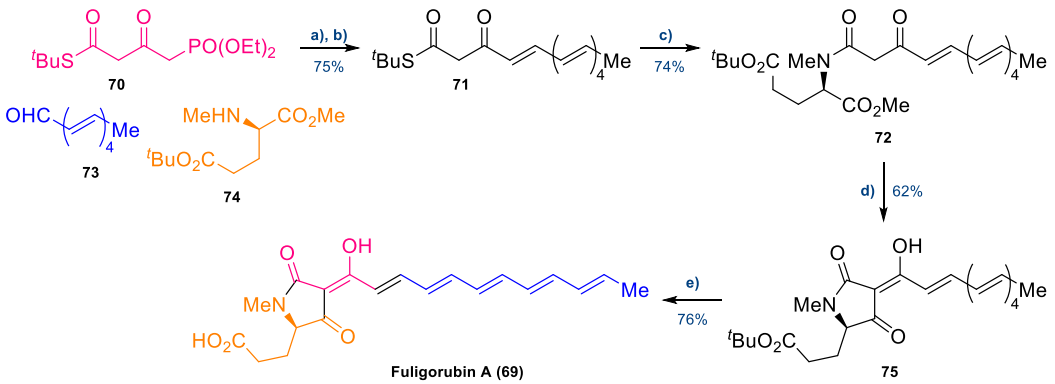
Cyclisierung benötigten basischen Bedingungen ist.[8] Zum anderen wird durch diese Herangehensweise das 3-Acyltetramsäuremotiv erst in den finalen Schritten der Synthese eingeführt, wodurch bekannte Probleme mit der Aufreinigung der Tetramsäuren, vor allem in Bezug auf die Säulenchromatographie mit Kieselgel,[13] umgangen werden können.

Die Verwendung von β-Ketoamiden als Intermediat zu 3-Acyltetramsäuren geht auf Lacey[54] zurück. Dieser setzte 1954 Aminoester mit Diketen **65** um. Die dabei generierten β-Ketoamide wurden dann anschließend in einer Dieckmann Kondensation zu den entsprechenden 3-Acyltetramsäuren umgesetzt. In Schema **9** ist dies beispielhaft für die Umsetzung von DL-Alaninhydrochlorid **66** mit Diketen **65** gezeigt.



Schema 9. Von Lacey etablierte Methode zur racemischen Darstellung von 3-Acetyltetramsäuren am Beispiel der Synthese von α-Acetyl-γ-methyltetramsäure **68**.[54]
Reagenzien und Bedingungen: a) NaOEt, EtOH dann **65** über 1 h bei < 10 °C, RT, 1 h; b) NaOEt, Benzol, rflx, üNa.

Die Frage der Racemisierung an C-5, welche in Bezug auf die enantiomerenreine Darstellung von entscheidender Bedeutung ist, wurde erst 1990 ausführlicher behandelt.[55] Poncet et al. konnten darin am Beispiel der Synthese von Tenuazonsäure zeigen, dass es unter Verwendung der von Lacey beschriebenen Cyclisierungsbedingungen zu Racemisierung an C-5 kommen kann. Jedoch nehmen die Autoren auch Bezug auf eine Veröffentlichung von Ley et al.,[56] denen die Synthese der Polyenoyltetramsäure Fuligorubin A (**69**) in enantiomerenreiner Form gelang (Schema **10**). Durch Verwendung des zuvor von ihnen publizierten[57] Thiophosphonats **70** konnte über eine *E*-selektive HWE-Reaktion der Thioester **71** aufgebaut und mittels Silber(I)-trifluoroacetat katalysierte Aminolyse in das β-Ketoamid **72** überführt werden. Die anschließende Dieckmann-Kondensation wurde, abweichend von Lacey, bei Raumtemperatur mit der sterisch anspruchsvolleren Base Kalium *tert*-butanolat durchgeführt. Damit konnte Stereoretention an C-5 erreicht und nach saurer Esterhydrolyse mit Ameisensäure der Naturstoff Fuligorubin A (**69**) enantiomerenrein erhalten werden.



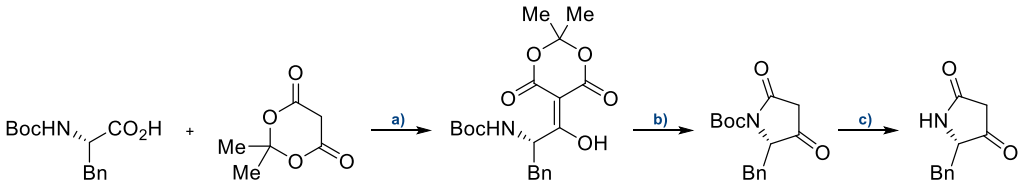
Schema 10. Racemisierungsfreie Synthese von Fuligorubin A (**69**) nach Ley.[56]
Reagenzien und Bedingungen: a) NaH, THF, 0 °C, 25 min; b) **71**, THF, 0 °C; c) $AgCO_2CF_3$, Na_2HPO_4, **74**, THF, RT, 3 h; d) KO^{t}Bu, ^{t}BuOH, RT, 30 min; e) HCO_2H, RT, 1 h.

Mit dieser erfolgreichen Synthese als Startpunkt untersuchten Ley et al. weitere β-Ketoamide auf deren Cyclisierungsverhalten. Dabei variierten sie auch die Ringschlussbedingungen bezüglich verwendeter Base, Reaktionszeit und Temperatur. Damit gelang es ihnen zu zeigen, dass *N*-substituierte β-Ketoamide bei Raumtemperatur unter Verwendung von Natriummethanolat ebenfalls racemisierungsfrei cyclisiert werden können,[58] womit der Grundstein für weitere enantioselektive Naturstoffsynthesen gelegt wurde.[59,60]

1.3.2 3-Acyltetramsäuren über 3-Acylierung freier Tetramsäuren

Eine andere Strategie zur Synthese von 3-Acyltetramsäuren stellt die nachträgliche 3-Acylierung freier Tetramsäuren dar. Eine erste Methode zur enantiomerenreinen Darstellung dieser 3-*H*-Tetramsäuren wurde 1987 von Jouin et al.[61] entwickelt (Schema **11**). Dabei werden *N*-geschützte Aminosäure, hier beispielhaft für Boc-Phenylalanin **(76)** gezeigt, mit Meldrumsäure (**77**) zum β-Oxoester **78** umgesetzt. Dabei bemerkten die Autoren, dass schon geringe Änderungen an den Reaktionsäquivalenten bzw. der Reaktionsführung enorme Auswirkungen auf die Anzahl an entstehenden Nebenprodukten haben können. Eine säulenchromatographische Aufreinigung des Meldrumsäurekonjugates **78** ist nur unter massiven Ausbeuteverlusten möglich, weswegen das erhaltene Rohprodukt weiter umgesetzt werden muss. Da beim anschließenden thermische Ringschluss zum Pyrrolidin-2,4-dion-System **79**, unter Aceton und CO_2 Abspaltung, die Anzahl an schwer abtrennbaren Nebenprodukten noch erhöht wird, ist es daher essentiell, dass das erhaltene Meldrumsäurekonjugat **78** möglichst rein eingesetzt werden kann. Von den beiden Aktivierungsreagenzien, die Jouin et al. getestet hatten, konnte die beste Ausbeute mit IPCF

anstelle von DCC erzielt werden. Die Gruppe um Ma[62] konnte jedoch 1996 zeigen, dass die niedrige Ausbeute, die unter Verwendung von DCC durch Jouin erzielt wurde, lediglich das Ergebnis einer suboptimalen Aufarbeitung des β-Oxoesters **78** war. Bei ansonsten gleichbleibender Reaktionsführung konnten sie durch Anpassung dieser eine beachtliche Ausbeutensteigerung nach thermischer Umsetzung zur Boc-Tetramsäure **79** erreichen. Eine letzte Verbesserung dieser Methodik wurde noch 2006 von Hosseini[63] vorgenommen, indem DCC durch das weniger giftige und leichter abzutrennende EDC·HCl, bei gleichbleibend guten Ausbeuten, substituiert werden konnte.



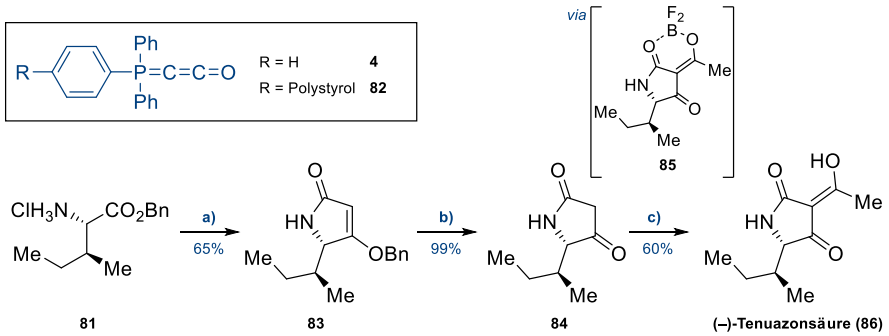
76 77 78 79 80

Gruppe	Reaktionsbedingungen	Prod.	Ausbeute
Jouin et al.	a) IPCF, DMAP, CH_2Cl_2, -5 °C, 3 h; b) MeOH, rflx, 20 min.	79	81% über 2 Stufen
	a) DCC, DMAP, CH_2Cl_2, RT, 3 h; b) MeOH, rflx, 20 min.	79	14% über 2 Stufen
Ma et al.	a) DCC, DMAP, CH_2Cl_2, RT, 3 h; b) MeOH, rflx, 30 min.	79	90% über 2 Stufen
Hosseini et al.	a) EDC•HCl, DMAP, CH_2Cl_2, 0 °C auf RT, üNa.; b) EtOAc, rflx, 30 min; c) 50% TFA in CH_2Cl_2, RT, 10 min.	80	91% über 3 Stufen

Schema 11. Entwicklung der Synthese von 3-*H*-Tetramsäuren mittles Meldrumsäure (**77**) über Jouin[61] und Ma[62] bis Hosseini.[63]

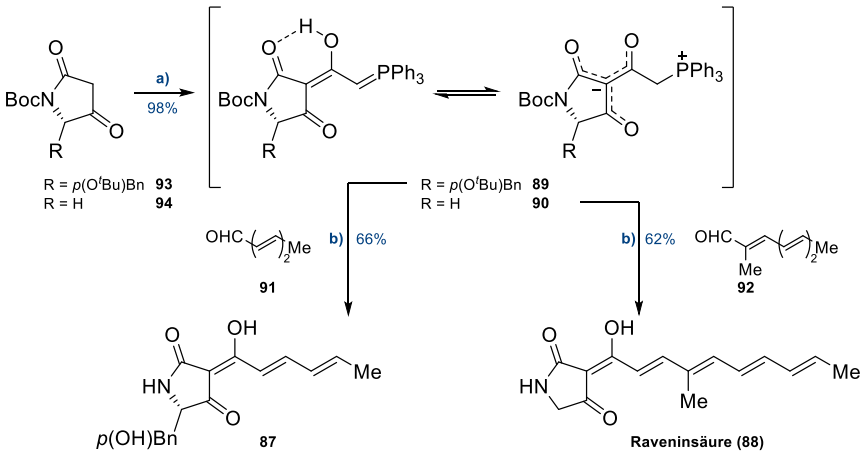
Eine alternative Möglichkeit zur Darstellung von 3-*H*-Tetramsäuren wurde 2004 von Schobert et al.[64] publiziert. Diese verwendet eine bereits 1996 von Löffler aus der gleichen Gruppe veröffentlichte Dominosynthese zur Darstellung von Tetramaten unter Verwendung von Ketenylidentriphenylphosphoran **4** (vgl. Schema **12**).[65] Basierend auf dieser wurde im ersten Schritt der Synthese L-Isoleucinbenzylester Hydrochlorid **(81)** mit einer weiterentwickelten, polymergebundenen Version dieses Phosphorans **82** umgesetzt. Durch Addition des Amins an die C=C Bindung des Phosphorans, gefolgt von einer intramolekularen Wittig Olefinierung, wurde damit das Tetramat **83** gebildet, welches über Paladium katalysierte Hydrogenolyse des Benzylethers in die 3-*H*-Tetramsäure **84** überführt werden konnte. Die nachfolgende 3-Acylierung geschah nach einem 1990 von Jones et al.[66] veröffentlichten Protokoll. In diesem werden freie Tetramsäuren wie **84** unter Zugabe der Lewissäure $BF_3 \cdot OEt_2$ und in Gegenwart eines Überschusses an Säurechlorid selektiv unter Bildung des BF_2-Komplexes **85** 3-acyliert. Dies ist in Schema **12** dargestellt. Dadurch, dass die 3-Acyltetramsäure hier bereits komplexiert vorliegt, wird außerdem die Aufreinigung der Verbindungen erleichtert. Durch anschließende Methanolyse (vgl. Loscher[60]) oder mittels Säure-Base Extraktion wie bei (–)-Tenuazonsäure

(**86**) können diese Komplexe dann in die gewünschten, enantiomerenreinen 3-Acyltetramsäuren überführt werden.



Schema 12. Synthese von (–)-Tenuazonsäure (**86**) nach Schobert,[64] unter Verwendung von polystyrolgebundenem Ketenylidentriphenylphosphoran **82** und anschließender Jones 3-Acylierung.
Reagenzien und Bedingungen: a) **82**, THF, 60 °C, 14 h; b) H_2, 5% Pd/C, MeOH, RT, 2 h; c) 1. $BF_3 \cdot OEt_2$, AcCl, 80 °C, 8 h; 2. 1% aq. NaOH.

Neben der relativ harschen 3-Acylierungsmethode nach Jones[66] wurde 2010 von Schlenk[67] eine alternative Methode vorgestellt, über die ein einfacher Zugang zu 3-Oligoenoyltetramsäuren möglich ist. Vorteil dieser Methodik ist dabei, dass der Seitenkettenaldehyd lediglich äquimolar zugegeben werden muss, was insbesondere bei aufwendiger zu synthetisierenden Seitenketten von großem Vorteil ist. Zudem können über diese Methode auch säurelabile Polyenoyl-Systeme hergestellt werden. In Schema **13** ist die Synthese einer Tyrosin-abgeleiteten 3-Dienoyltetramsäure **87** sowie die Synthese des Naturstoffes Raveninsäure (**88**) unter Verwendung dieser Strategie gezeigt. Die Boc-geschützten 3-*H*-Tetramsäuren, welche zuvor nach Hamilakis[68] synthetisiert wurden, konnten durch thermische Umsetzung mit Phosphoran **4** in das stabilisierte Ylid **89** bzw. **90** überführt werden. Dabei sind diese Ylide an sich nicht in der Lage, eine Wittig Olefinierung einzugehen, was durch Studien an Tetronsäureyliden, den Sauerstoffanaloga der Tetramsäuren, gezeigt wurde.[69] Daher ist es zur Aktivierung dieser Klasse von Yliden nötig, das chelatisierte Proton mittels einer geeigneten Base zu entfernen. Dies konnte durch Umsetzung mit Kalium *tert*-butanolat erreicht werden. Durch nachfolgende Zugabe der jeweiligen Aldehyde **91** bzw. **92** und anschließende saure Entschützung wurden die 3-Oligoenoyltetramsäure **87** sowie Raveninsäure (**88**) erhalten. Am Beispiel von **87** wurde zudem gezeigt, dass unter den verwendeten Reaktionsbedingungen keine Racemisierung an C-5 auftritt, womit diese Methode zur Synthese komplexerer 3-Acyltetramsäuren geeignet ist.



Schema 13. 3-Acylierung mit Stereoretention nach Schlenk[67] unter Verwendung von Ketenylidentriphenylphosphoran (**4**).
Reagenzien und Bedingungen: a) **4**, THF, rflx, 16 h; b) 1. KO^{t}Bu, THF, rflx, 20 min, dann **91**, rflx, 6 h; 2. 13% TFA in CH_2Cl_2, RT; b) analog bis auf **92** als Aldehyd.

2 KENNTNISSTAND UND ZIELSETZUNG

In Abbildung **5** sind vier aus verschiedenen Pilzen isolierte Zwischenmetaboliten der jeweiligen 2-Pyridonbiosynthese gezeigt. Diese Tyrosin-abgeleiteten 3-Acyltetramsäuren weisen dabei teilweise interessante biologische Aktivitäten auf. Auf Grund fehlender totalsynthetischer Zugänge zu den einzelnen Strukturen konnten jedoch bisher noch nicht alle diese Moleküle betreffenden offenen Fragen beantwortet werden. So ist die Stereochemie von Torrubiellon D (**1**) sowohl an C-5 als auch an C-14 unbekannt. Dasselbe ist für Militarinon C (**15**) und Fumosorinon A (**16**), ebenfalls an C-5, der Fall. Damit kann nicht eindeutig bestimmt werden, welches Stereoisomer die beobachteten biologischen Eigenschaften aufweist. Die Klasse der β-Hydroxytyrosin-abgeleiteten 3-Acyltetramsäuren, wie z.B. F-14329 (**9**), konnte zudem totalsynthetisch noch nicht erschlossen werden, was die Bestimmung der bisher erst unvollständig bekannten biologischen Funktion zusätzlich erschwert.

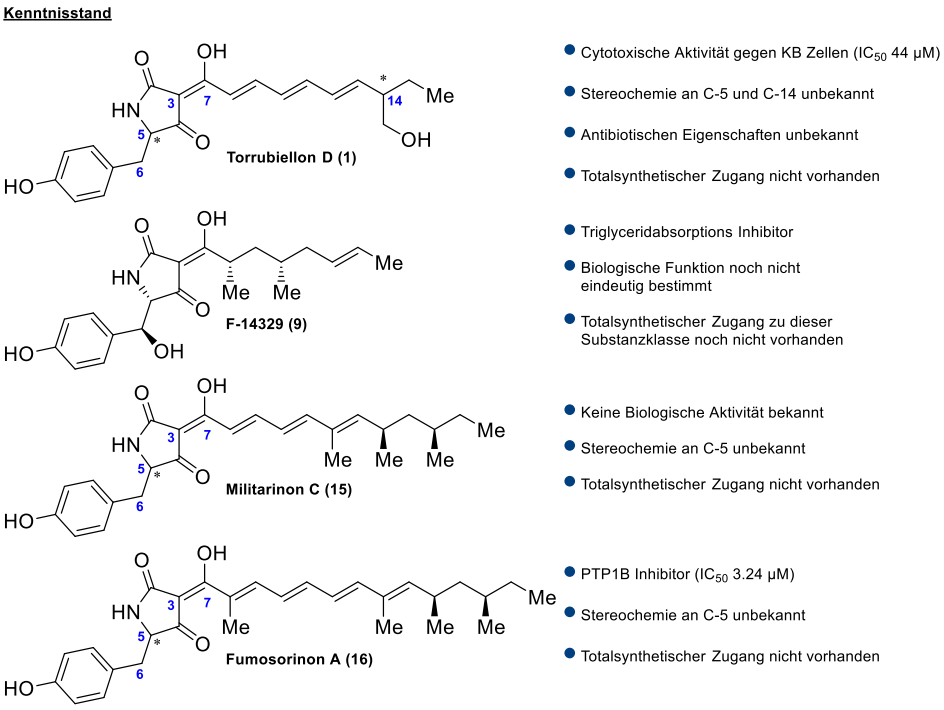


Abbildung 5. Die Zielverbindungen der vorliegenden Arbeit.

Im Rahmen dieser Arbeit sollten erstmalig verschiedene flexible Syntheserouten zu den in Abbildung **5** gezeigten 3-Acyltetramsäuren etabliert werden. Basierend auf diesen sollten anschließend die Strukturen der Naturstoffe durch Vergleich mit den synthetischen

Verbindungen aufgeklärt werden und im Fall von Torrubiellon D (**1**) zudem die antibiotischen Eigenschaften der Verbindung ermittelt werden.

3 SYNOPSIS

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

Ziel dieser Arbeiten war die Entwicklung flexibler, enantioselektiver Syntheserouten zur Darstellung der Tyrosin-abgeleiteten Naturstoffe Torrubiellon D (**1**), F-14329 (**9**), Militarinon C (**15**) und Fumosorinon A (**16**) (vgl. Abbildung **6**).
In diesem Rahmen wurde zuerst die Synthese von Torrubiellon D (**1**) entwickelt (vgl. Kapitel **6.1**). Die dabei gewonnenen Erfahrungen halfen anschließend, die Synthese von F-14329 (**9**) zu verwirklichen, so dass erstmalig eine β-Hydroxytyrosin-abgeleitete 3-Acyltetramsäure totalsynthetisch hergestellt werden konnte (vgl. Kapitel **6.2**). Im Zuge dieser Totalsynthese wurde mit *ortho*-Nitrobenzyl zudem eine in der Tetramsäurechemie zuvor unbekannte photolytisch abspaltbare Schutzgruppe eingeführt. Obgleich Untersuchungen während der Synthese von Militarinon C (**15**) zeigten, dass diese Schutzgruppe für Polyenoyltetramsäuren ungeeignet ist (vgl. Kapitel **6.3**), stellt die Etablierung von *ortho*-Nitrobenzyl für Tetramsäuren mit gesättiger Seitenkette eine entscheidende Neuerung dar. Des Weiteren konnte nach erfolgreicher Synthese von Militarinon C (**15**) und Fumosorinon A (**16**) deren Stereochemie an C-5 als (*S*) vorgeschlagen werden. Dies war durch Abgleich der Literaturdaten mit den experimentell ermittelten Daten möglich (vgl. Kapitel **6.3**). Im Fall von Torrubiellon D (**1**) war ein solcher Vorschlag nicht möglich, weswegen hier alle vier möglichen Stereoisomere synthetisiert werden mussten, die zudem mittels chiraler HPLC untersucht wurden (vgl. Kapitel **6.1**). Die genaue Identität des von Isaka publizierten[48] cytotoxisch aktiven Torrubiellon D Stereoisomers oder dessen Mischung mit einem weiteren konnte auf Grund nicht ausreichender Literaturdaten nicht eindeutig geklärt werden. Alle vier Torrubiellon D Stereoisomere wurden auf ihre antibiotischen Eigenschaften hin untersucht, wobei die Konfiguration an C-5 und C-14 entscheidenden Einfluss auf deren jeweilige Aktivität hatte (vgl. Kapitel **6.1**).

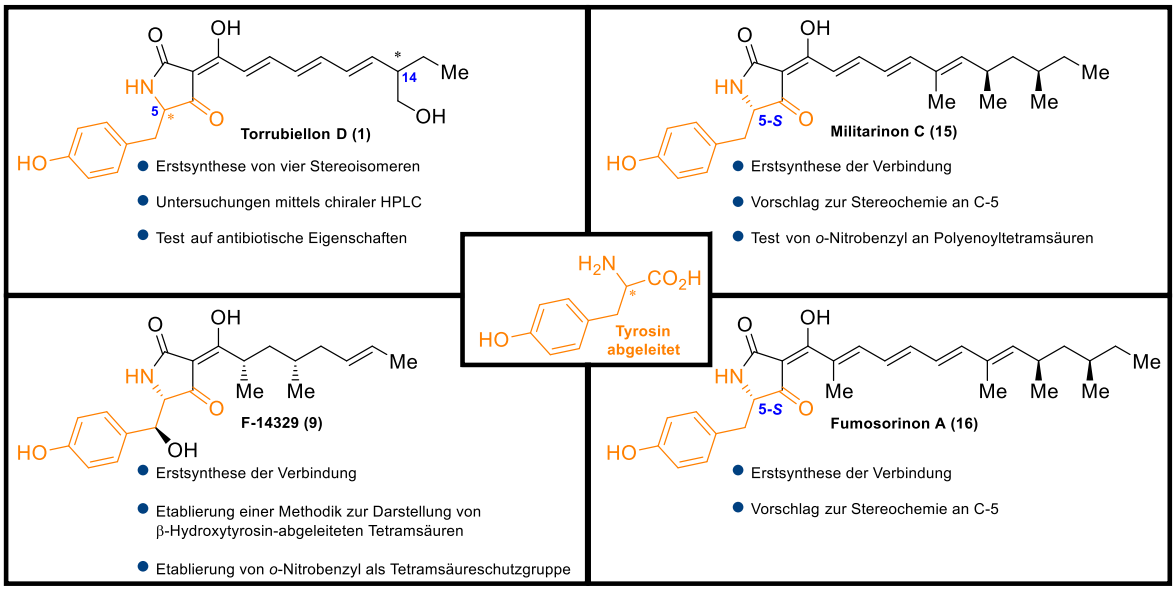


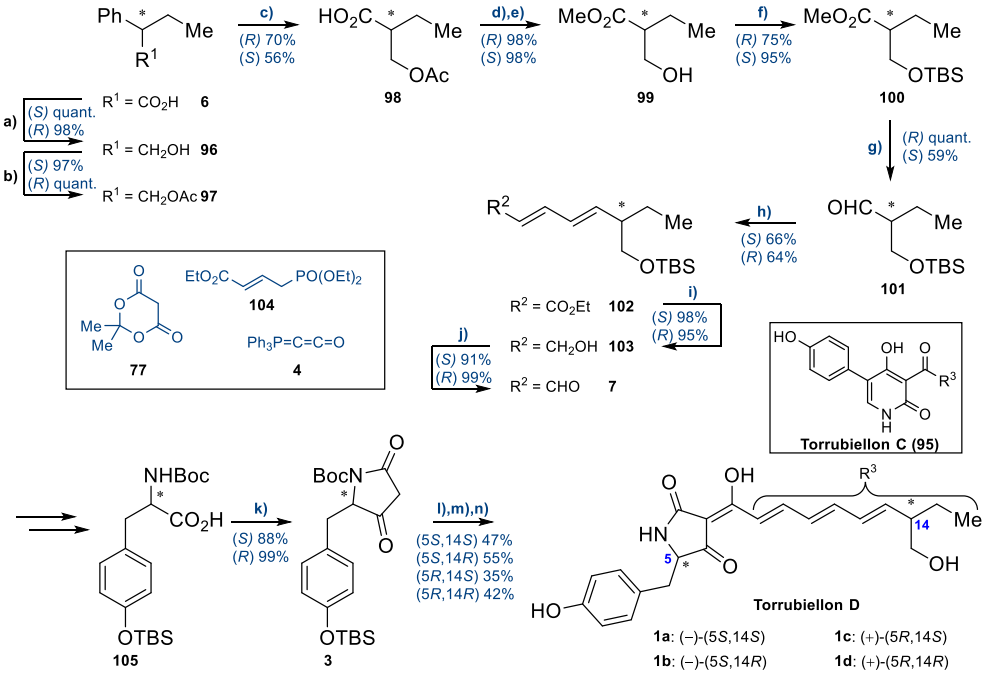
Abbildung 6. Erzielte Ergebnisse der vorliegenden Dissertation.

3.1 Synthese und antibakterielle Aktivität von vier Stereoisomeren des spinnenpathogenen Pilzmetaboliten Torrubiellon D (1)

Zur Darstellung von Torrubiellon D **(1)** sollte die unter Kapitel **1.3.2** vorgestellte Methode zur direkten 3-Acylierung von 3*H*-Tetramsäuren nach Schlenk[67] verwendet werden. Die dafür benötigte 3*H*-Tetramsäure wäre dabei, ausgehend von L- bzw. R-Tyrosin, nach Hosseini[63] unter Verwendung von Meldrumsäure (**77**) zugänglich. Das Stereozentrum an C-14 sollte dem chiralen Pool in Form von (*S*)- bzw. (*R*)-2-Phenylbuttersäure entnommen werden.

Da Jessen et al.[70] bei ihrer Synthese des 2-Pyridons Torrubiellon C (**95**), welches der biosynthetische Nachfolgemetabolit (vgl. Kapitel **1.2.2**) des zu synthetisierenden Torrubiellon D (**1**) ist, das Stereozentrum an C-14 mit (*R*) bestimmen konnten, sollten zunächst die beiden Torrubiellon D C-5-Epimere **1b** und **1d** dargestellt werden. Durch Vergleich mit den von Isaka[48] ermittelten analytischen Daten hätte es dann möglich sein sollen festzustellen, welches der beiden Epimere das natürliche Isolat darstellt.

Dafür wurde die in Schema **14** dargestellte Syntheseroute entwickelt, so dass beide Epimere über 13 Stufen mit bis zu 16% (für **1b**) dargestellt werden konnten.



Schema 14. Enantioselektive Synthese von vier Torrubiellon D Stereoisomeren **1a–d** über 13 Stufen mit einer Maximalausbeute von 16% (für **1b**).
Reagenzien und Bedingungen: a) $LiAlH_4$, Et_2O, rflx; b) $Cu(OTf)_2$ kat., Ac_2O, 0 °C auf RT; c) $RuCl_3$ kat., $NaIO_4$, MeCN/CCl_4/H_2O, RT; d) $TMSCHN_2$, Et_2O/MeOH, RT; e) K_2CO_3, MeOH, RT; f) TBSCl, Imidazol, DMF, RT; g) DIBAL-H, CH_2Cl_2, -78 °C; h) **104**, LiHMDS, THF, -78 °C, 10 min dann **101** auf RT; i) DIBAL-H, CH_2Cl_2, -78 °C; j) MnO_2, CH_2Cl_2, rt; k) i. Meldrumsäure (**77**), EDCxHCl, DMAP, 0 °C auf RT, ii. EtOAc, rflx; l) **4**, THF, rflx dann KO^{t}Bu, rflx dann **7**, rflx; m) TFA, CH_2Cl_2, RT; n) TFA, MeOH, H_2O, RT.

Die NMR-spektroskopischen Daten beider dargestellter Epimere **1b** und **1d** deckten sich sowohl untereinander als auch mit den Literaturdaten, weswegen zur endgültigen Bestimmung des natürlichen Isomers lediglich der von Isaka ermittelte Drehwert des natürlichen Isolats zu Rate gezogen werden konnte. Nachdem hier bei beiden C-5 Epimeren keine Übereinstimmung mit dem Literaturdrehwert erzielt werden konnte, wurden zusätzlich die dazugehörigen C-14 Epimere **1a** und **1c** dargestellt. Jedoch konnte auch hier der publizierte Wert nicht nachgewiesen werden (vgl. Tabelle **1**).

Tabelle 1. (Spezifische) Drehwerte der Torrubiellon D Stereoisomere **1a–d** (c = 0.12, MeOH).

	Isaka[48]	**1a**	**1b**	**1c**	**1d**
α		-0.62	-0.63	+0.64	+0.65
$[\alpha]_D^{23}$	-182	-517	-525	+533	+542

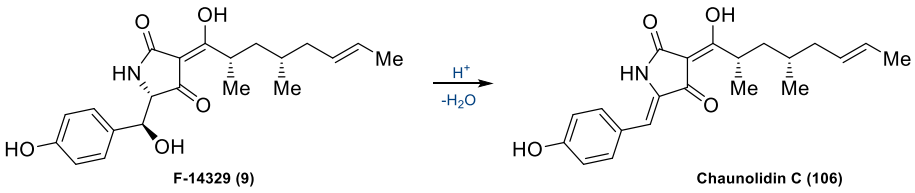
Um eventuelle Racemisierung an C-14 im Verlauf der Synthese auszuschließen, wurden zusätzlich chirale HPLC-Studien (vgl. Kapitel **6.1**) durchgeführt. Dadurch war es möglich zu zeigen, dass die verwendete Syntheseroute enantioselektiv abläuft.

Bzgl. des abweichenden Drehwertes des natürlichen Isolats lagen leider keine weiteren Literaturdaten vor, die es ermöglicht hätten, die Identität des natürlichen Isomers eindeutig zu bestimmen bzw. auszuschließen, dass während der Isolation teilweise Racemisierung an C-5 auftrat, was auf Grund der identischen NMR-Spektren der jeweiligen Epimere nicht aufgefallen wäre. Auch wäre es denkbar, dass lediglich eine unterschiedliche Tautomerenzusammensetzung während der Drehwertbestimmung von Isaka vorlag, was ebenfalls Auswirkungen auf die ermittelten Daten haben könnte.[11,12]

Von allen vier Stereoisomeren wurden am Helmholtz-Zentrum für Infektionsforschung in Braunschweig Tests auf antibiotische Wirkung durchgeführt, die zeigten, dass die unterschiedlich konfigurierten Zentren an C-5 und C-14 einen bedeutenden Einfluss auf die Wirkung der einzelnen Substanzen haben (vgl. Kapitel **6.1).**

3.2 Eine Syntheseroute zu β-Hydroxytyrosin-abgeleiteten Tetramsäuren: Die Totalsynthese des Pilzmetaboliten F-14329 (9)

Synthesen von β-Hydroxytyrosin-abgeleiteten Tetramsäuren waren vor dieser Arbeit noch nicht bekannt, obwohl bereits diverse Vertreter dieser Stoffklasse isoliert worden sind (vgl. Kapitel **1.2.2**, Abbildung **4**). Daher war es das Ziel, eine flexible Totalsynthese zu etablieren, welche den Zugang zu und damit die experimentelle Strukturaufklärung von Vertretern dieser Klasse ermöglicht. Im Gegensatz zur unter **3.1** und **6.1** vorgestellten Synthese von Torrubiellon D (**1**) sollte hierbei das 3-Acyltetramsäure-System von F-14329 (**9**) mittels Dieckmann Cyclisierung aufgebaut werden. Dies geschah aus dem einfachen Grund, dass die bereits für Torrubiellon D (**1**) erfolgreich angewandte Methode nach Schlenk[67] lediglich für Enoyl-Tetramsäuren verwendet werden kann. Die in Kapitel **1.3.2** vorgestellte Methode nach Jones[66] konnte nicht verwendet werden, da das β-Hydroxy-System der Zielverbindung im Sauren zu spontaner Dehydratisierung zu Chaunolidin C (**106**) neigt, wie Shang et al. bereits berichteten (vgl. Schema **15**).[46]



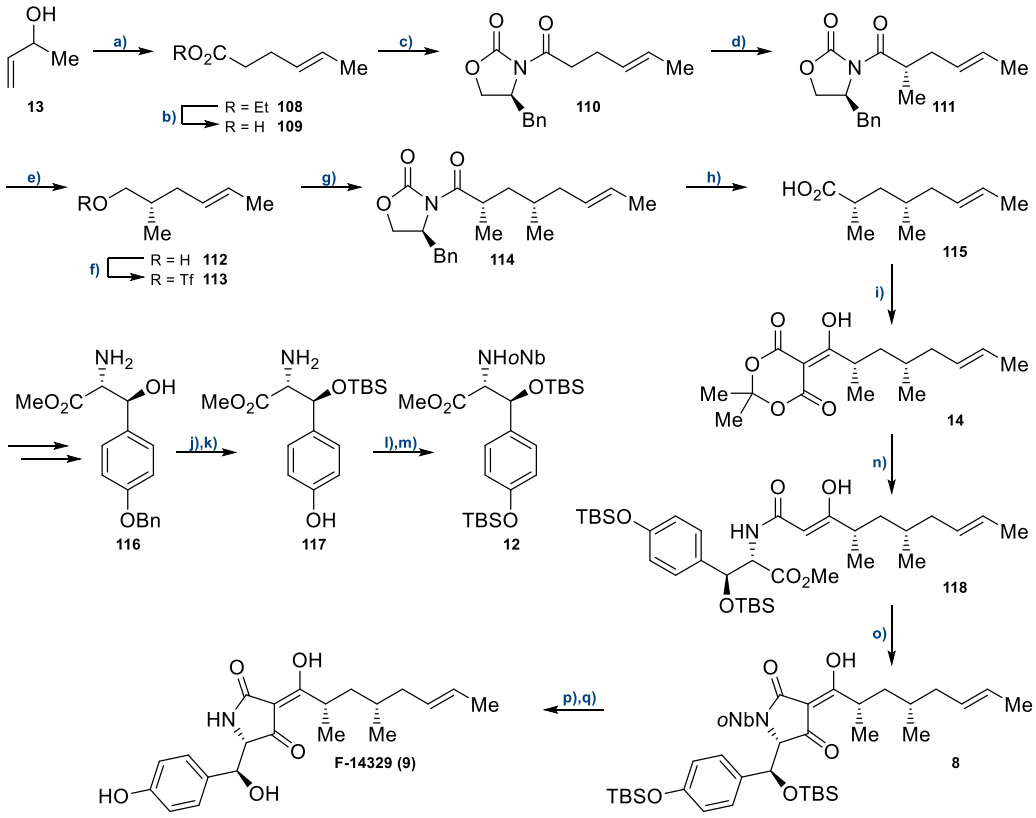
Schema 15. Dehydratisierung von F-14329 (**9**) zu Chaunolidin C (**106**).

Der Aufbau der Polyketidseitenkette wurde im Rahmen einer Kooperation mit R. Haase von diesem bis zum Meldrumsäurekonjugat **14** durchgeführt.

Im Laufe der Synthese traten immer wieder Schwierigkeiten auf (vgl. Kapitel **6.2**), welche eine Anpassung der Syntheseroute auf die jeweilige Problemstellung bedingten. Nachdem 2,4-Dimethoxybenzyl als Tetramsäureamid Schutzgruppe nicht verwendet konnte, wurde die aus der Peptidchemie bekannte, photolytisch abspaltbare *ortho*-Nitrobenzylschutzgruppe verwendet. Auf Grund der elektronenziehenden Eigenschaft dieser Gruppe war der Nukleophilitätsverlust am sekundären Amin **12** so groß, dass die unter Kapitel **1.3.1** vorgestellte Silber(I)-vermittelte Acylierungsmethode nach Ley[58] nicht mehr verwendet werden konnte. Deswegen wurde auf eine Meldrumsäure basierte, thermisch induzierte Stickstoffacylierung zurückgegriffen, die auch in der Literatur bereits erfolgreich verwendet wurde.[71,72]

Dadurch war es möglich, β-Ketoamid **107** aufzubauen und zu komplett geschütztem F-14329 **8** zu cyclisieren. Nach photolytisch induzierter *ortho*-Nitrobenzylabspaltung und Desilylierung

konnte damit erstmalig eine β-Hydroxytyrosin-abgeleitete Tetramsäure F-14329 (**9**) enantiomerenrein über 14 Stufen in einer Gesamtausbeute von 3.9% dargestellt werden (vgl. Schema **16**).



Schema 16. Erstsynthese einer β-Hydroxytyrosin-abgeleiteten Tetramsäure F-14329 (**9**) über 14 Stufen und 3.9% Gesamtausbeute in Kooperation mit R. Haase

Reagenzien und Bedingungen: a) $MeC(OEt)_3$, $EtCO_2H$, rflx, 1 h, 73%; b) KOH, EtOH, H_2O, RT, 20 min, 72%; c) PivCl, NEt_3, THF, 0 °C, 1 h, dann (*S*)-Benzyloxazolidinon, LiCl, RT, 1 h, 89%; d) NaHMDS, MeI, THF, -78 °C, 1 h, 84%; e) $LiBH_4$, Et_2O, MeOH, 0 °C, 35 min, 84%; f) Tf_2O, Pyridin, CH_2Cl_2, -78 °C, 90 min; g) (*R*)-4-Benzyl-3-propionyl-2-oxazolidinon, LDA, THF, -78 °C, 30 min, dann **113**, 4 h, 49% über 2 Stufen; h) BnOLi, THF, 0 °C, 2.5 h, dann KOH, MeOH, H_2O, RT, 3 d, 76% über 2 Stufen; i) EDC·HCl, DMAP, CH_2Cl_2, RT, 30 min, dann Meldrumsäure (**77**), 24 h, 99%; j) TBSOTf, NEt_3, CH_2Cl_2, -10 °C auf 4 °C, 16 h, 82%; k) 10% Pd/C, H_2, MeOH, RT, 15 h, 99%; l) TBSOTf, NEt_3, CH_2Cl_2, -10 °C auf 4 °C, 22 h, 82%; m) *ortho*-Nitrobenzaldehyd, $MgSO_4$, MeOH, AcOH, RT, 30 min, dann $NaBH_3CN$, 3 h, 76%; n) **14**, MS 3Å, Dioxan, rflx, 2.5 h; o) NaOMe, MeOH, RT, 10 min, 50% über 2 Stufen; p) hν, 366 nm 4 W, $MeCN/H_2O$, RT, 1 d, 72%; q) TBAF, AcOH, THF, 0 °C auf RT, 38 h, 81%.

3.3 Synthese der entomopathogenen Pilzmetaboliten Militarinon C (15) und Fumosorinon A (16)

Im Rahmen der Totalsynthesen der beiden Polyenoyltetramsäuren Militarinon C (**15**) und Fumosorinon A (**16**) sollten die Stereokonfiguration der Stereozentren an C-5 experimentell geklärt und am Beispiel von Militarinon C (**15**) zusätzlich die Anwendbarkeit der bei der Synthese von F-14329 (**9**) vorgestellten *ortho*-Nitrobenzyl Schutzgruppe an Polyenoyl-Systemen untersucht werden.

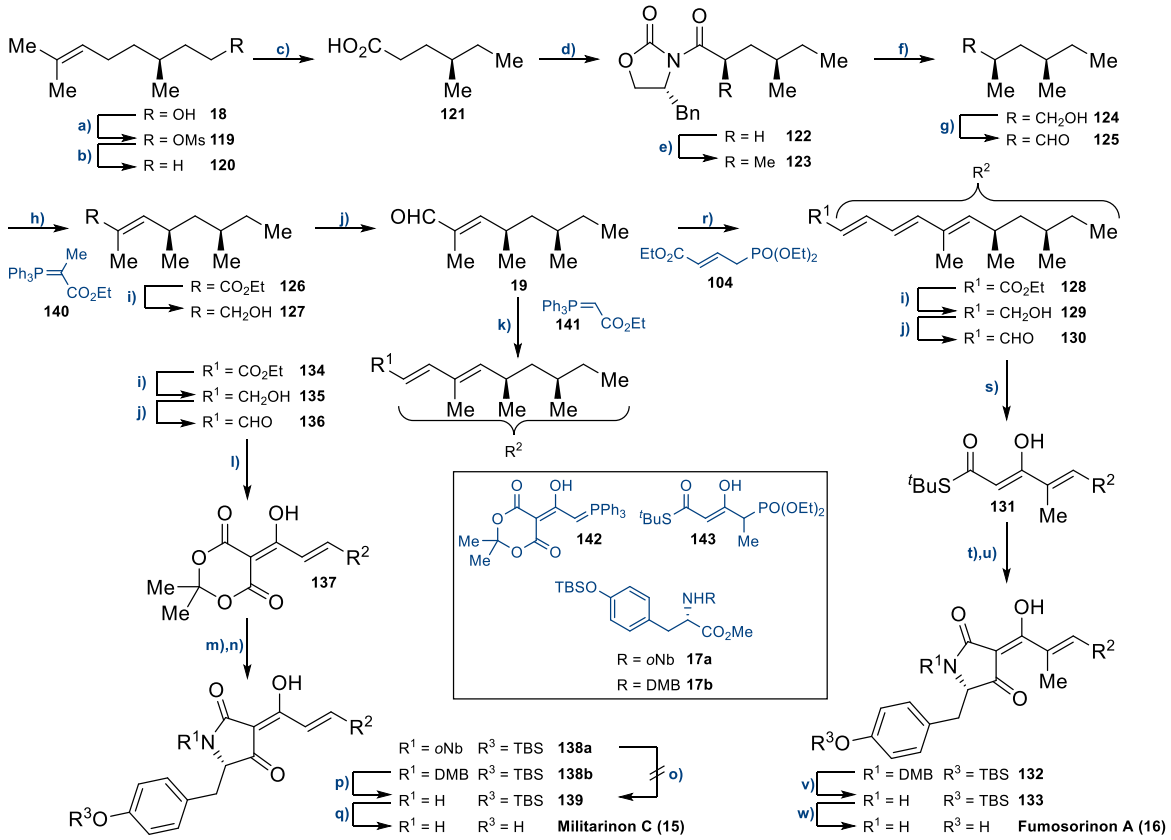
Dabei sollten beide Pyrrolidin-2,4-dion-Systeme, analog zur Synthese von F-14329 (**9**), mittels Dieckmann Cyclisierung geschlossen werden. Die Polyenoyl-Seitenketten **130** und **136** sollten, analog zur Synthese von Torrubiellon D (**1**) und der Literatur,[73,74] iterativ über HWE bzw. Wittig Olefinierungen, ausgehend von Intermediat **19,** aufgebaut werden. Intermediat **19** selbst sollte ausgehend von (*S*)-Citronellol (**18**) synthetisiert werden.

Die Synthese von (*S*)-Citronellol (**18**) bis zu Aldehyd **125** wurde von M. Weise im Rahmen ihrer Masterarbeit selbstständig geplant, durchgeführt und ausgewertet.

Die Darstellung der konjugierten Aldehyde **130** und **136** gelang ohne nennenswerte Schwierigkeiten. Die weitere Umsetzung von **136** geschah anschließend, im Gegensatz zu der des längeren Aldehyds **130,** nicht nach der bekannten Methode von Ley,[58] sondern nach einer von Lovmo et al.[75] entwickelten Vorschrift. Durch Umsetzung eines Aldehyds mit Meldrumsäureylid **142** können dabei konjugierte Meldrumsäurekonjugate der Art **137** erhalten und mittels Säure-Base-Extraktion aufgereinigt werden, was für die Synthese von **137** jedoch nicht ohne weiteres möglich war. Zum einen zeigte die Wittig-Olefinierung des Meldrumsäureylids **142** mit Aldehyd **136** keinen vollständigen Umsatz, was vermutlich der thermischen Instabilität des konjugierten Aldehyds **136** geschuldet ist. Ähnliches konnte bereits Schlessinger bei der Synthese von Tirandamycin A beobachten.[76] Zum anderen erwies sich auch die Aufreinigung der erhaltenen Mischung als schwierig, da auf Grund des amphiphilen Charakters des dargestellten Meldrumsäurekonjugats **137** eine Aufreinigung mittels Säure-Base-Extraktion, analog zu Lovmo,[75] nicht möglich war. Auch eine Aufreinigung mittels Säulenchromatographie konnte nicht durchgeführt werden, da Meldrumsäurekonjugate, wie bereits von Jouin[61] berichtet, an Kieselgel zur Zersetzung neigen. Somit musste die erhaltene Mischung aus Meldrumsäureylid **142**, Triphenylphosphinoxid und Meldrumsäurekonjugat **137** für die weiteren Umsetzungen verwendet werden. Damit war es möglich, sowohl die *ortho*-Nitrobenzyl als auch die 2,4-Dimethoxybenzyl geschützten 3-Acyltetramsäuren **138a** und **138b** herzustellen, was unter Verwendung der Methode von Ley[58] aus den bereits unter **3.2** bei der

Synthese von F-14329 (**9**) genannten Gründen nicht möglich gewesen wäre. Somit war es möglich, die photolytische Entschützung am Polyenoyl-System zu untersuchen, wobei sich jedoch zeigte, dass *ortho*-Nitrobenzyl hierfür nicht geeignet ist (vgl. Kapitel **6.3**).

Zusammenfassend konnten sowohl Militarinon C (**15**) als auch Fumosorinon A (**16**) totalsynthetisch hergestellt werden und über den Vergleich der erhaltenen experimentellen Daten, mit denen die aus der Literatur verfügbar sind, die zuvor nicht bekannten Konfigurationen an C-5 als (*S)* vorgeschlagen werden (vgl. Kapitel **6.3**).



Schema 17. Etablierung eines enantioselektiven, totalsynthetischen Zugangs zu den Polyenoyltetramsäuren Militarinon C (**15**) (18 Stufen, 2.5% Gesamtausbeute) und Fumosorinon A (**16**) (18 Stufen, 2.0% Gesamtausbeute) über das gemeinsame Intermediat **19** in Kooperation mit M. Weise.
Reagenzien und Bedingungen: a) MsCl, NEt_3, CH_2Cl_2, 0 °C auf RT, 3.75 h, quant.; b) $LiAlH_4$, THF, 0 °C auf RT, 16 h, quant.; c) $RuCl_3$ kat., $NaIO_4$, MeCN/CH_2Cl_2/H_2O, RT, 18 h, 64%; d) PivCl, NEt_3, THF, 0 °C, 25 min, dann (*R*)-Benzyloxazolidinon, LiCl, RT, 30 min, 88%; e) NaHMDS, THF, -78 °C, 15 min, dann MeI, -78 °C auf RT, 2.5 h, 90%, de 84%; f)$LiBH_4$, MeOH, Et_2O, 0 °C auf RT, 5 h, 95%; g) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C, 3 h; h) **140**, CH_2Cl_2, RT, 19 h, 70% über 2 Stufen, de 96%; i) DIBAL-H, CH_2Cl_2, -78 °C, 1 h, **126**/**128**/**134** 90%/85%/98%; j) MnO_2, CH_2Cl_2, RT, 18 h, **19**/**130**/**136** 83%/92%/96%; k) **141**, Toluol, rflx, 22 h, 68%, de 82%; l) **137**, Toluol, rflx, 22 h; m) **17a**/**17b**, MeCN, rflx, 1 h; n) NaOMe, MeOH, RT, 15 min, **138a**/**138b** 30%/25% über 3 Stufen; o) hν, 366 nm 4 W, MeCN/H_2O, RT, 4 d; p) 10% TFA in CH_2Cl_2, 0 °C auf RT, 1 h; q) KF, MeOH, RT, 1 h, 62% über 2 Stufen; r) **104**, NaH, THF, 0 °C, 30 min, dann **19**, RT, 1 h, 67%, de 95%; s) **143**, *n*-BuLi, THF, -78 °C, 15 min, dann **130**, -78 °C auf RT, 1.75 h, 95%; t) **17b**, NEt_3, AgCF3CO2, MS 4Å, THF, 0 °C, Lichtausschluss, 2.5 h, 89%; u) NaOMe, MeOH, RT, 20 min, quant.; v) 10% TFA in CH_2Cl_2, 0 °C auf RT, 0.5 h, 30%; w) KF, MeOH, RT, 0.5 h, 60%.

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5 DARSTELLUNG DES EIGENANTEILS

Die in dieser Dissertation präsentierten Publikationen wurden in Kooperation mit anderen Wissenschaftlern, allen voran Robert G. Haase, Marie Weise, Prof. Ursula Bilitewski und Prof. Rainer Schobert erarbeitet. Im Folgenden wird der Beitrag aller Koautoren zu den jeweiligen Arbeiten detailliert dargestellt.

zu Kapitel 6.1

Diese Arbeit wurde publiziert in Organic Letters (*Org. Lett.* **2016**, *18*, 1136 – 1139) unter dem Titel

„Synthesis and Antibacterial Activity of Four Stereoisomers of the Spider-Pathogenic Fungus Metabolite Torrubiellone D“

von den Autoren *Sebastian Bruckner, Ursula Bilitewski und Rainer Schobert**

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Diese Publikation wurde in Zusammenarbeit mit Prof. Ursula Bilitewski und Prof. Rainer Schobert erstellt. Die Syntheseplanung wurde in Zusammenarbeit mit Prof. Rainer Schobert vorgenommen Die synthetischen Arbeiten und deren analytische Auswertungen wurden von mir durchgeführt. Die HPLC Untersuchungen wurden ebenfalls von mir, mit Unterstützung der Firma Phenomenex, durchgeführt. Die biologischen Untersuchungen der Verbindungen wurden von Prof. Ursula Bilitewski durchgeführt.
Die Publikation wurde von mir in Zusammenarbeit mit Prof. Ursula Bilitewski und Prof. Rainer Schobert verfasst.

Geschätzter Eigenanteil: 80%

zu Kapitel 6.2

Diese Arbeit wurde publiziert in Chemistry – A European Journal (*Chem. Eur. J.* **2017**, *23*, 5692 – 5695) unter dem Titel

„A Synthetic Route to β-Hydroxytyrosine-Derived Tetramic Acids: Total Synthesis of the Fungal Metabolite F-14329“

von den Autoren *Sebastian Bruckner, Robert G. Haase und Rainer Schobert**

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Diese Publikation wurde in Zusammenarbeit mit Robert G. Haase und Prof. Rainer Schobert erstellt. Die Syntheseplanung wurde dabei von Robert G. Haase und mir, unter Anleitung von Prof. Rainer Schobert, vorgenommen. Die synthetische und analytische Arbeit wurde zwischen Robert G. Haase und mir zu jeweils 50% aufgeteilt, wobei Haase die funktionalisierten Acylseitenketten synthetisierte und von mir die Aminoesterbausteine dargestellt und die finalen Syntheseschritte zum fertigen Naturstoff durchgeführt wurden.
Die Publikation wurde von mir in Zusammenarbeit mit Robert G. Haase zu gleichen Teilen und in Zusammenarbeit mit Prof. Rainer Schobert verfasst.

Geschätzter Eigenanteil: 50%

zu Kapitel 6.3

Diese Arbeit wurde publiziert in The Journal of Organic Chemistry (*J. Org. Chem.* **2018**, *83*, 10805 – 10812) unter dem Titel

„Synthesis of the Entomopathogenic Fungus Metabolites Militarinone C and Fumosorinone A“

von den Autoren *Sebastian Bruckner, Marie Weise und Rainer Schobert**

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Diese Publikation wurde in Zusammenarbeit mit Marie Weise und Prof. Rainer Schobert erstellt. Marie Weise hat dabei die Synthese, unter Anleitung von Prof. Rainer Schobert, ausgehend von (*S*)-Citronellol bis Aldehyd **125** selbstständig geplant, durchgeführt und ausgewertet. Die restlichen synthetischen Arbeiten, Planungen und Auswertungen wurden anschließend von mir, unter Anleitung von Prof. Rainer Schobert, durchgeführt.
Diese Publikation wurde von mir in Zusammenarbeit mit Marie Weise und Prof. Rainer Schobert verfasst.

Geschätzter Eigenanteil: 70%

6 PUBLIKATIONEN

6.1 Synthesis and Antibacterial Activity of Four Stereoisomers of the Spider-Pathogenic Fungus Metabolite Torrubiellone D

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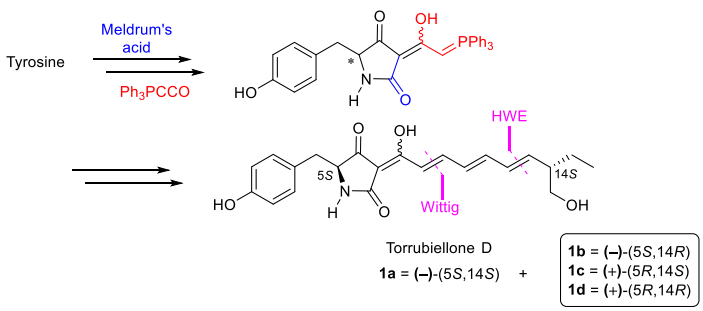

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Organic LETTERS

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Synthesis and Antibacterial Activity of Four Stereoisomers of the Spider-Pathogenic Fungus Metabolite Torrubiellone D

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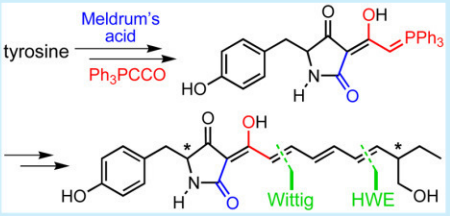
Supporting Information

ABSTRACT: Four stereoisomers of the spider-pathogenic fungus metabolite torrubiellone D were synthesized for the first time in 10% overall yield starting from L-tyrosine or D-tyrosine. The 3-decatrienoyl side chain was assembled and attached via (*E*)-selective HWE and Wittig olefinations. Their antibiotic activities against drug-susceptible *Escherichia coli* strains differed considerably.



Many fungi of the order Hypocreales are pathogenic to insects and feed on them.[1] They are also a rich source of structurally diverse metabolites that may contribute to the infestation of the host and to the defense of its resources against competitors.[1,2] These metabolites are therefore of particular interest as potential leads for new drugs and insecticides. As part of a screening program in Thailand,[3] Isaka et al.[4] assessed the metabolite profiles of 16 *Torrubiella* species,[5] the most prolific of which, *Torrubiella* sp. BCC 2165, was found to produce four hitherto unknown alkaloids, three 2-pyridones and a tetramic acid, torrubiellone D (**1**).

Their structures were elucidated except for the configuration of the stereocenters. A total synthesis of the pyridone (+)-torrubiellone C (**2**) by Gademann et al. proved that the natural (−)-enantiomer, the presumed metabolic product of the tetramic acid torrubiellone D (**1**), has an (*R*)-configured stereocenter in the side chain.[6] Cursory tests of compounds **1** and **2** on *Plasmodium falciparum*, *Mycobacterium tuberculosis*, and three cancer cell lines were negative.[4] We have now synthesized the four diastereomers **1a**−**d** in order to assign the stereochemistry of the natural product and also to evaluate their antibacterial activities (Figure 1).

First, the *N*,*O*-bisprotected tetramic acids (*S*)-**5** and (*R*)-**5** were prepared via a previously published general route[7] starting from enantiopure tyrosine as shown exemplarily for (*S*)-**5** in Scheme 1. L-Tyrosine was Boc-protected to give carbamate (*S*)-**3** which, in turn, was silylated to afford amino acid derivative (*S*)-**4**. This was cyclized to (*S*)-**5** with Meldrum's acid using a modification of Hosseini's protocol.[8]

The 3-decatrienoyl side chain of **1** was then attached to the tetramic acid **5** by first acylating the latter with the cumulated phosphorus ylide $Ph_3P{=}C{=}C{=}O$ to give a 3-acyl ylide which would be used to olefinate a suitably protected octadienal. By a similar approach, we previously synthesized ravenic acid.[9] The required octadienal **16** was prepared in both enantiomeric forms from purchasable enantiopure 2-phenylbutyric acids **6** as

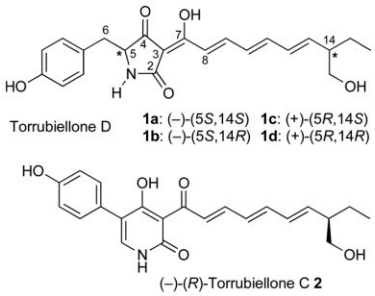


Figure 1. Structures of diastereoisomers of torrubiellone D (**1**) and of natural (−)-torrubiellone C (**2**).

outlined exemplarily for (*R*)-**16** in Scheme 2. Acid (*R*)-**6** was reduced with $LiAlH_4$ to give alcohol (*R*)-**7**, which was converted to the acetate (*R*)-**8** with acetic anhydride in the presence of catalytic copper(II) triflate according to a method by Firouzabadi.[10] Oxidative cleavage of the phenyl ring with $NaIO_4/RuCl_3$ gave the carboxylic acid (*S*)-**9** in 56% yield. The latter was treated with (trimethylsilyl)diazomethane and the resulting diester was selectively saponificated without prior purification to afford 2-(hydroxymethyl)butyrate (*S*)-**10** in 98% over the last two steps.[11] Silylation of the hydroxy group furnished TBS-ether (*S*)-**11**, the methoxycarbonyl residue of which was reduced with DIBAL-H in THF at −78 °C to give the aldehyde (*S*)-**12** in 59% yield. This aldehyde was then olefinated with the anion of phosphonate **13**, generated with LiHMDS in THF. The product ethyl dienoate (*R*)-**14**, obtained in 64% yield, was reduced in 95% yield to the alcohol (*R*)-**15**

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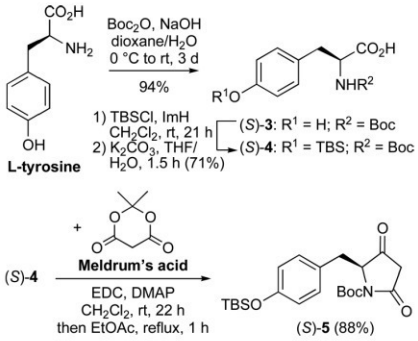
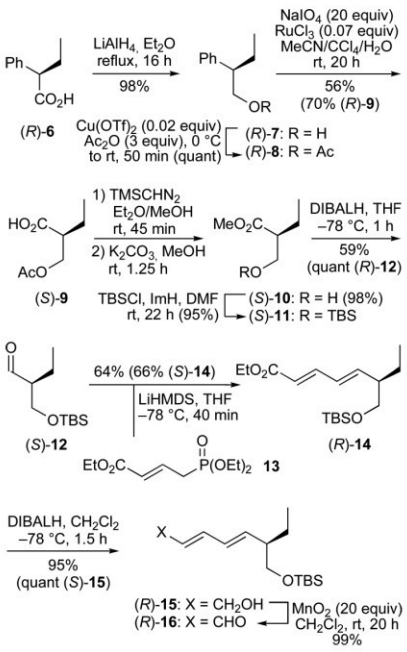
Scheme 1. Synthesis of *N,O*-Bisprotected Tetramic Acid (*S*)-5



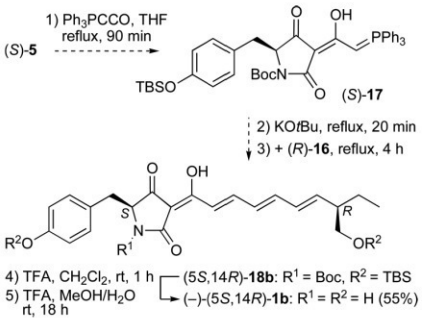
Scheme 2. Synthesis of the Side-Chain Precursor (*R*)-16



with DIBAL-H in dichloromethane. (*R*)-**15** was oxidized with MnO_2 to the dienal (*R*)-**16** almost quantitatively.

Finally, in a sequence of three consecutive reactions in one pot, this aldehyde was converted to the bisprotected tetramic acid (5*S*,14*R*)-**18b** which gave the torrubiellone D isomer (−)-(5*S*,14*R*)-**1b** in 55% overall yield after deprotection (Scheme 3). First, tetramic acid (*S*)-**5** was 3-acylated with Ph_3PCCO to afford the acyl ylide (*S*)-**17** which was deprotonated right away with potassium *tert*-butoxide to give a Wittig-active species of hitherto unknown structure. This, in turn, was treated with aldehyde (*R*)-**16**.[9] The resulting mixture was heated at reflux to afford compound (5*S*,14*R*)-**18b** as the product of an (*E*)-selective Wittig alkenation. It was deprotected stepwise, first with trifluoroacetic acid in dichloromethane and then with the same reagent in a methanol/water mixture to afford the target compound (−)-(5*S*,14*R*)-**1b**. The other three stereoisomers **1a**, **1c**, and **1d** were prepared analogously (cf. the Supporting Information).

Scheme 3. Attachment of the Side Chain via a 3-Acylylidation−Wittig Olefination Sequence



Since all four synthetic stereoisomers of torrubiellone D showed specific optical rotations which deviated from that reported by Isaka et al.[4] for their natural isolate (Table 1), we

Table 1. (Specific) Optical Rotations (*c* = 0.12, MeOH)

	Isaka[4]	1a	1b	1c	1d
α		−0.62	−0.63	+0.64	+0.65
$[\alpha]_D^{23}$	−182	−517	−525	+533	+542

confirmed their stereochemical identity and purity by analytical HPLC on a chiral Phenomenex Lux Amylose-1 column, in comparison to authentic diastereomeric mixtures. Figure 2 shows this for the (5*S*)-torrubiellones D **1a** and **1b** and a mixture of these synthesized from racemic aldehyde **16**.

As the topmost chromatogram, recorded of the diastereomeric mixture of (5*S*)-torrubiellones D, turned out to be an overlay of the chromatograms recorded of the pure synthetic (5*S*)-diastereomers **1a** and **1b**, we can rule out a side-chain racemization during the synthesis of the four stereoisomers. The additional peaks at earlier retention times in the chromatograms of **1a** and **1b** are additive in the chromatogram of the diastereomeric mixture and thus are very likely not impurities but tautomers or rotamers with respect to the C3−C7 bond of the 3-acyltetramic acid moiety. This assumption is also supported by the fact that all peaks showed the same characteristic UV absorption.

The optical rotation of Isaka's natural isolate deviates significantly from those of our pure synthetic stereoisomers. Optical rotations of 3-acyltetramic acids depend decisively on the solvent[12−14] and on the age of the sample solutions since these parameters govern the ratio of tautomers and rotamers whose individual specific optical rotations may vary considerably. Hence, it is hard to tell whether Isaka's natural isolate contained impurities, artifacts, several stereoisomers, or merely a different combination of tautomers or rotamers of one particular of the four possible stereoisomers. It is also worth noting that the configuration of the stereogenic center in the side chain has virtually no influence on the magnitude of the specific optical rotations of the four stereoisomers. Moreover, they all gave rise to virtually identical NMR spectra which are also congruent to the NMR data published by Isaka. The optical rotation of −182 quoted for his natural product isolate would best agree with a mixture of (5*S*)- and (5*R*)-stereoisomers since racemization at C5 is a well-known aspect of tetramic acid chemistry.

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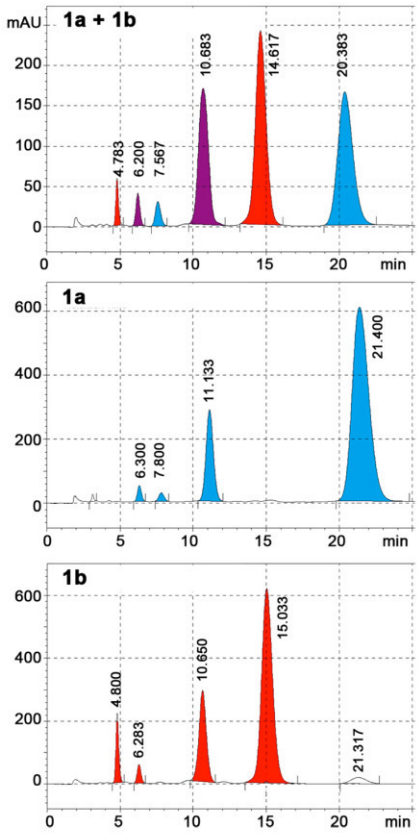

Figure 2. HPLC chromatograms for (5*S*)-torrubiellones D. (Top) Diastereomeric mixture of **1a** and **1b**; (middle) pure **1a**; (bottom) pure **1b** (Phenomenex Lux Amylose-1 100 × 4.6 mm chiral column, mobile phase 40% *n*-hexane, 60% ethanol with 0.1% TFA, flow rate 1 mL/min).

The four synthetic stereoisomers **1a**–**d** of torrubiellone D were finally tested for antibacterial activity against five different bacteria: the Gram-positive strains *Staphylococcus aureus* (DSM346) and *Enterococcus faecium* (DSM20477) and the Gram-negative strains *Escherichia coli* K12 wild-type, *Escherichia coli* Δ*To*lC mutant (JW5503), which lacks the ArcAB–TolC efflux system, and *Escherichia coli* D21f2 with truncated lipopolysaccharide (LPS) core (cf. the Supporting Information for experimental details). The four isomers displayed only weak activity against the Gram-positive bacteria with little variance between the compounds and the two strains. The *S. aureus* was slightly more susceptible to the (14*S*)-isomers **1a** and **1c** (Table 2). A more nuanced picture emerged from the tests with the Gram-negative *E. coli* strains. Wild-type *E. coli* K12 was not susceptible to any of the compounds, which was obviously due to insufficient penetration through the outer LPS layer and to efficient drug efflux pumps of the ArcAB–TolC type. The *E. coli* mutants which had a truncated LPS layer (D21f2) or lacked the TolC efflux pump (Δ*To*lC) were more susceptible than the K12 wild-type. The (5*R*)-isomers **1c** and **1d** gained most strongly from the absence of efflux pumps and reached IC_{50} values of ca. 13 μg/mL (i.e., ca. 35 μM) against *E. coli* Δ*To*lC.

Table 2. IC_{50} Values (μg/mL) of 1a–d for Various Bacteria[a]

	1a	1b	1c	1d
S. aureus	37	53	44	55
E. faecium	40	38	49	39
E. coli K12	>100	>100	>100	>100
E. coli Δ*To*lC	83	30	13	14
E. coli D21f2	62	41	37	39

[a]*S. aureus*: Gram-positive. *E. faecium*: Gram-positive. *E. coli* K12: wild-type, Gram-negative. *E. coli* Δ*To*lC: mutant lacking the ArcAB–TolC efflux system. *E. coli* D21f2: supersusceptible mutant with truncated lipopolysaccharide core.[15]

The (*S*,*S*)-isomer **1a** was least efficacious against both *E. coli* mutants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00245.

Experimental details of chemical syntheses and biological tests, characterizations, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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We thank Yasmin Wenzel and Max Niehage (Helmholtz Centre for Infection Research, Braunschweig, D) for their technical assistance with the microbiological tests.

■ DEDICATION

This paper is dedicated to Professor Steven Victor Ley (University of Cambridge) on the occasion of his 70th birthday.

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DOI: 10.1021/acs.orglett.6b00245
Org. Lett. 2016, 18, 1136−1139

Supporting Information

Synthesis and Antibacterial Activity of Four Stereoisomers of the Spider-Pathogenic Fungus Metabolite Torrubiellone D

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General

IR spectra were recorded with an FT-IR spectrophotometer equipped with an ATR unit. ^{1}H-NMR, ^{13}C-NMR and ^{31}P-NMR spectra were obtained using a Bruker DRX 500 and/or DRX 300 spectrometer. Chemical shifts are given in parts per million using the residual solvent peak as an internal standard acc. to Gottlieb, 7.26 ppm (proton) and 77.16 ppm (carbon) for $CDCl_3$ and 2.05 ppm (proton) and 206.26 and 29.84 ppm (carbon) for acetone-d_6.[1] Coupling constants (J) are quoted in Hz. Multiplicity abbreviation used: s singlet, d doublet, t triplet, q quartet and m multiplet. Mass spectra were obtained under EI (70 eV) conditions on a Thermo Finnigan MAT 8500 spectrometer using a MAT SS 300 data system. High resolution mass spectra were obtained with a UPLC/Orbitrap MS system in ESI mode. Optical rotations were measured at 589 nm (Na-D line) on a PerkinElmer 241 Polarimeter using solutions in chloroform and methanol. For chromatography silica gel 60 (230-400 mesh) was used. All reagents were purchased from commercial sources and were used without further purification. All anhydrous solvents were used as supplied, except tetrahydrofuran and dichloromethane which were freshly distilled according to standard procedures. Reactions were routinely carried out under an argon atmosphere unless stated otherwise. All glassware was flame-dried before use.

Chromatography: Analytical thin layer chromatography (TLC) was carried out using Merck Kieselgel 60GF_{254} pre-coated aluminium-backed plates and/or Merck 60 RP-18 F_{254S} foil plates. The compounds were visualised with UV light (254 nm and/or 360 nm) and/or ceric ammonium molybdate (CAM) and/or potassium permanganate.

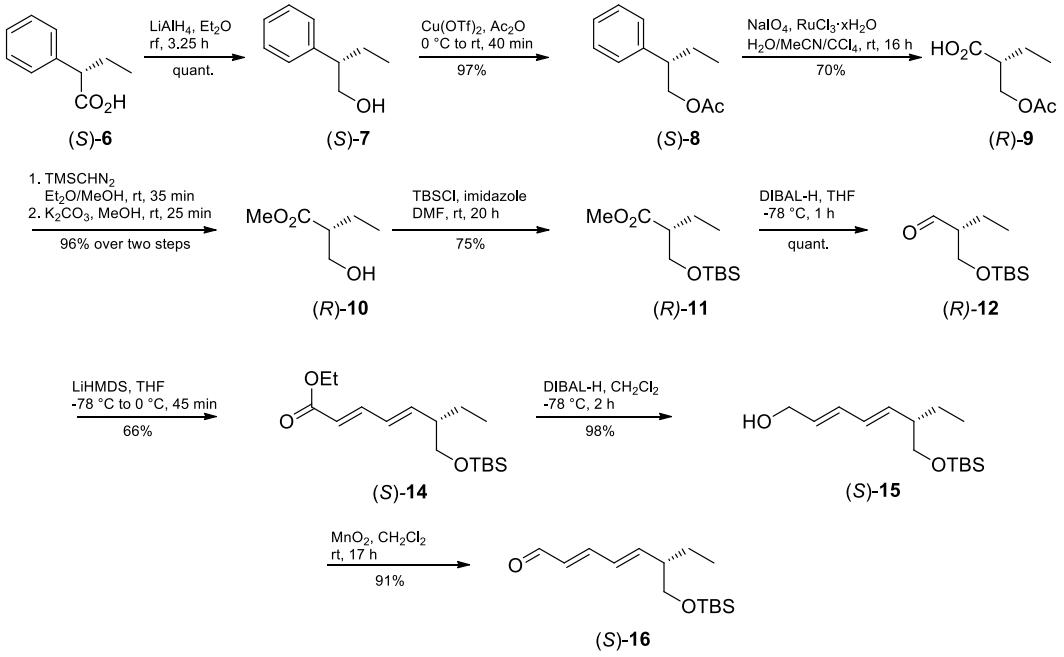
Flash chromatography was performed at medium pressure using dry packed Marchery-Nagel silica gel 60, pore size 40 – 63 µm with the eluent specified.

Analytical HPLC measurements were performed on a Beckman System Gold Programmable Solvent Module 126 using a Phenomenex Kinetex® C-18-HPLC column, length 250 x 4.6 mm, pore size 100 Å, particle size 5 µm. Detection by a Beckman Instruments Diode Array Detection Module 168. Chiral HPLC measurements were performed on a Beckman System Gold Programmable Solvent Module 125 using a Phenomenex Lux® Amylose-1-HPLC column, length 100 x 4.6 mm, pore size 100 Å, particle size 5 µm. Detection by a Beckman Instruments Diode Array Detection Module 168.

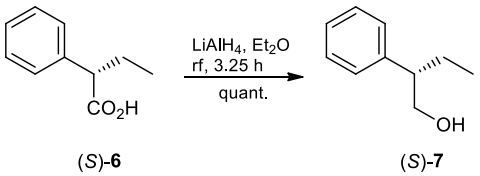
Preparative HPLC was carried out with a Knauer WellChrom K-1800 apparatus equipped with a Phenomenex Kinetex® C-18-HPLC-column, length 200 x 21.1 mm, pore size 100 Å, particle size 5µm. Detection was carried out using a Knauer WellChrom UV-detector K-2600. Program used for torrubiellone D purification: flow rate 14.95 mL/min, mobile phase 65% methanol 35% water with 0.1% formic acid for 7.5 min then to 95% methanol 5% water with 0.1% formic acid in 12.5 min for 40 min.

Procedures

Overview: Synthesis of (S,2E,4E)-6-(((tert-butyldimethylsilyl)oxy)methyl)octa-2,4-dienal (*S*)-16



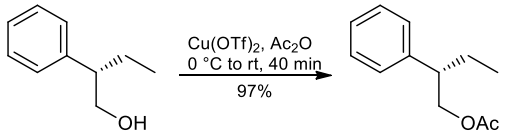
(*S*)-2-Phenylbutan-1-ol (*S*)-7



To a solution of (*S*)-(+)-2-phenylbutyric acid (*S*)-**6** (980 mg, 5.97 mmol, 1.00 eq) in absolute diethyl ether (50 mL) at 0 °C was added lithium aluminium hydride (569 mg, 15.00 mmol, 2.51 eq) and the mixture was heated at reflux for 3.25 h. Then aqueous citric acid (33% wt., 90 mL) was added and the mixture was stirred at ambient temperature for 3 h. The phases were separated and the aqueous phase was extracted with diethyl ether (2 x 150 mL). The combined organic phases were washed with aqueous citric acid (5% wt., 100 mL), saturated aqueous sodium hydrogen carbonate (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* as a colourless oil (895 mg, quant.); R_f = 0.5 (33% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{22}_D$ = +18.4 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 – 7.30 (m, 2H), 7.27 – 7.19 (m, 3H), 3.81 – 3.69 (m, 2H), 2.73 – 2.65 (m, 1H), 1.81 – 1.71 (m,

1H), 1.64 – 1.53 (m, 1H), 1.29 (br. s, 1H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.4, 28.8, 128.3, 126.9, 67.5, 50.6, 25.1, 12.1; IR (cm^{-1}, neat) *v* 3356, 2962, 2926, 2875, 1494, 1451, 1378, 1098, 1036, 759, 697; *m/z* (EI) 150 ([M], 13%), 119 ([M-CH_3O], 42%), 91 ([M^+-C_3H_8O], 100%). Data are consistent with those reported in literature.[2]

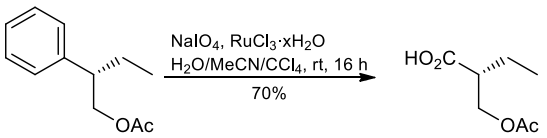
(*S*)-2-Phenylbutyl acetate (*S*)-8



(*S*)-**7** (*S*)-**8**

To a mixture of (*S*)-2-phenylbutan-1-ol (*S*)-**7** (888 mg, 5.91 mmol, 1.00 eq) and acetic anhydride (1.68 mL, 17.73 mmol, 3.00 eq) at 0 °C was added copper (II) triflate (43 mg, 0.12 mmol, 0.02 eq) and the mixture was stirred at ambient temperature for 40 min. Then diethyl ether (20 mL) and saturated aqueous sodium hydrogen carbonate (20 mL) were added, the phases were separated and the organic phase was washed with saturated aqueous hydrogen carbonate (3 x 20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* as a pale yellow oil (1.106 g, 97%); R_f = 0.7 (33% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{25}_D$ = +16.0 (c = 0.65 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 – 7.28 (m, 2H), 7.25 – 7.15 (m, 3H), 4.23 (dd, *J* = 10.8, 6.8 Hz, 1H), 4.19 (dd, *J* = 10.8, 6.9 Hz, 1H), 2.82 (dddd, *J* = 9.3, 6.9, 6.8, 5.2 Hz, 1H), 1.99 (s, 3H), 1.80 (dqd, *J* = 14.8, 7.3, 5.2 Hz, 1H), 1.61 (ddq, *J* = 14.8, 9.3, 7.3 Hz, 1H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 141.9, 128.5, 128.0, 126.8, 68.4, 46.8, 25.5, 11.9; IR (cm^{-1}, neat) *v* 2963, 1738, 1496, 1454, 1365, 1225, 1034, 759, 700; *m/z* (EI) 132 ([M^--$C_2H_3O_2$], 100%), 91 ([M^+-C_3H_8O], 100%). Data are consistent with those reported in literature.[3]

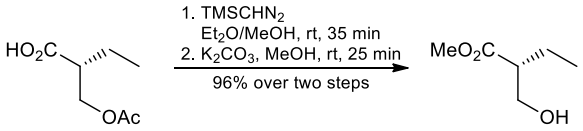
(*R*)-2-(Acetoxymethyl)butanoic acid (*R*)-9



(*S*)-**8** (*R*)-**9**

A mixture of (*S*)-2-phenylbutyl acetate (*S*)-**8** (1.100 g, 5.75 mmol, 1.00 eq), water (21.5 mL), acetonitrile (14.3 mL) and tetrachloromethane (14.3 mL) was treated with sodium periodate (24.597 g, 115 mmol, 20.00 eq) and ruthenium (III) chloride hydrate (84 mg, 0.40 mmol, 0.07 eq) and the resulting mixture was stirred at ambient temperature for 16 h. Dichloromethane (200 mL) and water (150 mL) were added, the phases were separated and the aqueous phase was extracted with dichloromethane (5 x 200 mL). The combined organic phases were washed with saturated aqueous sodium thiosulfate (80 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a dark pink oil, which was purified by flash chromatography on silica gel, eluting with 2% methanol in dichloromethane to give the *title compound* as a pale yellow oil (640 mg, 70%); R_f = 0.4 (10% methanol in dichloromethane, det. $KMnO_4$); $[\alpha]^{23}_D$ = -16.5 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.37 (br. s, 1H), 4.26 (dd, *J* = 11.0, 5.8 Hz, 1H), 4.23 (dd, *J* = 11.0, 7.8 Hz, 1H), 2.68 (dddd, *J* = 7.8, 7.6, 6.2, 5.8 Hz, 1H), 2.06 (s, 3H), 1.72 (ddq, *J* = 14.0, 7.6, 7.5 Hz, 1H), 1.63 (dqd, *J* = 14.0, 7.5, 6.2 Hz, 1H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.5, 171.0, 64.1, 46.2, 22.0, 21.0, 11.5; IR (cm^{-1}, neat) *v* 2968, 1740, 1707, 1463, 1367, 1224, 1040, 928, 824, 776; *m/z* (EI) 130 ([M^--C_2H_5], 7%), 117 ([M-C_2H_3O], 9%); HRMS (ESI) *m/z* [M-H]$^-$ calcd for $C_7H_{11}O_4^-$ 159.0652, found 159.0655. Data are consistent with those reported in literature.[4]

(*R*)-Methyl 2-(hydroxymethyl)butanoate (*R*)-10

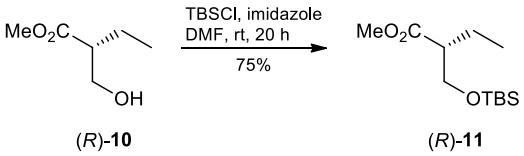


(*R*)-**9** (*R*)-**10**

A solution of (*R*)-2-(acetoxymethyl)butanoic acid (*R*)-**9** (640 mg, 4.00 mmol, 1.00 eq) in diethyl ether (7.8 mL) and methanol (2.6 mL) was treated dropwise with a solution of $TMSCH_2N_2$ in diethyl ether (2M, 2.6 mL, 5.2 mmol, 1.30 eq) and the resulting mixture was stirred at ambient temperature for 35 min. The solvent was removed *in vacuo* and the residual methyl ester was used in the next step without further purification. It was taken up in methanol (6 mL), potassium carbonate (553 mg, 4.00 mmol, 1.00 eq) was added and the mixture was stirred at ambient temperature for 25 min. Then water (30 mL) and diethyl ether (60 mL) were added, the phases were separated and the aqueous phase was extracted with diethyl ether (5 x 30 mL). The combined organic phases were dried (Na_2SO_4), silica gel (1.000 g) was added and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with 25% ethyl acetate in *n*-hexanes to give the *title compound* as a clear oil (505 mg, 96% over two steps); R_f = 0.3 (33% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{23}_D$ = +4.6 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.78 (dd, *J* = 11.0, 7.8 Hz, 1H), 3.72 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.71 (s, 3H), 2.52 (dddd, *J* = 7.8, 7.6, 6.2, 4.3 Hz, 1H), 2.24 (br. s, 1H), 1.67 (ddq, *J* = 14.5, 7.6, 7.5 Hz, 1H), 1.58 (dqd, *J* =

14.5, 7.5, 6.2 Hz, 1H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.9, 62.9, 51.8, 49.1, 21.8, 11.8; IR (cm^{-1}, neat) *v* 3443, 2935, 2880, 1717, 1436, 1379, 1264, 1196, 1170, 1047, 992, 798, 750; *m/z* (EI) 131 ([M^-], 1%), 102 ([M^--C_2H_5], 47%). Data are consistent with those reported in literature.[4]

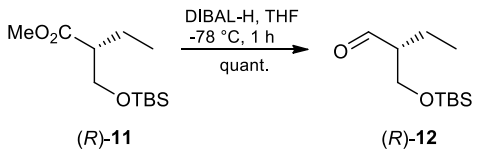
(*R*)-Methyl 2-((*tert*-butyldimethylsilyloxy)methyl)butanoate (*R*)-11



(*R*)-**10** (*R*)-**11**

To a solution of (*R*)-methyl 2-(hydroxymethyl)butanoate (*R*)-**10** (500 mg, 3.78 mmol, 1.00 eq) in DMF (20 mL) were added TBSCl (627 mg, 4.16 mmol, 1.10 eq) and imidazole (566 mg, 8.32 mmol, 2.20 eq) and the mixture was stirred at ambient temperature for 20 h. Then brine (20 mL) was added and the mixture was extracted with *n*-hexane (2 x 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil was purified by flash chromatography on silica gel, eluting with *n*-hexane → 1% diethyl ether in *n*-hexane → 2% diethyl ether in *n*-hexane to give the *title compound* as a clear oil (698 mg, 75%); R_f = 0.6 (10% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{26}_D$ = -10.5 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.76 (dd, *J* = 9.8, 7.9 Hz, 1H), 3.66 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.66 (s, 3H), 2.50 (dddd, *J* = 8.1, 7.9, 6.2, 5.8 Hz, 1H), 1.58 (ddq, *J* = 14.2, 8.1, 7.5 Hz, 1H), 1.53 (dqd, *J* = 14.2, 7.5, 6.2 Hz, 1H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.2, 64.0, 51.4, 50.3, 25.9, 21.7, 11.8, -5.4, -5.4; IR (cm^{-1}, neat) *v* 2956, 2928, 2858, 1739, 1463, 1435, 1388, 1256, 1196, 1174, 1095, 1006, 836, 776, 666; *m/z* (EI) 189 ([M-*t*Bu], 70%), 131 ([M-$SiMe_2$*t*Bu], 7%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{27}O_3Si^+$ 247.1724, found 247.1727. Data are consistent with those reported in literature.[5]

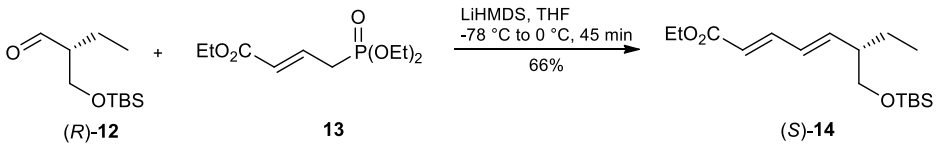
(*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)butanal (*R*)-12



(*R*)-**11** (*R*)-**12**

A solution of (*R*)-methyl 2-((*tert*-butyldimethylsilyloxy)methyl)butanoate (*R*)-**11** (616 mg, 2.50 mmol, 1.00 eq) in CH_2Cl_2 (25 mL) was treated dropwise at –78 °C with a solution of DIBAL-H in *n*-hexane (1M, 2.5 mL, 2.50 mmol, 1.00 eq) and the resulting mixture was stirred at –78 °C for 1 h. Aqueous citric acid (33% wt., 20 ml) was added and the mixture was stirred at ambient temperature for 1.25 h. Then diethyl ether (50 mL) and aqueous citric acid (33% wt., 20 mL) were added, the phases were separated and the organic phase was washed with brine (50 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* as a turbid oil (539 mg, quant.); R_f = 0.4 (6% diethyl ether in *n*-hexane, det. $KMnO_4$); $[\alpha]^{23}_D$ = -21.7 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.70 (d, *J* = 2.4 Hz, 1H), 3.86 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.84 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.34 (ddddd, *J* = 7.3, 6.6, 6.4, 5.1, 2.4 Hz, 1H), 1.71 (dqd, *J* = 14.0, 7.5, 7.3 Hz, 1H), 1.52 (dqd, *J* = 14.0, 7.5, 6.4 Hz, 1H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.1, 61.7, 55.9, 25.9, 18.7, 18.3, 11.6, -5.4; IR (cm^{-1}, neat) *v* 2958, 2929, 2858, 1728, 1463, 1389, 1362, 1253, 1098, 1054, 1006, 939, 834, 775, 667; *m/z* (EI) 159 ([M-*t*Bu], 79%). Data are consistent with those reported in literature.[6]

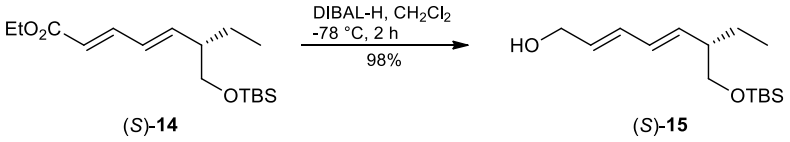
(*S*,2*E*,4*E*)-Ethyl 6-(((*tert*-butyldimethylsilyl)oxy)methyl)octa-2,4-dienoate (*S*)-14



To a solution of triethyl 4-phosphonocrotonate (1.854 g, 7.41 mmol, 3.00 eq) in THF (26 mL) at -78 °C was added a solution of LiHMDS in THF (1M, 7.41 mL, 7.41 mmol, 3.00 eq) and the mixture was stirred at -78 °C for 10 min. Then a solution of the aldehyde (*R*-**12** (536 mg, 2.47 mmol, 1.00 eq) in THF (34 mL) was added and the mixture was stirred at 0 °C for 45 min. After that saturated aqueous ammonium chloride (90 mL) and water (40 mL) were added as a quench and the mixture was extracted with diethyl ether (2 x 200 mL). The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo* and the residual orange oil was purified by flash chromatography on silica gel, eluting with 1.5% diethyl ether in *n*-hexane to give the *title compound* as a clear oil (513 mg, 66%); R_f = 0.3 (6% diethyl ether in *n*-hexane, det. UV_{254}); $[\alpha]^{23.5}_D$ = +24.8 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (dd, *J* = 15.4, 11.1 Hz, 1H), 6.20 (dd, *J* = 15.3, 11.1 Hz, 1H), 5.96 (dd, 15.3, 8.7 Hz, 1H), 5.80 (d, *J* = 15.4 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.56 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.53 (dd, *J* = 9.8, 6.0 Hz, 1H), 2.20 (ddddd, *J* = 8.7, 7.6, 6.0, 5.8, 5.2 Hz, 1H), 1.57 (dqd, *J* = 13.1, 7.6, 5.2 Hz, 1H), 1.30 (ddq, *J* = 13.1, 8.7, 7.6 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.87 (t, *J* = 7.6 Hz, 3H), 0.02 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5, 146.0, 145.1, 129.5, 119.7, 66.0, 60.3, 47.7, 26.0, 23.9, 18.4, 14.5, 11.8, -5.2; IR (cm^{-1}, neat) *v* 2957, 2931, 2858, 1715, 1644, 1618, 1464, 1368, 1302, 1257, 1220, 1182, 1140, 1097, 1046, 1000, 835,

775, 667; *m/z* (EI) 296 ([M^{-}-Me], 3%) 282 ([M^{-}-Et], 12%), 254 ([M^{-}-*t*Bu], 98%); HRMS (ESI) *m/z* [M+H]$^{+}$ calcd for $C_{17}H_{33}O_3Si^{+}$ 313.2193, found 313.2199.

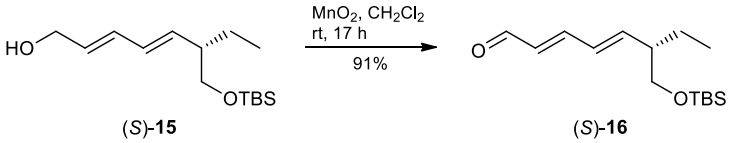
(*S*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyloxy)methyl)octa-2,4-dien-1-ol (*S*)-15



(*S*)-**14** (*S*)-**15**

To a solution of (*S*,2*E*,4*E*)-ethyl 6-(((*tert*-butyldimethylsilyl)oxy)methyl)octa-2,4-dienoate (*S*)-**14** (144 mg, 461 µmol, 1.00 eq) in dichloromethane (6.6 mL) at -78 °C was added a solution of DIBAL-H in hexane (1M, 0.97 mL, 970 µmol, 2.10 eq) and the mixture was stirred at -78 °C for 2 h. Then aqueous citric acid (33% wt., 10mL) was added as a quench and the mixture was stirred at ambient temperature for 25 min. Diethyl ether (20 mL) was added, the phases were separated and the aqueous phase was extracted with diethyl ether (10 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* as a clear oil (122 mg, 98%); R_f = 0.1 (10% diethyl ether in *n*-hexane, det. $KMnO_4$); $[\alpha]^{24}_D$ = +30.5 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.23 (dd, *J* = 15.1, 10.4 Hz, 1H), 6.08 (dd, *J* = 15.3, 10.4 Hz, 1H), 5.75 (dt, *J* = 15.1, 6.0 Hz, 1H), 5.52 (dd, *J* = 15.3, 8.6 Hz, 1H), 4.17 (d, *J* = 6.0 Hz, 2H), 3.53 (dd, *J* = 9.8, 6.1 Hz, 1H), 3.50 (dd, *J* = 9.8, 6.4 Hz, 1H), 2.15 – 2.08 (m, 1H), 1.62 – 1.54 (m, 1H), 1.31 – 1.19 (m, 2H), 0.88 (s, 9H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.0, 132.3, 130.6, 129.9, 66.5, 63.7, 47.3, 26.1, 24.1, 18.5, 11.8, -5.2; IR (cm^{-1}, neat) *v* 3317, 2957, 2929, 2857, 1729, 1463, 1361, 1252, 1086, 987, 939, 834, 774, 667; *m/z* (EI) 213 ([M-*t*Bu], 36%); HRMS (ESI) *m/z* [M+H]$^{+}$ calcd for $C_{15}H_{31}O_2Si^{+}$ 271.2088, found 271.1149.

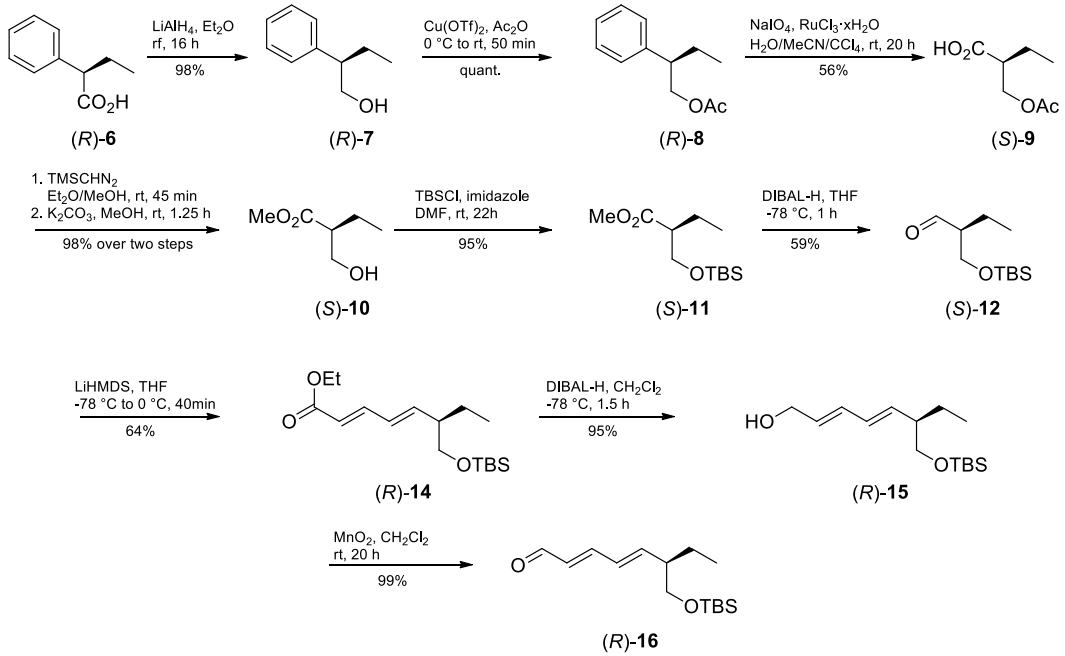
(*S*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyloxy)methyl)octa-2,4-dienal (*S*)-16



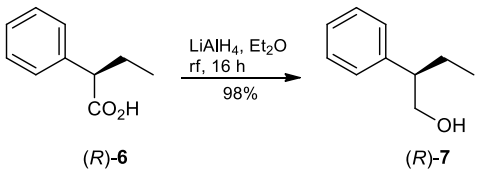
(*S*)-**15** (*S*)-**16**

To a solution of (*S*,2*E*,4*E*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)octa-2,4-dien-1-ol (*S*)-**15** (120 mg, 444 µmol, 1.00 eq) in dichloromethane (10 mL) was added manganese dioxide (771 mg, 8.87 mmol, 20.00 eq) and the mixture was stirred at ambient temperature for 17 h. Then the reaction mixture was filtered over a plug of celite and the plug was rinsed with dichloromethane (60 mL). The filtrate was concentrated *in vacuo* to give the *title compound* as a light yellow oil (109 mg, 91%); R_f = 0.4 (10% diethyl ether in *n*-hexane, det. $KMnO_4$); $[\alpha]^{23.5}_D$ = +36.3 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.55 (d, *J* = 7.9 Hz, 1H), 7.09 (dd, *J* = 15.4, 10.8 Hz, 1H), 6.35 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.13 (dd, *J* = 15.4, 8.7 Hz, 1H), 6.09 (dd, *J* = 15.3, 7.9 Hz, 1H), 3.60 (dd, *J* = 9.9, 5.7 Hz, 1H), 3.56 (dd, *J* = 9.9, 6.4 Hz, 1H), 2.29 – 2.22 (m, 1H), 1.63 – 1.55 (m, 1H), 1.40 – 1.31 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.1, 152.8, 148.8, 130.5, 129.7, 65.7, 47.9, 26.0, 23.8, 18.4, 11.8, -5.2; IR (cm^{-1}, neat) *v* 2958, 2929, 2857, 1686, 1642, 1463, 1254, 1165, 1098, 1009, 988, 836, 776, 666; *m/z* (EI) 211 ([M-*t*Bu], 42%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{29}O_2Si^+$ 269.1931, found 269.1928.

Overview: Synthesis of (R,2E,4E)-6-(((tert-butyldimethylsilyl)oxy)methyl)octa-2,4-dienal (*R*)-16



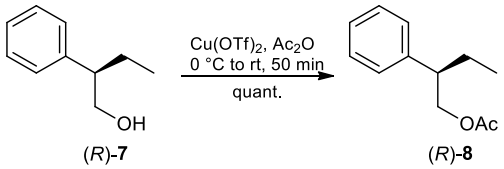
(*R*)-2-Phenylbutan-1-ol (*R*)-7



To a solution of (*R*)-(-)-2-phenylbutyric acid (*R*)-**6** (917 mg, 5.58 mmol, 1.00 eq) in absolute diethyl ether (50 mL) at 0 °C was added lithium aluminium hydride (531 mg, 14.02 mmol, 2.51 eq) and the mixture was heated at reflux for 16 h. Then aqueous citric acid (33% wt., 90 mL) was added and the mixture was stirred at ambient temperature for 3 h. The phases were separated and the aqueous phase was extracted with diethyl ether (2 x 150 mL). The combined organic phases were washed with aqueous citric acid (5% wt., 100 mL), saturated aqueous sodium hydrogen carbonate (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* as a colourless oil (825 mg, 98%); R_f = 0.5 (33% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{25}_D$ = -17.0 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 – 7.30 (m, 2H), 7.27 – 7.18 (m, 3H), 3.81 – 3.69 (m, 2H), 2.73 – 2.65 (m, 1H), 1.81 – 1.71 (m, 1H), 1.64 – 1.53 (m, 1H), 1.31 (br. s, 1H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.4, 128.8, 128.3, 126.8, 67.5, 50.6, 25.1, 12.1; IR (cm^{-1}, neat) *v* 3348, 2960, 2930, 2875, 1494, 1453, 1378, 1099,

1035, 759, 698; *m/z* (EI) 150 ([M], 13%), 119 ([M-CH_3O], 42%), 91 ([M^+-C_3H_8O], 100%). Data are consistent with those reported in literature.[7]

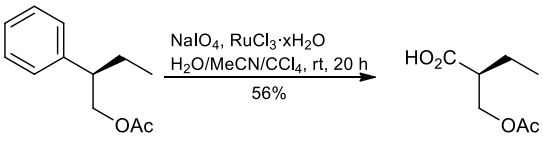
(*R*)-2-Phenylbutyl acetate (*R*)-8



(*R*)-**7** (*R*)-**8**

To a mixture of (*R*)-2-phenylbutan-1-ol (*R*)-**7** (823 mg, 5.48 mmol, 1.00 eq) and acetic anhydride (1.55 mL, 16.44 mmol, 3.00 eq) at 0 °C was added copper (II) triflate (40 mg, 0.11 mmol, 0.02 eq) and the resulting mixture was stirred at ambient temperature for 50 min. Then diethyl ether (20 mL) and saturated aqueous sodium hydrogen carbonate (20 mL) were added, the phases were separated and the organic phase was washed with saturated aqueous hydrogen carbonate (3 x 20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* as a pale yellow oil (1.052 g, quant.); R_f = 0.7 (33% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{23.5}_D$ = -14.5 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 – 7.15 (m, 5H), 4.23 (dd, *J* = 10.8, 6.8 Hz, 1H), 4.19 (dd, *J* = 10.8, 6.9 Hz, 1H), 2.82 (dddd, *J* = 9.3, 6.9, 6.8, 5.2 Hz, 1H), 1.99 (s, 3H), 1.80 (dqd, *J* = 14.8, 7.3, 5.2 Hz, 1H), 1.61 (ddq, *J* = 14.8, 9.3, 7.3 Hz, 1H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 141.9, 128.5, 128.0, 126.8, 68.4, 46.8, 25.5, 11.9; IR (cm^{-1}, neat) *v* 2966, 1739, 1496, 1454, 1365, 1228, 1036, 760, 701; *m/z* (EI) 132 ([M^+-$C_2H_3O_2$], 100%), 91 ([M^+-C_3H_8O], 100%). Data are consistent with those reported in literature.[8]

(*S*)-2-(Acetoxymethyl)butanoic acid (*S*)-9

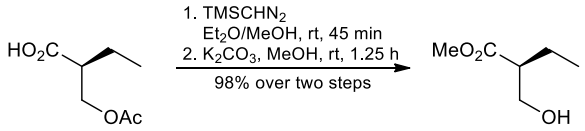


(*R*)-**8** (*S*)-**9**

To a solution of (*R*)-2-phenylbutyl acetate (*R*)-**8** (1.050 g, 5.46 mmol, 1.00 eq) in water (21.5 mL), acetonitrile (14.3 mL) and tetrachlormethane (14.3 mL) were added sodium periodate (23.314 g, 109 mmol, 20.00 eq) and ruthenium (III) chloride hydrate (79 mg, 0.38 mmol, 0.07 eq) and the resulting mixture was stirred at ambient temperature for 20 h. Then dichloromethane (200 mL) and water (150 mL)

were added, the phases were separated and the aqueous phase was extracted with dichloromethane (200 mL). The combined organic phases were washed with saturated aqueous sodium thiosulfate (80 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a dark pink oil, which was purified by flash chromatography on silica gel, eluting with 1.5% methanol in dichloromethane to give the *title compound* as a pale yellow oil (490 mg, 56%); R_f = 0.4 (10% methanol in dichloromethane, det. $KMnO_4$); $[\alpha]^{24}_D$ = +15.3 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.18 (br. s, 1H), 4.25 (dd, *J* = 11.0, 5.8 Hz, 1H), 4.22 (dd, *J* = 11.0, 7.8 Hz, 1H), 2.68 (dddd, *J* = 7.8, 7.6, 6.2, 5.8 Hz, 1H), 2.06 (s, 3H), 1.72 (ddq, *J* = 14.0, 7.6, 7.5 Hz, 1H), 1.63 (dqd, *J* = 14.0, 7.5, 6.2 Hz, 1H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.6, 171.0, 64.1, 46.2, 22.0, 21.0, 11.5; IR (cm^{-1}, neat) *v* 2972, 1740, 1709, 1463, 1367, 1225, 1041, 825, 776; *m/z* (EI) 130 ([M$^-$-C_2H_5], 7%), 117 ([M-C_2H_3O], 9%); HRMS (ESI) *m/z* [M-H]$^-$ calcd for $C_7H_{11}O_4^-$ 159.0663, found 159.0653.

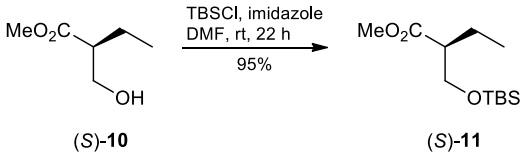
(*S*)-Methyl 2-(hydroxymethyl)butanoate (*S*)-10



(*S*)-**9** (*S*)-**10**

A solution of (*S*)-2-(acetoxymethyl)butanoic acid (*S*)-**9** (480 mg, 3.00 mmol, 1.00 eq) in diethyl ether (6.2 mL) and methanol (1.6 mL) was treated dropwise with a solution of $TMSCH_2N_2$ in diethyl ether (2M, 1.75 mL, 3.5 mmol, 1.17 eq) and the resulting mixture was stirred at ambient temperature for 45 min. The solvent was removed *in vacuo* and the residual methyl ester was used in the next step without further purification. It was taken up in methanol (4.5 mL), potassium carbonate (415 mg, 3.00 mmol, 1.00 eq) was added and the mixture was stirred at ambient temperature for 1.25 h. Then water (30 mL) and diethyl ether (60 mL) were added, the phases were separated and the aqueous phase was extracted with diethyl ether (5 x 30 mL). The combined organic phases were dried (Na_2SO_4), silica gel (1.000 g) was added and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with 25% ethyl acetate in *n*-hexanes to give the *title compound* as a clear oil (389 mg, 98% over two steps); R_f = 0.3 (2% methanol in dichloromethane, det. $KMnO_4$); $[\alpha]^{26}_D$ = -3.3 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.81 – 3.73 (m, 2H), 3.72 (s, 3H), 2.52 (dddd, *J* = 7.8, 7.6, 6.2, 4.3 Hz, 1H), 2.19 (br. s, 1H), 1.67 (ddq, *J* = 14.5, 7.6, 7.5 Hz, 1H), 1.59 (dqd, *J* = 14.5, 7.5, 6.2 Hz, 1H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.9, 62.9, 51.8, 49.0, 21.8, 11.8; IR (cm^{-1}, neat) *v* 3456, 2966, 1717, 1436, 1380, 1264, 1197, 1171, 1048, 992, 798, 750; *m/z* (EI) 102 ([M$^-$-C_2H_5], 47%); HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_6H_{13}O_3^+$ 133.0859, found 133.0860.

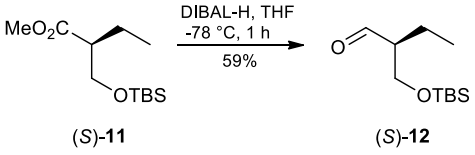
(*S*)-Methyl 2-((*tert*-butyldimethylsilyloxy)methyl)butanoate (*S*)-11



(*S*)-**10** (*S*)-**11**

To a solution of (*S*)-methyl 2-(hydroxymethyl)butanoate (*S*)-**10** (385 mg, 2.91 mmol, 1.00 eq) in DMF (15 mL) were added TBSCl (482 mg, 3.20 mmol, 1.10 eq) and imidazole (436 mg, 6.40 mmol, 2.20 eq) and the mixture was stirred at ambient temperature for 22 h. Then brine (15 mL) was added and the mixture was extracted with *n*-hexane (2 x 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil was purified by flash chromatography on silica gel, eluting with *n*-hexane → 1% diethyl ether in *n*-hexane → 2% diethyl ether in *n*-hexane to give the *title compound* as a clear oil (681 mg, 95%); R_f = 0.6 (10% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{27}_D$ = +10.1 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.77 (dd, *J* = 9.8, 7.9 Hz, 1H), 3.68 (s, 3H), 3.67 (dd, *J* = 9.8, 5.8 Hz, 1H), 2.51 (dddd, *J* = 8.1, 7.9, 6.2, 5.8 Hz, 1H), 1.60 (ddq, *J* = 14.2, 8.1, 7.5 Hz, 1H), 1.54 (dqd, *J* = 14.2, 7.5, 6.2 Hz, 1H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.3, 64.0, 51.5, 50.4, 25.9, 21.7, 11.8, -5.4; IR (cm^{-1}, neat) *v* 2954, 2858, 1739, 1463, 1435, 1388, 1255, 1196, 1174, 1094, 1005, 836, 776, 664; *m/z* (EI) 189 ([M-*t*Bu], 70%), 131 ([M-$SiMe_2$*t*Bu], 7%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{27}O_3Si^+$ 247.1724, found 247.1721. Data are consistent with those reported in literature.[5]

(*S*)-2-((*tert*- butyldimethylsilyloxy)methyl)butanal (*S*)-12

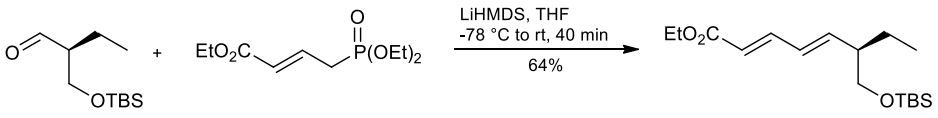


(*S*)-**11** (*S*)-**12**

A solution of (*S*)-methyl 2-((*tert*-butyldimethylsilyloxy)methyl)butanoate (*S*)-**11** (561 mg, 2.28 mmol, 1.00 eq) in CH_2Cl_2 (23 mL) at -78 °C was treated dropwise with a solution of DIBAL-H in *n*-hexane (1M, 2.25 mL, 2.25 mmol, 0.98 eq) and the resulting mixture was stirred at -78 °C for 1 h. Aqueous citric acid (33% wt., 20 ml) was added and the mixture was stirred at ambient temperature for 1.25 h. Diethyl ether (50 mL) and aqueous citric acid (33% wt., 20 mL) were added, the phases were separated and the organic phase was washed with brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give a light cloudy oil which was purified by flash chromatography on silica gel, eluting with 3% diethyl ether in

n-hexane to give the *title compound* as a clear oil (292 mg, 59%); R_f = 0.4 (6% diethyl ether in *n*-hexane, det. $KMnO_4$); $[\alpha]^{27}_D$ = +21.4 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.70 (d, *J* = 2.4 Hz, 1H), 3.86 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.84 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.34 (ddddd, *J* = 7.3, 6.6, 6.4, 5.1, 2.4 Hz, 1H), 1.71 (dqd, *J* = 14.0, 7.5, 7.3 Hz, 1H), 1.52 (dqd, *J* = 14.0, 7.5, 6.4 Hz, 1H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.1, 61.7, 55.9, 25.9, 18.7, 18.4, 11.6, -5.4; IR (cm^{-1}, neat) *v* 2956, 2930, 2861, 1729, 1463, 1387, 1359, 1253, 1102, 1052, 1006, 940, 836, 776; *m/z* (EI) 217 ([M^+], 3%), 159 ([M-*t*Bu], 4%). Data are consistent with those reported in literature.[9]

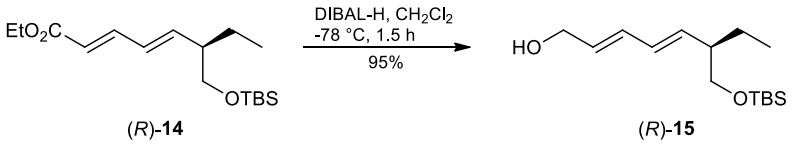
(*R*,2*E*,4*E*)-Ethyl 6-((*tert*-butyldimethylsilyloxy)methyl)octa-2,4-dienoate (*R*)-14



(*S*)-**12** **13** (*R*)-**14**

To a solution of triethyl 4-phosphonocrotonate (1.006 g, 4.02 mmol, 3.00 eq) in THF (15 mL) at -78 °C was added a solution of LiHMDS in THF (1M, 4.00 mL, 4.00 mmol, 3.00 eq) and the mixture was stirred at -78 °C for 10 min. Then a solution of the aldehyde (*S*)-**12** (290 mg, 1.34 mmol, 1.00 eq) in THF (18 mL) was added and the mixture was stirred at ambient temperature for 40 min. After that saturated aqueous ammonium chloride (90 mL) and water (40 mL) were added as a quench and the mixture was extracted with diethyl ether (2 x 200 mL). The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo* and the residual orange oil was purified by flash chromatography on silica gel, eluting with 1% diethyl ether in *n*-hexane → 3% diethyl ether in *n*-hexane to give the *title compound* as a clear oil (269 mg, 64%); R_f = 0.3 (6% diethyl ether in *n*-hexane, det. UV_{254}); $[\alpha]^{28}_D$ = -25.4 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (dd, *J* = 15.4, 11.1 Hz, 1H), 6.20 (dd, *J* = 15.3, 11.1 Hz, 1H), 5.96 (dd, 15.3, 8.7 Hz, 1H), 5.80 (d, *J* = 15.4 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.56 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.53 (dd, *J* = 9.8, 6.0 Hz, 1H), 2.20 (ddddd, *J* = 8.7, 7.6, 6.0, 5.8, 5.2 Hz, 1H), 1.57 (dqd, *J* = 13.1, 7.6, 5.2 Hz, 1H), 1.30 (ddq, *J* = 13.1, 8.7, 7.6 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.87 (t, *J* = 7.6 Hz, 3H), 0.02 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5, 146.0, 145.1, 129.5, 119.7, 66.0, 60.3, 47.7, 26.0, 23.9, 18.4, 14.5, 11.8, -5.2; IR (cm^{-1}, neat) *v* 2957, 2931, 2858, 1715, 1644, 1618, 1464, 1368, 1302, 1257, 1220, 1182, 1140, 1097, 1046, 1000, 835, 775, 667; *m/z* (EI) 297 ([M-Me], 3%) 282 ([M^+-Et], 8%), 255 ([M-*t*Bu], 100%);HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{17}H_{33}O_3Si^+$ 313.2193, found 313.2189. Data are consistent with those reported in literature.[9]

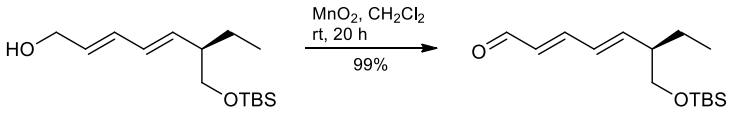
(*R*,2*E*,4*E*)-6-((*tert*-Butyldimethylsilyloxy)methyl)octa-2,4-dien-1-ol (*R*)-15



(*R*)-**14** (*R*)-**15**

To a solution of (*R*,2*E*,4*E*)-ethyl 6-(((*tert*-butyldimethylsilyl)oxy)methyl)octa-2,4-dienoate (*R*)-**14** (134 mg, 430 µmol, 1.00 eq) in dichloromethane (6.2 mL) at -78 °C was added a solution of DIBAL-H in hexane (1M, 0.90 mL, 900 µmol, 2.09 eq) and the mixture was stirred at -78 °C for 2 h. Then aqueous citric acid (33% wt., 10mL) was added as a quench and the mixture was stirred at ambient temperature for 10 min. Diethyl ether (20 mL) was added, the phases were separated and the aqueous phase was extracted with diethyl ether (20 mL). The combined organic phases were washed with aqueous citric acid (5% wt. 20 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* as a clear oil (110 mg, 95%); R_f = 0.1 (10% diethyl ether in *n*-hexane, det. $KMnO_4$); $[\alpha]^{24}_D$ = -28.8 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.22 (dd, *J* = 15.1, 10.4 Hz, 1H), 6.07 (dd, *J* = 15.3, 10.4 Hz, 1H), 5.75 (dt, *J* = 15.1, 6.0 Hz, 1H), 5.52 (dd, *J* = 15.3, 8.6 Hz, 1H), 4.17 (d, *J* = 6.0 Hz, 2H), 3.53 (dd, *J* = 9.8, 6.1 Hz, 1H), 3.49 (dd, *J* = 9.8, 6.4 Hz, 1H), 2.14 – 2.08 (m, 1H), 1.62 – 1.53 (m, 1H), 1.43 (br. s, 1H), 1.30 – 1.19 (m, 1H), 0.88 (s, 9H), 0.86 (t, *J* = 7.5 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.9, 132.2, 130.6, 129.9, 66.5, 63.7, 47.3, 26.1, 24.1, 18.5, 11.8, -5.2, -5.2; IR (cm^{-1}, neat) *v* 3338, 2957, 2929, 2857, 1463, 1381, 1252, 1085, 987, 939, 834, 774, 667; *m/z* (EI) 213 ([M-*t*Bu], 28%). Data are consistent with those reported in literature.[9]

(*R*,2*E*,4*E*)-6-((*tert*-Butyldimethylsilyloxy)methyl)octa-2,4-dienal (*R*)-16

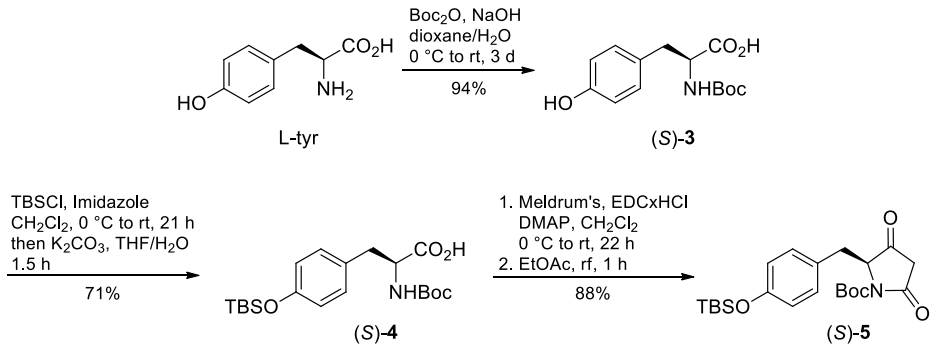


(*R*)-**15** (*R*)-**16**

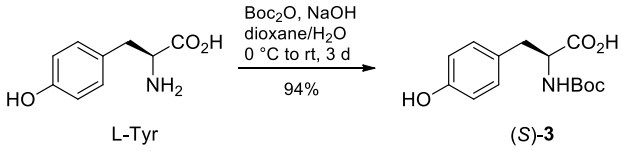
To a solution of (*R*,2*E*,4*E*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)octa-2,4-dien-1-ol (*R*)-**15** (107 mg, 396 µmol, 1.00 eq) in dichloromethane (10 mL) was added manganese dioxide (688 mg, 7.91 mmol, 20.00 eq) and the mixture was stirred at ambient temperature for 20 h. Then the reaction mixture was filtered over a plug of celite and the plug was washed with dichloromethane (60 mL). The filtrate was concentrated *in vacuo* to give the *title compound* as a light yellow oil (109 mg, 91%); R_f = 0.4 (10% diethyl ether in *n*-hexane, det. $KMnO_4$); $[\alpha]^{23.5}_D$ = -36.1 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.54 (d, *J* = 7.9 Hz,

1H), 7.08 (dd, *J* = 15.4, 10.8 Hz, 1H), 6.34 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.12 (dd, *J* = 15.4, 8.7 Hz, 1H), 6.09 (dd, *J* = 15.3, 7.9 Hz, 1H), 3.60 (dd, *J* = 9.9, 5.7 Hz, 1H), 3.56 (dd, *J* = 9.9, 6.4 Hz, 1H), 2.28 – 2.22 (m, 1H), 1.62 – 1.54 (m, 1H), 1.39 – 1.30 (m, 1H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.1, 152.8, 148.8, 130.5, 129.7, 65.7, 47.8, 26.0, 23.8, 18.4, 11.8, -5.3; IR (cm^{-1}, neat) *v* 2957, 2930, 2859, 1686, 1642, 1464, 1255, 1165, 1099, 1009, 988, 837, 776; *m/z* (EI) 211 ([M-*t*Bu], 25%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{29}O_2Si^+$ 269.1931, found 269.1929. Data are consistent with those reported in literature.[9]

Overview: Synthesis of N-(tert-butoxycarbonyl)-(5S)-5-((4-tert-butyldimethylsilyl)oxy)benzyl)-pyrrolidin-2,4-dione (*S*)-5

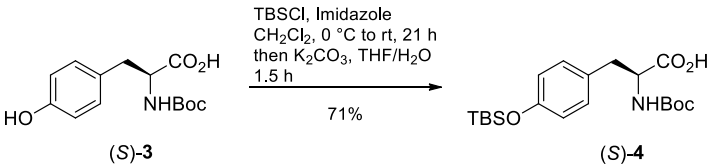


(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanoic acid (*S*)-3



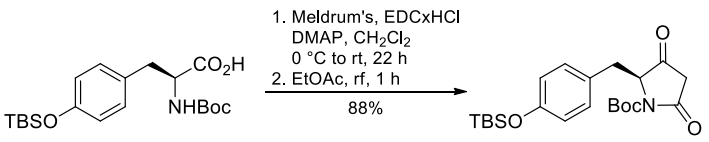
To a suspension of L-tyrosine (3 g, 16.56 mmol, 1.00 eq.) in 33% water in dioxane (120 mL) at 0 °C were added NaOH (1M, 16.6 mL, 16.6 mmol, 1.00 eq.) and di-*tert*-butyl dicarbonate (3.614 g, 16.56 mmol, 1.00 eq.) and the mixture was stirred for 3 d at ambient temperature. The dioxane was removed *in vacuo*, the aqueous phase was cooled to 0 °C and ethyl acetate (15 mL) was added. The pH was adjusted to 2 using aqueous potassium bisulfate (2M, 10 mL) and the mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a clear oil which was coevaporated with dichloromethane to give the *title compound* as a colorless ropy foam (4.400 g, 94%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (br, s, 1H), 6.98 (d, *J* = 7.9 Hz, 2H), 6.72 (d, *J* = 7.9 Hz, 2H), 5.10 – 5.02 (m, 1H), 4.61 – 4.52 (m, 1H), 3.09 – 2.98 (m, 1H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.1, 155.0, 130.7, 127.6, 115.8, 54.6, 37.2, 28.5, 14.3; IR (cm^{-1}, neat) *v* 3333, 2979, 1681, 11615, 1515, 1446, 1394, 1368, 1224, 1157, 1052, 827, 778. Data are consistent with those reported in literature.[10]

(*S*)-2-(*tert*-Butoxycarbonylamino)-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoic acid (*S*)-4



To a solution of L-Boc-tyrosine (*S*)-**3** (9.308 g, 33.09 mmol, 1.00 eq.) in dichloromethane (250 mL) at 0 °C were added imidazole (6.758 g, 99.27 mmol, 3.00 eq.) and TBSCl (10.972 g, 72.80 mmol, 2.20 eq.) and the mixture was stirred for 21 h at ambient temperature. Dichloromethane was removed *in vacuo* before water (200 mL), THF (100 mL) and potassium carbonate (2.3 g, 16.50 mmol, 0.50 eq.) were added and the mixture was stirred for 1.5 h at ambient temperature. Then the mixture was neutralized with HCl (0.5M, 66 mL) and the product was extracted with ethyl acetate (200 mL). The solvent was removed *in vacuo* and the residual yellow oil was purified by flash chromatography on silica gel, eluting with 10% ethyl acetate and 1% formic acid in *n*-hexane → 20% ethyl acetate and 1% formic acid in *n*-hexane to give the *title compound* after coevaporation with toluene as a colourless oily solid foam (9.257 g, 71%); R_f = 0.5 (80% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{24}_D$ = +15.4 (c = 1.00 $CHCl_3$);^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.45 (br. s, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.77 (d, *J* = 8.2 Hz, 2H), 5.05 – 4.83 (m, 1H), 4.69 – 4.44 (m, 1H), 3.19 – 2.79 (m, 2H), 1.42 (s, 9H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.8, 155.6, 154.9, 130.5, 128.6, 120.3, 80.4, 54.5, 37.1, 28.4, 25.8, 18.3, -4.3; IR (cm^{-1}, neat) *v* 2931, 2859, 1714, 1611, 1509, 1473, 1393, 1367, 1251, 1162, 1103, 1054, 1025, 912, 837, 779, 686, 631, 572; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{20}H_{32}NO_5Si^-$ 394.2055, found 394.2051. Data are consistent with those reported in literature.[11]

N-(*tert*-Butoxycarbonyl)-(5*S*)-5-((4-*tert*-butyldimethylsilyl)oxy)benzyl)-pyrrolidin-2,4-dione (*S*)-5

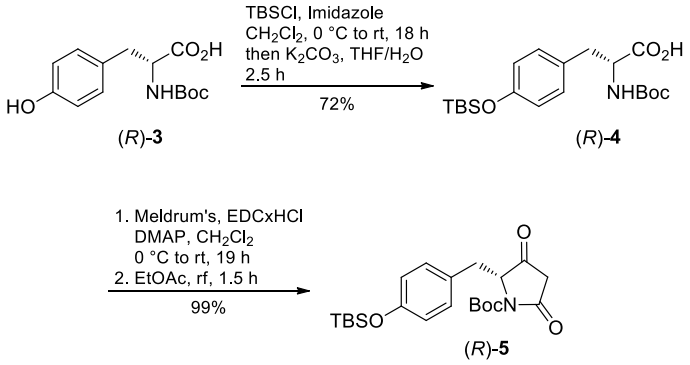


(*S*)-**4** (*S*)-**5**

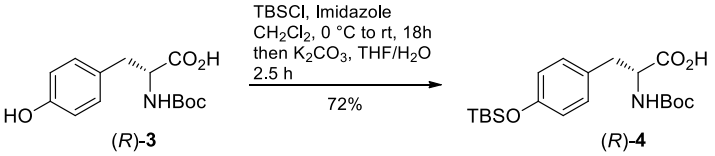
A solution of bisprotected tyrosine (*S*)-**4** (1 g, 2.53 mmol, 1.00 eq.) in dichloromethane (10 mL) at 0 °C was treated with Meldrum's acid (382 mg, 2.65 mmol, 1.05 eq.) and DMAP (464 mg, 3.80 mmol, 1.50 eq.). Then a suspension of EDCxHCl (583 mg, 3.04 mmol, 1.20 eq.) in dichloromethane (7 mL) was added drop-wise and the resulting mixture was stirred for 22 h at ambient temperature. Ethyl acetate (25 mL) and diethyl ether (20 mL) were added and the mixture was washed with water (20 mL), aqueous potassium bisulfate (5% wt., 2 x 30 mL), water (25 mL) and brine (30 mL). The organic phase was then dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. This oil was taken up in ethyl acetate (150 mL) and the solution was heated at reflux for 1 h before the solvent was removed *in vacuo* to give the *title compound* as a colorless solid foam (930 mg, 88%); R_f = 0.4 (10% methanol in dichloromethane, det. UV, CAM); $[\alpha]^{24}_D$ = +63.9 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 4.64 – 4.56 (m, 1H), 3.33 (dd, *J* = 14.2, 5.0 Hz, 1H), 3.14 (dd, *J* = 14.2, 2.9 Hz, 1H), 2.84 (d, *J* = 22.4 Hz, 1H), 2.23 (d, *J* = 22.4 Hz, 1H), 1.62 (s, 9H), 0.96 (s, 9H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$, 125

MHz) δ 204.6, 167.5, 155.4, 149.2, 131.1, 126.5, 120.7, 84.4, 68.6, 43.5, 35.9, 28.2, 25.8, 18.3, -4.3; IR (cm^{-1}, neat) *v* 2932, 1756, 1712, 1607, 1510, 1472, 1362, 1250, 1150, 1075, 912, 837, 809, 778, 686; HRMS (ESI) *m/z* [M+Na] calcd for $C_{22}H_{33}NNaO_5Si$ 442.2020, found 442.2014.

Overview: Synthesis of N-(tert-butoxycarbonyl)-(5R)-5-((4-tert-butyldimethylsilyl)oxy)benzyl)-pyrrolidin-2,4-dione (*R*)-5



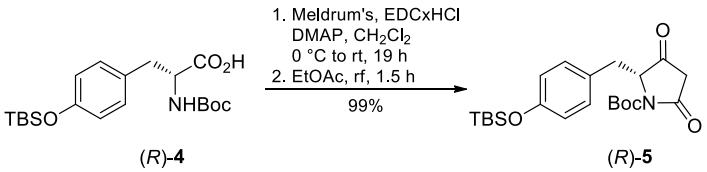
(*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoic acid (*R*)-4



To a solution of *R*-Boc-tyrosine (*R*)-**3** (1 g, 3.55 mmol, 1.00 eq.) in dichloromethane (36 mL) at 0 °C were added imidazole (725 mg, 10.65 mmol, 3.00 eq.) and TBSCl (1.070 g, 7.10 mmol, 2.20 eq.) and the mixture was stirred for 18 h at ambient temperature. A colorless solid formed which was filtered off and the filtrate was concentrated *in vacuo* to give a yellow oil. The oil was taken up in THF (12 mL) and water (24 mL) before potassium carbonate (246 mg, 1.78 mmol, 0.50 eq.) was added and the mixture was stirred at ambient temperature for 1.5 h. Then saturated aqueous ammonium chloride (150 mL) and ethyl acetate (200 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 200 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo to give a colourless oil. The oil was purified by flash chromatography on silica gel, eluting with 5% ethyl acetate and 0.1% formic acid in *n*-hexane → 10% ethyl acetate and 0.1% formic acid in *n*-hexane → 20% ethyl acetate and 0.1% formic acid in *n*-hexane → 25% ethyl acetate and 0.1% formic acid in *n*-hexane to give the *title compound* after coevaporation with toluene as a colorless ropy foam (1.006 g, 72%); R_f = 0.5 (80% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{24}_D$ = -16.2 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.11 (br. s, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 2H), 4.98 – 4.84 (m, 1H), 4.61 – 4.49 (m, 1H), 3.19 – 2.79 (m, 2H), 1.42 (s, 9H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.6, 155.6, 154.9, 130.5, 128.4, 120.3, 80.4, 54.5, 37.1, 28.4, 25.8, 18.3, -4.3; IR (cm^{-1}, neat) *v* 2931, 2859, 1714, 1610, 1509, 1473, 1393, 1368, 1251, 1163, 1103, 1054, 1026, 912,

837, 779, 687; HRMS (ESI) *m/z* [M-H]$^-$ calcd for $C_{20}H_{32}NO_5Si^-$ 394.2055, found 394.2051. Data were consistent with those reported in literature.[12]

N-(*tert*-Butoxycarbonyl)-(5*R*)-5-((4-*tert*-butyldimethylsilyl)oxy)benzyl)-pyrrolidin-2,4-dione (*R*)-5

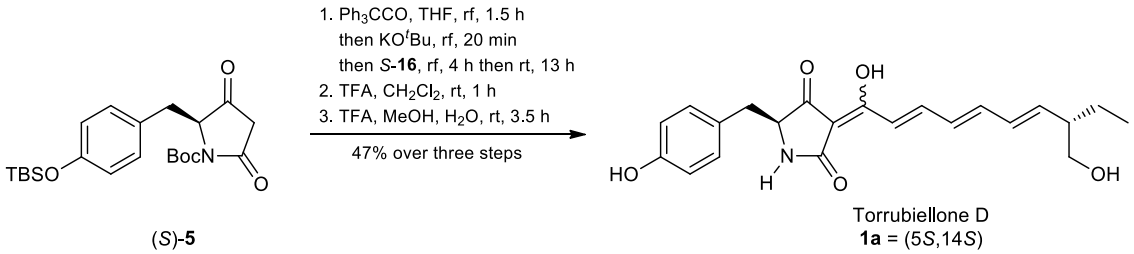


(*R*)-**4** (*R*)-**5**

To a solution of bisprotected tyrosine (*R*)-**4** (966 mg, 2.44 mmol, 1.00 eq.) in dichloromethane (17 mL) at 0 °C were added Meldrum's acid (369 mg, 2.56 mmol, 1.05 eq.) and DMAP (447 mg, 3.66 mmol, 1.50 eq.). Then a suspension of EDCxHCl (562 mg, 2.93 mmol, 1.20 eq.) in dichloromethane (7 mL) was added drop-wise and the mixture was stirred for 19 h while being allowed to reach ambient temperature. Ethyl acetate (25 mL) and diethyl ether (25 mL) were added and the mixture was washed with water (20 mL), saturated aqueous ammonium carbonate (2 x 50 mL), aqueous potassium bisulfate (5% wt. 2 x 30 mL), aqueous citric acid (5% wt., 20 mL), water (20 mL) and brine (20 mL). The organic phase was then dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. This oil was taken up in ethyl acetate (150 mL) and the resulting solution was heated at reflux for 1 h before the solvent was removed *in vacuo* to give the *title compound* as a colorless solid foam (1.012 g, 99%); R_f = 0.4 (10% methanol in dichloromethane, det. UV, CAM); $[\alpha]^{22}_D$ = -72.0 (c = 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 4.60 (ddd, *J* = 5.0, 2.8, 1.8 Hz, 1H), 3.33 (dd, *J* = 14.2, 5.0 Hz, 1H), 3.14 (dd, *J* = 14.2, 2.8 Hz, 1H), 2.84 (d, *J* = 22.3 Hz, 1H), 2.23 (dd, *J* = 22.3, 1.8 Hz, 1H), 1.62 (s, 9H), 0.95 (s, 9H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.6, 167.5, 155.4, 149.2, 131.0, 126.5, 120.7, 84.4, 68.6, 43.5, 35.9, 28.2, 25.8, 18.3, -4.3; IR (cm^{-1}, neat) *v* 2931, 1756, 1714, 1608, 1510, 1473, 1363, 1252, 1151, 1077, 912, 837, 809, 778, 686; HRMS (ESI) *m/z* [M+Na] calcd for $C_{22}H_{33}NNaO_5Si$ 442.2020, found 442.2014.

Syntheses of torrubiellones D 1a-d and of (–)-(5*S*,14*R/S*)-torrubiellone D 19

(5*S*,14*S*)-Torrubiellone D 1a

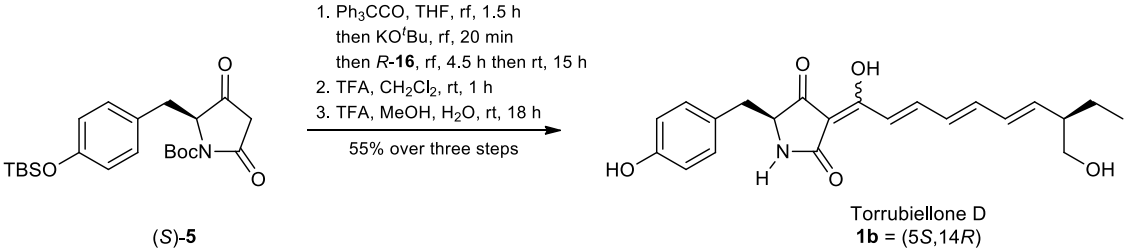


A solution of tetramic acid (*S*)-**5** (185 mg, 442 µmol, 1.10 eq) in THF (25 mL) at reflux was treated dropwise with a solution of ketenylidentriphenylphosphorane (134 mg, 442 µmol, 1.10 eq) in THF (10 mL) over 10 min and the resulting mixture was stirred at reflux for a further 1.5 h. Potassium *tert*-butanolate (50 mg, 442 µmol, 1.10 eq) was added and the mixture was stirred at reflux for 20 min. After that, a solution of aldehyde (*S*)-**16** (108 mg, 402 µmol, 1.00 eq) in THF (5 mL) was added dropwise over 5 min and the mixture was stirred at reflux for 4 h. It was then cooled to ambient temperature and stirred for 13 h before the solvent was removed *in vacuo* to leave an orange oil which was taken up in dichloromethane (20 mL). The resulting solution was washed with saturated aqueous ammonium chloride (30 mL), the aqueous phase was extracted with dichloromethane (4 x 30 mL), and the combined organic phases were concentrated *in vacuo* to give an orange oil which was purified by flash chromatography on RP-18 silica gel, eluting with 20% water in methanol → methanol. The product containing fractions were pooled and concentrated *in vacuo*. The remaining aqueous phase was repeatedly extracted with dichloromethane (2 x 15 mL), and the combined organic extracts were dried (Na_2SO_4) to give bisprotected (5*S*,14*S*)-torrubiellone D **18a** which was used in the next step without further purification.

The crude **18a** was taken up in 15% trifluoroacetic acid in dichloromethane (20 mL) and stirred at ambient temperature for 1 h, methanol was added, and the mixture was reduced to half its volume. Then trifluoroacetic acid (2 mL) and water (2 mL) were added and the resulting mixture was stirred at ambient temperature for 3.5 h. Toluene (20 mL) was added and the solvent was removed to leave half of the initial volume. Two phases had formed which were separated and the aqueous phase was extracted with dichloromethane (4 x 50 mL). The combined organic phases were concentrated *in vacuo* to give an oily yellow soild which was taken up in 35% water in methanol (40 mL) and purified by preparative HPLC. The product containing fractions were pooled, stripped of their methanol, and the aqueous phase was extracted with diethyl ether (5 x 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. This was taken up in methanol and filtered over Sephadex LH-20. The solvent was coevaporated with acetone to give the *title compound* as an amorphous orange-yellow solid (73 mg, 47% over three steps); $[\alpha]^{23}_D$ = -516 (c = 0.12 MeOH); ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.13 (br. s, 1H), 7.71 (br. s, 1H), 7.47 (dd, *J* = 15.2, 11.4 Hz, 1H), 7.12 (d, *J* = 15.2 Hz, 1H), 7.03

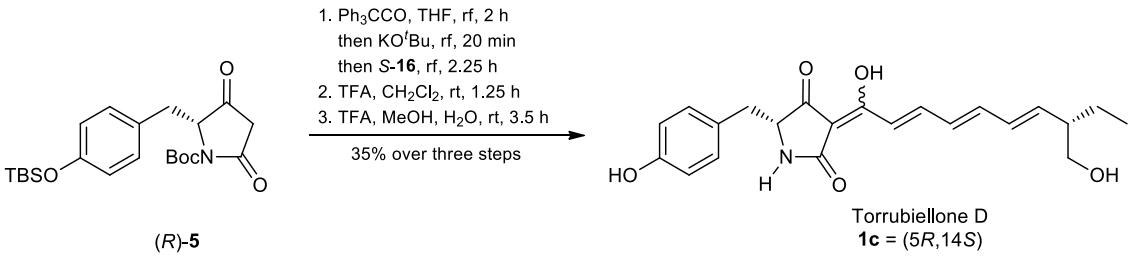
(d, *J* = 8.2 Hz, 2H), 6.83 (dd, *J* = 14.6, 11.1 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 2H), 6.53 (dd, *J* = 14.6, 11.4 Hz, 1H), 6.37 (dd, *J* = 15.2, 11.1 Hz, 1H), 5.97 (dd, *J* = 15.2, 8.8 Hz, 1H), 4.13 – 4.05 (m, 1H), 3.53 (d, *J* = 6.0 Hz, 2H), 3.04 (dd, *J* = 14.1, 3.9 Hz, 1H), 2.84 (dd, 14.1, 6.7 Hz, 1H), 2.28 – 2.19 (m, 1H), 1.68 – 1.56 (m, 1H), 1.39 – 1.24 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 195.2, 176.4, 173.9, 157.0, 145.0, 144.7, 144.6, 132.2, 131.6, 130.1, 127.9, 121.3, 116.0, 101.1, 65.7, 64.0, 48.9, 37.4, 24.6, 12.0; IR (cm^{-1}, neat) *v* 3279, 2919, 1652, 1588, 1550, 1515, 1425, 1367, 1225, 1170, 1007, 895, 869, 813; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{26}NO_5^+$ 384.1806, found 384.1795.

(5*S*,14*R*)-Torrubiellone D 1b



Analogously to **1a**, isomer **1b** (81 mg, 55% over three steps) was obtained as an amorphous orange-yellow solid from tetramic acid (*S*)-**5** (185 mg, 442 µmol, 1.15 eq), ketenylidentriphenylphosphorane (134 mg, 442 µmol, 1.15 eq), potassium *tert*-butanolate (50 mg, 442 µmol, 1.15 eq), and aldehyde (*R*)-**16** (103 mg, 384 µmol, 1.00 eq); $[\alpha]^{23}_D$ = -525 (c = 0.12 MeOH); ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.13 (br. s, 1H), 7.71 (br. s, 1H), 7.47 (dd, *J* = 15.2, 11.4 Hz, 1H), 7.12 (d, *J* = 15.2 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.83 (dd, *J* = 14.6, 11.1 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 2H), 6.53 (dd, *J* = 14.6, 11.4 Hz, 1H), 6.37 (dd, *J* = 15.2, 11.1 Hz, 1H), 5.97 (dd, *J* = 15.2, 8.8 Hz, 1H), 4.10 (br. s, 1H), 3.53 (d, *J* = 6.0 Hz, 2H), 3.03 (dd, *J* = 14.0, 4.3 Hz, 1H), 2.84 (dd, 14.0, 7.0 Hz, 1H), 2.28 – 2.19 (m, 1H), 1.67 – 1.57 (m, 1H), 1.38 – 1.28 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 195.2, 176.3, 173.9, 157.0, 145.0, 144.7, 144.6, 132.2, 131.6, 130.1, 127.9, 121.3, 116.0, 101.1, 65.7, 64.0, 48.9, 37.4, 24.6, 12.0; IR (cm^{-1}, neat) *v* 3236, 2921, 1643, 1586, 1543, 1515, 1424, 1368, 1224, 1169, 1006, 893, 867, 813; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{26}NO_5^+$ 384.1806, found 384.1806.

(5*R*,14*S*)-Torrubiellone D 1c

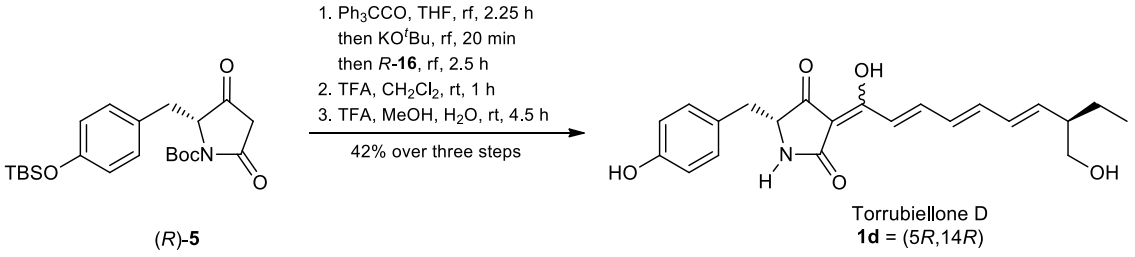


(*R*)-**5**

Torrubiellone D
1c = (5*R*,14*S*)

Analogously to **1a**, isomer **1c** (52 mg, 35% over three steps) was obtained as an amorphous orange-yellow solid from tetramic acid (*R*)-**5** (189 mg, 450 µmol, 1.15 eq), ketenylidentriphenylphosphorane (136 mg, 450 µmol, 1.15 eq), potassium *tert*-butanolate (51 mg, 450 µmol, 1.15 eq), and aldehyde (*S*)-**16** (105 mg, 391 µmol, 1.00 eq); $[\alpha]^{23}_{D}$ = +533 (c = 0.12 MeOH); ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.13 (br. s, 1H), 7.71 (br. s, 1H), 7.47 (dd, *J* = 15.2, 11.4 Hz, 1H), 7.12 (d, *J* = 15.2 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.83 (dd, *J* = 14.6, 11.1 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 2H), 6.53 (dd, *J* = 14.6, 11.4 Hz, 1H), 6.37 (dd, *J* = 15.2, 11.1 Hz, 1H), 5.97 (dd, *J* = 15.2, 8.8 Hz, 1H), 4.10 (dd, *J* = 6.0, 4.4 Hz, 1H), 3.53 (d, *J* = 6.0 Hz, 2H), 3.04 (dd, *J* = 14.2, 4.4 Hz, 1H), 2.83 (dd, 14.2, 6.9 Hz, 1H), 2.26 – 2.19 (m, 1H), 1.70 – 1.57 (m, 1H), 1.38 – 1.26 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 195.2, 176.4, 174.0, 157.0, 145.0, 144.7, 144.6, 132.2, 131.6, 130.1, 127.9, 121.3, 116.0, 101.1, 65.7, 64.0, 48.9, 37.4, 24.6, 12.0; IR (cm^{-1}, neat) *v* 3236, 2922, 1643, 1586, 1542, 1514, 1424, 1368, 1222, 1169, 1005, 893, 867, 810; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{26}NO_5^+$ 384.1806, found 384.1805.

(5*R*,14*R*)-Torrubiellone D 1d



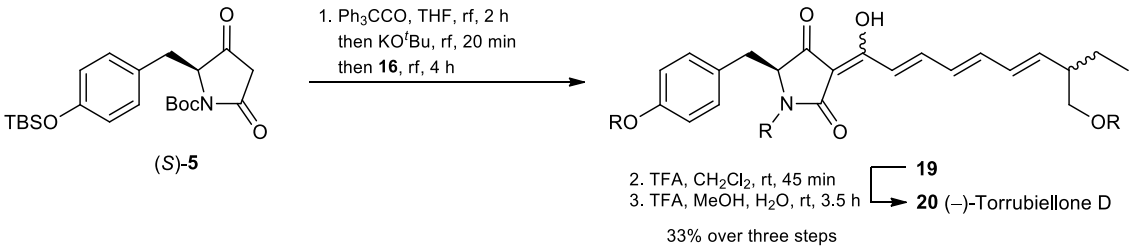
(*R*)-**5**

Torrubiellone D
1d = (5*R*,14*R*)

Analogously to **1a**, isomer **1d** (46 mg, 42% over three steps) was obtained as an amorphous orange-yellow solid from tetramic acid (*R*)-**5** (136 mg, 325 µmol, 1.15 eq), ketenylidentriphenylphosphorane (98 mg, 325 µmol, 1.15 eq), potassium *tert*-butanolate (36 mg, 325 µmol, 1.15 eq), and aldehyde (*R*)-**16** (76 mg, 283 µmol, 1.00 eq); $[\alpha]^{23}_{D}$ = +542 (c = 0.12 MeOH); ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.14 (br. s, 1H), 7.69 (br. s, 1H), 7.47 (dd, *J* = 15.2, 11.4 Hz, 1H), 7.13 (d, *J* = 15.2 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.82 (dd, *J* = 14.6, 11.1 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 2H), 6.53 (dd, *J* = 14.6, 11.4 Hz, 1H), 6.37 (dd, *J* = 15.2, 11.1 Hz, 1H), 5.96 (dd, *J* = 15.2, 8.8 Hz, 1H), 4.09 (br. s, 1H), 3.53 (d, *J* = 6.0 Hz, 2H), 3.04 (dd, *J* = 14.1,

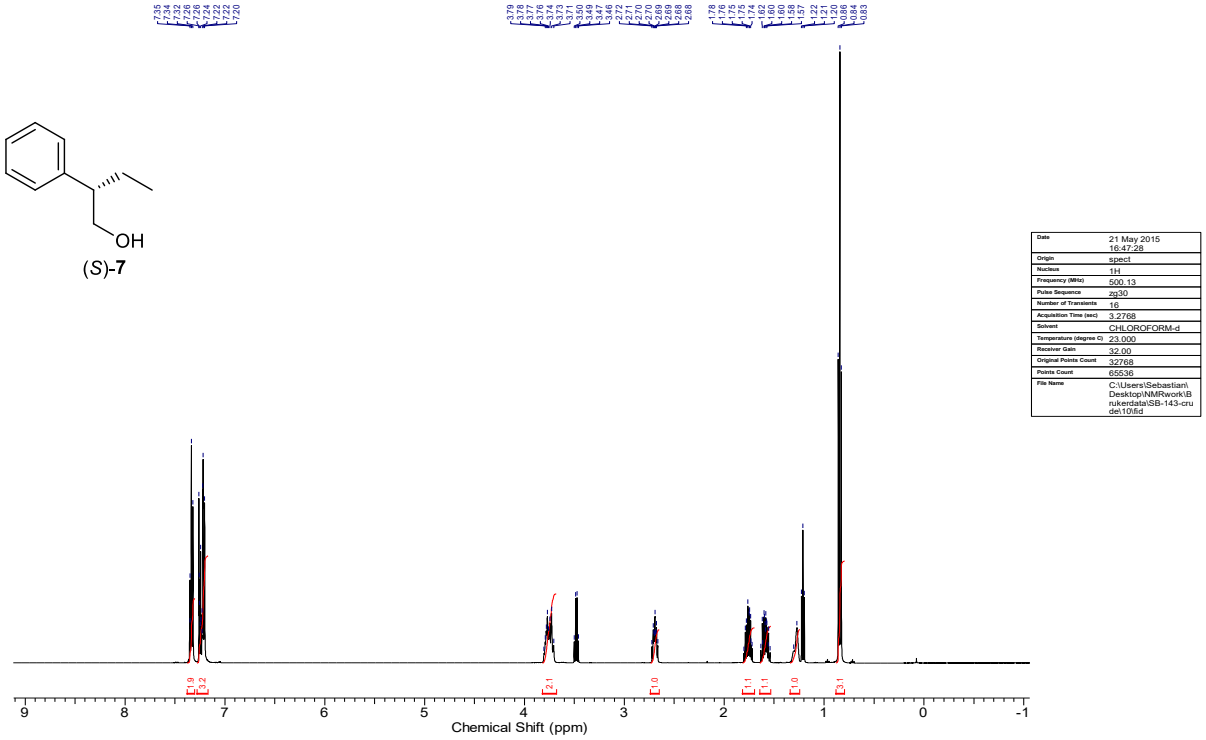
3.9 Hz, 1H), 2.83 (dd, 14.1, 6.7 Hz, 1H), 2.28 – 2.19 (m, 1H), 1.66 – 1.56 (m, 1H), 1.38 – 1.27 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 195.2, 176.4, 173.5, 157.0, 144.9, 144.6, 144.5, 132.2, 131.6, 130.2, 127.9, 121.5, 116.0, 101.1, 65.7, 64.0, 48.8, 37.5, 24.6, 12.0; IR (cm^{-1}, neat) *v* 3222, 2921, 1644, 1586, 1542, 1514, 1424, 1367, 1222, 1169, 1005, 893, 867, 813; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{22}H_{26}NO_5^+$ 384.1806, found 384.1806.

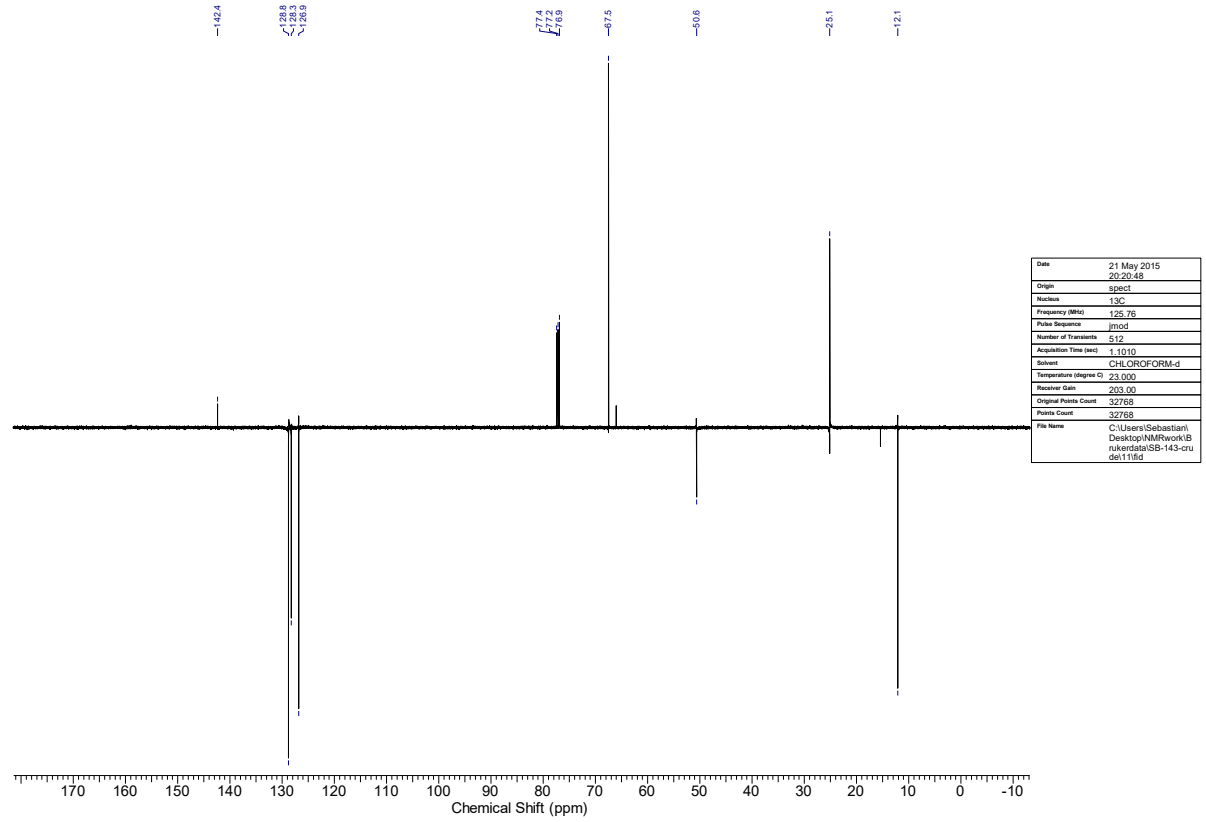
(–)-(5*S*,14*R/S)*-Torrubiellone D 19

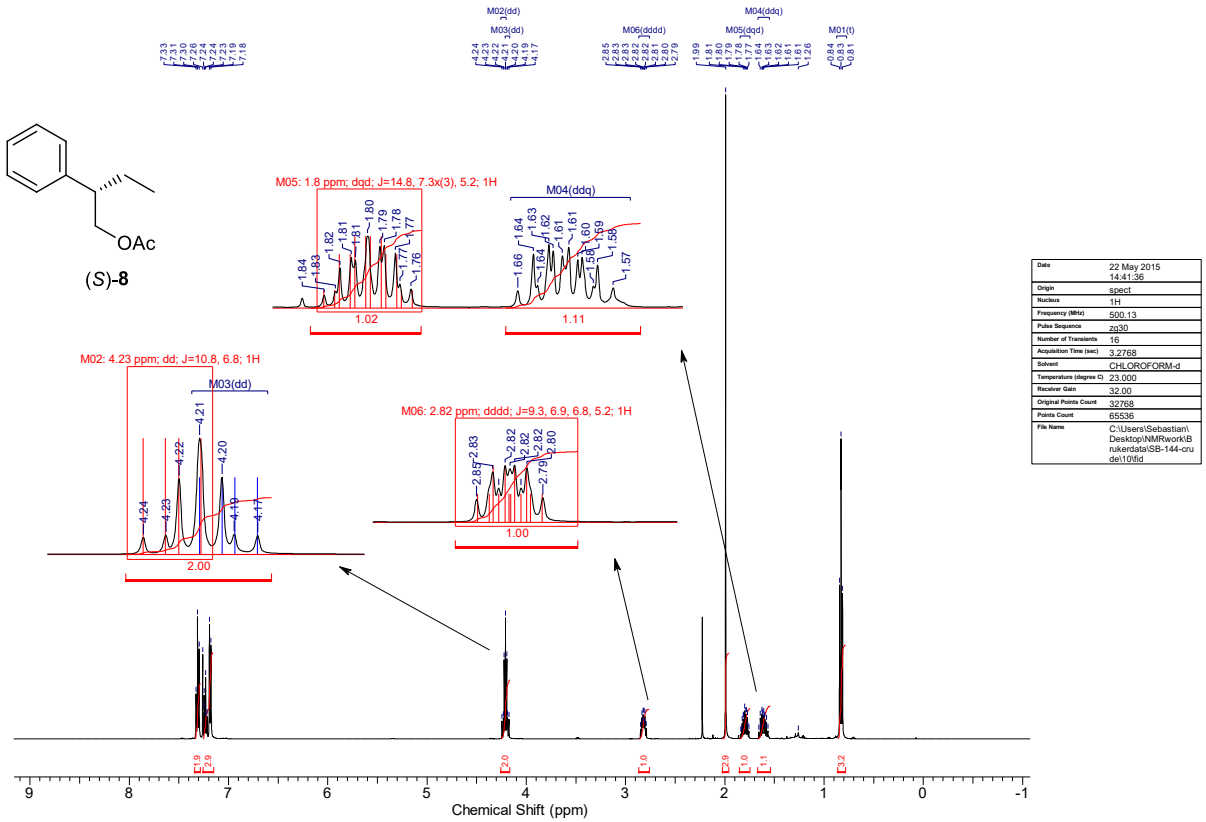


Analogously to **1a**, a 1:1-mixture of diastereoisomers **1a** and **1b** (61 mg, 33% over three steps) was obtained as an amorphous orange-yellow solid from tetramic acid (*S*)-**5** (200 mg, 477 µmol, 1.00 eq), ketenylidentriphenylphosphorane (146 mg, 482 µmol, 1.01 eq), potassium *tert*-butanolate (54 mg, 477 µmol, 1.00 eq), and racemic aldehyde (*R/S*)-**16** (128 mg, 477 µmol, 1.00 eq); ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.17 (br. s, 1H), 7.73 (br. s, 1H), 7.47 (dd, *J* = 15.3, 11.4 Hz, 1H), 7.12 (d, *J* = 15.3 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.82 (dd, *J* = 14.5, 10.9 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.53 (dd, *J* = 14.5, 11.4 Hz, 1H), 6.36 (dd, *J* = 15.2, 10.9 Hz, 1H), 5.97 (dd, *J* = 15.2, 8.7 Hz, 1H), 4.10 (br. s, 1H), 3.53 (d, *J* = 6.0 Hz, 2H), 3.04 (dd, *J* = 14.0, 3.8 Hz, 1H), 2.84 (dd, 14.0, 6.7 Hz, 1H), 2.28 – 2.19 (m, 1H), 1.66 – 1.56 (m, 1H), 1.38 – 1.27 (m, 1H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 195.3, 176.3, 173.9, 157.0, 145.0, 144.7, 144.6, 132.2, 131.6, 130.1, 127.8, 121.3, 115.9, 101.1, 65.7, 64.0, 48.8, 37.4, 24.6, 12.0; IR (cm^{-1}, neat) *v* 3212, 2929, 1645, 1587, 1545, 1515, 1427, 1369, 1226, 1170, 1007, 893, 868, 813.

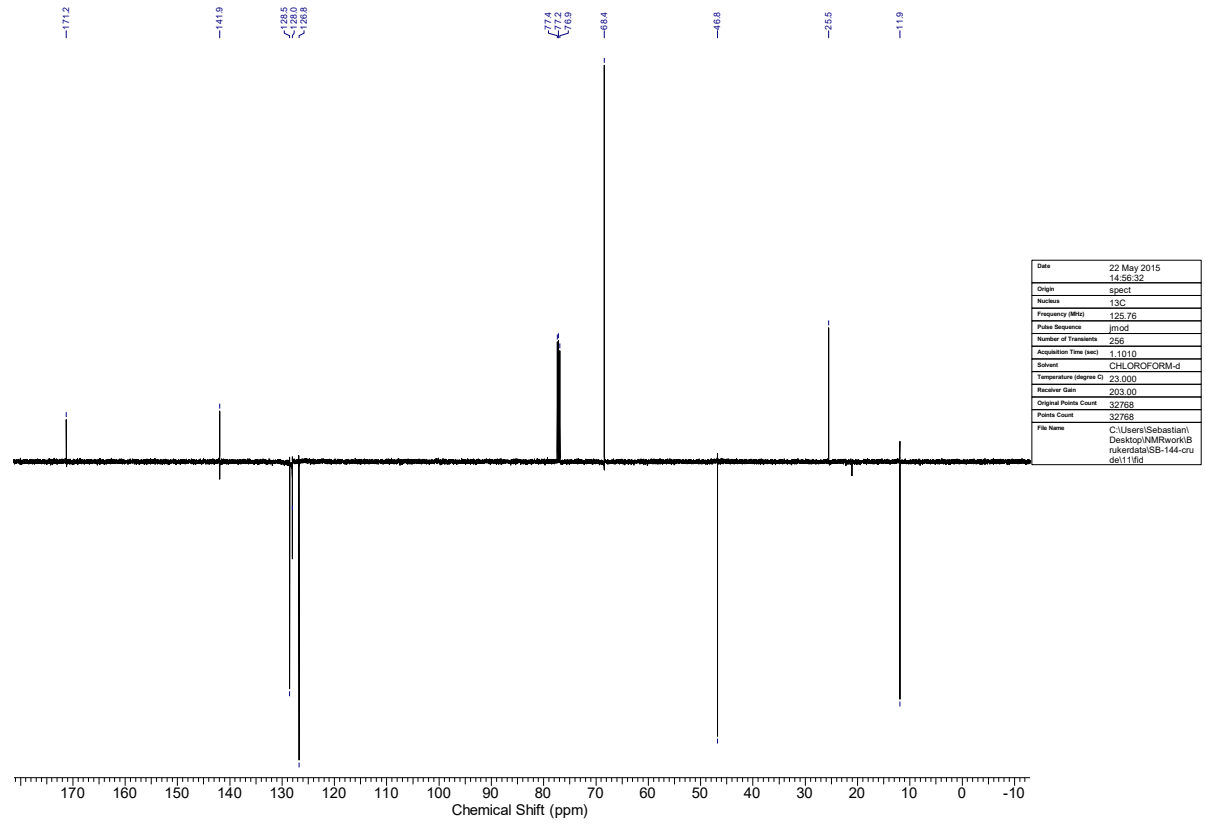
NMR Spectra and HPLC



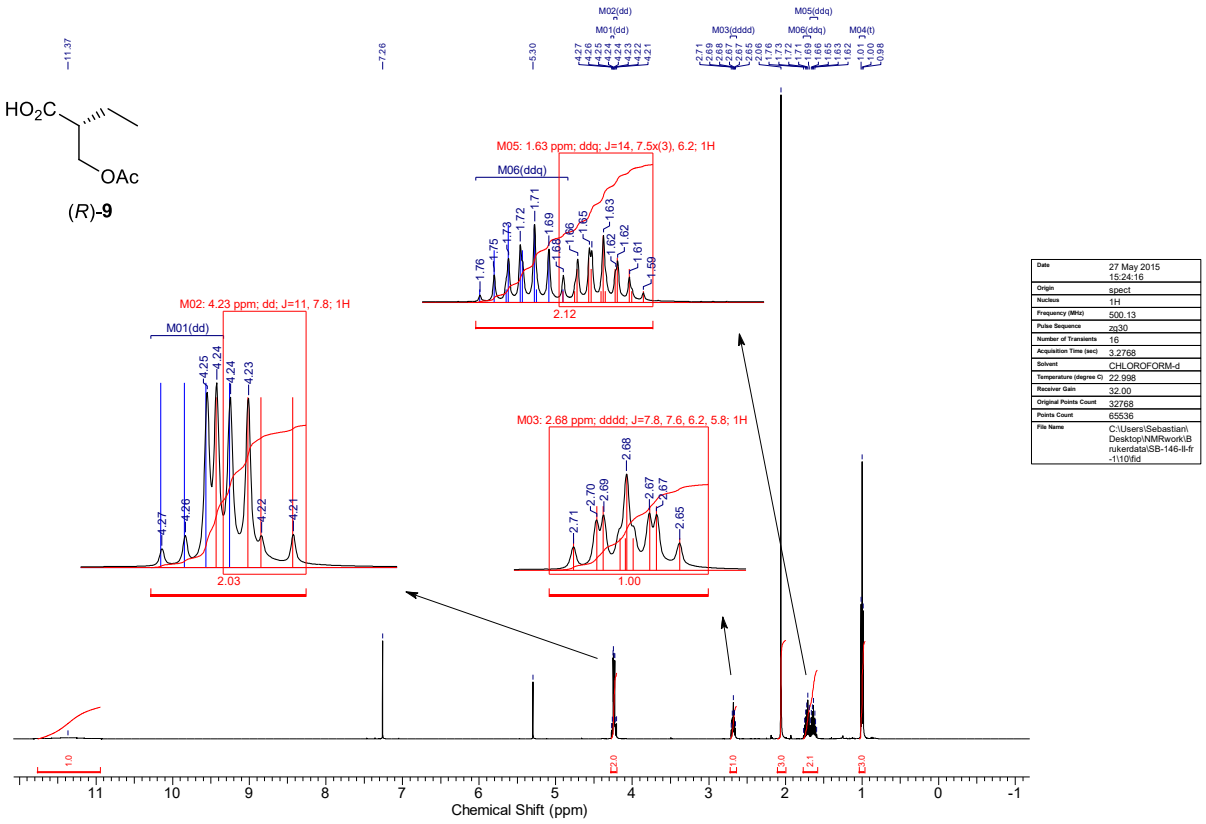


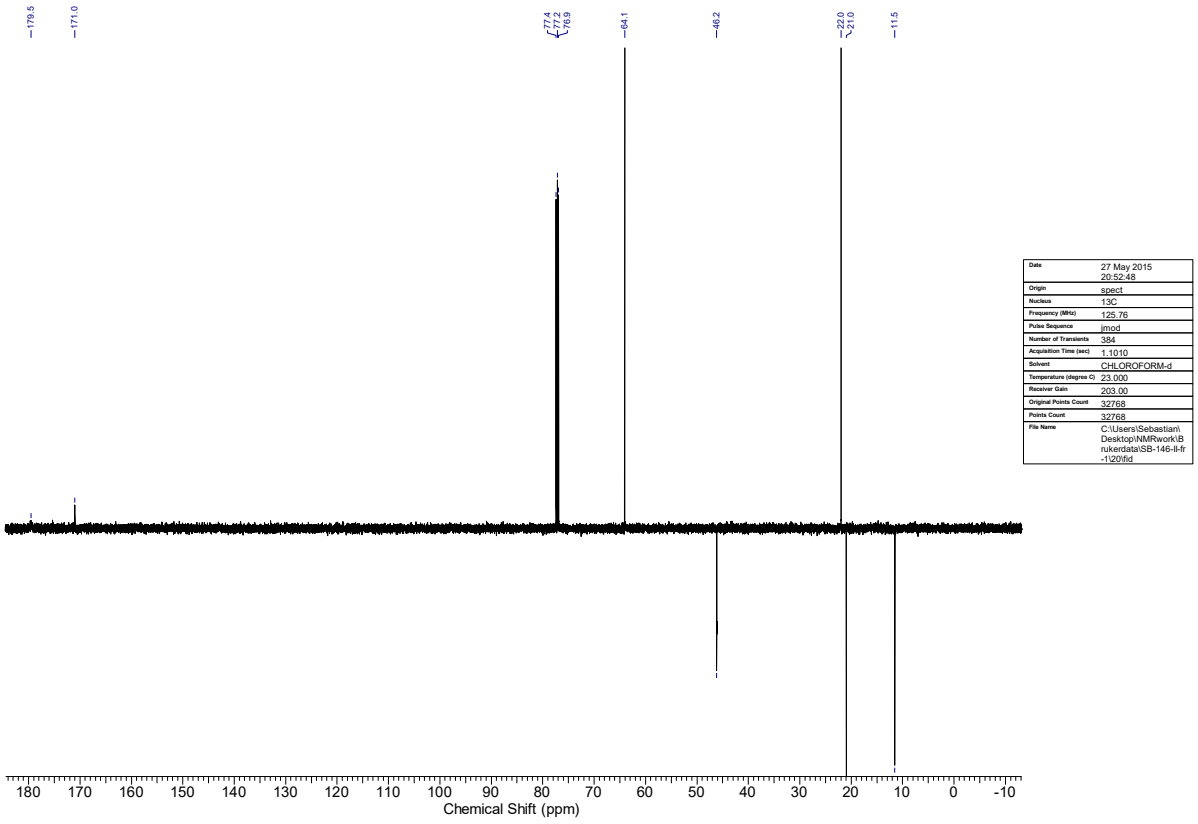


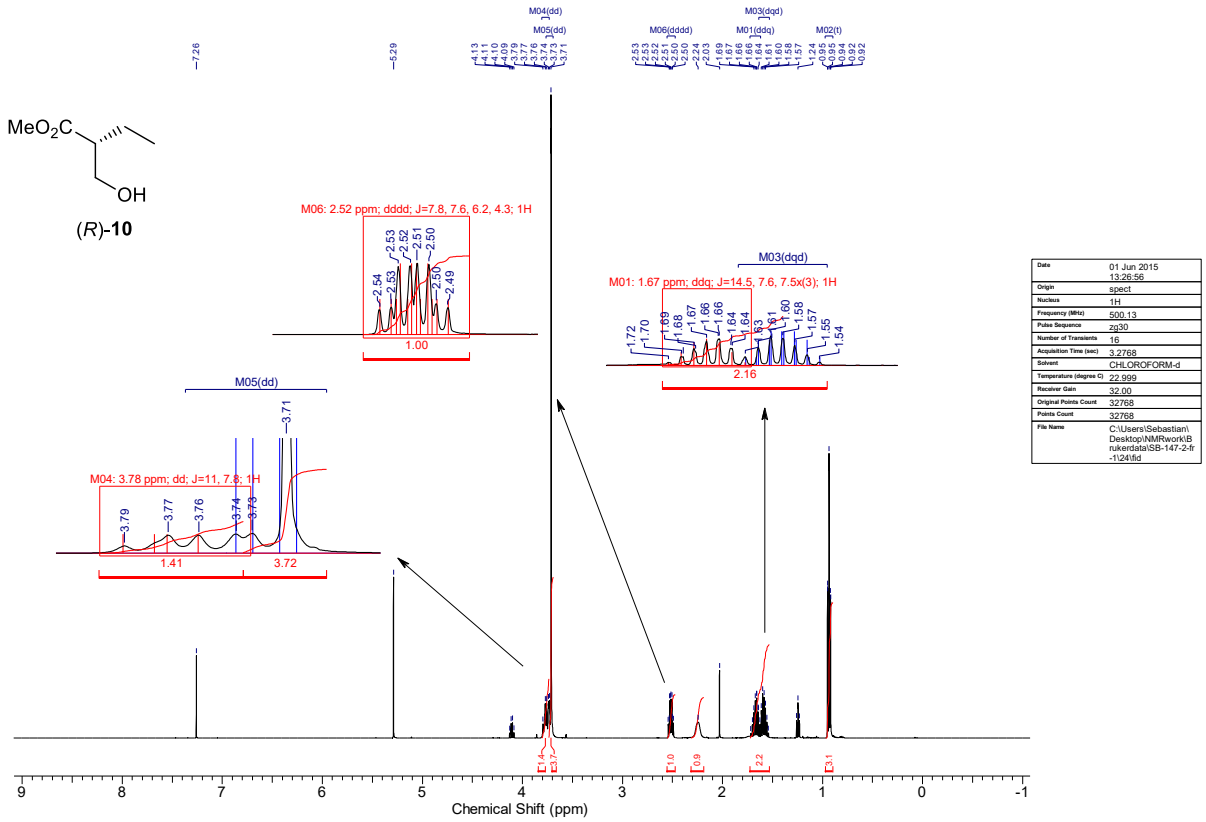
Date	22 May 2015 14:41:36
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	CHLOROFORM-d
Temperature (degree C)	23.000
Receiver Gain	32.00
Original Points Count	32768
Points Count	65536
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-144-crude\10\fid



Date	22 May 2015 14:56:32
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	jmod
Number of Transients	256
Acquisition Time (sec)	1.1010
Solvent	CHLOROFORM-d
Temperature (degree C)	23.000
Receiver Gain	203.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-144-crude\11\fid


HO2C
OAc
(R)-9
M05: 1.63 ppm; ddq; J=14, 7.5x(3), 6.2; 1H
M06(ddq)
2.12
M02: 4.23 ppm; dd; J=11, 7.8; 1H
M01(dd)
2.03
M03: 2.68 ppm; dddd; J=7.8, 7.6, 6.2, 5.8; 1H
1.00
Chemical Shift (ppm)


Chemical Shift (ppm)



Date	01 Jun 2015 13:26:56
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	CHLOROFORM-d
Temperature (degree C)	22.999
Receiver Gain	32.00
Original Points Count	32768
Points Count	32768
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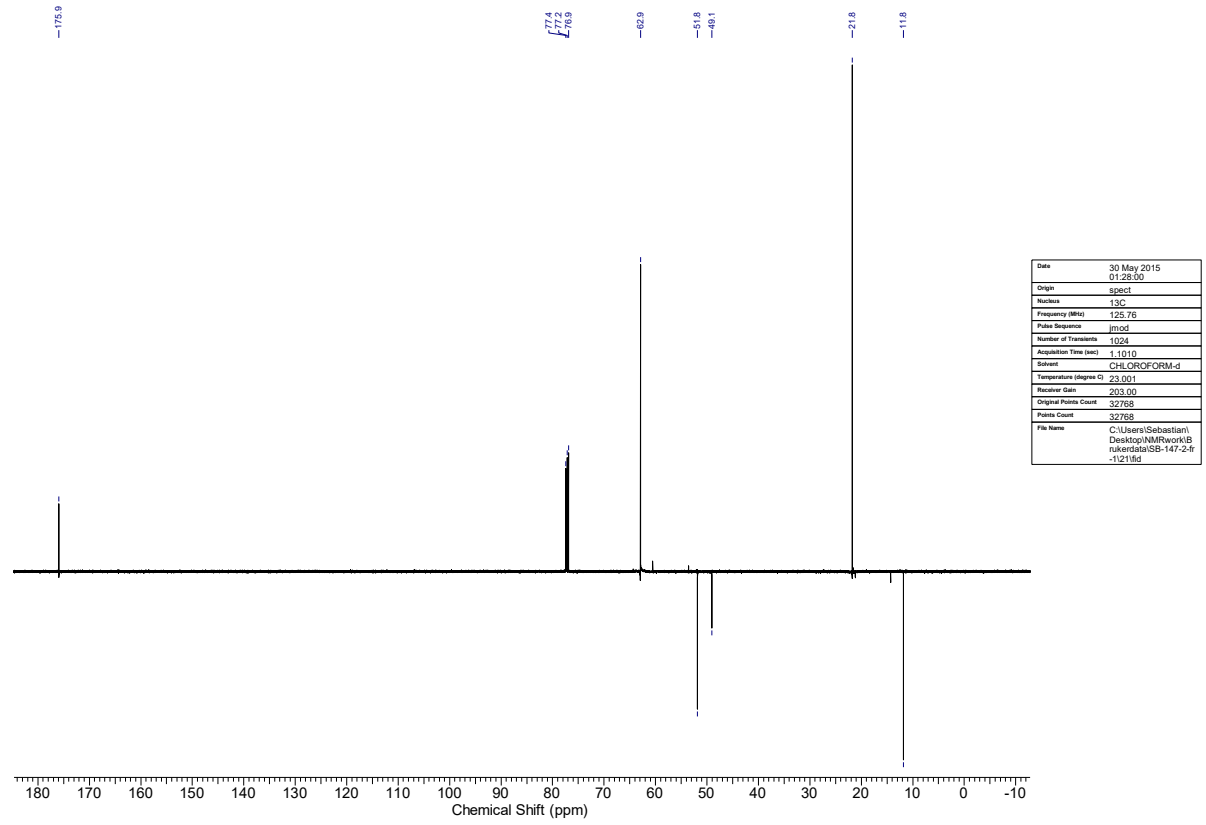

Date	30 May 2015 01:28:00
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	jmod
Number of Transients	1024
Acquisition Time (sec)	1.1010
Solvent	CHLOROFORM-d
Temperature (degree C)	23.001
Receiver Gain	203.00
Original Points Count	32768
Points Count	32768
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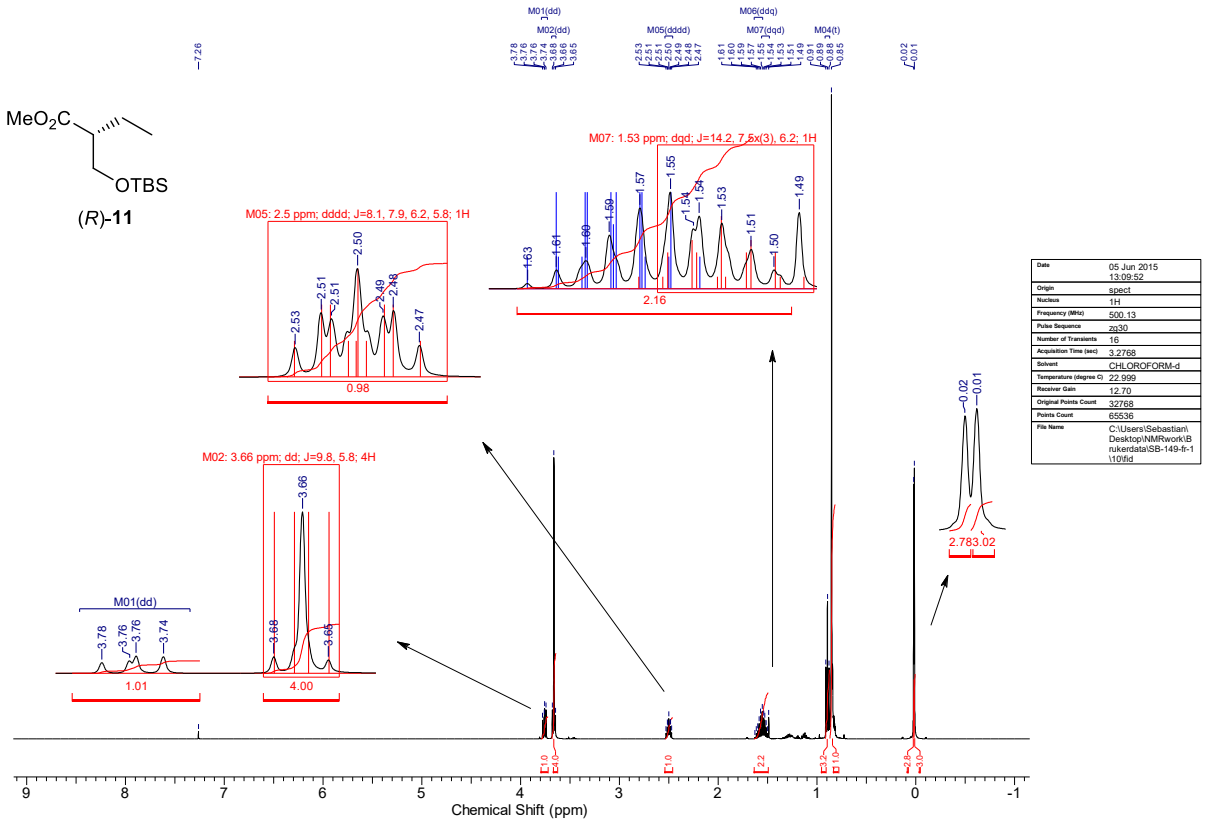
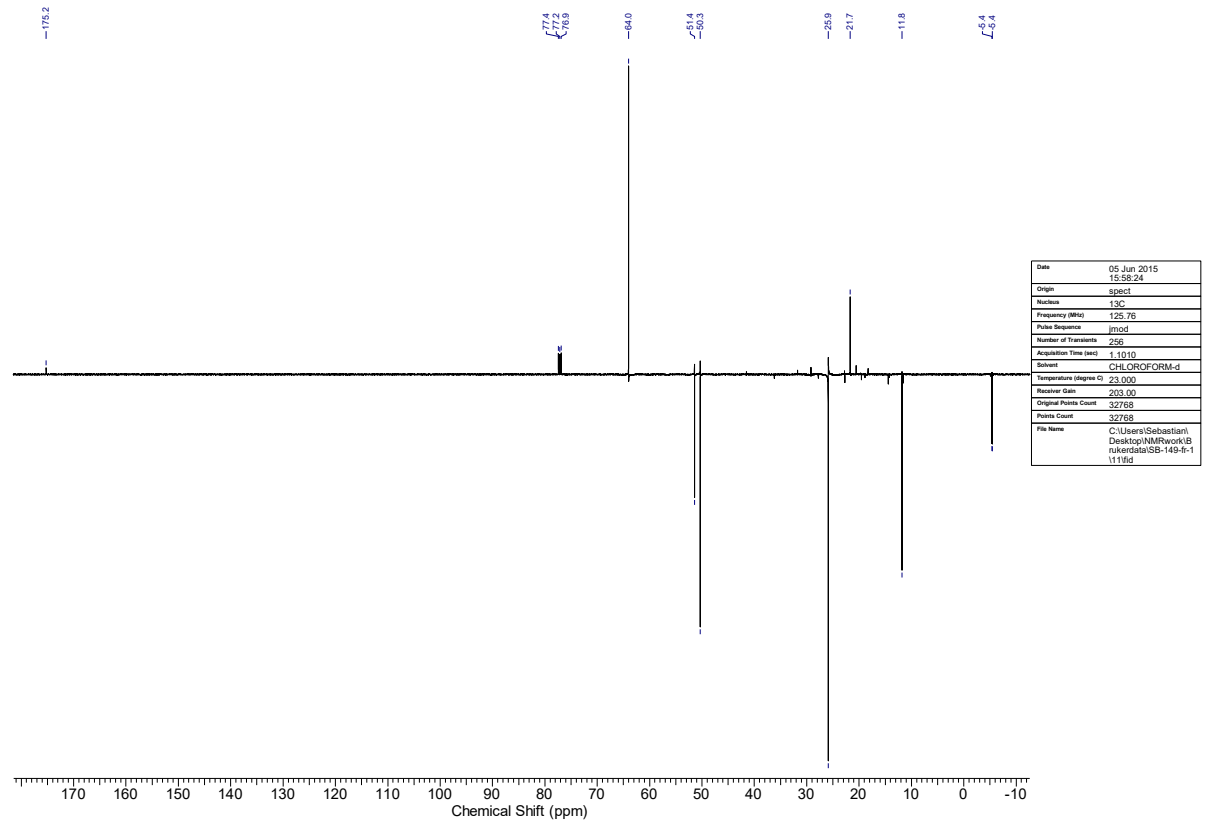
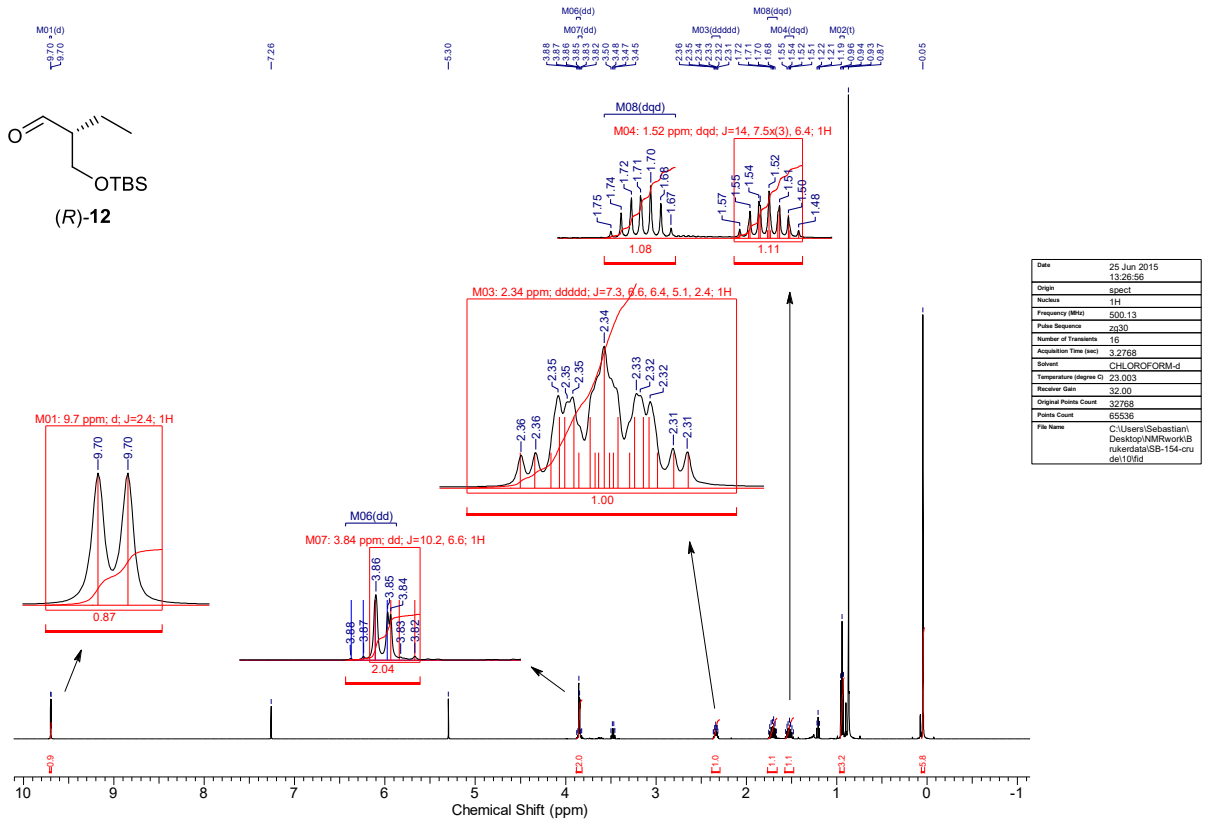
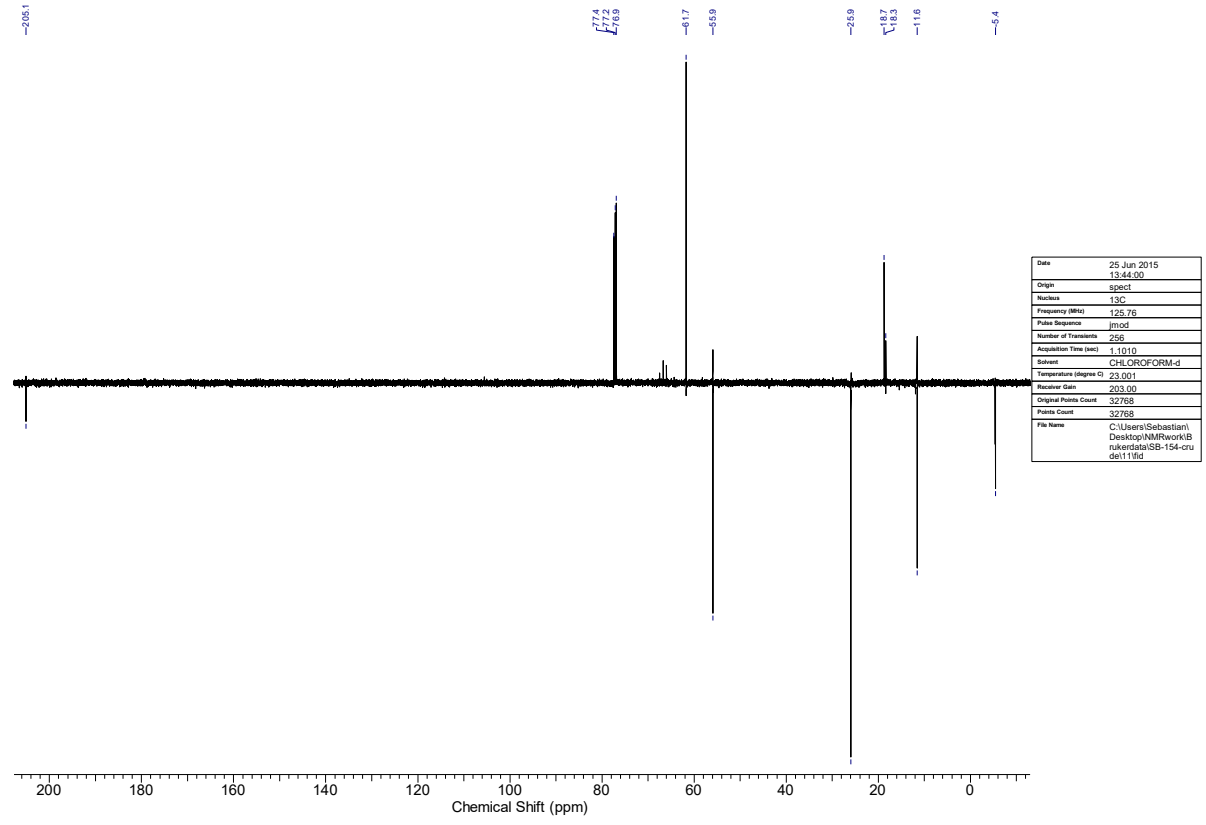
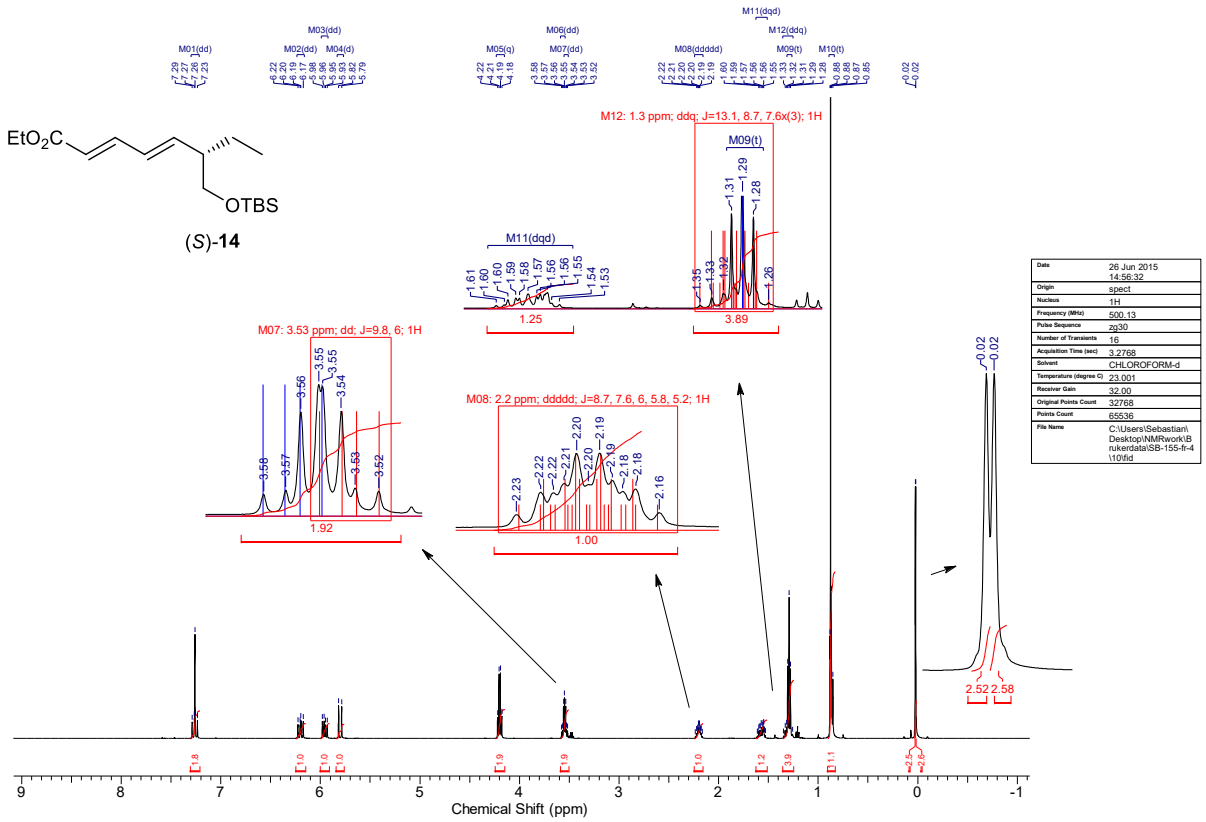
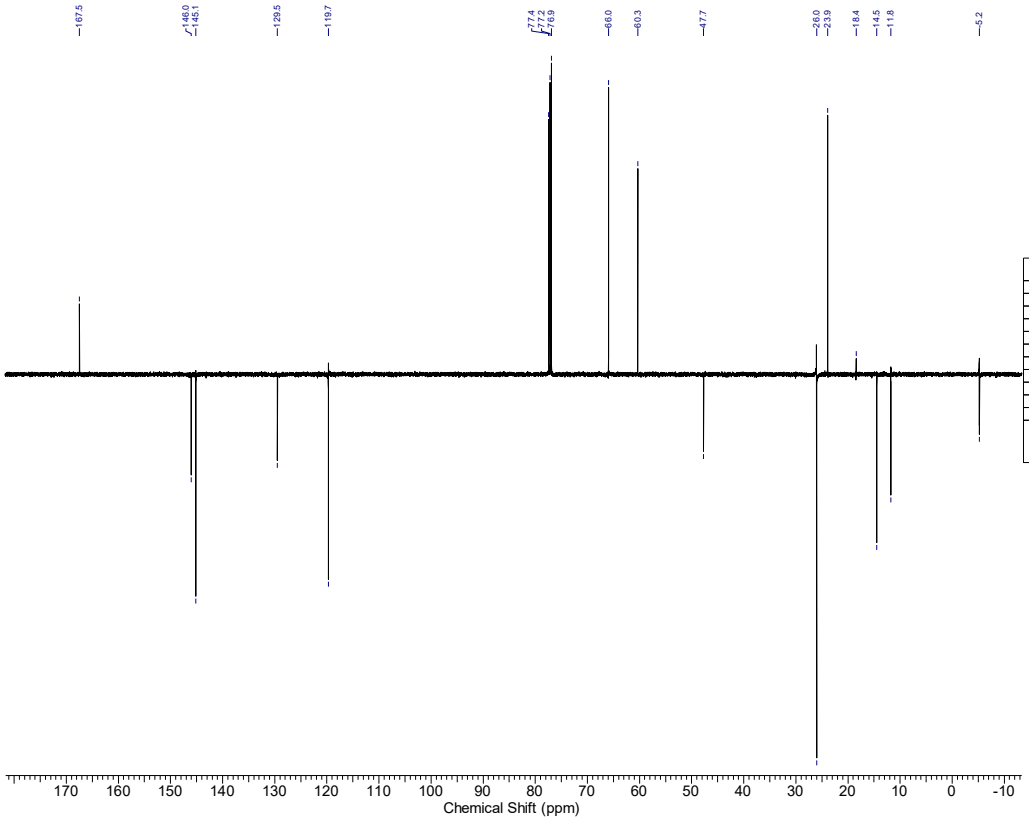

MeO2C
OTBS
(R)-11
M05: 2.5 ppm; dddd; J=8.1, 7.9, 6.2, 5.8; 1H
M07: 1.53 ppm; dqd; J=14.2, 7.5x(3), 6.2; 1H
M02: 3.66 ppm; dd; J=9.8, 5.8; 4H
M01(dd)
2.16
0.98
1.01
4.00
2.783.02
Chemical Shift (ppm)

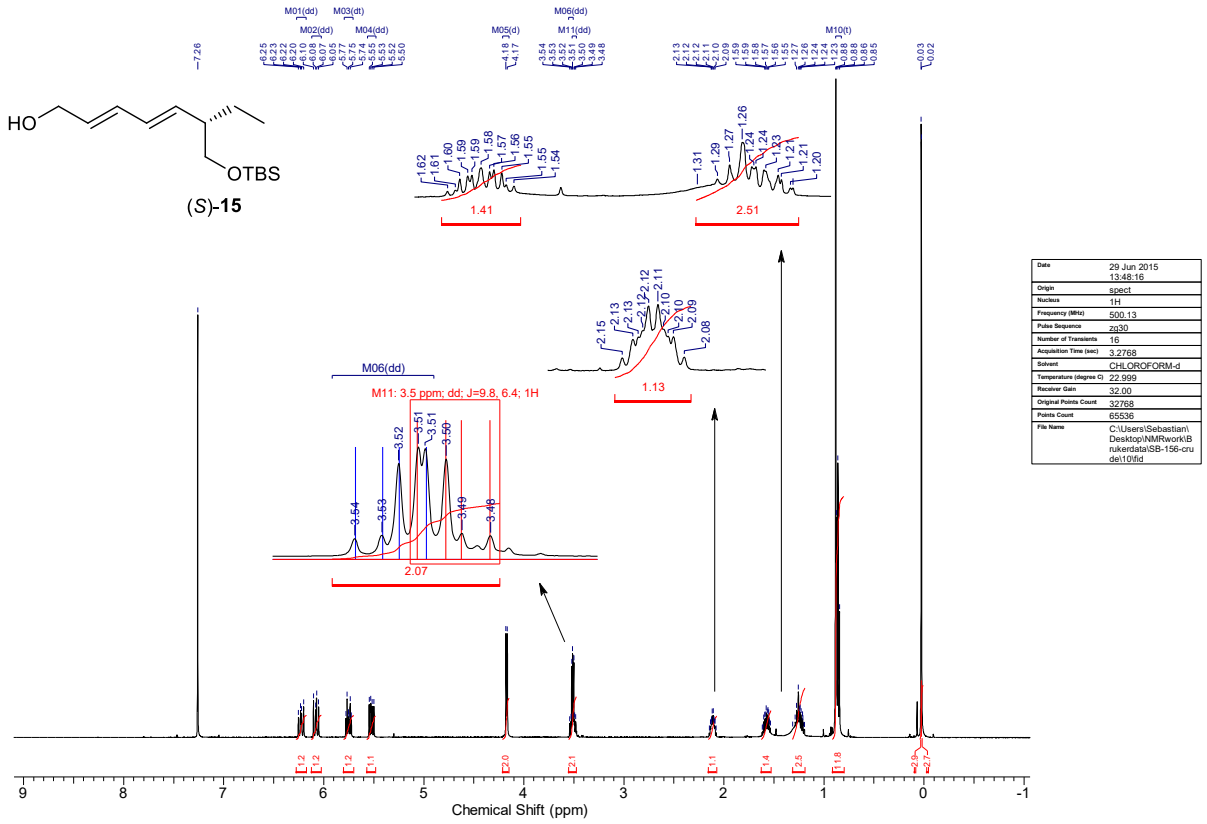

Chemical Shift (ppm)


M01(d)
M06(dd)
M07(dd)
M03(dddd)
M08(dqd)
M04(dqd)
M02(t)
OTBS
(R)-12
M08(dqd)
M04: 1.52 ppm; dqd; J=14, 7.5x(3), 6.4; 1H
1.08
1.11
M03: 2.34 ppm; ddddd; J=7.3, 6.6, 6.4, 5.1, 2.4; 1H
1.00
M01: 9.7 ppm; d; J=2.4; 1H
0.87
M06(dd)
M07: 3.84 ppm; dd; J=10.2, 6.6; 1H
2.04
Chemical Shift (ppm)
Date 25 Jun 2015 13:26:56
Origin spect
Nucleus 1H
Frequency (MHz) 500.13
Pulse Sequence zg30
Number of Transients 16
Acquisition Time (sec) 3.2768
Solvent CHLOROFORM-d
Temperature (degree C) 23.003
Receiver Gain 32.00
Original Points Count 32768
Points Count 65536
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-154-crude\10\fid


Chemical Shift (ppm)
Date 25 Jun 2015 13:44:00
Origin spect
Nucleus 13C
Frequency (MHz) 125.76
Pulse Sequence jmod
Number of Transients 256
Acquisition Time (sec) 1.1010
Solvent CHLOROFORM-d
Temperature (degree C) 23.001
Receiver Gain 203.00
Original Points Count 32768
Points Count 32768
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-154-crude\11\fid


EtO2C
OTBS
(S)-14
M12: 1.3 ppm; ddq; J=13.1, 8.7, 7.6x(3); 1H
M07: 3.53 ppm; dd; J=9.8, 6; 1H
M08: 2.2 ppm; ddddd; J=8.7, 7.6, 6, 5.8, 5.2; 1H
Chemical Shift (ppm)


Chemical Shift (ppm)



Date	29 Jun 2015 13:48:16
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	CHLOROFORM-d
Temperature (degree C)	22.999
Receiver Gain	32.00
Original Points Count	32768
Points Count	65536
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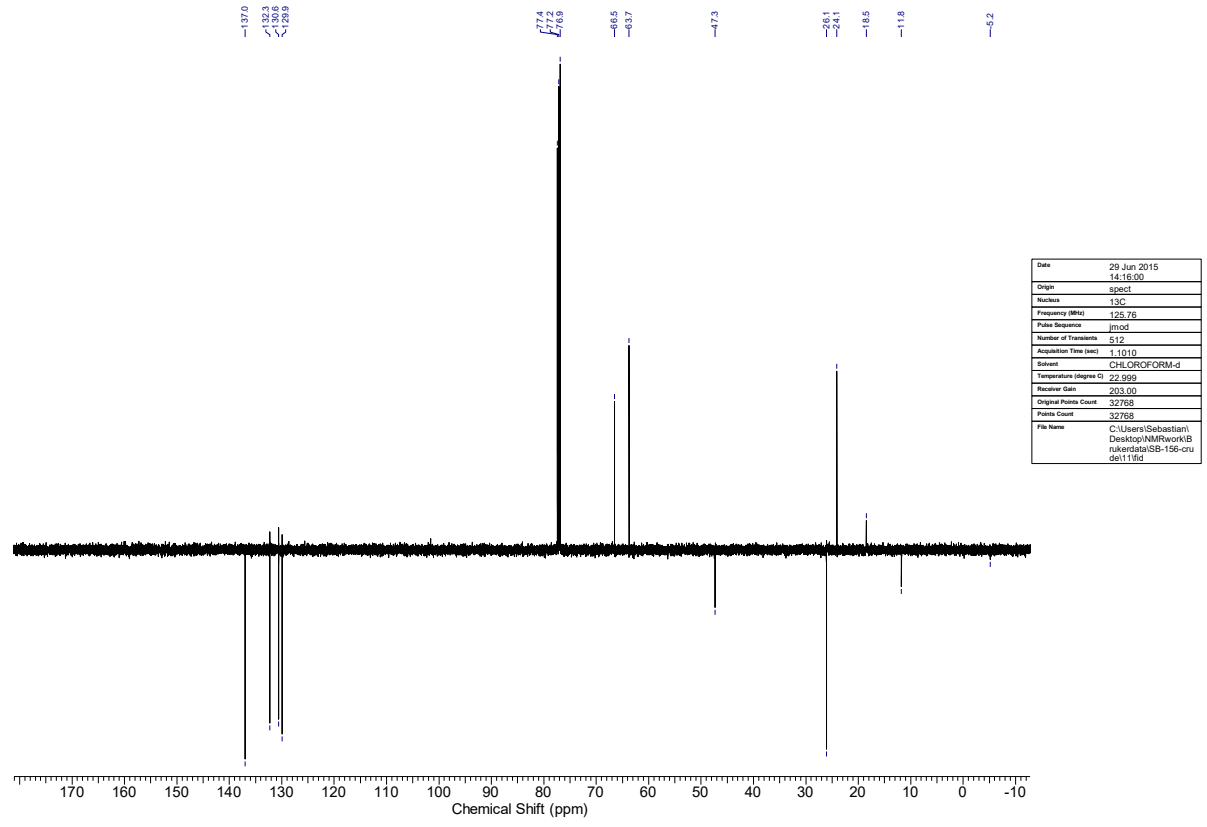
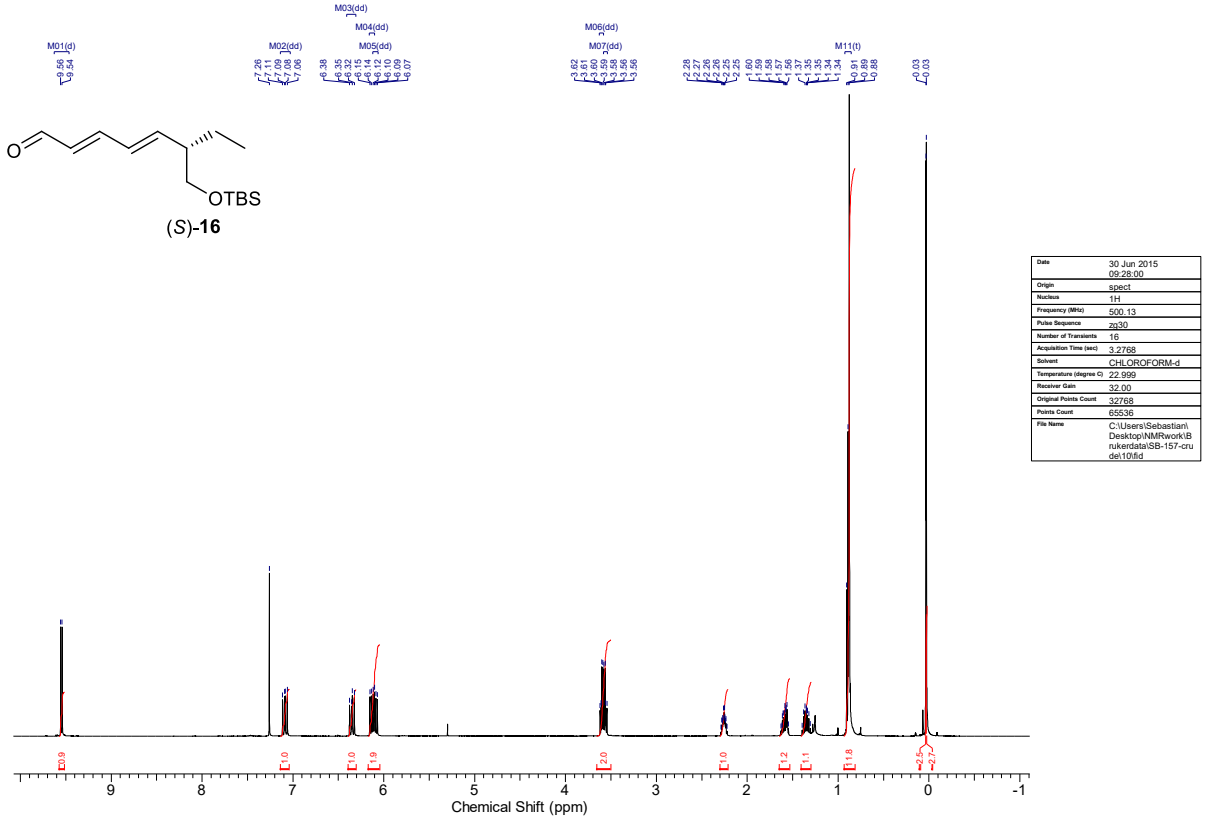
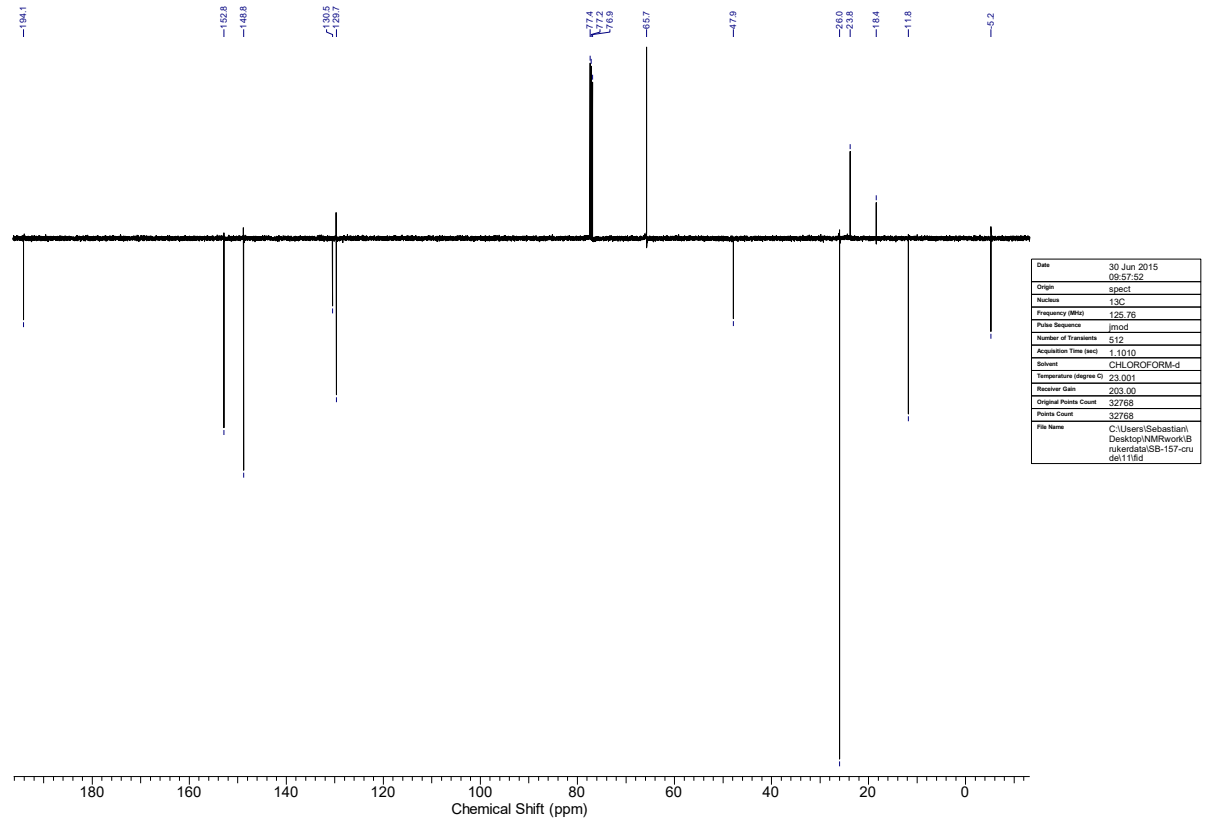


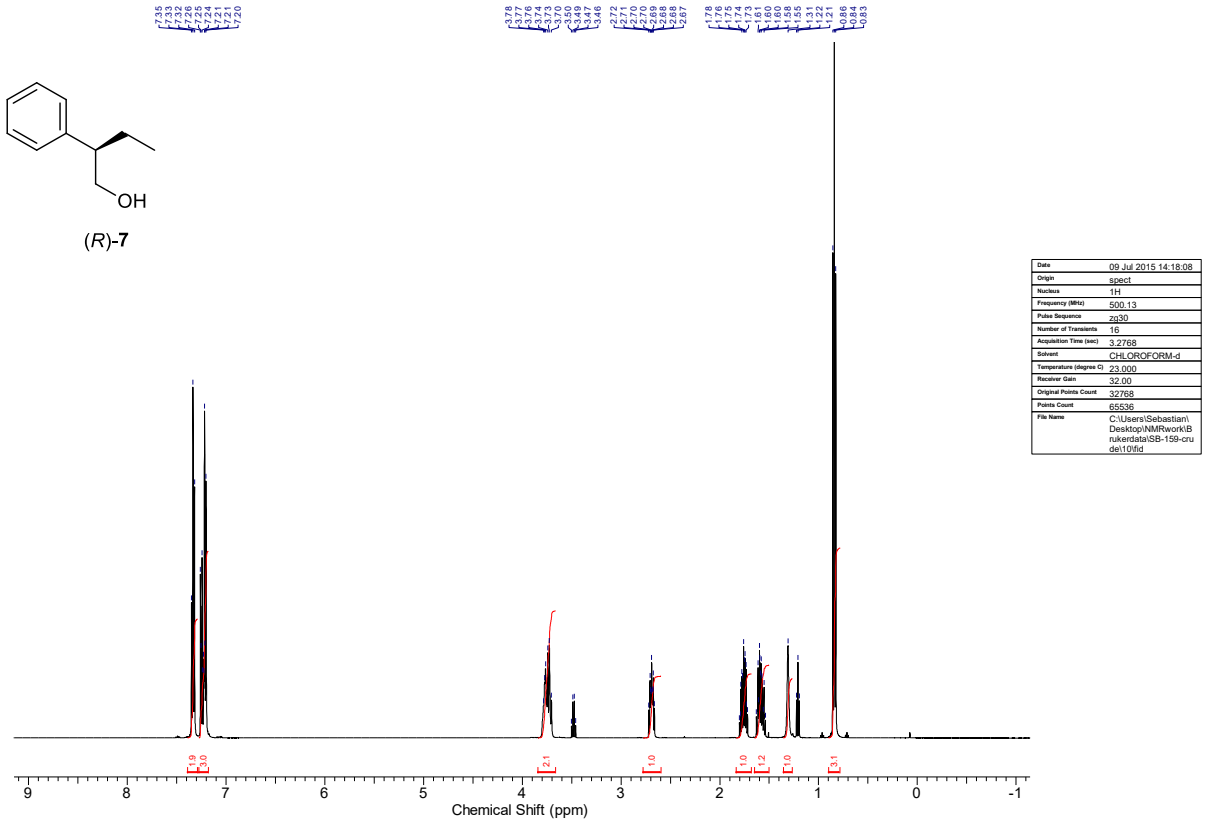
Date	29 Jun 2015 14:16:00
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	jmod
Number of Transients	512
Acquisition Time (sec)	1.1010
Solvent	CHLOROFORM-d
Temperature (degree C)	22.999
Receiver Gain	203.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-156-crude\11\fid



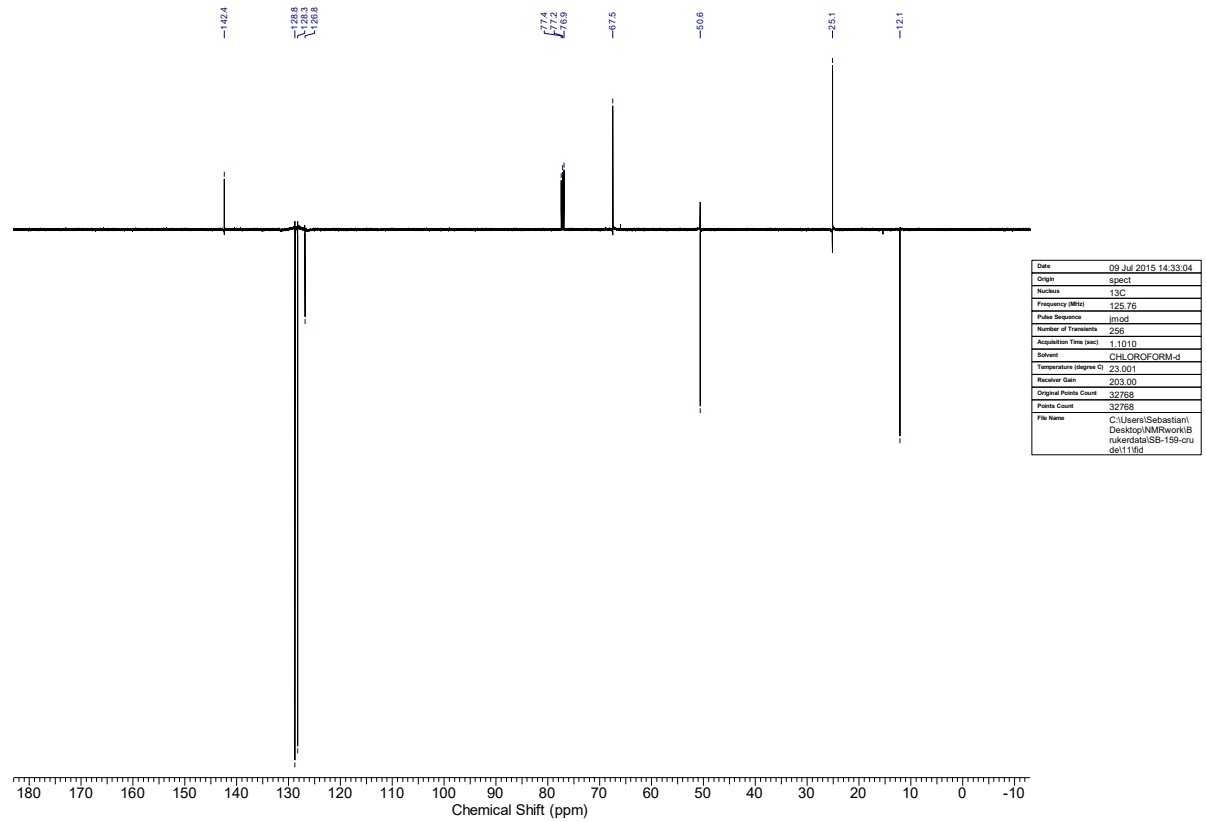
Date	30 Jun 2015 09:28:00
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	CHLOROFORM-d
Temperature (degree C)	22.999
Receiver Gain	32.00
Original Points Count	32768
Points Count	65536
File Name	C:\Users\Sebastian\Desktop\NMRwork\Bukerdata\SB-157-crude\10\fid



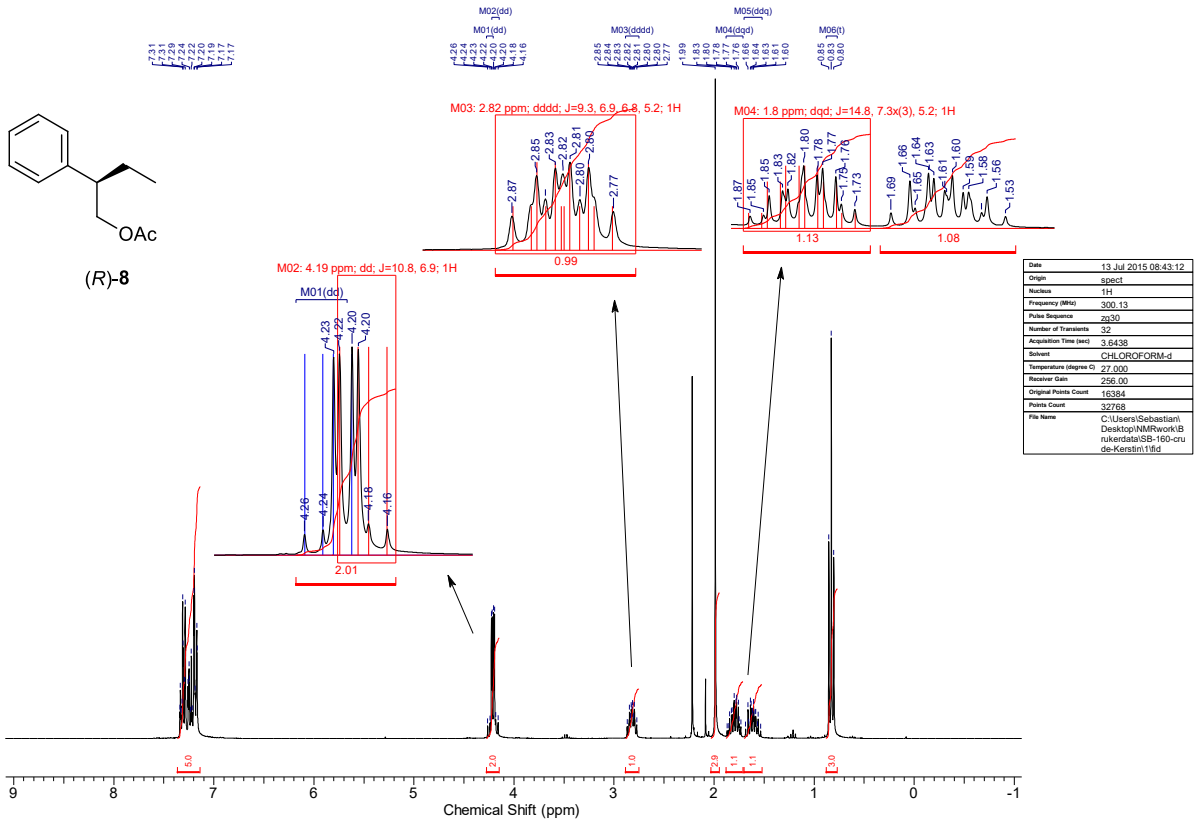
Date	30 Jun 2015 09:57:52
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	jmod
Number of Transients	512
Acquisition Time (sec)	1.1010
Solvent	CHLOROFORM-d
Temperature (degree C)	23.001
Receiver Gain	203.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Bukerdata\SB-157-crude\11\fid



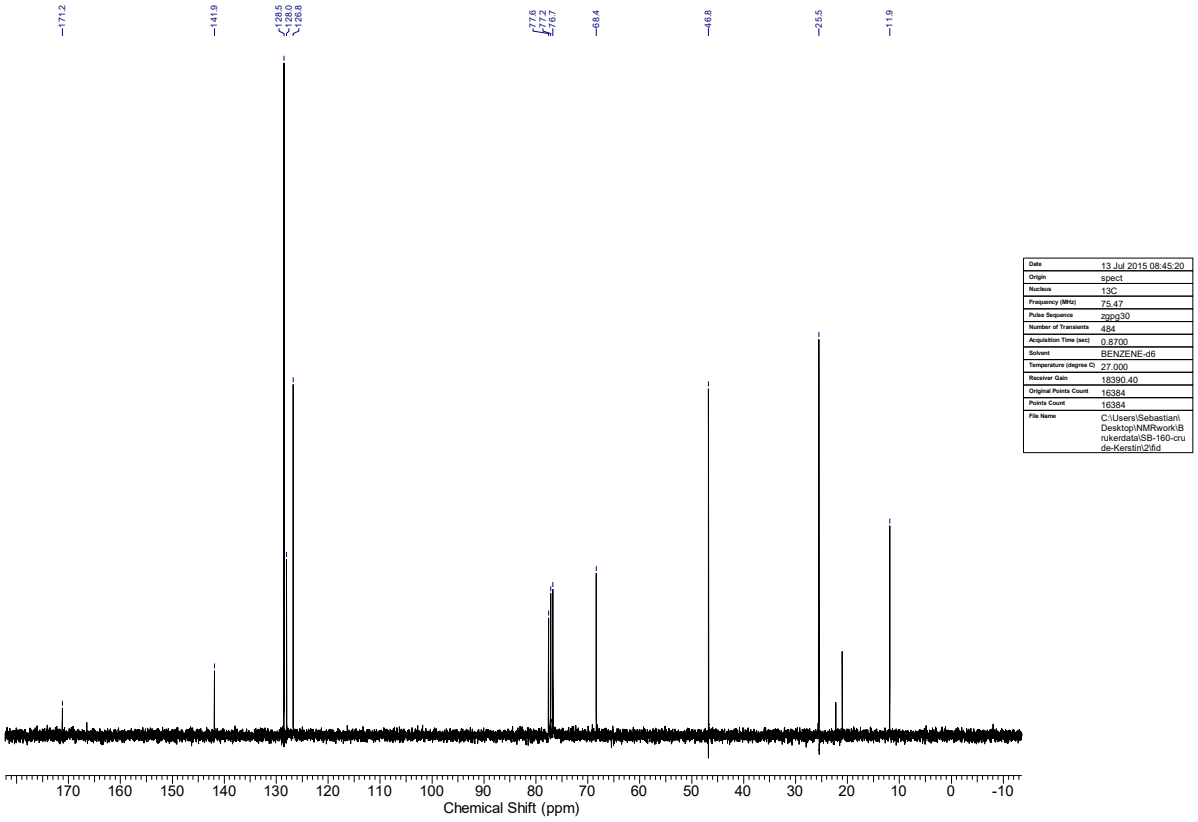
Date	09 Jul 2015 14:18:08
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	za30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	CHLOROFORM-d
Temperature (degree C)	23.000
Receiver Gain	32.00
Original Points Count	32768
Points Count	65536
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-159-crude\10\fid



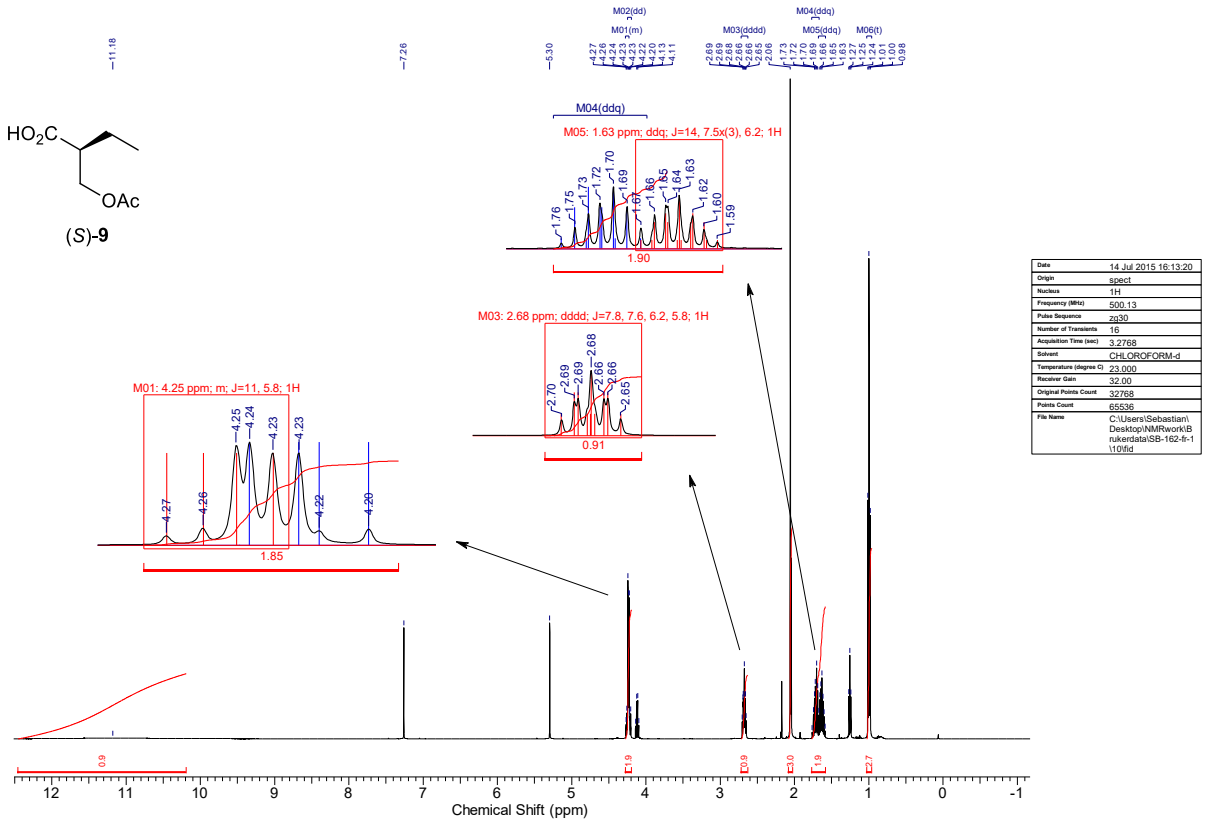
Date	09 Jul 2015 14:33:04
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	jmod
Number of Transients	256
Acquisition Time (sec)	1.1010
Solvent	CHLOROFORM-d
Temperature (degree C)	23.001
Receiver Gain	203.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-159-crude\11\fid



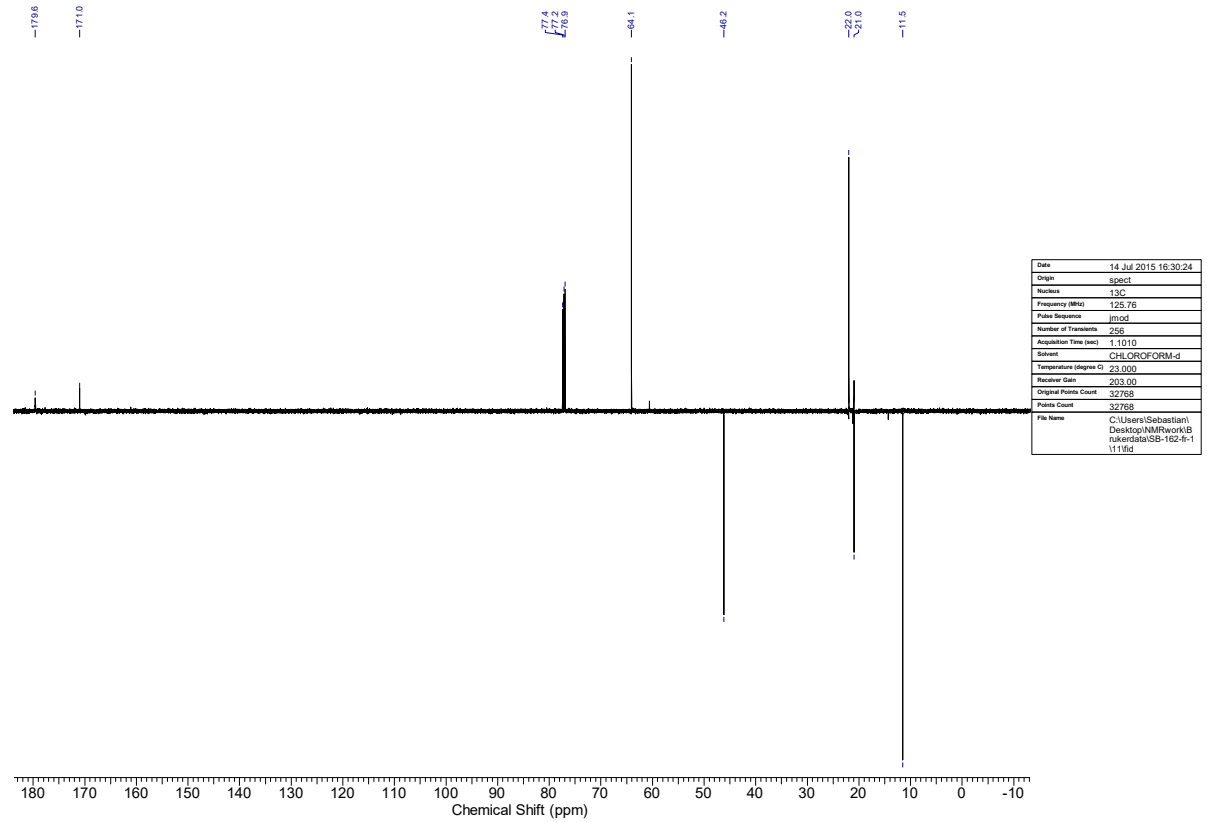
Date	13 Jul 2015 08:43:12
Origin	spect
Nucleus	1H
Frequency (MHz)	300.13
Pulse Sequence	zg30
Number of Transients	32
Acquisition Time (sec)	3.6438
Solvent	CHLOROFORM-d
Temperature (degree C)	27.000
Receiver Gain	256.00
Original Points Count	16384
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-160-crude-Kerstin\1\fid



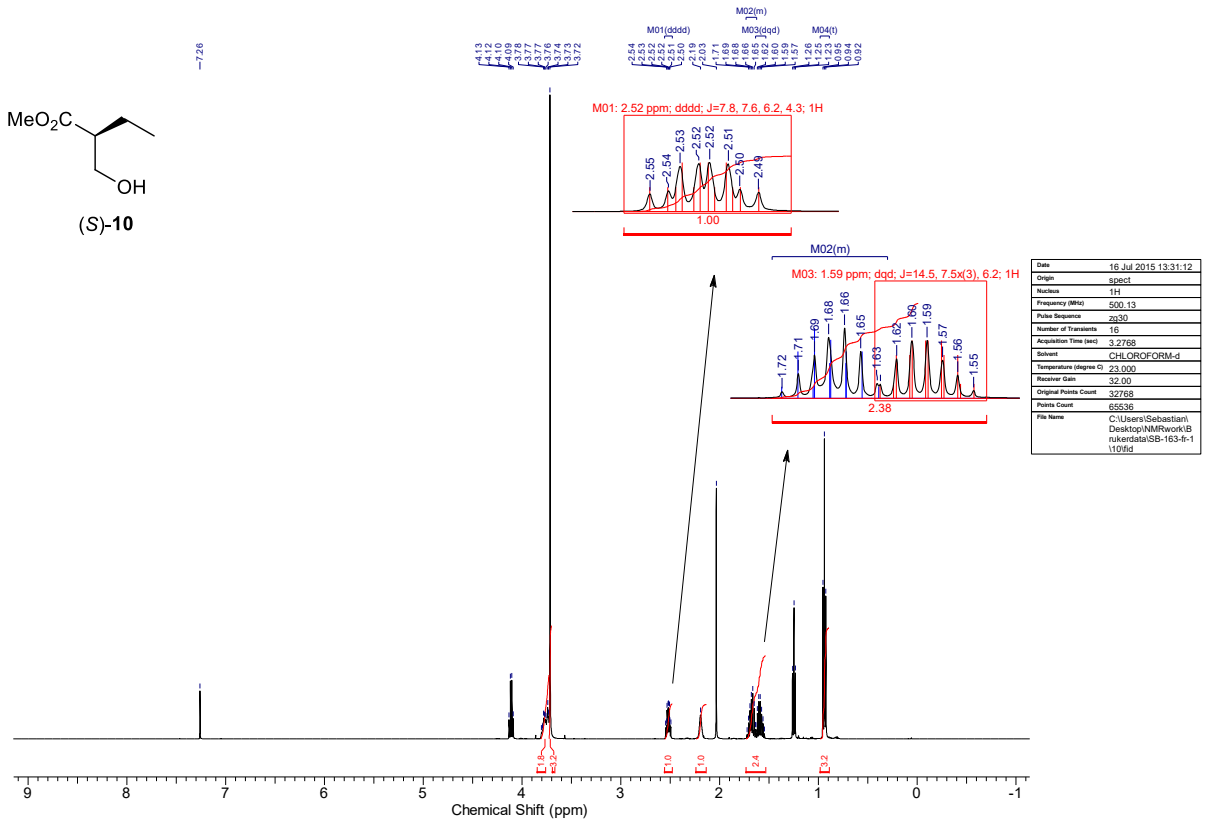
Date	13 Jul 2015 08:45:20
Origin	spect
Nucleus	13C
Frequency (MHz)	75.47
Pulse Sequence	zgpg30
Number of Transients	484
Acquisition Time (sec)	0.8700
Solvent	BENZENE-d6
Temperature (degree C)	27.000
Receiver Gain	18390.40
Original Points Count	16384
Points Count	16384
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-160-crude-Kerstin\2\fid

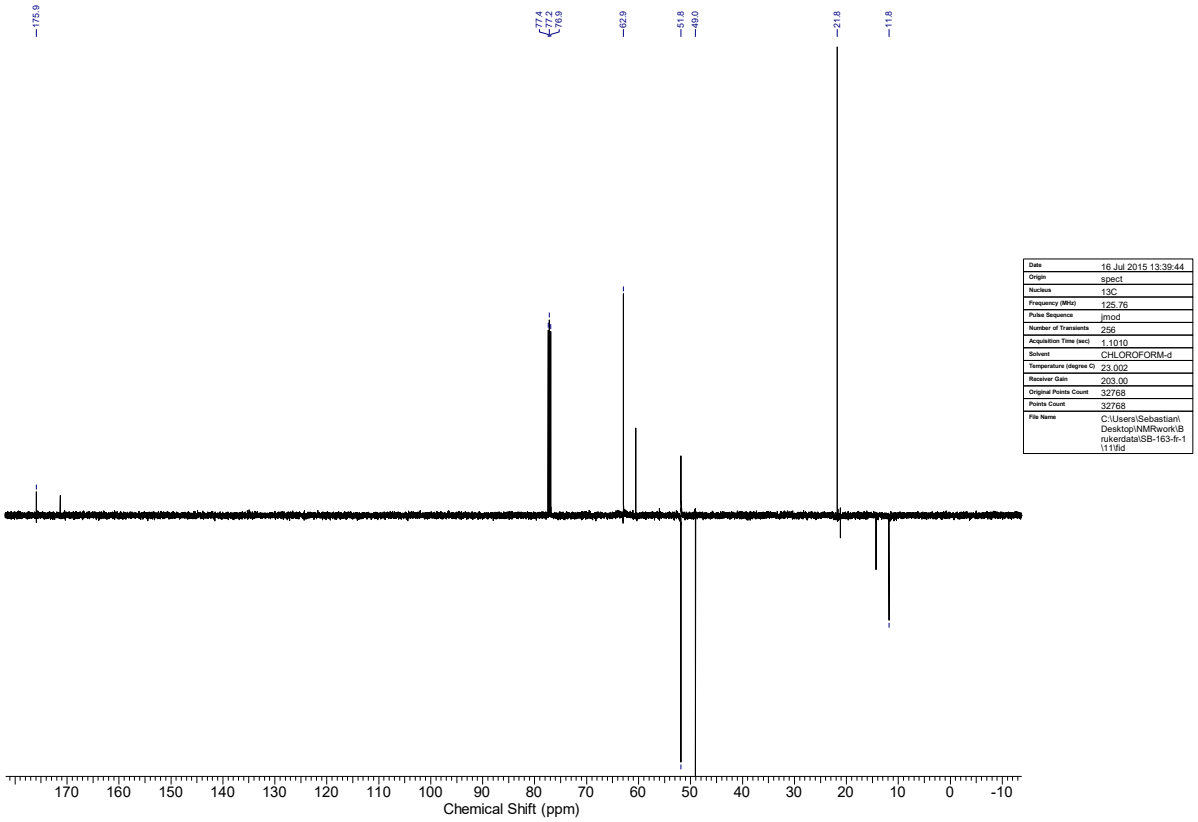


Date	14 Jul 2015 16:13:20
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	za30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	CHLOROFORM-d
Temperature (degree C)	23.000
Receiver Gain	32.00
Original Points Count	32768
Points Count	65536
File Name	C:\Users\Sebastian\Desktop\NMRwork\Bukerdata\SB-162-fr-1\10\fid

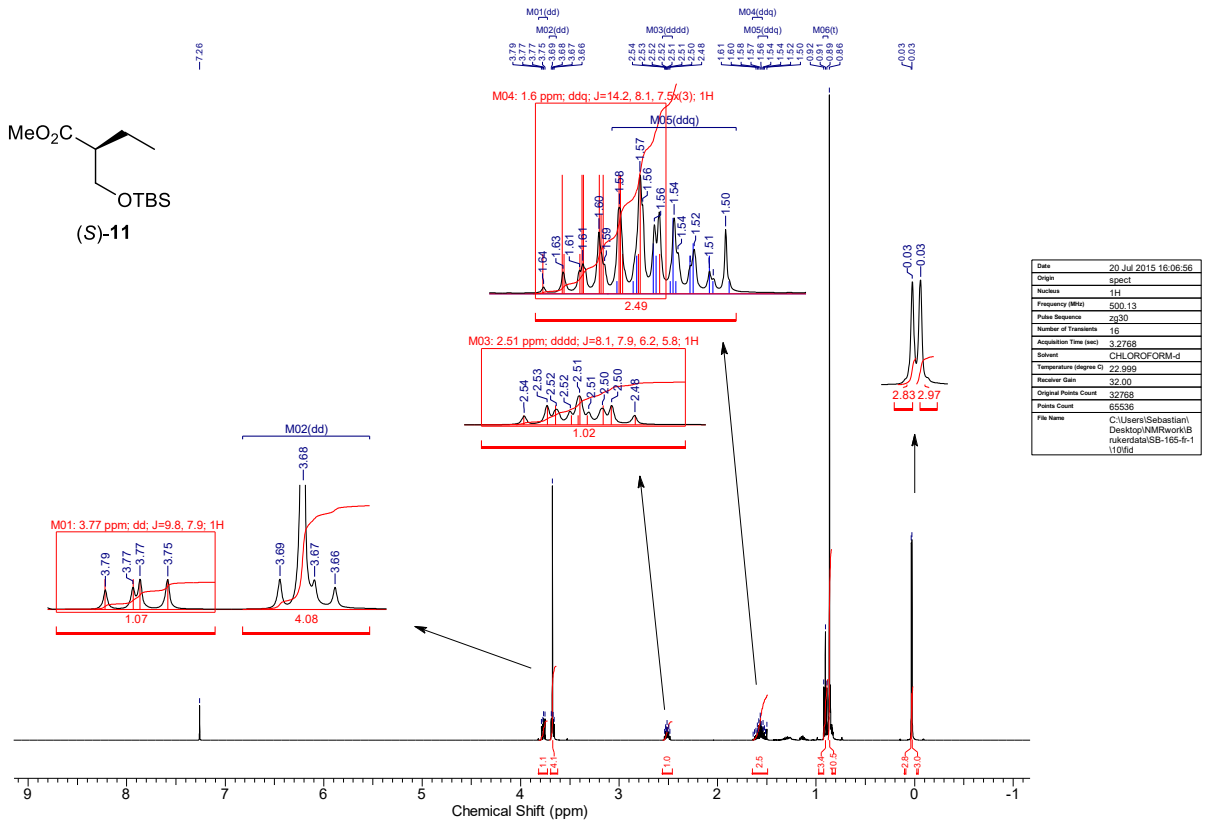


Date	14 Jul 2015 16:30:24
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	jmod
Number of Transients	256
Acquisition Time (sec)	1.1010
Solvent	CHLOROFORM-d
Temperature (degree C)	23.000
Receiver Gain	203.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Bukerdata\SB-162-fr-1\11\fid

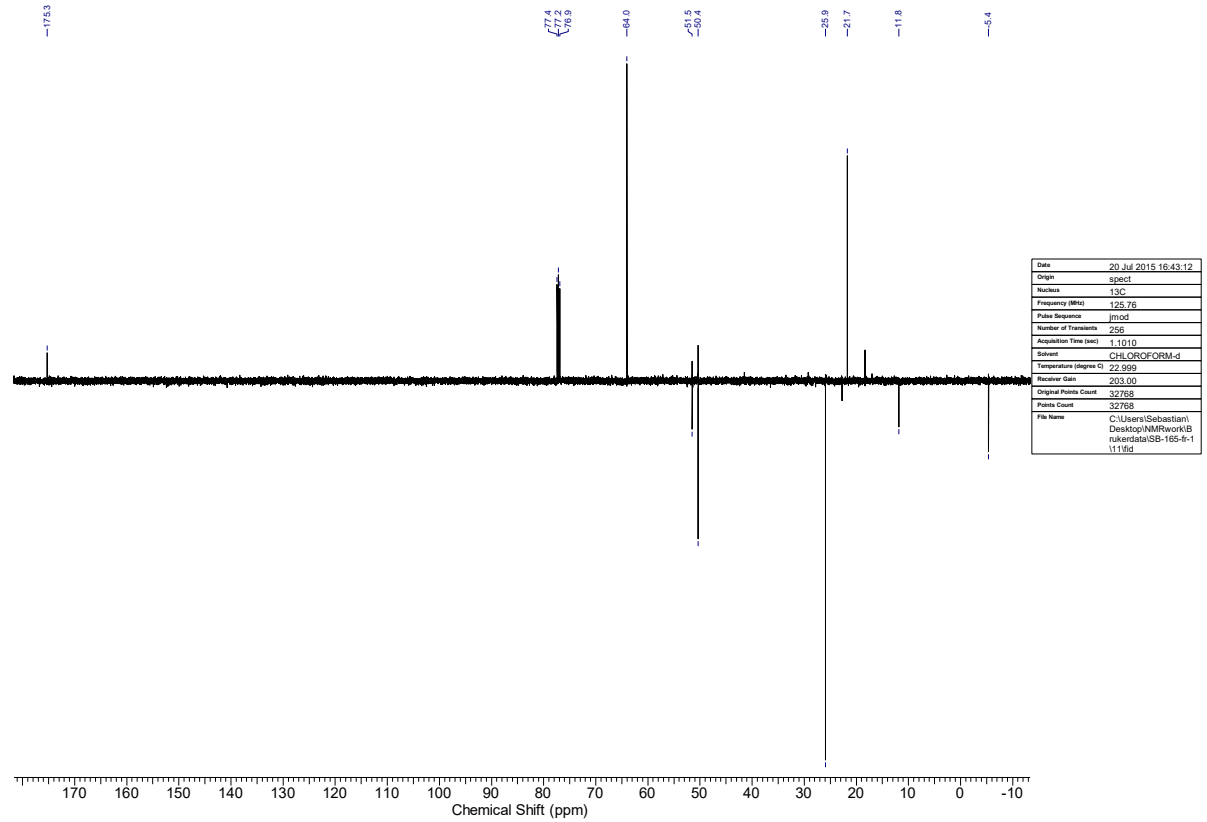

MeO2C
OH
(S)-10
M01: 2.52 ppm; dddd; J=7.8, 7.6, 6.2, 4.3; 1H
M02(m)
M03: 1.59 ppm; dqd; J=14.5, 7.5x(3), 6.2; 1H
Chemical Shift (ppm)


Chemical Shift (ppm)

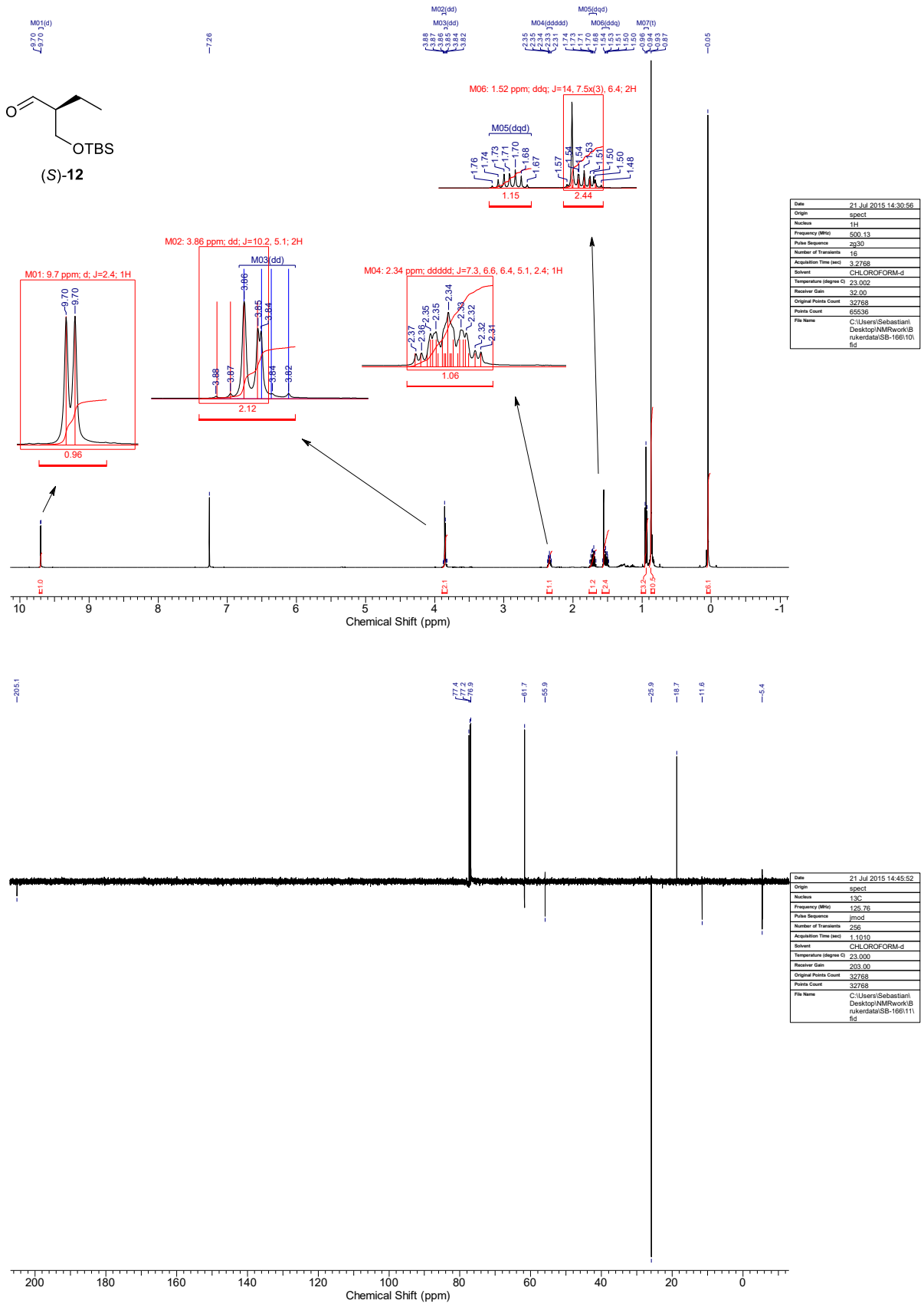
S38

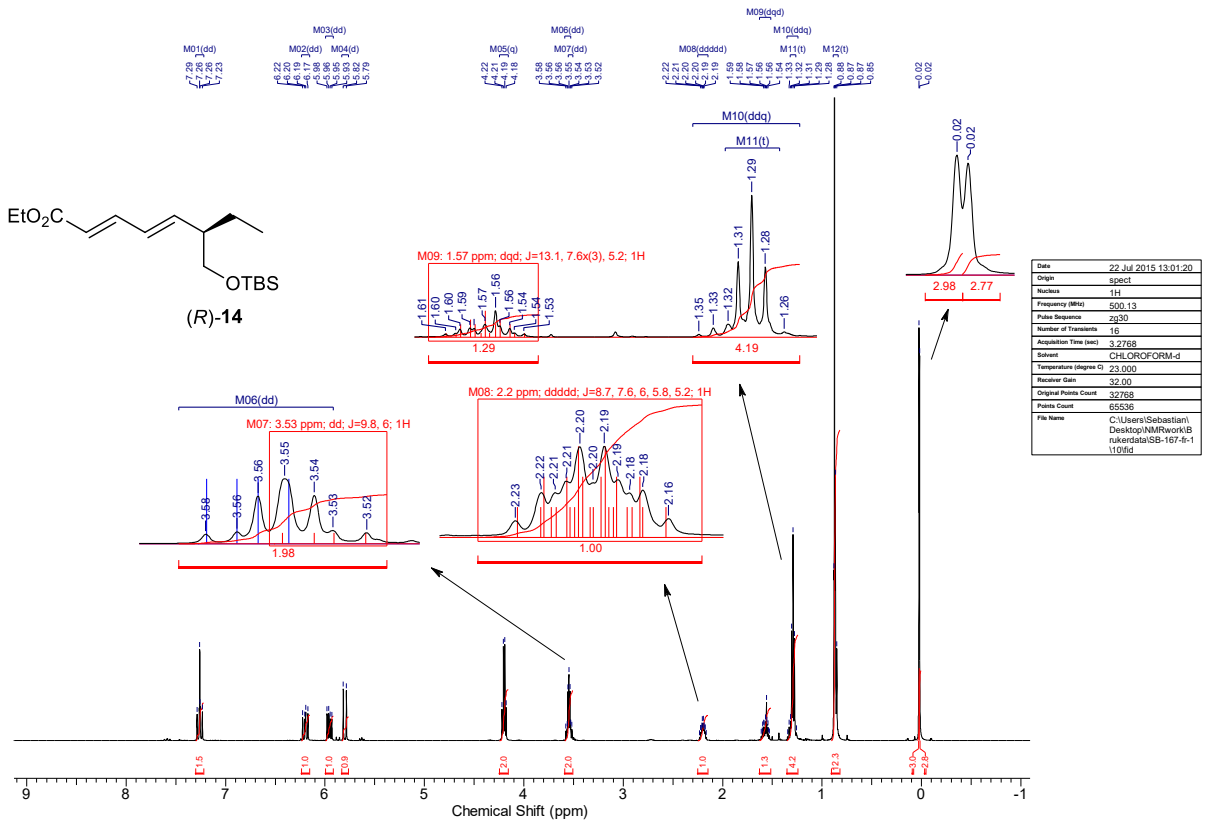


Date	20 Jul 2015 16:06:56
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	CHLOROFORM-d
Temperature (degree C)	22.999
Receiver Gain	32.00
Original Points Count	32768
Points Count	65536
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-165-fr-1\10\fid

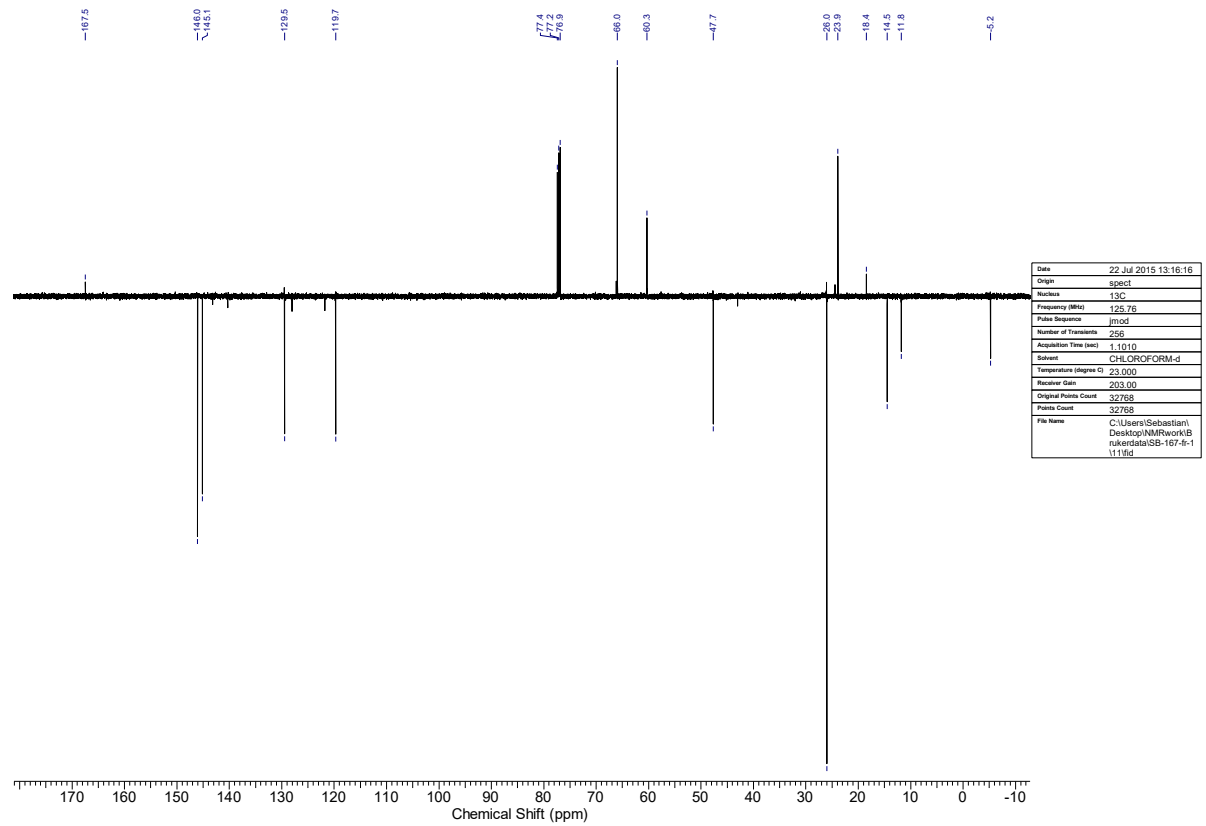


Date	20 Jul 2015 16:43:12
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	jmod
Number of Transients	256
Acquisition Time (sec)	1.1010
Solvent	CHLOROFORM-d
Temperature (degree C)	22.999
Receiver Gain	203.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-165-fr-1\11\fid

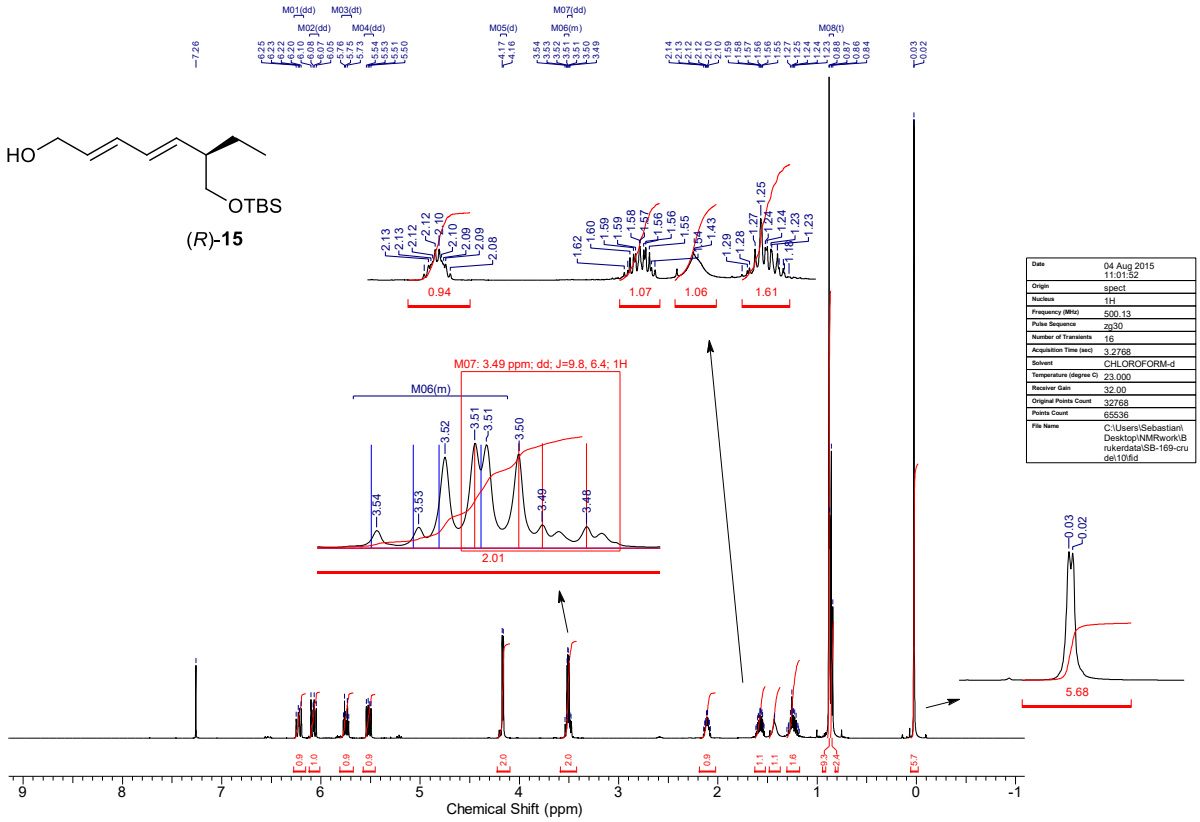

OTBS
(S)-12
M01: 9.7 ppm; d; J=2.4; 1H
M02: 3.86 ppm; dd; J=10.2, 5.1; 2H
M03(dd)
M04: 2.34 ppm; ddddd; J=7.3, 6.6, 6.4, 5.1, 2.4; 1H
M05(dqd)
M06: 1.52 ppm; ddq; J=14, 7.5x(3), 6.4; 2H
Chemical Shift (ppm)
Chemical Shift (ppm)

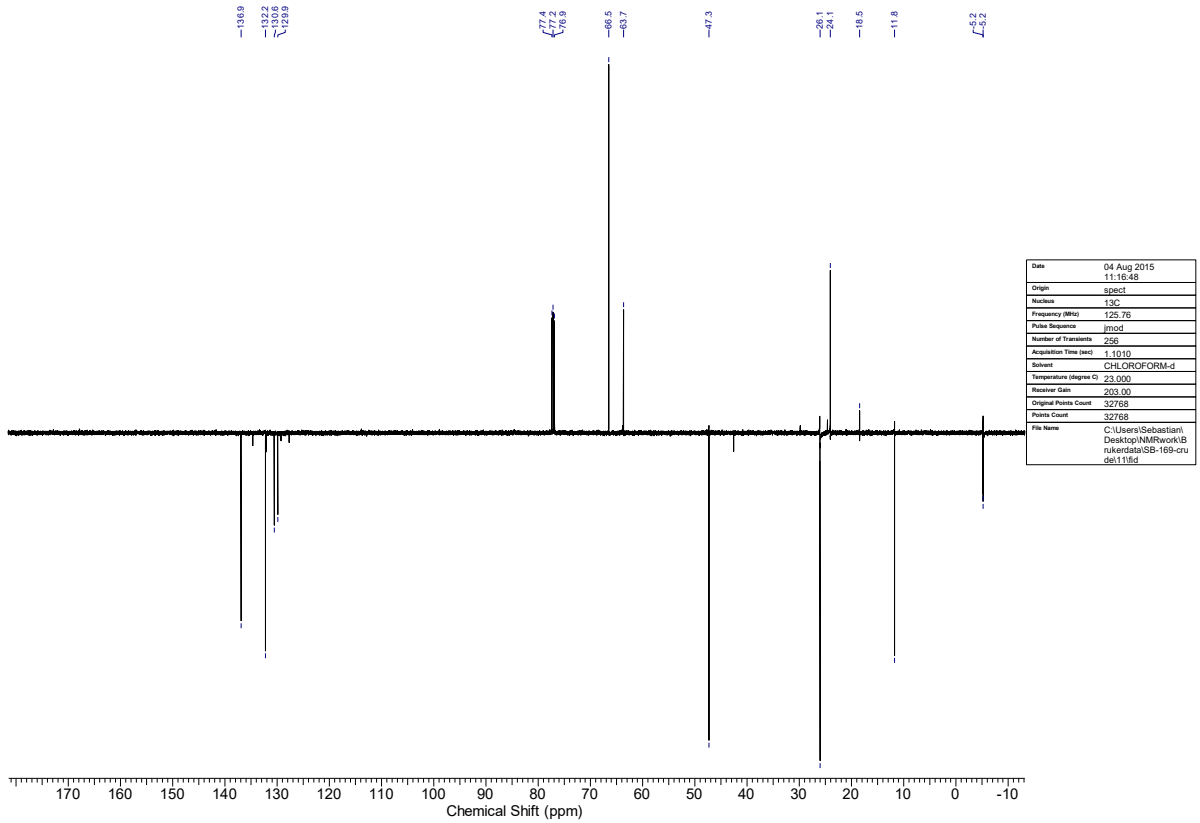


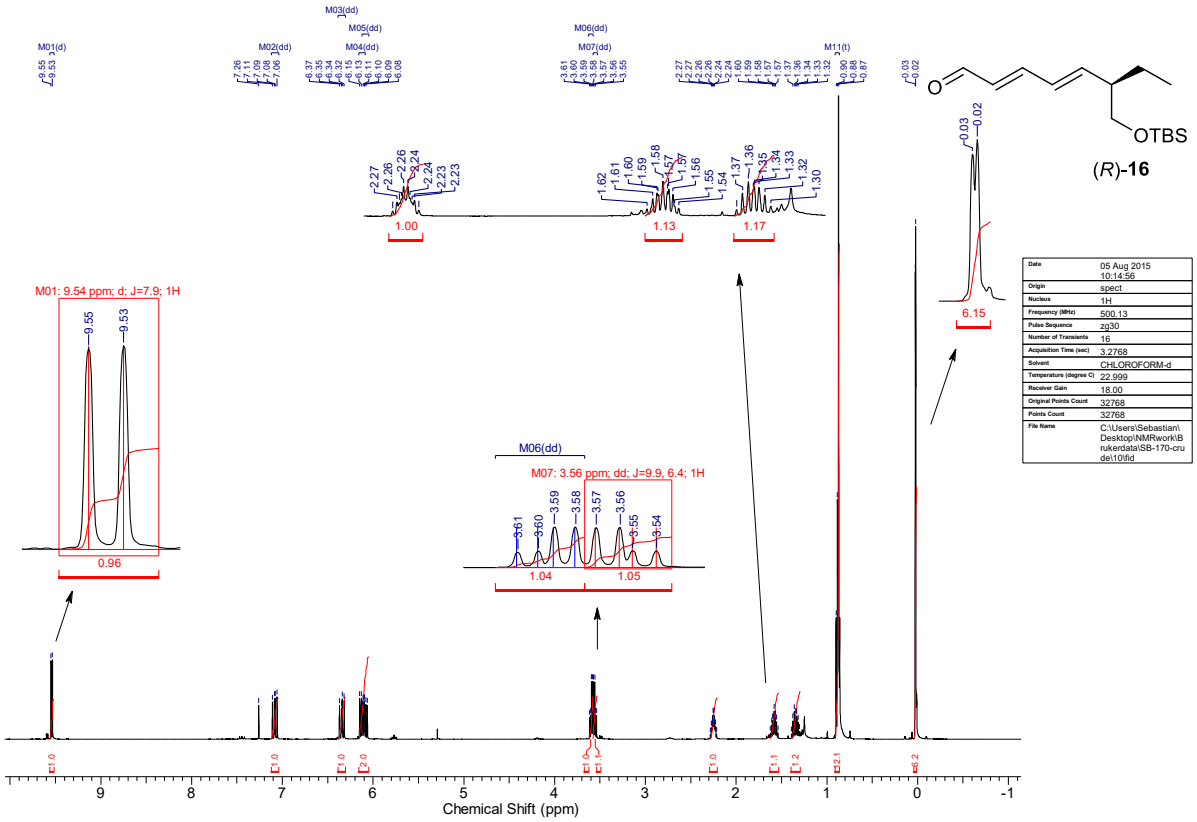
Date	22 Jul 2015 13:01:20
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	CHLOROFORM-d
Temperature (degree C)	23.000
Receiver Gain	32.00
Original Points Count	32768
Points Count	65536
File Name	C:\Users\Sebastian\Desktop\NMRwork\Bukerdata\SB-167-fr-1\10\fid



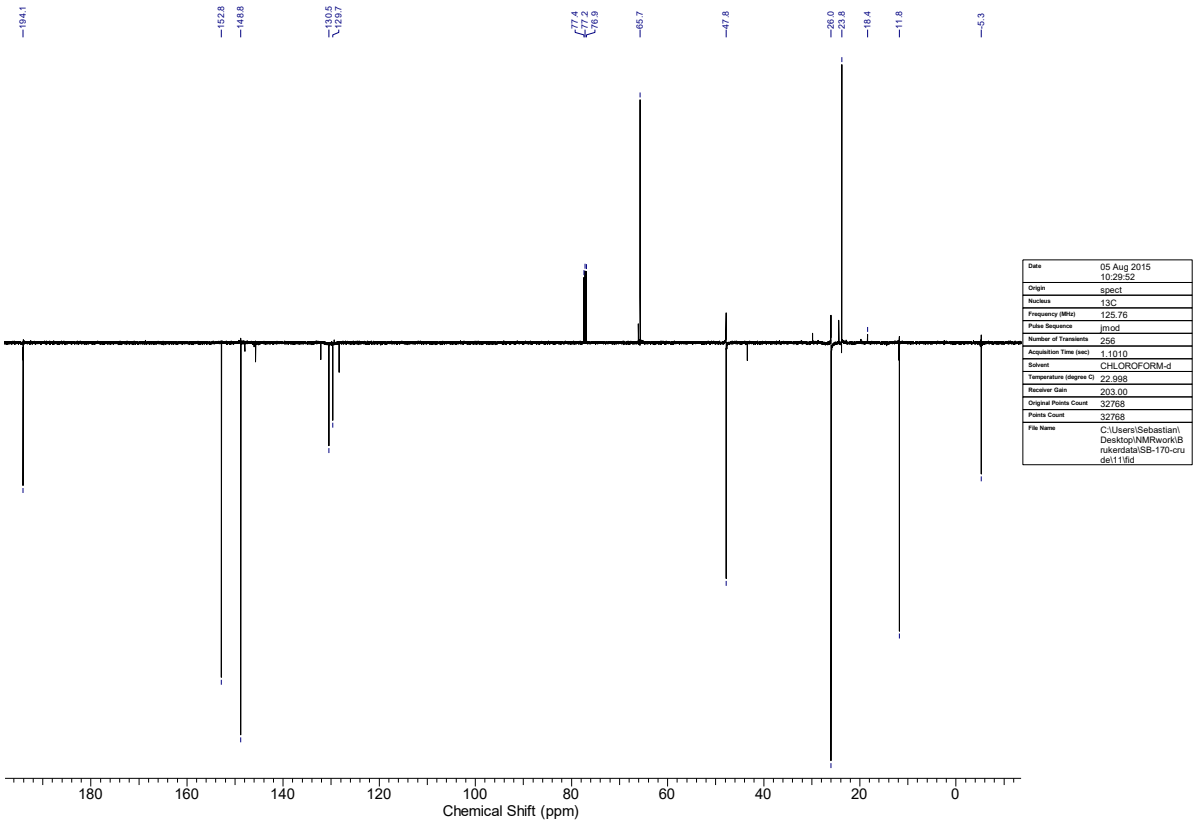
Date	22 Jul 2015 13:16:16
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	jmod
Number of Transients	256
Acquisition Time (sec)	1.1010
Solvent	CHLOROFORM-d
Temperature (degree C)	23.000
Receiver Gain	203.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Bukerdata\SB-167-fr-1\11\fid


HO
OTBS
(R)-15
M07: 3.49 ppm; dd; J=9.8, 6.4; 1H
M06(m)
2.01
0.94
1.07
1.06
1.61
5.68
Chemical Shift (ppm)

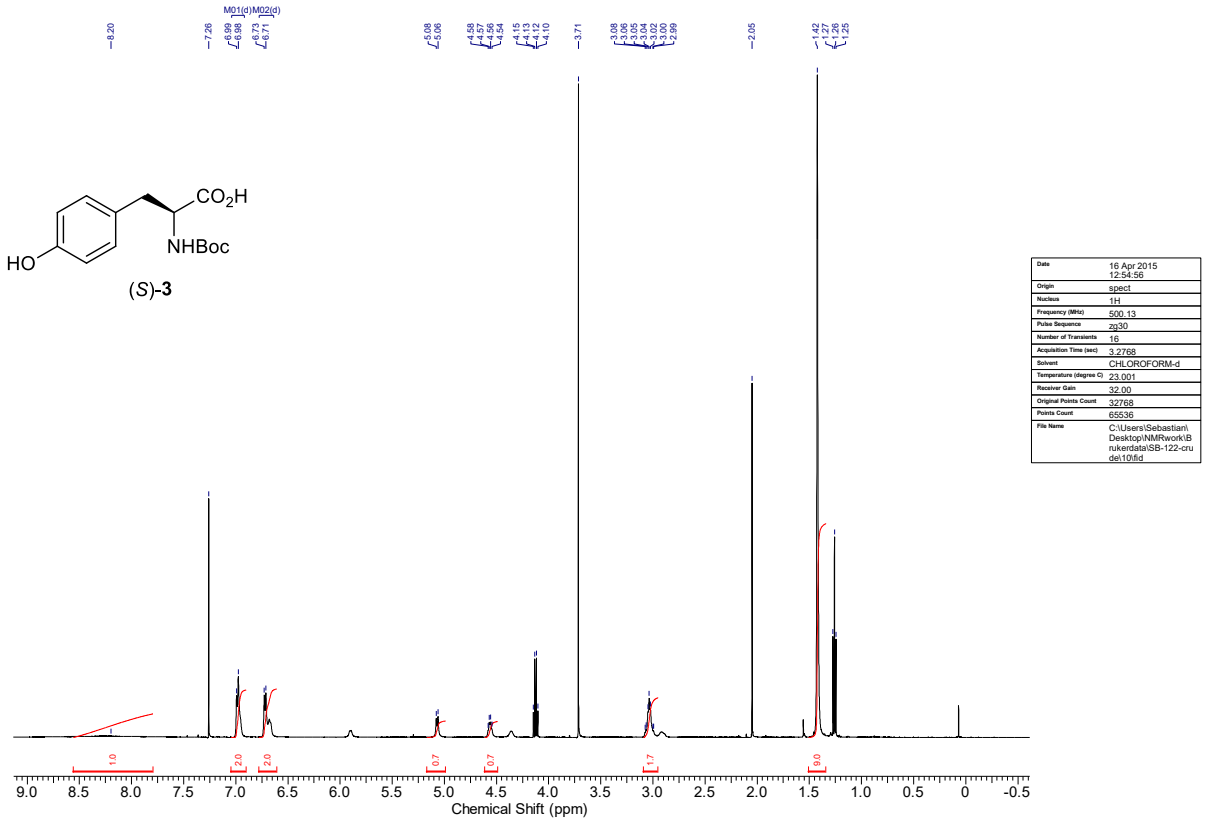

Chemical Shift (ppm)

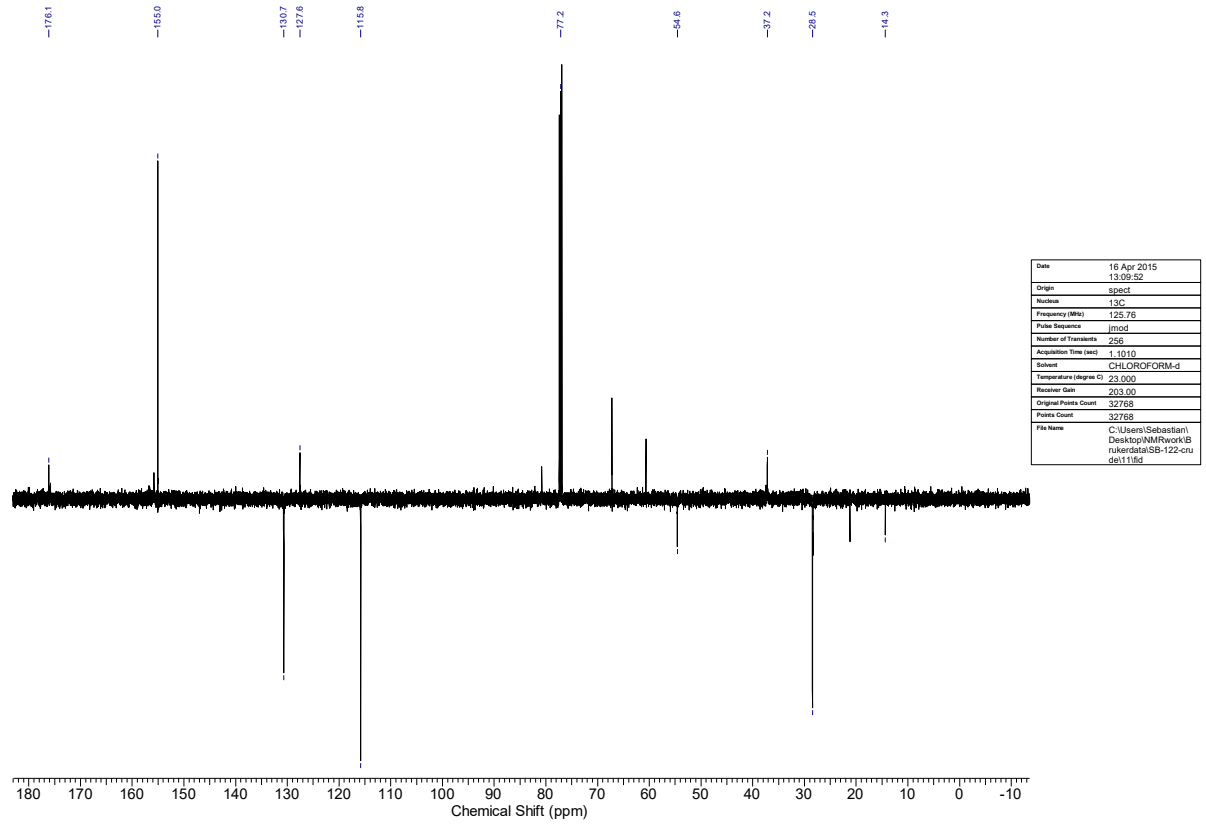


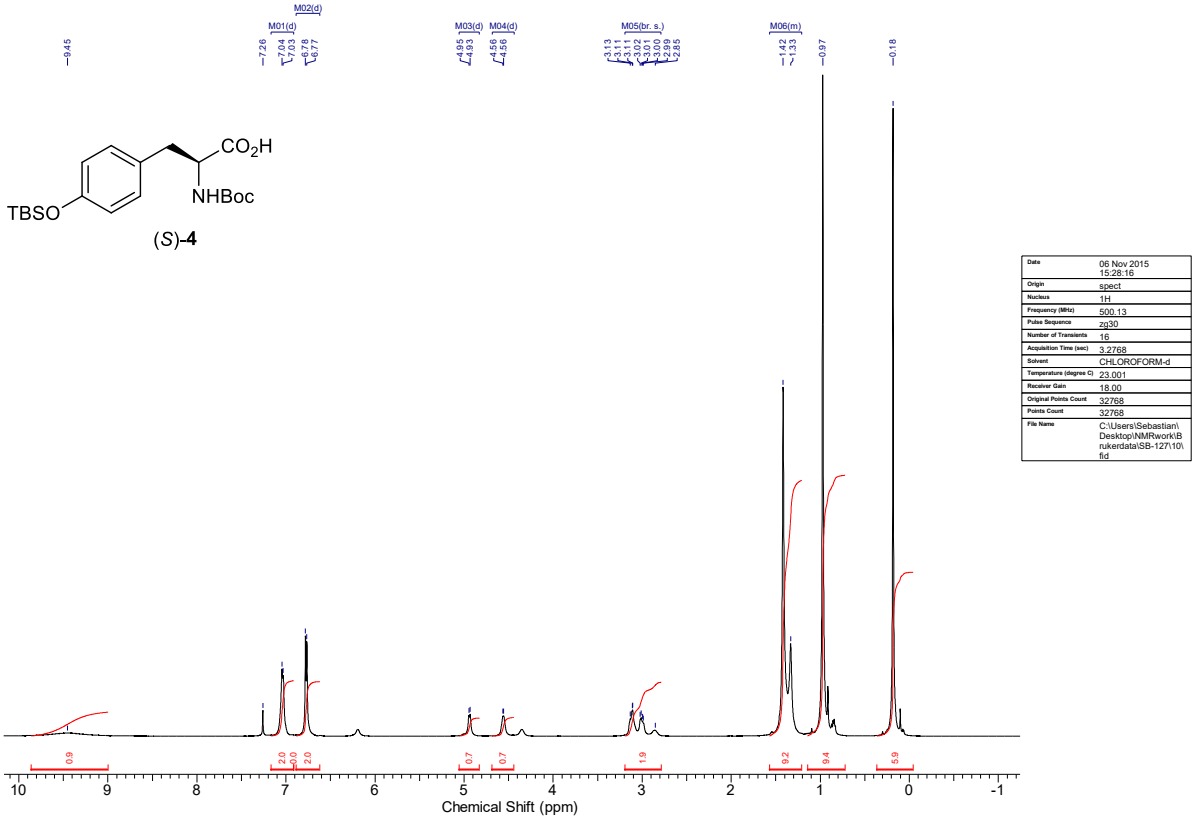
Date	05 Aug 2015 10:14:56
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	CHLOROFORM-d
Temperature (degree C)	22.999
Receiver Gain	18.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-170-crude\10\fid

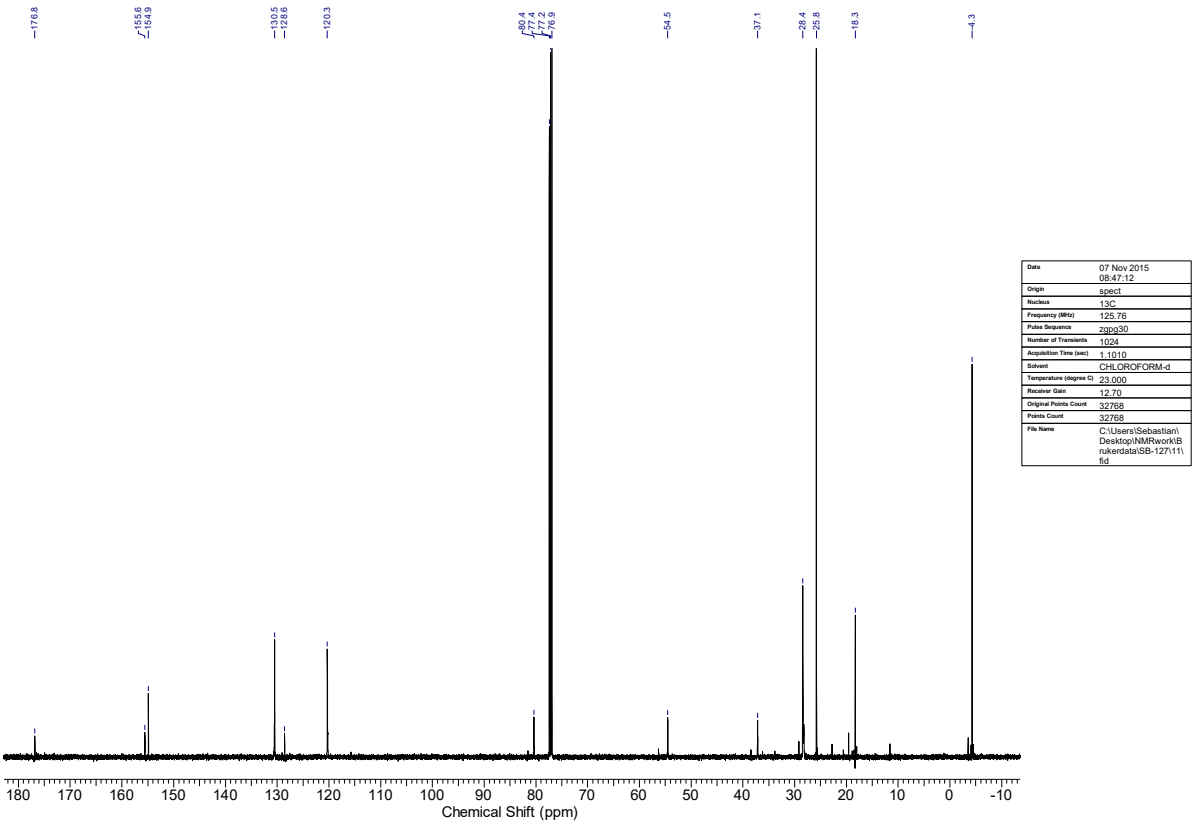


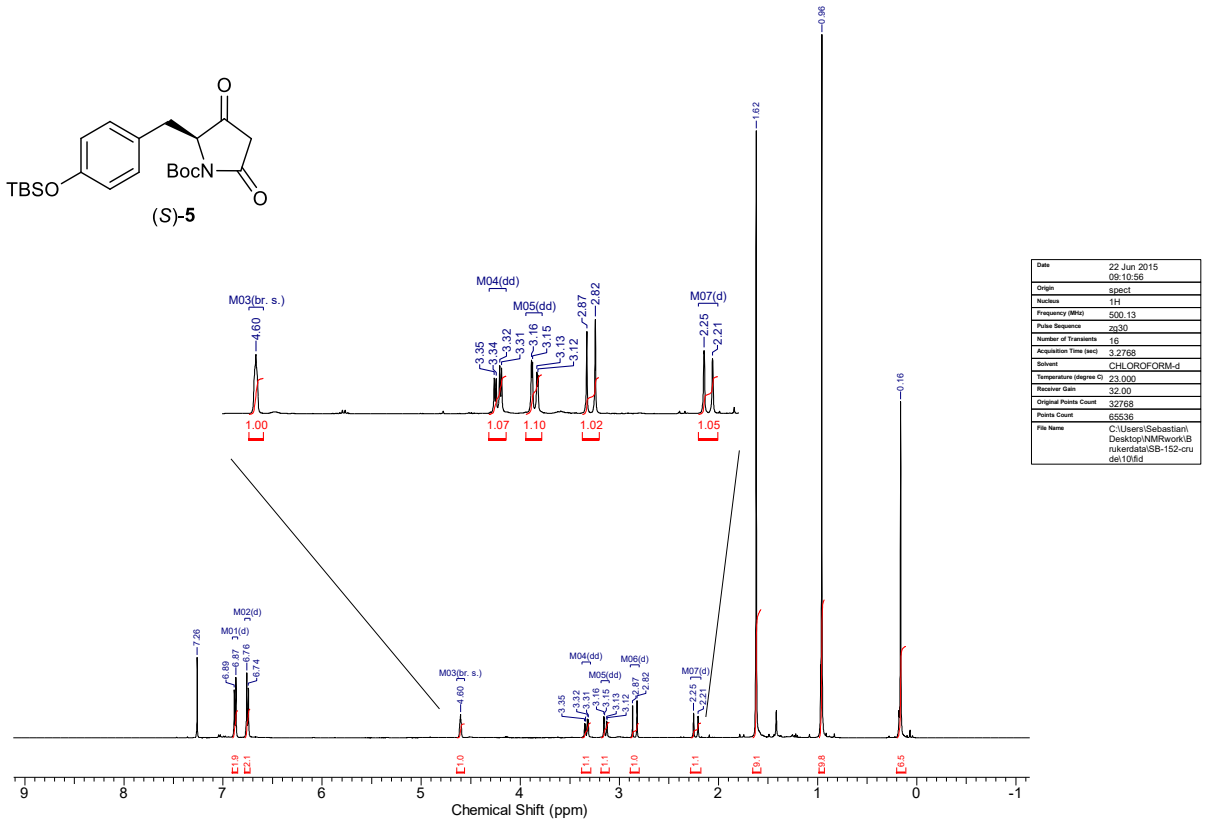
Date	05 Aug 2015 10:29:52
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	jmod
Number of Transients	256
Acquisition Time (sec)	1.1010
Solvent	CHLOROFORM-d
Temperature (degree C)	22.998
Receiver Gain	203.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-170-crude\11\fid

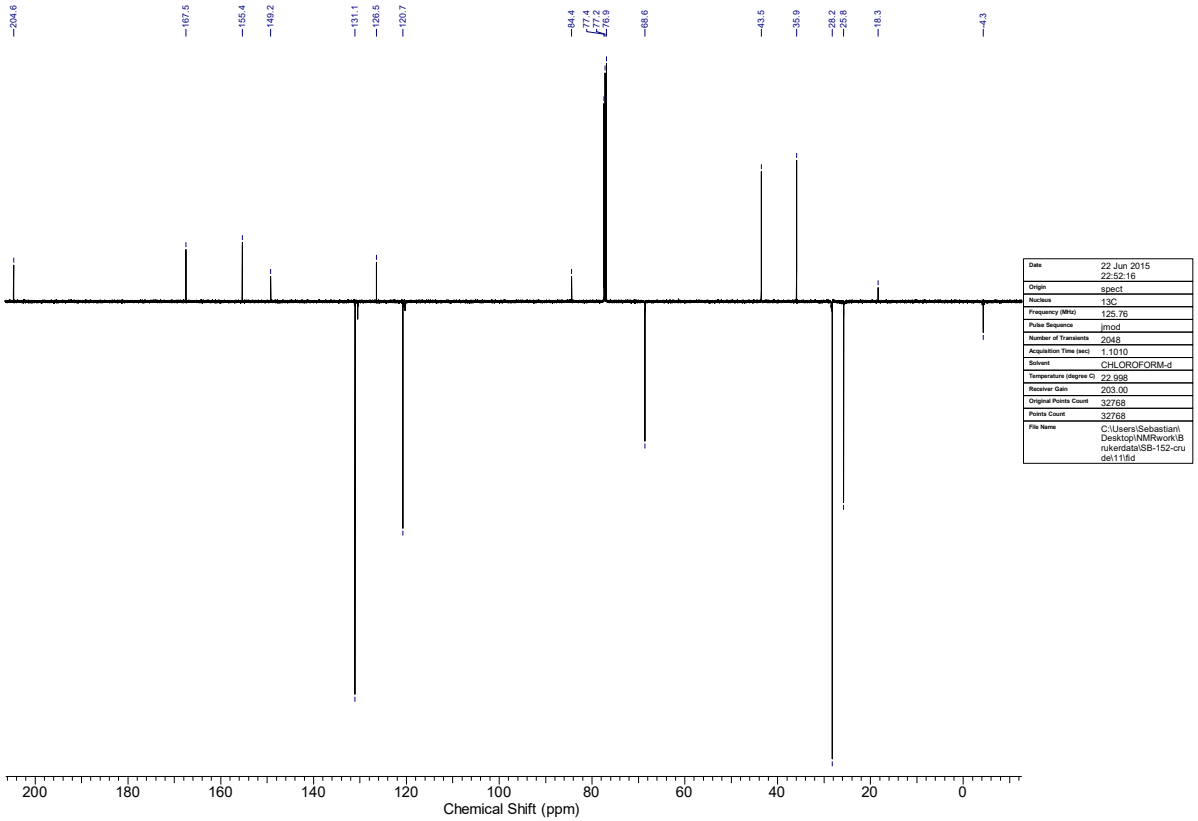

8.20
7.26
M01(d)M02(d)
6.99
6.98
6.73
6.71
5.08
5.06
4.58
4.57
4.56
4.54
4.15
4.13
4.12
4.10
3.71
3.08
3.06
3.05
3.04
3.02
3.00
2.99
2.05
1.42
1.27
1.26
1.25
CO2H
NHBoc
HO
(S)-3
Date 16 Apr 2015 12:54:56
Origin spect
Nucleus 1H
Frequency (MHz) 500.13
Pulse Sequence zg30
Number of Transients 16
Acquisition Time (sec) 3.2768
Solvent CHLOROFORM-d
Temperature (degree C) 23.001
Receiver Gain 32.00
Original Points Count 32768
Points Count 65536
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-122-crude\10\fid
1.0
2.0
2.0
0.7
0.7
1.7
9.0
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

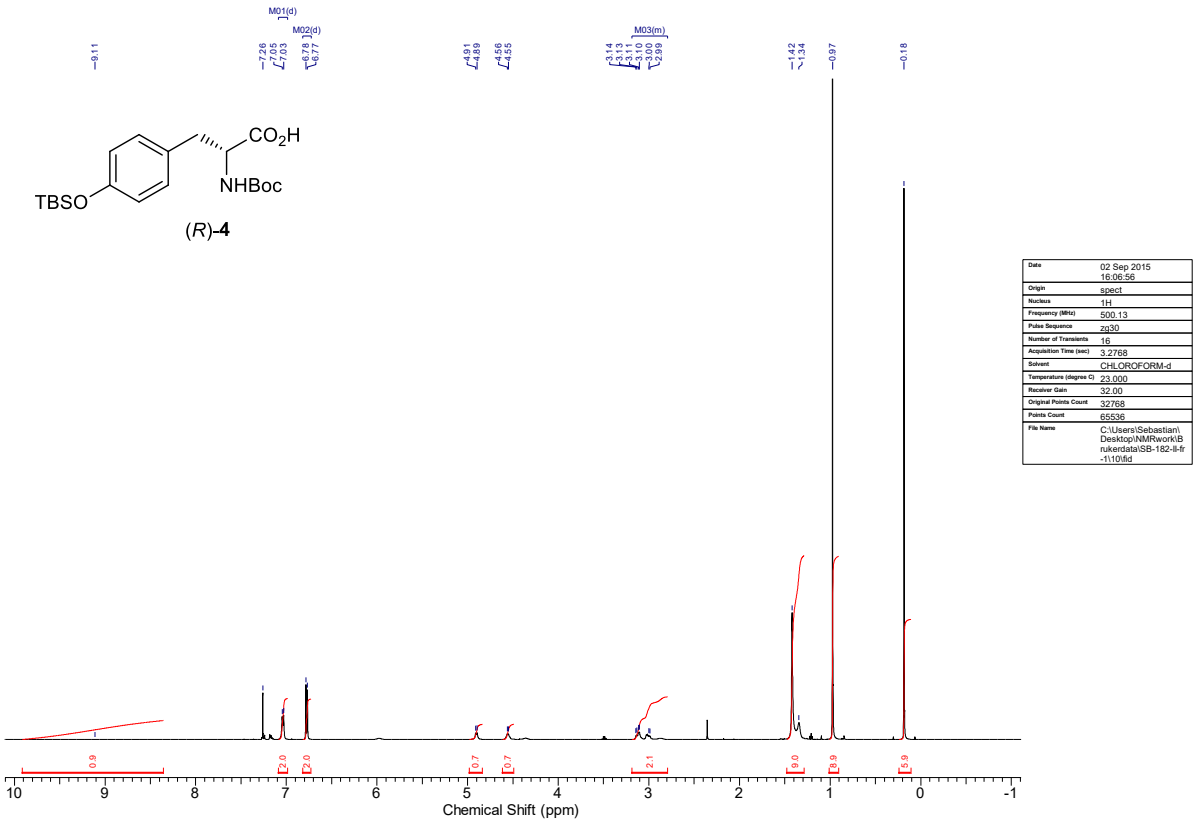

176.1
155.0
130.7
127.6
115.8
77.2
54.6
37.2
28.5
14.3
Date 16 Apr 2015 13:09:52
Origin spect
Nucleus 13C
Frequency (MHz) 125.76
Pulse Sequence jmod
Number of Transients 256
Acquisition Time (sec) 1.1010
Solvent CHLOROFORM-d
Temperature (degree C) 23.000
Receiver Gain 203.00
Original Points Count 32768
Points Count 32768
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-122-crude\11\fid
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

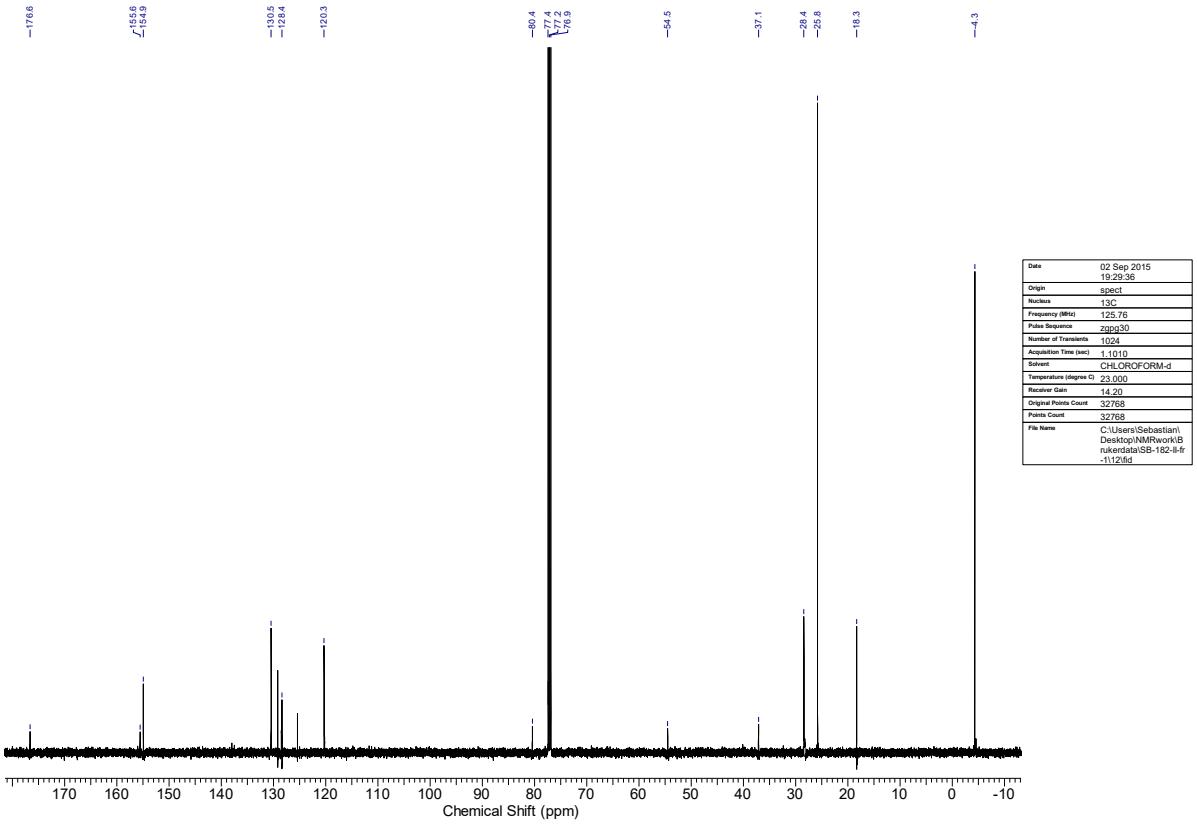

M02(d)
M01(d)
M03(d)
M04(d)
M05(br. s.)
M06(m)
9.45
7.26
7.04
7.03
6.78
6.77
4.85
4.83
4.56
4.56
3.13
3.11
3.11
3.02
3.01
3.00
2.88
2.85
1.42
1.33
0.97
0.18
CO2H
NHBoc
TBSO
(S)-4
Date 06 Nov 2015 15:28:16
Origin spect
Nucleus 1H
Frequency (MHz) 500.13
Pulse Sequence zg30
Number of Transients 16
Acquisition Time (sec) 3.2768
Solvent CHLOROFORM-d
Temperature (degree C) 23.001
Receiver Gain 18.00
Original Points Count 32768
Points Count 32768
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-127\10\fid
0.9
2.0
2.0
2.0
0.7
0.7
1.9
9.2
9.4
5.9
10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

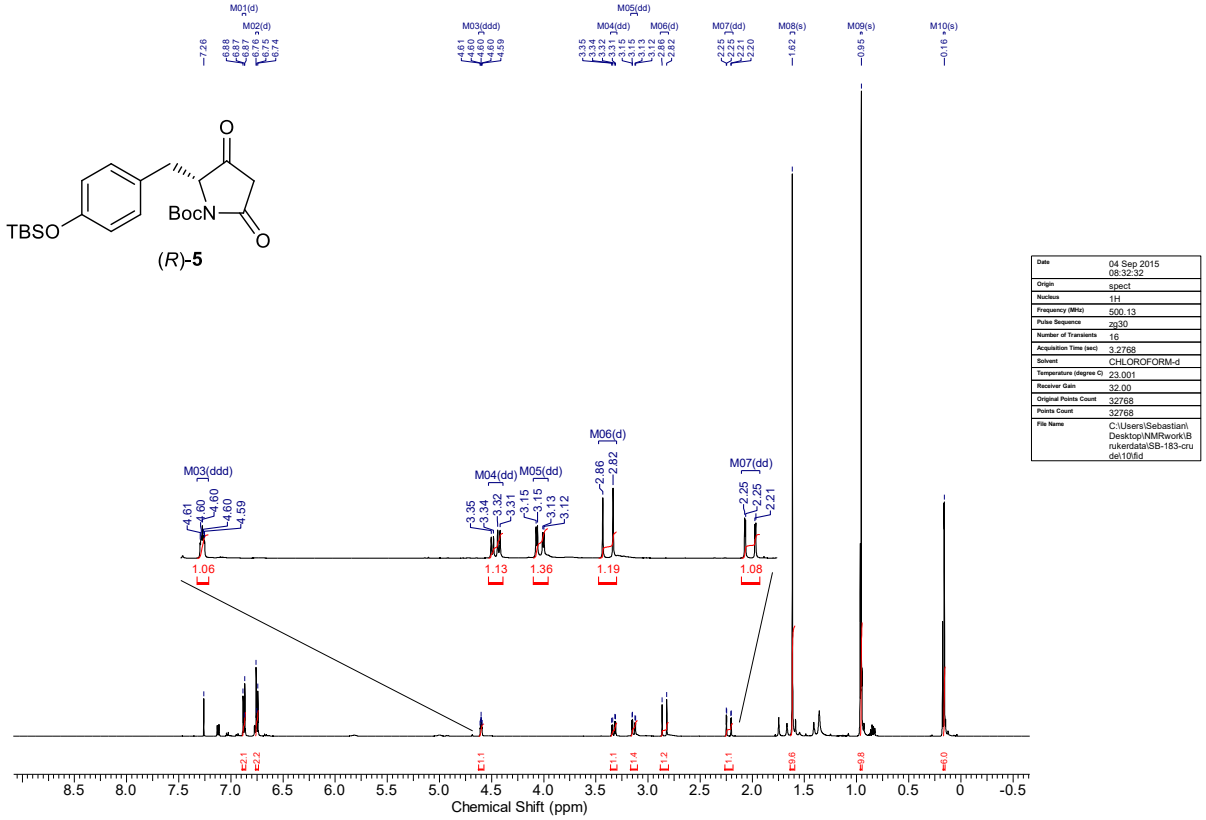

176.8
155.6
154.9
130.5
128.6
120.3
80.4
77.4
77.2
76.9
54.5
37.1
28.4
25.8
18.3
4.3
Date 07 Nov 2015 08:47:12
Origin spect
Nucleus 13C
Frequency (MHz) 125.76
Pulse Sequence zgpg30
Number of Transients 1024
Acquisition Time (sec) 1.1010
Solvent CHLOROFORM-d
Temperature (degree C) 23.000
Receiver Gain 12.70
Original Points Count 32768
Points Count 32768
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-127\11\fid
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


TBSO
BocN
O
O
(S)-5
M03(br. s.)
M04(dd)
M05(dd)
M07(d)
M02(d)
M01(d)
M06(d)
Chemical Shift (ppm)

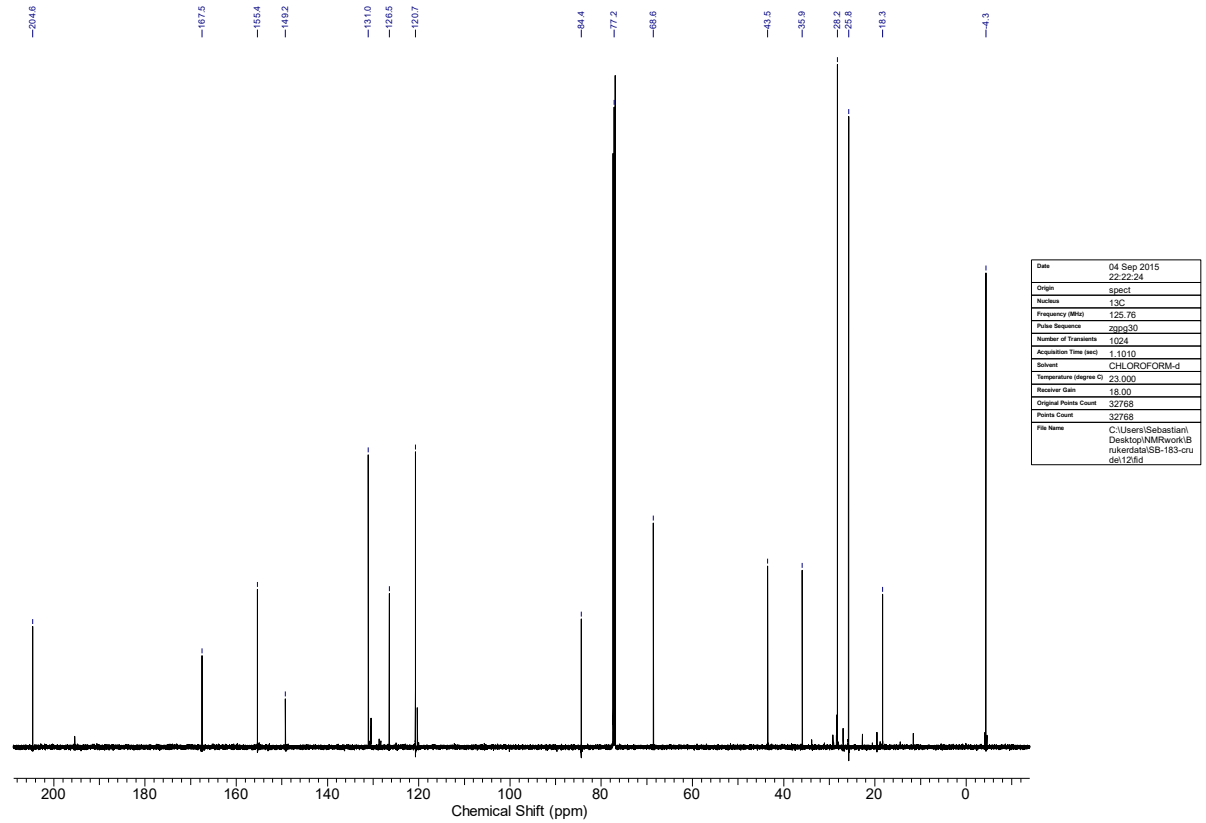

Chemical Shift (ppm)


M01(d)
M02(d)
M03(m)
9.11
7.26
7.05
7.03
6.79
6.77
4.91
4.89
4.56
4.55
3.14
3.13
3.11
3.10
3.00
2.99
1.42
1.34
0.97
0.18
CO2H
NHBoc
TBSO
(R)-4
Date 02 Sep 2015 16:06:56
Origin spect
Nucleus 1H
Frequency (MHz) 500.13
Pulse Sequence zg30
Number of Transients 16
Acquisition Time (sec) 3.2768
Solvent CHLOROFORM-d
Temperature (degree C) 23.000
Receiver Gain 32.00
Original Points Count 32768
Points Count 65536
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-182-II-fr-1\10\fid
0.9
2.0
2.0
0.7
0.7
2.1
9.0
8.9
5.9
Chemical Shift (ppm)

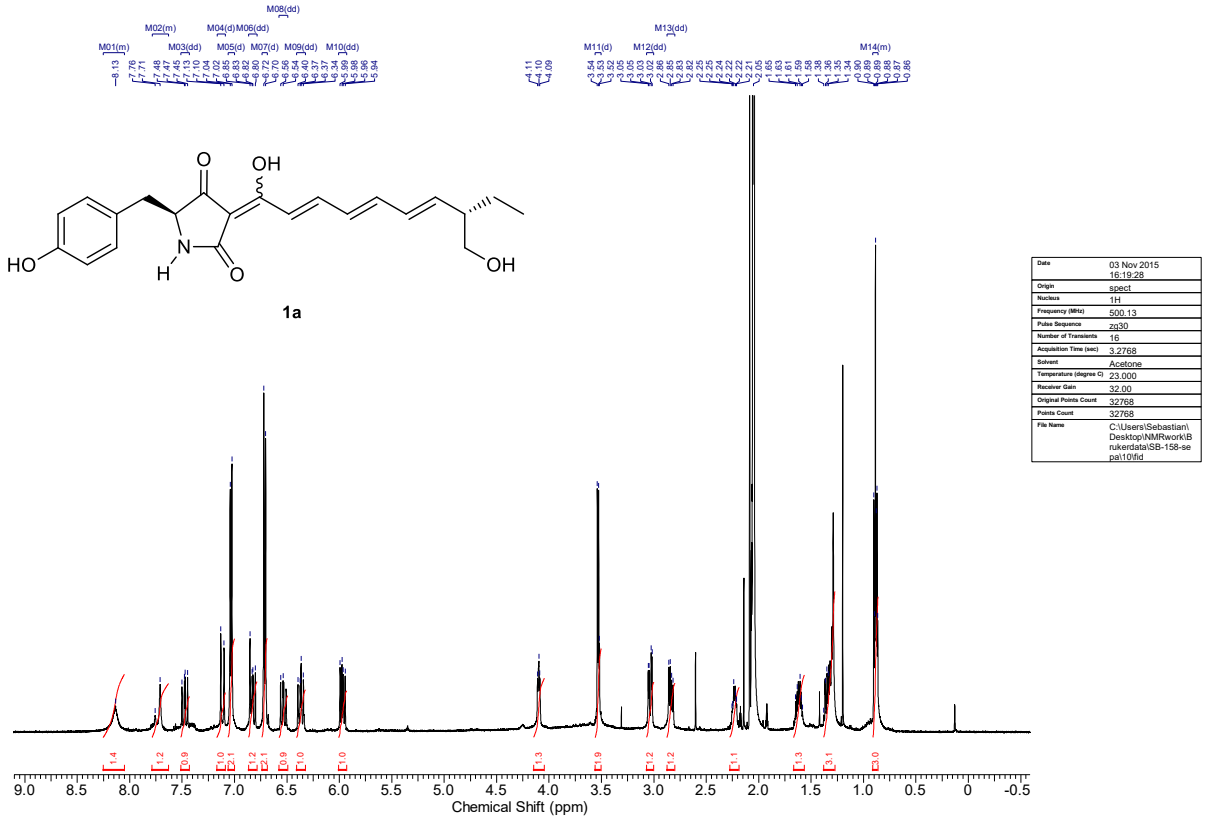

176.6
155.6
154.9
130.5
128.4
120.3
80.4
77.4
77.2
76.9
54.5
37.1
28.4
25.8
18.3
4.3
Date 02 Sep 2015 19:29:36
Origin spect
Nucleus 13C
Frequency (MHz) 125.76
Pulse Sequence zgpg30
Number of Transients 1024
Acquisition Time (sec) 1.1010
Solvent CHLOROFORM-d
Temperature (degree C) 23.000
Receiver Gain 14.20
Original Points Count 32768
Points Count 32768
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-182-II-fr-1\12\fid
Chemical Shift (ppm)



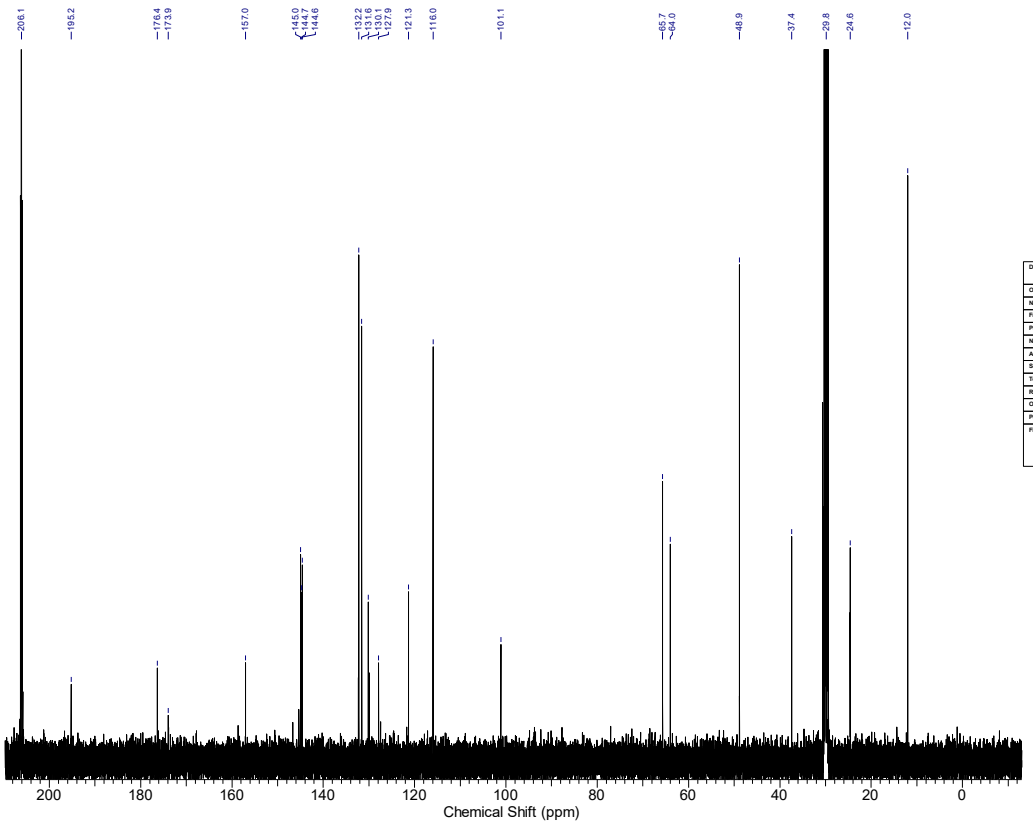
Date	04 Sep 2015 08:32:32
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	CHLOROFORM-d
Temperature (degree C)	23.001
Receiver Gain	32.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-183-crude\10\fid



Date	04 Sep 2015 22:22:24
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	zgpg30
Number of Transients	1024
Acquisition Time (sec)	1.1010
Solvent	CHLOROFORM-d
Temperature (degree C)	23.000
Receiver Gain	18.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-183-crude\12\fid



Date	03 Nov 2015 16:19:28
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	Acetone
Temperature (degree C)	23.000
Receiver Gain	32.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-158-sepa\10\fid



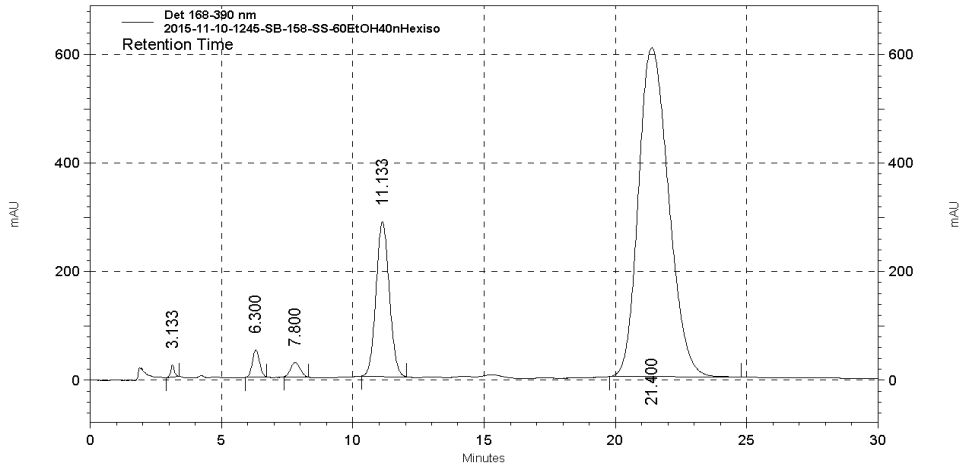
Date	03 Nov 2015 21:28:48
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	zgpg30
Number of Transients	3072
Acquisition Time (sec)	1.1010
Solvent	Acetone
Temperature (degree C)	23.000
Receiver Gain	22.60
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-158-sepa\11\fid

Custom Report

Data File:
C:\32Karat\Projects\Bruckner_Sebastian\Data\2015-11-10-1245-SB-158-SS-60EtOH40nHexiso

Method: C:\32Karat\Projects\Bruckner_Sebastian\Data\TestAuswertung SB-158.met

Instrument Name: HPLC2 (Offline)
Injection Volume: 20 µL
Concentration: 0.5 mg/mL
Analyst: Admin
Acquired: 11/10/2015 12:43:14 PM
Analyzed: 11/11/2015 2:16:55 PM
Printed: 11/11/2015 2:17:26 PM



Det 168-390 nm Results

Pk #	Time	Area	Height
1	3.133	210993	22086
2	6.300	949581	50047
3	7.800	669784	26737
4	11.133	9984812	284929
5	21.400	48415730	606285
Totals		60230900	990084

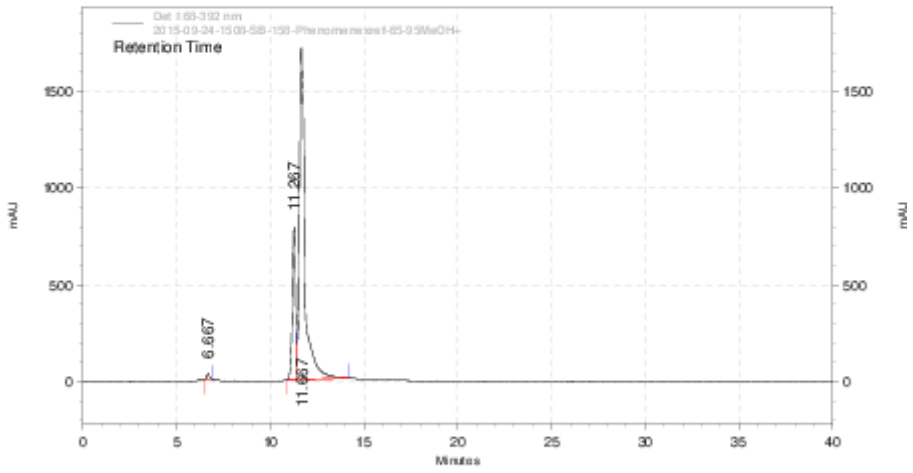
HPLC trace of (5*S*,14*S*)-torrubiellone D **1a**; (40% *n*-hexane, 60% ethanol (+0.1% TFA); 1 mL/min; Phenomenex Lux® Amylose-1 100x4.6mm)

Custom Report

Data File: C:\32Karat\Projects\Sebastian B\Data\2015-09-24-1508-SB-158-Phenomenexref-65-95MeOH+

Method: C:\32Karat\Projects\Sebastian B\Method\65MeOH(H2O)nach5in10auf100fuer40.met

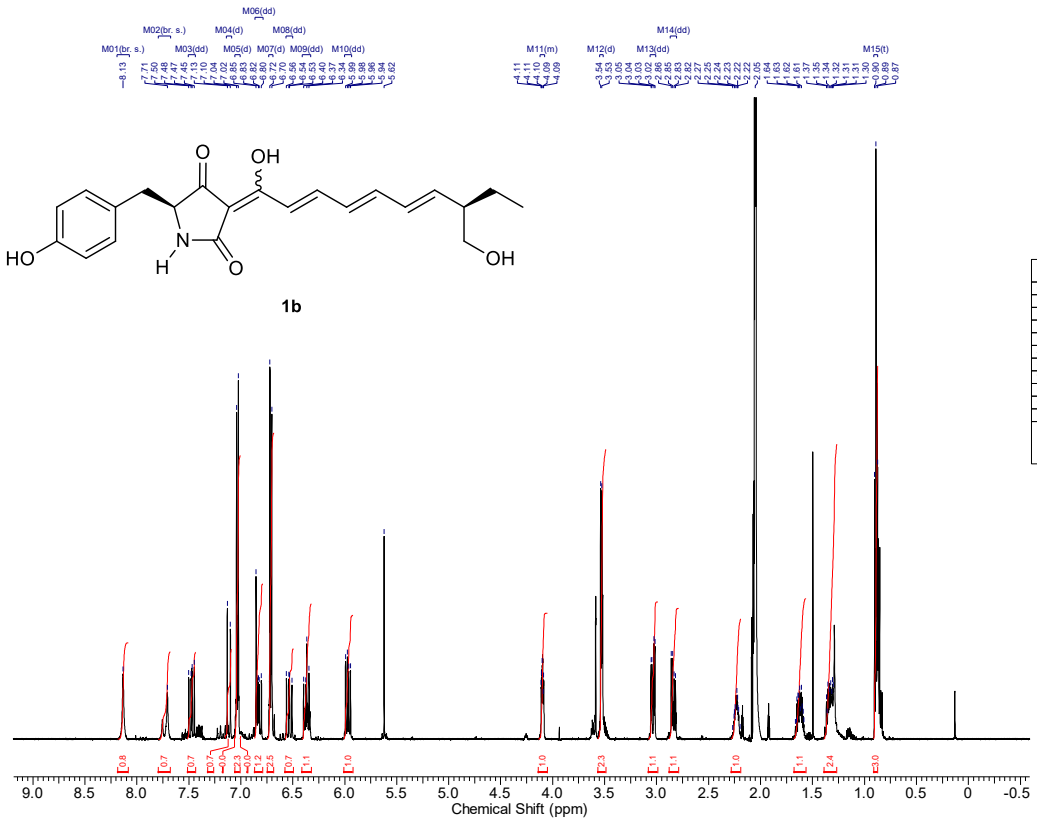
Instrument Name:System 1 (Offline)
Injection Volume: 20 µL
Concentration: 0.5 mg/mL
Analyst: Hoelzel
Acquired: 9/24/2015 3:10:29 AM
Analyzed: 11/11/2015 2:56:25 AM
Printed: 11/11/2015 2:57:13 AM



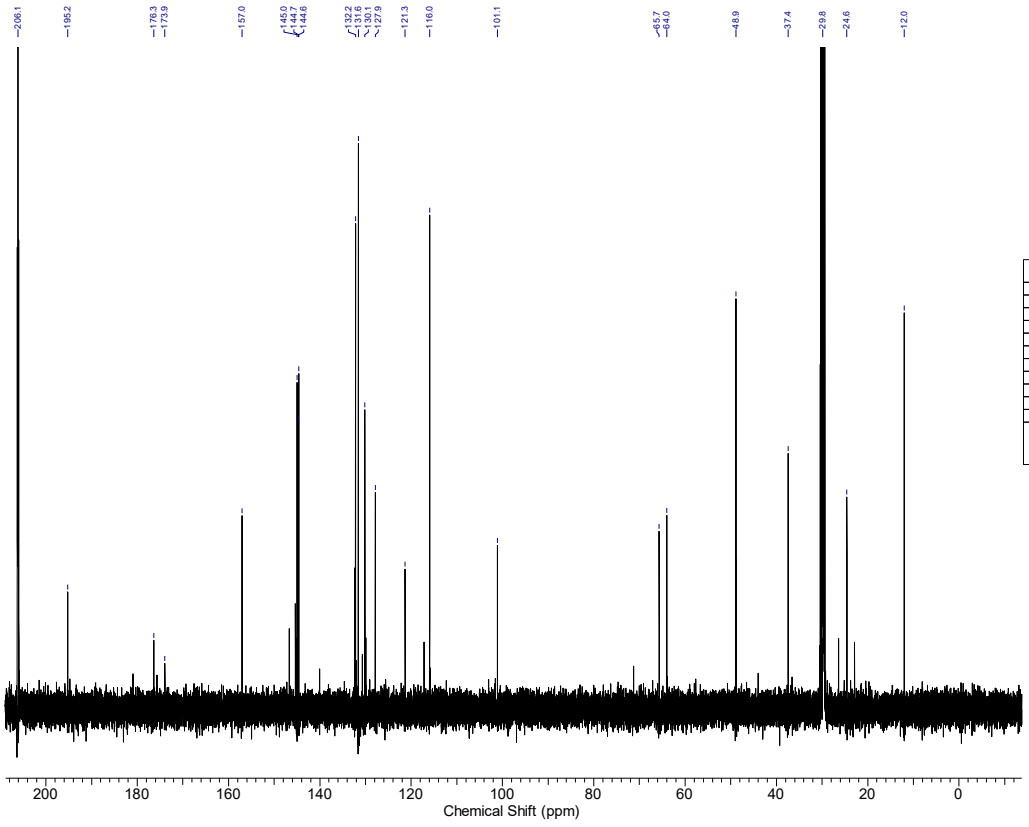
Det 168-392 nm Results

Pk #	Time	Area	Height
1	6.667	307578	30010
2	11.267	9361392	787639
3	11.667	35835226	1710728
Totals		45504196	2528377

HPLC trace of (5*S*,14*S*)-torrubiellone D **1a**; (65% MeOH in H_2O with 0.1% formic acid for 5 min then 95% MeOH in H_2O with 0.1% formic acid in 10 min for 25 min; 0.7 mL/min; Phenomenex Kinetex® C-18 250x4.6mm)



Date	30 Oct 2015 17:38:24
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	32
Acquisition Time (sec)	3.2768
Solvent	Acetone
Temperature (degree C)	22.999
Receiver Gain	32.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-171-re\20\fid



Date	30 Oct 2015 22:07:12
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	zgpg30
Number of Transients	4096
Acquisition Time (sec)	1.1010
Solvent	Acetone
Temperature (degree C)	23.000
Receiver Gain	25.40
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-171-re\21\fid

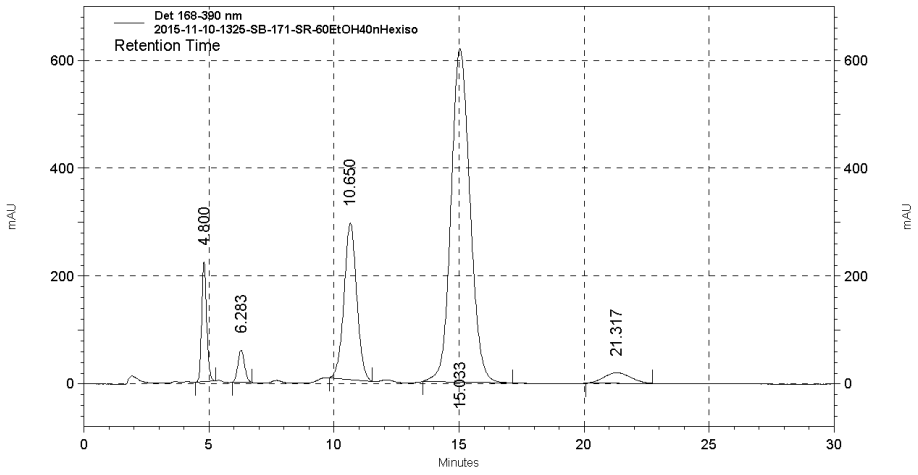
Page 1 of 1

Custom Report

Data File:
C:\32Karat\Projects\Bruckner_Sebastian\Data\2015-11-10-1325-SB-171-SR-60EtOH40nHexiso

Method: C:\32Karat\Projects\Bruckner_Sebastian\Data\TestAuswertung SB-158.met

Instrument Name: HPLC2 (Offline)
Injection Volume: 20 µL
Concentration: 0.5 mg/mL
Analyst: Admin
Acquired: 11/10/2015 1:23:50 PM
Analyzed: 11/11/2015 1:41:07 PM
Printed: 11/11/2015 1:43:25 PM



Det 168-390 nm Results

Pk #	Time	Area	Height
1	4.800	3073146	221758
2	6.283	1081785	59403
3	10.650	10256673	289890
4	15.033	32474365	617958
5	21.317	1429704	19520
Totals		48315673	1208529

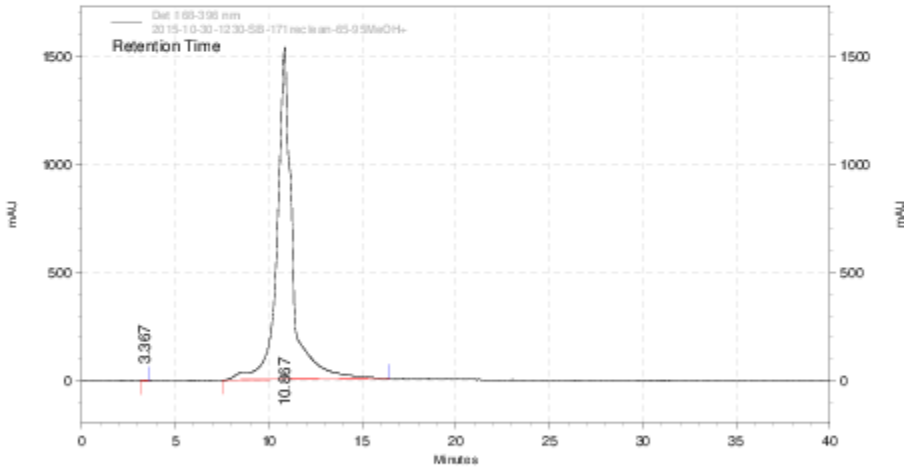
HPLC trace of (5*S*,14*R*)-torrubiellone D **1b**; (40% *n*-hexane, 60% ethanol (+0.1% TFA); 1 mL/min; Phenomenex Lux® Amylose-1 100x4.6mm)

Custom Report

Data File: C:\32Karat\Projects\Sebastian B\Data\2015-10-30-1230-SB-171reclean-65-95MeOH+

Method: C:\32Karat\Projects\Sebastian B\Method\65MeOH(H2O)nach5in10auf100fuer40.met

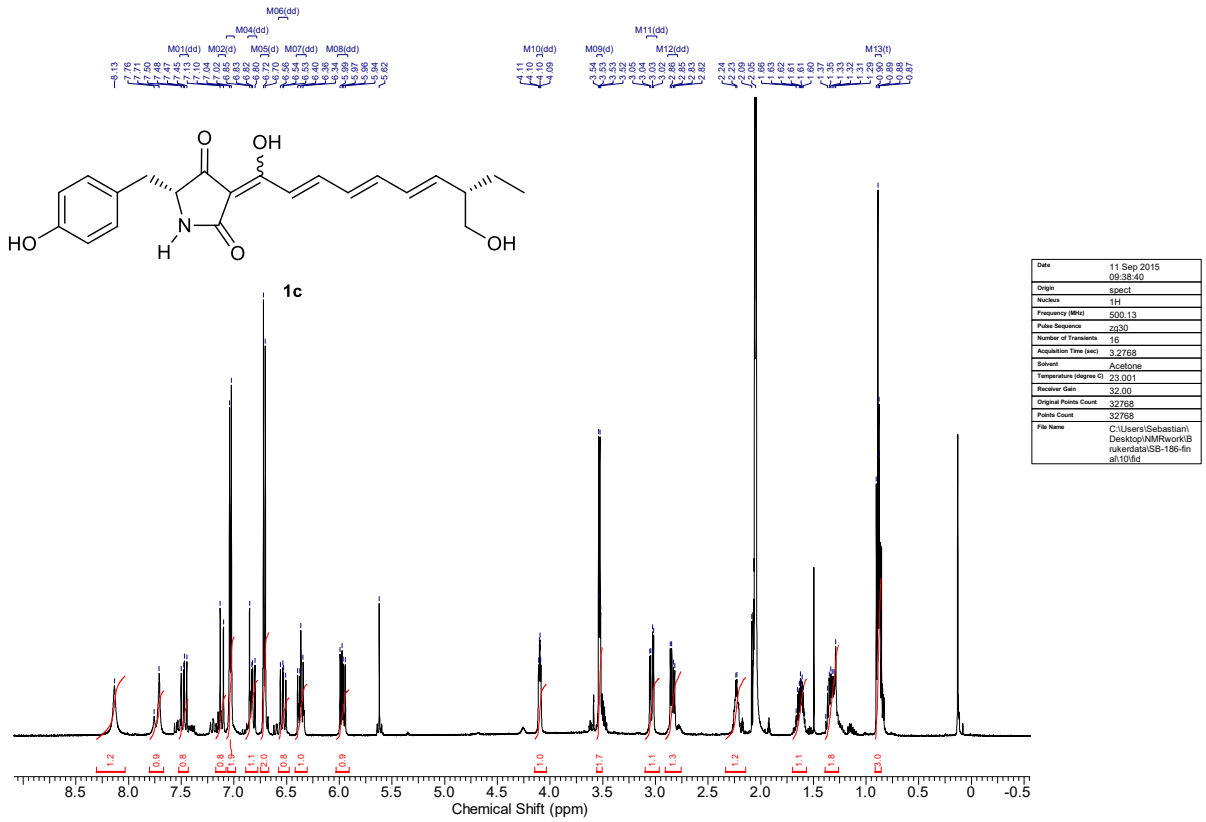
Instrument Name:System 1 (Offline)
Injection Volume: 20 µL
Concentration: 0.5 mg/mL
Analyst: Hoelzel
Acquired: 10/30/2015 12:29:06 AM
Analyzed: 11/11/2015 2:59:01 AM
Printed: 11/11/2015 2:59:26 AM

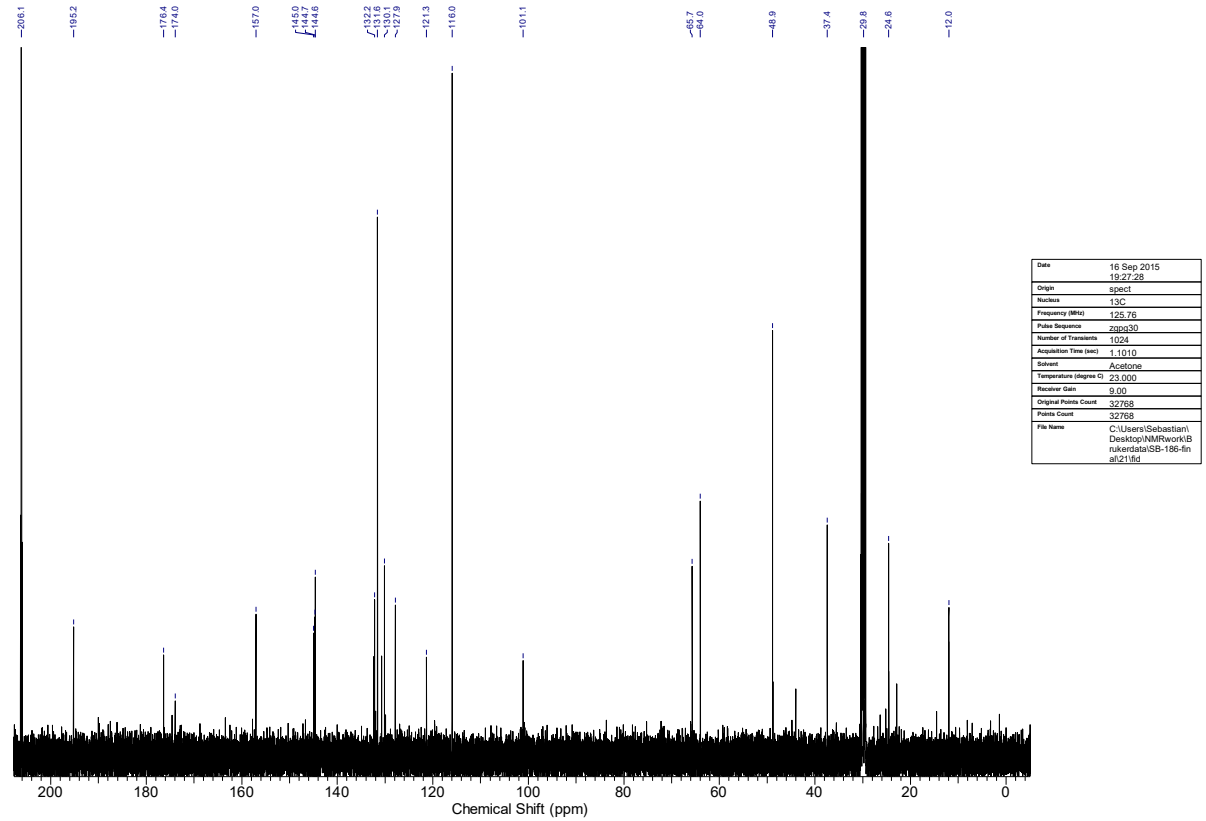


Det 168-396 nm Results

Pk #	Time	Area	Height
1	3.367	21614	2000
2	10.867	86973946	1536459
Totals		86995560	1538459

HPLC trace of (5*S*,14*R*)-torrubiellone D **1b**; (65% MeOH in H_2O with 0.1% formic acid for 5 min then 95% MeOH in H_2O with 0.1% formic acid in 10 min for 25 min; 0.7 mL/min; Phenomenex Kinetex® C-18 250x4.6mm)


M06(dd)
M04(dd)
M01(dd) M02(d) M05(d) M07(dd) M08(dd)
M10(dd) M09(d) M11(dd) M12(dd) M13(t)
O
OH
N
H
O
HO
OH
1c
Chemical Shift (ppm)
Date 11 Sep 2015 09:38:40
Origin spect
Nucleus 1H
Frequency (MHz) 500.13
Pulse Sequence zg30
Number of Transients 16
Acquisition Time (sec) 3.2768
Solvent Acetone
Temperature (degree C) 23.001
Receiver Gain 32.00
Original Points Count 32768
Points Count 32768
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-186-final\10\fid


206.1
195.2
176.4
174.0
157.0
145.0
144.7
144.6
132.2
131.6
130.1
127.9
121.3
116.0
101.1
65.7
64.0
48.9
37.4
29.8
24.6
12.0
Chemical Shift (ppm)
Date 16 Sep 2015 19:27:28
Origin spect
Nucleus 13C
Frequency (MHz) 125.76
Pulse Sequence zgpg30
Number of Transients 1024
Acquisition Time (sec) 1.1010
Solvent Acetone
Temperature (degree C) 23.000
Receiver Gain 9.00
Original Points Count 32768
Points Count 32768
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-186-final\21\fid

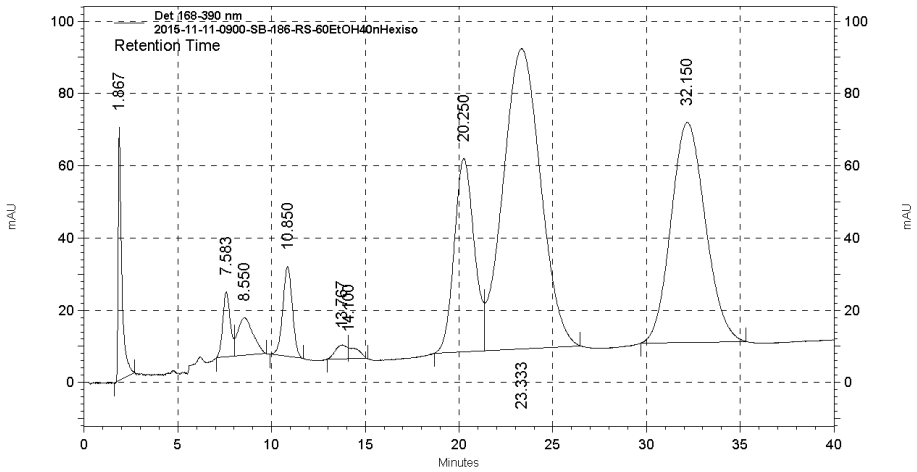
Page 1 of 1

Custom Report

Data File:
C:\32Karat\Projects\Bruckner_Sebastian\Data\2015-11-11-0900-SB-186-RS-60EtOH40nHexiso

Method: C:\32Karat\Projects\Bruckner_Sebastian\Data\TestAuswertung SB-158.met

Instrument Name: HPLC2 (Offline)
Injection Volume: 20 µL
Concentration: 0.5 mg/mL
Analyst: Admin
Acquired: 11/11/2015 9:07:00 AM
Analyzed: 11/11/2015 1:46:21 PM
Printed: 11/11/2015 1:47:03 PM



Det 168-390 nm Results

Pk #	Time	Area	Height
1	1.867	924928	70126
2	7.583	494417	17985
3	8.550	589781	10423
4	10.850	886284	24868
5	13.767	45438	3866
6	14.100	120370	2958
7	20.250	3971473	53450
8	23.333	11544753	83067
9	32.150	7750845	60912
Totals		26328289	327655

HPLC trace of (5*R*,14*S*)-torrubiellone D **1c**; (40% *n*-hexane, 60% ethanol (+0.1% TFA); 1 mL/min; Phenomenex Lux® Amylose-1 100x4.6mm)

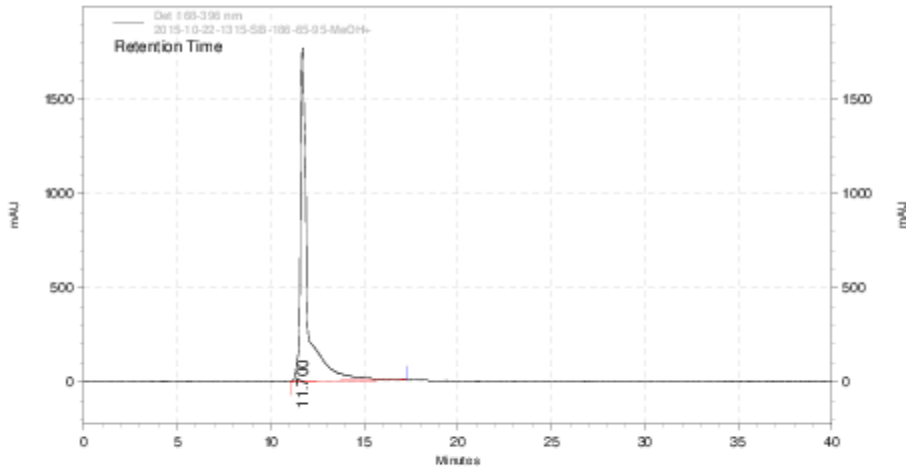
Page 1 of 1

Custom Report

Data File: C:\32Karat\Projects\Sebastian B\Data\2015-10-22-1315-SB-186-65-95-MeOH+

Method: C:\32Karat\Projects\Sebastian B\Method\65MeOH(H2O)nach5in10auf100fuer40.met

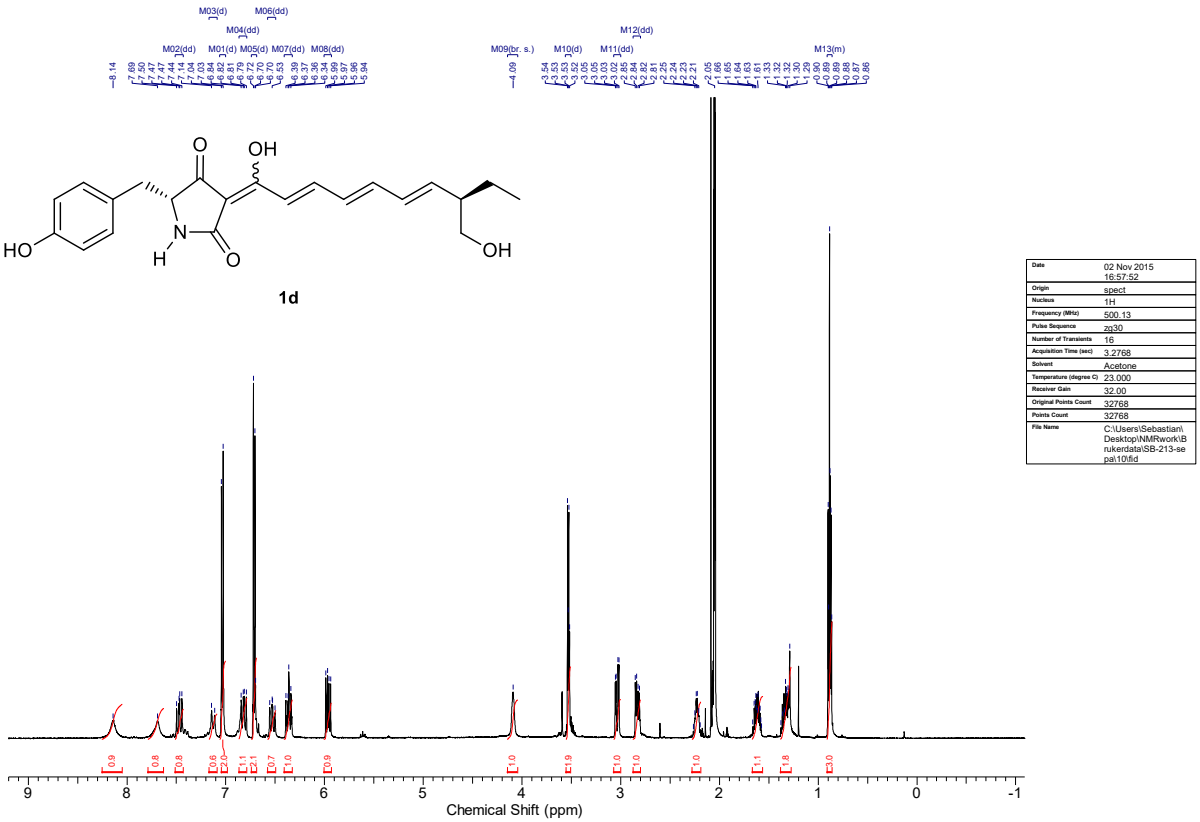
Instrument Name:System 1 (Offline)
Injection Volume: 20 µL
Concentration: 0.5 mg/mL
Analyst: Hoelzel
Acquired: 10/22/2015 1:19:38 AM
Analyzed: 11/11/2015 3:00:51 AM
Printed: 11/11/2015 3:01:10 AM

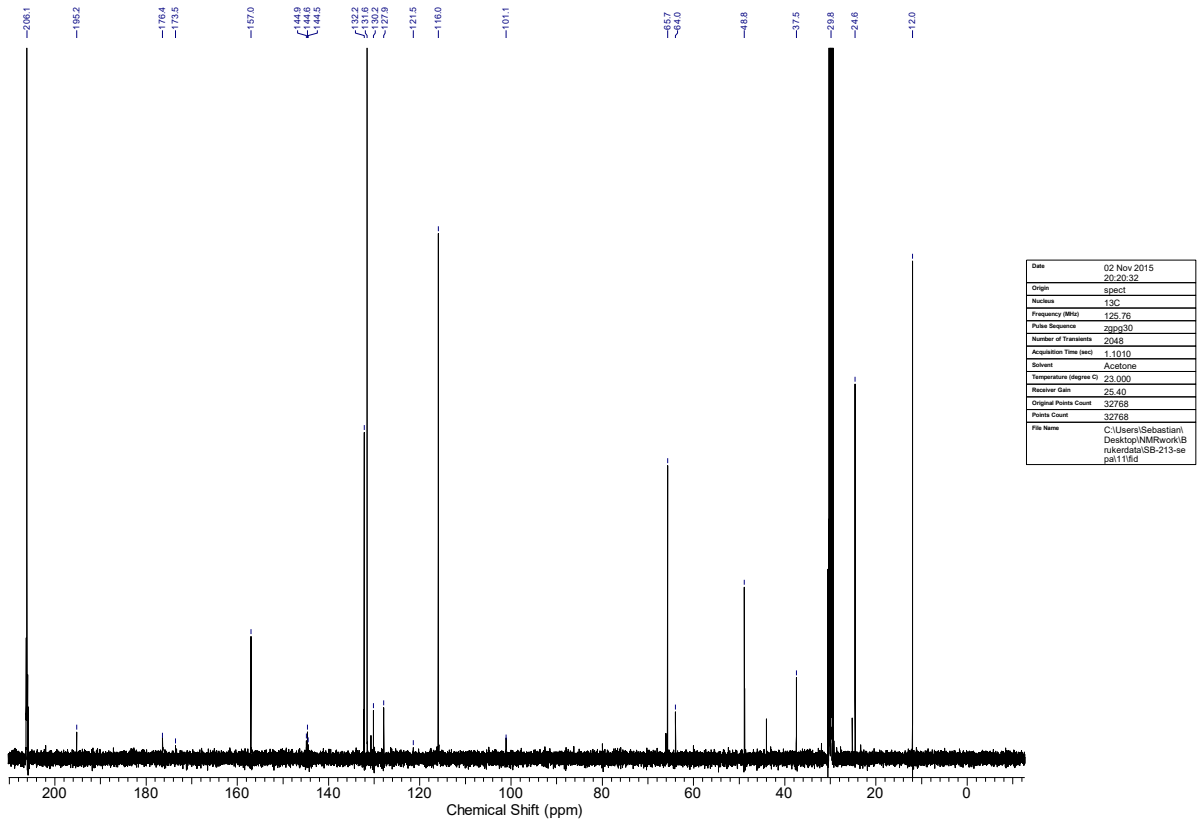


Det 168-396 nm Results

Pk #	Time	Area	Height
1	11.700	46610972	1770233
Totals		46610972	1770233

HPLC trace of (5*R*,14*S*)-torrubiellone D **1c**; (65% MeOH in H_2O with 0.1% formic acid for 5 min then 95% MeOH in H_2O with 0.1% formic acid in 10 min for 25 min; 0.7 mL/min; Phenomenex Kinetex® C-18 250x4.6mm)


M03(d)
M06(dd)
M04(dd)
M02(dd)
M01(d)
M05(d)
M07(dd)
M08(dd)
M09(br. s.)
M10(d)
M12(dd)
M11(dd)
M13(m)
8.14
7.69
7.50
7.47
7.47
7.44
7.14
7.04
7.03
6.84
6.82
6.79
6.72
6.70
6.53
6.39
6.37
6.34
6.00
5.99
5.97
5.96
5.94
4.09
3.54
3.53
3.53
3.52
3.05
3.03
3.02
2.84
2.82
2.51
2.25
2.24
2.23
2.21
2.05
1.66
1.65
1.64
1.63
1.61
1.33
1.32
1.30
1.29
0.90
0.89
0.89
0.88
0.87
0.86
O
OH
HO
N
H
O
OH
1d
Date 02 Nov 2015 16:57:52
Origin spect
Nucleus 1H
Frequency (MHz) 500.13
Pulse Sequence zg30
Number of Transients 16
Acquisition Time (sec) 3.2768
Solvent Acetone
Temperature (degree C) 23.000
Receiver Gain 32.00
Original Points Count 32768
Points Count 32768
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-213-sepa\10\fid
0.9
0.8
0.8
0.6
2.0
1.1
2.1
0.7
1.0
0.9
1.0
1.9
1.0
1.0
1.0
1.1
1.8
3.0
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)

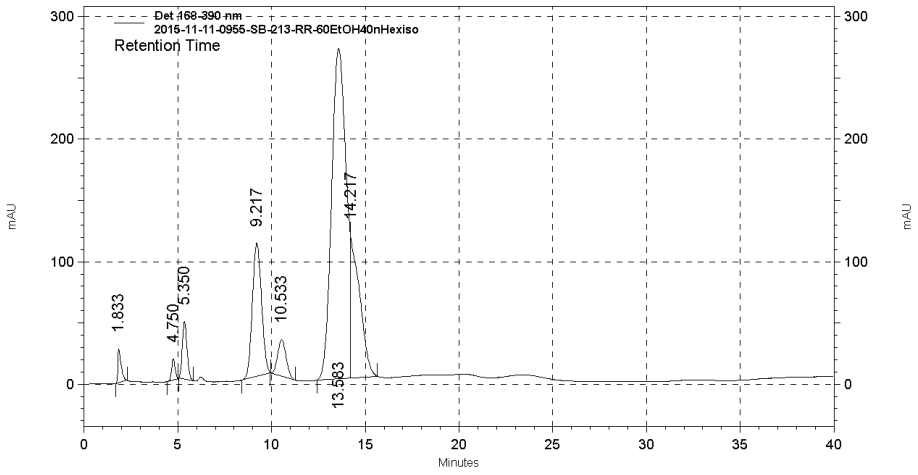

206.1
195.2
176.4
173.5
157.0
144.9
144.6
144.5
132.2
131.6
130.2
127.9
121.5
116.0
101.1
45.7
44.0
48.8
37.5
29.8
24.6
12.0
Date 02 Nov 2015 20:20:32
Origin spect
Nucleus 13C
Frequency (MHz) 125.76
Pulse Sequence zgpg30
Number of Transients 2048
Acquisition Time (sec) 1.1010
Solvent Acetone
Temperature (degree C) 23.000
Receiver Gain 25.40
Original Points Count 32768
Points Count 32768
File Name C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-213-sepa\11\fid
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

Custom Report

Data File:
C:\32Karat\Projects\Bruckner_Sebastian\Data\2015-11-11-0955-SB-213-RR-60EtOH40nHexiso

Method: C:\32Karat\Projects\Bruckner_Sebastian\Data\TestAuswertung SB-158.met

Instrument Name: HPLC2 (Offline)
Injection Volume: 20 µL
Concentration: 0.5 mg/mL
Analyst: Admin
Acquired: 11/11/2015 9:55:05 AM
Analyzed: 11/11/2015 1:49:15 PM
Printed: 11/11/2015 1:49:37 PM



Det 168-390 nm Results

Pk #	Time	Area	Height
1	1.833	334110	27525
2	4.750	215678	16920
3	5.350	824903	46924
4	9.217	3692999	108656
5	10.533	923120	29577
6	13.583	14467036	269367
7	14.217	3911450	115934
Totals		24369296	614903

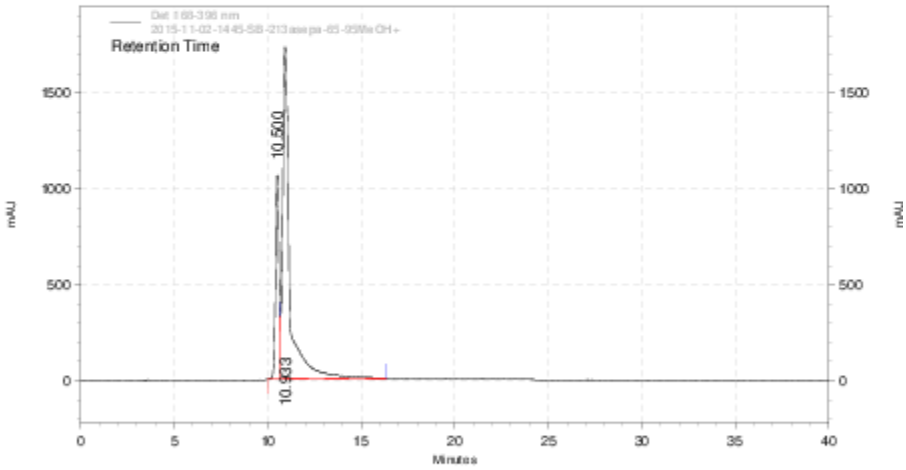
HPLC trace of (5*R*,14*R*)-torrubiellone D **1d**; (40% *n*-hexane, 60% ethanol (+0.1% TFA); 1 mL/min; Phenomenex Lux® Amylose-1 100x4.6mm)

Custom Report

Data File: C:\32Karat\Projects\Sebastian B\Data\2015-11-02-1445-SB-213asepa-65-95MeOH+

Method: C:\32Karat\Projects\Sebastian B\Method\65MeOH(H2O)nach5in10auf100fuer40.met

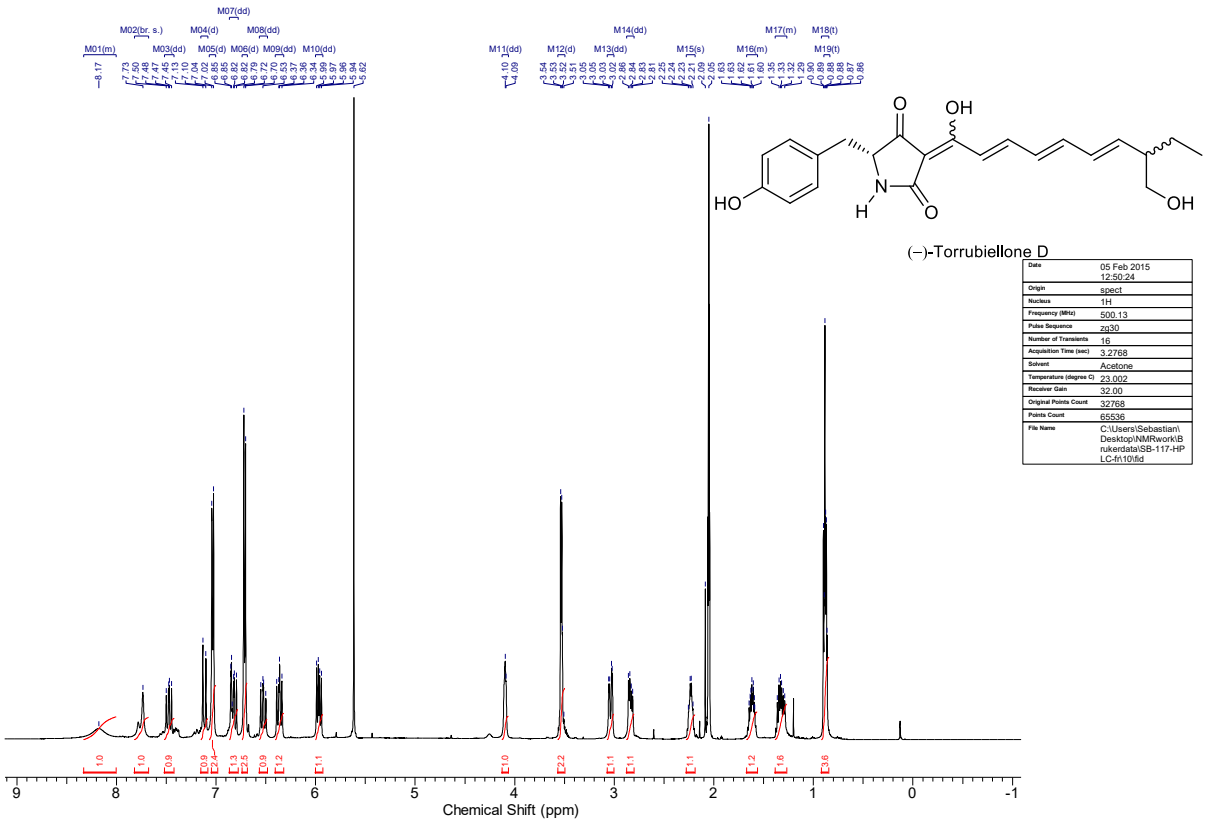
Instrument Name:System 1 (Offline)
Injection Volume: 20 µL
Concentration: 0.5 mg/mL
Analyst: Hoelzel
Acquired: 11/2/2015 2:44:05 AM
Analyzed: 11/11/2015 3:02:13 AM
Printed: 11/11/2015 3:02:30 AM



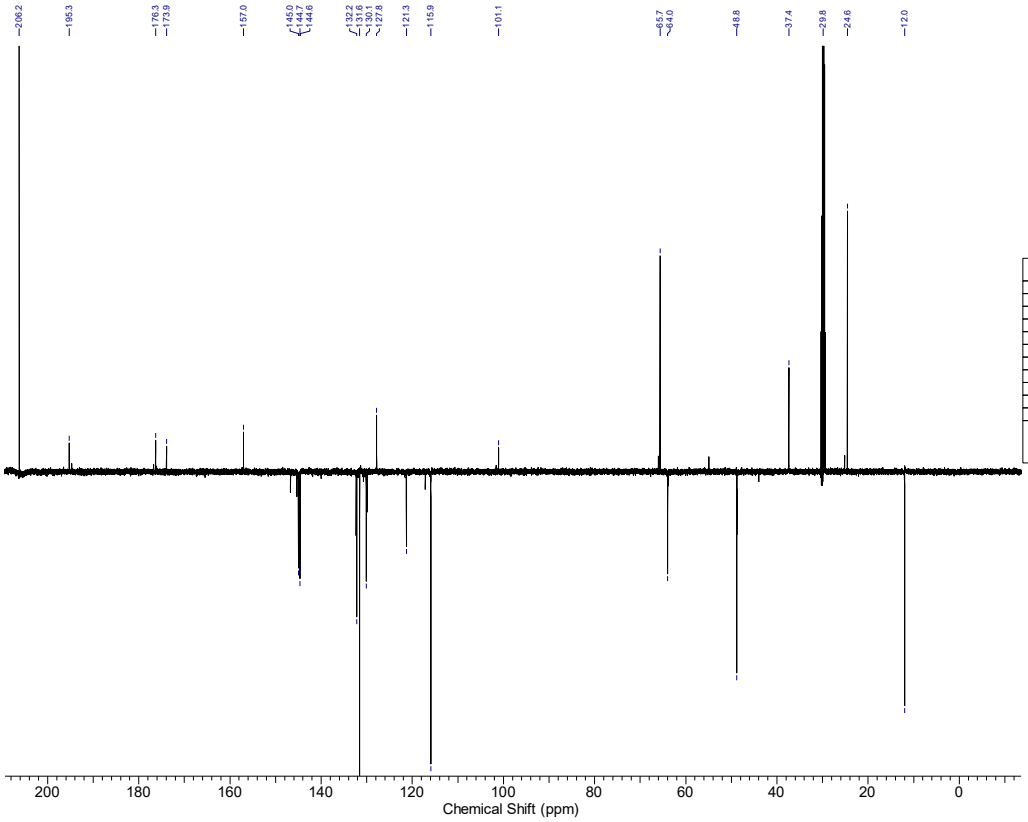
Det 168-396 nm Results

Pk #	Time	Area	Height
1	10.500	14116175	1062632
2	10.933	46216397	1732664
Totals		60332572	2795296

HPLC trace of (5*R*,14*R*)-torrubiellone D **1d**; (65% MeOH in H_2O with 0.1% formic acid for 5 min then 95% MeOH in H_2O with 0.1% formic acid in 10 min for 25 min; 0.7 mL/min; Phenomenex Kinetex® C-18 250x4.6mm)



Date	05 Feb 2015 12:50:24
Origin	spect
Nucleus	1H
Frequency (MHz)	500.13
Pulse Sequence	zg30
Number of Transients	16
Acquisition Time (sec)	3.2768
Solvent	Acetone
Temperature (degree C)	23.002
Receiver Gain	32.00
Original Points Count	32768
Points Count	65536
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-117-HPLC-fr110\fid



Date	05 Feb 2015 13:05:20
Origin	spect
Nucleus	13C
Frequency (MHz)	125.76
Pulse Sequence	jmod
Number of Transients	256
Acquisition Time (sec)	1.1010
Solvent	Acetone
Temperature (degree C)	23.000
Receiver Gain	203.00
Original Points Count	32768
Points Count	32768
File Name	C:\Users\Sebastian\Desktop\NMRwork\Brukerdata\SB-117-HPLC-fr111\fid

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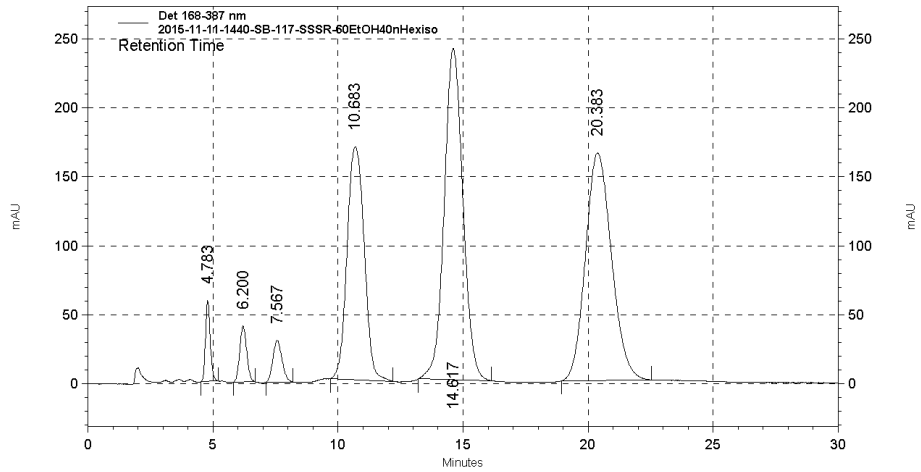
Custom Report

Data File:
C:\32Karat\Projects\Bruckner_Sebastian\Data\2015-11-11-1440-SB-117-SSSR-60EtOH40nHexiso

Method: C:\32Karat\Projects\Default\Methods\untitled.met

Instrument Name: HPLC1 (Offline)
Injection Volume: 20 µL
Concentration: 0.5 mg/mL
Analyst: Admin
Acquired: 11/11/2015 2:41:03 PM
Analyzed: 11/17/2015 9:08:37 AM
Printed: 11/17/2015 9:10:31 AM



Det 168-387 nm Results

Pk #	Time	Area	Height
1	4.783	777144	58659
2	6.200	779225	40385
3	7.567	758457	30109
4	10.683	8051434	168656
5	14.617	12452013	239912
6	20.383	11963041	164798
Totals		34781314	702519

HPLC trace of (–)-torrubiellone D; (40% *n*-hexane, 60% ethanol (+0.1% TFA); 1 mL/min; Phenomenex Lux® Amylose-1 100x4.6mm)

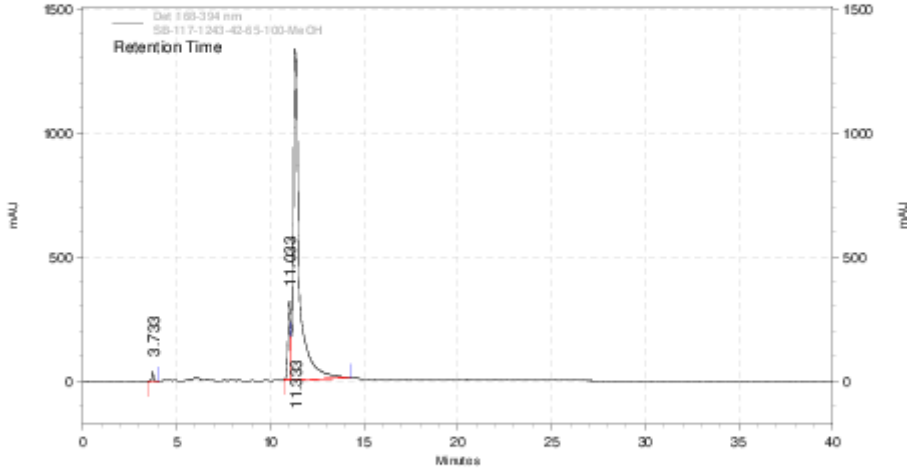
Page 1 of 1

Custom Report

Data File: C:\32Karat\Projects\Sebastian B\Data\SB-117-1243-42-65-100-MeOH

Method: C:\32Karat\Projects\Sebastian B\Method\65MeOH(H2O)nach5in10auf100fuer40.met

Instrument Name:System 1 (Offline)
Injection Volume: 20 µL
Concentration: 0.5 mg/mL
Analyst: Hoelzel
Acquired: 2/5/2004 1:53:01 AM
Analyzed: 11/11/2015 3:06:23 AM
Printed: 11/11/2015 3:06:32 AM



Det 168-394 nm Results

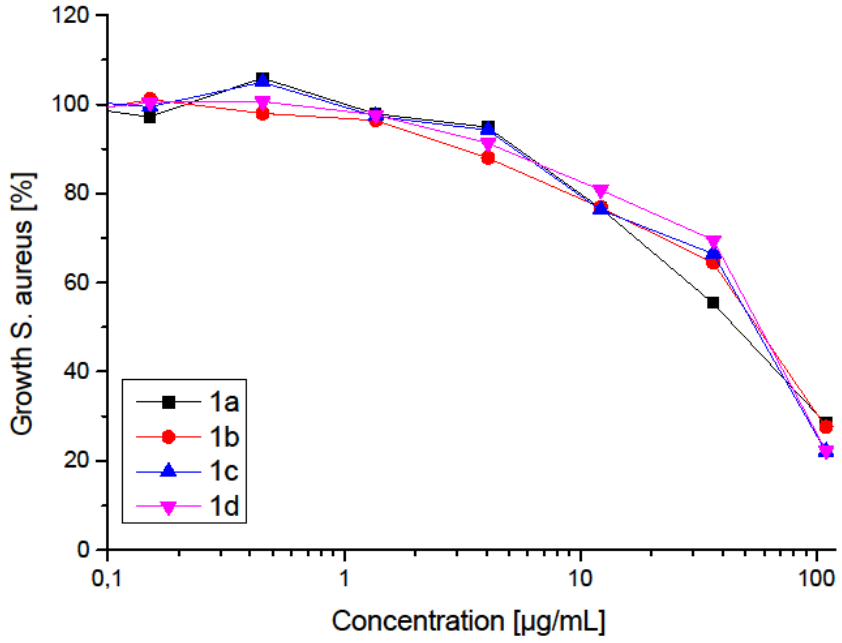
Pk #	Time	Area	Height
1	3.733	289030	40852
2	11.033	3338414	315532
3	11.333	29855112	1333285
Totals		33482556	1689669

HPLC trace of (–)-torrubiellone D; (65% MeOH in H_2O with 0.1% formic acid for 5 min then 95% MeOH in H_2O with 0.1% formic acid in 10 min for 25 min; 0.7 mL/min; Phenomenex Kinetex® C-18 250x4.6mm)

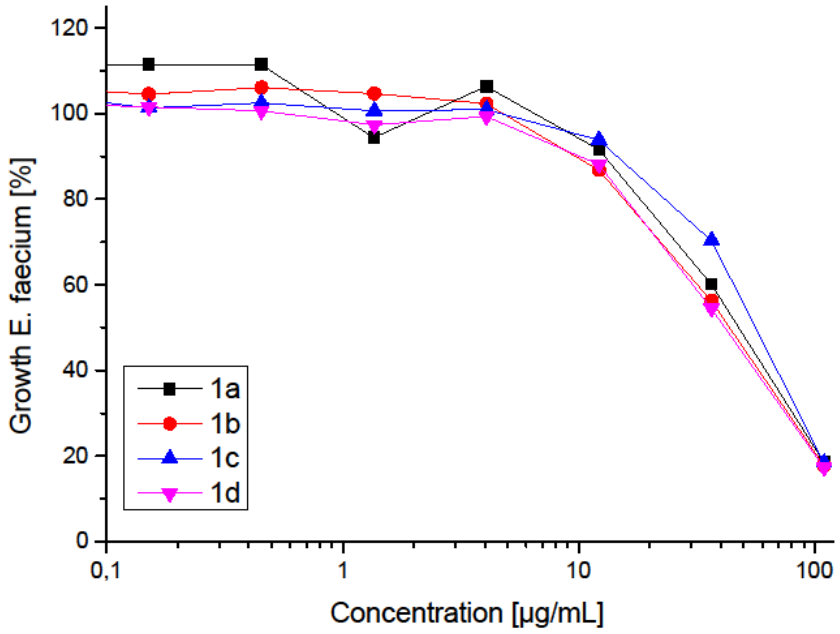
Antibiotic Tests

Staphylococcus aureus (DSM346), *Enterococcus faecium* (DSM20477), *Escherichia coli* K12, *Escherichia coli* Δ TolC (JW5503) and *Escherichia coli* D21f2 were cultivated in glucose-enriched T-medium (30g/l tryptic soy broth, 3g/l yeast extract and 10 % glucose). For all strains the same general procedure was followed to determine IC_{50}-values for each of the compounds: 200 mL medium were inoculated with a colony of the respective strain and incubated at 37 °C with shaking overnight. An aliquot of the overnight culture was diluted with fresh medium to obtain 50 mL with a start OD_{600} of 0.1. This culture was allowed to grow for another 1-2 h at 37 °C. The resulting culture was diluted with fresh medium so that 45 µl in the wells of a transparent 384 well microtiter plate resulted in an OD_{600} of approximately 0.1. 0.45 µl of the compound solutions were added from a compound master plate with the Selma96 semi-automated pipetting system, resulting in a maximum DMSO concentration of 1%. The compound master plate contained diluted DMSO solutions of the torrubiellones in triplicates. The maximum final concentration of the torrubiellones in the microbial cultures was 0.1 mg/mL. The bacterial suspensions were incubated with the compounds at 37 °C for 21 h. Bacterial growth was followed via determination of the optical density (OD) at 600 nm (turbidity) each hour using the microtiter plate reader µQuant™ from BioTek®. Blank and solvent controls were included on the microtiter plate. To compensate any solvent effects growth data were normalized to the growth data of the respective DMSO-containing cultures. From the dependence of growth from the compound concentrations IC_{50} values were determined as the concentration causing 50% growth inhibition by fitting the curves with the 4 parameter logistic nonlinear regression model.

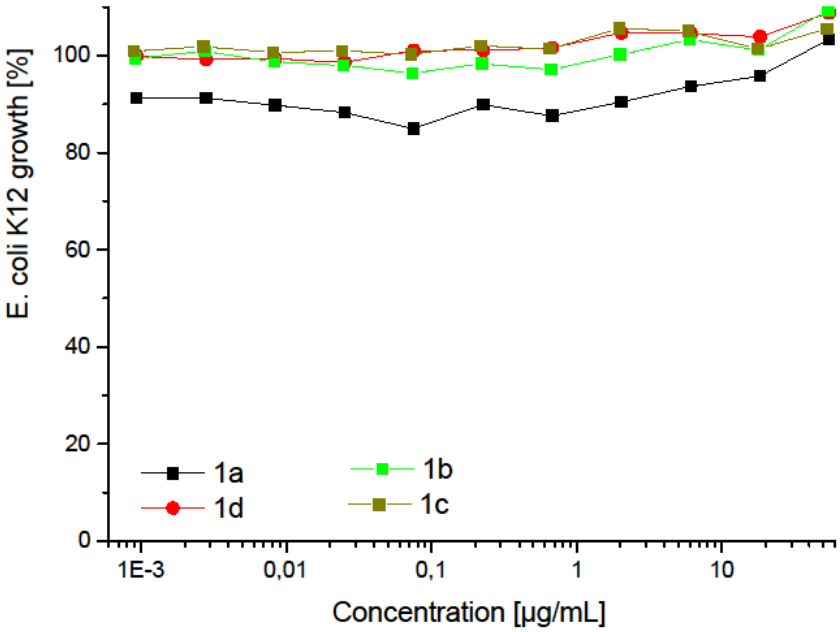
Staphylococcus aureus (DSM 346)



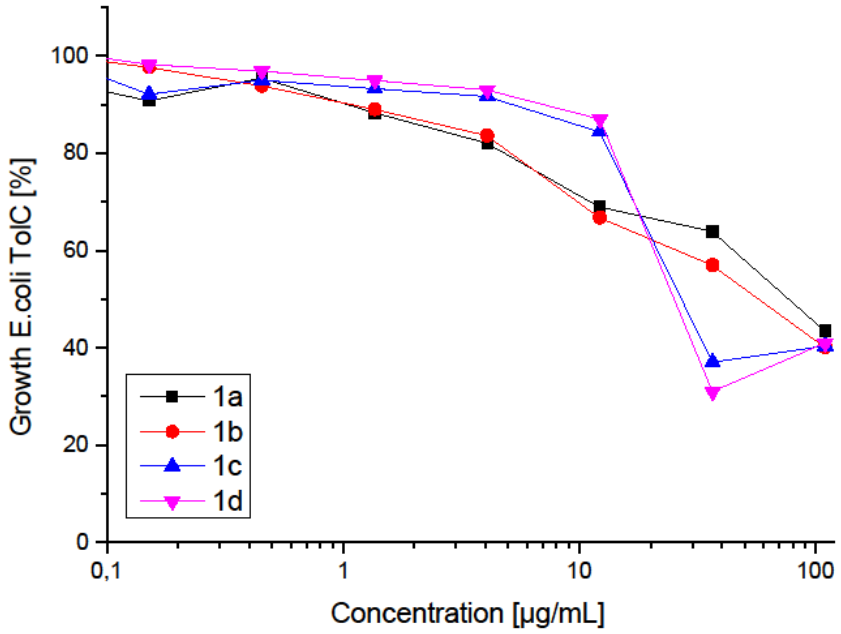
***Enterococcus faecium* (DSM 20477)**



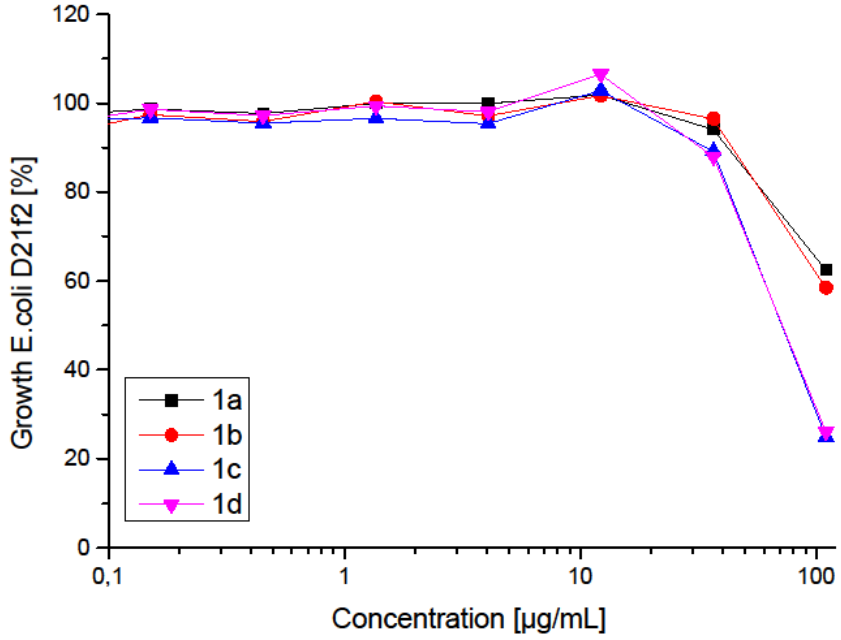
***Escherichia coli* K12**



***Escherichia coli* ΔTolC**



***Escherichia coli* D21f2**



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6.2 A Synthetic Route to β-Hydroxytyrosine-Derived Tetramic Acids: Total Synthesis of the Fungal Metabolite F-14329

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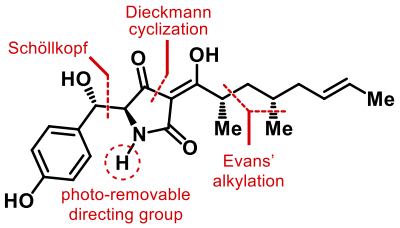

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Total Synthesis

A Synthetic Route to β-Hydroxytyrosine-Derived Tetramic Acids: Total Synthesis of the Fungal Metabolite F-14329

Sebastian Bruckner[+], Robert G. Haase[+], and Rainer Schobert*[a]

Abstract: 3-Acyltetramic acids derived from β-hydroxytyrosine are synthetically challenging. The first route to this structural motif, based upon a condensation between a Meldrum's acid conjugate bearing the acyl side chain, and a β-hydroxytyrosinate, N-protected by an *ortho*-nitrobenzyl group is presented. This group enables the Dieckmann cyclization of the resulting *N*-(β-ketoacyl)amino ester, after which it can be removed photolytically without compromising the delicate 3′-hydroxy group. This strategy was applied to the first total synthesis of the fungal metabolite F-14329 (**1**).

Tetramic acids are distinguished by a range of structural varieties, biological sources, and types of bioactivity. Numerous total syntheses and biosynthetic variations were reported.[1–3] 3-Acyltetramic acids derived from β-hydroxytyrosine are typically produced by fungi. The first derivative to be isolated by Hamburger et al. in 2003 was militarinone B (**2**), a metabolite of the fungus *Paecilomyces militaris* (Figure 1).[4] Four years later, Sankyo Co. Ltd. patented a biotechnological method for the production of F-14329 (**1**), a metabolite of a fungus *Chaunopycnis* sp., and they recommended its use "for the prophylactic and therapeutic treatment of obesity, diabetes, hypertension, and ischemic heart disease".[5] In the years to follow, more compounds of this class were found, most of them while studying the biosynthesis of pyridone alkaloids.[6–8] For instance, tolypocladenol B (**3**) was isolated from the fungus *Tolypocladium cylindrosporum* by Lou et al.[9] Capon et al. re-discovered F-14329 (**1**) together with closely related chaunolidines A (**4**) and B (**5**) in extracts of *Chaunopycnis* sp., found in the inner tissue of a pilmonate false limpet *Siphonaria* sp.[10] Prototenellin D (**6**) was identified as an intermediate in the biosynthesis of the 2-pyridone tenellin by the insect pathogenic fungus *Beauveria bassiana*.[7] Epicoccarine B (**7**) was isolated from a fungus *Epicoccum* sp. dwelling on the fruiting body of the tree fungus *Pholiota squarrosa*.[6] The structures and configurations of these compounds were determined by spectroscopy, X-ray crystallography, and circular dichroism. Despite their broad spectrum of bioactivities, no synthetic route to β-hydroxytyrosine-derived 3-acyltetramic acids has been reported, so far, probably owing to the incompatibility of their benzylic hydroxy group with the usual protocols of tetramic acid cyclization and acylation. We now developed a synthesis of F-14329 (**1**), which is flexible enough to open access to this important class of compounds.

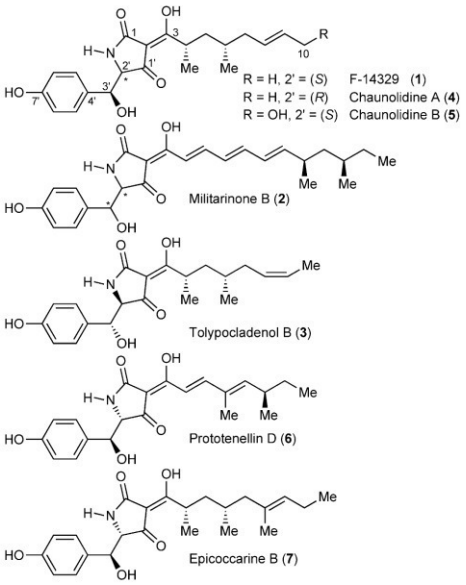

Figure 1. Structures of β-hydroxytyrosine derived tetramic acids.

Scheme 1 delineates the retrosynthetic approach. A late stage Dieckmann cyclization of an aptly protected *N*-β-ketoamide **8**, followed by mild deprotection, was used to afford target compound **1**. Precursor **8** should be accessible by *N*-acylation of a protected β-hydroxytyrosine **9** with a suitable β-ketoacyl derivative **10** of the required side chain, which could be a thioester, or a Meldrum's acid derivative. Amino acid **9** was to be built up, according to Schöllkopf, from bislactim ether **11** and *p*-methoxybenzaldehyde **12**. The side chain precursor **10** should be available from an α,γ-dimethyloctenoic acid **13**, the stereogenic centers of which could be established

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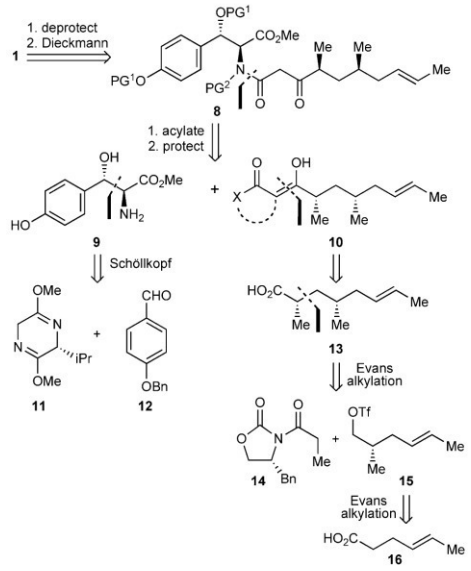
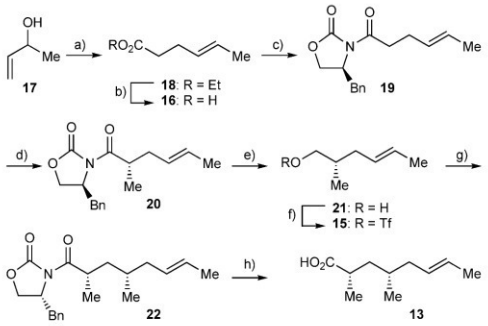
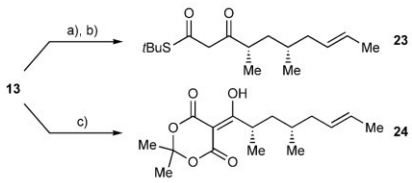


Scheme 1. Retrosynthetic approach to F-14329 (**1**).



Scheme 2. Synthesis of **13**. Reagents and conditions: a) $MeC(OEt)_3$, $EtCO_2H$, reflux, 1 h; 73%. b) KOH, EtOH, H_2O, RT, 20 min; 72%. c) PivCl, NEt_3, THF, 0 °C, 1 h; then (*S*)-benzyloxazolidinone, LiCl, RT, 1 h; 89%. d) NaHMDS, MeI, THF, −78 °C, 1 h; 84%. e) $LiBH_4$, Et_2O, MeOH, 0 °C, 35 min; 84%. f) Tf_2O, pyridine, CH_2Cl_2, −78 °C, 90 min. g) (*R*)-4-Benzyl-3-propionyl-2-oxazolidinone, LDA, THF, −78 °C, 30 min; then **15**, 4 h; 49% over 2 steps. h) BnOLi, THF, 0 °C, 2.5 h; then KOH, MeOH, H_2O, RT, 3 days; 76% over 2 steps. PivCl = pivaloyl chloride; NaHMDS = sodium bis(trimethylsilyl)amide; Tf_2O = triflic anhydride; LDA = lithium diisopropylamide.



Scheme 3. Syntheses of **23** and **24**. Reagents and conditions: a) CDI, THF, RT, 16 h. b) *tert*-Butylthioacetate, LDA, THF, −78 °C, 1 h; 46% over 2 steps. c) EDC·HCl, DMAP, CH_2Cl_2, RT, 30 min; then Meldrum's acid, 24 h; 99%. CDI = carbonyldiimidazole; EDC·HCl = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; DMAP = 4-dimethylaminopyridine.

by two consecutive Evans alkylation steps starting from hexenoic acid **16** and proceeding via chiral imide **14** and triflate **15**.

For the synthesis of the 3-acyl side chain precursor **13**, but-3-en-2-ol (**17**) was reacted with triethyl orthoacetate in an *E*-selective Johnson–Claisen rearrangement to afford ethyl hex-4-enoate (**18**) (Scheme 2). Its saponification gave carboxylic acid **16**, which was converted first into a mixed anhydride with pivalic acid, and then into an Evans imide **19**. Its deprotonation with NaHMDS at −78 °C and quenching of the resulting enolate with iodomethane left a separable mixture of two product diastereoisomers.

The major isomer **20** was cleaved with $LiBH_4$ at 0 °C to afford (2*S*,4*E*)-2-methylhex-4-enol (**21**), which was treated with triflic anhydride at −78 °C to afford the unstable triflate **15**. (*R*)-4-Benzyl-3-propionyl-2-oxazolidinone (**14**) was deprotonated with a small excess of LDA and the lithium enolate was quenched with freshly prepared triflate **15** to give imide **22**. Its cleavage with lithium benzylate followed by saponification of the resulting ester left (2*S*,4*S*,6*E*)-2,4-dimethyloct-6-enoic acid (**13**).

Considering that we intended to generate the 3-acyltetramic acid moiety of **1** by a Dieckmann cyclization, we converted acid **13** into two different β-ketoacyl derivatives, **23** and **24**, suitable for an N-acylation of an aptly substituted β-hydroxytyrosinate (Scheme 3). β-Ketothioester **23** was obtained by reacting acid **13** with 1,1′-carbonyldiimidazole according to Moody et al.,[11] to give the corresponding imidazolylacyl derivative, which was treated with the lithium salt of *tert*-butyl thioacetate. For the synthesis of derivative **24**, acid **13** was activated with EDC·HCl and then reacted with Meldrum's acid.

The stereogenic centers in the β-hydroxytyrosinate were introduced as described by Boger et al.[12] (Scheme 4). Aldehyde **12** was reacted with the (*R*)-configured Schöllkopf bislactim ether **11** to furnish the separable diastereomers **25** and **26** which were hydrolyzed to the optically pure β-hydroxytyrosinates **27** and **29**.[13]

The feasibility of an *N*-(β-keto)acylation of unprotected β-hydroxytyrosinates by a silver mediated aminolysis of thioester **23** according to the general protocol by Ley et al[14] was explored with methyl β-hydroxytyrosinate (**28**), prepared by debenzylation of the waste diastereomer **27** (Scheme 3, Scheme 4). β-Ketoamide **8′** was obtained as a crude product not amenable to further purification. An attempted cyclization of **8′** under conditions described in the literature for simple unprotected *N*-acyl tyrosinates[15] failed to give **31**, a diastereomer of F-14329 and chaunolidine A, but afforded the retro-aldol product **30** instead (Scheme 5).

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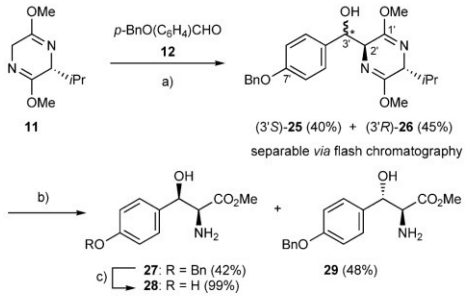
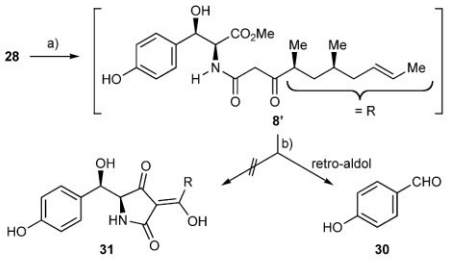


Scheme 4. Synthesis of β-hydroxytyrosinates **27** and **29**. Reagents and conditions: a) *n*BuLi, THF, −78 °C, 15 min; then **12**, 1.5 h. b) 0.25 M HCl, THF, MeCN, RT, 22 h. c) 10% Pd/C, H_2, MeOH, RT, 1 h.



Scheme 5. Failed cyclization of unprotected *N*-(β-ketoacyl)hydroxytyrosinate **8′**. Reagents and conditions: a) $AgCO_2CF_3$, MS 4 Å, NEt_3, **23**, THF, 0 °C, 1.5 h, light exclusion; 31% crude. b) KO*t*Bu, THF, RT, 5 min (MS = molecular sieve).

To favor Dieckmann cyclization over retro-aldol fragmentation, we introduced an *N*-2,4-dimethoxybenzyl (DMB) group, previously shown by Schlessinger et al. to render β-ketoamide anions more nucleophilic.[17] Moreover, nitrogen substituents larger than hydrogen are thought to promote the Dieckmann cyclization by changing the amide conformation from *trans* to *cis*, thus allowing for a sterically more favorable nucleophilic attack at the ester carbonyl (Figure 2). This assumption was first stated by Suzuki et al.[18] in their synthesis of the macrolactam macrocidin A, in which they noticed a conformational change in X-ray structures of acyclic precursors.

The introduction of an *N*-DMB group was possible only after protection of the β-hydroxy group. O-silylation and debenzylation of **29** gave aminoester **32** (Scheme 6). Its *N*-DMB protection and subsequent *N*-β-ketoacylation with thioester **23** gave a β-ketoamide (not shown) that decomposed like **8′** when treated with NaOMe. Apparently, in the presence of a β-hydroxy or β-silyloxy group, the phenolic OH group of tyrosine-derived *N*-β-ketoamides needs to be protected too, prior to the Dieckmann cyclization, in contrast to tyrosinates lacking the β-hydroxy function.[16] Hence, phenol **32** was first N-protected with 2,4-dimethoxybenzaldehyde/$NaBH_3CN$ and then O-silylated with TBSCl to give the fully protected aminoester **33**. Its Ley acylation with β-ketothioester **23** and subsequent basic cyclization of the crude intermediate β-ketamide **8** (PG^1 = TBS, PG^2 = DMB; PG = protecting group) afforded the protected F-14329 **35**. However, the DMB group of **35** could not be removed to give **36** without decomposition, neither under acidic, nor hydrogenolytic, nor oxidative conditions. This finding is in accordance with previously reported problems to deprotect the nitrogen of a tetramic acid bearing a saturated 3-acyl side chain,[18] whereas *N*-DMB residues of tetramic acids with unsaturated 3-acyl side chains were successfully removed

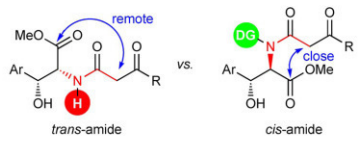
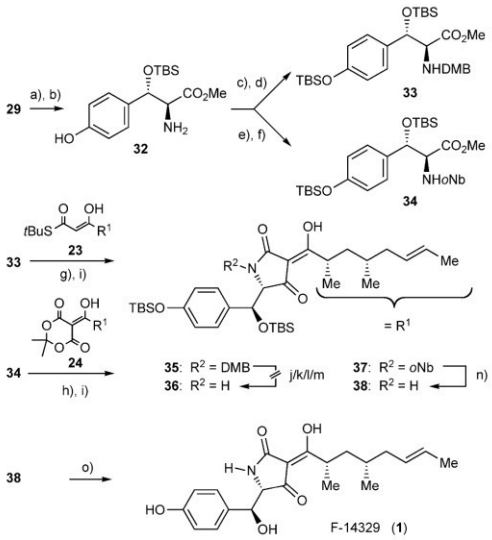


Figure 2. Predominant conformations of *N*-(β-ketoacyl)hydroxytyrosinates with and without directing group (DG).



Scheme 6. Synthesis of protected F-14329 **35**, failed deprotection, and synthesis of F-14329 (**1**). Reagents and conditions: a) TBSOTf, NEt_3, CH_2Cl_2, −10 °C→4 °C, 16 h; 82%. b) 10% Pd/C, H_2, MeOH, RT, 15 h; 99%. c) 2,4-dimethoxybenzaldehyde, MeOH, AcOH, RT, 30 min; then $NaBH_3CN$, 3 h; 51%. d) TBSCl, imidazole, CH_2Cl_2, RT, 19 h, 68%. e) TBSOTf, NEt_3, CH_2Cl_2, −10 °C→4 °C, 22 h; 82%. f) *o*-nitrobenzaldehyde, $MgSO_4$, MeOH, AcOH, RT, 30 min; then $NaBH_3CN$, 3 h; 76%. g) $AgCO_2CF_3$, MS 4 Å, NEt_3, **23**, THF, 0 °C, 1.5 h, light exclusion, 51% crude. h) **24**, MS 3 Å, dioxane, reflux, 2.5 h, 57% crude. i) NaOMe, MeOH, RT, 10 min; 50% (**35**)/54% (**37**) over 2 steps. j) 10% TFA in CH_2Cl_2, RT. k) $Pd(OH)_2$, NH_4HCO_2, MeOH, reflux. l) CAN, MeCN, H_2O, RT. m) DDQ, $CHCl_3$, CH_2Cl_2, H_2O, RT. n) *hν* 366 nm 4 W, MeCN, H_2O, RT, 1 d; 72%. o) TBAF, AcOH, THF, 0 °C→RT, 38 h; 81%. TBSOTf = *tert*-butyldimethylsilyl triflate; TBSCl = *tert*-butyldimethylsilyl chloride; TFA = trifluoroacetic acid; CAN = ceric ammonium nitrate; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TBAF = tetra-*n*-butylammonium fluoride.

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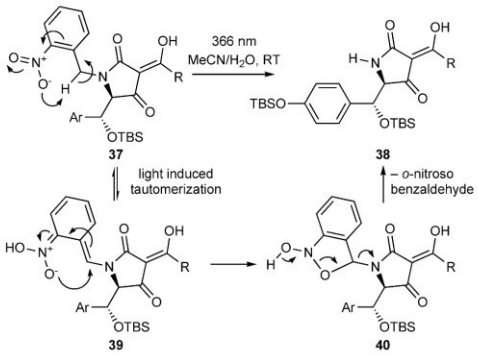
by trifluoroacetic acid.[17] So, in a new approach, the *ortho*-nitrobenzyl (*o*Nb) group was chosen for N-protection. Like the DMB group, it should favor a *cis* amide, yet may eventually be removed under neutral conditions. It was employed by Tatsu et al. as a photocleavable amide backbone protecting group.[19] Aminoester **32** was O-silylated with TBSOTf and N-protected with *ortho*-nitrobenzaldehyde/$NaBH_3CN$ to give fully protected aminoester **34** in 51% yield over four steps (Scheme 6). Although its silver-mediated acylation with thioester **23** failed, the reaction with Meldrum's acid conjugate **24** under conditions as described in a patented general protocol[20] for the acylation of secondary amines afforded β-ketoamide **8** (PG^1 = TBS, PG^2 = *o*Nb). Its Dieckmann cyclization without prior purification gave the triply protected F-14329 derivative **37** in 54% over two steps.

The *o*Nb group was removed by irradiating a solution of compound **37** in acetonitrile/water (9:1) with a 4 W lamp emitting light of wavelength 366 nm for 1 day. The resulting bis silyl ether **38** was desilylated using TBAF in THF, with acetic acid as a buffer, to yield F-14329 (**1**) in 81% after purification by MPLC, identical to the natural product as to NMR spectra and specific optical rotation.[21] A conceivable mechanism for the photolysis of the *o*Nb group, based on the studies of Il'ichev et al.[22] is shown in Scheme 7. Light-induced tautomerization of **37** could generate an activated intermediate **39** that undergoes cyclization with re-aromatization to intermediate **40**, which fragments to tetramic acid **38** and *o*-nitrosobenzaldehyde.



Scheme 7. Conceivable mechanism of the photolytic deprotection of **37**.

In summary, a synthetic route to β-hydroxytyrosine derived 3-acyltetramic acids was devised. It features the use of *ortho*-nitrobenzyl as an N-protecting and directing group, readily and selectively removable at a late stage without compromising the delicate β-hydroxy group and the configurational integrity of stereocenters. The fungal metabolite F-14329 (**1**) was prepared by this approach in 14 steps and 3.9% overall yield.

Conflict of interest

The authors declare no conflict of interest.

Keywords: chaunolidines · F-14329 · natural products · tetramic acids · total synthesis

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Supporting Information

A Synthetic Route to β-Hydroxytyrosine-Derived Tetramic Acids: Total Synthesis of the Fungal Metabolite F-14329

Sebastian Bruckner[+], Robert G. Haase[+], and Rainer Schobert*[a]

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Table of Contents

General

IR spectra were recorded with an FT-IR spectrophotometer equipped with an ATR unit. ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Bruker DRX 500 and/or DRX 300 spectrometer. Chemical shifts are given in parts per million using the residual solvent peak as an internal standard 7.26 ppm (proton) and 77.16 ppm (carbon) for $CDCl_3$, 3.31 ppm (proton) and 49.15 ppm (carbon) for CD_3OD and 2.50 ppm (proton) and 39.51 ppm (carbon) for DMSO-d_6. Coupling constants (*J*) are quoted in Hz. Multiplicity abbreviation used: s singlet, d doublet, t triplet, q quartet and m multiplet. High resolution mass spectra were obtained with a UPLC/Orbitrap MS system in ESI mode. Optical rotations were measured at 589 nm (Na-D line) on a PerkinElmer 241 Polarimeter. All reagents were purchased from commercial sources and were used without further purification. All anhydrous solvents were used as supplied, except tetrahydrofuran and dichloromethane which were freshly distilled according to standard procedures. Reactions were routinely carried out under an argon atmosphere unless stated otherwise. All glassware was flame-dried before use. Photolysis was performed using a Pro Collect UV tester with 366 nm and 4 W.

Chromatography: Analytical thin layer chromatography (TLC) was carried out using Merck Kieselgel 60GF_{254} pre-coated aluminium-backed plates and/or Merck 60 RP-18 F_{254S} foil plates. The compounds were visualised with UV light (254 nm and/or 360 nm) and/or ceric ammonium molybdate (CAM) and/or potassium permanganate.

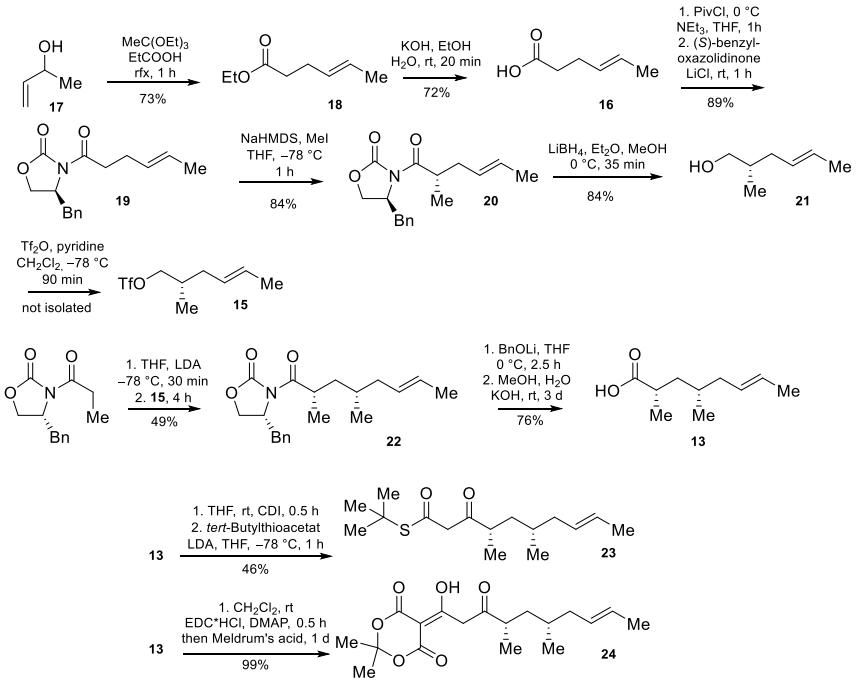
Flash chromatography was performed at medium pressure using dry packed Marchery-Nagel silica gel 60, pore size 40 – 63 µm with the eluent specified.

Analytical HPLC measurements were performed on a Beckman System Gold Programmable Solvent Module 126 using a Phenomenex Kinetex® C-18-HPLC column, length 250 x 4.6 mm, pore size 100 Å, particle size 5 µm. Detection by a Beckman Instruments Diode Array Detection Module 168. Detection by a Beckman Instruments Diode Array Detection Module 168.

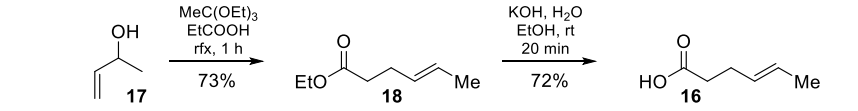
MPLC reversed phase chromatography was performed using a Büchi MPLC system with a "MN Polygo-prep® 100-50 C 18 endcapped" column, length 460 mm, diameter 49 mm. Detection by BÜCHI UV Photo-meter C-635.

Procedures

*Overview: Synthesis of β-Ketothio ester **23** and Meldrum's acid adduct **24***



Synthesis of (*E*)-hex-4-enoic acid 16

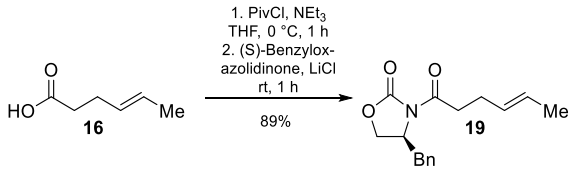


Chemical Formula: C_4H_8O Molecular Weight: 72,11 — Chemical Formula: $C_8H_{14}O_2$ Molecular Weight: 142,20 — Chemical Formula: $C_6H_{10}O_2$ Molecular Weight: 114,14

(±)-But-3-en-2-ol (**17**, 8.30 mL, 115 mmol, 1.00 eq.) was treated with triethyl orthoacetate (31.8 mL, 173 mmol, 1.50 eq.) and propionic acid (431 µL, 5.76 mmol, 0.05 eq.). After refluxing for 1 hour the generated ethanol was destilled off and the remaining mixture was treated with hydrochloric acid (200 mL, 0.50 M). After 1 hour the aqueos phase was extracted thrice with pentanes (3 x 100 mL), the combined organic layer washed with a K_2CO_3-solution (100 mL, saturated), dried with $MgSO_4$ and volatiles were removed under reduced pressure. The product was obtained as a colorless oil (11.9 g, 73%) and was used without further purification in the next step. Ethyl (*E*)-hex-4-enoate (**18**, 11.9 g, 84.0 mmol, 1.00 eq.) was dissolved in ethanol (70 mL) and treated with potassium hydroxide (7.07 g, 126 mmol, 1.50 eq.). After 20 minutes water (200 mL) was added, the aqueos layer was extracted twice with diethylether (2 x 50 mL) and the combined organic phases were disposed. Then the aqueos phase was set to ph=0 with sulfuric acid (2 M in H_2O, 40 mL) and extracted thrice with diethylether (3 x 50 mL). The combined organic phases were dried with $MgSO_4$ and volatiles were removed under reduced pressure. The product **16** was obtained as a pale yellowish oil was used without further purification (6.90 g, 72%). R_f = 0.20 (50% ethyl acetate in *n*-hexane, det. $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.59 - 11.99 (bs, 1 H), 5.38 - 5.56 (m, 2 H), 2.38 - 2.45 (m, 2 H), 2.27 - 2.35 (m, 2 H), 1.65 (dd, *J*=6.10, 0.92 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.7, 128.9, 126.6, 34.2, 27.7, 18.0.

^{1}H NMR data agree with those reported.[1]

Synthesis of (*S*,*E*)-4-benzyl-3-(hex-4-enoyl)oxazolidin-2-one 19



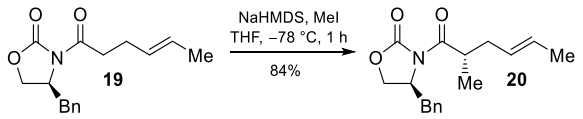
Chemical Formula: $C_6H_{10}O_2$
Molecular Weight: 114,14

Chemical Formula: $C_{16}H_{19}NO_3$
Molecular Weight: 273,33

A solution of (*E*)-hex-4-enoic acid (**16**, 6.45 g, 56.5 mmol, 1.00 eq.) in dry THF (200 mL) at 0 °C was treated with triethylamine (15.7 mL, 113 mmol, 2.00 eq.) and pivaloylchloride (6.95 mL, 56.5 mmol, 1.00 eq.). After one hour (*S*)-4-benzyl-2-oxazolidinone (10.0 g, 56.5 mmol, 1.00 eq.) and LiCl (2.40 g, 56.5 mmol, 1.00 eq.) were added and the suspension was warmed to room temperature for one hour. Water (200 mL) was added and the solution was concentrated under reduced pressure. The aqueos phase was extracted thrice with MTBE (3 x 100 mL), the combined organic phases washed with saturated $KHCO_3$ solution (100 mL), dried with $MgSO_4$ and volatiles were removed under reduced pressure. The obtained yellowish oil was recrystallized with *n*hexane/MTBE. The product **19** was then obtained as colorless needles and used without further purification (13.7 g, 89%). R_f = 0.46 (10% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{20}_D$ = +82.0 ° (c = 1.00 EtOH), Lit.[2] −80.6 (c=1.06 in CH_2Cl_2, enantiomer); mp = 70 °C, Lit[2] = 69,0-69,5 °C (enantiomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 - 7.36 (m, 2 H), 7.27 - 7.30 (m, 1 H), 7.18 - 7.25 (m, 2 H), 5.41 - 5.61 (m, 2 H), 4.64 - 4.71 (m, 1 H), 4.14 - 4.22 (m, 2 H), 3.30 (dd, *J*=13.4, 3.4 Hz, 1 H), 3.02 - 3.09 (m, 1 H), 2.92 - 3.01 (m, 1 H), 2.76 (dd, *J*=13.4, 9.8 Hz, 1 H), 2.35 - 2.42 (m, 2 H), 1.64 - 1.68 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 153.6, 135.4, 129.6, 129.3, 129.1, 127.5, 126.6, 66.3, 55.3, 38.0, 35.7, 27.3, 18.1; IR (cm^{-1}, neat) ν = 3032, 2956, 2915, 1784, 1701, 1458, 1438, 1390, 1374, 1353, 1324, 1300, 1275, 1243, 1200, 1117, 1048, 1014, 966, 905, 768, 747, 700, 635, 577, 561; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{20}O_3N^+$ 274.14377, found 274.14386.

Analytical data agree with those reported.[2]

Synthesis of (*S*)-4-benzyl-3-((*S*,*E*)-2-methylhex-4-enoyl)oxazolidin-2-one 20



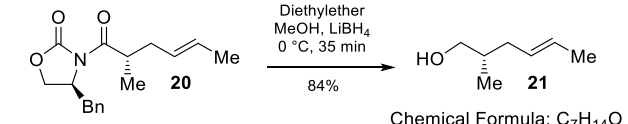
Chemical Formula: $C_{16}H_{19}NO_3$
Molecular Weight: 273,33

Chemical Formula: $C_{17}H_{21}NO_3$
Molecular Weight: 287,36

A solution of the oxazolidinone **19** (5.00 g, 18.3 mmol, 1.00 eq.) in dry THF (70 mL) at −78 °C was treated with sodium bis(trimethylsilyl)amide (2 M in THF, 10.4 mL, 20.8 mmol, 1.14 eq.). After 10 minutes iodomethane (6.29 mL, 101 mmol, 5.50 eq.) was added and the solution was stirred for 1 hour. Then ammonia (25% in water, 50 mL) and brine (50 mL) were added and the solution was warmed to room temperature. The aqueos phase was extracted thrice with *n*-pentane (3 x 100 mL), the combined organic phases dried with $MgSO_4$ and volatiles were removed under reduced pressure. The obtained yellowish oil was purified via column chromotagraphy (600 mL SiO_2, *hexanes*:ethylacetat 9:1) to yield the product **20** as a single diastereomer and a colorless oil (4.40 g, 84%). R_f = 0.55 (10% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{20}_D$ = +106.3 ° (c = 1.00 EtOH), Lit[2] −104 ° (c= 1.07 in CH_2Cl_2, enantiomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 - 7.37 (m, 2 H), 7.26 - 7.30 (m, 1 H), 7.19 - 7.24 (m, 2 H), 5.32 - 5.56 (m, 2 H), 4.66 (m, 1 H), 4.12 - 4.24 (m, 2 H), 3.76 (m, 1 H), 3.27 (dd, *J*=13.3, 3.2 Hz, 1 H), 2.77 (dd, *J*=13.3, 9.8 Hz, 1 H), 2.39 (m, 1 H), 2.12 (m, 1 H), 1.64 (dd, *J*=6.1, 1.2 Hz, 3 H), 1.21 (d, *J*=7.0 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 153.2, 135.5, 129.6, 129.1, 128.0, 127.8, 127.5, 66.2, 55.5, 38.1, 38.0, 36.6, 18.1, 17.1; IR (cm^{-1}, neat) ν = 3028, 2935, 2971, 2855, 1774, 1695, 1498, 1455, 1382, 1349, 1288, 1236, 1195, 1100, 1075, 1049, 1015, 967, 924, 838, 762, 746, 701, 623, 592; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{22}O_3N^+$ 288.15942, found 288.15894.

Analytical data agree with those reported.[2]

Synthesis of (*S*,*E*)-2-methylhex-4-en-1-ol 21



Chemical Formula: $C_{17}H_{21}NO_3$
Molecular Weight: 287,36

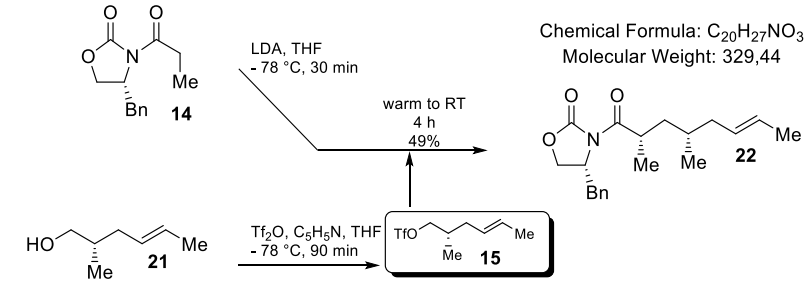
Chemical Formula: $C_7H_{14}O$
Molecular Weight: 114,19

A solution of the oxazolidinone **20** (10.6 g, 37.0 mmol, 1.00 eq.) in dieethylether (111 mL) an methanol (3.30 mL) at 0 °C was treated dropwise with lithium borohydride (4 M in THF, 7.90 mL, 0.85 eq.) over a period of 15 minutes. After additional 20 minutes reaction time sodium hydroxide (1 M, 10 mL) was added slowly and subsequently water (50 mL). The aqueos phase was extracted thrice with methylene chloride (3 x 100 mL), the combined organic phases dried with $MgSO_4$ and volatiles were removed under reduced pressure. The obtained oil was purified via column chromotagraphy (600 mL SiO_2, *hexanes*:ethylacetat 5:1) to yield the product **21** as a colorless oil (3.53 g, 84%). R_f = 0.50 (25% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{20}_D$ = −3.8 ° (c = 1.00 EtOH), Lit[2] + 2.5 ° (c= 1.08 CH_2Cl_2, enantiomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 - 5.54 (m, 2 H), 3.37 - 3.57 (m, 2 H), 2.04 - 2.13 (m, 1 H), 1.83 - 1.92 (m, 1 H), 1.61 - 1.74 (m, 4 H), 1.39 (bs, 1H), 0.90 (d, *J*=6.7 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.4, 126.7, 66.2, 36.7, 36.1, 18.1, 16.6; IR (cm^{-1}, neat) ν = 3328, 2964, 2919, 1454, 1377, 1030, 964, 613, 562. We were not able to measure the HRMS due to too low molecular weight.

Analytical data agree with those reported.[2]

Synthesis of (*4R*)-4-Benzyl-3-[(*2S*,*4S*,*6E*)-2,4-dimethyloct-6-enoyl]-oxazolidin-2-one 22

Chemical Formula: $C_{13}H_{15}NO_3$
Molecular Weight: 233,27



Chemical Formula: $C_{20}H_{27}NO_3$
Molecular Weight: 329,44

Chemical Formula: $C_7H_{14}O$
Molecular Weight: 114,19

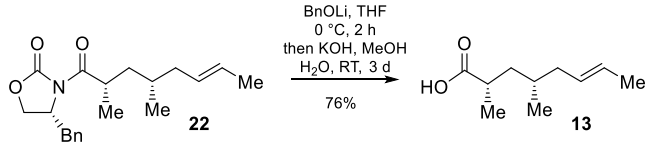
Chemical Formula: $C_8H_{13}F_3O_3S$
Molecular Weight: 246,24

A solution of alcohol **21** (3.53 mg, 30.9 mmol, 1.00 eq.) in dry methylene chloride (111 mL) at −78 °C was treated with pyridine (2.90 mL, 35.7 mmol, 1.15 eq.) and dropwise with trifluoromethanesulfonic anhydride (5.45 mL, 32.4 mmol, 1.05 eq.). After 90 minutes water (50 mL) and brine (20 mL) were added. The aqueos phase was extracted with *n*-pentane (200 mL), the organic phase dried with $MgSO_4$ and volatiles were removed under reduced pressure. The obtained trifluoromethanesulfonic ester **15** was immidietly used in the following reaction without further purification.

A solution of diisopropylamine (4.80 mL, 34.1 mmol, 1.10 eq.) in dry THF (50 mL) at −78 °C was treated with a *n*-butyllithium solution (2.2 M, 15.5 mL, 34.1 mmol, 1.10 eq.). After 30 minutes (*4R*)-4-Benzyl-3-propionyloxazolidin-2-one (**14**, 7.2 g, 31.0 mmol, 1.00 eq.) was added. After additional 30 minutes at −78 °C the trifluoromethanesulfonic ester **15** (6.40 g, 26.0 mmol, 0.84 eq.) was added and the mixture was slowly warmed to room temperature for 4 hours. After adding brine (100 mL) and water (20 mL) the aqueos phase was extracted twice with MTBE (2 x 200 mL) and once with methylene chloride (100 mL). The combined organic phases dried with $MgSO_4$ and volatiles were removed under reduced pressure. The obtained oil was purified via column chromotagraphy (800 mL SiO_2, *hexanes*:ethylacetat 11:1) to yield the product **22** as a colorless oil, which can be precipitated (MTBE/*n*hexanes) to yield a single diastereomer and colorless solid (4.20 g, 49%). R_f = 0.50 (10% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{20}_D$ = − 65.2 °

(c = 1.00 EtOH); mp = 54 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ, 7.30 - 7.36 (m, 2 H), 7.27 - 7.30 (m, 1 H), 7.19 - 7.25 (m, 2 H), 5.34 - 5.50 (m, 2 H), 4.69 (m, 1 H), 4.11 - 4.25 (m, 2 H), 3.87 - 4.01 (m, 1 H), 3.30 (dd, *J*=13.4, 3.4 Hz, 1 H), 2.73 (dd, *J*=13.4, 9.77 Hz, 1 H), 1.99 - 2.12 (m, 1 H), 1.75 - 1.93 (m, 2 H), 1.64 - 1.67 (m, 3 H), 1.46 - 1.57 (m, 1 H), 1.12 - 1.26 (m, 3 H), 0.90 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 153.1, 135.4, 129.5, 129.4, 129.0, 127.3, 126.4, 65.9, 55.4, 40.9, 39.9, 38.1, 35.2, 31.1, 19.7, 18.03, 18.00; IR (cm^{-1}, neat) ν = 2971, 2949, 2909, 2885, 2847, 1777, 1703, 1490, 1453, 1391, 1347, 1286, 1228, 1195, 1110, 1074, 1051, 1018, 966, 828, 763, 763, 740, 725, 697, 639, 572; HRMS (ESI) *m/z* [M +H]$^{+}$ calcd for $C_{20}H_{28}O_3N^{+}$ 330.20637, found 330.20578.

Synthesis of (2*S*,4*S*,*E*)-2,4-dimethyloct-6-enoic acid 13



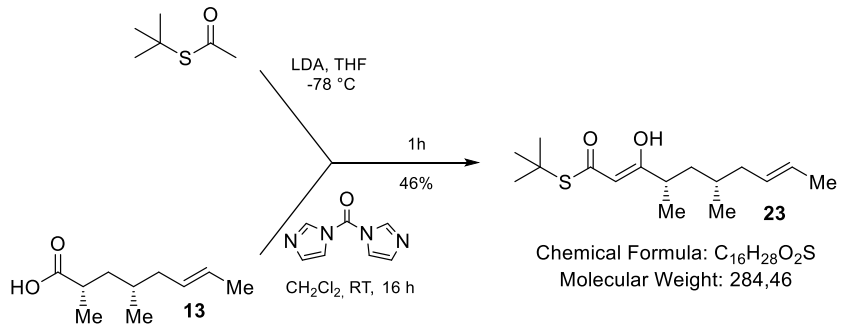
Chemical Formula: $C_{20}H_{27}NO_3$
Molecular Weight: 329,44

Chemical Formula: $C_{10}H_{18}O_2$
Molecular Weight: 170,25

A solution of benzyl alcohol (208 µL, 2.00 mmol, 2.00 eq.) in dry THF (10 mL) at 0 °C was treated with *n*-butyllithium (2.2 M in Hexan, 1.50 mmol, 1.50 eq.). Subsequently the oxazolidinone **22** (329 mg, 1.00 mmol, 1.00 eq.) was added. After 2 hours methanol (2 mL), water (2 mL) and KOH (2 M in water, 4.00 mmol, 2.00 mL, 4.00 eq.) were added and the solution was warmed to room temperature. After 3 days an ammonia chloride solution (50 mL, saturated) was added and the aqueos phase was extracted with MTBE (50 mL) and methylene chloride (50 mL). The combined organic phases dried with $MgSO_4$ and volatiles were removed under reduced pressure. The obtained oil was purified via column chromotagraphy (200 mL SiO_2, *hexanes*:ethylacetat 9:1) to yield the product **13** as a colorless oil (130 mg, 76%). R_f = 0.30 (10% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{20}_{D}$ = + 22.8 ° (c = 1.00 EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 - 12.33 (bs, 1 H), 5.31 - 5.49 (m, 2 H), 2.49 - 2.63 (m, 1 H), 1.91 - 2.03 (m, 1 H), 1.78 - 1.88 (m, 1 H), 1.68 - 1.77 (m, 1 H), 1.59 - 1.68 (m, 3 H), 1.44 - 1.59 (m, 1 H), 1.09 - 1.23 (m, 4 H), 0.89 (d, *J*=6.4 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.0, 129.3, 126.6, 40.8, 40.2, 37.4, 31.1, 19.4, 18.1, 17.9; IR (cm^{-1}, neat) ν = 3025, 2965, 2920, 1703, 1464, 1416, 1379, 1281, 1225, 1150, 1093, 965, 812, 642; HRMS (ESI) *m/z* [M +H]$^{+}$ calcd for $C_{10}H_{19}O_2$ 171.13796, found 171.13796.

Synthesis of *S*-(*tert*-butyl) (4*S*,6*S*,*E*)-4,6-dimethyl-3-oxodec-8-enethioate 23

Chemical Formula: $C_6H_{12}OS$
Molecular Weight: 132,22



Chemical Formula: $C_{10}H_{18}O_2$
Molecular Weight: 170,25

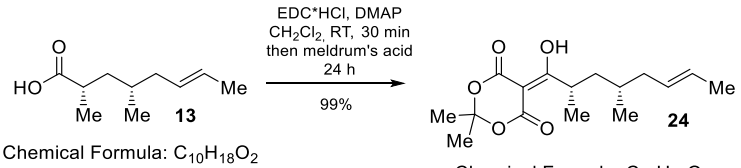
Chemical Formula: $C_{16}H_{28}O_2S$
Molecular Weight: 284,46

Solution 1:
A solution of (*2S*,*4S*,*E*)-2,4-dimethyloct-6-enoic acid (**13**, 550 mg, 3.23 mmol, 1.00 eq.) in dry CH_2Cl_2 (10 mL) at 0 °C was treated with carbonyldiimidazole (550 mg, 3.39 mmol, 1.05 eq.) and then stirred for 16 hours at room temperature. Then water (20 mL) was added and the aqueos phase was extracted twice with CH_2Cl_2 (2x 20 mL). The combined organic phase were dried with $MgSO_4$ and volatiles were removed under

reduced pressure. The obtained acyl imidazole was immidietly used in the following reaction without further purification (585 mg, 82%, 2.65 mmol).

Solution 2:
A solution of diisopropylamine (1.10 mL, 7.95 mmol, 3.00 eq.) in dry THF (10 mL) at −78 °C was treated with a *n-b*utyllithium (3.60 mL, 2.2 M in Hexan, 7.95 mmol, 3.00 eq.). After 20 minutes *S-tert*-butylthioacetate (1.05 g, 7.95 mmol, 3.00 eq.) was added and after additional 15 minutes the acquired acyl imidazole from solution 1 (585 mg, 2.66 mmol, 1.00 eq) was added. After 1 hour reaction time water (50 mL) and hydrochloric acid (1 M, 15 mL) were added and the aqueos phase is extracted twice with MTBE (2x 150 mL). The combined organic phases dried with $MgSO_4$ and volatiles were removed under reduced pressure. The obtained oil was purified via column chromotagraphy (200 mL SiO_2, *hexanes*:CH_2Cl_2 7:3) to yield the product **23** as a reddish oil (420 mg, 46% over 2 steps). R_f = 0.60 (30% CH_2Cl_2 in *n*-hexane, det. $KMnO_4$); $[\alpha]^{20}_D$ = − 4.1 ° (c=1.00 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.82 (s, 0.3 H), 5.26 - 5.40 (m, 2 H), 5.24 (s, 0.3 H), 3.45 - 3.60 (m, 1.4 H), 2.68 - 2.79 (m, 0.7 H), 2.17 (m, 0.3 H), 1.83 - 1.99 (m, 1 H), 1.73 (m, 1 H), 1.61 - 1.68 (m, 1 H), 1.59 (d, J=4.9 Hz, 3 H), 1.45 (s, 3 H), 1.35 - 1.42 (m, 7 H), 1.00 - 1.07 (m, 3 H), 0.93 - 1.00 (m, 1 H), 0.71 - 0.85 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.0/196.3, 192.5/180.2, 129.3/129.1, 126.6/126.4, 98.6, 56.7, 49.0/48.1, 44.3, 41.0/39.8, 40.2/39.5, 37.2, 30.72/30.69, 30.2/29.6, 19.7/19.4, 18.0, 19.0/16.8, written as keto-enol-pairs; IR (cm^{-1}, neat) ν = 2964, 2927, 1721, 1675, 1610, 1456, 1402, 1364, 1327, 1177, 1074, 966, 904, 846, 772, 716, 643, 588; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{29}O_2S^+$ 285.18828, found 285.18790.
Keto-enol tautomers were detected.

Synthesis of 5-((*2S*,*4S*,*E*)-1-hydroxy-2,4-dimethyloct-6-en-1-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 24

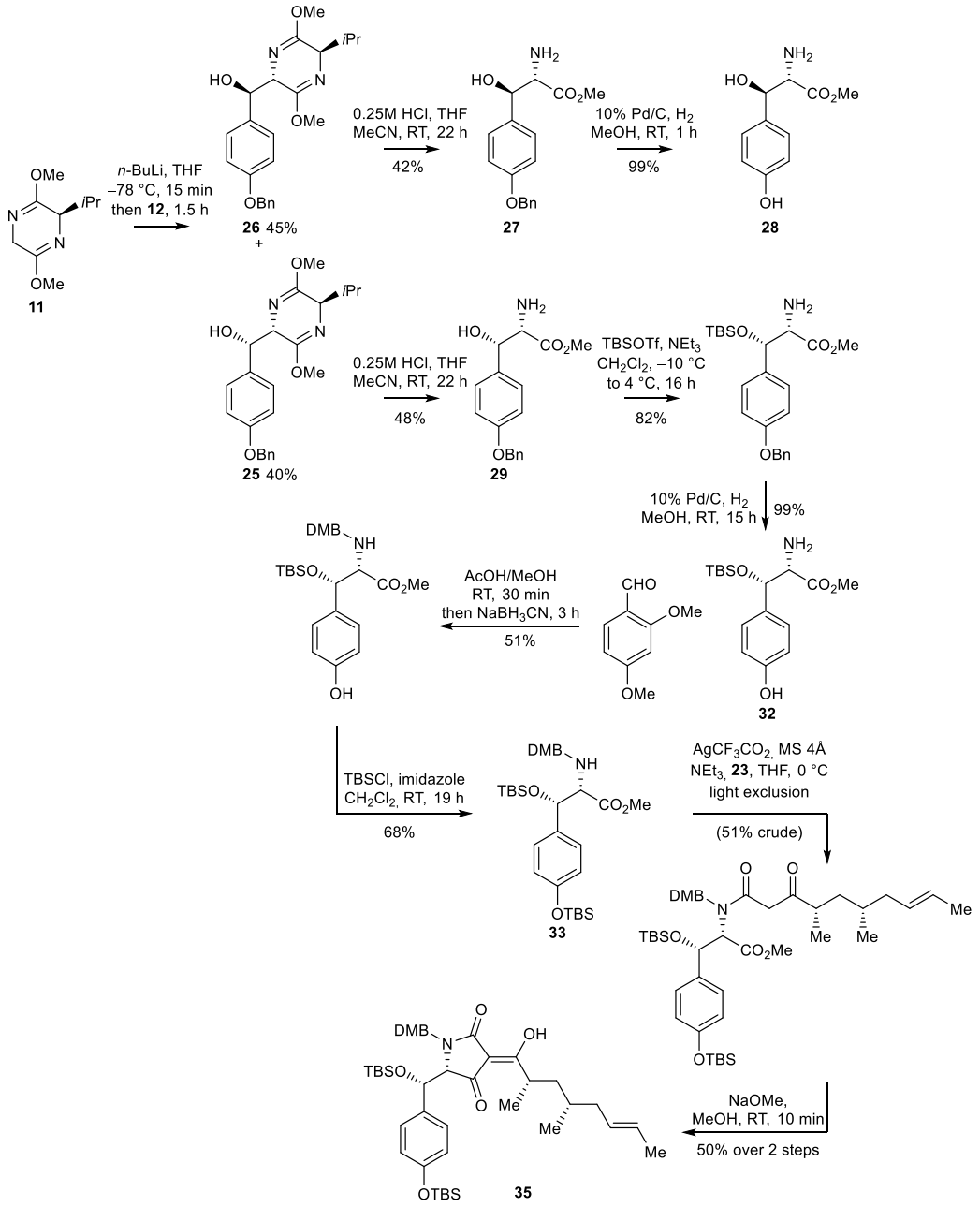


Chemical Formula: $C_{10}H_{18}O_2$
Molecular Weight: 170,25

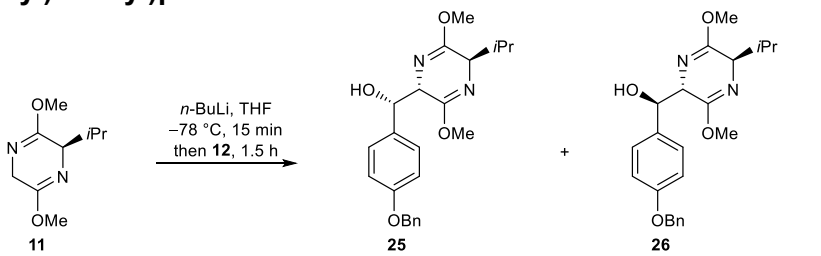
Chemical Formula: $C_{16}H_{24}O_5$
Molecular Weight: 296,36

To a solution of carbonic acid **13** (290 mg, 1.70 mmol, 1.00 eq) in dry CH_2Cl_2 (20 mL) EDC*HCl (391 mg, 2.04 mmol, 1.20 eq) and DMAP (290 mg, 1.70 mmol, 1.00 eq) were added. After 30 minutes meldrum's acid (270 mg, 1.87 mmol, 1.10 eq) was added and the solution was stirred for one day. Then the solution was diluted with MTBE (200 mL) and extracted twice with sulfuric acid (2x 100 mL, 0.5 M) and once with brine (100 mL). The organic phase was dried with $MgSO_4$, volatiles were evaporated and the product **24** was obtained as a colorless oil which was used without further purification (500 mg, 99%); $[\alpha]^{20}_D$ = − 5.1 ° (c=1.00 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz) δ 15.42 (s, 1 H), 5.28 - 5.55 (m, 2 H), 4.09 - 4.34 (m, 1 H), 1.92 - 2.05 (m, 1 H), 1.76 - 1.92 (m, 2 H), 1.73 (d, J=3.1 Hz, 6 H), 1.65 (dd, J=6.0, 1.1 Hz, 3 H), 1.34 - 1.47 (m, 1 H), 1.15 - 1.29 (m, 4 H), 0.86 (d, J=6.4 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.1, 170.9, 160.3, 129.3, 126.7, 104.8, 91.4, 40.8, 40.3, 35.8, 31.5, 27.1, 26.7, 19.7, 18.9, 18.1; IR (cm^{-1}, neat) ν = 2927, 1742, 1656, 1575, 1412, 1294, 1204, 1157, 1022, 966; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{25}O_5^+$ 297.16965, found 297.17080.

*Overview: Synthesis of β-hydroxy tyrosine amino ester and failed sequences towards F-14329 (**1**)*



Synthesis of 4-((*S*)-hydroxy((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)phenol 25 and 4-((*R*)-hydroxy((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)phenol 26



Chemical Formula: $C_9H_{16}N_2O_2$
Molecular Weight: 184,2390

Chemical Formula: $C_{23}H_{28}N_2O_4$
Molecular Weight: 396,49
40%

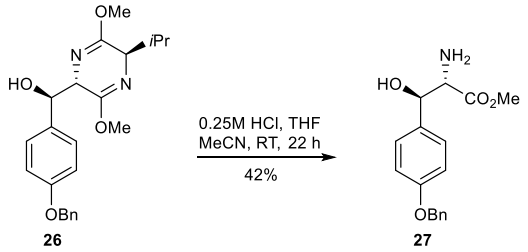
Chemical Formula: $C_{23}H_{28}N_2O_4$
Molecular Weight: 396,49
45%

Lactim ethers **25** and **26** were prepared according to literature procedure.[3]
Yield for **25**: 1.579 g, 40%; Data for **25**: R_f = 0.45 (2% Acetone in CH_2Cl_2, det. CAM); mp 84.8 °C; $[\alpha]^{23}_D$ = +68.4 (c = 0.70 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.30 - 7.45 (m, 5H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.15 (dd, *J* = 4.1, 9.2 Hz, 1H), 5.02 (s, 2H), 4.48 (dd, *J* = 3.8, 4.1 Hz, 1H), 3.85 (d, *J* = 9.2 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.40 (dd, *J* = 3.5, 3.8 Hz, 1H), 2.16 (dqq, *J* = 3.5, 6.7, 6.7 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.63 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 165.2, 160.5, 158.2, 137.0, 132.3, 128.6, 128.0, 127.7, 127.5, 114.1, 73.1, 69.9, 60.6, 60.5, 52.7, 52.1, 31.5, 19.0, 16.5; IR (cm^{-1}, neat) ν = 2945, 1694, 1610, 1510, 1456, 1435, 1383, 1305, 1238, 1194, 1173, 1142, 1113, 1011, 837, 736, 696, 639, 581; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{29}N_2O_4^+$ 397.2122, found 397.2117.

Yield for **26**: 1.783 g, 45%; Data for **26**: R_f = 0.22 (2% Acetone in CH_2Cl_2, det. CAM); $[\alpha]^{23}_D$ = − 10.3 (c = 0.70 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.32 - 7.46 (m, 5H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 5.06 (s, 2H), 5.05 (dd, *J* = 3.4, 7.8 Hz, 1H), 4.24 (dd, *J* = 3.4, 3.5 Hz, 1H), 3.78 (t, *J* = 3.5 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 2.93 - 2.99 (m, 1H), 2.22 (dqq, *J* = 3.5, 7.0, 7.0 Hz, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 165.9, 161.4, 158.2, 137.1, 134.0, 128.6, 128.0, 127.8, 127.5, 114.3, 74.1, 70.0, 61.1, 60.9, 52.7, 52.7, 31.7, 19.1, 16.8; IR (cm^{-1}, neat) ν = 2957, 1696, 1611, 1510, 1456, 1435, 1382, 1303, 1235, 1194, 1173, 1141, 1113, 1011, 862, 833, 793, 736, 697, 646; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{29}N_2O_4^+$ 397.2122, found 397.2117.

Analytical data agree with those reported.[3]

Synthesis of methyl (2*S*,3*R*)-2-amino-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate 27



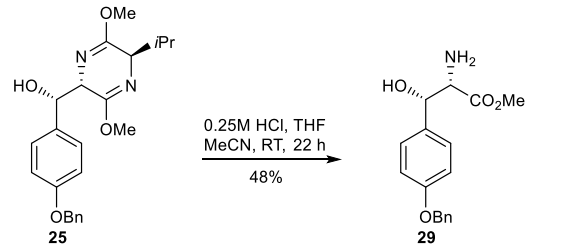
Chemical Formula: $C_{23}H_{28}N_2O_4$
Molecular Weight: 396,49

Chemical Formula: $C_{17}H_{19}NO_4$
Molecular Weight: 301,34

β-hydroxytyrosine methylester **27** was synthesized according to literature procedure.[3]
Yield for **27**: 578 mg, 42%; Data for **27**: R_f = 0.29 (6% MeOH in CH_2Cl_2, det. CAM); $[\alpha]^{23}_D$ = +20.0 (c = 1.90 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.30 - 7.46 (m, 5H), 7.27 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 5.06 (s, 2H), 4.83 (d, *J* = 4.9 Hz, 1H), 3.66 (s, 3H), 3.59 (d, *J* = 4.9 Hz, 1H), 1.66 (br. s., 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 173.8, 158.4, 136.9, 133.1, 128.6, 128.0, 127.5, 127.3, 114.8, 73.9, 70.0, 60.7, 52.2; IR (cm^{-1}, neat) ν = 3365, 2954, 1733, 1610, 1585, 1509, 1455, 1437, 1383, 1231, 1172, 1111, 1012, 915, 828, 737, 697; HRMS (ESI) *m/z* $[M +H]^+$ calcd for $C_{17}H_{20}NO_4^+$ 302.1387, found 302.1377.

Analytical data agree with those reported.[3]

Synthesis of methyl (2*S*,3*S*)-2-amino-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate 29



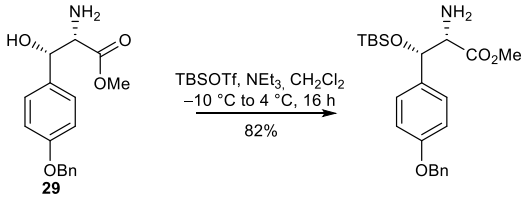
Chemical Formula: $C_{23}H_{28}N_2O_4$
Molecular Weight: 396,49

Chemical Formula: $C_{17}H_{19}NO_4$
Molecular Weight: 301,34

β-hydroxytyrosine methylester **29** was synthesized according to literature procedure.[3]
Yield for **29**: 341 mg, 48%; Data for **29**: R_f = 0.15 (6% MeOH in CH_2Cl_2, det. CAM); $[\alpha]^{23}_D$ = +15.7 (c = 2.70 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.30 - 7.44 (m, 5H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 5.05 (s, 2H), 4.90 (d, *J* = 6.1 Hz, 1H), 3.79 (d, *J* = 6.1 Hz, 1H), 3.70 (s, 3H), 1.59 (br. s., 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 173.7, 158.7, 136.9, 132.1, 128.6, 128.0, 127.6, 127.5, 114.8, 74.0, 70.0, 59.9, 52.1; IR (cm^{-1}, neat) ν = 3364, 2955, 1735, 1610, 1584, 1509, 1455, 1382, 1237, 1172, 1113, 1011, 835, 736, 696; HRMS (ESI) *m/z* $[M\text{-}H_2O+H]^+$ calcd for $C_{17}H_{18}NO_3^+$ 284.1281, found 284.1271.

Analytical data agree with those reported.[3]

Synthesis of methyl (2*S*,3*S*)-2-amino-3-(4-(benzyloxy)phenyl)-3-((*tert*-butyldimethylsilyl) oxy)propanoate



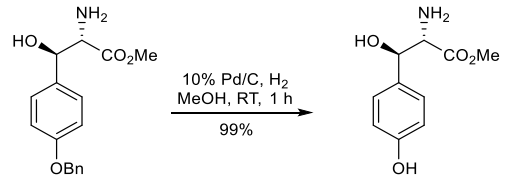
Chemical Formula: $C_{17}H_{19}NO_4$
Molecular Weight: 301,34

Chemical Formula: $C_{23}H_{33}NO_4Si$
Molecular Weight: 415,61

TBS protected β-hydroxytyrosine methylester was synthesized according to literature procedure.[3]
Yield for X: 612 mg, 82%; Data for X: R_f = 0.59 (50% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{23}_D$ = +53.4 (c = 0.30 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.30 - 7.46 (m, 5H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 5.05 (s, 2H), 4.76 (d, *J* = 6.7 Hz, 1H), 3.70 (s, 3H), 3.64 (d, *J* = 6.7 Hz, 1H), 0.85 (s, 9H), 0.02 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 173.7, 158.7, 137.0, 132.9, 128.7, 128.2, 128.1, 127.7, 114.6, 77.0, 70.0, 62.3, 51.9, 25.8, 18.2, -4.5, -5.2; IR (cm^{-1}, neat) ν = 2953, 2858, 1739, 1611, 1510, 1456, 1387, 1249, 1170, 1081, 1007, 837, 778, 737, 697; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{34}NO_4Si^+$ 416.2252, found 416.2243.

Analytical data agree with those reported.[3]

Synthesis of methyl (2*S*,3*R*)-2-amino-3-hydroxy-3-(4-hydroxyphenyl)propanoate 28

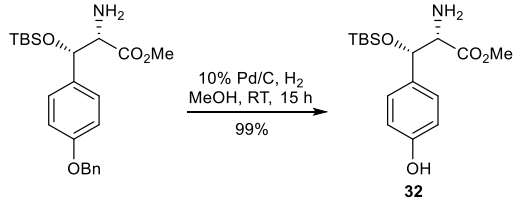


27
Chemical Formula: $C_{17}H_{19}NO_4$
Molecular Weight: 301,34

28
Chemical Formula: $C_{10}H_{13}NO_4$
Molecular Weight: 211,22

To a solution of benzyl ether **27** (120 mg, 398 µmol, 1.00 eq.) in methanol (5 mL) was added Pd/C (10%, 12 mg, 10% wt.) and the mixture was stirred under hydrogen atmosphere (1 atm) at ambient temperature for 1 h. Then the mixture was filtered over celite® and the celite® washed after with dichloromethane (50 mL). The resulting filtrate was concentrated *in vacuo* to give the *title compound* as pale-orange oil (84 mg, 99%); R_f = 0.25 (10% MeOH in CH_2Cl_2, det. CAM); $[\alpha]^{23}_D$ = +9.1 (c = 1.00 MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.18 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 4.83 (d, *J* = 4.9 Hz, 1H), 3.63 (s, 3H), 3.57 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.8, 158.3, 133.3, 128.6, 116.2, 75.9, 62.3, 52.5; IR (cm^{-1}, neat) ν = 3357, 2955, 1732, 1613, 1596, 1515, 1439, 1383, 1228, 1169, 1107, 1012, 911, 834, 777, 688, 642, 582; HRMS (ESI) *m/z* [M +H]$^+$ calcd for $C_{10}H_{14}NO_4^+$ 212.0917, found 212.0914.

Synthesis of (2*S*,3*S*)-methyl 2-amino-3-((*tert*-butyldimethylsilyl)oxy)-3-(4-hydroxy-phenyl)-propanoate 32

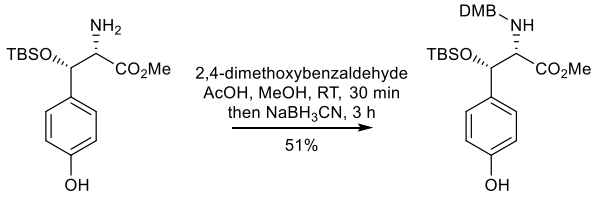


Chemical Formula: $C_{23}H_{33}NO_4Si$
Molecular Weight: 415,61

32
Chemical Formula: $C_{16}H_{27}NO_4Si$
Molecular Weight: 325,48

To a solution of (2*S*,3*S*)-methyl 2-amino-3-(4-(benzyloxy)phenyl)-3-((*tert*-butyldimethylsilyl)oxy)propanoate (356 mg, 856 µmol, 1.00 eq.) in MeOH p.a. (15 mL) was added 10% Pd/C (36 mg, 10%wt.) and the mixture was stirred under H_2 atmosphere (1 atm) for 15 h.
Then the mixture was filtered over celite® and the celite® washed after with dichloromethane (50 mL). The resulting filtrate was concentrated *in vacuo* to give the *title compound* as an off white solid foam (277 mg, 99%); R_f = 0.13 (50% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{23}_D$ = +37.6 (c = 0.25 MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 4.97 (d, *J* = 6.4 Hz, 1H), 3.91 (d, *J* = 6.4 Hz, 1H), 3.78 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), -0.14 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 171.4, 159.2, 130.5, 129.4, 116.5, 76.2, 61.6, 53.0, 26.1, 19.0, -4.6, -5.2; IR (cm^{-1}, neat) ν = 3263, 2930, 2857, 1741, 1614, 1516, 1440, 1362, 1252, 1169, 1082, 1006, 837, 778, 672; HRMS (ESI) *m/z* [M +H]$^+$ calcd for $C_{16}H_{28}NO_4Si^+$ 326.1782, found 326.1776.

Synthesis of methyl (2*S*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-((2,4-dimethoxybenzyl) amino)-3-(4-hydroxyphenyl)propanoate

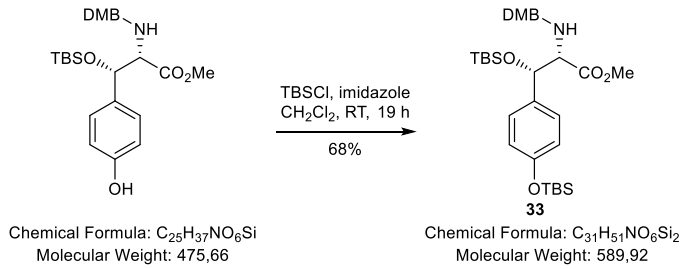


32
Chemical Formula: $C_{16}H_{27}NO_4Si$
Molecular Weight: 325,48

Chemical Formula: $C_{25}H_{37}NO_6Si$
Molecular Weight: 475,66

To a solution of amine **32** (301 mg, 925 µmol, 1.00 eq.) in 3% acetic acid in methanol (60 mL) was added 2,4-dimethoxybenzaldehyde (184 mg, 1.11 mmol, 1.20 eq.) and the mixture was stirred at ambient temperature for 30 min. Then $NaBH_3CN$ (87 mg, 1.39 mmol, 1.50 eq.) was added and stirring was continued for 3 h. After that sat. aq. $NaHCO_3$ (120 mL) and diethyl ether (200 mL) were added, the phases were separated and the aqueous phase was extracted with diethyl ether (125 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel, eluting with 6% acetone in dichloromethane to give the *title compound* as a colourless solid foam (223 mg, 51%); R_f = 0.29 (12% Acetone in CH_2Cl_2, det. CAM); $[\alpha]^{23}_D$ = +21.8 (c = 1.00 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.09 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 2H), 6.35 (dd, *J* = 2.4, 8.2 Hz, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 4.70 (d, *J* = 7.9 Hz, 1H), 3.77 (s, 3H), 3.64 - 3.70 (m, 3H), 3.67 (d, *J* = 13.7 Hz, 1H), 3.55 (s, 3H), 3.48 (d, *J* = 13.7 Hz, 1H), 3.37 (d, *J* = 7.9 Hz, 1H), 0.77 (s, 9H), -0.07 (s, 3H), -0.30 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 173.9, 160.3, 158.7, 155.9, 133.2, 130.8, 128.5, 119.5, 115.3, 103.5, 98.4, 76.1, 68.1, 55.5, 55.1, 51.8, 47.7, 25.7, 18.1, -4.5, -5.3; IR (cm^{-1}, neat) ν = 3318, 2956, 2857, 1743, 1614, 1590, 1508, 1463, 1362, 1290, 1259, 1208, 1157, 1135, 1082, 1036, 938, 836, 778; HRMS (ESI) *m/z* [M +H]$^+$ calcd for $C_{25}H_{38}NO_6Si^+$ 476.2463, found 476.2455.

Synthesis of methyl (2*S*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-3-(4-((*tert*-butyldimethylsilyl) oxy)phenyl)-2-((2,4-dimethoxybenzyl)amino)propanoate 33

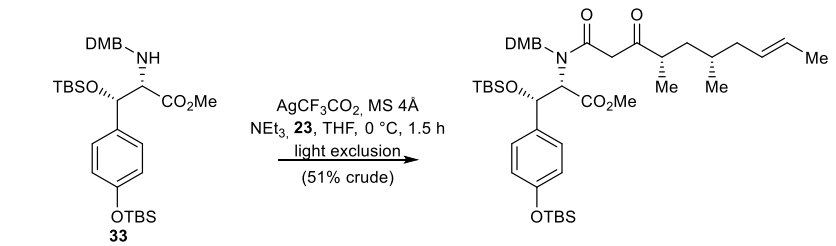


Chemical Formula: $C_{25}H_{37}NO_6Si$
Molecular Weight: 475,66

Chemical Formula: $C_{31}H_{51}NO_6Si_2$
Molecular Weight: 589,92

To a solution of phenol (130 mg, 273 µmol, 1.00 eq.) in dichloromethane (5 mL) were added TBSCl (45 mg, 300 µmol, 1.10 eq.) and imidazole (28 mg, 410 µmol, 1.50 eq.) and the mixture was stirred at ambient temperature for 19 h. Then, ethyl acetate (25 mL) and sat. aq. NH_4Cl (30 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a pale-yellow oil that was purified by flash chromatography on silica gel, eluting with 15% ethyl acetate in *n*-hexane to give the *title compound* as a clear oil (109 mg, 68%); R_f = 0.76 (40% ethyl acetate in *n*-hexane, det. CAM); $[\alpha]^{23}_D$ = +30.0 (c = 1.00 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.34 (dd, *J* = 2.4, 7.90 Hz, 1H), 6.30 (d, *J* = 2.4 Hz, 1H), 4.67 (d, *J* = 8.2 Hz, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.62 (d, *J* = 14.0 Hz, 1H), 3.55 (s, 3H), 3.45 (d, *J* = 14.0 Hz, 1H), 3.35 (d, *J* = 8.2 Hz, 1H), 1.79 (br. s., 1H), 0.97 (s, 9H), 0.77 (s, 9H), 0.19 (s, 6H), -0.07 (s, 3H), -0.31 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 174.1, 160.2, 158.7, 155.5, 134.5, 130.5, 128.5, 120.0, 119.8, 103.5, 98.4, 76.4, 68.2, 55.4, 55.1, 51.7, 47.5, 25.8, 25.7, 18.4, 18.1, -4.3, -4.6, -5.2; IR (cm^{-1}, neat) ν = 2931, 2859, 1739, 1610, 1508, 1464, 1253, 1208, 1158, 1080, 1039, 913, 837, 779; HRMS (ESI) *m/z* [M +H]$^+$ calcd for $C_{31}H_{52}NO_6Si_2^+$ 590.3328, found 590.3315.

Synthesis of (*S*,*Z*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)(4-((*tert*-butyldimethylsilyl)oxy) phenyl)methyl)-1-(2,4-dimethoxybenzyl)-3-((2*S*,4*S*,*E*)-1-hydroxy-2,4-dimethyloct-6-en-1-ylidene)pyrrolidine-2,4-dione 35

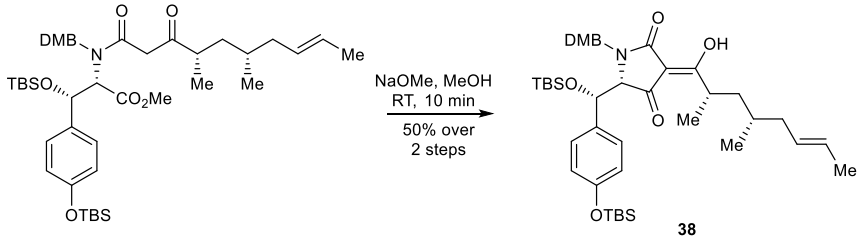


33

Chemical Formula: $C_{31}H_{51}NO_6Si_2$
Molecular Weight: 589,92

Chemical Formula: $C_{43}H_{69}NO_8Si_2$
Molecular Weight: 784,1940

To a solution of thioester **23** (47 mg, 166 µmol, 1.00 eq.) in THF (2.5 mL) were added MS 4Å, NEt_3 (0.09 mL, 664 µmol, 4.00 eq.) and a solution of amine **33** (108 mg, 183 µmol, 1.10 eq.) in THF (2.5 mL). The mixture was then cooled to 0 °C before $AgCF_3CO_2$ (55 mg, 249 µmol, 1.50 eq.) was added and the mixture was stirred at 0 °C under light exclusion for 1.5 h. Then diethyl ether (5 mL) was added and the mixture was filtered over celite ®. The celite ® was washed with diethyl ether (50 mL) and the combined filtrates were washed with sat. aq. NH_4Cl (30 mL), H_2O (30 mL) and brine (30 mL). The organic phase was then dried (Na_2SO_4) and concentrated *in vacuo* to give an orange oil that was purified by flash chromatography on silica gel, eluting with 10% ethyl acetate in *n*-hexane to give crude β-keto amide as a clear oil (67 mg, 51%); R_f = 0.39 (14% ethyl acetate in *n*-hexane, det. CAM). This was used in the next steps without further purification.



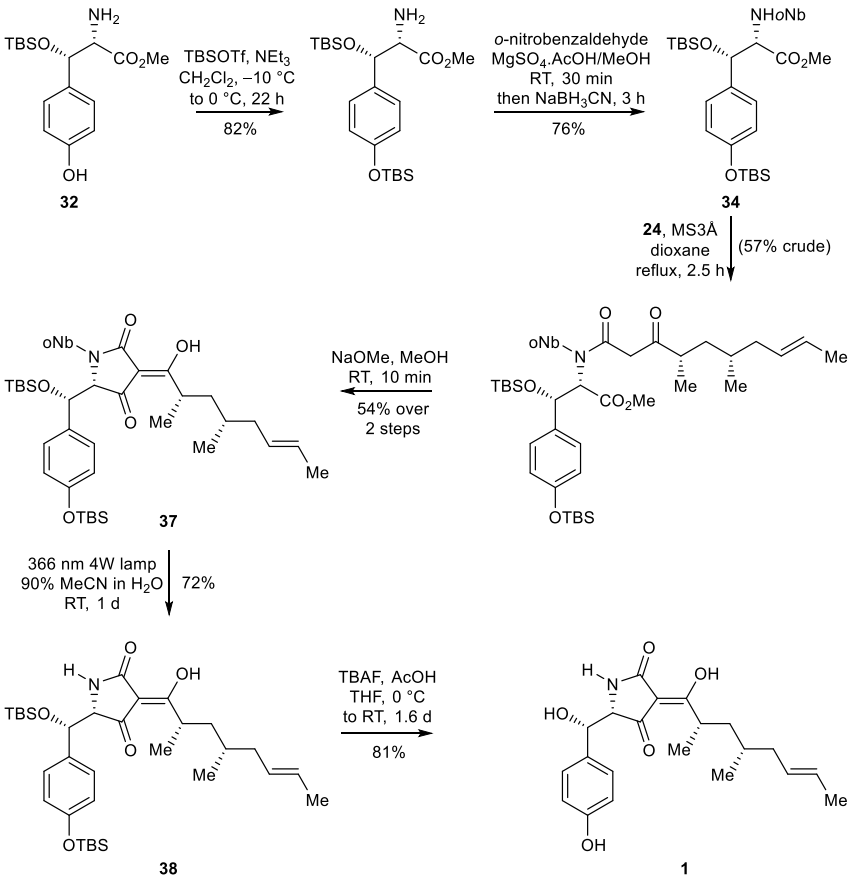
Chemical Formula: $C_{43}H_{69}NO_8Si_2$
Molecular Weight: 784,1940

38

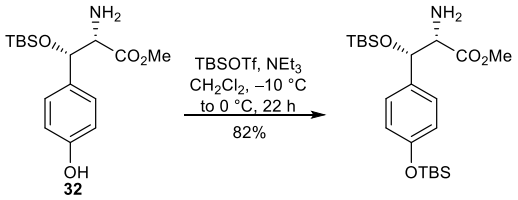
Chemical Formula: $C_{42}H_{65}NO_7Si_2$
Molecular Weight: 752,1520

To a solution of β-keto amide (67 mg, 85 µmol, 1.00 eq.) in methanol (8.5 mL) was added sodium methoxide (14 mg, 255 µmol, 3.00 eq.) and the mixture was stirred at ambient temperature for 10 min. Then
aq. HCl (1M, 10 mL) and ethyl acetate (15 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* as a pale-red oil (63 mg, 50% over 2 steps); R_f = 0.66 (25% ethyl acetate in *n*-hexane, det. CAM); $[\alpha]^{23}_D$ = − 95.6 (c = 1.00 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.17 (d, *J* = 9.2 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 6.42 - 6.48 (m, 2H), 5.28 - 5.42 (m, 2H), 5.18 (d, *J* = 2.4 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 1H), 4.71 (d, *J* = 14.6 Hz, 1H), 4.09 (d, *J* = 2.4 Hz, 1H), 3.80 - 3.81 (m, 3H), 3.79 (s, 3H), 3.59 - 3.69 (m, 1H), 1.88 - 1.95 (m, 1H), 1.68 - 1.79 (m, 2H), 1.62 (d, *J* = 5.5 Hz, 3H), 1.28 - 1.34 (m, 2H), 1.03 - 1.09 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 9H), 0.85 (s, 9H), 0.81 (d, *J* = 6.4 Hz, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.03 (s, 3H), -0.12 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 192.5, 190.9, 174.4, 160.8, 158.6, 155.4, 131.7, 131.1, 129.6, 128.1, 126.4, 119.6, 116.8, 104.0, 101.8, 98.6, 76.0, 70.7, 55.5, 55.3, 40.6, 40.4, 40.2, 33.7, 31.4, 25.8, 25.8, 19.5, 18.6, 18.4, 18.2, 18.1, -4.3, -4.6, -5.1; IR (cm^{-1}, neat) ν = 3630, 2930, 2856, 1707, 1610, 1508, 1463, 1254, 1209, 1158, 1109, 1081, 1037, 1005, 966, 911, 868, 836, 778, 682; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{42}H_{66}NO_7Si_2^+$ 752.4372, found 752.4355.

*Overview: Synthesis of F-14329 (**1**)*



Synthesis of (2*S*,3*S*)-methyl 2-amino-3-((*tert*-butyldimethylsilyl)oxy)-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate



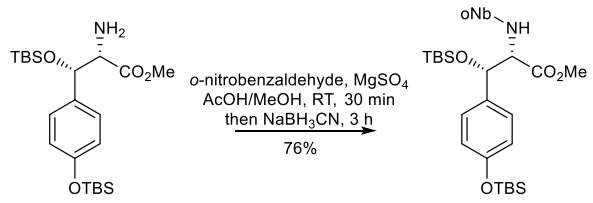
Chemical Formula: $C_{16}H_{27}NO_4Si$
Molecular Weight: 325,48

Chemical Formula: $C_{22}H_{41}NO_4Si_2$
Molecular Weight: 439,74

To a suspension of the phenol **32** (277 mg, 851 µmol, 1.00 eq.) in CH_2Cl_2 (20 mL) at -10 °C were added TBSOTf (1.36 mL, 4.255 mmol, 5.00 eq.) and NEt_3 (0.71 mL, 5.106 mmol, 6.00 eq.) and the brown solution was stirred at 0 °C for 22 h. Then sat. aq. $NaHCO_3$ (40 mL) and ethyl acetate (100 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 100 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an orange brown oil that was purified by flash chromatography on silica gel, eluting with 25% ethyl acetate in *n*-hexane to give the *title compound* as a pale yellow oil (307 mg, 82%); R_f = 0.47 (50% ethyl acetate in *n*-hexane, det. $KMnO_4$); $[\alpha]^{23}_D$ = +43.6 (c = 1.00 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.73 (d, *J* = 6.7 Hz, 1H), 3.69 (s, 3H), 3.63 (d, *J* = 6.7 Hz, 1H), 2.15 (br. s., 2H), 0.97 (s, 9H), 0.83 (s, 9H), 0.18 (s, 6H), 0.00 (s, 3H), -0.21 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$)

δ 173.6, 155.5, 133.2, 128.1, 119.8, 77.1, 62.1, 51.8, 25.7, 25.6, 18.2, 18.0, -4.4, -4.7, -5.3; IR (cm^{-1}, neat) ν = 2954, 2936, 2887, 2859, 1742, 1609, 1510, 1473, 1438, 1390, 1362, 1254, 1198, 1167, 1083, 1006, 913, 838, 805, 779, 684, 580, 564; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{42}NO_4Si_2^+$ 440.2647, found 440.2641.

Synthesis of (2*S*,3*S*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)-3-(4-((tert-butyldimethylsilyl) oxy)phenyl)-2-((2-nitrobenzyl)amino)propanoate 34



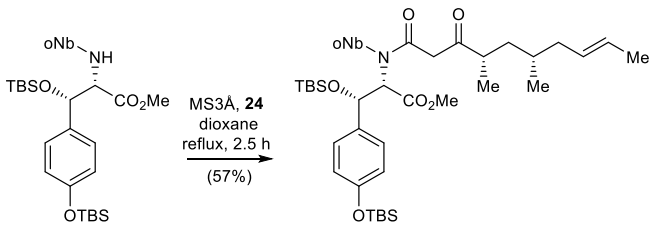
34

Chemical Formula: $C_{22}H_{41}NO_4Si_2$
Molecular Weight: 439,74

Chemical Formula: $C_{29}H_{46}N_2O_6Si_2$
Molecular Weight: 574,86

To a solution of amine (307 mg, 698 µmol, 1.00 eq.) in 3% acetic acid in methanol (35 mL) were added *ortho*-nitrobenzaldehyde (211 mg, 1.396 mmol, 2.00 eq.) and $MgSO_4$ (380 mg) and the mixture was stirred at ambient temperature for 30 min.
Then $NaBH_3CN$ (109 mg, 1.745 mmol, 2.50 eq.) was added and stirring continued for 3 h. After that sat. aq. $NaHCO_3$ (40 mL) and ethyl acetate (75 mL) were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (100 mL) and the combined organic phases were washed with brine (100 mL). After drying (Na_2SO_4) the solvent was removed *in vacuo* and the resulting yellow oil was purified by flash chromatography, eluting with 12% ethyl acetate in *n*-hexane to give the *title compound* as a pale yellow oil (289 mg, 76%); R_f = 0.54 (18% ethyl acetate in *n*-hexane, det. CAM); $[\alpha]^{23}_D$ = +53.3 (c = 1.00 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.88 (dd, *J* = 1.2, 7.9 Hz, 1H), 7.43 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 7.34 (ddd, *J* = 1.5, 7.6, 7.9 Hz, 1H), 7.31 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.67 (d, *J* = 7.9 Hz, 1H), 4.02 (d, *J* = 15.3 Hz, 1H), 3.82 (d, *J* = 15.3 Hz, 1H), 3.67 (s, 3H), 3.34 (d, *J* = 7.9 Hz, 1H), 2.16 (br. s, 1H), 0.98 (s, 9H), 0.79 (s, 9H), 0.19 (s, 6H), -0.04 (s, 3H), -0.28 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 174.1, 155.6, 148.9, 135.3, 134.4, 133.2, 131.0, 128.3, 127.9, 124.8, 119.9, 76.3, 68.5, 51.8, 48.9, 25.8, 25.7, 18.4, 18.1, -4.3, -4.3, -4.6, -5.2; IR (cm^{-1}, neat) ν = 2954, 2930, 2887, 2859, 1737, 1609, 1527, 1509, 1472, 1463, 1435, 1390, 1345, 1252, 1200, 1167, 1083, 1006, 911, 856, 836, 804, 778, 728, 703, 666, 634, 562; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{47}N_2O_6Si_2^+$ 575.2967, found 575.2956.

Synthesis of (*S*,*Z*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)(4-((*tert*-butyldimethylsilyl)oxy) phenyl)methyl)-3-((2*S*,4*S*,*E*)-1-hydroxy-2,4-dimethyloct-6-en-1-ylidene)-1-(2-nitrobenzyl) pyrrolidine-2,4-dione 37



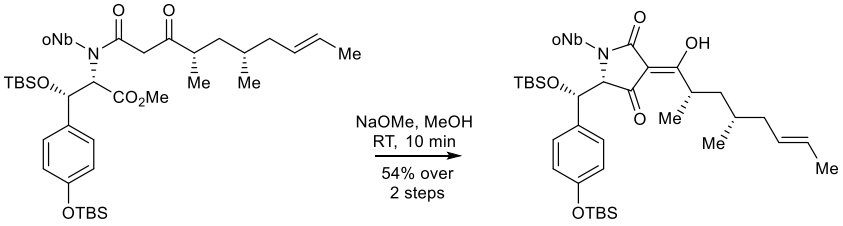
34

Chemical Formula: $C_{29}H_{46}N_2O_6Si_2$
Molecular Weight: 574,8650

Chemical Formula: $C_{41}H_{64}N_2O_8Si_2$
Molecular Weight: 769,1390

To a solution of amino ester **34** (289 mg, 503 µmol, 1.00 eq.) in dioxane (3 mL) with freshly activated mol sieves 3 Å at 50 °C was added a solution of Meldrum conjugate **24** (178 mg, 601 µmol, 1.19 eq.) in dioxane (3 mL) and the mixture was stirred at reflux for 2.5 h. After that the mol sieves were filtered off and the filtrate was concentrated *in vacuo*. The resulting orange oil was purified by flash chromatography on silica gel, eluting with 7% ethyl acetate in *n*-hexane to give crude β-keto amide as a pale-yellow oil (219 mg, 57%); R_f

= 0.17 (8% ethyl acetate in *n*-hexane, det. CAM). This was used in the next reaction without further purification.



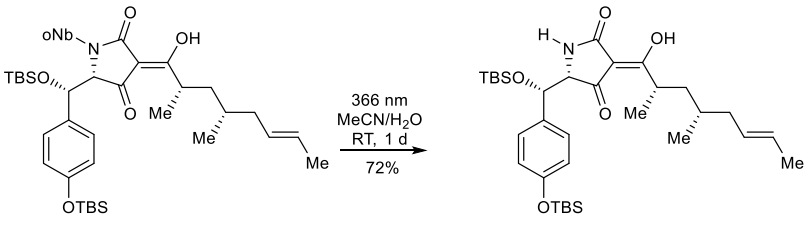
Chemical Formula: $C_{41}H_{64}N_2O_8Si_2$
Molecular Weight: 769,1390

37

Chemical Formula: $C_{40}H_{60}N_2O_7Si_2$
Molecular Weight: 737,0970

To a solution of β-keto amide (219 mg, 285 µmol, 1.00 eq.) in methanol (20 mL) was added sodium methoxide (77 mg, 1.425 mmol, 5.00 eq.) and the mixture was stirred at ambient temperature for 10 min. Then aq. citric acid (5%wt. 100 mL) and diethyl ether (50 mL) were added, the phases were separated and the aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic phases were washed with brine (150 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* as a pale yellow oil (198 mg, 54% over 2 steps); R_f = 0.35 (30% ethyl acetate in *n*-hexane, det. CAM); $[\alpha]^{23}_D$ = − 117.4 (c = 0.50 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 8.12 (dd, J = 1.2, 8.2 Hz, 1H), 7.62 (ddd, J = 1.2, 7.6, 7.6 Hz, 1H), 7.46 (ddd, J = 0.9, 7.6, 8.2 Hz, 1H), 7.18 (dd, J = 0.9, 7.6 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 5.48 (d, J = 17.4 Hz, 1H), 5.36 - 5.44 (m, 2H), 5.34 (d, J = 17.4 Hz, 1H), 5.24 (d, J = 2.4 Hz, 1H), 4.12 (d, J = 2.4 Hz, 1H), 3.65 - 3.74 (m, 1H), 1.94 - 2.01 (m, 1H), 1.72 - 1.83 (m, 2H), 1.64 (d, *J* = 5.2 Hz, 3H), 1.33 - 1.41 (m, 1H), 1.11 - 1.16 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 4H), 0.74 (s, 9H), 0.15 (s, 3H), 0.15 (s, 3H), -0.08 (s, 3H), -0.13 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 192.2, 191.6, 174.7, 155.7, 148.2, 133.9, 132.5, 130.7, 129.4, 128.4, 128.3, 128.0, 126.5, 125.7, 119.9, 101.0, 76.5, 70.9, 42.5, 40.4, 40.0, 33.9, 31.4, 25.8, 25.6, 19.6, 18.5, 18.4, 18.1, 18.0, -4.3, -4.8, -5.4; IR (cm^{-1}, neat) ν = 2956, 2931, 2859, 1710, 1651, 1609, 1530, 1509, 1463, 1340, 1257, 1208, 1168, 1109, 1082, 1006, 966, 912, 838, 807, 780, 728, 573; HRMS (ESI) *m/z* [M +Na]$^+$ calcd for $C_{40}H_{60}N_2NaO_7Si_2^+$ 759.3831, found 759.3820.

Synthesis of (*S*,*Z*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)(4-((*tert*-butyldimethylsilyl)oxy) phenyl)methyl)-3-((2*S*,4*S*,*E*)-1-hydroxy-2,4-dimethyloct-6-en-1-ylidene)pyrrolidine-2,4-dione 38



37

Chemical Formula: $C_{40}H_{60}N_2O_7Si_2$
Molecular Weight: 737,0970

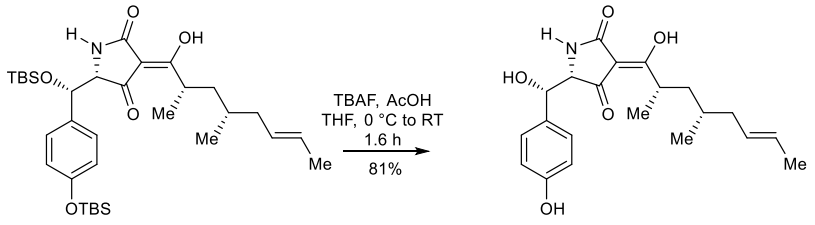
38

Chemical Formula: $C_{33}H_{55}NO_5Si_2$
Molecular Weight: 601,9750

A solution of fully protected F-14329 **37** (198 mg, 269 µmol, 1.00 eq.) in 90% acetonitrile in water was irradiated with a 4W blacklight lamp (366 nm) for 1 d. After that the solvent was removed *in vacuo* to give a brown oil that was purified by flash chromatography on RP-18 silica gel, eluting with 85% acetonitrile in water → 90% → 95% to give the *title compound* as an orange oil (117 mg, 72%); R_f = 0.35 (acetonitrile, det. UV_{254}); $[\alpha]^{23}_D$ = − 62.6 (c = 0.50 $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.09 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 6.41 (br. s, 1H), 5.30 - 5.42 (m, 2H), 5.11 (d, *J* = 3.7 Hz, 1H), 4.16 (d, *J* = 3.7 Hz, 1H), 3.55 - 3.63 (m, 1H), 1.87 - 1.95 (m, 1H), 1.67 - 1.79 (m, 2H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.25 - 1.33 (m, 1H), 1.04 - 1.09 (m, 1H), 0.93 (s, 9H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.12 (s, 6H), 0.05 (s, 3H), -0.10 (s, 3H); ^{3}C NMR (125 MHz,$CDCl_3$) δ 192.6, 192.5, 176.0, 155.6, 130.6, 129.4, 128.4, 126.4,

119.5, 101.5, 74.2, 68.5, 40.5, 40.0, 33.7, 31.4, 25.8, 25.8, 19.5, 18.6, 18.3, 18.2, 18.1, -4.3, -4.6, -5.0; IR (cm^{-1}, neat) ν = 2931, 2859, 1660, 1609, 1509, 1472, 1255, 1088, 915, 870, 838, 779, 662, 581, 556; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{33}H_{54}NO_5Si_2^+$ 600.3546, found 600.3551.

Synthesis of F-14329 (1)

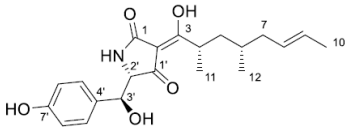


38
Chemical Formula: $C_{33}H_{55}NO_5Si_2$
Molecular Weight: 601,9750

1
Chemical Formula: $C_{21}H_{27}NO_5$
Molecular Weight: 373,4490

To a solution of TBS-protected F-14329 **38** (117 mg, 194 µmol, 1.00 eq.) in THF (1 mL) at 0 °C were added acetic acid (0.89 mL. 3.104 mmol,. 16.00 eq.) and a solution of TBAF in THF (1M, 2.33 mL, 2.330 mmol, 12.00 eq.) and the mixture was stirred at ambient temperature for 1.6 d. After that, aq. citric acid (5%wt. 25 mL) and ethyl acetate (25 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organic phases were washed with brine (25 mL), dried (Na_2SO_4) and concentrated from toluene and then from diethyl ether to give an orange oil that was purified by MPLC, eluting with 50% acetonitrile in water → 55% → 65% → 75% → acetonitrile. The product containing fractions were collected, acetonitrile was removed *in vacuo* and aq. citric acid (5%wt. 100 mL) was added. The aqueous phase was extracted with MTBE (3 x 250 mL), the combined organic phases were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* as a yellow oil (59 mg, 81%); $[\alpha]^{23}_D$ = -139.4 (c = 0.50 MeOH) {lit.[5] $[\alpha]^{23}_D$ = −140 (c = 0.05 MeOH)}; for NMR shifts see table 1, S13; IR (cm^{-1}, neat) ν = 3308, 2923, 2852, 1649, 1601, 1517, 1454, 1378, 1237, 1047, 967, 622; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{28}NO_5^+$ 374.1962, found 374.1954.

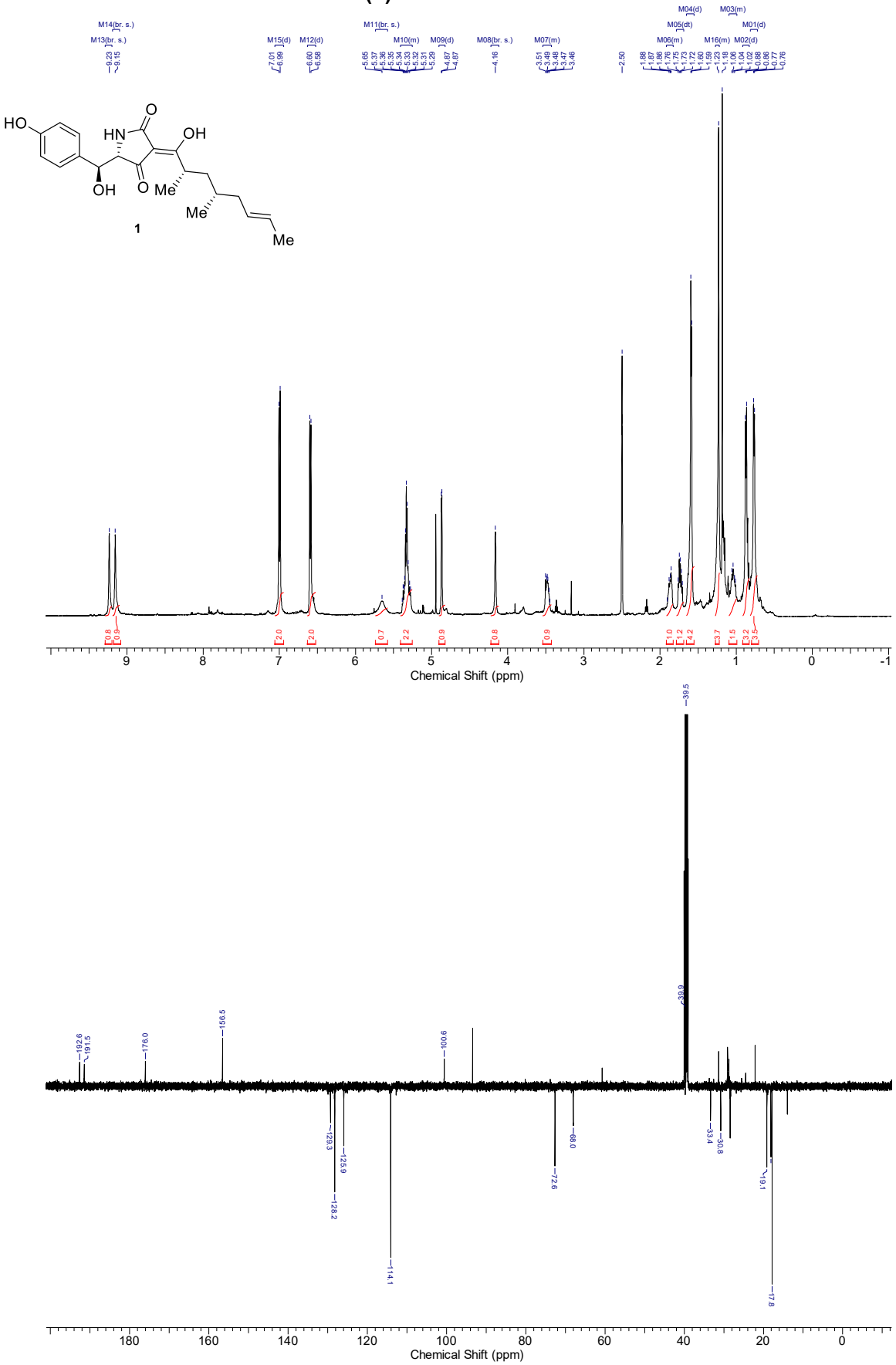
Table 1. Comparison of isolated[4] and synthetic F-14329 ^{13}C NMR shifts and ^{1}H NMR shifts and multiplet analysis.



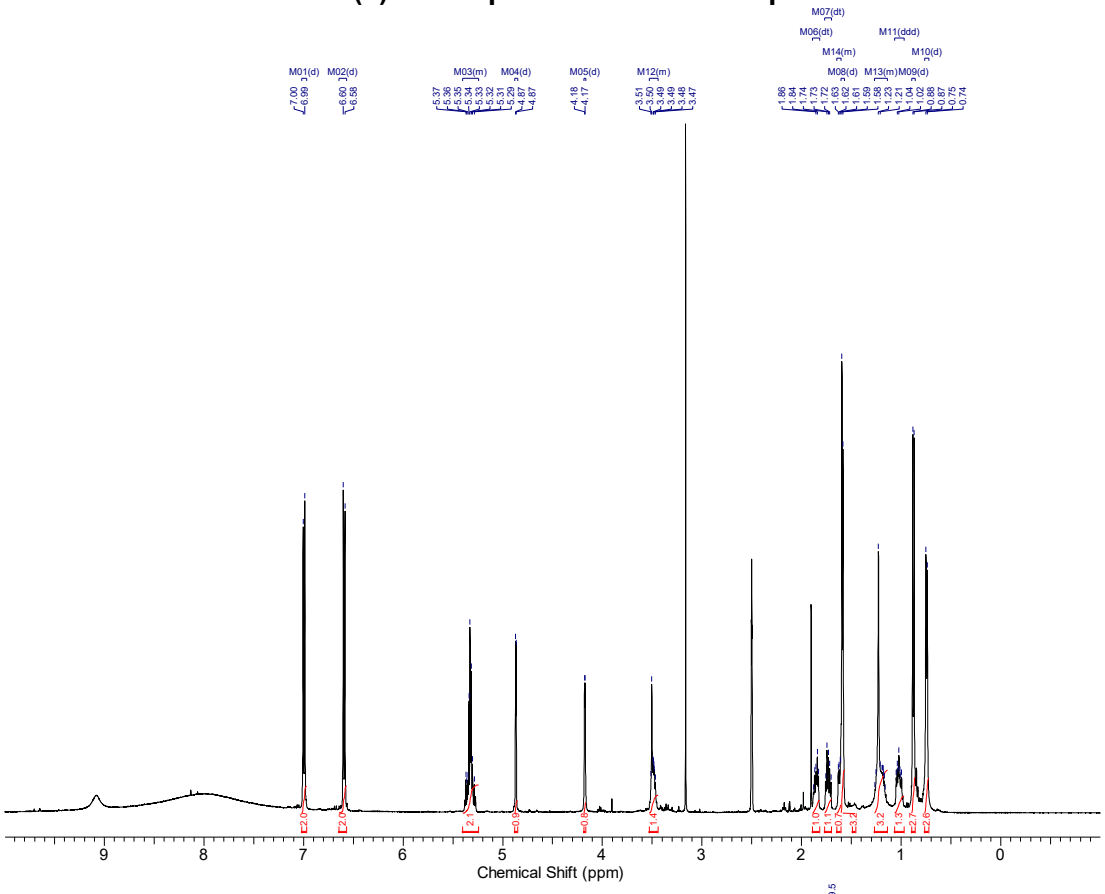
	natural F-14329 in DMSO d_6 Lit [4]		synthetic F-14329 in DMSO d_6		
Pos.	**δ_C**	**δ_H (mult. J[Hz])**	**δ_C**	**δ_H (mult. J[Hz])*+ TFA***	**δ_H (mult. J[Hz])**
1	176.0	-	176.0	-	-
2	100.6	-	100.6	-	-
3	191.5	-	191.5	-	-
4	33.4	3.49 (br m)	33.4	3.49 (br m)	3.48 (m)
5	39.8	1.62 (m)	39.9	1.59 (d, 5.2)	1.59 (d, 5.5)
5b	-	1.04 (m)	-	1.02 (ddd, 13.5, 9.1, 4.6)	1.03 (m)
6	30.8	1.24 (m)	30.8	1.24 (m)	1.25 (m)
7	39.9	1.86 (m)	39.9	1.86 (dt, 13.1, 6.0)	1.86 (m)
7b	-	1.74 (m)	-	1.73 (dt, 13.1, 6.6)	1.74 (m)
8	129.3	5.33 (m)	129,3	5.33 (m)	5.33 (m)
9	125.9	5.34 (m)	125.9	5.33 (m)	5.33 (m)
10	17.8	1.59 (d, 5,2)	17.8	1.59 (d, 5,2)	1.59 (d, 5,2)
11	18.1	0.88 (d, 6.3)	18.1	0.88 (d, 6.7)	0.88 (d, 6.3)
12	19.1	0.77 (d, 6.3)	19.1	0.75 (d, 6.7)	0.77 (d, 6.3)
1'	192.6	-	192.66	-	-
2'	68.0	4.16 (br. s)	68.0	4.18 (d, 3.0)	4.16 (br. s)
3'	72.6	4.87 (br. s)	72.6	4.87 (d, 3.0)	4.88 (br. s)
4'	129.3	-	129.3	-	-
'/9'	128.2	7.00 (d, 8.5)	128.2	7.00 (d, 8.5)	7.00 (d, 8.5)
6'/8'	114.1	6.59 (d, 8.5)	114.1	6.59 (d, 8.5)	6.59 (d, 8.5)
7'	156.5	-	156.57	-	-
3'-OH	-	5.65 (br. s)	-	not detected	5.66 (br. s)
7'-NH	-	9.23 (br. s)	-	not detected	9.23 (br. s)
-NH	-	9.14 (br. s)	-	not detected	9.15 (br. s)

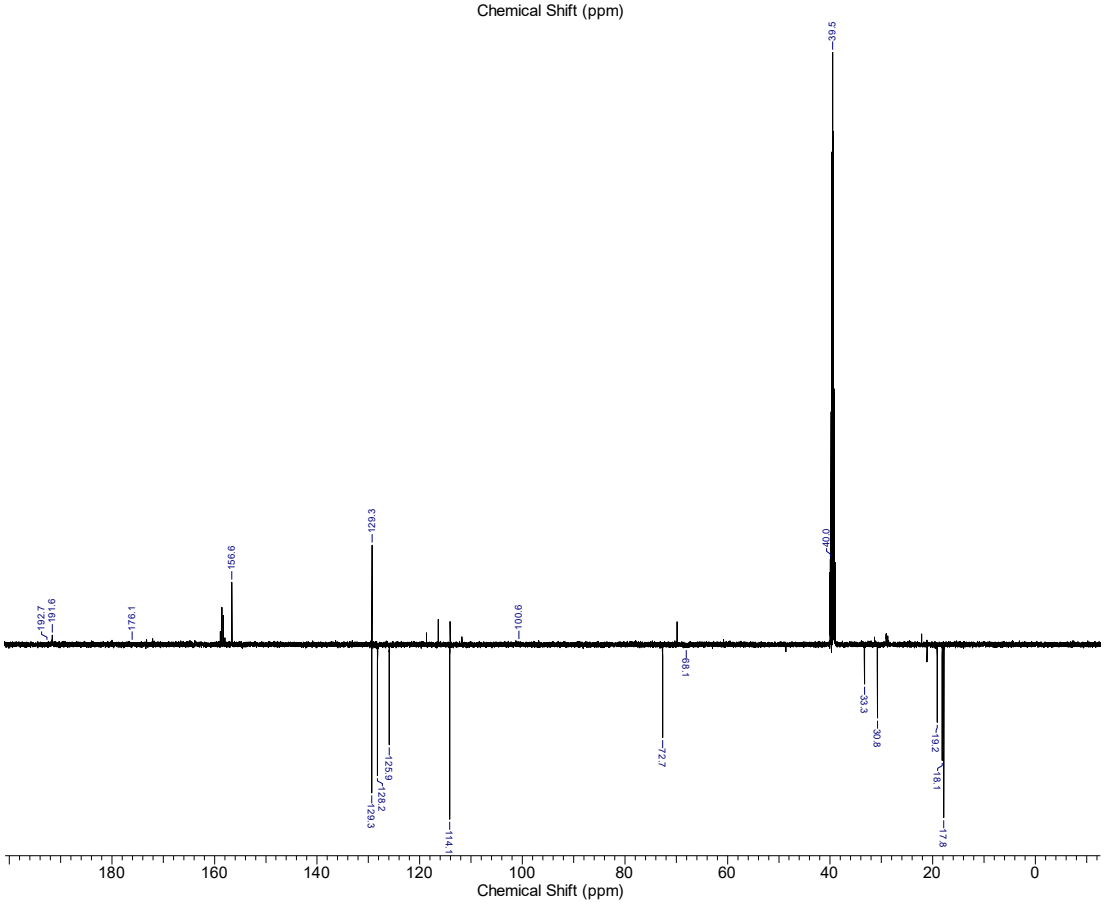
S18

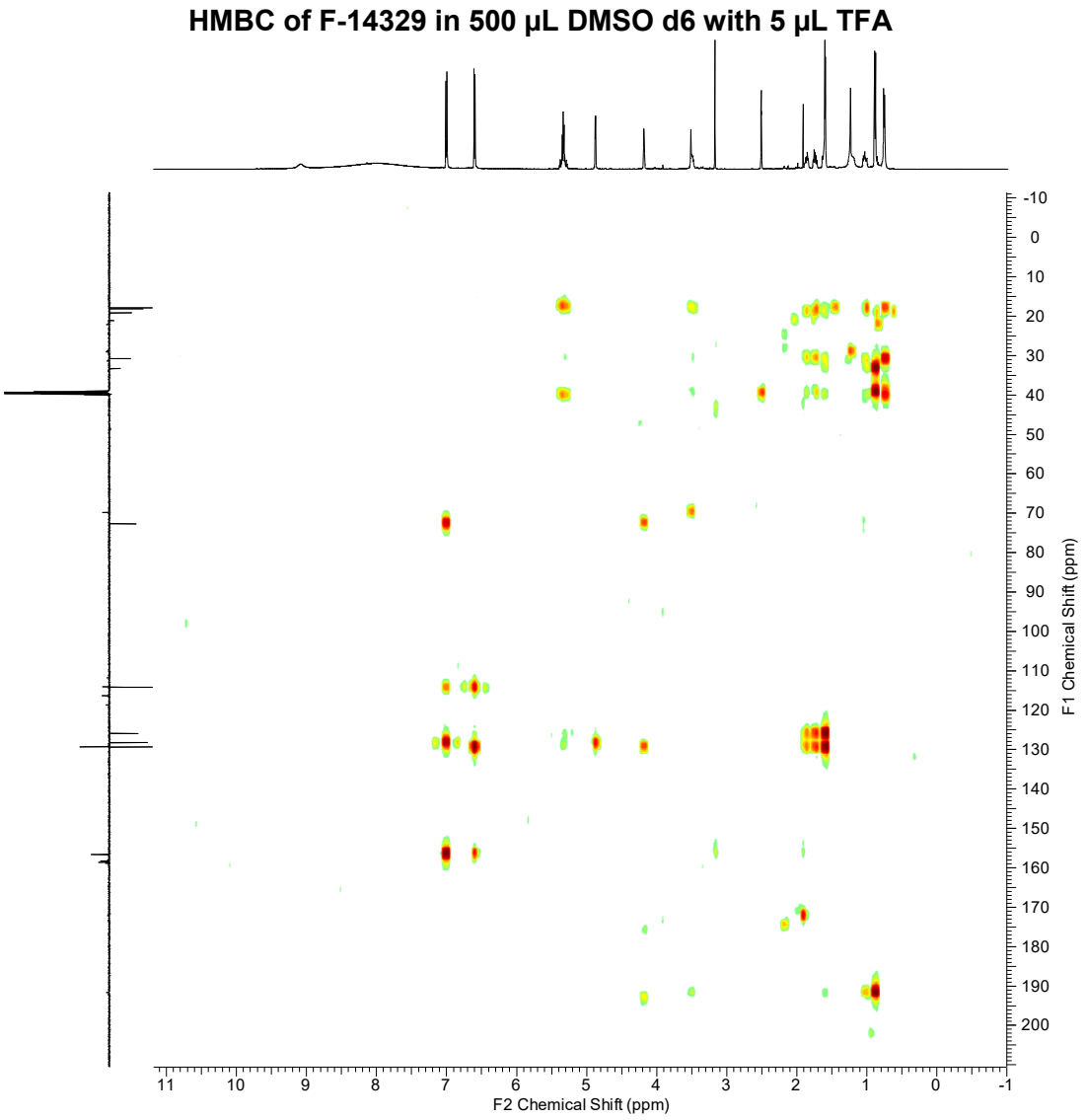
F-14329 (1) in DMSO d6 without TFA

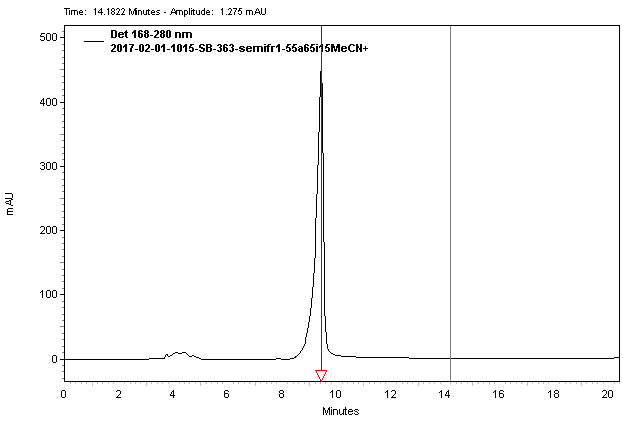


F-14329 (1) in 500 µL DMSO d6 with 5 µL TFA

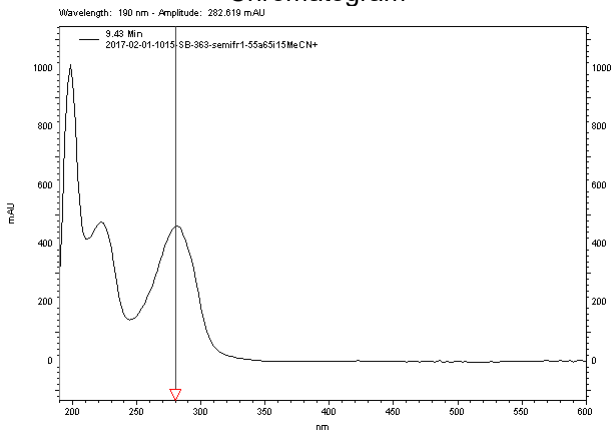





HMBC of F-14329 in 500 µL DMSO d6 with 5 µL TFA
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

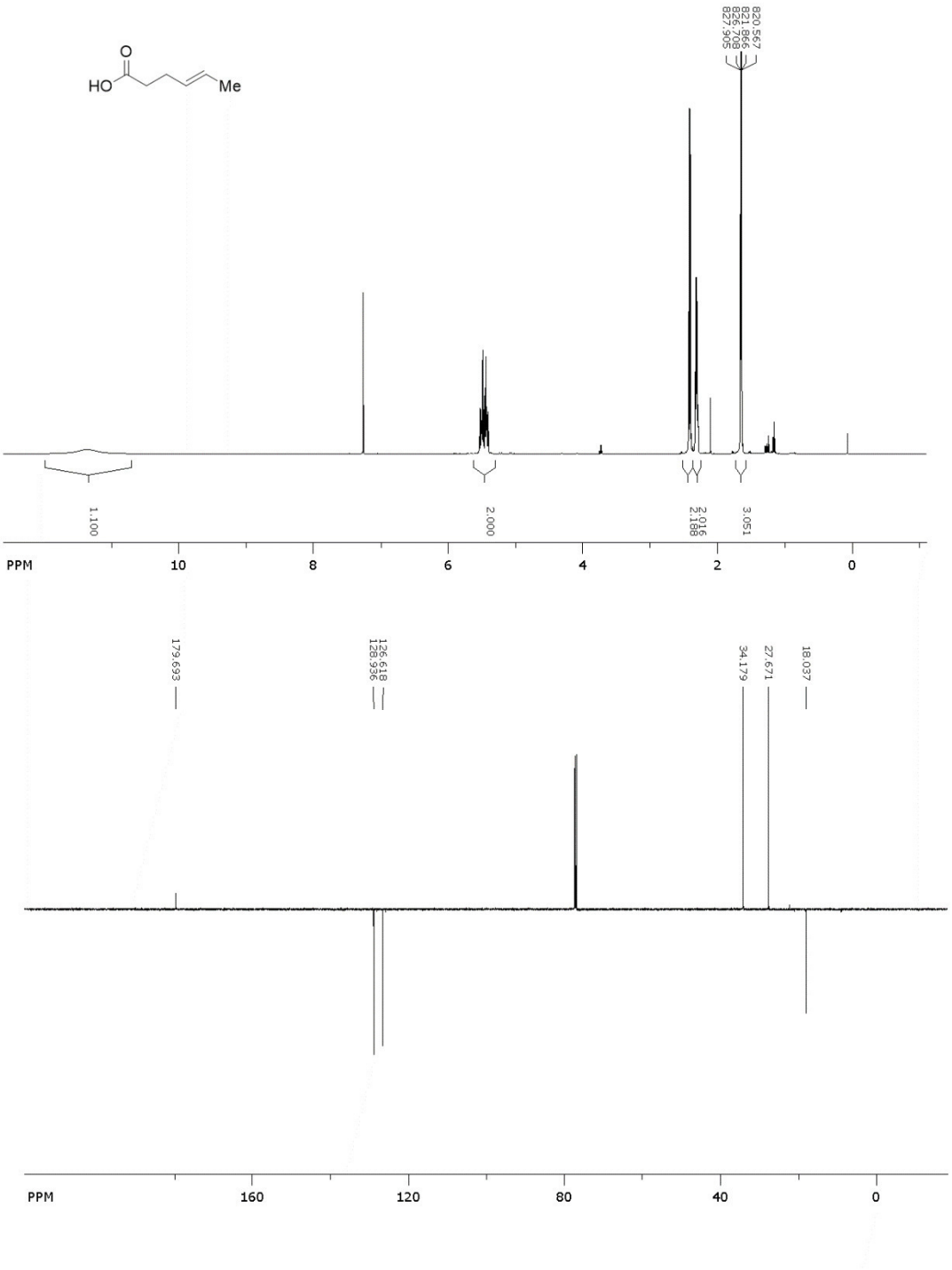


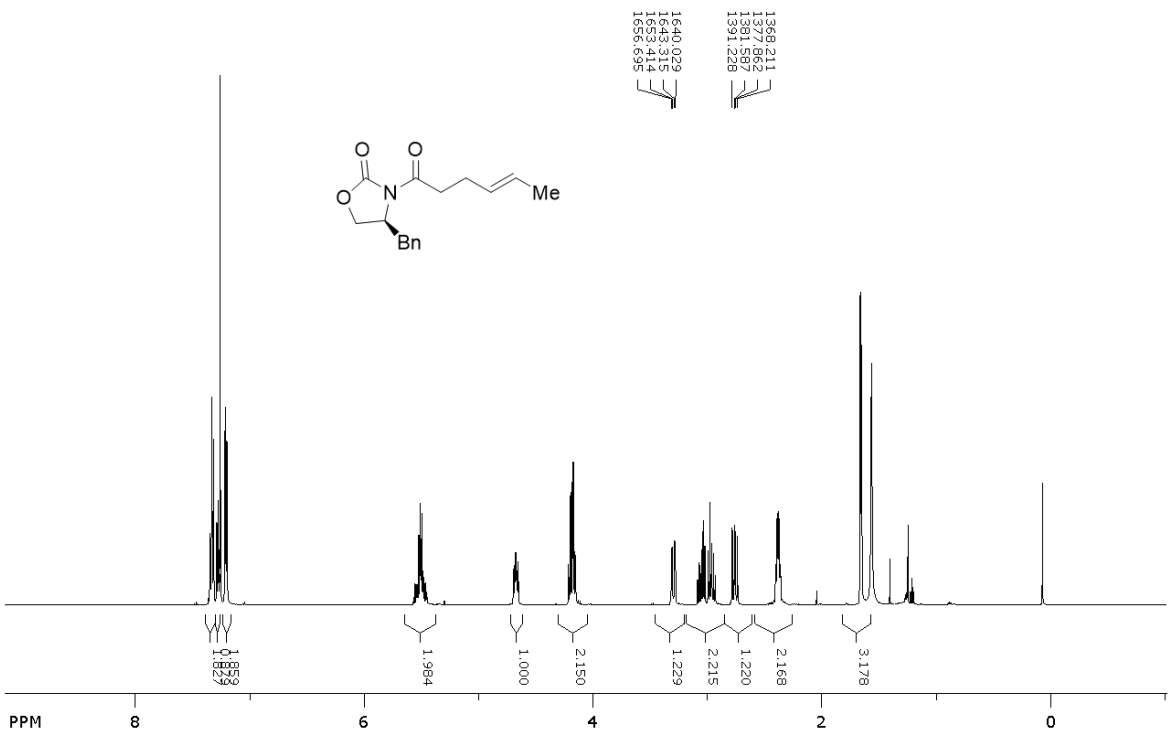
Chromatogram

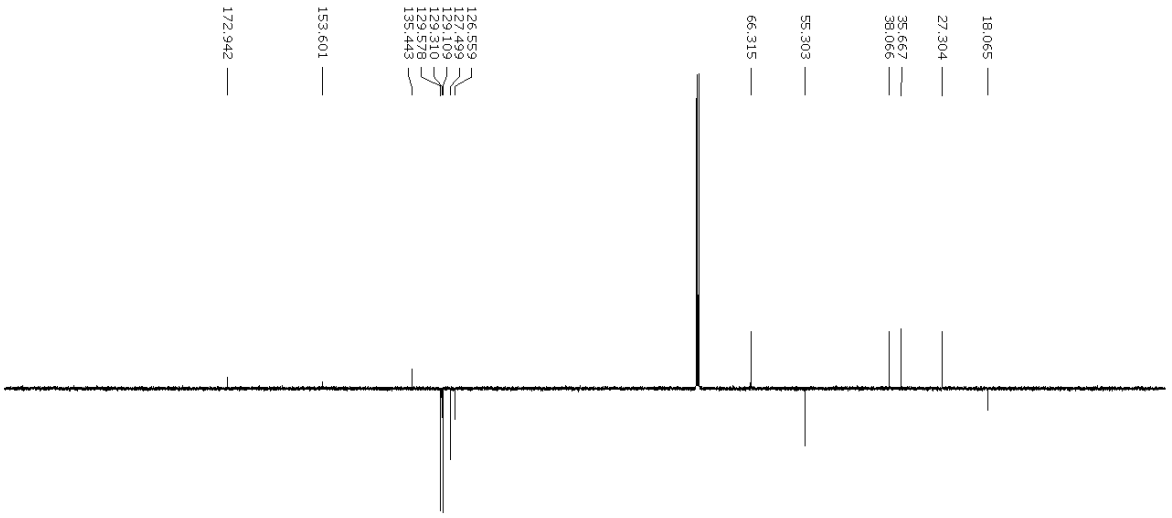


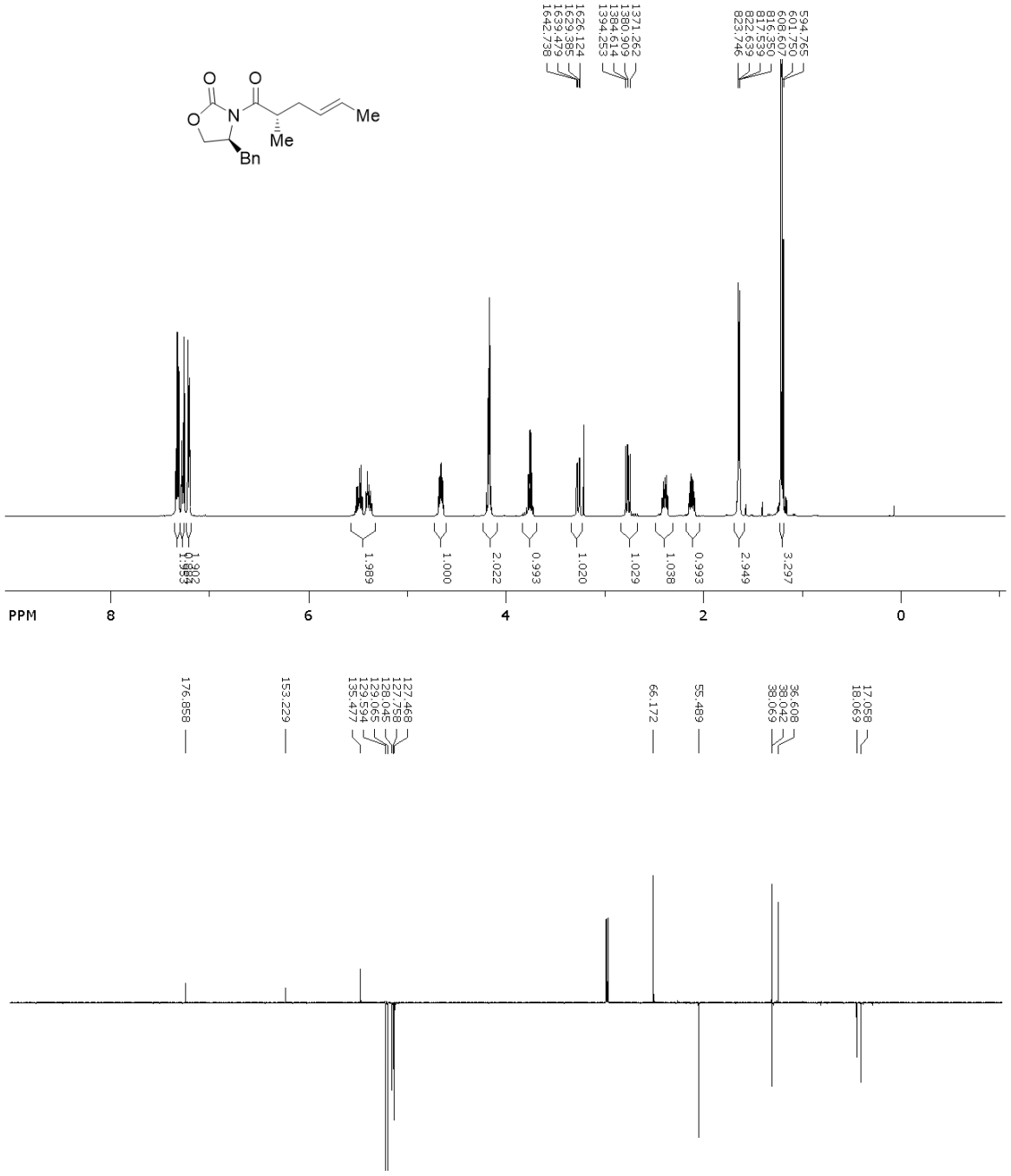
UV Absorption at 9.43 min

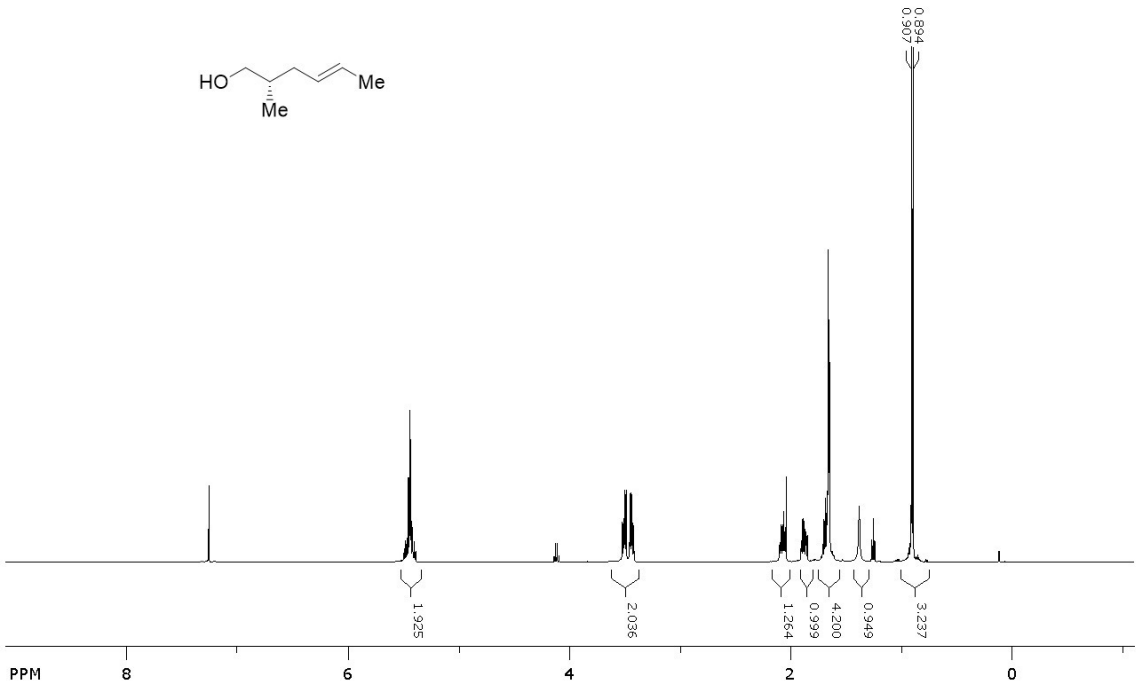
HPLC program: Start at 55% MeCN in H_2O with 0.1% constant HCO_2H acid modifier to 65% MeCN in 15 min to 100% MeCN in 1 min for 20 min; Flow-rate 0.7 mL/min, Column: Phenomenex Kinetex 5Cu C18 100A, 250 x 4.60 mm

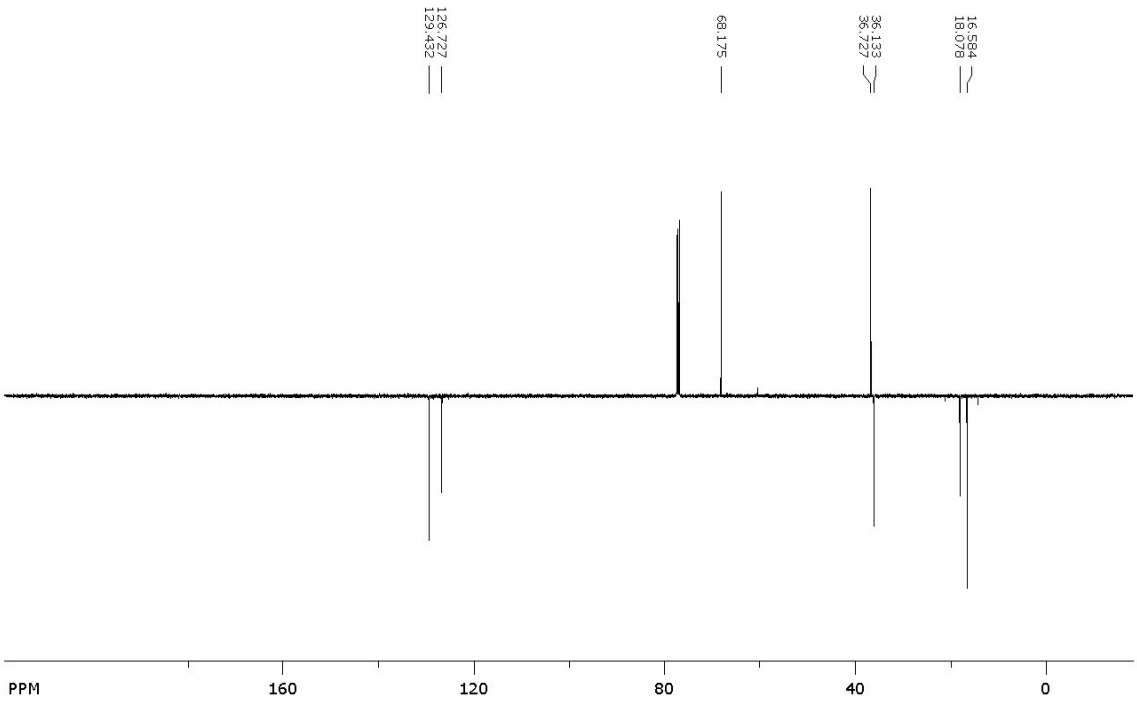

HO
O
Me
820.567
821.966
827.905
1.100
2.000
2.016
2.188
3.051
PPM
10
8
6
4
2
0
179.693
126.618
128.936
34.179
27.671
18.037
PPM
160
120
80
40
0

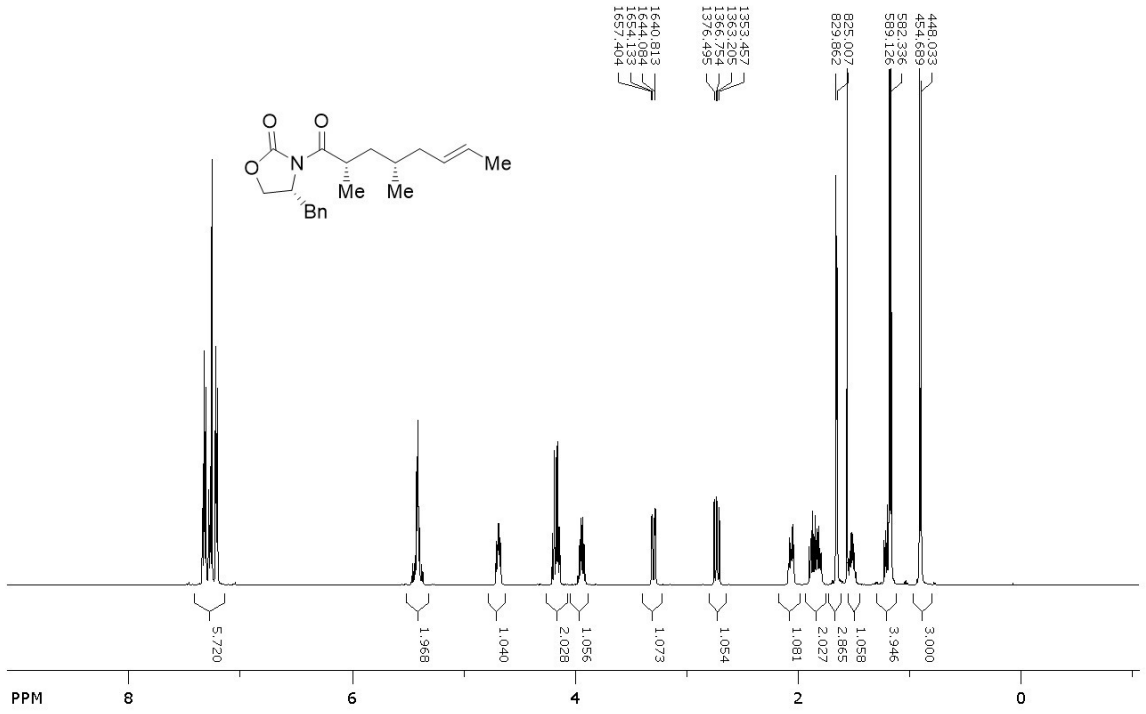

1640.029
1643.315
1653.414
1656.695
1368.211
1377.862
1381.587
1391.228
O
O
O
N
Me
Bn
1.827
1.850
1.984
1.000
2.150
1.229
2.215
1.220
2.168
3.178
PPM
8
6
4
2
0

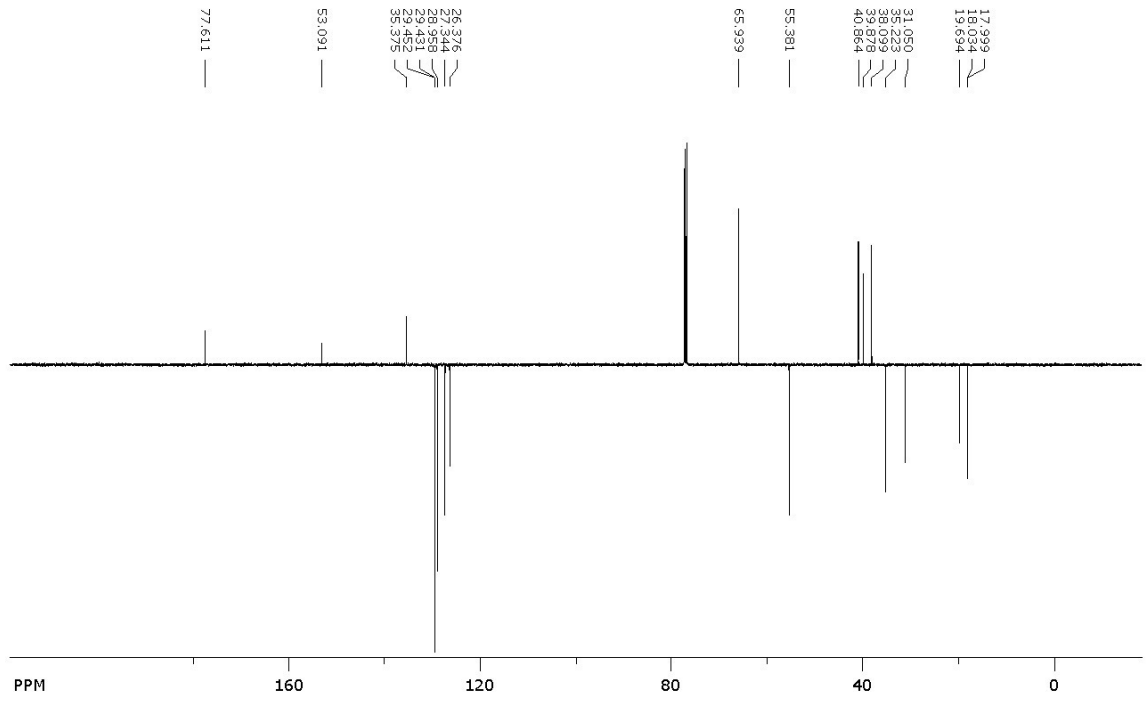

172.942
153.601
135.443
129.578
129.100
127.489
126.559
66.315
55.303
38.066
35.667
27.304
18.065

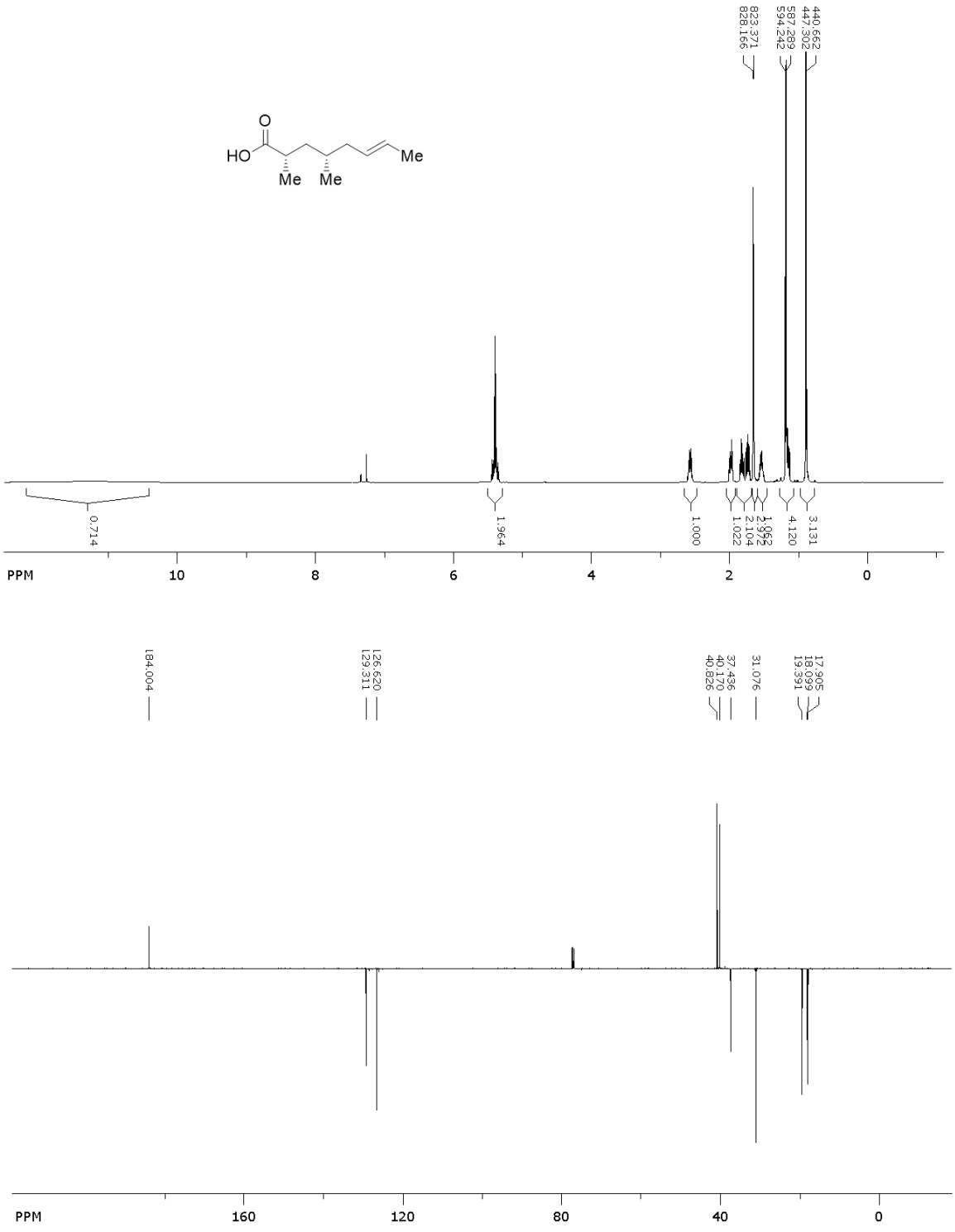

Me
Me
Bn
PPM
8
6
4
2
0

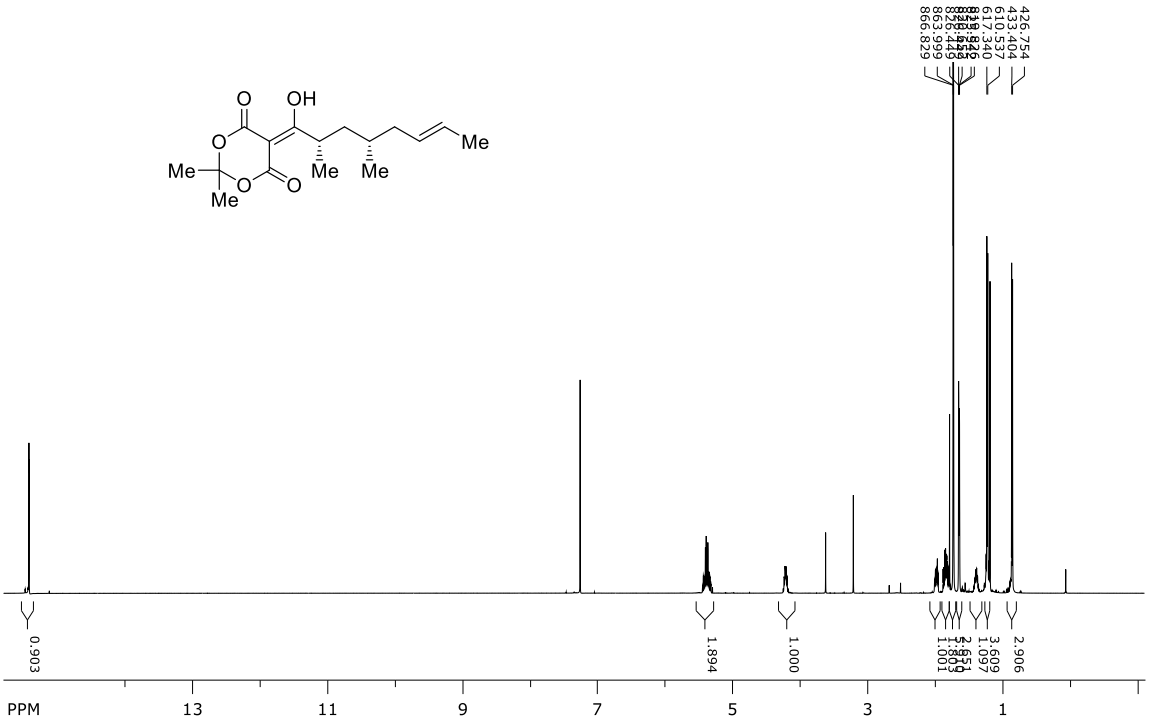

HO
Me
Me
0.894
0.907
1.925
2.036
1.264
0.999
4.200
0.949
3.237
PPM
8
6
4
2
0

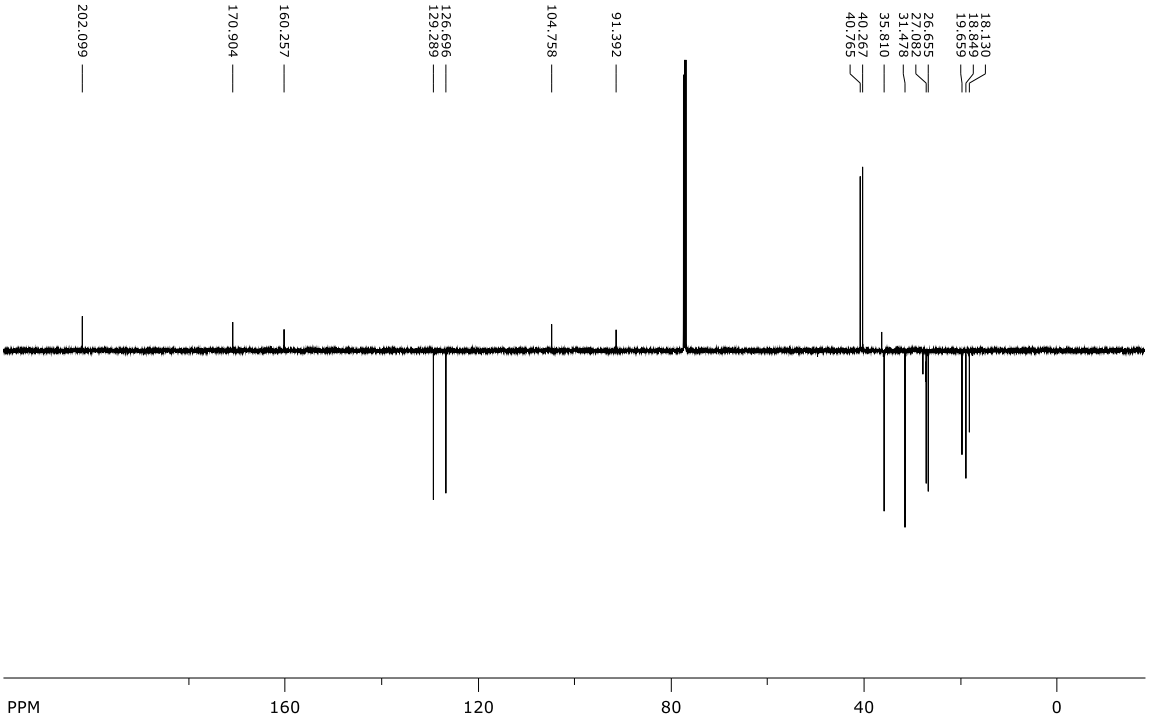

126.727
129.432
68.175
36.133
36.727
16.584
18.078
PPM
160
120
80
40
0

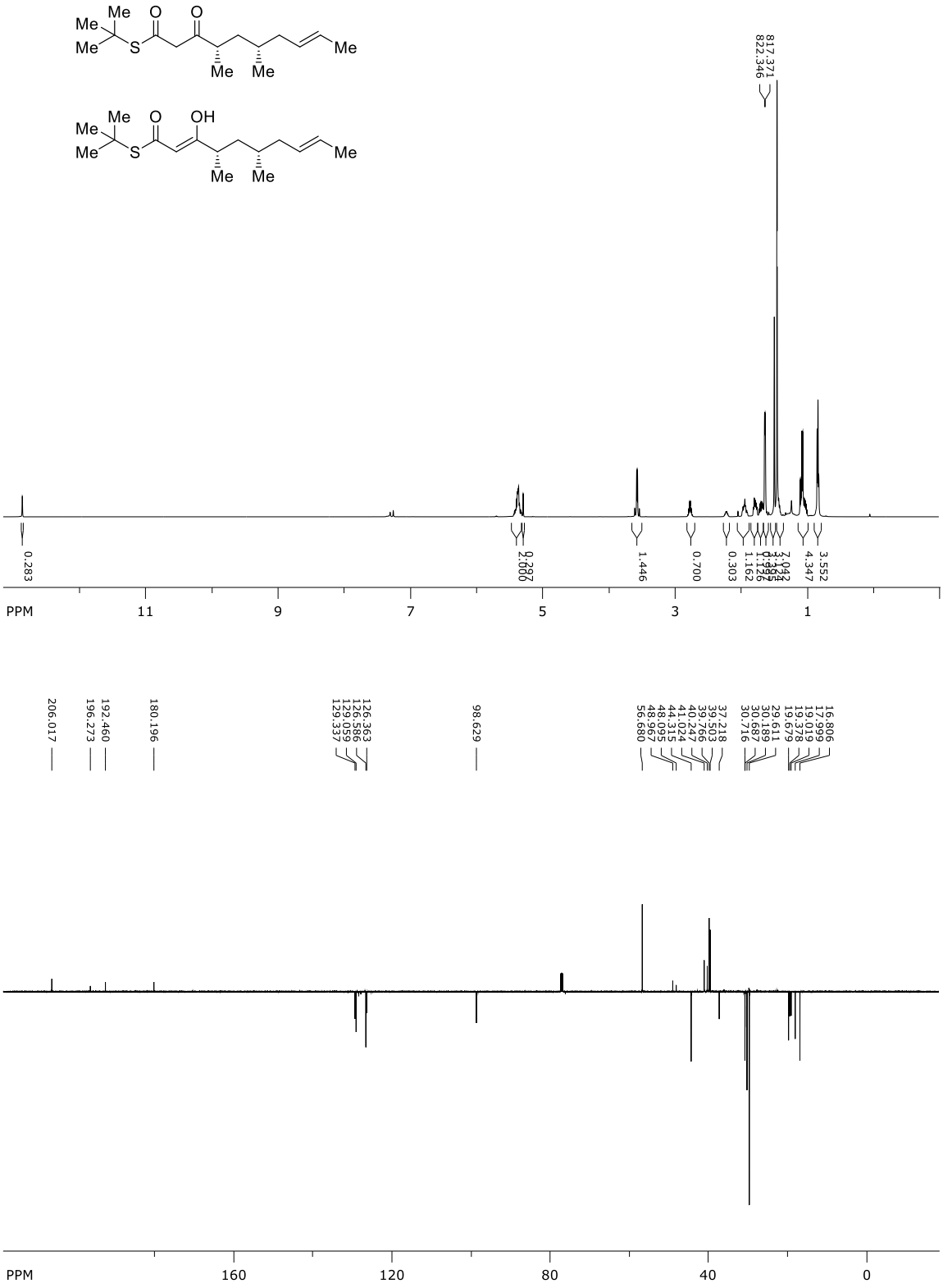

1657.404
1654.193
1640.813
1376.495
1366.754
1363.205
1353.457
829.862
825.007
589.126
582.336
454.689
448.033
Me
Me
Me
Bn
5.720
1.968
1.040
2.028
1.056
1.073
1.054
1.081
2.027
2.865
1.058
3.946
3.000
PPM
8
6
4
2
0

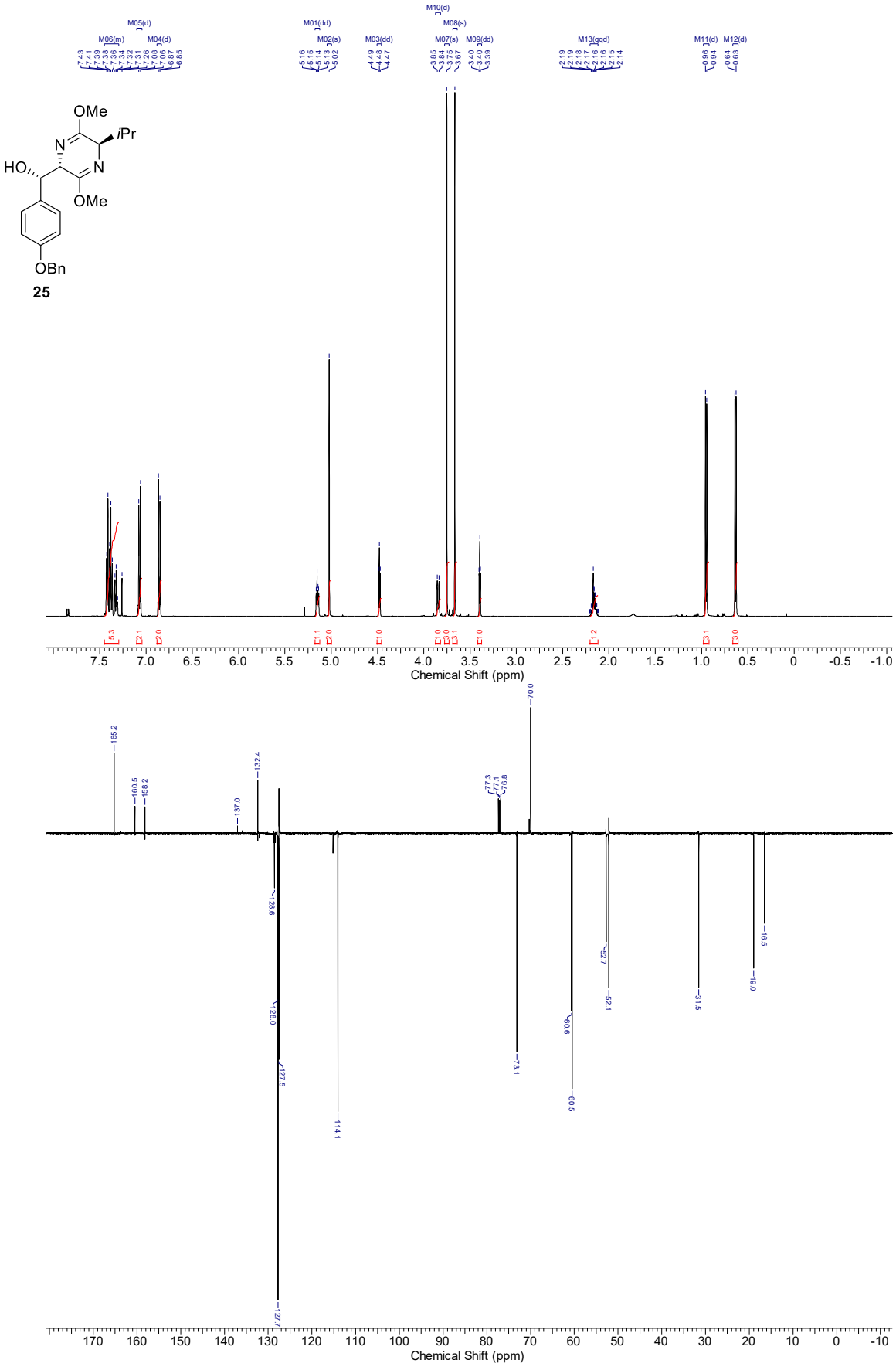

77.611
53.091
35.375
29.452
29.431
27.384
26.376
65.939
55.381
40.864
39.878
38.099
35.223
31.050
19.694
18.034
17.999
PPM
160
120
80
40
0

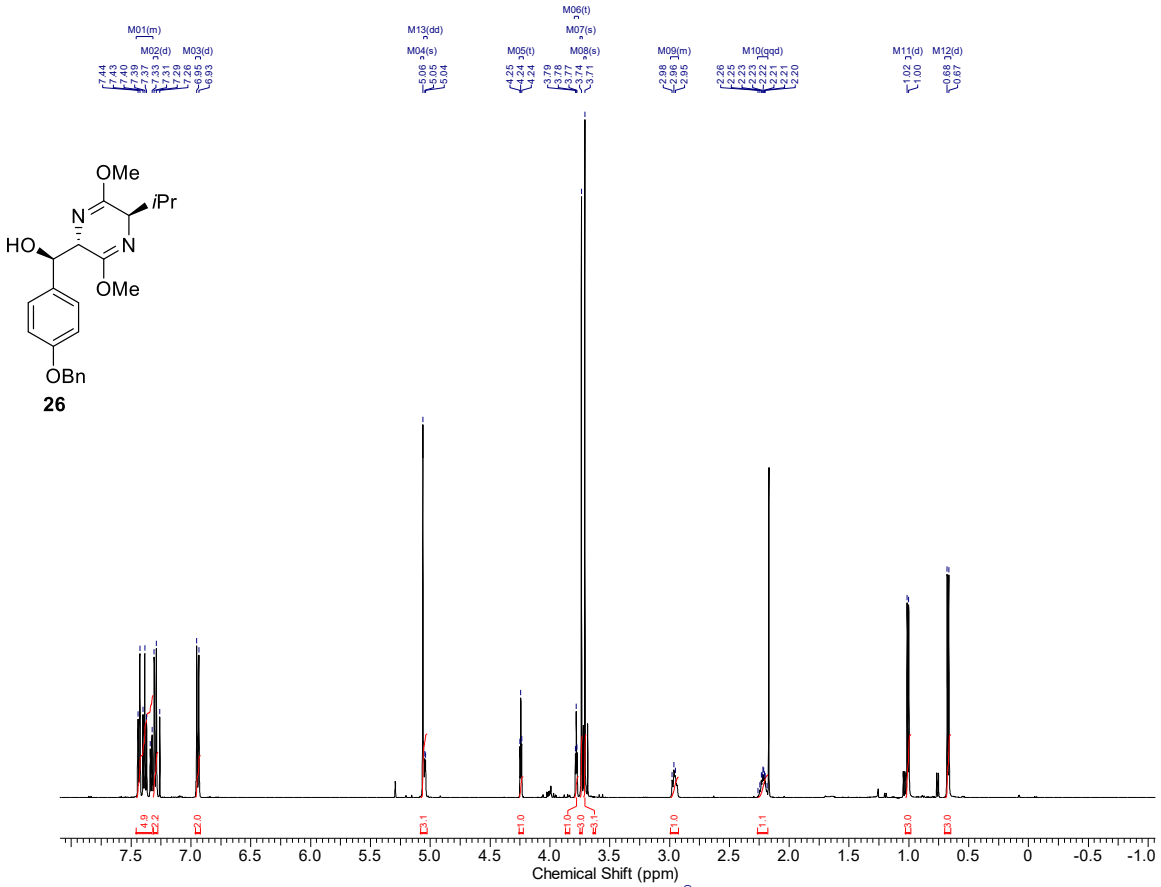

823.371
828.166
587.289
594.242
440.662
447.302
O
HO
Me
Me
Me
0.714
1.964
1.000
1.022
2.104
2.972
1.962
4.120
3.131
PPM
10
8
6
4
2
0
184.004
126.620
129.311
40.826
40.170
37.436
31.076
18.099
19.391
17.905
PPM
160
120
80
40
0

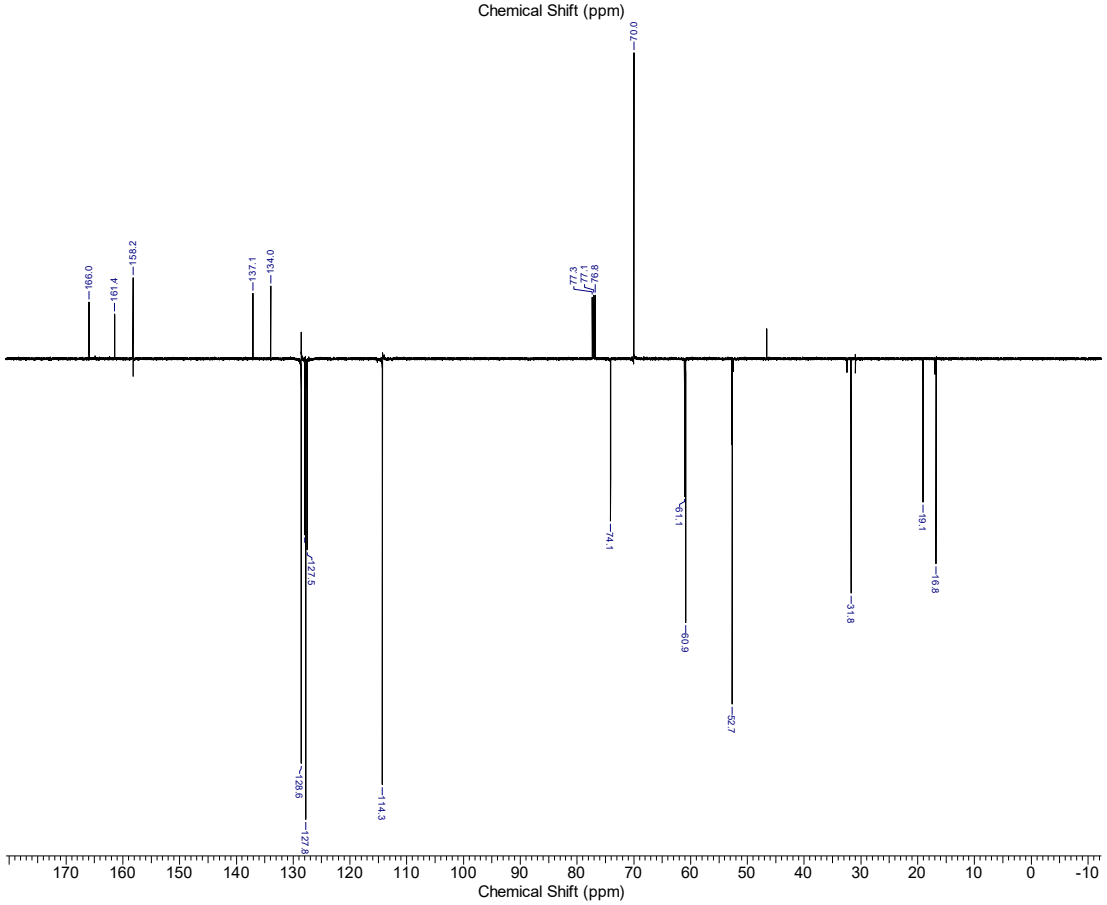

O
OH
O
Me
Me
Me
Me
O
O
Me
426.754
433.404
610.537
617.340
866.829
0.903
1.894
1.000
1.001
1.097
3.609
2.906
PPM
13
11
9
7
5
3
1

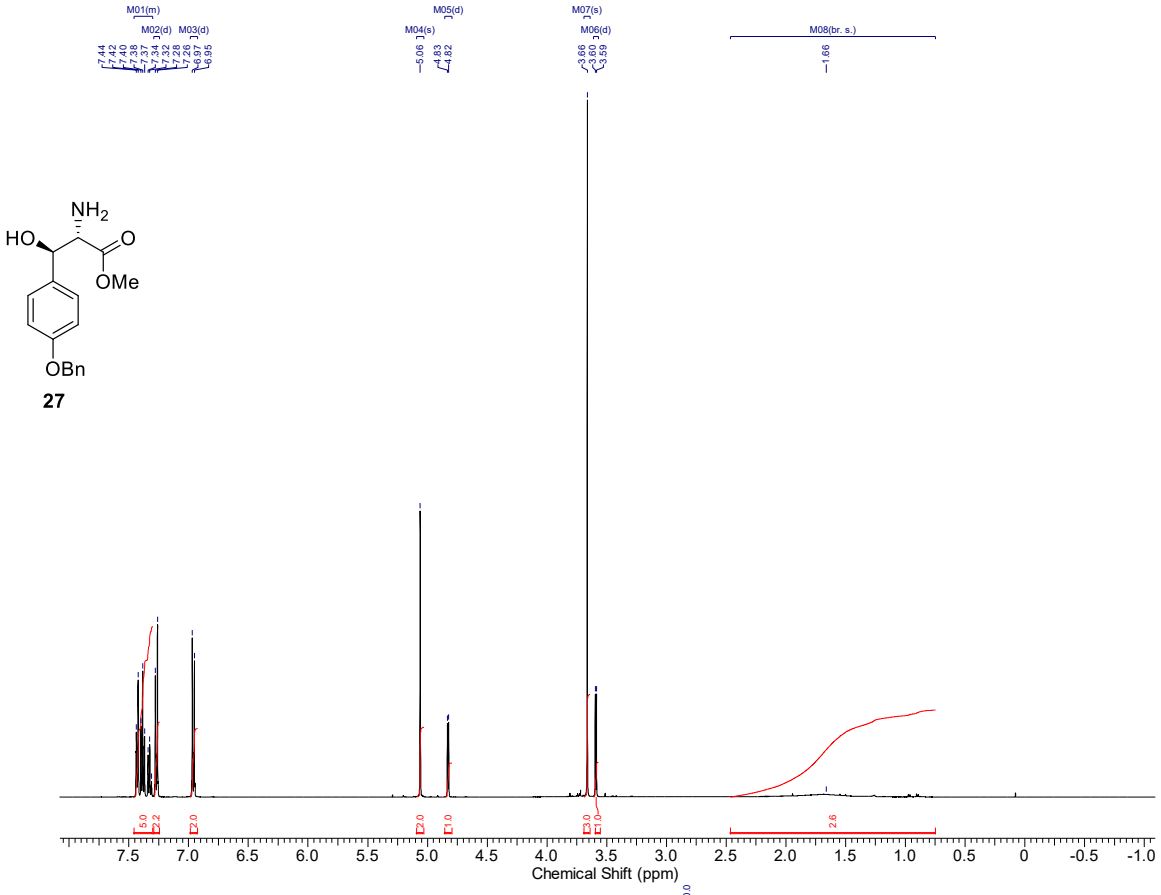

202.099
170.904
160.257
129.289
126.696
104.758
91.392
40.765
40.267
35.810
31.478
27.082
26.655
19.659
18.849
18.130
PPM
160
120
80
40
0


Me
Me
O
O
S
Me
Me
Me
Me
OH
817.371
822.346
0.283
2.000
2.087
1.446
0.700
0.303
1.162
1.126
3.042
4.347
3.552
PPM
11
9
7
5
3
1
206.017
196.273
192.460
180.196
129.337
129.059
126.586
126.363
98.629
56.680
48.967
48.095
44.315
41.047
40.047
39.766
39.503
37.218
30.716
30.687
30.189
29.611
19.679
19.378
19.019
17.959
16.806
PPM
160
120
80
40
0

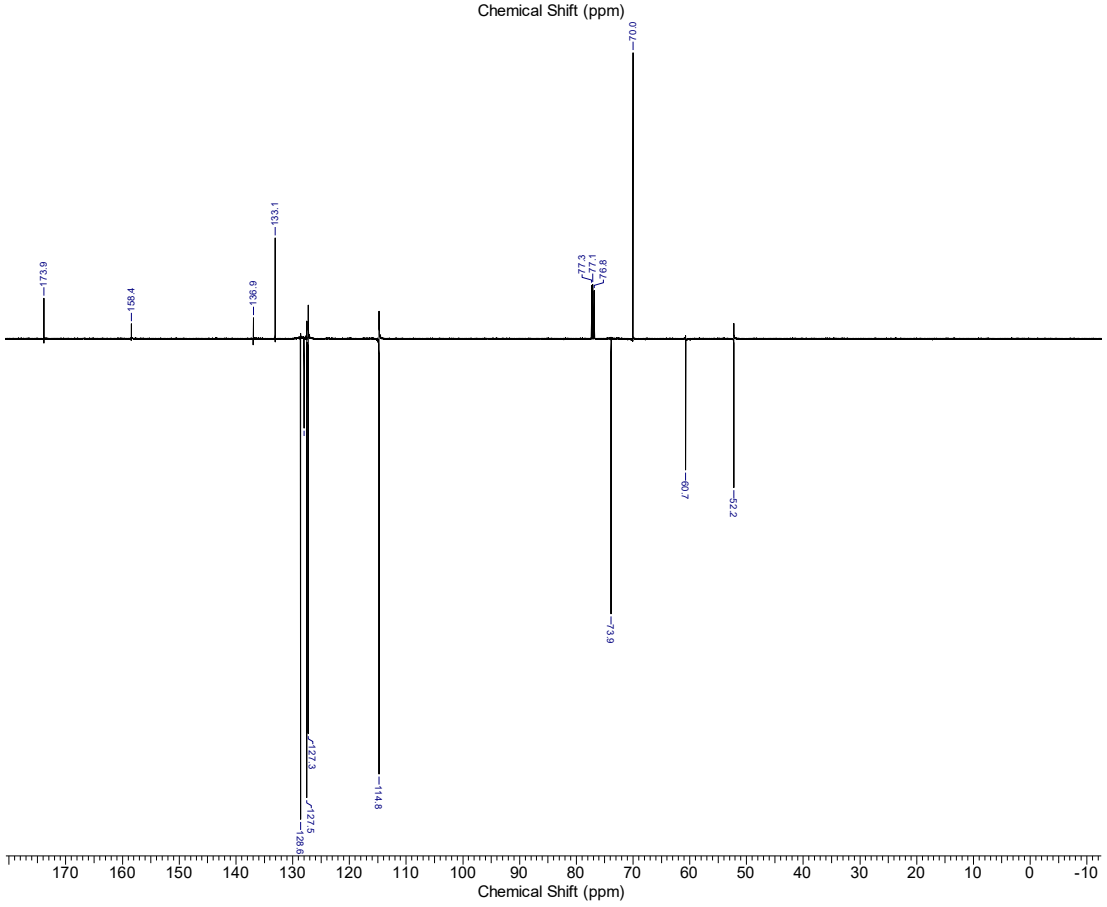

OMe
iPr
N
HO
N
OMe
OBn
25
Chemical Shift (ppm)
Chemical Shift (ppm)

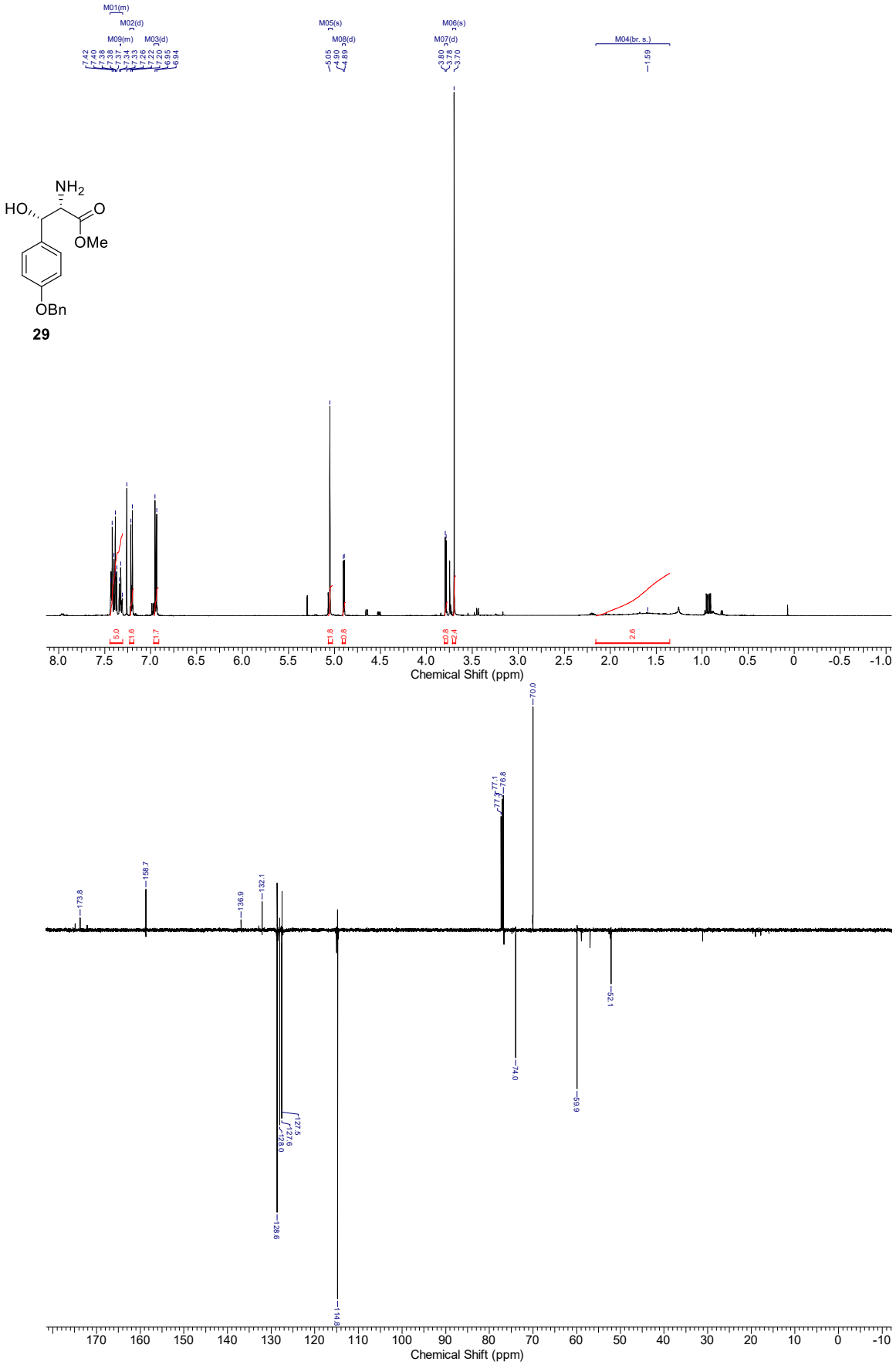

OMe
iPr
N
HO
N
OMe
OBn
26
Chemical Shift (ppm)

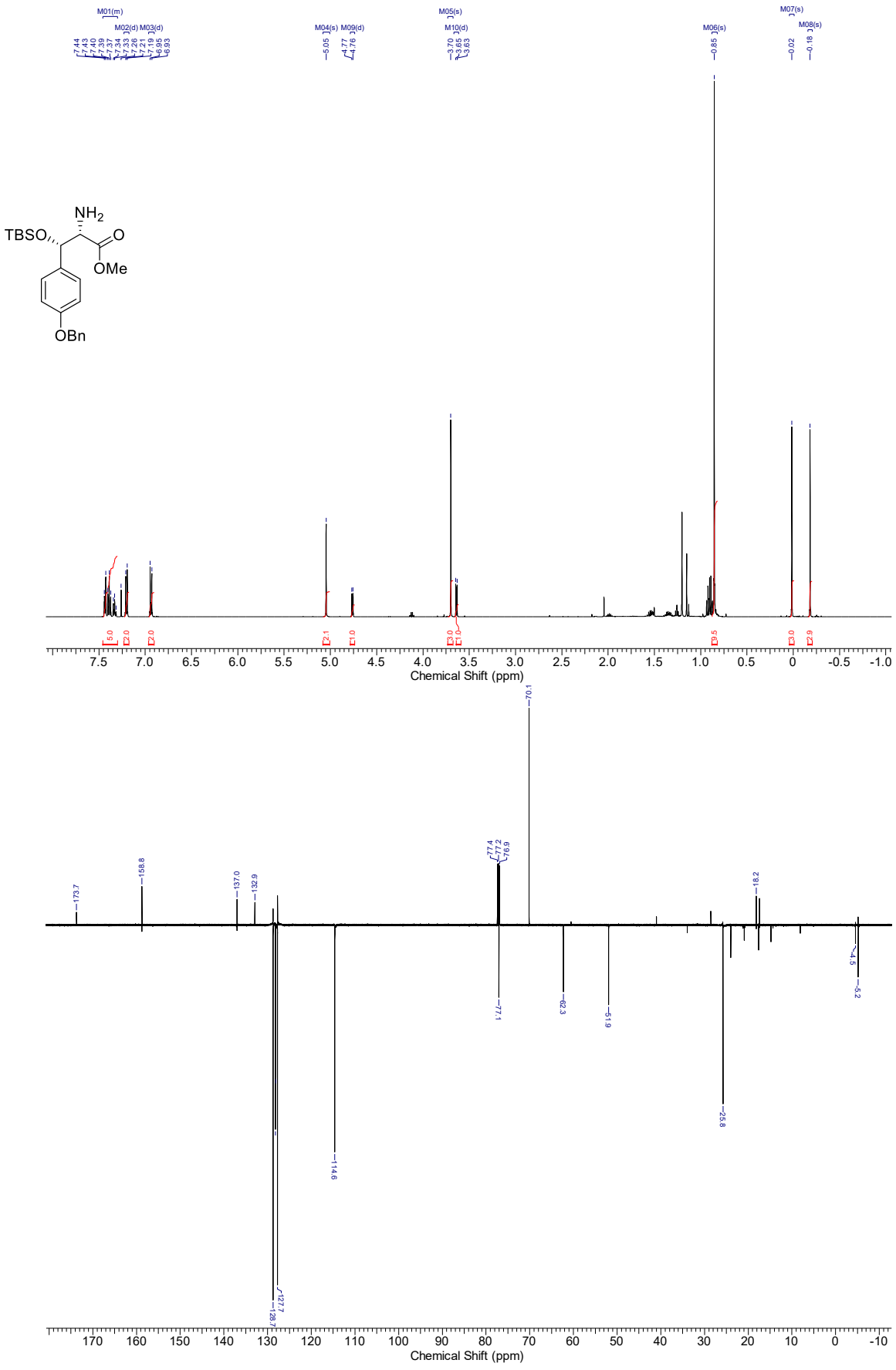

Chemical Shift (ppm)

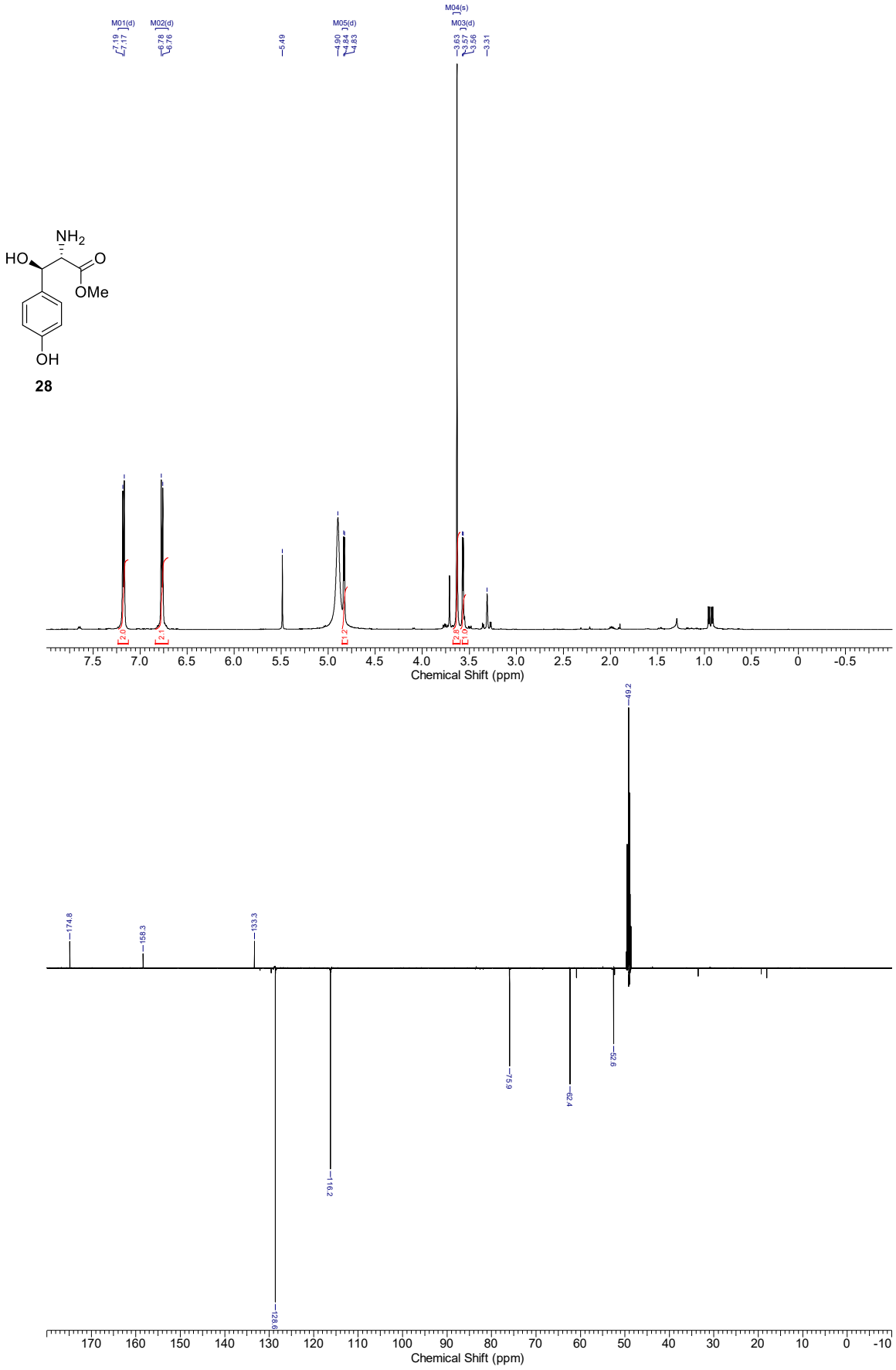

M01(m)
M02(d)
M03(d)
M04(s)
M05(d)
M06(d)
M07(s)
M08(br. s.)
NH2
HO
O
OMe
OBn
Chemical Shift (ppm)

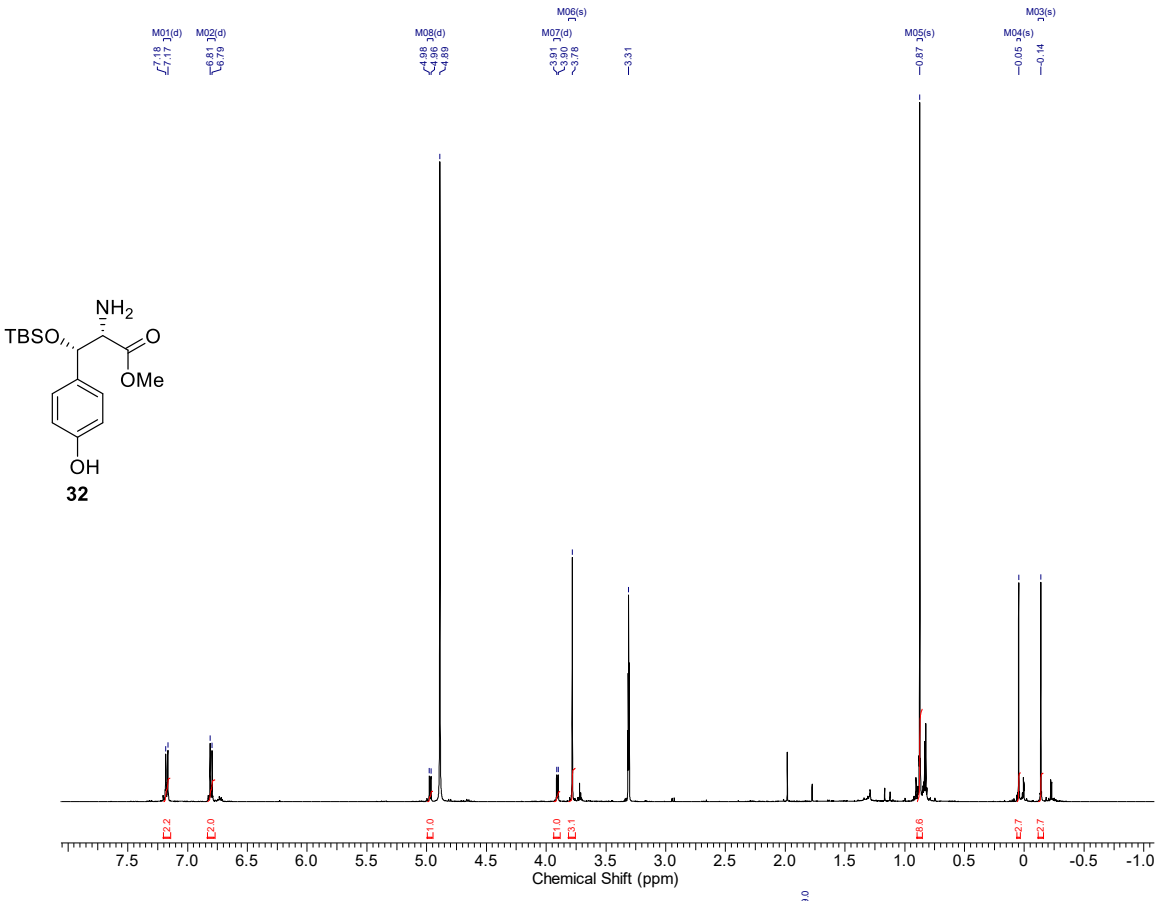
27

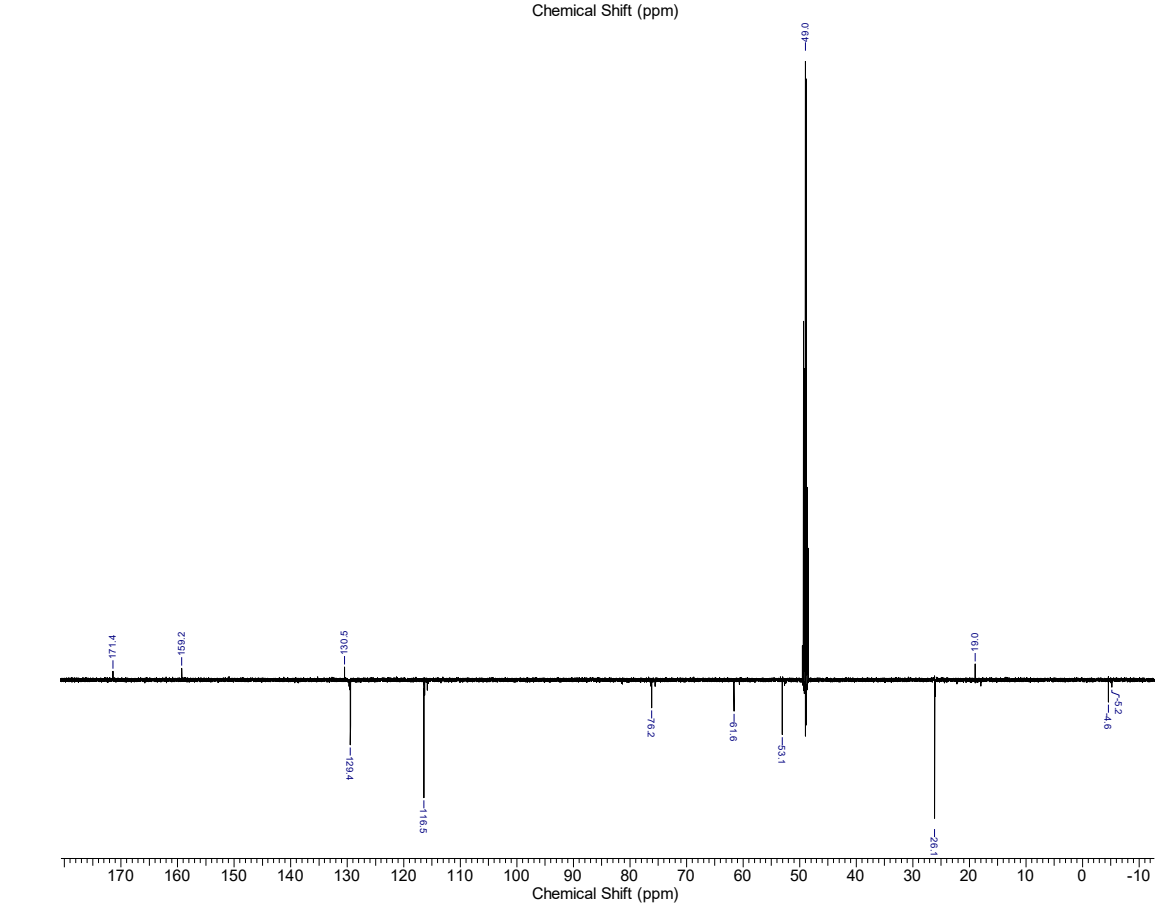

Chemical Shift (ppm)


M01(m)
M02(d)
M09(m)
M03(d)
M05(s)
M08(d)
M06(s)
M07(d)
M04(br. s.)
NH2
HO
O
OMe
OBn
29
Chemical Shift (ppm)
Chemical Shift (ppm)


NH2
TBSO
O
OMe
OBn
Chemical Shift (ppm)
Chemical Shift (ppm)

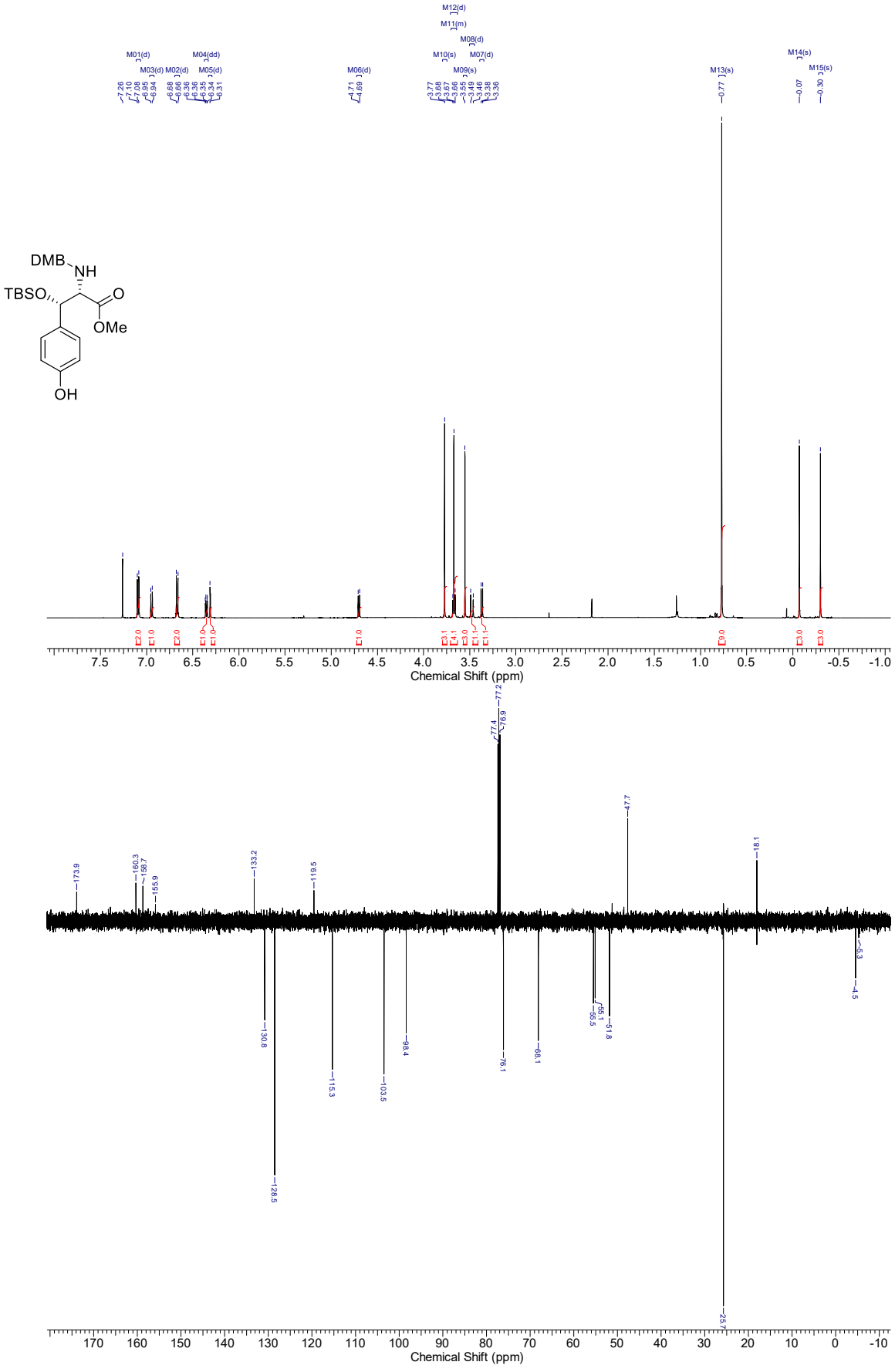

M01(d)
M02(d)
M05(d)
M04(s)
M03(d)
7.19
7.17
6.78
6.76
5.49
4.90
4.84
4.83
3.63
3.57
3.56
3.31
NH2
HO
O
OMe
OH
28
Chemical Shift (ppm)
174.8
158.3
133.3
116.2
128.6
71.9
62.4
52.6
49.2
Chemical Shift (ppm)

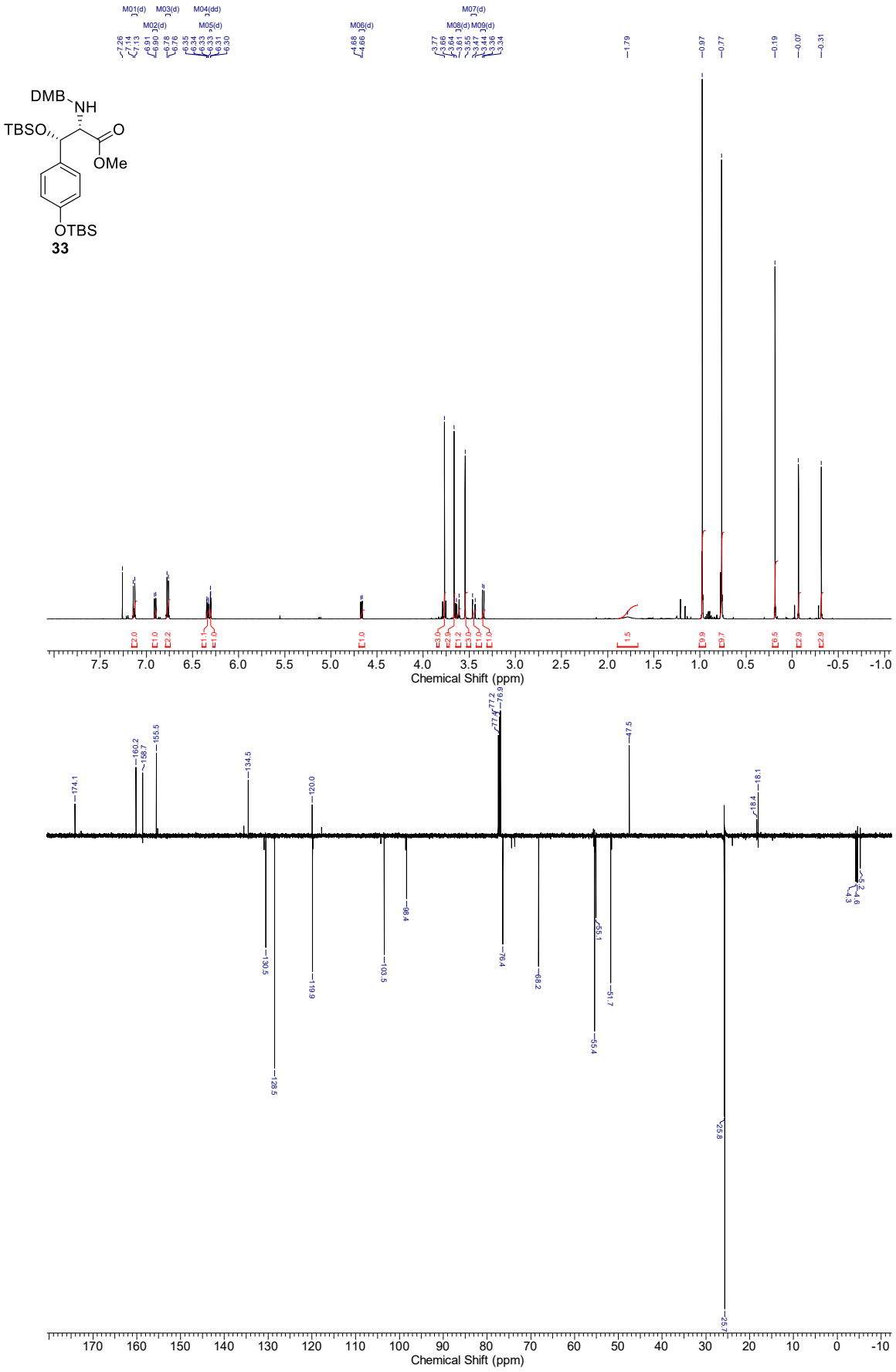

M01(d)
M02(d)
M08(d)
M07(d)
M06(s)
M05(s)
M04(s)
M03(s)
7.18
7.17
6.81
6.79
4.98
4.86
4.89
3.91
3.90
3.78
3.31
0.87
-0.05
-0.14
2.2
2.0
1.0
1.0
3.1
8.6
2.7
2.7
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5 -1.0
Chemical Shift (ppm)

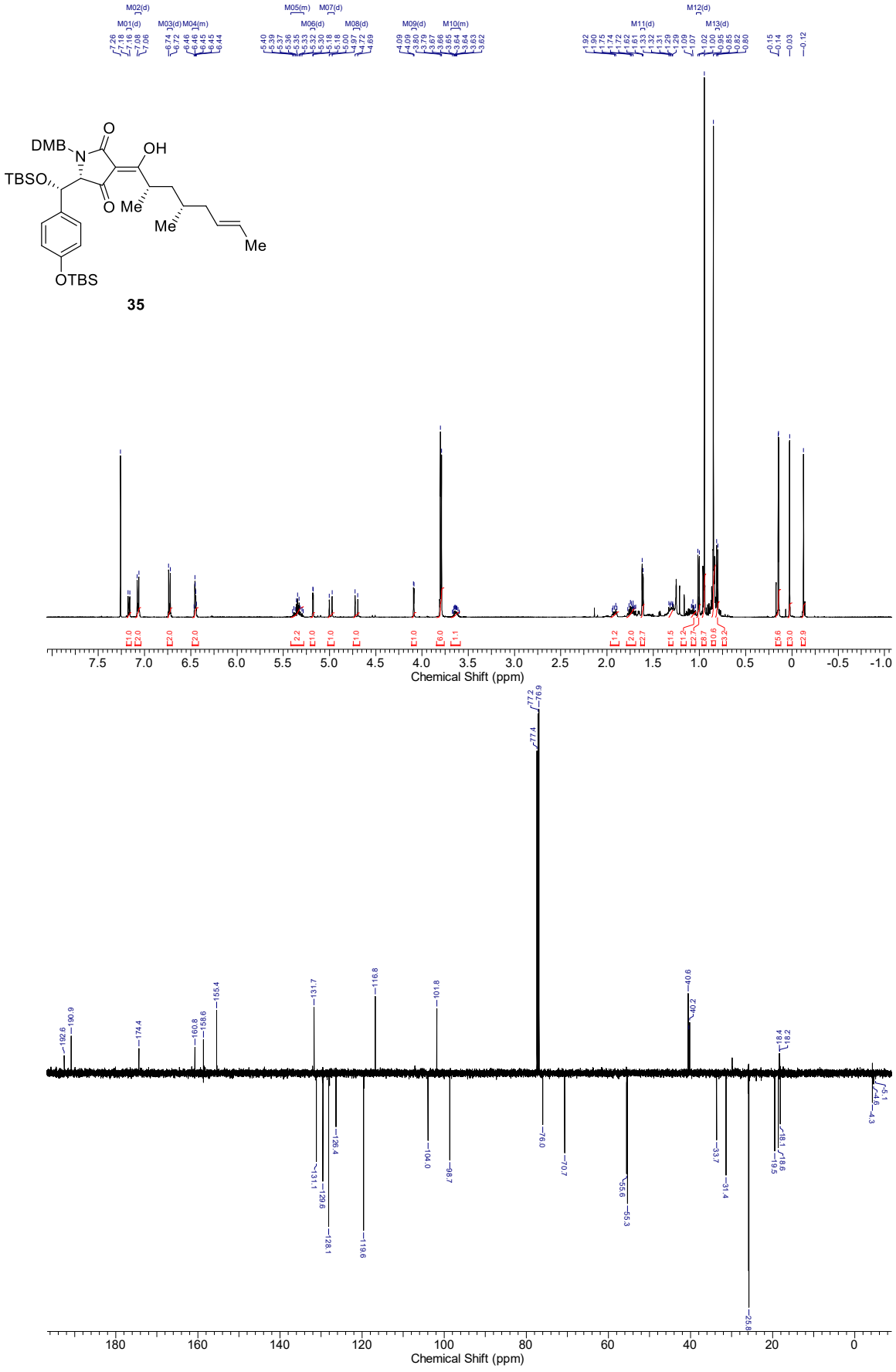

171.4
159.2
130.5
128.4
116.5
76.2
61.6
53.1
49.0
26.1
19.0
-5.2
-4.6
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

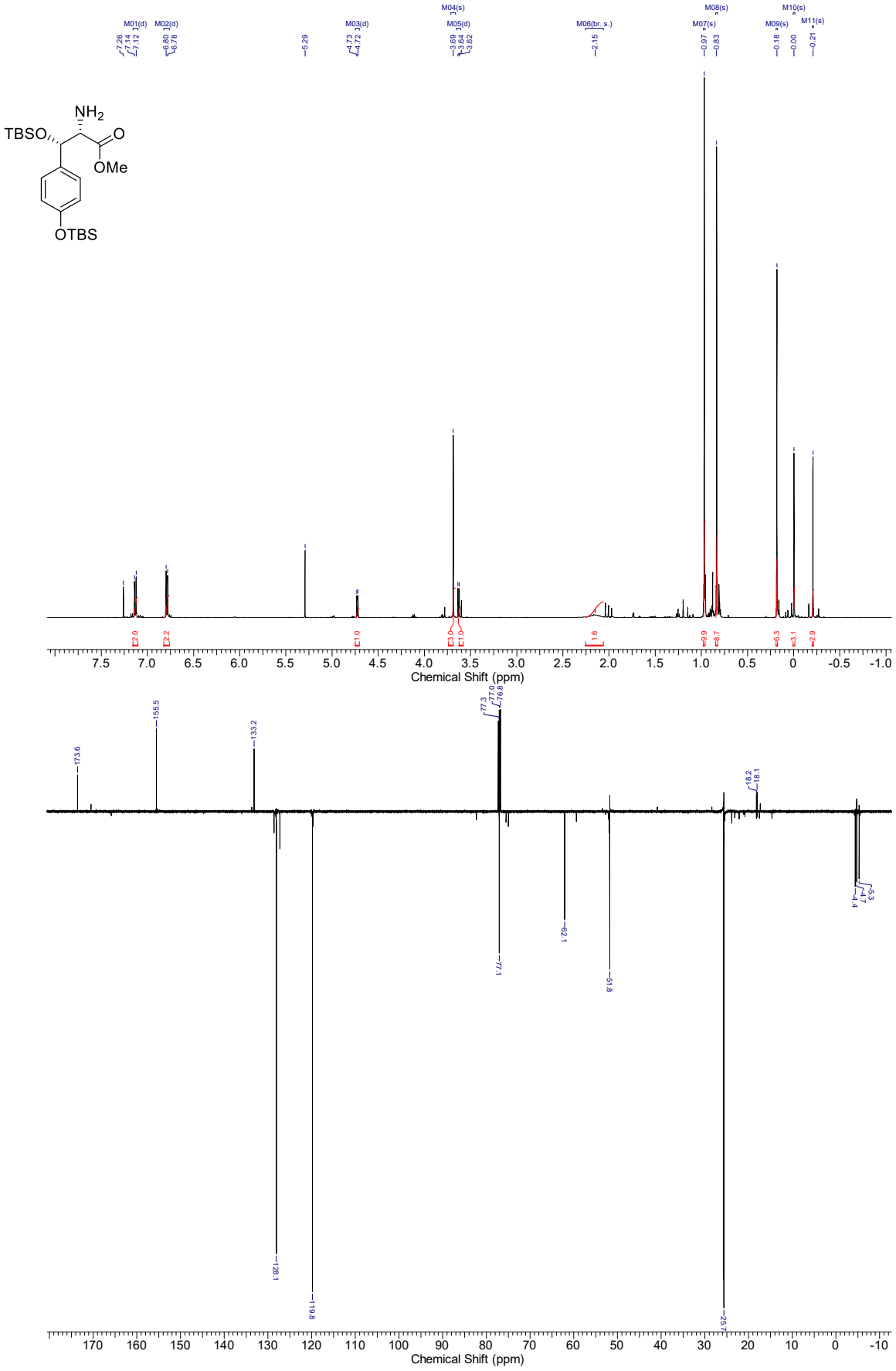
NH2
TBSO
O
OMe
OH

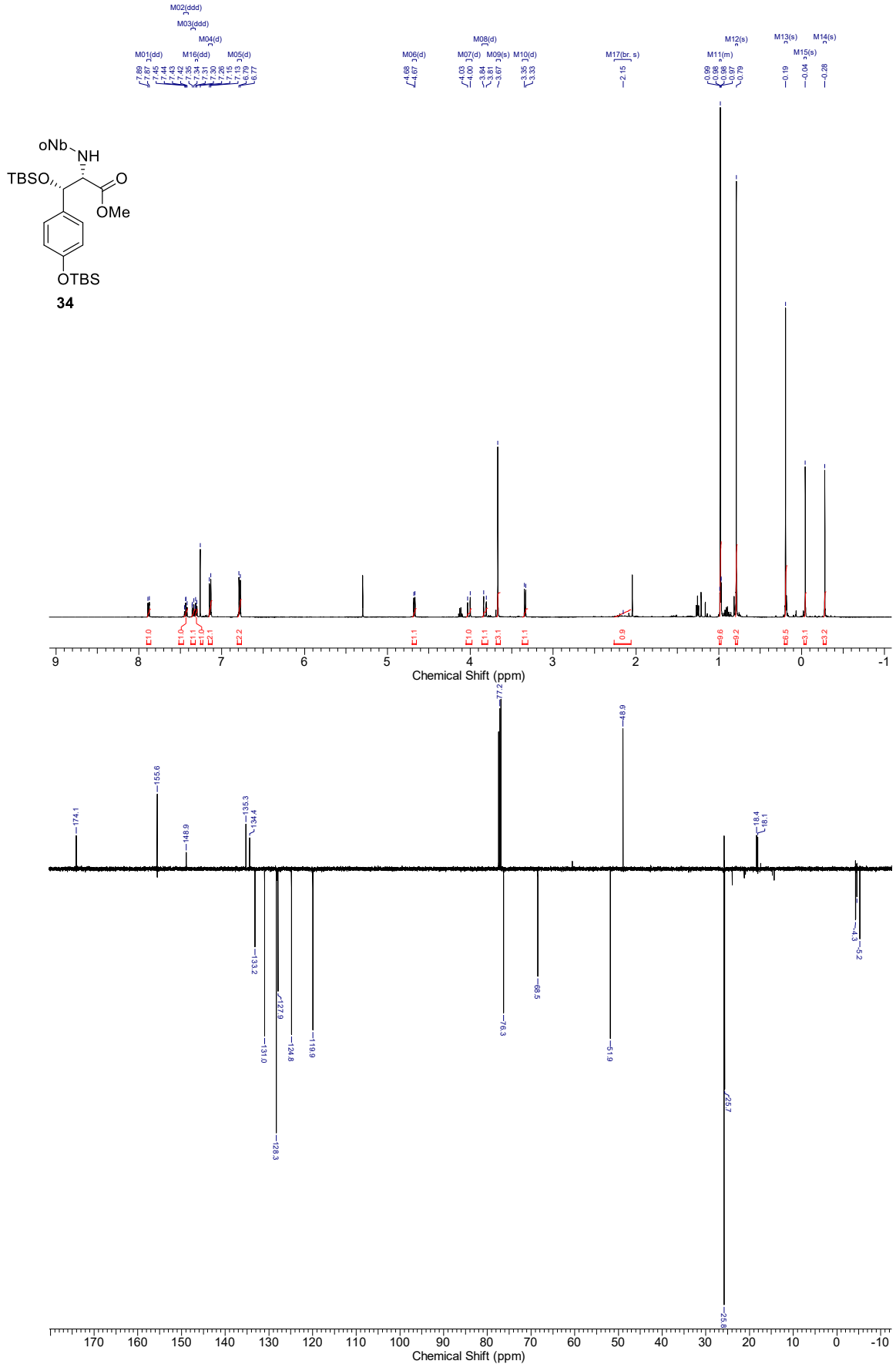
32

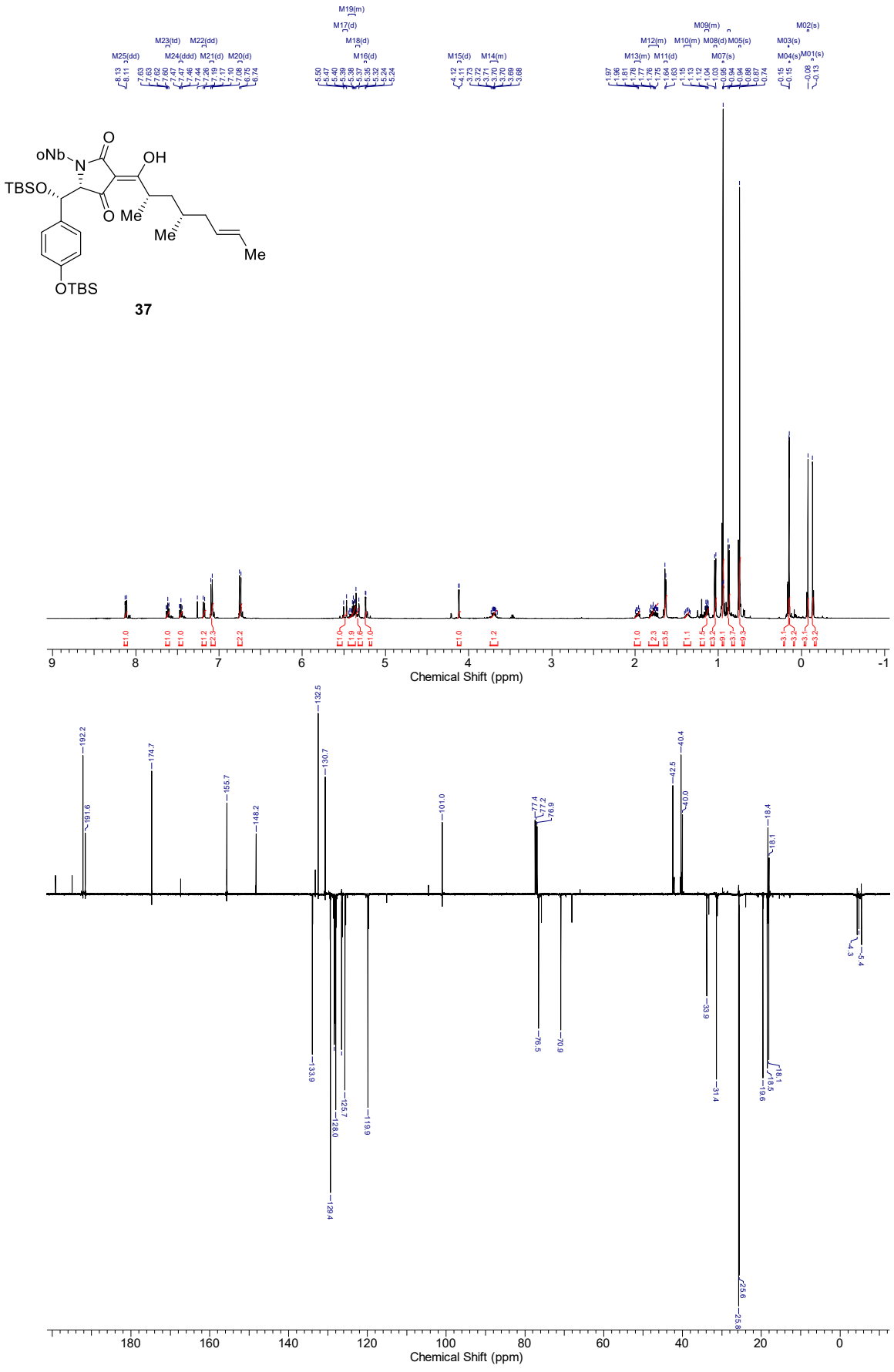

DMB
NH
TBSO
O
OMe
OH
Chemical Shift (ppm)
Chemical Shift (ppm)


DMB
NH
TBSO
O
OMe
OTBS
33
Chemical Shift (ppm)
Chemical Shift (ppm)

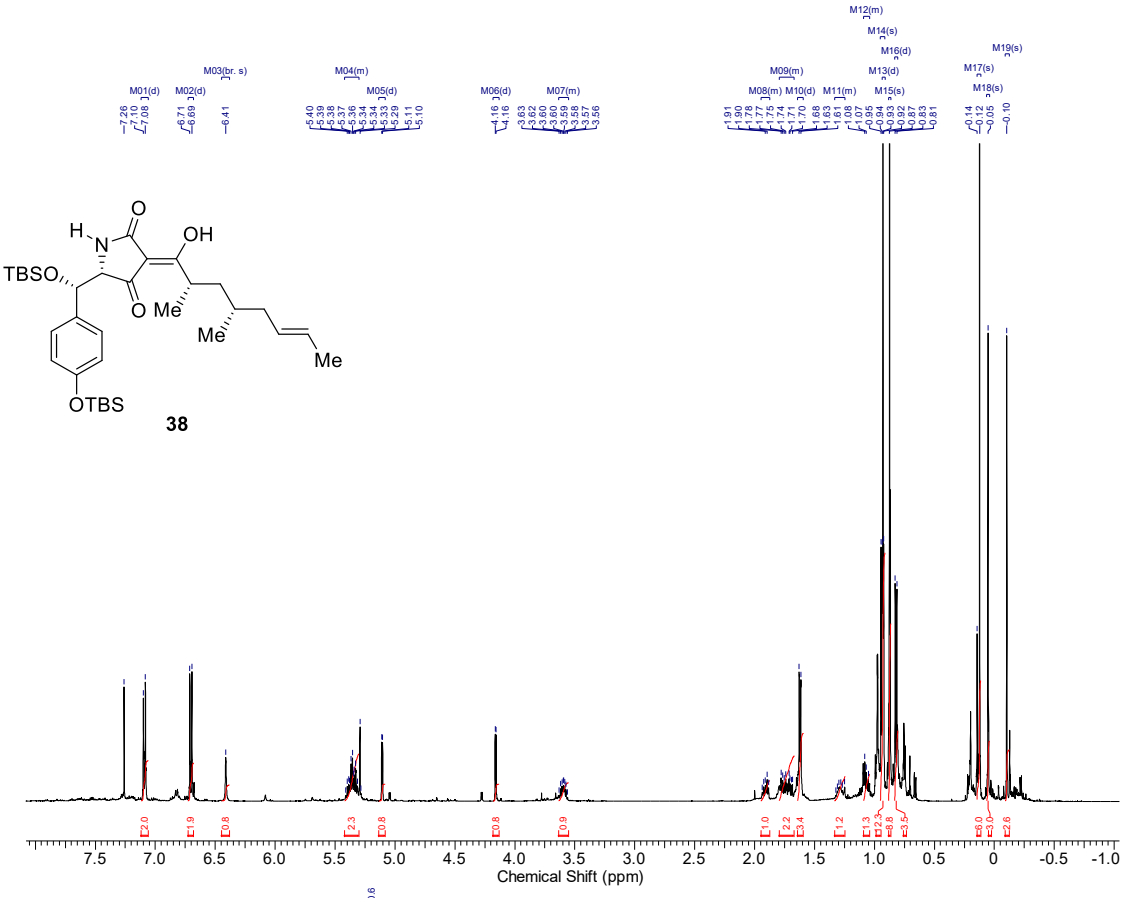

DMB
N
O
OH
TBSO
O
Me
Me
Me
OTBS
35
Chemical Shift (ppm)
Chemical Shift (ppm)

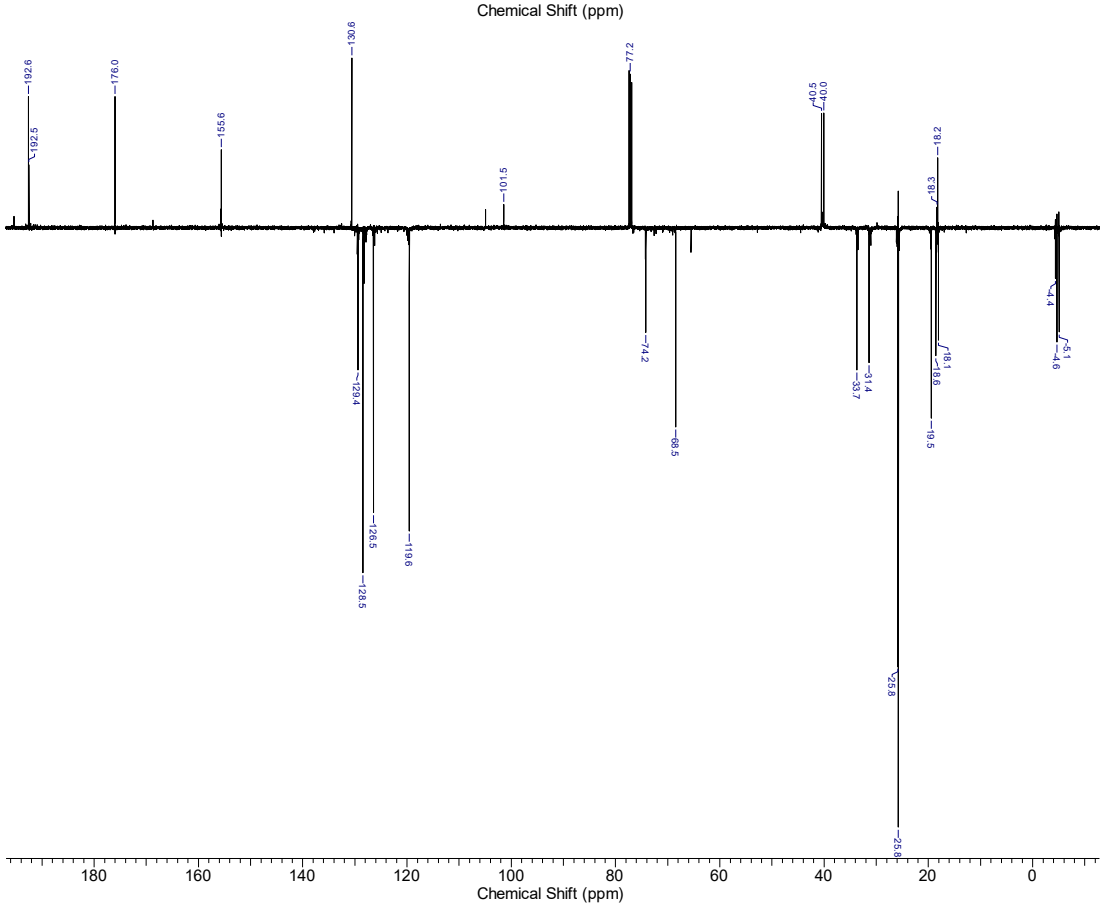

NH2
TBSO
O
OMe
OTBS
Chemical Shift (ppm)
Chemical Shift (ppm)


oNb
NH
TBSO
O
OMe
OTBS
34
Chemical Shift (ppm)
Chemical Shift (ppm)


oNb
N
O
OH
TBSO
O
Me
Me
Me
OTBS
Chemical Shift (ppm)
Chemical Shift (ppm)

37


M01(d)
M02(d)
M03(br. s)
M04(m)
M05(d)
M06(d)
M07(m)
M08(m)
M09(m)
M10(d)
M11(m)
M12(m)
M13(d)
M14(s)
M15(s)
M16(d)
M17(s)
M18(s)
M19(s)
H
N
O
OH
TBSO
O
Me
Me
Me
OTBS
38
Chemical Shift (ppm)


192.6
192.5
176.0
155.6
130.6
128.4
128.5
126.5
119.6
101.5
77.2
74.2
68.5
40.5
40.0
33.7
31.4
25.8
18.2
18.1
18.0
19.5
4.4
5.1
4.6
Chemical Shift (ppm)

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6.3 Synthesis of the Entomopathogenic Fungus Metabolites Militarinone C and Fumosorinone A

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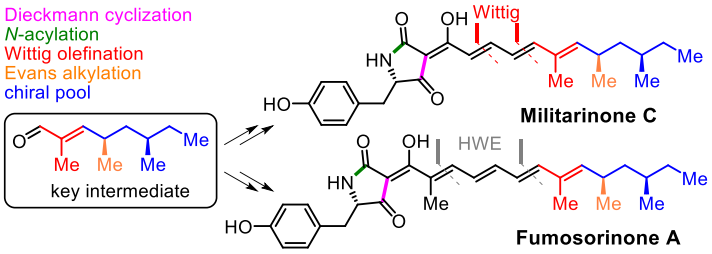

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Synthesis of the Entomopathogenic Fungus Metabolites Militarinone C and Fumosorinone A

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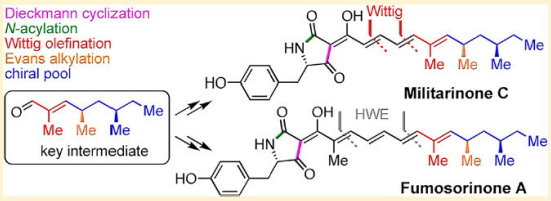
Supporting Information

ABSTRACT: Militarinone C and fumosorinone A, 3-oligoenoyltetramic acids produced by insect pathogenic fungi, were synthesized for the first time. The pyrrolidine-2,4-dione ring was closed through a late-stage Dieckmann condensation of *N*-(*β*-ketoacyl) derivatives of tyrosine, obtained by its acylation with either thioesters or Meldrum's acid derivatives bearing the *all-trans*-polyene side chain. The latter was built up from (*S*)-citronellol via an Evans methylation and Wittig or HWE olefinations.



INTRODUCTION

In 2002 Hamburger et al. reported the isolation of militarinone A (**1**), a neurotrophic 2-pyridone alkaloid, from the entomogenous fungus *Paecilomyces militaris*.[1] Shortly after, they also identified two yellow tetramic acids, militarinone B (**2**) and militarinone C (**3**), as cometabolites (Figure 1).[2] It is

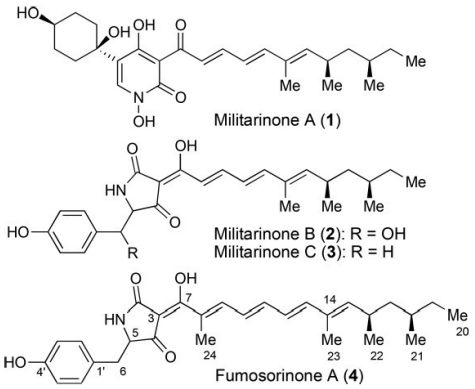


Figure 1. Structures of militarinones A−C (**1**-**3**) and fumosorinone A (**4**).

not uncommon that fungi produce mixtures of tyrosine-derived tetramic acids and 2-pyridones, e.g., the family of torrubiellones, metabolites of the fungus *Torrubiella sp.* BCC 2165,[3] or the (proto)tenellins, produced by the insect pathogenic fungus *Beauveria bassiana*. For the latter, Cox et al. established a radical oxidation−rearrangement conversion of the tetramic acid prototenellin D to the 2-pyridone tenellin.[4] In 2017, Zhang et al.[5] isolated fumosorinone A (**4**) from the entomogenous fungus *Isaria fumosorosea* and found it to inhibit (IC_{50} 3.24 μM) protein tyrosine phosphatase 1B (PTP1B), a major negative regulator[6] of the insulin signaling pathway. Such inhibitors are of interest as potential type II diabetes drugs since Klaman et al. had confirmed a higher sensitivity to insulin for mice deficient in PTP1B.[7] Herein we report short syntheses that procure both compounds in quantities sufficient to study their conversion to 2-pyridones.

RESULTS AND DISCUSSION

The retrosynthetic approach is outlined in Scheme 1. Both target compounds **3** and **4** were finished by a Dieckmann cyclization[8] of the respective functionalized *β*-ketoamide **5** or **6** followed by N,O-deprotection. These *β*-ketoamides were obtained by reaction of N,O-bisprotected methyl tyrosinates **7** with either Meldrum's acid derivative **8** or thioester **9** as N-acylating agents carrying the respective unsaturated side chain. The *β*-ketoesters **8** and **9** were accessible through consecutive Wittig or HWE olefinations of key aldehyde **10** which was built up from (*S*)-citronellol (**11**) using an Evans alkylation[9] to introduce the second methyl group and an *E*-selective Wittig olefination to establish the trisubstituted double bond.

(*S*)-Citronellol (**11**) was first converted to imide **15** following a modified route by Nishida et al.[10] (Scheme 2). It was quantitatively deoxygenated to alkene **13** in two steps via mesylation to give **12** which was reduced with $LiAlH_4$. Olefin **13** was subjected to a ruthenium-catalyzed oxidative cleavage according to a general procedure by Sharpless et al.[11] which afforded carboxylic acid **14**. This was converted to a mixed anhydride with pivaloyl chloride which was reacted with (*R*)-4-benzyloxazolidin-2-one to yield imide **15**. Its methylation at −78 °C gave the desired (*R*,*R*)-product **16** as a separable mixture of two diastereomers. Removal of the Evans auxiliary with $LiBH_4$/MeOH at 0 °C left enantiopure alcohol **17**. This was Swern oxidized to aldehyde **18** which was Wittig olefinated

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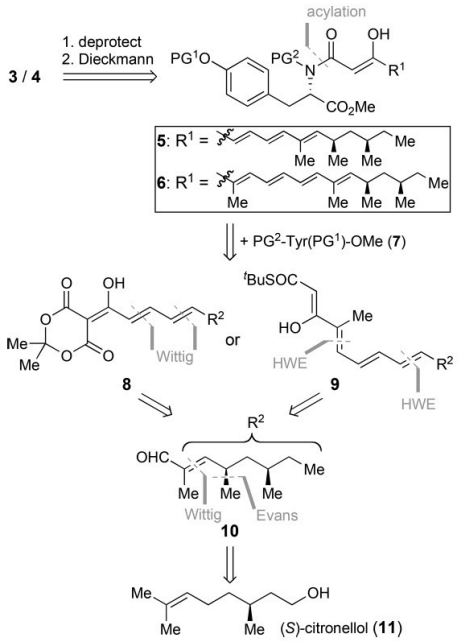
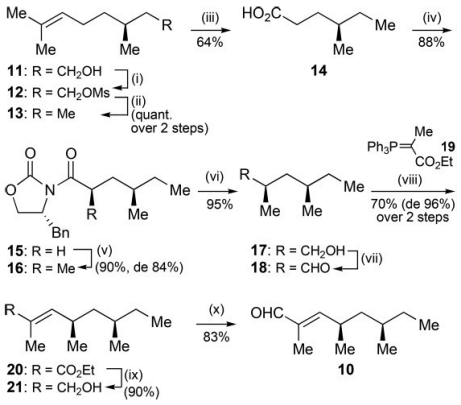
Scheme 1. Retrosynthesis of Militarinone C (3) and Fumosorinone A (4)



Scheme 2. [a] Synthesis of Key Aldehyde 10

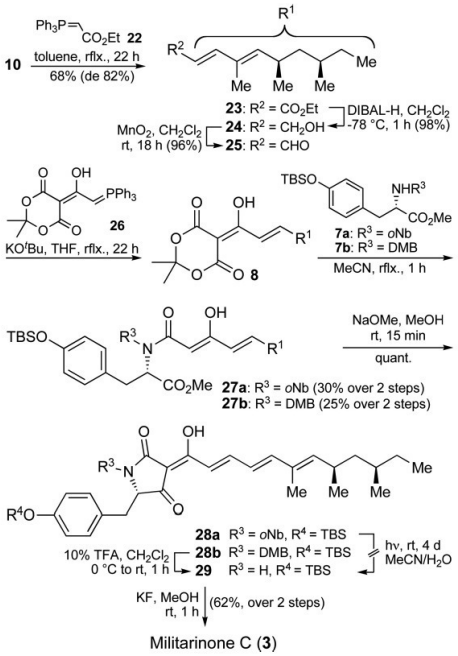


[a]Reagents and conditions: (i) MsCl, NEt_3, CH_2Cl_2, 0 °C to rt, 3.75 h; (ii) $LiAlH_4$, THF, 0 °C to rt, 16 h; (iii) $NaIO_4$ (4 equiv), $RuCl_3$ (2 mol %), $MeCN/CH_2Cl_2/H_2O$, rt, 18 h; (iv) PivCl, NEt_3, THF, 0 °C, 25 min, then LiCl, (*R*)-Evans oxazolidinone, rt, 30 min; (v) NaHMDS, THF, −78 °C, 15 min, then MeI, −78 °C to rt, 2.5 h; (vi) $LiBH_4$, MeOH, Et_2O, 0 °C to rt, 5 h; (vii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C, 3 h; (viii) + **19**, CH_2Cl_2, rt, 19 h; (ix) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; (x) MnO_2, CH_2Cl_2, rt, 18 h.

without purification to furnish ester **20** in 70% yield over two steps, following a protocol by Ding et al.[12] DIBAL-H reduction to alcohol **21** and its oxidation with MnO_2 afforded aldehyde **10** (10 steps, 25% relative to **11**).

For the synthesis of militarinone C (**3**), aldehyde **10** was elongated, analogously to aldehyde **18**, by a sequence of Wittig olefination with stabilized ylide **22** to give ester **23**, followed by its DIBAL-H reduction to alcohol **24**, and MnO_2 oxidation of the latter to aldehyde **25** (Scheme 3). This aldehyde was

Scheme 3. Synthesis of Militarinone C (3)



reacted with a Meldrum's acid-derived ylide **26**, applying a recent protocol by us,[13] to give *β*-ketoester **8**. Due to its decomposition on silica gel, the crude mixture of **8**, Ph_3PO, and some residual starting material was immediately reacted with either bisprotected methyl L-tyrosinate **7a** (R^3 = *o*-nitrobenzyl) or **7b** (R^3 = 2,4-dimethoxybenzyl). The resulting *β*-ketoamides **27** were treated with NaOMe in methanol to initiate a Dieckmann cyclization affording the respective bisprotected militarinone C **28** in quantitative yield. Unfortunately, irradiation of **28a**, which was previously successfully employed for the cleavage of an *o*Nb group on the nonoligoenoyl tetramic acid F-14329,[8] failed to give N-unprotected tetramic acid **29**. Besides requiring a longer reaction time (4 d vs 1 d), the photolytic deprotection of **28a** also led to cis−trans isomerizations of the 3-oligoenoyl side chain. Gratifyingly, deprotection of **28b** was readily achieved with 10% TFA in dichloromethane, leaving **29**, followed by desilylation to give militarinone C (**3**) in 62% over two steps after purification by MPLC. Its NMR data are in line with those reported[2] for the natural product (cf. Supporting Information Table S1), including the visibility of a second, minor tautomer in the NMR spectra. The specific optical rotation of our synthetic sample, $[\alpha]^{24}_D$ −310 (*c* 0.30, CH_3OH), differed distinctly from that of the natural isolate with $[\alpha]^{25}_D$ −430 (*c* 0.17, CH_3OH). However, because optical rotations of 3-acyltetramic acids are notorious for their volatility depending on many factors including the concentration and even age of the sample solution, they are not suited as proof of purity or identity. Although deviations between optical rotations of otherwise identical compounds have repeatedly been reported in the literature, e.g., lately for

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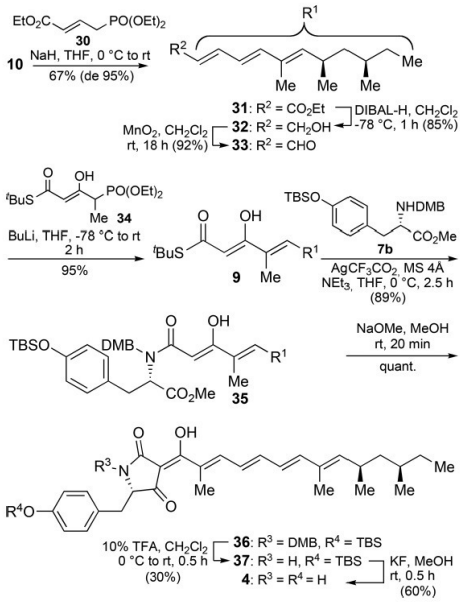
penicillinol A_2[14] and (−)-hymenosetin,[15] our synthesis of militarinone C supports, yet does not prove, the absolute configuration proposed in the literature for the natural product. An unambiguous proof would, for instance, require a comparison of circular dichroism spectra[15] of natural and synthetic samples (for an ECD spectrum of synthetic militarinone C (**3**) cf. Supporting Information).

For the synthesis of fumosorinone A (**4**), aldehyde **10** was submitted to a HWE olefination with phosphonate **30**, followed by a DIBAL-H reduction of product ester **31** to alcohol **32** and its oxidation with MnO_2 to aldehyde **33**, analogously to Dash et al.[16] (Scheme 4). Another HWE

Scheme 4. Synthesis of Fumosorinone A (4)



olefination with phosphonate **34**, according to Loscher et al.,[17] afforded thioester **9** in excellent 95% yield as a 2:3 keto/enol mixture. It was used to acylate aminoester **7b** in a surprisingly good yield of 89% according to Ley's silver(I)-mediated aminolysis protocol.[18] The resulting β-ketoamide **35** was cyclized quantitatively under mild conditions to give doubly protected fumosorinone A **36**. Due to its acid sensitivity, it had to be deprotected in two steps. Treatment with 10% TFA for only 30 min allowed the isolation of 30% TBS-protected fumosorinone A **37** aside of 30% recovered **36**. Desilylation of all accumulated **37** with KF in methanol finally yielded fumosorinone A (**4**) in 60% after semipreparative HPLC. It proved identical to the natural isolate in terms of NMR spectra (cf. Supporting Information Table S2) and also specific optical rotations ($[\alpha]^{24}_D$ −229 (*c* 0.20, CH_3OH) for synthetic and $[\alpha]^{20}_D$ −207 (*c* 0.1, CH_3OH) as reported for natural **4**).

■ CONCLUSIONS

In summary, fumosorinone A (**4**) and militarinone C (**3**) were each prepared in 18 steps and ca. 2% yield by N-acylating L-tyrosine esters with thioesters or 5-enoyl Meldrum's acids carrying the polyene side chains, followed by Dieckmann cyclization of the resulting β-ketoamides. The side chains were built up from (*S*)-citronellol via an Evans methylation and consecutive Wittig or HWE olefinations. The agreement (good in the case of **4**, reasonable for **3**) between NMR spectra and optical rotations of our synthetic products and those reported for the natural isolates at least does not rule out the origin of the latter from L-tyrosine. Studies of the conversion of compounds **3** and **4** to the respective 2-pyridones by means of radical oxidants are already underway.

■ EXPERIMENTAL SECTION

General Remarks. IR spectra were recorded with an FT-IR spectrophotometer equipped with an ATR unit. ^{1}H NMR and ^{13}C NMR spectra were obtained using a 500 MHz spectrometer. Chemical shifts are given in parts per million using the residual solvent peak as an internal standard 7.26 ppm (proton) and 77.16 ppm (carbon) for $CDCl_3$, 3.31 ppm (proton), and 47.60 ppm (carbon) for CD_3OD and 2.50 ppm (proton) and 39.51 ppm (carbon) for DMSO-d_6. Coupling constants (*J*) are quoted in hertz (Hz). Multiplicity abbreviation used: s singlet, d doublet, t triplet, q quartet, m multiplet, br broad. High resolution mass spectra were obtained with a UPLC/Orbitrap MS system in ESI mode. Optical rotations were measured at 589 nm (Na-D line). Photolysis was performed using a Pro Collect UV tester with 366 nm and 4 W.

Chemicals. All reagents were purchased from commercial sources and were used without further purification. All anhydrous solvents were used as supplied, except tetrahydrofuran, diethyl ether, and dichloromethane which were freshly distilled according to standard procedures. Reactions were routinely carried out under an argon atmosphere unless stated otherwise. All glassware was flame-dried before use.

Chromatography. Analytical thin layer chromatography was carried out using Merck silica gel $60GF_{254}$ precoated aluminum-backed plates and/or Merck 60 RP-18 F_{254S} foil plates. The compounds were visualized with UV light (254 nm and/or 360 nm) and/or ceric ammonium molybdate (CAM) and/or potassium permanganate and/or iodine on silica. Flash chromatography was performed at medium pressure using dry-packed Marchery-Nagel silica gel 60, pore size 40−63 μm, with the eluent specified. Analytical HPLC measurements were performed on a Beckman System Gold Programmable Solvent Module 126 using a Phenomenex Kinetex C-18-HPLC column, length 250 × 4.6 mm, pore size 100 Å, particle size 5 μm. Detection was by a Beckman Instruments Diode Array Detection Module 168. MPLC reversed phase chromatography was performed using a Büchi MPLC system with a "MN Polygroprep 100−50 C 18 end-capped" column, length 460 mm, diameter 49 mm. Detection was by a Büchi UV Photometer C-635. Semipreparative reversed phase HPLC was performed using an Amersham Biosciences ÄKTAbasic10 system with a Phenomenex Gemini-NX 5u C18 110A, 250 × 10.00 mm column. Detection was by an Amersham Biosciences ÄKTA UV-900 module.

Militarinone C (3). A solution of protected tetramic acid **28b** (107 mg, 156 μmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C and treated dropwise with 20% trifluoroacetic acid in CH_2Cl_2 (50 mL). The resulting mixture was stirred at ambient temperature for 1 h, sat. aqueous phosphate buffer (pH 7, 50 mL) was added, and the phases were separated. The organic phase was washed with the same buffer (2 × 50 mL) and aqueous $KHSO_4$ (5% wt, 50 mL) and then dried (Na_2SO_4) and concentrated in vacuo to give a mixture of *O*-TBS-protected tetramic acid **29** and militarinone C (**3**) as a yellow oil (93 mg) that was used in the next step without further purification.

The crude mixture of **29** and **3** was taken up in methanol p.a. (6 mL), a 10 M suspension of KF in methanol p.a. (624 μL, 6.24 mmol) was added, and the mixture was stirred at ambient temperature for 1 h. A 1 M aqueous HCl (20 mL) solution and brine (50 mL) were added, and the mixture was extracted with EtOAc (2 × 125 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil which was purified by MPLC on an RP-18 column, eluting with 75% methanol in H_2O (with 0.1% formic acid) to 95% methanol in 10 min with a flow rate of 240 mL/min. The

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product-containing fractions were collected, the methanol was removed in vacuo, and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with 1 M aqueous HCl (20 mL), dried (Na_2SO_4), and concentrated in vacuo to give militarinone C (**3**) as an orange-yellow solid foam (40.9 mg, 62% over two steps); $[\alpha]^{24}_D$ −310 (*c* 0.30, MeOH) (lit.[2] $[\alpha]^{24}_D$ −430.2 (*c* 0.17, MeOH)); IR ν_{max} 3284, 2959, 2923, 1587, 1551, 1515, 1463, 1429, 1373, 1226, 1172, 1105, 1031, 1000, 895, 868, 822, 733, 626 cm^{-1}; for NMR data cf. Supporting Information Table S1; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{34}NO_4^+$ 424.2482, found 424.2477.

Fumosorinone A (4). A solution of tetramic acid **36** (72 mg, 99 μmol) in CH_2Cl_2 (36 mL) was cooled to 0 °C and treated dropwise with 20% trifluoroacetic acid in CH_2Cl_2 (36 mL), and the mixture was stirred at ambient temperature for 30 min. Saturated aqueous phosphate buffer (pH 7, 100 mL) was added at 0 °C, the phases were separated, and the organic phase was washed with the same buffer (2 × 100 mL) and 1 M aqueous HCl (50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford an orange-yellow oil. It was purified by flash chromatography on RP-18 silica gel, eluting with 95% acetonitrile in H_2O to give *O*-TBS-protected tetramic acid **37** (16 mg, 30%) and residual starting material **36** (22 mg, 30%); R_f = 0.36 (8% MeOH in CH_2Cl_2). A solution of **37** (16 mg, 28 μmol) in MeOH (1.8 mL) was treated with a 10 M suspension of potassium fluoride in MeOH (199 μL, 1.99 mmol), and the mixture was stirred at ambient temperature for 30 min. Saturated aqueous NH_4Cl (20 mL) and 1 M aqueous HCl (10 mL) were added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to leave an orange-red oil which was filtered over Sephadex LH-20 (MeOH) to afford an orange-red oil upon evaporation. The oil was further purified by semipreparative HPLC (ÄKTA system, flow rate: 5 mL/min on a Phenomenex Gemini-NX 5u C18 110A, 250 × 10.00 mm column, one column volume (CV) at 70% MeCN in H_2O (with 0.1% formic acid), then three CV at 90% MeCN, t_{ret} = 11.7−12.6 min, UV_{det} = 414 nm) to give fumosorinone A (**4**) as a bright orange-yellow oil (7.7 mg, 60%); $[\alpha]^{24}_D$ −229 (*c* 0.20, MeOH) (lit.[5] $[\alpha]^{24}_D$ −207 (*c* 0.1, MeOH)); IR ν_{max} 3310, 2960, 2925, 1650, 1591, 1516, 1442, 1261, 1171, 988, 812, 620 cm^{-1}; for NMR data cf. Supporting Information Table S2; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{38}NO_4^+$ 464.2795, found 464.2785.

*Methyl (S)-3-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-2-((2-nitrobenzyl)amino)propanoate (**7a**).* A solution of L-tyrosine methyl ester hydrochloride (1.16 g, 5.00 mmol) in 3% acetic acid in methanol (100 mL) was treated with *o*-nitrobenzaldehyde (1.51 g, 10.00 mmol) and MS 3 Å (100 mg), and the resulting mixture was stirred at ambient temperature for 1 h. $NaBH_3CN$ (781 mg, 12.50 mmol) was added, and stirring was continued for 2 h. The molecular sieves were filtered off, and the reaction mixture was quenched with sat. aqueous $NaHCO_3$ (300 mL). Ethyl acetate (300 mL) was added, the phases were separated, and the organic phase was washed with brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellowish oil that was adsorbed on silica gel (wt ratio oil/silica 1:10) and purified by flash chromatography (silica gel, 1% MeOH in CH_2Cl_2 ⇒ 1.5% MeOH ⇒ 2% MeOH) to give *o*Nb-L-Tyr-OMe as a yellow oil (1.145 g, 69%); R_f = 0.30 (4% MeOH in CH_2Cl_2); $[\alpha]^{24}_D$ +33.6 (*c* 1.00, $CHCl_3$); IR ν_{max} 3324, 2953, 1732, 1613, 1596, 1578, 1516, 1444, 1344, 1206, 1173, 1107, 991, 829, 789, 731, 702, 666, 556 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.90 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.49 (ddd, *J* = 1.1, 7.2, 7.3 Hz, 1H), 7.46 (dd, *J* = 1.5, 7.3 Hz, 1H), 7.36 (ddd, *J* = 1.5, 7.2, 8.1 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 4.08 (d, *J* = 15.0 Hz, 1H), 3.93 (d, *J* = 15.0 Hz, 1H), 3.64 (s, 3H), 3.47 (dd, *J* = 6.1, 7.3 Hz, 1H), 2.91 (dd, *J* = 6.1, 13.4 Hz, 1H), 2.86 (dd, *J* = 7.3, 13.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.0, 155.0, 149.0, 134.9, 133.3, 131.2, 130.4, 128.5, 128.2, 124.9, 115.5, 62.6, 52.0, 49.2, 38.8; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}N_2O_5^+$ 331.1288, found 331.1284.

A solution of *o*Nb-L-Tyr-OMe (610 mg, 1.85 mmol) in CH_2Cl_2 p.a. (19 mL) was cooled to 0 °C and treated with imidazole (378 mg, 5.55 mmol) and TBSCl (613 mg, 4.07 mmol). The resulting mixture was stirred for 19 h while reaching room temperature. The mixture was filtered, the filtrate was taken up in CH_2Cl_2 (50 mL), the organic phase was washed with sat. aqueous NH_4Cl (100 mL), and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil that was purified by flash chromatography (silica gel, 12% ethyl acetate in hexane) to afford **7a** as a yellow oil (746 mg, 91%); R_f = 0.74 (hexane/EtOAc 1:1); $[\alpha]^{24}_D$ +26.8 (*c* 1.00, $CHCl_3$); IR ν_{max} 2954, 2931, 2858, 1737, 1609, 1580, 1527, 1510, 1471, 1444, 1346, 1255, 1200, 1170, 1131, 1105, 1007, 914, 840, 782, 729, 691, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, *J* = 8.2 Hz, 1H), 7.45−7.54 (m, 2H), 7.34−7.41 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 4.09 (d, *J* = 15.0 Hz, 1H), 3.92 (d, *J* = 15.0 Hz, 1H), 3.63 (s, 3H), 3.45 (dd, *J* = 6.4, 7.3 Hz, 1H), 2.91 (dd, *J* = 6.4, 13.7 Hz, 1H), 2.86 (dd, *J* = 7.3, 13.7 Hz, 1H), 2.07 (br. s, 1H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.9, 154.6, 149.1, 135.3, 133.2, 130.9, 130.3, 129.8, 128.0, 124.8, 120.1, 62.7, 51.9, 49.1, 39.1, 25.8, 18.3, −4.3; HRMS (ESI) *m* /*z* $[M + H]^+$ calcd for $C_{23}H_{33}N\ {}_2O_5Si^+$ 445.2153, found 445.2137.

*Methyl (S)-3-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-2-((2,4-dimethoxybenzyl)amino)propanoate (**7b**).* According to a modified literature procedure,[19] a suspension of L-tyrosine methyl ester hydrochloride (580 mg, 2.50 mmol) in CH_2Cl_2 (12 mL) was treated with imidazole (510 mg, 15.00 mmol) and TBSCl (452 mg, 6.00 mmol). The resulting mixture was stirred at room temperature for 19 h. Saturated aqueous $NaHCO_3$ (50 mL) was added, and the jellylike mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phases were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give an oil that was purified by flash chromatography (silica gel, 90% ethyl acetate in hexane) to afford L-Tyr(OTBS)-OMe as a clear oil (479 mg, 77%); R_f = 0.24 (hexane/EtOAc 1:4); $[\alpha]^{24}_D$ +10.0 (*c* 1.00, $CHCl_3$); IR ν_{max} 2954, 2931, 2893, 2858, 1739, 1609, 1509, 1472, 1464, 1438, 1252, 1195, 1169, 1109, 1102, 1008, 911, 837, 802, 779, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.03 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 3.70 (s, 3H), 3.68 (dd, *J* = 5.2, 7.6 Hz, 1H), 3.00 (dd, *J* = 5.2, 13.7 Hz, 1H), 2.80 (dd, *J* = 7.6, 13.7 Hz, 1H), 1.45 (br. s., 2H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.7, 154.7, 130.3, 129.9, 120.3, 56.1, 52.1, 40.5, 25.8, 18.3, −4.3.

A solution of L-Tyr(OTBS)-OMe (881 mg, 2.85 mmol) in 3% acetic acid in methanol (10 mL) was treated with 2,4-dimethoxybenzaldehyde (450 mg, 2.71 mmol), and the mixture was stirred at room temperature for 30 min. $NaBH(OAc)_3$ (804 mg, 3.79 mmol) was added, stirring continued for 1.5 h, and the reaction mixture was quenched with sat. aqueous $NaHCO_3$ (50 mL). The mixture was extracted with ethyl acetate (3 × 75 mL), and the combined organic phases were washed with brine (75 mL), dried (Na_2SO_4), and concentrated in vacuo to give an oil that was purified by flash chromatography (silica gel, 15% EtOAc with 0.5% NEt_3 in hexane ⇒ 30% EtOAc with 0.5% NEt_3) to leave **7b** as a clear oil (870 mg, 71%); R_f = 0.68 (hexane/EtOAc 1:1); $[\alpha]^{24}_D$ +1.98 (*c* 1.00, $CHCl_3$); IR ν_{max} 2952, 2931, 2858, 1735, 1611, 1589, 1508, 1463, 1438, 1418, 1278, 1250, 1207, 1156, 1132, 1104, 1036, 911, 835, 797, 779, 688, 634 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.02 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 6.36−6.40 (m, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 3.58 (s, 3H), 3.45 (t, *J* = 7.2 Hz, 1H), 2.89 (dd, *J* = 6.7, 13.4 Hz, 1H), 2.85 (dd, *J* = 7.6, 13.4 Hz, 1H), 1.87−2.05 (m, 1H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.2, 160.2, 158.7, 154.5, 130.5, 130.21, 130.17, 120.2, 120.1, 103.7, 98.5, 62.4, 55.5, 55.3, 51.7, 47.3, 39.1, 25.8, 18.3, −4.3.

*S-(tert-Butyl) (2Z,4E,6E,8E,10E,12R,14R)-3-Hydroxy-4,10,12,14-tetramethylhexadeca-2,4,6,8,10-pentaenethioate (**9**).* Following a general literature protocol,[17] thioester **9** (236 mg, 95%) was prepared from phosphonate **34** (289 mg, 889 μmol) and aldehyde **33** (140 mg, 635 μmol) as an orange-yellow oil and as a 2:3 keto/enol mixture; R_f = 0.86 (10% EtOAc in hexane); $[\alpha]^{24}_D$ −43.2 (*c* 0.50, $CHCl_3$); IR ν_{max} 2960, 2923, 2871, 1688, 1651, 1614, 1586, 1456, 1376, 1364, 1311, 1250, 1163, 1100, 1062, 986, 907, 859, 797, 769, 652 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 12.96 (s, 1H), 7.15 (d, *J* = 11.0 Hz, 1H),

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7.11 (d, J = 11.0 Hz, 1H), 6.22−6.75 (m, 8H), 5.57 (s, 1H, HCCOS enol), 5.41 (d, J = 9.8 Hz, 1H), 5.36 (d, J = 9.8 Hz, 1H), 3.88 (s, 2H, H_2CCOS keto), 2.56−2.69 (m, 2H), 1.92 (s, 3H), 1.86 (d, J = 0.9 Hz, 3H), 1.81 (d, J = 0.9 Hz, 3H), 1.80 (d, J = 0.9 Hz, 3H), 1.53 (s, 9H), 1.47 (s, 9H), 1.21−1.35 (m, 6H), 1.05−1.17 (m, 4H), 0.96 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H), 0.80−0.88 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.2, 193.6, 193.3, 169.6, 144.3, 143.2, 142.4, 141.8, 141.5, 139.9, 134.7, 132.6, 127.3, 127.2, 127.0, 126.4, 126.0, 98.1, 54.1, 49.0, 48.5, 45.0, 44.9, 32.5, 32.4, 30.84, 30.76, 30.35, 30.27, 30.25, 29.8, 21.63, 21.56, 19.2, 12.6, 12.4, 11.8, 11.5; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{38}O_2NaS^+$ 413.2485, found 413.2482.

*(4R,6R,E)-2,4,6-Trimethyloct-2-enal (**10**).* A solution of alcohol **21** (1.60 g, 9.37 mmol) in CH_2Cl_2 p.a. (94 mL) was treated with MnO_2 (29.48 g, 327.95 mmol), and the mixture was stirred at ambient temperature for 18 h and then filtered over Celite. The filtrate was concentrated in vacuo to give a clear liquid that was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to afford aldehyde **10** (1.31 g, 83%) as a clear oil; R_f = 0.38 (6% ethyl acetate in hexane); $[\alpha]^{24}_D$ −36.3 (c 1.00, $CHCl_3$) (lit.[20] $[\alpha]^{20}_D$ −43 (c 0.75, $CHCl_3$)); IR ν_{max} 2961, 2928, 2875, 2707, 1688, 1644, 1457, 1405, 1379, 1313, 1243, 1201, 1128, 1051, 1015, 874, 827, 805, 675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.38 (s, 1H), 6.21 (dd, J = 1.2, 10.1 Hz, 1H), 2.75−2.86 (m, 1H), 1.72−1.78 (m, 3H), 1.10−1.39 (m, 5H), 1.03 (d, J = 6.7 Hz, 3H), 0.81−0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.8, 161.0, 138.0, 44.1, 32.5, 31.4, 30.1, 20.5, 19.2, 11.4, 9.5.

*(S)-3,7-Dimethyloct-6-en-1-yl Methanesulfonate (**12**).* According to a literature procedure,[21] compound **12**[22] (4.67 g, 100%) was prepared from (*S*)-citronellol (**11**) (3.63 mL, 20.00 mmol), MsCl (1.6 mL, 21.00 mmol), and NEt_3 (2.9 mL, 21.00 mmol) as a yellow oil; R_f = 0.55 (hexane/EtOAc 5:1); $[\alpha]^{24}_D$ −2.11 (c 1.00, $CHCl_3$); IR ν_{max} 2964, 2914, 2859, 1456, 1378, 1351, 1333, 1171, 1036, 973, 938, 889, 818, 796, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.04−5.11 (m, 1H), 4.21−4.32 (m, 2H), 3.00 (s, 3H), 1.90−2.07 (m, 2H), 1.75−1.85 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.50−1.65 (m, 2H), 1.30−1.40 (m, 1H), 1.15−1.25 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 131.8, 124.4, 68.7, 37.5, 36.9, 36.0, 29.1, 25.9, 25.4, 19.3, 17.8.

*(R)-2,6-Dimethyloct-2-ene (**13**).* According to a literature protocol,[23] compound **13** (6.13 g, 100%) was prepared from **12** (10.30 g, 43.95 mmol) and $LiAlH_4$ (3.34 g, 88.00 mmol) as a clear oil; R_f = 0.89 (hexane); $[\alpha]^{24}_D$ −6.2 (c 1.00, $CHCl_3$) (lit.[24] $[\alpha]^{25}_D$ −7.55 (neat)); IR ν_{max} 2963, 2915, 2875, 2853, 1456, 1377, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.06−5.14 (m, 1H), 1.89−2.04 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.28−1.39 (m, 3H), 1.08−1.18 (m, 2H), 0.86 (d, J = 6.3 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 131.1, 125.3, 36.9, 34.2, 29.6, 25.9, 25.8, 19.3, 17.8, 11.5.

*(R)-4-Methylhexanoic Acid (**14**).* According to a modified literature protocol,[11] a solution of alkene **13** (6.15 g, 43.65 mmol) in CH_2Cl_2 p.a. (130 mL) was treated with acetonitrile p.a. (130 mL), H_2O (170 mL), $NaIO_4$ (37.35 g, 174.60 mmol), and $RuCl_3 \times H_2O$ (181 mg, 873 μmol, 2 mol %), and the mixture was stirred at ambient temperature for 18 h. $Na_2S_2O_3$ (3 g) was added, and the mixture was stirred for 15 min. The solids were filtered off, and the filtrate was concentrated in vacuo. A 1 M aqueous NaOH (100 mL) solution was added, and the resulting mixture was washed with diethyl ether (2 × 200 mL). The aqueous phase was acidified with 1 M aqueous HCl (175 mL), and the brown mixture was extracted with diethyl ether (3 × 200 mL). The combined organic phases were washed with aqueous $Na_2S_2O_3$ (20% wt, 2 × 150 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo to give acid **14** (3.66 g, 64%) as a brownish oil; R_f = 0.61 (hexane/EtOAc 4:1); $[\alpha]^{24}_D$ −10.9 (c 1.00, $CHCl_3$) (lit.[25] $[\alpha]^{10}_D$ −10.1 (c 1.00, $CHCl_3$)); IR ν_{max} 3042, 2962, 2931, 2876, 2654, 1705, 1463, 1413, 1380, 1281, 1250, 1216, 936 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.45 (br. s, 1H), 2.27−2.44 (m, 2H), 1.63−1.74 (m, 1H), 1.40−1.50 (m, 1H), 1.30−1.40 (m, 2H), 1.12−1.22 (m, 1H), 0.88 (d, J = 6.4 Hz, 3H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.6, 34.1, 32.0, 31.3, 29.2, 18.9, 11.4.

*(R)-4-Benzyl-3-((R)-4-methylhexanoyl)oxazolidin-2-one (**15**).* According to a literature procedure,[9] compound **15** (526 mg, 88%) was prepared from **14** (268 mg, 2.06 mmol), pivaloyl chloride (0.27 mL, 2.16 mmol), and (*R*)-benzyloxazolidin-2-one (383 mg, 2.16 mmol) as a colorless solid; R_f = 0.64 (hexane/EtOAc 4:1); $[\alpha]^{24}_D$ −56.9 (c 1.00, $CHCl_3$) (lit.[26] $[\alpha]^{27}_D$ −57.5 (c 1.00, $CHCl_3$)); mp 36−37 °C; IR ν_{max} 2961, 2925, 2874, 1777, 1698, 1455, 1384, 1351, 1324, 1280, 1210, 1194, 1138, 1097, 1052, 1015, 761, 741, 700, 628, 595, 564 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31−7.36 (m, 2H), 7.27−7.30 (m, 1H), 7.19−7.23 (m, 2H), 4.64−4.71 (m, 1H), 4.20 (dd, J = 7.6, 9.0 Hz, 1H), 4.16 (dd, J = 3.0, 9.0 Hz, 1H), 3.30 (dd, J = 3.3, 13.3 Hz, 1H), 2.99 (ddd, J = 5.4, 10.0, 16.7 Hz, 1H), 2.89 (ddd, J = 5.7, 9.8, 16.7 Hz, 1H), 2.76 (dd, J = 9.6, 13.3 Hz, 1H), 1.66−1.76 (m, 1H), 1.47−1.55 (m, 1H), 1.35−1.47 (m, 2H), 1.15−1.24 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9, 153.6, 135.5, 129.6, 129.1, 127.5, 66.3, 55.3, 38.1, 34.1, 33.5, 31.0, 29.4, 19.1, 11.5.

*(R)-4-Benzyl-3-((2R,4R)-2,4-dimethylhexanoyl)oxazolidin-2-one (**16**).* According to a literature procedure,[9] compound **16** (5.63 g, 90%) was prepared from **15** (5.98 g, 20.65 mmol) as a colorless solid of mp 32−33 °C; R_f = 0.54 (hexane/EtOAc 7:1); $[\alpha]^{24}_D$ −66.6 (c 1.00, $CHCl_3$) (lit.[27] $[\alpha]^{27}_D$ −68.6 (c 4.13, $CHCl_3$)); IR ν_{max} 2962, 2929, 2875, 1775, 1695, 1455, 1384, 1349, 1290, 1239, 1207, 1098, 1075, 1052, 1015, 971, 917, 761, 739, 701, 625, 593 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30−7.36 (m, 2H), 7.26−7.30 (m, 1H), 7.19−7.24 (m, 2H), 4.65−4.71 (m, 1H), 4.20 (dd, J = 7.4, 9.0 Hz, 1H), 4.17 (dd, J = 2.8, 9.0 Hz, 1H), 3.82−3.92 (m, 1H), 3.26 (dd, J = 3.1, 13.3 Hz, 1H), 2.76 (dd, J = 9.6, 13.3 Hz, 1H), 1.85 (ddd, J = 5.5, 8.6, 13.2 Hz, 1H), 1.29−1.43 (m, 2H), 1.22 (d, J = 6.8 Hz, 3H), 1.09−1.20 (m, 2H), 0.86 (d, J = 6.4 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.6, 153.2, 135.5, 129.6, 129.1, 127.5, 66.1, 55.5, 40.6, 38.0, 35.5, 32.4, 29.6, 19.5, 18.5, 11.4.

*(2R,4R)-2,4-Dimethylhexan-1-ol (**17**).* According to a literature procedure,[28] alcohol **17** (2.11 g, 95%) was prepared from **16** (5.19 g, 17.10 mmol) and $LiBH_4$ (4 M in THF, 4.9 mL, 19.67 mmol) as a clear oil; R_f = 0.33 (hexane/EtOAc 5:1); $[\alpha]^{24}_D$ +4.7 (c 1.00, $CHCl_3$) (lit. $[\alpha]_D$ +3.7 (c 1.67, $CHCl_3$)); IR ν_{max} 3342, 2959, 2915, 2875, 1462, 1378, 1028, 986, 612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.48−3.56 (m, 1H), 3.34−3.42 (m, 1H), 1.66−1.76 (m, 1H), 1.40−1.48 (m, 1H), 1.35−1.40 (m, 1H), 1.24−1.35 (m, 2H), 1.03−1.13 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.90 (s, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 68.6, 40.7, 33.3, 31.7, 29.2, 19.9, 17.4, 11.3.

*Triphenyl(1-ethoxycarbonylethyl)phosphorane (**19**).* According to literature procedure,[29] ylide **19**[30] (10.13 g, 50.00 mmol, 64%) was prepared as a beige solid from 2-bromoethyl propanoate (6.5 mL, 50.00 mmol) and PPh_3 (13.12 g, 50.00 mmol); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44−7.63 (m, 15H), 3.56−4.00 (m, 2H), 1.61 (d, J = 13.7 Hz, 3H), 0.22−0.92 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.8, 133.7, 131.7, 128.6, 128.5, 57.6, 12.8; IR ν_{max} 3055, 2979, 2927, 1626, 1589, 1571, 1484, 1435, 1381, 1365, 1310, 1298, 1185, 1158, 1087, 1071, 1029, 998, 950, 861, 773, 760, 747, 714, 692, 618, 576 cm^{-1}.

*Ethyl (4R,6R,E)-2,4,6-Trimethyloct-2-enoate (**20**).* According to a modified literature procedure,[12] a cooled (−78 °C) solution of oxalyl chloride (2.2 mL, 25.87 mmol) in CH_2Cl_2 (27 mL) was treated with a solution of dimethyl sulfoxide (2.9 mL, 40.43 mmol) in CH_2Cl_2 (13.5 mL), and the mixture was stirred at −78 °C for 30 min. A solution of alcohol **17** (2.11 g, 16.17 mmol) in CH_2Cl_2 (13.5 mL) was added, and stirring was continued at −78 °C for 30 min. NEt_3 (11.2 mL, 80.85 mmol) was added, and the mixture was stirred at −78 °C for 1 h before it was warmed to ambient temperature and stirred for 1 h. Then 1 M aqueous HCl (100 mL) was added, and the mixture was extracted with *n*-pentane (3 × 100 mL). The combined organic phases were washed with H_2O (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give aldehyde **18** as a pale-yellow liquid that was used in the next step without purification.

A solution of aldehyde **18** (2.07 g, 16.17 mmol) in CH_2Cl_2 p.a. (35 mL) was treated with $Ph_3P{=}C(CH_3)CO_2Et$ (**19**) (8.79 g, 24.26 mmol), and the mixture was stirred at ambient temperature for 19 h.

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The solvent was removed in vacuo to give a brownish oil that was purified by flash chromatography (silica gel, 2% diethyl ether in hexane) to give ester **20** (2.41 g, 70% over two steps) as an 98:2 mixture of *E*/*Z* isomers as a pale yellow liquid; R_f = 0.34 (2% diethyl ether in hexane); IR ν_{max} 2961, 2929, 2875, 1710, 1650, 1462, 1367, 1311, 1271, 1249, 1217, 1152, 1099, 1035, 991, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.50 (d, J = 9.8 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 2.56−2.64 (m, 1H), 1.84 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.20−1.34 (m, 3H), 1.08−1.18 (m, 2H), 0.98 (d, J = 6.4 Hz, 3H), 0.80−0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.7, 148.4, 126.3, 60.5, 44.3, 32.4, 31.0, 30.2, 20.7, 19.1, 14.4, 12.6, 11.4.

*(4R,6R,E)-2,4,6-Trimethyloct-2-en-1-ol (**21**).* [16] According to a modified literature procedure,[12] a cooled (−78 °C) solution of ester **20** (2.29 g, 10.79 mmol) in CH_2Cl_2 (36 mL) was treated with DIBAL-H (1 M in hexane, 27 mL, 26.98 mmol) using a syringe pump (2 mL/min). The mixture was stirred at −78 °C for 1 h, treated with aqueous citric acid (20% wt, 150 mL), stirred at room temperature for 20 min, and then extracted with ethyl acetate (3 × 150 mL). The combined organic phases were washed with aqueous citric acid (20% wt, 100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give a clear oil which was purified by flash chromatography (silica gel, 15% ethyl acetate in hexane) to afford alcohol **21** (1.66 g, 90%) as a clear oil; R_f = 0.31 (16% ethyl acetate in hexane); $[\alpha]^{24}_D$ −27.9 (c 1.00, $CHCl_3$); IR ν_{max} 3315, 2959, 2923, 2871, 1457, 1378, 1010, 850, 618 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.12 (dd, J = 1.2, 9.5 Hz, 1H), 3.99 (d, J = 5.8 Hz, 2H), 2.43−2.55 (m, 1H), 1.68 (d, J = 1.2 Hz, 3H), 1.23−1.31 (m, 3H), 1.01−1.16 (m, 2H), 0.92 (d, J = 6.7 Hz, 3H), 0.80−0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.25, 133.16, 69.3, 44.9, 32.2, 30.2, 29.7, 21.8, 19.3, 14.0, 11.4.

*Ethyl (2E,4E,6R,8R)-4,6,8-Trimethyldeca-2,4-dienoate (**23**).* According to a literature procedure,[12] compound **23** (990 mg, 68%) was prepared from **10** (1.03 g, 6.09 mmol) and Ph_3PCHCO_2Et (**22**) (4.24 g, 12.18 mmol) as a colorless oil; R_f = 0.32 (6% ethyl acetate in hexane); $[\alpha]^{24}_D$ −66.6 (c 1.00, $CHCl_3$) (lit.[12] $[\alpha]^{22.5}_D$ −41.8 (c 1.00, $CHCl_3$)); IR ν_{max} 2961, 2926, 2874, 1713, 1623, 1461, 1393, 1366, 1289, 1260, 1239, 1162, 1131, 1096, 1033, 982, 846 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, J = 15.6 Hz, 1H), 5.78 (d, J = 15.6 Hz, 1H), 5.63 (d, J = 9.8 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.58−2.70 (m, 1H), 1.76−1.80 (m, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.19−1.35 (m, 3H), 1.07−1.17 (m, 2H), 0.96 (d, J = 6.7 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 150.1, 148.9, 131.3, 115.6, 60.3, 44.6, 32.5, 31.0, 30.3, 21.2, 19.2, 14.5, 12.4, 11.4.

*(2E,4E,6R,8R)-4,6,8-Trimethyldeca-2,4-dien-1-ol (**24**).* Analogously to **21**, alcohol **24** (383 mg, 98%) was prepared as a colorless oil from ester **23** (477 mg, 2.00 mmol) and DIBAL-H (1 M in hexane, 5.0 mL, 5.00 mmol); R_f = 0.15 (16% ethyl acetate in hexane); $[\alpha]^{24}_D$ −40.3 (c 1.00, $CHCl_3$) (lit.[12] $[\alpha]^{22.5}_D$ −37.1 (c 1.00, $CHCl_3$)); IR ν_{max} 3313, 2960, 2923, 2871, 1651, 1457, 1377, 1097, 1024, 995, 964, 872, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.25 (qd, J = 0.8, 15.6 Hz, 1H), 5.71 (td, J = 6.1, 15.6 Hz, 1H), 5.23 (d, J = 9.8 Hz, 1H), 4.20 (dd, J = 0.8, 6.1 Hz, 2H), 2.53−2.65 (m, 1H), 1.76 (d, J = 1.2 Hz, 3H), 1.36 (br. s, 1H), 1.20−1.32 (m, 3H), 1.03−1.18 (m, 2H), 0.93 (d, J = 6.7 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H), 0.81 (d, J = 6.41 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.7, 137.4, 131.3, 125.1, 64.2, 45.0, 32.4, 30.4, 30.3, 21.7, 19.2, 12.8, 11.5.

*(2E,4E,6R,8R)-4,6,8-Trimethyldeca-2,4-dienal (**25**).* Analogously to **10**, aldehyde **25** (363 mg, 96%) was prepared as a colorless oil from alcohol **24** (383 mg, 1.95 mmol) and MnO_2 (3.39 g, 39.02 mmol); R_f = 0.55 (16% ethyl acetate in hexane); $[\alpha]^{24}_D$ −47.3 (c 1.00, $CHCl_3$) (lit.[12] $[\alpha]^{22.5}_D$ −61.4 (c 1.00, $CHCl_3$)); IR ν_{max} 2961, 2925, 2873, 2722, 1680, 1623, 1605, 1456, 1379, 1315, 1127, 1010, 969, 822, 595 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 9.55 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 15.6 Hz, 1H), 6.09 (dd, J = 7.9, 15.6 Hz, 1H), 5.76 (d, J = 9.8 Hz, 1H), 2.62−2.74 (m, 1H), 1.83 (d, J = 1.2 Hz, 3H), 1.19−1.39 (m, 3H), 1.10−1.19 (m, 2H), 1.00 (d, J = 6.7 Hz, 3H), 0.85 (t, J = 7.3 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.4, 158.4, 151.3, 132.0, 126.9, 44.5, 32.5, 31.3, 30.2, 21.1, 19.2, 12.6, 11.4.

*2,2-Dimethyl-5-(triphenylphosphoranylidene)acetyl-1,3-dioxan-4,6-dione (**26**).* According to a literature procedure,[13] ylide **26** (2.31 g, 56%) was prepared as a colorless solid from Meldrum's acid (1.32 g, 9.18 mmol) and ketenylidenetriphenylphosphorane (2.78 g, 9.18 mmol); IR ν_{max} 3062, 2984, 1685, 1626, 1587, 1573, 1548, 1516, 1375, 1314, 1272, 1258, 1204, 1175, 1158, 1104, 1055, 1029, 996, 985, 935, 86, 798, 783, 757, 747, 723, 716, 692, 659, 651, 579 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 13.53 (dd, J = 0.8, 2.9 Hz, 1H), 7.60−7.69 (m, 9H), 7.49−7.55 (m, 6H), 5.76 (dd, J = 2.9, 21.7 Hz, 1H), 1.70 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.9, 133.3 (d, J = 10.9 Hz), 133.0 (d, J = 2.7 Hz), 129.3 (d, J = 11.8 Hz), 124.9 (d, J = 91.7 Hz), 102.4, 57.0 (d, J = 108.1 Hz), 26.4.

*(5S,3Z)-5-(4-((tert-Butyldimethylsilyl)oxy)benzyl)-3-((2E,4E,6E,8R,10R)-1-hydroxy-6,8,10-trimethyldodeca-2,4,6-trien-1-ylidene)-1-(2-nitrobenzyl)pyrrolidine-2,4-dione (**28a**) and (5S,3Z)-5-(4-((tert-Butyldimethylsilyl)oxy)benzyl)-1-(2,4-dimethoxybenzyl)-3-((2E,4E,6E,8R,10R)-1-hydroxy-6,8,10-trimethyldodeca-2,4,6-trien-1-ylidene)pyrrolidine-2,4-dione (**28b**).* (A) A suspension of ylide **26** (790 mg, 1.77 mmol) and KO^{t}Bu (199 mg, 1.77 mmol) in THF (20 mL) was treated with a solution of aldehyde **25** (344 mg, 1.77 mmol) in THF (15 mL), and the resulting mixture was heated at reflux for 22 h. It was concentrated in vacuo, and the remainder was taken up in CH_2Cl_2 (150 mL) and sat. aqueous $NaHCO_3$ (100 mL). The phases were separated, and the organic one was washed with sat. aqueous $NaHCO_3$ (2 × 150 mL) and 1 M aqueous HCl (100 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give an inseparable mixture of 42% of Meldrum's acid derivative **8**, 42% PPh_3O, and 16% residual ylide **26**. It was taken up in acetonitrile p.a. (30 mL), and the resulting solution was split in two 15 mL portions which were used in the next step without further purification.

(B) The first 15 mL portion was treated with *o*Nb-L-Tyr(OTBS)-OMe **7a** (326 mg, 734 μmol, 1.00 equiv), the resulting mixture was heated at reflux for 1 h, and all volatiles were removed in vacuo to leave an orange oil that was purified by flash chromatography (silica gel, 30% EtOAc in hexane, R_f = 0.67) to give β-ketoamide **27a** as a yellow oil (161 mg, 30% over two steps) that was used in the next step without further purification.

The second 15 mL portion was reacted analogously with DMB-L-Tyr(OTBS)-OMe **7b** (381 mg, 829 μmol, 1.13 equiv) to give β-ketoamide **27b** as a yellow oil (120 mg, 25% over two steps) that was also used in the next step without further purification; R_f = 0.57 (30% EtOAc in hexane). (C) A solution of β-ketoamide **27a** (161 mg, 228 μmol) in methanol p.a. (23 mL) was treated with sodium methoxide (62 mg, 1.140 mmol), and the resulting mixture was stirred at ambient temperature for 15 min. A 1 M aqueous HCl (15 mL) solution and brine (10 mL) were added, and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to afford tetramic acid **28a** as a foamy orange yellow solid (152 mg, quant); R_f = 0.15 (30% EtOAc in hexane); $[\alpha]^{24}_D$ −415 (c 0.50, $CHCl_3$); IR ν_{max} 2957, 2927, 2857, 1698, 1645, 1626, 1592, 1556, 1525, 1510, 1443, 1353, 1338, 1305, 1259, 1173, 1120, 1001, 920, 875, 857, 839, 809, 781, 749, 727, 688, 608, 571 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.02 (dd, J = 1.2, 8.2 Hz, 1H), 7.58 (ddd, J = 1.2, 7.6, 7.6 Hz, 1H), 7.53 (dd, J = 11.3, 15.0 Hz, 1H), 7.44 (ddd, J = 1.2, 7.6, 8.2 Hz, 1H), 7.31 (dd, J = 1.2, 7.6 Hz, 1H), 7.17 (d, J = 15.0 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 15.3 Hz, 1H), 6.64 (d, J = 8.5 Hz, 2H), 6.43 (dd, J = 11.3, 15.3 Hz, 1H), 5.56 (d, J = 9.8 Hz, 1H), 5.22 (d, J = 17.1 Hz, 1H), 4.72 (d, J = 17.1 Hz, 1H), 4.00 (dd, J = 4.3, 5.2 Hz, 1H), 3.14 (dd, J = 4.3, 14.7 Hz, 1H), 3.04 (dd, J = 5.2, 14.7 Hz, 1H), 2.60−2.71 (m, 1H), 1.82 (s, 3H), 1.20−1.36 (m, 3H), 1.08−1.17 (m, 2H), 0.97 (d, J = 6.4 Hz, 3H), 0.94 (s, 9H), 0.81−0.87 (m, 6H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.7, 174.6, 173.9, 154.8, 149.5, 148.3, 147.9, 146.6, 133.9, 132.9, 132.1, 130.3, 129.4, 128.6, 127.6, 125.4, 125.2, 120.2, 119.8, 99.7, 66.0, 44.7, 41.1, 35.0, 32.5, 31.1, 30.2, 25.8, 21.3, 19.2, 18.3, 12.5, 11.4, −4.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{39}H_{53}N_2O_6Si^+$ 673.3667, found 673.3651.

Analogously, tetramic acid **28b** (113 mg, quant) was obtained as a solid yellow foam from β-ketoamide **27b** (120 mg, 167 μmol) and sodium methoxide (45 mg, 835 μmol); R_f = 0.41 (30% EtOAc in

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hexane); $[\alpha]^{24}_D$ −412 (*c* 0.50, $CHCl_3$); IR ν_{max} 2958, 2928, 2858, 1697, 1609, 1593, 1558, 1509, 1451, 1361, 1260, 1209, 1158, 1131, 1108, 1035, 1000, 915, 838, 782, 686, 610 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.44 (dd, *J* = 11.3, 15.0 Hz, 1H), 7.06−7.12 (m, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* = 15.3 Hz, 1H), 6.41−6.45 (m, 2H), 6.39 (dd, *J* = 11.3, 15.3 Hz, 1H), 5.51 (d, *J* = 9.8 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 1H), 4.19 (d, *J* = 14.6 Hz, 1H), 3.83−3.87 (m, 1H), 3.76−3.82 (m, 6H), 3.06−3.14 (m, 2H), 2.59−2.73 (m, 1H), 1.82 (s, 3H), 1.21−1.34 (m, 3H), 1.08−1.16 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.94 (s, 9H), 0.80−0.86 (m, 6H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.8, 173.8, 173.1, 160.9, 158.7, 154.6, 148.5, 147.2, 145.3, 132.9, 131.5, 130.7, 128.1, 125.3, 120.3, 120.1, 116.4, 104.4, 100.6, 98.5, 65.1, 55.51, 55.48, 44.7, 38.4, 34.4, 32.5, 31.0, 30.2, 25.8, 21.4, 19.2, 18.3, 12.5, 11.4, −4.3; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{41}H_{58}NO_6Si^+$ 688.4028, found 688.4031.

*Ethyl (2E,4E,6E,8R,10R)-6,8,10-Trimethyldodeca-2,4,6-trienoate (**31**).* According to a literature procedure,[16] ester **31** (248 mg, 67%) was prepared as a colorless oil from aldehyde **10** (235 mg, 1.394 mmol) and phosphonate **30** (1.12 g, 4.46 mmol); R_f = 0.40 (6% EtOAc in hexane); $[\alpha]^{24}_D$ −51.7 (*c* 1.00, $CHCl_3$) (lit.[16] $[\alpha]^{19}_D$ −41.8 (*c* 1.00, $CHCl_3$)); IR ν_{max} 2960, 2925, 2872, 1710, 1613, 1457, 1392, 1367, 1329, 1304, 1256, 1234, 1201, 1178, 1136, 1096, 1039, 996, 861, 718 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 (dd, *J* = 11.0, 15.3 Hz, 1H), 6.56 (d, *J* = 15.3 Hz, 1H), 6.22 (dd, *J* = 11.0, 15.3 Hz, 1H), 5.85 (d, *J* = 15.3 Hz, 1H), 5.44 (d, *J* = 9.8 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.55−2.69 (m, 1H), 1.80 (d, *J* = 1.2 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.20−1.33 (m, 3H), 1.07−1.17 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.80−0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5, 146.4, 145.6, 145.5, 132.3, 123.8, 119.6, 60.3, 44.8, 32.4, 30.8, 30.2, 21.5, 19.2, 14.5, 12.6, 11.4.

*(2E,4E,6E,8R,10R)-6,8,10-Trimethyldodeca-2,4,6-trien-1-ol (**32**).* Analogously to **21**, alcohol **32** (179 mg, 85%) was prepared as a colorless cloudy oil from ester **31** (226 mg, 948 μmol) and DIBAL-H (1 M in hexane, 2.4 mL, 2.40 mmol) in 179 mg (85%); R_f = 0.19 (16% EtOAc in hexane); $[\alpha]^{24}_D$ −37.5 (*c* 1.00, $CHCl_3$) (lit.[16] $[\alpha]^{20}_D$ −28.8 (*c* 1.00, $CHCl_3$)); IR ν_{max} 3306, 3024, 2959, 2922, 2870, 1625, 1455, 1376, 1309, 1087, 982, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.10−6.33 (m, 3H), 5.82 (td, *J* = 6.1, 15.2 Hz, 1H), 5.25 (d, *J* = 9.5 Hz, 1H), 4.19 (d, *J* = 6.1 Hz, 2H), 2.54−2.65 (m, 1H), 1.77 (d, *J* = 1.2 Hz, 3H), 1.22−1.31 (m, 3H), 1.04−1.16 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.79−0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.3, 138.9, 132.7, 132.1, 130.6, 125.3, 63.8, 45.0, 32.4, 30.5, 30.3, 21.7, 19.2, 12.7, 11.5.

*(2E,4E,6E,8R,10R)-6,8,10-Trimethyldodeca-2,4,6-trienal (**33**).* Analogously to **10**, aldehyde **33** (150 mg, 92%) was prepared as a yellowish oil from alcohol **32** (165 mg, 742 μmol) and MnO_2 (1.29 g, 14.84 mmol); R_f = 0.68 (16% EtOAc in hexane); $[\alpha]^{24}_D$ −49.4 (*c* 0.50, $CHCl_3$); IR ν_{max} 2960, 2925, 2874, 2730, 1676, 1603, 1457, 1377, 1315, 1159, 1129, 1114, 1009, 984, 858, 647 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.55 (d, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 11.0, 15.3 Hz, 1H), 6.68 (d, *J* = 15.3 Hz, 1H), 6.36 (dd, *J* = 11.0, 15.3 Hz, 1H), 6.16 (dd, *J* = 8.1, 15.1 Hz, 1H), 5.55 (d, *J* = 9.8 Hz, 1H), 2.60−2.72 (m, 1H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.21−1.35 (m, 3H), 1.09−1.17 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.80−0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.9, 153.5, 148.6, 147.5, 132.4, 130.5, 124.0, 44.7, 32.5, 31.0, 30.2, 21.4, 19.2, 12.6, 11.4; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{25}O^+$ 221.1900, found 221.1901.

*S-tert-Butyl-4-(diethoxyphosphoryl)-3-oxopentanethioate (**34**).* According to a literature procedure,[17] phosphonate **34**[31] (4.32 g, 59%) was prepared from bromopropionyl bromide (2.3 mL, 22.30 mmol) and Meldrum's acid (2.900 g, 20.20 mmol) as a pale orange oil and as a keto/enol mixture (5.6:1); IR ν_{max} 2966, 1723, 1674, 1614, 1478, 1456, 1398, 1365, 1314, 1250, 1163, 1016, 959, 836, 789, 688, 644, 591 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 13.01−13.06 (m, 1H), 5.42−5.47 (m, 1H), 4.06−4.16 (m, 4H), 4.03 (d, *J* = 15.3 Hz, 1H), 3.72 (d, *J* = 15.3 Hz, 1H), 3.46 (qd, *J* = 7.0, 26.2 Hz, 1H), 2.67 (qd, *J* = 7.3, 23.5 Hz, 1H), 1.41−1.50 (m, 9H), 1.35 (d, *J* = 7.0 Hz, 1H), 1.29−1.33 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.3 (d, *J* = 4.5 Hz), 192.9, 171.6 (d, *J* = 6.4 Hz), 101.0 (d, *J* = 7.3 Hz), 62.9 (dd, *J* = 18.2, 7.3 Hz), 58.3, 49.2, 48.5, 47.2 (d, *J* = 126.3 Hz), 38.9 (d, *J* = 135.3 Hz), 30.2, 29.7, 16.5 (d, *J* = 8.2 Hz), 12.7 (d, *J* = 5.4 Hz), 10.7 (d, *J* = 6.4 Hz).

*(5S,3Z)-5-(4-((tert-Butyldimethylsilyl)oxy)benzyl)-1-(2,4-dimethoxybenzyl)-3-((2E,4E,6E,8E,10R,12R)-1-hydroxy-2,8,10,12-tetramethyltetradeca-2,4,6,8-tetraen-1-ylidene)pyrrolidine-2,4-dione (**36**).* A mixture of thioester **9** (100 mg, 256 μmol), THF (3.2 mL), and 4 Å molecular sieves (powdered, 40 mg) was cooled to 0 °C and treated with a solution of DMB-L-Tyr(OTBS)-OMe **7b** (130 mg, 282 μmol), NEt_3 (0.14 mL, 1.024 mmol), and silver trifluoroacetate (113 mg, 512 μmol) in THF (3.2 mL). The mixture was stirred at 0 °C under exclusion of light for 2.5 h, diluted with diethyl ether (100 mL), and filtered over Celite. The filtrate was washed with sat. aqueous NH_4Cl (75 mL) and brine (75 mL), dried (Na_2SO_4), and concentrated in vacuo to give an orange oil. It was purified by flash chromatography (silica gel, 50% EtOAc in hexane; R_f = 0.76) to give β-ketoamide **35** as a yellow oil (173 mg, 89%) that was used in the next step without further purification. A solution of β-ketoamide **35** (159 mg, 209 μmol) in methanol (21 mL) was treated with sodium methoxide (56 mg, 1.05 mmol), and the mixture was stirred at ambient temperature for 20 min. Saturated aqueous NH_4Cl (40 mL) and 1 M aqueous HCl (30 mL) were added, the mixture was extracted with EtOAc (100 mL), and the organic phase was dried (Na_2SO_4) and concentrated in vacuo to give bisprotected fumosorinone A (**36**) as a red gum (149 mg, quant); R_f = 0.56 (50% EtOAc in hexane); $[\alpha]^{24}_D$ −367.1 (*c* 0.75, $CHCl_3$); IR ν_{max} 2958, 2928, 2859, 1652, 1611, 1590, 1544, 1508, 1452, 1389, 1361, 1255, 1209, 1171, 1158, 1119, 1034, 988, 913, 837, 807, 781, 725, 687, 640, 605, 578 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, *J* = 11.6 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.68−6.75 (m, 3H), 6.57 (dd, *J* = 11.6, 14.3 Hz, 1H), 6.41−6.49 (m, 3H), 6.31 (dd, *J* = 10.7, 15.0 Hz, 1H), 5.40 (d, *J* = 9.5 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 1H), 4.24 (d, *J* = 14.6 Hz, 1H), 3.82−3.86 (m, 1H), 3.78−3.82 (m, 6H), 3.15 (dd, *J* = 4.6, 14.3 Hz, 1H), 3.10 (dd, *J* = 4.0, 14.3 Hz, 1H), 2.56−2.70 (m, 1H), 1.95 (s, 3H), 1.81 (s, 3H), 1.22−1.35 (m, 3H), 1.06−1.17 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.95 (br. s., 9H), 0.85 (dd, *J* = 7.0, 7.6 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.6, 182.7, 175.9, 160.9, 158.7, 154.6, 144.1, 143.2, 142.9, 142.6, 132.7, 131.5, 130.8, 128.21, 128.18, 126.9, 126.3, 120.1, 116.4, 104.4, 99.4, 98.5, 64.5, 55.51, 55.49, 44.9, 38.7, 34.5, 32.4, 30.8, 30.2, 25.8, 21.5, 19.2, 18.3, 12.64, 12.61, 11.4, −4.32, −4.34; HRMS (ESI) *m* /*z* $[M + H]^+$ calcd for $C_{44}H_{62}NO_6Si^+$ 728.4341, found 728.4340.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01530.

NMR spectra of all compounds, HPLC chromatogramms of target compounds **3** and **4**, ECD spectrum of compound **3** (PDF)

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Notes

The authors declare no competing financial interest.

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Supporting Information

Synthesis of the Entomopathogenic Fungus Metabolites Militarinone C and Fumosorinone A

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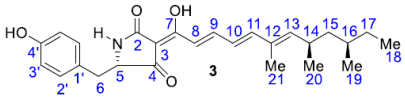
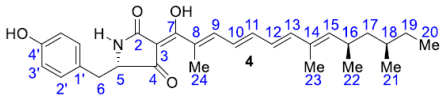
NMR Tables

Table S1. Comparison of isolated[1] and synthetic militarinone C (**3**). ^{13}C NMR shifts and ^{1}H NMR shifts and multiplet analysis.



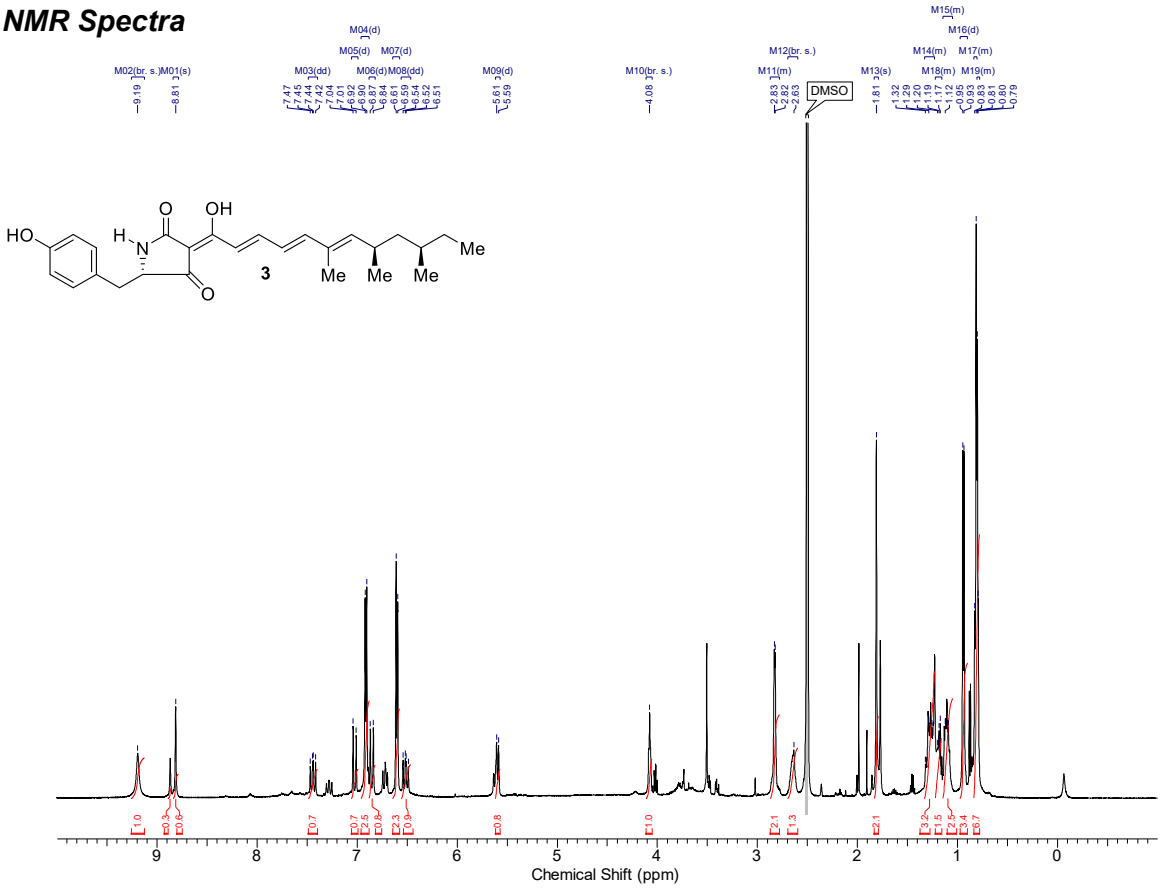
	Isolation in CD_3OD Lit[1]		Synthetic in CD_3OD	
No.	**δ_C**	**δ_H (Mult. J[Hz])**	**δ_C (Jmod)**	**δ_H (Mult. J[Hz])**
1-NH		8.75 (br. s)		8.81 (br. s)
2	175.0		175.0	
3	~100		100.0	
4	194.7		194.8	
5	62.2	4.05 (br. s)	62.3	4.08 (br. s)
6	35.8	2.82 (m)	35.8	2.83 (m)
7	172.5		172.4	
8	119.5	7.05 (br. s)	119.5	7.02 (d, 15.0)
9	144.5	7.42 (dd, 15.0, 11.4)	144.9	7.44 (dd, 15.0, 11.4)
10	125.1	6.48 (dd, 15.1, 11.4)	125.2	6.52 (dd, 15.1, 11.4)
11	148.4	6.82 (d, 15.1)	148.7	6.85 (d, 15.1)
12	132.7		132.9	
13	146.3	5.58 (d, 9.7)	146.6	5.60 (d, 9.7)
14	30.3	2.63 (m)	30.4	2.63 (m)
15a	44.0	1.11 (m)	44.1	1.11 (m)
15b		1.27 (m)		1.29 (m)
16	31.9	1.20 (m)	31.9	1.19 (m)
17a	29.5	1.11 (m)	29.6	1.11 (m)
17b		1.27 (m)		1.29 (m)
18	11.1	0.81 (m)	11.2	0.82 (m)
19	18.8	0.79 (m)	18.9	0.80 (m)
20	21.1	0.94 (d, 6.5)	21.1	0.94 (d, 6.5)
21	12.1	1.80 (br. s)	12.2	1.81 (br. s)
1'	125.9		125.8	
2'	130.5	6.91 (d, 8.4)	130.7	6.91 (d, 8.4)
3'	114.8	6.60 (d, 8.4)	114.8	6.60 (d, 8.4)
4'	155.8		155.9	
4'-OH		9.15 (s)		9.19 (br. s)

Table S2. Comparison of isolated[2] and synthetic fumosorinone A (**4**). ^{13}C NMR shifts and ^{1}H NMR shifts and multiplet analysis.



	Isolation in CD_3OD Lit[2]		Synthetic in CD_3OD	
No.	**δ_C (Dept)**	**δ_H (Mult. J[Hz])**	**δ_C (Jmod/HSQC/HMBC)**	**δ_H (Mult. J[Hz])**
2	174.8		not detected	
3	99.7		not detected	
4	194.1		193.8 (Jmod)	
5	61.6	4.05 (t, 4.8)	61.6 (HSQC)	4.06 (m)
6a	36.5	2.89 (dd, 14.1, 6.1)	36.3 (Jmod)	2.90 (dd, 14.1, 6.1)
6b		3.03 (dd, 14.1, 4.1)		3.01 (dd. 14.1, 4.1)
7	185.0		184.4 (HMBC)	
8	128.5		128.1 (HMBC)	
9	142.7	7.67 (d, 9.5)	142.8 (Jmod)	7.66 (br. s)
10	126.4	6.70 (dd. 15.2, 9.5)	126.6 (Jmod)	6.68 (dd, 15.2, 9.5)
11	142.8	6.70 (dd, 15.2, 9.5)	142.9 (Jmod)	6.73 (dd, 15.2, 9.5)
12	126.2	6.42 (dd, 15.2, 9.5)	126.2 (Jmod)	6.42 (dd, 15.2, 9.5)
13	142.8	6.54 (d, 15.2)	142.9 (Jmod)	6.55 (d, 15.2)
14	132.7		132.7 (Jmod)	
15	143.3	5.45 (d, 9.8)	143.3 (Jmod)	5.44 (d, 9.8)
16	30.5	2.68 (m)	30.5 (Jmod)	2.69 (m)
17a	44.6	1.16 (m)	44.6 (Jmod)	1.14 (m)
17b		1.34 (m)		1.32 (m)
18	32.3	1.34 (m)	32.3 (Jmod)	1.32 (m)
19a	29.8	1.16 (m)	29.9 (Jmod)	1.14 (m)
19b		1.34 (m)		1.32 (m)
20	10.3	0.88 (t, 7.4)	10.3 (Jmod)	0.88 (t, 7.4)
21	18.2	0.88 (d, 6.9)	18.1 (Jmod)	0.88 (d, 6.7)
22	20.4	0.98 (d, 6.6)	20.4 (Jmod)	0.98 (d, 6.6)
23	11.4	1.84 (s)	11.3 (Jmod)	1.84 (s)
24	11.2	1.95 (s)	11.1 (Jmod)	1.96 (s)
1'	126.4		126.1 (HMBC)	
2'	130.4	7.03 (d, 8.2)	130.5 (Jmod)	7.01 (d, 8.2)
3'	114.7	6.71 (d, 8.2)	114.6 (Jmod)	6.68 (d, 8.2)
4'	155.9		156.0 (Jmod)	

NMR Spectra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OH
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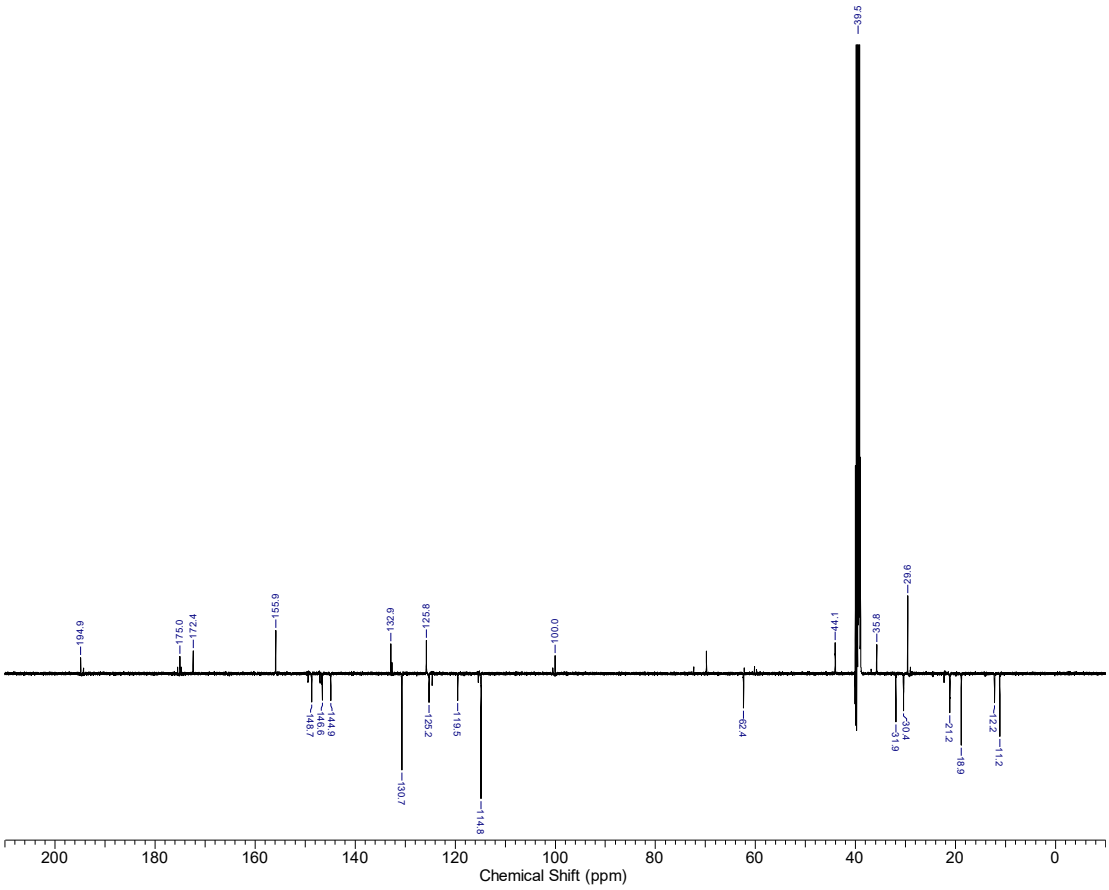
3
DMSO
Chemical Shift (ppm)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19.9
21.2
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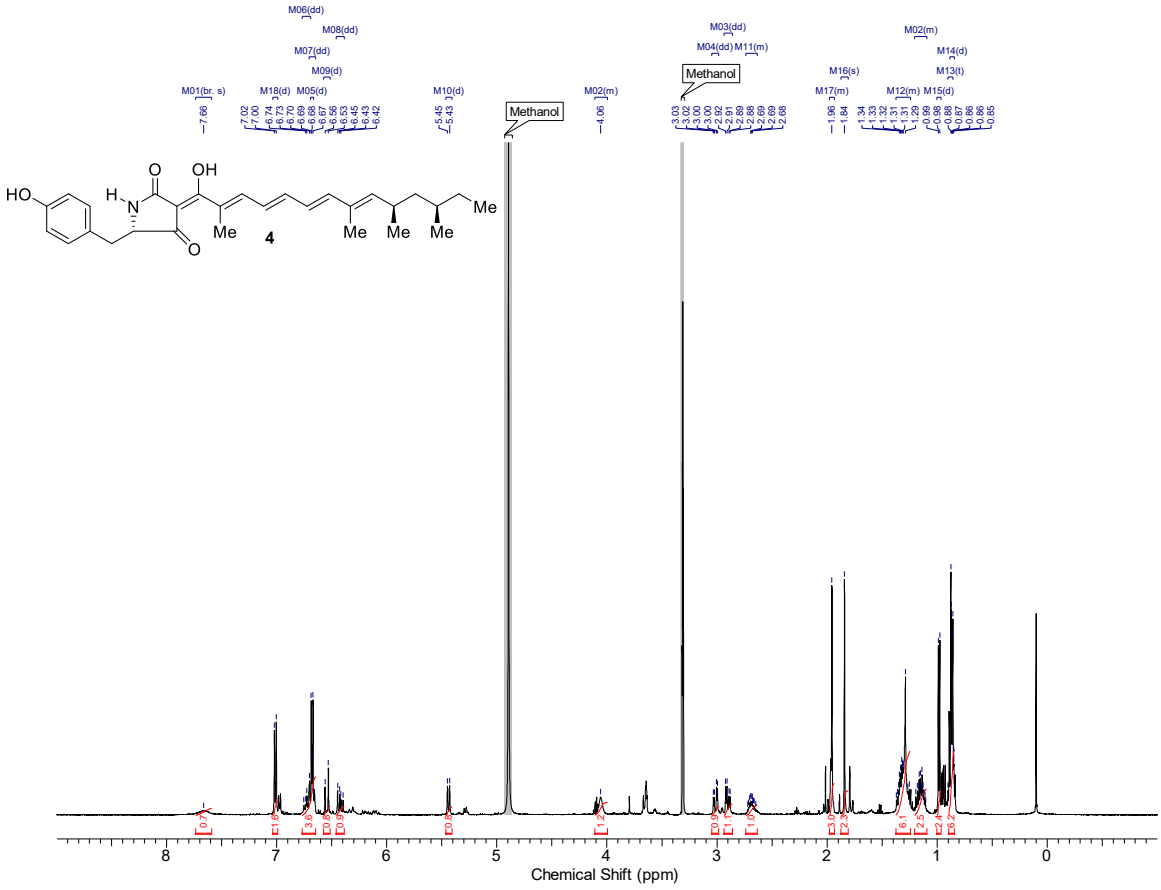
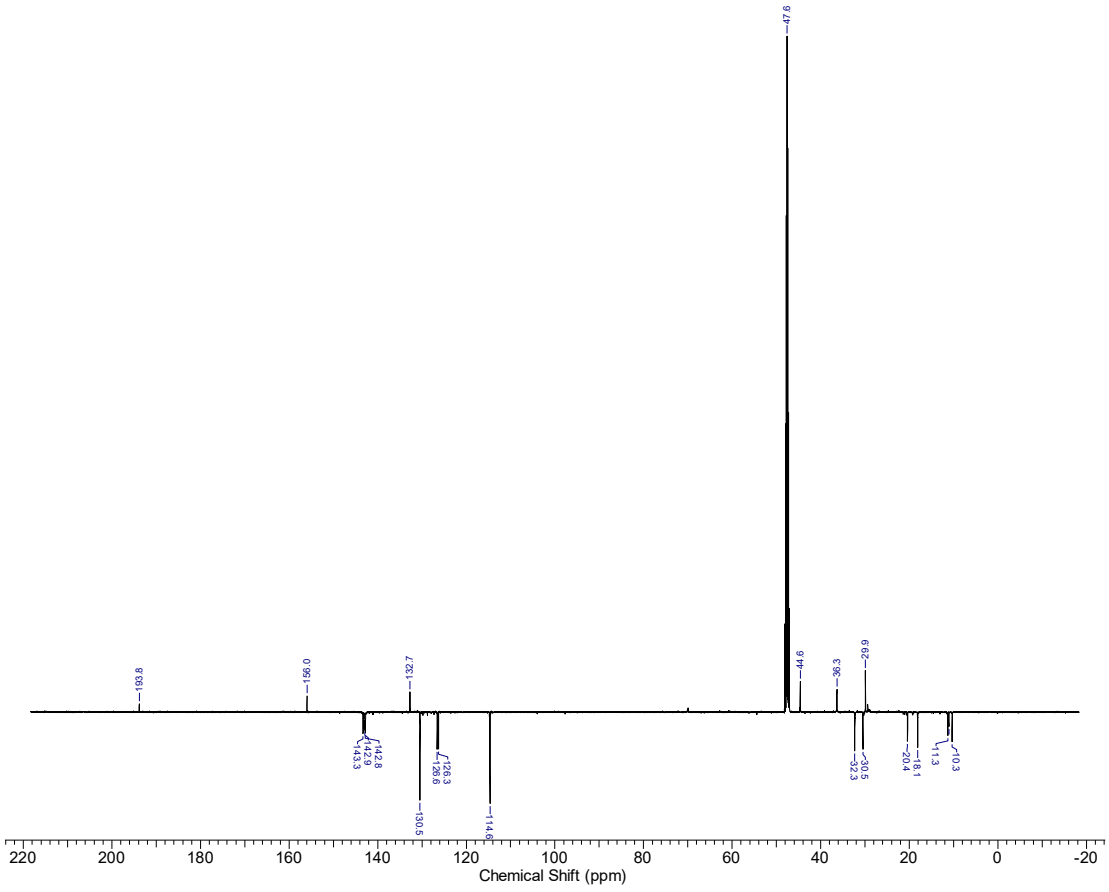
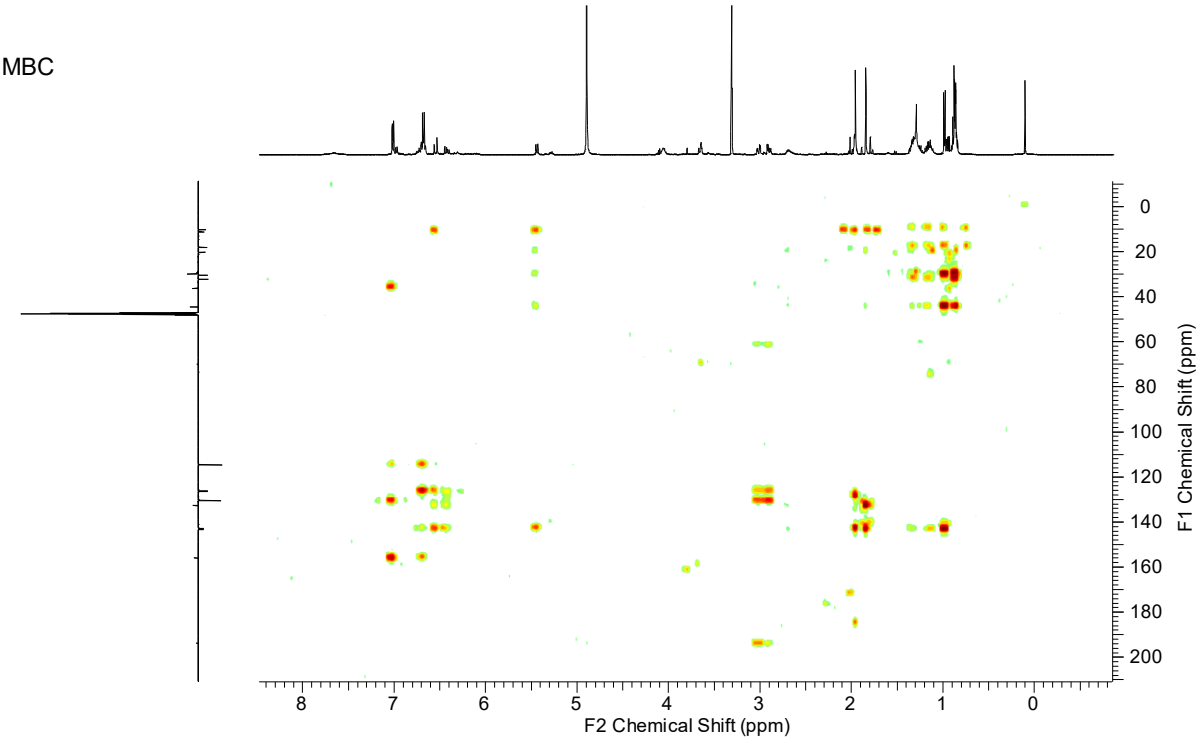
12.2
11.2
Chemical Shift (ppm)

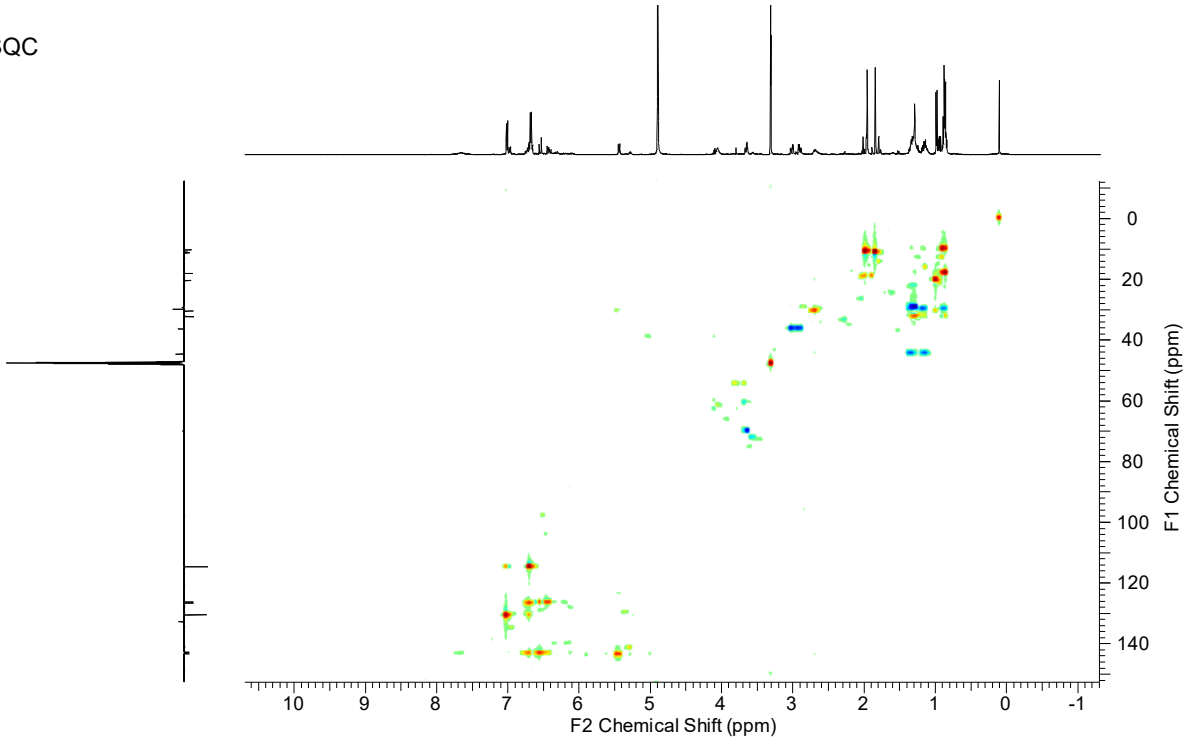

M06(dd)
M08(dd)
M07(dd)
M09(d)
M01(br. s)
M18(d)
M05(d)
M10(d)
M02(m)
M03(dd)
M04(dd)
M11(m)
Methanol
M16(s)
M17(m)
M12(m)
M15(d)
M14(d)
M13(t)
HO
O
OH
H
N
Me
Me
Me
Me
Me
O
4
Chemical Shift (ppm)

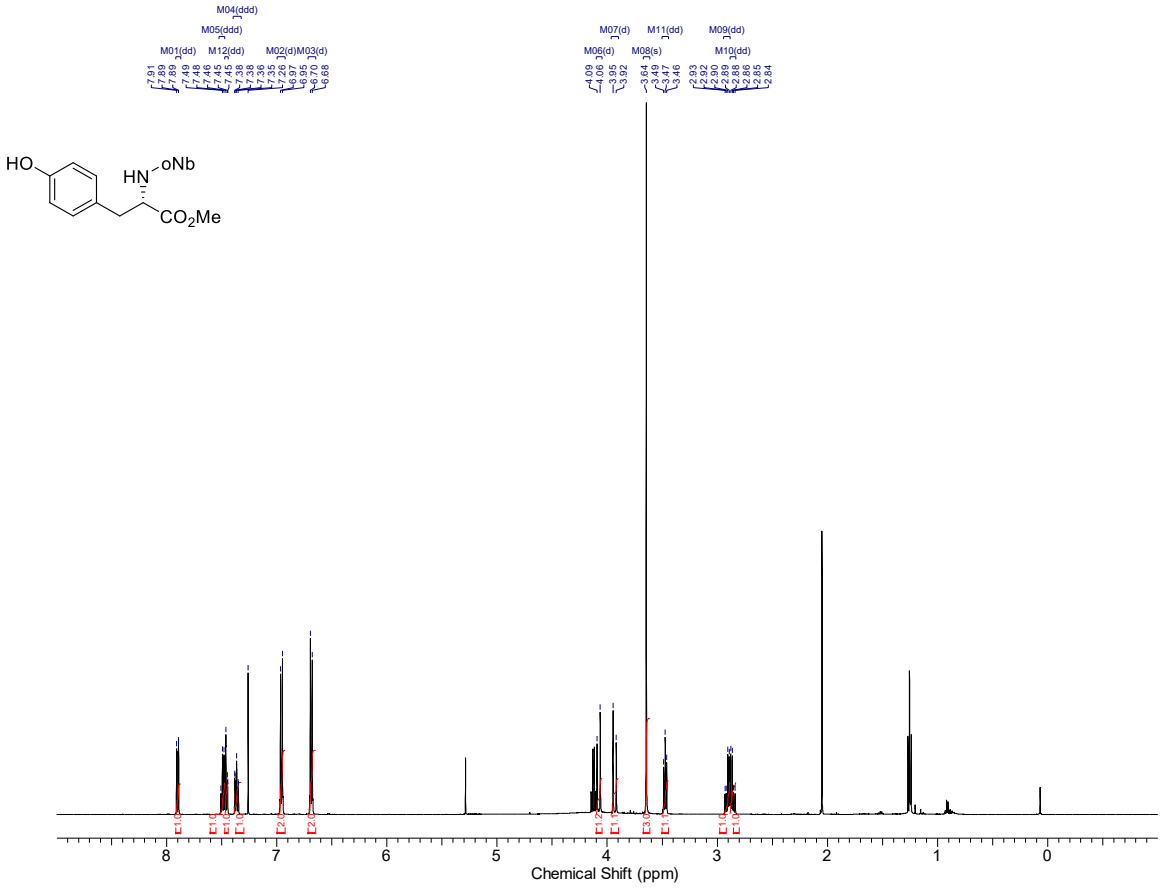

193.8
156.0
132.7
143.3
142.8
142.7
126.3
126.6
130.5
114.9
47.6
44.6
36.3
29.9
32.3
30.5
20.4
18.1
11.3
10.3
Chemical Shift (ppm)

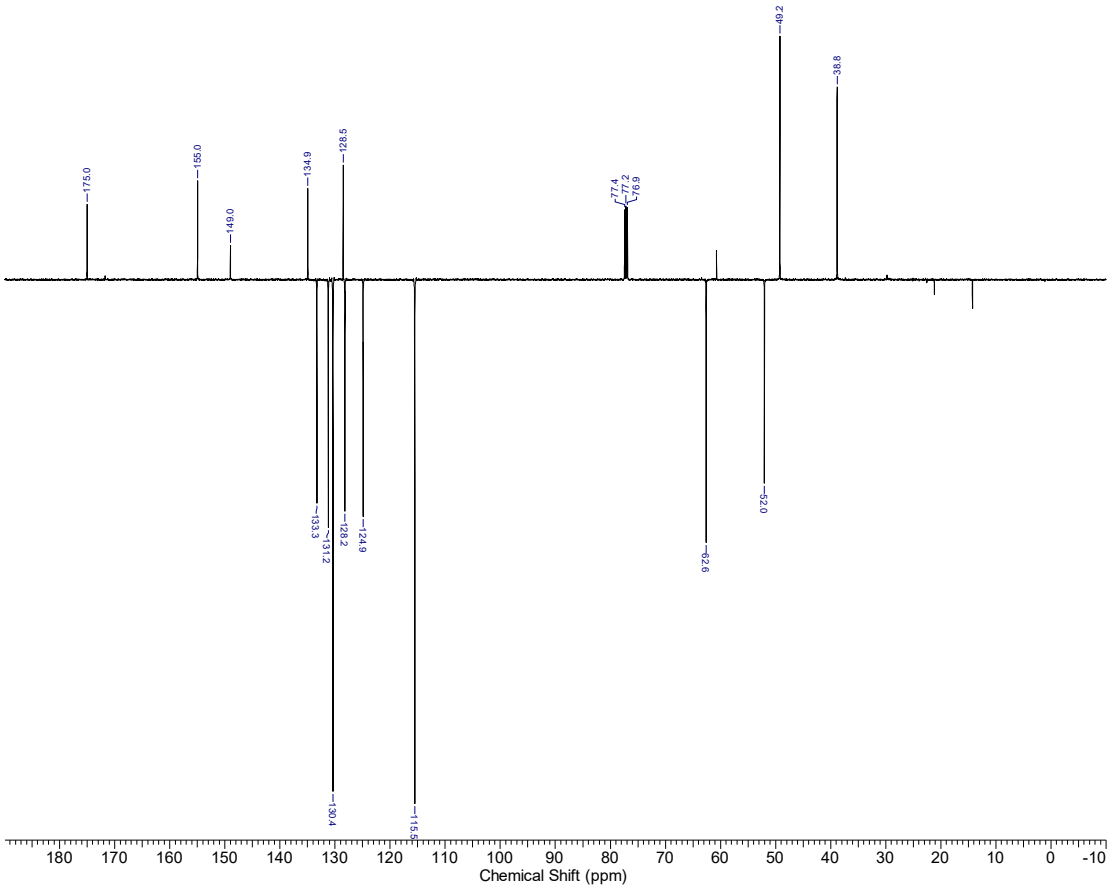
HMBC

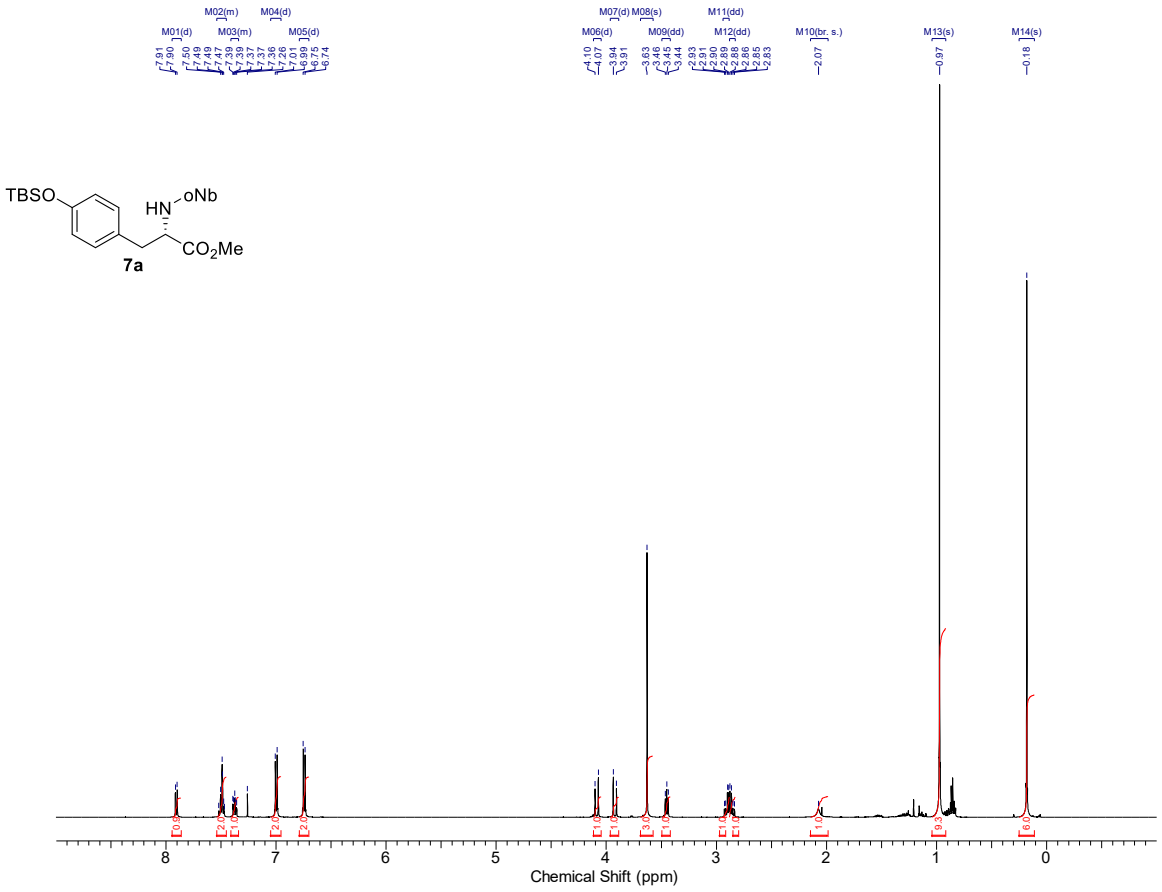

F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

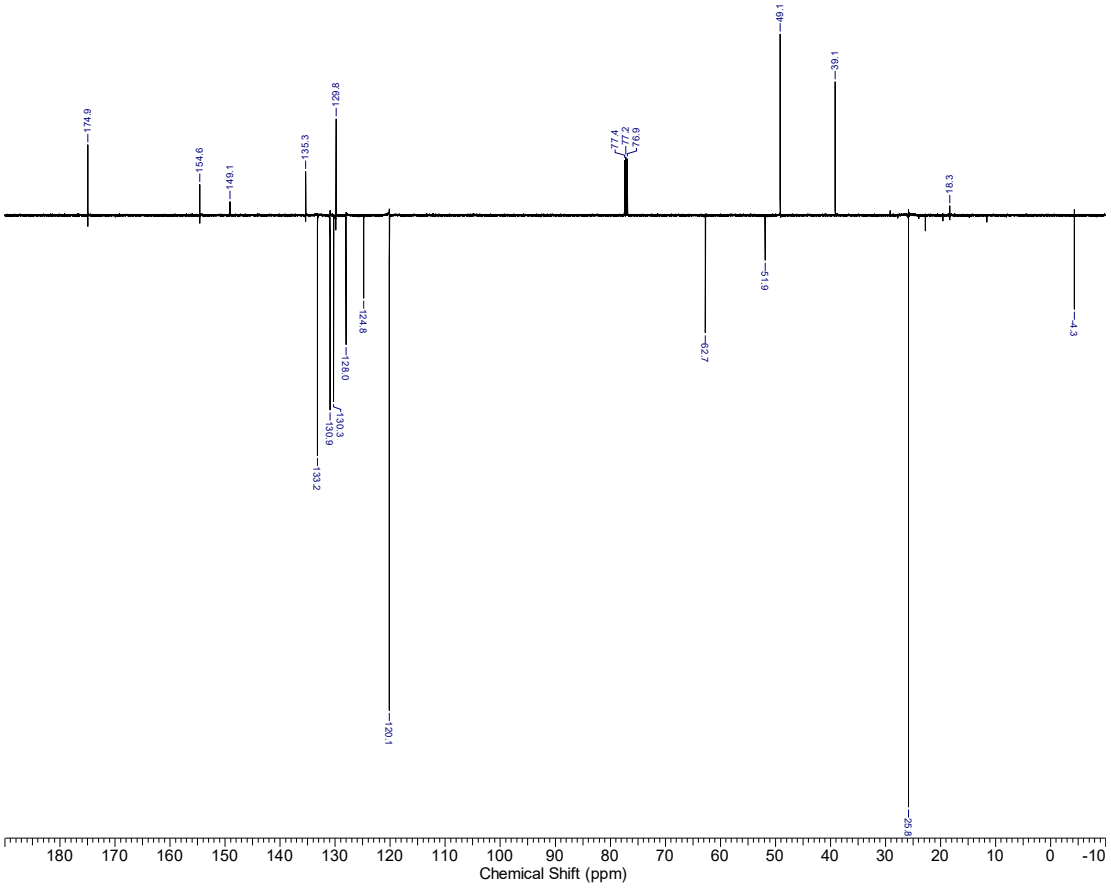
HSQC

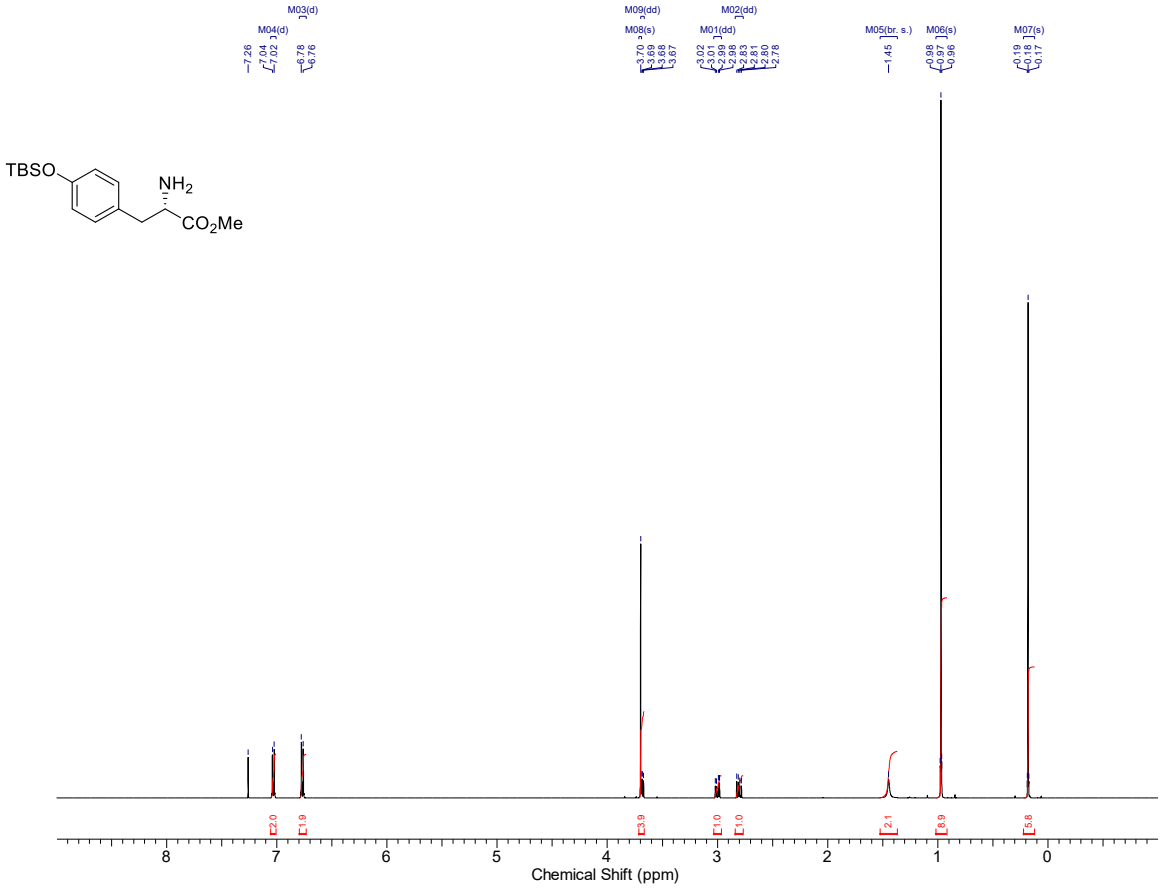

F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

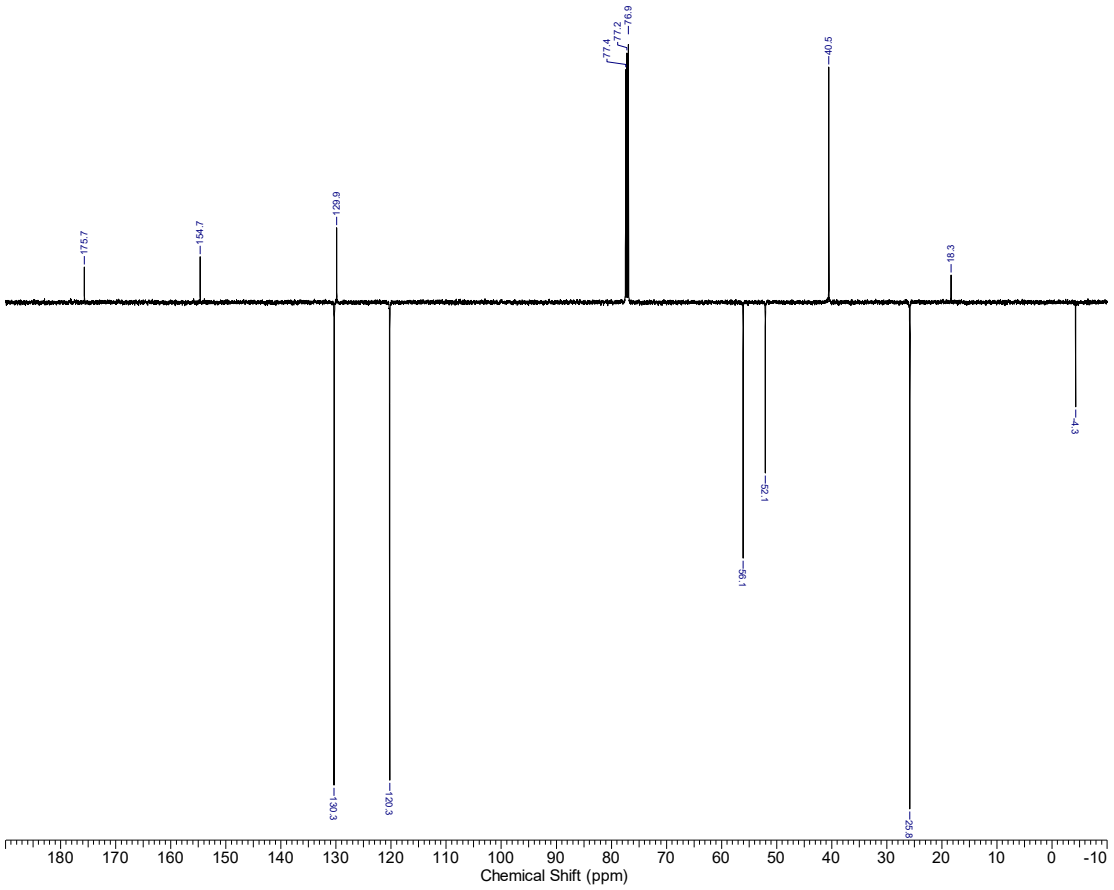

HO
HN
oNb
CO2Me
Chemical Shift (ppm)

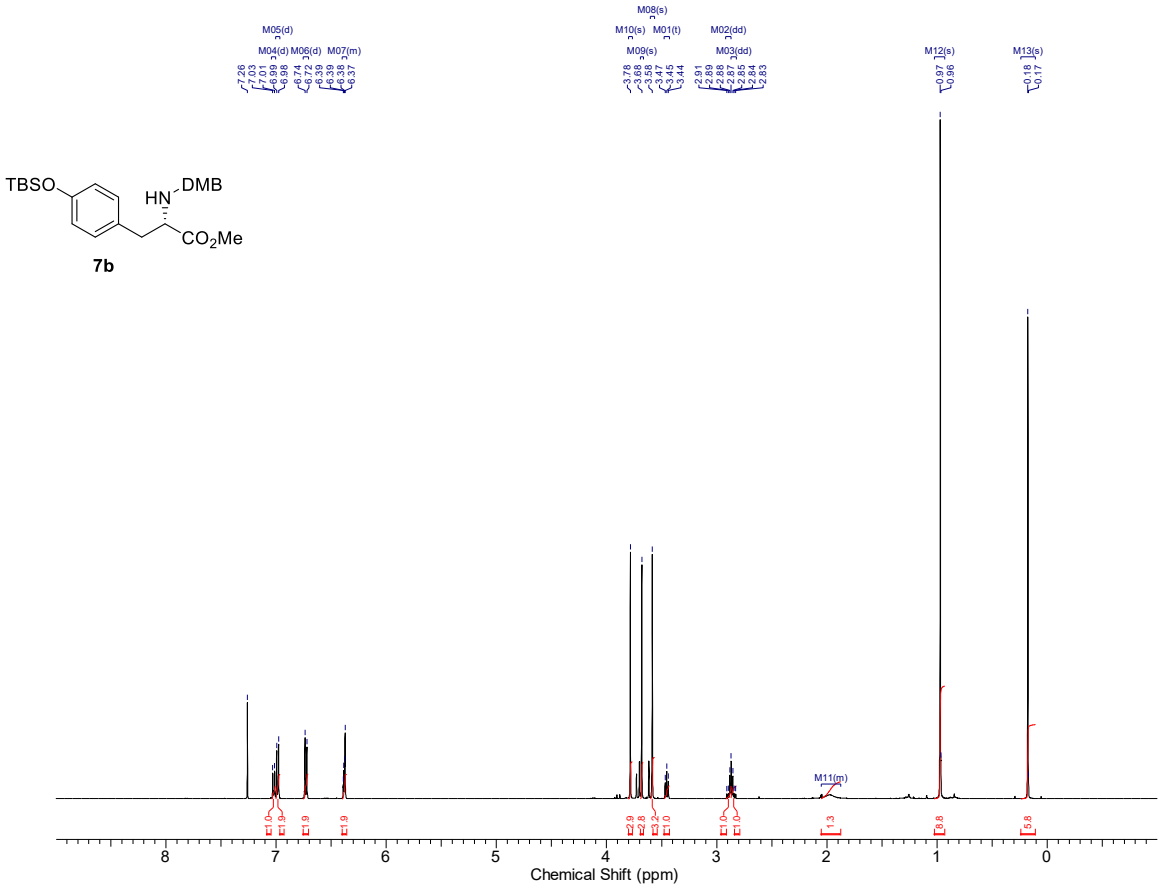

Chemical Shift (ppm)

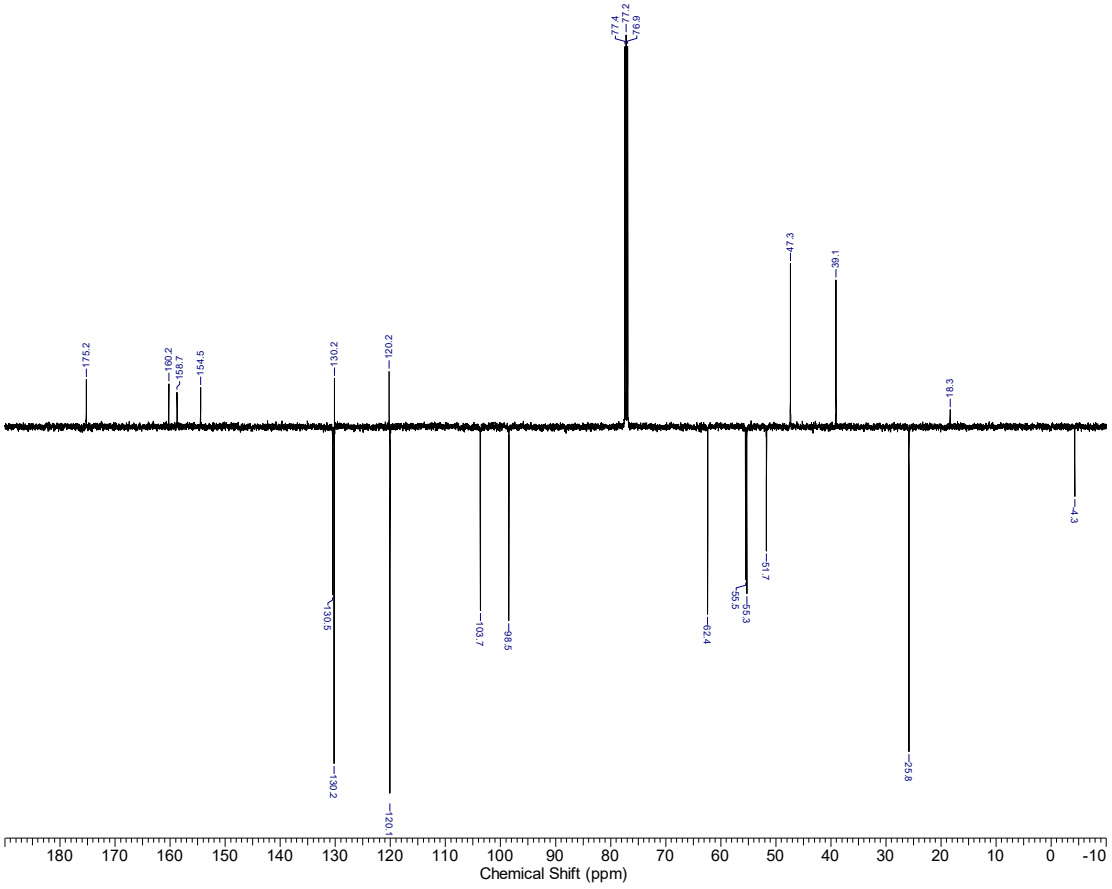

TBSO
HN
oNb
CO2Me
7a
Chemical Shift (ppm)

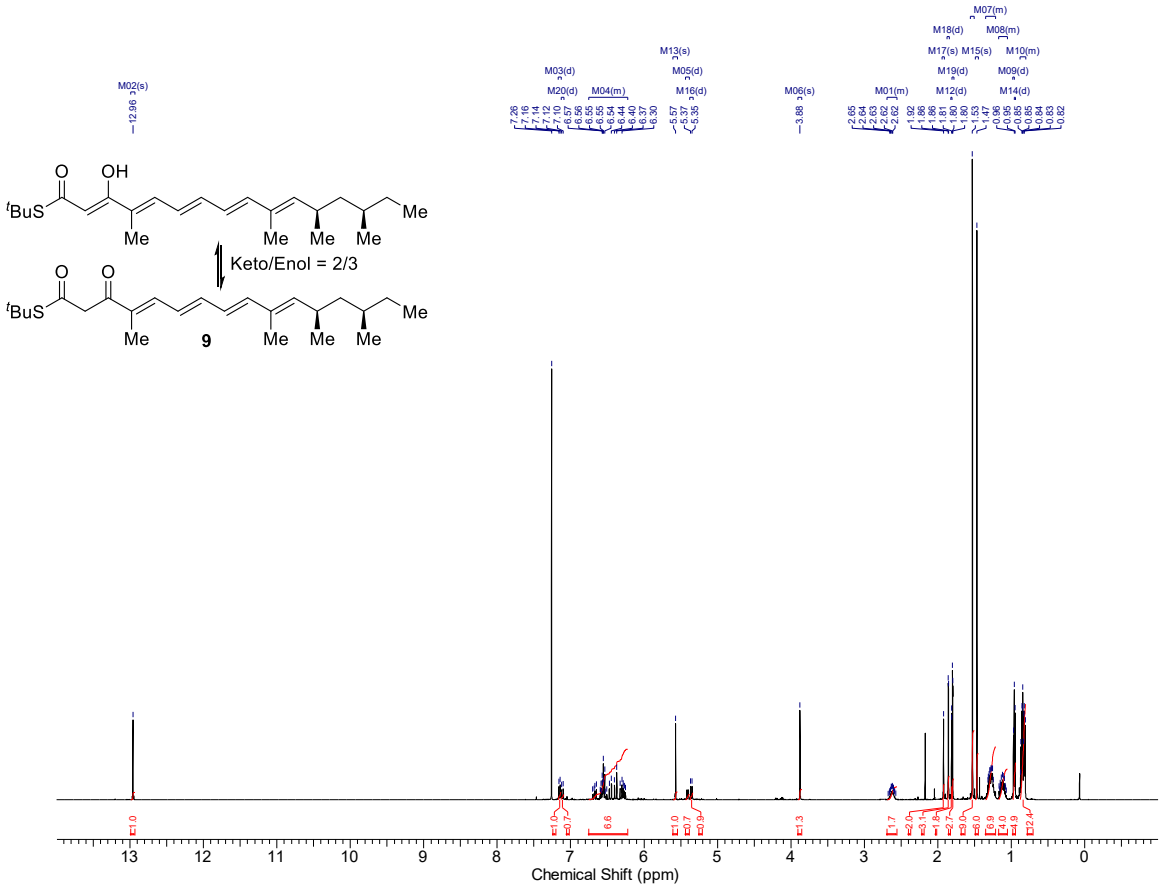

Chemical Shift (ppm)

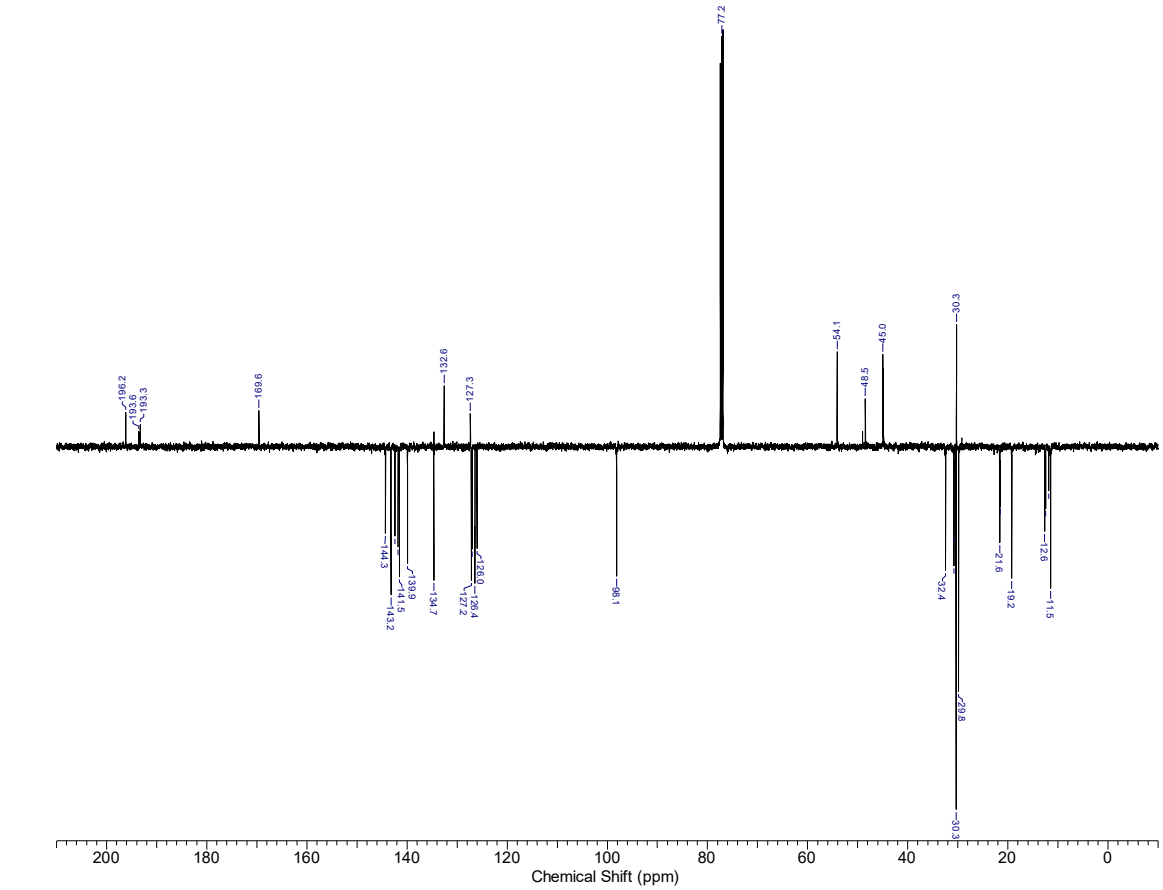

TBSO
NH2
CO2Me
Chemical Shift (ppm)

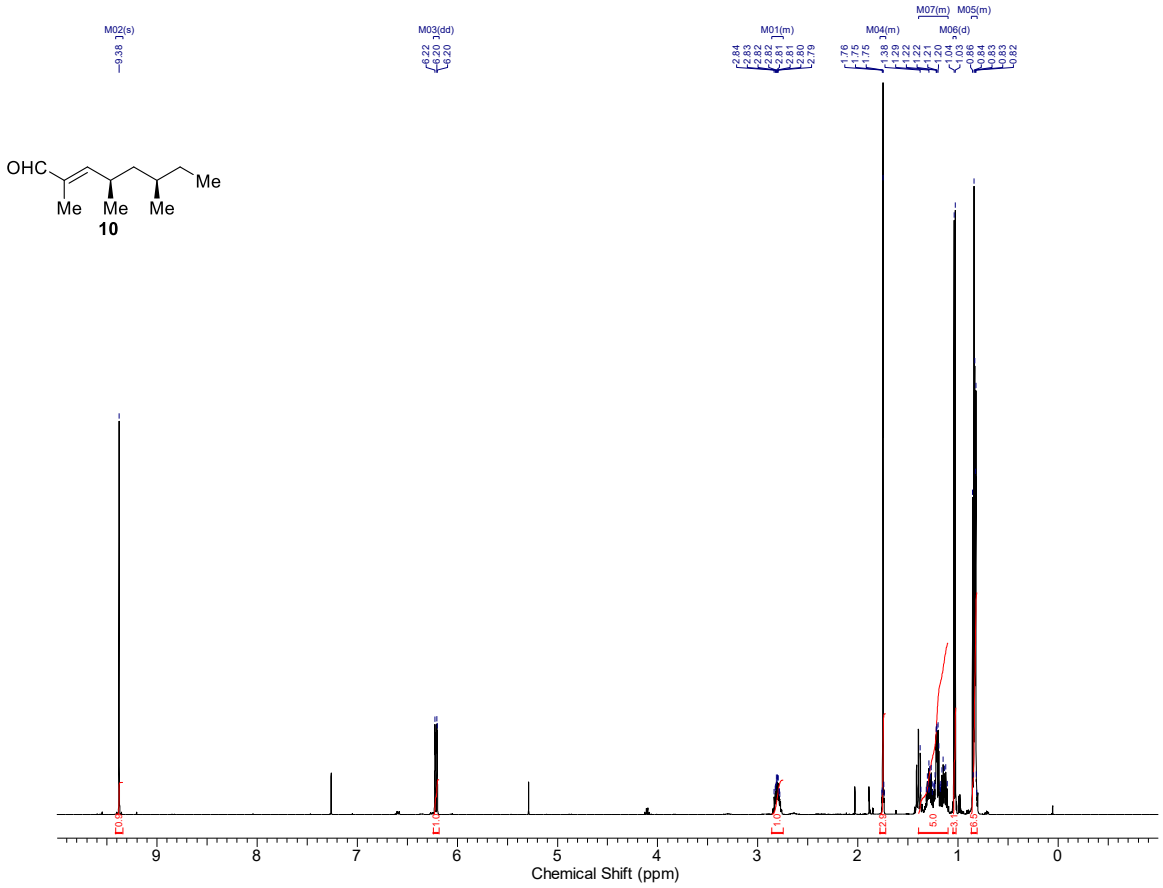

Chemical Shift (ppm)

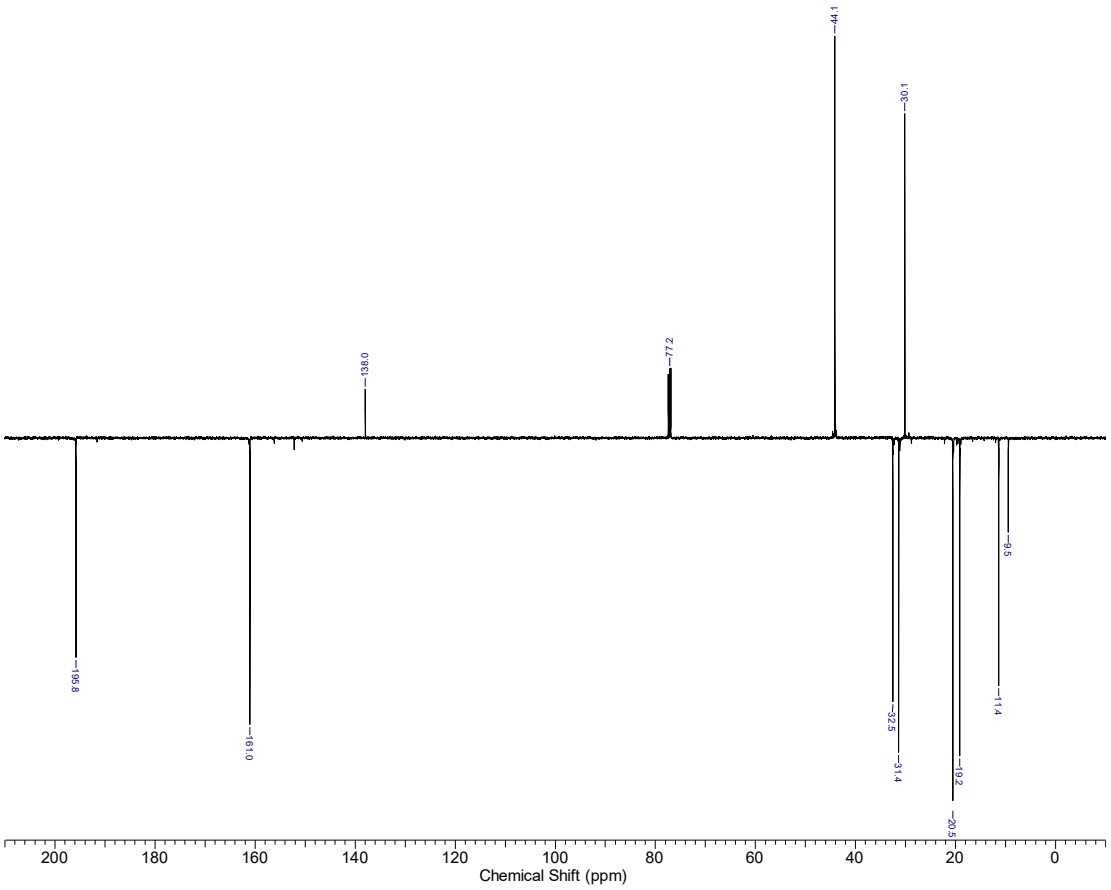

TBSO
HN
DMB
CO2Me
7b
Chemical Shift (ppm)

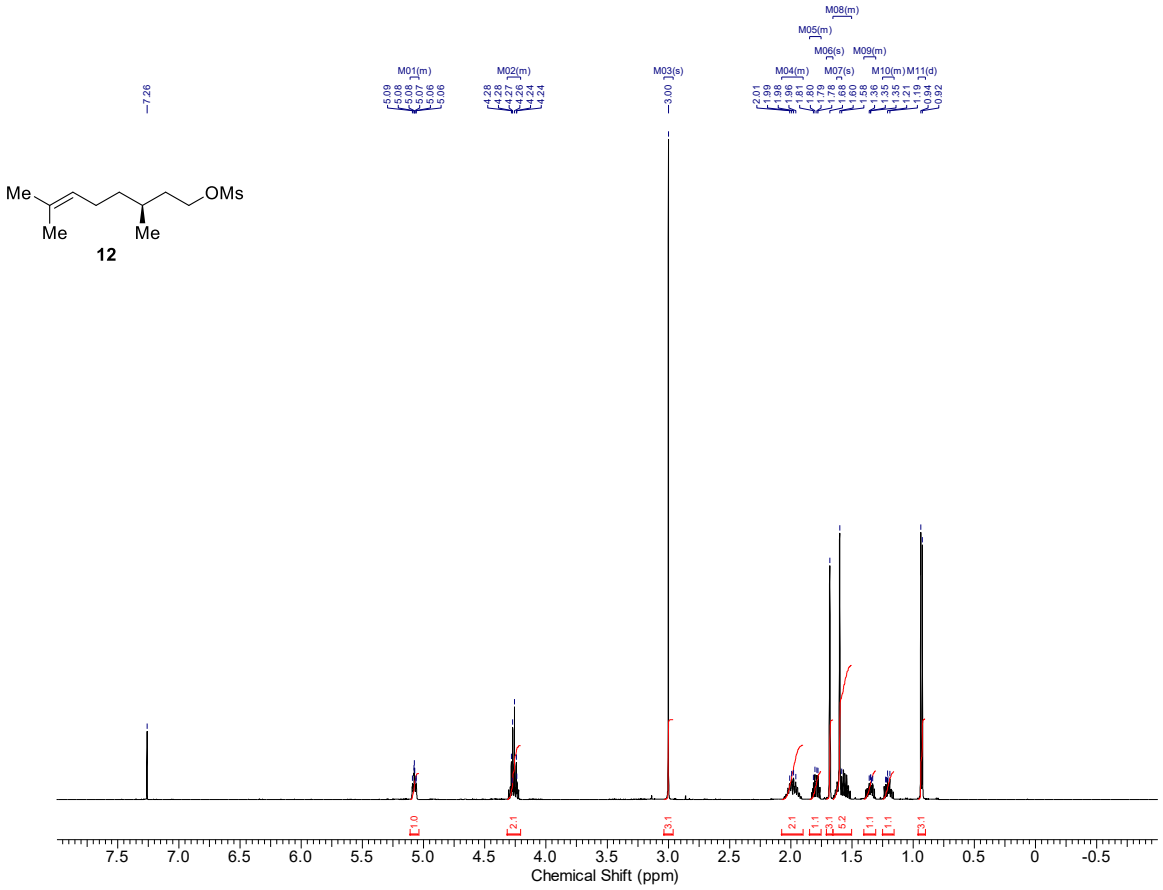

Chemical Shift (ppm)

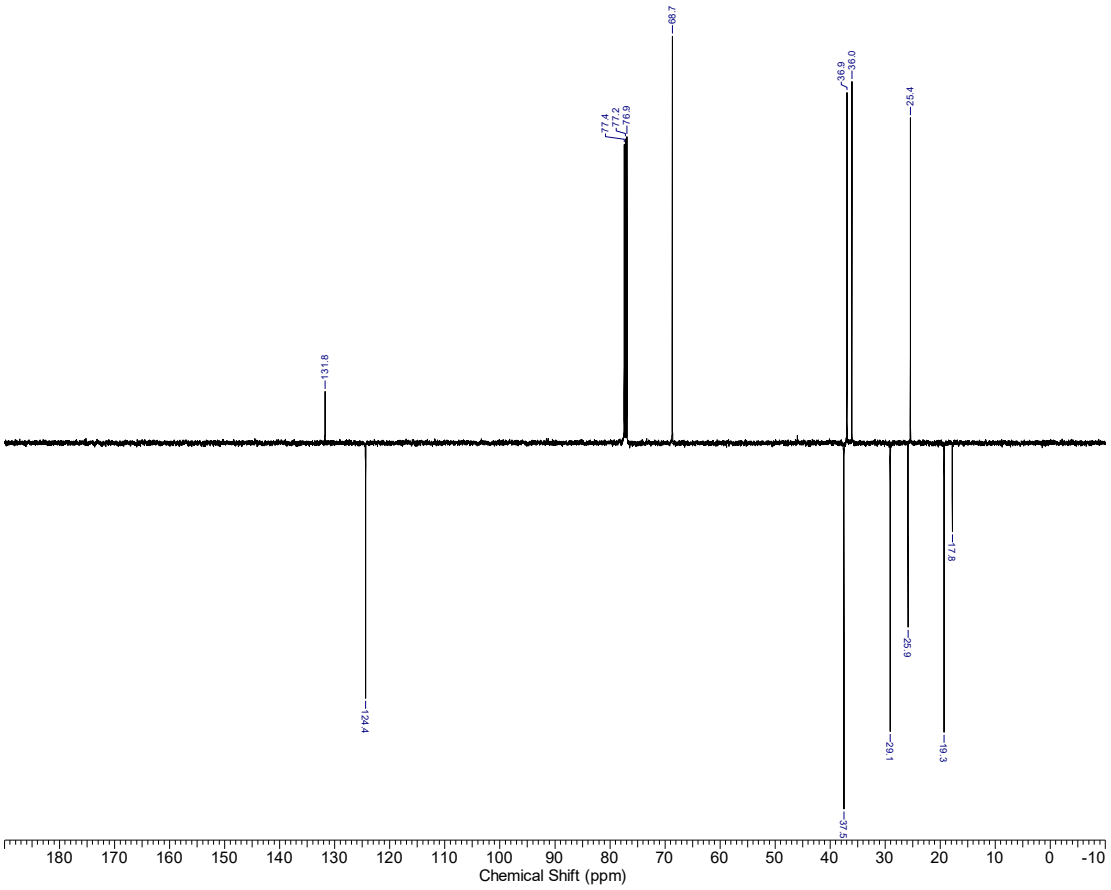

Keto/Enol = 2/3
Chemical Shift (ppm)

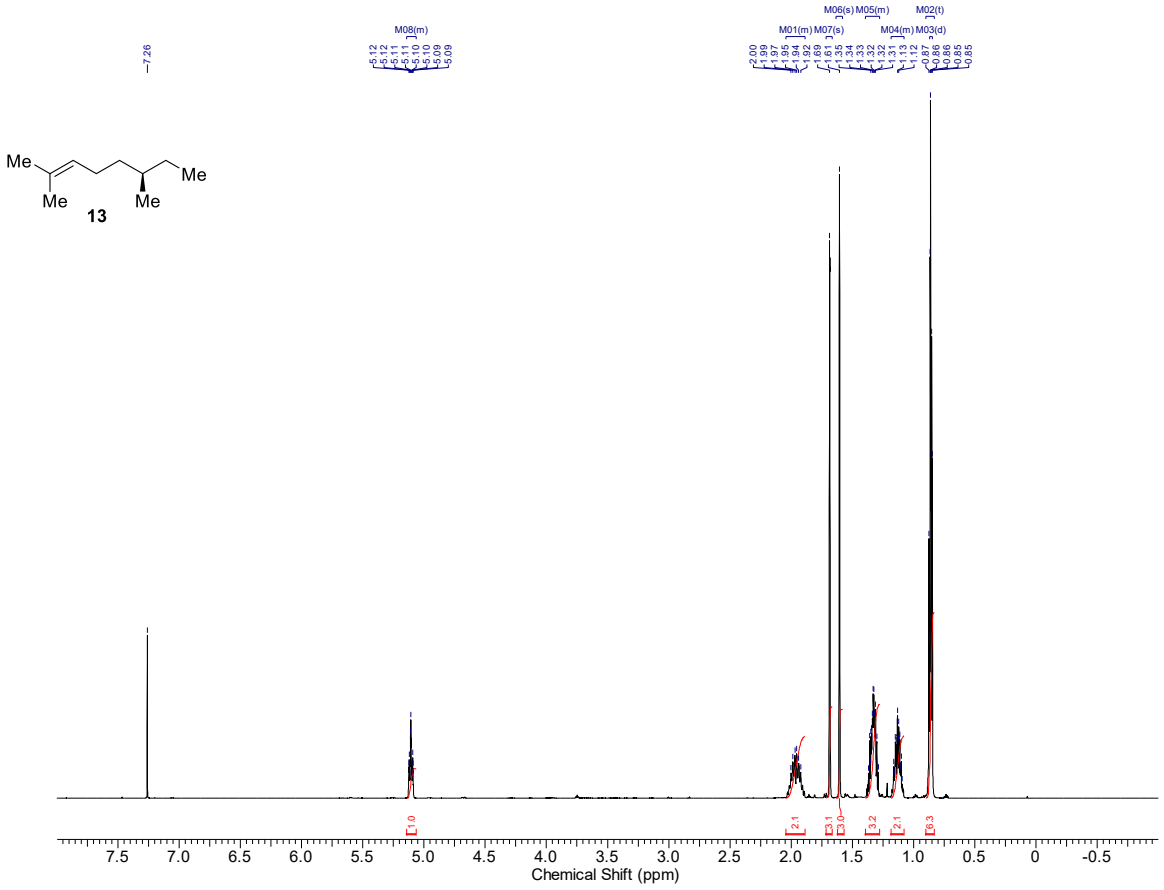

Chemical Shift (ppm)

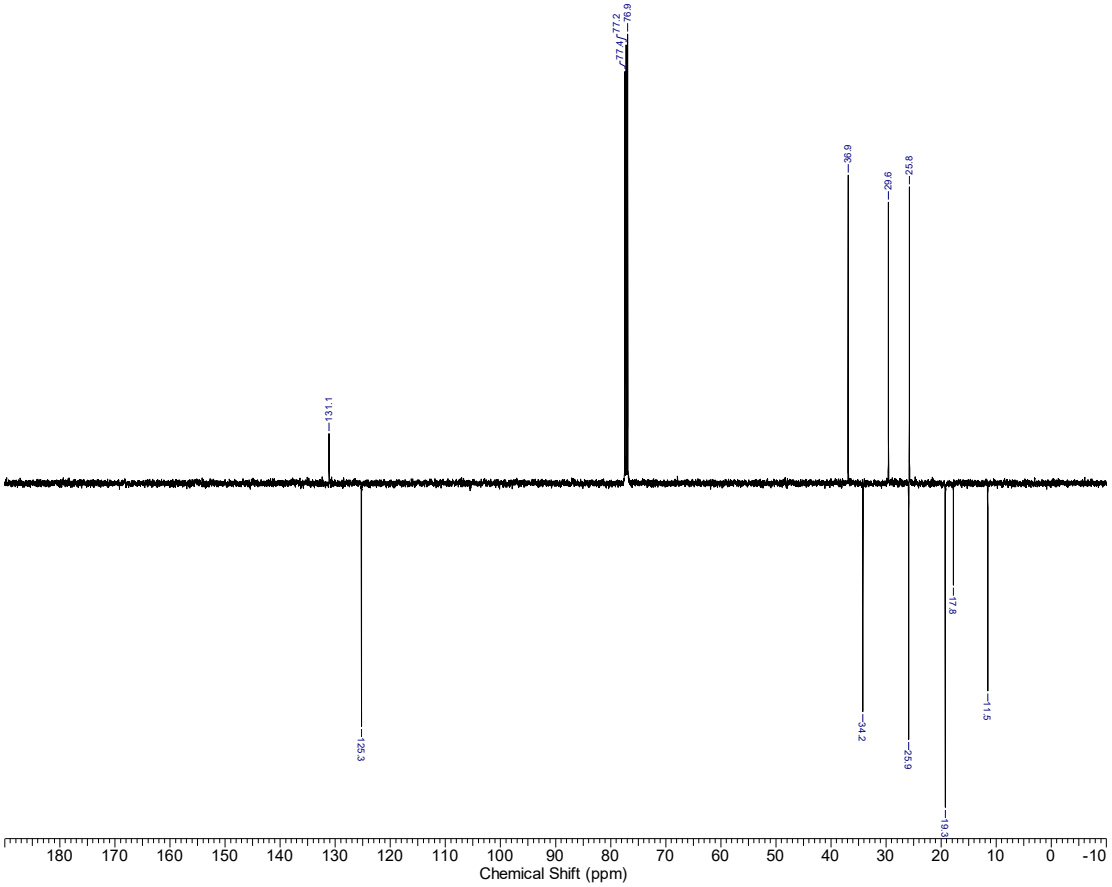

M02(s)
M03(dd)
M01(m)
M04(m)
M07(m)
M05(m)
M06(d)
OHC
Me
Me
Me
Me
10
Chemical Shift (ppm)

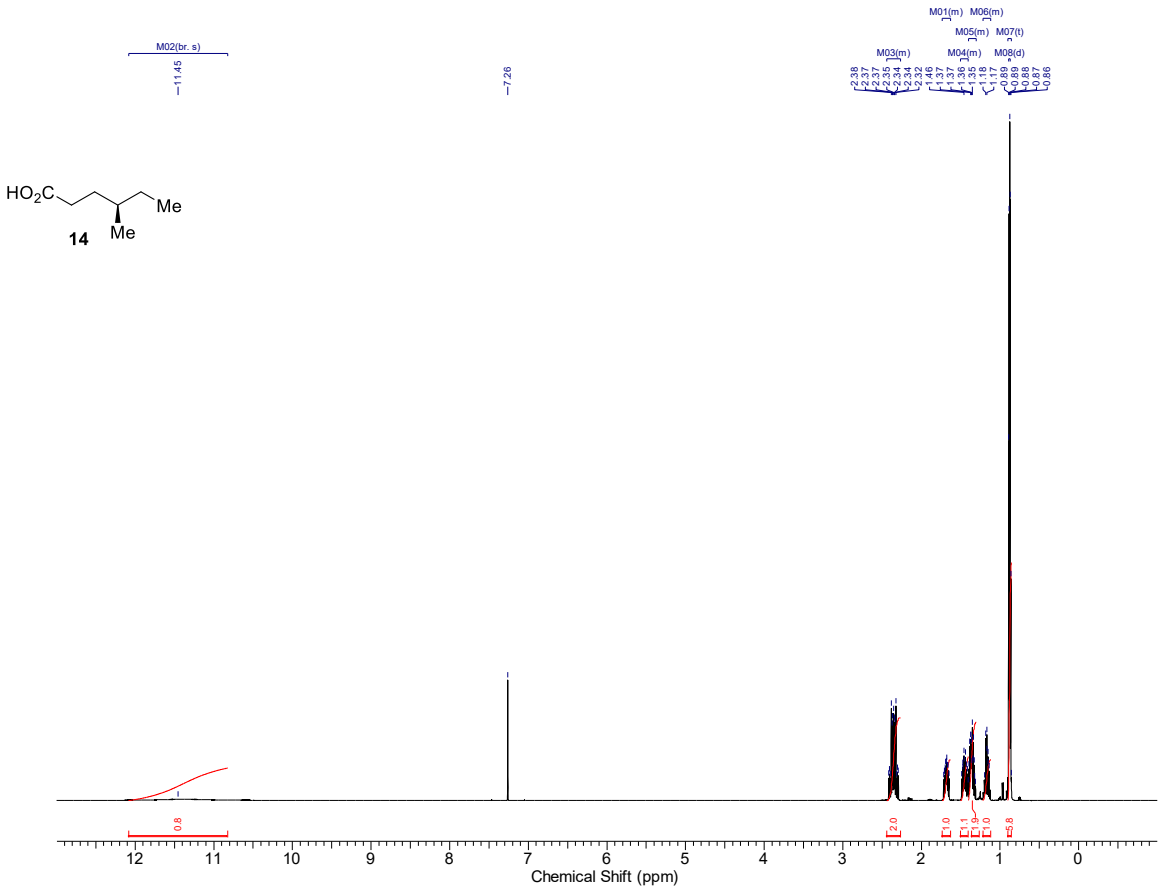

44.1
30.1
138.0
77.2
19.8
16.0
22.5
31.4
19.2
20.5
9.5
11.4
Chemical Shift (ppm)

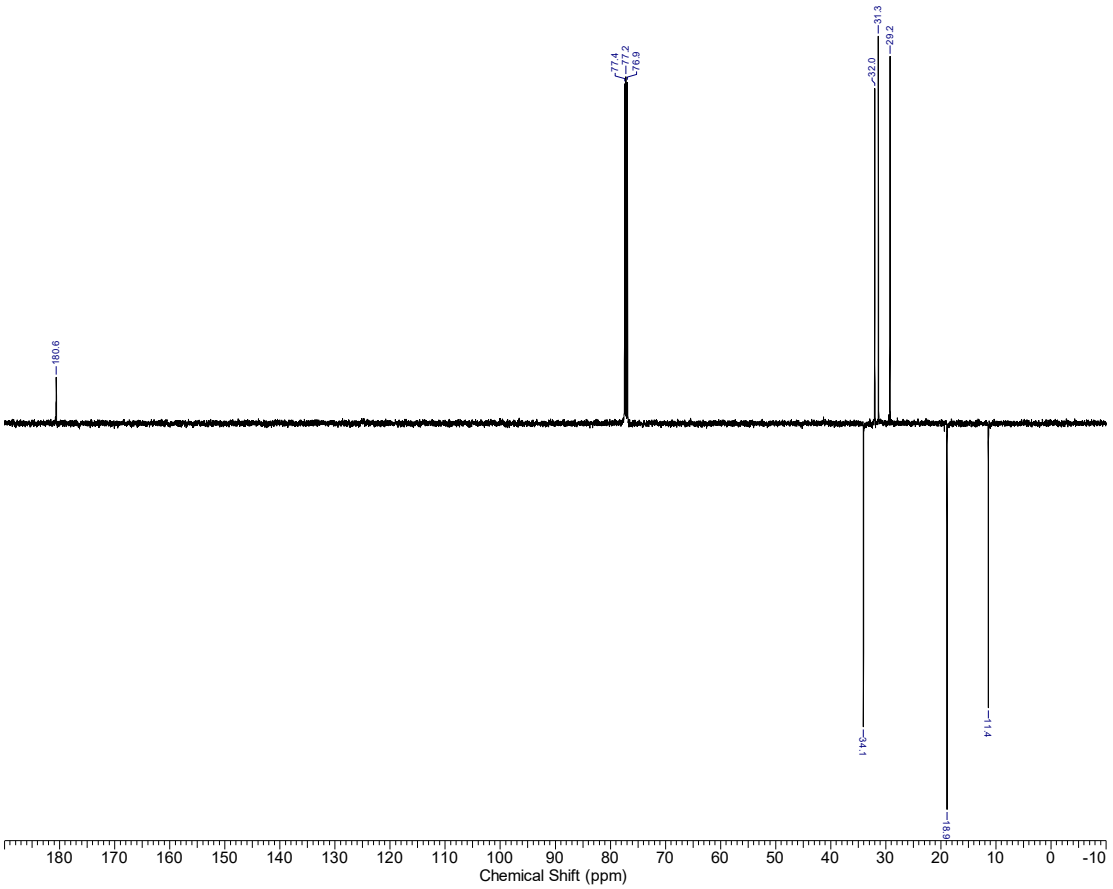

Me
OMs
Me
Me
12
Chemical Shift (ppm)

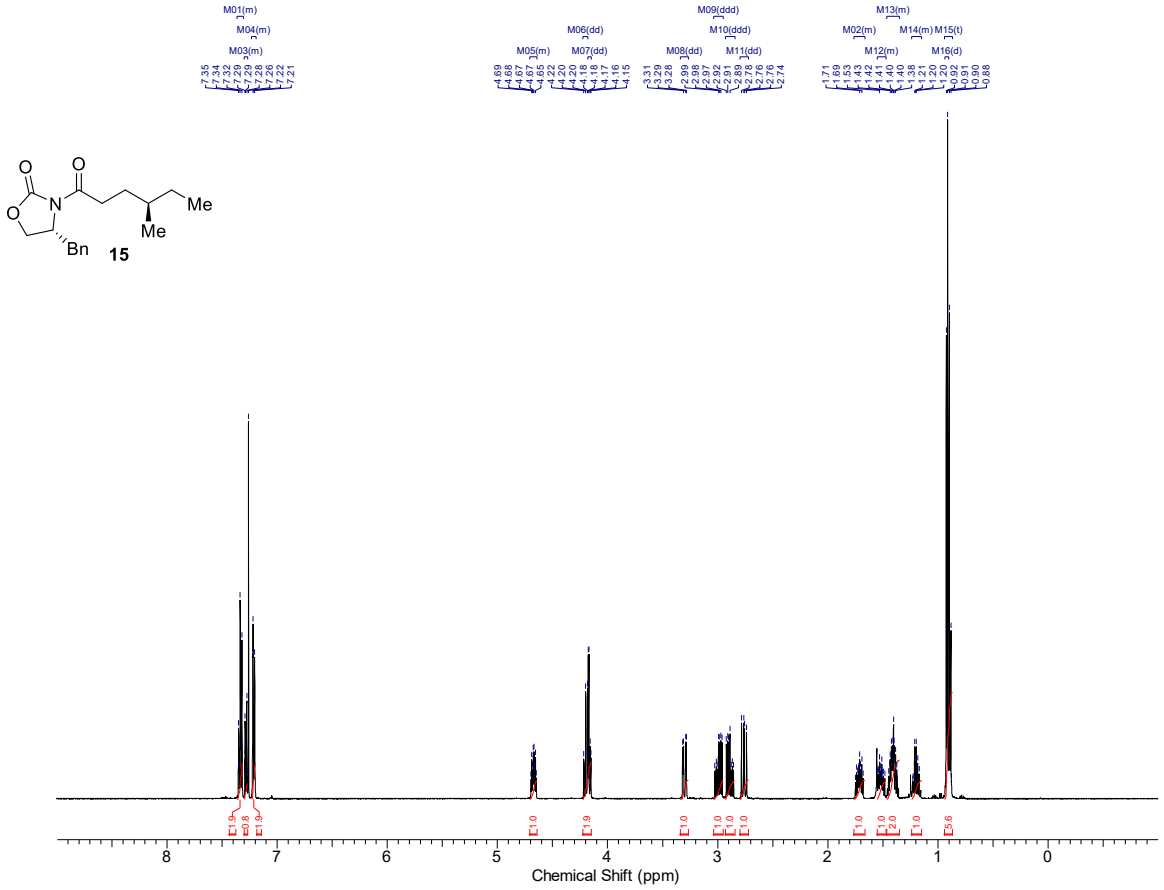

Chemical Shift (ppm)

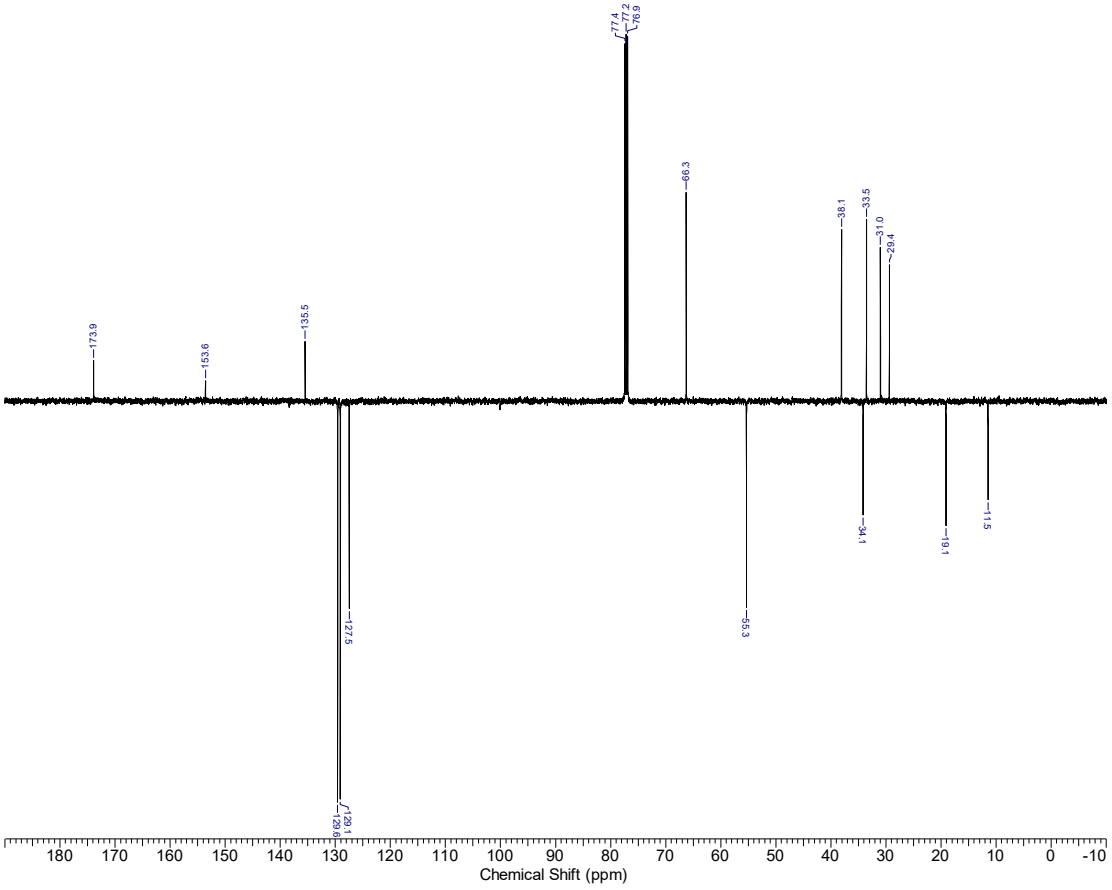

Me
Me
Me
Me
13
Chemical Shift (ppm)

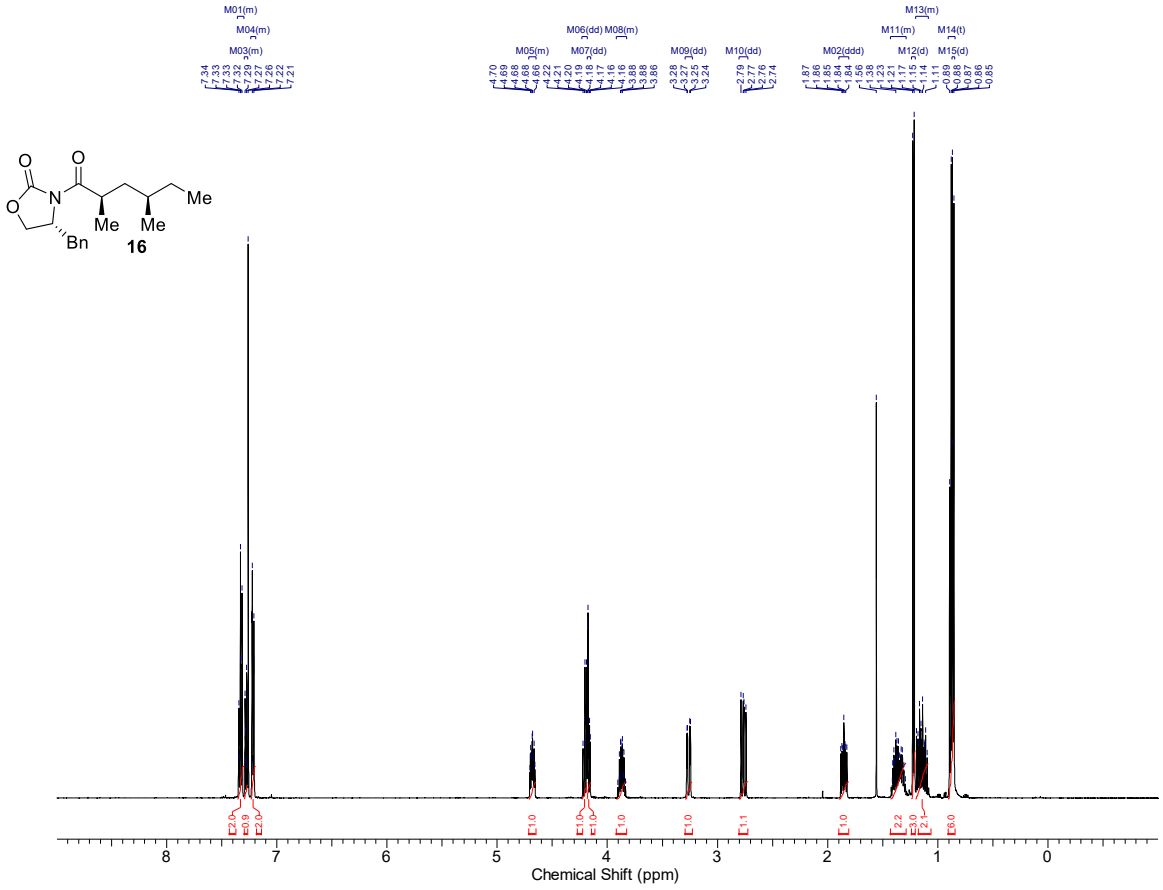

Chemical Shift (ppm)

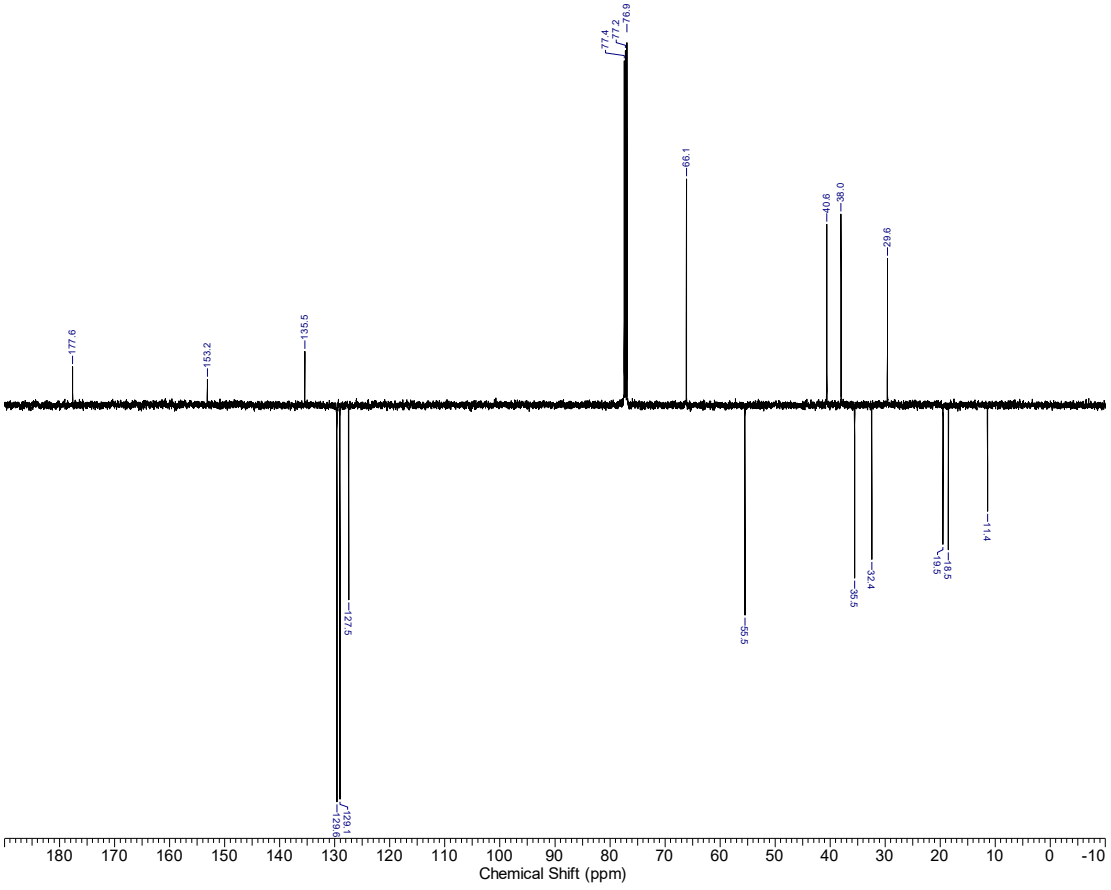

HO2C
Me
Me
14
M02(br. s)
11.45
7.26
M01(m)
M06(m)
M05(m)
M07(t)
M03(m)
M04(m)
M08(d)
2.38
2.37
2.37
2.35
2.34
2.34
2.32
1.46
1.37
1.37
1.36
1.35
1.18
1.17
0.89
0.89
0.88
0.87
0.86
0.8
2.0
1.0
1.1
0.9
1.0
5.8
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

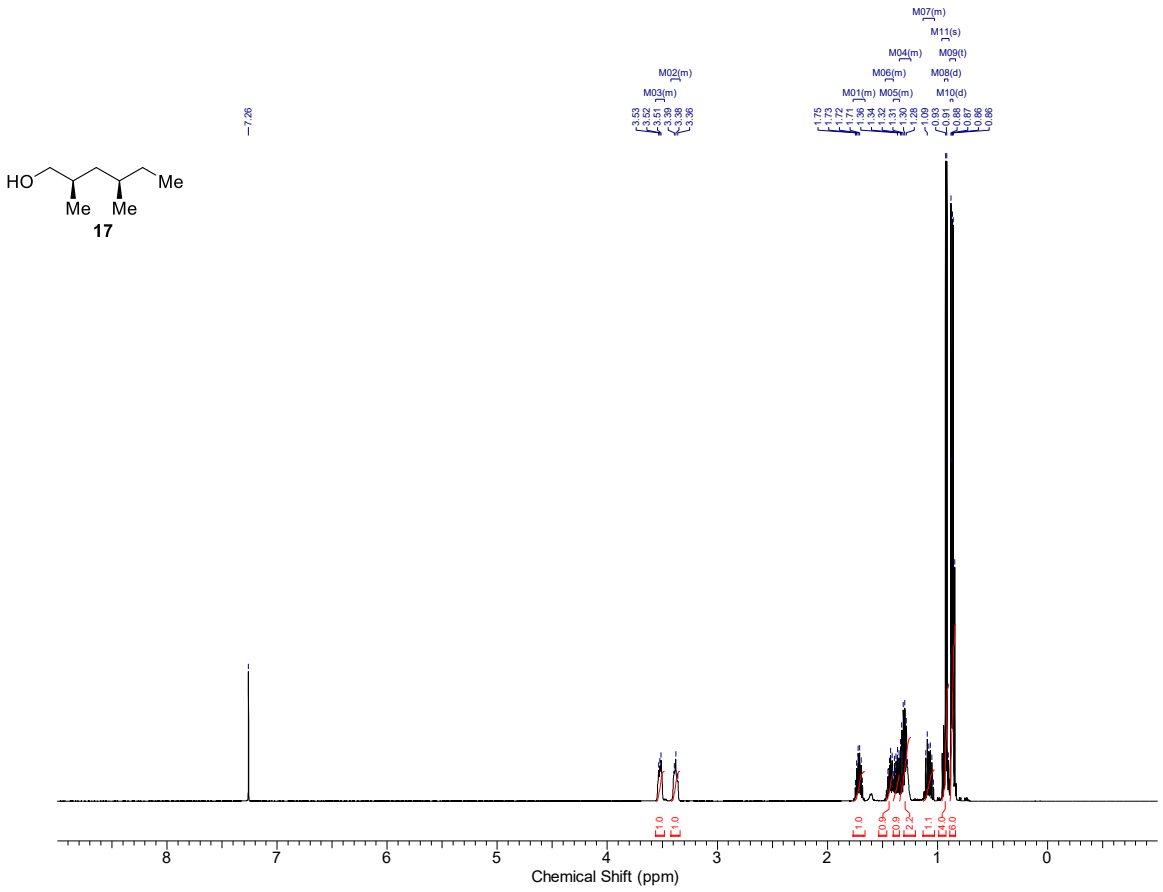

180.6
77.4
77.2
76.9
31.3
29.2
32.0
34.1
14.1
18.8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

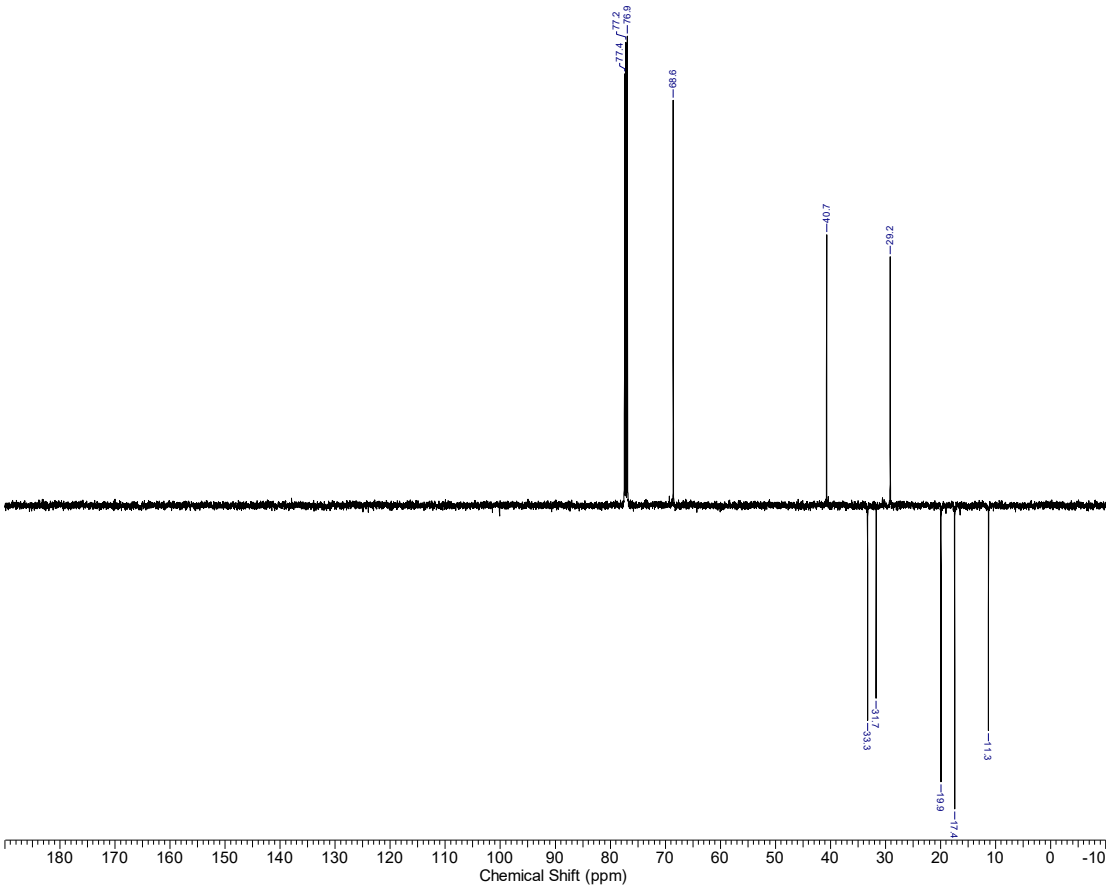

M01(m)
M04(m)
M03(m)
M06(dd)
M05(m)
M07(dd)
M09(ddd)
M10(ddd)
M08(dd)
M11(dd)
M13(m)
M02(m)
M14(m)
M15(t)
M12(m)
M16(d)
Me
Me
Bn
15
Chemical Shift (ppm)

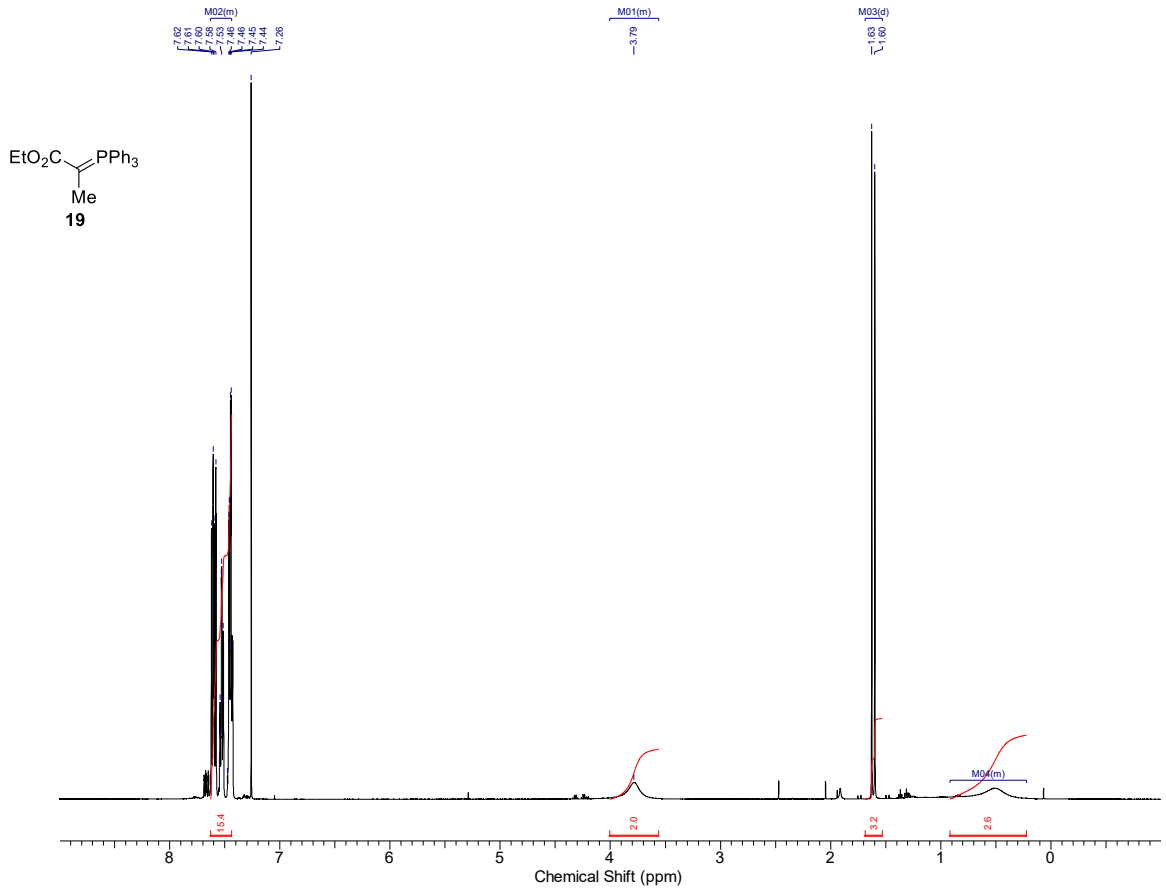

77.4
77.2
76.9
66.3
38.1
33.5
31.0
28.4
173.9
153.6
135.5
127.5
129.6
129.1
55.3
34.1
19.1
11.5
Chemical Shift (ppm)

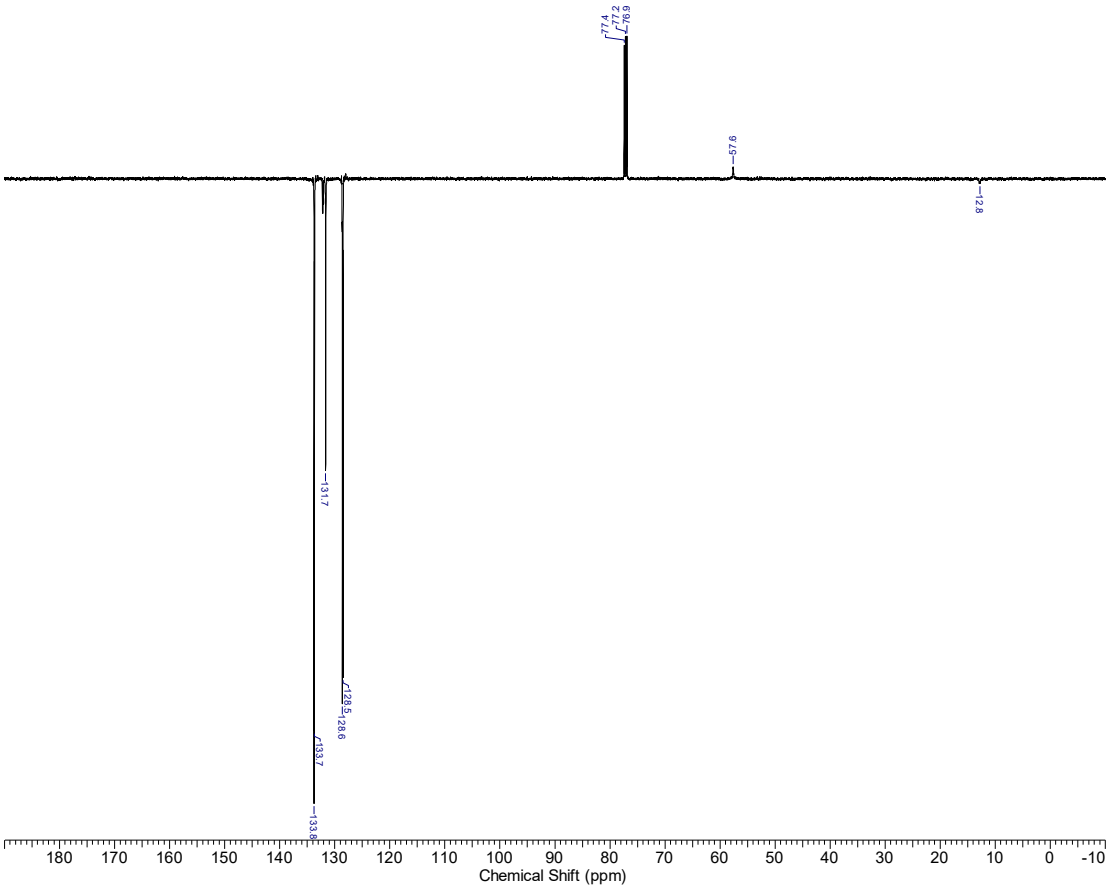

Me
Me
Me
Bn
16
Chemical Shift (ppm)

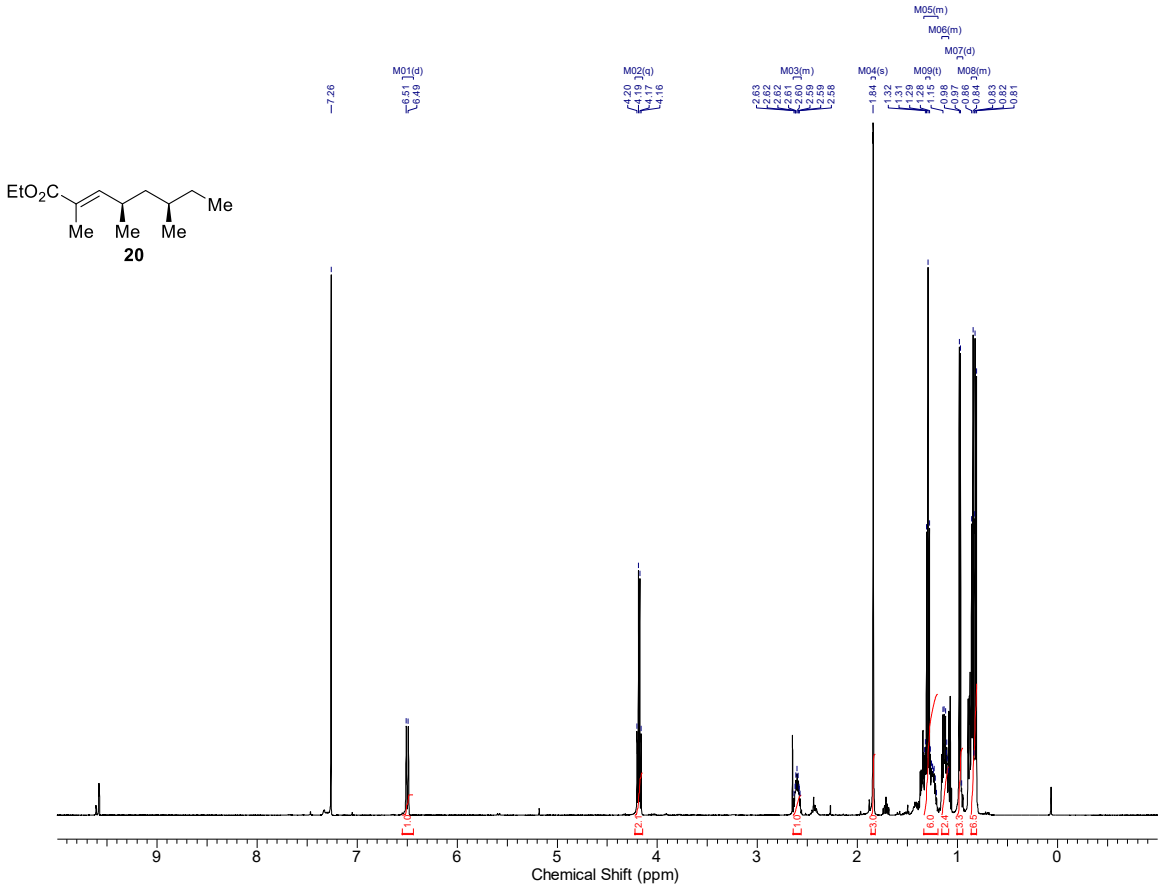

177.6
153.2
135.5
77.4
77.2
76.9
66.1
40.6
38.0
29.6
11.4
Chemical Shift (ppm)

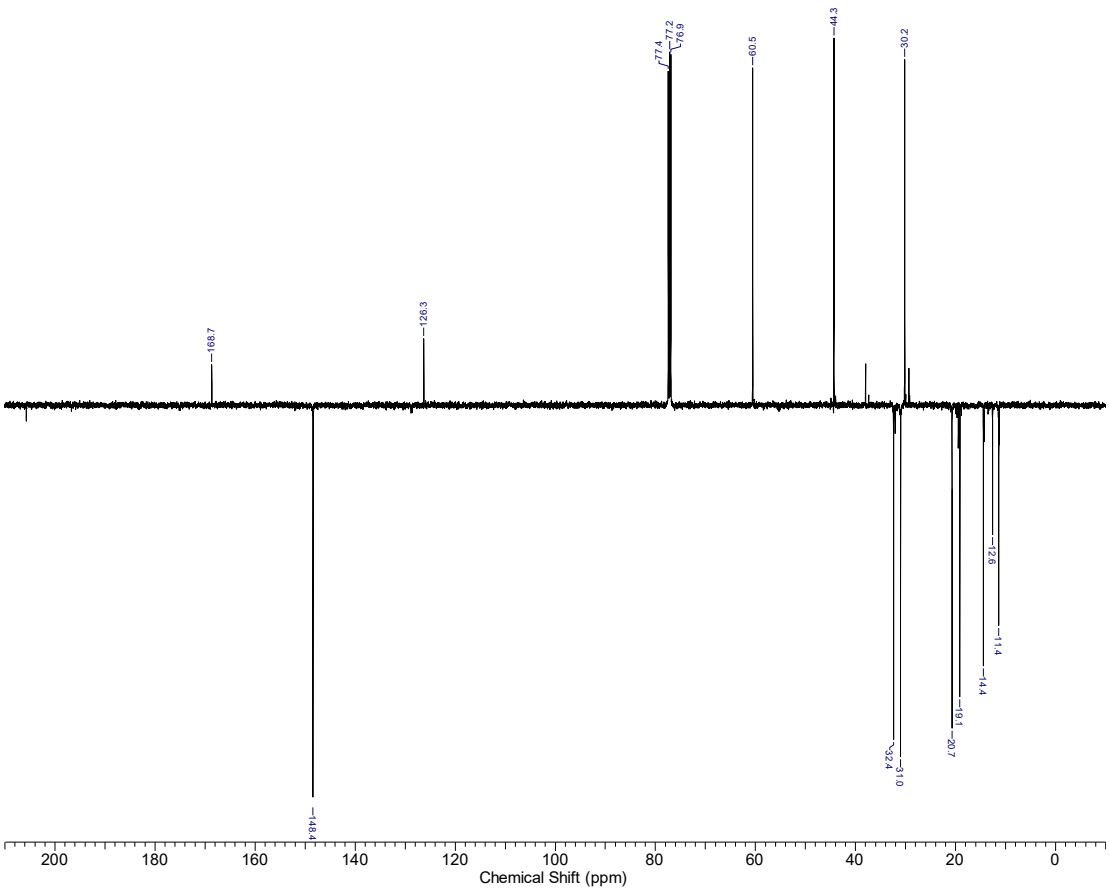

HO
Me
Me
Me
17
M07(m)
M11(s)
M04(m)
M09(t)
M02(m)
M06(m)
M08(d)
M03(m)
M01(m)
M05(m)
M10(d)
7.26
3.53
3.52
3.51
3.39
3.38
3.38
1.75
1.73
1.72
1.71
1.34
1.32
1.31
1.30
1.28
1.09
0.93
0.91
0.89
0.87
0.86
0.86
1.0
1.0
1.0
0.9
0.9
2.2
1.1
1.0
6.0
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

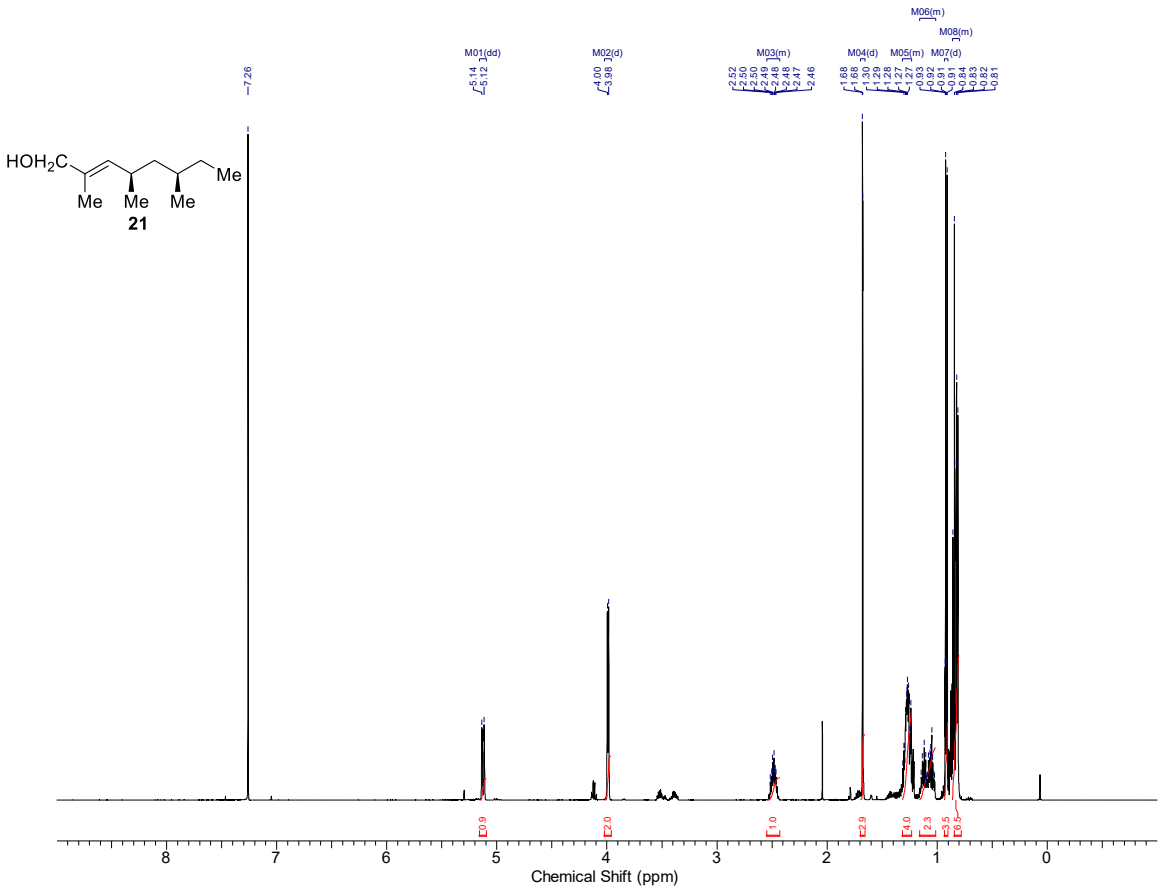

77.2
76.9
77.4
68.6
40.7
29.2
19.6
17.4
11.3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

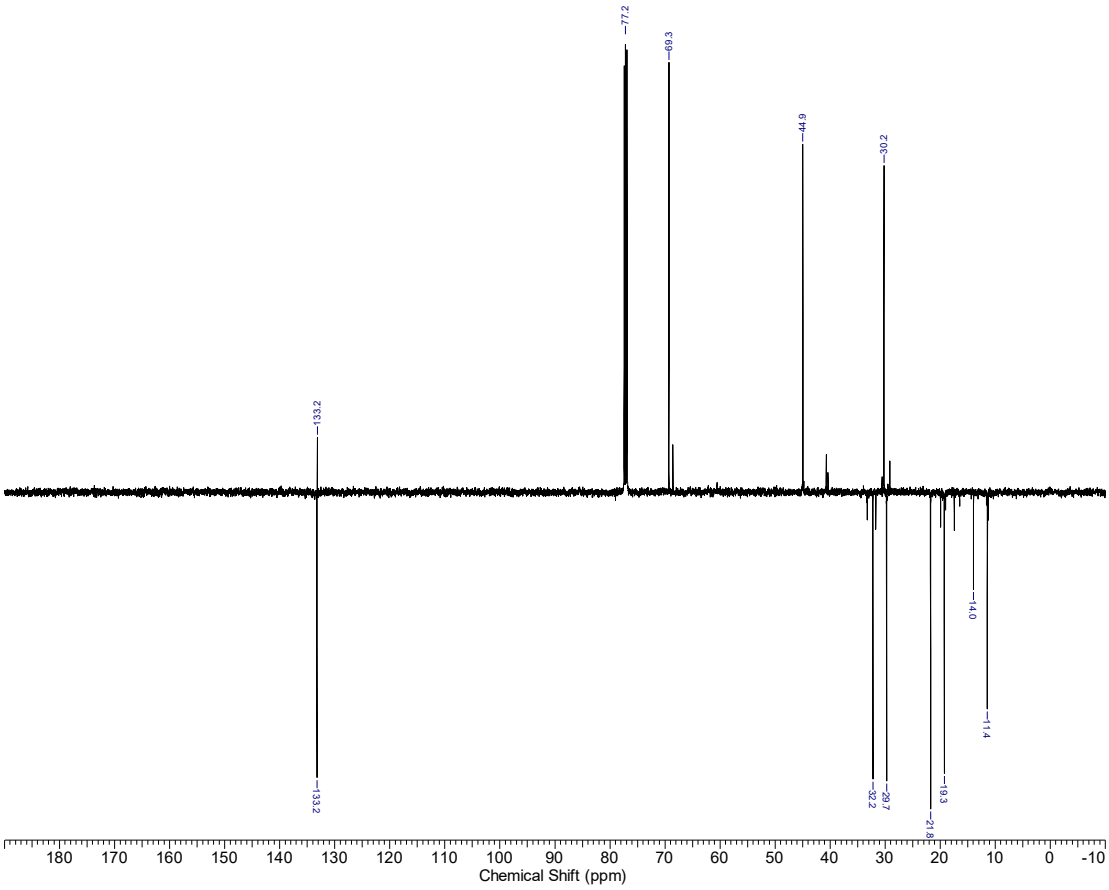

EtO2C
PPh3
Me
19
M02(m)
M01(m)
M03(d)
M04(m)
15.4
2.0
3.2
2.6
Chemical Shift (ppm)

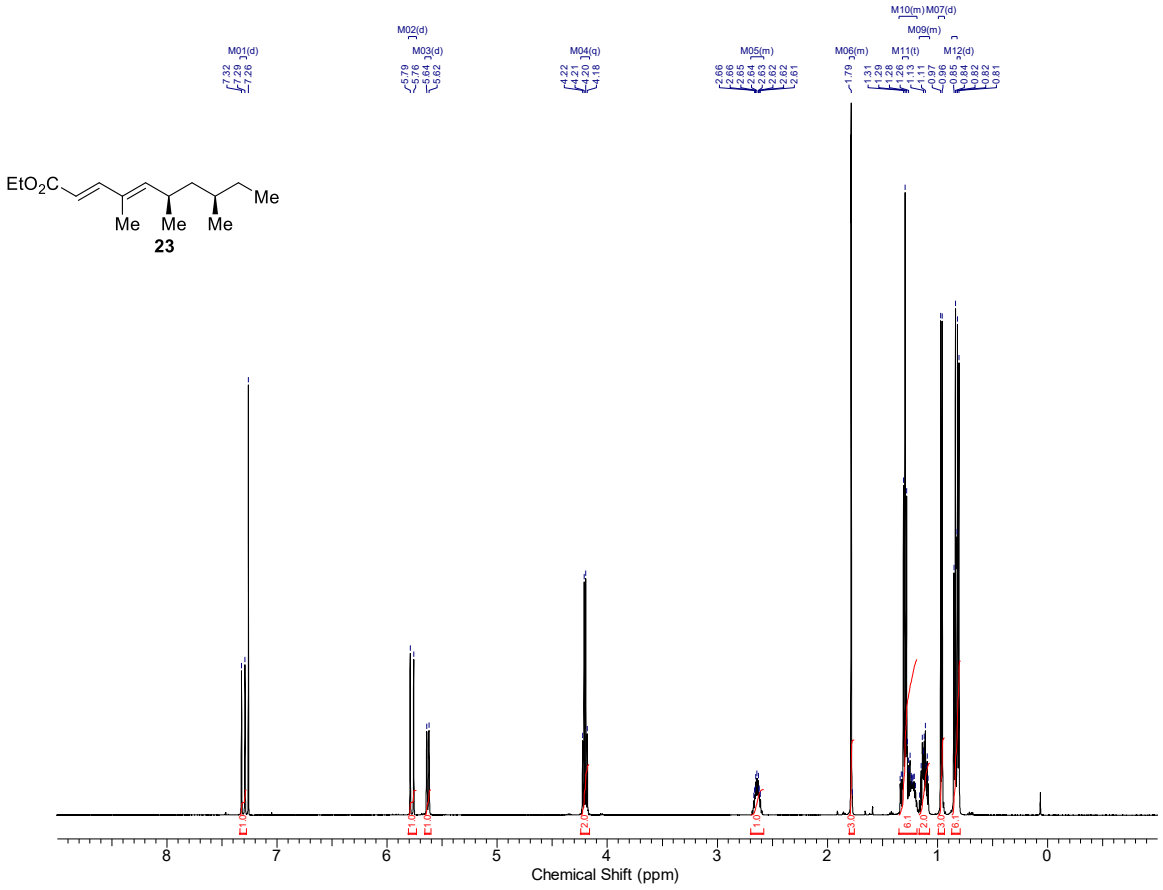

77.4
77.2
76.9
57.6
12.8
131.7
133.7
133.6
129.5
128.6
Chemical Shift (ppm)

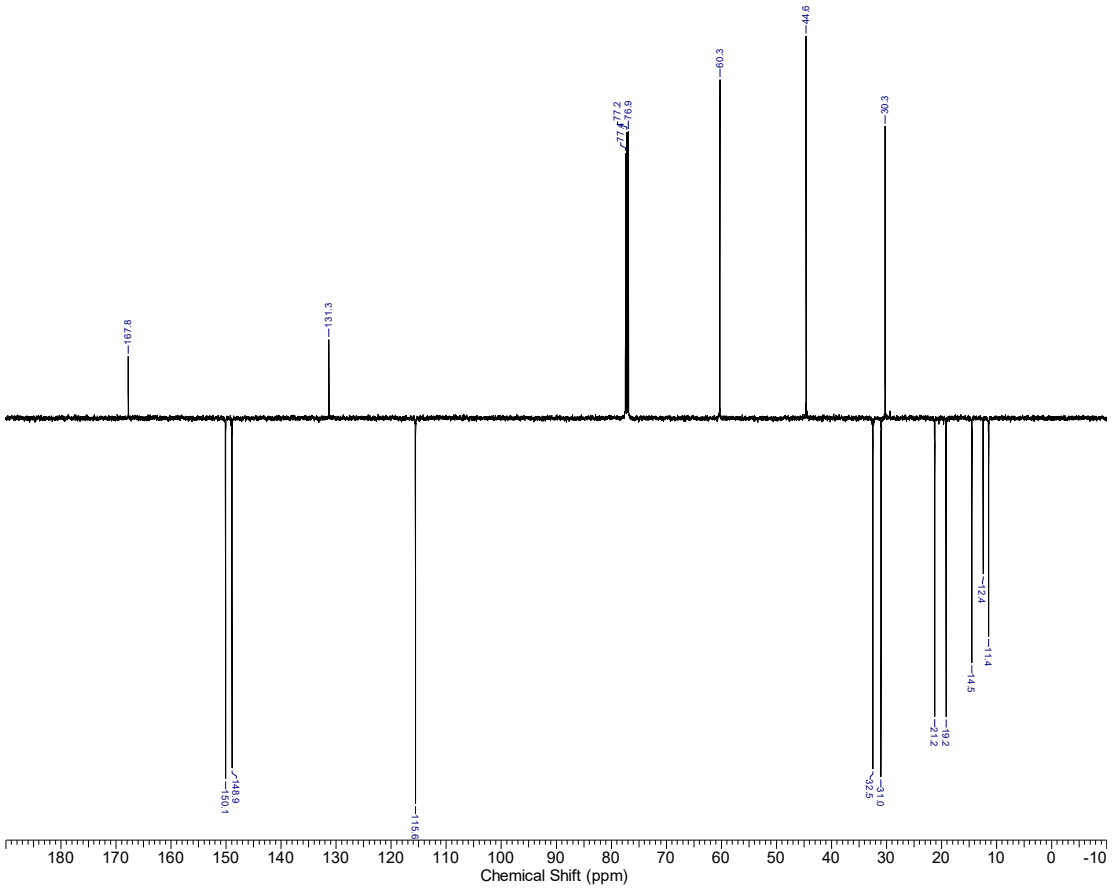

EtO2C
Me
Me
Me
Me
20
M01(d)
M02(q)
M03(m)
M04(s)
M05(m)
M06(m)
M07(d)
M08(m)
M09(t)
Chemical Shift (ppm)

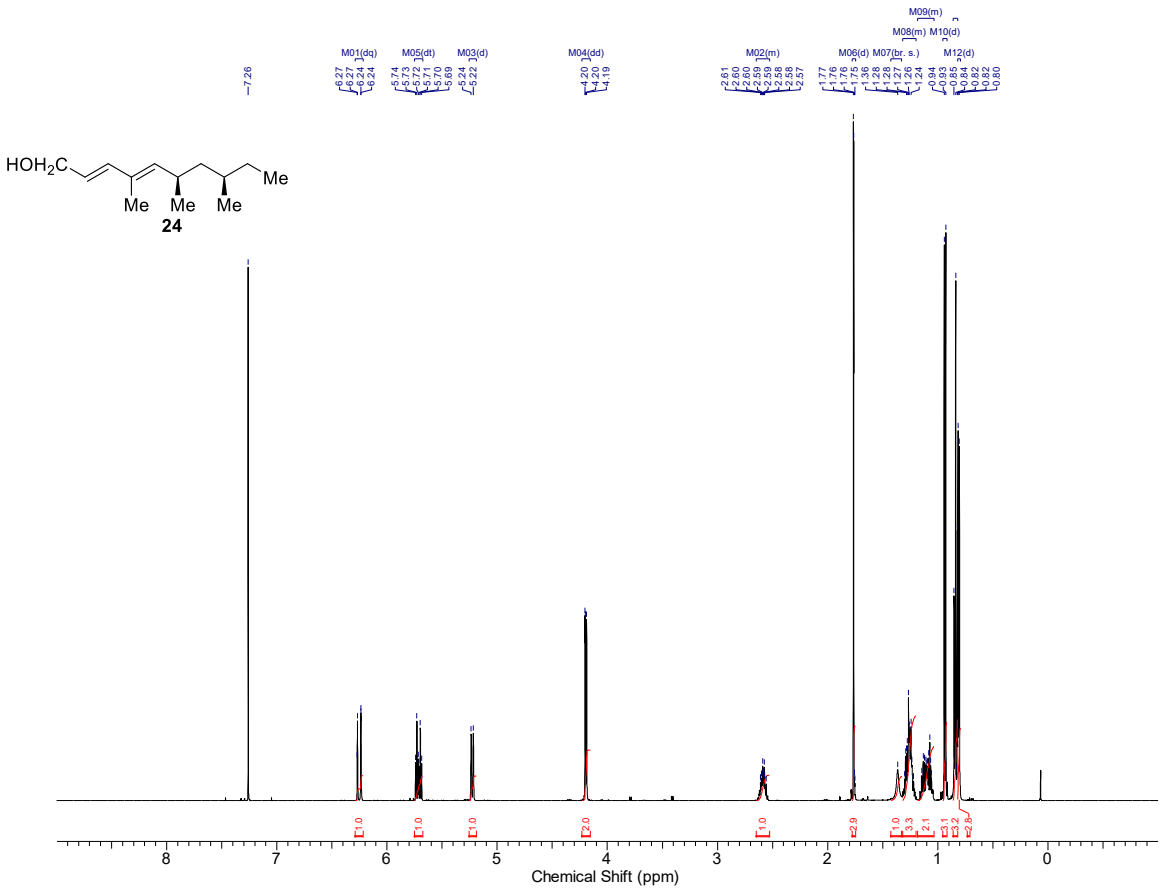

168.7
126.3
77.4
77.2
76.9
60.5
44.3
30.2
148.4
31.0
27.4
20.7
19.1
14.4
12.6
11.4
Chemical Shift (ppm)

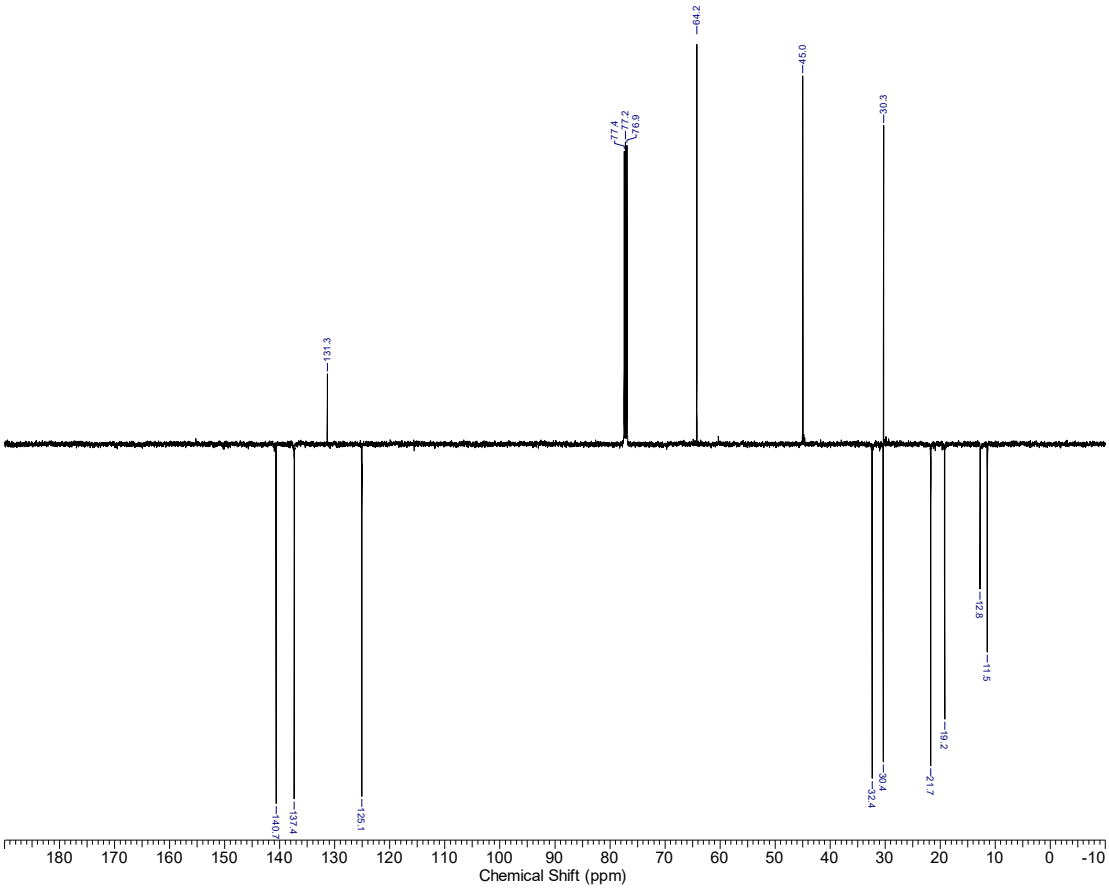

HOH2C
Me
Me
Me
Me
21
Chemical Shift (ppm)

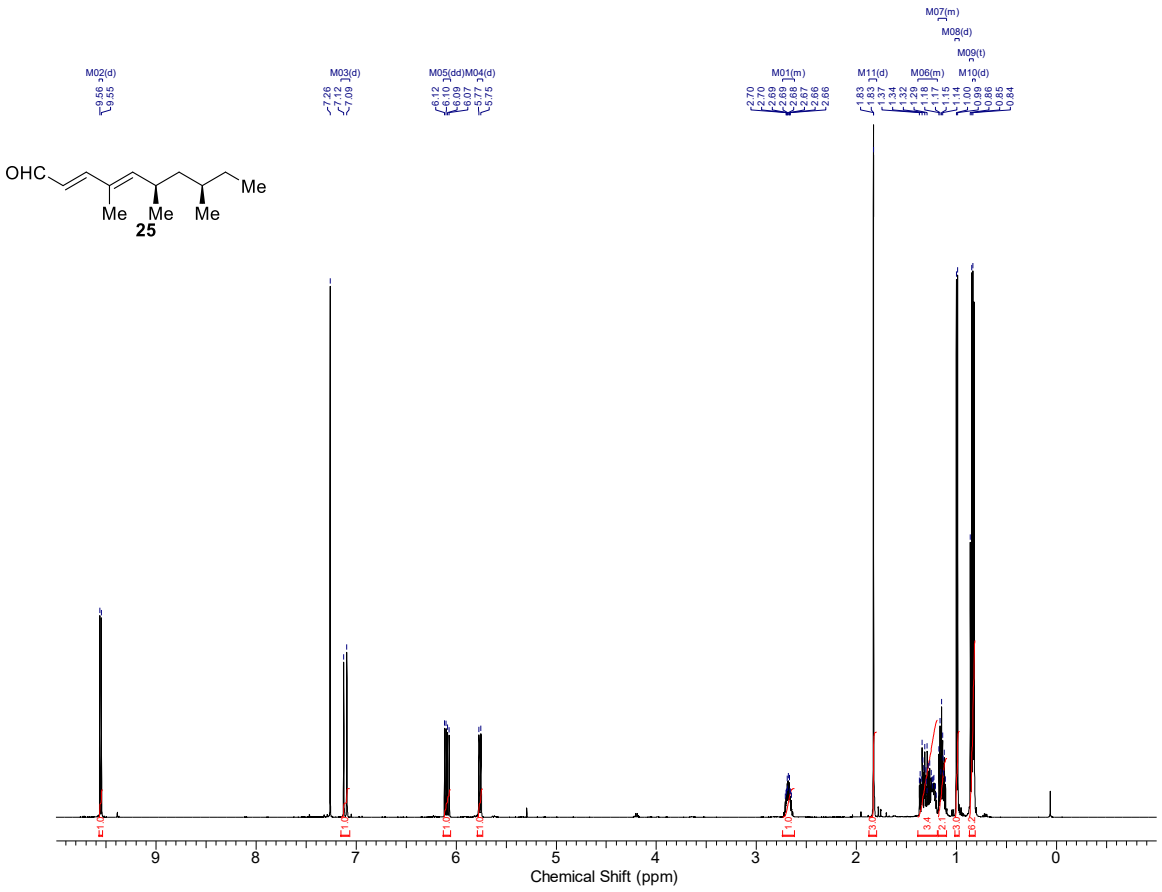

Chemical Shift (ppm)

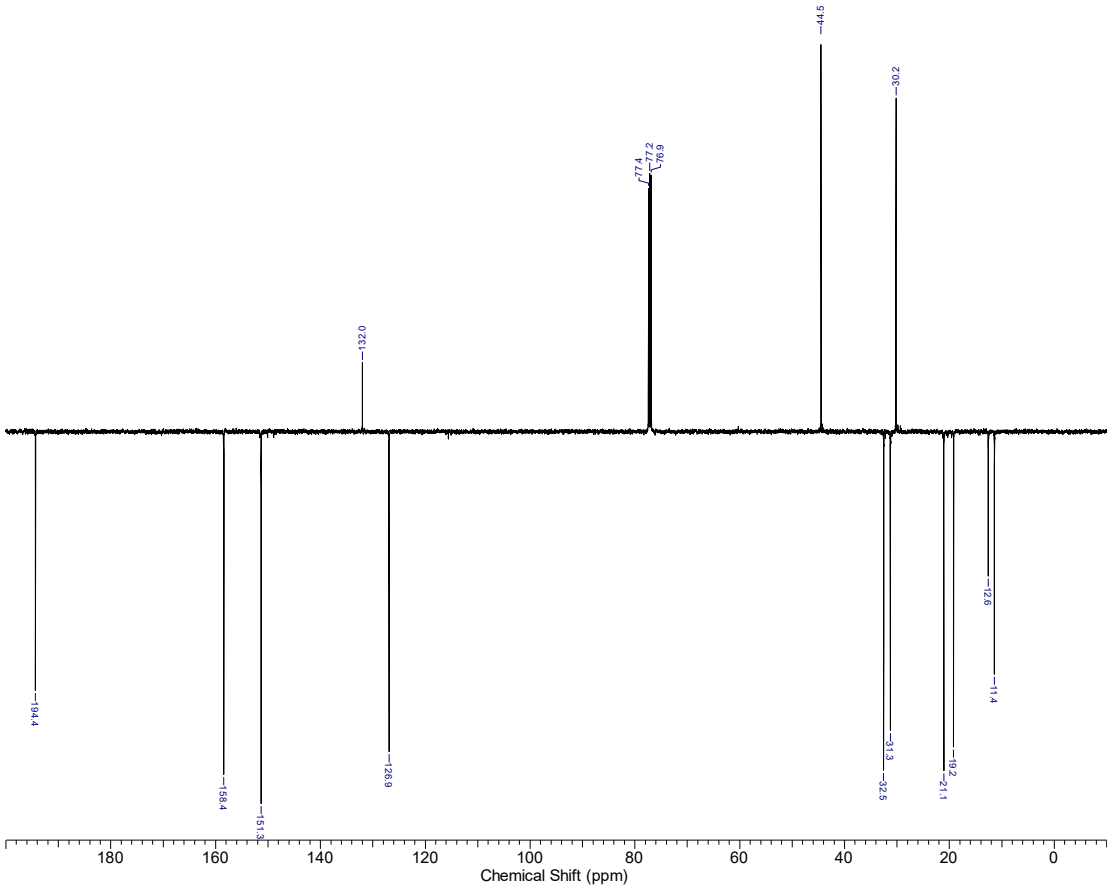

EtO2C
Me
Me
Me
Me
23
Chemical Shift (ppm)

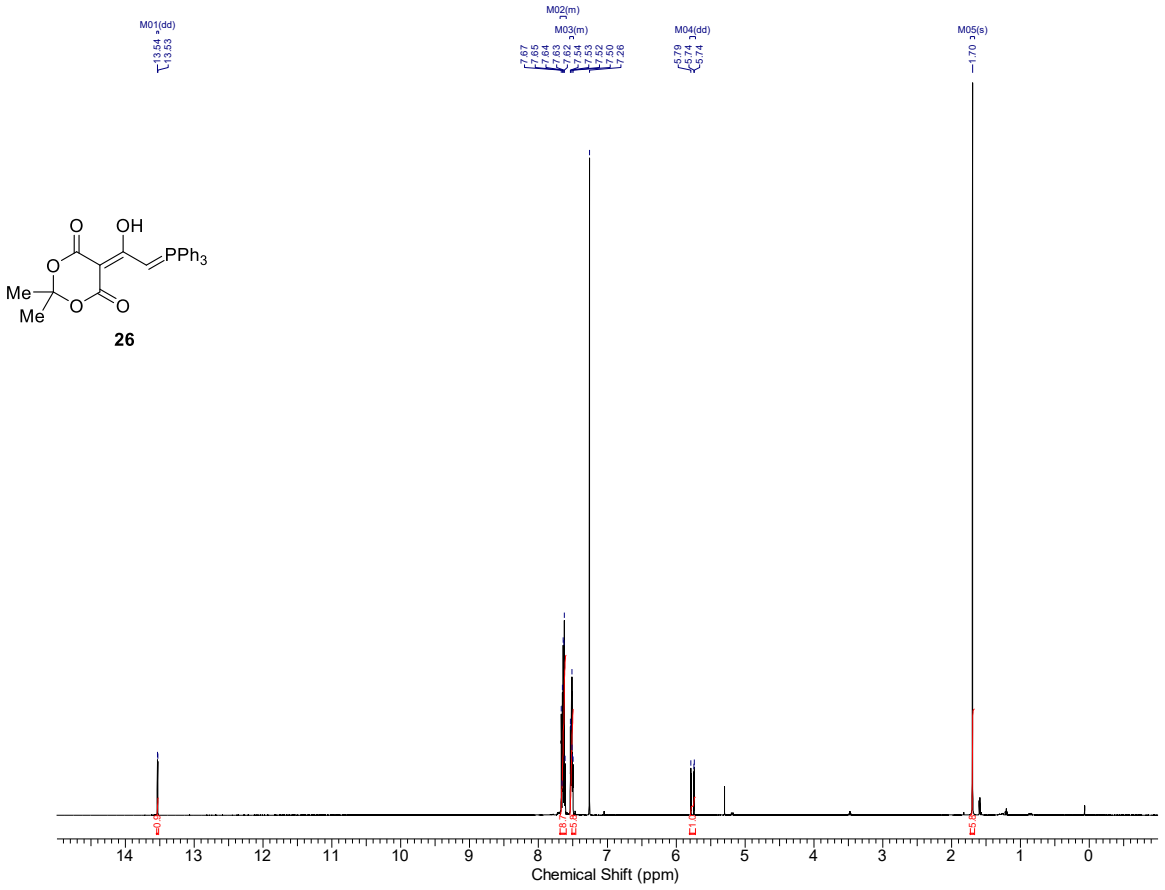

Chemical Shift (ppm)

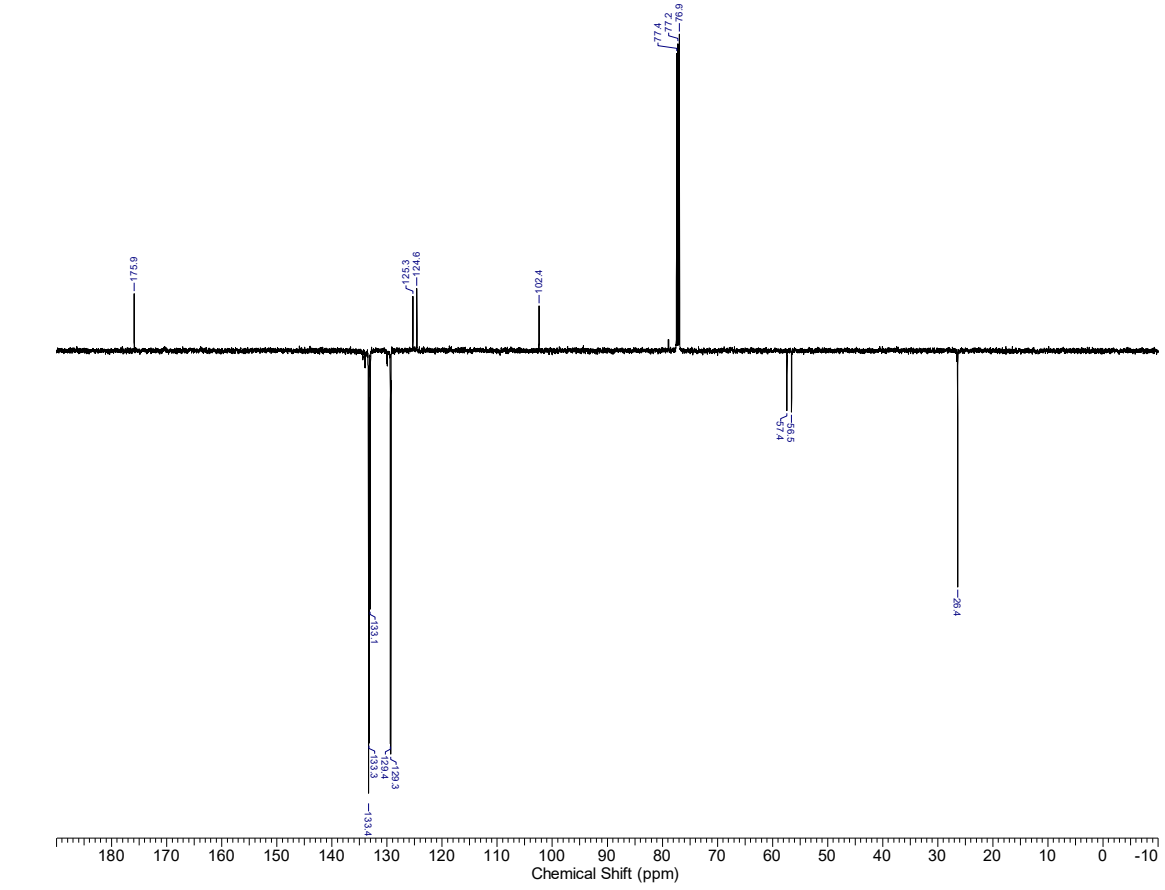

HOH2C
Me
Me
Me
Me
24
Chemical Shift (ppm)


Chemical Shift (ppm)

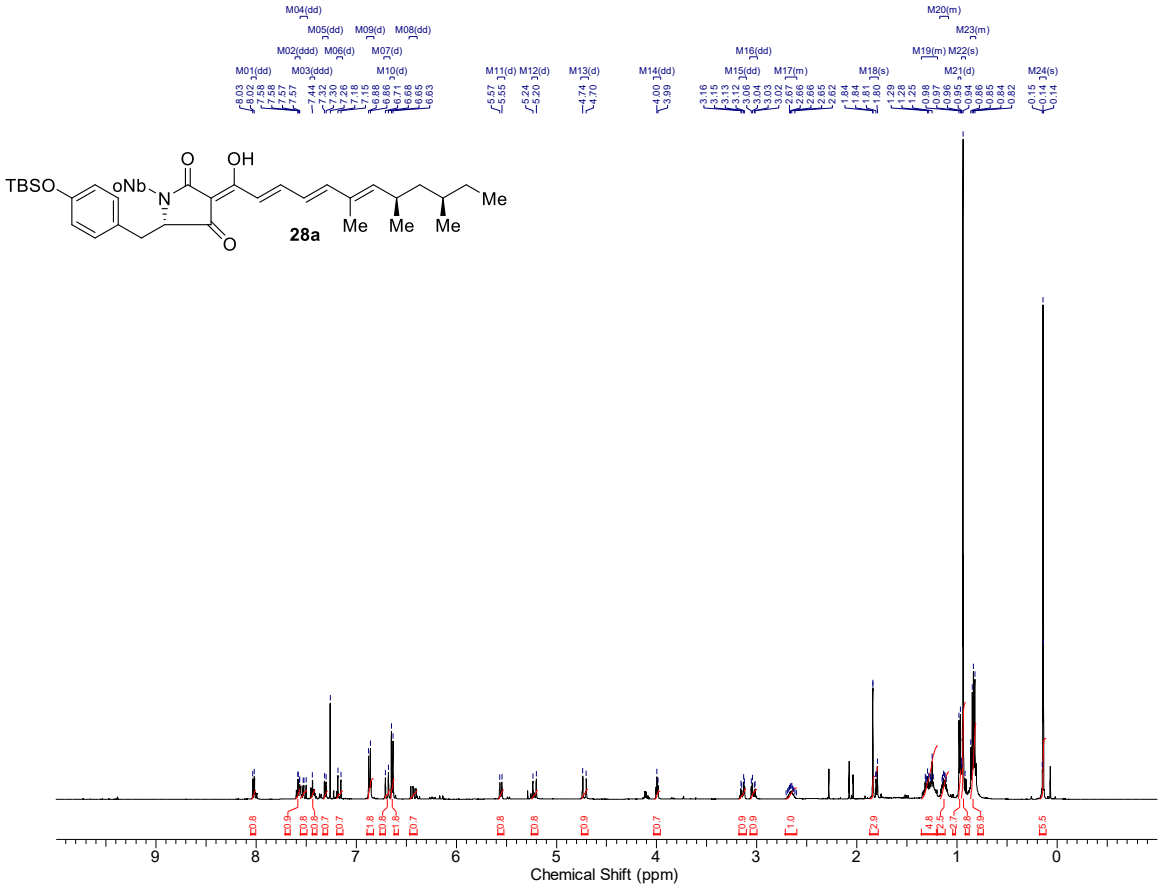

OHC
Me
Me
Me
Me
25
Chemical Shift (ppm)

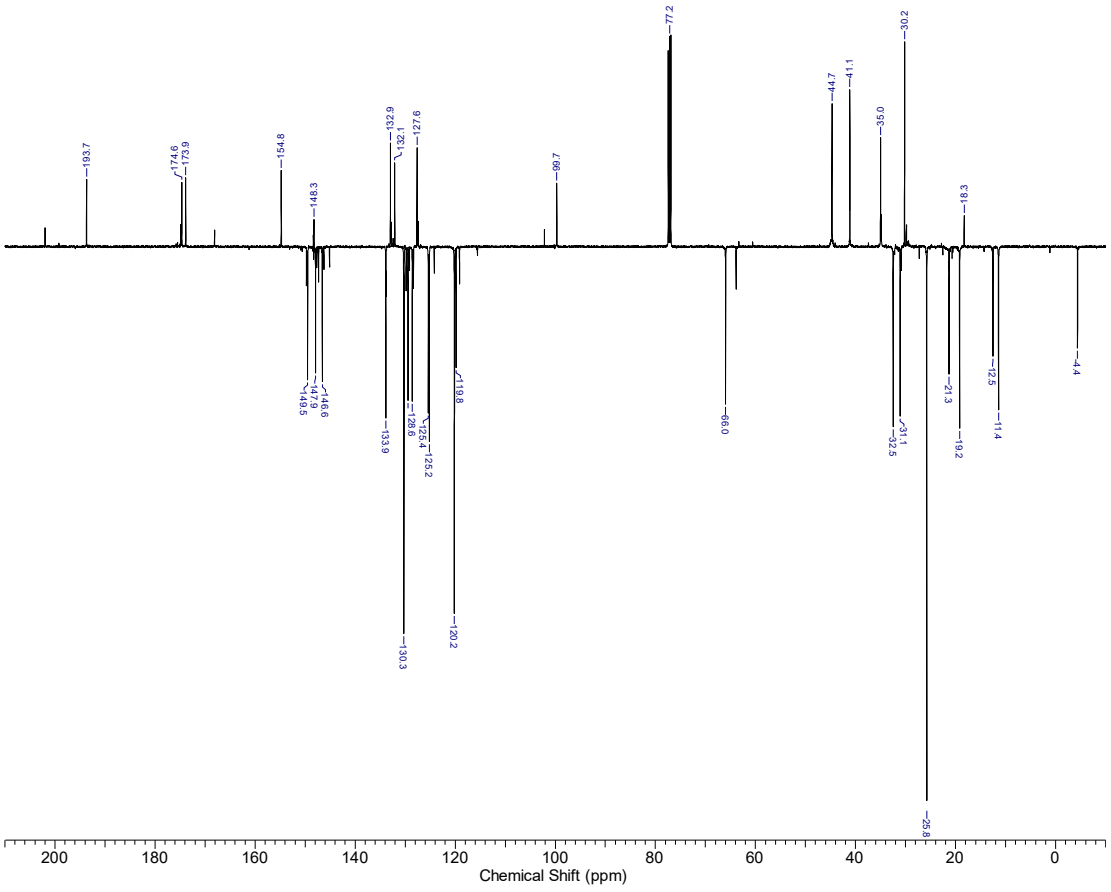

Chemical Shift (ppm)

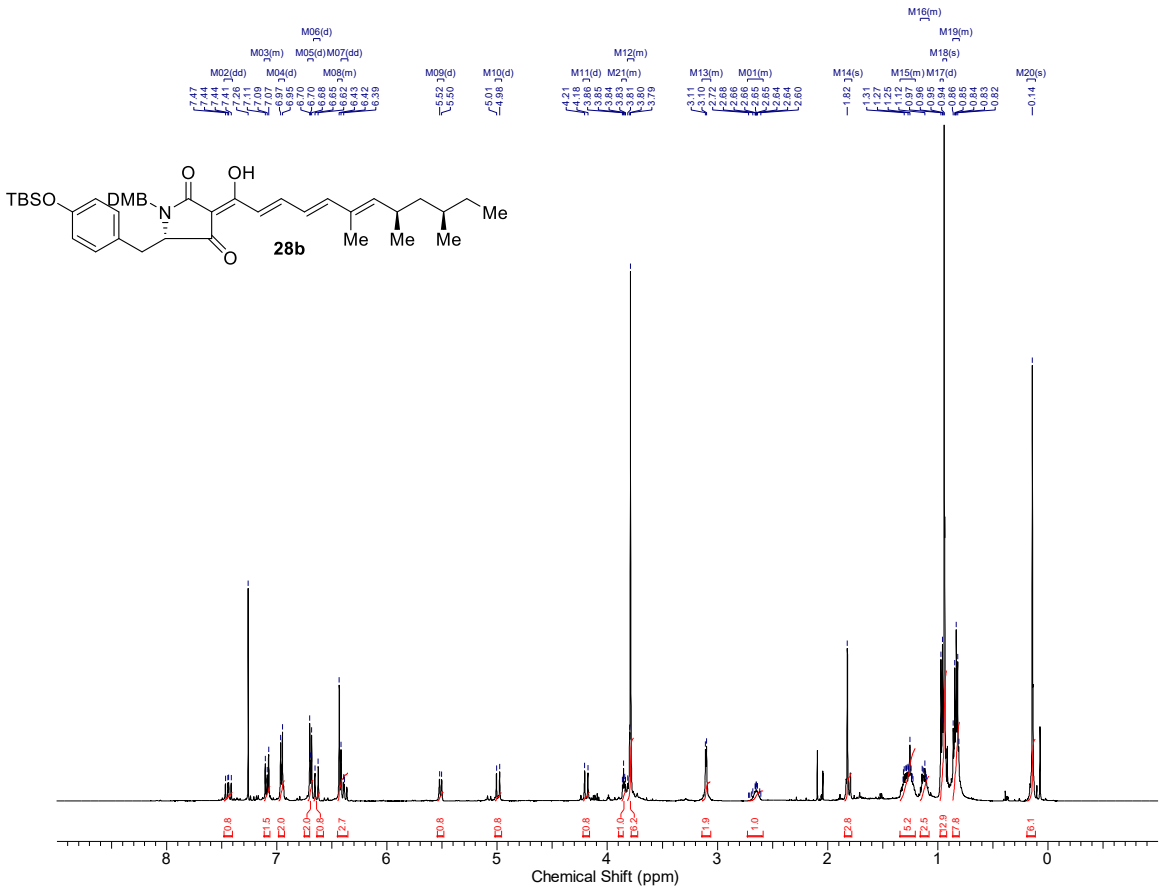

M01(dd)
13.54
13.53
M02(m)
M03(m)
7.67
7.65
7.64
7.63
7.62
7.54
7.53
7.52
7.50
7.26
M04(dd)
5.79
5.74
5.71
3.74
M05(s)
1.70
OH
PPh3
Me
Me
O
O
O
O
O
26
Chemical Shift (ppm)

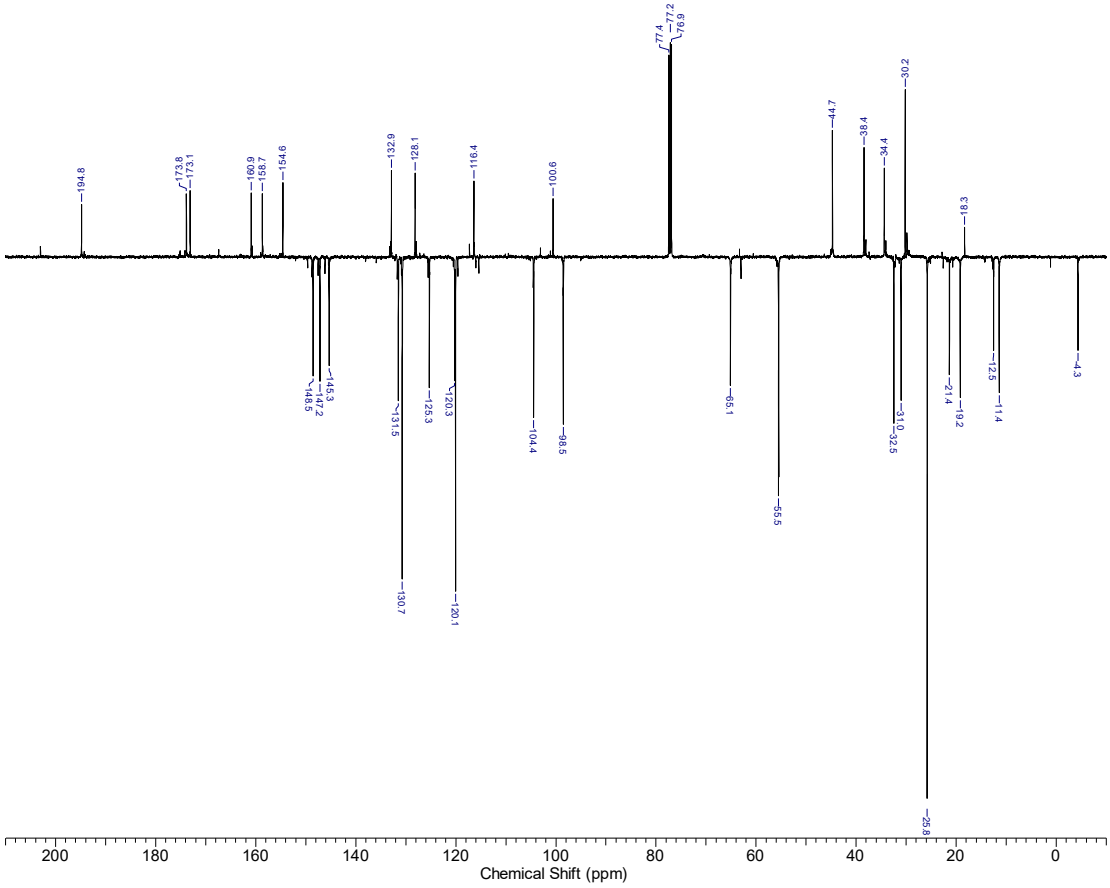

175.9
125.3
124.6
102.4
77.4
77.2
76.9
57.4
56.5
133.1
133.4
129.4
129.3
26.4
Chemical Shift (ppm)

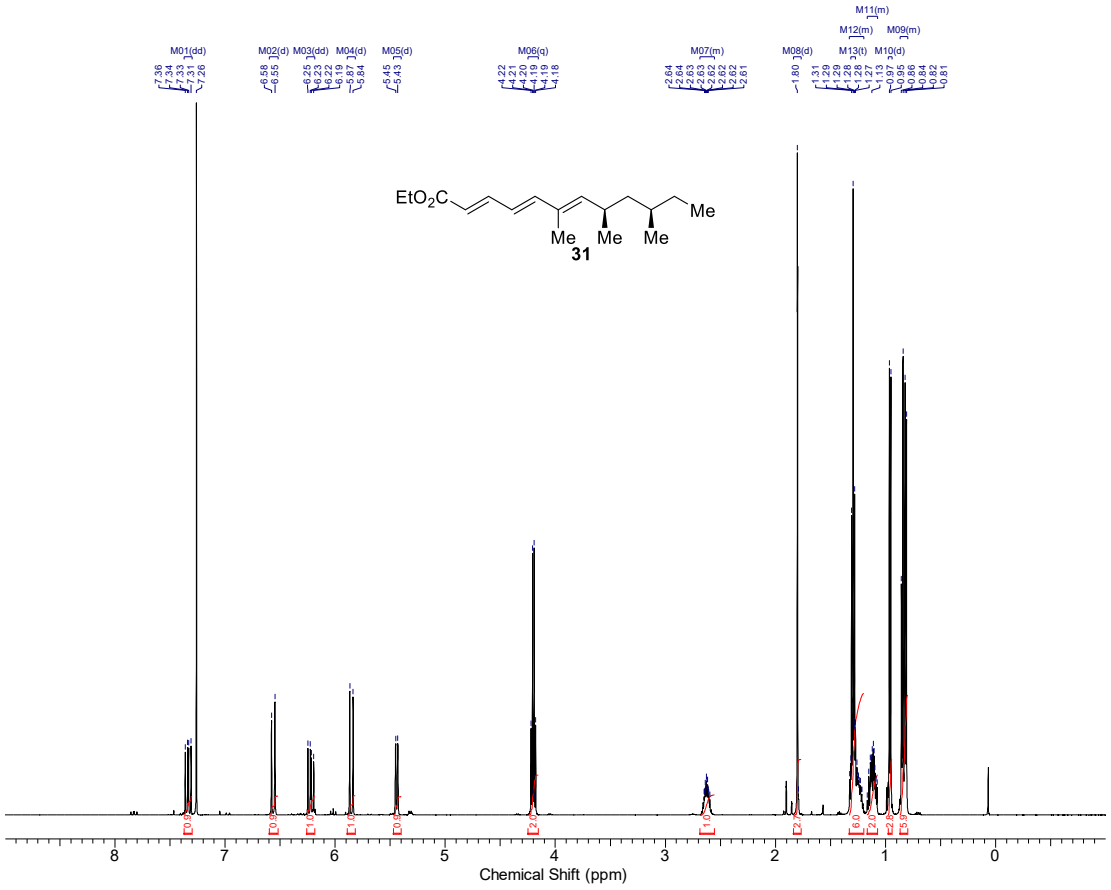
26

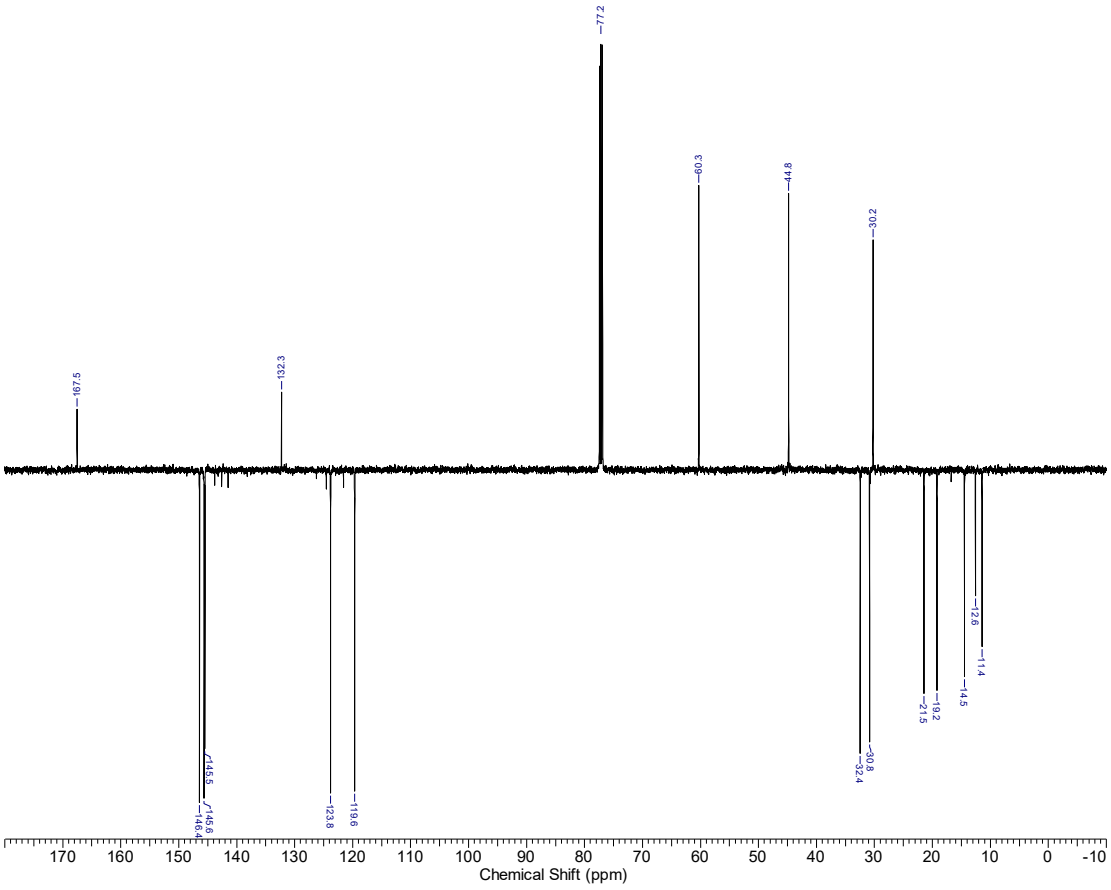

TBSO
oNb
N
O
OH
Me
Me
Me
Me
O
28a
Chemical Shift (ppm)

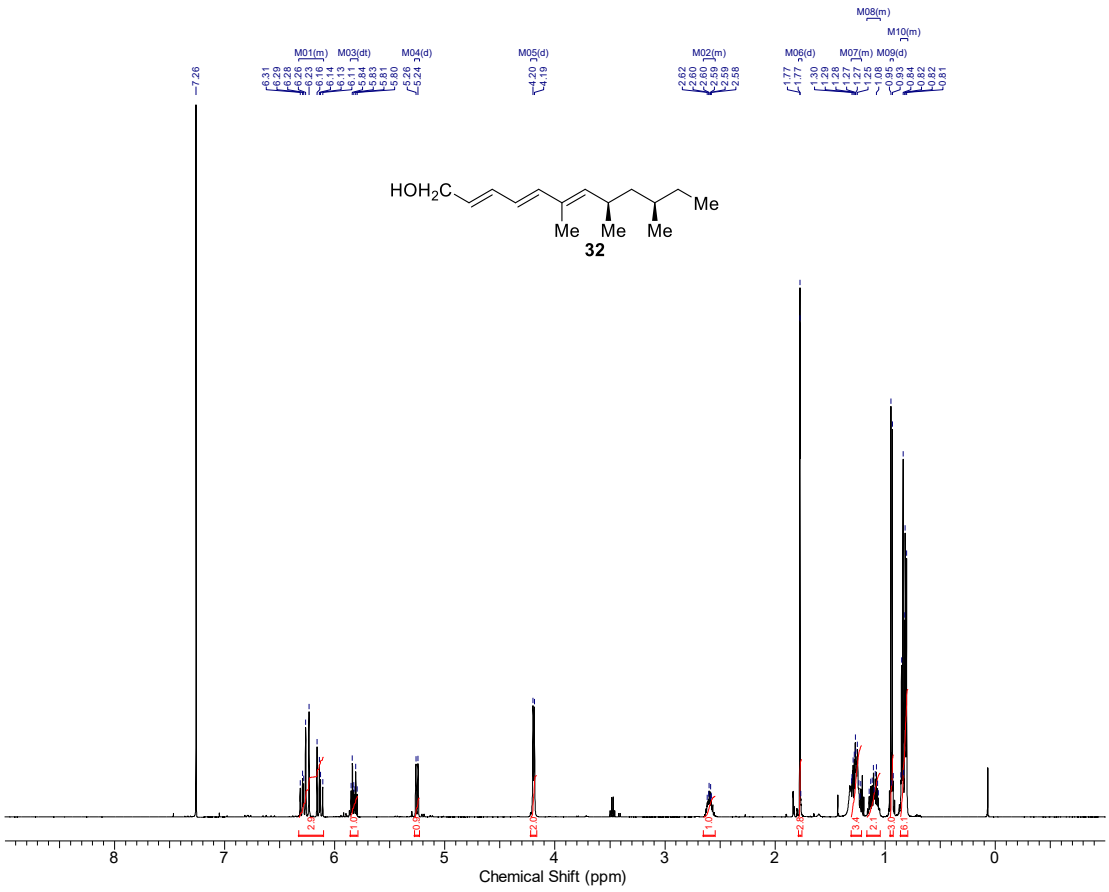

Chemical Shift (ppm)

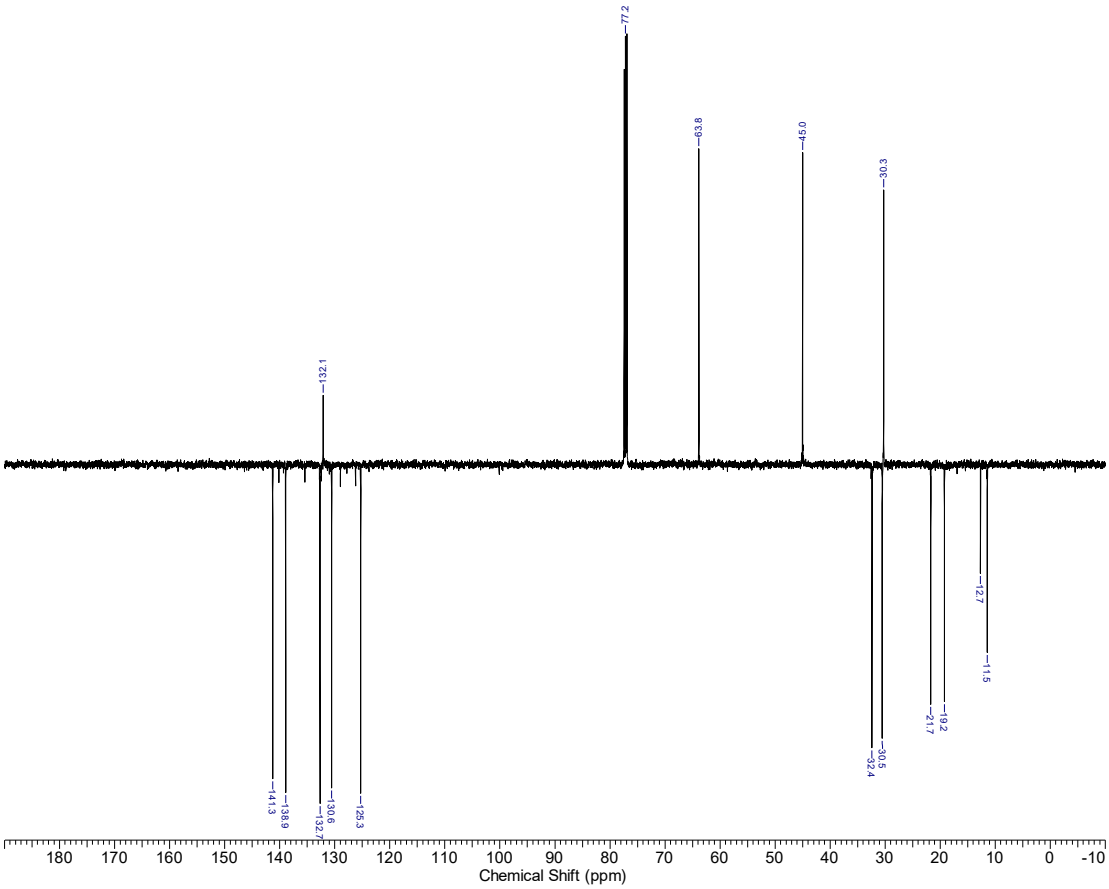

TBSO
DMB
N
O
OH
O
Me
Me
Me
Me
28b
Chemical Shift (ppm)

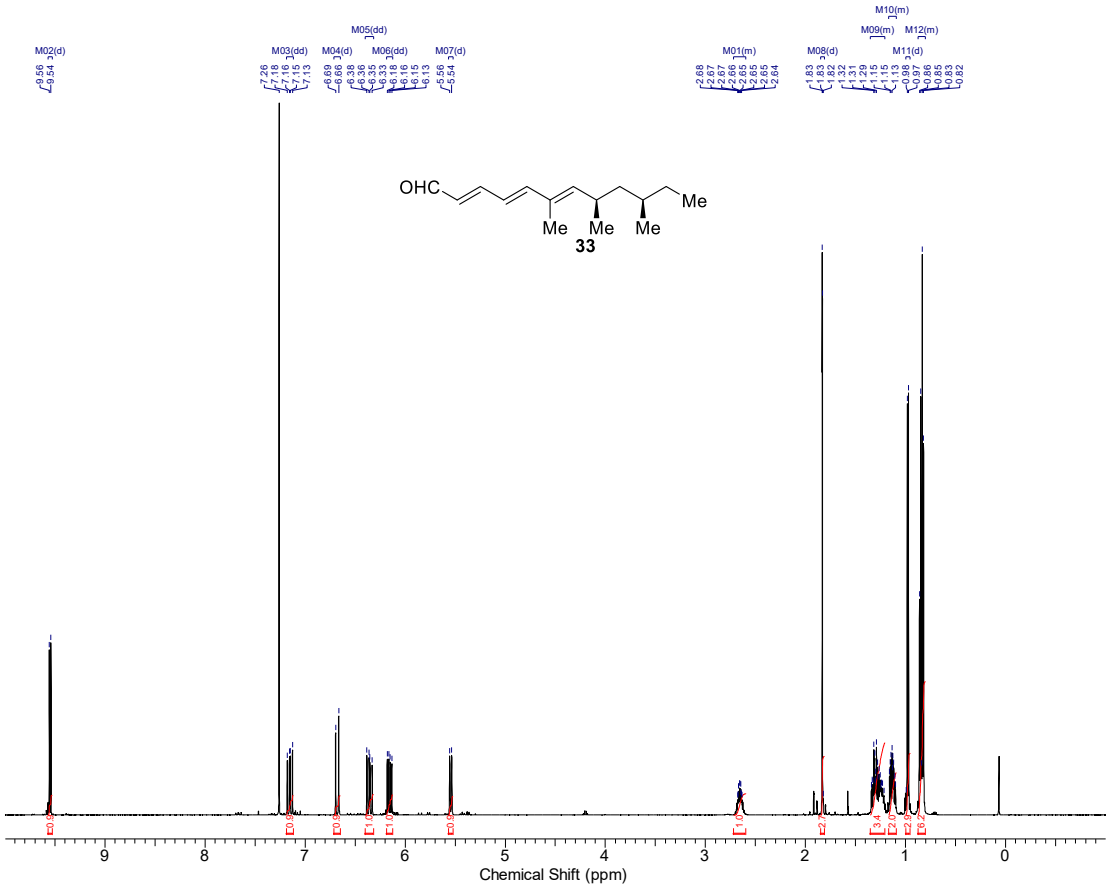

Chemical Shift (ppm)

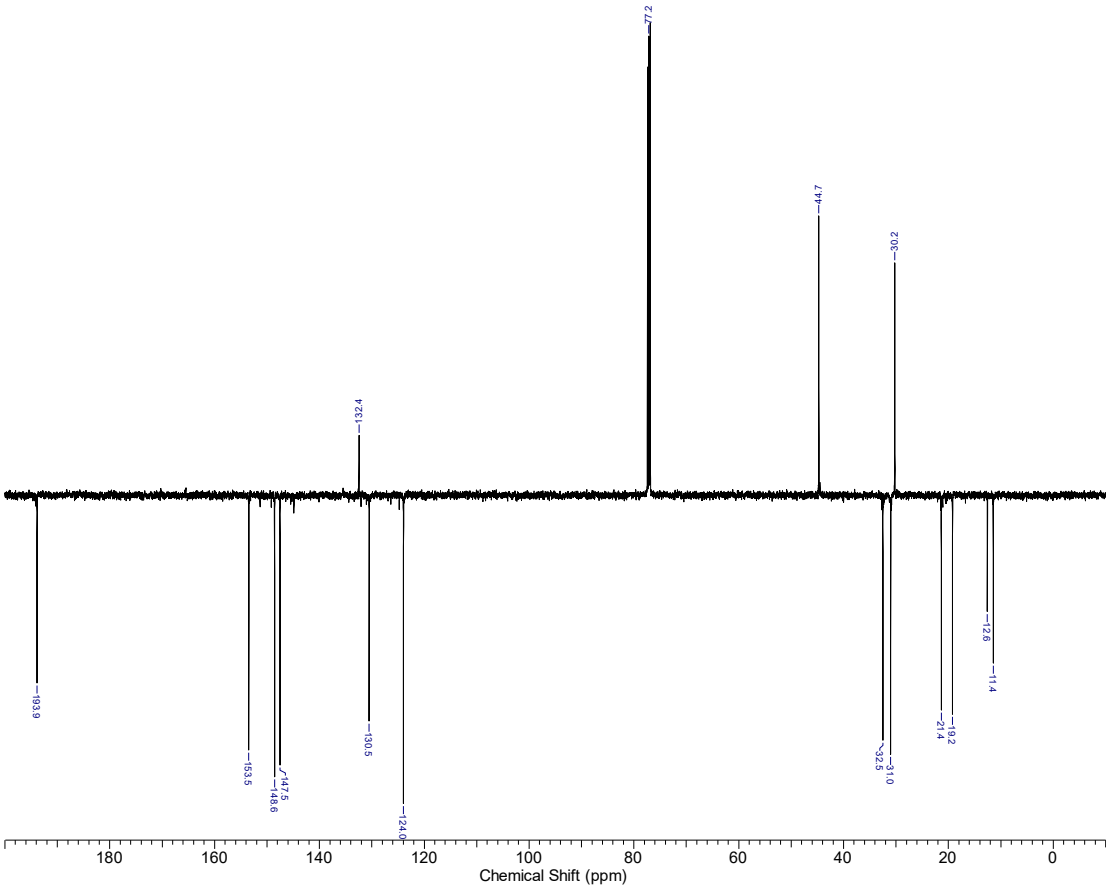

M01(dd)
M02(d)
M03(dd)
M04(d)
M05(d)
M06(q)
M07(m)
M08(d)
M09(m)
M10(d)
M11(m)
M12(m)
M13(t)
EtO2C
Me
Me
Me
Me
31
Chemical Shift (ppm)

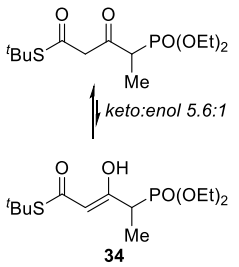

167.5
132.3
77.2
60.3
44.8
30.2
145.5
145.6
128.8
119.6
30.8
22.4
21.5
19.2
14.5
12.8
11.4
Chemical Shift (ppm)


HOH2C
Me
Me
Me
Me
32
Chemical Shift (ppm)

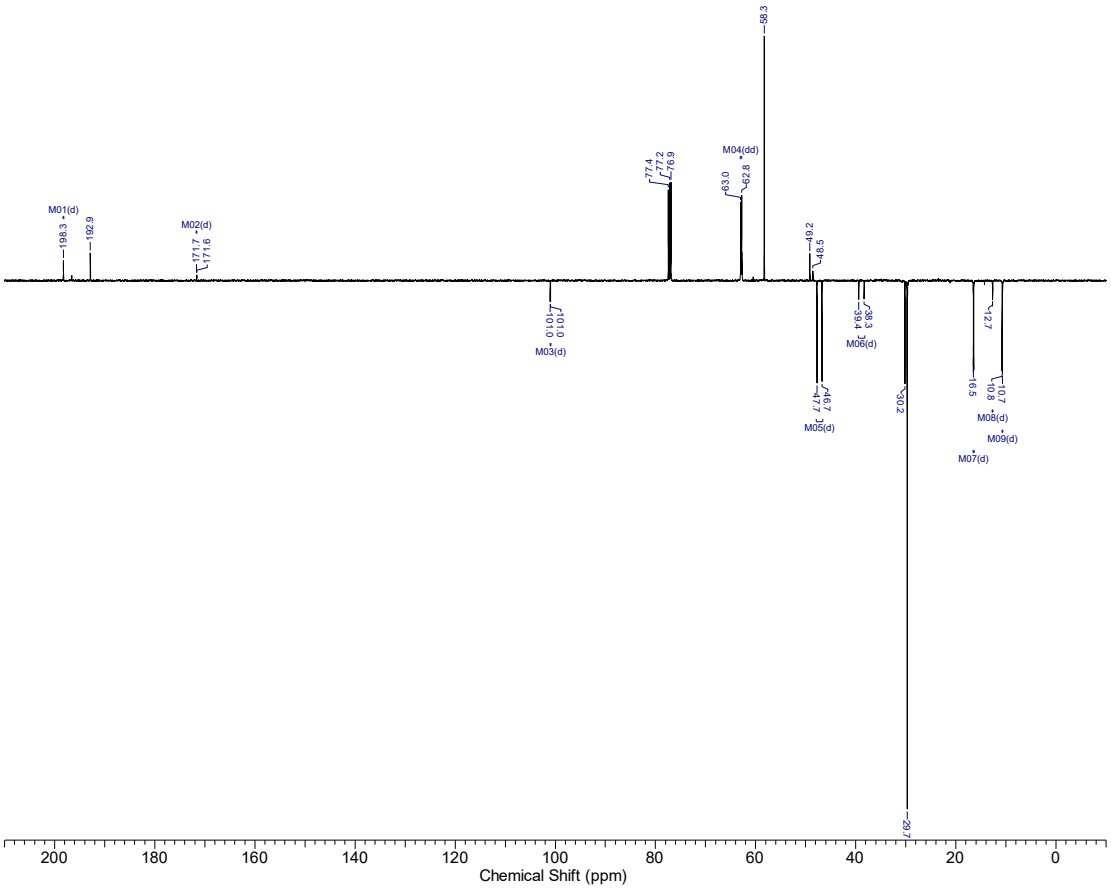

Chemical Shift (ppm)

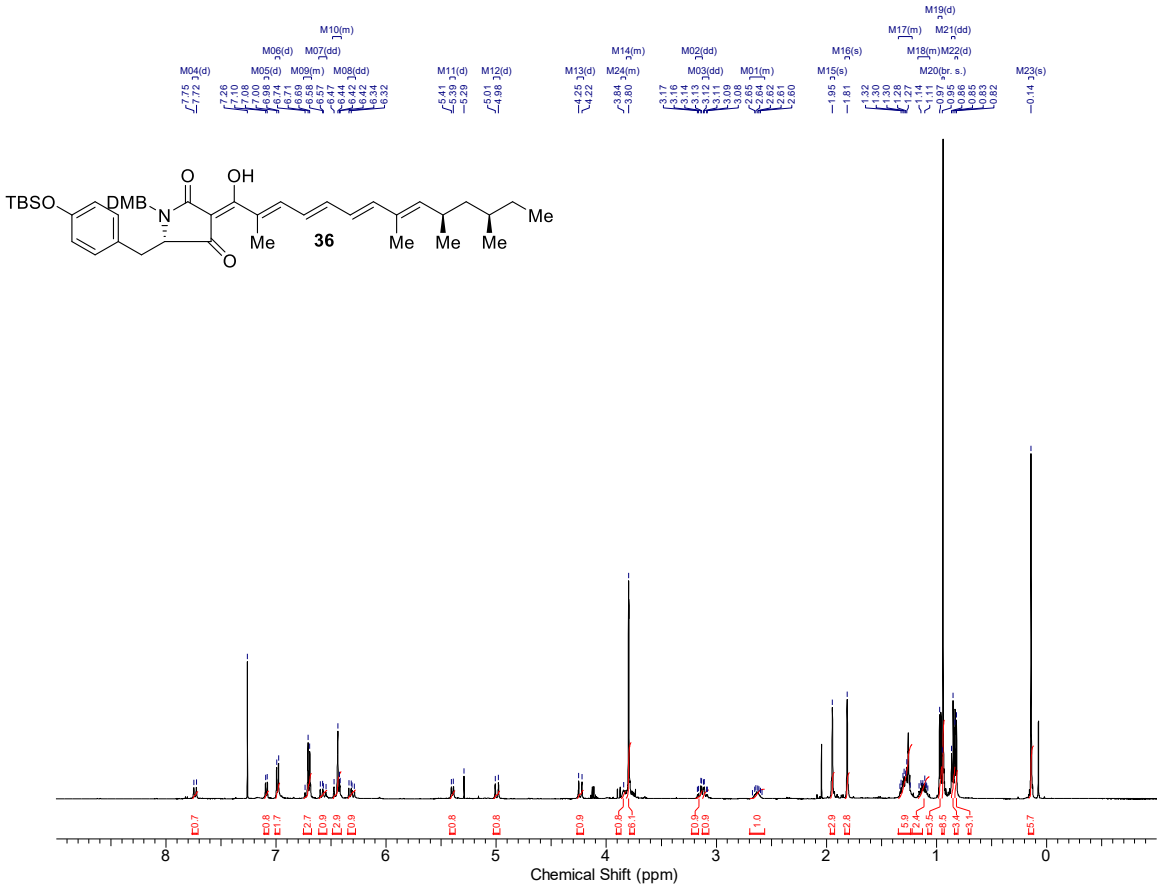

OHC
Me
Me
Me
Me
33
Chemical Shift (ppm)

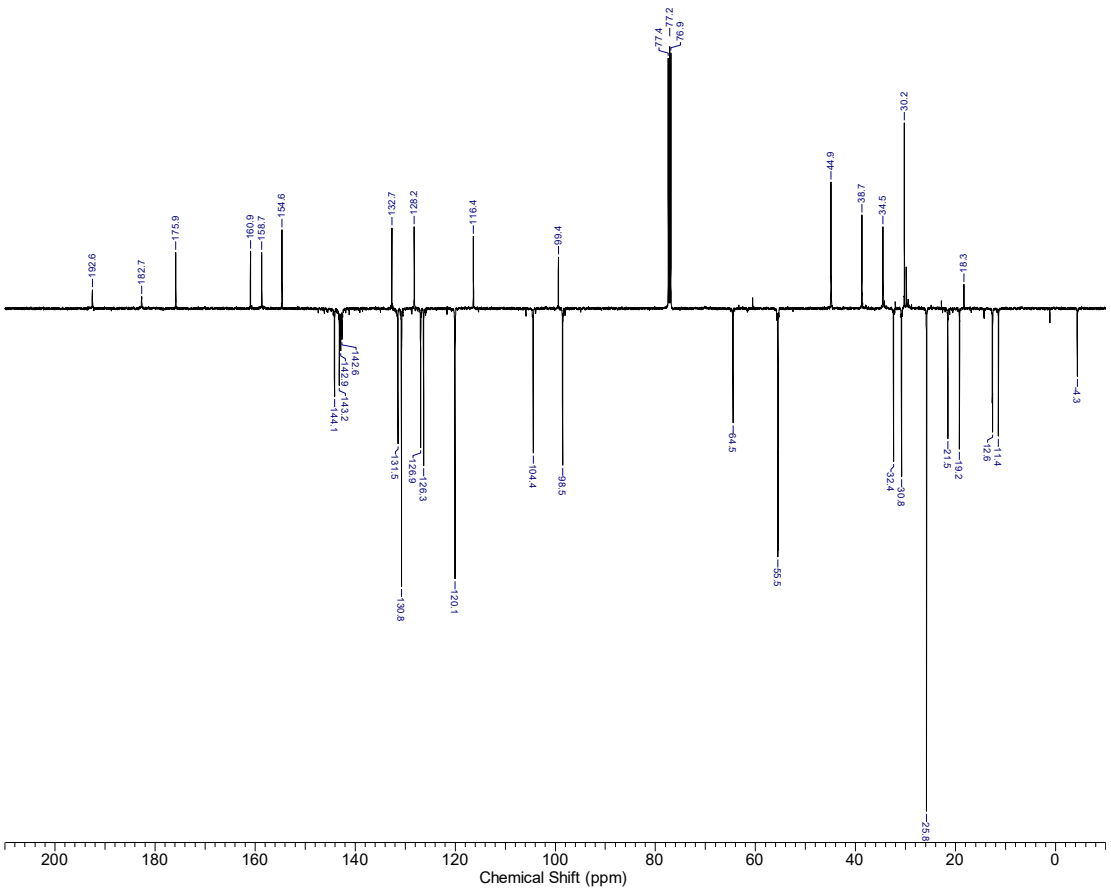

77.2
44.7
30.2
132.4
193.9
153.5
147.5
148.6
130.5
124.0
32.5
31.0
21.4
19.2
12.8
11.4
Chemical Shift (ppm)


tBuS
PO(OEt)2
Me
keto:enol 5.6:1
OH
34

Chemical Shift (ppm)


Chemical Shift (ppm)


TBSO
DMB
N
O
OH
Me
Me
Me
Me
Me
36
Chemical Shift (ppm)

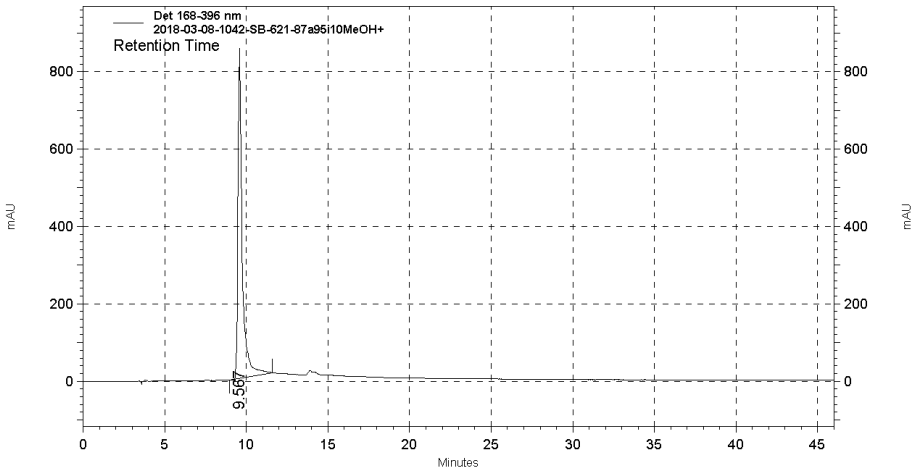

Chemical Shift (ppm)

HPLC Chromatogramms

Chromatogramm for Militarinone C (3)

Custom Report

Data File:	F:\2018-03-08-1042-SB-621-87a95i10MeOH+
Method:	87% MeCN in H2O (+0.1% formic acid) to 95% MeCN in 10 min
Flow Rate:	0.7 mL/min
Instrument Name:	System 1
Injection Volume:	20 µL
Concentration:	0.8 mg/mL in 87% MeCN in H2O (+0.1% formic acid)
Analyst:	Admin
Acquired:	7/26/2004 10:45:00 AM
Analyzed:	4/11/2018 9:51:25 AM
Printed:	4/11/2018 9:54:00 AM



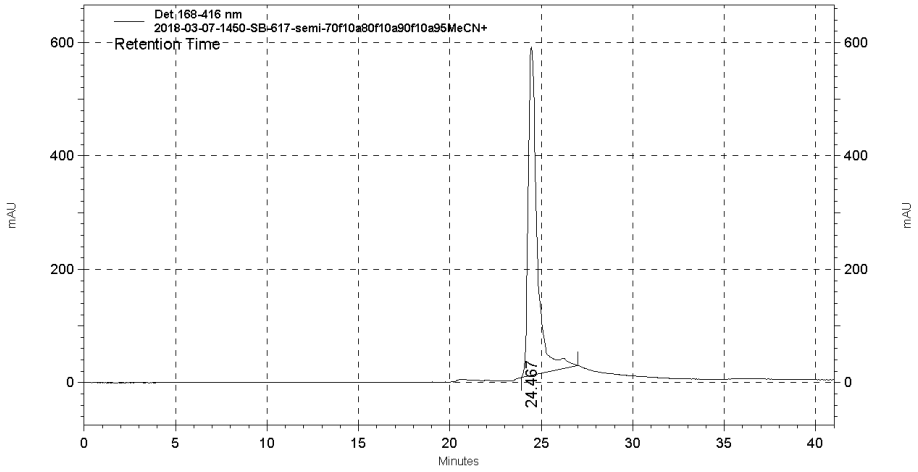
Det 168-396 nm
Results

Pk #	Time	Area	Height	Area Percent
1	9.567	15541914	852458	100.000
Totals		15541914	852458	100.000

Chromatogramm for Fumosorinone A (4)

Custom Report

Data File:	F:\2018-03-07-1450-SB-617-semi-70f10a80f10a90f10a95MeCN+
Method:	70% MeCN in H2O (+0.1% formic acid) hold for 10 min then 80% MeCN hold for 10 min then 90% MeCN hold for 10 min then 95% MeCN
Flow Rate:	0.7 mL/min
Instrument Name:	System 1
Injection Volume:	20 µL
Concentration:	0.7 mg/mL in 70% MeCN in H2O (+0.1% formic acid)
Analyst:	Admin
Acquired:	7/25/2004 2:55:38 PM
Analyzed:	4/11/2018 9:45:35 AM
Printed:	4/11/2018 9:50:20 AM



Det 168-416 nm
Results

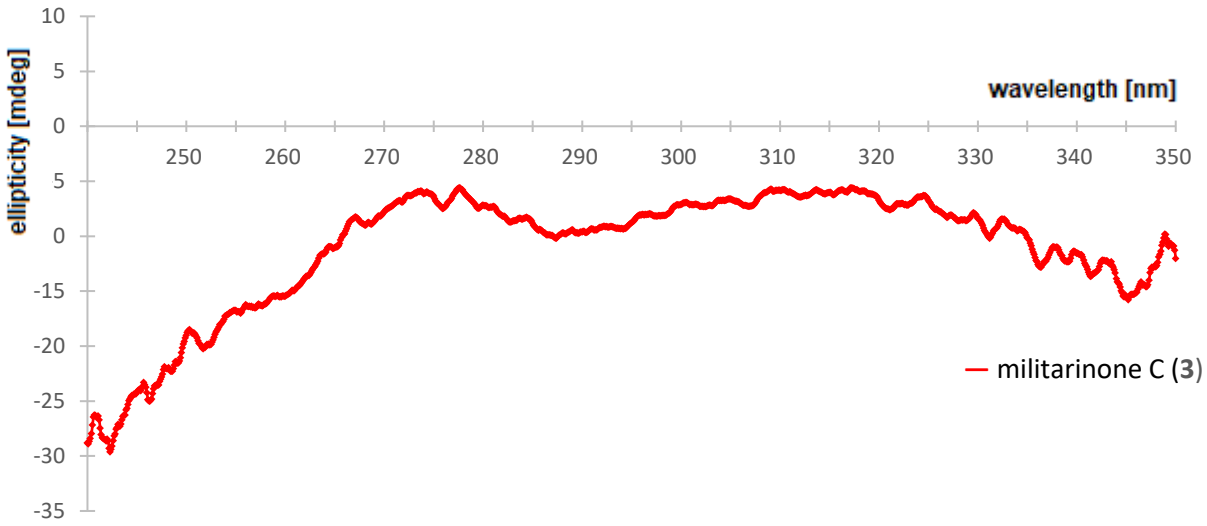
Pk #	Time	Area	Height	Area Percent
1	24.467	19585166	578646	100.000
Totals		19585166	578646	100.000

ECD Spectrum of Militarinone C (3)

The measurement was performed on a Jasco J-710 Spectropolarimeter at ambient temperature.

Sample concentration: 0.125 mg/mL in acetonitrile (HPLC grade)

Spectrum measurement parameters:	Sensitivity:	100 mdeg
	Start:	350 nm
	End:	240 nm
	Data Pitch:	0.1 nm
	Scanning Mode:	Continuous
	Scanning Speed:	100 nm/min
	Response:	1 sec
	Band Width:	1.0 nm
	Accumulation:	5



References

[1] Schmidt K., Riese U., Li Z., Hamburger M. *J. Nat. Prod.* **2003**, *66*, 378 – 383.

[2] Zhang J., Meng L.-L., Wei J.-J., Fan P., Liu S.-S., Yuan W.-Y., Zhao Y.-X., Luo D.-Q. *Molecules* **2017**, *22*, 2058.

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Damit nochmal an alle die es mir ermöglicht haben diese Arbeit zu vervollständigen und die ich vielleicht auch hier nicht erwähnt habe:

VIELEN DANK EUCH ALLEN!

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