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Total Synthesis and Biological Evaluation of (–)-Zampanolide, (–)-Dactylolide and of Analogs thereof

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Didier Zurwerra
Dipl. Chem. ETH Zurich

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citizen of
Mund/VS, Switzerland

accepted on the recommendation of

Prof. Dr. Karl-Heinz Altmann, examiner
Prof. Dr. Erick M. Carreira, co-examiner

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„Mut steht am Anfang des Handelns, Glück am Ende“

Demokrit

To my beloved family

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“Treasures from the Sea: Discovery and Total Synthesis of Ammosamides“

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ETH Zurich

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List of Poster Presentations

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Total Synthesis and SAR Studies of (–)-Zampanolide and (–)-Dactylolide
III EWDSy-Third European Workshop in Drug Synthesis, Siena **2010**

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Abstract

(–)-Zampanolide (**I**) and (+)-dactylolide (**II**) are structurally related polyketide-based macrolides that were isolated from two taxonomically different, geographically widely separated sponge species. Surprisingly, the absolute stereochemistry for the macrolactone core structure in **I** is opposite to that found in **II** (Figure 1).

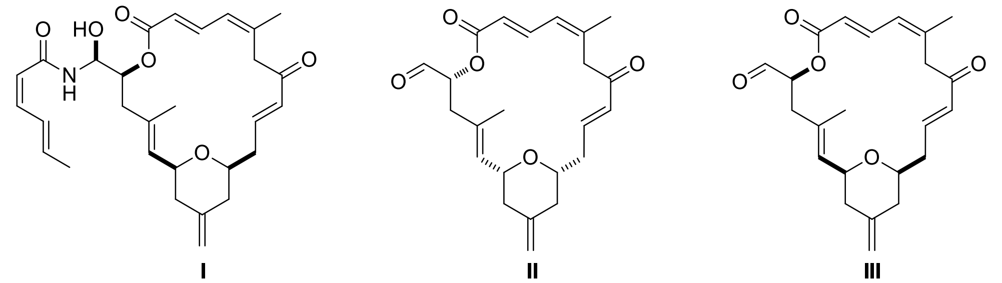


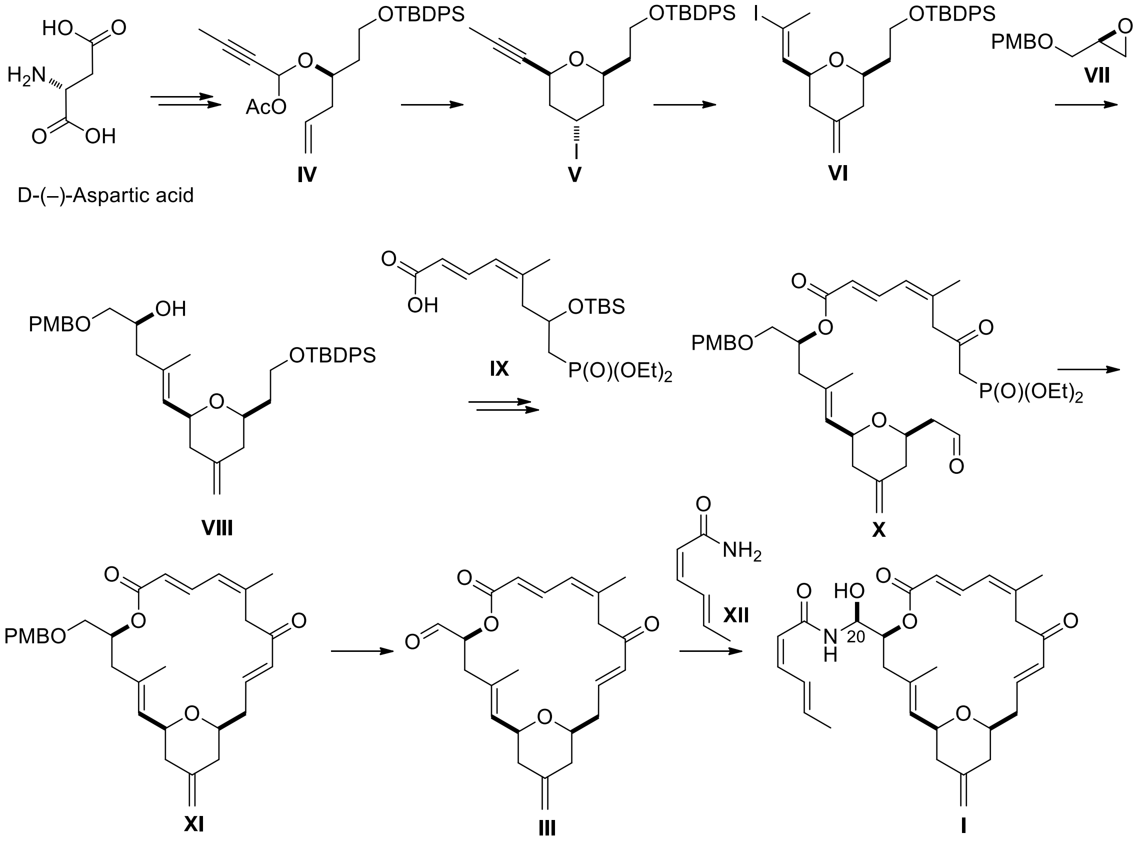
Figure 1: Structures of (–)-zampanolide (**I**), (+)-dactylolide (**II**) and (–)-dactylolide (**III**).

In contrast to the low nM cytotoxcicity of (–)-zampanolide (**I**), (+)-dactylolide (**II**) was found to be only a moderately potent inhibitor of human cancer cell growth with IC_{50}'s in the low μM range. This raised the question if the enhanced biological activity of (–)-zampanolide (**I**) over natural (+)-dactylolide (**II**) was related to the presence of the side chain or to the different absolute configuration of the macrolactone core (or perhaps both).

This research project was directed at the development of a new total synthesis of (–)-zampanolide (**I**) and (–)-dactylolide (**III**), which should provide the basis for the generation of derivatives for an initial structure-activity-relationship (SAR) study. Challenging architectural elements in (–)-zampanolide (**I**) are the unusual *N*-acyl hemiaminal side chain, the syn-substituted tetrahydropyran (THP) subring and the high degree of unsaturation.

Scheme 1 outlines key steps in the total synthesis of (–)-zampanolide (**I**) and (–)-dactylolide (**III**) starting from D-aspartic acid. The successful *Prins*-type cyclization with acetal **IV** provided access to THP derivative **V** as an advanced intermediate. Iodide displacement and olefination followed by acetylide reduction led to (*E*)-vinyl iodide **VI,** which was lithiated and coupled with PMB-protected (*R*)-glycidol (**VII**) to

give the secondary alcohol **VIII** in 14 steps and 17.2% overall yield from D-aspartic acid. Astonishingly, the BF_3-catalyzed epoxide opening reaction turned out to work only in toluene, a finding that was pivotal for the construction of derivatives. Since this epoxide opening reaction was problematic initially, an alternative synthesis for alcohol **VIII** was designed which required 22 steps (2.4% yield) for the longest linear sequence, starting from L-malic acid.


HO
O
H2N
O
OH
D-(−)-Aspartic acid
OTBDPS
O
AcO
IV
OTBDPS
O
I
V
I
OTBDPS
O
VI
PMBO
O
VII
PMBO
OH
OTBDPS
O
VIII
O
OH
OTBS
P(O)(OEt)2
IX
O
PMBO
O
O
P(O)(OEt)2
O
O
X
O
NH2
XII
O
PMBO
O
O
O
XI
O
O
O
O
O
III
O
HO
N
H
20
O
O
O
O
I

Scheme 1: Total synthesis of (–)-dactylolide (**III**) and (–)-zampanolide (**I**) starting from D-(–)-aspartic acid.

Alcohol **VIII** was esterified with acid **IX** (accessible from 2-butyn-1-ol in 10 steps and 25% yield) followed by elaboration of the ensuing ester into *β*-ketophosphonate aldehyde **X**. Macrocyclization was achieved by a *Horner-Wadsworth-Emmons* (*HWE*) reaction to afford macrocycle **XI** as a single isomer; **XI** could be readily converted into (–)-dactylolide (**III**), which was obtained in 4.8% yield in 20 steps for the longest linear sequence from D-aspartic acid. An aza-aldol reaction with aluminated (*Z*,*E*)-sorbamide **XII** followed by HPLC separation of the C20 epimers finally completed the synthesis of the natural product (–)-zampanolide (**I**) in 21 steps and 0.9% yield for the longest linear sequence from D-aspartic acid.

In vitro cytotoxicity analysis revealed (–)-zampanolide (**I**) to be highly potent with IC_{50} values in the low nM range (IC_{50}: 1–7 nM); this is in accord with literature data. The non-natural product (–)-dactylolide (**III**) revealed potency in the lower μM range (IC_{50}: 210–750 nM), which makes it slightly more potent than naturally occurring (+)-dactylolide (**II**). Thus, the presence of the side chain in (–)-zampanolide (**I**) is what determines its substantially higher potency over (+)-dactylolide (**II**), rather than the configuration of the macrocycle.

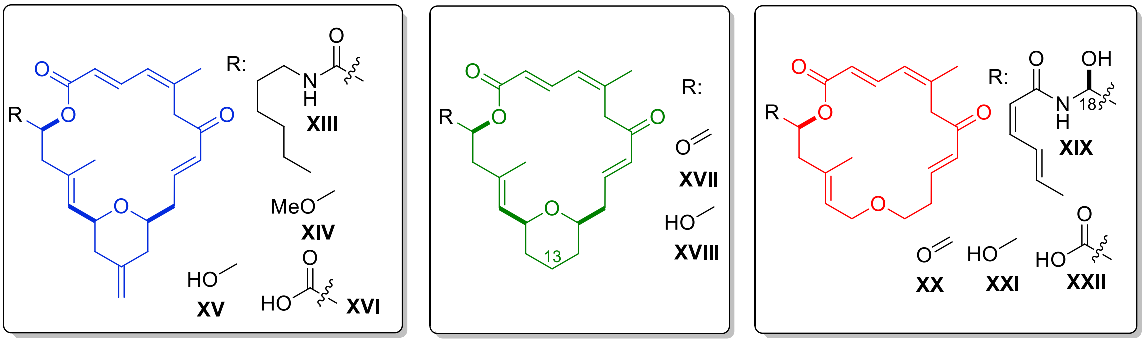


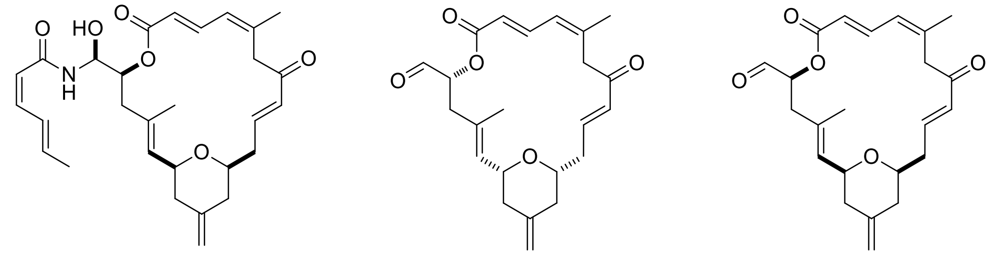
Figure 2: Collection of analogs and derivatives of I which include subring and side chain modifications.

The analogs and derivatives shown in Figure 2 emanated from the chemistry established in the course of the total synthesis work and represent the first analogs of **I** and **III** to be investigated. Comparison of the activity of (–)-dactylolide (**III**) with the corresponding primary alcohol **XV** shows that the aldehyde functionality is not required for biological activity. Interestingly, the removal of the C13 methylene group (analogs **XVII** and **XVIII**) did not affect cellular activity. The structurally less complex analogs lacking the THP subring (**XX** and **XXI**) were less potent inhibitors of cancer cell proliferation (IC_{50}: 1.9-4 μM). Astonishingly, however, upon introduction of the side chain in aldehyde **XX**, the potency increased to the level of (–)-dactylolide (**III**) (IC_{50}: 80–150 nM, tested for the C18 epimeric mixture). A loss in bioactivity (IC_{50}: > 7μM) was observed for acid derivatives **XVI** and **XXII** and other side chain modifications, such as methyl ether **XIV** or amide **XIII** (IC_{50}: 0.8–1.6 μM). Interestingly, the observed equal bioactivity of the aldehyde and the alcohol forms, i. e. **III** and **XV, XVII** and **XVIII** as well as **XX** and **XXI** suggests a general tendency, which appears to be independent of the macrocyclic core structure. Importantly, tubulin polymerization experiments clearly showed (–)-dactylolide (**III**) to be a new microtubule-stabilizer, similar to the more potent (–)-zampanolide (**I**).

This first SAR study on dactylolide/zampanolide-type structures corroborates the notion of the natural (*Z*,*E*)-sorbamide side chain to promote high cytotoxicity. A simplification of the THP subring seems possible, at least to some extent, without losing activity. The successful total synthesis of (–)-zampanolide (**I**) provides the basis for the construction of other derivatives for more detailed SAR investigations. This work thus highlights the power of diverted total synthesis for the generation of derivatives that would be inaccessible from the natural product by means of semi-synthesis.

Zusammenfassung

(−)-Zampanolid (**I**) und (+)-Dactylolid (**II**) sind strukturell verwandte, polyketidische Makrolaktone, welche aus taxonomisch verschiedenen, und in geographisch weit voneinander entfernt liegenden Regionen vorkommenden, Meeresschwämmen isoliert wurden. Überraschenderweise besitzt der Makrozyklus in **I** die entgegengesetzte absolute Stereochemie wie **II** (Figur 1).



I **II** **III**

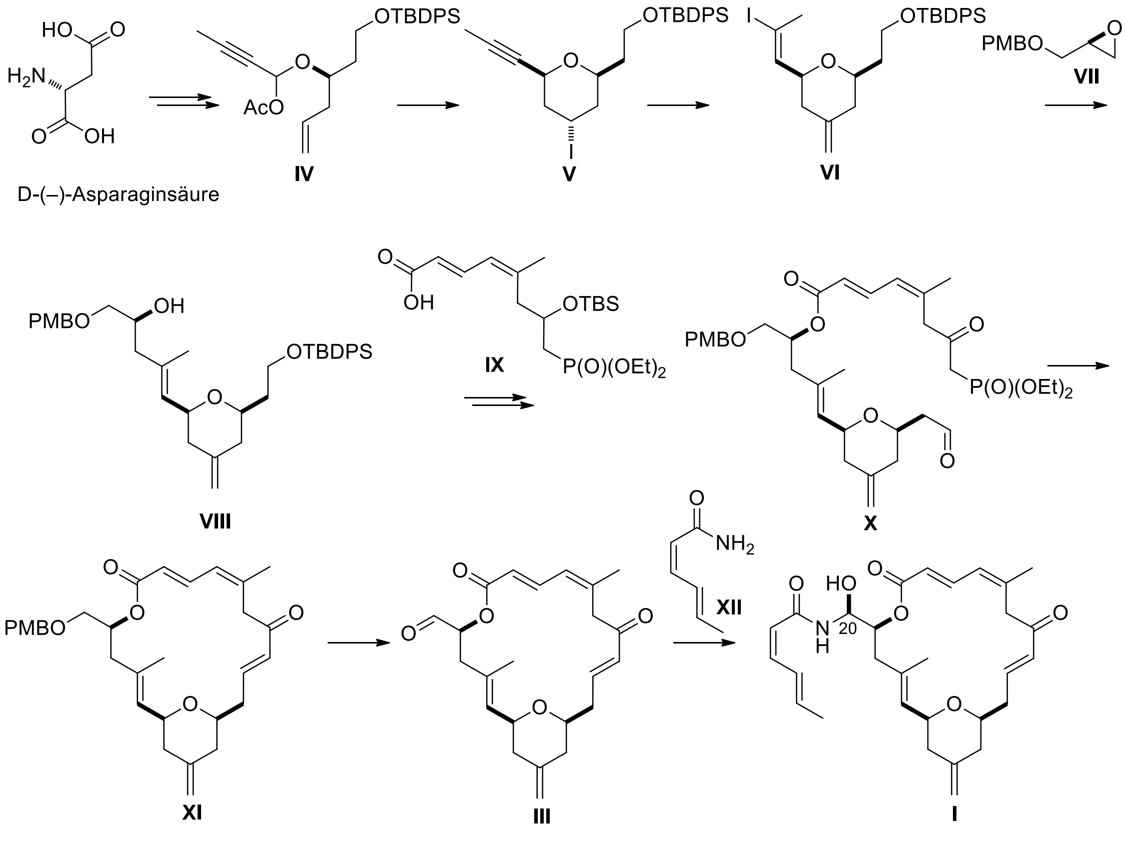
Figur 1: Strukturen von (–)-Zampanolid (**I**), (+)-Dactylolid (**II**) und (–)-Dactylolid (**III**).

Im Gegensatz zum hochpotenten (−)-Zampanolid (**I**), welches die Proliferation menschlicher Krebszellen mit IC_{50}-Werten im unteren nM Bereich hemmt, weist (+)-Dactylolid (**II**) mit IC_{50}-Werten im unteren µM Bereich nur eine moderate Aktivität gegen menschliche Krebszellen auf. Es stellte sich daher die Frage, ob der gravierende Unterschied in der biologischen Aktivität zwischen (−)-Zampanolid (**I**) und (+)-Dactylolid (**II**) auf das Vorhandensein der Seitenkette in ersterem oder auf die unterschiedliche Stereochemie der Makrozyklen in **I** und **II** zurückzuführen ist (oder vielleicht auf beides).

Ziel dieses Forschungsprojektes war die Entwicklung einer neuen Totalsynthese von (−)-Zampanolid (**I**) und (−)-Dactylolid (**III**) welche als Grundlage zur Herstellung von Derivaten für eine erste Studie zur Struktur-Aktivitäts-Beziehung dienen sollte. (−)-Zampanolid (**I**) vereint synthetisch interessante und herausfordernde Strukturelemente wie ein *N*-acyliertes Hemiaminal in der Seitenkette, einen syn-substituierten Tetrahydropyran (THP) Subring und einen hohen Anteil an C=C-Doppelbindungen.

Schema 1 zeigt die wichtigsten Schritte der Totalsynthese von (−)-Zampanolid (**I**) und (−)-Dactylolid (**III**) ausgehend von D-(−)-Asparaginsäure. Eine modifizierte *Prins* Zyklisierung mit dem acylierten Acetal **IV** lieferte das THP Derivat **V**. Nach dem

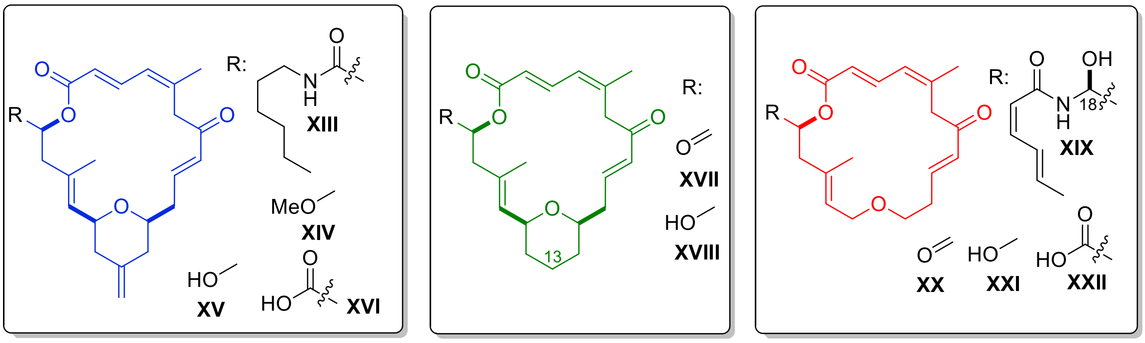
Ersatz des Iods durch Sauerstoff erfolgte eine Olefinierung mit anschliessender Reduktion der Acetylen-Untereinheit, was zum (*E*)-Vinyliodid **VI** führte. Dieses wurde in die lithiierte Verbindung überführt und mit PMB-geschütztem (*R*)-Glycidol (**VII**) zum sekundären Alkohol **VIII** umgesetzt, der somit ausgehend von D-Asparaginsäure in 14 Schritten und mit einer Gesamtausbeute von 17.2% erhalten wurde. Interessanterweise lief die BF_3-katalysierte Epoxidöffnung einzig in Toluol als Lösungsmittel ab, ein Ergebnis welches sich als ausschlaggebend für die Herstellung von Derivaten herausstellen sollte. Da sich die beschriebene Epoxidöffnung zu Beginn als äusserst schwierig erwies, wurde ein alternativer Zugang erarbeitet, welcher, ausgehend von L-Äpfelsäure, Alkohol **VIII** in 22 Stufen (2.4% Ausbeute) für die längste lineare Sequenz lieferte.


HO
O
H2N
O
OH
D-(–)-Asparaginsäure
OTBDPS
AcO
IV
OTBDPS
O
V
I
OTBDPS
VI
PMBO
O
VII
PMBO
OH
OTBDPS
VIII
O
OH
OTBS
IX
P(O)(OEt)2
PMBO
O
P(O)(OEt)2
X
PMBO
XI
III
NH2
XII
HO
N
H
20
I

Schema 1: Totalsynthese von (–)-Dactylolid (**III**) und (–)-Zampanolid (**I**) ausgehend von D-(–)-Asparaginsäure.

Alcohol **VIII** wurde mit Säure **IX** (zugänglich in 10 Schritten ausgehend von 2-Butin-1-ol in 25% Ausbeute) verestert. Nach Überführung in den *β*-Ketophosphonat Aldehyd **X** ermöglichte eine *Horner-Wadsworth-Emmons* (*HWE*) Makrozyklisierung als Schlüsselschritt den Zugang zum isomerenreinen Makrozyklus **XI**. Dieser konnte schliesslich leicht in (–)-Dactylolid (**III**) umgewandelt werden, welches in 4.8% Ausbeute über 20 Stufen (für die längste lineare Sequenz) erhalten wurde. Eine Aza-Aldol Reaktion mit aluminiertem (*Z*,*E*)-Sorbamid **XII** und anschliessende HPLC-Trennung der beiden C20 Epimeren führte schliesslich zum gewünschten Naturstoff (–)-Zampanolid (**I**), der somit ausgehend von D-Asparaginsäure über 21 Stufen und in 0.9% Gesamtausbeute für die längste lineare Sequenz erhalten wurde.

Studien zur *in vitro* Zytotoxizität von (–)-Zampanolid (**I**) ergaben eine Potenz im unteren nM Bereich (IC$_{50}$: 1–7 nM), was sich in Übereinstimmung mit Literaturwerten befindet. Nichtnatürliches (–)-Dactylolid (**III**) erwies sich als weniger aktiv, mit IC$_{50}$-Werten im tieferen μM Bereich (IC$_{50}$: 210–750 nM). **III** scheint somit geringfügig aktiver zu sein als der enantiomere Naturstoff (+)-Dactylolid (**II**). Die intrinsisch höhere Potenz von (–)-Zampanolid (**I**) im Vergleich zu (+)-Dactylolid (**II**) muss daher mit der Seitenkette verbunden sein.



Figur 2: Übersicht über Subring- und Seitekettenmodifikationen von **I**.

Die in Figur 2 dargestellten Derivate wurden auf der Basis der für **I** und **III** entwickelten Synthesestrategie hergestellt und sind die ersten Dactylolid/Zampanolid Analoga die je untersucht wurden. Ein Vergleich der IC$_{50}$-Werte für **III** und **XV** zeigt, dass das Vorhandensein einer Aldehydfunktion für die zelluläre Aktivität nicht kritisch ist. Interessanterweise weisen die C13 Desmethylen-Verbindungen **XVII** und **XVIII** in zellulären Versuchen identische Aktivitäten wie (–)-Dactylolid (**III**) bzw. **XV** auf. Die strukturell weniger komplexen Derivate ohne den THP Subring (**XX** und **XXI**), waren weniger aktive Inhibitoren der Krebszellproliferation (IC$_{50}$: 1.9–4 μM). Erstaunlicherweise ergab die Einführung der Seitenkette in Aldehyd **XX** ein sehr potentes Analogon (**XIX**), dessen Aktivität mit derjenigen von (–)-Dactylolid vergleichbar ist (IC$_{50}$-Werte von 80–150 nM für das getestete C18-Epimerengemisch). Auffallend war die geringere Bioaktivität (IC_{50}: > 7 μM) der Säurederivate **XVI** und **XXII**. Andere Seitenkettenmodifikationen wie in Methylether **XIV** oder Amid **XIII** führten zu moderaten Aktivitäten (IC_{50}: 0.8–1.6 μM). Die beobachtete gleiche Bioaktivität der jeweiligen Aldehyd- und Alkoholformen (Verbindungen **III** und **XV**, **XVII** und **XVIII** sowie **XX** und **XXI**) stellt einen generellen Trend dar, welcher unabhängig von der Struktur des Makrozyklus zu sein scheint.

Ein besonders bedeutsames Resultat der biologischen Profilierung von (–)-Dactylolid (**III**) ist die Tatsache, dass sich dieses in Tubulinpolymerisationsexperimenten als ein neuer Mikrotubulistabilisator erwies, was auch auf den potenteren Naturstoff (–)-Zampanolid (**I**) zutrifft. Die Ergebnisse dieser ersten Untersuchungen zu Struktur-Aktivitäts-Beziehungen bekräftigen die Auffassung, dass die hohe Zytotoxizität des (–)-Zampanolid (**I**) massgeblich von der natürlichen (*Z,E*)-Sorbamid Seitenkette abhängt. Eine Vereinfachung des THP Subrings erscheint dagegen ohne einen grossen Aktivitätsverlust möglich.

Die erfolgreiche Totalsynthese von (–)-Zampanolid (**I**) bietet die Grundlage für die Herstellung weiterer Derivate für eine tiefgehendere Struktur-Aktivitäts-Beziehungs Analyse. Zudem zeigt diese Arbeit wie es die divergierende Totalsynthese ermöglicht, Zugang zu Derivaten eines Naturstoffs zu erhalten, die durch Semisynthese ausgehend vom Naturstoff unzugänglich wären.

List of Abbreviations, Acronyms and Symbols

A

$[\alpha]_D^T$	specific rotation at temperature T at the sodium D line
Å	angstrom
Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	2,2′-azoisobutyronitrile
atm	atmosphere
ax	axial

B

BAIB	bisacetoxy iodobenzene
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2,2′-naphthol
BMS	borane methyl sulfide complex
br	broadened
brsm	based on recovered staring material
Bu	*n*-butyl
BVE	*n*-butyl vinyl ether

C

°C	degree centigrade
18-c-6	18-crown-6
calcd	calculated
cat.	catalytic
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid

D

δ	NMR chemical shift in ppm

d	standard day or doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclopropyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL–H	diisobutylaluminum hydride
DIC	1,3-diisopropylcarbodiimide
DIPCl	*B*-chloro-diisopinocampheyl borane
DIPEA	diisopropylethylamine
DMAP	4-*N*,*N*-dimethylamino pyridine
DME	1,2-dimethoxyethane (monoglyme)
DMF	*N*,*N*-dimethyl formamide
DMP	*Dess*–*Martin* periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPP	4,7-diphenyl-1,10-phenanthroline
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio

E

EDA	ethylenediamine
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact ionization
eq	equatorial
equiv	equivalent
Et	ethyl
eV	electronvolt

F

FDA	US Food and Drug Administration
FGI	Functional Group Interchange Transform

G

g	gram

H

h	hour
HATU	2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3 tetramethyluronium hexafluorophosphate
Hex	*n*-hexane
HFIP	1,1,1,3,3,3-hexafluoro isopropanol
HMPA	hexamethylphosphoramide
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz (s^{-1})

I

i	iso
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
ImH	imidazole
Ipc	isopinocampheyl

J

J	coupling constant

K

kcal	kilocalorie
KHMDS	potassium 1,1,1,3,3,3-hexamethyldisilazide

L

LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
LHMDS	lithium 1,1,1,3,3,3-hexamethyldisilazide

M

m	multiplet
M	molarity (moles$\cdot$l^{-1})
MDCKII	Madin Darbin canine kidney cells type II
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mmol	millimole
μM	micromolar
mol%	mole per cent
Mp	melting point
M.S.	molecular sieves
MS	mass spectrometry

N

n	normal
NaHMDS	sodium 1,1,1,3,3,3-hexamethyldisilazide
NCS	N-chlorosuccinimide
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NMO	*N*-methyl morpholine *N*-oxide
NOE	Nuclear Overhauser Effect
Nu	nucleophile

O

o	*ortho*

P

p	*para*
PCC	pyridinium chlorochromate
PG	protective group
Ph	phenyl
PMB	4-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	*n*-propyl
Proton Sponge®	*N*,*N*,*N′*,*N′*-tetramethyl-1,8-naphtalene-diamine
PS	polystyrene
p-TsOH	4-methylbenzenesulphonic acid
py	pyridine
pybox	bis(oxazolinyl)pyridine

Q

q	quartet
quant	quantitative

R

RCM	ring closing metathesis
RedAl®	sodium bis(2-methoxyethoxy)aluminumhydride
R_f	retention factor
RP	reverse phase
R_t	retention time
RT	room temperature

S

s	second or singlet
Sia	siamyl

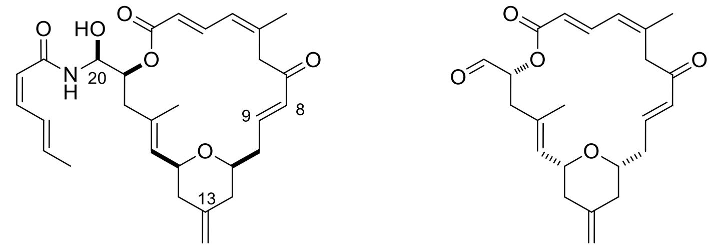
T

t	triplet
t	*tert*
T	temperature
TADDOL	2,2-dimethyl-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,3-dioxolane-4,5-dimethanol
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
2-Th	2-thienyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Tr	triphenylmethyl
Ts	4-methylphenyl sulfonyl

1. Introduction

1.1. Isolation and Initial Biological Evaluation of (+)-Dactylolide and (–)-Zampanolide

It was in the year of 1996 in which *Tanaka* and co-worker[1] first reported the antiproliferative activity of the novel marine macrolide (–)-zampanolide ((–)-1) (Figure 3), which was isolated from the sponge *Fasciospongia Rimosa* near Cape Zampa, Okinawa (Figure 4).[2] By means of HR-FABMS and applying extensive 2D-NMR techniques, *Tanaka* and co-worker were able to determine the relative stereochemistry of the macrolactone core structure, however, the stereochemistry at C-20 remained unassigned. (–)-**1** possesses a high degree of unsaturation, a 2,6-syn-substituted tetrahydropyran (THP) subring, with an exocyclic C=C double bond and a rather unusual *N*-hemiaminal side chain; the latter structural motif is only found in a limited number of other bioactive marine metabolites such as the antibiotic echinocandin[3] or the antitumor natural products mycalamide[4], spergualine[5] and upenamide[6] (Figure 5). The isolation procedure delivered 3.9 mg of (–)-zampanolide ((–)-**1**) from 480 gram of the sponge along with 13.7 mg of another highly active marine natural product, latrunculin A (**I-5**) (Figure 6).



(–)-Zampanolide ((–)-**1**) (+)-Dactylolide ((+)-**2**)

Figure 3: Molecular structures of (–)-zampanolide ((–)-**1**) and (+)-dactylolide ((+)-**2**).

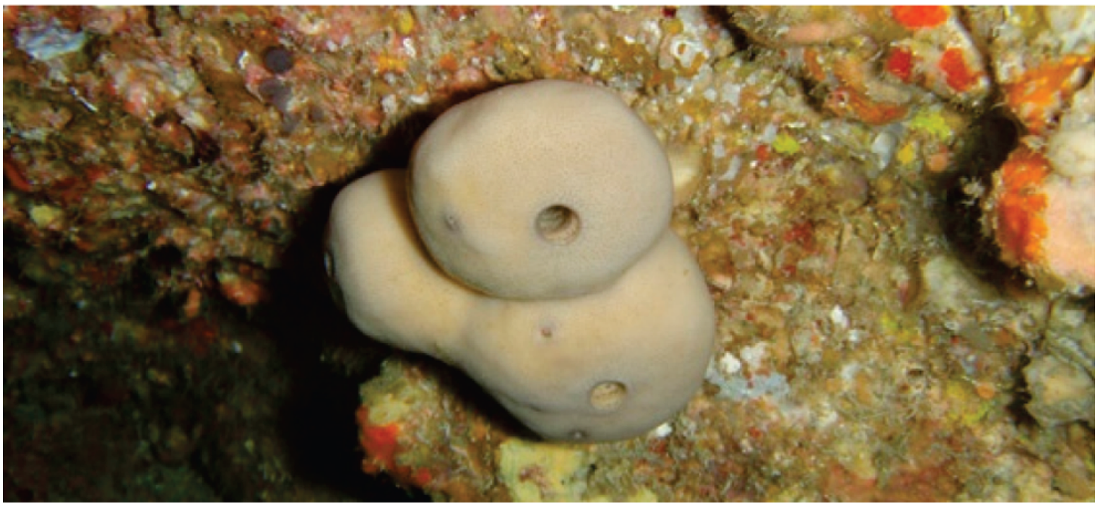
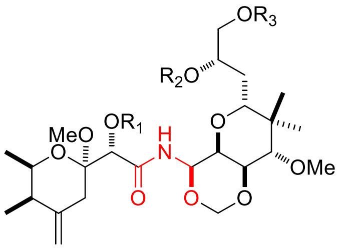


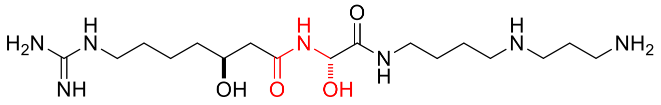
Figure 4: The marine sponge *Fasciospongia rimosa* found at Cape Zampa in Okinawa.[7]

Preliminary biological results revealed (–)-zampanolide ((–)-**1**) to be an effective inhibitor of cancer cell proliferation with *in vitro* IC_{50}'s between 1–5 ng/ml for P338 (leukemia), A549 (lung), HT29 (colon) and MEL28 (melanoma) cells. Five years later, in 2001, *Cutignano*[8] and co-workers reported the isolation and preliminary biological evaluation of the structurally related 20-membered marine macrolide (+)-dactylolide ((+)-**2**) (Figure 3), which was isolated from the sponge *Dactylospongia sp*. at Vanuatu



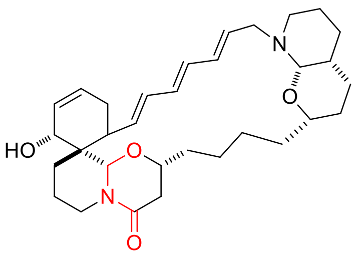
OR3
R2O
OR1
MeO
H
N
O
O
O
O
OMe

R_1=R_2=R_3=H: Mycalamide A (**I-1a**)
R_1=R_3=H, R_2=Me: Mycalamide B (**I-1b**)

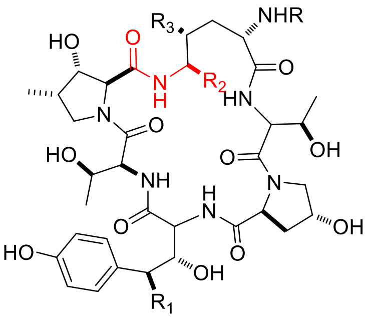


H2N
H
N
NH
OH
H
N
O
OH
O
N
H
H
N
NH2

(–)-Spergualin (**I-2**)



Upenamide (**I-3**)



R3
NHR
HO
O
N
H
R2
O
HN
N
O
HO
OH
O
NH
N
H
N
OH
O
O
HO
OH
R1

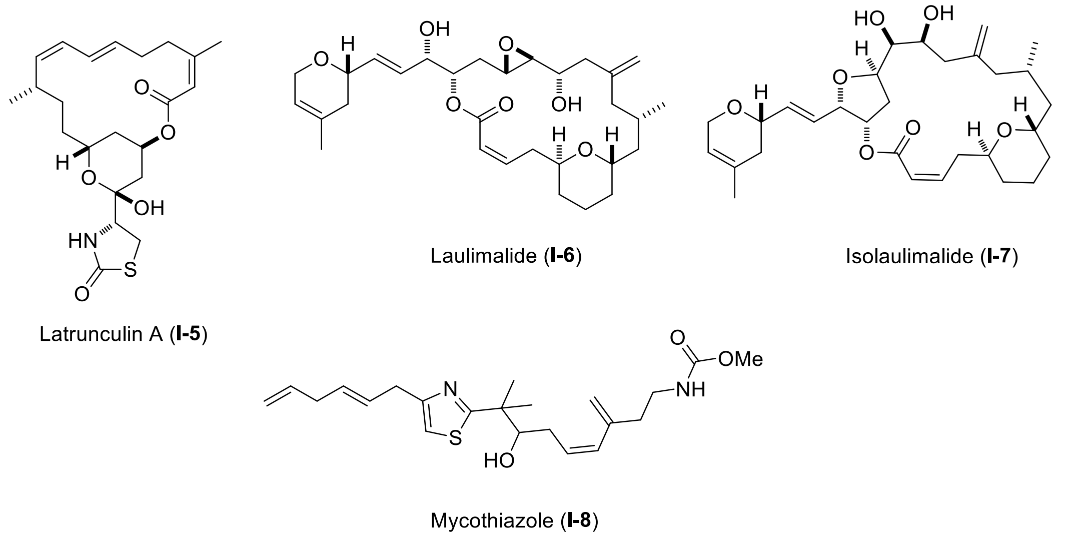
R_1=R_2=R_3=OH, R= Linoleic acid: Echinocandin B (**I-4a**)
R_1=R_2=R_3=OH, R= Stearic acid : Tetrahydroechinocandin B(**I-4b**)

Figure 5: Natural products containing *N*-hemiaminal motifs.

Islands along with a number of other macrolides, such as latrunculin A (**I-5**), laulimalide (**I-6**), isolaulimalide (**I-7**), and mycothiazole (**I-8**) (Figure 6).[8] However, (+)-dactylolide ((+)-**2**) is only a moderately potent inhibitor of human cancer cell growth with IC_{50}'s in the low μM range against the L1210 (mouse lymphocytic leukemia) and SK-OV-3 (ovarian tumor) cell lines (63% and 40% inhibition at 3.2 μg/mL, respectively).

In spite of the distant geographical location of the sponges from which (–)-zampanolide ((–)-**1**) and (+)-dactylolide ((+)-**2**) were isolated, their core structures initially were assumed to be identical. *Smith* and co-workers[9] where the first to show by way of total synthesis that the absolute configuration of the macrolactone core structure in (–)-zampanolide ((–)-**1**), however, is opposite to that found in natural (+)-dactylolide ((+)-**2**).

More recently, *Miller* and co-workers have reported the isolation of (–)-zampanolide ((–)-**1**) from the *Togan* sponge *Cacospongia mycofijiensis* (Figure 7) and they demonstrated the compound to be an efficient promotor of tubulin assembly.[10] In addition, the data revealed that (–)-zampanolide ((–)-**1**) is not a substrate for the P-glycoprotein (Pgp) efflux pump[10] thus indicating a potential for (–)-zampanolide ((–)-**1**) for the treatment of multidrug-resistant tumors.


Latrunculin A (**I-5**)

Laulimalide (**I-6**)

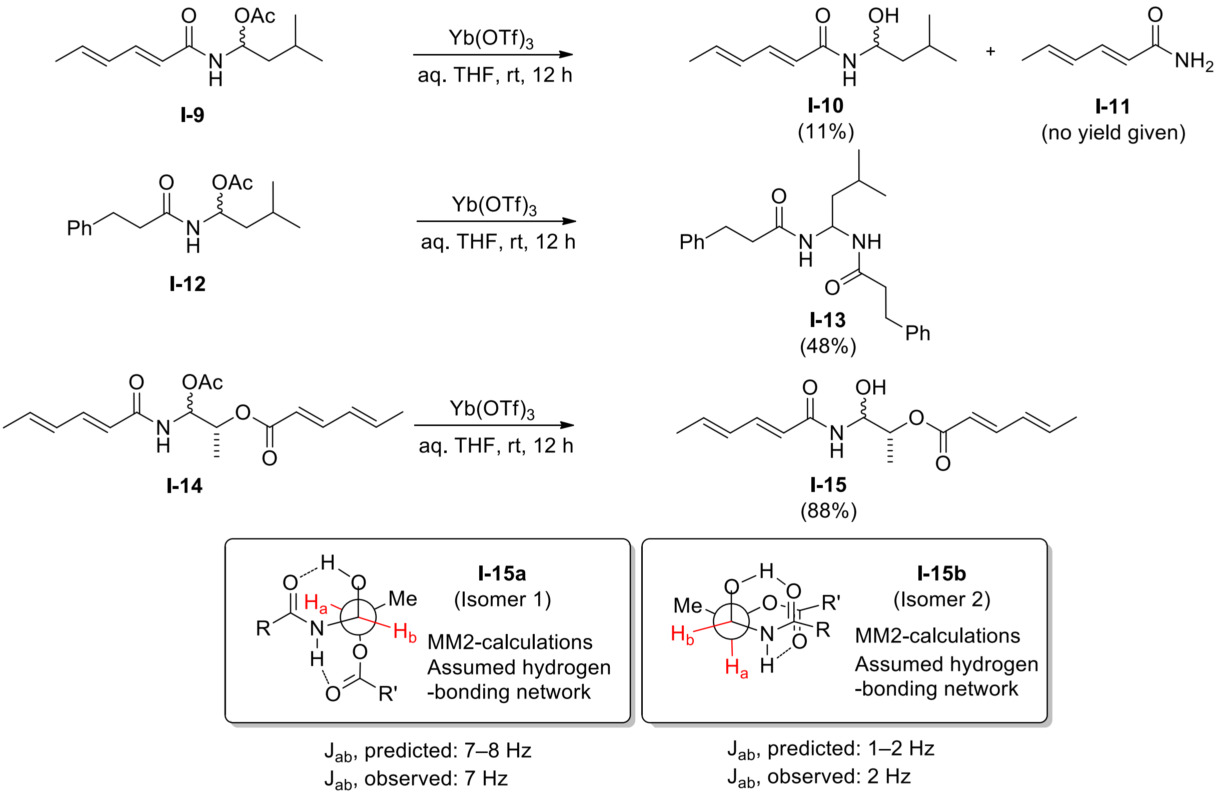
Isolaulimalide (**I-7**)

Mycothiazole (**I-8**)

Figure 6: Structures isolated from a sponge of the genus *Dactylospongia* along with (+)-dactylolide ((+)-**2**).[8]

Figure 7: Fijian sponge *Cacospongia mycofijiensis* from which (–)-zampanolide ((–)-**1**) has recently been isolated.[10-11]

The stability of (–)-zampanolide ((–)-**1**) with respect to the *N*-acyl hemiaminal substructure is astonishing since one might expect this functionality to exhibit a pH-dependent intrinsic instability. However, the presence of this moiety in several natural products could indicate that certain stabilizing elements are operative. For example, *Porco* and co-worker have proposed a hydrogen-bonding network as a plausible stabilizing element in the case of (–)-zampanolide ((–)-**1**),[12] as shown for model system **I-15** (Scheme 2**).** In their work towards the synthesis of (–)-zampanolide ((–)-**1**), sorbamide model substrates **I-9**, **I-12**, **I-14** were constructed to elaborate their stability during solvolysis. Interestingly, compounds **I-9** and **I-12**, could only be solvolyzed in poor yields (11–48%); however, model compound **I-14**, which resembles (–)-zampanolide ((–)-**1**) afforded alcohol **I-15** in excellent yield. Two hydrogen-bonding networks are present in **I-15,** which help stabilize the structure after hydrolysis of the acetate moiety as indicated in the *Newman* projections shown for both isomers of **I-15** in Scheme 2. Evidence comes from the predicted vicinal J_{ab}-coupling constant on the basis of the *Karplus* relationship[13] which is in agreement with the observed coupling constants of 2 Hz and 7 Hz, respectively for the individual isomers (Scheme 2). Further evidence was obtained by the measured down-field shift of 0.6-0.8 ppm of the hydrogen-bonded amide proton in **I-15** relative to the non-hydrogen-bonded amide proton in **I-10** which is in agreement with literature data for hairpin structures.[14]


I-9
Yb(OTf)3
aq. THF, rt, 12 h
I-10
(11%)
+
I-11
(no yield given)
I-12
Yb(OTf)3
aq. THF, rt, 12 h
I-13
(48%)
I-14
Yb(OTf)3
aq. THF, rt, 12 h
I-15
(88%)
I-15a
(Isomer 1)
MM2-calculations
Assumed hydrogen -bonding network
I-15b
(Isomer 2)
MM2-calculations
Assumed hydrogen -bonding network
Jab, predicted: 7–8 Hz
Jab, observed: 7 Hz
Jab, predicted: 1–2 Hz
Jab, observed: 2 Hz

Scheme 2: $Yb(OTf)_3$-mediated solvolysis of zampanolide model compounds.[12]

Interestingly, H-D exchange in **I-10** occurs at twice the rate of **I-15**, which lends further support to the presence of an intramolecular hydrogen-bonding network in (–)-zampanolide ((–)-**1**). Such a hydrogen-bonding network can cause structural rigidity, which not only helps to stabilize the whole molecular network in its natural environment and during isolation, but may also be elementary for the biological activity of (–)-zampanolide ((–)-**1**).

Hydrogen-bonding networks are not only important in defining secondary structures of proteins but might be a distinctive prerequisite for some natural products, e. g. for bafilomycin $A_{1,}$[15] to promote their biological effects.

1.2. The Non-Natural Product (–)-Dactylolide

The unexpected difference in the absolute stereochemistry of the macrolactone core structure between (–)-zampanolide ((–)-**1**) and (+)-dactylolide ((+)-**2**) leads to the question whether the intrinsically higher potency of (–)-zampanolide ((–)-**1**) is related to the presence of the hemiaminal side chain or is due to the opposite configurations of the 20-membered lactone core structures or both. The evaluation of the enantiomer of (+)-dactylolide ((+)-**2**), namely (–)-dactylolide ((–)-**2**) would allow to answer this question (Figure 8). Although the structural similarity between (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**) might imply a close biosynthetic relationship with (–)-zampanolide ((–)-**1**), (–)-dactylolide ((–)-**2**) has never been identified in any organism and it is unclear whether the compound in fact exists in nature.

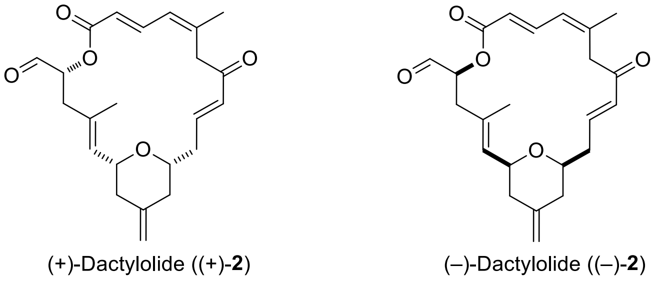
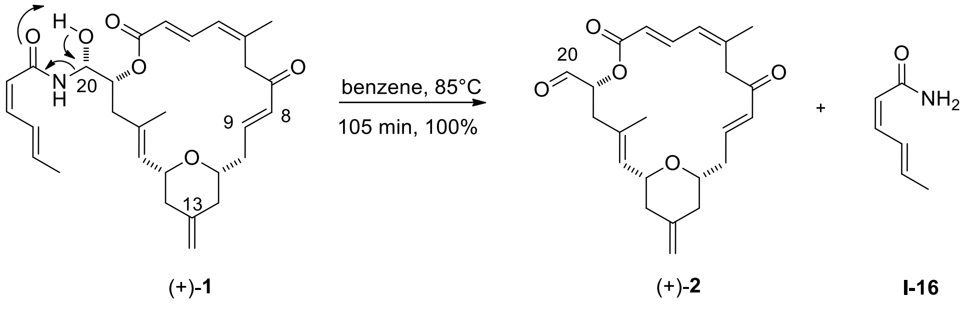


Figure 8: Natural occurring (+)-dactylolide ((+)-**2**) and its non-natural enantiomer (–)-dactylolide ((–)-**2**).

Smith and co-workers[9b] were able to show that by thermolysis of (+)-zampanolide ((+)-**1**) in benzene[1], the macrolactone aldehyde (+)-dactylolide ((+)-**2**) is obtained along with the (*Z*/*E*)-sorbamide side chain **I-16** (Scheme 3); this result can most probably be explained via a pseudo retro-ene reaction. Interestingly, base-promoted elimination (either with NEt_3, DBU or NaHMDS) did not lead to the anticipated fragmentation.



Scheme 3: Thermolysis of (+)-zampanolide ((+)-**1**) providing (+)-dactylolide ((+)-**2**) and the side chain **I-16**.

At the same time, *Tanaka* and co-workers[7] have recently reported that no trace of (–)-dactylolide ((–)-**2**) was detected upon exposure of either isolated (–)-zampanolide ((–)-**1**) or the whole sponge to the extraction conditions described by *Cutignano* and co-workers.[8] This shows that (–)-dactylolide ((–)-**2**) is not a degradation product of the natural product (–)-zampanolide ((–)-**1**), which leads to the assumption of distinctively different biosynthetic pathways for (–)-zampanolide ((–)-**1**) and (+)-dactylolide ((+)-**2**).[7]

---

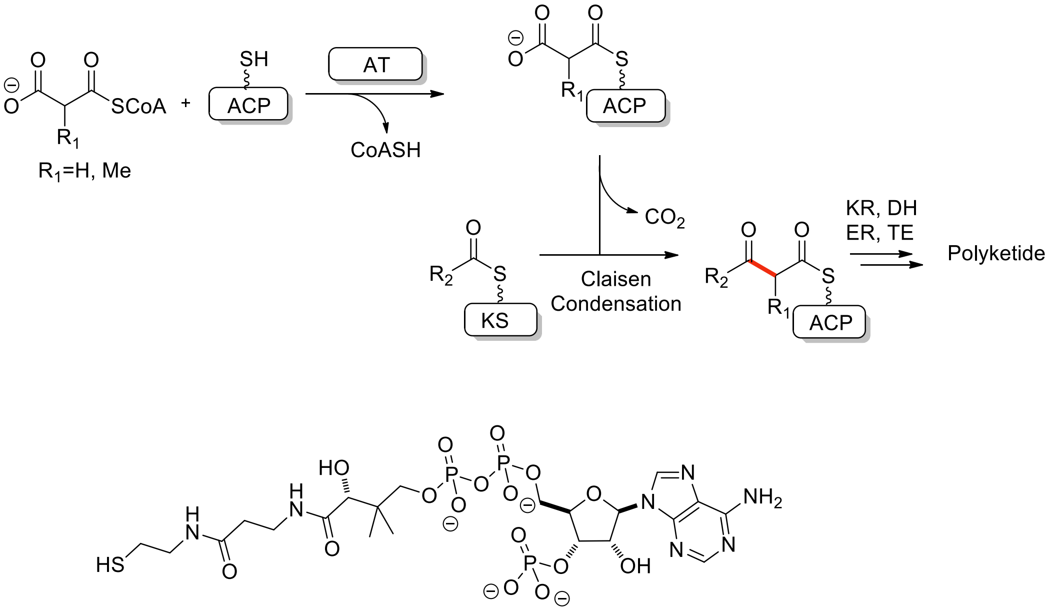
[1] (+)-Zampanolide ((+)-**1**) is not a known natural product.

The non-natural product (–)-dactylolide ((–)-**2**), therefore, is only accessible by way of synthesis. No targeted synthesis of (–)-dactylolide ((–)-**2**) had been reported in the literature at the outset of this Ph. D. project. In the meantime *Jennings* and co-workers have reported the synthesis and biological evaluation of synthetic (–)-dactylolide ((–)-**2**) and, interestingly, the data revealed that ((–)-**2**) is slightly more potent than natural (+)-dactylolide ((+)-**2**).[16] However, a direct comparison of the antiproliferative activity of (–)-dactylolide ((–)-**2**) and (+)-dactylolide ((+)-**2**) was only reported for the SK-OV-3 cell line, for which GI_{50} values were 1.8 μg/mL for ((–)-**2**) vs. 3.2 μg/mL for ((+)-**2**).[16] Given this minor difference in biological activity the significantly higher potency of (–)-zampanolide ((–)-**1**) compared to (+)-dactylolide ((+)-**2**) cannot be explained on the basis of the different configurations of their macrocyclic core structures. Thus, the hemiaminal side chain and perhaps associated, local conformational effects must be responsible for the profound difference in biological potency between (–)-zampanolide ((–)-**1**) and (+)-dactylolide ((+)-**2**).

1.3. The Biosynthesis of Polyketide Natural Products

Speculations about distinctly different biosynthetic pathways for (–)-zampanolide ((–)-**2**) and (+)-dactylolide ((+)-**2**) leads to the question of how nature, as an unrivalled chemist, creates macrocyclic lactones in general. This chapter provides a brief outline of the biosynthesis of polyketides in general and exemplifies the steps of the biosynthesis of the macrolide natural product 6-deoxyerythronolide B (**I-17**), which is the sugar-free core macrolactone of the important antibiotic erythromycin (Figure 9).[17]

Polyketide synthases (PKS) are large multifunctional polypeptides containing several enzymatic functions, also called domains, which are combined in modules. All macrolide modules contain in the minimum a β-keto acyl-CoA synthase (KS), an acyltransferase (AT) and an acyl carrier protein (ACP) as important enzymatic functions which allow the construction of the polyketide chain in a linear, uninterrupted way.[17c] Central for the build-up of the carbon skeleton is the *Claisen* reaction between an extender unit and the growing acyl chain (Scheme 4). The extender units, malonyl (R_1=H) or methylmalonyl (R_1=Me) are bound via a thioester bond to coenzyme A (CoA) and loaded to the acyl carrier protein (ACP) via the acyltransferase (AT) domain to produce the malonyl– or methylmalonyl-S-ACP. The KS domain not only catalyzes the decarboxylation reaction and provides the necessary C2-thioenolate nucleophile, it furthermore transfers the acyl chain from the active-site cysteine to the attacking C2-enolate under formation of a new C-C bond (highlighted in red in Scheme 4).[18]



Coenzyme A (CoA)

Scheme 4: Elongation of the KS-bound polyketide chain by the incorporation of C2-units either derived from malonyl- (R_1 = H) or from methylmalonyl-SCoA (R_1 = Me). The *Claisen* condensation is the central reaction for the formation of the new C-C bond (highlighted in red).[18] Further modifications of the *β*-keto group might involve the action of *β*-keto reductase (KR), dehydratase (DH), enoylreductase (ER) and thioesterase (TE) (explanation see text).[18]

PKS modules can be equipped with other domains which allow the stereoselective reduction of the *β*-keto group with NADPH to the hydroxyl group via the *β*-keto reductase (KR).[19] The elimination of the formal aldol product is promoted by the dehydratase (DH) giving the trans product exclusively which might further be reduced under the influence of the enoylreductase (ER) and NADPH giving access to the unsaturated product that would finally lead to the synthesis of fatty acids. All macrolactone PKS contain a thioesterase (TE) at the C terminus of the last module, which catalyzes the release of the polyketide chain from the PKS and its cyclization to the lactone moiety. In many cases, post-polyketide modifications are necessary to convert the macrolide into the final natural product.[17c]

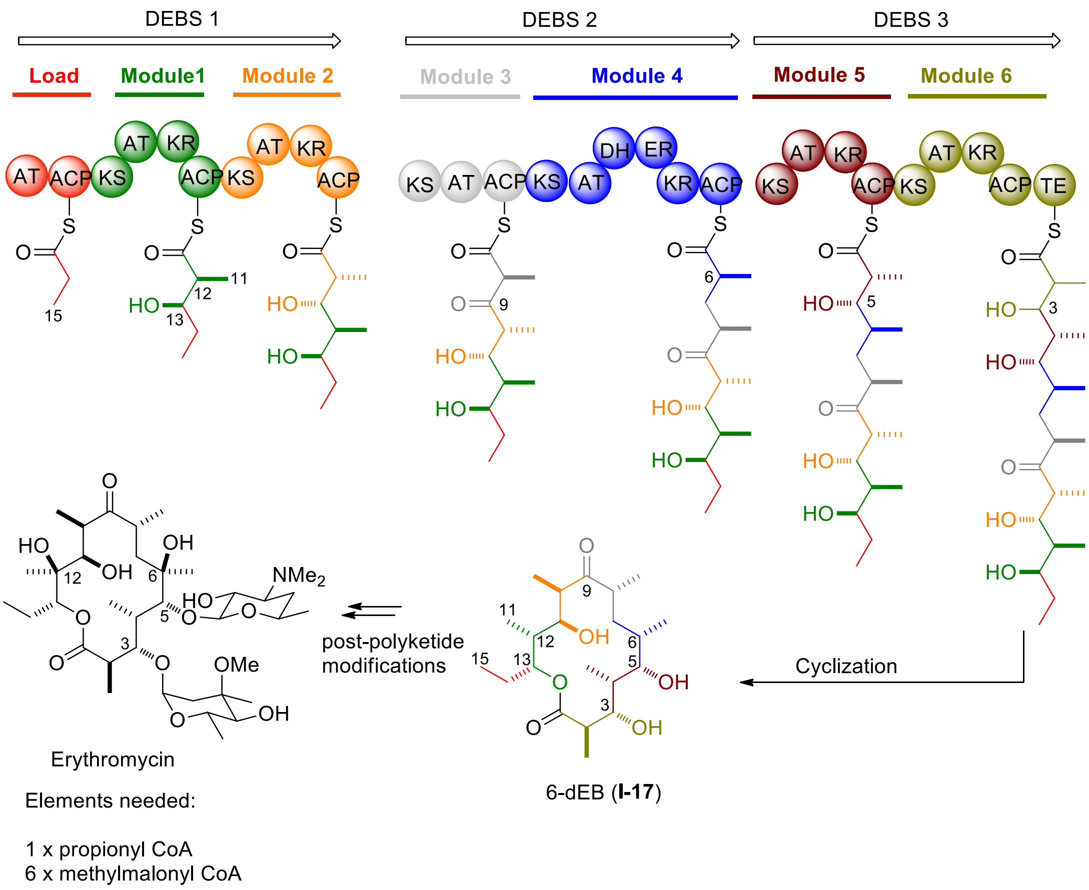

DEBS 1
DEBS 2
DEBS 3
Load
Module1
Module 2
Module 3
Module 4
Module 5
Module 6
AT
ACP
KS
KR
DH
ER
TE
S
O
HO
OH
NMe2
OMe
O
Erythromycin
Elements needed:
1 x propionyl CoA
6 x methylmalonyl CoA
post-polyketide modifications
Cyclization
6-dEB (I-17)

Figure 9: Organization of the polyketide synthase domains for the synthesis of DEB (**I-17**). The polyketide synthase (PKS) DEBS contains six elongation modules and a loading module. Each is responsible for a single elongation cycle of the polyketide chain and consists of a set of catalytic domains (highlighted in colored spheres).[17c]

The PKS involved in the biosynthesis of deoxyerythronolide B (DEB, (**I-17**)), specifically consists of six elongation modules and a loading module. A propionyl unit is bound to the AT domain which is transferred to the ACP domain in the loading module, highlighted in red (Figure 9).[17c] The propionyl residue is then transferred to the KS domain of module 1 under formation of the first C-C bond, which is followed by stereoselective reduction of the *β*-keto group by the KR domain. As indicated by the color code in Figure 9, the propionyl unit and the first extender unit become the C11-C15 sequence in the completed aglycone **I-17**. The acyl chain is then transferred to the KS of module 2 and condensed with the next methylmalonyl CoA extender unit affording the triketide; this is followed by reduction of the *β*-keto group by the KR2 domain. The next step needs the controlled interpolypeptide transfer of the growing acyl chain from the ACP of module 2 to the KS of module 3 followed by incorporation of the next methylmalonyl extender unit. The *β*-keto group is not reduced and forms the C9 keto group in **I-17**. After the fourth condensation the *β*-keto group is transformed into the methylene group at C7 by the KR4, DH4 and ER4 domains. The fifth and sixth condensations are each followed only by reduction of the *β*-keto group providing the C3 and C5 hydroxyl groups. The TE domain in module 6 catalyzes the release of the completed acyl chain from the PKS and promotes lactonization via attack of the C13 hydroxyl group. Post-polyketide modifications such as hydroxylation at C6 and C12 and glycosylation at C3 and C5 then complete the biosynthesis of erythromycin.[17c, 20] Overall the biosynthesis of erythromycin involves the separate synthesis of the aglycone and the sugars.

Recent developments in genetic engineering now allow the modifications of specific activities of individual PKS domains, thus changing the structure of the macrolide produced. *Jacobsen* and co-workers reported the artificial design of novel erythromycin analogs by combining chemical synthesis, genetics and fermentation.[21]

The biosyntheses of (–)-zampanolide ((–)-**1**) and (+)-dactylolide ((–)-**2**) must follow identical concepts as shown in Scheme 4 and Figure 9; however, their details, especially related to the incorporation of the unusual *N*-acyl hemiaminal side chain, remain unknown up to now.

1.4. Synthetic Efforts towards Zampanolide and Dactylolide

(–)-Zampanolide ((–)-**1**) and (+)-dactylolide ((+)-**2**) are interesting targets for total synthesis not only because the amounts of material that have been obtained from natural sources are insufficient for extensive biological evaluation, but also due to their appealing molecular architecture. (–)-Zampanolide ((–)-**1**) and (+)-dactylolide ((+)-**2**) contain a number of synthetically challenging structural moieties such as the uncommon *N*-acyl hemiaminal side chain, in case of (–)-zampanolide ((–)-**1**), the 2,6-bis-functionalized THP subring having an exocyclic methylene unit attached, as well as the various substituted C=C double bonds present in (*E*) and (Z) configurations.

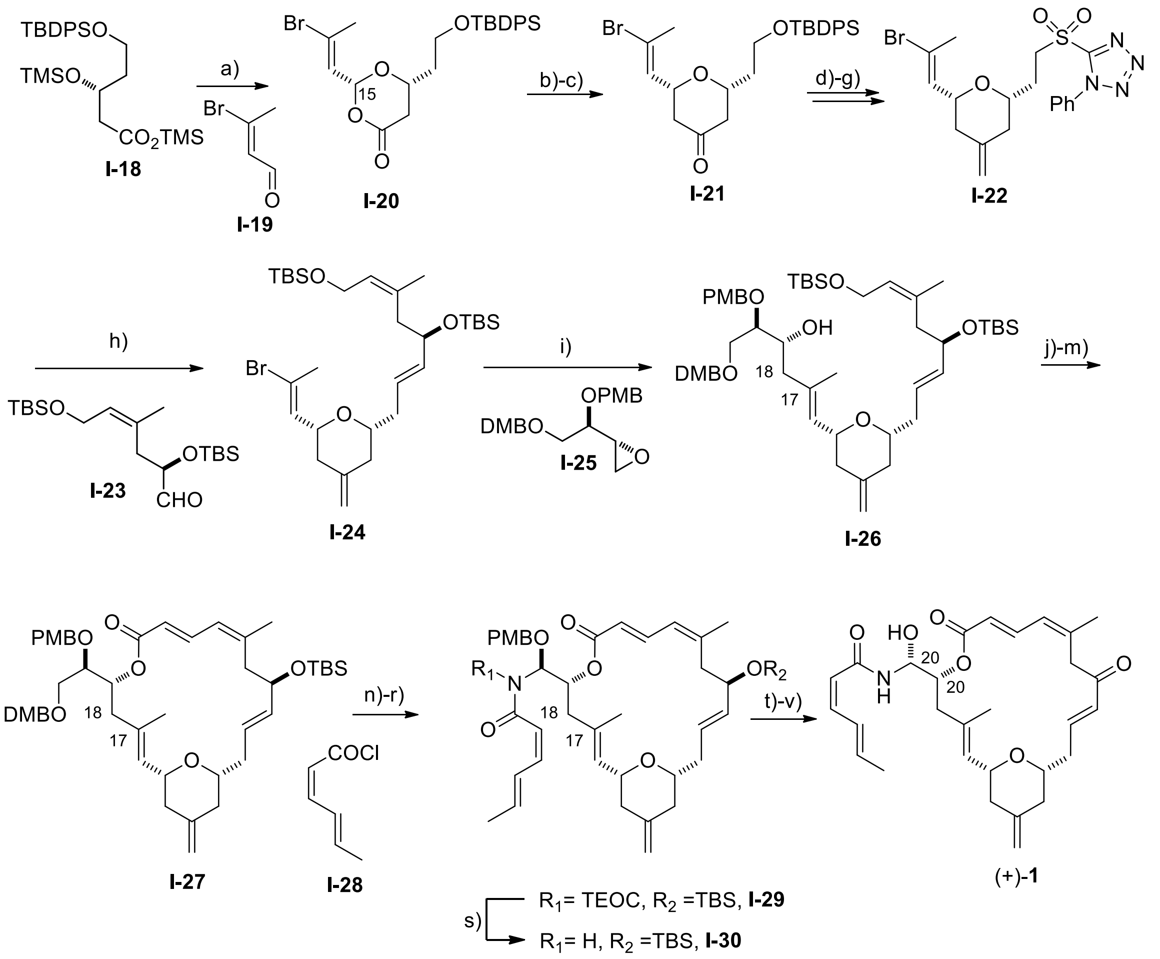
This section reviews the key strategic elements of previous syntheses by other groups listed in chronological order.

1.4.1. Synthesis of (+)-Dactylolide and (+)-Zampanolide by *Smith*

The first contributors in the field of zampanolide and dactylolide synthesis were *Smith* and co-workers who reported a unified strategy in which the synthesis of both (+)-dactylolide ((+)-**2**)[9b] and (+)-zampanolide ((+)-**1**)[9a, 9c] were addressed simultaneously. These early synthetic endeavors not only culminated in the development of an attractive approach to (+)-zampanolide ((+)-**1**) but also led to the establishment of the absolute stereochemistry of the natural product. Conceptual highlights in *Smith's* approach are the late-stage introduction of the side chain to an amine derived from a *Curtius*[22] rearrangement and the construction of the THP subring via a *Petasis-Ferrier*[23] cyclization as summarized in Scheme 5.

The application of the desired *Petasis-Ferrier* rearrangement required first the condensation between acid derivative **I-18** and unsaturated bromo aldehyde **I-19**, affording **I-20** as an inseparable 10:1 mixture of C15 epimers in favor of the desired isomer (Scheme 5). *Petasis* olefination followed by treatment with Me_2AlCl as the *Lewis* acid afforded the ketone **I-21** in 59% isolated yield as a pure stereoisomer. **I-21** in turn was readily converted into the sulfone **I-22** as the precursor for a *Julia-Kocienski* olefination[24] with aldehyde **I-23** which proceeded in high yield. The crucial epoxide opening with **I-25** turned out to be difficult and required extensive optimization. Eventually the use of the cyano-*Gilman* cuprate led to the desired alcohol **I-26** upon rigorous exclusion of oxygen.

A *HWE* cyclization was chosen to close the macrocycle through formation of the C2-C3 C=C double bond. Thus, **I-26** was converted to the corresponding phosphonate using *Steglich* conditions (DCC, DMAP), which was followed by base-induced macrocyclization to form the protected macrolactone **I-27**. Noteworthy is the failure to form the ester phosphonate under *Mitsunobu*[25] conditions (employing the C19 epimer of **I-26**), which led to retention of configuration at C19! Oxidative DMB removal, oxidation of the free alcohol to the carboxylic acid and conversion of the acid into the acyl azide set the stage for a *Curtius* rearrangement which afforded, after amide formation with acid chloride **I-28** the TEOC ester **I-29** in good yield (66%).

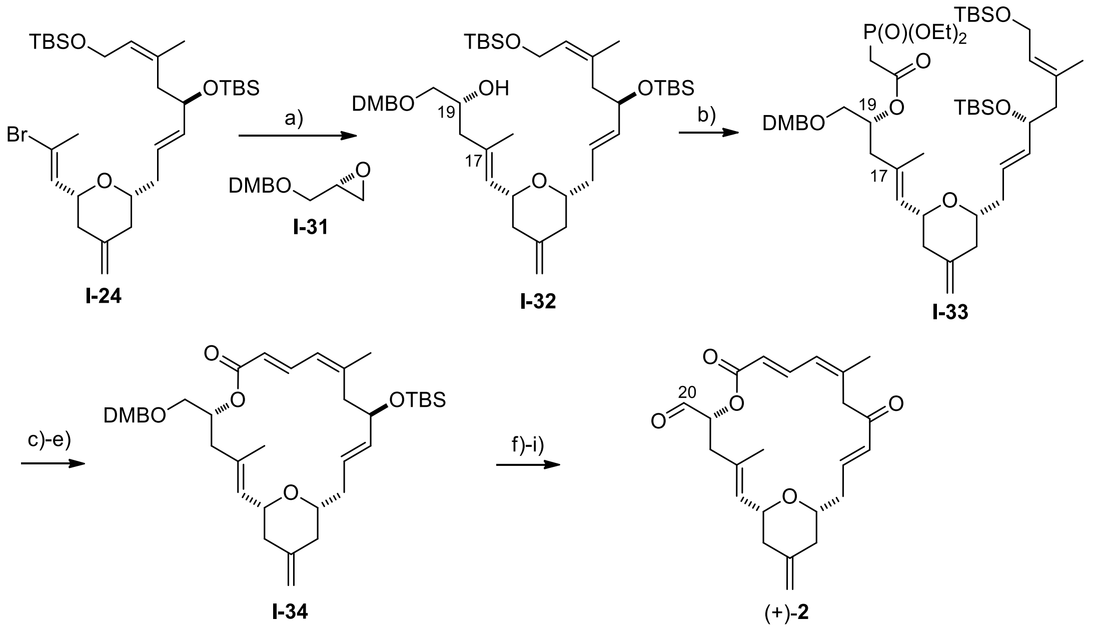

TBDPSO
TMSO
CO_2TMS
I-18
a)
Br
O
I-19
OTBDPS
15
I-20
b)-c)
I-21
d)-g)
Ph
I-22
h)
TBSO
OTBS
CHO
I-23
I-24
i)
OPMB
DMBO
I-25
PMBO
OH
18
17
I-26
j)-m)
I-27
COCl
I-28
n)-r)
R_1
N
OR_2
t)-v)
HO
20
H
(+)-1
s)
R_1= TEOC, R_2 =TBS, I-29
R_1= H, R_2 =TBS, I-30

Scheme 5: (a) TMSOTf, TfOH, CH_2Cl_2, –78 °C, **I-19**, dr 10:1 at C15, 82%; (b) Cp_2TiMe_2, THF, 65 °C, 19h, 72%; (c) Me_2AlCl, CH_2Cl_2, –78 to 0 °C, then $NaHCO_3$, NEt_3, 0 °C to RT, separation of C15-anti isomer, 59%; (d) $Ph_3P{=}CH_2$, THF, 0 °C to RT, 98%; (e) HF, CH_3CN, 97%; (f) DEAD, PPh_3, $C_{13}H_{19}N_5S$, 95%; (g) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, 69%; (h) KHMDS, THF, –78 °C then **I-23**, 88%; (i) *t*-BuLi (1.7 equiv), (2-Th)CuCNLi (1.05 equiv), Et_2O/THF, **I-25**, –45 °C to 0°C, 69-72%; (j) $HO_2CCH_2PO(OEt)_2$, DCC, DMAP, CH_2Cl_2, 94%; (k) HF•py, THF, 72%; (l) DMP, CH_2Cl_2, 92%; (m) NaHMDS, THF, 0.006M, –78 °C to RT, 72%; (n) DDQ, CH_2Cl_2, 59%; (o) DMP, CH_2Cl_2; (p) $NaClO_2$, Na_2HPO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 70% (2 steps); (q) i) *i*-Pr_2NEt, *i*-BuOCOCl, ii) NaN_3, H_2O, 0 °C, iii) toluene, heat, 15 min, iv)$TMSCH_2CH_2OH$, heat, 3h, 66%; (r) NaHMDS, THF, –78 °C, **I-28**, 58%; (s) TBAF, 0 °C, 93%; (t) TBAF, 81%; (u) DMP, CH_2Cl_2, quant.; (v) DDQ, CH_2Cl_2, pH7 buffer, RT, separation of epimers.

Protecting group removal was uneventful, except that the removal of the PMB group resulted in an unavoidable epimeric mixture at C20. The separation of the C20-epimers was possible by RP-HPLC, however, without indicating the exact analytical column used.

The natural product (+)-dactylolide ((+)-**2**) was obtained in full analogy to the approach towards (+)-zampanolide ((+)-**1**), by changing the epoxide from **I-25** to **I-31**

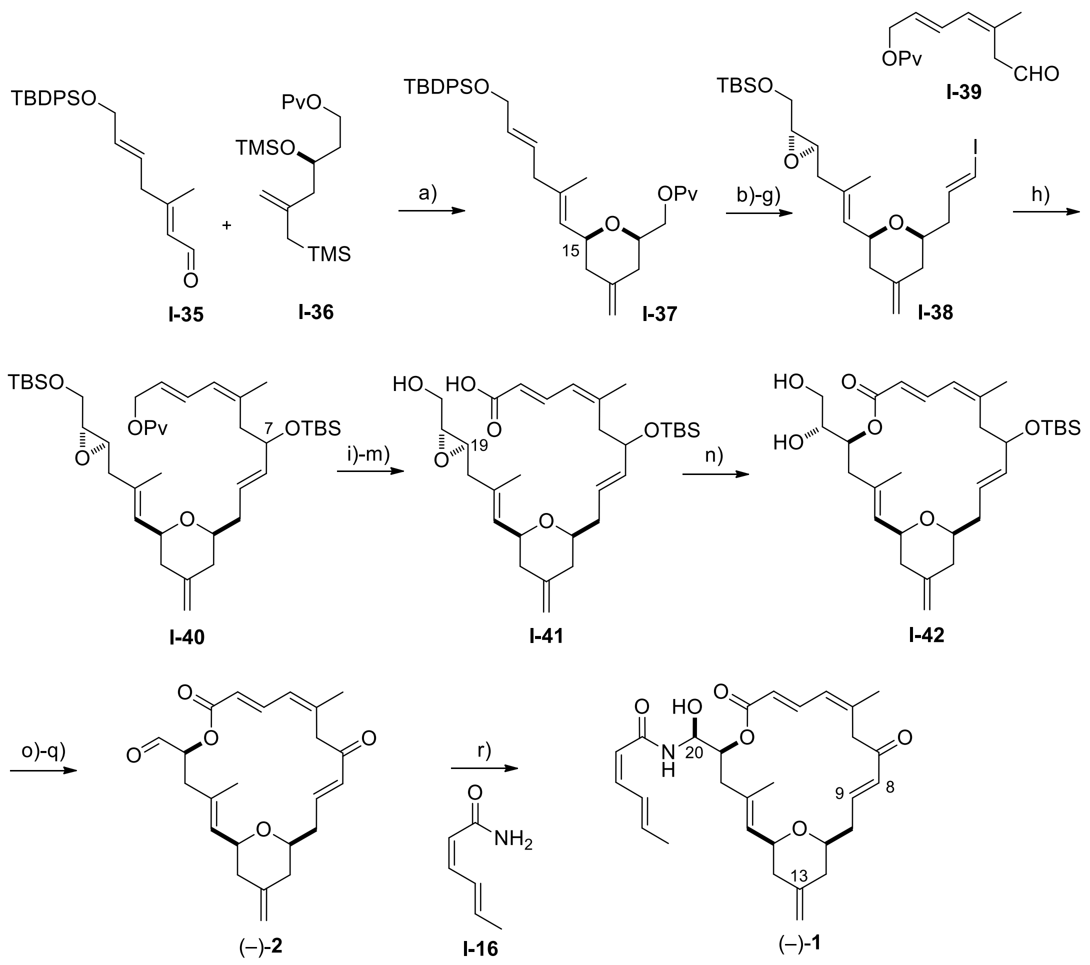
(Scheme 6). The efficiency of individual steps was similar to that in the case of (+)-zampanolide ((+)-**1**), albeit the epoxide opening reaction with DMB-protected (*S*)-glycidol (**I-31**) proceeded in only 40% yield or less.



Scheme 6: (a) *t*-BuLi (1.7 equiv), (2-Th)CuCNLi (1.05 equiv), Et_2O/THF, **I-31**, –45 °C to 0°C, 40%; (b) $HO_2CCH_2PO(OEt)_2$, DCC, DMAP, CH_2Cl_2, 96%; (c) HF•py, THF, 62%; (d) DMP, CH_2Cl_2, 95%; (e) NaHMDS, THF, 0.006M, –78 °C to RT, 72%; (f) TBAF, THF, rt, 62%; (g) DMP, CH_2Cl_2, 80%; (h) DDQ, CH_2Cl_2, wet H_2O, 90%; (i) DMP, CH_2Cl_2, 77%.

1.4.2. Synthesis of (–)-Dactylolide and (–)-Zampanolide by *Hoye*

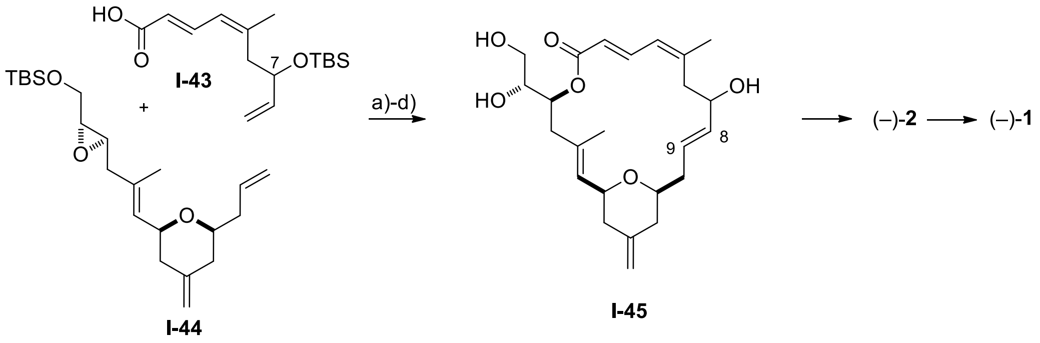
Shortly after the very first total synthesis by *Smith* and co-workers, *Hoye* and co-workers[26] reported an alternative approach that was based on macrocyclization through the regioselective Ti(O*i*-Pr)$_4$-mediated epoxide opening of a 2,3-epoxy alcohol (Scheme 7), an approach inspired by prior work by *Sharpless*.[27] A highly efficient *Hosomi-Sakurai* allylation[28] reaction between the unsaturated aldehyde **I-35** and allylsilane **I-36**, promoted by CSA under optimized conditions, provided the fully substituted THP subring of **I-37** in an elegant way. **I-37** was then functionalized to the TBS-protected vinyl iodide **I-38** which in turn was chosen to couple to the aldehyde fragment **I-39** via its lithium organyl giving rise to a 1:1 mixture of C7 epimers in **I-40**. This step was hampered by low yields, most probably due to the acidity of the aldehyde functionality and is the least efficient step in the synthesis.


TBDPSO
O
I-35
PvO
TMSO
TMS
I-36
a)
TBDPSO
OPv
15
O
I-37
b)-g)
TBSO
O
I
I-38
OPv
CHO
I-39
h)
TBSO
OPv
7
OTBS
I-40
i)-m)
HO
HO
O
19
OTBS
I-41
n)
HO
O
HO
O
OTBS
I-42
o)-q)
O
O
O
(–)-2
r)
O
NH2
I-16
O
HO
O
N
H
20
O
O
9
8
13
(–)-1

Scheme 7: (a) CSA (5 mol %), Et$_2$O, 78%; (b) DIBAL-H, CH$_2$Cl$_2$, 80%; (c) DMP, CH$_2$Cl$_2$, 82%; (d) CrCl$_2$, CHI$_3$, THF, 76%; (e) TBAF, THF, 72%; (f) *Sharpless* asymmetric epoxidation, –25 °C, 89%; (g) TBSCl, ImH, CH$_2$Cl$_2$, 98%; (h) *n*-BuLi, Et$_2$O, –78 °C; then **I-39**, Et$_2$O, 58%; (i) TBSOTf, 2,6-lutidine, –78 °C, CH$_2$Cl$_2$, 90%; (j) DIBAL-H, CH$_2$Cl$_2$, 97%; (k) MnO$_2$, CH$_2$Cl$_2$, 98%; (l) NaClO$_2$, NaH$_2$PO$_4$, *t*-BuOH/H$_2$O, 2-methyl-2-butene, 85%; (m) TBAF, THF, 52%; (n) Ti(O*i*-Pr)$_4$, CH$_2$Cl$_2$, 75 °C, 40% (30% recovered sm); (o) TBAF, THF, 85%; (p) 4-acetylamino-2,2,6,6- tetramethylpiperidine-1-oxoammonium tetrafluoroborate, SiO$_2$, CH$_2$Cl$_2$, 80%; (q) Pb(OAc)$_4$, benzene, 90%; (r) **I-16**, DIBAL-H, THF, RT then (–)-**2**.

The macrolactonization could be promoted by juxtaposition of reactants through coordination to the titanium center thus leading to the desired epoxide opening at C19 by the carboxylate group at elevated temperature (75 °C). However, macrolactone **I-42** still was obtained in only 40% yield along with recovered sm. Conversion of **I-42** into (–)-dactylolide ((–)-**2**) could then be accomplished by TBS removal, chemoselective allylic oxidation at C7 by the use of *Bobbitt's*[29] reagent (4-acetylamino-2,2,6,6–tetramethylpiperidine-1-oxoammonium tetrafluoro borate) and finally diol cleavage.

As an alternative approach, a ring-closing metathesis reaction (RCM) to form the C8-C9 C=C double bond was also established. To this end, acid **I-43** and epoxide **I-44** were first coupled via the intermolecular titanium-mediated epoxide opening reaction, affording higher yields (67%) as compared to the intramolecular case in **I-41**. RCM worked well for both C7-epimers which were both temporarily protected as their TBS ethers (Scheme 8). A non-selective aza-aldol reaction between (–)-dactylolide ((–)-**2**) and the aluminated side chain **I-16** (Scheme 7) afforded (–)-zampanolide ((–)-**1**) together with its C-20 epimer, which had to be separated by HPLC.



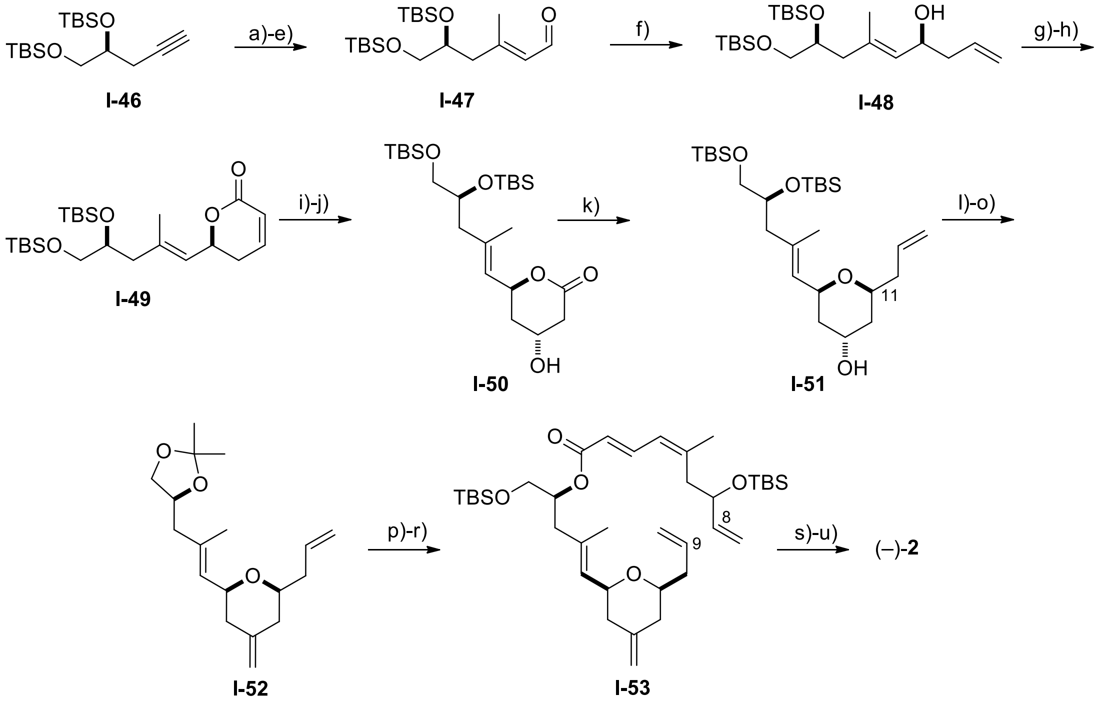
Scheme 8: (a) Ti(O*t*-Bu)$_4$, CH$_2$Cl$_2$, 75 °C, 67%; (b) BSA, benzene; (c) RuCHPhCl$_2$-(PCy$_3$)(H$_2$IMes), benzene, 60 °C, 77%; (d) TBAF, THF, 89%.

1.4.3. Synthesis of (–)-Dactylolide by *Jennings*

In 2005, *Jennings* and co-worker[30] reported the first targeted synthesis of (–)-dactylolide ((–)-**2**) which built up on the same RCM-macrocyclization concept at C8-C9 as employed by *Hoye*. The novelty in *Jennings'* contribution is found in the construction of the THP subring, which was based on an RCM approach to afford the unsaturated 6-membered lactone **I-49** followed by a *β*-C-glycosidation to form the C11 stereocenter (Scheme 9). The synthesis started from acetylene **I-46** which was readily converted to the unsaturated lactone **I-49**. The introduction of the exocyclic C=C double bond at C13 was achieved via the substrate controlled epoxidation in **I-49** and its regioselective opening with in situ generated PhSeNa[31] to produce, after reduction, **I-50**; the hydroxyl group was later converted to the desired methylene moiety.

A key step was the installment of the required allyl group via allyl-*Grignard* addition to the lactone carbonyl and subsequent reduction with Et$_3$SiH/TFA, thus forming the syn-substituted THP derivative **I-51**. The latter was elaborated into the

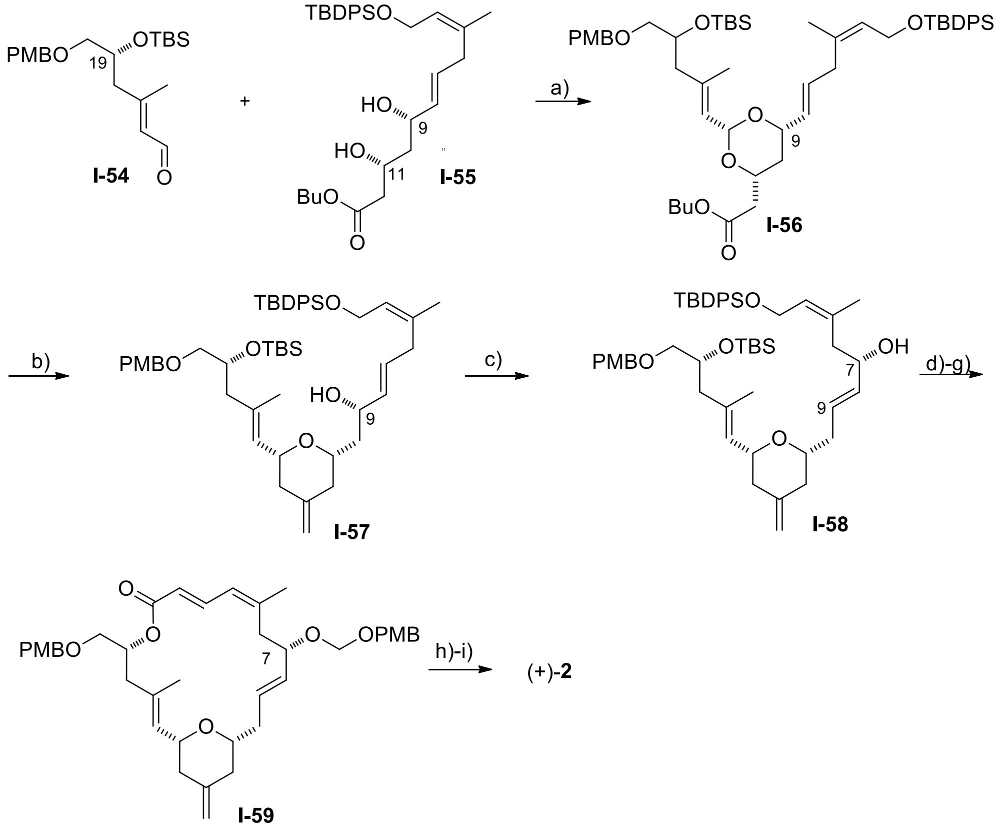
RCM substrate **I-53**, which was anticipated to from the C8-C9 C=C double bond in a similar way as reported by *Hoye*. Using *Grubbs'* 2nd generation catalyst[32] the macrolactone could then indeed be formed in excellent yield (93%).



Scheme 9: (a) *n*-BuLi, THF, –78 °C, then ClCOOEt, RT, quant.; (b) PhSH (1.2 equiv), NaOMe (5 mol %), MeOH, RT, 90%; (c) MeMgBr, CuI, THF, –78 °C to RT, 97%; (d) DIBAL-H; CH_2Cl_2, –78 °C, 95%; (e) PCC, NaOAc, CH_2Cl_2, RT, 94%; (f) (–)-Ipc$_2$BOMe, allylmagnesium bromide, Et_2O, 0 °C to RT, then **I-47**, –78 °C, 1 h; then H_2O_2, NaOH, H_2O/Et_2O, reflux, 3 h, 88%, 90% de; (g) acryloyl chloride, Et_3N, DMAP (5 mol %), CH_2Cl_2, RT, 16 h, 79%; (h) *Grubbs*' 2nd generation catalyst, CH_2Cl_2, reflux, 18 h, 96%; (i) H_2O_2, NaOH, MeOH, 0 °C to RT, 0.5 h, then benzene, reflux, 1 h, 83%; (j) $(PhSe)_2$, $NaBH_4$, EtOH, RT, then HOAc, 0 °C, 15 min, 78%; (k) allylmagnesium bromide, Et_2O, –78 °C, then Et_3SiH, TFA, CH_2Cl_2, –78 °C to –40 °C, 76%; (l) TBAF, THF; (m) 2,2-dimethoxypropane, *p*-TsOH (cat), CH_2Cl_2, RT, 16 h, 81% (2 steps); (n) PCC, NaOAc; CH_2Cl_2, RT, 74%; (o) $Ph_3P{=}CH_2$, THF, RT, 78%; (p) 1:1:1 TFA/EtOH/CH_2Cl_2, 0 °C; (q) TBSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to RT, 97% (2 steps); (r) **I-43**, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, toluene, RT, then the alcohol, DMAP, RT, quant.; (s) HCl, 4:1 MeOH/CH_2Cl_2, RT, 80%; (t) *Grubbs*' 2nd generation catalyst, CH_2Cl_2 (1 mM), RT, 93%; (u) DMP, CH_2Cl_2, 0 °C to RT, 90%.

1.4.4. Synthesis of (+)-Dactylolide by *Floreancig*

The *Floreancig*[33] synthesis of (+)-dactylolide ((+)-**2**) made extensive use of powerful asymmetric aldol methodology for the synthesis of advanced precursors, while an efficient *Peterson*-olefination/*Prins*-type cyclization was applied for THP ring construction (Scheme 10). Fragments **I-54** and **I-55** were needed to implement the projected cyclization strategy. Unsaturated aldehyde **I-54** was readily accessible via the Cu-pybox promoted vinylogous aldol[34] reaction that allowed the installation of the C19 stereocenter.

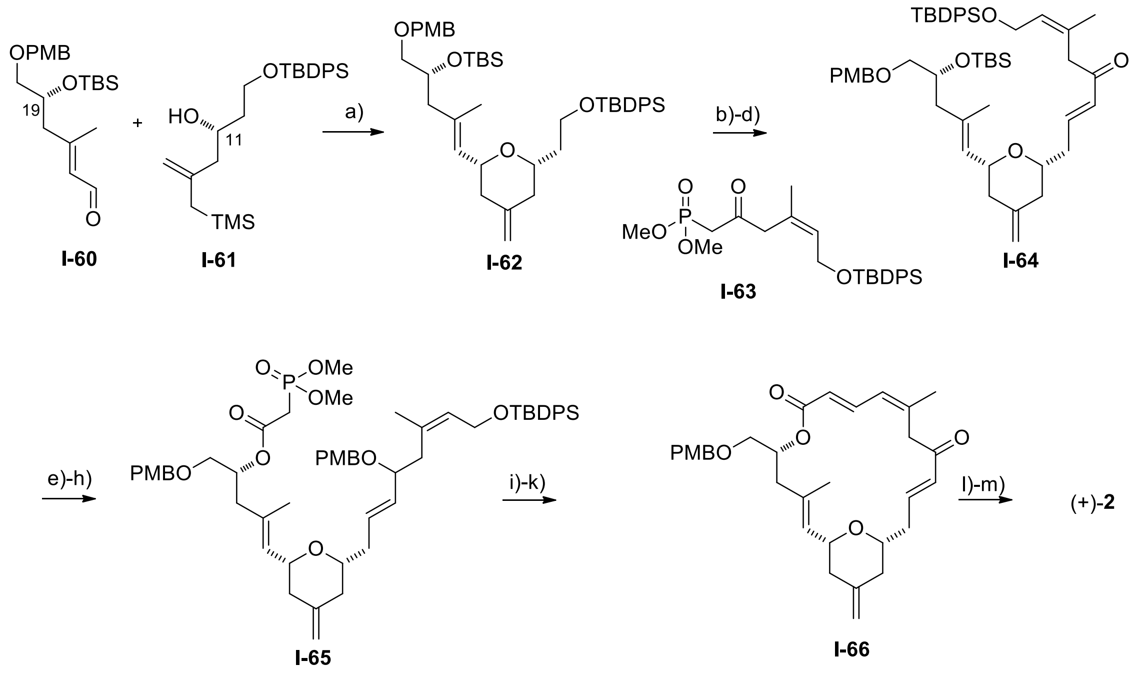


Scheme 10: (a) **I-55**, TMSCl, ImH, DMAP, DMF then **I-54**, TMSOTf, CH_2Cl_2, –78 °C, 83%; (b) $TMSCH_2MgCl$, $CeCl_3$, THF, –78 °C to RT, then py·HOTf, $MgSO_4$, CH_2Cl_2, 75%; (c) PhSeCN, Bu_3P, THF, then H_2O_2, py, THF, –30 °C, 62%; (d) $PMBOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, then HF·py, py, THF, 80%; (e) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 87%; (f) $HO_2CCH_2PO(OEt)_2$, DCC, DMAP, CH_2Cl_2, 95%; (g) NaHMDS, THF, –78 °C to 0 °C, 73%; (h) DDQ, CH_2Cl_2, buffer (pH 7), 63% (14% of C7 ketone); (i) DMP, CH_2Cl_2, 77%.

Butyl-protected diol **I-55** could be constructed by means of *Denmark's* bisphosphoramide[35] catalytic system for the creation of the C9 stereocenter which was followed by *syn*-reduction of the C11 keto group to the alcohol group. For the formation of the THP ring, fragments **I-54** and **I-55** were first linked via acetal formation, mediated by TMSOTf, followed by $CeCl_3$-mediated $TMSCH_2MgCl$ addition to the butylester, thus forming the carbinol. Upon treatment of this intermediate with py•HOTf and $MgSO_4$ a cascade of reactions is triggered where first the necessary allylsilane is formed which then reacts with the oxonium species derived from the cyclic acetal to produce **I-57**. The completely substituted THP subring with the exocyclic C=C double bond at C13 could be formed in a yield of 75% from **I-56**. The C9 hydroxyl group revealed in this process was then transposed though a selenium[36] version (PhSeCN, Bu_3P, H_2O_2) of the *Mislow-Evans* rearrangement[37] which proceeds via the conversion of the selenoxide to the selenate ester followed by hydrolysis, thus providing the transposed allylic alcohol **I-58**. PMB protection of the C7-OH group was difficult to achieve under acidic (PMBOC=(NH)CCl_3, BF_3•OEt_2) or basic conditions (NaH, NaI, PMBCl), but finally the conversion to the *p*-methoxybenzyloxymethyl ether proved to be feasible. The synthesis was then completed by applying a HWE-based macrocyclization at C2-C3 in analogy to *Smith*'s approach. Protecting group removal followed by oxidation finally afforded (+)-datcylolide ((+)-**2**).

1.4.5. Synthesis of (+)-Dactylolide by *Keck*

Motivated by their own development of methods for pyran annulations[38] and catalytic asymmetric allylations (CAA)[39], *Keck* and co-worker[40] reported a new total synthesis of (+)-dactylolide ((+)-**2**). Fragments **I-60** and **I-61** were designed for the projected pyran formation (Scheme 11). The stereocenter at C19 in fragment **I-60** was efficiently created via CAA using (*R*)-BINOL/Ti(O*i*-Pr)$_4$ (BITIP) as the catalyst. Allylsilane **I-61** could be created via a similar CAA in the presence of (*S*)-BITIP. Pyran annulation between **I-60** and **I-61** was efficiently promoted by TMSOTf affording **I-62** as a single stereoisomer in 85% yield. In contrast to the previously described approaches, the C8-C9 C=C double bond was efficiently created via a HWE reaction using β-keto phosphonate **I-63**, with *Paterson*'s[41] conditions (Ba(OH)$_2$) being superior over other methods such as *t*-BuOK or *Masamune*'s[42] conditions (CH_3CN, LiCl, *i*-Pr_2NEt). In the endgame, the keto moiety at C7 was first reduced under *Luche*[43] conditions, which was followed by applying *Smith*'s macrolactonization strategy where the C2-C3 C=C double bond was created via an intramolecular HWE reaction.

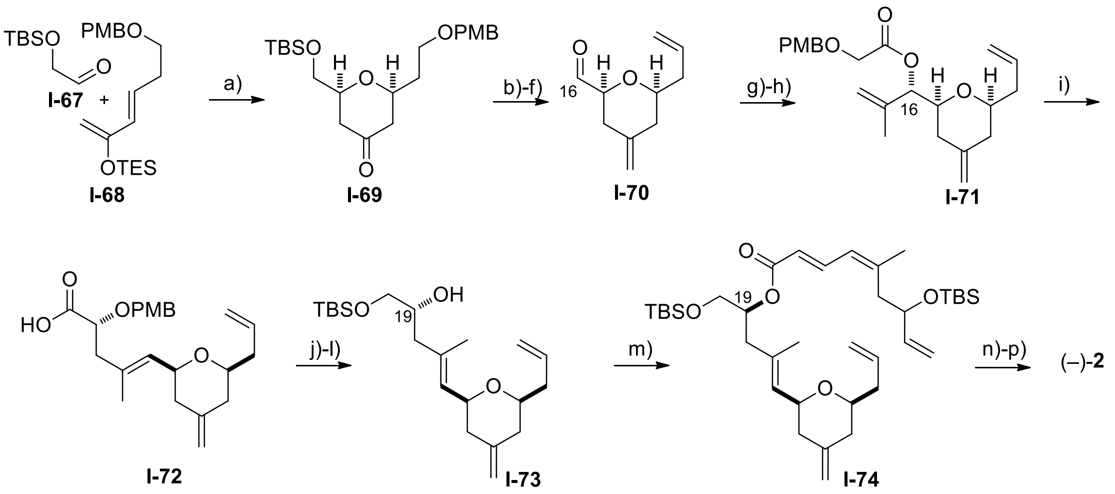


Scheme 11: (a) TMSOTf, Et_2O, –78 °C, 85%; (b) TBAF, AcOH, DMF, RT, 89%; (c) TPAP, NMO, 4 Å M.S., CH_2Cl_2, RT, not isolated; (d) **I-63**, $Ba(OH)_2$, wet THF, 0 °C to RT, 79% (2 steps); (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$; MeOH/THF (3/1), –30 °C; (f) KHMDS, PMBBr, THF, RT, 94% (2 steps); (g) PPTS, EtOH, RT, 74%; (h) $HO_2CCH_2PO(OEt)_2$, PS·DCC, DMAP, DMAP·HCl, $CHCl_3$, RT, quant.; (i) HF, py, CH_3CN/H_2O (20:1), 0°C, 74%; (j) TPAP, NMO, 4 Å M.S., CH_2Cl_2, RT, 86%; (k) NaHMDS, THF, 0 °C, 60%; (l) DDQ, CH_2Cl_2, RT, 84%; (m) DMP, CH_2Cl_2, RT, 91%.

1.4.6. Synthesis of (–)-Dactylolide by *McLeod*

McLeod and co-workers[44] developed an attractive alternative THP synthesis which was based on the *Jacobsen* catalytic asymmetric hetero *Diels-Alder* approach.[45] They also recognized a hidden retron in the C16-C19 region in (–)-dactylolide ((–)-**2**) which could be accessible via an *Ireland-Claisen* rearrangement.

The 2,6-disubstituted THP ring was efficiently accessed via chromium-catalyzed hetero *Diels-Alder* reaction between aldehyde **I-67** and diene **I-68** in 82% yield (Scheme 12). **I-69** was elaborated into the epimeric mixture **I-71** (*S*:*R* / 86:14) which was separable by means of HPLC. To trigger the *Ireland-Claisen* rearrangement[46], the glycol ester was transformed under kinetic conditions (LHMDS, TMSCl) into the corresponding (*Z*)-TMS-enol ether which smoothly underwent the [3,3]-sigmatropic rearrangement under very mild conditions (–78 °C to RT), as is usually observed for this transformation.[46-47] **I-72** was further converted into the partially protected diol **I-73**, which was coupled to unsaturated acid **I-43** (structure see Scheme 8) via a *Mitsunobu* reaction with concomitant inversion at C19. RCM again could be implemented as the macrocyclization principle at C8-C9 in **I-74** followed by elaboration into (–)-dactylolide ((–)-**2**). The need for isomer separation by HPLC at a relatively early stage of the synthesis (at **I-71**) represents a clear drawback of *McLeod's* approach.

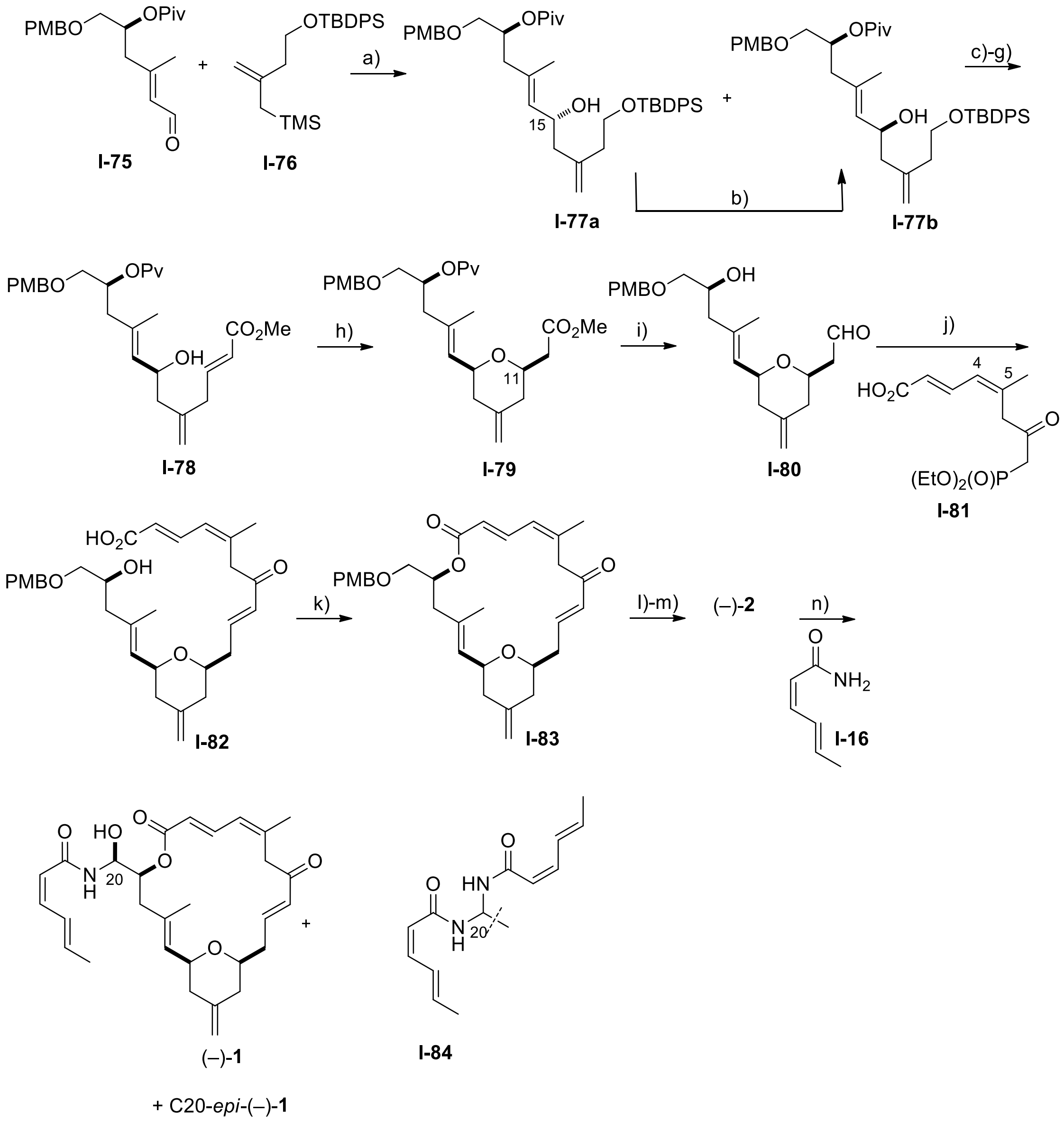


Scheme 12: (a) *Jacobsen's* chiral tridentate chromium(III) catalyst, 4 Å M.S., TBAF, AcOH, THF, 0°C, 82%; (b) DDQ, pH 7 buffer, CH_2Cl_2, 82%; (c) SO_3·py, NEt_3, CH_2Cl_2, DMSO; (d) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C to reflux; (e) TBAF, THF, 0 °C, 58% (3 steps); (f) SO_3·py, NEt_3, CH_2Cl_2, DMSO; (g) 2-bromopropene,*t*-BuLi, Et_2O, –78 °C, $MgBr_2$, 55%, 86:14 at C16 (*S*:*R*); (h) $PMBOCH_2COOH$, EDC, DMAP, NEt_3, CH_2Cl_2, 91%; (i) LHMDS; TMSCl, THF, –78 °C to RT then HCl; (j) LAH, Et_2O, 80% (2 steps); (k) TBSCl, NEt_3, CH_2Cl_2; (l) DDQ, pH 7 buffer, CH_2Cl_2, 74% (2 steps); (m) **I-43**, DEAD, PPh_3, toluene, 63%; (n) HCl, MeOH, CH_2Cl_2; (o) *Grubbs'* 2nd generation catalyst, CH_2Cl_2, 48% (2 steps); (p) DMP, $NaHCO_3$, CH_2Cl_2, 71%.

1.4.7. Synthesis of (–)-Dactylolide and (–)-Zampanolide by *Tanaka*

In 2009 *Tanaka* and co-workers[7], the original discoverers of (–)-zampanolide ((–)-**1**), reported their own synthetic approach to (–)-dactylolide ((–)-**2**) and (–)-zampanolide ((–)-**1**). Similarly as in the concept reported by *Hoye*[26] a late stage introduction of the side chain to the macrolactone moiety was envisaged. Ring closure was to be achieved by macrolactonization and an intramolecular hetero-*Michael* reaction was chosen to build up the THP subring.

Recent developments in palladium-mediated cross-coupling reactions on (*Z*)-bromoenynes[48] and methyl group installments by nickel-mediated *Kumada-Tamao-Corriu*[49] coupling, were exploited for the stereoselective construction of the tri-substituted C=C double bond at C4-C5. As illustrated in Scheme 13, unsaturated aldehyde **I-75** and allylsilane **I-76** were combined via an unselective *Hosomi-Sakurai* allylation affording a mixture of C15 epimers **I-77a** and **b**. The undesired isomer **I-77a** was converted to the desired **I-77b** by the use of a *Mitsunobu* reaction.


PMBO
OPiv
I-75
OTBDPS
TMS
I-76
a)
OH
15
I-77a
I-77b
b)
c)-g)
OPv
CO2Me
I-78
h)
11
I-79
i)
CHO
I-80
j)
HO2C
4
5
(EtO)2(O)P
I-81
I-82
k)
I-83
l)-m)
(–)-2
n)
NH2
I-16
HO
20
HN
I-84
(–)-1
+ C20-epi-(–)-1

Scheme 13: (a) SnCl$_4$, CH$_2$Cl$_2$, –78 °C 42% **I-77a** and 47% **I-77b**; (b) DEAD, PPh$_3$, AcOH, THF, then MeOH, K$_2$CO$_3$, 65% (2 steps); (c) EtOvinyl, PPTS, CH$_2$Cl$_2$; (d) TBAF, THF; (e) TEMPO, KBr, aq. NaClO, CH$_2$Cl$_2$; (f) Ph$_3$PCHCO$_2$Me, benzene; (g) PPTS, MeOH, 76% (5 steps); (h) LiHMDS (cat.), TMEDA, toluene, 60% syn, 34% anti, separation; (i) DIBAL-H, CH$_2$Cl$_2$, –78 °C, 92%; (j) **I-81**, Cs$_2$CO$_3$, *i*-PrOH, 89%; (k) ethoxyacetylene[RuCl$_2$(p-cymene)]$_2$, acetone then CSA, toluene, 48%; (l) DDQ, pH 7 buffer, CH$_2$Cl$_2$; (m) DMP, CH$_2$Cl$_2$, 87% (2 steps); (n) **I-16**, CSA, CH$_2$Cl$_2$; 12% for (–)-**1** along with 12% C20-*epi*-(–)-**1** and 16% for **I-84**.

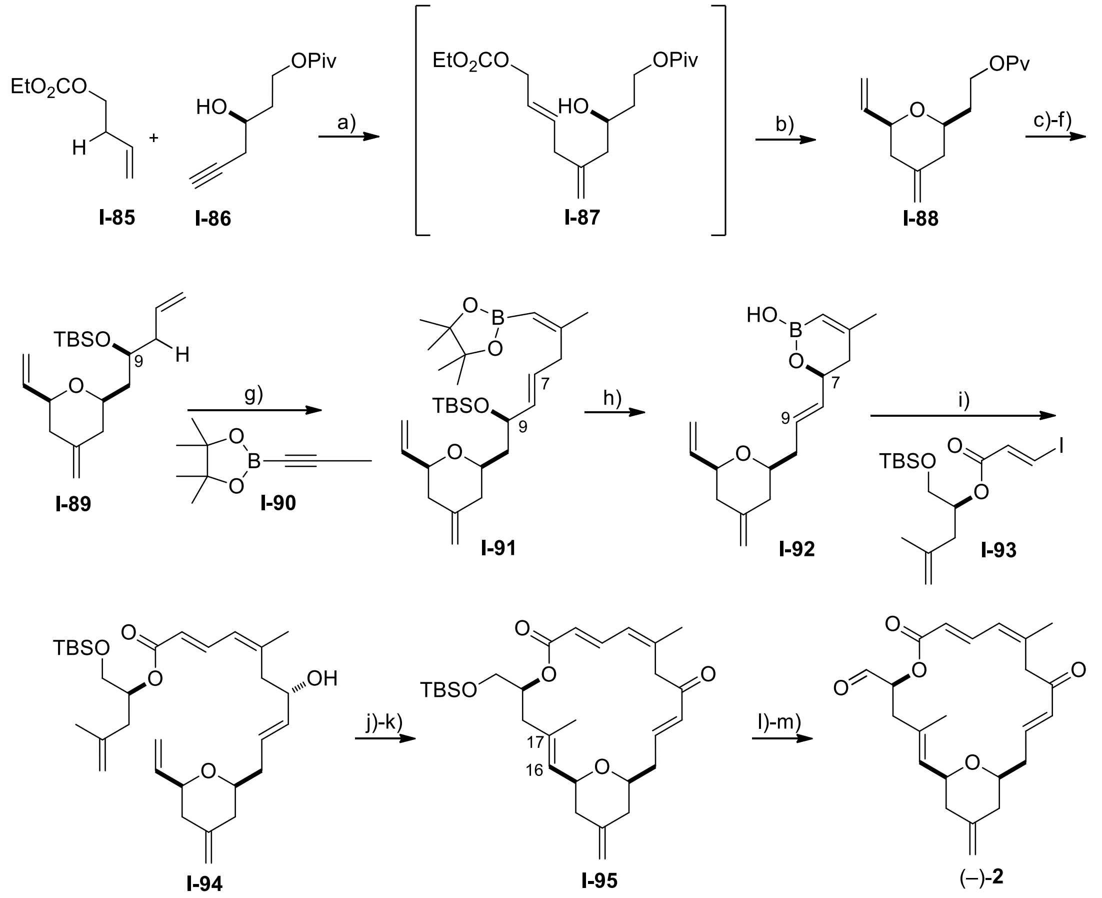
Functional group manipulation and 2-carbon extension led to **I-78**, which underwent THP ring closure, promoted by LiHMDS. The reaction produced a mixture of C11 isomers which had to be separated, to provide the desired isomer **I-79** in 60% yield. An intermolecular HWE reaction between aldehyde **I-80** and unsaturated acid **I-81** afforded seco-acid **I-82** in good yield (89%). Macrolactonization of unsaturated acid substrates under basic conditions can be problematic which is reflected in the low yield of 33% and 20% if *Yamaguchi's*[50] or *Shiina's*[51] method, respectively, for the ring closure of **I-82**. The best results for the macrolactonization of **I-82** were obtained with the *Trost-Kita*[52] protocol, which involves the use of an ethoxyacetylene [RuCl$_2$(*p*-cymene)]$_2$ catalyst with catalytic amounts of CSA; this approach afforded **I-83** in 48% yield. Acid-mediated installation of the side chain in (–)-dactylolide ((–)-**2**) afforded the natural product (-)-zampanolide ((–)-**1**) in 12% yield along with the C20-epimer and the bis-(*N*-acyl) product **I-84**.

1.4.8. Synthesis of (–)-Dactylolide by *Lee*

The latest synthesis in the field stems from *Lee* and co-workers[53], who have achieved the synthesis of (–)-dactylolide ((–)-**2**) based on the consecutive application of transition metal-catalyzed C-C and C-X bond forming reactions. As shown in Scheme 14 the syn-substituted THP subring was built up via *Trost's* ruthenium-catalyzed Alder ene reaction (RCAER),[54] between carbonate **I-85** and homopropargylic alcohol **I-86** promoted by [RuCp(CH$_3$CN)$_3$]PF$_6$ as the catalyst. The intermediate **I-87** thus formed underwent a palladium-catalyzed asymmetric allylic substitution[55] in the presence of the *Trost* ligand (+)-DPPBA[56] which gave THP derivative **I-88**. The overall transformation was best achieved using an improved one-pot protocol,[57] which provided **I-88** in 70 % over two steps from **I-85** and **I-86**.

Asymmetric allylation using *Leighton*'s protocol[58] and subsequent TBS-protection afforded **I-89** with a dr of 8:1. It remains unclear, why an asymmetric allylation method was employed in this step as the chiral center at C9 is destroyed after allylic transposition and oxidation to the C7 ketone moiety at a later stage of the synthesis. A second RCAER between olefin **I-89** and alkynyl boronate **I-90** then provided vinyl boronate **I-91** in a chemoselective manner and with the anticipated stereochemistry of the newly formed C=C double bond.

Rhenium-catalyzed allylic transposition[59] under concomitant TBS-removal formed the relatively unstable cyclic boronic acid half-ester **I-92** which was further elaborated into the unsaturated ester **I-94** via a *Suzuki* coupling reaction[60] with vinyl iodide **I-93,** thus liberating the hydroxyl group at C7. Macrocyclization was achieved via RCM-based formation of the C16-C17 C=C double bond with *Grubbs*' 2nd generation catalyst, although the yield was only moderate. TBS removal and oxidation then completed the total synthesis of (–)-dactylolide ((–)-**2**).


EtO2CO
H
+
HO
OPiv
a)
EtO2CO
HO
OPiv
b)
O
OPv
c)-f)
I-85
I-86
I-87
I-88
TBSO
9
H
O
I-89
g)
O
B
O
I-90
O
B
O
TBSO
9
7
O
I-91
h)
HO
B
O
7
9
O
I-92
i)
TBSO
O
O
I
I-93
TBSO
O
O
OH
O
I-94
j)-k)
O
O
TBSO
O
17
16
O
I-95
l)-m)
O
O
O
O
O
(–)-2

Scheme 14: (a) 7 mol% $[RuCp(CH_3CN)_3]PF_6$, acetone, RT; (b) 3 mol% $[Pd_2(dba)_3]\cdot CHCl_3$, 9 mol% (+)-DPPBA, CH_2Cl_2, –20 °C to RT, 70% (2 steps); (c) DIBAL-H, CH_2Cl_2, –78° C, 96%; (d) IBX, DMSO, 95%; (e) (*S*,*S*)-*Leighton* reagent, CH_2Cl_2, –10 °C, 85% (8:1 dr); (f) TBSCl, ImH, DMF, 98%; (g) **I-90**, 10 mol% $[RuCp(CH_3CN)_3]PF_6$, acetone, RT, 65% (78% brsm); (h) 10 mol% Re_2O_7, 65%; (i) $[Pd(PPh_3)_4]$, TlOEt, THF/H_2O (3:1), 79%; (j) DMP, CH_2Cl_2, 89%; (k) 10 mol% *Grubbs*' 2nd generation, 10 mol% benzoquinone, CH_2Cl_2, 65°C, 45% (l) HCl, MeOH, 95%; (m) DMP, py, CH_2Cl_2, 90%.

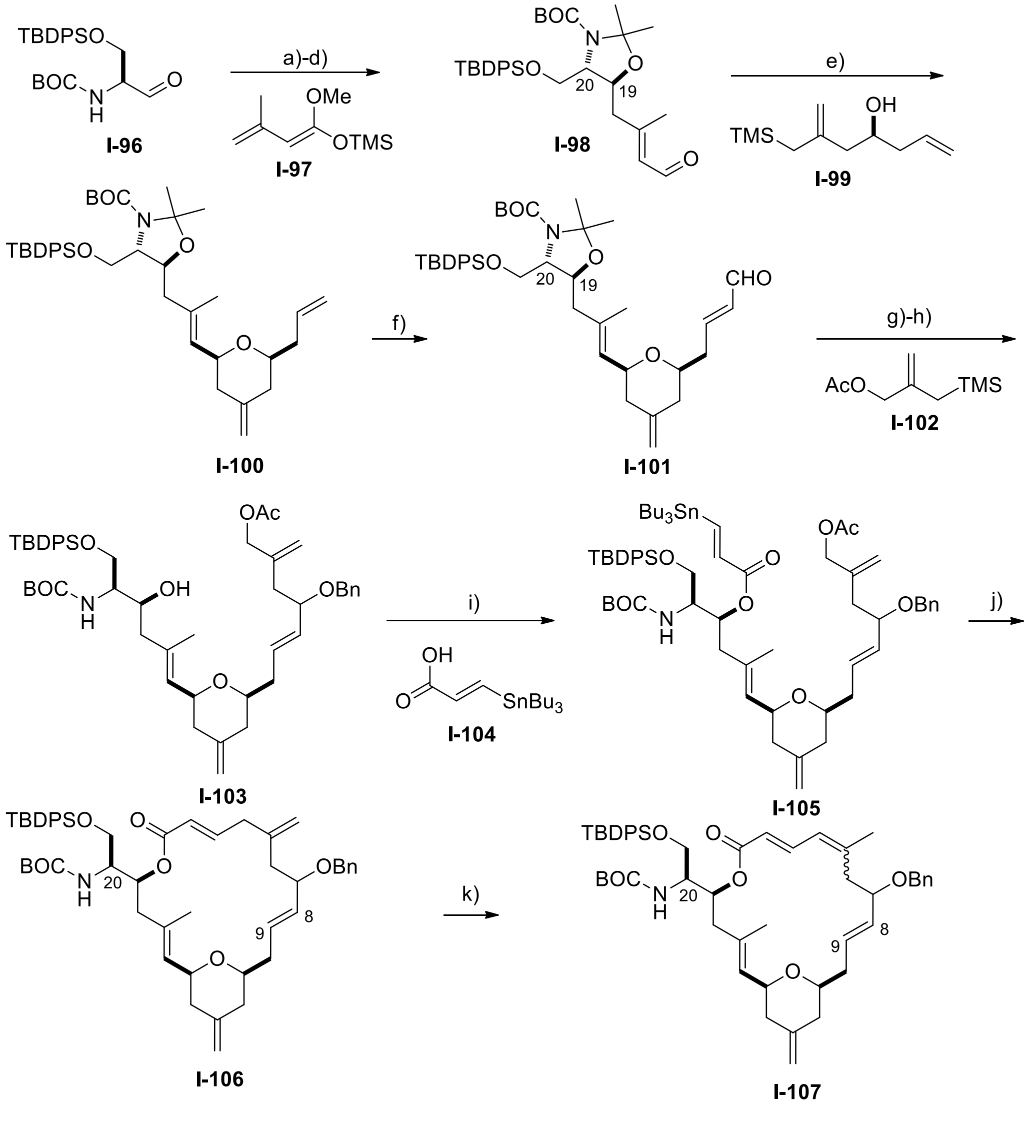
The creative use of transition metals such as palladium, rhenium and ruthenium to address key elements in the molecular skeleton in (–)-dactylolide-((–)-**2**), makes this total synthesis distinct from all previous approaches.

1.4.9. Synthetic Studies by *Porco*

The group of *Porco*[61] has not only reported studies regarding the assumed hydrogen-bonding network in (–)-zampanolide ((–)-**1**) (see Scheme 2, page 5), they have also devised a synthetic study towards (–)-zampanolide ((–)-**1**) (Scheme 15).

In this approach, an intramolecular *Stille*[62] coupling between the allylic acetate and the vinyl-tributyltin moieties in **I-105** was employed for ring closure to the macrolactone. The synthesis departs from serine-derived aldehyde **I-96**, which undergoes substrate-controlled vinylogous aldol reaction with silyl ketene acetal **I-**

97. DIBAL-H reduction of the ester moiety and oxidation using *Bobbitt*'s reagent[29] afforded **I-98** in good yields. *Hosomi-Sakurai* allylation with allylsilane **I-99** and cross-metathesis using acrolein afforded unsaturated aldehyde I-**101** which was further transformed into **I-105** through a second *Hosomi-Sakurai* allylation with allylsilane **I-102,** benzyl-protection, protecting group removal and esterification with unsaturated acid **I-104**.

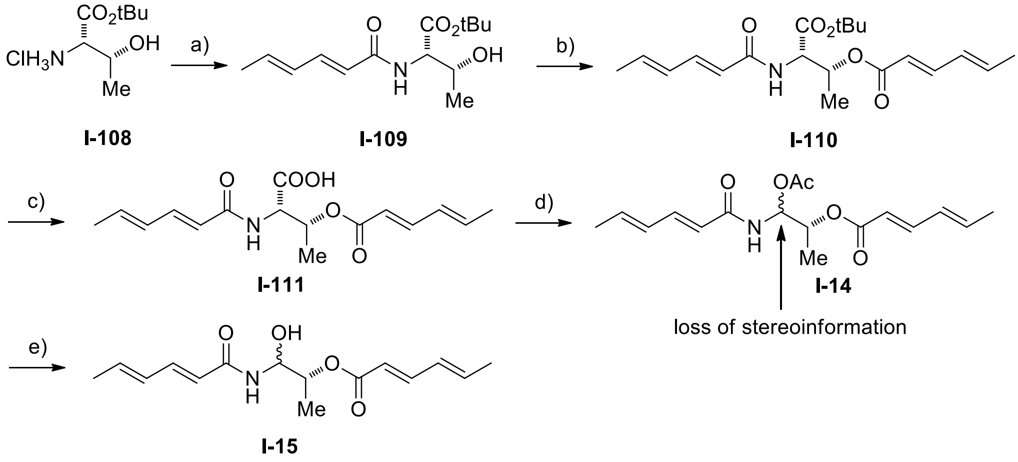


TBDPSO
BOC
N
H
O
I-96
a)-d)
OMe
OTMS
I-97
BOC
N
TBDPSO
O
20
19
O
I-98
e)
TMS
OH
I-99
I-100
f)
CHO
I-101
g)-h)
AcO
TMS
I-102
OAc
OH
OBn
I-103
i)
OH
O
SnBu3
I-104
Bu3Sn
I-105
j)
I-106
9
8
k)
I-107

Scheme 15: (a) I-97, Me_2AlCl, 2,6-di-*tert*-butyl-4-methyl pyridine, CH_2Cl_2, 69%; (b) $Me_2C(OMe)_2$, CSA, M.S., 84%; (c) DIBAL-H, CH_2Cl_2, –78 °C, 96%; (d) 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate 85%; (e) I-99, $Bi(OTf)_3$, DBMP, 4 Å, M.S., Et_2O, –78 °C, 77%; (f) acrolein, *Grubbs-Hoveyda* 2nd, CH_2Cl_2, reflux, 66%; (g) I-102, TMSOTf, BnOTMS, 2,6-di-*tert*-butyl-4-methyl pyridine, Et_2O, 79%; (h) formic acid, CH_2Cl_2, 60%; (i) I-104, DIC, DMAP, DMAP•HCl, CH_2Cl_2, 80%; (j) $Pd(PPh_3)_4$, *i*-Pr_2NEt, TBAI, toluene, 50%; (k) DBU, THF, 45 °C, quant., (*E*,*Z*):(*E*,*E*) 1:1.

Intramolecular *Stille* reaction did indeed afford macrocycle **I-106** in 50% yield. However, all attempts to isomerize **I-106** to the desired conjugated system having the desired (*EE:EZ*) olefin geometry met with failure. In the best case (DBU, THF, 45 °C) a 1:1 mixture of (*EE*:*EZ*) dienoate isomers **I-107** was obtained.

Were it possible to overcome this problem, the stage would be set for the introduction of the side chain, which was planned to be achieved via an oxidative decarboxylation-hydrolysis protocol, as described earlier for model substrate **I-15** (Scheme 16).[12]



Scheme 16: (a) sorbic acid, HOBT, EDC, DIEA, 96%; (b) sorbic acid, DIC, DMAP, DMAP·HCl, CH_2Cl_2, 97%; (c) TFA, Et_3SiH, CH_2Cl_2, 53%; (d) $Pb(OAc)_4$, $Cu(OAc)_2$, py, THF, 76%; (e) $Yb(OTf)_3$, wet THF, 12 h, 88%.

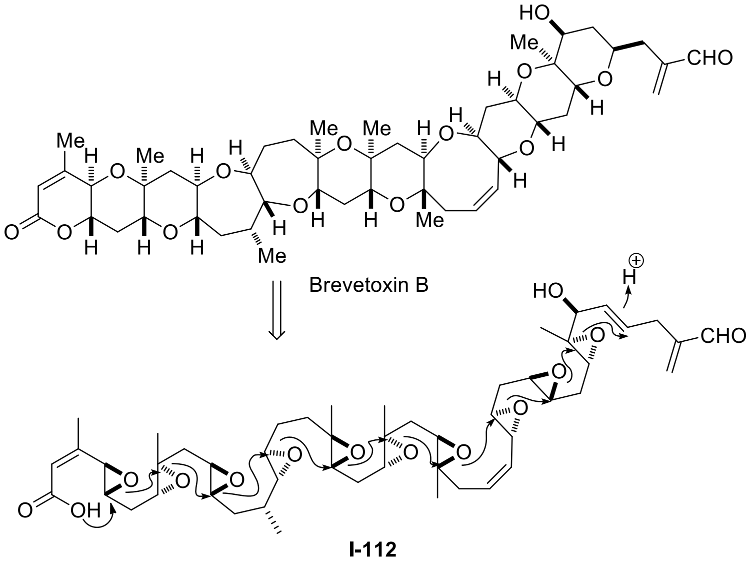
Having reviewed the existing approaches towards the synthesis of zampanolide and dactylolide, the next section will focus on strategies for the construction of syn-substituted 2,6-THP ring systems and their application to natural product total synthesis.

1.5. Methods for the Construction of 2,6-syn-Substituted THP Rings

A key structural element present in (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**) is the tri-substituted THP subring which poses a key synthetic challenge. As shown in the previous section, some established methods for THP ring construction have already found application in the total synthesis of zampanolide and dactylolide. In particular, this has involved cationic cyclization cascades proceeding via an oxonium ion species, such as the *Petasis-Ferrier* rearrangement, as applied by *Smith,*[9a] or *Hosomi-Sakurai*-type cyclizations as used by *Keck*[40] and *Hoye.*[26] A highly efficient *Prins-Peterson* cyclization cascade was applied by *Floreancig.*[33] Other creative approaches involved a hetero-*Diels-Alder* cyclization (*McLeod*[44]), the stereoselective reduction of a cyclic hemiketal (*Jennings*[30]), transition metal-catalyzed asymmetric allylic substitution (*Lee*[53]) or the hetero-*Michael* cyclization which was applied in *Tanaka's* synthesis.[7] In the following, other methodologies for THP ring construction will be briefly reviewed, however, without entering into a detailed discussion of each individual approach presented.

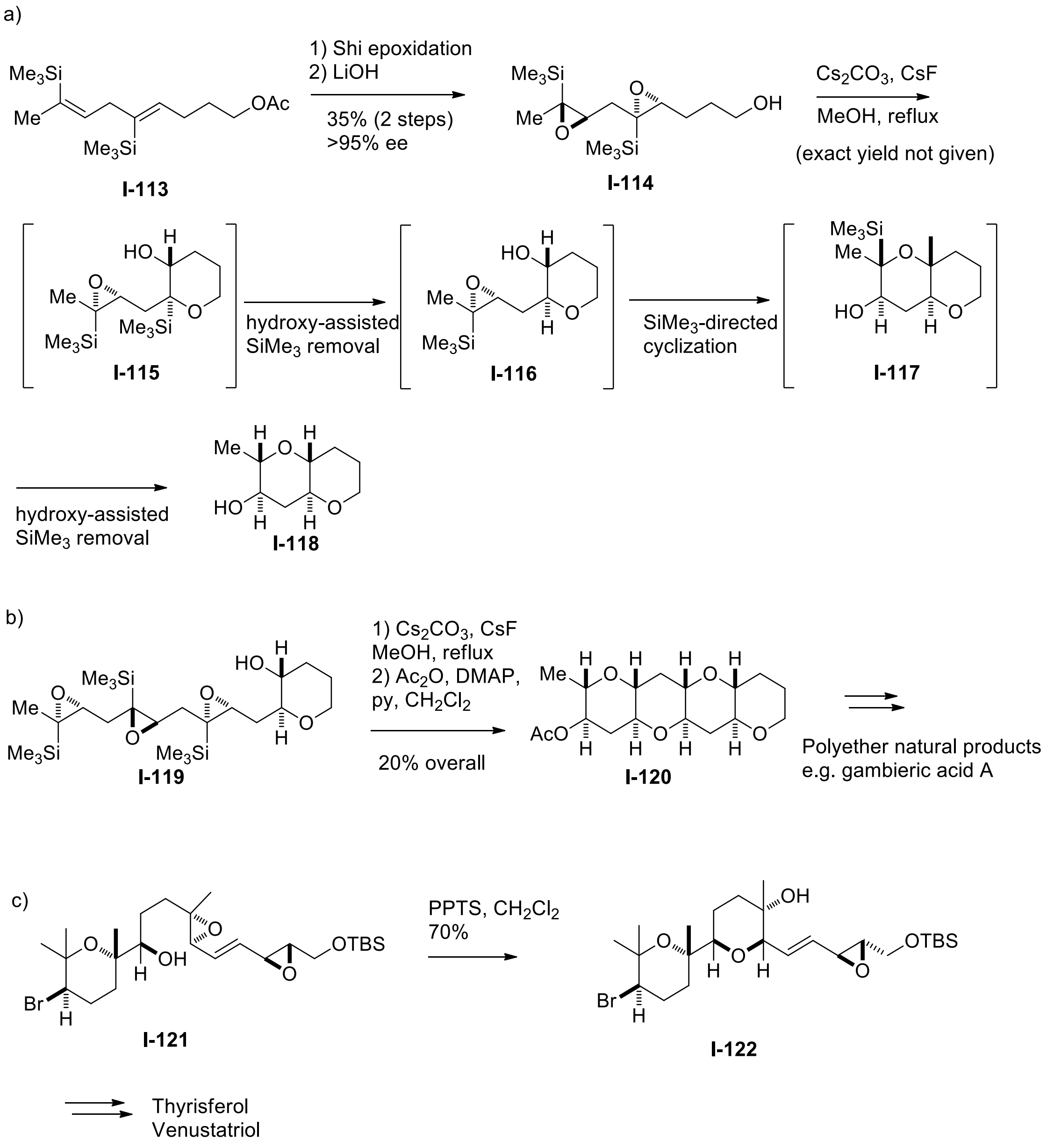
1.5.1. Cyclizations using Epoxide Opening

Polyether natural products such as brevetoxin, hemibrevetoxin, ciguatoxin, gambierol, maitotoxin and related structures have intrigued generations of chemists with their unique structural complexity and thus have inspired the development of new synthetic methods. This was greatly influenced by *Nakanishi's*[63] proposed biosynthesis of brevetoxin B in which a zip-type cascade reaction in **I-112** could explain the full construction of the polyether skeleton (Scheme 17). The acid functionality initiates the proton-catalyzed cascade reaction which proceeds via successive epoxide-openings. Many outstanding synthetic achievements have occurred in the field of polyether natural products over the last two decades which shall not be reviewed here (for an excellent review see *Nicolaou* et al.[64])



Scheme 17: Proposed zip-type polyepoxide-opening cascade for the biosynthesis of brevetoxin B.[63]

More recent work by *Jamison* and co-workers[65] exploits the directing effect of a Me_3Si substituent, which biases the regioselectivity of the epoxide opening reaction towards the formation of the THP vs. the THF ring and thus gives access of the THP diad **I-118** or tetrad **I-120** (Scheme 18). The latter, a structural motif that is present in many cyclic polyether natural products, had not been synthesized using an epoxide-opening cascade (for an excellent review on epoxide-opening cascades in the synthesis of polycyclic natural products see *Jamison* et al.[66]).


a)
Me3Si
Me
OAc
Me3Si
I-113
1) Shi epoxidation
2) LiOH
35% (2 steps)
>95% ee
Me3Si
Me
O
O
OH
Me3Si
I-114
Cs2CO3, CsF
MeOH, reflux
(exact yield not given)
HO
H
O
Me
Me3Si
Me3Si
O
I-115
hydroxy-assisted SiMe3 removal
HO
H
O
Me
Me3Si
H
O
I-116
SiMe3-directed cyclization
Me3Si
Me
O
HO
H
H
O
I-117
hydroxy-assisted SiMe3 removal
H
H
Me
O
HO
H
H
O
I-118
b)
Me3Si
O
Me
Me3Si
O
O
Me3Si
HO
H
O
H
I-119
1) Cs2CO3, CsF MeOH, reflux
2) Ac2O, DMAP, py, CH2Cl2
20% overall
H H H H
Me
O
O
AcO
O
O
O
H H H H
I-120
Polyether natural products e.g. gambieric acid A
c)
O
O
OH
H
O
OTBS
Br
H
I-121
PPTS, CH2Cl2
70%
OH
O
O
H
H
OTBS
O
Br
H
I-122
Thyrisferol
Venustatriol

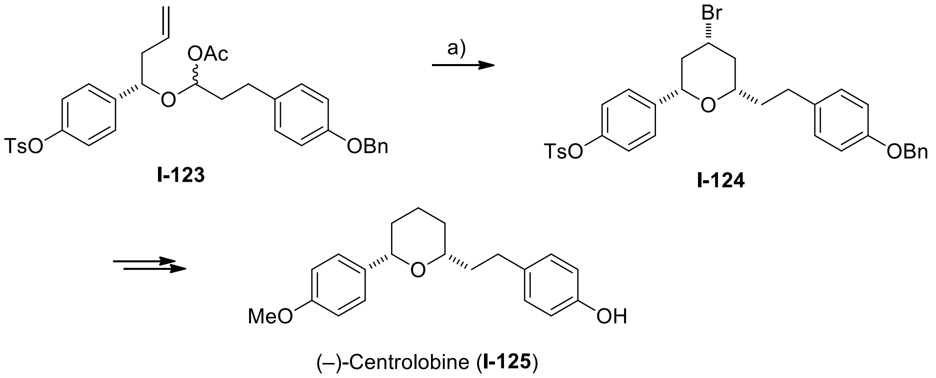
Scheme 18: a) Hydroxy-derived regioselective epoxide opening reaction for the formation of 2,6-syn substituted THP rings and the assembly into THP-diad **I-118**. b) Cascade reaction which led to the THP tetrad **I-120**, a structural motif found in many polyether natural products.[65b] c) *Brønsted*-acid mediated epoxide opening reaction towards thyrisferol and venustatriol.[68]

The model in Scheme 18a, explains the formation of THP diad **I-118** which should proceed via the intermediates **I-115**–**I-117.** Similar intermediates must be involved in the formation tetrad **I-120**. The exact mechanistic role of the Me3Si-directing group (as present in **I-115**) for the cascade reaction remains yet to be explored. Protodesilylation most likely proceeds through *Brook* rearrangement along with the stereospecific trapping by a proton, an event, which is suggested to take place before the next epoxide opening.[67]

The combination of a directing Me_3Si group, a Brønsted base, a fluoride source and a hydroxylic solvent enables cyclization cascades (such as for **I-114** and **I-119**) which emulates *Nakanishi's*[63] proposed biosynthetic pathway.[65b] This approach is significantly different from the rather established *Lewis* or *Brønsted* acid-mediated cyclizations, e. g. PPTS-catalyzed cyclization reaction in **I-121** (Scheme 18c).[68]

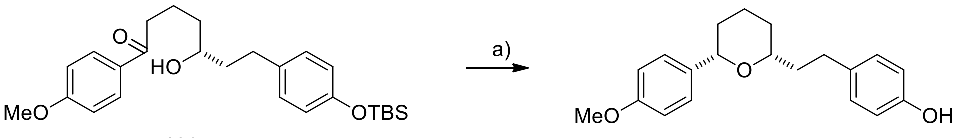
1.5.2. Cyclizations using Oxonium Ions

A classical approach to 2,6-syn-substituted THP is based on the *Prins* cyclization between an aldehyde and a homoallylic alcohol under *Lewis* acid or *Brønsted* acid catalysis, which most probably proceeds through a cationic intermediate. Based on the general principles of the classical *Prins* reaction, *Rychnovsky* and co-workers have recently developed a segment-coupling approach,[69] which leads to improved yields for cyclization and dramatically reduces the risk of partial racemization and exchange of alcohol and aldehyde chains leading to mixture of products.[70]



Scheme 19: Segment coupling approach in the synthesis of (–)-centrolobine (**I-125**). (a) $SnBr_4$, CH_2Cl_2, –78 °C, 83%, 94% ee.[71]

This concept was successfully applied by *Rychnovsky* to the synthesis of (–)-centrolobine (**I-125**) (Scheme 19) which is prone to racemization if classical *Prins* conditions are used.[71] The reduction of hemiacetals provides another interesting way to form THP rings as shown by an alternative synthesis of (–)-centrolobine (**I-125**) by *Evans* and co-workers (Scheme 20).[72] The use of catalytic $BiBr_3$ in combination with Et_3SiH not only promoted the cyclization but also led to the reduction of the acetal center to afford **I-125** (Scheme 20).

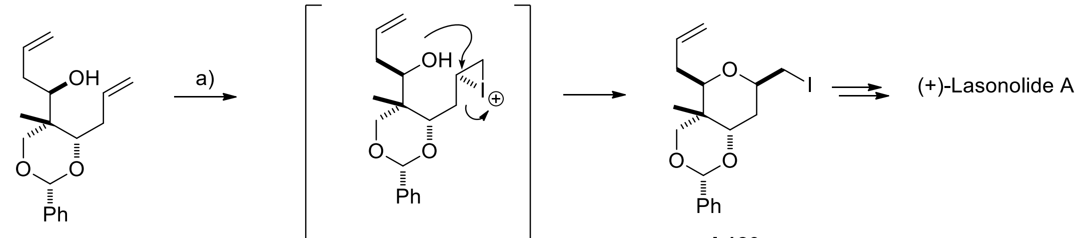


I-126 (–)-Centrolobine (**I-125**)

Scheme 20: Reductive cyclization with Et_3SiH catalyzed by $BiBr_3$. (a) $BiBr_3$ (cat.), Et_3SiH, CH_3CN, TBAF, 93%.

1.5.3. Cyclizations by other Onium Ions

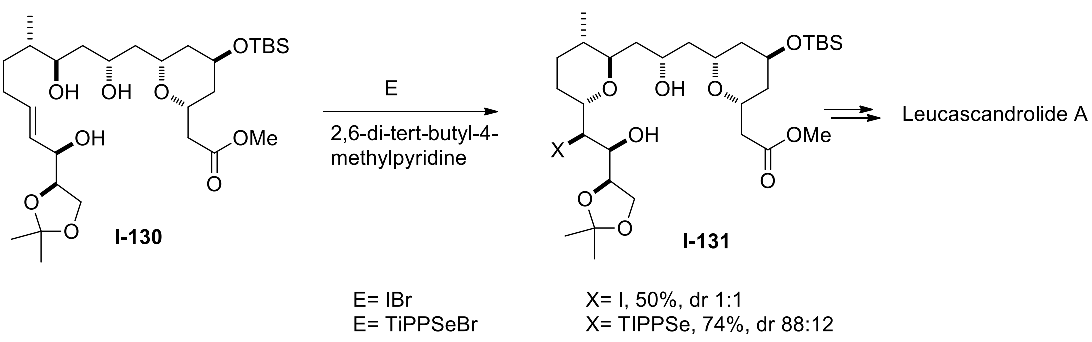
Reactive intermediates that are related to activated epoxides are well known and include bromonium or iodonium ions; these intermediates can be regioselectively opened by an adjacent hydroxyl group via 6-*exo*-tet haloetherification. *Kang*[73] has reported the successful construction of primary iodide **I-129** via the chemoselective iodoetherification as a key step in the synthesis of the antitumor agent (+)-lasonolide A (Scheme 21).



I-127 **I-128** **I-129**

Scheme 21: Iodetherification as key step to the iodinated THP fragment **I-129** towards (+)-lasonolide A. a) I_2, K_2CO_3, CH_3CN,– 30 to –20 °C, 95%.[73]

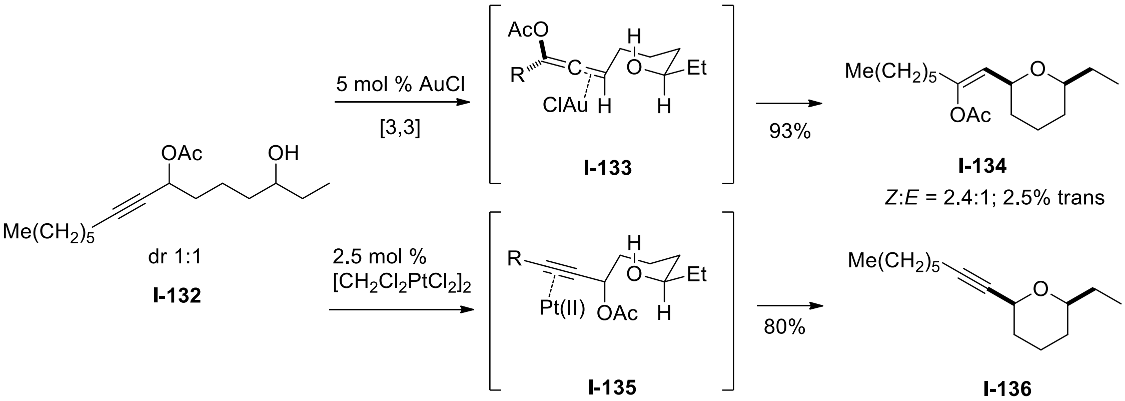
The concept of cyclization via reactive intermediates was also part of *Carreira's* approach towards leucascandrolide A (Scheme 22).[74] While iodolactonization of **I-130** with IBr resulted in a 1:1 mixture of syn:anti isomers **I-131** in moderate yield (50%), selenium-mediated etherification with TIPPSeBr (2,4,6-triisopropylphenyl selenyl bromide) was a breakthrough in the synthesis, as it not only resulted in an increased yield of **I-131** (74%), but also in improved diastereoselectivity (up to 88:12 in favor of the 2,6-anti diastereomer).


E
2,6-di-tert-butyl-4-methylpyridine
Leucascandrolide A
I-130
I-131
E= IBr
E= TiPPSeBr
X= I, 50%, dr 1:1
X= TIPPSe, 74%, dr 88:12

Scheme 22: Reactive onium species for the construction of the anti-substituted THP ring in the syntheis of leucascandrolide A by *Carreira*.[74]

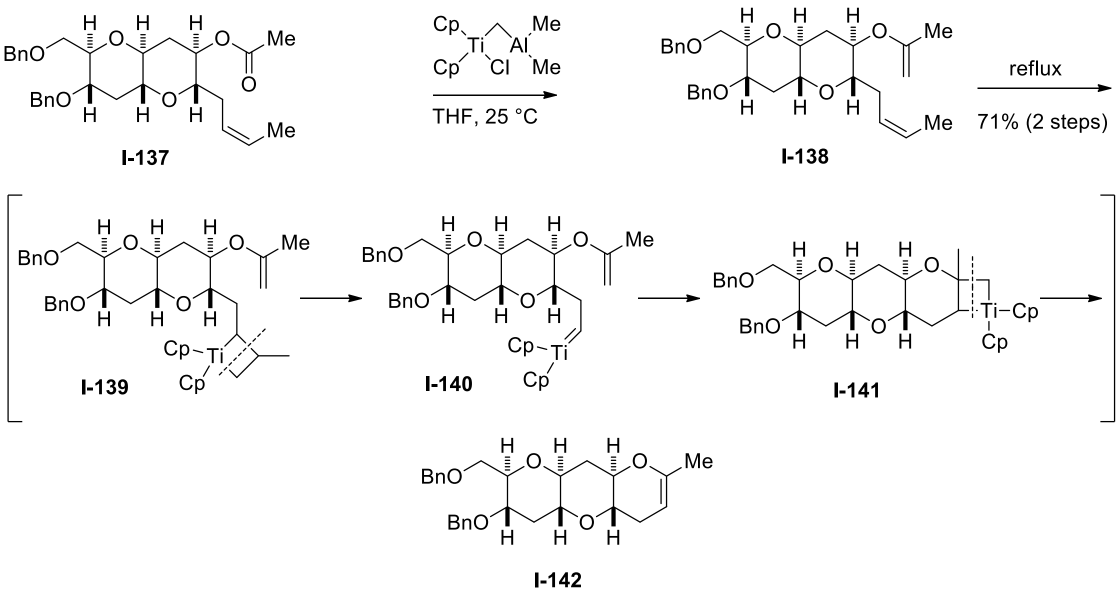
1.5.4. Metal-mediated Cyclizations

Transition metal-catalyzed reactions have dramatically changed modern organic synthesis. A novel metal-mediated method for THP ring formation from *ω*-hydroxy propargylic esters such as **I-132** was recently reported by *de Brabander* and co-workers[75] (Scheme 23). The incipient metal-complexed ester **I-132** may either deliver oxacylic enol acetate **I-134,** with AuCl as catalyst, or the propargylic substitution product **I-136**, when the reaction is catalyzed by a square planar platinum(II) complex, e.g. *Zeise* salt $[Cl_2Pt(CH_2CH_2)]_2$. The latter process affords similar products as the *Nicholas* reaction[76]. For the platinum (II)-catalyzed process a solvent-dependence was found where CH_2Cl_2 tends to give higher yields compared to the less ionizing solvent THF.


5 mol % AuCl
[3,3]
2.5 mol % [CH2Cl2PtCl2]2
I-132
dr 1:1
I-133
I-135
93%
80%
I-134
Z:E = 2.4:1; 2.5% trans
I-136

Scheme 23: Au(I) or Pt(II)-mediated cycloetherification either providing enolacetates **I-134** or propargyl ethers **I-136**.[75]

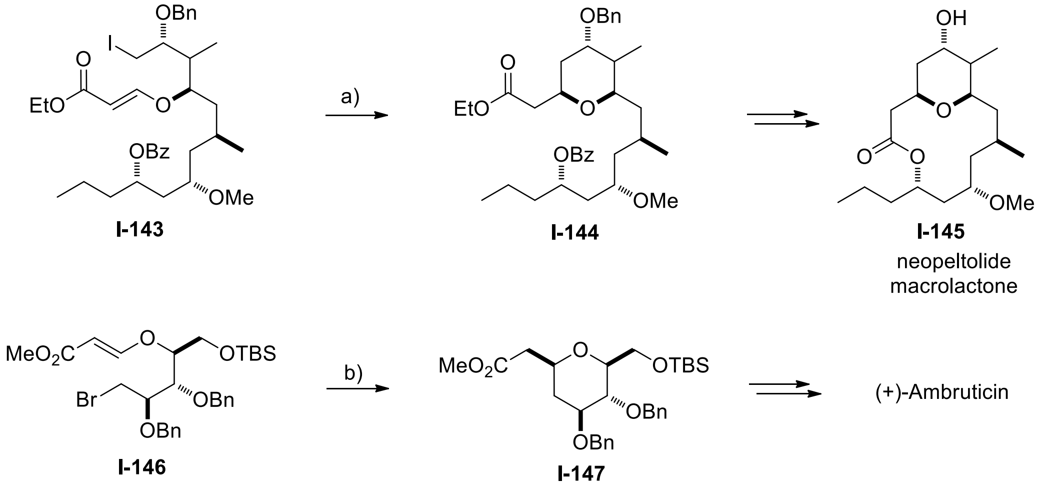
In earlier studies towards the total synthesis of the marine neurotoxin maitotoxin[77] *Nicolaou* and co-workers[78] reported the one pot conversion of **I-137** into cyclic enol ether **I-142** (Scheme 24). In this transformation the ester functionality is first converted into the enol ether **I-138** by means of the *Tebbe* reagent ($Cp_2TiCH_2ClAlMe_2$); reaction of **I-138** with a second equivalent of *Tebbe's* reagent at elevated temperature then leads to **I-142**, presumably via intermediates **I-139**–**I-141**.



Scheme 24: Titanium-mediated two step conversion of ester I-137 into cyclic enol ether I-142 as model system for the construction of polycyclic natural products.

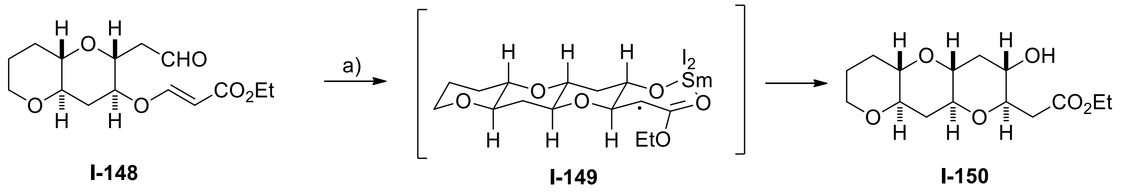
1.5.5. Radical Cyclizations

Radical cyclization is a powerful method and especially useful for the formation of small-sized rings. *Taylor* and co-workers[79] have reported a synthesis of neopeltolide macrolactone **I-145** in which the THP subring was constructed via 6-*exo*-trig radical cyclization of vinylogous carbonate **I-143** with AIBN and Bu_3SnH (Scheme 25). The reaction proceeded with high diastereoselectivity and excellent yield. A similar radical cyclization was employed by *Lee* and co-workers for the construction of the 2,6-syn-substituted THP derivative **I-147** in their synthesis of (+)-ambruticin.[80] Radical reactions are compatible with functional groups which are prone to elimination under anionic conditions. Therefore, attempts to cyclize **I-143** or **I-146** under anionic conditions would probably lead to loss of benzyl alcohol during halogen-metal exchange.


OBn
I
O
EtO
O
OBz
OMe
I-143
a)
OBn
O
EtO
O
OBz
OMe
I-144
OH
O
O
O
OMe
I-145
neopeltolide
macrolactone
MeO2C
O
OTBS
Br
OBn
OBn
I-146
b)
MeO2C
O
OTBS
OBn
OBn
I-147
(+)-Ambruticin

Scheme 25: Radical cyclization on vinylogous carbonates for the synthesis of neopeltolide[79] and ambruticin.[80] (a) AIBN, Bu_3SnH, toluene, reflux, 95%, 19:1 dr; (b) AIBN, Bu_3SnH, benzene, reflux, 95%.

The power of radical chemistry in THP ring formations is further illustrated by the conversion of vinylogous carbonate **I-148** into THP triad **I-150** in the presence of SmI_2 as reported by *Nakata* and co-workers (Scheme 26).[81] The reaction is completely regio- and stereoselective and most probably proceeds by a radical mechanism via intermediate **I-150**.


H
H
O
CHO
O
H
H
O
CO2Et
I-148
a)
H
H
H
I2
Sm
O
O
O
O
O
H
H
H
EtO
I-149
H
H
H
OH
O
O
O
H
H
H
CO2Et
I-150

Scheme 26: SmI_2-mediated reductive cyclization for the construction of fused polytetrahydropyran ring systems. (a) SmI_2, MeOH, THF, 0 °C, 86%.[81a]

1.6. Tubulin as the Cellular Target of (–)-Zampanolide

A recent report by *Miller* and co-workers[10] revealed (–)-zampanolide ((–)-**1**) to be a new microtubule stabilizer, i.e an agent which leads to the formation of microtubule bundles in cells and induces tubulin polymerization in purified tubulin preparations. Correspondingly, (–)-zampanolide ((–)-**1**) leads to cell arrest in the G2/M phase of the cell cycle and causes a dose-dependent shift of the equilibrium between soluble tubulin and its polymerized form to the polymer side inside cells, similar to paclitaxel.[10] Microtubules are a target of anticancer drugs and agents affecting microtubule dynamics have been a mainstay in the treatment of leukemia and solid tumors for many years.[82] These cellular components are required when it comes to regulating cellular processes such as trafficking of vesicles, organelles, cellular motility and chromosome segregation during mitosis. Together with actin and intermediate filaments, microtubules form the cytoskeleton.

Microtubules are heterodimers which derive from the association of α- and β-tubulin. The heterodimers assemble head-to-tail into linear protofilaments and polymerize further to from the characteristic hollow microtubule cylinder having an internal and external diameter of approximately 12 nm and 24 nm, respectively. The α-subunit points to the minus end of the cylinder, whereas the β-subunit is exposed at the plus end (Figure 10). The biological functions of microtubules are closely linked to their polymerization dynamics with two important dynamic behaviors being dynamic instability and treadmilling. Dynamic instability refers to the relatively rapid lengthening and shortening of microtubules at the plus end, whereas the controlled loss of tubulin subunits from the minus end with concurrent acquisition of tubulin at the plus end, without net change of microtubule mass, is termed treadmilling.[83] A microtubule population can either show only one of these two behaviors or both at the same time.

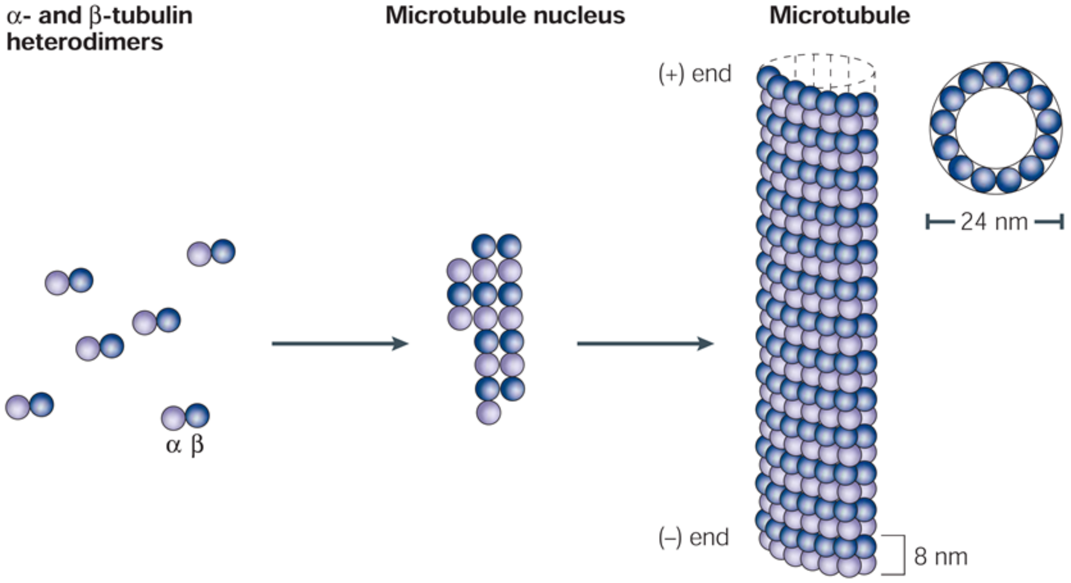


Figure 10: Assembly of heterodimers consisting of α- and β-tubulin units, into the microtubule composed of 13 protofilaments. The α-subunit is found at the (–)-end whereas β-tubulin is exposed at the (+)-end.[84]

Microtubule stability is largely dictated by GTP-binding and its hydrolysis to GDP. Two GTP-binding sites are found on tubulin; the β-site, which enables GTP-hydrolysis and the α-site, with no GTP hydrolysis. For the assembly of tubulin into microtubules, GTP must be bound to the β-tubulin end which is followed by the irreversible hydrolysis to GDP. The majority of the β-tubulin is in the GDP-bound form and capped with the GTP-bound β-tubulin at the plus end. If GTP on the β-tubulin end is hydrolyzed to GDP before another GTP-bound β-tubulin is added, the so exposed GDP-bound β-tubulin promotes a conformational change, which leads to a rapid microtubule depolymerization known as the microtubule catastrophe.[82] When cells enter mitosis the interphase microtubules depolymerize and the mitotic spindle (shown as yellow fibers in Figure 11) begins to form, which serves to separate the sister chromatids in a well-defined process culminating in cell division (Figure 11).[85]

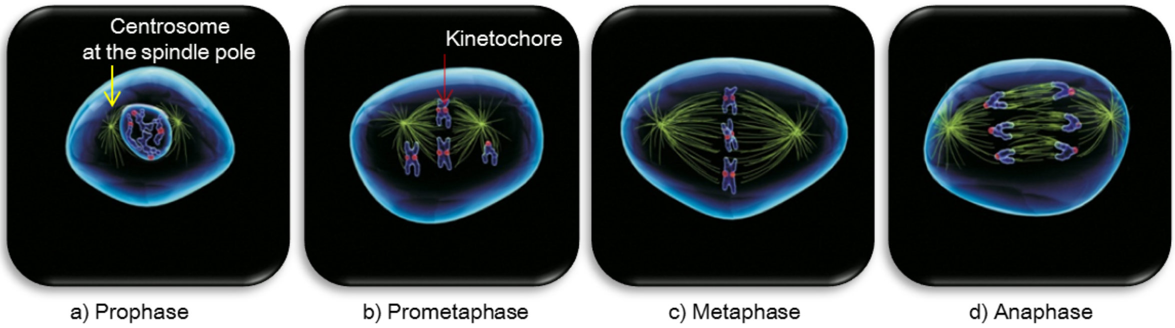


Figure 11[2]: Stages of the cell cycle influenced by microtubule dynamics. (a) In prophase, chromosomes begin to condense within the nuclear membrane. The centrosomes, which were replicated in interphase, are moved apart. (b) In prometaphase the nuclear envelope breaks down, chromosomes attach to spindle microtubules via their kinetochores and undergo active movement. (c) In metaphase, the condensed chromosomes have congressed to the equator and form the metaphase plate. The kinetochore microtubules attach sister chromatids to opposite poles of the spindle. (d) In anaphase the condensed duplicated chromosomes are moved apart from the central plane towards the spindle pole in order to form two new daughter cells.[84, 86]

Drugs targeting tubulin have been used as anticancer agents for over 20 years and are classified either as microtubule stabilizers or destabilizers. These drugs lead to an increase or decrease, respectively, of interphase microtubule mass at high concentrations. However, they inhibit mitosis at a 10-100 fold lower concentration via a mechanism of slowing microtubule dynamics thus leading to a blocking of the cell cycle and ultimately resulting in cell death by apoptosis.[87] [88]

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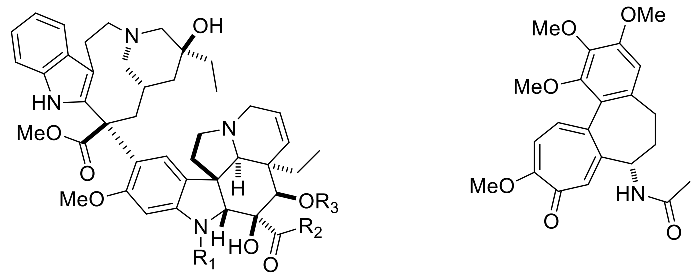
[2] Pictures reproduced with permission of Wellcome Images, 183 Euston Road, London NW1 2BE, UK; http://images.wellcome.ac.uk

1.6.1. Microtubule Destabilizers

Vinblastine (Velban®) and vincristine (Oncovin®) are two representatives of the vinca alkaloids, which were isolated from the periwinkle plant *Catharanthus roseus* and were first recognized for their myelosuppressive effects (Figure 12).[89] Since the 1960s, they have found clinical application for the treatment of childhood leukemia. Semi-synthetic second-generation compounds related to vinblastine, such as vindesine (Eldisine®), vinorelbine (Navelbine®) and vinflunine were developed for the treatment of a variety of cancers.[90]



Vinblastine (Velban®): R$_1$=Me, R$_2$=OMe, R$_3$=COCH$_3$
Vincristine (Oncovin®): R$_1$=CHO, R$_2$=OMe, R$_3$=COCH$_3$
Vindesine (Eldisine®): R$_1$=Me, R$_2$=NH$_2$, R$_3$=H

Colchicine

Figure 12: Vinca alkaloids and cholchicine as known microtubule destabilizers with binding sites on β-tubulin.

The vinca alkaloids bind to β-tubulin at the so called **vinca-binding site**, which is located near the GTP-binding site[91] at the exposed plus end of microtubules, at low, clinically relevant concentrations, thereby suppressing microtubule dynamics (see Figure 13a).[92] They also bind to soluble tubulin[93] and if sufficient drug is present, microtubule destabilization is observed. The interference of these agents with microtubule function is also the cause of common side effects in vinca-based chemotherapy, such as neuropathy and reversible myelosuppression.

Vinca alkaloid derivatives are used to treat a variety of specific cancers.[82] Vinblastine effectively treats advanced testicular cancer, lymphoma and Hodgkin's disease.[82] Vincristine is effectively used for the treatment of leukemias, lymphomas and sarcomas. Marqibo® (Tekmira), a liposomal sphingosomal sulfate formulation of vincristine, is currently in clinical trials for acute lymphoblastic leukemia.[94]

Vindesine is under investigation for the treatment of acute lymphocytic leukemia[94] and vinorelbine finds application in the treatment of non-small cell lung cancer.[94] Vinflunine showed improved efficacy in the treatment of a variety of tumors compared to vinblastine and is currently in clinical evaluation against solid tumors such as metastatic breast cancer.[94-95]

Hemiasterlin and dolastatin 10, two naturally occurring peptides, are known to bind to microtubules at or near the vinca-site. A synthetic derivative of hemiasterlin, E7974 (from Eisai) showed activity against bladder cancer in clinical phase I trials,[94] whereas a synthetic derivative of dolastatin 10, namely dolastatin 15, failed in clinical trials due to severe cardiac toxicity.[96] Halichondrin, a marine natural product belonging to the class of macrolide polyethers, has shown to be a noncompetitive inhibitor of vinca alkaloid binding due to an allosteric interaction with tubulin.[97]

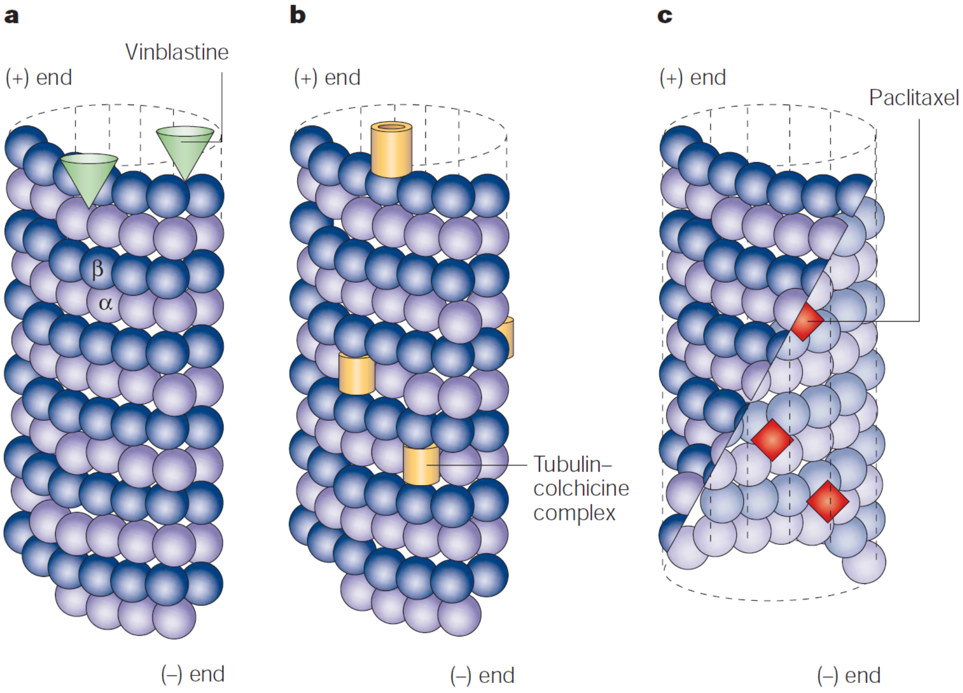


Figure 13: Interaction of antimitotic drugs with microtubules. (a) Vinblastine binds to a specific site at the microtubule plus end, thus suppressing microtubule dynamics. (b) Complexes of tubulin heterodimers with colchicine and integration into the microtubule polymer leading to the suppression of microtuble dynamics. (c) Paclitaxel binds to high-affinity sites at the interior surface of the microtubule suppressing its dynamic behavior.[84]

A structurally less complex analog, namely E7389 (Eribulin®) got FDA approval in 2010 to treat patients with metastatic breast cancer who have received at least two prior chemotherapy regimens for late-stage disease including anthracycline- and taxane-based chemotherapy. [98]

A second binding site of microtubule depolymerizers on β-tubulin is the **colchicine-site**. The natural product colchicine (Figure 12) binds to the β-subunit of unpolymerized tubulin units forming a stable complex, which inhibits microtubule dynamics upon binding at the microtubule plus end (Figure 13b).[99] Dose-related, severe toxicities prevented a therapeutic development in cancer, but colchicine finds application in the treatment of gout.[100] Combretastatin, a colchicine-related structure, binds to the colchicine binding-site and has shown the ability to selectively target and disrupt tumor vasculature.[101] The compound, in the form of the disodium phosphate prodrug combrestatatin A-4-phosphate (CA4P), is in clinical evaluation against solid tumors in combinations with paclitaxel, carboplatin or bevacizumab (Avastin®; Roche).[82, 94, 102] The compounds NPI-2358 (from Nereus) and SSR97225 (from Sanofi-Aventis) are two other colchicine site-binders which lead to a breakdown of tumor vasculature and a phase I study revealed good tolerability of NPI-2358 in patients with solid tumors or lymphoma.[94] The estrogen metabolite 2-methoxyestradiol (2ME2, Panzem®)[103] also binds to the colchicine site and has shown to inhibit angiogenesis,[104] however, with low bioavailability, most probably due to metabolism. A 2ME2 derivative with improved metabolic stability is currently in phase I studies for the treatment of advanced solid tumors.[105]

1.6.2. Microtubule Stabilizers

The only known microtubule binding site of microtubule-stabilizing agents is the **taxol-binding site**, which is located on β-tubulin and is utilized by the majority of microtubule-stabilizing natural products identified so far. Exceptions are laulimalide (structure see Figure 6 page 3) and peloruside A (structure on page 41); these agents do not bind to the taxol site, but exactly where they bind to tubulin has not been established.[106] In fact it has been suggested that peloruside A binds to α- rather than β-tubulin.

Apart from the natural product taxol itself (paclitaxel; Taxol®, Bristol-Myers-Squibb), which can be isolated from the bark of the pacific yew tree (Taxus brevifolia), the semi-synthetic taxol derivatives docetaxel (Taxotere®, Sanofi-Aventis) and cabazitaxel are in clinical use against breast and prostate cancer. Cabazitaxel only against metastatic hormon-resistant prostate cancer[90] (Figure 14).

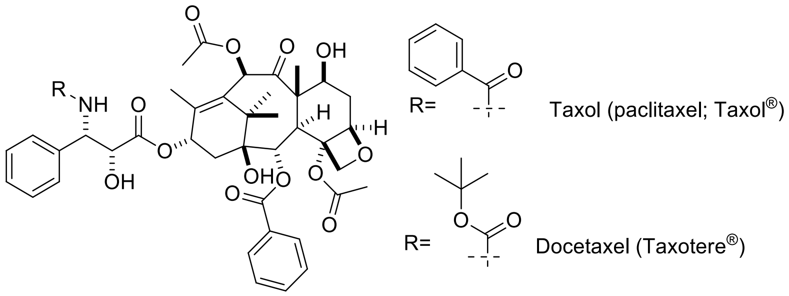


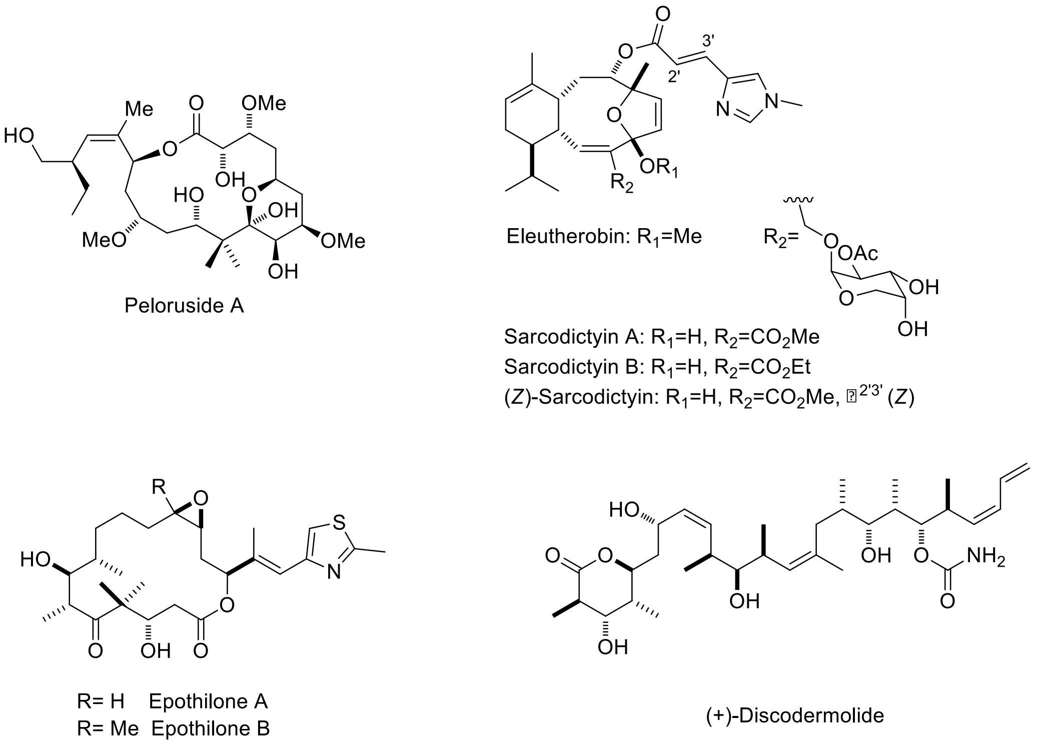
Figure 14: The taxanes as microtubule stabilizers with binding site on β-tubulin.

Taxol binds to the lumen of microtubules (Figure 13c) and stabilizes GDP-bound tubulin protofilaments.[107] It is thought that the compound gains access to the inner lumen through small pores in the microtubule wall or via fluctuations in the microtubule lattice.[108] At lower, clinically more relevant concentrations, taxol leads to decreased microtubule dynamics, similar as the previously described microtubule destabilizers, which results in aberrant spindle formation and the induction of apoptosis.[87] Impressively, it was found that only one taxol molecule per several hundred tubulin molecules in a microtubule reduced the rate of microtubule shortening by approximately 50%.[109] At higher taxol concentrations, the equilibrium is shifted from the soluble to the polymerized tubulin form leading to the bundling of interphase microtubules.

Similar to the vinca alkaloids, neurotoxicity and myelosuppression are side effects in the treatment with taxanes.[110] The poor solubility of taxol requires solubilizing formulations using cremophor (a castor oil derivative) which causes hypersensitivity and leads to a need for the pretreatment of patients. Derivatives with better solubility are Abraxane® (Abraxis), which is a taxol-albumin conjugate in clinical trials for the treatment of metatstatic breast cancer[94] and ANG1005 (Angiochem), a taxol-peptide conjugate.[111]

Resistance to paclitaxel can arise from overexpression of the P-glycoprotein (Pgp) drug transporter (belonging to the ATP-binding cassette (ABC)-transporter family). P-glycoprotein was the first ABC-transporter to be identified and is the product of the MDR1 gene.[112] Increased Pgp levels often lead to decreased intracellular drug levels and, thus, to resistance against drugs of different chemical structures, such as vinca alkaloids, taxol and many other common chemotherapeutics. Resistance to tubulin-interacting agents can also be mediated by overexpression of the βIII tubulin isotype.[113] Larotaxel® (Sanofi-Aventis) and TPI287 (Tapestry) are two derivatives being poor substrates for the Pgp multidrug transporter, thus circumventing taxol resistance. The former compound is currently in phase II trials for pancreatic cancer, the latter compound in phase II trials for prostate cancer.[114]

Other natural products promoting tubulin polymerization are epothilones, discodermolide, sarcodictyins, eleutherobin, peloruside, laulimalide, and, as the most recent addition to this group of natural products, zampanolide (Figure 15; for the structure of zampanolide see Figure 16).



Peloruside A

Eleutherobin: R_1=Me

Sarcodictyin A: R_1=H, R_2=CO_2Me
Sarcodictyin B: R_1=H, R_2=CO_2Et
(*Z*)-Sarcodictyin: R_1=H, R_2=CO_2Me, ▯$^{2'3'}$ (*Z*)

R= H Epothilone A
R= Me Epothilone B

(+)-Discodermolide

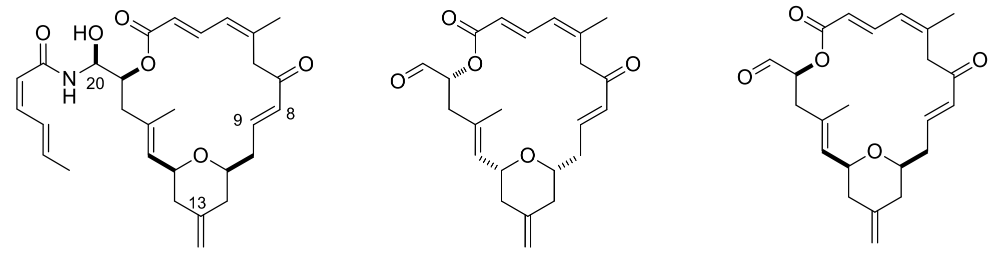
Figure 15: Structures of peloruside A, eleutherobin, sarcodictyins, epothilones and (+)-discodermolide.

Most of these compounds compete with taxol for binding to tubulin and thus are assumed to bind at or near the taxol-binding site. In contrast, laulimalide[115] and peloruside[106, 116] are not taxol-competitive (vide supra); for zampanolide no competition experiments with taxol have been reported. Epothilones are poor Pgp substrates and thus provide an alternative for growth inhibition of cells exhibiting taxol resistance.[117] The epothilone derivative ixabepilone (Ixempra®, Bristol-Myers-Squibb) was approved in 2007 for the treatment of metastatic or locally advanced taxane- and anthracycline-resistant breast cancer; it is associated with peripheral neuropathy as dose-limiting toxicity.[118] Epothilone B (patupilone),[119] ZK-EPO (sagopilone, Bayer)[120] are currently in clinical development.

Synergistic effects on microtubule dynamics have been reported for a combination of laulimalide and taxanes[121] (which bind to different sites on tubulin), as well as for discodermolide and paclitaxel (which are believed to bind to the same site).[122] In addition, combinations of taxanes with vinca alkaloids, estramustine or colchicine analogs have shown synergism *in vitro*.[114, 123] Although the exact mechanism(s) of synergism between drugs targeting tubulin remain(s) to be explored,[84] the effect offers the potential for improved efficacy and reduced side effects in patients due to the reduced concentrations needed of each single agent.

2. Aims and Scope

The work described in this thesis was largely triggered by the intriguing divergence in the absolute stereochemistry between the macrolactone core structures of (–)-zampanolide ((–)-**1**) and (+)-dactylolide ((+)-**2**) (Figure 16), which raised the question, if the difference in biological activity between (–)-zampanolide ((–)-**1**) and (+)-dactylolide ((+)-**2**) was related to the difference in the absolute stereochemistry of the macrolide ring or to the presence/absence of the hemiaminal side chain (or perhaps both). A primary objective of this thesis thus was the total synthesis of non-natural (–)-dactylolide ((–)-**2**), employing a strategy that would also provide a new and efficient route to (–)-zampanolide ((–)-**1**). The latter was hypothesized to be a microtubule-stabilizing agent, given its structural similarity with other marine microtubule stabilizers. The question of the antiproliferative activity of (–)-dactylolide ((–)-**2**) had not been addressed at the outset of this thesis and neither had the mode of action of (–)-zampanolide ((–)-**1**) been investigated.



(–)-Zampanolide ((–)-**1**) (+)-Dactylolide ((+)-**2**) (–)-Dactylolide ((–)-**2**)

Figure 16: Structures of natural occurring (–)-zampanolide ((–)-**1**), dactylolide ((+)-**2**) and unnatural (–)-dactylolide ((–)-**2**).

In the meantime the tubulin-polymerizing activity of (–)-zampanolide ((–)-**1**) has been discovered by *Miller* and co-workers[10] and the preliminary biological evaluation of unnatural (–)-dactylolide ((–)-**2**) has been reported.[16] The latter study revealed that the difference in absolute stereochemistry between the macrolactone core structure in (–)-zampanolide ((–)-**1**) and in (–)-dactylolide ((–)-**2**) cannot explain the inherent difference in biological potency between the natural products (–)-zampanolide ((–)-**1**) and (+)-dactylolide ((+)-**2**).

In a second phase of this thesis project the chemistry developed as part of the total synthesis work should then be exploited for the synthesis of a series of derivatives for structure-activity-relationship (SAR) studies. Ideally this would have led to the identification of structurally simpler analogs with similar potency as the parent compounds (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**), but accessible in a reduced number of synthetic transformations. Despite the synthetic efforts towards **1**[7, 9c, 26], (+)-**2**[9b, 9c, 33, 40] and (–)-**2**[7, 16, 26, 30, 44, 53] no derivatives of these macrolides have been reported so far.

The total synthesis to be developed was to be convergent in nature, in order to deal with a manageable number of steps for the longest linear sequence. Furthermore, it was to be flexible enough so as to still allow the exploration of alternative options to go forward even at a late stage, should obstacles arise.

3. Results and Discussion

3.1. First and Second Generation Approach towards (–)-Dactylolide and (–)-Zampanolide

3.1.1 First Generation Approach

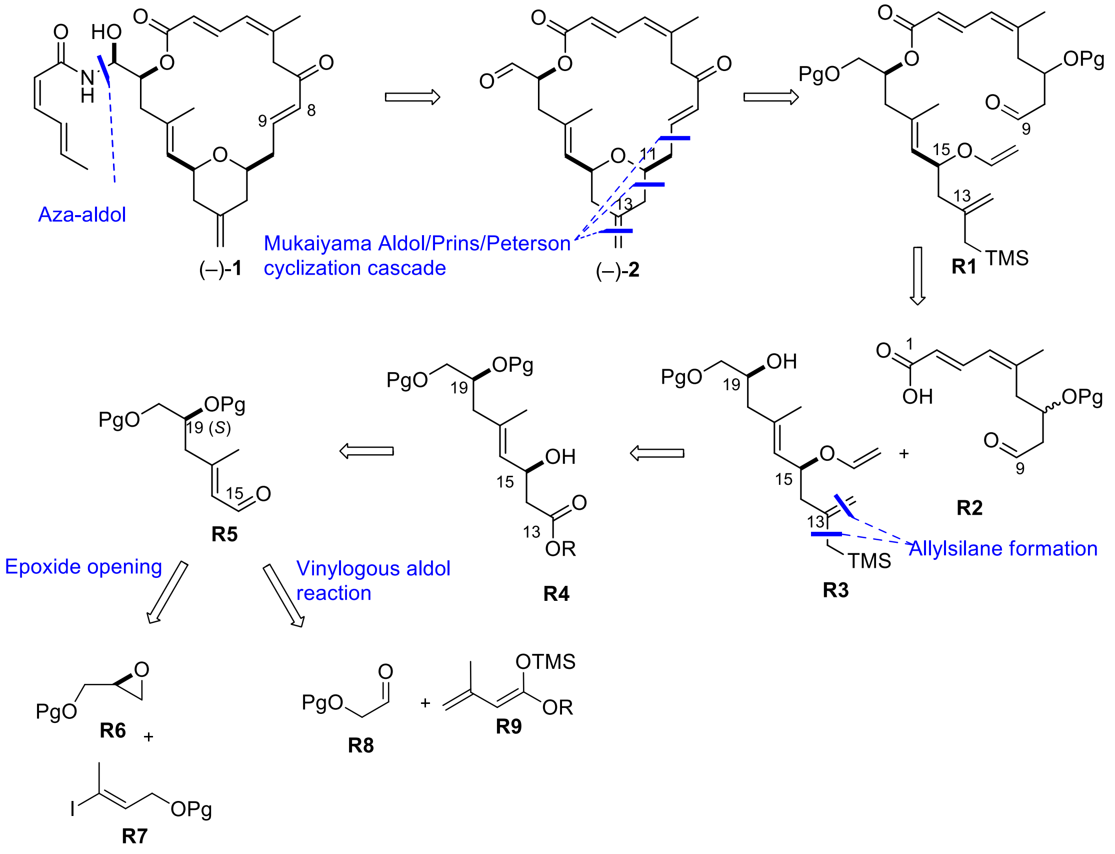
3.1.1.1 Retrosynthesis

Our various retrosyntheses of (–)-zampanolide ((–)-**1**)[3] were all based on a late-stage introduction of the side chain via an unselective aza-aldol reaction, similar to the approach by *Hoye;*[26] this would require a separation of C20 epimers. Retrosynthetically this leads directly to the macrolactone aldehyde (–)-dactylolide ((–)-**2**), the antipode of the naturally occurring (+)-dactylolide ((+)-**2**). Obviously, the synthesis had to be centered on the effective construction of the 2,6-syn-substituted THP subring, this being a crucial and challenging element in the structure. Our first generation retrosynthesis contemplated a *Mukaiyama* aldol[124]/*Prins* cyclization [125]/*Peterson*[126] olefination cyclization cascade, which has found application in a formal total synthesis of leucascandrolide A as reported by *Rychnovsky* and co-workers.[127] According to this approach macrocyclization and the build-up of the fully substituted THP ring would occur in one step (Scheme 27). This strategy would require an elimination of the so formed C9 hydroxyl group, in order to install the C8-C9 C=C double bond. Although this idea was highly appealing for the construction of (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**), it does bear limitations when it comes to the synthesis of analogs with modified THP subrings.

---

[3] The atom numbering used throughout this thesis for building blocks and intermediates always corresponds to the numbering of the natural product (–)-zampanolide ((–)-**1**).

To implement this cyclization strategy, a precursor such as **R1** would be needed with all the necessary functional groups present; this includes a vinyl ether moiety at C15, an allylsilane moiety at C13 and an aldehyde functionality at C9 (Scheme 27). Retro-cleavage of the ester group in **R1** provides acid **R2** and the secondary alcohol **R3**, which might in turn be derived from *β*-hydroxy ester **R4**; the latter is a retron for an aldol transform leading to unsaturated aldehyde **R5**. Analysis of **R5** revealed an epoxide opening between protected (*R*)-glycidol **R6** and a metallated-vinyl species[128], derived from (*E*)-vinyl iodide **R7**, as a feasible approach to install the chiral center at C19. Alternatively, a copper (I)-mediated asymmetric vinylogous aldol reaction[34, 129] between aldehyde **R8** and silyl ketene acetal **R9** would also deliver the stereocenter at C19 with concomitant formation of the unsaturated system.


Aza-aldol
(–)-1
Mukaiyama Aldol/Prins/Peterson cyclization cascade
(–)-2
R1
TMS
PgO
OPg
R2
R3
Allylsilane formation
R4
R5
19 (S)
Epoxide opening
Vinylogous aldol reaction
R6
R7
R8
R9
OTMS
OR

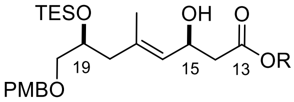
Scheme 27: First generation retrosynthesis of (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**). Pg = protecting group or H, which might vary independently.

The asymmetric vinylogous aldol reaction was only considered as a rescue strategy, since it had already been used in the synthesis of (+)-dactylolide ((+)-**2**) by

Floreancig[33] and co-workers, albeit with the opposite (i. e., (*R*)) stereochemistry at C19.

3.1.1.2 Attempts towards the Synthesis of Building Block R4

Based on the first generation retrosynthetic analysis outlined in Scheme 27, *β*-hydroxy ester **3** was required as an intermediate for the projected *Mukaiyama* aldol[124] /*Prins* cyclization[125b, 127]/*Peterson* olefination[126] cyclization cascade (Figure 17).



3

Figure 17: *β*-Hydroxy ester **3** as a crucial intermediate in the first generation approach towards (–)-zampanolide ((–)-**1**) and dactylolide ((–)-**2**), R = alkyl.

Although its structural complexity made fragment **3** look like a feasible synthetic target, efforts towards the development of a viable route to **R4**, respectively **R3**, turned out to be unsuccessful. This section provides a brief summary on some of these unsuccessful attempts. The initial approach for the construction of **3** were based on the idea of installing the tri-substituted C=C double bond via a ketone moiety at C17 as the precursor for an olefination reaction; this was to be followed by isomerization of the double bond into the main chain. The synthesis started from the readily available ethyl 4-chloroacetoacetate (Scheme 28) which was converted into PMB-ether **5**. An excess of base was necessary for the successful conversion to **5**, which involves formation of the sodium-enolate **4** followed by ether formation via displacement of chloride.[130] The stereocenter at C19 was installed by ruthenium-mediated asymmetric hydrogenation according to *Noyori*,[131] which worked in good yields and with acceptable enantioselectivity (90% ee).[4] A TES group was considered a suitable protecting group for the next transformations, which is why alcohol **6** was protected as its TES ether **7**.

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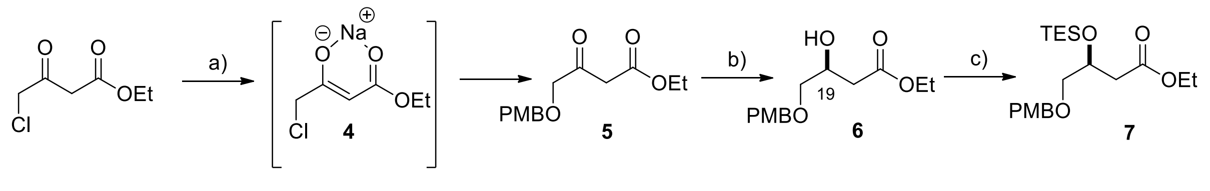
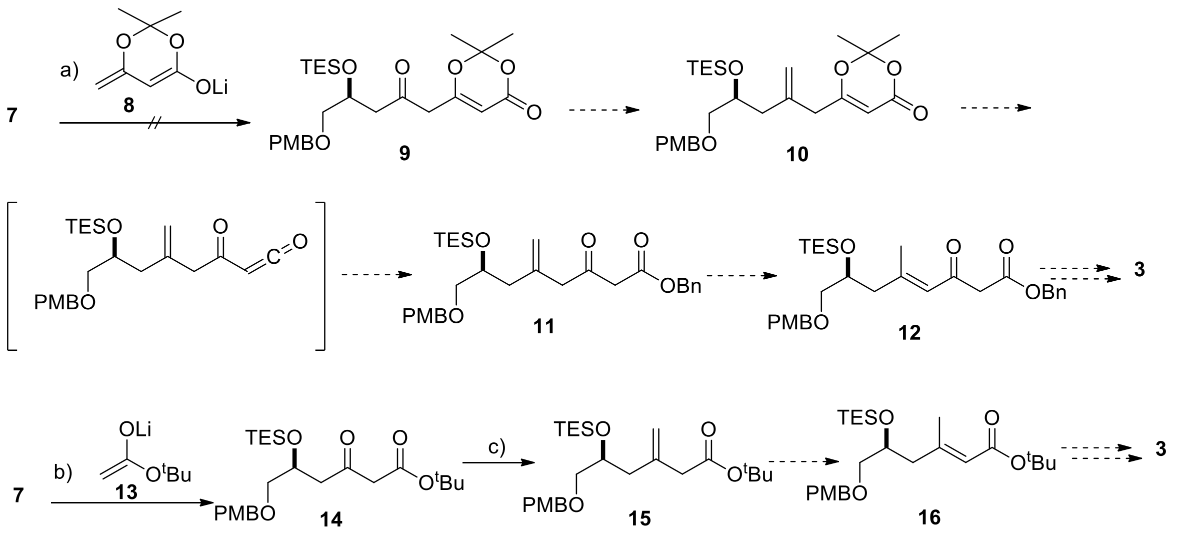
[4] Determined by chiral HPLC on Chiralcel OD-column; hexane/*i*-PrOH (84:16), 1 mL/min, 25 °C, 254 nm, R_t 6.80 min.



Scheme 28: (a) PMBOH, NaH (excess), toluene, RT, 78%; (b) RuCl(C_6H_6)/(*R*)-BINAP, H_2, 4 atm, EtOH, 105 °C, 87%, 90% ee; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 86%.

With **7** in hand, subsequent chain extension was to be accomplished via a *Claisen* condensation approach, either with a 4-carbon unit (derived from 2,2,6 trimethyl-1,3-dioxin-4-one) or with a 2-carbon unit (derived from *t*-butyl acetate) (Scheme 29).

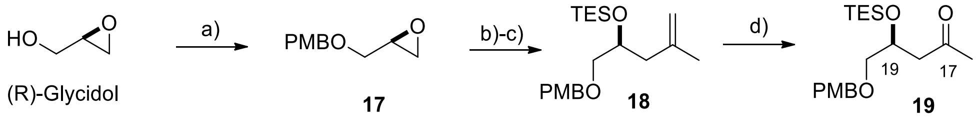


Scheme 29: (a) **8** (2 equiv), THF –40 °C; (b) **13** (2 equiv.), THF, –78 °C to –40 °C, 75%; (impure); (c) conditions see text.

The *Claisen* condensation between ester **7** and lithium dienolate **8** (readily prepared from 2,2,6-trimethyl-1,3-dioxin-4-one) was tested first, but no conversion to **9** was observed, even at elevated temperatures. Changing the counterion to sodium or the use of *Lewis* acids such as Me_2AlCl or $SnCl_4$[132] did not produce any of the desired product either. In contrast, addition of the lithium enolate of *t*-butyl acetate (**13**) to **7** afforded the *β*-keto ester **14,** although contaminated with unknown impurities which could not be removed.[130] For the installation of the tri- substituted C=C double bond in **3** we attempted the conversion of the keto group to a methylene group; the resulting **15** was then to be transformed to the *α*,*β*-unsaturated ester **16** via base-promoted transposition of the double bond, similar to the approach reported by *Keck*.[40] Unfortunately, methylenation of the keto group in **14** turned out to be impossible under any of the conditions tested, including the use of the *Wittig* reagent

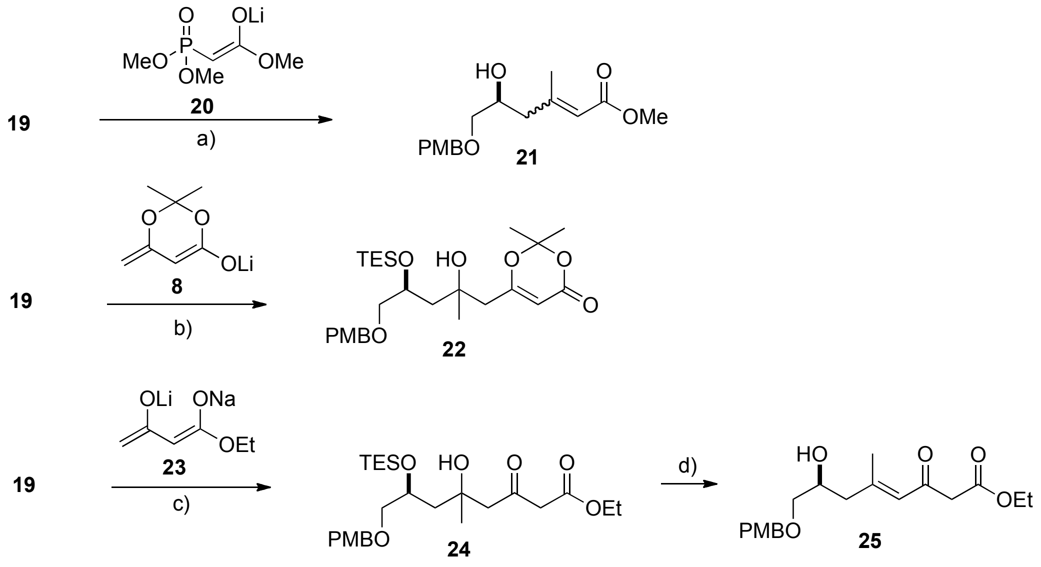
($Ph_3P=CH_2$)[133] and the titanium-based *Tebbe* ($Cp_2TiCH_2ClAlMe_2$)[134] and *Petasis* reagents (Cp_2TiMe_2),[135] which have found frequent application in the olefination of enolizable ketones, esters and lactones. Likewise, an attempted *Peterson* olefination using $TMSCH_2MgCl$ and $TMSCHLi{\cdot}CeCl_3$[126] did not provide olefin **15**. Starting material **14** was re-isolated in most cases. The unsuccessful conversion of **14** into **15** may be caused by an acid-base reaction between the olefination reagent and the *β*-keto ester moiety. Due to these problems we abandoned the *Claisen* approach towards **3**.

In a next approach we then explored the feasibility of the intermediacy of a methyl ketone moiety in the construction of the C16-C17 bond in **3,** either through *HWE* chemistry or via an appropriate nucleophile addition/elimination process. To test these ideas, ketone **19** was prepared starting from commercially available (*R*)-glycidol. The latter was first protected as its PMB ether **17** and then submitted to copper(I)-mediated epoxide opening with isopropenylmagnesium bromide[136] followed by TES protection of the secondary hydroxyl group formed (Scheme 30). Olefin oxidation in **18** was best conducted under conditions described by *Lemieux* and *Johnson*[137] ($NaIO_4$ and OsO_4) which afforded ketone **19** in good yields.



Scheme 30: (a) PMBCl, NaH, TBAI (cat.), DMF, 0 °C to RT, 82%; (b) isopropenylmagnesium bromide, CuI (10 mol%), THF, –40 °C, 99%; (c) TESCl, ImH, DMF, 0°C to RT, 1h, 94%; (d) i) OsO_4 (cat.), NMO, acetone/H_2O, RT, 4h, ii) $NaIO_4$, H_2O, RT, 12 h, 85% (2 steps).

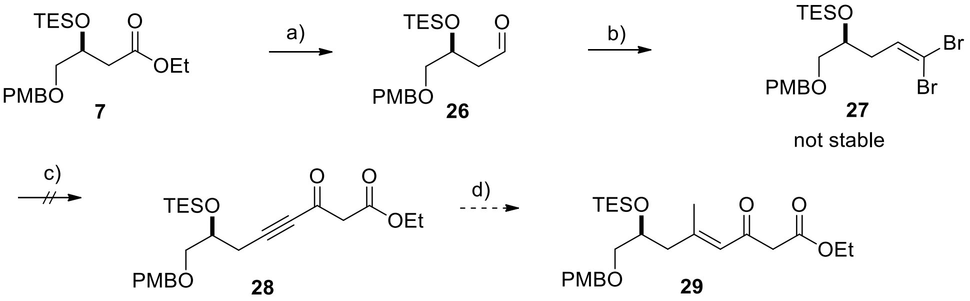
Ozonolysis was not compatible with the PMB group, leading to PMB cleavage and the formation of a series of unidentified side products which are not further specified. Having **19** in hand, the *HWE* chemistry was tried first, although being aware of the fact that *HWE* chemistry with ketones is distinctively different from that with aldehydes. Thus, while a plethora of references can be found for *HWE* reactions with aldehydes, similar transformations with ketones are limited to special cases. For example, *Avery*[138] and *Danishefsky*[139] have successfully applied *Wittig*-type chemistry for the installation of the thiazole side chain in the context of epothilone syntheses. In light of this, it was not too surprising that the anticipated reaction[140] between the lithium anion of trimethyl phosphonoacetate (**20**) and **19** only afforded traces of (desilylated) **21**, without any selectivity. Most probably the reagent **20** is too basic and underwent acid-base chemistry with **19** as the preferred reaction (Scheme 31).



Scheme 31: (a) **20**, THF, 0 °C to 45°C, traces of **21**, (*E*:*Z*) 1:1; (b) **8**, THF, –30 °C, 29%; (c) **23**, THF, –78 °C, 16%; (d) MsCl, NEt_3, CH_2Cl_2, 0 °C to 50 °C, 40%.

For an alternative use of **19**, an addition/elimination strategy with a C4 nucleophile was explored next. The addition of nucleophiles **8** and **23** indeed afforded the carbinols **22** and **24** respectively, although in low yields. Mesylation and subsequent base-induced elimination of the hydroxyl group in **24** proceed with concomitant loss of the silyl-protecting group to afford the unsaturated olefin **25** in 40% yield.[141] Although the ketone-addition-elimination sequence might have potentially been optimized, in light of the low yield for the addition step we decided not to pursue this approach further and instead try to find a higher-yielding approach to **3**.

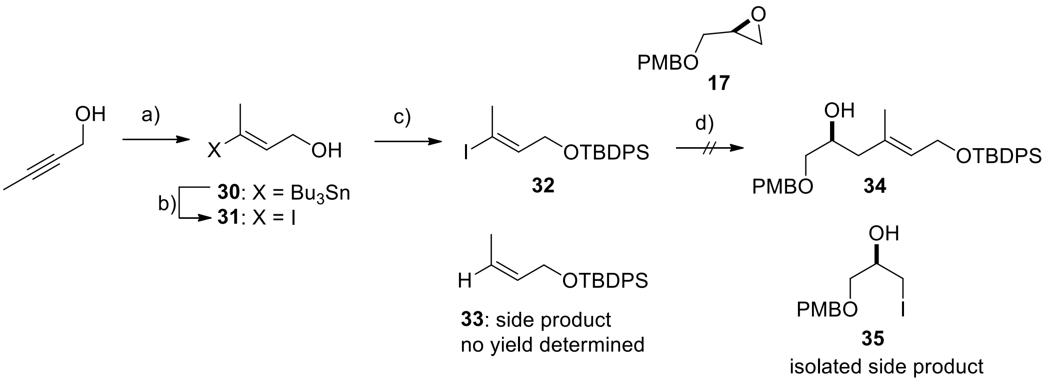
Yet an alternative way to create the tri-substituted C=C double bond at C16-C17 would be via an acetylenic ester moiety that would undergo copper(I)-catalyzed conjugate methyl addition,[142] a concept which was to be explored with intermediate **28** (Scheme 32). Starting from ester **7** geminal dibromide **27** was prepared via aldehyde **26**, employing the *Corey-Fuchs* protocol.[143] All attempts to isolate **27** were unsuccessful, due to its pronounced instability; this was also manifest during attempted aqueous workup, which resulted in complete decomposition. Filtration of the crude product of the *Corey-Fuchs* reaction over a plug of silica gel or celite, thus removing phosphine derivatives, did not improve the stability.



Scheme 32: (a) DIBAL-H, toluene, –80 °C, 95%; (b) CBr_4, PPh_3, NEt_3, CH_2Cl_2, 0 °C, used as crude; (c) i) *n*-BuLi, THF, –78 °C to 0 °C, ii) ethylmalonyl chloride; (d) i) PhSH, NaOMe, ii) MeMgBr, CuI.

The crude dibromide was thus tried to be directly converted to the lithium acetylide with *n*-BuLi, which should then be trapped with ethyl malonyl chloride as the electrophile. Unfortunately, none of the desired alkyne **28** could be obtained under these conditions (Scheme 32). It is conceivable that the enolizable electrophile ethyl malonyl chloride simply underwent an acid-base reaction with the acetylide. Choosing a non-enolizable electrophile such as ethyl chlorformate might have overcome this problem, but this strategy would have been close to the approach followed by *Jennings* in his synthesis of (–)-dactylolide ((–)-**2**)[30], which is why this alternative was considered largely redundant and, therefore, unattractive.

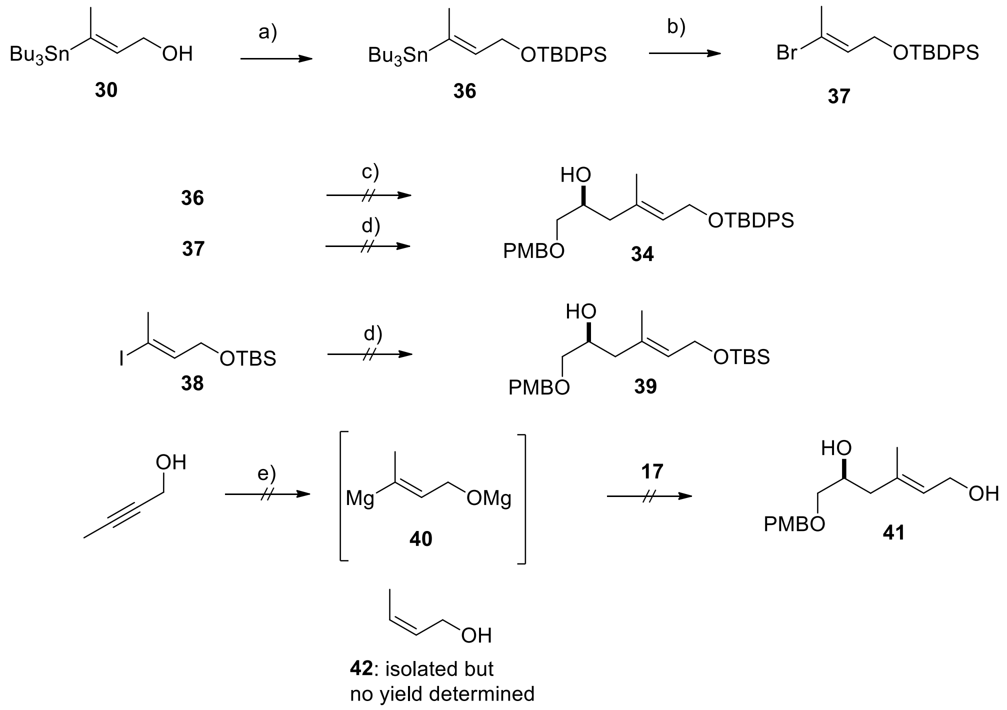
Perhaps the most direct approach to **3** would involve the formation of the C17-C18 bond in an epoxide opening reaction with an appropriate vinyl iodide, a concept that has been applied by *Smith* and co-workers at an advanced stage in the synthesis of (+)-zampanolide ((+)-**1**)[9a, 9c] and (+)-dactylolide ((+)-**2**).[9b] To explore this strategy for the synthesis of **3**, the $BF_3{\cdot}OEt_2$-mediated opening of epoxide **17** with lithiated (*E*)-vinyl iodide **32** was investigated (Scheme 33). The necessary (*E*)-vinyl iodide **32** was best prepared from 2-butyn-1-ol via a stannylcupration/iodination sequence.[144] The stannylcuprate $Bu_3Sn(Bu)CuCNLi_2$ afforded first the (*E*)-vinyl tin adduct **30** which underwent tin to iodide exchange to give **31** in high yields. In contrast, hydrozirconation by the use of the *Schwartz* reagent (Cp_2ZrHCl)[145] resulted in only partial conversion to **31**. Unfortunately, the initial trials to open epoxide **17** with lithiated vinyl iodide **32** under BF_3-catalysis in THF did not deliver the desired secondary alcohol **34,** but only led to the formation of iodohydrin **35**. As such, the formation of iodohydrin **35** by the *Lewis* acid-mediated epoxide opening with the iodide ion derived from the preceding halogen-lithium exchange was not entirely unexpected.



Scheme 33: (a) Bu_3SnH, *n*-BuLi, CuCN, MeOH (110 equiv), THF, –78 °C to –10 °C, 79%; (b) I_2, CH_2Cl_2, –78 °C, 94%; (c) TBDPSCl, NEt_3, DMAP (cat.), CH_2Cl_2, 91%; (d) *n*-BuLi or *t*-BuLi, THF, –78 °C, **17** then $BF_3{\cdot}OEt_2$. Other conditions: CuCN (cat.), CuI (cat.) or 2-ThCuCNLi in THF or Et_2O.

It was surprising, however, that **35** was the only epoxide opening product observed especially in light of the fact that similar transformations are precedented in the literature.[7] The halogen-lithium exchange step in **32** was not what was hampering the reaction and worked with equal efficacy with both *n*-BuLi and *t*-BuLi at low temperature (–78 °C, 15–30 min) as judged by TLC analysis that indicated the disappearance of **32** to a less polar product. Furthermore, product **33** was observed by ^{1}H-NMR analysis of the crude reaction mixture and in isolated, but impure fractions after flash chromatography.

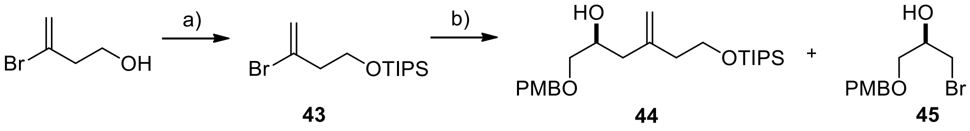
To evaluate whether there was a dependence of reaction outcome on the vinyl precursor, the corresponding (*E*)-vinyl tin species **36** and (*E*)-vinyl bromide **37**[9] were prepared and submitted to the conditions given in Scheme 33 ($BF_3{\cdot}OEt_2$, THF, –78 °C), but again no conversion to **34** took place (Scheme 34). It might be assumed that the organolithium species forms aggregates in ethereal solutions, which may not be able to react with epoxide **17**. HMPA is known to enhance rates of a variety of main group organometallic species, by dissociating, e. g., tetrameric MeLi or dimeric phenyllithium into monomeric species.[146] Thus, reactions were also carried out in the presence of HMPA as a co-solvent, but this did not lead to any improvements.



Scheme 34: (a) i) TBDPSCl, NEt_3, DMAP (cat.), CH_2Cl_2, RT, 95%; (b) Br_2, CH_2Cl_2, 0 °C, 98% (2 steps); c) *n*-BuLi, THF, –78 °C, **17**, then $BF_3{\cdot}OEt_2$; (d) *t*-BuLi, THF, –78 °C, **17**, then $BF_3{\cdot}OEt_2$; (e) *i*-BuMgBr, Cp_2TiCl_2 (cat.), 0 °C to RT, Et_2O, CuI (1 equiv) then **17**.

The efficiency of the organomagnesium derivative of **32** in the epoxide opening reaction was investigated after iodide to magnesium exchange with dibutyl isopropylmagnesate (i-PrBu$_2$MgLi).[147] Although complete exchange to the organomagnesium species occurred, as judged by the isolation of the reduced olefin **33** (again in impure form), the formation of **34** was not observed. In the context of organomagnesium chemistry, we also tried to apply the concept of hydromagnesiation in order to form the (*E*)-vinyl magnesium intermediate **40** directly from 2-butyn-1-ol. Although titanium-mediated hydromagnesiations have been reported,[148] the resulting magnesium species have not been widely used in synthesis, especially not for epoxide openings. 2-butyn-1-ol could indeed be reduced, at least partially, to the corresponding vinylmagnesium species **40**, as judged by the isolation of allylic alcohol **42** after aqueous workup and isolation (along with unreacted 2-butyn-1-ol). Unfortunately, none of the desired diol **41** as the formal product of the opening of epoxide **17** could be isolated (Scheme 34). Epoxide opening with **32** was also unsuccessful with catalytic or stoichiometric amounts of copper (I) (e.g. CuI, CuCN) or with mixed cuprate (2-ThCuCNLi).[149] Lastly, a change of the hydroxyl protecting group in **32** to the sterically less demanding TBS ether **38**

(Scheme 34) did not yield **39**. Interestingly, the lithium anion derived from vinyl bromide **43**, a regioisomer of **37**, readily reacted with epoxide **17** to the produce alcohol **44** with BF_3•OEt_2 in THF at –78 °C (Scheme 35). The remainder of the starting material was converted to the bromohydrin derivative **45**. One might speculate that the position of the double bond affects the stability and reactivity of lithium aggregates in solution. If this were true, however, one might have expected the addition of HMPA to affect the course of the reaction between lithiated **32** and **17**, which was not observed.



Scheme 35: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, quant; (b) *n*-BuLi, THF, –78 °C, **17**, then BF_3•OEt_2, 60%.

As will be discussed at a later stage, we were able eventually to identify conditions that led to successful opening of **17** with metallated vinyl species. At this point of the project, however, the epoxide opening approach was abandoned. Instead we turned to an approach where the stereocenter at C15 would be introduced via an asymmetric vinylogous aldol reaction with simultaneous introduction of the tri-substituted double bond.

The C2-symmetric complex [Cu((*S,S*)-Ph-pybox)]-$(SbF_6)_2$ is known to catalyse asymmetric aldol reactions with predictable stereochemical outcome.[34] As can be seen in Figure 18, the aldehyde chelates to the copper(II) center of the catalyst forming a square pyramidal complex. An aromatic protecting group (such as PMB) is essential for the necessary π-π stacking with the pyridine residue of the catalyst which biases the aldehyde into a conformation in which one side is shielded (the *re-face* in Figure 18) by the phenyl group pointing downwards. The nucleophile can only attack from the opposite side (the *si-face*) leading to the product **46** in high stereochemical purity.[34] This methodology has found application in natural product synthesis,[129] including the synthesis of (+)-dactylolide ((+)-**2**) as reported by *Floreancig*.[33]

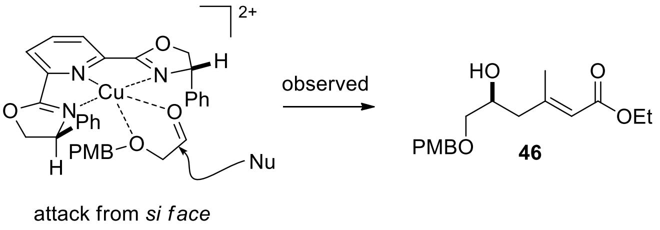
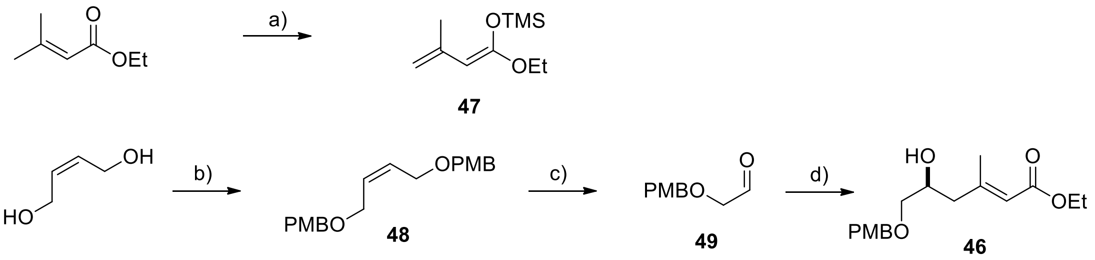


Figure 18: Model for the stereochemical outcome in the [Cu(S,S)-(Ph-pybox)]$^{2+}$-catalyzed aldol reaction. In this chelation model, the aldehyde is postulated to adopt the equatorial position and the PMB group the axial position which allows π-π stacking with the pyridine unit of the catalyst, thus leading to a defined stereochemical path in the aldol reaction.[34]

In our case, the necessary silyl ketene acetal **47** was readily obtained by the deprotonation of 3,3-dimethyl acrylate with LDA followed by treatment with TMSCl, under conditions different from those described in the literature (Scheme 36).[150] Thus, it was reported that HMPA is essential for the control of the olefin geometry in **47**. However, in trying to reproduce the literature data, an inseparable mixture of (*E*:*Z*) silyl ketene acetal isomers was obtained along with unreacted starting material, resulting in a yield lower than 50% for **47**. Interestingly, omitting HMPA not only increased the yield of **47** but also led to the formation of a single isomer (Scheme 36).

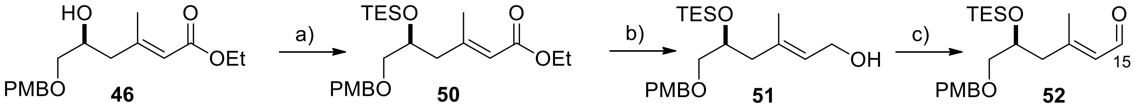


Scheme 36: (a) i) *n*-BuLi, *i*-Pr$_2$NH, THF, –78 °C, ii) TMSCl; 91%; (b) NaH, PMBCl, DMF, 0 °C to 10 °C, 98%; (c) i) AD-mix β, methansulfone amide, *t*-BuOH/H$_2$O (1:1), ii) NaIO$_4$, CH$_2$Cl$_2$/H$_2$O (5:1), 62% (2 steps); (d) i) (S,S)-Ph-pybox, CuCl$_2$, AgSbF$_6$, CH$_2$Cl$_2$, RT, ii) **49**, CH$_2$Cl$_2$, –78 °C, then **47**, CH$_2$Cl$_2$, 30 min to 4 h, –78 °C, iii) HCl (1N), THF, RT, 15–70% (2 steps), 90–93% ee.

The necessary aldehyde **49** was readily obtained via bis-PMB-protection of (*Z*)-but-2-ene-1,4-diol which was followed by *Lemieux-Johnson*[137] cleavage of the C=C double bond, which gave access to **49** in larger quantities (2.24 g). Noteworthy, oxidation of the C2 alcohol corresponding to **49** resulted in lower yields than C=C double bond cleavage in **48** for those oxidation reagents investigated, i. e., DMP[151], SO$_3$·py[152] and TPAP/NMO.[153]

With aldehyde **49** and silyl ketene acetal **47** in hand, the asymmetric vinylogous aldol reaction was explored next. The [Cu((S,S)-Ph-pybox)]$^{2+}$catalyst was generated in situ by mixing the ligand (*S,S*)-Ph-pybox and $CuCl_2$ in CH_2Cl_2 followed by addition of $AgSbF_6$ and filtration to remove solids such as AgCl. Although the conversion of aldehyde **49** was complete, the isolated yields of **46**, after TMS-ether cleavage, varied between 15–35% with 70% being the best yield for a single experiment. The stereochemical outcome of the reaction was acceptable (90-96% ee).[5] One explanation for the variable yields might be that a significant amount of water was still coordinated to $CuCl_2$ (although this was dried before use), which would give rise to the formation of trace amounts of HCl from unremoved AgCl, thus leading to side reactions.

Although the copper-mediated aldol reaction lacked reproducibility in terms of yield, substantial amounts of **46** could be prepared by this approach. This material was converted into TES-ether **50**, which was then elaborated into the unsaturated aldehyde **52** by reduction with LAH, to produce allylic alcohol **51**, followed by MnO_2-mediated oxidation (Scheme 37). The stage was thus set for the introduction of the new stereocenter at C15.



Scheme 37: (a) TESOTf, 2,6-dimethylpyridine, CH_2Cl_2, –78 °C, 90%; (b) LAH, Et_2O, 0 °C; (c) MnO_2, CH_2Cl_2, RT, 72% (2 steps).

In order to complete the construction of fragment **3** aldehyde **52** was to be submitted to asymmetric acetate aldol reaction, leading to the question which chiral auxiliary should be chosen. Among the various possibilities, our preference was for an ester bound auxiliary, which we felt might offer the opportunity for the direct conversion into the allylsilane moiety without FGI, which would not be possible, e. g, with *Evans* type imides. *Braun* and co-workers have reported the use of (*R*) and (*S*)-2-acetoxy-1,1,2-triphenylethanol as readily accessible chiral acetate moieties that provide access to the chiral *β*-hydroxy esters in good yields[154] and many successful applications of these precursors in synthesis have been documented.[155] Both auxiliaries **53** and **55** were prepared from commercially available methyl (*R*)- and (*S*)-

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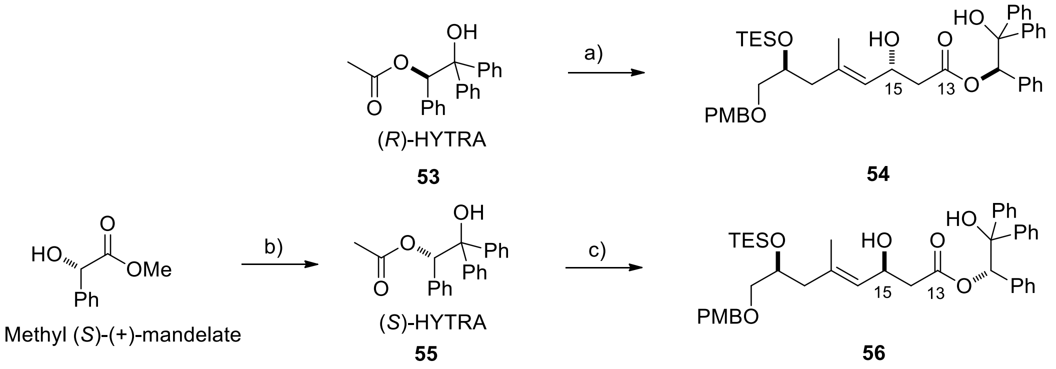
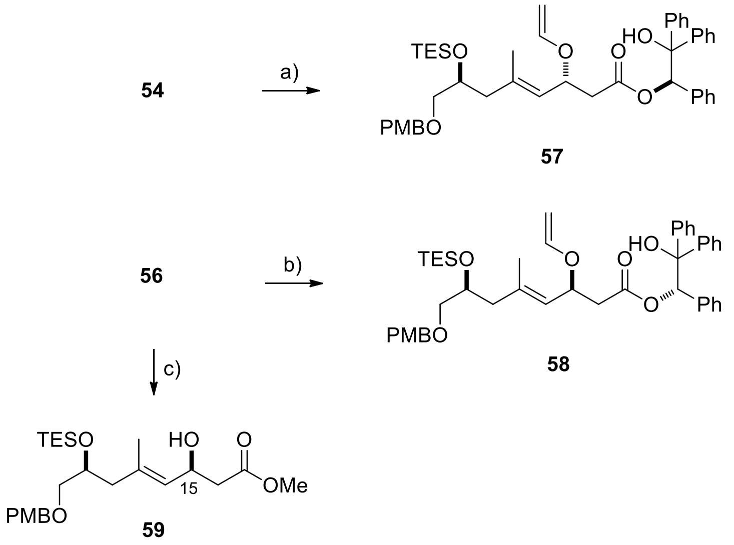
[5] Determined by chiral HPLC on a Chiralpak AD-H-column; hexane/*i*-PrOH (95:5), 1 mL/min, 25 °C, 254 nm, R_t 23.57 min.

mandelate, respectively, by two-fold addition of phenylmagnesium bromide and subsequent chemoselective acylation of the secondary hydroxyl group in good overall yields (Scheme 38).[156]



Scheme 38: (a) *n*-BuLi, *i*-Pr_2NH, **53**, THF, –78 °C then $MgBr_2$, –90 °C, then **52**, Et_2O, –130 °C, 79%, 8:1 dr; (b) phenylmagnesium bromide, THF, –78 °C, 60% (crystallization), ii) AcCl, pyridine, CH_2Cl_2, 0 °C, 72%; c) *n*-BuLi, *i*-Pr_2NH, **55**, THF, –78 °C then $MgBr_2$, –90 °C, then **52**, 2-methylbutane, –130 °C, max. 30%, 8:1 dr.

The feasibility of the acetate aldol reaction was first explored with (*R*)-HYTRA (**53**), which had already been available from other sources. Reaction of the corresponding acetate with aldehyde **52** gave the undesired C15 epimer **54** as the major product, as predicted. **54** was obtained in 79% yield as a mixture of diastereomers with a dr of approximately 8:1 in favor of desired **54** (as judged by ^{1}H-NMR analysis). In contrast, the aldol reaction with the acetate derived from (*S*)-HYTRA (**55**) proceeded sluggishly and afforded **56** in low yields only (max. 30%), as a diastereomeric mixture of 8:1 in favor of the desired **56**. Unfortunately, the reaction with both chiral acetates **53** and **55** lacked reproducibility in terms of yield. No differences were observed between the use of either commercial or freshly prepared $MgBr_2$ (produced from 1,2-dibromoethane and Mg) in the crucial transmetallation from lithium to magnesium. It is conceivable that the very low reaction temperature (–130 °C) required for high facial selectivity in the asymmetric aldol reaction negatively affected both yields and reproducibility, as the reaction mixture was never found to be a homogenous solution, regardless if Et_2O or 2-methylbutane were used as a co-solvent. It was thus clear that an alternative to the acetate aldol reaction would have to be found at a later stage of the project, should this strategy be pursued further.



Scheme 39: (a) (DPP)Pd(OCOCF$_3$)$_2$ (5 mol%), BVE, NEt$_3$, 40°C, 70%; (b) (DPP)Pd(OCOCF$_3$)$_2$ (5 mol%), BVE, NEt$_3$, 35°C, 6%; (c) NaOMe, MeOH, RT, 33%.

With minor quantities of **56** in hand we proceeded to explore the elaboration of this intermediate into building block **R-4** (see Scheme 27, page 44) as one of the immediate precursors for the projected *Mukaiyama* aldol/*Prins* cyclization/*Peterson* olefination cyclization cascade. In a first step this involved a palladium(II)-mediated transfer vinylation to install a vinyl ether moiety at C15 (Scheme 39 and Figure 19).[157] For hydroxy ester **54** a yield of 70% was obtained in this reaction, but the desired isomer **58** was obtained in only 6% from **56**. The reasons for this discrepancy have not been elucidated, but it seems unlikely that this result is related, at least not exclusively, to the difference in stereochemistry between **54** and **56**.

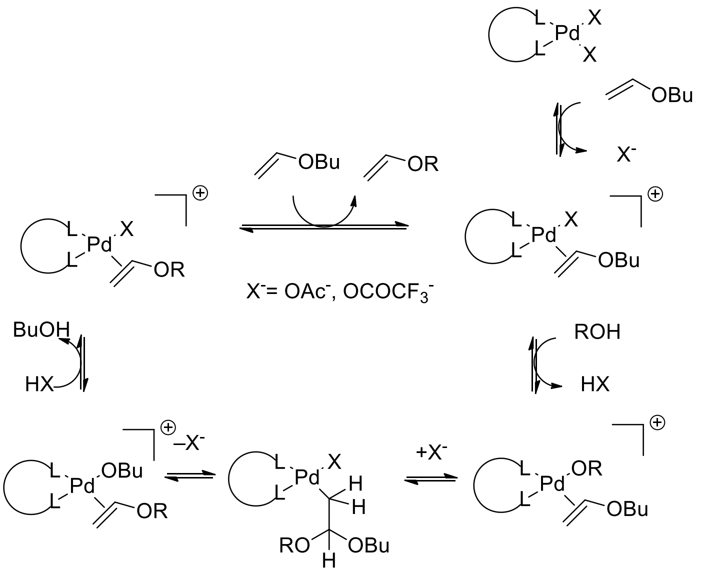
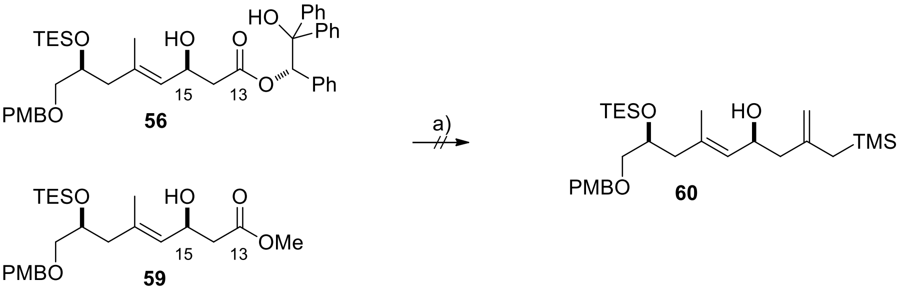


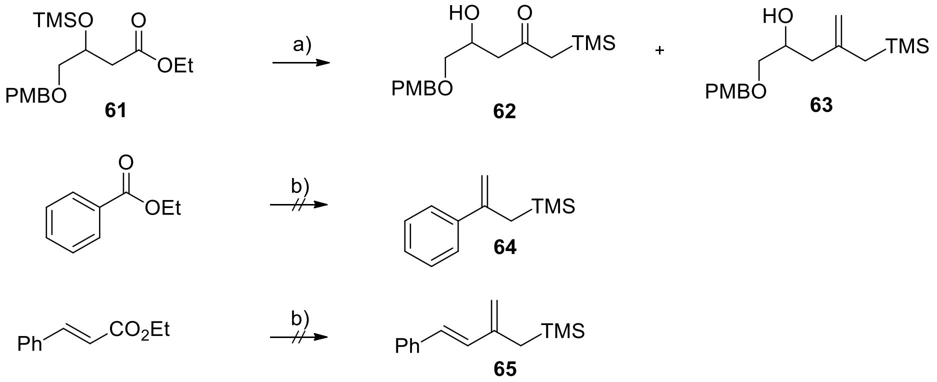
Figure 19: Proposed mechanism of the palladium-catalyzed transfer vinylation.

For the exploration of the next transformation, the installation of the allylsilane moiety, (*S*)-HYTRA ester (**56**) was also converted into methyl ester **59**, although in moderate yields. But neither **56** nor **59** underwent cerium-mediated allylsilane formation, independent of the source or the type of reagent (commercial grade $TMSCH_2MgCl$ or $TMSCH_2Li$; self-made $TMSCH_2MgCl$) (Scheme 40). It may well be that the C15 hydroxyl group in **56** and **59** would require protection for their successful conversion into the corresponding allylsilane. A charge-charge repulsion of the secondary alkoxide at C15 with the carbinol anion to be formed at C13 upon double attack of the nucleophile, could explain the failure in forming the desired allylsilane **60**.



Scheme 40: Unsuccessful allylsilane formation: (a) $TMSCH_2MgCl$, $CeCl_3$, THF, –78 °C to RT.

In light of the difficulties encountered in allylsilane formation, and with only minor amounts of **56** available, the reaction conditions reported by *Bunnelle* and co-worker[158] were then tested on simple systems such as TMS-protected *β*-hydroxy ester **61** (Scheme 41). After some optimization allylsilane **63** was obtained only in 42% yield in the maximum. In most cases, the conversion stopped after the addition of the first equivalent of the nucleophile at the stage of TMS ketone **62**. Likewise, the conversion of ethyl benzoate or ethyl cinnamate to the corresponding allylsilanes **64** and **65** was unsuccessful under a variety of conditions. Although being well-aware of alternative methods for the establishment of the allylsilane moiety, such as nickel-catalysed cross couplings of vinyl bromides or phosphates with $TMSCH_2MgCl$,[159] the cumulated difficulties encountered in the preparation of fragment **R4** (Scheme 27, page 44) finally led us to abandon our original concept of the synthesis of (–)-dactylolide ((–)-**2**) and (–)-zampanolide ((–)-**1**).

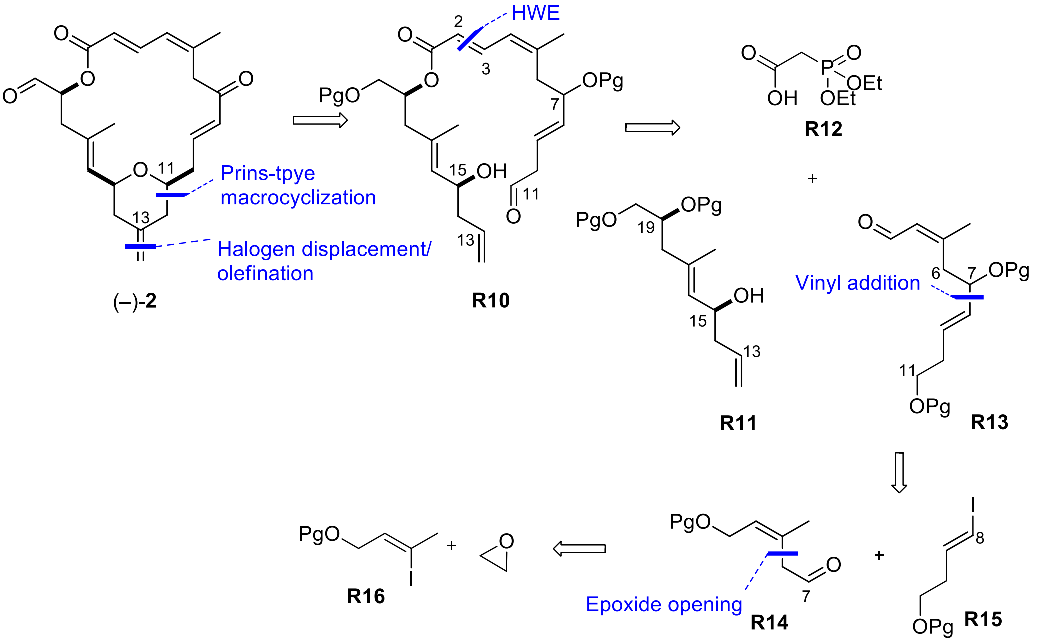


Scheme 41: (a) $TMSCH_2MgCl$, $CeCl_3$, THF, –78 °C to RT, 39-45% for **62** and 42% for **63**; (b) $TMSCH_2MgCl$, $CeCl_3$, THF, –78 °C to RT.

3.1.2 Second Generation Approach

3.1.2.1 Retrosynthesis

Our second generation approach still relied on THP subring formation via a *Prins*-type[160] reaction with concomitant macrocyclization (Scheme 42), but would not directly deliver a methylenated THP moiety. As a consequence, the required exocyclic C=C double bond at C13 would have to be installed at a subsequent stage. For example, one could imagine having a halogen at C13 which could be displaced and the displacement product further converted into the olefin. In that sense, ester **R10** (Scheme 42) with the necessary homoallylic alcohol group at C15 and the aldehyde functionality at C11 was considered an appropriate precursor for the elaboration of (–)-dactylolide ((–)-**2**). A *Horner-Wadsworth-Emmons* (*HWE*) reaction at the C2-C3 C=C double bond allows to generate three fragments, the homoallylic alcohol fragment **R11**, the acid phosphonate **R12**, and the unsaturated aldehyde **R13** (Scheme 42). The introduction of the (–)-zampanolide ((–)-**1**) side chain was still to be based on the aza-aldol reaction that was part of the first retrosynthetic analysis (Scheme 27, page 44).

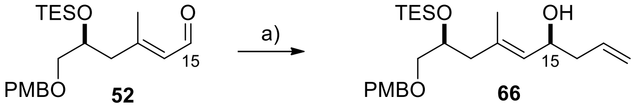


Scheme 42: Second generation retrosynthesis of (–)-dactylolide ((–)-**2**) based on a *Prins*-type macrocyclization approach. Pg = protecting group or H, which might vary independently.

These disconnections meet the requirements for a convergent approach and provide flexibility in the forward direction. Should the projected cyclization with **R10** prove to be problematic, there would still be the option to first form the THP subring with homoallylic alcohol **R11** and the appropriate aldehyde at C11, derived from **R13**, which could then be followed by the conversion into the macrocycle via a *HWE*-type macrocyclization (after deprotection at C19-O and esterification with acid phosphonate **R12**). **R11** should be accessible via an asymmetric allylation reaction leading to the unsaturated aldehyde **R5** as a precursor which in turn would be obtained as outlined in the first generation approach (Scheme 27, page 44). Fragment **R13** was deemed to be best accessible via the addition of a metallated vinyl species derived from **R15** to the aldehyde **R14**; a disconnection, which had already been reported earlier by *Hoye*[26] and *Jennings*.[16, 30] An epoxide opening reaction between oxirane and metallated (*Z*)-vinyl iodide **R16** followed by oxidation would provide access to the necessary aldehyde **R14**.

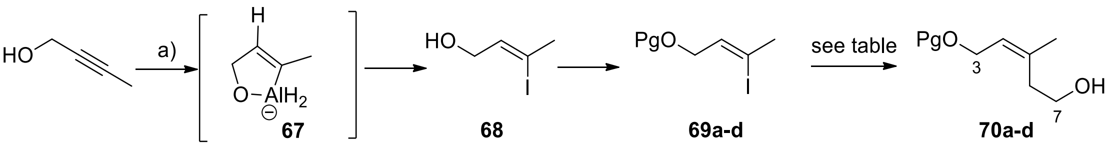
3.1.2.2 Building Block Synthesis

As outlined above, our second generation approach still foresaw the formation of the THP ring and closure of the macrocycle to occur in a single step. In contrast to the first generation approach, however, this new strategy would also provide the flexibility to first form the THP subring and then close the macrolactone ring via a *HWE*-type reaction at the C2-C3 C=C bond. One of the building blocks necessary for the implementation of this second generation strategy was homoallylic alcohol **66** (corresponding to building block **R11** in Scheme 42), which was obtained through allylation with *Brown's* chiral allyl-boron complex $(Ipc)_2$-B-allyl[161] in varying yields; a major problem being the inseparability of **66** from by-products after oxidative work-up (Scheme 43). The diastereoselectivity for the formation of **69** was not determined at this stage. An alternative allylation method might be needed should one intend the preparation of **66** on a larger scale.



Scheme 43: (a) (–)-DIPCl, allylmagnesium bromide, Et_2O, –100 °C to –78 °C then H_2O_2/NaOH, 38-57%.

Since **66** had been obtained in sufficient quantities and the optimization of the asymmetric allylation seemed feasible, we then focused on the synthesis of fragment **R13** (Scheme 42), which was planned to involve the addition of a vinyl species (corresponding to **R15**) to an aldehyde group at C7 (corresponds to **R14**). To this end, we started with the synthesis of the C3-C7 fragments **70**, which were obtained by homologation of protected (*Z*)-vinyl iodides **69** with oxirane. The latter were derived from 2-butyn-1-ol, which was reduced according to *Corey's* procedure[162] using $NaAlH_2(OCH_2CH_2OMe)_2$ (RedAl®) and treatment of the aluminated intermediate with iodine to provide (*Z*)-vinyl iodide **68** in good yields (83%) (Scheme 44). The reaction critically depends on neighbouring group participation by the hydroxyl group which binds to the aluminum source with concomitant intramolecular hydride transfer. Cyclic alkoxyaluminate **67** might be involved, which delivers (*Z*)-vinyl iodide **68** after iodinolysis.[163]



Scheme 44: (a) i) $NaAlH_2(OCH_2CH_2OMe)_2$, Et_2O, 0 °C to RT, ii) EtOAc, I_2, THF, 83%.

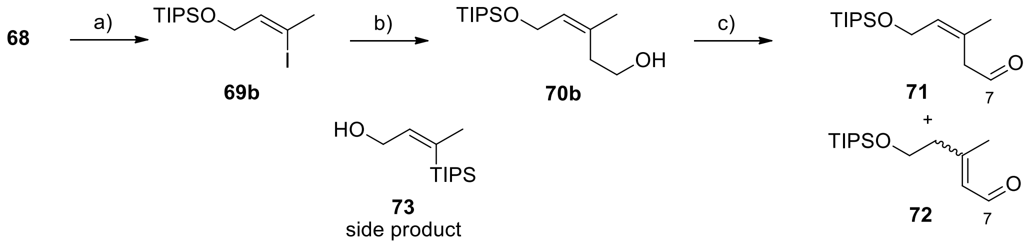
Protection of the hydroxyl group of **68** then led to **69a-d** and 2-carbon homologation of lithiated **69a-d** with oxirane gave primary alcohols **70**.[164] This latter step required significant optimization with regard to protecting group, solvent, and the lithium source (*n*-BuLi or *t*-BuLi). As shown in Table 1 the best yield was obtained for TIPS-protected **69b** in combination with the use of *t*-BuLi for the iodide to lithium exchange in the absence of *Lewis* acid. The reaction was also applicable to larger scale preparations (> 1g of **69b**) without reduction in yield.

Table 1: Conditions for the homologation of **69** with oxirane.[a]

Entry	Compound	Protecting group (Pg)	Reagent	Solvent	*Lewis* Acid	Yield[%]
1	**69a**	TBS	*n*-BuLi	Et_2O	$BF_3{\cdot}OEt_2$	24–29
2	**69b**	TIPS	*t*-BuLi	Et_2O	None	55–65
3	**69b**	TIPS	*t*-BuLi	Et_2O	$BF_3{\cdot}OEt_2$	0
4	**69c**	THP	*n*-BuLi	THF	None	33
5	**69d**	$MeOC(Me)_2$	*n*-BuLi	Et_2O	None	0–60
6	**69d**	$MeOC(Me)_2$	*n*-BuLi	Et_2O	$BF_3{\cdot}OEt_2$	0

[a] Reactions were performed at –78 °C with an excess of oxirane.

Vinyl silane **73** was observed as a side product, which is derived from a *retro-Brook* rearrangement,[165] probably being facilitated by the (*Z*)-olefin geometry in **73** (Scheme 45). The oxidation of **70b** to the *β,γ*-unsaturated aldehyde **71** was problematic, due to isomerization to the thermodynamically preferred *α,β*-unsaturated aldehyde **72**.



Scheme 45: (a) TIPSCl, ImH, CH_2Cl_2, RT, 97%; (b) *t*-BuLi, oxirane (excess), Et_2O, –78 °C to RT, 65%; (c) DMP, CH_2Cl_2, 90%.

Oxidation methods investigated for this transformation are summarized in Table 2. No significant difference between commercially available solid DMP and DMP in a CH_2Cl_2 solution was observed for the oxidation. The isomerization tendency of aldehyde **71** excluded prolonged storage and the compound was best used directly after preparation.

Table 2: Tested conditions for the oxidation of alcohol **70b** to aldehyde **71**.

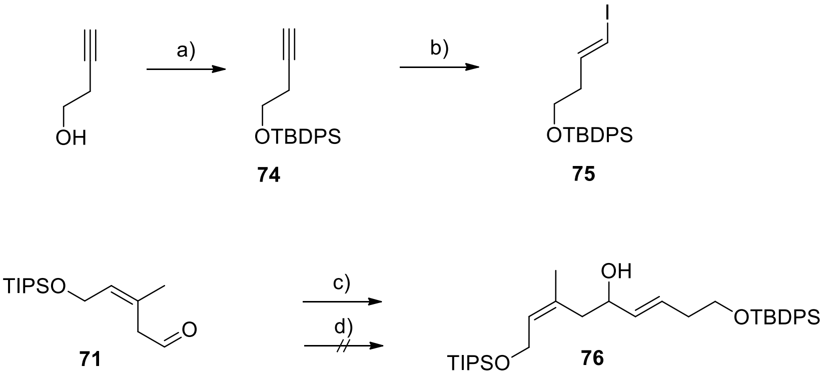
Entry	Reagent	Additive	Yield of 71 [%]
1	DMP	None	73–90
2	DMP	Py or K_2CO_3	52–67
3	PCC	NaOAc	39
4	TEMPO/BAIB	None	47
5	*Swern*[a]	None	22

[a] *Swern* oxidation conditions: $(COCl)_2$, DMSO, NEt_3).[166]

The purification procedure had an important influence on the yield of **71** and purification was best done by filtration over a short plug of silica gel. Significant isomerization of **71** to **72** was observed, if the purification took too long or if the stationary phase was deactivated with NEt_3 (1%). Optimized conditions for the oxidation of **71** to **72** comprised the use of DMP (1.3 equiv) in CH_2Cl_2 at RT for 1 h followed by filtration through a short plug of silica gel; using this procedure **71** was obtained in up to 90% yield. Although only minor amounts of **71** were prepared in each single experiment, these amounts were sufficient to study the addition of nucleophiles, in order to install the C8-C9 C=C bond.

The addition of the lithiated vinyl iodide **75** (prepared from **75** with *t*-BuLi) to the aldehyde **71** proceeded in yields between 43–49% for **76** (Scheme 46). Interestingly, the yield dropped to 33%, if Et_2O instead of THF was used as the solvent. The low yield for this reaction may be related to the isomerization tendency of **71** under basic conditions. This is in line with reports by *Hoye*,[26] *Jennings*[30] and *McLeod*[44] who observed only moderate yields for a similar aldehyde addition reaction with a metallated (*E*)-vinyl species used to install the C7 hydroxyl group in (–)-dactylolide

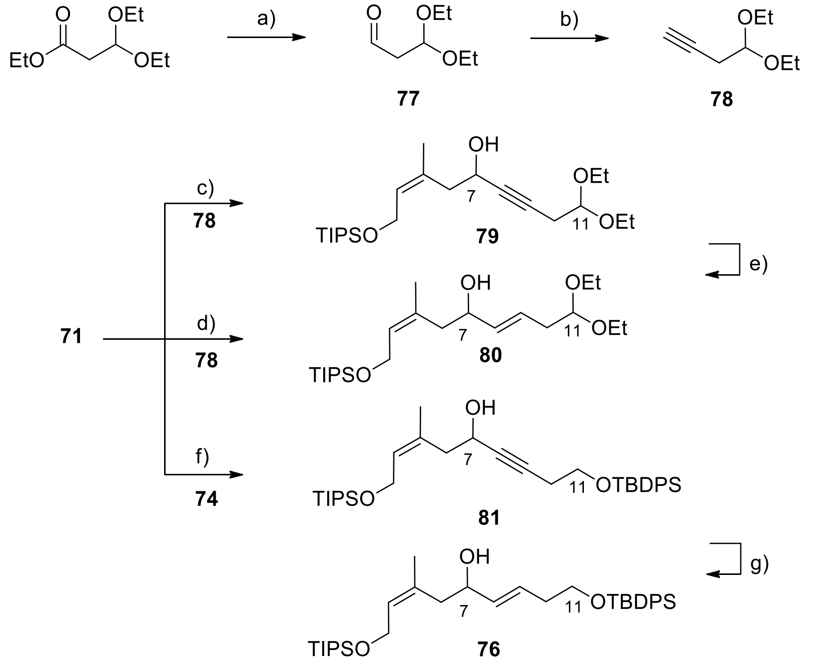
((–)-**2**). As less basic, but more nucleophilic vinyl species might help to improve the yield, we also investigated the conditions described by *Nozaki-Hiyama-Kishi* for the nickel-catalyzed additions (via $NiCl_2$, $CrCl_2$, DMSO);[167] however, this did not lead to an improvement of yields for **76**.



Scheme 46: (a) TBDPSCl, ImH, DMF, RT, 93%; (b) i) Cp_2ZrHCl, THF, RT, ii) I_2, THF, –78 °C, 96%; (c) *t*-BuLi, **75**, THF, –78 °C, 43–49%; (d) **74**, Cp_2ZrHCl, Et_2Zn, then **71**, THF, no conversion.

Likewise, the addition of a vinylzinc reagent, either prepared from lithiated vinyliodide **75** or derived from acetylide **74** via hydrozirconation and transmetallation with zinc proved to be unsuccessful.[168] In synthetic work towards novel terpenoids, *Escher* et al. have reported the quantitative addition of an acetylide, which is less basic compared to the corresponding lithium vinyl species, to an β,γ-unsaturated aldehyde having structural similarity to aldehyde **71**.[169] Based on this finding, we have investigated the addition of acetylenes **74** and **78** to aldehyde **71.** The latter would directly afford the necessary C11 aldehyde group, after acetal deprotection, which would be needed for the projected *Prins*-type macrocylization as outlined in Scheme 42 (page 59).

Indeed, the addition of acetylide **78** to **71** in THF was higher yielding than the addition of vinyllithium species **75** (Scheme 46). The same was true for the addition of **74** to **71** in monoglyme, which afforded propargylic alcohol **81** in even better yields (up to 73%) (Scheme 47). Unfortunately, the subsequent reductions to the (*E*)-configurated allylic alcohols **80** and **76**, using $NaAlH_2(OCH_2CH_2OMe)_2$ turned out to be low yielding. Only 52% yield was obtained for the reduction of **79** to **80** in THF as the best result, along with the elimination of ethanol as the main side reaction. The reduction of **81** to **76** in Et_2O was never complete and was accompanied by the loss of the TIPS group, if an excess of the reducing agent was used to enforce full conversion.

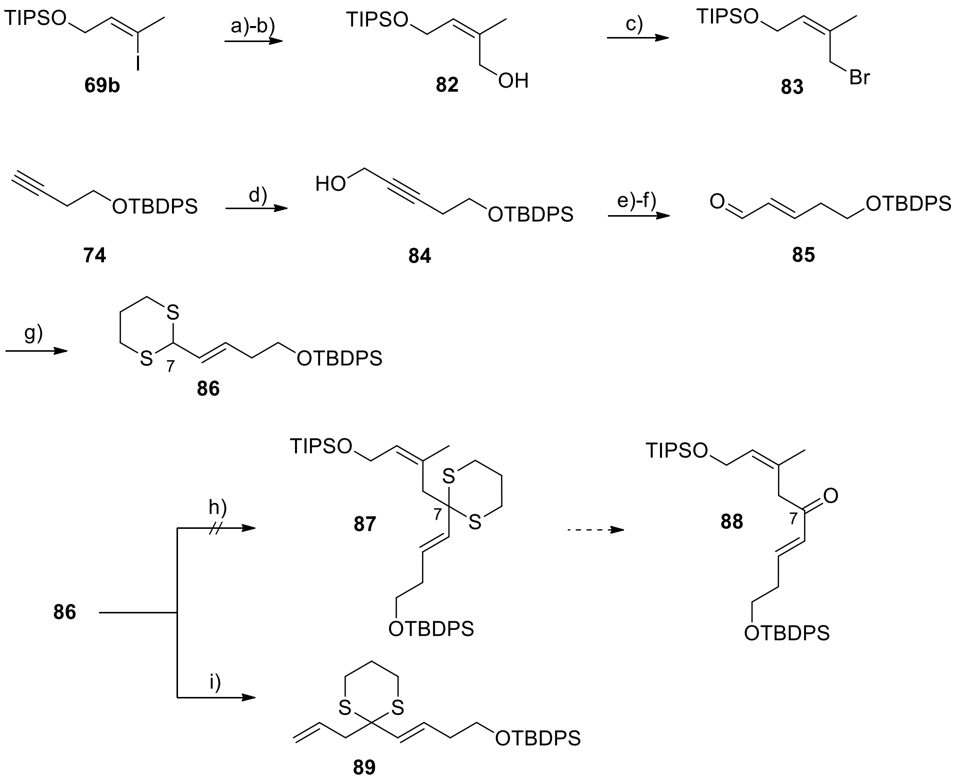


Scheme 47: (a) DIBAL-H, CH_2Cl_2, –78 °C, 50 %; (b) i) CBr_4, PPh_3, CH_2Cl_2, 0 °C, ii) *n*-BuLi, THF, –78 °C to 0 °C, 26% (2 steps); (c) **78**, *n*-BuLi, THF, –78 °C, 59–66%; (d) **78**, Cp_2ZrHCl, CH_2Cl_2, RT, then Me_2Zn, **71**, –78 °C, 13%; (e) $NaAlH_2(OCH_2CH_2OMe)_2$, THF, 0 °C to RT; H_2O, 52%; (f) **74**, *n*-BuLi, –40 °C, **71**, monoglyme, 58–73%; (g) $NaAlH_2(OCH_2CH_2OMe)_2$, Et_2O, incomplete conversion.

Thus, in spite of the higher yields in the addition step compared to the vinyllithium species, the acetylide addition/reduction concept did not offer any advantages over the simple addition of the vinyllihtium species to aldehyde **71**. Finally, we have also investigated an approach that was based on the concept of "Umpolung".[170] A dithiane group attached to C7 would not only act as a temporary protecting group for the ketone, it would also give the opportunity to introduce the remaining C3-C6 unit via an allylic alkylation (Scheme 48).

To implement the idea of an "Umpolung", two new fragments were needed, allyl bromide **83** and unsaturated dithiane **86** (Scheme 48). TIPS-protected allyl bromide **83** was obtained from (Z)-vinyl iodide **69b** by means of palladium(II)-mediated carbonylation[171] followed by reduction to the allylic alcohol **82** and bromination.[172] Fragment **86**, having C7 incorporated in a dithiane ring, could be accessed from TBDPS-protected acetylide **74** by homologation with paraformaldehyde to **84**, aluminum hydride-mediated reduction and oxidation to the unsaturated aldehyde

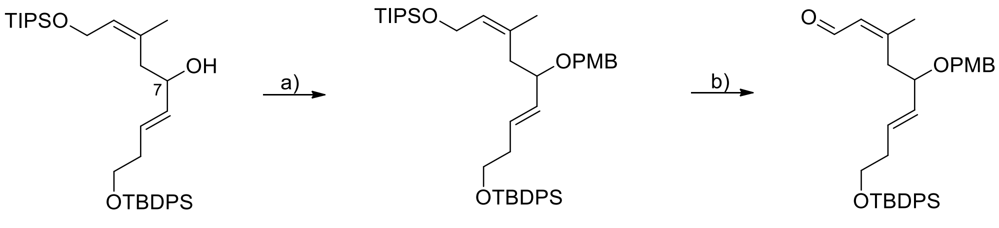
85 followed by magnesium-mediated dithiane formation[173] with propane-1,3-dithiol.



Scheme 48: (a) Pd(dppf)•CH_2Cl_2, CO (4 bar), MeOH, NEt_3, RT, 84%; (b) DIBAL-H, THF, –78 °C, 5–22%; (c) NBS, PPh_3, CH_2Cl_2, 0 °C, 58%; (d) *n*-BuLi, $(CHO)_n$, THF, –78 °C, 62%; (e) $NaAlH_2(OCH_2CH_2OMe)_2$, THF, 0 °C, H_2O; 75%; (f) MnO_2, CH_2Cl_2, RT, 87%; (g) propane-1,3-dithiol, $MgBr_2$•OEt_2, Et_2O, RT, 71–92%; (h) *n*-BuLi, THF, –78 °C, **83**, no conversion; (i) *n*-BuLi, THF, HMPA, –78 °C, CH_2=$CHCH_2Br$, incomplete conversion (yield not determined).

The allylic alkylation[174] between dithiane **86** and allyl bromide **83**, unfortunately, did not proceed and none of the desired coupling product **87**, which would give rise to the unsaturated ketone **88** after dithiane deprotection, was obtained. The alkylation of **86** with allyl bromide, as a simple test system, afforded at least some conversion to **89** along with side products, which were not characterized. These preliminary results indicated that the "*Umpolung*" approach was not a very promising concept to follow.

Even though rather low-yielding, the vinyllithium addition to aldehyde **71** provided sufficient amounts of secondary alcohol **76**, which allowed the investigation of the final functional group modifications that would lead to the carbon system of fragment **R13** (Scheme 42, page 59). This involved first the PMB-protection of the secondary hydroxyl group at C7. Being aware of problems encountered by *Keck* and co-workers during the acid-mediated PMB-protection of similar substrates as **76** with PMB-trichloroacetimidate or under standard ether forming conditions (KH, PMBBr),[40] we resorted to rather uncommon conditions (PMBBr and KHMDS/NEt_3 at low temperature) for the conversion of **76** into **90**.[175] PMB ether **90** was thus obtained in about 50% yield, but still containing impurities which were not characterized (Scheme 49).



76 **90** **91**

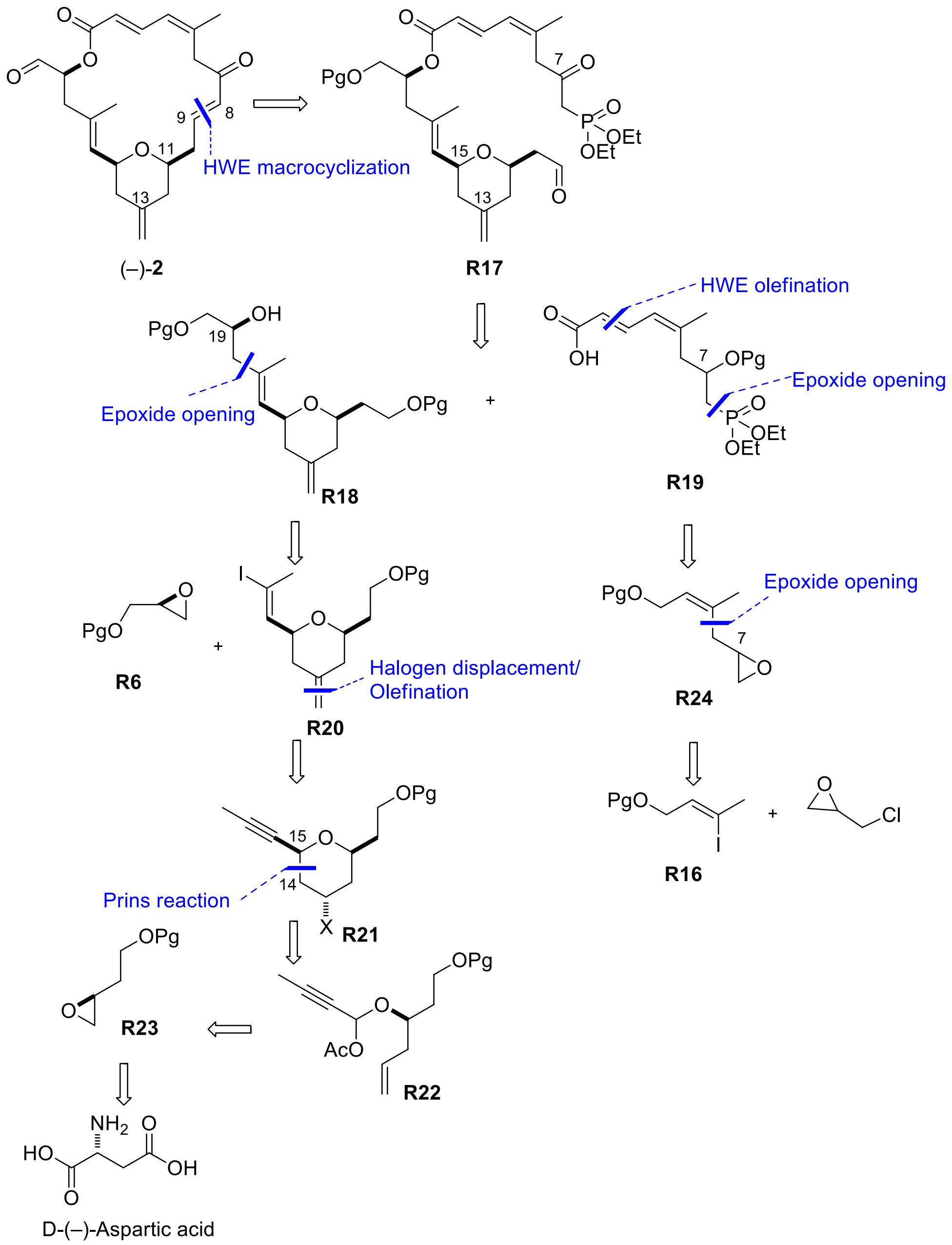
Scheme 49: (a) PMBBr, KMHDS, NEt_3, THF, –78 °C to 0 °C, 50 %, impure; (b) i) *p*-TsOH•H_2O, MeOH, RT, ii) DMP, CH_2Cl_2, RT, 48% (2 steps), impure.

TIPS deprotection (*p*-TsOH•H_2O, MeOH) followed by oxidation of the allylic alcohol afforded the unsaturated aldehyde **91** in 48% yield, although the compound was not entirely pure. **91** could not be separated from *p*-methoxy benzaldehyde, which was derived from *p*-methoxy benzylalcohol as one of the side products formed in the PMB-protection step. Although the conversion of **76** to **91** would still have scope for improvement, the second generation approach was abandoned for two main reasons. Firstly, the oxidation to *β,γ*-unsaturated aldehyde **71** (Scheme 45, page 61) suffered from isomerization to *α,β*-unsaturated aldehyde **72** which was hard to control. Secondly, the addition of lithiated vinyl iodide **75** to the aldehyde **71** (Scheme 46, page 63) only proceeded in moderate yields (43–49%), which would impede larger-scale preparations needed to finish the molecule.

3.2. Third Generation Approach

3.2.1. Retrosynthesis

In the third generation approach, macrocyclization was centered on an intramolecular *HWE* olefination for the closure of the 20-membered macrolide ring at the C8-C9 C=C double bond (Scheme 50). The introduction of the zampanolide side chain was still to be based on the aza-aldol reaction that was part of the first and the second generation approaches. The requisite *β*-keto phosphonate/aldehyde percursor **R17** would be obtained via esterification of alcohol **R18**, having the THP subring incorporated, and unsaturated acid **R19**.


(–)-2
HWE macrocyclization
R17
HWE olefination
Epoxide opening
R18
R19
Epoxide opening
R6
Halogen displacement/
Olefination
R20
Epoxide opening
R24
R16
Prins reaction
R21
R23
R22
D-(–)-Aspartic acid

Scheme 50: Third generation approach towards (–)-dactylolide ((–)-**2**), which is centered on a *HWE*-macrocyclization and an intramolecular *Prins*-type cyclization to form the THP subring. Pg = protecting group or H. Protecting groups can vary independently.

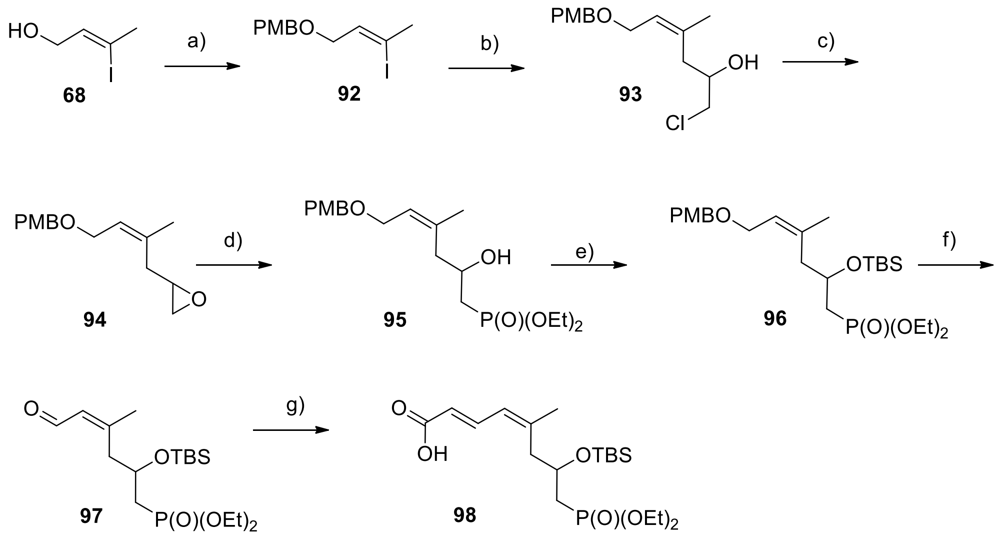
While *HWE*-based macrocyclizations involving the formation of the C=C double bond in *α,β*-unsaturated ketone units are well precedented in natural product synthesis, they have not been used extensively;[41, 176] in particular, and quite surprisingly, this strategy has not been employed in the context of zampanolide or dactylolide syntheses. Alcohol **R18** was envisioned to be accessible from protected

(*R*)-glycidol **R6** through regioselective epoxide opening with lithiated vinyl iodide **R20** (Scheme 33, page 50), although our previous unsuccessful attempts at epoxide opening of **17** with lithiated vinyl iodide **32** suggested that this step might require significant optimization. **R20** would be obtained by a *Prins*-type reaction with alkyne **R22** in order to deliver a 4-halo tetrahydropyran[69, 177] derivative **R21** via ring closure at the C14-C15 bond; the halogen substituent would then be elaborated into the desired methylene group at C13. Finally, **R22** would be derived from epoxide **R23** via a regioselective opening[178] followed by esterification with 2-butynoic acid and reductive acylation.[69a, 179] **R23**, in turn, might be accessible from D-aspartic acid[180] as a cheap starting material.

Acid **R19** was envisaged to be accessible from oxirane **R24** which itself would be derived from protected (*Z*)-vinyl iodide **R16** via reaction with epichlorohydrin[181] followed by conversion of the resulting chlorohydrin to a new oxirane.[182] This would be followed by an epoxide opening with lithiated diethylphosphite,[183] and finally, *HWE* reaction and ester hydrolysis. The successful implementation of this strategy would be especially suitable for the incorporation of modified THP subrings.

3.2.2. Synthesis of β-Hydroxy Phosphonate 98

As outlined above, one of the advanced intermediates for the implementation of our third generation approach towards (–)-dactylolide ((–)-**2**) and (–)-zampanolide ((–)-**1**) is fragment **R19**. Our synthetic endeavors started with (*Z*)-vinyl iodide **68** as an early intermediate (Scheme 51), which was obtained from 2-butyn-1-ol via *Corey*'s reductive alumination/iodination sequence (see also Scheme 44, page 60).[162] Subsequent PMB-protection with PMB-trichloroacetimidate[171, 184] then gave **92**, which was homologated through reaction with epichlorohydrin, i. e. following an analogous strategy as had been employed for the conversion of **69b** into **70b** (Scheme 45, page 61). The homologation reaction proved to be challenging, however, and no conversion to chlorohydrin **93** was observed upon formation of the vinyl lithium species (using *n*-BuLi) followed by treatment with racemic epichlorohydrin under *Lewis* acid catalysis (using $BF_3{\bullet}OEt_2$) in THF.



Scheme 51: (a) PMBO(C=N)CCl_3, PPTS (cat.), CH_2Cl_2/cyclohexane (1:1), RT, 90%; (b) *n*-BuLi, epichlorohydrin, BF_3·OEt_2, toluene, –85 °C, 60–70%; (c) KOH, EtOH, 0 °C, 89%; (d) diethylphosphite, *n*-BuLi, BF_3•OEt_2, THF, –78 °C, 80%; (e) TBSCl, ImH, DMAP, DMF, RT, 84%; (f) i) DDQ, CH_2Cl_2/H_2O (20:1), ii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78 °C to RT, 88% (2 steps); (g) i) triethyl phosphonoacetate, *n*-BuLi, THF, 0 °C, ii) NaOH, EtOH, 94% (2 steps).

While disappointing, this was also an intriguing finding, which seemed to parallel the early unproductive endeavours on *Lewis* acid-mediated epoxide opening reactions as described in section 3.1.1.2. All these previous experiments had been performed in THF, Et_2O or mixtures thereof as the only solvents (solvent mixtures). We then became aware of a report on the total synthesis of (+)-yatakemycin, where the opening of (*S*)-epichlorohydrin with an aryl-lithium species is described in toluene as the solvent, without any further comments on other solvent systems possibly investigated.[181] Based on this information, we investigated the use of toluene as the solvent for the conversion of **92** to **93** and indeed, the epoxide opening reaction proceeded smoothly, reproducibly providing **93** in yields between 60–70% on small scale (< 1 mmol). Yields could not be improved further by varying the temperature (–95 °C up to RT) or using other apolar solvent mixtures (Table 3). Increasing the number of equivalents of epichlorohydrin led to a higher conversion of **92,** while the use of more BF_3•OEt_2 was not beneficial. Varying the concentration of **92** in the range between 0.1M and 0.25M had no significant effect; however, the use of *n*-BuLi in general afforded higher yields of **93** than *t*-BuLi.

Table 3: Variation of reaction parameters for the reaction of vinyl iodide **92** with epichlorohydrin.[a]

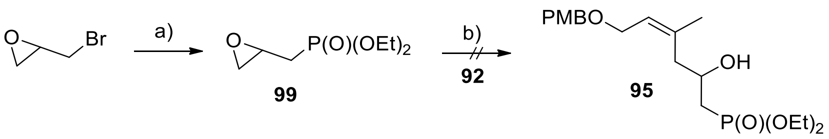
Entry	Solvent System	$BF_3 \cdot OEt_2$ [equiv]	Epichlorohydrin [equiv]	Yield of 93 [%]
1	THF	1	0.8	0
2	toluene	1.5	2.4	61
3	toluene	2.0	3.0	66
4	toluene	3.0	3.0	48
5	toluene	1.3	3.0	75
6	toluene	1.1	3.0	68[b]
7	toluene/Et_2O 1:1	3.0	3.0	29
8	toluene/cyclohexane 1:1	3.0	3.0	59
9	hexane/cyclohexane 1:1	3.0	3.0	18
10	toluene/hexane 10:1	3.0	3.0	29

[a] All reactions were conducted at –78 °C at concentrations of **92** between 0.1–0.25M. TLC-analysis after 5-10 min showed almost complete consumption of starting material **92**. No difference was observed if the reaction was stirred longer (2–3 h). [b] Reaction at –85°C afforded similar yield (2.99 mmol for **92**, 64%).

Collectively, the results of this optimization study suggest a slight excess of $BF_3 \cdot OEt_2$ (1.3 equiv) and an excess of epichlorohydrin (3 equiv) in toluene to be the best conditions, which afforded **93** in 75% as the highest yield in a single experiment (entry 5, Table 3). The procedure was also amenable to scale up, however with a slight erosion in yield (55 mmol scale of **92**, 50% yield for **93**).

The observation of this solvent effect was surprising and also led to the assumption that a change of ethereal solvents to toluene might also enable the conversion of (*E*)-vinyl iodide **32** to **34** (Scheme 33, page 50). Chlorohydrin **93** was converted to the epoxide **94** under basic conditions and the latter was regioselectively opened with lithiated diethylphosphite in THF,[183, 185] to afford the *β*-hydroxy phosphonate **95** in 80% yield (Scheme 51). A shorther approach to **95** would have been based on the opening of epoxy-phosphonate **99**[186] with lithiated **92** (Scheme

52); unfortunately, this transformation did not work either in THF or in toluene as the solvent.



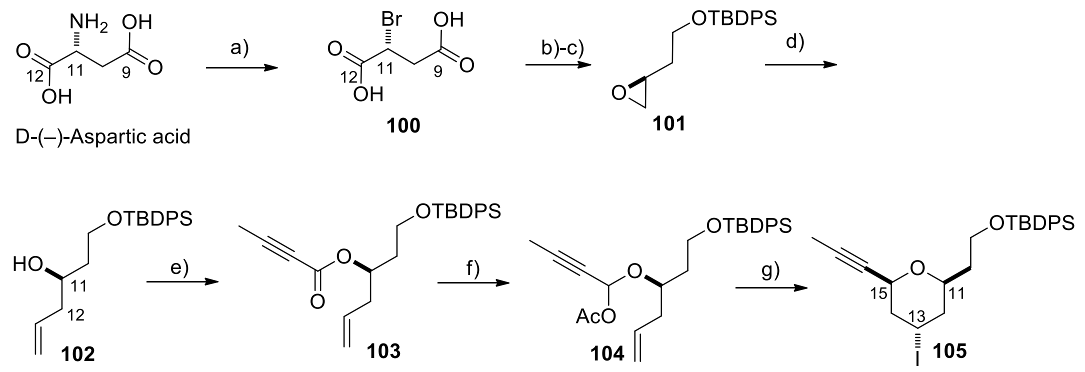
Scheme 52: Unsuccessful short approach to *β*-hydroxy phosphonate **95**: (a) $P(OMe)_3$, neat, 120 to 140 °C, 5 h, 26%; (b) *n*-BuLi, THF or toluene, $BF_3{\cdot}OEt_2$, –78 °C, no conversion.

TBS protection of secondary alcohol **95** under standard conditions (TBSCl, imidazole, DMF) was surprisingly slow and needed to be accelerated by the use of DMAP in order to achieve complete conversion (Scheme 51). PMB removal under oxidative conditions with DDQ[187] afforded a mixture of the unsaturated aldehyde **97** and the corresponding primary allylic alcohol. The mixture was submitted to *Swern*[166] oxidation conditions ($(COCl)_2$, DMSO, NEt_3) to give pure **97**. A two-step sequence involving *HWE* olefination using the lithium anion of triethyl phosphonoacetate[140] followed by hydrolysis then completed the synthesis of acid **98**. The sequence depicted in Scheme 51 was also suitable for large-scale preparations and provided **98** in multigram quantities; these were indeed needed to accomplish the total synthesis of (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**).

3.2.3. Synthesis of Alcohol 125

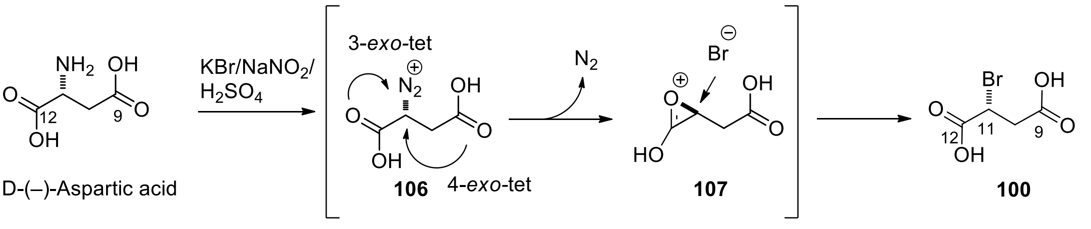
After having established a scalable route to acid **98** we next addressed the synthesis of homoallylic alcohol **R18** (Scheme 50), which again was centered around an epoxide opening reaction, in spite of the difficulties with this chemistry described in section 3.1.1.2. *Prins*-type reactions have gained significant importance in natural product synthesis, since the necessary homoallylic alcohol and aldehyde precursors are, in most cases, readily available by established methods, e.g. asymmetric allylations, vinyl lithium or vinyl *Grignard* additions to chiral epoxides.

Our synthetic work commenced with commercially available D-(–)-aspartic acid (Scheme 53); this was converted to homoallylic alcohol **102** via a three-step sequence which involved the substitution of the amino group with bromide under retention of configuration followed by borane reduction of both acid functionalities and treatment of the resulting diol with base (NaH) and TBDPSCl, which directly provided the TBDPS-protected epoxy alcohol **101**.[180]



Scheme 53: (a) KBr, H_2SO_4, $NaNO_2$, H_2O, 0 °C, 90%; (b) BH_3•THF or BH_3•DMS, THF, 0 °C to RT, 96%; (c) NaH, THF, then TBDPSCl, THF, 90%; (d) $CH_2CHMgBr$, CuI (cat.), THF, –55 to –30 °C, 98%; (e) 2-butynoic acid, DCC, DMAP, CH_2Cl_2, 0 °C to RT, 85%; (f) DIBAL-H then Ac_2O, pyridine, DMAP, CH_2Cl_2, –78 °C, 92% (dr 1.6:1); (g) TMSI (2.5 equiv), 2,6-dimethylpyridine (0.2 equiv), CH_2Cl_2, –19 °C, 85%.

Neighboring group-participation is the best explanation for the overall retention of configuration in the formation of bromide **100.** It may be assumed that the acid functionality at C12 displaces molecular nitrogen via 3-*exo*-tet cyclization compared to the kinetically less preferred 4-*exo*-tet[188] attack of the acid functionality at C9 (Scheme 54). This model is supported by the well established halogenation of bifunctional α-amino acids (i. e. amino acids without functional group-containing side chains)[189] which generally proceeds with retention of configuration.[190]

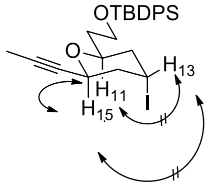


Scheme 54: Neighbouring group participation in the conversion of D-(–)-aspartic acid into **100**. 3-*exo*-tet attack of the acid group at C12 should be kinetically preferred over 4-*exo*-tet cyclization with the carboxylate at C9. Both pathways, however, would lead to retention of configuration.

A regioselective copper-mediated epoxide opening with vinyl magnesium bromide afforded **102** in multigram quantities.[178] This route profits from the readily available starting material and cheap bulk chemicals and allowed the preparation of **100–102** on multigram scale, thus making it a valuable alternative to asymmetric Brown allylation.[191]

To implement the intramolecular *Prins*-type reaction, we decided to rely on a segment-coupling approach as developed by Rychnovsky[69] as we felt that this should provide a higher yield for the cyclization reaction as such, which is often sub-optimal for reactions between homoallylic alcohols and aldehydes (for some applications of the segment-coupling approach see[71, 177, 179, 192]). **102** was thus esterified with 2-butynoic acid,[193] to give **103,** followed by reductive acylation to the acid-labile species **104** in reproducibly high yields. As the installation of the exocyclic C=C bond at C13 was planned after the *Prins*-type cyclization, both, a hydroxy or a halogen substituent at the 4-position of the THP ring would be suitable for the elaboration of the methylene group. This prospect gave flexibility in choosing *Lewis* or *Brønsted* acids to promote the cyclization of **104**.

By screening a number of conditions, it was found that the *Prins*-type cyclization of acylated acetal **104** was promoted most effectively by TMSI[177] as the *Lewis* acid, affording **105** in high yields and with the iodo substituent oriented anti to the substituents at positions C11 and C15, i. e. occupying an axial position (Scheme 53). 2,6-dimethylpyridine was used as an additive to suppress the possibly less selective HI-mediated cyclization.[177] The *anti*-orientation of the iodo group with substituents at C11 and C15 could be confirmed by NOE measurements as depicted in Figure 20.



105

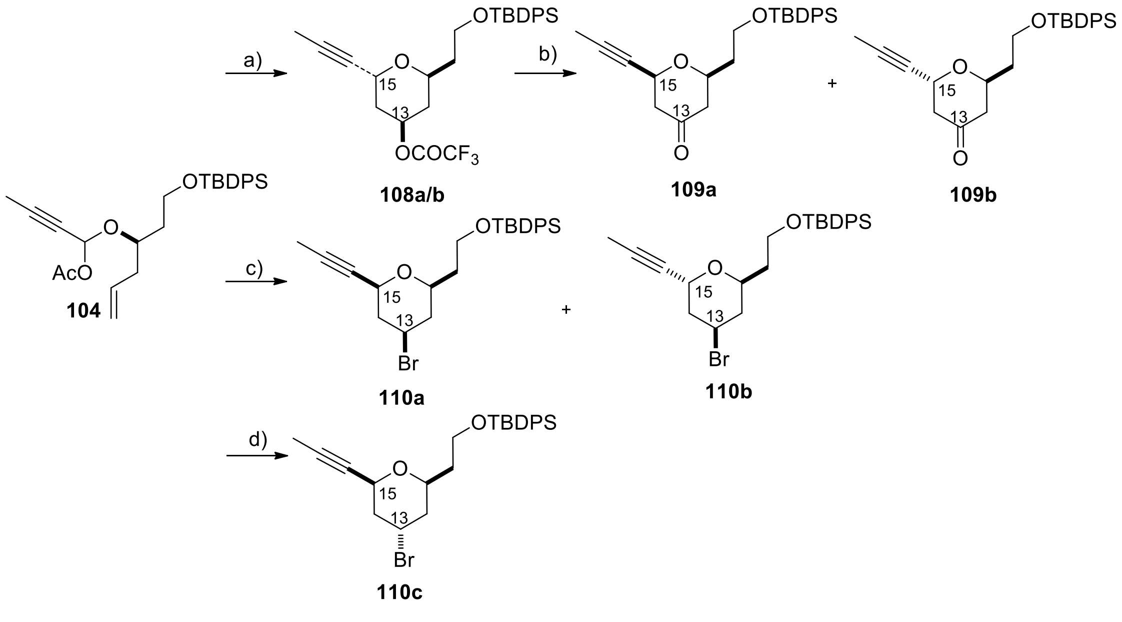
H_{13}: 4.83 ppm
observed NOE:
H11–H15

Figure 20: Key NOE's for THP derivative **105**.

No NOE's were observed between proton H11 and proton H13, or between protons H15 and H13, thus further supporting the stereochemical arrangement shown in Figure 20. Lastly, the chemical shift of 4.83 ppm for H13 was in accordance with literature data for an axially oriented iodo group on a THP ring.[177]

Initially, TFA was chosen to promote the cyclization of **104** (Figure 21, page 75, and Scheme 55), but this afforded a mixture of two isomers as judged by the chemical shifts of the CH_3 group at the acetylene moiety of 1.89 and 1.76 ppm after hydrolysis of **108a/b** and oxidation to the ketones **109a** and **109b** (in a ratio of 1:2). Compound **109b** was the major isomer, as judged by a comparison of chemical shifts for the CH_3 groups with other cyclization products depicted in Figure 21. Furthermore, the signal for axial H15 is shifted from 4.3 ppm in **109a** to 5.06 ppm in **109b,** where H15 adopts the equatorial position. Most probably, the trifluoroacetoxy group occupies an equatorial position in **108a/b,** based on literature evidence.[194]

Interestingly, the cyclization of **104** did not take place in the presence of $BF_3{\cdot}OEt_2$/AcOH, only decomposition of starting material was observed.[179] Similar to TFA, $SnBr_4$[71] led to a lack of selectvity at C15, as judged by the appearance of two CH_3 signals at 1.86 and 1.80 ppm in a ratio of approximately 1:1.7 in favor of the axial acetylide **110b** (Scheme 55). The signal for axially-oriented H15 was again shifted to the lower field from 4.63 ppm in **110a** to 4.73 ppm in **110b** but the difference in chemical shift is less pronounced than in the case of the ketones **109a/b**.



Scheme 55: Screening of the *Lewis* acids for the intramolecular Prins reaction: (a) TFA, CH_2Cl_2, 71%; (b) i) K_2CO_3, MeOH, RT (88%), ii) DMP, CH_2Cl_2, **109a**:**109b** (1:2); (c) $SnBr_4$, CH_2Cl_2, –78 °C, 69%,**110a**:**110b** (1:1.7); (d) TMSBr (24 equiv), 2,6-dimethylpyridine (0.2 equiv), CH_2Cl_2, 0 °C to RT, 4 h, 69%.

TMSBr-mediated cyclization afforded a single isomer, however the reaction was significantly slower compared to the TMSI-mediated cyclization (see Scheme 53).[177] In addition, a huge excess of TMSBr (ca. 24 equiv) was needed and prolonged stirring (4 h) was necessary for full conversion of **104** to **110c** (Scheme 55). Comparison of the proton spectra of **110c** with **105** revealed similar chemical shifts for the CH_3 group attached to the acetylene (1.86 ppm in **110c** and 1.87 in **105**; see Figure 21) as well as for H13 (4.7 ppm in **110c** and 4.83 ppm in **105**), which suggests that the bromo substituent at C13 occupies the axial position, as in the case of the iodo group in **105**.

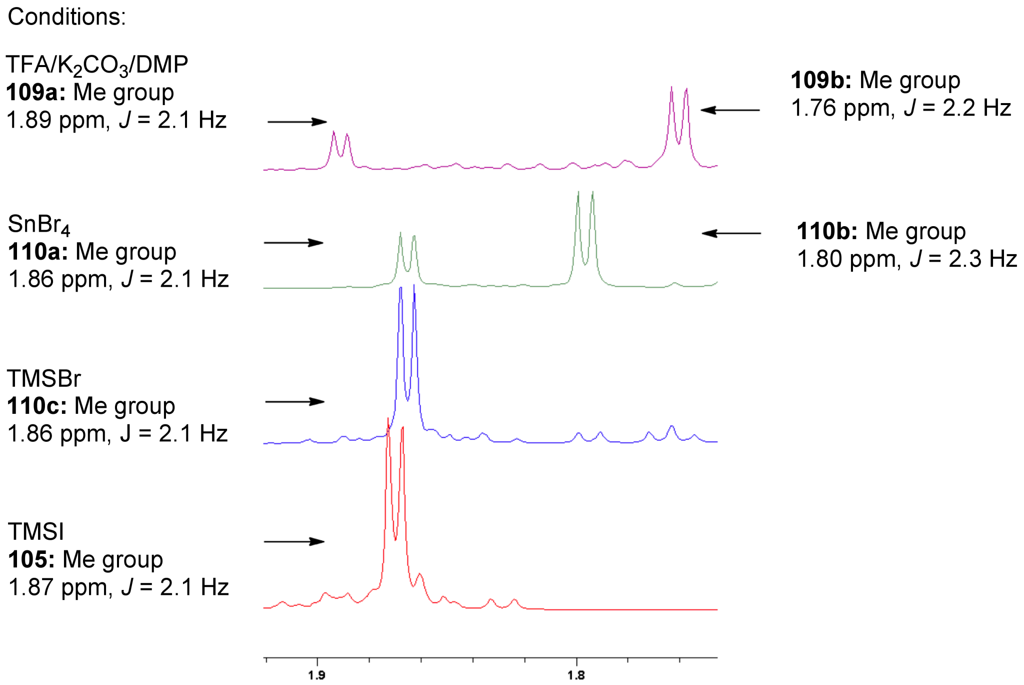
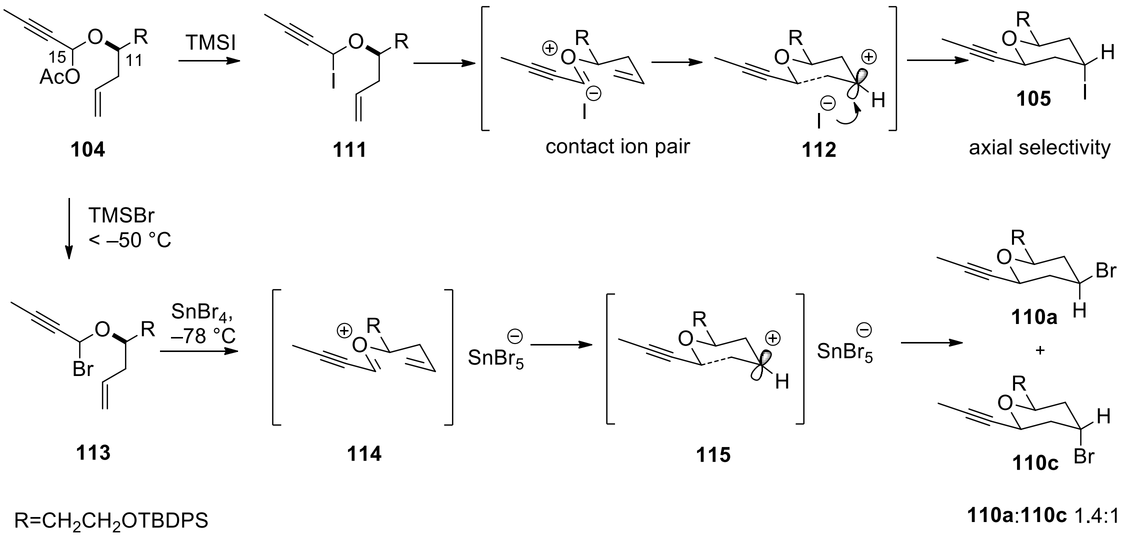


Figure 21: Influence of the *Lewis* acid on the stereochemical result during *Prins*-type cyclization of acylated acetal **104**: Cyclization promoted by TFA and $SnBr_4$ both afforded a lack of selectivity at C15 with the acetylide group preferring the axial orientation, as judged by ^{1}H-NMR analysis (see also Scheme 53 and Scheme 55).

The observation of axial selectivity for the TMSI/TMSBr mediated *Prins*-type reaction has been previously described by *Rychnovsky* and co-workers in their work on the solvolysis of α-bromo ethers.[177] The *syn*-arrangement of the subsitutents α to the oxygen in **105** is consistent with a cyclization via a chair-like conformation, where the existing stereocenter at C11 controls the formation of the new stereocenter at C15.

Scheme 56 might rationalize the observed stereochemical outcome of the cyclization reaction. The initially formed iodo ether **111** collapses to form a contact ion pair where the iodide can only attack in the pseudo axial orientation, thus leading to the observed axial selectivity in product **105**. The model depicted in Scheme 56 also provides a rationale for the observed equatorial selectivity in the *Prins*-type reaction promoted by $SnBr_4$. According to *Rychnovsky*, the treatment of α-bromo ether **113** with $SnBr_4$ leads to the formation of the solvent-separated ion pair **114** with $SnBr_5^-$ as the counterion, which preferentially attacks from the equatorial direction, leading to a reversal in selectivity (ratio of **110a**:**110c** = 1.4:1). An alternative explanation would be that the more stable $SnBr_5^-$ adduct, compared to the Br^- adduct, might have a later, more product-like, transition state which would favor the equatorial product.[177]

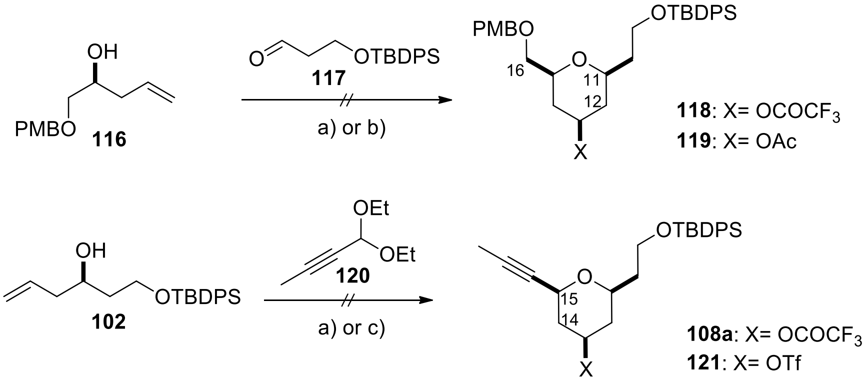


Scheme 56: Model for the observed axial selectivity in the segment-coupling *Prins*-type cyclization promoted by TMSI and $SnBr_4$.[177]

The poor stereoselectivity with regard to C15 in the *Prins*-type cyclizations of **104** promoted by TFA or $SnBr_4$ (Scheme 55) could be related to the small A-value of the acetylene residue which is around 0.4 kcal/mol[195] (for the case of cyclohexane; for an excellent review on the concept of A-values, see[196]). Thus, the results would imply that the reaction proceeds via a solvent-separated ion pair (similar to **114** in Scheme 56), where the acetylene group might adopt both, the pseudo equatorial and pseudo axial position during the reaction which then leads to the observed mixture of products.

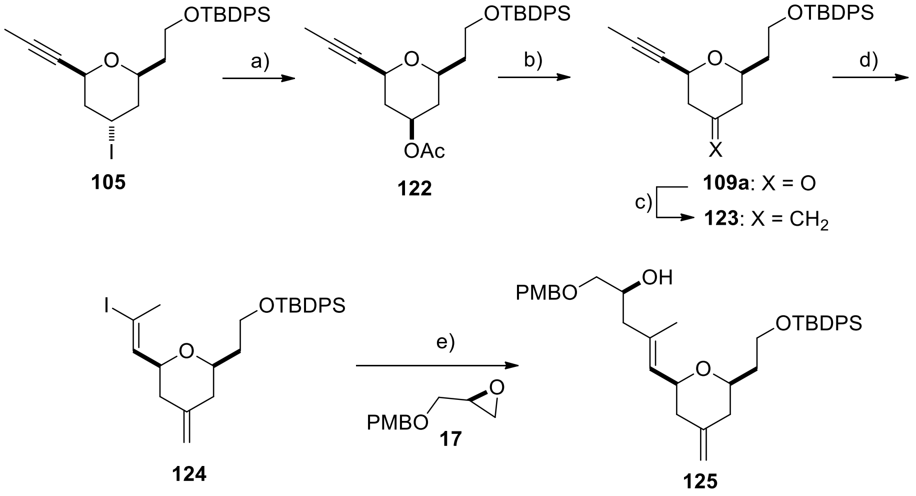
While most of the existing literature on *Prins*-type cyclizations is related to intermolecular[194b, 197] or intramolecular variants involving a homoallylic alcohol and an aldehyde[198] or enol ether[194a, 197d, 199] as starting materials, attempts to affect an intermolecular cyclization with homoallylic alcohol **116**[200] and aldehyde **117** did not afford the expected products **118** (TFA-promoted cyclization) or **119** (BF_3•OEt_2/AcOH-promoted cyclization) (Scheme 57). Likewise, the reaction of homoallylic alcohol **102** and an acetylenic aldehyde, masked as the diethoxy acetal **120**, did not give any of the cyclization products **108a** (TFA-promoted cyclization) or

121 (TMSOTf-promoted cyclization). The segment-coupling approach proved to be the best method to access the functionalized 2,6-syn-substituted THP ring that is present in (–)-zampanolide ((–)-**1**) and (–)-datcylolide ((–)-**2**).


OH
PMBO
116
O
OTBDPS
117
a) or b)
PMBO
16
O
11
12
X
OTBDPS
118: X= OCOCF3
119: X= OAc
OH
OTBDPS
102
OEt
OEt
120
a) or c)
O
15
14
X
OTBDPS
108a: X= OCOCF3
121: X= OTf

Scheme 57: Unsuccessful attempts on intermolecular *Prins*-type reactions. (a) TFA, CH_2Cl_2, –10 °C; (b) BF_3•OEt_2, AcOH, hexane, –78 °C; (c) TMSOTf, Et_2O, –78 °C.

Having the desired THP fragment **105** in hand we continued by establishing the C13 *exo*-methylene group via cesium-mediated acetate substitution,[192b] giving **122**, followed by ester hydrolysis under basic conditions and subsequent oxidation of the resulting free alcohol to ketone **109a** either with DMP or using the *Swern* protocol with similar efficiency (Scheme 58).


OTBDPS
O
I
105
a)
OAc
122
b)
X
109a: X = O
c)
123: X = CH2
d)
I
124
e)
PMBO
17
PMBO
OH
125

Scheme 58: (a) CsOAc, 18-c-6, toluene, 60 °C, 4d, 72%; (b) i) K_2CO_3, $MeOH/H_2O$ (20:1), RT, ii) DMP, 85% (2 steps); (c) $MePh_3PBr$, *n*-BuLi, THF, 0 to 50 °C, 94%; (d) i) Bu_3SnH, *n*-BuLi, CuCN, THF, MeOH, –78 °C, ii) NIS, THF, –17 °C, 97%; (e) *t*-BuLi,**17**, BF_3•OEt_2, toluene, –78 °C, 61%.

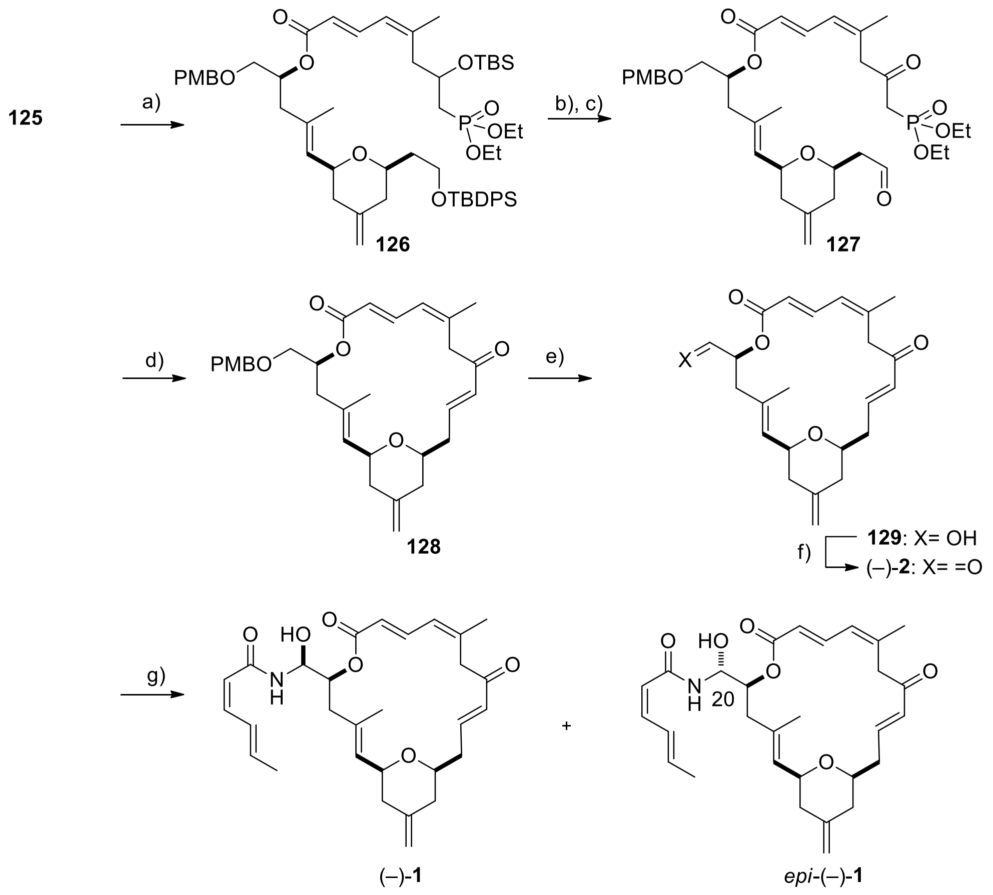
Finally, *Wittig* olefination provided **123** in good yields. The displacement of the iodo substituent in **105** proved to be difficult initially, since the reaction was hampered by the elimination to both possible cyclohexene derivatives which were identified by ^{1}H-NMR analysis of isolated but impure fractions after flash chromatography (for a more detailed discussion about this observation, the reader is referred to section 3.3.2, Scheme 72, page 91). Lowering the reaction temperature from 90 °C initially to 55–60 °C made it possible to obtain the desired acetate **122** as the major product, but at the price of longer reaction times (up to 4 d). The use of $AgOCOCF_3$[201] or $AgClO_4$[202] only resulted in elimination products, $PhI(OCOCF_3)_2$[203] gave no conversion at all and aqueous $CuSO_4$ in DMSO[204] afforded only side products that were not characterized.

Our next challenge was then to reduce the internal alkyne in **123** to the (*E*)-vinyl iodide **124,** which turned out to be a demanding transformation. Hydrozirconation with *Schwartz* reagent[145] afforded only unchanged starting material (THF, RT to 50 °C); in contrast, stannylcupration/iodination using $Bu_3Sn(Bu)CuCNLi_2$[144] and iodine (or NIS in both THF, CH_2Cl_2) gave the desired vinyl iodide **124** as a single isomer in good yields. We were then at the stage to couple the vinyllithium species derived from iodide **124** with PMB-protected (*R*)-glycidol (**17**), but initial attempts with $BF_3{\bullet}OEt_2$ catalysis delivered no product when THF, Et_2O or mixtures thereof were used as the solvent. In most cases, iodohydrin **35** (Scheme 33) was isolated next to deiodinated starting material **124**. These results parallelled those that we had obtained with attempted epoxide opening approaches earlier in the project (see Scheme 33). However, encouraged by the finding that the coupling of (*Z*)-vinyl iodide **92** with racemic epichlorohydrin in the synthesis of acid fragment **98** (Scheme 51) was successful in toluene, we investigated whether identical conditions might also work for the conversion of **124** into **125**.

We were then delighted to observe that the epoxide opening occurred instantaneously in toluene in the presence of $BF_3{\bullet}OEt_2$ as the *Lewis* acid, with 61% as the highest yield of **125** (Scheme 58). Toluene would not be expected to promote such kind of reactions, since it is not a typical solvent for stabilizing organometallic species. An explanation could be that the vinyl lithium species forms less stable aggregates in toluene than in ethereal solvents, and, thus, is available for epoxide opening more effectively. Although the coupling yield was moderate, the reaction between **124** and **17** was amenable to scale up and allowed the gram-wise preparation of **125**.

3.2.4. Completion of the Synthesis

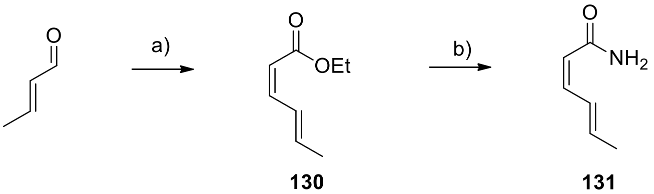
With alcohol **125** and acid **98** in hand, these building blocks were connected by *Yamaguchi* esterification[50] (Scheme 59), which gave ester **126** in higher yields than the more commonly used carbodiimide methods (DCC or EDCI); the latter delivered only traces of **126**. Global silyl removal using HF•py followed by one step oxidation of the resulting free diol to the β-keto phosphonate aldehyde **127** then set the stage for the crucial macrocyclization by means of an intramolecular *HWE* reaction.



Scheme 59: (a) **98**, 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, then **125**, toluene, RT, 85%; (b) HF•py, THF, 0 °C to RT, 85%; (c) DMP, CH_2Cl_2, RT, 74%; (d) $Ba(OH)_2 \cdot 0.8H_2O$, THF/H_2O (40:1), 0°C to RT, 81%; (e) DDQ, CH_2Cl_2/H_2O (5:1), RT, 82%; (f) DMP, CH_2Cl_2, 78%; (g) **131**, DIBAL-H then (–)-**2**, THF, RT, 18% for (–)-**1** and 12% for *epi*-(–)-**1**.

NaHMDS was tested first and indeed promoted macrocyclization of **127** to provide **128** as a single isomer, but in largely varying yields. In addition, long reaction times (up to 4 days) were needed and this was independent of the scale of the reaction (0.007 mmol to 0.046 mmol). The concentration was kept low (0.005M) to avoid polymerization of **127**. These disadvantages could be fully eliminated by the use of $Ba(OH)_2$,[41] which not only led to the reduction of the reaction time to 0.5–1 h, but under optimized conditions also afforded much higher yields (80%) reproducibly. In the largest single preparation, 430 mg of **127** were successfully converted into macrocycle **128** in 78% yield. PMB removal under oxidative conditions with DDQ and oxidation with DMP[151] then completed our new synthesis of (–)-dactylolide ((–)-**2**).[205]

In order to accomplish the synthesis of (–)-zampanolide ((–)-**1**), we relied on the known aza-aldol approach reported by *Hoye* and co-worker,[26] which is based on the unselective installation of the side chain starting from (–)-dactylolide ((–)-**2**) (Scheme 59). The preparation of the desired (*Z*,*E*)-sorbamide side chain **131** is shown in Scheme 60. The construction of **131** was based on the unselective *Wittig* reaction of crotonaldehyde and ethoxycarbonylmethylene-triphenylphosphorane followed by separation of the isomers by means of flash chromatography, which gave the desired isomer **130** in 23% yield. **130** was also accessible via *Still-Gennari*[206] olefination (yield not determined) but in terms of cost this approach is not attractive for upscaling. Aminolysis of **130** afforded satisfactory results by using *Weinreb's*[207] procedure ($NH_4Cl/AlMe_3$) and allowed the preparation of **131** in up to 70% yield without isomerization to the thermodynamically favored (*E*/*E*)-sorbamide**.** The use of NH_4OH[208] in EtOH afforded **131** in much lower yields (max. 11%).



Scheme 60: (a) Ethoxycarbonylmethylene-triphenylphosphorane, EtOH, RT, 23%; (b) NH_4Cl, $AlMe_3$, toluene, 50 °C, 70%.

Other methods tested, like amide formation from the acid corresponding to **130** with $NH_4Cl/DCC/NEt_3$[209] resulted in low conversion and the exclusive formation of the (*E*/*E*) isomer of **131**. This was also true for the conversion of **130** with Mg_3N_2[210] in MeOH, again leading to the exclusive formation of the undesired (*E*/*E*) isomer of **131** in 58% yield.

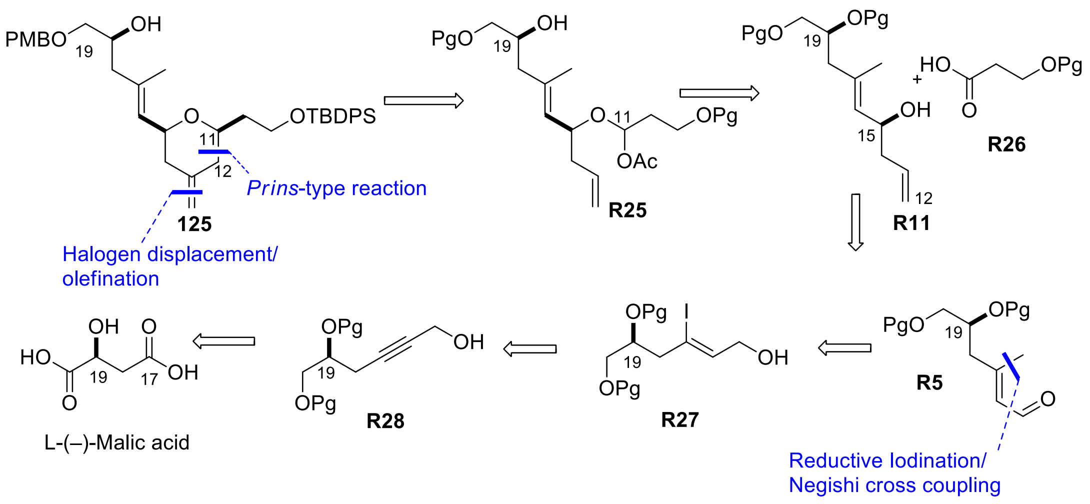
The addition of the aluminated amide **131** to (–)-dactylolide ((–)-**2**)[26, 208] afforded a mixture of the natural product (–)-zampanolide ((–)-**1**) and its C20-epimer *epi*-(–)-**1** in yields between 46% and 83%. A 1.1:1 mixture of epimers was obtained in favor of the desired epimer (–)-**1** as judged by comparison of ^{1}H-NMR data with those reported for (–)-**1**[1] isolated from natural sources and synthetic (–)-**1**.[7, 9c, 26] The separation of epimers was demanding and needed the development of a specific protocol, which involved firstly the purification of the (–)-zampanolide isomers (–)-**1** and *epi*-(–)-**1**) by flash chromatography on a silica stationary phase followed by separation of isomers using normal phase HPLC (Phenomenex Luna, 5µ NH_2) and lastly RP-HPLC purification of the individual epimers (–)-**1** and *epi*-(–)-**1** (Waters, symmetry®C18 5µm) (see Experimental Section). In that way pure (–)-zampanolide ((–)-**1**) and *epi*-(–)-**1** were finally obtained in 18% and 12% isolated yield, respectively, as spectroscopically pure products. The synthesis was reliable and provided the necessary amounts for the extensive biological evaluation. So far, more than 10 mg of the natural product (–)-zampanolide ((–)-**1**) have been made; likewise more than 5 mg of *epi*-(–)-**1** could be prepared, which represents the largest amounts of synthetic material reported so far for either epimer.

After having established a new and concise total synthesis of both (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**), an alternative synthesis for advanced fragment **125** was developed which is described in the following section.

3.3. Alternative Synthesis of Advanced Intermediate 125

3.3.1. Retrosynthesis

Before the discovery of the solvent effect that ultimately allowed the preparation of **125** from **124** through an epoxide opening reaction (section 3.2.3, Scheme 58), we had already started to explore an alternative route to **125**, as it was uncertain whether the epoxide opening approach would ultimately be successful. This alternative approach, obviously, did not include an epoxide opening step with a metallated vinyl species and was centered on the stepwise construction of the tri-substituted C=C double bond at C16-C17 and a segment coupling-based *Prins*-type approach towards the THP ring. The closure of the THP ring this time was designed to occur at the C11-C12 bond, which is different to the ring closure via the formation of the C14-C15 bond given in Scheme 50 (page 67). A suitable precursor for the attempted cyclization reaction would be acylated acetal **R25**, which might be obtained from homoallylic alcohol **R11** via esterification with the appropriate acid **R26** followed by reductive acylation[69, 179] (Scheme 61).

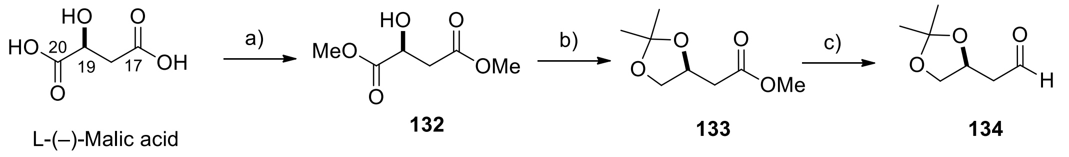

PMBO
OH
19
O
OTBDPS
11
12
Prins-type reaction
125
Halogen displacement/
olefination
PgO
OH
19
O
11
OPg
OAc
R25
PgO
19
OPg
HO
OPg
O
R26
OH
15
12
R11
OH
O
HO
19
17
OH
O
L-(–)-Malic acid
OPg
19
OH
OPg
R28
OPg
I
19
OH
OPg
R27
PgO
19
OPg
R5
O
Reductive Iodination/
Negishi cross coupling

Scheme 61: Alternative approach towards advanced intermediate **125**. Pg = protecting group or H, which might vary independently.

The construction of **R11** was redesigned omitting the unsatisfactory asymmetric vinylogous aldol reaction for the construction of the C19 stereocenter (see Scheme 36, page 53). The tri-substituted C=C double bond in **R11** was to be created from propargylic alcohol **R28** via reductive iodination followed by a *Negishi* cross-coupling[211] reaction for the installation of the methyl group.[212] **R28** could be derived from L-malic acid, a readily available starting material from the natural chiral pool. Although this linear route would require more synthetic steps compared to the epoxide opening approach and, thus, might be hampered by reduced overall yields and greater complexity, it was still deemed feasible. Furthermore, the availability of an alternative route to **125** provides more flexibility for the construction of derivatives.

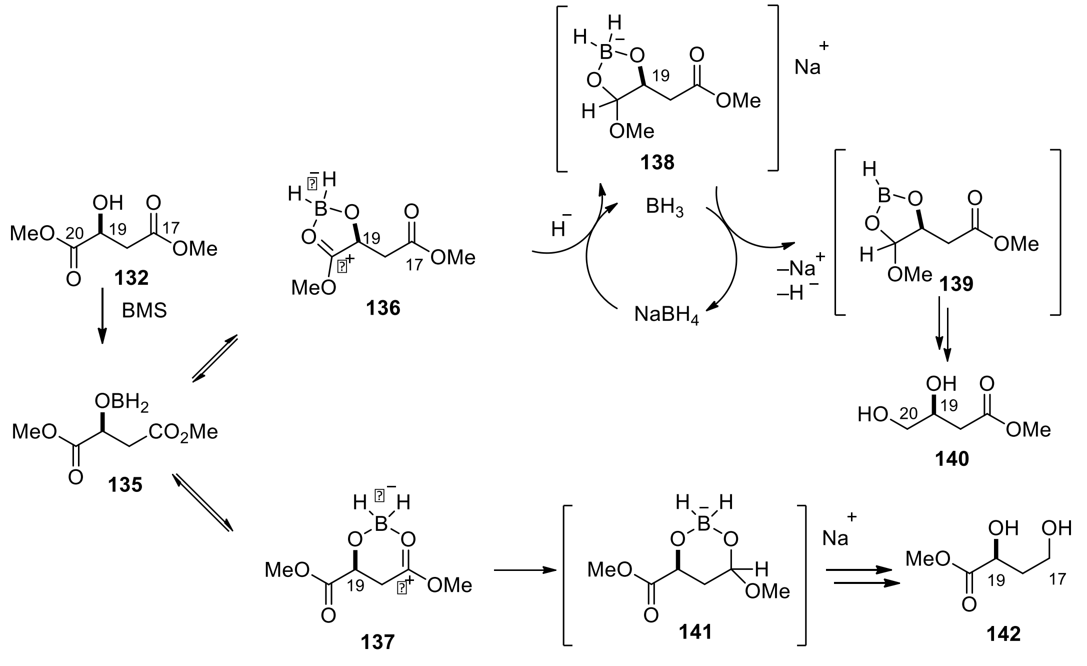
3.3.2. Malic Acid-based Synthesis of 125

The synthesis departed from commercially available L-malic acid as the source of the stereocenter at C19. Formation of the bis-methyl ester[213] **132** was followed by chemoselective reduction of the C20 ester functionality applying a procedure using BH_3 and catalytic amounts of $NaBH_4$, as reported by *Saito* and co-workers[214]. The crude diol was then protected as the acetonide **133**, which was isolated by distillation. Methyl ester **133** was then reduced to the aldehyde **134** with DIBAL-H in good yields (Scheme 62).



Scheme 62: (a) AcCl, MeOH, $HC(OMe)_3$, RT, 95%; (b) i) BH_3•DMS, $NaBH_4$ (cat.), THF, 0 °C to RT then MeOH, ii) $Me_2C(OMe)_2$, *p*-TsOH•H_2O, RT, 54% (2 steps); (c) DIBAL-H, CH_2Cl_2, –70 °C, 82%.

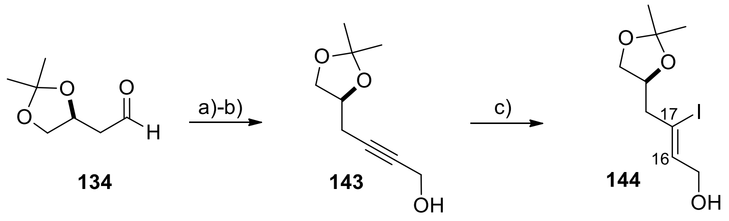
A mechanistic rationale for the chemoselective reduction of diester **132** is depicted in Scheme 63. After initial formation of an oxyborane intermediate with release of H_2, the boron atom intramolecularly coordinates to the carbonyl oxygen of either of the two ester groups of **135** to form the five or six-membered coordination products **136** or **137**, respectively.



Scheme 63: Proposed model which explains the chemoselective reduction of the C20 ester group compared to the C17 ester group. The five-membered chelation intermediate **136** is preferentially formed compared to the six-membered structure **137** for kinetic and steric reasons.

Reduction of **136** with $NaBH_4$ then leads to intermediate **138**; the latter undergoes loss of hydride, thus leading to dioxoborolane **139** and recovery of $NaBH_4$. **139** then collapses to give the aldehyde, which is then reduced via the same reductive cycle to produce diol **140**. The same mechanism is operative in the formation of alternative diol **142**, except that the reaction proceeds through intermediate **137**. Neighboring-group participation is most favored for the formation of five-membered rings as a result of the balance between strain energy and entropy factors under kinetically controlled conditions.[215] In addition, severe 1,3-diaxial interaction between the ester methyl group and the hydrogen on boron are operative in the transition state towards **141**, because of the short boron-oxygen bond. This 1,3-diaxial interaction are less pronounced in the transition state towards five-membered intermediate **138**, which makes this pathway more favorable.

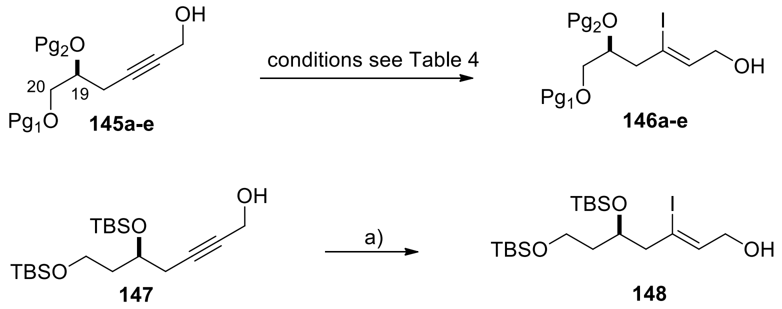
In a next step aldehyde **134** was converted into propargylic alcohol **143** by the *Corey-Fuchs* alkynylation[143] protocol (Scheme 64). This involved the formation of the geminal dibromide followed by elimination and trapping of the lithiated acetylide with paraformaldehyde to give alcohol **143**.[216] With **143** in hand, the stage was set for the stepwise construction of the C16-C17 tri-substituted C=C double bond. To this end **143** in a first step had to be transformed into (*Z*)-vinyliodide **144**; this could be achieved by reductive iodination using *Corey's* procedure[162] (for a similar transformation see Scheme 44, page 60).



134 **143** **144**

Scheme 64: (a) CBr_4, PPh_3, 2,6-dimethylpyridine, THF, 0 °C, 86%; (b) *n*-BuLi, THF, –78 °C then $(CHO)_n$, 64%; (c) $NaAlH_2(OCH_2CH_2OMe)_2$, THF, 0 °C to RT then EtOAc, I_2, THF, –78 °C, 75%.

As it turned out, the nature of the protecting groups at C20/C19 was crucial for the success of the reaction (Scheme 65 and Table 4), with acetonide protection of the diol moiety being essential for a high-yielding aluminum-mediated reduction (Scheme 64).



Scheme 65: Pg = Protecting group or H. (a) $NaAlH_2(OCH_2CH_2OMe)_2$ (3.33 M in toluene, 1.7 equiv), THF, RT; then NIS (1.8 equiv), THF, 30 min, 66%.[212]

Initially, PMB protection of the primary hydroxyl group at C20 was investigated in combination either with a TBS-protected or an unprotected hydroxyl group at C19. However, the PMB group proved to be unstable under the reaction conditions (entries 1 and 2, Table 4). The *bis*-TBS-protection strategy, unfortunately, resulted in low yields for the reductive iodination step (34% yield) (entry 3, Table 4).

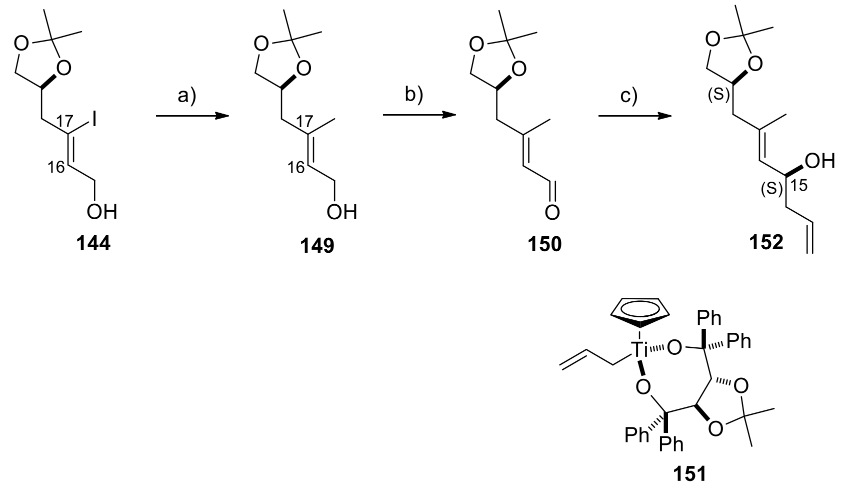
Table 4: Reductive iodination of propargylic alcohols **145a-e** (Scheme 65).[a]

Entry	Compound	Pg_1	Pg_2	Conditions	Result
1	**145a**	PMB	H	Red-Al®, RT, THF then I_2, –78 °C	PMB cleavage
2	**145b**	PMB	TBS	Red-Al®, RT, 12h, THF then I_2, –78 °C	PMB cleavage
3	**145c**	TBS	TBS	Red-Al®, RT, 50°C, 3 h, THF then I_2, –78 °C	up to 34%yield
4	**145d**	TIPS	H	Red-Al®, 50 °C, 3 h, THF then I_2, –78 °C	incomplete conversion
5	**145e**	Tr	H	Red-Al®, 50 °C, 2h, THF then I_2, –78 °C	incomplete conversion

[a] Red-Al® = $NaAlH_2(OCH_2CH_2OMe)_2$.

This result was surprising as literature precedence exists for the structurally related *bis*-TBS-protected diol **147,** which differs from bis-TBS-**145c** only by one CH_2 unit. *Nicolaou* and co-workers reported a yield of 66% for the transformation of substrate **147** into **148** (Scheme 65).[212] Protection of the primary hydroxyl group at C20 either as the TIPS or Trityl-ether did not afford complete conversion to the vinyl iodide. Only the protection of the diol as the acetonide finally led to a satisfactory yield of 75% for the reduction of **143** to **144** (Scheme 65).

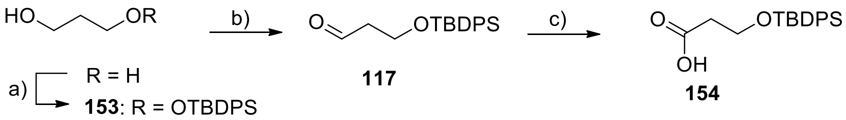
The C17 Me group was then installed via a *Negishi* cross-coupling in good yields, using Me_2Zn and $Pd(dppf)Cl_2$ as the catalyst,[212] thus installing the tri-substituted C=C double bond in **149** (Scheme 66). Temporary protection of the allylic hydroxyl group in **144** as its TMS ether was necessary in this transformation, in order to avoid reduction of the vinyl iodide. Methyl group introduction using Me_2CuLi[217] worked as well (64–77%), but was accompanied by partial reduction of vinyl iodide **144** to the olefin, which could not be separated from the desired product **149**. Oxidation of **149** under *Swern* conditions provided the unsaturated aldehyde **150** which was transformed into **152** through an asymmetric allylation reaction to set the stereocenter at C15.



Scheme 66: (a) i)TMSCl, NEt_3, ii) Me_2Zn, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, THF, 80 °C, iii) K_2CO_3 MeOH, RT, 81% (3 steps); (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78 °C, 84%; (c) **151**, Et_2O, –78 °C, 15 min, 80–97%.

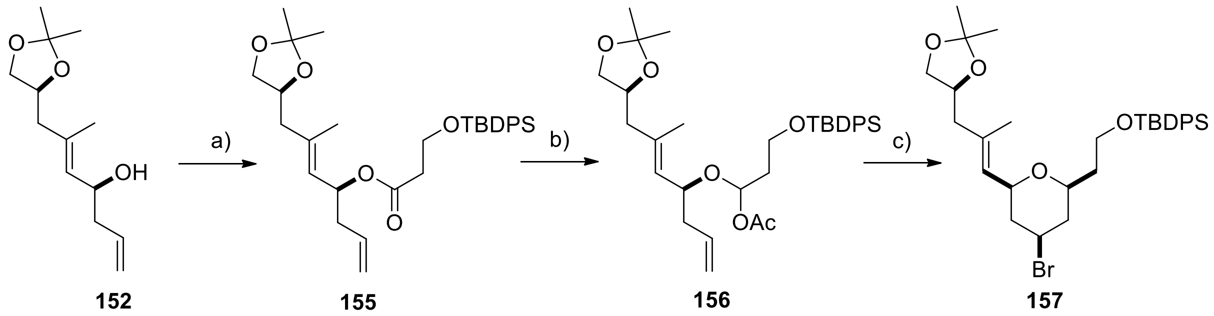
Initial experiments involved the use of the *Brown* allylation protocol with (–)-DIPCl and allylmagnesium bromide.[161, 218] However, these conditions afforded **152** with varying diastereoselectivities (up to 10:1) and highly variable yields (0–70%). These results were reminiscent of the experiments described in section 3.1.2.2 (Scheme 43) in which the *Brown* allylation also lacked reproducibility. Likewise, allylation under *Keck* conditions using (*S*)-BINOL/Ti(O*i*-Pr)$_4$[219] never resulted in complete conversion of aldehyde **150** (the stereoselectivity was not determined in this case). We were then delighted to find that the asymmetric allyltitanation with chiral cyclopentadienyl dialkoxyallyl titanium complex **151** as described by *Hafner* and *Duthaler*[220] provided the homoallylic alcohol **152** in high yields between 80 and 97%. Even more importantly, only the desired (*S*,*S*)-isomer was formed in the reaction, as judged by ^{1}H- and ^{13}C-NMR analysis, after short reaction times (15 min at –78 °C). The bidentate (*R*,*R*)-Taddol ligand could be recovered after NH_4F-workup. Collectively, these features made the allyltitanation superior over the other allylation methods explored. The protocol was also amenable to larger scale preparations and in a single run can provide more than 1 g of **152** as a single isomer without any erosion in yield compared to small scale trials.

The stage was now set for the construction of the THP subring, which again involved a *Prins*-type cyclization. In full analogy to the segment-coupling approach described above (see Scheme 53, page 72) homoallylic alcohol **152** was esterified with acid **154** (Scheme 68), which is readily available in three steps starting from propan-1,3-diol (Scheme 67). Reductive acylation of the ester **155** using DIBAL-H and treating the aluminated intermediate at low temperature sequentially with Ac_2O, pyridine and DMAP afforded the acylated acetal **156** in good yields as a mixture of epimers in a ratio of approximately 1.7:1 (Scheme 68).



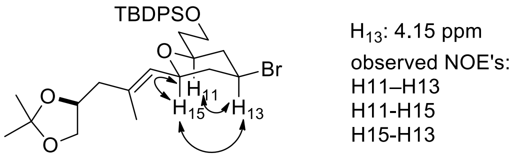
Scheme 67: (a) *n*-BuLi, TBDPSCl, THF, 60 °C, 97%; (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78 °C, 93%; (c) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*-BuOH/H_2O, RT, 82%.

The *Prins*-type reaction with **156** worked well, however, only if $SnBr_4$ was used as the *Lewis* acid. The acetonide was cleaved during the cyclization reaction and had to be re-installed to give the desired cyclization product **157** in 62% yield for the two steps.



Scheme 68: (a) **154**, EDCI, DMAP, CH_2Cl_2, 0 °C, 94%; (b) DIBAL-H then Ac_2O, pyridine, DMAP, CH_2Cl_2, –78 °C, 91%; (c) i) $SnBr_4$, CH_2Cl_2,– 78 °C, ii) $Me_2C(OMe)_2$, *p*-TsOH•H_2O, RT, 62% (2 steps).

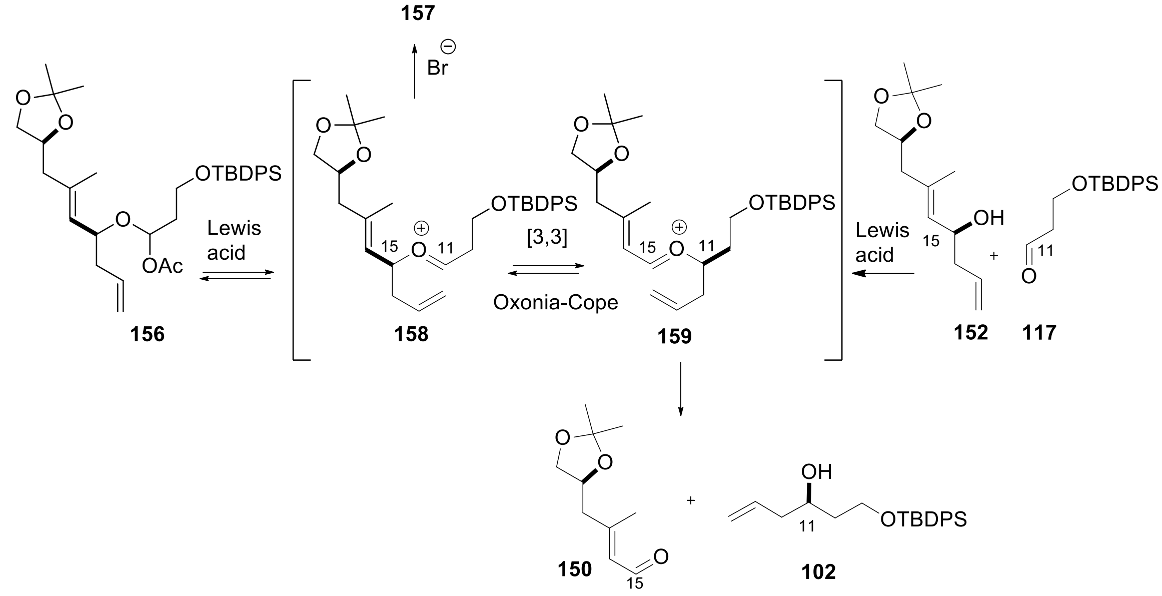
The anticipated all syn-configuration of the various stereocenters in the THP ring could be confirmed by NOE measurements (Figure 22). In addition, the chemical shift for H13 of 4.15 ppm is in accordance with literature data on an equatorially oriented bromo substituent on a THP ring.[179]


TBDPSO
O
Br
O
O
H11
H15
H13
H_{13}: 4.15 ppm
observed NOE's:
H11–H13
H11-H15
H15-H13

157

Figure 22: Key NOE's between H11, H13 and H15 which confirm the syn orientation of the substituents at C11 and C15.

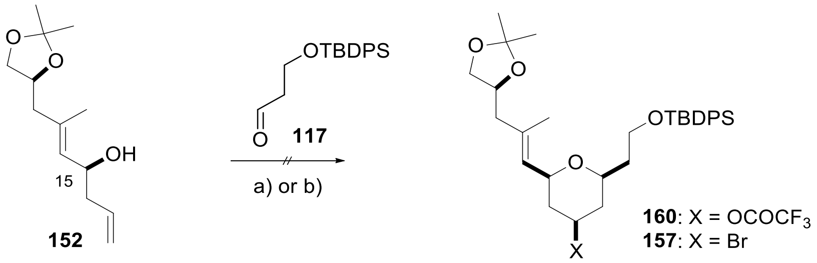
Interestingly, TMSI did not lead to the formation of the THP subring but rather afforded the homoallylic alcohol **102**, the unsaturated aldehyde **150** and the aldehyde **117,** which were identified by comparison of the ^{1}H-NMR spectra of the crude mixture after workup with the spectra of pure reference compounds, as well as by TLC-comparison of the crude reaction mixture with pure reference compounds (**102**, **117** and **150**); the stereochemistry of **102** was not established. The formation of these side products can be explained by an oxonia-*Cope* rearrangement[197b] of the initially formed oxonium ion **158** to **159** (Scheme 69).


157
Br
OTBDPS
OAc
Lewis acid
156
15
O
11
OTBDPS
158
[3,3]
Oxonia-Cope
15
O
11
OTBDPS
159
Lewis acid
15
OH
+
152
OTBDPS
11
O
117
+
OH
11
OTBDPS
150
15
102

Scheme 69: Oxonia-*Cope* rearrangement explains the formation of side products.

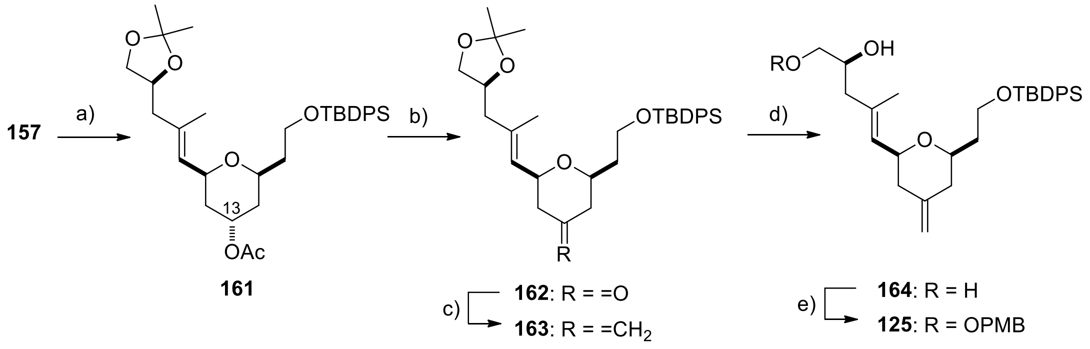
The oxonia-*Cope* rearrangement, in general, is not deleterious, but if cyclization is not fast enough or remains incomplete, the intermediate oxonium ion species **158** and **159** will decompose either during the reaction or while performing workup, leading to homoallylic alcohol **152** and aldehyde **117** (in the case of **158**) or, for **159**, to homoallylic alcohol **102** and aldehyde **150** as alternative products (Scheme 69). The oxonia-*Cope* rearrangement provides a rationale for the side-chain exchange as a potential side reaction in *Prins*-type cyclizations but can also explain why partial racemization is sometimes observed, dependent on the substrate (for a detailed mechanistic analysis see reference [70]). According to the work by *Rychnovsky* and co-workers, the segment-coupling approach should not only result in higher cyclization yields, it should also reduce the risk of epimerization.

Like TMSI, TMSBr, TMSOTf, $BF_3{\bullet}OEt_2/AcOH$, TFA, or $TFA/NaOCOCF_3$ did not lead to cyclization of **156**. As for the formation of **105**, attempts to access **157** (or the related trifluoroacetate **160**) by an intermolecular *Prins*-type reaction between homoallylic alcohol **152** and aldehyde **117** were unsuccessful. Again, the only observable product was homoallylic alcohol **102** (Scheme 70) as judged by ^{1}H-NMR analysis of isolated, but impure, **102**.



Scheme 70: (a) TFA, CH_2Cl_2, –10 °C; (b) $SnBr_4$, CH_2Cl_2, –78 °C.

Bromide **157** was then converted into the fully elaborated secondary alcohol **125** by installation of the exocyclic C=C double bond at C13 via the same sequence of reactions that had been previously used for iodide **105** (Scheme 58, page 77). Thus, cesium-mediated acetate substitution of bromide in **157** afforded acetate **161**, which was followed by base-promoted hydrolysis to the alcohol and subsequent oxidation to the ketone **162**. *Wittig* olefination gave olefin **163** in excellent yield (Scheme 71).

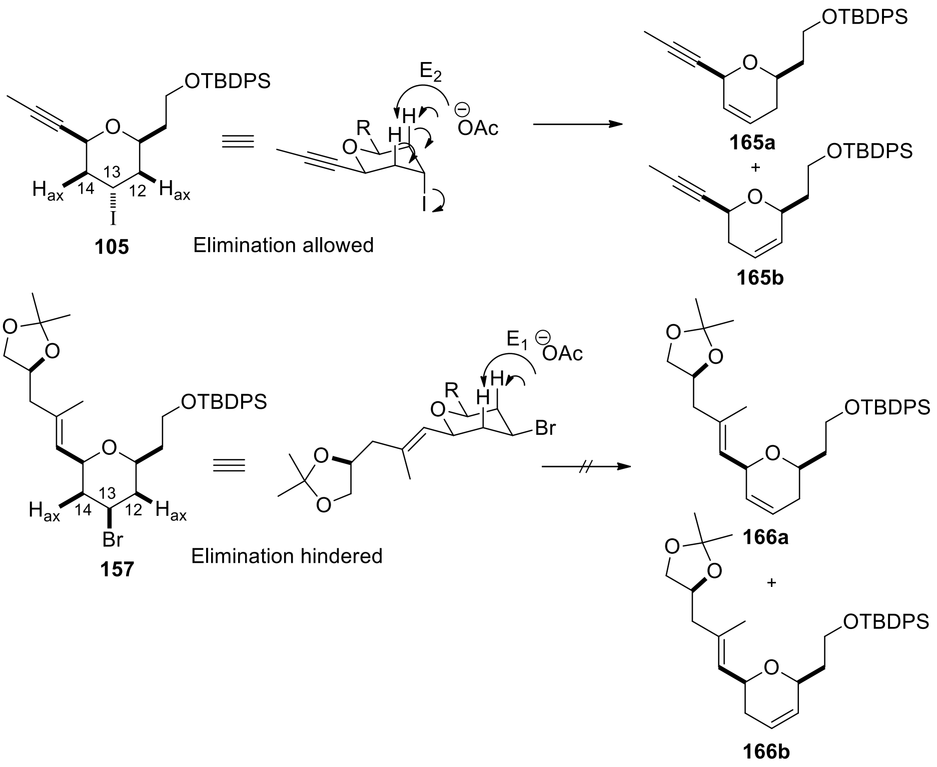


Scheme 71: (a) CsOAc, 18-c-6, toluene, 130 °C, 20 h, 88%; (b) i) K_2CO_3, $MeOH/H_2O$ (10:1), RT, ii) DMP, CH_2Cl_2, RT, 94% (2 steps); (c) $MePh_3PBr$, *n*-BuLi, THF, 0 to 45 °C, 92%; (d) $CuCl_2{\cdot}2H_2O$, MeOH, 60 °C, 84%; (e) Bu_2SnO, toluene, *Dean-Stark*, 140 °C, 1.5 d then PMBCl, TBAI, 120 °C, 1.5 h, 57%.

Attempts to install the exocyclic C=C double bond via exchange of bromide to lithium in **157** with *t*-BuLi and subsequent treatment with paraformaldehyde (which would then have to be followed by elimination) were unsuccessful; only bromide to lithium exchange occurred based on ^{1}H-NMR analysis of the isolated debrominated **157** in 53% yield. $CuCl_2{\cdot}2H_2O$-mediated acetonide cleavage[221] in **163** followed by regioselective PMB protection via a cyclic tin-acetal[222] intermediate completed the alternative synthesis of secondary alcohol **125** (Scheme 71). Opening of the cyclic PMP acetal of the diol moiety in **164** with $NaCNBH_3/HCl$[223] afforded a mixture of the corresponding primary and secondary alcohols with the desired **125** as the minor regioisomer.

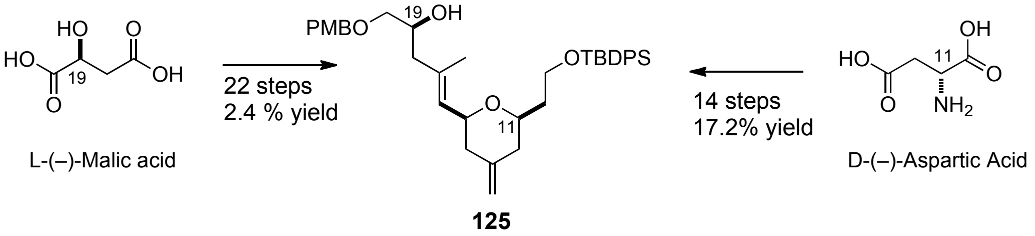
It is noteworthy that the bromide displacement step leading from **157** to **161** (Scheme 71), worked in higher yields compared with the iodide displacement in **105** (Scheme 58, page 77), where both elimination side products **165a** and **165b** were formed in significant amounts (Scheme 72). This difference in yield might be rationalized by the antiperiplanar orientation of the two axial H-atoms ($H12_{ax}$ and $H14_{ax}$) in iodide **105** which allows an E_2-type elimination to take place (Scheme 72).

An E_2-type elimination is not possible in bromide **157**. The reaction with bromide **157** can thus be conducted at higher temperature (130 °C, 20 h, 88%, Scheme 71), which in turn results in more efficient halide displacement and higher yields compared to the identical reaction with iodide **105** (60 °C, 4d, 72% in the best case, Scheme 58, page 77).


OTBDPS
O
13
14
12
H_{ax}
H_{ax}
I
105
≡
E_2
H
R
H
O
OAc
I
Elimination allowed
165a
+
165b
157
Br
Elimination hindered
E_1
Br
166a
+
166b

Scheme 72: Influence of the configuration of the C13 stereocenter on halogen displacement and elimination in iodide **105** and bromide **157**. The antiperiplanar orientation of the iodide in **105** relative to $H14_{ax}$ and $H12_{ax}$ allows an E_2-type elimination, which is not possible in **157**, having the bromide in the equatorial position.

The synthesis of alcohol **125** from L-malic acid required 22 steps for the longest linear sequence and gave the target compound in 2.4% overall yield. In comparison, the route described in section 3.2.3, which starts from D-aspartic acid, provided **125** in 17.2% yield with 14 steps for the longest linear sequence (Scheme 73). The D-aspartic acid-based approach thus proved to be significantly more efficient than the L-malic acid-based route. Samples of **125** obtained from either of the two approaches were identical with respect to all spectral and chiroptical properties.


HO
O
HO
19
OH
O
L-(–)-Malic acid
22 steps
2.4 % yield
PMBO
19
OH
OTBDPS
O
11
125
14 steps
17.2% yield
OH
HO
11
O
O
NH_2
D-(–)-Aspartic Acid

Scheme 73: Comparison of approaches leading to alcohol **125**. Advanced Intermediate **125** is accessible either from L-malic acid or D-aspartic acid.

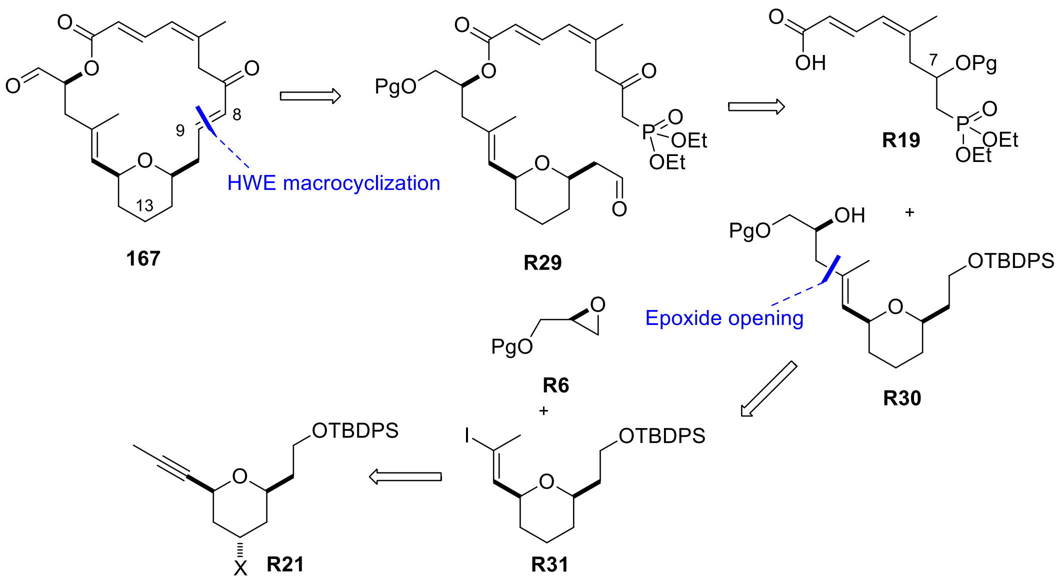
3.4. Synthesis of Analogs and Derivatives

At the outset of this work no data existed on which structural elements in (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**) are crucial for their activity. In light of this, the choice of analogs to be investigated in a first phase was somewhat arbitrary, but it seemed sensible to give priority to modifications that would reduce synthetic complexity. As a consequence, the work performed in this thesis has focused on modifications of the THP subring and the zampanolide side chain.

3.4.1. C13-Desmethylene-Dactylolide

3.4.1.1. Retrosynthesis

Our first target structure was the C13-desmethylene derivative of (–)-dactylolide ((–)-**2**), i. e. **167**. The synthesis of **167** was designed based on the same macrocyclization strategy as outlined in Scheme 50 for (–)-dactylolide ((–)-**2**), i. e. ring closure via an intramolecular *HWE* reaction using *β*-keto phosphonate aldehyde **R29**. The latter should be accessible from acid **R19** and the homoallylic alcohol **R30**, which differs from **R18** only in the exact structure of the THP subring (Scheme 50, page 67). **R30** might be obtained via an epoxide opening reaction between epoxide **R6** and a lithiated vinyl species derived from **R31**.

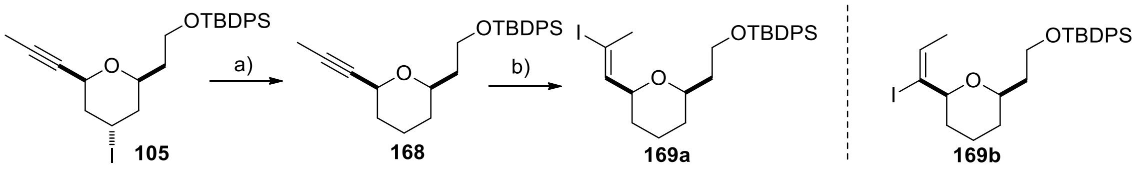


Scheme 74: Retrosynthesis of C13-desmethylene dactylolide (**167**). Pg = protecting group or H. Protecting groups can vary independently.

The latter would be obtained from the halogenated THP derivative **R21**, which was also a crucial intermediate in the synthesis of (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**).

3.4.1.2. Synthesis of C13-Desmethylene Dactylolide

The synthesis of **167** started with iodide **105**, which is an advanced intermediate in the synthesis of (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**) (see Scheme 53, page 72). Radical dehalogenation promoted by Bu_3SnH and AIBN[71] afforded the deiodinated THP derivative **168** without affecting the alkyne moiety by radical hydrostannylation.[144b] Dehalogenation with *t*-BuLi and aqueous workup resulted in significantly lower yields of **168** (not exceeding 35%). Acetylene **168** was then further elaborated by identical transformations as discussed in section 3.2.3 for intermediate **125** in the synthesis of (–)-dactylolide (–)-**2**/(–)-zampanolide (–)-**1**. In a first step this involved reduction to (*E*)-vinyl iodide **169**, a transformation that, similar to the reduction of acetylene **123**, again proved to be difficult.



Scheme 75: (a) Bu_3SnH, AIBN (cat.), toluene, 60 °C, 88%; (b) i) Bu_3SnH, *n*-BuLi, CuCN, THF, MeOH, –78 °C to –15 °C, ii) NIS, THF, –17 °C, 73% (only **169a**).

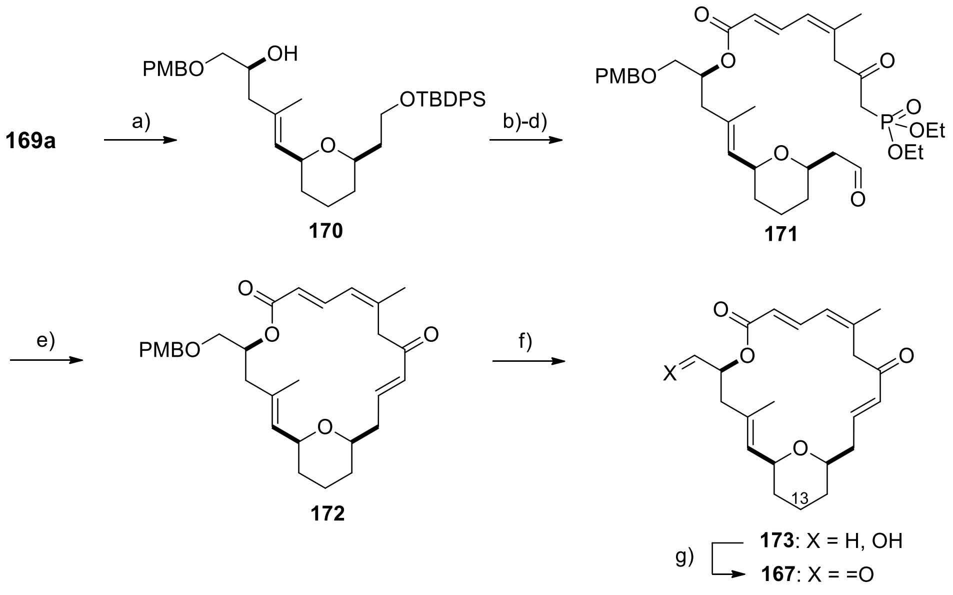
Table 5 summarizes the different methods investigated for the reduction step. Hydrzirconation/iodination[145], silylcupration/iodination[224] or palladium-mediated hydrostannylation followed by iodination[144] afforded low yields, lacked reproducibility or afforded mixtures of regiosiomers **169a/169b** (Scheme 75). Again a stannylcupration/iodination approach using the mixed cuprate $Bu_3Sn(Bu)CuCNLi_2$ proved to be most successful and afforded the desired isomer **169a** in good yields (Scheme 75).

Table 5: Evaluation of methods to reduce the internal acetylene in **168** (see Scheme 75).

Entry	Method	Conditions	Selectivity [169a:169b]	Yield [%][a]
1	Cp_2ZrHCl	THF or benzene, RT or 50°C, I_2, THF	3:1	18-60
2	$(PhMe_2Si)_2CuCNLi_2$	THF/Et_2O, –78 °C, NIS, HFIP	only **169a**	62
3	Bu_3SnH, $Pd(PPh_3)_2Cl_2$	Hexane, RT, NIS, THF	20:1 to 5.5:1	50-73
4	$Bu_3Sn(Bu)CuCNLi_2$ or $(Bu_3Sn)_2CuCNLi_2$	THF, –78 °C, 110 equiv MeOH, NIS, THF	only **169a**	73%

[a] Combined yield for both regioisomers **169a** and **169b**.

The crucial epoxide opening of **17** with lithiated **169a** catalyzed by BF_3•OEt_2 again worked only in toluene, however, with diminished yields of only 31–55% (Scheme 76), compared to the opening of **17** with lithiated **124** (Scheme 58, page 77).[205] No attempts were made to optimize the reaction conditions, in order to increase the yield. Other solvent systems tested like THF, CH_2Cl_2 or hexane afforded no product at all. Even the addition of a small percentage of an ethereal solvent to toluene results in a dramatic reduction in yield; thus, conducting the reaction in a mixture of toluene/Et_2O (10:1) only afforded 16% yield for **170**.



Scheme 76: (a) *t*-BuLi, **17**, BF_3•OEt_2, toluene, –78 °C, 31%; (b) **98**, 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, then **169a**, toluene, RT, 74%; (c) HF•py, THF, 0°C to RT, 80%; (d) DMP, CH_2Cl_2, RT, 72%; (e) NaHMDS, THF, –78 °C to RT, 2d, 49%; (f) DDQ, CH_2Cl_2/H_2O (5:1), RT, 72%; (g) DMP, CH_2Cl_2, 77%.

The secondary alcohol **170** was esterified with acid **98** under *Yamaguchi*[50] conditions, the ester was deprotected with HF•py and the resulting diol was oxidized with DMP, to give *β*-keto phosphonate aldehyde **171**. Macrocyclization was performed with NaHMDS and provided the PMB-protected macrolactone **172** in moderate yield (49%) after a reaction time of 2 days. The use of $Ba(OH)_2$ was not investigated in this case, but it is reasonable to assume that this would lead to an increase in yield, based on the results obtained for the cyclization of **127** to **128** (Scheme 59, page 79). PMB removal under oxidative conditions with DDQ followed by oxidation using DMP completed the synthesis of macrolactone **167**, which is the first derivative of (–)-dactylolide ((–)-**2**) to be reported.[205]

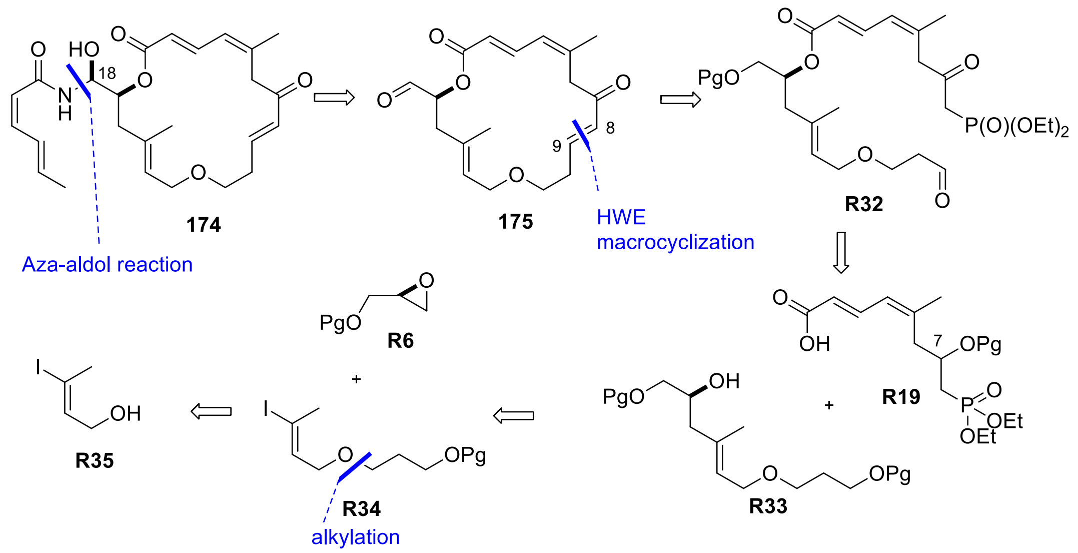
In summary, the strategy developed for the synthesis of the natural product (–)-zampanolide ((–)-**1**) could be successfully applied to the synthesis of the C13-desmethylene derivative **167**.[205] This strategy could also be pursued for the synthesis of analogs containing other types of THP sub-ring modifications.

3.4.2. Des-THP-(–)-Zampanolide

3.4.2.1. Retrosynthesis

Preliminary biological analysis of unnatural (–)-dactylolide ((–)-**2**) indicated a slightly increased potency over natural (+)-dactylolide ((+)-**2**), thus suggesting that the side chain and not the absolute stereochemistry of the macrolactone core structure must be responsible for the significantly higher biological potency of (–)-zampanolide ((–)-**1**) compared to (+)-dactylolide ((+)-**2**). We then asked the question whether a (–)-zampanolide ((–)-**1**) analog with a highly simplified macrolactone core structure could still retain significant activity. We thus designed the zampanolide analog **174**, having a simple ether bridge instead of the THP subring, which should be accessible in fewer steps compared to (–)-zampanolide ((–)-**1**) itself (Scheme 77).

Following the identical concept as for the synthesis of (–)-zampanolide ((–)-**1**), we planned to introduce the side chain via an aza-aldol reaction as the last step of the synthesis followed by separation of the formed C18-epimers. The macrocycle aldehyde, (–)-dactylolide derivative **175**, would be obtained again via an *HWE*-type macrocyclization approach by the formation of the C8-C9 C=C double bond.

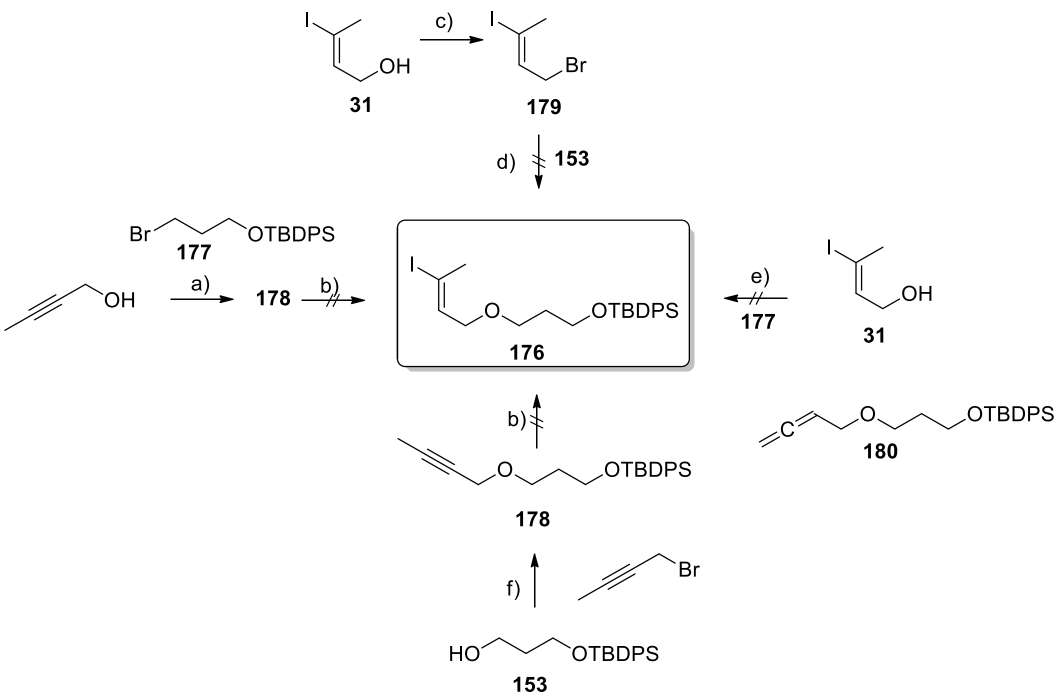


Scheme 77: Retrosynthesis of des-THP-zampanolide (**174**). Pg = protecting group or H. Protecting groups might vary independently.

The *β*-keto phosphonate aldehyde **R32**, which is needed for this transformation, could be obtained via esterification of secondary alcohol **R33** and unsaturated acid **R19**. The former might be formed via the epoxide opening reaction between epoxide **R6** and vinyl iodide **R34** which might itself be accessible from allylic alcohol **R35** via alkylation with an appropriate C3 unit.

3.4.2.2. Synthesis of Des-THP-Zampanolide

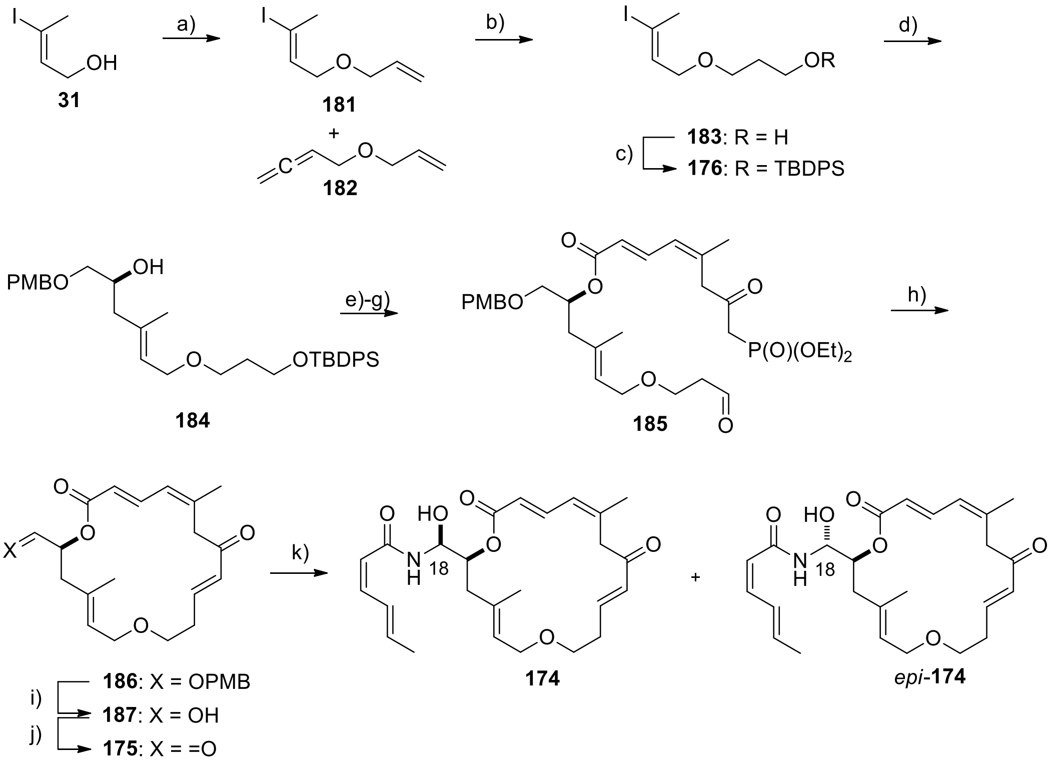
The synthesis des-THP-zampanolide (**174**) was conducted by *Florian D. Glaus* in the course of his master thesis. The synthesis was based on the same overall strategy that had been developed for (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**) and had also been successfully applied in the synthesis of the C13-desmethylene derivative **167** (Scheme 76). The distinguishing key building block for the synthesis of **174** was silyl-protected (*E*)-vinyl iodide **176**, whose synthesis proved to be more demanding than anticipated. Thus, initial attempts to form **176** by the approaches summarized in Scheme 78 were unsuccessful.



Scheme 78: (a) NaH then **177**, TBAI (cat.), DMF, RT, 38%; (b) i) Bu_3SnH, *n*-BuLi, CuCN, THF, MeOH, –78 °C to –15 °C; (c) PBr_3, Et_2O, 0 °C, 41%; (d) **153**, NaH, then **179**, THF, DMF, RT, 12h; (e) NaH then **177**, TBAI (cat.), DMF, RT; (f) NaH then 1-bromo-2-butyne, DMF, RT, 14 h, traces of **178**.

Although propargyl ether **178** could be obtained from 2-butyn-1-ol and bromide **177**, the subsequent attempted stannylcupration of the internal alkyne moiety in **178** only afforded recovered starting material. Attempted *Williamson* ether synthesis between allyl bromide **179** and primary alcohol **153** did not afford any of the desired product **176**, which was also true for allylic alcohol **31** and primary alkyl bromide **177**. In the latter case, allene **180** could be isolated and identified by ^1H- and ^{13}C-NMR analysis (yield was not determined). Similarly, only traces of **178** were formed if alcohol **153** was alkylated with 1-bromo-2-butyne as judged by ^1H-NMR analysis. The most effective way to construct **176** involved the allylation of vinyliodide **31** with allylbromide (Scheme 79) followed by hydroboration/oxidation. An excess of NaH (1.7 equiv) was required to promote the conversion of **31** to an extent that afforded synthetically useful amounts of **181**. Nevertheless, the conversion of **31** to **181** was never complete.

Allene **182** was observed as a side product (yield was not determined) as judged by NMR analysis of the crude reaction product in comparison with spectral data obtained for allene **180**. Distillation of the crude mixture of **181** and **182** afforded pure allylic ether **181** in moderate yield (42%). The primary hydroxyl group was installed by hydroboration of **181** with BH_3, which afforded primary alcohol **183** in acceptable yield (52%). In contrast, hydroborations with either $(Sia)_2BH$ or 9-BBN failed to convert **181**. TBDPS-protection then gave the desired (*E*)-vinyl iodide **176**.



Scheme 79: (a) NaH, CH_2CHCH_2Br, THF, 0 °C, 42%; (b) BH_3•THF, THF, 0 °C, $NaOH/H_2O_2$, 0°C, 52%; (c) TBDPSCl, DMAP (cat.), NEt_3, CH_2Cl_2, RT, 94%; (d) *t*-BuLi, **17**, BF_3•OEt_2, toluene, –78 °C, 61%; (e) **98**, 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, then **184**, toluene, RT, 81%; (f) HF•py, THF, 0°C to RT, 86%; (g) DMP, CH_2Cl_2, RT, 73%; (h) $Ba(OH)_2$•$0.8H_2O$, THF/H_2O (40:1), 0 °C to RT, 85%; (i) DDQ, CH_2Cl_2/H_2O (5:1), RT, 77%; (j) DMP, CH_2Cl_2, 75%; (k) **131**, DIBAL-H, RT, then **175**, THF, RT, 72% for the mixture of epimers (**174**:*epi*-**174**, 1.1:1).

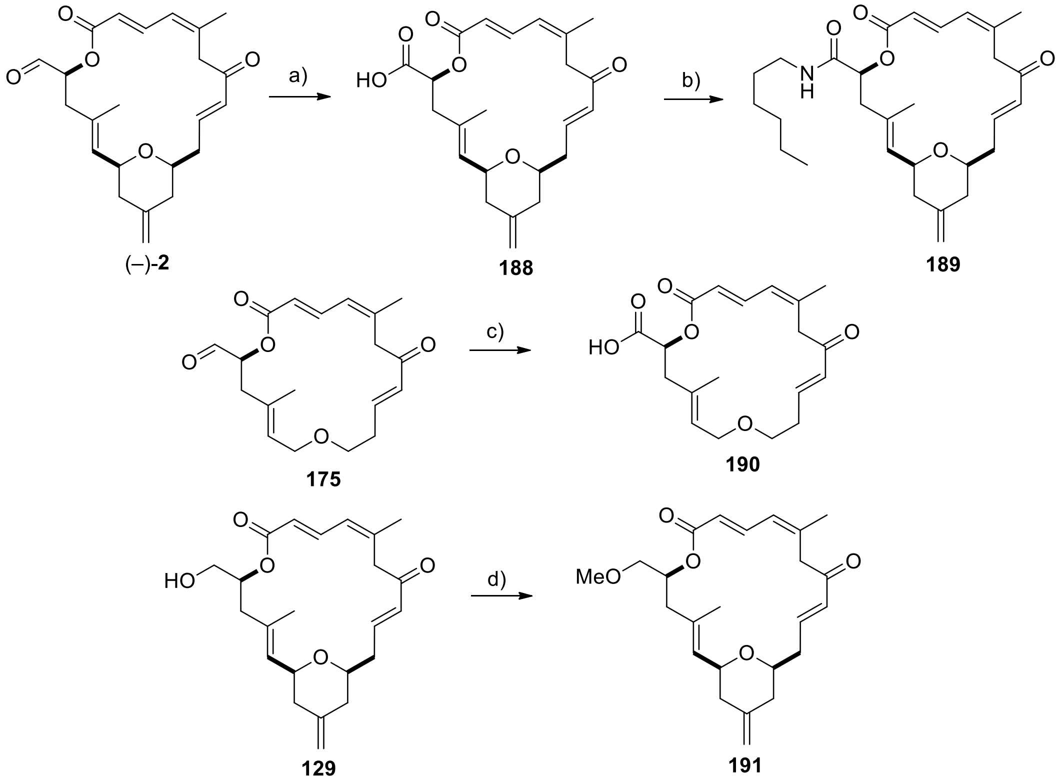
Epoxide opening of PMB-protected (*R*)-glycidol (**17**) with lithiated **176** in the presence of BF_3•OEt_2 proceeded smoothly in toluene and provided the coupling product **184** in 61% yield. This result is comparable with the yield obtained for the reaction of **17** with lithiated **124** under similar conditions in the case of the synthesis of (–)-dactylolide ((–)-**2**) (see Scheme 58, page 77).

Esterification of **184** with acid **98** under *Yamaguchi* conditions, global desilylation with HF•py and one-step oxidation of the resulting diol with DMP afforded *β*-keto phosphonate aldehyde **185** in good yields. This compound underwent macrocyclization very efficiently, to produce macrolactone **186** as a single isomer in 85% yield, if $Ba(OH)_2$ was used as the base. The use of NaHMDS afforded only low and irreproducible yields of **186**, which is similar to what had been observed for the corresponding NaHMDS-promoted macrocyclization of **127** to **128** (Scheme 59, page 79). PMB removal from **186** under oxidative conditions using DDQ followed by oxidation with DMP then gave des-THP-(–)-dactylolide (**175**) in 58% yield over two steps. Attachment of the (*Z*,*E*)-sorbamide side chain (**131**) was performed by aza-aldol reaction under identical conditions as those employed in the synthesis of (–)-zampanolide ((–)-**1**) (Scheme 59, page 79) which produced an epimeric mixture of **174** and *epi*-**174** (Scheme 79). Separation was possible again by using similar separation conditions as for the separation of (–)-zampanolide ((–)-**1**) and its C20-epimer *epi*-(–)-**1** (see page 79); this involved purification of the epimeric mixture via flash chromatography followed by separation of isomers using normal phase HPLC (Phenomenex Luna, 5µ NH_2, EtOH/hexane) and lastly RP-HPLC purification of the individual epimers **174** and *epi*-**174** (Waters, Symmetry®C18 5µm, ACN/H_2O) (see Experimental Section). Compound **174** could be obtained as a single isomer, whereas *epi*-**174** was contaminated with **174** (approximately as a 4:1 mixture), as judged by ^{1}H-NMR analysis. So far, the assignment of the C18 stereochemistry for the individual epimers is based only on comparision of ^{1}H-NMR data (in particular the signal of the NH proton) of the individual epimers with that for the natural product (–)-zampanolide ((–)-**1**) and its epimer *epi*-(–)-**1**.

3.4.3. Side Chain-Modified Analogs

Based on *Porco's* work on the possible hydrogen bonding network[12] associated with the side chain of (–)-zampanolide ((–)-**1**), it appeared sensible to evaluate a series of side chain-modified derivatives that would display different hydrogen-bonding properties. In light of this, we have investigated acid derivatives **188** and **190**, the latter having the simpler macrolactone core structure, as well as methoxy derivative **191** (Scheme 80). **188** and **190** were readily available by *Pinnick*[225] oxidation of (–)-dactylolide ((–)-**2**) and aldehyde **175**, respectively. Methyl ether **191**, was obtained from alcohol **129** by treatment with *Meerwein* salt (Me_3OBF_4).[226]

In addition, we have prepared derivative **189**, whose simple C6-alkyl side chain amide should mimic the natural (*Z*/*E*)-sorbamide side chain of (–)-zampanolide ((–)-**1**), however, with a different arrangement of hydrogen bond donor and acceptor groups. (–)-Zampanolide analog **189** was obtained from acid **188** by amide formation with hexylamine.



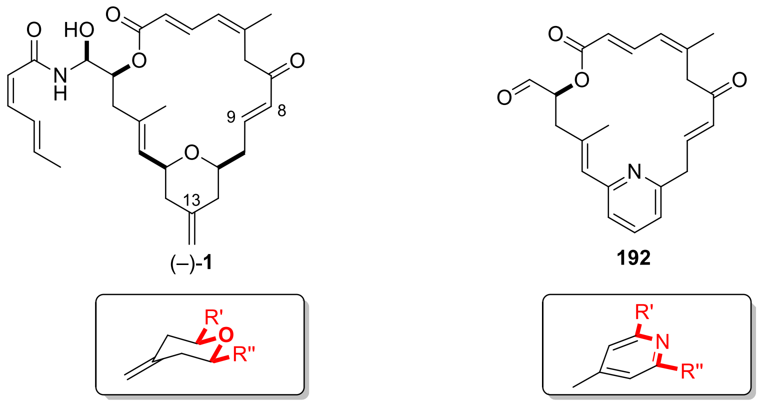
Scheme 80: (a) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, *t*-BuOH/H_2O (5:2), 2-methyl-2-butene, RT, 97%; (b) hexylamine, HATU, DIPEA, DMF, RT, 13%; (c) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, *t*-BuOH/H_2O (5:2), 2-methyl-2-butene, RT, 97%; (d) Me_3OBF_4, Proton Sponge®, CH_2Cl_2, RT, 83%.

3.4.4. Pyrido-(–)-Dactylolide

3.4.4.1. Retrosynthesis

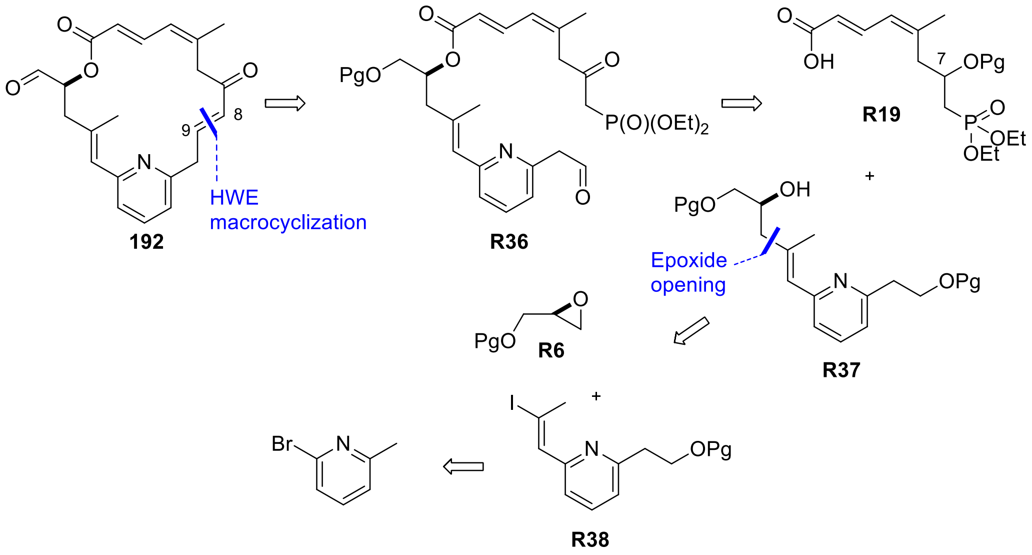
Conformational analysis of (–)-zampanolide ((–)-**1**)[1] and (+)-dactylolide ((+)-**2**)[8] has revealed the THP ring to be present in a chair conformation with the 2- and 6-substituents in equatorial orientations, thus leading to local flattening of the macrolactone around the oxygen atom of the THP subring. Similar conformational preferences should also apply to (–)-dactylolide ((–)-**2**).

Based on this analysis we asked the question whether a simple aromatic heterocycle, such as a pyridine ring, could potentially substitute for the THP subring, as it should lead to a similar geometry of the macrocycle in the immediate vicinity of the heteroatom (Scheme 81).


(–)-1
192
9
8
13
R'
R''
O
N

Scheme 81: The orientation of 2,6-syn substituents in the THP subring in (–)-zampanolide ((–)-**1**) will be retained upon replacement of the THP moiety by a pyridine ring.

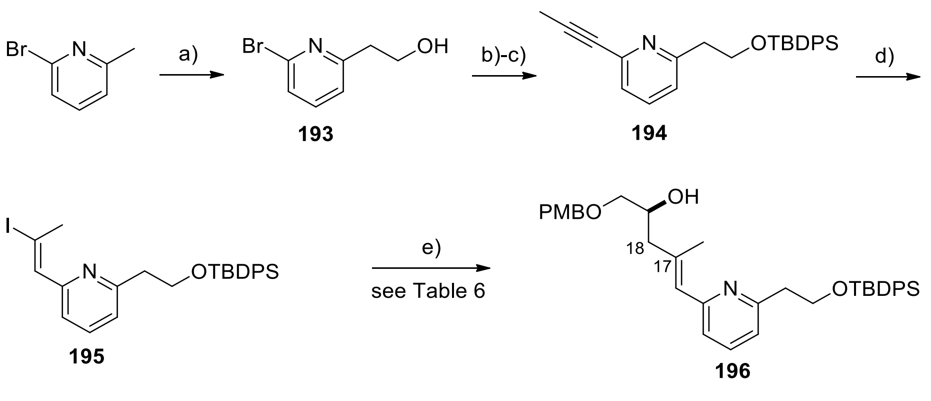
The synthesis of the corresponding (–)-dactylolide analog **192** would again follow the concept of *HWE*-macrocyclization at C8-C9, which retrosynthetically leads to *β*-keto phosphonate aldehyde **R36** as the cyclization precursor (Scheme 82). The known acid fragment **R19** and the secondary alcohol **R37**, having the pyridine ring incorporated, would be suitable building blocks for the assembly of **R36**. Alcohol **R37** is similar to intermediate **R18**; **R36** resembles **R17** (Scheme 50, page 67). **R37** might thus be accessible through the epoxide-opening with protected (*R*)-glycidol **R6** and lithiated (*E*)-vinyl iodide **R38**; the latter should be readily available from 2-bromo-6-methylpyridine.


192
9
8
HWE
macrocyclization
R36
PgO
P(O)(OEt)2
R19
OH
7
OPg
OEt
+
PgO
OH
Epoxide
opening
R37
OPg
R6
PgO
+
I
R38
OPg
Br
N

Scheme 82: Retrosynthesis of pyrido-dactylolide **192**. Pg = protecting group or H. Protecting groups might vary independently.

3.4.4.2. Towards the Synthesis of Pyrido-(–)-Dactylolide

As outlined above, the synthesis of pyrido-dactylolide **192** was to be based on the same concepts that had been successfully employed in the synthesis of (–)-dactylolide ((–)-**2**), (–)-zampanolide ((–)-**1**), C13-desmethylene dactylolide (**167**) and des-THP zampanolide (**174**). Therefore, the vinyl iodide **195** was needed as an intermediate, which would then be transformed into the secondary alcohol **196** via epoxide opening (Scheme 83). Following a procedure described in a patent the synthesis of vinyl iodide **195** started from commercially available 2-bromo-6-methylpyridine which was homologated to alcohol **193** by sequential treatment with LDA, DMF and $NaBH_4$ in 39% yield; thus well reproducing the reported yield of 45% (Scheme 83).[227] TBDPS protection and *Sonogashira* cross coupling[228] with propyne gave the desired acetylene **194** in good yield. **194** was reduced to the desired (*E*)-vinyl iodide **195** in 82% yield, employing our established stannylcupration/iodination sequence $Bu_3Sn(Bu)CuCNLi_2$ and quenching with iodine). Vinyl iodide **195** was then reacted with PMB-protected (*R*)-glycidol (**17**), again using a protocol that had been developed in the course of this thesis (*t*-BuLi, $BF_3•OEt_2$, toluene, –78 °C); this procedure did indeed afford the desired coupling product **196**, however, in a yield of only 15%.



Scheme 83: (a) i) *n*-BuLi, *i*-Pr_2NH, THF, –78 °C, ii) DMF, iii) MeOH, AcOH, $NaBH_4$, 39%; (b) TBDPSCl, NEt_3, DMAP, DMF, RT, 89%; (c) propyne, $PdCl_2(PPh_3)_2$, CuI, NEt_3, DMF, RT, 89%; (d) i) Bu_3SnH, *n*-BuLi, CuCN, MeOH, THF, –78 °C, 94%, ii) NIS, THF, –17 °C, 87%; (e) *t*-BuLi, **17**, $BF_3•OEt_2$, toluene, –78 °C, 30 %.

Since the yield for the epoxide opening reaction was too low to proceed with the synthesis, a screening of reaction conditions was performed, which included variations in *Lewis* acid, solvents additives and the concentration of vinyl iodide **195**. The results of this optimization study are summarized in Table 6.

Table 6: Screening of conditions for the reaction of vinyl iodide **195** with epoxide **17**.[a]

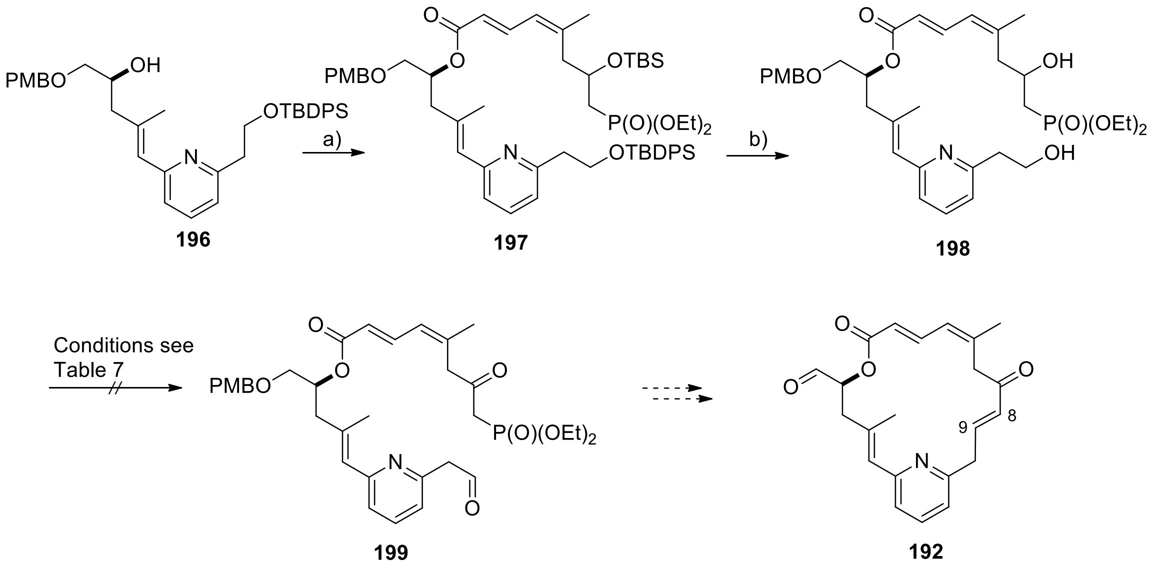
Entry	Solvent	Lewis acid	Additive	Concentration of 195	Scale of 195 [mg]	Yield of 196 [%]
1	toluene	BF_3•OEt_2	None	0.06	99	15
2	toluene	BF_3•OEt_2	None	0.024	38	8
3	toluene	BF_3•OEt_2	None	0.056	90[b]	8
4	THF	BF_3•OEt_2	None	0.03	40	0
5	toluene	BF_3•OEt_2	HMPA	0.04	65	0
6	THF	BF_3•OEt_2	HMPA	0.03	36	0
7	toluene	$TiCl_4$	None	0.02	25	10
8	toluene	None	HMPA (20% v/v)	0.015	30[c]	0
9	CH_2Cl_2	BF_3•OEt_2	None	0.023	37	0
10	toluene	BF_3•OEt_2	None	0.11	113	30
11	toluene	BF_3•OEt_2	None	0.20	160	16
12	toluene	BF_3•OEt_2	None	0.16	142	23
13	toluene	BF_3•OEt_2	THF (25%v/v)	0.10	101	23
14	THF	CuCN	No	0.07	106[d]	0
15	toluene	BF_3•OEt_2	No	0.15	548	20

[a] Typical reaction conditions involved the iodide to lithium exchange in **195** performed with *t*-BuLi followed by sequential addition of PMB-protected (*R*)-glycidol (**17**) (2.5 equiv) and *Lewis* acid (2.5 equiv). In general, HMPA (3 equiv) was added before the epoxide **17**. All reactions were carried out at –78 °C except for special cases such as: [b] –85 to –78 °C, [c] –78 °C to RT, HMPA added after epoxide **17**, [d] –78 °C to –20 °C. In entry 14, 2 equivalents of the vinyllithium reagent were used to form the homocuprate with respect to 1 equivalent of epoxide **17**. *Note:* The reverse addition, i.e. with the vinyllithium being added to a solution of epoxide **17** and BF_3•OEt_2, afforded no product (not shown in this Table).

The concentration of **195** seemed to be of only minor relevance for the reaction outcome. The addition of HMPA had no effect and the use of $TiCl_4$ as *Lewis* acid (entry 7, Table 6) or the use of a homocuprate (entry 14, Table 6) did not lead to formation of **196**. Changing the solvent from toluene to THF or CH_2Cl_2 resulted in no conversion to **196**. It thus seemed that the initial conditions (*t*-BuLi, BF_3•OEt_2, toluene) were still the best, although the product was consistently obtained in low yields only. So far, 30% yield for **196** (entry 10, Table 6) was the highest yield obtained under standard conditions (BF_3•OEt_2, toluene, –78 °C), but yields in the vicinity of 20% were in fact more common.

The reasons for the low yield for **196** might perhaps be ascribed to the deactivation of the nucleophile due to BF_3–coordination to the nitrogen lone pair of the pyridine ring. The number of BF_3-equivalents used for the conversion of **195** into **196** (see Table 6) corresponded to the optimized conditions which had been developed in the synthesis of (–)-dactylolide ((–)-**2**) for the similar transformation of **124** to **125** (Scheme 58, page 77) and thus was deemed best not to be varied at this stage.

Although secondary alcohol **196** was accessible in only minor amounts, the material available was converted to ester **197** according to the *Yamaguchi* protocol (Scheme 84).[50] This was followed by global silyl deprotection with HF•pyridine to provide diol **198** with good yields. The oxidation to the mixed *β*-keto phosphonate/aldehyde **199** using DMP, surprisingly, afforded no product, which is in marked contrast to previous results obtained with related substrates in the course of the synthesis of (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**) (Scheme 59, page 79), C13-desmethylene dactylolide (**167**) (Scheme 76, page 94) and des-THP zampanolide (**174**) (Scheme 79, page 98).



Scheme 84: (a) **98**, 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, then **196**, toluene, RT, 73%; (b) HF•py, THF, 0°C to RT, 84%.

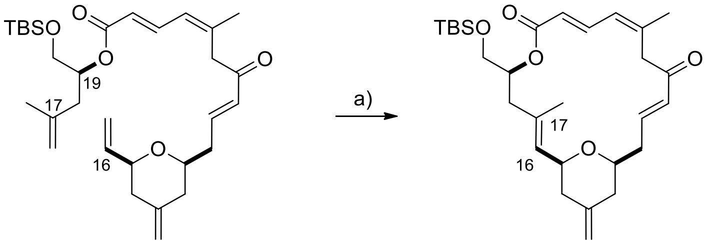
TLC analysis revealed that several polar products had formed, relative to diol **198**, upon addition of DMP; *Swern* oxidation conditions gave only recovered starting material **198**, while TPAP/NMO led to decomposition. A number of other common oxidation methods were tested, but in no case was the desired *β*-keto-phosphonate/aldehyde **199** formed (Table 7).

Table 7: Attempted oxidation of diol **198**.[a]

Entry	Oxidant/(Additive)	Equivalents	Mass(m/z)	Yield of 199 [%]
1	DMP	6	No	0
2	DMP, $NaHCO_3$	6	No	0
3	PS-IBX	10	643	0
4	BAIB, TEMPO	4	643	0
5	CrO_3•py	10	No	0
6	PCC	5	643	0
7	TPAP, NMO	5	No	0
8	Swern	4	No	**198** back
9	NCS, Me_2S	10	No	0
10	SO_3•py, DMSO	10	No	**198** back
11	P_2O_5, DMSO, NEt_3	5	643	0
12	DMP/(TFA)	6/(3)	643	0
13	DMP/(BF_3•OEt_2)	6/(4.5)	No	0
14	DMP/(HBF_4•OEt_2)	6/(1.5)	No	0
15	DMP/(HCl (2N))	6/(11)	No	0

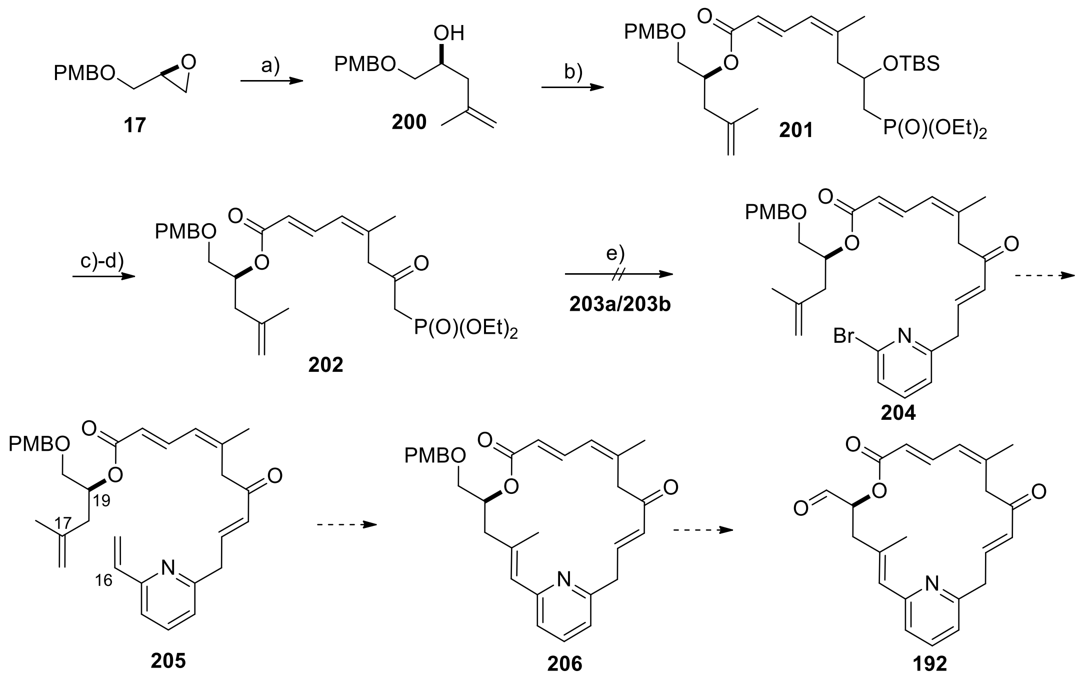
[a] Mass spectroscopy of the reaction mixture was used to follow product formation; the mass of 643 (m/z) corresponds to the mono-oxidized product, 641(m/z) would correspond to the mass of desired product **199**.

The lone pair of the pyridine nitrogen could potentially form a hydrogen bond with the primary alcohol moiety in **198** or interact with the "active principle" of the oxidant. Although it was not entirely clear how this might impact the oxidation reaction, we investigated, whether blocking the nitrogen-lone pair might lead to formation of **199**. As it turned out, however, the addition of either *Brønsted* or *Lewis* acids did not result in the formation of the desired oxidation product **199** (Table 7, entries 12–15). While permanent blockage of the pyridine nitrogen by *N*-oxidation might have been another option worth investigating, uncertainties about the compatibility of conditions required for *N*-oxide reduction with other structural features of the molecule at a late stage of the synthesis led us not to pursue this approach. Rather, we decided to change the overall strategy for the assembly of the desired pyridine derivative **192**, such that ring closure would be attempted by macrocylization through RCM between C16 and C17.This idea was inspired by the latest total synthesis of (–)-dactylolide ((–)-**2**) reported in the literature, which is based on the analogous ring closure (Scheme 85).[53]



Scheme 85: Macrocyclization approach by *Lee* and co-workers, based on RCM at C16-C17. (a) 10 mol% *Grubbs'* 2nd generation catalyst, 10 mol% benzoquinone, CH_2Cl_2, 65 °C, 45%.[53]

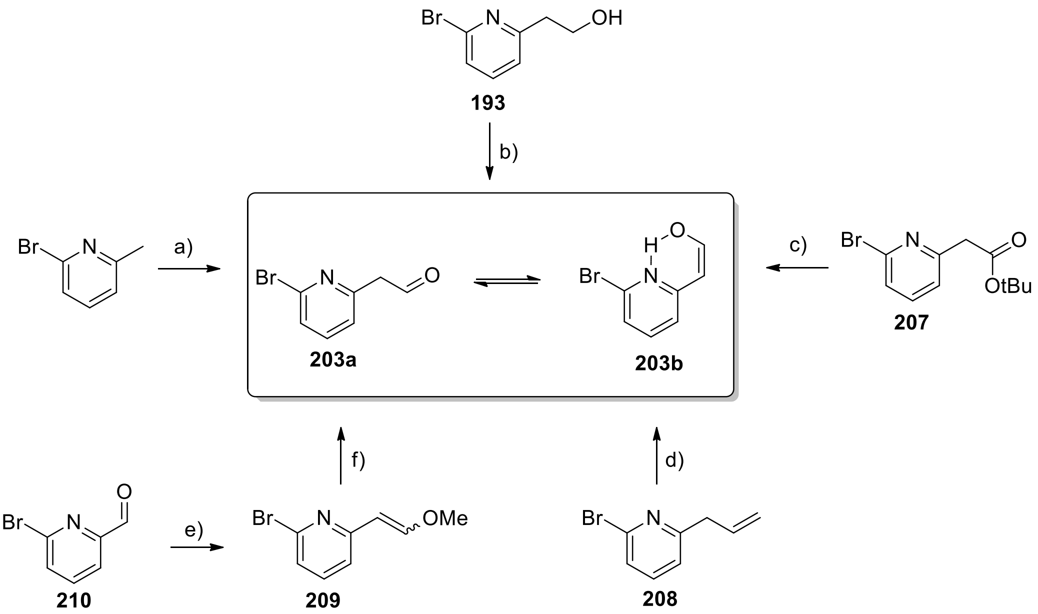
As illustrated in Scheme 86 the pyridine fragment was to be introduced relatively late in the synthesis via an intermolecular *HWE* olefination between *β*-keto phosphonate **202** and aldehyde **203a** (see Scheme 87), which would then be followed by the installation of the vinyl group in **204** and finally RCM to establish the C16-C17 C=C double bond. Alternatively, the vinyl group might have been installed before the *HWE* olefination. The synthesis of the *β*-keto phosphonate **202** was achieved starting from PMB-protected (*R*)-glycidol (**17**), which was transformed into the secondary alcohol **200** via a copper(I)-mediated epoxide opening with *iso*-propenylmagnesium bromide. Alcohol **200** was then further elaborated into **202** in good overall yields (Scheme 86).


PMBO
O
17
a)
OH
PMBO
200
b)
PMBO
O
O
OTBS
P(O)(OEt)2
201
c)-d)
PMBO
O
O
O
P(O)(OEt)2
202
e)
203a/203b
PMBO
O
O
O
Br
N
204
PMBO
O
O
19
17
O
16
N
205
PMBO
O
O
O
N
206
O
O
O
O
N
192

Scheme 86: (a) *iso*-propenylmagnesium bromide, CuI (10 mol%), THF, –40 °C, 98%; (b) **98**, 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, then **200**, toluene, RT, 83%; (c) HF•py, THF, 0°C to RT, 91%; (d) DMP, CH_2Cl_2, RT, 79%; (e) **203a**/**203b**, $Ba(OH)_2 \cdot 0.8H_2O$, THF/H_2O (40:1), 0 °C to RT, no reaction.

While **202** was thus readily available, the synthesis of aldehyde **203a**, unexpectedly, turned out to be difficult. The treatment of primary alcohol **193** with DMP afforded a product which might have been the desired aldehyde **203a,** based on NMR analysis of the crude reaction mixture after workup, but that could not be isolated in pure form.

Thus other methods for the preparation of **203a** were explored which are summarized in Scheme 87. This included the formylation of 2-bromo-6-methylpyridine, which only afforded a mixture of unidentifiable compounds. More promising though, was the reduction of *t*-butyl ester **207** to the aldehyde. This afforded a mixture of two inseparable products, according to NMR analysis, in low combined yield (15%, ca. 90% purity).



Scheme 87: Attempts to obtain the desired *β*-pyridine aldehyde: (a) i) *n*-BuLi, *i*-Pr_2NH (2 equiv), THF, –78 °C, ii) DMF, no clear assignment; (b) DMP, CH_2Cl_2, RT, yield not determined; (c) DIBAL-H, CH_2Cl_2, –78 °C, 15%, ca. 90% purity; (d) i) AD-mix β, *t*-BuOH/H_2O, RT, ii) $NaIO_4$, CH_2Cl_2,H_2O, yield not determined; (e) $Ph_3PCH_2OCH_3Cl$, *n*-BuLi, 0 °C, 72%, 1.1:1 mixture of olefins; (f) HCl, THF, 80 °C, 35%, ca. 90% purity.

Figure 23 shows the ^{1}H-NMR spectrum of the purified product mixture **203a** and **203b**, which suggests that aldehyde **203a** (signal at 9.9 ppm) may be present in equilibrium with its tautomer **203b** (signal at 12.4 ppm, which might be assigned to the enol hydroxyl group) in a ratio of 1.2:1 in favor of aldehyde **203a**. A higher yielding approach to the product mixture **203a/b** (35% yield, ca. 90% purity) was the hydrolysis of enolether **209** (obtained from 6-bromo-pyridine-2-carbaldehyde (**210**) by *Wittig* reaction with $Ph_3P{=}CHOCH_3$). NMR analysis revealed however, a different ratio of 1:1.4[6] in favor of the enol form **203b** (spectrum not shown). *Lemieux-Johnson* cleavage of olefin **208**, afforded the same product mixture **203a/b** although in impure form (yield was not determined) (Scheme 87).

We speculated whether the mixture of tautomers **203a** and **203b** would still undergo the planned intermolecular *HWE* reaction with *β*-keto phosphonate **202**; the aldehyde **203a** would react with **202** and thus shifting the equilibrium from enol **203b** to the aldehyde **203a**. The presumed tautomeric mixture of **203a/203b** (derived from the hydrolysis of enolether **209**, ca. 90% purity), unfortunately, did not undergo

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[6] The difference in the ratio for **203a/b** for the epimeric mixture is most likely related to the difference in concentrations of prepared samples for NMR data acquisition.

Ba(OH)$_2$-promoted *HWE* reaction with *β*-keto phosphonate **202** (Scheme 86, page 107). These difficulties suggested that access to pyrido-dactylolide **192** would require the development of an alternative synthesis, which would not have been possible within the timeframe of this Ph. D. thesis. The synthesis of **192** was thus abandoned.

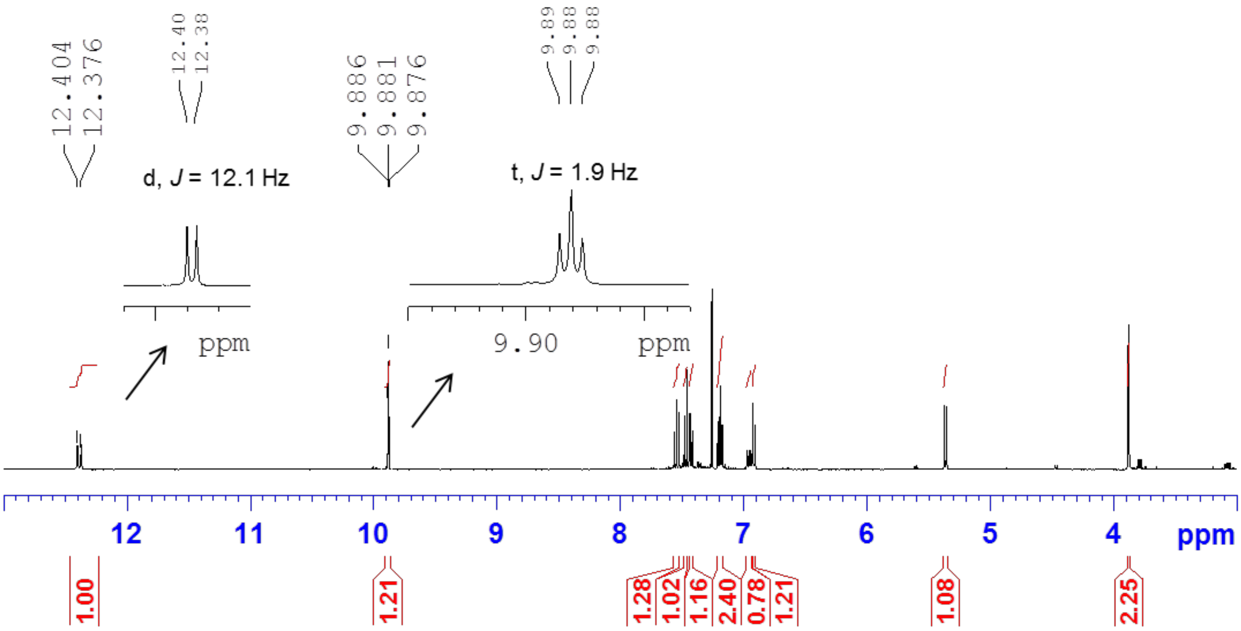

Figure 23: ^{1}H-NMR spectrum of the presumed tautomeric mixture of **203a** and **203b** (in a ratio of approximately 1:1.2) derived from reduction of *t*-butyl ester **207**. The spectrum was recoded in CDCl$_3$.The signal at 9.9 ppm (t, *J* = 1.9 Hz) corresponds to the aldehyde form **203a**, the signal at 12.4 ppm (d, *J* = 12.1 Hz) to the enol form **203b**. It may be speculated that the enol tautomer prefers the hydrogen-bonded (*Z*)-enol form, however, with no experimental evidence.

3.5. Biological Evaluation[7]

This section describes the results of the first SAR study conducted on zampanolide/dactylolide-type structures. This has included the assessment of antiproliferative activities and effects on tubulin polymerization, the determination of microtubule-binding affinities, and the investigation of Pgp-mediated efflux. The actual biological experiments were all carried out by collaborators.

3.5.1. *In Vitro* Antiproliferative Activity

The *in vitro* antiproliferative effects of (–)-zampanolide ((–)-**1**), (–)-dactylolide ((–)-**2**) and the various analogs prepared in this Ph. D. thesis were investigated in the group of *Prof. Dr. Jürg Gertsch* at the University of Bern. The results of these experiments are summarized in Table 8.

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[7] For a detailed experimental description see Experimental Section and references given.

Table 8: Cancer cell growth inhibition by (–)-zampanolide ((–)-**1**), dactylolide ((–)-**2**) and their analogs (IC$_{50}$ values in nM).[a]

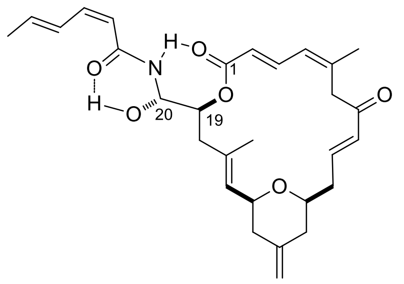
Compounds	**IC$_{50}$**	**IC$_{50}$**	**IC$_{50}$**	**IC$_{50}$**
	A549 (lung)	**MCF-7 (breast)**	**HTC116 (colon)**	**PC3 (prostate)**
(–)-**1**[b]	3.2±0.4	6.5±0.7	7.2±0.8	2.9±0.4
epi-(–)-**1**[b]	53.0±5.9	42.0±9.3	88.3±5.1	50.4±11.7
(–)-**1**:*epi*-(–)-**1**	39.0±8.1	26.5±4.9	23.9±7.5	53.7±13.8
(–)-**2**	301.5±4.3	247.6±2.6	210.4±4.7	750.6±69.4
129	127.5±2.9	106.0±3.6	155.8±2.1	319.5±26.1
167	149±12.8	68±5.6	249.5±28.2	nd[c]
173	189±19.3	114.4±10.2	74.1±1.5	104±4.1
175	3′921±216	2′894±144	2′653±68	4′021±102
187	2′378±70	3′891±102	1′846±92	3′051±178
174:*epi*-**174**	113±5	149±7	81±3	92±4
188	9′732±260	7′624±303	12′733±379	9′338±242
189	1′072±103	1′489±83	1′603±122	1′274±117
190	>20µM	>20µM	>20µM	>20µM
191	973±90	1′138±72	1′204±63	829±27

[a] Cells were exposed to the test compounds for 72 h. Cell numbers were estimated by quantification of the protein content of fixed cells by methylene blue staining (see references[229]). Values shown represent the means of three independent experiments (± standard deviation). [b] IC$_{50}$ values were also acquired for the leukemia cell line U937 and found to be 1.3±0.08 nM for (–)-**1** and 19.2±0.8 nM for *epi*-(–)-**1**. [c] nd = not determined.

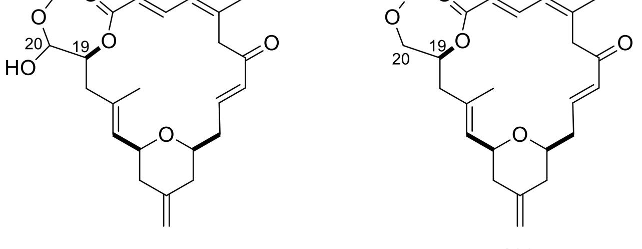
Synthetic (–)-zampanolide ((–)-**1**) possesses potent antiproliferative activity with IC$_{50}$′s in the low nM range, which is in line with the effects reported for (–)-zampanolide ((–)-**1**) isolated from *Fasciospongia rimosa*[1] and *Cacospongia mycofijiensis,*[10] and also with data reported very recently for synthetic (–)-**1**.[7] C20-*epi*-(–)-**1** is less active by a factor of about 10 which is also true for the mixture of (–)-**1**:*epi*-(–)-**1** (approximately 1.1:1) obtained in the unselective aza-aldol reaction. (–)-

Dactylolide ((–)-**2**) is significantly less potent than (–)-zampanolide ((–)-**1**) with IC_{50} values in the range of 210 to 750 nM. These data are in agreement with literature data on other cell lines.[16] The literature data also indicate that naturally occurring (+)-dactylolide ((+)-**2**) is slightly less potent than unnatural (–)-dactylolide ((–)-**2**), although a direct comparison is only available for the SK-OV-3 cell line.[16] As we did not have access to natural (+)-dactylolide ((+)-**2**) we were not able to carry out any comparative experiments. Overall, the data clearly indicate that the side chain is the crucial element for the enhanced potency of (–)-zampanolide ((–)-**1**) over (+)-dactylolide ((+)-**2**), while the absolute stereochemistry of the macrocyclic core structure is less important.

Interestingly, alcohol **129** showed at least the same potency as the parent compound (–)-dactylolide ((–)-**2**), with IC_{50} values between 106 and 320 nM. Based on this result, one could speculate that in solution the aldehyde functionality of (–)-dactylolide ((–)-**2**) is present as its hydrate, allowing a similar hydrogen-bonding network as might be present in alcohol **129** (Figure 24), or with the hydroxyl group being involved in interactions with the target protein tubulin.



(–)-Zampanolide ((–)-**1**)



Hydrate of (–)-Dactylolide ((–)-**2**)

129

Figure 24: Hypothetical hydrogen-bonding networks in (–)-zampanolide ((–)-**1**), (–)-dactylolide ((–)-**2**) and in alcohol **129**.

As discussesd in the introduction, *Porco* and co-worker[12] have described a 6-membered hydrogen-bonding network between the side chain amide carbonyl of (–)-

zampanolide ((–)-**1**) and the OH group at C20 as well as a 7-membered hydrogen-bonding network between the amide NH and the lactone carbonyl functionality at C1 as important structural motifs (Figure 24 and Scheme 2, page 5). The 7-membered hydrogen-bonding network could also be present in the hydrate form of (–)-dactylolide ((–)-**2**), thus stabilizing a particular conformation. The existence of such hydrogen bonding networks in aqueous solution, however, and their potential relevance for the biological activity of zampanolide/dactylolide remain to be established.

In this context it should also be noted that blocking the hydrogen-bonding donor capability of alcohol **129** with a methyl group only leads to a moderate loss in cellular potency, with IC_{50} values for methyl ether **191** being between 0.83 and 1.2 μM. Independent of the biological significance of this finding it should be pointed out that (–)-dactylolide ((–)-**2**) shows a pronounced tendency for hemiacetal formation based on NMR analysis of (–)-dactylolide ((–)-**2**) in EtOH-d_6. The aldehyde signal was almost invisible in the ^{1}H- and ^{13}C-NMR spectra which were acquired immediately after sample preparation. Furthermore, a new set of signals at 4.7 ppm in the ^{1}H-NMR spectrum was observed which was present as two overlapping doublets with identical *J*-coupling constants (5.4 Hz) in a ratio of ca. 2:1 (Figure 25).

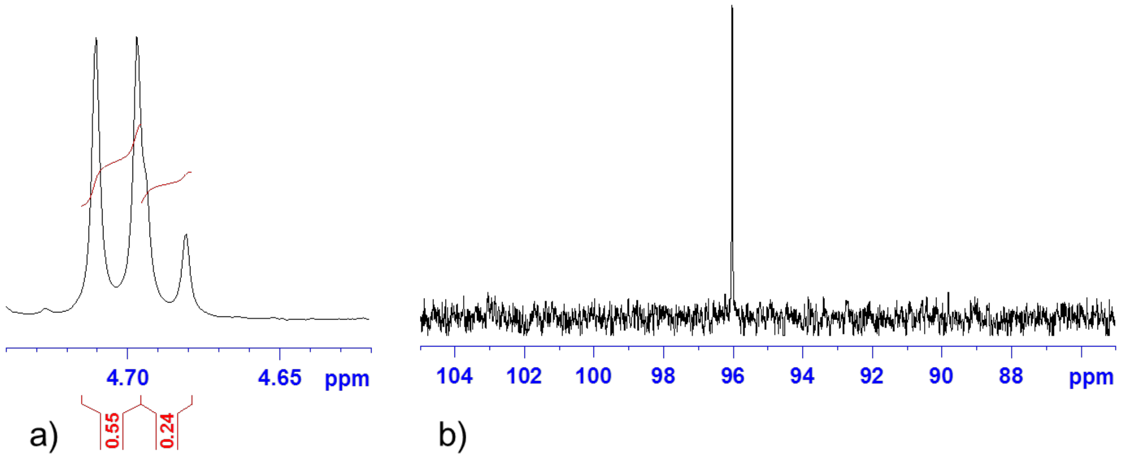


Figure 25: Selected signals from the NMR spectra of (–)-dactylolide ((–)-**2**) acquired in EtOH-d_6 immediately after sample preparation; a) ^{1}H-NMR signal at 4.7 ppm and b) ^{13}C-NMR signal at 96 ppm, presumably corresponding to the C20-H of an ethyl hemiacetal.

These signals coupled to a new signal at 96 ppm in the ^{13}C-NMR spectrum (as determined by HSQC analysis) and correspond to a new C-H group which was not present in ^{1}H- and ^{13}C- NMR spectra recorded in $CDCl_3$. These observations strongly suggest hemiacetal formation of (–)-dactylolide ((–)-**2**) at C20 in EtOH-d_6 (or less likely, acetal formation). As for (–)-dactylolide ((–)-**2**) and alcohol **129**, the evaluation of the C13-desmethylene derivatives revealed no difference between the aldehyde **167** and alcohol **173** (structures see Scheme 76, page 94) with IC_{50}'s between 68 and 250 nM. Furthermore, both compounds **167** and **173** seem to be equally potent as (–)-dactylolide ((–)-**2**) and alcohol **129**, respectively[205]. This finding in fact led to the design of the dramatically simplified des-THP analogs of (–)-zampanolide (**174**) and (–)-dactylolide (**175**) (structures see Scheme 79, page 98). Aldehyde **175** and alcohol **187** were equally potent with IC_{50} values in the range between 1.8 and 4 μM, and thus are less potent than (–)-dactylolide ((–)-**2**) only by a factor of about 10 (Table 8).

More interestingly, however, was the observation that the epimeric mixture of **174** and *epi*-**174** possessed IC_{50} values between 81–150 nM. This mixture was significantly more potent than aldehyde **175**, which correlates well with the higher activity of (–)-zampanolide ((–)-**1**) compared to (–)-dactylolide ((–)-**2**). Intriguingly, **174**/*epi*-**174** even appears to be slightly more potent than (–)-dactylolide ((–)-**2**), in spite of a substantial simplification of the macrolactone core structure. The biological analysis of the individual epimers **174** and *epi*-**174** is currently ongoing.

Acid **188** showed IC_{50} values in the range between 7.6 and 12.7 μM only, while acid **190**, which lacks the THP subring, is even less potent (IC_{50} values higher than 20 μM) (structures see Scheme 80, page 100). It remains to be established whether the reduced cellular activity of carboxylic acids, compared to the corresponding alcohols, is due to poor cellular uptake or due to weak or absent interaction with the molecular target(s). In contrast to the above acidic analogs, alkyl amide **189**, whose alkyl group exhibits similar lipophilicity as the natural side chain of (–)-zampanolide ((–)-**1**), is active with IC_{50} values between 1 and 1.6 μM. However, given the loss in activity relative to (–)-zampanolide ((–)-**1**) the C20-side chain of **189** is not an adequate replacement of the natural side chain.

3.5.2. Tubulin Polymerization

For (–)-dactylolide ((–)-**2**), alcohol **129,** and the C13-desmethylene derivatives **167** and **173** we have determined their ability to induce tubulin polymerization.

Table 9: Induction of tubulin polymerization by (–)-dactylolide ((–)-**2**) and derivatives using 2 or 5 μM of the test compound (values in %).[a]

	(–)-2	129	167	173	EpoA
2 μM	41	63	74	69	82
5 μM	68	80	88	83	91

[a] Induction of tubulin polymerization of porcine brain microtubule protein (10 μM) relative to the effect of 25 μM of epothilone B.

All four compounds showed significant tubulin-polymerizing activity (Table 9), which establishes for the first time that the non-natural product (–)-dactylolide ((–)-**2**), like (–)-zampanolide ((–)-**1**), is a microtubule stabilizer.

3.5.3. Interactions with Microtubules

The microtubule-binding of several of the compounds prepared in this thesis has been investigated in the group of Dr. *José Fernando Díaz* at the Centro de Investigaciones Biológicas in Madrid, Spain.[8] These experiments have shown that (–)-zampanolide ((–)-**1**), (–)-dactylolide ((–)-**2**), alcohol **129**, and desmethylene dactylolide all bind to microtubules at the taxol binding site, as they can all displace the pre-bound fluorescently labelled taxol derivative Flutax-2[9]. Preliminary apparent binding constants K_a are $3x10^7$ M^{-1} at 35 °C for (–)-zampanolide ((–)-**1**), $3x10^6$ M^{-1} for both (–)-dactylolide ((–)-**2**) and alcohol **129**, and $3x10^5$ M^{-1} for desmethylene analog **167** (for experimental details, including the concentrations of Flutax-2, test compounds and taxol binding sites, see[230]). In addition, the independent evaluation of the antiproliferative activity of (–)-zampanolide ((–)-**1**) and (–)-datylolide ((–)-**2**) by *Díaz* and co-workers confirmed our own data.

Figure 26 shows the kinetics of the loss of binding sites for the fluorescin-labelled taxol derivative Flutax-2 on stabilized microtubules after incubation with (–)-zampanolide ((–)-**1**) and selected analogs. Synthetic (green circles in Figure 26) and natural (–)-zampanolide ((–)-**1**) (cyan circles) both completely block Flutax-2 binding to microtubules within the dead time of the method (30 minutes), i. e. the compound cannot be displaced from microtubules even by a large excess of Flutax-2. Blocking kinetics is slower for C20-*epi*-zampanolide (*epi*-(–)-**1**) (blue circles), (–)-dactylolide ((–)-**2**) (red circles) and its alcohol derivative **129** (yellow circles), but blockage is still apparent. In contrast, the C13-desmethylene (–)-dactylolide derivatives **167** (pink circles) and **173** (orange circles) (structures see Scheme 76, page 94) do not block binding of Flutax-2. These data suggest that all compounds investigated, with the exception of **167** and **173**, bind to microtubules in an irreversible fashion. For **167** and **173** binding may be either reversible or the reaction with microtubules may be simply too slow to prevent Flutax-2 binding within the timeframe of the experiment.

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[8] Unpublished results reproduced with permission from Dr. *J. F. Díaz.*

[9] Flutax-2=7-*O*-[*N*-(2,7-difluoro-4-fluoresceincarbonyl)-L-alanyl]taxol.

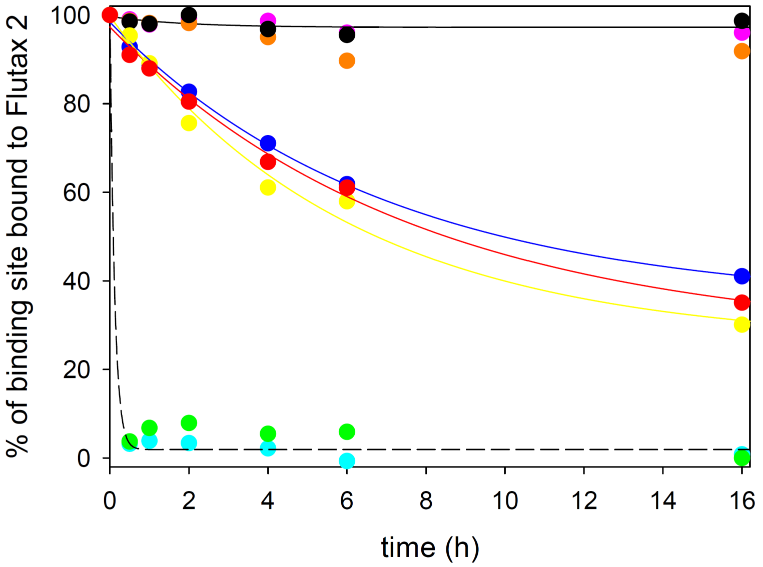


Figure 26: Kinetics of inhibition of Flutax-2 binding to crosslinked microtubules by (–)-zampanolide ((–)-**1**) and its analogs. DMSO control (black circles), **167** (pink circles), **173** (orange circles), C20-zampanolide epimer (*epi*-(–)-**1**) (blue circles), (–)-dactylolide ((–)-**2**) (red circles), **129** (yellow circles), synthetic (–)-zampanolide ((–)-**1**) (green circles) and isolated (–)-zampanolide ((–)-**1**) (cyan circles). Solid lines represent the fitted decay of Flutax-2 binding sites on microtubules incubated with DMSO (black line), with C20-*epi*- (–)-**1** (blue line), with (–)-dactylolide ((–)-**2**) (red line) and with **129** (yellow line). Dashed line represents the fitted decay of binding sites incubated with (–)-zampanolide ((–)-**1**). For experimental details, see[231].

Data from MS sequencing of chymotrypsin-digested tubulin samples derived from (–)-zampanolide- and (–)-dactylolide-treated microtubules have confirmed that both compounds form covalent adducts with tubulin, presumably by reaction with tyrosine 224 in β-tubulin. This residue is located in the taxol-binding site as shown in the ribbon diagram of the α,β-tubulin dimer with docetaxel bound in Figure 27.[232]

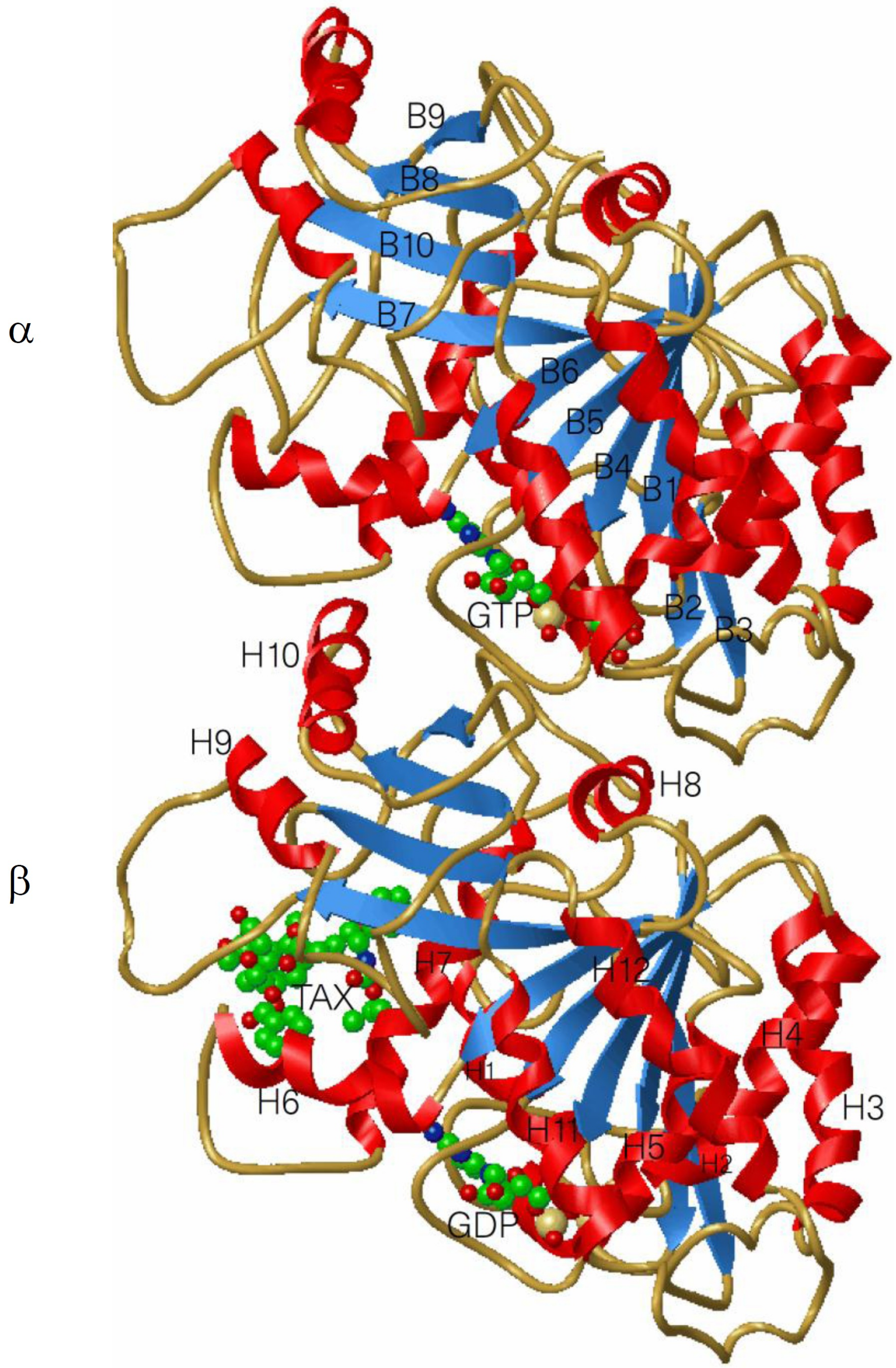
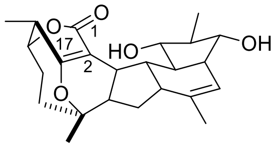


Figure 27: Ribbon diagram of the tubulin dimer showing α-tubulin with bound GTP (top), and β-tubulin containing GDP and docetaxel (bottom). Labels for strands (in the α-subunit) and helices (in the β-subunit) are included.[232]

The covalent modification of a tyrosine residue is, although surprising, not implausible. Cyclostreptin (Figure 28), a natural product isolated from *Streptomyces* sp. 9885 has been previously found to covalently modify Tyr220 and Asn228 residues of β-tubulin in stabilized microtubules or Tyr220 only in unpolymerized tubulin, presumably through 1,4-addition to the *Michael* acceptor system formed by C17, C2 and C1.[231] The reactive site(s) in (–)-zampanolide/(–)-dactylolide remain to be determined.



Cyclostreptin

Figure 28: Structure of cyclostreptin, a potent natural product isolated from *Streptomyces* sp. 9885, which covalenty modifies β-tubulin.[231]

3.5.4. Pgp-Susceptibility of (–)-Dactylolide Derivative 129

According to the recent report by *Miller* and co-workers (–)-zampanolide ((–)-**1**) appears not to be a substrate for the ATP-dependent P-glycoprotein (Pgp) efflux pump,[10] as the compound retains its activity against Pgp-overexpressing ovarian cancer cells, which are resistant to taxol. Pgp-mediated efflux reduces intracellular drug concentrations, thus leading to multidrug-resistance (MDR) of cancer cells, which causes failure of many forms of chemotherapy.

In collaboration with *Denise Ilgen*[10] from the group of Prof. Dr. *Heidi Wunderli-Allenspach*, the Pgp-mediated efflux of alcohol **129** (structure see Figure 24 , page 111) was studied in a cell monolayer efflux assay.[233] Passive permeation of alcohol **129** was determined as the apparent permeability coefficient (P_{app}) across polarized cell monolayers (MDCKII) in the absorptive (apical-to-basal, A→B) and secretory (basal-to-apical, B→A) direction, which provides information on the absorption of the compound investigated. In cells overexpressing Pgp (MDCKII-hMDR1), the protein is localized on the apical surface of the cells monolayer, thus reducing transport of the substrate in the apical-to-basal direction and increasing transport in the basal-to-apical direction. Comparison of B→A:A→B ratios measured in parental (MDCKII) and Pgp-overexpressing cells (MDCKII-hMDR1) provides evidence for the involvement of Pgp-mediated efflux as shown in Figure 29.

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[10] Unpublished results reproduced with permission from *Denise Ilgen*. This section is partially adapted from the Ph. D. Thesis of *Denise Ilgen*.

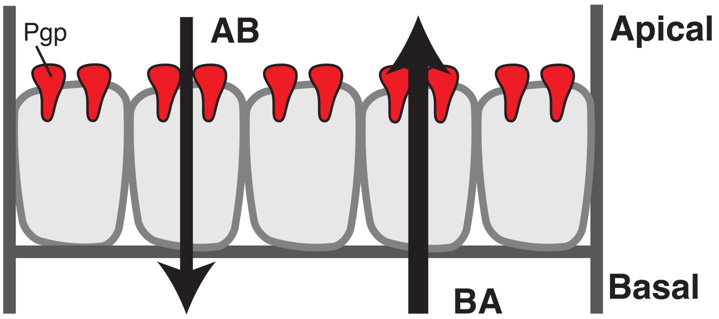


Figure 29: Cell monolayer efflux assay - Schematic representation of the method to evaluate Pgp susceptibility: The net apparent permeability coefficient (Perm$_{app}$) for compounds across polarised cell monolayers (MDCKII-hMDR1 cells) in the absorptive (apical-to-basal, A→B) and the secretory (basal-to-apical, B→A) direction is measured. A comparison of the B→A:A→B ratios obtained in parental and Pgp-overexpressing cells defines the involvement of Pgp-mediated efflux.

Judging by the data summarized in Figure 30 as well as in Table 10 and Table 11, alcohol **129** possesses moderate permeability in the cell assay.

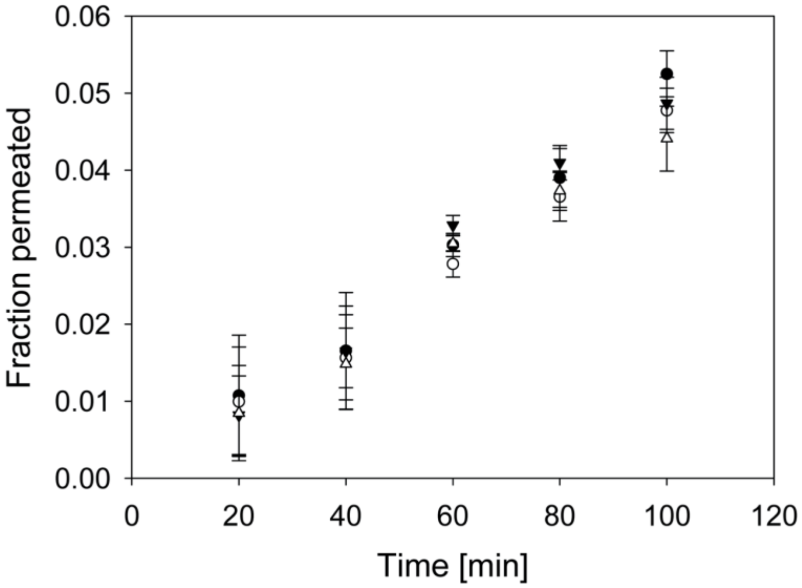


Figure 30: Permeation of alcohol **129** across MDCKII-hMDR1 cells: Alcohol **129** was measured at a concentration of 50 μM. Closed symbols represent apical-to-basal and open symbols basal-to-apical transport. Circles represent MDCKII-hMDR1 and triangles MDCKII cell lines. No difference in transport rates was found for **129** between the apical and basal compartment and between the parental cells and Pgp-overexpressing cells. Data represent mean values and standard deviation from three cell inserts.

The apparent permeability coefficient (apical-to-basal) (P$_{app}$ A→B) for **129** is higher than for vinblastine, being a known poorly permeable drug. The efflux ratio of ~0.9, suggests that **129** is not a Pgp-substrate, since no increased transport in the basal-to-apical direction was observed (Table 11). Usually, a B→A:A→B ratio of >3.0 would indicate that a drug or a xenobiotic is a Pgp-substrate.[233]

Table 10: Apparent permeation coefficients of tubulin-targeting agents.[a]

Drug	P_{app} x 10^{-6} [cm/s] MDCKII-hMDR1 (A→B)	 (B→A)	P_{app} x 10^{-6} [cm/s] MDCKII (A→B)	 (B→A)
vinblastine	0.72±0.10	3.15±0.26	1.21±0.03	1.13±0.02
129	6.54±0.35	5.74±0.82	6.21±0.17	5.45±0.64

[a] **129** was investigated at a concentration of 50 μM. For comparison, the known Pgp-substrate vinblastine was investigated at a concentration of 25 μM. Data represent mean values and standard deviation from three cell inserts.

In contrast to alcohol **129**, the well-established Pgp-substrate vinblastine showed a significantly increased P_{app} (B→A), resulting in an efflux ratio of 4.49 (Table 11). The recovery of **129** was ~77.5%, which excludes the possibility of loss of compound during the measurement.

Table 11: Efflux ratios of microtubule-targeting agents.[a]

Drug	P_{app} (B→A)/ P_{app} (A→B) MDCKII-hMDR1	P_{app} (B→A)/ P_{app} (A→B) MDCKII
vinblastine	4.49±1.02	0.94±0.01
129	0.88±0.08	0.88±0.08

[a] **129** was measured at a concentration of 50 μM, the known Pgp-substrate vinblastine was investigated at a concentration of 25 μM. Data represent mean values and standard deviation from three cell inserts.

Overall, the data suggest that **129** is a moderately permeable compound and not affected by Pgp-mediated efflux. This supports the notion, at least indirectly, that the related natural product (–)-zampanolide ((–)-**1**) is a non-Pgp substrate, which could, therefore, have potential for the treatment of Pgp-expressing tumors.

4. Conclusions and Outlook

The synthetic endeavours described in this Ph. D. thesis have led to new total syntheses of the marine natural product (–)-zampanolide ((–)-**1**) and the structurally related non-natural product (–)-dactylolide ((–)-**2**). These syntheses have provided substantial amounts of both products for biological testing, thus either overcoming the paucity of isolated material (in case of (–)-**1**) or providing access to a compound which, so far, has not been isolated from nature.

The synthesis of (–)-zampanolide ((–)-**1**) included the late-stage addition of the (*Z*,*E*)-sorbamide side chain to the aldehyde functionality of (–)-dactylolide ((–)-**2**) followed by the separation of the two C20 epimers formed. This afforded the natural product (–)-zampanolide ((–)-**1**) as well as its C20 epimer *epi*-(–)-**1**. (–)-Dactylolide ((–)-**2**) was accessed via a highly efficient *HWE*-based macrocyclization between C8 and C9, an approach that had remained unexplored in the construction of dactylolide/zampanolide. The synthesis was amenable to scale-up and allowed the preparation of (–)-zampanolide ((–)-**1**) and (–)-dactylolide ((–)-**2**) in quantities that have not been reported previously.

An important element in the synthesis of (–)-zampanolide ((–)-**1**) and also its derivatives was an epoxide opening reaction to form the C17-C18 bond, a reaction which was highly sensitive to the solvent used. Surprisingly, toluene was the only solvent which allowed the regioselective opening of PMB-protected (*R*)-glycidol (**17**) with lithiated vinyl iodide **124**, thus providing access to advanced intermediate **125**. While two routes have been developed to alcohol **125**, one from D-aspartic acid and one from L-malic acid, the D-aspartic acid-based route was clearly more efficient. Both routes to **125** were centered on the use of *Prins*-type cyclizations for the construction of the THP subring, which was accomplished in high yields and selectivities.

The exploitation of the epoxide opening chemistry allowed the construction of a series of analogs with THP subring modifications, such as the C13-desmethylene derivatives **167** and **173** and the simple ether analogs **174**, *epi*-**174**, **175** and **187**. Synthetic (–)-zampanolide ((–)-**1**) showed IC_{50} values between 1 and 7 nM in cancer cell proliferation assays, thus confirming the data reported in the original isolation work. No confirmatory evidence for this activity had been available at the outset of this project, but has been reported with newly synthesized and isolated material in the very recent past. (–)-Zampanolide ((–)-**1**) is a much more potent inhibitor of human cancer cell growth than (–)-dactylolide ((–)-**2**) with IC_{50} values between 210 and 750 nM. Based on a comparison with literature data (although for different cell lines), (–)-dactylolide ((–)-**2**) appears to be slightly more potent than the natural product (+)-dactylolide ((+)-**2**). Again, no biological data had been available in the literature for (–)-dactylolide ((–)-**2**) prior to the start of this project, but cellular activity data for the compound have been reported recently (and match with our own findings). These findings establish the need for the side chain in (–)-zampanolide ((–)-**1**) as a crucial element for high antiproliferative activity, and imply that the absolute stereochemistry of the macrolactone core structure is largely unimportant.

Significantly, both synthetic (–)-zampanolide ((–)-**1**) as well as (–)-dactylolide ((–)-**2**) could be demonstrated to bind to microtubules and to induce tubulin polymerization (only investigated for (–)-dactylolide-((–)-**2**)). The interactions of these compounds with the tubulin/microtubule system had been unknown at the outset of this project and for (–)-dactylolide ((–)-**2**) had not been reported before publication of our own work. For (–)-zampanolide ((–)-**1**) its tubulin-polymerizing activity has been established by *Miller* and colleagues only very recently.

The evaluation of cell growth inhibition by the series of analogs of (–)-zampanolide ((–)-**1**)/(–)-dactylolide ((–)-**2**) prepared in this thesis represents the first SAR study on these structures. Our data have revealed no obvious difference in antiproliferative activity between aldehyde ((–)-**2**, **167**, **175**) and alcohol (**129**, **173**,

187) forms of dactylolide-type structures; likewise the C13-methylene group is not essential for activity. Most impressive among the various analogs studied was the structurally less complex (–)-zampanolide ((–)-**1**) analog **174**, which was found to be at least as potent as (–)-dactylolide ((–)-**2**) (as a mixture of epimers at C18). The biological evaluation of **174** and *epi*-**174** is currently ongoing.

Our initial SAR data suggest that a reduction of structural complexity in the THP subring region of (–)-zampanolide ((–)-**1**) can lead to analogs which still exhibit potent cellular activity. With regard to side chain modifications it remains to be explored whether the unsaturation in the (*Z*,*E*)-sorbamide side chain of (–)-zampanolide ((–)-**1**) is important or if an analog with a simpler, saturated version, would be equally potent as (–)-zampanolide ((–)-**1**).

It is evident that more derivatives must be investigated for a deeper understanding of the structural requirements for potent biological effects by zampanolide- and dactylolide-type structures. Such additional analogs may also include hybrid structures with structural elements of other tubulin-targeting natural products. Experiments along these lines are currently ongoing in our laboratory.

5. Experimental Section

5.1. General Methods

All solvents used for reactions were purchased as anhydrous grade from Fluka (puriss.; dried over molecular sieves; H_2O <0.005%) and used without further purification. Solvents for extractions, flash column chromatography (FC) and thin layer chromatography (TLC) were purchased as commercial grade and distilled prior to use. All non-aqueous reactions were performed under an argon atmosphere using flame-dried glassware and standard syringe/septa techniques. All commercially available reagents were used without further purification, unless otherwise noted. In general, reactions were magnetically stirred and monitored by TLC performed on Merck TLC aluminum sheets (silica gel 60 F_{254}). Spots were visualized with UV light (□ = 254 nm) or through staining with $Ce_2(SO_4)_3$/phosphomolybdic acid/H_2SO_4 (CPS) or $KMnO_4$/K_2CO_3. Chromatographic purification of products (FC) was performed using Fluka silica gel 60 for preparative column chromatography (particle size 40–63 µm).

Melting points were obtained in open capillary tubes using a Büchi melting point apparatus B-540 and are uncorrected.

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$, MeOH-d_4 and DMSO-d_6 (unless otherwise noted) on Bruker AV-400 400 MHz and AV-500 500 MHz instruments at room temperature. Chemical shifts (δ) are reported in ppm and are referenced to the solvent signal as an internal standard ($CDCl_3$ δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C, MeOH-d_4 δ = 3.31 ppm for ^{1}H, δ = 49.00 ppm for ^{13}C, DMSO-d_6 δ = 2.50 ppm for ^{1}H, δ = 39.52 ppm for ^{13}C). All ^{13}C-NMR spectra were measured with complete proton decoupling. Data for NMR spectra are reported as follows: s =

singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad signal, J = coupling constant in Hz.

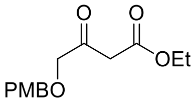
Infrared spectra (IR) were recorded on a Jasco FT/IR-6200 instrument as thin film. Resonance frequencies are given as wavenumbers in cm^{-1}.

Optical rotations were measured on a Jasco P-1020 polarimeter operating at the sodium D line with a 10 mm or 100 mm path length cell and are reported as follows: $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\boldsymbol{T}}$, concentration (g/100 mL), and solvent.

Mass spectra were recorded by the ETH Zurich MS service; HRMS (ESI) spectra were obtained on a Bruker Daltonics maxis (UHR-TOF) and HRMS (EI) on a Waters Micromass AutoSpec Ultima instrument.

HPLC analyses were carried out on a Hitachi Elite LaChrom apparatus. (autosampler: L-2200, pump: L-2130, diode array detector: L-2450). Conditions, columns, wavelenghts and retention times (R_t) are indicated for the specific case.

5.2. Characterization of Compounds from the First and Second Generation Approaches



Ethyl 4-((4-methoxybenzyl)oxy)-3-oxobutanoate (5).[11] A flask, equipped with a thermometer and an addition funnel, was charged with NaH (55%, 7.42 g, 169.86 mmol, 2.3 equiv) followed by toluene (100 mL). 4-methoxybenzyl alcohol (9.63 mL, 77.21 mmol, 1.05 equiv) was added slowly at room temperature so that the interior temperature did not exceed 25 °C. The suspension was stirred for 1 h at room temperature followed by addition of ethyl 4-chloroacetoacetate (10 mL, 73.53 mmol, 1 equiv) over 20 min having a water bath applied (the temperature stayed at 26 °C). Stirring was continued for 13 h at room temperature then citric acid (1 M, 78 mL) was added dropwise using an addition funnel. After effeverscence ceased, the phases were separated followed by extraction of the aqueous phase with toluene (2 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:5→1:1) was performed twice which afforded **5** (15.0 g, 56.36 mmol, 73%) as a yellow oil.

TLC: $R_f = 0.42$ (EtOAc/Hex 1:3, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): $\delta = 7.28$-7.25 (m, 2 H), 6.91-6.87 (m, 2 H), 4.52 (s, 2 H), 4.17 (q, *J* = 7.2, 2 H), 4.10 (s, 2 H), 3.80 (s, 3 H), 3.51 (s, 2 H), 1.25 (t, *J* = 7.2, 3 H).

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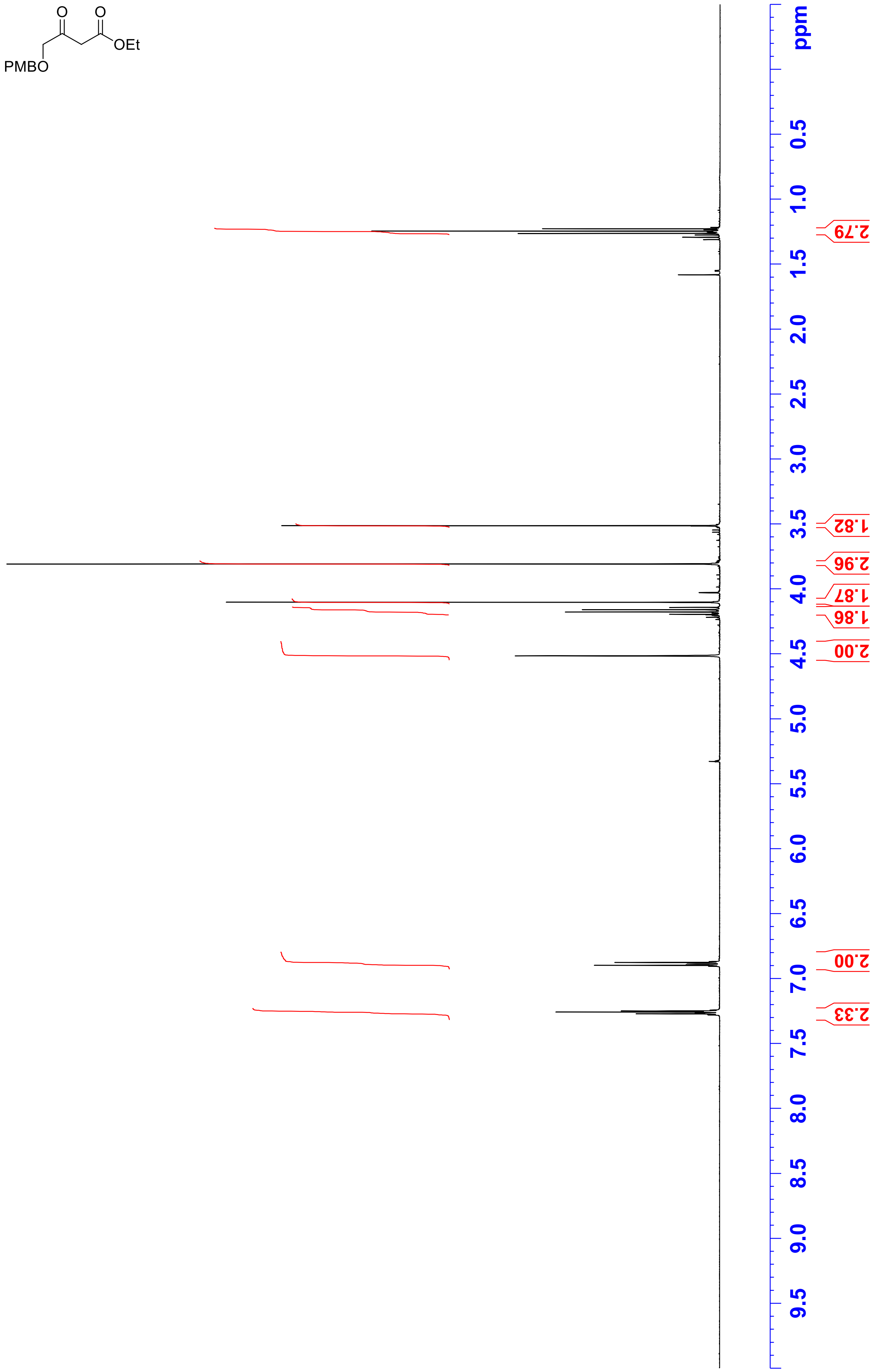
[11] Adapted from the procedure of the described benzyl derivative of **5**: G. Beck, H. Jendralla, K. Kesseler, *Synthesis* **1995**, *1995*, 1014–1018. See also M. Inman, C. J. Moody, *J. Org. Chem.* **2010**, *75*, 6023-6026.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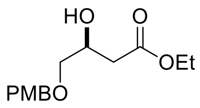

(*S*)-Ethyl 3-hydroxy-4-((4-methoxybenzyl)oxy)butanoate (6).[12] *R*-BINAP (13.9 mg, 0.023 mmol, 0.006 equiv) and $[Ru(C_6H_6)Cl]_2$ (4.5 mg, 0.008 mmol, 0.003 equiv) were suspended in dry DMF (1 mL) then stirring was continued for 15 min at room temperature followed by heating to 100 °C and stirring was continued for 5 min. The brownish solution formed, was allowed to cool to room temperature. This solution was added via needle/syringe to a degased solution (three cycles of argon flow and vacuum) of **5** (1.011 g, 3.77 mmol, 1 equiv) in dry EtOH (10 mL) placed in a high pressure apparatus. The atmosphere was replaced by H_2 (4 atm) followed by the application of a heating bath (105 °C) and stirring was continued for 17 h. The reaction mixture was allowed to cool to room temperature then concentrated under reduced pressure followed by purification using flash chromatography (EtOAc/Hex 1:2) affording **6** (0.85 g, 3.17 mmol, 84%) as a dark-yellow oil.

The ee was determined as 90% as determined by chiral HPLC on Chiralcel OD-column: hexane/*i*-PrOH, (84:16), 1 mL/min, 25 °C, 254 nm, R_t 6.80 min.

Alternative workup: After EtOH was removed under reduced pressure, the curde oil was redissolved in Et_2O and treated with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure followed by purification using flash chromatography (EtOAc/Hex 1:3) to give **6** as a dark-yellow oil.

TLC: R_f = 0.21 (EtOAc/Hex 1:3, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.27-7.23 (m, 2 H), 6.89-6.86 (m, 2 H), 4.49 (s, 2 H), 4.25-4.18 (m, 1 H), 4.15 (q, *J* = 7.2, 2 H), 3.80 (s, 3 H), 3.49 (dd, *J* = 9.6, 4.5, 1 H), 3.44 (dd, *J* = 9.6, 6.0, 1 H), 2.97 (d, *J* = 4.3, 1 H), 2.52 (d, *J* = 6.3, 1 H), 1.26 (t, *J* = 7.2, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 172.3, 159.5, 130.1, 129.5, 114.0, 73.2, 73.0, 67.4, 60.8, 55.4, 38.4, 14.3.

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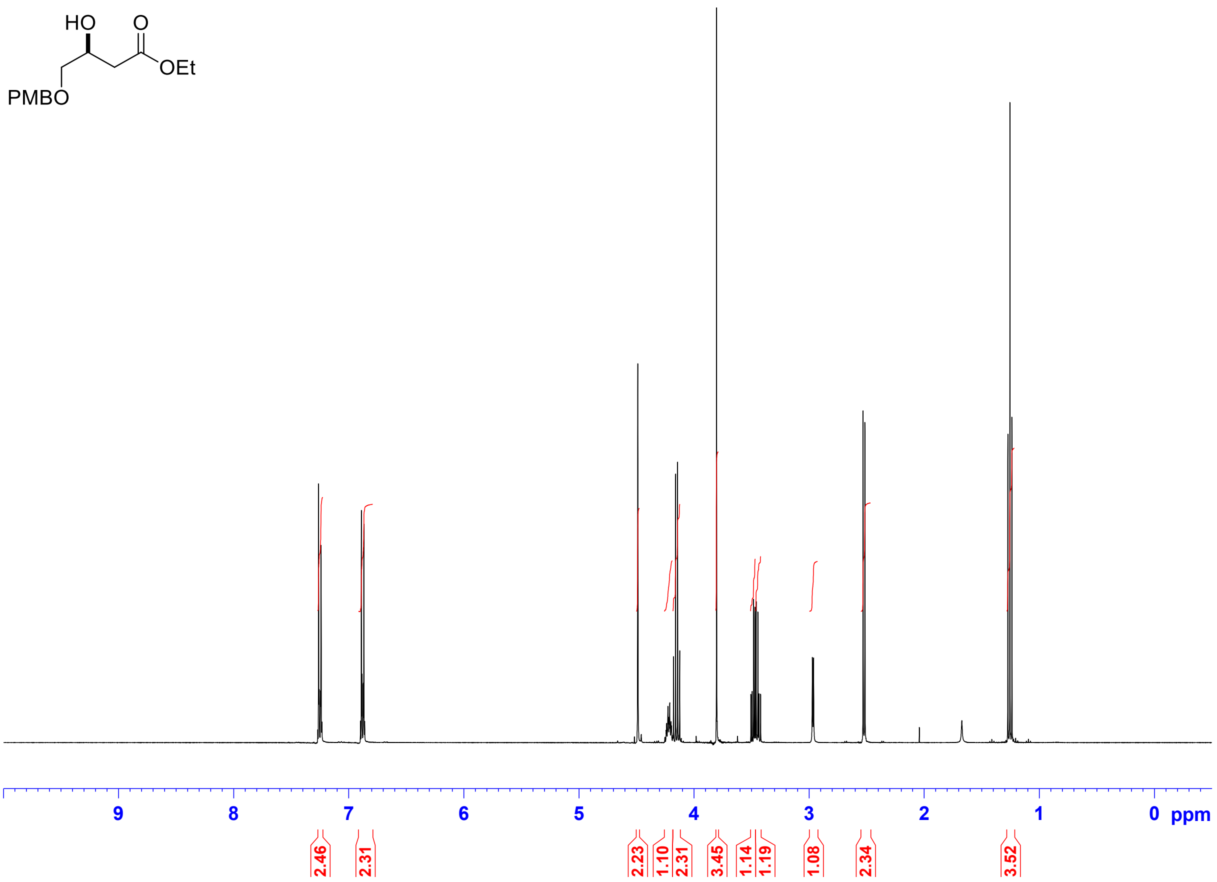
[12] For similar transformation see: G. Beck, H. Jendralla, K. Kesseler, *Synthesis* **1995**, *1995*, 1014–1018.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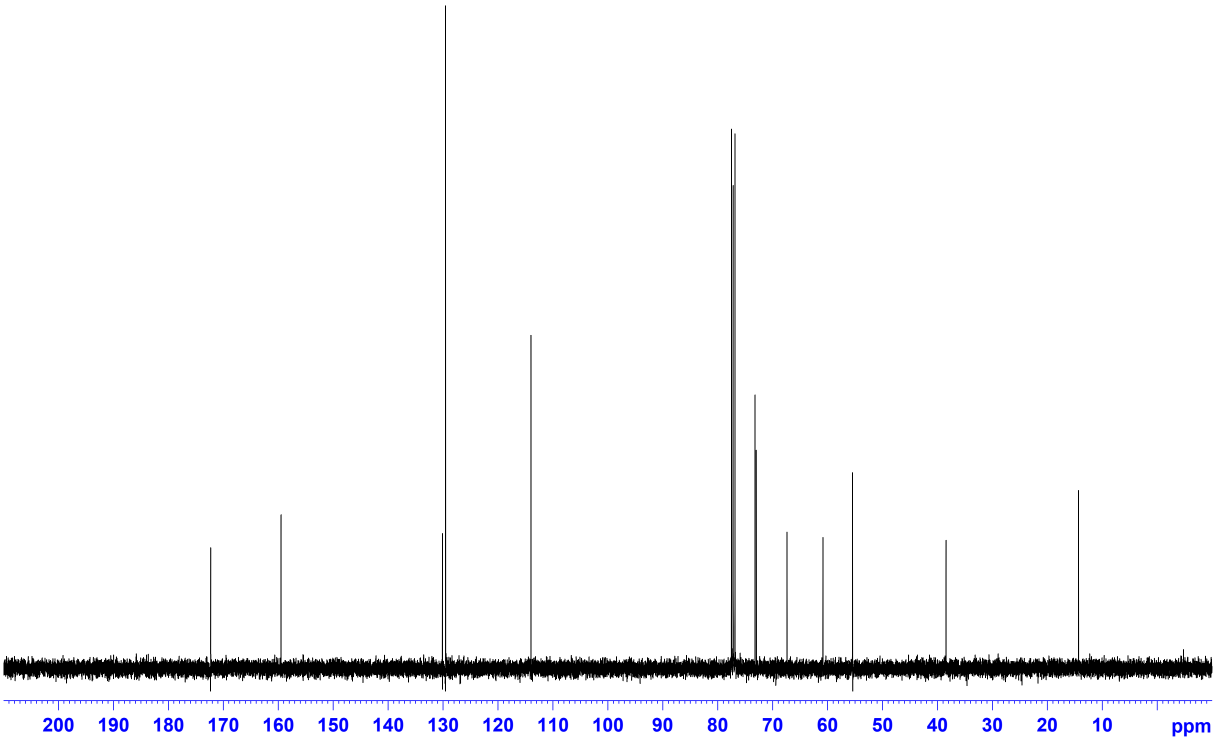
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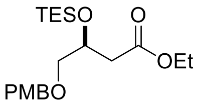
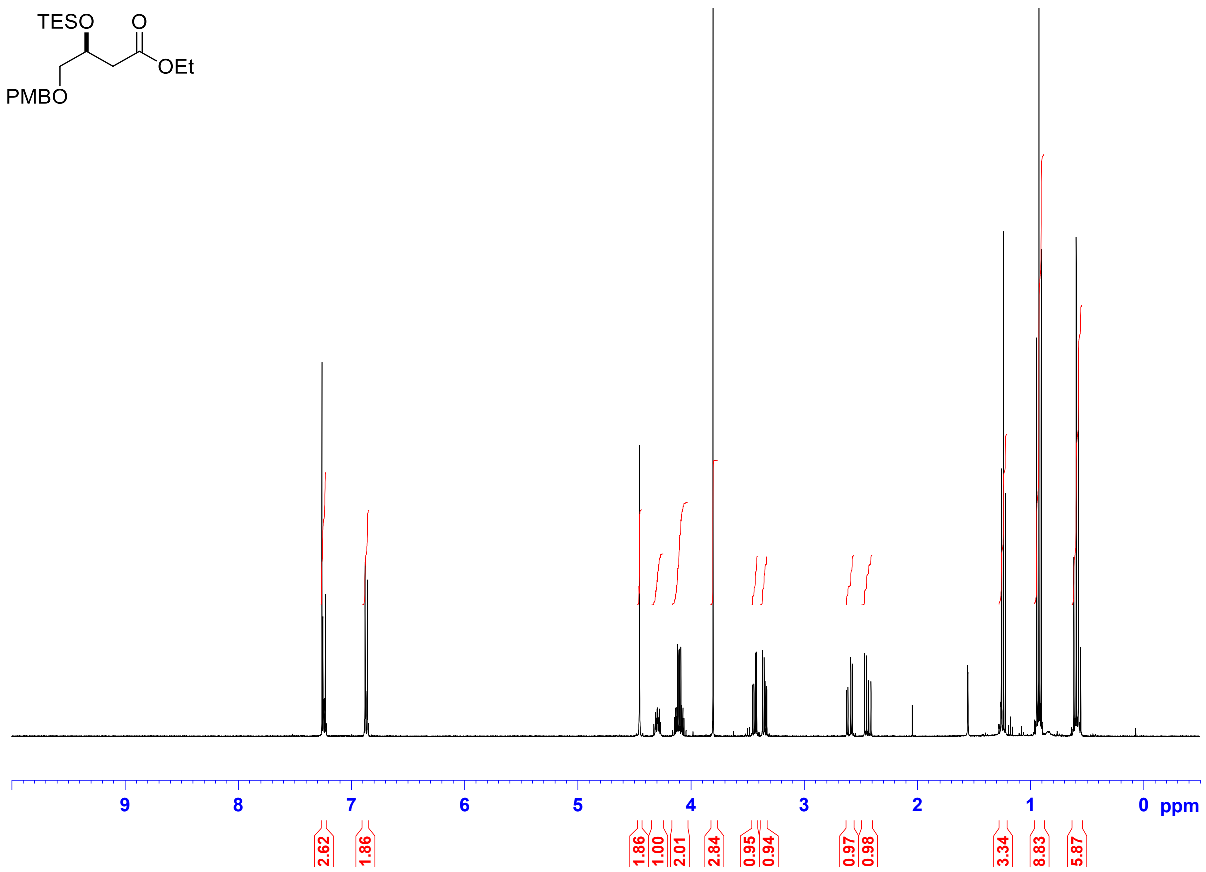
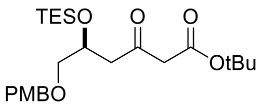


(*S*)-Ethyl 4-((4-methoxybenzyl)oxy)-3-((triethylsilyl)oxy)butanoate (7). To a solution of **6** (0.95 g, 3.54 mmol, 1.0 equiv) in dry DMF (3 mL) was added ImH (0.29 g, 4.25 mmol, 1.2 equiv) followed by TESCl (0.66 mL, 3.89 mmol, 1.1 equiv) at 0 °C. Stirring was continued for 15 min at the temperature followed by stirring at room temperature for another 1 h. MeOH (5 mL) was added and stirring was continued for 5 min more then the solution was added to H_2O (10 mL) followed by addition of Et_2O. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure followed by purification using flash chromatography (EtOAc/Hex 1:20) to give **7** (1.12 g, 2.92 mmol, 83%) as a colorless oil.

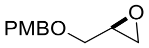
TLC: R_f = 0.67 (EtOAc/Hex 1:3, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.27-7.22 (m, 2 H), 6.89-6.86 (m, 2 H), 4.49 (s, 2 H), 4.33-4.27 (m, 1 H), 4.16-4.04 (m, 2 H), 3.80 (s, 3 H), 3.44 (dd, *J* = 9.6, 5.3, 1 H), 3.35 (dd, *J* = 9.6, 6.2, 1 H), 2.60 (dd, *J* = 15.1, 4.8, 1 H), 2.52 (dd, *J* = 15.1, 7.8, 1 H), 1.26 (t, *J* = 7.2, 3 H), 0.92 (t, *J* = 8.0, 9 H), 0.62-0.55 (m, 6 H).





(*S*)-*tert*-Butyl 6-((4-methoxybenzyl)oxy)-3-oxo-5-((triethylsilyl)oxy)hexanoate (14). To a solution of *i*-Pr$_2$NH (0.038 mL, 0.29 mmol, 2.2 equiv) in THF (0.5 mL) was added *n*-BuLi (1.6M, 0.18 mL, 0.29 mmol, 2.2 equiv) at 0 °C. The solution was then stirred for 30 min at 10 °C and then cooled to –78 °C followed by addition of *t*-BuOAc (0.039 mL, 0.287 mmol, 2.2 equiv). The flask was immersed into an icebath (0 °C), stirred for 5 min and then placed again into a bath at –78 °C. Stirring was continued for 30 min then a solution of **7** (50 mg, 0.13 mmol, 1 equiv) in THF (0.3 mL) was slowly added. The temperature was then allowed to warm to –40 °C and stirring was continued for 30 min. Saturated aqueous NH$_4$Cl (10 mL) was added as well as EtOAc then the phases were separated followed by extraction of the aqueous phase with EtOAc (3 x 15 mL). The combined organic phases were dried over MgSO$_4$, concentrated under reduced pressure and then purified using flash chromatography (EtOAc/Hex 1:15) which gave **14** (150.6 mg, 0.33 mmol, 75%) as a dark oil along with unidentified impurities. Analytical data are given in comparison with a related structure.[14]

TLC: $R_f = 0.16$ (EtOAc/Hex 1:10, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): $\delta = 7.25$-7.21 (m, 2 H), 6.88-6.85 (m, 2 H), 4.43 (s, 2 H), 4.35-4.29 (m, 1 H), 3.80 (s, 3 H), 3.40 (dd, *J* = 9.6, 5.1, 1 H), 3.35 (s, 2 H), 3.33 (dd, *J* = 9.6, 5.8, 1 H), 2.76 (dd, *J* = 15.9, 5.4, 1 H), 2.68 (dd, *J* = 15.9, 7.0, 1 H), 1.46 (s, 9 H), 0.94-0.89 (m, 9 H), 0.64-0.55 (m, 6 H).



(*S*)-2-((4-Methoxybenzyloxy)methyl)oxirane (17).[15] To a suspension of NaH (60% in mineral oil, 0.73 g, 18.07 mmol, 1.20 equiv) in dry DMF (15 mL) at 0 °C was added a solution of (*R*)-glycidol (1.16 g, 15.06 mmol, 1.00 equiv) in DMF (2 mL). After stirring for 30 min at 0 °C 4-methoxybenzyl chloride (2.83 g, 18.07 mmol, 1.20 equiv) was added slowly followed by a spatula tip of TBAI and the mixture was allowed to warm to room temperature. After 20 h H_2O (20 mL) was added carefully followed by EtOAc (10 mL); the phases were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure, and the residue was purified by flash chromatography (EtOAc/Hex 1:10→1:5→1:3) to give **17** (2.24 g, 11.5 mmol, 76%) as a colorless oil.

TLC: $R_f = 0.31$ (EtOAc/Hex 1:3, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): $\delta = 7.29$-7.26 (m, 2 H), 6.90-6.86 (m, 2 H), 4.54 (d, *J* = 11.6, 1 H), 4.49 (d, *J* = 11.6, 1 H), 3.81 (s, 3 H), 3.73 (dd, *J* = 11.4, 3.1, 1 H), 3.42 (dd, *J* = 11.4, 5.8, 1 H), 3.19-3.15 (m, 1 H), 2.79 (dd, *J* = 5.0, 4.2, 1 H), 2.60 (dd, *J* = 5.1, 2.7, 1 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): $\delta = 159.5$, 130.1, 129.6, 114.0, 73.1, 70.7, 55.4, 51.0, 44.5. **IR** (thin film): $\tilde{\nu} = 2999$, 2934, 2836, 1731, 1612, 1512, 1464, 1384, 1301, 1244, 1174, 1086, 1031, 818 cm^{-1}. **HRMS** (EI): calcd for $C_{11}H_{14}O_3$ $[(M)^+]$: 194.0937; found: 197.0938. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –5.98° (c 0.98, $CHCl_3$).

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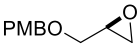
[14] For transformation and analytical data of a similar compound, see: G. Beck, H. Jendralla, K. Kesseler, *Synthesis* **1995**, *1995*, 1014–1018.

[15] The reaction works also in THF but in lower yields (up to 54%). For synthetic procedure and analytical data, see: K. C. Nicolaou, K. C. Fylaktakidou, H. Monenschein, Y. Li, B. Weyershausen, H. J. Mitchell, H.-x. Wei, P. Guntupalli, D. Hepworth, K. Sugita, *J. Am. Chem. Soc.* **2003**, *125*, 15433-15442.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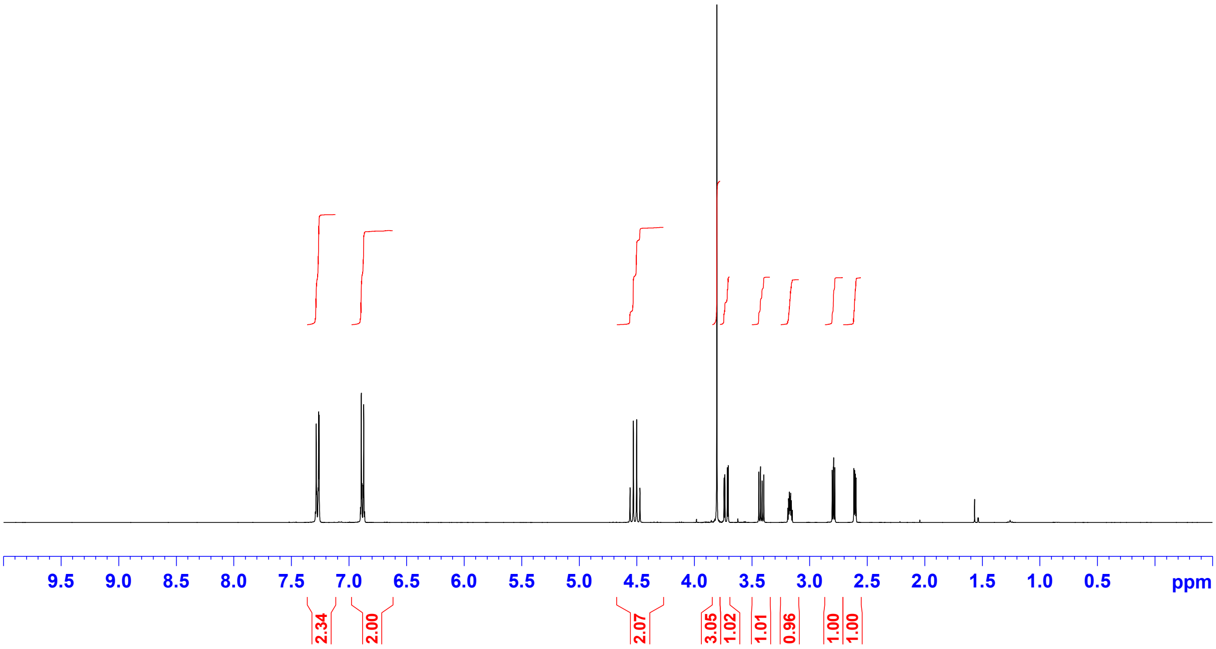
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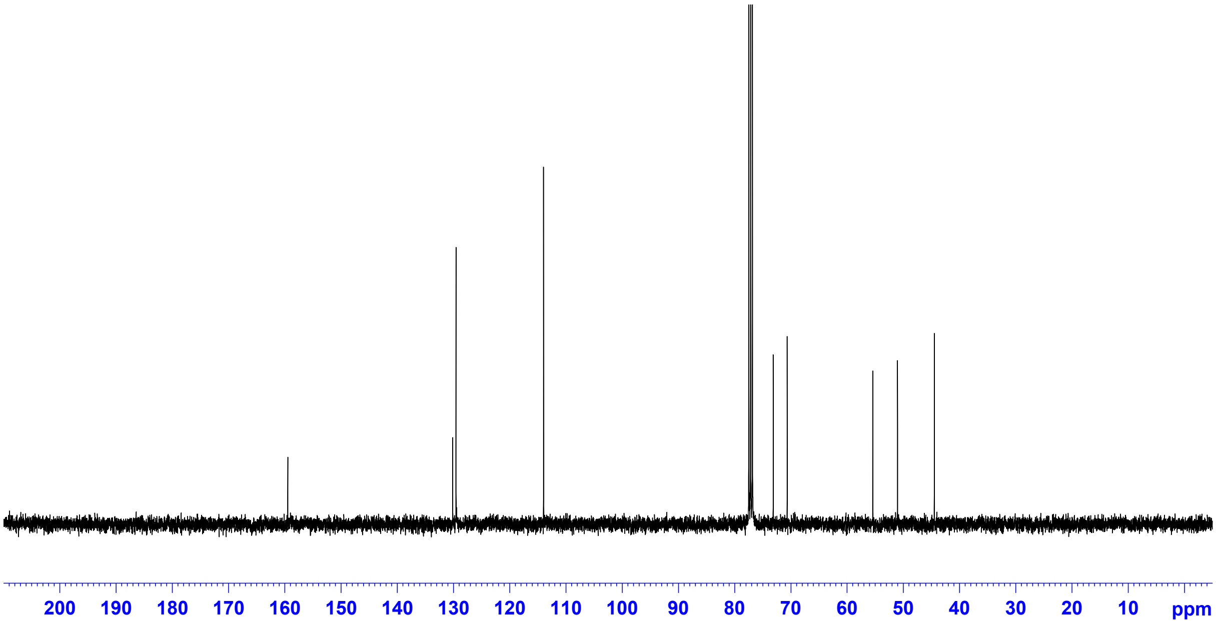
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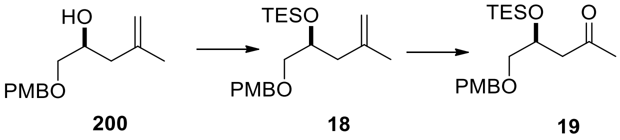
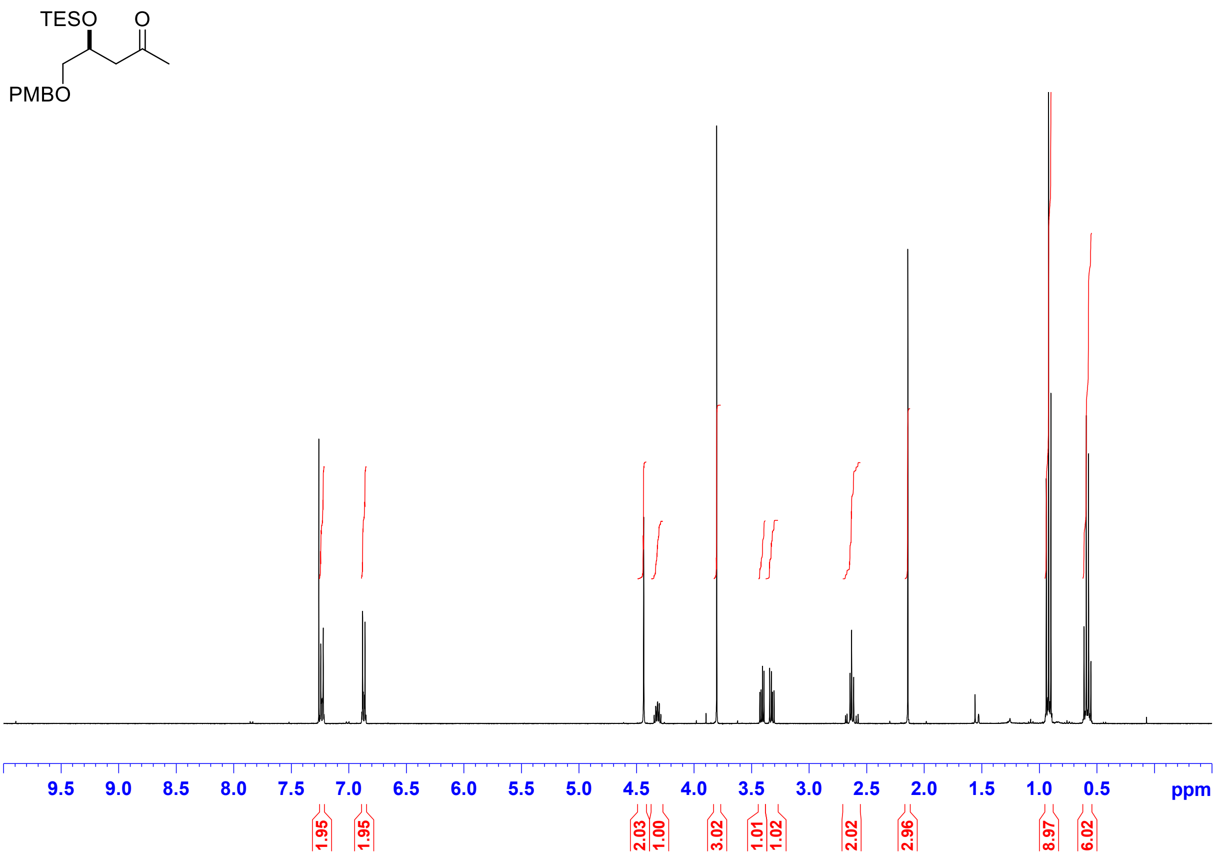


(*S*)-5-((4-Methoxybenzyl)oxy)-4-((triethylsilyl)oxy)pentan-2-one (19). To a solution of secondary alcohol **200** (1.0 g, 4.24 mmol, 1 equiv) in dry DMF (3 mL) at 0 °C was added ImH (0.35 g, 5.12 mmol, 1.2 equiv) followed by TESCl (0.79 mL, 4.65 mmol, 1.1 equiv). Stirring was continued for 15 min then the cooling bath was removed and stirring was continued at room temperature for another 45 min. MeOH (0.05 mL) was added and after 10 min more, the solution was added to H_2O (10 mL) followed by addition of Et_2O (ca. 20 ml). The phases were separated followed by extraction of the aqueous phase with Et_2O (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 10 mL) and once with brine (10 mL) then dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:10) afforded **18** (1.39 g, 3.695 mmol, 94%) as a pale-yellow oil.

To a solution of **18** (95.1 mg, 0.27 mmol, 1 equiv) in acetone (3 mL) was added H_2O (0.6 mL). NMO (41.3 mg, 0.35 mmol, 1.3 equiv) was added followed by a solution of OsO_4 (2.5% in *t*-BuOH, 0.15 mL, 0.027 mmol, 0.1 equiv) at room temperature and stirring was continued for 4 h. $NaIO_4$ (143 mg, 0.67 mmol, 2.47 equiv) was added followed by H_2O (0.5 mL) and stirring was continued at room temperature for 12 h. The reaction mixture was then poured in H_2O (20 mL), followed by addition of Et_2O (ca. 10 mL) and separation of phases. The aqueous phase was extracted with Et_2O (3 x 10 mL) then the combined organic phases were washed with saturated aqueous $Na_2S_2O_3$ (10 mL) and once brine (10 mL) then dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:10) gave **19** (81.3 mg, 0.23 mmol, 85%) as a dark oil.

TLC: R_f = 0.53 (EtOAc/Hex 1:3, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.25-7.21 (m, 2 H), 6.89-6.85 (m, 2 H), 4.44 (s, 2 H), 4.35-4.29 (m, 1 H), 3.80 (s, 3 H), 3.41 (dd, *J* = 9.7, 4.9, 1 H), 3.33 (dd, *J* = 9.7, 5.9, 1 H), 2.68-2.58 (m, 2 H), 2.14 (s, 3 H), 0.92 (t, *J* = 7.9, 9 H), 0.58 (q, *J* = 7.9, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 207.6, 159.3, 130.4, 129.4, 113.9, 74.0, 73.1, 68.1, 55.4, 48.9, 31.6, 6.9, 5.0.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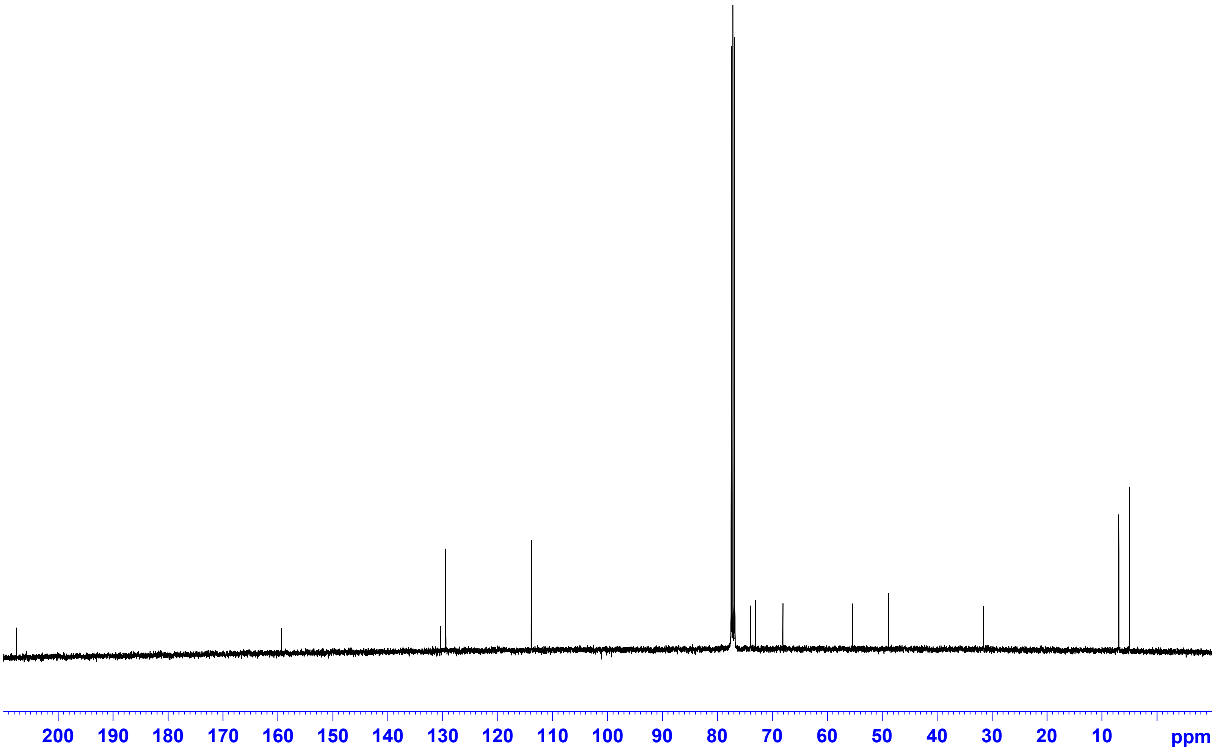
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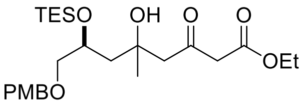
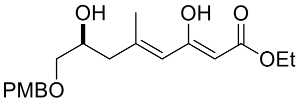


(7*S*)-Ethyl 5-hydroxy-8-((4-methoxybenzyl)oxy)-5-methyl-3-oxo-7-((triethylsilyl)oxy) octanoate (24). To a suspension of NaH (60%, 4.1 mg, 0.168 mmol, 1.17 equiv) in dry THF (0.5 mL) was added ethyl acetoacetate (0.021 mL, 0.16 mmol, 1.1 equiv) at –30 °C and stirring was continued for 15 min. A solution of *n*-BuLi (1.6M, 0.11 mL, 0.168 mmol, 1.17 equiv) was added and stirring was continued for 15 min more. A solution of **19** (51.1 mg, 0.145 mmol, 1.0 equiv) in dry THF (0.2 mL) was added dropwise then stirring was continued for 3 h at that temperature. HCl (2N, 2mL) was added followed by Et_2O (5 mL) then the mixture was allowd to warm to room temperature and the phases were separated. The organic phase was washed with H_2O (3 x 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:5) afforded **24** (22.1 mg, 0.045 mmol, 29%) as a pale-yellow oil.

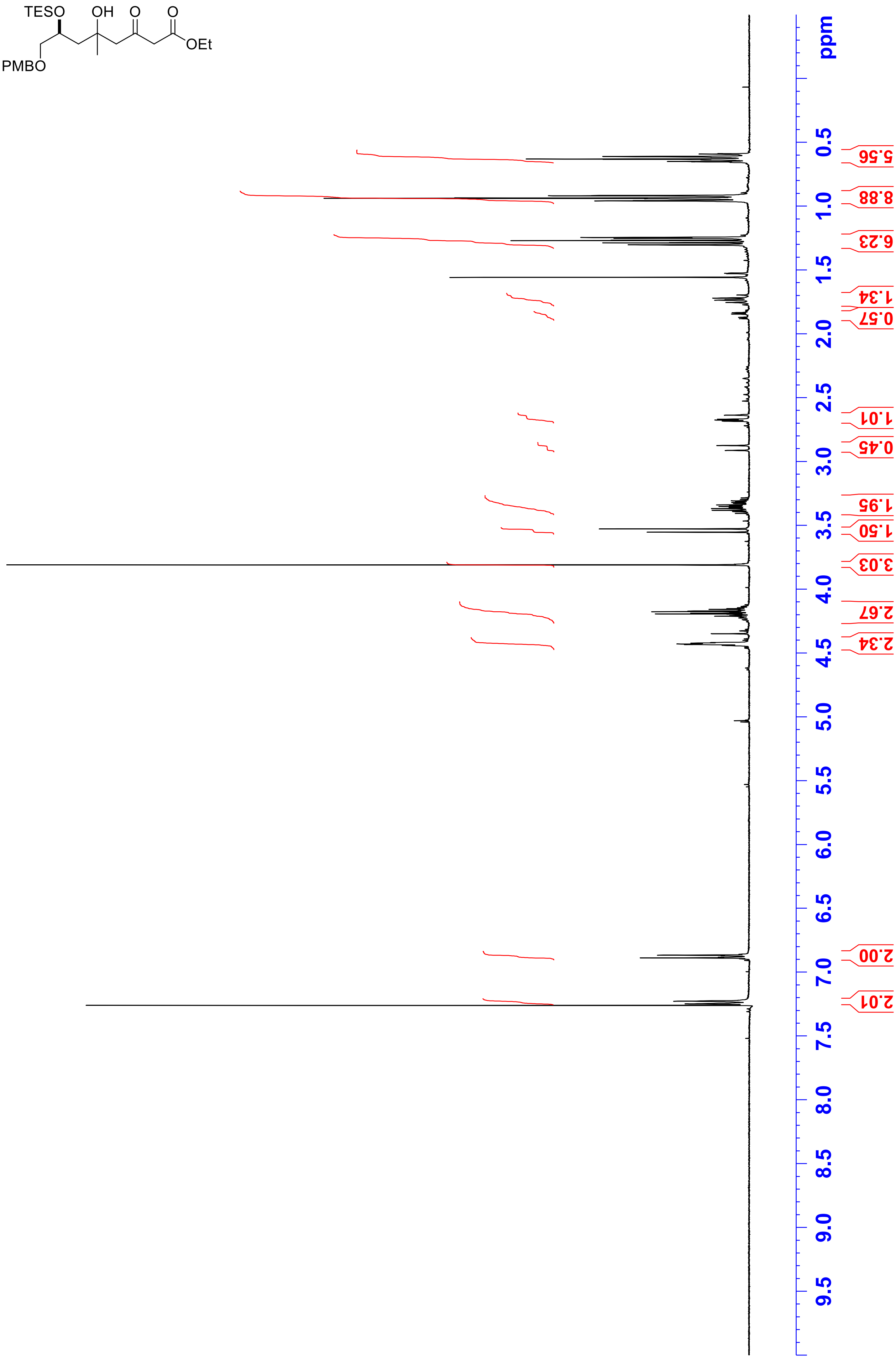
TLC: R_f = 0.36 (EtOAc/Hex 1:3, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.25-7.22 (m, 2 H), 6.89-6.86 (m, 2 H), 4.46-4.39 (m, 2 H), 4.24-4.14 (m, 3 H), 3.81 (s, 3 H), 3.54 (d, *J* = 10.3, 1.5 H), 3.41-3.29 (m, 2 H), 2.90 (d, *J* = 15.0, 0.45 H), 2.69-2.64 (m, 1 H), 1.86 (dd, *J* = 14.5, 4.1, 0.5 H), 1.77-1.70 (m, 1 H), 1.30-1.25 (m, 6 H), 0.96-0.92 (m, 9 H), 0.66-0.60 (m, 6 H).



(S,2Z,4E)-Ethyl 3,7-dihydroxy-8-((4-methoxybenzyl)oxy)-5-methylocta-2,4-dienoate (25). To a solution of **24** (6 mg, 0.012 mmol, 1 equiv) in dry CH_2Cl_2 (0.5 mL) was added NEt_3 (3.4 µL, 0.025 mmol, 2.05 equiv) at 0 °C followed by MsCl (1.2 µL, 0.015 mmol, 1.2 equiv). The cooling bath was removed then the solution was stirred at room temperature for 12 h, then more NEt_3 (1.7 µL, 0.013 mmol, 1 equiv) was added and stirring was continued for 18 h more. The solution was heated to 50 °C and stirring was continued for 1 d, then the solution was allowed to cool to RT followed by addition of saturated aqueous NH_4Cl (1 mL). The phases were separated then the aqueous phase was extracted with Et_2O (3 x 5 mL), the combined organic phases were dired over $MgSO_4$ and concentrated under reduced pressure.

Purification using flash chromatography (EtOAc/Hex 1:10) afforded **25** (1.7 mg, 0.005 mmol, 40%) as an oil. According to ^{1}H-NMR analysis, **25** exclusively exists as the enol tautomer.

TLC: R_f = 0.46 (EtOAc/Hex 1:5, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.29-7.28 (m, 1 H), 7.27-7.25 (m, 2 H), 6.91-6.87 (m, 2 H), 5.20 (s, 1 H), 4.53 (s, 2 H), 4.20-4.15 (m, 1 H), 4.13 (q, *J* = 7.2, 2 H), 3.80 (s, 3 H), 3.62 (dd, *J* = 10.4, 5.4, 1 H), 3.56 (dd, *J* = 10.4, 4.8, 1 H), 2.40-2.33 (m, 1 H), 2.15 (dd, *J* = 17.7, 4.0, 1 H), 1.93 (s, 3 H), 1.26 (t, *J* = 7.2, 3 H).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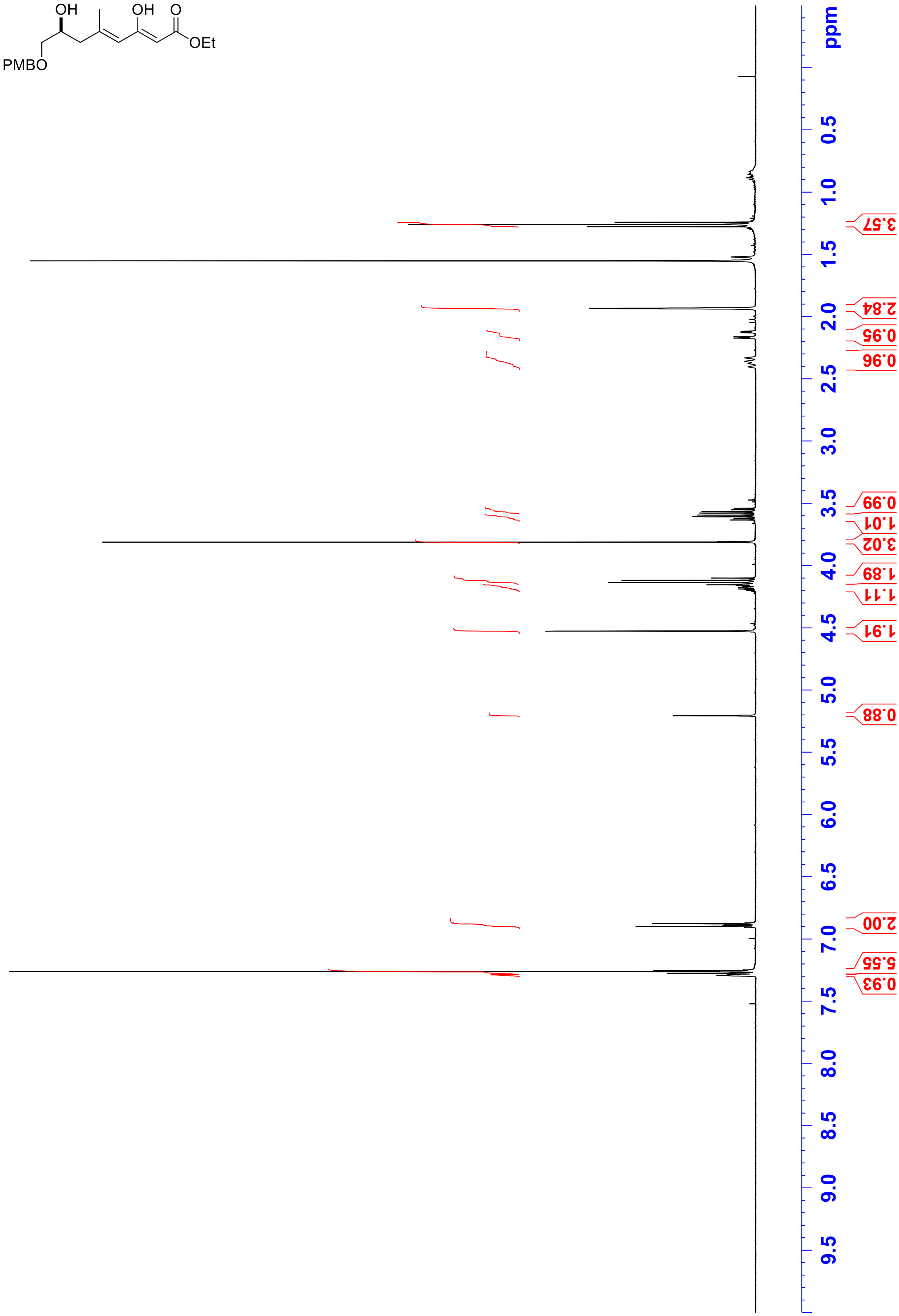
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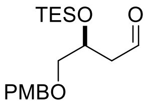
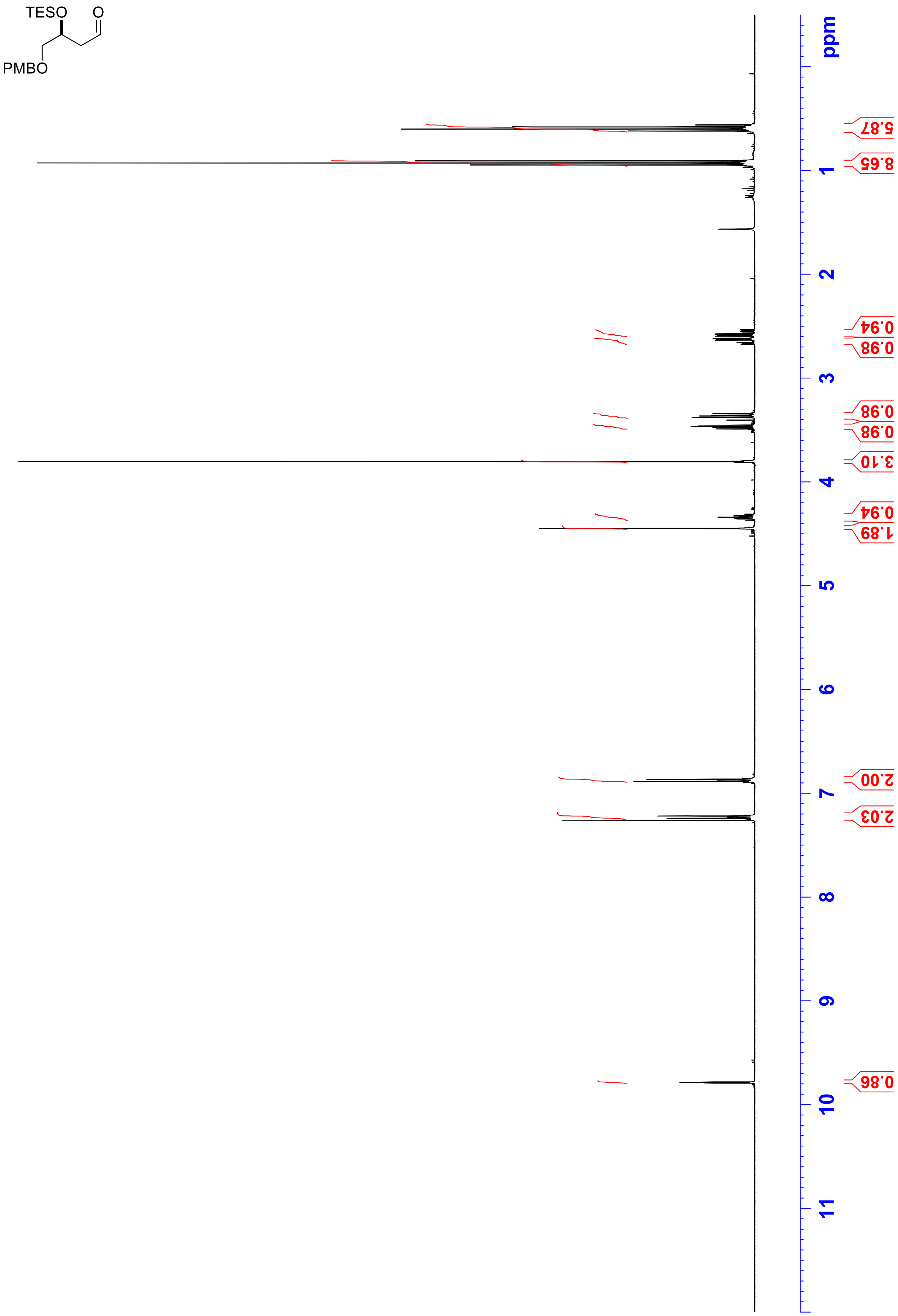


(*S*)-4-((4-Methoxybenzyl)oxy)-3-((triethylsilyl)oxy)butanal (26). To a solution of **7** (0.5 g, 1.3 mmol, 1 equiv) in dry toluene (10 mL) was added a solution of DIBAL-H (1M in toluene, 1.32 ml, 1.32 mmol, 1.01 equiv) slowly over 15 min at –80 °C. After all reagent was added, another portion of DIBAL-H (0.4 mL) was added. Immediately after this, MeOH (ca. 5 mL) was added then the reaction mixture was allowed to warm to room temperature. Et_2O (10 mL) was added followed by NaOH (0.5M, 10 mL). After separation of phases, the aqueous phase was extracted with Et_2O (3 x 10 mL) then the combined organic phases were washed sequentially with NaOH (0.5M, 10 mL), H_2O (10 mL) and brine (10 mL). Drying over $MgSO_4$, concentration under reduced pressure and purification using flash chromatography (EtOAc/Hex 1:6) afforded **26** (417.8 mg, 1.23 mmol, 95%) as a colorless oil.

TLC: R_f = 0.46 (EtOAc/Hex 1:5, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.78 (dd, *J* = 2.5, 2.4, 1 H), 7.25-7.21 (m, 2 H), 6.89-6.85 (m, 2 H), 4.45 (s, 2 H), 4.37-4.31 (m, 1 H), 3.80 (s, 3 H), 3.47 (dd, *J* = 9.5, 5.0, 1 H), 3.36 (dd, *J* = 9.5, 6.4, 1 H), 2.65 (ddd, *J* = 16.0, 5.3, 2.3, 1 H), 2.57 (ddd, *J* = 16.0, 6.6, 2.6, 1 H), 0.92 (t, *J* = 8.0, 9 H), 0.62-0.56 (m, 6 H).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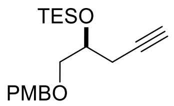
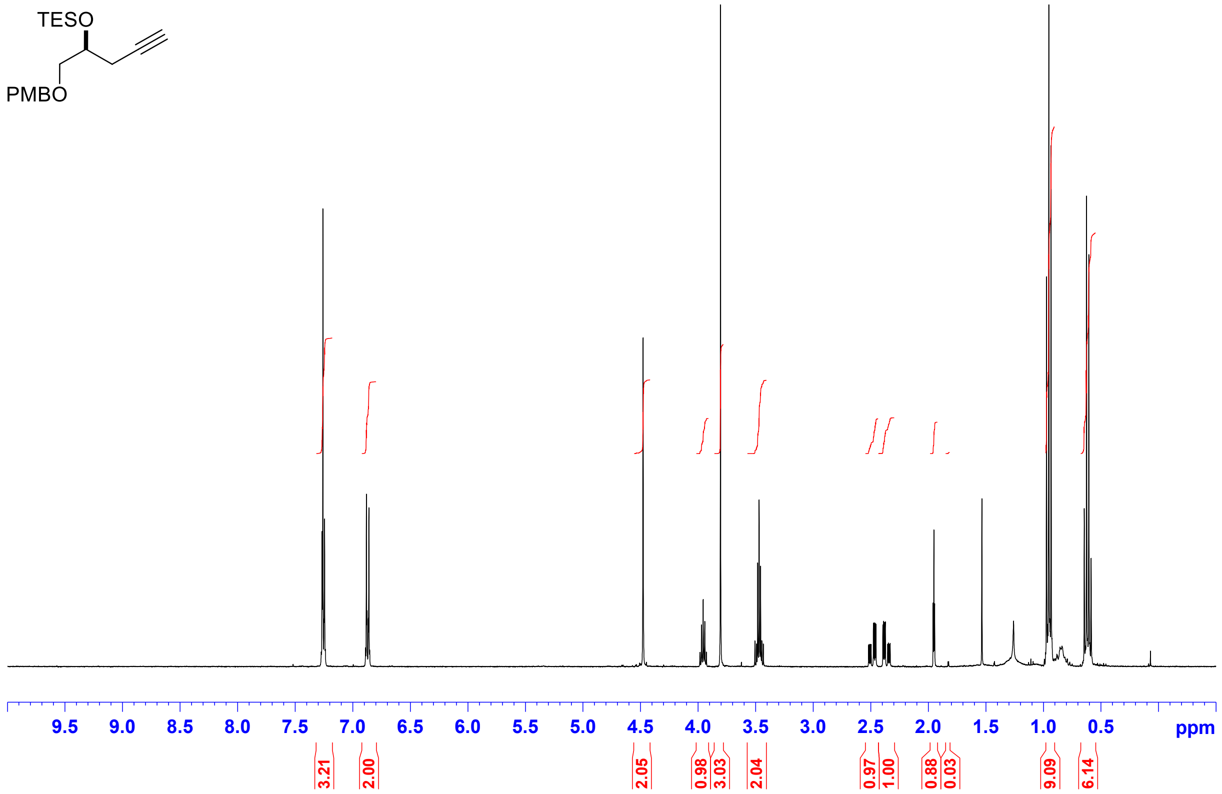


(*S*)-Triethyl((1-((4-methoxybenzyl)oxy)pent-4-yn-2-yl)oxy)silane (A).[234] To a solution of the epoxide **17** (232.7 mg, 1.20 mmol, 1 equiv) in dry DMSO (1 mL) and dry THF (1 mL) was added LiCCH•EDA (256 mg, 2.4 mmol, 2 equiv) in one portion at –2 °C (ice/NaCl). Stirring was continued for 1 h at room temperature then ice and HCl (2N) were carefully added. The mixture was filtered over Celite followed by separation of phases then the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure followed by purification using flash chromatography (EtOAc/Hex 1:3) to give the secondary alcohol (218.7 mg, 0.99 mmol, 83%) as a pale-yellow oil.

To a solution of secondary alcohol (203.6 mg, 0.923 mmol, 1 equiv) in dry CH_2Cl_2 (3 mL) at –78 °C was added 2,6-dimethylpyridine (0.16 mL, 1.39 mmol, 1.5 equiv) followed by TESOTf (0.27 mL, 1.2 mmol, 1.3 equiv). Stirring was continued for 1 h then MeOH (2 mL) was added and after 10 min more, saturated aqueous NH_4Cl (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure followed by purification using flash chromatography (EtOAc/Hex 1:20) to give **A** (293.6 mg, 0.88 mmol, 95%) as a colorless oil.

TLC: R_f = 0.65 (EtOAc/Hex 1:10, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.27-7.24 (m, 2 H), 6.89-6.85 (m, 2 H), 4.48 (s, 2 H), 3.96 (q, *J* = 5.5, 1 H), 3.81 (s, 3 H), 3.47 (ddd, *J* = 14.5, 9.7, 5.4, 2 H), 2.48 (ddd, *J* = 16.9, 6.1, 2.6, 1 H), 2.36 (ddd, *J* = 16.8, 5.9, 2.8, 1 H), 1.95 (t, *J* = 2.6, 1 H), 0.95 (t, *J* = 7.9, 9 H), 0.62 (q, *J* = 7.9, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.3, 130.6, 129.4, 113.9, 81.5, 73.3, 73.2, 70.2, 70.0, 55.5, 24.9, 6.9, 5.0.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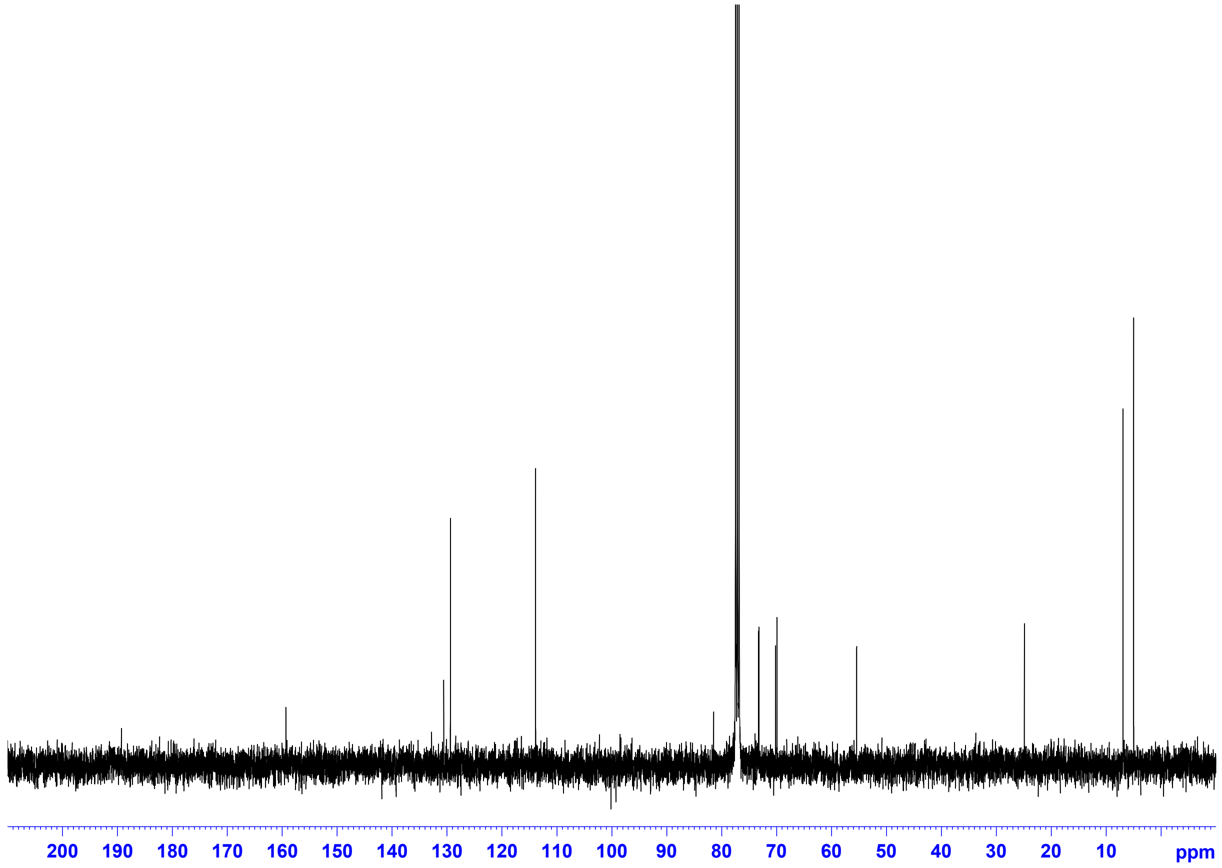
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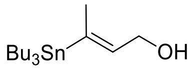
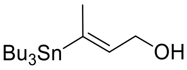


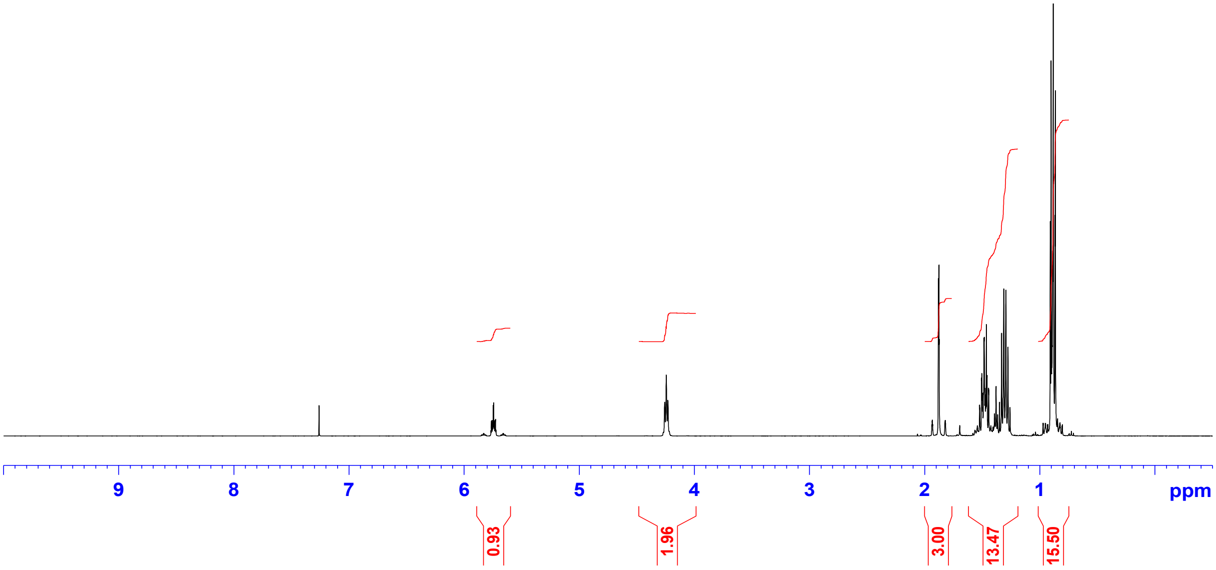
(*Z*)-3-(Tributylstannyl)but-2-en-1-ol (30).[144b] To a suspension of CuCN (2.37 g, 26.5 mmol, 2.0 equiv) in THF (100 mL) at –78 °C was added a solution of *n*-BuLi (1.6M in hexane, 33.2 mL, 53.07 mmol, 4.0 equiv). After 5 min the flask was immersed in a cooling bath at –40 °C and kept at this temperature for 10 min. The almost clear solution was then re-cooled to –78 °C, producing a slightly heterogenous mixture, and Bu_3SnH (14.3 mL, 53.07 mmol, 4.0 equiv) was added dropwise, resulting in the immediate formation of a yellow turbid solution with liberation of some gas. After 10 min at –78 °C the mixture was stirred for 5 min at –40 °C, giving an almost clear golden-yellow solution, and then re-cooled to –78 °C. MeOH (59 mL, 1.46 mol, 110.0 equiv) was added under vigorous stirring, the mixture was stirred for 10 min at –78 °C then warmed to –40 °C and kept there for 15 min, which afforded a clear red solution. This solution was re-cooled to –78 °C followed by addition of 2-butyne-1-ol (1 mL, 13.27 mmol, 1.0 equiv) then stirring was continued at that temperature for 10 h then the flask was immersed into a cooling bath of –10 °C and stirring was continued for 1 h more. MeOH (20 mL) was added and after 5 min, the mixture was added to a stirred mixture of saturated aqueous NH_4Cl (400 mL) and 25% aqueous NH_4OH (40 mL) then stirring was continued for 20 min leading to two clear phases. The phases were separated then the aqueous phase was extracted with EtOAc (3 x 50 mL), the combined organic extracts were dried over $MgSO_4$ followed by concentration under reduced pressure. Purification of the residue by flash chromatography on deactivated silica (Hex→EtOAc/Hex 1:10, 1%(v/v) NEt_3) gave **30** (3.8 g, 10.53 mmol, 79%) as a pale-yellow oil. This material was immediately used in the next step.

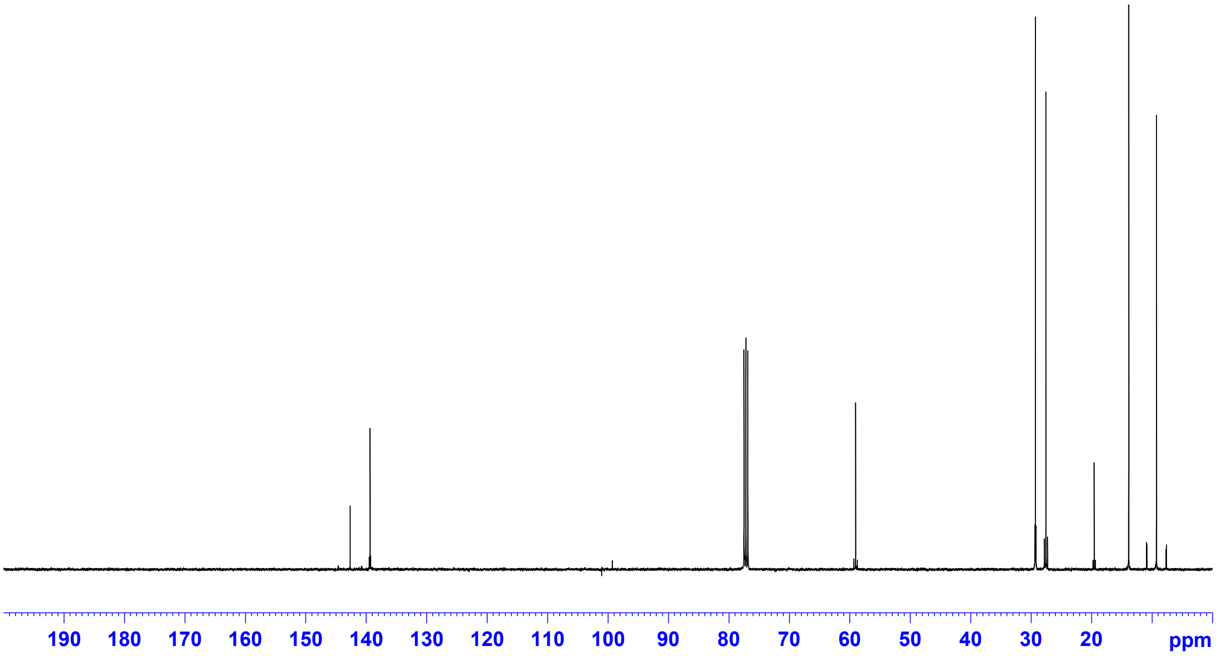
Note: 2-butyne-1-ol can also be added at –40 °C to the cuprate solution followed by performing the reaction at –10 °C which gives full conversion within 1 h in similar yield for **30**.

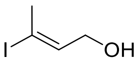
TLC: R_f = 0.44 (EtOAc/Hex 1:5, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.75 (tq, *J* = 6.7, 1.9, *J* ^{1}H-^{117}Sn = *J* ^{1}H-^{119}Sn = 67.5, 1 H), 4.25 (t, *J* = 5.9, 2 H), 1.89-1.88 (m, ^{1}H-^{117}Sn = *J* ^{1}H-^{119}Sn = 44.9, 3 H), 1.57-1.46 (m, 7 H), 1.36-1.27 (m, 6 H), 0.92-0.87 (15 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 142.7, 139.4, 59.1, 29.3 (*J* ^{13}C-^{117}Sn = *J* ^{13}C-

^{119}Sn = 19.8), 27.5 (J ^{13}C-^{117}Sn = J ^{13}C-^{119}Sn = 55.0), 19.5, 13.8, 9.2. **IR** (thin film): $\tilde{\nu}$ = 3298, 2955, 2923, 2871, 2852, 1463, 1376, 1059, 1003, 874, 865 cm^{-1}. **HRMS** (EI): calcd for $C_{12}H_{25}OSn$ [(M–C_4H_9)$^+$]: 305.0922; found: 305.0921.



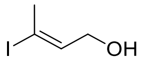






(*E*)-3-Iodobut-2-en-1-ol (31). To a solution of **30** (7.41 g, 20.5 mmol, 1.0 equiv) in THF (100 mL) at –78 °C was added a solution of iodine (6.25 g, 24.6 mmol, 1.2 equiv) in THF (100 mL) dropwise via an addition funnel. The resulting orange-brown solution was stirred at –78 °C for 10 min before it was warmed to room temperature where saturated aqueous $Na_2S_3O_3$ (100 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added. Phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). Saturated aqueous KF (50 mL) was added to the combined organic phases, leading to the formation of a white precipitate. The mixture was vigorously stirred for 30 min and then filtered over a plug of celite, followed by elution with EtOAc. Phases were separated and the aqueous phase was extracted with EtOAc (1 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/Hex 1:5→1:3) afforded vinyl iodide **31** (3.83 g, 19.3 mmol, 94%) as a yellow oil.

TLC: R_f = 0.46 (EtOAc/Hex 1:3, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 6.41-6.37 (m, 1 H), 4.09-4.06 (m, 2 H), 2.45-2.44 (m, 3 H), 1.75-1.72 (m, 1 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 139.8, 98.6, 60.0, 28.1. **IR** (thin film): $\tilde{\nu}$ = 3298, 2916, 2872, 1636, 1423, 1376, 1218, 1096, 1059, 998 cm^{-1}. **HRMS** (EI): calcd for C_4H_7IO [M^+]: 197.9537; found: 197.9539.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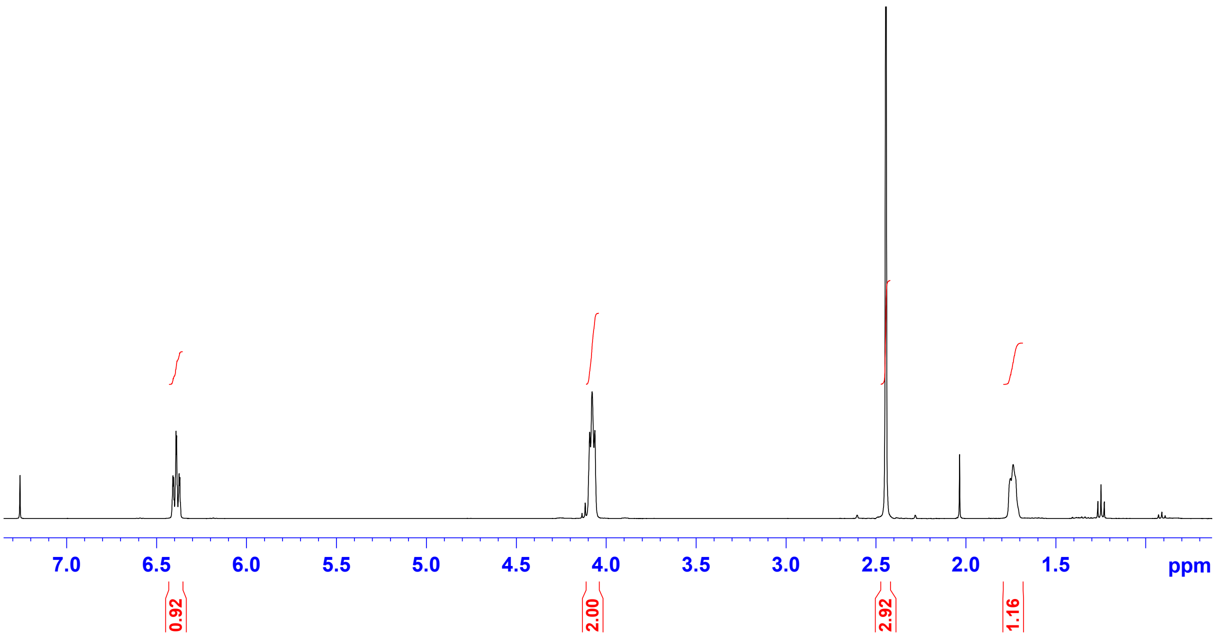
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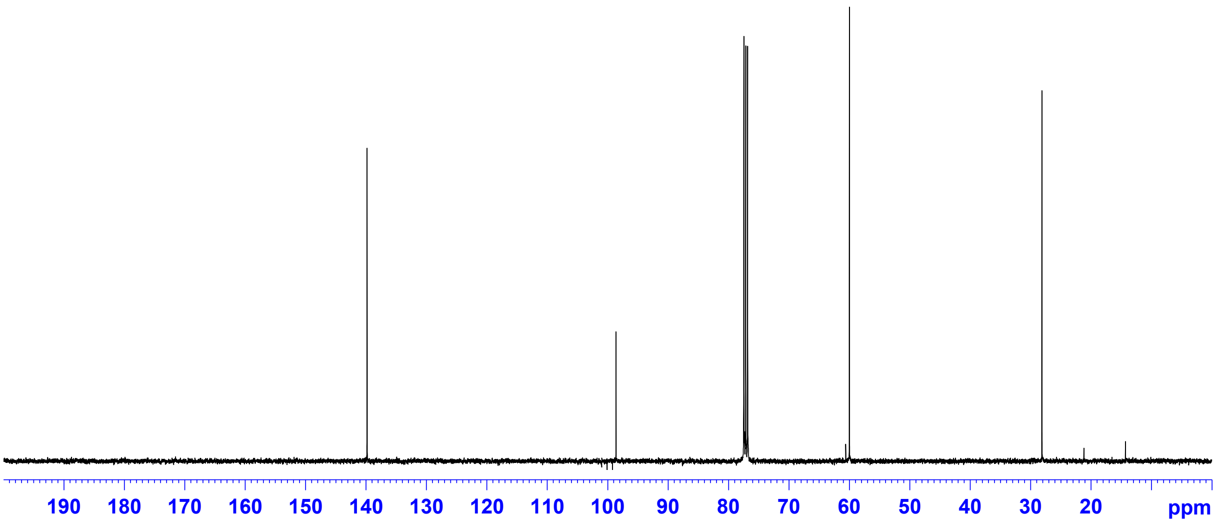
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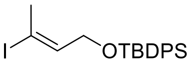
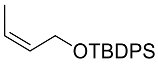


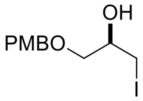
(*E*)-*tert*-Butyl((3-iodobut-2-en-1-yl)oxy)diphenylsilane (32).[19] To a solution of **31** (893 mg, 4.5 mmol, 1.0 equiv) in dry CH_2Cl_2 (20 mL) was added NEt_3 (0.81 mL, 5.85 mmol, 1.3 equiv) followed by TBDPSCl (1.28 mL, 4.96 mmol, 1.1 equiv) and a small amount (spatula tip) of DMAP at room temperature affording a complete soluition. Stirring was continued for 21 h then saturated aqueous $NaHCO_3$ (10 mL) was added followed by separation of phases and extraction with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:100→1:50) gave **32** (1.86 g, 4.27 mmol, 95%) as a colorless oil.

TLC: R_f = 0.81 (EtOAc/Hex 1:20, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.86-7.65 (m, 4 H), 7.46-7.37 (m, 6 H), 6.35 (tq, J = 6.6, 1.5, 1 H), 4.12 (dq, J = 6.5, 0.8, 2 H), 2.19-2.18 (m, 3 H), 1.05 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 140.3, 135.7, 133.6, 129.9, 127.9, 96.6, 61.5, 28.1, 26.9, 19.3.

Side products in the unsuccessful epoxide opening reaction (Scheme 33, page 50):



(*Z*)-(But-2-en-1-yloxy)(*tert*-butyl)diphenylsilane (33). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.71-7.67 (m, 4 H), 7.42-7.36 (m, 6 H), 5.66-5.58 (m, 1 H), 5.53-5.43 (m, 1 H), 4.28-4.25 (m, 2 H), 1.48-1.46 (m, 3 H), 1.05 (s, 9 H).



(*R*)-1-Iodo-3-((4-methoxybenzyl)oxy)propan-2-ol (35). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.27-7.24 (m, 2 H), 6.91-6.87 (m, 2 H), 4.49 (s, 2 H), 3.81 (s, 3 H), 3.80-3.74 (m, 1 H), 3.55 (d, J = 5.1, 2 H), 3.33 (dd, J = 10.2, 5.6, 1 H), 3.26 (dd, J = 10.2, 5.9, 1 H), 2.51 (d, J = 5.7, 1 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.6, 129.8, 129.6, 114.1, 73.3, 72.4, 70.1, 55.4, 9.5.

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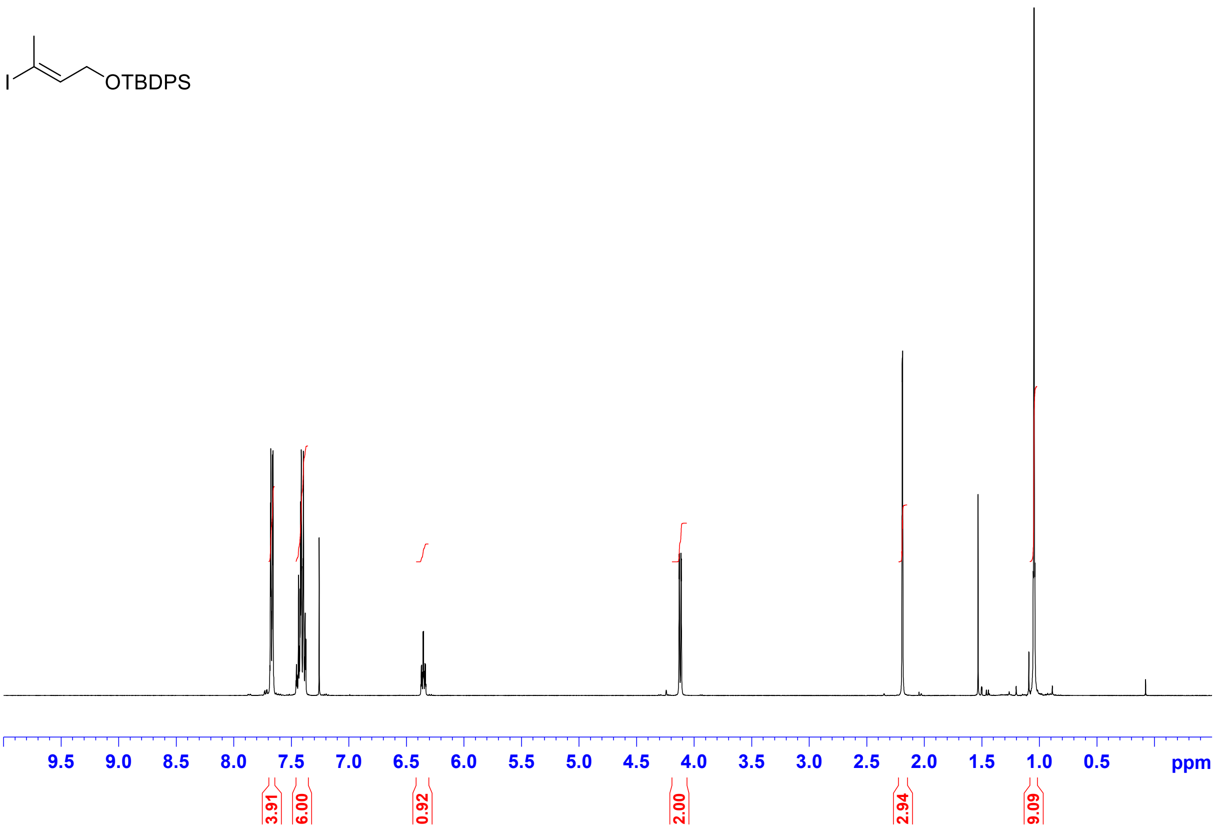
[19] For analytical data see also: J. Lee, J. S. Panek, *Org. Lett.* **2009**, *11*, 4390-4393.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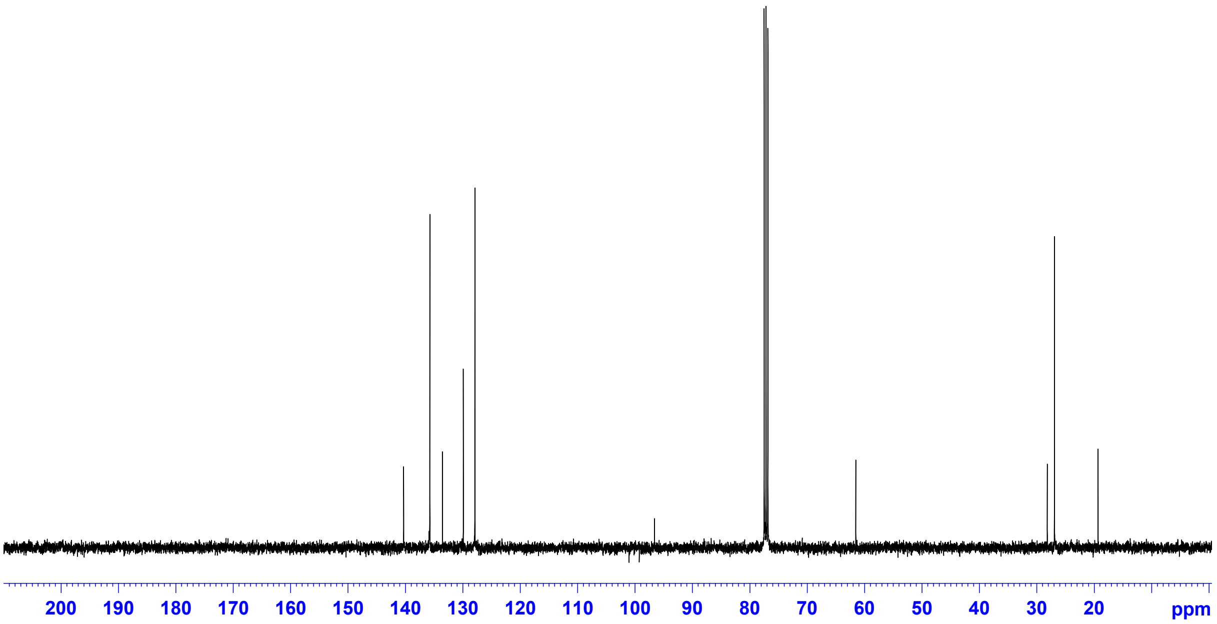
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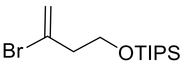
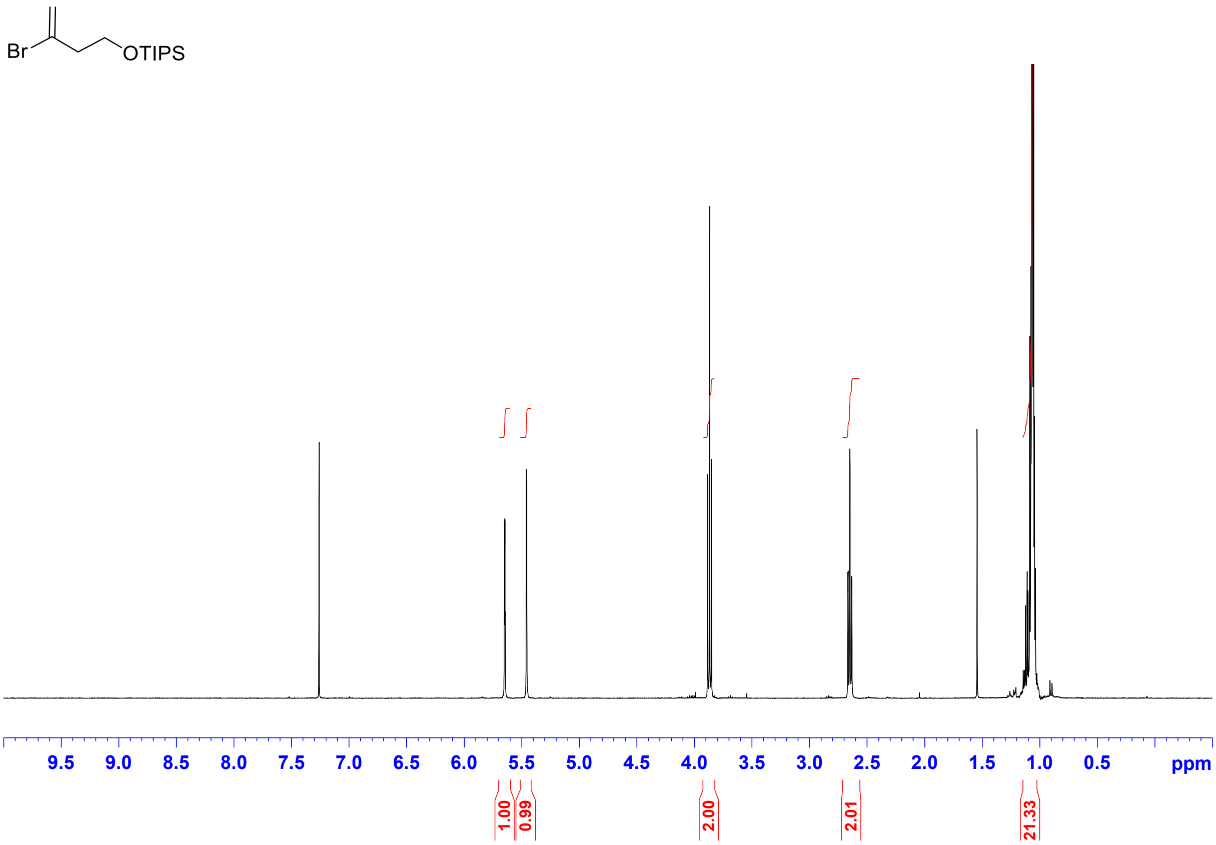


((3-Bromobut-3-en-1-yl)oxy)triisopropylsilane (43). To a solution of 3-bromo-3-butene-1-ol (0.2 mL, 2.01 mmol, 1.0 equiv) in dry CH_2Cl_2 (5 mL) at –78 °C was added 2,6-dimethylpyridine (0.35 mL, 3.02 mmol, 1.5 equiv) followed by TIPSOTf (0.59 mL, 2.2 mmol, 1.1 equiv). The solution was stirred for 1.5 h then allowed to warm to room temperatue. MeOH (5 mL) was added and stirring was continued for 10 min more. Saturated aqueous NH_4Cl (10 mL) and EtOAc (5 mL) were added followed by separation of phases and extraction with EtOAc (3 x 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:100→1:10) gave **43** (0.612 g, 1.99 mmol, 99%) as a colorless oil.

TLC: $R_f = 0.94$ (EtOAc/Hex 1:3, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): $\delta = 5.65$ (q, J = 1.3, 1 H), 5.46 (d, J = 1.5, 1 H), 3.89 (t, J = 6.4, 2 H), 2.65 (dt, J = 6.4, 1.0, 2 H), 1.14-1.04 (m, 21 H).**^{13}C-NMR** (100 MHz, $CDCl_3$): $\delta = 131.0$, 118.5, 61.4, 45.1, 18.1, 12.1.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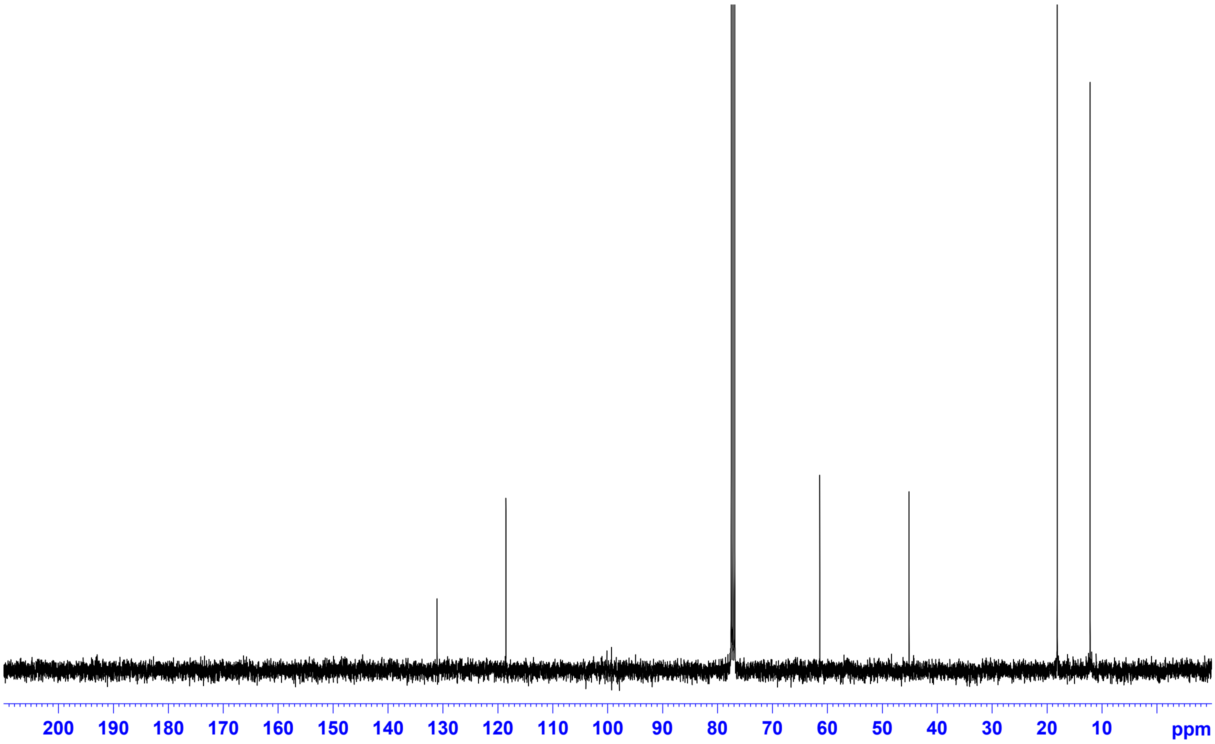
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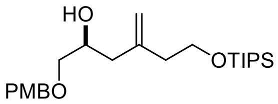
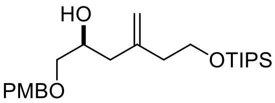


(*S*)-1-((4-Methoxybenzyl)oxy)-4-methylene-6-((triisopropylsilyl)oxy)hexan-2-ol (44). To a solution of **43** (190 mg, 0.62 mmol, 1.21 equiv) in dry THF (4 mL) was added a solution of *n*-BuLi (1.6M in hexane, 0.39 mL, 0.62 mmol, 1.2 equiv) at –78 °C and stirring was continued for 30 min at that temperature. BF_3•OEt_2 (0.078 mL, 0.062 mmol, 1.2 equiv) was then added followed by a solution of the epoxide **17** (100 mg, 0.52 mmol, 1 equiv) in dry THF (1 mL). Stirring was continued for 4 h while the flask was slowly allowed to warm to room temperature in the cooling bath. Saturated aqueous NH_4Cl (10 mL) was added as well as EtOAc then the phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:6) gave **44** (130.6 mg, 0.31 mmol, 60%) as a colorless oil.

TLC: R_f = 0.50 (EtOAc/Hex 1:3, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.28-7.25 (m, 2 H), 6.90-6.87 (m, 2 H), 4.90 (br. s, 2 H), 4.49 (s, 2 H), 4.00-3.94 (m, 1 H), 3.81 (s, 3 H), 3.80 (t, *J* = 6.7, 2 H), 3.48 (dd, *J* = 9.4, 3.9, 1 H), 3.37 (dd, *J* = 9.5, 7.0, 1 H), 2.43 (br. s, 1 H), 2.32-2.29 (m, 2 H), 2.26 (dd, *J* = 14.1, 5.3, 1 H), 2.20 (dd, *J* = 14.1, 8.3, 1 H), 1.12-1.01 (m, 21 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 130.3, 129.5, 114.1, 114.0, 74.0, 73.2, 68.7, 62.9, 55.4, 40.9, 39.4, 18.2, 12.1.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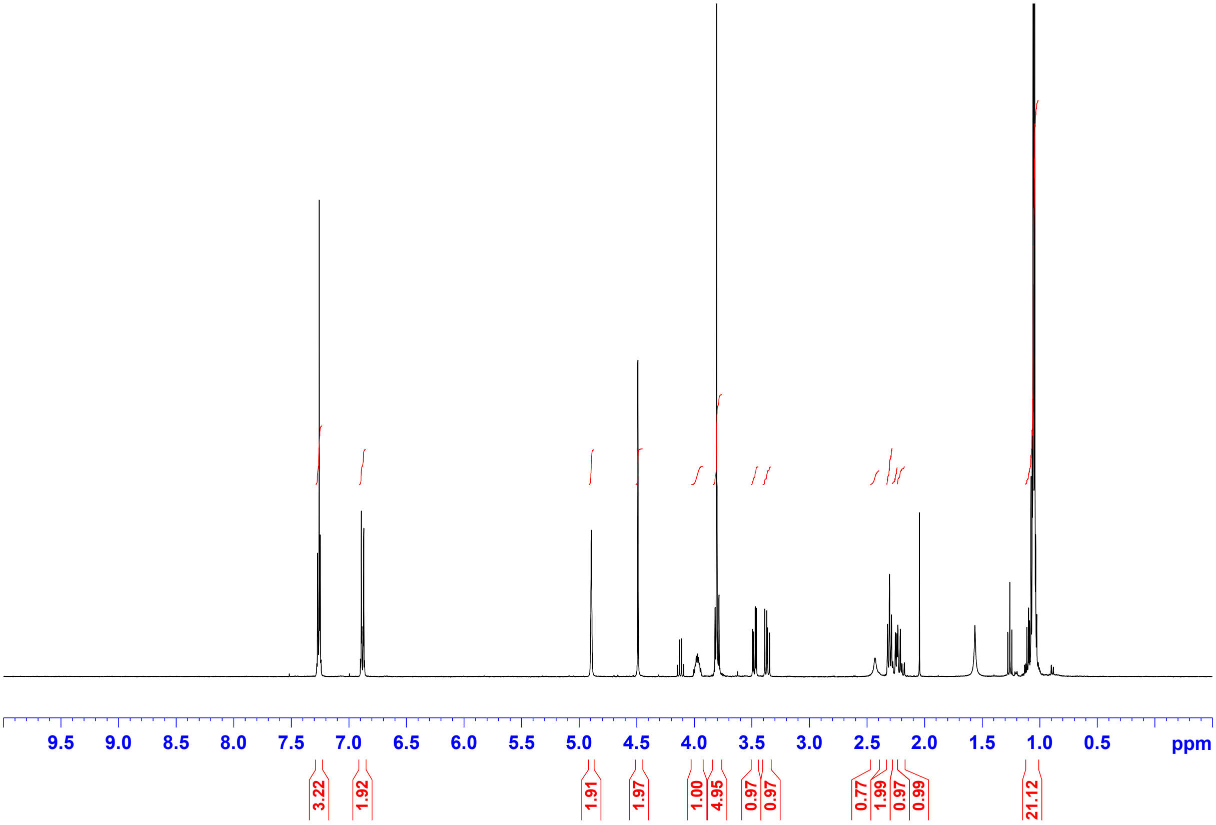
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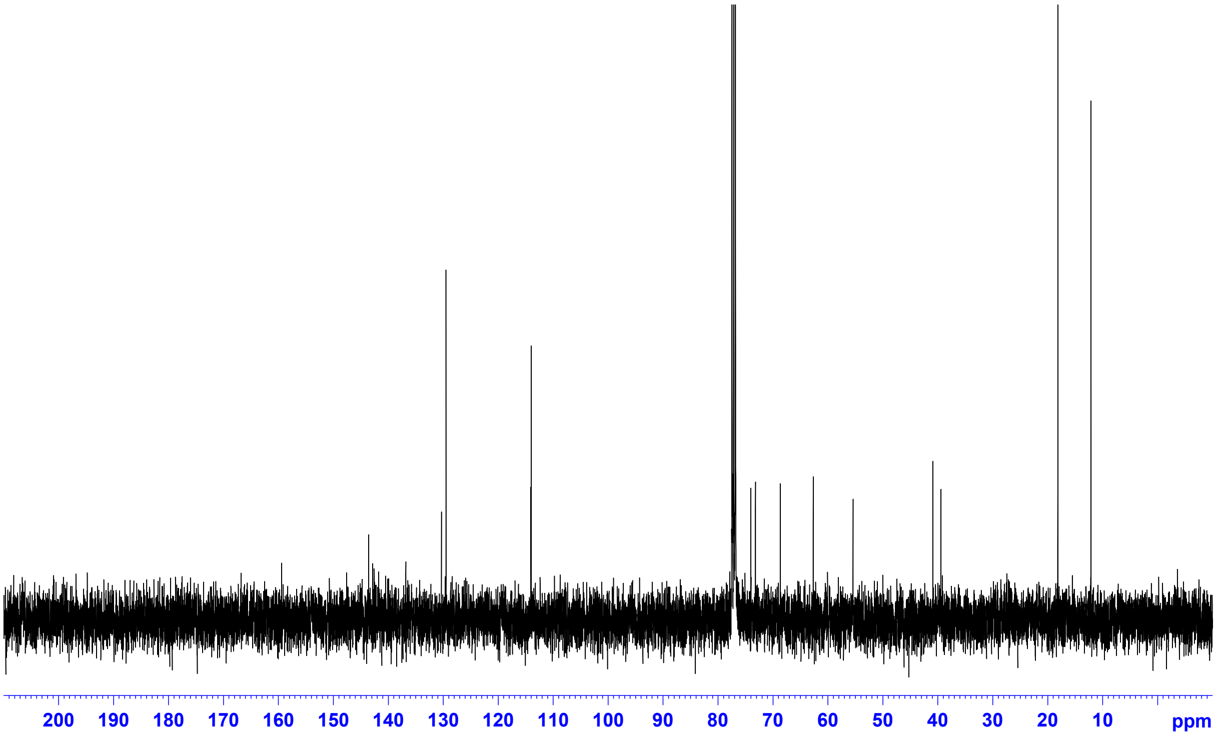
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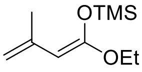

(*Z*)-((1-Ethoxy-3-methylbuta-1,3-dien-1-yl)oxy)trimethylsilane (47).[20] To a solution of *i*-Pr$_2$NH (2.88 mL, 22 mmol, 1.1 equiv) in dry THF (20 mL) was added *n*-BuLi (1.6M in hexane, 2.88 mL, 22 mmol, 1.1 equiv) at –78 °C. The flask was immersed into an icebath (0 °C) an stirring was continued for 30 min then cooled to –78 °C followed by addition of 2.8 mL of 3,3-dimethyl acrylate (keep interior temperature lower than –70 °C during addition). Stirring was continued for 30 min then TMSCl (4 mL, 31.3 mmol, 1.6 equiv) was added dropwise leading to a white suspension which was allowed to warm to room temperature over 1 h. The suspension was concentrated under reduced pressure followed by ventialation with argon. Pentane (150 mL) was added to the white residue followed by filtration under reduced pressure (argon flow). The liquid was concentrated under reduced pressure affording a yellow oil, which was purified by bulb-to-bulb distillation affording **47** (3.63 g, 18.1 mmol, 91%) as a colorless liquid.

Note: Perform all transformations, including ventialation at the Rotavap, under a protective atmosphere using argon.

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 4.77-4.75 (m, 1 H), 4.53-4.51 (m, 1 H), 4.23 (s, 1 H), 3.79 (q, *J* = 7.1, 2 H), 1.93-1.92 (m, 3 H), 1.30 (t, *J* = 7.1, 3 H), 0.24 (s, 9 H). **^{13}C-NMR** (100 MHz, CDCl$_3$): δ = 156.7, 140.7, 107.3, 81.1, 63.6, 23.9, 14.6, 0.6.

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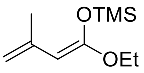
[20] R. V. Hoffman, H. O. Kim, *J. Org. Chem.* **1991**, *56*, 1014-1019 (modified procedure).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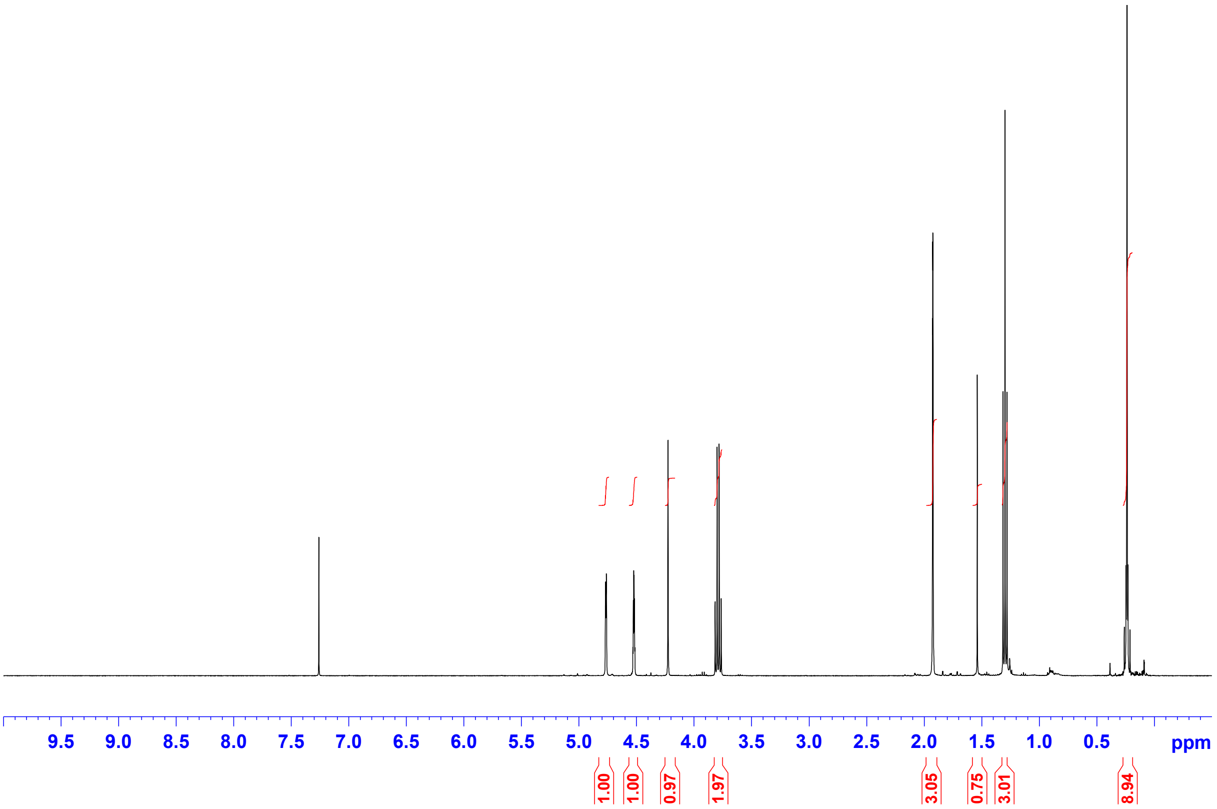
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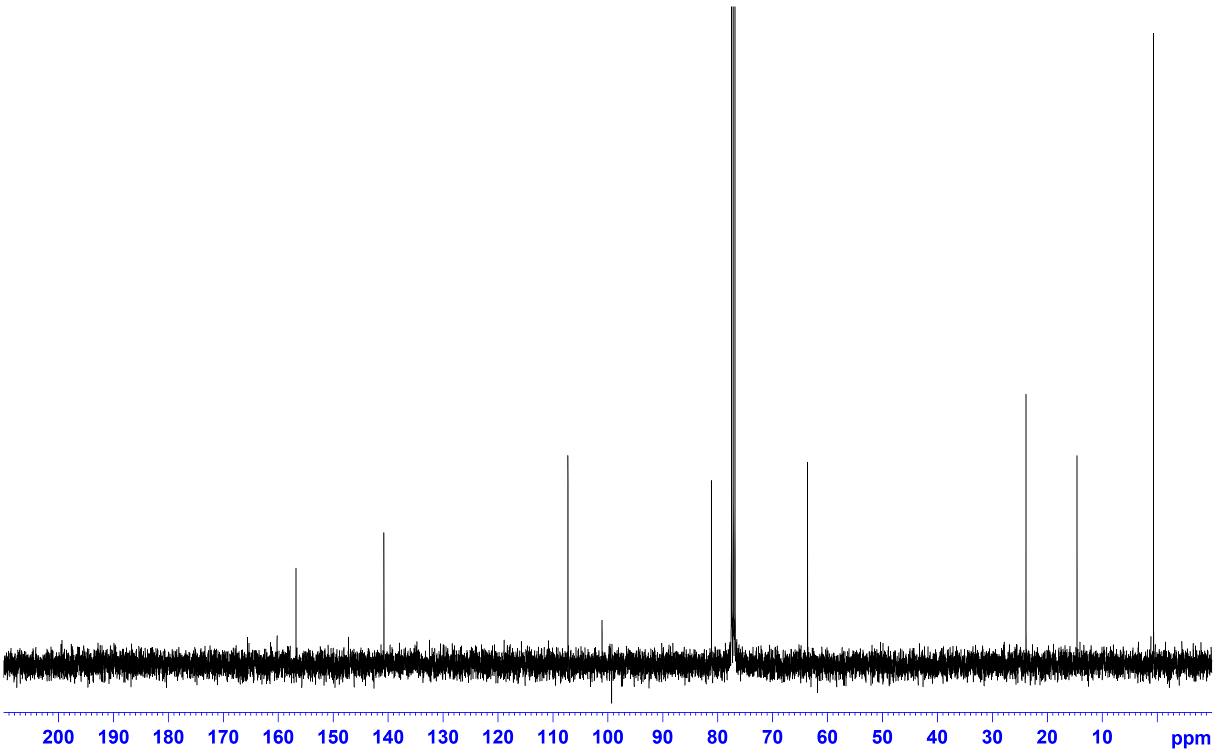
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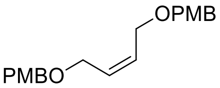
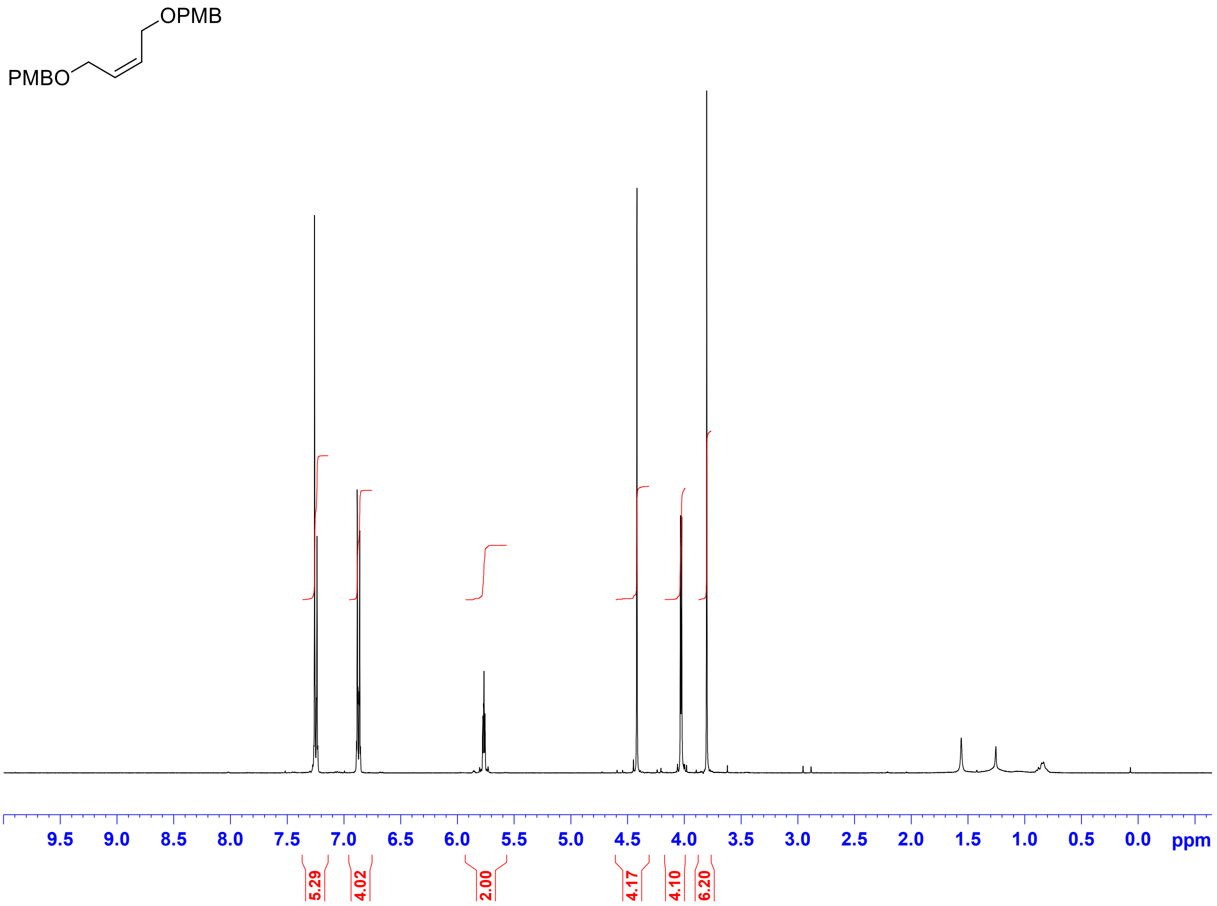


(*Z*)-1,4-Bis((4-methoxybenzyl)oxy)but-2-ene (48).[235]NaH (60%, 1.85 g, 46.35 mmol, 2.2 equiv) was added to dry DMF (25 mL) at 0 °C. 2-butene-1,4-diol (1.7 mL, 21.07 mmol, 1 equiv) was added slowly under effervescence and stirring was continued for 30 min at that temperature. PMBCl (6 mL, 44.25 mmol, 2.1 equiv) was added to the suspension then sirring was continued for 3 h at ca. 10 °C (water/ice) followed by careful addition of saturated aqueous NH_4Cl (30 mL). After effervescence ceased, Et_2O was added followed by sepratation of phases then the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:5→1:3→1:1) gave **48** (6.76 g, 20.6 mmol, 98%) as a pale-yellow oil.

TLC: R_f = 0.88 (EtOAc/Hex 1:1, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.27-7.23 (m, 4 H), 6.89-6.85 (m, 4 H), 5.80-5.73 (2 H), 4.42 (s, 4 H), 4.03-4.02 (m, 4 H), 3.80 (s, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.6, 130.5, 129.5, 114.3, 72.0, 65.7, 55.4.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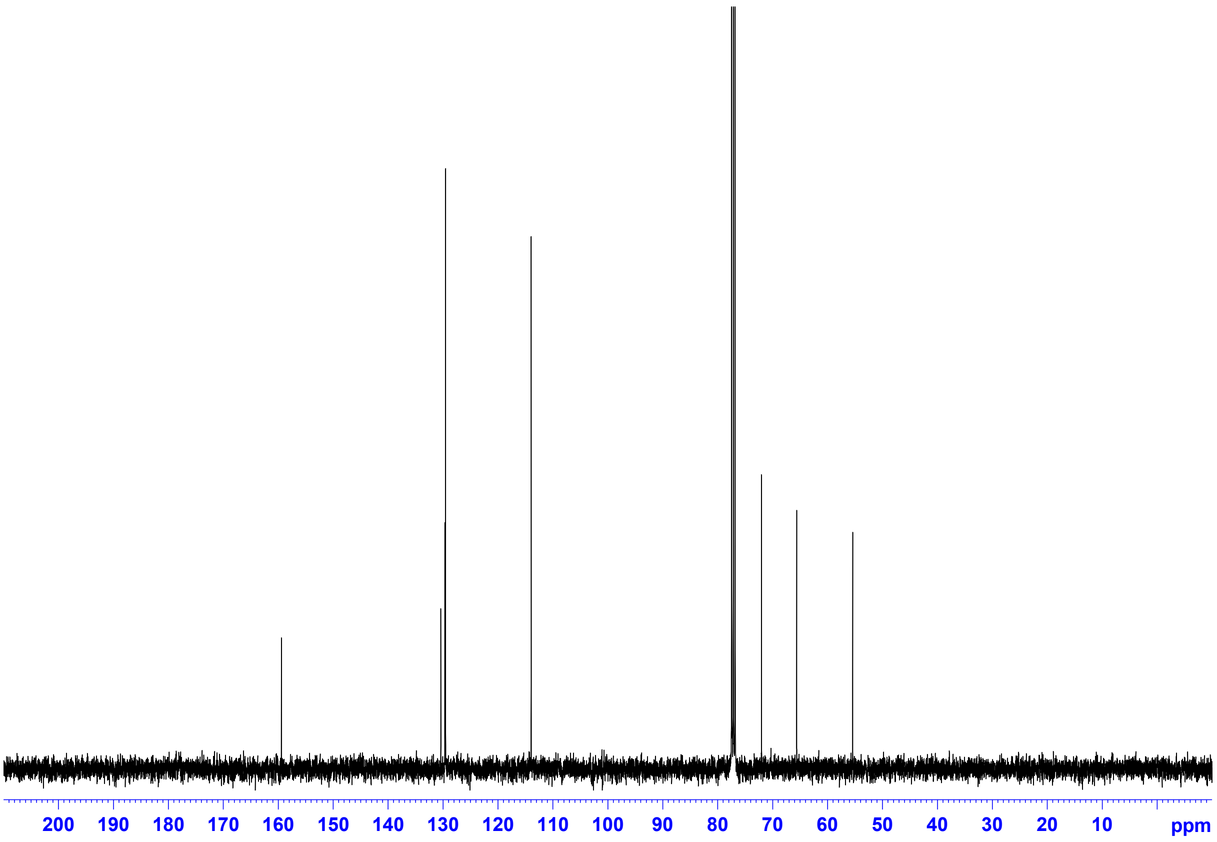
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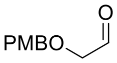

2-((4-Methoxybenzyl)oxy)acetaldehyde (49).[21] To a stirred mixture of *t*-BuOH (30 mL) and H_2O (30 mL) at 0 °C was added AD-mix β (1.4 g/mmol substrate, 14.0 g, 10.0 mmol, 1 equiv) followed by addition of neat **48** (3.28 g, 9.99 mmol, 1 equiv) (syringe rinsed with few *t*-BuOH) and methylsulfonamide (0.95 g, 9.99 mmol, 1 equiv). The orange-colored suspension was allowed to warm to RT and stirred for 17 h. The mixture was cooled to 0 °C then Na_2SO_3 (7.5 g) was added then the cooling bath was removed and stirring was continued for 30 min. Phases were separated then the aqueous phase was extracted with EtOAc (3 x 30 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL) followed by addition of $NaIO_4$ (2.14 g, 9.99 mmol, 1 equiv) and H_2O (25 mL). Stirring was continued for 50 min, then the reaction mixture was poured in H_2O (20 mL), the phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (10 mL) and once with brine (10 mL) then dried over $MgSO_4$ and concentrated under reduced pressure. Purification by bulb-to-bulb distiallation afforded **49** (2.24 g, 12.4 mmol, 62%) as a colorless oil.

TLC: R_f = 0.60 (EtOAc/Hex 1:1, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.70 (br. s, 1 H), 7.30-7.27 (m, 2 H), 6.92-6.88 (m, 2 H), 4.57 (s, 2 H), 4.07-4.06 (m, 2 H), 3.81 (s, 3 H).

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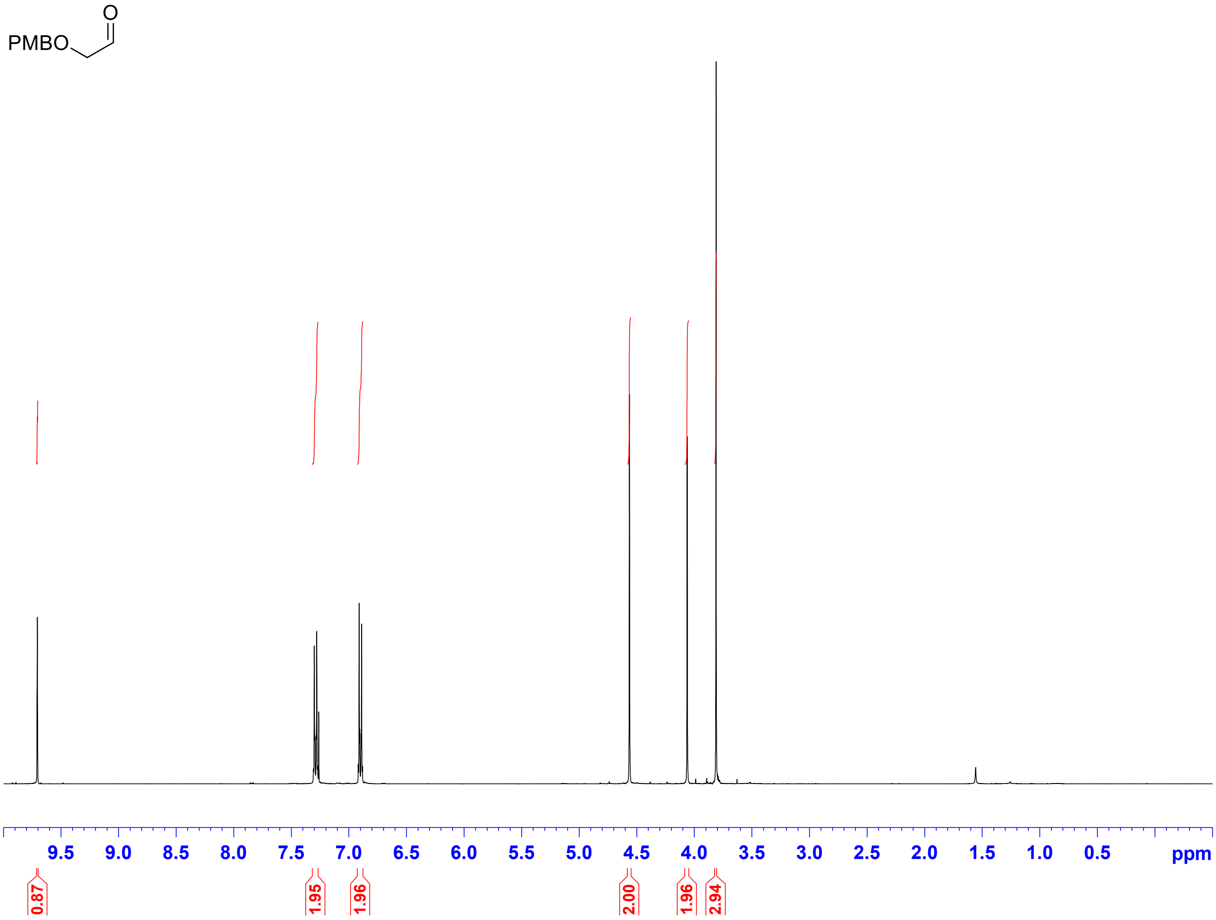
[21] Experimental procedure and analytical data: D. L. Aubele, S. Wan, P. E. Floreancig, *Angew. Chem. Int. Ed.* **2005**, *44*, 3485-3488.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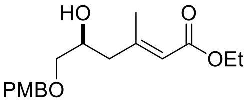

(*S*,*E*)-Ethyl 5-hydroxy-6-((4-methoxybenzyl)oxy)-3-methylhex-2-enoate (46).[22] To (*S*,*S*)-bis-(phenyloxazolinyl)pyridine (40 mg, 0.11 mmol, 0.05 equiv) was added $CuCl_2$ (14.8 mg, 0.11 mmol, 0.05 equiv) and CH_2Cl_2 (4 mL) giving a fluorescent green suspension which was stirred for 1 h at RT. A solution of $AgSbF_6$ (76 mg, 0.22 mmol, 0.1 equiv) in CH_2Cl_2 (2 mL) was added giving immediately a blue suspension. Stirring was continued for 2 h at RT in the dark then stirring was stopped and the blue supernatant was transferred via Teflon cannula to an oven-dried Pasteur pipette, equipped with cotton, and filtered under a flow of argon directly into the dried reaction flask.

The blue clear solution was cooled to –78 °C followed by addition of a solution of the aldehyde **49** (0.4 g, 2.21 mmol, 1 equiv) in CH_2Cl_2 (3 mL) which resulted in a color change from blue to turquoise. After 15 min, neat **47** (5.33 mg, 2.6 mmol, 1.2 equiv) was added dropwise over 30 min which resulted in a dark-green solution after the addition was completed. Stirring was continued for 4 h at –78 °C then the cooling bath was removed followed by addition of Et_2O (10 mL) giving a mixture which was filtered over a pad of silica and washed with Et_2O (50 mL). The solution was concentrated under reduced pressure, the residue dissolved in THF (50 mL) followed by addition of HCl (1N, 30 mL) and stirring was continued for 30 min at RT. Et_2O (30 mL) was added then the phases were separated followed by extraction of the aqueous phase with Et_2O (3 x 30 mL). The combined organic phases were washed once with saturated aqueous $NaHCO_3$ (30 mL), once with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:3→1:1) gave **46** (477 mg, 1.55 mmol, 70%) as a colorless oil.

TLC: R_f = 0.20 (EtOAc/Hex 1:3, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.27-7.24 (m, 2 H), 6.91-6.87 (m, 2 H), 5.73 (q, *J* =1.2, 1 H), 4.52-4.45 (m, 2 H), 4.14 (q, *J*

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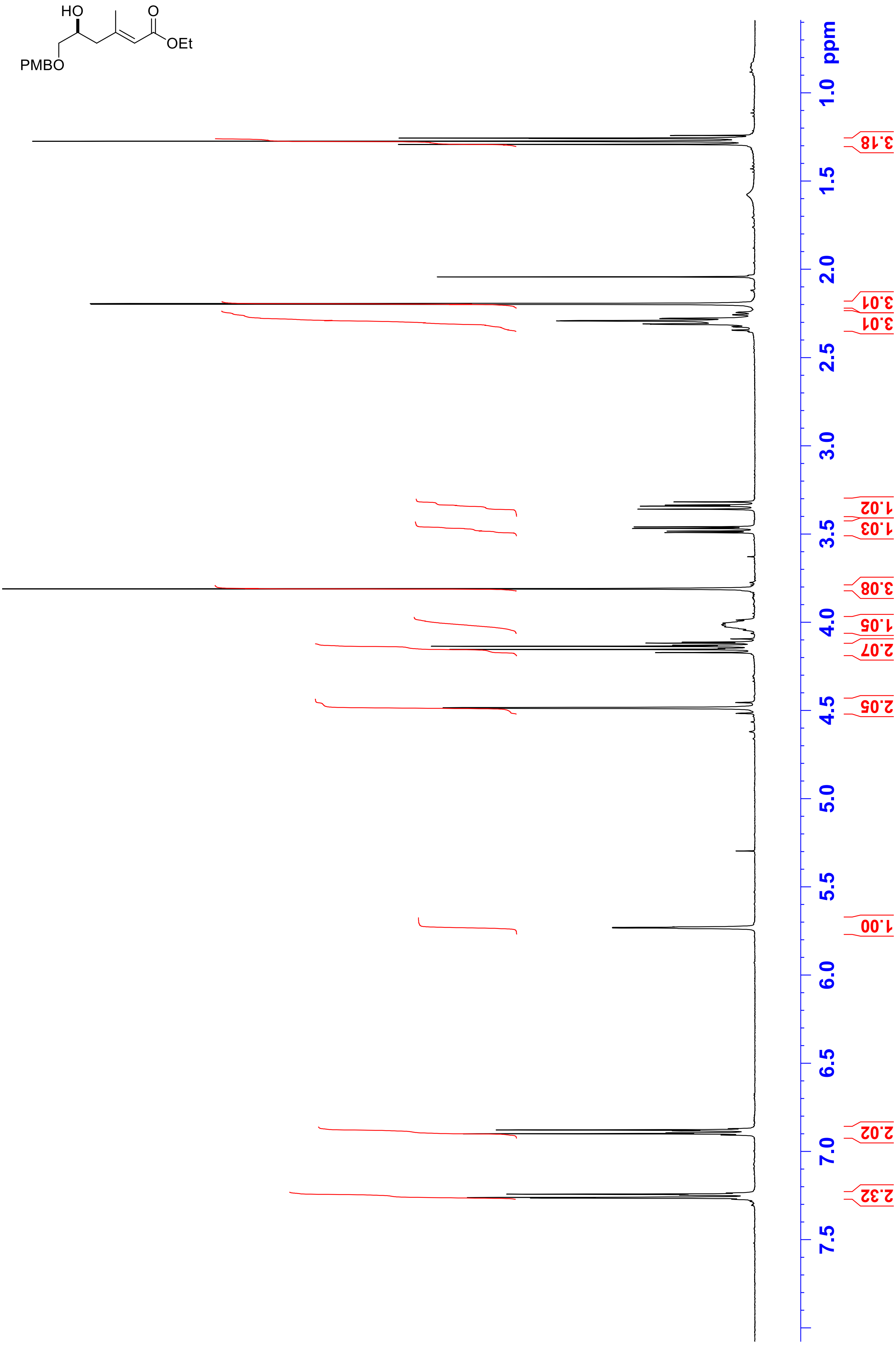
[22] Experimental procedure and analytical data: D. L. Aubele, S. Wan, P. E. Floreancig, *Angew. Chem. Int. Ed.* **2005**, *44*, 3485-3488. See as well: D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669-685.

= 7.1, 2 H), 4.05-3.98 (m, 1 H), 3.81 (s, 3 H), 3.47 (dd, *J* = 9.5, 3.4, 1 H), 3.34 (dd, *J* = 9.5, 7.1, 1 H), 2.34-2.24 (m, 3 H), 2.19 (d, *J* = 1.3, 3 H), 1.27 (t, *J* = 7.1, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 166.6, 159.6, 155.8, 130.0, 129.6, 118.3, 114.1, 73.7, 73.3, 68.5, 59.6, 55.4, 44.8, 19.1, 14.5.

The ee was determined to be 93% (but varied usually between 90–93%) by HPLC analysis using a Chiralpak AD-H-column: hexane/*i*-PrOH, (95:5); 1 mL/min; 25 °C, 254 nm, R_t 23.57 min.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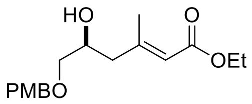
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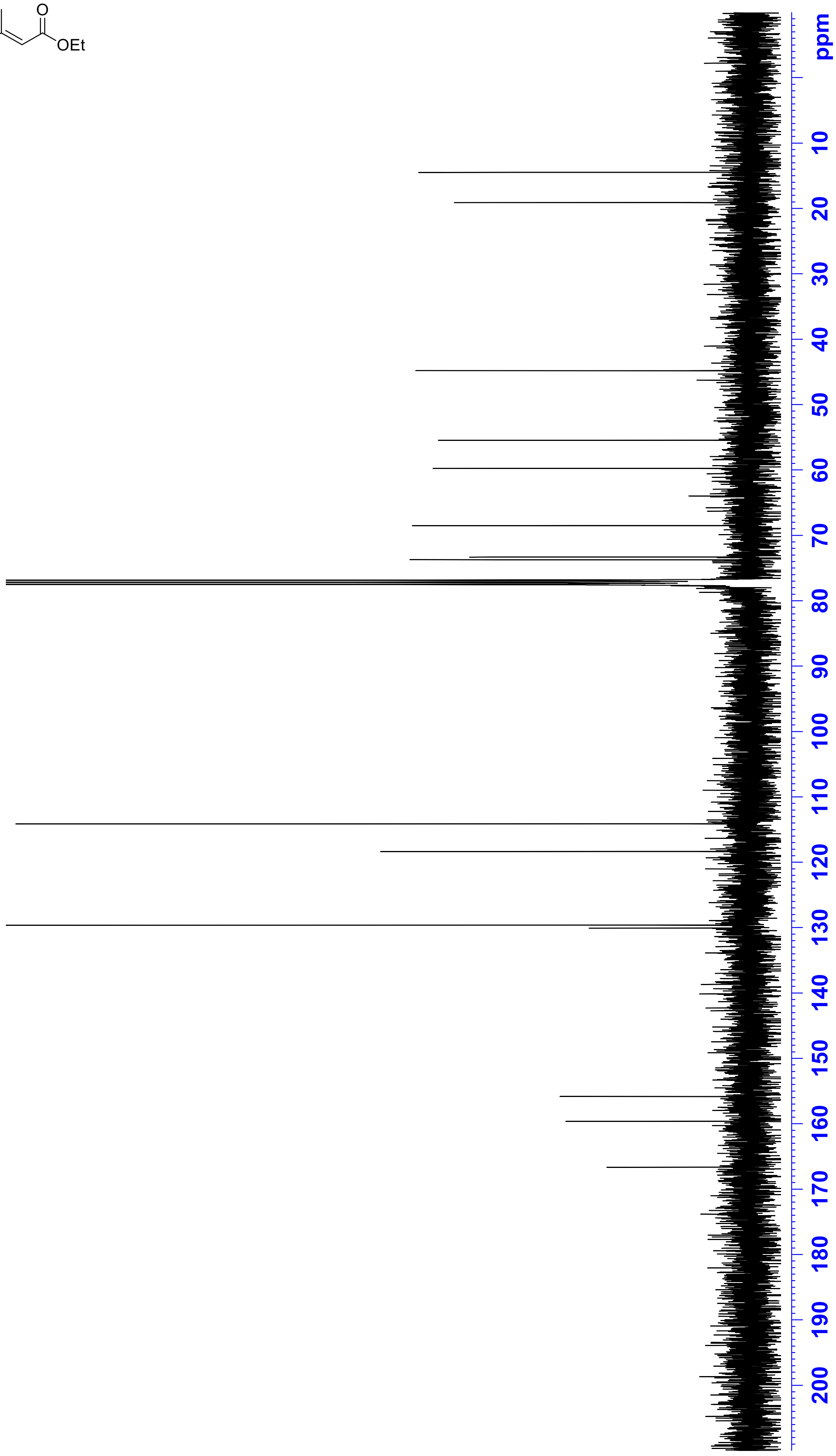
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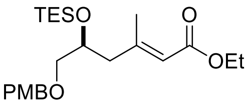
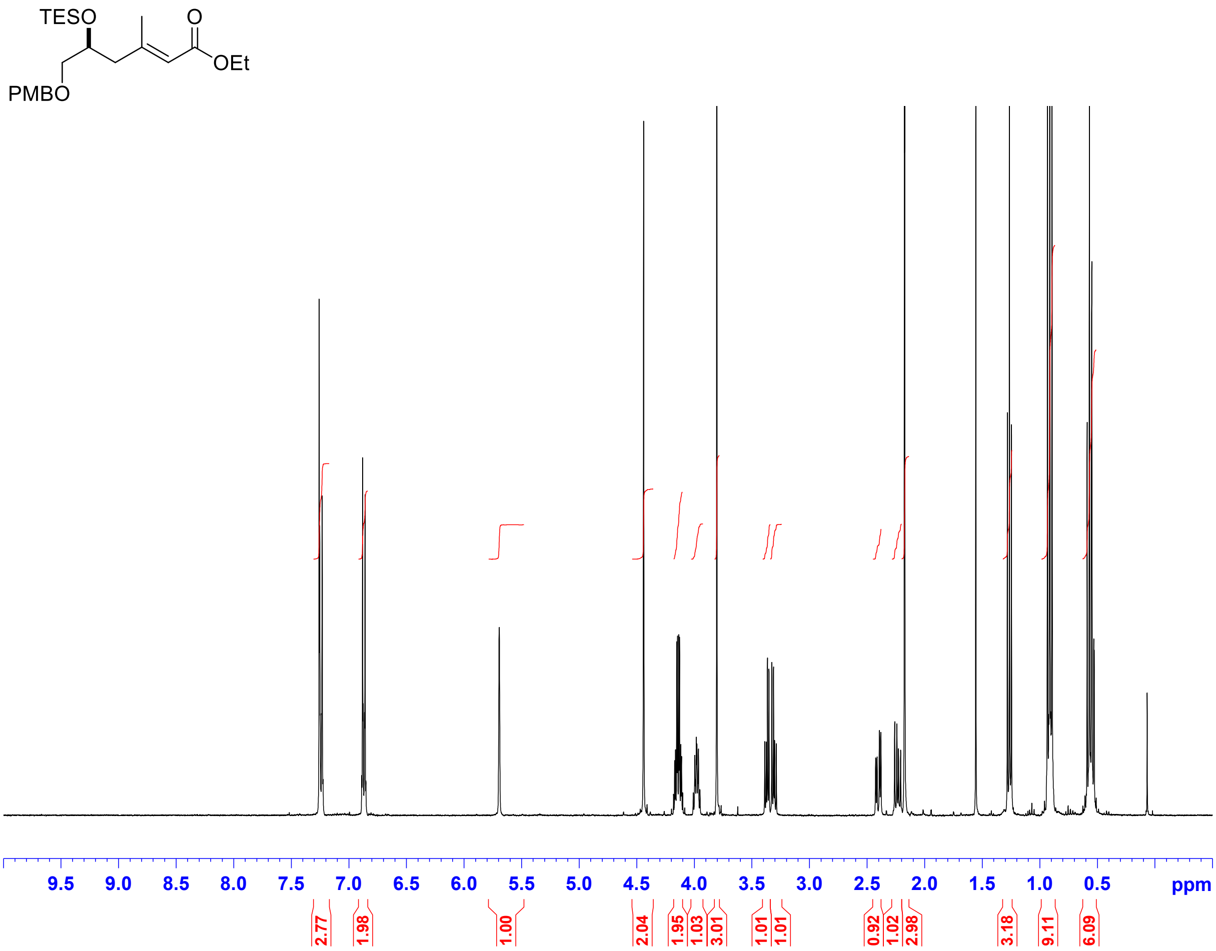


(*S*,*E*)-Ethyl 6-((4-methoxybenzyl)oxy)-3-methyl-5-((triethylsilyl)oxy)hex-2-enoate (50). To a solution of **46** (741.4 mg, 2.4 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL) at –78 °C was added 2,6-dimethylpyridine (0.42 mL, 3.6 mmol, 1.5 equiv) followed by TESOTf (0.57 mL, 2.53 mmol, 1.05 equiv). MeOH (2 mL) was added after 45 min followed by saturated aqueous NH_4Cl (10 mL). Phases were separated then the aqueous phase was extracted with Et_2O (3 x 10 mL) then the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:10) afforded **50** (0.91 g, 2.15 mmol, 90%) as a colorles oil.

TLC: R_f = 0.67 (EtOAc/Hex 1:3, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.26-7.23 (m, 2 H), 6.88-6.85 (m, 2 H), 5.69 (q, *J* =1.1, 1 H), 4.44 (s, 2 H), 4.18-4.10 (m, 2 H), 3.98 (dq, *J* = 7.4, 5.2, 1 H), 3.81 (s, 3 H), 3.37 (dd, *J* = 9.5, 5.3, 1 H), 3.31 (dd, *J* = 9.5, 5.6, 1 H), 2.40 (dd, *J* = 13.4, 4.8, 1 H), 2.24 (dd, *J* = 13.4, 7.6, 1 H), 2.17 (d, *J* = 1.1, 3 H), 1.26 (t, *J* = 7.1, 3 H), 0.91 (t, *J* = 7.8, 9 H), 0.59-0.53 (m, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 166.9, 159.3, 156.6, 130.5, 129.5, 118.5, 113.9, 74.1, 73.2, 70.0, 59.5, 55.4, 46.4, 19.7, 14.5, 7.0, 5.1.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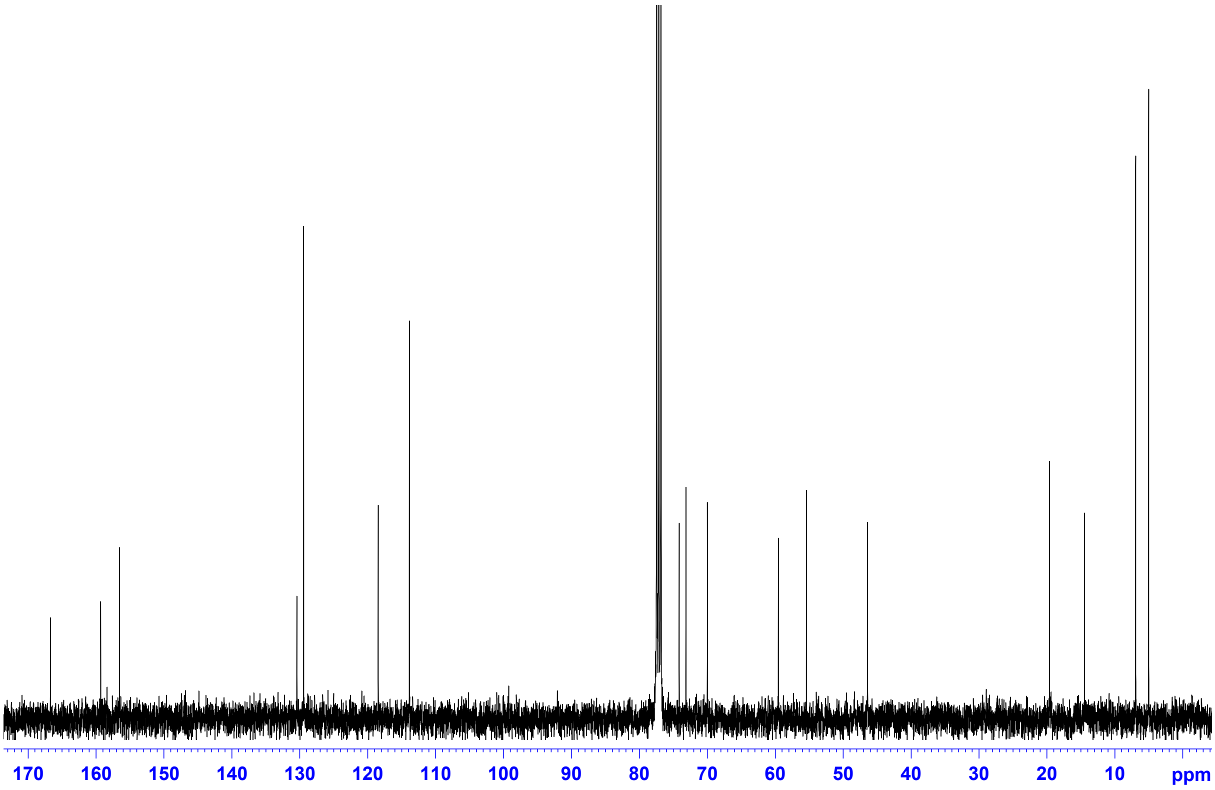
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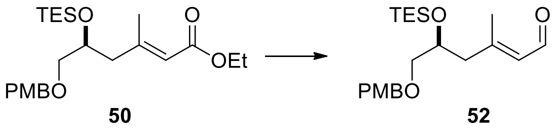
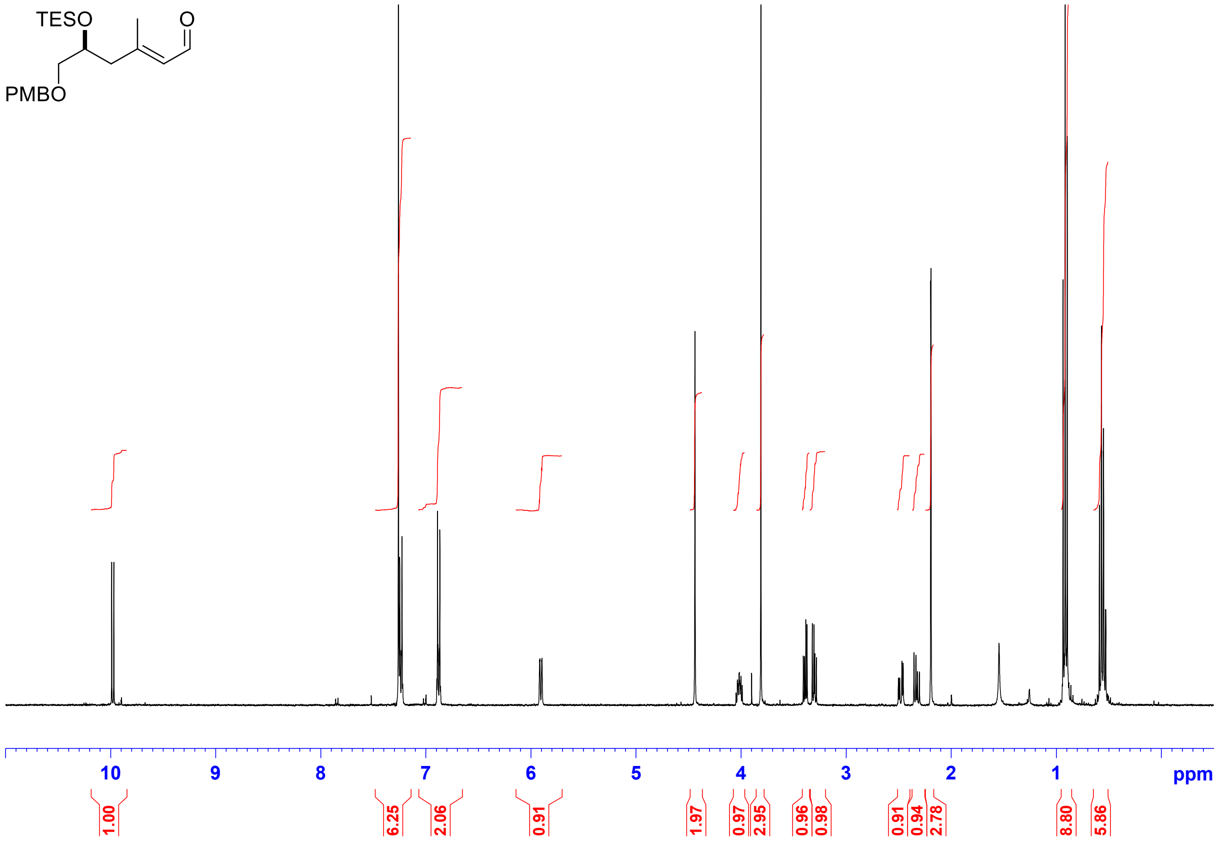


(*S*,*E*)-6-((4-Methoxybenzyl)oxy)-3-methyl-5-((triethylsilyl)oxy)hex-2-enal (52). A solution of LAH (1M in THF, 0.51 mL, 0.51 mmol, 2.0 equiv) was diluted with dry Et_2O (2 mL) and cooled to 0 °C. Then, a solution of **50** (108 mg, 0.26 mmol, 1.0 equiv) in dry Et_2O (1 mL) was added and stirring was continued for 30 min. Saturated aqueous Rochelle salt (15 mL) was carefully added then the mixture was stirred at room temperature for 15 min. Phases were separated then the aqueous phase was extracted with Et_2O (3 x 10 mL), the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The oil was dissolved in dry CH_2Cl_2 (1 mL) and transferred to a flask which was charged with MnO_2 (activated, 220 mg, 2.55 mmol, 10 equiv) and CH_2Cl_2 (2 mL) and stirring was continued under argon for 16 h at room temperature. The black suspension was filtered through a pad of celite and washed with EtOAc followed by concentration of the organic filtrate under reduced pressure. Purification by flash chromatography (EtOAc/Hex 1:10) gave **52** (69.1 mg, 0.183 mmol, 72%) as a colorless oil.

TLC: R_f = 0.53 (EtOAc/Hex 1:3, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.98 (d, *J* = 8.1, 1 H), 7.25-7.23 (m, 2 H), 6.89-6.86 (m, 2 H), 5.90 (dq, *J* = 8.0, 1.0, 1 H), 4.43 (s, 2 H), 4.05-3.99 (m, 1 H), 3.81 (s, 3 H), 3.39 (dd, *J* = 9.3, 5.1, 1 H), 3.30 (dd, *J* = 9.3, 6.3, 1 H), 2.47 (dd, *J* = 13.2, 4.5, 1 H), 2.33 (dd, *J* = 13.3, 7.7, 1 H), 2.19 (d, *J* = 1.1, 3 H), 0.91 (t, *J* = 8.0, 9 H), 0.59-0.53 (m, 6 H).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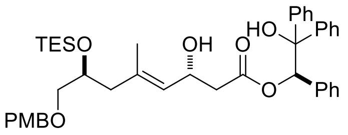

(3*R*,7*S*,*E*)-(*R*)-2-Hydroxy-1,2,2-triphenylethyl 3-hydroxy-8-((4-methoxybenzyl)oxy)-5-methyl-7-((triethylsilyl)oxy)oct-4-enoate (54).[23] To a solution of *i*-Pr$_2$NH (0.29 mL, 2.2 mmol, 12.2 equiv) in dry THF (4 mL) was added *n*-BuLi (1.6M in hexane, 1.38 mL, 2.2 mmol, 12.2 equiv) at 0 °C. Stirring was continued for 1 h then the solution was transferred via Teflon cannula to (*R*)-HYTRA (**53**) (332 mg, 1 mmol, 5.6 equiv) in dry THF (5 mL) then stirring was continued while the rection mixture was warmed to 0 °C giving an orange solution. Stirring was continued for 1 h at 0 °C.

To magnesium turnings (53 mg, 2.2 mmol, 12.2 equiv) in dry THF (5 mL) was added 1,2-dibromoethane (0.19 mL, 2.2 mmol, 12.2 equiv) then the suspension was heated to reflux until complete consumption of magnesium, then the grey slurry was allowed to cool to RT.

The freshly prepared Li-enolate solution of **53** was added to the cooled MgBr$_2$ suspension at –90 °C using a Teflon cannula followed by addition of Et$_2$O (20 mL). The mixture was then cooled to –130 °C (N$_2$/aceton) then a precooled solution (–78 °C) of **52** (68.2 mg, 0.18 mmol, 1 equiv) in dry THF (2 mL) was added via a Teflon cannula. Stirring was continued for 2 h, then saturated aqueous NH$_4$Cl (50 mL) was added as well as H$_2$O (30 mL). Phases were separated then the aqueous phase was extracted with Et$_2$O (3 x 30 ml), the combined organic phases were washed H$_2$O (30 mL) water, dried over MgSO$_4$ and purified using flash chromatography (EtOAc/Hex 1/6→1/1) which gave **54** (101.6 mg, 0.143 mmol, 79%, ca. 8:1 dr). Spectroscopic data are reported for the diastereomeric mixture.

TLC: R$_f$ = 0.23 (EtOAc/Hex 1:3, UV, KMnO$_4$). **^{1}H-NMR** (400 MHz, CDCl$_3$): δ = 7.59-7.56 (m, 2 H), 7.38-7.35 (m, 2 H), 7.30-7.27 (m, 1 H), 7.25-7.10 (m, 10 H), 7.08-7.04 (m, 2 H), 6.86-6.81 (m, 2 H), 6.72 (s, 0.12 H), 6.71 (s, 0.78 H), 5.07 (dq, *J* = 8.5, 1.1, 1 H), 4.55 (dt, *J* = 8.8, 3.3, 1 H), 4.42 (s, 2 H), 3.91-3.84 (m, 1 H), 3.80 (s, 2.62 H), 3.79 (s, 0.35

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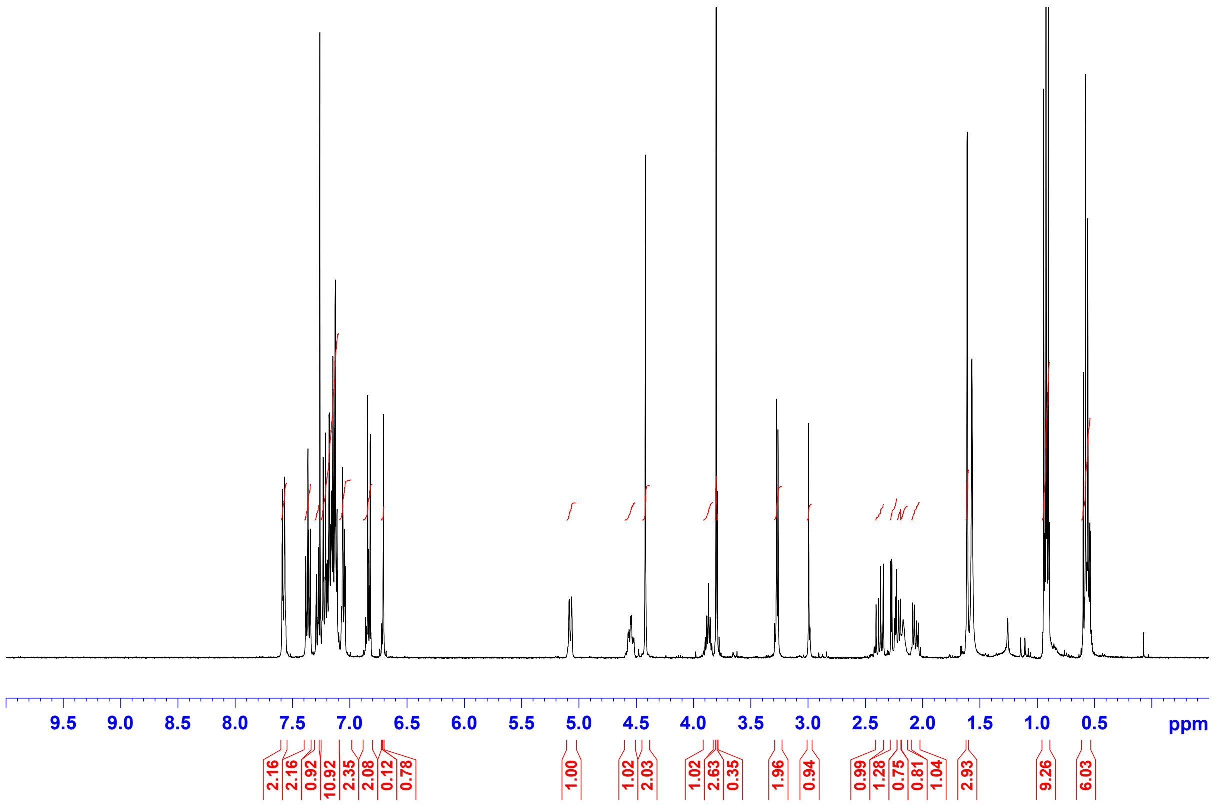
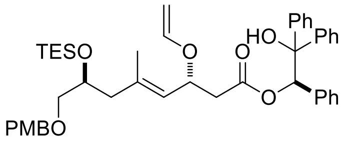
[23] a) U. Mahler, R. M. Devant, M. Braun, *Chem. Ber.* **1988**, *121*, 2035-2044. b) M. Braun, S. Graf, *Org. Synth.* **1995**, *72*, 38-47. c) M. Braun, B. Mai, D. Ridder, *Eur. J. Org. Chem.* **2001**, *2001*, 3155-3160.

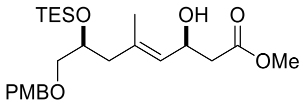
H), 3.27 (d, *J* = 5.1, 2 H), 2.99 (s, 0.78 H), 2.98 (s, 0.13 H), 2.38 (dd, *J* = 16.0, 8.9, 1 H), 2.24 (dd, *J* = 16.0, 3.5, 1 H), 2.22 (dd, *J* = 13.6, 6.5, 1 H), 2.17 (br. s, 1 H), 2.06 (dd, *J* = 13.7, 6.5, 1 H), 1.61 (d, *J* = 1.2, 3 H), 0.92 and 0.91 (t, *J* = 7.9, 9 H), 0.59-0.54 (m, 6 H).





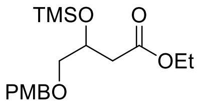
(3*R*,7*S*,*E*)-(*R*)-2-Hydroxy-1,2,2-triphenylethyl 8-((4-methoxybenzyl)oxy)-5-methyl-7-((triethylsilyl)oxy)-3-(vinyloxy)oct-4-enoate (57). Pd(OCOCF$_3$)$_2$ (1 mg, 0.003 mmol, 0.04 equiv) and 4,7-diphenyl-phenanthroline (1 mg, 0.003 mmol, 0.04 equiv) were dissolved in BVE (1.5 mL, excess) at room temperature. The yellow-brown suspension was heated to 40 °C to give a solution. To the yellow solution was added NEt$_3$ (ca. 1µL) followed by **54** (42.3 mg, 0.059 mmol, 1 equiv) (dissolved in ca. 0.5 mL of BVE). Stirring was continued at 40 °C for 17 h then the heating bath was removed and the solution was allowed to cool to room temperature. Concentration under reduced pressure followed by purification using flash chromatography on a deactivated stationary silica phase (EtOAc/Hex 1:5, 2% NEt$_3$ (v/v)) gave **57** (30.3 mg, 0.041 mmol, 70%, ca. 8:1 dr) as a pale-yellow solid. Spectroscopic data is reported for the diastereomeric mixture.

TLC: R_f = 0.72 (EtOAc/Hex 1:3, UV, KMnO$_4$). **^{1}H-NMR** (400 MHz, CDCl$_3$): δ = 7.56-7.53 (m, 2 H), 7.36-7.32 (m, 2 H), 7.28-7.21 (m, 3 H), 7.17-7.03 (m, 10 H), 6.87-6.83 (m, 2 H), 6.67 (s, 0.79 H), 6.66 (s, 0.18 H), 6.17 (dd, *J* = 14.1, 6.8, 0.11 H), 6.02 (dd, *J* = 14.1, 6.7, 0.89 H), 5.02-5.00 (m, 1 H), 4.73 (dt, *J* = 8.6, 4.6, 1 H), 4.45-4.37 (m, 2 H), 4.13-4.09 (m, 1 H), 3.91-3.87 (m, 2 H), 3.80 (s, 2.67 H), 3.78 (s, 0.38 H), 3.27 (d, *J* = 5.2, 2 H), 3.00 (s, 1 H), 2.55 (dd, *J* = 15.6, 8.6, 1 H), 2.27 (dd, *J* = 15.6, 4.6, 1 H), 2.25 (dd, *J* = 13.4, 6.4, 1 H), 2.11 (dd, *J* = 13.4, 5.9, 1 H), 1.66 (d, *J* = 1.1, 2.68 H), 1.57 (d, *J* = 1.1, 0.38 H), 0.93 and 0.92 (t, *J* = 7.9, 9 H), 0.57 (q, *J* = 7.9, 6 H).



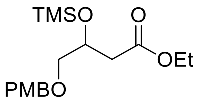
(3*S*,7*S*,*E*)-Methyl 3-hydroxy-8-((4-methoxybenzyl)oxy)-5-methyl-7-((triethylsilyl)oxy)oct-4-enoate (59). To solution of **56** (25.7 mg, 0.036 mmol, 1 equiv) in dry MeOH (1 mL) at room temperature was added NaOMe (2.3 mg, 0.044 mmol, 1.2 equiv) and stirring was continued for 14 h. Saturated aqueous NH_4Cl (5 mL) was added then the phases were separated followed by extraction of the aqueous phase with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:5) to give **59** (5.6 mg, 0.012 mmol, 33%). Spectroscopic data are reported for the diastereomeric mixture (exact ratio was not determined).

TLC: R_f = 0.28 (EtOAc/Hex 1:3, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.25-7.23 (m, 2 H), 6.88-6.83 (m, 2 H), 5.25-5.21 (m, 1 H), 4.80-4.74 (m, 1 H), 4.44 (s, 2 H), 3.95-3.89 (m, 1 H), 3.80 (s, 3 H), 3.71 (s, 0.72 H), 3.70 (s, 2.16 H), 3.33-3.31 (m, 2 H), 2.50 (dd, *J* = 16.2, 8.6, 1 H), 2.50-2.46 (m, 1 H), 2.41 (dd, *J* = 16.2, 4.1, 1 H), 2.27 (dd, *J* = 13.4, 6.4, 1 H), 2.13 (dd, *J* = 13.5, 6.6, 1 H), 1.73-1.71 (m, 3 H), 0.93 and 0.92 (t, *J* = 8.0, 9 H), 0.61-0.54 (m, 6 H).



Ethyl 4-((4-methoxybenzyl)oxy)-3-((trimethylsilyl)oxy)butanoate (61). A solution of **5** (1.05 g, 3.9 mmol, 1.0 equiv) in EtOH (15 mL) was cooled to 0 °C followed by slow addition of $NaBH_4$ (117 mg, 3.1 mmol, 0.8 equiv) so that the interior temperature stayed at 0 °C. Stirring was continued for 15 min at that temperature then saturated aqueous NH_4Cl (2 mL) was added under stirring as well as EtOAc (5 mL). Phases were separated then the aqueous phase was extracted with EtOAc (3 x 10 mL). The collected organic phases were dried over $MgSO_4$ and then concentrated under reduced pressure. The crude alcohol was dissolved in dry CH_2Cl_2 (15 mL) then cooled to –78 °C followed by addition of 2,6-dimethylpyridine (0.9 mL, 7.76 mmol, 2.0 equiv) and TMSOTf (1.05 mL, 5.4 mmol, 1.4 equiv). The cooling bath was removed then the solution was allowed to warm to room temperature. After a total of 90 min, MeOH (1 mL) was added followed by saturated aqueous NH_4Cl (5 mL) then the phases were separated. The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic phases were dried over $MgSO_4$ and concentrated under resduced pressure. Purification by flash chromatography (EtOAc/Hex 1:10) gave **61** (989.9 mg, 2.91 mmol, 75%) as a colorless oil.

TLC: R_f = 0.55 (EtOAc/Hex 1:3, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.25-7.23 (m, 2 H), 6.89-6.85 (m, 2 H), 4.46 (br. s, 2 H), 4.32-4.26 (m, 1 H), 4.16-4.06 (m, 2 H), 3.80 (s, 3 H), 3.41 (dd, *J* = 9.7, 5.5, 1 H), 3.34 (dd, *J* = 9.7, 5.7, 1 H), 2.57 (dd, *J* = 15.1, 4.5, 1 H), 2.42 (dd, *J* = 15.1, 8.2, 1 H), 1.24 (t, *J* = 7.2, 3 H), 0.1 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 171.7, 159.3, 130.4, 129.4, 113.9, 73.8, 73.1, 68.7, 60.5, 55.4, 40.5, 14.4, 0.36.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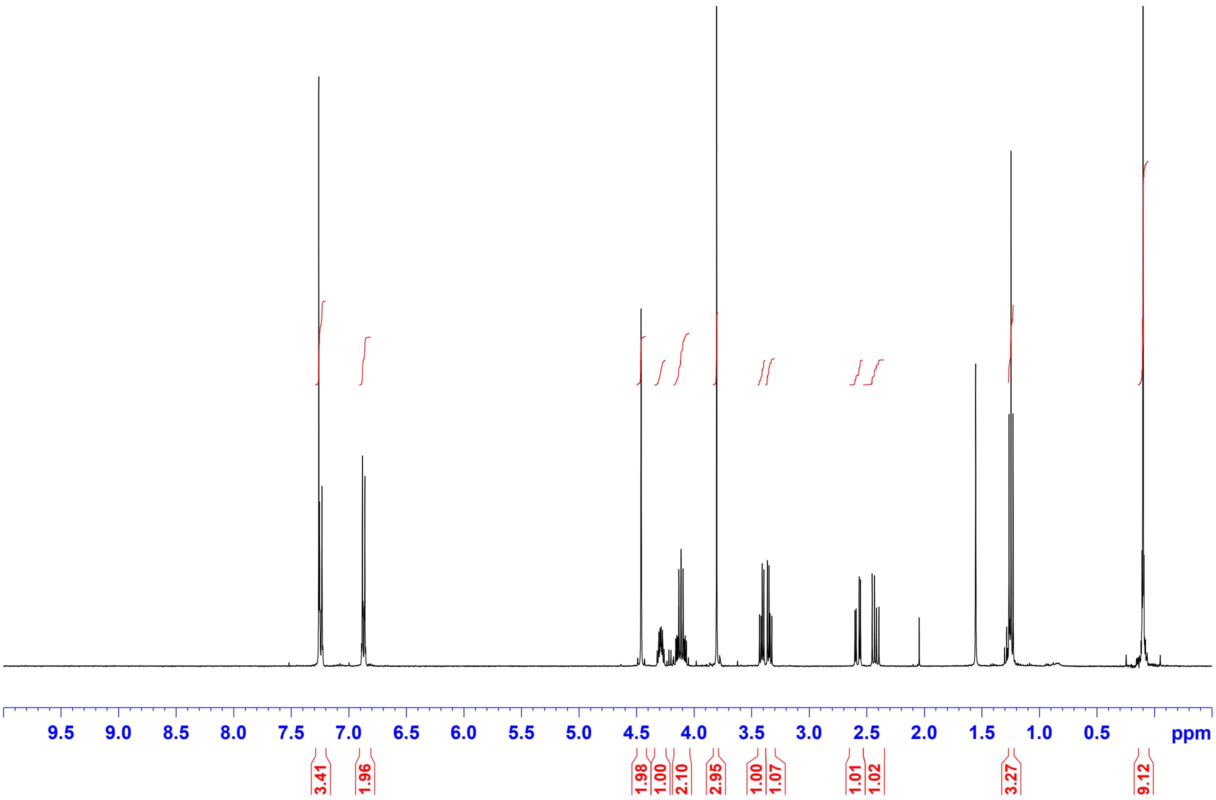
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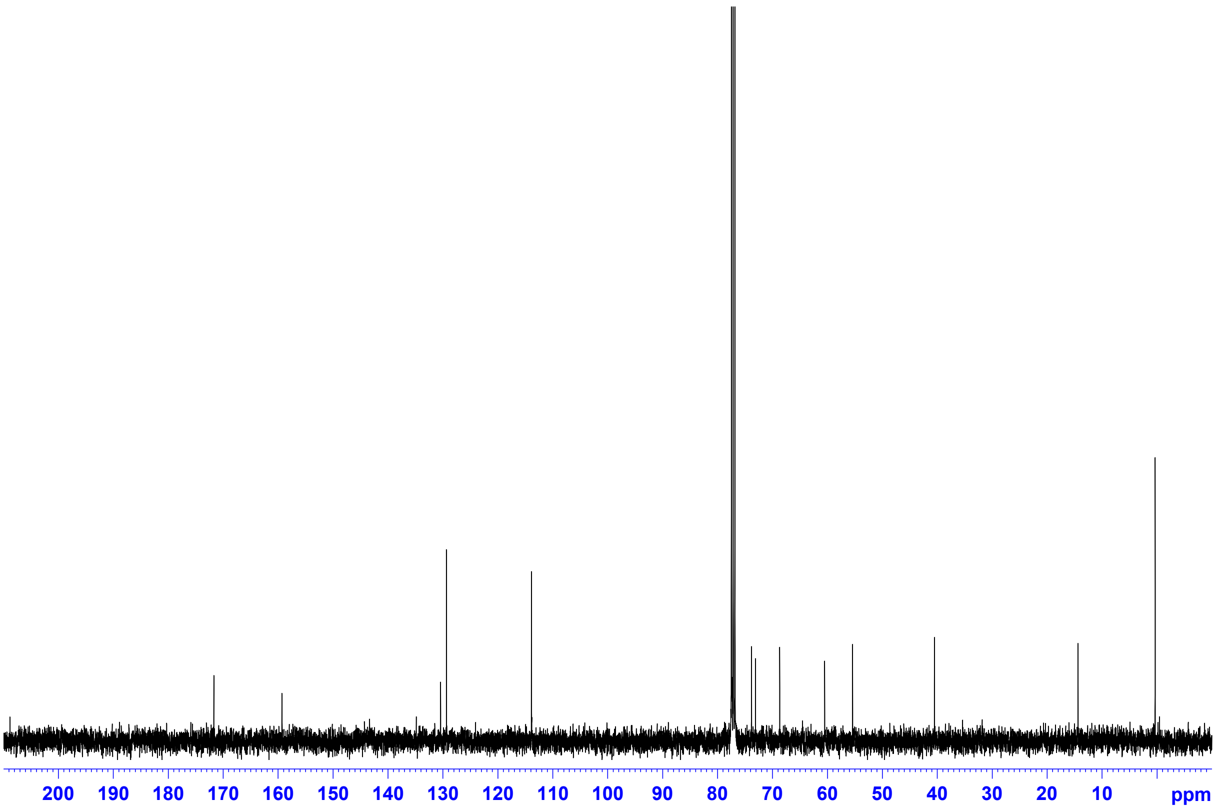
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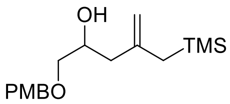
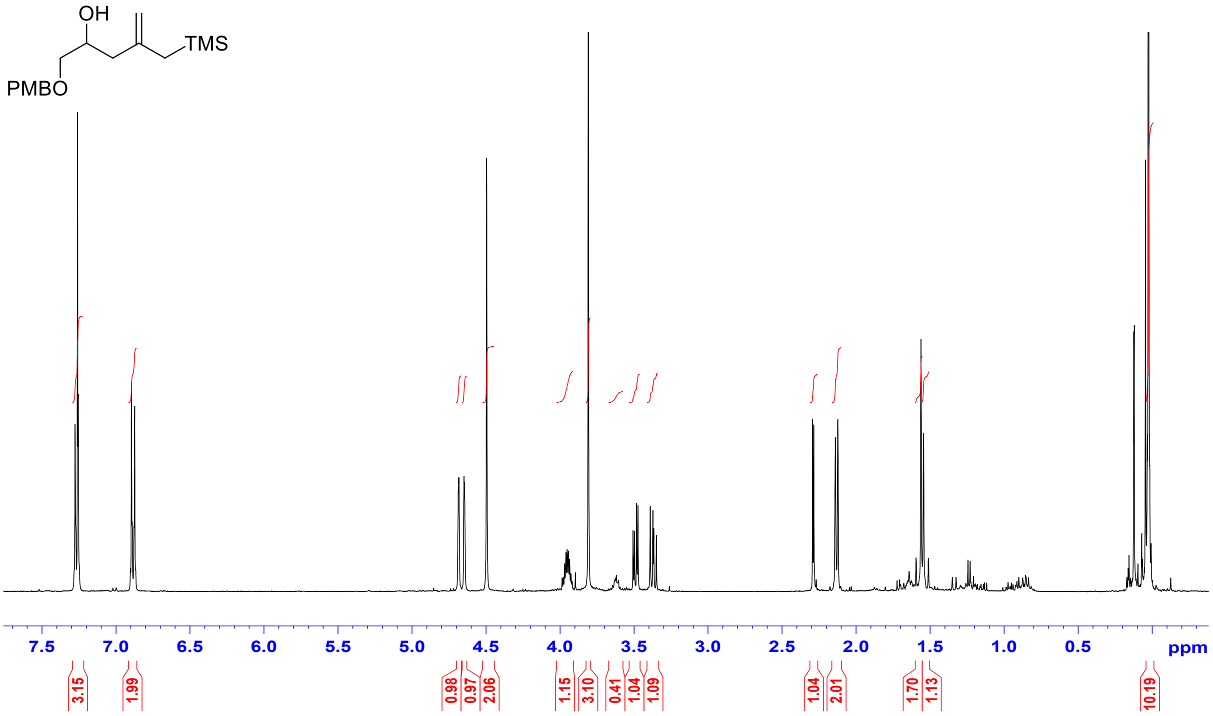


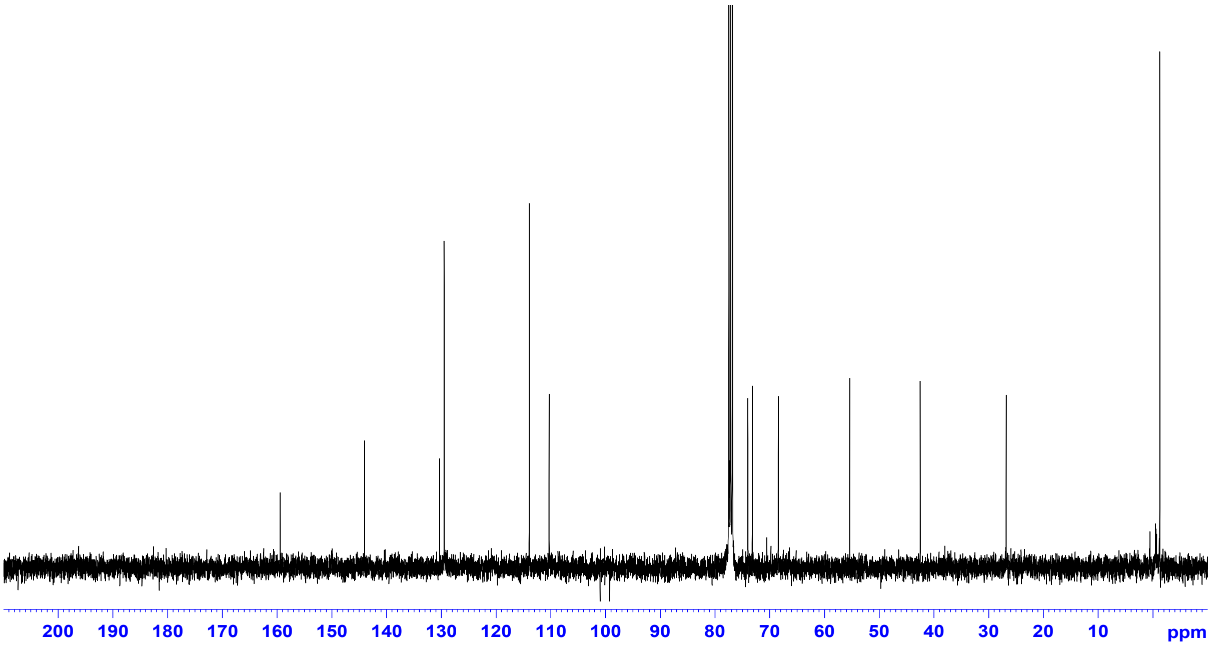
4-Hydroxy-5-((4-methoxybenzyl)oxy)-1-(trimethylsilyl)pentan-2-one (63).[158] To a two-necked dry flask, charged with a magnetic stirring bar and an argon in-outlet, was added $CeCl_3 \cdot (H_2O)_7$ (1.54 g, 4.18 mmol, 4 equiv) then the flask was heated to 145 °C under vigorous stirring for 2 h applying a high vacuum ($p < 10^{-1}$ mbar), giving an off-white powder. The flask was cooled to room temperature, ventilated with argon followed by addition of dry THF (10 mL) then stirring was vigorously continued at room temperature for 2 h.

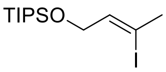
A freshly prepared solution of $TMSCH_2MgCl$ (ca. 1M in Et_2O) was made by applying the following procedure: To a two-necked flask, equipped with an addition funnel and an reflux condenser, was added magnesium turnings (240 mg, 10 mmol) then the flask was set under vacuum and flame-dried for ca. 3 min. $TMSCH_2Cl$ (1.4 ml, 9.93 mmol) and dry Et_2O (8.6 mL) were placed in the addition funnel followed by addition of app. 2 ml of this solution to the magnesium at room temperature. After the reaction had started, the rest of the solution was carefully added over ca. 30 min, which led to the almost complete consumption of magnesium. The so obtained Grignard solution was app. 1M in concentration.

The prepared pale-yellow solution of $TMSCH_2MgCl$ (ca. 1M in Et_2O, 4.18 ml, 4.18 mmol, 4 equiv) was added slowly to the $CeCl_3$-slurry at –78 °C (interior temperature must be below –60 °C). Stirring was continued for 20 min followed by addition of a solution of **61** (0.355 g, 1.05 mml, 1 equiv) in dry THF (1 mL). The mixture was then allowed to warm to room temperature over night. Stirring was continued for 16 h in total which afforded a tan suspension. The mixture was cooled to 0 °C then a precooled solution of HCl (1N, 8 mL, 8 mmol, 8 equiv) at 0 °C was added and vigorously stirred until a yellow solution was formed. The phases were separated then the aqueous phase was extracted twice with Et_2O, the combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and purified by flash chromatography (EtOAc/Hex 1:5) giving **63** (134.7 mg, 0.44 mmol, 42%) as a pale-yellow oil.

TLC: R_f = 0.78 (EtOAc/Hex 1:3, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.28-7.26 (m, 2 H), 6.90-6.87 (m, 2 H), 4.69-4.68 (m, 1 H), 4.65-4.64 (m, 1 H), 4.50 (br. s, 2 H), 3.98-3.92 (m, 1 H), 3.81 (s, 3 H), 3.49 (dd, J = 9.6, 3.6, 1 H), 3.37 (dd, J = 9.6, 7.1, 1 H), 2.29 (d, J = 3.0, 1 H), 2.15-2.12 (m, 2 H), 1.56-1.56 (m, 1 H), 1.55-1.51 (m, 1 H), 0.03 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.4, 144.0, 130.3, 129.5, 114.0, 110.4, 74.0, 73.2, 68.5, 55.4, 42.5, 26.8, -1.2.







(*Z*)-((3-Iodobut-2-en-1-yl)oxy)triisopropylsilane (69b).[25] To a solution of alcohol **68** (387 mg, 1.95 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL) was added 2,6-dimethylpyridine (0.45 mL, 3.90 mmol, 2 equiv) at –78 °C, followed by addition of TIPSOTf (0.55 mL, 2.54 mmol, 1.3 equiv). The mixture was allowed to warm to room temperature after 30 min then MeOH (1 mL) was added and stirring was continued for 30 min more. Saturated aqueous NH_4Cl (10 mL) was added then the phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hex 1:100) to give **69b** (0.60 g, 1.69 mmol, 87%) as a colorless oil that turns red after few days even after storage in the dark.

TLC: R_f = 0.90 (EtOAc/Hex 1:10, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.73 (tq, *J* = 5.1, 1.6, 1 H), 4.24 (dq, *J* = 5.1, 1.6, 2 H), 2.51 (q, *J* = 1.6, 3 H), 1.14-1.06 (m, 21 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.9, 98.6, 68.9, 33.6, 18.1, 12.1.

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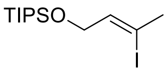
[25] For analytical data, see: Y. Hayashi, M. Shoji, H. Ishikawa, J. Yamaguchi, T. Tamura, H. Imai, Y. Nishigaya, K. Takabe, H. Kakeya, H. Osada, *Angew. Chem. Int. Ed.* **2008**, *47*, 6657-6660.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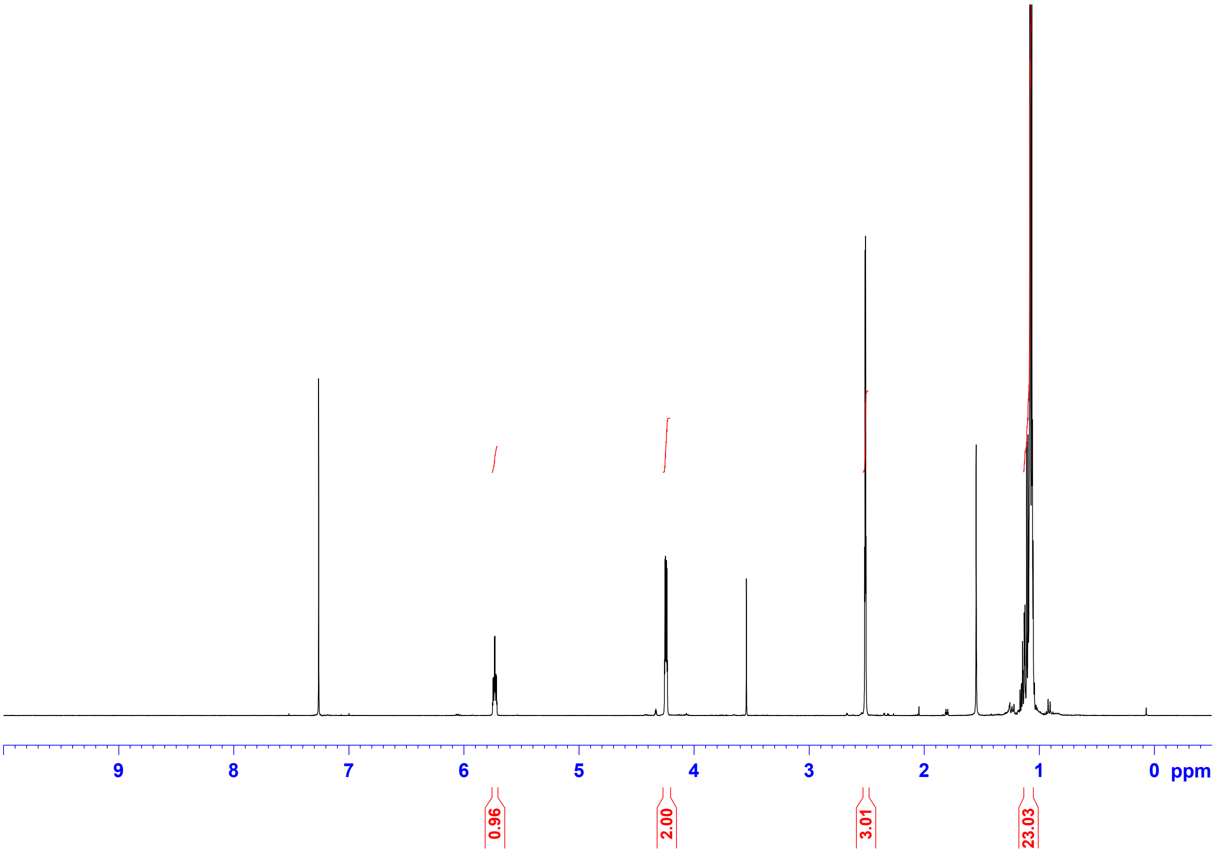
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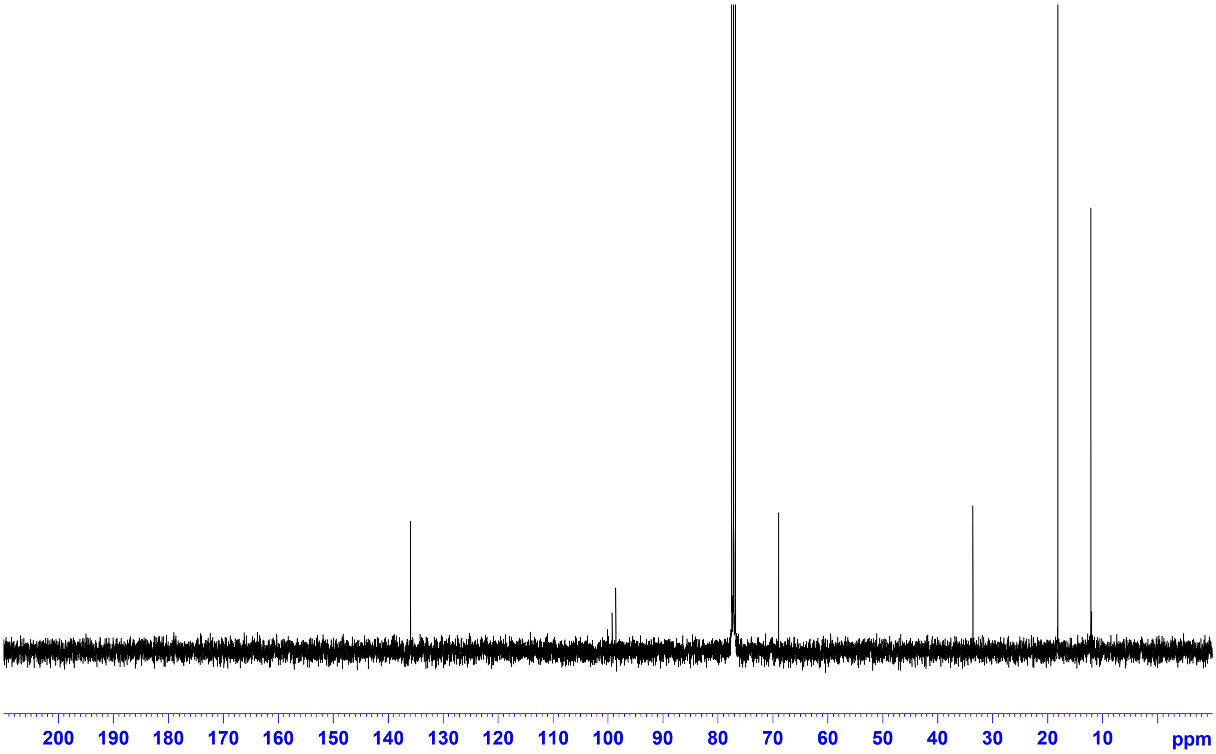
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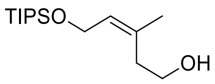
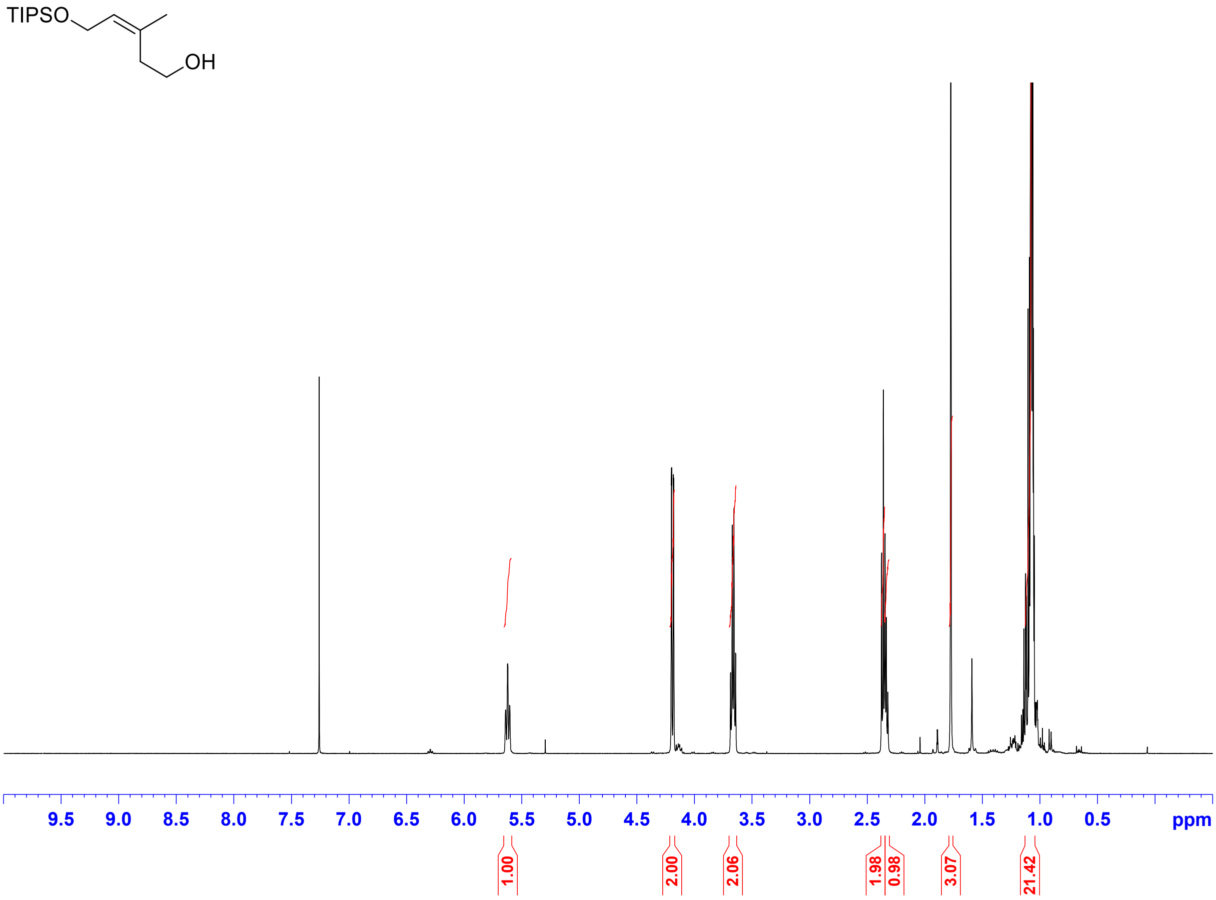


(*Z*)-3-Methyl-5-((triisopropylsilyl)oxy)pent-3-en-1-ol (70b). To a solution of **69b** (2.03 g, 6.5 mmol, 1 equiv) in dry Et_2O (25 mL) was added *t*-BuLi (1.6M in pentane, 8.55 mL, 13.65 mmol, 2.1 equiv) dropwise at –78 °C affording a pale-yellow solution. Stirring was continued for 20 min then oxirane was condensed directly into the reaction mixture, which was allowed to warm to room temperature and stirring was continued for 13 h affording an orange solution. After that time, saturated aqueous NH_4Cl (20 mL) was added then the phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAcHex 1:10→1:6) and afforded **70b** (1.15 g, 4.23 mmol, 65%) as an orange oil.

TLC: $R_f = 0.33$ (EtOAc/Hex 1:5, CPS, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.62 (t, *J* = 7.4, 1 H), 4.19 (dd, *J* = 7.0, 0.8, 2 H), 3.66 (q, *J* = 6.1, 2 H), 2.36 (t, *J* = 6.1, 2 H), 2.33 (t, *J* = 5.7, 1 H), 1.78-1.77 (m, 3 H), 1.13-1.04 (m, 21 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 136.5, 127.2, 59.9, 59.3, 35.4, 23.6, 18.1, 12.1.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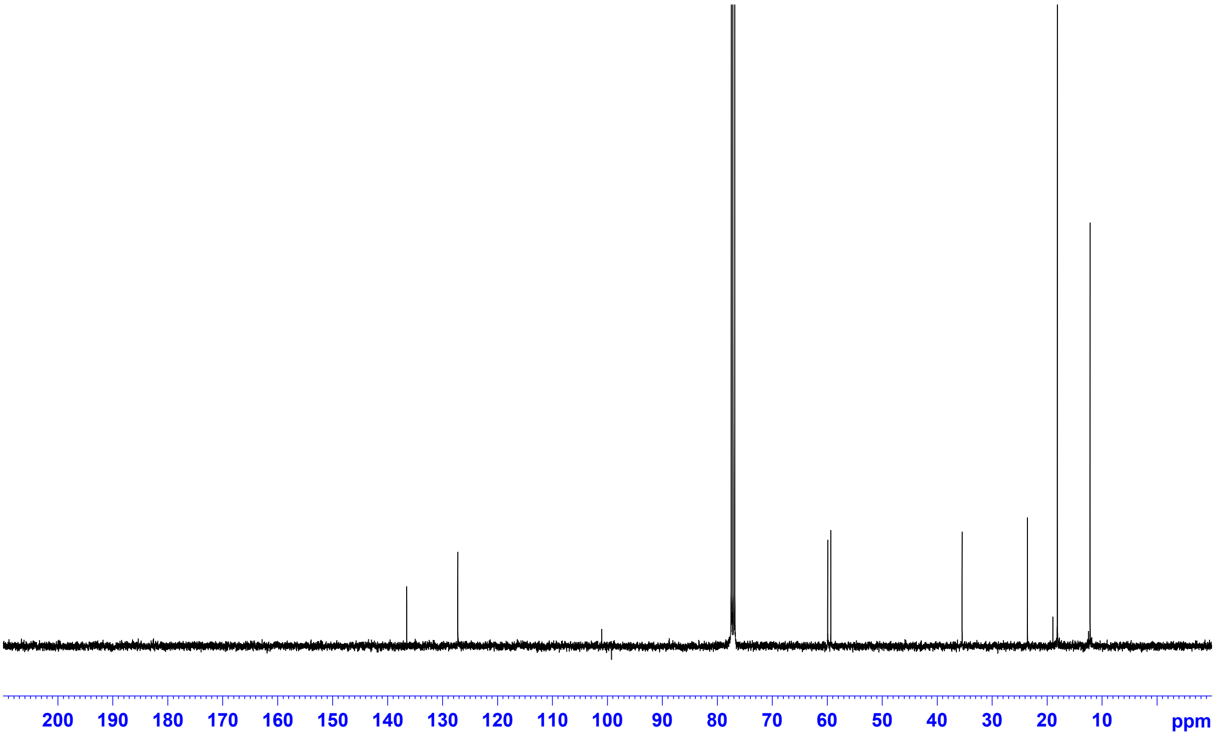
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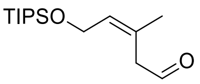
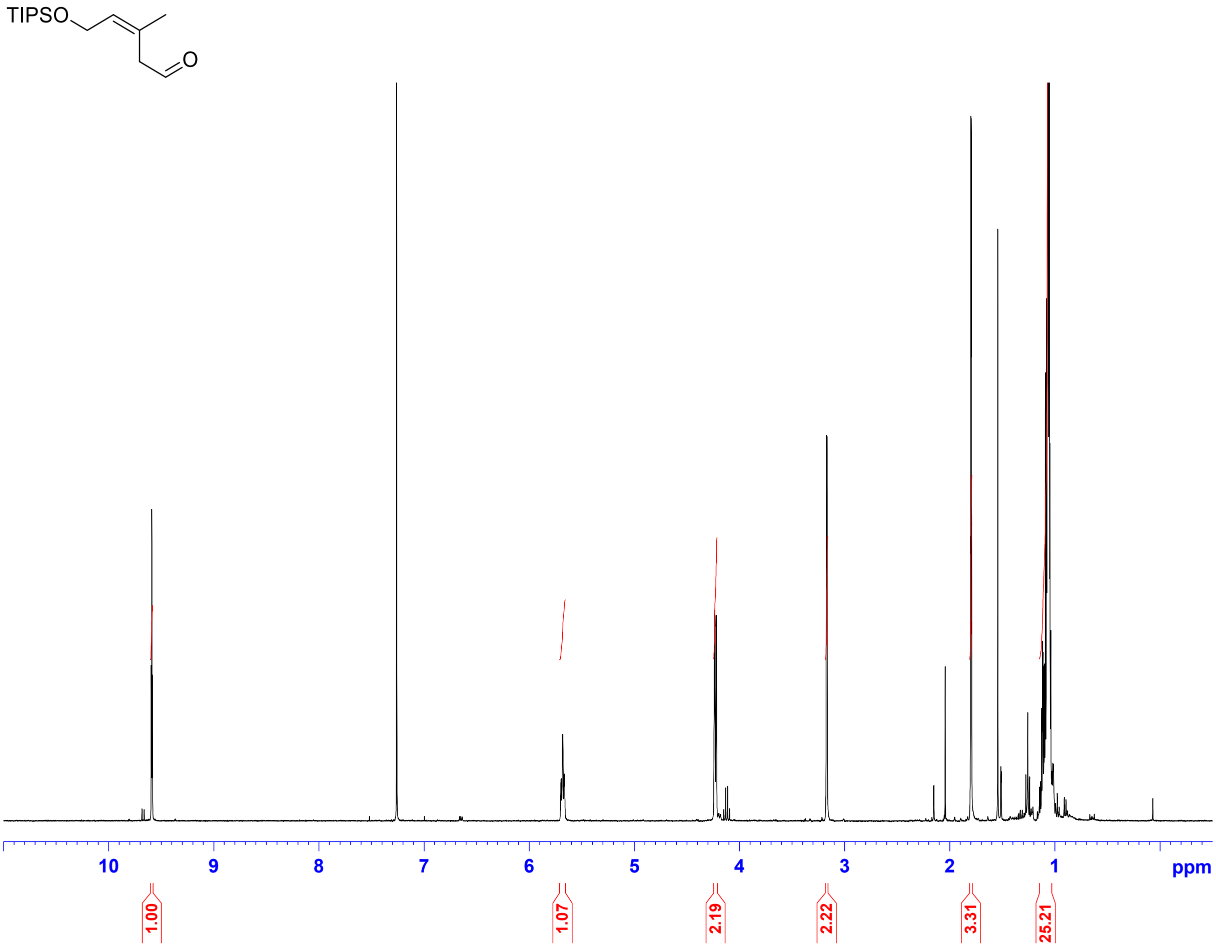


(*Z*)-3-Methyl-5-((triisopropylsilyl)oxy)pent-3-enal (71). To a solution of alcohol **70b** (66 mg, 0.24 mmol, 1 equiv) in dry CH_2Cl_2 (2 mL) was added DMP (133 mg, 0.32 mmol, 1.3 equiv) at 0 °C affording a pale-yellow to colorless suspension immediately. Stirring was continued for 45 min then saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL) were added. Stirring was continued for 10 min, when two almost clear phases had formed. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic extracts were washed once with brine (5 ml) then were dried over $MgSO_4$ and concentred under reduced pressure to a white solid. This solid was redissolved in few CH_2Cl_2 followed by purification over a plug of silica (EtOAc/Hex 1:2, 30 ml) giving **71** (61 mg, 0.23 mmol, 93%) as a pale-yellow.

TLC: R_f = 0.50 (EtOAc/Hex 1:10, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.59 (t, *J* = 2.3, 1 H), 5.70-5.66 (m, 1 H), 4.23 (dq, *J* = 6.4, 1.2, 2 H), 3.17 (d, *J* = 2.3, 2 H), 1.80 (q, *J* = 1.6, 3 H), 1.12-1.05 (m, 21 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 199.2, 130.0, 128.3, 60.2, 47.9, 24.6, 18.2, 12.1.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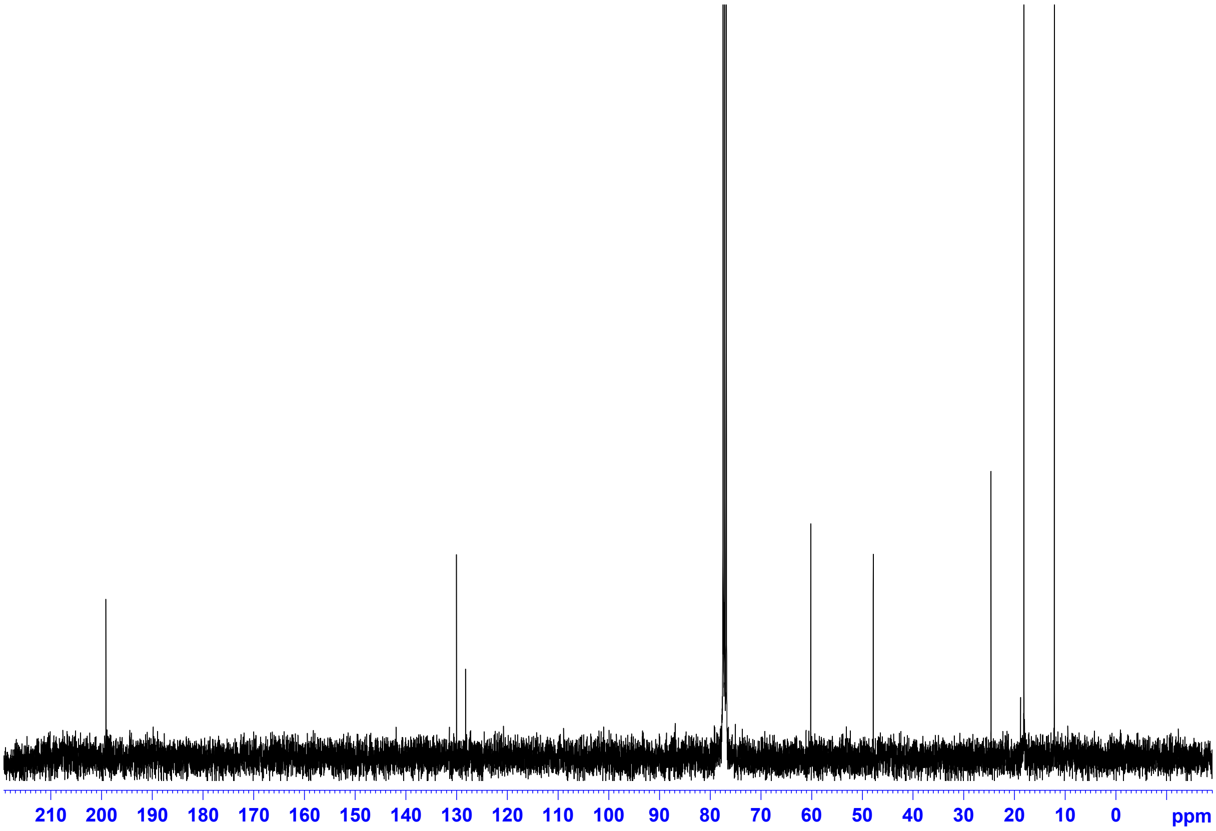
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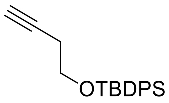

(But-3-yn-1-yloxy)(*tert*-butyl)diphenylsilane (74).[26] To a solution of 3-butyne-1-ol (1 mL, 13.21 mmol, 1 equiv) in DMF (10 mL) at room temperature was added sequentially TBDPSCl (3.4 mL, 14.5 mmol, 1.1 equiv) and ImH (1.8 g, 26.4 mmol, 2 equiv) and stirring was continued for 1 h. MeOH (6 ml) was added then mixture was poured into a stirred solution of **s**aturated aqueous NH_4Cl (30 mL) and H_2O (20 mL) which was followed by addition of EtOAc. Then the phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure followed by purification using flash chromatography (EtOAc/Hex 1:50) affording **74** (3.78 g, 12.27 mmol, 93%) as a colorless oil.

TLC: R_f = 0.59 (EtOAc/Hex 1:30, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4 H), 7.46-7.37 (m, 6 H), 3.79 (t, *J* = 7.1, 2 H), 2.45 (dt, *J* = 7.1, 2.7, 2 H), 1.95 (t, *J* = 2.6, 1 H), 1.06 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.7, 133.7, 129.8, 127.8, 81.6, 69.5, 62.4, 26.9, 22.7, 19.4.

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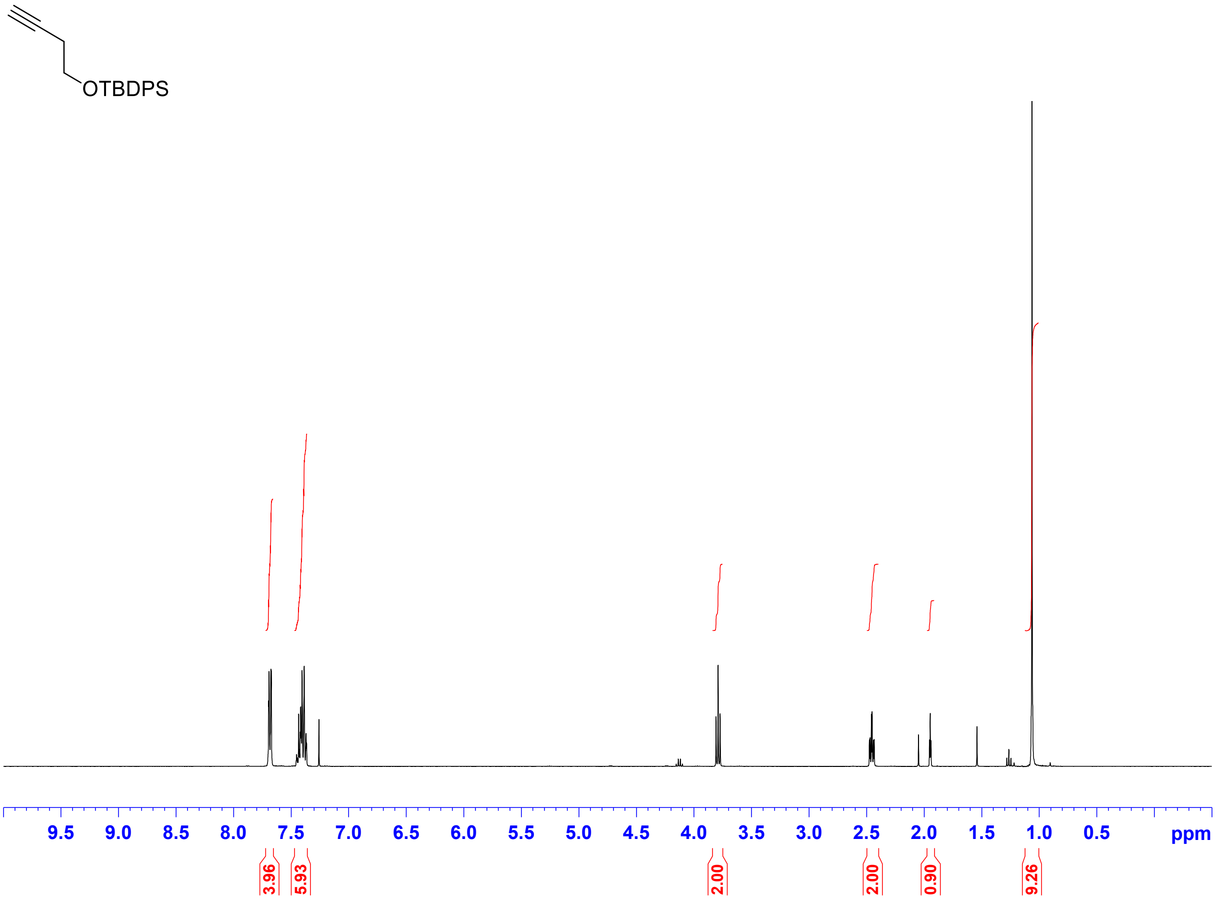
[26] For analytical data, see: T. J. Greshock, D. M. Johns, Y. Noguchi, R. M. Williams, *Org. Lett.* **2008**, *10*, 613-616.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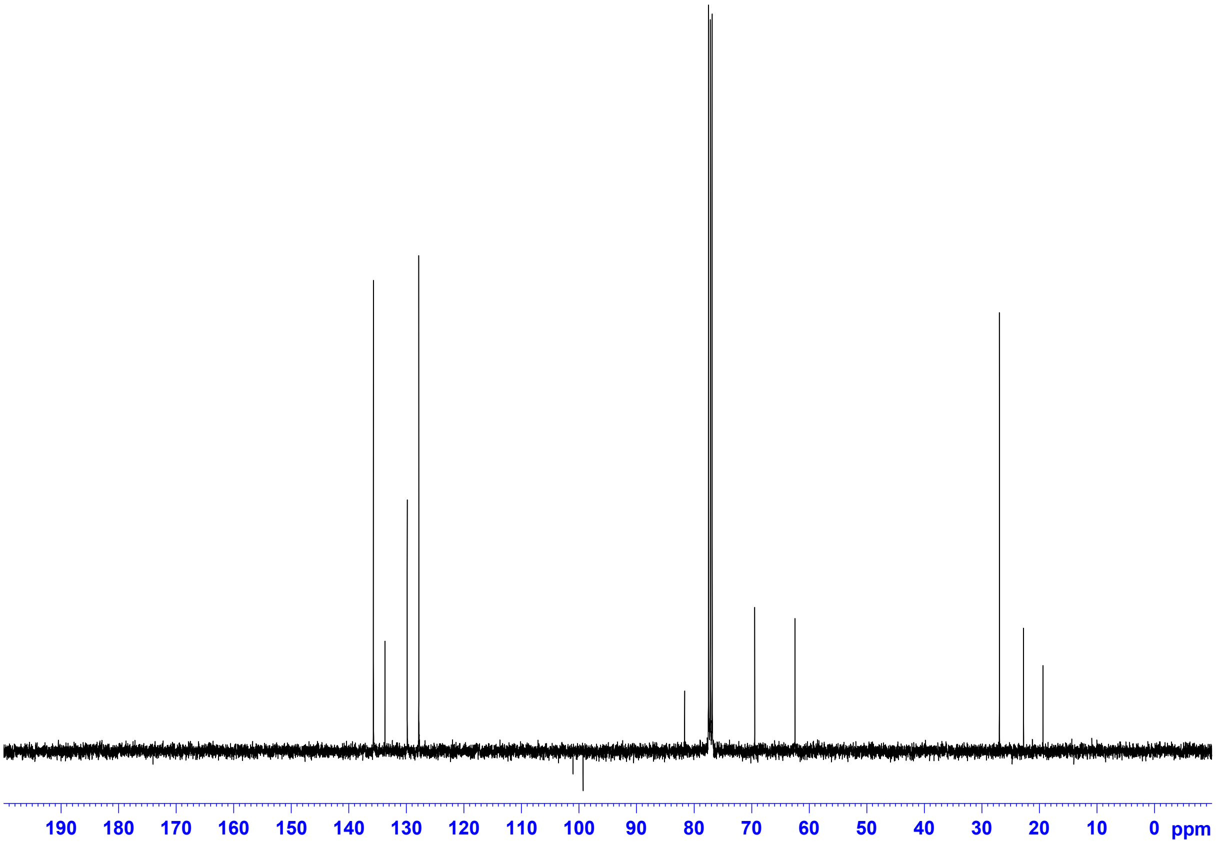
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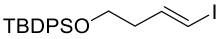

(But-3-yn-1-yloxy)(*tert*-butyl)diphenylsilane (75).[27] To a suspension of Cp_2ZrHCl (1.03 g, 3.97 mmol, 1.22 equiv) in dry THF (10 ml) was added as solution of **74** (1.0 g, 3.25 mmol, 1 equiv) in dry THF (2 mL) at RT and stirring was continued in the dark for 30 min giving a dark-yellow mixture. Another portion of Cp_2ZrHCl (0.46 g, 1.78 mmol, 0.55 equiv) was added and stirring was continued for 15 min more. The yellow-colored mixture was the cooled to –78 °C followed by slow addition of a solution of iodine (1.07 g, 4.23 mmol, 1.3 equiv) in dry THF (5 mL). Stirring was continued for 15 min then the cooling bath was removed and mixture was allowed to warm to room temperature. The reaction mixture was poured onto a stirred solution of saturated aqueous $Na_2S_2O_3$ (40 mL) and H_2O (20 ml). The phases were separated and the organic phase dried over $MgSO_4$ and concentred under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:50) afforded **75** (1.36 g, 3.11 mmol, 96%) as a pale-yellow oil.

TLC: R_f = 0.75 (EtOAc/Hex 1:10, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 4 H), 7.45-7.37 (m, 6 H), 6.53 (dt, *J* = 14.4, 7.3, 1 H), 6.08-6.04 (m, 1 H), 3.69 (t, *J* = 6.4, 2 H), 2.31-2.26 (m, 2 H), 1.05 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 143.5, 135.7, 133.8, 129.8, 127.9, 76.7, 62.5, 39.3, 27.0, 19.3.

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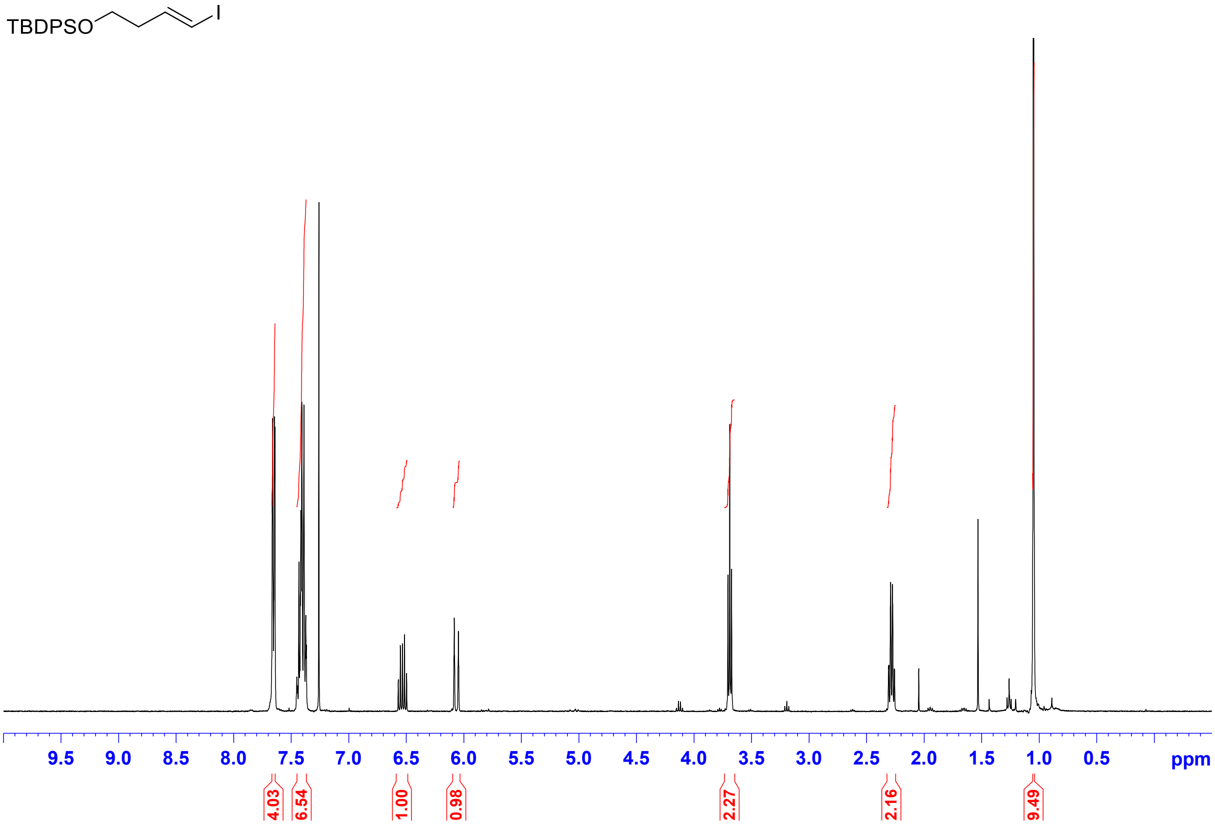
[27] For analytical data, see: T. A. Dineen, W. R. Roush, *Org. Lett.* **2003**, *5*, 4725-4728.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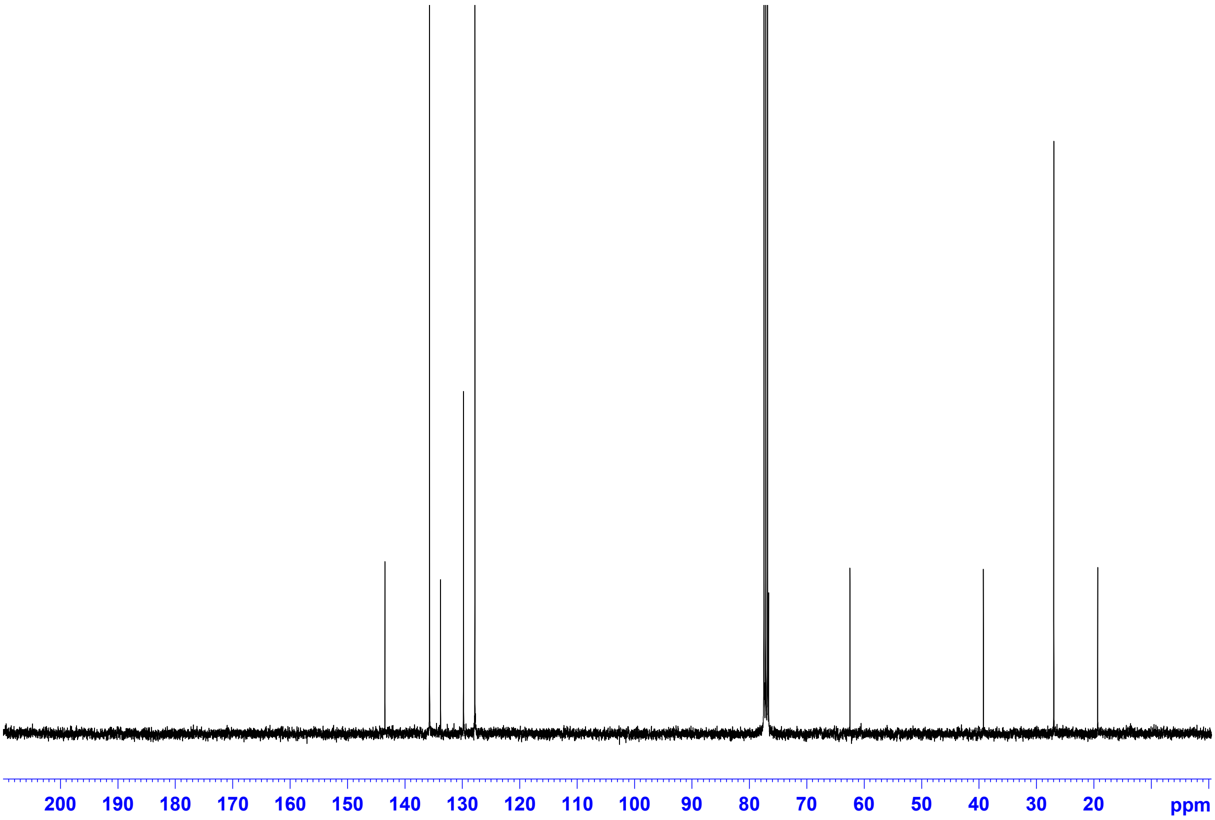
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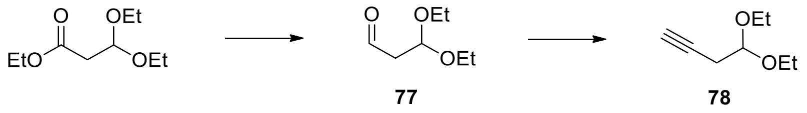

4,4-Diethoxybut-1-yne (78).[28] To a solution of ethyl 3,3-diethoxypropionate (1 mL, 5.1 mmol, 1 equiv) in dry CH_2Cl_2 (10 mL) was added a solution of DIBAL-H (5.1 mL, 5.1 mmol, 1 equiv) slowly at –78 °C, so that the interior temperature stays lower then –65 °C. Stirring was continued for 45 min then the flask was immersed into an ice bath followed by addition of saturated aqueous Rochelle salt (15 mL) and stirring was continued for 10 min then the mixture was filtered over basic celite (coarse 535, pH>8) and washed with CH_2Cl_2. The phases were separated then the the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:10→1:5), which gave the aldehyde **77** (0.37 g, 2.51 mmol, 50%) as a colorless oil.

A solution of CBr_4 (2.54 g, 7.65 mmol, 1.5 equiv) in dry CH_2Cl_2 (20 mL) was cooled to 0 °C followed by addition of PPh_3 (4.0 g, 15.4 mmol, 3.1 equiv). Stirring was continued for 5 min then a solution of the prepared aldehyde **77** in dry CH_2Cl_2 (5 mL) was added followed by stirring at that temperature for 45 min. After that time, the mixture was poured onto ice-cooled hexane (100 mL) followed by filtration over a pad of silica and washing with EtOAc/Hex (1:1) (200 mL). Concentration under reduced pressure afforded a pale-yellow liquid which was used without further purification. The crude dibromide was dissolved in dry THF (20 ml) followed by addition of *n*-BuLi (1.6M in hexane, 6.7 mL, 10.77 mmol, 2.1 equiv) at –78 °C and stirring was continued for 20 min then the flask was immersed into a cooling bath (0 °C) and stirring was continued for another 20 min. Saturated aqueous $NaHCO_3$ (20 mL) and H_2O (10 mL) as well as Et_2O (10 mL) were added then the phases were separated and the aqueous phase extracted with Et_2O (2 x 10 mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated under reduced pressure. Purification using bulb-to-bulb distillation (6 mbar, 100-110 °C) afforded **78** (187 mg, 1.32 mmol, 26%, 2 steps) as a colorless oil.

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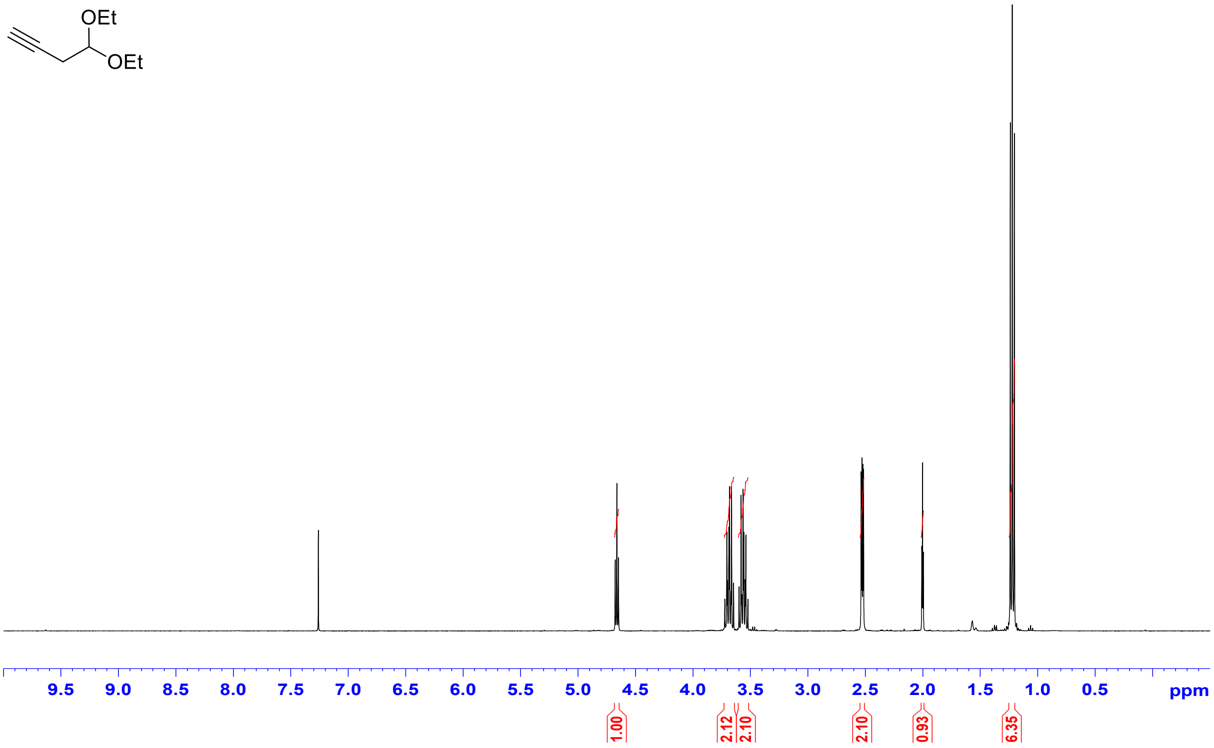
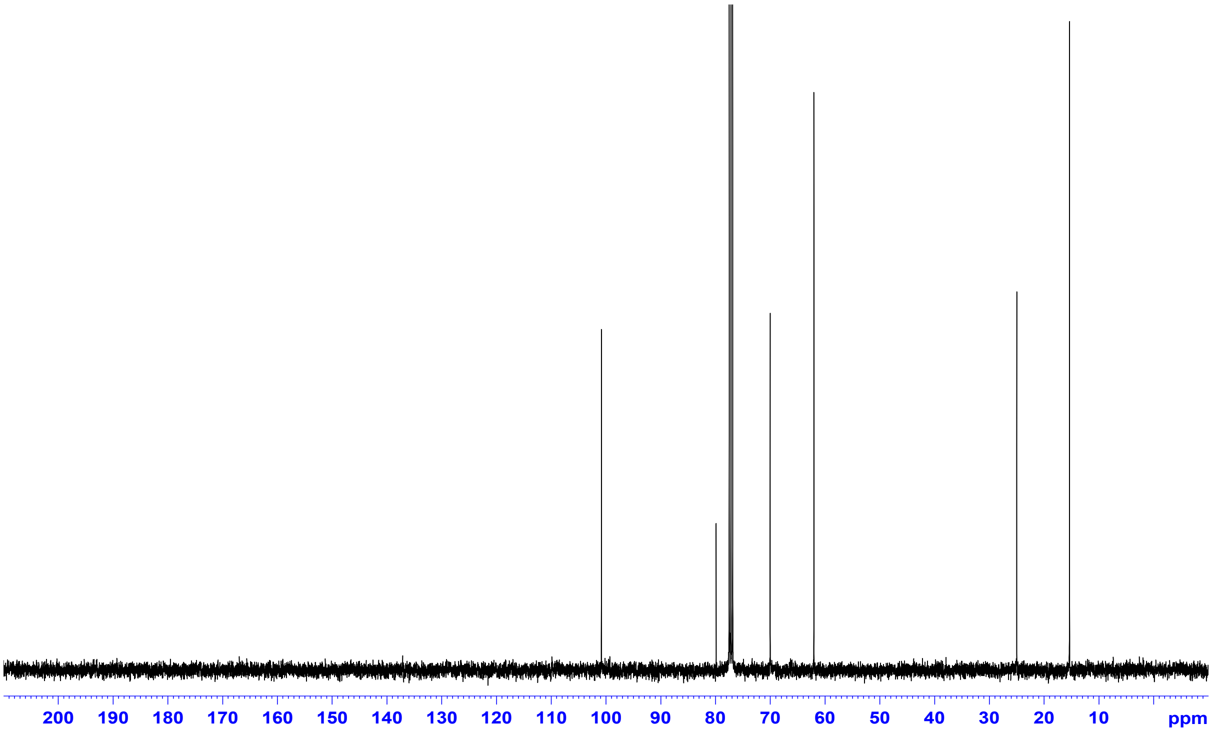
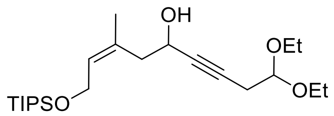
[28] Direct conversion of 3-bromopropyne and triethyl orthofromate catalyzed by aluminum powder and $HgCl_2$ afforded the title compound **78** in 76% yield, see:I. Beaudet, A. Duchêne, J.-L. Parrain, J.-P. Quintard, *J. Organomet. Chem.* **1992**, *427*, 201-212.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.66 (t, *J* = 5.6, 1 H), 3.69 (dq, *J* = 9.4, 7.1, 2 H), 3.56 (dq, *J* = 9.4, 7.1, 2 H), 2.53 (dd, *J* = 5.7, 2.8, 2 H), 2.0 (t, *J* = 2.7, 1 H), 1.22 (t, *J* = 7.1, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 100.8, 79.9, 70.0, 62.0, 25.0, 15.4.

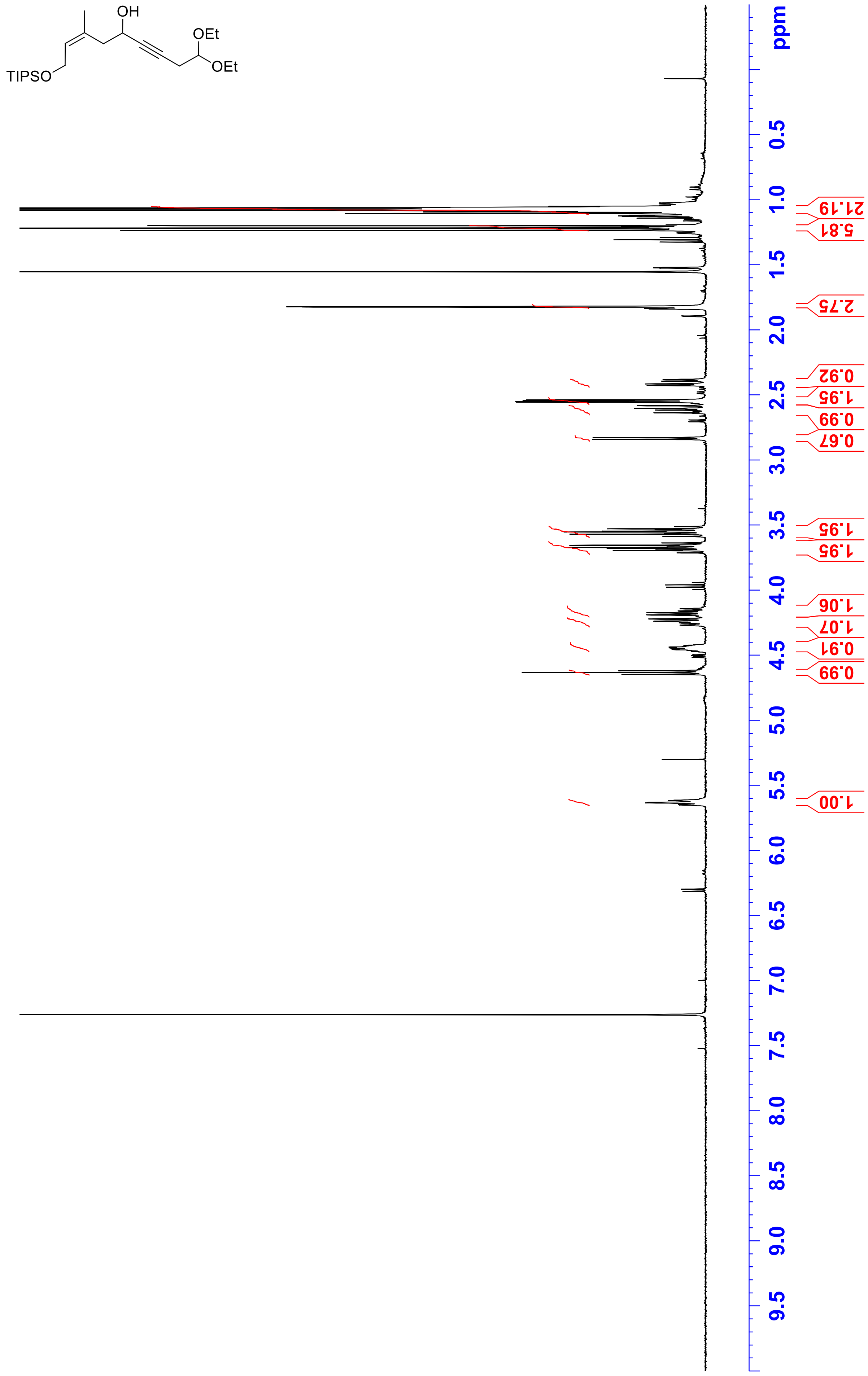






(*Z*)-9,9-Diethoxy-3-methyl-1-((triisopropylsilyl)oxy)non-2-en-6-yn-5-ol (79). To a solution of **78** (43 mg, 0.3 mmol, 1.4 equiv) in dry THF (1 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 0.19 mL, 0.30 mmol, 1.4 equiv) at –78 °C and stirring was continued for 20 min. After that time, a solution of **71** (57 mg, 0.21 mmol, 1 equiv) in dry THF (1 mL) was added slowly and stirring was continued for 3 h then the cooling bath was removed and stirring was continued until room temperature was reached. Brine (10 mL) and H_2O (1 mL) were added followed by Et_2O (5 mL) then the phases were separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:9) giving **79** (58 mg, 0.14 mmol, 66%) as an oil.

TLC: R_f = 0.26 (EtOAc/Hex 1:5, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.64-5.60 (m, 1 H), 4.63 (t, *J* = 5.7, 1 H), 4.47-4.42 (m, 1 H), 4.27-4.22 (m, 1 H), 4.19-4.14 (m, 1 H), 3.68 (dq, *J* = 9.4, 7.2, 2 H), 3.55 (dq, *J* = 9.4, 7.2, 2 H), 2.83 (d, *J* = 5.5, 1 H), 2.61 (dd, *J* = 13.4, 8.3, 1 H), 2.55 (dd, *J* = 5.7, 2.1, 2 H), 2.40 (dd, *J* = 13.4, 5.0, 1 H), 1.83-1.82 (m, 3 H), 1.22 (t, *J* = 7.1, 6 H), 1.11-1.06 (m, 21 H).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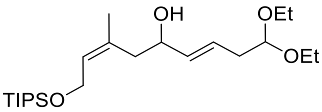
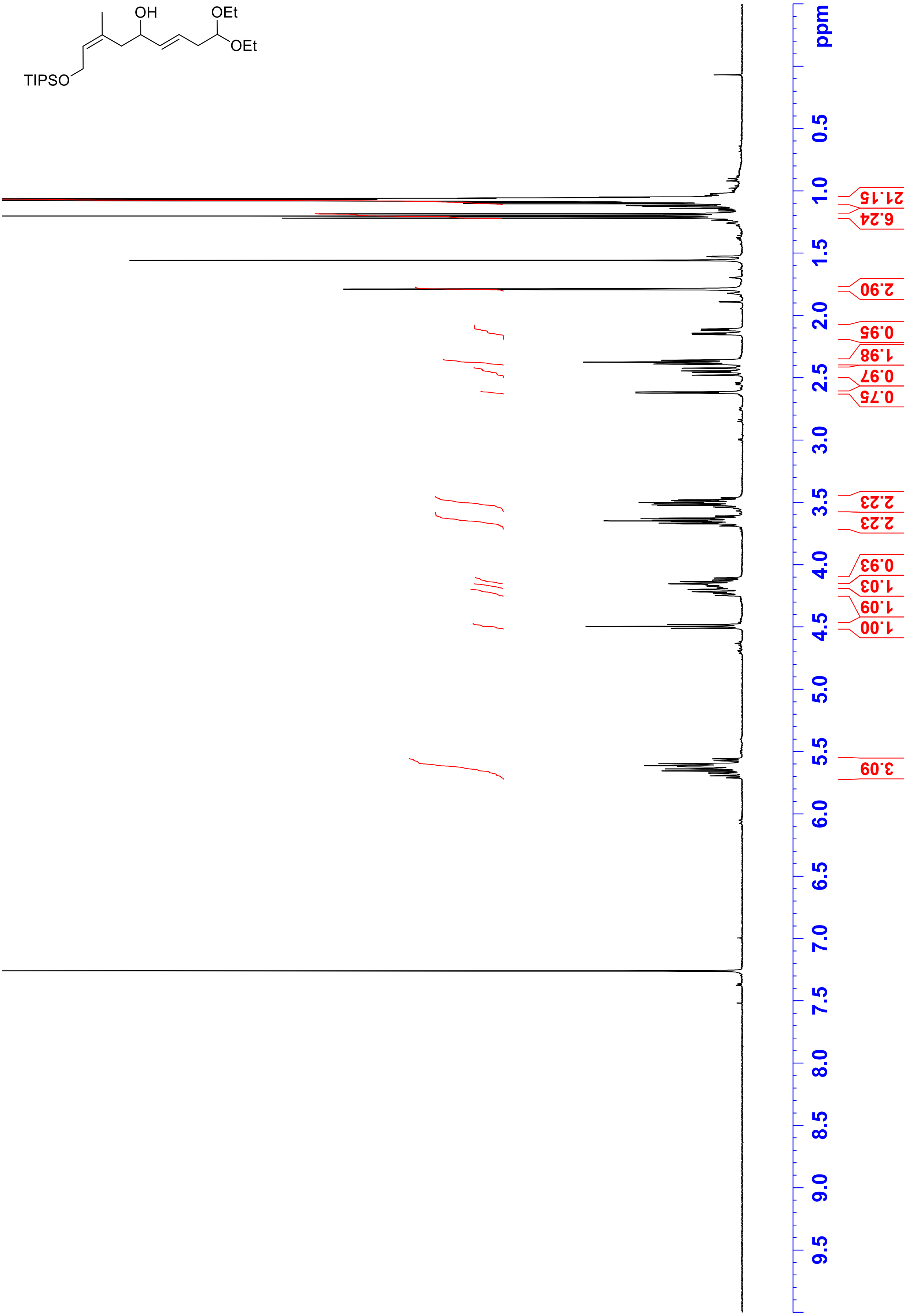


(2*Z*,6*E*)-9,9-Diethoxy-3-methyl-1-((triisopropylsilyl)oxy)nona-2,6-dien-5-ol (80). To a solution of **79** (56.9 mg, 0.138 mmol, 1 equiv) in dry THF (1 mL) was added RedAl® (65% in toluene, 0.07 mL, 0.23 mmol, 1.66 equiv) at 0 °C then the cooling bath was removed and stirring was continued for 3 h followed by addition of a second portion of RedAl® (65% in toluene, 0.07 mL, 0.23 mmol, 1.66 equiv). Stirring was continued for 1 h more then saturated aqueous Rochelle salt (5 mL) was added as well as Et_2O (5 ml) and stirring was continued until two clear phases were formed. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:6) afforded **80** (30 mg, 0.07 mmol, 52%) as an oil.

TLC: R_f = 0.42 (EtOAc/Hex 1:3, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.71-5.56 (m, 3 H), 4.50 (t, *J* = 5.9, 1 H), 4.23 (dd, *J* = 12.1, 7.2, 1 H), 4.18-4.14 (m, 1 H), 4.13 (dd, *J* = 12.2, 6.9, 1 H), 3.65 (ddq, *J* = 9.4, 7.0, 2.3, 2 H), 3.50 (ddq, *J* = 9.4, 7.0, 1.5, 2 H), 2.61 (d, *J* = 3.7, 1 H), 2.45 (dd, *J* = 13.4, 9.1, 1 H), 2.38 (t, *J* = 6.2, 2 H), 2.13 (dd, *J* = 13.4, 4.0, 1 H), 1.79 (br. s, 3 H), 1.20 (t, *J* = 7.0, 6 H), 1.11-1.05 (m, 21 H).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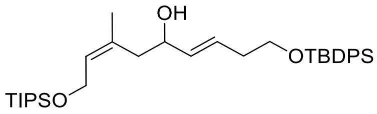
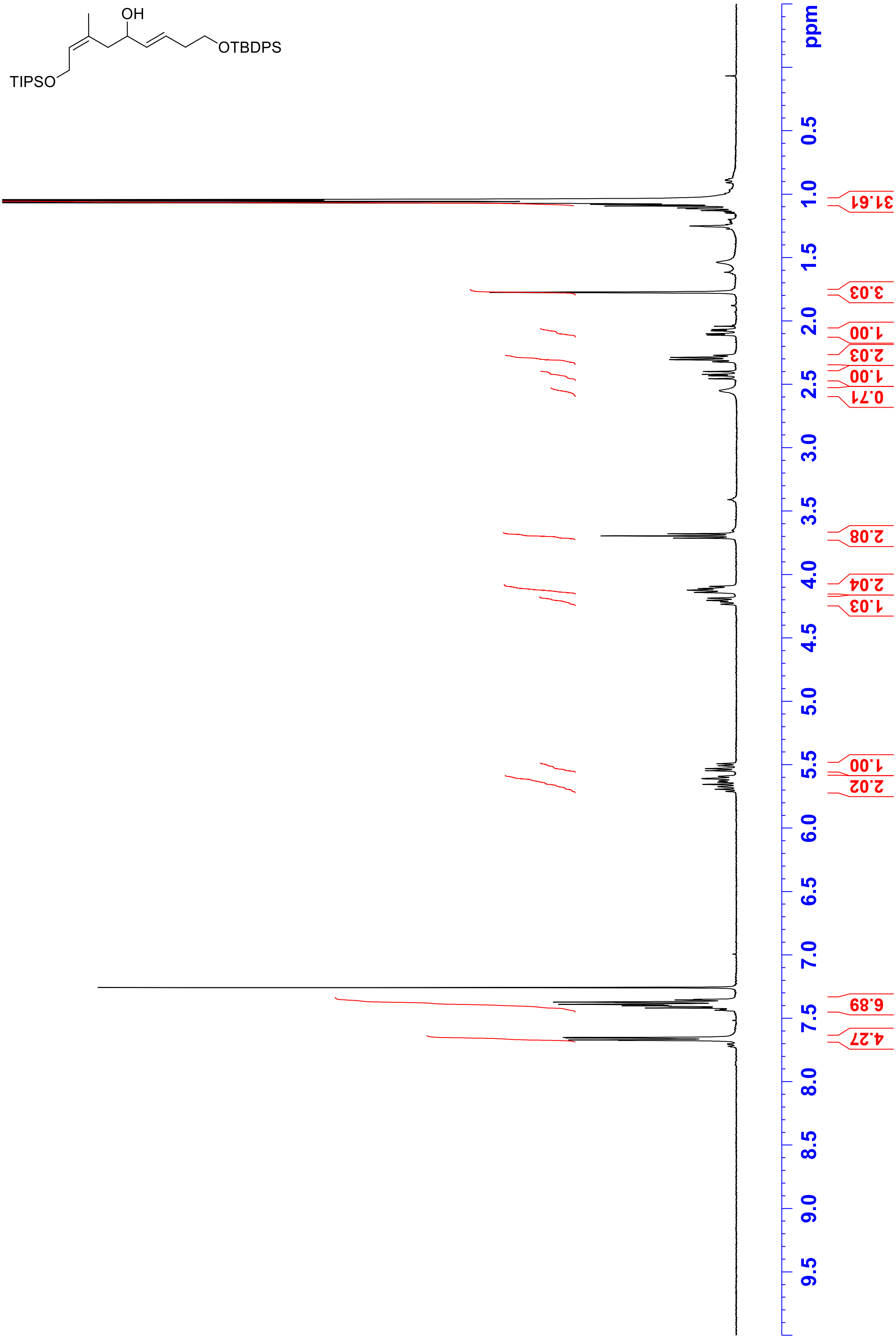


(6*Z*,10*E*)-3,3-Diisopropyl-2,7,16,16-tetramethyl-15,15-diphenyl-4,14-dioxa-3,15-disilaheptadeca-6,10-dien-9-ol (76). To a solution of **75** (63 mg, 0.14 mmol, 1.2 equiv) in dry Et_2O (2 mL) was added *t*-BuLi (1.7M in pentane, 0.17 mL, 0.29 mmol, 2.5 equiv) at –78 °C then stirring was continued for 30 min. This solution was cannulated into a solution of **71** (31 mg, 0.12 mmol, 1 equiv) in Et_2O (1 mL) and stirring was continued for 1.5 h then the cooling bath was removed and stirring was continued until room temperature was reached. Saturated aqueous NH_4Cl (3 mL) was added then the phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:30→1:20) giving **876** (22.0 mg, 0.04 mmol, 33%) as a pale-yellow oil.

TLC: R_f = 0.30 (EtOAc/Hex 1:10, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68-7.64 (m, 4 H), 7.43-7.35 (m, 6 H), 5.72-5.60 (m, 2 H), 5.55-5.49 (m, 1 H), 4.21 (dd, *J* = 11.9, 7.1, 1 H), 4.14-4.09 (m, 2 H), 3.70 (t, *J* = 6.8, 2 H), 2.60 (br. s, 1 H), 2.43 (dd, *J* = 13.4, 9.3, 1 H), 2.32-2.27 (m, 2 H), 2.09 (dd, *J* = 13.6, 4.0, 1 H), 1.77 (s, 3 H), 1.11-1.04 (m, 30 H).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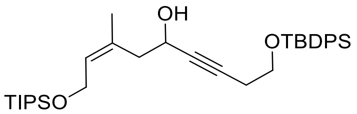
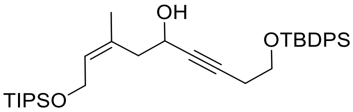


(*Z*)-3,3-Diisopropyl-2,7,16,16-tetramethyl-15,15-diphenyl-4,14-dioxa-3,15-disilaheptadec-6-en-10-yn-9-ol (81). To a solution of **74** (61 mg, 0.20 mmol, 1.3 equiv) in dry Et_2O (1 mL) was added *n*-BuLi (1.6M in hexane, 0.13 mL, 0.20 mmol, 1.3 equiv) at –78 °C then stirring was continued for 20 min. A solution of **76** (41 mg, 0.15 mmol, 1 equiv) in Et_2O (1 mL) was added dropwise and stirring was continued for 30 min at that temperature. Then the cooling bath was removed and stirring was continued for 2.5 h more. Saturated aqueous NH_4Cl (2 mL) was added as well as H_2O (1 ml) then the phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure followed by purification using flash chromatography (EtOAc/Hex 1:20) giving **81** (50.6 mg, 0.087 mmol, 58%) as a pale-yellow oil.

TLC: R_f = 0.25 (EtOAc/Hex 1:3, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68-7.66 (m, 4 H), 7.45-7.36 (m, 6 H), 5.61 (t, *J* = 6.6, 1 H), 4.42-4.36 (m, 1 H), 4.23 (dd, *J* = 12.1, 6.9, 1 H), 4.14 (dd, *J* = 12.9, 6.9, 1 H), 3.76 (t, *J* = 7.2, 2 H), 2.79 (d, *J* = 5.3, 1 H), 2.58 (dd, *J* = 13.4, 8.5, 1 H), 2.48 (dt, *J* = 7.2, 1.8, 2 H), 2.35 (dd, *J* = 13.4, 4.9, 1 H), 1.79 (s, 3 H), 1.10-1.04 (m, 30 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.7, 135.2, 133.8, 129.8, 128.2, 127.8, 82.6, 81.9, 62.6, 60.2, 59.5, 41.2, 27.0, 24.2, 23.1, 19.4, 18.2, 12.1.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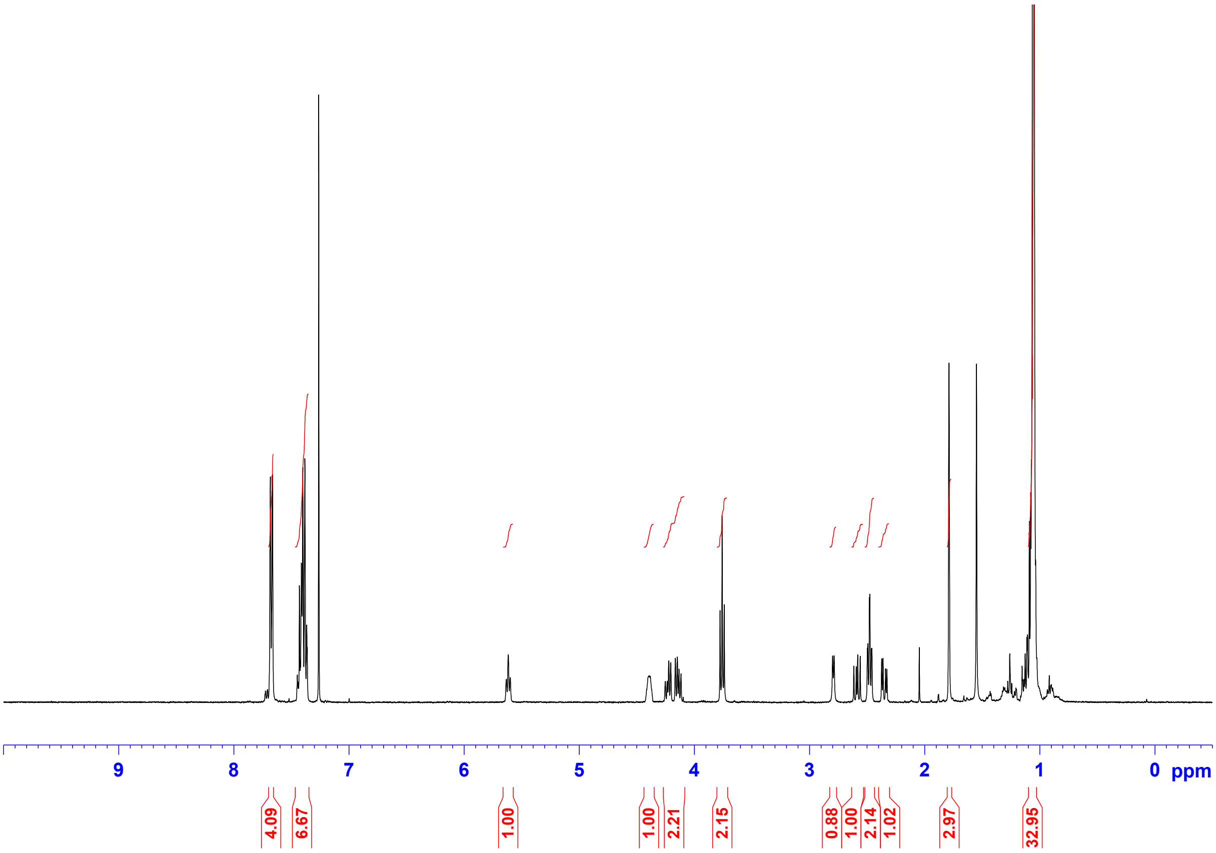
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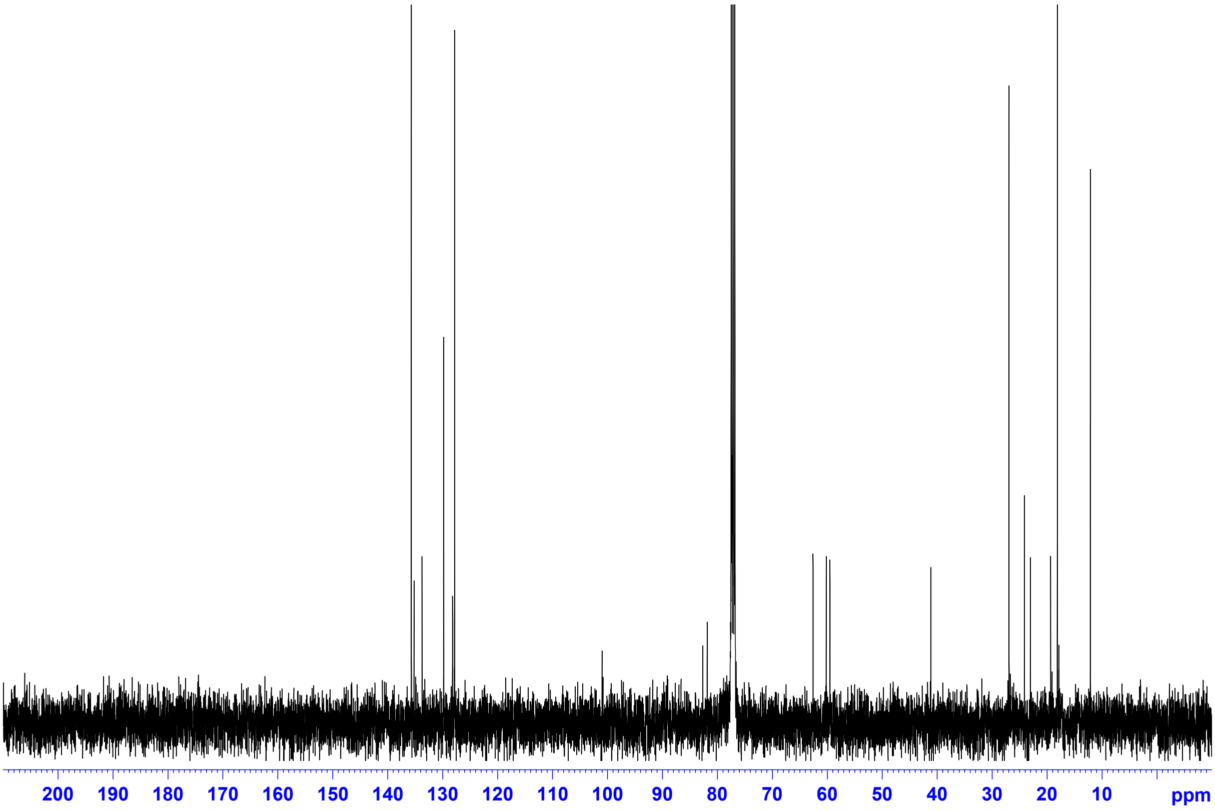
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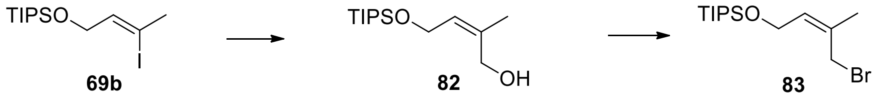

(*Z*)-((4-Bromo-3-methylbut-2-en-1-yl)oxy)triisopropylsilane (83).[29] In a high-pressure apparatus was placed a solution fo vinyl iodide **69** (506.7 mg, 1.43 mmol, 1 equiv) in dry MeOH (20 mL) followed by addition of NEt_3 (0.59 mL, 4.23 mmol, 3 equiv) and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (50 mg, 0.07 mmol, 0.05 equiv). The atmosphere was replaced by CO (4 atm) and stirring was continued for 7 h at room temperature. After that time, the reaction mixture was diluted with Et_2O (10 mL) then saturated aqueous NH_4Cl was added so that two phases were formed. The phases were separated and the organic phase was washed once with brine then dried over $MgSO_4$ and concentrated under reduced pressure. The solid was suspended in Et_2O then filtered over celite and washed with Et_2O followed by concentration under reduced pressure affording the curde product which was used without purification.

A solution of the methoxy ester in dry THF (15 mL) was cooled to –78 °C followed by addition of $LiAlH_4$ (2M in THF, 1.6 mL, 3.2 mmol, 2.2 equiv). Stirring was continued for 20 min then the cooling bath was removed and the flask immersed into an icebath. After 1 h more, the solution was slowly added to a vigorously stirred mixture of saturated aqueous Rochelle salt (50 mL) and Et_2O (20 mL) and stirring was continued for 45 min then the phases were separated. The aqueous phase was extracted with EtOAc (2 x 20 mL) then the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:5) afforded the alcohol **82** (82.4 mg, 0.32 mmol, 22%) as a pale-yellow oil.

To a solution of the alcohol **82** (78.8 mg, 0.3 mmol, 1 equiv), in dry CH_2Cl_2 (5 mL) was added PPh_3 (88 mg, 0.34 mmol, 1.1 equiv) followed by NBS (60 mg, 0.34 mmol, 1.1 equiv) at 0 °C and stirring was continued for 30 min then more PPh_3 (16 mg, 0.06 mmol, 0.2 equiv) and NBS (11 mg, 0.06 mmol, 0.2 equiv) were added so that approximately 1.3 equiv of each reagent was present. After ca. 10 min saturated aqueous NH_4Cl (5 mL) and H_2O (2 mL) were added followed by separation of phases. The aqueous phase was extracted with EtOAc (2 x 5 mL) then the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:100) afforded **83** (55.4 mg, 0.17 mmol, 58%) as a colorless oil.

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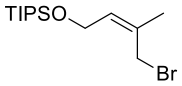
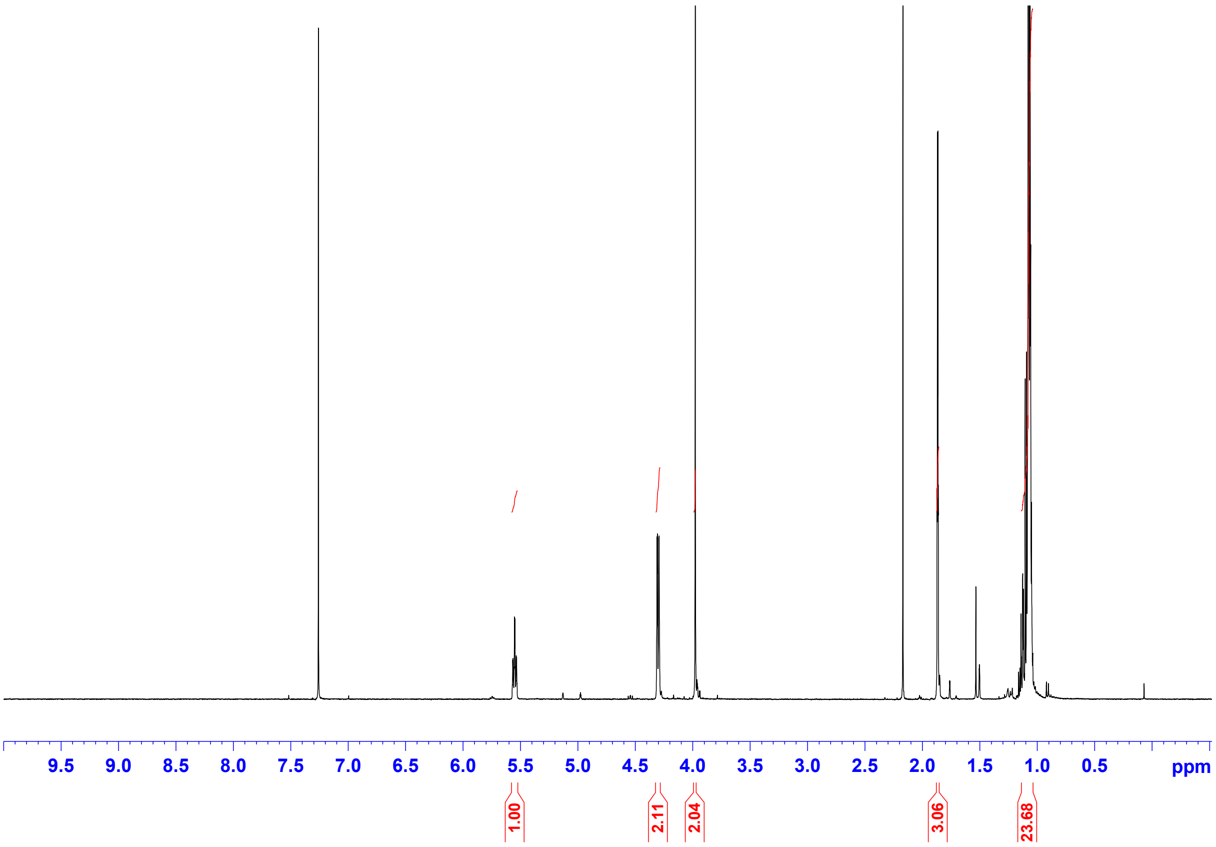
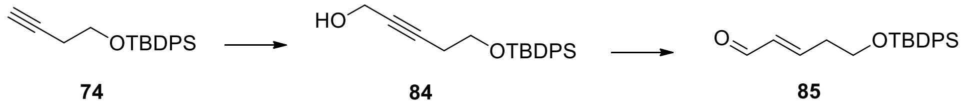
[29] For experimental procedure with respect to the palladium-mediated carbonlyation/reduction see : A. Chau, J.-F. Paquin, M. Lautens, *J. Org. Chem.* **2006**, *71*, 1924-1933.

TLC: R_f = 0.84 (EtOAc/Hex 1:10, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.55 (tq, *J* = 6.2, 1.4, 1 H), 4.30 (dq, *J* = 6.1, 1.3, 2 H), 3.98 (s, 2 H), 1.87 (q, *J* = 1.4, 3 H), 1.14-1.04 (m, 21 H).





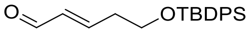


(*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)pent-2-enal (85). To a solution of **74** (913 mg, 2.96 mmol, 1 equiv) in dry THF (10 mL) was added a solution of *n*-BuLi (1.6M in hexane, 2.05 mL, 3.25 mmol, 1.1 equiv) at –78 °C then stirring was continued for 30 min followed by addition of paraformaldehyde (214 mg, 7.13 mmol, 2.4 equiv) in one portion. Stirring was continued for 20 h while the reaction mixture was slowly allowed to warm to room temperature. Saturated aqueous NH_4Cl (10 mL) and H_2O (2 mL) were added followed by separation of phases and extraction with Et_2O (2 x 10 mL) then the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1/5) afforded the propargylic alcohol **84** (625.6 mg, 1.84 mmol, 62%) as a colorless oil.

To a solution of the alcohol **84** (589 mg, 1.74 mmol, 1 equiv) in dry THF (10 ml) was added RedAl® (65% in toluene, 0.78 mL, 2.6 mmol, 1.5 equiv) at 0 °C then the cooling bath was removed and stirring was continued for 2.5 h at room temperature. Saturated aqueous Rochelle salt (10 mL) was slowly added as well as H_2O (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure followed by purification using flash chromatography (EtOAc/Hex 1:5) giving the allylic alcohol (443 mg, 1.30 mmol, 75%) as a colorless oil.

To a solution of the allylic alcohol (437.1 mg, 1.28 mmol, 1 equiv) was added activated MnO_2 (1.16 g, 13.3 mmol, 10.4 equiv) and stirring was continued under argon for 21 h at RT. Filtration over a pad of celite followed by washing with CH_2Cl_2 (200 mL) and concentration under reduced pressure afforded an oil which was purified using flash chromatography (EtOAc/Hex 1:20→1:10) giving the unsaturated aldehyde **85** (375 mg, 1.11 mmol, 87%) as a yellow oil.

TLC: $R_f = 0.55$ (EtOAc/Hex 1:5, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): $\delta = 9.48$ (d, $J = 7.9$, 1 H), 7.66-7.62 (m, 4 H), 7.47-7.37 (m, 6 H), 6.84 (dt, $J = 15.8, 7.0$, 1 H), 6.15 (ddt, $J = 15.8, 7.9, 1.5$, 1 H), 3.83 (t, $J = 6.1$, 2 H), 2.58-2.53 (m, 2 H), 1.06 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): $\delta = 194.1$, 155.6, 135.7, 134.6, 133.6, 130.0, 127.9, 62.2, 36.1, 27.0, 19.3.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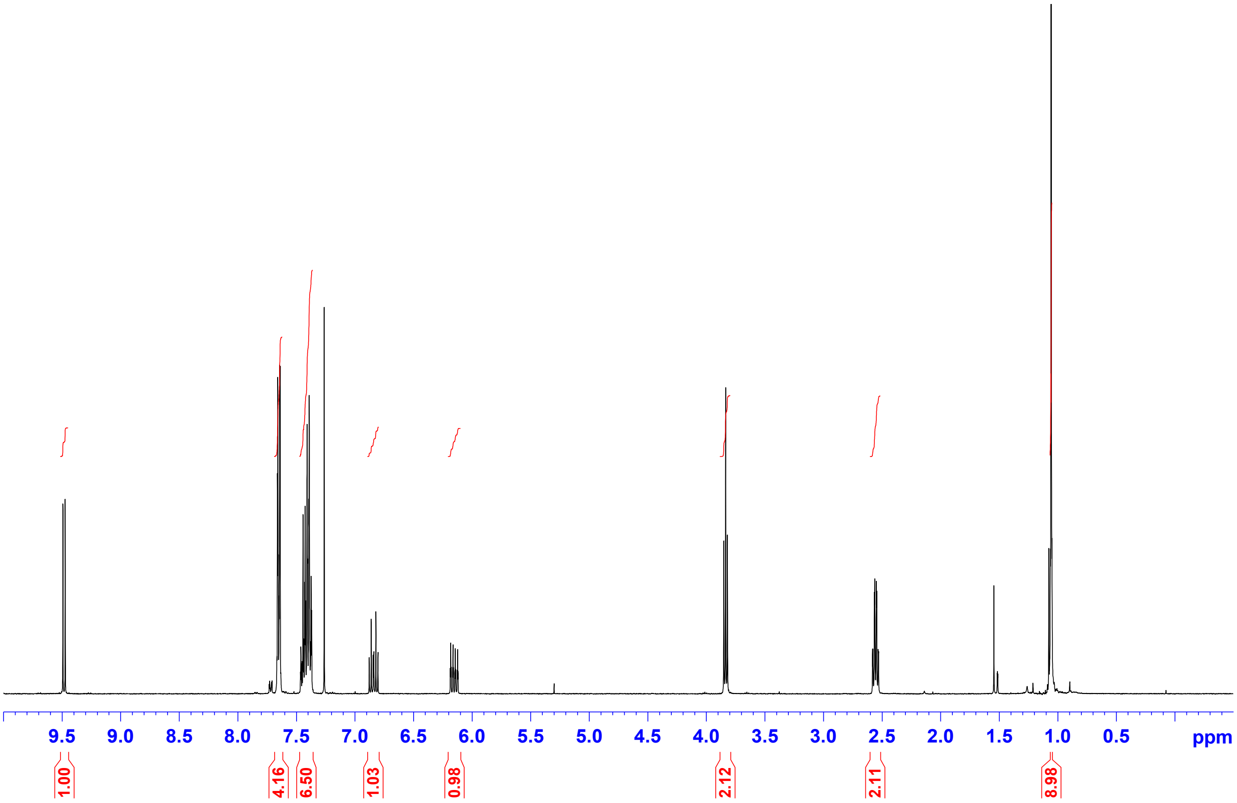
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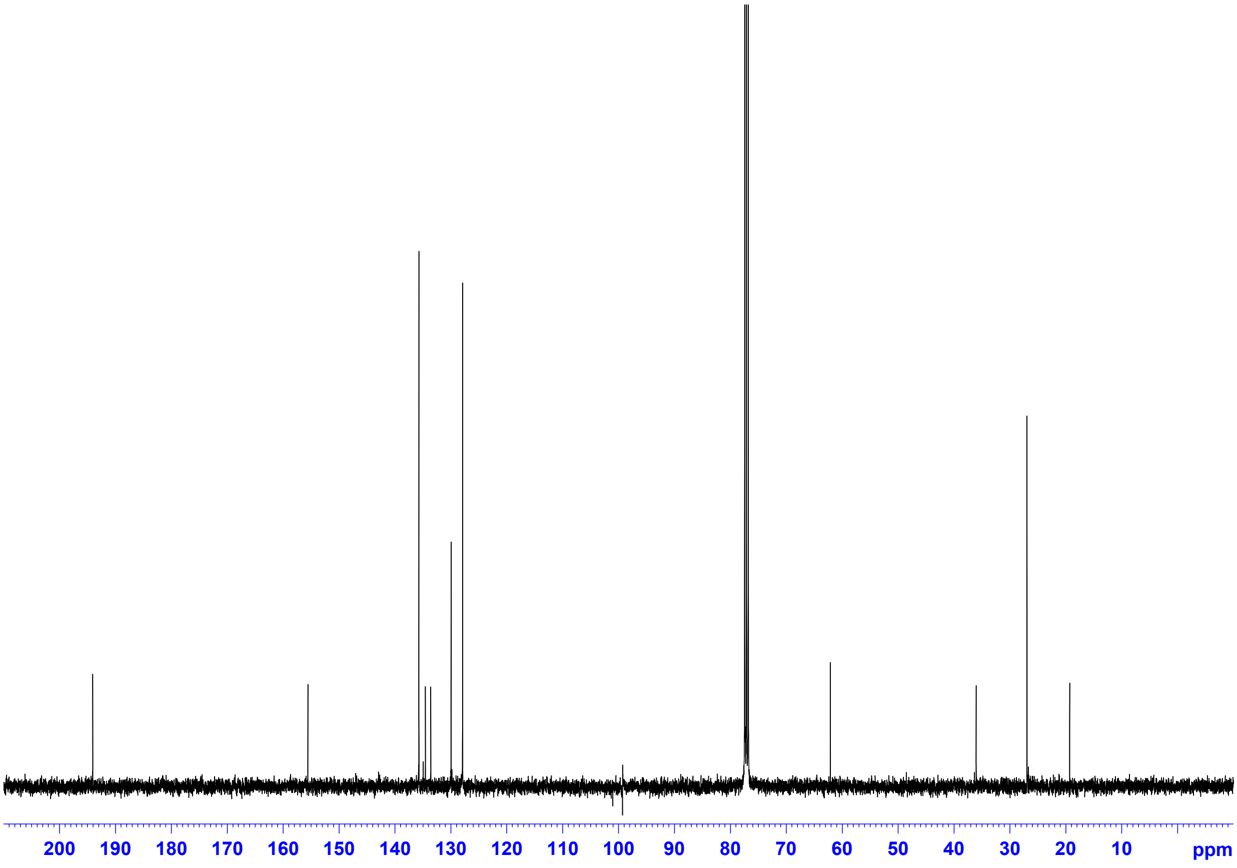
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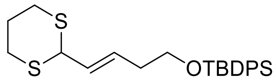
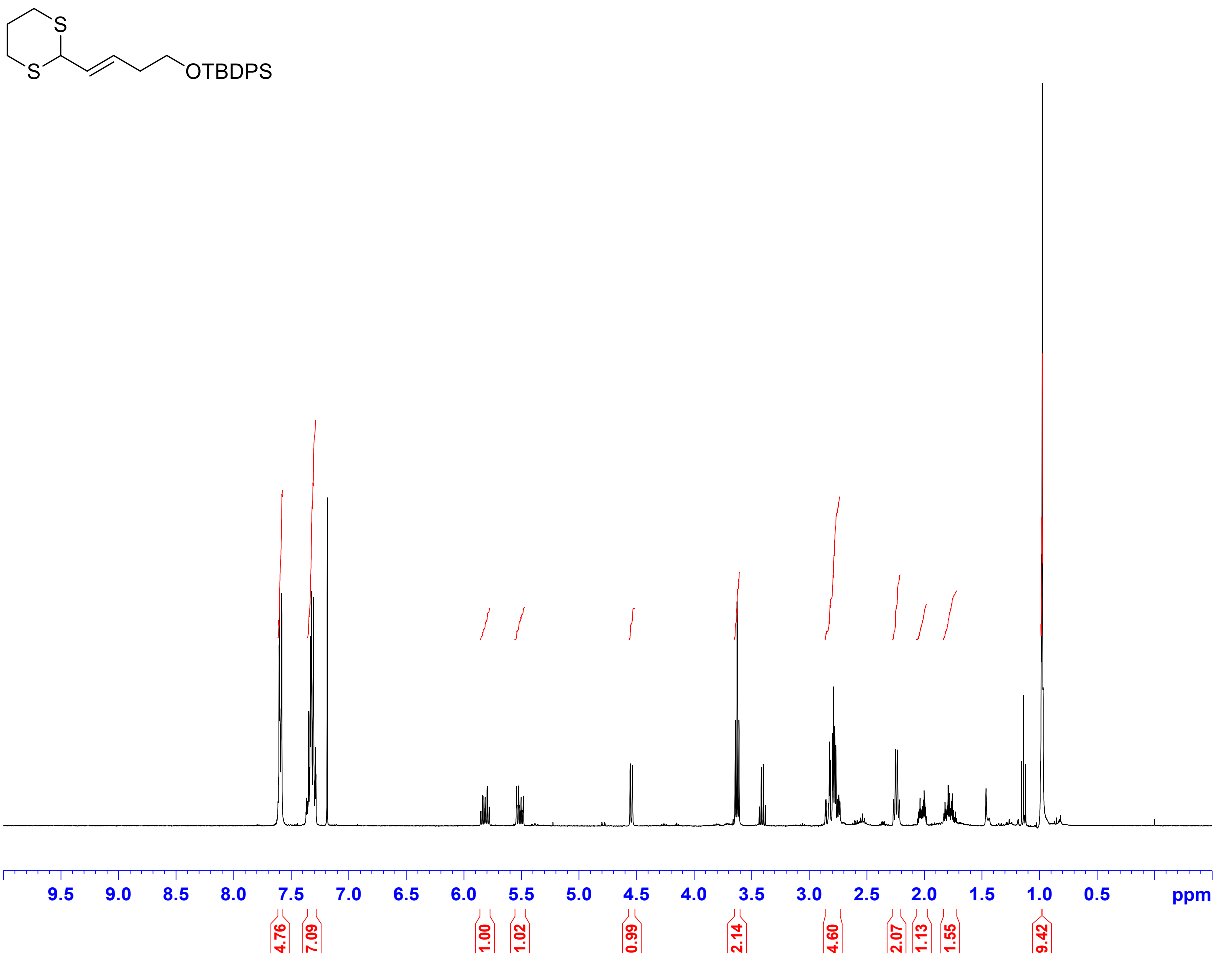


(*E*)-((4-(1,3-Dithian-2-yl)but-3-en-1-yl)oxy)(*tert*-butyl)diphenylsilane (86). To a solution of 1,3-propanedithiol (0.023 mL, 0.23 mmol, 1.2 equiv) in dry Et_2O (1 mL) was added $MgBr_2{\bullet}OEt_2$ (69 mg, 0.27 mmol, 1.4 equiv) followed by a solution of **85** (65 mg, 0.192 mmol, 1 equiv) in dry Et_2O (1 mL) at room temperature. Stirring was continued for 20 min then trioxane (18 mg, 0.2 mmol, 1.05 equiv) was added and stirring was continued for 30 min more, affording an off-white suspension. Saturated aqueous NH_4Cl (5 mL) and H_2O (1 mL) were added followed by EtOAc (5 mL) then separation of phases and extraction with EtOAc (2 x 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure then purified using flash chromatography (EtOAc/Hex 1:20) giving **86** (71.2 mg, 0.17 mmol, 86%) as a viscous, colorless oil.

TLC: R_f = 0.66 (EtOAc/Hex 1:5, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.61-7.58 (m, 4 H), 7.37-7.28 (m, 6 H), 5.82 (ddt, *J* = 15.5, 6.9, 1.0, 1 H), 5.51 (ddt, *J* = 15.4, 7.5, 1.2, 1 H), 4.54 (d, *J* = 7.6, 1 H), 3.62 (t, *J* = 6.7, 2 H), 2.86-2.73 (m, 4 H), 2.24 (dq, *J* = 6.8, 0.9, 2 H), 2.06-1.98 (m, 1 H), 1.83-1.72 (m, 1 H), 0.97 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.8, 134.0, 131.9, 129.7, 128.8, 127.8, 63.4, 47.9, 35.9, 30.5, 27.1, 25.5, 19.3.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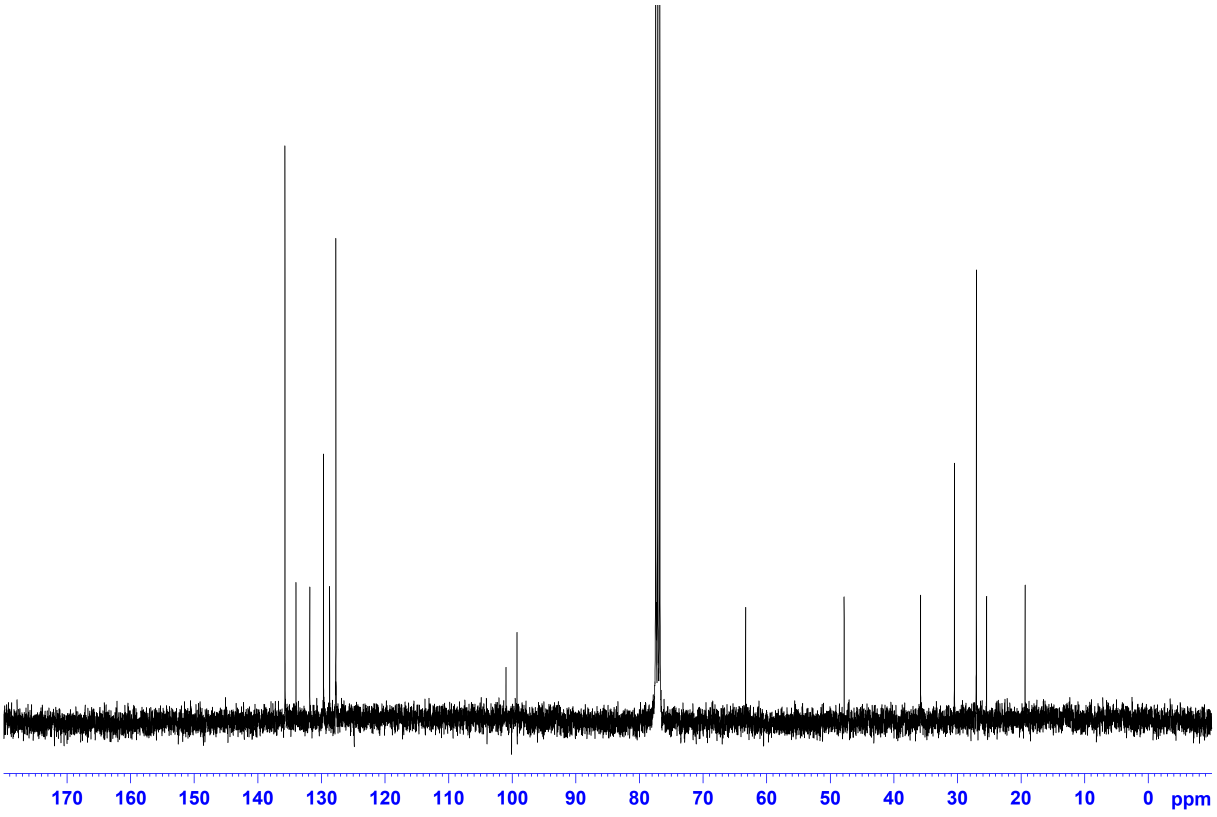
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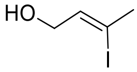
5.3. Characterization of Compounds from the Third Generation Approach

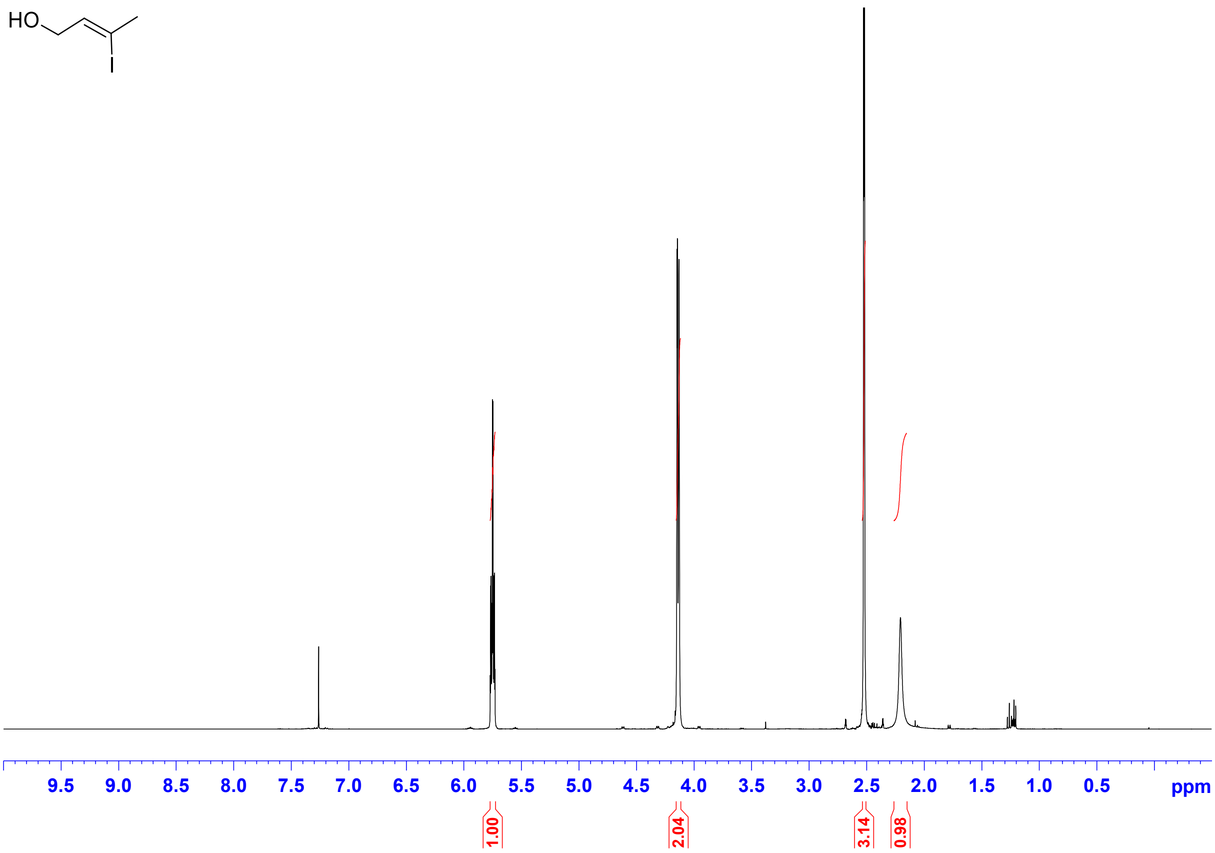
5.3.1. Synthesis of Unsaturated Acid 98



(*Z*)-3-Iodobut-2-en-1-ol (68).[162] A solution of Red-Al® (3.4M in toluene, 64 mL, 218 mmol, 1.50 equiv) in a two-necked dry flask charged with a magnetic stirring bar, a reflux condenser, an addition funnel and an argon in/outlet was diluted with Et_2O (150 mL) and then cooled to 0 °C. A solution of 2-butyn-1-ol (10.17 g, 145.10 mmol, 1.00 equiv) in Et_2O (150 mL) was added dropwise via the addition funnel. After stirring at 0 °C for 30 min the reaction mixture was allowed to warm to room temperature (CAUTION: exothermicity after ca. 1.5 h !). After 15 h a white suspension had formed that was cooled to 0 °C; EtOAc (100 mL) was then slowly added via the addition funnel. A solution of iodine (55.3 g, 218 mmol, 1.50 equiv) in THF (150 mL) was then slowly added at –78 °C. After completion of the addition, the addition funnel was rinsed with THF (75 mL). After warming to room temperature the mixture was carefully added to a stirred mixture of saturated aqueous $Na_2S_2O_3$ (200 mL) and saturated aqueous Rochelle salt (200 mL) followed by addition of EtOAc (100 mL). After stirring at room temperature for 30 min two clear phases were obtained that were separated. The aqueous phase was extracted with EtOAc (3 x 100 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:6→1:3→1:1) gave **68** (25.25 g, 127.6 mmol, 88%) as a yellow oil.

Note: The product is not stable upon prolonged storage at room temperature.

TLC: R_f = 0.36 (EtOAc/Hex 1:3, UV, $KMnO_4$ or CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.75 (tq, *J* = 5.9, 1.5, 1 H), 4.14 (dq, *J* = 6.0, 1.3, 2 H), 2.52 (q, *J* = 1.3, 3 H), 2.20 (br s, 1 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ =134.3, 102.5, 67.4, 33.7. **IR** (thin film): $\tilde{\nu}$ = 3313, 2950, 2911, 2871, 1720, 1649, 1426, 1375, 1256, 1222, 1073, 1005 cm^{-1}. **HRMS** (EI): calcd for C_4H_6IO [M^+]: 197.9458; found: 197.9537.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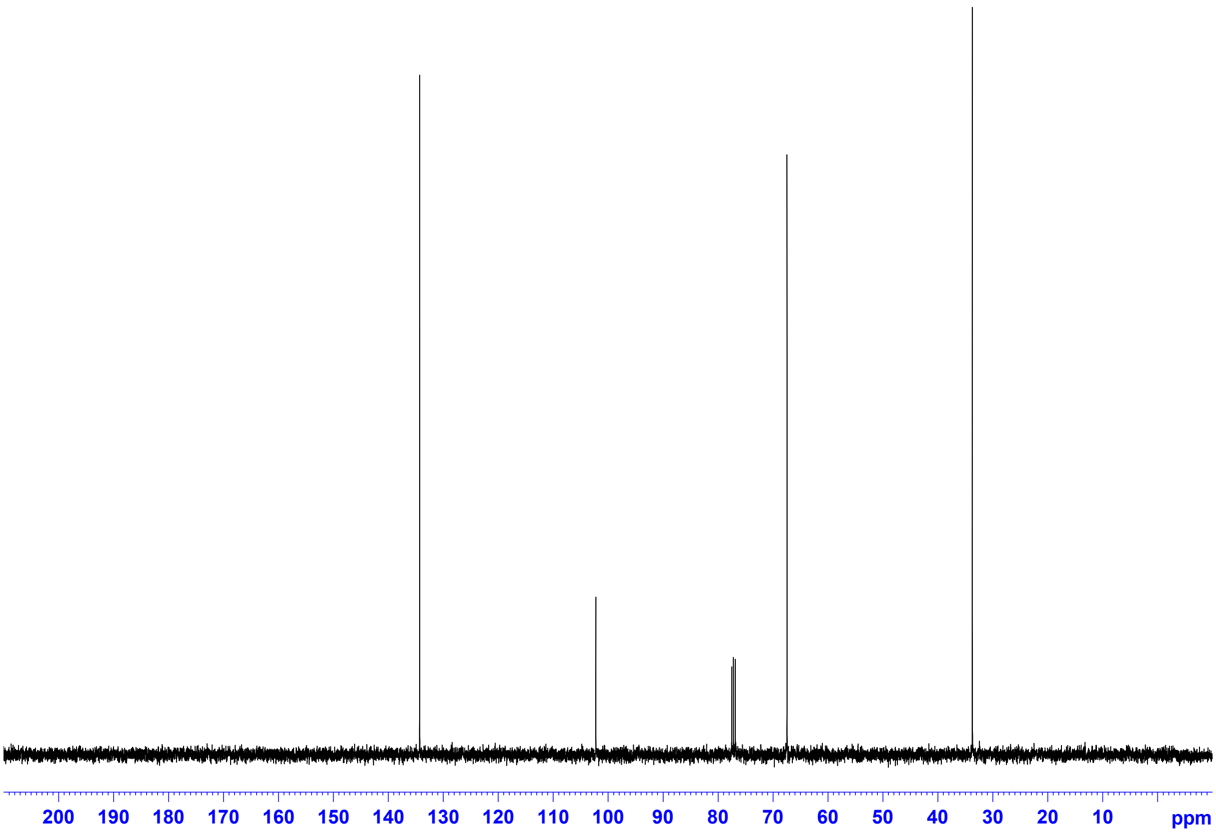
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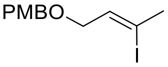
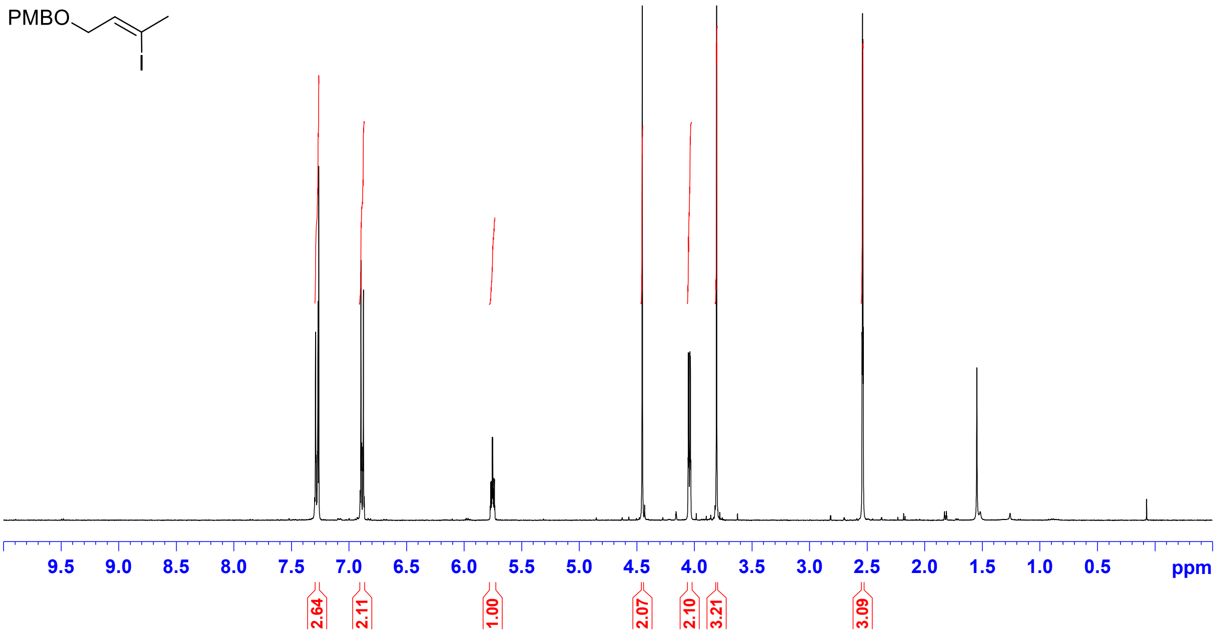


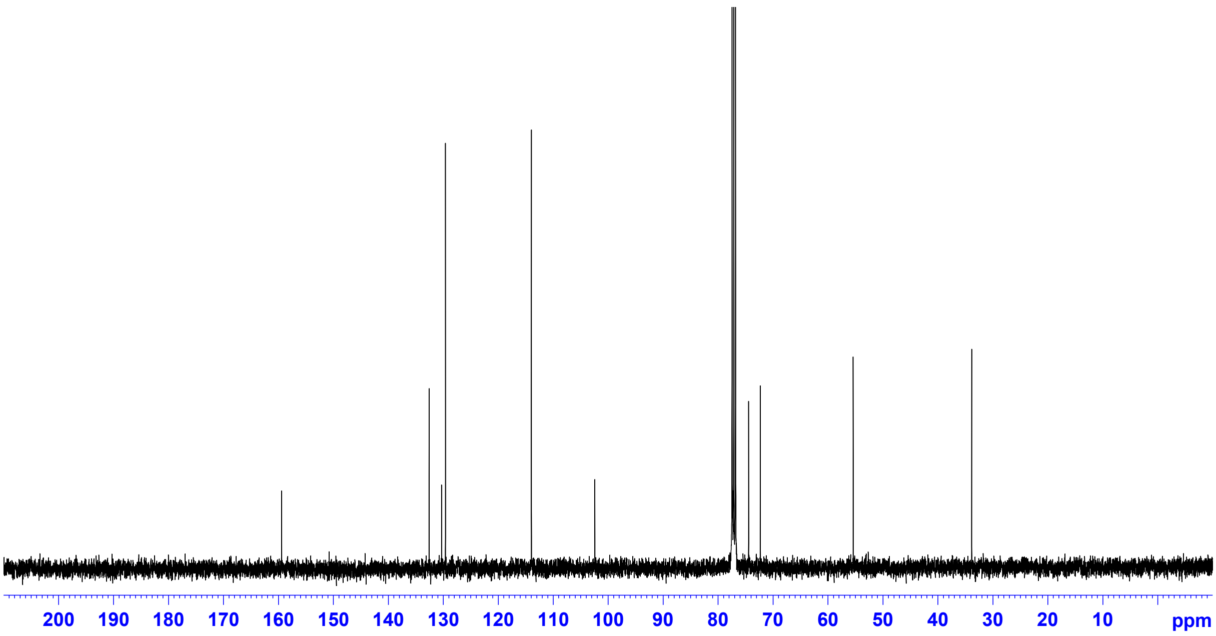
(*Z*)-1-((3-Iodobut-2-enyloxy)methyl)-4-methoxybenzene (92).

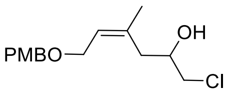
Preparation of PMB-trichloroacetimidate:[184] A solution of 4-methoxybenzyl alcohol (13.82 g, 100.00 mmol, 1.00 equiv) in Et_2O (15 mL) was added to a stirred suspension of NaH (60% in mineral oil, 0.40 g, 10.00 mmol, 0.10 equiv) in Et_2O (70 mL) at 0 °C. After the effervescence had ceased, stirring was continued for a total of 30 min. Neat Cl_3CCN (10.53 mL, 105 mmol, 1.05 equiv) was then added dropwise, resulting in the formation of a pale yellow solution (with the interior temperature was kept between 0–8 °C) and the pale orange suspension was stirred at 0 °C for a total of 45 min. The mixture was then allowed to warm to room temperature and was concentrated under reduced pressure. The tan residue was treated with pentane (100 mL) and MeOH (0.40 mL, 10.00 mmol, 0.10 equiv), the mixture was stirred for 2 min at room temperature, and the solid material was removed by filtration and treated with pentane (washed once 100 mL). The combined filtrate and washing was conentrated under reduced pressure and the yellow residue was purified by flash chromatography (EtOAc/Hex 1:10→1:5, 1% NEt_3 (v/v) to deactivate the stationary phase) giving PMB-trichloroacetimidate (24.63 g, 87.16 mmol, 87%) as a yellow oil that could be stored in the freezer over months and without loss of reactivity.

To a solution of **68** (1.02 g, 5.15 mmol, 1.00 equiv) in cyclohexane (20 mL) and CH_2Cl_2 (10 mL) was added neat PMB-trichloroacetimidate dropwise at 0 °C followed by PPTS (0.12 g, 0.48 mmol, 0.10 equiv) (a clear solution was obtained after ca. 5 min). The cooling bath was removed and a white precipitate began to form. After 16 h saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL) were added to the pale yellow mixture. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:20) provided **92** (1.47 g, 4.64 mmol, 90%) as a pale yellow oil.

TLC: R_f = 0.75 (EtOAc/Hex 1:5, UV, $KMnO_4$ or CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.29-7.27 (m, 2 H), 6.90-6.86 (m, 2 H), 5.75 (tq, *J* = 5.7, 1.5, 1 H), 4.45 (s, 2 H), 4.04 (dq, *J* = 5.7, 1.4, 2 H), 3.80 (s, 3 H), 2.54 (q, *J* = 1.4, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ =159.4, 132.6, 130.3, 129.6, 114.0, 102.4, 74.5, 72.3, 55.4, 33.9. **IR** (thin film): $\tilde{\nu}$ = 2998, 2951, 2933, 2911, 2852, 1649, 1611, 1585, 1510, 1462, 1440, 1427, 1353, 1245, 1173, 1092, 1057, 1034, 817 cm^{-1}. **HRMS** (EI): calcd for $C_{12}H_{15}IO_2$ [M$^+$]: 318.0117; found: 318.0112.

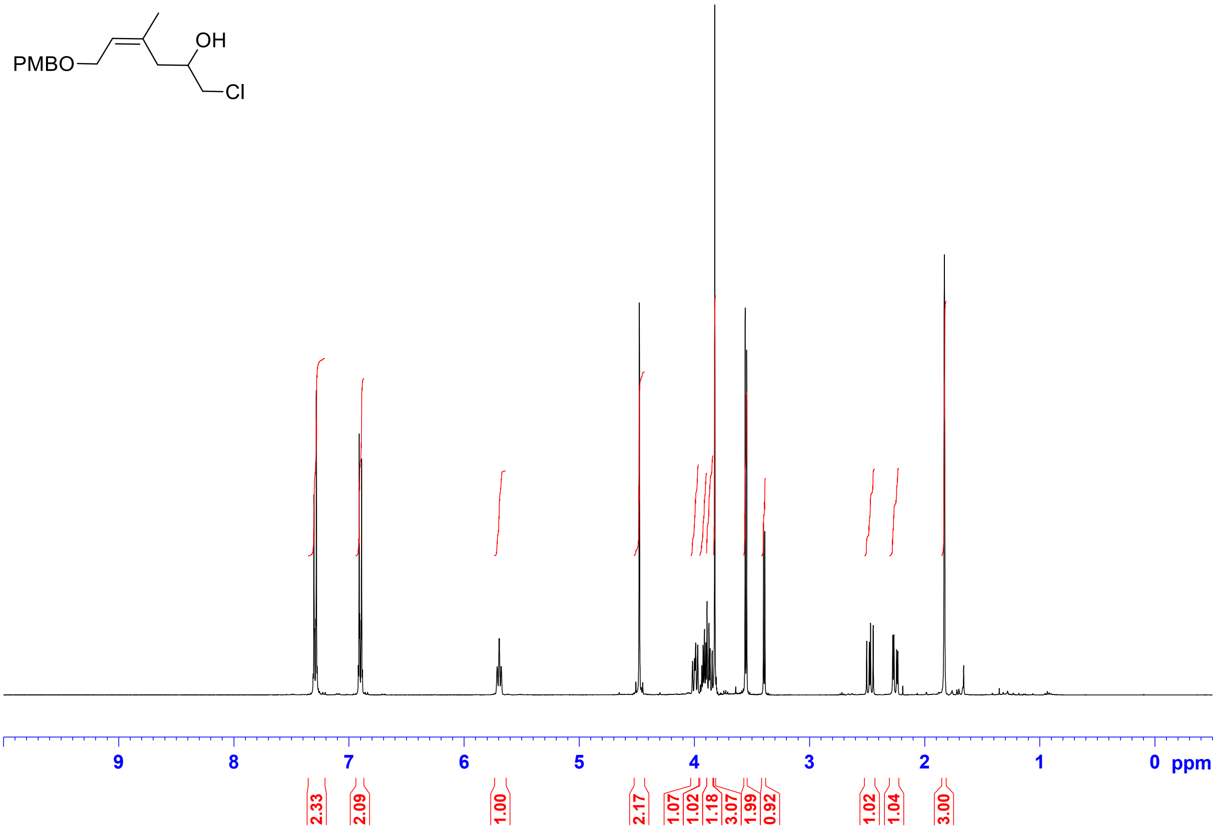






(*Z*)-1-Chloro-6-(4-methoxybenzyloxy)-4-methylhex-4-en-2-ol (93). To a solution of **92** (952.20 mg, 2.99 mmol, 1.00 equiv) in toluene (15 mL) was added *n*-BuLi (1.6M in hexane, 2.05 mL, 3.29 mmol, 1.10 equiv) dropwise at –85 °C. After 30 min freshly distilled epichlorohydrin (0.70 mL, 8.98 mmol, 3.00 equiv) was added followed by $BF_3{\cdot}OEt_2$ (0.50 mL, 3.89 mmol, 1.30 equiv.). After additional 15 min saturated aqueous $NaHCO_3$ (15 mL), H_2O (10 mL), and EtOAc (20 mL) were added and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL); the combined organic extracts were washed once with brine (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:5→1:3) afforded **93** (544.2 mg, 1.91 mmol, 64%) as a colorless oil.

TLC: R_f = 0.28 (EtOAc/Hex 1:3, UV, $KMnO_4$ or CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.30-7.28 (m, 2 H), 6.92-6.88 (m, 2 H), 5.69 (t, *J* = 7.0, 1 H), 4.48 (s, 2 H), 3.99 (dd, *J* = 11.2, 7.1, 1 H), 3.95-3.89 (m, 1 H), 3.87 (dd, *J* = 11.0, 7.3, 1 H), 3.82 (s, 3 H), 3.55 (d, *J* = 5.2, 2 H), 3.39 (d, *J* = 4.9, 1 H), 2.47 (dd, *J* = 13.5, 9.2, 1 H), 2.26 (dd, *J* = 13.5, 4.1, 1 H), 1.83 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ =159.5, 139.0, 129.9 (3xC), 124.4, 114.0 (2xC), 72.5, 68.8, 65.2, 55.4, 49.9, 37.4, 23.8. **IR** (thin film): $\tilde{\nu}$ = 3404, 2954, 2935, 2911, 2858, 2837, 1612, 1513, 1464, 1442, 1380, 1361, 1301, 1246, 1173, 1063, 1032, 819 cm^{-1}. **HRMS** (ESI): calcd for $C_{15}H_{21}ClNaO_3$ [$(M+Na)^+$]: 307.1077; found: 307.1071.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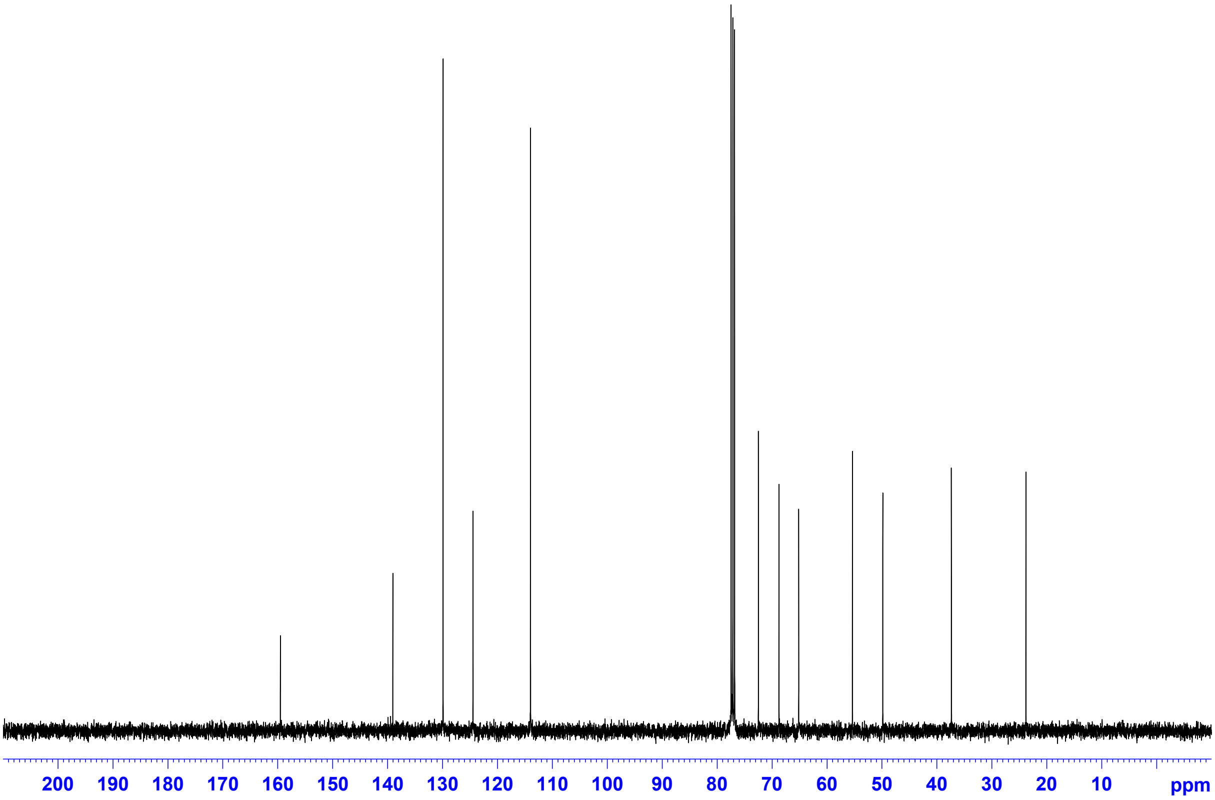
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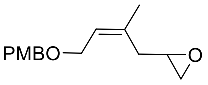
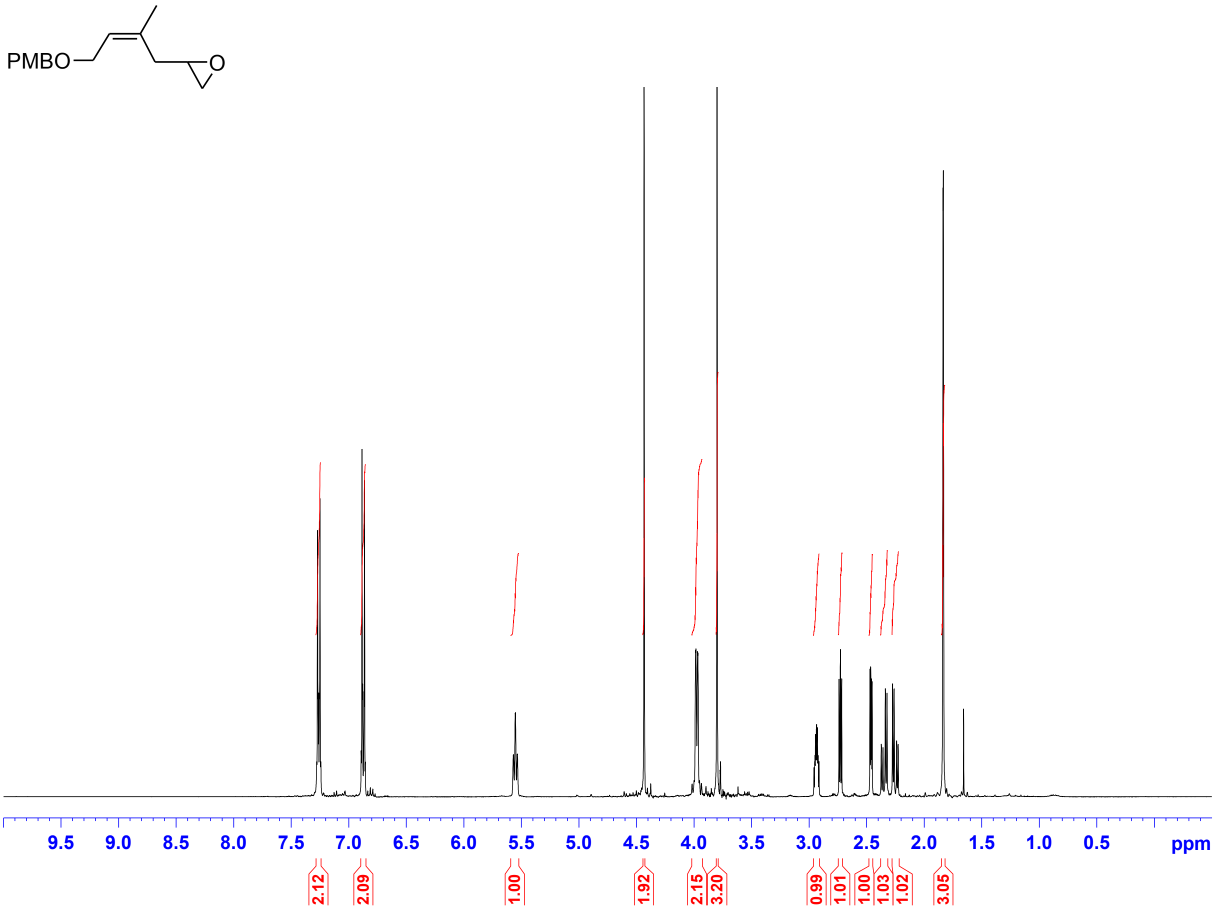


(*Z*)-2-(4-(4-Methoxybenzyloxy)-2-methylbut-2-enyl-)oxirane (94). To a solution of **93** (2.67 g, 9.38 mmol, 1.00 equiv) in EtOH (100 mL) was added crushed KOH (0.59 g, 10.50 mmol, 1.10 equiv) at 0 °C and the mixture was stirred for 20 h at 0 °C. It was then concentrated under reduced pressure and the residue was partitioned between H_2O (10 mL) and EtOAc (20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL); the combined organic extracts were washed once with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:5→1:3) afforded **94** (2.08 g, 8.39 mmol, 89%) as a colorless oil.

TLC: R_f = 0.44 (EtOAc/Hex 1:3, UV, $KMnO_4$ or CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ =7.28-7.24 (m, 2 H), 6.89-6.85 (m, 2 H), 5.55 (t, *J* = 6.8, 1 H), 4.43 (s, 2 H), 4.02-3.94 (m, 2 H), 3.80 (s, 3 H), 2.96-2.91 (m, 1 H), 2.73 (dd, *J* = 4.9, 4.0, 1 H), 2.46 (dd, *J* = 5.0, 2.6, 1 H), 2.34 (dd, *J* = 14.2, 5.9, 1 H), 2.25 (dd, *J* = 14.2, 5.3, 1 H), 1.83 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ =159.3, 136.3, 130.6, 129.5, 124.3, 113.9, 72.0, 66.0, 55.4, 51.2, 46.9, 35.2, 24.5. **IR** (thin film): $\tilde{\nu}$ = 3039, 2934, 2853, 1612, 1511, 1454, 1442, 1301, 1245, 1173, 1072, 1034, 819 cm^{-1}. **HRMS** (ESI): calcd for $C_{15}H_{20}NaO_3$ [$(M+Na)^+$]: 271.1305; found: 271.1305.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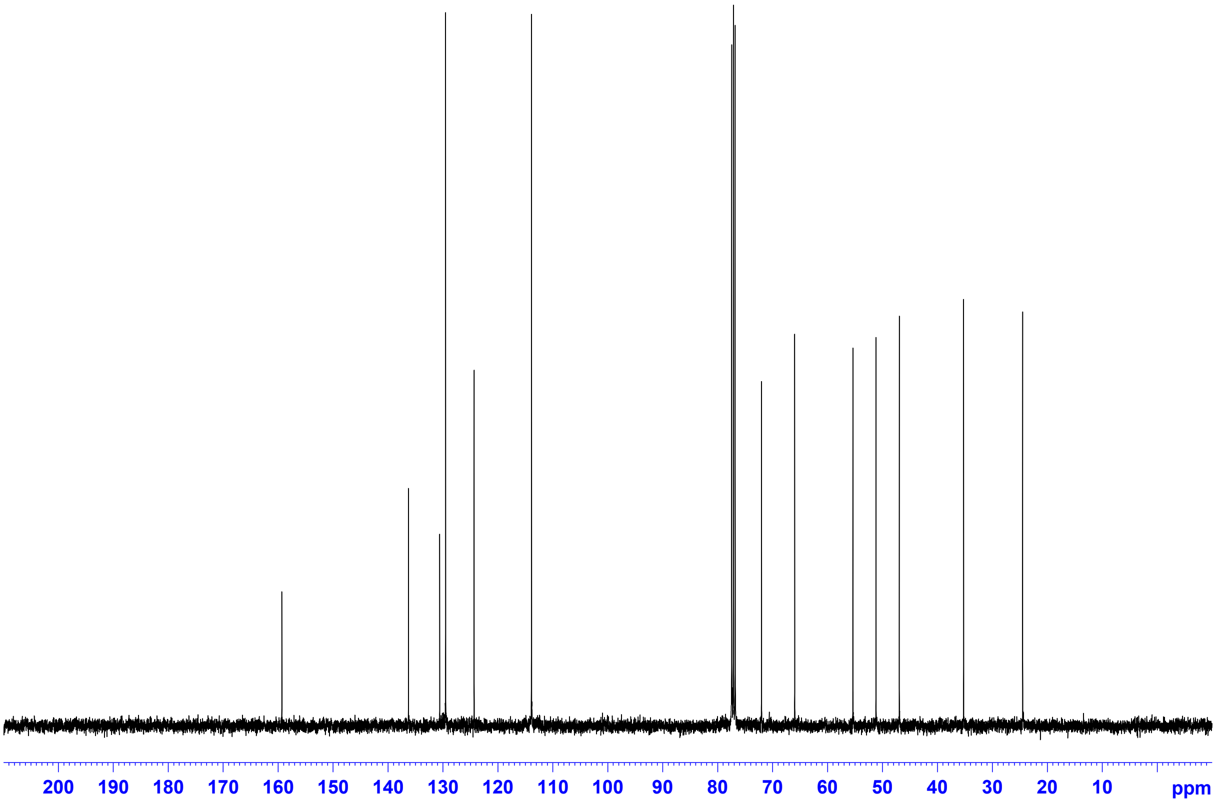
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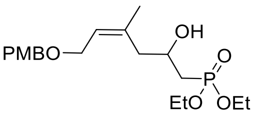

(*Z*)-Diethyl 2-hydroxy-6-(4-methoxy benzyloxy)-4-methyl hex-4-enyl phosphonate (95).[30] To a solution of diethylphosphite (3.48 g, 25.17 mmol, 3.00 equiv) in THF (55 mL) was added *n*-BuLi (1.6M in hexane, 15.70 mL, 25.17 mmol, 3.00 equiv) at –78 °C (interior temperature reached around –60 °C during addition). After 30 min a solution of **94** (2.08 g, 8.39 mmol, 1.00 equiv) in THF (15 mL) was added slowly followed by $BF_3•OEt_2$ (3.2 mL, 25.17 mmol, 3.00 equiv.). After 6 h at –78 °C saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was allowed to reach room temperature. The phases were separated, the aqueous phase was extracted with Et_2O (3 x 40 mL), and the combined organic extracts were washed once with brine (10 mL) and dried over $MgSO_4$. Concentration of the solution under reduced pressure and purification of the residue by flash chromatography (EtOAc→EtOAc/acetone 5:1) afforded **95** (2.58 g, 6.68 mmol, 80%) as a pale yellow oil.

TLC: R_f = 0.27 (EtOAc, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.27-7.24 (m, 2 H), 6.89-6.85 (m, 2 H), 5.61 (t, *J* = 7.0 Hz, 1 H), 4.43 (s, 2 H), 4.15-4.06 (m, 5 H), 3.99-3.90 (m, 2 H), 3.80 (s, 3 H), 3.55 (br. s, 1 H), 2.41 (ddd, *J* = 13.5, 8.2, 1.5, 1 H), 2.24 (dd, *J* = 13.5, 5.2, 1 H), 1.99-1.83 (m, 2 H), 1.79 (d, *J* = 1.1, 3 H), 1.32 (td, *J* = 7.1, 1.7, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.4, 138.0, 130.4, 129.7, 124.8, 113.9, 72.3, 65.8, 64.8 (d, *J* = 4.2), 62.0 (d, *J* = 6.1), 61.9 (d, *J* = 6.7), 55.4, 41.0 (d, *J* = 15.2), 33.8 (d, *J* = 138.8), 24.0, 16.5 (d, *J* = 6.0). **IR** (thin film): $\tilde{\nu}$ = 3386, 2931, 1612, 1513, 1443, 1365, 1245, 1023, 958, 818 cm^{-1}. **HRMS** (ESI): calcd for $C_{19}H_{31}NaO_6P$ $[(M+Na)^+]$: 409.1750; found: 409.1758.

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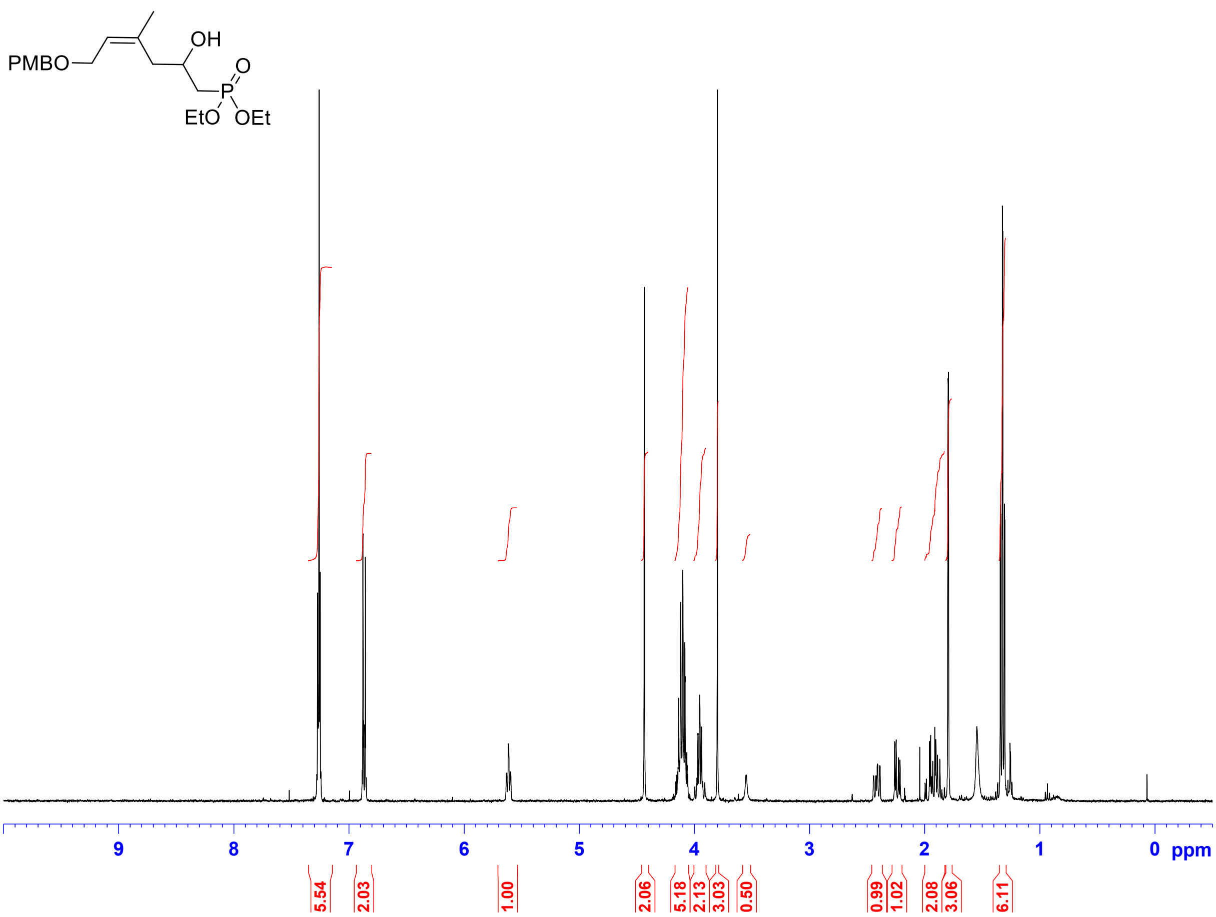
[30] For NMR data of β-hydroxy phosphonates: E. Zymanczyk-Duda, B. Lejczak, P. Kafarski, J. Grimaud, P. Fischer, *Tetrahedron* **1995**, *51*, 11809-11814.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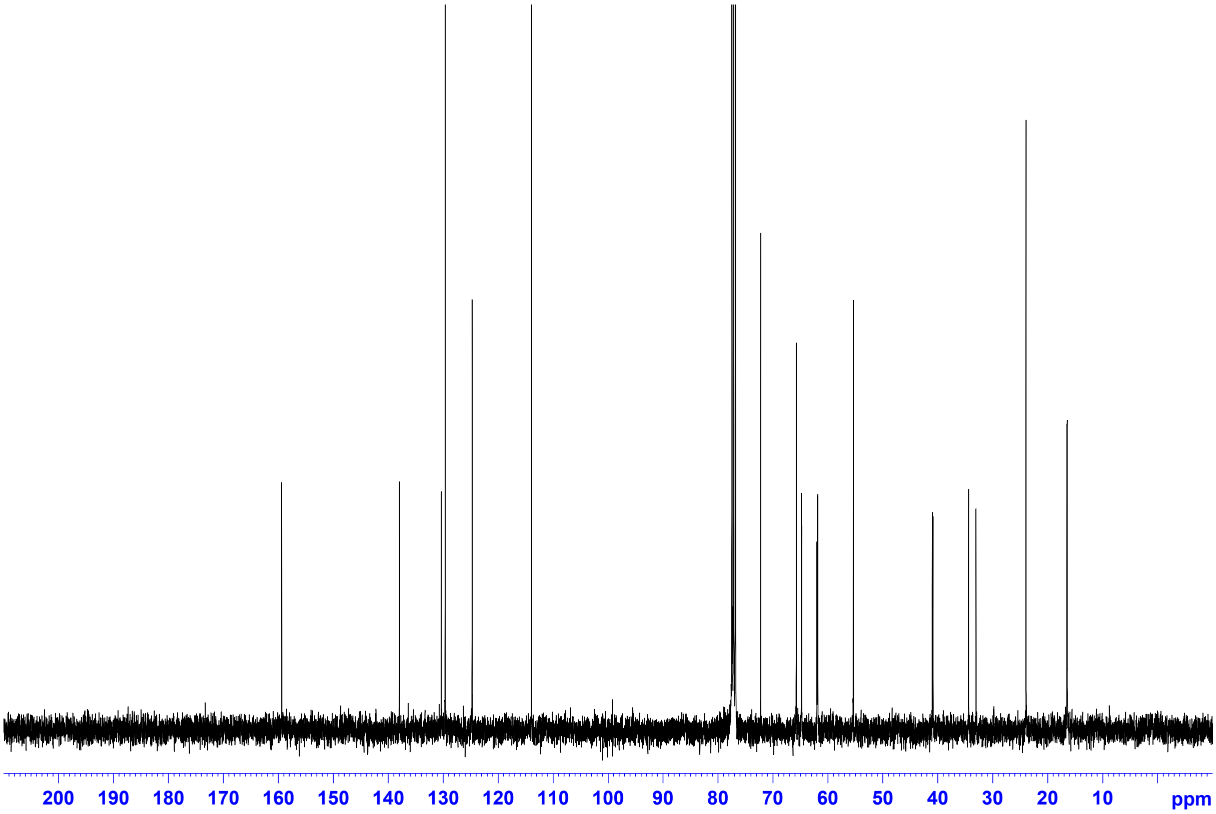
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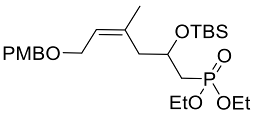
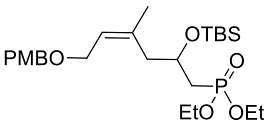


(*Z*)-Diethyl2-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)-4-methyl hex-4-enylphosphonate (96). To a solution of **95** (2.56 g, 6.62 mmol, 1.00 equiv) in DMF (15 mL) were added sequentially ImH (2.70 g, 40 mmol, 6.00 equiv), DMAP (0.80 g, 6.62 mmol, 1.00 equiv) and TBSCl (3.00 g, 20 mmol, 3.00 equiv) at room temperature. The mixture formed was stirred for 1.5 d; H_2O (20 mL) and Et_2O (20 mL) were then added, the phases were separated, and the organic phase was extracted with H_2O (2 x 10 mL). The combined aqueous extracts were then re-extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 2:1→5:1) afforded **96** (2.78 g, 5.55 mmol, 84%) as a colorless oil.

TLC: R_f = 0.70 (EtOAc, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.27-7.24 (m, 2 H), 6.87-6.84 (m, 2 H), 5.50 (t, *J* = 6.7 Hz, 1 H), 4.41 (s, 2 H), 4.16-4.03 (m, 6 H), 3.96 (dd, *J* = 11.7, 6.5, 1 H), 3.79 (s, 3 H), 2.43 (dd, *J* = 13.5, 4.8, 1 H), 2.27 (ddd, *J* = 13.5, 7.8, 1.8, 1 H), 2.03-1.87 (m, 2 H) 1.77 (d, *J* = 1.1, 3 H), 1.31 (td, *J* = 7.0, 1.2, 6 H), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.02 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ =159.3, 137.0, 130.8, 129.5, 124.9, 113.9, 72.1, 67.0, 66.5, 61.5 (d, *J* = 6.6), 55.4, 41.4 (d, *J* = 6.4), 34.9 (d, *J* = 136.1), 26.0, 24.4, 18.0, 16.6 (d, *J* = 6.1), 16.6 (d, *J* = 6.1), -4.5, -4.6. **IR** (thin film): $\tilde{\nu}$ = 2954, 2929, 2856, 1613, 1513, 1471, 1389, 1246, 1025, 958, 936, 808, 776 cm^{-1}. **HRMS** (EI): calcd for $C_{21}H_{36}O_6PSi$ [$(M-C_4H_9)^+$]: 443.2013; found: 443.2014.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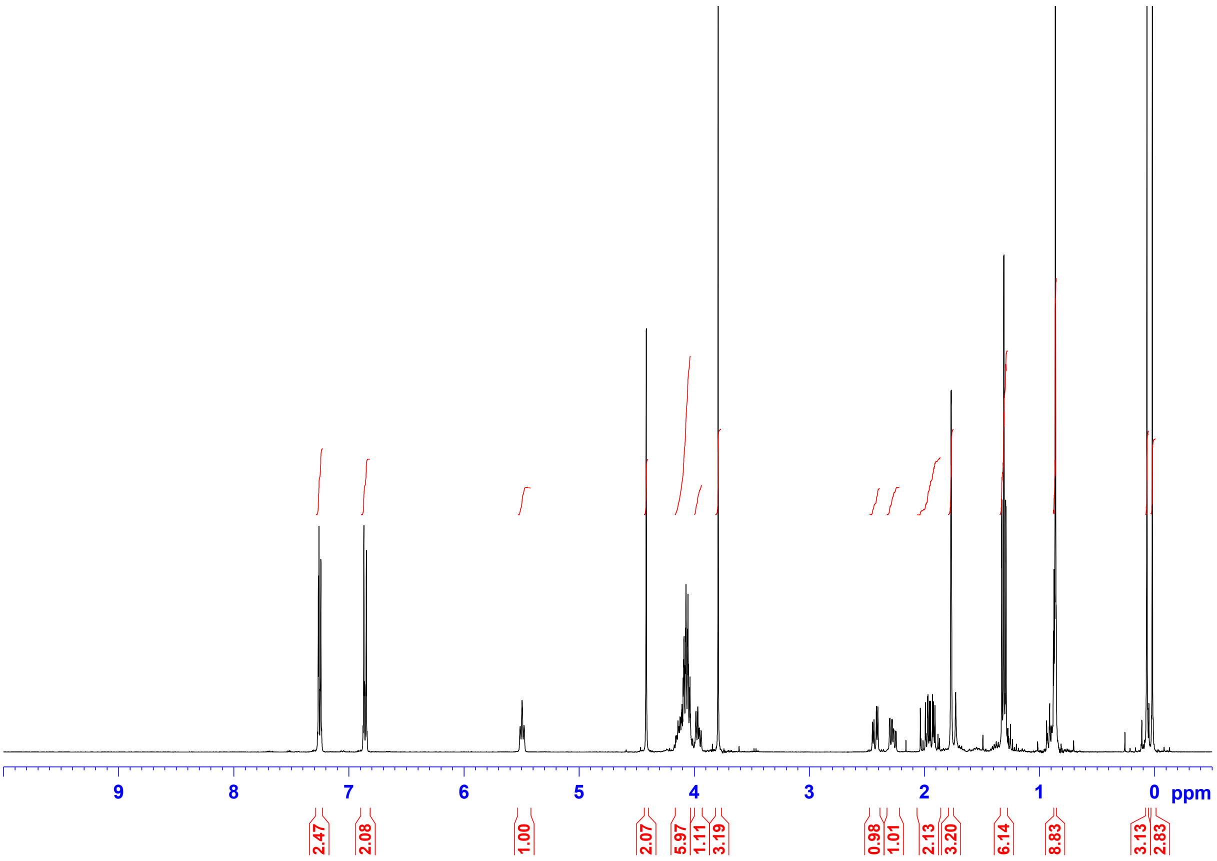
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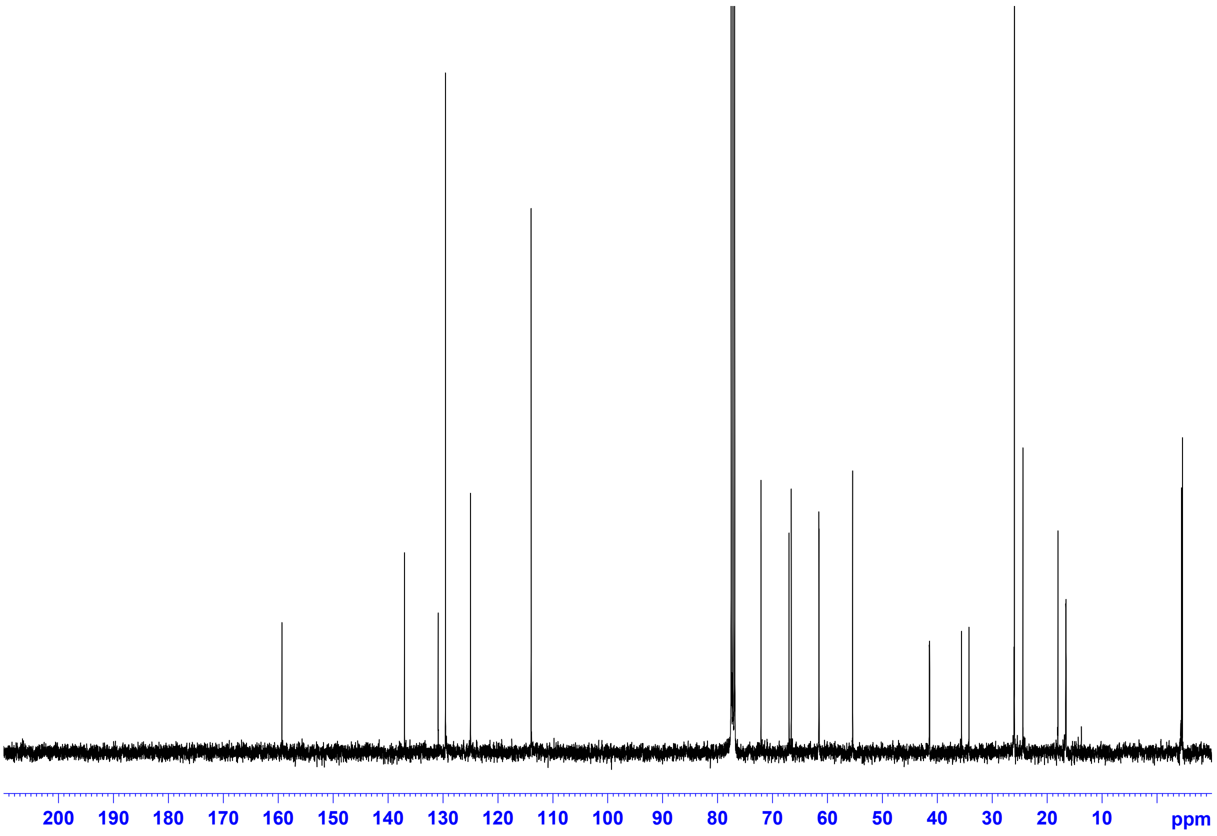
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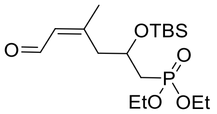
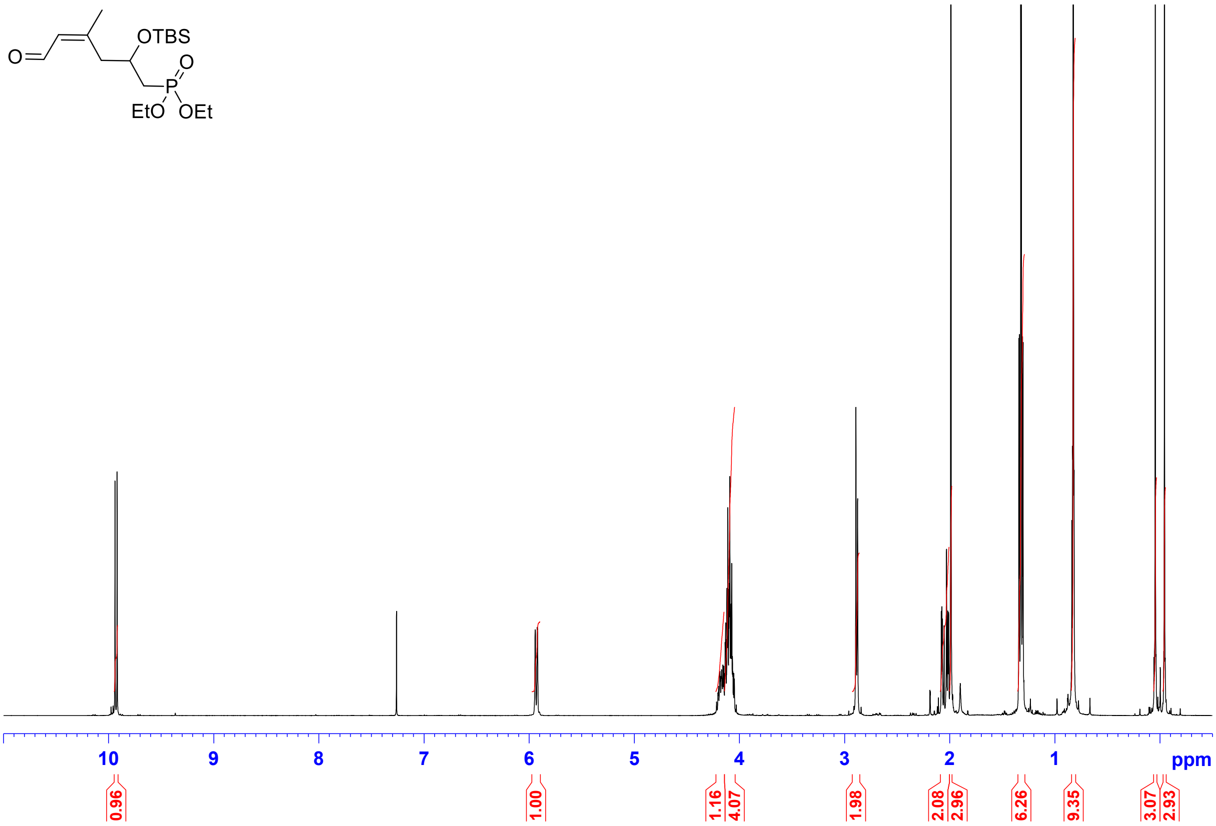


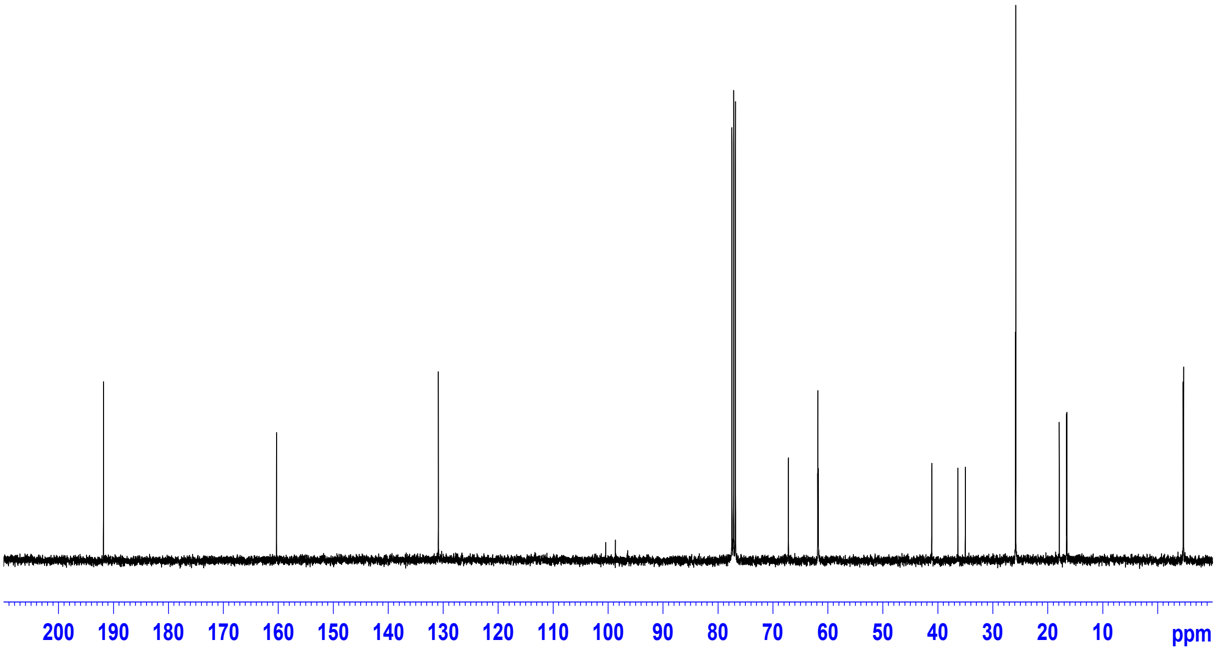
(*Z*)-Diethyl 2-(*tert*-butyldimethyl silyloxy)-4-methyl-6-oxohex-4-enyl phosphonate (97). To a solution of **96** (2.60 g, 5.19 mmol, 1.00 equiv) in CH_2Cl_2 (40 mL) was added H_2O (2 mL) followed by DDQ (1.77 g, 7.80 mmol, 1.50 equiv; added in 3 equal portions in 10 min intervals) at 0 °C under vigorous stirring. After 90 min the orange-tan coloured mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL), CH_2Cl_2 (50mL) and H_2O (10 mL). The clear phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude pale red oil, which contained the deprotected primary alcohol as well as the corresponding aldehyde, was directly used in the subsequent oxidation step.

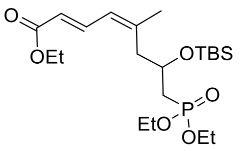
To a stirred solution of oxalylchloride (0.50 mL, 5.71 mmol, 1.10 equiv) in CH_2Cl_2 (10 mL) was slowly added a solution of DMSO (0.81 mL, 11.40 mmol, 2.20 equiv) in CH_2Cl_2 (1 mL) at –78 °C. After 10 min, a solution of the crude alcohol/aldehyde in CH_2Cl_2 (20 mL) was added and stirring was continued for another 30 min. NEt_3 (3.60 mL, 26.00 mmol, 5.00 equiv) was then added and after 15 additional min at –78 °C the mixture was allowed to warm to room temperature. After 1.5 h the yellow solution was diluted with H_2O (10 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 3:1→5:1→6:1) gave **97** (1.72 g, 4.54 mmol, 88% over two steps) as a pale red oil.

Note: The aldehyde decomposes upon prolonged storage at room temperature.

TLC: R_f = 0.42 (EtOAc/Hex 5:1, UV, $KMnO_4$ or CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.93 (d, J = 8.2, 1 H), 5.93 (d, J = 8.2, 1 H), 4.21-4.13 (m, 1 H), 4.14-4.04 (m, 4 H), 2.90-2.88 (m, 2 H), 2.08-2.00 (m, 2 H), 1.99 (d, J = 1.3, 3 H), 1.32 (td, J = 7.1, 2.0, 6 H), 0.82 (s, 9 H), 0.05 (s, 3 H), -0.04 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 191.8, 160.3, 130.9, 67.2 (d, J = 2.2), 61.9 (d, J = 6.8), 61.8 (d, J = 6.8), 41.1 (d, J = 2.2), 35.7 (d, J = 134.9), 25.9, 25.8, 17.9, 16.6 (d, J = 6.2), -4.6, -4.7. **IR** (thin film): $\tilde{\nu}$ = 2954, 2857, 1674, 1472, 1463, 1392, 1251, 1151, 1048, 1021, 959, 936, 835, 826, 775 cm^{-1}. **HRMS** (EI): calcd for $C_{13}H_{26}O_5PSi$ [(M-C_4H_9)$^+$]: 321.1282; found: 321.1282.

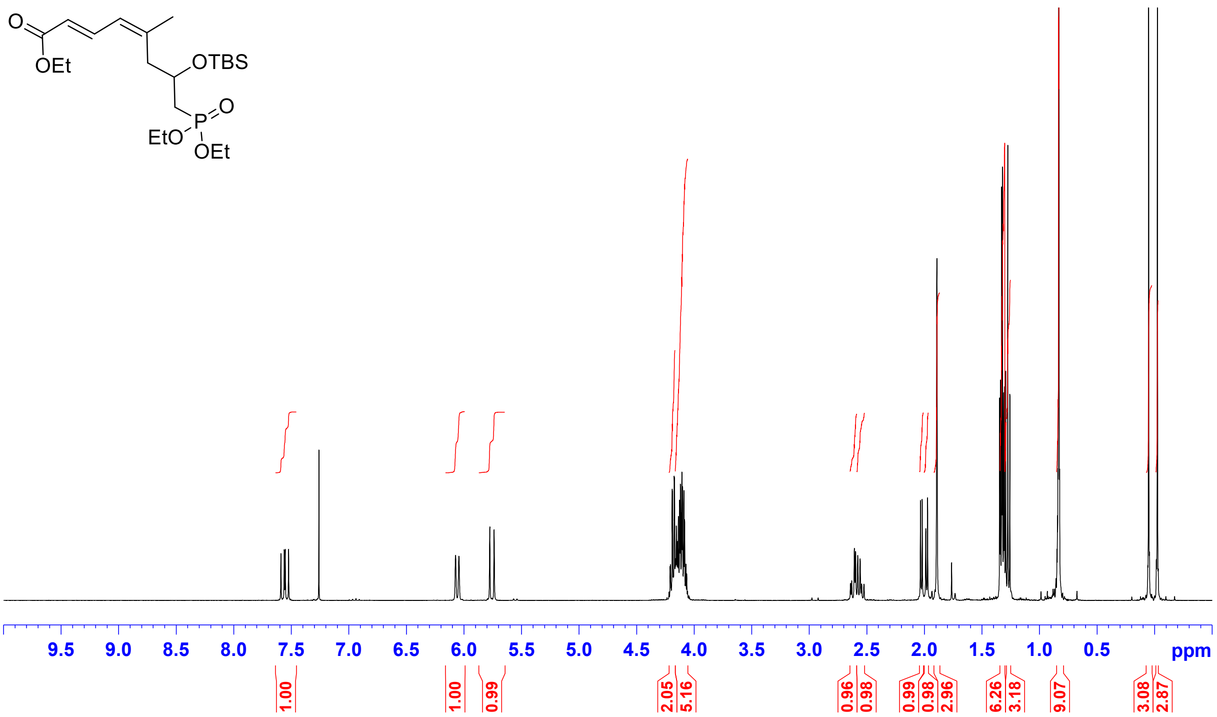






(2*E*,4*Z*)-Ethyl 7-(*tert*-butyldimethylsilyloxy)-8-(diethoxy phosphoryl)-5-methylocta-2,4-dienoate (D). To a solution of triethyl phosphonoacetate (1.17 mL, 5.90 mmol, 1.30 equiv) in THF (10 mL) was added *n*-BuLi (1.6M in hexane, 3.55 mL, 5.67 mmol, 1.25 equiv) at 0 °C. After stirring for 30 at min 0 °C a solution of **97** (1.72 g, 4.54 mmol, 1.00 equiv) in THF (10 mL) was added, resulting in the formation of pale yellow-orange solution, which was stirred at 0 °C for 1.5 h. Saturated aqueous NH_4Cl (20 mL), H_2O (5 mL) and EtOAc (5 mL) were then added, the phases were separated and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hex 2:1) to afford **D** (1.96 g, 4.38 mmol, 97%) as a pale purple oil.

TLC: R_f = 0.54 (EtOAc/Hex 5:1, UV, $KMnO_4$ or CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.56 (dd, J = 15.2, 11.6, 1 H), 6.06 (d, J = 11.5, 1 H), 5.76 (d, J = 15.2, 1 H), 4.18 (dq, J = 7.1, 1.4, 2 H), 4.16-4.07 (m, 5 H), 2.62 (dd, J = 13.4, 4.2, 1 H), 2.55 (dd, J = 13.4, 8.1, 1 H), 2.03 (d, J = 6.2, 1 H), 1.98 (d, J = 6.2, 1 H), 1.89 (s, 3 H), 1.33 (td, J = 7.1, 2.8, 6 H), 1.28 (t, J = 7.1, 3 H), 0.83 (s, 9 H), 0.05 (s, 3 H), -0.02 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 167.5, 146.1, 141.0, 126.8, 119.8, 67.0, 61.7 (d, J = 6.5), 60.2, 41.7 (d, J = 5.1), 35.3 (d, J = 135.3), 25.9, 25.3, 17.9, 16.6 (d, J = 6.1), 14.5, -4.6, -4.7. **IR** (thin film): $\tilde{\nu}$ = 2980, 2955, 2929, 2905, 2857, 1711, 1636, 1472, 1390, 1367, 1252, 1146, 1046, 1021, 934, 836, 808, 775 cm^{-1}. **HRMS** (ESI): calcd for $C_{21}H_{42}O_6PSi$ [(M+H)$^+$]: 449.2483; found: 449.2471.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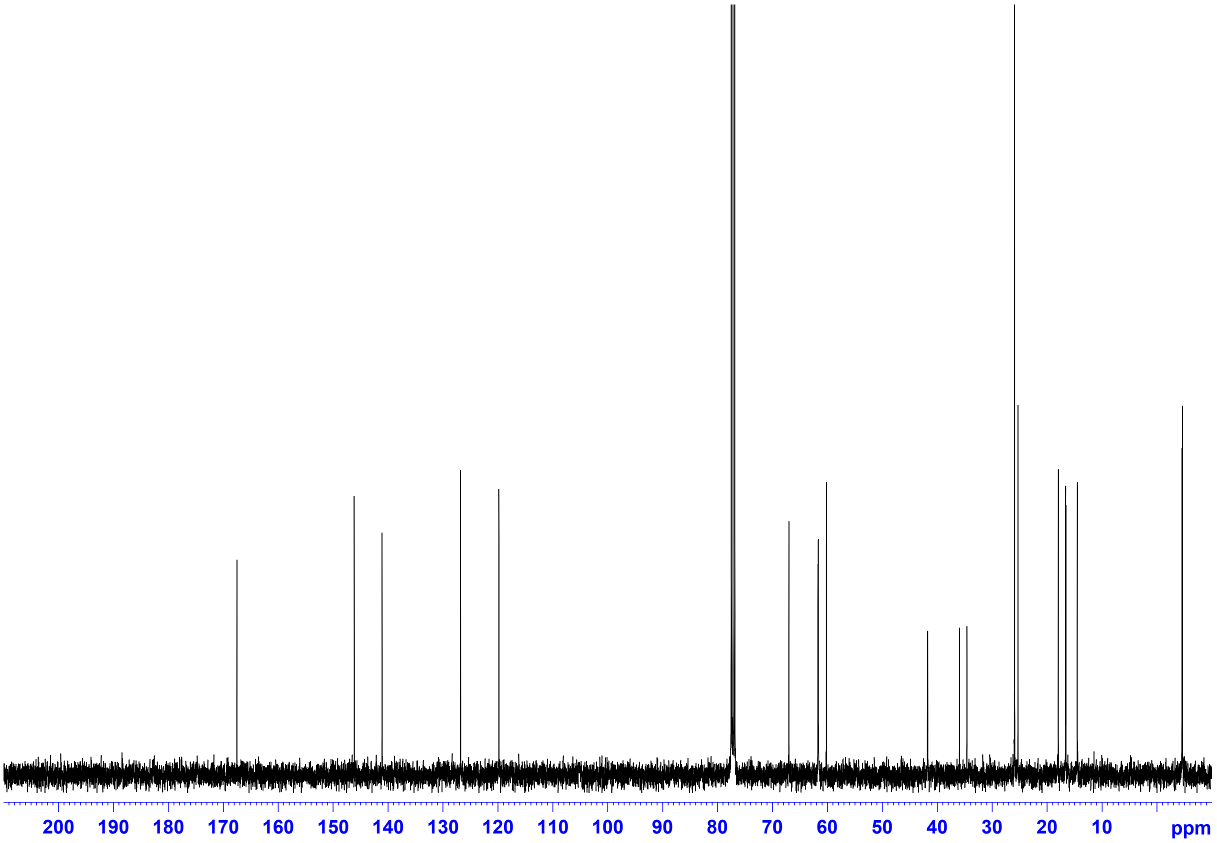
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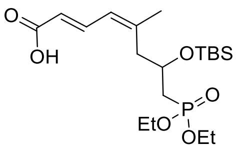
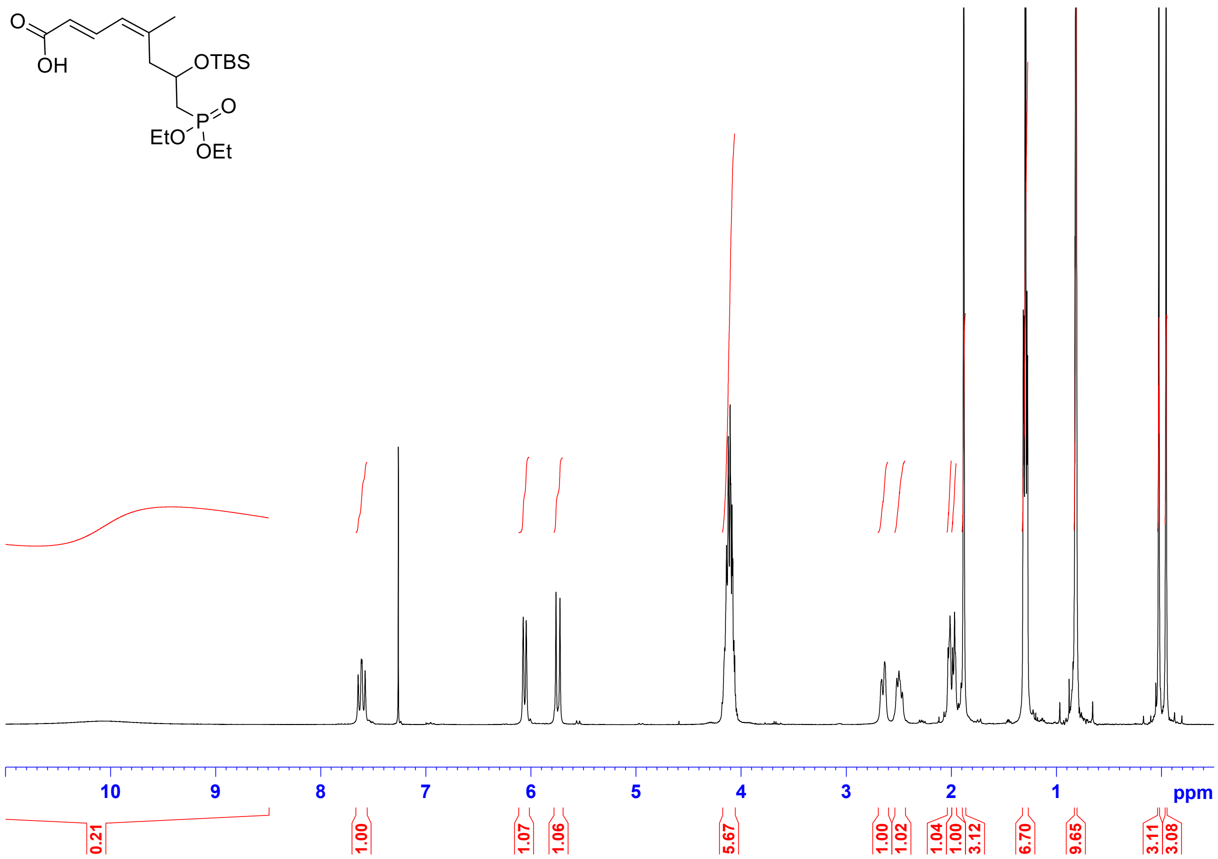


(2*E*,4*Z*)-7-(*tert*-Butyldimethylsilyloxy)-8-(diethoxyphosphoryl)-5-methylocta-2,4-dienoic acid (98). To a solution of **D** (1.41 g, 3.13 mmol, 1.00 equiv) in EtOH (24 mL) was added 1.0M aqueous NaOH (9.40 mL, 9.40 mmol, 3.00 equiv) at 0 °C. The cooling bath was removed after 5 min and the yellow solution at was stirred at room temperature for 25 h. The reaction was then quenched by the addition of 2.0M aqueous HCl (4.70 mL, 9.40 mmol, 3.00 equiv). Subsequently, EtOAc (20 mL) and brine (20 mL) were added, the phases were separated, and the aqueous phase was extracted with EtOAc (4 x 20 mL). The combined organic extracts were dried over MgSO$_4$ and evaporated under reduced pressure. The residue was dried in high vacuum to give crude **98** (1.27 g, 3.03 mmol, 97%) which was used in the next step without further purification.

TLC: $R_f = 0.46$ (EtOAc, UV, KMnO$_4$). **^{1}H-NMR** (400 MHz, CDCl$_3$): $\delta = 10.1$ (br s, 1 H), 7.61 (dd, $J = 15.0, 11.9$, 1 H), 6.06 (d, $J = 11.7$, 1 H), 5.74 (d, $J = 15.0$, 1 H), 4.17-4.05 (m, 5 H), 2.65 (d, $J = 13.0$, 1 H), 2.49 (dd, $J = 13.0, 8.2$, 1 H), 2.03-2.00 (m, 1 H), 1.98-1.96 (m, 1 H), 1.88 (s, 3 H), 1.29 (td, $J = 7.2, 2.8$, 6 H), 0.81 (s, 9 H), 0.02 (s, 3 H), -.0.04 (s, 3 H). **^{13}C-NMR** (100 MHz, CDCl$_3$): $\delta = 172.0$, 146.9, 142.2, 126.6, 119.9, 67.2, 62.0 (d, $J = 6.3$), 41.6 (d, $J = 3.4$), 35.0 (d, $J = 136.3$), 25.8, 25.5, 17.9, 16.5 (d, $J = 6.2$), -4.7, -4.8. **IR** (thin film): $\tilde{\nu} = 2954$, 2929, 2857, 1703, 1636, 1391, 1251, 1200, 1149, 1046, 1019, 935, 808, 774 cm^{-1}. **HRMS** (ESI): calcd for $C_{19}H_{37}O_6NaPSi$ [(M+Na)$^+$]: 443.1989; found: 443.1989.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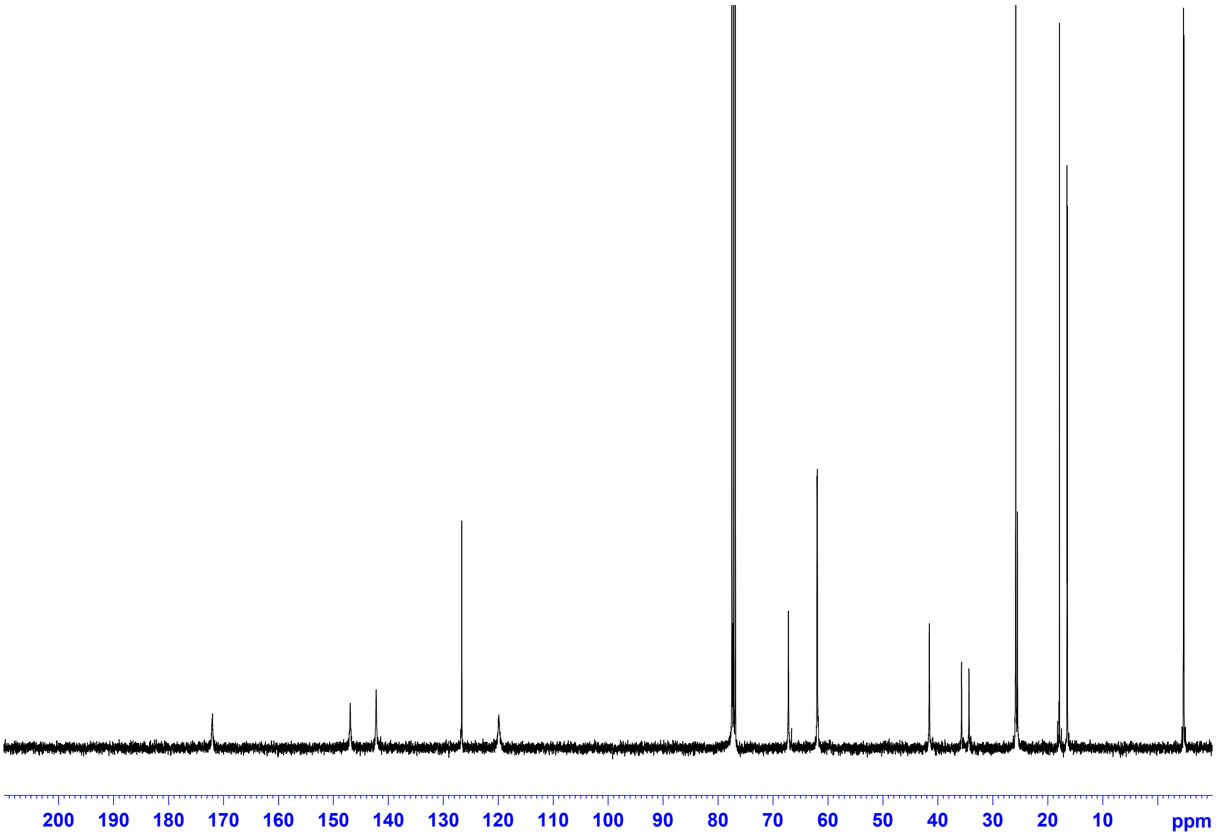
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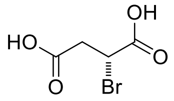
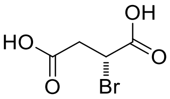
5.3.2. Synthesis of Alcohol 125



(*R*)-2-Bromosuccinic acid (100).[180] To a solution of D-aspartic acid (5.00 g, 37.56 mmol, 1.00 equiv) in H_2SO_4 (13.3 mL of conc. H_2SO_4, 250 mmol, 6.60 equiv, in 100 mL of H_2O) at –5 °C (NaCl/ice) was added KBr (20.11 g, 169 mmol, 4.5 equiv) followed by slow addition of a solution of $NaNO_2$ (4.6 g, 68.7 mmol, 1.80 equiv.) in H_2O (9 mL) during 1 h (ATTENTION: Nitrous gases are formed and an experimental set-up with a washing flask should be used!). After 3 h at 0 °C the brown mixture was extracted with EtOAc (4 x 60 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure, to give **100** (6.67 g, 33.89 mmol, 90%) as a yellow solid. The compound was used without purification.

TLC: R_f = 0.52 (EtOAc/Hex 1:1, 5% AcOH, UV, $KMnO_4$). **Mp**: 166-167 °C. **^{1}H-NMR** (400 MHz, MeOH-d_4): δ = 5.00 (br. s, 2 H), 4.59 (dd, J = 8.7, 6.3, 1 H), 3.22 (dd, J = 17.2, 8.7, 1 H), 2.98 (dd, J = 17.2, 6.3, 1 H). **^{13}C-NMR** (100 MHz, MeOH-d_4): δ = 173.2, 172.3, 40.7, 40.1. **IR** (thin film): $\tilde{\nu}$ = 3010, 2902, 2642, 2532, 1700, 1418, 1404, 1303, 1287, 1185, 935, 648 cm^{-1}. **HRMS** (ESI): calcd for $C_4H_4BrO_4$ [$(M-H)^-$]: 194.9298; found: 194.9298. $[\alpha]_D^{24}$: +60.83° (c = 0.90, MeOH).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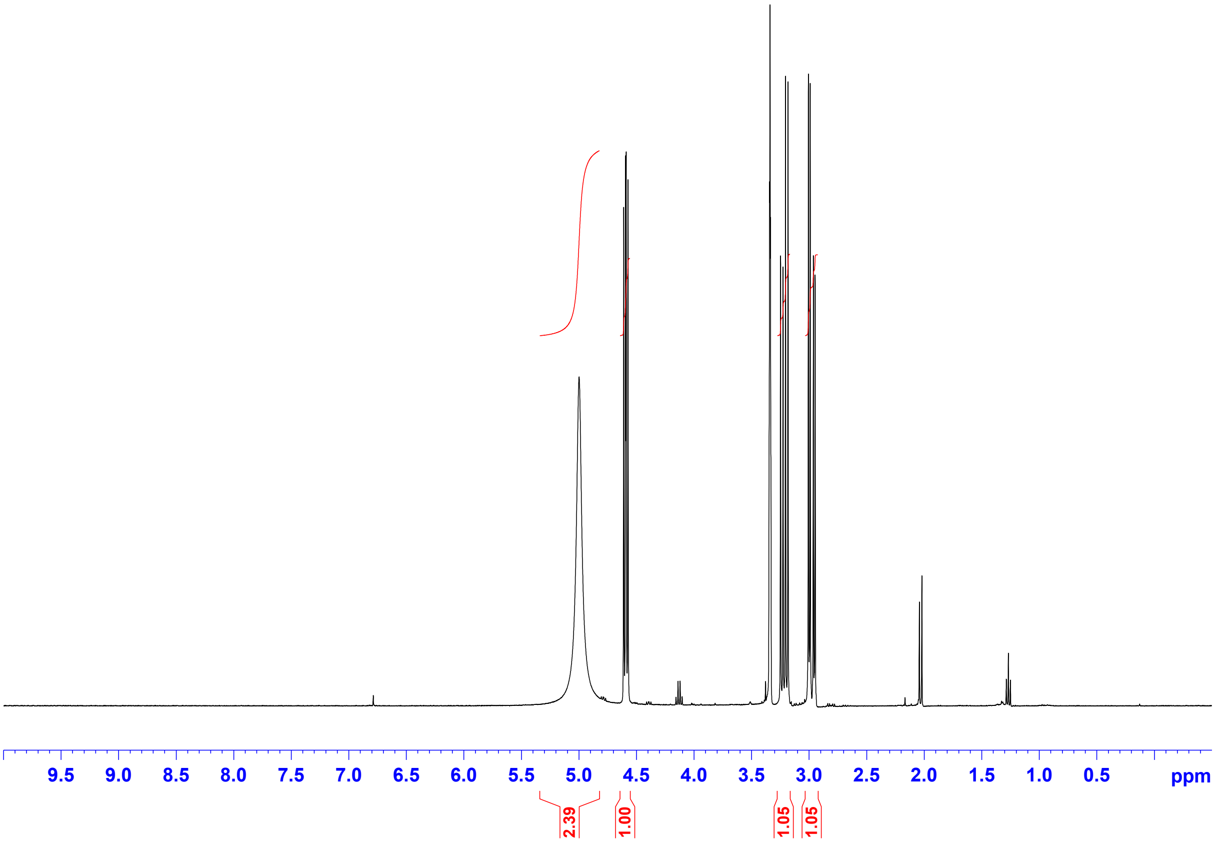
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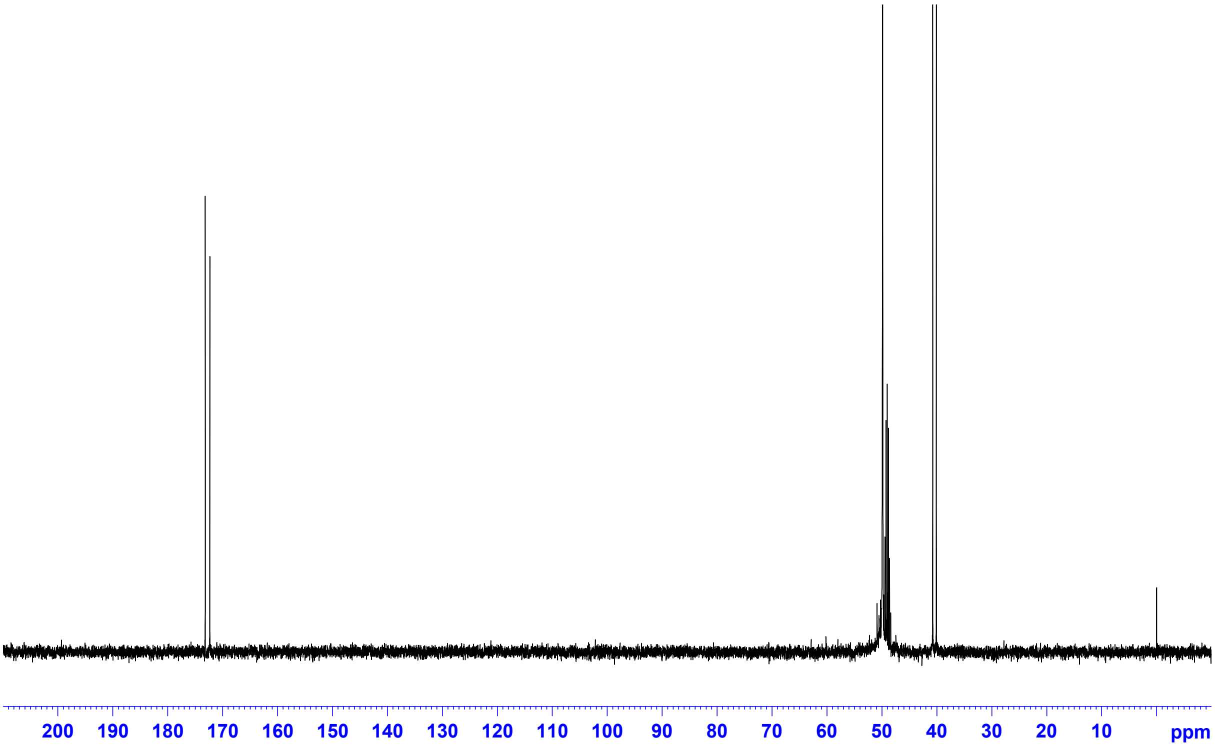
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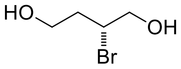
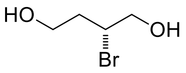


(*R*)-2-Bromobutane-1,4-diol (B). To a solution of **100** (6.64 g, 33.7 mmol, 1.00 equiv) in dry THF (90 mL) was added a solution of BH_3 (1M in THF, 100 mL, 100 mmol, 3 equiv) slowly via a dropping funnel during 1 h at 0 °C. The yellow solution formed was stirred for 1 h at 0 °C and the cooling bath was removed; after 15 min a white precipitate was formed (exothermic process). Stirring was continued for additional 1.5 h, then the mixture was cooled to 0 °C and H_2O (5 mL) and K_2CO_3 (10 g) were slowly added. The suspension was stirred for 10 min at room temperature, then filtered and the residue was washed with Et_2O (3 x 50 mL). Concentration of the solution under reduced pressure and purification of the residue by flash chromatography (EtOAc/MeOH 50:1) afforded **B** (5.47 g, 32.38 mmol, 96%) as a yellow oil.

Note: The reaction also works well with neat BMS in around 93% yield. It is advisable to extend the initial cooling period, if the reaction is performed on larger scale and at higher concentrations, due to substantial exothermicity!

TLC: R_f = 0.53 (EtOAc/MeOH 50:1, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.28 (dq, J = 8.1, 5.3, 1 H), 3.88-3.74 (m, 4 H), 3.45 (br. s, 1 H), 3.00 (br. s, 1 H), 2.15 (ddt, J = 15.0, 8.1, 4.9, 1 H), 2.10-2.02 (m, 1 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 67.2, 60.1, 54.7, 37.9. **IR** (thin film): $\tilde{\nu}$ = 3307, 2935, 2886, 1452, 1419, 1378, 1052, 1023, 639 cm^{-1}. **HRMS** (ESI): calcd for $C_4H_9BrNaO_2$ [$(M+Na)^+$]: 190.9678; found: 190.9667. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$**:** +33.30° (c = 15.19, $CHCl_3$).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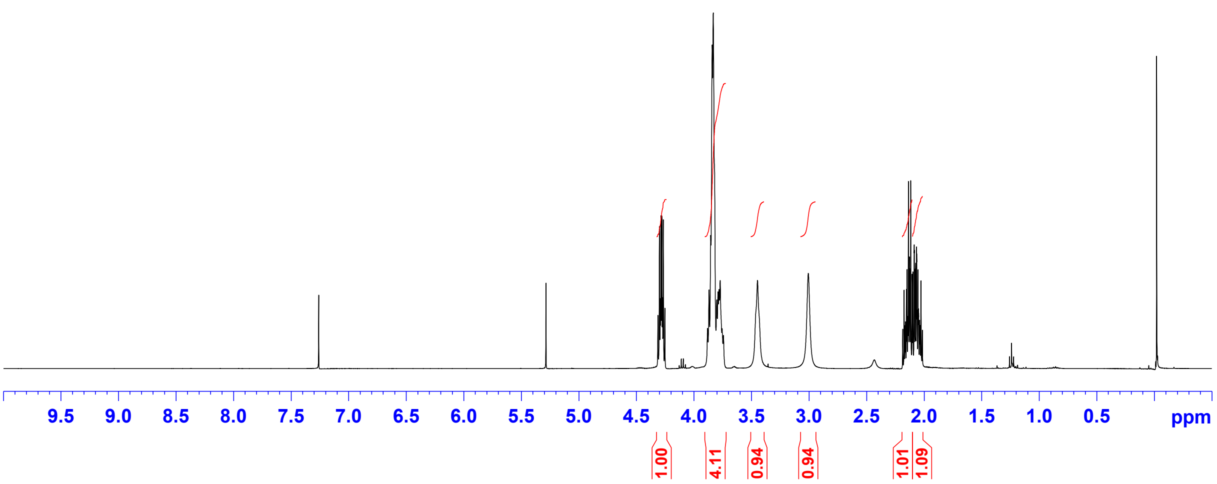
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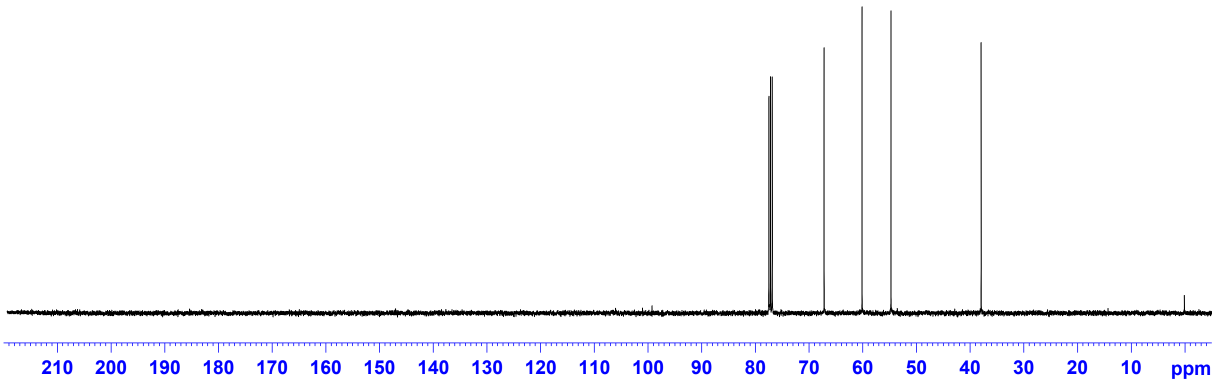
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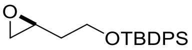

(*S*)-*tert*-Butyl-(2-(oxiran-2-yl)ethoxy)diphenylsilane (101).[32] To a suspension of NaH (60% in mineral oil, 2.74 g, 68.5 mmol, 3.00 equiv) in THF (30 mL) at –16 °C (NaCl/ice) was added a solution of **B** (3.86 g, 22.83 mmol, 1.00 equiv) in THF (20 mL) over a 15 min period, during which the temperature rose to –10 °C. A solution of TBDPSCl (6.59 g, 23.97 mmol, 1.05 equiv) in THF (15 mL) was added at that temperature after 30 min and the cooling bath was removed. After additional 45 min, H_2O (20 mL) was added carefully at 0 °C followed by saturated aqueous NH_4Cl (20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hex 1:20) to give **101** (6.73 g, 20.61 mmol, 90%) as a colorless oil that converts to a white solid upon storage.

TLC: R_f = 0.51 (EtOAc/Hex 1:10, UV, CPS). **Mp**: 39.7-41.2 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68-7.65 (m, 4 H), 7.45-7.36 (m, 6 H), 3.87-3.78 (m, 2 H), 3.12-3.07 (m, 1 H), 2.78 (dd, J = 5.1, 4.1, 1 H), 2.51 (dd, J = 5.1, 2.8, 1 H), 1.80-1.75 (m, 2 H), 1.06 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.7, 135.7, 133.8, 133.8, 129.8, 127.8, 61.0, 50.2, 47.4, 35.8, 26.9, 19.3. **IR** (thin film): $\tilde{\nu}$ = 3070, 2956, 2930, 2857, 1472, 1427, 1389, 1110, 823, 738, 701 cm^{-1}. **HRMS** (ESI): calcd for $C_{20}H_{26}NaO_2Si$ [$(M+Na)^+$]: 349.1594; found: 349.1592. $[\alpha]_D^{24}$: –6.74° (c = 1.87, $CHCl_3$).

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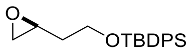
[32] For analytical data, see also: S. Hanessian, A. Tehim, P. Chen, *J. Org. Chem,* **1993**, *58*, 7768-7781.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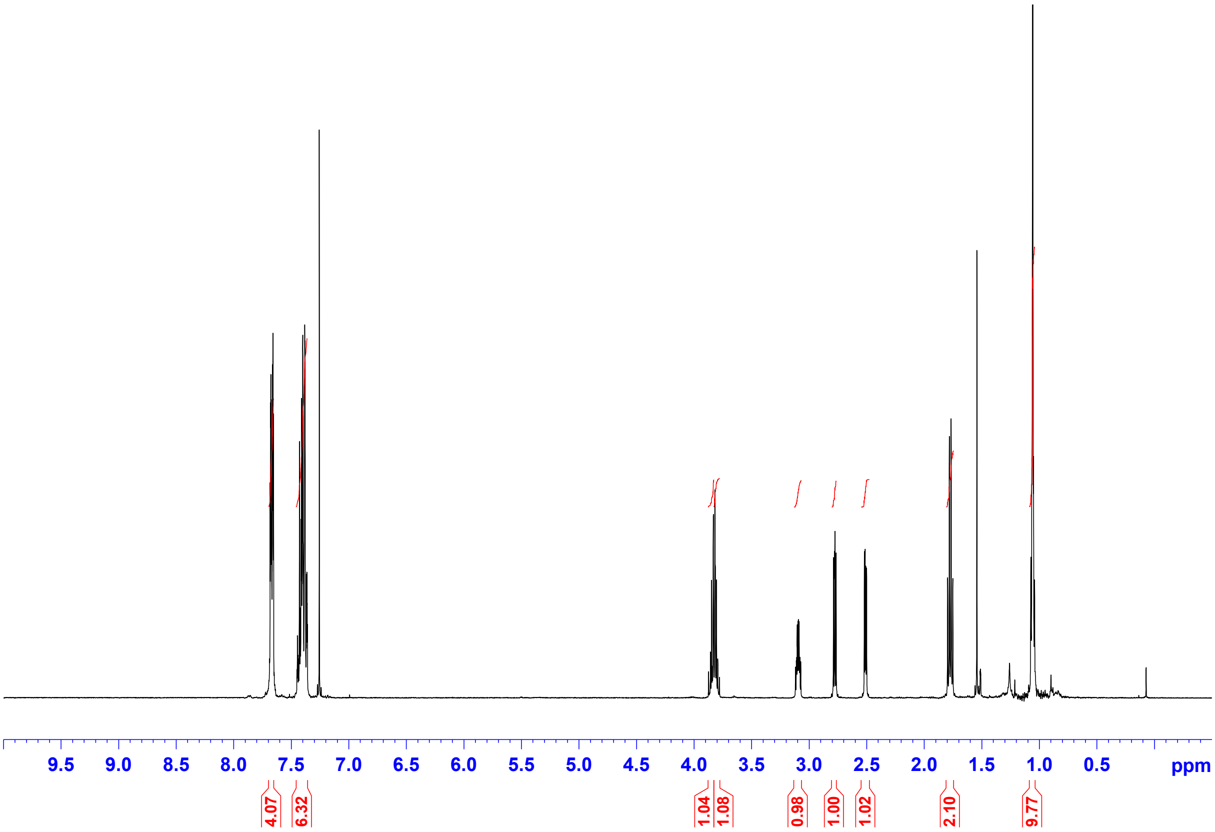
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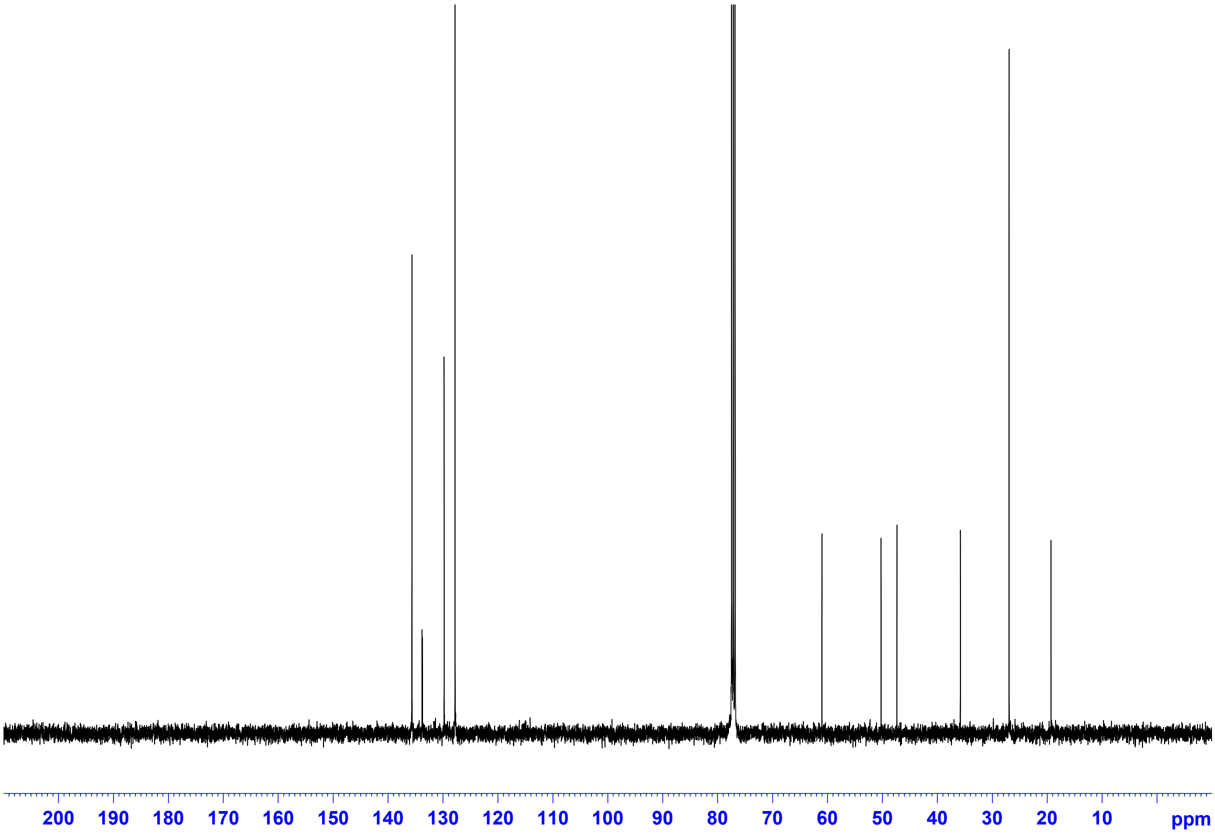
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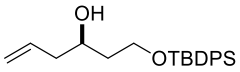
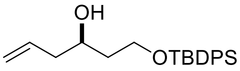


(*R*)-1-(*tert*-Butyldiphenylsilyloxy)hex-5-en-3-ol (102).[178] To a solution of vinylmagnesium bromide (1M in THF, 40.5 mL, 40.5 mmol, 2.00 equiv) was added CuI (395 mg, 2.03 mmol, 0.10 equiv) at –60 °C. After 5 min a solution of **101** (6.62 g, 20.28 mmol, 1.00 equiv) in THF (25 mL) was added, such that the interior temperature did not exceed –55 °C. The temperature was then allowed to rise slowly to –30 °C over a period of 1.5 h; then saturated aqueous NH_4Cl (50 mL) was added slowly followed by H_2O (20 mL). The cooling bath was removed, the mixture was stirred for 15 min, 25% aqueous NH_4OH (10 mL) was added and stirring was continued for additional 10 min. The phases were separated, the blue aqueous phase was extracted with EtOAc (3 x 30mL), and the combined organic phases were dried over $MgSO_4$. Concentration of this solution under reduced pressure and purification of the residue by flash chromatography (EtOAc/Hex 1:10→1:5) afforded **102** (7.07 g, 19.94 mmol, 98%) as a pale-yellow, viscous oil.

TLC: R_f = 0.40 (EtOAc/Hex 1:5, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 4 H), 7.46-7.38 (m, 6 H), 5.85 (ddt, *J* = 17.1, 10.2, 7.2, 1 H), 5.14-5.08 (m, 2 H), 4.00-3.93 (m, 1 H), 3.91-3.81 (m, 2 H), 3.15 (d, *J* = 2.6, 1 H), 2.33-2.21 (m, 2 H), 1.78-1.65 (m, 2 H), 1.06 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.7, 135.7, 135.1, 133.2, 133.1, 129.9, 127.9, 117.5, 71.0, 63.5, 42.1, 38.0, 27.0, 19.2. **IR** (thin film): $\tilde{\nu}$ = 3446, 3071, 2953, 2930, 2857, 1472, 1427, 1390, 1361, 1108, 1077, 997, 914, 822, 737, 700, 613, 503, 487 cm^{-1}. **HRMS** (ESI): calcd for $C_{22}H_{30}NaO_2Si$ [$(M+Na)^+$]: 377.1907; found: 377.1903. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +4.31° (c = 1.34, $CHCl_3$).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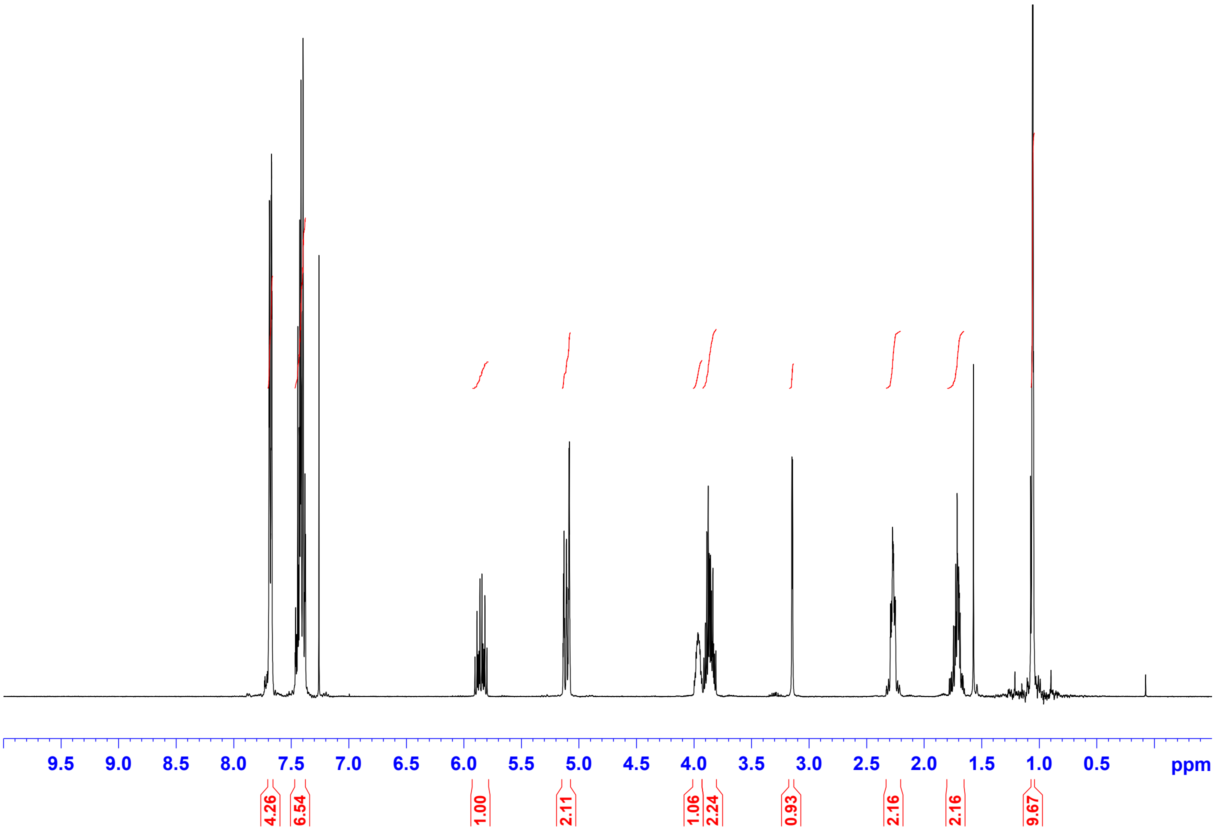
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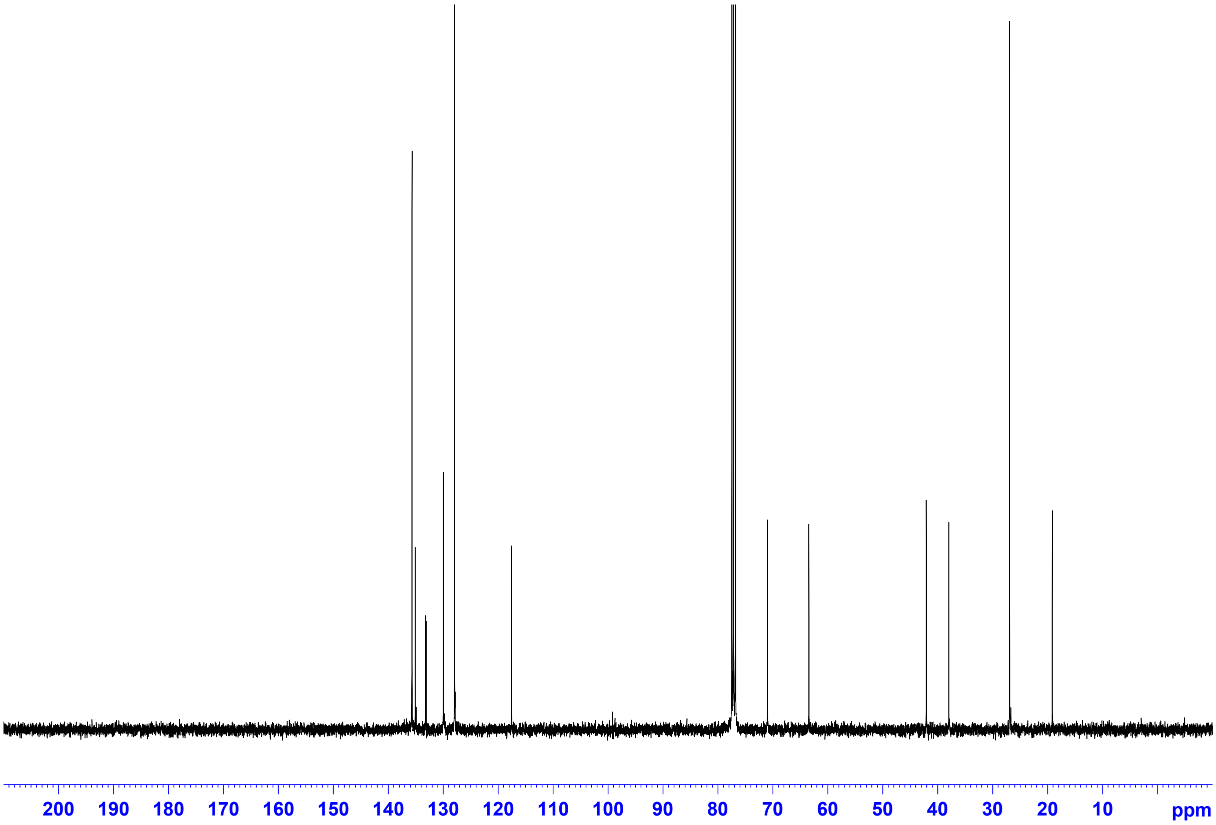
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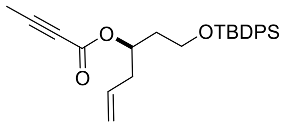
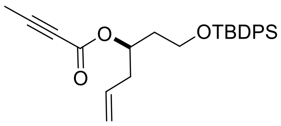


(*R*)-1-(*tert*-Butyldiphenylsilyloxy)hex-5-en-3-yl but-2-ynoate (103). To a solution of **102** (1.84 g, 5.2 mmol, 1.00 equiv) in dry CH_2Cl_2 (15 mL) were added sequentially DMAP (65 mg, 0.52 mmol, 0.10 equiv), 2-butynoic acid (0.49 g, 5.70 mmol, 1.10 equiv), and a solution of DCC (1.30 g, 6.30 mmol, 1.20 equiv) in CH_2Cl_2 (15 mL) at 0 °C. The suspension formed was allowed to warm to room temperature and stirring was continued for 16 h. Et_2O (100 mL) was then added, the mixture was filtered, and the filter cake was washed with Et_2O (50 mL). The filtrate was concentrated under reduced pressure to give a brown-red oil that was again treated with Et_2O (100 mL) followed by re-filtration of the mixture and washing of the precipitate with Et_2O (50 mL). The combined filtrate and washing were concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc/Hex 1:30→1:20), to give **103** (1.87 g, 4.44 mmol, 85%) as a colorless oil.

TLC: R_f = 0.44 (EtOAc/Hex 1:10, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.65 (m, 4 H), 7.46-7.37 (m, 6 H), 5.77 (ddt, J = 17.4, 9.7, 7.0, 1 H), 5.29-5.23 (m, 1 H), 5.13-5.07 (m, 2 H), 3.77-3.68 (m, 2 H), 2.46-2.34 (m, 2 H), 1.98 (s, 3 H), 1.89-1.83 (m, 2 H), 1.07 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 153.3, 135.7, 135.6, 133.8, 133.6, 133.2, 129.7, 127.8, 118.2, 85.3, 72.8, 72.6, 60.0, 38.6, 36.1, 26.9, 19.2, 3.9. **IR** (thin film): $\tilde{\nu}$ = 3071, 3050, 2957, 2359, 2342, 2243, 1706, 1472, 1428, 1389, 1249, 1110, 1063, 700 cm^{-1}. **HRMS** (ESI): calcd for $C_{23}H_{27}O_3Si$ [$(M-CH_3H_5)^+$]: 379.1730; found: 379.1724. $[\alpha]_D^{24}$: –18.04° (c = 0.93, $CHCl_3$).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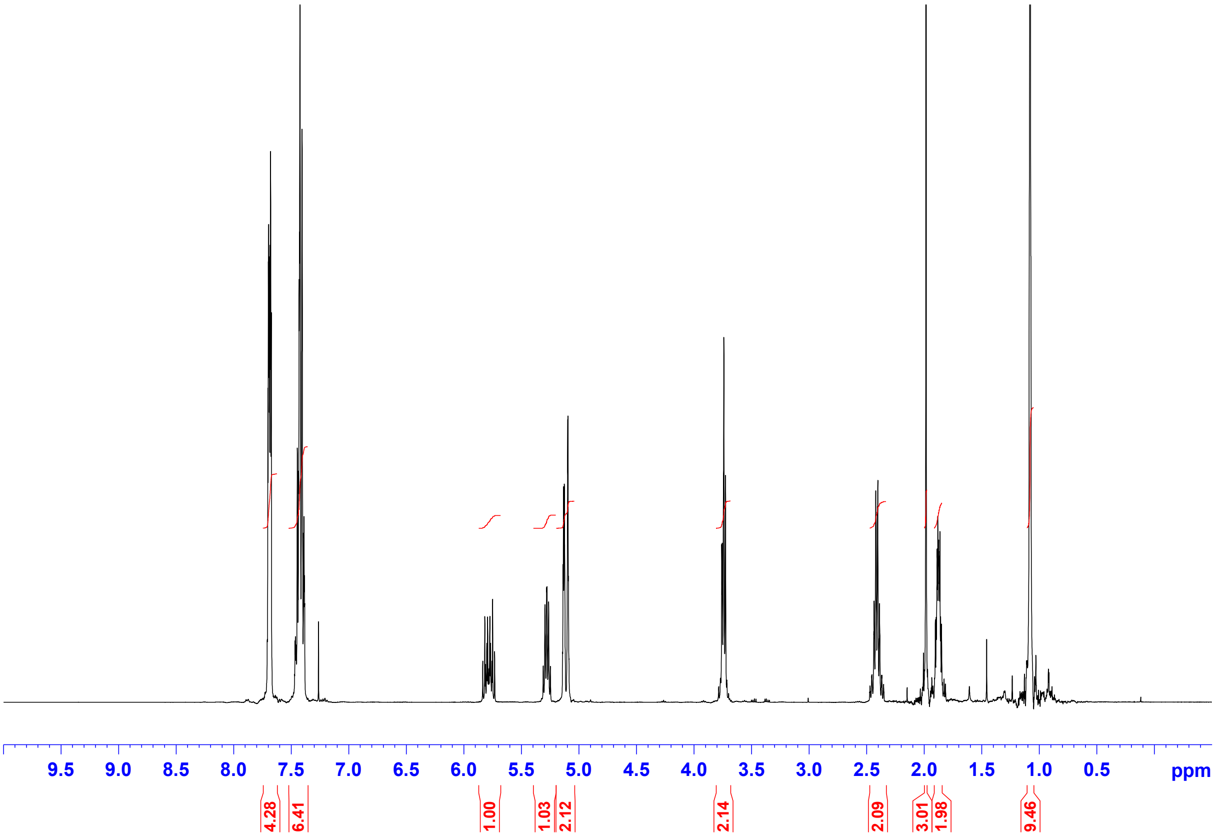
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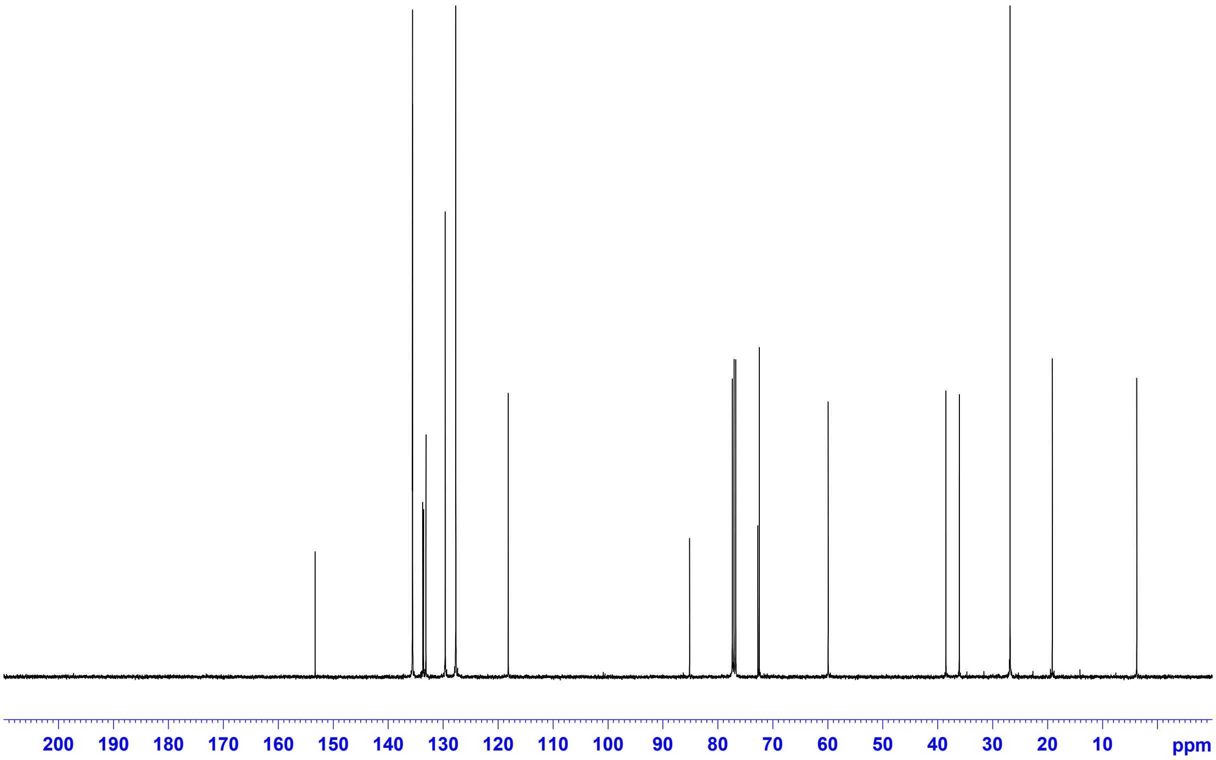
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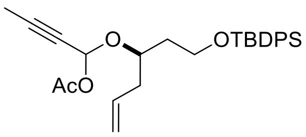
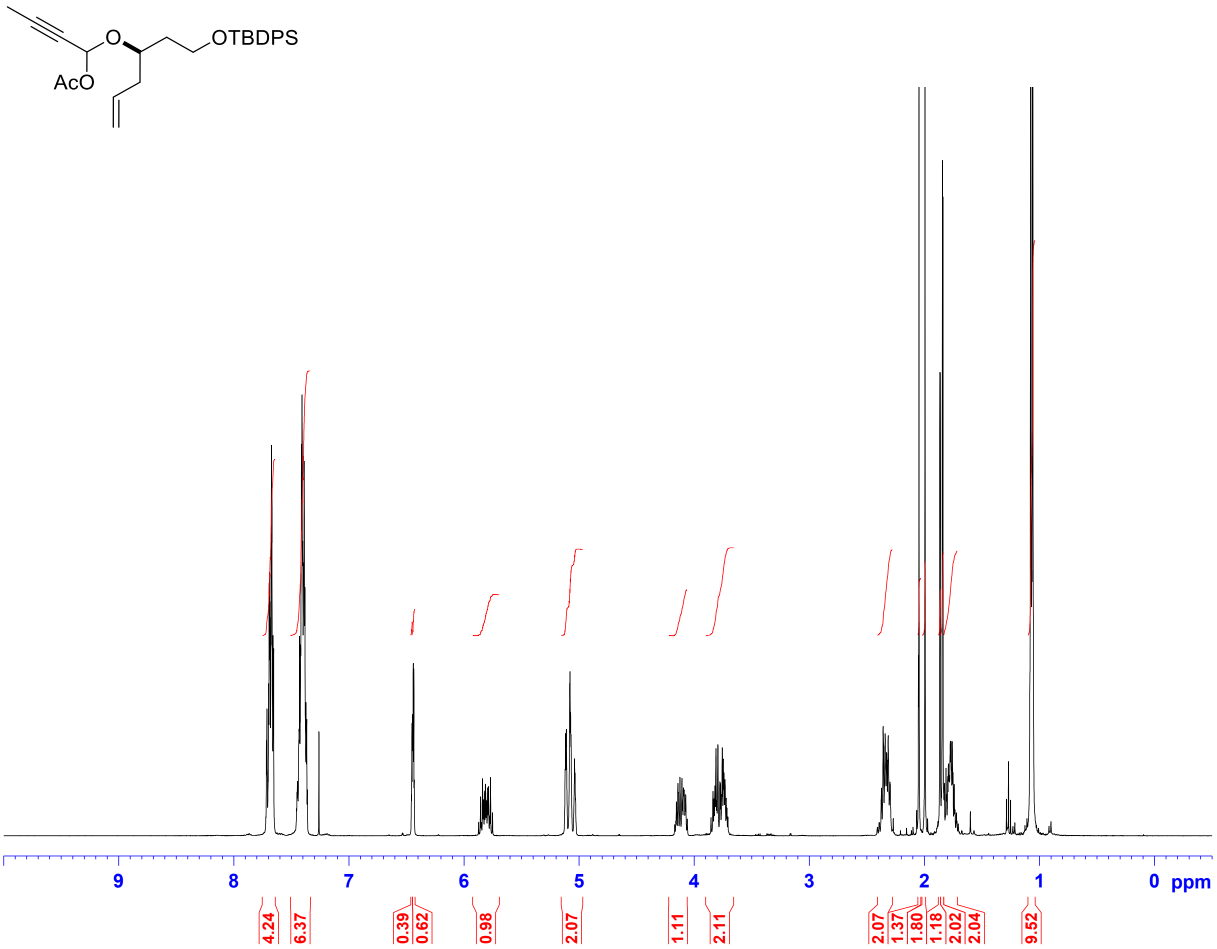


1-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)hex-5-en-3-yloxy)but-2-ynyl acetate (104). To a solution of **103** (1.77 g, 4.20 mmol, 1.00 equiv) in CH_2Cl_2 (40 mL) at –78 °C was added slowly DIBAL-H (1M in toluene, 8.40 mL, 8.40 mmol, 2.00 equiv); after 30 min pyridine (1 mL, 12.60 mmol, 3.00 equiv), DMAP (1.54 g, 12.60 mmol, 3.00 equiv), and Ac_2O (2.37 mL, 25.20 mmol, 6.00 equiv) were added seqentially at –78 °C and the mixture was stirred at that temperature for 22 h. Saturated aqueous NH_4Cl (20 mL) and saturated aqueous Rochelle salt (40 mL) were added at –78 °C and the mixture was allowed to warm to room temperature. Vigorous stirring was continued for 90 min in a beaker, resulting in the formation of two clear phases that were readily separable. The aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 x 20mL) and brine (10 mL, once), and then dried over $MgSO_4$. Concentration of the solution under reduced pressure and purification of the residue by flash chromatography on a deactivated stationary silica phase (EtOAc/Hex 1:30→1:20, 2% NEt_3 (v/v)) afforded **104** (1.80 g, 3.87 mmol, 92%) as a 1.6:1 mixture of diastereomers as a colorless, viscous oil. Spectroscopic data are reported for the diastereomeric mixture.

TLC: R_f = 0.40 (EtOAc/Hex 1:10, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.72-7.66 (m, 4 H), 7.45-7.36 (m, 6 H), 6.45 (q, *J* = 1.8, 0.37 H), 6.44 (q, *J* = 1.8, 0.63 H), 5.87-5.75 (m, 1 H), 5.12-5.02 (m, 2 H), 4.17-4.06 (m, 1 H), 3.85-3.71 (m, 2 H), 2.41-2.30 (m, 2 H), 2.05 (s, 1.12 H), 1.99 (s, 1.88 H), 1.86 (d, *J* = 1.8, 1.15 H), 1.84 (d, *J* = 1.8, 1.85 H), 1.83-1.71 (m, 2 H), 1.07 (s, 3.38 H), 1.06 (s, 5.62 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 169.9, 169.7, 135.7, 135.7, 135.6, 135.6, 134.5, 134.1, 134.0, 133.9, 133.9, 129.7, 129.7, 129.7, 127.8, 127.8, 118.0, 117.2, 87.2, 86.2, 83.1, 82.9, 76.4, 74.9, 74.4, 74.1, 60.6, 60.3, 39.7, 39.2, 37.4, 37.4, 27.0, 26.9, 21.2, 21.2, 19.3, 19.3, 3.7, 3.7. **IR** (thin film): $\tilde{\nu}$ = 3072, 2956, 2857, 2259, 1740, 1472, 1370, 1228, 1082, 903, 822, 701 cm^{-1}. **HRMS** (ESI): calcd for $C_{28}H_{36}NaO_4Si$ [$(M+Na)^+$]: 487.2281; found: 487.2265. $[\alpha]_D^{24}$: –19.24° (c = 0.99, $CHCl_3$).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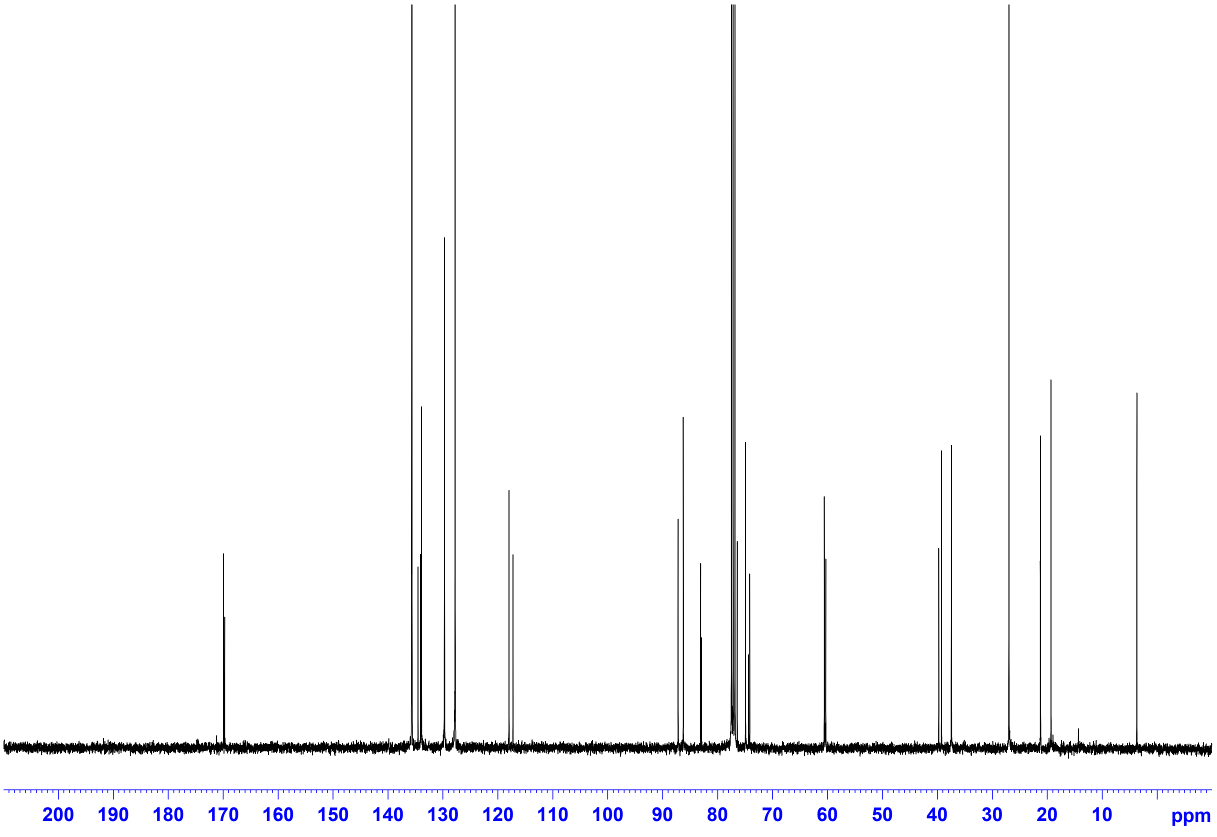
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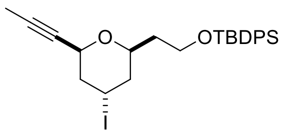

***tert*-Butyl-(2-((2*S*,4*S*,6*S*)-4-iodo-6-(prop-1-ynyl)tetrahydro-2H-pyran-2-yl) ethoxy)diphenylsilane (105)**. To a solution of **104** (1.79 g, 3.85 mmol, 1.00 equiv) in CH_2Cl_2 (55 mL) at –19 °C (NaCl/ice) was added 2,6-dimethylpyridine (0.09 mL, 0.77 mmol, 0.20 equiv) followed by slow addition of TMSI (1.37 mL, 9.62 mmol, 2.50 equiv).[34] The cooling bath was removed after 10 min and the yellow solution was allowed to warm to room temperature. After a total of 45 min saturated aqueous $NaHCO_3$ (20 mL) was carefully added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:30→1:20) afforded **105** (1.78 g, 3.34 mmol, 85%) as a pale-yellow, viscous oil. Material obtained in this way is generally contaminated by 2-3% of aldehyde **117**. Spectroscopic data for **105** were acquired with a pure sample.

TLC: R_f = 0.45 (EtOAc/Hex 1:10, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.71-7.67 (m, 4 H), 7.44-7.36 (m, 6 H), 4.83 (quin, *J* = 3.1, 1 H), 4.57 (br. dquin, *J* = 10.8, 2.1, 1 H), 4.21-4.15 (m, 1 H), 3.86 (ddd, *J* = 10.5, 8.2, 4.9, 1 H), 3.73 (dt, *J* = 10.3, 5.4, 1 H), 2.16 (dq, *J* = 14.8, 2.3, 1 H), 1.99 (ddd, *J* = 14.7, 2.4, 2.1, 1 H), 1.93-1.82 (m, 2 H), 1.87 (d, *J* = 2.1, 3 H), 1.69 (ddt, *J* = 13.7, 8.3, 5.3, 1 H), 1.57-1.50 (m, 1 H), 1.07 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.7, 135.7, 134.1, 133.9, 129.7, 127.8, 127.8, 81.5, 77.9, 71.1, 65.1, 60.1, 41.8, 40.3, 38.3, 29.3, 27.0, 19.4, 3.8. **IR** (thin film): $\tilde{\nu}$ = 3070, 2953, 2856, 2360, 2341, 1472, 1427, 1389, 1232, 1107, 1095, 1049, 822, 737, 702 cm^{-1}. **HRMS** (EI): calcd for $C_{22}H_{24}IO_2Si$ [$(M-C_4H_9)^+$]: 475.0590; found: 475.0585. $[\alpha]_D^{24}$: –3.30° (c =1.00, $CHCl_3$).

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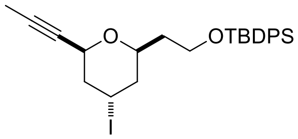
[34] The conversion of **104** (0.06 mmol) proceeds with identical efficacy if less TMSI (1.3 equiv) is used, however, this was not tested on larger scale.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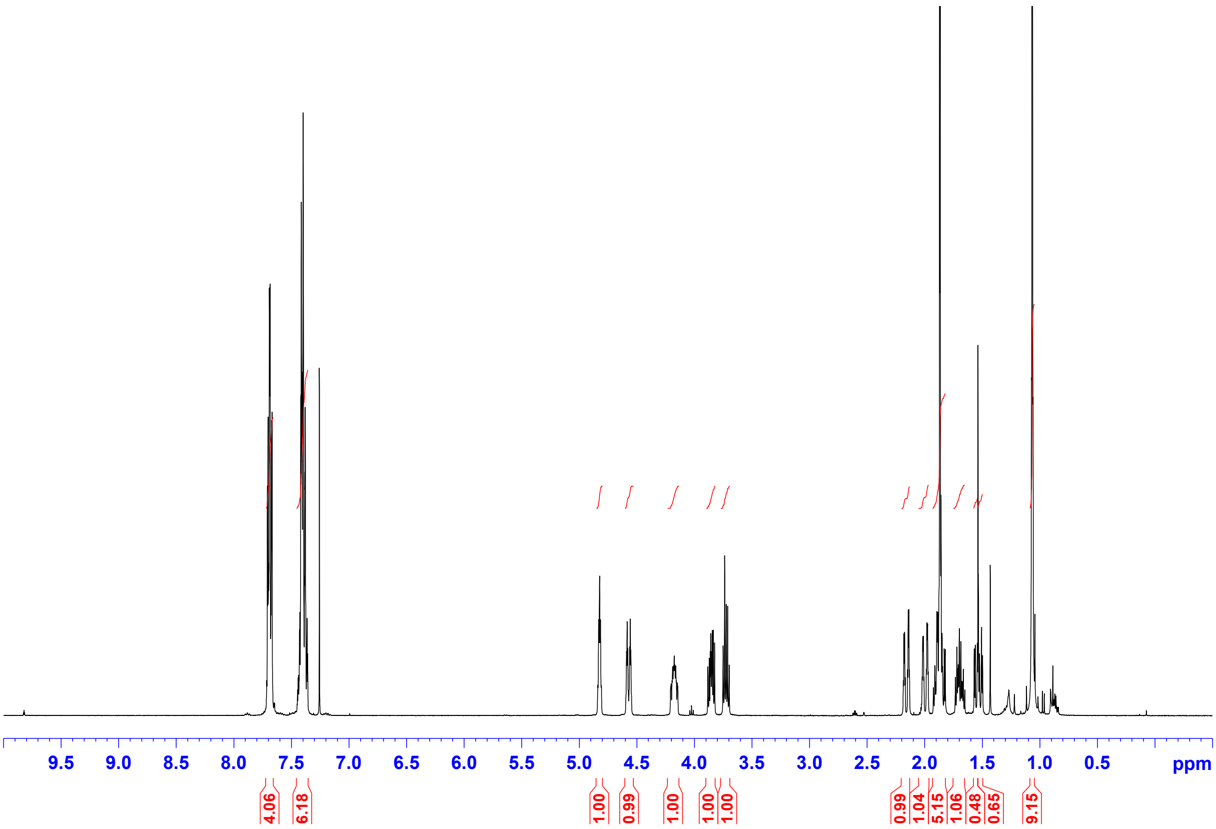
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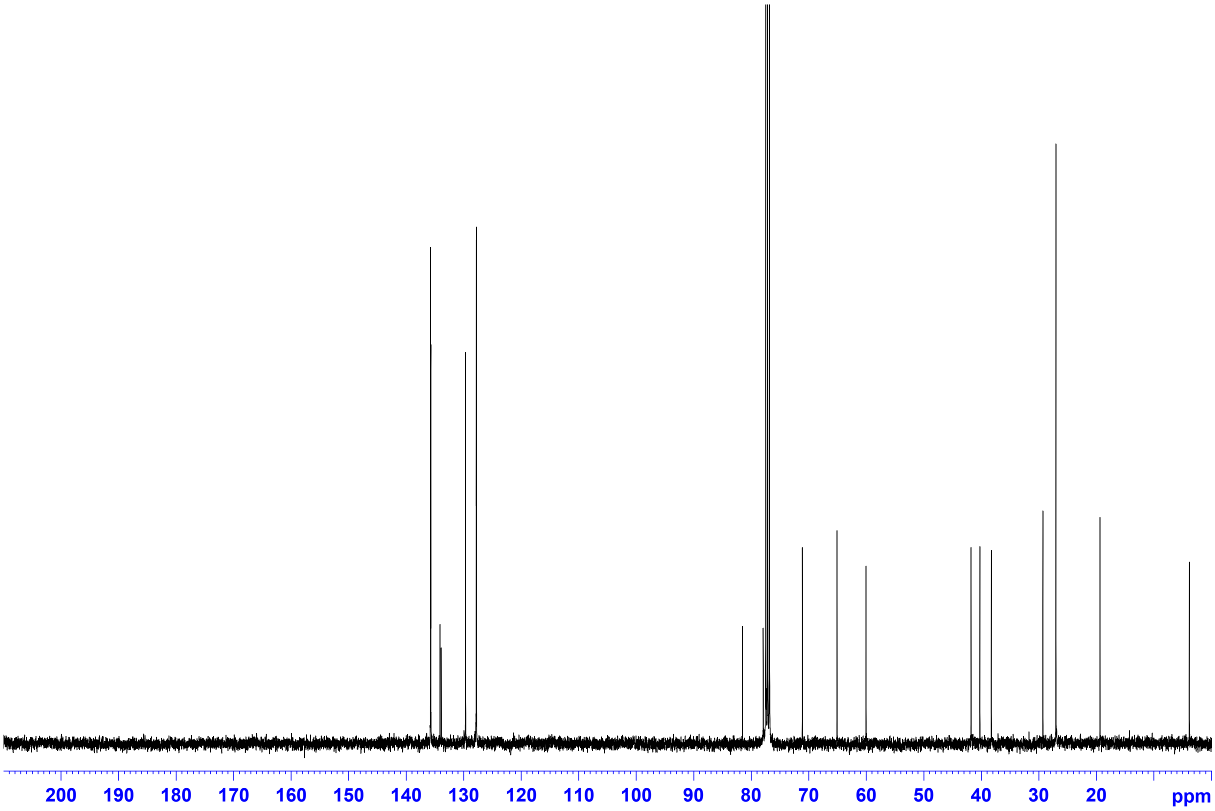
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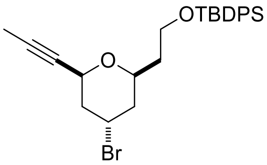
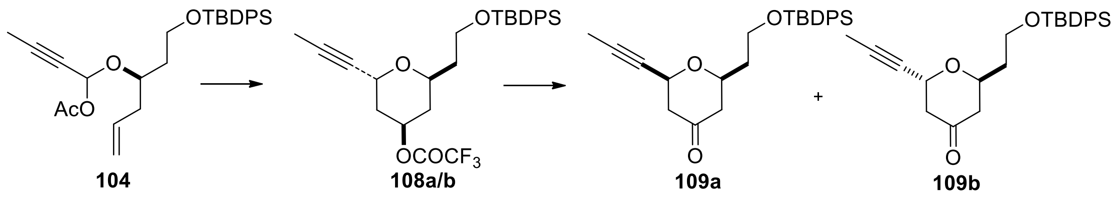


(2-((2*S*,4*S*,6*S*)-4-romo-6-(prop-1-yn-1-yl)tetrahydro-2H-pyran-2-yl)ethoxy)(*tert*-butyl)diphenylsilane (110c). To a solution of **104** (42.1 mg, 0.09 mmol, 1.0 equiv) in CH_2Cl_2, 1 mL) at 0 °C was added 2,6-dimethylpyridine (2.1 μl, 0.018 mmol, 0.2 equiv) followed by slow addition of TMBr (0.03 mL, 0.027 mmol, 2.50 equiv). The cooling bath was removed after 5 min and the yellow solution was allowed to warm to room temperature. After 1.75 h, more TMSBr (0.03 mL, 0.027 mmol, 2.50 equiv) was added at room temperature. Stirring was continued for 30 min more then more TMSBr (0.06 mL, 0.054 mmol, 5.0 equiv) was added. After 4 h in total, a last portion of TMSBr (0.16 mL, 1.21 mmol, 13.3 equiv) was added which resulted in the almost complete consumption of **104**. The yellow solution was poured carefully in saturated aqueous $NaHCO_3$ (10 mL) followed by addition of CH_2Cl_2 (10 mL) and after 5 min, the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:30) afforded **110c** (30 mg, 0.062 mmol, 69%) as a colorless, viscous oil. Material obtained in this way was contaminated by 4% of aldehyde **117**.

TLC: R_f = 0.32 (EtOAc/Hex 1:10, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.70-7.66 (m, 4 H), 7.44-7.36 (m, 6 H), 4.70 (quin, *J* = 3.1, 1 H), 4.63 (dquin, *J* = 10.6, 2.1, 1 H), 4.24-4.17 (m, 1 H), 3.85 (ddd, *J* = 10.3, 8.0, 4.8, 1 H), 3.73 (dt, *J* = 10.3, 5.4, 1 H), 2.16 (dq, *J* = 14.9, 2.2, 1 H), 2.08 (ddd, *J* = 14.8, 10.8, 3.3, 1 H), 2.02-1.97 (m, 1 H), 1.90-1.82 (m, 1 H), 1.86 (d, *J* = 2.1, 3 H), 1.76 (ddd, *J* = 14.7, 11.0, 3.3, 1 H), 1.72-1.64 (m, 1 H), 1.06 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.7, 135.7, 134.1, 133.9, 129.7, 127.8, 127.8, 81.5, 78.0, 69.8, 63.7, 60.1, 49.6, 40.7, 39.2, 38.4, 27.0, 19.4, 3.9.



(2*S*,6*S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-6-(prop-1-yn-1-yl)dihydro-2H-pyran-4(3H)-one (109a). To a solution of **104** (45.7 mg, 0.098 mmol, 1 equiv) in CH_2Cl_2 (1.0 mL) was added a solution of TFA (0.073 mL, 0.98 mmol, 10 equiv) in CH_2Cl_2 (0.1 mL) at 0 °C giving a pale-yellow solution. Stirring was continued for 30 min then all starting material was consumed according to TLC analysis. Saturated aqueous $NaHCO_3$ (10 mL) was added as well as CH_2Cl_2 (5 mL) then the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5mL) then the combined organic phases were washed with brine (2 x 5 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:50) gave a mixture of **108a** and **b** (36 mg, 0.07 mmol, 71%) as a pale-yellow oil.

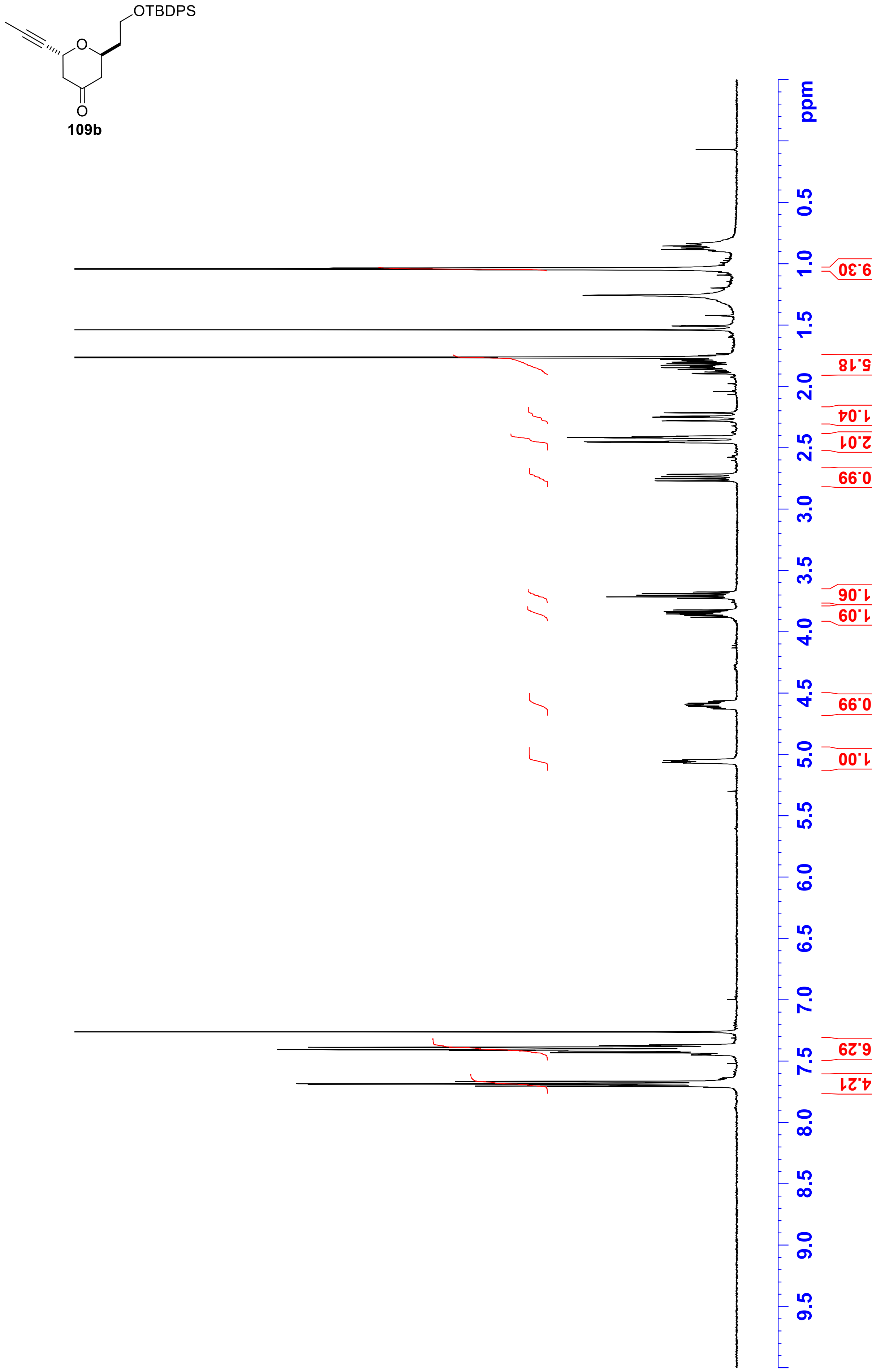
To a solution of **108a/b** (36 mg, 0.07 mmol, 1 equiv) in MeOH (0.6 mL) was added K_2CO_3 (20 mg, 0.14 mmol, 2 equiv) and stirring was continued at room temperature for 45 min. The mixture was diluted with H_2O (5 mL) then Et_2O was added followed by separation of phases. The aqueous phase was extracted with Et_2O (3 x 5 ml) then the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:3) afforded a mixture of the secondary alcohol from of **108a/b** (25.7 mg, 0.061 mmol, 88%) as a colorless oil.

To a solution of the alcohol mixture (25.7 mg, 0.061 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added a solution of DMP (15% in CH_2Cl_2, 0.2 mL). Stirring was continued at room temperature for 2.5 h then TLC (EtOAc/Hex 1:5) analysis indicated complete conversion of the alcohols and the formation of two new products. CH_2Cl_2 (5 mL) was added as well as saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The two clear phases were separated, then the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were dried over $MgSO_4$. Purification using flash chromatography (EtOAc/Hex 1:30→1:10) afforded two products **109 a** and **b** which were partially separable. A combined yield was not calculated in this trial but is in the range of 90%, as calculated by the indentical transformation in a separate trial.

Analytical data for **109a**: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.63 (m, 4 H), 7.45-7.36 (m, 6 H), 4.29 (ddq, *J* = 10.3, 4.1, 2.1, 1 H), 3.93-3.83 (m, 2 H), 3.75 (dt, *J* = 10.4, 5.3, 1 H), 2.61 (dd, *J* =15.0, 10.5, 1 H), 2.56 (ddd, *J* = 15.0, 4.0, 1.6, 1 H), 2.39 (ddd, *J* = 14.6, 2.6, 1.6, 1 H), 2.29 (dd, *J* = 14.6, 11.6, 1 H), 1.97-1.88 (m, 1 H), 1.89 (d, *J* = 2.1, 3 H), 1.82-1.73 (m, 1 H), 1.04 (s, 9 H).

Note: Analytical data of **109a** (^{1}H-NMR) was identical to the data which were obtained form compound derived from the acetate substitution of iodide **105** (Scheme 58, page 77).

Analytical data for **109b**: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.71-7.66 (m, 4 H), 7.45-7.36 (m, 6 H), 5.07-5.04 (m, 1 H), 4.63-4.56 (m, 1 H), 3.85 (ddd, *J* = 10.2, 8.4, 4.8, 1 H), 3.70 (dt, *J* = 10.3, 5.2, 1 H), 2.77-2.72 (m, 1 H), 2.46-2.41 (m, 2 H), 2.28-2.22 (m, 1 H), 1.89-1.75 (m, 2 H), 1.77 (d, *J* = 2.2, 3 H), 1.04 (s, 9 H).



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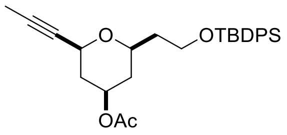
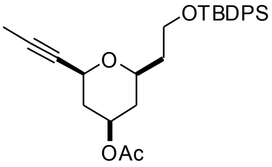
109b



(2*S*,4*R*,6*S*)-2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-6-(prop-1-ynyl)tetrahydro-2H-pyran-4-yl acetate (122). To a solution of **105** (1.57 g, 2.95 mmol, 1.00 equiv) in toluene (130 mL) was added a solution of 18-c-6 (3.12 g, 11.80 mmol, 4.00 equiv) in toluene (20 mL) followed by CsOAc (5.67 g, 29.53 mmol, 10.00 equiv) at room temperature and the mixture was heated to 60 °C for 4 d. After cooling to room temperature H_2O (50 mL) and EtOAc (50 mL) were added, the phases were separated, and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic extract were washed once with brine (30 mL), dried over $MgSO_4$ and the solution was concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:25→1:10) afforded **122** (987 mg, 2.12 mmol, 72%) as a colorless, viscous oil.

TLC: R_f = 0.29 (EtOAc/Hex 1:10, UV, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 4 H), 7.44-7.36 (m, 6 H), 4.86 (tt, *J* = 11.3, 4.8, 1 H), 4.09 (dquin, *J* = 11.6, 2.1, 1 H), 3.87 (ddd, *J* = 10.3, 8.3, 4.9, 1 H), 3.72 (dt, *J* = 10.3, 5.4, 1 H), 3.67-3.61 (m, 1 H), 2.18 (dddd, *J* =12.6, 4.9, 2.4, 2.1, 1 H), 2.04 (s, 3 H), 1.94 (dddd, *J* = 12.3, 4.8, 2.4, 1.8, 1 H), 1.89-1.82 (m, 1 H), 1.86 (d, *J* = 2.1, 3 H), 1.72 (ddt, *J* = 14.1, 8.4, 5.4, 1 H), 1.64 (dd, *J* = 23.9, 11.5, 1 H), 1.31 (dd, *J* = 23.6, 11.5, 1 H), 1.05 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 170.5, 135.7, 135.7, 134.9, 134.1, 133.9, 129.7, 129.7, 127.8, 81.2, 77.7, 72.6, 69.7, 66.2, 60.0, 38.8, 38.4, 37.1, 27.0, 21.3, 19.3, 3.8. **IR** (thin film): $\tilde{\nu}$ = 3071, 2956, 2856, 2360, 2342, 1740, 1472, 1428, 1389, 1237, 1109, 1063, 1031, 907, 822 cm^{-1}. **HRMS** (ESI): calcd for $C_{22}H_{24}IO_2Si$ [$(M+Na)^+$]: 487.2281; found: 487.2275. $[\alpha]_D^{24}$: –10.84° (c = 2.39, $CHCl_3$).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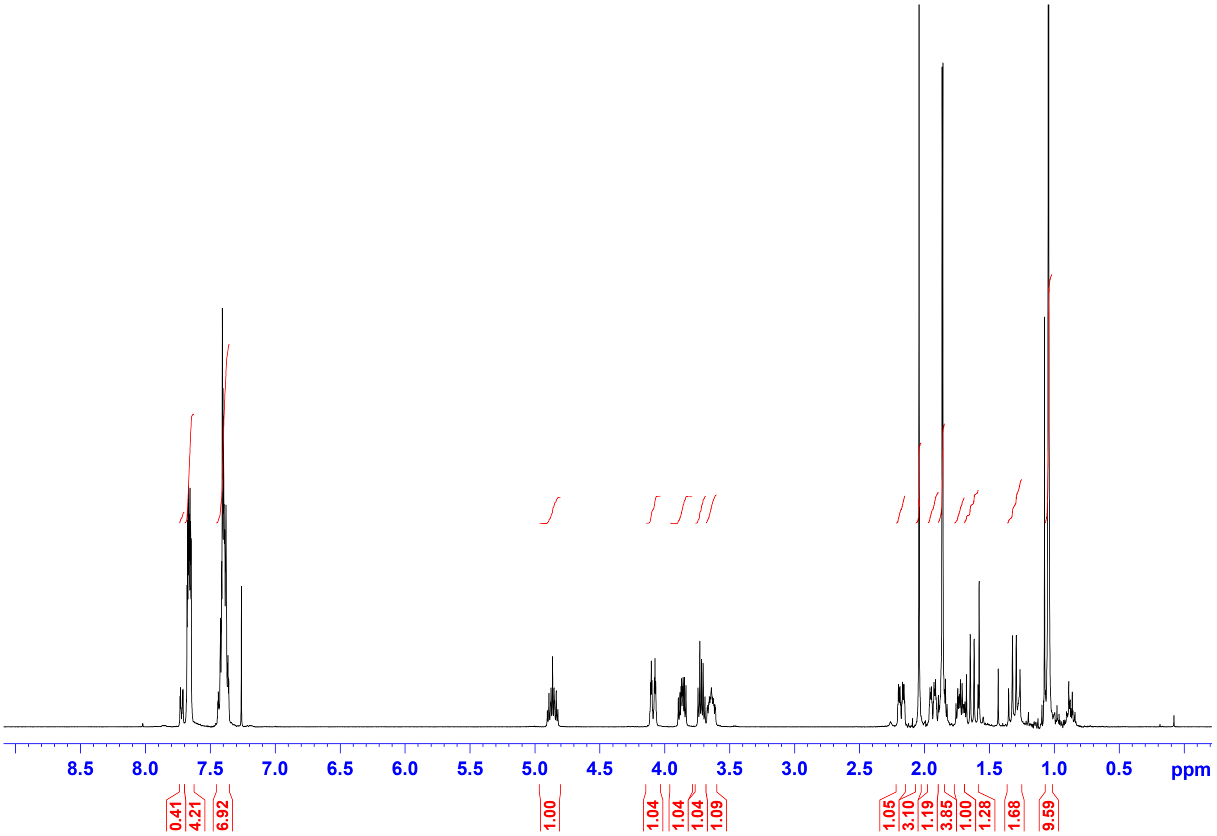
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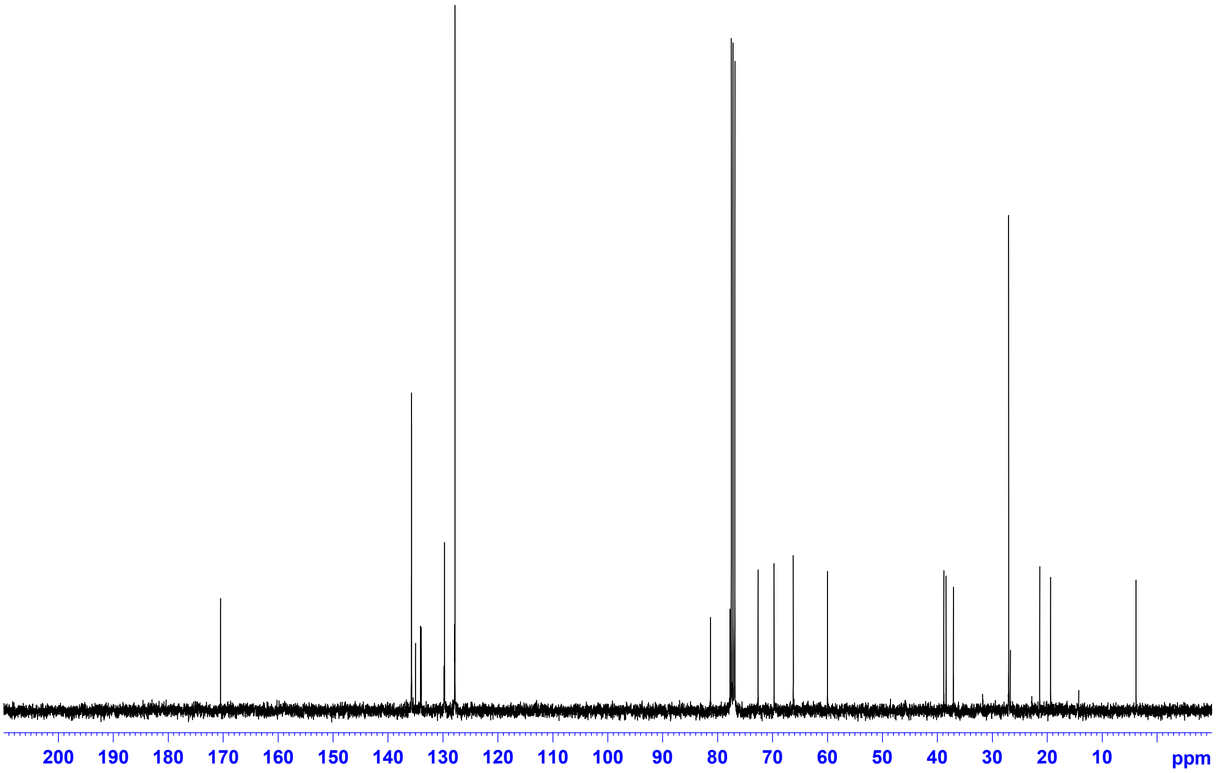
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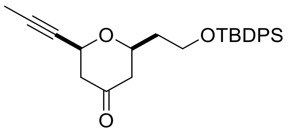
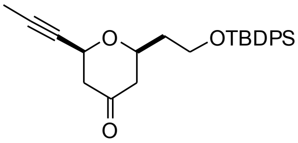


(2*S*,6*S*)-2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-6-(prop-1-ynyl)dihydro-2H-pyran-4(3H)-one (109a). To a stirred solution of **122** (0.96 g, 2.07 mmol, 1.00 equiv) in MeOH (40 mL) were added K_2CO_3 (2.86 g, 20.70 mmol, 10.00 equiv) and H_2O (2 mL) and stirring was continued for 6 h. Brine (20 mL) and EtOAc (20 mL) were then added and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (20 mL) and DMP (1.32 g, 3.10 mmol, 1.50 equiv) was added in two equal portions (with the second portion added after 30 min) and the mixture was stirred for 3 h. A mixture of saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10mL) was then added and stirring was continued for 10 min. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:10→1:5) gave **109a** (733.8 mg, 1.75 mmol, 85% for two steps) as a colorless oil.

Note: Swern oxidation using 1.5 equiv of oxalylchloride, 3 equiv of DMSO and 5 equiv of NEt_3 gave comparable overall yields and could be more suitable for large scale preparations.

TLC: R_f = 0.33 (EtOAc/Hex 1:5, UV, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.63 (m, 4 H), 7.45-7.36 (m, 6 H), 4.29 (ddq, *J* = 10.3, 4.1, 2.1, 1 H), 3.93-3.83 (m, 2 H), 3.75 (dt, *J* = 10.4, 5.3, 1 H), 2.61 (dd, *J* =15.0, 10.5, 1 H), 2.56 (ddd, *J* = 15.0, 4.0, 1.6, 1 H), 2.39 (ddd, *J* = 14.6, 2.6, 1.6, 1 H), 2.29 (dd, *J* = 14.6, 11.6, 1 H), 1.97-1.88 (m, 1 H), 1.89 (d, *J* = 2.1, 3 H), 1.82-1.73 (m, 1 H), 1.04 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 205.6, 135.7, 135.7, 133.8, 133.8, 129.8, 129.8, 127.9, 83.0, 77.0, 73.8, 67.3, 59.7, 48.3, 47.8, 39.1, 27.0, 19.3, 3.9. **IR** (thin film): $\tilde{\nu}$ = 2955, 2927, 2856, 1722, 1473, 1427, 1337, 1227, 1109, 1086, 702 cm^{-1}. **HRMS** (ESI): calcd for $C_{26}H_{32}NaO_3Si$ [$(M+Na)^+$]: 443.2013; found: 443.1999. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –26.81° (c = 0.97, $CHCl_3$).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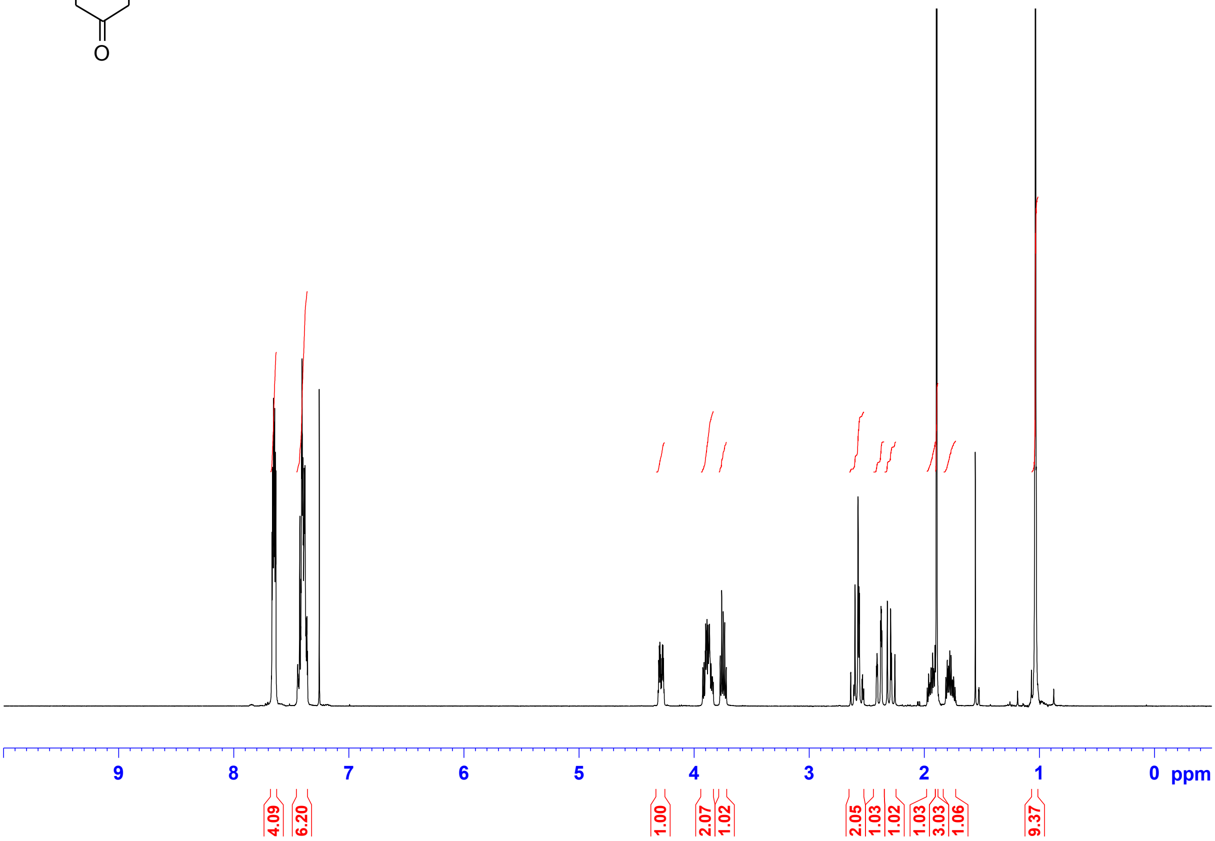
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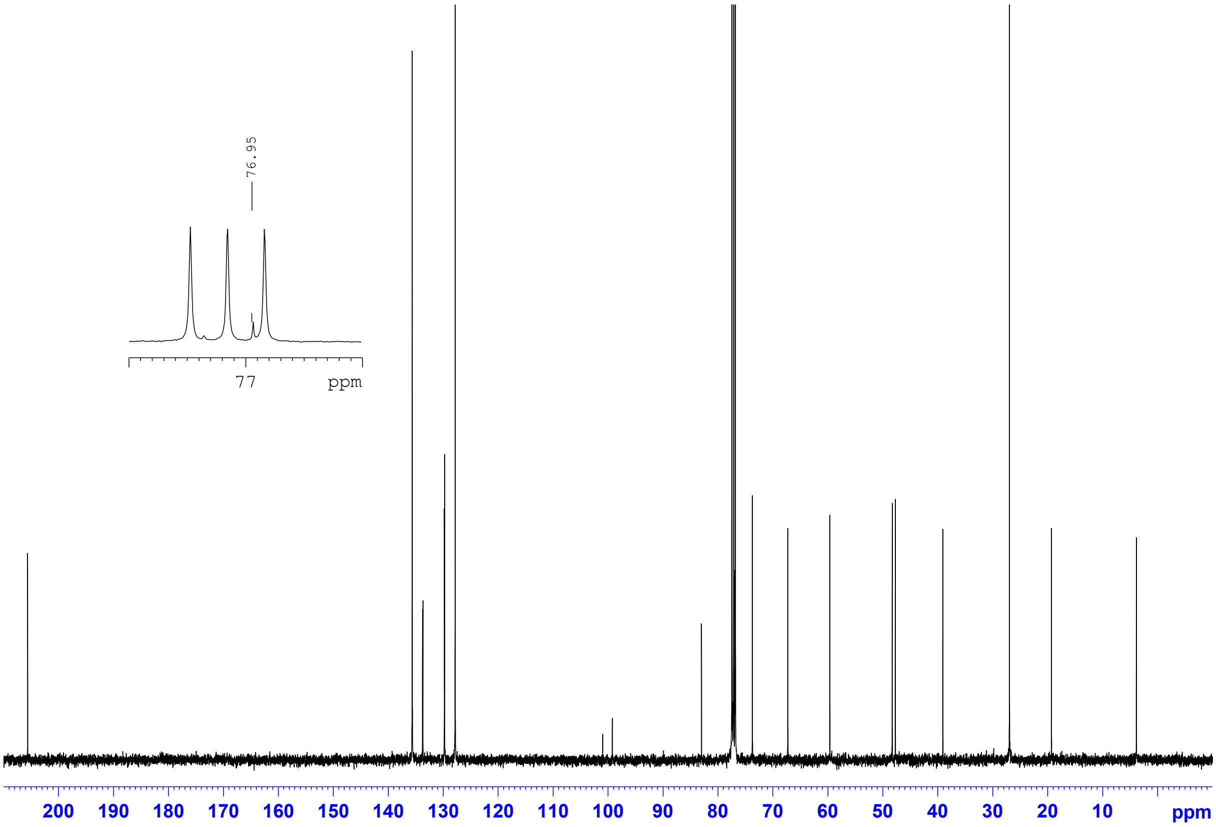
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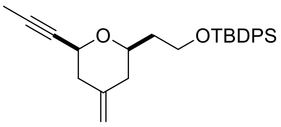
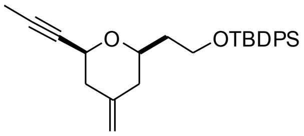


***tert*-Butyl-(2-((2*R*,6*S*)-4-methylene-6-(prop-1-ynyl-)tetrahydro-2H-pyran-2-yl)ethoxy-) diphenylsilane (123)**. To a solution of MePh$_3$PBr (1.20 g, 3.38 mmol, 2.00 equiv) in THF (20 mL) was added *n*-BuLi (1.6M in hexane, 2.00 mL, 3.20 mmol, 1.90 equiv) at –78 °C. After stirring for 15 min at –78 °C the temperature was allowed to rise to 0 °C; stirring was continued for 30 min, then a solution of **109a** (0.71 g, 1.69 mmol, 1.00 equiv) in THF (10 mL) was added and the mixture was then heated to 50 °C for 90 min. After cooling to room temperature H$_2$O (10 mL) and EtOAc (10 mL) were added, the phases were separated, and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO$_4$ and the solution was concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:100→1:50) gave **123** (0.66 g, 1.58 mmol, 94%) as a colorless oil.

TLC: R_f = 0.62 (EtOAc/Hex 1:10, UV, CPS). **^{1}H-NMR** (400 MHz, CDCl$_3$): δ = 7.68-7.65 (m, 4 H), 7.44-7.35 (m, 6 H), 4.76-4.74 (m, 2 H), 4.00 (ddq, *J* = 11.0, 2.4, 2.1, 1 H), 3.87 (ddd, *J* = 10.2, 8.1, 5.0, 1 H), 3.74 (dt, *J* =10.2, 5.5, 1 H), 3.56-3.50 (m, 1 H), 2.43-2.39 (m, 1 H), 2.36-2.29 (m, 1 H), 2.24-2.20 (m, 1 H), 2.00-1.93 (m, 1 H), 1.92-1.85 (m, 1 H), 1.88 (d, *J* = 2.1, 3 H), 1.78-1.70 (m, 1 H), 1.04 (s, 9 H). **^{13}C-NMR** (100 MHz, CDCl$_3$): δ = 143.5, 135.7, 135.7, 134.1, 134.0, 129.7, 129.7, 127.8, 109.6, 81.2, 78.5, 75.6, 69.0, 60.3, 42.0, 40.5, 39.1, 27.0, 19.3, 3.9. **IR** (thin film): $\tilde{\nu}$ = 3071, 2944, 2931, 2857, 2360, 2342, 1651, 1472, 1427, 1389, 1345, 1110, 1089, 1060, 998, 894, 823, 702 cm^{-1}. **HRMS** (ESI): calcd for $C_{27}H_{35}O_2Si$ [(M+H)$^+$]: 419.2401; found: 419.2404. $[\alpha]_D^{24}$: –3.42° (c = 0.55, CHCl$_3$).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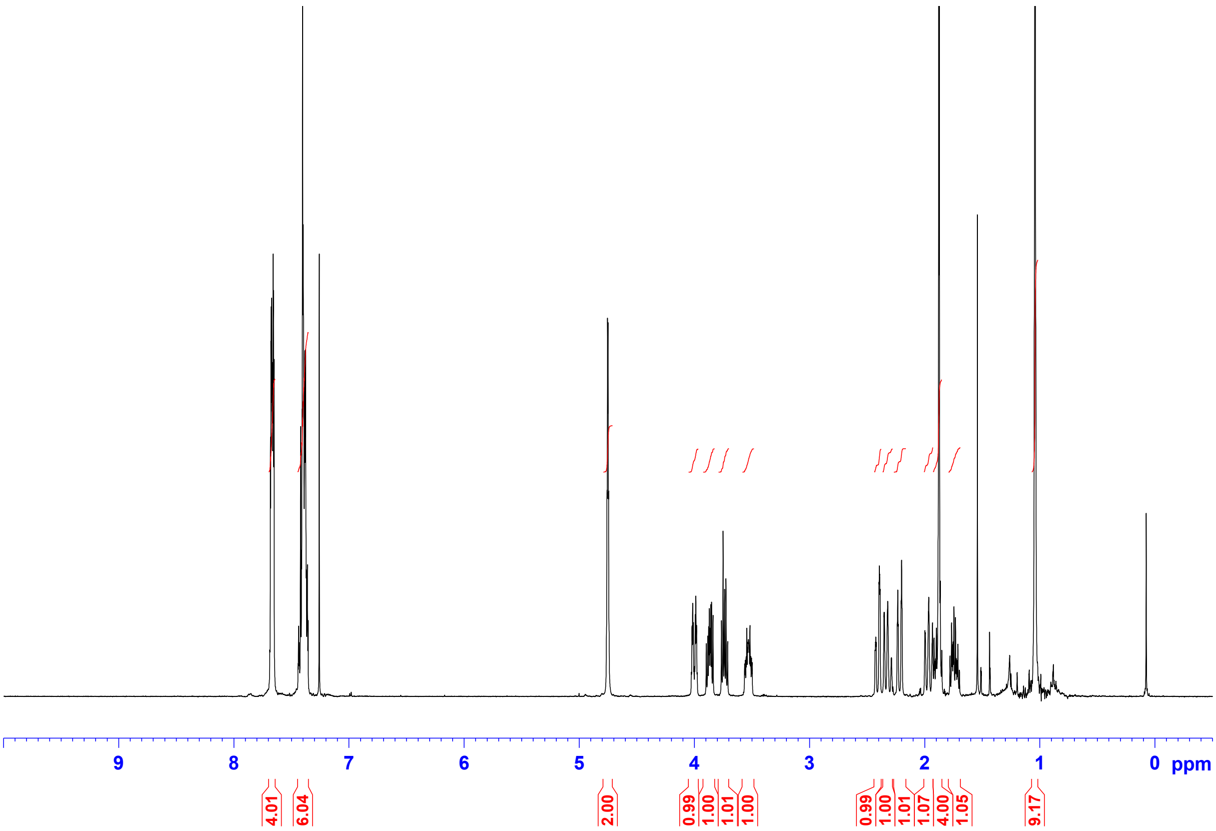
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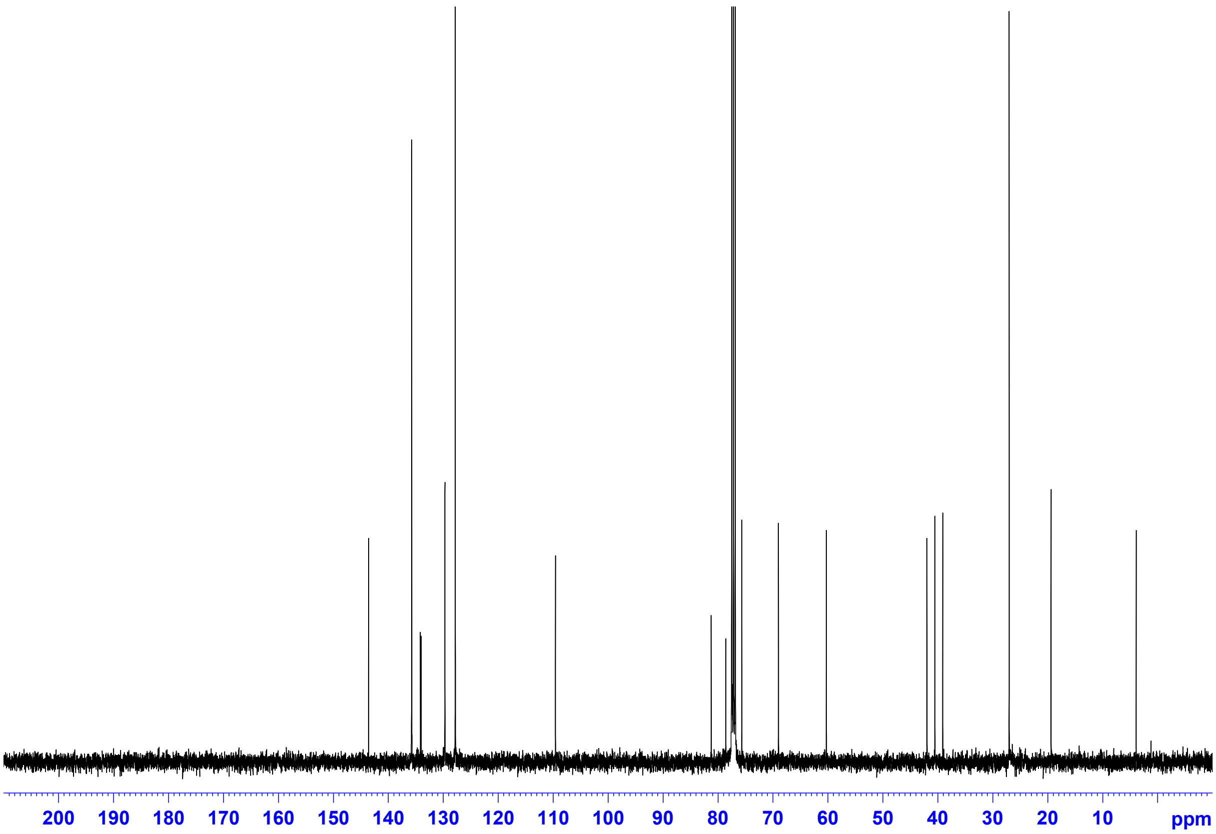
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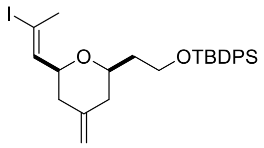
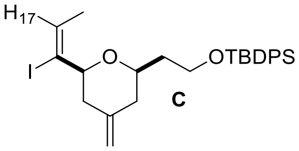


***tert*-Butyl-(2-((2*R*,6*S*)-6-((*E*)-2-iodoprop-1-enyl)-4-methylenetetrahydro-2H-pyran-2-yl)ethoxy) diphenylsilane (124)**. To a suspension of CuCN (668 mg, 7.42 mmol, 5.00 equiv) in THF (16 mL) at –78 °C was added a solution of *n*-BuLi (1.6M in hexane, 9.30 mL, 14.82 mmol, 10.00 equiv). After 5 min the flask was immersed in a cooling bath at –40 °C, resulting in the formation of a pale-yellow, almost clear solution. The mixture was cooled back to –78 °C after 10 min, which made it become slightly heterogenous. Neat Bu_3SnH (4.00 mL, 14.82 mmol, 10.00 equiv.) was then added dropwise, immediately leading to a turbid yellow solution with liberation of gas. After 20 min at –78 °C the mixture was stirred for 5 min at –40 °C, giving an almost clear golden-yellow solution. After 10 min at –40 °C the solution was cooled back to –78 °C followed by addition of MeOH (6.60 mL, 163.00 mmol, 110.00 equiv) under vigorous stirring. After 10 min at –78 °C the flask was immersed in a cooling bath at –40 °C; the reaction mixture now was a clear red solution. After 10 min at –40 °C this solution was cooled back to –78 °C and a solution of **123** (0.62 g, 1.48 mmol, 1.00 equiv) in THF (10 mL) was added. The mixture was stirred for 15 h, during which period the temperature was allowed to rise to –15 °C. Saturated aqueous NH_4Cl (30 mL) and 25% aqueous NH_4OH (6 mL) were then added together with EtOAc (20 mL). Stirring was continued for 30 min, the two almost clear phases were separated, and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, the solution was concentrated under reduced pressure. Purification of the residue by flash chromatography on deactivated silica (Hex→EtOAc/Hex 1:100→1:50, 1% (v/v) NEt_3) gave the vinylstannane (1.02 g, 1.43 mmol, 97%) as a pale-yellow oil that was used immediately.

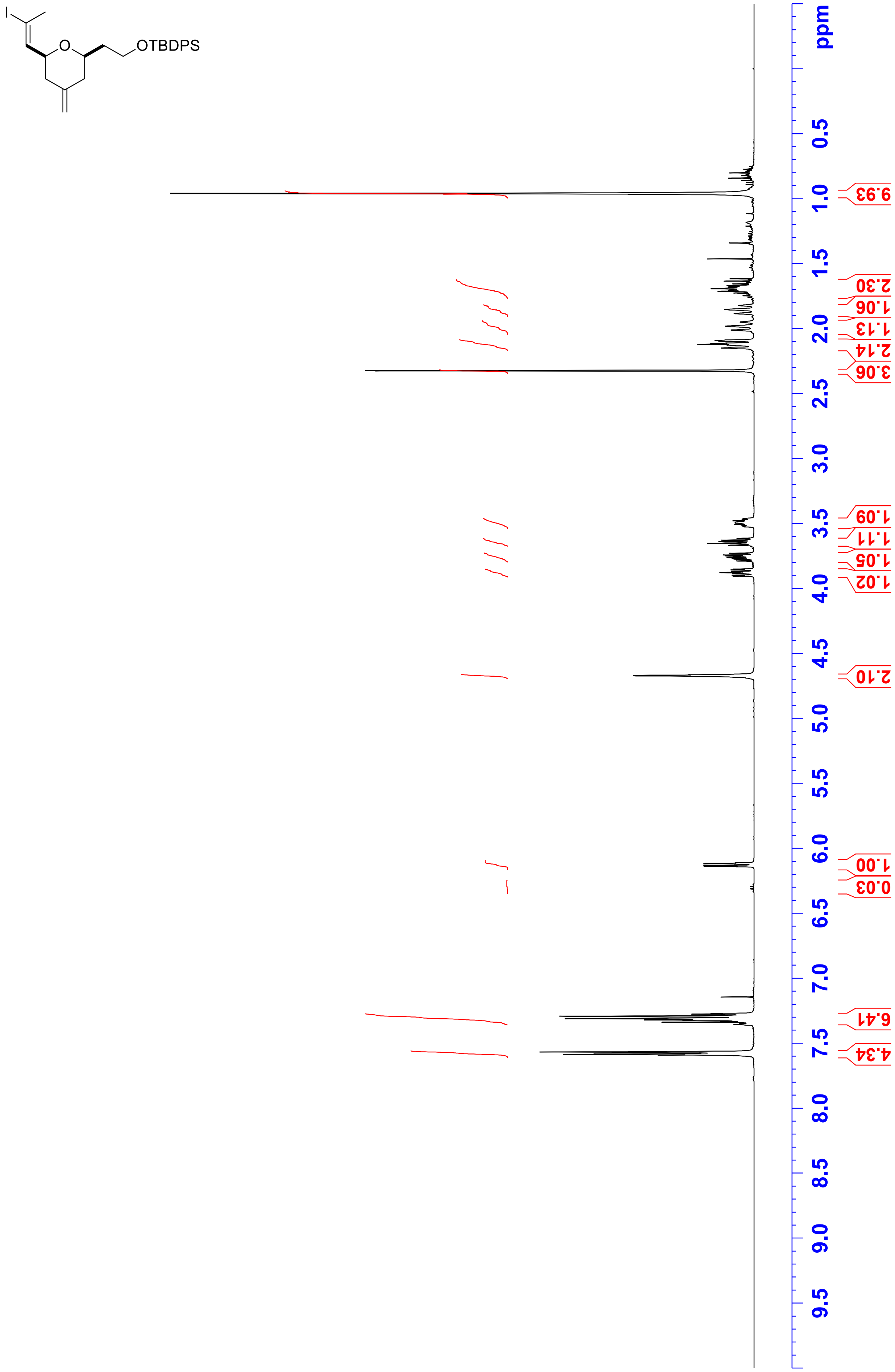
A solution of the above vinylstannane in THF (11 mL) was cooled to –17 °C (NaCl/ice) followed by addition of NIS (0.49 g, 2.10 mmol, 1.50 equiv) in THF (2 mL), to give an almost clear yellow solution. After 20 min a mixture of saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) was added followed by EtOAc (5 mL). Stirring was continued for 2 min until two clear, colorless phases were formed. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by flash chromatography (Hex/EtOAc 1:100) to afford the desired product **124** (0.79 g, 1.44 mmol, quant.) as a pale yellow oil.

TLC: R_f = 0.64 (EtOAc/Hex 1:20, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4 H), 7.47-7.38 (m, 6 H), 6.24 (dq, *J* = 7.7, 1.5, 1 H), 4.81-4.77 (m, 2 H), 3.99 (ddd, *J* =10.8, 7.7, 2.6, 1 H), 3.87 (ddd, *J* = 10.1, 8.1, 5.4, 1 H), 3.76 (dt, *J* = 10.1, 5.6, 1 H), 3.64-3.57 (m, 1 H), 2.44 (d, *J* = 1.5, 3 H), 2.27-2.20 (m, 2 H), 2.13-2.06 (m, 1 H), 2.00-1.94 (m, 1 H), 1.87-1.73 (m, 2 H), 1.08 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 141.6, 135.6, 135.6, 134.0, 133.9, 129.7, 127.7, 109.3, 98.5, 76.3, 75.3, 60.2, 40.6, 40.4, 39.0, 28.8, 26.9, 19.3. **IR** (thin film): $\tilde{\nu}$ = 3070, 2931, 2890, 2856, 1651, 1472, 1427, 1360, 1105, 1087, 998, 858, 700 cm^{-1}. **HRMS** (ESI): calcd for $C_{27}H_{36}IO_2Si$ [$(M+H)^+$]: 547.1524; found: 547.1503. $[\alpha]_D^{24}$: +4.90° (c =1.81, $CHCl_3$).

Note: The ^{1}H-NMR spectrum indicated the presence of ca. 3 % of the undesired regioisomer **C** (H17: δ = 6.45-6.39 (m, 1 H)):



C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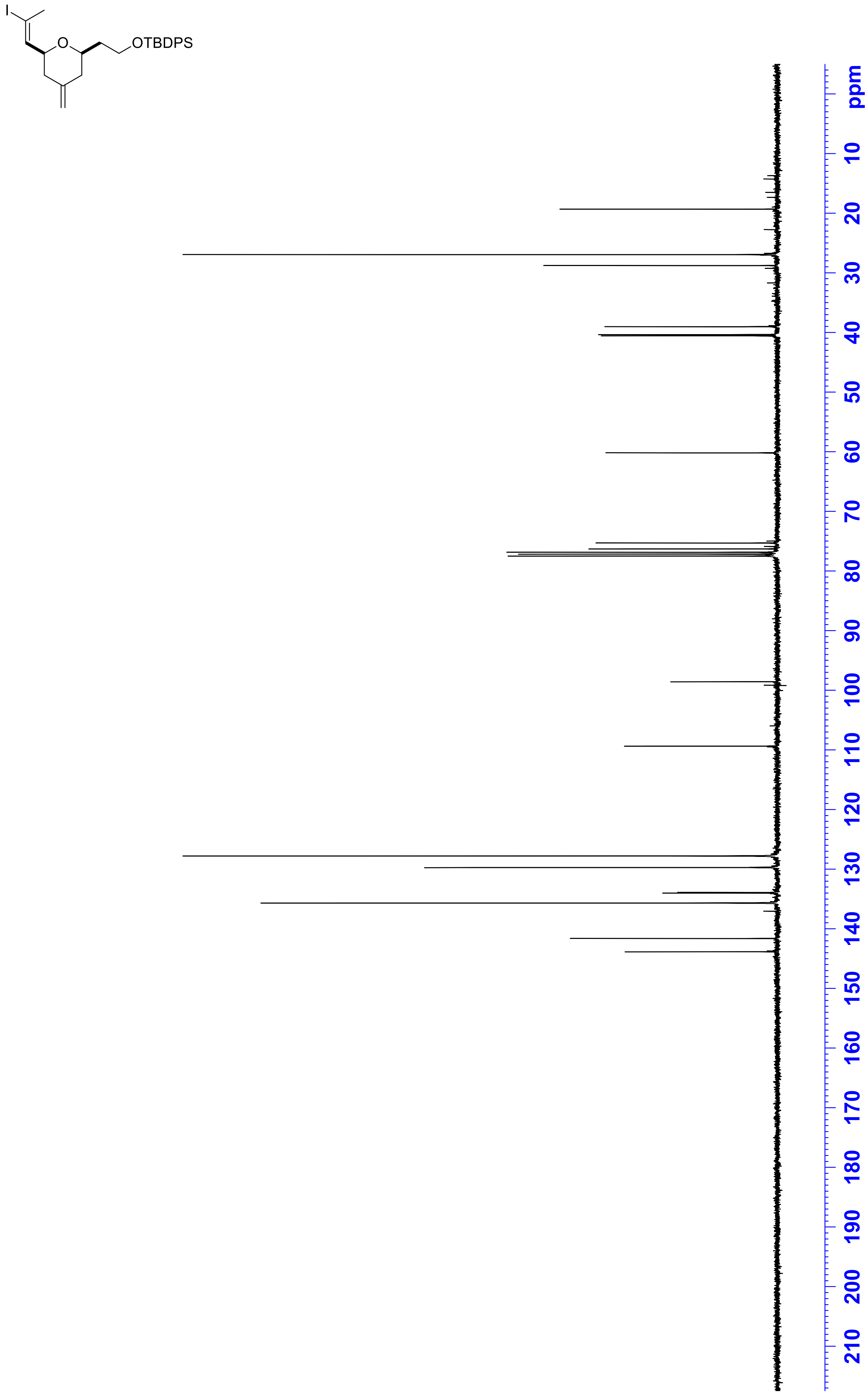
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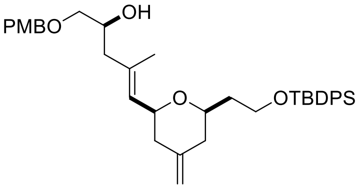
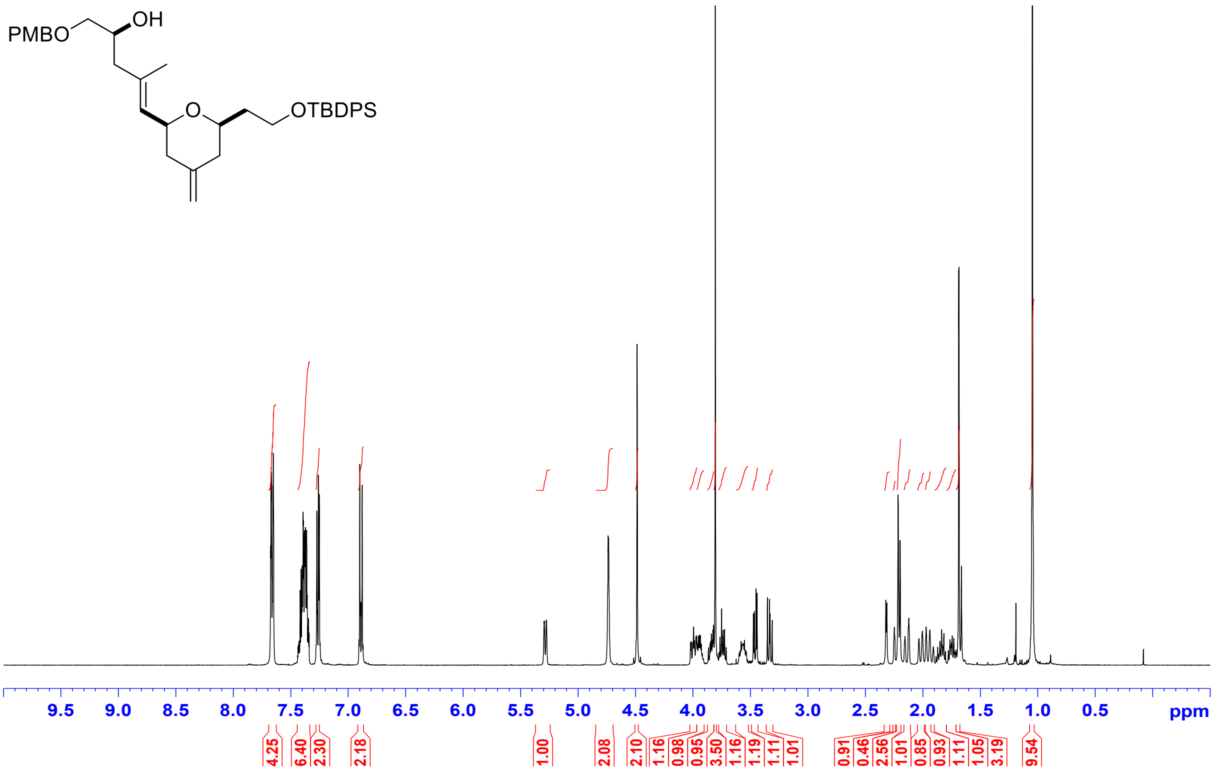
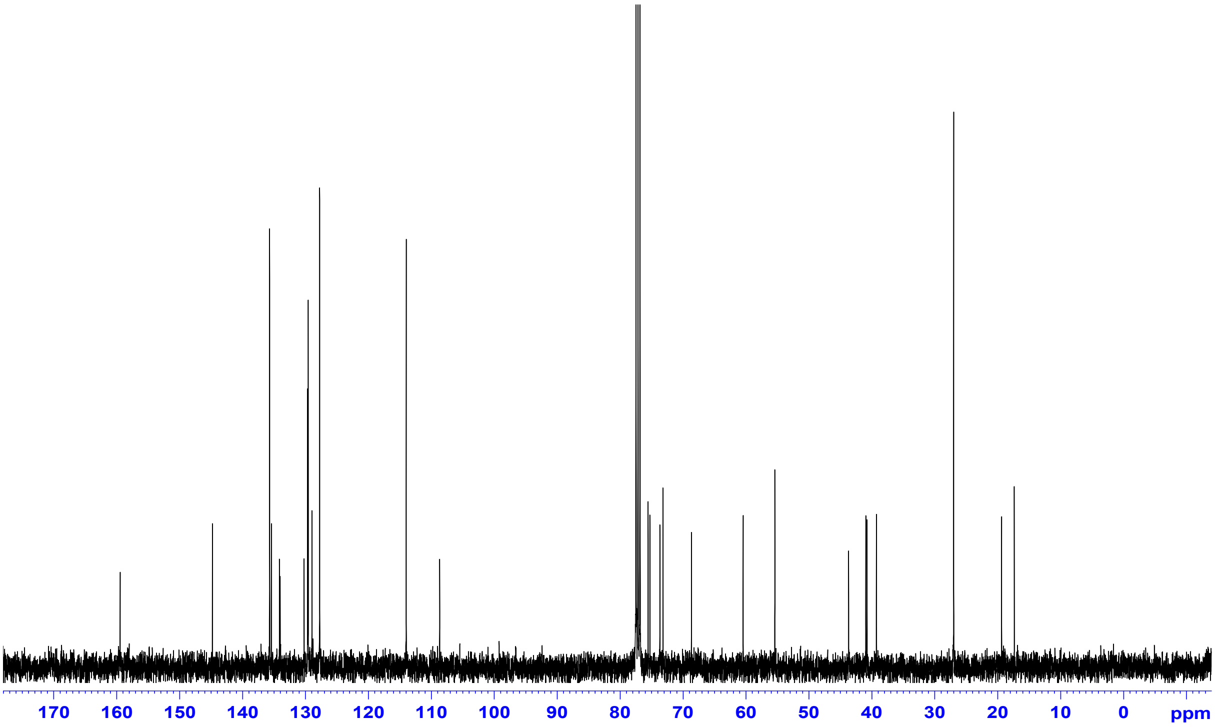


(*S*,*E*)-5-((2*S*,6*R*)-6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-2H-pyran-2-yl)-1-(4-methoxybenzyloxy)-4-methylpent-4-en-2-ol (125). Vinyl iodide **124** (385 mg, 0.70 mmol, 1.00 equiv, azeotropically dried once with 2 mL of acetonitrile or toluene right before use) was dissolved in dry toluene (7 mL) and the solution was cooled to –78 °C. *t*-BuLi (1.6M in pentane, 0.88 mL, 1.41 mmol, 2.00 equiv) was then added and the near colorless solution was stirred for 30 min; it was then cooled to around –85 to –90 °C with liquid nitrogen and a solution of **17** (342 mg, 1.76 mmol, 2.50 equiv, azeotropically dried once with 2 mL of acetonitrile or toluene right before use) in dry toluene (2 mL) was added followed by BF_3•OEt_2 (0.22 mL, 1.76 mmol, 2.50 equiv; addition ca. 1 min after the addition of **17**) giving a pale yellow solution. Stirring was continued at –78 °C for 1 h; then the cooling bath was removed and saturated aqueous $NaHCO_3$ (10 mL) and 10 mL of EtOAc were added. After the mixture had reached room temperature, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure, and the residue purified by flash chromatography (EtOAc/Hex 1:5→1:4) to give **125** (264.2 mg, 0.43 mmol, 61%) as a colorless oil.

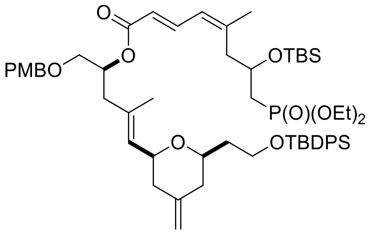
Note: Chromatographic separation was difficult and two purification runs were needed in order to remove the iodohydrine **35** derived from competing epoxide opening by iodide.

TLC: R_f = 0.17 (EtOAc/Hex 1:5, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ =7.68-7.65 (m, 4 H), 7.44-7.34 (m, 6 H), 7.28-7.24 (m, 2 H), 6.90-6.87 (m, 2 H), 5.29 (dq, *J* = 7.7, 1.2, 1 H), 4.75-4.73 (m, 2 H), 4.49 (s, 2 H), 3.99 (ddd, *J* =10.9, 7.7, 2.7, 1 H), 3.98-3.91 (m, 1 H), 3.84 (ddd, *J* = 10.1, 8.0, 5.5, 1 H), 3.80 (s, 3 H), 3.74 (dt, *J* = 10.1, 5.7, 1 H), 3.60-3.54 (m, 1 H), 3.46 (dd, *J* = 9.5, 3.5, 1 H), 3.33 (dd, *J* = 9.5, 7.1, 1 H), 2.31 (d, *J* = 3.5, 1 H), 2.25-2.22 (m, 1 H), 2.20 (d, *J* = 6.8, 2 H), 2.16-2.12 (m, 1 H), 2.04-2.00 (m, 1 H), 1.97-1.90 (m, 1 H), 1.89-1.80 (m, 1 H), 1.77-1.71 (m, 1 H), 1.69 (d, *J* = 1.2, 3 H), 1.05 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.4, 144.7, 135.7, 135.7, 135.4, 134.1, 134.0, 130.2, 129.7, 129.5, 129.0, 127.7, 127.7, 114.0, 108.7, 75.5, 75.3, 73.7, 73.2, 68.6, 60.4, 55.4, 43.7, 41.0, 40.7, 39.2, 27.0, 19.4, 17.3. **IR** (thin film): $\tilde{\nu}$ = 3070, 2932, 2857, 1612, 1513, 1471, 1427, 1247, 1106, 1087, 1058, 1036, 998, 821, 702 cm^{-1}. **HRMS** (ESI): calcd for $C_{38}H_{50}NaO_5Si$ [(M+Na)$^+$]: 637.3320; found: 637.3322. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$= +5.97° (c = 0.88, CHCl$_3$).





5.3.3. Completion of (–)-Dactylolide and (–)-Zampanolide

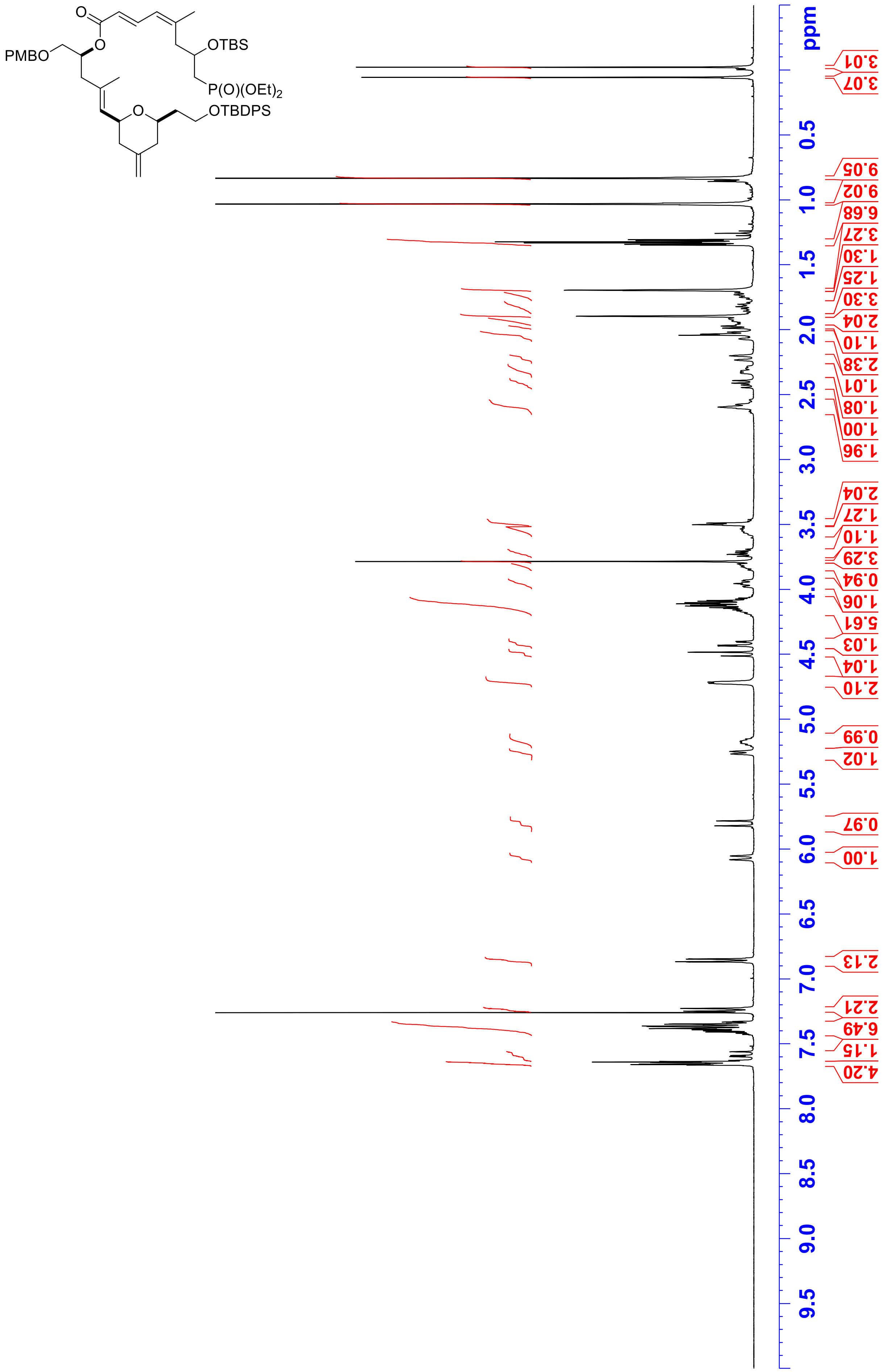


(2*E*,4*Z*)-((*S*,*E*)-5-((2*S*,6*R*)-6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-4-methylene tetrahydro-2H-pyran-2-yl)-1-(4-methoxybenzyloxy)-4-methylpent-4-en-2-yl)7-(*tert*-butyldimethylsilyloxy)-8-(diethoxyphosphoryl)-5-methylocta-2,4-dienoate (126). To a solution of **98** (218 mg, 0.52 mmol, 1.20 equiv, co-evaporated once with 2 mL of acetonitrile immediately before use) in toluene (3 mL) was added NEt_3 (0.16 mL, 1.12 mmol, 2.60 equiv) followed by 2,4,6-trichlorobenzoyl chloride (0.1 mL, 0.65 mmol, 1.5 equiv) giving a pale yellow mixture. After 1.5 h at room temperature, a solution of **125** (266 mg, 0.43 mmol, 1.00 equiv, co-evaporated once with 2 mL of acetonitrile) and DMAP (53 mg, 0.43 mmol, 1.00 equiv, mixture sonicated to produce a clear solution) in toluene (1 mL; plus additional 1.5 mL form rinsing) was added, immediately leading to a yellow suspension. After stirring at room temperature for 18 h saturated aqueous $NaHCO_3$ (5 mL), H_2O (5 mL), and EtOAc (5 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure, and the residue was purified by flash chromatography (EtOAc/Hex 1:3→1:2→1:1) to give **126** (375.9 mg, 0.37 mmol, 85%) as a pale yellow, viscous oil.

Note: Conversion is complete or near to completeness after 1–2 h, judged by TLC analysis.

TLC: R_f = 0.54 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 4 H), 7.59 (dd, *J* = 15.3, 11.9, 1 H), 7.43-7.32 (m, 6 H), 7.25-7.22 (m, 2 H), 6.87-6.84 (m, 2 H), 6.07 (d, *J* = 11.8, 1 H), 5.80 (d, *J* = 15.2, 1 H), 5.26 (d, *J* = 7.8, 1 H), 5.21-5.14 (m, 1 H), 4.73-4.71 (m, 2 H), 4.50 (d, *J* = 11.8, 1 H), 4.42 (dd, *J* = 11.8, 2.6, 1 H), 4.19-4.07 (m, 5 H), 3.96 (ddd, *J* = 10.9, 7.8, 2.6, 1 H), 3.85-3.80 (m, 1 H), 3.78 (s, br, 3 H), 3.72 (dt, 10.2, 5.5, 1 H), 3.60-3.51 (m, 1 H), 3.51-3.46 (m, 2 H), 2.64-2.54 (m, 2 H), 2.42

(dd, *J* = 13.7, 7.8, 1 H), 2.31 (ddd, *J* = 13.7, 5.7, 2.2, 1 H), 2.22 (d, *J* = 13.1, 1 H), 2.05 (d, *J* = 13.1, 1 H), 2.03-2.02 (m, 1 H), 1.99-1.97 (m, 1 H), 1.97-1.91 (m, 2 H), 1.89 (s, 3 H), 1.87-1.79 (m, 1 H), 1.76-1.71 (m, 1 H), 1.70 (s, 3 H), 1.32 (dt, *J* = 7.1, 3.0, 6 H), 1.03 (s, 9 H), 0.83 (s, 9 H), 0.06 (s, 3 H), -0.02 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$; due to the diastereomeric nature of the product, the number of signals in the ^{13}C-spectrum exceeds the number of carbon atoms): δ = 166.8, 159.1, 146.3, 144.7, 141.4 (2), 135.6, 135.6, 134.6 (2), 134.1, 133.9, 130.3, 129.6, 129.4 (2C), 129.3 (2C), 127.7 (2C), 126.8, 119.7, 113.9, 108.6, 75.5, 75.2, 72.9 (2C), 71.4, 71.3, 70.1 (2C), 66.9, 61.6 (d, *J* = 6.5) (2C), 60.4 (2C), 55.3, 41.7, 40.9, 40.8, 40.7, 39.2, 35.2 (d, *J* = 135), 26.9, 25.9, 25.1, 21.1, 19.3, 17.9, 17.3 (2C), 16.5 (d, *J* = 6.3), -4.6, -4.7. **IR** (thin film): $\tilde{\nu}$ = 2952, 2930, 2893, 2857, 1710, 1636, 1612, 1514, 1248, 1146, 1111, 1089, 1049, 1024, 823, 703 cm^{-1}. **HRMS** (ESI): calcd for $C_{57}H_{85}NaO_{10}PSi_2$ [(M+Na)$^+$]: 1039.5311; found: 1039.5309. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +9.46° (c = 1.03, $CHCl_3$).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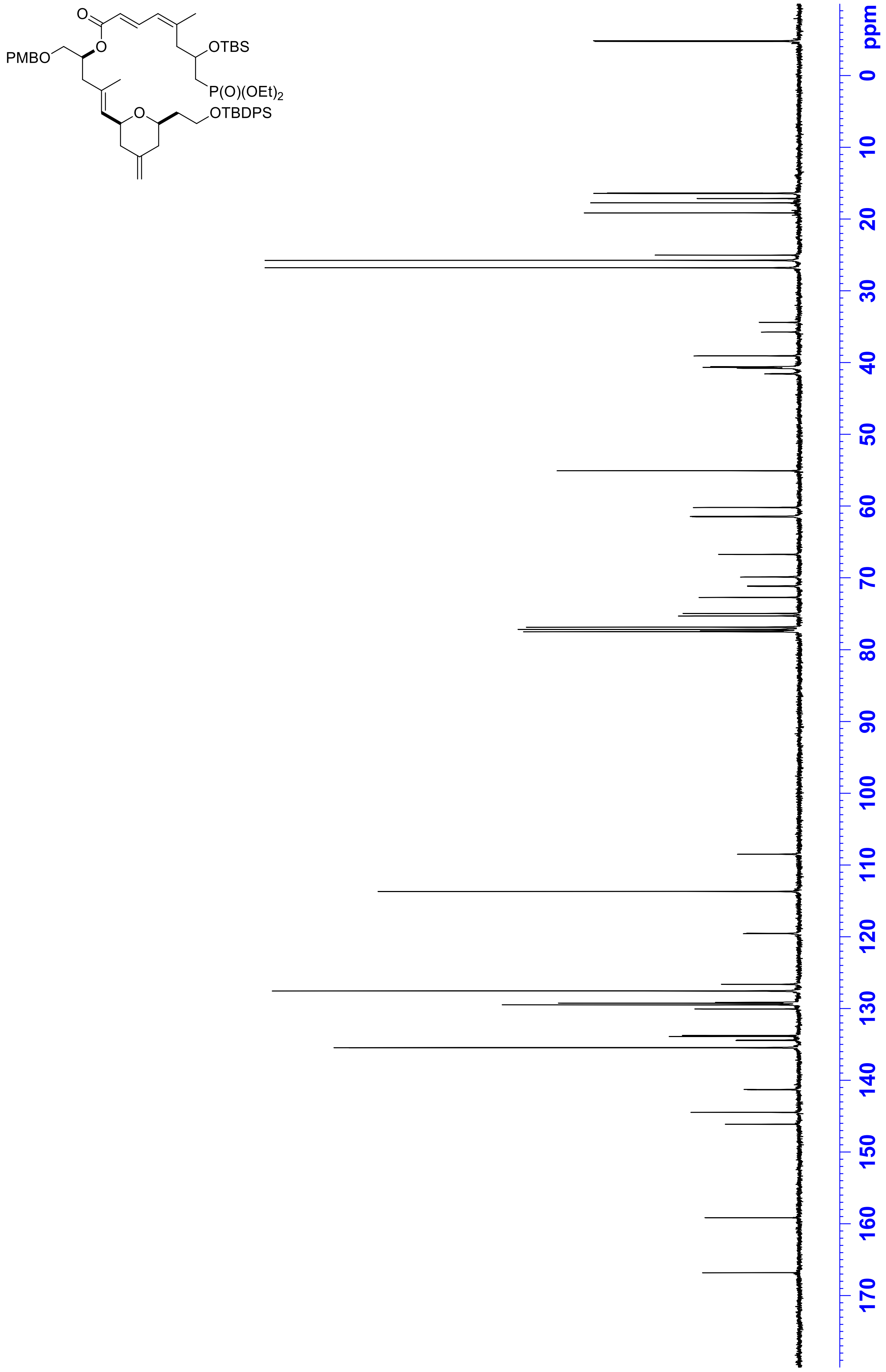
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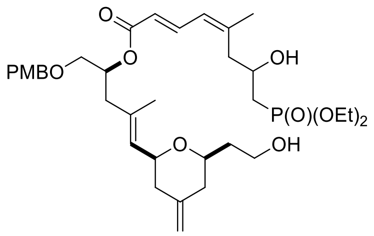
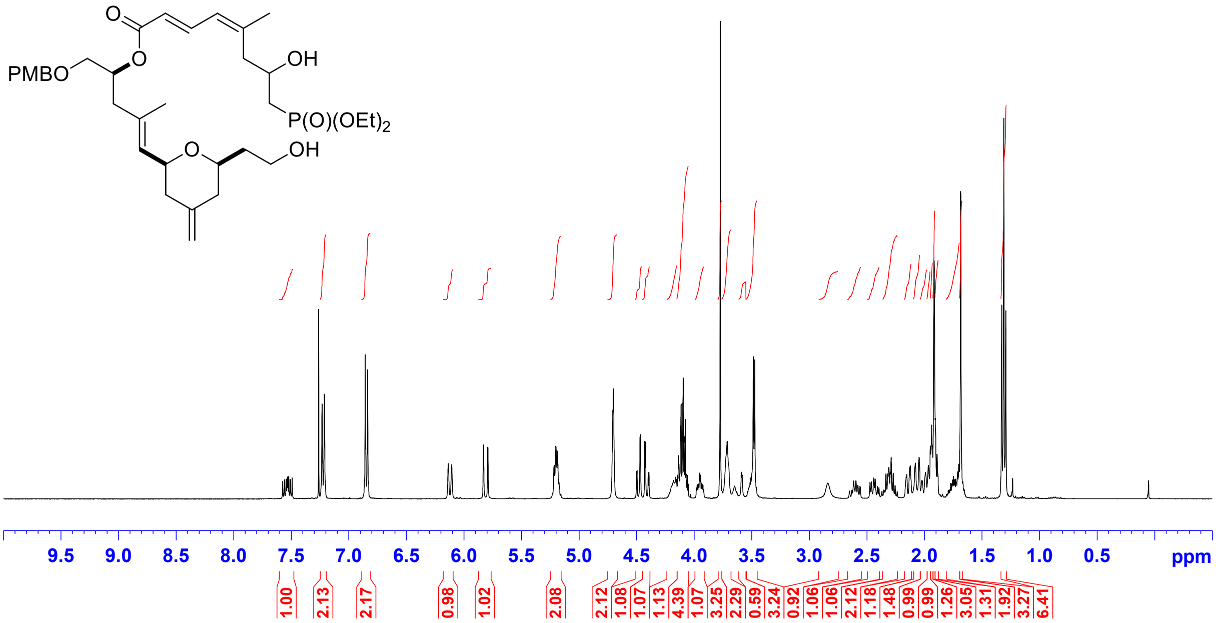
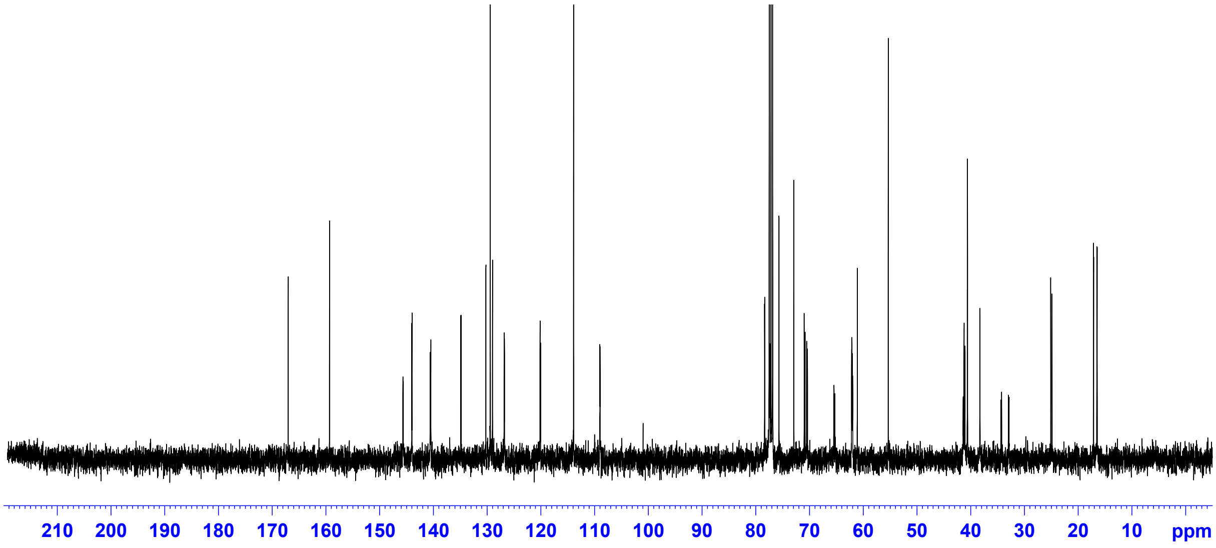


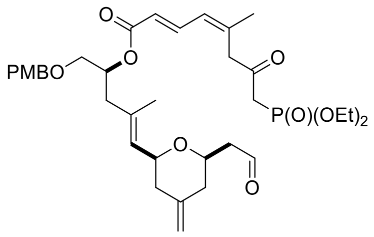
***(2E,4Z)-((S,E)*-5-((2*S*,6*R*)-6-(2-Hydroxyethyl)-4-methylenetetrahydro-2H-pyran-2-yl)-1-(4-methoxy benzyloxy)-4-methylpent-4-en-2-yl)-8-(diethoxyphosphoryl)-7-hydroxy-5-methyl-octa-2,4-dienoate (E)**. To a stirred solution of **126** (27.3 mg, 0.027 mmol, 1.00 equiv) in THF (1 mL) in a plastic tube was added 70% HF•py (0.27 mL) at 0 °C (ice/H_2O). The cooling bath was removed after 5 min and stirring was continued at room temperature for 14 h. The solution was then carefully added to a vigorously stirred mixture of saturated aqueous $NaHCO_3$ (20 mL) and EtOAc (10 mL) until two clear phases had formed (ca. 15 min). The phases were separated, the aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) followed by drying over $MgSO_4$. Concentration under reduced pressure and purification using flash chromatography (EtOAc→EtOAc/acetone 1:1) afforded **E** (15.1 mg, 0.023 mmol, 85%) as a pale yellow, viscous oil.

Note: The use of less concentrated aqueous $NaHCO_3$ is not recommended for workup, since not all HF may be neutralized, which would in turn lead to decomposition of the product during concentration under reduced pressure. In any case the pH of the aqueous phase should be determined after workup and should not be acidic!

TLC: R_f = 0.71 (EtOAc/acetone 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.53 (ddd, *J* = 15.0, 11.6, 6.1, 1 H), 7.23-7.20 (m, 2 H), 6.86-6.83 (m, 2 H), 6.12 (d, *J* = 11.6, 1 H), 5.81 (d, *J* = 15.1, 1 H), 5.23-5.16 (m, 2 H), 4.71-4.69 (m, 2 H), 4.48 (dd, *J* = 11.8, 1.5, 1 H), 4.41 (dd, *J* = 11.8, 2.7, 1 H), 4.42-4.11 (m, 1 H), 4.17-4.05 (m, 4 H), 3.98-3.91 (m, 1 H), 3.77 (s, 3 H), 3.74-3.69 (m, 2 H), 3.60-3.56 (m, 1 H), 3.54-3.46 (m, 3 H), 2.89-2.76 (br s, 1 H), 2.60 (ddd, *J* = 15.2, 14.5, 8.1, 1 H), 2.47-2.40 (m, 1 H), 2.37-2.24 (m, 2 H), 2.17-2.12 (m 1 H), 2.09-2.04 (m, 1 H), 2.03-1.98 (m, 1 H), 1.98-1.95 (m, 1 H), 1.95-1.93 (m, 1 H), 1.92 (s, 3 H), 1.91-1.88 (m, 1 H), 1.81-1.70 (m, 2 H), 1.69, 1.68 (d, *J* = 1.1, 3 H), 1.31 (t, *J* = 7.1, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$; due to the diastereomeric nature of the product, the number of signals in the ^{13}C-spectrum exceeds the number of carbon atoms): δ = 167.0, 159.3, 145.7, 145.6, 144.0 (2C), 140.6, 140.5, 134.9, 134.8, 130.2, 129.4, 129.0, 126.8 (2C), 120.1, 120.0, 113.9, 109.0 (2C), 78.3 (2C), 75.7, 72.9 (2C), 71.0, 70.8, 70.5, 70.4, 65.4 (d, *J* = 5.1), 65.3 (d, *J* = 5.1), 62.1 (d, *J* = 6.5), 62.0 (d, *J* = 6.5), 61.1, 55.3, 41.3 (d, *J* = 6.2), 41.2 (d, *J* = 6.2), 41.2, 41.0, 40.6, 40.6, 38.3, 38.2, 33.6 (d, *J* = 138), 33.5 (d, *J* = 138), 25.1, 24.8, 17.2, 17.1, 16.5 (d, *J* = 6.0) (2C). **IR** (thin film): $\tilde{\nu}$ = 3388, 2935, 2909, 2864, 1707, 1633, 1612, 1513, 1442, 1367, 1247, 1222, 1148, 1023, 975, 890, 802 cm^{-1}. **HRMS** (ESI): calcd for $C_{35}H_{54}O_{10}P$ [(M+H)$^+$]: 665.3449; found: 665.3442. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –8.11° (c = 0.99, CHCl$_3$).

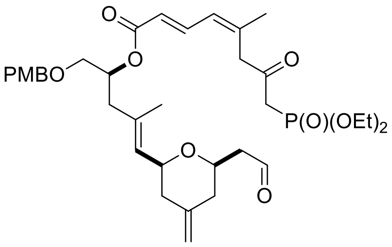






(2*E*,4*Z*)-((*S*,*E*)-1-(4-Methoxybenzyloxy)-4-methyl-5-((2*S*,6*R*)-4-methylene-6-(2-oxoethyl)tetrahydro-2H-pyran-2-yl)pent-4-en-2-yl)-8-(diethoxyphosphoryl)-5-methyl-7-oxoocta-2,4-dienoate (127). To a solution of **E** (15 mg, 0.023 mmol, 1.00 equiv) in CH_2Cl_2 (1 mL) was added DMP (67 mg, 0.16 mmol, 7.00 equiv; added in three equal portions in 30 min intervals) at room temperature. After 3 h stirring at room temperature, a mixture of CH_2Cl_2 (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and saturated aqueous $Na_2S_2O_3$ (5 mL) and stirring was continued for 10 min, when two almost clear phases had formed. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were dried over $MgSO_4$. Concentration of the solution under reduced pressure and purification of the residue by flash chromatography (EtOAc, 1% AcOH to deactivate the stationary phase) gave **127** (11.1 mg, 0.017 mmol, 74%) as a colorless oil.

TLC: R_f = 0.53 (EtOAc, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.75 (t, *J* = 2.2, 1 H), 7.38 (dd, *J* = 15.1, 11.7, 1 H), 7.24-7.20 (m, 2 H), 6.87-6.83 (m, 2 H), 6.19 (d, *J* = 11.7, 1 H), 5.85 (d, *J* = 15.1, 1 H), 5.21-5.17 (m, 2 H), 4.77-4.74 (m, 2 H), 4.48 (d, *J* = 11.8, 1 H), 4.40 (d, *J* = 11.8, 1 H), 4.19-4.12 (m, 4 H), 3.98 (ddd, *J* = 11.6, 7.7, 2.7, 1 H), 3.84-3.79 (m, 1 H), 3.78 (s, 3 H), 3.61 (s, 2 H), 3.48 (d, *J* = 4.7, 2 H), 3.12 (s, 1 H), 3.07 (s, 1 H), 2.62 (ddd, *J* = 16.4, 7.6, 2.5, 1 H), 2.48 (ddd, *J* = 16.4, 4.9, 1.9, 1 H), 2.36 (dd, *J* = 13.6, 6.8, 1 H), 2.28 (dd, *J* = 13.6, 6.8, 1 H), 2.25-2.21 (m, 1 H), 2.10-2.05 (m, 1 H), 2.00-1.97 (m, 1 H), 1.94-1.91 (m, 1 H), 1.88 (s, 3 H), 1.68 (d, *J* = 1.2, 3 H), 1.33 (t, *J* = 7.1, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 201.1, 198.2 (d, *J* = 6.5), 166.8, 159.4, 143.3, 141.0, 139.8, 135.1, 130.2, 129.4, 128.7, 127.5, 121.2, 113.9, 109.6, 75.7, 73.4, 72.9, 71.2, 70.3, 62.9 (d, *J* = 6.5), 55.4, 49.7, 47.7, 42.3 (d, *J* = 128), 41.0, 40.4, 40.3, 25.0, 17.2, 16.4 (d, *J* = 6.2). **IR** (thin film): $\tilde{\nu}$ = 2980, 2936, 2906, 2865, 1713, 1638, 1612, 1513, 1364, 1247, 1150, 1019, 971, 893 cm^{-1}. **HRMS** (ESI): calcd for $C_{35}H_{50}O_{10}P$ [$(M+H)^+$]: 661.3136; found: 661.3154. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +6.22° (c = 1.53, $CHCl_3$).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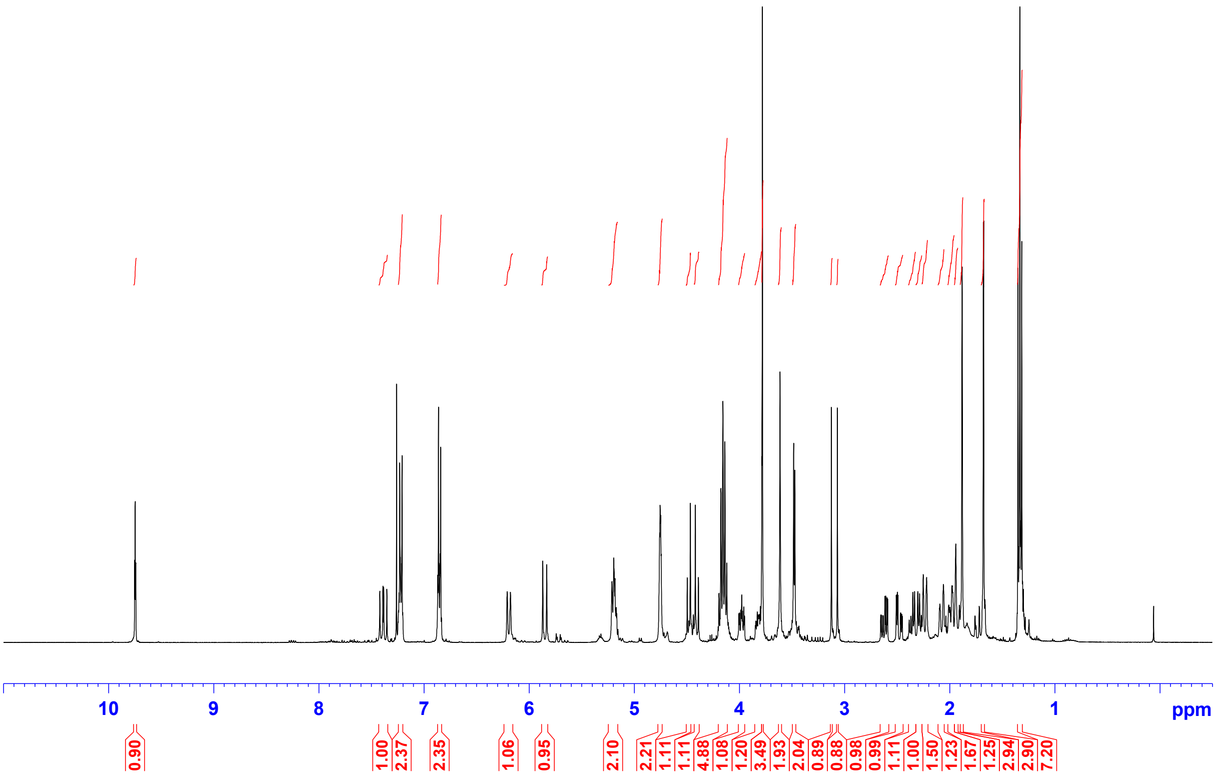
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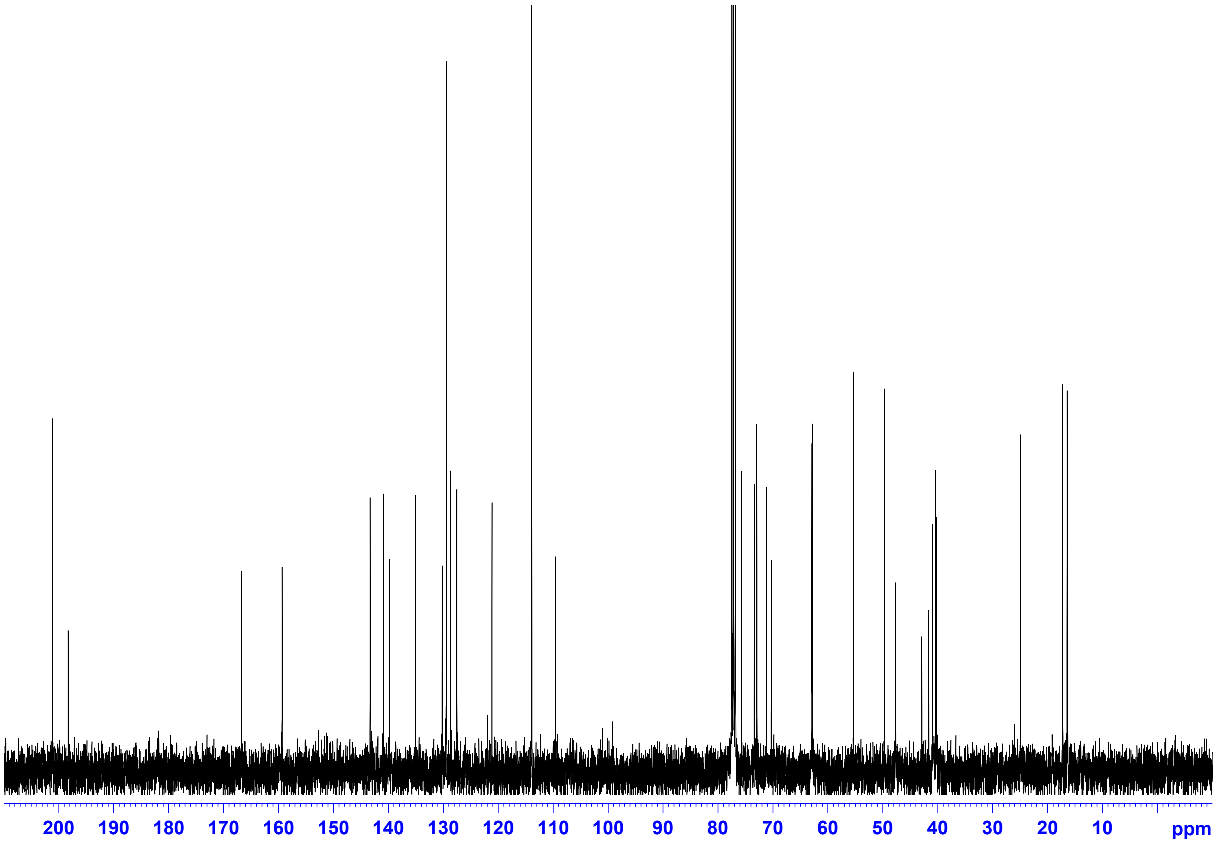
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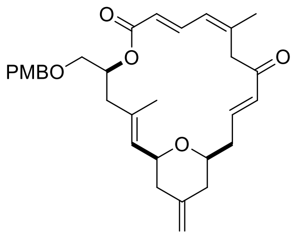
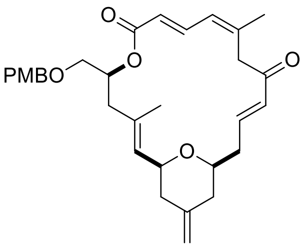


(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*S*)-5-((4-Methoxybenzyloxy)methyl)-3,11-dimethyl-19-methylene-6,21-dioxa bicyclo [15.3.1]henicosa-2,8,10,14-tetraene-7,13-dione (128). To a stirred solution of **127** (7.2 mg, 0.011 mmol, 1.00 equiv, co-evaporated before use with 1 mL of toluene) in THF (2 mL) at –78 °C was added a solution of NaHMDS (1 M in THF, 0.013 mL, 0.013 mmol, 1.20 equiv, diluted with 1 mL of THF). The solution turned orange immediately. Stirring was continued while the cooling bath was slowly allowed to warm to room temperature. After 3.5 d, H_2O (5 mL) and EtOAc (5 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 5 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:4) afforded **128** (2.54 mg, 0.005 mmol, 46%) as a colorless oil.

Note: Varying yields between 20% and 80% were observed independent of the scale of the reaction.

Alternative procedure using $Ba(OH)_2 \cdot 0.8H_2O$:[41b, 236] To a stirred solution of **127** (62.2 mg, 0.094 mmol, 1.00 equiv, co-evaporated with 3 mL of toluene immediately before use) in THF (31 mL) was added H_2O (0.8 mL) followed by freshly activated $Ba(OH)_2 \cdot 0.8H_2O$ at 0 °C. The cooling bath was removed after 30 min and stirring was continued at room temperature for additional 30 min more; Et_2O (30 mL) were then added and the solution was washed first with saturated aqueous $NaHCO_3$ (2 x 10 mL) and then with brine (1 x 10 mL). The clear organic phase was dried over $MgSO_4$ and concentrated. The resulting yellow oil was purified by flash chromatography (EtOAc/Hex 1:3) to afford **128** (38.6 mg, 0.076 mmol, 81%) as a colorless oil.

TLC: R_f = 0.40 (EtOAc/Hex 1:3, UV, $KMnO_4$, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.62 (dd, *J* = 15.1, 11.6, 1 H), 7.27-7.24 (m, 2 H), 6.90-6.86 (m, 2 H), 6.83 (ddd, *J* = 16.2, 9.8, 4.4, 1 H), 6.10 (d, *J* = 11.6, 1 H), 5.94 (d, *J* = 15.1, 1 H), 5.92 (d, *J* = 16.4, 1 H), 5.40-5.34 (m, 1 H), 5.17 (dd, *J* = 8.1, 0.9, 1 H), 4.74-4.70 (m, 2 H), 4.52 (d, *J* = 11.8, 1 H), 4.48 (d, *J* = 11.8, 1 H), 4.17 (d, *J* = 13.6, 1 H), 3.96 (ddd, *J* = 11.3, 8.1, 2.5, 1 H), 3.81 (s, 3 H), 3.58 (dd, *J* = 10.4, 6.0, 1 H), 3.51 (dd, *J* = 10.4, 4.9, 1 H), 3.30-3.24 (m, 1 H), 3.00 (d, *J* = 13.5, 1 H), 2.37 (dddd, *J* = 15.0, 10.1, 4.4, 2.0, 1 H), 2.26-2.20 (m, 1 H), 2.20 (d, *J* = 6.7, 2 H), 2.16-2.11 (m, 1 H), 2.11-2.05 (m, 1 H), 1.97-1.89 (m, 2 H), 1.79 (s, 3 H), 1.70 (d, *J* = 1.1, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ =198.3, 166.9, 159.4, 146.5, 143.9, 142.9, 139.4, 132.6, 131.6, 130.2, 129.5, 129.5, 125.6, 121.3, 114.0, 109.1, 76.7, 76.1, 73.1, 71.6, 69.6, 55.4, 45.2, 42.8, 41.1, 40.9, 40.4, 23.6, 16.8. **IR** (thin film): $\tilde{\nu}$ = 3016, 2923, 2852, 1713, 1668, 1635, 1614, 1513, 1463, 1360, 1281, 1249, 1215, 1176, 1152, 1086, 1035, 978 cm^{-1}. **HRMS** (ESI): calcd for $C_{31}H_{38}NaO_6$ [(M+Na)$^+$]: 529.2561; found: 529.2571. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –158.79° (c = 0.25, $CHCl_3$).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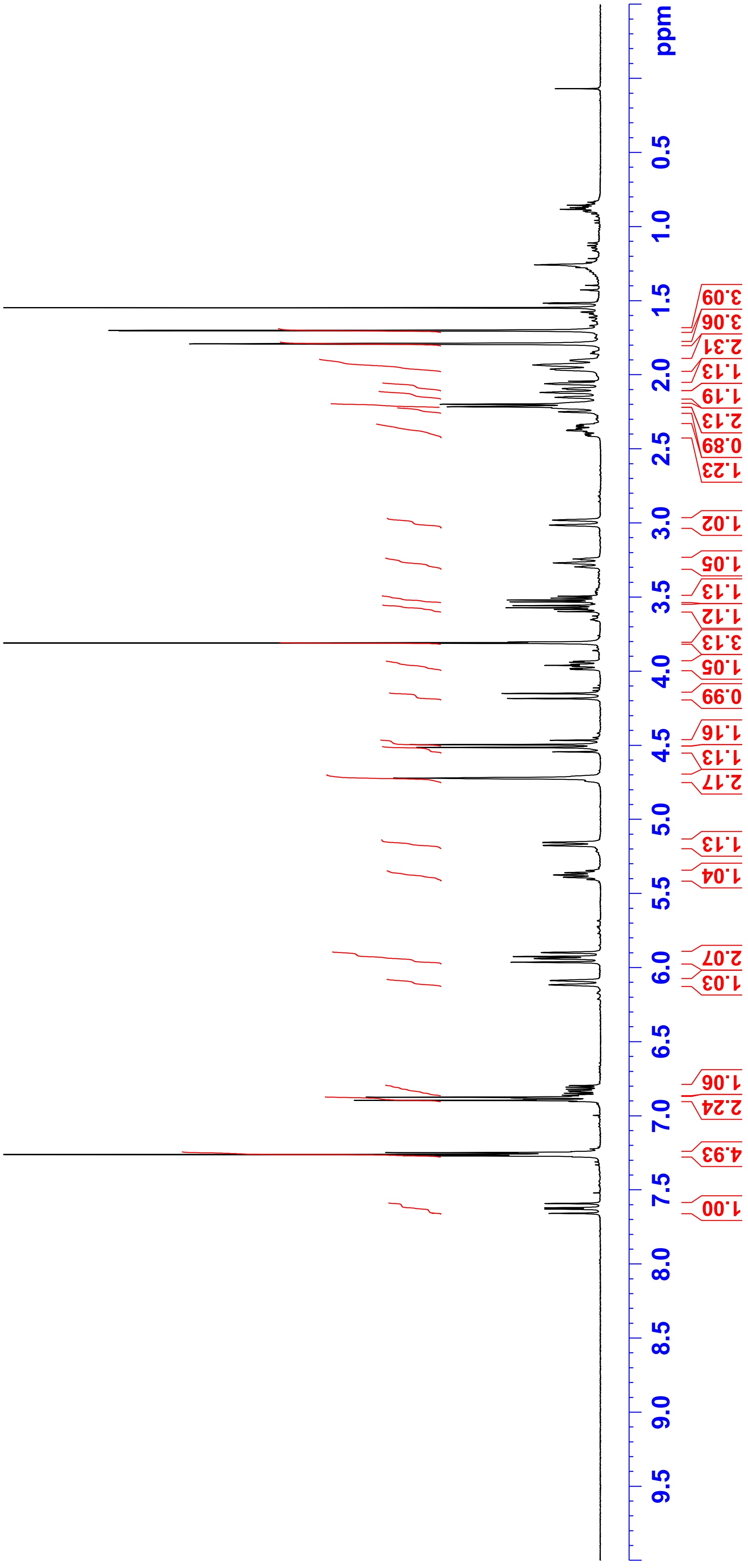
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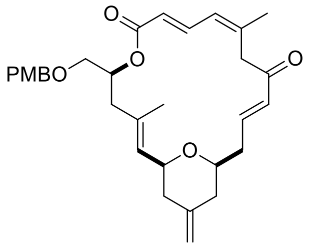
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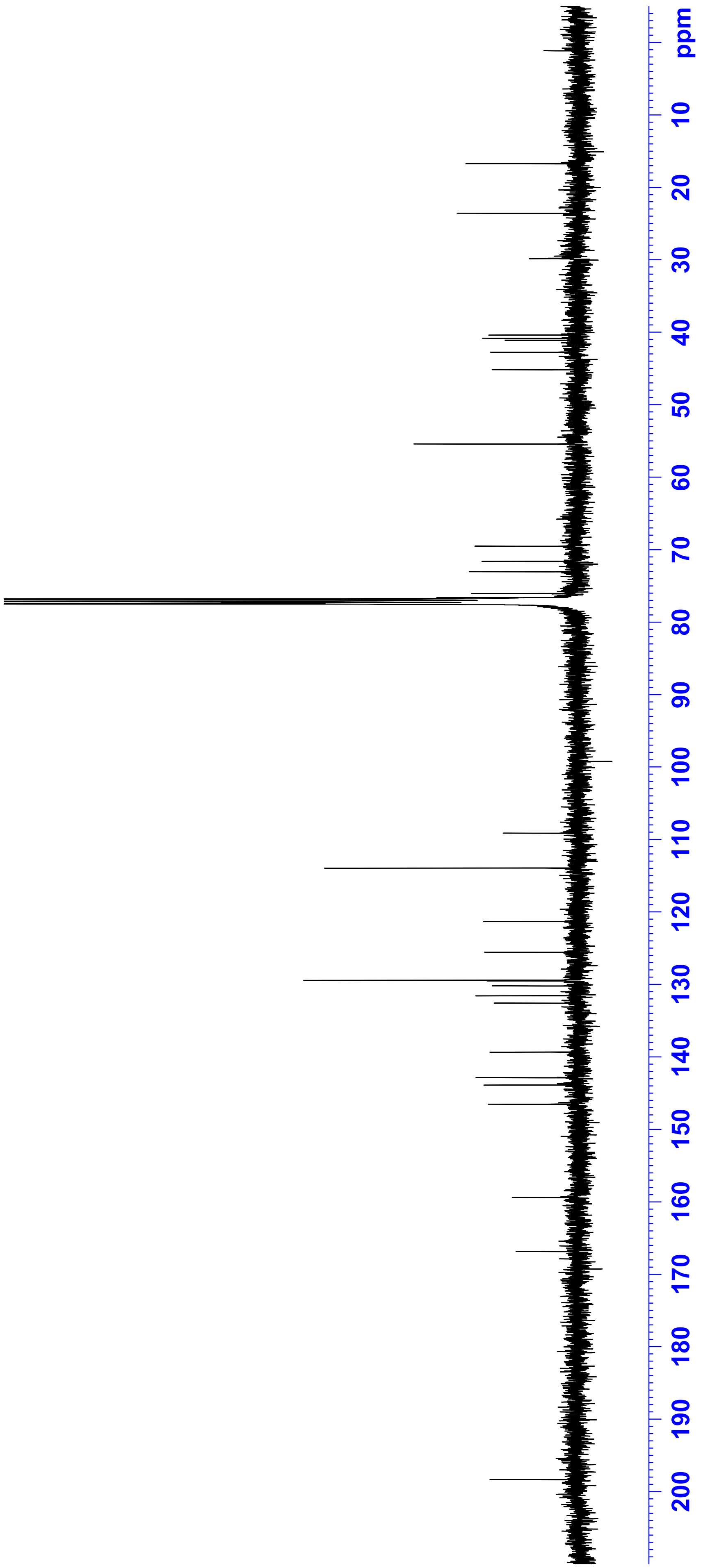
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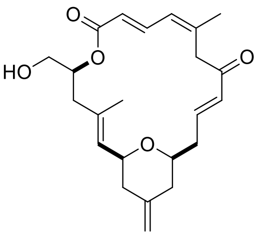
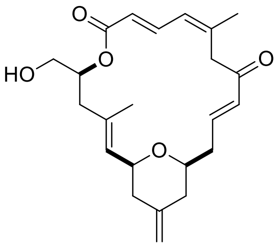


(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*S*)-5-(Hydroxymethyl)-3,11-dimethyl-19-methylene-6,21-dioxabicyclo [15.3.1]henicosa-2,8,10,14-tetraene-7,13-dione (129). To a solution of **128** (4 mg, 0.008 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) was added H_2O (0.1 mL) followed by DDQ (5.4 mg, 0.024 mmol, 3.50 equiv) at room temperature. The mixture was vigorously stirred for 3 h; then saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:3→1:2) delivered **129** (2.49 mg, 0.0064 mmol, 82%) as a colorless solid.

TLC: R_f = 0.30 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 15.1, 11.6, 1 H), 6.84 (ddd, *J* = 16.2, 9.6, 4.6, 1 H), 6.11 (d, *J* =11.7, 1 H), 5.94 (d, *J* = 15.1, 1 H), 5.93 (d, *J* = 16.5, 1 H), 5.28 (dddd. *J* = 10.8, 5.9, 4.1, 2.1, 1 H), 5.19 (d, *J* = 8.0, 1 H), 4.73 (d, *J* = 1.6, 1 H), 4.73 (d, *J* = 1.6, 1 H), 4.14 (d, *J* = 13.7, 1 H), 3.97 (ddd, *J* = 11.2, 8.2, 2.7, 1 H), 3.77- 3.70 (m, 2 H), 3.29 (ddt, *J* = 11.8, 9.5, 2.1, 1 H), 3.04 (d, *J* = 13.7, 1 H), 2.38 (dddd, *J* = 15.1, 10.1, 4.6, 2.0, 1 H), 2.30-2.08 (m, 5 H), 1.98-1.91 (m, 2 H), 1.81 (s, 3 H), 1.73 (d, *J* = 1.2, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 198.1, 167.1, 146.5, 143.9, 143.3, 139.8, 132.6, 131.6, 129.6, 125.6, 121.0, 109.2, 76.7, 76.1, 71.9, 65.4, 45.2, 42.1, 41.1, 40.8, 40.3, 23.7, 16.8. **IR** (thin film): $\tilde{\nu}$ = 3389, 2925, 2853, 1715, 1669, 1634, 1553, 1449, 1436, 1357, 1280, 1259, 1148, 1086, 1049, 1019, 976, 799 cm^{-1}. **HRMS** (ESI): calcd for $C_{23}H_{30}NaO_5$ [$(M+Na)^+$]: 409.1985; found: 409.1983. $[\alpha]_D^{24}$: –136.26° (c = 0.11, $CHCl_3$).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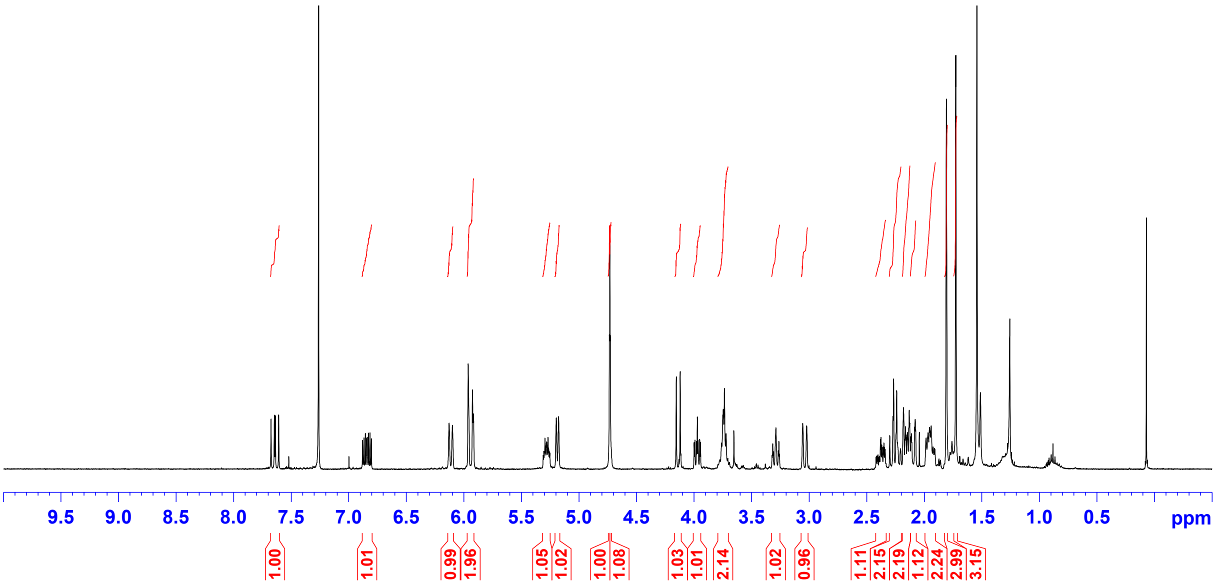
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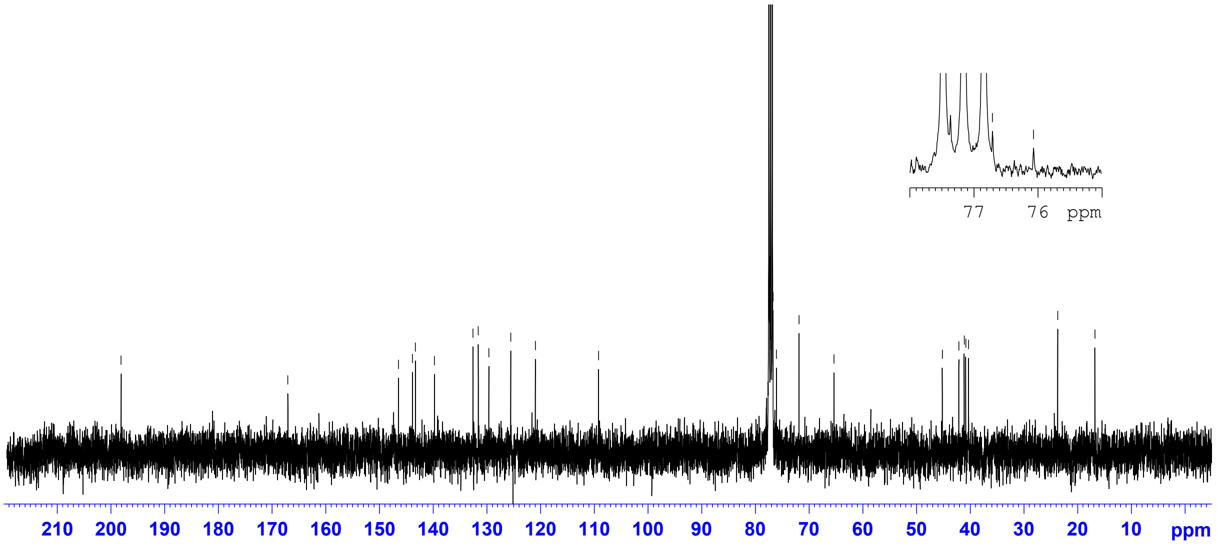
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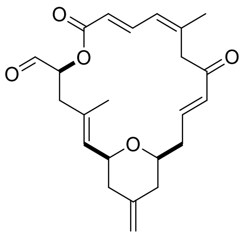
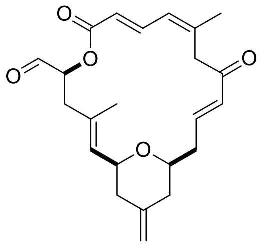


(–)-Dactylolide ((–)-2). To a stirred solution of **129** (2.33 mg, 0.006 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) was added DMP (15 mg, 0.036 mmol, 6.00 equiv; added in 3 equal portions in 20 min intervals) at room temperature and stirring was continued for 60 min then a mixture of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL) was added and stirring was continued for 10 min until two clear phases were formed. The phases were separated then the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure then purified using flash chromatography (EtOAc/Hex 1:3) affording (–)-dactylolide ((–)-**2**) (1.8 mg, 0.0048 mmol, 78%) of a colorless solid.

Note: The compound is stable in DMSO according to NMR.

TLC: R_f = 0.57 (EtOAc/Hex 1:1, UV, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.67 (s, 1 H), 7.63 (dd, *J* = 15.1, 11.6, 1 H), 6.85 (ddd, *J* = 16.2, 8.6, 6.0, 1 H), 6.16 (d, *J* = 11.7, 1 H), 6.03-5.94 (m, 2 H), 5.32 (dd, *J* = 11.3, 2.5, 1 H), 5.24 (d, *J* = 8.0, 1 H), 4.75 (d, *J* = 1.6, 1 H), 4.75 (d, *J* = 1.6, 1 H), 3.97 (ddd, *J* = 11.5, 8.1, 2.7, 1 H), 3.94 (d, *J* = 14.3, 1 H), 3.33 (ddt, *J* = 11.1, 8.7, 2.7, 1 H), 3.24 (d, *J* = 14.5, 1 H), 2.55 (d, *J* = 14.3, 1 H), 2.36-2.28 (m, 3 H), 2.19-2.15 (m, 1 H), 2.14-2.09 (m, 1 H), 1.99-1.93 (m, 2 H), 1.87 (s, 3 H), 1.72 (d, *J* = 0.9, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 199.2, 197.6, 166.4, 146.1, 144.2, 143.6, 140.6, 131.6, 131.1, 130.7, 125.7, 119.9, 109.5, 76.6, 75.9, 75.5, 45.0, 40.9, 40.6, 39.9, 39.8, 24.3, 16.2. **IR** (thin film): $\tilde{\nu}$ = 2936, 2858, 1733, 1716, 1706, 1670, 1635, 1438, 1355, 1278, 1256, 1144, 1086, 1050, 978, 890 cm^{-1}. **HRMS** (ESI): calcd for $C_{23}H_{28}NaO_5$ [$(M+Na)^+$], 407.1829, found: 407.1820. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –258.33° (c = 0.11, MeOH).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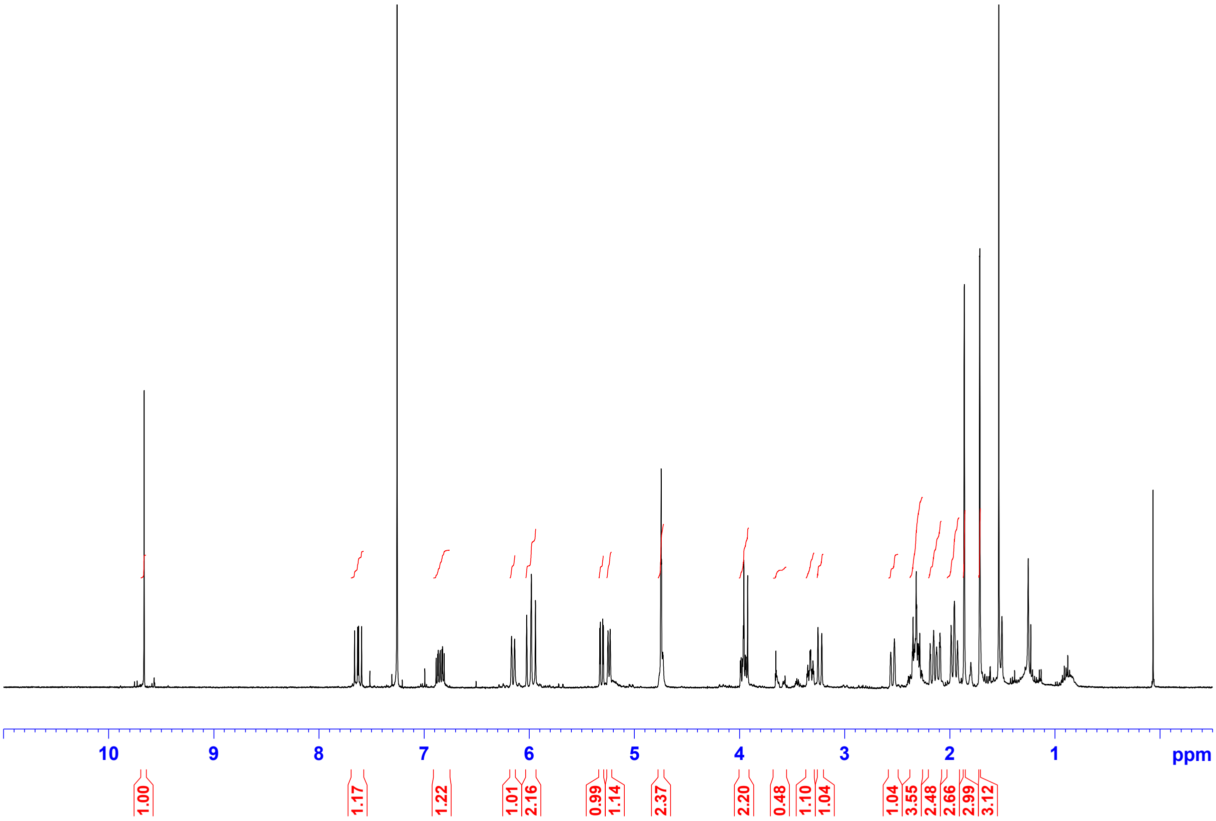
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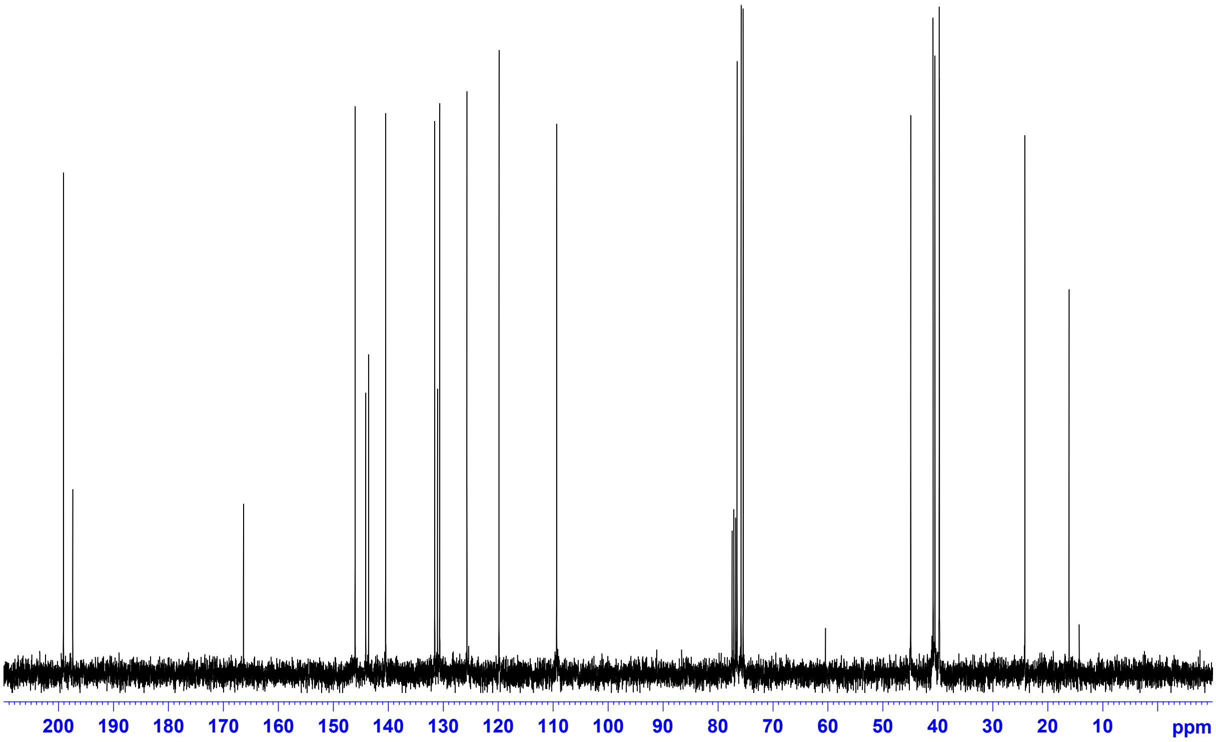
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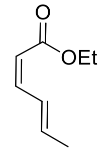
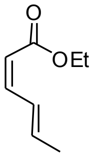


(2Z,4E)-Ethyl hexa-2,4-dienoate (130). To a mixture of carbethoxymethylene-triphenylphosphorane (11.74 g, 33.7 mmol, 1 equiv) in EtOH (100 mL) was added crotonaldehyde (4.13 mL, 50.55 mmol, 1.5 equiv) and stirring was continued at room temperature for 16 h affording a complete solution under slight exothermicity. The crude solution was concentrated to a yellow oil, which was titurated with Hex/EtOAc (50:1) giving a white precipitate. Filtration and washing with Hex/EtOAc (50:1) gave a yellow liquid with some precipitates after concentration under reduced pressure. The procedure was repeated once more leading to a yellow oil. Purification using flash chromatography (EtOAc/Hex 1:50, 25 cm silica, 6 cm column) led to the separation of isomers along with some mixed fractions. The more apolar compound was the desired isomer **130** which was obtained as a pale-yellow liquid (1.09 g, 7.77 mmol, 23%).

TLC: R_f = 0.67 (EtOAc/Hex 1:10, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.44-7.33 (m, 1 H), 6.53 (t, *J* = 11.4, 1 H), 6.11-6.02 (m, 1 H), 5.54 (dq, *J* = 11.4, 0.8, 1 H), 4.17 (q, *J* = 7.2, 2 H), 1.87 (dd, *J* = 7.0, 1.6, 3 H), 1.29 (t, *J* = 7.2, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 166.7, 145.2, 140.3, 128.5, 115.5, 59.9, 18.7, 14.4. **IR** (thin film): $\tilde{\nu}$ = 2982, 2937, 2913, 1712, 1639, 1603, 1418, 1388, 1175, 1126, 1030, 998, 962, 944, 835 cm^{-1}. **HRMS** (ESI): *m/z*: calcd for $C_8H_{12}NaO_2[(M+Na)^+]$: 163.0730; found: 163.0737.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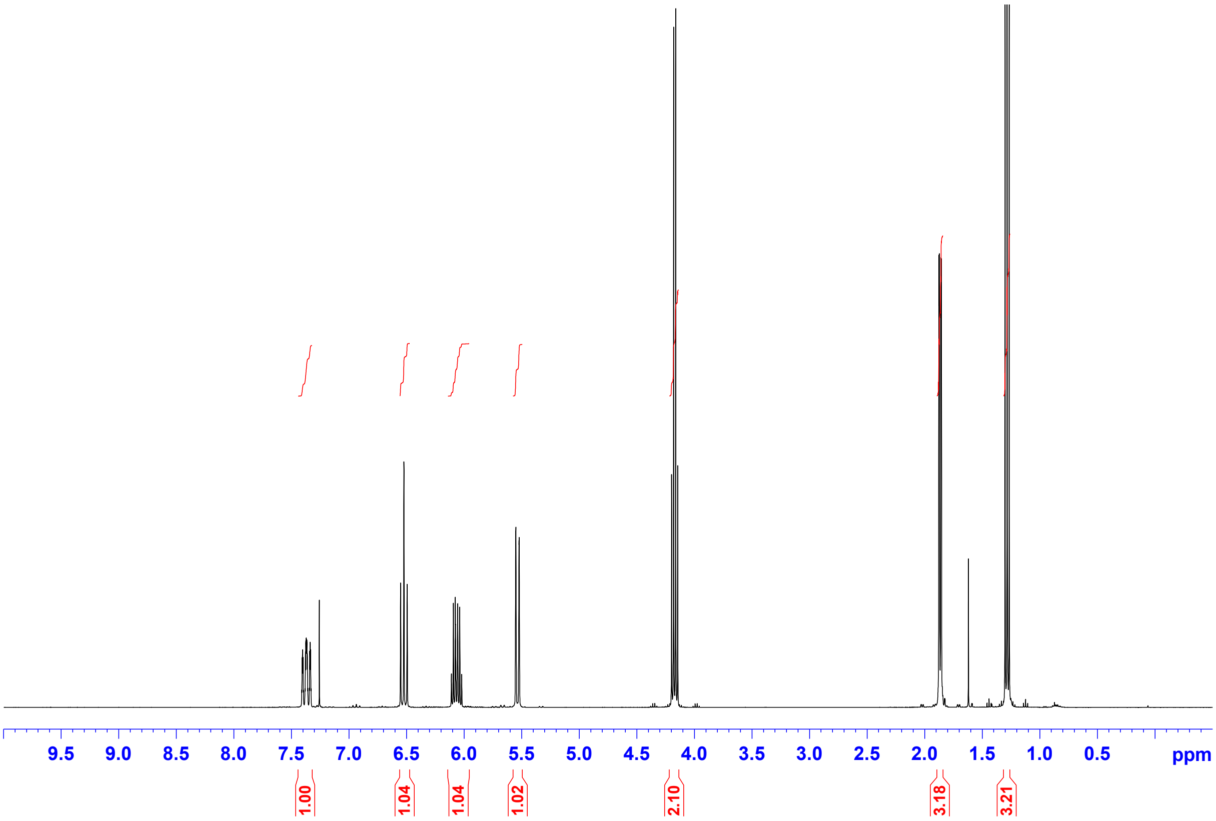
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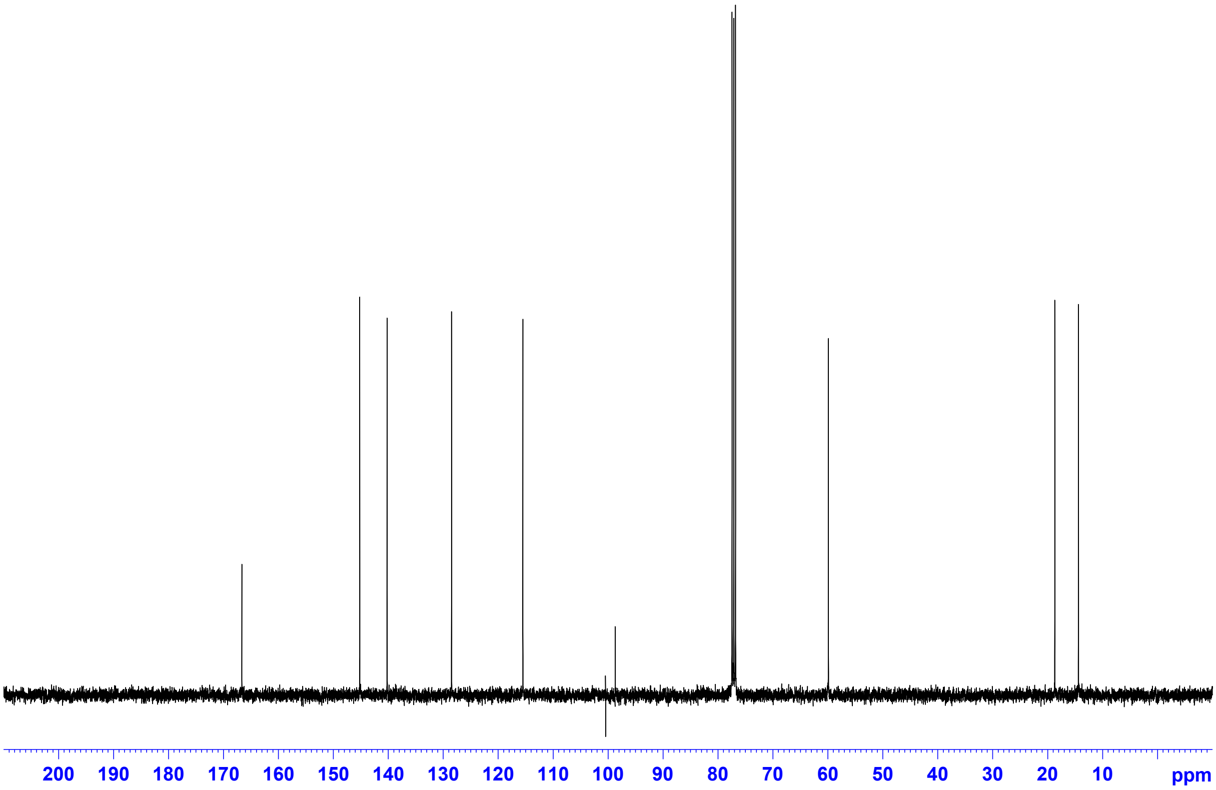
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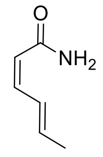
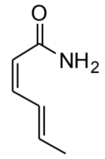


(2*Z*,4*E*)-Hexa-2,4-dienamide (131). To a suspension of NH_4Cl (292 mg, 5.45 mmol, 2.5 equiv) in toluene (5 mL) was added $AlMe_3$ (2M in toluene, 2.7 mL, 5.45 mmol, 2.5 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and after ca. 5 min a solution of **130** (306 mg, 2.18 mmol, 1 equiv) in toluene (2 mL) was added and the clear pale-yellow solution was then heated to 50 °C for a total of 24 h leading to a red mixture. The heating bath was removed and the mixture allowed to cool to room temperature then was poured carefully to a stirred mixture of saturated aqueous Rochelle salt (50 mL) and EtOAc (50 mL) and stirring was continued for 30 min. The phases were separated then the aqueous phase was extracted with EtOAc (2 x 20 mL) then the combined organic phases were dried over $MgSO_4$ and purified using flash chromatography (EtOAc/Hex 3:1) giving a pale-yellow to white solid that was purified again (EtOAc/Hex 2:1) giving **131** (169.8 mg, 1.53 mmol, 70%) as a colorless solid.

TLC: R_f = 0.44 (EtOAc/Hex 5:1, UV, $KMnO_4$ or CPS). **Mp**: 112.1-114.6 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.46-7.38 (m, 1 H), 6.43 (t, *J* = 11.4, 1 H), 6.07-5.98 (m, 1 H), 5.52 (dq, *J* = 11.4, 0.8, 1 H), 5.40 (br. s, 2 H), 1.86 (dd, *J* = 6.9, 1.6, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 168.7, 142.9, 139.2, 128.3, 117.2, 18.6. **IR** (thin film): $\tilde{\nu}$ = 344, 3160, 1662, 1592, 149, 1426, 1328, 1306, 1000, 959, 813 cm^{-1}. **HRMS** (EI): *m/z*: calcd for $C_6H_9NO[(M)^+]$: 111.0679; found: 111.0679.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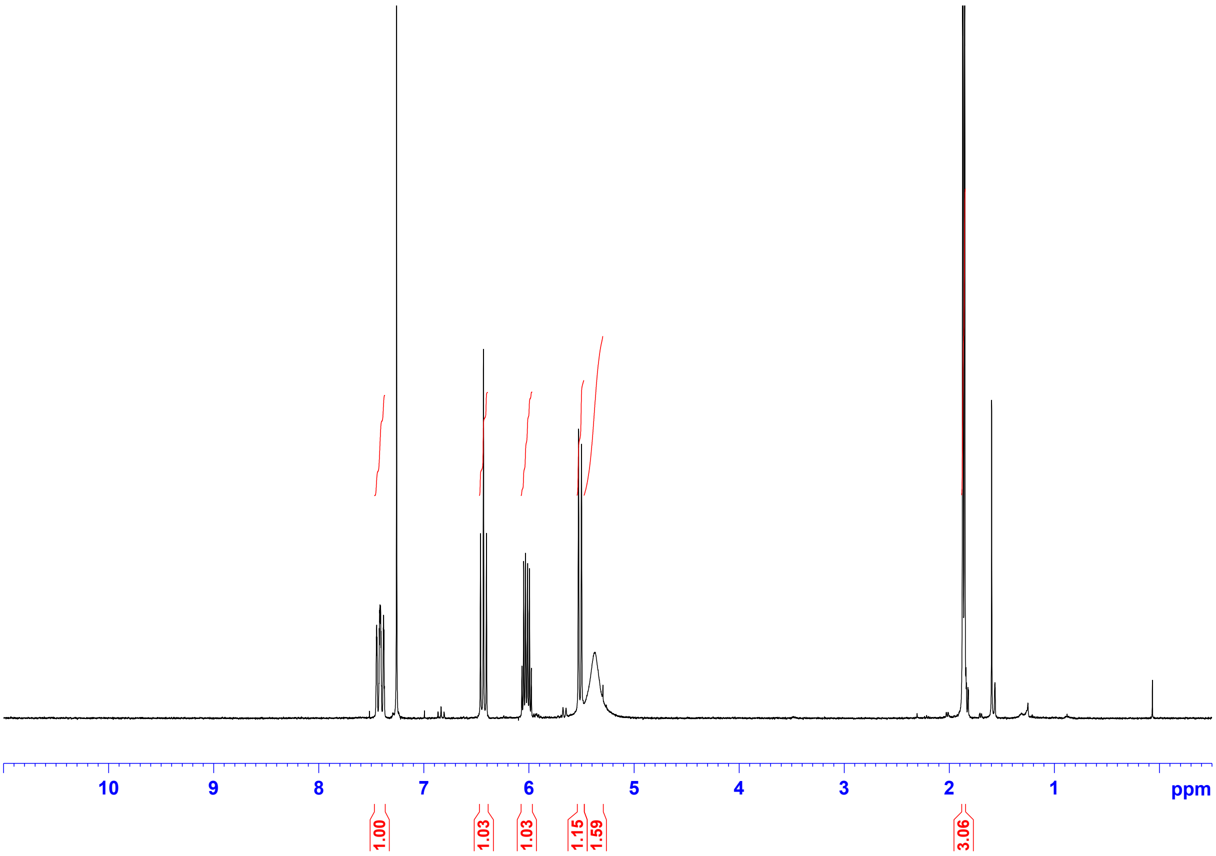
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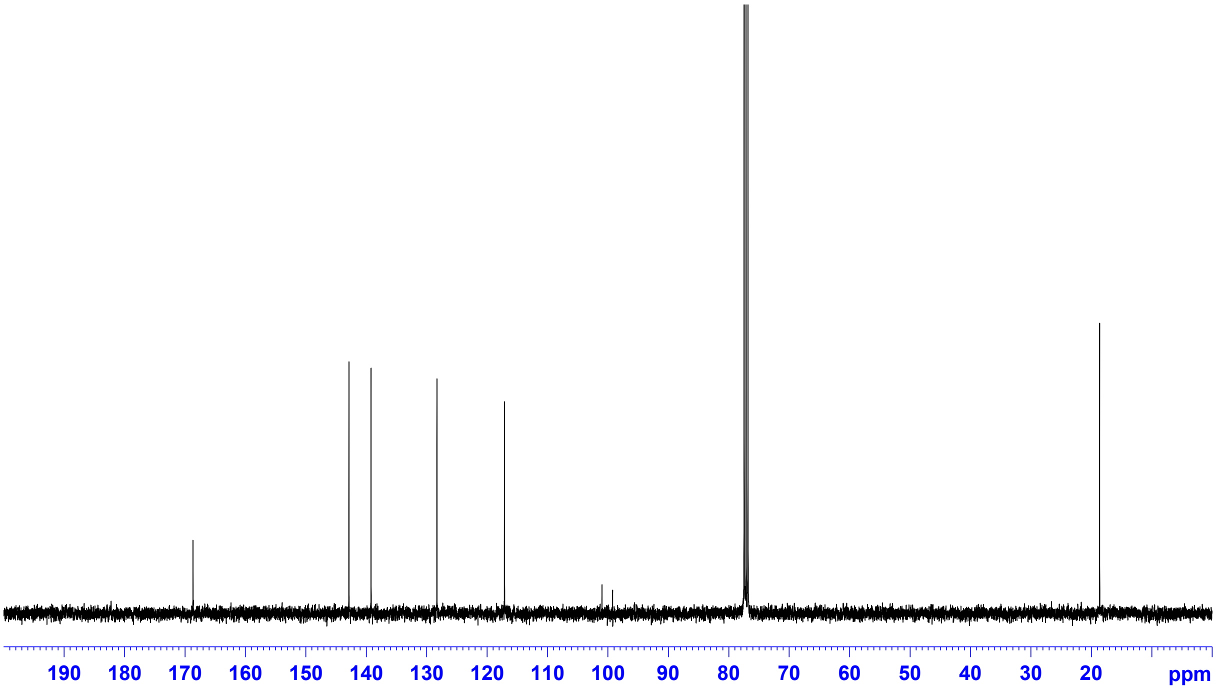
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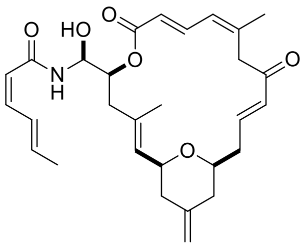

(–)-Zampanolide ((–)-1). To a solution of the side chain amid **131** (36.6 mg, 0.33 mmol, 4.6 equiv) in THF (2 mL) was added DIBAL-H (1M in CH_2Cl_2, 0.27 mL, 0.27 mmol, 3.76 equiv) and stirring was continued at room temperature for 45 min. After that time a solution of (–)-dactylolide ((–)-**2**) (27.6 mg, 0.072 mmol, 1 equiv) in THF (1 mL, flask rinsed twice with 0.5 mL of THF) was added. Stirring was continued for a total of 3 h then saturated aqueous Rochelle salt (10 mL) was added as well as EtOAc (10 mL) and stirring was continued for 15 min then brine (10 mL) was added followed by separation of phases and extraction with EtOAc (3 x 5 mL). The combined organic phases were dried over $MgSO_4$ and purified using flash chromatography on deactivated stationary phase (EtOAc/Hex 1:3→1:1, 2% NEt_3 (v/v)) giving (–)-zampanolide ((–)-**1**) (16.4 mg, 0.033 mmol, 46%) as a mixture of both C20 epimers as a pale-yellow foam. Both epimers could be separated by HPLC on normal phase[39] (compound is concentrated in EtOH, Phenomenex Luna, 5µ NH_2, 10x150 mm, EtOH/Hex (1:9), 4 mL/min, 25 °C, 266 nm, R_t = 7.6 min [(–)-zampanolide ((–)-**1**)], R_t = 8.5 min [C20-epi-(–)-**1**)] followed by RP-HPLC purification of the individual epimers (–)-**1** and epi-(–)-**1** (Waters, Symmetry®C18, 5µm, 7.8 x 100 mm, ACN/H_2O (1:1), 3 mL/min, 30 °C, 266 nm, R_t =10.2 min for both epimers). After lyophilisation, 6.4 mg (0.013 mmol, 18%) of (–)-zampanolide and 4.4 mg (0.0089 mmol, 12%) of C20-epi-zampanolide were obtained.

TLC: R_f = 0.40 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (500 MHz, DMSO-d$_6$): δ = 8.35 (d, *J* = 8.9, 1 H), 7.51 (dd, *J* = 14.9, 11.8, 1 H), 7.45 (dd, *J* = 14.9, 11.8, 1 H), 6.75 (ddd, *J* = 16.3, 8.6, 5.7, 1 H), 6.36 (t, *J* = 11.3, 1 H), 6.20 (d, *J* = 11.9, 1 H), 6.18 (br. s, 1 H), 6.00-5.94 (m, 1 H), 5.95 (d, *J* = 15.9, 1 H), 5.93 (d, *J* = 15.1, 1 H), 5.65 (d, *J* = 11.4, 1 H), 5.32 (dd, *J* = 8.4, 6.4, 1 H), 5.10 (d, *J* = 7.7, 1 H), 4.96 (dd, *J* = 10.2, 6.2, 1 H), 4.73 (br. s, 2 H), 4.13 (d, *J* = 14.2, 1 H), 3.86 (ddd, *J* = 11.4, 7.7, 1.8, 1 H), 3.26 (t, *J* = 10.1, 1 H),

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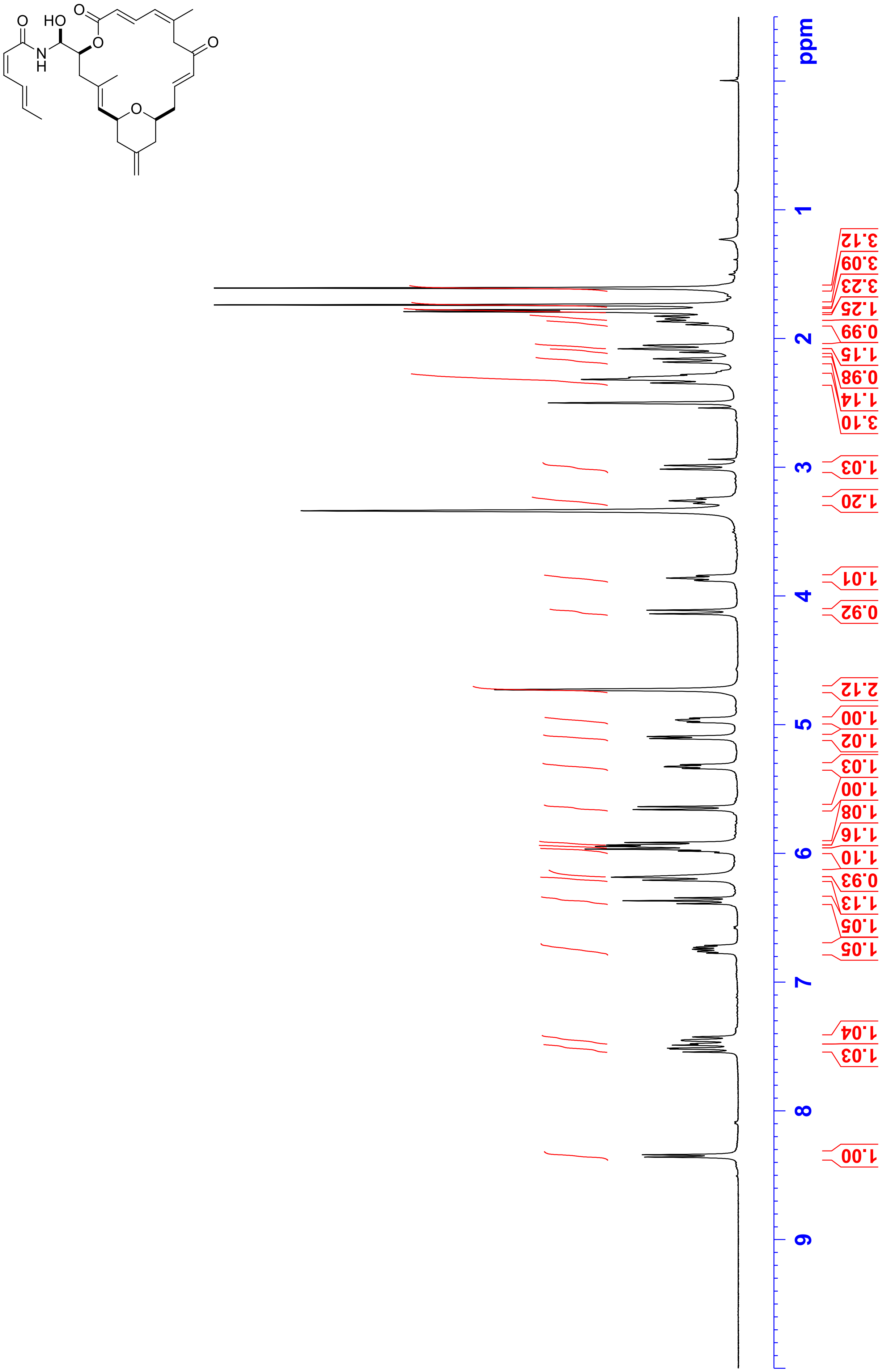
[39] For analytical run under normal phase conditions, use: Phenomenex Luna, 3µ NH_2, 4.6x150 mm, EtOH/Hex (1:9), 1 mL/min, 20 °C.

3.00 (d, *J* = 14.3, 1 H), 2.35-2.26 (m, 3 H), 2.17 (d, *J* = 12.7, 1 H), 2.11-2.05 (m, 2 H), 1.89-1.86 (m, 1 H), 1.85-1.82 (m, 1 H), 1.79 (d, *J* = 6.7, 3 H), 1.74 (s, 3 H), 1.61 (s, 3 H). **^{13}C-NMR** (125 MHz, DMSO-d$_6$): δ = 197.3, 165.6, 165.3, 145.9, 143.8, 143.0, 140.6, 139.5, 137.2, 132.5, 130.9, 129.0, 128.6, 125.1, 120.7, 119.2, 109.0, 76.0, 75.1, 72.9, 72.0, 44.9, 40.9, 40.3, 40.3, 39.3, 23.6, 18.3, 16.7. **IR** (thin film): $\tilde{\nu}$ = 3325, 3015, 2960, 2924, 2853, 1708, 1664, 1634, 1604, 1520, 1431, 1355, 1281, 1259, 1213, 1147, 1085, 1050, 1034, 1025, 802 cm^{-1}. **HRMS** (ESI): *m/z*: calcd for $C_{29}H_{38}NO_6$ [(M+H)$^+$]: 496.2694; found: 496.2681. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –241.33° (c = 0.18 in $CHCl_3$, deactivated before use over basic Alox). **RP-HPLC** (analytical column): Merck, Hibar Purospher®STAR RP-18e, 5µm, 4.6 x 150 mm, ACN/H_2O (1:1), 1 mL/min, 30 °C, 266 nm, R$_t$=16.4 min.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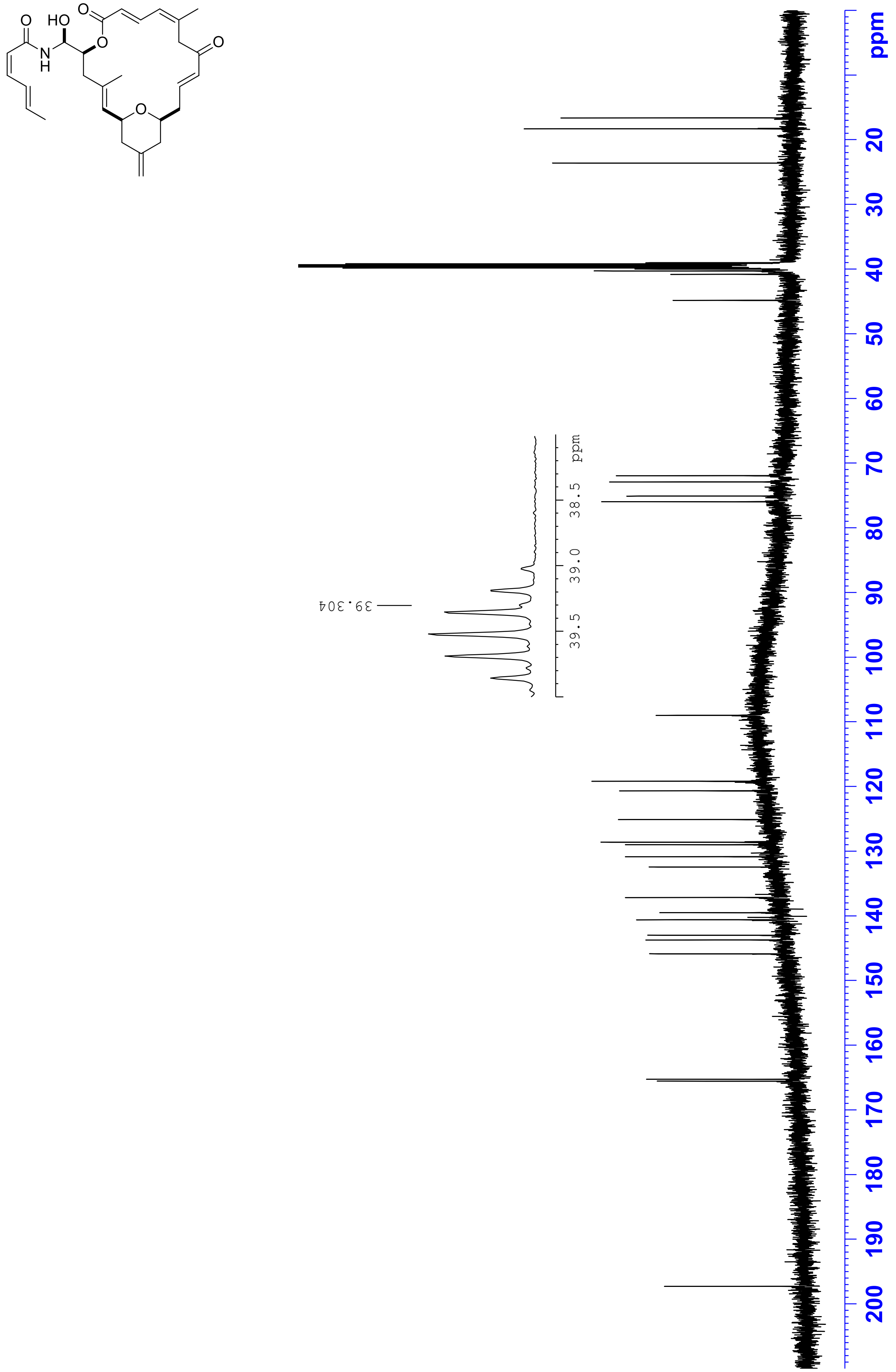
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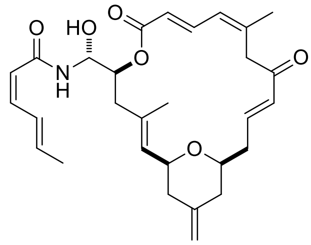

(–)-Zampanolide epimer C20-*epi*-(–)-1.[40] **TLC**: R_f = 0.40 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, DMSO-d_6): δ = 8.39 (d, J = 9.0, 1 H), 7.48 (dd, J = 15.1, 11.5, 1 H), 7.47-7.42 (m, 1 H), 6.74 (ddd, J = 16.1, 8.3, 5.7, 1 H), 6.41 (t, J = 11.3, 1 H), 6.22 (d, J = 11.5, 1 H), 6.03-6.01 (m, 1 H), 6.01-5.97 (m, 1 H), 5.98 (d, J = 14.8, 1 H), 5.93 (d, J = 16.2, 1 H), 5.65 (d, J = 11.4, 1 H), 5.33 (dd, J = 8.9, 6.0, 1 H), 5.07 (d, J = 7.9, 1 H), 5.02 (ddd, J = 9.8, 5.9, 2.9, 1 H), 4.72 (br. s, 2 H), 4.16 (d, J = 14.1, 1 H), 3.87 (ddd, J = 11.0, 8.2, 2.4, 1 H), 3.27-3.22 (m, 1 H), 2.91 (d, J = 14.2, 1 H), 2.33-2.27 (m, 2 H), 2.18-2.09 (m, 3 H), 2.07-2.03 (m, 1 H), 1.87-1.79 (m, 2 H), 1.80 (dd, J = 6.8, 1.1, 3 H), 1.75 (s, 3 H), 1.62 (s, 3 H). **^{13}C-NMR** (125 MHz,DMSO-d_6): δ = 197.4, 165.9, 165.2, 146.0, 143.7, 142.7, 140.9, 138.9, 137.4, 132.0, 130.9, 129.1, 128.6, 125.2, 121.3, 119.1, 109.0, 75.9, 75.2, 72.8, 71.8, 44.9, 40.6, 40.3, 40.3, 39.3, 23.5, 18.4, 16.4. **IR** (thin film): $\tilde{\nu}$ =3325, 2962, 2927, 2853, 1714, 1654, 1634, 1520, 1431, 1355, 1280, 1259, 1213, 1147, 1085, 1048, 1034, 1024 cm^{-1}. **HRMS** (ESI): *m/z*: calcd for $C_{29}H_{37}NNaO_6$ [$(M+Na)^+$]: 518.2513; found: 518.2518. $[\alpha]_D^{24}$: –172.92° (c = 0.65 in $CHCl_3$, deactivated over Alox before use). **RP-HPLC** (analytical column): Merck, Hibar Purospher®STAR RP-18e, 5µm, 4.6 x 150 mm, ACN/H_2O (1:1), 1 mL/min, 30 °C, 266 nm, R_t=16.4 min.

Note: Both compounds, (–)-zampanolide ((–)-**1**) and C20-*epi*-(–)-**1** are stable in DMSO as judged by RP-HPLC analysis (see method above).

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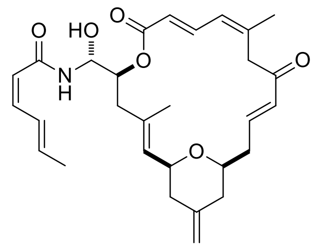
[40] For both compounds (–)-zampanolide ((–)-**1**) and C20-*epi*-(–)-**1**, a change in color of the initially colorless DMSO-d_6 solutions to purple was sometimes observed, after having conducted NMR experiments with a large number of scans (> 1k). This color change was associated with a reduction in purity and individual compounds had to be re-purified by means of RP-HPLC to provide pure samples for biological evaluation. The reason for this change in color remains unkown.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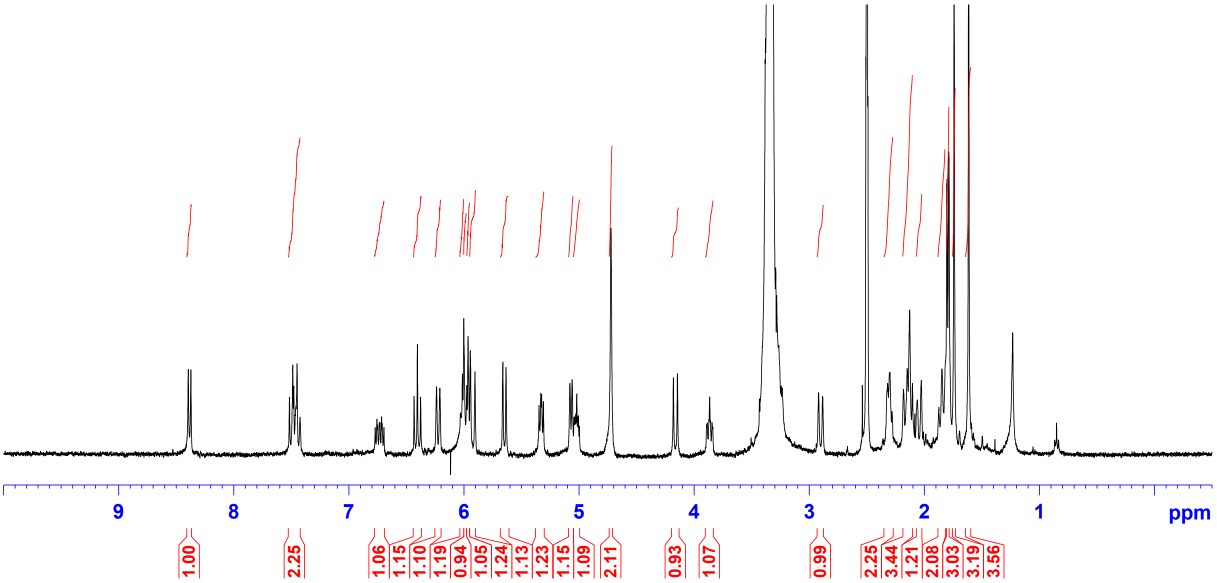
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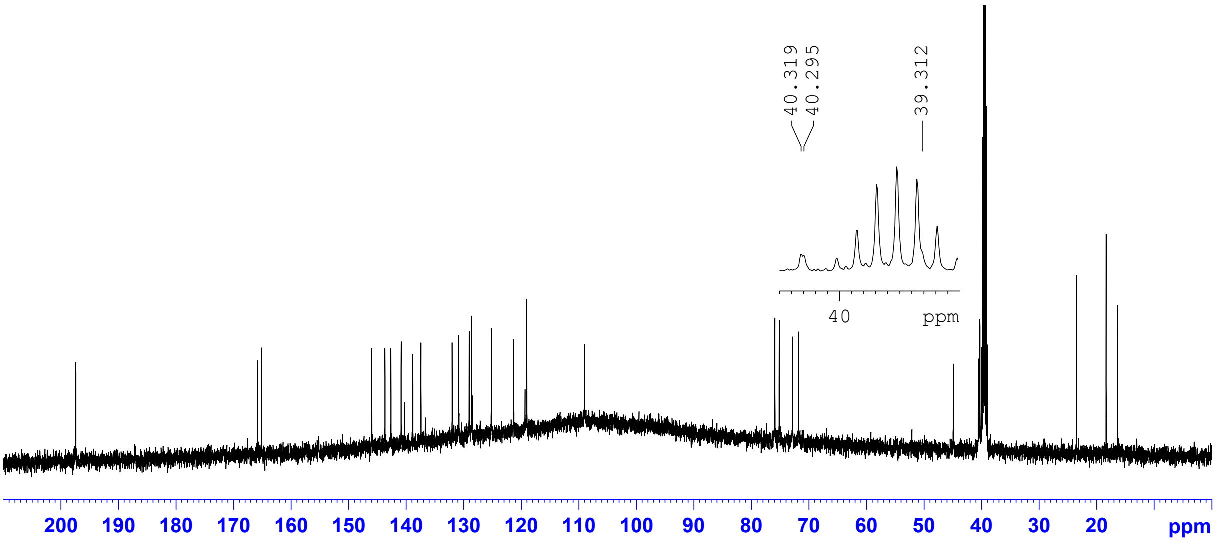
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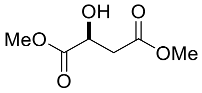
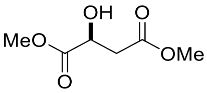
5.4. Alternative Synthesis of Alcohol 125



(*S*)-Dimethyl 2- hydroxysuccinate (132).[213] To a three-necked flask, flushed with argon, was added acetyl chloride (5.34 mL, 75 mmol, 0.37 equiv) to MeOH (70 mL) at 0 °C. The solution was allowed to warm to room temperature and after 20 min, L-malic acid (33.44 g, 249.4 mmol, 1 equiv) followed by $HC(OMe)_3$ (55 mL, 498 mmol, 1.96 equiv) were added to this solution. The resultant solution was stirred at room temperature overnight under an atmosphere of argon. After 22 h, the volatiles were removed under reduced pressure followed by drying of the crude for 2 h under high vacuum. The residue was distilled using bulb-to-bulb distillation (150 °C, ca. $5 \cdot 10^{-1}$ mmbar and ice/H_2O cooling) to afford **132** (38.349 g, 236.52 mmol, 95%) as a colorless oil. The product can be stored in the fridge over a prolonged time.

TLC: R_f = 0.44 (EtOAc/Hex 1:1, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.53-4.49 (m, 1 H), 3.82 (s, 3 H), 3.72 (s, 3 H), 3.19 (d, J = 5.4, 1 H), 2.87 (dd, J = 16.5, 4.3, 1 H), 2.79 (dd, J = 16.5, 6.1, 1 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 173.8, 171.1, 67.4, 53.0, 52.2, 38.6. **IR** (thin film): $\tilde{\nu}$ = 3480, 2956, 1731, 1439, 1366, 1265, 1214 cm^{-1}. **HRMS** (ESI): *m/z*: calcd for $C_6H_{10}NaO_5$ [$(M+Na)^+$]: 185.0420; found: 185.0421.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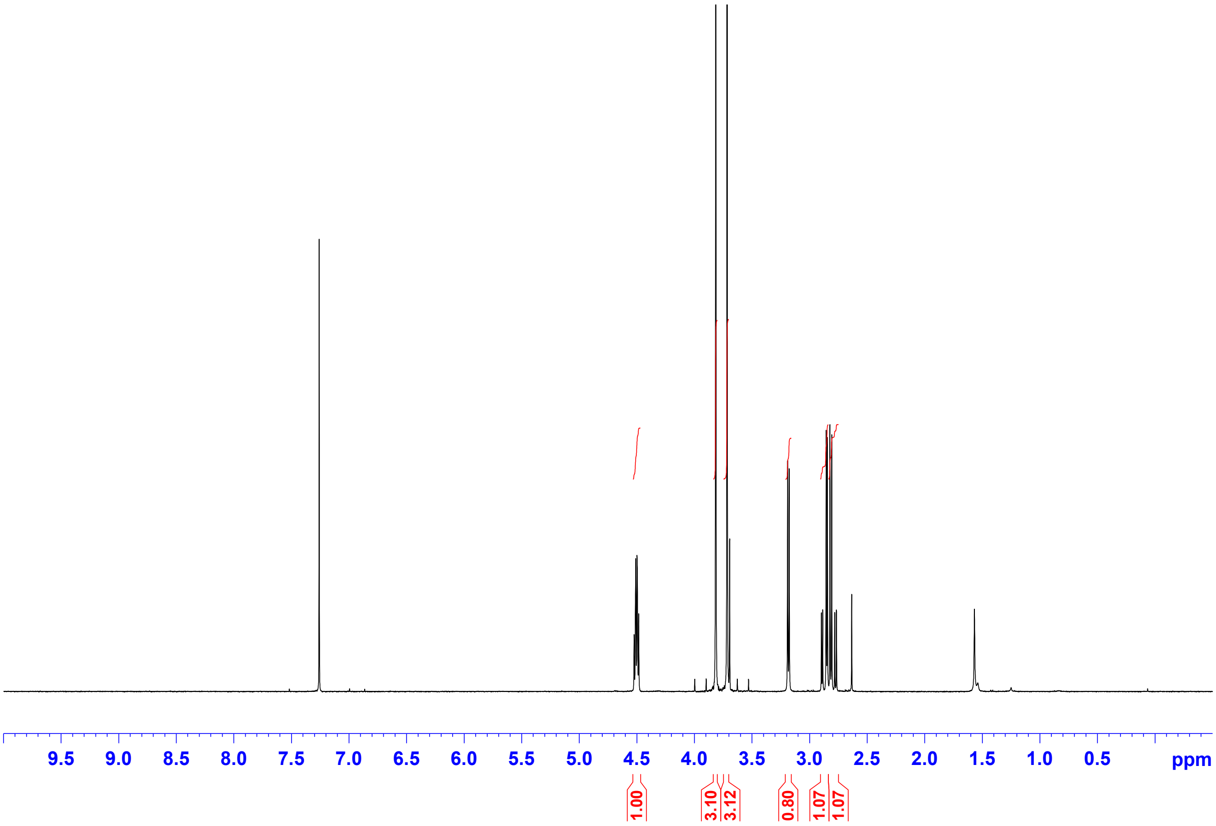
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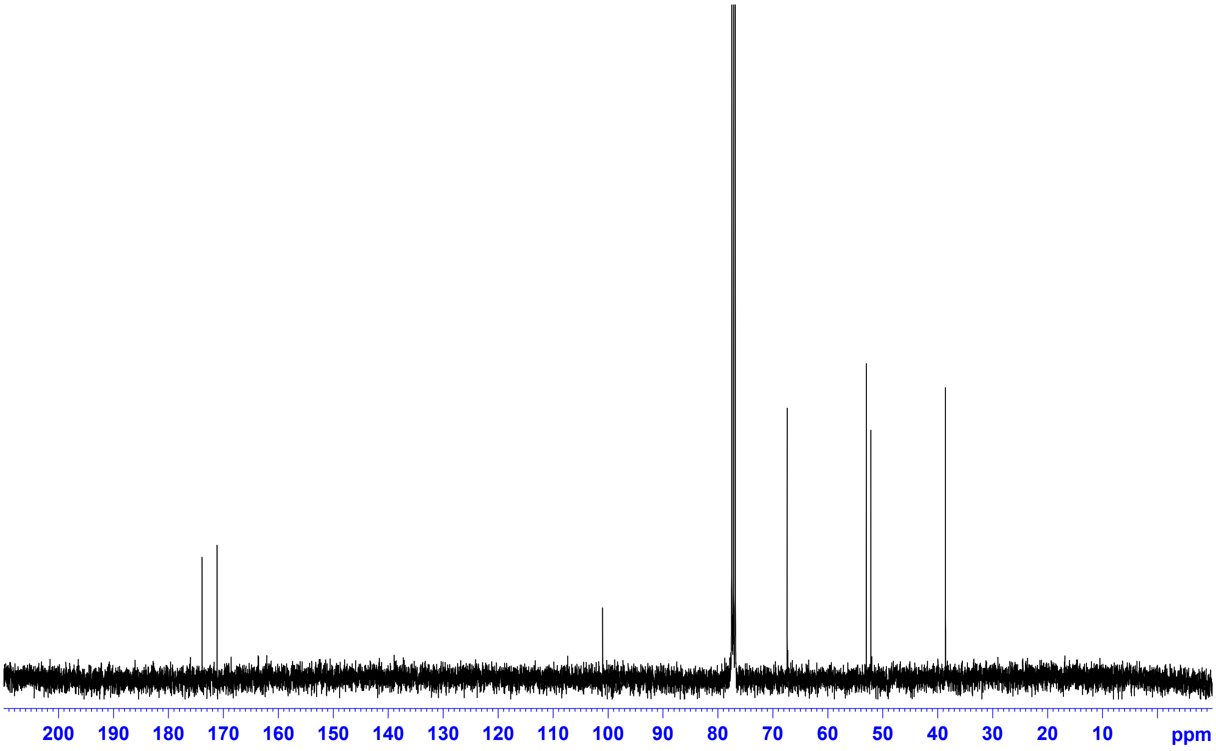
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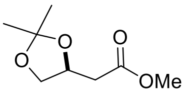

(*S*)-Methyl 2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetate (133).[42] To a flame-dried, three-necked flask, charged with a magnetic stirring bar and an argon in/outlet was added **132** (30 g, 185 mmol, 1 equiv) in dry THF (150 mL) followed by slow addition of BMS (18.5 mL, 194 mmol, 1.05 equiv) at 0 °C. Hydrogen started to evolve slowly, after the evolution of gas ceased (ca. 60 min), $NaBH_4$ (280 mg, 7.6 mmol, 0.04 equiv) was added in one portion under vigorous stirring. The cooling bath was removed after 1 h at 0 °C and stirring was continued at room temperature for 2 h more. Dry MeOH (50 mL) was added slowly then stirring was continued at room temperature for 30 min. The crude was concentrated under reduced pressure, then co-evaporated sequentially with MeOH (3 x 100 mL) and with toluene (2 x 100 mL) giving a pale-yellow oil after drying at high vacuum for 2 h. The crude viscous oil was then dissolved in acetone (200 mL) then *p*-TsOH•H_2O (3.5 g, 20.45 mmol, 0.11 equiv) was added followed by $Me_2C(OMe)_2$ (35 mL) and stirring of the white-colored mixture was continued at room temperature for 1 h. Saturated aqueous $NaHCO_3$ (100 mL) was added as well as H_2O (10 mL) and Et_2O (ca. 100 mL). Phases were separated, the aqueous phase was extracted with Et_2O (3 x 60 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:5→1:3) afforded **133** (17.4 g, 99.8 mmol, 54%) as a colorless oil. Alternative isolation procedure involves a bulb-to-bulb distillation (120-130°C at 3 mbar, use two bulbs).

Note: It is recommended to use this two-step sequence and not to isolate the diol after borane-reduction since the diol is very water-soluble and isolation of the crude diol by distillation resulted in a significantly lower yield.

TLC: R_f = 0.40 (EtOAc/Hex 1:3, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.51-4.44 (m, 1 H), 4.16 (dd, *J* = 8.4, 6.1, 1 H), 3.70 (s, 3 H), 3.65 (dd, *J* = 8.4, 6.4, 1 H), 2.72 (dd, *J* = 15.9, 6.4, 1 H), 2.53 (dd, *J* = 15.9, 7.1, 1 H), 1.42 (s, 3 H), 1.36 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 171.2, 109.4, 72.2, 69.3, 51.9, 39.0, 27.0, 25.7. **IR** (thin film): $\tilde{\nu}$ =

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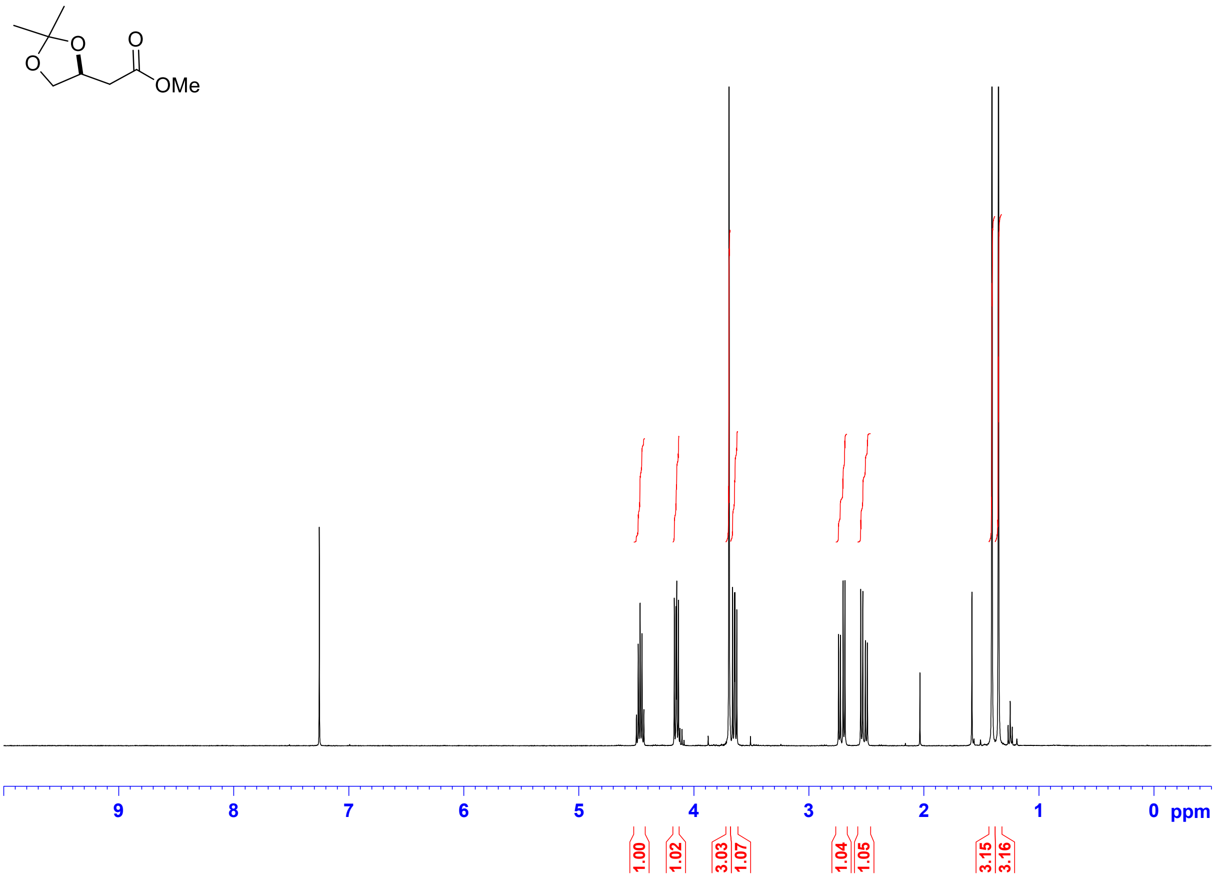
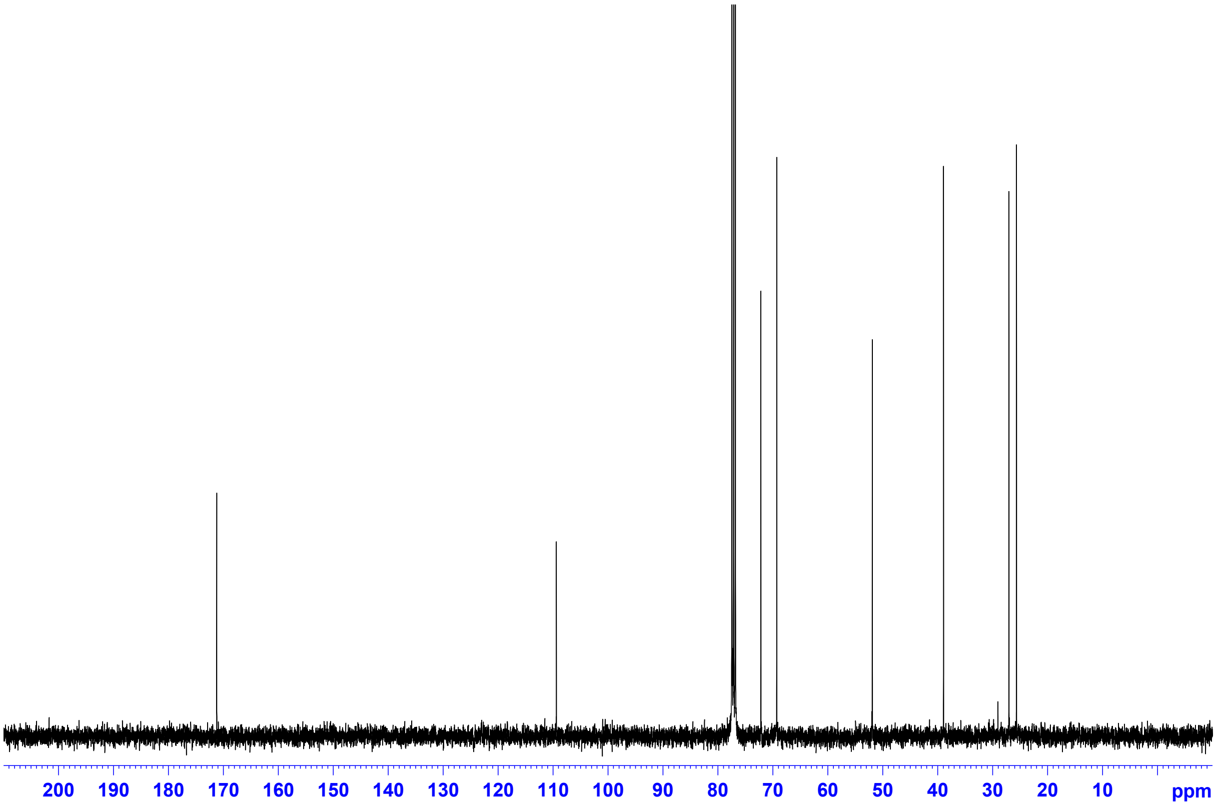
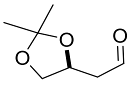
[42] Experimental procedure and analytical data, see: S. Saito, T. Ishikawa, A. Kuroda, K. Koga, T. Moriwake, *Tetrahedron* **1992**, *48*, 4067-4086.

2988, 2955, 1736, 1438, 1380, 1371, 1207, 1171, 1157, 1063 cm^{-1}. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +18.08° (c = 1.58 in $CHCl_3$).







(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acetaldehyde (134).[43] To a solution of **133** (19.97 g, 114.65 mmol, 1 equiv) in dry CH_2Cl_2 (500 mL) was added a solution of DIBAL-H (1M in CH_2Cl_2, 120 mL, 120 mmol, 1.05 mmol) via an addition funnel at –78 °C so that the interior temperature did not exceed –70 °C. 15 min after the addition was completed, the cooling bath was removed then saturated aqueous Rochelle salt (300 mL) was added slowly. Stirring was continued for 90 min resulting in the formation of two clear phases. The phases were separated then the aqueous phase was extracted using Et_2O (2 x 50 mL), the combined organic phases were dried over $MgSO_4$ and purification using bulb-to-bulb distillation (120–130 °C at 6 mmbar) afforded **134** (13.51 g, 93.7 mmol, 82%) as a colorless oil.

TLC: $R_f = 0.30$ (EtOAc/Hex 1:3, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.81 (t, d = 1.5, 1 H), 4.53 (quint, *J* = 6.4, 1 H), 4.20 (dd, *J* = 8.4, 6.1, 1 H), 3.60 (dd, *J* = 8.4, 6.8, 1 H), 2.84 (ddd, *J* = 17.2, 6.6, 1.8, 1 H), 2.64 (ddd, *J* = 17.2, 6.2, 1.4, 1 H), 1.42 (s, 3 H), 1.37 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 200.1, 109.4, 70.8, 69.3, 48.0, 27.0, 25.6. **IR** (thin film): $\tilde{\nu}$ = 2989, 1724, 1380, 1372, 1248, 1215, 1157, 1051 cm^{-1}.

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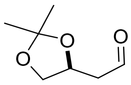
[43] For analytical data, see: A. Erkkilä, P. M. Pihko, *J. Org. Chem.* **2006**, *71*, 2538-2541.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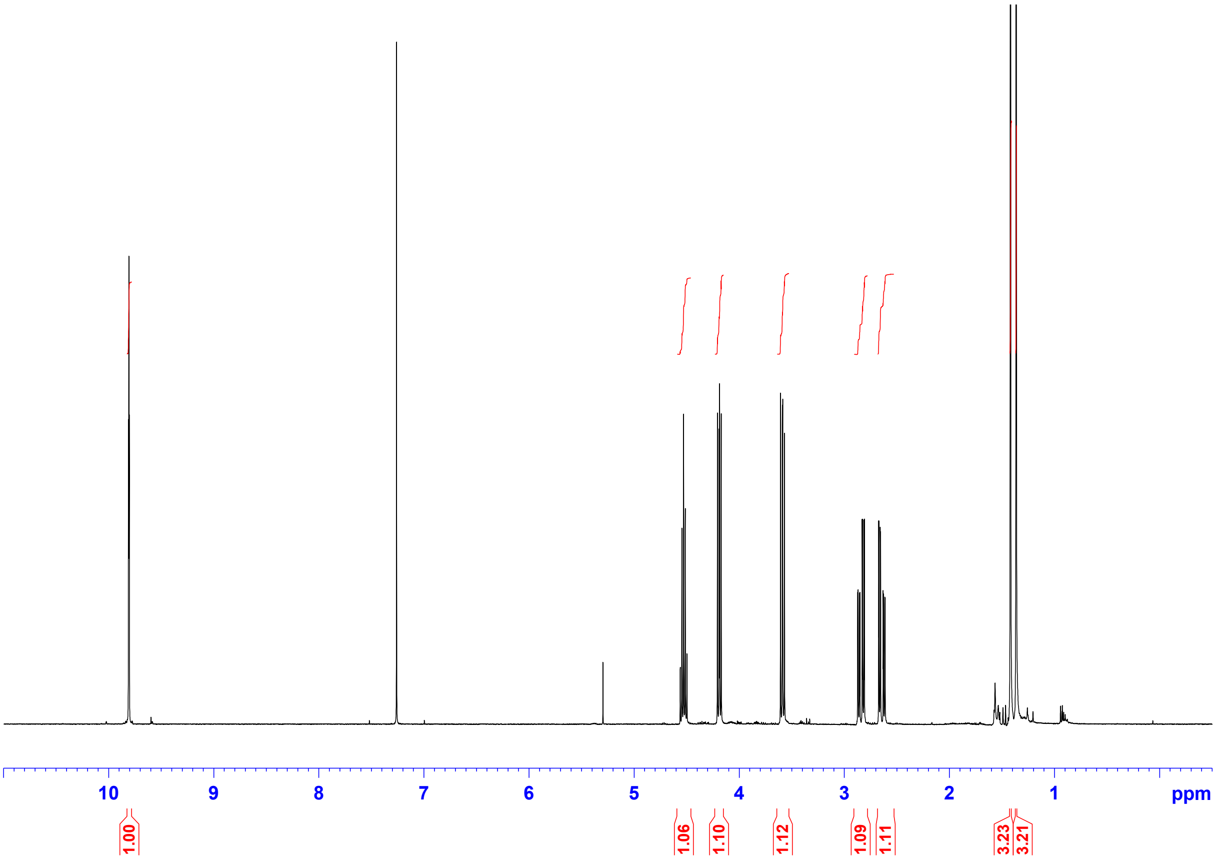
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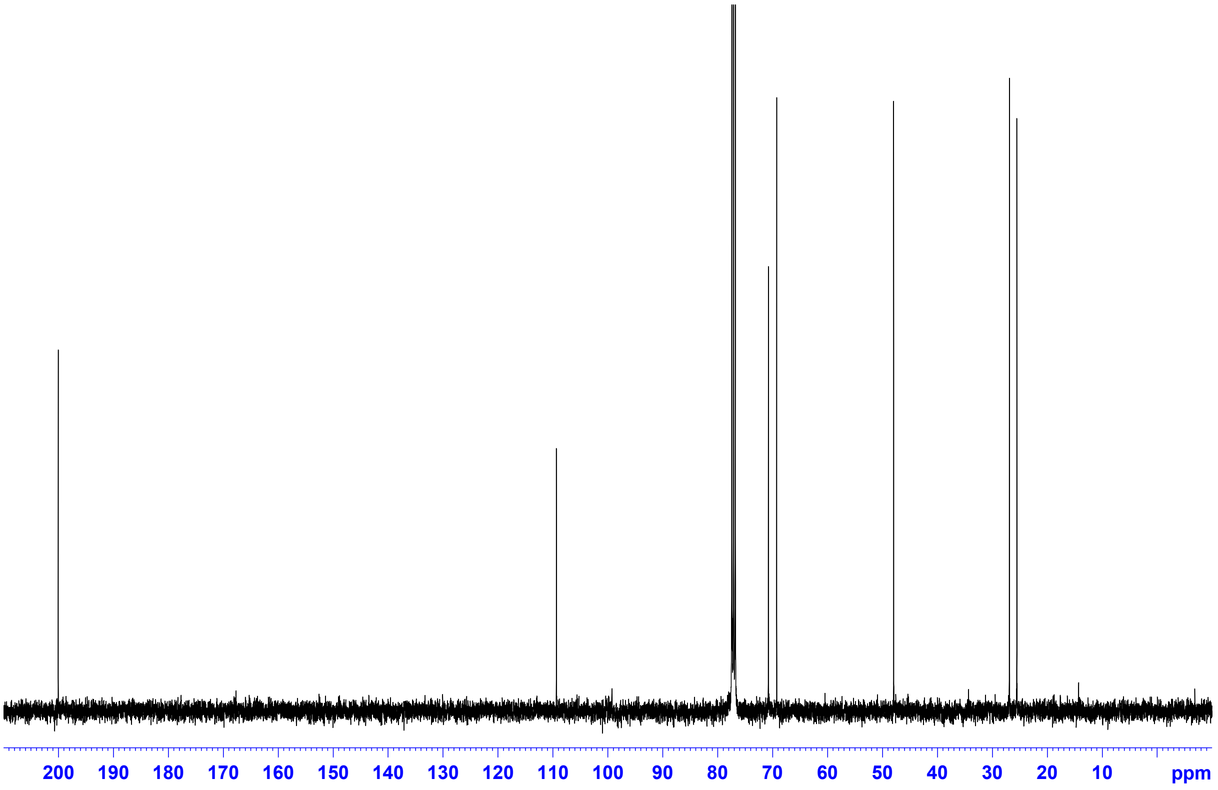
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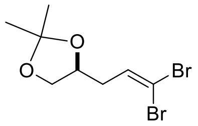
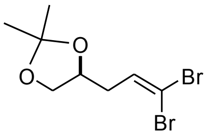


(*S*)-4-(3,3-Dibromoallyl)-2,2-dimethyl-1,3-dioxolane (F). To a flame-dried three-necked flask, charged with a magnetic stirring bar, an addition funnel and argon in/outlet, was added CBr_4 (46.6 g, 140.5 mmol, 1.5 equiv) and dry CH_2Cl_2 (400 mL) followed by PPh_3 (68.0 g, 259 mmol, 2.7 equiv) at 0 °C giving an orange solution followed by 2,6-dimethylpyridine (15 mL, 140.6 mmol, 1.5 equiv) affording a dark mixture that was stirred for 10 min. A solution of **134** (13.5 g, 93.71 mmol, 1 equiv) in dry CH_2Cl_2 (90 mL) was added via an addition funnel (rinsed with 10 mL of dry CH_2Cl_2) then the mixture was stirred for 10 min more, after the addition was completed. The tan mixture was then poured into hexane (400 mL) giving a brown precipitate, which was filtered off over a pad of silica and washed with EtOAc/Hex (1:1, 1000 mL). The filtrate was concentrated under reduced pressure followed by addition of hexane (300 mL) which resulted in a white precipitate that was suspended in Et_2O (200 mL) followed by filtration and washing of the solid residue with hexane (100 mL) and Et_2O (100 mL). Concentration under reduced pressure then again treating the residue with hexane (100 mL) afforded a white precipitate that was filtered off. After concentration under reduced pressure, the pale-yellow oil obtained did not form any white precipitates when treated again with hexane. Purification using flash chromatography (EtOAc/Hex 1:20→1:10) of the concentrated oil containing 2,6-dimethylpyridine afforded **F** (24.27 g, 80.32 mmol, 86%) as a colorless oil.

TLC: R_f = 0.42 (EtOAc/Hex 1:10, UV, $KMnO_4$ or CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 6.47 (t, J = 7.1, 1 H), 4.17 (quint, J = 6.1, 1 H), 4.03 (dd, J = 8.1, 6.2, 1 H), 3.58 (dd, J = 8.2, 6.6, 1 H), 2.42-2.30 (m, 2 H), 1.41 (d, J = 0.5, 3 H), 1.33 (d, J = 0.5, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ =134.1, 109.5, 91.1, 73.9, 68.7, 37.3, 26.9, 25.6. **IR** (thin film): $\tilde{\nu}$ = 2985, 2935, 2877, 1455, 1379, 1369, 1249, 1213, 1153, 1057, 839 cm^{-1}. **HRMS** (ESI): calcd for $C_8H_{12}Br_2NaO_2$ [(M+Na)$^+$]: 320.9096; found: 320.9101. $[\alpha]_D^{24}$= –3.00° (c = 2.06 in $CHCl_3$).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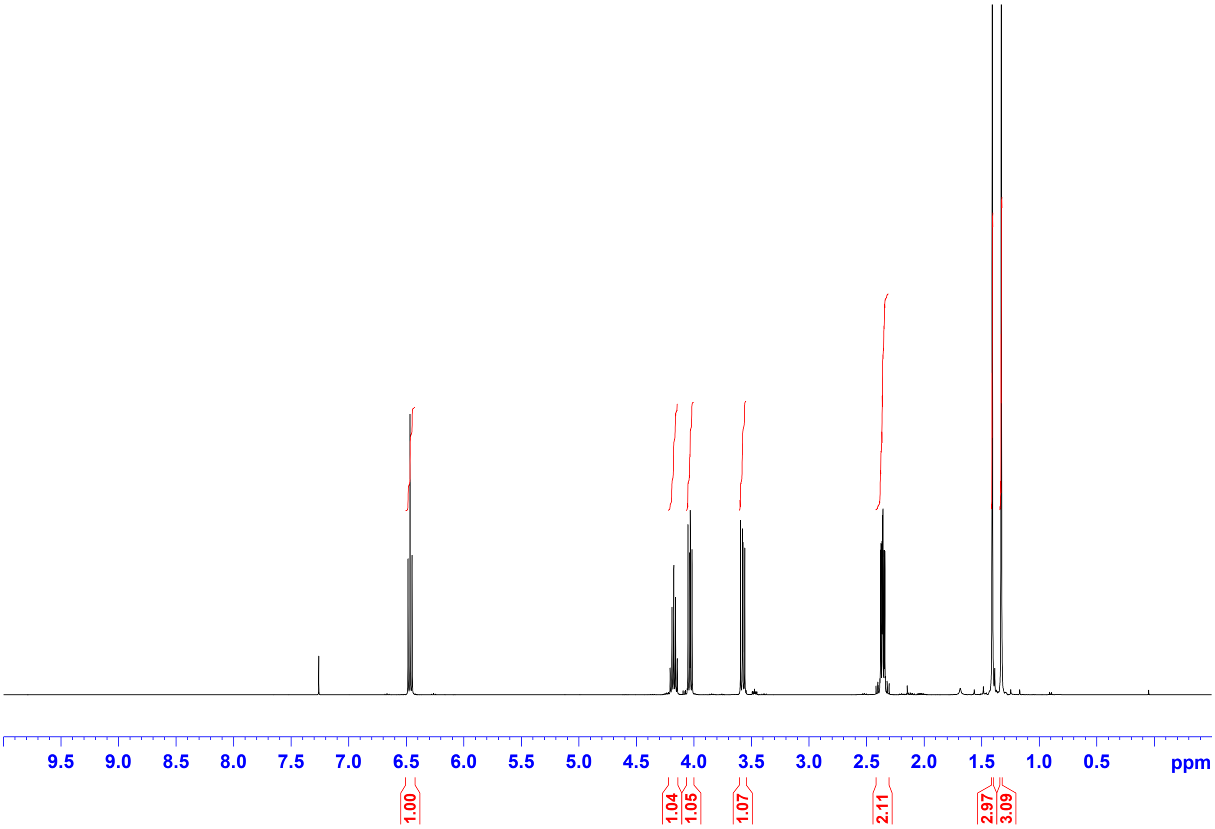
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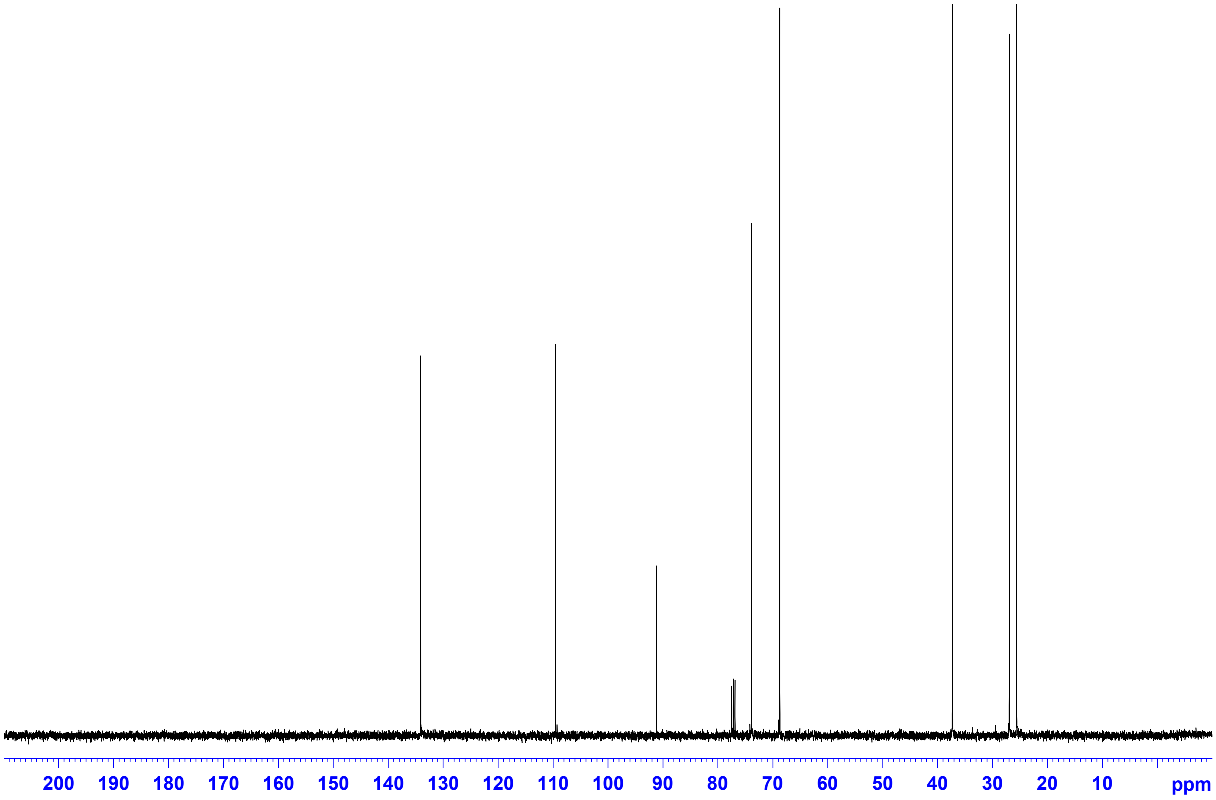
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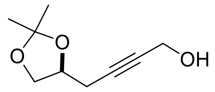
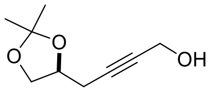


(*S*)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol (143). To a flame-dried three-necked flask, charged with a magnetic stirring bar, an addition funnel and argon in/outlet, was added **F** (24.03 g, 80.09 mmol, 1 equiv) in dry THF (400 mL) followed by *n*-BuLi (1.6M in hexane, 105.0 mL, 168.2 mmol, 2.1 equiv) via an addition funnel at –78 °C (interior temperature raised to –65 °C during addition). After 20 min, the flask was immersed into an icebath (0 °C) and stirring was continued for 30 min more. The pale-yellow solution was cooled back to –78 °C followed by addition of paraformaldehyde (4.81 g, 160.18 mmol, 2 equiv) and stirring was continued for 1 h at that temperature then the tiny suspension was allowed to warm to room temperature. Stirring was continued for a total of 20 h then saturated aqueous NH_4Cl (100 mL) was added followed by H_2O (50 mL) and EtOAc (100 mL) then extraction with EtOAc (3 x 50 mL), followed by drying over $MgSO_4$ and concentration under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:10→1:1) gave **143** (8.74 g, 51.3 mmol, 64%) as a pale-yellow oil. Unreacted acetylene (volatile) was recovered as a pale-yellow oil in 927 mg.

Note: Acetylene intermediate stains well with CPS but is not UV-active.

TLC: R_f = 0.48 (EtOAc/Hex 1:1, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.26-4.24 (m, 2 H), 4.25-4.20 (m, 1 H), 4.10 (dd, *J* = 8.4, 6.1, 1 H), 3.76 (dd, *J* = 8.3, 6.1, 1 H), 2.57 (ddt, *J* = 16.7, 5.3, 2.2, 1 H), 2.46 (ddt, *J* = 16.7, 7.3, 2.2, 1 H), 1.56 (br. s, 1 H) 1.44 (s, 3 H), 1.36 (d, *J* = 0.6, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 109.8, 81.9, 80.3, 74.2, 68.9, 51.4,27.0,25.7,24.2.**IR**(thinfilm):$\tilde{\nu}$ = 3426, 2986, 2934, 2875, 1371, 1255, 1213, 1154, 1064, 1013 cm^{-1}. **HRMS** (ESI): calcd for $C_9H_{14}NaO_3$ [$(M+Na)^+$]: 193.0835; found: 193.0827. $[\alpha]_D^{24}$: +31.94° (c = 0.84 in $CHCl_3$).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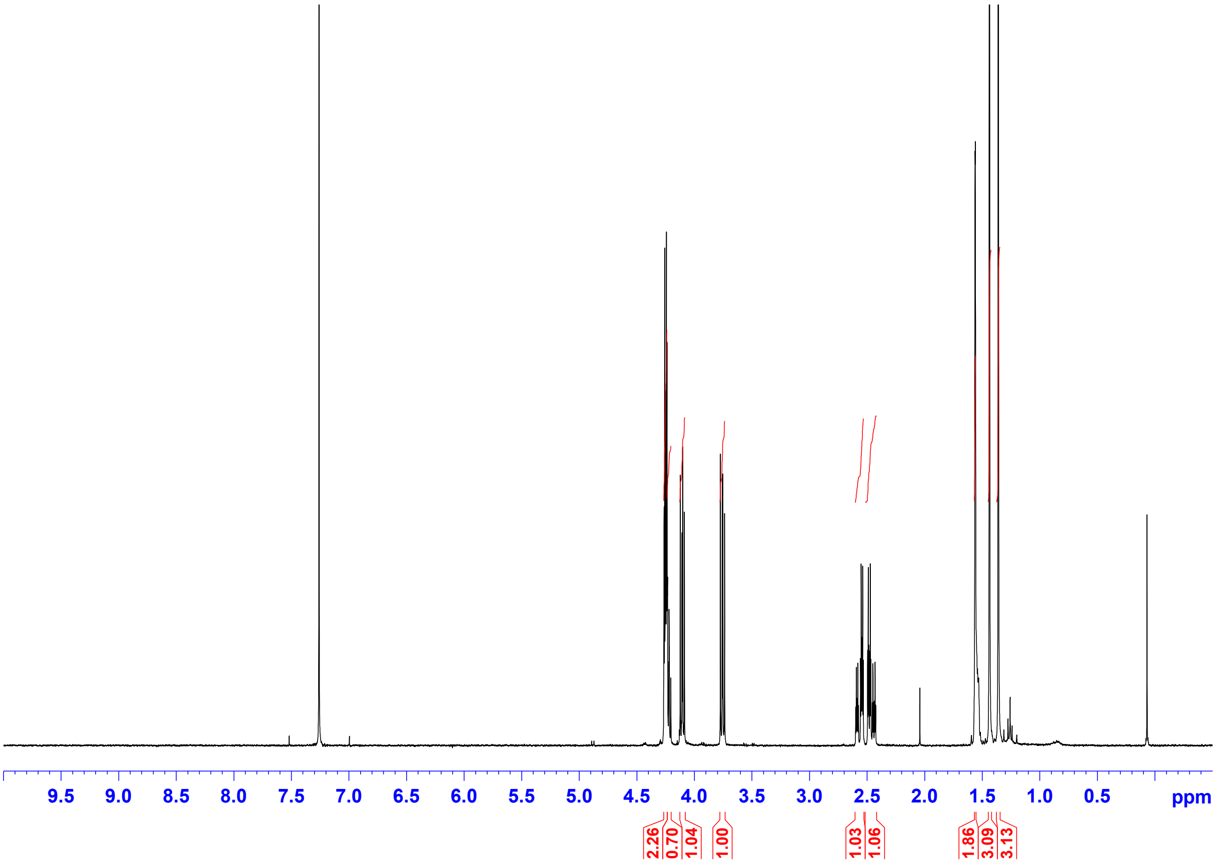
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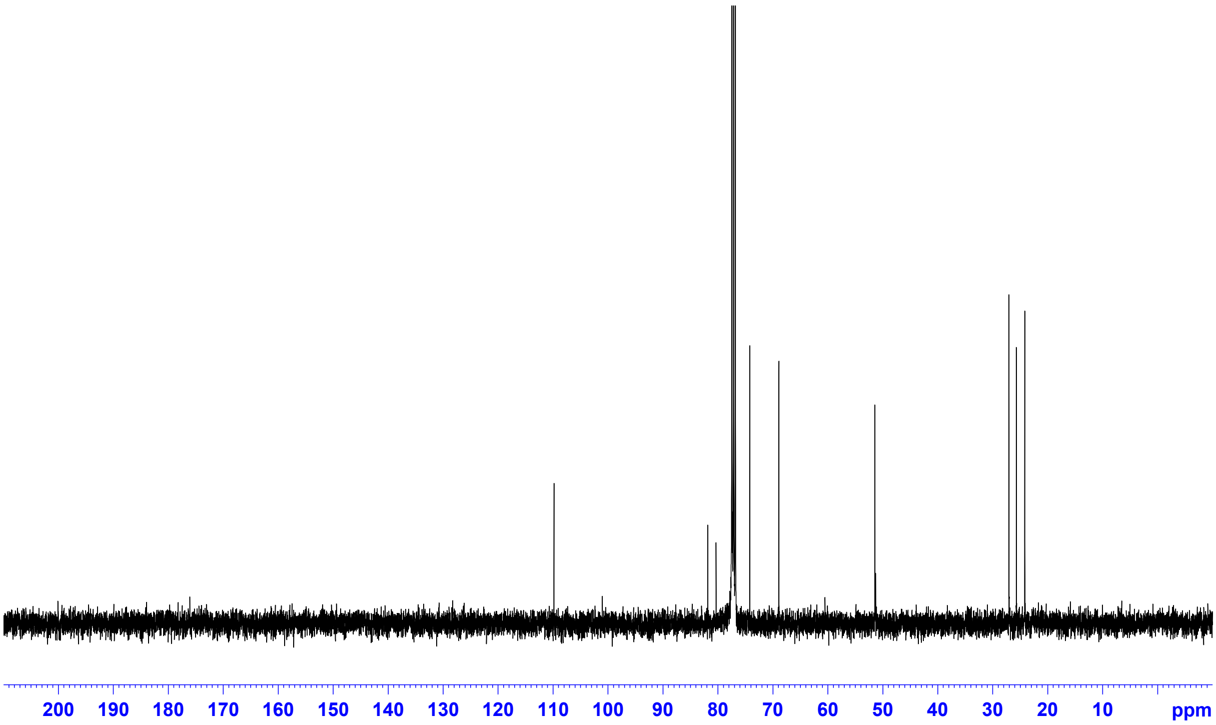
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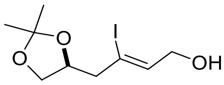
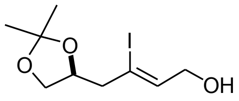


(*S*, *Z*)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-iodobut-2-en-1-ol (144). To a flame-dried three-necked flask, charged with a magnetic stirring bar, an addition funnel and argon in/outlet, was added **143** (8.74 g, 51.3 mmol, 1 equiv) in dry THF (100 mL) followed by a solution of RedAl® (3.4M in toluene, 22.6 mL, 77 mmol, 1.5 equiv) at 0 °C (ice bath). After 5 min the cooling bath was removed and stirring was continued at room temperature for 45 min (the reaction mixture got exothermic). The solution was cooled to 0 °C (ice bath) followed by slow addition of dry EtOAc (70 mL) via an addition funnel. After 5 min iodine (19.5 g, 77 mmol, 1.5 equiv), dissolved in dry THF (100 mL), was added via addition funnel (which was rinsed with dry THF (20 mL)) at –78 °C. After the addition was completed, the cooling bath was removed and the mixture was allowed to warm to room temperature then saturated aqueous $Na_2S_2O_3$ (200 mL) and saturated aqueous Rochelle salt (200 mL) were added followed by EtOAc (100 mL). After 30 min, two clear phases were obtained which were separated. The aqueous phase was extracted with EtOAc (3 x 50 mL) then the combined organic phases were dried over $MgSO_4$ followed by purification using flash chromatography (EtOAc/Hex 1:6→1:3→1:1) giving **144** (11.49 g, 38.54 mmol, 75%) as a yellow oil.

TLC: R_f = 0.63 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.95 (tt, *J* = 5.7, 1.2, 1 H), 4.38 (dq, *J* = 6.7, 6.0, 1 H), 4.21-4.11 (m, 2 H), 4.06 (dd, *J* = 8.3, 6.1, 1 H), 3.61 (dd, *J* = 8.3, 6.1, 1 H), 2.85 (ddq, *J* = 14.5, 7.1, 1.0, 1 H), 2.64 (ddq, *J* = 14.5, 5.8, 1.0, 1 H), 2.93 (t, *J* = 5.5, 1 H), 1.40 (s, 3 H), 1.34 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 136.9, 109.5, 102.5, 74.6, 68.5, 67.3, 49.4, 27.1, 25.7. **IR** (thin film): $\tilde{\nu}$ = 3352, 2958, 2930, 2878, 1647, 1456, 1420, 1258, 1220, 1069, 1022 cm^{-1}. **HRMS** (ESI): *m/z*: calcd for $C_9H_{16}IO_3$ [(M+H)$^+$]: 299.0139; found: 299.0124. $[\alpha]_D^{24}$: –10.10° (c = 1.94 in $CHCl_3$).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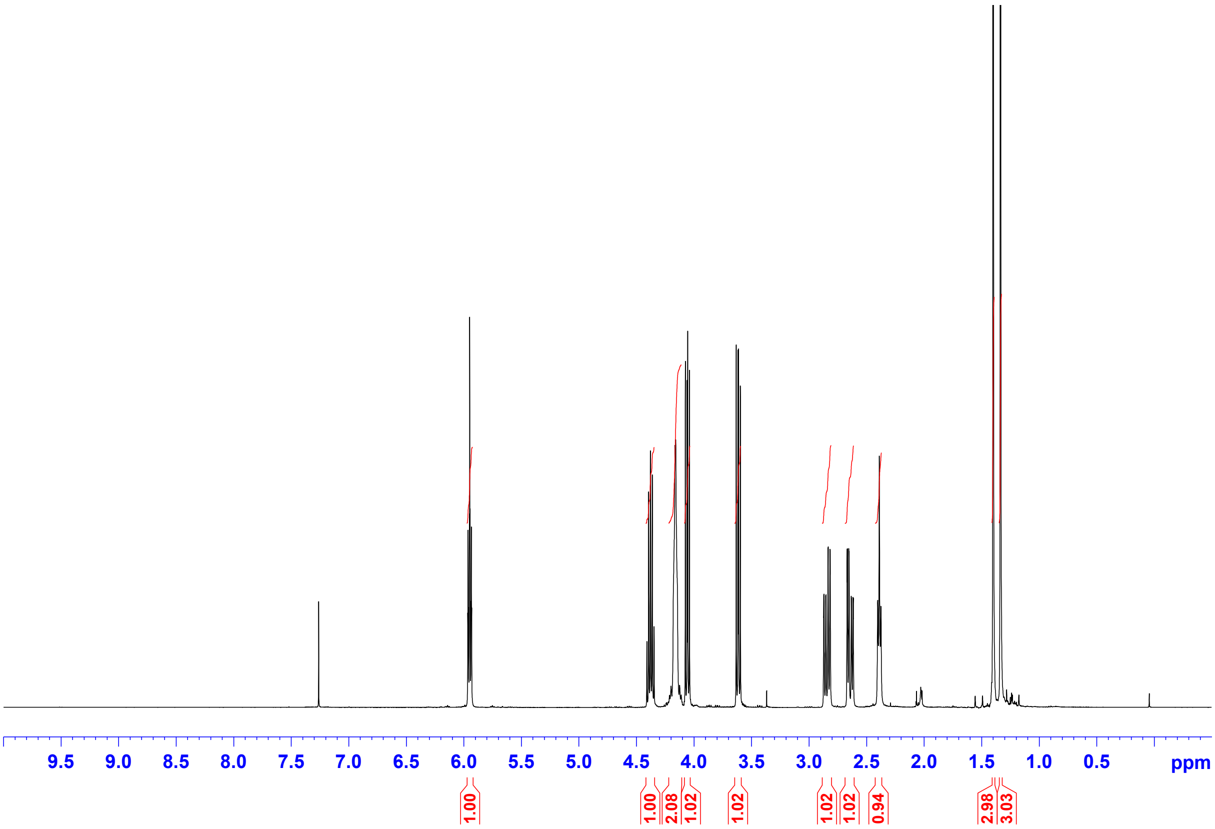
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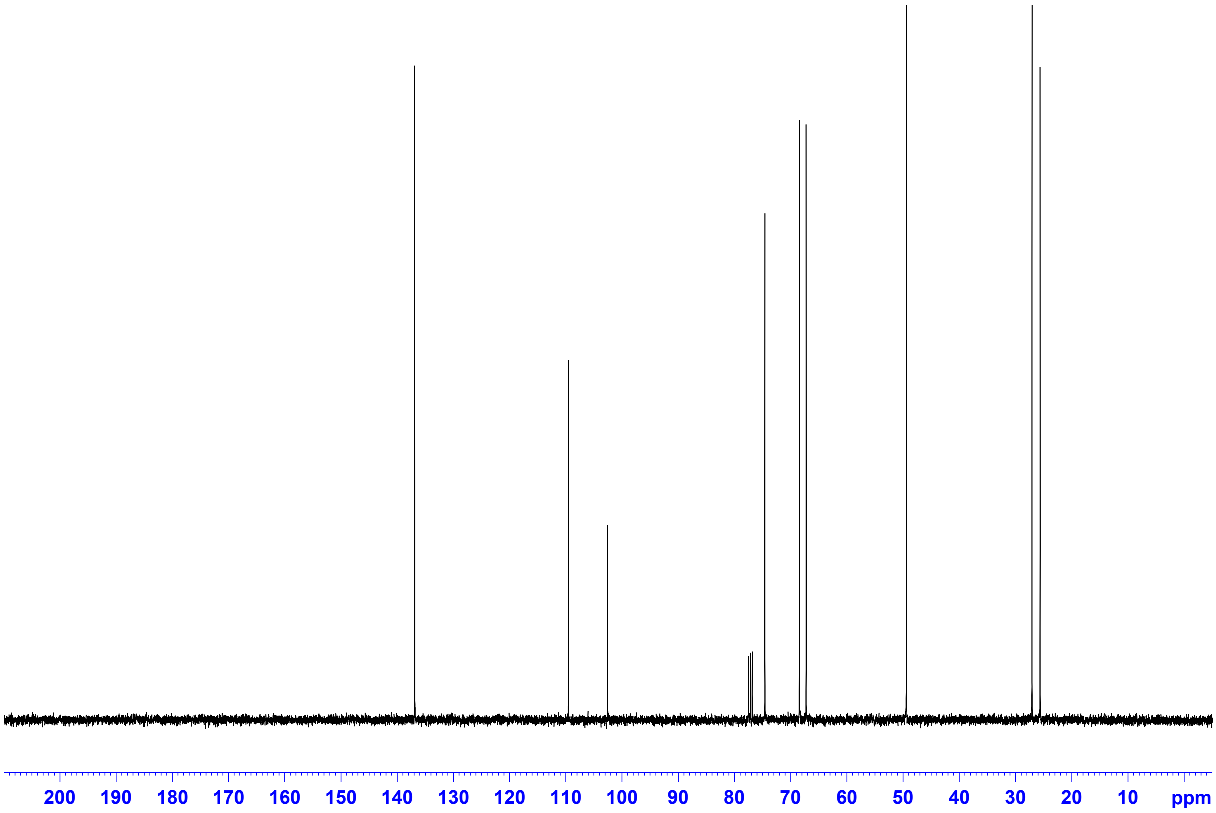
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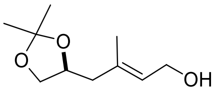
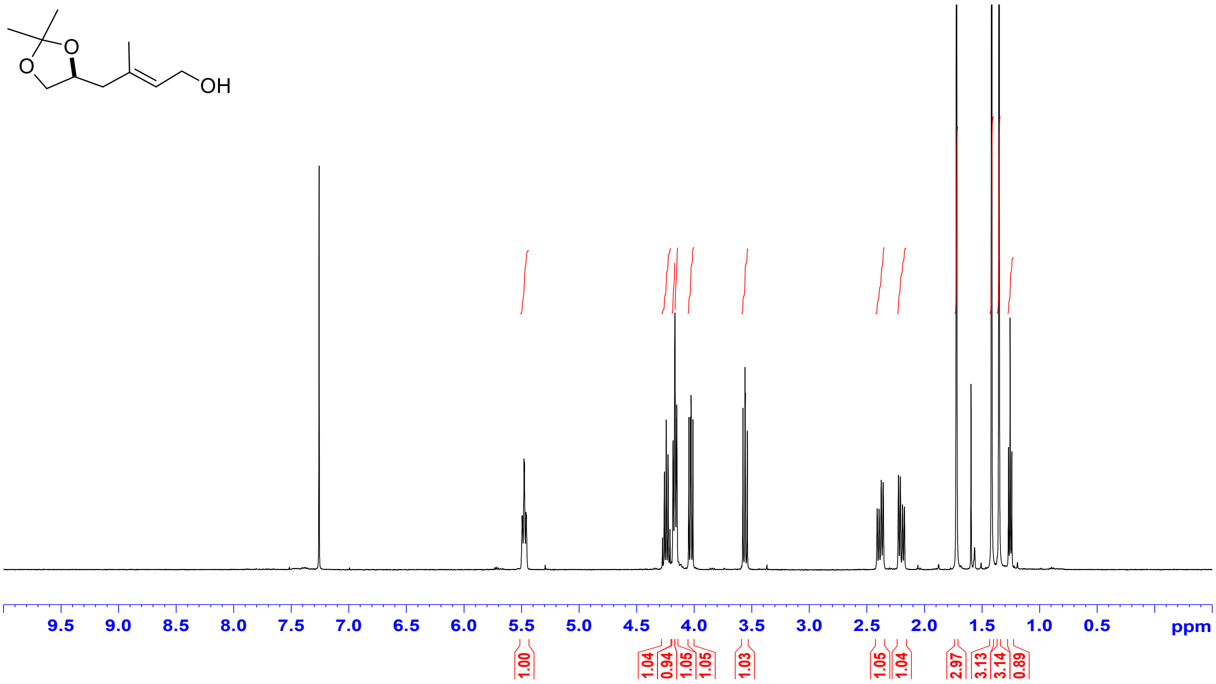
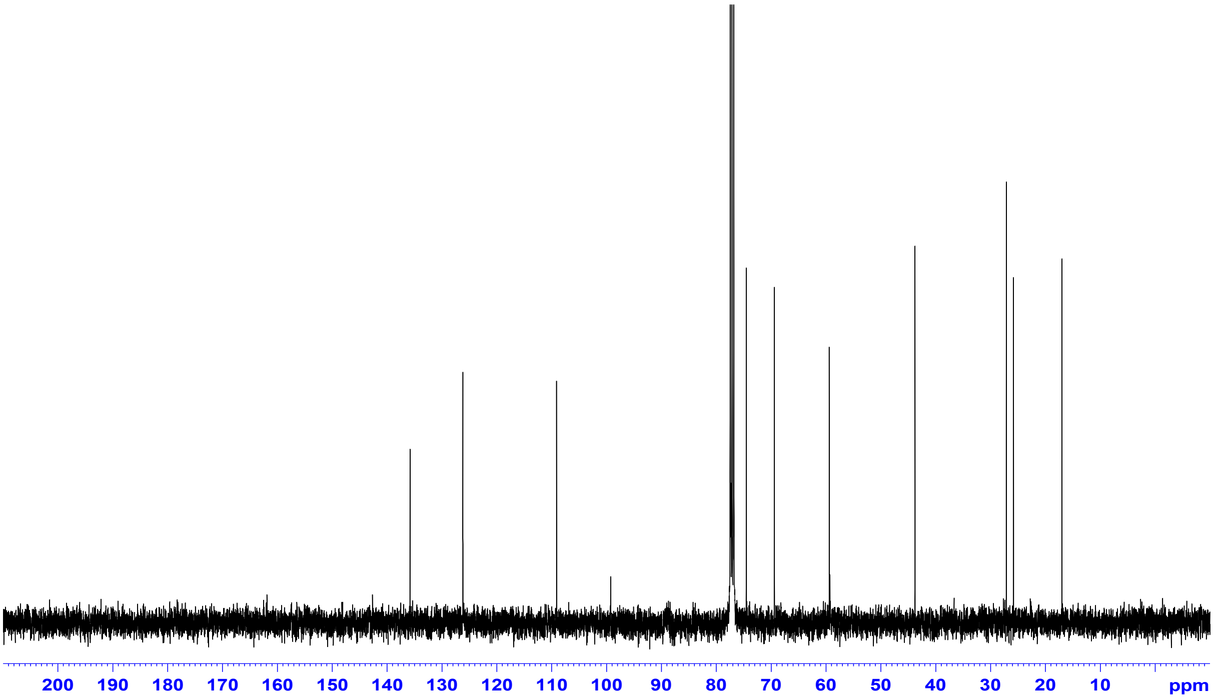


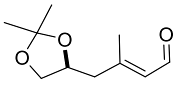
(*S*,*E*)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methylbut-2-en-1-ol (149). To a three-necked, flame-dried flask, charged with a magnetic stirring bar, a reflux condenser and an argon in-outlet, was added **144** (11.49 g, 38.54 mmol, 1 equiv) in dry THF (150 mL) followed by addition of NEt_3 (26.7 mL, 192.7 mmol, 5 equiv). The solution was cooled to 0 °C (icebath) then TMSCl (9.8 mL, 77.1 mmol, 2 equiv) was added giving a white precipitate immediately. Stirring was continued for 2 h then phosphate buffer (pH 7.2, 50 mL) was added followed by separation of phases and extraction of the aqueous phase with Et_2O (2 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure giving the crude TMS ether as a pale-yellow oil.

The resulting crude TMS ether was dissolved in degassed THF (150 mL, argon bubbled through the solvent for 15 min) at room temperature followed by addition of $Pd(dppf)Cl_2{\bullet}CH_2Cl_2$ (2.29 g, 2.81 mmol, 0.07 equiv) and a solution of Me_2Zn (1.2M in toluene, 64.2 mL, 77.1 mmol, 2 equiv) leading to a complete yellow solution immediately. The solution was heated to 80 °C and stirring was continued for 1 d. The heating bath was removed then saturated aqueous NH_4Cl (100 mL) was carefully added followed by addition of Et_2O (100 mL). Phases were separated then the aqueous phase was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure giving a yellow oil with some dark solids. The crude was suspended in dry MeOH (100 mL) and K_2CO_3 (5.86 g, 42.4 mmol, 1.01 equiv) was added then stirring was continued at room temperature for 1.5 h. The crude was concentrated under reduced pressure then H_2O (100 mL) was added followed by Et_2O (200 mL). Phases were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL) and once with CH_2Cl_2 (50 mL), then the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:2→1:1→2:1) afforded **149** (5.82 g, 31.25 mmol, 81%) as an orange oil.

TLC: R_f = 0.35 (EtOAc/Hex 1:1, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.48 (tq, *J* = 6.9, 1.2, 1 H), 4.28-4.21 (m, 1 H), 4.18 (br. d, *J* = 6.1, 1 H), 4.16 (br. d, *J* = 6.4, 1 H), 4.03 (dd, *J* = 8.0, 6.0, 1 H), 3.56 (dd, *J* = 8.0, 7.1, 1 H), 2.39 (dd, *J* = 14.1, 6.8, 1 H), 2.20 (dd, *J* = 14.1, 6.4, 1 H), 1.72 (s, 3 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 1.24 (t, *J* = 5.6, 1 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.8, 126.2, 109.1, 74.5, 69.4, 59.4, 43.7, 27.1, 25.8, 17.0. **IR** (thin film): $\tilde{\nu}$= 3417, 2962, 2902, 1448, 1376, 1241, 1029 cm^{-1}. **HRMS** (ESI): calcd for $C_{10}H_{18}NaO_3$ [$(M+Na)^+$]: 209.1148; found: 209.1154. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +2.04° (c = 0.50 in $CHCl_3$).

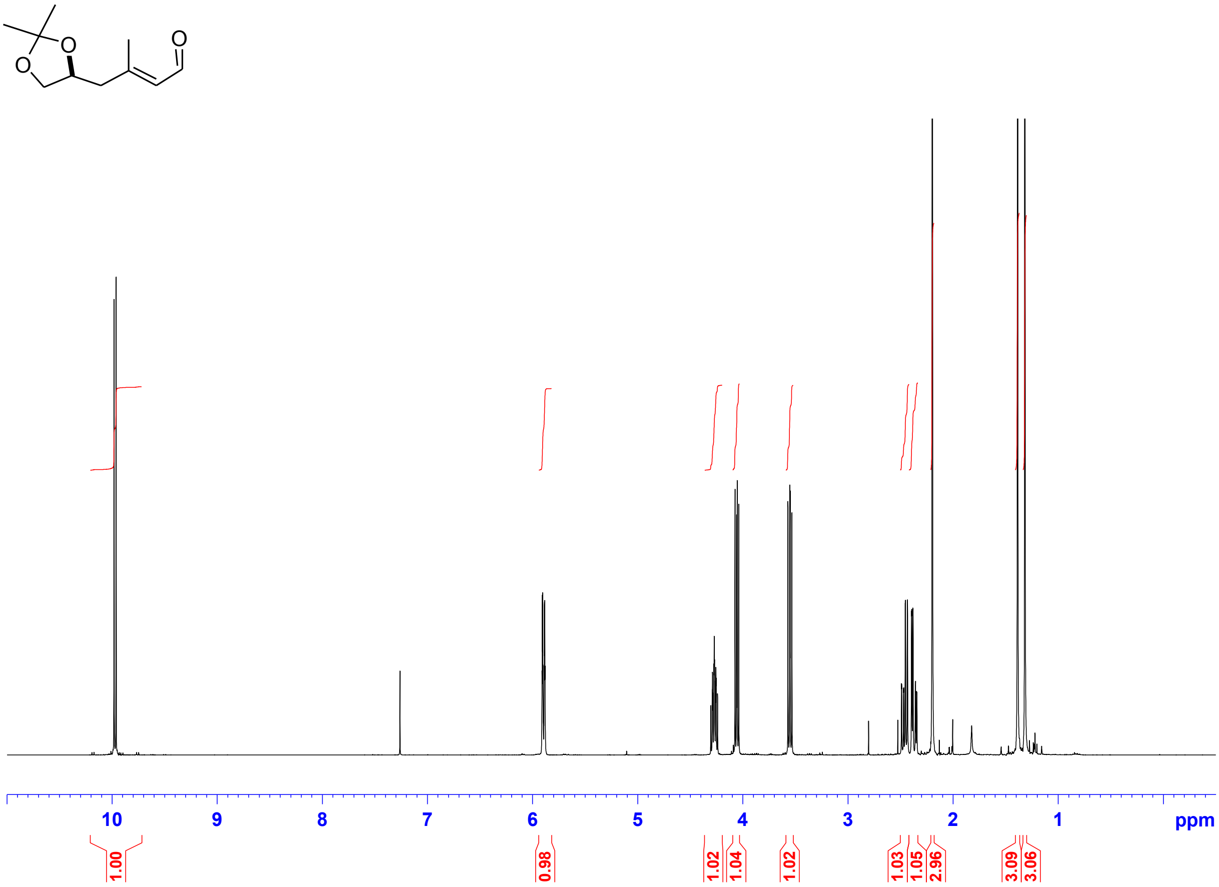






(*S*,*E*)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methylbut-2-enal (150). To a three-necked, flame-dried flask, charged with a magnetic stirring bar and an argon in-outlet, was added oxalyl chloride (3.2 mL, 37.2 mmol, 1.2 equiv) in dry CH_2Cl_2 (120 mL) then cooled to –78 °C. Dry DMSO (5.5 mL, 77.53 mmol, 2.5 equiv) was added dropwise giving a clear solution under effeverscence (which ceased after few seconds). After 20 min, a solution of the alcohol **149** (5.77 g, 31.01 mmol, 1 equiv) in dry CH_2Cl_2 (25 mL, flask rinsed with 1x5 mL of CH_2Cl_2) was added dropwise giving an off-white suspension. The suspension was stirred for 30 min at –78 °C then NEt_3 (15 mL, 108 mmol, 3.5 equiv) was slowly added. After 10 min, the thick suspension formed was allowed to warm to room temperature and stirring was continued for a total of 30 min. Saturated aqueous NH_4Cl (50 mL) was added as well as H_2O (10 mL) then the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) then the combined organic phases were dried over $MgSO_4$. Purification using flash chromatography (EtOAc/Hex 2:3) afforded **150** (4.78 g, 25.92 mmol, 84%) as a yellow oil that does not smell of sulphur derivatives if drying at the Rotavap was continued for ca. 30-45 min.

TLC: R_f = 0.55 (EtOAc/Hex 1:1, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.97 (d, J = 7.9, 1 H), 5.91-5.87 (m, 1 H), 4.31-4.24 (m, 1 H), 4.06 (dd, J = 8.2, 6.0, 1 H), 3.55 (dd, J = 8.2, 6.7, 1 H), 2.46 (ddd, J = 14.5, 8.1, 0.9, 1 H), 2.37 (ddd, J = 14.5, 5.2, 0.9, 1 H), 2.20 (d, J = 1.3, 3 H), 1.39 (s, 3 H), 1.32 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 191.0, 159.4, 129.1, 109.6, 73.7, 69.2, 44.7, 27.0, 25.6, 18.1. **IR** (thin film): $\tilde{\nu}$ = 2987, 2937, 2883, 1716, 1693, 1644, 1436, 1372, 1249, 1214, 1110 cm^{-1}. **HRMS** (ESI): calcd for $C_{10}H_{16}NaO_3$ [$(M+Na)^+$]: 207.0992; found: 207.0984. $[\alpha]_D^{24}$: –26.08° (c = 2.19 in $CHCl_3$).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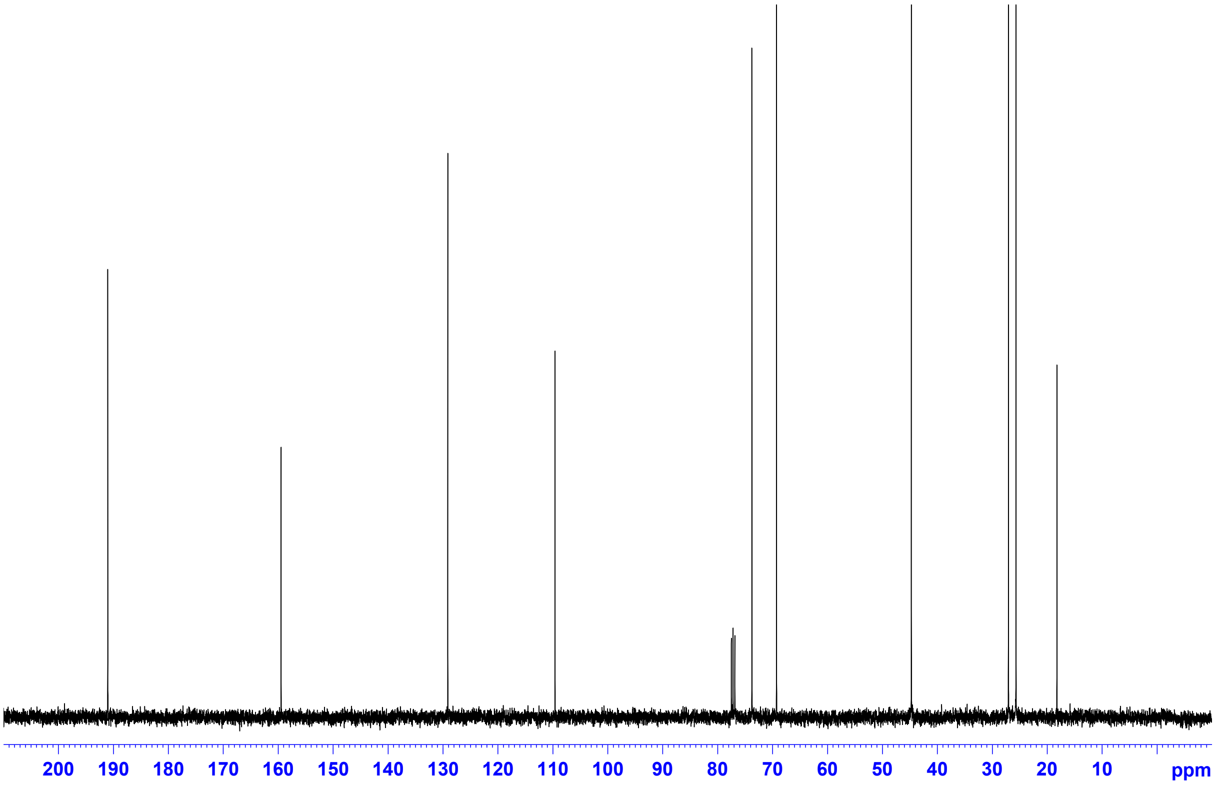
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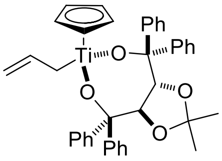
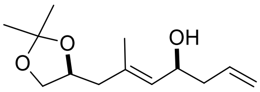


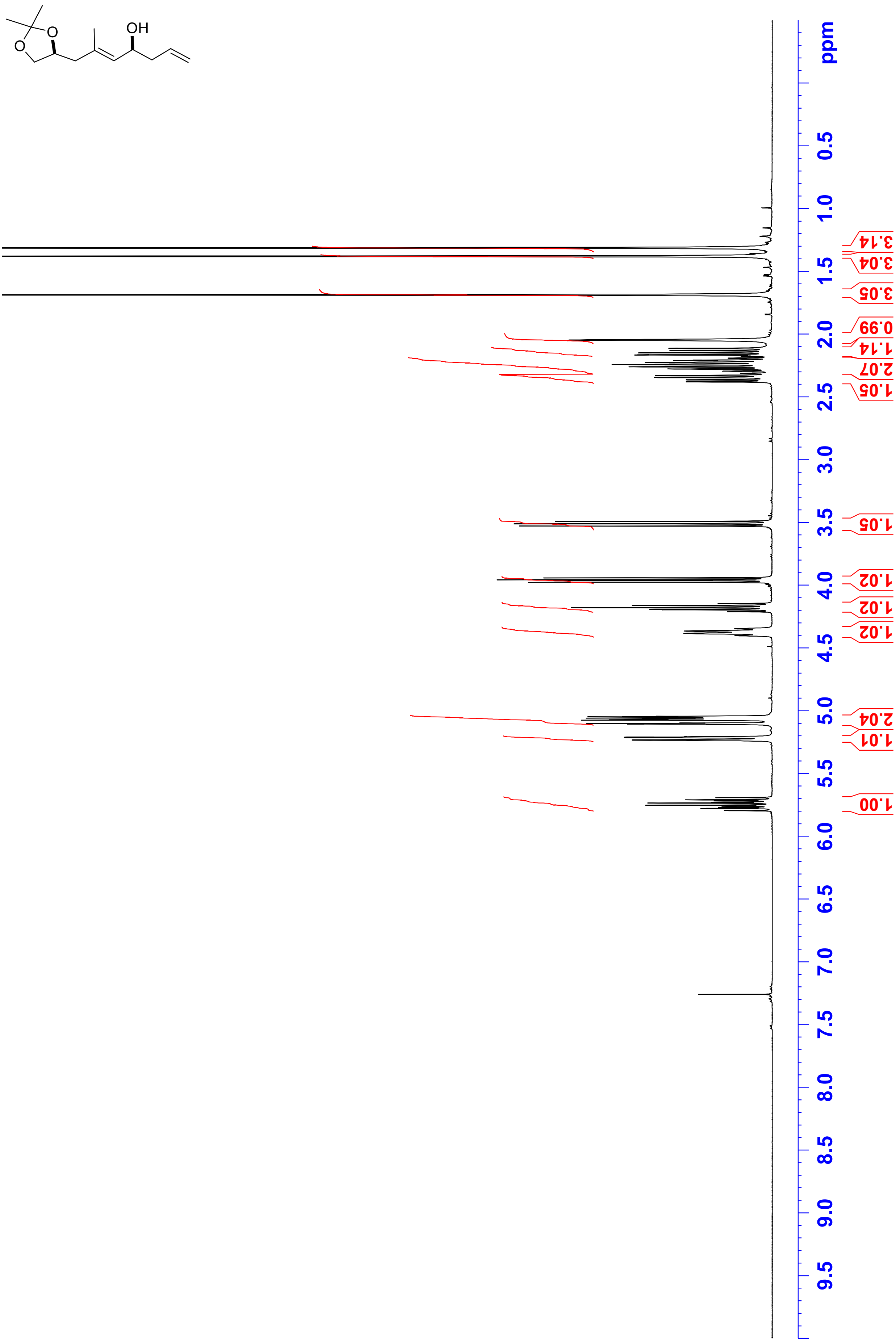
Synthesis of chiral auxiliary: (–)-(*R*,*R*)-Taddol-CpTiCl (151).[220] To a one-necked flame-dried flask, charged with a magnetic stirring bar, an argon in-outlet and a soxhlet extractor (equipped with 6 g MgO which was dried over 2.5 h at ca. 33 mbar/400 °C via heatgun which was applied ca. all 15 min) was added $CpTiCl_3$ (2.40 g, 10.92 mmol, 1 equiv, commercially available and used without further purification) to dry cyclohexane (120 mL) followed by addition of (–)-(*R*,*R*)-Taddol (5.10 g, 10.92 mmol, 1 equiv) then a heating bath was applied (140 °C bath temperature). The heating bath was removed after 30 h then the solvent was removed under reduced pressure and the yellow-brown fluffy residue was kept under argon, stored in the freezer and used without further purification.



(*S*,*E*)-7-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-methylhepta-1,5-dien-4-ol (152). To a three-necked flame-dried flask, charged with a magnetic stirring bar and an argon in-outlet was added allylmagnesium bromide (0.95M in THF, 8.9 mL, 8.46 mmol, 1.4 equiv) over ca. 10 min to a solution of **151** (5.56 g, 9.06 mmol, 1.5 equiv) in Et_2O (100 mL) at 0 °C (icebath) resulting first in an orange solution with tiny precipitates which then turned into a dark mixture. After having stirred for 1.25 h, the suspension formed was cooled to –78 °C which resulted in the formation of a more turbid suspension. This was followed by addition of a solution of **150** (1.11 g, 6.04 mmol, 1 equiv) in Et_2O (15 mL) (flask rinsed with 5 mL of Et_2O) so that the interior temperature stayed lower than –71 °C. A change in color to a bright tan mixture was observed immediately with more precipitates during the addition; those precipitates persisted after the addition was completed. The cooling bath was removed after 15 min then a solution of aqueous NH_4F (60 mL, 45% (g/v)) was added. Stirring was continued at room temperature over night for 14 h giving an almost colorless mixture. Filtration over celite, washing with Et_2O (1 x 60 mL), separation of phases and extraction of the aqueous phase with Et_2O (2 x 50 mL) followed by drying of the combined organic phases over $MgSO_4$ and purification by flash chromatography (EtOAc/Hex 1:3□1:1, change of gradient when the product appears as judged by TLC analysis) afforded **152** (1.098 g, 4.85 mmol, 80%) as a pale-orange oil.

Note: Only one isomer is present as judged by NMR after isolation.

TLC: R_f = 0.20 (EtOAc/Hex 1:3, UV, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.80-5.69 (m, 1 H), 5.24-5.20 (m, 1 H), 5.11-5.04 (m, 2 H), 4.40-4.35 (m, 1 H), 4.21-4.15 (m, 1 H), 3.96 (dd, J = 8.1, 6.0, 1 H), 3.51 (dd, J = 8.1, 7.0, 1 H), 2.35 (dd, J = 13.7, 6.3, 1 H), 2.31-2.17 (m, 2 H), 2.14 (ddd, J = 7.1, 3.7, 0.8, 1 H), 2.05 (br. s, 1 H), 1.69 (d, J = 1.4, 3 H), 1.38 (s, 3 H), 1.31 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 134.6, 134.4, 130.1, 117.9, 109.1, 74.5, 69.3, 67.6, 43.9, 42.1, 27.1, 25.8, 17.2. **IR** (thin film): $\tilde{\nu}$ = 3422, 2984, 2934, 1670, 1643, 1440, 1379, 1370, 1249, 1215, 1156, 1062, 1045, 996 cm^{-1}. **HRMS** (ESI): calcd for $C_{13}H_{22}NaO_3$ [$(M+Na)^+$]: 249.1461; found: 249.1458. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$= –12.55° (c = 1.55 in $CHCl_3$).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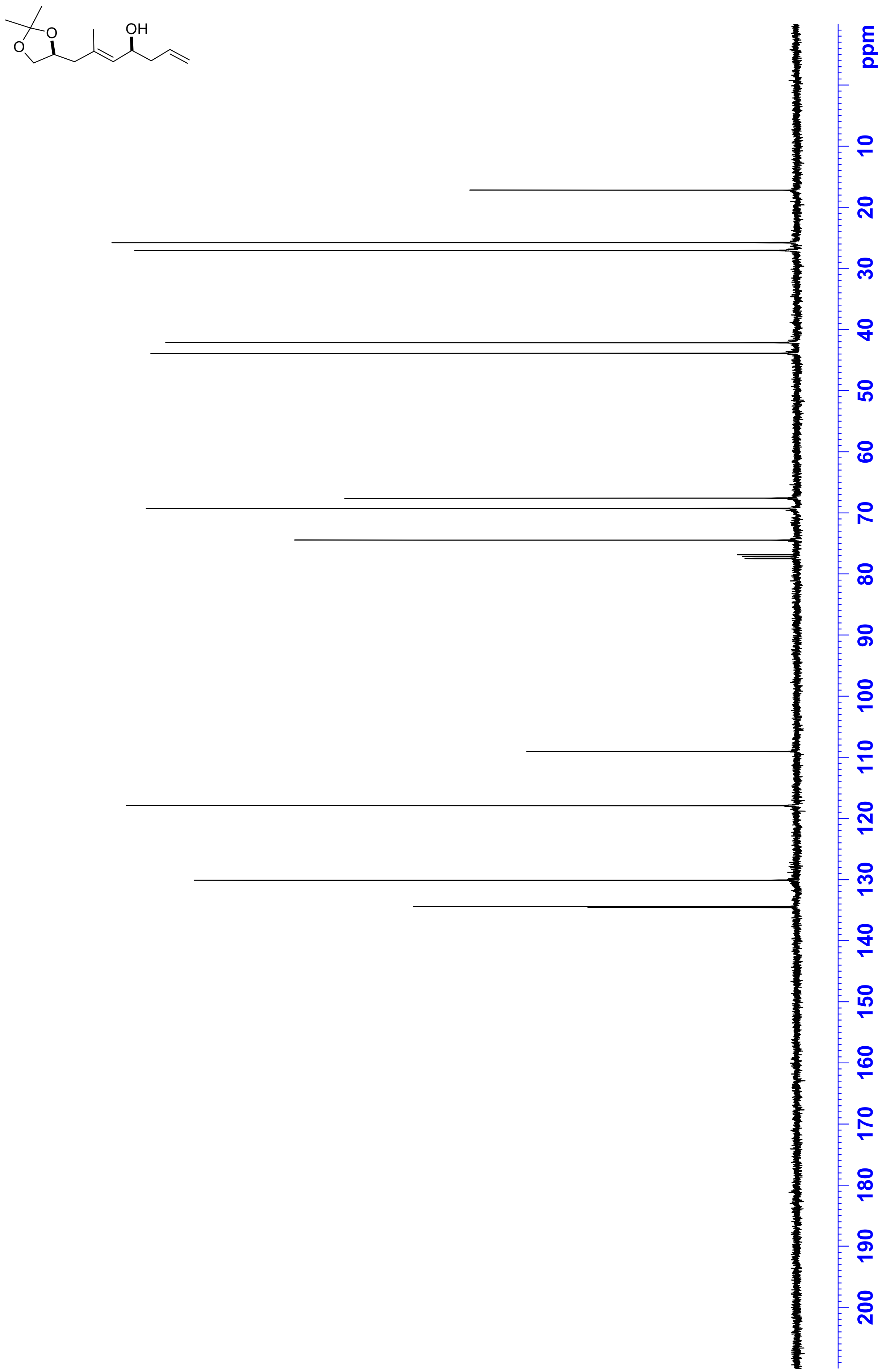
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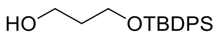
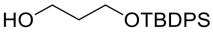


3-(*tert*-Butyldiphenylsilyloxy)propan-1-ol (153). To a solution of propane-1,3-diol (3.0 mL, 41.7 mmol, 1.0 equiv) in THF (75 mL) at –78 °C was added *n*-BuLi (1.6M in hexane, 26.3 mL, 42.1 mmol, 1.0 equiv) followed by TBDPSCl (11.6 g, 42.1 mmol, 1.01 equiv). After stirring for 15 min at –78 °C, the mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 15 h, heated to 60 °C for 4 h and then stirred at room temperature for additional 16 h. EtOAc (100 mL) and H_2O (100 mL) were then added then the phases were separated and the aqueous phase was extracted with EtOAc (3 x 75 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (EtOAc/Hex 1:3) afforded **153** (12.8 g, 40.5 mmol, 97%) as a colorless oil which became solid upon standing.

TLC: R_f = 0.45 (EtOAc/Hex 1:3, UV, $KMnO_4$). **Mp**: 42-43 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.70-7.68 (m, 4 H), 7.47-7.38 (m, 6 H), 3.87-3.84 (m, 4 H), 2.38 (br. s, 1 H), 1.84-1.79 (m, 2 H), 1.07 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.7, 133.4, 129.9, 127.9, 63.4, 62.1, 34.4, 27.0, 19.2. **IR** (thin film): $\tilde{\nu}$ = 3369, 3071, 3049, 2930, 2857, 1472, 1427, 1107, 1086, 965, 822 cm^{-1}. **HRMS** (EI): calcd for $C_{15}H_{17}O_2Si$ [$(M–C_4H_9)^+$]: 257.0993; found: 259.0993.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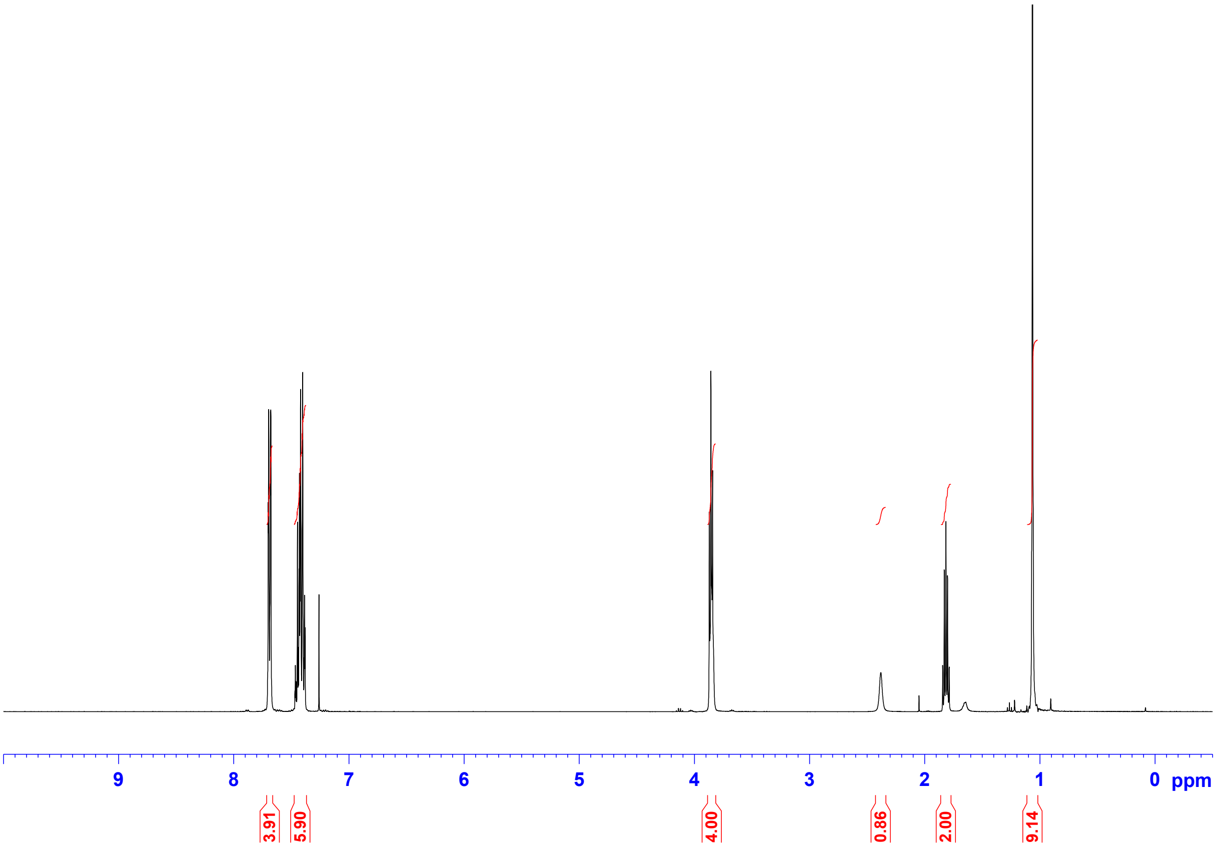
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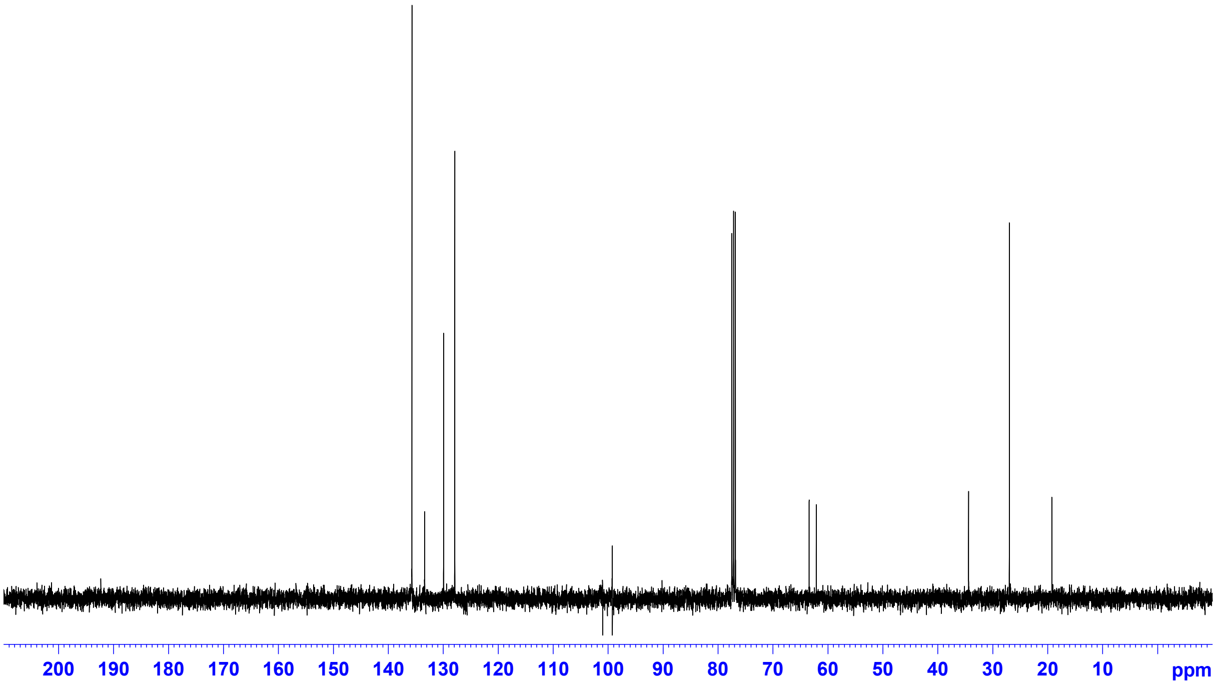
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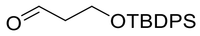
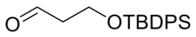


3-(*tert*-Butyldiphenylsilyloxy)propanal (117). To a three-necked flame-dried flask, charged with a magnetic stirring bar and an argon in-outlet, was added oxalyl chloride (0.98 mL, 11.62 mmol, 1.2 equiv) in dry CH_2Cl_2 (40 mL) which was then cooled to –78 °C. DMSO (1.72 mL, 24.2 mmol, 2.5 equiv) was added dropwise giving a clear solution under effeverscence (which ceased after few seconds). After 30 min, a solution of the **153** (3.05 g, 9.68 mmol, 1.0 equiv) in dry CH_2Cl_2 (15 mL) was added (flask rinsed with 5 mL of CH_2Cl_2) dropwise giving an off-white suspension. The suspension was stirred for 30 min at –78 °C then NEt_3 (6 mL, 43.6 mmol, 4.5 equiv) was added slowly. After 10 min more, the suspension was allowed to warm to room temperature and stirring was continued for a total of 60 min. Saturated aqueous NH_4Cl (15 mL) was added then the phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were washed once with H_2O (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:5) afforded **117** (2.82 g, 9.02 mmol, 93%) as a pale-yellow oil after drying at high vacuum.

TLC: R_f = 0.52 (EtOAc/Hex 1:3, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.83 (t, *J* = 2.2, 1 H), 7.69-7.66 (m, 4 H), 7.47-7.38 (m, 6 H), 4.04 (t, *J* = 2 H), 2.61 (dt, *J* = 6.0, 2.2, 2 H), 1.05 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 202.0, 135.7, 133.4, 130.0, 127.9, 58.4, 46.5, 26.9, 19.3. **IR** (thin film): $\tilde{\nu}$ = 3072, 3015, 2998, 2857, 1727, 1472, 190, 1106, 823 cm^{-1}. **HRMS** (EI): calcd for $C_{15}H_{15}O_2Si$ [$(M–C_4H_9)^+$]: 255.0836; found: 255.0836.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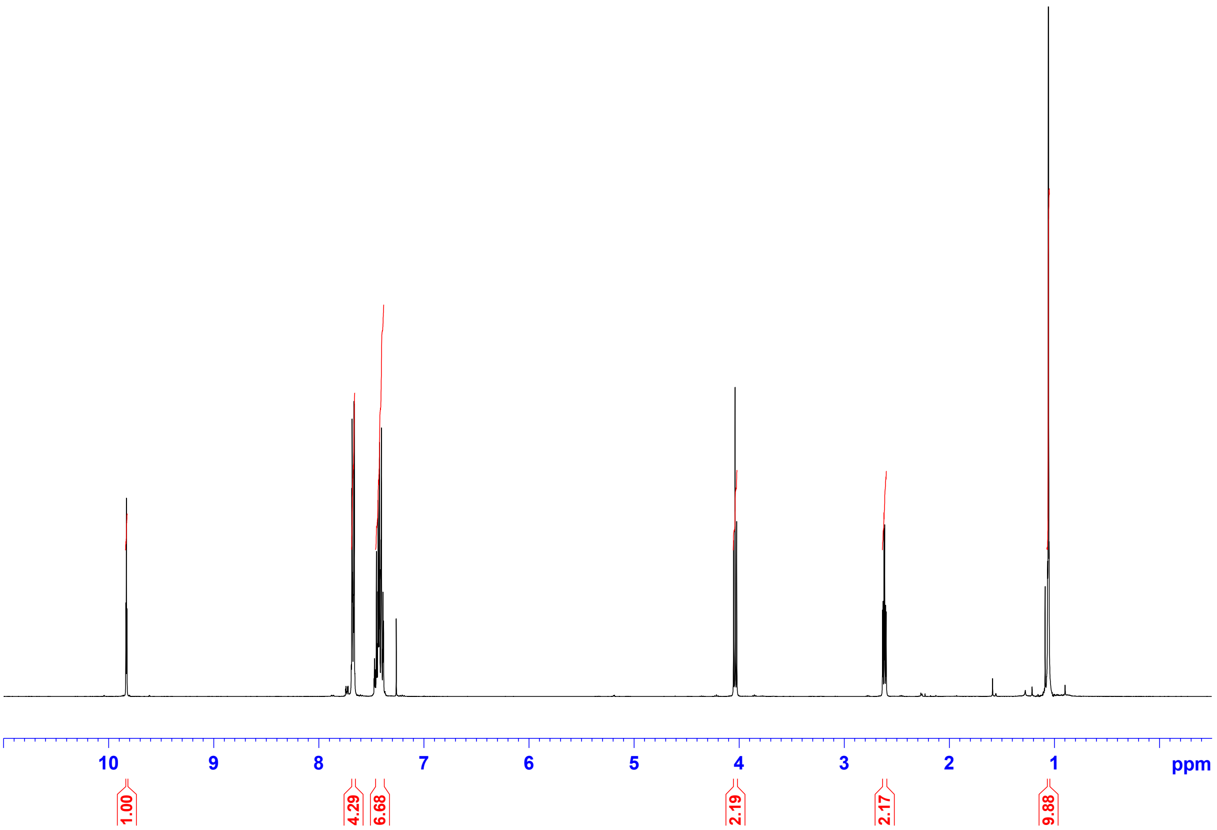
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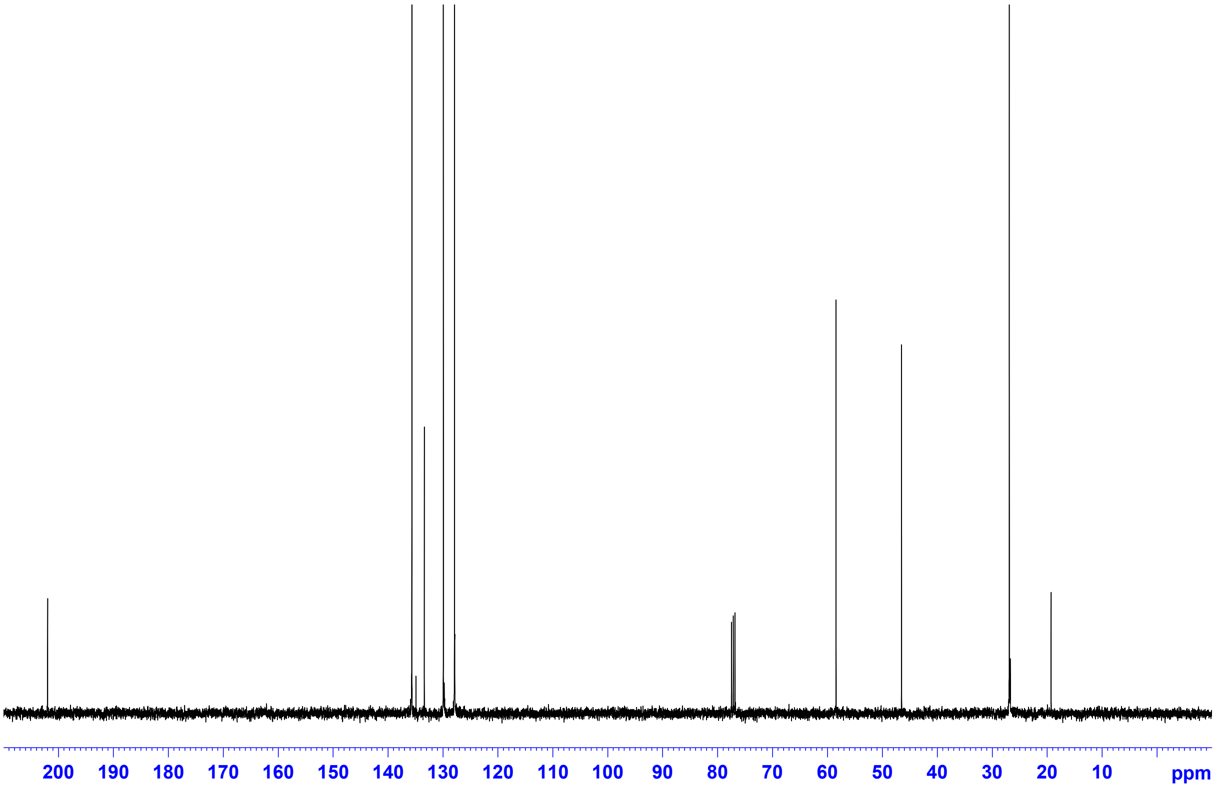
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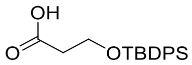
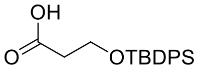


3-(*tert*-Butyldiphenylsilyloxy)propanoic acid (154). To a two-necked flask, charged with a magnetic stirring bar, was added **117** (2.82 g, 9.02 mmol, 1 equiv) and *t*-BuOH (150 mL). A solution of $NaClO_2$ (8.15 g, 90.2 mmol, 10.0 equiv) and $NaH_2PO_4 \bullet H_2O$ (8.70 g, 63.14 mmol, 7.0 equiv) in H_2O (60 mL) was added slowly using an addition funnel (added over ca. 5 min) at room temperature giving a yellow reaction mixture under slight exothermicity and the formation of a yellow gas. In order to remove the yellow gases (most probably Cl_2O and Cl_2) partially, a washing flask containg saturated aqueous $NaHCO_3$ was linked to the flask then N_2 was bubbled through the solution for 15 min. The crude was diluted with H_2O (200 mL) then Et_2O (100 mL) was added and the phases were separated. The aqueous phase was acidified to pH 4 using aqueous HCl (2N) (ca. 8 mL) and extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over $MgSO_4$, concentrated giving a colorless oil and purified by flash chromatography (EtOAc/Hex 1:3, 1% MeOH) giving **154** (2.4 g, 7.44 mmol, 82%) as a colorless oil that changed to a white crystalline solid upon longer storage.

TLC: R_f = 0.43 (EtOAc/Hex 1:3, 1% MeOH, UV, $KMnO_4$). **Mp**: 96.1-98.0 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 10.65 (br. s, 1 H), 7.71-7.68 (m, 4 H), 7.47-7.38 (m, 6 H), 3.98 (t, J = 6.5, 2 H), 2.63 (t, J = 6.3, 2 H), 1.07 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): □ = 177.9, 135.7, 133.4, 129.9, 127.9, 59.7, 37.7, 26.9, 19.3. **IR** (thin film): $\tilde{\nu}$ = 3050, 2886, 1713, 1427, 1104, 940 cm^{-1}. **HRMS** (EI): calcd for $C_{15}H_{15}O_3Si$ $[(M–C_4H_9)^+]$: 271.0785; found: 271.0785.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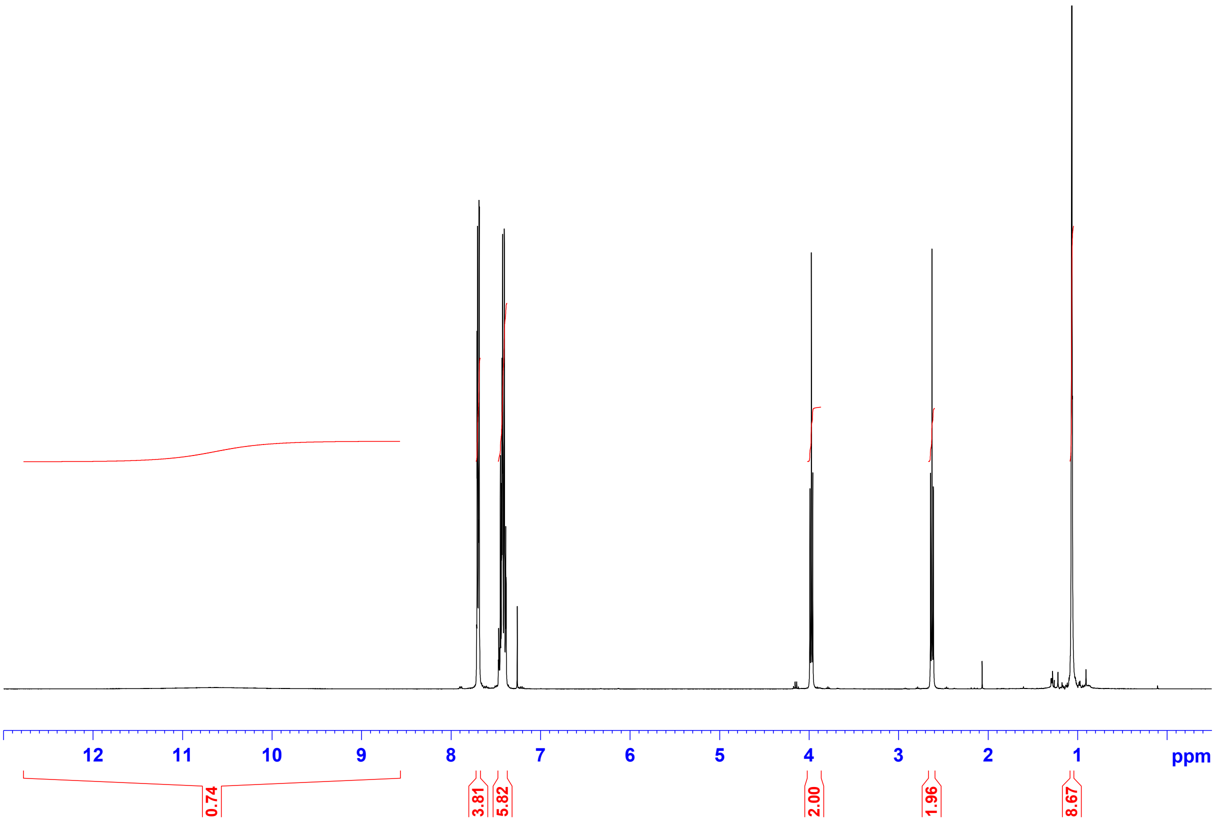
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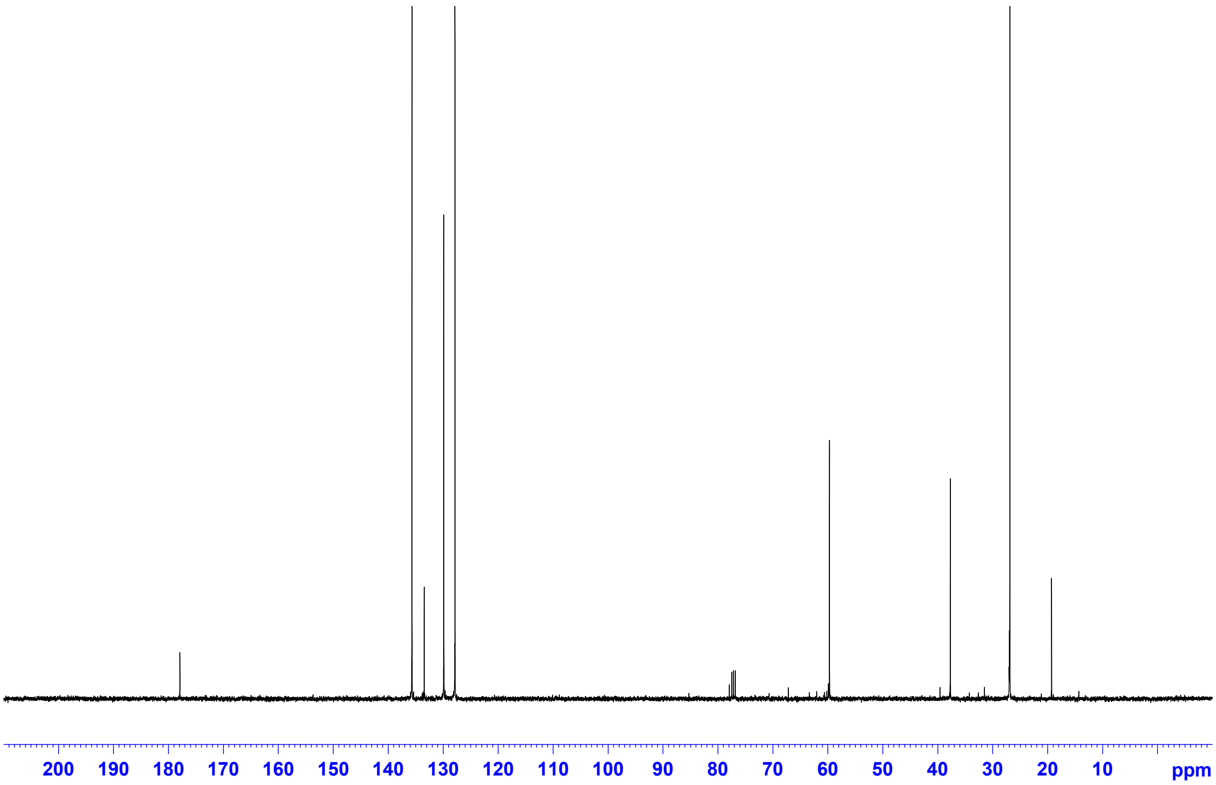
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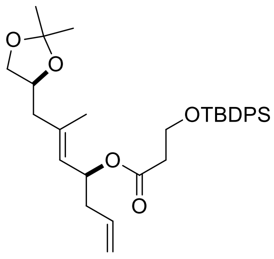
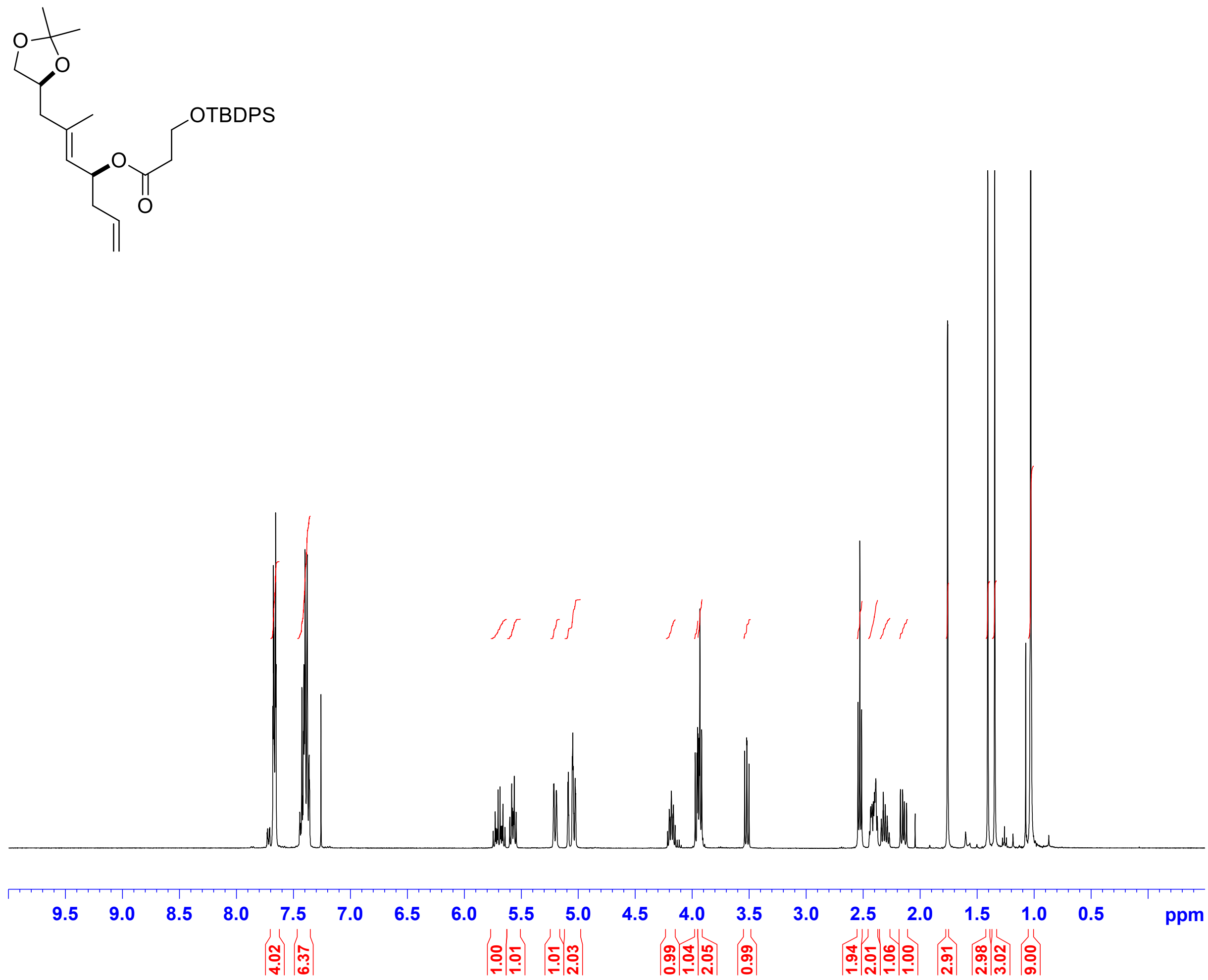


(*S*,*E*)-7-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-methylhepta-1,5-dien-4-yl 3-((*tert*-butyldiphenylsilyl)oxy)propanoate (155). To a solution of **154** (2.18 g, 6.63 mmol, 1.15 equiv) and **152** (1.31 g, 5.76 mmol, 1 equiv) in dry CH_2Cl_2 (40 mL) at 0 °C was added DMAP (0.70 g, 5.76 mmol, 1 equiv) followed by EDCI (1.58 g, 7.66 mmol, 1.3 equiv; weight in under argon). The cooling was removed after 15 min and stirring was continued at room temperature for 17 h in total then saturated aqueous NH_4Cl (20 mL) was added followed by CH_2Cl_2 (20 mL) then the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over $MgSO_4$ and purified using flash chromatography (EtOAc/Hex 1:25→1:10→1:5), which afforded **155** (2.89 g, 5.39 mmol, 94%) as a colorless, viscous oil.

TLC: R_f = 0.28 (EtOAc/Hex 1:10, UV, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68-7.65 (m, 4 H), 7.45-7.36 (m, 6 H), 5.69 (ddt, J = 17.5, 10.2, 7.0, 1 H), 5.57 (dt, J = 9.0, 6.6, 1 H), 5.23-5.19 (m, 1 H), 5.10-5.02 (m, 2 H), 4.22-4.15 (m, 1 H), 3.96 (dd, J = 8.1, 6.0, 1 H), 3.93 (t, J = 6.5, 2 H), 3.52 (dd, J = 8.1, 7.2, 1 H), 2.53 (t, J = 6.3, 2 H), 2.45-2.38 (m, 2 H), 2.34-2.27 (m, 1 H), 2.15 (dd, J = 13.8, 7.9, 1 H), 1.76 (d, J = 1.2, 3 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.03 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 171.1, 137.0, 135.7, 133.7, 133.3, 129.8, 127.8, 125.8, 118.0, 109.1, 74.7, 70.4, 69.3, 60.1, 43.9, 39.5, 38.3, 27.1, 26.9, 25.9, 19.3, 17.7. **IR** (thin film): $\tilde{\nu}$ = 3072, 2931, 2858, 1733, 1472, 1379, 1254, 1179, 1107, 1061, 859 cm^{-1}. **HRMS** (ESI): calcd for $C_{32}H_{48}NO_5Si$ [$(M+NH_4)^+$]: 554.3296; found: 554.3293. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –2.33° (c = 1.23 in $CHCl_3$).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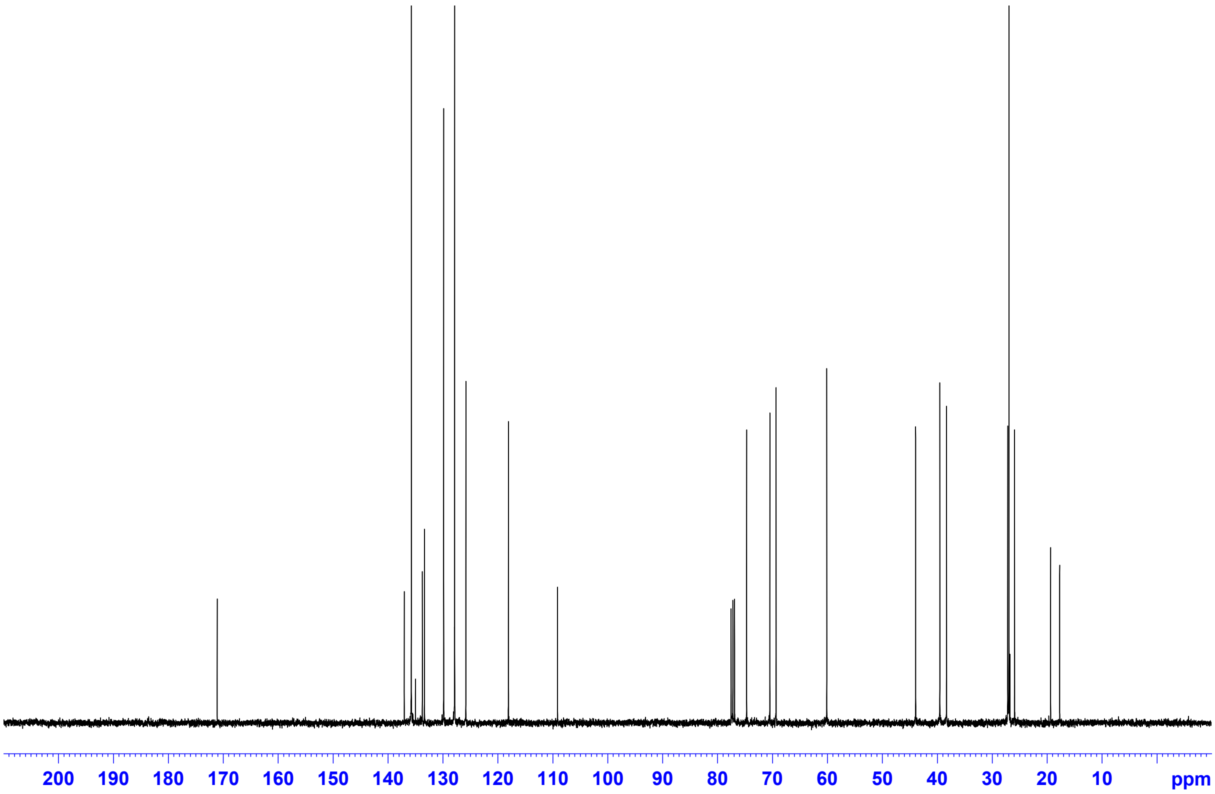
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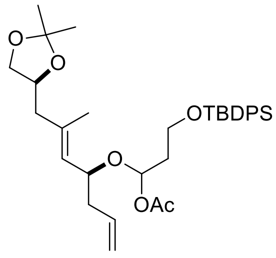
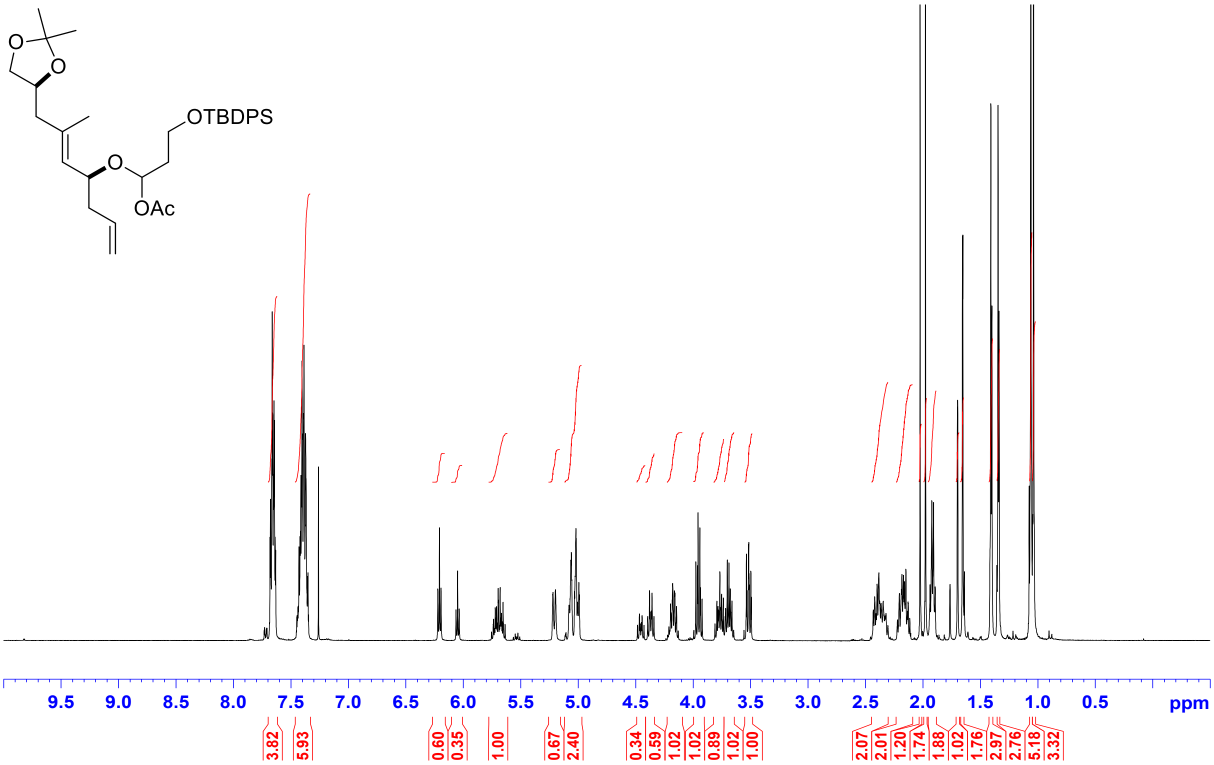
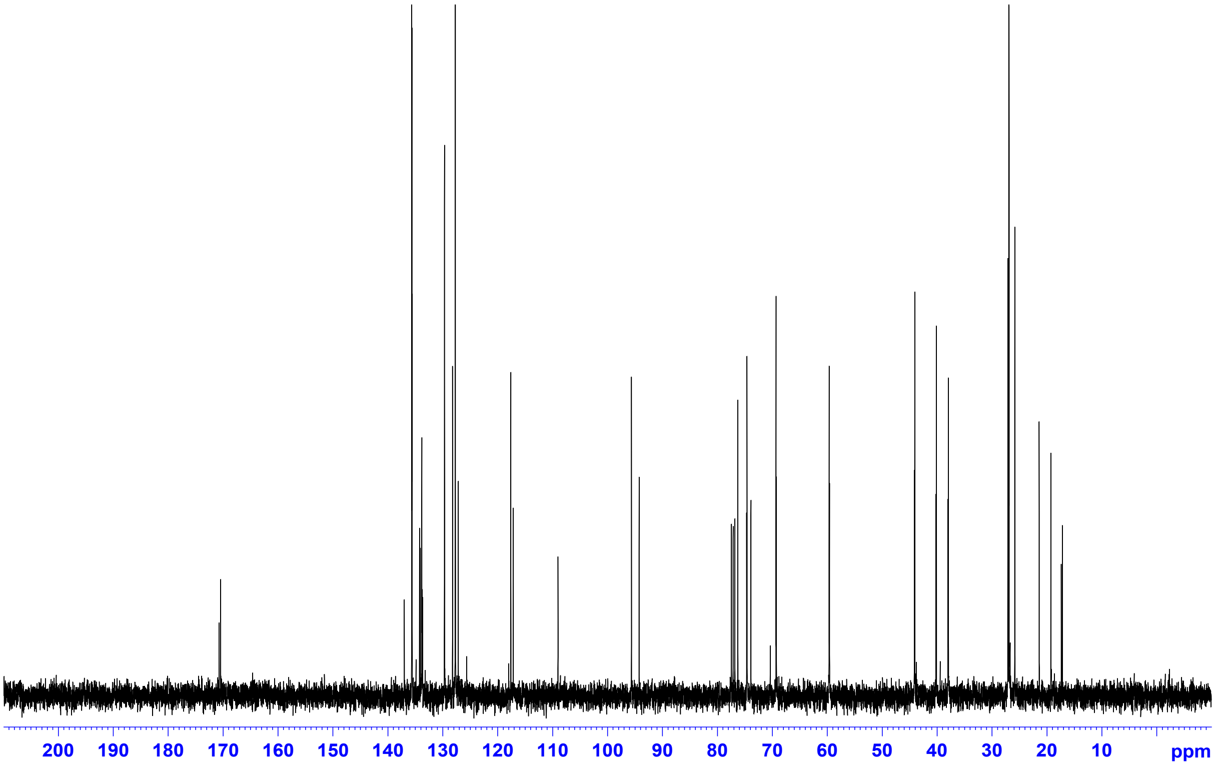
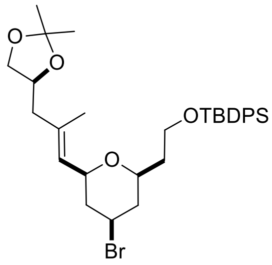


3-((*tert*-Butyldiphenylsilyl)oxy)-1-(((*S*,*E*)-7-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-methylhepta-1,5-dien-4-yl)oxy)propyl acetate (156). To a solution of **155** (1.35 g, 2.52 mmol, 1.00 equiv) in dry CH_2Cl_2 (30 mL) at –78 °C was added slowly DIBAL-H (1M in toluene, 5.04 mL, 5.04 mmol, 2.00 equiv); after 30 min, pyridine (0.61 mL, 7.56 mmol, 3.00 equiv), DMAP (920 mg, 7.56 mmol, 3.00 equiv) and Ac_2O (1.42 mL, 15.1 mmol, 6.00 equiv) were added seqentially at –78 °C and the mixture was stirred at that temperature for 22 h. Saturated aqueous NH_4Cl (20 mL) and saturated aqueous Rochelle salt (20 mL) were added at –78 °C and the mixture was allowed to warm to room temperature. Vigorous stirring was continued for 2 h in a beaker, resulting in the formation of two clear phases that were readily separable. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (1 x 10 mL), and then dried over $MgSO_4$. Concentration of the solution under reduced pressure and purification of the residue by flash chromatography on a deactivated stationary silica phase (EtOAc/Hex 1:10, 2% NEt_3 (v/v)) afforded **156** (1.336 g, 2.30 mmol, 91%) in a 1.7:1 mixture of diastereomers as a colorless, viscous oil. Spectroscopic data are reported for the diastereomeric mixture.

TLC: R_f = 0.78 and 0.74 (EtOAc/Hex 1:3, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68-7.63 (m, 4 H), 7.45-7.35 (m, 6 H), 6.21 (t, *J* = 5.7, 0.6 H), 6.05 (t, *J* = 5.7, 0.35 H), 5.75-5.64 (m, 1 H), 5.23-5.19 (m, 0.67 H), 5.11-4.98 (m, 2.4 H), 4.45 (dt, *J* = 9.2, 6.6, 0.34 H), 4.37 (dt, *J* = 8.8, 6.5, 0.59 H), 4.24-4.13 (m, 1 H), 3.95 (dt, *J* = 8.1, 5.8, 1 H), 3.81-3.74 (m, 1 H), 3.72-3.65 (m, 1 H), 3.55-3.49 (m, 1 H), 2.43-2.31(m, 2 H), 2.22-2.10 (m, 2 H), 2.03 (s, 1.20 H), 1.98 (s, 1.74 H), 1.95-1.89 (m, 2 H), 1.69 (d, *J* = 1.2, 1 H), 1.65 (d, *J* = 1.2, 1.76 H), 1.42-1.40 (m, 3 H), 1.35-1.33 (m, 3 H), 1.06 (s, 5.2 H), 1.04 (s, 3.3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 170.7, 170.4, 137.0, 135.7, 135.7, 135.6, 135.6, 134.3, 134.1, 133.9, 133.8, 133.8, 133.7, 129.7, 129.7, 128.3, 127.8, 127.2, 117.6, 117.2, 109.0, 109.0, 95.6, 94.2, 76.3, 74.7, 74.6, 73.9, 69.3, 69.3, 59.7, 59.6, 44.1, 44.0, 40.2, 40.1, 38.0, 37.9, 27.1, 27.1, 26.9, 26.9, 26.9, 25.8, 25.8, 21.4, 21.4, 19.3. **IR** (thin film): $\tilde{\nu}$ = 2984, 2932, 2858, 1736, 1428, 1370, 1238, 1108, 1065, 1006, 924, 824, 701 cm^{-1}. **HRMS** (ESI): calcd for $C_{34}H_{48}NaO_6Si$ [(M+Na)$^+$]: 603.3112; found: 603.3126. $[\alpha]_D^{24}$: –12.88° (c = 0.78 in $CHCl_3$).



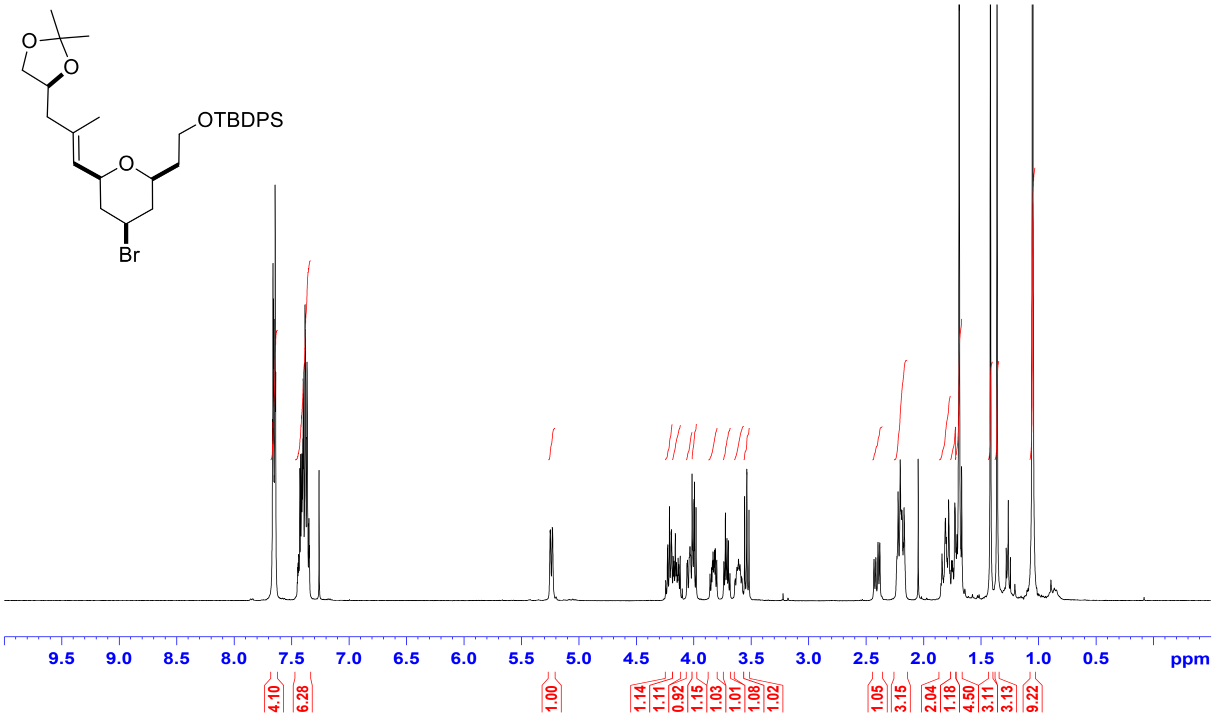


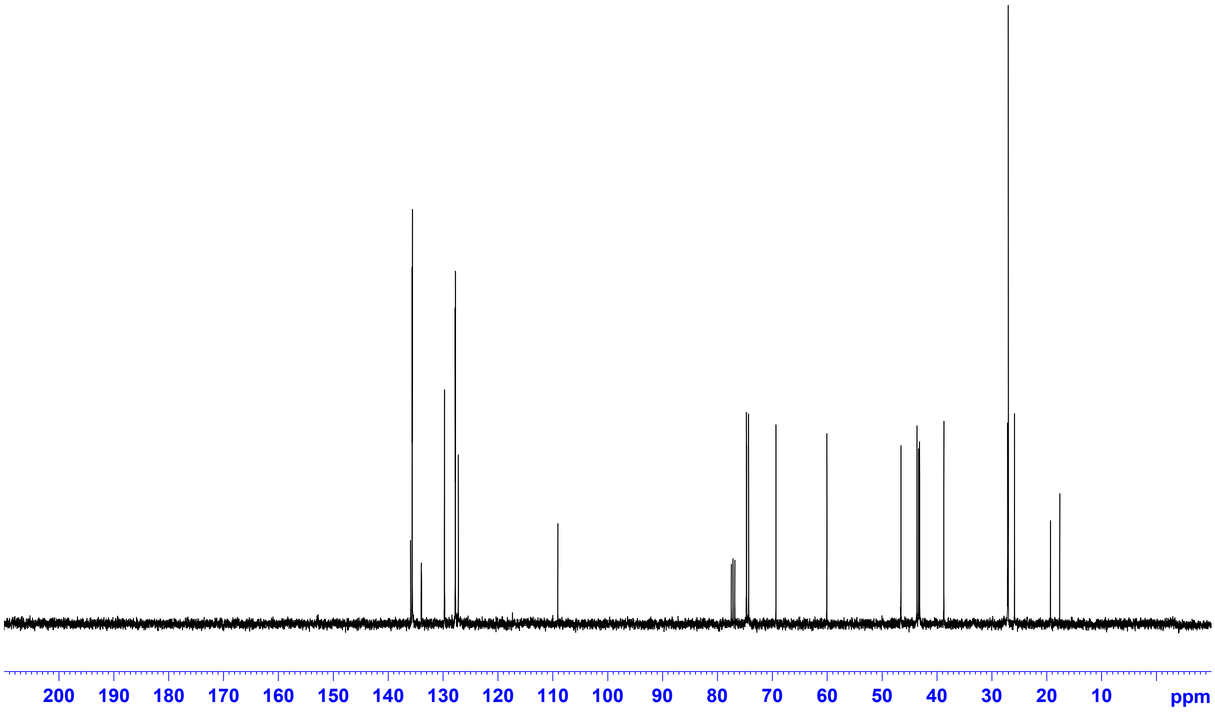


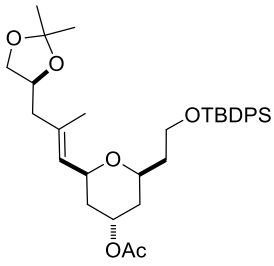
(2-((2*S*,4*R*,6*S*)-4-Bromo-6-((*E*)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methyl prop-1-en-1-yl)tetrahydro-2H-pyran-2-yl)ethoxy)(tert-butyl)diphenylsilane (157). To a solution of **156** (1.336 g, 2.30 mmol, 1 equiv) in dry CH_2Cl_2 (12 mL) at –78 °C was added dropwise a solution of $SnBr_4$ (3.03g, 6.9 mmol, 3 equiv; dissolved in 6 mL of dry CH_2Cl_2, 1.15M). The solution turned pale-yellow after few seconds. The cooling bath was removed after 90 min then H_2O (20 mL) was added and stirring was continued at room temperature for 30 min then saturated aqueous $NaHCO_3$ (20 mL) was added giving some effervescence. Stirring was continued for 30 min more leading to two separated phases. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give a colorless oil. Purification using flash chromatography (EtOAc/Hex 1:10→3:1) gave the acetonide-deprotected diol of **157** (859.6 mg, 1.53 mmol, 66%) as a colorless oil.

This diol (859.6 mg, 1.53 mmol) was dissolved in $Me_2C(OMe)_2$ (20 mL) at room temperature followed by addition of *p*-TsOH•H_2O (320 mg, 1.68 mmol, 1.1 equiv) giving a yellow solution. Saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (10 mL) were added after 20 min then the phases were separated and the aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic phases were dried over $MgSO_4$ concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:10) affording **157** (859.5 mg, 1.43 mmol, 62% over two steps) as a pale-yellow oil after drying.

TLC: R_f = 0.50 (EtOAc/Hex 1:5, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 4 H), 7.45-7.34 (m, 6 H), 5.25-5.22 (m, 1 H), 4.24-4.18 (m, 1 H), 4.18-4.12 (m, 1 H), 4.06-4.01 (m, 1 H), 4.00 (dd, *J* = 8.0, 5.9, 1 H), 3.83 (ddd, *J* = 10.3, 8.1, 5.0, 1 H), 3.71 (dt, *J* = 10.3, 5.5, 1 H), 3.64-3.58 (m, 1 H), 3.54 (dd, *J* = 8.0, 7.3, 1 H), 2.40 (dd, *J* = 13.9, 6.3, 1 H), 2.24-2.16 (m, 3 H), 1.85-1.76 (m, 2 H), 1.76-1.67 (m, 2 H), 1.69 (d, *J* = 1.1, 3 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.05 (s, 9 H). **^{13}C-NMR** (100 MHz, CDCl$_3$): δ = 135.9, 135.7, 135.6, 134.0, 133.9, 129.8, 129.7, 127.8, 127.7, 127.2, 109.1, 74.7, 74.7, 74.3, 69.3, 60.1, 46.6, 43.6, 43.3, 43.1, 38.7, 27.1, 27.0, 25.9, 19.4, 17.7. **IR** (thin film): $\tilde{\nu}$ = 2954, 2930, 2857, 1472, 1428, 1378, 1369, 1244, 1213, 1156, 1110, 1058, 999, 845, 822, 701 cm^{-1}. **HRMS** (ESI): calcd for $C_{32}H_{49}BrNO_4Si$ [(M+NH$_4$)$^+$]: 618.2609; found: 618.2607. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\boldsymbol{24}}$: –23.24° (c = 1.29 in CHCl$_3$).

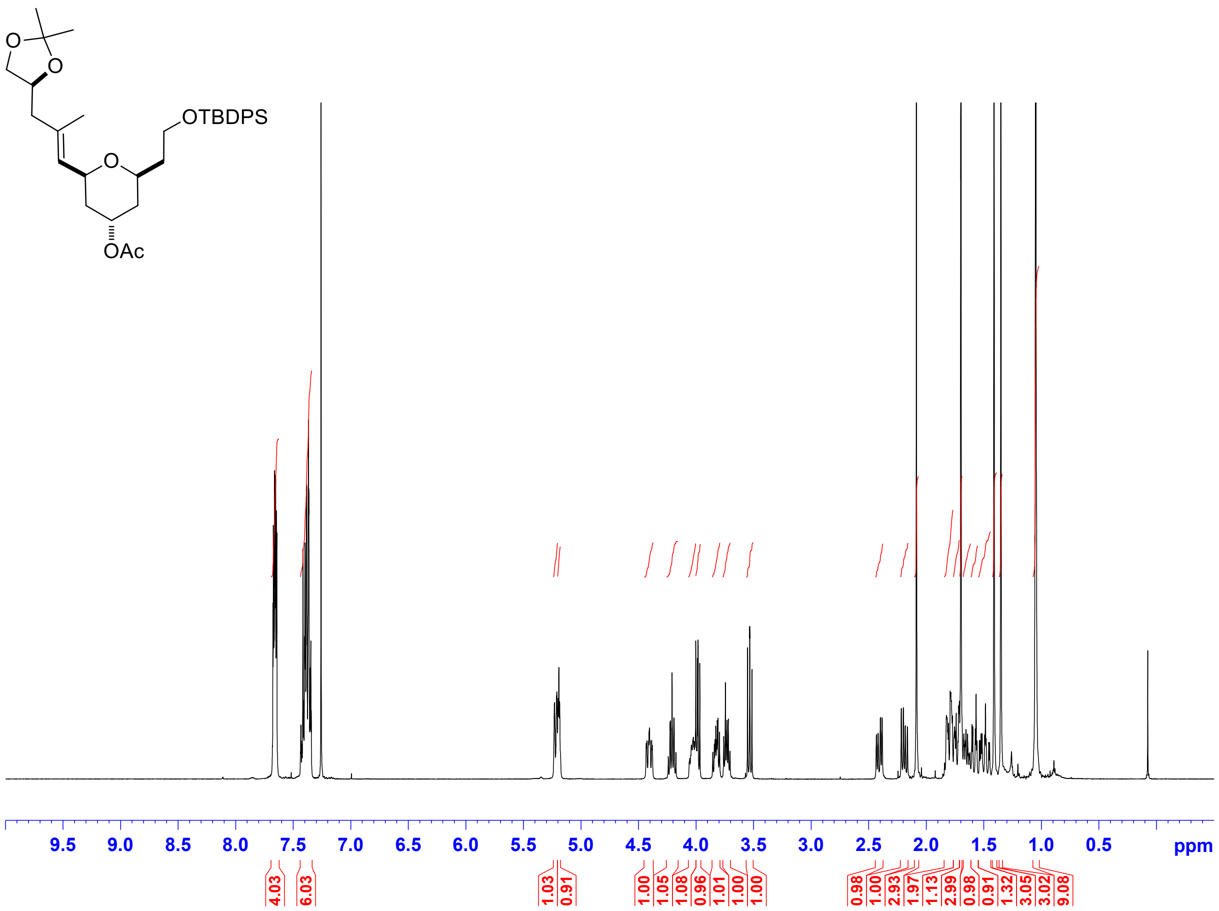






(2*S*,4*S*,6*S*)-2-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-6-((E)-3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylprop-1-en-1-yl)tetrahydro-2H-pyran-4-yl acetate (161). To a solution of **157** (859.5 mg, 1.43 mmol, 1 equiv) in dry toluene (10 mL) was added 18-c-6 (3.78 g, 14.3 mmol, 10 equiv) in dry toluene (5 mL) followed by CsOAc (2.74 g, 14.3 mmol, 10 equiv). The mixture was heated to 130 °C (bath temperature) and stirring was continued for 20 h, then the cooling bath was removed and the mixture was allowed to cool to room temperature then partitioned between H_2O (20 mL) and EtOAc (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 20mL), the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:5) giving **161** (734 mg, 1.26 mmol, 88%) as a colorless oil.

TLC: R_f = 0.17 (EtOAc/Hex 1:5, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 4 H), 7.44-7.34 (m, 6 H), 5.24-5.20 (m, 1 H), 5.19 (q, *J* = 2.9, 1 H), 4.41 (ddd, *J* = 11.5, 7.7, 2.1, 1 H), 4.21 (ddd, *J* = 13.2, 7.1, 6.2, 1 H), 4.06-3.99 (m, 1 H), 3.99 (dd, *J* = 8.1, 5.9, 1 H), 3.83 (ddd, *J* = 10.3, 7.9, 5.4, 1 H), 3.73 (dt, *J* = 10.2, 5.8, 1 H), 3.53 (dd, *J* = 8.0, 7.2, 1 H), 2.41 (dd, *J* = 13.9, 6.0, 1 H), 2.19 (dd, *J* = 13.9, 7.3, 1 H), 2.09 (s, 3 H), 1.84-1.76 (m, 2 H), 1.76-1.71 (m, 1 H), 1.70 (s, 3 H), 1.68-1.62 (m, 1 H), 1.61-1.55 (m, 1 H), 1.54-1.44 (m, 1 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.05 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 170.5, 135.9, 135.7, 135.6, 134.1, 134.0, 129.7, 129.7, 128.1, 127.7, 127.7, 109.0, 74.8, 69.5, 69.3, 69.1, 68.2, 60.3, 43.7, 38.9, 35.8, 35.4, 27.1, 26.9, 25.9, 21.4, 19.4, 17.7. **IR** (thin film): $\tilde{\nu}$ = 3075, 2931, 2857, 1737, 1472, 1428, 1369, 1237, 1215, 1109, 1088, 1049, 1016, 822, 701 cm^{-1}. **HRMS** (ESI): calcd for $C_{34}H_{52}NO_6Si$ [$(M+NH_4)^+$]: 598.3558; found: 598.3561. $[\alpha]_D^{24}$: +4.03° (c = 2.06 in $CHCl_3$).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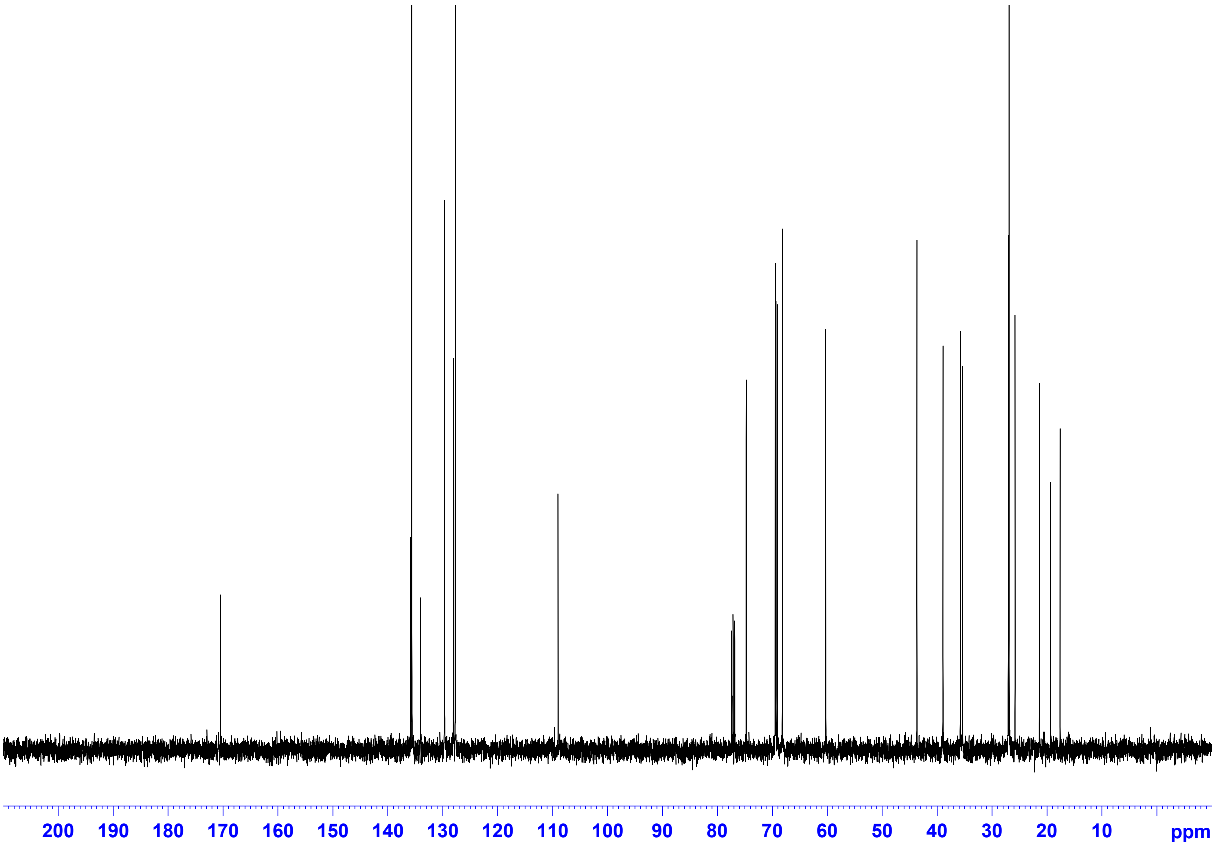
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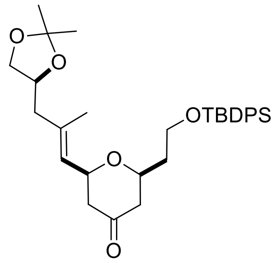
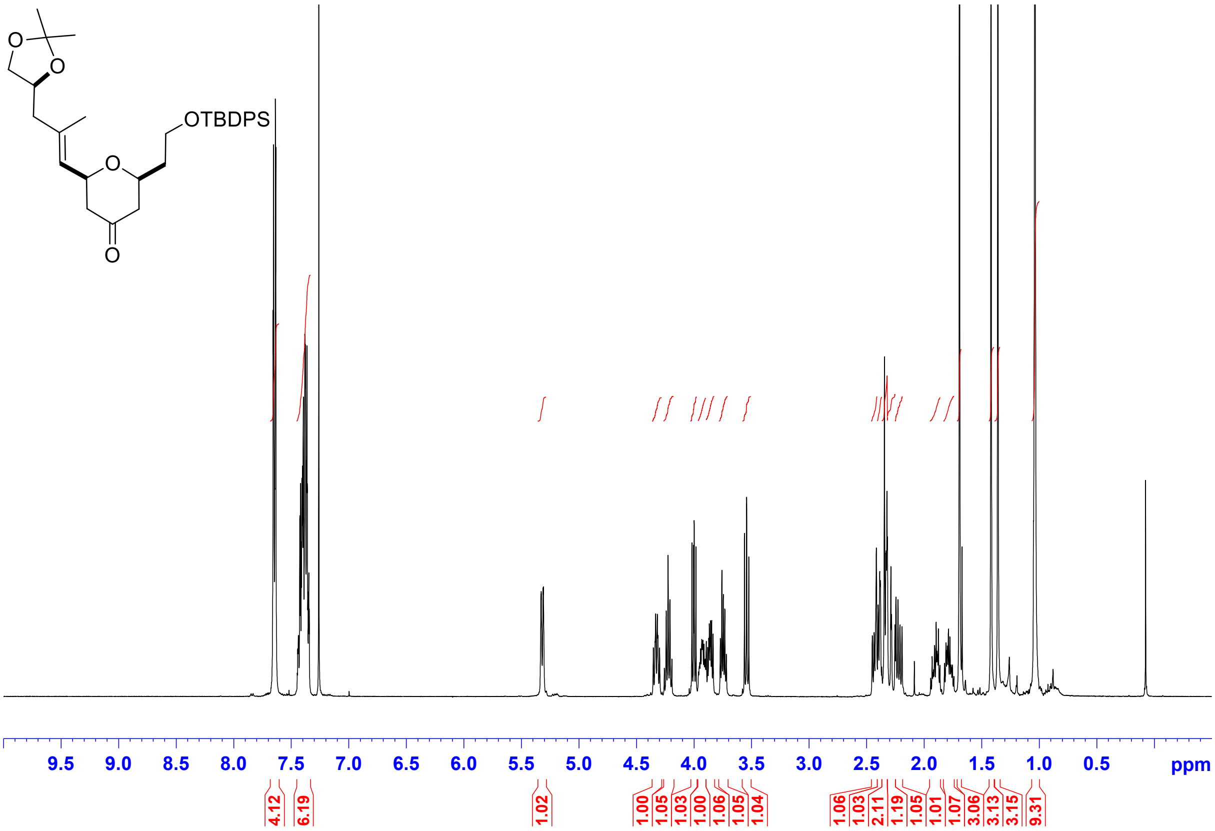
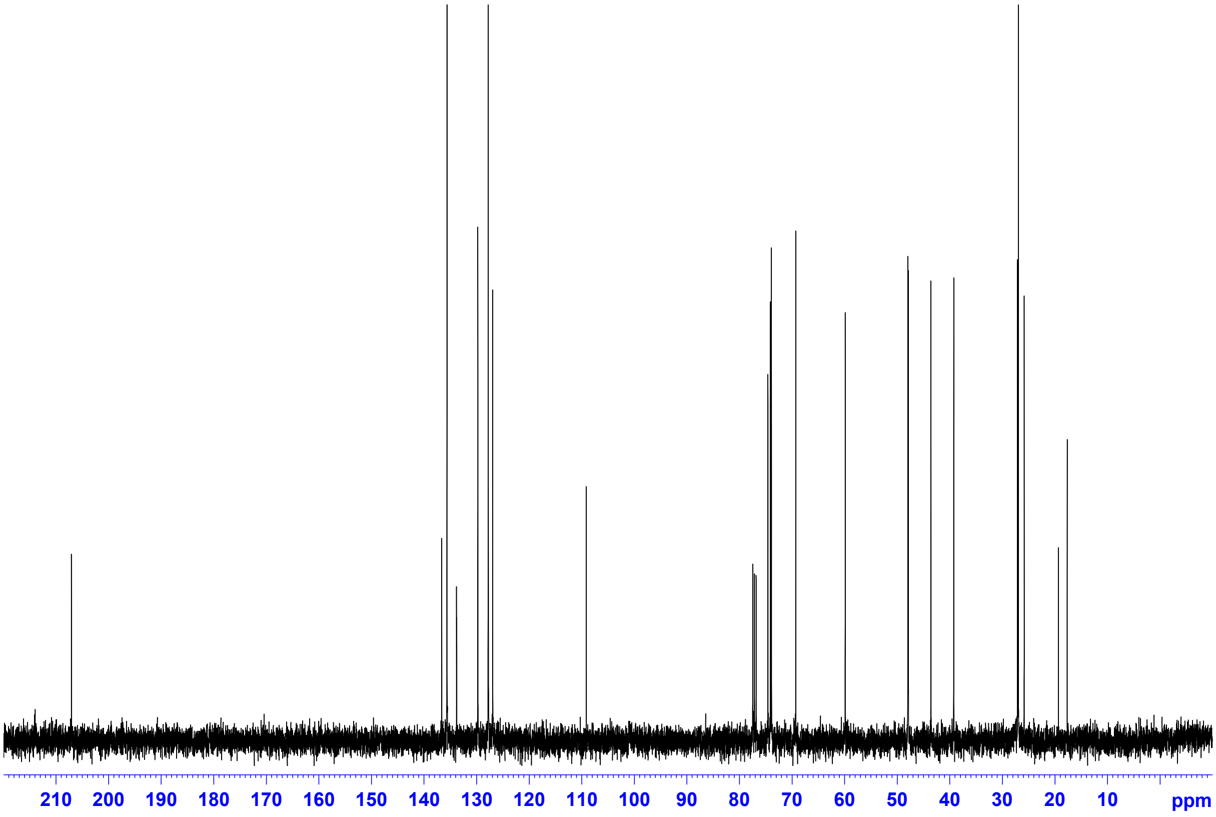


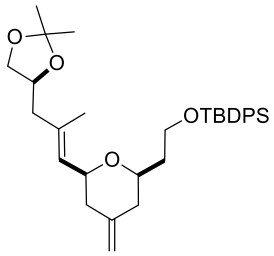
(2*S*,6*S*)-2-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-6-((*E*)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylprop-1-en-1-yl)dihydro-2H-pyran-4(3H)-one (162).To a solution of **161** (734 mg, 1.26 mmol, 1 equiv) in MeOH (20 mL) and H_2O (2 mL) was added K_2CO_3 (1.76 g, 12.6 mmol, 10 equiv) and stirring was continued at room temperature for 4 h. The mixture was concentrated under reduced pressure then partitioned between EtOAc (10 mL) and brine (10 mL). The phases were separated then the aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic phases were dried over $MgSO_4$ then concentrated under reduced pressure giving the alcohol as the crude oil. This was suspended in CH_2Cl_2 (10 mL) followed by addition of solid DMP (800 mg, 1.89 mmol, 1.5 equiv) and stirring was continued for 30 min at room temperature then saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) as well as CH_2Cl_2 (10 mL) were added then stirring was continued for 15 min giving two colorless phases which were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL), the combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) then dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:10→1:5) afforded **162** (636 mg, 1.18 mmol, 94%) as a colorless oil.

TLC: R_f = 0.50 (EtOAc/Hex 1:3, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.63 (m, 4 H), 7.44-7.34 (m, 6 H), 5.34-5.30 (m, 1 H), 4.32 (dt, *J* = 8.0, 6.0, 1 H), 4.26-4.19 (m, 1 H), 4.00 (dd, *J* = 8.1, 5.9, 1 H), 3.96-3.90 (m, 1 H), 3.86 (ddd, *J* = 10.3, 8.3, 4.8, 1 H), 3.74 (dt, *J* = 10.3, 5.4, 1 H), 3.54 (dd, *J* = 8.0, 7.2, 1 H), 2.43 (dd, *J* = 13.9, 6.3, 1 H), 2.41-2.37 (m, 1 H), 2.34-2.32 (m, 2 H), 2.29 (dd, *J* = 14.3, 11.7, 1 H), 2.22 (dd, *J* = 13.9, 7.0, 1 H), 1.94-1.86 (m, 1 H), 1.82-1.74 (m, 1 H), 1.69 (d, *J* = 1.1, 3 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.04 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 207.1, 136.6, 135.7, 135.6, 133.8, 133.8, 129.8, 129.8, 127.8, 127.8, 126.9, 109.1, 74.6, 74.1, 73.9, 69.3, 59.9, 48.0, 47.9, 47.9, 43.6, 39.3, 27.1, 27.0, 25.8, 19.3, 17.7. **IR** (thin film): $\tilde{\nu}$ = 2983, 2957, 2931, 2857, 1720, 1472, 1428, 1379, 1369, 1321, 1255, 1111, 1089, 1063, 998, 823, 737, 703 cm^{-1}. **HRMS**

(ESI): calcd for $C_{32}H_{45}O_5Si$ [(M+H) $^+$]: 537.3031; found: 537.3026. $[\alpha]_D^{24}$: –5.40° (c = 1.33 in $CHCl_3$).

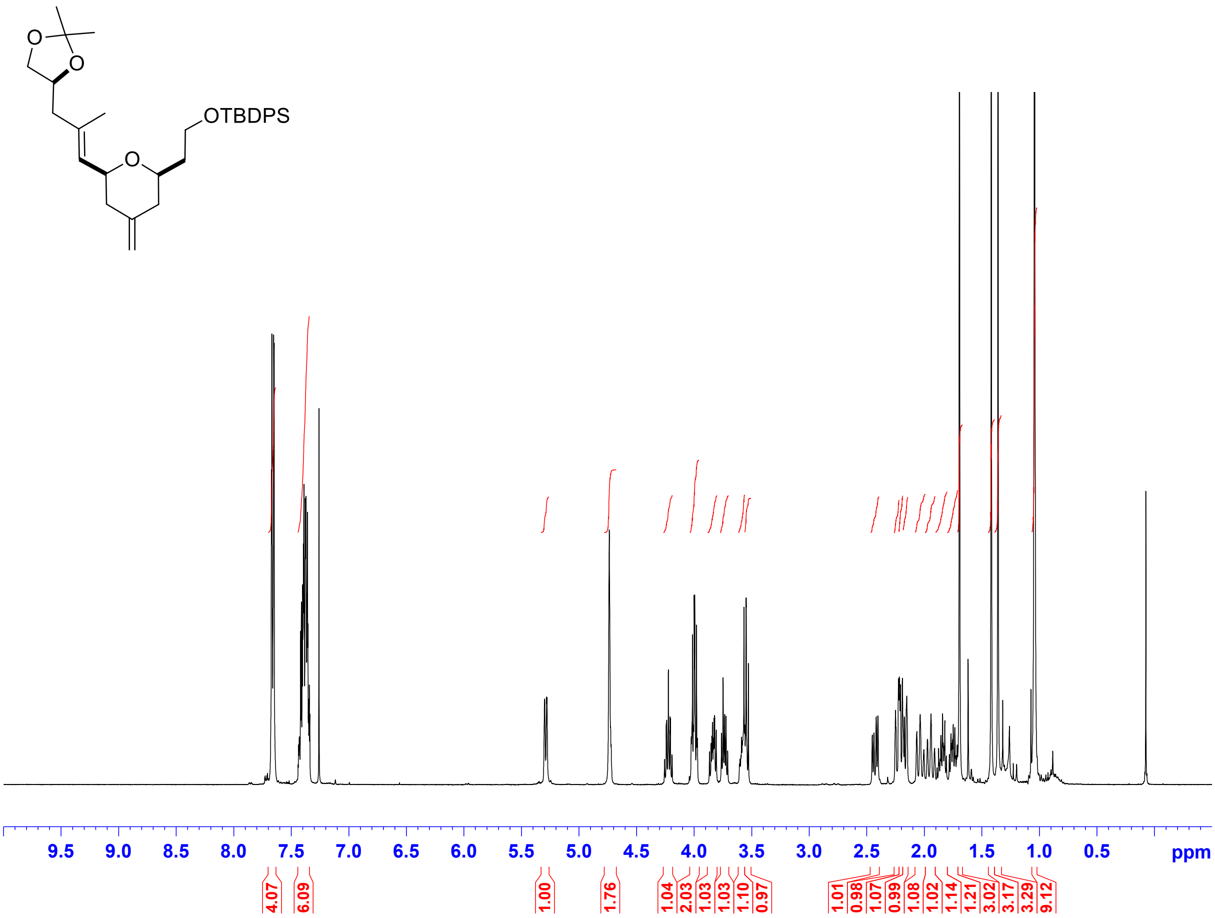






***tert*-Butyl(2-((2*R*,6*S*)-6-((*E*)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylprop-1-en-1-yl)-4-methylenetetrahydro-2H-pyran-2-yl)ethoxy)diphenylsilane (163)**. To a two-necked flame-dried flask, charged with a magnetic stirring bar, a reflux condenser and an argon in/outlet, was added $MePh_3PBr$ (863 mg, 2.42 mmol, 2.1 equiv) in dry THF (15 mL) followed by cooling to –78 °C. A solution of *n*-BuLi (1.6M in hexane, 1.4 mL, 2.24 mmol, 1.9 equiv) was added and stirring was continued for 5 min then the mixture was warmed to 0 °C and stirring was continued for further 30 min giving a yellow suspension. A solution of **162** (636 mg, 1.18 mmol, 1 equiv) in dry THF (5 mL) was added at 0 °C giving an orange mixture immediately. The flask was immersed into a heating bath at 45 °C. Stirring was continued for 45 min in total under heating then the heating bath was removed and brine (10 mL) as well as EtOAc (10 mL) were added followed by separation of phases and extraction of the aqueous phase with EtOAc (2 x 5 mL). The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:10) giving **163** (582 mg, 1.09 mmol, 92%) as a colorless oil.

TLC: R_f = 0.45 (EtOAc/Hex 1:5, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68-7.65 (m, 4 H), 7.44-7.34 (m, 6 H), 5.31-5.27 (m, 1 H), 4.74 (s, 2 H), 4.22 (ddd, *J* = 13.2, 7.5, 5.9, 1 H), 4.03-3.97 (m, 2 H), 3.84 (ddd, *J* = 10.1, 7.9, 5.3, 1 H), 3.74 (dt, *J* = 10.1, 5.6, 1 H), 3.61-3.56 (m, 1 H), 3.55 (dd, *J* = 8.0, 7.4, 1 H), 2.43 (dd, *J* = 13.9, 6.0, 1 H), 2.26-2.22 (m, 1 H), 2.22-2.19 (m, 1 H), 2.19-2.15 (m, 1 H), 2.07-1.99 (m, 1 H), 1.98-1.91 (m, 1 H), 1.89-1.81 (m, 1 H), 1.79-1.71 (m, 1 H), 1.70 (d, *J* = 1.2, 3 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.05 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 144.8, 135.7, 135.7, 135.5, 134.2, 134.1, 129.7, 129.7, 128.4, 127.7, 127.7, 109.1, 108.7, 75.5, 75.3, 74.8, 69.4, 60.5, 43.7, 41.0, 40.8, 39.2, 27.1, 27.0, 25.9, 19.4, 17.7. **IR** (thin film): $\tilde{\nu}$ = 3072, 2984, 2933, 2890, 1740, 1472, 1428, 1370, 1240, 1158, 1110, 1089, 1061, 998, 890, 822, 735 cm^{-1}. **HRMS** (ESI): calcd for $C_{33}H_{50}NO_4Si$ [$(M+NH_4)^+$]: 552.3504; found: 552.350. $[\alpha]_D^{24}$: +11.48° (c = 0.93 in $CHCl_3$).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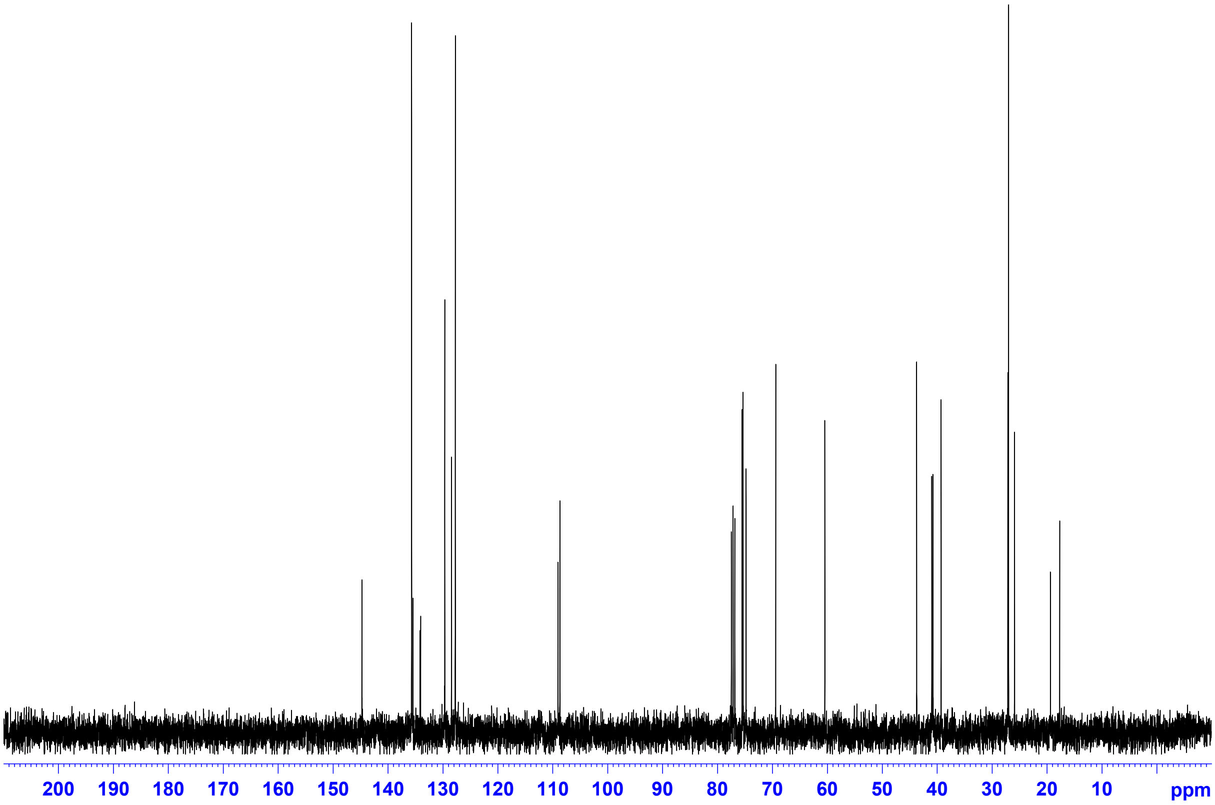
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.07
6.09
1.00
1.76
1.04
2.03
1.03
1.03
1.10
0.97
1.01
0.98
1.07
0.99
1.08
1.02
1.14
1.21
3.02
3.17
3.29
9.12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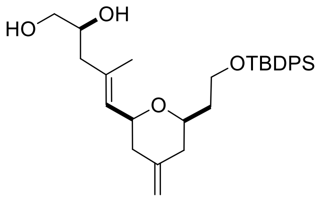
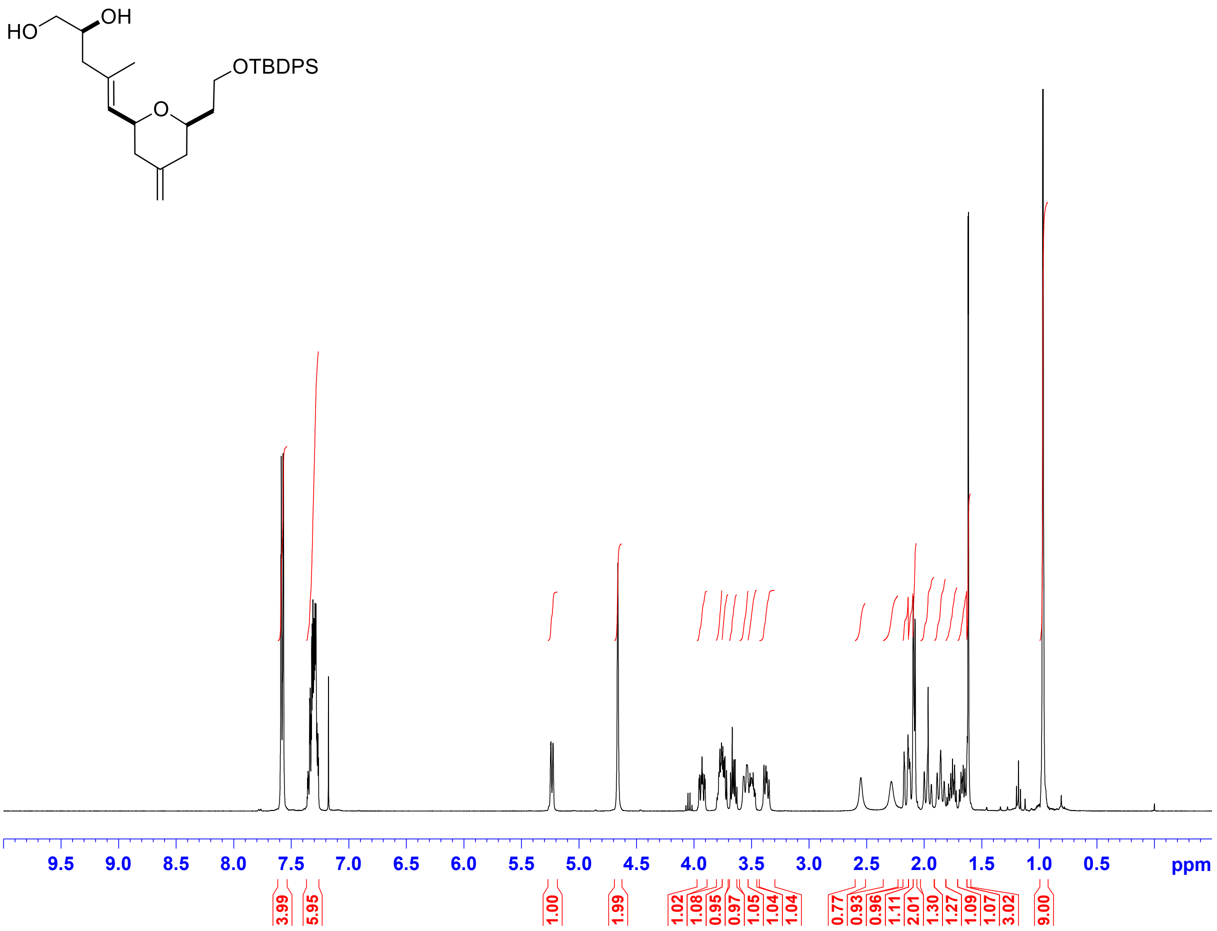
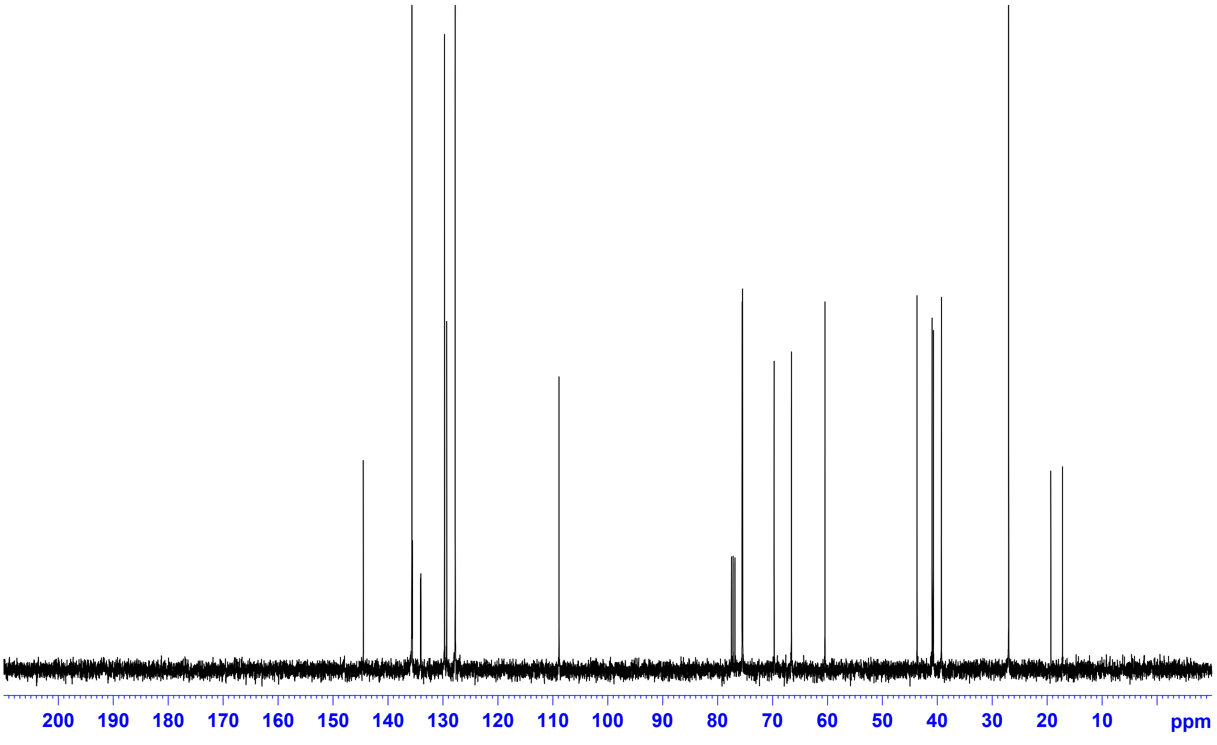
ppm

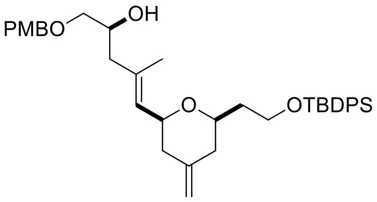


(*S*,*E*)-5-((2*S*,6*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-4-methylenetetrahydro-2H-pyran-2-yl)-4-methylpent-4-ene-1,2-diol (164). To a solution of **163** (581 mg, 1.09 mmol, 1 equiv) dissolved in MeOH (15 mL) was added $CuCl_2{\bullet}2H_2O$ (927 mg, 5.44 mmol, 5 equiv) then the green solution formed was heated to 60 °C for 1 h then the heating bath was removed and $NaHCO_3$ (1 g) was added. Water (10 mL) was added carefully and after the evolution of gas ceased, EtOAc (20 mL) was added then the phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:1→2:1) giving **164** (453 mg, 0.917 mmol, 84%) as a colorless oil that solidified upon standing at room temperature.

TLC: R_f = 0.39 (EtOAc/Hex 3:1, UV, CPS). **Mp**: 79.1-84.2 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.60-7.56 (m, 4 H), 7.36-7.26 (m, 6 H), 5.26-5.22 (m, 1 H), 4.67 (s, 2 H), 3.93 (ddd, *J* = 11.2, 7.6, 2.7, 1 H), 3.80-3.76 (m, 1 H), 3.76-3.72 (m, 1 H), 3.66 (dt, *J* = 10.2, 5.7, 1 H), 3.58-3.53 (m, 1 H), 3.53-3.47 (m, 1 H), 3.37 (dd, *J* = 11.1, 6.9, 1 H), 2.55 (br. s, 1 H), 2.29 (br. s, 1 H), 2.18-2.13 (m, 1 H), 2.13-2.10 (m, 1 H), 2.10-2.07 (m, 2 H), 2.01-1.93 (m, 1 H), 1.89-1.82 (m, 1 H), 1.80-1.72 (m, 1 H), 1.69-1.63 (m, 1 H), 1.62 (d, *J* = 1.2, 3 H), 0.97 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 144.5, 135.7, 135.7, 135.6, 134.1, 134.0, 129.7, 129.3, 127.7, 108.8, 75.5, 75.4, 69.7, 66.6, 60.4, 43.7, 40.9, 40.7, 39.2, 27.0, 19.4, 17.2. **IR** (thin film): $\tilde{\nu}$ = 3395, 3071, 2931, 2890, 2857, 1427, 1389, 1361, 1309, 1260, 1189, 1160, 1106, 1088, 1106, 1088, 1056, 1007, 998, 907, 892, 822, 734, 701 cm^{-1}. **HRMS** (ESI): calcd for $C_{30}H_{43}O_4Si$ [(M+H)$^+$]: 495.2925; found: 495.2928.$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –0.94° (c = 0.68 in $CHCl_3$).


HO
OH
OTBDPS
O
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.99 5.95 1.00 1.99 1.02 1.08 0.95 0.97 1.05 1.04 1.04 0.77 0.93 0.96 1.11 2.01 1.30 1.27 1.09 1.07 3.02 9.00

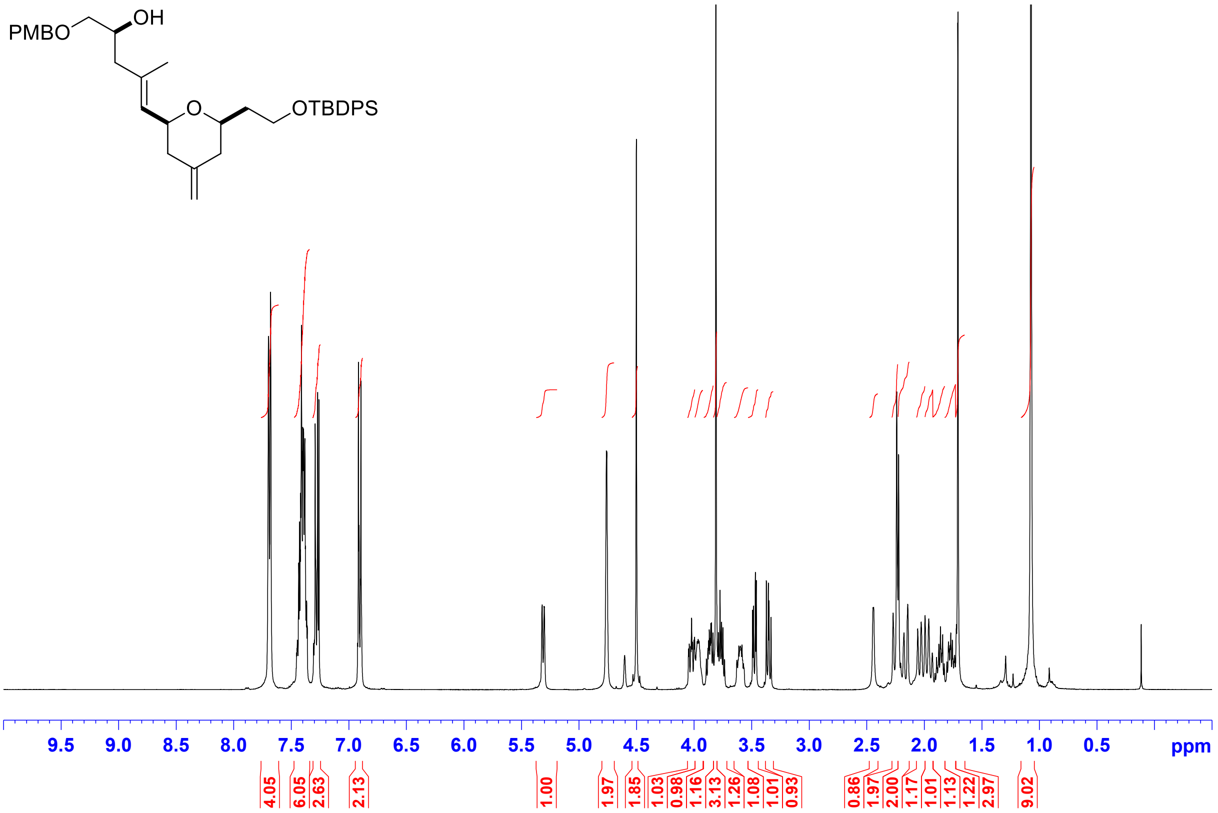

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

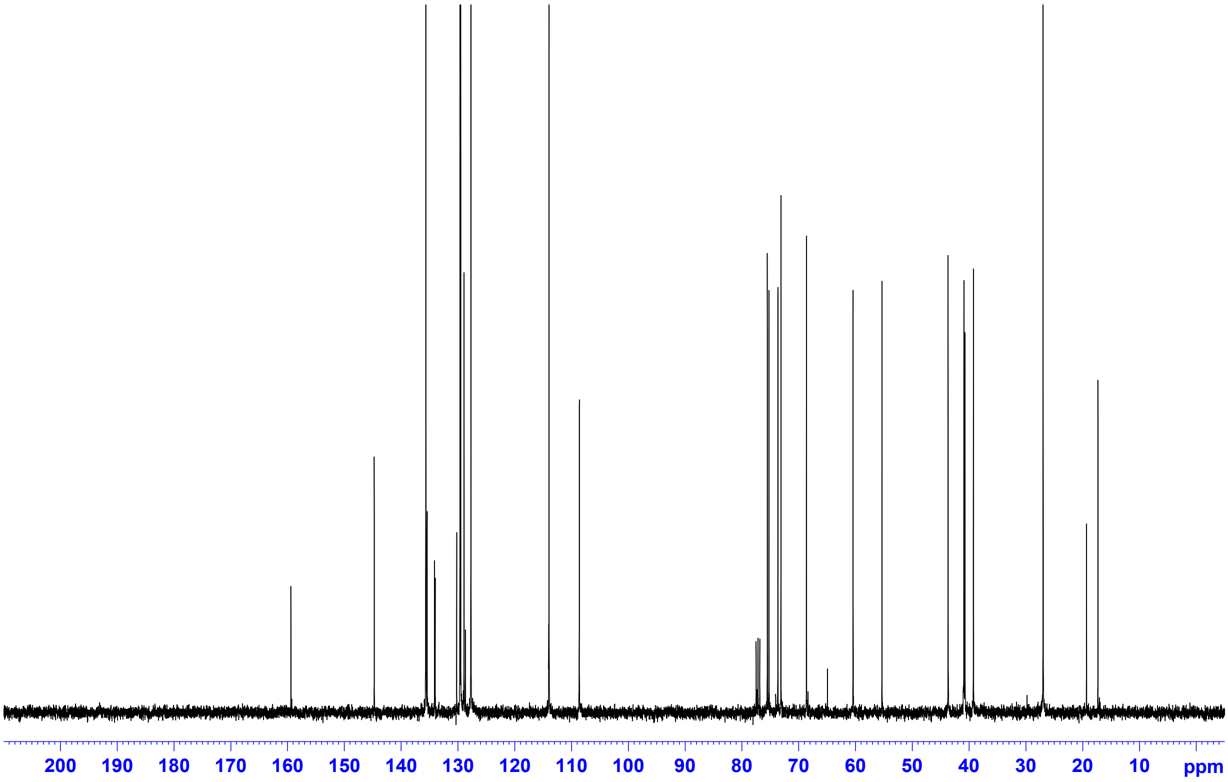


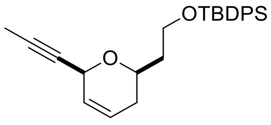
(*S*,*E*)-5-((2*S*,6*R*)-6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-2H-pyran-2-yl)-1-(4-methoxybenzyloxy)-4-methylpent-4-en-2-ol (125). To a two-necked flame-dried flask, charged with a magnetic stirring bar, a reflux condenser and a *Dean-Stark* apparatus, was added **164** (138.5 mg, 0.28 mmol, 1 equiv) in dry toluene (5 mL) followed by Bu_2SnO (77 mg, 0.31 mmol, 1.1 equiv) then the mixture was stirred at reflux (bath temperature was set to 140 °C) for 1.5 d giving a clear, pale-yellow solution. The heating bath was removed and the solution was allowed to cool to room temperature followed by addition of TBAI (145 mg, 0.39 mmol, 1.4 equiv) and PMBCl (61 mg, 0.39 mmol, 1.4 equiv). The mixture was heated to reflux (120 °C bath tempearture) for 1.5 h giving a brownish solution. The heating bath was removed and the solution was allowed to cool to room temperature then EtOAc (10 mL) and brine (10 mL) were added as well as H_2O (10 mL) followed by separation of phases. The aqueous phase was extracted with EtOAc (2 x 5 mL) then the combined organic phases were dried over $MgSO_4$ and purified using flash chromatography (EtOAc/Hex 1:5, 20 cm height, 2 cm width) affording the complete separation from the other regioisomer, which was formed as the minor isomer as judged by TLC analysis. **125** (98.3 mg, 0.160 mmol, 57%) was obtained as a pale-yellow oil.

Note: Samples of **125** obtained from L-malic acid was identical with respect to all spectral and chiroptical properties to samples of **125** obtained from D-aspartic acid.

TLC: R_f = 0.14 (EtOAc/Hex 1:5, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4 H), 7.45-7.35 (m, 6 H), 7.29-7.26 (m, 2 H), 6.91-6.88 (m, 2 H), 5.28 (d, *J* = 7.7, 1 H), 4.77-4.74 (m, 2 H), 4.50 (s, 2 H), 4.03 (ddd, *J* =10.9, 7.7, 2.7, 1 H), 3.99-3.93 (m, 1 H), 3.85 (ddd, *J* = 10.1, 8.0, 5.5, 1 H), 3.81 (s, 3 H), 3.76 (dt, *J* = 10.1, 5.8, 1 H), 3.62-3.56 (m, 1 H), 3.47 (dd, *J* = 9.5, 3.5, 1 H), 3.35 (dd, *J* = 9.5, 7.0, 1 H), 2.44 (br. s, 1 H), 2.26-2.21 (m, 1 H), 2.20 (d, *J* = 6.8, 2 H), 2.18-2.14 (m, 1 H), 2.06-1.99 (m, 1 H), 1.99-1.92 (m, 1 H), 1.90-1.82 (m, 1 H), 1.79-1.72 (m, 1 H), 1.71 (d, *J* = 1.2, 3 H), 1.07 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.4, 144.8, 135.7, 135.6, 135.4, 134.1, 134.0, 130.2, 129.6, 129.5, 128.9, 127.7, 127.7, 113.9, 108.6, 75.5, 75.2, 73.6, 73.1, 68.6, 60.4, 55.3, 43.7, 40.9, 40.7, 39.2, 26.9, 19.3, 17.3. **IR** (thin film): $\tilde{\nu}$ = 3432, 3070, 2932, 2857, 1612, 1513, 1471, 1427, 1247, 1106, 1088, 1058, 1037, 998, 822, 701 cm^{-1}. **HRMS** (ESI): calcd for $C_{38}H_{50}NaO_5Si$ [(M+Na)$^+$]: 637.3320; found: 637.3326. $[\alpha]_D^{24}$: +6.03° (c = 0.98 in $CHCl_3$).

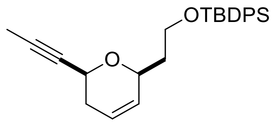






165a

+



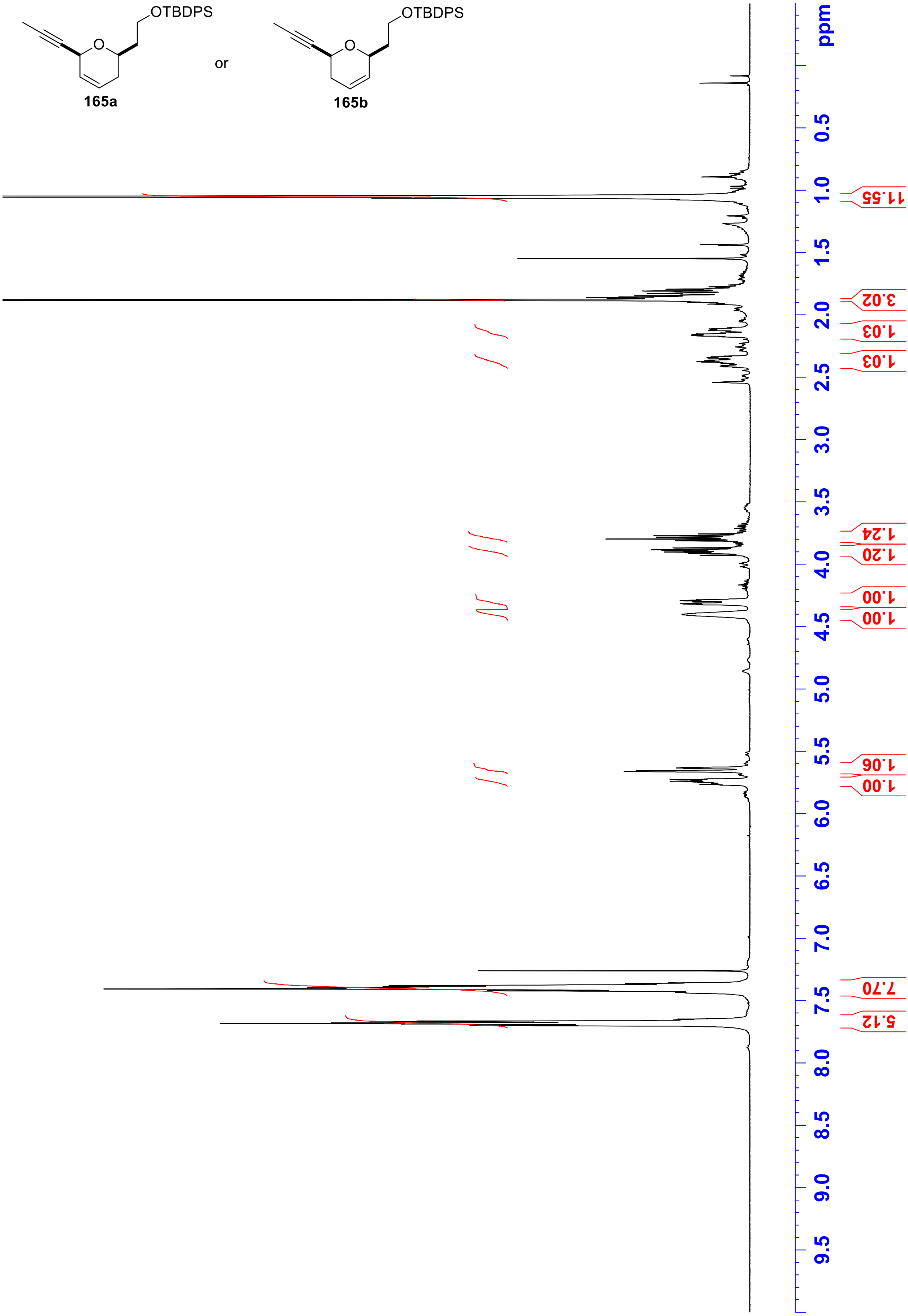
165b

Analytical data for elimination products **165a** and **165b** (see Scheme 72, page 91). Which spectrum belongs to which molecule was not established.

Product 1: TLC: R_f = 0.27 (EtOAc/Hex 1:20, UV, CPS). **^{1}H-NMR** (400 MHz, CDCl$_3$): δ = 7.71-7.64 (m, 4 H), 7.44-7.36 (m, 6 H), 5.77-5.72 (m, 1 H), 5.66-5.63 (m, 1 H), 4.43-4.37 (m, 1 H), 4.33-4.28 (m, 1 H), 3.86 (ddd, J = 10.3, 7.7, 5.6, 1 H), 3.78 (dt, J =10.4, 5.7, 1 H), 2.42-2.33 (1 H), 2.18-2.10 (m, 1 H), 1.88 (d, J = 2.1, 3 H), 1.87-1.79 (m, 2 H), 1.05 (s, 9 H).

Product 2: TLC: R_f = 0.20 (EtOAc/Hex 1:20, UV, CPS). **^{1}H-NMR** (400 MHz, CDCl$_3$): δ = 7.71-7.64 (m, 4 H), 7.44-7.36 (m, 6 H), 5.87-5.82 (m, 1 H), 5.69-5.66 (m, 1 H), 5.08-5.03 (m, 1 H), 4.88-4.84 (m, 1 H), 3.85-3.81 (m, 1 H), 3.69 (dd, J = 7.0, 5.9, 1 H), 2.32-2.21 (1 H), 2.08-1.99 (m, 1 H), 1.87 (d, J = 2.3, 3 H), 1.85-1.75 (m, 2 H), 1.05 (s, 9 H). This product was a mixture of **165a** and **b** (1:1).

The spectrum given on next page, represents product 1, which is either **165 a** or **165b**.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165a
or
OTBDPS
O
165b
ppm
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1.5
2.0
2.5
3.0
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4.5
5.0
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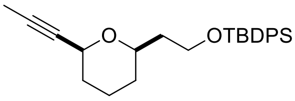
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
11.55
3.02
1.03
1.03
1.24
1.20
1.00
1.00
1.06
1.00
7.70
5.12

5.5. Synthesis of Analogs and Derivatives

5.5.1. C13-Desmethylene-Dactylolide (167)



***tert*-Butyldiphenyl(2-((2*R*,6*S*)-6-(prop-1-ynyl)tetrahydro-2H-pyran-2-yl)ethoxy-)silane (168)**. To a solution of **105** (316.20 mg, 0.59 mmol, 1.00 equiv) in toluene (5 mL) was added Bu_3SnH (0.18 mL, 0.07 mmol, 1.10 equiv) and a catalytic amount of AIBN. The solution was heated to 60 °C for 30 min; then the heating bath was removed and a solution of saturated aqueous KF[45] (10 mL) was added followed by EtOAc (5 mL). The mixture was stirred for 30 min at room temperature, the phases were separated, and the aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:50) afforded **168** (211.2 mg, 0.52 mmol, 88%) as a colorless oil that converted to a colorless solid at room temperature.

TLC: R_f = 0.69 (EtOAc/Hex 1:10, UV, CPS). **Mp**: 68-69 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68-7.65 (m, 4 H), 7.44-7.35 (m, 6 H), 4.05 (ddq, *J* = 11.0, 2.4, 2.1, 1 H), 3.86 (ddd, *J* = 10.2, 8.0, 5.1, 1 H), 3.71 (dt, *J* =10.2, 5.6, 1 H), 3.59-3.53 (m, 1 H), 1.87-1.75 (m, 3 H), 1.86 (d, *J* = 2.1, 3 H), 1.72-1.63 (m, 1 H), 1.61-1.47 (m, 3 H), 1.28-1.19 (m, 1 H), 1.04 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 135.7, 135.6, 134.1, 134.0, 129.6, 129.6, 127.7, 80.4, 79.2, 75.0, 68.4, 60.3, 39.2, 33.0, 31.0, 27.0, 23.6, 19.3, 3.8. **IR** (thin film): $\tilde{\nu}$ = 3071, 2930, 2856, 2367, 2342, 1474, 1428, 1312, 1197, 1078, 822 cm^{-1}. **HRMS** (EI): calcd for $C_{22}H_{25}O_2Si$ [$(M-C_4H_9)^+$]: 349.1618; found: 349.1619. $[\alpha]_D^{24}$: –44.35° (c = 1.09, $CHCl_3$).

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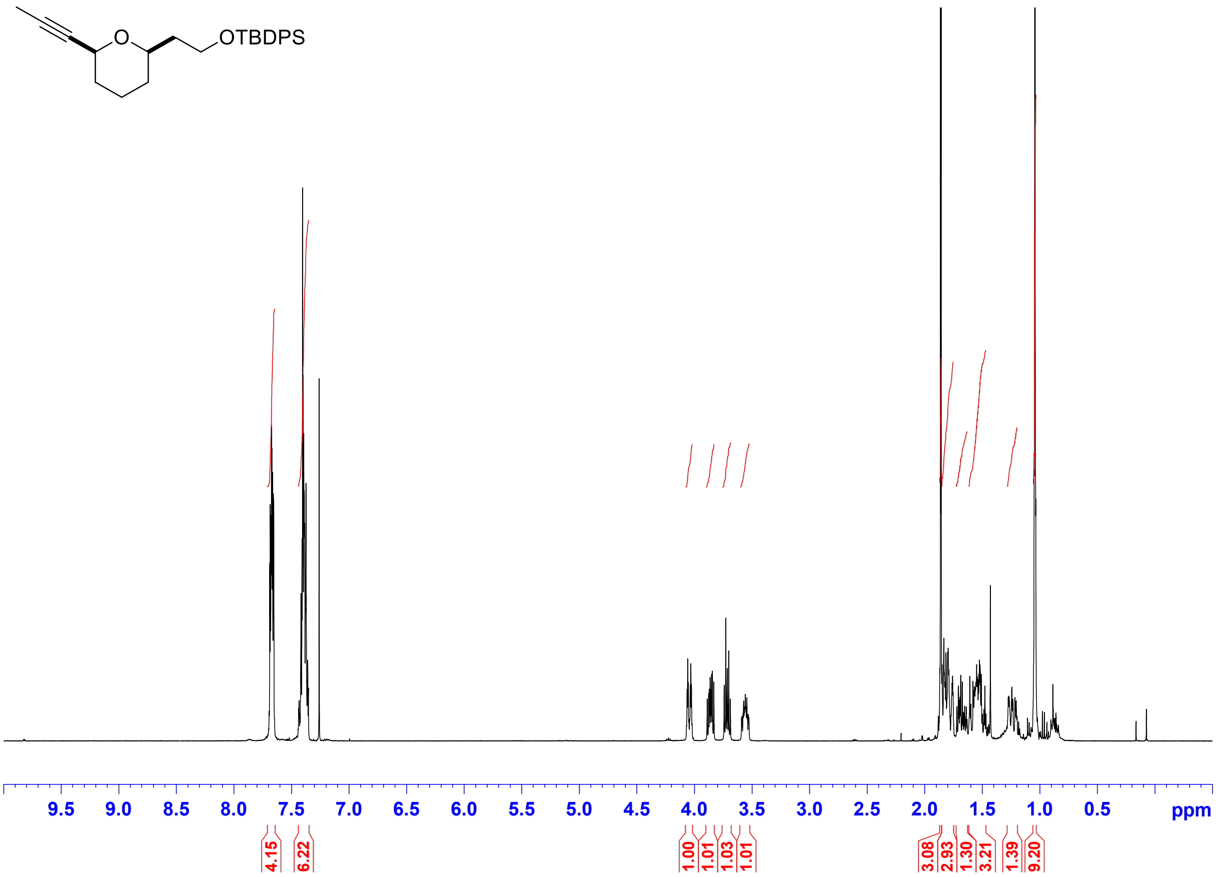
[45] The use of KF-Workup is described in R. Askani, U. Keller, *Liebigs Ann. Chem.* **1988**, 61. The reaction works also on larger scale for **105** (2.9 mmol) without reduced yield.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2.93
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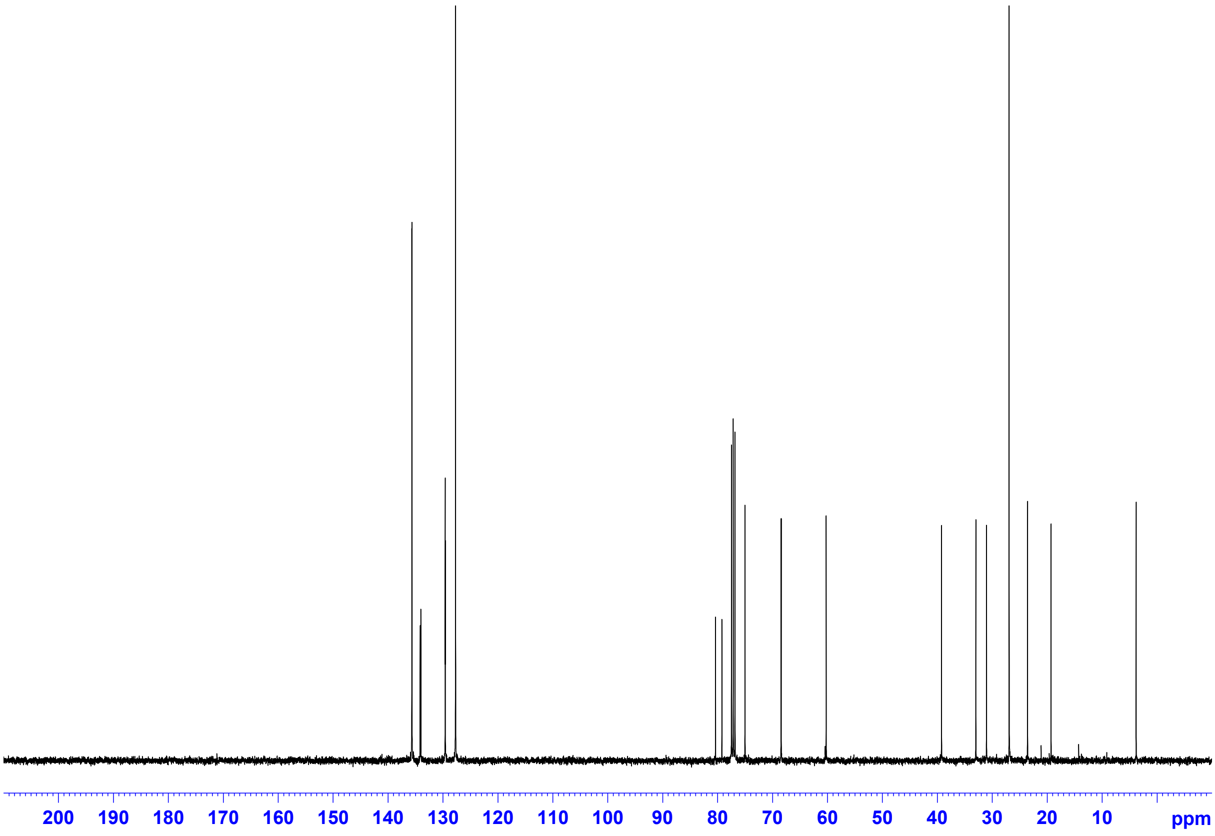
3.21
1.39
9.20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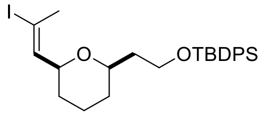
ppm

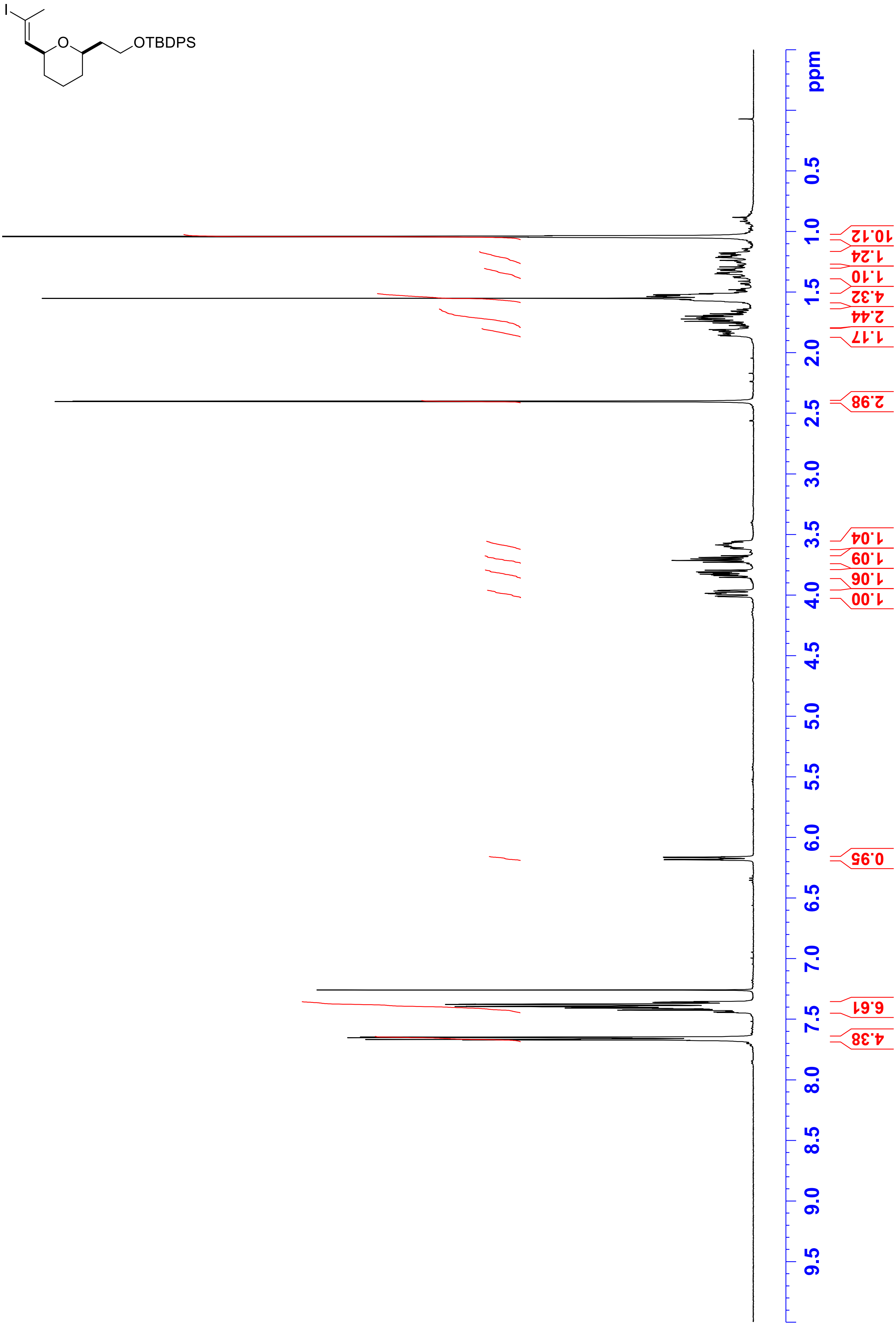


***tert*-Butyl-(2-((2*R*,6*S*)-6-((*E*)-2-iodoprop-1-enyl)tetrahydro-2H-pyran-2-yl)ethoxy-)diphenylsilane (169a)**. To a suspension of CuCN (385 mg, 4.30 mmol, 10.0 equiv) in THF (8 mL) at –78 °C was added a solution of *n*-BuLi (1.6M in hexane, 5.40 mL, 8.60 mmol, 20.0 equiv). After 5 min the flask was immersed in a cooling bath at –40 °C and kept at this temperature for 10 min. The almost clear solution was then was re-cooled to –78 °C, producing a slightly heterogenous mixture, and Bu_3SnH (2.30 mL, 8.60 mmol, 20.00 equiv) was added dropwise, resulting in the immediate formation of a yellow turbid solution with liberation of some gas. After 20 min at –78 °C the mixture was stirred for 15 min at –40 °C, giving an almost clear golden-yellow solution, which was then re-cooled to –78 °C. MeOH (1.90 mL, 47.30 mmol, 110.0 equiv) was added under vigorous stirring, the mixture was stirred for 10 min at –78 °C, warmed to –40 °C and kept there for 20 min giving a red solution, which was re-cooled to –78 °C. A solution of **168** (175 mg, 0.43 mmol, 1.00 equiv) in THF (5 mL) was then added and the mixture was stirred for 1.5 d, with the temperature being allowed to gradually rise to –15 °C. Saturated aqueous NH_4Cl (10 mL) and 25% aqueous NH_4OH (1 mL) were then added together with EtOAc (10 mL), the mixture was stirred for 30 min at room temperature and two almost clear phases were formed that were separated. The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic extracts were dried over $MgSO_4$, and the solution was concentrated under reduced pressure. Purification of the residue by flash chromatography on deactivated silica (Hex→EtOAc/Hex 1:100→1:50, 1%(v/v) NEt_3) gave the (*E*)-vinyl stannane (223 mg, 0.32 mmol, 74%) as a colorless oil. This material was immediately used in the next step.

A solution of the above (*E*)-vinyl stannane (223 mg, 0.32 mmol, 1.00 equiv) in THF (3 mL) was cooled to –17 °C (NaCl/ice) and a solution of NIS (108 mg, 0.48 mmol, 1.50 equiv) in THF (1 mL) was added. After 20 min a mixture of saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) was added followed by EtOAc (5 mL). Stirring was continued for 5 min until two clear, colorless phases had formed; the pases were separated, the aqueous phase was extracted with EtOAc

(3 x 5 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (Hex/EtOAc 1:100) gave **169a** (166 mg, 0.31 mmol, 98%, 73% for both steps) as a pale yellow oil.

TLC: R_f = 0.72 (EtOAc/Hex 1:20, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 4 H), 7.44-7.35 (m, 6 H), 6.17 (dq, J = 7.7, 1.5, 1 H), 3.99 (ddd, J =11.2, 7.7, 2.1, 1 H), 3.83 (ddd, J = 10.1, 8.1, 5.5, 1 H), 3.70 (dt, J = 10.2, 5.6, 1 H), 3.62-3.56 (m, 1 H), 2.40 (d, J = 1.5, 3 H), 1.86-1.80 (m 1 H), 1.79-1.65 (m, 2 H), 1.58-1.51 (m, 3 H), 1.38-1.31 (m, 1 H), 1.24-1.18 (m, 1 H), 1.04 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 142.5, 135.7, 135.7, 134.1, 134.1, 129.7, 127.7, 98.5, 75.9, 74.6, 60.3, 39.3, 31.4, 31.3, 28.8, 27.0, 23.6, 19.4. **IR** (thin film): $\tilde{\nu}$ = 3070, 2931, 2856, 1472, 1428, 1260, 1197, 1105, 1076, 1036, 822, 799 cm^{-1}; **HRMS** (ESI): calcd for $C_{26}H_{35}INaO_2Si$ [$(M+Na)^+$]: 557.1343; found: 557.1305. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –33.02° (c = 0.44, $CHCl_3$).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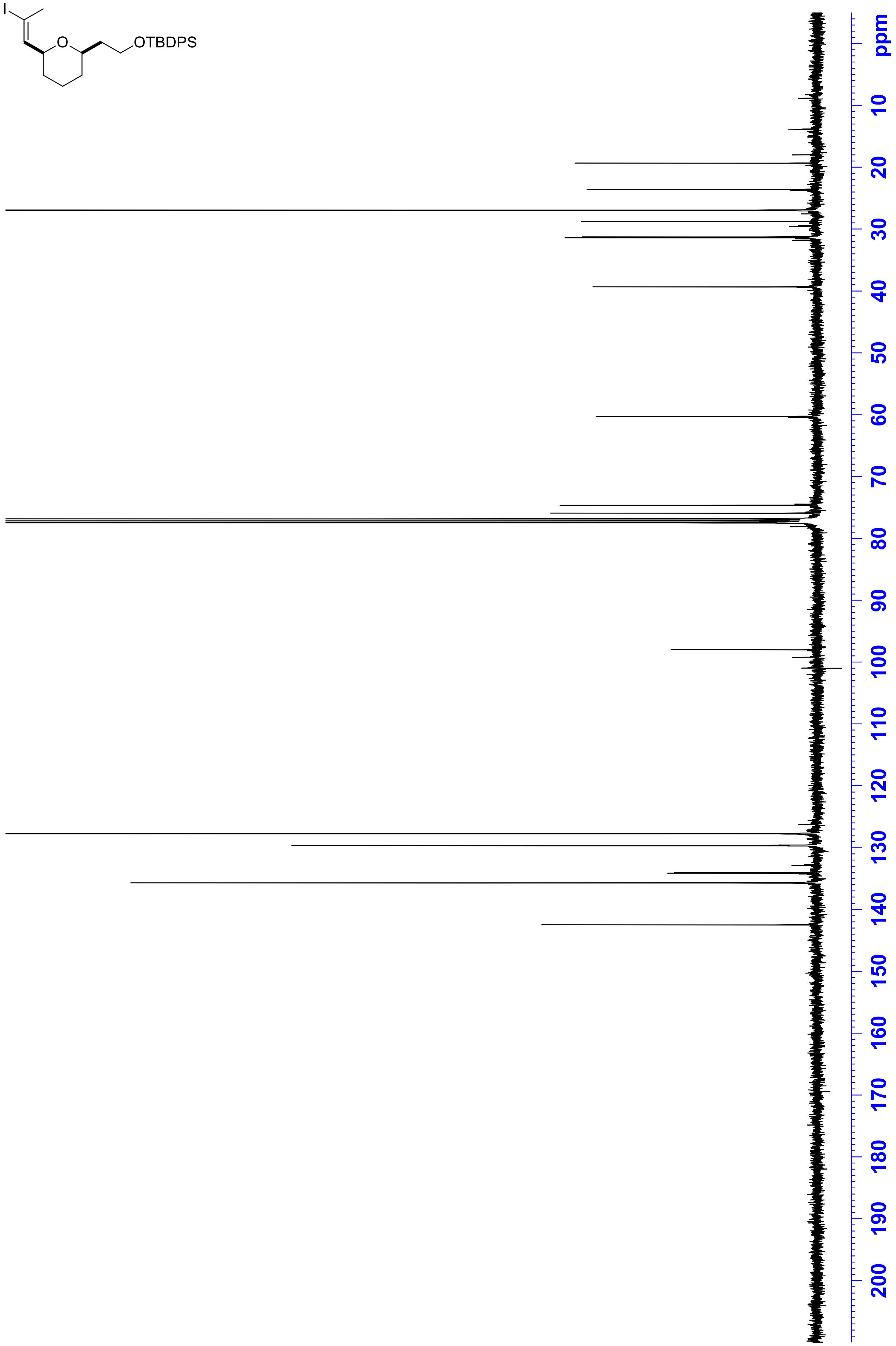
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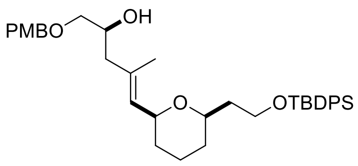
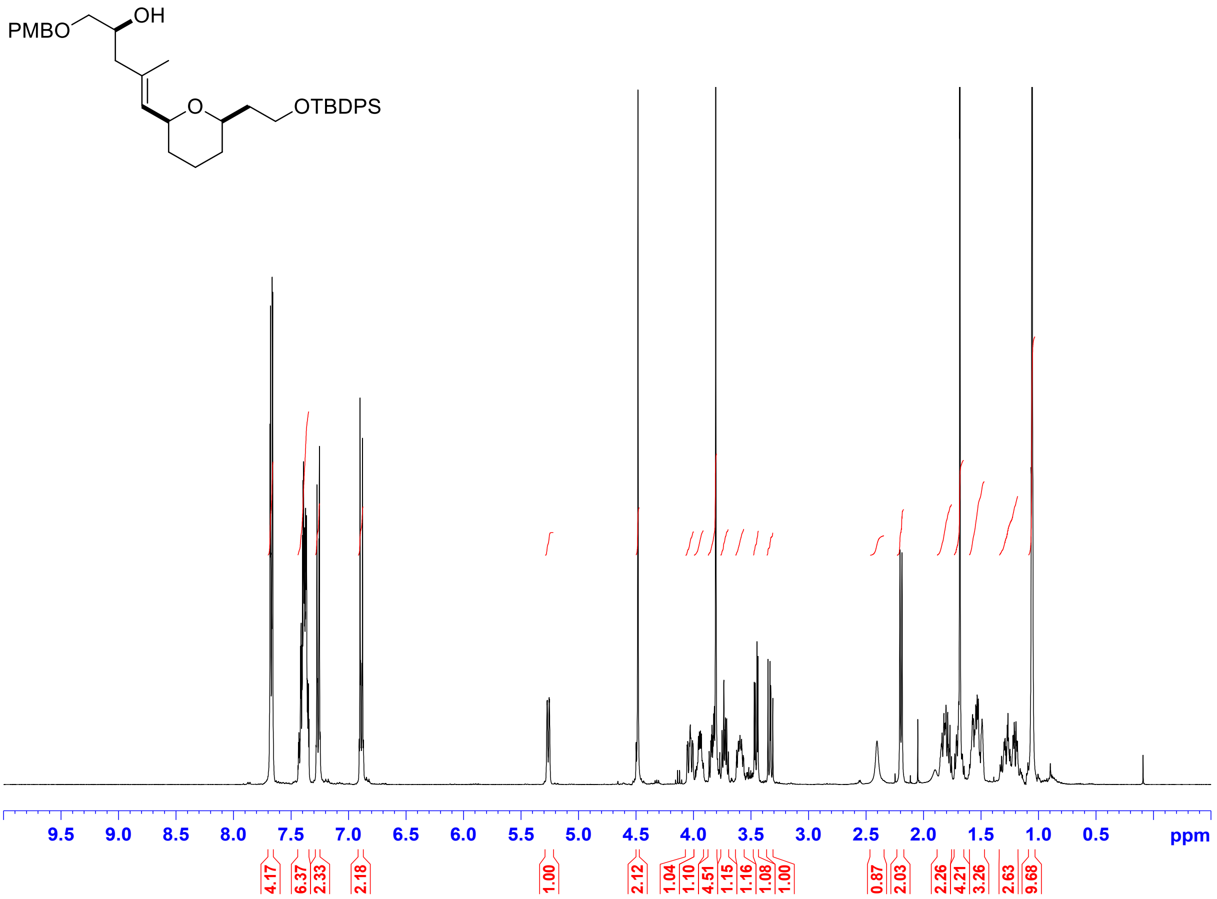


(*S*,*E*)-5-((2*S*,6*R*)-6-(2-(*tert*-Butyldiphenylsilyloxy-)ethyl-)tetrahydro-2H-pyran-2-yl)-1-(4-methoxybenzyloxy)-4-methylpent-4-en-2-ol (170). To a solution of **169a** (165.7 mg, 0.31 mmol, 1.00 equiv) in toluene (1 mL) was added *t*-BuLi (1.6M in pentane, 0.33 mL, 0.53 mmol, 1.70 equiv) at –78 °C. The near colorless solution was stirred for 30 min at –78 °C and then further cooled to around –85 °C. A solution of **17** (161 mg, 0.83 mmol, 2.70 equiv) in toluene (1.5 mL) was then added, followed, after 1 min, by $BF_3{\bullet}OEt_2$ (0.10 mL, 0.77 mmol, 2.50 equiv), which produced a pale yellow solution. The mixture was stirred for 1 h at –78 °C; the cooling bath was then removed and saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (10 mL) were added. After the mixture had reached room temperature, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure, and the residue was purified by flash chromatography (EtOAc/Hex 1:7→1:5) to give **170** (58.3 mg, 0.097 mmol, 31%) as a colorless oil.

Note: Flash chromatography is difficult and needed to be performed twice (see comments for compound **125**, section 5.3.2, page 222), in order to remove the iodohydrine **35** derived from competing epoxide opening by iodide.

TLC: R_f = 0.28 (EtOAc/Hex 1:3, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.69-7.66 (m, 4 H), 7.44-7.34 (m, 6 H), 7.28-7.25 (m, 2 H), 6.90-6.87 (m, 2 H), 5.27 (dq, *J* = 7.7, 1.2, 1 H), 4.49 (s, 2 H), 4.03 (ddd, *J* =11.2, 7.6, 2.3, 1 H), 3.99-3.92 (m, 1 H), 3.84 (ddd, *J* = 10.3, 7.9, 5.5, 1 H), 3.80 (s, 3 H), 3.73 (dt, *J* = 10.2, 5.7, 1 H), 3.63-3.57 (m, 1 H), 3.46 (dd, *J* = 9.5, 3.5, 1 H), 3.33 (dd, *J* = 9.6, 7.1, 1 H), 2.41 (br. s, 1 H), 2.20 (d, *J* = 6.9, 2 H), 1.86-1.76 (m, 2 H), 1.73-1.65 (m, 1 H), 1.68 (d, *J* = 1.2, 3 H), 1.60-1.48 (m, 3 H), 1.34-1.17 (m, 2 H), 1.06 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.4, 135.7, 135.6, 134.6, 134.2, 134.1, 130.2, 129.8, 129.6, 129.5, 127.7, 113.9, 74.9, 74.5, 73.7, 73.1, 68.6, 60.5, 55.4, 43.7, 39.5, 31.8, 31.4, 27.0, 23.8, 19.4, 17.3. **IR** (thin film): $\tilde{\nu}$ = 3442, 2931, 2856, 1612, 1513, 1429, 1388, 1302, 1247, 1110, 1037, 821, 702 cm^{-1}. **HRMS** (ESI): calcd for $C_{37}H_{50}NaO_5Si$ [(M+Na)$^+$]: 625.3320; found: 625.3320. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –5.02° (c = 0.43, $CHCl_3$).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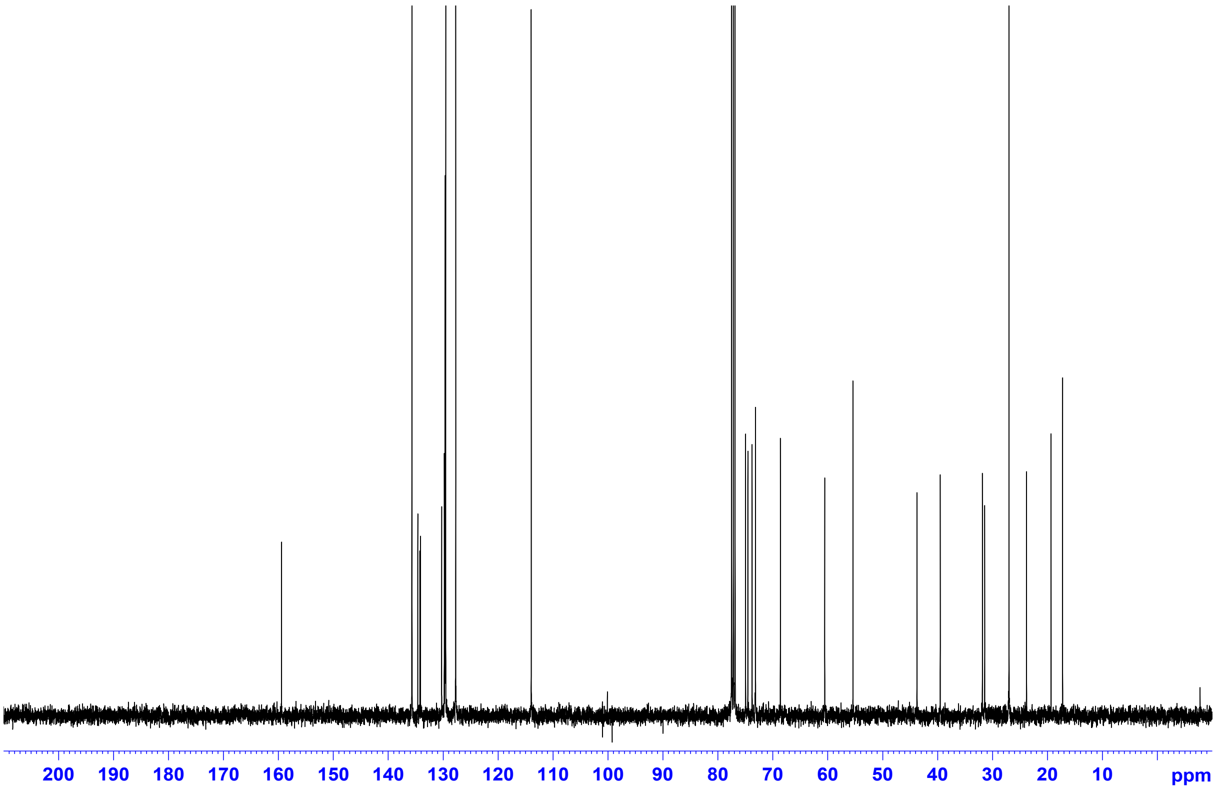
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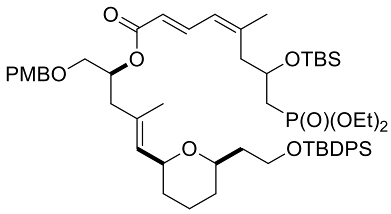
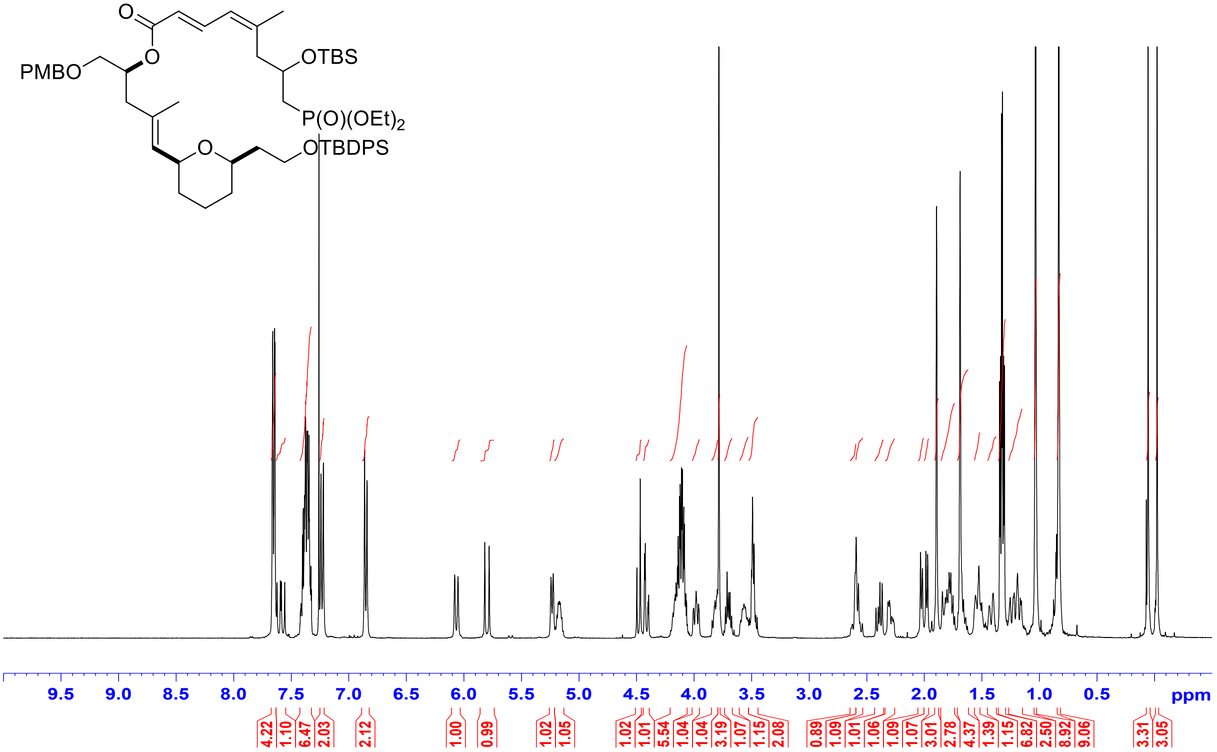
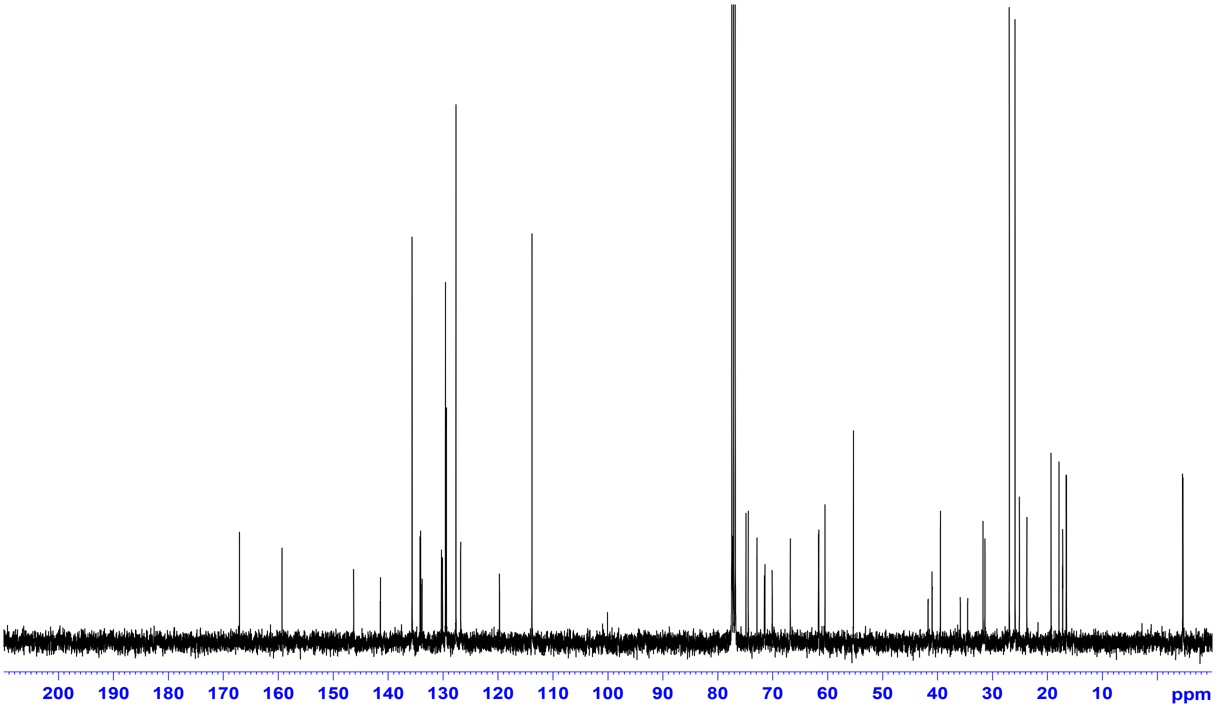
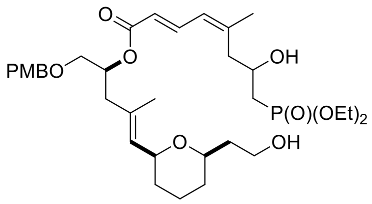


(2*E*,4*Z*)-((*S*,*E*)-5-((2*S*,6*R*)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)tetrahydro-2H-pyran-2-yl)-1-(4-methoxybenzyloxy)-4-methylpent-4-en-2-yl) 7-(*tert*-butyl dimethyl silyloxy)-8-(diethoxyphosphoryl)-5-methylocta-2,4-dienoate (G). To a solution of **98** (82.8 mg, 0.20 mmol, 1.55 equiv) in toluene (1 mL) was added NEt_3 (0.06 mL, 0.39 mmol, 3.20 equiv) followed by 2,4,6-trichlorobenzoyl chloride (0.038 mL, 0.24 mmol, 1.90 equiv) at room temperature. The almost clear pale yellow solution was stirred for 1 h; then a solution of alcohol **170** (76.8 mg, 0.127 mmol, 1.00 equiv) and DMAP (23 mg, 0.19 mmol, 1.50 equiv) in toluene (1 mL (the mixture was sonicated to produce a clear solution); plus 2 x 0.5 mL for rinsing)) was added, resulting in the immediate formation of an off-white suspension. After 18 h saturated aqueous $NaHCO_3$ (5 mL) and EtOAc (5 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/Hex 1:3→1:1) afforded ester **G** (96.6 mg, 0.096 mmol, 74 %) as a colorless oil.

TLC: R_f = 0.54 (EtOAc/hexane 1:1, UV, $KMnO_4$ or CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 4 H), 7.59 (dd, *J* = 15.3, 11.9, 1 H), 7.43-7.32 (m, 6 H), 7.25-7.22 (m, 2 H), 6.87-6.84 (m, 2 H), 6.07 (d, *J* = 11.8, 1 H), 5.80 (d, *J* = 15.2, 1 H), 5.23 (d, *J* = 7.8, 1 H), 5.21-5.14 (m, 1 H), 4.48 (d, *J* = 11.7, 1 H), 4.41 (dd, *J* = 11.8, 2.6, 1 H), 4.20-4.06 (m, 5 H), 4.01-3.95 (m, 1 H), 3.84-3.78 (m, 1 H), 3.78 (s, 3 H), 3.71 (dt, 10.2, 5.6, 1 H), 3.60-3.53 (m, 1 H), 3.52-3.45 (m, 2 H), 2.64-2.59 (m, 1 H), 2.56 (dd, *J* = 13.4, 7.9. 1 H), 2.40 (dd, *J* = 13.6, 8.0, 1 H), 2.30 (ddd, *J* = 13.8, 5.9, 2.2, 1 H), 2.03 (d, *J* = 6.4, 1 H), 1.98 (d, *J* = 6.4, 1 H), 1.89 (s, 3 H), 1.85-1.74 (m, 3 H), 1.71-1.63 (m, 1 H), 1.69 (s, 3 H), 1.58-1.49 (m, 1 H), 1.44-1.40 (m, 1 H), 1.33 (dt, *J* = 7.1, 2.9, 6 H), 1.26-1.16 (m, 2 H), 1.04 (s, 9 H), 0.83 (s, 9 H), 0.06 (s, 3 H), -0.02, (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$; due to the diastereomeric nature of the product, the number of signals in the ^{13}C-spectrum exceeds the number of carbon atoms): δ = 167.1, 159.3, 146.3, 141.5, 141.4, 135.7, 135.6, 134.2, 134.1, 133.9, 133.8, 130.3, 130.1 (2C), 129.6, 129.4 (2C), 127.7, 126.8, 119.8, 119.7, 113.9, 74.9, 74.5, 72.9 (2C), 71.5 (2C), 70.1 (2C), 66.8, 61.7 (d, *J* = 6.5) (2C), 60.5, 55.3, 41.8, 41.7, 41.0 (2C), 39.5, 35.2 (d, *J* = 135.0), 31.7, 31.4, 27.0, 25.9, 25.1, 23.8, 19.3, 17.9, 17.3 (2C), 16.5 (d, *J* = 6.3), -4.6, -4.7. **IR** (thin film): $\tilde{\nu}$ = 2930, 2856, 1710, 1636, 1612, 1513, 1472, 1363, 1302, 1248, 1146, 1026, 936, 823, 775, 703 cm^{-1}. **HRMS** (ESI): calcd for $C_{56}H_{85}NaO_{10}PSi_2$ $[(M+Na)^+]$: 1027.5311; found: 1027.5315. $[\alpha]_D^{24}$: +1.30° (c = 1.30, $CHCl_3$).



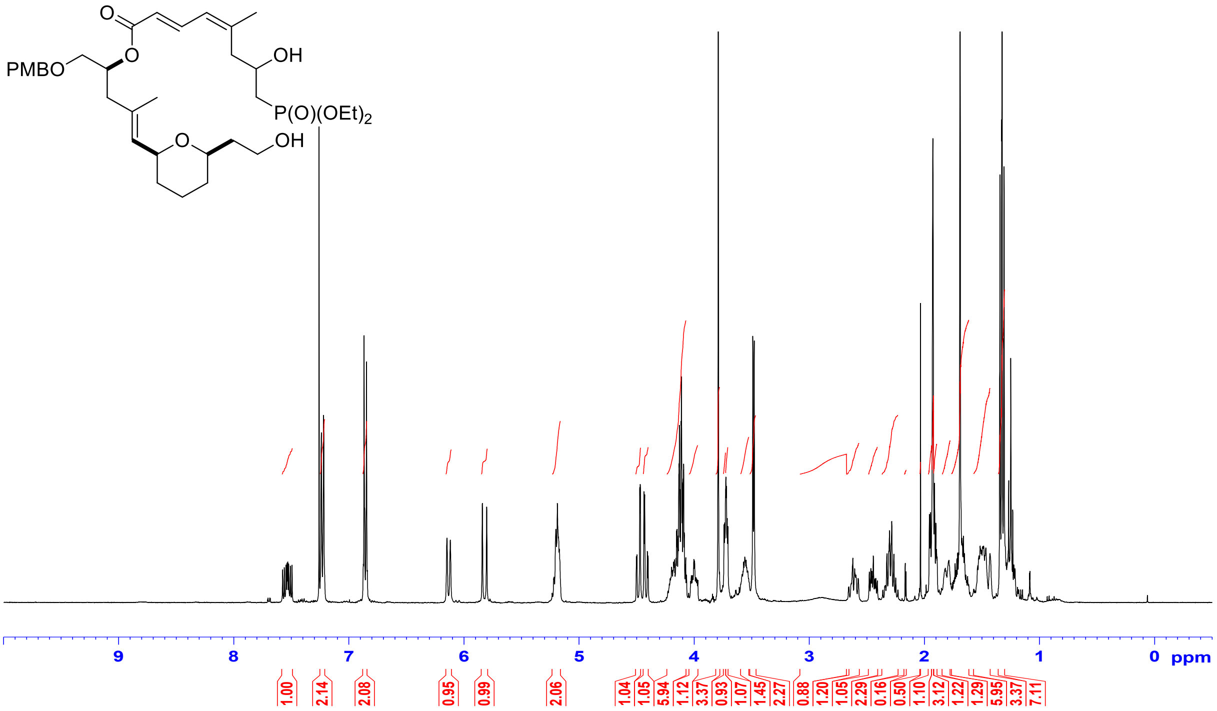


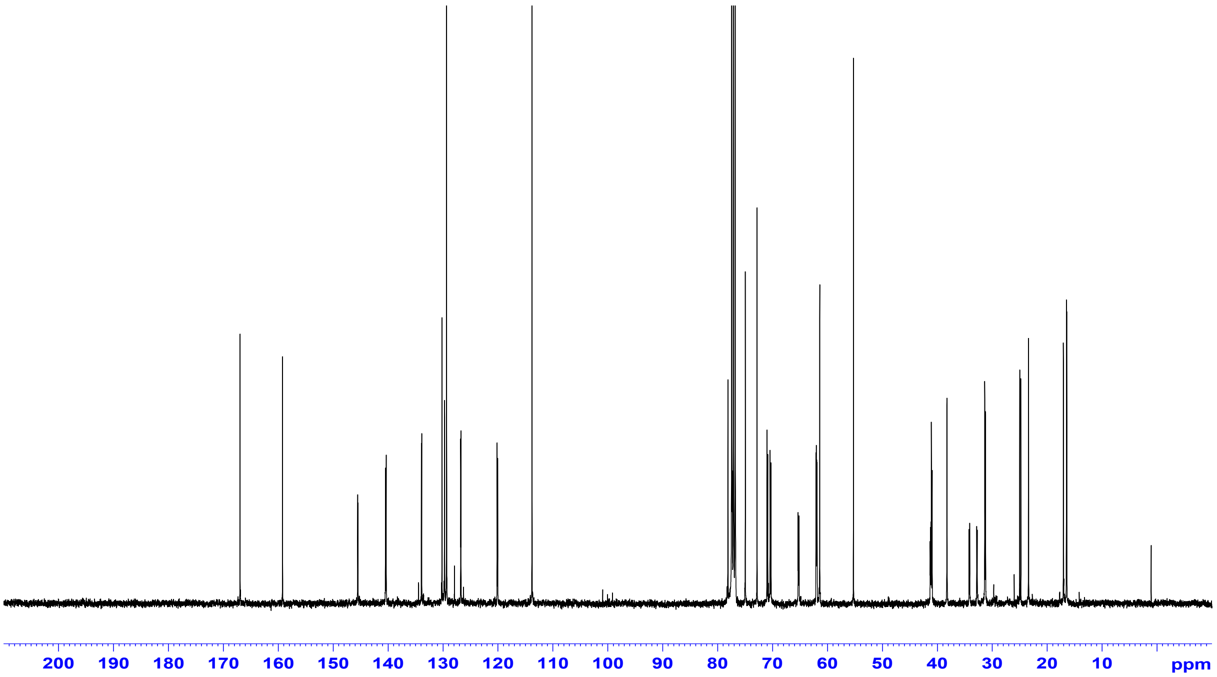


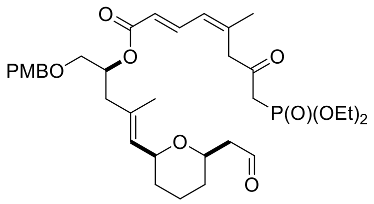
(2*E*,4*Z*)-((*S*,*E*)-5-((2*S*,6*R*)-6-(2-Hydroxyethyl)tetrahydro-2H-pyran-2-yl)-1-(4-methoxybenzyloxy)-4-methylpent-4-en-2-yl) 8-(diethoxyphosphoryl)-7-hydroxy-5-methylocta-2,4-dienoate (H). To a solution of **G** (96.90 mg, 0.096 mmol, 1.00 equiv) in THF (4 mL) in a polypropylene tube was added 70% HF•py (1 mL) at 0 °C (ice). The cooling bath was removed after 5 min and stirring was continued at room temperature for 20 h. The solution was then carefully added to a vigorously stirred mixture of saturated aqueous $NaHCO_3$ (50 mL) and EtOAc (10 mL); after ca. 15 min two clear phases had formed which were separated. The aqueous phase was extracted with EtOAc (4 x 10 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1x 5 mL) and dried over $MgSO_4$. Concentration under reduced pressure and purification of the residue by flash chromatography (EtOAc→EtOAc/acetone 1:1) afforded **H** (50.6 mg, 0.078 mmol, 80%) as a colorless, viscous oil.

Note: The use of less concentrated aqueous $NaHCO_3$ is not recommended for workup, since not all HF may be neutralized, which would in turn lead to decomposition of the product during concentration under reduced pressure. In any case the pH of the aqueous phase should be determined after workup and should not be acidic!

TLC: R_f = 0.33 (EtOAc/acetone 1:1, UV, $KMnO_4$ or CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.54 (ddd, *J* = 14.7, 11.6, 6.0, 1 H), 7.24-7.21 (m, 2 H), 6.87-6.84 (m, 2 H), 6.13 (d, *J* = 11.7, 1 H), 5.82 (d, *J* = 15.1, 1 H), 5.23-5.16 (m, 2 H), 4.48 (dd, *J* = 11.8, 2.0, 1 H), 4.42 (dd, *J* = 11.8, 2.5, 1 H), 4.23-4.15 (m, 1 H), 4.18-4.07 (m, 4 H), 4.03-3.97 (m, 1 H), 3.79 (s, 3 H), 3.73-3.64 (m, 3H), 3.62 (br s, 1H), 3.60-3.52 (m, 1H), 3.48 (d, *J* = 4.8, 2H), 2.98 (br s, 1H), 2.66-2.57 (m, 1H), 2.45 (ddd, *J* = 13.6, 9.1, 5.5, 1 H), 2.36-2.23 (m, 2 H), 1.96-1.89 (m, 2 H), 1.93 (s, 3 H), 1.81-1.75 (m, 1 H), 1.75-1.61 (m, 2 H), 1.67 (d, *J* = 1.0, 3 H), 1.52-1.40 (m, 3 H), 1.31, 1.30 (2 x t, *J* = 7.1, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$; due to the diastereomeric nature of the product, the number of signals in the ^{13}C-spectrum exceeds the number of carbon atoms): δ = 167.0, 159.3, 145.6, 145.5, 140.5, 140.4, 134.0, 133.9, 130.2, 129.8, 129.7, 129.4, 126.8 (2C), 120.2, 120.1, 113.8, 78.2, 78.1, 75.0, 72.9, 71.1, 70.9, 70.5, 70.3, 65.4 (d, J = 5.0), 65.2 (d, J = 5.0), 62.1 (d, J = 6.6), 62.0 (d, J = 6.6), 61.4, 55.3, 41.3 (d, J = 5.9), 41.2 (d, J = 5.9), 41.1, 41.0, 38.3 (2C), 33.6 (d, J = 138.0), 33.5 (d, J = 138.0), 31.4 (2C), 31.3, 31.2, 25.0, 24.8, 23.4 (2C), 17.1 (2C), 16.5 (d, J = 6.2) (2C). **IR** (thin film): $\tilde{\nu}$ = 3398, 2929, 2857, 1707, 1633, 1612, 1513, 1367, 1301, 1247, 1148, 1025, 974, 818 cm^{-1}. **HRMS** (ESI): calcd for $C_{34}H_{53}NaO_{10}P$ [$(M+Na)^+$]: 675.3269; found: 675.3278. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –10.42° (c = 1.02, $CHCl_3$).

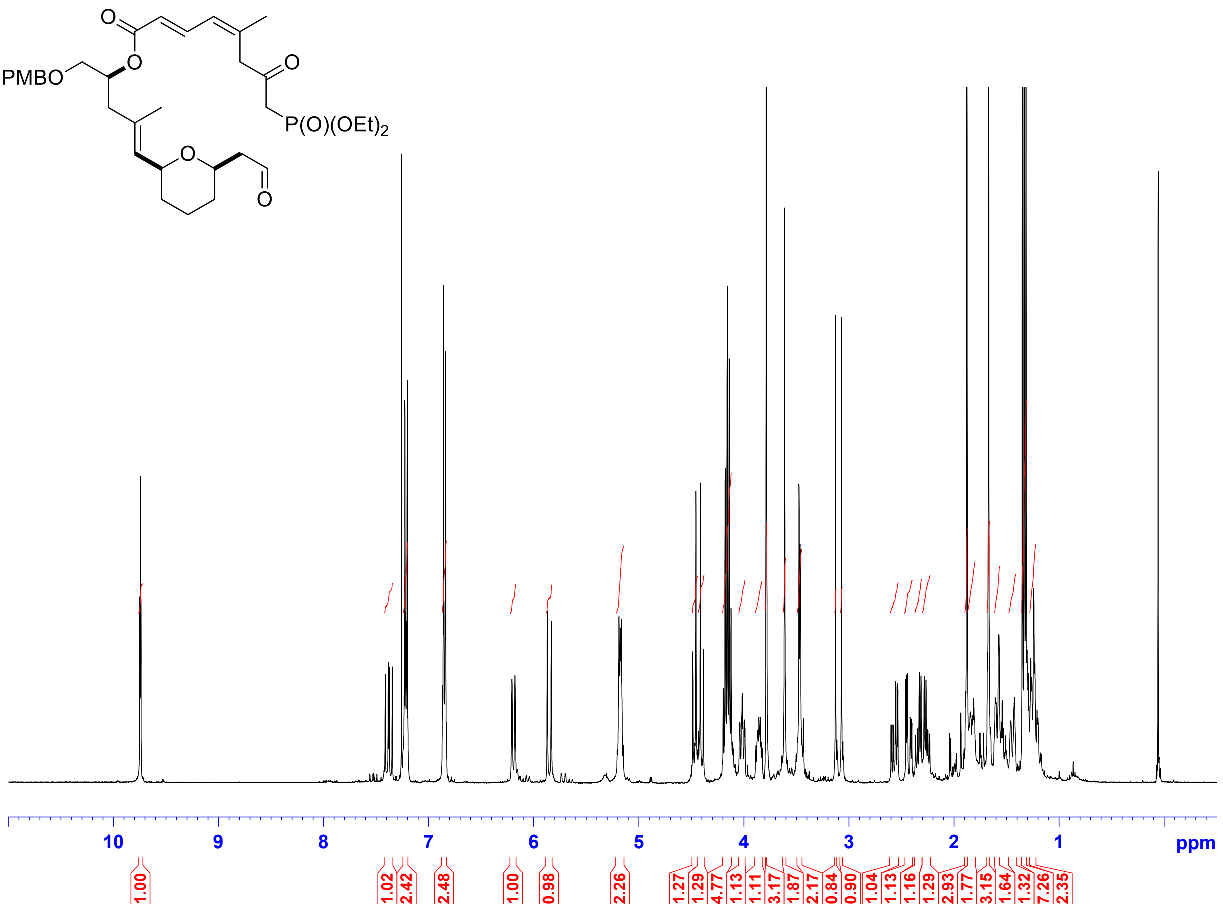






(2*E*,4*Z*)-((*S*,*E*)-1-(4-Methoxybenzyloxy)-4-methyl-5-((2*S*,6*R*)-6-(2-oxoethyl) tetrahydro-2H-pyran-2-yl)pent-4-en-2-yl) 8-(diethoxyphosphoryl)-5-methyl-7-oxo octa-2,4-dienoate (171). To a stirred solution of **H** (32.30 mg, 0.05 mmol, 1.00 equiv) in CH_2Cl_2 (1 mL) was added DMP (126 mg, 0.297 mmol, 6.00 equiv, addition in two equal portions, second addition after 30 min) at room temperature. After 3 h CH_2Cl_2 (5 mL) and a mixture of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL) were added then stirring was continued for 10 min, when two clear phases had formed. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic extracts were dried over $MgSO_4$. Concentration under reduced pressure and purification of the residue by flash chromatography (EtOAc, 1% AcOH to deactivate the stationary phase) gave **171** (23.3 mg, 0.036 mmol, 72%) as a pale yellow oil.

TLC: R_f = 0.33 (EtOAc, UV, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.74 (t, *J* = 2.2, 1 H), 7.38 (dd, *J* = 15.1, 11.7, 1 H), 7.24-7.20 (m, 2 H), 6.87-6.83 (m, 2 H), 6.19 (d, *J* = 11.5, 1 H), 5.85 (d, *J* = 15.1, 1 H), 5.21-5.15 (m, 2 H), 4.47 (d, *J* = 11.8, 1 H), 4.40 (d, *J* = 11.8, 1 H), 4.19-4.12 (m, 4 H), 4.02 (ddd, *J* = 11.2, 7.7, 2.3, 1 H), 3.89-3.83 (m, 1 H), 3.79 (s, 3 H), 3.62 (br. s, 2 H), 3.49-3.44 (m, 2 H), 3.13 (s, 1 H), 3.07 (s, 1 H), 2.57 (ddd, *J* = 16.3, 7.7, 2.5, 1 H), 2.43 (ddd, *J* = 16.3, 4.9, 2.0, 1 H), 2.34 (dd, *J* = 13.7, 6.9, 1 H), 2.26 (dd, *J* = 13.7, 7.0, 1 H), 1.88 (s, 3 H), 1.86-1.81 (m, 2 H), 1.67 (d, *J* = 1.2, 3 H), 1.62-1.56 (m, 1 H), 1.47-1.43 (m, 1 H), 1.33 (t, *J* = 7.1, 6 H), 1.28-1.20 (m, 2 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 201.8, 198.3 (d, *J* = 6.8), 166.8, 159.3, 140.9, 139.8, 134.3, 130.2, 129.5, 129.4, 127.6, 121.2, 113.9, 75.1, 72.9, 72.9, 71.3, 70.3, 62.9 (d, *J* = 6.5), 55.4, 50.1, 47.7, 42.2 (d, *J* = 127), 41.0, 31.2, 31.1, 25.0, 23.4, 17.2, 16.4 (d, *J* = 6.0). **IR** (thin film): $\tilde{\nu}$ = 2977, 2932, 2915, 2858, 1714, 1638, 1612, 1514, 1440, 1365, 1248, 1020, 971 cm^{-1}. **HRMS** (ESI): calcd for $C_{34}H_{50}O_{10}P$ [$(M+H)^+$]: 649.3136; found: 649.3158. $[\alpha]_D^{24}$: –0.76° (c = 1.15, $CHCl_3$).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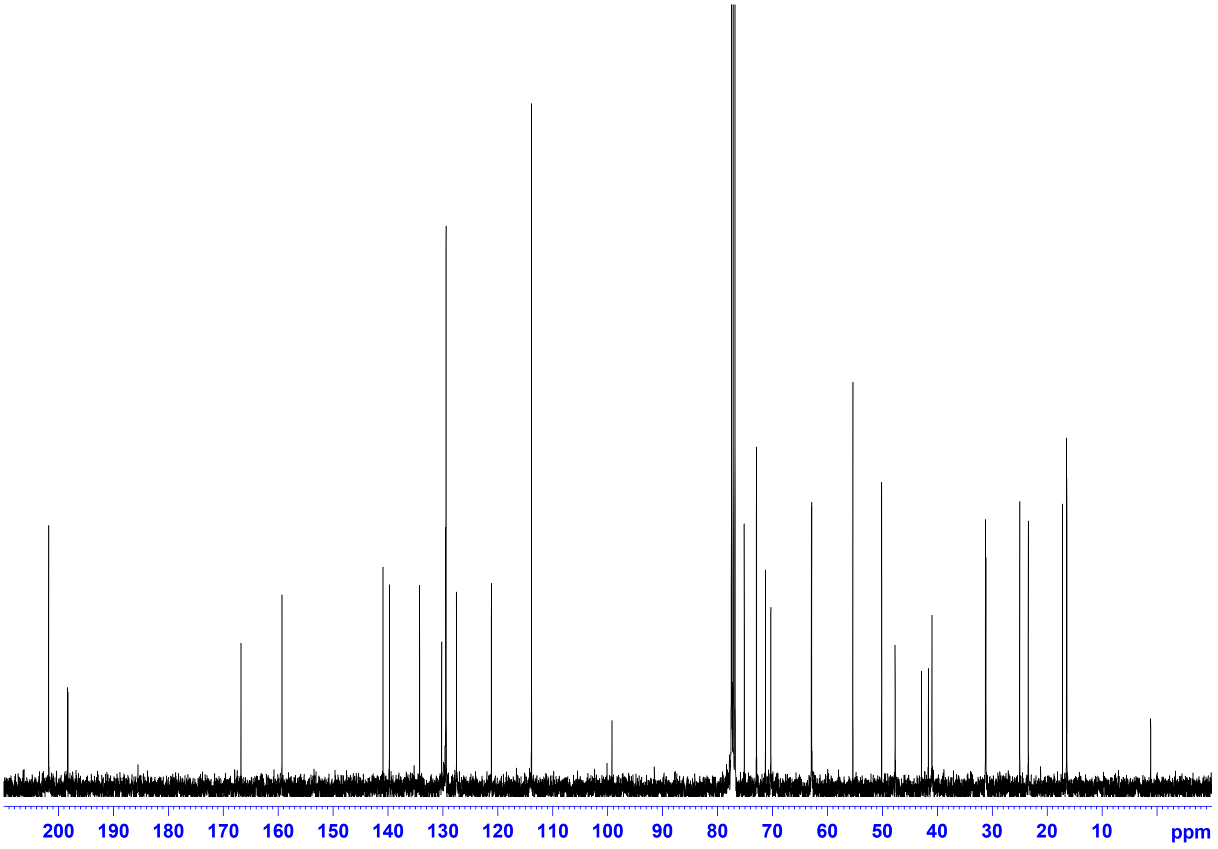
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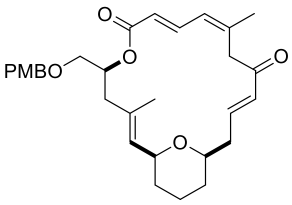
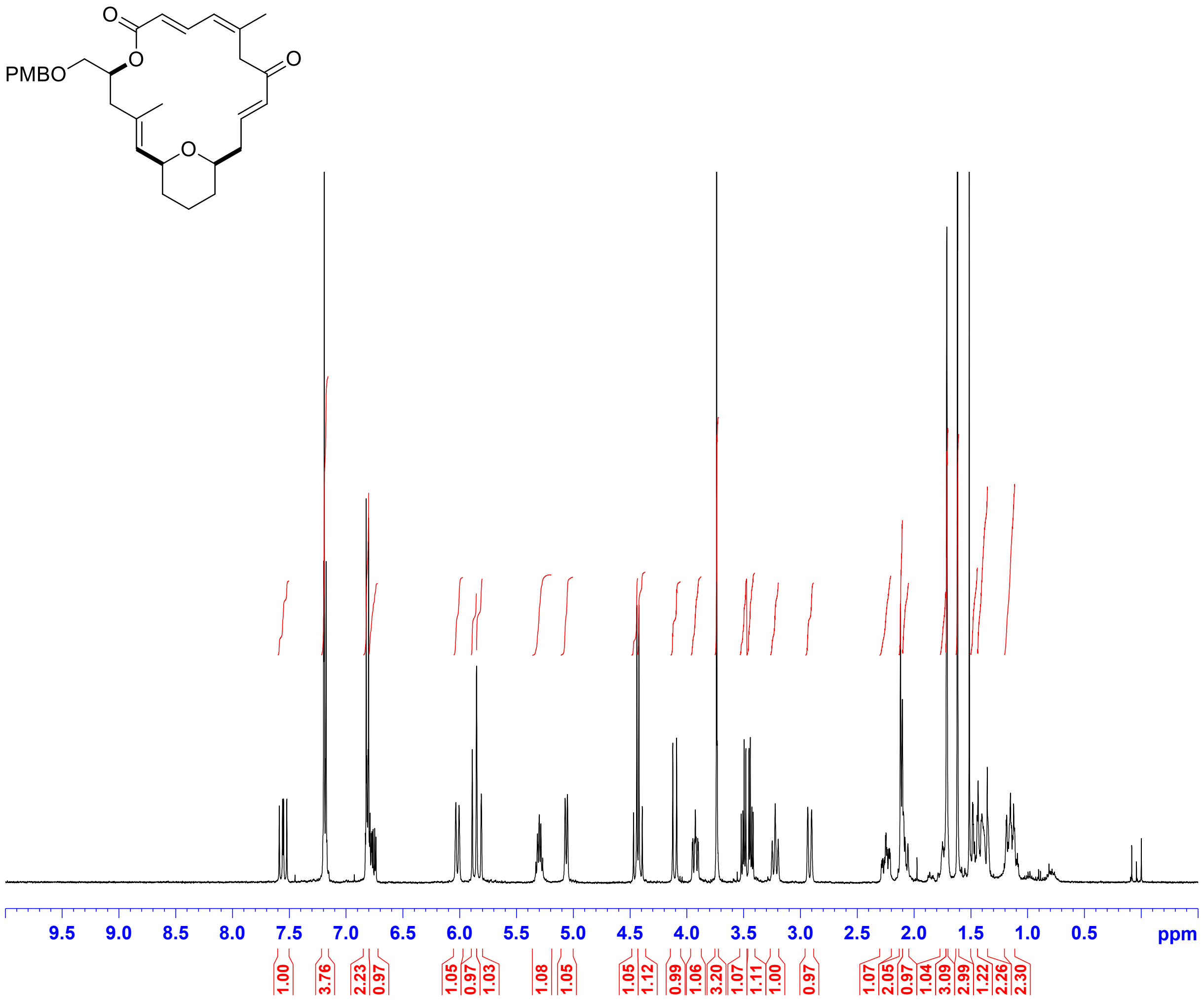


(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*R*)-5-((4-Methoxybenzyloxy)methyl)-3,11-dimethyl-6,21-dioxabicyclo [15.3.1]henicosa-2,8,10,14-tetraene-7,13-dione (172). To a solution of **171** (22.9 mg, 0.035 mmol, 1.00 equiv, co-evaporated before use with 1 mL of dry toluene) in THF (18 mL) was added a solution of NaHMDS (1M in THF, 0.05 mL, 0.05 mmol, 1.40 equiv, diluted with 5 mL of THF) at –78 °C; an orange color was produced immediately. Stirring was continued while the cooling bath was slowly allowed to warm to room temperature. After 2 d saturated aqueous NH_4Cl (5 mL), H_2O (1 mL) and EtOAc (5 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/Hex 1:4) afforded **172** (8.6 mg, 0.017 mmol, 49%) as a colorless oil.

Note: Varying yields between 49% and 90% were observed independent of the scale of the reaction.

TLC: R_f = 0.35 (EtOAc/Hex 1:3, UV, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.62 (dd, *J* = 15.1, 11.6, 1 H), 7.27-7.24 (m, 2 H), 6.89-6.87 (m, 2 H), 6.84 (ddd, *J* = 16.5, 9.8, 4.3, 1 H), 6.09 (d, *J* = 11.6, 1 H), 5.94 (d, *J* = 15.1, 1 H), 5.90 (d, *J* = 16.5, 1 H), 5.40-5.34 (m, 1 H), 5.13 (dd, *J* = 8.0, 0.9, 1 H), 4.52 (d, *J* = 11.8, 1 H), 4.48 (d, *J* = 11.8, 1 H), 4.18 (d, *J* = 13.5, 1 H), 3.99 (ddd, *J* = 11.3, 8.0, 2.3, 1 H), 3.81 (s, 3 H), 3.57 (dd, *J* = 10.4, 6.0, 1 H), 3.50 (dd, *J* = 10.4, 4.9, 1 H), 3.32-3.26 (m, 1 H), 2.99 (d, *J* = 13.6, 1 H), 2.32 (dddd, *J* = 15.0, 10.1, 4.4, 2.0, 1 H), 2.19-2.17 (m, 2 H), 2.17-2.12 (m, 1 H), 1.83-1.79 (m, 1 H), 1.78 (s, 3 H), 1.69 (d, *J* = 1.2, 3 H), 1.55-1.51 (m, 1 H), 1.51-1.42 (m, 2 H), 1.27-1.18 (m, 2 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 198.5, 166.9, 159.4, 147.2, 142.8, 139.3, 131.6, 131.3, 130.3, 130.3, 129.4, 125.6, 121.4, 114.0, 76.1, 75.4, 73.0, 71.7, 69.6, 55.4, 45.1, 42.8, 40.7, 32.0, 31.7, 23.6, 23.5, 16.7. **IR** (thin film): $\tilde{\nu}$ = 2978, 2932, 2915, 2858, 1714, 1638, 1612, 1514, 1365, 1248, 1151, 1020, 972 cm^{-1}. **HRMS** (ESI): calcd for $C_{30}H_{39}O_6$ [(M+H)$^+$]: 495.2741; found: 495.2741. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –198.92° (c = 0.36, $CHCl_3$).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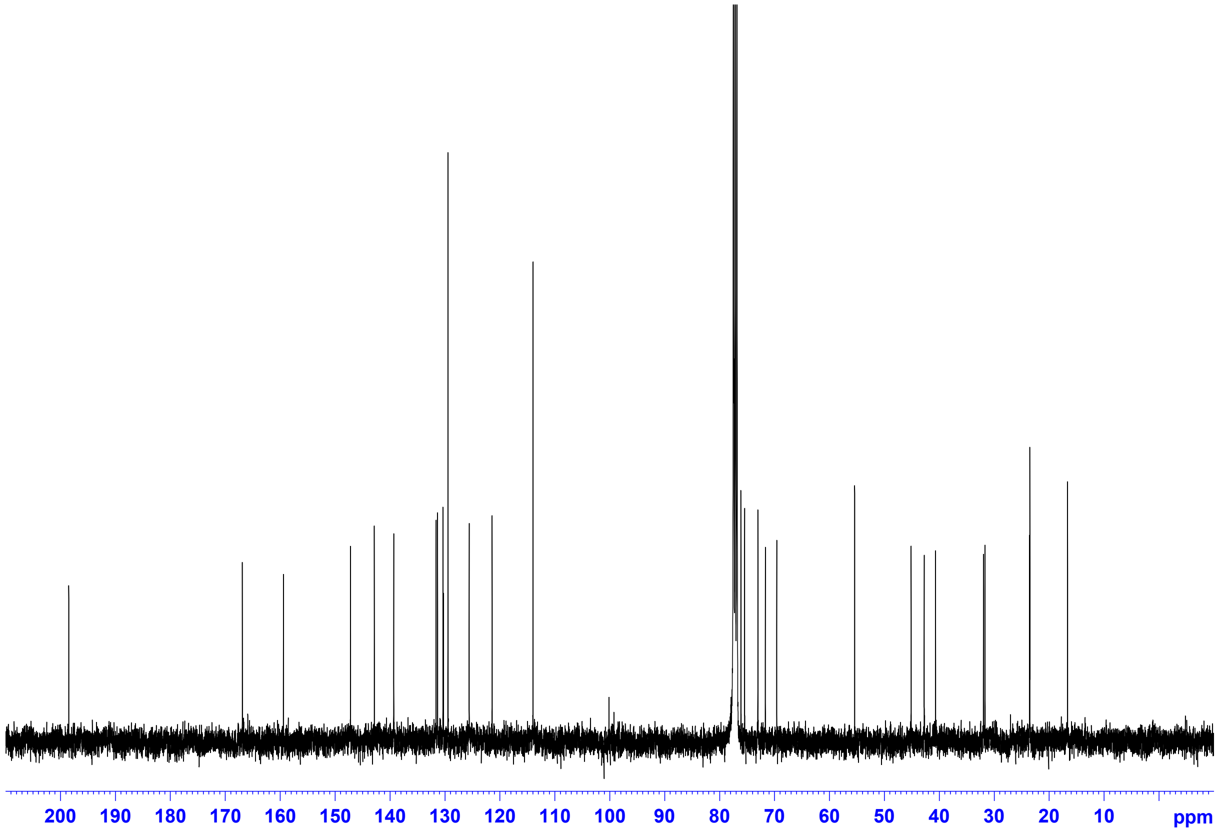
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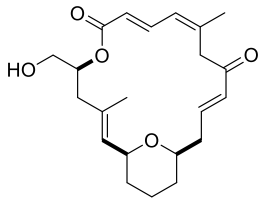
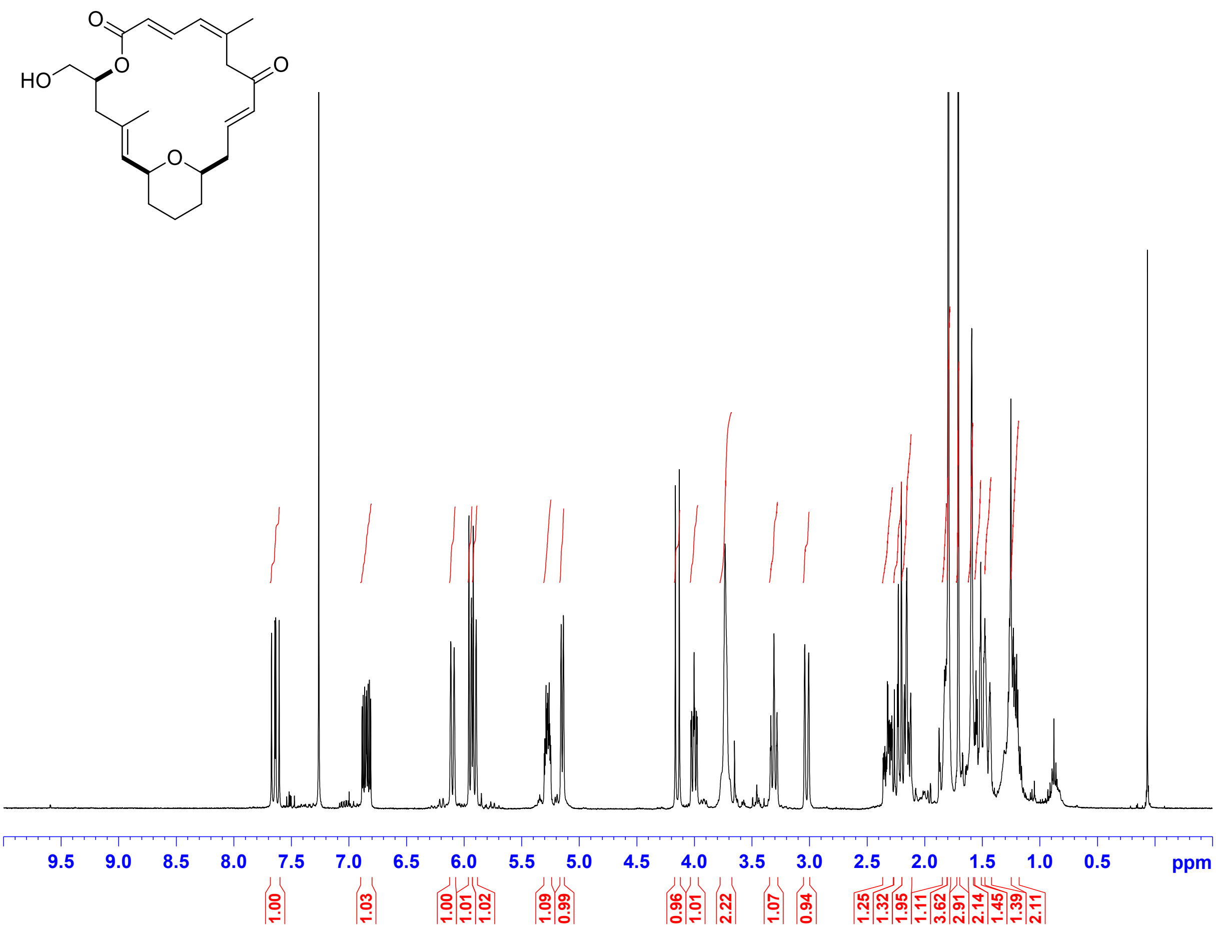


(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*R*)-5-(Hydroxymethyl)-3,11-dimethyl-6,21-dioxabicyclo [15.3.1]henicosa-2,8,10,14-tetraene-7,13-dione (173). To a solution of **172** (8.6 mg, 0.017 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) was added H_2O (0.1 mL) followed by DDQ (12 mg, 0.052 mmol, 3.00 equiv) at room temperature. The mixture was vigorously stirred for 2 h; then saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the reisdue by flash chromatography (EtOAc/Hex 1:2→1:1) delivered **173** (4.7 mg, 0.013 mmol, 72%) as an amorphous off-white solid.

TLC: R_f = 0.41 (EtOAc/Hex 1:1, UV, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 15.1, 11.5, 1 H), 6.85 (ddd, *J* = 16.2, 9.7, 4.6, 1 H), 6.09 (d, *J* = 11.9, 1 H), 5.94 (d, *J* = 15.1, 1 H), 5.94-5.89 (m, 1 H), 5.27 (dddd, *J* = 10.6, 5.9, 4.1, 2.2, 1 H), 5.15 (d, *J* = 8.0, 1 H), 4.15 (d, *J* = 13.7, 1 H), 4.00 (ddd, *J* = 11.2, 8.0, 2.3, 1 H), 3.77-3.69 (m, 2 H), 3.34-3.28 (m, 1 H), 3.02 (d, *J* = 13.7, 1 H), 2.32 (dddd, *J* = 15.0, 10.2, 4.5, 2.0, 1 H), 2.23 (dd, *J* = 13.6, 10.8, 1 H), 2.19-2.12 (m, 2 H), 1.84-1.81 (m, 1 H), 1.79 (s, 3 H), 1.71 (d, *J* = 1.1, 3 H), 1.62-1.58 (m, 2 H), 1.56-1.50 (m, 1 H), 1.48-1.42 (m, 1 H), 1.25-1.17 (m, 2 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 198.3, 167.1, 147.2, 143.3, 139.7, 131.6, 131.3, 130.4, 125.5, 121.0, 76.2, 75.4, 71.9, 65.4, 45.1, 42.1, 40.6, 31.9, 31.7, 23.7, 23.6, 16.7. **IR** (thin film): $\tilde{\nu}$ = 3445, 2931, 2856, 1715, 1668, 1635, 1437, 1359, 1280, 1209, 1177, 1150, 1044, 979 cm^{-1}. **HRMS** (ESI): calcd for $C_{22}H_{30}NaO_5$ [(M+Na)$^+$]: 397.1985; found: 397.1981. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –163.24° (c = 0.18, $CHCl_3$).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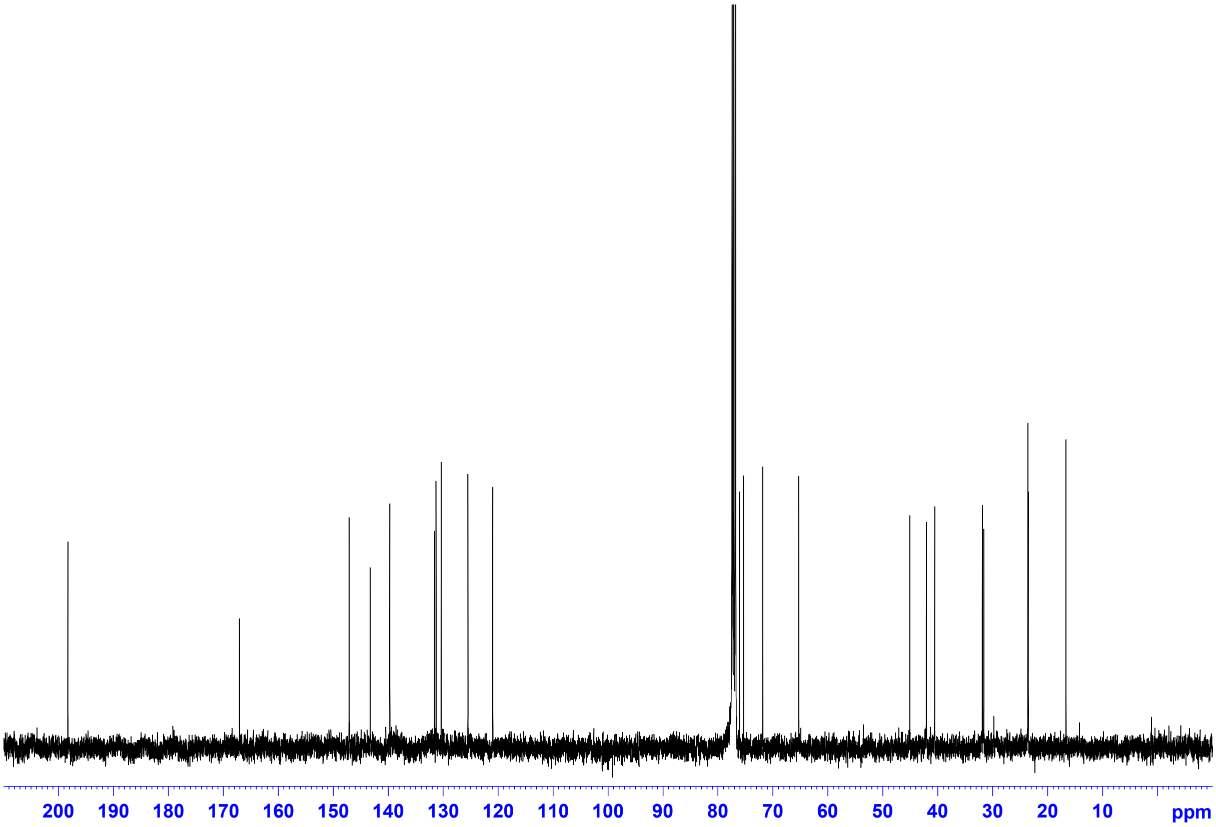
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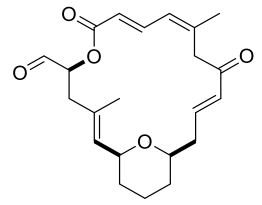
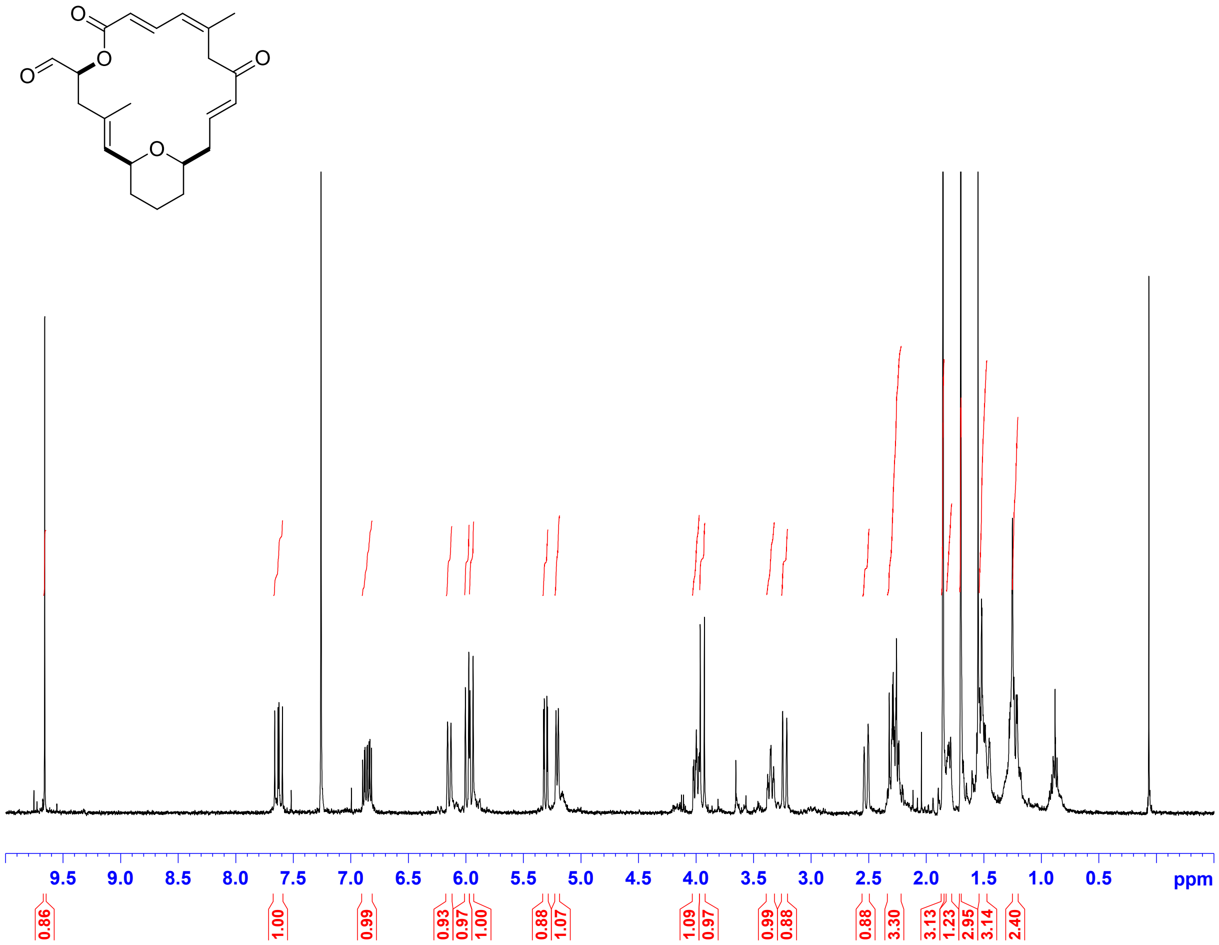


(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*R*)-3,11-Dimethyl-7,13-dioxo-6,21-dioxabicyclo [15.3.1]henicosa-2,8,10,14-tetraene-5-carbaldehyde (167). To a stirred solution of **173** (4.7 mg, 0.013 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) was added DMP (22 mg, 0.05 mmol, 4.00 equiv, addition in 2 equal portions, the second portion added after 20 min) and stirring was continued for 60 min. A mixture of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL) was then added together with CH_2Cl_2 (5 mL) and stirring was continued for 10 min, when two practically clear phases had formed. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/Hex 1:5→1:3→1:1) afforded **167** (3.7 mg, 0.01 mmol, 77%) as a semi-solid.

TLC: R_f = 0.53 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.67 (s, 1 H), 7.63 (dd, *J* = 15.2, 11.7, 1 H), 6.85 (ddd, *J* = 16.2, 8.7, 6.0, 1 H), 6.14 (d, *J* = 11.7, 1 H), 5.98 (d, *J* = 16.2, 1 H), 5.96 (d, *J* = 15.2, 1 H), 5.31 (dd, *J* = 11.3, 2.5, 1 H), 5.20 (d, *J* = 8.0, 1 H), 4.00 (ddd, *J* = 11.5, 8.0, 2.4, 1 H), 3.95 (d, *J* = 14.4, 1 H), 3.35 (ddt, *J* = 11.8, 8.9, 2.5, 1 H), 3.23 (d, *J* = 14.4, 1 H), 2.52 (d, *J* = 14.1, 1 H), 2.33-2.22 (m, 3 H), 1.86 (s, 3 H), 1.83-1.77 (m, 1 H), 1.71 (d, *J* = 0.9, 3 H), 154-1.47 (m, 3 H), 1.28-1.21 (m, 2 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 199.3, 197.7, 166.5, 146.8, 144.2, 140.5, 131.5, 131.4, 130.1, 125.7, 120.0, 76.1, 75.6, 75.3, 45.0, 40.1, 39.9, 31.8, 31.4, 24.2, 23.5, 16.1. **IR** (thin film): $\tilde{\nu}$ = 2929, 2855, 1715, 1669, 1635, 1437, 1354, 1279, 1257, 1208, 1146, 1078, 1045, 979 cm^{-1}. **HRMS** (ESI): calcd for $C_{22}H_{29}O_5$ [(M+H)$^+$]: 373.2010; found: 373.2021. $[\alpha]_D^{24}$: –236.81° (c = 0.23, $CHCl_3$).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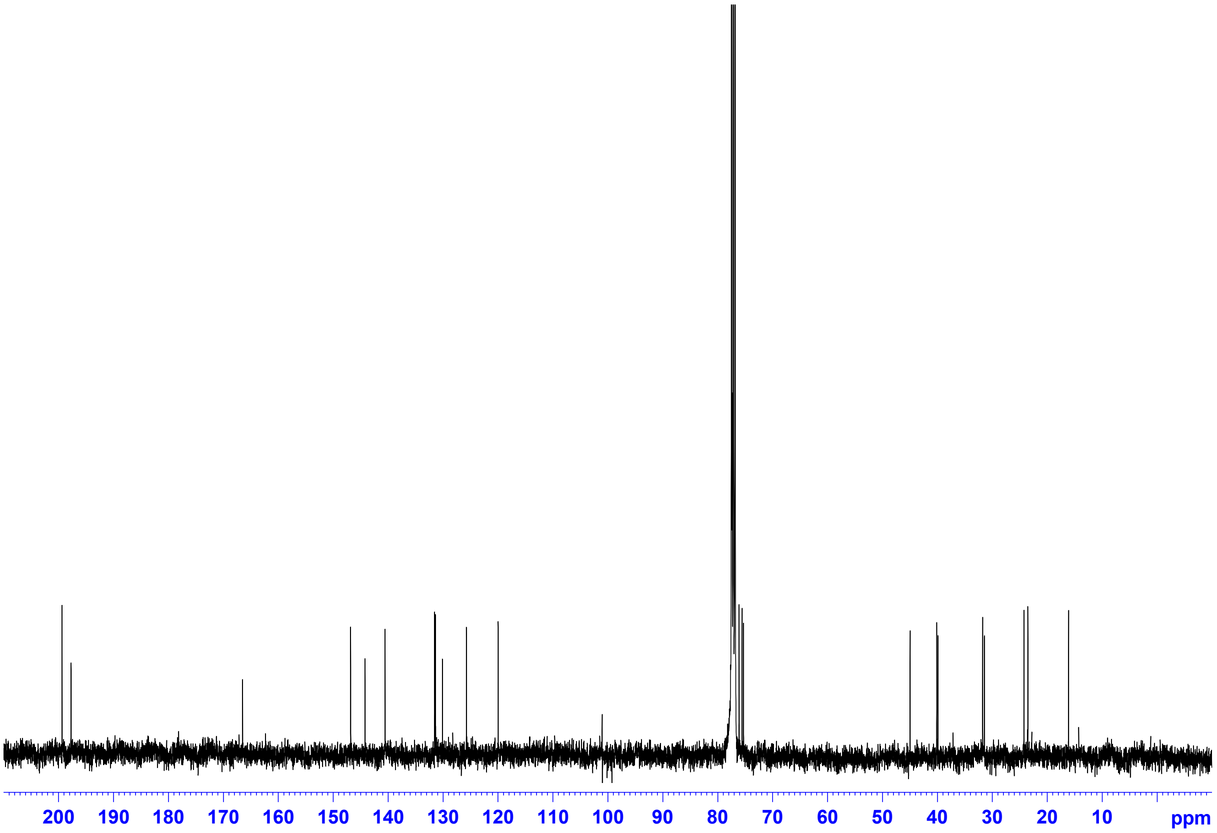
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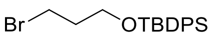
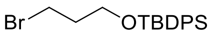
5.5.2. Des-THP-(–)-Zampanolide (174)



(3-Bromopropoxy)(*tert*-butyl)diphenylsilane (177). To a solution of 3-bromo-1-propanol (3.0 mL, 35.1 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added sequentially NEt_3 (6.3 mL, 45.6 mmol, 1.3 equiv), TBDPSCl (10.6 g, 38.6 mmol, 1.1 equiv) and DMAP (0.21 g, 1.8 mmol, 0.05 equiv). The solution was stirred for 18 h at room temperature. Saturated aqueous $NaHCO_3$ (100 mL) was added then the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (Hex→EtOAc/Hex 1:10) afforded **177** (12.3 g, 32.7 mmol, 93%) as a colorless oil.

TLC: R_f = 0.35 (EtOAc/Hex 1:100; UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.69-7.66 (m, 4 H), 7.46-7.37 (m, 6 H), 3.79 (t, J = 5.7, 2 H), 3.59 (t, J = 6.6, 2 H), 2.11-2.05 (m, 2 H), 1.06 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 135.7, 133.7, 129.8, 127.8, 61.5, 35.6, 30.7, 27.0, 19.4. **IR** (thin film): $\tilde{\nu}$ = 3070, 2958, 2930, 2857, 1472, 1427, 1389, 1105, 822, 700 cm^{-1}. **HRMS** (EI): calcd for $C_{15}H_{16}BrOSi$ [$(M-C_4H_9)^+$]: 319.0154; found: 319.0150.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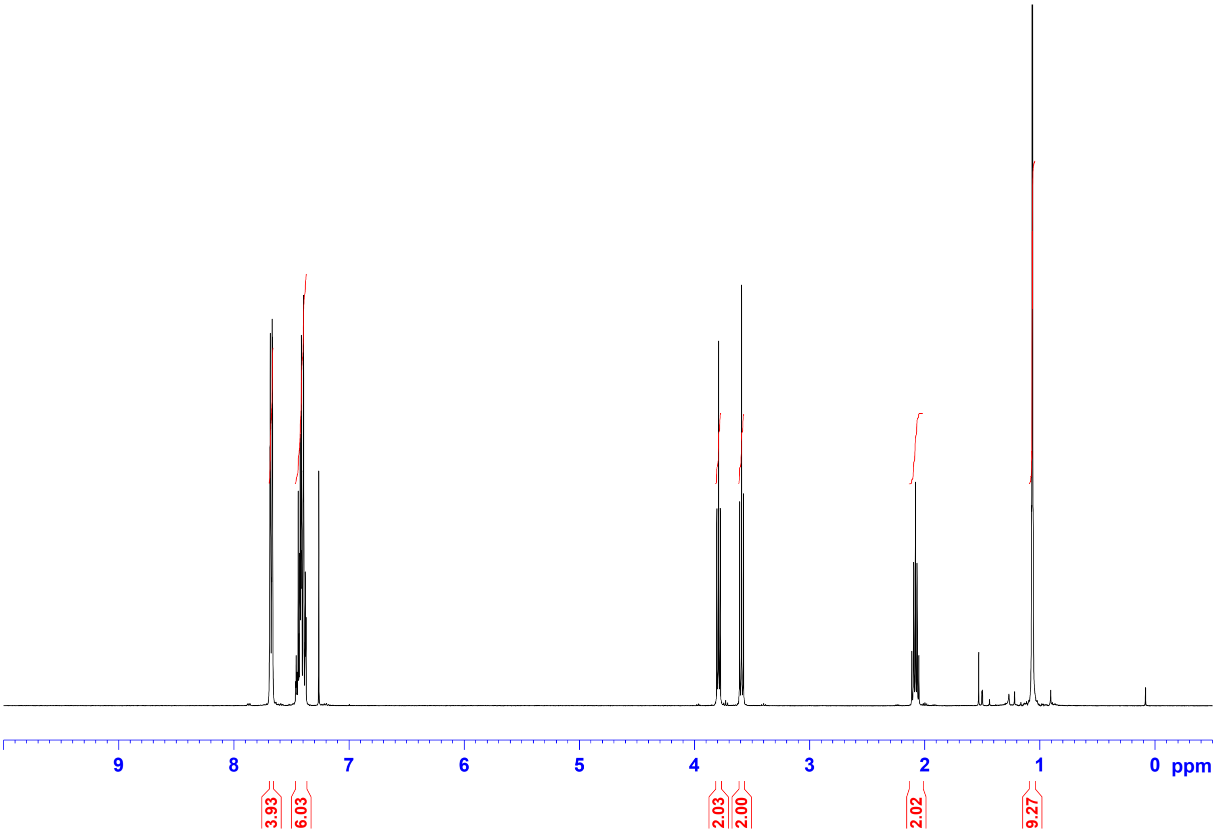
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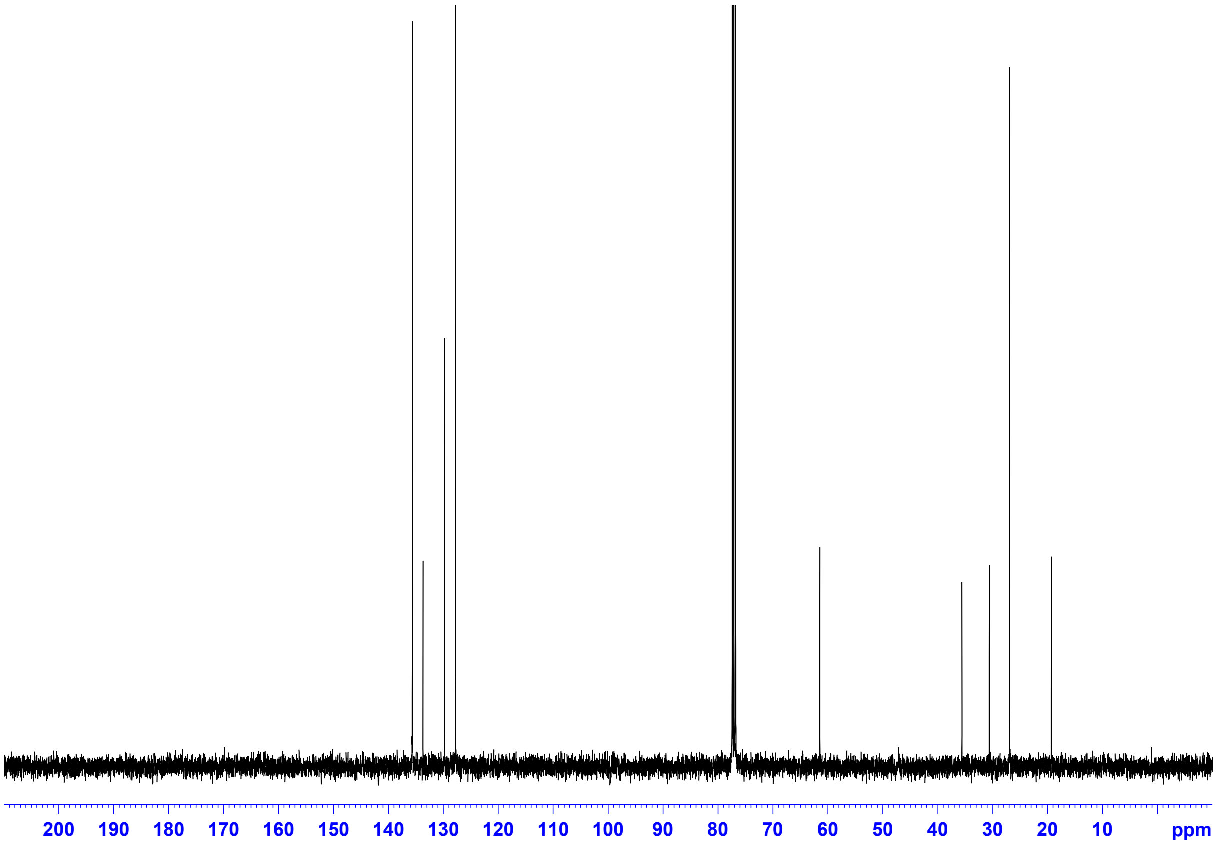
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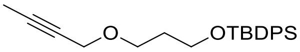
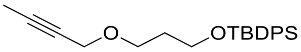


(3-(But-2-ynyloxy)propoxy)(*tert*-butyl)diphenylsilane (178). To a suspension of NaH (27.6 mg, 0.69 mmol, 1.3 equiv) in DMF (1.5 mL) at 0 °C was added 2-butyn-1-ol (45.6 mg, 0.64 mmol, 1.2 equiv) dropwise. The mixture was stirred at 0 °C for 20 minutes then a solution of **177** (201 mg, 0.53 mmol, 1.0 equiv) in DMF (0.5 mL; the vial was rinsed twice with 0.5 mL of DMF) followed by TBAI (19.6 mg, 0.05 mmol. 0.1 equiv.) were added. The cooling bath was removed and the mixture was stirred for 15 h at room temperature. EtOAc (5 mL) was added followed by water (5 mL). Phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water (2 x 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (Hexane→EtOAc/Hex 1:200) afforded **178** (73.2 mg, 0.20 mmol, 38%) as a colorless oil.

TLC: R_f = 0.33 (EtOAc/Hex 1:20; UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 4 H), 7.45-7.36 (m, 6 H), 4.07 (q, *J* = 2.3, 2 H), 3.78 (t, *J* = 6.1, 2 H), 3.64 (t, *J* = 6.4, 2 H), 1.88-1.83 (m, 2 H), 1.85 (t, *J* = 2.3, 3 H), 1.06 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 135.7, 134.1, 129.7, 127.7, 82.3, 75.5, 66.8, 60.8, 58.8, 32.7, 27.0, 19.4, 3.7. **IR** (thin film): $\tilde{\nu}$ = 3071, 2955, 2929, 2856, 1472, 1427, 1389, 1361, 1089, 822, 736 cm^{-1}. **HRMS** (EI): calcd for $C_{23}H_{31}O_2Si$ [(M+H)$^+$]: 367.2088; found: 367.2084.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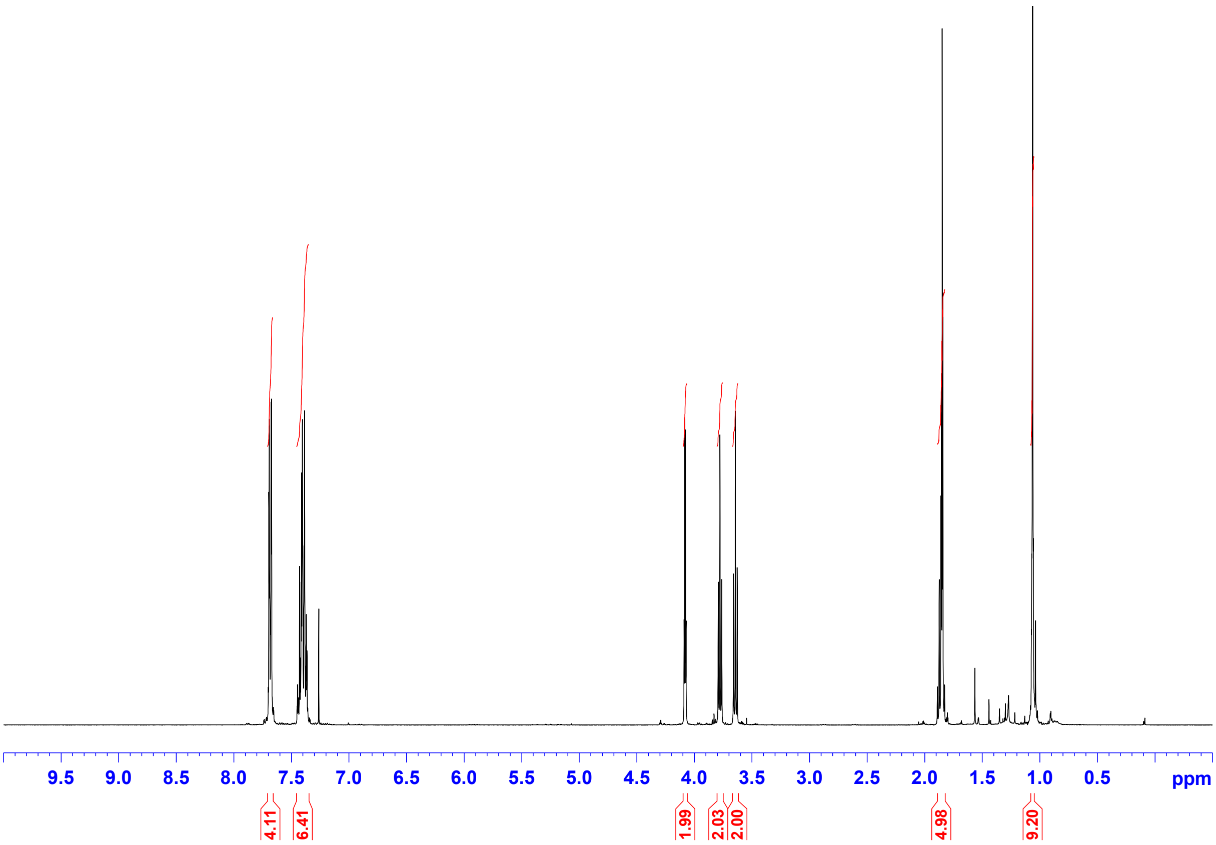
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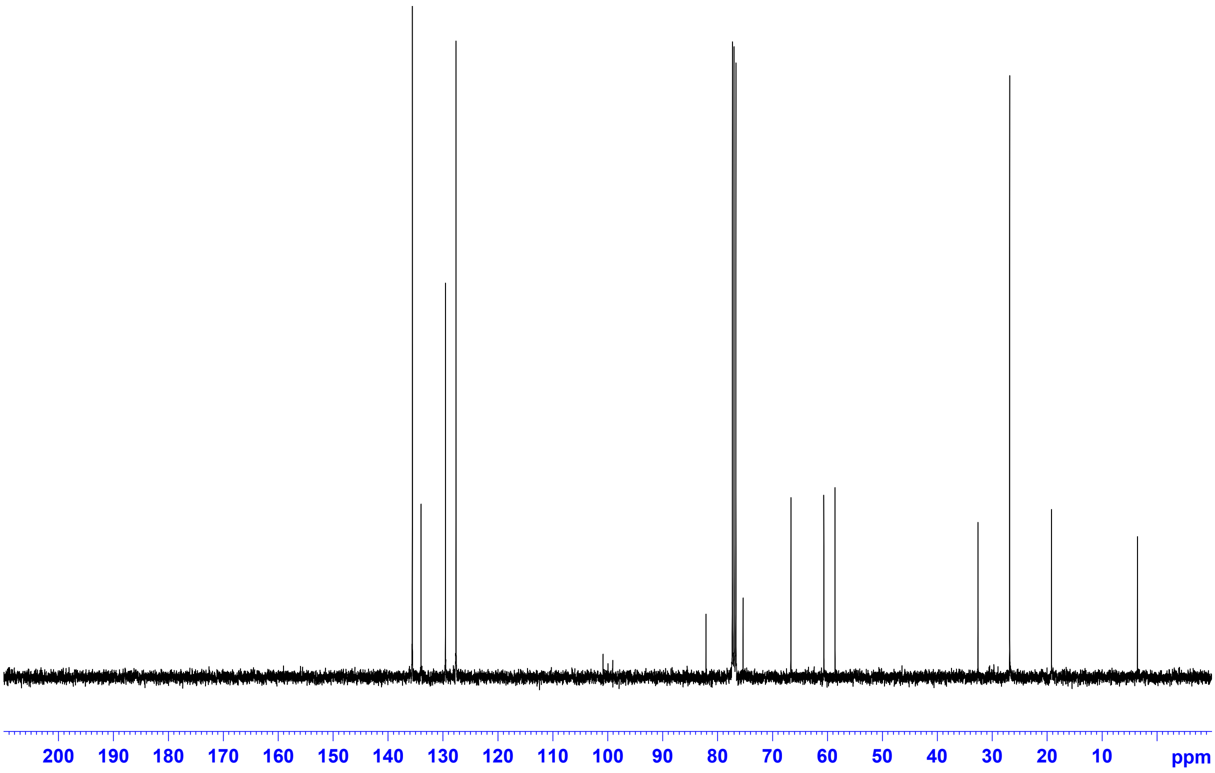
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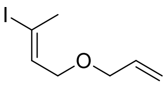

(*E*)-1-(Allyloxy)-3-iodobut-2-ene (181). To a suspension of NaH (60% dispersion in mineral oil, 1.31 g, 32.9 mmol, 1.7 equiv) in THF (200 mL) at 0 °C was added alcohol **31** (3.83 g, 19.3 mmol, 1.0 equiv) dissolved in THF (10 mL; the flask was rinsed three times with 3 mL of THF) dropwise. The mixture was stirred at 0 °C for 20 min and then allylbromide (1.8 mL, 21.3 mmol, 1.1 equiv) was added neat. The resulting yellow mixture was stirred at 0 °C for 7 h before H_2O (100 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure, followed by bulb-to-bulb distillation (30-90 °C at 5 mbar),[46] then the residue left was filtered over a pad of silica gel (EtOAc/Hex 1:2) to afford alkene **181** (1.95 g, 8.20 mmol, 42%) as a yellow oil.

TLC: R_f = 0.43 (EtOAc/Hex 1:20, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 6.34 (tq, *J* = 6.9, 1.5, 1 H), 5.94-5.85 (m, 1 H), 5.30-5.25 (m, 1 H), 5.22-5.18 (m, 1 H), 3.96 (dt, *J* = 5.78, 1.4, 2 H), 3.94-3.91 (m, 2 H), 2.44-2.43 (m, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 137.7, 134.5, 117.6, 98.9, 71.2, 66.8, 28.3. **IR** (thin film): $\tilde{\nu}$ = 2955, 2924, 2856, 1732, 1659, 1640, 1457, 1363, 1249, 1108, 1051, 991, 915. **HRMS** (EI): calcd for C_4H_6IO [$(M–C_3H_5)^+$]: 196.9458; found: 196.9460.

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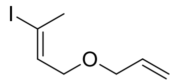
[46] Buld-to-bulb distillation allowed the removal of the allene side product **182** (no spectral data acquired).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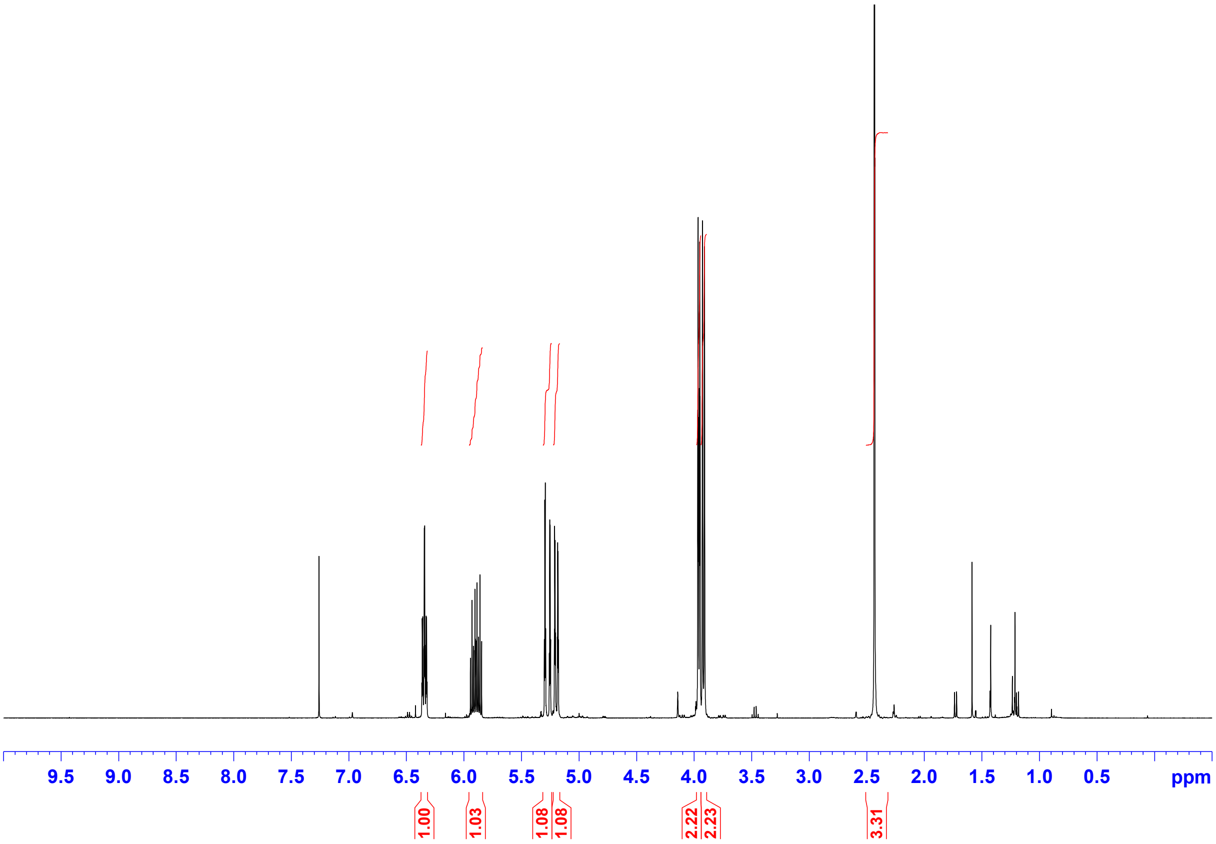
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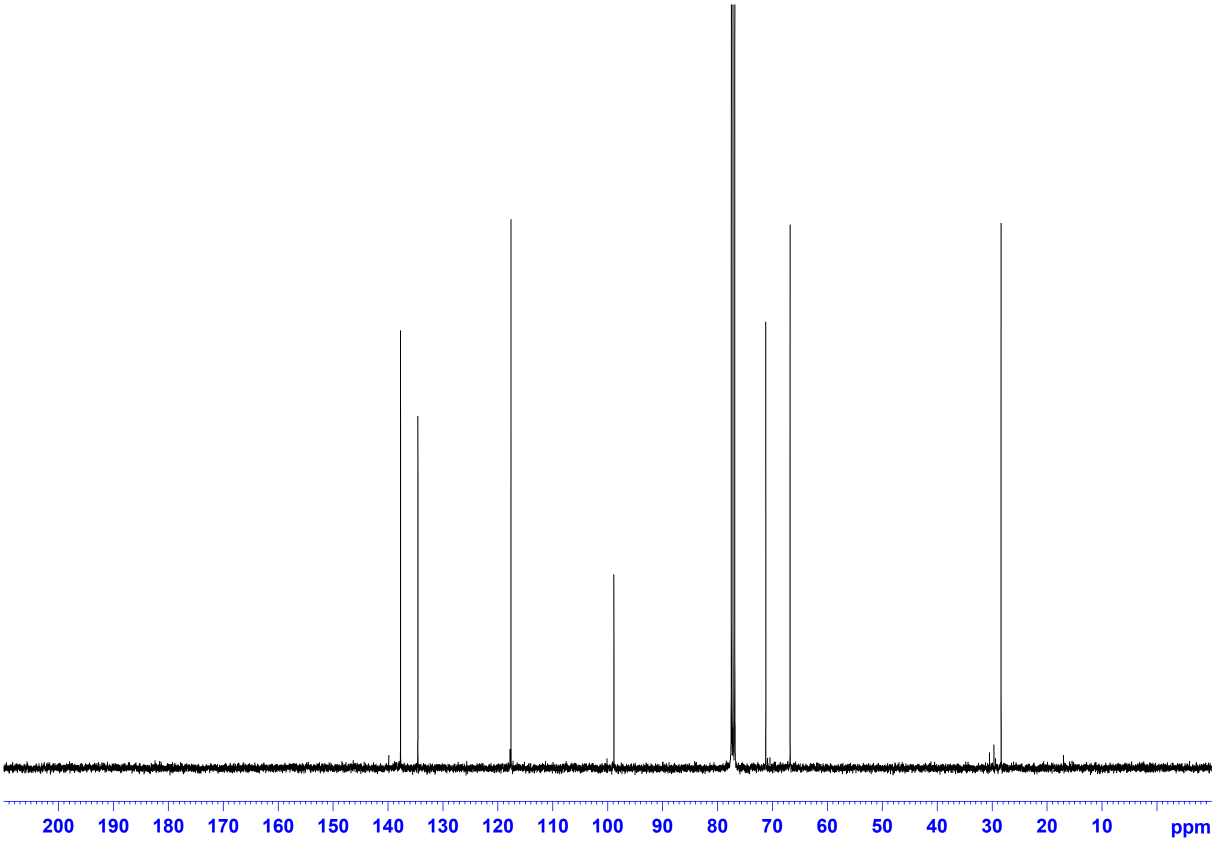
1.08
1.08
2.22
2.23
3.31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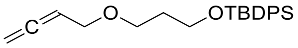
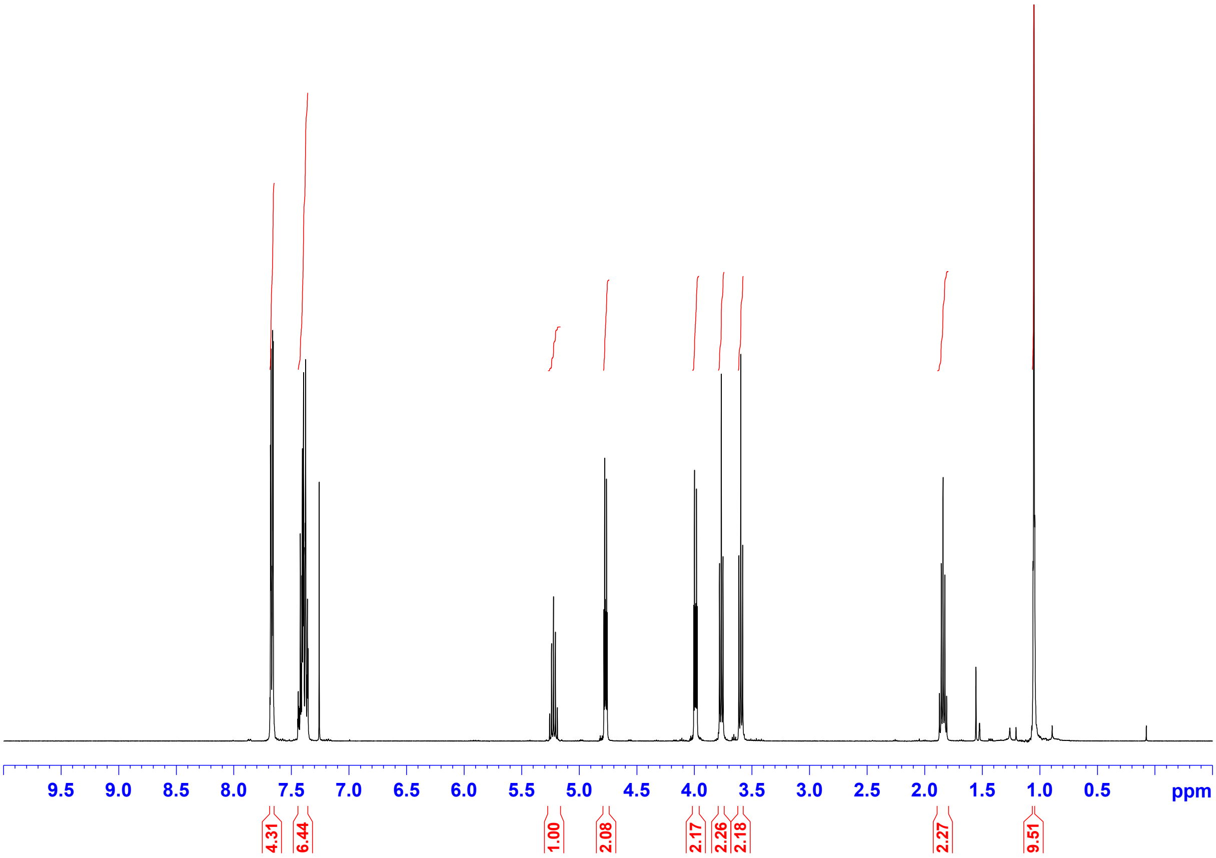
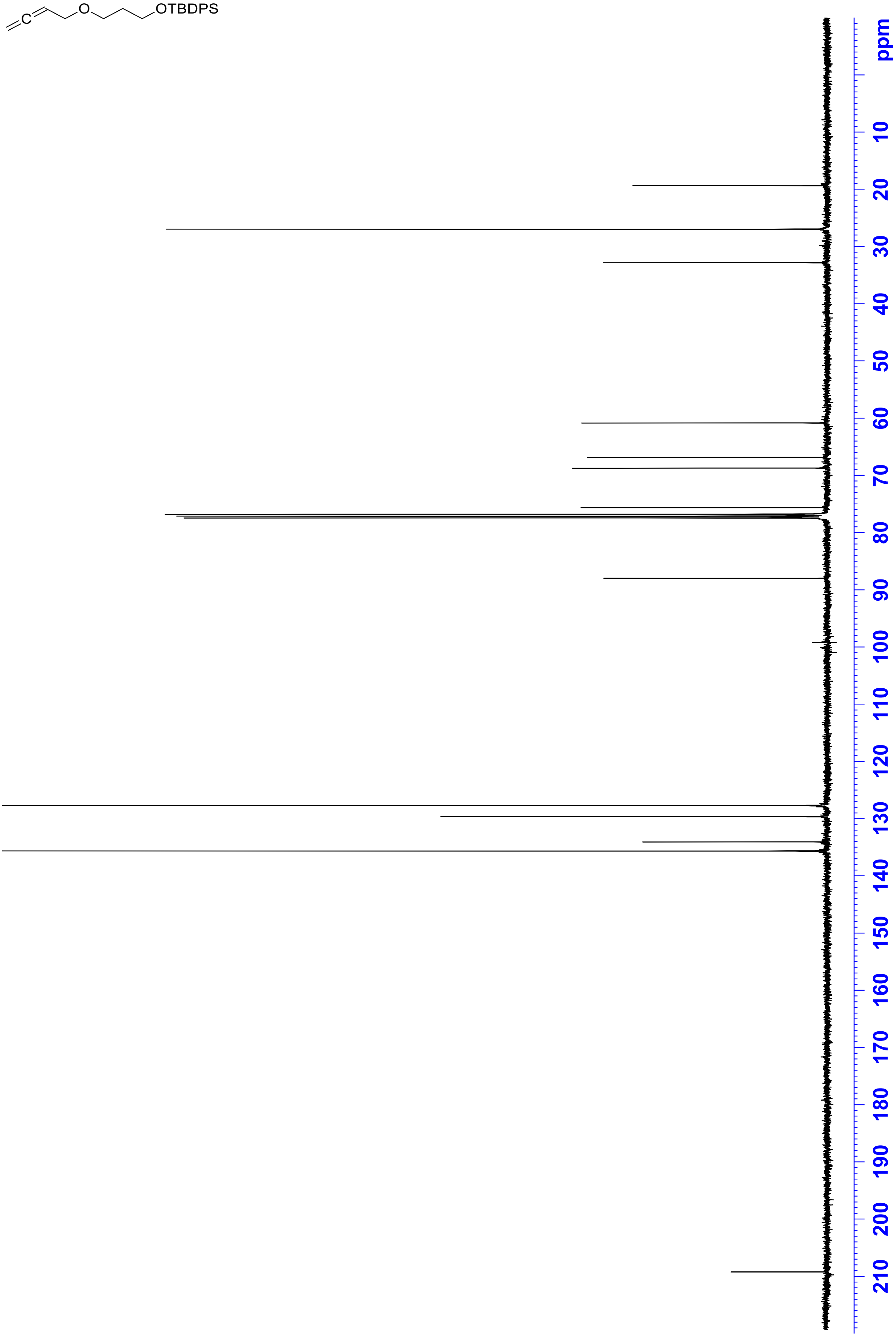


(3-(Buta-2,3-dien-1-yloxy)propoxy)(*tert*-butyl)diphenylsilane.

TLC: R_f = 0.31 (EtOAc/Hex 1:20, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.69-7.66 (m, 4 H); 7.44-7.36 (m, 6 H), 5.23 (q, *J* = 6.8, 1 H), 4.77 (dt, *J* = 6.6, 2.5, 2 H), 3.99 (dt, *J* = 6.8, 2.5, 2 H), 3.77 (t, *J* = 6.0, 2 H), 3.60 (t, *J* = 6.4, 2 H), 1.84 (q, *J* = 6.3, 2 H), 1.05 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 209.3, 135.7, 134.1, 129.7, 127.7, 88.1, 75.7, 68.8, 66.9, 60.1, 32.9, 27.0, 19.4. **IR** (thin film): $\tilde{\nu}$ = 3071, 2930, 2857, 1956, 1472, 1427, 1361, 1089, 1007, 843, 700 cm^{-1}. **HRMS** (EI): calcd for $C_{23}H_{31}O_2Si$ [(M+H)$^+$]: 367.2086; found: 367.2088.

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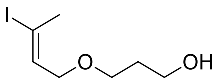
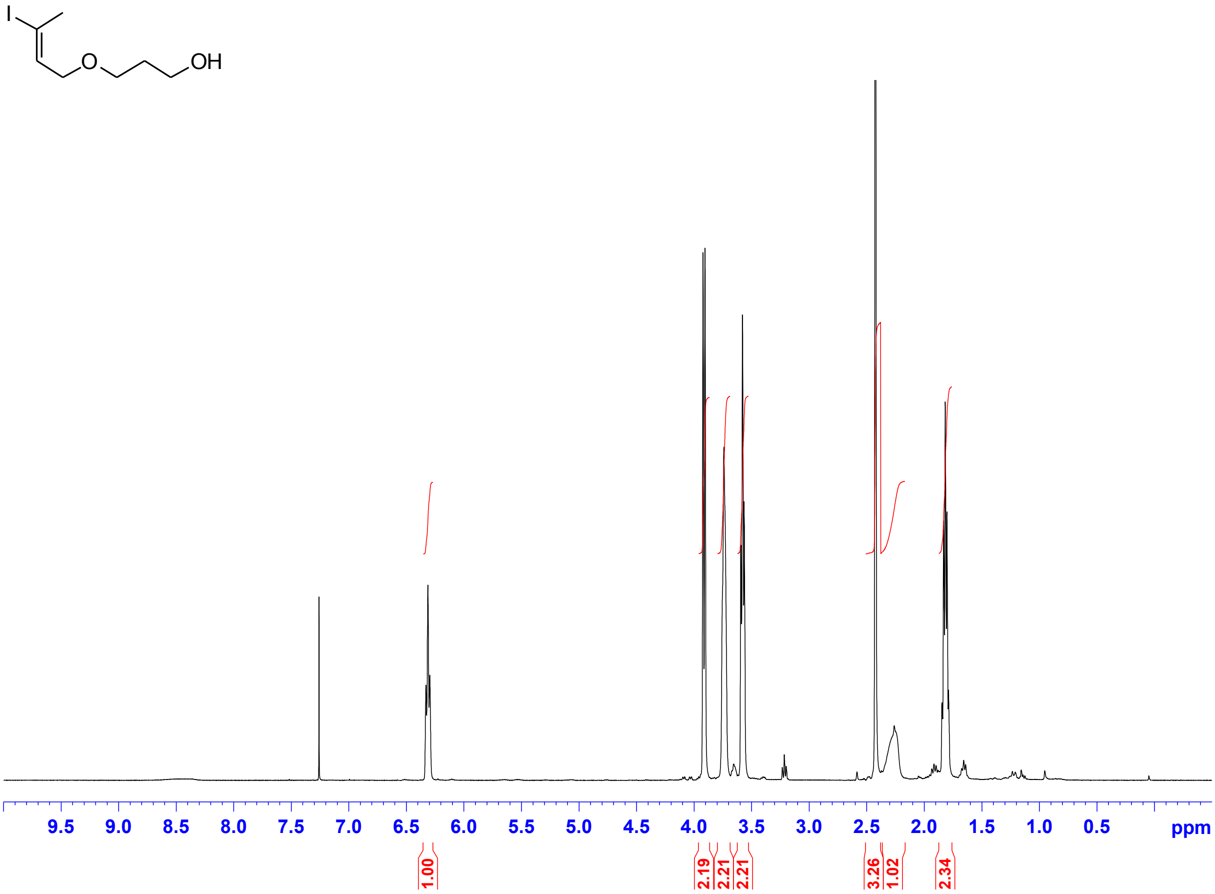


(*E*)-3-(3-Iodobut-2-enyloxy)propan-1-ol (183). To a solution of alkene **181** (596 mg, 2.50 mmol, 1.0 equiv) in THF (60 mL) at 0 °C was added BH_3•THF (1M in THF, 3.85 mL, 3.85 mmol, 1.5 equiv). After stirring for 30 min at room temperature, additional BH_3•THF (1.25 mL, 1.25 mmol, 0.5 equiv) was added. The solution was stirred at room temperature for 45 min more before H_2O (6 mL), 10% aqueous NaOH (8.5 mL) and 30% aqueous H_2O_2 (8.5 mL) were added carefully at 0 °C, whereby a white solid formed. The mixture was allowed to warm slowly to room temperature in the cooling bath. After 13 h, H_2O (50 mL) was added and stirring was continued until effervescence ceased. Phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (EtOAc/Hex 1:5→1:1) yielded **183** (332 mg, 1.30 mmol, 52%) as an orange-red oil.

TLC: R_f = 0.38 (EtOAc/Hex 1:1, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 6.33 (tq, *J* = 6.8, 1.5, 1 H), 3.94-3.92 (m, 2 H), 3.79-3.75 (m, 2 H), 3.60 (t, *J* = 5.9, 2 H), 2.45-2.44 (m, 3 H), 2.07-2.05 (m, 1 H), 1.87-1.81 (m, 2 H), 1.56 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 137.4, 99.0, 69.4, 67.9, 61.9, 32.1, 28.3. **IR** (thin film): $\tilde{\nu}$ = 3374, 2944, 2922, 2864, 1636, 1425, 1376, 1362, 1267, 1239, 1105, 1052, 1018, 972, 947, 917, 823 cm^{-1}. **HRMS** (EI): calcd for $C_7H_{13}IO_2$ [M$^+$]: 255.9955; found: 255.9959.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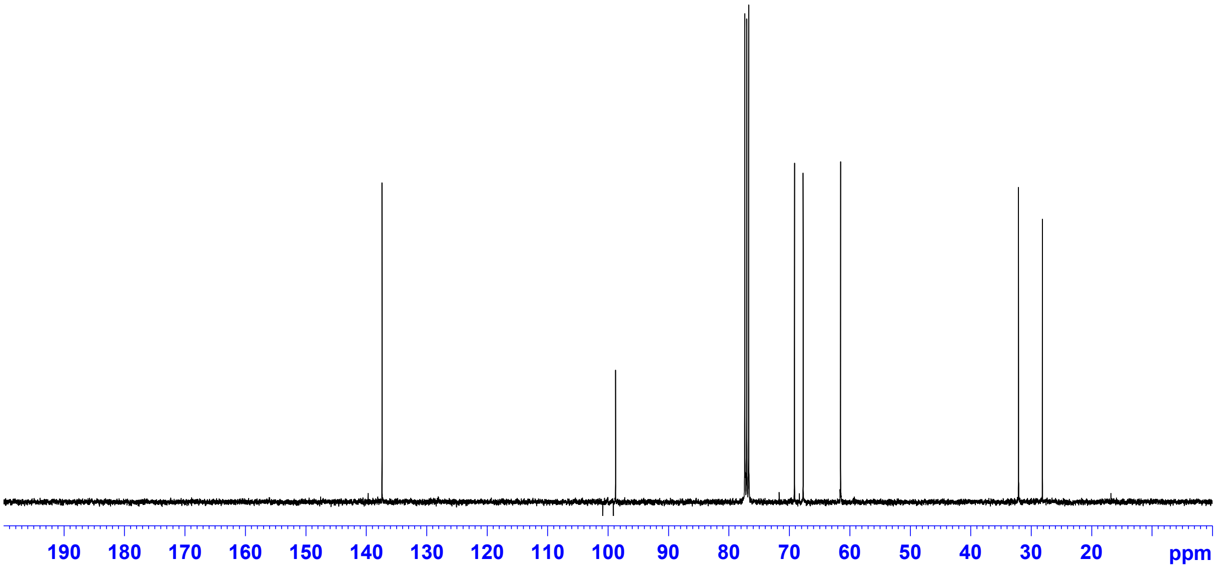
2.34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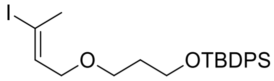
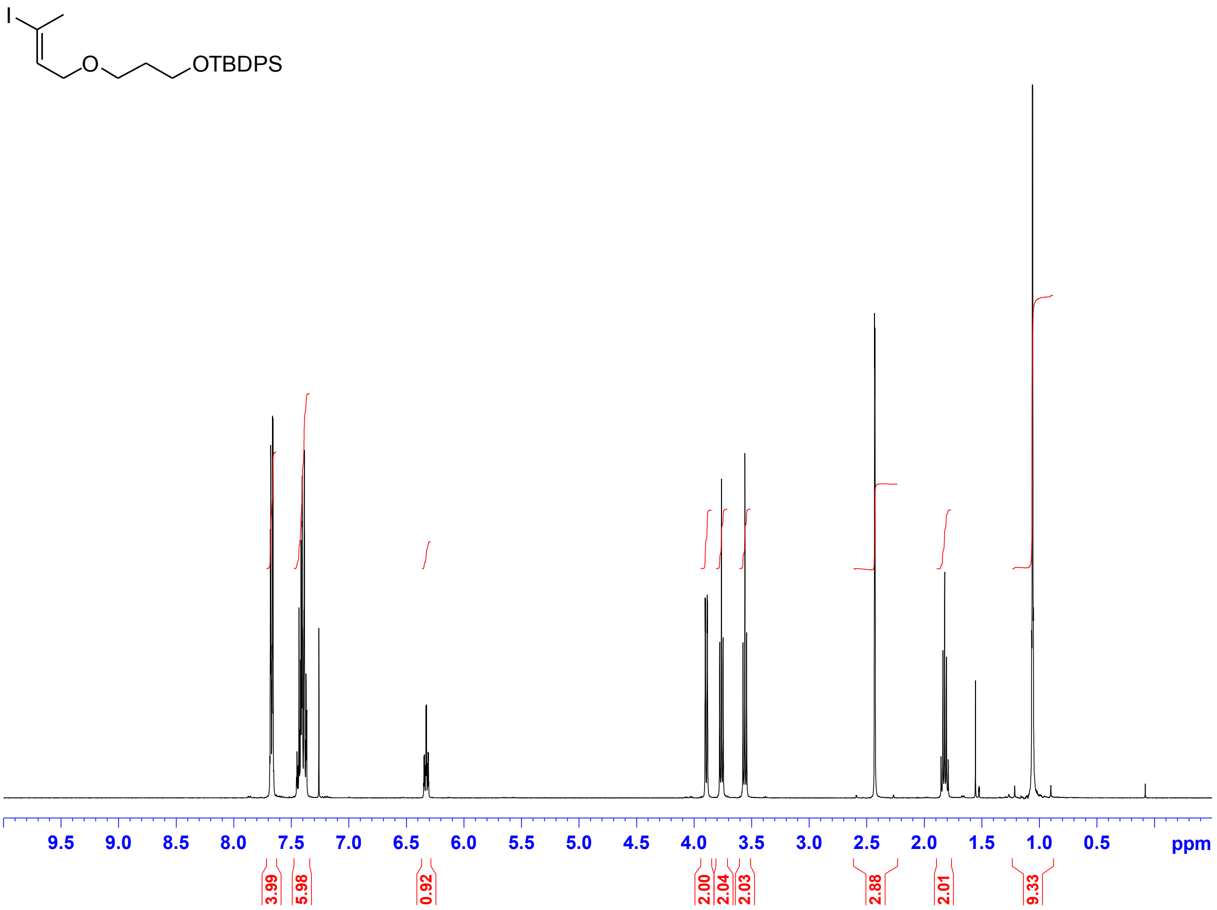


(*E*)-*tert*-Butyl(3-(3-iodobut-2-enyloxy)propoxy)diphenylsilane (176). To a solution of alcohol **183** (332 mg, 1.30 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at room temperature were added sequentially NEt_3 (0.23 mL, 1.69 mmol, 1.3 equiv), TBDPSCl (392 mg, 1.43 mmol, 1.1 equiv) and DMAP (7.94 mg, 0.06 mmol, 0.05 equiv). The solution was stirred at room temperature for 69 h and then saturated aqueous $NaHCO_3$ (10 mL) was added. Phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 100:1→50:1) yielded **176** (602 mg, 1.22 mmol, 94%) as a yellow oil.

TLC: R_f = 0.37 (EtOAc/Hex 1:20, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.69-7.65 (m, 4 H), 7.45-7.36 (m, 6 H), 6.33 (tq, *J* = 6.8, 1.5, 1 H), 3.90-3.88 (m, 2 H), 3.76 (t, *J* = 6.1, 2 H), 3.56 (t, *J* = 6.3, 2 H), 2.43 (m, 3 H), 1.85-1.79 (m, 2 H), 1.06 (s, 1 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 138.0, 135.7, 134.0, 129.7, 127.8, 98.4, 67.7, 67.2, 60.7, 32.8, 28.3, 27.0, 19.4. **IR** (thin film): $\tilde{\nu}$ = 3070, 2929, 2856, 1636, 1472, 1427, 1361, 1188, 1104, 822 cm^{-1}. **HRMS** (ESI): calcd for $C_{23}H_{32}IO_2Si$ [$(M+H)^+$]: 495.1211; found: 495.1210.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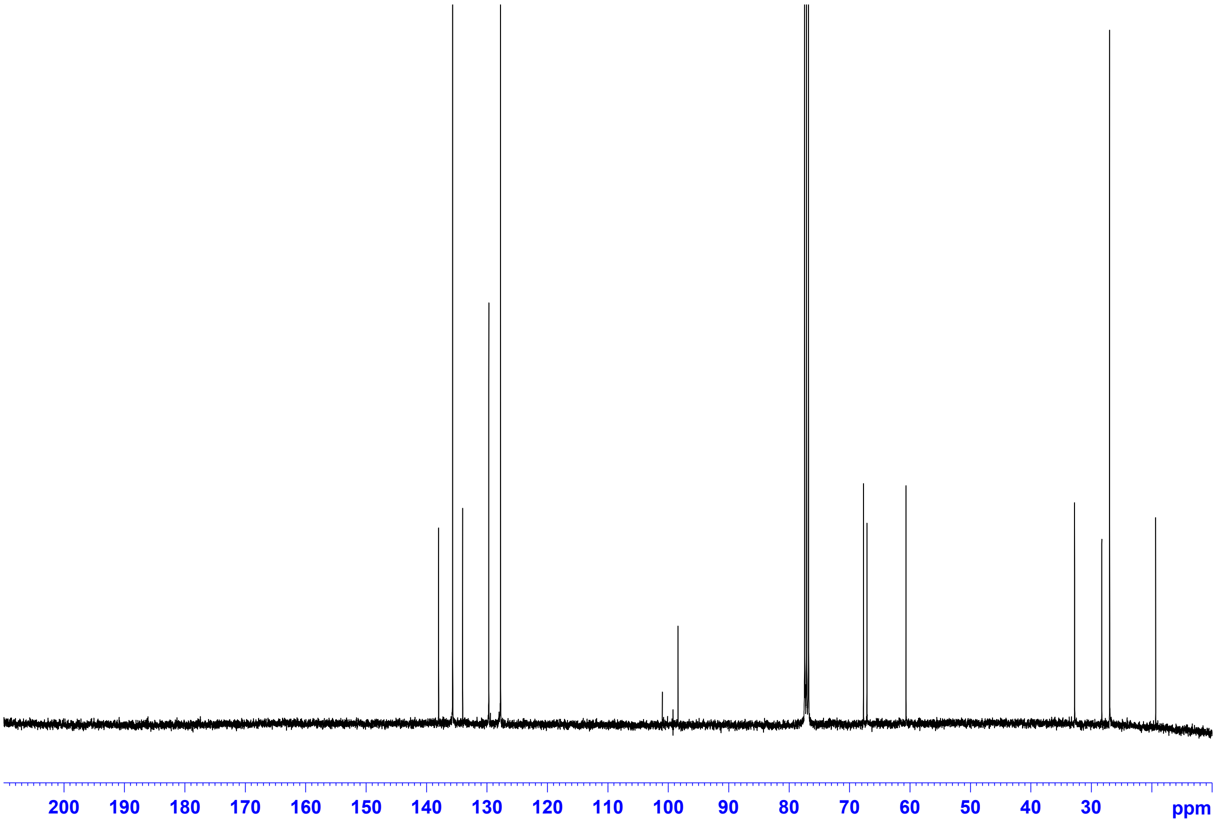
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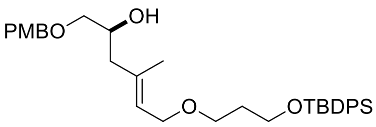
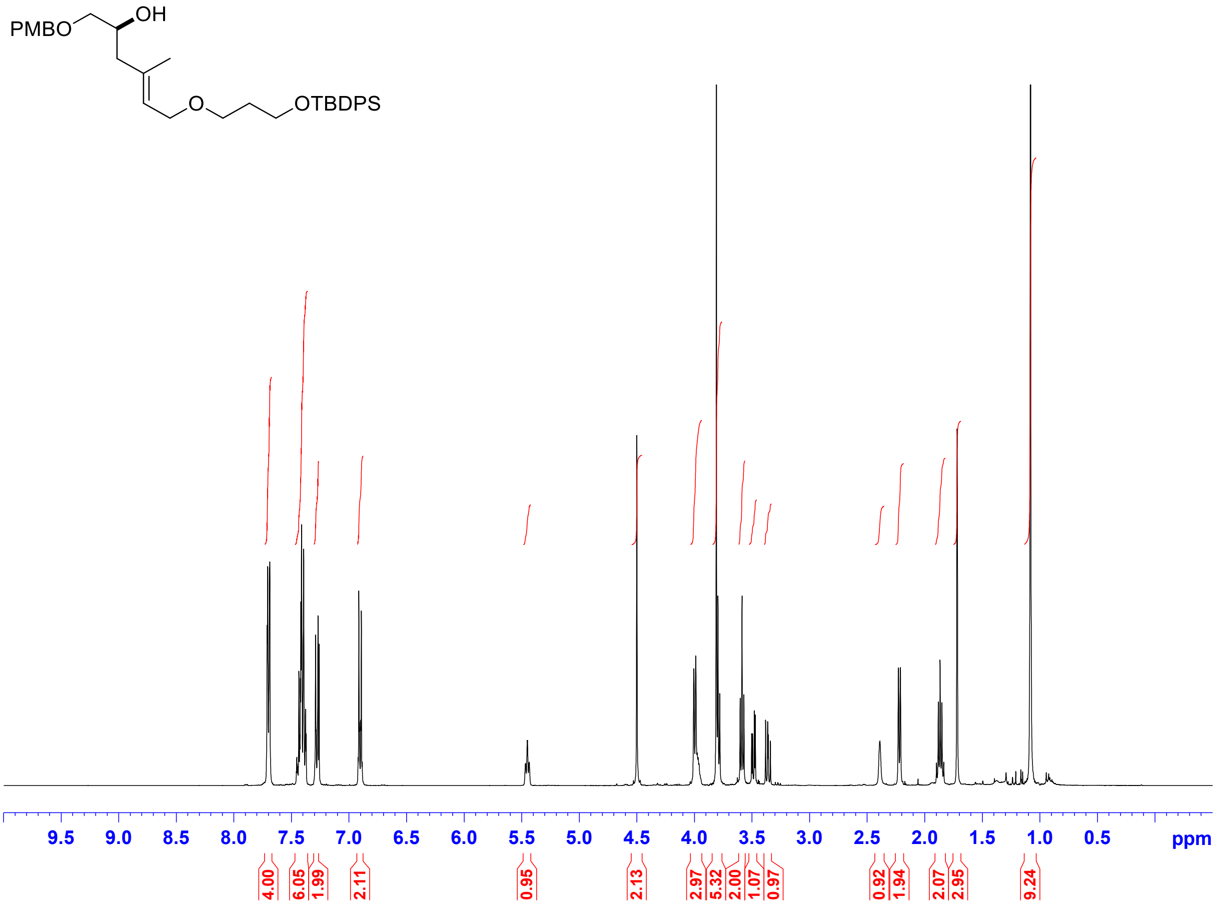


(*S*,*E*)-1-(4-Methoxyphenyl)-6,15,15-trimethyl-14,14-diphenyl-2,9,13-trioxa-14-silahexadec-6-en-4-ol (184). To a solution of vinyliodide **176** (494 mg, 2.00 mmol, 1.0 equiv; coevaporated twice with 3 mL of acetonitrile) in toluene (17 mL) at –78 °C was added *t*-BuLi (1.6M in pentane, 2.5 mL, 4.00 mmol, 2.0 equiv) giving an almost clear solution. After stirring for 45 min at –78 °C, the reaction was cooled to –90 °C. Epoxide **17** (1.04 g, 5.34 mmol, 2.7 equiv; coevaporated twice with 1 mL of acetonitrile) dissolved in toluene (5 mL; the vial was rinsed three times with 1 mL toluene) was added dropwise in a way that the interior temperature did not exceed –78 °C. The reaction solution was recooled to –90 °C before BF$_3$•OEt$_2$ (0.53 mL, 4.2 mmol, 2.1 equiv) was added dropwise. The solution was stirred at –78 °C for 6 h before EtOAc (30 mL) and saturated aqueous NaHCO$_3$ (75 mL) were added. Phases were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried over MgSO$_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/Hex 1:5→1:1) yielded secondary alcohol **184** (615 mg, 1.23 mmol, 61%) as a colorless oil.

TLC: R_f = 0.40 (EtOAc/Hex 1:3, UV, CPS). **^{1}H-NMR** (400 MHz, CDCl$_3$): δ = 7.72-7.68 (m, 4 H), 7.46-7.37 (m, 6 H), 7.30-7.27 (m, 2 H), 6.92-6.89 (m, 2 H), 5.47-5.44 (m, 1 H), 4.50 (s, 2 H), 4.02-3.95 (m, 3 H), 3.81-3.78 (m, 5 H), 3.59 (t, *J* = 6.4, 2 H), 3.49 (dd, *J* = 9.6, 3.5, 1 H), 3.36 (dd, *J* = 9.6, 7.2, 1 H), 2.39 (br. s, 1 H), 2.22 (d, *J* = 6.7, 2 H), 1.90-1.84 (m, 2 H), 1.72 (s, 3 H), 1.08 (s, 9 H). **^{13}C-NMR** (100 MHz, CDCl$_3$): δ = 159.4, 136.0, 135.6, 134.0, 130.2, 129.6, 129.5, 127.7, 124.5, 113.9, 74.0, 73.1, 68.4, 67.3, 67.1, 60.9, 55.3, 43.7, 32.9, 26.9, 19.3, 16.7. **IR** (thin film): $\tilde{\nu}$ = 3445, 3070, 2929, 2856, 1613, 1513, 1463, 1427, 1247, 1105, 1087 cm^{-1}. **HRMS** (ESI): calcd for C$_{34}$H$_{50}$NO$_5$Si [(M+NH$_4$)$^+$]: 580.3453; found: 580.3454. $[\alpha]_D^{24}$: –1.14 (c = 0.96, CHCl$_3$).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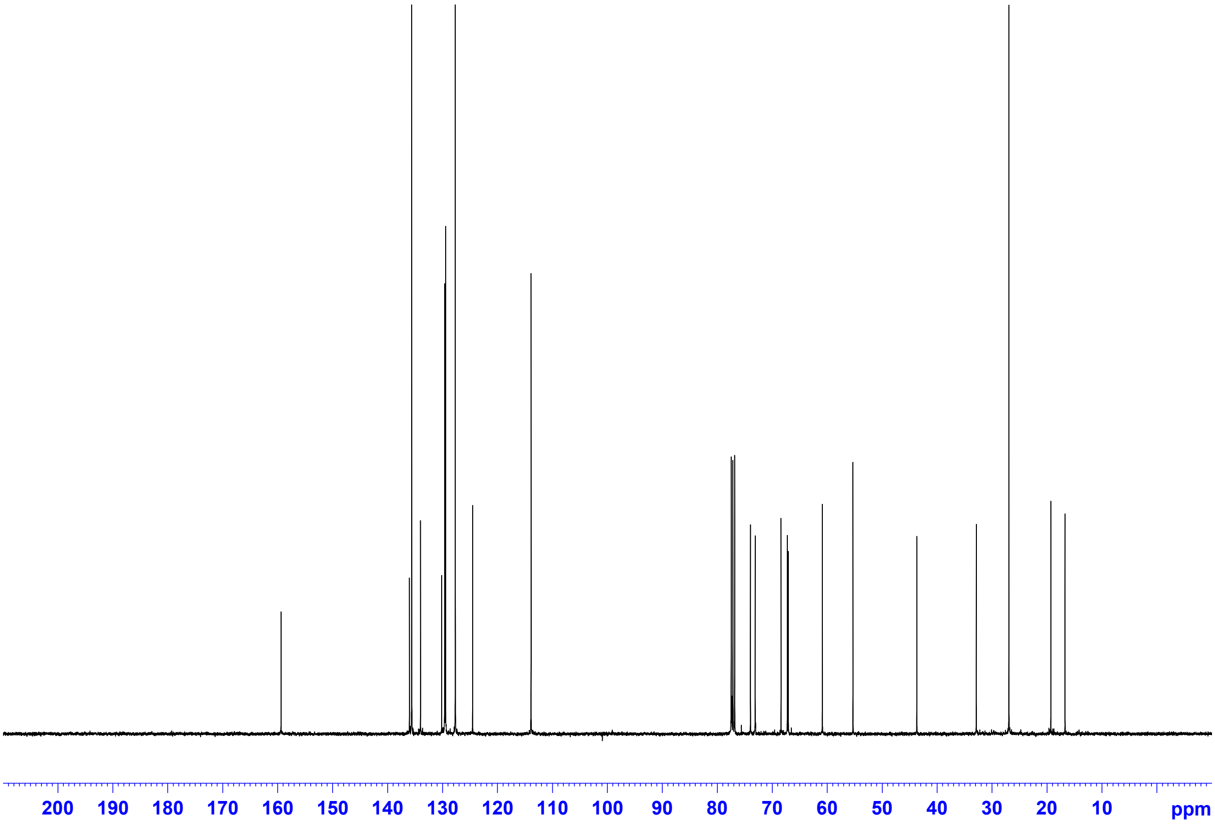
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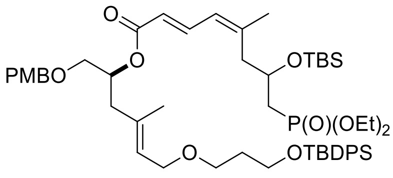
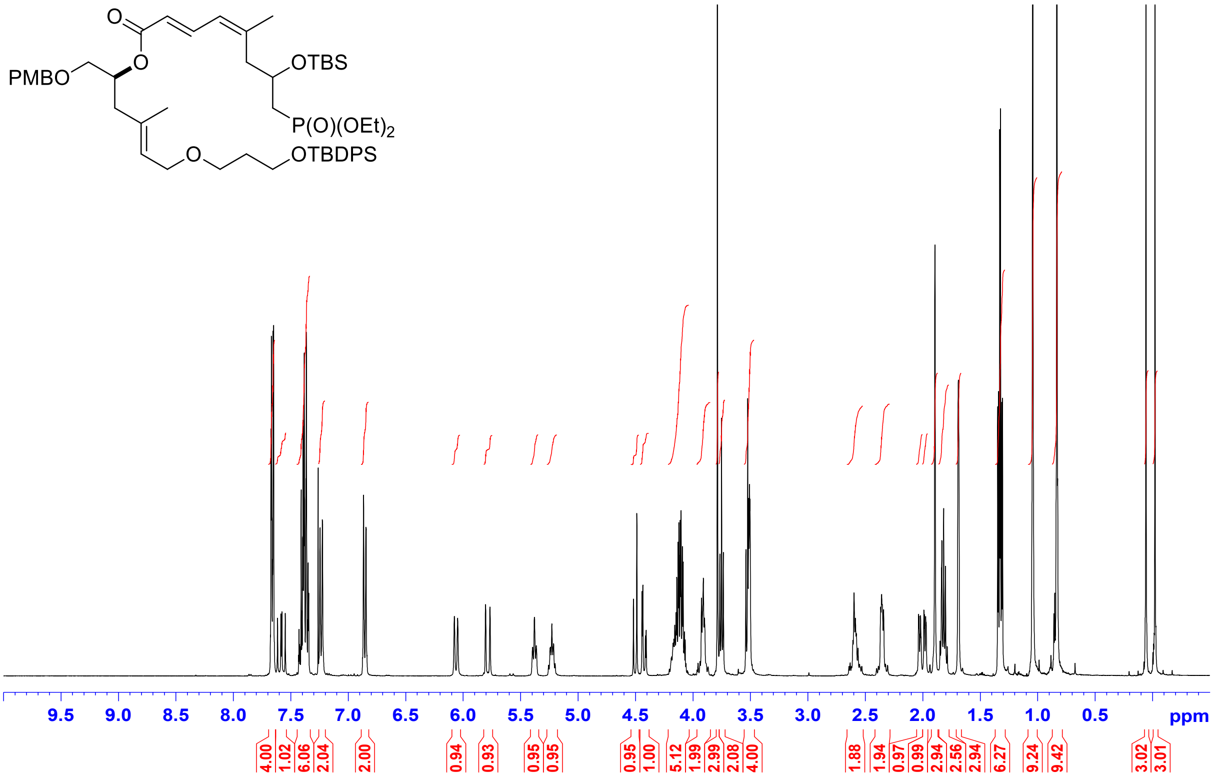
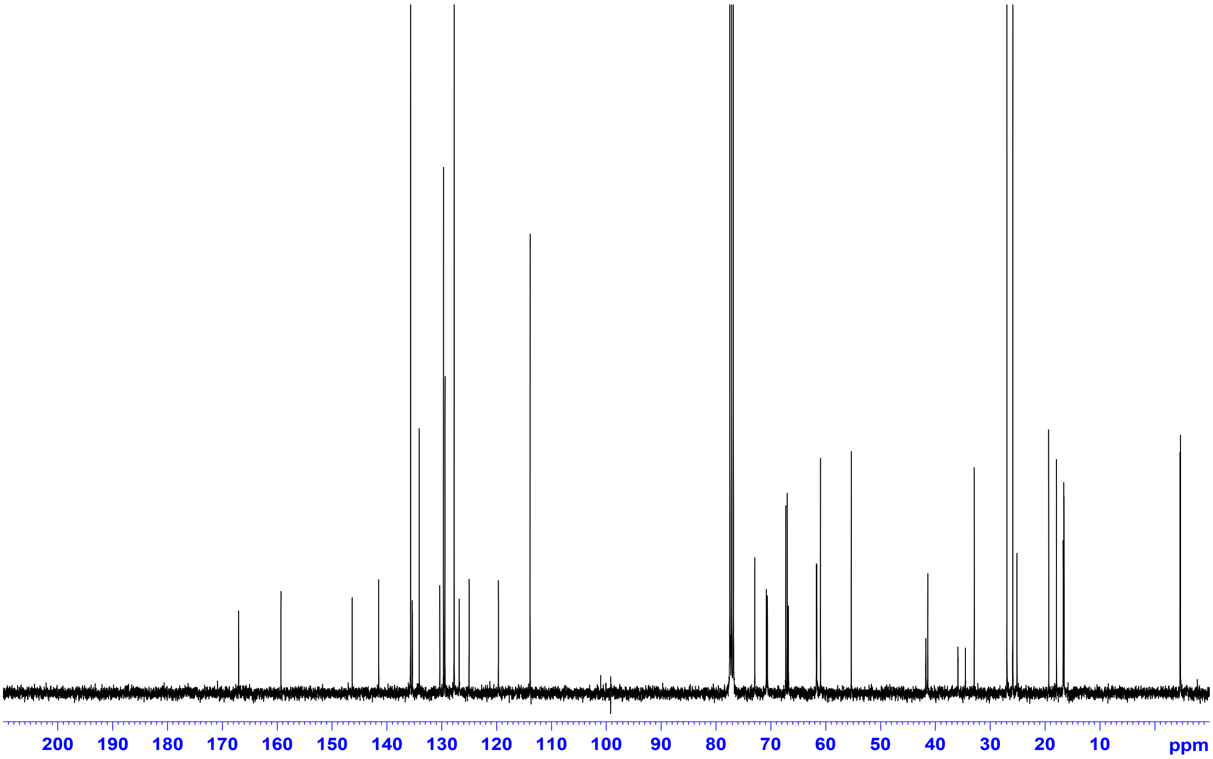
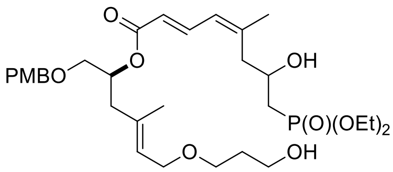


(2*E*,4*Z*)-((*S*,*E*)-1-(4-Methoxyphenyl)-6,15,15-trimethyl-14,14-diphenyl-2,9,13-trioxa-14-silahexadec-6-en-4-yl)-7-(tert-butyldimethylsilyloxy)-8-(diethoxy phosphoryl)-5-methylocta-2,4-dienoate (I). To a solution of acid **98** (51.6 mg, 0.12 mmol, 1.4 equiv; coevaporated twice with 0.5 mL of acetonitrile) in toluene (1.2 mL) was added NEt_3 (37 µL, 0.27 mmol, 3.0 equiv) followed by 2,4,6-trichlorobenzoyl chloride (24 µL, 0.15 mmol, 1.8 equiv) giving a pale-yellow mixture. After stirring for 90 min at room temperature, a solution of **184** (49.3 mg, 0.09 mmol, 1.0 equiv; coevaporated with 0.5 mL of acetonitrile) and DMAP (12.5 mg, 0.10 mmol, 1.2 equiv) in toluene (0.2 mL; ultrasound was used to achieve a complete solution) was added, giving immediately a yellow suspension. The reaction was stirred at room temperature for 19 h, then H_2O (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and EtOAc (5 mL) were added. Phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/Hex 1:3→1:2→1:1) yielded ester **I** (68.5 mg, 0.07 mmol, 81%) as a mixture of diastereoisomers in a 1:1 ratio as a pale-yellow, viscous oil.

TLC: R_f = 0.30 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68-7.64 (m, 4 H), 7.58 (dd, *J* = 15.0, 11.6, 1 H), 7.43-7.34 (m, 6 H), 7.24-7.22 (m, 2 H), 6.87-6.84 (m, 2 H), 6.06 (d, *J* = 11.6, 1 H), 5.78 (d, *J* = 15.1, 1 H), 5.38 (t, *J* = 6.5, 1 H), 5.25-5.20 (m, 1 H), 4.50 (d, *J* = 11.8, 1 H), 4.42 (dd, *J* = 11.6, 2.7, 1 H), 4.20-4.04 (m, 5 H), 3.96-3.87 (m, 2 H), 3.79 (s, 3 H), 3.78 (s, 3 H) 3.75 (t, *J* = 6.1, 2 H), 3.54-3.50 (m, 4 H), 2.64-2.53 (m, 2 H), 2.40-2.30 (m, 2 H), 2.04-1.97 (m, 2 H), 1.89 (s, 3 H), 1.85-1.79 (m, 2 H), 1.69 (br. s, 3 H), 1.32 (td, *J* = 7.1, 2.9, 6 H), 1.04 (s, 9 H), 0.83 (s, 9 H), 0.06 (s, 3 H), -0.02 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$; due to the diastereomeric nature of the product, the number of signals in the ^{13}C-spectrum exceeds the number of carbon atoms): δ = 167.0, 167.0, 159.3, 146.3, 146.3, 141.5, 135.7, 135.4, 135.3, 134.1, 130.3, 129.6, 129.4, 129.4, 127.7, 126.8, 126.8, 125.0, 125.0, 119.6, 113.9, 72.9, 72.9, 70.8, 70.8, 70.6, 70.6, 67.3,67.0, 66.8, 66.8, 61.7 (d, *J* = 6.6), 61.7 (d, *J* = 6.6), 60.9, 55.4, 41.7, 41.4, 35.2 (d, J = 135.5), 35.2 (d, J = 135.5), 32.9, 27.0, 25.9, 25.1, 25.1, 19.3,17.9, 16.7, 16.7, 16.6 (d, J = 5.9), -4.6, -4.7. **IR** (thin film): $\tilde{\nu}$ = 3070, 3049, 2954, 2929, 2856, 1710, 1636, 1612, 1514, 1472, 1463, 1428, 1362, 1248, 1146, 1111, 1089, 1048, 1023, 978, 958, 937, 822 cm^{-1}. **HRMS** (ESI): calcd for $C_{53}H_{85}NO_{10}PSi_2$ [(M+NH$_4$)$^+$]: 982.5444; found: 982.5428. $[\alpha]_D^{24}$: +1.93 (c = 1.00, CHCl$_3$).



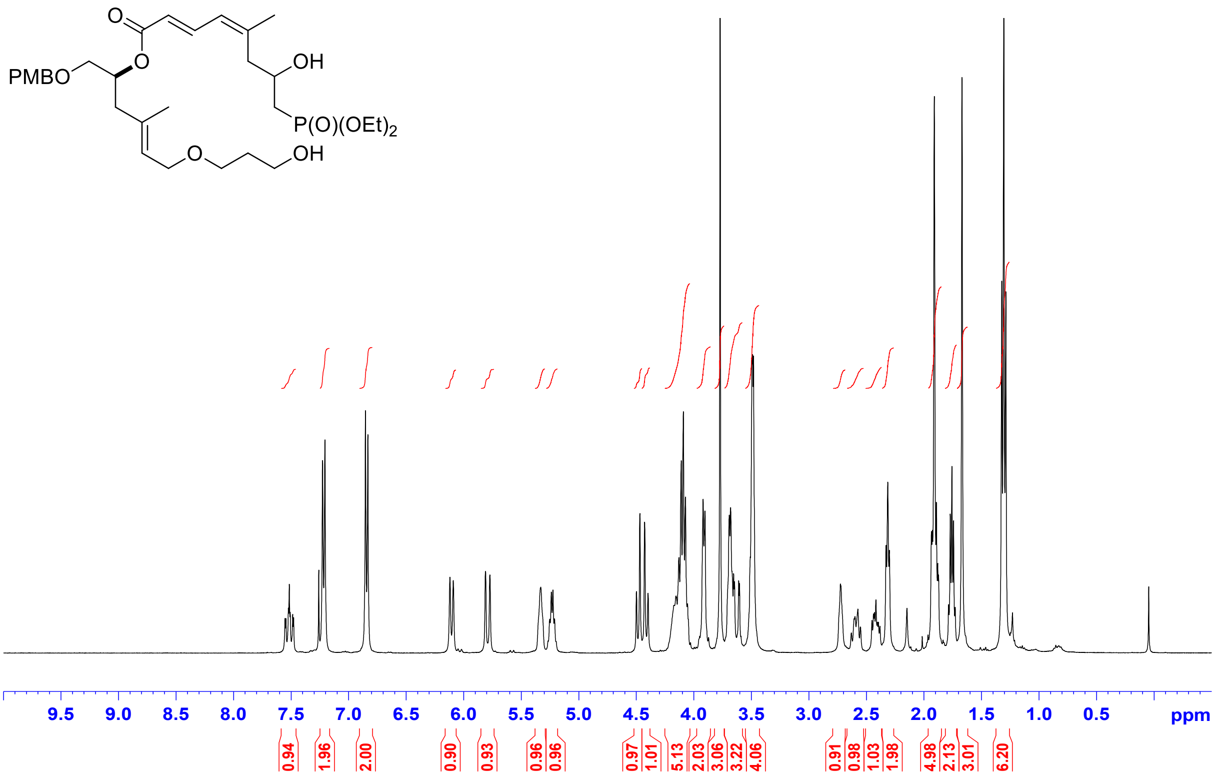


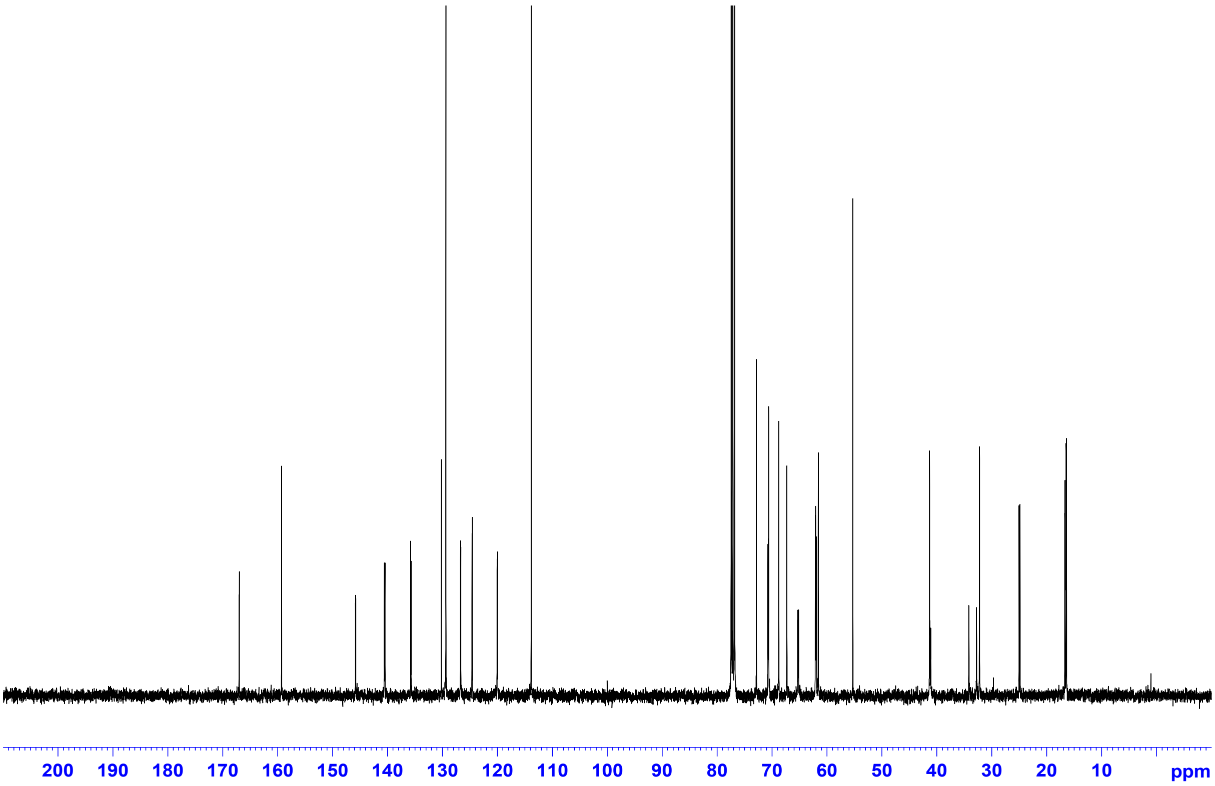


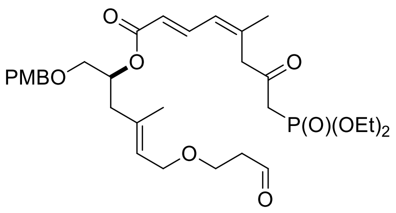
(2*E*,4*Z*)-((*S*,*E*)-6-(3-Hydroxypropoxy)-1-(4-methoxybenzyloxy)-4-methylhex-4-en-2-yl) 8-(diethoxyphosphoryl)-7-hydroxy-5-methylocta-2,4-dienoate (J). To a solution of **I** (542 mg, 0.56 mmol) in THF (22 mL) at 0 °C in a 50 mL plastic tube was added carefully HF•pyridine (70% HF in pyridine, 5.6 mL). After 5 min at 0 °C, the cooling bath was removed and the solution was stirred at room temperature for 16 h. The reaction was transferred dropwise to a stirring solution of saturated aqueous $NaHCO_3$ (450 mL) and EtOAc (250 mL). The phases were separated and the aqueous phase was extracted with EtOAc (4 x 100 mL). The pH value of the aqueous phase was above 8. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (EtOAc→EtOAc/acetone 1:1) yielded diol **J** (294 mg, 0.48 mmol, 86%) as a mixture of diastereoisomers in a 1:1 ratio as a colorless oil .

Note: The use of less concentrated aqueous $NaHCO_3$ is not recommended for workup, since not all HF may be neutralized, which would in turn lead to decomposition of the product during concentration under reduced pressure. In any case the pH of the aqueous phase should be determined after workup and should not be acidic!

TLC: R_f = 0.40 (EtOAc/acetone 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.55-7.48 (m, 1 H), 7.23-7.21 (m, 2 H), 6.85-6.83 (m, 2 H), 6.11 (d, *J* = 11.6, 1 H), 5.79 (d, *J* = 15.1, 1 H), 5.35-5.31 (m, 1 H), 5.27-5.20 (m, 1 H), 4.49 (d, *J* = 11.8, 1 H), 4.42 (d, *J* = 11.9, 1 H), 4.20-4.05 (m, 5 H), 3.96-3.87 (m, 2 H), 3.77 (s, 3 H), 3.71-3.61 (m, 3 H), 3.51-3.48 (m, 4 H), 2.73 (br. s, 1 H), 2.63-2.55 (m, 1 H), 2.45-2.38 (m, 1 H), 2.33-2.30 (m, 2 H), 1.94-1.87 (m, 5 H), 1.79-1.73 (m, 2 H), 1.67 (s, 3 H), 1.31 (t, *J* = 7.1, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$; due to the diastereomeric nature of the product, the number of signals in the ^{13}C-spectrum exceeds the number of carbon atoms): δ = 167.0, 167.0, 159.3, 145.8, 145.8, 145.8, 145.8 140.6, 140.5, 135.8, 135.7, 130.2, 129.4, 126.7, 126.7, 124.6, 124.5, 120.0, 120.0, 113.8, 72.9, 70.8, 70.7, 70.7, 68.8, 67.3, 65.4 (d, *J* = 4.8), 65.2, (d, *J* = 4.8), 62.1 (d, *J* = 6.3), 62.0 (d, *J* = 6.3), 61.6, 61.6, 55.3, 41.3 (d, *J* = 5.1), 41.2 (d, *J* = 5.1), 33.5 (d, J = 138.2), 33.5 (d, J = 139.0), 32.3, 25.1, 24.9, 16.8, 16.7, 16.5 (d, J = 5.9), 16.5 (d, J = 5.9). **IR** (thin film): $\tilde{\nu}$ = 3386, 2979, 2932, 2909, 2863, 1707, 1633, 1611, 1513, 1442, 1367, 1302, 1275, 1246, 1221, 1147, 1075, 1023, 973, 893 cm^{-1}. **HRMS** (ESI): calcd for [(M+NH$_4$)$^+$]: 635.2956; found: 635.2963. $[\alpha]_D^{24}$: –6.49 (c = 1.11, CHCl$_3$).

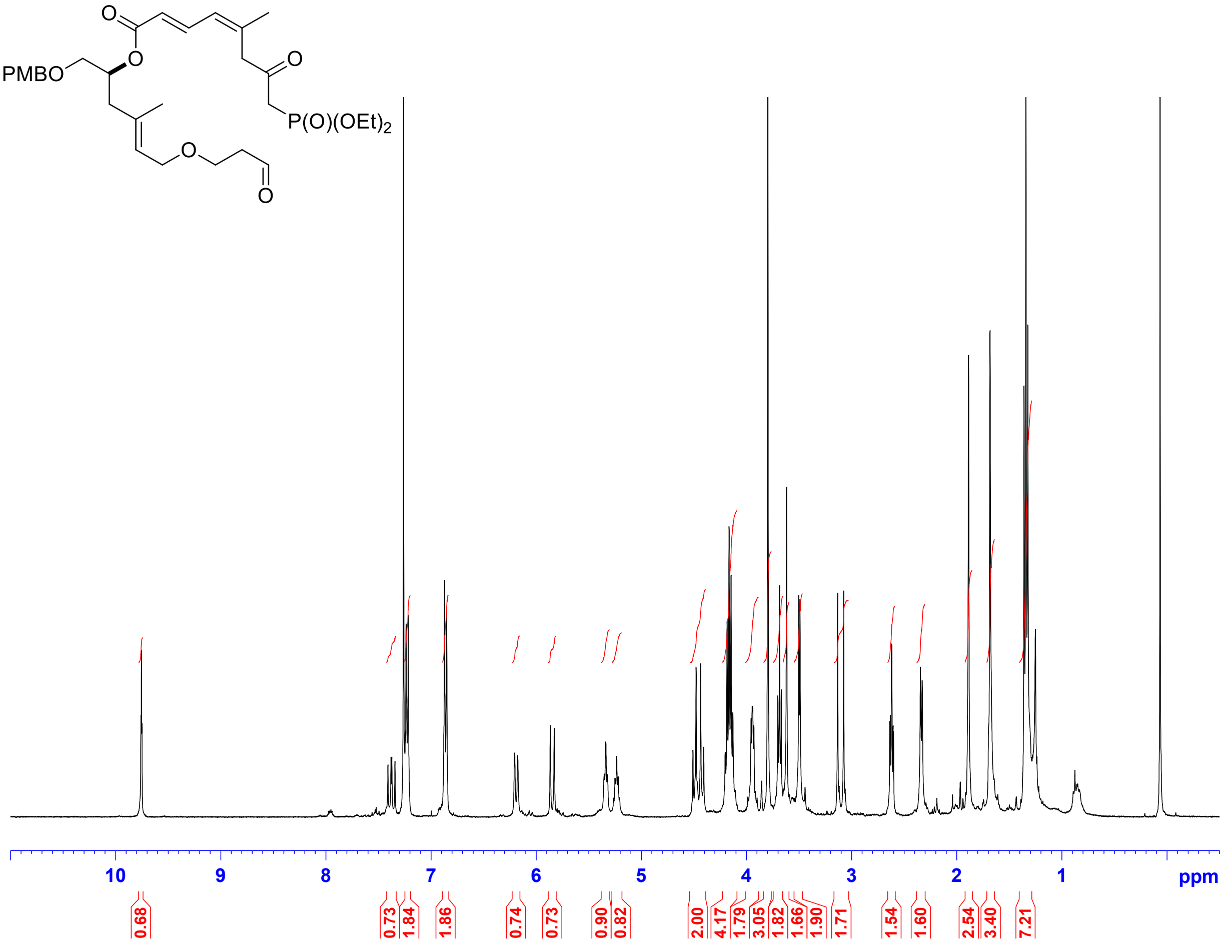






(2*E*,4*Z*)-((*S*,*E*)-1-(4-Methoxybenzyloxy)-4-methyl-6-(3-oxopropoxy)hex-4-en-2-yl) 8-(diethoxy phosphoryl) - 5-methyl-7-oxoocta-2,4-dienoate (185). To a solution of diol **J** (155 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added solid DMP (323 mg, 0.76 mmol, 3.0 equiv) giving a white mixture after 15 min. A second portion of DMP (323 mg, 0.76 mmol, 3.0 equiv) was added after 30 min. After a total of 90 min, the reaction mixture was poured into a stirred mixture of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL). Stirring was continued for 30 min, then the almost clear phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc, 1% (v/v) AcOH was used to buffer the stationary phase) afforded **185** (113.2 mg, 0.19 mmol, 73%) as a yellow oil after coevaporation with toluene (1x5 mL).

TLC: R_f = 0.49 (EtOAc, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.75 (t, *J* = 1.8, 1 H), 7.38 (dd, *J* = 15.1, 11.7, 1 H), 7.24-7.22 (m, 2 H), 6.88-6.84 (m, 2 H), 6.19 (d, *J* = 11.7, 1 H), 5.85 (d, *J* = 15.1, 1 H), 5.35-5.32 (m, 1 H), 5.26-5.21 (m, 1 H), 4.49 (d, *J* = 11.9, 1 H), 4.42 (d, *J* = 11.7, 1 H), 4.20-4.11 (m, 4 H), 3.99-3.90 (m, 2 H), 3.80 (s, 3 H), 3.69 (t, *J* = 6.2, 2 H), 3.62 (br. s, 2 H), 3.55 (d, *J* = 4.8, 2 H), 3.10 (d, *J* = 22.8, 2 H), 2.62 (dt, *J* = 6.1, 1.8, 2 H), 2.34 (d, *J* = 6.8, 2 H), 1.89 (s, 3 H), 1.68 (s, 3 H), 1.34 (t, *J* = 7.1, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 201.4, 198.2 (d, *J* = 6.6), 166.7, 159.3, 141.1, 139.8, 136.0, 130.2, 129.4, 127.5, 124.4, 121.0, 113.9, 72.9, 70.8, 70.7, 67.4, 63.6, 62.9 (d, *J* = 6.6), 55.4, 47.6, 44.0, 42.3 (d, *J* = 127.1), 41.4, 25.0, 16.7, 16.4 (d, *J* = 5.9). **IR** (thin film): $\tilde{\nu}$ = 2977, 2929, 2911, 2862, 1713, 1638, 1612, 1586, 1513, 1455, 1443, 1391, 1364, 1302, 1248, 1173, 1150, 1113, 1093, 1019, 970, 847, 818 cm^{-1}. **HRMS** (ESI): calcd for $C_{31}H_{45}NaOP$ [$(M+Na)^+$]: 631.2643; found: 631.2649. $[\alpha]_D^{24}$: –11.89 (c = 0.62, $CHCl_3$).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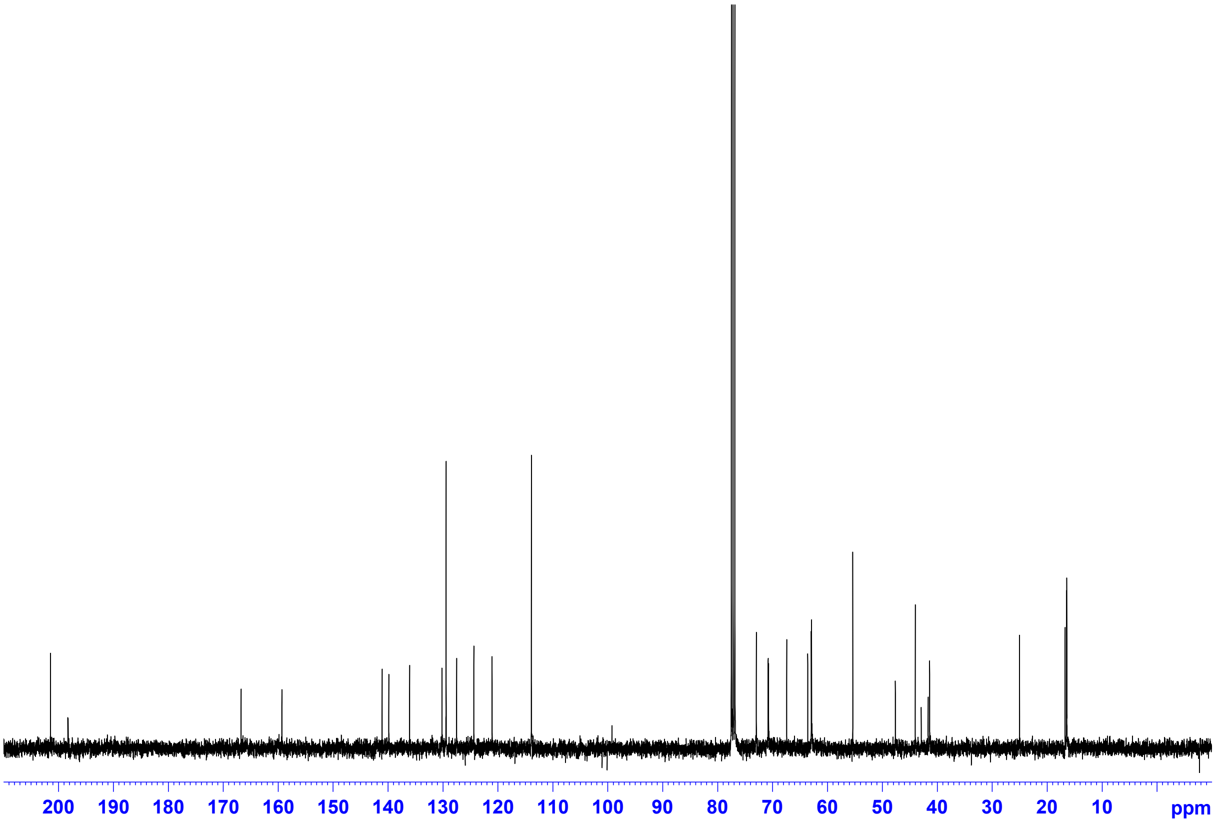
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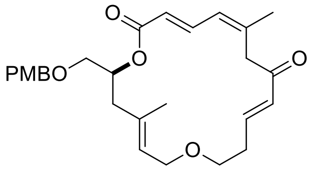
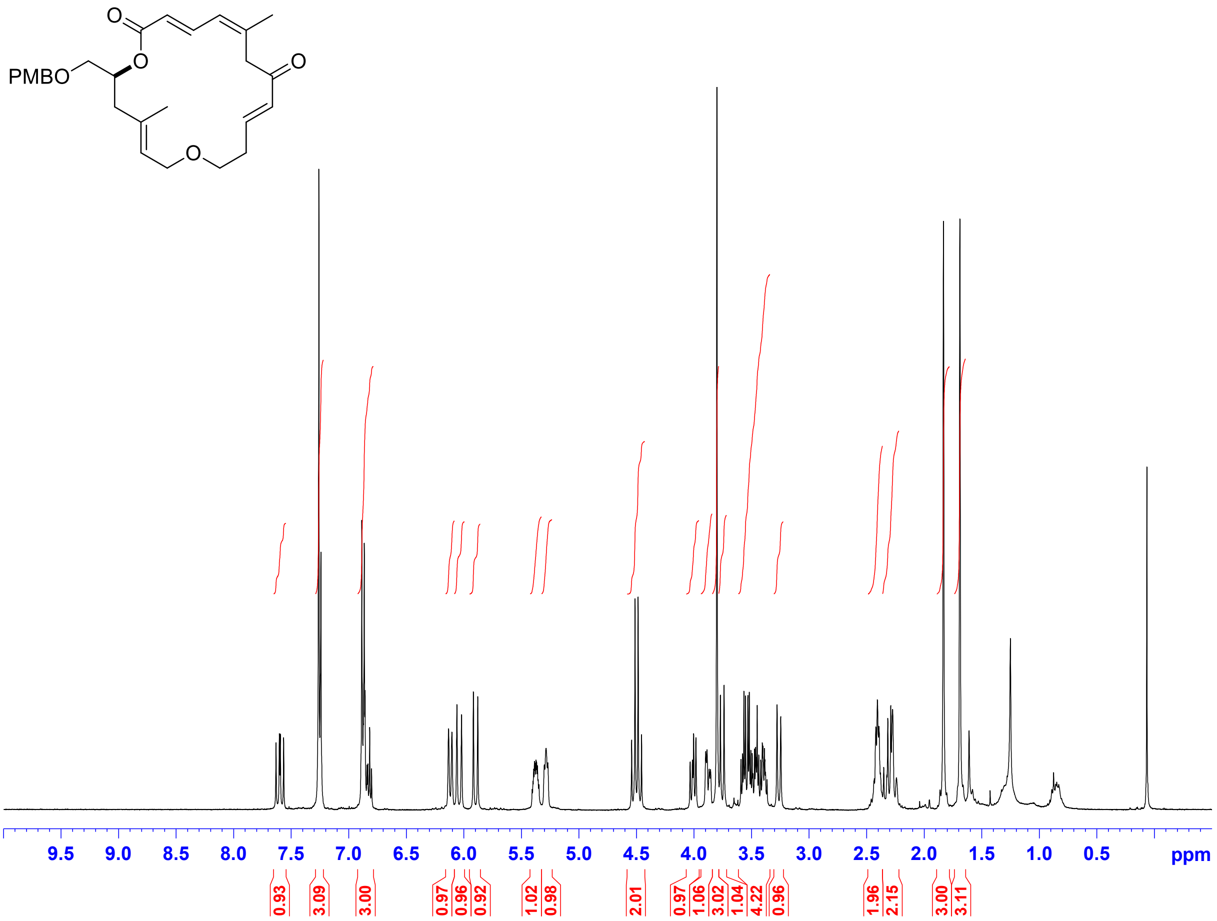


(*S*,3*E*,9*E*,11*Z*,15*E*)-6-((4-Methoxybenzyloxy)methyl)-4,12-dimethyl-1,7-dioxacyclooctadeca-3,9,11,15-tetraene-8,14-dione (186). To a solution of phosphonate **185** (216.1 mg, 0.355 mmol, 1.0 equiv; coevaporated once with 2 mL of toluene right before use) in THF (300 mL) and H_2O (7.5 mL) was added freshly activated $Ba(OH)_2 \cdot H_2O$ (53 mg, 0.284 mmol, 0.8 equiv) at 0 °C. The mixture turned yellow then orange after few minutes. The cooling bath was removed after 30 min then stirring was continued for a total of 3 h resulting in a pale-orange mixture. Et_2O (50 mL) was added then saturated aqueous $NaHCO_3$ (50 mL). Phases were separated then the organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) and with brine (50 mL). The combined aqueous phases were washed once with Et_2O (20 mL) then the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure giving a yellow oil. Purification using flash chromatography (EtOAc/Hex 1:3→1:1) afforded **186** (136.9 mg, 0.30 mmol, 85%) as a pale-yellow oil.

TLC: R_f = 0.50 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.60 (dd, *J* = 15.2, 11.6, 1 H), 7.26-7.24 (m, 2 H), 6.89-6.80 (m, 3 H), 6.12 (d, *J* = 11.6, 1 H), 6.04 (d, *J* = 16.2, 1 H), 5.90 (d, *J* = 15.2, 1 H), 5.41-5.35 (m, 1 H), 5.30-5.27 (m, 1 H), 4.53 (d, *J* = 11.8, 1 H), 4.47 (d, *J* = 11.8, 1 H), 4.01 (dd, *J* = 12.1, 8.0, 1 H), 3.88 (dd, *J* = 12.1, 4.7, 1 H), 3.80 (s, 3 H), 3.76 (d, *J* = 12.8, 1 H), 3.59-3.37 (m, 4 H), 3.26 (d, *J* = 12.8, 1 H), 2.48-2.38 (m, 2 H), 2.35-2.24 (m, 2 H), 1.83 (s, 3 H), 1.69 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 197.1, 166.7, 159.4, 146.8, 142.4, 139.5, 134.6, 130.3, 130.2, 129.5, 125.9, 124.9, 121.3, 114.0, 73.0, 71.6, 69.7, 67.8, 67.8, 55.4, 45.9, 42.0, 33.0, 24.1, 16.7. **IR** (thin film): $\tilde{\nu}$ = 3009, 2999, 2959, 2916, 2857, 1708, 1667, 1633, 1613, 1586, 1513, 1456, 1441, 1360, 1301, 1279, 1247, 1208, 1173, 1148, 1089, 1033, 976, 890, 846, 819 cm^{-1}. **HRMS** (ESI): calcd for $C_{27}H_{34}NaO_6$ [$(M+Na)^+$]: 477.2248; found: 477.2230. $[\alpha]_D^{24}$: –76.05 (c = 0.61, $CHCl_3$).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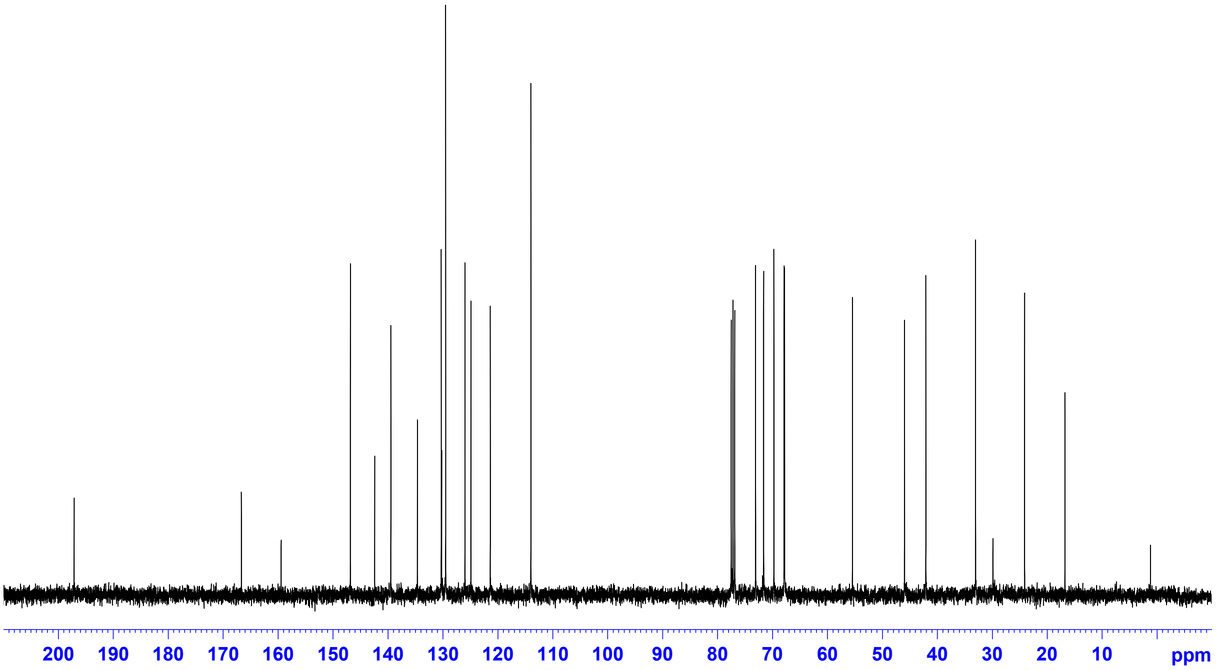
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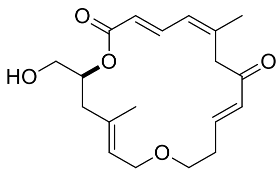
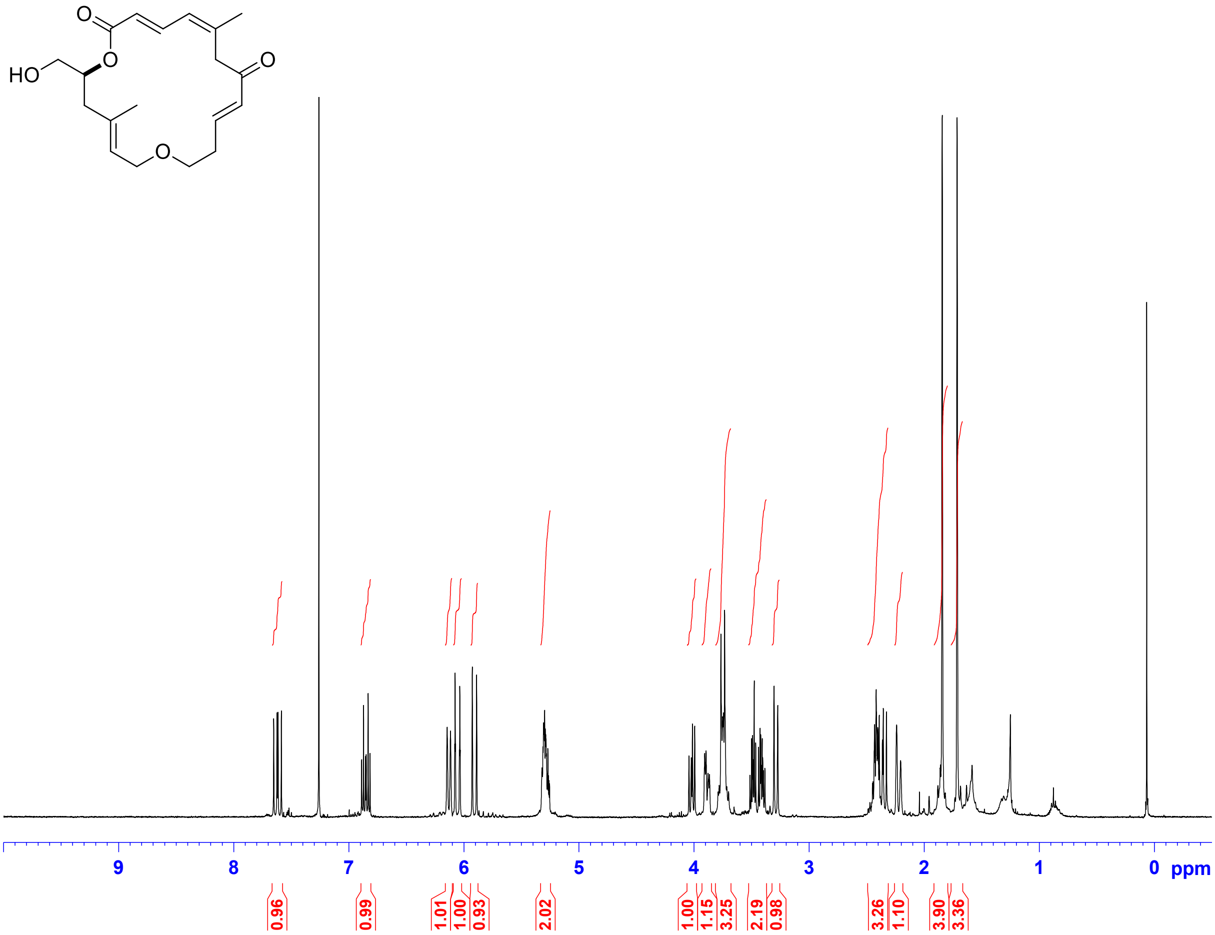


(*S*,3*E*,9*E*,11*Z*,15*E*)-6-(Hydroxymethyl)-4,12-dimethyl-1,7-dioxacyclooctadeca-3,9,11,15-tetraene-8,14-dione (187). To a solution of **186** (72 mg, 0.158 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was added H_2O (0.8 mL) followed by DDQ (72 mg, 0.32 mmol, 2.0 equiv) and stirring was vigorously continued at room temperature for 60 min giving a tan-yellow mixture with dark-red aqueous parts. The reaction mixture was added to saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (5 mL). Phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (EtOAc/Hex 1:1) yielded **187** (40.7 mg, 0.122 mol, 77%) as a pale-yellow oil.

TLC: R_f = 0.19 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.62 (dd, *J* = 15.1, 11.6, 1 H), 6.85 (dt, *J* = 16.2, 6.6, 1 H), 6.13 (d, *J* = 11.5, 1 H), 6.06 (dt, *J* = 16.2, 1.5, 1 H), 5.91 (d, *J* = 15.2, 1 H), 5.32-5.25 (m, 2 H), 4.02 (dd, *J* = 12.0, 7.9, 1 H), 3.91-3.86 (m, 1 H), 3.79-3.70 (m, 3 H), 3.51-3.38 (m, 2 H), 3.29 (d, *J* = 12.9, 1 H), 2.49-2.33 (m, 3 H), 2.22 (d, *J* = 13.8, 1 H), 1.84 (s, 3 H), 1.71 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 197.0, 167.1, 146.8, 142.8, 139.8, 134.3, 130.3, 125.9, 125.0, 121.0, 72.2, 68.0, 67.8, 65.5, 46.0, 41.5, 33.0, 24.1, 16.8. **IR** (thin film): $\tilde{\nu}$ = 3442, 2929, 2855, 1703, 1693, 1667, 1631, 1437, 1380, 1359, 1279, 1258, 1208, 1174, 1148, 1113, 1088, 1059, 1038, 976, 936, 891 cm^{-1}. **HRMS** (ESI): calcd for $C_{19}H_{26}NaO_5$ [$(M+Na)^+$]: 357.1672; found: 357.1666. $[\alpha]_D^{24}$: –74.67 (c = 0.29, $CHCl_3$).



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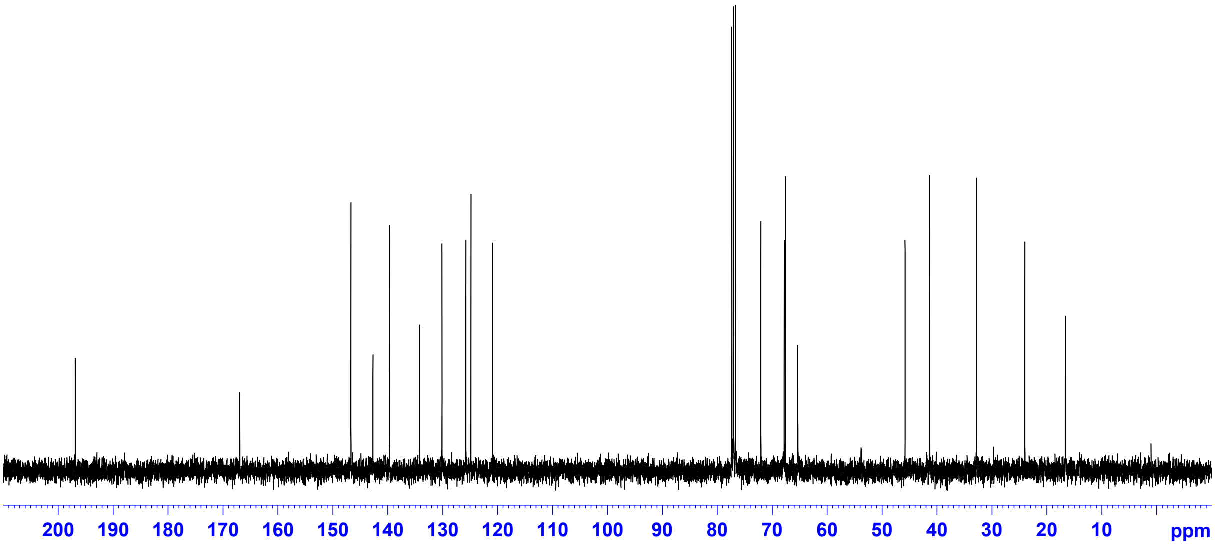

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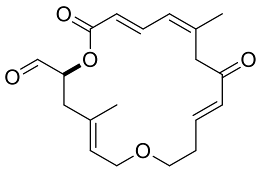
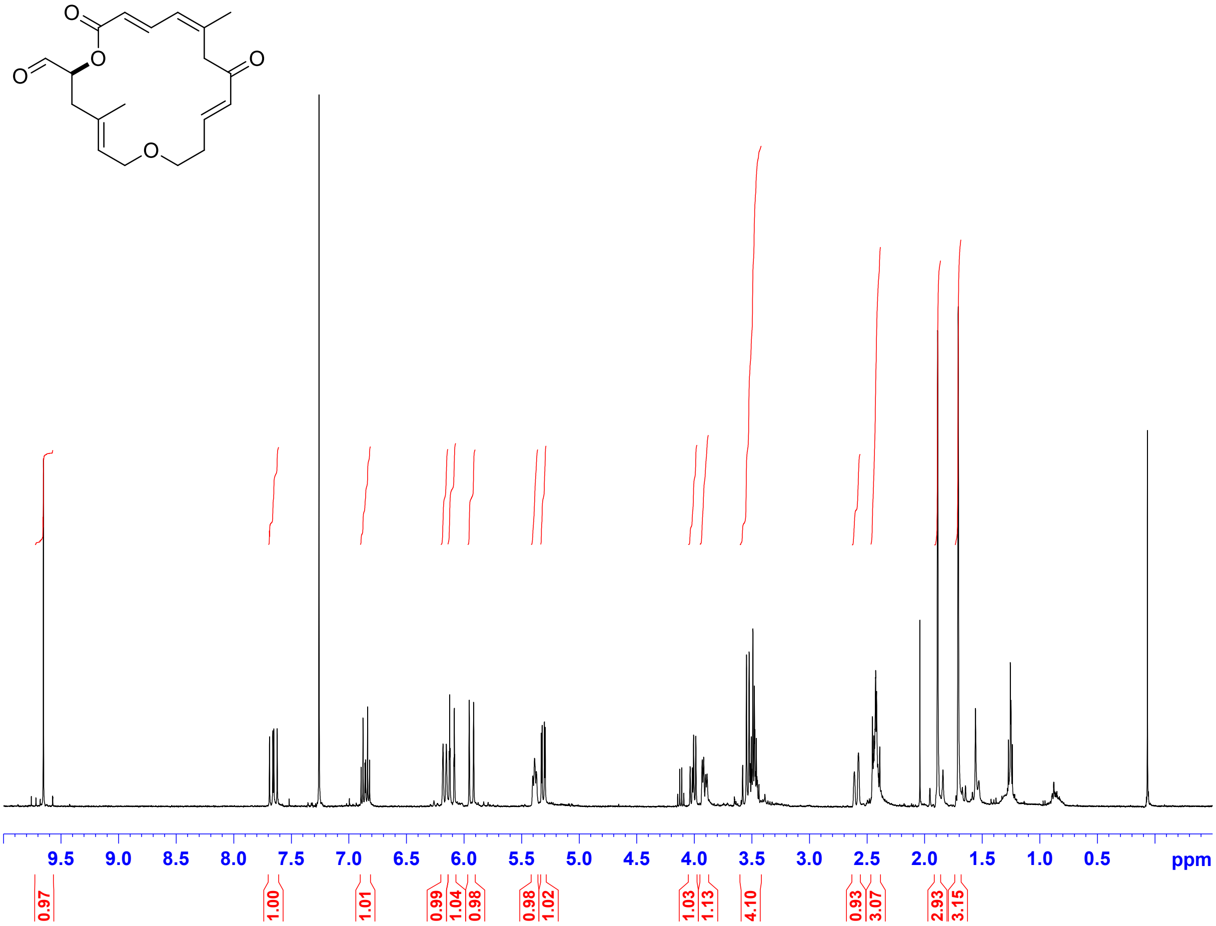


(*S*,4*E*,10*E*,14*Z*,16*E*)-4,14-Dimethyl-12,18-dioxo-1,7-dioxacyclooctadeca-4,10,14,16-tetraene-2-carbaldehyde (175). To a solution of alcohol **187** (40.7 mg, 0.122 mol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) was added solid DMP (156 mg, 0.37 mmol, 3.0 equiv) splitted in two equal portions; the second portion added after 10 min. Stirring was continued for a total of 30 min at room temperature then saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL) were added and stirring was continued for 15 min leading to a clear organic phase and a turbid aqueous phase. Phases were separated then the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 x 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:2→1:1) yielded **175** (30.5 mg, 0.092 mmol, 75%) as a pale-yellow semisolid.

TLC: R_f = 0.37 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 7.66 (dd, *J* = 15.2, 11.6, 1 H), 6.86 (dt, *J* = 16.2, 6.7, 1 H), 6.19-6.15 (m, 1 H), 6.10 (dt, *J* = 16.2, 1.5, 1 H), 5.94 (d, *J* = 15.2, 1 H), 5.43-5.37 (m, 1 H), 5.33-5.30 (m, 1 H), 4.01 (dd, *J* = 12.0, 7.8, 1 H), 3.93-3.89 (m, 1 H), 3.58-3.44 (m, 4 H), 2.61-2.58 (m, 1 H), 2.47-2.37 (m, 3 H), 1.89 (s, 3 H), 1.71 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 199.0, 196.6, 166.3, 146.8, 143.8, 140.5, 133.1, 130.5, 126.0, 125.9, 120.0, 75.8, 67.9, 67.5, 45.7, 39.2, 32.9, 24.5, 16.4. **IR** (thin film): $\tilde{\nu}$ = 3424, 2957, 2921, 2853, 1732, 1706, 1668, 1632, 1456, 1437, 1377, 1356, 1317, 1258, 1206, 1174, 1143, 1112, 1080, 1026, 976, 888, 800 cm^{-1}. **HRMS** (ESI): calcd for $C_{19}H_{24}NaO_5$ [$(M+Na)^+$]: 355.1516; found: 355.1523. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{24}}$: –50.49 (c = 0.44, $CHCl_3$).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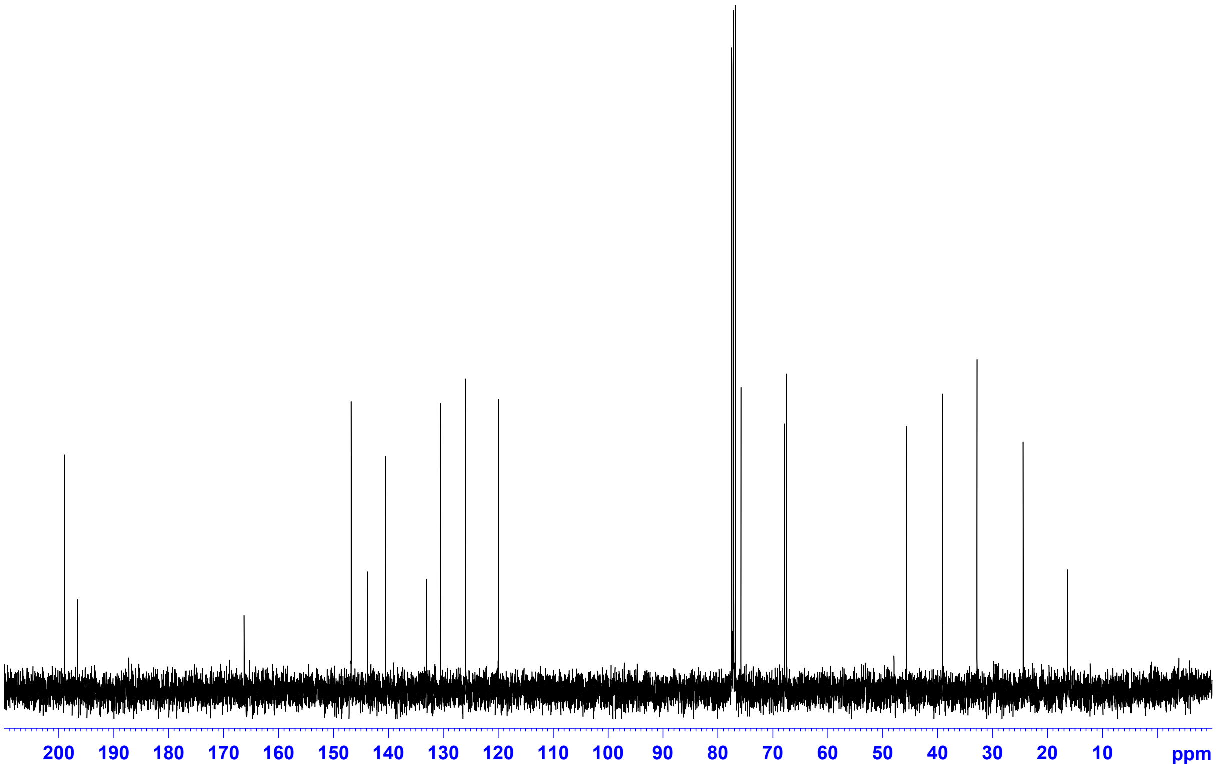
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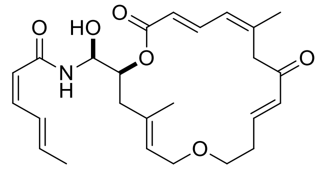

(2*Z*,4*E*)-N-((*S*)-((*S*,4*E*,10*E*,14*Z*,16*E*)-4,14-Dimethyl-12,18-dioxo-1,7-dioxacyclo octadeca-4,10,14,16-tetraen-2-yl)(hydroxy)methyl)hexa-2,4-dienamide (174). To a solution of amide **131** (19.3 mg, 0.174 mmol, 2.86 equiv) in dry THF (1.5 mL) was added DIBAL-H (1M in toluene, 0.15 mL, 0.15 mmol, 2.47 equiv) at 0 °C giving a colorless solution. Stirring was continued for 45 min, then a solution of aldehyde **175** (20.2 mg, 0.06 mol, 1 equiv) in THF (0.5 mL, the flask was rinsed with THF (2 x 0.5 mL)) was added dropwise. In the course of the reaction, an orange color was formed. Stirring was continued for a total of 5 h then saturated aqueous Rochelle salt (10 mL) was added as well as EtOAc (5 mL). Stirring was continued for 15 min and then two clear phases were formed. Phases were separated and the aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification using flash chromatography on a deactivated stationary phase (CH_2Cl_2/MeOH 20:1, 1% NEt_3 (v/v), 2 cm diameter, 12 cm height) afforded a mixture of **174**:*epi*-**174** (19.5 mg, 0.048 mmol, 72%, 1.1:1 ratio). Both epimers could be separated by HPLC on normal phase[47] (compound is concentrated in EtOH for injection, Phenomenex Luna, 5μ NH_2, 10 x 150 mm, EtOH/Hex (1:9), 3.5 mL/min, 20 °C, 266 nm, R_t = 11.9–12.6 min (**174**), R_t = 12.9–13.8 min (*epi*-**174**) and lastly RP-HPLC purification of the individual epimers (Waters, Symmetry®C18, 5μm, 7.8 x 100 mm, ACN/H_2O (45:55), 2.5 mL/min, 30 °C, 266 nm, R_t = 5.45 min for both epimers). Yields for the individual epimers were not calculated.

TLC: R_f = 0.24 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, DMSO-d$_6$): δ = 8.32 (d, *J* = 8.8, 1 H), 7.56 (dd, *J* = 15.0, 11.8, 1 H), 7.46 (dd, *J* = 14.5, 11.7, 1 H), 6.80 (dt, *J* = 16.1, 6.7, 1 H), 6.37 (dd, *J* = 11.4, 11.2, 1 H), 6.19 (d, *J* = 11.8, 1 H), 6.16 (br. s, 1 H), 6.02 (d, *J* = 16.1, 1 H), 5.96 (dd, *J* = 15.1, 7.1, 1 H), 5.91 (d, *J* = 15.1, 1 H), 5.65 (d, *J* = 11.4, 1 H), 5.38-5.35 (m, 1 H), 5.23-5.20 (m, 1 H), 4.98 (ddd, *J* = 10.1, 5.8, 2.1, 1 H), 3.95

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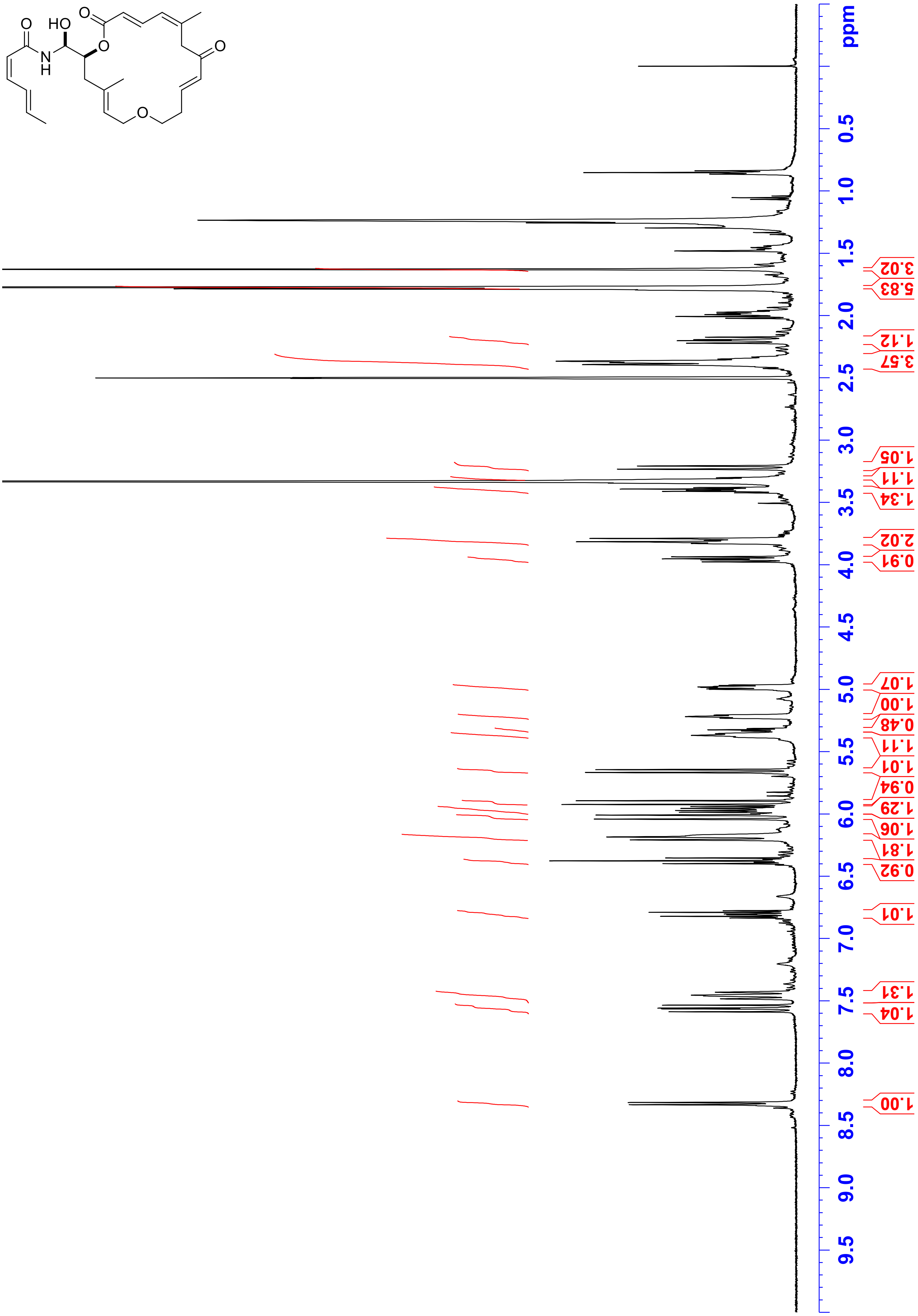
[47] Retentions times were rather susceptible to the injection volume. For analytical run under normal phase conditions, use: Phenomenex Luna, 3μ NH_2, 4.6 x 150 mm, EtOH/Hex (1:9), 1 mL/min, 20 °C.

(dd, *J* = 12.2, 8.0, 1 H), 3.83-3.80 (m, 1 H), 3.80 (d, *J* = 13.1, 1 H), 3.40 (dt, *J* = 9.4, 5.9, 1 H), 3.34-3.31 (m, 1 H), 3.21 (d, *J* = 13.1, 1 H), 2.42-2.33 (m, 3 H), 2.20 (dd, *J* = 14.1, 10.0, 1 H), 1.78-1.77 (m, 6 H, 2 x CH_3), 1.63 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 196.3, 165.6, 165.3, 146.4, 142.3, 140.7, 139.8, 137.3, 134.4, 129.9, 128.6, 125.6, 124.6, 120.7, 119.1, 72.9, 72.2, 66.9, 66.6, 45.1, 40.0, 32.3, 24.0, 18.3, 16.7. **IR** (thin film): $\tilde{\nu}$ = 3351, 2925, 2853, 1697, 1664, 1634, 1603, 1569, 1457, 1437, 1279, 1260, 1084, 1052 cm^{-1}. **HRMS** (ESI): calcd for $C_{25}H_{33}NNaO_6$ [$(M+Na)^+$]: 466.2200; found: 466.2192. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{24}}$: –12.38 (c = 0.15, EtOH). **RP-HPLC** (analytical column): Merck, Hibar Purospher®STAR RP-18e, 5µm, 4.6 x 150 mm, ACN/H_2O (1:1), 1 mL/min, 30 °C, 266 nm, R_t = 4.6 min. Alternative method: ACN/H_2O (1:9) to ACN (100%, 10 min) to ACN/H_2O (1:9, 15 min), 1 mL/min, 30 °C, 266 nm, R_t = 8.8-9.0 min.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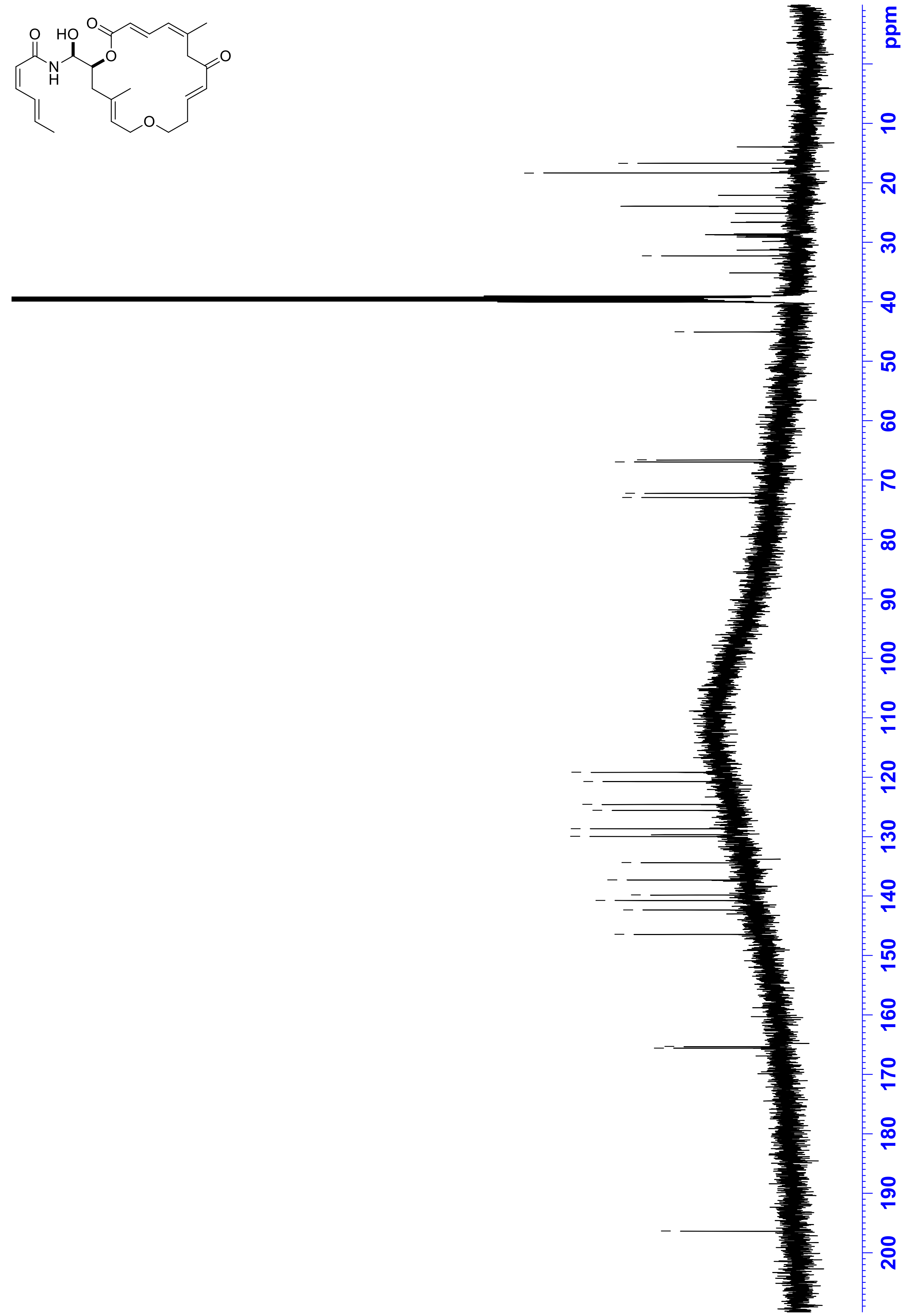
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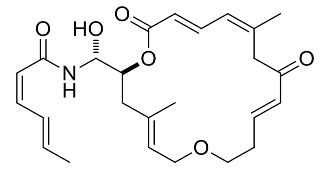

(2*Z*,4*E*)-N-((*R*)-((*S*,4*E*,10*E*,14*Z*,16*E*)-4,14-Dimethyl-12,18-dioxo-1,7-dioxacyclooctadeca-4,10,14,16-tetraen-2-yl)(hydroxy)methyl)hexa-2,4-dienamide (*epi*-174).[48]
TLC: R_f = 0.24 (EtOAc/Hex 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, DMSO-d_6): δ = 8.45 (d, *J* = 8.9, 1 H), 7.55 (dd, *J* = 15.1, 11.6, 1 H), 7.48-7.43 (m, 1 H), 6.76 (dt, *J* = 16.2, 6.7, 1 H), 6.40 (dd, *J* = 11.3, 11.2, 1 H), 6.22 (d, *J* = 11.7, 1 H), 6.09 (br. s, 1 H), 6.00 (d, *J* = 16.1, 1 H), 6.00-5.95 (m, 1 H), 5.96 (d, *J* = 15.1, 1 H), 5.65 (d, *J* = 11.4, 1 H), 5.37-5.34 (m, 1 H), 5.21-5.19 (m, 1 H), 5.06 (dd, *J* = 12.7, 6.3, 1 H), 3.94 (dd, *J* = 12.4, 7.9, 1 H), 3.89 (d, *J* = 13.0, 1 H), 3.80 (dd, *J* = 12.7, 4.4, 1 H), 3.38 (dt, *J* = 9.5, 5.9, 1 H), 3.33-3.29 (m, 1 H), 3.12 (d, *J* = 13.1, 1 H), 2.41-2.31 (m, 2 H), 2.20 (d, *J* = 6.9, 1 H), 1.79 (dd, *J* = 6.9, 1.2, 3 H), 1.77 (s, 3 H), 1.62 (s, 3 H), (a single proton is missing which could not be assigned). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 196.4, 165.8, 165.2, 146.4, 140.9, 140.3, 139.3, 137.4, 134.1, 129.6, 128.6, 125.6, 124.5, 121.2, 119.1, 72.9, 71.8, 67.1, 66.7, 45.3, 39.8, 32.3, 23.8, 18.4, 16.4. **HRMS** (ESI): calcd for $C_{25}H_{33}NNaO_6$ [$(M+Na)^+$]: 466.2200; found: 466.2197. **RP-HPLC** (analytical column): Merck, Hibar Purospher®STAR RP-18e, 5µm, 4.6 x 150 mm, ACN/H_2O (1:1), 1 mL/min, 30 °C, 266 nm, R_t = 4.6 min. Alternative method: ACN/H_2O (1:9) to ACN (100%, 10 min) to ACN/H_2O (1:9, 15 min), 1 mL/min, 30 °C, 266 nm, R_t = 8.8-9.0 min.

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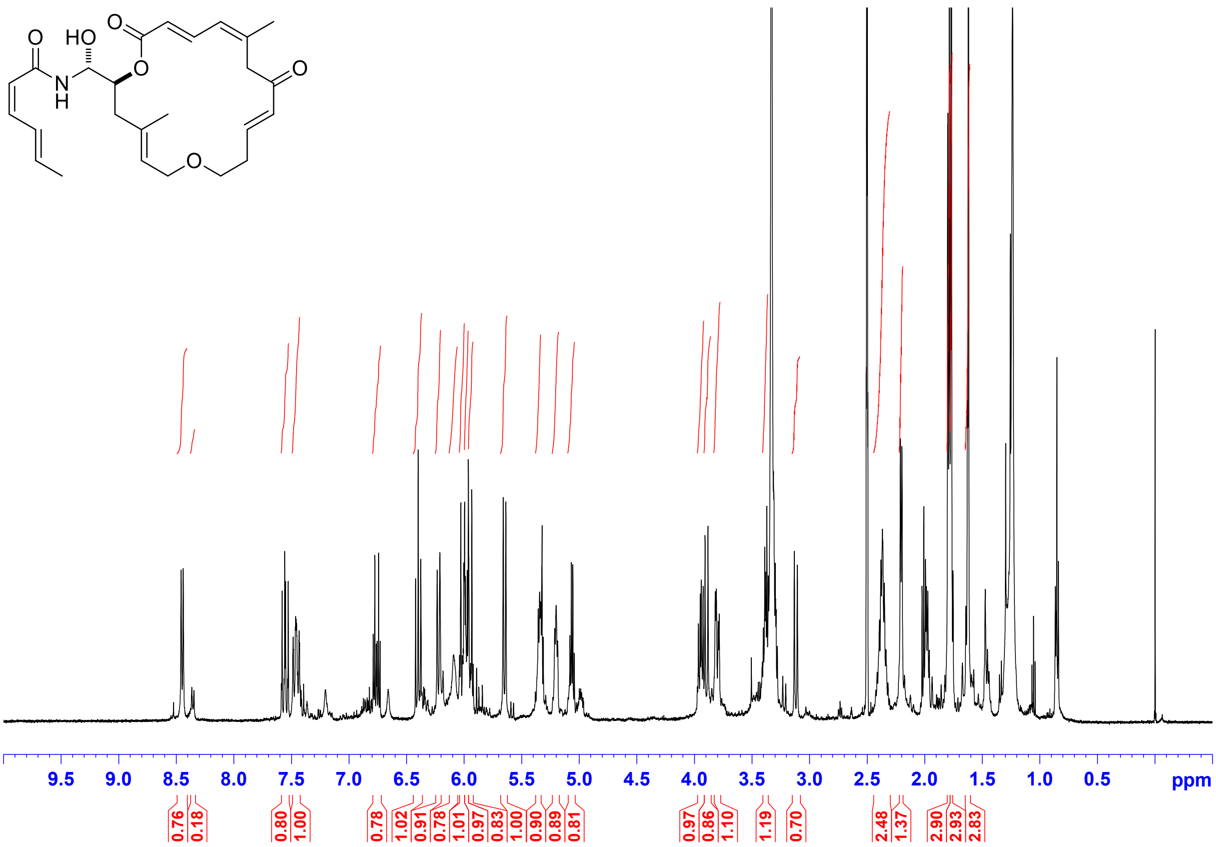
[48] The same change in color for DMSO-d_6 solutions of **174** and *epi*-**174** was observed as in the case of (–)-zampanolide ((–)-**1**) and *epi*-(–)-**1**, again with a slight loss in purity; RP-HPLC purification had to be repeated after NMR experiments.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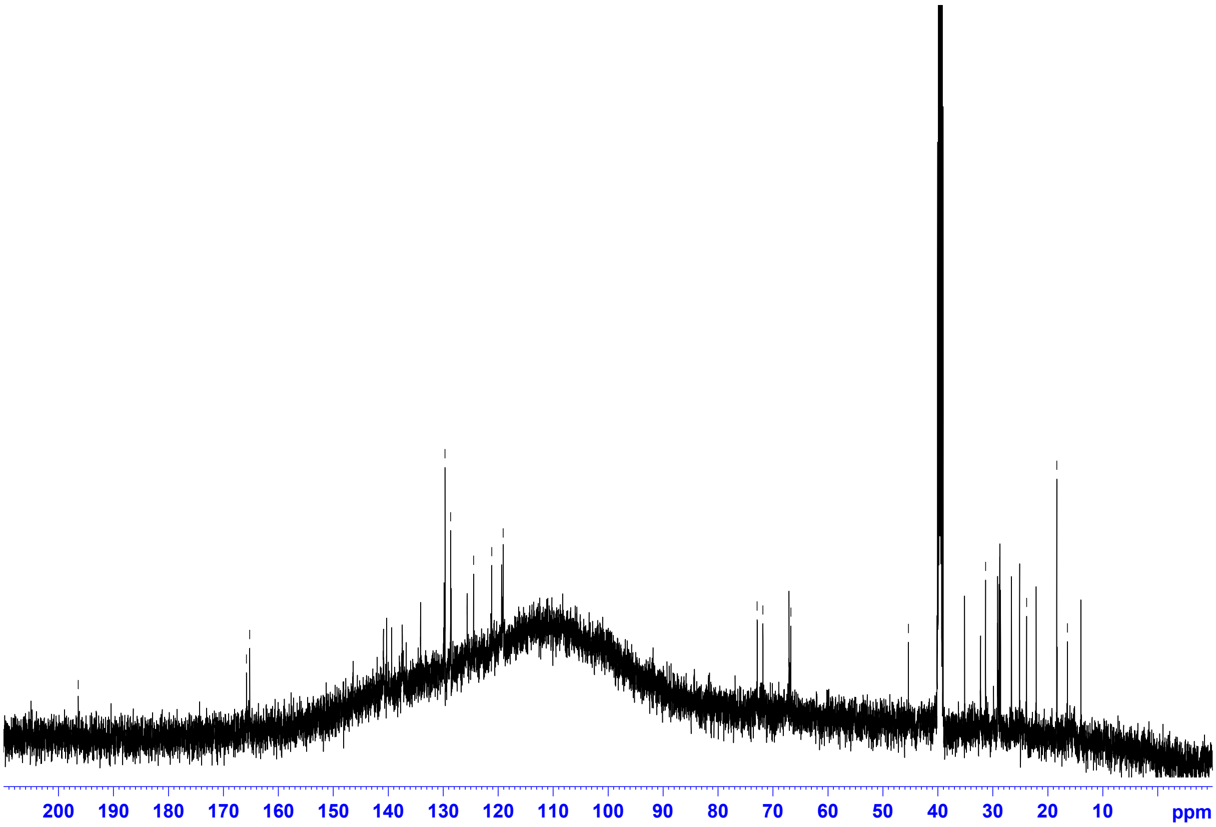
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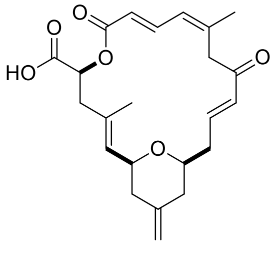
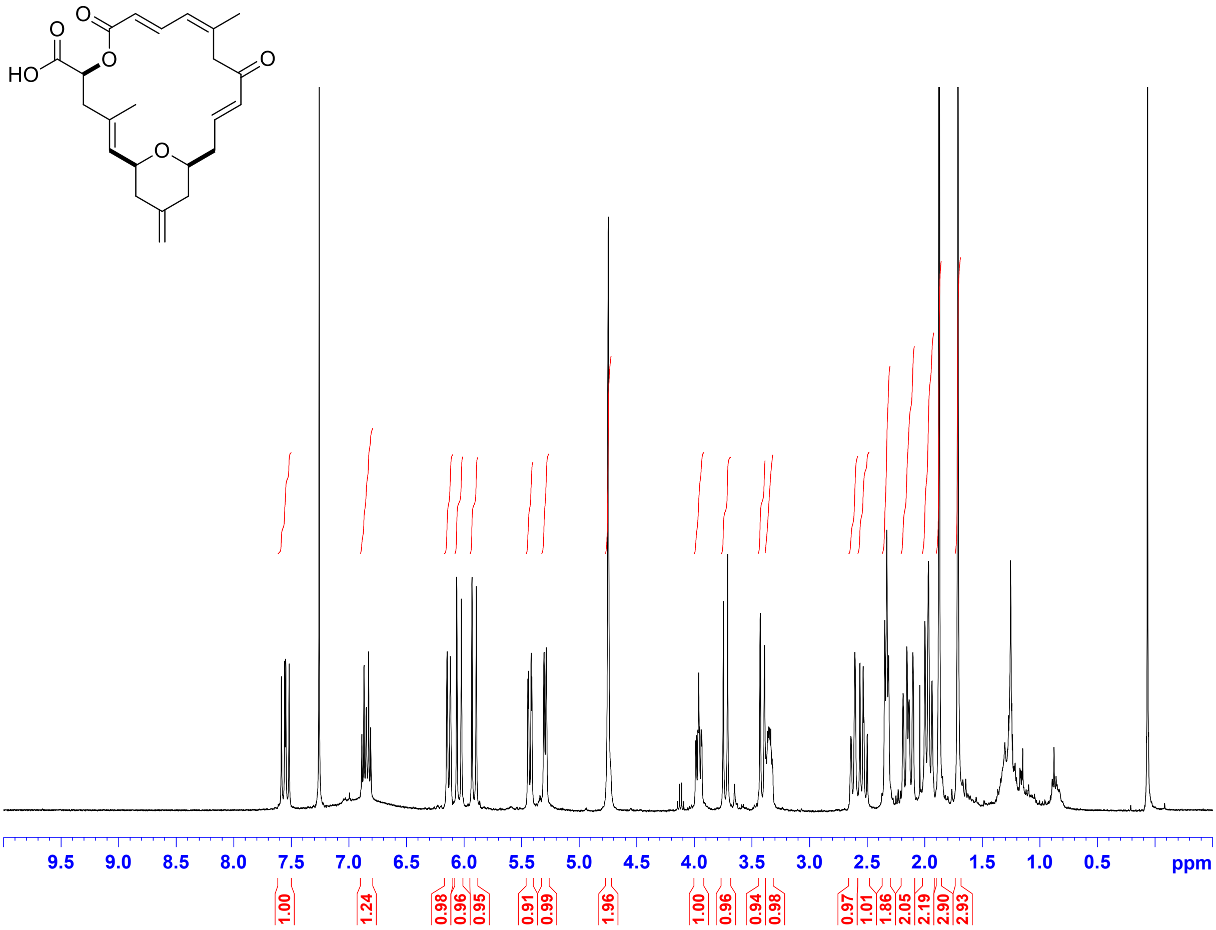
5.5.3. Side Chain-Modified Analogs



(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*S*)-3,11-Dimethyl-19-methylene-7,13-dioxo-6,21 dioxa bicyclo [15.3.1] henicosa-2,8,10,14-tetraene-5-carboxylic acid (188). To a solution of (–)-dactylolide ((–)-**2**) (9.5 mg, 0.0247 mmol, 1 equiv) in *t*-BuOH (3 mL) and 2-methyl-2-butene (2 mL, 18.88 mmol, 764 equiv) was slowly added a solution of $NaClO_2$ (22.3 mg, 0.247 mmol, 10 equiv) and $NaH_2PO_4{\bullet}H_2O$ (27.3 mg, 0.198 mmol, 8 equiv) in H_2O (1.2 mL) at room temperature giving a colorless mixture. The crude was diluted after 40 min with brine (10 mL) and then the phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ concentrated under reduced pressure and purified by flash chromatography (EtOAc, 0.5% AcOH) giving **188** (9.6 mg, 0.024 mmol, 97%) after coevaporation with toluene (1 x 2 mL).

TLC: R_f = 0.31 (EtOAc/0.5% AcOH, UV, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 15.1, 11.7, 1 H), 6.85 (dt, *J* = 16.2, 7.2, 1 H), 6.13 (d, *J* = 11.8, 1 H), 6.04 (d, *J* =16.1, 1 H), 5.91 (d, *J* = 15.5, 1 H), 5.43 (dd, *J* = 11.3, 2.6, 1 H), 5.30 (d, *J* = 7.9, 1 H), 4.75 (s, 2 H), 3.96 (ddd, *J* = 11.1, 7.9, 2.5, 1 H), 3.73 (d, *J* = 14.8, 1 H), 3.41 (d, *J* = 14.8, 1 H), 3.39-3.32 (m, 1 H), 2.63 (br. d, *J* = 13.5, 1 H), 2.53 (dd, *J* = 14.1, 11.3, 1 H), 2.35-2.30 (m, 2 H), 2.19-2.15 (m, 1 H), 2.14-2.09 (m, 1 H), 2.00-1.93 (m, 2 H), 1.87 (s, 3 H), 1.71 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 197.4, 174.6, 166.2, 145.8, 143.8, 143.7, 140.3, 131.7, 131.2, 130.7, 126.0, 120.2, 109.5, 76.5, 75.8, 69.1, 45.0, 41.8, 40.8, 40.5, 39.4, 24.5, 16.1. **IR** (thin film): $\tilde{\nu}$ = 3020, 2936, 1714, 1711, 1635, 1436, 1355, 1258, 976, 889, 752 cm^{-1}. **HRMS** (ESI): calcd for $C_{23}H_{28}NaO_8[(M+Na)^+]$: 423.1778; found: 423.1767. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –68.82 (c 0.49 in $CHCl_3$).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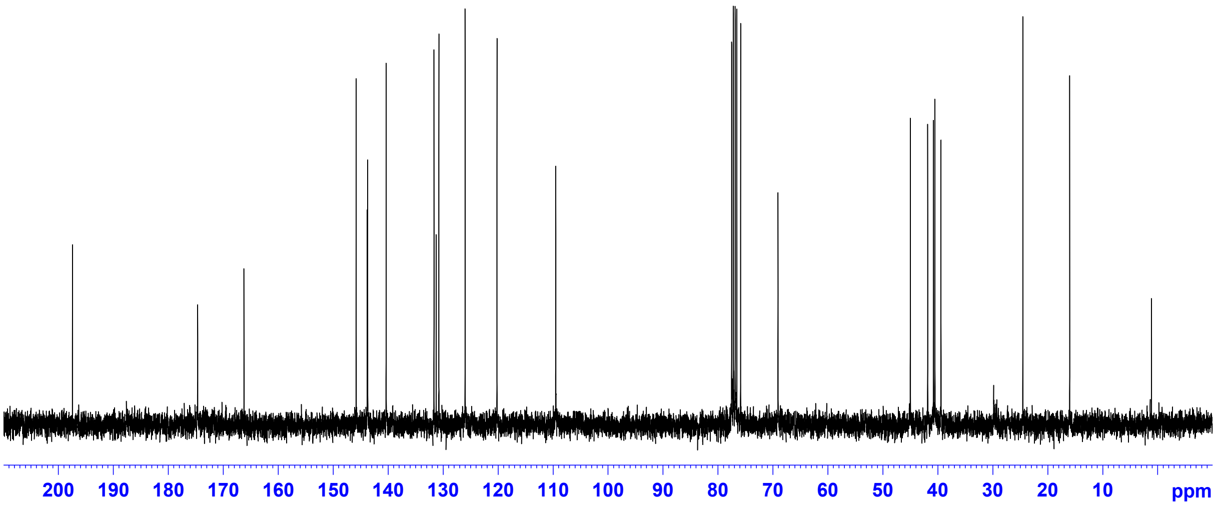
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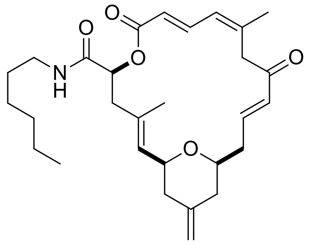
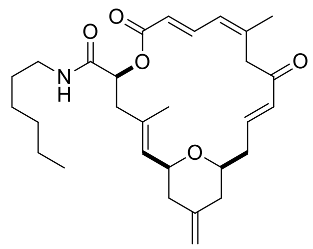


(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*S*)-*N*-Hexyl-3,11-dimethyl-19 - methylene - 7,13 - dioxo - 6,21 - dioxa bicyclo [15.3.1] henicosa-2,8,10,14-tetraene-5-carboxamide (189). To a solution of **188** (26 mg, 0.065 mmol, 1 equiv) in dry DMF (2 mL) was added HATU (27.4 mg, 0.072 mmol, 1.1 equiv) and DIPEA (0.023 mL, 0.13 mmol, 2 equiv) giving a yellow solution. After 10 min, neat hexylamine (0.026 mL, 0.195 mmol, 3 equiv; freshly distilled right before use) was added. Stirring was continued for a total of 16 h then H_2O (5 mL) was added followed by Et_2O (5 mL). The phases were separated then the aqueous phase was extracted with Et_2O (3 x 5 mL) and the combined organic phases were washed with H_2O (2 x 5 mL). The aqueous phase had to be reextracted with CH_2Cl_2 (2 x 5 mL) then the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:5→1:3) giving **189** (4.1 mg, 0.0085 mmol, 13%) as a yellow oil.

TLC: R_f = 0.15 (EtOAc/Hex 1:3, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.70 (dd, *J* = 15.1, 11.6, 1 H), 6.82 (ddd, *J* = 16.4, 9.5, 4.7, 1 H), 6.23-6.19 (m, 1 H), 6.14 (d, *J* = 11.5, 1 H), 5.97 (d, *J* = 14.9, 1 H), 5.93 (d, *J* = 16.0, 1 H), 5.56 (dd, *J* = 11.2, 2.1, 1 H), 5.18 (d, *J* = 8.1, 1 H), 4.75-4.71 (m, 2 H), 4.19 (d, *J* = 13.8, 1 H), 3.97 (ddd, *J* = 11.2, 8.1, 2.6, 1 H), 3.32-3.24 (m, 3 H), 3.01 (d, *J* = 13.7, 1 H), 2.74 (d, *J* = 13.7, 1 H), 2.34 (dddd, *J* = 14.8, 10.0, 4.8, 1.8, 1 H), 2.28-2.25 (m, 1 H), 2.24-2.21 (m, 1 H), 2.17-2.13 (m, 1 H), 2.12-2.07 (m, 1 H), 1.99-1.88 (m, 2 H), 1.83 (s, 3 H), 1.74 (d, *J* = 0.9, 3 H), 1.55-1.48 (m, 3 H), 1.35-1.28 (m, 8 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 197.8, 169.6, 165.5, 146.6, 144.6, 143.7, 140.9, 132.6, 131.7, 130.1, 125.3, 119.7, 109.3, 76.7, 76.0, 71.1, 45.1, 43.7, 41.1, 40.8, 40.3, 39.5, 31.6, 29.7, 26.7, 23.9, 22.7, 16.4, 14.1. **IR** (thin film): $\tilde{\nu}$ = 3336, 2929, 2859, 1717, 1668, 1635, 1533, 1436, 1355, 1277, 1256, 1206, 1176, 1141, 1117, 1086, 1053, 977, 888 cm^{-1}. **HRMS** (ESI): calcd for $C_{29}H_{42}NO_5[(M+H)^+]$: 484.3057; found: 484.3057. $[\alpha]_D^{24}$: –166.22 (c = 0.82 in $CHCl_3$).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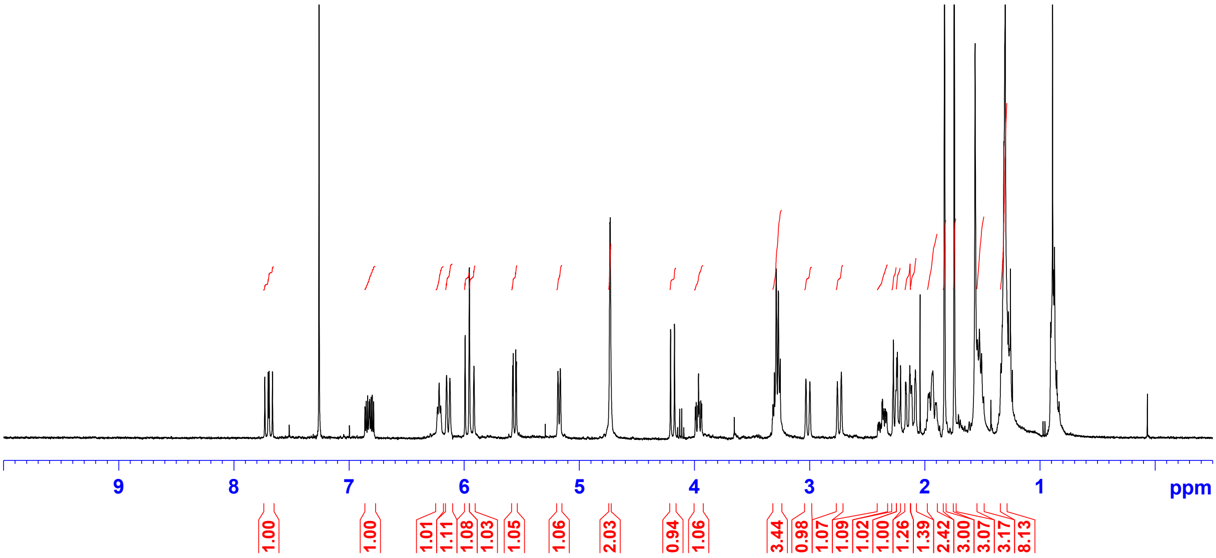
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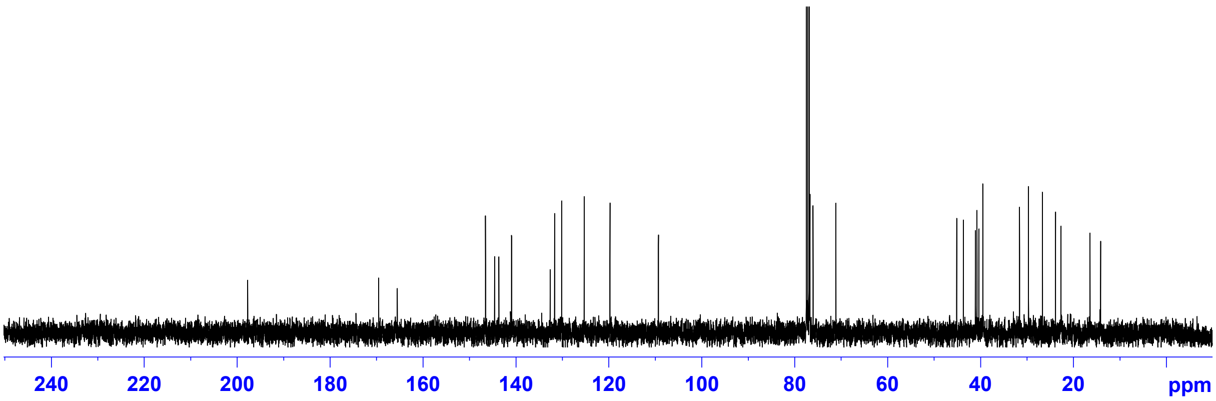
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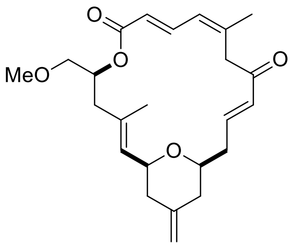
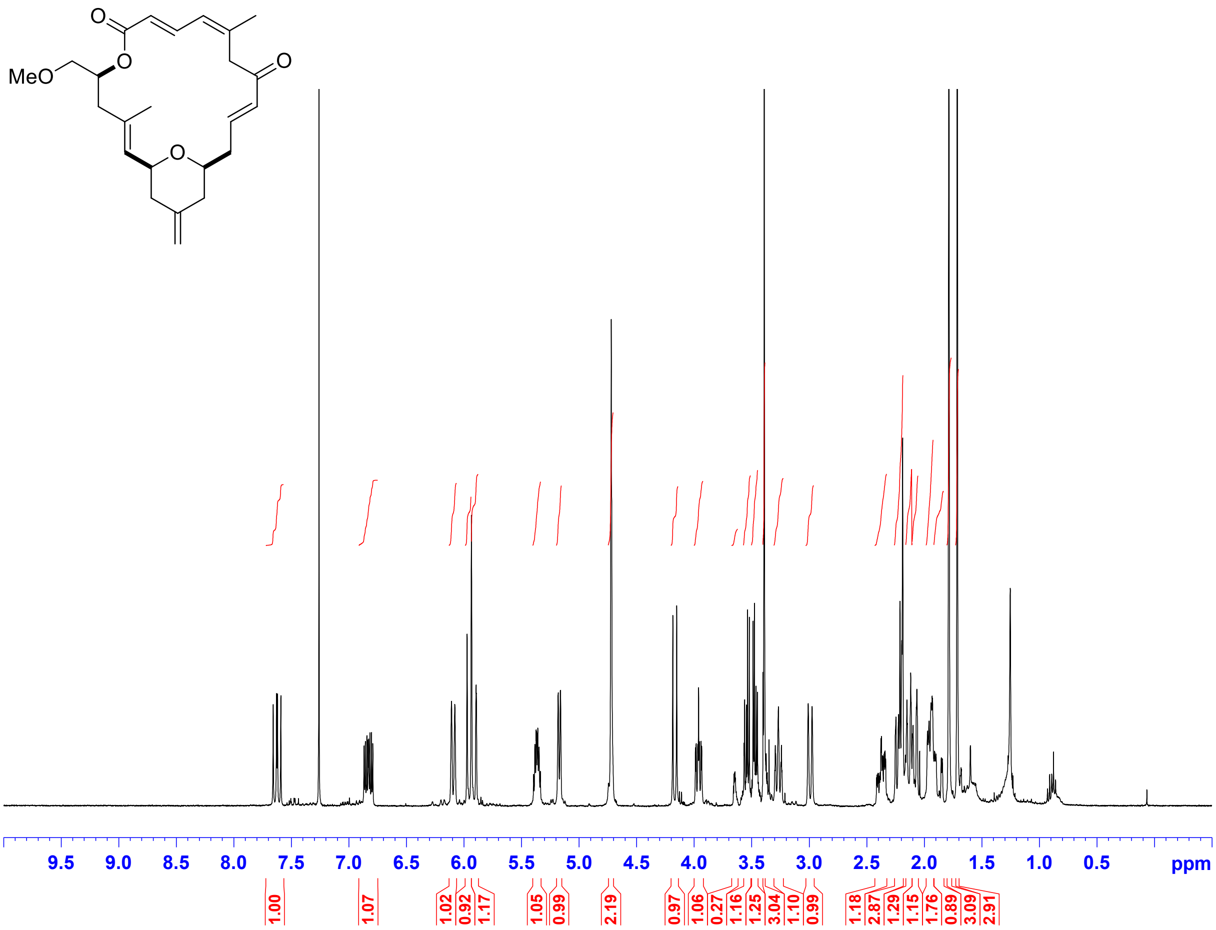


(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*S*)-5-(Methoxymethyl) - 3,11 - dimethyl - 19 - methylene -6,21-dioxa bicyclo [15.3.1] henicosa-2,8,10,14-tetraene-7,13-dione (191). To a suspension of Me_3OBF_4 (13.8 mg, 0.093 mmol, 5 equiv) in dry CH_2Cl_2 (0.5 mL) was added a solution of **129** (7.2 mg, 0.0186 mmol, 1 equiv) in dry CH_2Cl_2 (0.5 mL; flask rinsed with dry CH_2Cl_2 (2 x 0.2 mL)) followed by Proton Sponge™ (20 mg, 0.093 mmol, 5 equiv) leading to a yellow-orange mixture after 30 min. Saturated aqueous NH_4Cl (10 mL) was added after 1.5 h as well as CH_2Cl_2 (5 mL). The phases were separated then the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic phases were washed with brine (5 mL) then dried over $MgSO_4$ and concentrated under reduced pressure. In order to remove the Proton Sponge™, the crude product was diluted with CH_2Cl_2 then washed with aqueous HCl (1N, 2 x 5 mL). The organic phase was dried over $MgSO_4$ then concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:5) giving **191** (6.2 mg, 0.0155 mmol, 83%) as a colorless oil.

TLC: R_f = 0.31 (EtOAc/Hex 1:3, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.62 (dd, *J* = 15.1, 11.6, 1 H), 6.83 (ddd, *J* = 16.2, 9.5, 4.6, 1 H), 6.09 (d, *J* = 11.1, 1 H), 5.95 (d, *J* = 15.1, 1 H), 5.91 (d, *J* = 16.5, 1 H), 5.39-5.33 (m, 1 H), 5.19-5.15 (m, 1 H), 4.73-4.71 (m, 2 H), 4.17 (d, *J* = 13.6, 1 H), 3.96 (ddd, *J* = 11.3, 8.3, 2.6, 1 H), 3.54 (dd, *J* = 10.4, 6.1, 1 H), 3.47 (dd, *J* = 10.4, 4.6, 1 H), 3.39 (s, 3 H), 3.30-3.24 (m, 1 H), 2.99 (d, *J* = 13.5, 1 H), 2.37 (dddd, *J* = 15.3, 10.1, 4.4, 1.9, 1 H), 2.25-2.21 (m, 1 H), 2.21-2.18 (m, 2 H), 2.16-2.11 (m, 1 H), 2.11-2.06 (m, 1 H), 1.98-1.87 (m, 2 H), 1.79 (s, 3 H), 1.71 (d, *J* = 1.2, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 198.3, 166.9, 146.5, 143.9, 142.9, 139.4, 132.5, 131.6, 129.6, 125.6, 121.3, 109.1, 76.7, 76.1, 74.6, 69.3, 59.4, 45.2, 42.6, 41.1, 40.9, 40.4, 23.6, 16.8. **IR** (thin film): $\tilde{\nu}$ = 2978, 2935, 2871, 1715, 1669, 1634, 1434, 1357, 1279, 1255, 1203, 1175, 1145, 1118, 1086, 1052, 977, 889 cm^{-1}. **HRMS** (ESI): calcd for $C_{24}H_{32}NaO_5[(M+Na)^+]$: 423.2124; found: 423.2147. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$= –269.21 (c = 0.23 in $CHCl_3$).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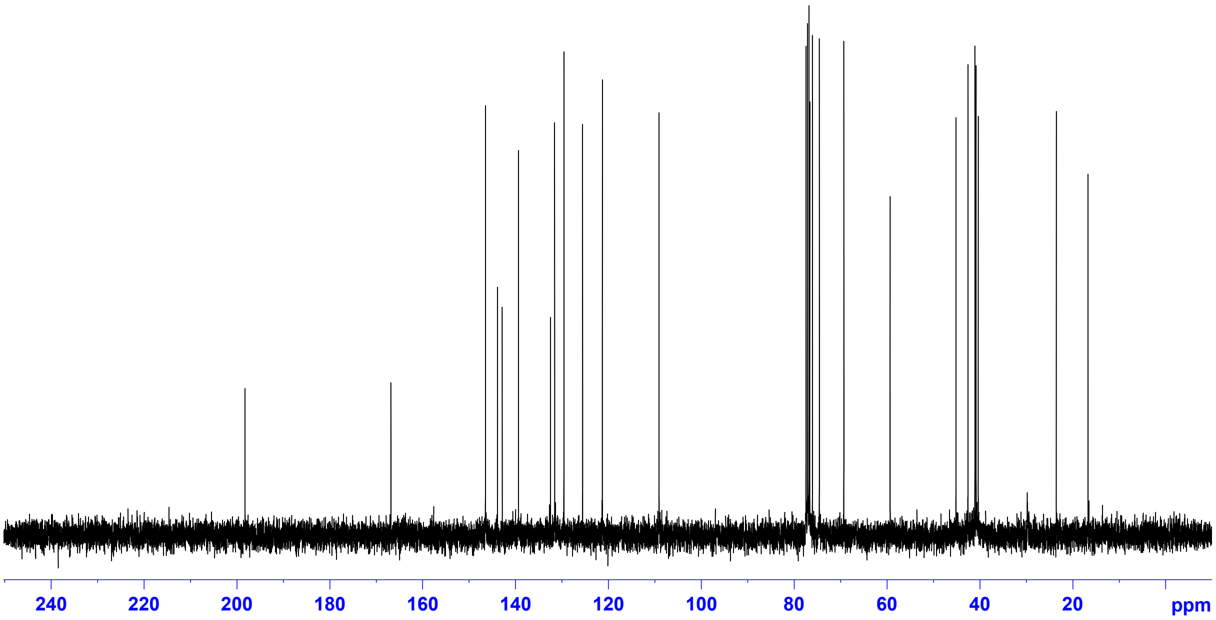
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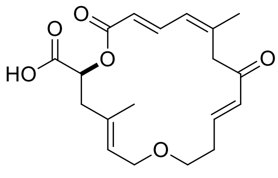
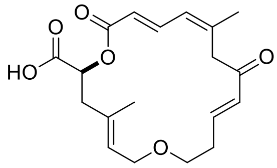


(*S*,4*E*,10*E*,14*Z*,16*E*)-4,14-Dimethyl-12,18-dioxo-1,7-dioxacyclooctadeca-4,10,14,16-tetraene-2-carboxylic acid (190). To solution of **175** (8.9 mg, 0.027 mmol, 1 equiv) in *t*-BuOH (0.5 mL) and 2-methyl-2-butene (0.5 mL, 4.72 mmol, 175 equiv) was added a solution of $NaClO_2$ (24.5 mg, 0.27 mmol, 10 equiv) and KH_2PO_4 (29 mg, 0.21 mmol, 8 equiv) in H_2O (0.2 mL) slowly at room temperature, giving a pale-yellow reaction mixture that decolorized after few minutes. Stirring was continued for 20 min then the mixture was diluted with brine (10 mL) and the phases separated. The aqueous phase was extracted with EtOAc (3 x 10 mL) then the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified twice by flash chromatography (EtOAc/MeOH/AcOH 10:1:0.1) giving **190** (9.1 mg, 0.026 mmol, 97%).

TLC: R_f = 0.17 (EtOAc/AcOH 200:1, UV, CPS or $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.62 (dd, *J* = 14.9, 11.5, 1 H), 7.26-7.15 (m, 1 H), 6.84 (dt, *J* = 16.0, 6.8, 1 H), 6.14 (d, *J* = 11.4, 1 H), 6.14-6.09 (m, 1 H), 5.88 (d, *J* = 15.1, 1 H), 5.44-5.39 (m, 1 H), 5.35 (dd, *J* = 9.7, 3.7, 1 H), 4.01 (dd, *J* = 11.9, 7.9, 1 H), 3.93 (dd, *J* = 12.0, 5.1, 1 H), 3.67 (d, *J* = 13.5, 1 H), 3.52-3.47 (m, 2 H), 3.38 (d, *J* = 13.5, 1 H), 2.68-2.57 (m, 2 H), 2.47-2.40 (m, 2 H), 1.88 (s, 3 H), 1.72 (s, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 196.7, 174.8, 166.1, 146.8, 143.4, 140.3, 133.6, 130.6, 126.1, 125.8, 120.3, 69.4, 67.8, 67.3, 45.7, 41.3, 32.8, 24.5, 16.3. **IR** (thin film): $\tilde{\nu}$ = 3163, 2975, 2924, 2859, 1711, 1695, 1669, 1631, 1435, 1382, 1353, 1269, 1251, 1180, 1146, 1113, 1073, 975, 708 cm^{-1}. **HRMS** (ESI): calcd for $C_{19}H_{24}NaO_6[(M+Na)^+]$: 371.1465; found: 371.1473. $[\alpha]_D^{24}$= +230.31 (c= 0.065 in $CHCl_3$).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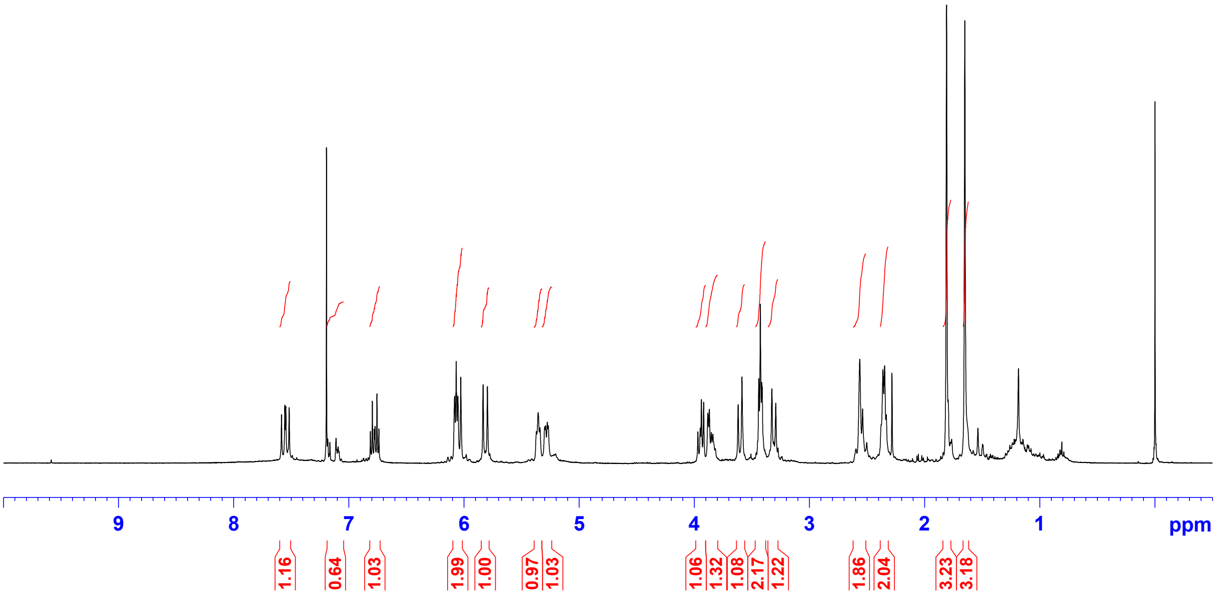
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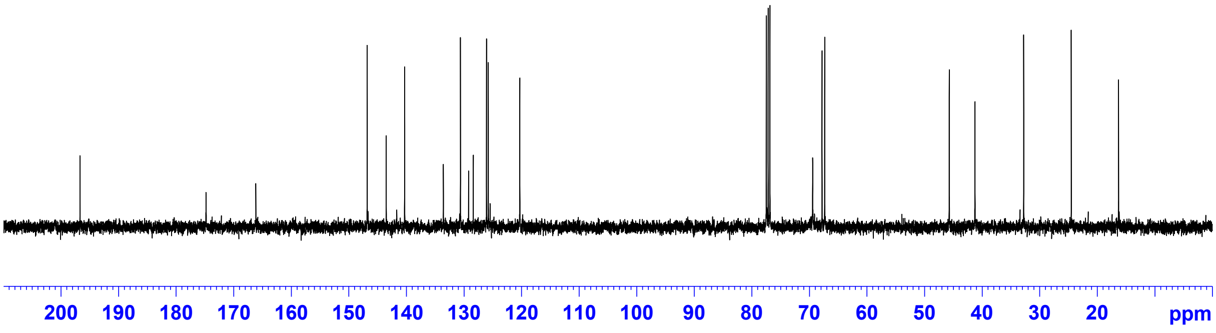
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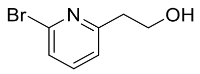
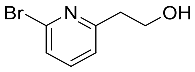
5.5.4. Towards the Synthesis of Pyrido-(–)-Dactylolide (192)



2-(6-Bromopyridin-2-yl)ethanol (193).[227] To a solution of diisopropylamine (6.5 mL, 46.2 mmol, 2 equiv) in dry THF (50 mL) was added a solution of *n*-BuLi (1.6M in hexane, 28.9 mL, 46.2 mmol, 2 equiv) at 0 °C (icebath). The solution was stirred for 30 min then cooled to –78 °C followed by addition of 2-bromo-6-methylpyridine (0.5 mL, 23.1 mmol, 1 equiv) in dry THF (10 mL). 30 min later, DMF (1.79 mL, 23.1 mmol, 1 equiv) was added and stirring was continued for 90 min more. Sequential addition of MeOH (24 mL), AcOH (1.32 mL, 23.1 mmol, 1 equiv) and NaBH$_4$ (0.87 g, 23.0 mmol, 0.95 equiv) resulted in an orange mixture that was allowed to warm to room temperature during 2 h. Saturated aqueous NaHCO$_3$ (50 mL) was slowly added followed by EtOAc (50 mL) and H$_2$O (50 mL). Phases were separated then the aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic phases were washed with brine (1 x 10 mL), then dried over MgSO$_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:1→2:1) afforded **193** (1.82 g, 8.98 mmol, 39%) as a yellow oil.

TLC: R$_f$ = 0.28 (EtOAc/Hex 1:1, UV, KMnO$_4$). **^{1}H-NMR** (400 MHz, CDCl$_3$): δ = 7.47 (dd, J =7.9, 7.7, 1 H), 7.34 (d, J = 7.9, 1 H), 7.14 (d, J = 7.7, 1 H), 4.00 (q, J = 5.8, 2 H), 3.09 (t, J = 5.8, 1 H), 3.00 (d, J = 5.8, 1 H), 2.99 (d, J = 5.7, 1 H). **^{13}C-NMR** (100 MHz, CDCl$_3$): δ = 161.7, 141.5, 138.9, 126.0, 122.5, 61.6, 39.5. **IR** (thin film): $\tilde{\nu}$ = 3355, 2957, 2933, 2880, 1648, 1582, 1552, 1437, 1404, 1226, 1177, 1157,1122, 10 47 cm^{-1}. **HRMS** (EI): calcd for C$_7$H$_8$BrNO [(M)$^+$]: 200.9784; found: 200.9784.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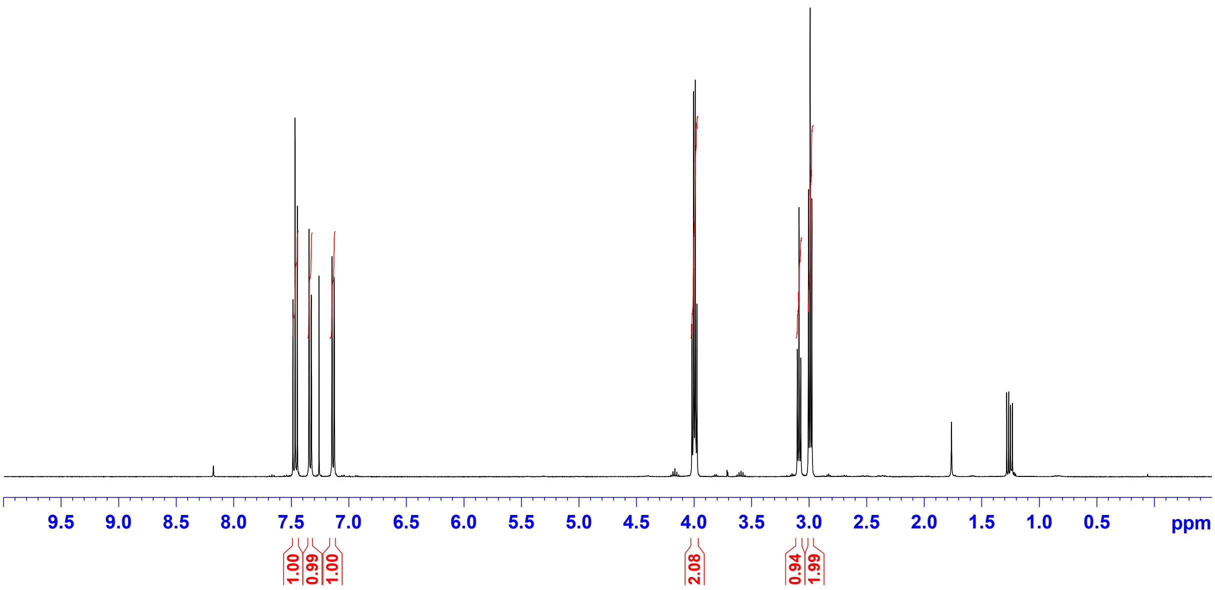
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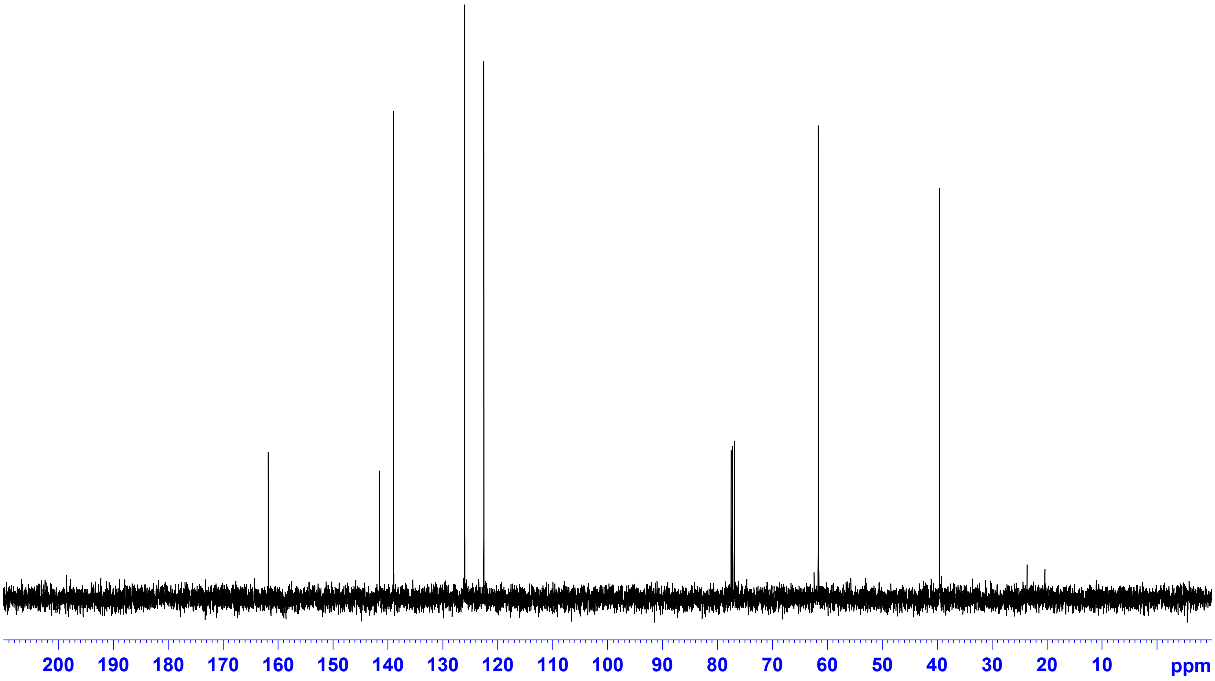
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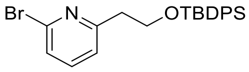
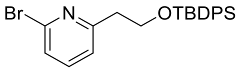


2-Bromo-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)pyridine (K). To a solution of **193** (1.81 g, 8.98 mmol, 1 equiv) in dry DMF (20 mL) was added NEt_3 (1.37 mL, 9.88 mmol, 1.1 equiv) followed by TBDPSCl (2.56 mL, 9.88 mmol, 1.1 equiv) giving a clear solution. DMAP (1.1 g, 8.98 mmol, 1 equiv) was added resulting in the formation of a turbid mixture under slight exothermicity. Stirring was continued for 1 h then H_2O (50 mL) followed by Et_2O (50 mL) were added. Phases were separated then the aqueous phase was extracted with Et_2O (3 x 20 mL); the combined organic phases were then washed with H_2O (1 x 20 mL) followed by washing of the aqueous phase with Et_2O (1 x 20 mL). The combined organic phases were dried over $MgSO_4$, then concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:50) giving **K** (3.49 g, 7.91 mmol, 89%) as a colorless oil.

TLC: R_f = 0.48 (EtOAc/Hex 1:10, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.57-7.54 (m, 4 H), 7.44 (dd, *J* = 7.7, 7.6, 1 H), 7.43-7.33 (m, 6 H), 7.33 (d, *J* = 7.7, 1 H), 7.18 (d, *J* = 7.6, 1 H), 4.00 (t, *J* = 6.1, 2 H), 3.00 (t, *J* = 6.1, 2 H), 0.98 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 161.5, 141.7, 138.3, 135.7, 133.7, 129.7, 127.8, 125.7, 123.2, 63.2, 41.2, 26.9, 19.3. **IR** (thin film): $\tilde{\nu}$ = 3070, 2958, 2929, 2857, 1582, 1553, 1472, 1437, 1426, 1105, 1094, 1082 cm^{-1}. **HRMS** (EI): calcd for $C_{19}H_{17}BrNOSi$ [$(M-C_4H_9)^+$]: 382.0257; found: 382.0258.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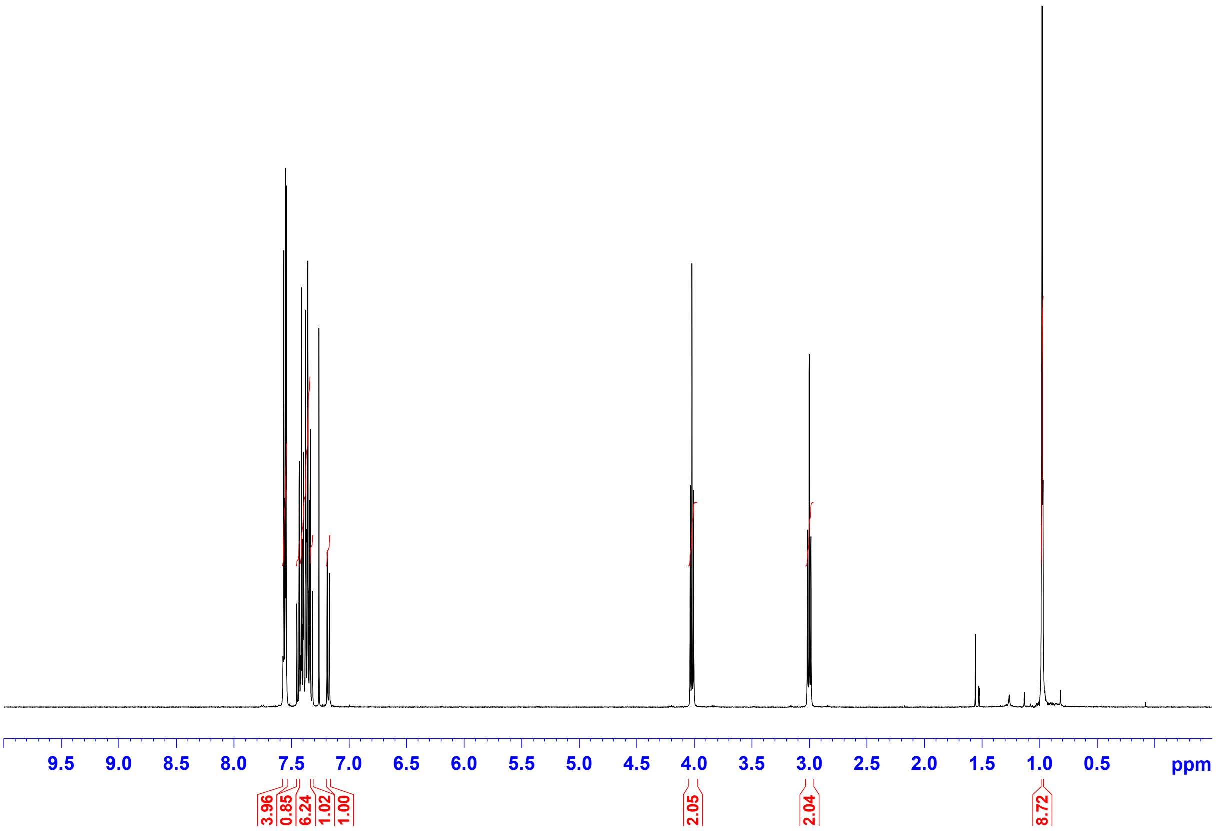
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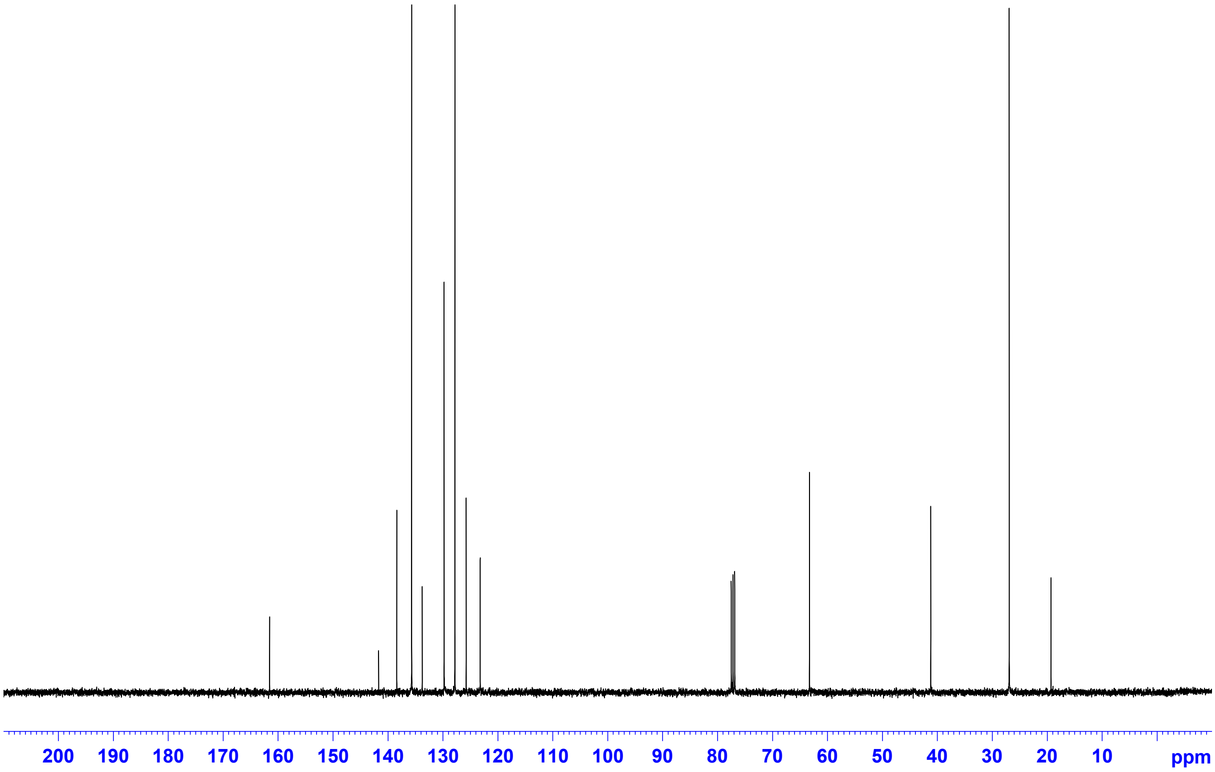
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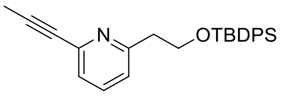
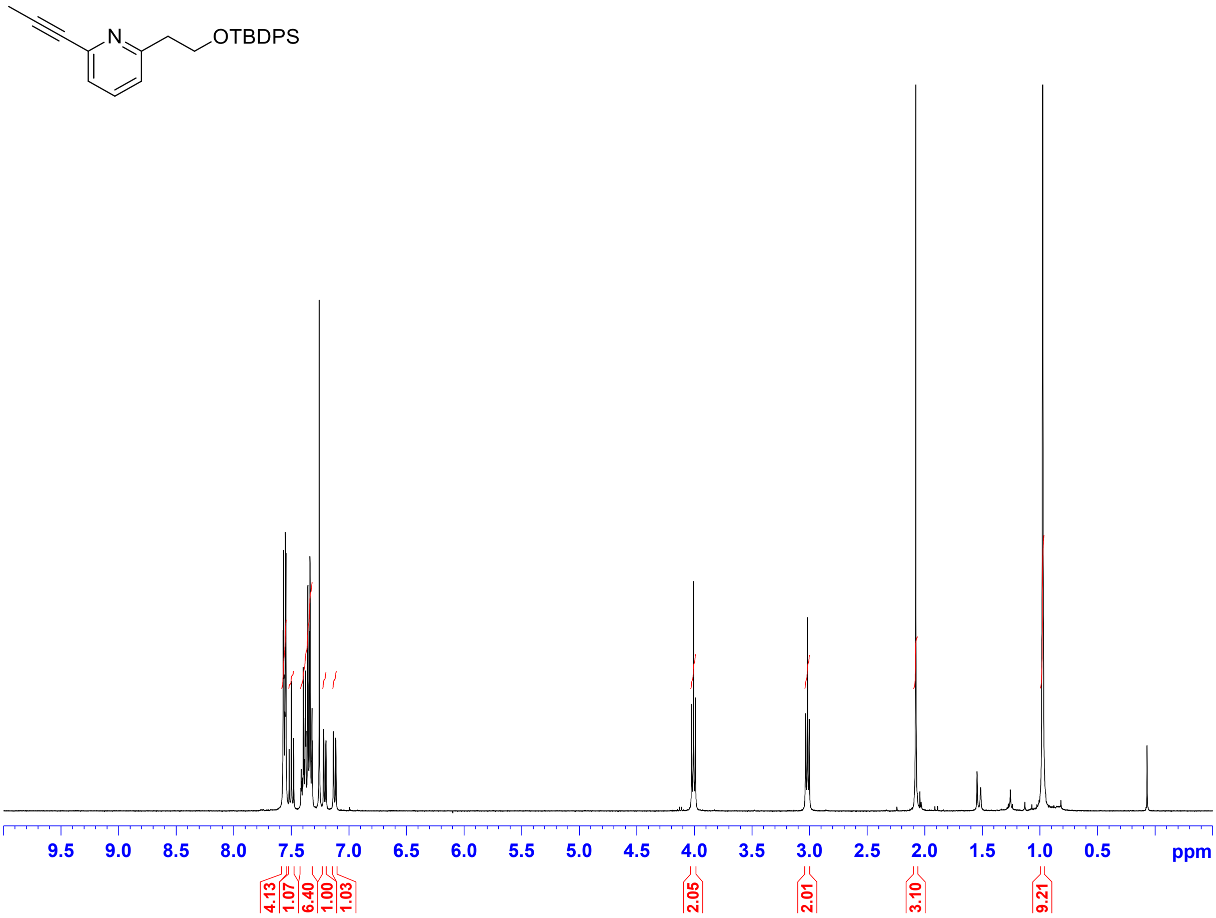


2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-6-(prop-1-ynyl)pyridine (194). To a solution of **K** (3.48 g, 7.91 mmol, 1 equiv) in dry DMF (75 mL, degassed for 5 min with argon) was added diisopropylamine (22 mL, 158.2 mmol, 20 equiv) followed by CuI (0.15 g, 0.79 mmol, 0.1 equiv) and $PdCl_2(PPh_3)_2$ (0.28 g, 0.40 mmol, 0.05 equiv) giving a clear golden-yellow solution. A balloon, containing propyne gas, was applied leading to a black solution under slight exothermicity. Stirring was continued for 60 min then a new ballon containing propyne was applied. After a total of 90 min, Et_2O (200 mL) was added then the organic phase was washed with H_2O (3 x 25 mL). The aqueous phase was washed with Et_2O (1 x 20 mL) then the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:5) giving **194** (3.05 g, 7.63 mmol, 97%) as a dark-orange oil.

TLC: R_f = 0.48 (EtOAc/Hex 1:5, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.57-7.54 (m, 4 H), 7.50 (dd, *J* = 7.9, 7.8, 1 H), 7.41-7.32 (m, 6 H), 7.21 (d, *J* = 7.8, 1 H), 7.13 (d, *J* = 7.9, 1 H), 4.00 (t, *J* = 6.4, 2 H), 3.02 (t, *J* = 6.3, 2 H), 2.08 (s, 3 H), 0.98 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 160.0, 143.4, 136.1, 135.6, 133.9, 129.6, 127.7, 124.4, 123.1, 86.2, 80.0, 63.6, 41.7, 26.9, 19.3, 4.5. **IR** (thin film): $\tilde{\nu}$ = 3070, 2958, 2930, 2856, 2241, 2235, 1583, 1567, 1472, 1449, 1427, 1105, 1084, cm^{-1}. **HRMS** (EI): calcd for $C_{26}H_{28}NOSi$ [$(M-H)^+$]: 398.1935; found: 398.1935.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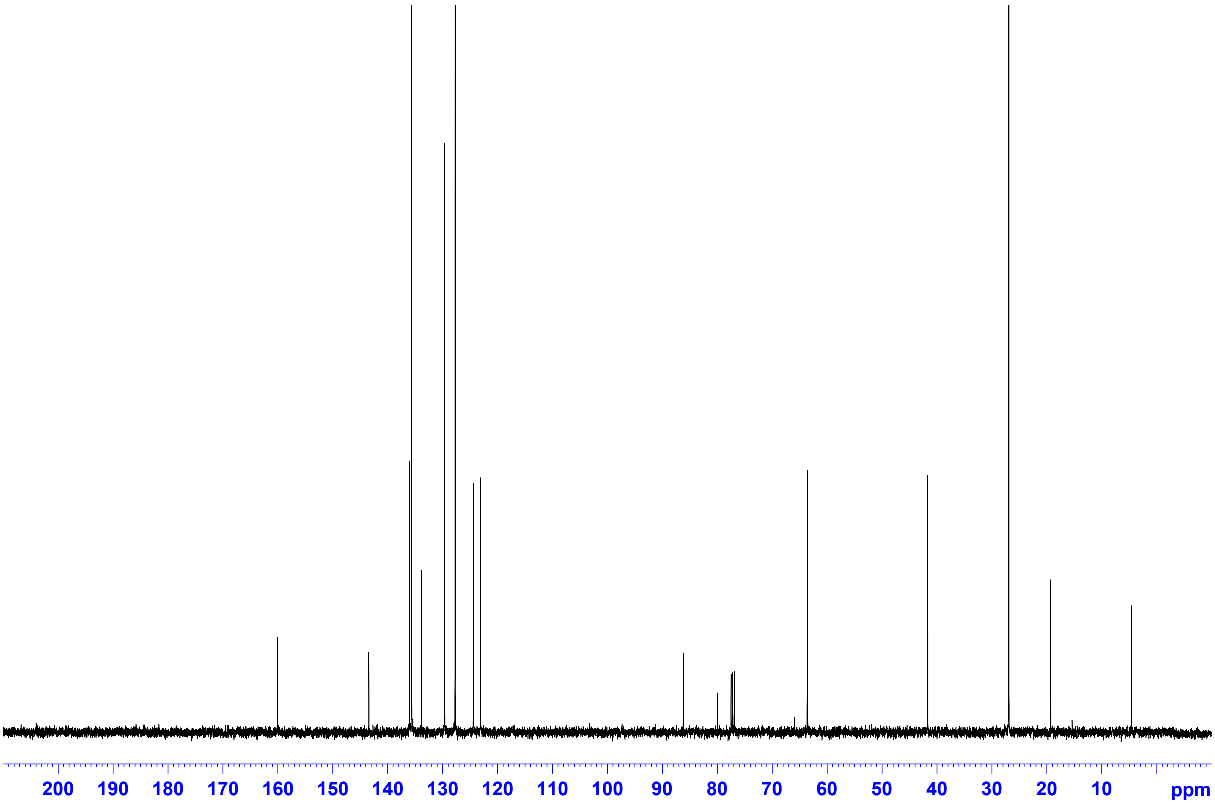
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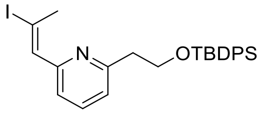
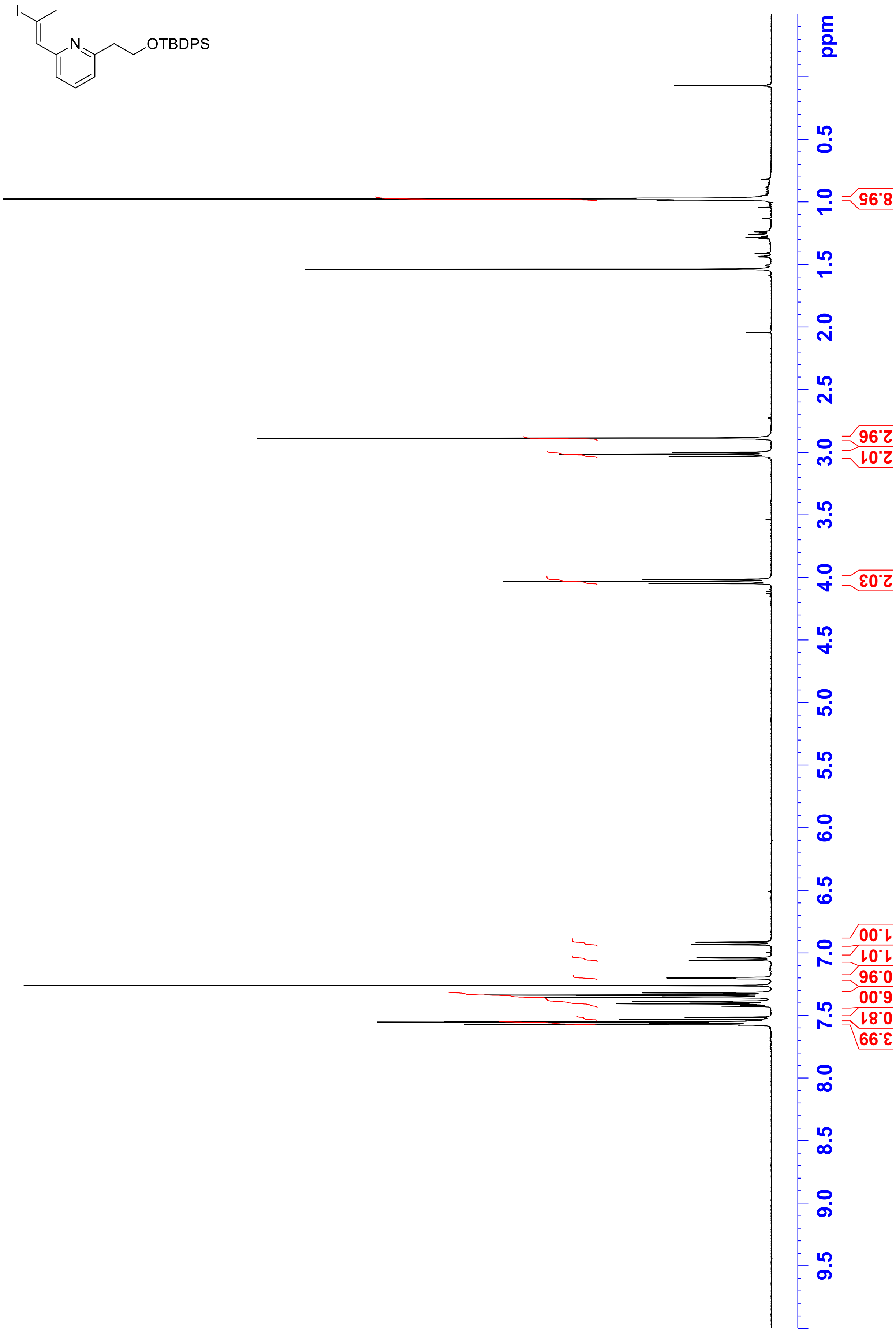


(*E*)-2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-6-(2-iodoprop-1-enyl)pyridine (195). To a suspension of CuCN (901 mg, 10.06 mmol, 2.00 equiv) in THF (100 mL) at –78 °C was added a solution of *n*-BuLi (1.6M in hexane, 12.6 mL, 20.11 mmol, 4 equiv). After 5 min, the flask was immersed into a cooling bath at –40 °C where a pale-yellow, almost clear solution was formed. This was cooled back to –78 °C after 10 min giving a clear solution. Then neat Bu_3SnH (5.40 mL, 20.11 mmol, 4.00 equiv) was added dropwise giving a yellow turbid solution immediately with some liberation of gas. After 30 min at –78 °C the mixture was stirred for 20 min at –40 °C giving a clear golden-yellow solution. The solution was cooled back to –78 °C followed by addition of MeOH (22.00 mL, 553.00 mmol, 110.00 equiv) under vigorous stirring giving a pale orange solution. 20 min later, the flask was immersed into a cooling bath at –40 °C giving a clear red solution and after 20 min more this solution was cooled back to –78 °C followed by addition of a solution of **194** (2.00 g, 5.03 mmol, 1.00 equiv) in dry THF (10 mL, rinsed with additional dry 2 x 2 mL of THF). The mixture was stirred for 1 h then the flask was immersed into a cooling bath at –30 °C and stirring was continued for 16 h. Saturated aqueous NH_4Cl (100 mL) and 25% aqueous NH_4OH (20 mL) were then added as well as EtOAc (50 mL). Stirring was continued for 60 min then two almost clear phases were formed that were separated. The aqueous phase was extracted with EtOAc (3 x 50 mL) then the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification using flash chromatography on deactivated silica (Hex→EtOAc/Hex 1:20, 1% (v/v) NEt_3) afforded the vinylstannane (3.275 g, 4.74 mmol, 94%) as a yellow oil that was immediately used.

A solution of vinylstannane (3.97 g, 5.76 mmol, 1 equiv) in THF (50 mL) was cooled to –17 °C (NaCl/ice) followed by addition of NIS (1.94 g, 8.60 mmol, 1.50 equiv) in THF (10 mL) giving an almost clear yellow solution. After 20 min, a mixture of saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous $NaHCO_3$ (20 mL) was added followed by EtOAc (10 mL). Stirring was continued for 10 min until two clear, colorless phases were formed then a solution of saturated aqueous KF (20 mL) was added and stirring was continued for 30 min more. Phases were separated then the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure followed by purification using flash chromatography (Hex/EtOAc 1:50) giving **195** (2.65 g, 5.02 mmol, 87%) as an orange oil.

TLC: R_f = 0.73 (EtOAc/Hex 1:10, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.59-7.56 (m, 4 H), 7.53 (dd, *J* = 7.7, 7.7, 1 H), 7.43-7.33 (m, 6 H), 7.21 (q, *J* = 1.5, 1 H), 7.05 (d, *J* = 7.7, 1 H), 6.93 (d, *J* = 7.7, 1 H), 4.05 (t, *J* = 6.5, 2 H), 3.03 (d, *J* = 6.5, 2 H), 2.90 (d, *J* = 1.5, 3 H), 0.99 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.2, 155.6, 139.7, 136.4, 135.7, 133.9, 129.7, 127.7, 122.2, 121.6, 105.3, 63.7, 41.7, 30.8, 26.9, 19.3. **IR** (thin film): $\tilde{\nu}$ = 3071, 2956, 2929, 2856, 1622, 1580, 1567, 1472, 1448, 1427, 1105, 1087, 1066 cm^{-1}. **HRMS** (ESI): calcd for $C_{22}H_{21}INOSi$ [$(M-C_4H_9)^+$]: 470.0432; found: 470.0432.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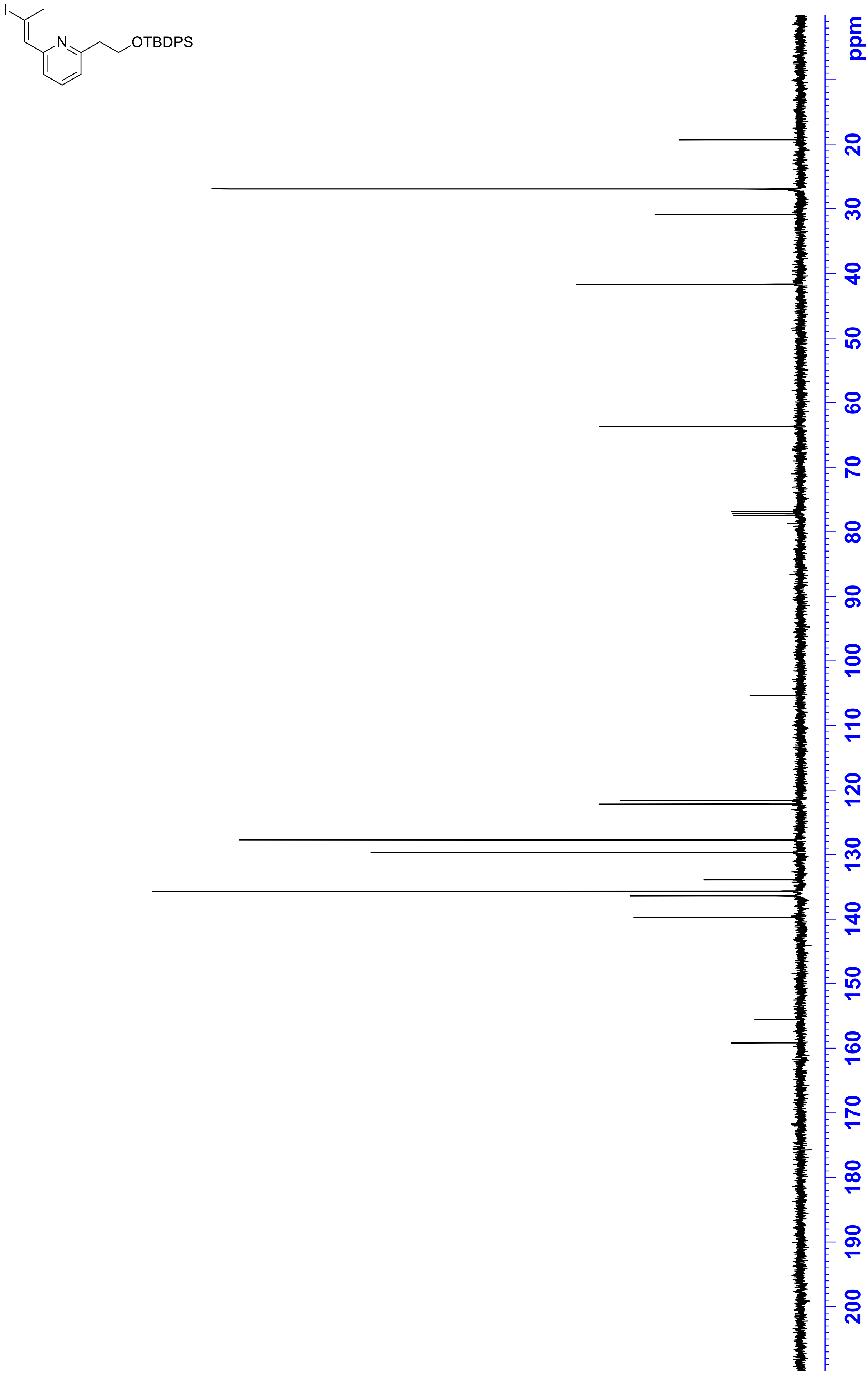
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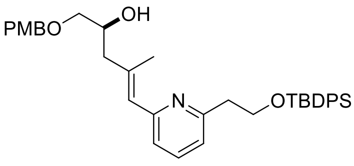
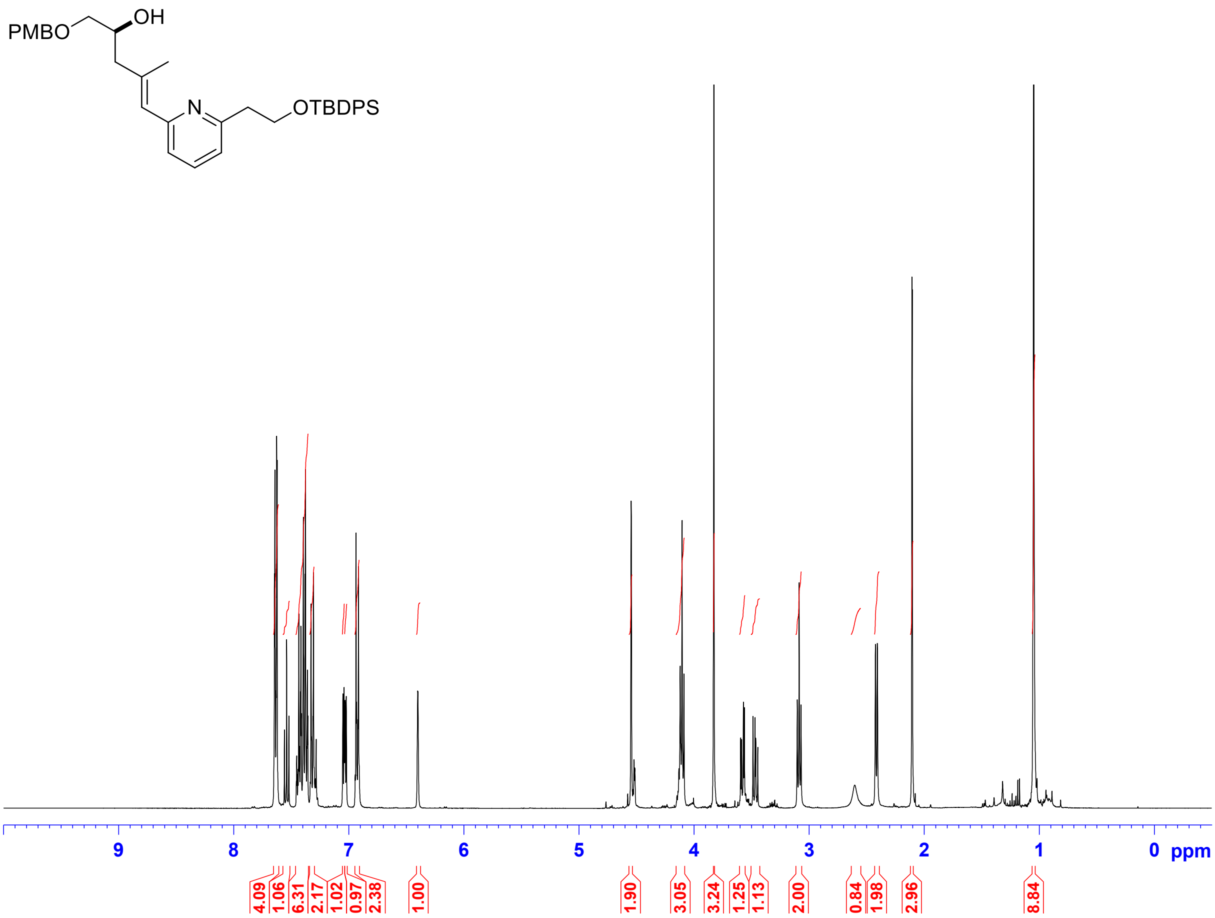


(*S*,*E*)-5-(6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)pyridin-2-yl)-1-(4-methoxy benzyloxy)-4-methylpent-4-en-2-ol (196). A solution of **195** (548.00 mg, 1.04 mmol, 1.00 equiv) in dry toluene (5 mL) was cooled to –78 °C followed by addition of *t*-BuLi (1.6M in pentane, 1.33 mL, 2.10 mmol, 2.00 equiv). Stirring was continued for 30 min followed by addition of a solution of **17** (504.60 mg, 2.59 mmol, 2.50 equiv, azeotropically dried once with 5 mL of toluene right before use) in dry toluene (2 mL) followed by addition of BF_3•OEt_2 (0.33 mL, 2.59 mmol, 2.50 equiv) after 1 min giving a tiny suspension. Stirring was continued at –78 °C for 1 h then the cooling bath was removed followed by addition of saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (5 mL). After the mixture reached room temperature, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified using flash chromatography (EtOAc/Hex 1:3) giving **196** **(**124.4 mg, 0.20 mmol, 20%) as a colorless oil.

TLC: R_f = 0.15 (EtOAc/Hex 1:3, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.65-7.62 (m, 4 H), 7.54 (dd, *J* = 7.8, 7.7, 1 H), 7.46-7.36 (m, 6 H), 7.33-7.31 (m, 2 H), 7.04 (d, *J* = 7.8, 1 H), 7.03 (d, *J* = 7.7, 1 H), 6.94-6.91 (m, 2 H), 6.40-6.39 (m, 1 H), 4.55 (br. s, 2 H), 4.15-4.10 (m, 1 H), 4.10 (t, *J* = 6.6, 2 H), 3.83 (s, 3 H), 3.58 (dd, *J* = 9.5, 3.6, 1 H), 3.47 (dd, *J* = 9.5, 7.0, 1 H), 3.09 (t, *J* = 6.6, 2 H), 2.61 (br. s, 1 H), 2.42 (d, *J* = 6.7, 2 H), 2.11 (d, *J* = 1.3, 3 H), 1.05 (s, 9 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.4, 158.7, 156.4, 139.9, 135.9, 135.6, 133.9, 130.2, 129.6, 129.5, 127.7, 127.6, 121.6, 121.1, 113.9, 74.0, 73.2, 68.7, 63.8, 55.3, 45.4, 41.7, 26.9, 19.3, 18.6. **IR** (thin film): $\tilde{\nu}$ = 2956, 2931, 2857, 1586, 1570, 1513, 1454, 1428, 1247, 1105, 1087, 1036, 907. **HRMS** (ESI): calcd for $C_{37}H_{46}NO_4Si$ [$(M+H)^+$]: 596.3191; found: 596.3188. $[\alpha]_D^{24}$: –6.04 (c = 2.55 in $CHCl_3$).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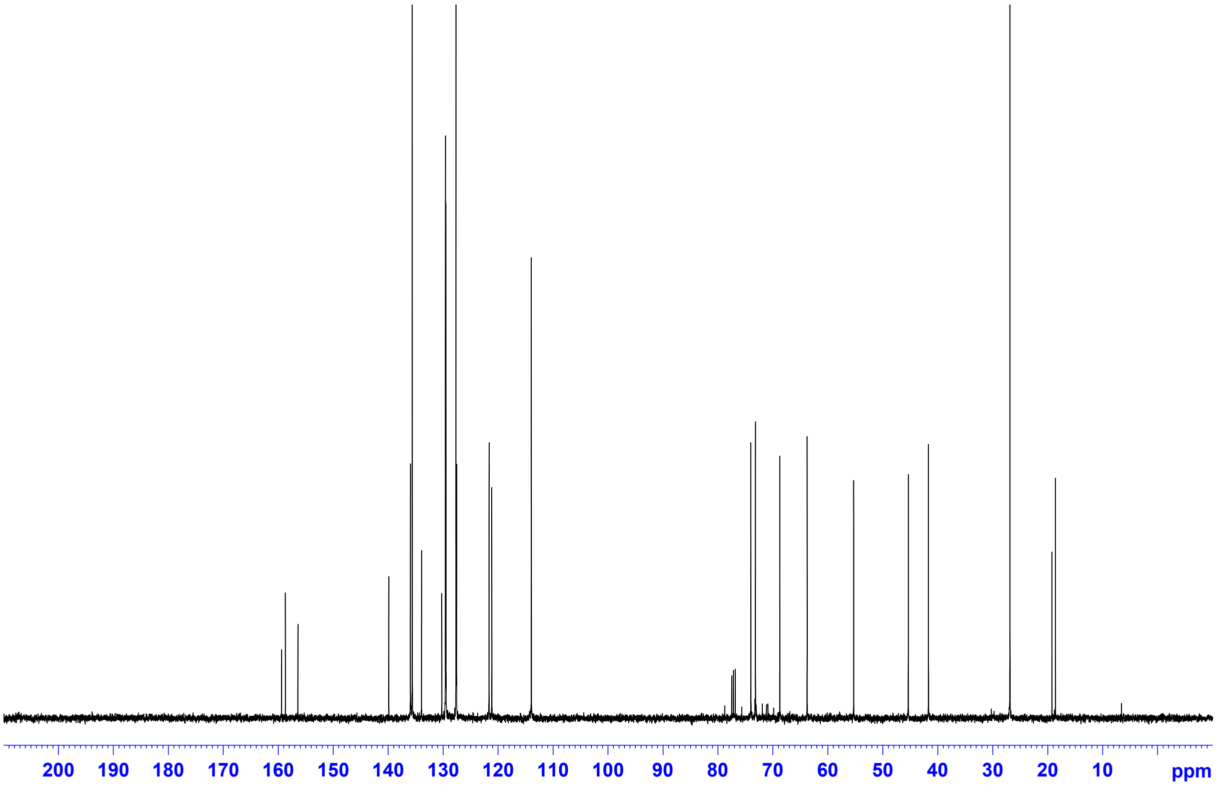
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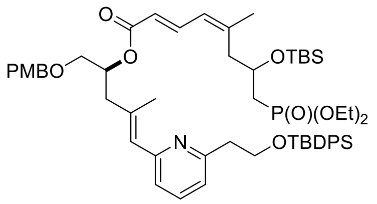
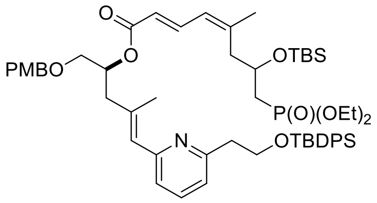
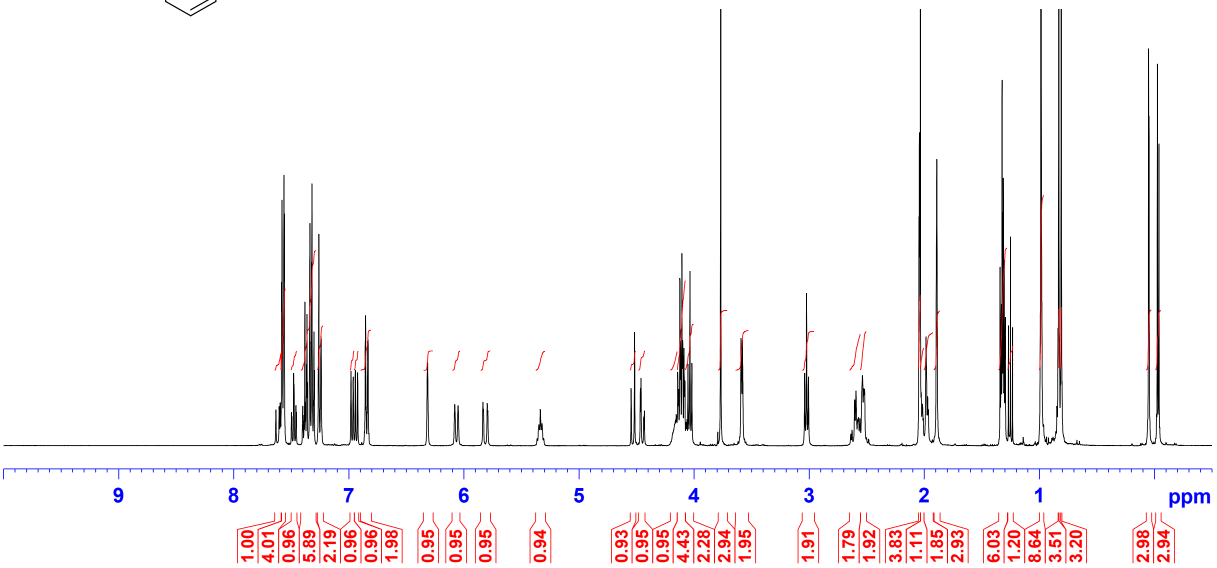


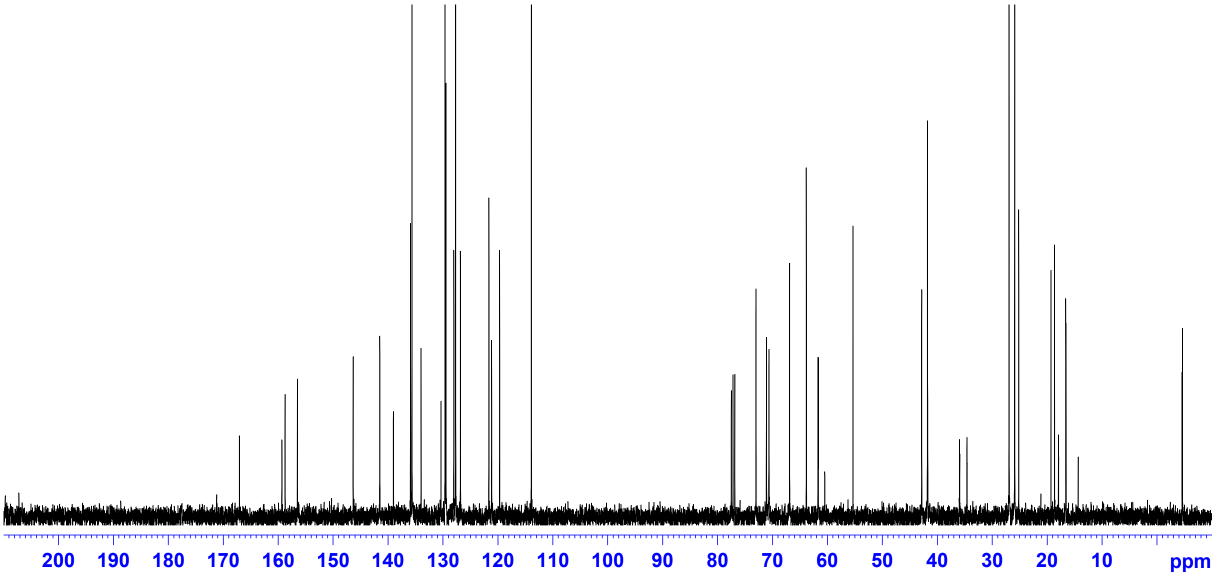
(2*E*,4*Z*)-((*S*,*E*)-5-(6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)pyridin-2-yl)-1-(4-methoxybenzyloxy)-4-methylpent-4-en-2-yl) 7-(*tert*-butyldimethylsilyloxy)-8-(diethoxyphosphoryl)-5-methylocta-2,4-dienoate (197). To a solution of **98** (244 mg, 0.58 mmol, 1.30 equiv) in toluene (5 mL) was added NEt$_3$ (0.19 mL, 1.34 mmol, 3 equiv) followed by addition of 2,4,6-trichlorobenzoyl chloride (0.12 mL, 0.76 mmol, 1.70 equiv) at room temperature. The almost clear pale-yellow solution was stirred for 1 h then a solution of alcohol **196** (266.5 mg, 0.447 mmol, 1.00 equiv) and DMAP (82 mg, 0.67 mmol, 1.50 equiv, use ultrasound to enable the formation of a complete solution) in toluene (6 mL) was added followed by rinsing with toluene (2 x 0.5 mL) giving an off-white suspension immediately. After 1.5 h, saturated aqueous NaHCO$_3$ (10 mL), H$_2$O (10 mL) and EtOAc (10 mL) were added followed by separation of phases. The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic phases were dried over MgSO$_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 1:1) afforded ester **197** (326 mg, 0.327 mmol, 73 %) as a pale-yellow oil.

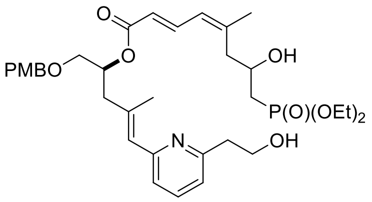
TLC: R$_f$ = 0.28 (EtOAc/hexane 1:1, UV, KMnO$_4$ or CPS). **^{1}H-NMR** (400 MHz, CDCl$_3$): δ = 7.60 (dd, *J* = 15.4, 11.9, 1 H), 7.58-7.56 (m, 4 H), 7.48 (dt, *J* = 7.7, 1.8, 1 H), 7.40-7.29 (m, 6 H), 7.27-7.23 (m, 2 H), 6.97 (d, *J* = 7.6, 1 H), 6.93 (d, *J* = 7.9, 1 H), 6.86-6.83 (m, 2 H), 6.32 (br. s, 1 H), 6.06 (d, *J* = 11.9, 1 H), 5.84-5.79 (m, 1 H), 5.37-5.31 (m, 1 H), 4.53 (d, *J* = 11.9, 1 H), 4.45 (dd, *J* = 11.9, 2.4, 1 H), 4.20-4.12 (m, 1 H), 4.14-4.08 (m, 4 H), 4.04 (t, *J* = 6.6, 2 H), 3.77-3.76 (m, 3 H), 3.60-3.57 (m, 2 H), 3.03 (t, *J* = 6.6, 2 H), 2.60 (dt, *J* = 13.5, 4.5, 2 H), 2.55-2.49 (m, 2 H), 2.05-2.04 (m, 4 H), 2.03-2.01 (m, 1 H), 1.99-1.96 (m, 2 H), 1.89 (br. s, 3 H), 1.34-1.30 (m, 6 H), 1.25 (dd, *J* = 7.3, 7.1, 1 H), 0.99 (s, 9 H), 0.83 (s, 3 H), 0.81 (s, 3 H), 0.05-0.04 (m, 3 H), –0.02- –0.04 (m, 3 H). **^{13}C-NMR** (100 MHz, CDCl$_3$; due to the diastereomeric nature of the product, the number of signals in the ^{13}C-spectrum exceeds the number of carbon atoms): δ = 167.0 (2C), 159.3, 158.7, 156.5, 146.3, 141.5, 139.0 (2C), 135.9, 135.6, 130.3, 129.6, 129.4 (2C), 128.0, 127.7, 126.8, 121.6, 121.1, 119.7, 113.9, 73.0 (2C), 71.1 (2C), 70.6 (2C), 66.9, 63.8, 61.7 (d, *J* = 6.3), 61.6

(d, *J* = 6.3), 55.3, 42.8, 41.8, 35.3 (d, *J* = 135.8), 35.2 (d, *J* = 135.8), 26.9, 25.9, 25.8, 25.1, 19.3, 18.6, 16.5 (d, *J* = 6.1) (2C), –4.6, –4.7. **IR** (thin film): $\tilde{\nu}$ = 2955, 2929, 2857, 1711, 1636, 1612, 1584, 1570, 1513, 1472, 1453, 1429, 1390, 1363, 1303, 1248, 1146, 1087, 1048, 1025 cm^{-1}. **HRMS** (ESI): calcd for $C_{56}H_{81}NO_9PSi_2$ [(M+H)$^+$]: 998.5182; found: 998.5161. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –3.85 (c = 0.69 in $CHCl_3$).





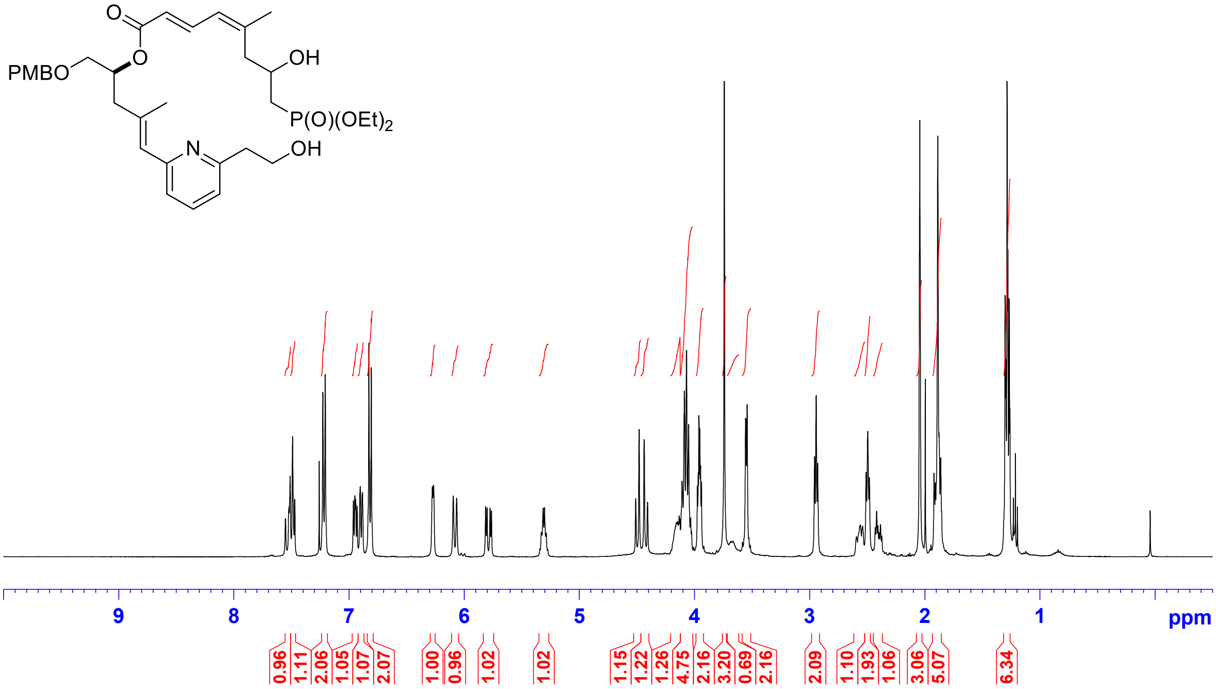


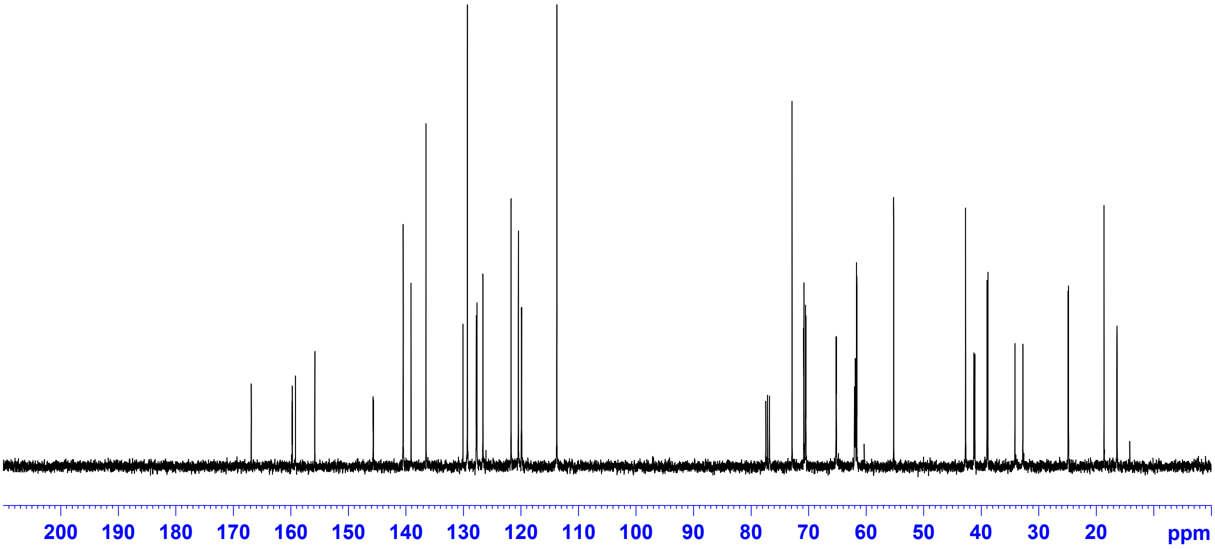


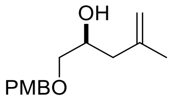
(2*E*,4*Z*)-((*S*,*E*)-5-(6-(2-Hydroxyethyl)pyridin-2-yl)-1-(4-methoxybenzyloxy)-4-methylpent-4-en-2-yl) 8-(diethoxyphosphoryl)-7-hydroxy-5-methylocta-2,4-dienoate (198). To a one-necked 50 mL-plastic tube, flooded with argon, was added **197** (326 mg, 0.327 mmol, 1 equiv) dissolved in dry THF (20 mL) followed by addition of HF•py (70% HF, 4 mL) slowly at room temperature. After 22 h, the solution was carefully added to a vigorously stirred mixture of saturated aqueous $NaHCO_3$ (200 mL) and EtOAc (50 mL) then stirring was continued for 10 min leading to two clear phases. The pH value of the aqueous phase was above 8. The phases were separated and the aqueous phase extracted with EtOAc (3 x 10 mL) then the combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 x 5 mL) followed by drying over $MgSO_4$. Concentration under reduced pressure and purification using flash chromatography (EtOAc→EtOAc/acetone 1:1) afforded **198** (177 mg, 0.274 mmol, 84%) as a pale-yellow oil.

Note: The use of less concentrated aqueous $NaHCO_3$ is not recommended for workup, since not all HF may be neutralized, which would in turn lead to decomposition of the product during concentration under reduced pressure. In any case the pH of the aqueous phase should be determined after workup and should not be acidic!

TLC: R_f = 0.30 (EtOAc/acetone 1:1, UV, $KMnO_4$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.52 (dd, *J* = 15.3, 11.9, 1 H), 7.51-7.47 (m, 1 H), 7.23-7.20 (m, 2 H), 6.94 (dd, *J* = 7.7, 4.8, 1 H), 6.89 (dd, *J* = 7.7, 1.5, 1 H), 6.83-6.80 (m, 2 H), 6.27 (d, *J* = 4.5, 1 H), 6.08 (d, *J* = 11.8, 1 H), 5.79 (dd, *J* = 15.1, 4.6, 1 H), 5.35-5.27 (m, 1 H), 4.49 (d, *J* = 11.8, 1 H), 4.42 (d, *J* = 11.8, 1 H), 4.20-4.12 (m, 1 H), 4.11-4.02 (m, 5 H), 3.96 (dt, *J* = 5.7, 2.9, 2 H), 3.74 (s, 3 H), 3.70-3.65 (m, 1 H), 3.59-3.52 (m, 2 H), 2.94 (t, *J* = 5.5, 2 H), 2.60-2.53 (m, 1 H), 2.51-2.48 (m, 2 H), 2.40 (dt, *J* = 13.5, 4.6, 1 H), 2.05-2.03 (m, 3 H), 1.92-1.85 (m, 5 H), 1.30-1.26 (m, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$; due to the diastereomeric nature of the product, the number of signals in the ^{13}C-spectrum exceeds the number of carbon atoms): δ = 166.9, 166.9, 159.8, 159.8, 159.2, 155.9, 145.7, 145.7, 140.5, 139.1, 136.5, 130.1, 129.3, 127.8, 127.7, 126.7, 126.6, 121.7, 120.5, 120.0, 119.9, 113.8, 72.9, 70.9, 70.8, 70.6, 70.5, 65.3, 65.2, 62.1 (d, *J* = 6.5), 62.0 (d, *J* = 6.5), 61.9, 61.9, 61.7, 61.6, 55.2, 42.8, 41.3, 41.1, 39.0, 38.9, 33.5 (d, *J*= 138.5), 24.9, 24.8, 18.7, 16.4 (d, *J* = 6.0), 16.4 (d, *J* = 6.0). **IR** (thin film): $\tilde{\nu}$ = 3382, 2929, 2909, 2864, 1706, 1634, 1612, 1585, 1570, 1514, 1454, 1367, 1302, 1275, 1248, 1222, 1148, 1026, 974 cm^{-1}. **HRMS** (ESI): calcd for $C_{34}H_{49}O_9P$ [(M+H)$^+$]: 646.3139; found: 646.3139. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –16.59 (c = 2.11 in $CHCl_3$).

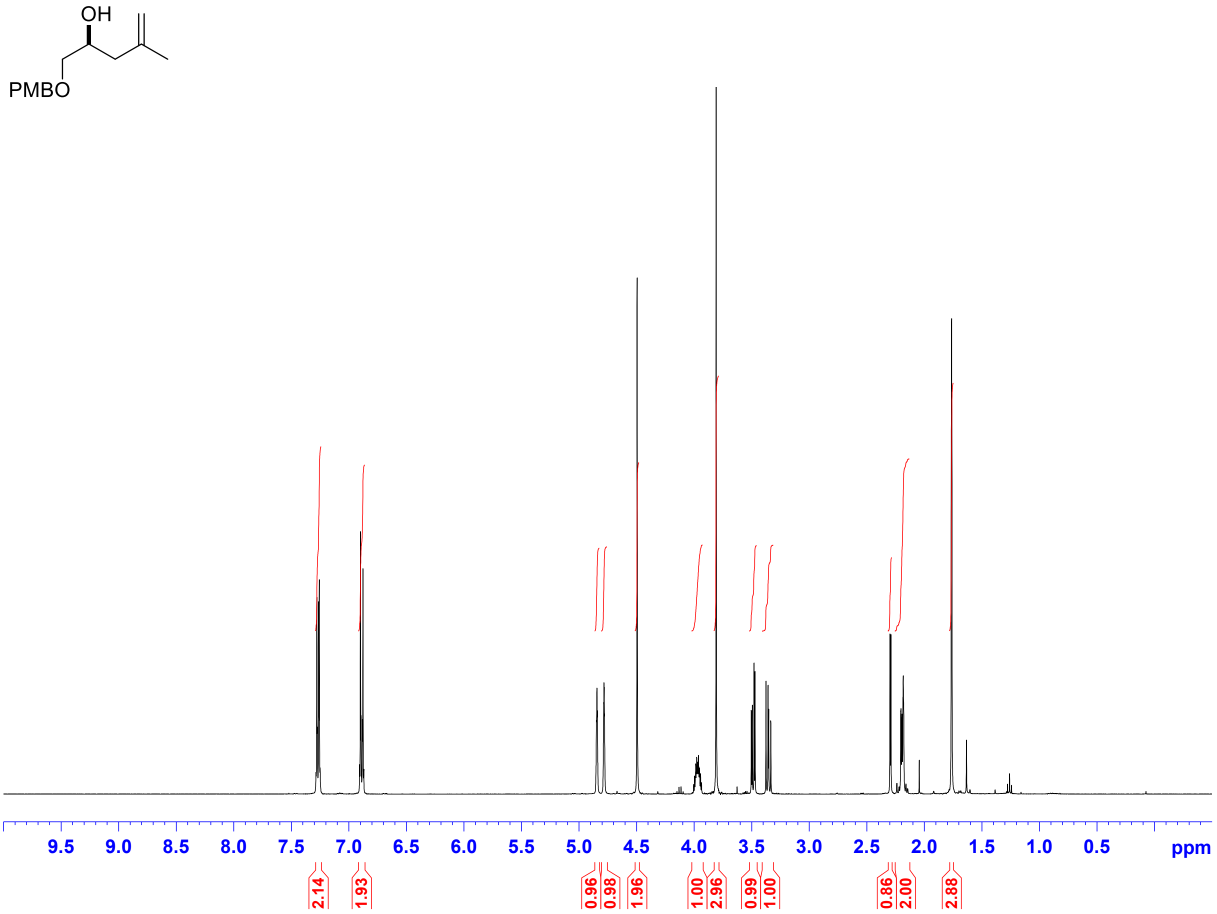






(*S*)-1-(4-Methoxybenzyloxy)-4-methylpent-4-en-2-ol (200). To a solution of isopropenylmagnesium bromide (0.5M in THF, 15.46 mL, 7.73 mmol, 1.5 equiv) at –40 °C was added CuI (99 mg, 0.52 mmol, 0.1 equiv) in one portion. The yellow suspension formed was stirred for 30 min then a solution of **17** (972.4 mg, 5.15 mmol, 1 equiv) in dry THF (2 mL) was added dropwise. The mixture was allowed to warm to room temperature during 1 h then the mixture was carefully poured into a vigorously stirred mixture of saturated aqueous NH_4Cl (10 mL) and Et_2O (20 mL). The phases were separated then the aqueous phase was extracted with Et_2O (3 x 10 mL), the combined organic phases were washed with saturated aqueous NH_4Cl (5 mL) concentrated under reduced pressure giving **200** (1.2 g, 0.51 mmol, 98%) as a pale-yellow oil, which was used without further purification.

TLC: R_f = 0.27 (EtOAc/Hex 1:3, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.28-7.25 (m, 2 H), 6.91-6.87 (m, 2 H), 4.85-4.84 (m, 1 H), 4.79-4.77 (m, 1 H), 4.49 (s, 2 H), 4.00-3.94 (m, 1 H), 3.81 (s, 3 H), 3.49 (dd, *J* = 9.5, 3.5, 1 H), 3.35 (dd, *J* = 9.5, 7.2, 1 H), 2.29 (d, *J* = 3.2, 1 H), 2.24-2.15 (m, 2 H), 1.77-1.76 (m, 3 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.4, 142.3, 130.3, 129.5, 114.0, 113.3, 74.1, 73.2, 68.3, 55.4, 42.1, 22.6. **IR** (thin film): $\tilde{\nu}$ = 3466, 2933, 2906, 2859, 2837, 1648, 1612, 1586, 1512, 1456, 1442, 174, 1363, 1301, 1245, 1173, 890, 818 cm^{-1}. **HRMS** (ESI): calcd for $C_{14}H_{21}O_3$ [$(M+H)^+$]: 237.1485; found: 237.1484. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +1.39 (c = 1.33 in $CHCl_3$).


OH
PMBO
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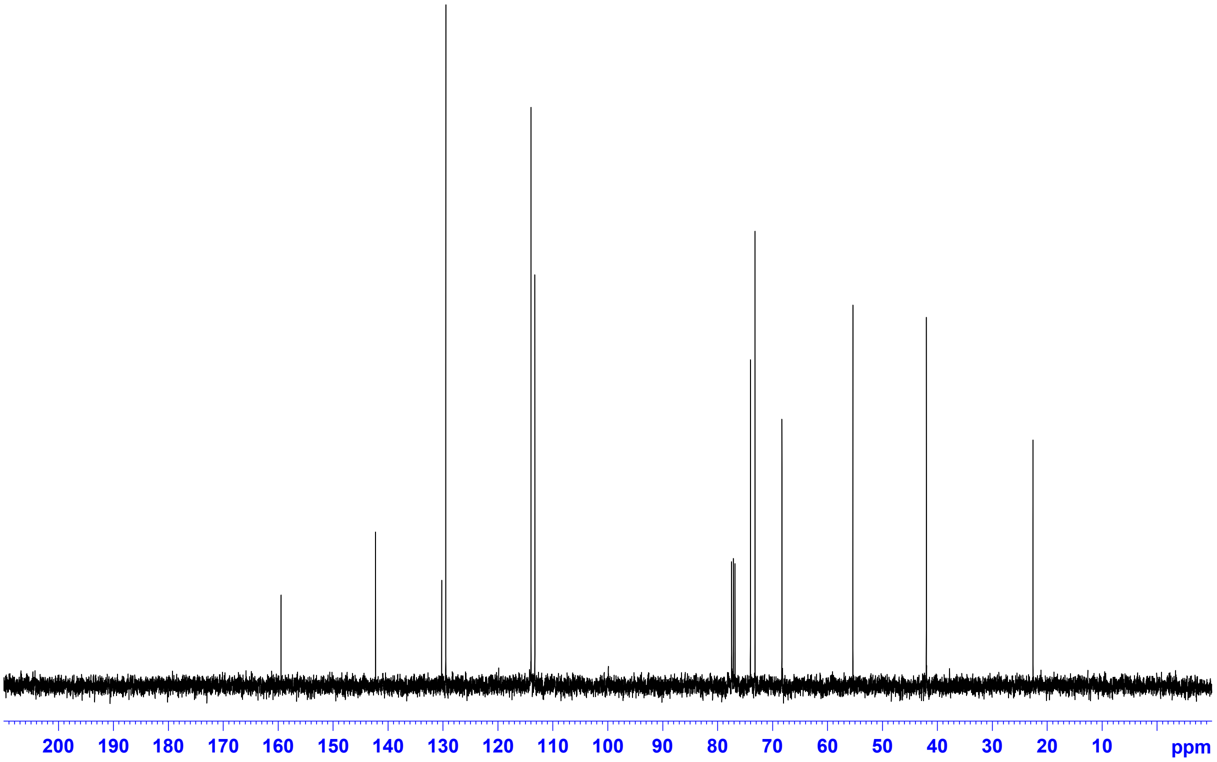
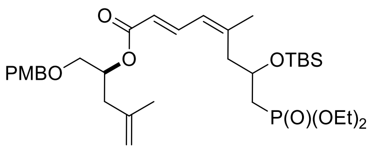
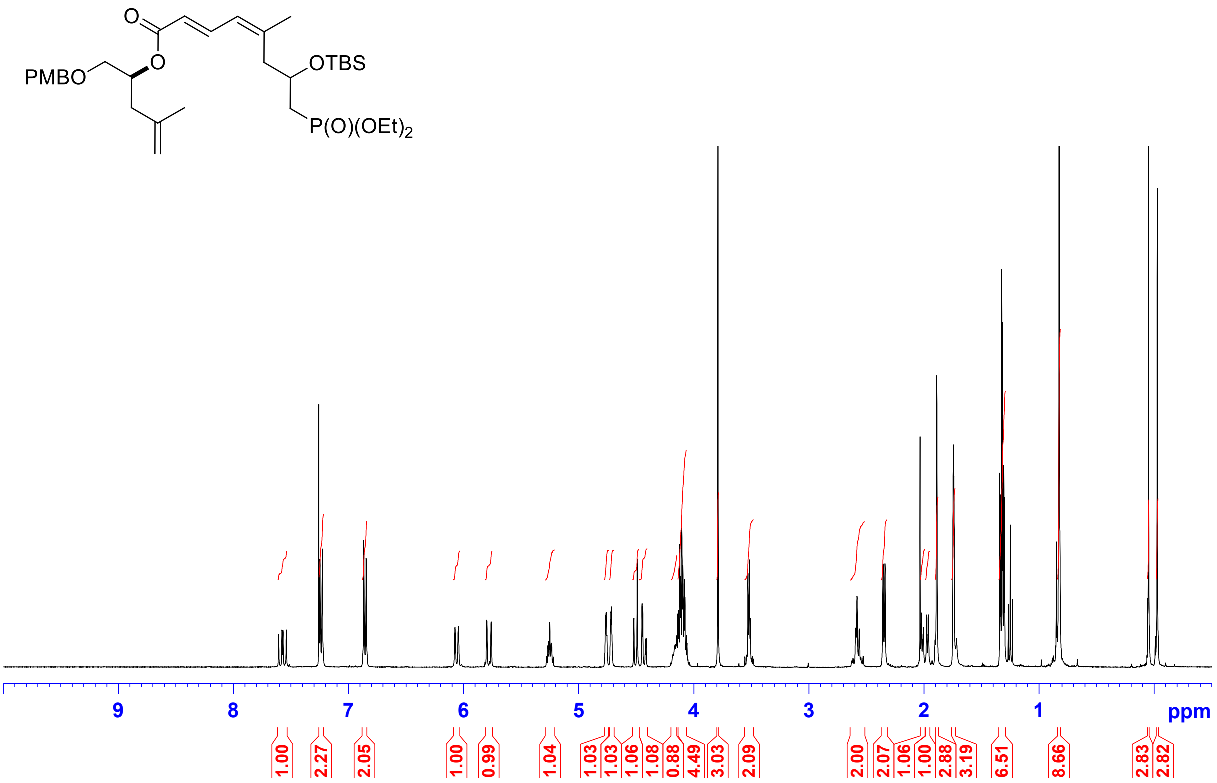
2.14
1.93
0.96
0.98
1.96
1.00
2.96
0.99
1.00
0.86
2.00
2.88

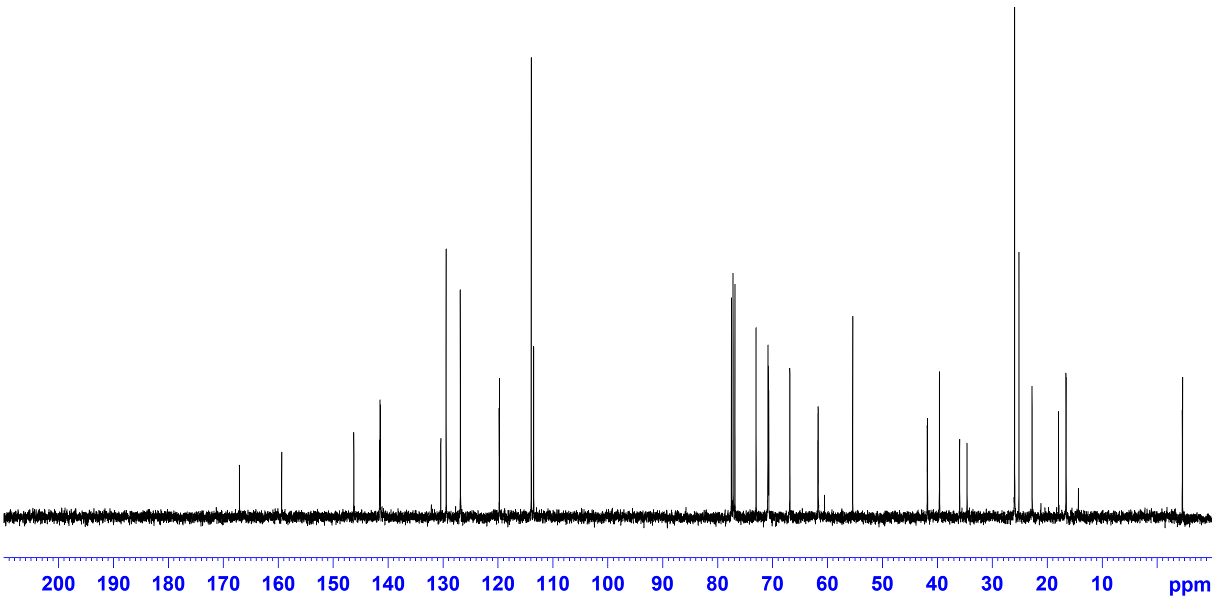

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

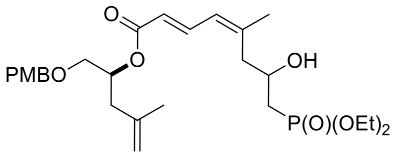


(2*E*,4*Z*)-((*S*)-1-(4-Methoxybenzyloxy)-4-methylpent-4-en-2-yl) 7-(*tert*-butyl dimethylsilyloxy)-8-(diethoxyphosphoryl)-5-methylocta-2,4-dienoate (201). To a solution of **98** (462 mg, 1.09 mmol, 1.20 equiv) in toluene (5 mL) was added NEt$_3$ (0.57 mL, 4.12 mmol, 3 equiv) followed by addition of 2,4,6-trichlorobenzoyl chloride (0.24 mL, 1.55 mmol, 1.70 equiv) at room temperature. The pale-yellow solution was stirred for 1 h then a solution of alcohol **200** (216.6 mg, 0.92 mmol, 1.00 equiv) and DMAP (167 mg, 1.37 mmol, 1.50 equiv, use ultrasound to enable the formation of a complete solution) in toluene (5 mL) was added followed by rinsing of the flask with toluene (2 x 0.5 mL) giving an off-white suspension immediately. Stirring was continued for 1 h then saturated aqueous NaHCO$_3$ (20 mL), H$_2$O (10 mL) and EtOAc (10 mL) were added followed by separation of phases. The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic phases were dried over MgSO$_4$ and concentrated under reduced pressure. Purification using flash chromatography (EtOAc/Hex 3:1) afforded **201** (486 mg, 0.76 mmol, 83%) as a pale-yellow oil.

TLC: R_f = 0.51 (EtOAc/Hex 3:1, UV, CPS). **^{1}H-NMR** (400 MHz, CDCl$_3$): δ = 7.58 (dd, *J* = 15.1, 11.6, 1 H), 7.25-7.22 (m, 2 H), 6.88-6.84 (m, 2 H), 6.06 (d, *J* = 11.6, 1 H), 5.78 (d, *J* = 15.1, 1 H), 5.28-5.22 (m, 1 H), 4.77-4.75 (m, 1 H), 4.73-4.70 (m, 1 H), 4.51 (d, *J* = 11.7, 1 H), 4.43 (dd, *J* = 11.7, 2.5, 1 H), 4.20-4.12 (m, 1 H), 4.15-4.05 (m, 4 H), 3.79 (s, 3 H), 3.56-3.48 (m, 2 H), 2.63-2.53 (m, 2 H), 2.35 (d, *J* = 6.8, 2 H), 2.03-2.00 (m, 1 H), 1.98-1.96 (m, 1 H), 1.89 (s, 3 H), 1.76-1.73 (m, 3 H), 1.32 (dt, *J* = 7.1, 2.8, 6 H), 0.83 (s, 9 H), 0.05 (s, 3 H), –0.03 (s, 3 H). **^{13}C-NMR** (100 MHz, CDCl$_3$; due to the diastereomeric nature of the product, the number of signals in the ^{13}C-spectrum exceeds the number of carbon atoms): δ = 167.1, 167.0, 159.3, 146.2, 141.5, 141.5, 141.4, 141.4, 130.4, 129.4, 126.8, 119.7, 119.7, 113.9, 113.5, 113.5, 73.0, 73.0, 70.8, 70.8, 70.7, 70.7, 66.9, 66.8 61.7 (d, *J* = 6.5), 61.7 (d, *J* = 6.5), 55.4, 41.8, 41.8, 39.6, 39.6, 35.3 (d, *J* = 135.3), 35.3 (d, *J* = 135.3), 25.9, 25.9, 25.1, 22.7, 22.7, 17.9, 16.6 (d, *J* = 6.1), –4.6, –4.6. **IR** (thin film): $\tilde{\nu}$ = 2955, 2929, 2857, 1710, 1636, 1612, 1513, 1472, 1464, 1443, 1367, 1302, 1367, 1302, 1248, 1147, 1048, 1024, 977, 962, 936, 890, 836, 823, 809, 751 cm^{-1}. **HRMS** (ESI): calcd for $C_{33}H_{55}O_8PSi$ [(M)$^+$]: 638.3398; found: 638.3398.$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: – 3.72 (c = 1.27 in $CHCl_3$).





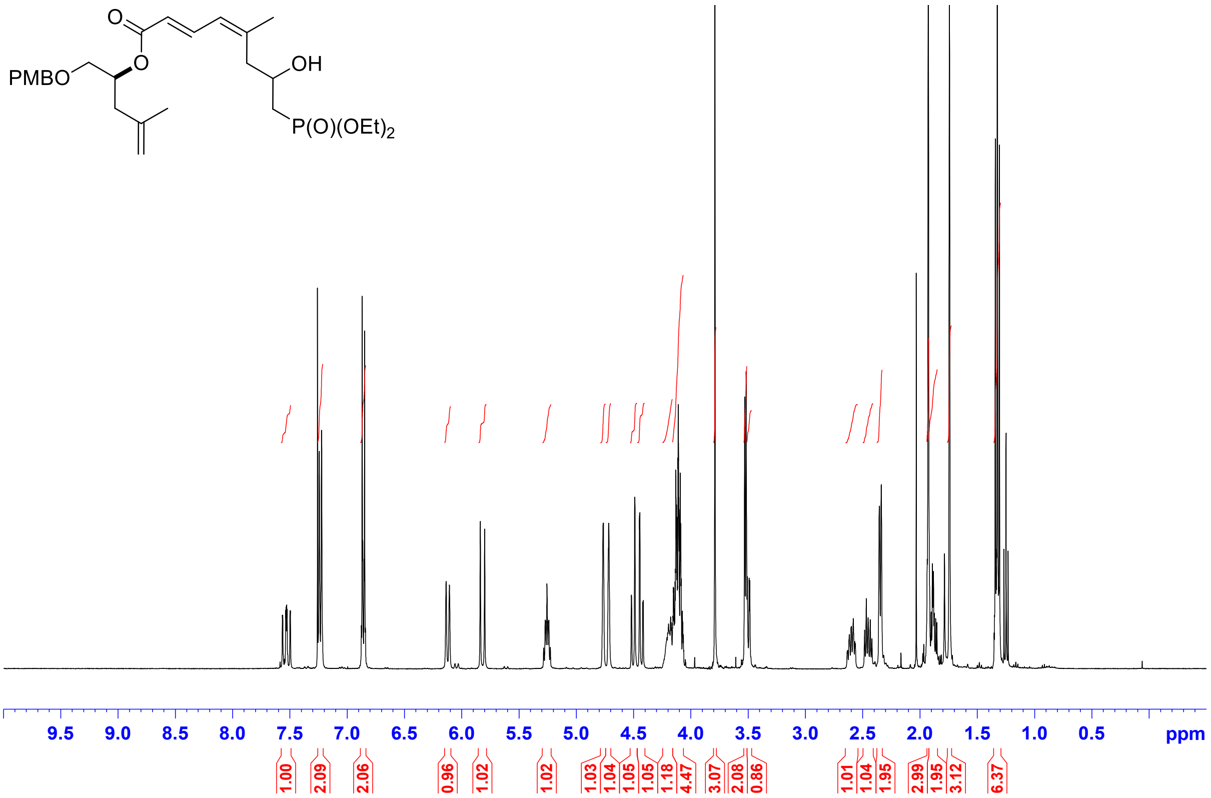


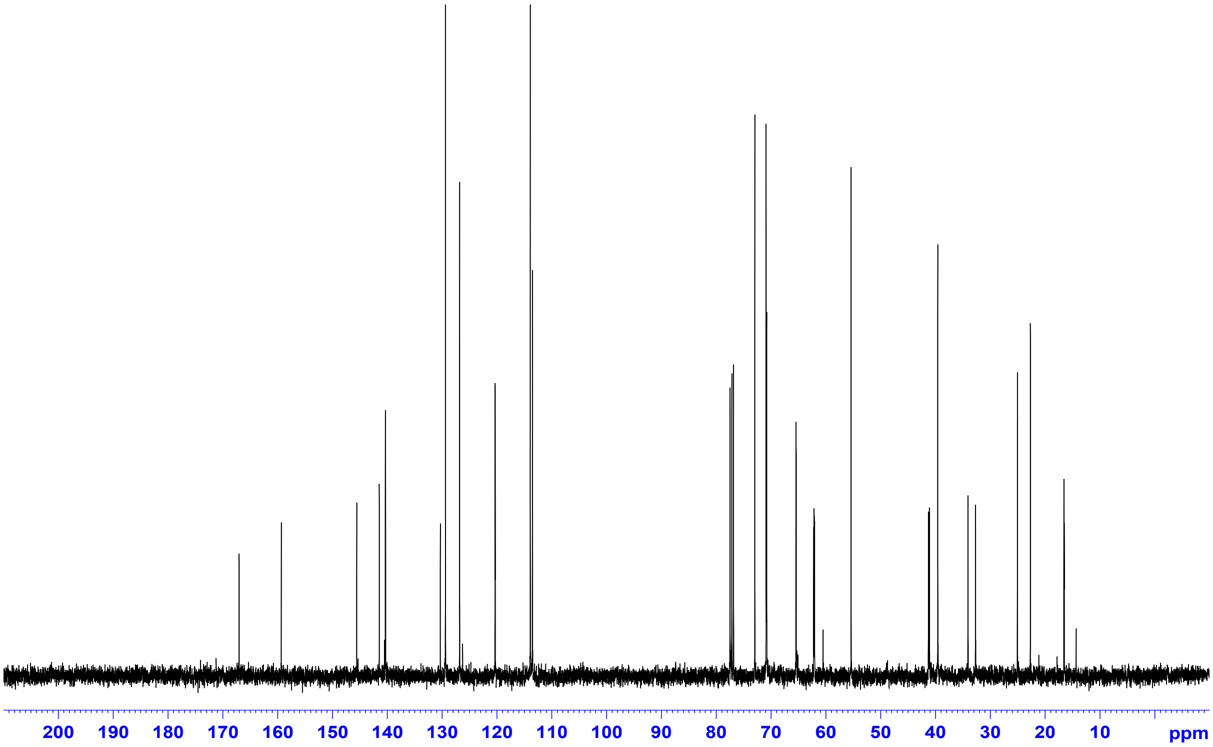
(2*E*,4*Z*)-(*S*)-1-((4-Methoxybenzyl)oxy)-4-methylpent-4-en-2-yl 8-(diethoxy phosphoryl)-7-hydroxy-5-methylocta-2,4-dienoate (L). To a one-necked 50 mL-plastic tube, flooded with argon, was added **201** (469.8 mg, 0.735 mmol, 1 equiv) dissolved in dry THF (20 mL) followed by addition of HF•py (70% HF, 2.7 mL) slowly at room temperature. After 12.5 h, the solution was carefully added to a vigorously stirred mixture of saturated aqueous $NaHCO_3$ (200 mL) and EtOAc (50 mL) then stirring was continued for 10 min leading to two clear phases. The pH value of the aqueous phase was above 8. The phases were separated and the aqueous phase extracted with EtOAc (3 x 10 mL) then the combined organic phases were washed with saturated aqueous $NaHCO_3$ (1 x 50 mL) followed by drying over $MgSO_4$. Concentration under reduced pressure and purification using flash chromatography (EtOAc→EtOAc/acetone 1:1) afforded **L** (349.1 mg, 0.665 mmol, 91%) as a pale-yellow oil.

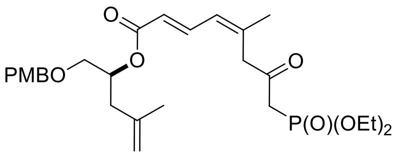
Note: The use of less concentrated aqueous $NaHCO_3$ is not recommended for workup, since not all HF may be neutralized, which would in turn lead to decomposition of the product during concentration under reduced pressure. In any case the pH of the aqueous phase should be determined after workup and should not be acidic!

TLC: R_f = 0.62 (EtOAc/acetone 1:1, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.53 (ddd, *J* = 15.2, 11.8, 1.5, 1 H), 7.25-7.21 (m, 2 H), 6.88-6.84 (m, 2 H), 6.12 (d, *J* = 11.8, 1 H), 5.82 (d, *J* =15.2, 1 H), 5.29-5.23 (m, 1 H), 4.78-4.75 (m, 1 H), 4.72-4.71 (m, 1 H), 4.50 (d, *J* = 11.7, 1 H), 4.43 (dd, *J* = 11.7, 1.5, 1 H), 4.24-4.14 (m, 1 H), 4.18-4.05 (m, 4 H), 3.79 (s, 3 H), 3.53-3.51 (m, 2 H), 3.50 (dd, *J* = 8.5, 2.5, 1 H), 2.64-2.56 (m, 1 H), 2.45 (dt, *J* = 6.1, 3.5, 1 H), 2.36-2.33 (m, 2 H), 1.93 (br. s, 3 H), 1.93-1.85 (m, 2 H), 1.74 (br. s, 3 H), 1.32 (t, *J* = 7.2, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$; due to the diastereomeric nature of the product, the number of signals in the ^{13}C-spectrum exceeds the number of carbon atoms): δ = 167.1, 167.0, 159.3, 145.6, 141.5, 141.5, 140.4, 140.3, 130.3, 129.4, 126.8, 120.3, 120.3, 113.9, 113.5, 73.0, 70.9, 70.8, 70.8, 65.5, 65.4, 62.2 (d, *J* = 6.5), 62.1 (d,

J = 6.5), 55.4, 41.3, 41.1, 39.6, 33.4 (d, J = 138.5), 25.1, 25.0, 22.7, 16.6 (d, J = 6.2), 16.5 (d, J = 6.2). **IR** (thin film): $\tilde{\nu}$ = 3367, 2981, 2932, 2908, 2864, 1707, 1634, 1612, 1513, 1443, 1367, 1247, 1219, 1148, 1024, 973, 751 cm^{-1}. **HRMS** (ESI): calcd for $C_{27}H_{42}O_8P[(M+H)^+]$: 525.2612; found: 525.2621. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: – 4.21 (c = 1.17 in $CHCl_3$).

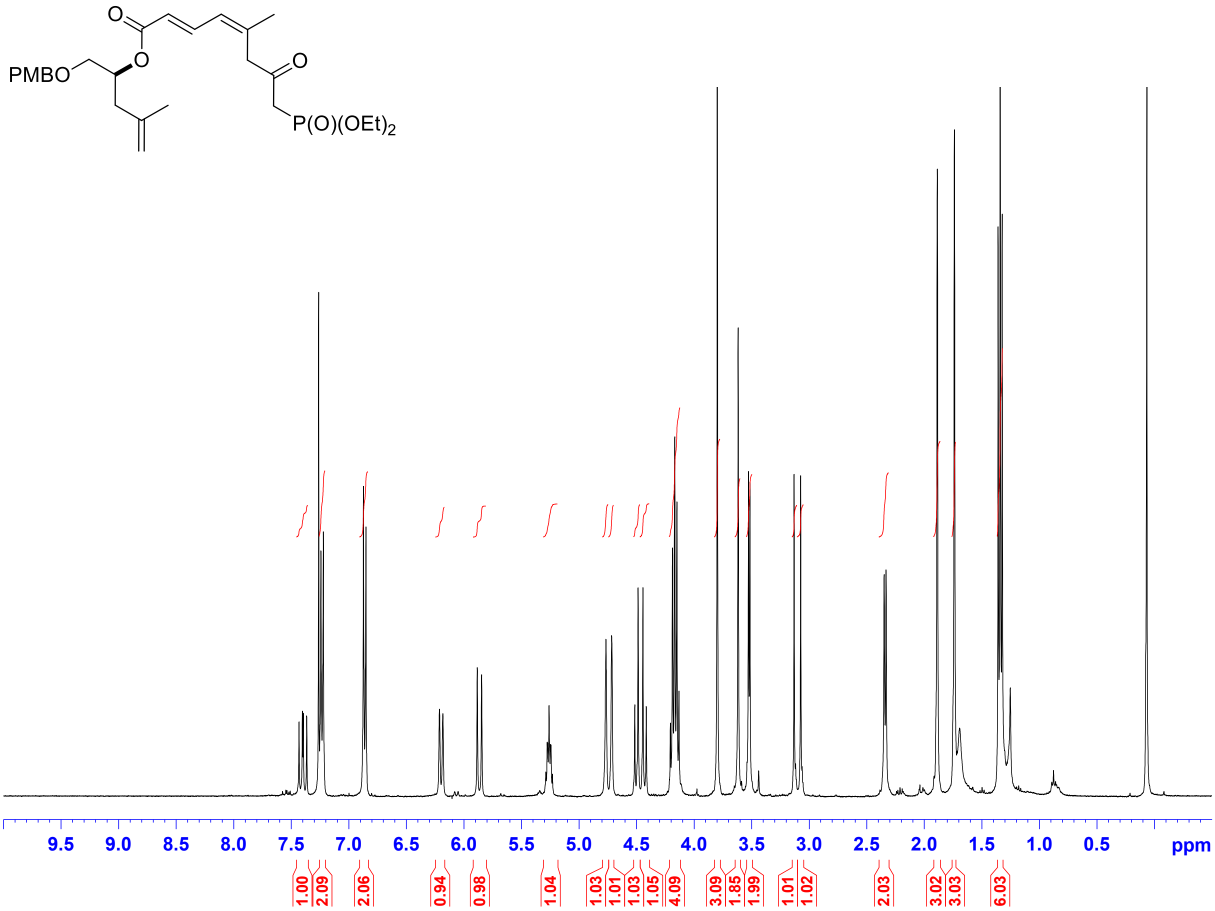






(2*E*,4*Z*)-(*S*)-1-((4-Methoxybenzyl)oxy)-4-methylpent-4-en-2-yl 8-(diethoxy phosphoryl)-5-methyl-7-oxoocta-2,4-dienoate (202). To a solution of **L** (327.1 mg, 0.624 mmol, 1 equiv) dissolved in dry CH_2Cl_2 (6 mL) was added DMP (396 mg, 0.935 mmol, 1.5 equiv) at room temperature giving a white-yellow mixture immediately. The mixture was poured after 45 min onto a stirred mixture of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL) then CH_2Cl_2 (10 mL) were added and stirring was continued for 60 min but separation of two phases did not work. The mixture was filtered over celite and washed with CH_2Cl_2 then two clear phases were formed. Separation of phases then the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL), the combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 x 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure giving a colorless oil. Purification using flash chromatography (EtOAc) afforded **202** (250.6 mg, 0.479 mmol, 77%) as a yellow oil.

TLC: R_f = 0.58 (EtOAc, UV, CPS). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 15.1, 11.8, 1 H), 7.25-7.21 (m, 2 H), 6.88-6.84 (m, 2 H), 6.19 (d, *J* = 11.8, 1 H), 5.86 (d, *J* =15.1, 1 H), 5.29-5.23 (m, 1 H), 4.76 (br. s, 1 H), 4.71 (br. s, 1 H), 4.50 (d, *J* = 11.8, 1 H), 4.43 (d, *J* = 11.7, 1 H), 4.21-4.13 (m, 4 H), 3.79 (s, 3 H), 3.62 (br. s, 2 H), 3.52 (d, *J* = 5.0, 2 H), 3.13 (br. s, 1 H), 3.07 (br. s, 1 H), 2.43 (d, *J* = 6.7, 2 H), 1.89 (s, 3 H), 1.73 (s, 3 H), 1.34 (t, *J* = 7.1, 6 H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 198.3, 138.2, 166.8, 159.4, 141.4, 140.8, 139.7, 130.3, 129.4, 127.6, 121.3, 113.9, 113.5, 73.0, 70.9, 70.8, 62.9 (d, *J* = 6.5), 55.4, 47.7, 42.3 (d, *J* = 127.9), 39.6, 25.0, 22.7, 16.5 (d, *J* = 6.1). **IR** (thin film): $\tilde{\nu}$ = 2972, 2912, 2859, 1711, 1639, 1612, 1513, 1443, 1365, 1247, 1150, 1019 cm^{-1}. **HRMS** (ESI): calcd for $C_{27}H_{40}O_8P[(M+H)^+]$: 523.2455; found: 523.2465. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: – 7.42 (c = 0.77 in $CHCl_3$).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5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.09
2.06
0.94
0.98
1.04
1.03
1.01
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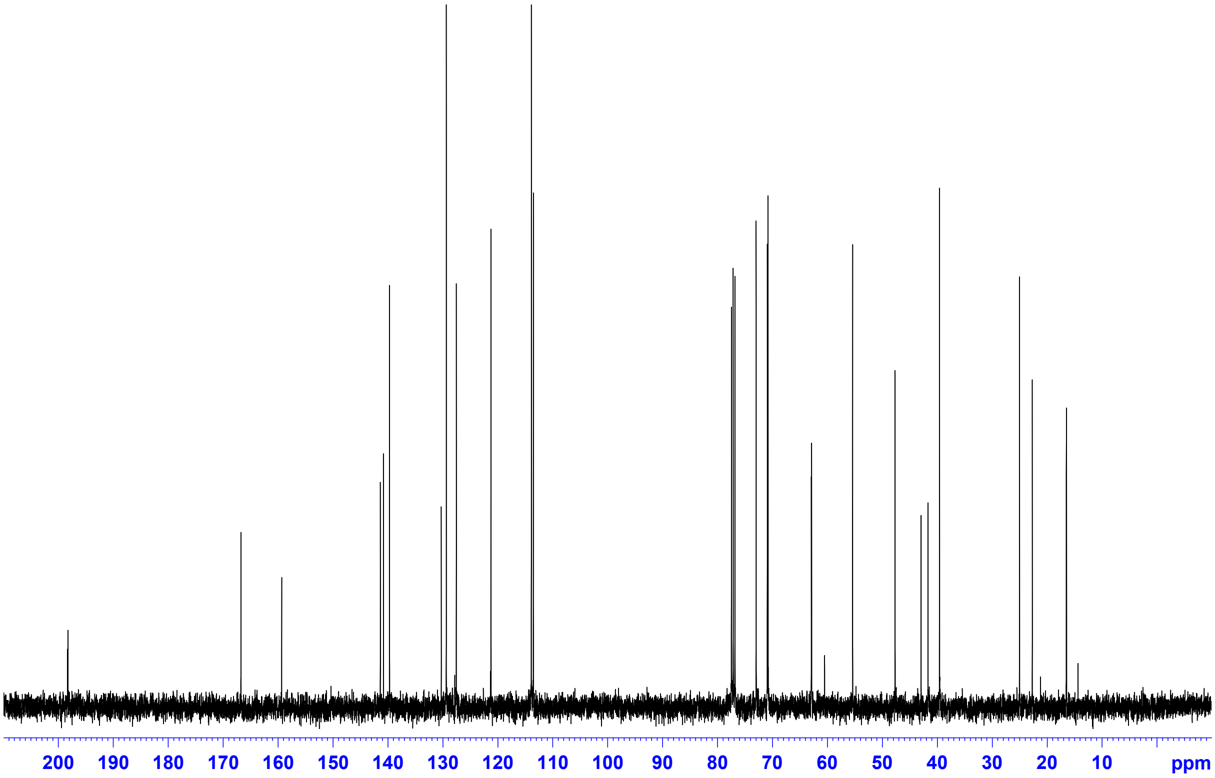
3.02
3.03
6.03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180
170
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150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

5.6. **Determination of Cell Proliferation and Tubulin Polymerization**[50]

5.6.1. Cell Proliferation Assay

Inhibition of cell proliferation was determined in the MCF-7, (breast), A549 (lung), and HCT-116 (colon), PC3 (prostate) and U937 (leukemia) (only for (–)-zampanolide ((–)-**1**)) cell lines, which were obtained as a kind gift from Markus Wartmann (Novartis Institute for Biomedical Research (NIBR) Basel, Switzerland). Cells were maintained in a 5% CO_2 humidified atmosphere at 37 °C in RPMI medium 1640 (Gibco BRL) containing 10% fetal bovine serum, penicillin (100 U/ml) and streptomycin (100 μg/ml) (Gibco BRL). Cells were seeded at 1.5×10^3/well into 96-well microtiter plates and incubated overnight. Compounds were added in serial dilutions on day 1. Subsequently, the plates were incubated for two population doublings (72 h) and then fixed with 3.3% v/v glutaraldehyde, washed with water and stained with 0.05% methylene blue. After washing, the dye was eluted with 3% (v/v) HCl and the optical density (OD) measured at 665 nm with a TECAN GeniosPro (Switzerland). IC_{50} values were determined with Graphpad Prism 4 using the formula $(OD_{treated}-OD_{start})/(OD_{control}-OD_{start})\times100$. The IC_{50} is the drug concentration for which the total cell number per well corresponds to 50% of the cell number in untreated control cultures (100%) at the end of the incubation period.

5.6.2. Tubulin Polymerization

Isolation and purification of α,β-tubulin from pig brain was performed as in literature.[229b] For the polymerization assay freshly thawed tubulin was centrifuged at 5000 *g* for 5 min at 5 °C and then incubated with additional BRB80 buffer and test compound (added as an appropriate aliquot of a 2mM stock solution in DMSO). Compounds were added to the tubulin solution (10μM) on ice and no GTP/glutamate was added to ligand-driven polymerizations. The final volume of the polymerization solution was 100 μL and the tubulin concentration was 10μM in all experiments. Experiments were performed in a 96-well quartz plate. In negative control experiments plain DMSO was substituted for the compound solution (to a final DMSO concentration of 2%). For positive control experiments polymerization was induced through the addition of GTP/glutamate (0.5mM/0.4M final concentration). The polymerization was monitored by following the increase in absorption at 340 nm in a temperature-controlled TECAN GeniosPro (Switzerland) spectrophotometer. The temperature was set to room temperature (actual measuring temperature was 24–27 °C). The concentration of DMSO was found to be highly critical, as DMSO concentrations >2 % induced considerable microtubule formation, depending on the tubulin batch. The maximal polymerization (P_{max}) was obtained by measuring the maximal absorption at 340 nm using increasing amounts of compounds (1, 3, 4, 5, 7, 10, 15, 20, 25 μM). All compounds showed a P_{max} at equimolar or close to equimolar tubulin:drug ratios. The concentration required to induce 50% of maximal tubulin polymerization achievable with the respective compound (EC_{50}) was calculated from a concentration-effect curve using Graphpad Prism 4. All experiments, including both negative (untreated tubulin) and vehicle controls, were carried out in triplicate. Experiments were performed with at least two different tubulin batches.

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[50] For experimental procedure and details, see: S. A. Dietrich, R. Lindauer, C. Stierlin, J. Gertsch, R. Matesanz, S. Notararigo, J. F. Díaz, K.-H. Altmann, *Chem. Eur. J.* **2009**, *15*, 10144-10157.

5.6.3. Monolayer Efflux Assay across MDCKII-hMDR1 cells[52]

The monolayer efflux assay was used for assessment of susceptibility to Pgp-mediated transport. Polarized epithelial MDCKII and MDCKII-hMDR1 cells overexpressing human Pgp were grown on semipermeable filters, localized on the apical surface of the cells and reduce transport in the apical-to-basal direction and increase transport of Pgp substrates in the basal-to-apical direction. Cell monolayers were washed twice with pre-warmed EBSS and equilibrated for 30 minutes with pre-warmed transport buffer (HBSS containing 10 mM HEPES, pH 7.4) at 37 °C on a platform shaker. The volumes of the apical and basal chambers were 2.5 mL and 3 mL, respectively. Stock solutions at a concentration of 1mM in ultrapure water and of 20mM in ethanol or methanol (both HPLC grade) were prepared for water-soluble and poorly water-soluble compounds, respectively. The monolayer efflux assay was initiated by adding 10 to 50μM drug in transport buffer to either the apical (for apical to basal transport, A→B) or basal (for basal to apical transport, B→A) compartment.

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[52] For experimental procedure and details, see: D. I. Ilgen, Ph. D. Thesis, ETH Zurich (Zurich), **2010**.

The 6-well plates were incubated for 100 minutes at 37 °C while shaking. At 20 minutes intervals, aliquots of 100 μL were removed from the basal (for A→B transport) or from the apical (for B→A transport) compartment. At the end of the experiment, an aliquot was also removed from the donor compartment (apical for A→B or basal for B→A transport) for analysis of the drug recovery. Experiments were performed in triplicates for each drug per experiment. For HPLC/MS/MS analysis, samples were diluted 1:5 in methanol (HPLC grade) and the drug concentration was determined as described below.

5.6.4. Quantification of drugs by HPLC/MS/MS

The concentration of drugs was determined by LC/MS/MS with a 2759 HPLC (Waters) equipped with a XTerra C8 column (3.5 μM, 1x50 mm, Waters) and a MS Quattro Micro Mass detector (Waters). The samples were eluted with a linear gradient of 95% ultrapure water/5% acetonitrile to 100% acetonitrile. Transition monitored as well as optimized cone voltage and collision energy is presented in Table 12. A solvent delay of 5 minutes was set for alcohol **129** in order to include an additional clean-up step using the built-in divert valve controlled by the MassLynx software (Waters). Peak areas of obtained chromatograms were integrated using the MassLynx software. Drug concentrations were calculated via an appropriate calibration curve (0.5–5 μM, n=5).

Table 12: HPLC/MS/MS parameters for alcohol **129**.

Compound	Cone Voltage	Collision Enegrgy	Retention time
129	20 eV (positive mode)	m/z 387 m/z 369, 10 eV m/z 147, 15 eV m/z 197, 20 eV	~14.8 0–25 min run

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During my Ph. D. education I was teaching assistant in practical courses for undergraduate students of Pharmaceutical Sciences as well as involved in lectures. Furthermore, I was responsible for the supervision of one master student.

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