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***Total Synthesis of Isoxeniolide A and Studies
Towards the Total Synthesis of Acalycixeniolide F***

A thesis submitted to attain the degree of
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presented by

LEO BETSCHART

MSc ETH Zurich

born on May 10th 1985

citizen of Hünenberg ZG, Switzerland

accepted on the recommendation of

Prof. Dr. Karl-Heinz Altmann

Prof. Dr. Jeffrey W. Bode

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"You can't give her that!" she screamed. "It's not safe!"

"IT'S A SWORD", said the Hogfather. "THEY'RE NOT MEANT TO BE SAFE."

"She's a child!" shouted Crumley.

"IT'S EDUCATIONAL."

"What if she cuts herself?"

"THAT WILL BE AN IMPORTANT LESSON."

Terry Pratchett, *Hogfather*, 1997

fürs Chuzeners

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Abstract

Abstract

Xenicane diterpenoids represent a large class of marine natural products with more than 100 known members, many of which display anticancer activity. A strained monocarbocyclic 9-membered ring-system (Fig. 1), generally featuring an *E*-double bond, is the unifying structural motif of the xenicane class of natural products.

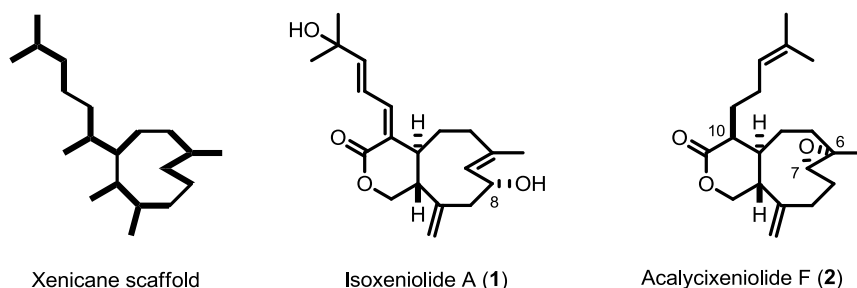


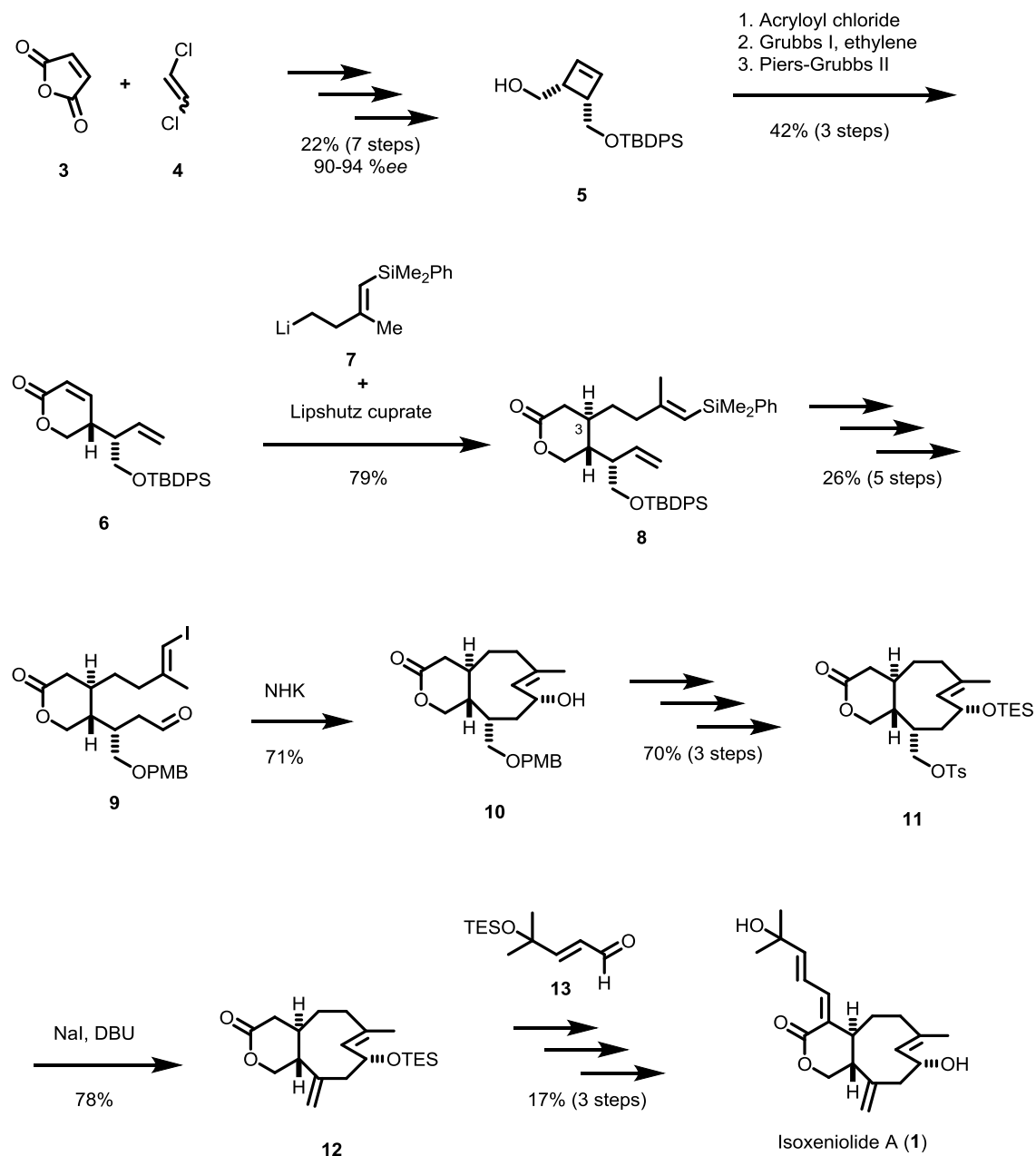
Fig. 1: Structure of the xenicane scaffold and the two targets structures pursued in this PhD thesis.

Isoxeniolide A (**1**) is an 8-hydroxyxenicane and was first isolated in 1979 from *Xenia novaebritanniae* by Braekman. The compound was later shown to induce weak antiproliferative effects in a number of tumor cell lines. Acalycixeniolide F (**2**) was obtained from a sample of *Acanthogorgia inermis* (formerly *Acalycigorgia*) and showed strong cytotoxicity against K562 leukemia cells with an LC_{50} of 0.2 $\mu\text{g/mL}$. It incorporates an interesting C6-C7 *trans*-epoxide and a C10 stereocenter. No information on their biological mode of action is available for either of these two natural products.

In light of their challenging structures and their interesting biological activity, we embarked on a total synthesis of **1** and **2**, neither of which had been synthesized at the outset of our work. In fact, no literature precedence existed for the construction of any 8-hydroxyxenicane, such as **1**. We aimed at the development of a unified approach for the synthesis of both target structures via a common intermediate. The synthetic strategy should also allow access to other xenicane family members and potentially to xenicane analogs. Sufficient quantities of material were to be produced to conduct biological profiling of both compounds.

Highly enantioenriched building block **5** (Scheme 1) was accessible in 7 steps from maleic anhydride (**3**) and 1,2-dichloroethene (**4**). Key transformations were a [2+2]-photocycloaddition and the desymmetrization of a *meso*-cyclobutene derivative with *Pseudomonas fluorescens* lipase. Continuing from intermediate **5**, α,β -unsaturated lactone **6** was produced in a three-step sequence of acrylate ester formation, ring-opening metathesis

(ROM) and finally ring-closing metathesis (RCM) catalyzed by the Piers-Grubbs 2nd generation catalyst. Diastereoselective *Michael* addition of a higher-order Lipshutz cuprate derived from alkyllithium species **7** installed the C3-stereocenter. The precursor of **7** was synthesized in 64% yield over 5 steps. After a number of functional group adjustments, aldehyde **9** was obtained, which efficiently underwent intramolecular *Nozaki-Hiyama-Kishi* reaction.



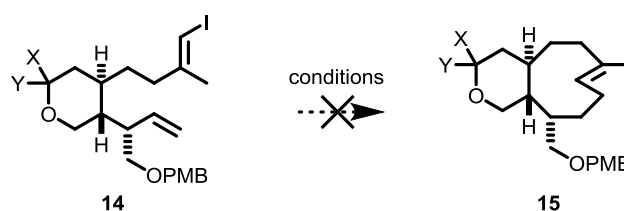
Scheme 1: Total synthesis of isoxeniolide A (**1**).

Cyclononanol **10** was obtained as a single stereoisomer and the structural assignment was confirmed by X-ray crystallography. In three further steps, we arrived at tosylate **11** and using a one-pot iodide formation/elimination procedure, the exocyclic double bond of **12** was

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installed in good yield. Completion of the total synthesis entailed an aldol addition, *syn*-elimination and removal of the silyl protecting groups. The longest linear sequence in the synthesis of isoxeniolide A (**1**) was 24 steps with an overall yield of 0.2%. The total step count was 35, whereof 5 steps were needed for the synthesis of the vinylsilane fragment and additional 6 steps (33% yield) for the side chain aldehyde **13**.

Attempts to synthesize the acalcixeniolide core **15** (Scheme 2) via an alkyl-B *Suzuki* reaction of substrates **14** have been unsuccessful so far. Hydroboration was demonstrated to work and failure of the organoboranes to undergo transmetalation is suspected to be the underlying cause that prevents the desired transformation.



Scheme 2: Failed B-alkyl *Suzuki* reaction. X = H and Y = OMe; X = H and Y = OTBS; X = H and Y = OTIPS; Y, X = O.

As an alternative strategy, deoxygenation of **10** and a number of related structures **16-18** (Fig. 2) was investigated. These attempts have either resulted in decomposition of the material or no reaction at all.

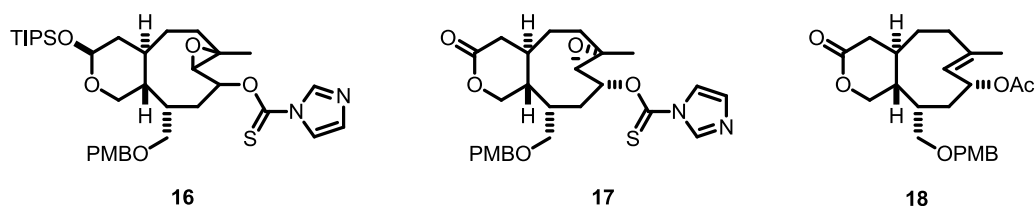


Fig. 2: Substrates that failed to undergo deoxygenation on the cyclononene moiety.

Zusammenfassung

Diterpenoide vom Xenican-Typ bilden eine mehr als 100 bekannte Verbindungen umfassende Klasse mariner Naturstoffe, die vornehmlich aus weichen Korallen und grünen Algen isoliert wurden. Das gemeinsame Strukturmerkmal dieser Naturstoffe ist ein hochgradig gespannter neungliedriger Ring (Abb. 1), der in der Regel eine *E*-konfigurierte Doppelbindung aufweist. Für viele dieser Substanzen wurde eine Aktivität gegen Krebszellen nachgewiesen.

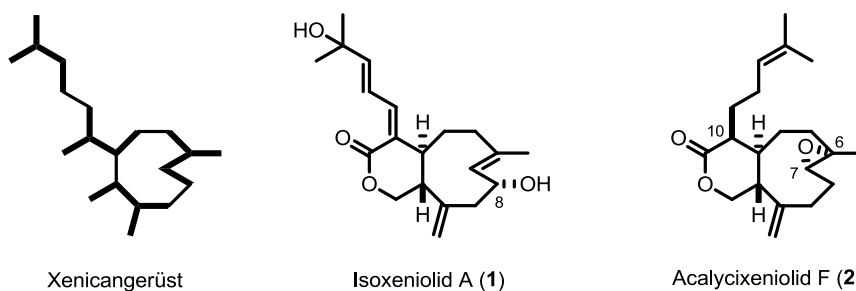


Abb. 1: Struktur des Xenicangerüsts und der beiden in dieser Doktorarbeit angestrebten Zielstrukturen.

Isoxeniolid A (**1**) ist ein 8-Hydroxyxenican und wurde erstmals im Jahre 1979 von *Braekman* aus *Xenia novaebritanniae* isoliert. Spätere Untersuchungen zeigten, dass die Verbindung eine schwache antiproliferative Wirkung auf verschiedene Krebszelllinien aufweist. Acalycixeniolid F (**2**) wurde in einer Probe von *Acanthogorgia inermis* (ursprünglich *Acalycigorgia*) gefunden und besitzt stark cytotoxische Eigenschaften. So beträgt z. B. der LC_{50} -Wert gegen K562 Leukämiezellen 0.2 $\mu\text{g/mL}$. Die Substanz enthält eine strukturell interessante, *trans*-konfigurierte Epoxidgruppierung; im Vergleich mit **1** weist **2** ausserden ein zusätzliches Stereozentrum auf (C10). Der biologische Wirkungsmechanismus beider Substanzen ist bisher ungeklärt.

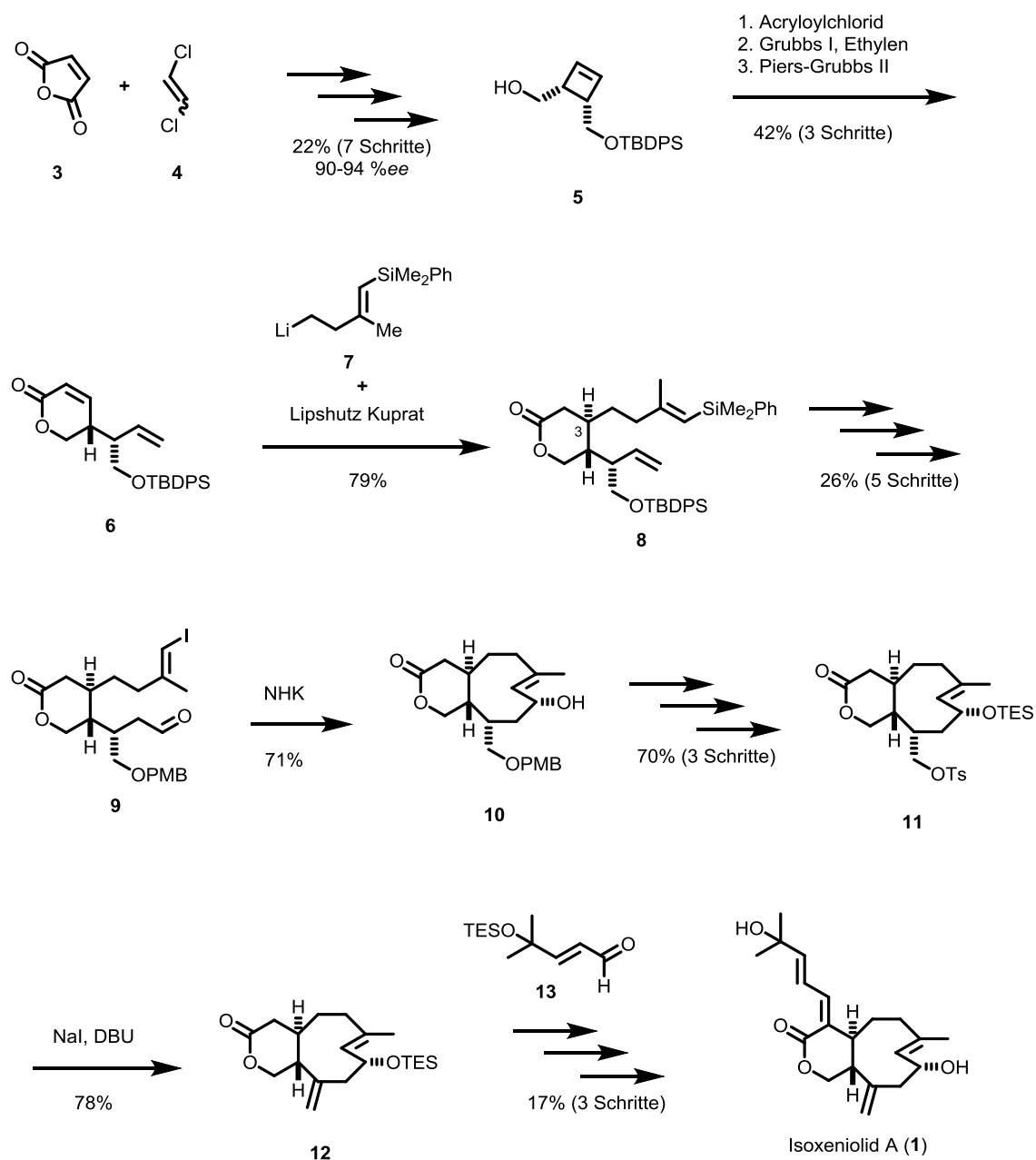
Inspiziert von den spannenden strukturellen Merkmalen und den vielversprechenden biologischen Eigenschaften beider Verbindungen, haben wir die Totalsynthese von **1** und **2** in Angriff genommen. Ein Blick in die chemische Literatur vor Beginn unserer Studien zeigte, dass die Zielstrukturen – und generell die Unterklasse der 8-Hydroxyxenicanen - synthetisches Neuland repräsentierten.

Ziel dieser Doktorarbeit war die Entwicklung eines neuartigen synthetischen Ansatzes, mittels welchem die beiden Zielstrukturen über ein gemeinsames Zwischenprodukt hergestellt werden können. Zusätzlich sollte die Synthesestrategie neue Möglichkeiten für den Zugang zu

Zusammenfassung

weiteren Mitgliedern der Xenicanfamilie sowie zu vereinfachten Analoga eröffnen. Darüber hinaus sollten genügend grosse Substanzmengen für die biologische Profilierung der beiden Naturstoffe hergestellt werden.

Der enantiomerenangereicherte Baustein **5** (Schema 1) wurde in einer 7-stufigen Synthese ausgehend von Maleinsäureanhydrid (**3**) und 1,2-Dichloroethen (**4**) hergestellt. Die Schlüsselschritte der Sequenz bildeten eine [2+2]-Photocycloaddition, sowie die Desymmetrisierung eines *meso*-Cyclobutenderivats durch eine Lipase aus *Pseudomonas fluorescens*.

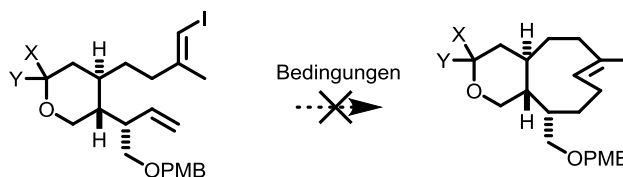


Schema 1: Totalsynthese von Isoxeniolid A (**1**).

Das einfach-geschützte Diol **5** wurde dann in den folgenden 3 Schritten in das sechsgliedrige α,β -ungesättigte Lacton **6** überführt: (1) Bildung des Acrylatesters; (2) Ringöffnungsmetathese; und (3) Ringschlussmetathese mit dem Piers-Grubbs Katalysator der zweiten Generation. Die Umsetzung des Lactons **6** mit dem aus dem Alkylolithium **7** gebildeten entsprechenden Lipshutzkuprat höherer Ordnung lieferte in einer diastereoselektiven *Michael*-Addition **8**. Die Vorstufe zu **7** wurde ausgehend von 3-Butynol in 5 Schritten und 64%-iger Gesamtausbeute hergestellt. Durch Anpassungen der funktionellen Gruppen konnte **8** in den Aldehyd **9** überführt werden, der in zuverlässiger Weise mittels intramolekularer *Nozaki-Hiyama-Kishi*-Reaktion zum Ringschluss gebracht werden konnte. Die Ringschlussreaktion lieferte das Cyclononenol **10** als ein einziges Stereoisomer, dessen Struktur durch Röntgenstrukturanalyse eindeutig nachgewiesen werden konnte. Drei weitere Schritte führten zum Tosylat **11**, das über eine *Finkelstein*-Reaktion und anschliessende Eliminierung im Eintopfverfahren in guter Ausbeute in das Alken **12** umgewandelt wurde. Die Synthese von **1** wurde schliesslich über eine Aldolreaktion, eine *syn*-Eliminierung und zuletzt das Entfernen der Silylschutzgruppen erfolgreich abgeschlossen.

Die längste lineare Reaktionssequenz für die Synthese von Isoxeniolid A (**1**) betrug 24 Schritte, wobei das Zielprodukt in einer Gesamtausbeute von 0.2% erhalten wurde. Insgesamt umfasst die Synthese 35 Schritte, wovon 5 für die Synthese des Vinylsilanfragments notwendig waren und 6 weitere (33% Ausbeute) für den Aufbau des Seitenkettenaldehyds **13**.

Alle Versuche das Oxabicyclo[7.4.0]nonen Derivat **15** mittels intramolekularer Alkyl-B *Suzuki* Reaktion (Schema **2**) aus dem Vinyljodid **14** herzustellen verliefen bisher erfolglos. Die dem Ringschluss vorangehende Hydroborierung konnte dabei eindeutig als Ursache ausgeschlossen werden. Die experimentellen Ergebnisse lassen vermuten, dass die angestrebte Transformation aufgrund eines Problems im Transmetallierungsschritt nicht ablaufen kann.



Schema 2: Gescheiterte Alkyl-B *Suzuki* Reaktion. X = H und Y = OMe; X = H und Y = OTBS; X = H und Y = OTIPS; Y, X = O..

Zusammenfassung

Als mögliche Alternative zum Ringschluss via Kreuzkupplung wurde die Deoxygenierung von **10** und einigen verwandten Strukturen **16-18** (Abb. 2) untersucht. All diese Versuche führten jedoch entweder zur vollständigen Zersetzung der Edukte oder es wurde keine Reaktion beobachtet.

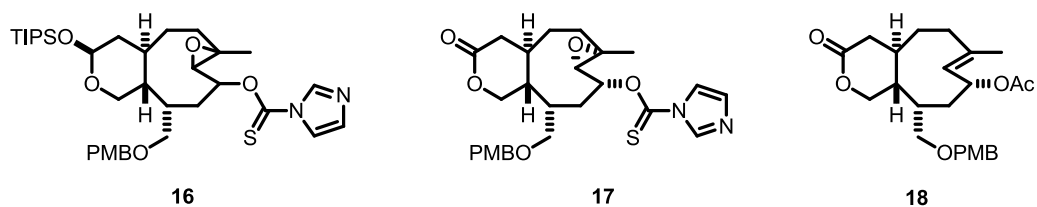


Abb. 2: Verbindungen von welchen die überzählige Hydroxy-Gruppe nicht entfernt werden konnte.

List of Abbreviations, Acronyms and Symbols

Ø	diameter
(l)	liquid
[c]	concentration
[O]	oxidation
°C	degree Celsius
9-BBN	9-borabicyclo[3.3.1]nonane
Å	Ångstrom
Ac	acetyl
acac	acetyl acetate
AIBN	azobisisobutyronitrile
API	active pharmaceutical ingredient
aq.	aqueous
BMEA	bis(methoxyethyl)amine
br	broad
brsm	by recovery of starting material: Yield = %Product / (100 - %Recovered)
cat.	catalytic
CDI	carbonyl diimidazole
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	day or doublet
dba	dibenzylideneacetone
DBB	di-tert-butylbiphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
δ	NMR chemical shift in ppm
DIBAL-H	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine; Hünig's base
DMAP	4-dimethylamino pyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
DOSP	1-[[4-dodecylphenyl]sulfonyl]proline
dppb	1,4-bis-diphenylphosphinobutane
dppf	(ferrocene-1,1'-diyl)bis(diphenylphosphine)
dr	diastereomeric ratio
EC50	half maximal effective concentration
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
ee	enantiomeric excess
EI	electron ionization
ent-	enantiomer of

List of Abbreviations, Acronyms and Symbols

eq.	equivalent
<i>er</i>	enantiomeric ratio
ESI	electrospray ionization
esp	$\alpha,\alpha,\alpha,\alpha$ -tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
FC	flash chromatography
g	gram
G-I	Grubbs 1 st generation catalyst
G-II	Grubbs 2 nd generation catalyst
h	hour
He	hexanes
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HG-I	Hoveyda-Grubbs 1 st generation catalyst
HG-II	Hoveyda-Grubbs 2 nd generation catalyst
h ν	UV/VIS irradiation
HPLC	high-pressure liquid chromatography
HRMS	high-resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
<i>i</i>	iso
IC50	half maximal inhibitory concentration
Im	imidazolyl
ImH	imidazole
<i>i</i> Pr	iso-propyl
IR	infra-red
<i>J</i>	coupling constant
LDA	lithium diisopropylamide
LG	leaving group
LiHMDS	lithium hexamethyldisilazide
M	molar
m	meter or multiplet
<i>m</i>	meta
MALDI	matrix-assisted laser desorption/ionization
<i>m</i> -CPBA	meta-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
Mes	mesitylene, 2,4,6-trimethylphenyl
MHz	megaHertz
min	minute
Mp.	melting point
MPPIM	methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4-carboxylate
Ms	methanesulfonyl
MS	mass spectrometry or molecular sieves
n.d.	not determined
NIS	N-iodo succinimide
nm	nanometer
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide

NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Np	naphthalenide
<i>o</i>	<i>ortho</i>
OPP	pyrophosphate
ORTEP	oak ridge thermal ellipsoid plot
<i>p</i>	<i>para</i>
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PFL	<i>Pseudomonas fluorescens</i> lipase
PG	protecting group
PG-II	Piers-Grubbs 2 nd generation catalyst
Ph	phenyl
PhH	benzene
PhMe	toluene
pin	pinacol, 2,3-dimethyl-2,3-butanediol
Piv	trimethyl acetyl
PMB	<i>para</i> -methoxy benzyl
PMP	<i>para</i> -methoxy phenyl
PPTS	pyridinium <i>p</i> -toluene sulfonate
py	pyridine
q	quartet
quant.	quantitative
rac	racemic
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminumhydride
R _f	retention factor
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerization
rt	ambient temperature
s	second or singlet
sat.	saturated
sec	secondary
SFC	supercritical fluid chromatography
siamyl	sec-isopentyl
SM	starting material
t	triplet or time
T	temperature
TADDOL	2,2-dimethyl- α,α',α' -tetraphenyl-1,3-dioxolane-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBDPS	tert-butyl diphenyl silyl
TBS	tert-butyl dimethyl silyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-yloxy
tert	tertiary
TES	triethyl silyl

List of Abbreviations, Acronyms and Symbols

Tf	trifluoromethane sulfonyl
THF	tetrahydrofuran
thienyl	thiophen-2-yl
TIPS	triisopropyl silyl
TLC	thin layer chromatography
TMS	trimethyl silyl
TPAP	tetrapropylammonium perruthenate
Ts	p-toluene sulfonyl
UV	ultra violet

1. Introduction¹

*“And seeing ignorance is the curse of God,
Knowledge the wing wherewith we fly to heaven.”*

William Shakespeare, Henry IV, Part 2

¹ Chapters 1.1 and 1.2 have been adapted from a review article by L. Betschart & K.-H. Altmann, entitled “Xenicane Natural Products: Biological Activity and Total Synthesis”.^[357] The content is slightly abridged and adapted to cover the scope of this work. However, it contains additional references to include current developments. Please consult the published version for the full account. DOI: [10.2174/1381612821666151002112607](https://doi.org/10.2174/1381612821666151002112607)

1.1 Natural Products in Drug Discovery and Development

Biologically active natural products play an important role in drug discovery,^[1,2] either as immediate drug candidates or as lead structures for the development of new drugs with novel carbon scaffolds or other unique structural characteristics.^[3–5] At a different level, natural products, or related (semi)synthetic derivatives, can also serve as vital molecular probes for biological investigations.^[6,7] In comparison to typical synthetic small molecules, natural products have been suggested to feature higher hit rates in high-throughput screening campaigns,^[7,8] although this notion has to be treated with caution, as publicly available data on this question are scarce and as a “hit rate” obviously depends on the specific criteria that are applied to define a screening hit.

Independent of these ambiguities, there are a number of reasons why natural products should exhibit a high propensity to interact with biological macromolecules, in particular with proteins. Foremost among these is the fact that secondary metabolites in the course of their biosynthesis and when exerting their biological function extensively interact with cellular proteins; thus, they occupy biologically relevant chemical space and as a consequence can be considered validated starting points for biomedical research (in terms of identifying ligands that modulate protein function).^[9–11] Further, the frequent occurrence of sp³-carbon-rich three-dimensional scaffolds allows for a fine-tuned spatial arrangement of the functional groups that interact with target biomacromolecules, leading to high affinity and also specificity of the binding interaction in many cases.^[8]

1.1.1 Natural Product-Based Drugs in Cancer Therapy

Cancer is the major leading cause of death worldwide, with lung and breast cancer showing the highest number of incidents.^[12] Over the last 60 years a number of natural product derived drugs have found their way into the clinic and into cancer patients. To illustrate the importance of natural products in cancer chemotherapy, a selection of these compounds, and if applicable their compound of origin, are depicted in Fig. 3.

The *Vinca* alkaloid vinblastine (**19**) is representative of the earliest class of anti-cancer agents to be identified by means of activity-guided fractionation and was obtained from the Madagascar periwinkle (*Catharanthus roseus*).^[13] Among other therapeutic applications the

compound has been used for the treatment of *Hodgkin's* lymphoma, testicular cancer and *Kaposi's* sarcoma.^[14] The compound acts through inhibition of tubulin polymerization.^[13]

The natural product mitomycin C (**20**), originally isolated from *Streptomyces caespitosus*, is used in combination therapies for a variety of cancer types.^[14] The compound was FDA-approved in 1974^[15] and acts as a DNA cross-linker, thus leading to cytotoxicity.^[16]

Taxol (**21**) was discovered in 1966 in the bark of the Pacific yew tree (*Taxus brevifolia*), but only saw its FDA-approval in 1992.^[17] It is used for the treatment of ovarian, breast, and non-small cell lung cancer, *Kaposi's* sarcoma and other cancer types. The agent exerts its effect by binding to microtubules, stabilizing their structures and thus preventing mitosis. Its binding site is distinct from that of the *Vinca* alkaloids.^[18] Due to the low isolation yield from the bark and because the tree is killed in the process, the drug is produced industrially by semisynthesis from a closely related natural product named 10-deacetyl baccatin III - the latter featuring the complete terpenoid core structure of the drug molecule.^[14] The precursor can be obtained sustainably and in bulk quantities from the needles of the European yew tree (*Taxus baccata*).^[13] There are a large number of man-made taxol derivatives that have found application in the clinic as exemplified by docetaxel (**22**).^[17]

The alkaloid camptothecin (**23**) was first found in the Chinese tree *Camptotheca acuminata* in 1958.^[13] It showed excellent antitumor activity in animal models, but displayed very unfavourable physicochemical properties and strong toxic side effects.^[19] When its mechanism of action was determined to be inhibition of DNA topoisomerase I, interest in this compound was renewed.^[14] The derivative topotecan (**24**) was approved for use against ovarian, cervical and small-cell lung cancer and another derivatives of camptothecin (**23**) which is called irinotecan (not depicted) has found its way into the clinic as well.^[20]

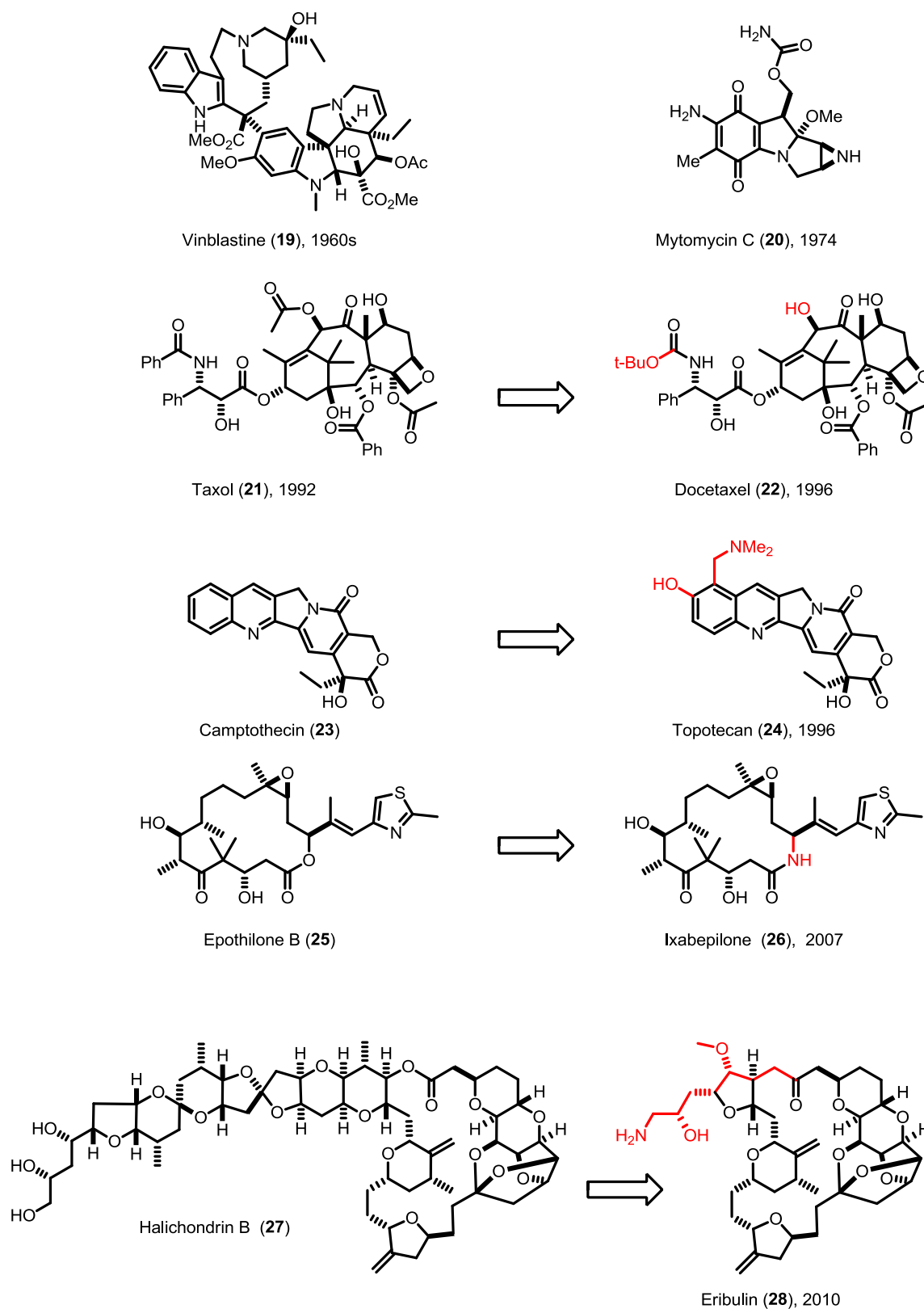


Fig. 3: Natural products (all black colored) and natural product derivatives (red color shows deviation from natural product) in cancer drug discovery. The year next to a molecule's name indicates the year of its approval as a drug. Natural products **23**, **25** and **27** are not approved for clinical use.

Epothilone B (**25**) was isolated from the myxobacterium *Sorangium cellulosum* in 1987.^[21] While the parent compound **25** is not used as a drug, its amide derivative ixabepilone (**26**) was approved by the FDA for the treatment of metastatic or locally advanced breast cancer.^[14] A crucial characteristic of epothilone-derived drugs is their retained activity on tumors that are resistant towards paclitaxel.^[19] This is intriguing in light of the fact that epothilones display the same mechanism of action and are binding to the same site on tubulin as the taxanes.^[21]

The polyether halichondrin B (**27**) was found in 1986 in the marine sponge *Halichondria okadai* using a bioassay-guided fractionation.^[22] The compound displayed nanomolar activity against melanoma and leukemia cell lines.^[22] Its mechanism of action is similar, but distinct from that of the *Vinca* alkaloids.^[14] Given the large and complex structure of halichondrin B (**27**), it took years of research and the synthesis of a great number of derivatives to develop the simplified analog eribulin (**28**).^[23] Despite its much smaller size and complexity when compared to the parent compound, eribulin (**28**) represents the most complex small molecule drug industrially produced and also comprises the longest synthetic sequence of an API.^[24] Eribulin (**28**) is approved for the treatment of metastatic breast cancer.^[19]

1.1.2 Bioactive Marine Natural Products and Their Role in Drug Discovery

The work described in this PhD thesis is centered on two natural products of the xenicane family of diterpenoids (*vide infra*). Xenicanes are exclusively of marine origin and, therefore, this section shall provide some background on the peculiarities of marine natural products (compared to their terrestrial counterparts). Natural products of marine origin hold a distinct position in the context of drug discovery, due to the great diversity in their structures and biological activities. Organisms belonging to the kingdoms *Archaea*, *Bacteria*, *Protozoa*, *Chromista*, and *Fungi* as well as many *Algae*, and lower animals of the phyla *Porifera* and *Cnidaria* are not equipped with any physical means of protection.^[25] Instead, they release secondary metabolites, *e.g.* toxins,^[26] as a chemical way of defense.^[27] These substances can either be synthesized by the organism itself or by an associated symbiont, but they can also be acquired from other organisms by feeding.^[4]

When compared to their terrestrial counterparts, a higher incidence of significant bioactivity has been noted for marine natural products and this is often associated with a high degree of chemical novelty; *i.e.* many newly discovered bioactive marine natural products display novel

types of chemical structures.^[11,28] While the ocean harbors many creatures we have not been closely interacting with for ages,^[26] eukaryotic physiology evolved in our early marine ancestors and is highly conserved.^[8] These two facts combined might partly explain the large number of novel mechanisms of action found for marine natural products.^[11] Moreover, it is speculated that their often extremely high potency could be traced back to the high dilution in ocean water.^[4]

Marine organisms are the source of an ever increasing number of new structures, with more than 1100 and 1300 new compounds described in 2013^[29] and 2014^[30], respectively. The discovery of new marine natural products is fueled by a tremendous number of new marine species that are discovered every year as well as the increased efficiency of genome sequencing, which enables the identification of an ever growing number of biosynthetic gene clusters.^[11] Increasingly, samples from previously difficult-to-access regions are investigated and improved spectroscopic methods allow for structure elucidation with trace amounts of unknown substances.^[11] Not only does the use of data-driven methods facilitate the identification of bioactive compounds,^[31] but also the dereplication of known natural products.^[32] At the same time, the elucidation of molecular targets and mechanisms of action is becoming both faster and more material-efficient.^[33,34] Notwithstanding these recent advances, the set of organisms that has been scrutinized so far for bioactive secondary metabolites is still very limited and much yet remains to be discovered.^[29]

In light of the intriguing and often unique biological profiles of marine secondary metabolites, it is not surprising that they have also served as starting points for successful drug development, although the number of marine natural product-derived marketed drugs at this point in time is still limited. This includes the anticancer drugs trabectedin, which is an unmodified natural product (ecteinascidin-743) that is, however, produced by semisynthesis from a terrestrial natural product (cyanosafracin B),^[7,35] the abovementioned eribulin (**28**)^[35] and the antibody-drug conjugate brentuximab vedotin; the latter contains a derivative of the marine natural product auristatin as the active drug payload.^[35] The only marine-derived drug that has been approved so far outside of the oncology area is ziconotide,^[35] a peptide from a cone snail that is used for the treatment of pain. Many more compounds that are derived from marine natural products are in various stages of clinical development.^[35–38]

1.1.3 Synthetic Chemistry and Natural Product-Based Medicinal Research

Biomedical investigations of natural products of marine origin are often hampered by the general paucity of material for broad-based profiling. While the demand is high,^[26] the supply of material is often difficult and non-sustainable;^[7] in addition, even the sheer cost of collecting a marine organism as the source of the desired material can be a prohibitive factor.^[26] Some marine bacteria can be fermented on large scale, as is the case for the industrial production of salinosporamide.^[11] On the other hand, more delicate organisms like sponges are difficult to cultivate.^[26] Additionally, under breeding conditions, relevant gene clusters may remain silent, which has been resolved by mixed fermentation, in some cases.^[11]

In this context, chemical synthesis of natural products has an important role to play in the chemical biology of natural products and also in natural product-based drug discovery. While it is true that synthetic routes to elaborate carbon scaffolds and/or complex stereochemical arrays often take a long time to establish and may deliver only small quantities of material^[8] (although frequently more than is available from the natural source), chemical synthesis not only allows access to the natural product itself, but it also wields the potential to deliver structures not easily accessible by derivatization or modification of an isolated natural product.^[11] A potent carbon skeleton can be a valuable starting point for drug discovery *via* both simple functional group interconversions as well as *via* appending chain elements.^[8] Truncation^[39,40] (the most prominent example being eribulin^[11]) or hypermodification (examples are bryologs^[41] or hypermodified epothilone analogs^[42]) of a natural product core structure can lead to improved biological^[8] and/or pharmacological^[26] properties, while at the same time facilitating synthetic access.^[8]

1.2 Xenicane Diterpenoids

Out of the vast array of structures produced by marine organisms, the work described in this PhD thesis is focused on two natural products of the xenicane family. A large number of members of this natural product family have been isolated and evaluated for their respective biological activities (*cf.* section 1.2.3, p. 14ff). While these biological properties spanned a broad range including antibacterial action, modulation of superoxide production and ichthyotoxicity, the most frequently observed effects (>66% of instances) were cytotoxic and antiproliferative in nature. This suggests that xenicane natural products represent interesting tool compounds for cancer research and, in some cases, could also serve as lead structures for anticancer drug discovery. In spite of this potential, however, the chemistry and biology of xenicane diterpenoids have not been explored extensively.

This chapter provides a brief introduction into the basic structural features and the biogenesis of natural products of the xenicane family, followed by an overview of bioactive compounds related to xeniolide A (**30**, Fig. 5) and their potential mechanisms of action (where investigated). In addition, selected xenicane family members that are structurally distinct from xeniolide A will also be discussed.

1.2.1 Structural Classes and Origin of Xenicanes

Xenicane diterpenoids (also referred to as Xenia diterpenoids^{II}) are a diverse group of marine natural products featuring a 9-membered carbocyclic ring as the defining structural element (Fig. 4).^[43] With a small number of exceptions, most of the xenicanes also bear C6-C7 *E*-configured double bond.

In the seminal report on the isolation of xenicin (**29**), which was the first xenicane diterpenoid to be discovered in 1977 by *Schmitz, van der Helm* and co-workers,^[44] the name “xeniane” was proposed for the carbon skeleton shown in Fig. 1, but this term has been used in the literature only sparsely. More than a hundred xenicane-type diterpenoids have been isolated since the discovery of xenicin (**29**) almost 40 years ago.

^{II} “Xenia diterpenoids” is a collective term that is defined by species of origin rather than specific structural features. Therefore, compounds that are commonly referred to as xenia diterpenoids include xenicanes, xeniaphyllanes and also other types, such as prenylated germacrene type structures.^[70]

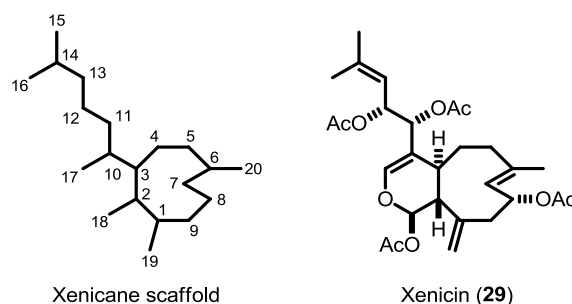


Fig. 4. The xenicanane carbon skeleton and the structure of xenicin (**29**).

For the majority of xenicanane diterpenoids, carbon atoms 17 and 18 are connected by an oxabridge, giving rise to (mostly) bicyclic, but also polycyclic structures. Depending on the nature of the additional 6-membered ring, such 11-oxa-bicyclo[7.4.0]tridecane-based xenicanane diterpenoids can be divided into two distinct structural sub-classes that are referred to as xenicins^{III} and xeniolides, respectively (**Fig. 5**).

Xenicanane diterpenoids of the xenicin sub-class are characterized by the presence of a dihydropyran moiety fused to the 9-membered ring, with xenicin (**29**) as the prototypical example. Common differences amongst xenicin-type compounds relate to the degree of acetylation and hydroxylation as well as the configuration of the acetyl acetal moiety.

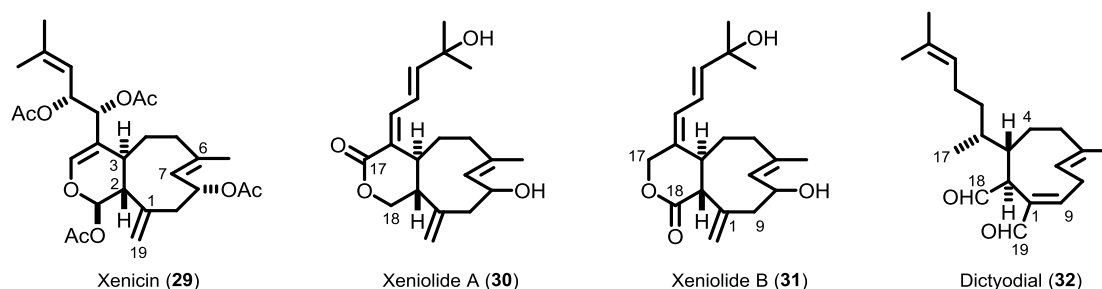


Fig. 5. Four representative members of the xenicanane family of diterpenoids: Xenicin (**29**) belongs to the xenicin sub-class, xeniolides A (**30**) and B (**31**) are prototypical xeniolides and dictyodial (**32**) is a monocyclic xenicanane. Throughout this work, the xenicanane numbering suggested by *Vanderah et al.* will be used.^[44]

Compared to xenicins, xeniolides incorporate a δ -lactone ring in place of the pyranoside moiety, with either C17 or C18 being oxidized to the carbonyl group of the ester moiety (*cf.*

^{III} Xenicins have also been referred to as xenicanes.^[63]

Fig. 1 for numbering); the former arrangement, which we found to be more frequent^{IV}, is present, *e.g.*, in xeniolide A (**30**) (Fig. 5), which was isolated in 1978 from *Xenia macrospiculata*^[45] and thus belongs to the earliest xenicane diterpenoids to be discovered. The presence of a C1-C19 exocyclic methylene group is a common feature of xenicins and xeniolides. Much of the structural variation within these two sub-classes of xenicane diterpenoids is accounted for by the number, position and geometry of unsaturations in the side chain, but also the possible epoxidation of the typical C6-C7 double bond. Moreover, a common structural modification is hydroxylation at C8.

In addition to xenicins and xeniolides, a few examples of bicyclic xenicane diterpenoids with an oxa-bridge between C18 and C19 have also been described. These compounds are related to a larger set of monocyclic xenicane diterpenoids with C18 and/or C19 oxidized to the alcohol, aldehyde or acid state, without these carbons being part of a second ring. Additionally, a C1-C9 double bond is a prevalent feature. The first monocyclic xenicane diterpenoid to be discovered was dictyodial (**32**) (Fig. 5), which was first isolated in 1979 from *Dictyota crenulata*^[46] and contains an unmodified C17 methyl group. However, other variants of monocyclic xenicane diterpenoids have been isolated subsequently with further oxidative modifications of the xenicane skeleton at C17 and/or C4.

So far, xenicane diterpenoids have been discovered exclusively in marine organisms. Most of the compounds discussed in this work have been isolated from soft corals of the genera *Xenia* and *Acanthogorgia*^V (formerly *Acalycigorgia*). Other, minor sources of active compounds include soft corals of the genera *Asterospicularia*^[47–49], *Capnella*^[50], *Eleutherobia*^[51], *Acanthoprimnoa*^[52], *Alcyonium*^[53], *Anthelia*^[53], and *Clavularia*^[54]. Many of the compounds related to dictyodial (**32**) are found in brown algae of the genus *Dictyota* (which includes the defunct genera *Dilophus*^[55–57] and *Glossophora*^[58]) and to a much smaller extent in sea slugs of the genus *Aplysia*^[46] and brown algae of the genus *Padina*^[59].

^{IV} A Reaxys Chemistry Database search on June 7th, 2016 gave the following numbers of hits: 60 publications with 176 xenicane structures (*Mosher* esters and total syntheses were excluded); xeniolide A type: 53 hits, 34 thereof bioactive; xeniolide B type: 25 hits, 10 thereof bioactive; xenicin type: 86 hits, 45 thereof bioactive; structures combining a xeniolide A type lactone moiety with structural characteristics of dictyodial (**32**): 9 hits, 2 thereof bioactive; others with a C17-C18 oxa-bridge and C17 acetal, 3 hits, 2 thereof bioactive.

^V "*Acanthogorgia* Gray, 1857". WoRMS Editorial Board (2016). World Register of Marine Species. Available from <http://www.marinespecies.org> at VLIZ. Accessed August 1, 2016

Importantly, the absolute configuration of the xenicane skeleton may vary between individual members of the family, depending on the producing organism. More specifically, the available data for the absolute configuration of xenicanes from different sources suggest that compounds obtained from brown algae and those from soft corals exhibit opposite configurations of both their C2 and C3 stereocenters^{vi}. Therefore, compounds obtained from algae are treated as a separate subclass in this chapter, with antipodal absolute stereochemistry to that from soft corals.

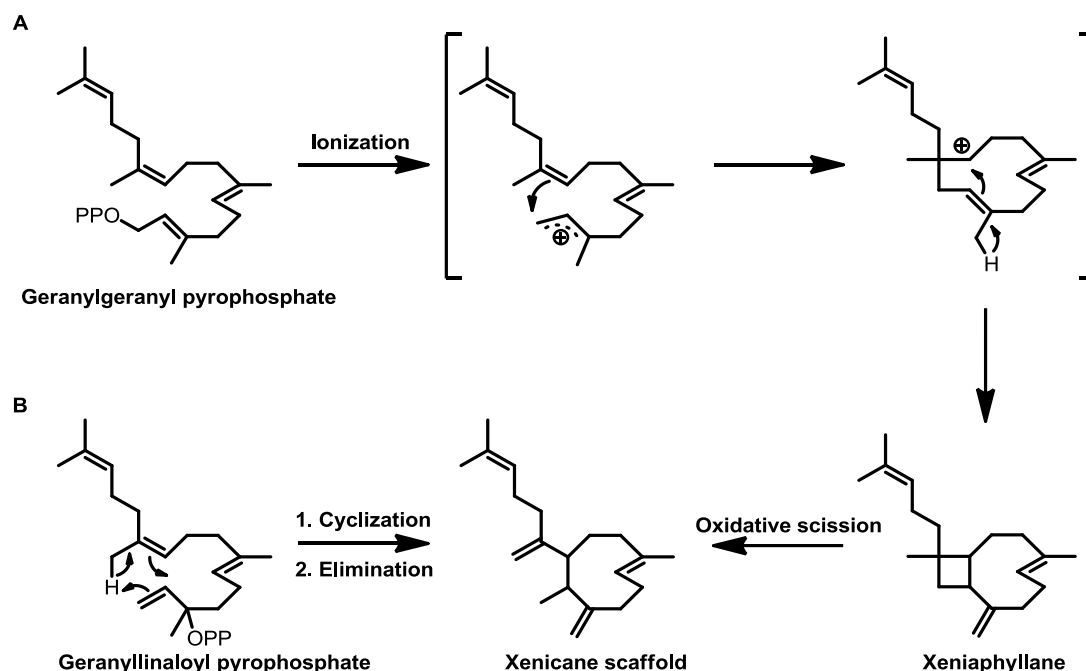
1.2.2 Biogenesis and Closely Related Natural Product Scaffolds

While significant advances have been made in our understanding of biosynthetic pathways in terrestrial organisms, the biosynthesis of marine natural products remains poorly understood even today. To a large extent, this is related to difficulties in the cultivation of certain marine organisms, which has proven to be extremely demanding.^[60–62] Growth rates are often slow^[63] and large seasonal variations in terpene content have been noted for specimens of *Xenia macrospiculata*.^[45] To date, only one single example of a xenicane diterpenoid that has been obtained by cultivation (of *Xenia elongata*) has been reported.^[64] Lastly, in most cases, it remains unclear whether the macroorganism harboring a secondary metabolite in fact produces the compound by itself or if it rather originates from an associated symbiotic microorganism.^[65] For example, it is likely, but not proven, that the sea slug *Aplysia depilans* acquires xenicane diterpenoids from brown algae that are part of their diet.^[46] In a chemotaxonomic investigation of *Dictyota dichotoma*, extreme variations in the distribution of secondary metabolites served as a basis for the suggestion that *Dictyota dichotoma* is in fact a collection of different species.^[66] To date, there still remains a gap in knowledge of pathways as well as relevant gene clusters for xenicane synthesis.

According to the biogenetic isoprene rule,^[67] xenicanes are regular, *i.e.* non-rearranged diterpenes. The biogenesis of xenicane diterpenoids has been suggested to proceed from geranylgeranyl pyrophosphate or geranylgeranyl pyrophosphate as precursors.^[44] In analogy

^{vi} Thus, it has been established by a combination of Mosher ester analysis, chemical correlation studies and total synthesis that xenicin (**1**), which originates from soft corals, and dictyodial (**4**), which so far has so been obtained only from brown algae, exhibit opposite configurations of their C2 and C3 stereocenters.^[110,111] A 2*S*,3*S* configuration as in dictyodial (**4**) has also been established for two closely related xenicanes from the brown algae *Glossophora kuntii* and *Dictyota* sp., respectively, by means of X-ray crystallography.^[358] In addition, for the brown alga-derived 4-hydroxydictyolactone (**83**, Fig. 12) the corresponding configurational assignment was confirmed by total synthesis.^[129,130] On the other hand, the 2*R*,3*R* configuration in soft coral-derived xenicanes has been corroborated by the total synthesis of three different xeniolide-type structures (*cf.* section 4).

to the biogenesis of caryophyllene,^[68] cyclization of a linear allylic cation has been proposed (Scheme 3, pathway **A**). After initial formation of a xeniaphyllane, oxidative scission of the cyclobutane ring would deliver the xenicane scaffold.^[44] Alternatively, direct ring-closure in a formal ene-reaction might take place (Scheme 3, pathway **B**). The typical exocyclic methylene group would then arise by elimination of the tertiary hydroxy group.^[44] The fact that xeniaphyllanes have been co-isolated with xenicanes^[45,69] may be taken to infer that the “xeniaphyllane pathway” **A** represents the more likely process for the formation of the 9-membered ring. However, this finding does not conclusively rule out alternative pathways, such as the pathway **B**. Therefore, the exact sequence of steps involved in the formation of the 9-membered ring at this point still remains elusive.



Scheme 3. Alternative hypothetical pathways for the biogenesis of xenicane diterpenoids: **A**. Cyclization followed by oxidative cleavage of the cyclobutane ring.^[44] **B**. Direct cyclization and elimination.^[44] OPP: pyrophosphate.

Soft corals have been found to produce a variety of diterpenoids that bear a close structural relationship to xenicanes, but cannot be classified as such (Fig. 6). For example, xeniaphyllenol (**33**) from *Xenia macrospiculata* incorporates an additional C10-C18 bond when compared with the xenicane parent structure and, thus, can formally be considered a prenylated caryophyllene.^[69] As indicated above, compounds of this type have been co-isolated with xenicanes in a number of instances.^[45,69–71] When compared to the xeniaphyllenol scaffold, the structure of sarcoglance (**34**) features an additional 5-membered carbocycle, which

formally arises from the formation of a C-C bond between C13 and C18. Biogenetically, **34** and related products may be derived either from a xeniaphyllane or from a cembrane precursor.^[72] In contrast to the previous examples, the carbon scaffold of antheliolide A (**35**) is not that of a typical C20 diterpene, but incorporates an additional acetoacetate moiety.^[73,74] It has been speculated that oxidation of xeniaphyllenol to the corresponding C18-hydroxy C17-aldehyde followed by aldol reaction/lactonization with an acetoacetyl derivative and a final formal [4+2] cycloaddition would constitute a plausible biogenetic relationship between xenicanes and antheliolide A (**35**).^[63] In fact, this sequence has been exploited in *Corey's* total synthesis (p. 24ff) of antheliolide A (**35**).^[75]

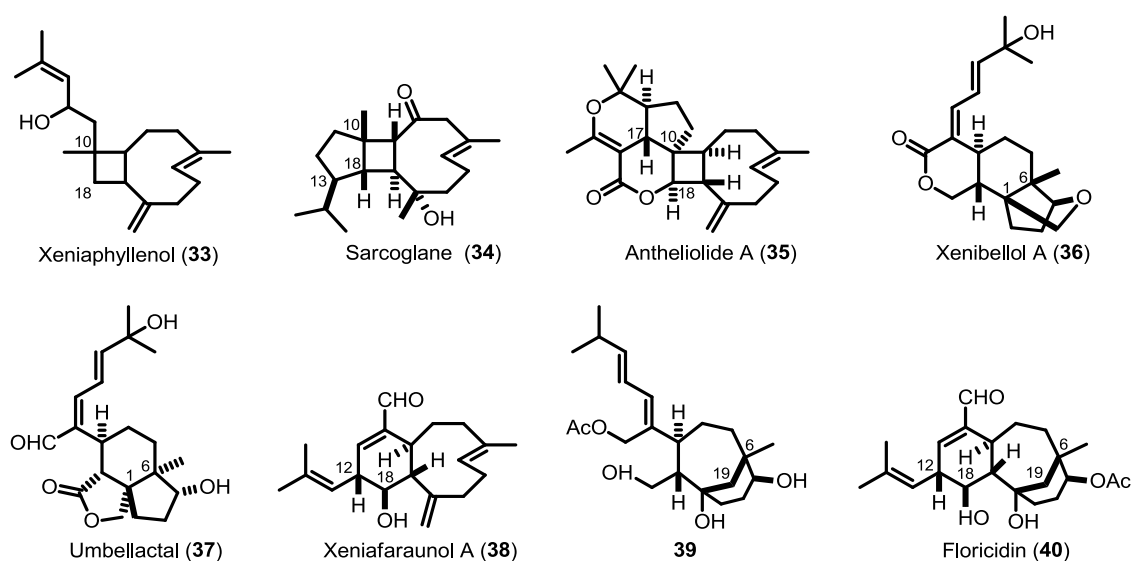


Fig. 6. Diterpenes from soft corals that show a close structural relationship with xenicane diterpenoids.

Xenibellol A (**36**)^[76] and umbellactal (**37**)^[77] illustrate the possible diversification of the xenicane-type carbon scaffold into structures with a C1-C6 transannular fusion. Xeniafaraunol A (**38**) incorporates an additional C12-C18 connection, which produces a bicyclo[7.4.0]tridecadiene carbon skeleton.^[78] Unnamed diterpenoid **39** displays an alternative transannular ring-fusion pattern compared to **36** and **37** with a C6-C19 bond.^[79] Interestingly, this cyclization mode was also observed as a side reaction during an HCl-mediated deprotection of a methyl acetal during the synthesis of coraxeniolide A (*cf.* p. 27ff).^[80] The same motif is also found as part of floricidin (**40**), where it occurs in combination with a cyclohexene ring as it is present in **38**.^[81]

1.2.3 Biologically Active Xenicanes

Given the general propensity of marine natural products to exert, sometimes very potent, biological effects and in light of the diversity of structures among xenicane diterpenoids, it is reasonable to expect that some of these compounds would exhibit interesting biological activities that might be exploited in chemical biology and potentially for drug discovery. To shed some light on this question, in the following section the reported biological activities of individual xenicane diterpenoids will be reviewed and a critical assessment of the available data will be attempted. Unfortunately, no biological data (neither negative nor promising) can be found in the literature for a significant number of xenicanes; for older compounds in particular, isolation and structure elucidation work has often not been accompanied by the assessment of biological activity (or the data were not included in the corresponding publications). Notably, in the more recent literature the number of reports that include biological data on newly isolated compounds has significantly increased. It needs to be stressed, however, that even for those xenicanes where biological data are available in the literature, profiling was generally performed only in a limited set of assays. One notable exception is a report by *König et al.* that describes the evaluation of close to 70 natural products (including xenicanes **32**, **70** and **80**) against a panel of 13 cancer cells lines, different variants of *Plasmodium falciparum*, as well as strains of *Penicillium oxalicum*, *Bacillus subtilis*, *Micrococcus luteus* and *Escherichia coli*.^[82] Given the range of effects observed for those xenicanes that have been subjected to biological testing (*vide infra*), it is well conceivable, and even likely, that many of the xenicanes that are not discussed here may harbor biological properties that have yet to be unraveled.

In the first part of the discussion, the biological activities of xeniolides, as the largest group of known bioactive metabolites of the xenicane family of diterpenoids, will be summarized. This will be followed by a small collection of xenicin-type structures and some important xenicanes originating from *Phaeophyceae* (brown algae) whose absolute configuration is opposite to that of the structures produced by soft corals. Finally, a number of diverse structures will be touched upon that do not fit into any of the above categories, but nicely illustrate the structural variety of this diterpenoid class. It should be noted here that stereocenters, especially in the C10 side chain, have not always been assigned in the isolation literature. This partial lack of stereochemical information is reflected in several of the structural drawings

depicted in the following subsections. Absolute stereochemistry was adapted according to the organism of origin.

1.2.3.1 Xeniolides

As illustrated by the structures depicted in Fig. 7, a significant sub-group of bioactive xeniolides incorporates a potentially reactive α,β -unsaturated lactone moiety, with the conjugated exocyclic double bond being either *cis*- or *trans*-configured. The former group of structures includes isoxeniolide A (**1**) and epoxyisoxeniolide (**41**), which were both obtained from *Xenia novaebritanniae*^[83] and were the first xeniolides to be discovered after the prototypical xeniolides A and B.^[45] They were later re-isolated from *Xenia* sp. and reported to “show an $IC_{50} > 1 \mu g/mL$ against mouse (P-388) and human (A-549, HT-29, MEL-28) tumor cell lines”.^[84] Unfortunately, these data are not very informative, but the wording may suggest that the compounds displayed only low antiproliferative activity.

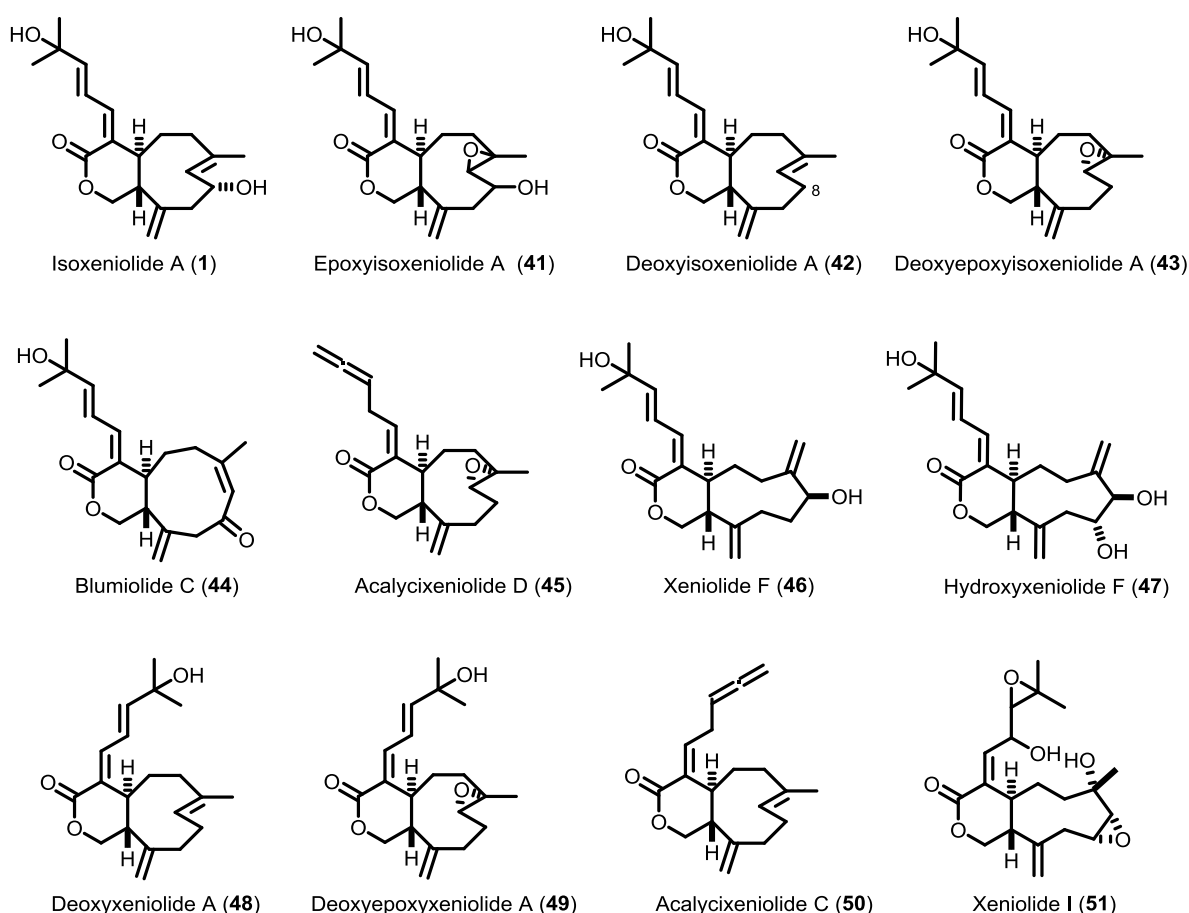


Fig. 7. Xeniolide A-related natural products incorporating an α,β -unsaturated lactone ring.

The stereochemistry of the epoxyalcohol moiety of **41** has not been assigned, but likely is a combination of the stereochemical features found in compounds **1** and **43**. The corresponding

8-deoxyxenicanes **42** and **43** were isolated from *Xenia blumi* and exhibited moderate cytotoxicity against HT-29 colon cancer cells with ED₅₀ values in the single digit µg/mL range.^[85] Additionally, epoxide **43** was found to be similarly active against P-388 leukemia cells;^[85] this compound has also been isolated from a different unspecified *Xenia* species.^[86] Significantly higher potency has been reported for blumiolide C (**44**) with ED₅₀ values against the HT-29 colon carcinoma and P-388 mouse leukemia cell lines in the sub-µg/mL range;^[85] blumiolide C (**44**) was isolated from both *Xenia blumi*^[85] and *Xenia* sp.^[86] and contains an unusual Z-double bond as part of the 9-membered ring. Surprisingly, synthetic **44** was found to be less potent against the HCT-116 colon carcinoma and A549 lung carcinoma cell lines than what might have been expected based on the data reported in the context of the isolation work (IC₅₀ values > 10 µM).^[87] An α,β-unsaturated lactone moiety with a *cis*-configured conjugated exocyclic double bond is also found in acalcixeniolide D (**45**), which is a norditerpenoid lacking one of the side chain carbon atoms. It was discovered in a sample of *Acanthogorgia inermis* and effected low cytotoxicity against K562 leukemia cells.^[88,89] Xeniolide F (**46**) and its hydroxylated version **47** were co-isolated with **1** and **41** and as for the latter, no conclusive information is available on the antiproliferative activity of **46** and **47**.^[84] Notably, **46** was also found in the same specimen of *Xenia* sp. as **43**.^[86] Abstraction of one proton from the methyl group on the cyclononane ring, accompanied by opening of the epoxide moiety, might be the chemical link between these two natural products.^[71,90]

In contrast to the various xeniolides discussed above, xeniolides **48** to **51** all incorporate a *trans*-configured exocyclic double bond in conjugation with a lactone carbonyl group. Deoxyxeniolide A (**48**), which is a double bond isomer of **42**, was first found in *Xenia* sp. and showed detectable, but low antibiotic activity against *Micrococcus luteus*, *Bacillus subtilis*, and *Staphylococcus aureus*.^[91] An independent source of **48** proved to be *Acanthogorgia inermis*; in the context of the isolation of **48** from this latter organism the compound was found to display very strong cytotoxicity against K562 leukemia cells with an LC₅₀ of 0.04 µg/mL.^[92] Its epoxide **49**, an isomer of **43**, was isolated from *Xenia blumi* and found to have moderate cytotoxicity (single digit µg/mL ED₅₀ values) against human HT-29 colon cancer and mouse P-388 leukemia cells;^[85] **49** has also been isolated from *Xenia florida*.^[93] Acalcixeniolide C (**50**) was obtained from *Acanthogorgia* sp.^[94–96] and showed biological activities ranging from moderate cytotoxicity against mouse P388 leukemia cells, to low, but detectable activity in a sea urchin (*Hemicentrotus pulcherrimus*) egg assay, to antifungal activity against *Mortierella*

ramannianus and *Penicillium chrysogenum*.^[94] The highly oxidized and structurally unusual xeniolide I (**51**) was extracted from *Xenia novaebritanniae* and showed moderate antibacterial activity against *Escherichia coli* and *Bacillus subtilis*.^[97]

Fig. 8 depicts a series of xeniolides bearing a stereogenic center in the α -position to the lactone carbonyl group rather than an sp^2 carbon as part of an exocyclic double bond. These compounds are referred to as acalcixeniolides. As the first representatives of the group, the norditerpenoids acalcixeniolides A (**55**) and B (**56**) were isolated from the gorgonian *Acanthogorgia inermis*.^[98] In fact, all of the compounds shown in Fig. 8 originate from *Acanthogorgia inermis*, except for **60** and **61**, which have been isolated from *Acanthogorgia* sp.

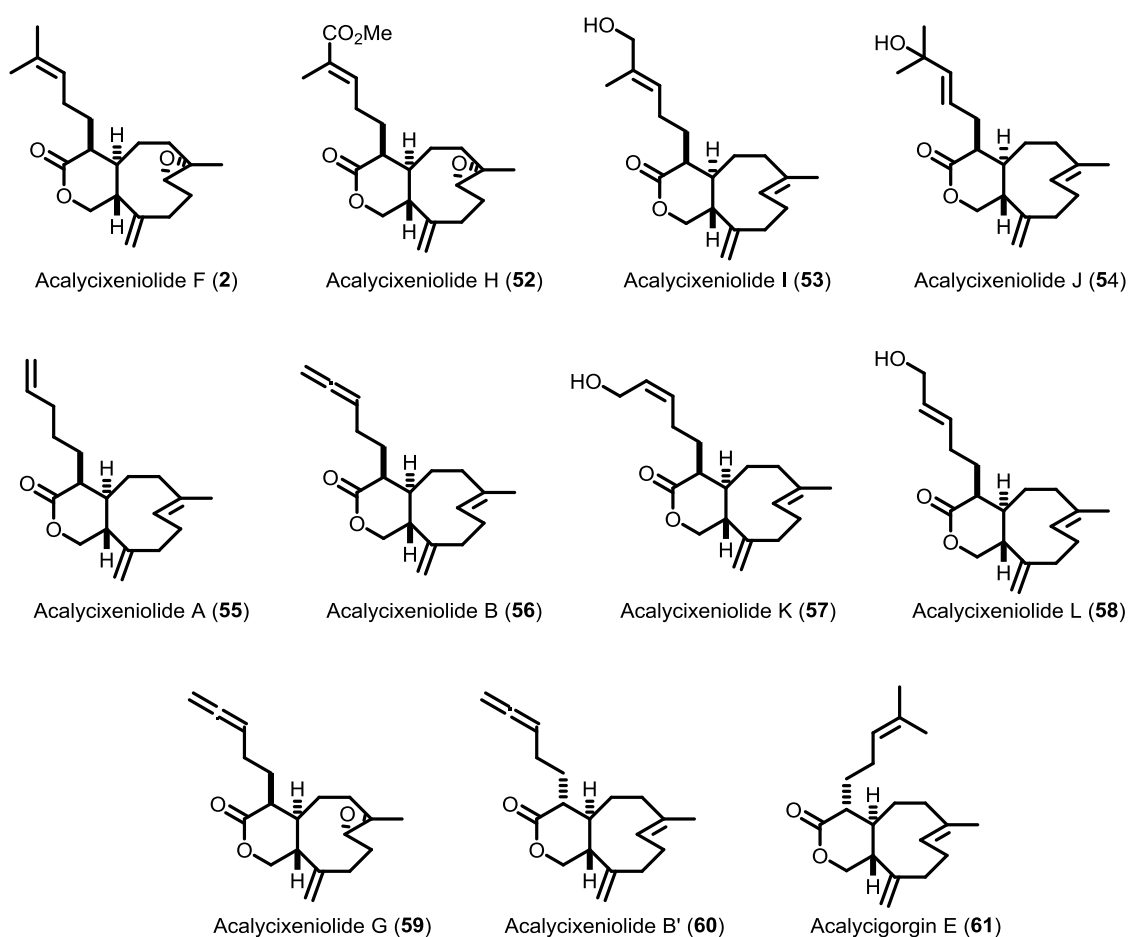


Fig. 8. Xeniolide A-related bioactive natural products bearing a stereogenic center in the α -position of the lactone moiety.

Epoxide acalcixeniolide F (**2**) was co-isolated with **45** and showed strong cytotoxicity against K562 leukemia cells (LC_{50} of 0.2 $\mu\text{g/mL}$).^[88,89] Acalcixeniolide H (**52**) was found in a different specimen of the same species, but was less active than **2** (LC_{50} against K562 leukemia cells of

3.9 $\mu\text{g/mL}$). The two constitutional isomers acalcixeniolide I (**53**) and J (**54**) were co-isolated with **52**; their antiproliferative activity against K562 cells was similar to that of **52**.^[92] Acalcixeniolide A (**55**) and B (**56**), which are norxeniolides, were reported to inhibit the cell division of fertilized eggs of the starfish *Asterina pectinifera* with ED_{50} values of 20 and 5 $\mu\text{g/mL}$, respectively.^[98] Two additional norxeniolides, acalcixeniolides K (**57**) and L (**58**), were found in the same coral material as **52**, **53** and **54**. Their side chains feature a *cis*- and *trans*-configured allylic alcohol moiety, respectively; **57** and **58** inhibit the growth of K562 leukemia cells with IC_{50} values of 1.5 and 1.8 $\mu\text{g/mL}$, respectively.^[92] Acalcixeniolide G (**59**), the epoxide of **56**, was co-isolated with **45** and **2** and was reported to be moderately cytotoxic towards K562 leukemia cells.^[88,89] Acalcixeniolide B' (**60**) is the α -epimer of **56** and was isolated together with **50**.^[94–96] A range of biological tests revealed moderate cytotoxicity against P388 leukemia cells ($\text{IC}_{50} < 2.5 \mu\text{g/mL}$), and very low activity in a sea urchin egg assay; the compound also showed antifungal activity against *Mortierella ramannianus* and *Penicillium chrysogenum*.^[94] Acalcigorgin E (**61**), the non-epoxidized epimer of **2**, was found in an unidentified *Acanthogorgia* species. It inhibited cell division of fertilized ascidian (*Styela partita*) eggs at 8 $\mu\text{g/mL}$ and displayed moderate toxicity in a brine shrimp lethality bioassay.^[96]

While all xeniolides discussed so far had C17 oxidized to the lactone carbonyl group, bioactive variants have also been isolated where the ester linkage in the lactone ring is located between C18 and the bridging oxygen atom (*i.e.* C18 is present in the carbonyl oxidation state). As can be seen from Fig. 9, these compounds are related to the xeniolide B (**31**) (Fig. 5), for which no biological data have been reported so far. An unrelated but important fact about xeniolide B (**31**) is its limited stability: “Even at -20° in the dark xeniolide B decomposes slightly already after 24 hours.”^[45] For none of the other B-type xeniolides similar descriptions can be found in the literature, but it may well be that biological effects described for these compounds are associated with this phenomenon. 9-Deoxyxeniolide E (**62**)^{VII} and its epoxide congener **63** were obtained from *Xenia umbellata*. Both xenicanes **62** and **63** exerted weak cytotoxic effects against A549 lung adenocarcinoma and HT-29 colon cancer cells (IC_{50} values between 10 and 20 $\mu\text{g/mL}$, except for **63** against HT-29 cells, where the IC_{50} has been reported to be 7.7 $\mu\text{g/mL}$); the antiproliferative activity was somewhat more pronounced against P-388 leukemia

^{VII} This name does not follow the *Vanderah* numbering system.

cells.^[99] Blumiolide B (**64**) was isolated from *Xenia blumi* and showed moderate antiproliferative activity against P-388 mouse and K562 human leukemia cells (single digit $\mu\text{g/mL}$ IC_{50} values).^[85] Finally, xeniolide G (**65**) from *Xenia umbellata* represents a peroxo version of **64** and showed strong antiproliferative activity against P-388 mouse leukemia cells (ED_{50} 0.04 $\mu\text{g/mL}$); the activity was significantly less pronounced against the solid tumor cell lines HT-29 (ED_{50} 8.31 $\mu\text{g/mL}$) and A549 (ED_{50} 4.77 $\mu\text{g/mL}$).^[99]

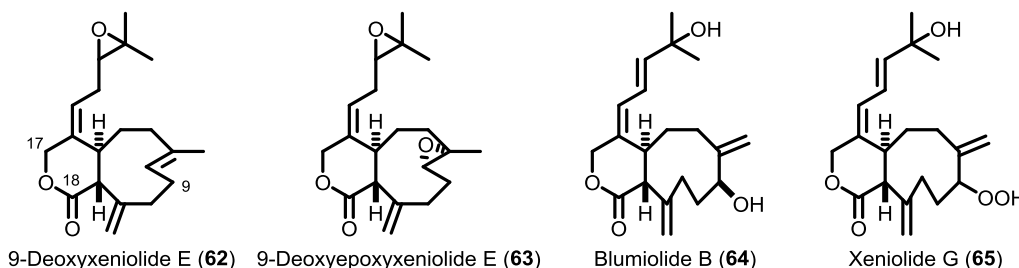


Fig. 9. Selection of xeniolide B-related bioactive natural products.

1.2.3.2 Xenicins

As outlined above, the xenicin sub-class of xenicane diterpenoids is distinct from the xeniolides by the presence of a pyranose moiety in place of a 6-membered lactone ring. In Fig. **10**, a selection of xenicin-type compounds is depicted that serves two distinct purposes: (1) illustrate the structural variations within the xenicin sub-class and (2) highlight some of the more potent compounds. Waixenicin A (**66**) has been found in a number of soft corals^[95,96,100–102] and strongly and selectively inhibited transient receptor potential melastatin 7 (TRPM7) channels. In addition, it showed antiproliferative effects in Jurkat T-cell lymphoma and RBL1 cells.^[101] The norxenicane ginamallene (**67**) was isolated from *Acanthogorgia* sp.^[94–96,103] and shows a range of biological activities: strong growth inhibitory activity against P388 mouse leukemia cells (IC_{50} 0.27 $\mu\text{g/mL}$),^[94] activity in a sea urchin egg assay,^[94] antifungal activity^[94] and ichthyotoxicity^[103]. Triacetate **68** has been isolated from *Asterospicularia laurae*; the compounds exhibited cytotoxicity on P388D1 mouse lymphoma cells with an IC_{50} value of 0.1 $\mu\text{g/mL}$.^[47,49] Asterolaurin A (**69**) is a highly oxidized diterpenoid from *Asterospicularia laurae*; the compound showed moderate antiproliferative activity against HepG2 human liver carcinoma cells (IC_{50} 8.9 μM).^[48] Desoxyhavannahine A (**70**) has been obtained from numerous sources^[104,105] and is one of the rare examples of a biochemically well-profiled xenicane.^[27,106,107] The compound was tested against a panel of 10 cancer cells lines and

showed strong antiproliferative activity against Col2 cells (ED_{50} 0.6 $\mu\text{g/mL}$), while antiproliferative activity was good to moderate against P-388, ZR-75-1, Lu1, Mel2, KB-V1, LNCaP tumor cells (ED_{50} values between 1 and 10 $\mu\text{g/mL}$).^[82]

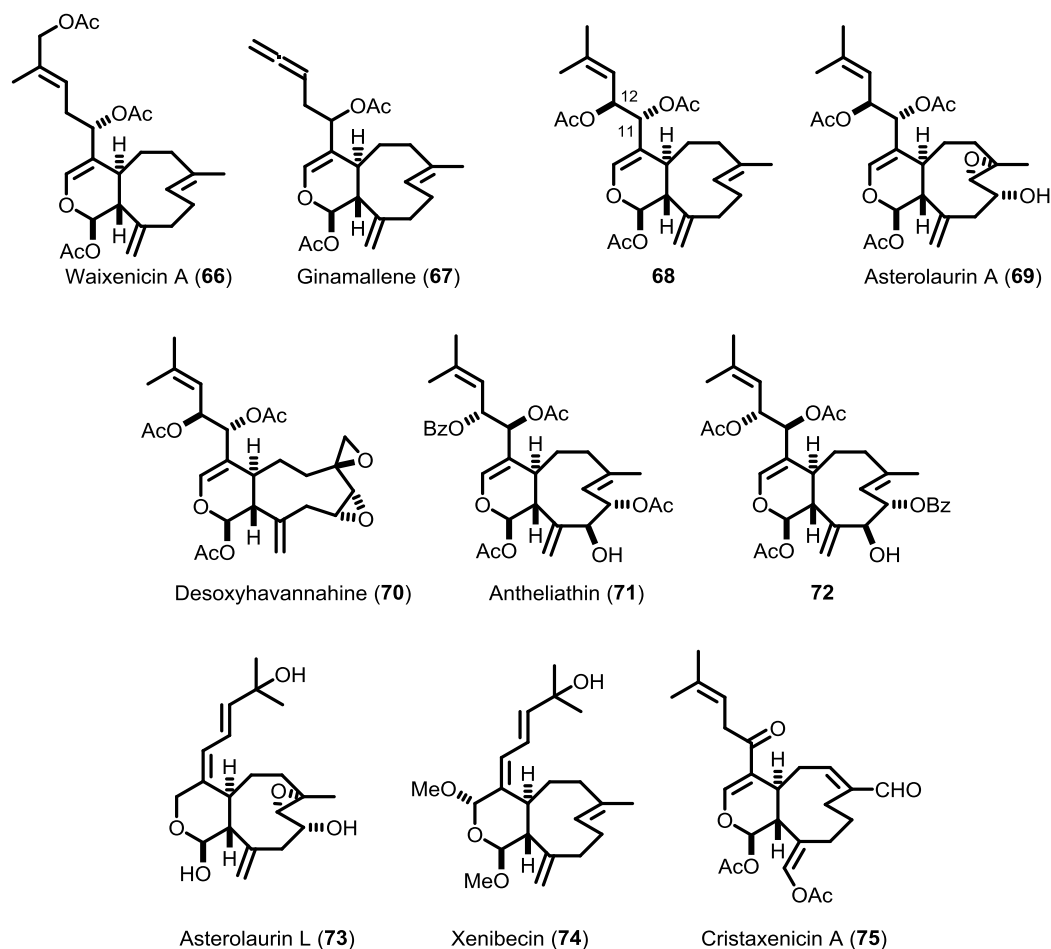


Fig. 10. C11-acetylated xenicin-type bioactive natural products.

Antheliatin (**71**), from *Anthelia glauca*, showed significant antiproliferative effects against P-388, A-549 and MEL-28 cells, with IC_{50} values close to 1 $\mu\text{g/mL}$; 10-fold higher potency was observed against HT-29 human colon carcinoma cells.^[53] Likewise, the corresponding constitutional isomer **72**, which was isolated from *Clavularia inflata* var. *luzoniana*, inhibited the growth of P-388 and HT-29 cells with IC_{50} values of 0.5 and 1.2 $\mu\text{g/mL}$, respectively.^[54] The closely related asterolaurin L (**73**) was found in a specimen of *Asterospicularia laurae*. Xenicane **73** displayed moderate antiproliferative effects against the cancer cells lines Hep-2, Daoy, MCF-7 and WiDr (single digit $\mu\text{g/mL}$ ED_{50} values).^[108] The bis-acetal xenibecin (**74**), which has been obtained from *Xenia umbellata*,^[99] is unlikely to be an isolation artifact, since no methanol was used during extraction and purification of the compound. It displayed moderate antiproliferative activity against P-388 mouse leukemia cells (ED_{50} 3.96 $\mu\text{g/mL}$); weaker effects

were found against the solid tumor cell lines HT-29 and A549.^[99] Cristaxenicin A (**75**), from *Acanthoprimnoa cristata*, is structurally unique among xenicins, with C11, C19 and C20 all being present at the carbonyl oxidation level. The compound possesses very strong antiprotozoal activity against *Leishmania amazonensis* and a slightly weaker effect on *Trypanosoma congolense*; in contrast, it showed only marginal antimalarial potency against *Plasmodium falciparum*.^[52,109] Xenicane **75** also inhibited the growth of P388 and HeLa cells with single digit μM IC_{50} values.^[52]

1.2.3.3 Other Xenicane Structures from Soft Corals

The compounds selected for this subsection (Fig. 11) serve to illustrate both structural variety and interesting biological activity. All these natural products were isolated from soft corals, but do not share the typical structural features that define xeniolides and xenicin-type structures. Xenitacin (**76**), from *Xenia umbellata*, inhibited the growth of P-388, HT-29, and A549 cells with single digit $\mu\text{g}/\text{mL}$ ED_{50} values.^[99] Bisepoxide **77** from *Xenia elongata* proved to be an inducer of apoptosis. Interestingly, the compound embodies the only xenicane effecting selective inhibition of HDAC6, albeit at very high concentrations.^[64] Novaxenicin B (**78**), from *Xenia novaebritanniae*, has been reported to induce apoptosis in transformed mammalian cells with $\mu\text{g}/\text{mL}$ potency.^[97] Structurally, **78** is closely related to **51**. Norxenicane xenibellal (**79**), which has been obtained from *Xenia umbellata*, exhibited moderate antiproliferative effects against P-388 cells.

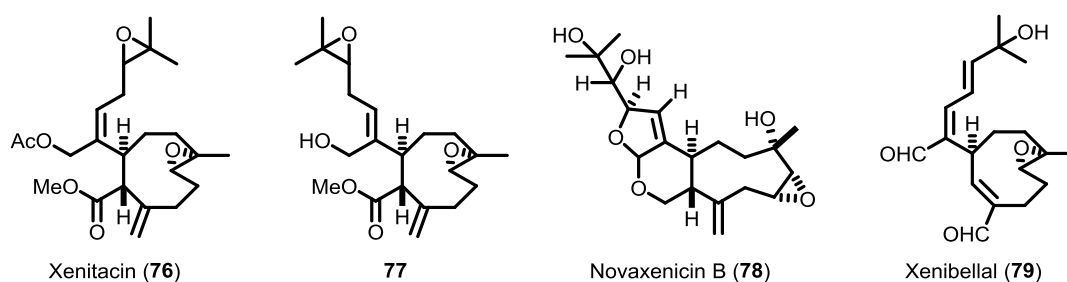


Fig. 11. Bioactive xenicanes lacking the C17-C18 oxa-bridge and the polycyclic novaxenicin B (**78**).

1.2.3.4 Xenicanes from *Phaeophyceae*

As highlighted earlier in this review, the absolute configuration of dictyodial (**4**) (Fig. 12), which so far has been isolated only from brown algae, is opposite to that of the soft coral metabolite

xenicin (**1**).^[110,111] Together with other data on the absolute configuration of xenicanes from soft corals and brown algae (*cf.* section 1.2.1), this finding suggests that xenicanes from brown algae are generally antipodal to their soft coral counterparts. For this reason, brown algae-derived xenicanes are treated here as a separate structural class (Fig. **12**).

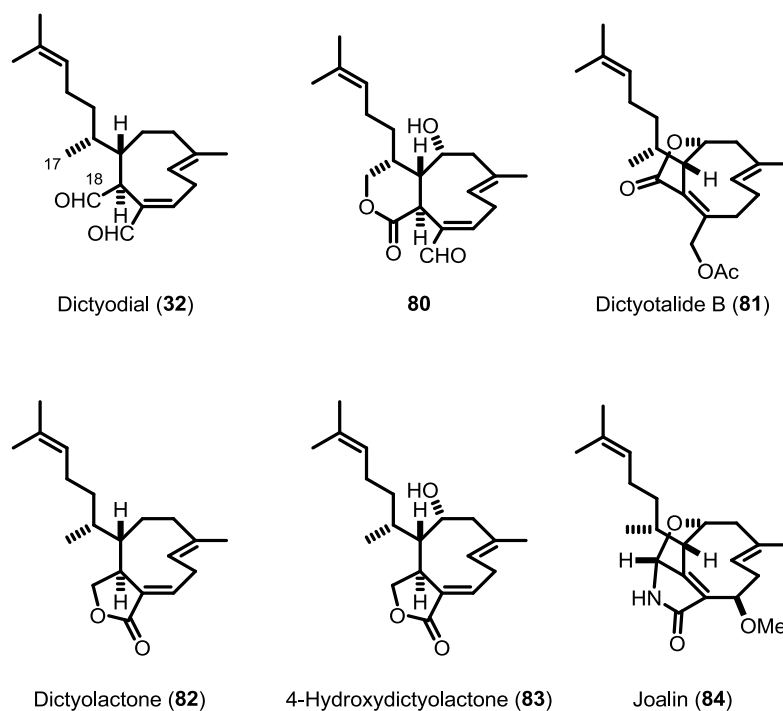


Fig. 12. Selected bioactive xenicanane diterpenoids from brown algae.

Dictyodial (**4**) was the first xenicanane of this series to be isolated^[46] and over time it has been reisolated from a variety of organisms.^[46,58,112–120] It is one of the most broadly profiled xenicanes and its biological effects include antibacterial and antifungal activity,^[46] moderate antiproliferative activity^[82] and inhibition of HIV-reverse transcriptase.^[112,116] The unnamed compound **80** from *Dictyota Divaricata* incorporates a xeniolide B-type lactone ring;^[121] however, the α,β -unsaturated aldehyde moiety as well as the C4 hydroxy group are features that are not usually present in the typical xeniolide B-type structures that originate from soft corals. Diterpenoid **80** was tested against a panel of 10 cancer cells lines and displayed moderate antiproliferative effects against P-388, KB, KB-V1, LNCaP, and ZR-75-1 cells.^[82] Dictyotalide B (**81**), from *Dictyota dichotoma*, inhibited the growth of B16 mouse melanoma cells with IC₅₀ values of 0.58 $\mu\text{g/mL}$ ^[122] and displayed weak activity against a number of other cancer cell lines.^[123] Dictyolactone (**82**) was first discovered in a sea hare, which is known to feed on algae of the genus *Dictyota*. Chemical correlation with **4** revealed the same absolute stereochemistry.^[46] Over time it was shown to display strong antifeeding properties,^[57]

algicidal effects,^[124] moderate effectiveness against a dinoflagellate^[124] and cytotoxic effects against P-388 and KB cells in the single digit $\mu\text{g/mL}$ range, while the IC_{50} value against the NSCLC cell line N6-L16 was $0.3 \mu\text{g/mL}$.^[123] 4-Hydroxydictyolactone (**83**) was first described as man-made^[125,126] and only later isolated as a genuine natural product from *Dictyota* sp.^[127] Very recently, the compound was determined to exhibit only weak antiproliferative effects against the cancer cell lines SF-268, MCF-7, H460, HT-29 and normal mammalian CHO-K cells.^[128] Fully synthetic **83** has been produced, but to date, no biological profiling of this material has been reported.^[129,130] The exceptional joalin (**84**), from *Dictyota* sp., epitomizes the only nitrogen-containing xenicane reported to date. The nitrogen atom is part of an amide group, but is also involved in a mixed *N,O*-acetal, with the acetal carbon being connected to an unusual bridgehead double bond. This compound has been reported to be mildly cytotoxic on the L1210 mouse leukemia cell line.^[131]

1.2.4 Conclusions

The xenicane diterpenoids constitute a diverse class of marine natural products with a range of biological activities and new members of this family continue to be isolated every year. At this point in time, however, only a minority of these compounds has been subjected to broader biological evaluation. So far, biological studies of xenicane diterpenoids have mostly been limited to the assessment of their *in vitro* antiproliferative effects against cancer cells. The biological effects that have been reported for in this area are mostly weak to moderate, but a number of compounds, such as **48**, **65**, **67**, **68**, **70**, and **81**, have also been shown to exert potent activity and, thus, may represent interesting biological probes or leads for drug discovery. However, even for these most promising cases, nothing is known about the molecular mechanism of action of the compounds.

Very little is known at this point about the chemical or the metabolic stability of xenicane diterpenoids. In some cases, the double bond in the cyclononene ring has been observed to react with atmospheric oxygen and spontaneously form the frequently observed epoxides.^[132] No studies have been reported on the metabolism of xenicanes either in rodent or in human systems (*e.g.*, plasma or liver microsomes). It is also important to note that a large number of xenicanes is equipped with potentially reactive structural elements. In particular, many xeniolides include an α,β -unsaturated lactone ring and may thus readily react with biological

nucleophiles (such as, *e.g.*, the SH groups of cysteines). While such reactive functionalities might be crucial for (a desired) biological activity, they could also be associated with non-specific effects as a potential source of toxicity in animals or humans. Overall, a significant amount of future research on the biochemical and cellular effects of xenicane diterpenoids is still required, in order to determine their potential as tools for chemical biology or as lead structures for drug discovery.

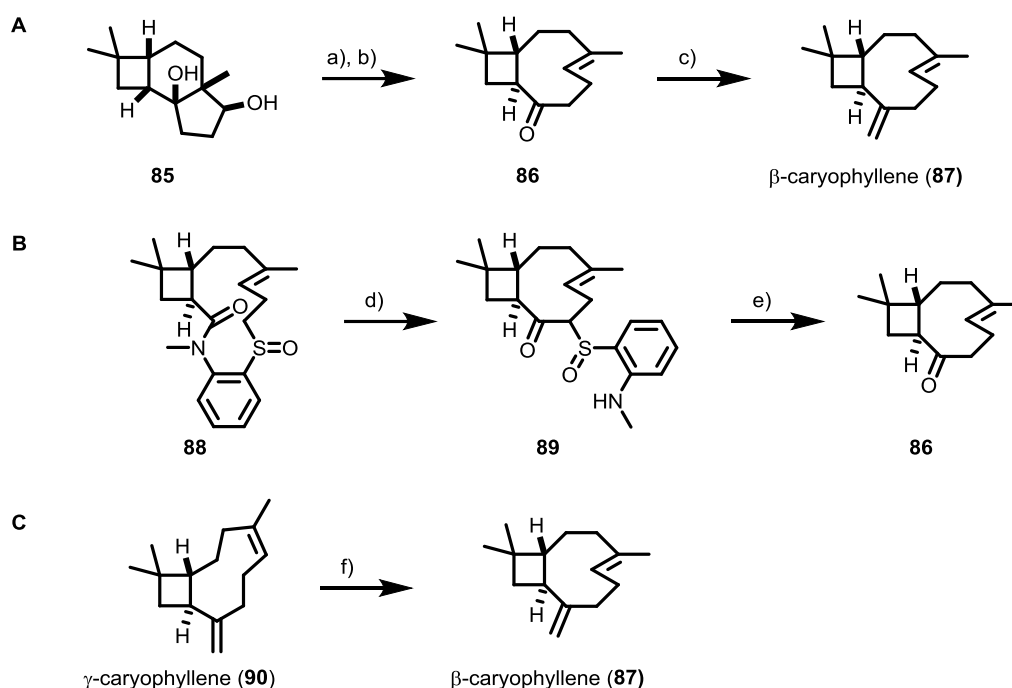
1.3 Relevant Synthetic Work^{VIII}

Long before the discovery of the first member of the xenicane family, the plant-derived caryophyllenes were identified.^[133] As a consequence, early synthetic work aimed at the construction of *Z*- and *E*-configured cyclononenes preceded the isolation of the first xenicanes by more than a decade. Some of this work showcases methods that might also be applicable for the synthesis of xenicanes and in some cases clearly has provided inspiration in the latter area (*vide infra*). Therefore, a very brief overview on key steps in the total synthesis of natural products featuring *E*-configured double bonds as part of a nine-membered carbocyclic ring (not limited to caryophyllene (**87**)) will be given. This is followed by an account of completed total syntheses of xenicane natural products. Finally, some studies related to xenicane synthesis that have not resulted in the total synthesis of a natural product are given for reference.

1.3.1 Synthetic Work on Non-Xenicane *E*-Cyclononenes

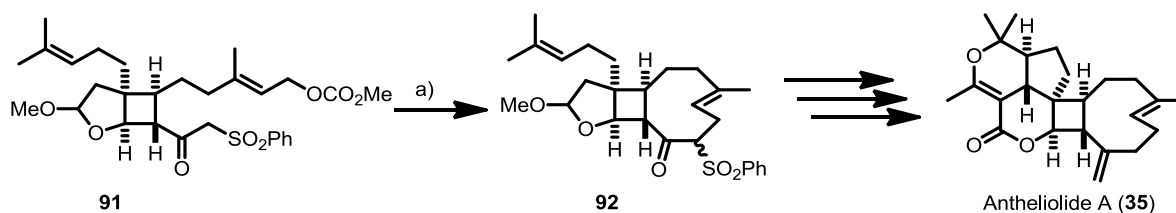
Corey *et al.* published the first total synthesis of β -caryophyllene (**87**) in 1963 (Scheme **4A**).^[134,135] Key to their success was a *Grob*-fragmentation of a secondary tosylate derived from tricyclic precursor **85**. A Wittig olefination of **86** gave the natural product (**87**). It needs to be highlighted that with the epimeric configuration at the secondary hydroxy group in **85**, the *Z*-cyclononene could be cleanly obtained, paving the way for the synthesis of γ -caryophyllene (**90**).

^{VIII} Magauer and coworkers have also reviewed the synthesis of caryophyllanes and xenicanes some related compounds.^[359]



Scheme 4: Selected steps in the total syntheses of caroyphyllene. Reagents and conditions: (a) TsCl (2 eq.), py, CH_2Cl_2 , 0 °C, 30 min, rt, 24 h, 93%; (b) NaH (7.3 eq.), *t*-BuOH, DMSO, 20 °C, 17 h, 100%; (c) Ph_3PCH_2 , DMSO, 100%; (d) LDA (10 eq.), HMPA, THF, -78 °C, 30 min, 0 °C, 30 min, 98% crude; (e) Na-amalgam, Na_2HPO_4 , MeOH, 0 °C, 30 min, Na-amalgam, 30 min, 70% (2 steps); (f) hv, rt, 65 h, 10%, 32% recovered SM.

Ohtsuka and coworkers chose a ring-contraction strategy (Scheme 4B) in their synthesis of β -caryophyllene (87).^[136] Compound 88 had the *E*-olefin geometry already in place. Deprotonation at the α -position of the sulfoxide moiety in the 13-membered lactam produced an anion that efficiently underwent intramolecular acylation. The resulting cyclononenone 89 was reductively desulfurized giving intermediate 86, which intercepted the *Corey* route.



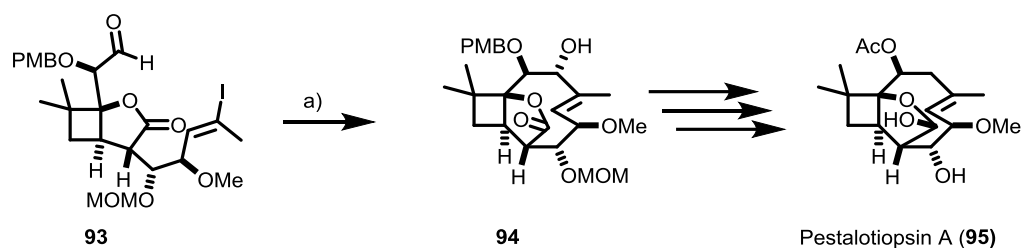
Scheme 5: Key step in *Corey*'s synthesis of antheliolide A (35). Reagents and conditions: (a) $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, dppb, DBU, THF, 55 °C, 2 h, 75%;

Suginome et al. opted for a total synthesis of γ -caryophyllene (90) and transformed the *Z*-cyclononene into the corresponding *E*-isomer (Scheme 4C).^[137] This was achieved by irradiation with a high pressure mercury arc in the presence of methyl benzoate as a sensitizer

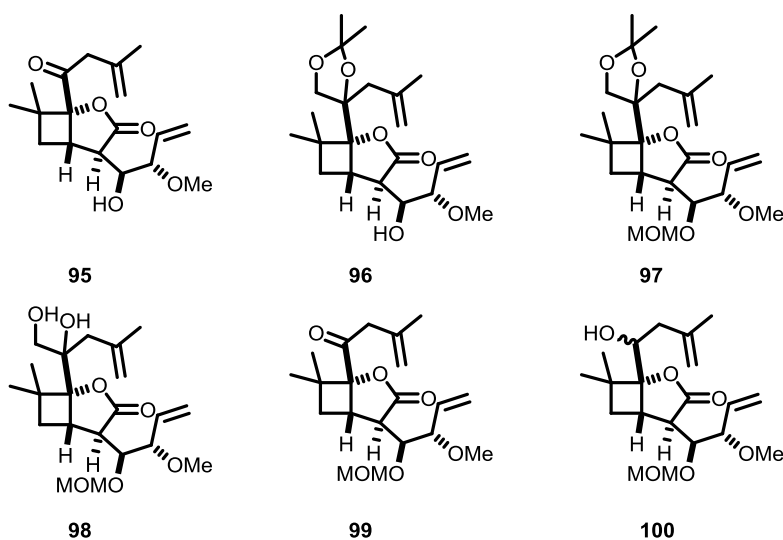
to photochemically isomerize the double bond. However, the yield of β -caryophyllene (**87**) was disappointingly low, as was the recovery of the starting γ -caryophyllene (**90**).

In *Corey's* total synthesis of the xeniaphyllane-congener antheliolide A (**35**), an intramolecular Pd-mediated allylation reaction of β -keto sulfone **91** was employed to form the 9-membered ring of **92** (Scheme 5).^[75] The product was obtained as a single double bond isomer.

In their total synthesis of pestalotiopsin A (**95**), *Tadano* and coworkers described the use of a *Nozaki-Hiyama-Kishi* reaction of iodide **93** as an enabling transformation (Scheme 6).^[138,139] The product **94** was obtained in good yield, but the reaction also produced a notable amount of the epimer at the newly generated allylic stereocenter.



Scheme 6: Key step in *Tadano's* synthesis of pestalotiopsin A. Reagents and conditions: (a) CrCl_2 (8.7 eq.), NiCl_2 (0.1 eq.), DMSO, 50 °C, 15.5 h, 73%, 14% epimer.



Scheme 7: Substrates that failed to undergo RCM in Paquette's studies towards ent-**95**.

Paquette et al. reported some findings of their studies towards the total synthesis of the unnatural enantiomer^{IX} of pestalotiopsin A (Scheme 7).^[140] Key transformation of their

^{IX} At the time, the absolute configuration of pestalotiopsin A was unknown. It was established via total synthesis by the group of *Tadano*.^[138]

synthetic plan was to be an RCM-reaction. However, none of the substrates prepared (**95-100**) could be coerced into undergoing the desired transformation.

1.3.2 Completed Total Syntheses of Xenicanes

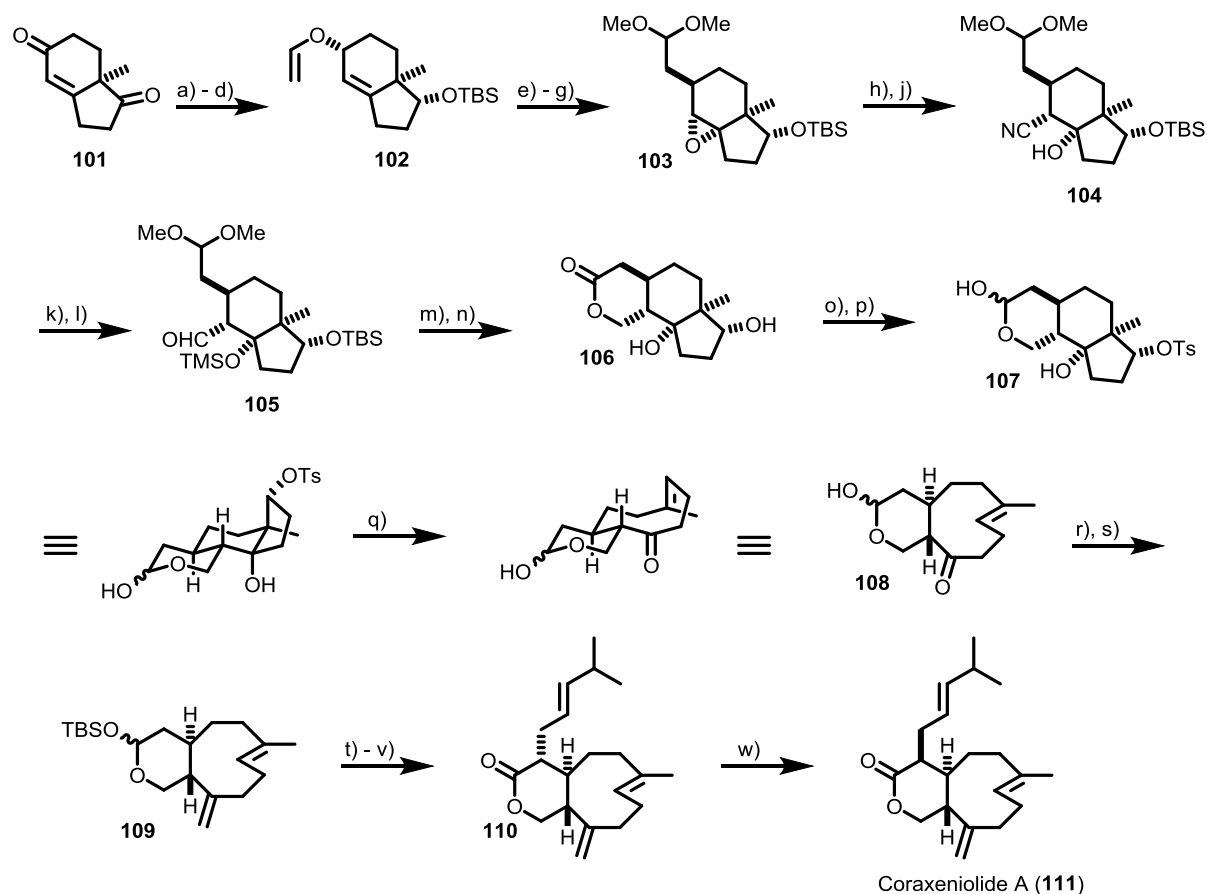
To date, coraxeniolide A (**111**), blumiolide C (**44**) and 4-hydroxydictyolactone (**83**) are the only xenicane diterpenoids for which successful total syntheses have been reported. These syntheses will be summarized in the following. Where appropriate, reference to related work will be given, but without thorough discussion. Regrettably, synthetic material has been subjected to biological reevaluation only in the case blumiolide C (**44**).

1.3.2.1 *Leumann and Pfander's Synthesis of Coraxeniolide A*

It took some 18 years from the first isolation of a xenicane family member in 1977^[44] until publication of the first synthetic studies towards this compound class. Only in 1995, *Pfander* reported the first synthesis of a bicyclic xenicane ring system, which could potentially serve as a basis for the synthesis of a number of xenicane terpenoids.^[141] Building on this initial work, *Leumann* and *Pfander* were indeed able to elaborate the total synthesis of coraxeniolide A in 2000 (Scheme **8**).^[80] Key to the success of the synthesis was a carefully implemented Grob fragmentation to install the 9-membered ring, while controlling the *E* geometry of the double bond. This strategy was inspired by *Corey's* elegant work on β -caryophyllene (Scheme **4A**, p.25).

The starting point for the synthesis of coraxeniolide A by *Leumann* and *Pfander's* group was the *Hajos-Parrish* diketone **101**^[142] that could be converted into allyl vinyl ether **102** in 55% overall yield in a four-step sequence involving chemo- and diastereoselective reduction of the non-conjugated keto functionality, TBS-protection of the ensuing alcohol, 1,2-reduction of the enone moiety, and mercury(II) acetate-mediated transesterification with ethylvinyl ether. Vinyl ether **102** underwent MgClO_4 -mediated diastereoselective [1,3] sigmatropic rearrangement to an aldehyde in excellent yield (83%); remarkably, no chromatographic purification was required up to this point in the synthesis. Conversion of the aldehyde into the corresponding dimethyl acetal followed by epoxidation of the double bond then led to a separable 11:1 mixture of epoxide diastereomers with the desired isomer **103** as the major

product in 65% overall yield from vinyl ether **102**. Regioselective epoxide opening in **103** with lithium cyanide in THF was followed by treatment of the ensuing cyanohydrin with ethanolic potassium hydroxide, which induced equilibration at the nitrile-bearing stereocenter through a reversible retro-aldol/aldol sequence to produce a separable mixture of the desired *exo* isomer **104** and *epi*-**104** in a 3:1 ratio. Following protection of the tertiary alcohol moiety as a TMS ether, reduction of the nitrile group furnished aldehyde **105** in 44% yield from **103**.



Scheme 8. *Leumann and Pfander's* total synthesis of coraxeniolide A. Reagents and conditions: (a) NaBH_4 , EtOH, 94%; (b) TBSCl, ImH, DMAP, CH_2Cl_2 , 82%; (c) LiAlH_4 , Et_2O , 90%; (d) $\text{C}_2\text{H}_5\text{OC}_2\text{H}_3$, $\text{Hg}(\text{OAc})_2$, 80%; (e) $\text{Mg}(\text{ClO}_4)_2$, CH_3NO_2 , 83%; (f) $\text{CH}(\text{OCH}_3)_3$, montmorillonite clay K-10, Et_2O , 98%; (g) *m*-CPBA, CH_2Cl_2 , 80%; (h) LiCN, THF, 84%; (j) KOH, EtOH, 69%; (k) TMSCl, ImH, DMAP, CH_2Cl_2 , 99%; (l) DIBAL-H, hexane 76%; (m) NaBH_4 , EtOH, 89%; (n) (i) HCl, THF; (ii) Ag_2CO_3 on Celite, benzene; 61% (2 steps); (o) TsCl, pyridine, CHCl_3 , 92%; (p) DIBAL-H, CH_2Cl_2 , 98%; (q) NaH, DMSO, 88%; (r) TBSCl, ImH, CH_2Cl_2 , 98%; (s) $\text{TiCp}_2\text{-CH}_2\text{ClAlMe}_3$, THF, py, 70%; (t) TBAF, THF, 85%; (u) Ag_2CO_3 on Celite, benzene, 89%; (v) LDA, 1-bromo-4-methylpent-2-ene, THF, DMPU, 42% **110**, 7% **111**; (w) TBD, MePh, 60% **111**, 20% **110** recovered.

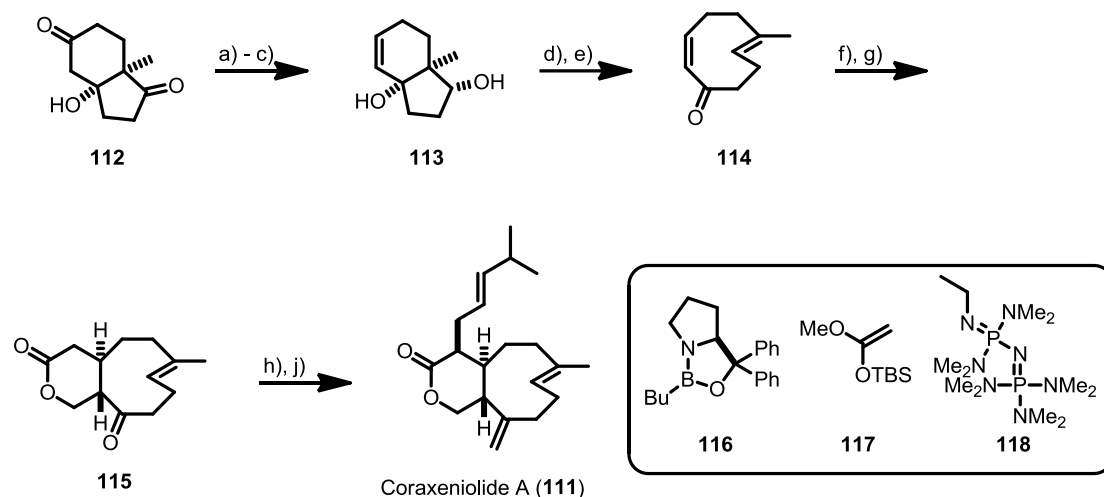
Reduction of **105** with sodium borohydride followed by treatment of the resulting alcohol with aqueous HCl in THF, which resulted in the cleavage of all protecting groups, gave a lactol that was directly oxidized to lactone **106** with *Fétizon's* reagent. Selective tosylation of the secondary hydroxy group and re-reduction of the lactone ring to a lactol then provided sulfonate **107** as the substrate for the crucial *Grob* fragmentation^x. In the event, treatment of **107** with sodium hydride in dimethyl sulfoxide cleanly delivered the desired 9-membered ketone **108** in 88% yield. The conversion of the C1 keto group in **108** into the required alkene moiety could be achieved by *Tebbe* olefination, but only after prior protection of the lactol as a TBS-ether (to give **109**). The olefination reaction was not possible at the lactone oxidation level and gave very poor yields when the lactol was protected as a methyl acetal. Removal of the TBS-group with tetrabutylammonium fluoride and subsequent *Fétizon* oxidation delivered the complete bicyclic core structure of the target molecule. Finally, the installation of the side chain involved deprotonation of the α -position of the lactone ring with lithium diisopropylamide and alkylation with 1-bromo-4-methylpent-2-ene. While the reaction as such proceeded cleanly, the stereoselectivity in the alkylation step, unfortunately, was biased towards the undesired *anti*-isomer **110** (crude *dr* = 5.7:1), which led to the isolation of pure **111** in only 7% yield, together with 42% of (pure) **110**. In addition, **110** could be epimerized with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) to provide a 3:1 mixture of coraxeniolide A (**111**) and **110**; separation of the mixture gave 60% of pure **111** (based on the starting epimer **110**).

1.3.2.2 Corey's Total Synthesis of Coraxeniolide A

In 2008, *Corey* and *Larionov*^[143] reported an extension of the group's previous work on caryophyllenes.^[134,135] Similar to *Leumann* and *Pfander's* approach, *Corey* and *Larionov* exploited diketone **112** (Scheme 9) as the source of chirality;^[142] diketone **112** was regio- and stereoselectively reduced to the corresponding cyclohexanol, which was then further transformed into diol **113** by dehydration under *Mitsunobu* conditions. Trimethylsilyl protection of the tertiary hydroxy group, stereoselective *CBS*-reduction of the carbonyl group with catalyst **116** and removal of the TMS group with Et₃N·3HF afforded diol **113** in 31% overall

^x The *Grob*-fragmentation could also be realized with the tosylated lactone or the methyl-protected lactol. Attempts to cleave the methyl acetal after successful olefination of the ketone resulted in transannular cyclization as it is found, e.g., in **39** and **40** (cf. Fig. 3).

yield from diketone **112**. Tosylation and *Grob* fragmentation cleanly delivered optically active cyclononadienone **114**. Notably, the chirality of the precursor is transferred into conformational chirality, which is retained at temperatures below 23 °C.



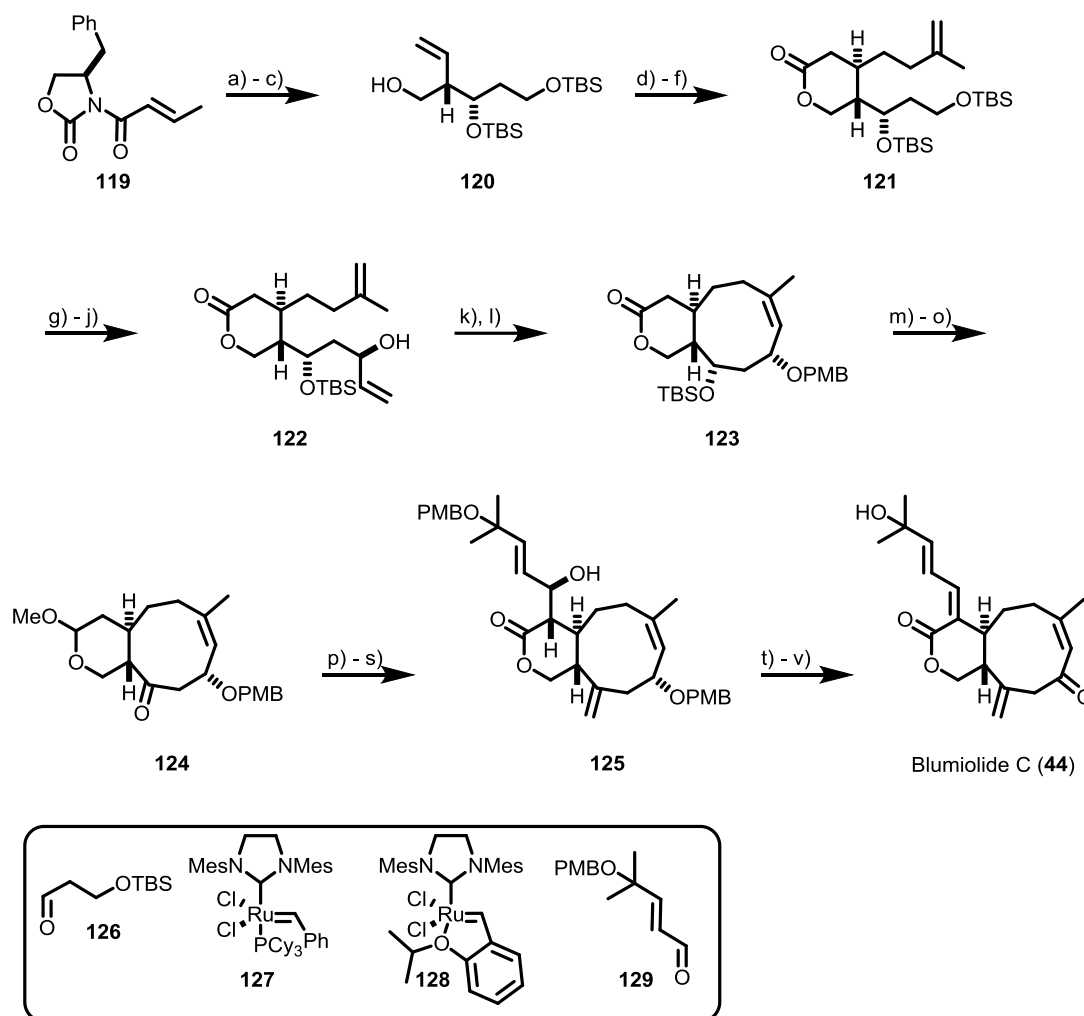
Scheme 9. Corey's total synthesis of coraxeniolide A. Reagents and conditions: (a) NaBH₄, AcOH, 86%; (b) (i) DEAD, PPh₃, THF; (ii) TMS-ImH, THF, TBAF, 61%; (c) (i) **116**, BH₃·Me₂S, THF; (ii) Et₃N·3HF, THF, 60% (2 steps); (d) TsCl, py, 75%; (e) NaH, DMF, 93%; (f) Ph₃CClO₄, **117**, (ClCH₂)₂, 64%; (g) NaOtC₅H₁₁, THF, CH₂O, 59%; (h) PPh₃CH₂, THF, 61%; (j) (i) LiHMDS, THF, 1-iodo-4-methylpent-2-ene; (ii) **118**, PhMe, 62% (2 steps, *dr* 4:1).

Trityl perchlorate-mediated *Michael* addition of silyl ketene acetal **117** to **114** installed the β-stereogenic center of the ensuing ester. Careful site-selective deprotonation of the addition product (NaOtC₅H₁₁, -60 °C to -30 °C, 5h) followed by reaction with formaldehyde gave a hydroxymethylated intermediate which spontaneously cyclized to lactone **115**. The latter was obtained in 38% yield from **114**. The olefination problems encountered by *Leumann* and *Pfander* were circumvented by the use of a salt free phosphorane to establish the xenicane core. Deprotonation with lithium hexamethyldisilazide and reaction of the ester enolate with 1-iodo-4-methylpent-2-ene produced a 1:6 mixture of epimeric alkylation products with coraxeniolide A (**111**) as the minor isomer. However, this mixture, after removal of unreacted starting material, could be equilibrated with the *Schwesinger* phosphazene P2-Et (**118**) as a base providing a 4:1 mixture of isomers in favor of **111**. The latter was finally obtained in 50% yield (62% yield based on recovered starting material). To this day *Corey's* innovative approach to a complete xenicane bicycle remains unrivaled in elegance. A similar approach to a chiral bicycle by *Williams* did not culminate in the synthesis of a natural product, but is mentioned here for completeness.^[144–146] Also, in a thesis by *Carr* from the University of Alabama studies

on a Grob-Fragmentation for the synthesis of xenicanes are described. However, they did not bear fruit.^[147]

1.3.2.3 Altmann's Total Synthesis of Blumiolide C

Altmann's synthesis of blumiolide C (Scheme 10)^[87] started with an *Evans* aldol addition of benzyloxazolidinone **119** to TBS-protected 3-hydroxypropanal **126**. The resulting homoallylic alcohol functionality was masked as a TBS-ether and reductive removal of the auxiliary with lithium borohydride gave **120** in 68% from **119**. A sequence of esterification of **120** with acryloyl chloride, ring-closing metathesis (RCM) with *Grubbs* 2nd generation catalyst (**127**), and CuI-mediated 1,4-addition of isopentenyl magnesium bromide to the resulting α,β -unsaturated lactone cleanly provided **121** with complete *anti* stereoselectivity and 62% yield for the three-step sequence from **120**. Cleavage of the primary TBS-ether followed by *Swern* oxidation gave an aldehyde that was reacted with a mixture of ZnCl₂ and vinylmagnesium chloride to produce allylic alcohol **122** as an inconsequential 5:1 mixture of diastereoisomers. Omitting the zinc additive, the addition suffered from low yields and side product formation. The free hydroxy group was protected as a *para*-methoxybenzyl ether under acidic conditions and RCM catalyzed by *Hoveyda-Grubbs* 2nd generation catalyst (**128**) under high dilution conditions gave the desired bicycle **123** in a very acceptable yield of 66%. PMB-protection turned out to be crucial for successful ring-closure and the *Z* configured olefin was observed exclusively. Reduction of the lactone moiety and transformation of the resulting lactol to the corresponding methyl acetal, removal of the TBS-group and oxidation then led to ketone **124**. Addition of a methyl *Grignard* reagent and dehydration of the ensuing tertiary alcohol with *Martin's* sulfurane installed the *exo* double bond; this was followed by hydrolysis of the methyl acetal and subsequent *Ley* oxidation, thus re-establishing the lactone moiety. Aldol addition of the corresponding lithium enolate to enal **129** produced **125**, which contains the fully elaborated carbon skeleton of the target structure (50% yield). The stereoselective dehydration of **125** required extensive experimentation, but was eventually achieved by the combined use of DCC and CuCl₂. Removal of the two protecting groups and *Dess-Martin* oxidation of the secondary alcohol finally completed the total synthesis of blumiolide C (**44**).

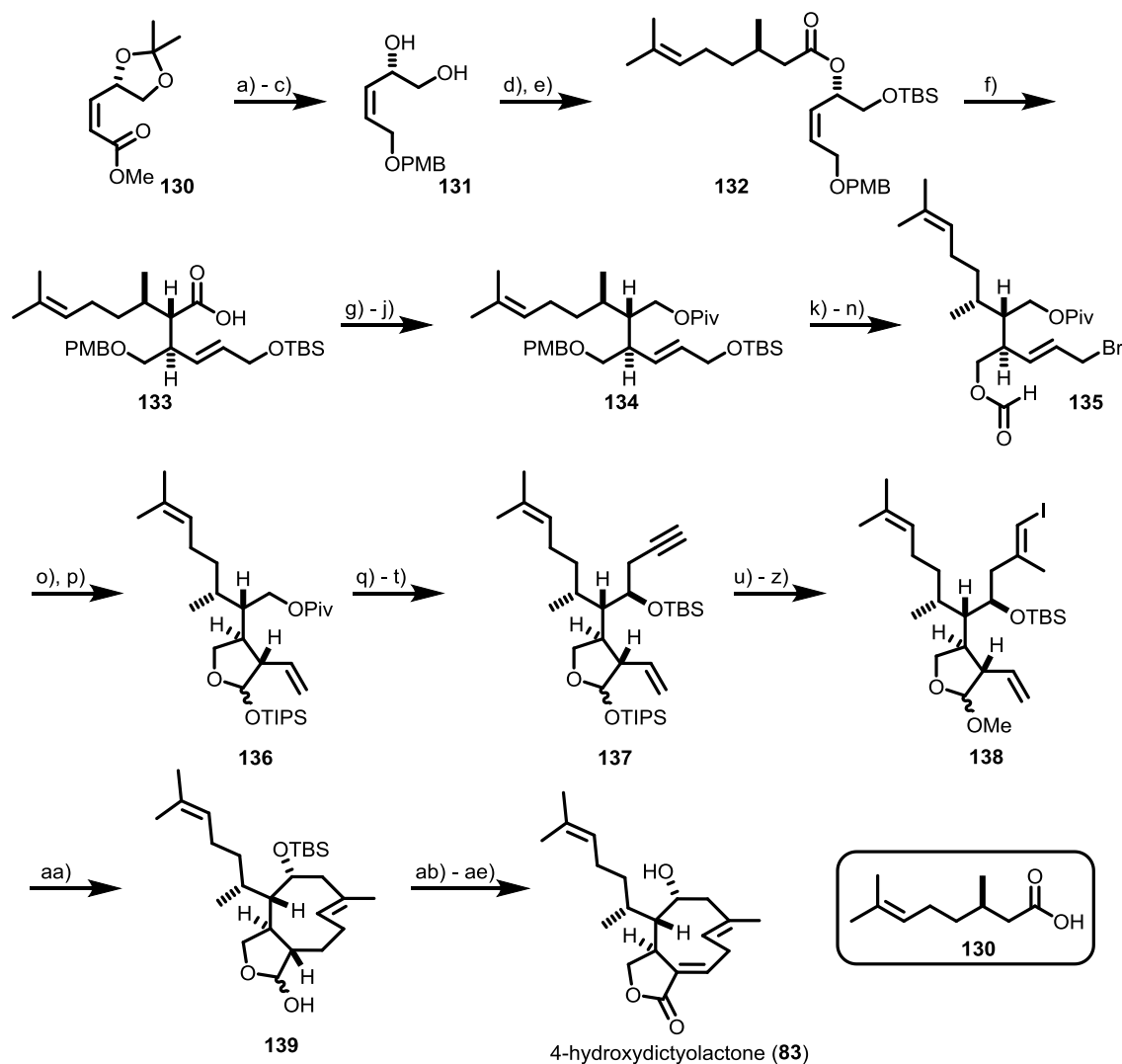


Scheme 10. Altmann's total synthesis of blumiolide C. Reagents and conditions: (a) Bu_2BOTf , Et_3N , **126**, CH_2Cl_2 , 95%; (b) TBSOTf , 2,6-lutidine, CH_2Cl_2 , 93%; (c) LiBH_4 , MeOH (1 eq.), Et_2O , 77%; (d) $\text{CH}_2=\text{CHC}(\text{O})\text{Cl}$, Et_3N , DMAP, CH_2Cl_2 , 75%; (e) **127**, CH_2Cl_2 , 92%; (f) $\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{MgI}$, CuI , Et_2O , 90%; (g) CSA, $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (1:1), 90%; (h) DMSO , $(\text{COCl})_2$, Et_3N , 93%; (j) $\text{CH}_2=\text{CHMgCl}$, ZnCl_2 , THF, 62% (*dr* 5:1); (k) $\text{PMBOC}(\text{=NH})\text{CCl}_3$, cyclohexane, PPTS (3 mol%), 68%; (l) **128**, PhMe , 66%; (m) (i) DIBAL-H , CH_2Cl_2 , (ii) MeOH , PPTS (5 mol%), 73% (two steps, *dr* 1:1); (n) TBAF (2 eq.), THF, 90%; (o) TPAP, NMO, 4 Å MS, CH_2Cl_2 , 80%; (p) MeMgBr , Et_2O , 75%; (q) Martin's sulfurane, CH_2Cl_2 , 86%; (r) (i) 48% aq. HF, MeCN/THF (5:1), (ii) TPAP, NMO, 4 Å MS, CH_2Cl_2 , 73% (two steps); (s) LDA (3 eq.), THF, then **129**, 50%; (t) neat DCC, CuCl_2 , 90%; (u) DDQ, $\text{CH}_2\text{Cl}_2/\text{phosphate buffer}$ (20:1), 68%; (v) DMP, CH_2Cl_2 , 85%.

1.3.2.4 Williams' Total Synthesis of 4-Hydroxydictyolactone

As shown in Scheme 11, Williams' synthesis of 4-hydroxydictyolactone (**83**)^[129,130] started from known enoate **130**, which is accessible in three steps from (D)-mannitol. A sequence of 1,2-

reduction, PMB-protection of the ensuing alcohol and cleavage of the acetonide moiety delivered mono-protected triol **131** in 95% yield.



Scheme 11. Williams' total synthesis of 4-hydroxydictyolactone. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2 , 98%; (b) PMBCl, NaH, DMF, 97%; (c) 1M HCl, MeOH, 100%; (d) TBSCl, ImH, CH_2Cl_2 , 92%; (e) **150**, EDCI, DMAP, CH_2Cl_2 , 97%; (f) TMSCl, Et_3N , -78°C , then LDA, -78°C , then reflux, 85%, *dr* 94:6; (g) MeI, K_2CO_3 , DMF, 97%; (h) DIBAL-H, CH_2Cl_2 , 100%; (j) PivCl, pyridine, CH_2Cl_2 , 95%; (k) DDQ, pH 7.0 buffer, CH_2Cl_2 , 76%; (l) formic acid, EDCI, DMAP, CH_2Cl_2 , 96%; (m) $\text{Bu}_4\text{N}^+ \text{Ph}_3\text{SiF}_2^-$, AcOH, THF, 99%; (n) CBr_4 , PPh_3 , CH_2Cl_2 ; (o) CrCl_2 , THF, 92% (two steps), *dr* > 95:5 at C19; (p) TIPSOTf, 2,6-lutidine, CH_2Cl_2 , 0°C , 90% (q) DIBAL-H, CH_2Cl_2 , 96%; (r) TPAP, NMO, 4 Å MS, CH_2Cl_2 , 99%; (s) propargyl bromide, Mg^0 , HgCl_2 , Et_2O , -20°C , 96% (t) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 94%; (u) $\text{Me}_3\text{SiSnBu}_3$, $\text{Pd}(\text{PPh}_3)_4$, THF, 85%; (v) I_2 , 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2 , 93%; (w) MeLi, CuI, THF, 98%; (x) NIS, MeCN, 82% (y) TBAF, THF, 95%; (z) PPTS, MeOH, 99%; (aa) (i) 9-BBN (1.5 equiv), THF, (ii) $\text{Pd}(\text{PPh}_3)_4$ (0.5 equiv), NaOH (5.0 equiv), MeCN/ H_2O (15:1), [0.005 M], 85°C , (iii) aq. AcOH, THF, 66% (ab) TPAP, NMO, 4 Å MS, CH_2Cl_2 , 79% (ac) TBAF, THF, 83%; (ad) (i) LDA, THF, (ii) PhSeBr; (ae) (i) *m*-CPBA, CH_2Cl_2 , -78°C , (ii) Et_3N , 55% (two steps).

The primary hydroxy group was protected as a TBS-ether and esterification of the secondary hydroxy group with (*R*)-citronellic acid **140** furnished allylic ester **132**. The latter served as substrate for an *Ireland-Claisen* rearrangement to produce **133**. Using carefully chosen conditions, the rearranged carboxylic acid was obtained in 85% yield and in a diastereomeric ratio of 94:6. The newly formed carboxyl group was then methylated, the ester moiety was reduced to the alcohol level and the hydroxy group masked as a pivalate **134**. Oxidative removal of the PMB-group gave an alcohol that was converted into a formate ester, followed by cleavage of the TBS-ether and transformation of the resulting alcohol into the corresponding bromide **135**. Intramolecular *Nozaki-Hiyama-Kishi* allylation with **135** and TIPS-protection furnished the 5-membered cyclic acetal **136** as a 9:1 mixture of anomers (83% from the free alcohol); importantly, the crucial tertiary stereocenter could be generated with complete selectivity. After reductive cleavage of the pivalate ester and *Ley* oxidation, the resulting aldehyde was reacted with allenylmagnesium bromide assisted by mercury dichloride to produce a homopropargylic alcohol with a *dr* of 84:16 and in excellent yield of 96%. The newly generated alcohol functionality was protected as a TBS-ether to furnish **137**. The terminal triple bond was then transformed into the *E*-configured vinyl iodide functionality in a four-step sequence of palladium-catalyzed *syn*-stannylsilylation followed by tin-iodide exchange, reaction with a methyl cuprate and a silicon-iodine exchange. The overall yield was 64% and the longer sequence was necessary, because the classical Negishi carboalumination protocol selectively funneled all the starting material into a synthetic dead end. The TIPS-ether was cleaved and the hydroxy group was re-protected as a less bulky methyl acetal (**138**). This enabled successful hydroboration of the terminal double bond with 9-BBN and intramolecular *Suzuki*-coupling with Pd(PPh₃)₄ (instead of the more common Pd(dppf)Cl₂ catalyst) to close the 9-membered ring; only the desired *E*-cyclononene was formed in the reaction. Subsequent hydrolysis of the methyl acetal produced lactol **139** in 66% yield (2 steps) after extensive experimentation. The latter was transformed into the corresponding lactone by *Ley* oxidation. Finally, TBS-cleavage followed by α -phenylselenylation, oxidation and elimination furnished 4-hydroxydictyolactone (**83**).

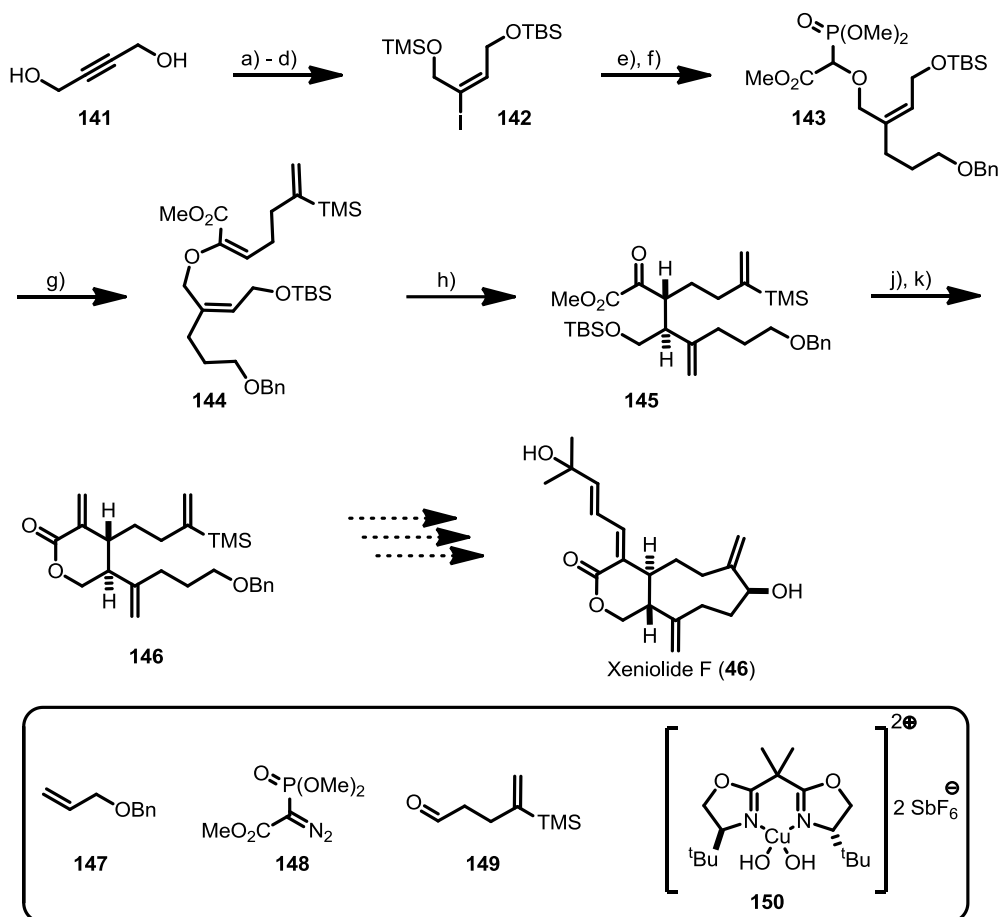
1.3.3 Other Work Related to Xenicane Synthesis

The following section will provide an overview on some other studies in the context of xenicane synthesis. Apart from the two reports by the group of *Hiersemann*, this information has not found its way into the peer-reviewed literature.

1.3.3.1 *Hiersemann's Approach Towards Xeniolide F*

Hiersemann and *Pollex*^[148] reported an approach to an advanced synthetic intermediate in a projected synthesis of xeniolide F (**46**), which is centered on metal-catalyzed enantioselective transformations to establish the stereochemistry at the C2 and C3 bridgehead carbons of the bicyclic xeniolide core structure (Scheme 6). The synthesis started from but-2-ynediol **141** which was subjected to palladium-mediated *syn* hydrostannylation followed by selective protection of the sterically less encumbered hydroxyl group as a TBS-ether. Iodine-tin exchange delivered an allylic alcohol in 74% over 3 steps; TMS-protection of the second hydroxy group then gave vinyl iodide **142**. *Suzuki* cross-coupling of crude **142** with the boronate derived from allyl benzyl ether **147**, followed by removal of the TMS group, and clean rhodium-catalyzed OH-insertion of a carbene generated from trimethyl diazophosphonoacetate **148** then led to phosphonate **143**. *Horner-Wadsworth-Emmons* olefination with aldehyde **149** produced allyl vinyl ether (**144**) in 87% yield with an *E/Z* ratio of 9:1 at the newly formed double bond. Intermediate **144** underwent a catalytic *Claisen* rearrangement in the presence of the copper bisoxazoline complex **150**, which installed the two vicinal stereogenic centers of **145** in 64% yield with an enantiomeric excess > 99 % and a diastereomeric ratio > 19:1. It is of note that the absolute configuration of **145** is opposite to that of the natural product, but both enantiomers of the catalyst are available.^{XI} Reaction with methylenetriphenylphosphorane and subsequent acid-catalyzed lactonization gave advanced intermediate **146**. The α,β -unsaturated lactone ring was found to be incompatible with the desired transformation of the vinylsilane into an iodide. These problems could not be resolved^[149] and no direct follow-up publication to this work has appeared.

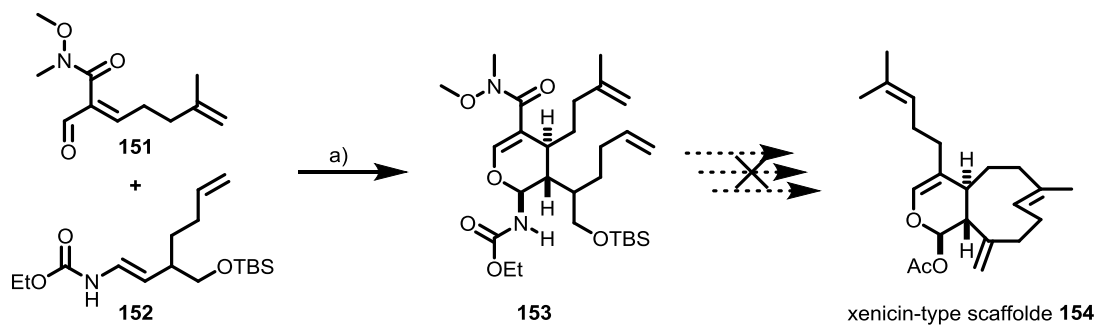
^{XI} The enantiomer of the ligand in depicted for **150** is the cheaper one by a factor of 3.5. Source: <http://www.tcichemicals.com> (accessed June 8th 2016).



Scheme 12. Hiersemann's approach towards the synthesis of xeniolide F. Reagents and conditions: (a) Bu_3SnH , $(\text{PPh}_3)_2\text{PdCl}_2$, THF, 87%, (b) TBSCl, ImH, THF, 88%, (c) I_2 , CH_2Cl_2 , 97%, (d) TMSCl, Et_3N , CH_2Cl_2 , (e) (i) **147**, 9-BBN, THF (ii) **142**, (dppf) PdCl_2 , NaOH, PhMe, H_2O , (iii) K_2CO_3 , MeOH, 60% (4 steps) (f) **148**, $\text{Rh}(\text{OAc})_4$, $(\text{ClCH}_2)_2$, 62%, (g) (i) LDA, THF, (ii) **149**, 87%; (h) **150**, 4 Å MS, CH_2Cl_2 , 64%, *de* > 90%, *ee* > 99%, (j) PPh_3CH_2 , THF, 68%; (k) HF·pyridine, THF, 77%.

1.3.3.2 Funk's Studies Towards Xenicins

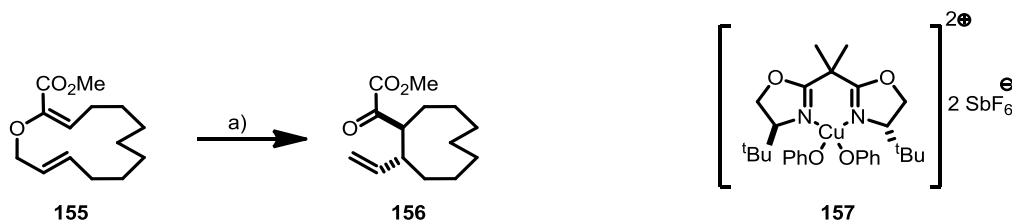
Funk and Aungst Jr. have reported in a thesis on a hetero-Diels-Alder approach to xenicin-type scaffolds **154** (Scheme 13).^[150] Under high-pressure, α,β -unsaturated aldehyde **151** underwent cycloaddition with ene-carbamate **152** to produce the protected aminal **153** in good yield. However, all attempts to functionalize **153** and related structures exclusively led to decomposition.



Scheme 13: Hetero-*Diels-Alder* approach to xenicin type oxo-cyclohexenes. Reagents and conditions: (a) CH_2Cl_2 , rt, 12 kbar, 2 d, 73%, *dr* 2.3:1.

1.3.3.3 Hiersemann's Model Studies Towards Xeniolide F

Hiersemann and Jaschinski have reported on a model study also directed at the synthesis of xeniolide F (**46**), with a slightly changed strategy:^[151] Instead of closing the nonacycle after installation of the stereogenic centers (*cf.* Scheme **12**), the precursor for a transannular *Claisen* rearrangement was a 13-membered ring (**155**) that was contracted to a 9-membered ring product (**156**).



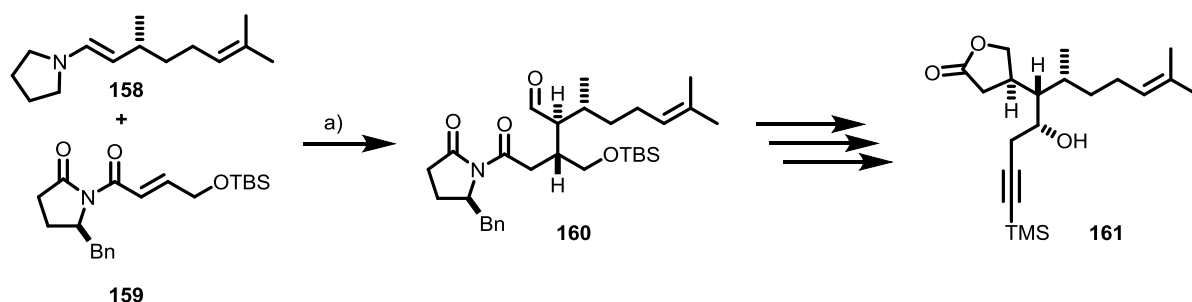
Scheme 14: Ring-contraction approach to cyclononanes. Reagents and conditions: (a) **157**, 4 Å MS, $(\text{CH}_2\text{Cl})_2$, 87%, *dr* 83:17, *ee* > 98%.

This process is catalyzed by Cu-complex **157**, which provides both excellent yields and enantioselectivity, and good diastereoselectivity. Nonetheless, the substrates described in this later work do not bear functionality that would make them amenable for the subsequent elaboration into a xenicane-type natural product.

1.3.3.4 Christmann's Studies Towards 4-Hydroxydictyolactone

Christmann and Könning have reported in a thesis on studies towards 4-hydroxydictyolactone (**83**).^[152] For the overall disconnections, they were building on the impressive groundwork by

Williams. A stereoselective Michael addition (Scheme 15) of an enamine **158**^{xii} to chiral α,β -unsaturated imide building block **159** installed two of the final 4 stereogenic centers with excellent yield and selectivity. Intermediate **160** was taken 3 steps further to intermediate **161**, the last intermediate described. The development of a new oxidation methodology^[153,154] for the 4-step synthesis of **159** merits to be highlighted, as does the brevity and efficiency with 9 steps to **161** with an overall yield of 11%.



Scheme 15: Michael-addition approach to dictyota xenicanes. Reagents and conditions: (a) $\text{Ti}(\text{OiPr})_3\text{Cl}$, auxiliary **159**, CH_2Cl_2 /hexanes 1:2, 0 °C, 5 min, enamine **158**, CH_2Cl_2 , 0 °C, 5 h, 91% (*dr* 95:5).

1.3.4 Conclusions

A more detailed exploration of xenicanane diterpenoids at the biochemical and cellular level in undoubtedly requires efficient synthetic access to these structures. From a synthetic point of view, the sub-class that poses the greatest challenge are the xenicins, owing to both the presence of an unsaturated pyranoside moiety as well as the very diverse oxidation patterns. Other than the studies of *Funk*, no work on xenicin-type structures has been reported. The seminal work of *Pfander* and *Leumann* broke ground for the synthesis of xeniolide natural products. Their results provided valuable information about possible side reactions and incompatibilities of the *E*-cyclononene scaffold, but also revealed the undesired stereoselectivity during late-stage side chain introduction. *Corey*'s work on coraxeniolide A (**111**) represents a hallmark of creativity and brevity in accessing xeniolide-type structures. However, the synthesis of more highly oxidized or scaffold-modified congeners *via* the *Corey* route would still appear to be difficult. Also, the problem of efficient and stereoselective introduction of the side chain still remained unsolved in the *Corey* synthesis. Altmann showcased the first successful closure of a xenicanane cyclononene in good yield and with

^{xii} **82** was derived from (*R*)-(+)-citronellal.

complete Z-selectivity during the total synthesis of blumiolide C (**44**). This is remarkable by itself, when also considering the complete inertness of all substrates **95-100** that were subjected to metathesis conditions in *Paquette's* studies towards *ent*-pestalotiopsin A, it highlights the powerful influence of substrate on the outcome of such an RCM. In principle, *Williams'* approach to 4-hydroxydictyolactone, could provide a useful platform also for the synthesis of a variety of related natural products, but the approach suffers from a high step count. *Christmann* has reported some promising work to improve on these shortcomings. However, no follow-up on the thesis work of *Könning* is available. With regard to step efficiency, also *Hiersemann's* methodology seems promising, but this work still awaits completion. In summary, the synthesis of highly strained xenicane diterpenoids with their diverse arrays of reactive functionalities still remains a formidable challenge and scalable and efficient approaches for their synthesis still need to be developed.

2 Aims and Scope

“Confidence is the feeling you have before you fully understand the situation.”

Gerhard Müller, Closing Remarks, Swiss Course on Medicinal Chemistry, 2014

The principal goal of this PhD thesis was to develop a unifying approach for the synthesis of xeniolide A-type structures. Target molecules were the two natural products isoxeniolide A (**1**) and acalcixeniolide F (**2**) (Fig. 13).

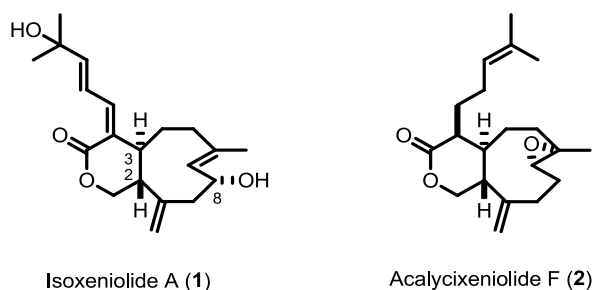


Fig. 13: The two main target-molecules of this work.

With exception of *Altmann's* work,^[87] which paved the way towards the synthesis of the rare Z-cyclononenes, the synthesis of natural products incorporating an 8-hydroxylated xenicane scaffold, as in **1**, has not been described so far. In contrast, for the synthesis of structures like **2** precedence exists in the work of *Leumann* and *Pfander*^[80,141] as well as *Corey*.^[143] Building on this work, a multitude of acalcixeniolides (*cf.* Fig. 8) as well as other xeniolides could theoretically be produced.

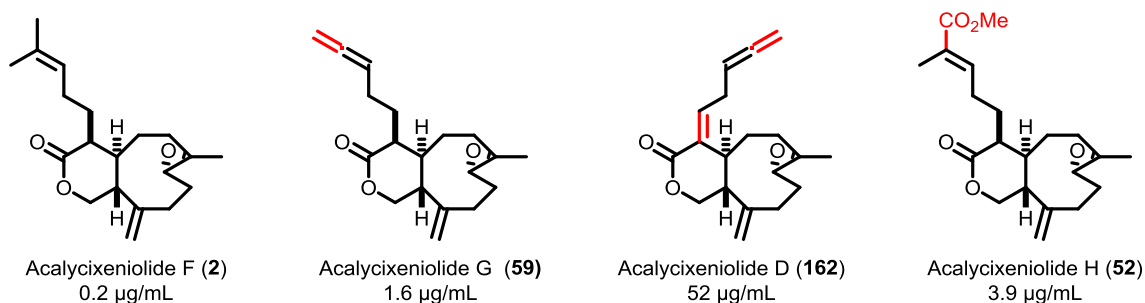


Fig. 14: Selected acalcixeniolides and their respective activities against the human leukemia cell-line K562.

Acalcixeniolide F (**2**) was selected as a target for total synthesis due to its interesting chiral epoxide moiety, but also because of its potent *in vitro* activity (Fig. 14). The compound strongly inhibits the proliferation of leukemia cells *in vitro* (Fig. 14).^[88,89] Comparing the structures and activities of compounds **2**, **59**,^[88,89] **162**^[88,89] and **52**,^[92] all of which have been co-isolated from the same biological source, reveals the following trends: An allene instead of a prenyl side-chain, as in acalcixeniolide G (**59**), leads to a approximately tenfold reduction in activity. Moreover, an added degree of unsaturation adjacent to the ester moiety, as in

acalcixeniolide D (**162**), further decreases potency by a factor of around thirty. On the other hand, if the prenyl group is oxidized to the acid level, as found in acalcixeniolide H (**52**), the activity decreases around twenty-fold compared to **2**. Based on this very limited data set, the orientation of the side-chain seems to have a more profound impact on cytotoxicity than the substitution pattern. The mode of action has not been elucidated for any of the compounds. Establishing an efficient total synthesis for **2** would provide a basis for the synthesis of analogs and derivatives for SAR investigations and target identification studies.

The new synthetic approach for both of the target xenicanes **1** and **2** should comprise the following features: (1) enantiocontrol; (2) relative stereocontrol for the C2,C3-array as well as for C8 in compound **1**; (3) complete control of the *E*-olefin geometry in the 9-membered ring; (4) **1** and **2** should be accessible from a common intermediate; (5) possibility to modify other parts of the scaffold, such as C9, C19 and C20 or the carbon-count in the medium-sized ring.

In addition the following points were deemed desirable, but not mandatory: (1) possible access to the other enantiomer; (2) possible access to the *Z*-isomer.

After successful completion of both synthetic targets, and given sufficient time, the synthesis of the selection of acalcixeniolides depicted in Fig. **14** was to be a secondary goal.

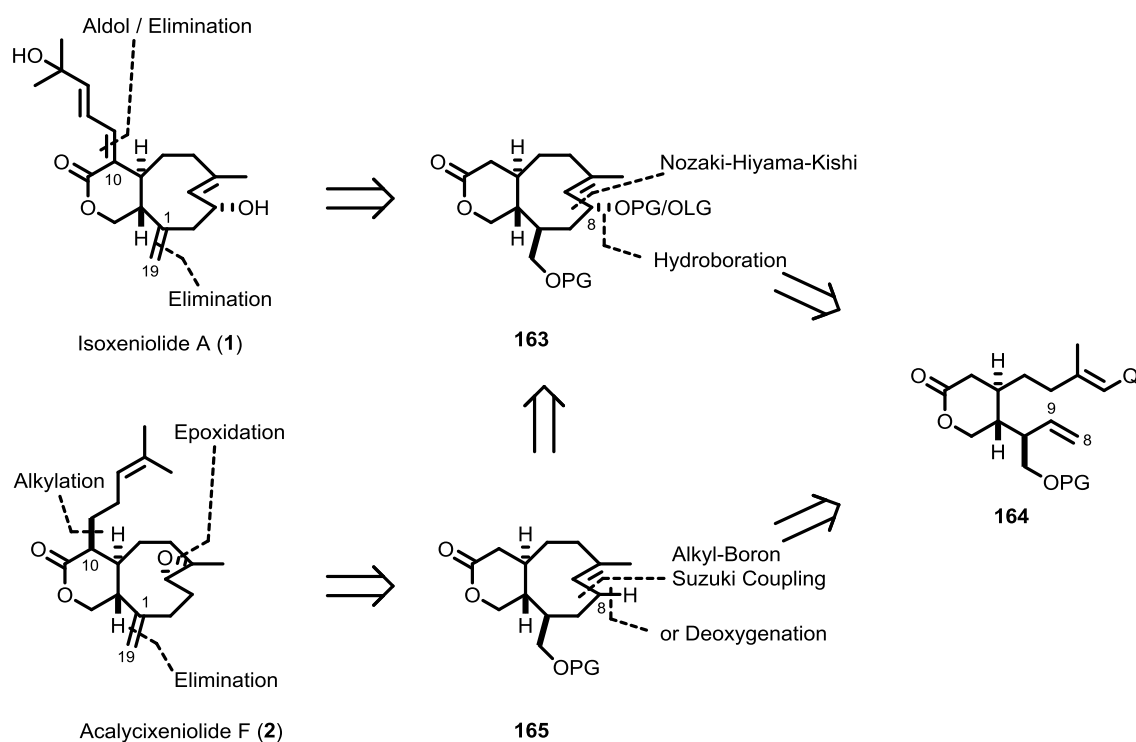
3 Results and Discussion

*“Good judgment comes from experience,
and a lot of that comes from bad judgment.”*

Anon

3.1 General Retrosynthetic Considerations

The main retrosynthetic disconnections for both isoxeniolide A (**1**) and acalcixeniolide F (**2**) via a common precursor **164** are depicted in Scheme 16. Isoxeniolide A (**1**) can be traced back to protected bicyclic structure **163**, by means of an aldol transform with an appropriately protected aldehyde for introduction of the C10 side chain^{XIII} and an elimination transform for installation of the C1-C19 exocyclic alkylidene functionality. In a similar fashion, completion of the synthesis of acalcixeniolide F (**2**) from cyclononene **165** was to entail an elimination reaction to install the C1-C19 exocyclic double bond and stereoselective attachment of the C10 side chain using enolate chemistry. Compared to isoxeniolide A (**1**), however, the stereoselective epoxidation of the trisubstituted C6-C7 double bond in the 9-membered ring is additionally required at some stage during the transformation of **165** into the natural product.



Scheme 16: Overall retrosynthetic analysis of isoxeniolide A (**1**) and acalcixeniolide F (**2**). PG: Protecting group; LG: Leaving group; Q: I, OTf, SiR₃, SnR₃.

The allylic hydroxyl group in **163** represents a retron for the addition of a vinyl metal species to an aldehyde. In the synthetic direction this motif was to be built up by hydroboration/oxidation of the C8-C9 vinyl group, followed by a *Nozaki-Hiyama-Kishi*

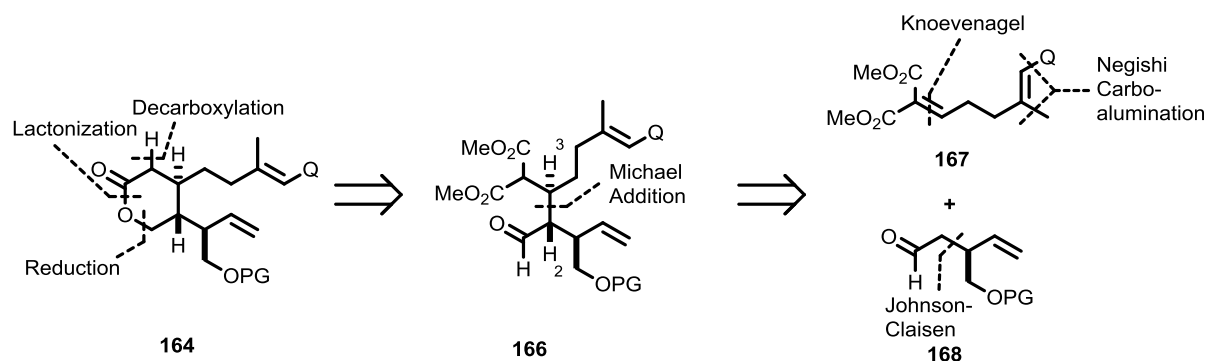
^{XIII} xenicane numbering, cf. Fig. 4, p.5.

cyclization starting from a suitable precursor of the form **164** e.g. vinyl iodide, triflate, silane or stannane. The double bond in **165** can either be considered a retron for a deoxygenation reaction or for an alkyl-vinyl cross coupling. Synthetically, cyclononene **165** can either be accessed from precursor **164** by hydroboration and alkyl-boron *Suzuki* reaction or, with additional steps, by removal of the C8-hydroxy group of **163** via a suitable leaving group.

In light of our interest in the effect of different side chain modifications on the biological activity of xenicanes, the introduction of the side chain was to be carried out at a very late stage of the synthesis. Both the groups of *Corey* and *Leumann* found it necessary to equilibrate the epimerize the chiral center on C10 to produce the natural product coraxeniolide A. In previous syntheses, introduction of the exocyclic methylene group at C1 starting from a carbonyl-group was shown to be highly substrate dependent; extensive experimentation was required to install this feature.^[80,87,143] Accordingly, in our synthetic design, we chose to introduce the required carbon atom at a very early stage of the synthesis and transform it into the required methylene group later. To this end, we planned to eliminate a primary hydroxy group rather than using carbonyl olefination methodology. At the planning stage it was not obvious if the configuration of the protected hydroxymethyl group as depicted in structures **163**, **164** and **165** would allow for elimination, or whether it would be necessary to use the corresponding epimers.

3.2 First Generation Synthetic Approach to Building Block **164**: Attempted Synthesis of Lactone **164** via a *Michael* Addition Strategy

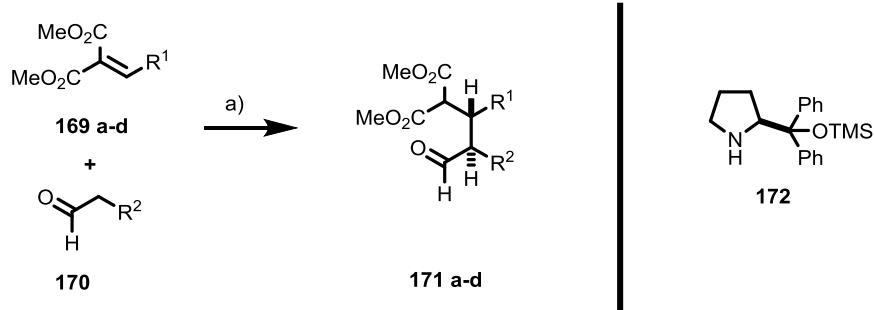
Our first strategy for synthesizing **164** revolved around a *Michael* addition reaction as the enabling transformation. Reaction of an aldehyde of the form **168** to an alkylidene malonate such as **167** (Scheme **17**) would establish the two vicinal stereogenic centers of intermediate **166** (C2 and C3). Reduction of the aldehyde, lactonization and decarboxylation would produce key intermediate **164**. For the synthesis of the α,β -unsaturated malonate, we projected a *Knoevenagel* condensation; the *E*-vinyl iodide geometry in the requisite aldehyde would be controlled through use of *Negishi's* protocol for carboalumination and iodination. Therefore, the heteroatom Q would be an iodine atom, but in case of chemical incompatibility, it could also be another group (OTf, SiR₃, SnR₃) that would later be transformed into an iodide.



Scheme 17: First generation retrosynthetic analysis of building block **164**. PG: Protecting group; Q: I, OTf, SiR₃, SnR₃.

Literature precedence for enantio- and diastereoselective Michael additions of aldehydes onto alkylidene malonates was found in a recent report by *Córdova* and coworkers (Table 1).^[155] Using the *Jørgensen-Hayashi* catalyst (**172**)^[156,157] a number of substrates underwent this transformation with excellent enantioselectivity, moderate to good diastereoselectivity and fair to good yields.

Table 1: Enantioselective Michael addition reported by *Córdova*.^[155]



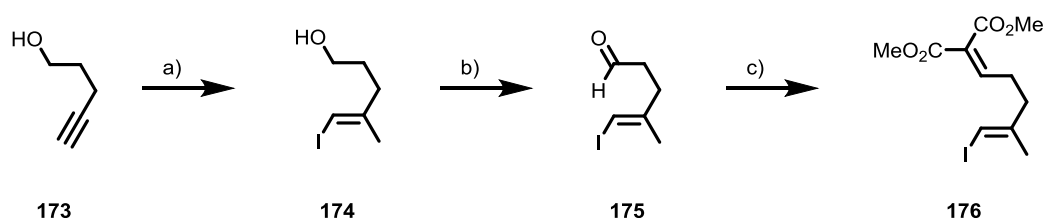
Entry	R ¹	R ²	Time (h)	Yield (%)	<i>d.r.</i>	<i>ee</i> (%)
a	4-(NO ₂)C ₆ H ₄	Et	16	77	14:1	99
b	4-(NO ₂)C ₆ H ₄	Bn	48	73	8:1	98
c	4-(NO ₂)C ₆ H ₄	allyl	48	86	6:1	98
d	<i>n</i> -Pr	Me	48	84	4:1	95

Reagents and conditions: (a) malonate **169** (1.0 eq.), aldehyde **170** (2.0 eq.), **172** (0.2 eq.), CHCl₃ (0.25 M), +4 °C.^[155]

Even though *Córdova's* studies were largely limited to the addition of propanal to aromatic alkylidene malonates, a small subset of substrates shone some light on the reactivity of non-aromatic aldehydes (entries **1-3**). In addition, one single example of an *n*-propylalkylidene malonate (entry **4**) hinted at the possibility that this transformation might be possible with both R^1 and R^2 being alkyl.

3.2.1 Synthesis of Fragment **176**

Synthesis of fragment **176** started from pent-4-yn-1-ol (**173**) with a zirconium catalyzed *Negishi* carboalumination reaction as the first step, followed by quenching of the vinyl aluminate with iodine (Scheme **18**).



Scheme 18: Reagents and conditions: (a) (i) AlMe_3 (3 eq., in hexanes), Cp_2ZrCl_2 (0.25 eq.), CH_2Cl_2 , 0 °C, 10 min, rt, 12 d, (ii) I_2 , THF, -78 °C, 1 h, 98%; (b) $(\text{COCl})_2$ (1.2 eq.), DMSO (2.2 eq.), Et_3N (5 eq.), CH_2Cl_2 , -78 °C, 1 h, 66%; (c) TiCl_4 (2 eq.), **175** (1.05 eq.), dimethyl malonate (1 eq.), pyridine (4 eq.), CH_2Cl_2 , 2 °C to rt, 3 d, 78%.

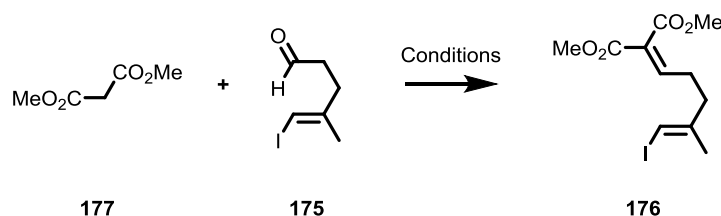
The procedure was carried out according to a report by *Pattenden*^[158], but incorporating two distinct changes. Firstly, an extended reaction time of at least 5 days was required to reach full conversion in the hydrozirconation step; which stands in strong contrast to 20 hours described by *Pattenden*. Shorter reaction times resulted in the presence of unreacted **173**, which was separable, but the desired iodo olefin was only produced in 70% yield (which is what has been reported in the literature). A longer reaction time obviated the need for flash chromatography and the yield increased to 98%. Secondly, the purity of **174** was higher when it was not subjected to chromatography. This is likely due to the material decomposing to a small extent on silica.

Parikh-Doering oxidation^[159] of alcohol **174** was ineffective and gave only marginal conversion, with a 20% isolated yield of the desired aldehyde **175**, accompanied by 76% of recovered starting alcohol. This problem was overcome by using a *Swern* oxidation^[160], which delivered

iodoaldehyde **175** in 65% overall yield in 2 steps. This was more favorable than the 2-step yield of 55% that was obtained when iodoalcohol **174** was chromatographed, despite a more efficient *Swern* oxidation in the latter case.

Knoevenagel condensation of **175** with dimethyl malonate to produce *Michael* acceptor **176** (the optimal conditions already shown in Scheme **18**) required extensive experimentation (Table **2**). A first attempt using TiCl_4 solution in CH_2Cl_2 and pyridine in THF^[161] led to almost complete conversion (entry **1**), but low yield and purity of isolated product. Formation of a number of by-products was observed by TLC. Lowering the temperature to 0 °C, while doubling the reaction time (entry **2**) still gave low purity and even lower yields.

Table 2: Optimisation of the *Knoevenagel* condensation between dimethyl malonate and aldehyde **175**.



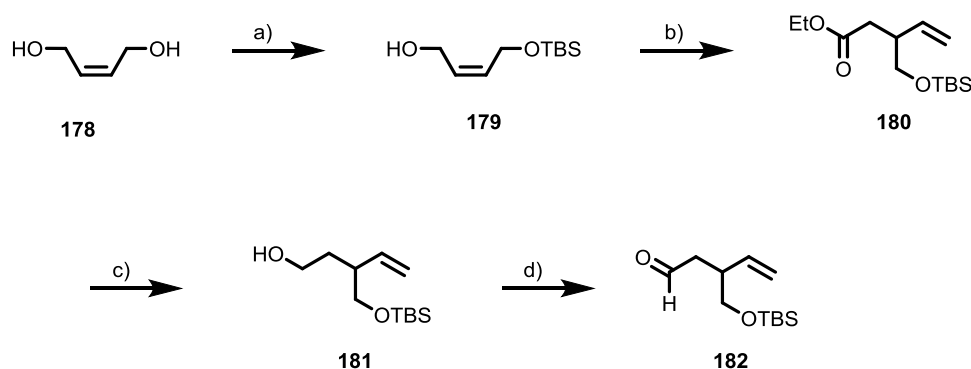
Entry	Conditions	Solvent	Time	Temperature	Yield
1	TiCl_4 in CH_2Cl_2 , py	THF	2 d	0 °C to rt	43 %
2	TiCl_4 in CH_2Cl_2 , py	THF	4 d	0 °C	18 %
3^A	piperidinium acetate	THF	2 h	0 °C	decomposition
4^B	(<i>L</i>)-proline	DMSO	10 h	rt	decomposition
5	TiCl_4 in CCl_4 , pyridine	THF	2 d	0 °C to rt	8 %
6^C	AlCl_3 , NEt_3	THF	5 h	0 °C to rt	decomposition
7^D	TiCl_4 in CH_2Cl_2 , py	dioxane	2 d	0 °C to rt	40 %
8^{D,E}	TiCl_4 in CH_2Cl_2 , py;	dioxane	2.5 d	0 °C to rt	23 %
9^{D,F}	TiCl_4 in CH_2Cl_2 , py;	dioxane	2.5 d	0 °C to rt	80 %
10^{D,F}	TiCl_4 in CH_2Cl_2 , py;	dioxane	2 d	0 °C to rt	78 %

Unless otherwise noted, condensations were performed with 0.95 eq. **177**. **A**: 1.1 eq. **177**; **B**: 2 eq. **177**; **C**: 1 eq. **177**; **D**: quench with pH 7 phosphate buffer; **E**: chromatography with NEt_3 ; **F**: chromatography with acetic acid.

Attempts to catalyze the condensation with either piperidinium acetate^[162], proline^[163] or aluminium trichloride^[164] (entries **3**, **4** and **6**) were futile and decomposition of the starting material was observed. Using a freshly-prepared solution of neat TiCl_4 in tetrachloromethane^[161] (entry **5**), the yield was even lower yield than with a commercially available solution in dichloromethane. While performing a mini-workup for a TLC sample (entry **7**), the reaction was quenched with pH 7 phosphate buffer, which decreased the number and intensity of byproducts on TLC. All the following reactions were thus quenched with buffer to give a neutral work-up, but this did not result in any improvement of yield and purity of the isolated product. In two follow-up experiments, the solvent for chromatography was either buffered with triethyl amine or acetic acid (entries **8** and **9**). Buffering with base dramatically lowered yield as well as purity, while addition of acid doubled the yield to give around 80 %, which was reproducible on larger scale (entry **10**). While the yield could be improved, a small percentage of unidentified impurities was not removable from the product **176**, despite extensive chromatography.

3.2.2 Synthesis of Fragment **182**

The synthesis of the known aldehyde **182** (Scheme **19**) departed from readily available (*Z*)-butene-1,4-diol (**178**), which was mono-protected^[165] by deprotonation with *n*-BuLi, followed by reaction with TBSCl. Propionic acid-catalyzed^[166] *Johnson-Claisen* rearrangement of **179** with triethyl orthoacetate under continuous removal of ethanol produced **180** in very good yield (82%).



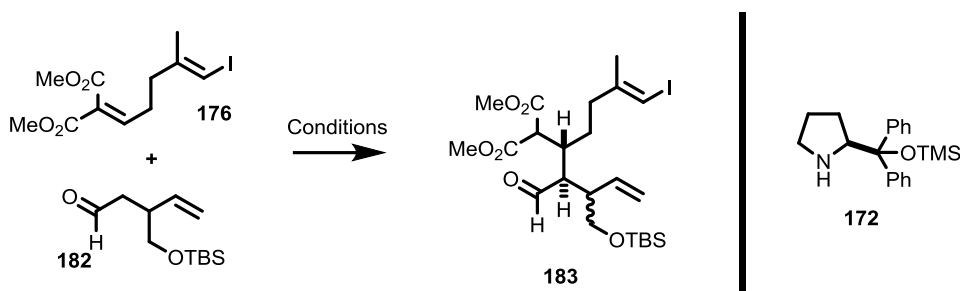
Scheme 19: Reagents and conditions: *n*-BuLi (1.05 eq.), TBSCl (1.0 eq.), THF, 0 °C to rt, 1 h, 0 °C, 1 h, rt, 88%; (b) $(\text{EtO})_3\text{CMe}$ (5 eq.), propionic acid (0.25 eq.), 155 °C, 6 h, 82%; (c) DIBAL-H, THF, -78 to 0 °C, 2 h, 93%; $(\text{COCl})_2$ (1.2 eq.), DMSO (2.5 eq.), Et_3N (5 eq.), CH_2Cl_2 , -78 °C, 30 min, 92%

Prior experiments with hydroquinone^[167] as a proton source had provided a yield of 54% at best, even with a large excess of *ortho*-ester and prolonged reaction time. **180** was reduced to the alcohol **181** with diisobutylaluminium hydride^{XIV} and the resulting primary alcohol was oxidized under *Swern* conditions to give aldehyde **182** in 86% overall yield from ester **180**. Direct reduction of **180** to **182**^[167] was attempted, but did not succeed.

3.2.3 Studies on the Union of Building Blocks **176** and **182**

With malonate **176** and aldehyde **182** in hand, a variety of conditions for the projected *Michael* addition was investigated (Table 3). Following the protocol reported by *Córdova*^[155], a 2:1 mixture of racemic aldehyde **182** and malonate **176** was treated with 0.2 equivalents of *Jørgensen's* catalyst **172** in acetonitrile at 4 °C (entry 1).

Table 3: Conditions investigated for organocatalytic conjugate addition of aldehyde **182** to alkylidene malonates **176**.



Entry	Catalyst / loading	Solvent	Time	Yield	Stability of Malonate
1	172 0.2 eq.	MeCN	7d	29%	decomposes
2	172 0.2 eq.	5 % EtOH H ₂ O	3d	14%, partly decomposed	stable
3	172 0.4 eq.	CH ₂ Cl ₂	10d	60%	stable
4	172 0.4 eq.	MeOH 1 eq. AcOH	22d	not determined, impure	decomposes
5	(L)-Proline 0.4 eq.	DMF	22d	5-10% conversion	stable

Entry **1** was carried out at 0 °C, all other experiments at rt. Yields refer to the mass recovery of product mixtures.

^{XIV} Procedure adapted from a similar substrate.^[360]

Conversion to **183** was very sluggish, with only traces of a new compound being detectable by TLC after 1 day. After 3 days, iodo malonate **176** started to decompose and at some point after 4 or 5 days, the reaction came to a complete halt. The isolated material was an inseparable mixture of different 1:1 adducts of **176** and **182**, as determined by ^1H NMR. Four major aldehyde peaks could be observed in a 1:3:2:1 ratio (Fig. **15.1**). In addition, an unidentifiable decomposition byproduct of aldehyde **182** was isolated, which was also formed under all other reaction conditions shown in Table **3**. Because the yield obtained under the conditions described by Cordoba suggested both low turnover rate and number of the catalyst, either more catalyst or higher temperature were hypothesized to lead to an improved reaction outcome. As a consequence, subsequent experiments were performed at ambient temperature. With 5 % ethanol in water (entry **2**) as a solvent, malonate **176** stayed intact throughout the reaction. However, conversion was again low and essentially the same product distribution (1:2:3:1) was observed as with acetonitrile as the solvent, judged by the aldehyde signals in the ^1H NMR spectrum of the inseparable product mixture (Fig. **15.2**). Interestingly, however, from a comparison of the integrals in the aldehyde, the olefinic and the silyl-region of the spectrum, it was determined that the products were in fact 1:2 adducts of **176** and **182**. This stands in contrast to entry **1**, but goes in line with a later observation with substrate **185** (next section), where the ratio was confirmed by HRMS. Despite looking pure on TLC, the mixture was determined to be partly decomposed by ^1H NMR.

In CH_2Cl_2 (entry **3**), malonate **176** was again stable and a higher yield for the mixture of products was obtained. This material contained at least 5 different isomers as judged by the signals of the aldehyde, the methyl group and the iodovinyl proton in the ^1H NMR spectrum and approximately represented a 2:3:6:5:2 mixture (Fig. **15.3**). This experiment produced 1:1 adducts of the two starting materials. Performing the reaction in methanol with one equivalent of acetic acid (entry **4**) gave low conversion and led to decomposition of malonate **176**, as judged by TLC analysis. On account of the low conversion, it was not possible to separate the product mixture completely from the starting **176**. Integration of the ^1H NMR signals suggested a 2:2:1 mixture of products (Fig. **15.4**), which were again 1:2 adducts of **176** and **182**. Finally, an experiment with proline in dimethylformamide (entry **5**) gave only traces of conversion even after several weeks and no attempts were made to isolate the product.

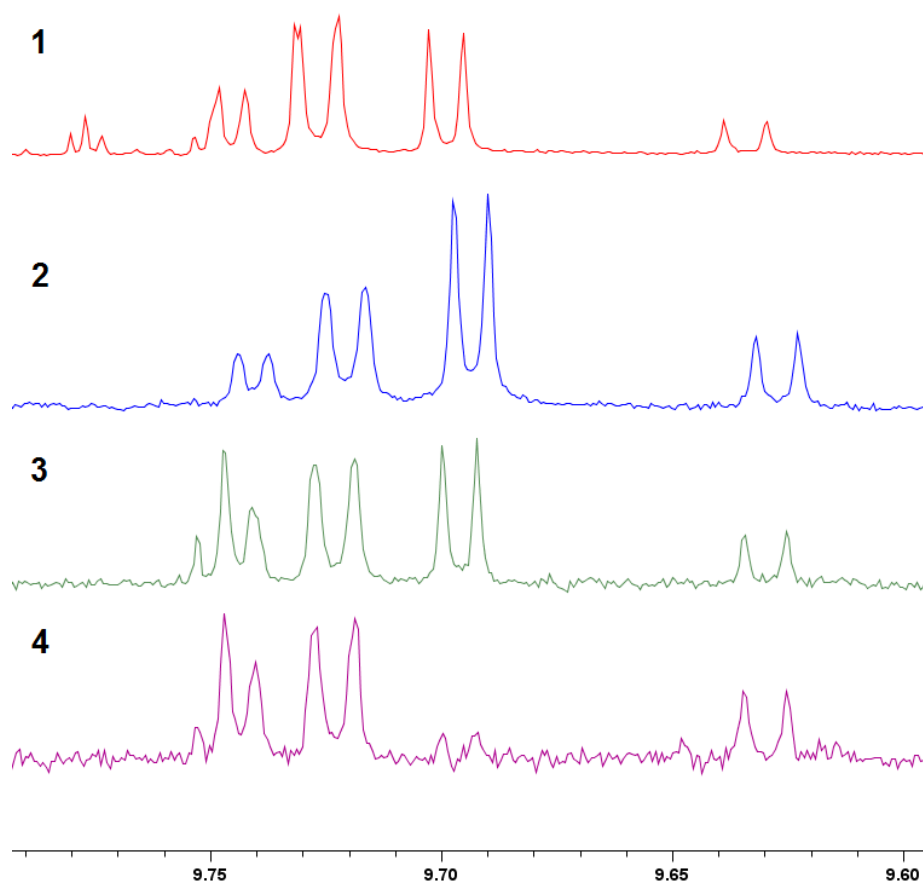
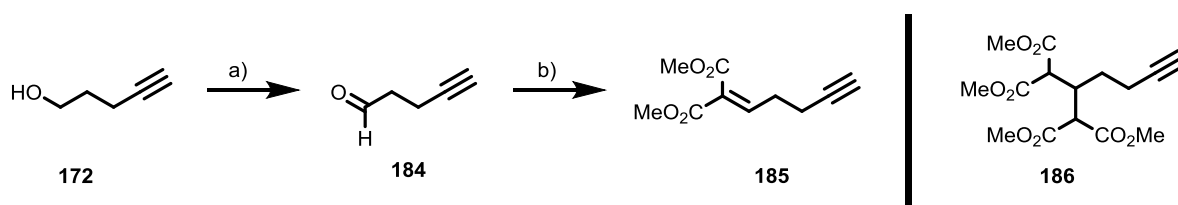


Fig. 15: Products mixtures of the Michael addition were assessed by ^1H NMR spectra of the aldehyde region. Top to bottom correspond to entries 1-4.

In summary, the following conclusions derive from the results presented in this section: (1) The stability of malonate **176** during the *Michael* addition is limited and strongly dependent on the reaction solvent, (2) conversion is generally low and the type of product formed is also solvent-dependent; (3) the selectivity of the addition was low, with between 3 to 5 major products being detectable in the reaction mixture. Since aldehyde **182** was used as a racemate, a theoretical maximum of 8 stereoisomeric products is possible, which represent 4 pairs of enantiomers; however, up to 5 sets of signals were visible in the NMR spectrum of the product mixture obtained in the reactions between **182** and **176**, which points to the interference of additional reaction pathways.

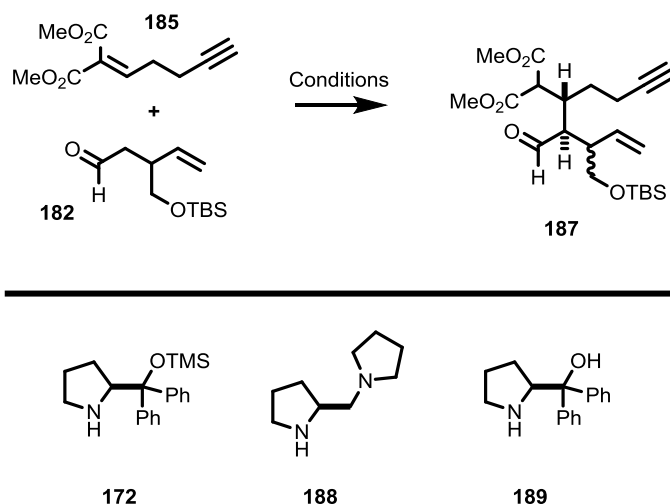
3.2.4 Investigation of Alternative Alkylidene Malonate **185**

Malonate **185** (Scheme **20**) bearing a terminal alkyne moiety was envisioned to be a more stable alternative to iodo malonate **176** and allow for further functionalization at a later stage. Its synthesis started from pent-4-yn-1-ol (**173**), which was oxidized to aldehyde **184** under Swern^[160] conditions. Due the volatility of this aldehyde, the yield of **184** varied between 34 and 59%. When aldehyde **184** was subjected to Knoevenagel^[161] condensation with dimethyl malonate, the yield of the desired product **185** was low and the material had to be exposed to vacuum for a prolonged period of time so as to completely remove residual dimethyl malonate. Moreover, a small amount of a side product was observed that was tentatively assigned as **186**, the product of a Michael addition of dimethyl malonate onto **185**.



Scheme 20: Reagents and conditions: (a) (COCl)₂ (1.2 eq.), DMSO (2.2 eq.), Et₃N (5 eq.), CH₂Cl₂, -78 °C, 1 h, 59%; (b) TiCl₄ (2 eq.), **184** (1.05 eq.), dimethyl malonate (1 eq.), pyridine (4 eq.), CH₂Cl₂, 2 °C to rt, 3 d, 44%.

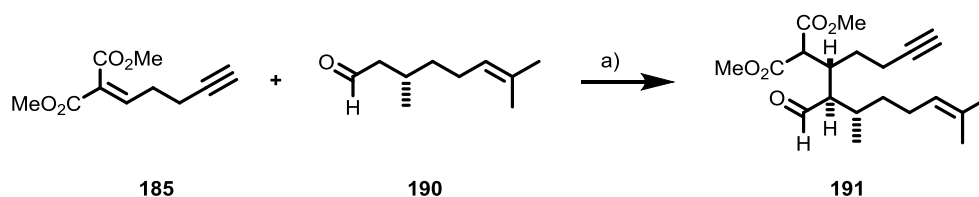
With alkylidene malonate **185** in hand, the critical *Michael* addition was investigated (Table **4**). Again, two equivalents of racemic aldehyde **182** were employed in the reaction, in the presence of different catalysts at ambient temperature. Of the catalysts investigated, only **172** (entries **1** and **2**) led to formation of 1:1 adducts of the two fragments. In both cases, however, the yield was only around 50% and the selectivity of the reaction was poor. According to the aldehyde signals in the ¹H and ¹³C NMR spectra, 4 different isomers were obtained. Considering the ratio of isomers and the overall yield, 14% of each of the major isomers and 8 % of the minor isomer was obtained. The use of catalyst **188** (entry **3**) gave a mixture of isomers which incorporated two equivalents of the aldehyde **182** and one equivalent of malonate **185**, as judged by ¹H NMR and HRMS. This finding is in line with the formation of 2:1 adducts previously observed for malonate **176**. The exact nature of the product was not further investigated. No traces of the desired product were observed. Catalysts **189** (entry **4**) gave no conversion.

Table 4: Conditions used for attempted Michael addition of aldehyde **182** to alkylidene malonates **185**.

Entry	Catalyst	Solvent	Time	Temperature	Product (ratio of isomers)
1	172 (0.4 eq.)	CH ₂ Cl ₂	17 d	rt	48% (3:3:3:2)
2	172 (0.4 eq.)	CHCl ₃	18 d	rt	52% (2:2:2:1)
3	188 (0.4 eq.)	MeCN	12 d	rt	Undesired product
4	189 (0.4 eq.)	CHCl ₃	18d	rt	No reaction

3.2.5 Michael Addition of an Enantiopure Aldehyde

A structural comparison of substrate **182** with the aldehydes used by Córdova^[155] led to the notion that the size of the β-substituent might be accountable for the lack of conversion and selectivity in the organocatalytic *Michael* addition of aldehyde **182**. In order to corroborate this hypothesis, the reaction was also investigated with (*S*)-citronellal **190** as an enantiopure β-chiral aldehyde with a small methyl substituent. Indeed, the isolated yield of the reaction with malonate **185** dramatically increased to 93 % (Scheme 21).

**Scheme 21:** Reagents and conditions: (a) malonate **185** (1.0 eq.), aldehyde **190** (2.0 eq.), **172** (0.4 eq.), CH₂Cl₂ (0.25 M), rt, 13 d, 95%, *dr* 2:1.

However, two diastereoisomers of **191** were formed in a 1:2 ratio, which is comparable to the ratio of the major isomers in the reaction of **185** with aldehyde **182**. This finding indicates that the size of the β -substituent on the aldehyde exerts a strong effect on the yield of the reaction, while it apparently does not affect the diastereochemical bias to a large extent. It should also be noted that a strict comparison between the reactions with racemic aldehyde **182** and citronellal is not possible, as two equivalents of enantiopure citronellal were used, while only one equivalent of each enantiomer of **182** was present in the reaction mixture.

3.2.6 Conclusions

No synthetically useful conditions for the Michael addition of aldehyde **182** to alkylidene malonates **176** and **185** could be identified. This outcome was attributed to the low reactivity of aldehyde **182**, which is likely caused by the size of the β -substituent. As a consequence, the Michael addition approach towards **164** was abandoned. Nevertheless, the results obtained in the experiments described in this subchapter deserve some specific comments. Firstly, from a mechanistic perspective, the reaction of **185** with (*R*)-citronellal would have provided insights into matched/mismatched interactions between aldehyde and catalyst. Such experiments were not carried out at the time, in light of the significant effort that had already been expended on the Michael addition approach without success. Secondly, in light of the high conversion of citronellal, the latter might have shown improved selectivity and still maintained good conversion when lowering the temperature again to 0 °C. However, it needs to be noted that in the example reported by *Córdova* (Table 1, entry 4, Me and *n*-Pr), despite excellent enantioselectivity and yield, diastereoselectivity was a modest 4:1 in the case of both substituent being alkyl ones.

In a later phase of this thesis (section 3.6.1, p. 95ff) it was found that in a structural motif **192** (Fig. 16) the presence of the TBS-ether (PG = TBS) would not allow for hydroboration/oxidation of the double bond, while the corresponding PMB-ether (PG = PMB) gave good results. Therefore, the reactivity problems encountered with **182** in the *Michael* addition might be overcome by a change of the protecting group from TBS to PMB or Bn. In this context it should also be noted that a scalable preparation of both enantiomers of the Taniguchi lactone **193** *via* resolution was recently reported by Kieseritzky and coworkers^[168]. This compound might be a useful starting point for the synthesis of PMB- or Bn-protected aldehydes of type **168**.

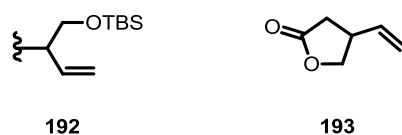
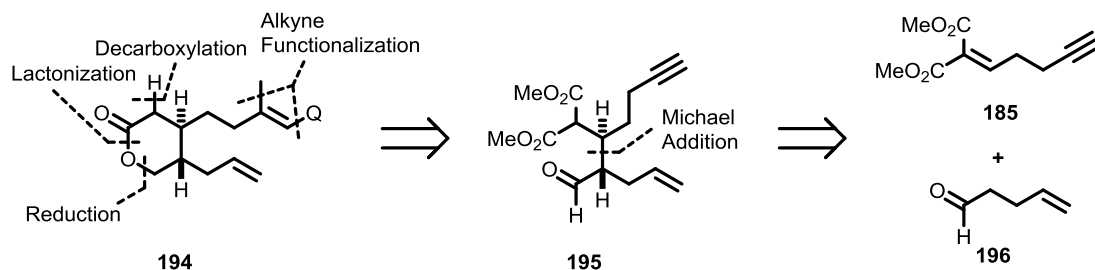


Fig. 16: Structural motif **192** and Taniguchi lactone **193**.

In view of the results obtained with citronellal, the approach pursued here for the synthesis of **164** should be well suited for the synthesis of simplified building block **194** *en route* to xenicane analogs lacking the exocyclic methylene group (Scheme **22**). Simple aldehyde **196** should undergo Michael addition with alkylidene malonate **185** or a silyl-protected version thereof to produce **195**. A sequence of reduction, lactonization, decarboxylation and alkyne functionalization would give access to **194**, which is the des-(hydroxymethyl) version of building block **164** (Scheme **16**).

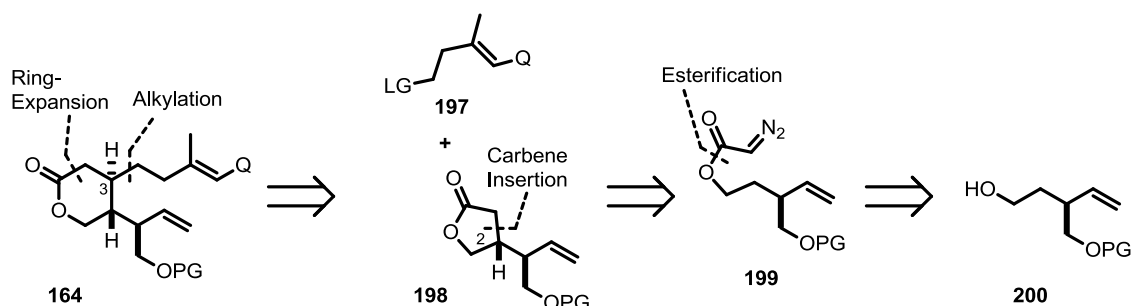


Scheme 22: Potential application of the organocatalyzed *Michael* addition for the synthesis of C1-des-methylene xenicanes.

3.3 Second Generation Synthetic Approach Towards Building Block **164**: Short Study on the Potential Elaboration of **181** into **164**

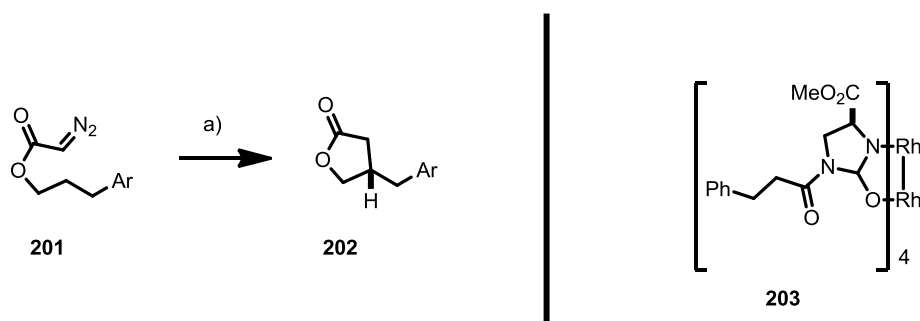
After abandoning the *Michael* addition strategy, we hypothesized that a fragment of the form **200** (Scheme **23**) might represent a useful starting point to access **164** via an alternative strategy. Retrosynthetically, **164** is disconnected into ring-contracted intermediate **198** that could be alkylated in a diastereoselective fashion with an electrophile **197** to establish the C3-stereocenter. Possible transforms for the ring-expansion were found to be *Kowalski* homologation^[169–171] with LiCHBr₂, or, alternatively, a sequence of reduction to the lactol followed by reaction with an appropriate C₁-*Wittig* reagent such as PPh₃CHOMe and further manipulations on the ensuing enol ether. **199** should be accessible from **200** by esterification with a suitable diazoacetylating agent. A synthetic route to enantiomerically pure **200** via

resolution has been reported.^[172] Diastereoselective C-H insertion of a carbene derived from **199** will close the γ -lactone ring and install the chirality at C2.



Scheme 23: Access to building block **164** via diastereoselective C-H insertion and ring-expansion. PG: Protecting group; LG: Leaving group; Q: I, OTf, SiR₃, SnR₃.

The concept was inspired by a report of *Doyle, Bode* and coworkers, who had described enantioselective C-H insertions with diazo acetates like **201** to form γ -lactones **202** (Scheme **24**).^[173,174] The chiral dimeric rhodium catalyst Rh₂(4S-MPPIM)₄ **203** served as a mediator for this transformation.

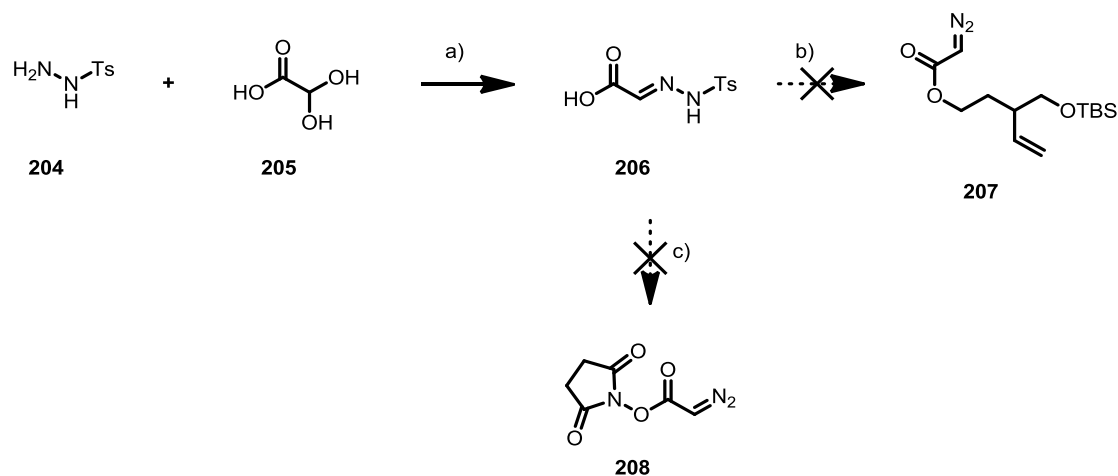


Scheme 24: Enantioselective C-H insertion reported by Doyle. Reagents and conditions: (a) **203** (0.02 eq.), CH₂Cl₂, reflux, 59-76% yield, 91-97% *ee*. Ar: Aryl.

This reaction is notable for the following features: Preference of γ - over δ -lactone formation, although the benzylic position is highly activated; high yields and enantioselectivities; absence of carbene reaction with the electron-rich aromatic ring system; and up to 10% of β -lactone formation as the main by-product. We hypothesized that it might be possible to either achieve diastereoselective C-H insertion with **199** using an achiral catalyst, or alternatively, override a potential substrate inherent lack in selectivity by means of a chiral catalyst. By the time of the writing of this work, *Carreira* had reported diastereoselective C-H insertion for the formation of cyclopentanones in the context of prostaglandine synthesis.^[175,176]

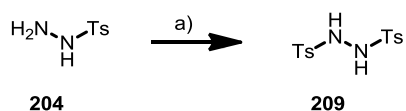
3.3.1 Synthesis of Diazo Acetate **206**

Tosylhydrazonoacetic acid **206** (Scheme **25**) was prepared according to the method of *Blankley* and *House*^[177,178] using a procedure reported by *Wulff*^[179]. The low yield in the reaction of tosyl hydrazide **204** with glyoxylic acid **205** could likely be improved by a change of the crystallization process. Attempts to directly esterify alcohol **181** with acid **206** did not lead to any notable conversion, while the starting materials decomposed over time. A procedure of *Badet*^[180] for conversion of **206** into *N*-hydroxysuccinimidyl diazoacetate **208** could not be reproduced. Only intractable mixtures of products were isolated.



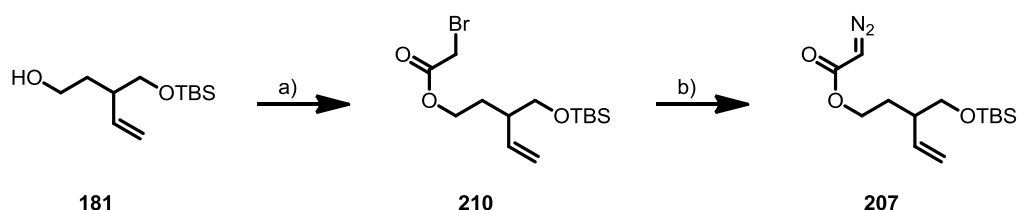
Scheme 25: Attempted synthesis of diazo acetate **206**. Reagents and conditions: (a) **204** (1 eq.), **205** (1 eq.), HCl (0.32 eq.), H₂O, 65 °C, 15 min, 31%; (b) (i) **181** (1 eq.), EDCI (1. Eq.), *N*-hydroxy succinimide (1.05 eq.), dioxane, 15 °C, 15 min, then rt or (ii) **181** (1 eq.), EDCI (1. Eq.), DMAP (1.05 eq.), THF, 0 °C, 15 min, then rt; (c) (i) DCC (1. Eq.), *N*-hydroxy succinimide (1.00 eq.), dioxane, 15 °C, 15 min, rt, 4 h.

As a possible alternative, we turned our attention to *Fukuyama's* method^[181], which provides access to diazo acetates from the corresponding α -bromo acetates (Table **5**). The requisite 1,2-ditosyl hydrazide reagent was prepared according to the literature procedure^[181] (Scheme **26**).



Scheme 26: Reagents and conditions: (a) H₂NNHTs, pyridine, CH₂Cl₂, rt, 1.5 h, 80%.

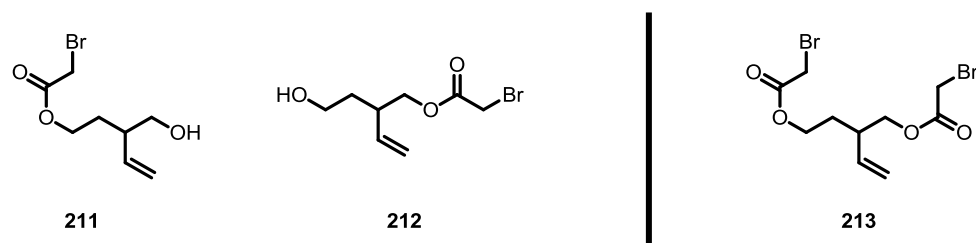
Using bromoacetyl bromide and sodium hydrogen carbonate (Table **5**, entry **1**), only traces of a less polar product were formed according to TLC. After work-up, the material was directly reacted with ditosyl hydrazide (**209**) to give only a 10 % overall yield of the desired product.

Table 5: Bromoacetylation of **181** and preparation of diazo compound **206**.

Entry	Base (eq.)	bromoacetyl bromide (eq.)	Solvent	Yield 210	Yield 207
1	NaHCO ₃ (2.2)	1.1	MeCN	n. d.	10 %
2	Na ₂ CO ₃ (10)	1.5	MeCN	46 %	n. d.
3	Pyridine (10) DMAP (0.1)	1.1	MeCN	33 %	27 %
4	DIPEA (10) DMAP (0.1)	1.1	CH ₂ Cl ₂	decomposition	decomposition

Reagents and conditions: (a) bromoacetyl bromide, base; (b) **209** (2 eq.), DBU (5 eq.), THF, 0 °C, 10 min.

The two byproducts formed during the bromo acetate formation under the conditions of entry 1 in Table 5 were isolated and tentatively assigned to be a regioisomeric mixture of TBS-deprotected bromoacetates **211** and **212**; and bisbromo acetate **213** (Fig. 17).

**Fig. 17:** Byproducts obtained during bromoacetylation of **181**.

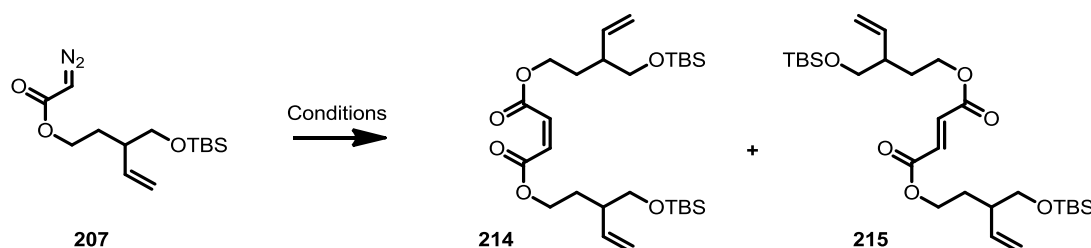
In an attempt to prevent TBS-ether cleavage by free hydrogen bromide, the base was changed to sodium carbonate (entry **2**) and used in larger excess. Even though the isolated yield for the esterification step under these conditions was 46 % (entry **2**), the same side products were still present as judged by TLC. Using pyridine and DMAP (entry **3**), the formation of side products was suppressed, but the yield was lower, despite full conversion. This might have been caused by residual organic base reacting with the product upon removal of the solvent. The use of Hünig's base (entry **4**) only delivered intractable tar.

3.3.2 Attempted Carbene Insertion with **206**

In spite of the low yields in the synthesis of diazo acetate **206**, sufficient material could be secured to execute preliminary experiments on the projected carbene insertion (Table 6). The first attempt was made with the dinuclear rhodium tetraacetate complex $\text{Rh}_2(\text{OAc})_4$ ^[173,174] in refluxing dichloromethane, to which the substrate was added manually (entry 1). The only isolable product obtained from this reaction was tentatively assigned to be **215** (Table 6). The dimerization of carbenes derived from diazo acetates as a sole reaction pathway had previously been observed in some cases by *Doyle* and coworkers.^[182] In contrast, they described successful C-H insertion of diazo acetoacetates.^[182]

Hudlicky^[183] has reported a procedure for the formation of cyclopropane-annulated butanones from diazo ketones, using the readily available $\text{Cu}_2(\text{acac})_2$ complex for generating the necessary carbene. However, in our case (entry 2), reacting substrate and catalyst in high dilution (0.04 mM) at elevated temperature, simply resulted in carbene dimerization to produce the corresponding maleate and fumarate derivatives **214** and **215**, respectively (Table 6). Apart from the two main products, only decomposed material was isolated. Slow addition^[173,174] of the substrate to a boiling solution of the dimeric rhodium catalyst (entry 3), gave no dimer but decomposed starting material.

Table 6: Attempts on formation of the γ -lactone and products isolated.



Entry	Catalyst	Loading / eq.	Solvent	Temperature	Addition mode	Products
1	$\text{Rh}_2(\text{OAc})_4$	0.05	CH_2Cl_2	40 °C	dropwise, by hand	Traces of 215
2	$\text{Cu}_2(\text{acac})_2$	0.1	MePh	112 °C	premix and stir	28 % of 214 traces of 215 and decomposition
3	$\text{Rh}_2(\text{OAc})_4$	0.04	CH_2Cl_2	40 °C	dropwise, syringe pump, 3h	decomposition

3.3.3 Conclusions

Due to the promising initial results obtained with the approach described in the next subchapter **3.4**, the studies on carbene insertion were stopped. In hindsight, the difficulties to access diazo acetate **206** clearly prevented effective and thorough screening of the projected C-H activation reaction. As indicated above (section 3.2.5), the choice of a TBS-ether as a hydroxy protecting group in **206** might have been suboptimal, although this was only discovered in a later phase of the project (section 3.6.1, p. 95ff). In addition, the TBS group exhibited low compatibility with the *Fukuyama* protocol for diazo acetate formation, probably due to HBr release in the course of the reaction. One possible alternative to synthesize **206** directly from **206** could involve the use of diazoacetyl chloride (**216**)^[177,184] (Fig. **18**). Other options to access **206** include prior formation of an acetate bearing an electron-withdrawing group^[185] and subsequent *Regitz* diazo transfer^[186]. Illustrative examples of potential activated acetates include acetoacetate **217**^[187], benzoylacetate **218**^[188], trifluoroacetoacetate **219**^[189] or methyl malonate **220**^[190,191]. Whereas compounds such as **217** to **219** are known to be easily deacylated after diazo transfer, the malonate **220** would likely require more forcing conditions for decarboxylation. On the other hand, the presence of the carbomethoxy group would facilitate α -alkylation of the C-H insertion product (*cf.* **Scheme 23**).

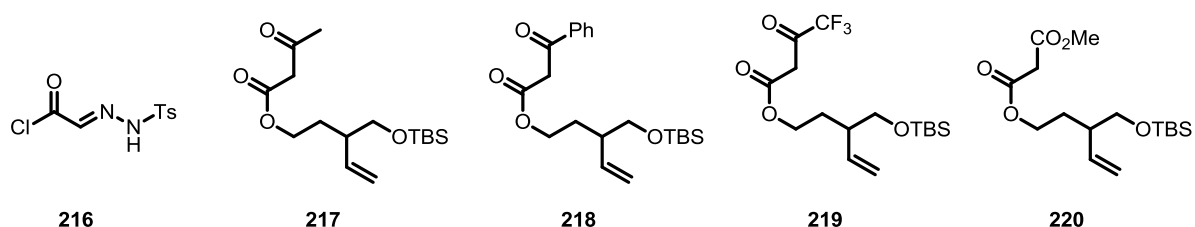


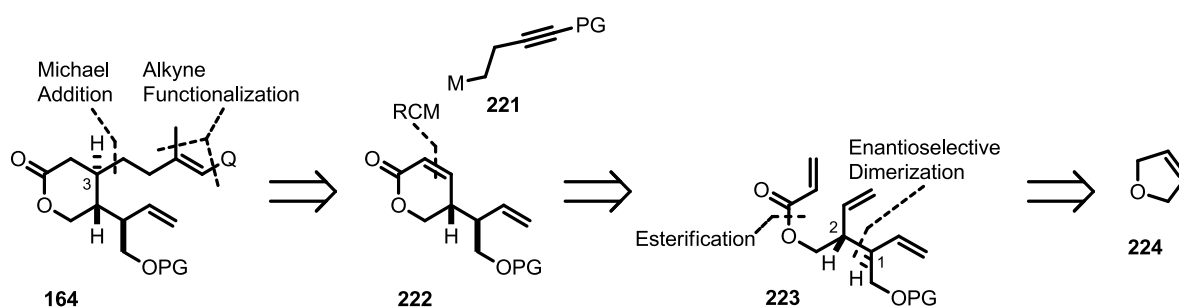
Fig. 18: Possible alternative intermediates *en route* to **206**.

Since the initially screened catalyst systems did not produce the targeted γ -lactone, the next step would be to test the diastereoselective carbene insertion using a more stable and selective catalyst such as $\text{Rh}_2(\text{esp})_2$ (developed by *Du Bois* and coworkers).^[192] Alternatively, the use of chiral mediators such as *Davies'* $\text{Rh}_2(\text{DOSP})_4$ class of catalysts might display the desired reactivity and selectivity profile.^[193]

In conclusion, a more efficient synthesis of diazo acetate **206** should be feasible, more experimentation might be warranted to assess the feasibility of the projected (stereoselective) carbene insertion reaction. However, due to more promising results in other areas, these studies were no longer within the scope of this thesis.

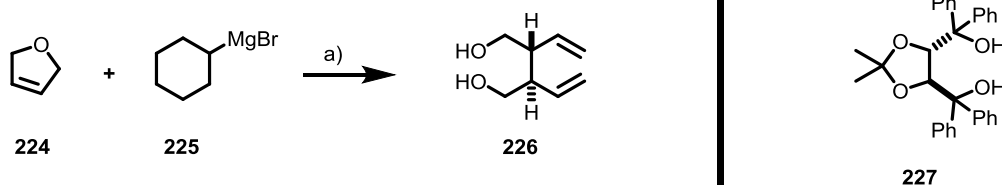
3.4 Third Generation Synthetic Approach Towards Building Block **164**: Studies on the Synthesis of Enoate **258** via a C_2 symmetric Fragment

In parallel to the studies on the synthesis of diazo acetate **206**, an alternative strategy to access building block **164** was scrutinized (Scheme 27). The two key disconnections were inspired by our work in the context of the structurally related blumiolide C:^[87] Michael addition to establish the C3-stereogenic center and RCM to form a 6-membered enoate. In the forward synthetic direction, acrylate **223** would be subjected to RCM conditions, and the resulting α,β -unsaturated δ -lactone **222** would undergo *Michael* addition with a homopropargylic species of type **221**. Functionalization of the newly appended alkyne would finally give access to **164**. A literature survey revealed that the parent free diol of **223** can be traced back to 2,5-dihydrofuran (**224**) via a dimerization transform. The advantage of this plan clearly resides in the C_2 -symmetric nature of dimerization product, which already contains the chiral information of C1 and C2.



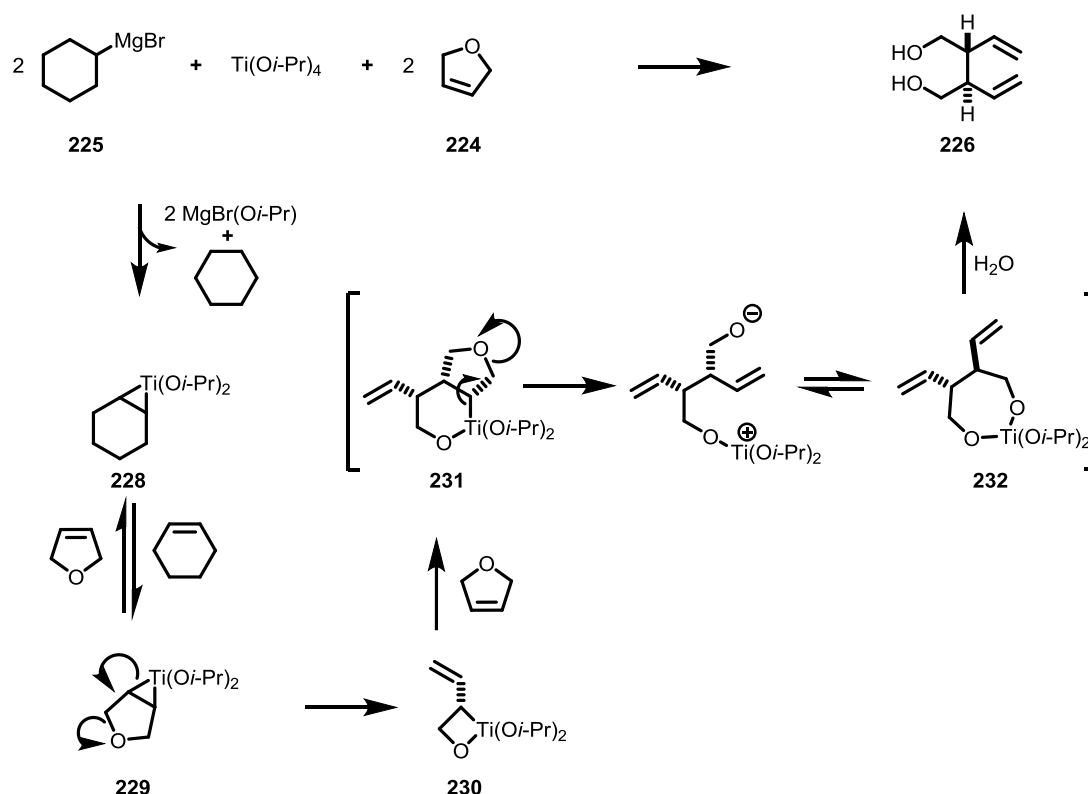
Scheme 27: Third generation retrosynthetic analysis of building block **164**. RCM: Ring-closing metathesis; PG: Protecting group; Q: Q: I, OTf, SiR₃, SnR₃; M: Li, Mg, Cu

Racemic and enantioselective versions of the dimerization of furan to produce **226** have been reported by the group of *De Meijere*^[194] (Scheme 28). As a drawback of this methodology, the stoichiometric use of the *in situ* formed chiral titanium bis-TADDOLate complex needs to be highlighted. In addition, it seems that the stereochemical correlation between catalyst and product has not been rigorously determined. Moreover, the product was reported to contain bicyclohexyl as a byproduct, which could not be separated by distillation.



Scheme 28: Enantioselective ring-opening dimerization of furan according to *De Meijere*. Reagents and conditions: (a) **224** (2 eq.), **225** (3 eq.), $\text{Ti}(\text{O}i\text{-Pr})_4$ (1 eq.), **227** (2 eq.) THF/PhH, 0 °C, 36 h, 35%, 94% *ee*.

The following mechanism for this transformation has been suggested by *De Meijere* (Scheme 29). It starts by exchange of one alkoxy-ligand of the Ti-complex for a cyclohexyl-group. As proposed for the Kulinkovich reaction,^[195] abstraction of a proton at the α -position of the σ -bound alkyl moiety by a second equivalent of the Grignard reagent leads to titanacyclopropane complex **228**. This π -complex undergoes ligand-exchange with dihydrofuran **224**, producing intermediate **229**.



Scheme 29: Mechanistic rationale for Ti-catalyzed formation of dimer **226**.^[194]

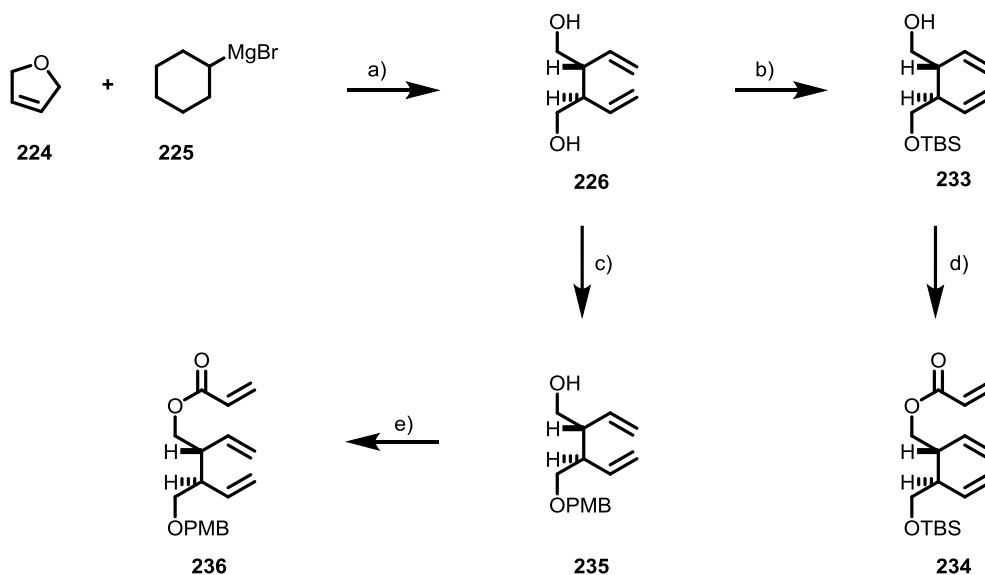
Unimolecular fragmentation (enantioselective step!) irreversibly gives alkoxyallyl complex **230**. Via a diastereoselective insertion reaction of a second equivalent of **224**, the all-*cis*

stereochemistry in alkoxyalkyl compound **231** is established. A second fragmentation step opens both rings before forming chelated product **232**. Finally, hydrolysis of the complex releases dimer **226**.

3.4.1 Synthesis of Racemic **226** and Optimization of the RCM.

Our first synthetic steps on this route were directed at racemic **226** (Scheme 30). Due to the high catalyst loading needed for the enantioselective version of this reaction, we first wanted to explore the synthesis with racemic material. In a later phase, this material would be needed as a standard for chiral GC-analysis.

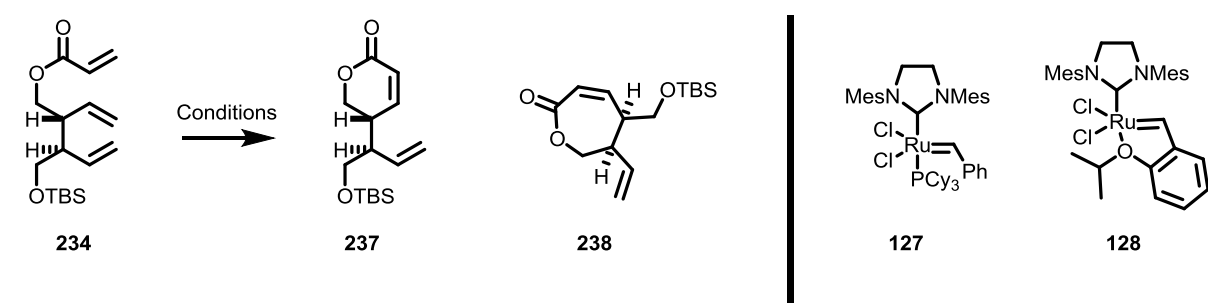
After some experimentation, it was found that the synthesis of racemic **226** from **224** could be slightly improved by the following measures: First of all, slow addition of the *Grignard* reagent and lower temperature (-12 °C instead of 0 °C, as reported) helped to compensate for the strong exothermicity of the reaction, minimizing the formation of byproducts. Secondly, quenching the reaction with 2 M HCl facilitated the work-up procedure by reducing the amounts of insoluble precipitates.



Scheme 30: Synthesis of TBS- and PMB- protected RCM-precursors **234** and **236**. (a) **224** (2 eq.), $\text{Ti}(\text{O}i\text{-Pr})_4$ (1 eq.), **225** (3 eq., slow addition), THF, -12 °C, 30 min, rt, 12 h, 60%; (b) *n*-BuLi (1.05 eq.), TBSCl (1.0 eq.), THF, rt, 1 h, 88%; (c) (i) PMPCH(OMe)₂ (1.1 eq.), TsOH·H₂O (0.01 eq.), 4 Å MS, MePh, rt, 22 h, (ii) DIBAL-H (1.25 eq.), MePh, 0 °C, 1 h, 91% (2 steps); (d) acryloyl chloride (4 eq.), DIPEA (7 eq.), DMAP (0.2 eq.), CH₂Cl₂, -78 °C to rt, 1.5 h, 84%; (e) acryloyl chloride (4 eq.), DIPEA (7 eq.), DMAP (0.2 eq.), CH₂Cl₂, -78 °C, 74%.

Thirdly, owing to the high polarity of the product, the use of EtOAc rather than Et₂O as a solvent for extraction was much more efficient. The biscyclohexyl byproduct could not be detected or visualized on TLC, but we found it to be easily removed by coevaporation with methanol; apparently the two form an azeotrope. Under these optimized conditions racemic **226** was finally obtained in pure form in 60% yield. Monodeprotonation of **226** and reaction with TBSCl gave **233** in 88% yield. This was treated with acryloyl chloride and Hünig's base to furnish the TBS-protected RCM-precursor **234**. Alternatively, **226** was converted into mono-PMB-ether **235** in 91% overall yield via formation of the cyclic 7-membered acetal and its subsequent reduction with diisobutylaluminium hydride to produce **235**. Acrylate formation was then carried out as before to yield **236**.

Table 7: RCM of **234** and structure of catalysts used.

						
Entry	Catalyst (eq.)	Solvent	[c]	Temperature	Time	Yield
1	127 (0.05)	CH ₂ Cl ₂	0.0046 M	50 °C	26 h	20%
2	128 (0.05)	(CH ₂ Cl) ₂	0.0046 M	80 °C	20 h	12%
3	127 (0.05)	(CH ₂ Cl) ₂	0.0046 M	80 °C	4 d	30%
4	127 (0.2)	CH ₂ Cl ₂	0.046 M	40 °C.	46 h	decomp.
5	127 (0.1)	MePh	0.046 M	111 °C	4 d	18%
6	128 (0.1)	MePh	0.046 M	111 °C	30 h	20%

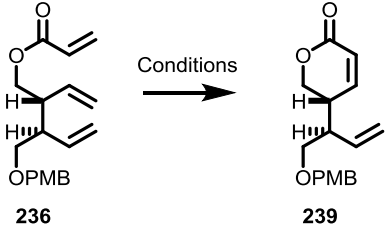
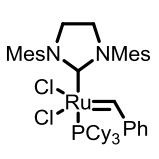
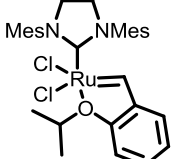
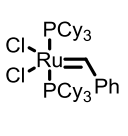
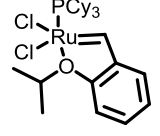
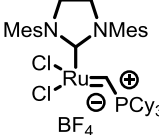
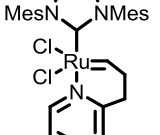
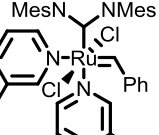
The yields represent isolated yield.

Different conditions were then screened to effect the desired ring-closing metathesis of **234** (Table 7). As can be seen from Table 7, neither Grubbs 2nd generation catalyst **127** nor Hoveyda-Grubbs 2nd generation catalyst **128** under different conditions led to formation of

preparatively useful amounts of the desired product. Moreover, in all cases using chlorinated solvents, the product was a 5:1 mixture of lactone **237** and its constitutional isomer **238**.

The best result was obtained with catalyst **128** in 1,2-dichloroethane, which gave 30 % of the desired product. The reactions were run in sealed microwave vials and it needs to be noted that after removing samples for TLC-analysis, the septum needed to be replaced. If not, the color of the reaction mixture turned brown very quickly, which indicated decomposition of the catalyst.

Table 8: RCM screening of **236** and structure of catalysts used.

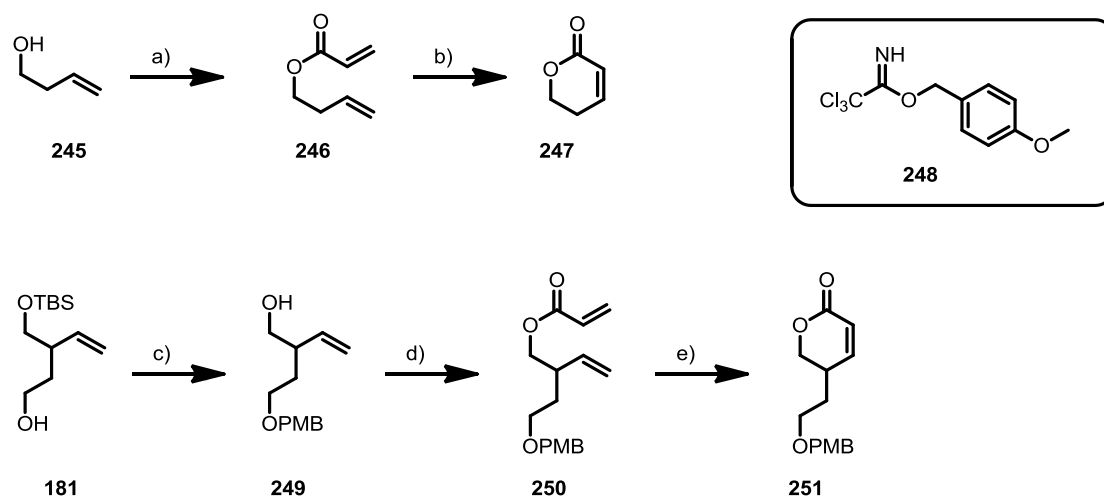
<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  <p>236 → 239</p> </div> <div style="border-left: 1px solid black; padding-left: 20px;"> <div style="display: grid; grid-template-columns: repeat(4, 1fr); gap: 10px;"> <div style="text-align: center;">  <p>127</p> </div> <div style="text-align: center;">  <p>128</p> </div> <div style="text-align: center;">  <p>240</p> </div> <div style="text-align: center;">  <p>241</p> </div> <div style="text-align: center;">  <p>242</p> </div> <div style="text-align: center;">  <p>243</p> </div> <div style="text-align: center;">  <p>244</p> </div> </div> </div> </div>						
Entry	Catalyst (eq.)	Solvent	[c]	Temperature	Time	Conversion(TLC)
1	241, 243, 244 (0.2)	CH ₂ Cl ₂	0.01 M	40 °C	24 h	no conversion
2	127, 128, 240, 242 (0.2)	CH ₂ Cl ₂	0.01 M	40 °C	24 h	< 10 %, byproducts
3	243 (0.2)	MePh	0.01 M	70 °C.	24 h	no conversion
4	127, 240, 241, 242, 244 (0.2)	MePh	0.01 M	70 °C	24 h	< 10 %, byproducts
5	128 (0.2)	MePh	0.01 M	70 °C	24 h	10-15%, byproducts

Only one catalyst was used in each experiment, but for reasons of clarity, the experiments are grouped to entries according to the observed range in conversion.

Following these rather unsatisfactory results, ring-closing metathesis of PMB-protected acrylate **236** was investigated (Table 8). A screening using stock solutions of the substrate in two standard solvents^[196] in combination with seven different catalysts was carried out.

Conversion was judged after 24 h of reaction time by analyzing samples of 1 μ L in parallel on TLC. The best result was obtained with Hoveyda-Grubbs 2nd generation catalyst **128** in toluene, but only with a marginal 10-15 % conversion (entry 5).

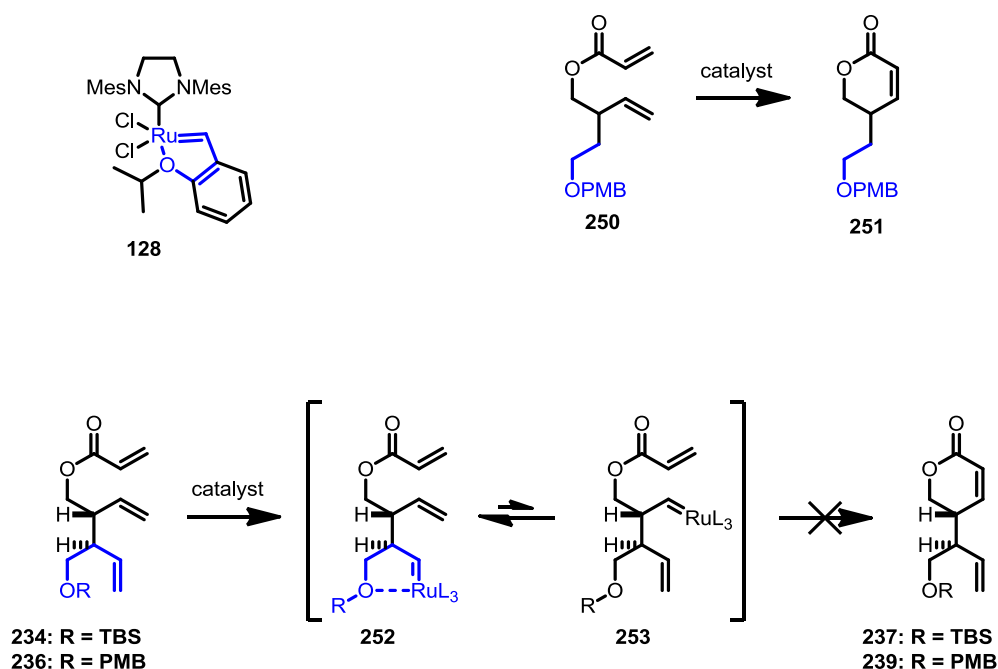
The lack of efficiency in this ring-closure raised some suspicion, since previous work in the group on RCM with a very similar substrate had not caused any problems. To ensure that the reason for the failure of the RCM were substrate-specific and not in any way related to the quality of the solvents or catalysts used, two simple test-substrates were synthesized and subjected to RCM (Scheme 31). Commercially available homoallyl alcohol (**245**) was treated with acryloyl chloride and Hünig's base to give the volatile and strongly smelling acrylate **246** with some residual diethyl ether and ethyl acetate. With catalyst **127**, this material smoothly underwent complete conversion to the desired lactone **247**, as determined on TLC by comparison to commercial material. Isolation, however, proved less successful, due to the volatility and the small scale of the reaction.



Scheme 31: Synthesis of RCM control substrates and successful RCM thereof. Reagents and conditions: (a) DIPEA (7 eq.), DMAP (0.2 eq.), acryloyl chloride (4 eq.), CH₂Cl₂, -78 °C to rt, yield not determined; (b) **127** (0.1 eq.), CH₂Cl₂, 23 °C, 24 h, 100% conversion, 15% isolated; (c) (i) **248** (1.25 eq.), CSA (0.05 eq.), CH₂Cl₂, (ii) MeOH, CSA (20%), one-pot, 76 %; (d) DIPEA (7 eq.), DMAP (0.2 eq.), acryloyl chloride (4 eq.), CH₂Cl₂, -78 °C, 5min, rt, 1h, 60%; (e) **127** (0.1 eq.), CH₂Cl₂, 40 °C, 64 h, 60%.

In parallel, the more elaborate test-substrate **251** was synthesized from **181**, the latter being available from the approach described in section 3.2.1. Alcohol **181** was protected with a PMB-group under acidic conditions using PMB-trichloroacetimidate **248**. After complete protection, the TBS-group was removed in the same pot to produce **249**. Acrylate **250** was then accessed as previously described for **234** and **236**. Ring closing metathesis showed quantitative conversion, but much lower isolated yield of **251**. Nevertheless, this time the desired product was isolated in 60% yield, supporting the notion that the reluctance of **234** and **236** to undergo RCM must be substrate-inherent.

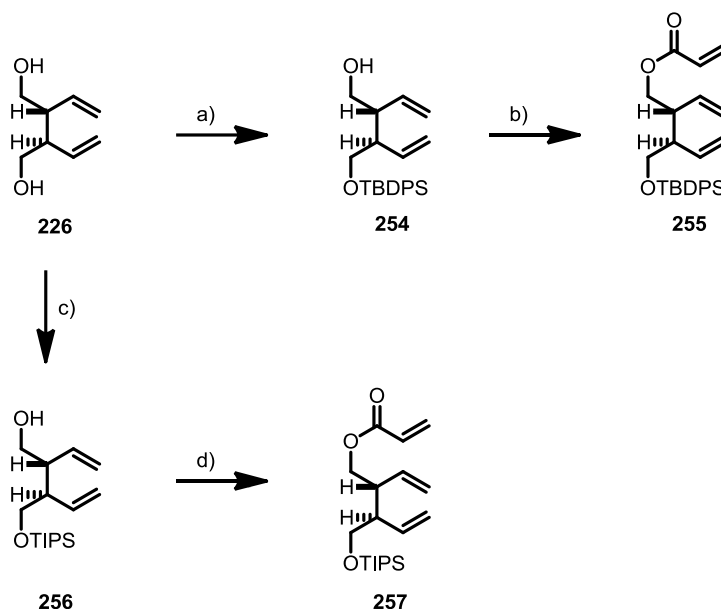
A possible rationale for these experimental findings is revealed by the comparison of the structure of the substrates with that of Hoveyda-Grubbs 2nd generation catalyst **128** (Scheme 32), which features a 5-membered metallacycle. In a similar manner, substrates **234** and **236** might replace a ligand on the ruthenium catalyst and form cyclic intermediates of the form **252**. Stabilized by the chelate effect, **252** is unlikely to form the isomeric carbene **253**, which is required for ring-closure to give **237** or **239**. The acrylic olefin is the least reactive towards the metathesis catalysts, therefore the intermediacy of **253** is likely to be crucial.



Scheme 32: Possible explanation for the failure of RCM of the TBS- and PMB-protected substrate

In contrast to **234** and **236**, **250** is not adorned with a vinyl group that could lead to formation of an intermediate like **252**, so the RCM can proceed with ease. The fact that the PMB-protected substrate **236** is even less reactive than the TBS-analog **234** further supports the

above hypothesis. The steric bulk of the aryl ring is kept at distance with a methylene spacer, whereas the bulky silane is directly attached to the oxygen; therefore, chelate **252** is likely to be more stable and less reactive for the PMB-group.



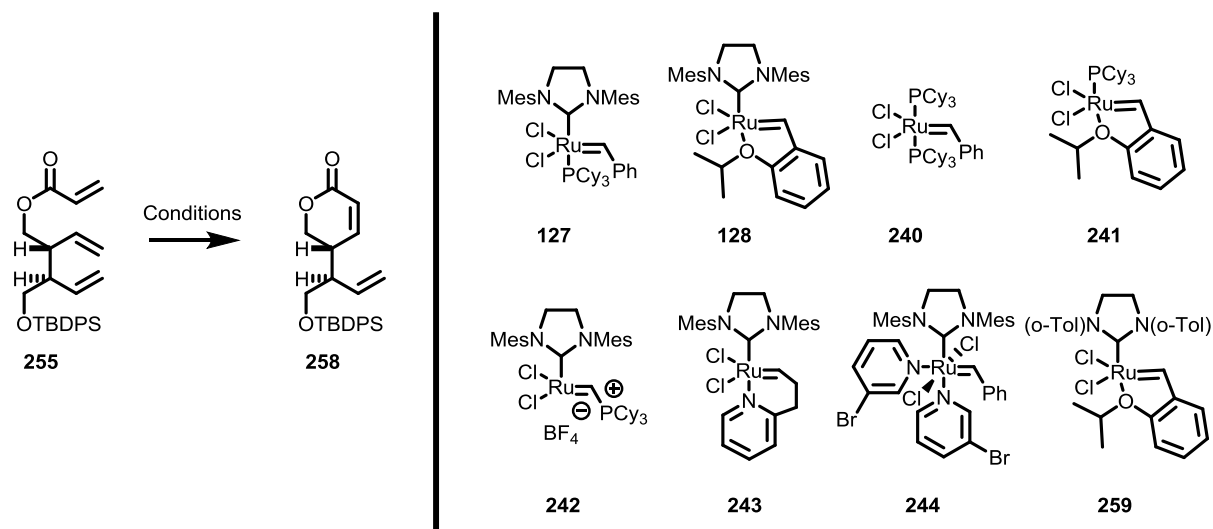
Scheme 33: Synthesis of TBDPS- and TIPS-protected RCM-precursors **255** and **257**. Reagents and conditions: (a) *n*-BuLi (1.05 eq.), TBDPSCI (1.0 eq.), THF, 0 °C, 5 min, rt, 1 h, 79%; (b) acryloyl chloride (4 eq.), DIPEA (7 eq.), DMAP (0.2 eq), CH₂Cl₂, -78 °C to rt, 1.5 h, 82%; (c) *n*-BuLi (1.05 eq.), TIPSCI (1.0 eq.), THF, rt, 3 d, 88%; (d) acryloyl chloride (4 eq.), DIPEA (7 eq.), DMAP (0.2 eq), CH₂Cl₂, -78 to 5 °C, 86%.

According to the hypothesis formulated before, the introduction of a more sterically demanding protecting group at the oxygen should facilitate the desired RCM. Hence, in a similar fashion to **234** and **236**, the TBDPS- and TIPS-protected congeners of **234** were synthesized (Scheme 33). TBDPS-protection was carried using *n*-butyl lithium as a base and gave **254** in good yield (79%). The latter was converted into acrylate **255** in the same way as described before. Likewise, TIPS-protection and acrylate formation of **226** provided RCM substrate **257** in 76% overall yield from **226**.

An array of eight catalysts and two solvents^[196] were screened for RCM of acrylate **255** (Table 9). As can be seen from Table 9, half of the catalysts studied gave either none of the product or only traces thereof after 24 h (entries 1,2,4 and 5). Grubbs and Hoveyda-Grubbs 2nd generation catalysts **127** and **128** as well as Piers-Grubbs 2nd generation catalysts **242** were effective in producing the desired compound in either solvent (entries **3** and **6**). Grubbs 3rd

generation catalyst **244** led to substantial amounts of desired product only in CH₂Cl₂, whereas **259**, the *ortho*-tolyl carbene variant of the Hoveyda-Grubbs 2nd generation catalyst was only active in toluene.

Table 9: Screening of conditions for RCM of acrylate **255**.



Entry	Catalyst (eq.)	Solvent	[c]	Temperature	Time	Product
1	241, 243, 259 (0.2)	CH ₂ Cl ₂	0.01 M	40 °C	24 h	no conversion
2	240 (0.2)	CH ₂ Cl ₂	0.01 M	40 °C	24 h	traces
3	127, 128, 242, 244 (0.2)	CH ₂ Cl ₂	0.01 M	40 °C	24 h	30-70 %, byproducts
4	243 (0.2)	MePh	0.01 M	70 °C.	24 h	no conversion
5	240, 241, 244 (0.2)	MePh	0.01 M	70 °C	24 h	traces, byproducts
6	127, 128, 242, 259 (0.2)	MePh	0.01 M	70 °C	24 h	10-50%, byproducts
7	242 (0.05 + 0.10)	CH ₂ Cl ₂	0.02 M	40 °C	72 h	65%, isolated
8	242 (0.2)	CH ₂ Cl ₂	0.02 M	40 °C	48 h	67%, isolated

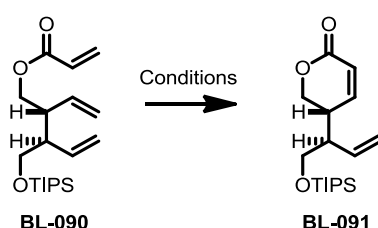
Conversion was judged by TLC, except entries **7** and **8**, which represent isolated yields.

In CH₂Cl₂, Piers-Grubbs 2nd generation catalyst **242**^[197] was found to be the most active and produced minimal amounts of by-products. In toluene, catalyst **259** was the most active, but concomitantly produced several additional products (as indicated by TLC analysis). Increased formation of by-products in reactions performed in toluene was a general trend and may be attributed to the elevated temperature. In a preparative experiment (entry **7**), an attempt to

lower the catalyst loading of **242** to 5 mol% was ineffective; only trace conversion was observed after 24 h and addition of another 0.1 equivalents of catalyst was necessary to drive the reaction to completion. With 0.2 equivalents of catalyst, the reaction worked reliably, also on a larger scale (entry **8**).

After the successful implementation of the RCM with the TBDPS-protected substrate **255**, the corresponding TIPS-derivative **257** was investigated for its ability to undergo RCM (Table **10**) in dichloromethane. The results with this acrylate were comparable with the ones for the TBDPS-protected substrate **255**. Again, catalysts **127**, **128** and **244** showed notable conversion (entry **3**) and catalyst **242** (entry 4) proved superior in affecting the desired reaction. Conversion seemed slightly lower than for the TBDPS-case.

Table 10: Screening for RCM of acrylate **257**.



Entry	Catalyst (0.2 equiv.)	Solvent	[c]	Temperature	Time	Product
1	241, 243	CH ₂ Cl ₂	0.01 M	40 °C	24 h	no conversion (TLC)
2	240, 259	CH ₂ Cl ₂	0.01 M	40 °C	24 h	traces (TLC)
3	127, 128, 244	CH ₂ Cl ₂	0.01 M	40 °C	24 h	30-50 % (TLC), byproducts
4	242	CH ₂ Cl ₂	0.01 M	40 °C.	24 h	more than 50% (TLC)

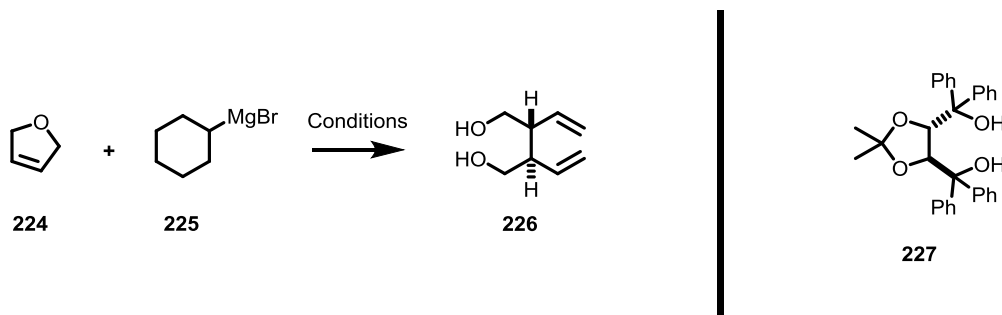
Conversion were judged by TLC .cf. Table **9** for catalyst structures.

3.4.2 Attempted Enantioselective Dimerization

With reasonably satisfactory conditions for the RCM step established, the enantioselective ring-opening dimerization of **224** was investigated (Table **11**). Using the improved conditions for the racemic version of the reaction, attempted dimerization at - 12 °C gave no conversion to the desired product, even after warming to ambient temperature (entry **1**). Exactly following the protocol of *De Meijere* and running the reaction at 0 °C, improved the result slightly; but only traces of the desired product were observed and isolated after 3 days (entry

2). An attempt was then made using more rigorously anhydrous conditions, *i.e.* employing freshly distilled titanium isopropoxide and using a shortpath distillation apparatus for distilling off the isopropanol by-product instead of an argon-flushed rotary evaporator (entry 3). However, the result was only marginally affected. A report from Seebach^[198], which demonstrated the mono titanium TADDOL complex to be more active and selective in additions of organozinc compounds to aldehydes, prompted the use of only one equivalent of TADDOL (entry 4).

Table 11: Variations on literature conditions for enantioselective dimerization.



entry	T (°C)	Ti (source)	227 (eq.)	Grignard	Removal of ⁱ PrOH	Yield
1	-12 to rt	Ti(O ⁱ Pr) ₄	2 eq.	commercial	rotavap	no reaction
2	0	Ti(O ⁱ Pr) ₄	2 eq.	commercial	rotavap	2%
3	0	Ti(O ⁱ Pr) ₄ freshly distilled	2 eq.	commercial	distillation under Ar	3%
4	0	Ti(O ⁱ Pr) ₄ freshly distilled	1 eq.	commercial	distillation under Ar	8%
5	0	Ti(O ⁱ Pr) ₄ freshly distilled	1 eq.	fresh	distillation under Ar	8%
6	0	Ti(O ⁱ Pr) ₄ freshly distilled	2 eq.	fresh	distillation under Ar	3%
7	0	CpTiCl ₃	1 eq.	fresh	distillation under Ar	no reaction

This led to higher conversion, but still, product was only isolated in an unsatisfactory yield of 8%. Next, the commercial cyclohexylmagnesium bromide was replaced by a freshly prepared reagent, which did not change the outcome of the experiment (entry 5). As a control, the racemic version of the reaction was performed again and could easily be reproduced in 45 % yield. In another attempt, after azeotropic removal of isopropanol, the bis-TADDOL complex was triturated with diethyl ether, as was described by Seebach^[199,200] (entry 6). This led to no

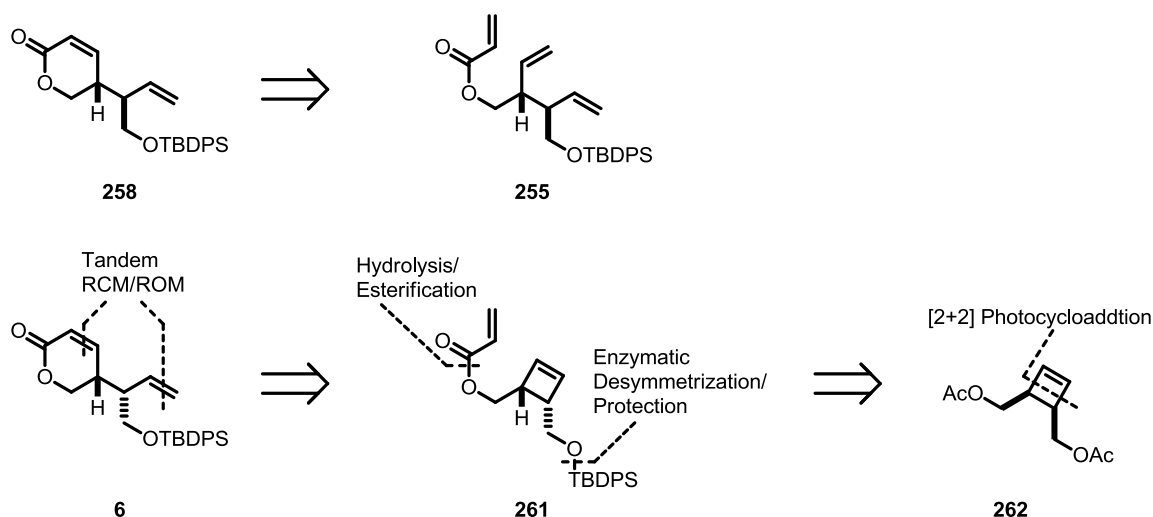
improvement, either. Due to the large conformational similarity^[198], one last attempt was then made, using cyclopentadienyltitanium trichloride as a titanium source and forming the same mono-TADDOL complex which is used as a precursor for the *Duthaler-Hafner* reagent^[201]. Unfortunately, this complex also proved to be catalytically inactive (entry **7**).

These unsatisfactory results led us to us to abandon the enantioselective dimerization reaction and find an alternative access for the RCM substrate. It is also of note, that for reaction of 1 g of dihydrofuran, a striking 6.6 g of TADDOL are required for formation of the catalyst. Despite the fact that the chiral ligand can be recovered, this would have been very problematic operationally on a larger scale.

3.5 Synthesis of Key Intermediate **290** and Related Studies

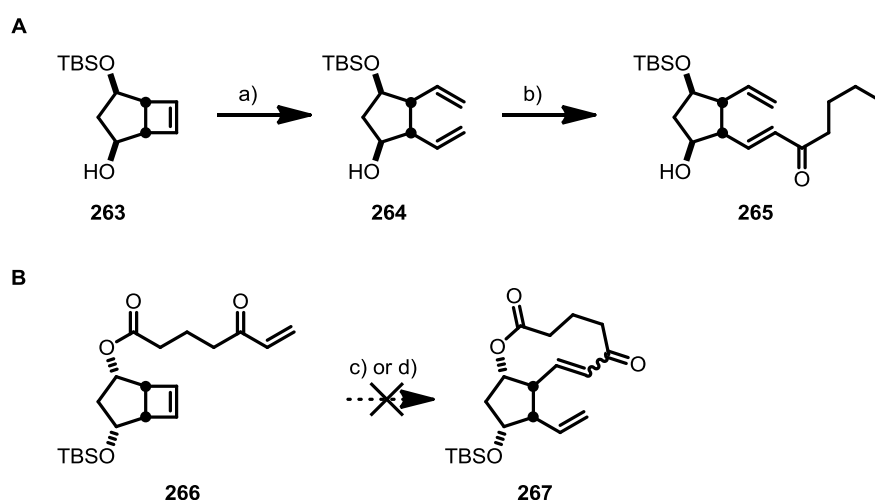
3.5.1 Fourth Generation Synthetic Approach via Building Block **6**.

Given the fact that conditions had been successfully established for the conversion of **255** and **257** into the desired α,β -unsaturated lactones by means of RCM, subsequent efforts were directed at the identification of alternative diene presursors (in place of **255/257**) for this critical transformation. In this context, our attention was drawn to cyclobutene derivative **261** (Scheme **34**), which should be accessible from *meso*-diacetate **262** by means of a known enzymatic saponification reaction^[202], followed by TBDPS-protection and acrylate formation. Evidently, the choice of TBDPS as protecting group was based on the findings described in the previous subchapter. A number of syntheses of cyclobutene derivative **262** have been described, all using a [2+2]-photocycloaddition as a key step. The preparation of the enantiomer of **261** has been reported in the literature, making use of an enzymatic esterification reaction.^[203]



Scheme 34: Fourth generation retrosynthetic analysis via building block **6**. RCM: Ring-closing metathesis; ROM: Ring-opening metathesis.

In addition to control over absolute stereochemistry, we anticipated a potential improvement in reactivity during the metathesis reaction, due to the release in ring-strain. *Snapper's* group has previously investigated the phenomenon of strain-release tandem ring-opening/cross metathesis reactions using cyclobutene substrates. In this context, the ability of the ring-opened vinylidene ruthenium adduct to preferably undergo cross metathesis with a terminal olefin as opposed to ring-opening polymerization is of note.^[204,205] However, there was a caveat: Enones had proved to be very recalcitrant to the tandem reaction conditions. This was exemplified by the overall transformation of cyclobutene derivative **263** to enone **265** (Scheme **35A**). A one-pot process was not feasible; only ring-opening metathesis polymerization (ROMP)-products were observed. However, when starting olefin **263** was ethenolyzed to intermediate **264**, using Grubbs 1st generation catalyst, the desired cross metathesis could subsequently be effected with pure **264** in the presence of Hoveyda-Grubbs 2nd generation catalyst.^[206] Comparable results were obtained with a number of closely related bicyclo[3.2.0]heptenes.^[207] *Snapper* also reported failure to achieve tandem ROM/RCM of substrate **266** was another finding (Scheme **35B**). Instead of the desired 10-membered ring-product, ROMP was the main reaction pathway and, under an atmosphere of ethylene, dimerization of the starting material was observed.^[207]



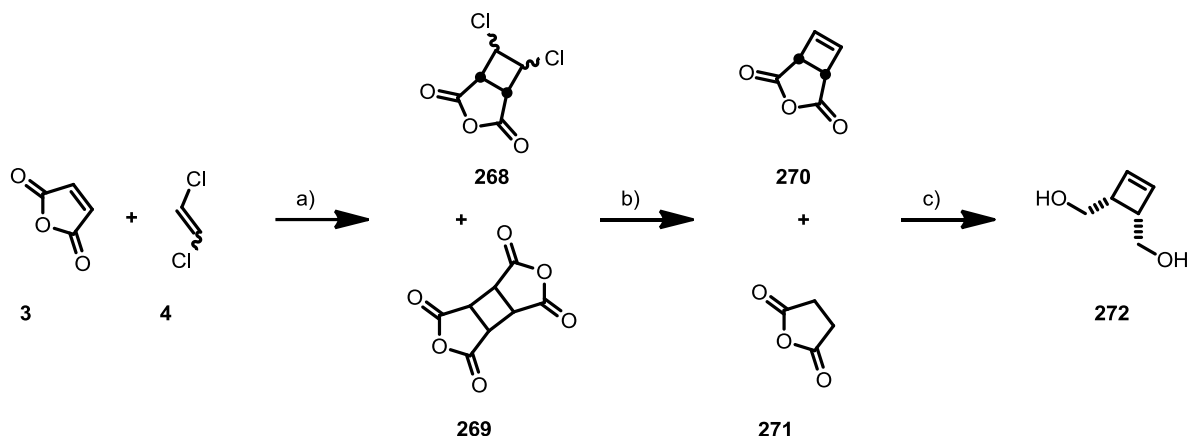
Scheme 35: Examples of successful and attempted metathesis by *Snapper*.^[206,207] Reagents and conditions: (a) ethylene, **240** (0.05 eq.), benzene (0.01 M), 87%; (b) oct-1-en-3-one, **128** (0.05 eq.), CH₂Cl₂ (0.2 M), 40 °C, 70-90%; (c) **240** (0.05 eq.), CH₂Cl₂ (0.022 M), ROMP product; (d) ethylene, **240** (0.05 eq.), CH₂Cl₂ (0.022 M), 17% dimer.

For the 6-membered ring that was to be formed in the transformation of **261** into **6**, however, we anticipated a more favorable outcome than in *Snapper's* case, due to the greater ease of formation of a 6-membered vs. a 10-membered ring. Moreover, based on *Snapper's* findings, a stepwise sequence of ROM and RCM could be a viable alternative, if cyclobutene ring-opening and subsequent RCM would not take place under the same conditions. We were also cognisant of the fact that **6** is diastereomeric to **258** and, thus, might display different or no reactivity in the metathesis step. This was a point to be addressed early on.

3.5.2 Synthesis of *Meso*-Diol **272**

The synthesis of diol **272** (Scheme **36**) started from commercially available maleic anhydride (**3**) and *trans*-1,2-dichloroethene (**4**).^[208] Under irradiation a mixture containing all possible isomers of cycloadduct **268** was formed. Reproducibility of the reaction was poor - sometimes complete consumption of the starting anhydride was observed within 4 days and other times it took up to 7 days. The outcome did not improve when the reaction mixture was degassed or when dichloride **4** was filtered through aluminium oxide prior to the reaction. Two different sources of light were investigated: A high pressure mercury arc or an array of 260-400 nm cold cathodes. Reaction rates were comparable, but it was noted that when using the cold cathodes, visible amounts of a precipitate were formed that were removed by decanting.

Apart from a mixture of isomers of **268**, the main constituent of this solid was tentatively assigned to be dimer **269** on the basis of a single resonance at 4.11 ppm in the ^1H NMR spectrum (d_6 -acetone). The literature report described purification of **268** by trituration of the crude material with diethyl ether. In our hands, this only led to formation of a slurry, therefore the crude product was directly used for the following step.



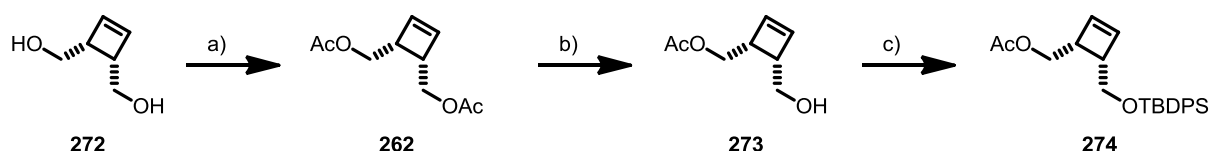
Scheme 36: Synthesis of *meso*-diol **272**. Reagents and conditions: (a) $h\nu$, EtOAc, 4 to 7 d, 36-87% (NMR yield); (b) Zn^0 , Ac_2O , MePh, 85 °C, 1-4 d; (c) LiAlH_4 (1.65 eq.), THF, 65 °C, 31% (3 steps).

Crude vicinal dichloride **268** was dissolved in a mixture of toluene and acetic anhydride and reacted with zinc powder as a reducing agent to give **270**. Mechanical stirring was crucial to keep the metal suspended and to avoid cake formation. This step displayed issues of reproducibility as well: Sometimes it was completed within 21 h, other times it took 3 d until all the starting material had reacted. Often, additional zinc and acetic anhydride were needed to push the reaction to completion. In our last batch, we found that after stalling, addition of 0.05 eq. of acetic acid pushed the reaction to completion without the need of adding any other reagents. It appears conceivable at this point that the use of clean and dry acetic anhydride in fact does not allow the reaction to proceed, whereas residual acetic acid serves as a beneficial acid catalyst. The crude anhydride was reduced to diol **272** with lithium aluminium hydride in boiling THF. At this stage, all the impurities could be chromatographically removed and the desired **272** was obtained in yields between 15 and 35% over 3 steps. The reduction was initially carried out in Et_2O according to the method of *Neidlein*^[209] and the reaction turned out to be a slurry/suspension. THF ^[210] was later found to be superior, since it would give a homogenous reaction mixture and could be heated to higher temperatures.

Purification of the zinc reduction product was first performed via sublimation as previously described.^[208] Typically the product was contaminated with succinic anhydride, which co-sublimed and was derived from maleic anhydride. However, yields were low and substantial amount of the crude cyclobutene **270** seemed to have decomposed to intractable black tar during purification. Therefore, we tested direct LiAlH₄-reduction of the crude material, which gave comparable results. We surmise that sublimation of **270** in small batches might be a means of reducing decomposition and improving the overall yield substantially.

3.5.3 Desymmetrization of *Meso*-Diol **272**

With the cyclobutene **272** in hand, the enzymatic desymmetrization was investigated (Scheme 37). Diol **272** was exhaustively acetylated^[203] with acetic anhydride in pyridine. One of the acetate groups in **262** could then be selectively removed according to the method of *Harvey* and *Crout*^[202] to give chiral acetate **273**. This enantioselective hydrolysis reaction was performed with commercially available *Pseudomonas fluorescens* lipase in a neutral buffered medium. The released acetic acid was continuously neutralized by addition of sodium hydroxide from an automated titration apparatus and the amount of base used served as a direct measure of reaction progress. Since spontaneous racemization of *ent*-**273** over time had been reported,^[211] the material was immediately protected as the TBPDS ether **274**.



Scheme 37: Desymmetrization of diol **272** and protection to prevent racemization. Reagents and conditions: (a) Ac₂O, pyridine, rt, 14 h, 91%; (b) *Pseudomonas fluorescens* lipase, buffer pH 7 (67 mM), neutralization with NaOH (1 M), rt, yields *cf.* Table 12 ; (c) TBDPSCl (1.1 eq.), ImH (3.7 eq.), DMF, rt, 32 h, 97%.

Harvey and *Crout*^[202] reported a yield of 75% and an *ee* > 97% when the reaction was stopped after addition of 0.8 eq. of base. Only 86% *ee* with no given yield was observed with 1 eq. of base as the endpoint of reaction. We were not able to reproduce this result and obtained 92% *ee* when stopping at 0.8 eq. base (entry 1). A comparable level of enantioselectivity was obtained for each subsequent batch, even if the total amount of base was increased to 0.95 eq. (entries 2-5); the *er* varied from 97:3 to 95:5, but yields were higher if more base was

added. The yields obtained for **273** covered a range from 69% to 81%. In all cases, at least 10% of starting material **262** was recovered and the product of two-fold saponification **272** was observed, too.

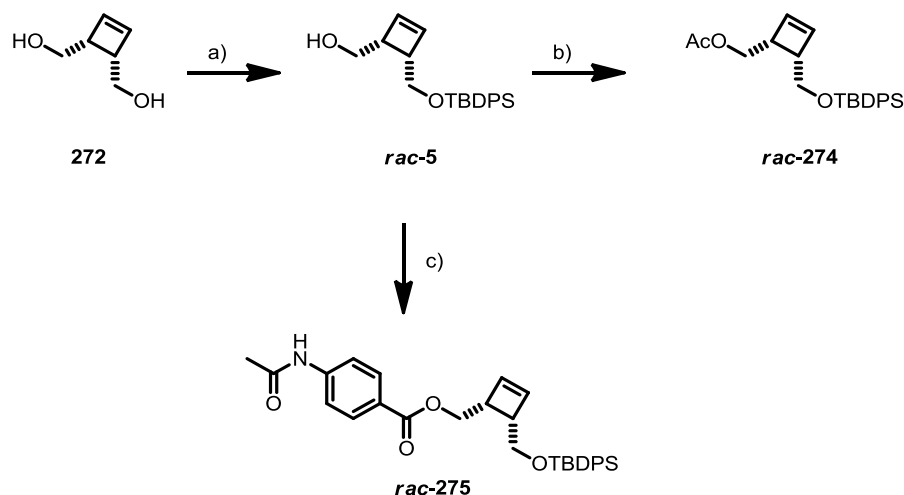
Table 12: Yield and enantiopurity observed in different batches of **273** and recovery of starting **262** and diol **272**.

entry	conversion / %	273 / %	<i>ee</i> / %	262 / %	272 / %
1	80	61	94	20	n.d.
2	95	77	92	11	n.d.
3	95	82	92	11	4
4	96	72	90	10	5
5	95	69	90	19	4

All yields refer to isolated material. Enantiomeric excess was determined by HPLC or SFC of derivative **275** (*vide infra*). n.d. = not determined.

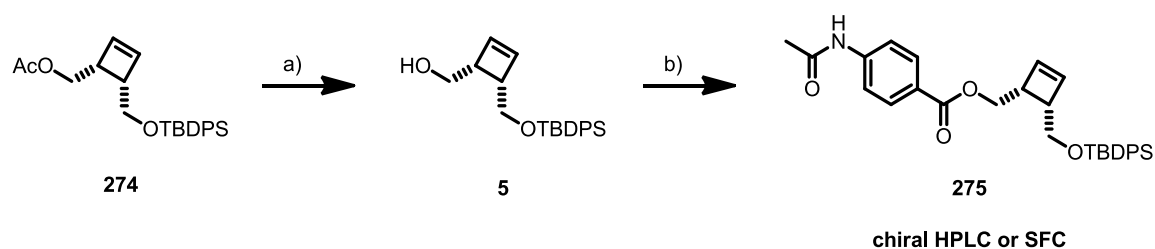
A drop in pH-value was noted when adding the enzyme to the reaction mixture. While no correlation was found between the mass of enzyme added and the amount of base needed to neutralize this initial drop, it might reflect a change in the quality of the enzyme over time and account for some of the variability.

Because cyclobutenes can easily undergo ring-opening to dienes under thermal conditions^[210], GC was not an option for the determination of enantiopurity, instead liquid chromatography was the method of choice. A small amount of **272** was mono-TBDPS protected^[165] to give *rac*-**5** (Scheme 38). Via acylation of the hydroxy group, derivatives *rac*-**274** and *rac*-**275** were accessible. However, neither the free primary alcohol *rac*-**5** (Scheme 40) nor the corresponding acetate *rac*-**274** could be resolved by chiral HPLC. Moreover, for both compounds UV-absorption was poor, thus affecting sensitivity of detection, and very short retention times were observed on the available columns. Neither a *p*-nitro benzoate derivative nor a mixture of diastereomeric MTPA esters could be separated on a chiral column, either. *Para*-acetamido benzoate *rac*-**275** solved both the problem of too low polarity and the issue of poor UV absorption. For this derivative, the two enantiomers could be cleanly separated by HPLC. In a later phase of the project, *ee* determination was performed using SFC.



Scheme 38: Synthesis of standards tested for chiral HPLC/SFC. Reagents and conditions: (a) *n*-BuLi, TBDPSCI, THF, 0 °C, 30 min, rt, 2.5 h, 66%; (b) Ac₂O (2.2 eq), pyridine (3.1 eq.), rt, 18 h, 62%; (c) 4-acetamidobenzoic acid, EDCI, DMAP, rt, 25%.

For each batch of **274**, a small sample was saponified and transformed into *p*-acetamido benzoate **275** (Scheme 39). This material was analyzed by HPLC or SFC, before the synthesis was continued.

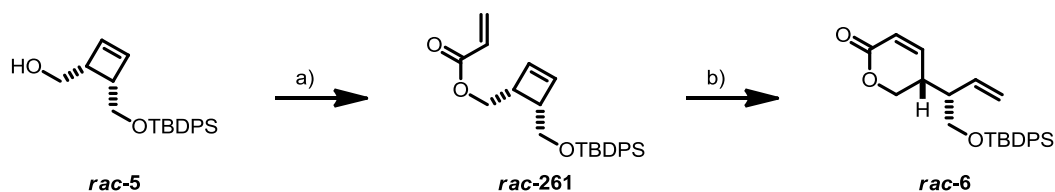


Scheme 39: Standard procedure for *ee* determination of chiral material. Reagents and conditions: (a) K₂CO₃ (0.2 eq), MeOH, rt, 5 h, quant.; (b) 4-acetamidobenzoic acid, EDCI, DMAP, rt, 65-90%.

When producing intermediate **5** on larger scale, we noted a drop in optical rotation. Because mono-acetate **273** had been reported to racemize over time^[211] and since silyl groups can migrate, especially under basic conditions,^[212] we tested for potential racemization via migration of the TBDPS group under saponification conditions. This was again performed by chiral HPLC analysis of derivative **275** and, gratifyingly, no erosion of absolute stereochemistry was observed.

3.5.4 Optimization of the Metathesis Reaction

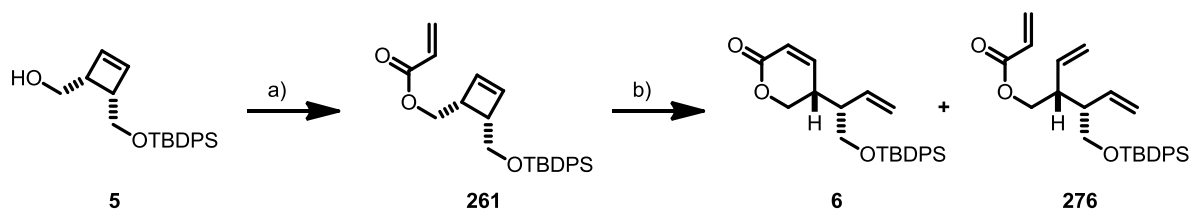
In parallel with the development of the method for the determination of the enantiopurity of **274**, some of the racemic material was used for a preliminary investigation of the desired tandem metathesis reaction. **Rac-5** was thus reacted with acryloyl chloride and Hünig's base under standard conditions^[213] to give acrylate **rac-261** in 75% yield (Scheme 40). A TLC-screening for the feasibility of the tandem metathesis was then carried out. To this end, a stock solution of the substrate was added to 0.2 eq. portions of eight different catalysts (Table 9, p. 72) in HPLC vials and the mixture was stirred at 40 °C for 26.5 h. Conversion to **rac-6** was judged by analyzing equal aliquots of the reaction mixtures on TLC and monitoring for a product with comparable polarity as **258** (*vide supra*).



Scheme 40: Synthesis of racemic acrylate **261** and TLC screening of tandem ROM/RCM. Reagents and conditions: (a) acryloyl chloride (4 eq.), DIPEA (7 eq.), DMAP (0.2 eq), CH_2Cl_2 , -78 to -5 °C, 3.5 h, 75%; (b) **127** - **259** (0.2 eq.), CH_2Cl_2 (0.01 M), 40 °C, 26.5 h, only putatively observed in TLC, not isolated.

A product spot within the predicted R_f range was observed for all catalysts except **243** and **244**. Best conversions were achieved in the order Hoveyda-Grubbs 1st generation > Grubbs and Hoveyda-Grubbs 2nd generation >> Grubbs 1st generation catalyst. It needs to be noted that for the three most active catalysts no trace of starting material was left; at the same time the metathesis of cyclobutene **rac-261** in all cases, produced a number of side or decomposition products, that were weakly visible as streaks in TLC. This phenomenon had not been observed with substrate **255**.

After the enantiomeric excess of **274** had been established as being satisfactory, the metathesis reaction was investigated more closely. Using the standard method, small batches of **261** were prepared (Scheme 41) and used within two or three days. This was based on the observation that some of the remaining starting material for the racemic metathesis screening had polymerized in its neat form when stored at ambient temperature.



Scheme 41: Formation of **261** and conditions for attempted tandem ROM/RCM. Reagents and conditions: (a) acryloyl chloride (4 eq.), DIPEA (7 eq.), DMAP (0.2 eq), CH₂Cl₂, -78 to -5 °C, 3.5 h, 75%; (b) Catalyst (*cf.* Table 13), CH₂Cl₂, 40 °C, isolated yields. n.d. = not determined.

In the first attempt (Table 13, entry 1) using HG-I as the best catalyst identified in the screening with *rac*-**261**, only traces of enoate **6** were isolated. Despite looking homogeneous on TLC, the material contained additional impurities as revealed by ¹H NMR. Unfortunately, the material corresponding to *rac*-**261** on TLC had completely decomposed. For catalyst G-I (entry 2), which had also been shown to be active in the initial screening, and which is much cheaper than any of the *N*-heterocyclic carbene-bearing ruthenium-based metathesis catalysts, the product was again largely contaminated with impurities and the yield was low; however, the unreacted starting material had remained intact. Based on the work of *Snapper*^[206,207] we then investigated the effect of ethylene as an additive with the HG II catalyst (entry 3). Some conversion to the desired product was observed by TLC, but only decomposed material could be isolated. Surprisingly, what had been presumed to be recovered unreacted starting material **261** proved to be clean triene **276** (Scheme 41).

Table 13: Conditions attempted for tandem ROM/RCM of **261**.

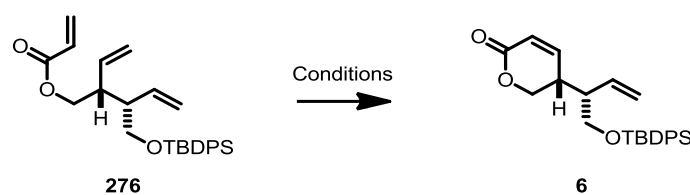
Entry	Catalyst (mol-%)	[c] /mM	T / °C	t / h	261 / %	6 / %	276 / %
1	HG I (20)	10	40	24	-	< 16 %, impure	-
2	G I (20)	10	40	24	40 %	< 10 %, impure	-
3	HG I (20), ethylene	7	40	24	-	-	82%
4	HG I (10), ethylene	12	40	7	-	-	84%
5	PG II (20), ethylene	2	40	16	n.d. content 2/3	trace	n.d. content 1/3
6	G-I (6), ethylene	5	40	7	-	-	90%
7	G-I (6), ethylene	30	rt	3	-	-	94%

All yields refer to isolated material. n.d. = not determined.

Increasing the substrate concentration and lowering the catalyst loading (entry **4**) led to a much faster reaction with a comparable yield of **276**. Piers-Grubbs II catalyst, which had delivered best results for the formation of the 6-membered enoate from **255**, under an atmosphere of ethylene produced only traces of the desired tandem metathesis product **6** (entry **5**). NMR analysis of the crude mixture revealed around 33% conversion to **276**. In view of the cost for scaling up this reaction, G-I catalyst (entry **6**) was tested and, when compared to the HG II catalyst, gave both better yields and faster conversion at lower catalyst loadings and even at lower concentration. By increasing the concentration, the reaction became very fast even at ambient temperature (entry **7**). Unfortunately, while the isolated product of a large-scale reaction (entry **7**) was dried *in vacuo* to remove all residual solvent, the material partly polymerized. Accordingly, for subsequent scale-up reactions, yields were not determined for **261** and **276** but only at the stage of **6**. The latter is bench stable for longer periods of time, as exemplified by a small sample stored on the bench top for 6 months without showing any signs of decomposition or change. In later operations on large scale, the catalyst loading could be decreased to 4.5 mol-%, at the cost of prolonged reaction times between 24 to 36 h.

Acrylate **276** was subjected to the best set of conditions found for RCM with **255** (Table 9, p. 72). The reaction was carried out using **P-G II** catalyst in a sealed tube over 3 days (Table 14, entry **1**) and provided **6** in 69% yield along with 25% of unreacted starting material. However, high loading (0.2 eq.) of the expensive catalyst had to be used, which might pose a problem when large amounts of this material would have to be produced in the future.

Two experiments were carried out to determine whether the use of certain additives might increase conversion and allow for lowering of the catalyst loading. Following a procedure described by *Ghosh* and coworkers, G-I was used in combination with titanium tetraisopropoxide as an additive (entry **2**) to prevent formation of unproductive chelates.^[214] Unfortunately, no more than 10 % conversion was observed by TLC. *Lipshutz* and coworkers combined G-II with copper(I) iodide as a phosphine scavenger, forming highly active iodo ruthenium complexes in ethereal solvents. The latter were reported to be efficient catalysts for demanding cross metathesis with electron-deficient olefins.^[215] With acrylate **276**, no reaction was observed (entry **3**). It was anticipated, that increasing the concentration of the substrate while maintaining the concentration of the catalyst might be a way of lowering the catalyst loading (entry **4**).

Table 14: Reagents and conditions for optimization of the ring-closing metathesis of **276**.

Entry	Conditions (eq.)	Solvent	[c] / mM	T / °C	T / h	Product
1	P-G II (0.2)	CH ₂ Cl ₂	10	40 °C	68	69 % + 25 % SM
2	G-I (0.16), Ti(OiPr) ₄ (4)	CH ₂ Cl ₂	7	40 °C	24	10 % conversion (TLC)
3	G- II (0.1), CuI (1.4)	Et ₂ O	7	40 °C	7	no reaction
4	P-G II (0.05)	CH ₂ Cl ₂	28	40 °C	120	<18 %
5	P-G II (0.20), 20 mbar vacuum	dichloro-benzene	10	40 °C	24	25 % + 15 % SM
6	P-G II (0.20)	CH ₂ Cl ₂	15	40 °C	96	>45%, >25% recovered
7	P-G II (4*0.5 portions), freeze and thaw	CH ₂ Cl ₂	15	40 °C	65	>81%

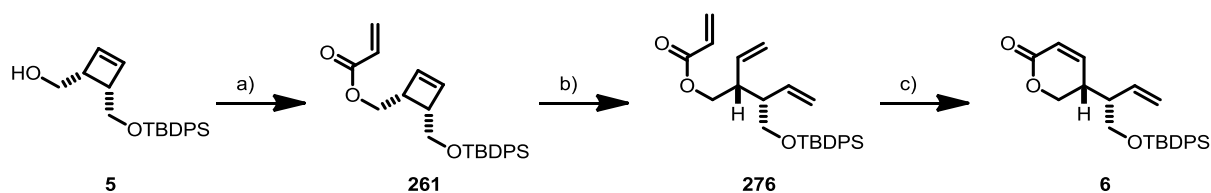
All yields refer to isolated material unless otherwise stated.

This was not successful. Since the reaction was carried out in a closed vessel, it was speculated that the build-up of ethylene might affect the chemical equilibrium and not allow for complete conversion. Per molecule of starting material, one molecule of ethylene is produced. To test this, the reaction was carried out in high-boiling *o*-dichlorobenzene under reduced pressure (entry **5**). Conversion was not improved in comparison to the sealed vessel. Additionally, purification and work-up were more tedious with the high-boiling solvent.

Part of the polymerized **276** described above could be reused. It was extracted with benzene and a sample was evaporated to assess mass recovery. The material contained visible solid pieces, therefore purity was likely lower than 95%. With this material, a 100 mg scale reaction was performed, using P-G II (entry **6**). The reaction stalled after 1 d and was left to stir further without any change. Considering the unknown purity of the starting material, a yield higher than 45% was determined and more than 25% of **276** was recovered. Competing catalyst decomposition was the next possibility to be investigated. Instead of adding 0.2 eq. in one portion at the outset of the reaction, PG-II was added in 4 batches of 5 mol% each. This indeed

improved conversion and more than 90%^{xv} of **6** was obtained on a 600 mg scale. These findings are in line with results disclosed by Piers subsequent to our studies on **276**,^[216] which showed that while initiation with PG-II is very fast, this catalyst also undergoes relatively rapid thermal unimolecular decomposition.

At this point, It was decided that, for the time being, subsequent steps of the synthesis deserved more attention before the RCM was to be investigated any further. Due to the risk of polymerization, during the overall process from cyclobutene **5** to enoate **6** (Scheme 42), the intermediates **261** and **276** were never evaporated to dryness. Instead, they were kept in solution and solvent switches were performed where appropriate. On larger scale, the catalyst loading could be lowered to 12 mol% and it was found that a minimum of 2.5 mol% was required per portion to obtain useful boosts in conversion. In addition, degassing the solvent by freeze and thaw (3 cycles) was beneficial for reproducibility. When this was omitted, the reaction was observed to stall at around 10% conversion, notwithstanding addition of more catalyst. Operationally, two different protocols were used: (1) Substrate **6** was dissolved and degassed; catalyst was added using a small volume of non-degassed solvent. (2) Substrate was dissolved; catalyst was added using a small volume of solvent; the mixture was degassed immediately. Because variability of yield was high, we observed no clear difference using either protocol. However, in the preparation of our last batch of **6** a color change from green during the first cycle to brown during the second cycle was observed.



Scheme 42: Overall solution for acrylation RCM sequence. Reagents and conditions. (a) acryloyl chloride (2 eq.), DIPEA (3.5 eq.), DMAP (0.2 eq), CH₂Cl₂, -78 °C, 20 min; (b) G-I (0.04 eq.), ethylene, rt, CH₂Cl₂, 26 h; (c) PG-II (0.12 eq.), CH₂Cl₂, 40 °C, 44 h, 46% (3 steps) and 4% (3 steps) recovery of **276**.

While the origin of this color change is unknown at this point, this observation could suggest that it might be beneficial to separately degas the substrate solution, and to dissolve and add

^{xv}The yield was calculated assuming 100% purity of the starting material. Because there were solid pieces of polymers visible, the actual purity was lower and thus the actual yield must have been higher.

the catalyst with previously degassed solvent.^{xvi} Finally, the isolation of lactone **6** shall be commented. Several rounds of chromatography were required for removal of the ruthenium catalyst and its decomposition products. This would change the color of the material from black to a light yellow or light brown. Attempted catalyst removal by filtration through cellite did not improve the process. Moreover, some fraction of the product were contaminated by an impurity that was extremely hard to separate on silica. This contaminant was very UV-active, but not detectable by NMR. Batches containing said impurity did perform identical to “TLC-clean” material in subsequent steps.

3.5.5 Conjugate Addition to **6** and Elaboration into **290**.

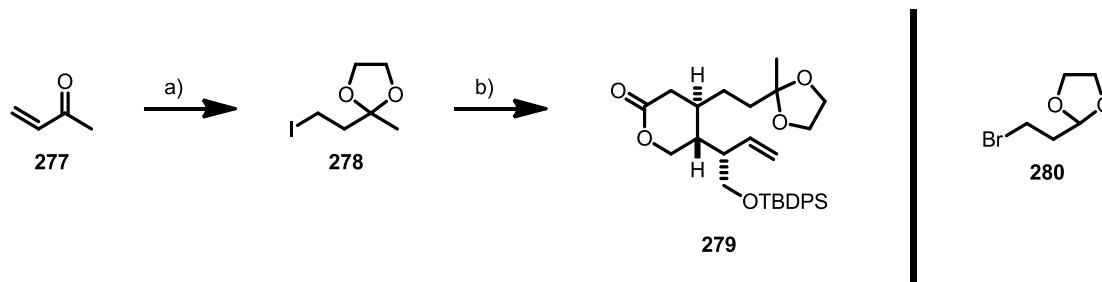
With sufficient amounts of δ -lactone **6** in hand, stereocontrolled introduction of a vinyl iodide functionality was explored. In the course of these studies different tactics were evaluated and the results of these efforts are summarized chronologically in this section.

3.5.5.1 Synthesis of an *E/Z* Mixture of **164**

Our first experiments were centered around a *Takai* olefination of a ketone derived from **279** (Scheme **43**). Known iodide **278** was prepared according to a one-pot procedure by *Larson* and *Klesse*.^[217] The yield was much lower than reported, despite the use of freshly distilled methylvinyl ketone **277**. It is likely that residual HCl in the chloro silane was interfering with the reaction and that the latter must be distilled immediately prior to use. An alternative procedure was reported by *Stowell* and coworkers, involving first treatment with hydroiodic acid and ketal formation in a second step.^[218] This turned out to be much more laborious, without providing any improvement in yield. Nevertheless, acceptable quantities of iodide **278** were secured, due to the ready availability of the starting materials. The next transformation entailed halogen-lithium exchange of iodide **278**, transmetallation with *Lipshutz*’s “cuprate in a bottle”^[219,220] and finally conjugate addition to enoate **6**. The *Lipshutz* reagent was chosen for its high reactivity and because only one equivalent of precious functionalized

^{xvi} In both metathesis steps, we attempted quench of the catalyst with ethyl vinyl ether prior to purification, but no discernible effect was observed.

organolithium is needed per equivalent of higher-order cuprate, which would play an important role when working on larger scale.

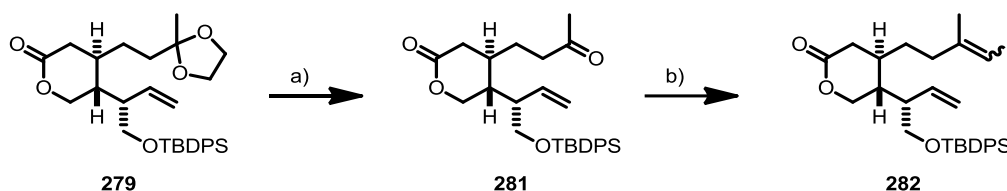


Scheme 43: Synthesis and attachment of building block **278**. Reagents and conditions: (a) (i) NaI (1.2 eq.), TMSCl (1.2 eq.), MeCN, rt, 5 min, (ii) ethylene glycol, 5 min, 17%; (b) (i) **278** (4 eq.), *t*-BuLi (8.2 eq.), Et₂O, -78 °C, 2h, (ii) LiCu(thienyl)CN (4.2 eq.), -78 °C, 3h, (iii) **6** (1 eq.), -78 °C, 2h, -45 °C, 14 h, rt, 5 h, 81%.

Initially, halogen-lithium exchange of **278** was problematic. Adaption of a procedure by Gampe^[221] for lithiation of closely related bromide **280**, which involved addition of *t*-BuLi to a cooled 0.5 M solution of the bromoacetal in Et₂O, led to formation of a white and insoluble precipitate in the case of **278**. The mixture did not lead to strong coloring, which is typically observed upon addition of 1,10-phenanthroline to alkyl lithium species.^[222] Inspired by the work of Bailey and Punzalan,^[223] we found experimentally that acetonide **278** would successfully undergo halogen-lithium exchange at a concentration lower than 0.12 M, while higher concentrations would only lead to decomposition. After transmetalation to Lipshutz's cuprate, the addition to **6** worked smoothly and ketal **279** was obtained in good yield^{xvii} as the only observable isomer by ¹H NMR. The chemical shifts and coupling constants of the diagnostic α- and δ-protons of the lactone ring were in excellent agreement with intermediates in the synthesis of blumiolide C.^[87] Relative configuration was assigned based on this observation and confirmed unambiguously at a later stage (Fig. 20, p. 109).

Hydrolysis of the acetonide according to a procedure of MaGee and Shannon to liberate ketone **281** was uneventful (Scheme 44).^[224] Unsurprisingly, Takai olefination^[225] produced an 1/1 mixture of *E*- and *Z*-isomers of **282**. Nevertheless, this material was valuable for scouting the subsequent steps for functionalization of the terminal C8-C9 vinyl group.

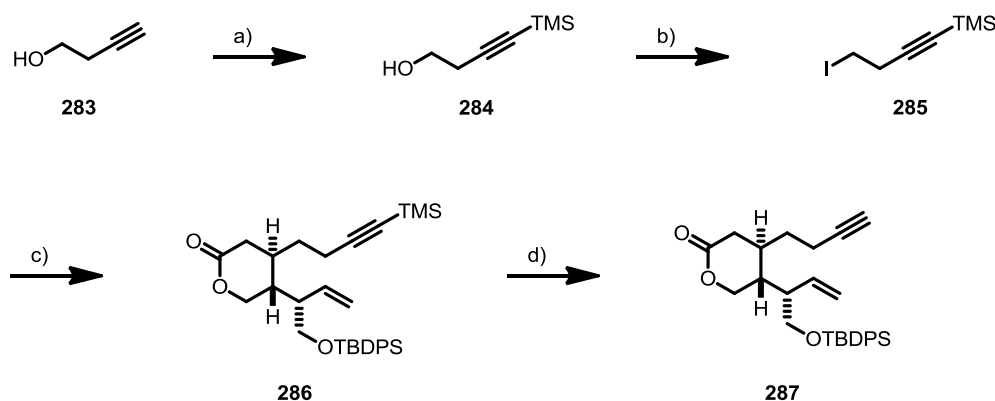
^{xvii} It proved to be crucial to open the reaction mixture to air after quenching with NH₃. Otherwise the blue NH₃ complex did not form and the isolated material would retain a strong brown color.



Scheme 44: Synthesis of *E/Z*-mixture of iodide **282**. Reagents and conditions: (a) PPTS (0.1 eq.), MeCN/H₂O 4:1, 85 °C, 7 h, 98%; (b) CHI₃ (2 eq.), CrCl₂ (6 eq.), THF, 0 °C, 10 min, rt, 21 h, 61% (*E:Z* 1.1:1), 10% **281** recovered.

3.5.5.2 Synthesis of *E*-**164** via Functionalization after Conjugate Addition

In the second synthesis of **290** (Scheme **45** and Scheme **46**), the plan already outlined earlier (Scheme **27**, p. 64) was realized: Conjugate addition of a homopropargylic fragment and subsequent elaboration of the terminal triple bond to produce vinyl iodide **282** as a single isomer. The synthesis started from commercially available homopropargylic alcohol **283**. The latter was doubly silylated, followed by acidic quench to cleave the silicon-oxygen-bond to produce protected alkyne **284** in good yield (85%).^[226] Using an *Appel*-like reaction, the hydroxy group was substituted to give known iodide **285**.^[227]

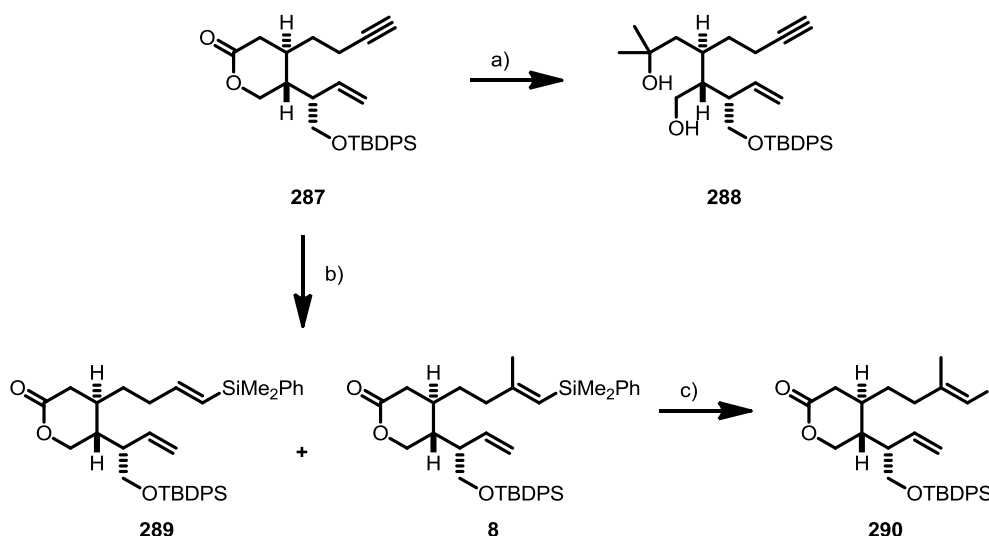


Scheme 45: Synthesis of fragment **285** and attachment to enoate **6**. Reagents and conditions: (a) *n*-BuLi (2.2 eq.), TMSCl (2.2 eq.), -78 to 0 °C, 3 h, HCl, 0 °C, 30 min, 85%; (b) I₂ (1.1 eq.), ImH (3 eq.), PPh₃ (1.2 eq.), CH₂Cl₂, 0 °C, 5.5 h, 89%; (c) (i) *t*-BuLi (6 eq.), **285** (3 eq.), Et₂O, -78 °C, 20 min, 0 °C, 10 min, (ii) LiCu(thienyl)CN (3.24 eq.), -78 °C, 10 min, 0 °C, 1 h 15 min, (iii) **6** (1 eq.), -78 °C, 11 min, 0 °C, 1 h 25 min, 90%; (d) (i) K₂CO₃ (4 eq.), MeOH, rt, 4h 20 min, (ii) AcOH (36 eq.), PhMe, rt, 17 h, 76%.

For the conjugate addition of iodide **285** to **6**, a procedure by Overman was adapted,^[228] wherein lithiation involved adding the iodide to a cooled solution of *t*-BuLi in a mixture of pentane and Et₂O. When lithiation was carried out in the reverse manner, as previously

described for **278**, the reagent decomposed and did not transmetallate to copper. The resulting homopropargylic lithium species was converted into a higher order cuprate,^[219,220] which was reacted with enoate **6** to give saturated lactone **286** the as a single isomer^{XVIII} in 90% yield^{XVII}. The silyl protecting group was removed in basic methanol to liberate the terminal alkyne **287**.^[229] It is worth mentioning that the lactone was also partly hydrolyzed. Upon complete TMS-removal, the reaction mixture was therefore treated *in situ* with an excess acetic acid to restore the lactone moiety.

A first attempt to convert alkyne **287** into an E-vinyl iodide was made using *Negishi's* protocol for zirconocene-catalyzed carboalumination with subsequent iodine quench (Scheme 46).^[230] Literature precedence for this endeavor in the presence of a lactone ring was rather thin: Only *Romo* and coworkers had described one single example of a sequence of carboalumination, transmetallation of the resulting vinyl aluminate with ZnCl_2 and *Negishi* coupling to a vinyl iodide for a γ -lactone ring-containing substrate; however, the yield of this transformation was very low (12%).^[231] For our substrate, the material isolated after exposure to AlMe_3 and treatment with iodine did not correspond to the desired iodide **290**.

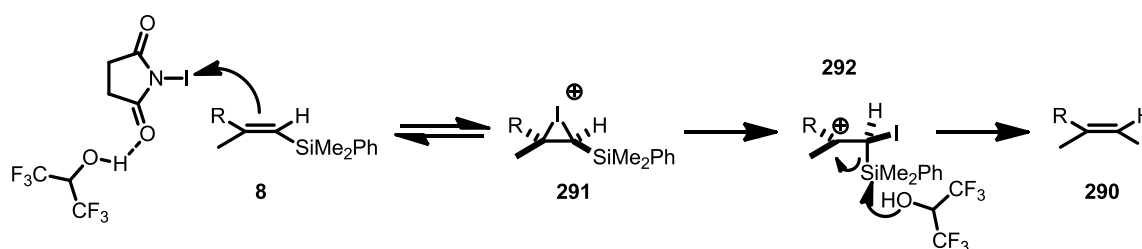


Scheme 46: Functionalization of alkyne **287**. Reagents and conditions: (a) (i) AlMe_3 (3 eq., in hexanes), Cp_2ZrCl_2 (1 eq.), CH_2Cl_2 , 0 °C, 5 min, rt, 23 h, (ii) I_2 , THF, -78 °C to rt, 1 h, 51%; (b) (i) Li^0 (9 eq.), Me_2PhSiCl (3 eq.), -10 °C, 5 h, (ii) CuCN (1.5 eq.), -10 °C, 40 min, (iii) **287** (1 eq.), -78 °C, 50 min, (iv) MeI (7.5 eq.), -78 °C to 0 °C, 3 h, 64%; (c) NIS (1.15 eq.), Ag_2CO_3 (0.3 eq.), HFIP, 0 °C, 93%.

^{XVIII} As observed by ^1H NMR.

Rather, the tertiary alcohol **288** had been formed, which is the product of two-fold methyl addition to the lactone. A solution to this problem was found in *Fleming's* protocol^[232,233] for silylcupration of alkynes and further reaction with methyl iodide as an electrophile^{XVII}. After some experimentation, best results were obtained if methyl iodide was purified by filtration over alox and distillation on the day of use. Otherwise, *des*-methyl compound **289** would be present as a chromatographically inseparable bulk contaminant of the desired silane **8**. Attempted silyl- to iodide-exchange on alkene **8** with elemental iodine did not lead to any conversion. This was overcome by using a combination of *N*-iodo succinimide in 1,1,1,3,3,3-hexafluoro-2-propanol^[234] with silver carbonate^[235] as an additive. Omitting the silver salt would lead to an intermediate purple color during the reaction and reduce the overall yield.

The iodination reaction of **174** with NIS proceeded very rapidly and was often completed in less than 10 minutes. However, despite complete conversion, in several instances starting material was again detectable by TLC after quenching. A look at the putative mechanism^[234] of the silicon-iodine exchange might help rationalizing this observation (Scheme 47).

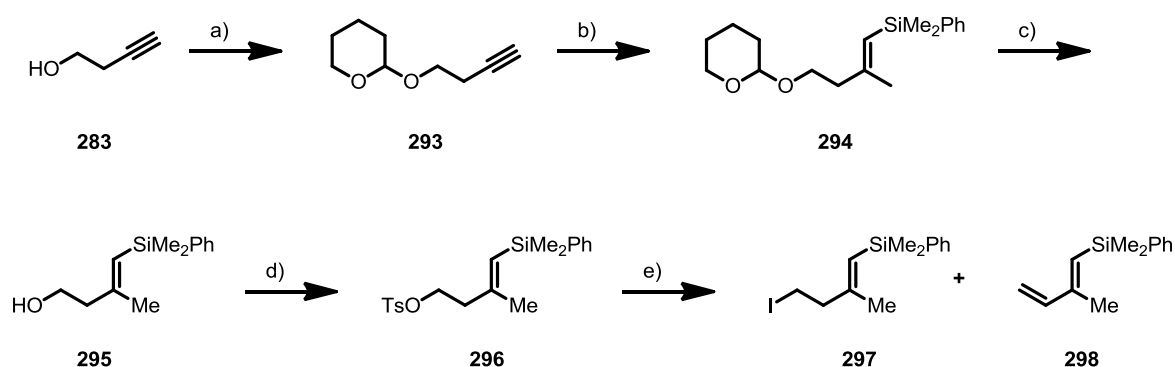


Scheme 47: Putative mechanism of silyl-iodine exchange by Zakarian.^[234]

NIS is thought to be activated by hydrogen bonding to the solvent and the electrophilic iodine atom is attacked by the double bond of vinyl silane **8**. Epiiodonium-ion **291** undergoes opening and rotation around approx. 30° to give intermediate **292**, wherein the empty orbital on the tertiary carbocation is aligned with the silicon group. Silicon serves as an electrofuge and reacts with the solvent to give a silyl-HFIP ether as well as vinyl iodide **290**. A possible explanation might be that the iodonium species **291** is formed rapidly but only slowly reacts to the product. Direct spotting onto silica plates likely leads to direct formation of **290**, whereas upon premature aqueous quench the intermediate decays back to **8**.

3.5.5.3 Synthesis of *E*-164 via Conjugate Addition of a Preformed *E*-Olefin

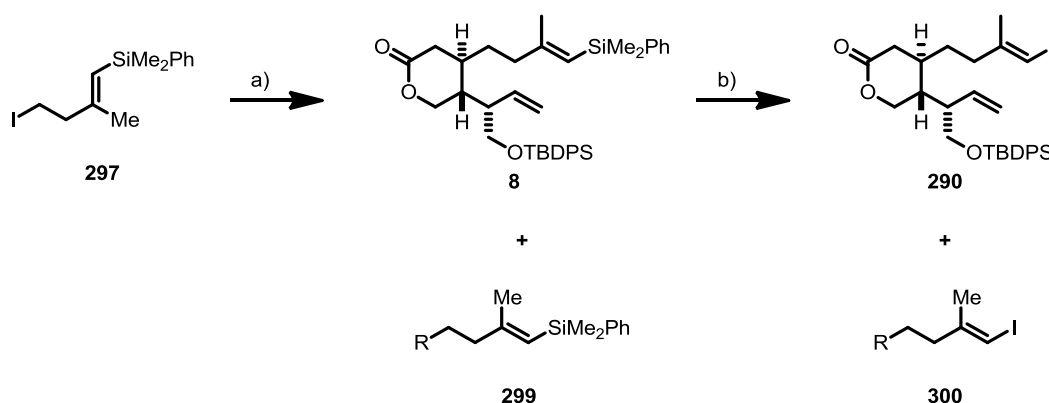
After successful carbosilylation of **287**, the question arose if the overall synthesis could be streamlined by including the carbosilylation step into the sequence leading up to the halogen-lithium exchange and perform the *Michael* addition onto lactone **6** with a preformed vinyl silane. This would remove two steps from the longest linear sequence and add convergence by means of a simple tactical change. Synthesis of iodo vinyl silane **297** (Scheme 48), the precursor for the necessary alkyl lithium species, had been described by *Taber*^[236]. The compatibility of vinyl silane building blocks with halogen-lithium exchange conditions has been demonstrated by the groups of Oshima (-SiMe₂Ph)^[237] and of Nicolaou (-SiMe₃)^[238,239]. However, in both cases, vinyl iodides were used. It was, therefore, unclear, whether these previous findings would also apply for **297**, since alkyl iodides require much more forcing conditions for lithiation than their vinyl counterparts.^[223]



Scheme 48: Synthesis of fragment **297**. Reagents and conditions: (a) 3,4-Dihydro-2*H*-pyran (1.05 eq.), TsOH·H₂O (0.01 eq.), CH₂Cl₂, 0 °C, 1h, 94%; (b) (i) Li⁰ (7.5 eq.), Me₂PhSiCl (2.5 eq.), -10 °C, 4.5 h, (ii) CuCN (1.12 eq.), -20 °C, 15 min, (iii) **293** (1 eq.), -78 °C, addition time 50 min, then 20 min (iv) MeI (6.25 eq.), -78 °C, addition over 40 min, then 30 min, to 0 °C over 40 min, 98%; (c) TsOH·H₂O (1 eq.), EtOH, rt, 2 h, 81%; (d) TsCl (eq.), DMAP (eq.), Et₃N (eq.), CH₂Cl₂, rt, 14 h, 94%; (e) NaI (10 eq.), Cu⁰ (0.05 eq.), acetone, 92%, 5% **298**.

Homopropargyl alcohol **283** was protected as tetrahydropyranoside **293** in very good yield.^[240] *Fleming's* method^[232,233] delivered the vinyl silane **294** almost quantitatively^{XVII}, but again, the use of freshly purified methyl iodide was crucial. Removal of the THP group gave a comparably moderate yield of the free alcohol (81%), with the remaining 20% of material being unaccounted for. It is possible that **295** undergoes protodesilylation to give a product that is either volatile or is able to form an azeotrope with ethanol. In the subsequent tosylation reaction, the excess of triethylamine could be reduced from 100 to 10 equivalents compared

to *Taber's* work. The quality of the tosyl chloride employed had a great influence on the yield of tosylate **296** and was best purified by recrystallization prior to use. Further reaction of the tosylate with free chloride was observed as a trace side reaction and gave the very apolar homoallylic chloride, which was detectable on TLC. If present, this impurity was not removed but also reacted in the following *Finkelstein* reaction to give iodide **297** in 80 to 82% yield. Between 3 and 12% of inseparable diene **298** was concomitantly formed in each batch. At this point, it should be noted that whereas THP-ether **294** was stable in the fridge over months, alcohol **295**, tosylate **296** and iodide **297** display decreasing stability (in that order). Alcohol **295** turned yellow within days in the freezer at -15 °C and a small amount of another compound was formed over time.



Scheme 49: Improved synthesis of iodide **290**. Reagents and conditions: (a) (i) *t*-BuLi (3.5 eq.), **297** (1.8 eq.), Et₂O, -78 °C, 2 h, (ii) LiCu(thienyl)CN (1.91 eq.), -78 °C, 8 min, 0 °C, 2 h, (iii) **6** (1 eq.), -78 °C to -60 °C over 1 h, 0 °C, 20 min, 79%; (b) NIS (1.15 eq.), Ag₂CO₃ (0.3 eq.), HFIP, 0 °C, 10min, 88%, 11% **8** recovered. R = unidentified.

Tosylate **296** decayed even faster, becoming brown in the process. Iodide **297** proved to be particularly sensitive: In one instance, the latter was visually observed to completely decompose within 15-25 seconds (colorless to brown/black), due to residual HCl in deuteriochloroform. On the other hand, under vacuum (10-40 mbar), it could be stored in bulk for more than a week under ambient atmosphere in daylight with no detectable decomposition. As a consequence, THP-ether **294** was produced in large batches and converted into iodide **297** only when needed. The presence of diene **298** did not interfere with the lithiation/conjugate addition sequence^[228] (Scheme **49**) and silane **8** was obtained in good to moderate yield^{XVII}. Around 5-10% of an unknown impurity of the form **299** was always

present, which structurally resembled the silane fragment, but could not be separated or identified. At the stage of **290**, this impurity had also undergone iodination to **300** and was easily removed by prolonged exposure to vacuum.

3.5.6 Conclusions

Some of the steps described in this chapter will still require some improvement for optimal scalability.

So far we were able to produce sufficient quantities of *meso*-cyclobutenediol **272**, but the sequence was low-yielding, suffered from poor reproducibility and required tedious purification. A viable approach to address the shortcomings of the current process could be the direct reaction of maleic anhydride **3** and acetylene to produce cyclobutene derivative **270**.^[241] However, this alternative approach would require the availability of a specialized quartz reactor^[242] that allows for effective and continuous cooling; otherwise the safety of the process cannot be guaranteed.^[208] Since no such equipment was available, **270** was accessed via the longer sequence so far.

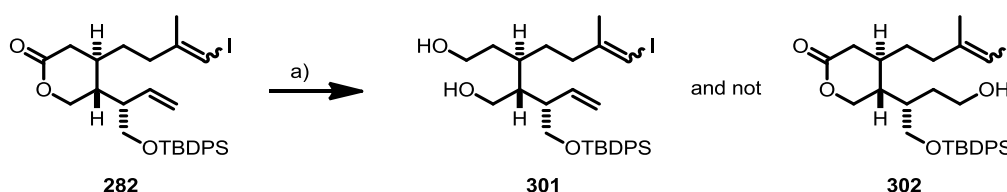
The catalyst loading of the metathesis step is high (12%), which makes this step a very expensive one, since it lies early in the synthetic sequence. Moreover, the large catalyst loading affects the isolation of lactone **6**, because the catalyst-derived decomposition products have to be chromatographically removed. Since a substantial amount of experimentation was required to obtain meaningful conversion, the purification process was so far not investigated in great detail. Possible improvements for the removal of ruthenium species might be found in treatment with reagents such as $\text{P}(\text{CH}_2\text{OH})_3$, DMSO, $\text{PO}(\text{Ph})_3$, amino-substituted vinyl ethers, mercaptonicotinic acid or *N*-acetyl cysteine.^[243] It should also be noted that Piers has reported that catalyst lifetime can be improved by a factor of around 40 by the exchange of the standard bis-mesitylene *N*-heterocyclic carbene with a bulkier 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene.^[216] While modified catalysts of this type are not commercially available so far and require demanding synthesis in a glove box, they might be a promising option for lowering the catalyst loading in the future.

3.6 Cyclononene Formation via *Nozaki-Hiyama-Kishi* Reaction

With the *E/Z*-mixture of iodides **282** and pure *E*-iodide **290** in hand, the possibility to functionalize the terminal C8-C9 double via hydroboration and oxidation was assessed. Successful execution of this transformation would be of paramount importance to both main strategies: Firstly, it would provide access to a primary alcohol as a precursor to the aldehyde in the key *Nozaki-Hiyama-Kishi* ring-closure. Secondly, hydroboration was to be the first stage in the planned alkyl-boron *Suzuki*-coupling. As a consequence, with proof of successful hydroboration, investigation of the following cross-coupling stage would be facilitated due to one possible factor for failure being ruled out.

3.6.1 Initial Hydroboration Studies on the *E/Z* Mixture **282**

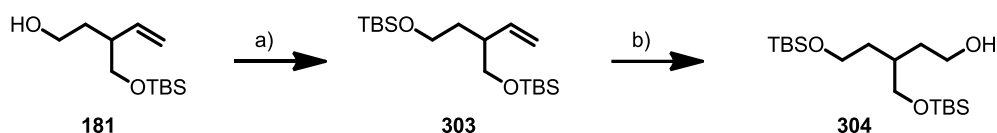
The *E/Z* mixture **282** underwent reaction with 9-BBN only very slowly even upon prolonged heating (Scheme 50). After oxidative workup with sodium perborate, only a small amount of product was isolated. Yet, the spectral data of this impure material did not match the expected structure of **302**, but was tentatively assigned to be diol **301**. The alpha protons of the lactone had vanished, two more signals were visible in the alcohol region of the ^1H NMR and surprisingly, the olefin had remained untouched.



Scheme 50: Attempted hydroboration/oxidation of **282**. Reagents and conditions: (a) (i) 9-BBN (1.5 eq.), THF, 70 °C, 24 h, (ii) $\text{NaBO}_3 \cdot 4 \text{H}_2\text{O}$, 50 °C, 3h, 36% **301**.

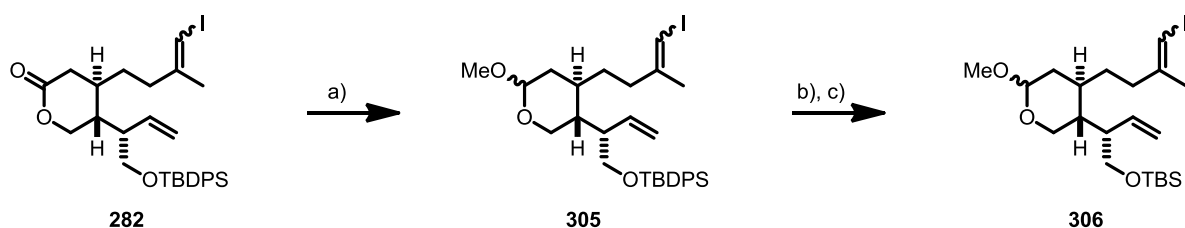
Since a large protecting group had been experimentally determined to be crucial for blocking the vinyl group during RCM, we reasoned that for the same reason, hydroboration was now hampered. This prompted us to test the efficiency of the smaller TBS-ether on the hydroxymethyl group in this reaction. While testing the quality of the hydroborating agent on standard substrates, the sodium perborate work-up^[244] was found to be more sluggish and lower yielding when compared to the traditional basic hydrogen peroxide.^[245]

Alcohol **181**, which was still available from the approach described in subchapter 3.2.2 (p. 51), was TBS-protected to give olefin **303** (Scheme 51). It served as a simplified model analog of intermediate **282**. Hydroboration and oxidation^[245] cleanly provided alcohol **304** in 70% yield. When performed at room temperature, the reaction was lower yielding and showed increased formation of side products.



Scheme 51: Hydroboration of a simplified model system. Reagents and conditions: (a) TBSCl (1.2 eq.), ImH (3.7 eq.), CH₂Cl₂, rt, 3 d, 95%; (b) (i) 9-BBN (1.5 eq.), THF, 40 °C, 18 h, (ii) NaOH (1.5 eq.), MeOH (14 eq.), H₂O₂ (4.4 eq.), 70%.

Due to the limited literature precedence,^[246] we expected that concomitant reduction of the lactone would again be a problem, even with a smaller TBS group. Therefore the lactone was reduced using DIBAL-H and the corresponding methyl pyranoside **305** was formed in good yield (Scheme 52). The TBDPS group was removed with tetrabutylammonium fluoride;^[247] somewhat surprisingly, the vinyl iodide functionality survived the presence of the very basic TBAF when the reaction mixture was directly evaporated to dryness, displaying no signs of decomposition. However, significant amounts of residual Bu₄N⁺-species were present in the deprotected product after column chromatography. Treatment of this material with TBSCl then gave pure TBS-ether **306** in 90% over two steps.

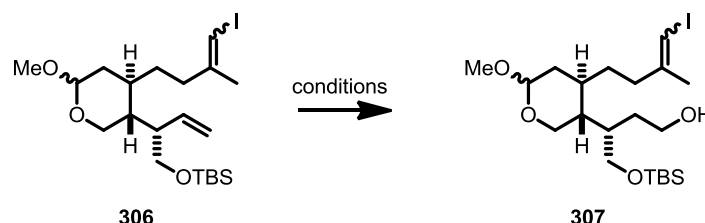


Scheme 52: Protection of the lactone and introduction of a smaller protecting group. Reagents and conditions: (a) (i) DIBAL-H (2 eq.), CH₂Cl₂, -78 °C, 40 min, (ii) PPTS (0.05 eq.), MeOH, rt, 30 h, 82% (2 steps); (b) TBAF (2 eq.), THF, rt, 22h, (c) TBSCl (2.7 eq.), ImH (6.8 eq.), CH₂Cl₂, rt, 25 h, 90% (2 steps).

TBS-ether **306** did not undergo hydroboration under any of the conditions investigated (Table 15). Even the use of a large excess of 9-BBN and prolonged heating gave no conversion (entry 1). To ensure that the quality of the starting material was not at fault, it was freshly purified prior to use and azeotropically dried with benzene (entry 2); this did not change the outcome.

Likewise, both the sterically less demanding borane·THF-complex or the bulky disiamyl borane^[248] (entries **3** and **4**) failed to react. Finally, attempted formation of an alkylboronic pinacol ester^[249] catalyzed by Wilkinson's catalyst^[250–253] failed, too (entry **5**).

Table 15: Conditions used for attempted hydroboration of **306**.

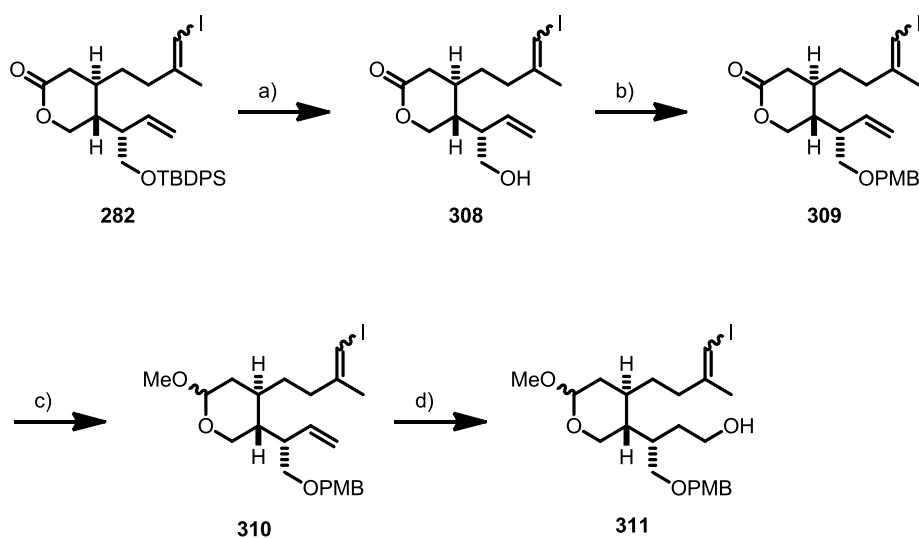


Entry	Conditions	Temperature	Time	Product
1	9-BBN (7.5 eq.)	45 °C	45 h	No conversion
2^a	9-BBN (2.5 eq.)	rt 45 °C	5 h 14 h	No conversion
3	BH ₃ (1 eq.)	rt 45 °C	23 h 24 h	No conversion
4	1) BH(siamyl) ₂	rt 45 °C	23 h 24 h	No conversion
5	1) BH(pin), RhCl(PPh ₃) ₃	rt	4 h	No conversion

All reactions performed in THF. ^a **306** was repurified and coevaporated with benzene just prior to reaction. pin: pinacol

In light of the above results, our attention was shifted to PMB as a hydroxy protecting group, because the latter had demonstrated the most pronounced interference with the RCM reaction (*cf.* Table **8**, p. 68), indicating that it allowed excellent access for the ruthenium catalyst. Starting again from **282**, the TBS group was removed using *Olah's* HF·pyridine^[254,255] since the methyl acetal was not yet present and to avoid the presence of residual ammonium salts (**Scheme 52**). Free alcohol **308** was protected under mildly acidic conditions using PMB-trichloroacetimidate **248** to give PMB-ether **309**.^[256] The yield of this step could not be determined because of residual trichloroacetamide. The latter was visible as a solid impurity and showed identical retention as **309** on silica gel for all eluent systems tested. DIBAL-H reduction to the lactol was directly followed by installation of the methyl acetal to give **310** in 73% yield for the three-step sequence from **282**. Hydroboration^[245] of **310** was found to be feasible at room temperature, when performed at high enough concentrations (> 0.05 M). At lower concentrations the reaction was very slow and did not go to completion, as indicated

by reisolation of unreacted starting material. It needs to be noted, that on TLC, material with identical retention as the starting material was still observed, even when the reaction was complete. This is due to some borane decomposition product forming on TLC. Even after chromatography, we were unable to obtain pure alcohol **311** in this reaction, due to sluggish oxidation of the borane. Because of the small scale and small volume of solvent in the initial test reactions, the mixture after hydroboration was always diluted with the extraction solvent diethyl ether before oxidative work-up. In a later phase of the project, this was found to be responsible for the slow oxidation; only THF as a solvent permits clean oxidation. An anomeric mixture of the pure *E*-isomer of alcohol **311** was later inadvertently obtained from **313** via simultaneous hydroboration/lactone reduction and acetal formation during workup (Scheme 59, p. 105). Spectral comparison with this pure *E*-vinyl iodide **326** confirmed the identity of half the material present in **311**.



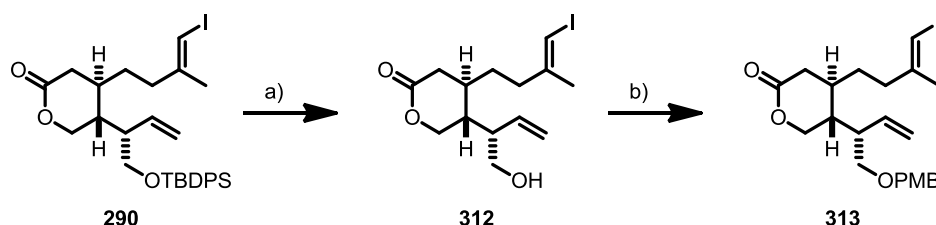
Scheme 53: Synthesis and hydroboration of PMB-protected methyl pyranoside **311**. Reagents and conditions: (a) HF·py, THF, 0 °C, 5 min, rt, 16 h, 93%; (b) **248** (1.52 eq.), CSA (0.05 eq.), CH₂Cl₂, rt, 3 d; (c) (i) DIBAL-H (1.5 eq.), CH₂Cl₂, -78 °C, 20 min, (ii) PPTS (0.10 eq.), MeOH, rt, 19 h, 73% (3 steps); (d) (i) 9-BBN (1.2 eq.), THF, rt, 38 h, (ii) NaOH (1.2 eq.), MeOH (80 eq.), H₂O₂ (4.1 eq.), 60-80% estimated.

3.6.2 Follow-up Hydroboration Studies Starting from Pure *E*-iodide **290**

After the first studies on the hydroboration reaction, we turned our attention to the further elaboration of the pure *E*-vinyl iodide **290** (subsections 3.5.5.2 and 3.5.5.3, p. 89ff). Since the PMB group had proved to be optimal for access of the borane to the vinyl group in **310**, it was to be used also in experiments with the pure *E*-vinyl iodide. At the time, the sluggish reaction

producing impure alcohol **311** was attributed to some instability of the methyl acetal. This notion seemed to be supported by the fact that, that the attempted removal of a similar methyl acetal moiety as in **310/311** had led to to a transannular cyclization in Leumann's synthesis of coraxeniolide A. As a consequence, the methyl pyranoside was to be replaced by a silyl protected lactol moiety.

HF·pyridine^[254,255] mediated removal of the TBDPS group (Scheme 54) went uneventfully and could be effected using only a small excess of fluoride within a reasonable timeframe; provided the concentration of **290** in the reaction mixture was at least 0.3 M. The work-up procedure for primary alcohol **312** (*i.e.* **E-308**) could be improved by using saturated a KHCO₃ solution^[257] instead of the usual NaHCO₃, which reduced the volume of the aqueous phase by a factor of 2.5. This greatly simplified extractive isolation of the product.



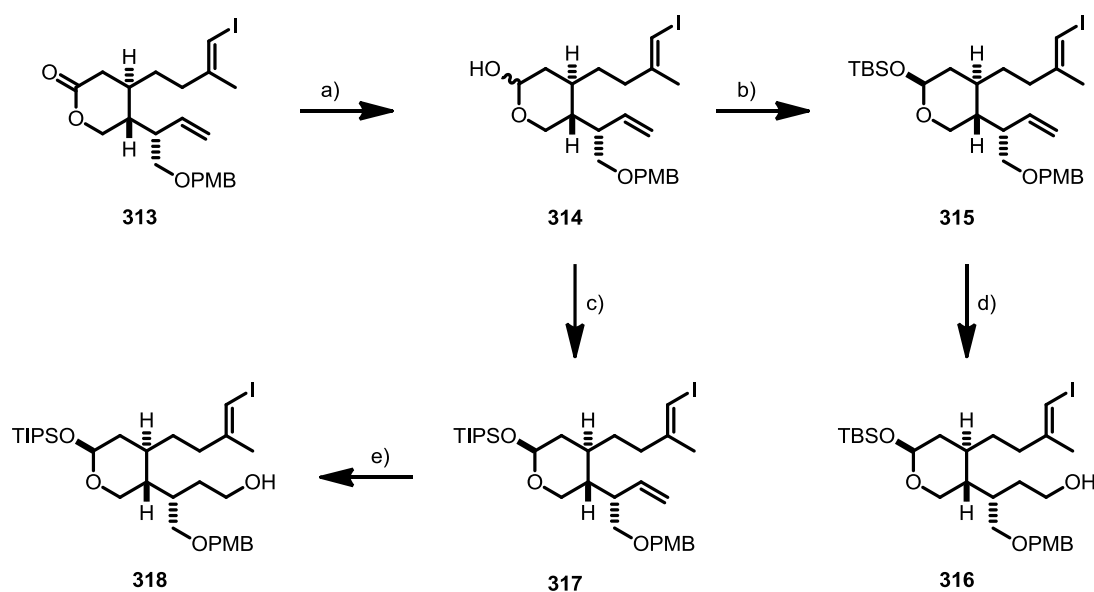
Scheme 54: Synthesis of pure *E*-iodide **313**. Reagents and conditions: (a) HF·py (4.2 eq. based on HF), THF, rt, 18 h, 82%; (b) **248** (1.50 eq.), TMSOTf (0.05 eq.), CH₂Cl₂, -78 °C, 40 min, 61 %, 12% impure **313**, 8% **312**.

Free alcohol **312** was protected with a PMB group under acidic conditions to deliver ether **313**. It was produced on larger scale than the previously described **309** and over time three distinct problems became apparent in this step: Firstly, the reaction was slow and did not reach completion, usually stalling at around 80% conversion. Secondly, with the standard acid catalyst CSA, concomitant decomposition of the starting material was a major pathway, requiring tedious chromatography for purification. Lastly, trichloroacetamide was a bulk contaminant in the product and proved to be very hard to remove due to identical R_f-value.

A series of Brønsted acids^[258] was then screened as catalysts for the etherification reaction, including PPTS, TFA, TfOH, MsOH and TsOH·H₂O, but none of those provided a notable improvement over CSA. In fact, the milder Brønsted acid PPTS^[258] even led to lower conversion and increased decomposition compared to CSA. After some experimentation, the use of the Lewis acid TMSOTf at low temperature^[259] was found to overcome the slow conversion

problem and to greatly reduce side product formation. A partial solution for the removal of trichloroacetamide was found using an EtOAc/PhMe solvent system for chromatography. This allowed for separation of most of this byproduct due to a difference in solubility, while the compound was inseparable from the product on TLC. To simplify purification, PMB-protection under acidic conditions is traditionally executed in a mixture of cyclohexane and dichloromethane; trichloroacetamide is largely insoluble in this solvent mixture and most of this byproduct can be removed by simple filtration.^[260] In the case of ether **313**, this practice failed, due to the similar polarity of product and contaminant: When trichloroacetamide precipitated, large proportions of the oily intermediate **313** were associated with the solids formed and it was not possible to achieve reasonable recovery without redissolving most of the undesired solid.

Early on, a potential alternative was envisioned to be PMB-protection using basic conditions (NaH, PMBCl^[261], TBAI^[262]), but this led to incomplete conversion of around 30%; starting material and product had partly decomposed.



Scheme 55: Synthesis and hydroboration of two silyl-protected pyranosides. Reagents and conditions: (a) DIBAL-H (2.0 eq.), CH₂Cl₂, -78 °C, 25 min, 96%; (b) TBSCl (1.2 eq.), ImH (1.3 eq.), CH₂Cl₂, rt, 1 h 15 min, 85%, 4% minor anomer; (c) TIPSCl (1.8 eq.), ImH (2.1 eq.), DMAP (0.26 eq.), CH₂Cl₂, rt, 22 h, 66%; (d) (i) 9-BBN (2.5 eq.), THF, 0 °C, 4 min, rt, 24 h, (ii) NaOH (2.5 eq.), MeOH (80 eq.), H₂O₂ (7.2 eq.), 45%; (e) (i) 9-BBN (2 eq.), THF, 0 °C, 2 min, rt, 3 h 15 min, (ii) NaOH (2 eq.), MeOH (80 eq.), H₂O₂ (6 eq.), 74%

Reduction^[87] of lactone **313** provided the corresponding lactol **314** (Scheme 55) as an amorphous solid composed of an approximately 1:1 mixture of anomers. Unfortunately,

attempts to obtain a single crystal for X-ray diffraction were unproductive. The lactol was protected either as the corresponding TBS-ether^[263] **315** or TIPS-ether^[264] **317**; the smaller protecting group giving a higher yield. The minor anomers were separable by chromatography, but since the minor isomer of **318** contained inseparable impurities, it was discarded. When subjected to a hydroboration and oxidation^[245] sequence, both silyl pyranosides produced the corresponding alcohols **318** and **316**. Because of concomitant decomposition, the yield of the TBS-protected version (45%) was substantially lower than for the TIPS-variant (75%).

The stereochemistry of the silyl lactols **315** and **319** was assigned in analogy to structurally related compounds bearing all equatorial substituents (Fig. 19). For compounds such as **315**, anomeric ¹H NMR shifts of 4.52–4.74 ppm have typically been observed, with the two coupling constants ranging from 7.9–9.4 and 1.4–2.1 Hz, respectively.^[263,265] The larger coupling constant is characteristic for a *trans*-arrangement of two vicinal protons and is thus a defining feature. For the major product a chemical shift of 4.52 ppm was measured with coupling constants of 9.4 and 2.1 Hz, which fits well into the expected region. There is no directly applicable literature precedence for the proposed minor isomer. The values measured were 5.16 ppm for the chemical shift of the anomeric proton and a single coupling constant of 2.2 Hz. Assuming a chair conformation also for this isomer, two dihedral angles of around 60° between the anomeric and the two neighbouring protons are expected, leading to a coupling in the range of 2–4 Hz according to the Karplus relation^[266].

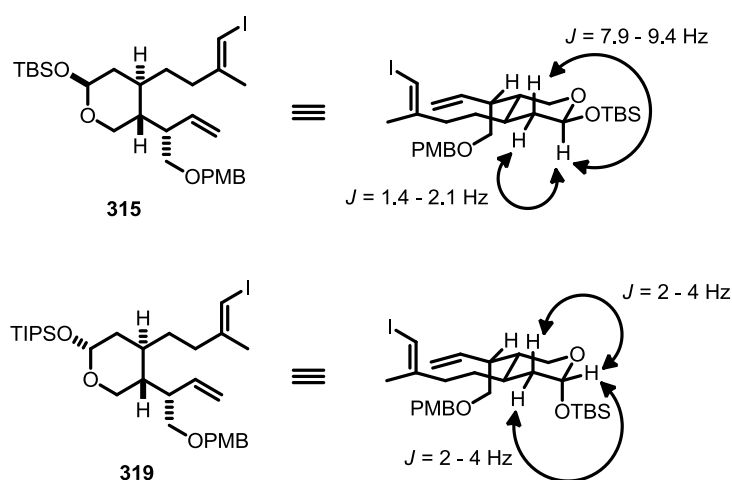
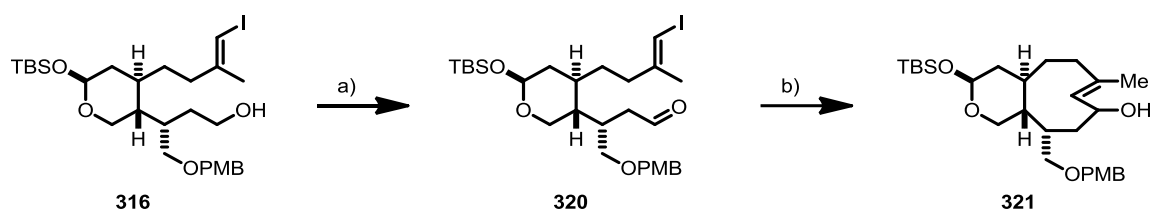


Fig. 19: Rationale for assignment of the relative stereochemistry of the two isomers **315** and **319**.

The stereochemistry of the two isomers of **317** was assigned in analogy to that of **315**. For both **315** and **317**, ring-closure via alkyl-B Suzuki coupling was investigated (section 3.8.1, p. 120ff).

3.6.3 Nozaki-Hiyama-Kishi Reactions of Silyl-Pyranosides

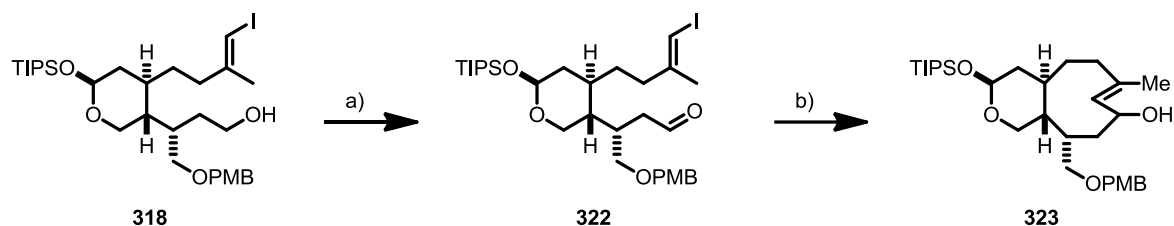
The small amount of primary alcohol **316** was oxidized to aldehyde **320** using a large excess of Dess-Martin periodinane^[267] (Scheme 56). The reaction had to be buffered with pyridine^[268] to obtain a clean product, otherwise the material would decompose completely. A dilute solution of the aldehyde was subjected to a Nozaki-Hiyama-Kishi reaction^[138,139] to close the 9-membered ring and form cyclononenol **321**.



Scheme 56: Ring-closure of TBS- protected lactol. Reagents and conditions: (a) DMP (20 eq.), py (80 eq.), CH₂Cl₂, 15 h, 66%; (b) CrCl₂ (36.2 eq.), NiCl₂ (0.06 eq.), DMSO, 50 °C, 64%.

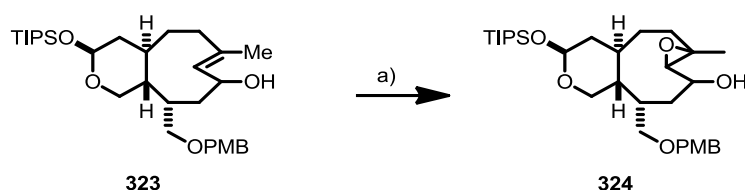
A large excess of chromium was used, so as to ensure adequate nickel content (0.1-1 % with respect to Cr). Notably, the reaction had to be conducted at 50 °C, but did still not go to completion; at ambient temperature, no conversion was observed. The possible formation of a cyclic dimer was refuted by HRMS. As the scale for the initial experiments was very small, the possible formation of two diastereomeric products could not be unequivocally excluded by ¹H NMR spectroscopy.

A later comparison with **323** revealed the suspected isomer peaks to be decomposition products. As had been experienced previously with alcohol **316**, aldehyde **320** and allylic alcohol **321** were very prone to decomposition, especially in presence of trace amounts of acid, *e.g.* in untreated CDCl₃. Due to the observed larger stability of the TIPS-congeners, the TBS-pyranoside route was abandoned at this point.



Scheme 57: Ring-closure of TIPS-protected lactol. Reagents and conditions: (a) DMP (3 eq.), py (10 eq.), *t*-BuOH (10 eq.), CH₂Cl₂, 78%; (b) CrCl₂ (18 eq.), NiCl₂ (0.07 eq.), DMSO, 50 °C, 47% (2 cycles).

Primary alcohol **318** was oxidized to aldehyde **322**, using a very rapid *t*-BuOH accelerated^[267] and pyridine-buffered^[268] Dess-Martin oxidation (**Scheme 57**). Initial attempts at the NHK-reaction with this substrates gave unsatisfactory results and only around 30% of product. No obvious benefits were observed by changing the quench from ammonium chloride to *Rochelle's* salt; both led to formation of a precipitate and emulsion. A substantial improvement was found in the use of a 0.1 M EDTA solution to quench the reaction, producing a homogenous purple to black solution of Cr ions. Addition of 4-*t*-Bu-pyridine has been reported to enable recalcitrant NHK-reactions.^[269] In our case, only marginal conversion was observed under these conditions and the starting iodide **322** was isolated unchanged. Resubmitting the recovered material to NHK conditions, but omitting the 4-*t*-Bu-pyridine, partial conversion was observed and product **323** was obtained in 47% overall yield for both cycles. In the second round, the unreacted starting material had completely decomposed under the reaction conditions. It was later found that for reproducible results, freshly opened bottles of DMSO should be used within approximately a week and the solvent should be degassed just prior to use. After chromatography and appearing homogeneous by TLC, **323** was still contaminated with 7% of another similar compound. When this material was converted into epoxide **324** (**Scheme 58**), it became apparent that **324** had been the very impurity detected in **323**.



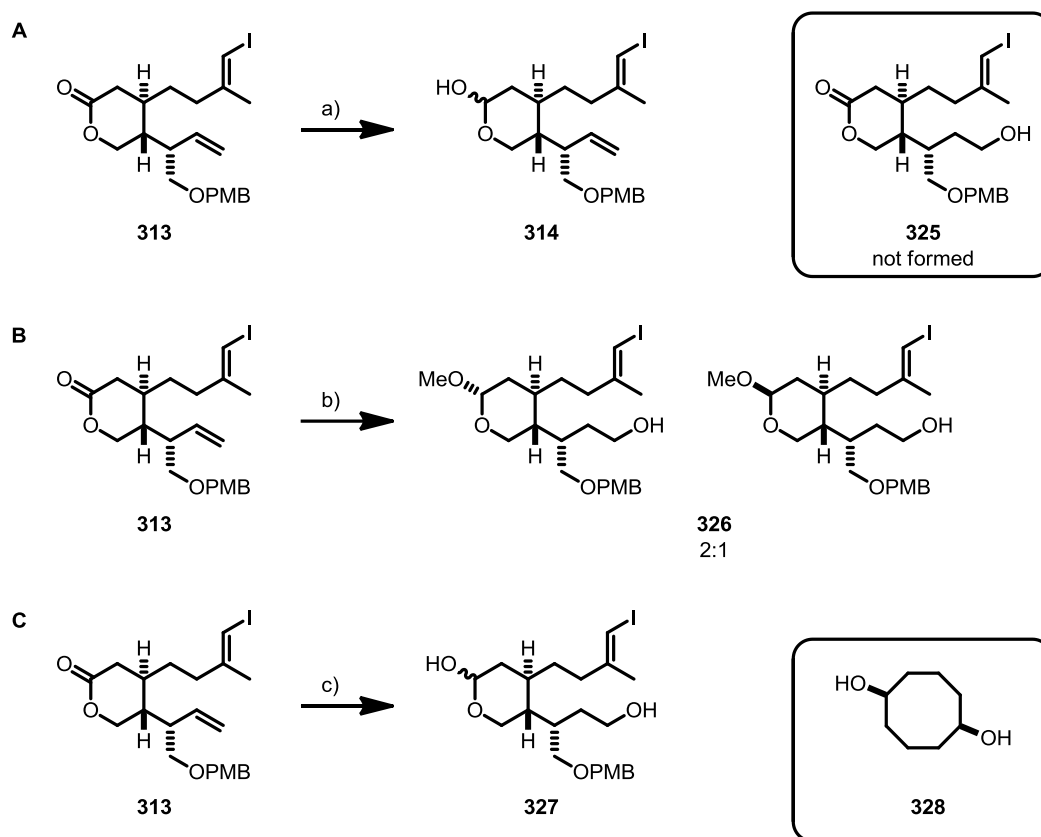
Scheme 58: Epoxidation of **323**. Reagents and conditions: (a) *m*-CPBA (3 eq.), Na₂HPO₄ (3.6 eq.), CH₂Cl₂, 0 °C, 70, 65%.

This finding highlights the highly strained nature of cyclononenol **323**; it implies that the compound is able to react with atmospheric oxygen as a means of strain release and this very strain might account for its defiance to undergo ring-closure. A subsequent reevaluation of the spectra of TBS-protected cyclononenol **321** revealed characteristic epoxide peaks, as well.

Before closure of the 9-membered ring, reactions of the TIPS-protected substrates gave visibly higher yields. Afterwards and against all expectations, the TIPS-series did not display improved stability. Despite the compounds appearing to be pure on TLC, NMR spectroscopy would always reveal the presence of impurities/decomposition. After some further attempts to functionalize the available epoxide **324** (section 3.8.2, p. 122ff), this route was thus abandoned.

3.6.4 Hydroboration/Oxidation of Lactone **313** and Ring-Closure

Bearing in mind the problems with the stability of the silyl pyranosides, and after gathering experience in effecting clean hydroboration/oxidation reactions^[245], the project took a necessary step back and oxofunctionalization of the lactone-based terminal olefin **313** was evaluated. Initial experiments on the hydroboration/oxidation of **313** with 1.1 eq. of 9-BBN (Scheme **59A**) did not lead to the desired primary alcohol **325**, but instead produced small amounts of the lactol **314** as well as some recovered starting material. It thus became clear, that reduction of the carbonyl group in the lactone ring was faster than the desired hydroboration. Reaction with an excess of $\text{BH}_3\cdot\text{THF}$ followed by oxidation, did produce trace amounts of the desired alcohol **325**; upon isolation this material was determined to be mostly decomposed.



Scheme 59: (a) 9-BBN (1.1 eq.), THF, -78 °C, 1 min, rt, 2 h 30 min, (ii) NaOH (1.1 eq.), MeOH (80 eq.), H₂O₂ (3.84 eq.), 26% **314**, 19% **313**; (b) 9-BBN (3 eq.), THF, -78 °C, 1 min, rt, 4 h, (ii) MeOH (80 eq.), rt, 35 min, (iii) NaOH (3 eq.), H₂O₂ (8.4 eq.), rt, 79%; (c) 9-BBN (2.25 eq.), THF, -78 °C, 2 h 30 min, (ii) MeOH (80 eq.), NaOH (2.25 eq.), 0 °C to rt, 30 min, (iii) H₂O₂ (6.6 eq.), 0 °C to rt, 30 min 81%;

Hydroboration using a 3-fold excess of 9-BBN surprisingly delivered a 2:1 anomeric mixture of methyl acetals **326** (Scheme **59B**), which is the pure *E*-isomer of the previously described *E/Z*-mixture **311** (Scheme **53**, p.98). On the basis of ¹H NMR chemical shifts and coupling constants^[270] as well as ¹³C chemical shifts^[271], the axial anomer was assigned to be the major one. Formation of the methyl acetal can be rationalized by formation of 9-borabicyclo[3.3.1]nonan-9-ol via hydrolysis and acetal formation is catalyzed by this borinic acid after quenching the reaction with methanol. The material for this reaction had not been subjected to the usual azeotropic drying procedure with benzene, which clearly accounts for the presence of residual water, as NaOH was only added 30 min after quenching with MeOH. As a consequence, in subsequent reactions, olefin **313** was always azeotropically dried before reaction, and both MeOH and NaOH were added simultaneously during the quench, which reproducibly delivered compound **327** in good yield (81%) (Scheme **59C**). Cyclooctane-1,5-diol

328 was the expected byproduct of this reaction and relatively hard to separate from the product. Lowering the excess of 9-BBN to 2.25 eq. eased isolation of diol **327** to some extent.

With diol **327** in hand, simultaneous oxidation to the lactone and the aldehyde was probed on small scale (Table **16**). This approach proved to be problematic, because for most of the experiments compiled in Table **16**, large amounts of byproducts were formed that were tedious to remove chromatographically. To complicate matters further, in most cases impurities were still detected in the isolated product by ^1H NMR, even when the material appeared homogeneous by TLC (exceptions are highlighted below). At a later stage, these impurities were found not to interfere with the next step. The use of unbuffered Dess-Martin periodinane^[267] gave incomplete conversion and formation of intractable byproducts (entry **1**) as well as trace amounts of impure **329**. Buffering the DMP oxidation with pyridine^[268] (entry **2**) improved the overall yield, but the amount of removable byproducts was not lowered and conversion was still very slow. Reaction of buffered Dess-Martin periodinane with *t*-BuOH^[267] prior to addition of **327**, slightly reduced the degree of byproduct formation and accelerated the reaction (entry **3**). However, portionwise addition of a large excess of the oxidant was still required to achieve full conversion. The use of pyridinium chlorochromate (entry **4**) produced large amounts of both the desired product and undesired byproducts (around 1:1 ratio); but it was necessary to stir the reaction overnight to go to completion. Both these aspects were deemed unsatisfactory and no attempts were made to isolate the product. The milder pyridinium dichromate (entry **5**) produced the purest material in the first series of experiments, as it contained only traces of the typical inseparable contaminants. Swern oxidation^[160] (entry **6**) of **327** selectively gave aldehyde **329**, albeit in low yield and purity. Oxidation of this product with buffered Dess-Martin periodinane and *tert*-butanol (entry **7**) led to a 1:1 mixture (TLC) of the desired product and a separable impurity; this material was discarded due to the expected low 2-step yield. Fétizon oxidation^[272,273] (entry **8**) of **327** at 120 °C **cleanly!!!** oxidized the lactol moiety while the primary hydroxy group remained unchanged. A combination of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and (diacetoxyiodo)benzene (DAIB)^[274,275] is frequently used for the oxidation of lactols to lactones and after repeated chromatography, **325** was obtained in very low yield, but in excellent purity (entry **9**).

Table 16: Reagents and conditions tested for double oxidation of diol **327**.

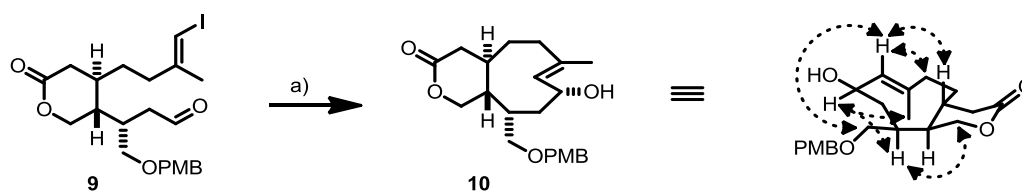
Entry	Conditions	Solvent	Product	Yield
1	Dess-Martin	CH ₂ Cl ₂	9	< 24%
2	Dess-Martin, pyridine	CH ₂ Cl ₂	9	< 46%
3	Dess-Martin, pyridine, <i>t</i> -BuOH	CH ₂ Cl ₂	9	< 55%
4	PCC, 4Å MS	CH ₂ Cl ₂	9	n.d.
5	PDC, 4Å MS	CH ₂ Cl ₂	9	< 44%, slightly impure
6	Swern	CH ₂ Cl ₂	329	<35%
7	329 , Dess-Martin, pyridine, <i>t</i> -BuOH	CH ₂ Cl ₂	9 : by-product 1:1	n.d.
8	Ag ₂ CO ₃ , Cellite, 120 °C	Toluene	325	66%, pure
9	DAIB, TEMPO	CH ₂ Cl ₂	325	30%, pure
10	DAIB, TEMPO, Yb(OTf) ₃	CH ₂ Cl ₂	325	Very low conversion, no clean reaction, n.d.
11	325 , Dess-Martin, pyridine, <i>t</i> -BuOH	CH ₂ Cl ₂	9 , trace of by-product	n.d., AlOx column destroyed material
12	TPAP (0.1 eq.), NMO (5 eq.), 4Å MS	CH ₂ Cl ₂	9 , trace of by-product	50%, purity 94%
13	TPAP (0.1 eq.), NMO (5 eq.), 4Å MS	CH ₂ Cl ₂	9 , trace of by-product	70%

All products contained inseparable impurities unless otherwise noted. Entries 7 and 11 used **329** and **325** as starting materials, respectively. n.d. = not determined.

Using the same mixture with added Yb(OTf)₃^[276] (entry **10**), produced a number of different byproducts and the material was discarded. The product from the experiment in entry **9** was oxidized employing the accelerated Dess-Martin conditions (entry **11**) and only traces of separable byproduct were observed by TLC. However, the reaction was very slow and a large excess of Dess-Martin periodinane was needed to drive the reaction to completion. Even though 2D TLC of the crude product obtained in this reaction indicated no decomposition, it was suspected that the low yield might have been caused by the instability of the product

during column chromatography. As an alternative, purification on neutral aluminum oxide was thus attempted, but no product was obtained. Finally, Ley's conditions^[277,278] (entry **12**) converted diol **327** to the desired intermediate **9** within 15 minutes, showing no formation of the inseparable byproduct and only small amounts of a partly separable one. By using a simple silica plug filtration for purification, yields of 65-70% were routinely obtained (entry **13**). Obviously, the impurity with the close R_f -value was not removed by filtration, but, as mentioned before, this was found not to interfere with the next step. On larger scale, the reaction was best cooled with an ambient temperature water bath and the catalyst was added in several portions to control the slight exothermicity. Performing the reaction at 0 °C was no option as the process became very slow.

In light of the observed low yields and instability of **9** on silica gel, the aldehyde was always immediately used for the next step. When subjected to *Nozaki-Hiyama-Kishi* conditions, formation of one single isomer was observed (Scheme **60**). NOESY correlations suggested the relative configuration of the newly formed stereogenic center to be as depicted in **10**. Yields varied between 57 and 75%.



Scheme 60: Ring-closure of aldehyde **9** and key NOE interactions within allylic alcohol **10**. Reagents and conditions: (a) CrCl_2 (7.5 eq.), NiCl_2 (0.06 eq.), DMSO, rt, 71%.

In those cases where better yields were obtained, the reaction was usually progressing more quickly and complete conversion was achieved in 80 min. In other cases, the reaction stalled at a certain point and could not be pushed to completion. In one single case, the reaction did not proceed at all, and no intact starting material could be recovered after 15 h. The color of the reaction mixtures varied between black, turquoise and olive green, but there was no obvious correlation between coloring and the conversion/yield obtained for individual reactions. Literature reports on the successful formation of cyclononenols refer to substrate concentrations between 5 mM^[138] and 40 mM^[139]. Initially, we started at concentrations of **9** of 3.3 mM, but since no dimer formation was observed, later experiments were performed at 20 mM. While up to a 100-fold excess of Cr had to be used on small scale for practical purposes

(exact Ni content), the excess of Cr could be reduced to 7.5 eq. when reactions were performed on 100 mg scale and larger. Quenching with EDTA gave homogenous purple to black solutions of Cr(II)-ions, often-times accompanied by a small amount of insoluble green Cr(III) salts that were best removed by filtration. On larger scale, quenching was highly exothermic and was thus best carried out by pouring the reaction mixture into an ice-cooled EDTA solution. The catalytic version^[279,280] of the NHK as developed by *Fürstner* was also investigated, but did not lead to any conversion; rather, slow decomposition of **9** was observed. This finding was not surprising, given the sensitive nature of the substrate. Due to the low concentration in DMSO, the product had to be extracted from large volumes of aqueous solution. We thus tested for the possible *in situ* formation of the corresponding silyl ether, in order to reduce product polarity and the volume of the organic solvent required for extraction. However, only trace conversion was observed.

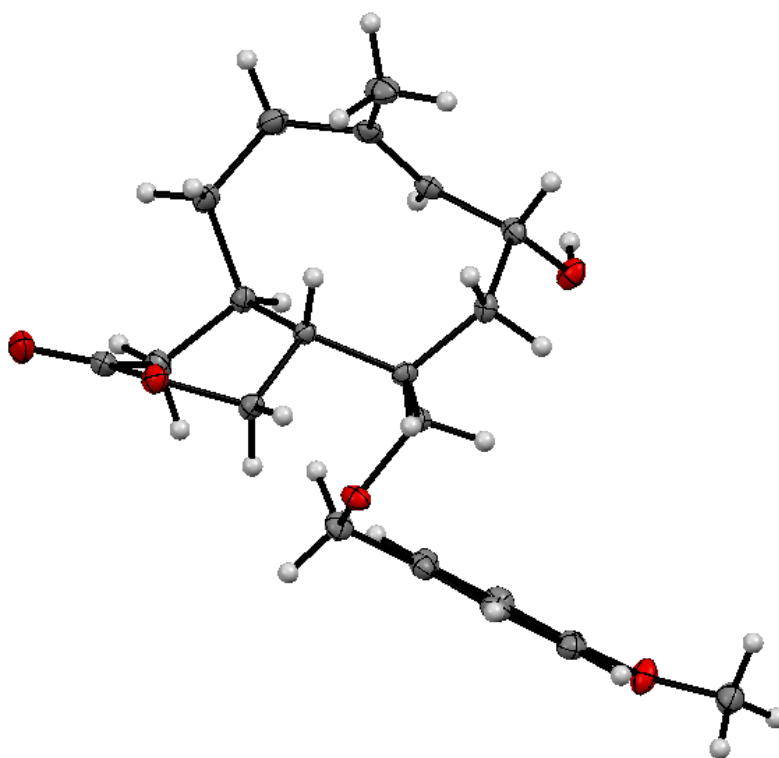


Fig. 20: ORTEP representation of cyclononenol **10** determined by X-ray diffraction. Thermal ellipsoids drawn at 50% probability

After having secured larger quantities of **10**, formation of a white grainy solid was observed upon evaporation of a solution in diethyl ether. Through subsequent crystallization trials it

was eventually found that crystals suitable for X-ray diffraction could be obtained by slow solvent evaporation from a solution of **10** in fluorobenzene. As depicted below (Fig. 20), the X-ray crystal structure of **10** independently confirmed the previous NOE-based assignment of the configuration of the newly formed C8 stereocenter bearing the allylic hydroxy group. In addition, the structure also highlights the correct relative configuration of the other stereocenters.

3.6.5 Conclusions

The route developed to effect the desired *NHK*-reaction of PMB-protected aldehyde **9** still holds potential for further improvement: The yield of the PMB-protection (Scheme 54) is still unsatisfactory for a transformation considered to be routine and the same applies to the removal of the trichloroacetamide byproduct. The group of *Dudley* has successfully established pyridine-based reagents **361** for Bn protection^[281,282] and lepidine-based PMB-donors for the installation of PMB groups^[283] under neutral conditions (Fig. 21). The byproducts of these reactions have polarities that are generally different from those of the Bn/PMB-ethers formed and might be easier to remove also in our case. Paquette has adapted the lepidine system for the protection under acidic conditions.^[284] An easier and cheaper alternative might be the PMB hydroxypyridine **363**.^[285]

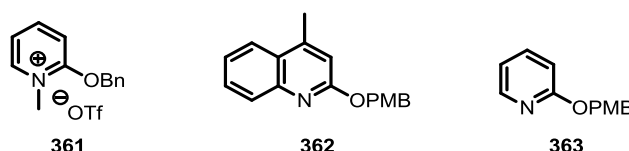


Fig. 21: Dudley's reagents **361**^[281,282] and **362**^[283] for benzyl- and PMB-ether formation, respectively, under neutral conditions. **363** might be an alternative for **362**.

As for the ring-closure to **10** (Scheme 60) itself, the following aspects might warrant some further investigation: The use of DMSO as a reaction solvent necessitates dilution with a large excess of aqueous solution to enable extraction of the product. Because of this, an increase in substrate concentration^[286] holds the greatest potential for improving product recovery and ease the handling. No efforts have so far been expended on the investigation of any reaction solvent other than DMSO, which may not be optimal. Other possible solvents for the *NHK* reaction include DMF^[287], DMF·Me₂S^[288], THF^[286,289,290], DME^[286,291,292], EtCN^[289] and MeCN.^[293,294] Preferably, a solvent that can be removed by evaporation should be used. When

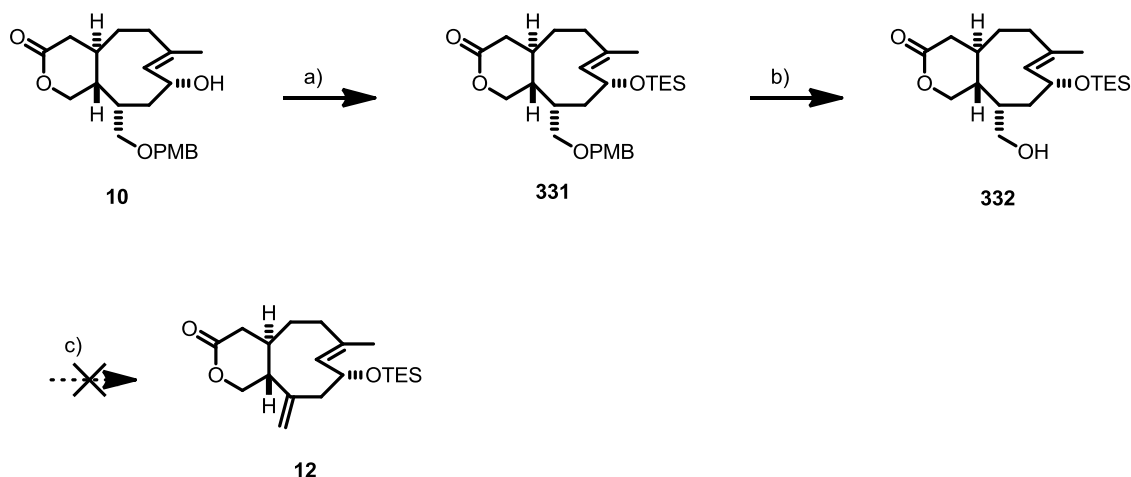
suspending CrCl_2 in DMSO, formation of hard lumps was observed that could be broken down only partly by stirring with extreme vigor. This aggregation in the solid state might limit the actual fraction of accessible Cr and thus decrease reactivity. Using an additive such as 4-*t*-Bu-pyridine^[269] to render the reaction more homogeneous has not been explored for aldehyde **9**. Alternatively, a reinvestigation of the catalytic version of the NHK reaction using different Cr(II)-^[292,293] and Ni(II)-complexes^[292–294] might allow to overcome this problem and also enable a reduction of the metal-loading. Kishi has also reported an air-stable heterobimetallic construct for very easy to perform coupling reactions.^[291]

3.7 Completion of the Total Synthesis of Isoxeniolide A

Starting from cyclonenol **10**, two structural features were missing for the completion of the synthesis of isoxeniolide A: The exocyclic alkylidene group and $\alpha,\beta,\gamma,\delta$ -unsaturated appendage to the lactone.

3.7.1 Introduction of the Exocyclic Double Bond

Oxabicyclo[7.4.0]nonene **10** was first protected as a TES ether **331** (Scheme 61) and the primary hydroxyl group was liberated using DDQ^[295] under buffered conditions to give alcohol **332**.



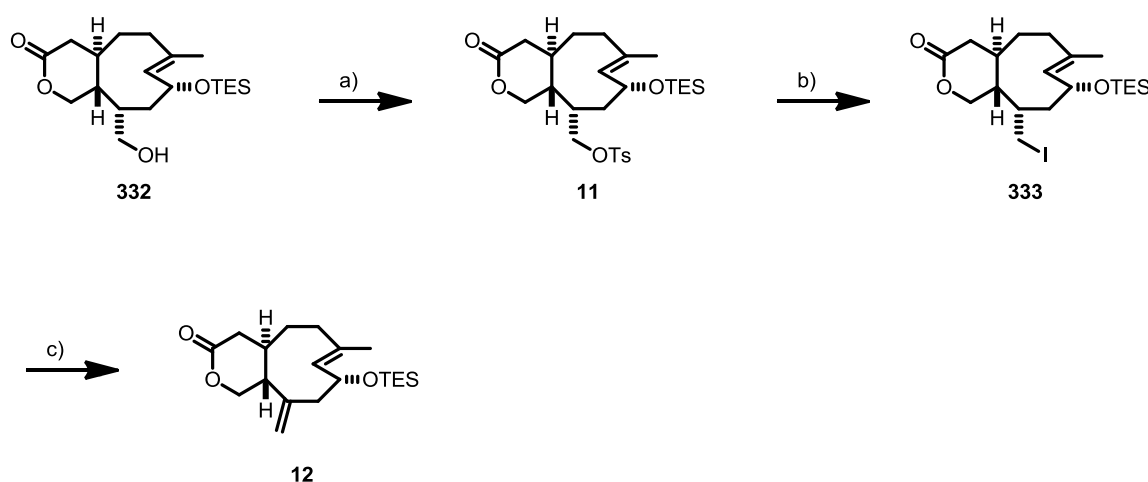
Scheme 61: Preparing the substrate for installation of the exocyclic double bond. Reagents and conditions: (a) TESCl (1.1 eq.), ImH (3.7 eq.), CH₂Cl₂, 4 h, 85%; (d) DDQ (2.14 eq.), buffer pH 7, CH₂Cl₂, 0 °C, 5 min, rt, 1 h 45 min, 93%; (c) cf. text for a description of the conditions used.

We first attempted a *Grieco-Sharpless* elimination^[296–298], a reaction that has been successfully employed for the formation of 1,1-disubstituted double bonds in the context of a number of complex molecule syntheses.^[299–302] In the case of primary alcohol **332**, no reaction was observed. Recovery of **332** was rendered impossible by the presence of decomposition products derived from the excess *o*-nitrophenyl selenocyanate, which could not be separated from the starting material. The use of rigorously purified *o*-nitrophenyl selenocyanate reagent did not change the outcome. We hypothesized that PBu₃ as an activating agent might be too sterically demanding to access the encumbered primary alcohol. The much smaller PMe₃ has also been used in *Grieco-Sharpless* reactions.^[303–306] However, using this reagent on **332**, no

change in reactivity was observed and recovery of the starting material still remained impossible.

As an alternative, we envisioned transforming the alcohol into a suitable leaving group and effecting elimination through the use of a strong base. Work by *Agosta* and coworkers had shown that primary tosylates and iodides undergo efficient elimination using DBU in DMF.^[307] Furthermore, a natural product synthesis by *Iwata's* group provided an example of direct elimination using a mesylate with DBU in toluene.^[308]

Bearing these pieces of information in mind, we carried out tosylation of alcohol **332** (Scheme 62). Tosyl chloride of excellent purity was paramount to obtain good yields in this transformation. The reaction was very slow and took almost one day to go to completion. This finding was not surprising, in light of the inertness of alcohol **332** observed in the *Grieco-Sharpless* reaction. An attempt to access iodide **333** via *Finkelstein* reaction of tosylate **11** gave no conversion at room temperature, even in the presence of a large excess of NaI. Only when this mixture was heated to 50 °C, the product was obtained in moderate yield. When iodide **333** was treated with DBU in refluxing toluene, TLC (falsely) indicated no reaction, even upon prolonged heating. However, the reisolated material contained no more iodide, but traces of the desired diene **12** and some unrelated decomposition products. A tentative structural assignment was based on the presence of the characteristic ¹H NMR signals of the geminal olefin protons.

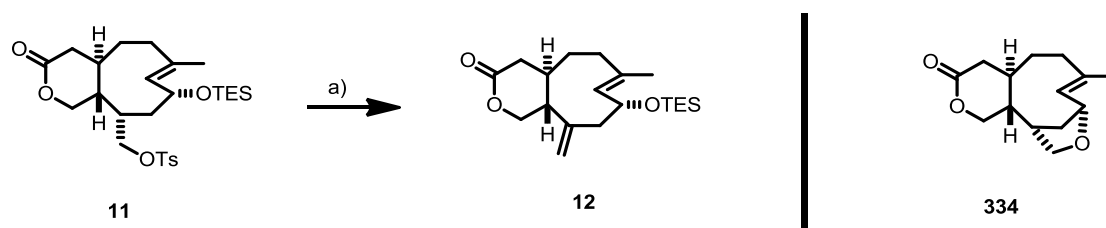


Scheme 62: Installation of the exocyclic double bond – initial results. Reagents and conditions: (a) TsCl (3 eq.), NEt₃ (6 eq.), DMAP (0.5 eq.), CH₂Cl₂, rt, 20 h, 89%; (d) NaI (200 eq.), Cu (0.2 eq.), acetone, 50 °C, 4 h, 59%; (c) DBU (12 eq.), toluene, 80 °C, 3h, 85 °C, 3 d, traces.

These initial results suggested that the desired elimination was possible, at least to some extent, and it revealed that formation of the iodide via a 2-step process would be associated with a substantial loss of material. However, attempts at the direct formation of iodide **333** from **332** via an *Appel*-like reaction using I₂, PPh₃ and ImH were unsuccessful. This reaction was not investigated further because the desired iodide **333** and PPh₃ display almost identical R_f values on TLC. *Agosta* and coworkers reported a one-pot two-step procedure where a tosylate is first transformed into the iodide with NaI in DMF at 50 °C and, after 4-6 h, DBU is added and the temperature is raised to 80 °C for elimination.^[307] A report by the group of *Maier* suggested that elimination can also be induced by heating tosylates in the presence of NaI and DBU in glyme.^[309,310] Further literature precedent was available for one-pot substitution/eliminations reactions in DMF^[311].

After some experimentation, *Maier's* one-pot procedure for formation of the double bond could be successfully implemented (Scheme **63**). Both, rigorously anhydrous conditions and freshly distilled DBU were crucial for reproducible results. Moreover, a reaction time of at least 2 h, preferably 3 h was important. While the intermediate iodide **333** is completely formed within 1 h, additional time is needed for full conversion to **12**. At this point, some additional comments are warranted on problems encountered during the double bond formation process. After securing larger batches of tosylate **11**, we found that this compound is very prone to decomposition^{xix} and is best used immediately. The purity of the tosylate greatly affected formation of diene **12**. When partially decomposed material (66% purity) was subjected to the one-pot elimination conditions for only 1 h, the reaction was largely funneled along a pathway producing tricyclic compound **334** in 50% yield. The pathway to this product likely comprises loss of the TES-protecting group, followed by an S_N2-reaction of the allylic hydroxy group with either a tosyloxy or iodide anion as a leaving group. In addition, 16% of diene **12** and around 10% of a mixture containing mostly iodide **333** and traces of the desired product was isolated from this reaction.

^{xix} About 1/3 of the material decomposed overnight in the fridge under argon.



Scheme 63: One-pot 2-step transformation of tosylate **11** into **12** and the structure of undesired byproduct **334**. Reagents and conditions: (a) NaI (5 eq.), DBU (3 eq.), DME, 90 °C, 3 h, 78%.

The structure of **334** was assigned by NMR spectroscopy and HRMS (Fig. 22). Two likely conformations for the cyclononene ring of the proposed structure were modelled: one with the C20 methyl group oriented in the opposite direction with respect to the lactone β -proton, one with the methyl group and β -proton aligned. Energies of these two conformations were minimized by an MM2 force field method.^{xx}

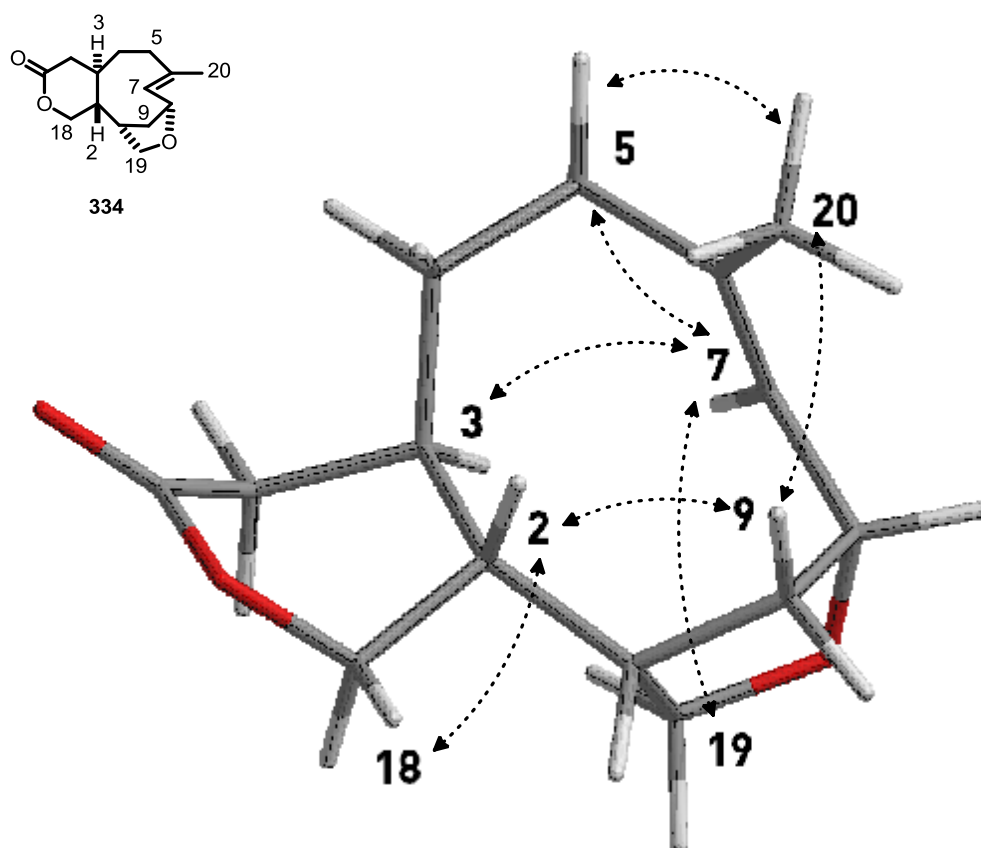


Fig. 22: Structure and modelled conformation of tricyclic compound **334**. The numbering corresponds

^{xx} CambridgeSoft ChemBio3D, V.12.0.2.1076

to the xenicane system. NOE contacts for the conformational assignment are highlighted with arrows.

In a comparison of both conformers with the experimental NOE data observed, the 3-dimensional structure depicted in Fig. 22 was determined to be very likely. In this context, NOE interactions C20-C9, C3-C7 and C7-C19 are of diagnostic relevance, since they rule out the other conformer. When comparing the modelled 3D-structure of **334** to the X-ray structure of **10** (Fig. 20), it seems that both molecules adopt an almost identical conformation of the oxabicyclo[7.4.0]nonene system. Because the allylic hydroxy group of alcohol **10** is already in close spatial proximity of the electrophilic position, only a small conformational change is necessary for ring-closure and allowed for efficient reaction.

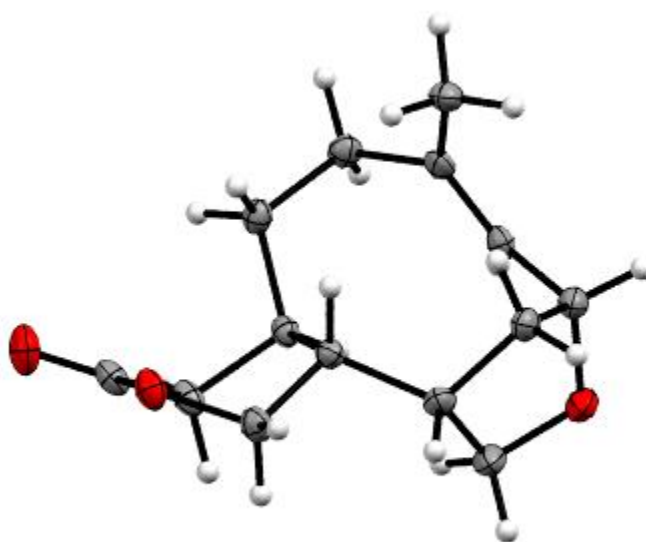


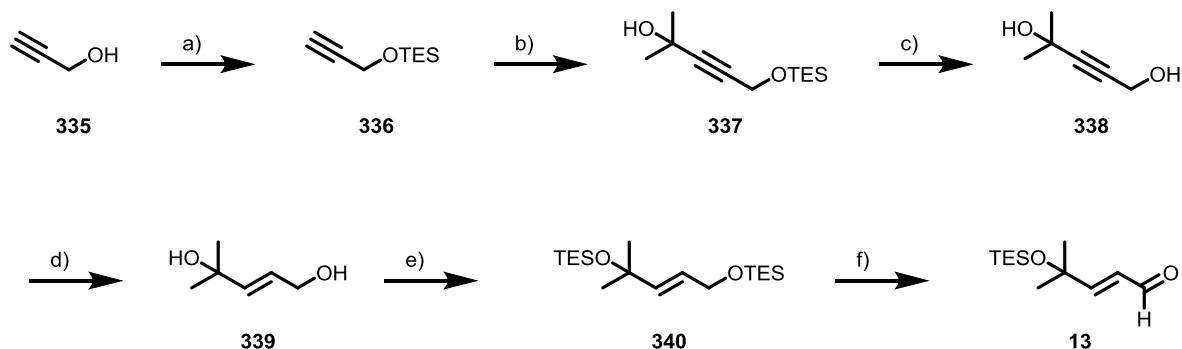
Fig. 23: ORTEP representation of tricyclic byproduct **334** determined by X-ray diffraction. Thermal ellipsoids drawn at 50% probability

The absolute structure of **334** and its proposed conformation were unambiguously confirmed by single crystal X-ray analysis in a later phase of the project.

3.7.2 Synthesis of Side Chain **13** and Assembly of Isoxeniolide A

As discussed in chapter 3.1, p.46f), attachment of the C10-side chain was planned to be carried out via an aldol reaction, followed by stereoselective dehydration to control for the olefin geometry; a sequence inspired by previous work in the group on blumiolide C. Since the protecting group strategy for isoxeniolide A (**1**) had relied on a TES-protection of the allylic

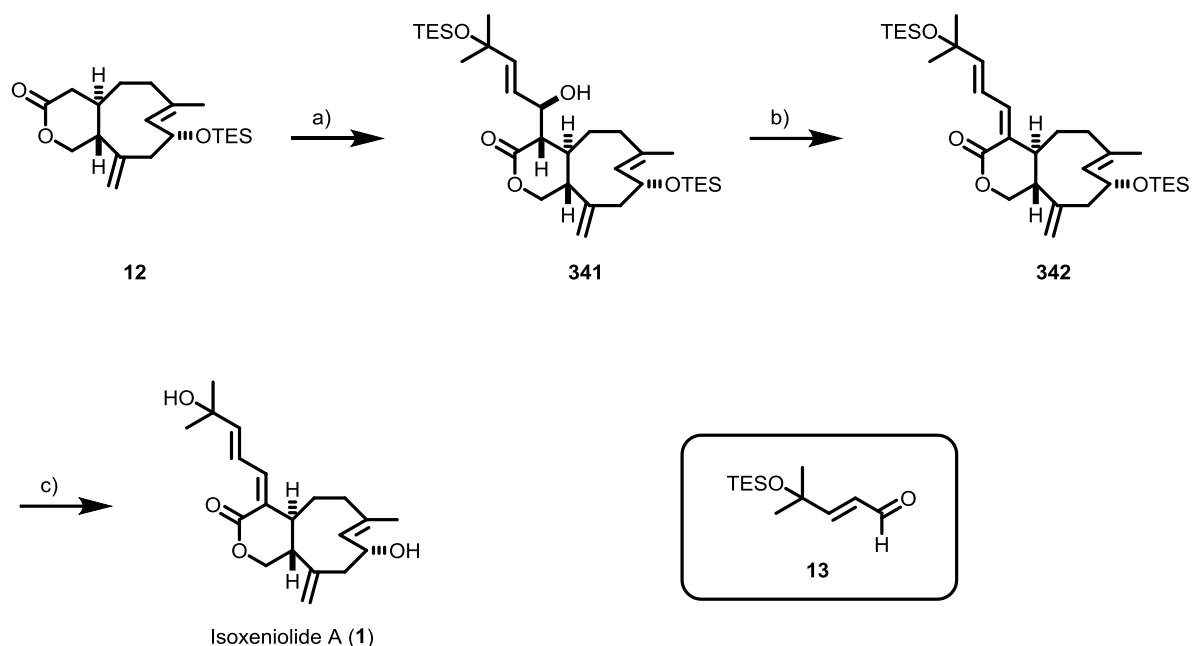
hydroxy group on C8 during the final stages of the synthesis, we planned to use TES-protected aldehyde **13** as the side chain precursor (**Scheme 64**).



Scheme 64: Synthesis of aldehyde **13** from propargyl alcohol (**335**). Reagents and conditions: (a) TESCl (1.1 Eq.), ImH (3.7 eq.), CH₂Cl₂, 0 °C, 5 min, rt, 2 min; (b) (i) *n*-BuLi (1.1 eq.), THF, -20 °C, 15 min, (ii) acetone (1.5 eq.), 30 min, 78% (2 steps); (c) PPTS (0.5 eq.), MeOH/THF (2:1), rt, 12 min, 85%; (d) LiAlH₄ (4 eq.), THF, 0 °C, 15 min, to rt, 45 min, 73% (e) TESCl (3 Eq.), ImH (4.6 eq.), DMAP (0.2 eq.), CH₂Cl₂, rt, 1 h 20 min; 96%; (f) (COCl)₂ (4.4 eq.), DMSO (10 eq.), Et₃N (20 eq.), CH₂Cl₂, -78 °C to rt, 1 h, 70%.

TES-ether **337** was available in our laboratories from other studies and had been synthesized in a 2-step sequence: Propargyl alcohol (**335**) was TES-protected^[312] to give silyl ether **336**, which, after deprotonation with *n*-BuLi, was reacted with acetone to install the dimethylcarbinol moiety of **337**^[313] in 83% overall yield. The silyl group was removed under weakly acidic conditions^[314] to provide diol **338**.^[315] Reduction of the triple-bond with LiAlH₄^[316] furnished known *E*-olefin **339**^[317] as a single isomer. The diol was doubly TES-protected leading to compound **340**. Simultaneous TES-deprotection/*Swern* oxidation^[318] produced unsaturated aldehyde **13**.

For the union of aldehyde **13** with lactone **12**, the latter was deprotonated with LiHMDS at low temperature and the enolate was then treated with an excess of aldehyde **13** (Scheme **65**). The reaction did not reach full conversion, even after slowly warming to -10 °C. The desired product was obtained in 29 % yield as a single stereoisomer, along with 42% of recovered starting material **12**. The *syn*-elimination on aldol product **341** was performed employing a combination of EDCI and CuCl₂ in toluene. Surprisingly, this *Ohmizu* variant^[319,320] of the *Corey* dehydration procedure^[321,322] led to complete reaction in less than half an hour, which is much faster than the 2 h described by *Ohmizu*.



Scheme 65: Completion of the total synthesis of isoxeniolide A. Reagents and conditions: (a) LiHMDS (2.9 eq.), THF, -78°C , 1 h, **13** (1.5 eq.), 2 h, -78°C to -10°C over 20 min, 29%, 42% recover of **12**; (b) EDCI^{xxi} (5 eq.), CuCl_2 (cat.), PhMe, 80°C , 26 min, 76%; (c) $\text{Et}_3\text{N}\cdot 3\text{HF}$ (9 eq.), THF, rt, 2 d, 80%.

Dienoate **342** was found to be a single double-bond-isomer with the geometry depicted, based on the comparison of NMR chemical shifts as well as coupling constants with the corresponding literature values for xeniolide A (**30**) and isoxeniolide A (**1**).^[83] The two newly formed stereogenic centers in **341** were tentatively assigned using the following rationale: Aldehyde **13** was expected to approach from the more accessible face of the enolate, the same side where the lactone β -proton is oriented. The same stereochemical bias has been observed by *Leumann and Pfander*, *Altmann and Corey*. To be in accordance with the *syn*-selectivity of the elimination step, the β -hydroxy group must have the configuration shown in **341**. While *mono*-deprotection of bis-TES-ether **342** was observed to be complete within 2 h at ambient temperature, it took 2 d for complete liberation of the second hydroxy group. It is reasonable to assume that the secondary TES-ether reacts much faster, but we have not confirmed this by isolation of the corresponding intermediate. Isoxeniolide A (**1**) was obtained in good yield and this deprotection-step concluded the total synthesis. ^1H and ^{13}C NMR were in agreement with the values reported by *Braekman*.^[83] Optical rotation of the synthetic product $[\alpha]^{20}_{\text{D}} = +19.22^{\circ}$ ($c = 0.385$, MeOH) displayed the same sign, but differed from the

^{xxi} Use of the salt free variant of this reagent is mandatory; otherwise no reaction occurs.

literature value ($[\alpha] = +50^\circ$ ($c=0.655$, MeOH)) in magnitude. The reasons for this discrepancy are not clear.

3.8 Studies Towards the Total Synthesis of Acalycixeniolide F

3.8.1 Attempted Cyclononene Formation via Alkyl-Boron *Suzuki* Reaction

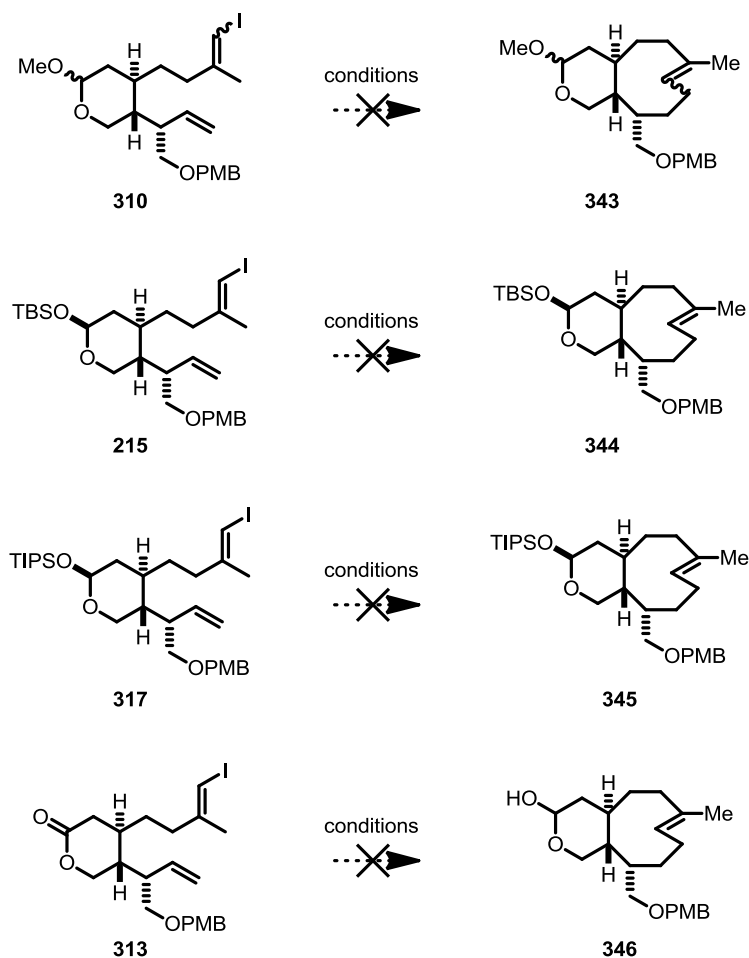
The substrates described in chapter 3.6, which were suitable for hydroboration/oxidation, were also investigated for their ability to undergo intramolecular alkyl-B *Suzuki*-coupling, after being subjected to hydroboration conditions. None of these attempts were fruitful, but the methods employed will be shortly summarized and some further background will be given. Our initial investigations started with the mixture of *E*- and *Z*-iodides **310** (Scheme 66). After the olefin had undergone complete hydroboration, the mixture was quenched with degassed NaOH and treated with Pd(PPh₃)₄ in a solvent mixture of MeCN/H₂O/THF 10:1:1. These conditions had been used by Williams^[129,130] (Scheme 11, p.33) for the very challenging cyclononene formation in the synthesis of 4-hydroxydictyolactone (**83**).

In the case of methyl pyranoside **310**, no formation of a well-defined product was observed. Instead, the material decomposed to a number of different compounds as observable by TLC. When isolated, for most of them the NMR spectra still showed the presence of the anomeric proton on the pyran-ring, but no traces of the terminal vinyl group and no signals corresponding to the vinyl iodide were found. In general, alkyl-B *Suzuki*-couplings are executed with Pd(dppf)Cl₂ as a catalyst, due to reduced β-hydride elimination and improved performance in the transmetallation step, compared to Pd-complexes lacking a chelating ligand.^[323] Because the addition of AsPh₃ has been reported by Johnson^[324,325] to increase turnover rate and lead to cleaner *Suzuki*-couplings, we tried Johnson's combination on substrate **310** using a solvent mixture of DMF/H₂O/THF 10:1:1. The reaction again led to a large number of products as judged by TLC and, after oxidative workup, only decomposition products were obtained, even though the mass of the desired product was present in a number of fractions from the flash chromatography (according to LCMS).

For TBS-protected pyranoside **315**, three attempts using standard conditions for *Suzuki*-couplings were made: First, the conditions described by Williams with Pd(PPh₃)₄ and NaOH were investigated. As a second set, the conditions of Johnson using Pd(dppf)Cl₂, Cs₂CO₃ and AsPh₃ were employed. Lastly, the combination of Pd(dppf)Cl₂, TIOEt and AsPh₃ (as pioneered by Danishefsky^[326]) was explored. None of these experiments delivered any trace of the desired product. The iodide functionality had disappeared after the reaction as well as the TBS

group and the borane was usually still present. This indicates that failed transmetalation is likely responsible for the unsuccessful reaction.

Attention was then turned to the TIPS-pyranoside **317**. For this substrate we focused on the combination Pd(dppf)Cl₂, AsPh₃ and TIOEt. Once, slow addition of the borate species to the catalyst was tried and in a second experiment, borate and catalyst were mixed immediately. In both cases, no well-defined product was formed and a large content of residual borane was observed in all fractions after chromatography. This underscores the hypothesis that failed transmetalation is responsible for the lack of success in this reaction.



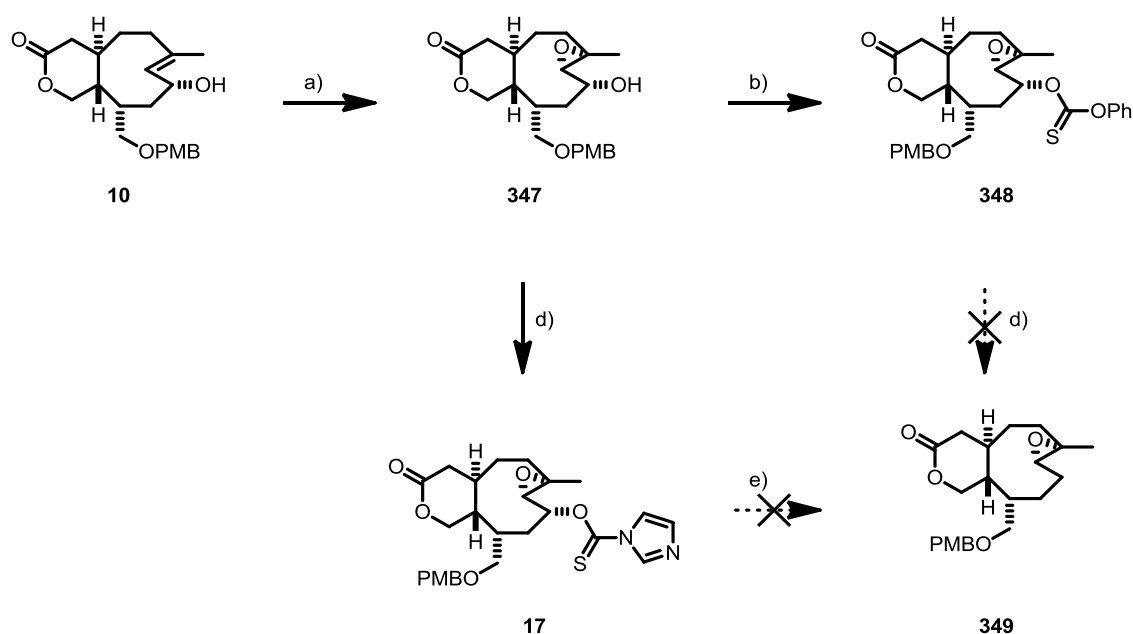
Scheme 66: Substrates for attempted alkyl-B Suzuki reactions to close the 9-membered ring. Reagents and conditions are described in the text.

Due to the presence of the lactone moiety, compound **313** did not seem to be a promising candidate for an alkyl-B Suzuki coupling. Therefore, only a single attempt was made on this substrate using Williams conditions. However, complete decomposition was observed in this experiment.

We suspect that the intermediate boranes formed upon reaction of **315** or **313** with 9-BBN adopt a very specific conformation to accommodate the large borabicyclononane moiety and that this spatial arrangement does not permit the catalyst to approach the boron-bearing carbon atom and insert. Conversely, the peroxide used for oxidative cleavage of the borane is very small and can easily attack boron. In light of the disappointing results described above, efforts of achieving 9-membered ring-formation via cross-coupling came to a halt. All material of intermediates **315**, **317** and **313** was instead used for the *NHK*-studies described in sections 3.6.3 and 3.6.4.

3.8.2 Attempted Deoxygenation of Epoxyalcohols via *Barton-McCombie* Reaction

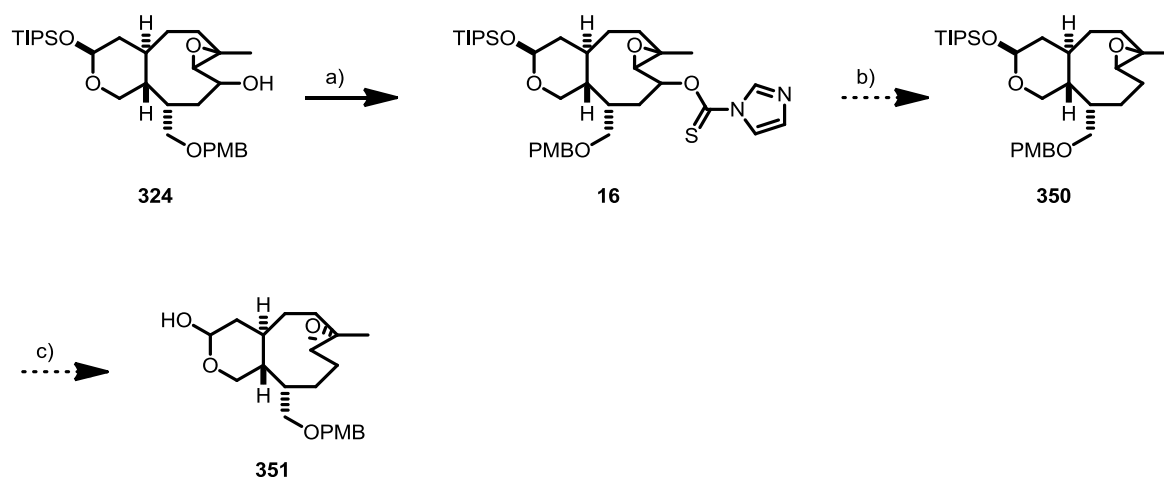
We envisioned deoxygenation of the *NHK* products **323** and **10** as a viable alternative to the defiant *Suzuki* coupling. **10** was thus treated with *m*-CPBA to give epoxide **347** in almost quantitative yield (Scheme 67). Due to the strained nature of the cyclononene system and the presence of the allylic hydroxyl group, this reaction proceeded extremely fast. The relative stereochemistry was assigned based on the disposition of the double-bond both in the solid state and solution (*cf.* Fig. 20).



Scheme 67: Attempted deoxygenation from allylic alcohol **10**. Reagents and conditions: (a) *m*-CPBA (1.5 eq.), Na₂HPO₄ (2.25 eq.), 0 °C, 17 min, 98%; (b) Cl(CS)OPh (3 eq.), py (4 eq.), CH₂Cl₂, rt, 14 h, 59%; (c) (CS)Im₂ (3 eq.), DMAP (0.5 eq.), CH₂Cl₂, rt, 13 h, 88%; (d); Bu₃SnH (6 eq.), AIBN (0.3 eq.), PhH, 80 °C, 5 h; (e) *cf.* text.

Epoxyalcohol **347** was converted into the corresponding thionocarbonate^[327] **348** and imidazolyl thionocarbamate^[328] **17** in moderate and very good yields, respectively. Radical deoxygenation of thionocarbonate **348** was attempted under thermal conditions using Bu₃SnH as a reductant and AIBN as a radical starter.^[327] Unfortunately, upon heating to the required 80 °C for radical initiation through AIBN cleavage, the material was slowly transformed into a multitude of decomposition products. With **17**, which was available in slightly larger quantity, two different sets of conditions were tested: We attempted photoredox deoxygenation mediated by Ir(ppy)₃ and blue LED-light, using Bu₃N and *Hantzsch* ester as additives and degassed MeCN as a solvent.^[329,330] The use of Bu₃SnH with Et₃B as a radical starter was also investigated.^[331] In the photochemically initiated reaction, the starting material took several hours to disappear, whereas in the borane-initiated reaction it had reacted within 15 min. However, in both cases, no trace of the desired product could be isolated. In one of the attempts on photochemical reduction, the imidazolidine did not react. An attempt to recover the material showed that the imidazolyl carbamate moiety is not stable to aqueous work-up. Due to a lack of material for further studies, the deoxygenation of derivatives of epoxyalcohol **347** was so far not continued.

Further studies on the removal of the C8 hydroxy group were also undertaken with the small amount of hydroxyepoxide **324** (Scheme 58, p. 103).



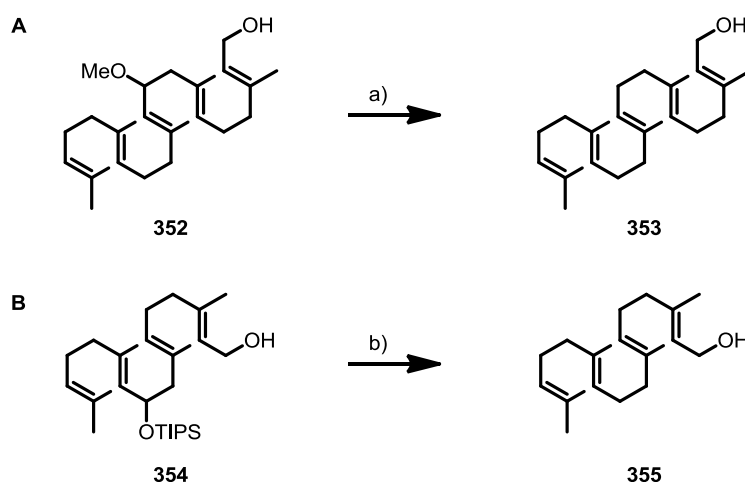
Scheme 68: Attempted deoxygenation from epoxyalcohol **324**. Reagents and conditions: (a) (CS)Im₂ (3 eq.), DMAP (0.5 eq.), CH₂Cl₂, 83%; (b) Bu₃SnH (2.2 eq.), Et₃B (2.2 eq.), PhH, 8-82%; (c) TBAF (270 eq.), AcOH (30 eq.), THF, 2 h, traces.

To this end, **324** was cleanly transformed into imidazolyl *O*-thionocarbamate **16** (Scheme 68) and radical deoxygenation using Bu₃SnH and Et₃B as a radical initiator produced a compound tentatively assigned^{xxii} as **350** on a 3 mg scale.

The reproducibility of this reaction was poor, however; an experiment on the same scale and under identical conditions gave only a small amount of product as well as a number of inseparable decomposition products. This material could not be purified further to permit collection of meaningful analytical data for structure assignment. Thus, we attempted TBAF-mediated removal of the silyl group, which was slow and required a large excess of reagent, but the reaction seemed to be clean by TLC. However, the amount of product obtained was too small to determine its identity. Due to the paucity of material for epoxyalcohol **324**, this route was not yet further pursued.

3.8.3 Allylic Deoxygenation via Metal Reduction

As a possible alternative to the attempted deoxygenation reactions described in the previous section, we turned our attention to alkali metal reductions. This was inspired by a report by Corey in the context of polyprenoid synthesis (Scheme 69).



Scheme 69: Allylic deoxygenation by Corey.^[332,333] Reagents and conditions: (a) (i) *n*-BuLi, THf, -78 °C (ii) Li⁰/EtNH₂, THF, -78 °C, 96%; (b) identical conditions, 90%.

^{xxii} Tentative assignment was based on NMR: Disappearance of the C8 proton in the region 5.44 ppm of the ¹H NMR spectrum was noted. This proton was also absent in the HSQC spectrum. There were however two distinct signals corresponding to epoxides, indicating partial isomerization.

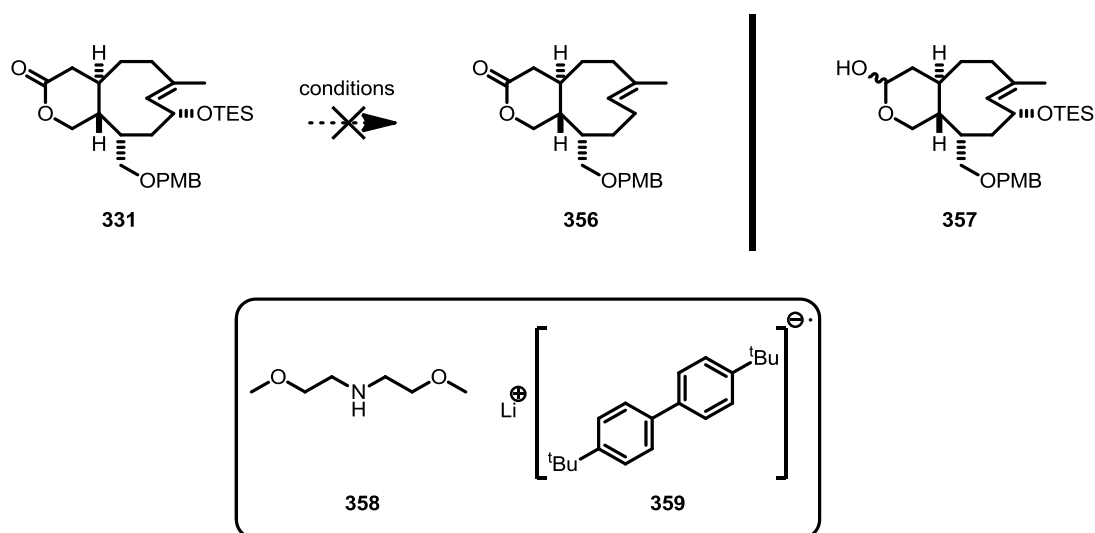
In this work, the secondary allylic methoxy ether **352**, after deprotonation of the primary hydroxy group with *n*-BuLi, was transformed into the corresponding reduced compound **353** (**A**) by titration with $\text{Li}^0/\text{EtNH}_2$ in THF.^[332] Likewise the siloxy group of polyene **354** was reductively removed to furnish product **355**.^[333]

A further survey of the literature revealed that this methodology had been applied previously for the reductive opening of 5,6-dihydro-2*H*-pyrans^[334] and, more importantly, that allylic acetate derivatives^[335,336] of complex terpenes had been shown to be suitable substrates for this type of deoxygenation.

Literature precedence for the stability of 6-membered lactones towards reductive conditions was available.^[337] We attempted to effect allylic deoxygenation using some conditions developed by the group of *Donohoe*, because the requisite EtNH_2 that had been used in the earlier work above was not commercially available any more at the time.^{xxiii} *Donohoe* and coworkers have conducted extensive studies on *Birch*-type reductions using much milder reagent combinations. Notable developments include the introduction of BMEA (**358**)^[338,339] as a milder proton source, use of LiNp ^[339,340] as a soluble one-electron source and LiDBB (**359**)^[341,342] as a further improved version of the latter.

Our first attempt included titration of a THF solution of allylic siloxane **331** with LiDBB (**359**) at $-78\text{ }^\circ\text{C}$ until a strong color persisted (4 eq.), when the reaction mixture was immediately quenched (Scheme **70**). Almost no conversion was observed and the main products were lactol **357** and another well-defined apolar product to which no structure could be assigned so far. In a second experiment, a mixture of siloxane **331** and 6.3 eq. of BMEA (**358**) was titrated with LiDBB (**359**) at $-20\text{ }^\circ\text{C}$ until the blue color disappeared (only very slowly; 20 eq. of **359** were added). By TLC, spots corresponding to **331** and **357** were observed in a ca. 3:1 ratio. The unidentified byproduct observed previously was present as a contaminant in the recovered starting material.

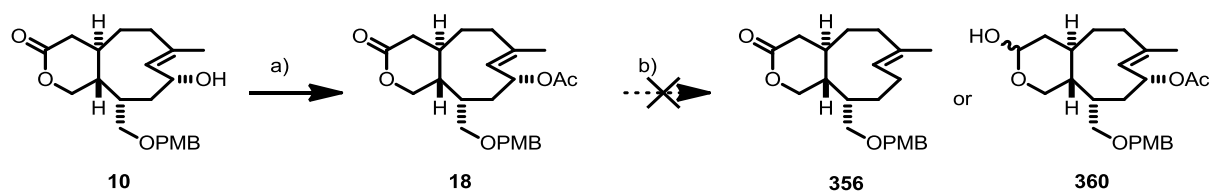
^{xxiii} Written statement from Aldrich: Due to change in EU legislation, the compound would not be available for an unspecified period of time. (22th March 2016)



Scheme 70: Attempted removal of the allylic ether functionality of **331**. Lactol **357** was the only identifiable byproduct. Conditions: *cf.* text.

Finally, a mixture of siloxane **331** and 3.2 eq. of BMEA (**358**) was added dropwise to a solution of 10 eq. LiDBB (**359**) at $-78\text{ }^{\circ}\text{C}$. Upon stirring for 15 min, the color turned orange, but only formation of lactol **357** was observed under these conditions. The structure of **357** was confirmed by independent synthesis from **331** with DIBAL-H.

Acetate **18** (Scheme **71**) was synthesised from allylic alcohol **10** as a substrate for deoxygenation that would feature a better leaving group. An attempt to remove the allylic acetate group using Birch conditions gave only marginal conversion and the only distinct product observed was putative lactol **360**.



Scheme 71: Synthesis of acetate **18** and attempted allylic deoxygenation. Reagents and conditions: (a) Ac_2O (2.4 eq.), Et_3N (3.2 eq.), DMAP (0.8 eq.), $-15\text{ }^{\circ}\text{C}$ to rt, 14 h, 87%; (b) Na^0 , NH_3 (l), $-78\text{ }^{\circ}\text{C}$, 5 min.

4 Conclusions & Outlook

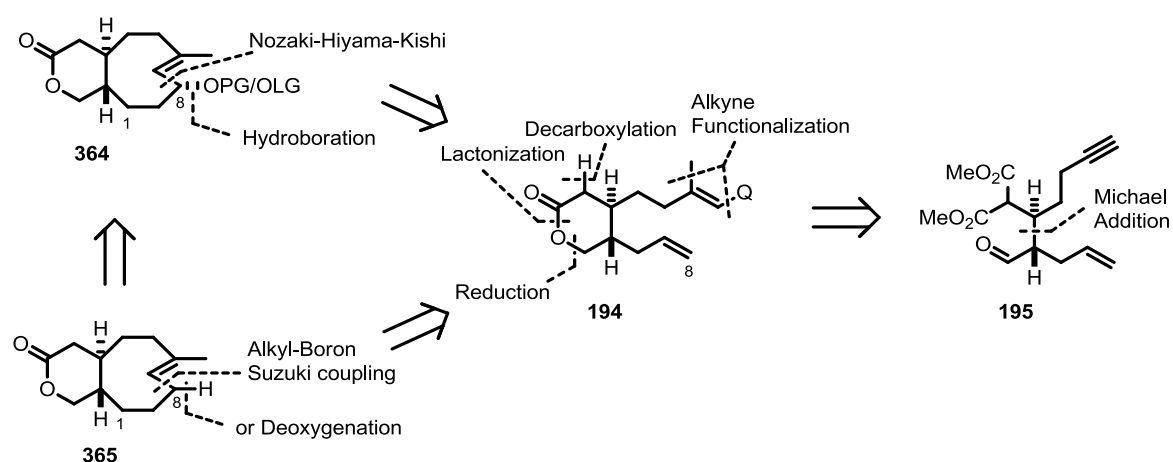
"Ich isä de mii Fänz drheimä widär"

Xavier Koller, Der schwarze Tanner, 1985

In the first part of this chapter, the total synthesis of isoxeniolide A (**1**) that has been elaborated in this thesis is summarized and critically discussed and a number of points are made on the failed initial strategies. Strong emphasis is put on possible solutions or alternative strategies for aspects that warrant further improvement. The second part contains a synopsis of the studies towards the total synthesis of acalcixeniolide F (**2**) and directions for future work is given. In the third sub-chapter, the chemistry developed throughout this thesis work is put into perspective with the initially stated goals and with the previously summarized literature on xenicane synthesis. Finally, an overview of target structures that have now come within synthetic reach is given.

4.1 Conclusions and Discussion of Isoxeniolide A Synthesis

In subchapter **3.2** we described our attempts to build up key intermediate **164** via an organocatalyzed *Michael* addition. Because these studies did not bear fruits, a separate conclusion section is included at the end of the subchapter itself (p. 57ff). *Córdova's* methodology^[155] might nevertheless be useful for the synthesis of xenicane analogs lacking the exocyclic methylene group attached to C1 (Scheme **72**). This notion is based on the finding that aliphatic aldehydes such as citronellal efficiently undergo *Michael* addition to alkylidene malonates. In order to illustrate this idea, two simplified core structures **364** and **365** are depicted below, corresponding to isoxeniolide A (**1**) and acalcixeniolide F (**2**), respectively.



Scheme 72: Potential application of the organocatalyzed *Michael* addition for the synthesis of C1-des-methylene xenicanes. PG: Protecting group; LG: Leaving group.

For the studies described in subchapter **3.3**, a conclusion is also given at the end of the respective subchapter (p. 63ff). In our opinion, these investigations have no immediate relevance for further work on xenicane synthesis.

In subchapter **3.4**, RCM for the formation of 6-membered lactone intermediates of type **222** (Fig. **24**) was investigated. This approach was eventually abandoned because the precursor could not be produced as a single enantiomer. Nevertheless, TBDPS and TIPS were identified as the optimal protecting group and Piers-Grubbs 2nd generation catalyst was found to be the best catalyst for the desired transformation. Both these findings were successfully implemented in the route that ultimately led to the total synthesis of isoxeniolide A (**1**).

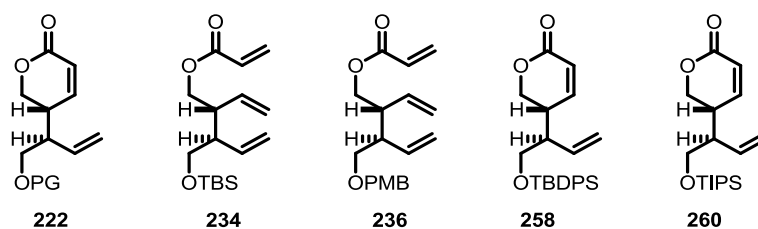
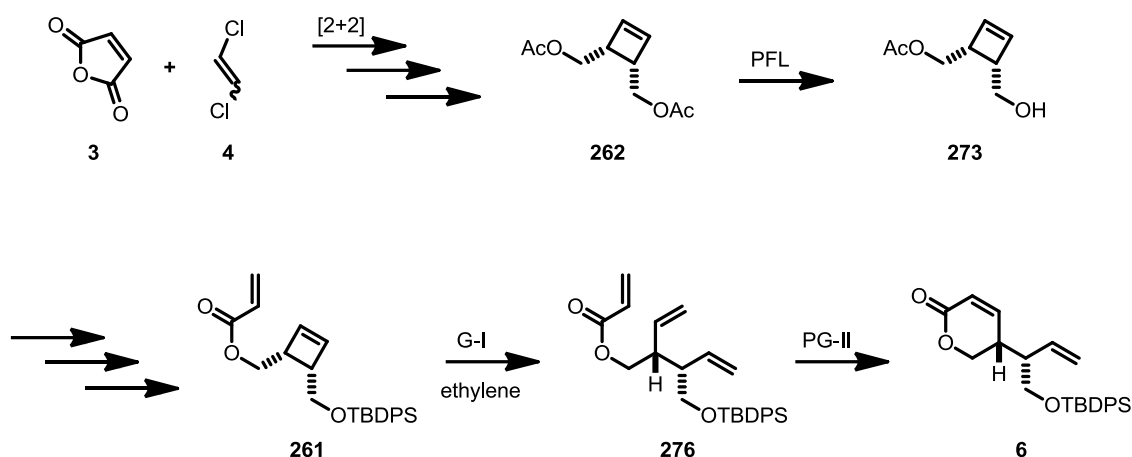


Fig. 24: Substrates **234** and **236** were unsuitable for the planned RCM. Lactones **258** and **260** could be accessed in synthetically useful yields/conversions.

Chapter **3.5** describes a changed synthetic plan, wherein the initial target lactone **258**, was replaced by the corresponding epimer **6**. The synthetic route made use of a [2+2]-photocycloaddition between 1,2-dichloroethene and maleic anhydride. Subsequent functional group manipulations and enantioselective enzymatic hydrolysis of *meso*-diester **262** gave the highly enantiomerically enriched mono-acetate **273**, which could then be elaborated into **6** (Scheme **73**). Even though the literature procedures for the synthesis of *meso*-cyclobutene bisacetate **262** were not fully reproducible and involved cumbersome purifications, the compound could be prepared on a decagram scale. The *meso*-compound was reliably desymmetrized by a *Pseudomonas fluorescens* lipase-mediated saponification reaction. The *ee* of the enzymatic hydrolysis product was found to be $\geq 90\%$ for all batches produced. Chiral alcohol **273** was easily converted into acrylate **261**. While the tandem ring-opening/ring-closing metathesis from **261** to **6** could not be implemented on a preparatively useful preparative scale, a two-step approach involving ethenolysis of the cyclobutene ring followed by RCM of triene **276** provided efficient access to lactone **6**.

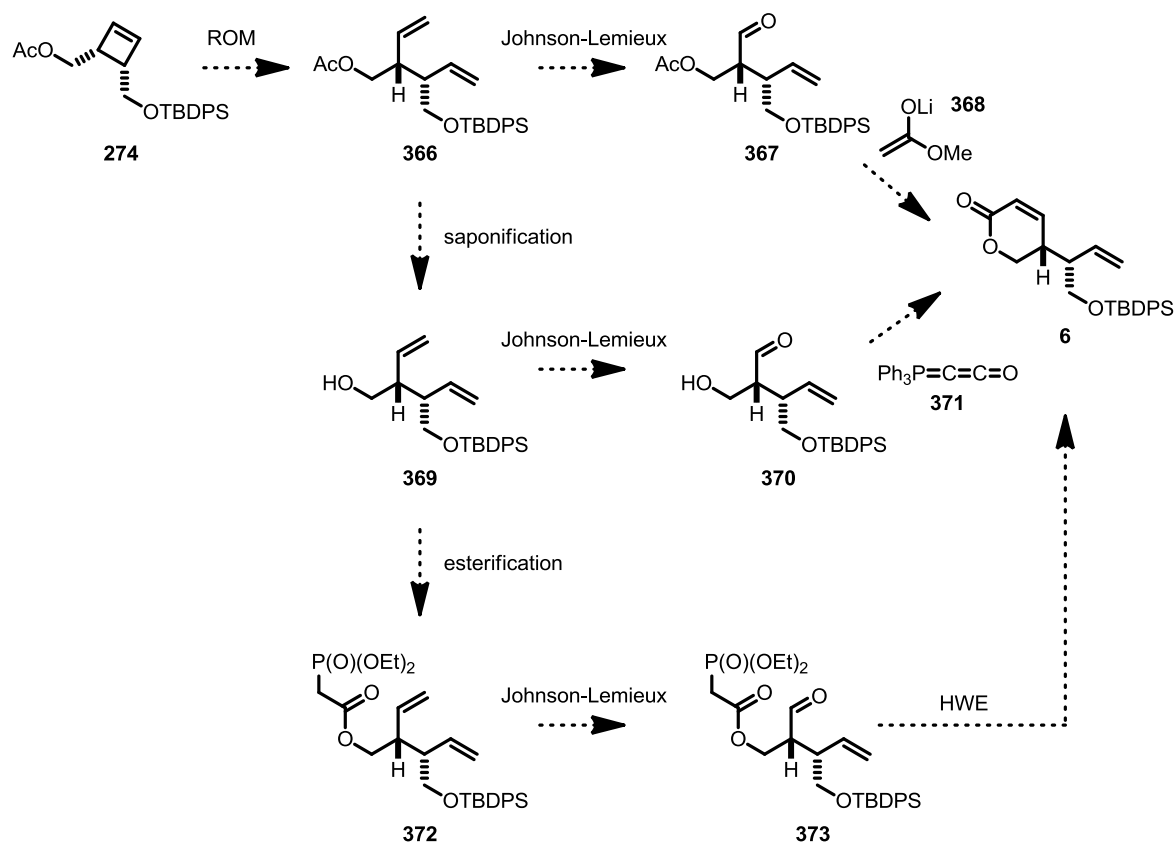


Scheme 73: Key steps in the synthesis of highly enantioenriched lactone **6**.

Competing catalyst decomposition was identified as a reason for the incomplete conversion encountered and the problem was solved by portion-wise addition of catalyst. All intermediate acrylate esters were found to be prone to polymerization and, as a consequence, were always handled in solution.

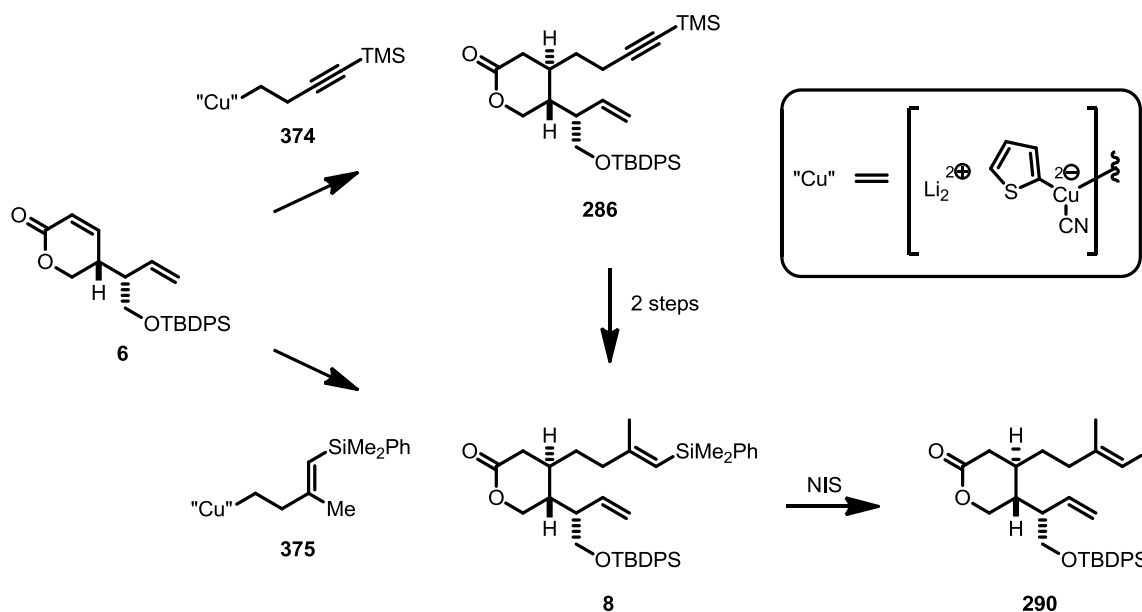
Overall, the three-step sequence from cyclobutene **261** to lactone **6** represented the critical bottleneck in the synthesis of isoxeniolide **A** described in this PhD thesis, even though the overall yield of 46% represents a good 77% average yield per step. However, the required catalyst loading of 12% of PG-II for the ring-closing step is unfavourably high; given the fact that less than half of the number of steps for the longest linear sequence to isoxeniolide **A** (**1**) have been covered at the stage of **6**, the RCM needs to be performed with a large mass of catalyst, rendering this step very expensive.

Instead of pursuing the RCM pathway to Intermediate **6** any further, it might well be worth considering distinct tactics to convert chiral cyclobutene **274** into lactone **6** (Scheme **74**). Thus, **274** could first be opened to **366** by ethenolysis. In presence of the large TBDPS group it might then be possible to selectively convert the more accessible double bond in **366** (or related compounds) into a carbonyl functionality as found in **367**, **370** or **373**. These aldehydes should be accessible by using the *Johnson-Lemieux*^[343] or a related protocol.^[344] *Keck* has reported a one-pot two-step protocol for the synthesis of **6**-type lactones from α -chiral acetates using lithium enolates **368**, which might be applicable to **367**. *Andrus* has used ketene reagent **371** to effect acylation immediately followed by *Wittig* ring-closure, which might also be possible for **370**.^[345] Formation of phosphonoacetate **372**, and intramolecular *Horner-Wadsworth-Emmons* cyclization^[346] of aldehyde **373** would constitute a third option.



Scheme 74: Possible alternative strategies for the construction of lactone **6**.

The vinyl iodide appendage in **290** was first produced from the corresponding ketone using a *Takai* olefination reaction, providing an almost equal mixture of *E* and *Z* isomers. In a second approach, with *E*-vinyl silane **8** as an intermediate (Scheme **75**), this moiety was installed by conjugate addition of organocuprate **374** to **6**, conversion of the ensuing addition product **286** into vinyl silane **8** by deprotection/carbosilylation. Building on these findings, the synthesis could be rendered more convergent in a third approach, which entailed *Michael* addition of organocuprate **375**, the latter featuring the preformed olefin geometry. The three-step synthesis from **6** to **8** gave an overall yield of 44%, while the one-step attachment of building block **375** to **286** delivered **8** in 63-79%. Vinyl silane **8** could reliably be transformed into the corresponding iodide **290**. To the best of our knowledge, **375** represents the first example of a bifunctional alkyl cuprate/vinyl silane linchpin fragment.



Scheme 75: First and second generation synthesis of isomerically pure **290** from **6**.

Chapter **3.6** describes the search for a substrate that would undergo the projected hydroboration/oxidation reaction, which revealed a number of valuable insights. First of all, TBDPS-ether **282** and TBS-ether **306** (Fig. **25**) both were found to be completely resistant to hydroboration. The latter was surprising, since in a simplified model system the corresponding TBS-ether (but not the TBDPS-ether) could be hydroborated successfully. While the PMB-protected methyl pyranoside **310** allowed for successful hydroboration with 9-BBN, this compound was not further pursued as a possible intermediate, due to the issues encountered by *Leumann* and coworkers with the cleavage of a related methyl acetal as part of their work on coraxeniolide A.^[80] Compounds **315**, **317** and **313** underwent hydroboration successfully and were all investigated further. However, the two silyl pyranosides and related compounds showed relatively poor stability. For lactone **313**, reduction of the lactone carbonyl group was faster than hydroboration of the double bond. With an excess of borane, reduction and hydroboration could be effected simultaneously.

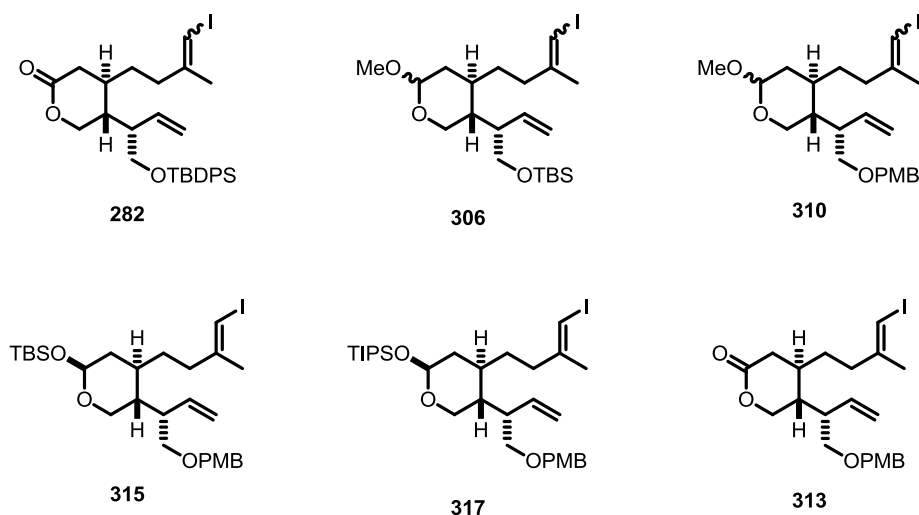
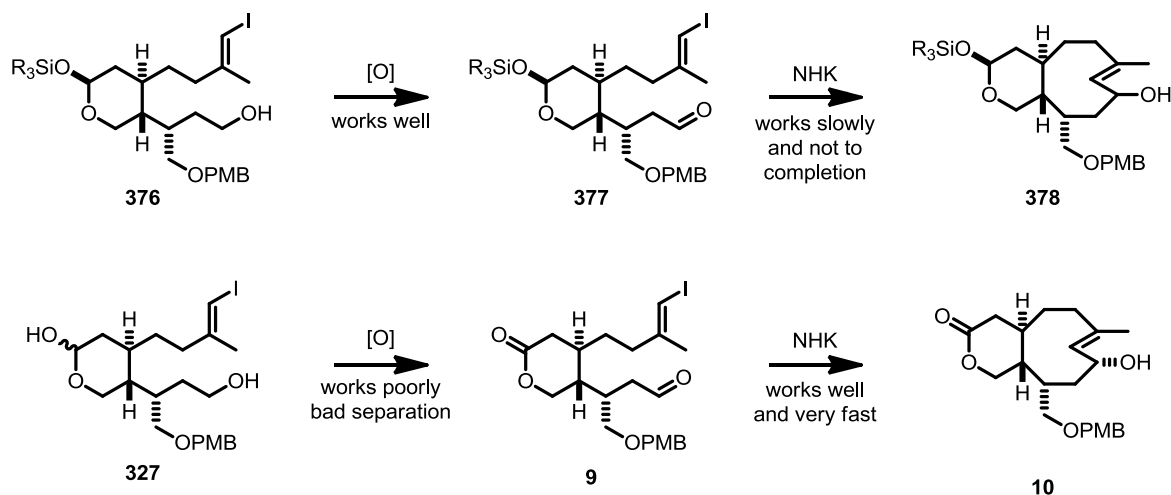


Fig. 25: Substrates tested for their ability to undergo hydroboration.

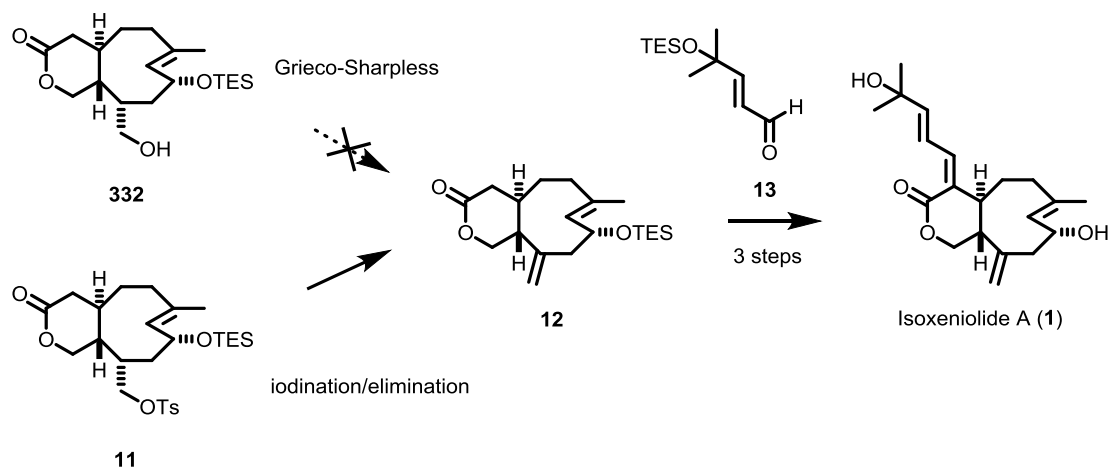
Opposing behavior was observed for silylated pyranosides **376** and the corresponding lactol **327** (Scheme 76) in the oxidation/cyclization sequence leading from the monocyclic hydroboration product to the 11-oxa-bicyclo[7.4.0]tridecene system: Oxidation of **376** was fast and gave aldehydes **377** in good isolated yields. However, ring-closure of the latter required forcing conditions, did not go to completion and the products **378** are so strained that they are prone to spontaneous partial epoxidation by atmospheric oxygen.



Scheme 76: Effect of pyrane-ring on oxidation, stability and ring-closure.

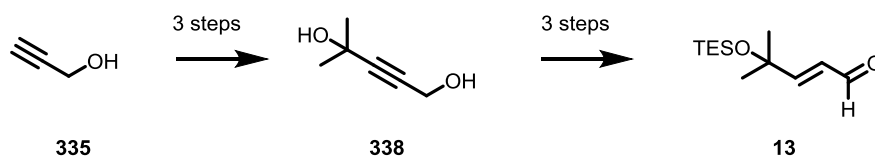
On the other hand, for lactol **327**, only TPAP produced fast and useful double oxidation to aldehyde **9**. This compound was found to decompose rapidly during chromatography on silica. Although not entirely pure, however, **9** would undergo quick ring-closure to give cyclononenol **10**, whose configuration was ascertained by X-ray analysis.

The work described in chapter 3.7 demonstrated that failure to install the exocyclic alkylidene group of the xenicane core via the *Grieco-Sharpless* protocol (Scheme 77) could be overcome using a very sensitive one-pot *Finkelstein*/elimination sequence. Addition of the lithium enolate of TES-protected xenicane core **12** to aldehyde **13** was stereoselective, producing one single product. Selective *syn*-elimination of the aldol product installed the side chain of isoxeniolide A. The formation of this conjugated double bond proceeded very fast and cleanly delivered one single product. When compared to the result observed for the corresponding aldol step in the synthesis of blumiolide C (50%)^[87], the yield of 29% (50% brsm) for the aldol reaction of **12** was unfavourably low. A possible remedy might be found in transmetallation of the lithium enolate with ZnCl₂, which was reported by *Corey* to effect very efficient aldol additions of γ -lactones to unsaturated aldehydes.^[322] In addition, *Ito et al.* have successfully used Bu₂BOTf and DIPEA for soft enolization and with these boron enolates, high yielding aldol additions to acrolein were performed.^[347,348]



Scheme 77: Completion of the isoxeniolide A synthesis.

Aldehyde **13** (Scheme 78), the requisite precursor for the side chain, was easily synthesized in 6 steps, in 35% overall yield. By using a one-step approach from **335** to **338**,^[315] the number of manipulations could in principle be reduced by 2 steps.



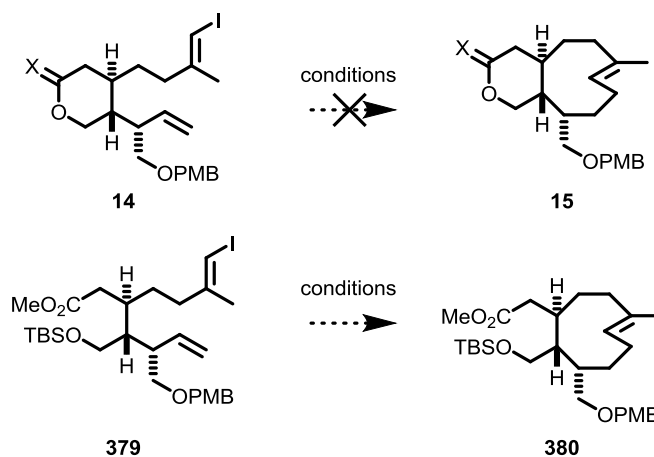
Scheme 78: Synthesis of aldehyde **13**.

The natural product was synthesized in 35 steps in total, whereof 24 steps were part of the longest linear sequence; 5 steps were needed for the synthesis of the vinylsilane fragment and additional 6 steps for the side chain aldehyde.

4.2 Conclusions and Discussion of Attempted Acalcixeniolide F Synthesis

The total synthesis of acalcixeniolide F could not be completed, since we were unable to forge its cyclononene core-structure. Different methods for ring-closure as well as the deoxygenation of 8-hydroxyxeniolide-type scaffolds were investigated. Some of the substrates inspected still warrant further experimentation before completely discarding them; others have displayed underlying issues that are unlikely to be overcome.

The projected *Suzuki* coupling of substrates **14** (Scheme 79) did not produce even traces of products **15**. Part of this failure can likely be attributed to the limited stability of some of the substrates, *e. g.* the silyl protected lactols. In many of the attempted cross coupling reactions, we observed the presence of residual organo-boron contaminants in all the products isolated. This suggests that transmetalation is the critical step for the ring closure.



Scheme 79: Failed Suzuki coupling of **14** for formation of the 9-membered ring **15**. Possible alternative substrate **379**. X = H and OMe; H and OTBS; H and OTIPS; O.

In order to investigate this further, alternative and more stable substrates are worth considering. An example is given with ester **379**, which should be accessible from lactone **313** by a sequence of saponification, TBS protection and ester formation. This substrate should be less easily reduced during hydroboration than the corresponding lactone, and it possesses additional degrees of freedom, which might facilitate access of the Pd-catalyst to the

organoborane species. Both these features might permit a more meaningful investigation of the cross coupling reaction. *Buchwald's* monodentate biaryl ligands SPhos or XPhos have proved to be valuable tools for the cross-couplings of sterically highly demanding substrates^[349] and therefore may represent another opportunity to overcome the issues observed with our substrates.

Attempt to effect deoxygenation of an isoxeniolide type scaffold so far proved to be fruitless. Imidazolyl thionocarbamate **16** (Fig. 26) could be deoxygenated, but the process was only poorly reproducible. In view of the limited stability of the silylated lactols, the uncertainty of the outcome of the deoxygenation reaction, and of the long step count, this route is not of real interest for the synthesis of acalcixeniolide F. Thionocarbamate **17** decomposed under all conditions investigated for deoxygenation. Thiono carbonate **348** seemed to have better stability properties, but due to a lack of material, this compound could not be investigated in any detail. Under milder conditions than those employed in a single experiment, this compound might undergo the desired transformation and should therefore be revisited.

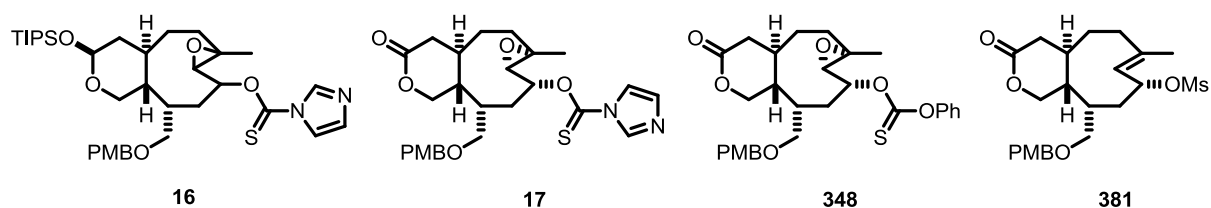


Fig. 26: Previously investigated **16** and **17** and proposed substrates **348** and **381** for further deoxygenation studies.

Other than the classical *Barton-McCombie* method, we found a report by the group of *Kim* wherein $(\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$ is used as a mild initiator for radical deoxygenations of thionocarbonates and other radical precursors.^[350] This might work more reliably than the Et_3B used so far.

The results of our studies aiming at the removal of allylic TES or acetate groups in the 9-membered ring provided only the product of lactone reduction, even in the presence of a large excess of reducing agent. This strategy should be reinvestigated using substrates with a better allylic leaving group, such as a mesylate **381**, the corresponding tosylate or a carbamate. Should this change of substrate bring about the desired deoxygenation, the resulting lactol product could easily be reoxidized to the desired lactone.

4.3 Conclusions on the Overall Strategy

When comparing the findings of our experimental work with the goals stated at the beginning of this thesis, the results are as follows: Generic key intermediate **164** (Fig. 27) of our retrosynthetic plan was realized with key building **313**, which, in addition, is epimeric at C1. We have developed a scalable synthesis of this compound featuring very good enantioselectivity and complete control of the stereogenic centers at C1, C2 and C3. The vinyl iodide functionality was installed as a single *E*-olefin isomer. The approach used for attachment of the latter is modular and opens opportunities for the introduction of a number of possible modifications in the C4-C7 region: For example, the C6-C7 *Z*-isomer can be accessed, replacement or removal of the C20 methyl group is possible and the length of the C4-C5 linker could be changed to modulate the size of the carbocycle. C8, C9 and C19 of intermediate **313** possess functionalities that might be used for the introduction of additional modification in the synthesis of xenicane analogs, be that in the form of simplified derivatives or even in the form of more complex natural products. **10**, which corresponds to planning stage intermediate **163**, was accessed from **313** in 3 steps. The compound was produced as a single stereoisomer on C8, a result which we speculate to be the consequence of a matching conformational bias of the C1-C3 sterotriad.

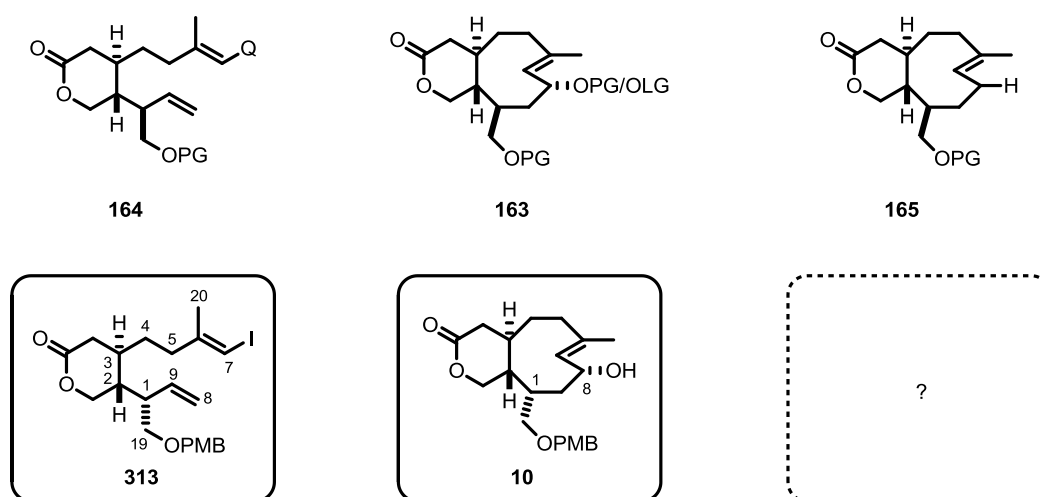


Fig. 27: Comparison of retrosynthetic key intermediates (top) with the corresponding completed synthetic work (bottom).

One of the main findings of this project involves the strategic late-stage introduction of the C19 methylene group via elimination from the primary hydroxy group. After extensive experimentation, an efficient method for this transformation was found, which completed the

isoxeniolide A core structure, and after some elaboration, enable access to the natural product itself. However, both during the RCM-step in the synthesis of intermediate **313** and also in the hydroboration reaction leading up to **10**, the presence of the hydroxymethyl group caused major complications and necessitated careful adjustment of the protecting group strategy. Thus, while this feature adds a lot of value to the synthetic scheme by opening possibilities for derivatisation, it also was the underlying cause of major roadblocks and dead ends encountered during this synthetic journey.

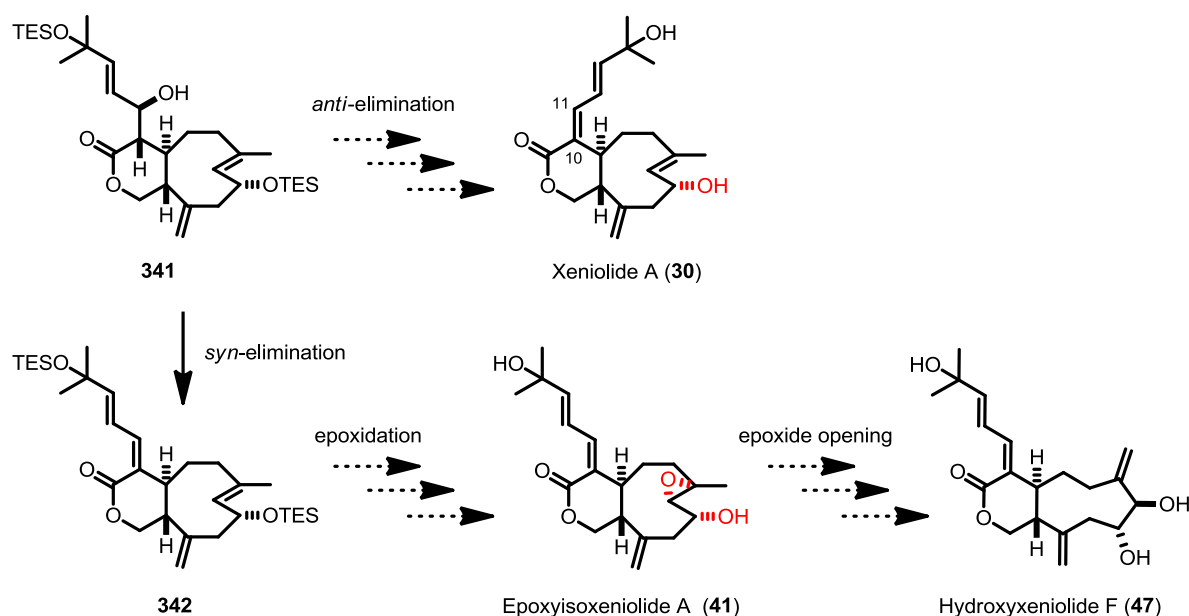
We were so far unable to produce an intermediate corresponding to generalized structure **165**, neither by *Suzuki* cyclization nor by deoxygenation. However, in view of the experimental evidence gathered so far, we do not rule out that a transformation of structure **164** or **163** into an acalcixeniolide core **165** should be feasible - given some further perseverance.

As a final note, we would like to highlight two additional features of the synthetic route described here: (1) The enzymatic desymmetrization methodology that was used allows access to the enantiomeric series of compounds. (2) The overall strategy makes use of a temporary stereogenic center and functional handle, the C19 hydroxymethyl moiety. This functionality, in combination with the aforementioned point might render our approach an interesting chemical starting point for the synthesis of enantiomeric xenicanes from *Phaeophyceae* (sub-section 1.2.3.4, p. 21ff).

4.4 Future Potential of this Project

The chemistry described in this thesis should permit access to a number of 8-hydroxylated xeniolide natural products (Scheme **80**). The prototypical xeniolide A (**30**) and epoxyisoxeniolide A (**41**) are immediate choices, since for both these compounds, the stereochemistry at C8 has not been assigned; for **41** this is additionally true for the epoxide functionality. Xeniolide A (**30**) only differs from isoxeniolide A (**1**) in the configuration of the C10-C11 double bond. This functionality might be installed via transformation of the C11-hydroxy group of **341** into a suitable leaving group *e. g.* a tosylate, followed by base-mediated *anti*-elimination.^[322] The case is more complex for epoxide **41**. It has been shown that isoxeniolide (**1**) cannot be directly epoxidized by *m*-CPBA to produce **41**, but instead decomposes.^[83] It is unclear whether this finding is due to the choice of reagent, due to interference of the C1-19 double bond, or if this is somehow related to the presence of the

the conjugated diene functionality. Studies on this epoxidation reaction will provide valuable information on the reactivity of individual functional groups in the xeniolide scaffold. It may well be that partial deprotection of **342** and hydroxy-guided epoxidation of the cyclononenol might circumvent decomposition. The spontaneous epoxidation of synthetic **321** and **323** that we have observed is a phenomenon that has previously been reported in the literature.^[132] Selective epoxidation of the xenicane cyclononene might even be possible by simple treatment of the natural product with oxygen in solution. Hydroxyxeniolide F (**47**) is a closely related structure to **41**. The stereochemistry is likely the same and it might be accessible via opening of the epoxide in **41**. This transformation has precedent in the aluminium oxide-catalyzed opening of xeniaphyllane epoxides^[71] and in the BuLi-mediated opening of caryophyllene epoxides.^[90]



Scheme 80: Putative structures and potential synthetic strategies toward 8-hydroxylated xeniolides. Red color indicates speculative stereochemical assignment by us.

Close structural relationship to xeniolide A is also found in the collection of xeniolides depicted below (Fig. **28**), for all of which no biological data are available. Asterolaurins I (**382**),^[351] J (**383**)^[351] and F (**384**)^[48] all bear the same configuration for the side chain double bond. Because MeOH was used for the isolation of **382** and **383**, they may well represent artifacts of isolation and could be derived from **30** or the corresponding epoxide, respectively. Access to **384** could follow the strategy towards xeniolide A, but would necessitate the synthesis of a protected α -hydroxy aldehyde building block. Dihydroxeniolide A (**385**)^[352] features a side

chain double bond that is unusual for not being in conjugation with the lactone carbonyl. Synthetic access to this motif in a stereodefined manner might pose a formidable challenge.

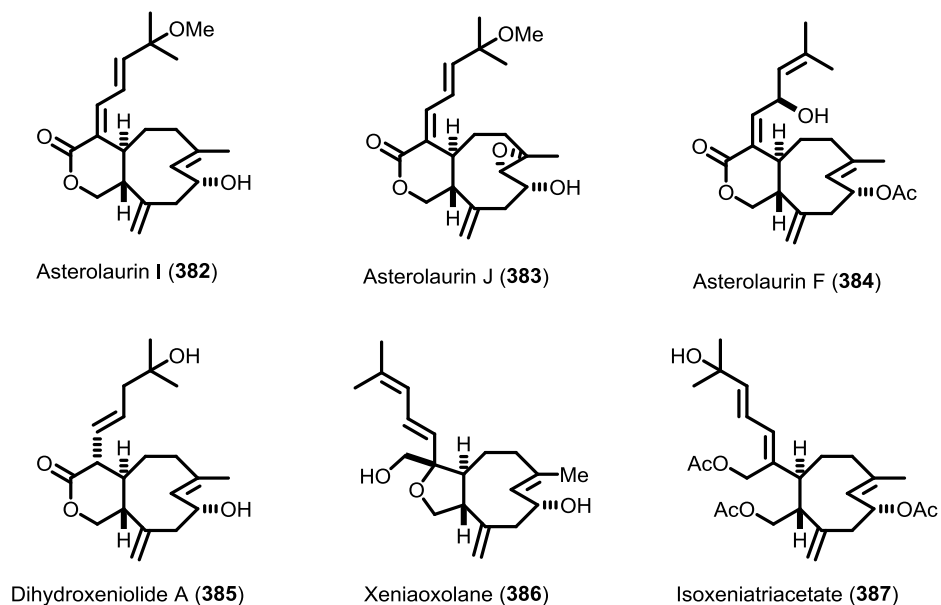


Fig. 28: Additional 8-hydroxy xeniolides and the related compound xeniaoxalone.

Xeniaoxolane (**386**)^[353] was co-isolated with (**30**) and also synthesized from the latter by means of exhaustive reduction with LiAlH_4 and acid-mediated cyclization. Finally, the monocyclic natural product isoxeniatriacetate (**387**)^[352] could be accessed via reduction and acetylation from isoxeniolide A (**1**).

5 Experimental Section

„Und ds'Biär vermischt sich mit äm Bluät.“

Mani Matter, Si hei dr Wilhalm Täll ufgfüert

5.1 General Methods

All non-aqueous reactions were performed under an argon atmosphere using flame-dried glassware and standard syringe/septa techniques. CH_2Cl_2 , THF and Et_2O used for reactions were distilled under argon prior to use (CH_2Cl_2 from CaH_2 , THF and Et_2O from Na/benzophenone). All other absolute solvents were purchased as anhydrous grade from Fluka or Acros (puriss.; dried over molecular sieves; $\text{H}_2\text{O} < 0.005\%$) and used without further purification unless otherwise stated. Solvents for extractions, flash column chromatography (FC) and thin layer chromatography (TLC) were purchased as commercial grade; hexanes, Et_2O and EtOAc were distilled prior to use. All other commercially available reagents were used without further purification unless otherwise stated. Reactions were magnetically stirred and monitored by TLC performed on Merck TLC aluminum sheets (silica gel 60 F254). Spots were visualized with UV light ($\lambda = 254 \text{ nm}$) or through staining with $\text{KMnO}_4/\text{K}_2\text{CO}_3$ and in rare cases $\text{Ce}_2(\text{SO}_4)_3$ /phosphomolybdic acid/ H_2SO_4 (CPS) or vanillin/ H_2SO_4 /EtOH. Chromatographic purification of products (FC) according to the method of Still^[354] was performed using Fluka silicagel 60 or Silicycle Silia Flash® P60 for preparative column chromatography (particle size 40-63 μm) unless otherwise stated. For automated titrations a setup from Metrohm was used: A combination of Titrando 801 and 836 coupled to a Dosimo 800 unit was operated with a touch control system. Photochemical reactions were either carried out in a Rayonet Photoreactor equipped with 16 RPR-3000 (~260-400nm) cold cathodes or mediated by a Hanau TQ 150 high-pressure mercury arc connected to a Hanau Q150 power supply.

Melting points were obtained in open capillary tubes using a Büchi melting point apparatus B-540 and are uncorrected. **^1H - and ^{13}C -NMR spectra** were recorded in CDCl_3 , CD_3OD or C_6D_6 , (CD_3) $_2\text{COD}$ are reported in ppm and are referenced to chloroform (δ 7.26 ppm for ^1H , δ 77.16 ppm for ^{13}C), MeOH (δ 3.31 ppm for ^1H , δ 49.00 ppm for ^{13}C) or benzene (δ 7.16 ppm for ^1H , δ 128.06 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, m = multiplet, br = broad signal, J = coupling constant in Hz

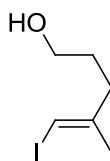
Infrared spectra (IR) were recorded on a Jasco FT/IR-6200 instrument. Resonance frequencies are given as wavenumbers in cm^{-1} .

Optical rotations were measured on a Jasco P-1020 polarimeter or on an Anton-Paar MCP 300 at the sodium D line with a 10 or 100 mm path length cell and are reported as follows: (concentration (g/100 mL), and solvent).

High resolution mass spectra (HRMS) were recorded on one of the following devices by the ETH Zürich MS service (Louis Bertschi, Rolf Häfliger and Oswald Greter under the direction of Dr. Xiangyang Zhang): Waters' AutoSpec Ultima (EI), Bruker's maXis (ESI) or Bruker's solariX (MALDI) AutoSpec Ultima spectrometer (EI), respectively.

5.2 Preparations and Analytical Data

174 (E)-5-iodo-4-methylpent-4-en-1-ol

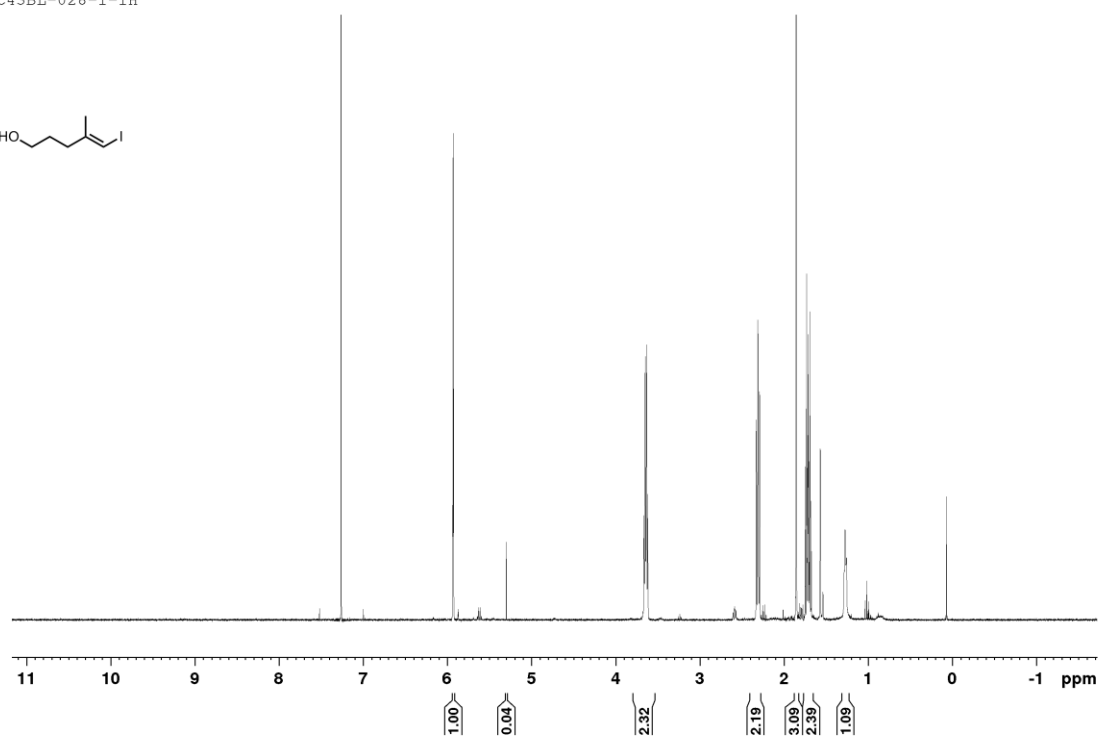
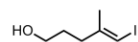


$C_6H_{11}IO$
Exact Mass: 225.9855
MW: 226.0554

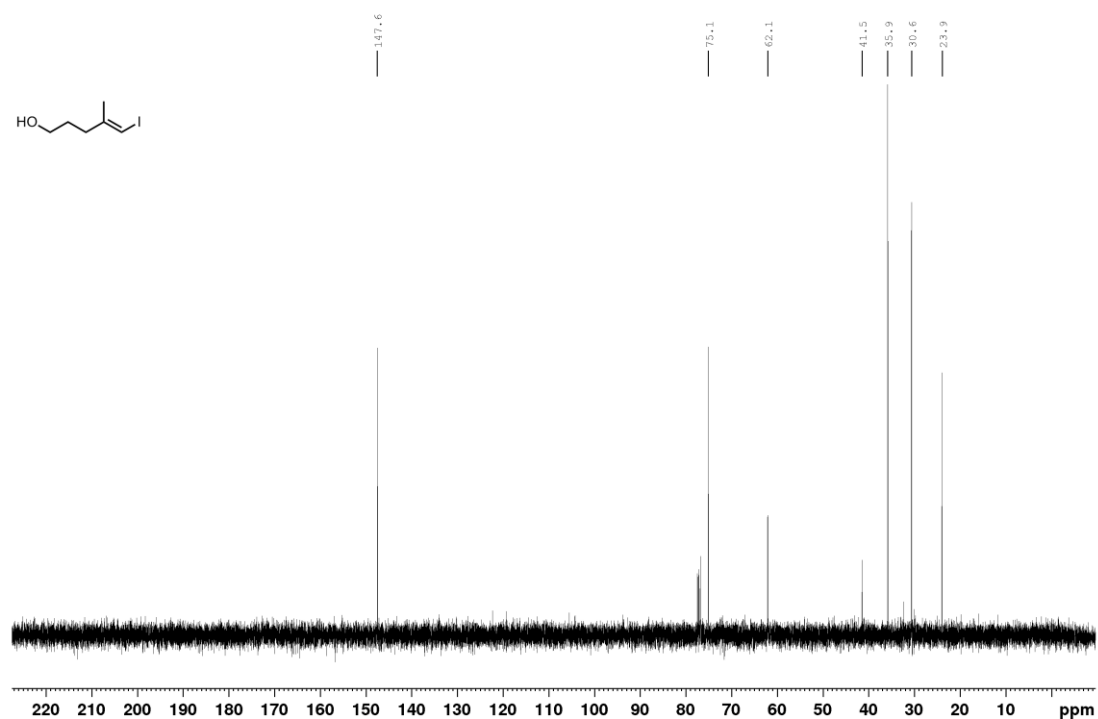
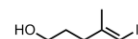
At ambient temperature, a solution of trimethylaluminium (8.9 mL, 2.0 M, 17.8 mmol, 3 eq.) in hexanes was added dropwise over 25 min to a stirred solution of zirconocene dichloride (339 mg, 1.49 mmol, 0.25 eq., weighed in a glovebox) in dry CH_2Cl_2 (15 mL) with an argon balloon. The mixture was stirred for 15 min, then cooled to 0 °C and a solution of pent-4-yn-1-ol (0.55 mL, 5.94 mmol, 1 eq.) in dry CH_2Cl_2 (4 mL) was added dropwise over 15 min. The rubber septum was replaced with a glass stopper and the yellow mixture was stirred at room temperature for 12 days, upon which it turned into a golden solution and conversion to vinyl aluminate was complete. (careful quenching of a sample with 2 M HCl and comparison of the resulting 4-methylpent-4-en-1-ol with the starting alkyne by TLC with EtOAc:hexanes 1:3). The mixture was then cooled to -78 °C and a solution of iodine (1.81 g, 7.13 mmol, 1.2 eq.) in dry THF (7 mL) was added dropwise over 1 h. The mixture was stirred for further 1 h, then allowed to warm to 0 °C in an ice bath and then K_2CO_3 (2.0 mL, aq., sat.) was added cautiously while keeping the internal temperature at more or less 0 °C. Et_2O (20 mL) was added, the slurry was stirred for 30 min, celite and magnesium sulfate were added and the mixture was filtered through a pad of celite and rinsed with (5x30 mL) ether until no more product could be detected by TLC. The solvent was evaporated to give vinyl iodide **174** as a slightly yellow oil (1.32 g, 98%) which was used crude for the next step. The title compound was product was sufficiently pure to be used without purification. **Comment:** Purification over silica gel did decrease the purity due to decomposition. Analytical data was in agreement with the literature.^[158]

1H NMR: ($CDCl_3$, 400 MHz) δ = 5.93 (sextet, J = 1.1 Hz, 1 H), 3.64 (dd, J = 11.7, 6.2 Hz, 2 H), 2.30 (td, J = 7.5, 1.1 Hz, 2 H), 1.85 (d, J = 1.1 Hz, 3 H), 1.75-1.67 (m, 2 H), 1.27 (triplett-like, br, 1 H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 147.6, 75.1, 62.1, 35.9, 30.6, 23.9 **HRMS (EI):** calc. for $[M]^+$: 225.9859, found 225.9849; **HRMS (EI):** calc. for $[M]^+$: 225.9859, found 225.9849; **Rf-value:** 0.16 (EtOAc:hexanes 1:3), starting alkyne: 0.16, quenched des-iodo compound: 0.23.

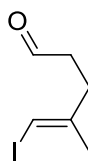
C43BL-028-1-1H



C43BL-028-1



175 (E)-5-iodo-4-methylpent-4-enal



Exact Mass: 223.9698

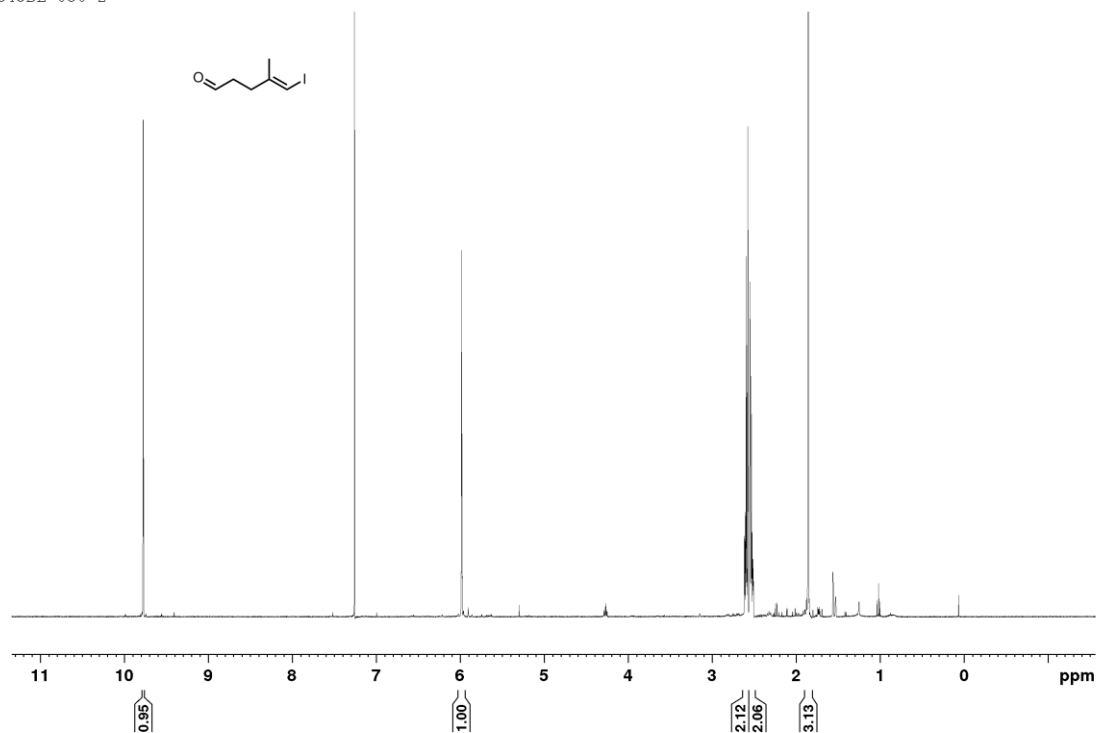
MW: 224.0395

To a solution of oxalyl chloride (0.60 mL, 6.98 mmol, 1.2 eq.) in CH_2Cl_2 (8.7 mL) at -78°C was added dropwise a solution of dimethylsulfoxide (0.91 mL, 12.8 mmol, 2.2 eq.) in CH_2Cl_2 (9.3 mL). After 5 min, a solution of **174** (1.31 g, 5.82 mmol) in CH_2Cl_2 (7.6 mL) was added (and rinsed with 1 mL CH_2Cl_2). The reaction mixture was stirred for 30 min at -78°C and triethylamine (4.04 mL, 29.1 mmol, 5 eq.) was added in 1 portion, upon which the reaction turned into a white jelly. CH_2Cl_2 (20 mL) was added slowly and after 1 h at -78°C , the mixture was put into an ambient temperature H_2O bath. It was diluted with CH_2Cl_2 (50 mL) and the organic layer was successively washed with NH_4Cl (3x7.5 mL, aq., sat.) and brine (6.5 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure, which led to formation of a small amount of precipitate. This was suspended in the mobile phase and purified by FC (EtOAc:hexanes 1:10) gave the title compound as a clear, yellow liquid (868 mg, 66%).^x

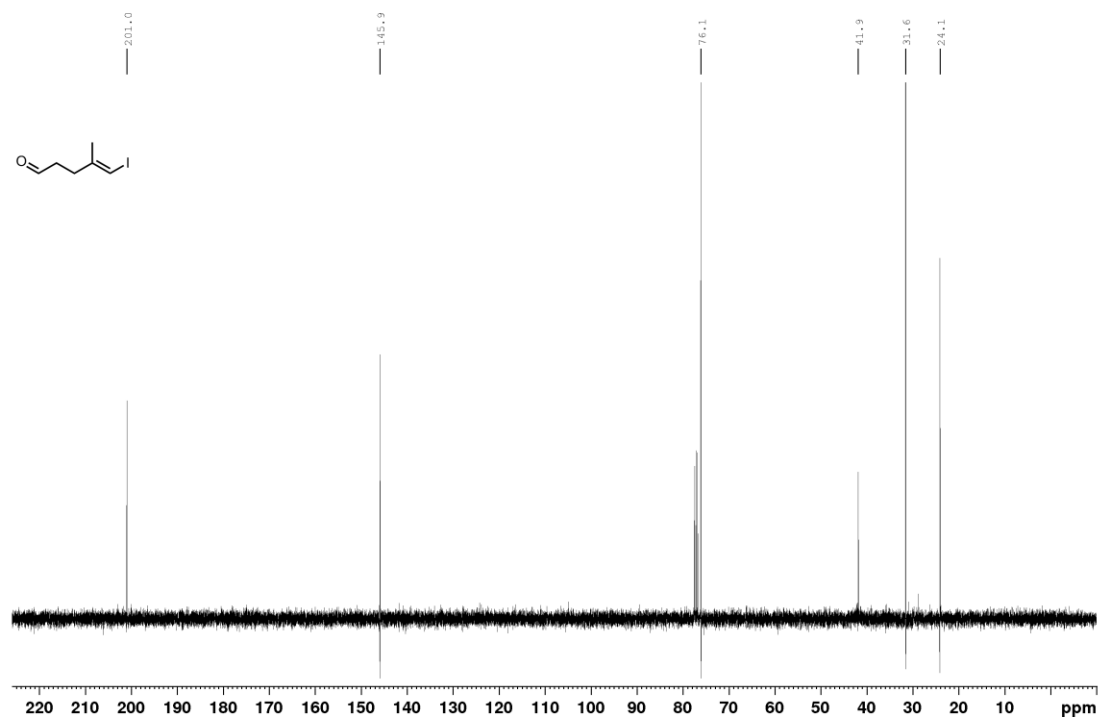
^1H NMR: (CDCl_3 , 400 MHz) δ = 9.78 (t, J = 1.4 Hz, 1H), 5.98 (sextett, J = 1.1 Hz, 1H), 2.63–2.49 (m, 2H), 2.56 (ddt, J = 16.6, 6.0, 1.3 Hz, 2H), 1.85 (d, J = 1.1 Hz, 3H); **^{13}C NMR:** (CDCl_3 , 100 MHz) δ = 201.0, 145.9, 76.1, 41.9, 31.6, 24.1; **HRMS (EI):** calc. for $[\text{M}-\text{I}]^+$: 97.0648, found 97.0652; calc. for $[\text{M}-\text{H}]^+$: 222.9614, found 222.9614; **IR (neat):** 2912, 2823, 2723, 1720, 1440, 1409, 1377, 1355, 1268, 1143, 1066, 899, 859, 768, 683, 667; **Rf-value:** 0.49 (EtOAc:hexanes 1:3).

^x This compound had previously been reported in several instances,^[361–365] but none of them containing any experimental and analytical data.

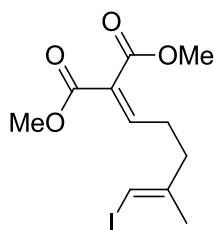
C45BL-030-2



C45BL-030-2



176 (E)-dimethyl 2-(5-iodo-4-methylpent-4-en-1-ylidene)malonate

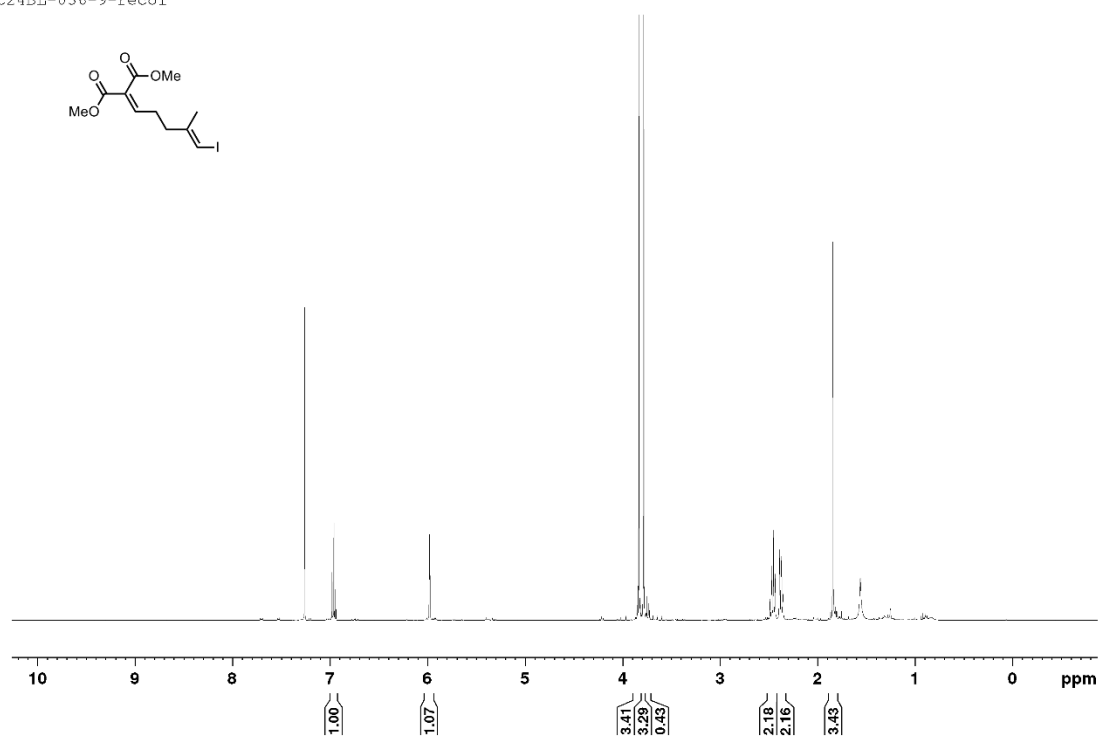
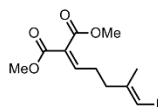


$C_{11}H_{15}IO_4$
Exact Mass: 338.0015
MW: 338.1389

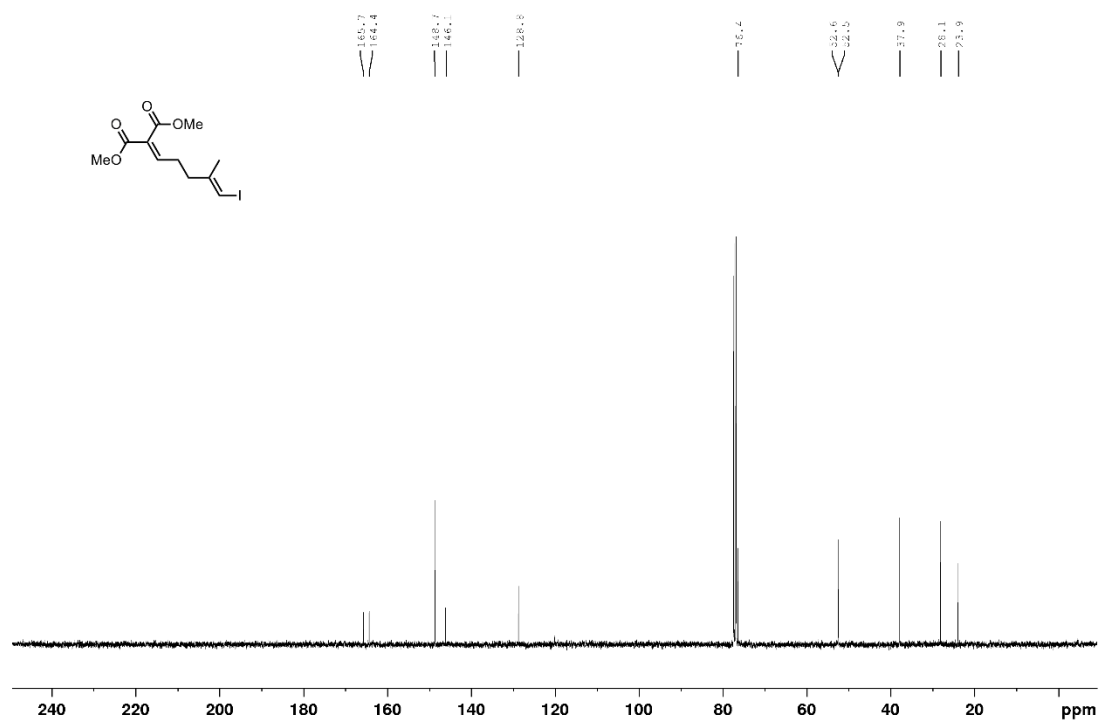
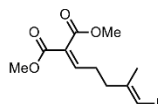
To 1,4-dioxane (3.8 mL) at 5 °C was added a solution of $TiCl_4$ (1.95 mL, 1.95 mmol, 1M in CH_2Cl_2 , 2 eq.), giving a bright yellow solid which melted at 8-9 °C to yield a bright yellow suspension. **175** (231 mg, 1.03 mmol, 1.05 eq.) in 1,4-dioxane (0.7 mL and rinsed with 0.25 mL) and neat malonic acid dimethylester (1.16 mL, .98 mmol, 1 eq.) were added to give a bright yellow solution. A solution of pyridine (0.32 mL, 3.93 mmol, 4 eq.) in 1,4-dioxane (0.7 mL) was added via a syringe pump over 60 min at 2 °C. After 50 % of addition the solution had turned a strong orange color. After 2h the mixture had a temperature of 5 °C and was let to warmed up overnight in the cooling bath. It was stirred for a total of 52 h during which it turned an opaque beige colour. The reaction was quenched with phosphate buffer (1.05 mL, pH 7.2) and H_2O (0.25 mL, the H_2O did not dissolve precipitates), the phases were separated and the aqueous phases was extracted with Et_2O (3x2.3 mL). The combined organic phases were washed with brine (1.05 mL), dried over Na_2SO_4 and the solvent was removed to give a brown liquid. FC (Et_2O : pentane 1:10 + 1% AcOH) gave title compound as a yellow oil. It was contaminated with an inseparable impurity that was used for the subsequent steps (257 mg, 78%).

Comment: A small amount of an analytical sample was obtained by FC (Toluene: hexanes 7:3 + 1% AcOH); **1H NMR:** ($CDCl_3$, 400 MHz) δ = 6.96 (t, J = 7.6 Hz, 1H), 5.98 (q, J = 1.1 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.50-2.42 (m, 2H), 2.40-2.34 (m, 2H), 1.84 (d, J = 1.0 Hz, 3H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 165.7, 164.4, 148.7, 146.1, 128.8, 76.4, 52.6, 52.5, 37.9, 28.1, 23.9; **HRMS (EI):** calc. for $[M]^+$: 338.0010, found 338.0009; calc. for $[M-I]^+$: 211.0965, found 211.0967; calc. for $[M-MeOH-HI]^+$: 179.0703, found 179.0708; **IR (neat):** 2952, 2929, 2852, 2359, 2336, 1723, 1646, 1619, 1435, 1372, 1260, 1226, 1197, 1144, 1095, 1060, 984, 930, 830, 801, 768, 731, 667; **Rf-value:** 0.48 ($EtOAc$:hexanes 1:3).

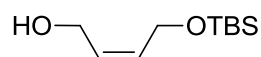
C24BL-036-9-recol



C24BL-036-9-recol/8



179 (Z)-4-((tert-butyldimethylsilyl)oxy)but-2-en-1-ol

Chemical Formula: C₁₀H₂₂O₂Si

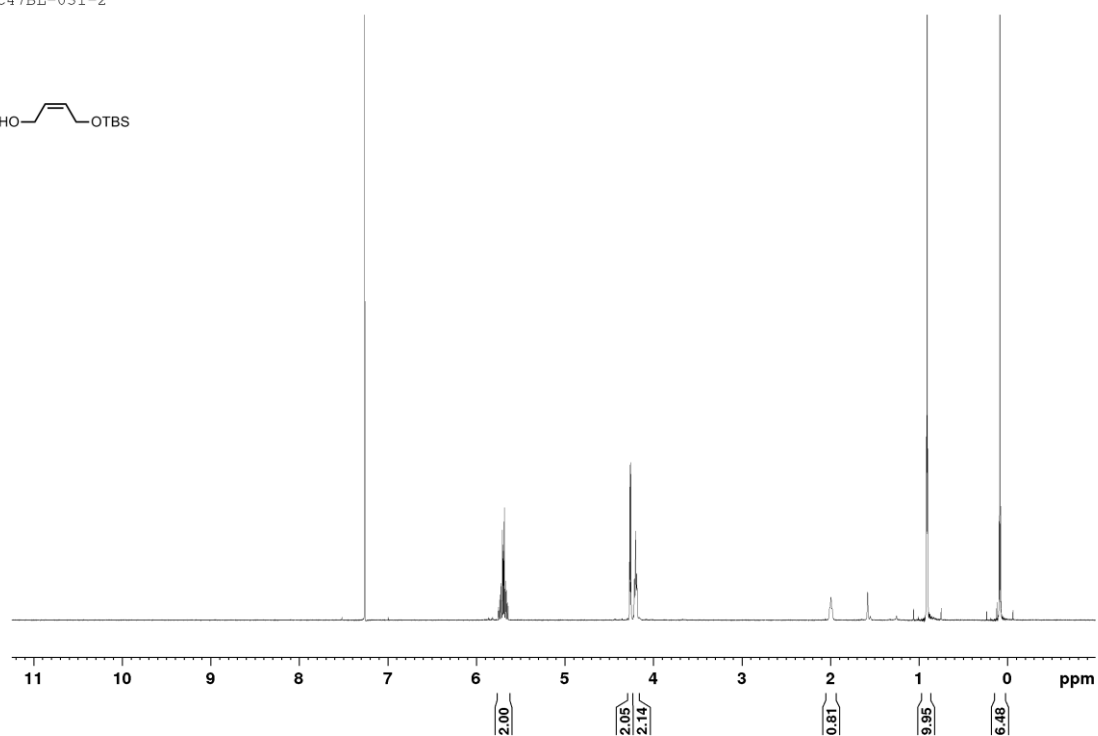
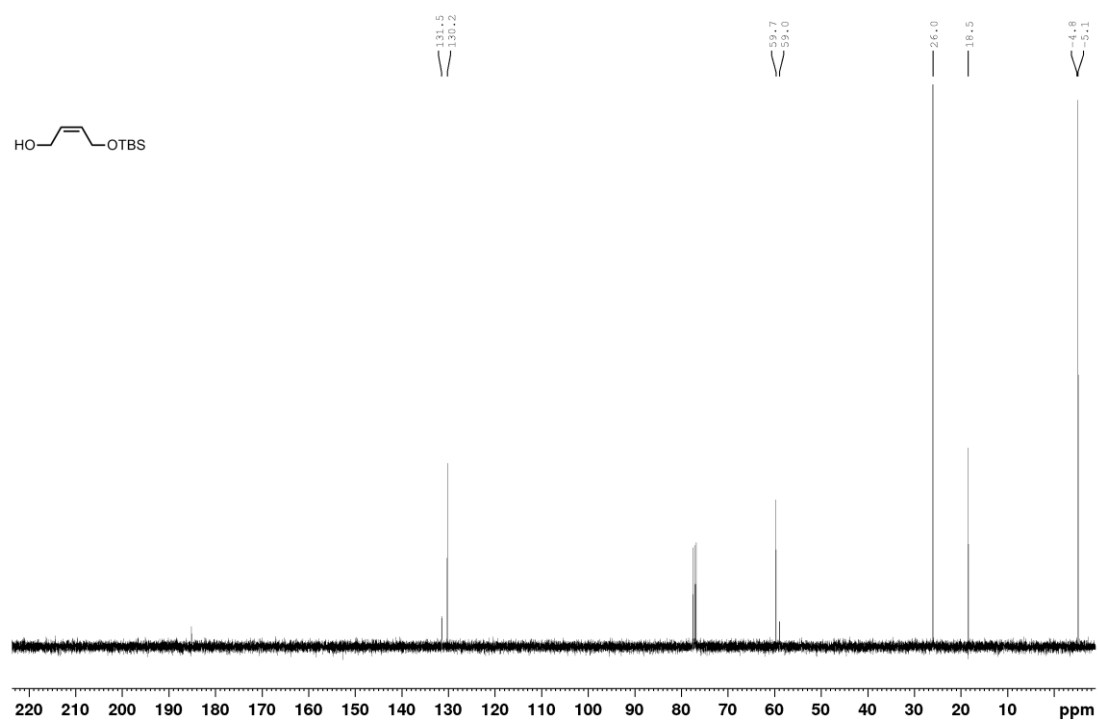
Exact Mass: 202.1389

Molecular Weight: 202.3660

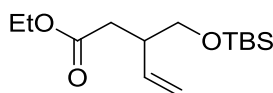
To a solution of (Z)-but-2-ene-1,4-diol (11.00 g, 124.8 mmol, 1 eq.) in dry THF (500 mL) was added *n*-BuLi (82 mL, 1.6 M in hexanes, 131 mmol, 1.05 eq.) in an ambient temperature H₂O bath. A cloudy white suspension formed. The mixture was cooled 0 °C, solid *t*-butyldimethylchlorosilane (18.81 g, 124.8 mmol, 1 eq.) was added in one portion and the cloudy mixture was stirred for 1h, followed by another 1 h at ambient temperature during which it turned into a clear golden solution. The reaction was concentrated by rotary evaporation, before quenching by addition of H₂O (20 mL) and diluting with EtOAc (150 mL). Phases were separated and the aqueous layer was extracted with EtOAc (3x50 mL). The combined organic extracts were dried over MgSO₄, filtered, rinsed with EtOAc (200 mL) and concentrated under reduced pressure. FC (EtOAc:hexanes 1:3 to 1:1) delivered **179** as a slightly yellow oil (22.08 g, 88%). Analytical data was in agreement with the literature.^[166]

¹H NMR: (CDCl₃, 400 MHz) δ = 5.76-5.63 (m, 2H), 4.28-4.26 (m, 1H), 4.26-4.24 (m, 1H), 4.20 (t, *J* = 5.5 Hz, 2H), 1.99 (t, br, *J* = 5.5 Hz, 1H), 0.91 (s, 9H), 0.09 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 131.5, 130.2, 59.7, 59.0, 26.0, 18.5, -4.8, -5.1; **HRMS (ESI-TOF):** calc. for [M+Na]⁺: 225.1281, found 225.1282; **Rf-value:** 0.49 (EtOAc:hexanes 1:1); 0.66 (EtOAc:hexanes 3:1).

C47BL-031-2

pnmr_13C_1024 CDCl₃ /v pkanmr 53

180 (+/-) Ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-enoate

Chemical Formula: C₁₄H₂₈O₃Si

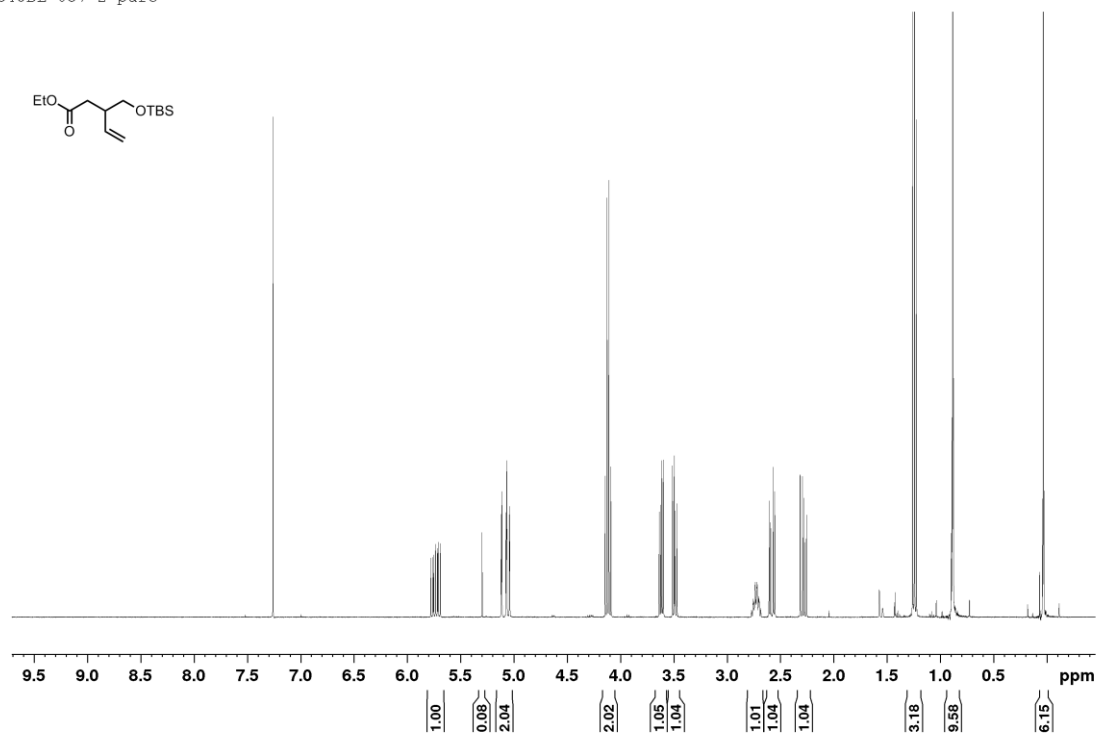
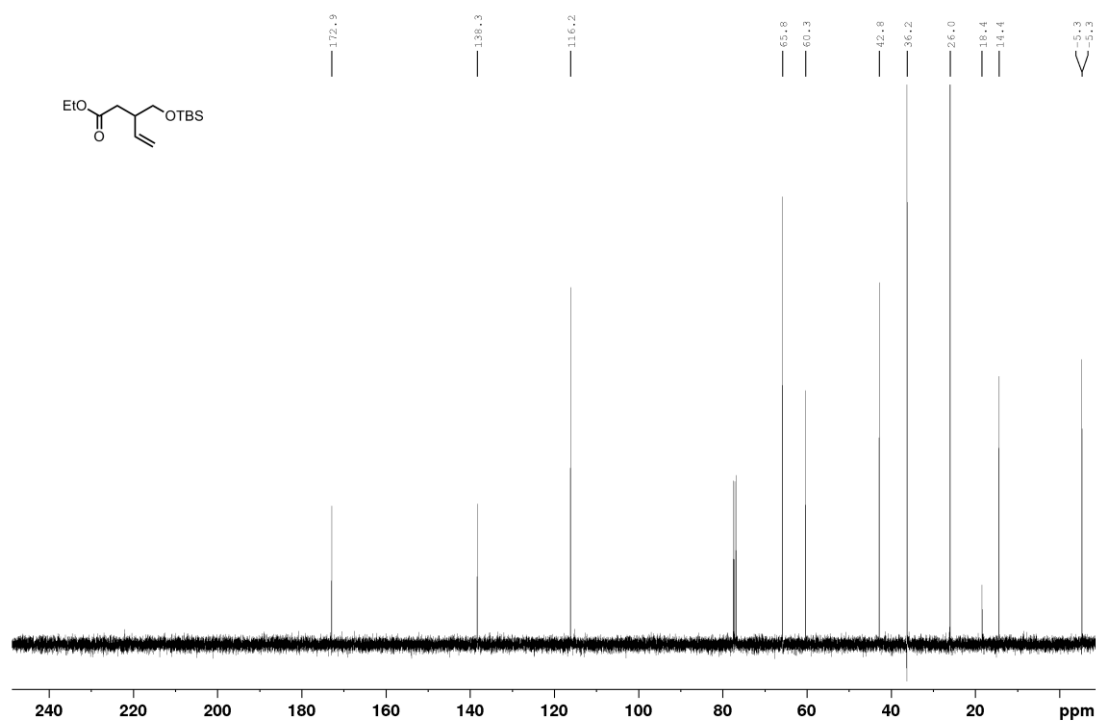
Exact Mass: 272.1808

Molecular Weight: 272.4558

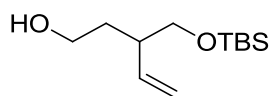
Through a solution of allylic alcohol **179** (5 g, 24.71 mmol, 1 eq.) and propionic acid (0.46 mL, 6.18 mmol, 0.25 eq.) in triethyl orthoacetate (22.6 mL, 123.5 mmol, 5 eq.) was bubbled argon for 15 min, then it was heated to 150°C for 6h with constant stirring while distilling of the resulting ethanol (3.15 mL, 54 mmol, approx. 2 eq.) with a Dean-Stark trap. The excess triethyl orthoacetate was distilled off at reduced pressure (0.27 mbar from r.t. to 55 °C) and the residue was purified by FC (Et₂O:hexanes 1:40) to deliver the title compound as a clear colourless liquid (5.546 g, 82 %). Analytical data was in agreement with the literature.^[166]

¹H NMR: (CDCl₃, 400 MHz) δ = 5.73 (ddd, *J* = 17.4, 10.4, 7.8 Hz, 1H), 5.09 (dt, *J* = 17.4, 1.6 Hz, 1H), 5.05 (ddd, *J* = 10.4, 1.5, 0.8 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.62 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.49 (dd, *J* = 9.9, 6.8 Hz, 1H), 2.78-2.67 (m, *broad, sextett-like*, *J* = 6.8 Hz, 1H), 2.58 (dd, *J* = 15.4, 5.8 Hz, 1H), 2.28 (dd, *J* = 15.3, 8.4 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 172.9, 138.3, 116.2, 65.8, 60.3, 42.8, 36.2, 26.0, 18.4, 14.4, -5.3 (2 signals); **HRMS (EI):** calc. for [M-tBu]⁺: 215.1098, found 215.1093; calc. for [M-OEt]⁺: 227.1462, found 227.1466; calc. for [M-Me]⁺: 257.1567, found 257.1569; **Rf-value:** 0.79 (EtOAc:hexanes 1:1).

C48BL-037-2-pure

pnmr_13C_1024 CDCl₃ /v pkanmr 14

181 (+/-) 3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-en-1-ol

Chemical Formula: C₁₂H₂₆O₂Si

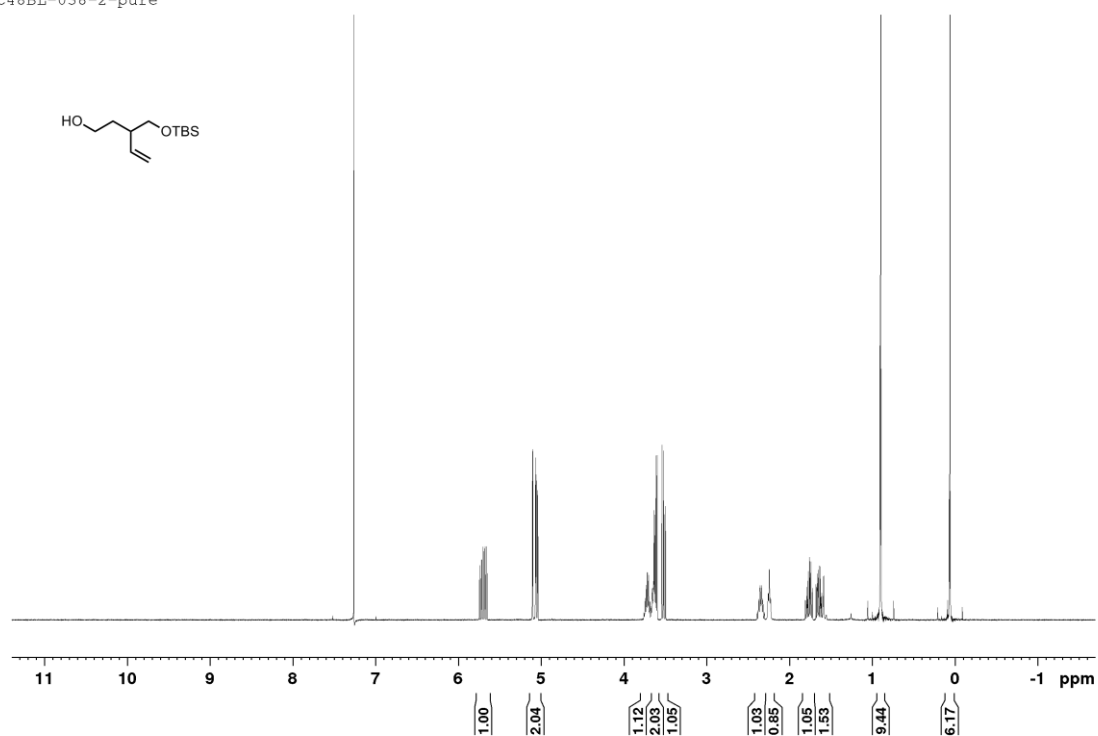
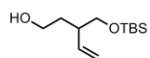
Exact Mass: 230.1702

Molecular Weight: 230.4191

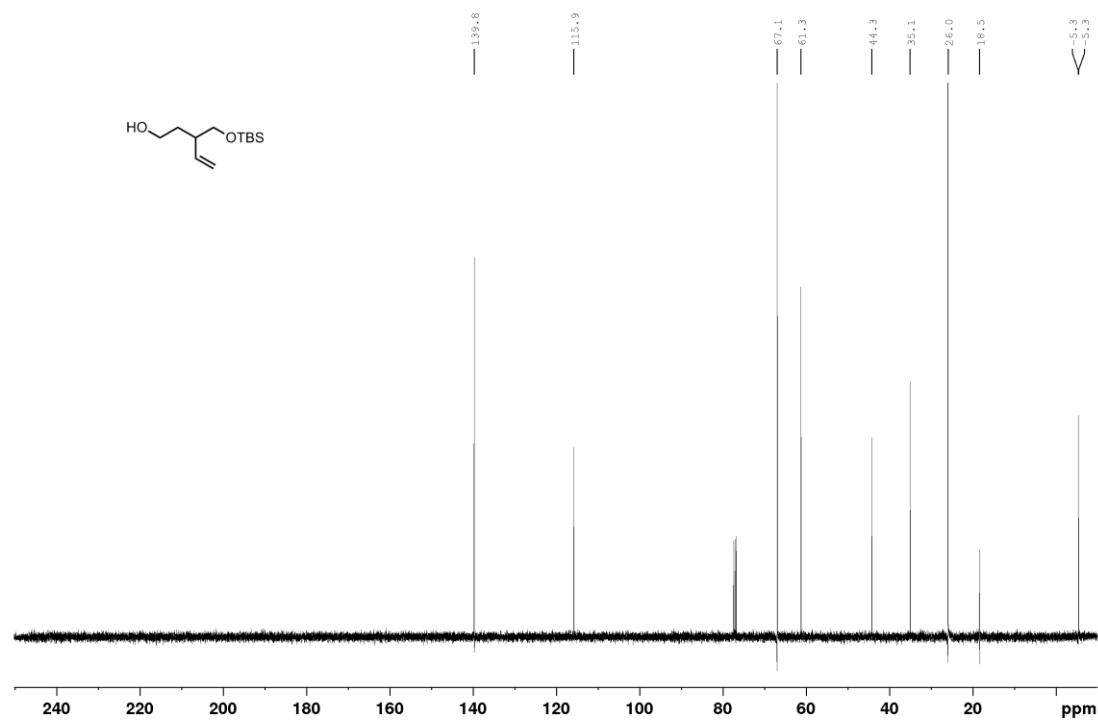
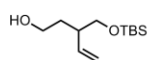
To alcohol 180 (3.71 g, 17.3 mmol, 1eq.) in THF (86 mL) at -78 °C was dropwise added DIBAL-H (31.7 mL, 38.0 mmol, 1.2 M in Toluene, 2.2 eq.), carefully keeping internal temperature below -65 °C. After 30 min at -78 °C, the mixture was put into an ice bath and stirred for 2h. It was quenched by careful addition of MeOH (5.8 mL) at -78 °C, then a saturated Rochelle's salt solution (58 mL) was added at 0 °C. After stirring for 3 h, Et₂O (33 mL) was added, the phases were separated and the organic phase was extracted with Et₂O (4x33 mL). The combined organic phases were washed with NH₄Cl (297 mL, aq., sat.) and brine (29 mL) and dried over MgSO₄. FC (EtOAc:hexanes 1:10 to EtOAc:Hexanes 1:7) gave the title compound as a colorless liquid (3.713 g, 93 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 5.70 (ddd, *J* = 17.3, 10.3, 8.4 Hz, 1H), 5.08 (ddd, *J* = 17.2, 1.8, 1.0 Hz, 1H), 5.05 (ddd, *J* = 10.4, 1.8, 0.6 Hz, 1H), 3.71 (*septett, broad*, *J* = 5.6 Hz, 1H), 3.68-3.59 (m, 1H), 3.62 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.52 (dd, *J* = 10.0, 7.2 Hz, 1H), 2.40-2.29 (m, 1H) 2.24 (t, *J* = 5.4 Hz, 1H, OH), 1.76 (ddt, *J* = 7.6, 6.1, 5.8 Hz, 1H), 1.69-1.58 (m, 1H) 0.90 (s, 9H), 0.06 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 139.8, 115.9, 67.1, 61.3, 44.3, 35.1, 26.0, 18.3, -5.3 (2 signals); **HRMS (ESI-TOF):** calc. for [M+H]⁺: 231.1775, found 231.1779; **IR (neat):** 3341 (br), 2954, 2929, 2886, 2857, 1642, 1471, 1421, 1388, 1361, 1253, 1101, 1053, 1003, 973, 939, 914, 833, 813, 774, 666; **Rf-value:** 0.57 (EtOAc:hexanes 1:1); 0.49 (EtOAc:hexanes 1:3).

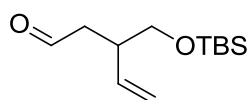
C48BL-038-2-pure



C48BL-038-2-pure



182 (+/-) 3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-enal

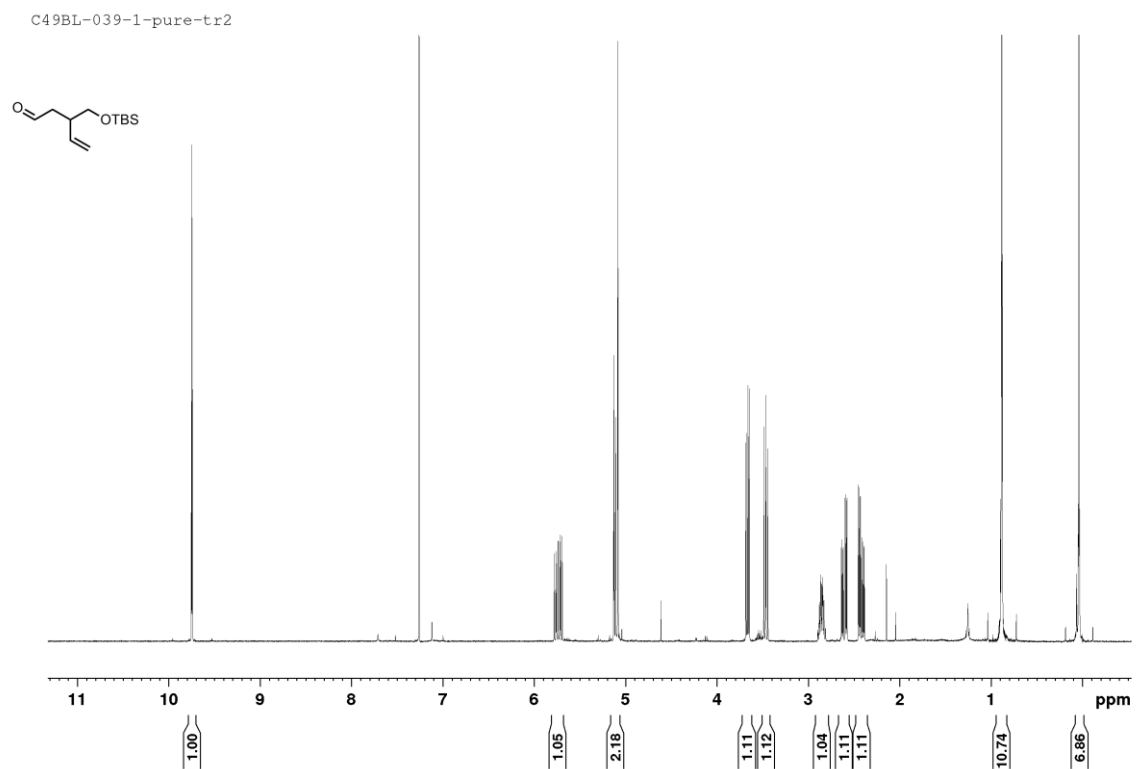
Chemical Formula: C₁₂H₂₄O₂Si

Exact Mass: 228.1546

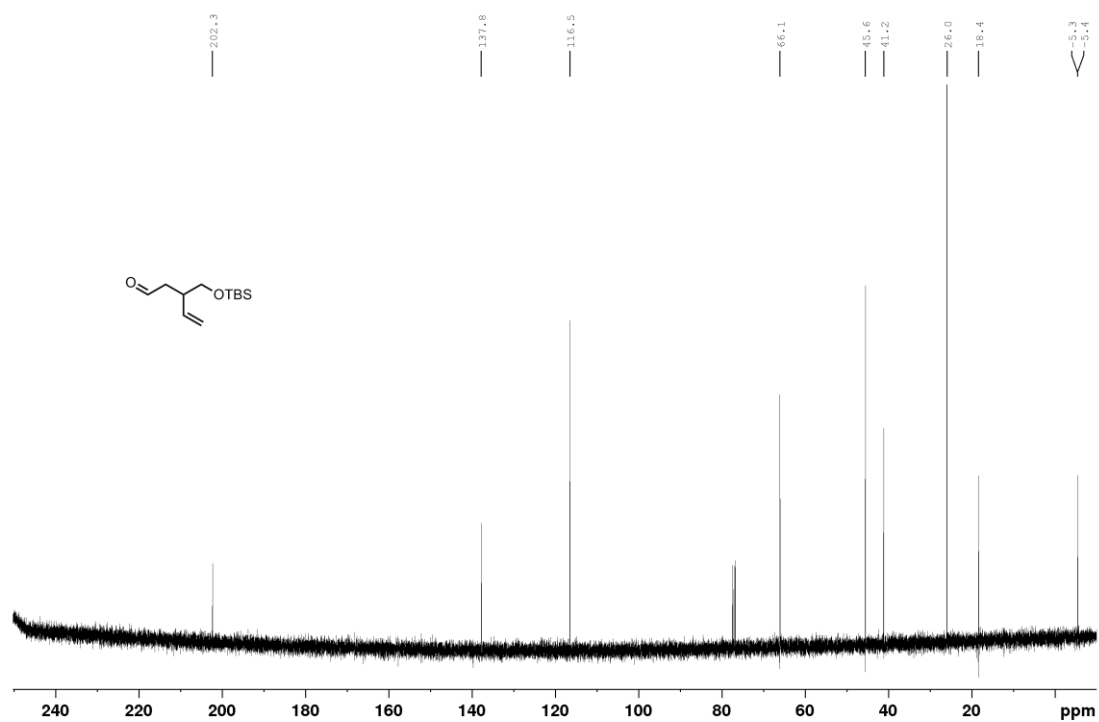
Molecular Weight: 228.4033

To a solution of oxalyl chloride (0.12 mL, 1.37 mmol, 1.2 eq.) in CH₂Cl₂ (1.71 mL) at -78 °C was added dropwise a solution of dimethylsulfoxide (0.18 mL, 2.51 mmol, 2.2 eq.) in CH₂Cl₂ (1.83 mL). After 10 min, a solution of **181** (263 mg, 1.14 mmol, 1 eq.) in CH₂Cl₂ (1.48 mL) was added and rinsed with CH₂Cl₂ (2x1.5 mL). The reaction mixture was then stirred for 25 min at -78 °C and Et₃N (0.79 mL, 5.7 mmol, 5 eq.) was added in one portion. After 30 min at -78 °C, the mixture was put into an ambient temperature H₂O bath, quenched with NH₄Cl (2.1 mL, aq., sat.) and diluted with CH₂Cl₂ (9.6 mL). H₂O (0.45 mL) was added to dissolve the precipitates, the phases were separated and the organic layer was successively washed with NH₄Cl (2.1 mL, aq., sat.) and brine (2.1 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure, which lead to formation of a small amount of precipitate. This was suspended in the mobile phase and purified by FC (EtOAc:hexanes 1:10) to give the title compound as a clear, yellow liquid (239 mg, 92%). Analytical data was in agreement with the literature.^[355]

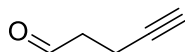
¹H NMR: (CDCl₃, 400 MHz) δ = 9.75 (t, *J* = 2.3 Hz, 1H), 5.74 (ddd, *J* = 17.2, 10.6, 7.6 Hz, 1H), 5.12 (dt, *J* = 7.6, 1.3 Hz, 1H), 5.08 (d, *J* = 1.0 Hz, 1H), 3.66 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.46 (dd, *J* = 9.6, 7.7 Hz, 1H), 2.90-2.80 (m, 1H), 2.61 (ddd, *J* = 16.4, 6.3, 2.4 Hz, 1H), 2.42 (ddd, *J* = 16.4, 7.3, 2.3 Hz, 1H); 0.88 (s, 9H). 0.04 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 202.3, 137.8, 116.5, 66.1, 45.6, 41.2, 26.0, 18.4, -5.3, -5.4; **HRMS (ESI-TOF):** calc. for [M-H]⁺: 227.1462, found 227.1465; **IR (neat):** 2954, 2929, 2887, 2858, 1727, 1472, 1409, 1389, 1361, 1253, 1099, 1027, 1005, 918, 834, 814, 775, 668; **Rf-value:** 0.67 (EtOAc:hexanes 1:1); 0.44 (EtOAc:hexanes 1:10).



pnmr_13C_256 CDCl3 /v pkanmr 27



184 pent-4-ynal

Chemical Formula: C₅H₆O

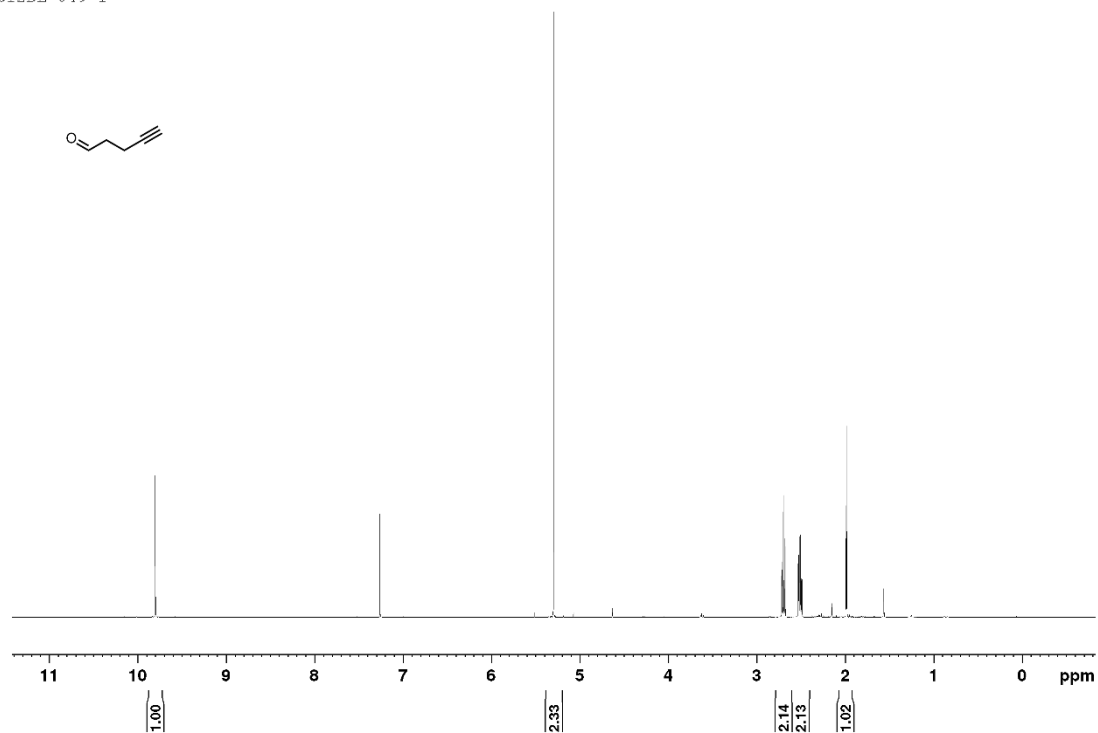
Exact Mass: 82.0419

Molecular Weight: 82.1005

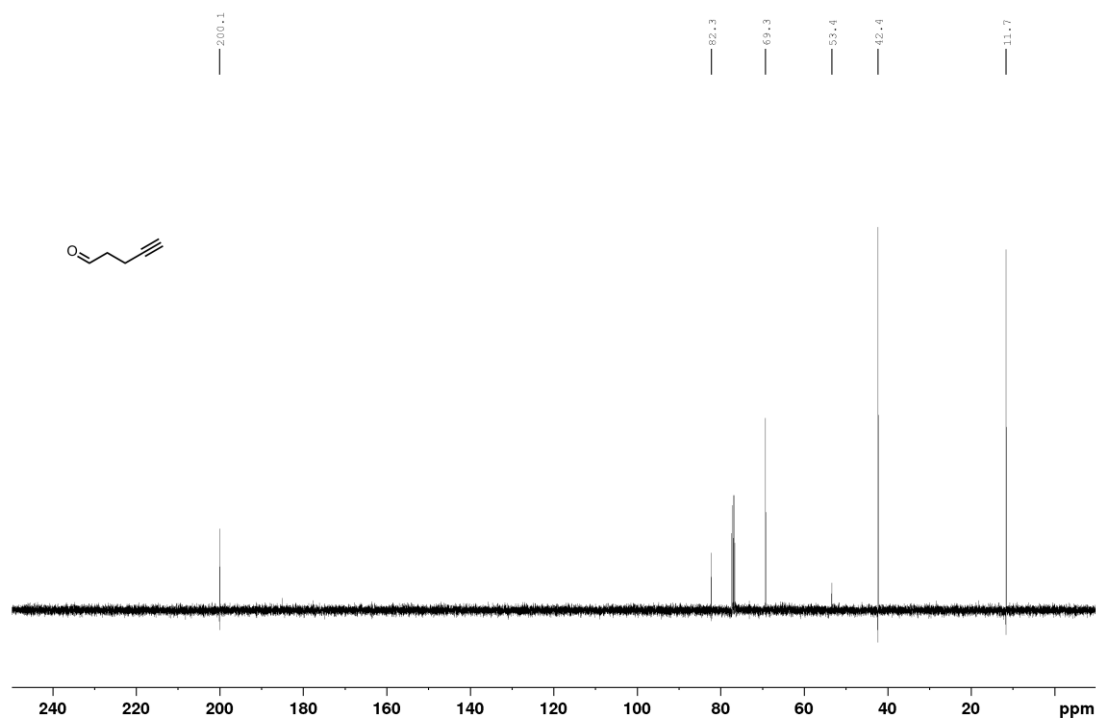
To a solution of oxalyl chloride (1.23 mL, 14.27 mmol, 1.2 eq.) in CH₂Cl₂ (18 mL) at –78 °C was added dropwise a solution of DMSO (1.86 mL, 26.15 mmol, 2.2 eq.) in CH₂Cl₂ (19 mL). After 5 min, a solution of pent-4-yn-1-ol (1.1 mL, 11.89 mmol, 1 eq.) in CH₂Cl₂ (16 mL) was added. The reaction mixture was then stirred for 30 min at –78 °C and Et₃N (8.3 mL, 59.4 mmol, 5 eq.) was added in one portion. After 1 h min at –78 °C, the mixture was put into an ambient temperature H₂O bath, quenched with saturated aqueous NH₄Cl (15 mL) and diluted with CH₂Cl₂ (102 mL). H₂O (2 mL) was added to dissolve the precipitates, the phases were separated and the organic layer was successively washed with NH₄Cl (2x15 mL, aq., sat.) and brine (10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by FC (CH₂Cl₂) to give the title compound as a clear, yellow liquid (1.21 g, contains 47% w/w of the aldehyde and 53 % CH₂Cl₂, corrected yield = 59%)

¹H NMR: (CDCl₃, 400 MHz) δ = 9.80 (t, *J* = 1.1 Hz, 1H), 2.70 (t, *J* = 7.1 Hz, 2H), 2.51 (td, *J* = 7.1, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 200.1, 82.3, 69.3, 42.4, 11.7; **HRMS (EI):** calc. for [M-H]⁺: 81.0335, found 81.0334; **IR (neat):** 3292, 2922, 1746, 1722, 1245, 1069, 637; **Rf-value:** 0.37 (EtOAc:hexanes 1:3); 0.62 (CH₂Cl₂).

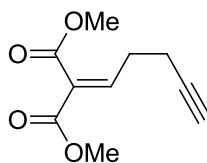
C12BL-049-1



C12BL-049-1



185 Dimethyl 2-(pent-4-yn-1-ylidene)malonate

Chemical Formula: C₁₀H₁₂O₄

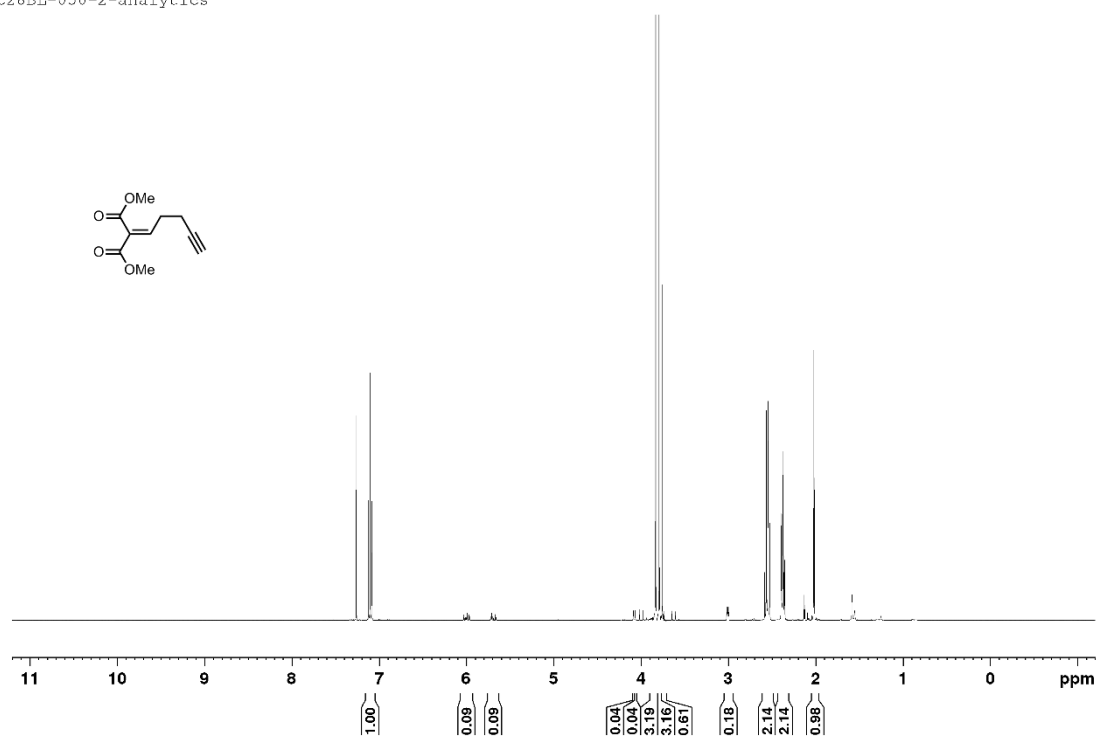
Exact Mass: 196.0736

Molecular Weight: 196.1999

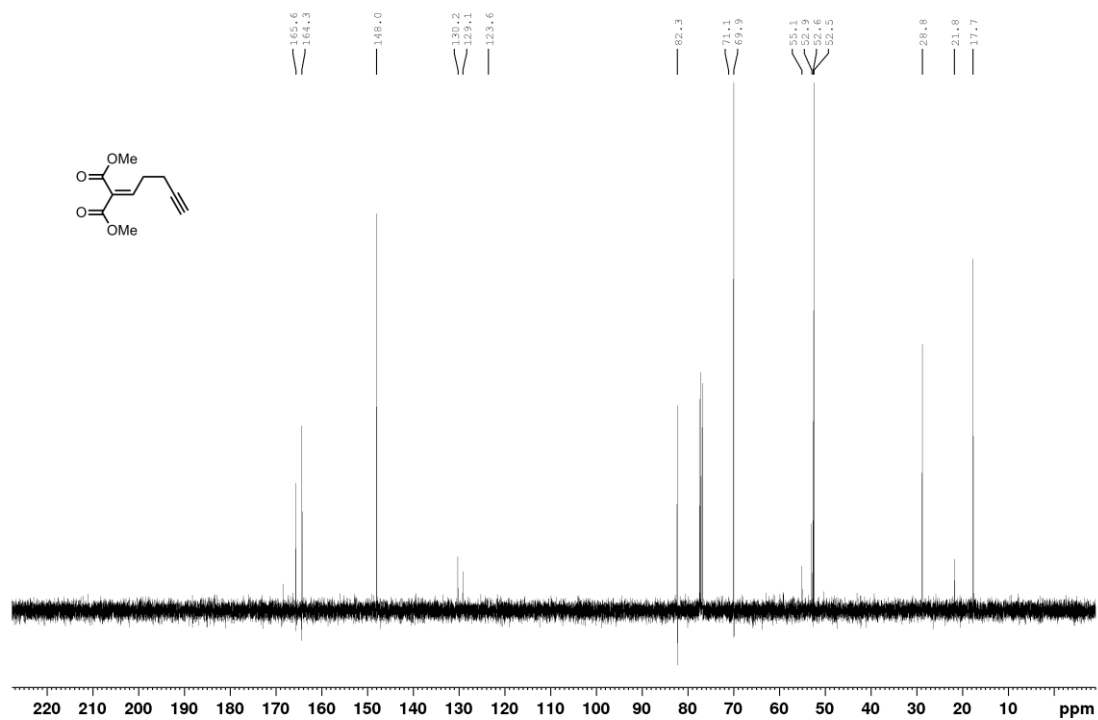
The reaction of **184** was carried out as described above for the synthesis of **176** from **175**. FC (Et₂O:pentane 1:10 + 1% AcOH) gave 44% of the desired compound after evacuating under high-vacuum overnight to remove residual dimethylmalonate. The material was contaminated with another inseparable substance (purity around 92%). In addition, traces of **186** were isolated (*vide infra*) that were contaminated with some aromatic impurity.

¹H NMR: (CDCl₃, 400 MHz) δ = 7.10 (t, J = 7.6 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.55 (q, J = 7.3 Hz, 2H), 2.37 (td, J = 7.0, 2.6 Hz, 2H), 2.02 (t, J = 2.6 Hz, 1H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 165.6, 164.3, 148.0, 129.1, 82.3, 69.9, 52.6, 52.5, 28.8, 17.7; **HRMS (ESI-TOF):** calc. for [M-NH₄]⁺: 214.1074, found 214.1076; **IR (neat):** 3287, 2955, 1722, 1649, 1436, 1370, 1268, 1219, 1197, 1094, 1061, 646; **Rf-value:** 0.47 (EtOAc:hexanes 1:3).

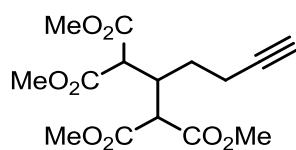
C28BL-050-2-analytics



C28BL-050-2-analytics



186 Tetramethyl 2-(but-3-yn-1-yl)propane-1,1,3,3-tetracarboxylate

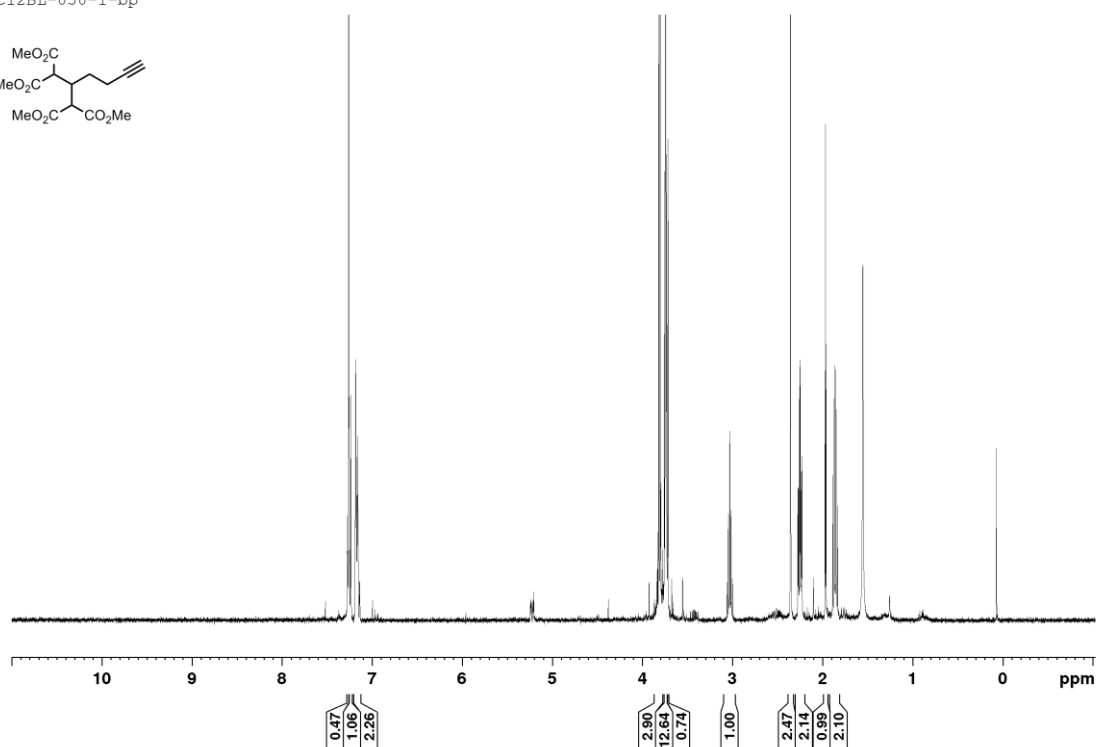
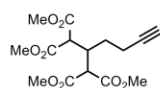
Chemical Formula: C₁₅H₂₀O₈

Exact Mass: 328.1158

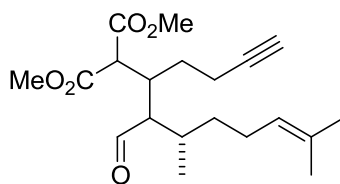
Molecular Weight: 328.3145

¹H NMR: (CDCl₃, 400 MHz) δ = 3.74 (d, J = 1.0 Hz, 12H), 3.03 (quint, J = 6.0 Hz, 1H), 2.36 (s, 2H), 2.25 (td, J = 7.5, 2.6 Hz, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.86 (m, q-like, 2H); **Rf-value:** 0.27 (EtOAc:hexanes 1:3)

C12BL-050-1-bp



191 dimethyl 2-((7S)-6-formyl-7,11-dimethyldodec-10-en-1-yn-5-yl)malonate

Chemical Formula: C₂₀H₃₀O₅

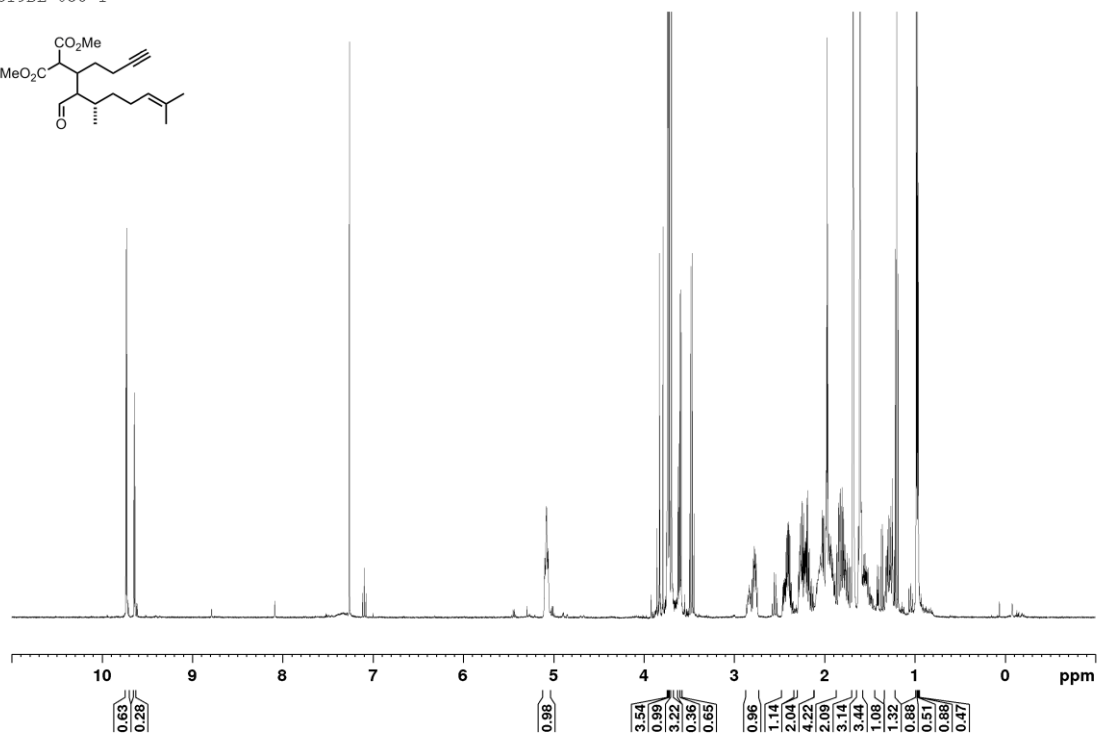
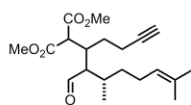
Exact Mass: 350.2093

Molecular Weight: 350.4492

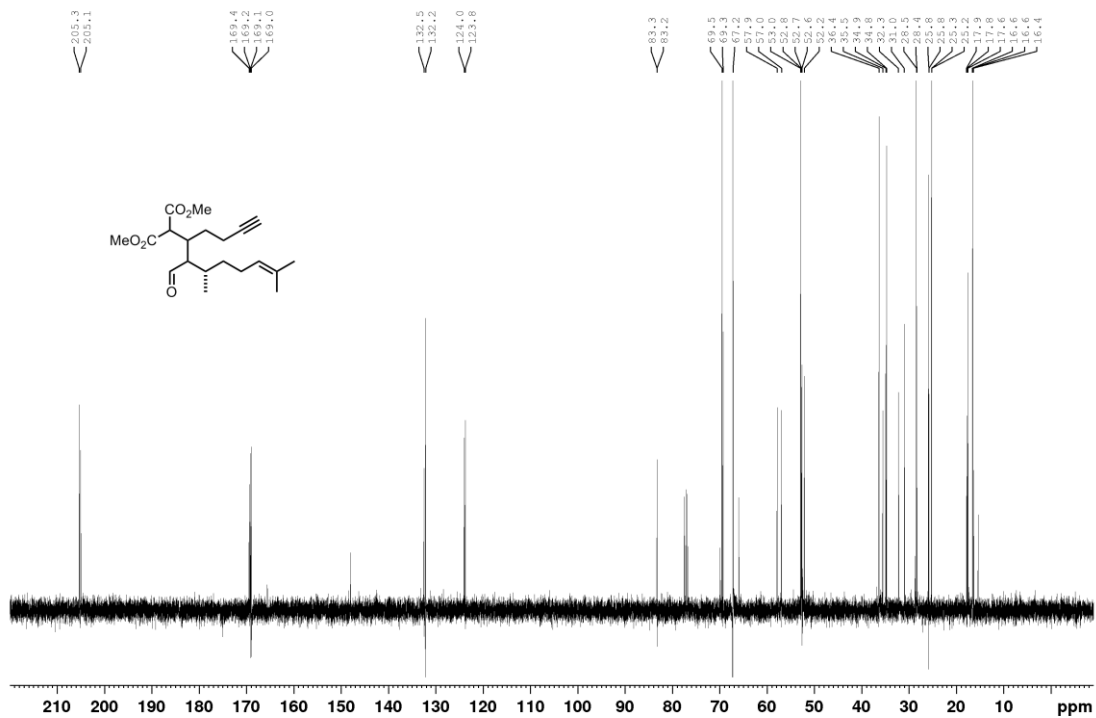
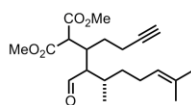
Malonate **185** (15 mg, 0.077 mmol, 1 eq.), citronellal (23.6 mg, 0.153 mmol, 2 eq.) and (S)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (10 mg, 0.031 mmol, 0.4 eq.) were combined in an HPLC vial and CH₂Cl₂ (0.31 mL) was added. The vial was closed with parafilm and stirred for 13d at ambient temperature. The solvent was removed by rotary evaporation and the material was directly purified by FC (Et₂O:hexanes 1:10 to 1:8 to 1:7) and gave 27.3 mg of a product mixture. The material still contained starting malonate (around 6-7 %) and other minor impurities. (purity maximum 93%, yield: 95-98%) Two doublet signals are visible in the aldehyde region of ¹H NMR. The ratio is 1:2 and likely represents the diastereomeric ratio. ¹³C spectra shows most signals twice, again hinting at two isomers.

¹H NMR: (CDCl₃, 400 MHz) δ = 9.73 (d, J = 3.9 Hz, 0.7 H), 9.64 (d, J = 3.8 Hz, 0.3 H), 5.12-5.04 (m, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.61 (d, J = 4.4 Hz, 0.3 H), 3.59 (d, J = 5.5 Hz, 0.6 H), 2.88-2.73 (m, 1H), 2.47-2.33 (m, 1H), 2.30-2.12 (m, 2H), 2.11-1.87 (m, 4H), 1.87-1.70 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58-1.45 (m, 1H), 1.33-1.22 (m, 1H), 0.97 (d, J = 6.9 Hz, 1.8 H), 0.97 (d, J = 6.8 Hz, 1 H); ¹³C NMR: (CDCl₃, 100 MHz) δ = 205.3, 205.1, 169.4, 169.2, 169.1, 169.0, 132.5, 132.2, 124.0, 123.8, 83.3, 83.2, 69.5, 69.3, 67.2, 57.9, 57.0, 53.0, 52.8, 52.7, 52.6, 52.2, 36.4, 35.5, 34.9, 34.8, 32.3, 31.0, 28.5, 28.4, 25.8 (2 signals), 25.3, 25.2, 17.9, 17.8, 17.6, 16.6 (2 signals), 16.4; HRMS (MALDI): calc. for [M+NH₄]⁺: 368.2431, found 368.2431; Rf-value: 0.29 (EtOAc:hexanes 1:5).

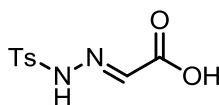
C19BL-058-1



C19BL-058-1-pure



206 (E)-2-(2-tosylhydrazono)acetic acid

Chemical Formula: C₉H₁₀N₂O₄S

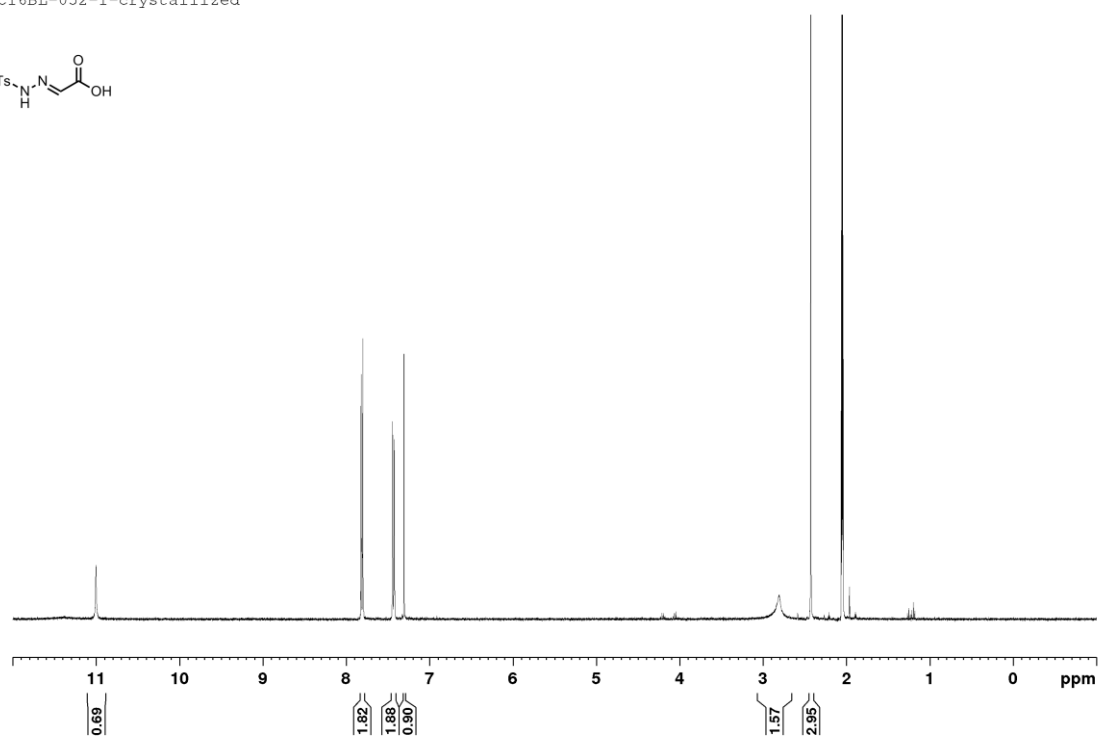
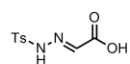
Exact Mass: 242.0361

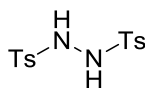
Molecular Weight: 242.2517

Glyoxylic acid monohydrate (2.572 g, 13.97 mmol, 50 %) was dissolved in H₂O (14.55 mL). The mixture was stirred at 65 °C and a warm suspension (approximately 65 °C) of *p*-toluenesulfonyl hydrazide in hydrochloric acid (aq., 1.81 mL conc. HCl and 6.92 mL H₂O) was added. The reaction mixture was stirred at 65 °C for 15 min, allowed to cool to room temperature gradually until all of the oil solidified. The flask was kept in a refrigerator overnight. The crude product was collected on filter paper, washed with cold water, and dried for 2 days in open air followed by exposure to high vacuum overnight. The material was dissolved in boiling EA, some drops of hot hexanes were added until it became slightly cloudy and drops of hot EA were added to just completely dissolve it. It was then left to crystallize in the freezer and washed with ice cold ETOA/hexanes (30 mL, 1:1). The title compound was obtained as a white powder (1.034 g, 31 %).

¹H NMR: (d₆-acetone, 400 MHz) δ = 11.00 (s, br, 1H), 7.84-7.78 (m, 2H), 7.46-7.40 (m, 2H), 7.31 (t, *J* = 0.7 Hz, 1H), 2.81 (s, br, 1H), 2.43 (s, 3H); **m.p.:** 151.5-153 °C (lit.: 150-152 °C)^[179].

C16BL-052-1-crystallized



209 4-methyl-*N'*-tosylbenzenesulfonohydrazideChemical Formula: C₁₄H₁₆N₂O₄S₂

Exact Mass: 340.0551

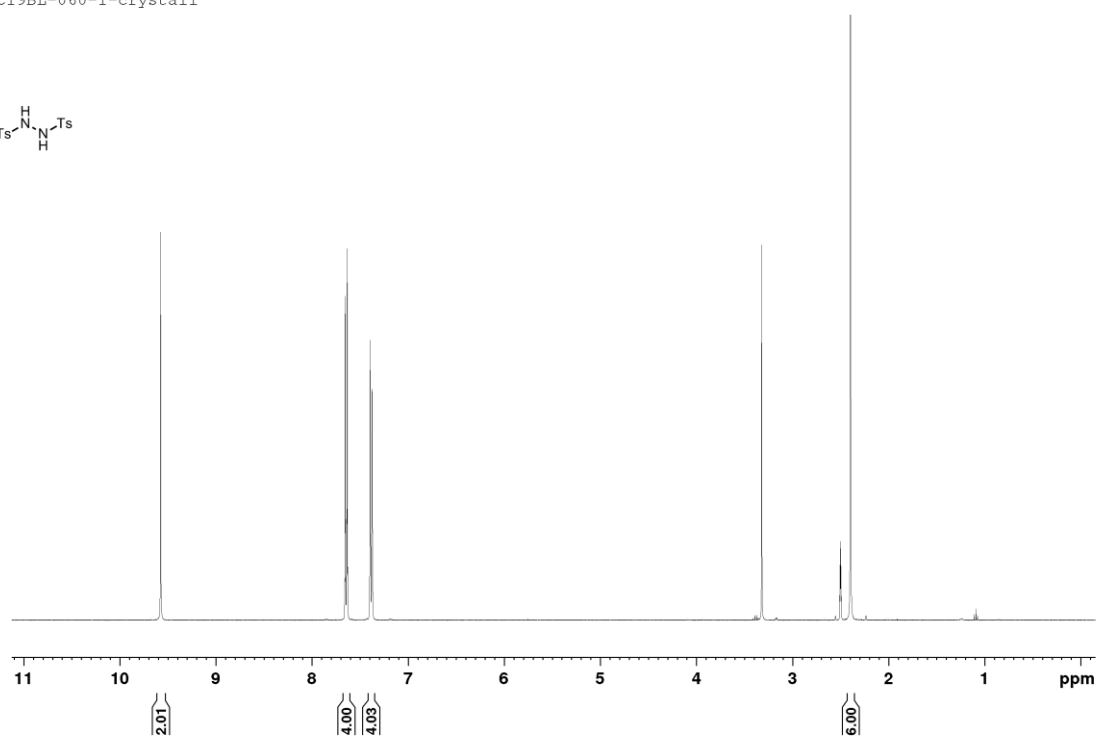
Molecular Weight: 340.4178

A flame-dried, 500-mL, round-bottomed flask fitted with a magnetic stirbar was charged with *p*-toluenesulfonyl hydrazide (9.32 g, 50.1 mmol, 1 eq.) and *p*-toluenesulfonyl chloride (14.31 g, 75.1 mmol, 1.5 eq.) in CH₂Cl₂ (50 mL). The stirred suspension was stirred at room temperature while pyridine (6.1 mL, 75.1 mmol, 1.5 eq.) was added dropwise over 1 min. During the addition, the reaction mixture became homogenous and turned yellow. White precipitate was observed within 3 minutes and the reaction mixture was stirred for 1.5 h. Et₂O (200 mL) and H₂O (100 mL) were added and stirring was continued at 0 °C for 22 min. The white solid which had precipitated was collected in a Büchner funnel using suction filtration and washed with Et₂O (100 mL). The solid thus obtained was dissolved in boiling MeOH (400 mL). After cooling to the room temperature, a precipitate appeared. Some MeOH (around 200 mL) was removed by rotary evaporation and the mixture was cooled to 4 °C overnight. The precipitate was collected in a Büchner funnel using suction filtration and washed with cold MeOH (20 mL) and Et₂O (100 mL) to give *N,N'*-ditosylhydrazine as white needles, which was then dried on high vacuum for 5 h (13.66 g, 80%).

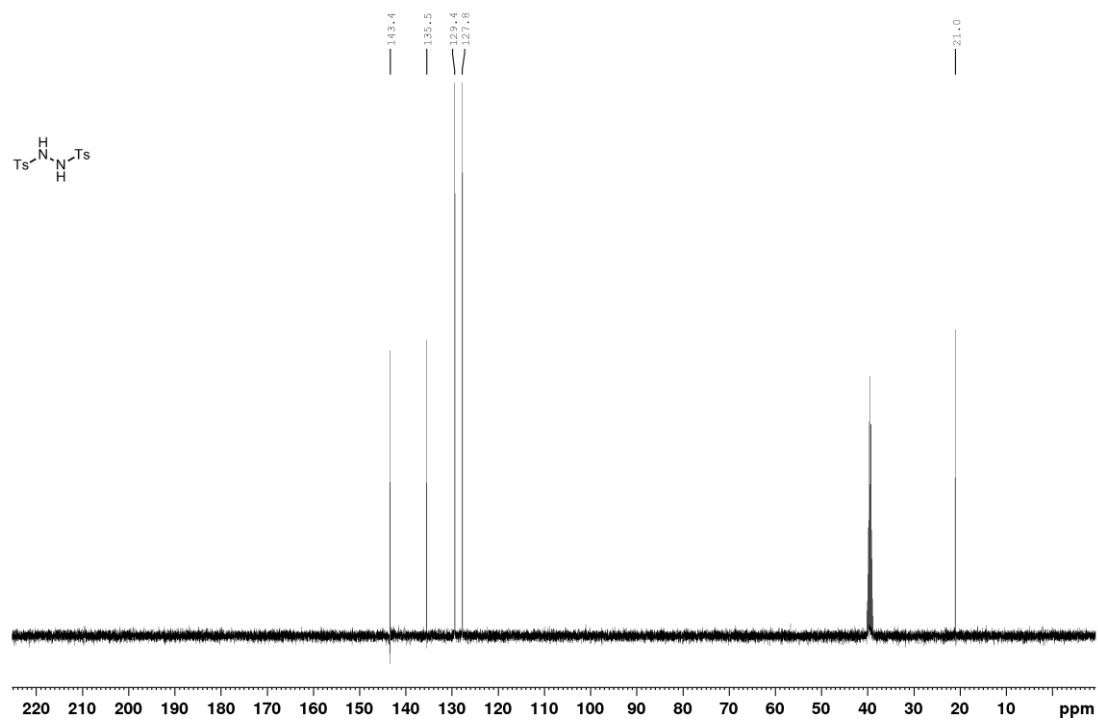
¹H NMR: (d₆-DMSO, 400 MHz) δ = 9.58 (s, 2H), 7.64 (d, *J* = 8.3 Hz, 4H), 7.38 (d, *J* = 8.3 Hz, 4H), 2.40 (s, 6H)^y; **¹³C NMR:** (DMSO-d₆, 100 MHz) δ = 143.4, 135.5, 129.4, 127.8, 21.0; **HRMS (MALDI):** calc. for [M-Na]⁺: 363.0449, found 363.0444; **IR (neat):** 3228, 3203, 1957, 1329, 1186, 1171, 1088, 813, 803; **m.p.:** decomposition starts between 212 and 215 °C (reported 209 °C).

^y In the analytical section of the original publication, the DMSO chemical shift was assigned to the water peak, which explains the difference in chemical shift.

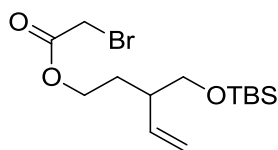
C19BL-060-1-crystall



C19BL-060-1-crystall



210 3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-en-1-yl 2-bromoacetate

Chemical Formula: C₁₄H₂₇BrO₃Si

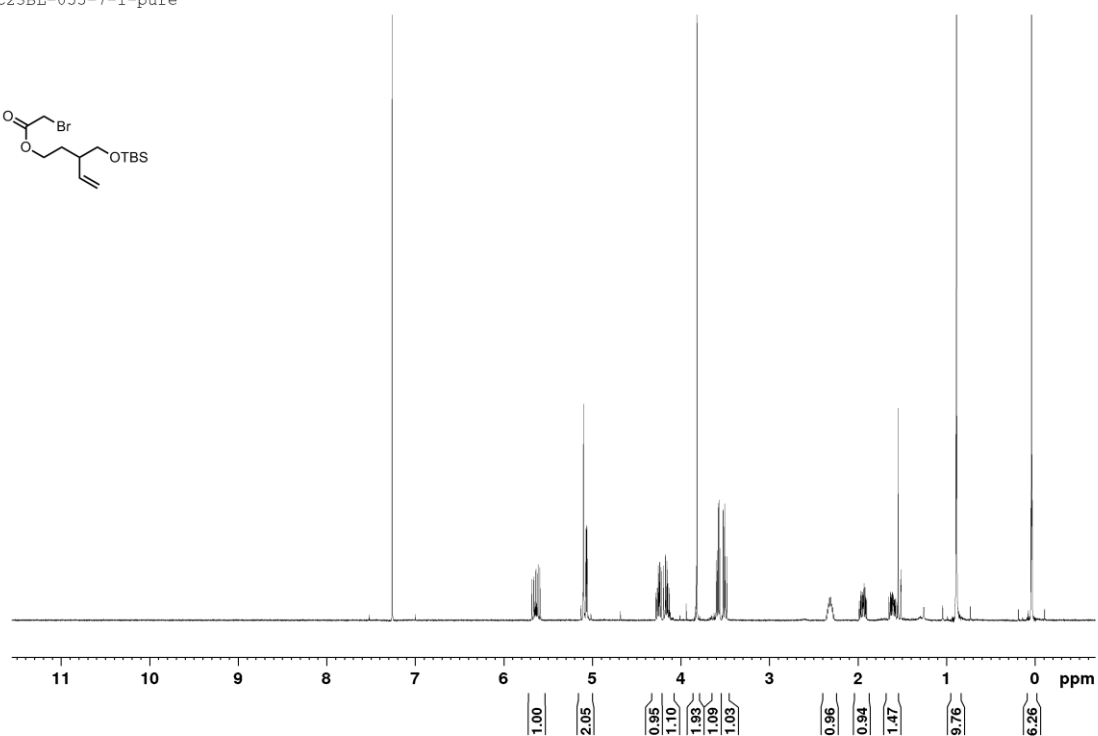
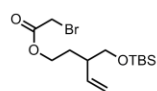
Exact Mass: 350.0913

Molecular Weight: 351.3519

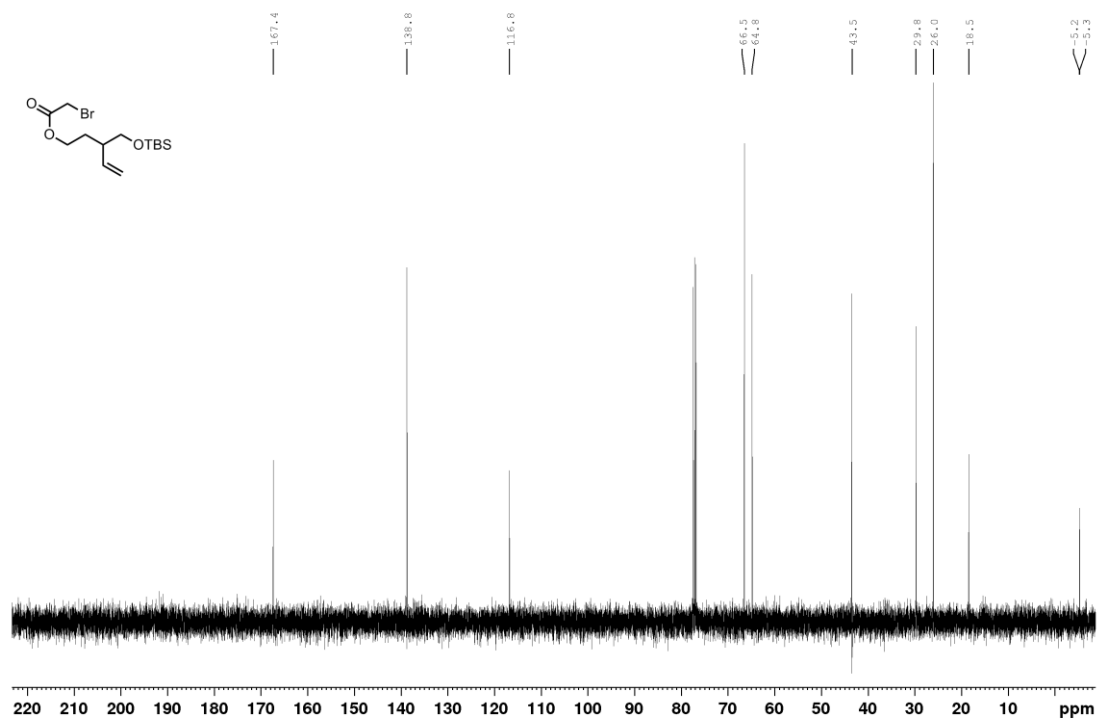
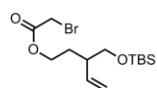
Alcohol **181** (50.2 mg, 0.217 mmol) was dissolved in acetonitrile (1.08 mL) and Na₂CO₃ (230 mg, 2.17 mmol, 10 eq.) was added in one go. At 0 °C, bromoacetyl bromide (29 µL, 0.326 mmol, 1.5 eq.) was added slowly. TLC of the reaction showed the desired product, deprotected starting material, starting material and bis acetylated diol. After warming up to ambient temperature and continued stirring for 2 d, the reaction was quenched with H₂O (1 mL). The mixture was extracted with CH₂Cl₂ (3x10 mL). The organic phase was washed with brine, dried over MgSO₄ and the solvent was evaporated. Purification by FC (silica gel; EtOAc:Hexanes 1:7) gave the clean title compound (35.1 mg, 46 %) as a clear colorless oil.

¹H NMR: (CDCl₃, 400 MHz) δ = 5.69-5.58 (m, 1H), 5.11-5.09 (m, 1H), 5.08-5.05 (m, 1H), 4.25 (ddd, 10.8, 7.2, 5.5, *J* = Hz, 1H), 4.16 (ddd, *J* = 10.8, 7.7, 6.8 Hz, 1H), 3.82 (s, 2H), 3.58 (dd, *J* = 9.9, 5.3 Hz, 1H), 3.50 (dd, *J* = 9.9, 6.6 Hz, 1H), 2.37-2.26 (m, 1H) 1.94 (dtd, *J* = 14.0, 7.5, 4.6 Hz, 1H), 1.61 (dddd, *J* = 9.6, 6.7, 5.5, 4.4 Hz, 1H). 0.89 (s, 9H), 0.04 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 167.4, 138.8, 116.8, 66.5, 64.8, 43.5, 29.8, 26.0 (2C), 18.5, -5.2, .5.3; **HRMS (ESI-TOF):** calc. for [M-Na]⁺: 373.0805, found 373.0799; **IR (neat):** 2955, 2929, 2896, 2857, 1738, 1471, 1463, 1278, 1254, 1162, 1105, 1004, 993, 918, 834, 775, 666; **Rf-value:** 0.70 (EtOAc:hexanes 1:3), 0.61 (EtOAc:hexanes 1:5)

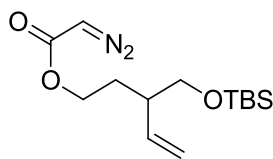
C23BL-055-7-1-pure



C23BL-055-7-1-pure



206 3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-en-1-yl 2-diazoacetate

Chemical Formula: C₁₄H₂₆N₂O₃Si

Exact Mass: 298.1713

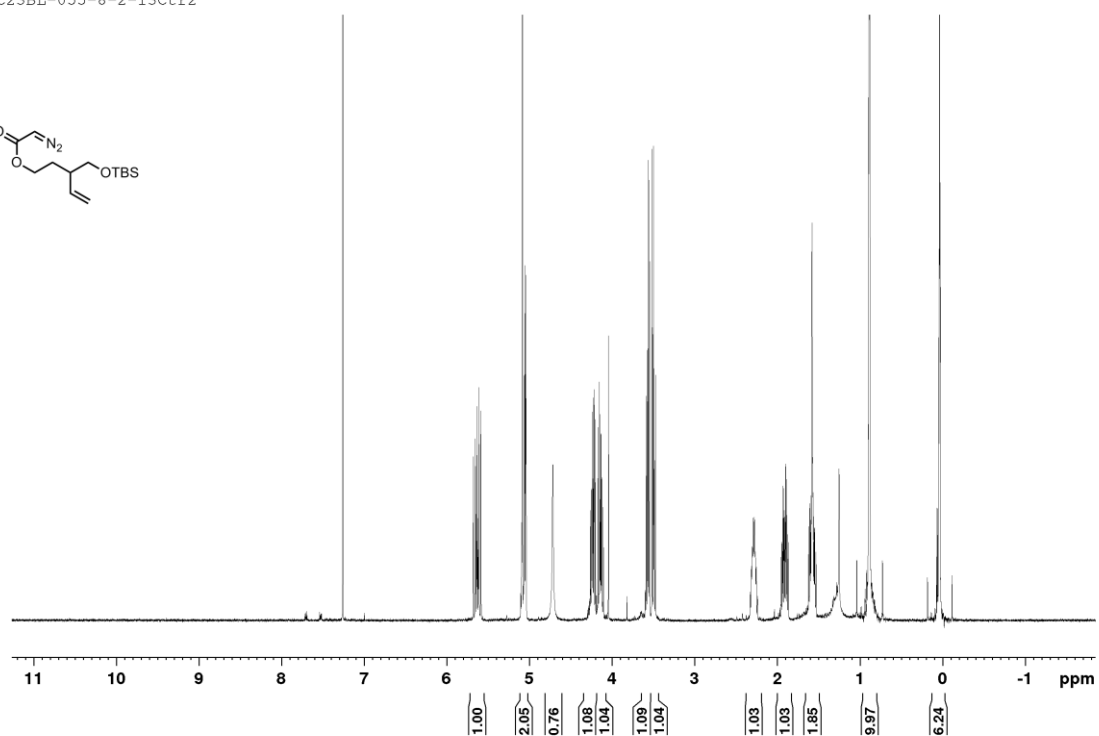
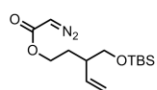
Molecular Weight: 298.4533

¹H NMR: (CDCl₃, 400 MHz) δ = 5.69-5.58 (m, 1H), 5.11-5.07 (m, 1H), 5.07-5.03 (m, 1H), 4.72 (s, br, 1H), 4.28-4.19 (m, 1H), 4.19-4.09 (m, 1H), 3.57 (dd, J = 9.9, 5.5 Hz, 1H), 3.49 (dd, J = 9.9, 6.5 Hz, 1H), 2.34-2.23 (m, 1H), 1.91 (dtd, 13.9, 7.5, 4.6 Hz, 1H), 1.63-1.52 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 167 (only visible in HMBC), 139.0, 116.6, 66.5, 63.4, 46.3, 43.6, 30.1, 26.0, 18.5, -5.2, -5.3; **HRMS (ESI-TOF):** calc. for [M-Na]⁺: 321.1605, found 321.1510; **IR (neat):** 2955, 2930, 2898, 2858, 2361, 2337, 2110, 1698, 1468, 1396, 1361, 1251, 1184, 1102, 1083, 1005, 918, 837, 777, 741, 669; **Rf-value:** 0.57 (EtOAc:hexanes 1:3), 0.54 (EtOAc:hexanes 1:5)

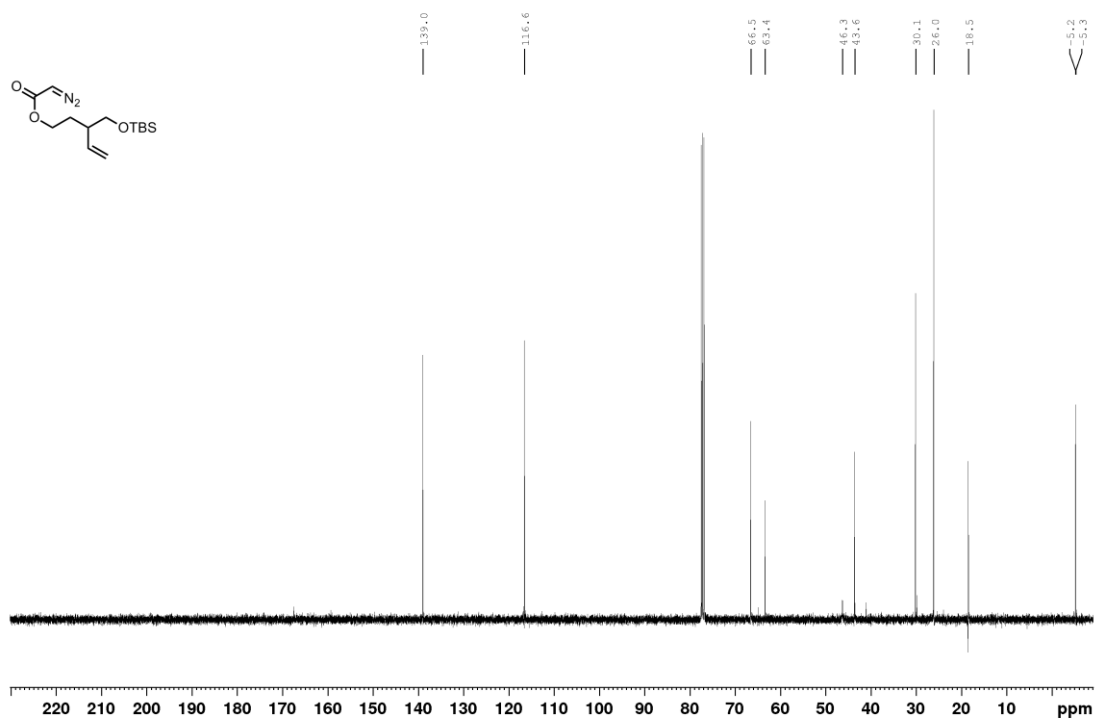
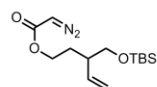
Alcohol **181** (51.3 mg, 0.223 mmol) was dissolved in acetonitrile (1.08 mL) and pyridine (0.18 mL, 2.17 mmol, 10 eq.) was added followed by DMAP (2.7 mg, 22 μ mol, 0.1 eq.). At 0 °C, bromoacetyl bromide (21 μ L, 0.24 mmol, 1.1 eq.) was added slowly. After warming removing the cooling bath and stirring at ambient temperature for 1 h, the reaction was diluted with Et₂O (20 mL), then quenched with NH₄Cl (2 mL, aq., sat.). Phases were separated and the aqueous phase was washed with Et₂O (2x10 mL) and the combined organic phases were washed with NH₄Cl (2 mL, aq., sat.), brine (2 mL) and then dried over MgSO₄. Purification by FC (EtOAc:Hexanes 1:7) gave the intermediate bromo acetate (25.3 mg, 33%) as clear colorless oil.

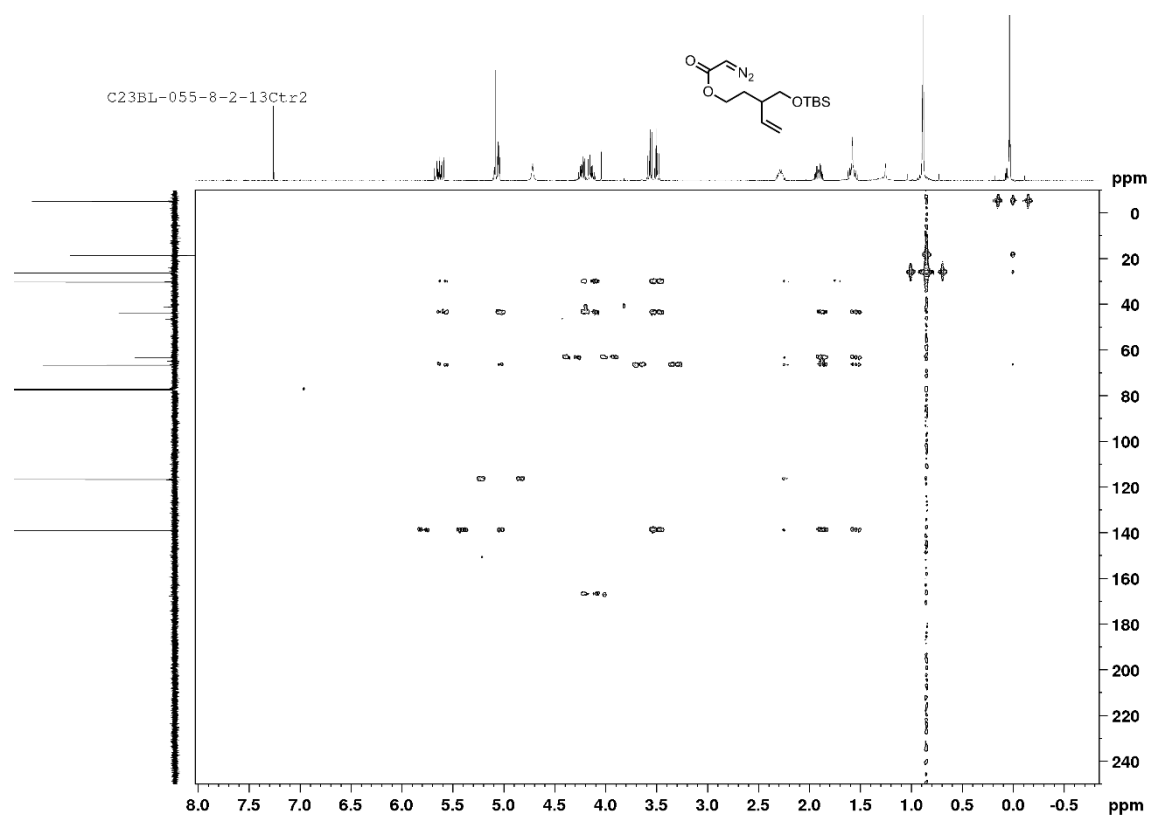
The bromoacetate was dissolved in THF (0.36 mL), **209** (50 mg, 0.14 mmol, 2 eq.) were added and the mixture was cooled to 0 °C. DBU (54 μ L, 0.36 mmol, 5 eq.) was added dropwise and the mixture turned from colorless to yellow within 10 min. It was quenched with NaHCO₃ (0.4 mL, aq., sat.), extracted with Et₂O (3x5 mL). The combined organic phases were washed with brine (0.4 mL) and dried over MgSO₄. The solvent was evaporated and the crude material purified by FC (EtOAc:Hexanes 1:10) to give the title compound (17.6 mg, 27 % overall).

C23BL-055-8-2-13Ctr2

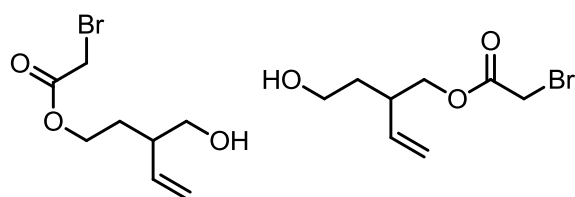


C23BL-055-8-2-13Ctr2





211 and 212: 3-(hydroxymethyl)pent-4-en-1-yl 2-bromoacetate

Chemical Formula: $C_8H_{13}BrO_3$

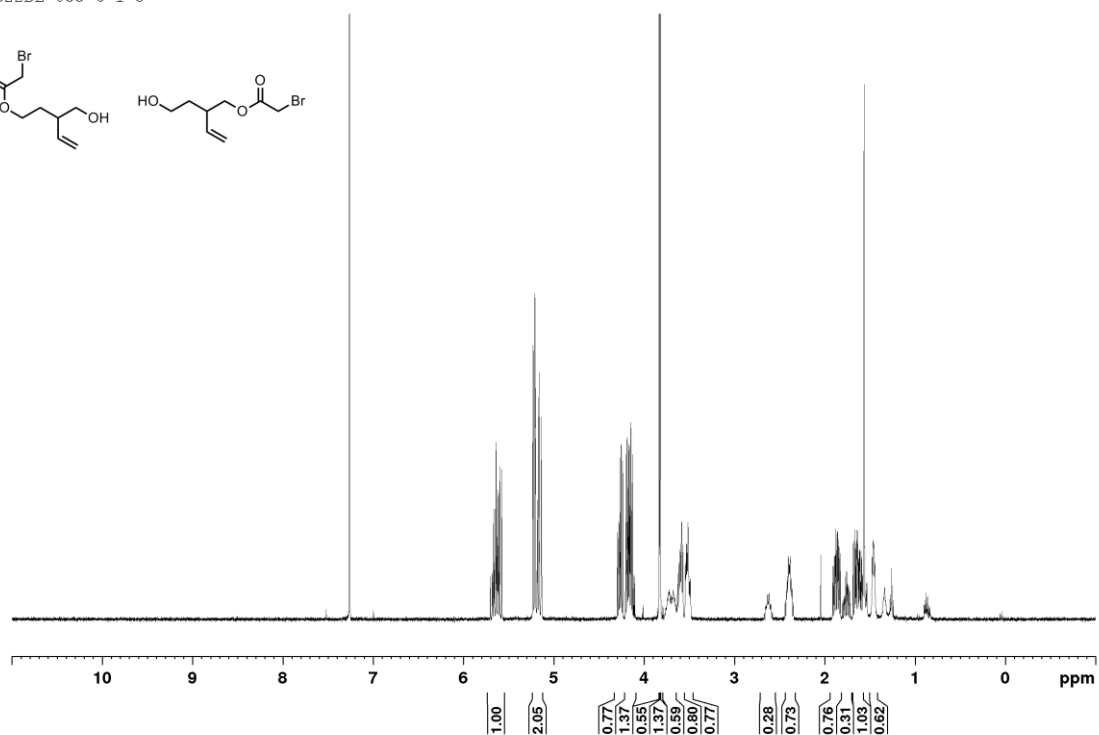
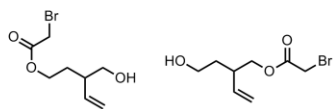
Exact Mass: 236.0048

Molecular Weight: 237.0910

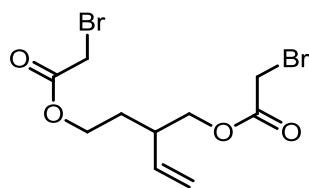
181 (50 mg, 0.22 mmol) was dissolved in MeCN (1.08 mL) and $NaHCO_3$ (40 mg, 0.48 mmol, 2.2 eq.) was added in one portion. After cooling to 0 °C, bromoacetyl bromide (21 μ L, 0.24 mmol, 1.1 eq.) was added slowly. After stirring for 30 min at 0 °C, cooling was removed and the mixture was stirred for further 3 h. Shortly after warming, a white precipitate was observed. The reaction was quenched with H_2O (1 mL) and extracted with CH_2Cl_2 (3x5 mL). The organic phase was washed with brine (1mL), dried over $MgSO_4$ and the solvent was evaporated. Half of the crude material was purified by FC (silica gel; EtOAc:Hexanes 1:5 to 1:1 to give first **213** and a mixture of regioisomers **211** and **212**.

1H NMR: ($CDCl_3$, 400 MHz) δ = 5.71-5.56 (m, 1H), 5.24-5.12 (m, 2H), 4.27 (ddd, J = 11.0, 6.9, 5.6 Hz, 0.8H), 4.21-4.09 (m, 1.4H), 3.83 (s, 0.6 H), 3.82 (s, 1.4 H), 3.79-3.69 (m, 0.6H), 3.69-3.55 (m, 0.8H), 3.55-3.46 (m, 0.8H), 2.68-2.57 (m, 0.3H), 2.44-2.33 (m, 0.7H), 1.92-1.82 (m, 0.8H), 1.81-1.71 (m, 0.3H), 1.69-1.57 (m, 1H), 1.46 (dd, J = 6.7, 4.6 Hz, 0.6H); **Rf-value:** 0.04 (EtOAc:hexanes 1:5)

C22BL-055-6-1-3



213 2-vinylbutane-1,4-diyl bis(2-bromoacetate)

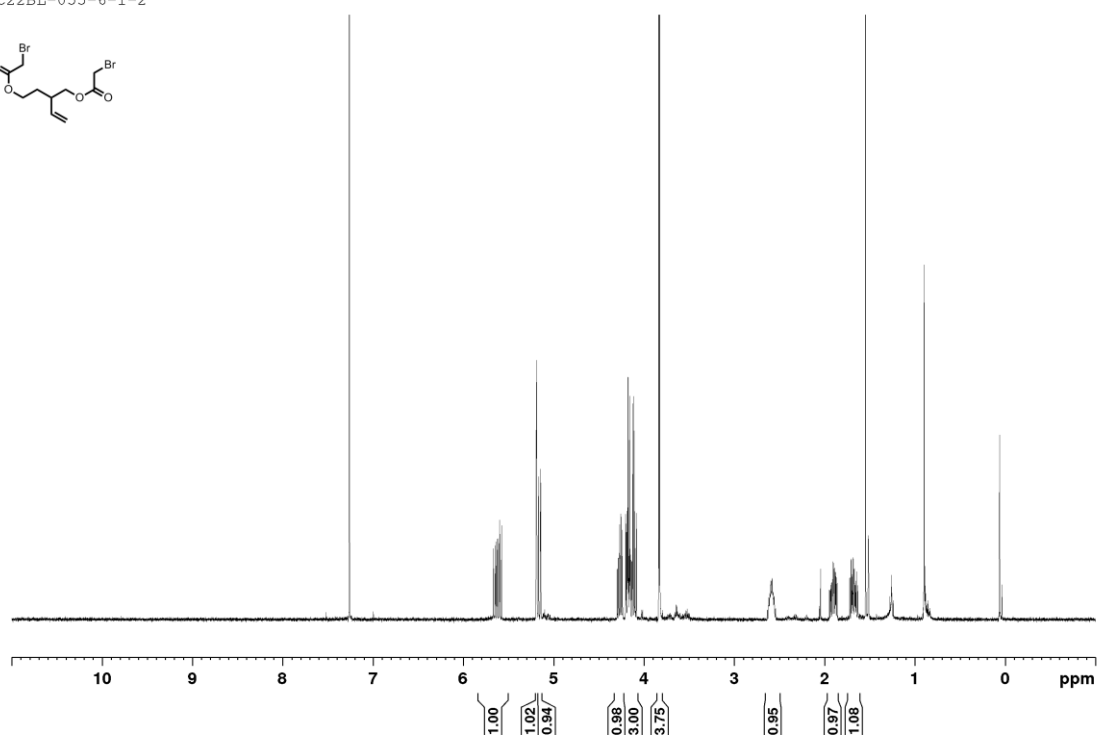
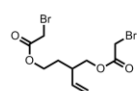
Chemical Formula: $C_{10}H_{14}Br_2O_4$

Exact Mass: 355.9259

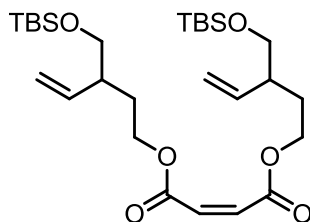
Molecular Weight: 358.0238

1H NMR: ($CDCl_3$, 400 MHz) δ = 5.62 (ddd, J = 16.9, 8.6, 10.6 Hz, 1 H), 5.20-5.18 (m, 1H), 5.18-5.13 (m, 1H), 4.27 (ddd, J = 11.1, 6.6, 5.5 Hz, 1 H), 4.21-4.07 (m, 3H), 3.84 (s, 2H), 3.83 (s, 2H), 2.64-2.53 (m, 1H), 1.95-1.85 (m, 1H), 1.73-1.62 (m, 1H); **Rf-value:** 0.24 (EtOAc:hexanes 1:5)

C22BL-055-6-1-2



214 bis(3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-en-1-yl) maleate

Chemical Formula: $C_{28}H_{52}O_6Si_2$

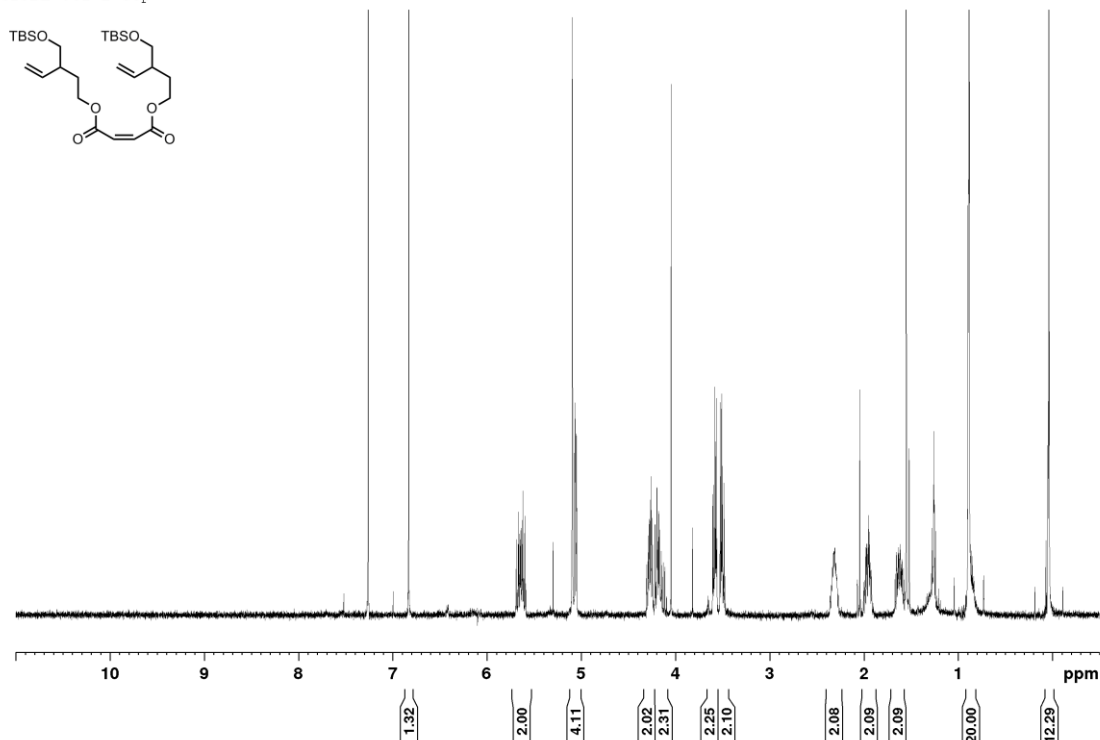
Exact Mass: 540.3302

Molecular Weight: 540.8799

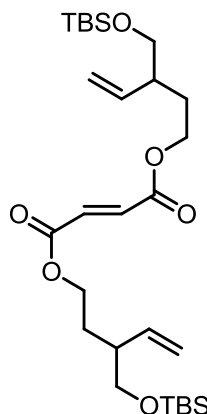
A solution of the 206 (7.6 mg, 25.5 μ mol) in toluene (0.51 mL) was refluxed with copper(II) acetoacetate (0.7 mg, 2.5 μ mol, 0.1 eq.) in a sealed microwave vial for 20.5 h at 112 $^{\circ}$ C. After removal of the solvent, the residue was directly purified by FC (Et₂O:hexanes 1:15, then EtOAc:hexanes 1:10) to first give the title compound (1.9 mg, 28%) and some traces of the isomer **215**.

¹H NMR: (CDCl₃, 400 MHz) δ = 6.83 (s, 2H), 5.70-5.58 (m, 2H), 5.11-5.08 (m, 2H), 5.08-5.04 (m, 2H), 4.31-4.22 (m, 2H), 4.22-4.08 (m, 2H), 3.61-3.55 (m, 2H), 3.54-3.46 (m, 2H), 2.37-2.26 (m, 2H), 2.01-1.90 (m, 2H), 1.68-1.57 (m, 2H), 0.89 (s, 18H), 0.04 (s, 12H); **HRMS (ESI-TOF):** calc. for [M+H]⁺: 541.3375, found 541.3378; **Rf-value:** 0.77 (EtOAc:hexanes 1:5)

C23BL-061-2-top



215 bis(3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-en-1-yl) fumarate

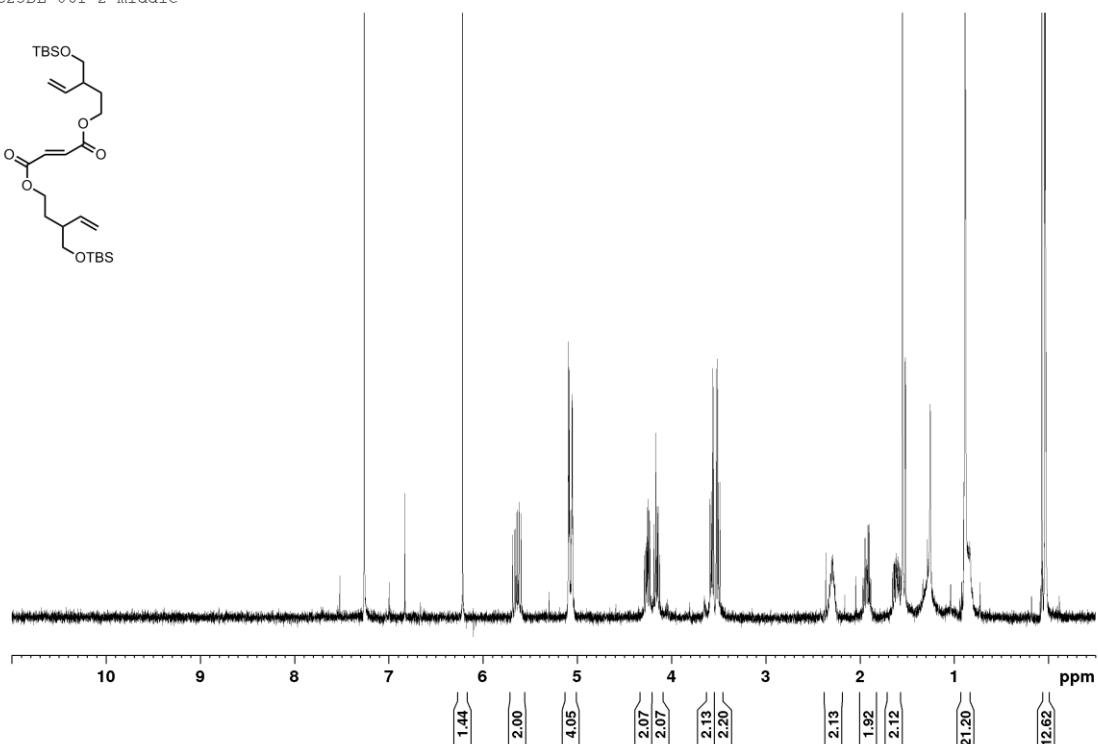
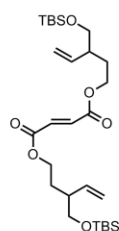
Chemical Formula: $C_{28}H_{52}O_6Si_2$

Exact Mass: 540.3302

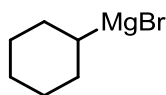
Molecular Weight: 540.8799

1H NMR: ($CDCl_3$, 400 MHz) δ = 6.22 (s, 2H), 5.64 (ddd, J = 17.7, 9.8, 8.5 Hz, 2H), 5.10-5.07 (m, 2H), 5.07-5.04 (m, 2H), 4.26 (ddd, J = 10.9, 7.6, 5.5 Hz, 2H), 4.15 (dt, J = 10.9, 7.4 Hz, 2H), 3.57 (dd, J = 9.8, 5.5 Hz, 2H), 3.51 (dd, J = 9.8, 6.3 Hz, 2H), 2.35-2.24 (m, 2H), 1.98-1.86 (m, 2H), 1.67-1.56 (m, 2H), 0.88 (s, 18H), 0.03 (s, 12H); **HRMS (ESI-TOF):** calc. for $[M+Na]^+$: 563.3195, found 563.3194; **Rf-value:** 0.61 (EtOAc:hexanes 1:5)

C23BL-061-2-middle



225 Cyclohexyl magnesium bromide

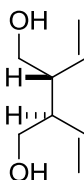
**BL-096**Chemical Formula: $C_6H_{11}BrMg$

Exact Mass: 185.9895

Molecular Weight: 187.3605

To a flame-dried Mg turnings (3.13 g, 129 mmol, 1.05 eq.) was added THF (13 mL). Dibromoethane (0.11 mL, 1.2 mmol, 0.1 eq) were added and the flask was gently heated to reflux with a heat gun. A first portion (6 mL) of a solution of bromocyclohexane (15 mL, 123 mmol, 1 eq.) in THF (32 mL) was added to initiate the Grignard. The rest of the material was added at a speed to ensure gentle refluxing. Heating was continued at 70 °C for 2 h, followed by 100 °C for 1h. The stock solution was transferred into a flame dried flask. A lot of the Grignard reagent crystallized, therefore more THF (20 mL) and dry benzene (20 mL) were added and the solution was sonicated for 1h, to dissolve all the solids. Before dilution and sonication, the concentration of the black solution was 1.5 M according to titration with *s*-BuOH/Phenanthroline.^[222] Afterwards the concentration was 1.1 M.

226: (+/-)-(trans)-2,3-divinylbutane-1,4-diol

Chemical Formula: $C_8H_{14}O_2$

Exact Mass: 142.0994

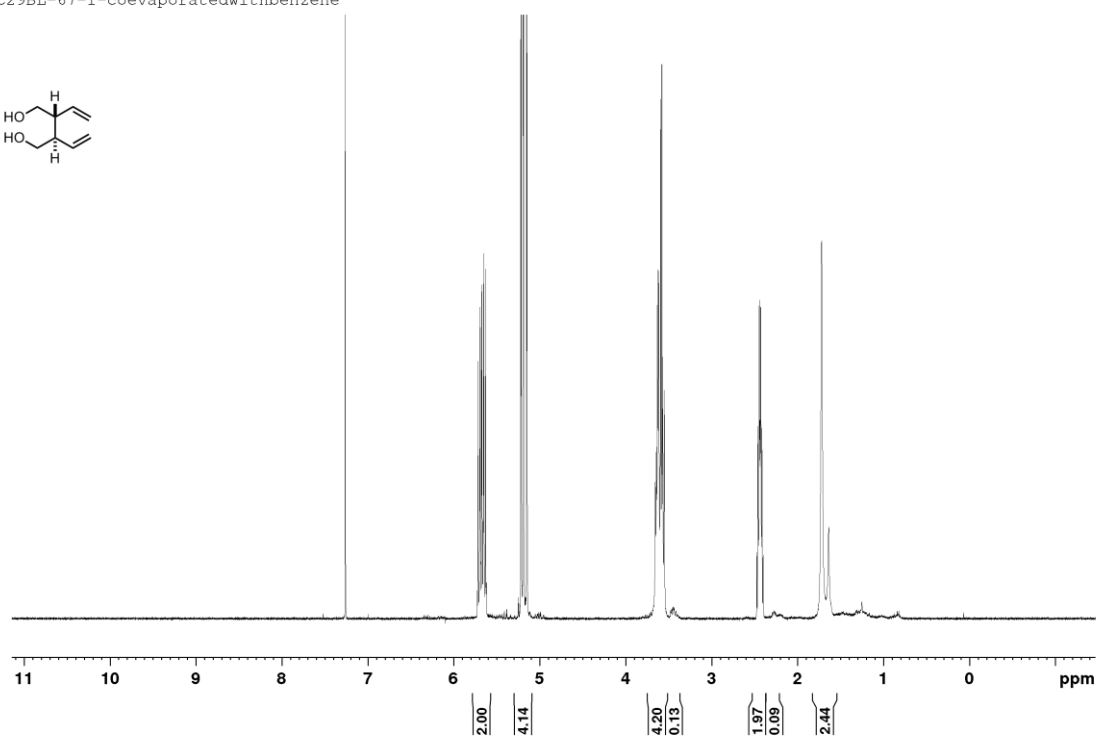
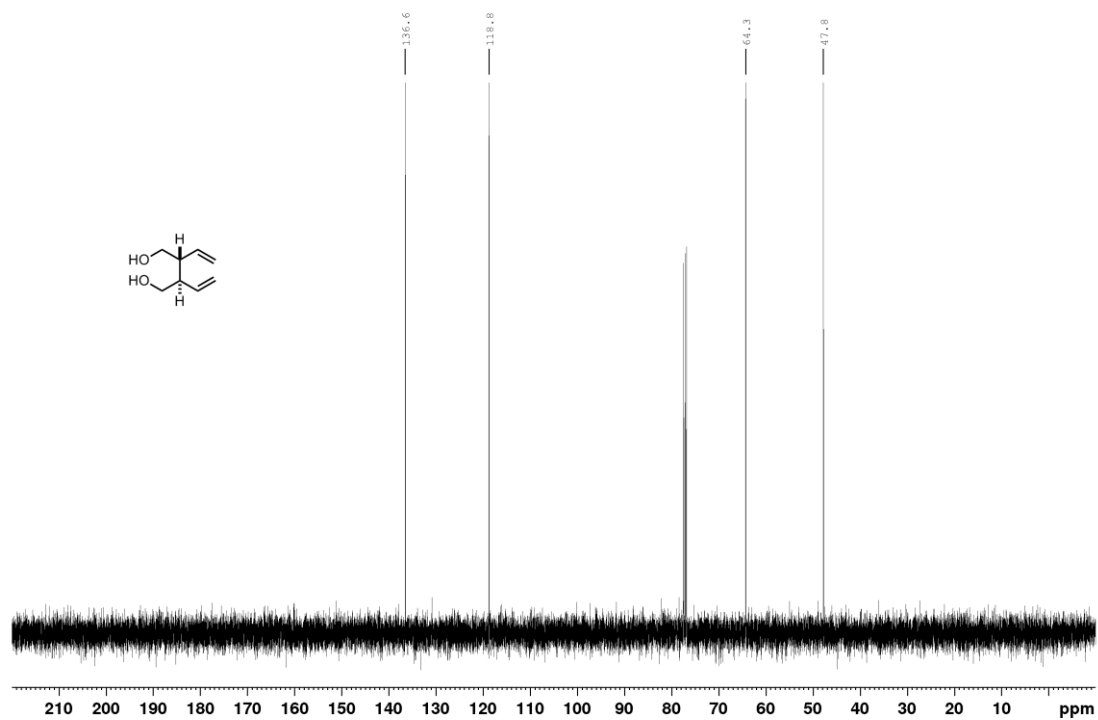
Molecular Weight: 142.1956

A flame dried 40 mL flask was charged with tetraisopropyloxytitanium (2.16 mL, 7.13 mmol, 1 eq., purified 2 months before by coevaporating 10 mL with 50 mL benzene and subsequent distillation under high vacuum @ 120 °C), followed by THF (1.43 mL) and lastly 2,5-dihydrofuran (1.08 mL, 14.27 mmol, 2 eq.). This colourless mixture was cooled to -12 °C (cryostat) and a commercially available solution of cyclohexylmagnesium bromide (21.4 mL, 21.4 mmol, 3 eq., TCI, slightly brown, but very clear), was added dropwise over 70 min (glass syringe, syringe pump, 0.3 mL/min). The mixture turned first yellow, then a cloudy dark brown and was stirred for 30 min at low temperature. After that, cooling was turned off and the material was warmed up to 20 °C in the bath, then the acetone bath was exchanged for a H₂O

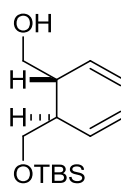
bath. The mixture was stirred overnight, during which some gelatinous precipitates formed on the wall of the flask and the mixture had turned a dark brown. While immersed in the H₂O bath, the mixture was diluted with Et₂O (15 mL) and slowly quenched with HCl (15 mL, 2M, aq.). **The quench raised temperature to 30 °C** but no higher and a caramel-colored precipitate formed. H₂O was added and more Et₂O, but the precipitate did not dissolve. The phases were separated and to the aqueous phase was again added ether. After 1h, the precipitates had still not dissolved. The material was pushed through a plug of celite, then extracted with CH₂Cl₂ (6x25 mL). pH was adjusted to 7 with 1M HCl. The aqueous phase was extracted with EtOAc (5 x 25 mL). The combined organic extracts were, dried over Na₂SO₄ and evaporated to dryness to give a slightly yellow oil. This was purified by FC (EtOAc:Hexanes 1:1 to 3:1 to 5:1 to give the title compound contaminated with dicyclohexyl. The material was transferred into another flask with MeOH and concentrated. This completely removed the dicyclohexyl contaminant and gave the title compound as a clear colourless oil (613 mg, 60 %). Some mixed fractions contaminated with a slightly less polar compound (R_f=0.34) were obtained. Comparison by ¹H NMR later revealed this to be the corresponding *meso*-compound.

¹H NMR: (CDCl₃, 400 MHz) δ = 5.67 (ddd, *J* = 17.0, 10.4, 6.6 Hz, 2H), 5.21 (dd, *J* = 10.4, 1.8 Hz, 2H), 5.17 (dd, *J* = 17.0, 1.8 Hz, 2H), 3.62 (dd, *J* = 10.8, 5.4 Hz, 2H), 3.57 (dd, *J* = 10.8, 6.8 Hz, 2H), 2.48-2.39 (m, 2H), 1.72 (s, *br*, 2H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 136.6, 118.8, 64.3, 47.8; **HRMS (EI):** calc. for [M-CH₃O]⁺: 111.0804, found 111.0805; **HRMS (ESI):** calc. for [M+H]⁺: 143.1067, found 143.1065; **IR (neat):** 3329, 2925, 2876, 1639, 1425, 1039, 993, 915, 780, 720; **R_f-value:** 0.27 (EtOAc:hexanes 3:1)

C29BL-67-1-coevaporatedwithbenzene

pnmr_13C_1024 CDCl₃ /v pkanmr 18

233 (+/-)- (2R,3R)-3-(((tert-butyldimethylsilyl)oxy)methyl)-2-vinylpent-4-en-1-ol

Chemical Formula: C₁₄H₂₈O₂Si

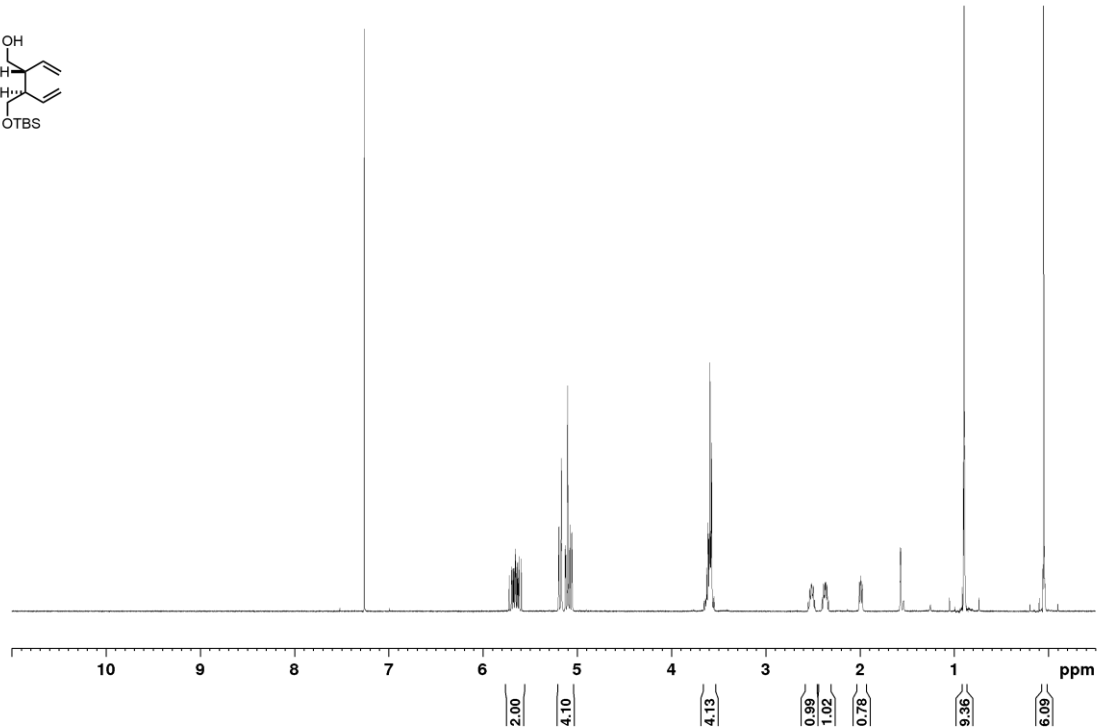
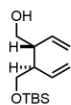
Exact Mass: 256.1859

Molecular Weight: 256.4564

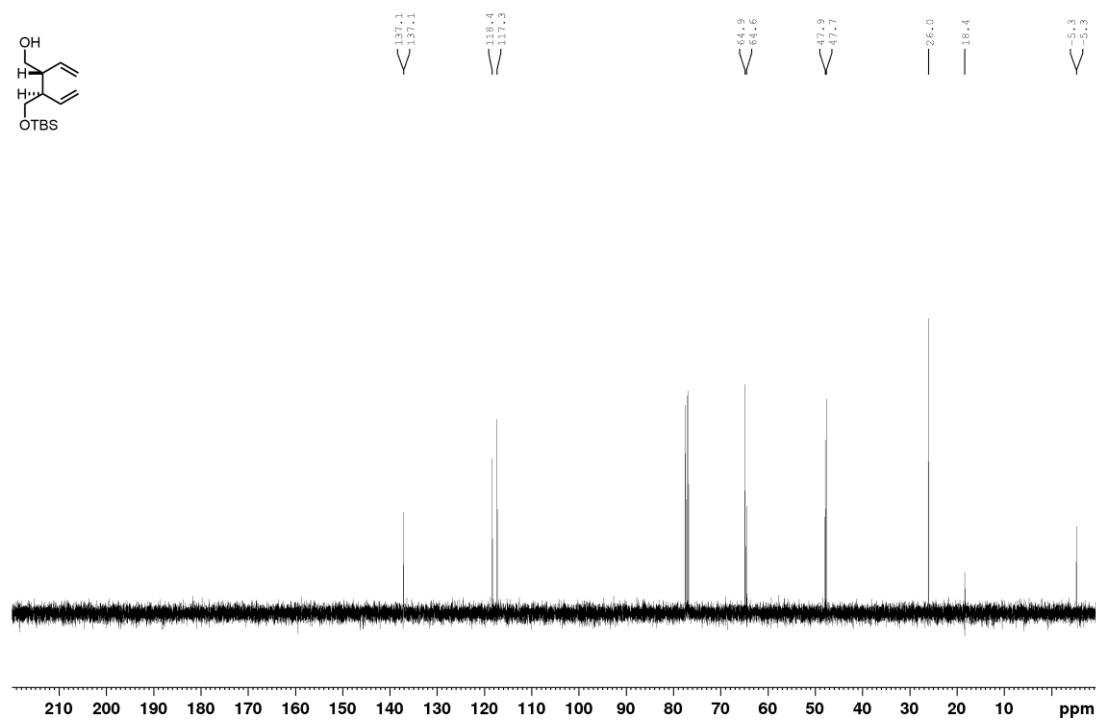
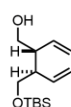
To a solution of diol **226** (50 mg, 0.352 mmol, 1 eq.) in THF (1.4 mL) in a ambient temperature water bath was added *n*-BuLi (0.23 mL, 1.6 M in hexanes, 0.369 mmol, 1.05 eq.). TBSCl (53 mg, 0.352 mmol, 1 eq) was added in one portion and the mixture was stirred at ambient temperature for 1 h. Reaction was quenched by addition of water (0.3 mL). THF was removed by rotary evaporation and the material was dissolved in EtOAc (1.5 mL) and diluted with H₂O (0.3 mL), since the water had partly evaporated. Phases were separated and the aqueous layer was extracted with EtOAc (3x1.5 mL). The combined organic extracts were washed with brine (1 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by FC (EtOAc:Hexanes 1:5) to give the title compound as a clear, colourless oil (78.9 mg, 88%).

¹H NMR: (CDCl₃, 400 MHz) δ = 5.73-5.58 (m, 2H), 5.21-5.11 (m, 2H), 5.11-5.04 (m, 2H), 3.66-3.54 (m, 4H), 2.56-2.47 (m, 1H), 2.41-2.32 (m, 1H), 1.99 (dd, *J* = 7.4, 5.1 Hz, 1H), 0.89 (s, *br*, 9H), 0.05 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 137.1 (2 signals), 118.4, 117.3, 64.9, 64.6, 47.9, 47.7, 26.0, 18.4, -5.3 (2 signals); **HRMS (EI):** calc. for [M-C(CH₃)₃]⁺: 199,1149, found 199.1148; **HRMS (ESI):** calc. for [M+H]⁺: 257.1931, found 257.1934; **IR (neat):** 2954, 2929, 2885, 2858, 1471, 1464, 1425, 1388, 1361, 1253, 1090, 1052, 995, 937, 917, 884, 834, 814, 774, 719, 665; **Rf-value:** 0.27 (EtOAc:hexanes 1:10)

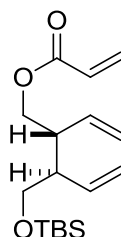
C29BL-068-1-pure



C29BL-068-1-pure



234 (+/-)-(2R,3R)-3-(((tert-butyldimethylsilyl)oxy)methyl)-2-vinylpent-4-en-1-yl acrylate

Chemical Formula: C₁₇H₃₀O₃Si

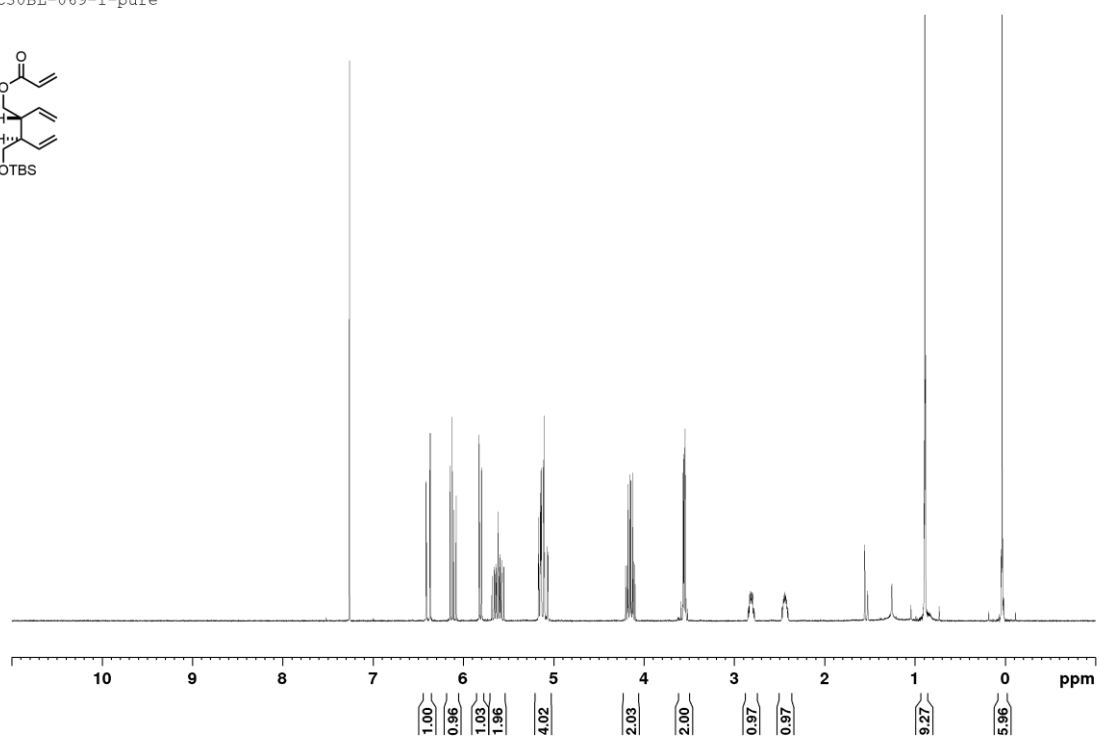
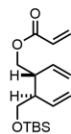
Exact Mass: 310.1964

Molecular Weight: 310.5038

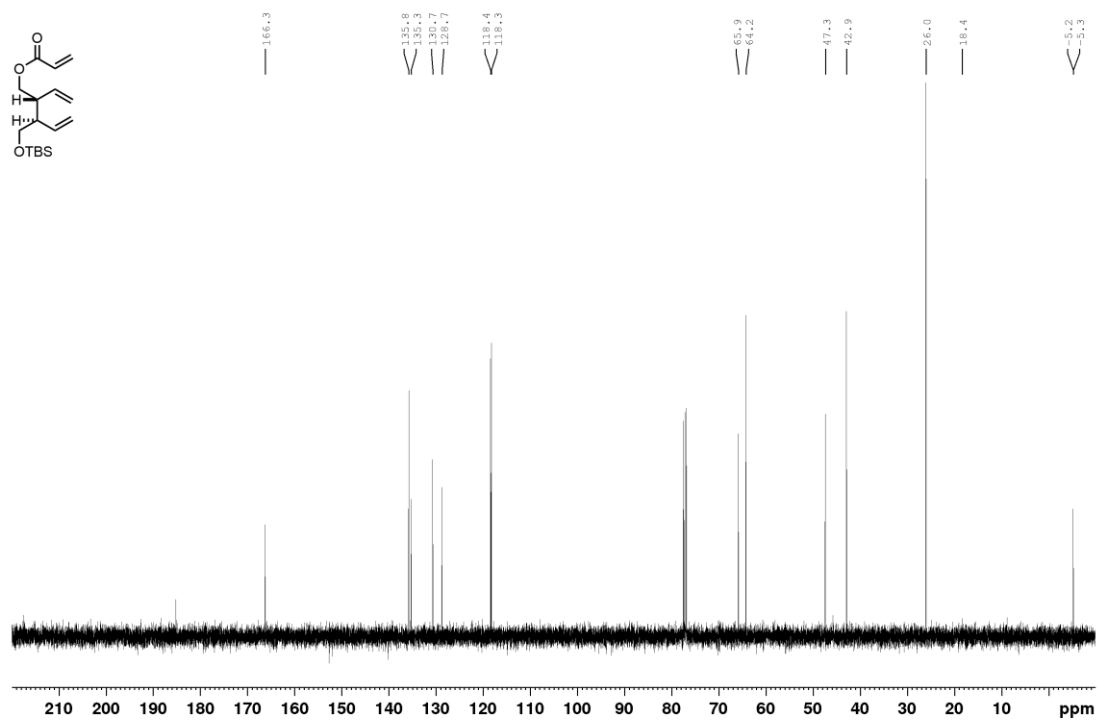
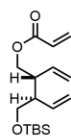
To a solution of alcohol **233-1** (74.2 mg, 0.289 mmol, 1 eq.) in CH₂Cl₂ (3.3 mL) was added DMAP (7 mg, 0.058 mmol, 0.2 eq.) and it was cooled to -78°C. DIPEA (0.35 mL, 2.03 mmol, 7 eq.) was quickly added, then dropwise acryloyl chloride (0.09 mL, 1.16 mmol, 4 eq.). The resulting mixture was let to warm up slowly to 5° in the acetone bath after the dry ice had been removed (took around 1.5 h and turned the mixture into a slight orange color). Reaction was quenched by addition of NH₄Cl (1 mL), which warmed it immediately to 20 °C. The suspension formed was diluted with Et₂O (35 mL) and some drops of water to dissolve all the precipitates. Phases were separated and the organic phase was washed NH₄Cl (2x1 mL), NaHCO₃ (1 mL) and finally brine (1 mL). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc:hexanes 1:10) to give the pure title compound as a slightly yellow oil (75.2 mg, 84%).

¹H NMR: (CDCl₃, 400 MHz) δ = 6.39 (dd, *J* = 17.4, 1.5 Hz, 1H), 6.11 (dd, *J* = 17.4, 10.4 Hz, 1H), 5.81 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.69-5.54 (m, 2H), 5.18-5.05 (m, 4H), 4.18 (dd, *J* = 11.0, 7.4 Hz, 1H), 4.12 (dd, *J* = 11.0, 7.0 Hz, 1H), 3.56 (d, *J* = 2.5 Hz, 1H), 3.54 (d, *J* = 1.1 Hz, 1H), 2.86-2.79 (m, 1H), 2.48-2.39 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 166.3, 135.8, 135.3, 130.7, 128.7, 118.4, 118.3, 65.9, 64.2, 47.3, 42.9, 26.0, 18.4, -5.2, -5.3; **HRMS (ESI):** calc. for [M+Na]⁺: 333.1856, found 333.1859; **IR (neat):** 2955, 2929, 2896, 2858, 1728, 1637, 1471, 1464, 1425, 1406, 1388, 1295, 1256, 1185, 1094, 1061, 986, 966, 919, 836, 809, 774, 720, 664; **Rf-value:** 0.53 (EtOAc:hexanes 1:10)

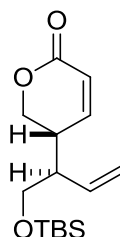
C30BL-069-1-pure



C30BL-069-1-pure



237 (+/-)-(R)-5-((R)-1-((tert-butyldimethylsilyl)oxy)but-3-en-2-yl)-5,6-dihydro-2H-pyran-2-one



Chemical Formula: C₁₅H₂₆O₃Si

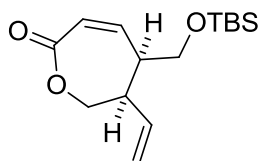
Exact Mass: 282.1651

Molecular Weight: 282.4506

To neat acrylate **234** (10 mg, 32.2 μ mol) in a sealed microwave tube under argon was added Hoveyda Grubb's 2nd generation catalyst (1 mg, 0.05 eq.) in 3 mL dichloroethane (freshly distilled from CaH₂ and subjected to 3 cycles of freeze and thaw) and rinsed with 2x2mL). The microwave vial was quickly opened and fitted with a new, unpierced lid. The green, clear solution was stirred at 80 °C for 4 d, during which the color turned from slightly green into slightly brown. The mixture was cooled to rt and concentrated in vacuo. The brown to black residue was purified by FC (EtOAc:hexanes 1:15) to recover clean starting material (4.3 mg, 43%) and give an inseparable 5:1 mixture of **237** and **238** (2.7 mg, 30%).

¹H NMR: (CDCl₃, 400 MHz) δ = 6.91 (dd, J = 9.9, 3.6 Hz, 1H), 6.01 (dd, J = 9.9, 2.1 Hz, 1H), 5.69 (ddd, J = 17.2, 10.3, 9.1 Hz, 1H), 5.21-5.09 (m, 2H), 4.46 (ddd, J = 11.2, 5.2, 1.0 Hz, 1H), 4.28 (dd, J = 11.2, 8.2 Hz, 1H), 3.72 (dd, J = 10.4, 4.5 Hz, 1H), 3.62 (dd, J = 10.4, 6.2 Hz, 1H), 2.90-2.82 (m, 1H), 2.35-2.26 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 164.0, 149.1, 135.7, 121.2, 118.8, 69.9, 64.2, 47.3, 34.4, 26.0, 18.4, -5.4 (2 signals); **HRMS (MALDI):** calc. for [M+H]⁺: 283.1724, found 283.1724; **IR (neat):** 2954, 2929, 2895, 2857, 2360, 2339, 1733, 1470, 1397, 1361, 1256, 1226, 1165, 1099, 1003, 924, 836, 778, 668; **Rf-value:** 0.34 (EtOAc:hexanes 1:5)

238 (+/-)- (5R,6R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-6-vinyl-6,7-dihydrooxepin-2(5H)-one



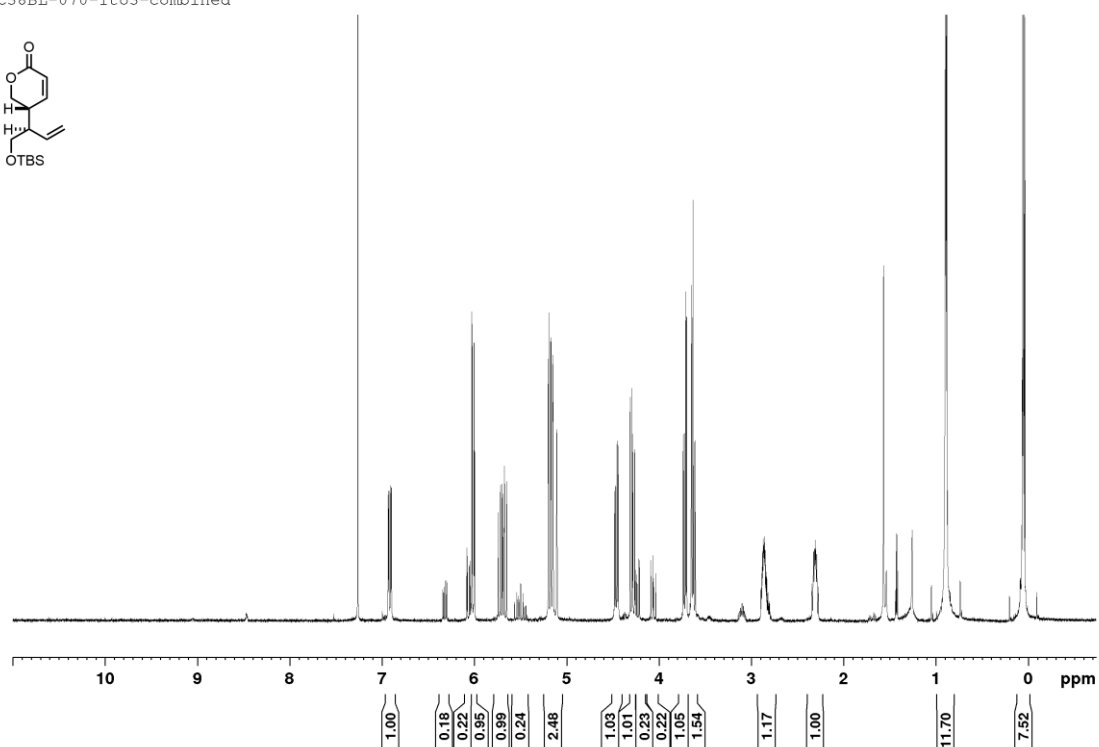
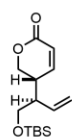
Chemical Formula: C₁₅H₂₆O₃Si

Exact Mass: 282.1651

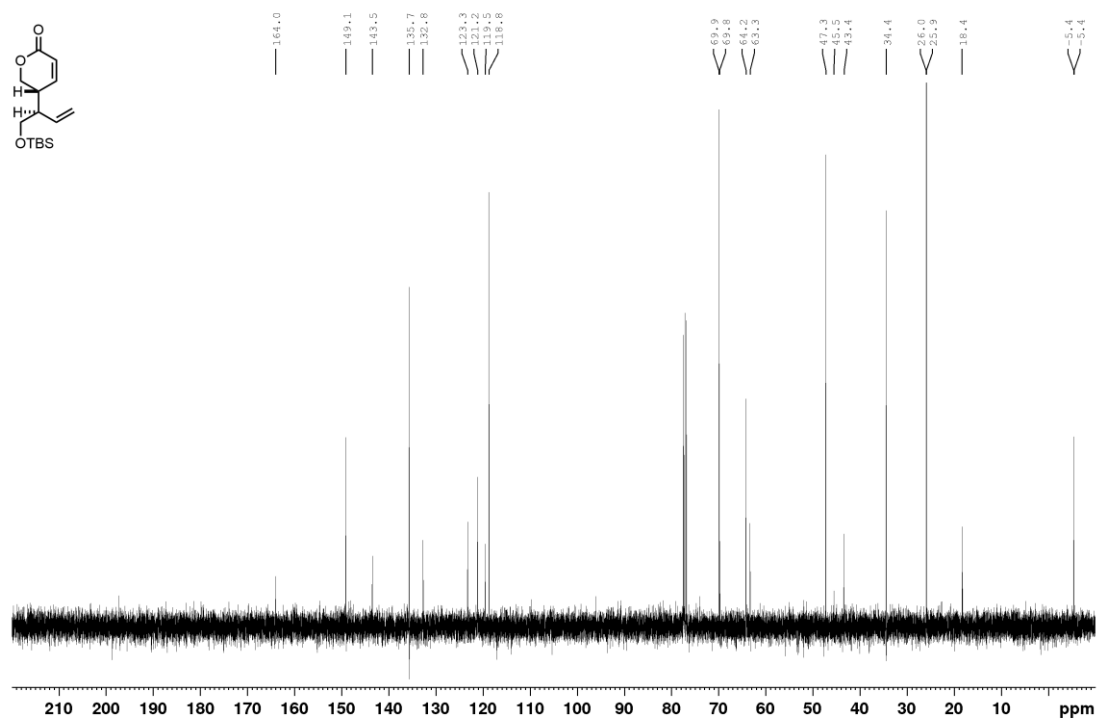
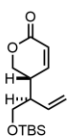
Molecular Weight: 282.4506

¹H NMR: (CDCl₃, 400 MHz): 6.32 (dd, *J* = 11.5, 5.1 Hz, 1H), 6.06 (dd, *J* = 10.5, 2.4 Hz, 1H), 5.57-5.42 (m, 1H), 5.21-5.09 (underlying, 2H), 4.23 (dd, *J* = 12.2, 5.2 Hz, 1H), 4.06 (dd, *J* = 12.2, 10.0 Hz, 1H), 3.66-3.60 (underlying, 1H), 3.15-3.05 (m, 1H), 2.85-2.78 (m, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); **¹³C NMR:** (carbonyl not found) 143.5, 132.8, 123.0, 119.5, 69.8, 63.3, 45.5, 43.4, 25.9, 18.3, -5.3 (only 1 signal visible)

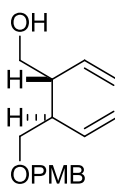
C38BL-070-1to3-combined



C38BL-070-1to3-combined



235 (+/-)-(2R,3R)-3-(((4-methoxybenzyl)oxy)methyl)-2-vinylpent-4-en-1-ol

Chemical Formula: C₁₆H₂₂O₃

Exact Mass: 262.1569

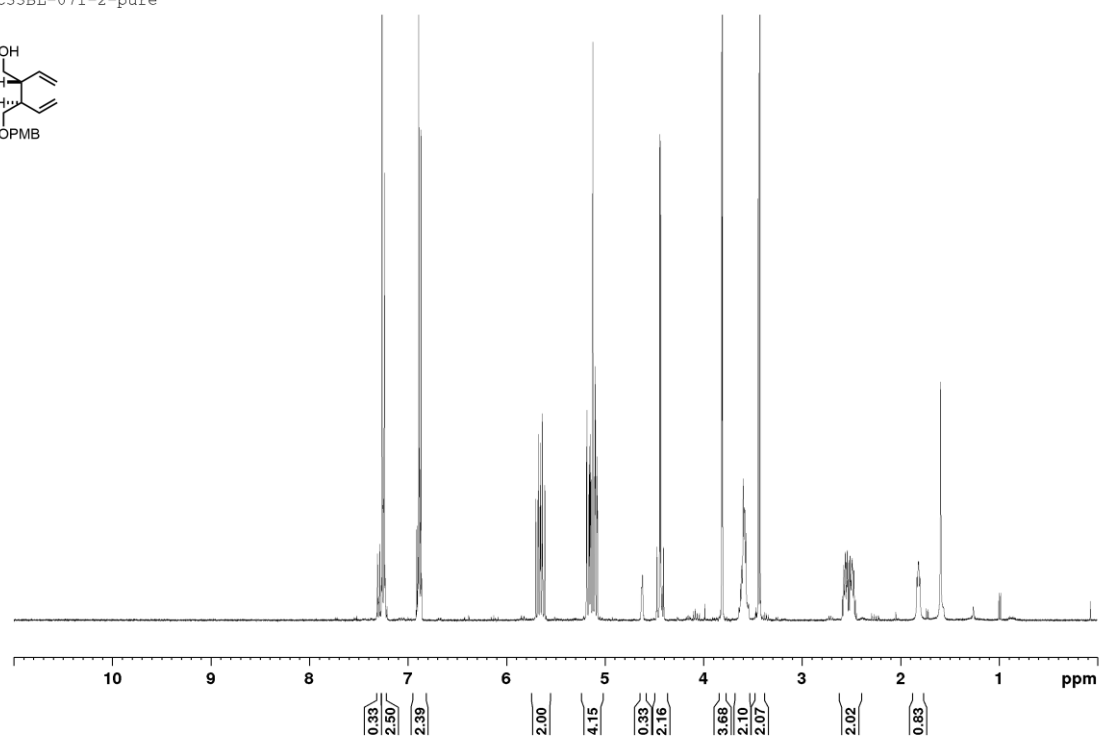
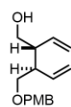
Molecular Weight: 262.3441

To a solution of **226** (160 mg, 1.135 mmol, 1 eq.) in toluene (1.41 mL) was added anisaldehyde dimeylacetal (0.22 mL, 1.24 mmol, 1.1 eq.), followed by TsOH·H₂O (1 mg). Molecular sieves (20 pieces, 4Å, granules, quickly heated to 300 with a heat gun under high vacuum) were added and the mixture was stirred at ambient temperature for 22 h. A white turbid precipitate formed during this time. The material was transferred into another flask, the molecular sieves were rinsed three times with toluene and the mixture was concentrated. The turbid oily material was directly subjected to the next reaction. **R_f-value of intermediate:** 0.54 (EtOAc:hexanes 1:10). The crude acetal was dissolved in toluene (7 mL) and cooled in an ice bath to 0 °C. DIBAL-H (1.17 mL, 1.2 M in MePh, 1.25 eq.) was added quickly. The reaction mixture was stirred at 0 °C for 1 h. Conversion was not complete, so additional DIBAL-H (0.25 mL, 0.27 eq.) was added. After 20 min, a very small amount of starting material remained, so a last portion of DIBAL (0.25 mL, 0.27 eq.) was added. After 10 min of stirring, the mixture was cooled in an ice/water bath. Methanol (0.1 mL, 2.2 eq.) was added dropwise slowly, so that the foam did not reach the top of the flask. Then HCl (7.6 mL, 2 M, aq.) was added, followed by Et₂O (20 mL). The mixture was stirred for about 10 min until the aqueous phase turned clear and slightly yellow. Phases were separated and the aqueous phase was extracted with Et₂O (2x20 mL). The combined organic phases were washed with NaHCO₃ (5.7 mL, aq., sat., evolution of gas), then brine (5.7 mL), dried over MgSO₄, filtered and concentrated. The material was purified by flash chromatography (EtOAc:hexanes 1:3) to give the title compound as a clear colorless oil (269 mg, 91%)

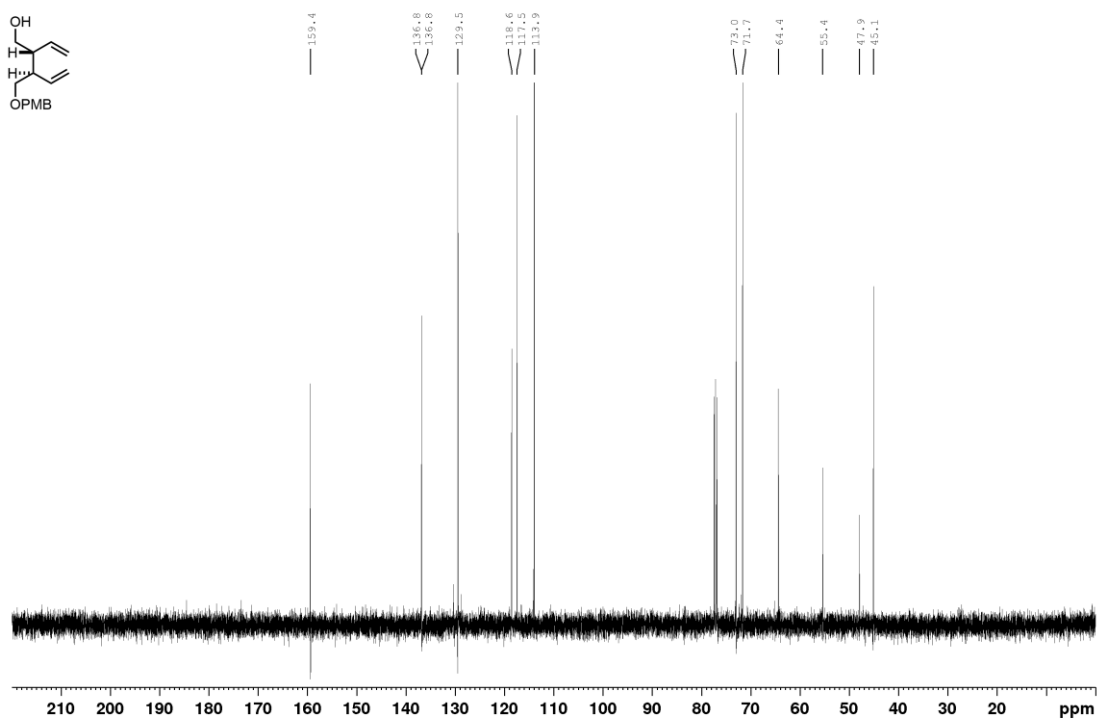
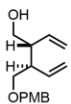
¹H NMR: (CDCl₃, 400 MHz) δ = 7.27-7.22 (m, 2H), 6.90-6.87 (m, 2H), 5.71-5.60 (m, 2H), 5.20-5.06 (m, 4H), 4.44 (dd, *J* = 15.3, 11.6 Hz, 2H), 3.81 (s, 3H), 3.65-3.52 (m, 2H), 3.44 (s, 1H), 3.42 (s, 1H), 2.60-2.44 (m, 2H), 1.82 (dd, *J* = 7.1, 5.1 Hz, 1H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 159.4, 136.8 (2 signals), 129.5, 118.6, 117.5, 113.9, 73.0, 71.7, 64.4, 55.4, 47.9, 45.1; **HRMS (MALDI):** calc. for [M+H]⁺: 263.1642, found 263.1642; **IR (neat):** 3406, 2934, 2904, 2862, 2838, 1637,

1612, 1586, 1512, 1464, 1443, 1424, 1362, 1301, 1245, 1211, 1174, 1083, 1033, 996, 953, 917, 845, 818, 756, 724, 716; **Rf-value:** 0.48 (EtOAc:hexanes 1:1)

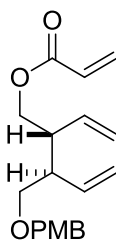
C33BL-071-2-pure



C33BL-071-2-pure



236 (+/-)-(2R,3R)-3-(((4-methoxybenzyl)oxy)methyl)-2-vinylpent-4-en-1-yl acrylate

Chemical Formula: C₁₉H₂₄O₄

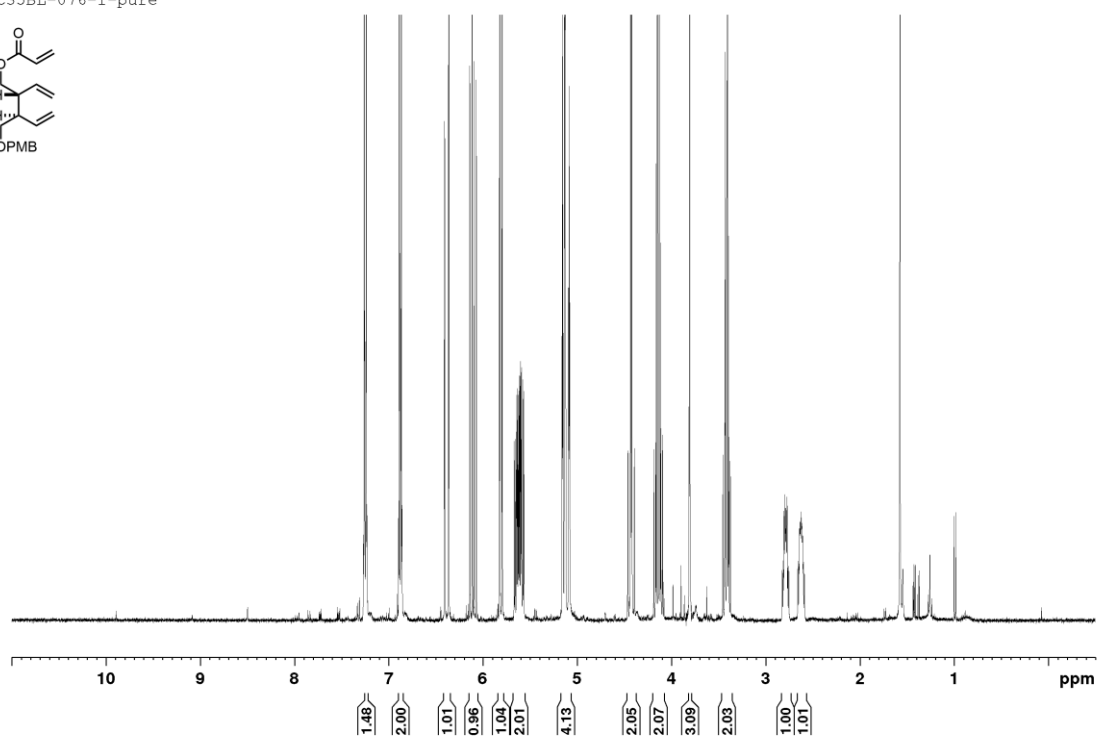
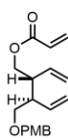
Exact Mass: 316.1675

Molecular Weight: 316.3915

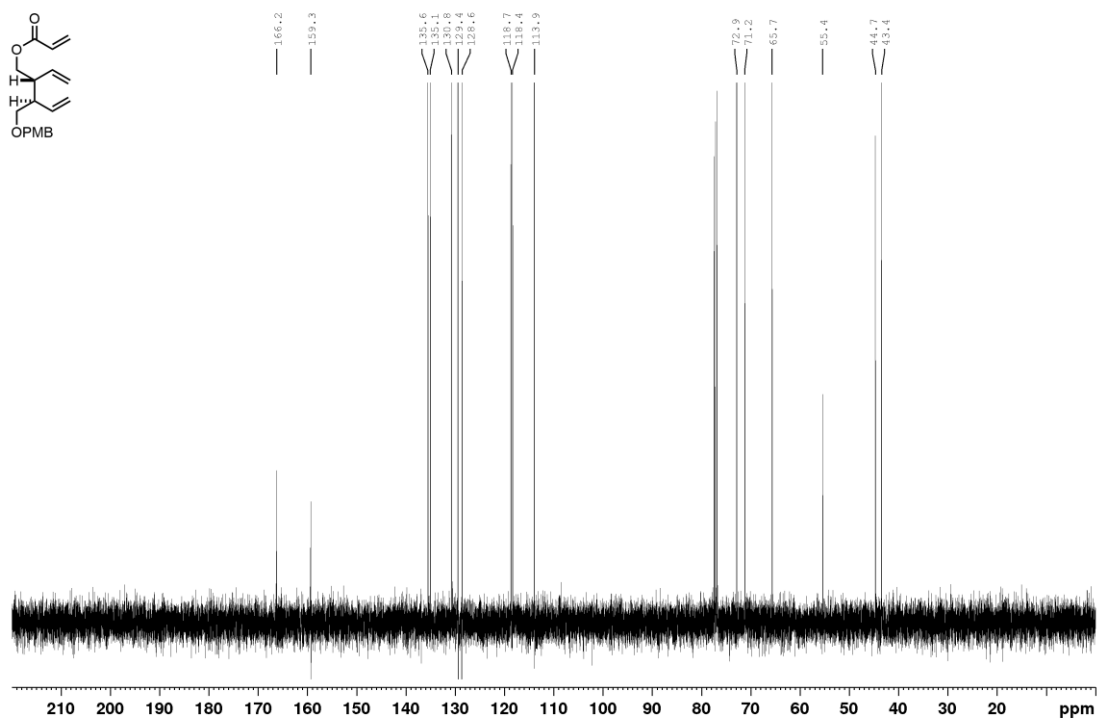
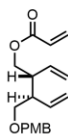
To a solution of 235 (49.2 mg, 0.188 mmol, 1 eq.) in CH₂Cl₂ was added DMAP (4.6 mg, 37.5 μmol, 0.2 eq.) and it was cooled to -78°C. DIPEA (0.23 mL, 1.31 mmol, 7 eq.) was quickly added, then dropwise acryloyl chloride (0.06 mL, 0.75 mmol, 3 eq.), upon which it turned cloudy. The resulting mixture was let to warm up slowly overnight, during which the mixture changed into a cloudy strong yellow color. Reaction was quenched by addition of NH₄Cl (1 mL, sat., aq.). The suspension formed was diluted with Et₂O (35 mL) and some drops of water to dissolve all the precipitates. Phases were separated and the organic phase was washed NH₄Cl (2x1 mL, sat., aq.), then NaHCO₃ (1 mL, sat., aq.) and finally brine (1 mL). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by FC (Et₂O:hexanes 1:10) to give the title compound as a slightly yellow oil (43.8 mg, 74%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.27-7.22 (m, 2H), 6.90-6.85 (m, 2H), 6.38 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.10 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.81 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.68-5.56 (m, 2H), 5.17-5.14 (m, 1H), 5.14-5.11 (m, 2H), 5.10-5.07 (m, 1H), 4.43 (dd, *J* = 16.5, 11.6 Hz, 2H), 4.16 (dd, *J* = 10.9, 7.5 Hz, 1H), 4.11 (dd, *J* = 10.9, 7.1 Hz, 1H), 3.81 (s, 3H), 3.43 (dd, *J* = 9.3, 7.8 Hz, 1H), 3.39 (dd, *J* = 9.4, 6.4 Hz, 1H), 2.83-2.74 (m, 1H), 2.66-2.58 (m, 1H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 166.2, 159.3, 135.6, 135.1, 130.8, 129.4, 128.6, 118.7, 118.4, 113.9, 72.9, 71.2, 65.7, 55.4, 44.7, 43.4; **HRMS (ESI-TOF):** calc. for [M+Na]⁺: 339.1567, found 339.1567; **IR (neat):** 3076, 2853, 2838, 1723, 1636, 1613, 1586 1512, 1464, 1444, 1423, 1406, 1361, 1297, 1246, 1184, 1090, 1061, 1034, 987, 920, 846, 809, 757, 731; **Rf-value:** 0.66 (EtOAc:hexanes 1:3)

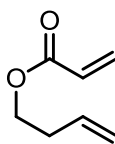
C35BL-076-1-pure



C35BL-076-1-pure



246 but-3-en-1-yl acrylate

Chemical Formula: C₇H₁₀O₂

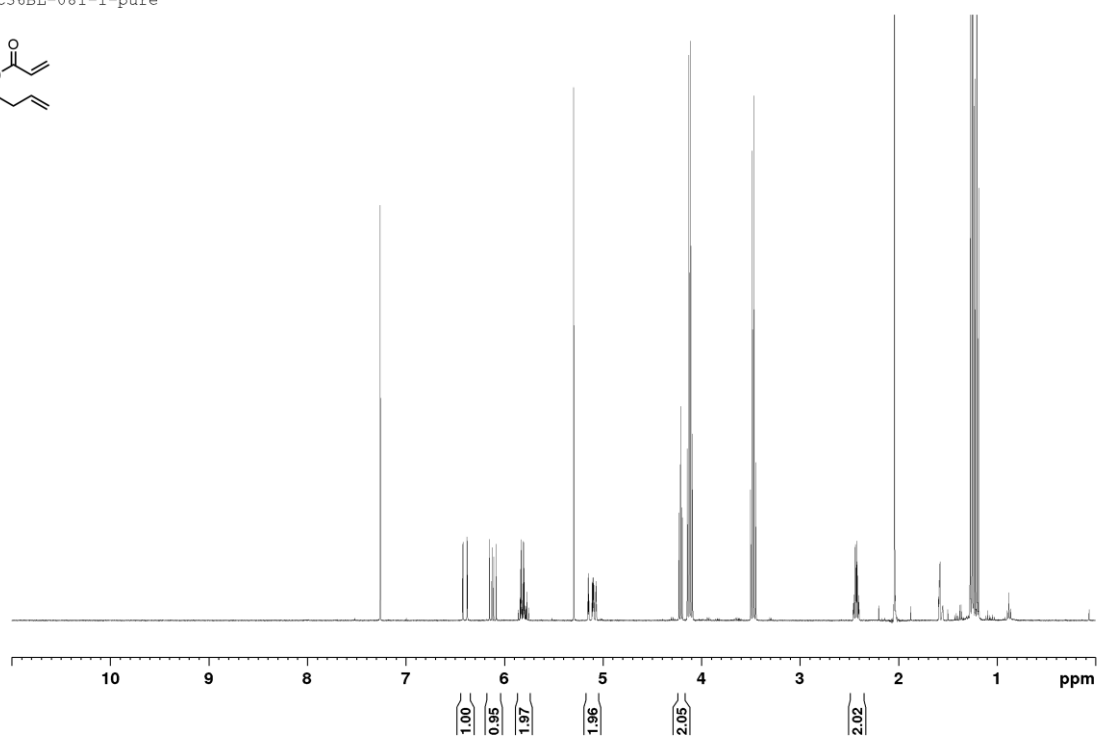
Exact Mass: 126.0681

Molecular Weight: 126.1531

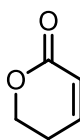
To a solution of homoallyl alcohol (200 mg, 2.77 mmol, 1 eq.) in CH₂Cl₂ (32 mL) was added DMAP (68 mg, 0.55 mmol, 0.2 eq.) and it was cooled to -78°C. DIPEA (3.4 mL, 19.4 mmol, 7 eq.) was quickly added, then dropwise acryloyl chloride (0.09 mL, 11.1 mmol, 4 eq.), upon which it turned cloudy. The resulting mixture was let to warm up to -20 °C over 3h, during which the mixture changed into a cloudy strong yellow color. Reaction was quenched by addition of NH₄Cl (12 mL, sat., aq.). The suspension formed was diluted with Et₂O (420 mL) and some drops of water to dissolve all the precipitates. Phases were separated and the organic phase was washed NH₄Cl (2x12 mL, sat., aq.), then NaHCO₃ (12 mL, sat., aq.) and finally brine (12 mL). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by FC (Et₂O:pentane 1:10) to give the title compound as a strongly odorous yellow oil (yield not determined, contained residual Et₂O, EtOAc CH₂Cl₂).

Rf-value: 0.44 (Et₂O:pentane 1:0), 0.91 (Et₂O neat)

C36BL-081-1-pure



247 5,6-dihydro-2H-pyran-2-one

Chemical Formula: C₅H₆O₂

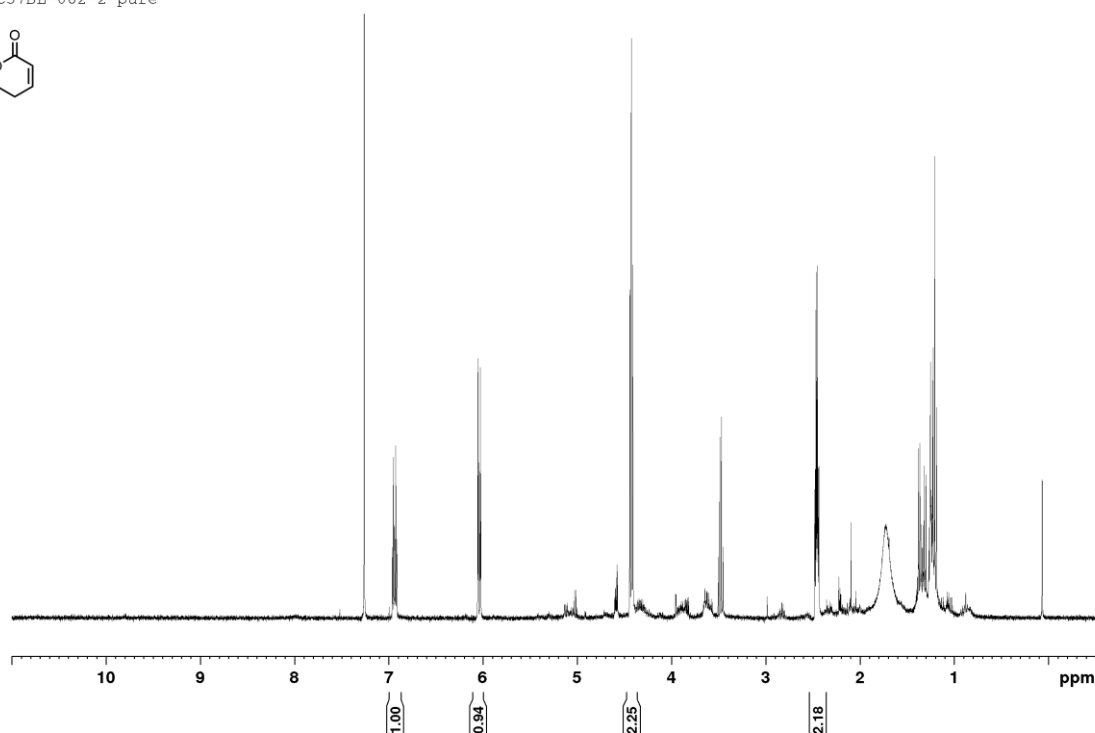
Exact Mass: 98.0368

Molecular Weight: 98.0999

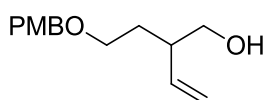
To Grubb's 2nd generation catalyst (5.4 mg, 6.4 μ mol, 0.1 eq.) in a sealed HPLC vial under argon was added 1.27 mL of a solution of acrylate **246** (8.8 mg in 1.4 mL CH₂Cl₂). The top of the vial was sealed with parafilm and the mixture was stirred at 40 °C for 64 h. TLC showed more than 90 % conversion (co-spotted with a sample commercially available product). The brown-black reaction mixture was quenched with ethyl vinyl ether (0.3 mL), stirred for 10 min, then concentrated *in vacuo*. The black residue was purified by FC (neat Et₂O) to give the title compound (2.9 mg, 29%).

Rf-value: 0.34 (Et₂O neat)

C37BL-082-2-pure



249 (+/-)-2-(2-((4-methoxybenzyl)oxy)ethyl)but-3-en-1-ol

Chemical Formula: C₁₄H₂₀O₃

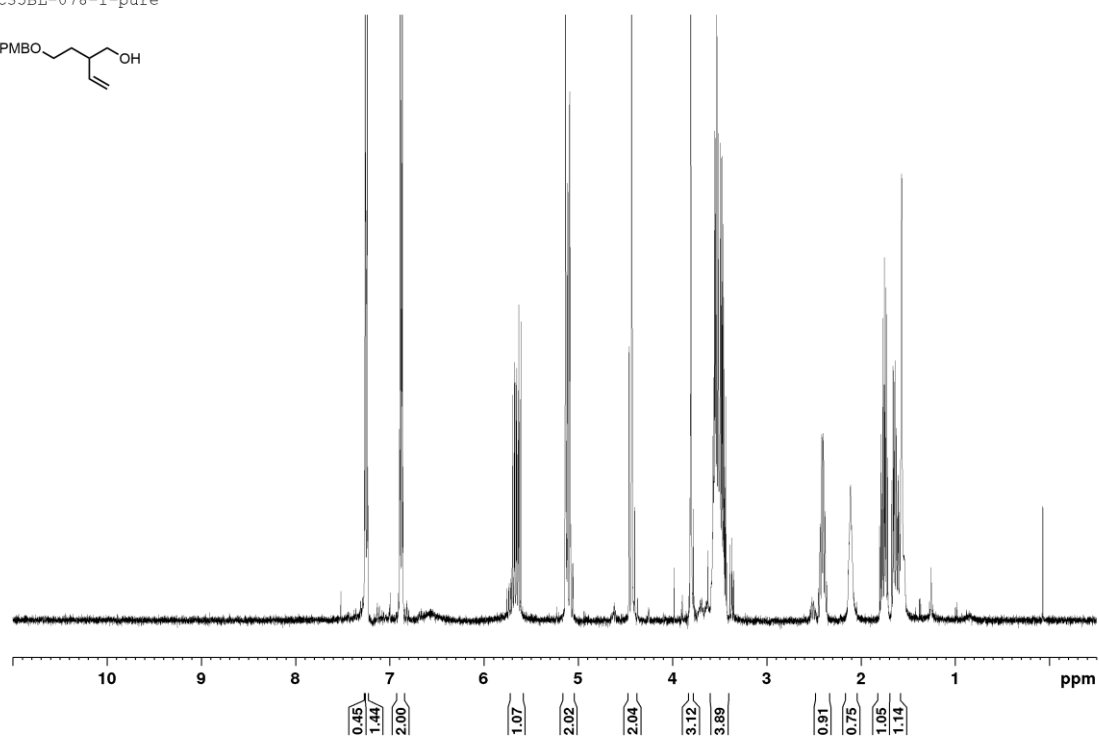
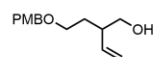
Exact Mass: 236.1412

Molecular Weight: 236.3068

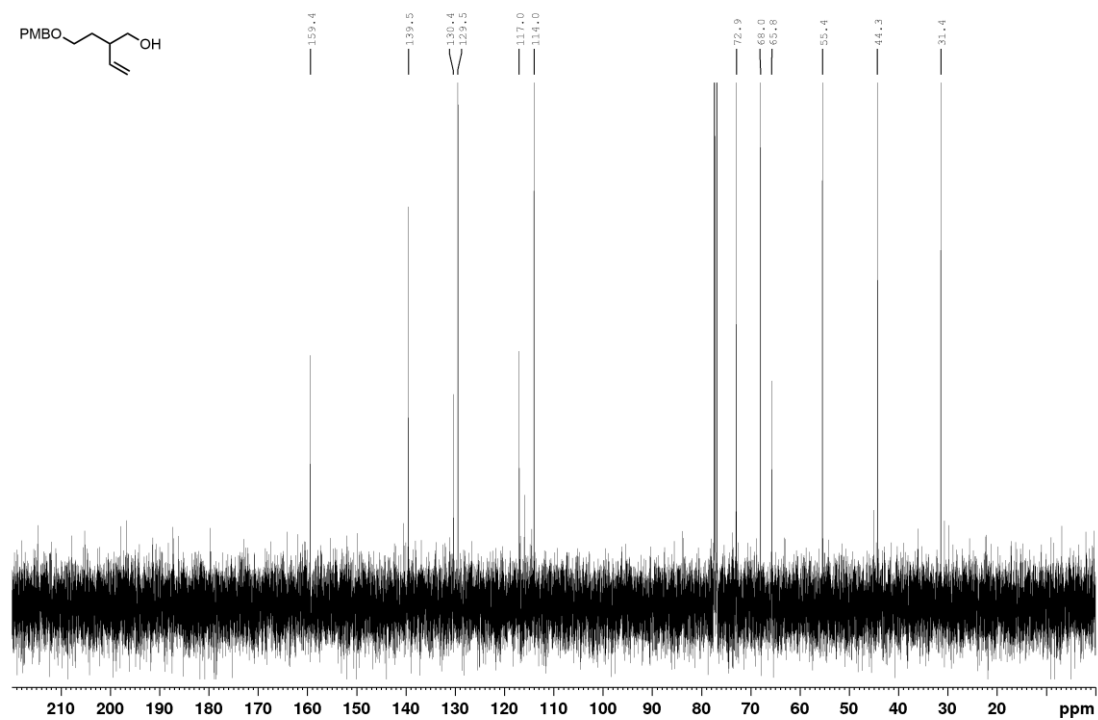
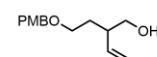
To a solution of alcohol **181** (200 mg, 0.868 mmol, 1 eq.) in CH₂Cl₂ (0.83 ml) was added solid (-)-CSA (10.1 mg, 43 μmol, 0.05 eq.). The reaction mixture was cooled to 0 °C, then a solution of *p*-methoxybenzyltrichloroacetimidate **248** (307 mg, 1.09 mmol, 1.25 eq.) in CH₂Cl₂ (0.41 mL) was added dropwise and rinsed with CH₂Cl₂ (0.41 mL). The mixture was allowed to warm to room temperature in the bath overnight and stirring was continued for a total of 17 h. Then MeOH (4 mL) was added all at once, followed by additional CSA (30 mg, 129 μmol, 0.15 eq.). After 20 min, all the doubly protected material had reacted, the material was concentrated *in vacuo* and directly loaded onto a column. Purification by FC (EtOAc:hexanes) gave the title compound as a clear, slightly yellow oil (150.2 mg, 76 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.28-7.22 (m, 2H), 6.91-6.85 (m, 2H), 5.65 (ddd, *J* = 16.8, 10.7, 8.3 Hz, 1H), 5.15-5.07 (m, 2H), 4.47-4.39 (dd-like multiplet, 2H), 3.80 (s, 1H), 3.60-3.42 (m, 4H), 2.42 (sextet, *J* = 6.9 Hz, 1H), 2.11 (s, *br*, 1H), 1.76 (ddt, *J* = 14.2, 8.0, 5.8 Hz, 1H), 1.63 (ddt, *J* = 14.2, 7.7, 5.6 Hz, 1H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 159.4, 139.5, 130.4, 129.5, 117.0, 114.0, 72.9, 68.0, 65.8, 55.4, 44.3, 31.4; **HRMS (EI):** calc. for [M]⁺: 236.1407, found 236.1404; **IR (neat):** 3370, 3184, 3074, 2934, 2861, 2838, 1726, 1640, 1612, 1587, 1512, 1464, 1442, 1421, 1363, 1301, 1245, 1210, 1174, 1079, 1033, 998, 917, 821, 779, 756, 684, 672, 637; **R_f-value:** 0.4 (EtOAc:hexanes 1:1)

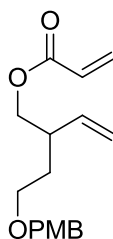
C35BL-078-1-pure



C35BL-078-1-pure



250 (+/-)-2-(2-((4-methoxybenzyl)oxy)ethyl)but-3-en-1-yl acrylate

Chemical Formula: C₁₇H₂₂O₄

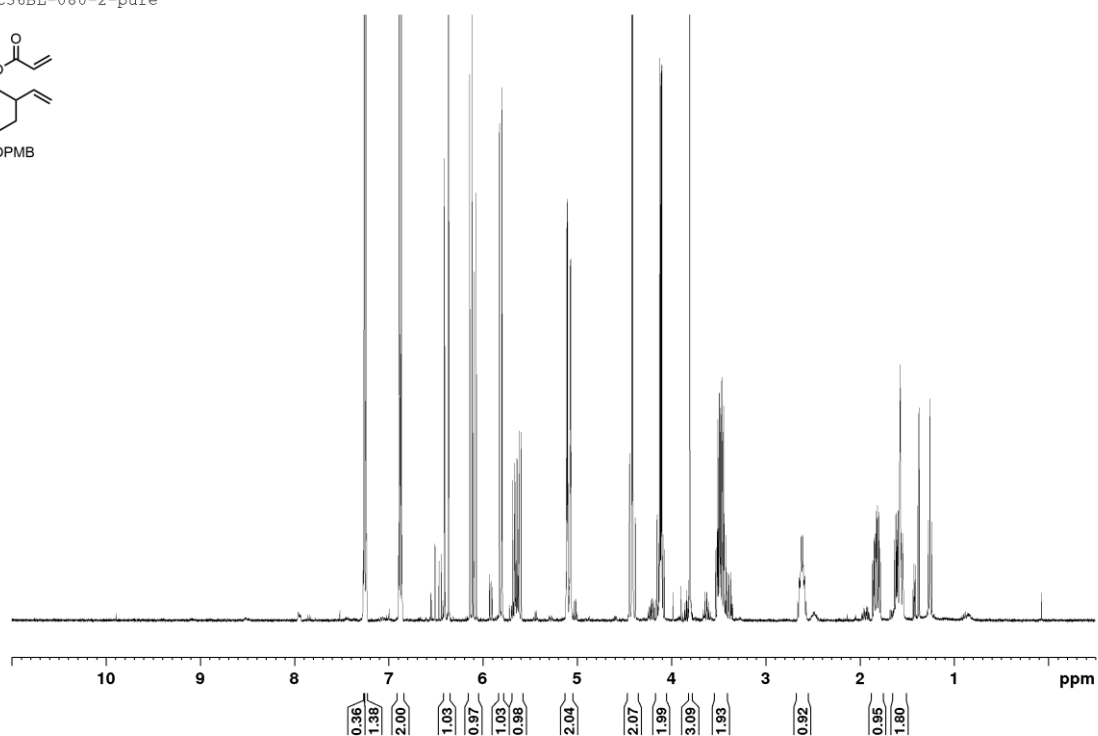
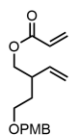
Exact Mass: 290.1518

Molecular Weight: 290.3542

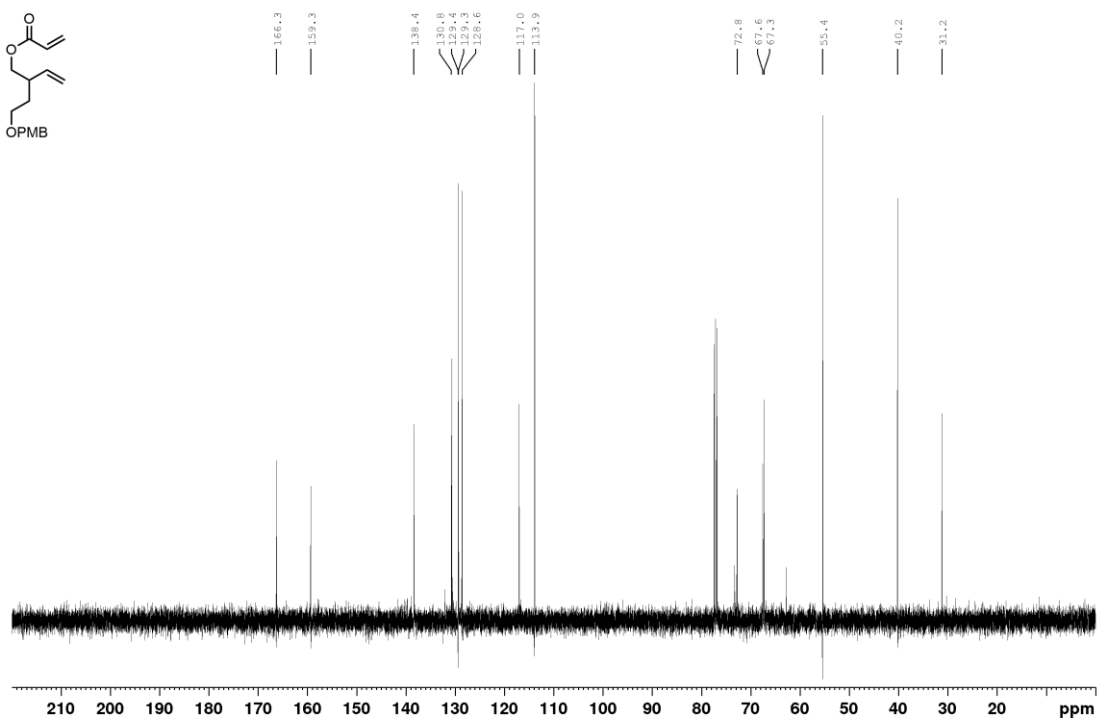
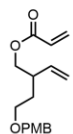
To a solution of **249** (50 mg, .212 mmol, 1 eq.) in CH₂Cl₂ (2.43 mL) was added DMAP (5.2 mg, 42 μmol, 0.2 eq.) and it was cooled to -78°C. DIPEA (0.26 mL, 1.5 mmol, 7 eq.) was quickly added, then dropwise acryloyl chloride (0.07 mL, 0.85 mmol, 4 eq.), upon which it turned cloudy. The resulting mixture was stirred for 1 h at ambient temperature then quenched by addition of NH₄Cl (1 mL, sat., aq.). The suspension formed was diluted with Et₂O (35 mL) and some drops of water to dissolve all the precipitates. Phases were separated and the organic phase was washed NH₄Cl (2x1 mL sat., aq.), then NaHCO₃ (1 mL, sat., aq.) and finally brine (1 mL). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by FC (Et₂O:hexanes 1:10) to give the title compound as a clear colorless oil (38.5 mg, purity 95%, 60%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.28-7.22 (m, 2H), 6.90-6.85 (m, 2H), 6.39 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.10 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.81 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.65 (ddd, *J* = 17.6, 9.9, 8.5 Hz, 1H), 5.13-5.09 (m, 1H), 5.09-5.05 (m, 1H), 4.41 (dd, *J* = 14.8, 11.5 Hz, 2H), 4.13 (dd, *J* = 10.9, 6.8 Hz, 1H), 4.09 (dd, *J* = 10.9, 6.1 Hz, 1H), 3.80 (s, 1H), 3.50 (ddd, 9.3, 6.8, 5.5 Hz, 1H), 3.45 (ddd, 9.3, 7.6, 6.4 Hz, 1H), 2.67-2.54 (m, 1H), 1.87-1.77 (m, 1H), 1.64-1.56 (m, 1H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 166.3, 159.3, 138.4, 130.8, 129.4, 129.3, 128.6, 117.0, 113.9, 72.8, 67.6, 67.3, 55.4, 40.2, 31.2; **HRMS (EI):** calc. for [M+H]⁺: 291.1591, found 291.1591; **IR (neat):** 3076, 2937, 2859, 1723, 1636, 1613, 1586, 1512, 1464, 1406, 1364, 1297, 246, 1184, 1093, 1059, 1034, 985, 919, 809, 756, 707, 688, 666, 638; **Rf-value:** 0.52 (EtOAc:hexanes 1:3)

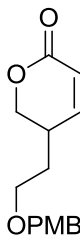
C36BL-080-2-pure



C36BL-080-2-pure



251 (+/-)-5-(2-((4-methoxybenzyl)oxy)ethyl)-5,6-dihydro-2H-pyran-2-one

Chemical Formula: C₁₅H₁₈O₄

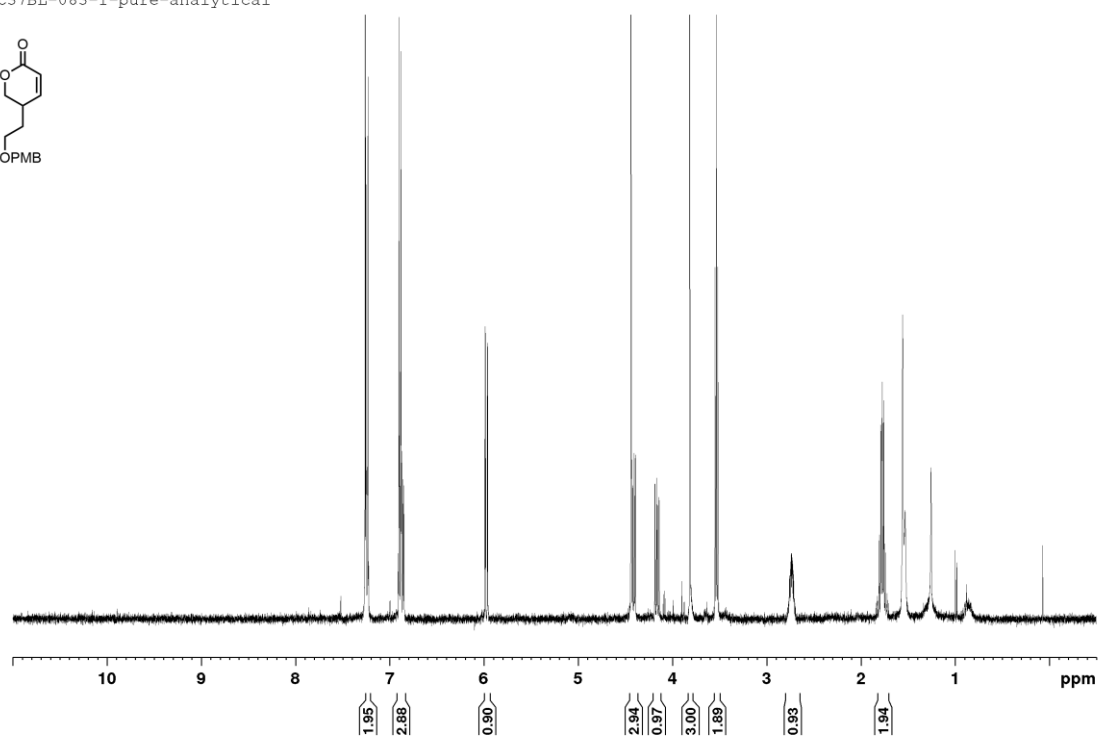
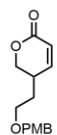
Exact Mass: 262.1205

Molecular Weight: 262.3010

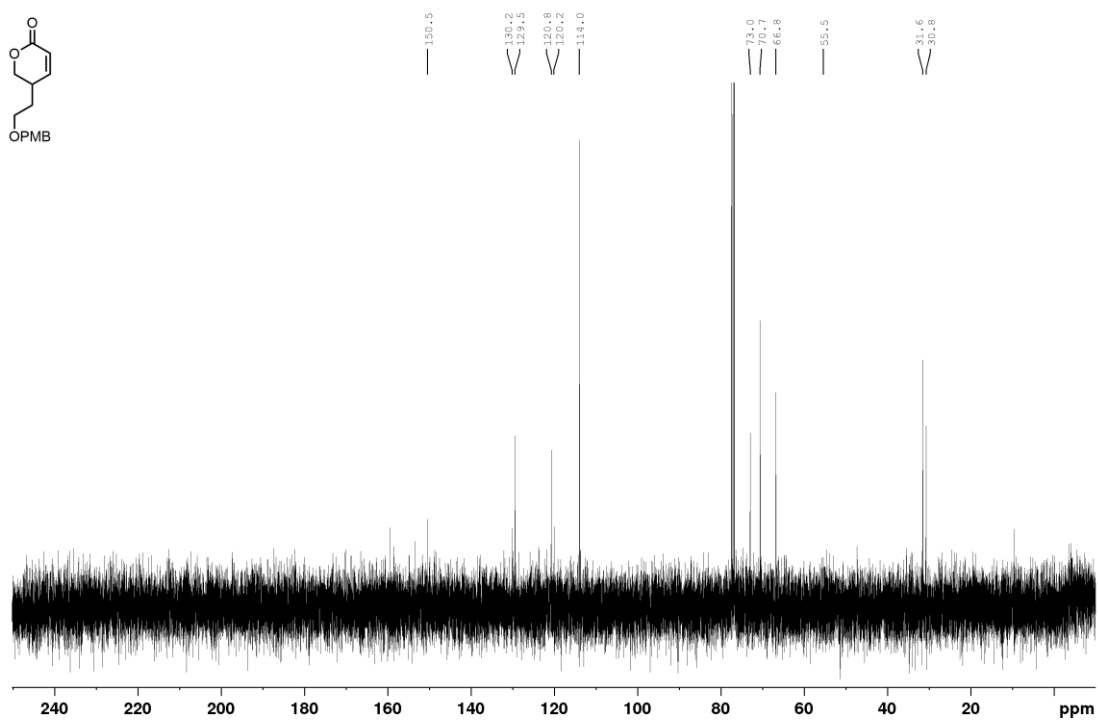
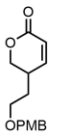
Grubb's 2nd generation catalyst (2.9 mg, 3.4 μ mol, 0.1 eq.) was weighed into an HPLC vial under normal atmosphere, equipped with a stir bar and gently flushed with argon before the lid was closed. The lid was sealed with parafilm on the side. 0.69 mL of a solution of **250** were added (to 18.4 mg of starting material under Argon was added 1.27 mL dichloromethane). The septum of the lid was sealed off with parafilm. The solution was stirred at 40 °C for 64 h. Ethylvinyl ether (0.15 mL) was added and stirred for 5 min, then the mixture was directly purified by FC (pure CH₂Cl₂, then EtOAc:hexanes 1:1) to give the title compound as a clear colorless oil (5.4 mg, 60 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.27-7.21 (m, 2H), 6.92-6.86 (m, 2H), 6.89-6.84 (m, 1H), 5.97 (dd, J = 9.8, 1.8 Hz, 1H), 4.44 (s, 2H), 4.41 (ddd, J = 11.2, 4.8, 0.7 Hz, 1H), 4.16 (ddd, J = 11.2, 6.8, 0.5 Hz, 1H), 3.81 (s, 3H), 3.53 (t, J = 5.9 Hz, 2H), 2.78-2.68 (m, 1H), 1.85-1.70 (m, 2H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 159.2, 150.5, 130.2, 129.5, 120.8, 120.2, 114.0, 73.0, 70.7, 66.8, 55.5, 31.6, 30.8; **HRMS (MALDI-TOF):** calc. for [M+Na]⁺: 285.1097, found 285.1097; **IR (neat):** 2923, 2855, 2357, 2326, 1724, 1650, 1612, 1586, 1558, 1541, 1512, 1464, 1398, 1366, 1301, 1245, 1174, 1087, 1031, 931, 818, 789, 757, 693; **Rf-value:** 0.39 (EtOAc:hexanes 1:1)

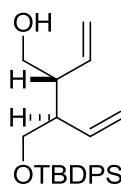
C37BL-083-1-pure-analytical



C37BL-083-1-pure-analytical



254 (+/-)-(2R,3R)-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2-vinylpent-4-en-1-ol

Chemical Formula: C₂₄H₃₂O₂Si

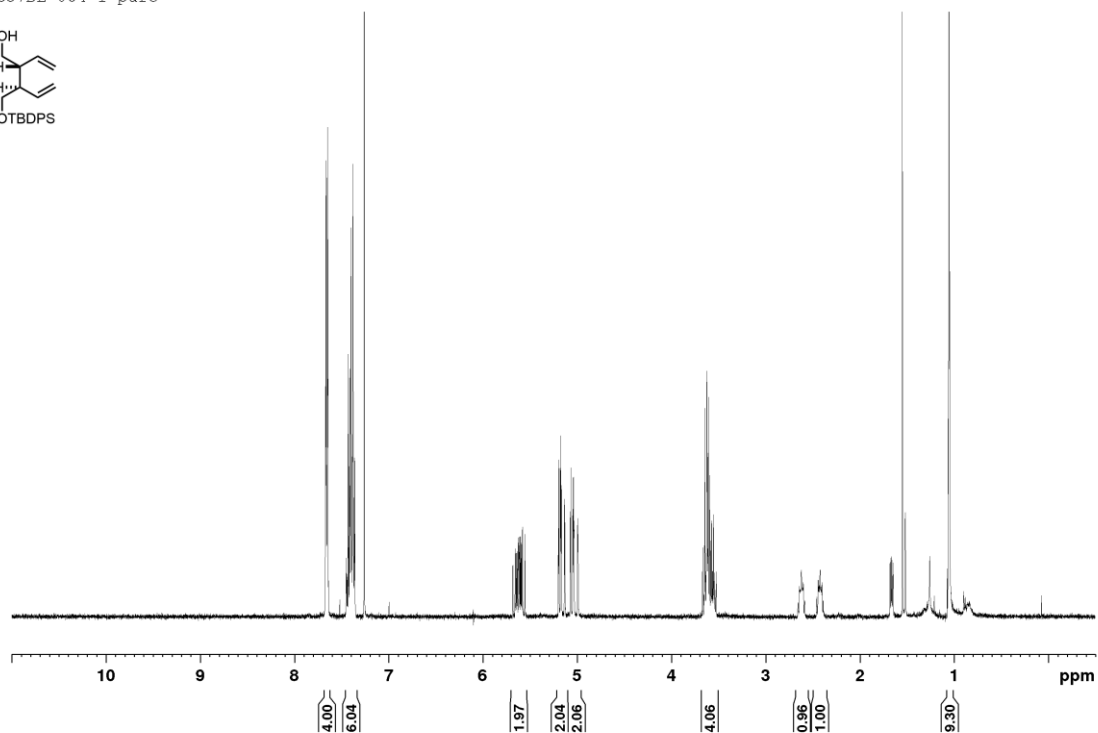
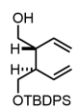
Exact Mass: 380.2172

Molecular Weight: 380.5952

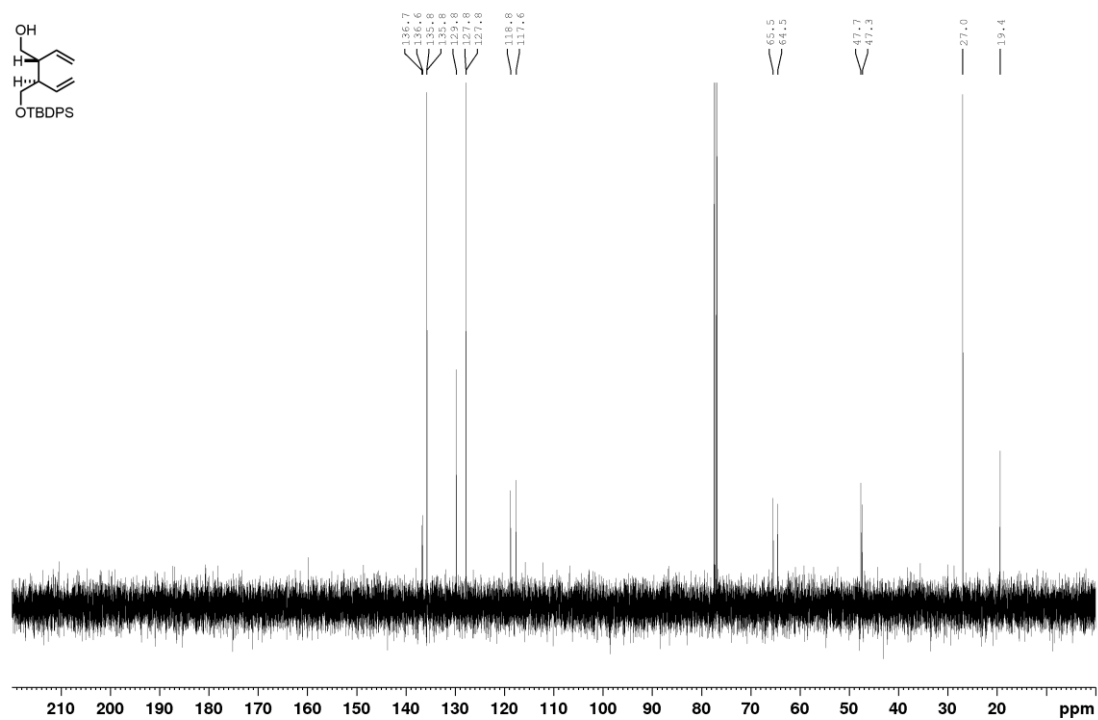
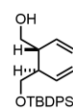
To a solution of **226** (100 mg, 0.70 mmol, 1 eq.) in THF (2.81 mL) in an ice bath was added *n*-BuLi (0.46 mL, 1.6 M in hexanes, 0.74 mmol, 1.05 eq.). Solid DMAP (17.2 mg, 0.14 mmol, 0.2 eq.) was added, then TBDPSCI (0.19 mL, 0.70 mmol, 1 eq.) was added dropwise and the mixture was stirred at ambient temperature for 20 h. Reaction seemed mostly complete by TLC and was quenched by addition of water (1 mL). The solvent was removed by rotary evaporation and material was dissolved in EtOAc (3 mL), phases were separated and aqueous layer was extracted with EtOAc (3x3 mL). The combined organic extracts were washed with brine (1 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by FC (EtOAc:hexanes 1:7) to give the title compound as a clear, colourless oil (212.1 mg, 79 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.68-7.63 (m, 4H), 7.46-7.35 (m, 6H), 5.62 (dddd, *J* = 17.0, 13.9, 10.3, 9.3 Hz, 2H), 5.18 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.15 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.06 (dd, *J* = 10.4, 1.9 Hz, 1H), 5.01 (dd, *J* = 17.1, 1.9 Hz, 1H), 3.68-3.51 (m, 4H), 2.66-2.57 (m, 1H), 2.47-2.37 (m, 1H), 1.65 (dd, *J* = 8.0, 4.5 Hz, 1H), 1.05 (s, 9H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 136.7, 136.6, 135.8 (2 signals), 129.8, 127.8 (2 signals), 118.8, 117.6, 65.5, 64.5, 47.7, 47.3, 27.01, 19.4; **HRMS (MALDI-TOF):** calc. for [M+H]⁺: 381.2244, found 381.2244; **IR (neat):** 3391, 3072, 3050, 2999, 2957, 2931, 2858, 2361, 1639, 1590, 1472, 1427, 1389, 1361, 1307, 1261, 1188, 1108, 1085, 996, 917, 823, 802, 739, 701; **Rf-value:** 0.29 (EtOAc:hexanes 1:5)

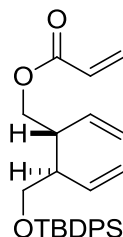
C37BL-084-1-pure



C37BL-084-1-pure



255 (+/-)-(2R,3R)-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2-vinylpent-4-en-1-yl acrylate



Chemical Formula: $C_{27}H_{34}O_3Si$

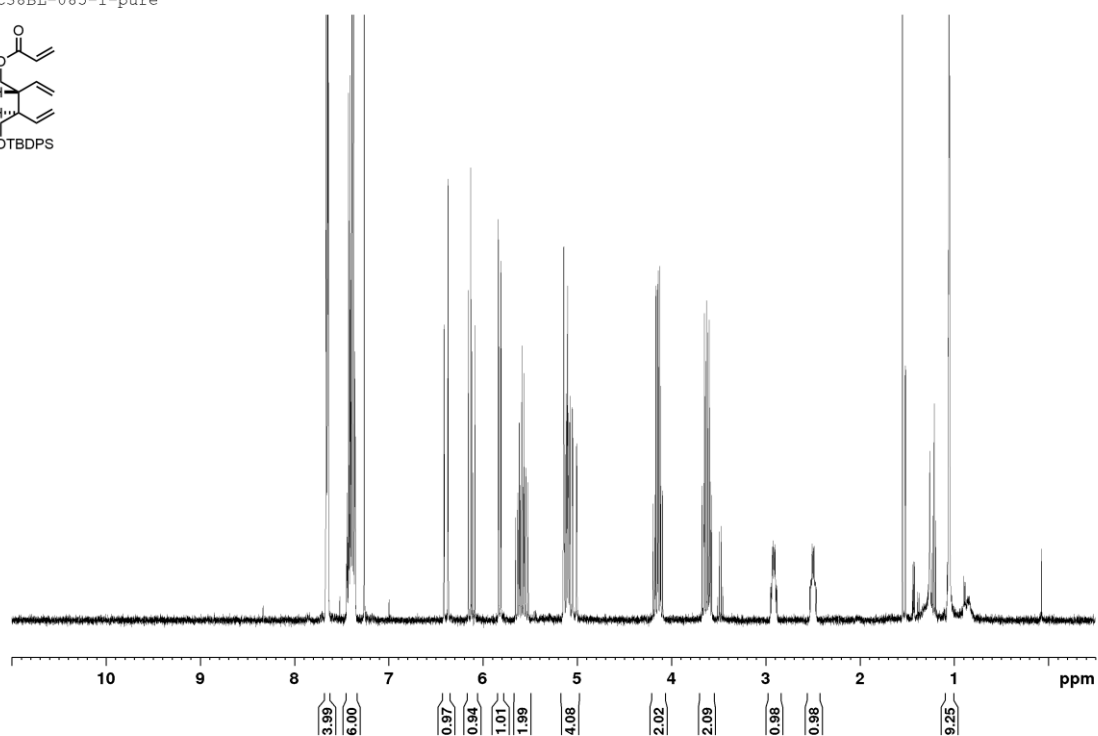
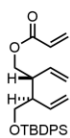
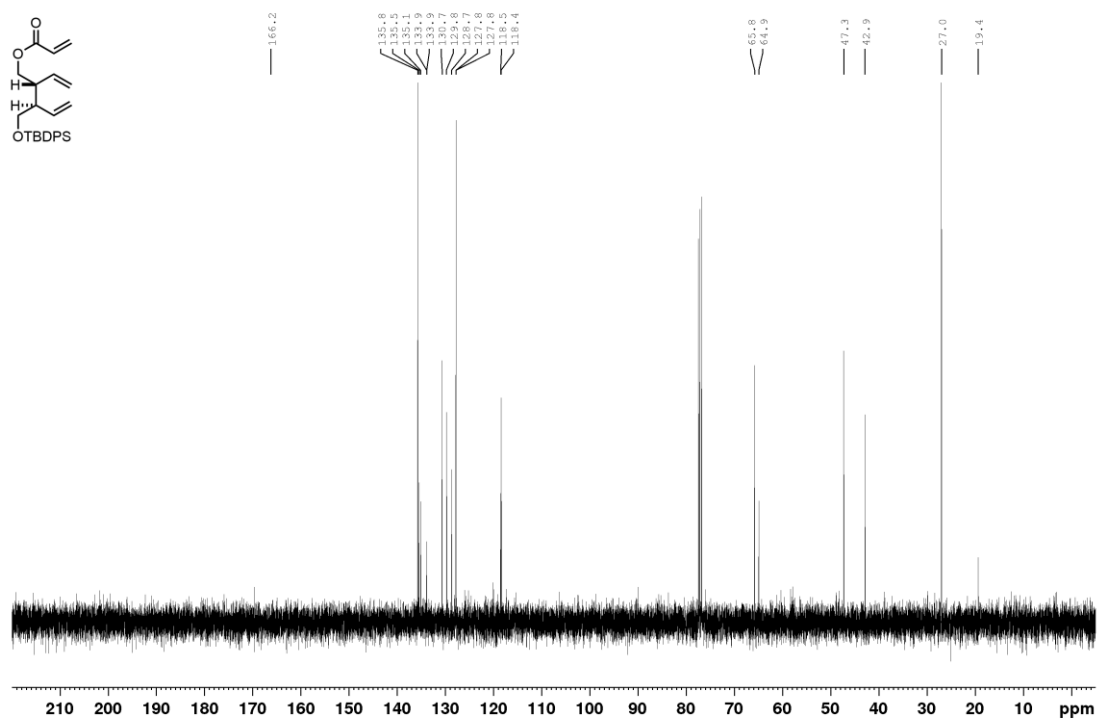
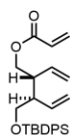
Exact Mass: 434.2277

Molecular Weight: 434.6426

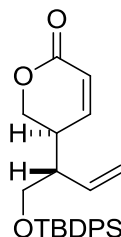
To a solution of **254** (62 mg, 0.13 mmol, 1 eq.) in CH_2Cl_2 was added DMAP (4 mg, 33 μ mol, 0.2 eq.) and it was cooled to $-78^\circ C$. DIPEA (0.2 mL, 1.14 mmol, 7 eq.) was quickly added, then dropwise acryloyl chloride (0.05 mL, 0.65 mmol, 4 eq.). The resulting mixture was let to warm up slowly to 5° in the acetone bath after the dry ice had been removed (took around 1.5 h and turned the mixture into a slight yellow color). Reaction was quenched by addition of NH_4Cl (1 mL, sat., aq.), which warmed it immediately to $20^\circ C$. The suspension formed was diluted with Et_2O (35 mL) and some drops of water to dissolve all the precipitates. Phases were separated and the organic phase was washed NH_4Cl (2x1 mL, sat., aq.), then $NaHCO_3$ (1 mL, sat., aq.) and finally brine (1 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by FC (Et_2O :hexanes 1:10) to give the title compound as a clear colorless oil (57.8 mg, 82 %).

1H NMR: ($CDCl_3$, 400 MHz) δ = 7.68-7.63 (m, 4H), 7.45-7.34 (m, 6H), 6.39 (dd, J = 17.4, 1.5 Hz, 1H), 6.12 (dd, J = 17.4, 10.4 Hz, 1H), 5.82 (dd, J = 10.4, 1.5 Hz, 1H), 5.61 (ddd, J = 17.0, 10.5, 9.3 Hz, 1H), 5.56 (ddd, J = 17.0, 10.0, 9.7 Hz, 1H), 5.16-4.99 (m, 4H), 4.17 (dd, J = 10.9, 7.3 Hz, 1H), 4.11 (dd, J = 11.0, 7.2 Hz, 1H), 3.65 (dd, J = 10.1, 8.1 Hz, 1H), 3.59 (dd, J = 10.1, 5.9 Hz, 1H), 2.96-2.87 (m, 1H), 2.54-2.45 (m, 1H), 1.05 (s, 9H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 166.2, 135.8, 135.5, 135.1, 133.9 (2 signals), 130.7, 129.8, 128.7, 127.8 (2 signals), 118.5, 118.4, 65.8, 64.9, 47.3, 42.9, 27.0, 19.4; **HRMS (MALDI-TOF):** calc. for $[M+H]^+$: 435.2350, found 435.2351; **IR (neat):** 3072, 3051, 2956, 2929, 2857, 2363, 2338, 1727, 1636, 1590, 1470, 1427, 1405 1390, 1361, 1295, 1268, 1185, 1109, 1089, 1062, 986, 921, 823, 808, 739, 701, 612; **Rf-value:** 0.53 ($EtOAc$:hexanes 1:10)

C38BL-085-1-pure

pnmr_13C_1024 CDCl₃ /v pkanmr 5

258 (+/-)-(R)-5-((R)-1-((tert-butyldiphenylsilyl)oxy)but-3-en-2-yl)-5,6-dihydro-2H-pyran-2-one



Chemical Formula: C₂₅H₃₀O₃Si

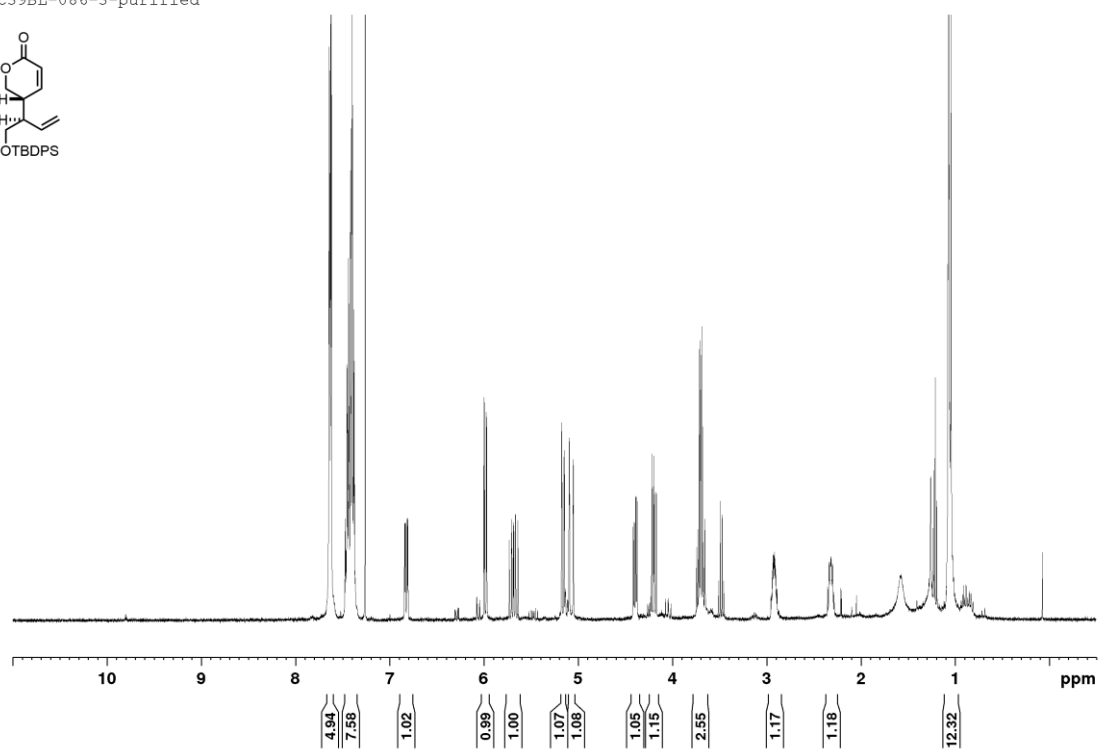
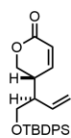
Exact Mass: 406.1964

Molecular Weight: 406.5894

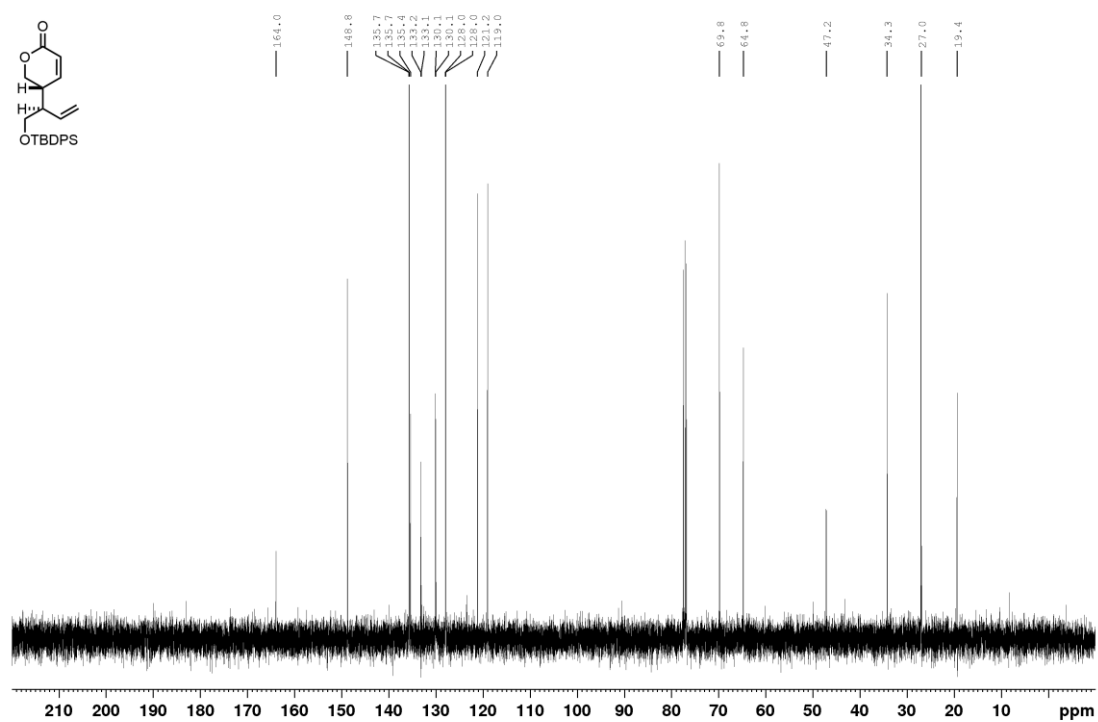
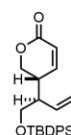
Piers Grubbs 2nd generation catalyst (41.5 mg, 48.3 μ mmol, 0.2 eq.) was weighed in a glove box into a microwave vial, equipped with stir bar and closed. Acrylate **255** (105 mg, 0.242 mmol, 1 eq.) was dissolved in CH₂Cl₂ (4 mL) and added to the catalyst, then rinsed with CH₂Cl₂ (2x1 mL). Since the solution was a strong black, it was diluted with CH₂Cl₂ (6 mL). A new unpierced lid was fitted to the vial and the golden brown solution was stirred at 40 °C for 48 h. Vinyl ethyl ether (2.42 mL) was added and stirring continued for 20 min. The material was cooled to ambient temperature and directly filtered through a plug of silica (1 cm \varnothing x5 cm heiht) in a column with CH₂Cl₂ (approx. 45 ml to get all the material out). The solvent was removed and the residue was purified by FC (Et₂O:hexanes 1:15, then EtOAc:hexanes 1:5) to give title compound as a clear colorless oil (66.1 mg, 67 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.67-7.60 (m, 4H), 7.48-7.35 (m, 6H), 6.82 (dd, J = 9.9, 3.5 Hz, 1H), 5.98 (dd, J = 9.9, 2.1 Hz, 1H), 5.68 (ddd, J = 17.1, 10.2, 9.2 Hz, 1H), 5.16 (dd, J = 10.3, 1.4 Hz, 1H), 5.07 (dq, J = 17.1, 0.7 Hz, 1H), 4.39 (ddd, J = 11.2, 5.2, 1.0 Hz, 1H), 4.19 (dd, J = 11.1, 8.3 Hz, 1H), 3.72 (dd, J = 10.6, 4.8 Hz, 1H), 3.67 (dd, J = 10.6, 6.3 Hz, 1H), 2.96-2.87 (m, 1H), 2.36-2.27 (m, 1H), 1.07 (s, 9H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 164.0, 148.8, 135.7 (2 signals), 135.4, 133.2, 133.1, 130.1 (2 signals), 128.0 (2 signals), 121.2, 119.0, 69.8, 64.8, 47.2, 34.3, 27.0, 19.4; **HRMS (ESI-TOF):** calc. for [M+Na]⁺: 429.1856, found 429.1848; **IR (neat):** 3072, 3049, 3014, 2998, 2956, 2931, 2893, 2858, 1730, 1640, 1589, 1486, 1470, 1428, 1392, 1361, 1329, 1273, 1262, 1227, 1187, 1161, 1105, 1083, 1028, 997, 924, 875, 822, 793, 864, 740, 701, 667, 613, 586; **Rf-value:** 0.18 (EtOAc:hexanes 1:52)

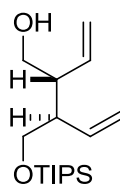
C39BL-086-3-purified



C39BL-086-3-purified



256 (+/-)-(2R,3R)-3-(((triisopropylsilyl)oxy)methyl)-2-vinylpent-4-en-1-ol

Chemical Formula: C₁₇H₃₄O₂Si

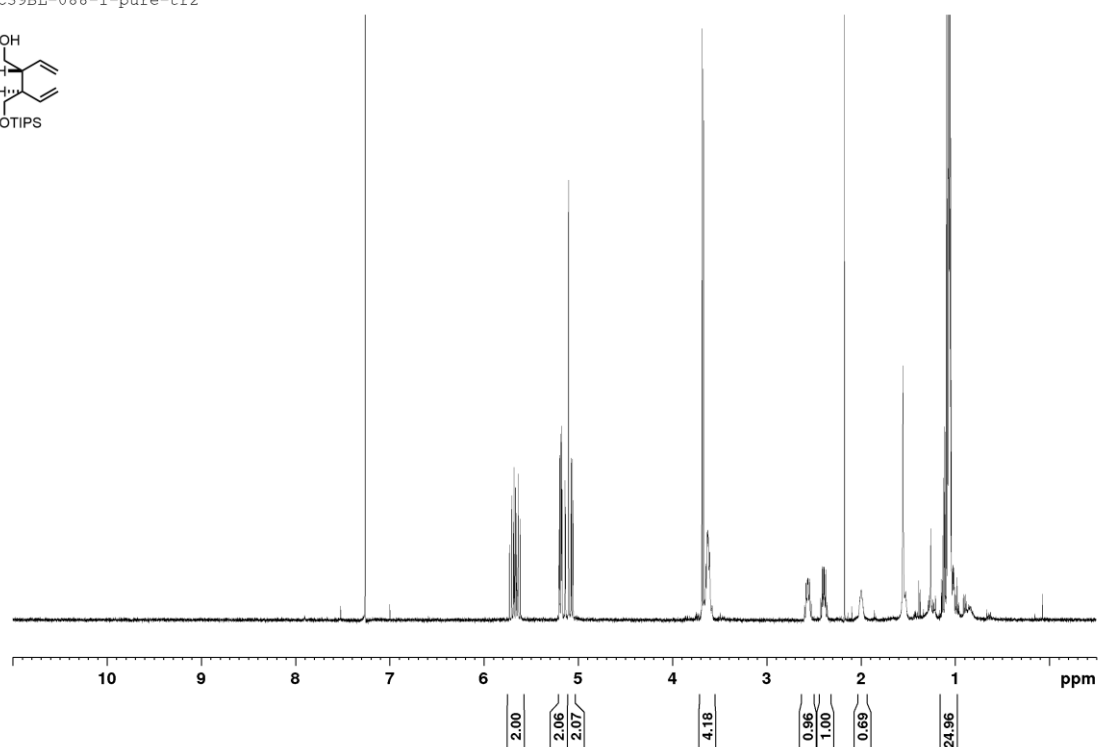
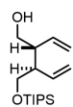
Exact Mass: 298.2328

Molecular Weight: 298.5362

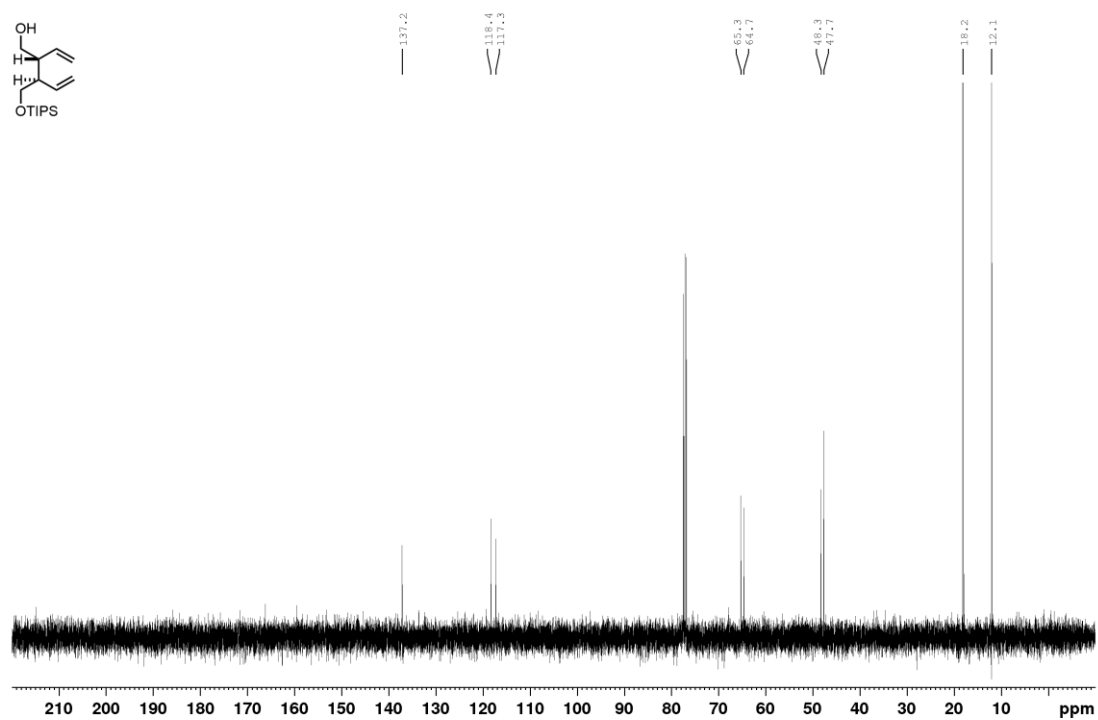
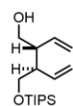
To a solution of **226** (53 mg, 0.37 mmol, 1 eq.) in THF (1.5 mL) in an ice bath was added *n*-BuLi (0.24 mL, 1.6 M in hexanes, 0.39 mmol, 1.05 eq.). TIPSCl (0.08 mL, 0.37 mmol, 1 eq.) was added dropwise and the mixture was stirred at ambient temperature for 3 d. Quenched by addition of water (1 mL). Solid NaCl was added, to brine the THF into the organic phase and the material was diluted with EtOAc (3 mL), phases were separated and aqueous layer was extracted with EtOAc (3x3 mL). The combined organic extracts were washed with brine (1 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by FC (EtOAc:hexanes1:10) to give the title compound as a clear, colourless oil (98.3 mg, 88 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 5.74-5.60 (m, 2H), 5.18 (dd, *J* = 10.5, 2.0 Hz, 1H), 5.16 (ddd, *J* = 17.1, 2.0, 0.8 Hz, 1H), 5.10 (s, 1H), 5.06 (dd, *J* = 7.0, 2.0 Hz, 1H), 3.68 (s, 1H), 3.67 (s, 1H), 3.65-3.56 (m, 2H), 2.61-2.51 (m, 1H), 2.43-2.33 (m, 1H), 1.99 (s, *br*, 1H), 1.10-1.03 (m, 21H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 137.2, 118.4, 117.3, 65.3, 64.7, 48.3, 47.7, 18.2, 12.1; **HRMS (MALDI-TOF):** calc. for [M+Na]⁺: 321.2220, found 321.2224; **IR (neat):** 3375, 3077, 2943, 2893, 2866, 2357, 2338, 1639, 1464, 1424, 1384, 1248, 1102, 1066, 994, 917, 881, 833, 788, 718, 680, 657; **Rf-value:** 0.38 (EtOAc:hexanes 1:5)

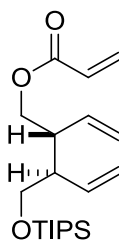
C39BL-088-1-pure-tr2



C39BL-088-1-pure-tr2



257 (+/-)-(2R,3R)-3-(((triisopropylsilyl)oxy)methyl)-2-vinylpent-4-en-1-yl acrylate

Chemical Formula: $C_{20}H_{36}O_3Si$

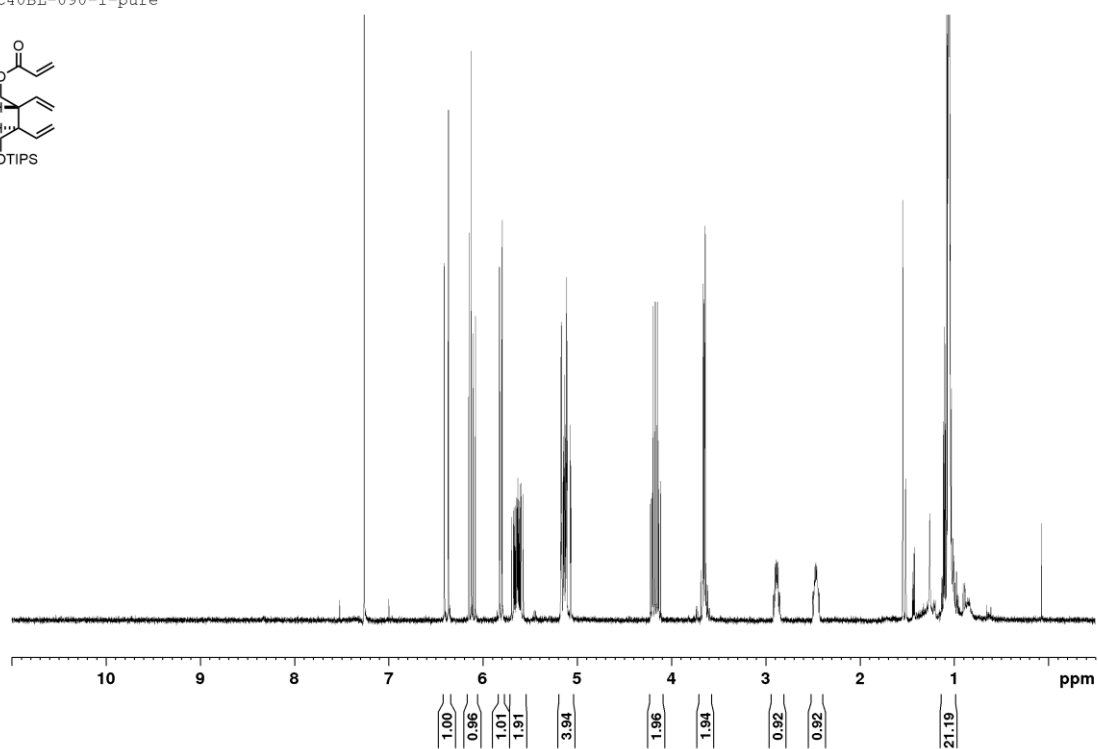
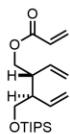
Exact Mass: 352.2434

Molecular Weight: 352.5835

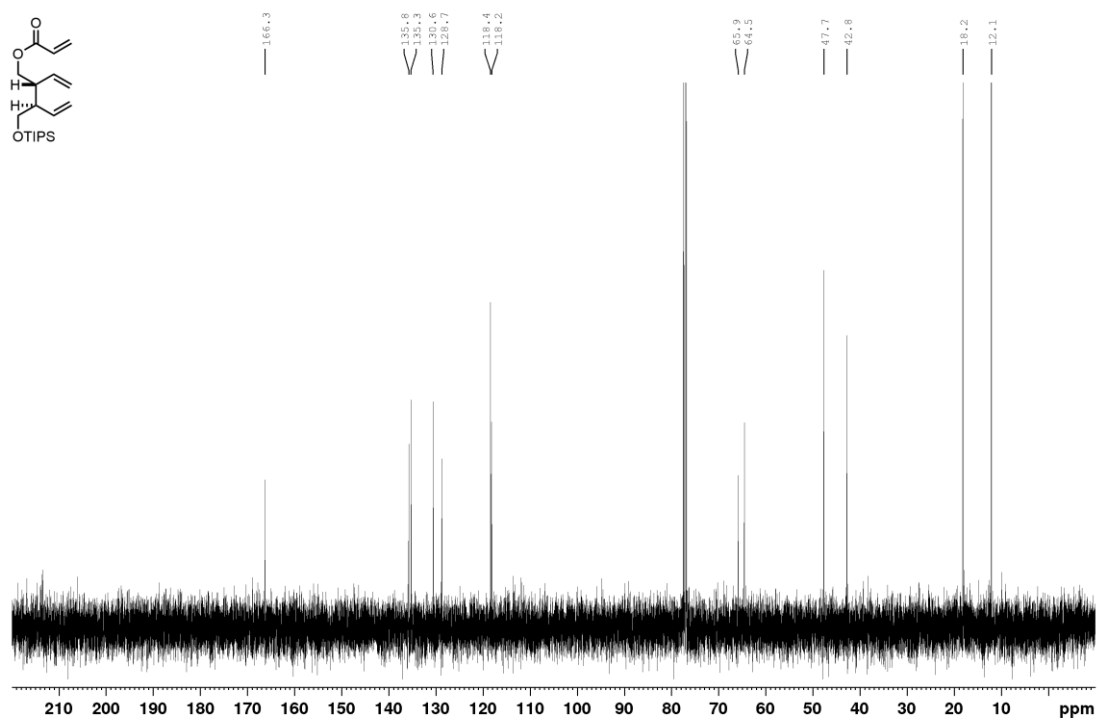
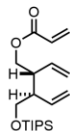
To a solution of **256** (51.2 mg, 0.17 mmol, 1 eq.) in CH_2Cl_2 (2 mL) was added DMAP (4.2 mg, 34 μ mol, 0.2 eq.) and it was cooled to $-78^\circ C$. DIPEA (0.2 mL, 1.14 mmol, 7 eq.) was quickly added, then dropwise acryloyl chloride (55 μ L, 0.69 mmol, 4 eq.). The resulting mixture was let to warm up slowly to 5° in the acetone bath after the dry ice had been removed (took around 1.5 h and turned the mixture into a slight orange color). Reaction was quenched by addition of NH_4Cl (1 mL, sat., aq.), which warmed it immediately to $20^\circ C$. The suspension formed was diluted with Et_2O (35 mL) and some drops of water to dissolve all the precipitates. Phases were separated and the organic phase was washed NH_4Cl (2x1 mL, sat., aq.), then $NaHCO_3$ (1 mL, sat., aq.) and finally brine (1 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by FC ($EtOAc$:hexanes 1:15) to give the title compound as a clear colorless oil (51 mg, 86%).

1H NMR: ($CDCl_3$, 400 MHz) δ = 6.39 (dd, J = 17.4, 1.5 Hz, 1H), 6.11 (dd, J = 17.4, 10.4 Hz, 1H), 5.81 (dd, J = 10.4, 1.5 Hz, 1H), 5.71-5.56 (m, 2H), 5.18-5.15 (m, 1H), 5.14 (dd, J = 4.8, 1.9 Hz, 1H), 5.13-5.05 (m, 2H), 5.17 (ddd, J = 24.3, 10.9, 7.2 Hz, 2H), 3.69-3.59 (m, 2H), 2.92-2.83 (m, 1H), 2.51-2.41 (m, 1H), 1.12-1.02 (m, 21H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 166.3, 135.8, 135.3, 130.6, 128.7, 118.4, 118.2, 65.9, 64.5, 47.7, 42.8, 18.2, 12.1; **HRMS (ESI-TOF):** calc. for $[M+Na]^+$: 375.2326, found 375.2321; **IR (neat):** 3079, 2943, 2894, 2867, 1730, 1637, 1464, 1425, 1407, 1384, 1295, 1269, 1185, 1100, 1062, 986, 965, 919, 881, 808, 791, 719, 681, 657; **Rf-value:** 0.68 ($EtOAc$:hexanes 1:5)

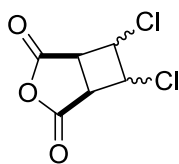
C40BL-090-1-pure



C40BL-090-1-pure



268 (1R,5S)-6,7-dichloro-3-oxabicyclo[3.2.0]heptane-2,4-dione

Chemical Formula: C₆H₄Cl₂O₃

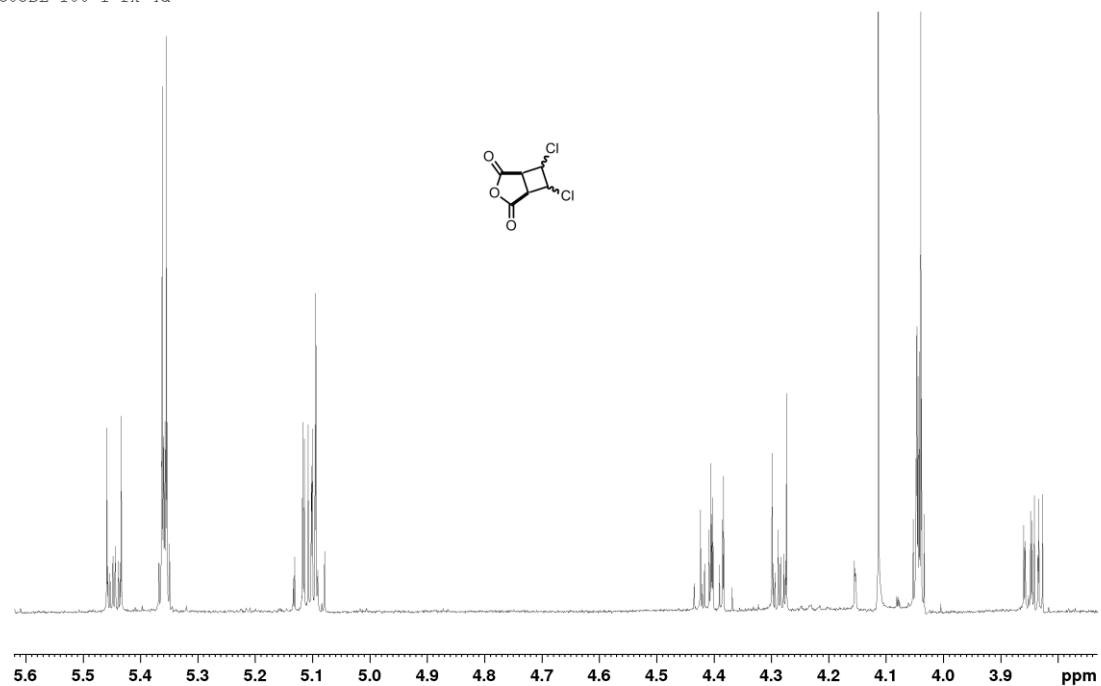
Exact Mass: 193.9537

Molecular Weight: 195.0002

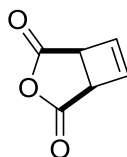
A solution of maleic anhydride (**3**) (18.86 g, 192 mmol, 1 eq.) and (*E*)-1,2-dichloroethene (**4**) (16.5 mL, 215 mmol, 1.12 eq., filtered through a plug of neutral alox before use) in EtOAc (240 mL) was irradiated in a quartz reaction vessel under argon at ambient temperature with a Rayonet Photoreactor equipped with 16 RPR-3000 (~260-400nm) cold cathodes. The vessel was constantly cooled by a stream of cooling water. Reaction control: Aliquots of 0.05 mL evaporated. ¹H NMR in d₆-acetone: Comparing integral of maleic anhydride (7.34 ppm) with the isomeric signals of the protons geminal to chlorine (5.45 ppm, 5.36 ppm, 5.10 ppm). After 7 d, the reaction had stalled, the material was transferred into another flask with further EtOAc and the solvent was removed, first by normal rotary evaporation and afterwards by high vacuum rotary evaporation. The crude material was obtained as a sticky beige solid that was directly used for the next step (total weight 27.4 g, around 17.9 g of **268** (corresponds to 65% purity and 48% yield), 1.4 g of dimerized maleic anhydride **269** (7% yield) and 8.1 g of unreacted maleic anhydride **3** (43% recovery)

¹H NMR: ((CD₃)₂CO, 400 MHz) δ = 5.47-5.43 (m, 2H), 5.38-5.34 (m, 2H), 5.14-5.07 (m, 2H), 4.44-4.36 (m, 1H), 4.31-4.27 (m, 2H), 4.06-4.03 (m, 2H), 3.87-3.82 (m, 1H)

C03BL-100-1-rk-4d



270 (1R,5S)-3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione

Chemical Formula: C₆H₄O₃

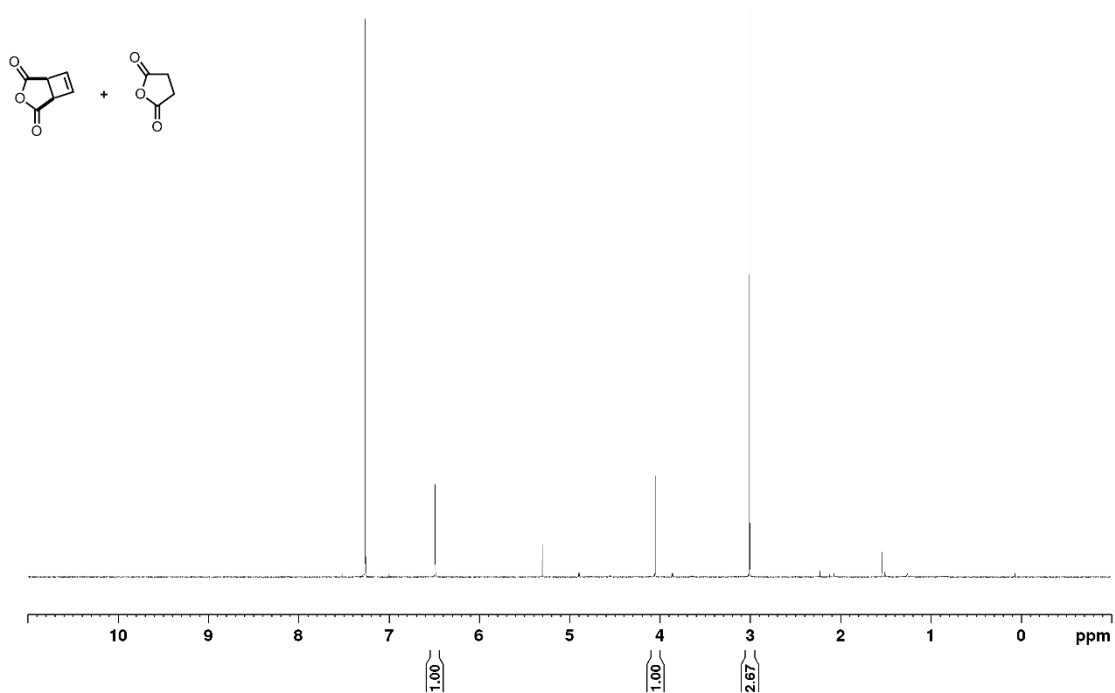
Exact Mass: 124.0160

Molecular Weight: 124.0942

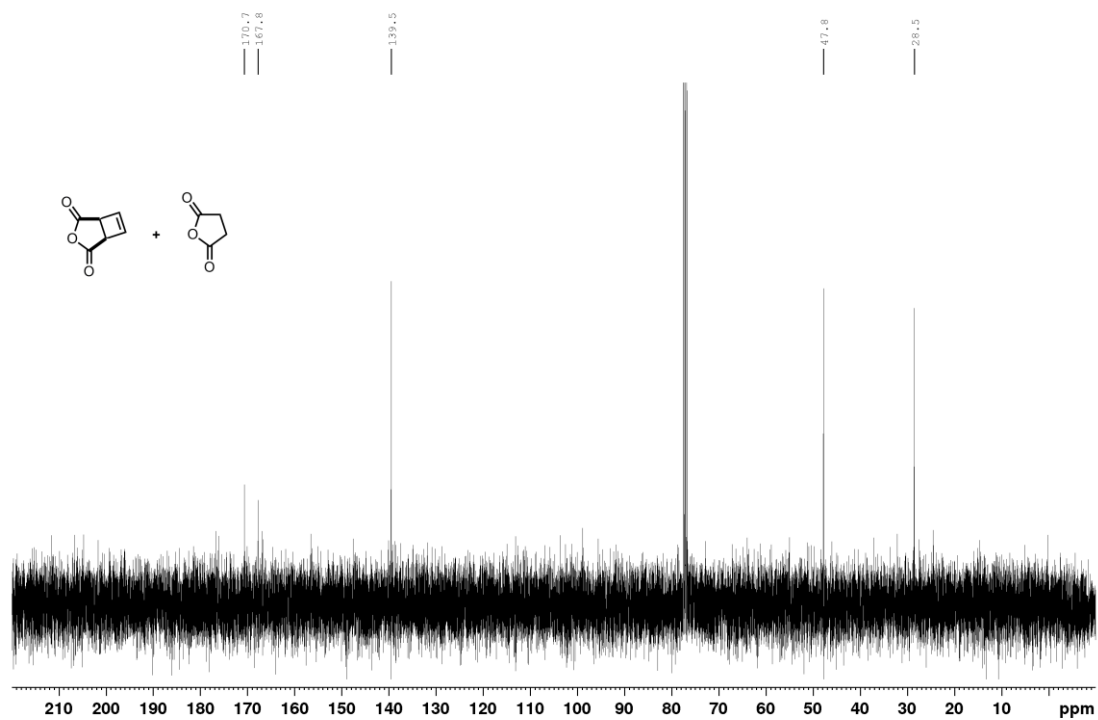
Crude **268** (27.44 g, contained 17.9 g=1 eq. of **268**, 65% purity) was suspended in a mixture of MePh (58 mL) and Ac₂O and transferred into a 500 mL flask equipped with a mechanical stirrer. It was rinsed (2x45 mL) with MePh:Ac₂O 5:4 and warmed to 40 °C to dissolve all of the mixture. Zinc dust (50.8 g, 4.3 eq., >=98% Acros, < 10 μm) was added in one portion while stirring vigorously (450 rpm) and the mixture was warmed to 85 °C. Over time, seven more portion of zinc (50 g each) were added as well as additional Ac₂O (3x20 mL) and MePh (40 mL). The mixture was stirred at 85 °C for 24 h and at 90 °C for 25 h. It was filtered through a large pad of cellite and rinsed with portions of toluene (16x50 mL) until the filtrate displayed no more yellow/orange color. The solvent was removed by first rotary evaporation (40 °C, 75 mbar and later down to 30 mbar) to give an orange oil. It was transferred into a smaller flask and rinsed with toluene (50 mL), evaporated again for 30 min and carefully connected to high vacuum (0.05 mbar). It was warmed to 50 °C and finally to 60 °C for 30 min. Some product had sublimed up to the neck of the flask (white needles). Upon cooling under vacuum part of the material solidified, giving an orange oil with large amounts of black/brownish crystalline solids. (29.9 g). As calculated by NMR cointegration: contains 10.7 g of **270** (36 % w/w), 2.0 g (7% w/w) of succinic anhydride, 8.4 g (29% w/w) of dimerized maleic anhydride and around 8.7 g (29% w/w) of acetic anhydride (were not removable even by prolonged evacuation).

¹H NMR: (CDCl₃, 400 MHz) δ = 6.49 (s, 2H), 4.05 (s, 2H)

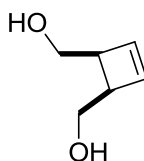
C05BL-101-1-distilled



C05BL-101-1-distilled



272 Cyclobut-3-ene-1,2-diylldimethanol

Chemical Formula: $C_6H_{10}O_2$

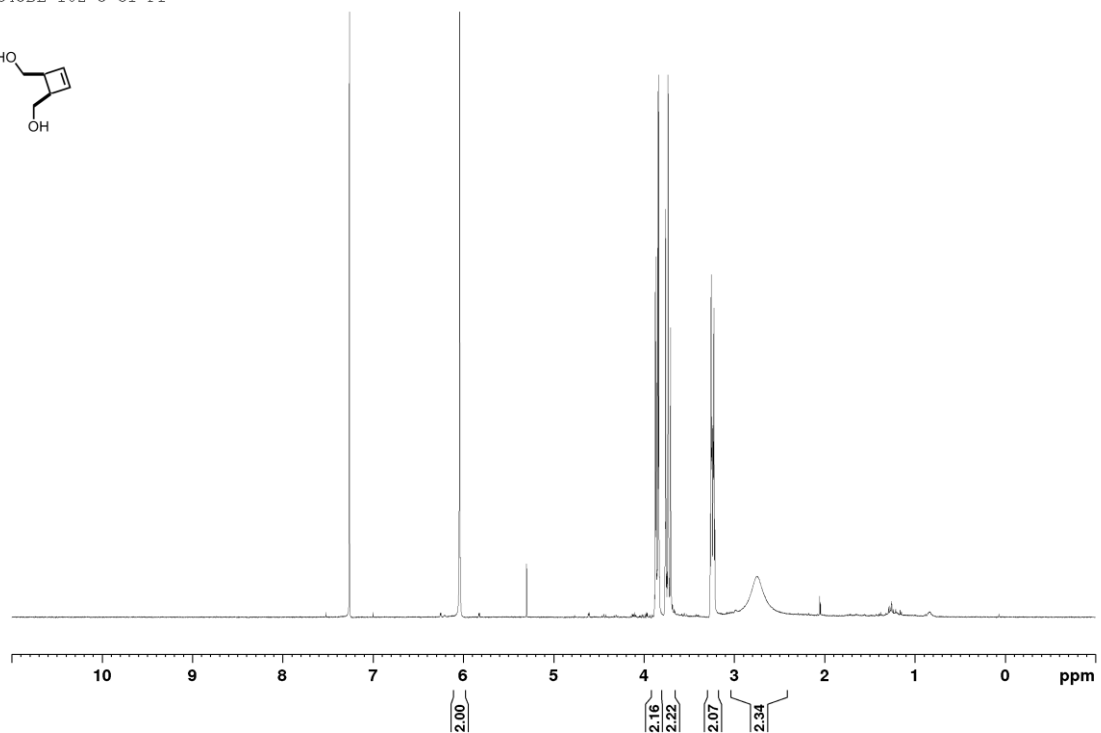
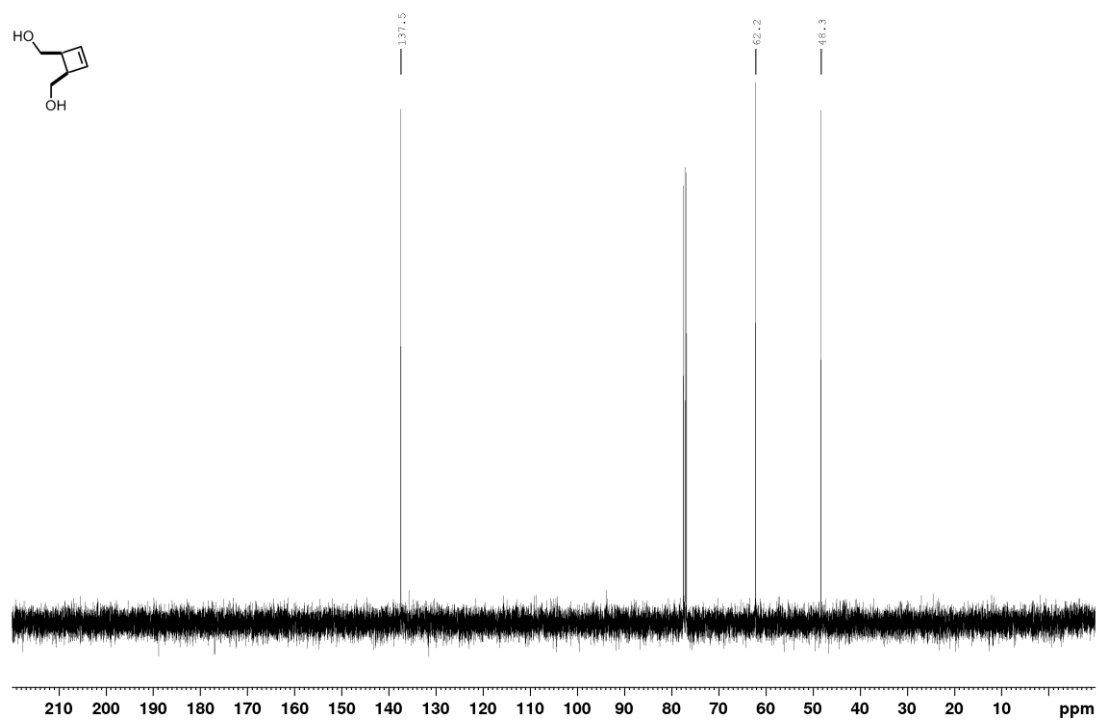
Exact Mass: 114.0681

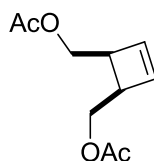
Molecular Weight: 114.1424

$LiAlH_4$ (15 g, 297 mmol) was suspended in THF (around 400 mL) and immersed in an ice bath. **270** (29.9 g, 36 % purity, 10.7 g effectively=86.3 mmol) in 75 mL THF was added with a slow stream. It was rinsed with THF (24 mL) upon which some foaming of the light brown solution was observed. More portions of THF (3x6 mL) were used for rinsing residual SM. Internal temperature did rise to 15 °C during the addition. The solution was warmed to reflux (66 °C, bath temperature 86 °C) and stirred for 45 min during which it turned into a dark brown color. Heating was turned off and the mixture was let to cool down in the oil bath and stirred for 16 h upon which it turned black. $LiAlH_4$ was quenched by dropwise addition of MeOH (26 mL) at -78 °C (only small increase in internal temperature) and warmed to 0 °C in an ice bath. It was slowly poured into a solution of Rochelle's salt (500 mL, sat. aq.) during which some light foaming was observed. It was rinsed with additional solution of Rochelle's salt (3x200 mL+150 mL, sat. aq.). The grey suspension was mechanically stirred (800 rpm) and an increase in temperature to 40 °C was observed. THF was removed by rotary evaporation, EtOAc (300 mL) was added and the mixture was filtered. Phases were separated and the aqueous phase was extracted with EtOAc (4x300 mL). Dried over Na_2SO_4 , filtered and rinsed with EtOAc (300 mL). Solvent was removed and the crude residue was purified by silica plug filtration (4 cm \varnothing x 5 cm height, EtOH:EtOAc 1:9) to remove all the baseline material from the product (first 450 mL contained all the product). The material was repurified by FC (EtOAc:hexanes 1:1) to give the title compound as a slightly yellow oil (5.04 g, 23% over three steps) as well as notable amounts of product containing around 5% of an impurity as an orange oil (1.7 g, 8%).

1H NMR: ($CDCl_3$, 400 MHz) δ = 6.04 (s, 2H), 3.85 (dd, J = 11.5, 4.1 Hz, 2H), 3.77-3.69 (m, 2H) 3.27-3.20 (m, 2H), 2.75 (s, br, 2H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 137.5, 62.2, 48.3; **HRMS (EI):** calc. for $[M-CH_3O]^+$: 83.0491, found 83.0491; **IR (neat):** 3296, 3046, 2912, 1436, 1369, 1335, 1289, 1229, 1189, 1155, 1109, 1057, 1019, 942, 815, 713, 630, 621; **Rf-value:** 0.29 (EtOAc:hexanes 3:1)

C45BL-102-5-C1-Pr

pnmr_13C_1024 CDCl₃ /v pkanmr 8

262 meso-cyclobut-3-ene-1,2-diylbis(methylene) diacetate^[203]Chemical Formula: C₁₀H₁₄O₄

Exact Mass: 198.0892

Molecular Weight: 198.2158

Diol **272** (10.2 g, 89.5 mmol, 1 eq.) was dissolved in pyridine (22.5 mL, 277 mmol, 3.1 eq.) and cooled to 0 °C in an ice bath. Ac₂O (18.5 mL, 194 mol, 2.17 eq.) was added quickly. After 5 min, the flask was moved into a water bath. It was stirred for 1 h, transferred into a vigorously stirred solution of NaHCO₃ (380 mL, sat., aq.) and the reaction vessel was rinsed with 250 mL CH₂Cl₂. After stirring for 30 min, no more effervescence was observable. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic solution was washed with HCl (380 mL, 1 M), water (380 mL), brine (200 mL), dried over Na₂SO₄ and evaporated. The residue was purified by FC (Et₂O:hexanes 1:3) to give the title compound as a clear colorless oil (15.26, 91 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 6.12 (s, 2H), 4.24-4.18 (m, 4H), 3.9-3.22 (m, 2H), 2.06 (s, 6H);

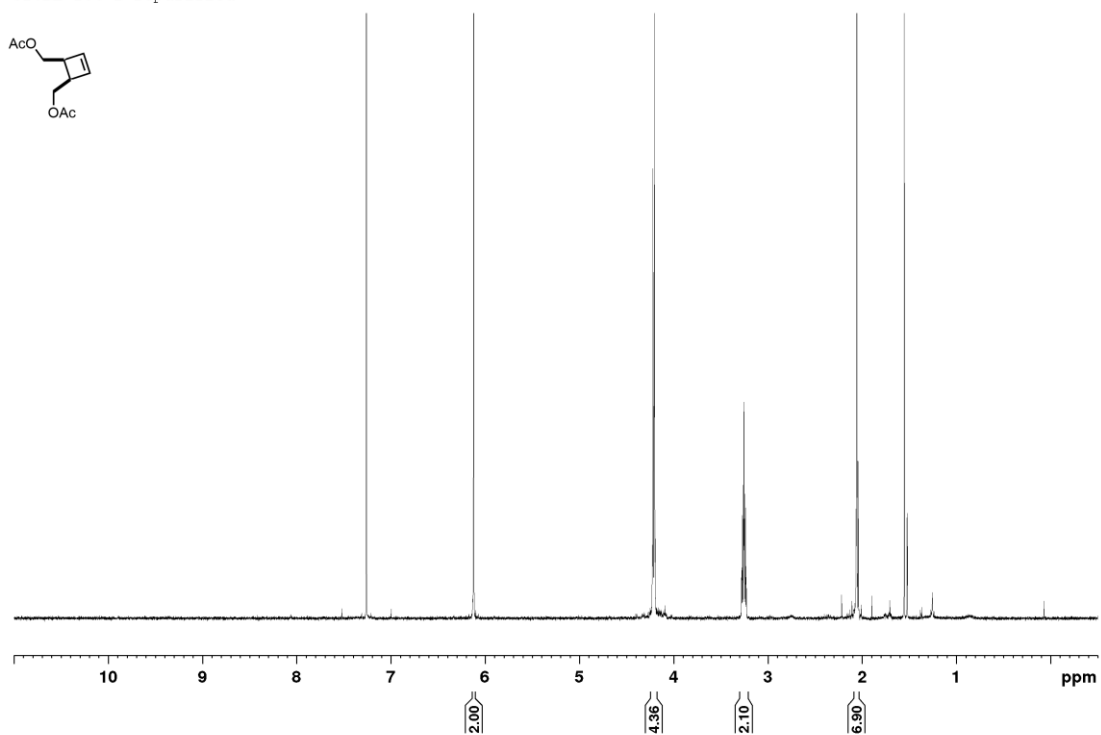
¹³C NMR: (CDCl₃, 100 MHz) δ = 171.1, 138.0, 64.1, 44.5, 21.1; **HRMS (ESI-TOF):** calc. for [M-

Na]⁺: 221.0784, found 221.0785; **IR (neat):** 2956, 2902, 2364, 2340, 1735, 1470, 1454, 1436,

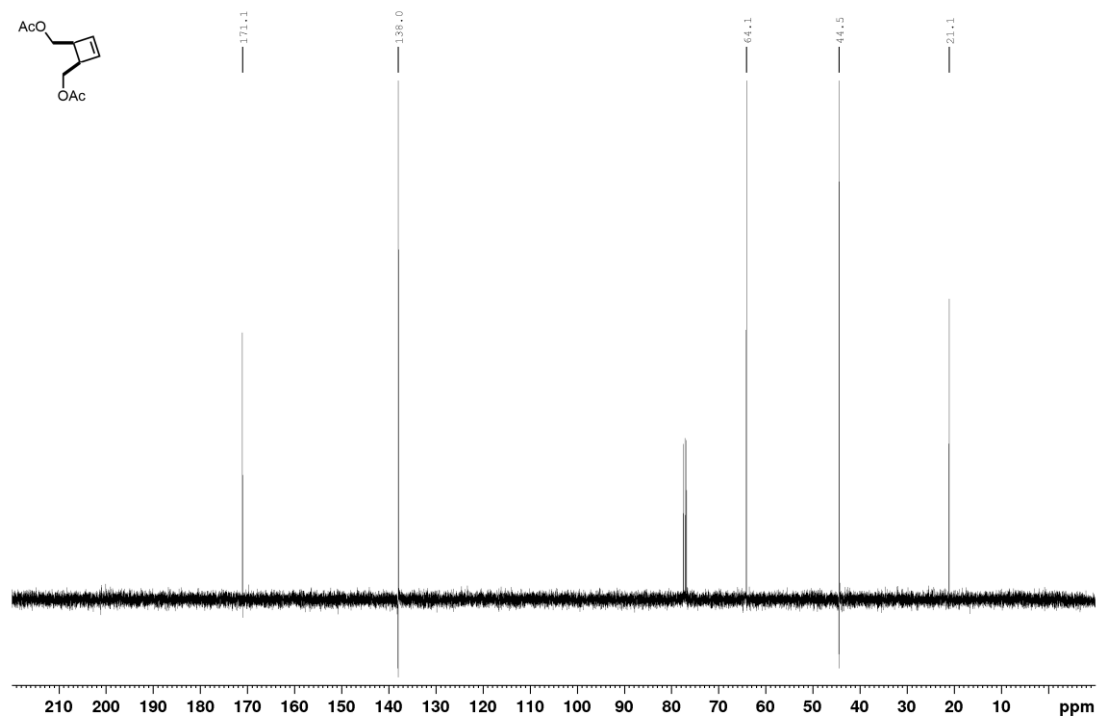
1384, 1365, 1222, 1166, 1113, 1029, 972, 930, 884, 852, 784, 738, 634, 605; **Rf-value:** 0.17

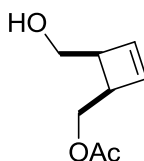
(EtOAc:hexanes 1:3)

C16BL-106-2-repurified



C06BL-106-1-pure



273 ((1R,4S)-4-(hydroxymethyl)cyclobut-2-en-1-yl)methyl acetate^[202]Chemical Formula: C₈H₁₂O₃

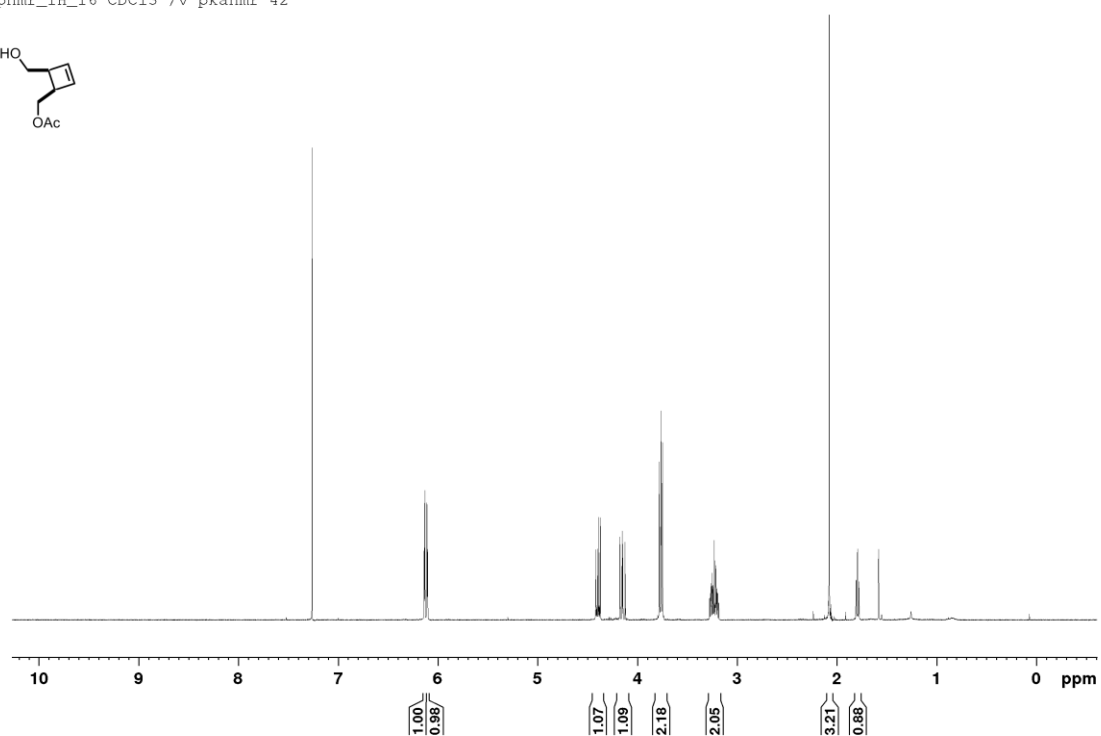
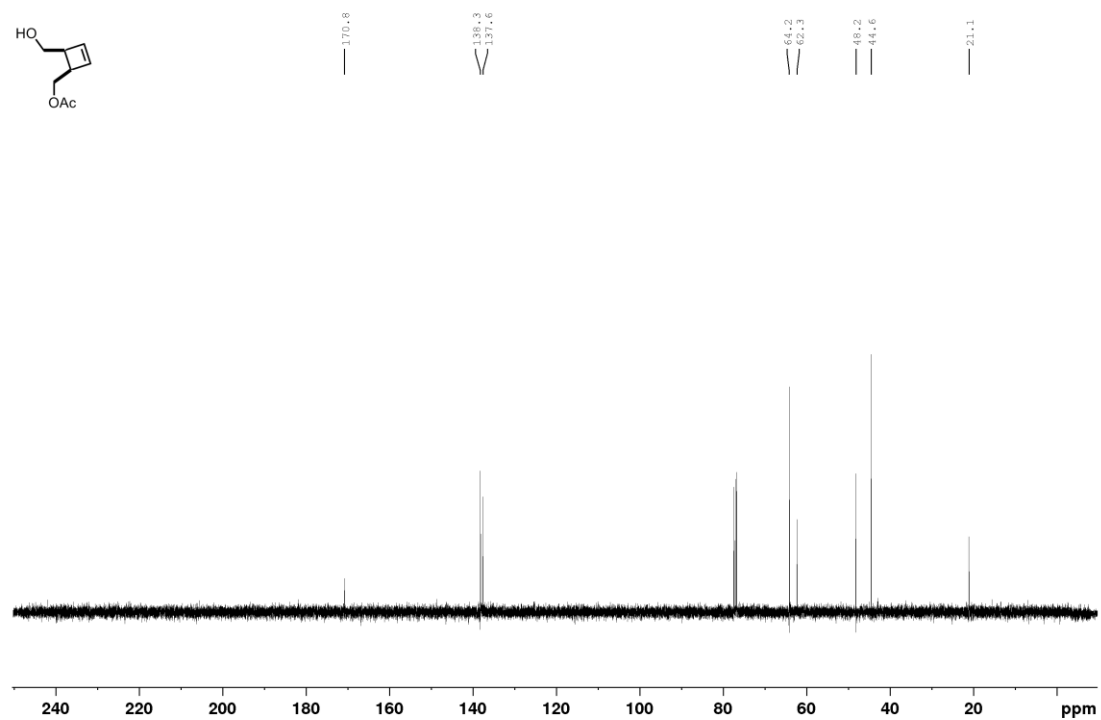
Exact Mass: 156.0786

Molecular Weight: 156.1791

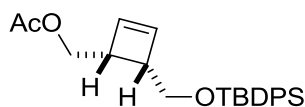
Diacetate **BL 106** (15.2 g, 76.4 mmol) was vigorously stirred in phosphate buffer pH 6.97 (350 mL, 67 mM, slightly below pH 7) was titrated with an automatic titration system (STAT function) up to pH 7 using 1 M NaOH. Amano Lipase from *Pseudomonas fluorescens* (534 mg, Aldrich) was added. The reaction was stirred for 12 h 20 min (up to 95 % conversion by titration, 72.68 mL NaOH). The solution was saturated with NaCl and extracted a variety of solvents. In most cases an emulsion formed that could only be broken by filtration through celite. The order of solvents was: CHCl₃ (100 mL), EtOAc (250 mL), EtOAc:Et₂O (150 mL, 2:1), CHCl₃ (200 mL), EtOAc:Et₂O (4x200 mL). The combined organic phases were washed with brine (20 mL) and dried over Na₂SO₄. The crude product was purified by two rounds of FC (EtOAc:Hexanes 1:1 to 3:1 to neat EtOAc) to recover pure **262** as a clear, colorless oil (1.74 g, 11%), give the title compound **273** as clear, slightly yellow oil (9.77 g, 82%) and clean diol **272** as a slightly yellow oil (320 mg, 4%). Because compound **273** had been reported to racemize over time, it was immediately converted to TBDPS-ether **274**.

¹H NMR: (CDCl₃, 400 MHz) δ = 6.13 (dd, *J* = 2.9, 0.7 Hz, 1H), 6.11 (dd, *J* = 2.9, 0.8 Hz, 1H), 4.39 (ddd, *J* = 5.8, 5.7, 2.6 Hz, 1H), 4.15 (ddd, *J* = 11.4, 9.0, 1.8 Hz, 1H), 3.77 (d, *J* = 6.4 Hz, 1H), 3.75 (d, *J* = 6.3 Hz, 1H), 3.28-3.17 (m, 2H), 2.07 (s, 3H), 1.79 (t, *J* = 5.9 Hz, 1H); ¹³C NMR: (CDCl₃, 100 MHz) δ = 170.8, 138.3, 137.6, 64.2, 62.3, 48.2, 44.6, 21.1; HRMS (ESI-TOF): calc. for [M+Ag]⁺: 262.9832, found 262.9837; IR (neat): 3435, 2902, 1734, 1367, 1232, 1027, 971, 735, 607

[α]_D²⁰ = +9.5 ± 0.2° (c = 2.0, CHCl₃); Rf-value: 0.31 (EtOAc:hexanes 1:1)

pnmr_1H_16 CDCl₃ /v pkanmr 42pnmr_13C_1024 CDCl₃ /v pkanmr 7

274 ((1R,4S)-4-(((tert-butyldiphenylsilyl)oxy)methyl)cyclobut-2-en-1-yl)methyl acetate



Chemical Formula: C₂₄H₃₀O₃Si

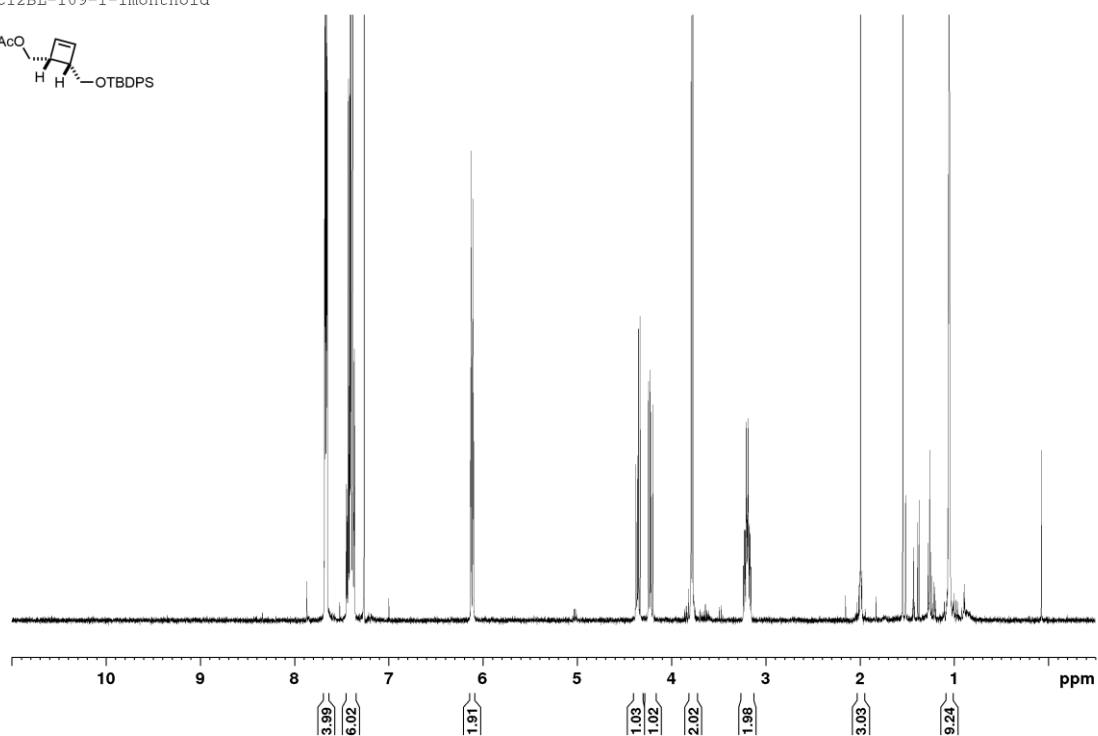
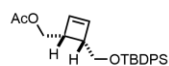
Exact Mass: 394.1964

Molecular Weight: 394.5787

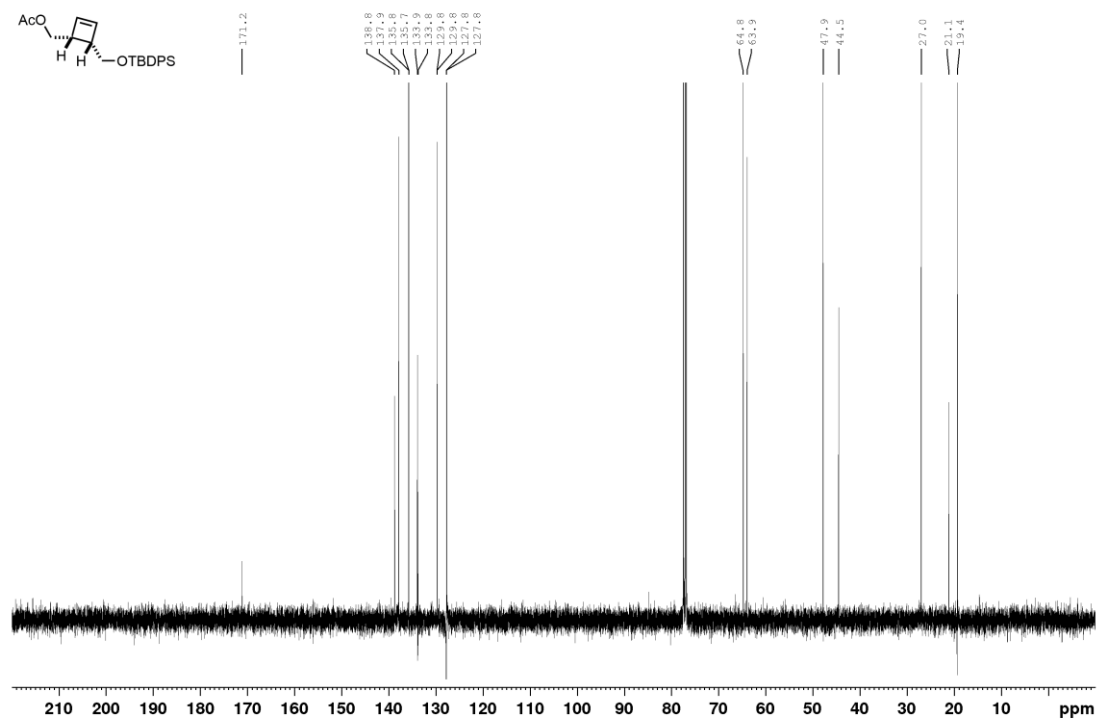
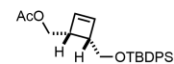
To a solution of alcohol **273** (4.56 g, 29.2 mmol, 1 eq.) in DMF (34 mL) at ambient temperature was added TBDPSCI (8.2 mL, 32.1 mmol, 1.1 eq.) immediately followed by imidazole (7.35 g, 108.0 mmol, 3.3 eq.), both in one portion. The reaction was stirred for 32 h and diluted with Et₂O (340 mL). The mixture was washed sequentially with 173 mL of each citric acid (10 %, aq.), water, NaHCO₃ (sat., aq.) and brine. The solution was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by FC (Et₂O:hexanes1:15) to give the title compound as clear, colorless and viscous oil (11.19 g, 97 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.71-7.64 (m, 4H), 7.46-7.35 (m, 6H), 6.12 (dd, *J* = 2.9, 0.6 Hz, 1H), 6.10 (d, *br*, *J* = 2.9 Hz, 1H), 4.35 (dd, *J* = 11.0, 6.7 Hz, 1H), 4.22 (dd, *J* = 11.1, 7.4 Hz, 1H), 3.78 (d, *J* = 6.8 Hz, 2H), 3.24-3.14 (m, 2H), 1.99 (s, 3H), 1.05 (s, 9H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 171.2, 138.8, 137.9, 135.8, 135.7, 133.9, 133.8, 129.8 (2 signals), 127.8 (2 signals), 64.8, 63.9, 47.9, 44.5, 27.0, 21.1, 19.4; **HRMS (ESI/MALDI-TOF):** calc. for [M+H]⁺: 395.2037, found 395.2037; calc. for [M+Na]⁺: 417.1856, found 417.1857; **IR (neat):** 3070, 3049, 2957, 2930, 2895, 2858, 2359, 1740, 1471, 1447, 1428, 1385, 1362, 1229, 1194, 1108, 1082, 1056, 1031, 1008, 1000, 970, 937, 851, 822, 776, 737, 700; **[α]_D²⁰** = +6.29 ± 0.05° (*c* = 1.16, CHCl₃); **Rf-value:** 0.32 (Et₂O:hexanes 1:10)

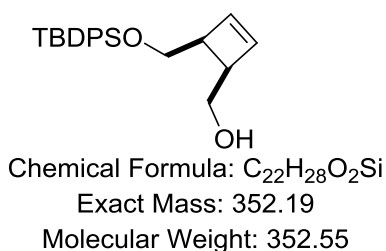
C12BL-109-1-1monthold



C12BL-109-1-1monthold

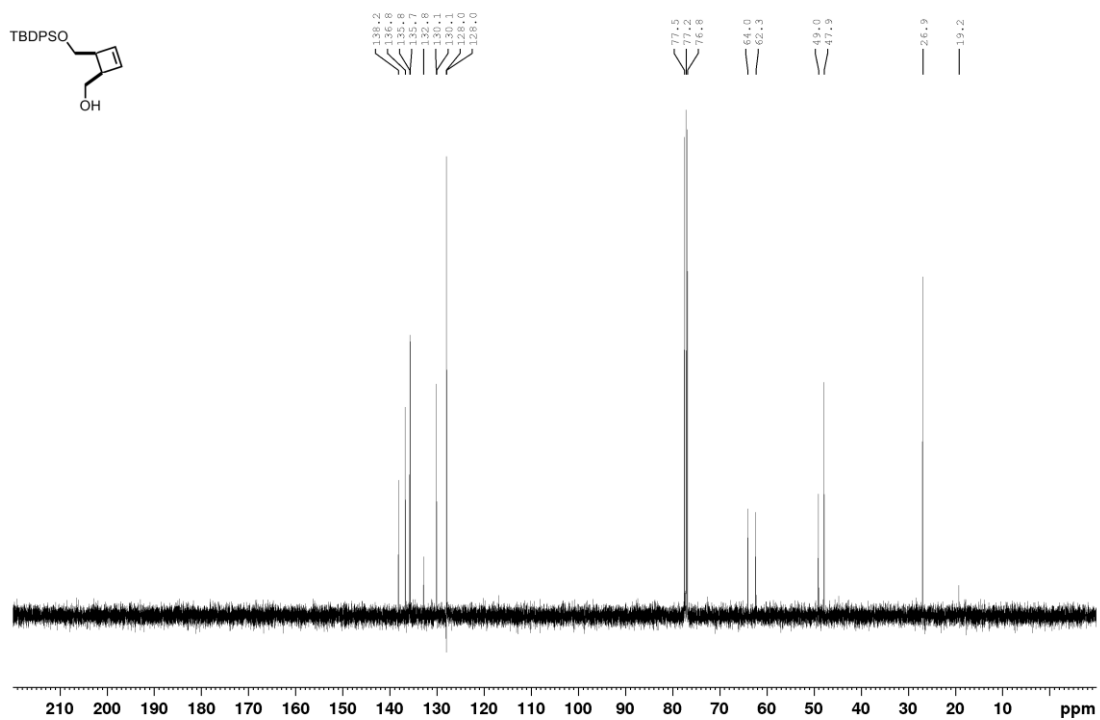
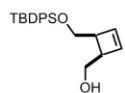
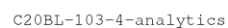
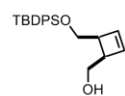


5 (+)-((1S,4R)-4-(((tert-butyldiphenylsilyl)oxy)methyl)cyclobut-2-en-1-yl)methanol

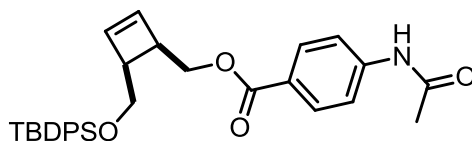


To a solution acetate **274** (22.16 g, 56.16 mmol, 1 eq.) in MeOH (320 mL, HPLC grade, new bottle) was added K₂CO₃ (695 mg) and the mixture was stirred at ambient temperature for 5 h. It was quenched with phosphate buffer (100 mL, pH 7, 0.5 M) in which NaH₂PO₄ (1.224 g, anhydrous, 10.1 mmol, 0.18 eq.) was dissolved. Water was added until all the precipitates dissolved and the solvent was removed by rotary evaporation (foaming!). Et₂O (200 mL) was added, the phases were separated and the aqueous phase was extracted with ether (3x200 mL). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄ filtered, and concentrated under reduced pressure. The crude product was purified by repeated FC (1:8 EtOAc:hexanes) to give large amount of pure title compound as well as impure material contaminated with an apolar impurity (R_f=0.41, EtOAc:hexanes 1:3). The impure material was repeatedly chromatographed to give additional title compound. The pure material was obtained as clear, slightly yellow and viscous oil that solidified upon standing (19.71 g, 100).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.72-7.67 (m, 4H), 7.49-7.38 (m, 6H), 6.04 (dd, *J* = 2.9, 0.8 Hz, 1H), 5.86 (dd, *J* = 2.9, 0.8 Hz, 1H), 3.85-3.76 (m, 5H, 2 CH₂ and 1 OH), 3.36-3.29 (m, 1H), 3.25-3.15 (m, 1H), 1.05 (s, 9H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 138.2, 136.8, 135.8, 135.7, 132.8, 132.8, 130.1 (2 signals), 128.0 (2 signals), 64.1, 62.3, 49.0, 47.9, 26.9, 19.2 (weak, but visible in HMBC); **HRMS (ESI-TOF):** calc. for [M+H]⁺: 353.1931, found 353.1930; **IR (neat):** 3466, 3070, 3045, 2962, 2930, 2906, 2877, 2858, 1588, 1483, 1470, 1444, 1428, 1393, 1382, 1363, 1287, 1256, 1190, 1145, 1106, 1069, 1042, 1025, 1009, 997, 969, 937, 824, 786, 760, 742, 723, 689, 622, 614; **[α]_D²⁰** = +6.71 ± 0.01° (c = 1.01, CHCl₃); **Mp:** 59-60 °C; **R_f-value:** 0.69 (EtOAc:hexanes 1:1), 0.35 (EtOAc:hexanes 1:3)



275 ((1R,4S)-4-(((tert-butyldiphenylsilyl)oxy)methyl)cyclobut-2-en-1-yl)methyl 4-acetamidobenzoate



Chemical Formula: $C_{31}H_{35}NO_4Si$

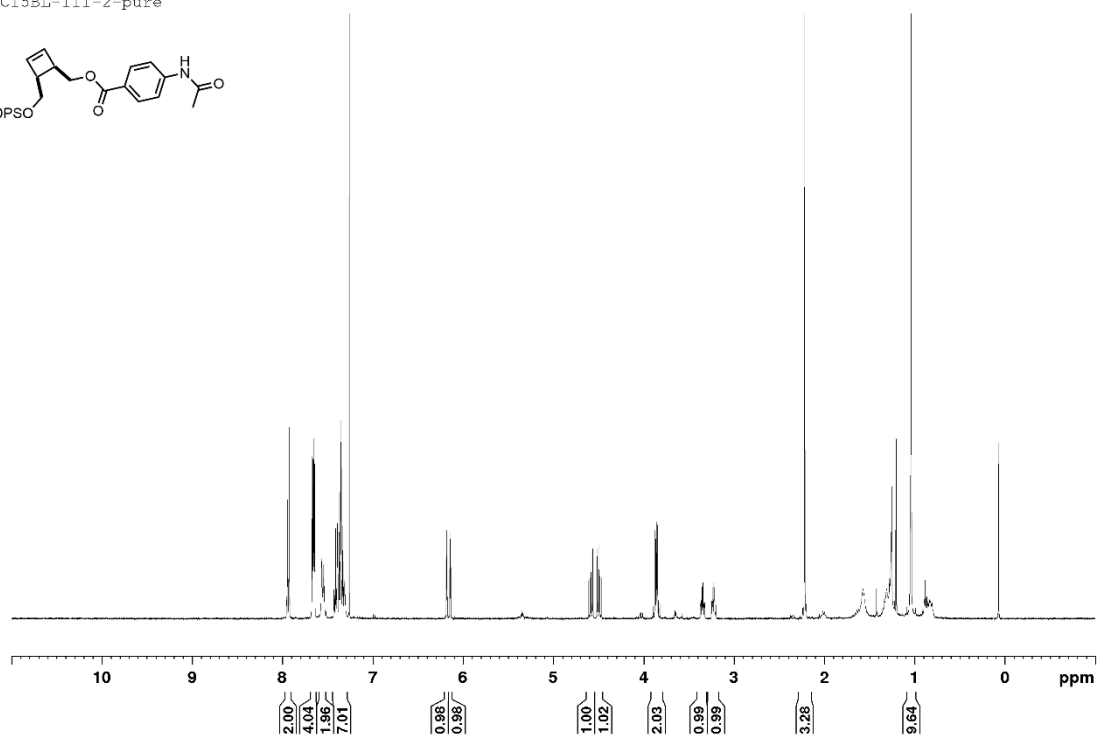
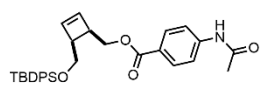
Exact Mass: 513.2335

Molecular Weight: 513.6994

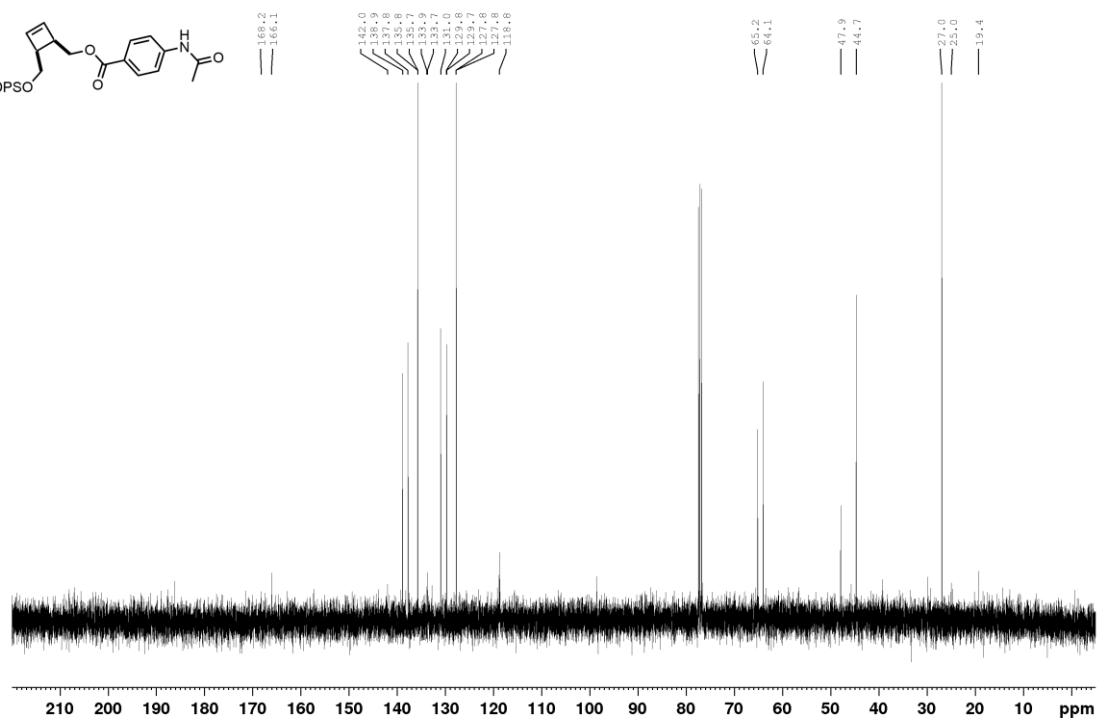
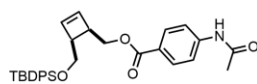
To crude **5** (10 mg, 28.4 μ mol, 1 eq.), was added in that order DMAP (4.2 mg, 34 μ mol, 1.2 eq.), CH_2Cl_2 (0.28 mL), 4-acetamidobenzoic acid (6.7 mg, 34 μ mol, 1.2 eq.) and EDCI (6.4 mg, 34 μ mol, 1.2 eq.). The suspension was stirred for 15 h, during which the material dissolved completely and all the SM had disappeared. Reaction was diluted with Et_2O (5 mL) and quenched with NH_4Cl (0.5 mL, aq., sat.). Dilution with water (0.5 mL) dissolved all the precipitates and the phases were separated. Around 1.5 mL of the organic phase was spilled, thus accounting for the low overall yield. The aqueous phase was extracted with Et_2O (2x5mL), the combined organic phases were washed with a mixture of NH_4Cl (0.5 mL, aq., sat.) and water (0.5 mL), brine (1 mL) and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by FC (EtOAc:hexanes1:1) to give the title compound as a non-clear, colourless oil (8.6 mg, 90 %).

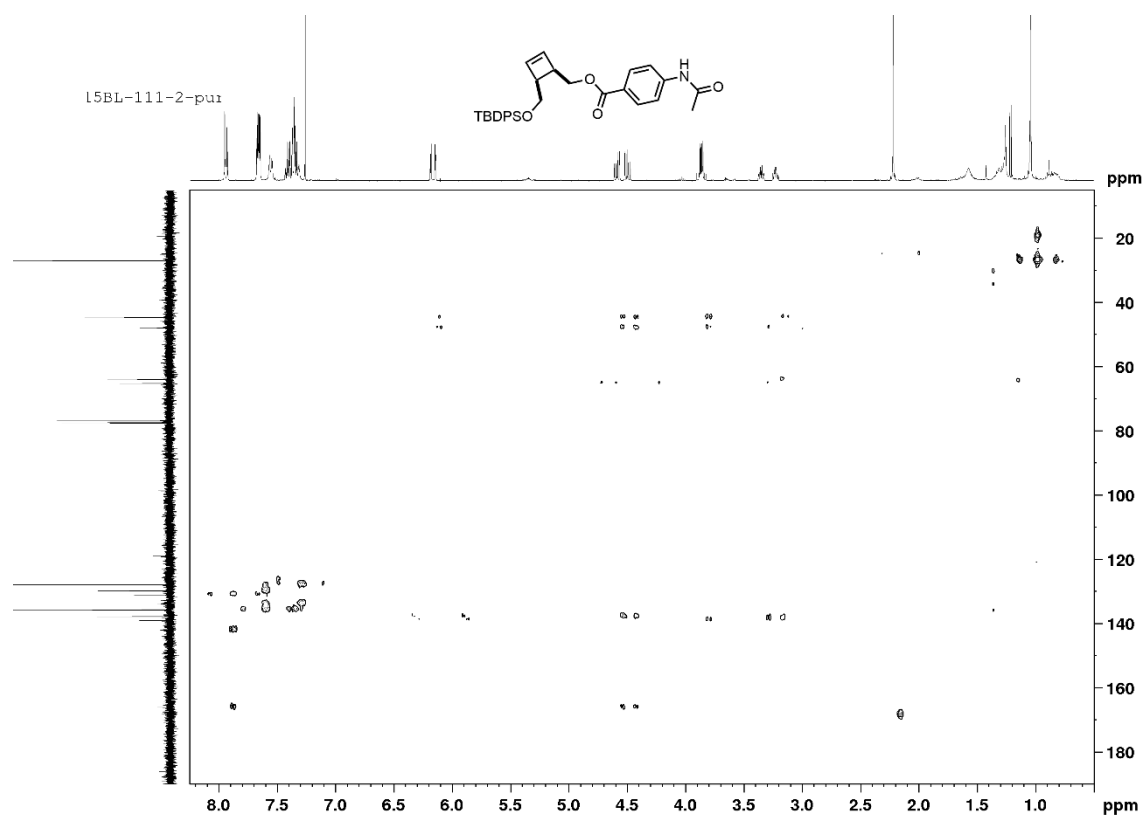
1H NMR: ($CDCl_3$, 400 MHz) δ = 7.97-7.91 (m, 2H), 7.69-7.63 (m, 4H), 7.55 (d, br, J = 8.5 Hz, 2H), 7.44-7.29 (m, 7H), 6.18 (dd, J = 3.0, 0.9 Hz, 1H), 6.14 (d, J = 3.0 Hz, 1H), 4.59 (dd, J = 11.1, 7.0 Hz, 1H), 4.49 (dd, J = 11.1, 7.2 Hz, 1H), 3.88 (dd, J = 10.6, 7.4 Hz, 1H), 3.84 (dd, J = 10.5, 6.5 Hz, 1H), 3.38-3.32 (m, 1H), 3.26-3.19 (m, 1H), 2.22 (s, 3H), 1.04 (s, 9H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 168.2, 166.1, 142.0, 138.9, 137.8, 135.8, 135.7, 133.9, 133.7, 131.0, 129.8, 129.7, 127.8, 127.8, 118.8, 65.2, 64.1, 47.9, 44.7, 27.0, 25.0, 19.4; **HRMS (MALDI/ESI):** calc. for $[M+Na]^+$: 536.2228, found 536.2227; **IR (neat):** 3321, 3071, 3049, 2959, 2926, 2856, 2369, 1714, 1678, 1599, 1532, 1467, 1427, 1406, 1375, 1316, 1261, 1173, 1105, 1015, 919, 858, 819, 798, 772, 738, 701, 647, 610, 580, 505, 456, 431, 413; **$[\alpha]^{20}_D$** = +0.2 $^\circ$ (c = 0.275, $CHCl_3$); **Rf-value:** 0.20 (EtOAc:hexanes 1:1)

C15BL-111-2-pure

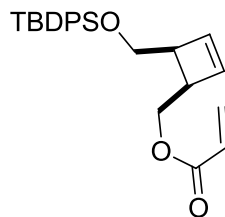


C15BL-111-2-pure





261 ((1R,4S)-4-(((tert-butyldiphenylsilyl)oxy)methyl)cyclobut-2-en-1-yl)methyl acrylate

Chemical Formula: C₂₅H₃₀O₃Si

Exact Mass: 406.1964

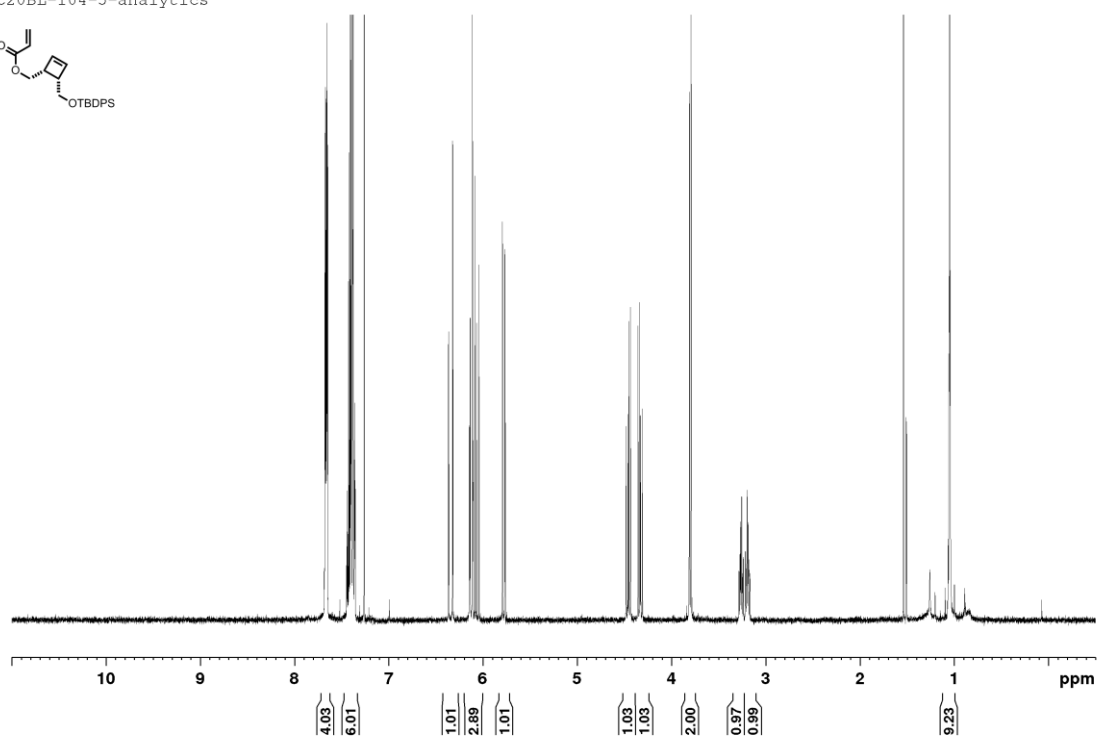
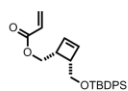
Molecular Weight: 406.5894

A solution of **5** (19.71 g, 55.9 mmol) in CH₂Cl₂ (500 mL, fresh bottle over MS) was cooled to -78 °C and DIPEA (20.5 mL, 117.4 mmol, 2.1 eq.) was quickly added, then dropwise via an addition funnel a solution of acryloyl chloride (5.5 mL, 67.1 mmol, 1.2 eq., freshly distilled (from 0.5 g hydroquinone per 200 mL) CH₂Cl₂ (45 mL) over 30 min. The addition funnel was rinsed with CH₂Cl₂ (2x5 mL) and the mixture was stirred at -78 °C for 30 min, quenched by addition of NH₄Cl (100 mL, sat., aq.) and diluted with water (24 mL) and hexane (200 mL). It was warmed to ambient temperature in the rotary evaporator bath and the dichloromethane was distilled off. The mixture was diluted with Et₂O (400 mL) and the phases were separated. The organic phase was subsequently washed with NH₄Cl (2x20 mL, sat., aq.), then NaHCO₃ (20 mL, sat., aq.) and finally brine (20 mL). Each of the aqueous phases was backextracted with Et₂O (200 mL). Since there was still product in the aqueous phases, each of them was sequentially backextracted with first a mixture of EtOAc/MePh (200 mL, 1:1) and secondly EtOAc/MTBE (200 mL, 1:1). The ether phases and the EtOAc containing phases were separately dried (MgSO₄) and filtered. The ether phases were evaporated down to around 70 mL, the EtOAc phases were evaporated to dryness (since toluene might elute both the SM and PR simulatenously). The residue was purified by FC (Et₂O:hexanes 1:10 to 1:5 to EtOAc:hexanes 1:3 to 1:1) to give the title compound (as a solution in hexanes, usually around 80%) and recover some pure starting material **5** (0.57 g, 3%). **Note: If concentrated, this compound is prone to polymerization.**

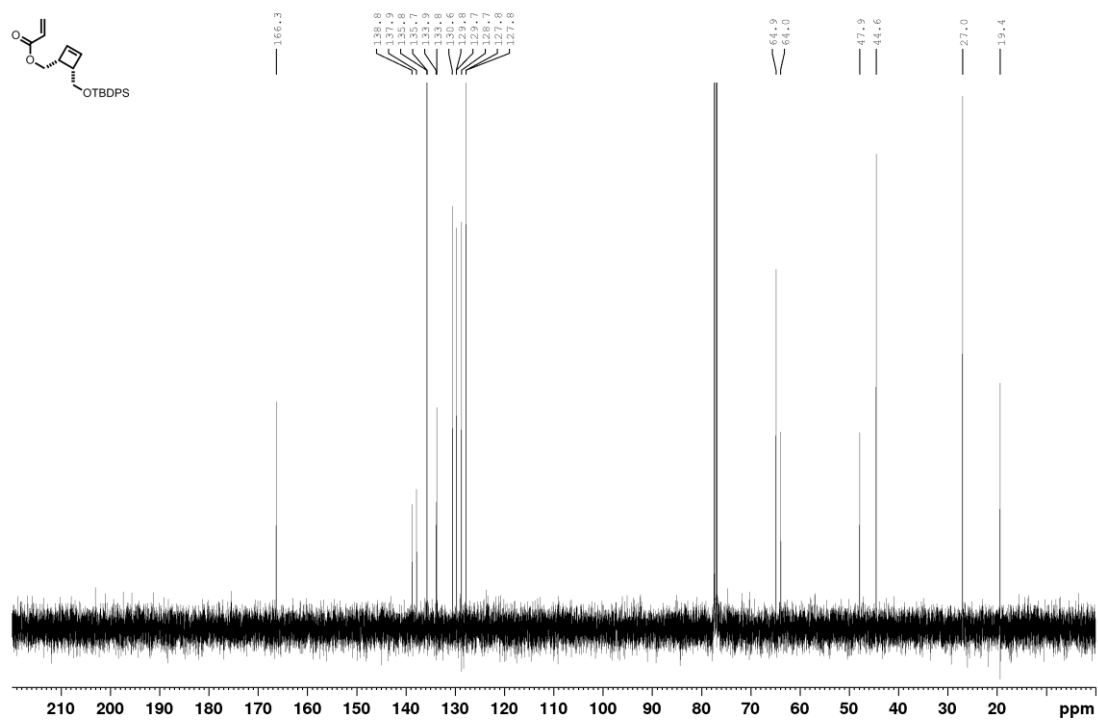
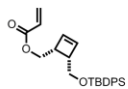
¹H NMR: (CDCl₃, 400 MHz) δ = 7.69-7.64 (m, 4H), 7.45-7.35 (m, 6H), 6.34 (dd, *J* = 17.4, 1.5 Hz, 1H), 6.14 (dd, *J* = 2.8, 0.7 Hz, 1H), 6.12-6.10 (m, 1H), 6.08 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.78 (dd, *J* = 1.5, 10.4 Hz, 1H), 4.48 (dd, *J* = 11.1, 6.9 Hz, 1H), 4.33 (dd, *J* = 11.1, 7.4 Hz, 1H), 3.80 (d, *J* = 6.9 Hz, 2H), 3.29-3.23 (m, 1H), 3.22-3.16 (m, 1H), 1.05 (s, 9H); ¹³C NMR: (CDCl₃, 100 MHz) δ = 166.3, 138.8, 137.9, 135.8, 135.7, 133.9, 133.8, 130.6, 129.8, 128.7 (2 signals), 127.8 (2

signals), 64.9, 64.0, 47.9, 44.6, 27.0, 19.4; **HRMS (ESI-TOF)**: calc. for $[M+H]^+$: 407.2037, found 407.2030; calc. for $[M-C_3H_3O_2]^+$: 335.1826, found 335.1822; **IR (neat)**: 3070, 3049, 2957, 2931, 2894, 2858, 2369, 2339, 2333, 1725, 1634, 1622, 1469, 1427, 1406, 1388, 1363, 1293, 1269, 1185, 1108, 1081, 1052, 1002, 983, 938, 886, 821, 811, 777, 736 702, 611; $[\alpha]^{20}_D = +5.21 \pm 0.05^\circ$ ($c = 1.03$, $CHCl_3$); **Rf-value**: 0.34 (Et₂O:hexanes 1:10)

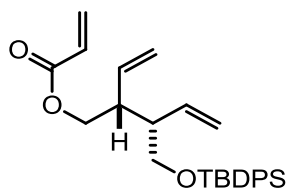
C20BL-104-5-analytics



C20BL-104-5-analytics



276 (2R,3S)-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2-vinylpent-4-en-1-yl acrylate

Chemical Formula: $C_{27}H_{34}O_3Si$

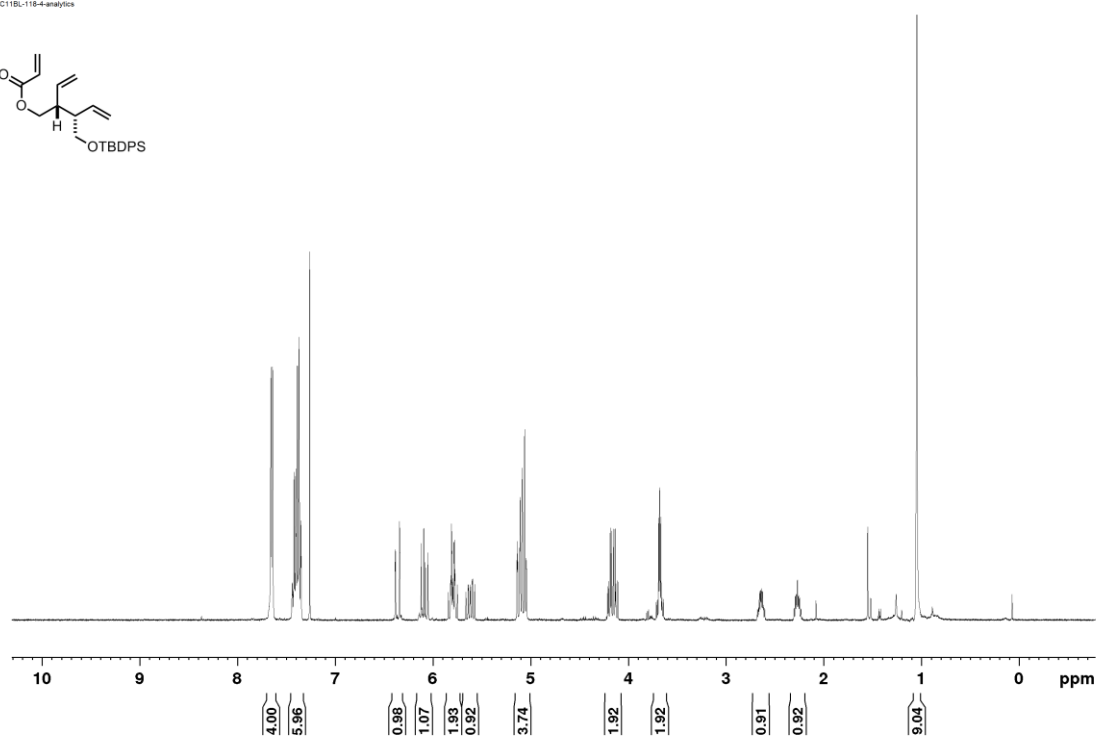
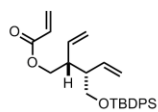
Exact Mass: 434.2277

Molecular Weight: 434.6426

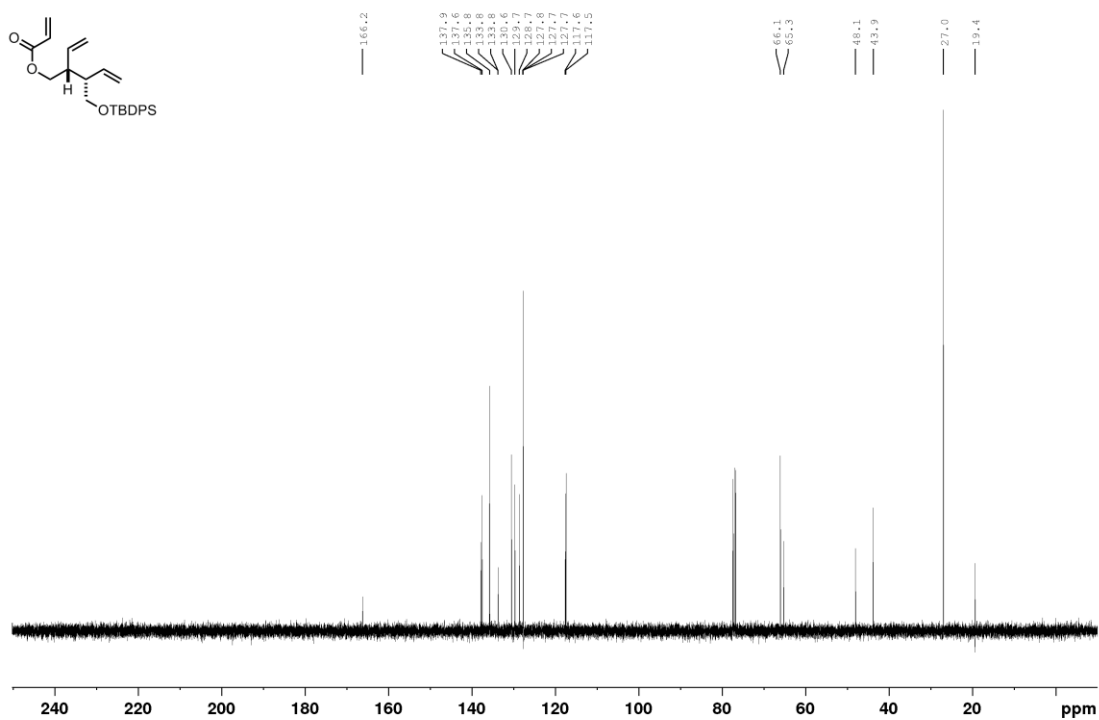
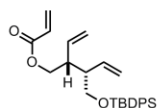
261 in a minimal residue of hexane (around 40 mL) was placed under an atmosphere of argon and dissolved in CH_2Cl_2 (230 mL, over MS, stabilized) and transferred via cannula into a two-necked round bottom flask equipped with a rubber septum and a three-way tap. Both an ethylene bottle and a balloon (Orsatblase, supplier: Faust) as an ethylene reservoir were connected to the tap. The SM was rinsed with CH_2Cl_2 (4x24 mL). The solution was subjected to 3 cycles of freeze and thaw, then flooded with ethylene. Grubbs I (1.1 g, 0.03 eq.) in CH_2Cl_2 (12 mL) was sparged with ethylene for 1 min and transferred into the reaction vessel. It was rinsed with CH_2Cl_2 (2x6 mL). The mixture was stirred for 7 h, by which time the ethylene was used and the balloon was refilled. After 12 h Grubbs I (0.55 g, 0.015 eq.) was added in CH_2Cl_2 (6 mL, rinsed with 2x3 mL), warmed reaction to 35 °C and stirred for another 16 h. The material was directly flushed through a plug of silica (8 cm \varnothing ; height 8 cm with 3 cm of cellite on top, eluent 1:10 Et_2O :hexanes for flushing). The resulting solution of **276** obtained had a slightly golden color. **Note: If concentrated, this compound is prone to polymerization.**

1H NMR: ($CDCl_3$, 400 MHz) δ = 7.69-7.62 (m, 4H), 7.45-7.34 (m, 6H), 6.36 (dd, J = 17.4, 1.4 Hz, 1H), 6.08 (dd, J = 17.3, 10.4 Hz, 1H), 5.79 (ddd, J = 17.0, 9.9, 9.8 Hz, 1H), 5.79 (dd, J = 10.4, 1.4 Hz, 1H), 5.62 (ddd, J = 16.7, 10.0, 9.4 Hz, 1H), 5.15-5.03 (m, 2H), 4.19 (dd, J = 11.0, 4.6, 1H), 4.13 (dd, J = 11.0, 7.6, 1H), 3.72 -3.63 (m, higher order pattern, 2H), 2.69-2.59 (m, 1H), 2.32-2.22 (m, 1H), 1.05 (s, 9H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 166.2, 137.9, 137.6, 135.8, 133.8, 133.8, 130.6, 129.7, 128.7, 127.8, 127.7, 127.7, 117.6, 117.5, 66.1, 65.3, 48.1, 43.9, 27.0, 19.4; **HRMS (ESI-TOF):** calc. for $[M+H]^+$: 435.2350, found 435.2348; calc. for $[M-Acrylate]^+$: 363.2139, found 363.2140; **IR (neat):** 3072, 3051, 2956, 2931, 2893, 2858, 1726, 1638, 1469, 1425, 1406, 1363, 1294, 1270, 1188, 1107, 1063, 988, 918, 881, 821, 807, 740, 702, 611; **$[\alpha]^{20}_D$** = $-5.00 \pm 0.03^\circ$ (c = 0.555, $CHCl_3$); **Rf-value:** 0.31 in EtOAc:hexanes 1:10

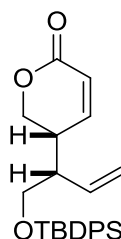
C11BL-118-4-analytics



C11BL-118-4-analytics



6 (R)-5-((S)-1-((tert-butyldiphenylsilyl)oxy)but-3-en-2-yl)-5,6-dihydro-2H-pyran-2-one



Chemical Formula: $C_{25}H_{30}O_3Si$

Exact Mass: 406.1964

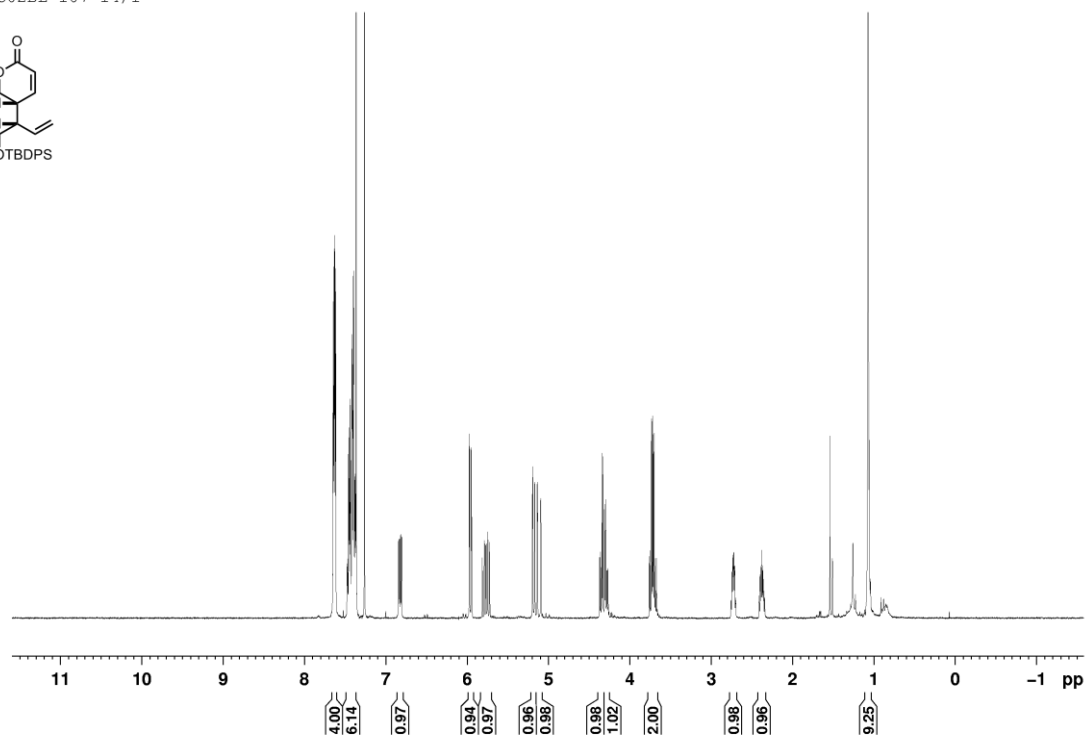
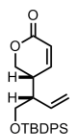
Molecular Weight: 406.5894

A flame dried 2 L flask equipped with a reflux condenser was charged with CH_2Cl_2 (around 400 mL, bottled, over MS). **276** (around 60 mL of a solution in hexanes) was diluted with PhH (100 mL) and coevaporated to around 60 mL volume. This process was repeated once more. The solution was transferred via canula into the reaction flask and rinsed with CH_2Cl_2 (3x50 mL). Piers Grubbs 2nd generation catalyst (1.15 g, 0.03 eq.) was weighed in a glove box into a 25 mL round bottom flask and closed with a septum. The catalyst was dissolved in CH_2Cl_2 (12.5 mL), transferred into the reaction mixture and rinsed with CH_2Cl_2 (6.25 mL). The mixture was subjected to two cycles of freeze and thaw, the first time the color being olive green, the second time beige brown. After observing the brown color, the intended third cycle was omitted and the mixture was stirred at 40 °C. Conversion was assessed by evaporating 0.4 mL aliquots to dryness and measuring 1H NMR: (Pr, 6.82 ppm, 1H), (SM, 6.36 ppm, 1H). After 16 h, 23 h and 38 h another portion of catalyst (1.15 g, 0.03 eq., each time) was added in CH_2Cl_2 (12.5 mL + 6.25 mL). After 44 h, the material was loaded onto a column without concentrating and purified by FC (3 cm cellite on top, conditioned and first eluted with CH_2Cl_2 , then Et_2O :hexanes 1:5, Et_2O :hexanes 3:8, then 2:6). Mixed fractions were repurified by FC (Et_2O :hexanes 3:5, then 1:4 $EtOAc$:hexanes) to recover give pure **276** (0.91 g, 4 %), provide clean product (2.62 g, 12% over 3 steps) and a larger batch of product (7.65 g, 34%) that contained a strongly UV active impurity, but was clean by 1H NMR. The latter batch behaved identical in subsequent reactions.

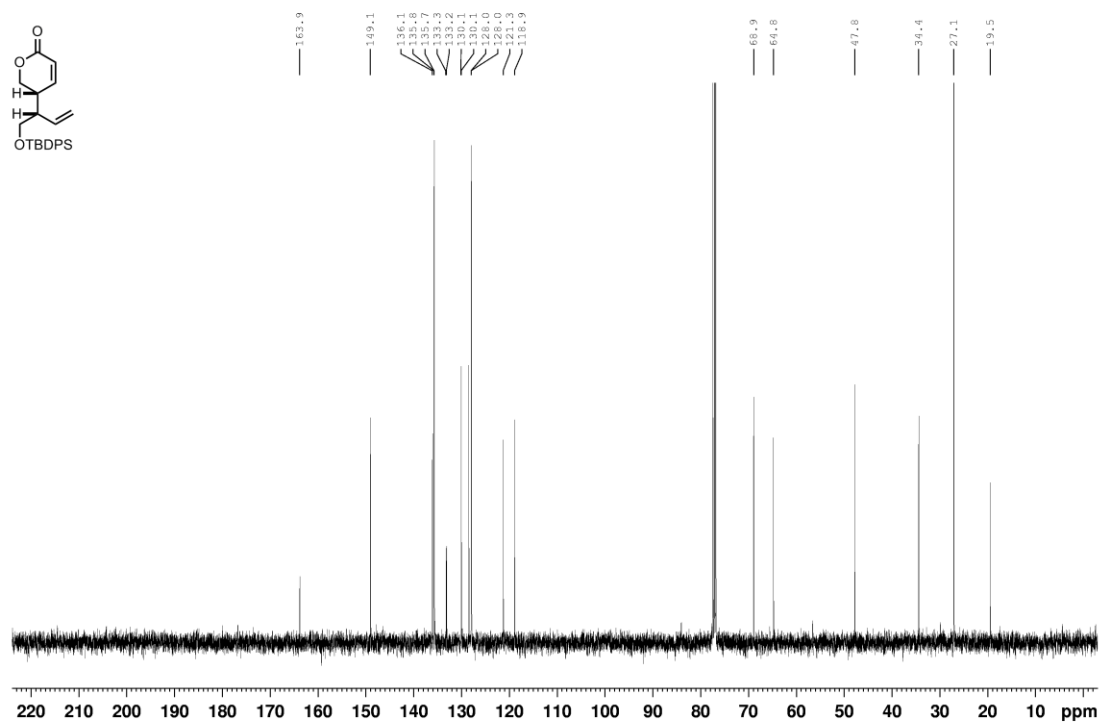
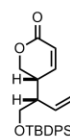
1H NMR: ($CDCl_3$, 400 MHz) δ = 7.66-7.61 (m, 4H), 7.48-7.36 (m, 6H), 6.82 (dd, J = 9.9, 4.7 Hz, 1H), 5.96 (dd, J = 9.9, 1.5 Hz, 1H), 5.77 (ddd, J = 17.1, 10.3, 9.6 Hz, 1H), 5.18 (dd, J = 10.3, 1.5 Hz, 1H), 5.11 (ddd, J = 17.1, 1.5, 0.7 Hz, 1H), 4.35 (dd, J = 11.3, 4.7 Hz, 1H), 3.74 (dd, J = 10.4, 4.5 Hz, 1H), 3.69 (dd, J = 10.5, 5.2 Hz, 1H), 2.77-2.69 (m, 1H), 2.42-2.33 (m, 1H), 1.07 (s, 9H);

¹³C NMR: (CDCl₃, 100 MHz) δ = 163.9, 149.1, 136.1, 135.8, 135.7, 133.3, 133.2, 130.1, 130.1, 128, 128, 121.3, 118.9, 68.9, 64.8, 47.8, 34.4, 27.1, 19.5; **HRMS (ESI-TOF):** calc. for [M-Na]⁺: 424.2302, found 424.2306; **IR (neat):** 3070, 2934, 2892, 2859, 2353, 1729, 1591, 1467, 1426, 1388, 1272, 1226, 1105, 1081, 997, 926, 821, 742, 701, 612; **[α]²⁴_D** = +56.51 \pm 0.03° (c = 0.78, CHCl₃); **Rf-value:** 0.32 (EtOAc:hexanes 1:3)

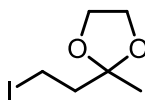
C02BL-107-14/1



C02BL-107-14/2



278 2-(2-iodoethyl)-2-methyl-1,3-dioxolane

Chemical Formula: $C_6H_{11}IO_2$

Exact Mass: 241.9804

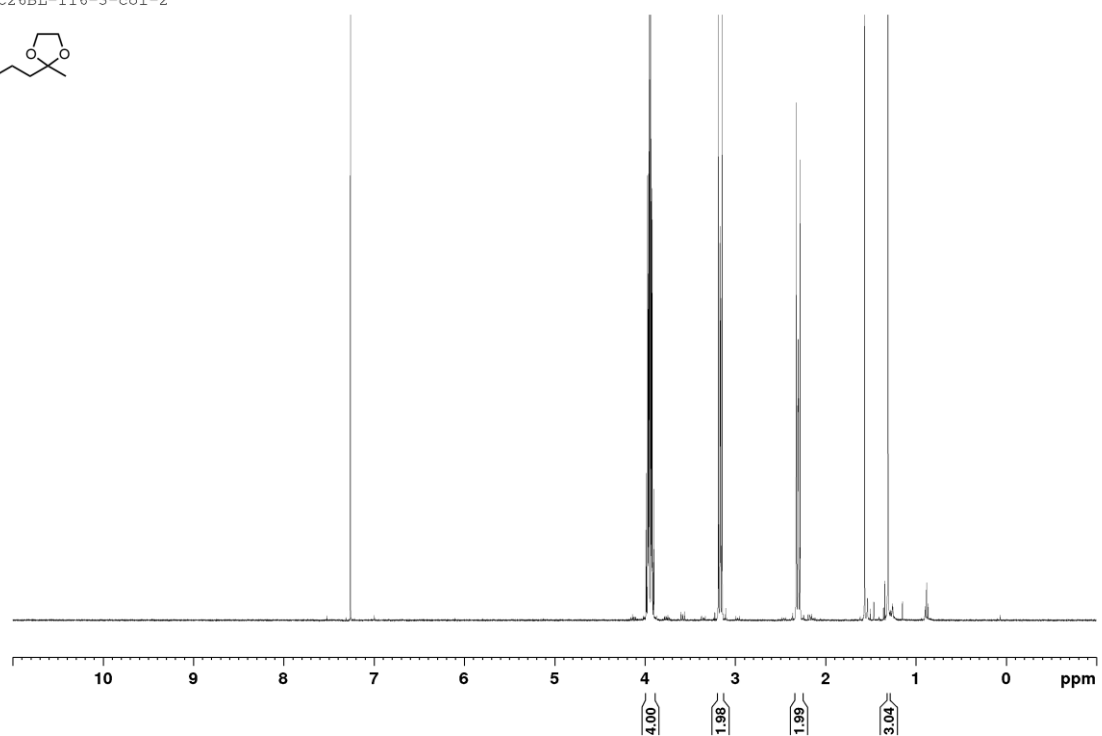
Molecular Weight: 242.0548

To a solution of NaI (18 g, 120 mmol, 1.26 eq., dried @ 70 °C in vacuum overnight) and 3-buten-2-one (8.11 mL, 95 mmol, 1 eq., freshly distilled from CaH_2 and K_2CO_3 , 200 mbar, around 70-75 °C) in MeCN (250 mL, technical grade, fresh bottle) was rapidly added with vigorous stirring TMSCl (15.2 mL, 120 mmol, 1.26 eq.). The resulting off-white cloudy solution was stirred for 5 min and ethylene glycol (6.7 mL, 120 mmol, 1.26 eq.) was added rapidly followed by stirring for 5 min, after which time the now dark yellow brown reaction mixture was poured onto $NaHCO_3$ (100 mL, aq., 5%) overlaid with pentane (300 mL). This produced after thorough mixing three distinct liquid phases. The aqueous, undermost layer was removed, and the remaining organic phases were washed with $Na_2S_2O_3$ (100 mL, aq., 5%), and then with brine (100-mL portions) until only a single organic phase was remaining. This required around twelve washes. The pentane layer directly concentrated. It was purified twice by flash chromatography (Aluminium oxide, 1:10 Et_2O :pentane) to give the title compound as a colorless oil (4.58 g, 17%).

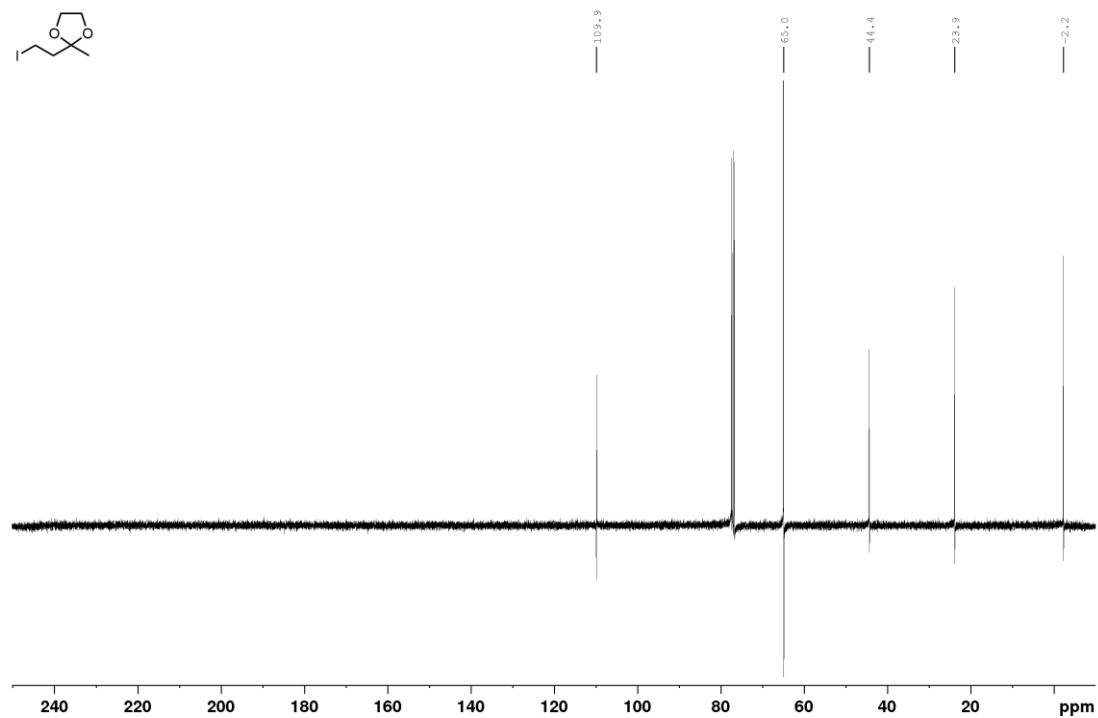
1H NMR: ($CDCl_3$, 400 MHz) δ = 3.99-3.89 (higher order coupling pattern, 4H), 3.19-3.13 (higher order coupling pattern, 2H), 2.32-2.27 (higher order coupling pattern, 2H), 1.31 (s, 3H); **^{13}C**

NMR: ($CDCl_3$, 100 MHz) δ = 109.9, 65.0, 44.4, 23.9, -2.2

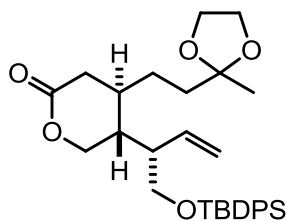
C26BL-116-3-col-2



C26BL-116-3-col-2



279 (4R,5R)-5-((S)-1-((tert-butyldiphenylsilyl)oxy)but-3-en-2-yl)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)tetrahydro-2H-pyran-2-one



Chemical Formula: C₃₁H₄₂O₅Si

Exact Mass: 522.2802

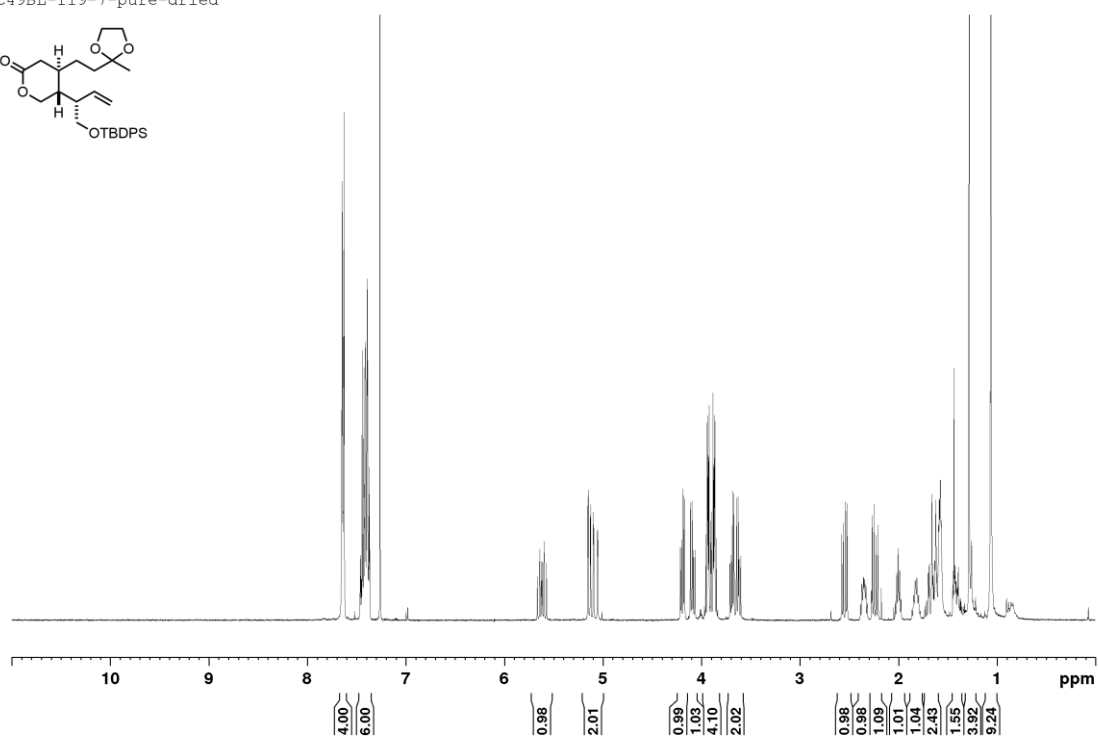
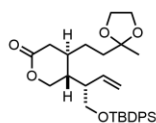
Molecular Weight: 522.7477

278 (136 mg, 0.92 mmol, 4 eq., bulk coevaporated twice with benzene) in Et₂O (10.7 mL) in a 100 mL Schlenk flask was cooled to -78 °C and added was t-BuLi (1.08 mL, 8.2 eq., Aldrich, 1.74 M in pentane, titrated directly before use) over 3 min letting it flow along the wall of the flask. After complete addition, the solution was till clear with no precipitate. Stirred at this temperature for 1 h 40 min (was then white cloudy). Warmed to ambient temperature in a water bath for 5 min, cooled again and added was lithium 2-thienylcyanocuprate (3.86 mL, 0.966 mmol, 4.2 eq. 0.25 M in THF) along the wall of the flask, a small amount of light green precipitate was visible. The mixture was stirred for 3 h. **6** (100 mg, 0.23 mmol, 1 eq.) was weighed in a flask, coevaporated with benzene twice and put under an atmosphere of argon. It was added to the reaction mixture in Et₂O (1 mL + 1 mL rinsing). The solution turned clear yellow upon addition and was stirred for 2 h 15 min at -78 °C, then transferred into an *i*-PrOH bath @ -45 °C. After stirring overnight, the yellow solution with some yellow precipitates on the flask wall was warmed to ambient temperature and stirred for 5 h, during which it stayed yellow. It was quenched with sat. NH₄Cl/ 25% NH₃ (18 mL, 1:1) and the solution was stirred for 30 min, then diluted with 20 mL EtOAc. Phases were separated, the organic phase was washed again with NH₄Cl/25% NH₃ (6 mL, 1:1) and washed with brine (6 mL). The aqueous washes were extracted with EtOAc (10 mL, TLC indicated some residual product) and this organic phase was washed with brine (2x2 mL). The combined organic phases were dried over MgSO₄ and rinsed with EtOAc (20 mL). The crude product was purified by two rounds of FC (Et₂O:hexanes 7:10 to 1:1 to 6:5 and again Et₂O:hexanes 7:5) to give the title compound as a clear colorless oil (97.7 mg, 81%).

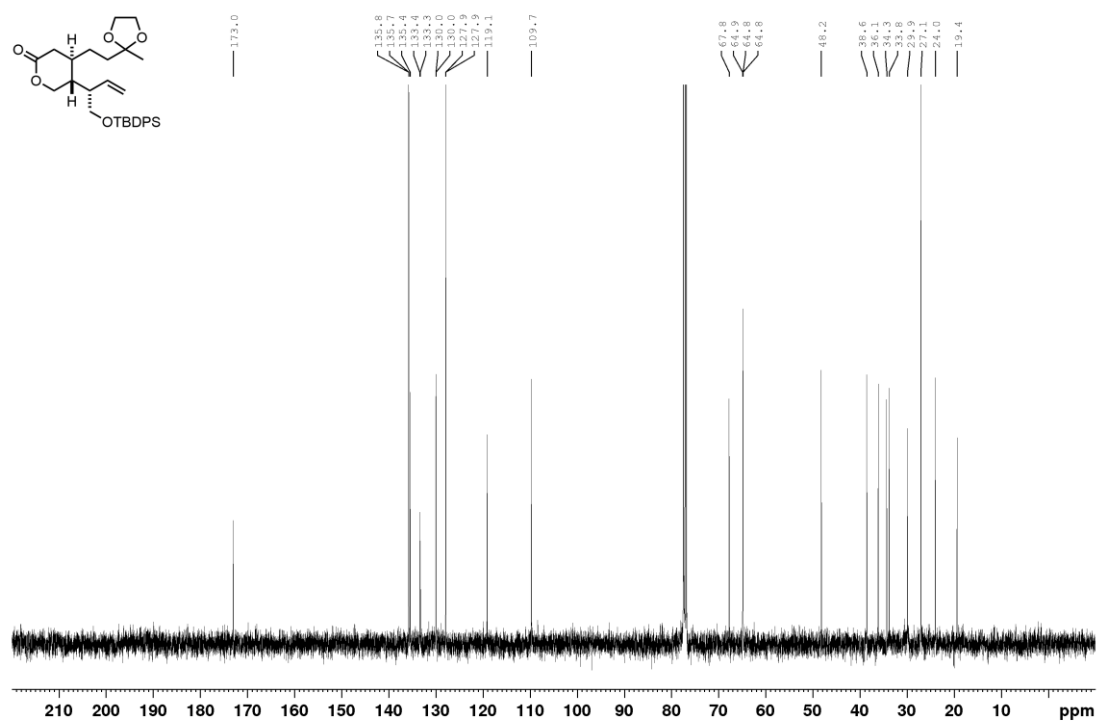
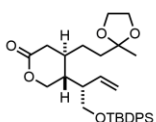
¹H NMR: (CDCl₃, 400 MHz) δ = 7.67-7.61 (m, 4H), 7.47-7.35 (m, 6H), 5.62 (dt, *J* = 17.0, 9.9 Hz, 1H), 5.14 (dd, *J* = 10.3, 1.8 Hz, 1H), 5.07 (ddd, *J* = 17.0, 1.7, 0.6 Hz, 1H), 4.19 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.09 (dd, *J* = 11.7, 6.8 Hz, 1H), 3.97-3.83 (m, 4H), 3.69 (dd, *J* = 10.4, 5.3 Hz, 1H), 3.62

(dd, $J = 10.4, 7.1$ Hz, 1H), 2.55 (dd, $J = 15.8, 6.6$ Hz, 1H), 2.40-2.29 (m, 1H), 2.24 (dd, $J = 15.8, 7.5$ Hz, 1H), 2.04-1.96 (m, 1H), 1.87-1.76 (m, 1H), 1.70-1.6 (m, 2H), 1.45-1.33 (m, 2H), 1.28 (s, 3H), 1.06 (s, 9H); $^{13}\text{C NMR}$: (CDCl_3 , 100 MHz) $\delta = 173.0, 135.8, 135.7, 135.4, 133.4, 133.3, 130.0$ (2 signals), 127.9 (2 signals), 119.1, 109.7, 67.8, 64.9, 64.8 (2 signals), 48.2, 38.6, 36.1, 34.3, 33.8, 29.9, 27.1, 24.0, 19.4; **HRMS (ESI-TOF)**: calc. for $[\text{M}+\text{NH}_4]^+$: 540.3140, found 540.3140; calc. for $[\text{M}-\text{Ph}]^+$: 445.2405, found 445.2406; **IR (neat)**: 2930, 2858, 1750, 1472, 1428, 1377, 1255, 1220, 1048, 998, 922, 857, 823, 741, 613; $[\alpha]^{20}_{\text{D}} = -26.42^\circ$ ($c = 1.02, \text{CHCl}_3$); **Rf-value**: 0.39 (EtOAc:hexanes 1:1)

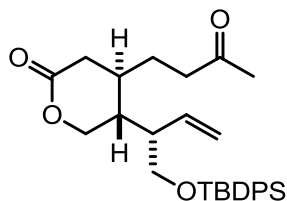
C49BL-119-7-pure-dried



C49BL-119-7-pure-dried



281 (4R,5R)-5-((S)-1-((tert-butyldiphenylsilyl)oxy)but-3-en-2-yl)-4-(3-oxobutyl)tetrahydro-2H-pyran-2-one



Chemical Formula: C₂₉H₃₈O₄Si

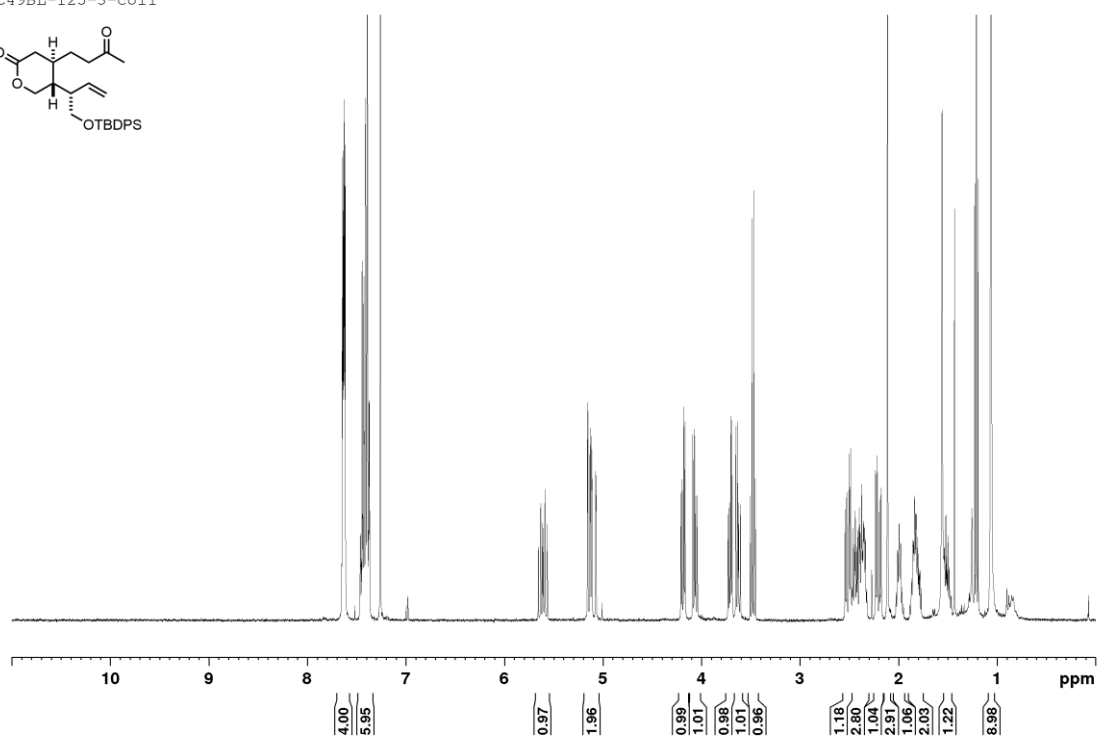
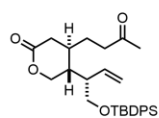
Exact Mass: 478.2539

Molecular Weight: 478.6951

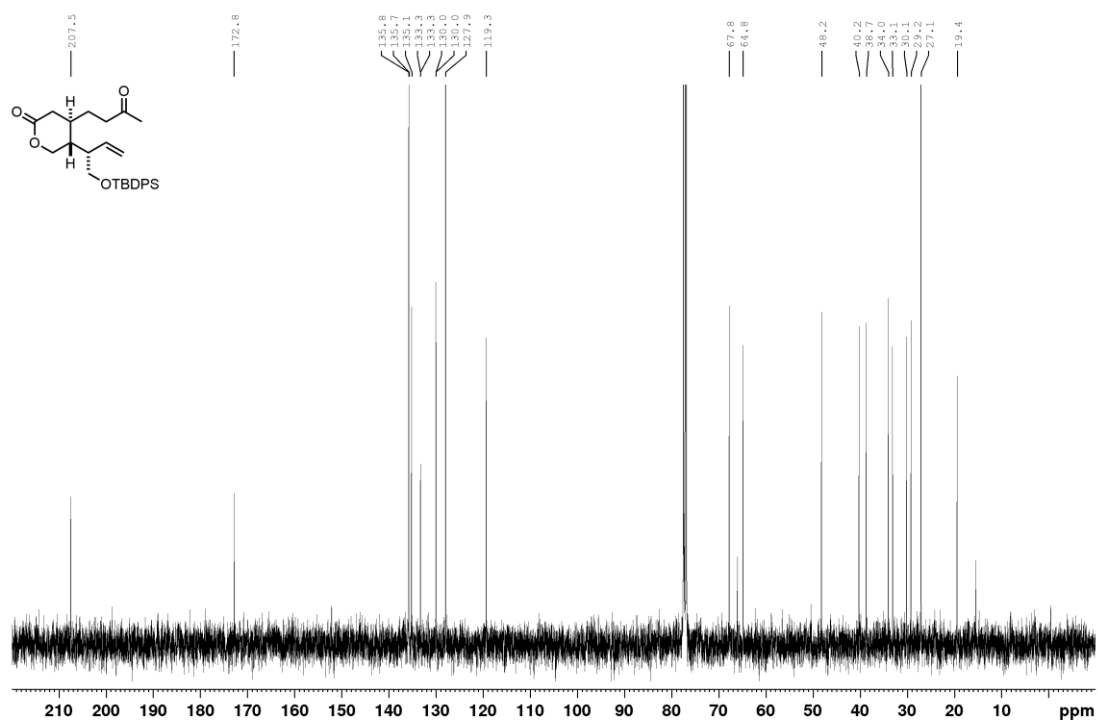
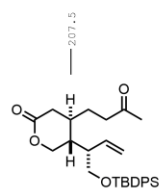
To acetal **279** (147 mg, 0.281 mmol, 1 eq.) in MeCN/H₂O (14.1 mL, 4:1) was added a PPTS (7.1 mg, 28 μ mol, 0.1 eq.). The reaction mixture was stirred at 85 °C for 7 h, cooled to ambient temperature and concentrated in vacuo. To the residue (around 4 mL aq.) was added NaCl and CH₂Cl₂ (15 mL). Phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2x15mL). The combined organics were washed with brine (7.5 mL), dried over MgSO₄, and filtered, and the solvent was removed in vacuo. It was purified by FC (Et₂O:hexanes 7:5 to neat Et₂O) to give the title compound as a copper colored viscous oil (132 mg, 98%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.66-7.60 (m, 4H), 7.48-7.35 (m, 6H), 5.61 (dt, J = 17.0, 9.9 Hz, 1H), 5.14 (dd, J = 10.3, 1.8 Hz, 1H), 5.09 (ddd, J = 17.0, 1.6, 0.5 Hz, 1H), 4.19 (dd, J = 11.7, 5.0 Hz, 1H), 4.06 (dd, J = 11.7, 7.3 Hz, 1H), 3.71 (dd, J = 10.4, 5.2 Hz, 1H), 3.63 (dd, J = 10.4, 7.3 Hz, 1H), 2.51 (dd, J = 15.7, 6.7 Hz, 1H), 2.48-2.31 (m, 3H), 2.20 (dd, J = 15.7, 6.9 Hz, 1H), 2.11 (s, 3H), 2.03-1.94 (m, 1H), 1.89-1.76 (m, 2H), 1.55-1.45 (m, 1H), 1.06 (s, 9H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 207.5, 172.8, 135.8, 135.7, 135.1, 133.3 (2 signals), 130.0 (2 signals), 127.9 (2 signals), 119.3, 67.8, 64.8, 48.2, 40.2, 38.7, 34.0, 33.1, 30.1, 29.2, 27.1, 19.4; **HRMS (ESI-TOF):** calc. for [M+NH₄]⁺: 496.2878, found 496.2870; calc. for [M-Ph]⁺: 401.2143, found 401.2145; **IR (neat):** 2930, 2858, 1748, 1715, 1472, 1428, 1359, 1261, 1164, 1008, 998, 923, 823, 741, 701, 613; **$[\alpha]^{20}_D$** = -27.88° (c = 1.07, CHCl₃); **Rf-value:** 0.34 (EtOAc:hexanes 1:1)

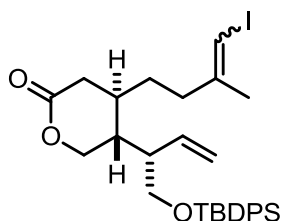
C49BL-125-3-col1



C49BL-125-3-col1



282 (4R,5R)-5-((S)-1-((tert-butyldiphenylsilyl)oxy)but-3-en-2-yl)-4-(4-iodo-3-methylbut-3-en-1-yl)tetrahydro-2H-pyran-2-one



Chemical Formula: $C_{30}H_{39}IO_3Si$

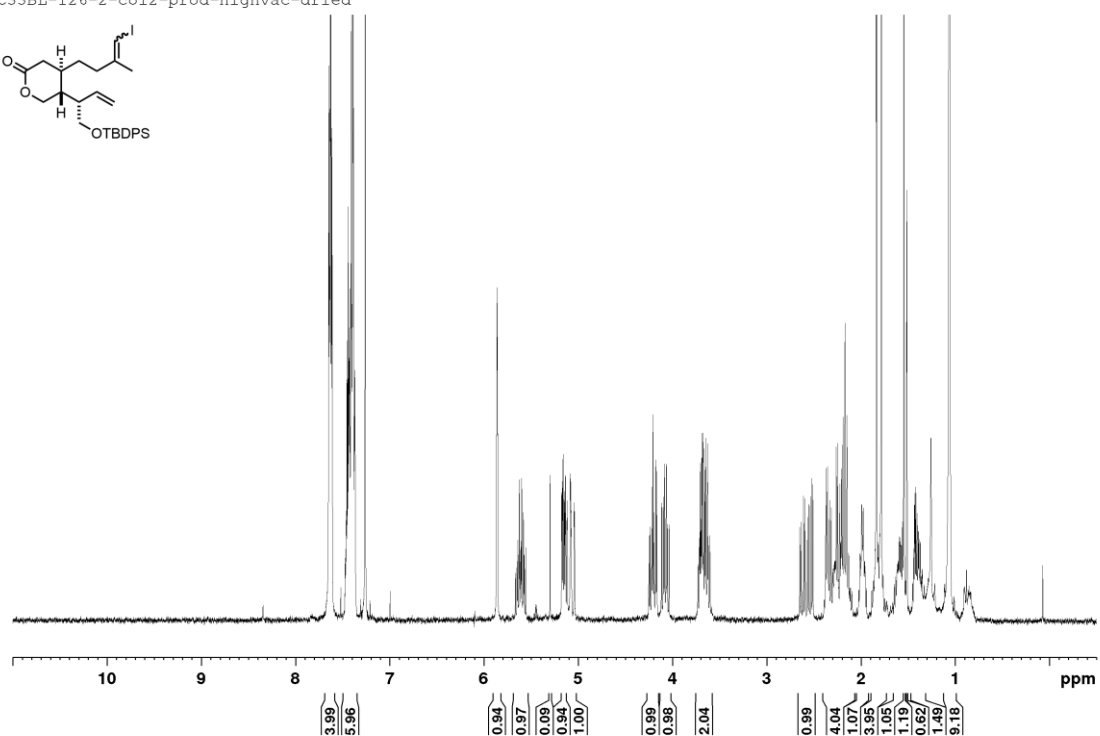
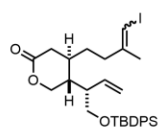
Exact Mass: 602.1713

Molecular Weight: 602.6188

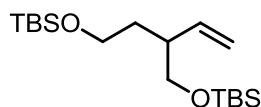
A 10 mL round bottom flask was heat-gun dried and put under vacuum. In a glovebox it was charged with $CrCl_2$ (206 mg, 1.65 mmol, 6 eq.). This was suspended in THF (1 mL) at 0 °C and dropwise was added iodoform (220 mg, 0.55 mmol, 3 eq.) in THF (1 mL) and rinsed with THF (1 mL). The mixture turned a strong orange then burgundy within a minute. **281** (132 mg, 0.276 mmol, 1 eq.) in THF (1 mL+2x1mL) was added and rinsed. The mixture was warmed to ambient temperature after 10 min. and stirred for a total of 21 h during which the mixture had turned into a rusty red color. The mixture was poured into water/sat. aq. $Na_2S_2O_3$ (8 mL, 1:1) and extracted with Et_2O (4x10 mL). The green organic layer was washed twice with 6 mL of an aqueous mixture (5:5:2 water/brine/ $Na_2S_2O_3$). It was dried over anhydrous $MgSO_4$ and filtered. The residue was purified by FC (Et_2O :hexanes 1:1 to neat Et_2O) to give the title compound as a slightly yellow oil (100.6 mg, 61%) as well as some recovered **281** as a clear, colorless oil (8.7 mg, 7%).

1H NMR: ($CDCl_3$, 400 MHz) δ = 7.67 (m, 4H), 7.48-7.35 (m, 6H), 5.88-5.84 (m, 1H), 5.61 (dtd, J = 16.7, 10.0, 6.7 Hz, 1H), 5.15 (ddd, J = 10.2, 4.9, 1.7 Hz, 1H), 5.08 (ddd, J = 13.6, 1.6, 0.6 Hz, 1H), 4.21 (ddd, J = 16.9, 11.8, 5.0 Hz, 1H), 4.08 (td, J = 12.3, 7.5 Hz, 1H), 3.74-3.59 (m, 2H), 2.58 (ddd, J = 32.8, 15.8, 6.8 Hz, 1H), 2.29 (ddd, J = 44.0, 15.8, 7.0 Hz, 1H), 2.40-2.07 (m, 3H), 2.05-1.93 (m, 1H), 1.90-1.70 (m, 1H), [1.83 (d, J = 1.4 Hz) and 1.78 (d, J = 0.9 Hz), 3H], 1.66-1.55 (m, 1H), 1.46-1.32 (m, 1H), 1.06 (s, 2 signals, 9H); **Rf-value:** 0.50 ($EtOAc$:hexanes 1:3), 0.13 (Et_2O :hexanes 1:3), 0.31 (Et_2O :hexanes 1:1)

C33BL-126-2-col2-prod-highvac-dried



303 2,2,3,3,10,10,11,11-octamethyl-6-vinyl-4,9-dioxa-3,10-disiladodecane

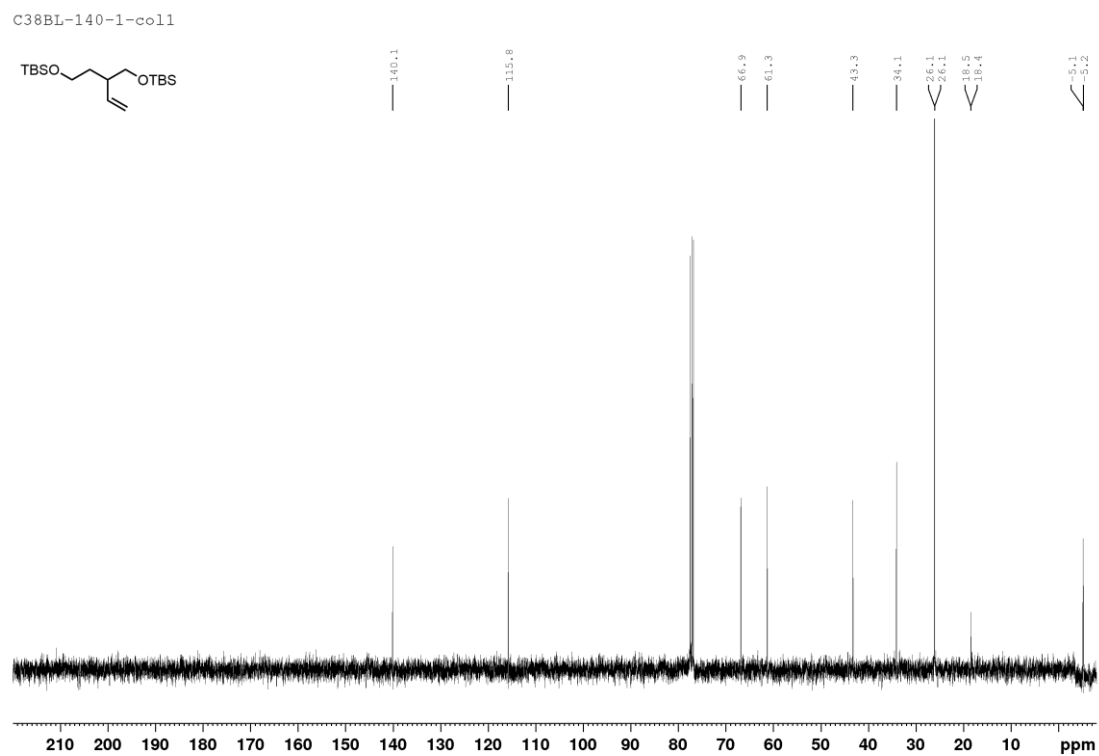
Chemical Formula: $C_{18}H_{40}O_2Si_2$

Exact Mass: 344.2567

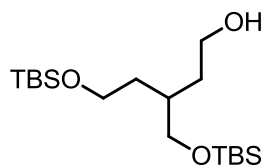
Molecular Weight: 344.6800

To a solution of alcohol **181** (200 mg, 0.868 mmol, 1 eq.) in CH_2Cl_2 (8.5 mL) at ambient temperature was added imidazole (219 mg, 3.21 mmol, 3.7 eq.) followed by TBSCl (157 mg, 1.04 mmol, 1.2 eq.). The reaction mixture quickly turned cloudy and was stirred for 3 days over the weekend. The mixture was diluted with CH_2Cl_2 (50 mL) and washed sequentially with NH_4Cl (3x5 mL, sat., aq., 1 mL H_2O was added to the first wash), $NaHCO_3$ (2x5 mL sat., aq.) and brine (5 mL). The solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by FC (Et_2O :hexanes 1:40) to give the pure title compound as a clear, colorless liquid (285.5 mg, 95 %).

1H NMR: ($CDCl_3$, 400 MHz) δ = 5.70-5.69 (m, 1H), 5.07-5.03 (m, 1H), 5.03-5.00 (m, 1H), 3.68-3.54 (m, 2H), 3.55-3.47 (m, 2H), 2.37-2.25 (m, 1H), 1.80-1.71 (m, 1H), 1.59-1.39 (m, 1H), 0.89 (2xs, 18H), 0.04 (s, 6H), 0.03 (s, 6H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 140.1, 115.8, 66.9, 61.3, 43.3, 34.1, 26.1 (2 signals), 18.5, 18.4, -5.1 (2 signals), -5.2 (2 signals); **HRMS (ESI-TOF):** calc. for $[M+Na]^+$: 345.2640, found 345.2643; **IR (neat):** 2954, 2931, 2892, 2858, 2364, 1468, 1387, 1362, 1253, 1094, 1005, 940, 915, 775, 666; **Rf-value:** 0.84 ($EtOAc$:hexanes 1:10), 0.60 (Et_2O :hexanes 1:20)



304 5-((tert-butyldimethylsilyl)oxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)pentan-1-ol

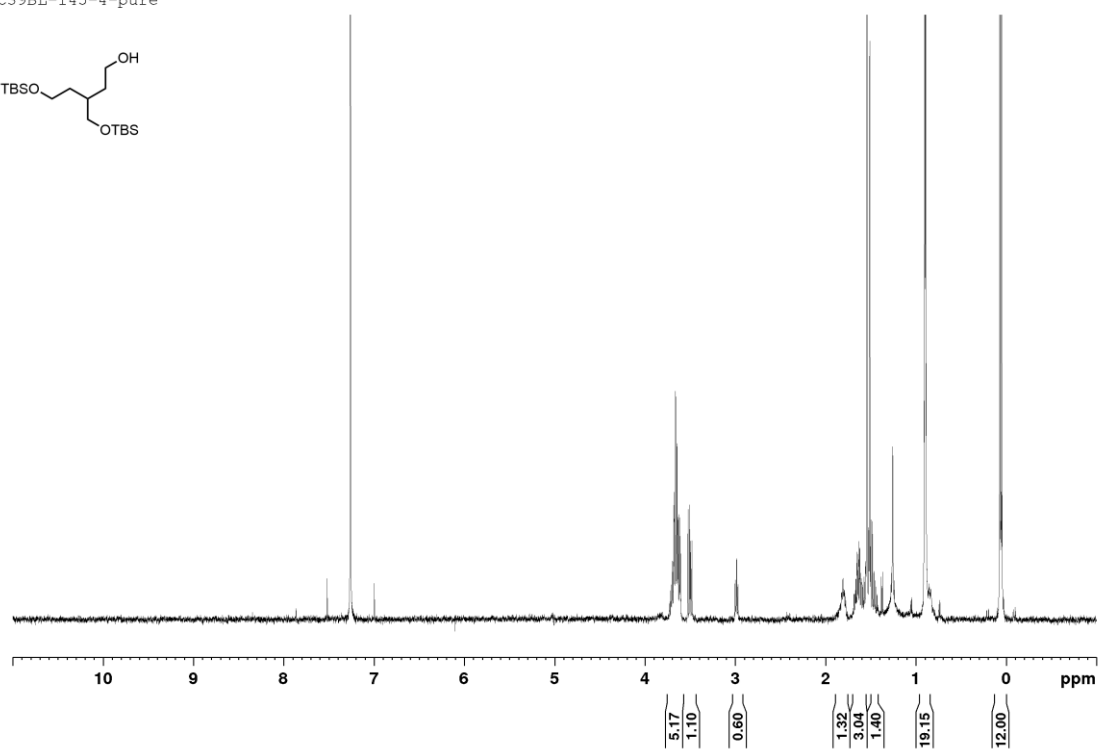
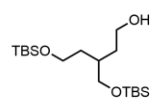
Chemical Formula: C₁₈H₄₂O₃Si₂

Exact Mass: 362.2672

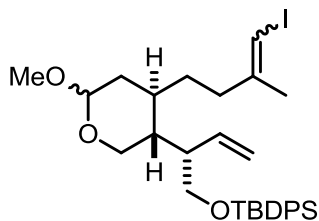
Molecular Weight: 362.6953

An oven-dried microwave vial was flushed with Argon, capped and further flushed with Argon through a syringe needle. **303** (172.8 mg, 58 μ mol, 1 eq.) was dried on the vacuum for 2 h and added was THF (2.5 mL). 0.3 mL of this stock solution was transferred to the microwave vial. 9-BBN (30.5 mg, 0.25 mmol) was dissolved in a small amount of THF by sonication, then filled up to 1 mL in a volumetric flask. 9-BBN solution (0.35 mL, 87 μ mol, 1.5 eq.) was added to the starting material dropwise at ambient temperature, upon which some effervescence was observable. The clear solution was stirred at 45 °C for 18 h, with good conversion, but still some SM visible. 9-BBN was quenched by dropwise addition of MeOH (33 μ L, 14 eq.), NaOH (3 M, 29 μ L, 1.5 eq.) and H₂O₂ (30 %, 26 μ L, 4.4 eq.). The mixture was then stirred for 2 h at 45 °C. brine (1 mL) and water (0.5 mL) were added and the mixture was extracted with Et₂O (3x5 mL). The organic phases were washed with brine (1 mL) and dried over MgSO₄. The solvent was removed and the crude material was purified by FC (EtOAc:hexanes1:10) to give the pure title product as clear colorless oil (14.7 mg, 70 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 3.73-3.59 (m, 5H), 3.50 (dd, J = 10.1, 7.0 Hz, 1H), 2.99 (t, J = 6.0 Hz, 0.6H, OH), 1.89-1.75 (m, 1H), 1.70-1.55 (m, 3H), 1.50-1.42 (m, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.07 (s, 6H), 0.05 (s, 6H); **Rf-value:** 0.27 (EtOAc:hexanes 1:5)



305 tert-butyl((((2S)-2-((3R,4R)-4-(4-iodo-3-methylbut-3-en-1-yl)-6-methoxytetrahydro-2H-pyran-3-yl)but-3-en-1-yl)oxy)diphenylsilane



Chemical Formula: $C_{31}H_{43}IO_3Si$

Exact Mass: 618.2026

Molecular Weight: 618.6613

A stock solution of lactone **282** (49.2 mg) CH_2Cl_2 (0.7 mL) prepared. 0.36 mL of this solution were transferred into a dried flask (25.3 mg, 43 μ mol, 1 eq.) under argon and cooled to $-78^\circ C$. DIBAL-H (52 μ L, 52 μ L, in CH_2Cl_2 , 1.25 eq.) was added dropwise. After 15 min, reaction was still incomplete. Additional DIBAL-H (15 μ L, 0.36 eq.) was added. 15 min later conversion was still not quite complete, so again DIBAL-H (15 μ L, 0.36 eq.) was added. After 10 min, all the SM had disappeared. It was quenched with acetone (50 μ L), then Rochelle's salt solution (1 mL, sat., aq.) was added, followed by EtOAc (5 mL). It was stirred for 1 h, until the two phases were clear. Phases were separated and the aqueous phase was extracted with EtOAc (2x5 mL). The combined organic extracts were washed with brine (1 mL), then dried over $MgSO_4$ and the solvent was evaporated. The resulting crude lactol was obtained as clear, colorless oil (24.3 mg, 97%) and was used for the methyl acetal formation without purification.

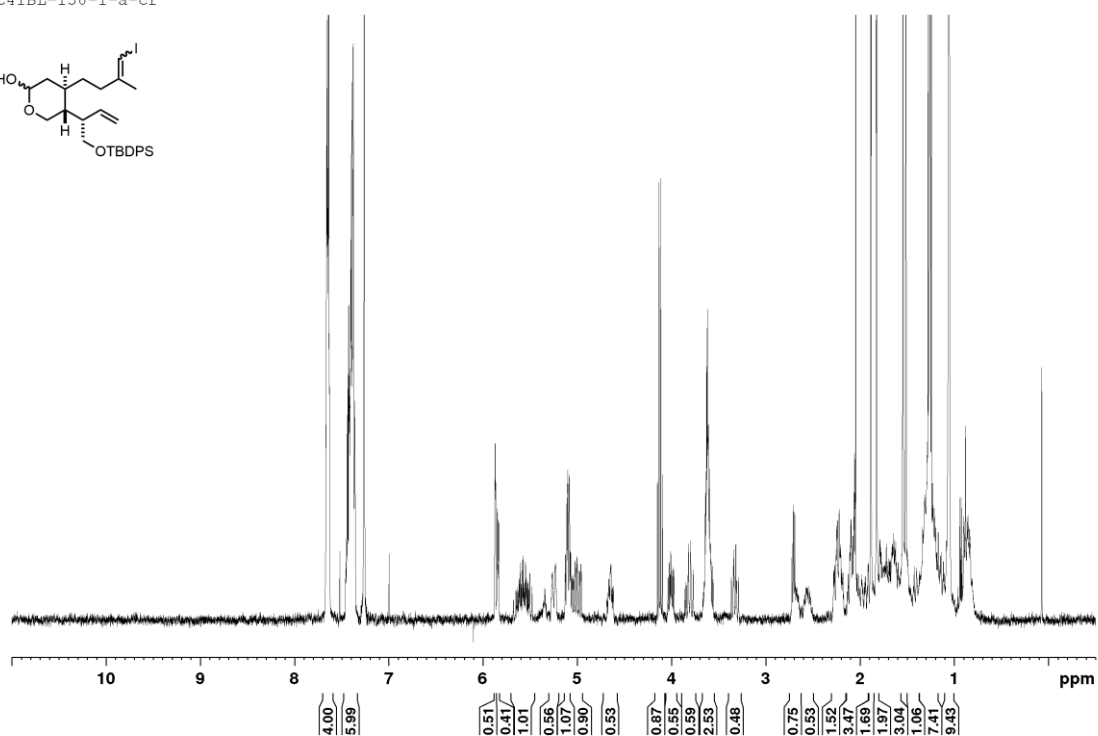
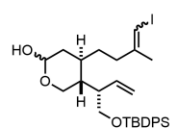
1H NMR: ($CDCl_3$, 400 MHz) δ = 7.68-7.62 (m, 4H), 7.47-7.34 (m, 6H), 5.89-5.86 (m, 0.5H), 5.86-5.82 (m, 0.5H), 5.70-5.47 (m, 1H), 5.25 (d, br, J = 12.2 Hz, 0.5H), 5.14-5.08 (m, 1H), 5.08-4.95 (m, 1H), 4.79-4.61 (m, 0.5H), 4.05-3.97 (m, 0.5H), 3.86-3.75 (m, 0.5H), 3.67-3.55 (m, 2.5H), 3.33 (td, J = 11.7, 8.5 Hz, 0.5H), 2.74-2.62 (m, 0.75H), 2.62-2.49 (m, 0.5H), 2.30-2.15 (m, 1.5H), the remaining aliphatic signals were not assigned except the two methyl groups signals 1.88 (d, J = 1.3 Hz) and 1.83 (t, J = 1.2 Hz) and the *t*-Bu group 1.05 (s, 9H); **Rf-value:** 0.21 (EtOAc:hexanes 1:3)

To a solution of the crude lactol in MeOH (0.3 mL) was added a solution of PPTS (0.5 mg, 2.1 μ mol, 0.05 eq.) in MeOH (0.05 mL) and and rinsed with MeOH (0.05 mL). The mixture was stirred at ambient temperature for 30 h. The reaction was quenched with $NaHCO_3$ (2 mL, sat., aq., gave cloudy solution) and diluted with water (1 mL). Extracted with EtOAc (3x5 mL). The combined organic extracts were washed with $NaHCO_3$ (1 mL, sat., aq.), brine (1 mL), dried over

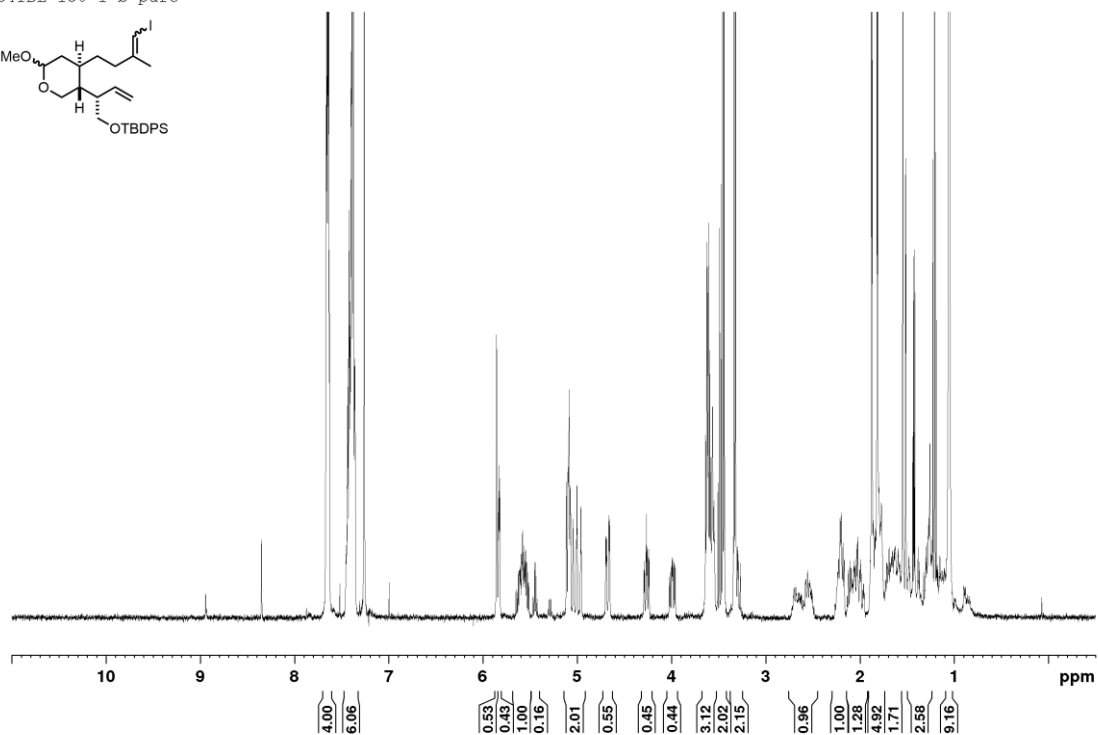
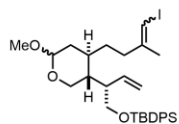
MgSO₄ and evaporated. The crude material was purified by FC (1:10 Et₂O:hexanes) to give the title compound as a clear, colorless oil (21.2 mg, 82%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.68-7.62 (m, 4H), 7.47-7.34 (m, 6H), 5.87-5.84 (m, 0.5H), 5.84-5.81 (m, 0.5H), 5.66-5.49 (m, 1H), 5.13-4.95 (m, 2H), 4.71-4.64 (m, 0.5H), 4.26 (ddd, J = 11.0, 8.7, 2.6 Hz, 0.5H), 3.99 (ddd, J = 11.6, 9.4, 4.3 Hz, 0.5H), 3.48 (dd, J = 14.0, 7.0 Hz, 1H) 3.45 (s, 0.5H), 3.44 (s, 0.5H), 3.34 (s, 1H), 3.32 (s, 1H), 2.74-2.58 (m, 1H), 2.28-2.15 (m, 1H), 2.15-1.92 (m, 1.3H), 1.92-1.74 (m, 2H), 1.87 (t, J = 1.6 Hz, 1.5H), 1.81 (dd, J = 1.0, 2.8 Hz, 1.5H), 1.73-1.55 (m, 2H), 1.50-1.24 (m, 2H), (1.06 (s), 1.06 (s), 1.05 (s), 1.05 (s) total 9H); **Rf-value:** 0.62 (EtOAc:hexanes 1:3), 0.41 (EtOAc:hexanes 1:10)

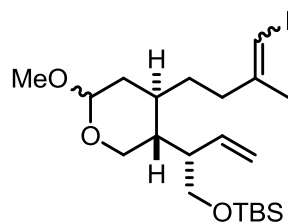
C41BL-150-1-a-cr



C41BL-150-1-b-pure



306 tert-butyl(((2S)-2-((3R,4R)-4-(4-iodo-3-methylbut-3-en-1-yl)-6-methoxytetrahydro-2H-pyran-3-yl)but-3-en-1-yl)oxy)dimethylsilane

Chemical Formula: C₂₁H₃₉IO₃Si

Exact Mass: 494.1713

Molecular Weight: 494.5225

A stock solution of **305** (16.4 mg) in 2.62 mL THF was prepared and part of this solution (0.16 mL) was used for another a different experiment. To the rest of the solution, a stirbar was added, followed by dropwise addition of TBAF (0.05 mL, 50 μ mol, 1 M in THF, ABCR). The mixture was stirred for 22 h, then the stir bar was removed, rinsed with Et₂O and the solvent was evaporated. The resulting slightly yellow residue was purified by FC (1:3 EtOAc:hexanes to 1:2) to give the title compound as a clear colorless oil (8.9 mg), which was contaminated with residual ammonium salts and used for the next step without further purification.

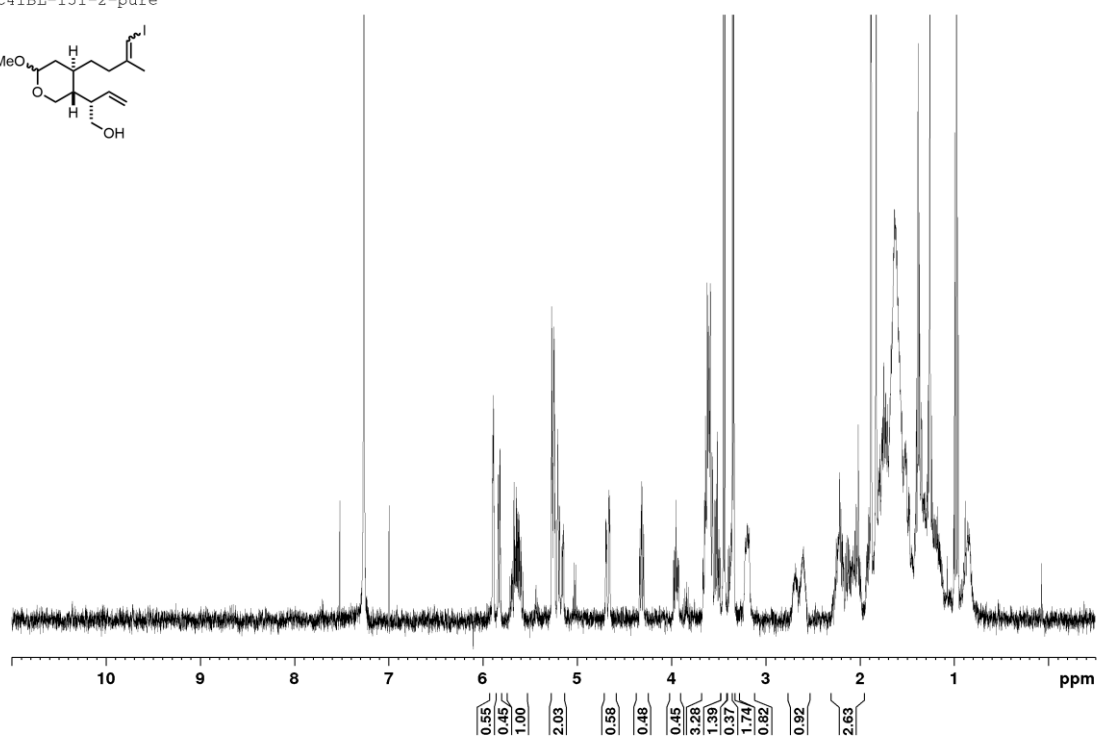
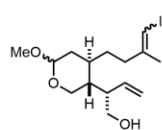
¹H NMR: (CDCl₃, 400 MHz) δ = 5.91-5.87 (m, 0.5H), 5.85-5.83 (m, 0.25H), 5.83-5.81 (m, 0.25H), 5.72-5.55 (m, 1H), 5.28-5.13 (m, 2H), 4.70-4.64 (m, 0.5H), 4.34-4.28 (m, 0.5H), 3.99-3.91 (m, 0.5H), 3.67-3.48 (m, 3H), 3.44 and 3.45 (s, 1.4H), 3.41-3.33 (m, 0.5H), 3.35 and 3.34 (s, 1.6 H), 3.24-3.17 (m, 1H), 2.74-2.54 (m, 1H), aliphatic region could not be clearly identified;

Rf-value: 0.06 (EtOAc:hexanes 1:3), 0.32 (EtOAc:hexanes 1:1)

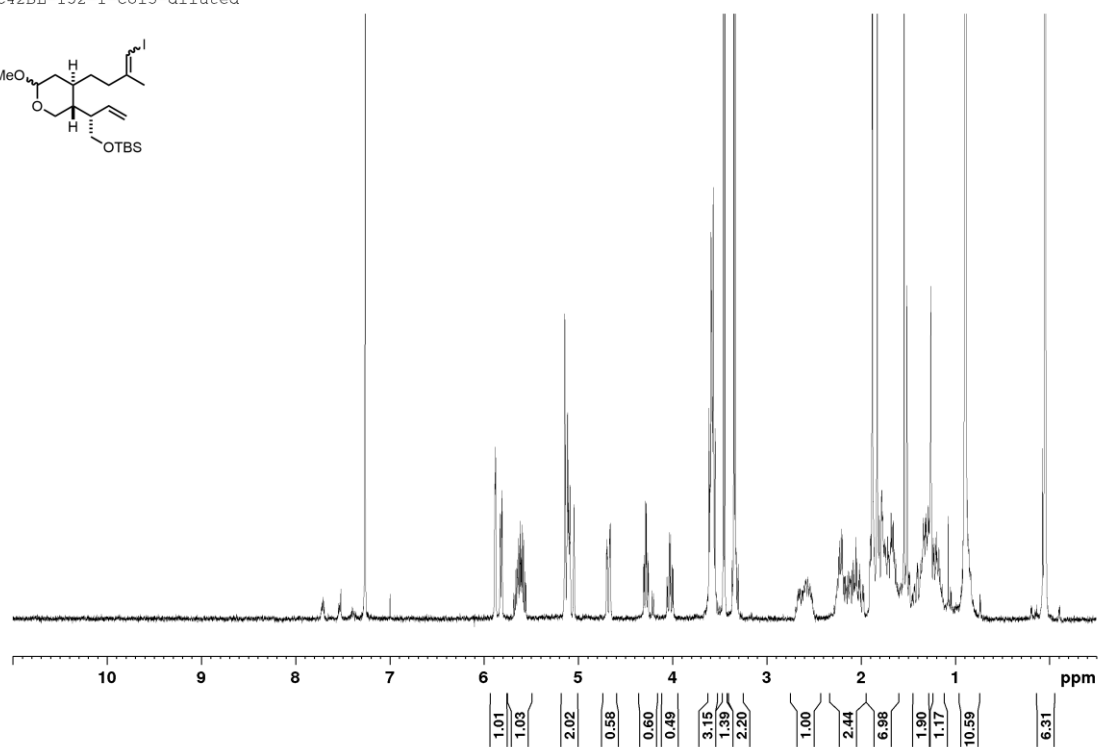
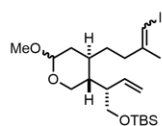
To a solution of the impure alcohol (9.0 mg, 24.5 μ mol, 1 eq.) in CH₂Cl₂ (0.25 mL) at ambient temperature was added imidazole (8.4 mg, 3.7 eq.) followed by TBSCl (5 mg, 1.2 eq.). The reaction mixture quickly turned cloudy and was stirred for 5 h. Additional TBSCl (2 mg) and CH₂Cl₂ (0.25 mL) was added and stirring continued for another 1 h. Conversion was still incomplete. Additional TBSCl (3 mg) and imidazole (3 mg) were added and the mixture was stirred for a total of 25 h. The mixture was diluted with EtOAc (10 mL), quenched with NH₄Cl (1 mL, sat., aq., drops of H₂O were added until the aqueous layer became clear) and the phases were separated. The organic layer was washed sequentially with NH₄Cl (2x5 mL, sat., aq.) and brine (1 mL). The solution was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by FC (Et₂O:hexanes 1:7) to give the title compound.

¹H NMR: (CDCl₃, 400 MHz) δ = 5.90-5.86 (m, 0.5H), 5.84-5.82 (m, 0.25H), 5.82-5.79 (m, 0.25H), 5.69-5.54 (m, 1H), 5.15-5.03 (m, 2H), 4.68 (ddd, J = 12.6, 3.2, 1.1 Hz, 0.5H), 4.28 (td, J = 8.6, 2.6 Hz, 0.5H), 4.02 (td, J = 11.3, 4.3 Hz, 0.5H), 3.63-3.53 (m, 3H), 3.46 and 3.44 (s, total 1.4H), 3.40-3.25 (m, 0.5 H), 3.35 and 3.33 (s, total 1.6H), 2.70-2.48 (m, 1H), 2.30-1.95 (m, 2H), 1.95-1.60 (m, 4H), 1.88 (t, J = 1.1 Hz, 1.4 H), 1.83 (d, J = 0.9 Hz, 1.6H), 1.45-1.28 (m, 2H), 1.24-1.12 (m, 1H), 0.89 and 0.88 (s, total 9H), 0.05 and 0.04 (3 s, 6H); **Rf-value:** 0.58 (EtOAc:hexanes 1:3), 0.53 and 0.48 (Et₂O:hexanes 1:5)

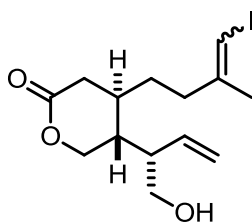
C41BL-151-2-pure



C42BL-152-1-col3-diluted



308 (4R,5R)-5-((S)-1-hydroxybut-3-en-2-yl)-4-(4-iodo-3-methylbut-3-en-1-yl)tetrahydro-2H-pyran-2-one



Chemical Formula: C₁₄H₂₁IO₃

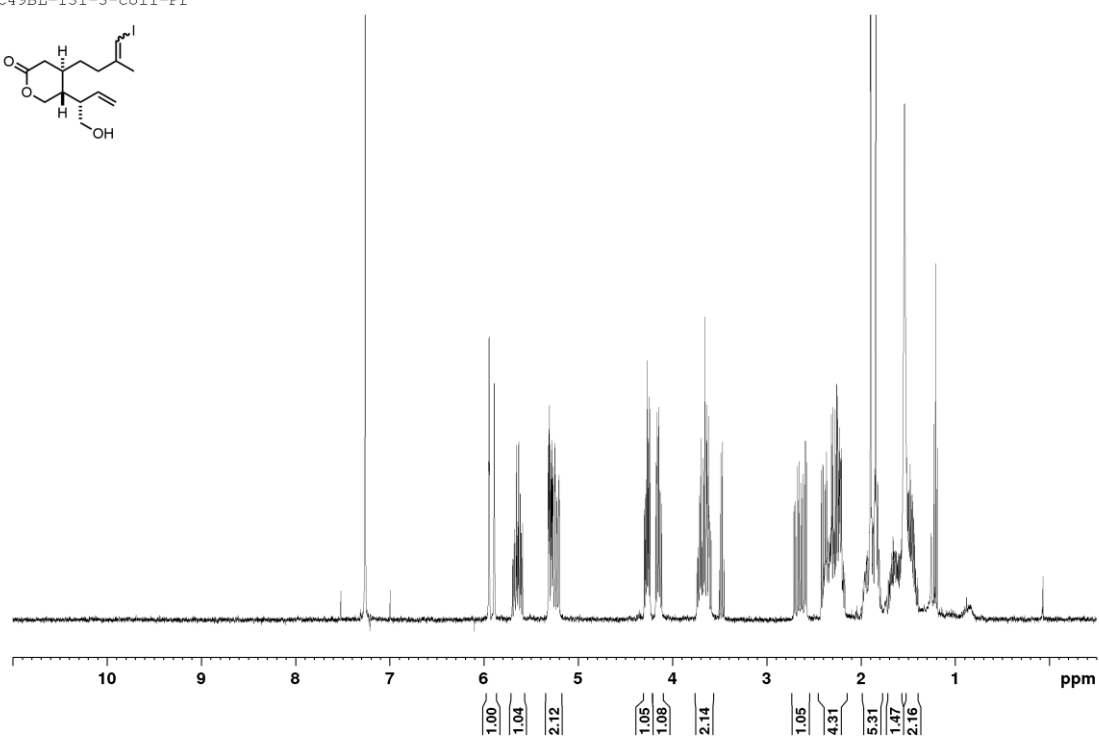
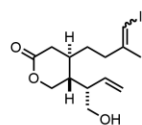
Exact Mass: 364.0535

Molecular Weight: 364.2192

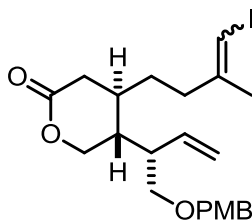
282 (100.6 mg, 167 μ mol, 1 eq.) was dissolved in THF (2.5 mL), transferred into a plastic centrifugal tube and rinsed with THF (2x2 mL). The tube was put into an ice bath and slowly added was HF \cdot py (0.83 mL, 70 W/V%) dropwise. After 2 h of stirring in the ice bath, the same volume of HF \cdot py was added again. The cooling bath was removed after 5 min and stirring was continued at ambient temperature for a total of 16 h. The solution was then carefully added to a vigorously stirred mixture of NaHCO₃ (125 mL, aq., sat.) and EtOAc (65 mL) until two clear phases had formed (ca. 30 min). The phases were separated, the aqueous phase was extracted with EtOAc (3 x 65 mL), the combined organic extracts were washed with saturated aqueous NaHCO₃ (40 mL), brine (10 mL) followed by drying over MgSO₄. The crude was concentrated under reduced pressure and purified by FC (1:1 EtOAc:hexanes) to give the title compound as clear, slightly yellow and viscous oil (56.7 mg, 93 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 5.95 (q, J = 1.1 Hz, 0.5H), 5.89 (q, J = 1.4 Hz, 0.5H), 5.71-5.58 (m, 1H), 5.30 (dd, J = 10.3, 1.6 Hz, 0.5H), 5.29 (dd, J = 10.3, 1.6 Hz, 0.5H), 5.25 (ddd, J = 17.0, 1.6, 0.6 Hz, 0.5H), 5.22 (ddd, J = 17.1, 1.7, 0.7 Hz, 0.5H), 4.28 (dd, J = 11.9, 4.7 Hz, 0.5H), 4.26 (dd, J = 11.9, 4.7 Hz, 0.5H), 4.19-4.11 (m, 1H), 3.75-3.58 (m, 2H), 2.68 (dd, J = 15.9, 6.6 Hz, 0.5H), 2.61 (dd, J = 15.7, 6.7 Hz, 0.5H), 2.39 (dd, J = 15.7, 7.0 Hz, 0.5H), 2.43-2.15 (m, 3H), 2.28 (dd, J = 15.6, 6.7 Hz, 0.5H), 1.99-1.77 (m, 2H), 1.90 (d, J = 1.5 Hz, 1.5H), 1.84 (d, J = 1.0 Hz, 1.5H), 1.72-1.57 (m, 1H), 1.52-1.39 (m, 2H); **Rf-value:** 0.17 (EtOAc:hexanes 1:1)

C49BL-131-3-coll-Pr



309 (4R,5R)-4-(4-iodo-3-methylbut-3-en-1-yl)-5-((S)-1-((4-methoxybenzyl)oxy)but-3-en-2-yl)tetrahydro-2H-pyran-2-one



Chemical Formula: $C_{22}H_{29}IO_4$

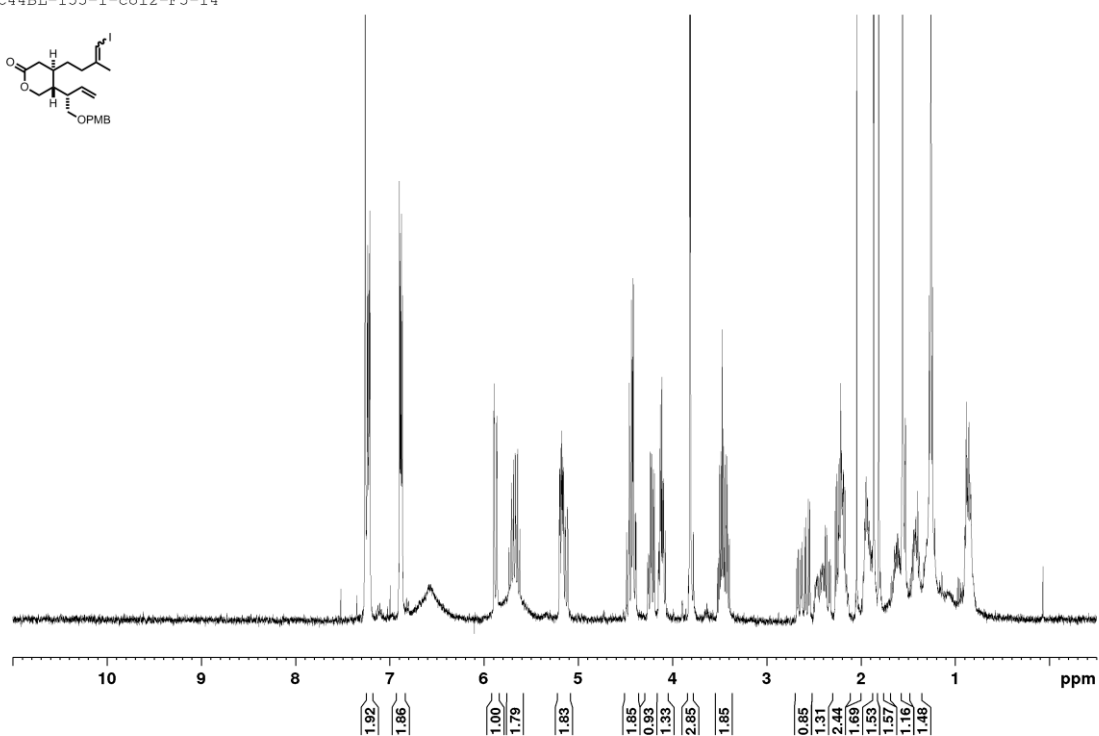
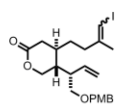
Exact Mass: 484.1111

Molecular Weight: 484.3677

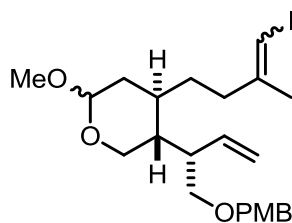
To alcohol **308** (56.7 mg, 156 μmol , 1 eq.) in CH_2Cl_2 (1.05 mL) was added p-methoxybenzyltrichloroacetimidate **248** (55.3 mg, 0.19 mmol, 1.25 eq.) in CH_2Cl_2 (0.5 mL+2x0.5 mL). The mixture was stirred at ambient temperature, then was added solid (-)-CSA (1.8 mg, 0.05 eq.). The yellow mixture was stirred for 3 days. Since it was still incomplete, more **248** (11.4 mg, 0.25 eq.) was added. No appreciable change had occurred after 5 h, so the solution was directly loaded onto a column and purified by several rounds of FC (EtOAc:hexanes 1:1; again with EtOAc:hexanes 1:5 to 1:3 to 1:1 and a thir time with Et_2O :hexanes 2:1) to give the title compound as a partial solid, contaminated with trichloroacetamide (114 mg material, would correspond to >150% yield). The material was used for the synthesis of **310**.

^1H NMR: (CDCl_3 , 400 MHz) δ = 7.25-7.20 (m, 2H), 6.91-6.85 (m, 2H), 5.89 (q, J = 1.0 Hz, 0.5H), 5.86 (q, J = 1.4 Hz, 0.5H), 5.74-5.61 (m, 1H), 5.21-5.10 (m, 2H), 4.47 (d, J = 11.6 Hz, 0.5H), 4.45 (d, J = 11.6 Hz, 0.5H), 4.41 (d, J = 11.7 Hz, 0.5H), 4.40 (d, J = 11.6 Hz, 0.5H), 4.24 (dd, J = 11.9, 4.6 Hz, 0.5H), 4.21 (dd, J = 12.0, 4.7 Hz, 0.5H), 4.16-4.06 (m, 1H), 3.82 and 3.81 (2s, total 3H), 3.53-3.39 (m, 2H), 2.65 (dd, J = 15.8, 6.5 Hz, 0.5H), 2.57 (dd, J = 15.7, 6.6 Hz, 0.5H), 2.52-2.30 (m, 1H), 2.35 (dd, J = 15.9, 6.7 Hz, 0.5H), 2.30-2.12 (m, 2H), 2.24 (dd, J = 15.8, 6.7 Hz, 0.5H), 2.00-1.88 (m, 2H), 1.86 (d, J = 1.4 Hz, 1.5H), 1.81 (d, J = 0.9 Hz, 1.5H), 1.69-1.57 (m, 1H), 1.48-1.36 (m, 1H); **Rf-value:** 0.64 (EtOAc:hexanes 1:1), 0.27 (Et_2O :hexanes 2:1)

C44BL-155-1-col12-F5-14



310 (4R,5R)-4-(4-iodo-3-methylbut-3-en-1-yl)-2-methoxy-5-((S)-1-((4-methoxybenzyl)oxy)but-3-en-2-yl)tetrahydro-2H-pyran



Chemical Formula: $C_{23}H_{33}IO_4$

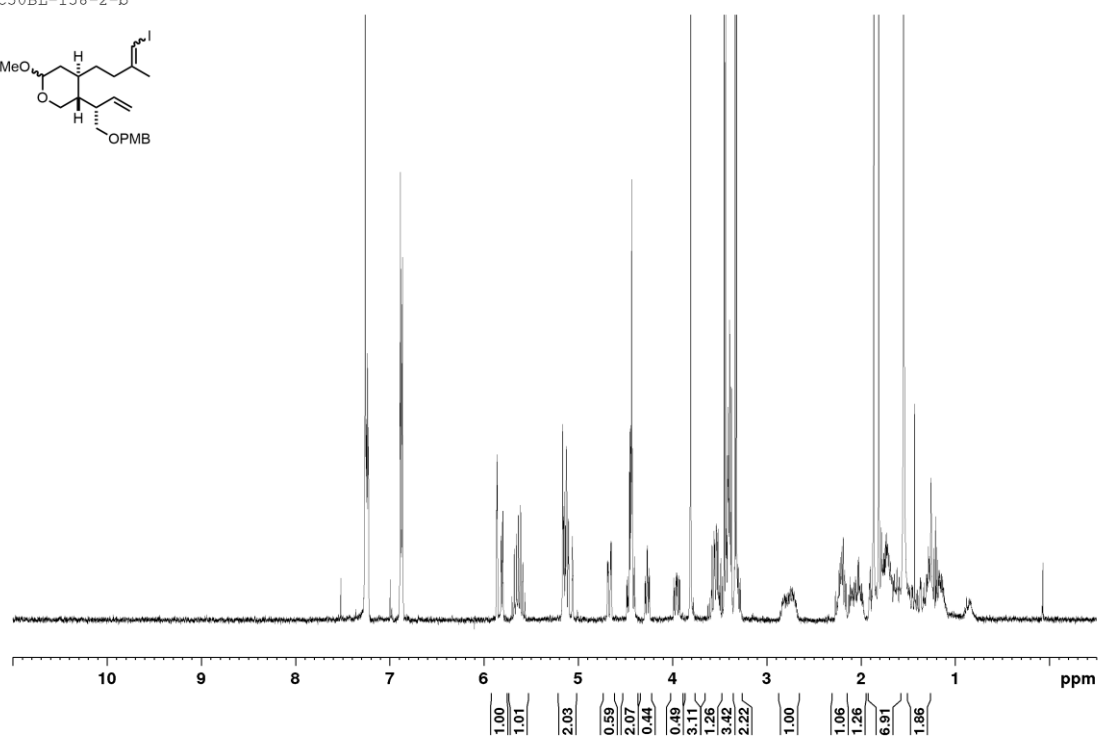
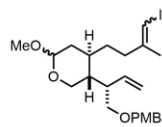
Exact Mass: 500.1424

Molecular Weight: 500.4102

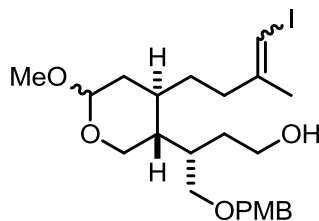
The stoichiometry of the reaction was calculated with a 100 % yield of **309** (156 μ mol). However, the actual content was likely lower. Impure lactone **309** (156 μ mol) was dissolved in CH_2Cl_2 (1.37 mL) and cooled to $-78^\circ C$. DIBAL-H (0.24 mL, 234 μ mol, 1.5 eq., 1 M in CH_2Cl_2) was added dropwise. After 20 min, the reaction was complete and it was quenched with acetone (0.02 mL, 156 μ mol, 1 eq.) and Rochelle's salt (1 mL, sat., aq.). The mixture was diluted with EtOAc (5 mL) and stirred for 8 h 30 min. Phases were separated and the aqueous phase was extracted with EtOAc (2x5 mL). The combined organic extracts were washed with brine (1 mL), then dried over $MgSO_4$ and the solvent was evaporated. The resulting crude lactol was purified by several rounds of FC (2:1 Et_2O :hexanes, again with 4:3 Et_2O :hexanes and again with 1:2 Et_2O :hexanes to neat Et_2O) to give the lactol as a white solid (61.6 mg, (81% over 2 steps from **308**). **Rf-value**: 0.38 ($EtOAc$:hexanes 1:1). To a solution of the pure lactol in MeOH (1.4 mL) was added solid PPTS (0.4 mg, 16 μ mol, 0.05 eq.). The mixture was stirred at ambient temperature for 19 h. Toluene was added (10 mL) and the solution was concentrated to 1 mL. Directly loaded on column and purified by FC (2:5 Et_2O :hexanes) to give the title compound as a clear colorless oil (57.1 mg, 73% over 3 steps from **308**).

1H NMR: ($CDCl_3$, 400 MHz) δ = 7.26-7.22 (m, 2H), 6.90-6.85 (m, 2H), 5.88-5.85 (m, 0.5H), 5.83-5.81 (m, 0.25H), 5.81-5.79 (m, 0.25H), 5.71-5.56 (m, 1H), 5.18-5.05 (m, 2H), 4.67 (dd, J = 13.2, 3.2 Hz, 0.5H), 4.49-4.39 (m, 2H), 4.27 (td, J = 8.3, 2.4 Hz, 0.5H), 3.95 (ddd, J = 11.5, 9.9, 4.1 Hz, 0.5H), 3.81 (2 signals, s, 3H), 3.63-3.48 (m, 1H), 3.48-3.36 (m, 3.5H), 3.36-3.27 (m, 2H), 2.87-2.66 (m, 1H), 2.28-2.15 (m, 1H), 2.15-1.95 (m, 2H), 1.92-1.58 (m, 4H), 1.86 (dd, J = 1.3, 0.7 Hz, 1.5H), 1.81 (d, J = 1.0 Hz, 1.5H), 1.51-1.26 (m, 2H); **Rf-value**: 0.72 ($EtOAc$:hexanes 1:1)

C50BL-158-2-b



311 (3S)-3-((3R,4R)-4-(4-iodo-3-methylbut-3-en-1-yl)-6-methoxytetrahydro-2H-pyran-3-yl)-4-((4-methoxybenzyl)oxy)butan-1-ol



Chemical Formula: C₂₃H₃₅IO₅

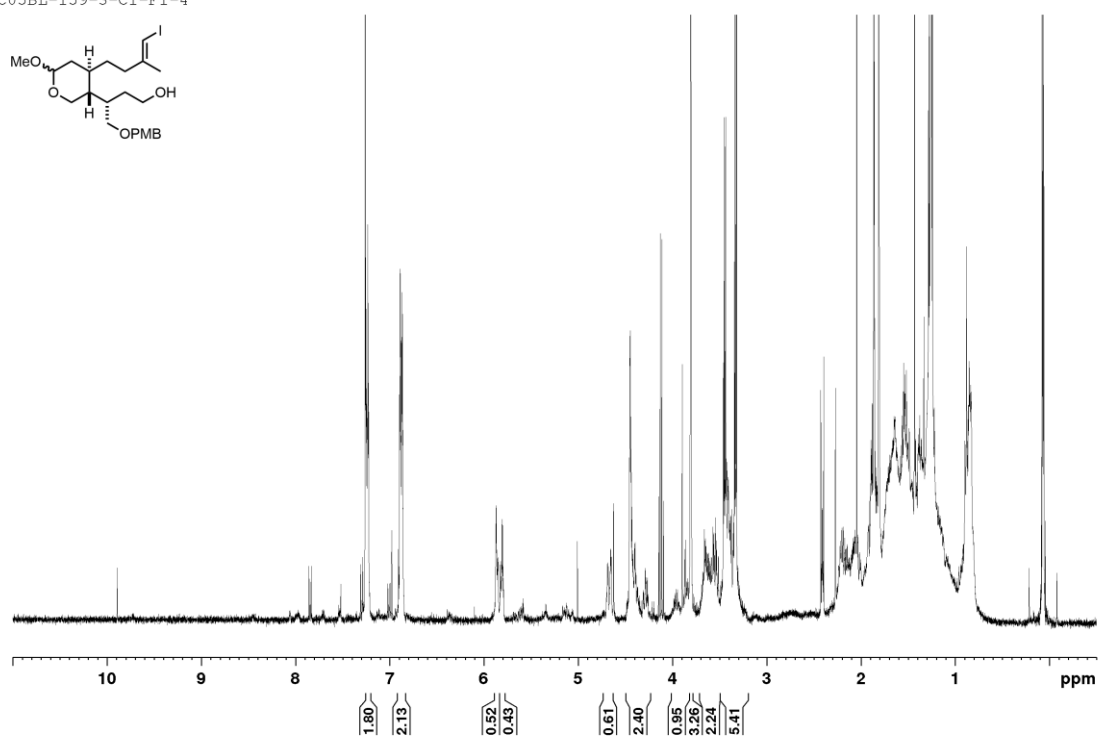
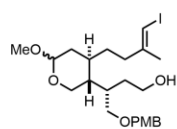
Exact Mass: 518.1529

Molecular Weight: 518.4255

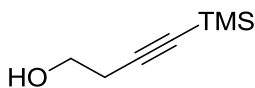
310 (9.1 mg, 18.2 μ mol, 1 eq.) was coevaporated with MePh in a Schlenk flask. 9-BBN (26.2 mg, 0.2 mmol) was dissolved in a small amount of THF by sonication, then filled up to 2 mL in a dry volumetric flask. An aliquot of of this 9-BBN solution (0.21 mL, 22 μ mol, 1.2 eq.) was added to the starting material dropwise at ambient temperature. The walls of the flask were rinsed with THF (0.06 mL) and the solution was stirred at ambient temperature for 38 h without the SM completely disappearing. The reaction was diluted with Et₂O (1 mL) and after cooling to 0 °C, it was quenched by dropwise addition of MeOH (59 μ L, 80 eq.), NaOH (3 M, 7 μ L, 1.2 eq.) and H₂O₂ (8 μ L, 4.08 eq., 30 %). The mixture was stirred at ambient temperature for 30 min, then for 30 min at 45 °C and finally evaporated to dryness. Brine (1 mL) and some drops of water were added and the mixture was extracted with Et₂O (3x5 mL). The organic phases were washed with brine (1 mL), dried over MgSO₄ and evaporated. The crude material was purified by FC (1:1 EtOAc:hexanes) provided the title compound contaminated with aliphatic impurities (10.3 mg, estimated purity, around 60-80%). **It was later observed, that oxidative workup did not work that well (sluggish and/or incomplete) in Et₂O. Therefore after completion of the reaction, if dilution is necessary, THF has to be used.**

¹H NMR: (CDCl₃, 400 MHz) δ = 1.26-1.21 (m, 2H), 6.91-6.85 (m, 2H), 5.89-5.84 (m, 0.5H), 5.84-5.78 (m, 0.5H), 4.71-4.63 (m, 0.5H), 4.49-4.23 (m, 2.25H), 4.02-3.78 (m, 1H), 3.81 and 3.80 (s, 3H), 3.71-3.50 (m, 2H), 3.50-3.20 (m, 5.5H), the aliphatic region contains major a large amount of impurities and could not be assigned. The terminal double bond had clearly disappeared, while the methyl acetal, the PMB-group and the vinyl iodide were still intact; **Rf-value:** 0.34 and 0.27 (EtOAc:hexanes 1:1)

C05BL-159-3-C1-F1-4



284 4-(trimethylsilyl)but-3-yn-1-ol

Chemical Formula: C₇H₁₄OSi

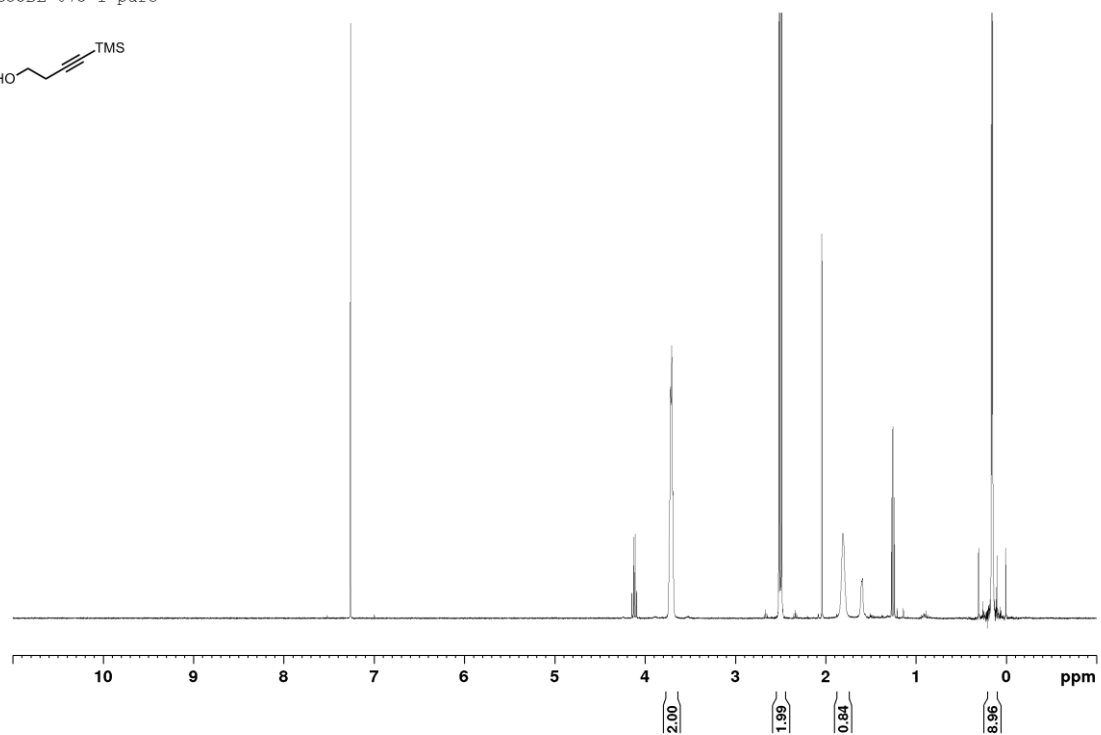
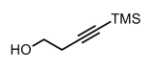
Exact Mass: 142.0814

Molecular Weight: 142.2710

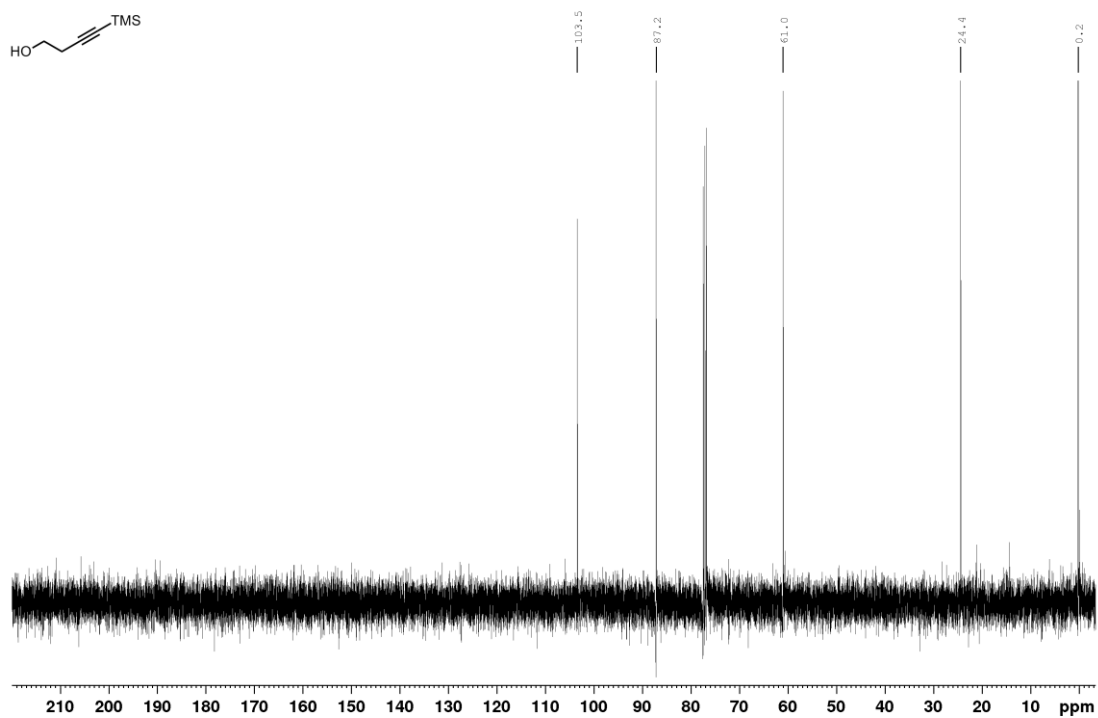
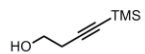
3-Butyn-1-ol (2.16 mL, 28.5 mmol, 1 eq.) was dissolved in THF (290 mL) and cooled to -78 °C. *n*-BuLi (39.2 mL, 1.6 M in hexanes, 2.2 eq.) was added, while keeping temperature constant. The solution turned cloudy during the process. The mixture was stirred for 2 h at -78 °C. Neat TMSCl (8.21 mL, 2.2 eq.) was added dropwise and the mixture was warmed to 0 °C over 1 h. The reaction was quenched with HCl (9 mL, aq., 2 M) and stirred for 30 min. The solution was extracted with Et₂O, washed with NaHCO₃, brine and dried over MgSO₄. The solvent was evaporated and FC (EtOAc:hexanes 1:3) gave the title compound as a viscous colorless oil (3.44 g, 85%).

¹H NMR: (CDCl₃, 400 MHz) δ = 3.75-3.67 (m, 2H), 2.51 (t, *J* = 6.3 Hz, 2H), 1.81 (s, *br*, 1H), 0.16 (s, 9H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 103.5, 87.2, 61.0, 24.4, 0.2; **HRMS (EI):** calc. for [M-CH₃]⁺: 127.0574, found 127.0574; **IR (neat):** 3340, 2959, 2899, 2360, 2337, 2176, 1411, 1331, 1249, 1186, 1053, 1029, 892, 837, 759, 759, 698, 639; **Rf-value:** 0.60 (EtOAc:hexanes 1:1)

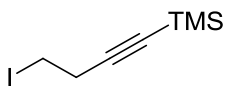
C35BL-075-1-pure



C35BL-075-1-pure



285 (4-iodobut-1-yn-1-yl)trimethylsilane

Chemical Formula: C₇H₁₃BrSi

Exact Mass: 203.9970

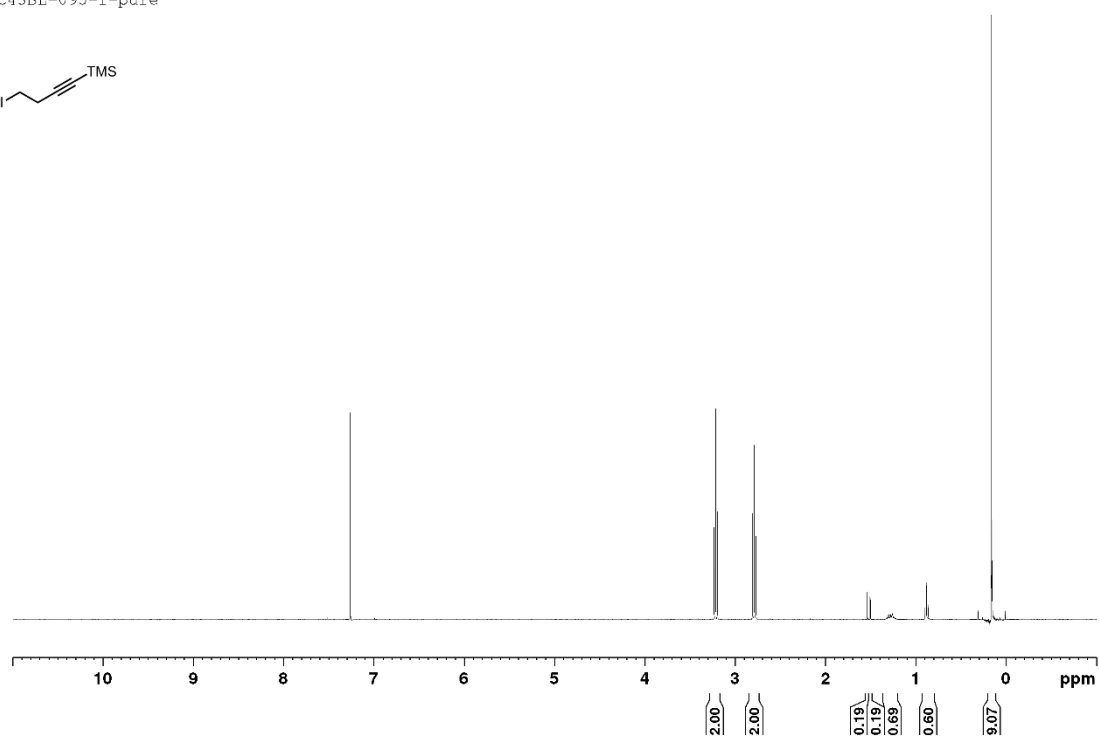
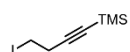
Molecular Weight: 205.1676

Iodine (1.96 g, 7.73 mmol, 1.1 eq.) was added to a solution of imidazole (1.44 g, 21.1 mmol, 3.0 eq.) and PPh₃ (2.21 g, 8.43 mmol, 1.2 eq.) in CH₂Cl₂ (40 mL) at 0 °C. The solution was stirred for 5 min, and **284** (1 g, 7.03 mmol, 1 eq.) in CH₂Cl₂ (8 mL), was added slowly. The reaction mixture was stirred for 5.5 h with the exclusion of light. Cellite was added, the solvent was removed and the solid was rinsed with first 2 mL ether then hexane. The solvent was removed, the crude product was purified by FC (neat pentane) gave the desired product as a colorless oil (1.29 g, 89 %). The values of the NMR spectra are in accordance with reported literature data.^[227]

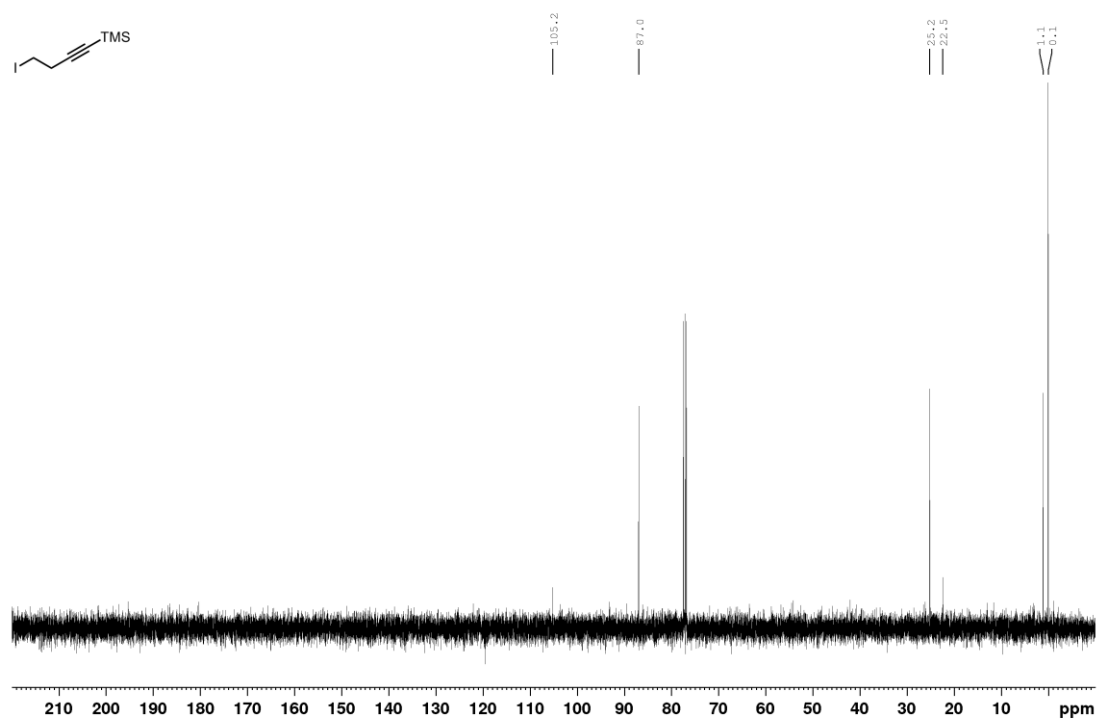
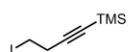
¹H NMR: (CDCl₃, 400 MHz) δ = 3.22 (t, *J* = 7.5 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 0.16 (s, 3H); **¹³C**

NMR: (CDCl₃, 100 MHz) δ = 105.2, 87.0, 25.2, 1.1, 0.1; **Rf-value:** 0.69 (EtOAc:hexanes 1:5)

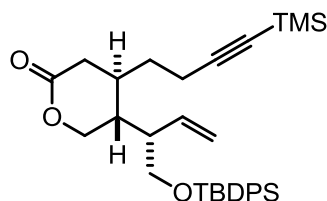
C43BL-095-1-pure



C43BL-095-1-pure



286 (4R,5R)-5-((S)-1-((tert-butyldiphenylsilyl)oxy)but-3-en-2-yl)-4-(4-(trimethylsilyl)but-3-yn-1-yl)tetrahydro-2H-pyran-2-one



Chemical Formula: $C_{32}H_{44}O_3Si_2$

Exact Mass: 532.2829

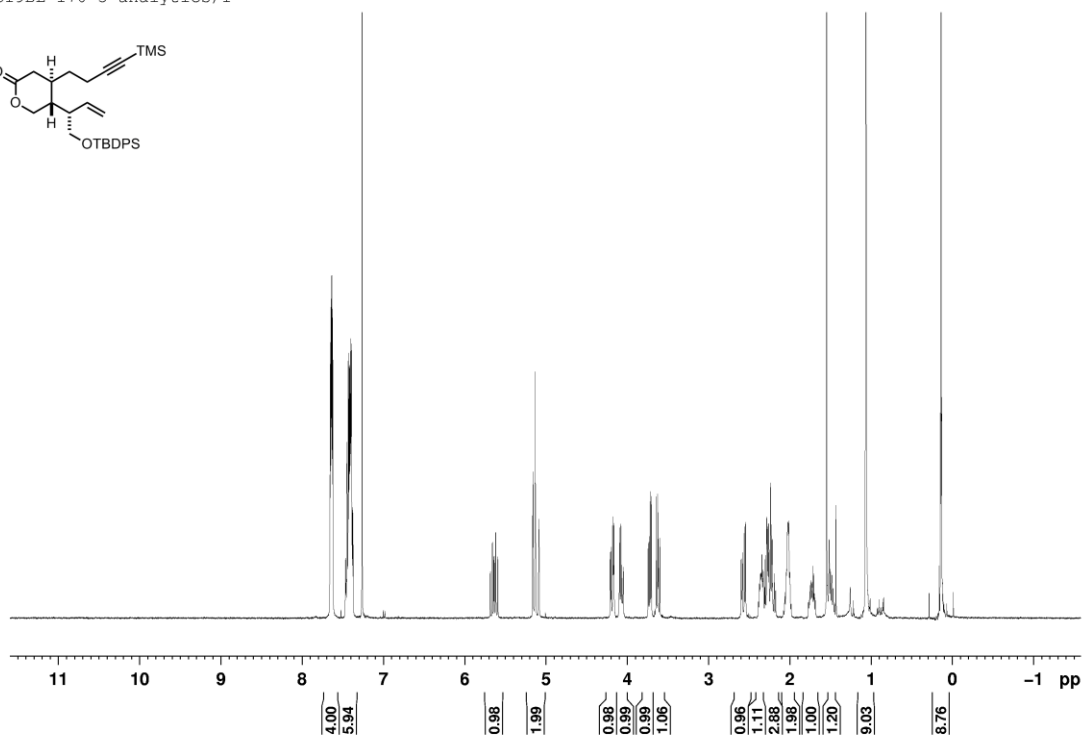
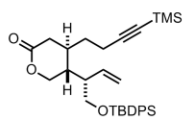
Molecular Weight: 532.8610

A solution of 1-iodo-4trimethylsilyl-3-pentyne **285** (538 mg, 2.13 mmol coevaporated with benzene before weighing, 3.06 eq.) in Et_2O (2 mL) was added dropwise over 5 min to a solution of *t*-BuLi (1.97 mL, 4.12 mmol, 5.97 eq., 2.09 M solution in pentane, titrated before use, Aldrich) and dry Et_2O (2 mL) at $-78^\circ C$. After stirring the turbid solution for 18 min, it was put into an ice bath and left for 10 min, during half of which it had turned a clear golden color. It was put into $-78^\circ C$ bath and after 3 min, a solution of lithium 2-thienylcyanocuprate (9.9 mL, 2.5 mmol, 3.24 eq., 0.25 M solution in THF, Aldrich) was added dropwise at $-78^\circ C$ over 9 min, turning the solution brown greenish. The solution was then kept at $0^\circ C$ for 1 h 15 min and, then clear chocolate brown, cooled again to $-78^\circ C$. A solution of **6** (309 mg, 0.76 mmol, coevaporated with benzene before use) in dry Et_2O (2 mL+2x2 mL) was added and rinsed over 5 min (turned yellow). The solution was stirred at $-78^\circ C$ for further 11 min, then at $0^\circ C$ for 1 h 25 min. After 40 min of this time, TLC indicated little of the UV active starting material and showed already mainly the smeary product spot with the same R_f -value. Quenched with NH_4Cl (7.5 mL, aq., sat.) and diluted with NH_3 (7.5 mL, 25 %). It turned a brown cupric color. Some water (5 mL) was added and gave some grey brown precipitate. It was filtered through cellite and rinsed with $EtOAc$ (2x50 mL). By contact with air, the color of the aqueous phase turned the typical blue and was backextracted with $EtOAc$ (20 mL). The combined organic phases were washed with a mixture of 25 mL brine and 1 mL $Na_2S_2O_3$ and finally dried over $MgSO_4$. The brown crude residue was purified by several rounds of FC (Et_2O :hexanes 1:10 to 1:5 to 2:5 to neat Et_2O) to give the title compound as a clear slightly copper colored oil (364.8 mg, 90 %).

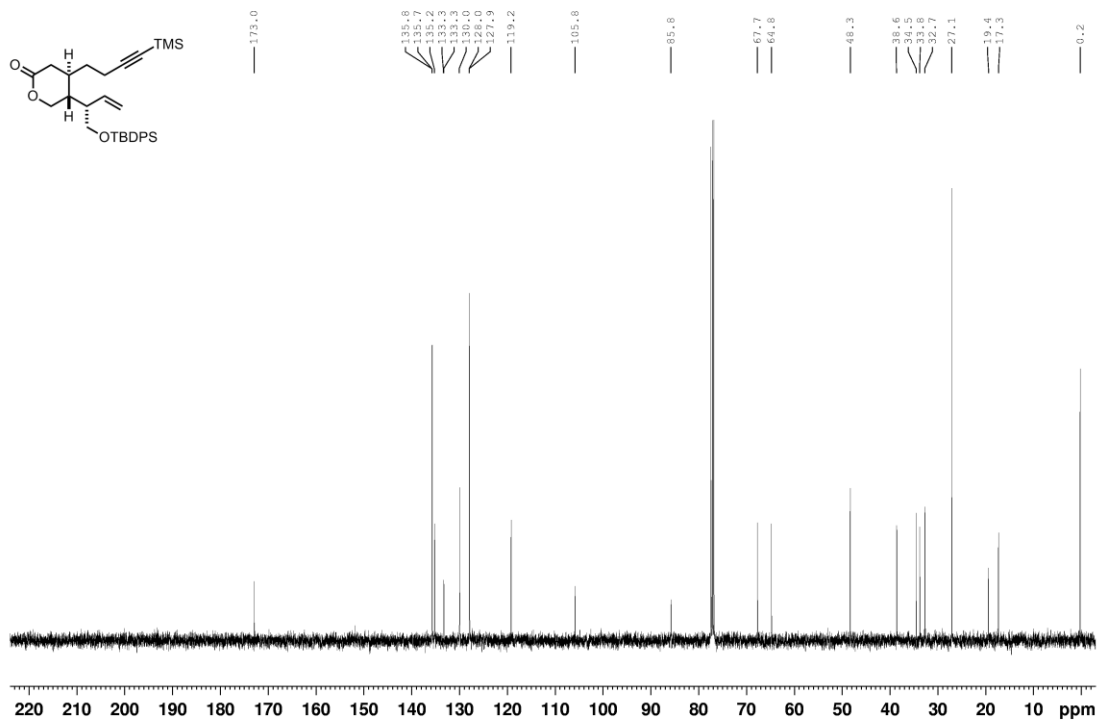
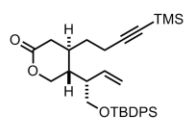
1H NMR: ($CDCl_3$, 400 MHz) δ = 7.67-7.61 (m, 4H), 7.48-7.36 (m, 6H), 5.64 (dt, J = 17.0, 9.9 Hz, 1H), 5.15 (dd, J = 10.4, 1.8 Hz, 1H), 5.11 (dd, J = 17.2, 1.5 Hz, 1H), 4.19 (dd, J = 11.7, 4.7 Hz, 1H), 4.07 (dd, J = 11.7, 7.2 Hz, 1H), 3.73 (dd, J = 10.5, 5.0 Hz, 1H), 3.62 (dd, J = 10.4, 7.2 Hz, 1H), 2.57 (dd, J = 15.5, 6.5 Hz, 1H), 2.40-2.32 (m, 1H), 2.32-2.16 (m, 3H), 2.09-1.97 (m, 2H), 1.78-

1.68 (m, 1H), 1.54-1.44 (m, 1H), 1.06 (s, 9H), 0.14 (s, 9H); ^{13}C NMR: (CDCl_3 , 100 MHz) δ = 173, 135.8, 135.7, 135.2, 133.3, 133.3, 130.0 (2 signals), 128.0, 127.9, 119.2, 105.8, 85.8, 67.7, 64.8, 48.3, 38.6, 34.5, 33.8, 32.7, 27.1, 19.4, 17.3, 0.2; **HRMS (ESI-TOF)**: calc. for $[\text{M}+\text{Na}]^+$: 555.2722, found 555.2721; **IR (neat)**: 2958, 2930, 2900, 2858, 2173, 1749, 1472, 1428, 1390, 1250, 1111, 1075, 1047, 999, 909, 841, 823, 760, 730, 701, 646, 613; $[\alpha]^{24}_{\text{D}}$ = -14.62° (c = 0.502, CHCl_3); **Rf-value**: 0.15 (EtOAc:hexanes 1:5)

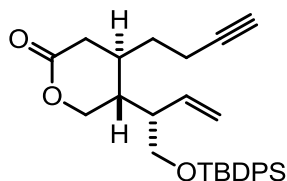
C19BL-170-3-analytics/1



C19BL-170-3-analytics/5



287 (4R,5R)-4-(but-3-yn-1-yl)-5-((S)-1-((tert-butyldiphenylsilyl)oxy)but-3-en-2-yl)tetrahydro-2H-pyran-2-one



Chemical Formula: $C_{29}H_{36}O_3Si$

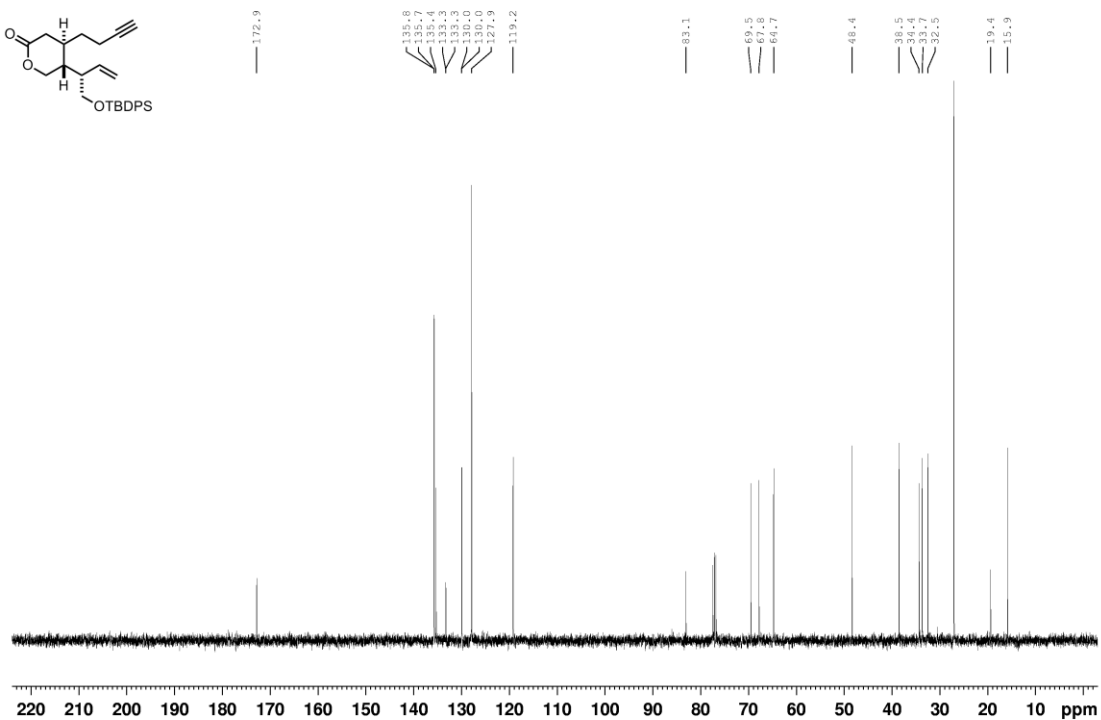
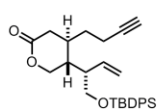
Exact Mass: 460.2434

Molecular Weight: 460.6798

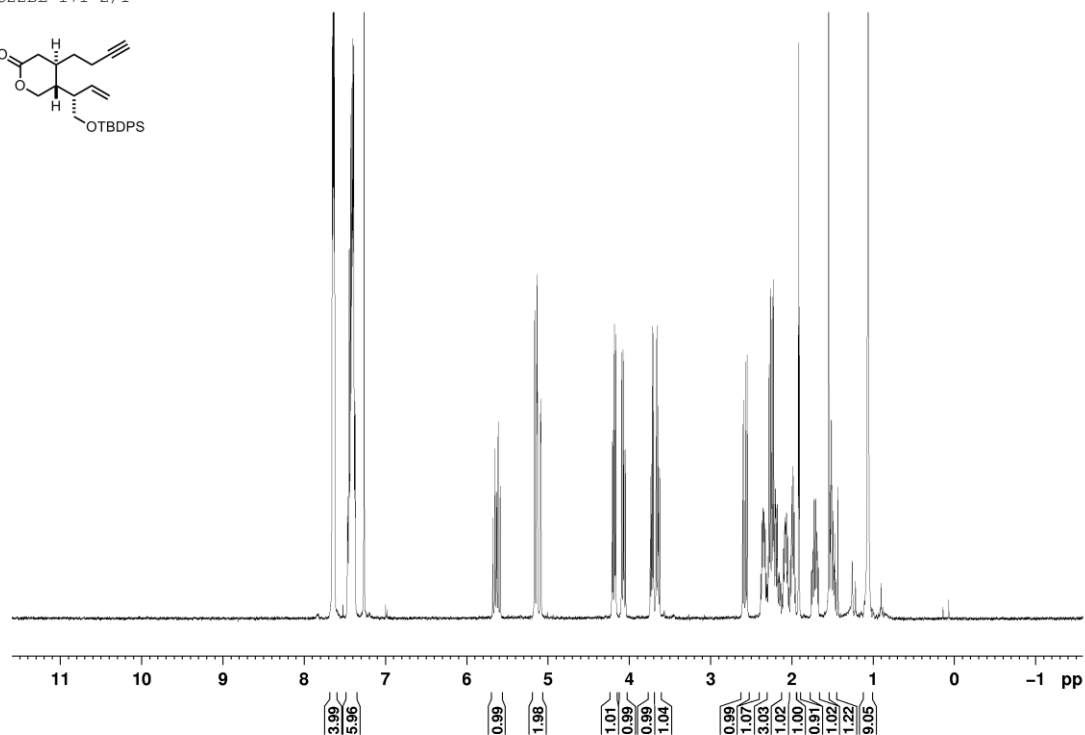
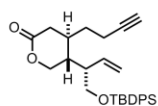
286 (198.6 mg, 0.373 mmol, 1 eq.) was dissolved in MeOH (3.7 mL). Solid K_2CO_3 (208 mg, 1.49 mmol, 4 eq.) was added in one portion and the suspension was stirred for 4 h 20 at ambient temperature. After addition of the base, the suspension had turned turbid very quickly. AcOH (0.77 mL) was added, upon which the solution turned clear. MePh (5 mL) was added and the mixture was evaporated to dryness (twice). The material was dissolved in EtOAc (3.7 mL) and added was again AcOH (0.77 mL). Stirred for 17 h. Added were water (1 mL) and brine (1 mL) and it was diluted with EtOAc (10 mL). No organic material was left in the aqueous phase. Phases were separated and the organic phase was washed with $NaHCO_3$ (1 mL, sat. aq., effervescence observed). The solution was dried over $MgSO_4$, evaporated and the crude product was purified by two rounds of FC (Et_2O :hexanes3:5) to give the title compound as a clear, colorless oil (129.7 mg, 76 %).

1H NMR: ($CDCl_3$, 400 MHz) δ = 7.67-7.61 (m, 4H), 7.47-7.36 (m, 6H), 5.63 (dt, J = 16.9, 9.9 Hz, 1H), 5.15 (dd, J = 10.3, 1.7 Hz, 1H), 5.11 (dd, J = 17.1, 1.5 Hz, 1H), 4.19 (dd, J = 11.7, 5.0 Hz, 1H), 4.07 (dd, J = 11.8, 7.4 Hz, 1H), 3.72 (dd, J = 10.4, 5.2 Hz, 1H), 3.65 (dd, J = 10.4, 6.9 Hz, 1H), 2.58 (dd, J = 15.7, 6.8 Hz, 1H), 2.39-2.30 (m, 1H), 2.30-2.13 (m, 3H), 2.13-2.03 (m, 1H), 2.03-1.95 (m, 1H), 1.91 (t, J = 2.6 Hz, 1H), 1.77-1.66 (m, 1H), 1.54-1.45 (m, 1H), 1.07 (s, 9H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 172.9, 135.8, 135.7, 135.4, 133.3 (2 signals), 130 (2 signals), 127.9 (2 signals), 119.2, 83.1, 69.5, 67.8, 64.7, 48.4, 38.5, 34.4, 33.7, 32.5, 19.4, 15.9; **HRMS (ESI-TOF):** calc. for $[M+Na]^+$: 483.2325, found 483.2326; **IR (neat):** 3303, 3072, 3050, 2998, 2956, 2930, 2857, 2368, 1749, 1639, 1589, 1472, 1427, 1390, 1361, 128, 1260, 1187, 1157, 1108, 1075, 998, 920, 822, 802, 737, 701, 634, 612, 553; **$[\alpha]^{24}_D$** = -17.24° (c = 0.535, $CHCl_3$); **Rf-value:** 0.69 (EtOAc:hexanes 1:1)

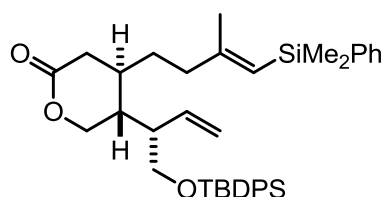
C22BL-171-2/2



C22BL-171-2/1



8 (4R,5R)-5-((S)-1-((tert-butyldiphenylsilyl)oxy)but-3-en-2-yl)-4-((E)-4-(dimethyl(phenyl)silyl)-3-methylbut-3-en-1-yl)tetrahydro-2H-pyran-2-one



Chemical Formula: $C_{38}H_{50}O_3Si_2$

Exact Mass: 610.3298

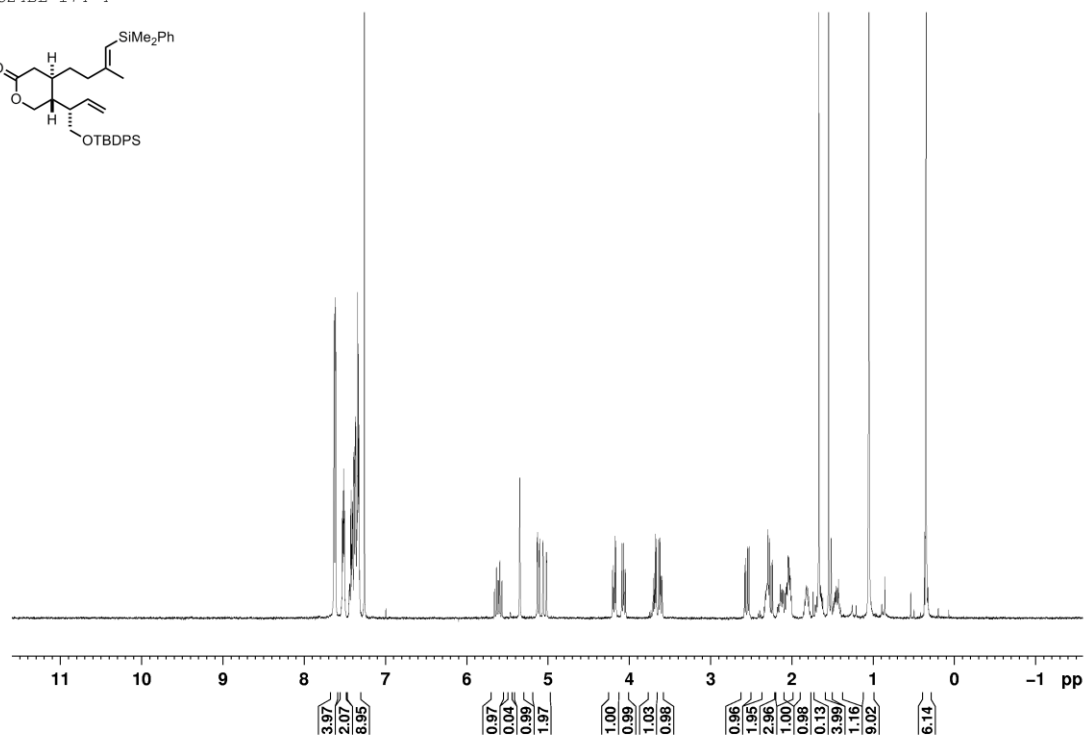
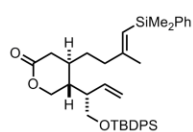
Molecular Weight: 610.9728

A solution of iodide **297** (2.48 g, 97 % pure, prepared and purified two days prior and afterwards stored at ambient temperature under vacuum) in dry ether (7 mL and 2*2mL for rinsing) was added dropwise to a solution of tert-butyllithium (8.45 mL, 1.68 M solution in pentane, titrated before use, Aldrich) and Et₂O (10 mL) at -78 °C over 12 min. After stirring the cloudy yellow solution for 2 h, a solution of lithium 2-thienylcyanocuprate (30.8 mL, 0.25 M solution in THF, Aldrich) was added dropwise at -78 °C over 14 min during which the color first turned yellow/greenish, then grey yellowish. After 8 min, the solution was warmed to 0 °C, and the now clear yellow solution was maintained at this temperature for 2 h and turned caramel brown. It was cooled to -78 °C, and a solution of **6** (1.646 g) in dry Et₂O (11 mL) was added dropwise fast (turned strong yellow) and rinsed with 3*5.5 mL. After 1h temperature had risen to -60 °C and only traces of SM were visible by TLC. After stirring at 0 °C for 20 min, it was quenched with saturated aqueous NH₄Cl (30 mL), warmed to ambient temperature and opened to air. 30 mL 25% NH₃ and 100 mL EtOAc were added and it was stirred until a strong blue color developed. The aqueous phase was separated and extracted with 100 mL EtOAc. The combined organic phases were washed with 60 mL sat. NH₄Cl/25% NH₃ 1:1, then 30 mL brine and dried over MgSO₄. After the solution was concentrate by rotary evaporation, the brown residue was purified by flash chromatography (Et₂O:hexanes 1:5 to 1:3) to give the title compound as a clear, slightly yellow and highly viscous, oil (1.962 g, 79%)

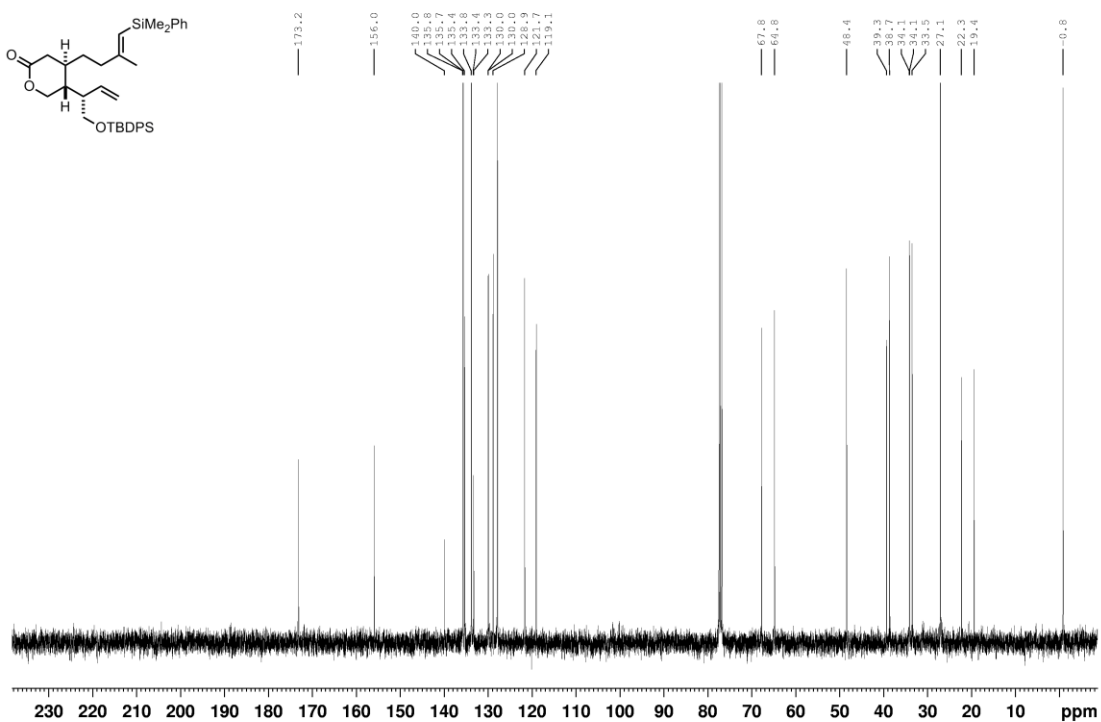
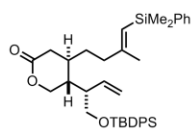
¹H NMR: (CDCl₃, 400 MHz) δ = 7.66-7.59 (m, 4H), 7.55-7.48 (m, 2H), 7.46-7.31 (m, 9H), 5.61 (dt, J = 17.0, 9.9 Hz, 1H), 5.35 (s, 1H), 5.12 (dd, J = 10.3, 1.7 Hz, 1H), 5.04 (dd, J = 17.1, 1.5 Hz, 1H), 4.19 (dd, J = 11.7, 5.0 Hz, 1H), 4.07 (dd, J = 11.7, 7.2 Hz, 1H), 3.69 (dd, J = 10.4, 5.2 Hz, 1H), 3.61 (dd, J = 10.4, 7.2 Hz, 1H), 2.56 (dd, J = 15.7, 6.9 Hz, 1H), 2.35-2.26 (m, 1H), 2.27 (dd, J = 15.7, 7.1 Hz, 1H), 2.20-2.10 (m, 1H), 2.10-1.98 (m, 2H), 1.87-1.76 (m, 1H), 1.72-1.60 (m, 1H), 1.67 (s, 3H), 1.50-1.28 (m, 1H), 1.05 (s, 9H), 0.35 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 173.2,

156.0, 140.0, 135.8, 135.7, 135.4, 133.8, 133.4, 133.3, 130.0 (2 signals), 128.9, 121.7, 119.1, 67.8, 64.8, 48.4, 39.3, 38.7, 34.1 (2 signals), 33.5, 27.1, 22.3, 19.4, -0.8; **HRMS (ESI-TOF)**: calc. for $[M+H]^+$: 611.3371, found 611.3360; **IR (neat)**: 3068, 2952, 2930, 2859, 259, 25, 1749, 1615, 1470, 1427, 1388, 1251, 1107, 1000, 913, 823, 782, 731, 699, 646, 612; $[\alpha]^{24}_D = -27.00 \pm 0.2^\circ$ (c = 0.36, CHCl_3); **Rf-value**: 0.27 (EtOAc:hexanes 1:5)

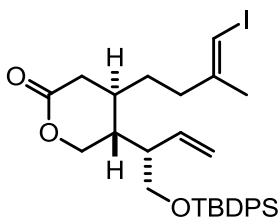
C24BL-174-4



C24BL-174-4



290 (4R,5R)-5-((S)-1-((tert-butyldiphenylsilyl)oxy)but-3-en-2-yl)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)tetrahydro-2H-pyran-2-one



Chemical Formula: $C_{30}H_{39}IO_3Si$

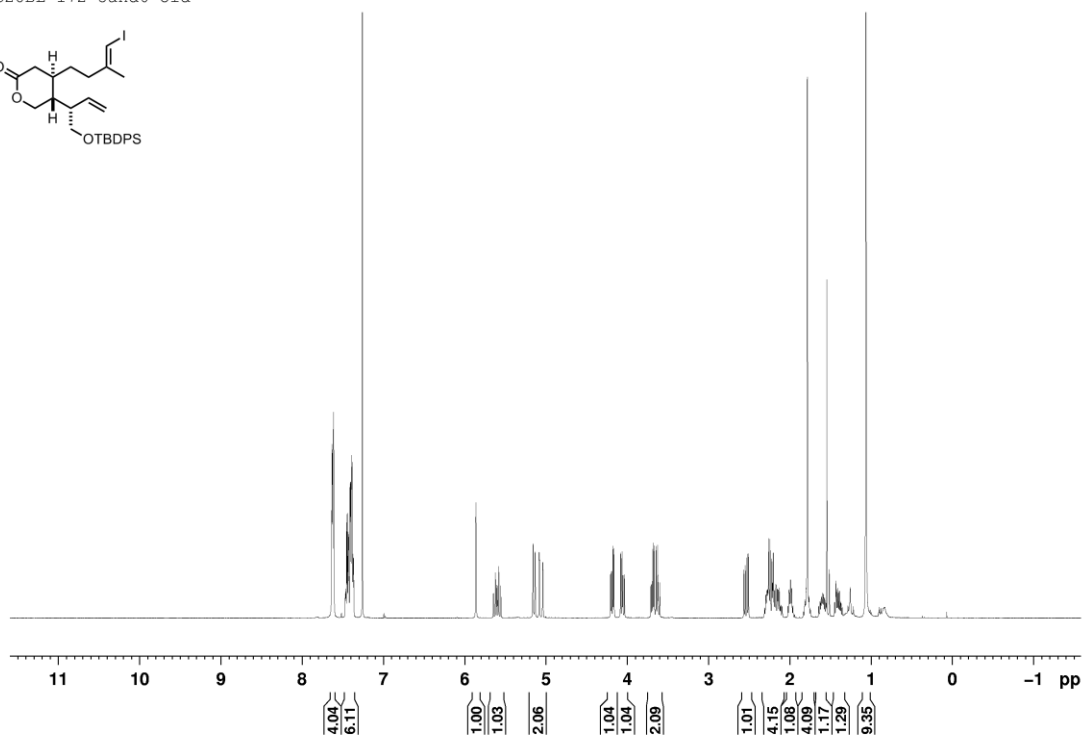
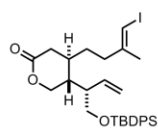
Exact Mass: 602.1713

Molecular Weight: 602.6188

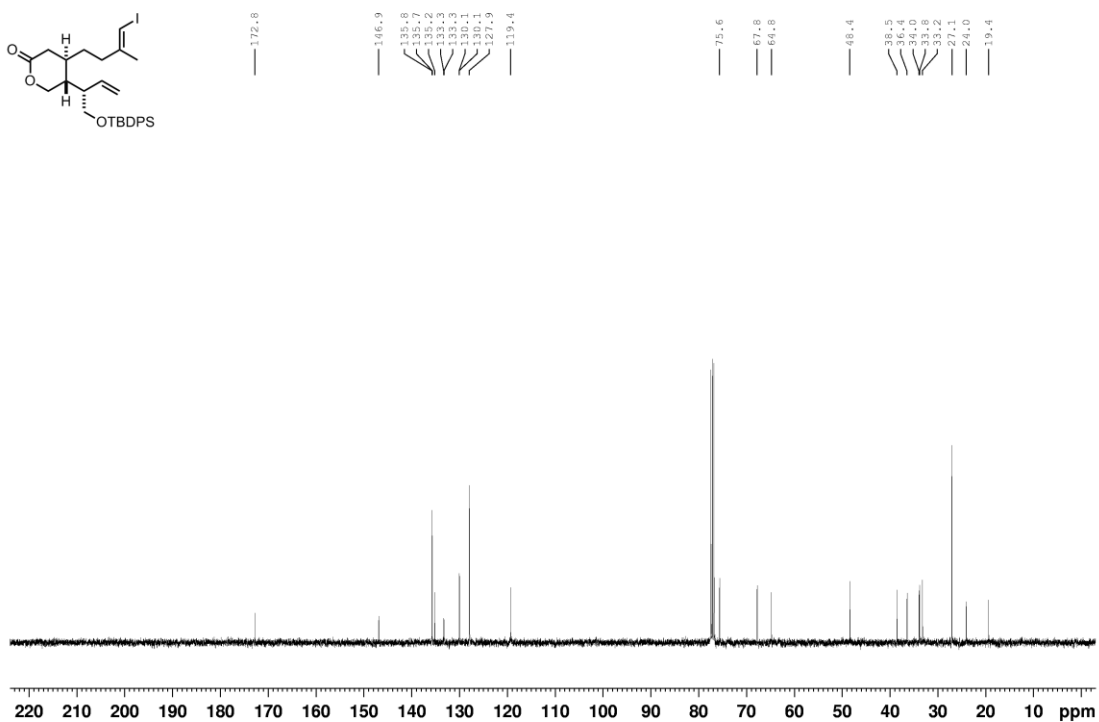
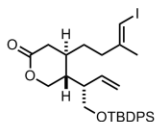
8 (1.962 g, 3.21 mmol) was dissolved in HFIP (30 mL, pushed through alox and distilled under argon). It was cooled to 0 °C. Silver carbonate (266 mg, 0.3 eq.) was added. To the slightly rusty brown solution was added NIS (868 mg, 1.2 eq.) in one portion. The color changed to slightly pink during the course of the reaction, but then ended at slightly yellow. All SM was gone after 3 min (time of first TLC). The reaction was quenched by addition of sat. aq. $Na_2S_2O_3$ (151 mL, higher density than CH_2Cl_2), stirred until all the color disappeared and extracted with first CH_2Cl_2 (300+2x150 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a brown oil accompanied by white solid (probably succinimide). The crude product was purified by several rounds of FC (EtOAc:He 1:5) to give the title compound as a clear yellow oil (1.699 g, 88%) and recover some SM as a brown oil (207 mg, 11 %).

1H NMR: ($CDCl_3$, 400 MHz) δ = 7.65-7.60 (m, 4H), 7.48-7.36 (m, 6H), 5.86 (d, J = 0.9 Hz, 1H), 5.60 (dt, J = 17.0, 9.9 Hz, 1H), 5.15 (dd, J = 10.3, 1.7 Hz, 1H), 5.06 (dd, J = 17.0, 1.3 Hz, 1H), 4.19 (dd, J = 11.7, 5.0 Hz, 1H), 4.06 (dd, J = 11.7, 7.5 Hz, 1H), 3.69 (dd, J = 10.5, 5.3 Hz, 1H), 3.62 (dd, J = 10.5, 7.2 Hz, 1H), 2.54 (dd, J = 15.7, 6.8 Hz, 1H), 2.32-2.08 (m, 3H), 2.23 (dd, J = 15.7, 6.9 Hz, 1H), 2.03-1.95 (m, 1H), 1.84-1.74 (m, 1H), 1.78 (d, J = 0.8 Hz, 3H), 1.66-1.55 (m, 1H), 1.46-1.34 (m, 1H), 1.06 (s, 9H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 172.8, 146.9, 135.8, 135.7, 135.2, 133.3 (two signals visible), 130.1 (two signals visible), 127.9 (two coinciding signals), 119.4, 75.6, 67.8, 64.8, 48.4, 38.5, 36.4, 34.0, 33.8, 33.2, 27.1, 24.0, 19.4; **HRMS (ESI-TOF):** calc. for $[M+Na]^+$: 625.1605, found 625.1321; **IR (neat):** 3064, 2925, 2860, 2356, 2345, 1747, 1467, 1430, 1385, 1264, 1183, 1103, 1000, 923, 818, 746, 699, 612, 558; **$[\alpha]^{24}_D$** = $-31.89 \pm 0.15^\circ$ (c = 1.205, $CHCl_3$); **Rf-value:** 0.17 (EtOAc:hexanes 1:5)

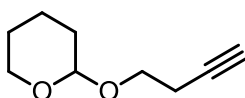
C28BL-172-5and6-old



C28BL-172-5and6-old



293 2-(but-3-yn-1-yloxy)tetrahydro-2H-pyran

Chemical Formula: C₉H₁₄O₂

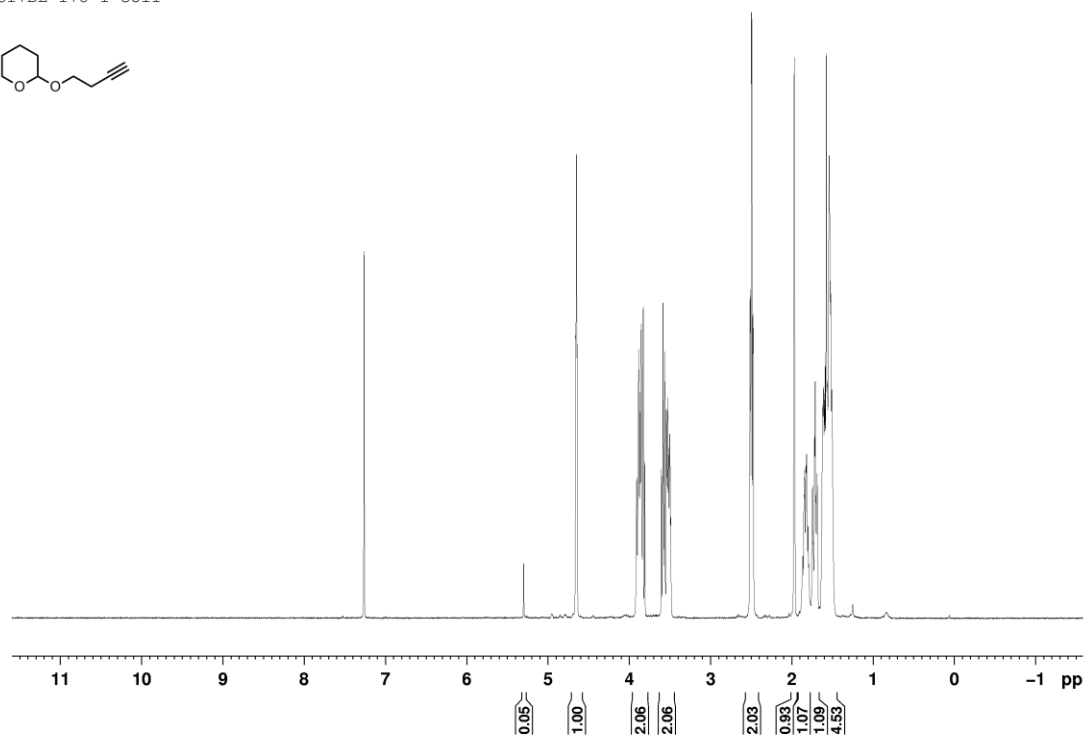
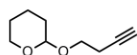
Exact Mass: 154.0994

Molecular Weight: 154.2063

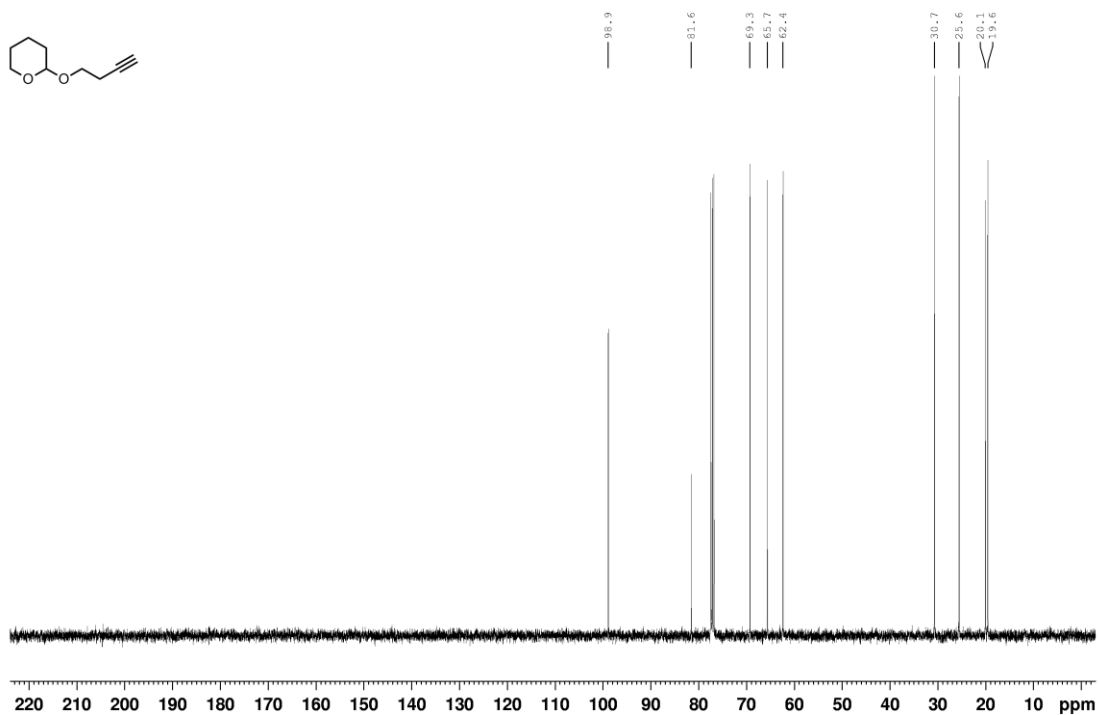
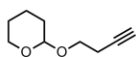
To a mixture of but-3-yn-1-ol (11 mL, 145 mmol, 1 eq.) and 4,5-dihydro-2H-pyran (14 mL, 153 mmol, 1.05 eq.) in CH₂Cl₂ (230 mL) at 0 °C was added TsOH•H₂O (284 mg, 1.45 mmol, 0.01 eq.) was added. The mixture was stirred at this temperature for 60 min. After 15 min, more than 90 % of the SM had already been converted. NaOH (110 mL, 1 M, aq.) was added and stirred for 30 min. Phases were separated and the organic phase was dried over MgSO₄, filtered and rinsed with CH₂Cl₂ (100 mL). The solvent was evaporated and the crude product was purified by FC (CH₂Cl₂) to the title compound as clear colorless oil (21.0 g, 94%). Prolonged rotary evaporation was necessary to remove all the residual solvent.

¹H NMR: (CDCl₃, 400 MHz) δ = 4.65-7.61 (t, *J* = 3.3 Hz, 1H), 3.93-3.79 (m, 2H), 3.62-3.43 (m, 2H), 2.50 (td, *J* = 7.0, 2.2 Hz, 2H), 1.97 (s, *br*, 1H), 1.90-1.77 (m, 1H), 1.77-1.67 (m, 1H), 1.65-1.47 (m, 4H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 98.9, 81.6, 69.3, 65.7, 62.4, 30.7, 25.6, 20.1, 19.6; **HRMS (EI):** calc. for [M-H]⁺: 153.0910, found 153.0910; **Rf-value:** 0.56 (EtOAc:hexanes 1:3); **Density:** 0.964 g/mL (23 °C)

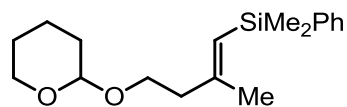
C17BL-175-1-coll



C17BL-175-1-coll/7



294 (E)-dimethyl(2-methyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-1-en-1-yl)(phenyl)silane



Chemical Formula: C₁₈H₂₈O₂Si

Exact Mass: 304.1859

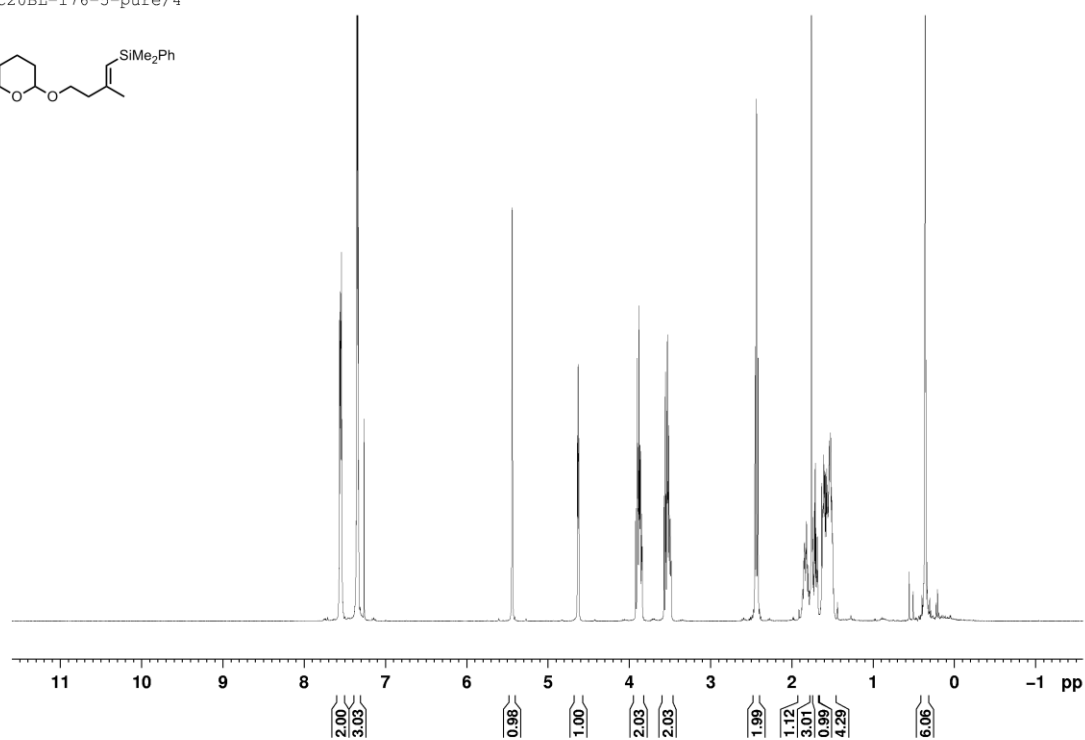
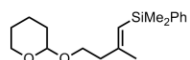
Molecular Weight: 304.4992

Lithium metal pellets (8.43 g, 1.22 mol, 7.5 eq. Aldrich) were suspended in THF (420 mL) and cooled to -10 °C. Neat phenyldimethylchlorosilane (67.4 mL, 405 mmol, 2.5 eq.) was added dropwise over 10 min. The solution started to darken within 10 minutes and was stirred for 4 h 30 min. CuCN (16.31 g, 183 mmol, 1.13 eq., Aldrich, used as received, stored in a glove box) was suspended in THF (280 mL) at 0 °C. The solution of the silane was cooled to -20 °C, taken out of the cooling bath and was quickly transferred to the copper via cannula, rinsed with 3x20 mL THF and stirred for 15 min. The mixture was cooled to -78 °C, and a solution of **293** (27 mL, 162 mmol, 1 eq.) in THF (210 mL) was added dropwise (addition funnel) and rinsed with THF (3x10) over 50 min (internal temperature below -71 °C). The mixture was stirred for 20 min (TLC indicated consumption of **293**), and iodomethane (144 mL, 1.013 mol, 6.25 eq., pushed through a plug of neutral activated aluminum oxide Ø= 1cm, length 5cm and distilled under argon prior to use) was added dropwise over 40 min. The first 10 mL had to be added very slowly due to strong exothermicity, then the rate of addition could be increased. After 30 min cooling was removed, after 40 min, internal temperature had reached 4 °C. The mixture was quenched by transfer into a 1:1 mixture of sat. NH₄Cl/25 %NH₃ (1L), rinsed with 1:1 sat. NH₄Cl/25 %NH₃ (2x200 mL), diluted with EtOAc (700 mL). After stirring vigorously and open to air overnight, the mixture had turned blue. Cellite was added and it was filtered. The phases were separated and the aqueous phase and the filter cake were extracted with EtOAc (2x200 mL). The combined organic phases were first stirred with sat. NH₄Cl/25 %NH₃ (140 mL, 1:1), and secondly with a mixture of brine (105 mL) and Na₂S₂O₃ (14 mL). The solution was dried over MgSO₄ and concentrated. The material was purified by two rounds of FC (hexanes to 1:25 Et₂O:hexanes to 1:12.5 to 1:9 to 1:4) to give the title compound as a clear, slightly green-yellow oil (52.23 g, 98%).

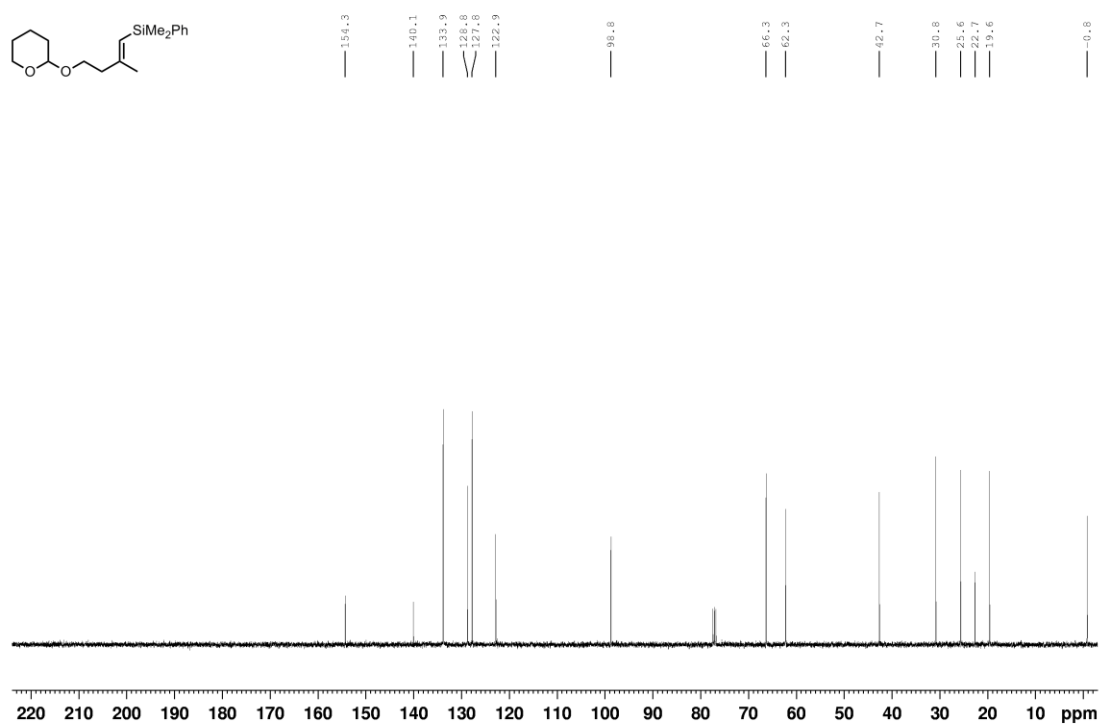
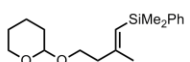
¹H NMR: (CDCl₃, 400 MHz) δ = 7.59-7.51 (m, 2H), 7.38-7.31 (m, 3H), 5.44 (d, *J* = 0.6 Hz, 1H), 4.63 (t, *J* = 3.5 Hz, 1H), 3.93-3.83 (m, 2H), 3.58-3.47 (m, 2H), 2.44 (t, *J* = 7.1 Hz, 2H), 1.92-1.78 (m, 1H), 1.76 (s, 3H), 1.75-1.67 (m, 1H), 1.65-1.47 (m, 4H), 0.36 (s, 6H); **¹³C NMR:** (CDCl₃, 100

MHz) δ = 154.3, 140.1, 133.9, 128.8, 127.8, 122.9, 98.8, 66.3, 62.3, 42.7, 30.8, 25.6, 22.7, 19.6, -0.8; **HRMS (EI)**: calc. for $[M-CH_3]^+$: 289.1618, found 289.1619, weak signal; **HRMS (ESI)**: calc. for $[M+Na]^+$: 327.1758, found 327.1751; **Rf-value**: 0.51 (EtOAc:hexanes 1:5)

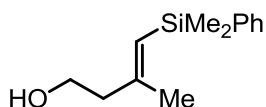
C20BL-176-5-pure/4



C20BL-176-5-pure/3



295 (E)-4-(dimethyl(phenyl)silyl)-3-methylbut-3-en-1-ol

Chemical Formula: C₁₃H₂₀OSi

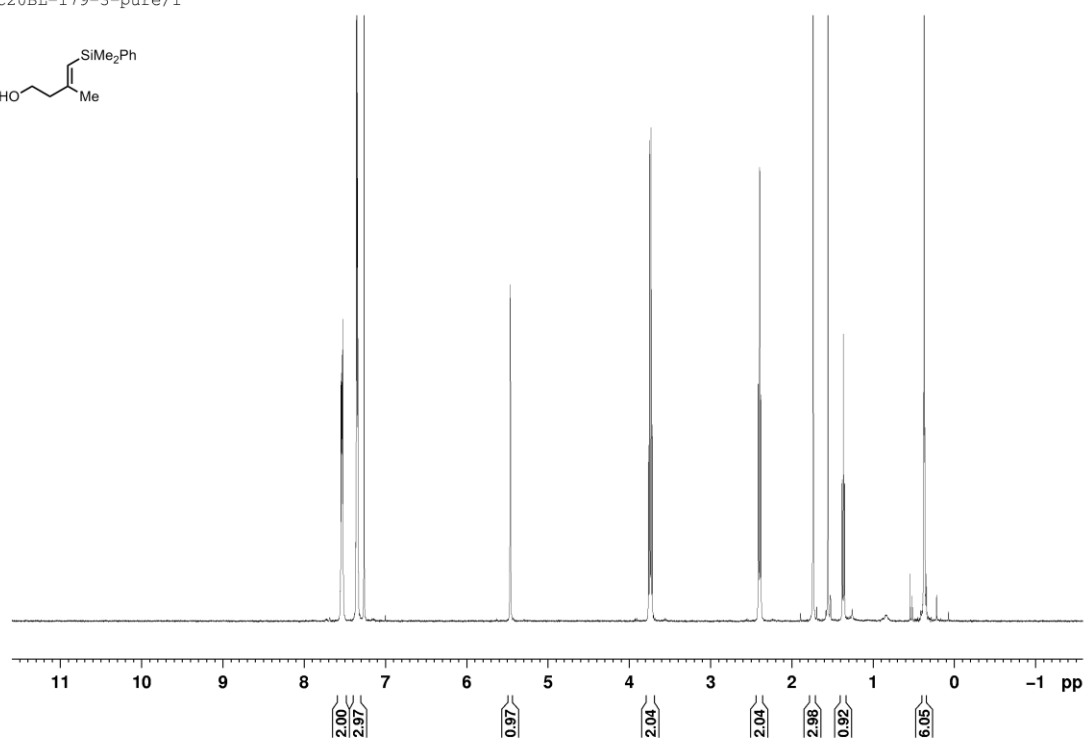
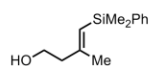
Exact Mass: 220.1283

Molecular Weight: 220.3828

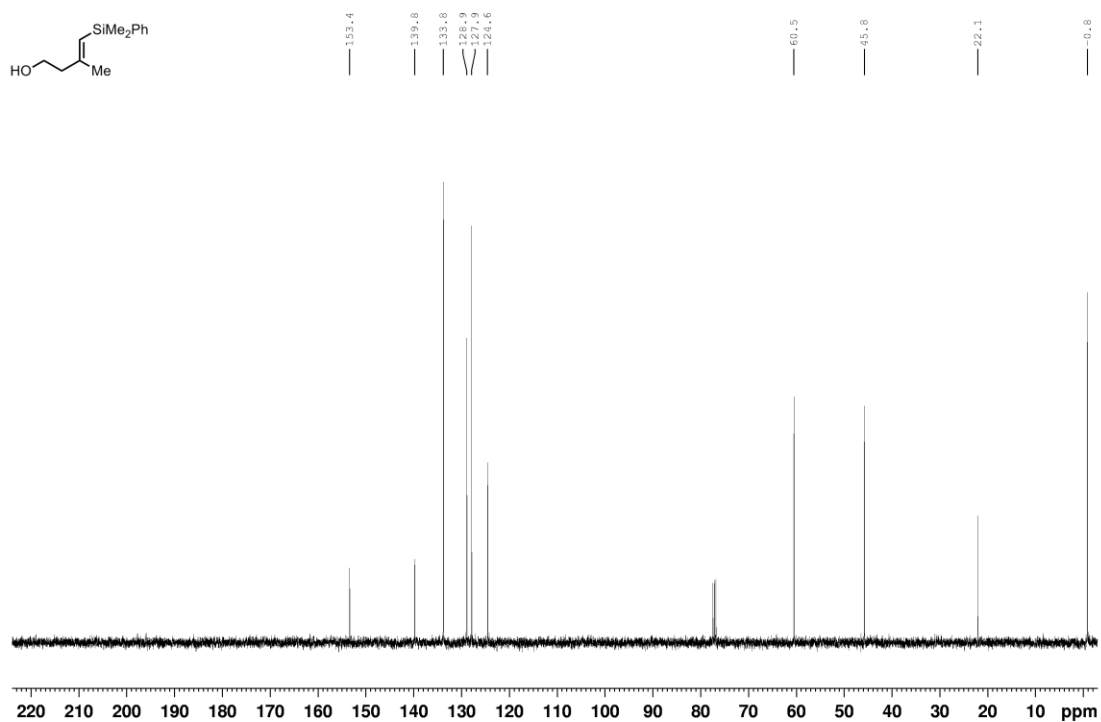
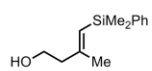
To THP ether **294** (2.0 g, 6.57 mmol, 1 eq.) in ethanol (100 mL) was added TsOH·H₂O (1.25 g, 6.57 mmol, 1 eq.) and it was stirred for 2 h at ambient temperature. The mixture was diluted with phosphate buffer (130 mL, pH 7, 0.5 M) and Na₂HPO₄•12H₂O (2.352 g, 1 eq.) was added. The ethanol was removed by rotary evaporation (foaming) and the aqueous phase was extracted with EtOAc (1x100 mL and 2x50 mL). The organic phase was dried over Na₂SO₄ and concentrated. Purification by FC (EtOAc:hexanes 1:6 to 1:5 to 1:1) gave the title compound as a clear, colorless oil (1.167 g, 81%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.56-7.50 (m, 2H), 7.38-7.32 (m, 3H), 5.46 (d, *J* = 0.6 Hz, 1H), 3.74 (q, *J* = 6.2 Hz, 2H), 2.40 (td, *J* = 6.3, 0.6 Hz, 2H), 1.74 (s, 3H), 1.37 (t, *J* = 5.8 Hz, 1H), 0.37 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 153.4, 139.8, 133.8, 128.9, 127.9, 124.6, 60.5, 45.8, 22.1, -0.8; **HRMS (EI):** calc. for [M-CH₃]⁺: 205.1043, found 205.1044; **R_f-value:** 0.10 (EtOAc:hexanes 1:5)

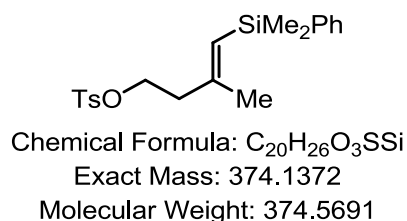
C20BL-179-3-pure/1



C20BL-179-3-pure/2



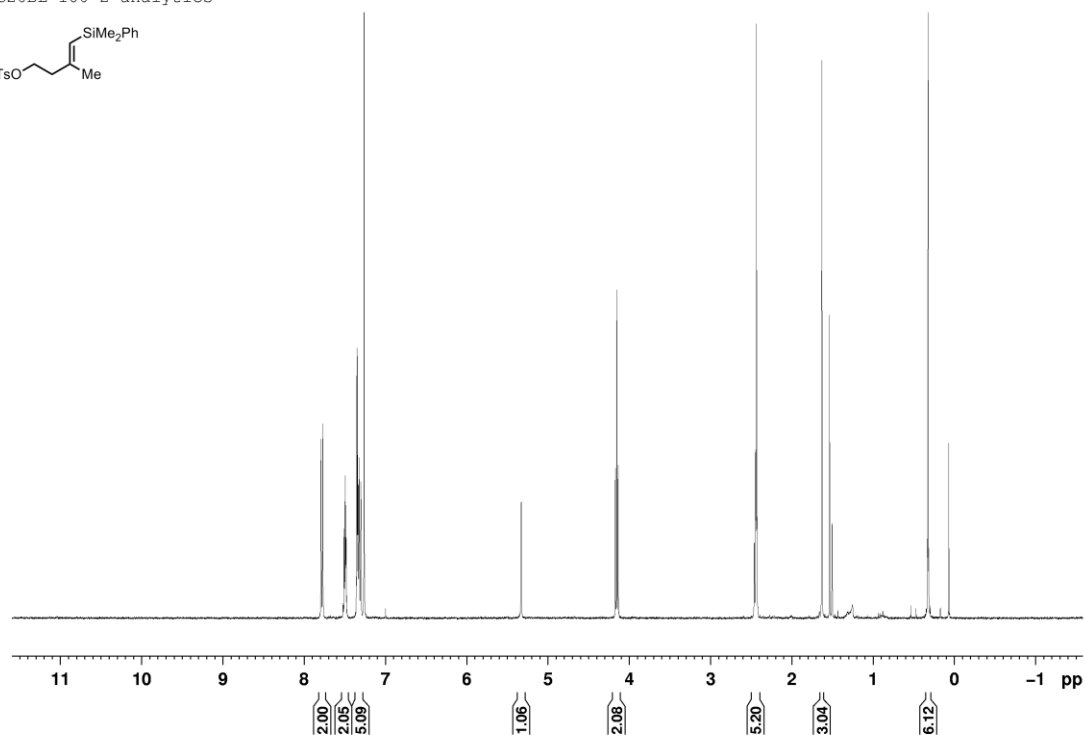
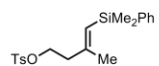
296 (E)-4-(dimethyl(phenyl)silyl)-3-methylbut-3-en-1-yl 4-methylbenzenesulfonate



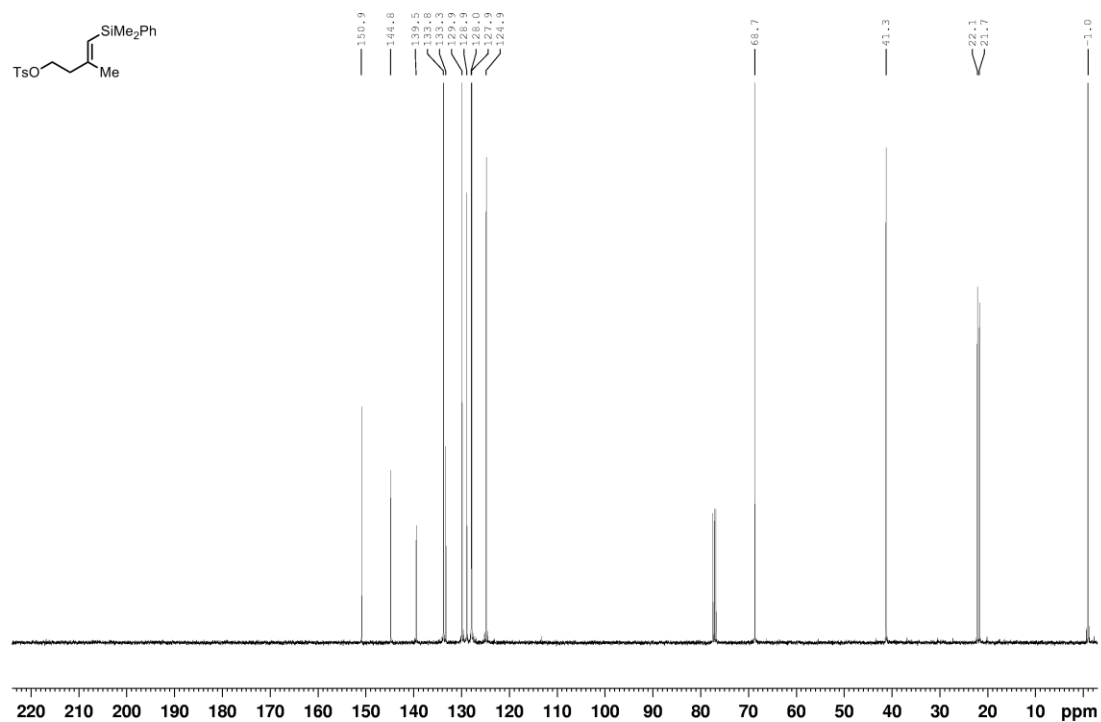
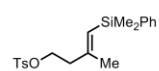
To a solution of **295** (2.10 g, 9.53 mmol, 1 eq.) and DMAP (230 mg, 1.91 mmol, 0.2 eq.) in Et₃N (13 mL, 95.3 mmol, 10 eq.) and CH₂Cl₂ (48 mL) was added TsCl (2.51 g, 13.2 mmol, 1.38 eq.) and the mixture turned a strong yellow color within a few minutes. It was stirred for 14 h at room temperature and the brown reaction mixture was partitioned between NH₄Cl (50 mL, sat., aq.), water (30 mL) and EtOAc (100). The aqueous phase was extracted with EtOAc (2x50 mL) and the combined organic extract were washed with sat. NH₄Cl/brine (1:1, 20 mL), then brine (20 mL), dried over Na₂SO₄ and concentrated. FC (loading with CH₂Cl₂, elution with Et₂O:hexanes 1:24 to 1:12) gave the title compound as a clear, colorless oil (3.344 g, 94 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.81-7.76 (m, 2H), 7.52-7.57 (m, 2H), 7.37-7.29 (m, 5H), 5.33 (d, *J* = 0.8 Hz, 1H), 4.16 (t, *J* = 6.9 Hz, 2H), 2.45 (td, *J* = 6.9, 0.9 Hz, 2H), 2.44 (s, 3H), 1.63 (s, 3H), 0.32 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 150.9, 144.8, 139.5, 133.8, 133.3, 129.9, 128.9, 128, 127.9, 124.9, 68.7, 41.3, 22.1, 21.7, -1.0; **Rf-value:** 0.36 (EtOAc:hexanes 1:5)

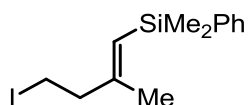
C20BL-180-2-analytics



C20BL-180-2-analytics



297 (E)-(4-iodo-2-methylbut-1-en-1-yl)dimethyl(phenyl)silane

Chemical Formula: $C_{13}H_{19}ISi$

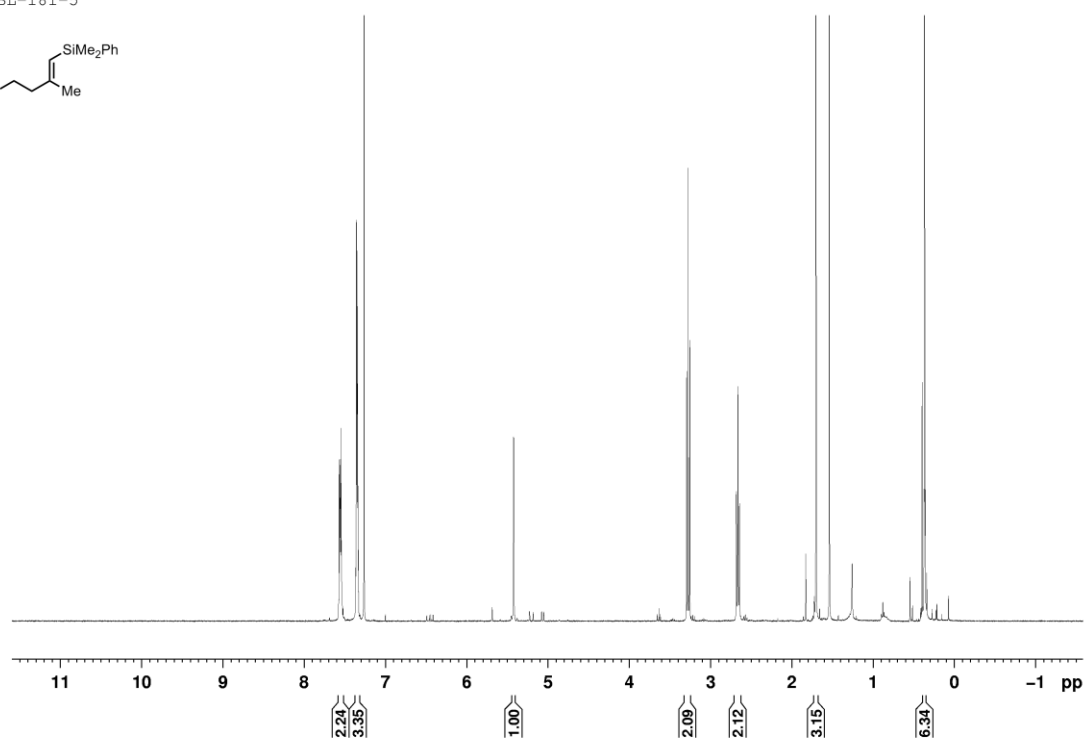
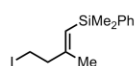
Exact Mass: 330.0301

Molecular Weight: 330.2799

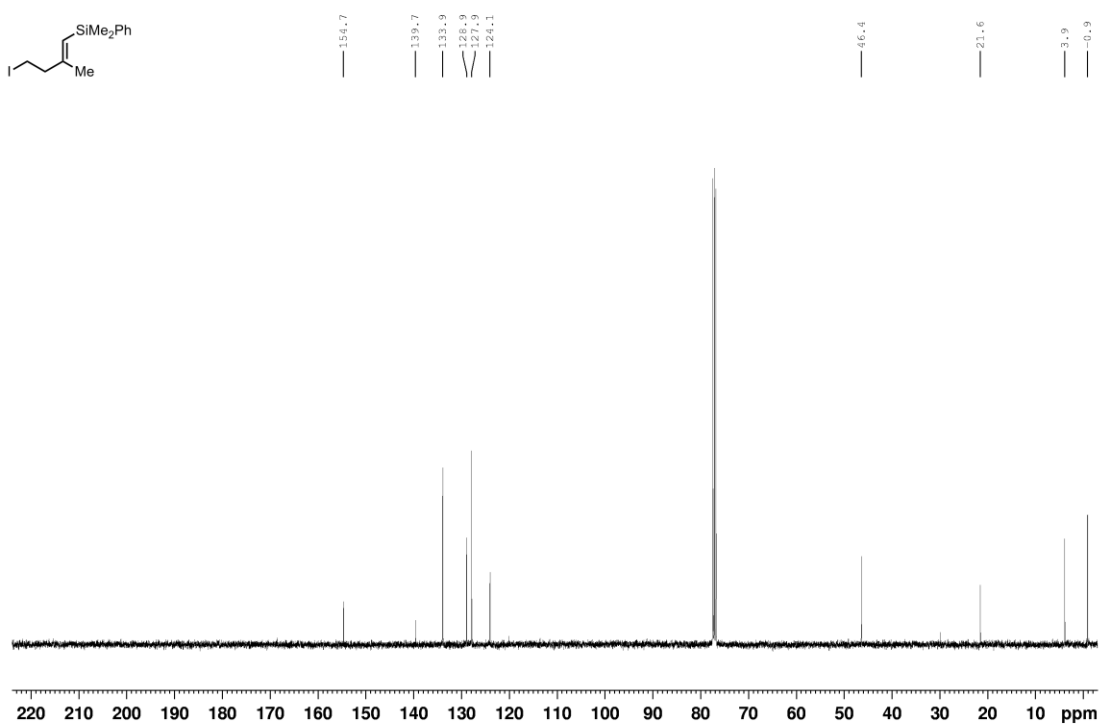
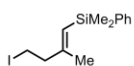
Tosylate **296** (28.0 g, 74.8 mmol, 1 eq.) was dissolved in acetone (380 mL) and put into a water bath. A mixture of NaI (113 g, 748 mmol, 10 eq., dried under 1 mbar vacuum at 120 ° for 8 h) and copper powder (390 mg, 3.74 mmol, 0.05 eq.) was added. The solution of SM quickly turned a slight brown, which was soon replaced by the red color of the copper powder. The slurry was stirred for 18 h. The mixture was diluted with toluene (400 mL), which gave a very fine dispersion and evaporated to a volume of around 100 mL. Silica gel column was conditioned (Et₂O:hexanes 1:20) and topped with sand (3 cm). Dry silica gel (100 mL) was added to the crude slurry and the slurry was directly loaded onto column, it was rinsed with toluene (6x50 mL), then topped with sand (3 cm). Elution with first toluene, then Et₂O:hexanes 1:20. The small amount of impure material obtained was repurified by FC (Et₂O:hexanes 1:25). The title compound was obtained as a clear, slightly yellow and thick oil (24.02 g, purity 95%, 5% of inseparable diene, corrected yield 92%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.57-7.53 (m, 2H), 7.38-7.32 (m, 3H), 5.42 (d, J = 0.9 Hz, 1H), 3.28 (t, J = 7.6 Hz, 2H), 2.66 (td, J = 7.6, 0.9 Hz, 2H), 1.70 (d, J = 0.6 Hz, 3H), 0.37 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 154.7, 139.7, 133.9, 128.9, 127.9, 124.1, 46.4, 21.6, 3.9, -0.9; **Rf-value:** 0.68 (EtOAc:hexanes 1:10)

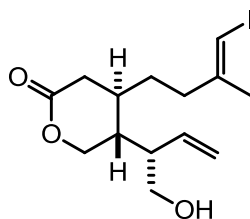
BL-181-5



BL-181-5



312 (4R,5R)-5-((S)-1-hydroxybut-3-en-2-yl)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)tetrahydro-2H-pyran-2-one



Chemical Formula: C₁₄H₂₁IO₃

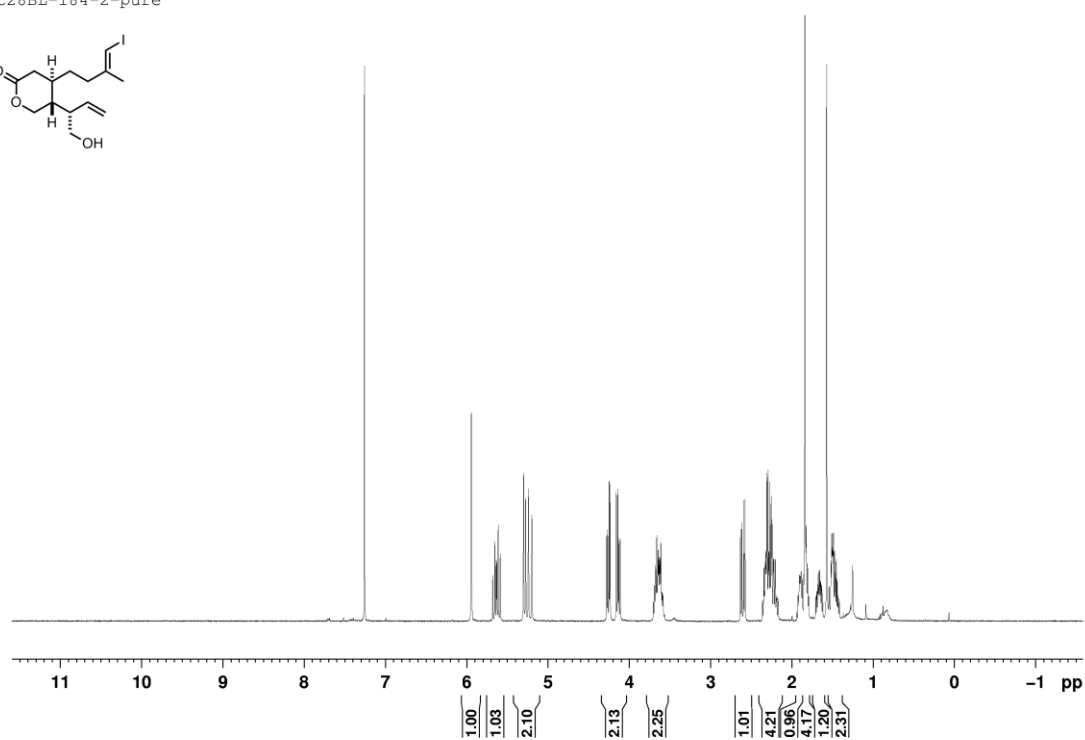
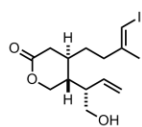
Exact Mass: 364.0535

Molecular Weight: 364.2192

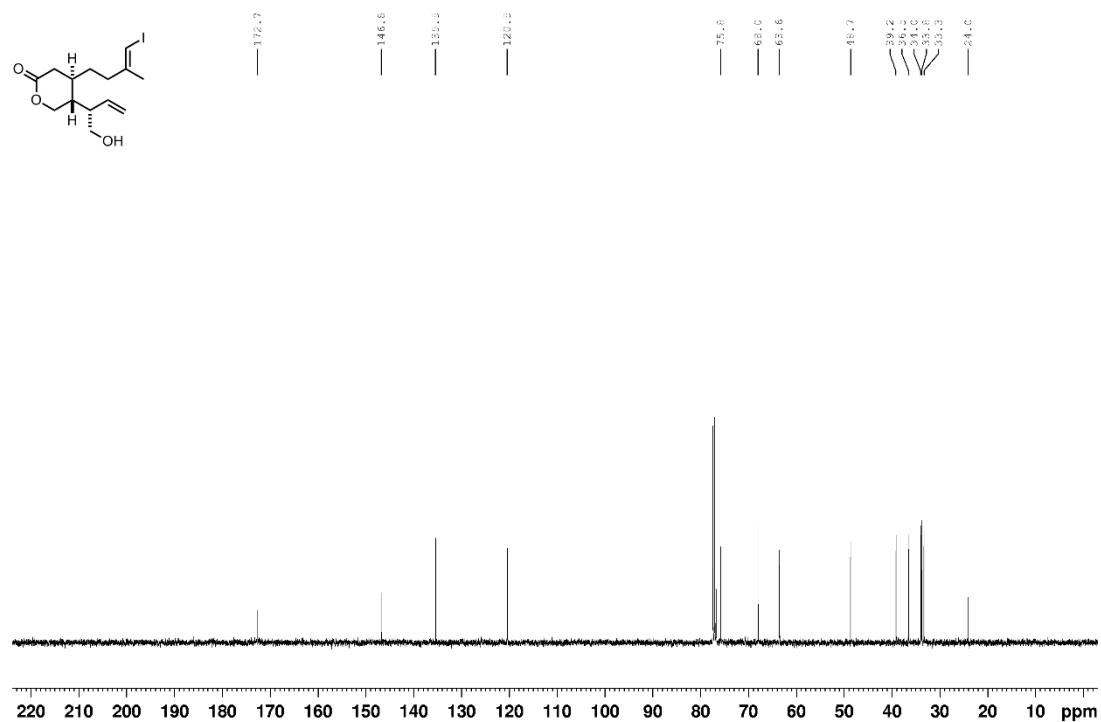
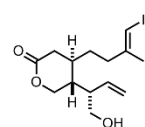
290 (12.09 g) was dissolved in THF (40 mL), and the solution was equally distributed among 4 argon flushed plastic centrifugal tubes (50 mL) and rinsed with THF (2x13 mL). To each vial was added HF·py (5 mL each, 70 W/V%) quickly dropwise at room temperature. After 17.5 h of stirring, the solutions were added carefully to a vigorously stirred solution of KHCO₃ (560 mL, sat., aq.) by syringe, then rinsed with KHCO₃ (small portions of total 60mL, sat. aq.) and EtOAc (300 mL). The mixture was stirred for 2 h and checking the pH gave a value of approx. 9. The aqueous phase was saturated with solid NaCl, separated and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with KHCO₃ (50 mL, sat. aq., saturated with NaCl), brine (50 mL) followed by drying over MgSO₄. The solution was concentrated under reduced pressure and purified by FC (loaded and eluted with EtOAc:hexanes 1:1 to 3:1). The pure product was dried on high vacuum overnight to remove residual pyridine. The title compound was obtained as a clear, orange, very viscous oil (5.98 g, 82%).

¹H NMR: (CDCl₃, 400 MHz) δ = 5.94 (d, *J* = 0.9 Hz, 1H), 5.64 (dt, *J* = 17.0, 9.9 Hz, 1H), 5.29 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.22 (dd, *J* = 17.1, 1.0 Hz, 1H), 4.26 (dd, *J* = 11.8, 4.8 Hz, 1H), 4.14 (dd, *J* = 11.8, 7.2 Hz, 1H), 3.72-3.55 (m, 2H), 2.60 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.37-2.14 (m, 3H), 2.28 (dd, *J* = 15.6, 6.7 Hz, 1H), 1.95-1.86 (m, 1H), 1.86-1.78 (m, 1H), 1.84 (d, *J* = 1.0 Hz, 3H), 1.72-1.61 (m, 1H), 1.53-1.40 (m, 2H, CH and OH); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 172.7; 146.8; 135.5; 120.5; 75.8, 68.0; 63.6; 48.7; 39.2; 36.5; 34.0; 33.8; 33.3; 24.0; **HRMS (ESI-TOF):** calc. for [M+Na]⁺: 387.0428, found 387.0428; **IR (neat):** 3438, 3071, 2918, 2353, 2332, 2189, 2063, 1990, 1916, 1849, 1730, 1641, 1429, 1386, 1264, 1184, 1145, 1047, 923, 830, 758, 670, 656; **[α]_D²³** = +32.7 ± 0.6° (c = 0.32, CHCl₃); **Rf-value:** 0.17 (EtOAc:hexanes 1:1)

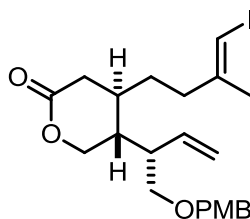
C28BL-184-2-pure



C28BL-184-2-pure



313 (4R,5R)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)-5-((S)-1-((4-methoxybenzyl)oxy)but-3-en-2-yl)tetrahydro-2H-pyran-2-one



Chemical Formula: C₂₂H₂₉IO₄

Exact Mass: 484.1111

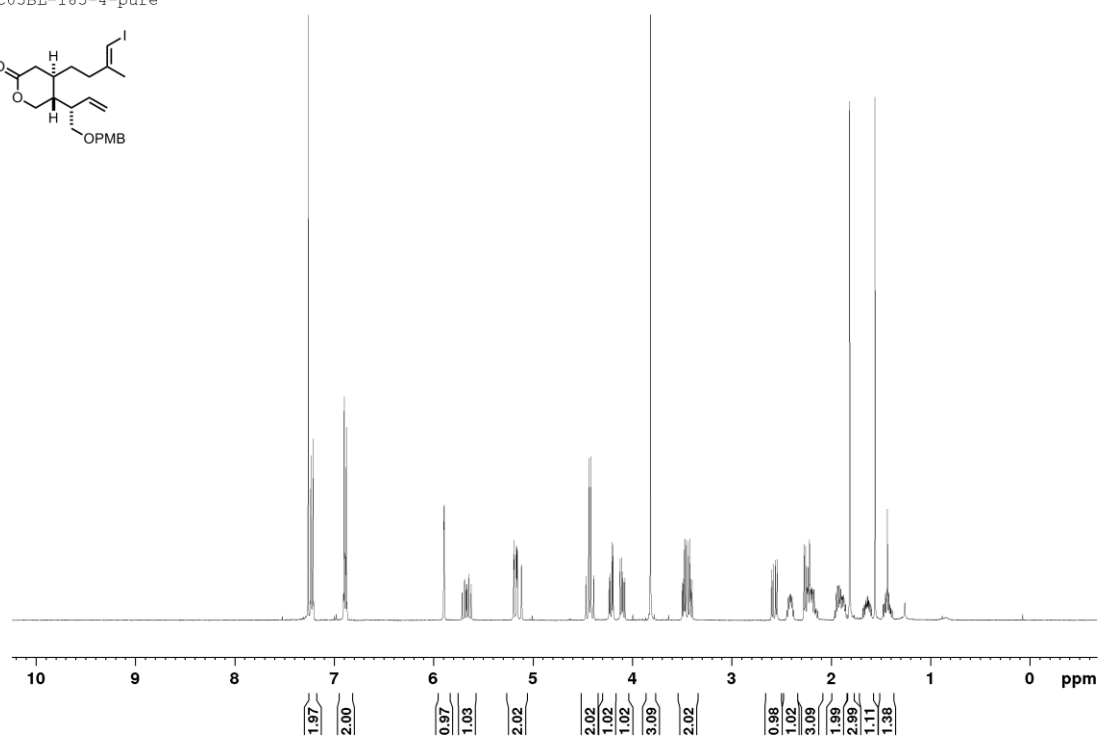
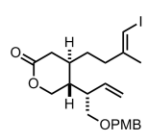
Molecular Weight: 484.3677

312 (5.98 g, 16.4 mmol, 1 eq.) was dissolved in CH₂Cl₂ (20 mL). *para*-methoxytrichloroacetimidate **248** (6.96 g, 24.6 mmol, 1.5 eq.) was added in CH₂Cl₂ (21 mL+ 2x20 mL rinsing). The mixture was cooled to -78 °C and added was TMSOTf (0.05 mL, 0.279 mmol, 0.017 eq.). After 17 min, additional TMSOTf (0.1 mL, 0.558 mmol, 0.034 eq.) was added and the solution immediately turned cloudy. The mixture was stirred for 25 min, Et₃N (0.64 mL, 1.64 mmol, 0.1 eq.) was added and it was left to warm to ambient temperature. Cyclohexane (120 mL) was added and the mixture was filtered. The filter cake was rinsed with cyclohexane:CH₂Cl₂ (3x60 mL, 2:1), MgSO₄ and cellite were added and it was filtered again. Unfortunately, material was sticking to the filter cake and necessitated rinsing off with cyclohexane:CH₂Cl₂ (3x55 mL, 7:1). The solution was diluted with toluene (40 mL) and all the more volatile solvents were removed. The solution was directly loaded onto a column and purified by several rounds of FC (neat toluene to EtOAc:toluene 1:10 to 1:5 to EtOAc:hexanes 1:3 and finally 3:1). The pure title compound was obtained as a yellow oil (4.87 g, 61% yield), accompanied by two batches of lower purity, one containing trichloroacetamide, the other PMB₂O (6% estimated yield each) and some pure starting **312** as a yellow oil (0.5 g, 8%)

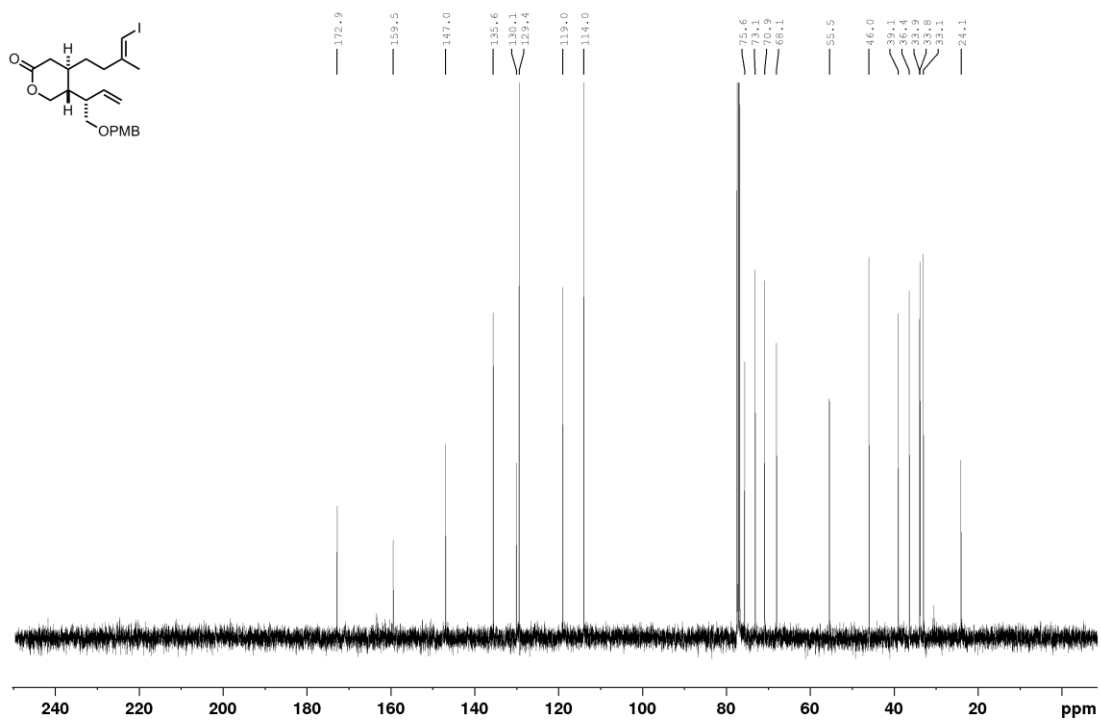
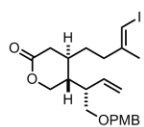
¹H NMR: (CDCl₃, 400 MHz) δ = 7.25-7.20 (m, 2H), 6.91-6.86 (m, 2H), 5.89 (q, *J* = 1.0 Hz, 1H), 5.67 (ddd, *J* = 17.1, 10.2, 9.5 Hz, 1H), 5.18 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.13 (ddd, *J* = 17.2, 1.4, 0.4 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.21 (dd, *J* = 11.7, 4.8 Hz, 1H), 4.10 (dd, *J* = 11.7, 7.3 Hz, 1H), 3.82 (s, 3H), 3.48 (dd, *J* = 9.5, 5.1 Hz, 1H), 3.42 (dd, *J* = 9.5, 6.8 Hz, 1H), 2.57 (dd, *J* = 15.7, 6.6 Hz, 1H), 2.45-2.37 (m, 1H), 2.24 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.28-2.11 (m, 2H), 1.98-1.84 (m, 2H), 1.81 (d, *J* = 1.0 Hz, 3H), 1.69-1.58 (m, 1H), 1.48-1.37 (m, 1H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 172.9, 159.5, 147.0, 135.6, 130.1, 129.4, 119.0, 114.0, 75.6, 73.1, 70.9, 68.1, 55.5, 46.0, 39.1, 36.4, 33.9, 33.8, 33.1, 24.1; **HRMS (ESI-TOF):** calc. for [M+Na]⁺: 507.1003, found 507.1002; calc. for [M+K]⁺: 523.0742, found 523.0740; **IR (neat):** 3071, 2998,

2912, 2856, 2362, 2338, 1638, 1612, 1586, 1512, 1458, 1358, 1300, 1175, 1143, 1078, 1000, 923, 820, 762, 720, 712, 706, 697, 667, 564; $[\alpha]^{20}_{\text{D}} = -29.1 \pm 0.05^\circ$ ($c = 1.05$, CH_2Cl_2); **Rf-value:** 0.58 (EtOAc:hexanes 1:1)

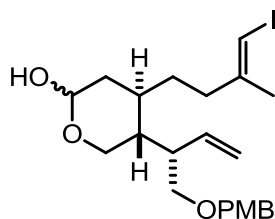
C05BL-185-4-pure



C05BL-185-4-pure



314 (4R,5R)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)-5-((S)-1-((4-methoxybenzyl)oxy)but-3-en-2-yl)tetrahydro-2H-pyran-2-ol



Chemical Formula: C₂₂H₃₁IO₄

Exact Mass: 486.1267

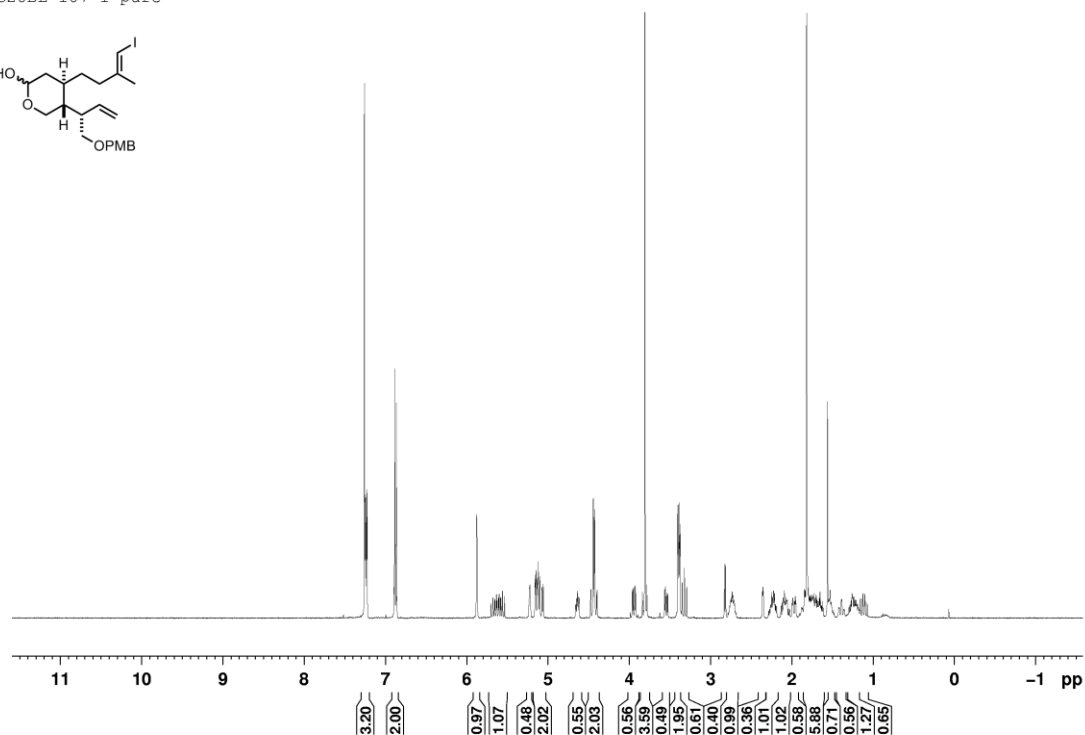
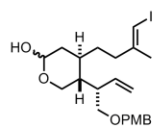
Molecular Weight: 486.3836

313 (267.8 mg, .553 mmol) was dissolved in CH₂Cl₂ (4.85 mL) and cooled to -78 °C. DIBAL-H in CH₂Cl₂ (0.61 mL, 1.0 M, 1. Eq.) was added dropwise. After 20 min, more DIBAL (0.6 mL, 0.1 eq.) was added, upon which TLC showed complete conversion. Acetone (0.02 mL, 1 eq.) was added, then sat. Rochelle's salt solution (2 mL). the mixture was warmed to ambient temperature in a water bath and diluted with EtOAc (10 mL). After 45 min, the solution had turned clear. The phases were separated and the aqueous phase was extracted with 2x5 mL EtOAc. It was dried over MgSO₄ and the solvent was evaporated to give the title compound as a clear, colorless and sticky oil, whichn solidified upon storage to a white non-crystalline material (257.9 mg, 96%).

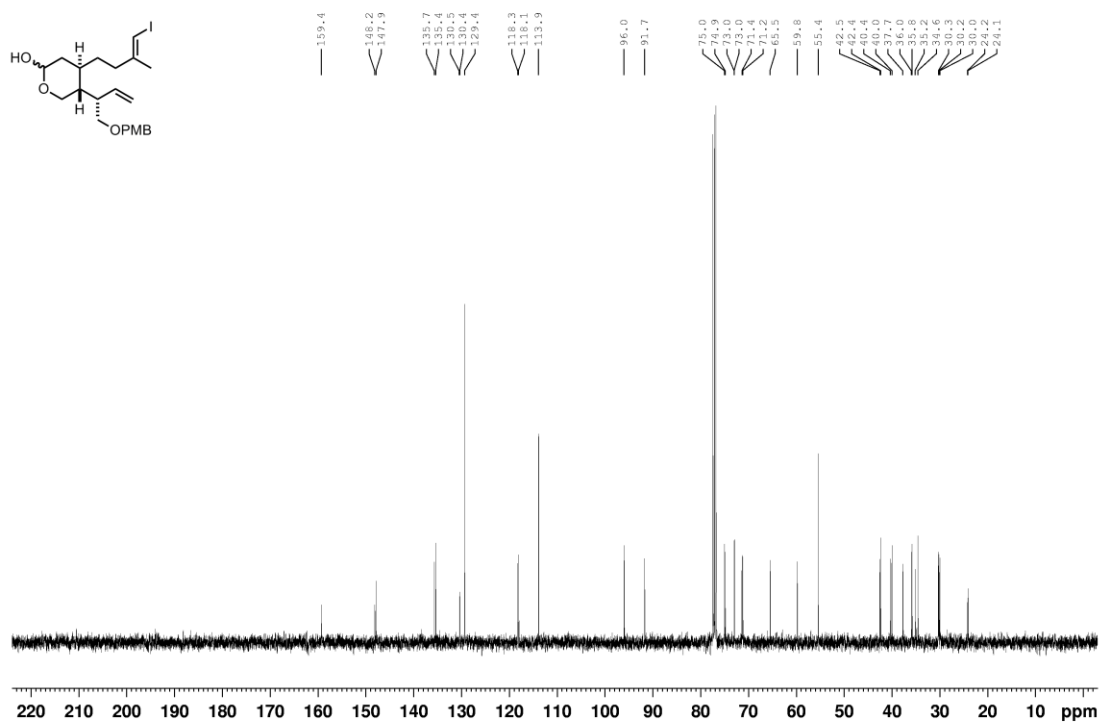
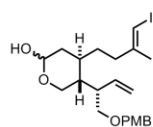
¹H NMR: (CDCl₃, 400 MHz) δ = 7.27-7.21 (m, 2 H), 6.90-6.85 (m, 2H), 5.88 (d, *J* = 1.1 Hz, 1H), 5.66 (ddd, *J* = 17.1, 10.2, 9.4 Hz, 0.5 H), 5.58 (ddd, *J* = 17.1, 9.6, 0.7 Hz, 0.5 H), 5.25-5.20 (m, br, 0.5 H), 5.14 (ddd, *J* = 10.4, 4.0, 1.7 Hz, 1H), 5.09 (ddd, *J* = 17.1, 5.8, 1.0 Hz, 1H), 4.64 (ddd, *J* = 9.1, 5.9, 2.3 Hz, 0.5 H), 4.46 (dd, strong roof effect, *J* = 11.7, 1.3 Hz, 1H), 4.41 (dd, strong roof effect, *J* = 11.7, 2.8 Hz, 1H), 3.94 (ddd, *J* = 20.1, 12.8, 8.6 Hz, 0.6H), 3.85-3.77 (m, 0.6 H), 3.81 (s, 3H), 3.55 (dd, *J* = 11.2, 4.2 Hz, 0.5H) 3.39 (m, quartet like, apparent *J* = 3.5 Hz, 2H), 3.32 (t, *J* = 11.1 Hz, 0.6 H), 2.82 (d, *J* = 6.1 Hz, 0.4H, OH), 2.80-2.67 (m, 1H), 2.36 (d, *J* = 3.2, 1.7 Hz, 0.4 H, OH), 2.30-2.17 (m, 1H), 2.15-2.01 (m, 1H), 1.97 (ddd, *J* = 12.6, 3.6, 2.5 Hz, 0.6H), 1.86-1.60 (m, 2.9 H), 1.82 (s, 3H), 1.56-1.48 (m, 0.7 H), 1.44-1.34 (m, triplet-like, 0.6 H), 1.31-1.17 (m, 1.3 H), 1.12 (td, *J* = 9.3, 12.2 Hz, 0.5 H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 159.4, 148.2, 147.9, 135.7, 135.4, 130.5, 130.4, 129.4, 118.3, 118.1, 113.9, 96.0, 91.7, 75.0, 74.9, 73.0 (2 distinct signals), 71.4, 71.2, 65.5, 59.8, 55.4, 42.5, 42.4, 40.4, 40.0, 37.7, 36.0, 35.8, 35.2, 34.6, 30.3, 30.2, 30.0, 24.2, 24.1; **HRMS (MALDI/ESI):** calc. for [M+Na]⁺: 509.1159, found 509.1158, calc. for [M+K]⁺: 525.0899, found 525.0898; **IR (neat):** 3343, 3055, 2967, 2921, 2856, 1728, 1694, 1609, 1585, 1509, 1453, 1390, 1375, 1357, 1300, 1268, 1251, 1238, 1207, 1183, 1172, 1140,

1123, 1119, 1109, 1077, 1030, 1014, 999, 953, 945, 926, 816, 885, 845, 831, 812, 802, 767, 754, 707, 664, 637; $[\alpha]^{20}_{\text{D}} = -22.34^{\circ}$ ($c = 1.02$, CHCl_3); **m.p.:** 57-60 °C (no decomposition); **Rf-value:** 0.42 (EtOAc:hexanes 1:1)

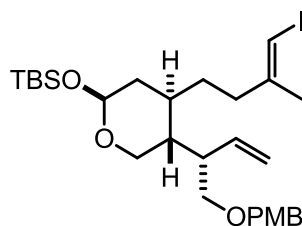
C28BL-187-1-pure



C28BL-187-1-pure



315 tert-butyl(((4R,5R)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)-5-((S)-1-((4-methoxybenzyl)oxy)but-3-en-2-yl)tetrahydro-2H-pyran-2-yl)oxy)dimethylsilane



Chemical Formula: $C_{28}H_{45}IO_4Si$

Exact Mass: 600.2132

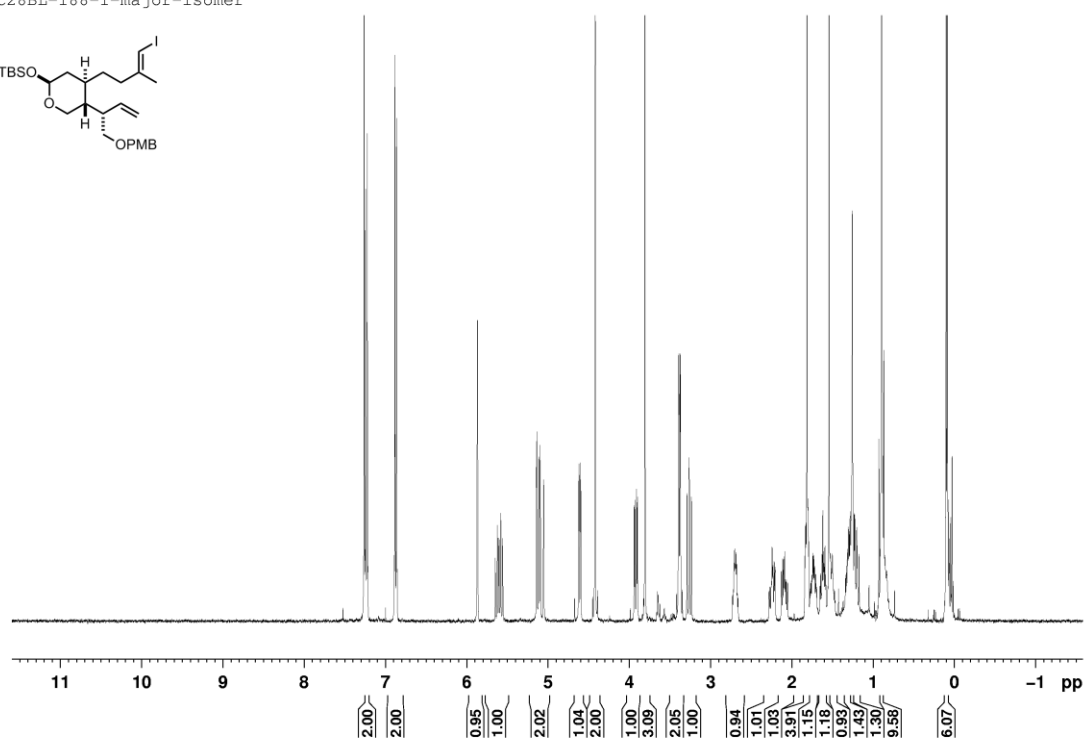
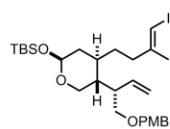
Molecular Weight: 600.6445

Lactol **314** (126 mg, 0.259 mmol, 1 eq.) was dissolved in CH_2Cl_2 (0.56 mL) and added was imidazole (24.2 mg, 0.356 mmol, 1.37 eq.). The solution was cooled to 0 °C and TBSCl (45.7 mg, 0.303 mmol, 1.17 eq.) was added in one portion. The solution turned immediately cloudy and was put into a water bath after 2 min. After 1 h 15 min, no more SM was detectable. Diluted with Et_2O (3 mL) and stirred for another 1.5 h. Quenched by addition of NH_4Cl (1 mL, sat., aq.) and diluted with H_2O (0.1 mL) and Et_2O (7 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3x5 mL). The combined organic phases were sequentially washed with NH_4Cl (2x1 mL, sat., aq.) and brine (1 mL). It was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by four rounds of FC (Et_2O :hexanes 2:5 and three times Et_2O :hexanes 1:10) to give the title compound as a clear colorless oil (132.5 mg, 85%) as well as some of the minor isomer as a clear, colorless oil (6.7 mg, 4%).

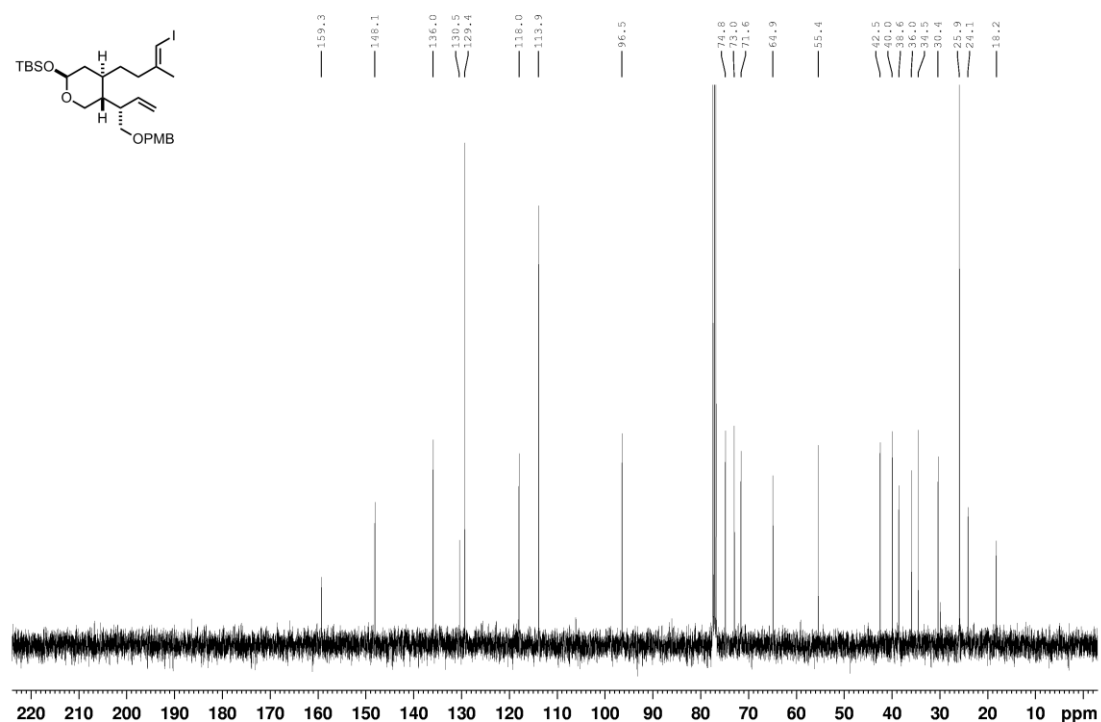
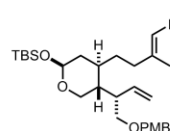
1H NMR: ($CDCl_3$, 400 MHz) δ = 7.26-7.21 (m, 2H), 6.90-6.85 (m, 2H), 5.87 (d, J = 0.8 Hz, 1H), 5.60 (dt, J = 16.9, 9.8 Hz, 1H), 5.13 (dd, J = 10.4, 1.8 Hz, 1H), 5.08 (dd, J = 17.2, 1.3 Hz, 1H), 4.61 (dd, J = 8.5, 2.3 Hz, 1H), 4.42 (triplet like, higher order, apparent J = 12.1 Hz, 2H), 3.92 (dd, J = 11.6, 4.1 Hz, 1H), 3.81 (s, 3H), 3.38 (quartet like, higher order, 2H), 3.26 (dd, J = 11.3, 10.5 Hz, 1H), 2.74-2.65 (m, 1H), 2.30-2.19 (m, 1H), 2.14-2.04 (m, 1H), 1.86-1.78 (m, 1H), 1.81 (d, J = 0.8 Hz, 3H), 1.78-1.68 (m, 1H), 1.63 (tt, J = 15.1, 4.0 Hz, 1H), 1.54-1.45 (m, 1H), 1.35-1.27 (m, 1H), 1.24-1.16 (m, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 159.3, 148.1, 136, 130.5, 129.4, 118, 113.9, 96.5, 74.8, 73, 71.6, 64.9, 55.4, 42.5, 40, 38.6, 36, 34.5, 30.4, 25.9, 24.1, 18.2, -4.1, -5.1; **HRMS (MALDI/ESI):** calc. for $[M+Na]^+$: 624.2056, found 624.2059; **IR (neat):** 2928, 2855, 1613, 1512, 1462, 1388, 1366, 1294, 1249, 1165, 1073, 1038,

996, 919, 838, 778, 709, 673, 577, 517; $[\alpha]^{20}_{\text{D}} = -34.98 \pm 0.26^\circ$ ($c = 0.595$, CHCl_3); **Rf-value:** 0.68 (EtOAc:hexanes 1:1)

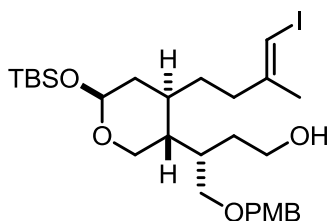
C28BL-188-1-major-isomer



C28BL-188-1-major-isomer



316 (S)-3-((3R,4R,6S)-6-((tert-butyldimethylsilyl)oxy)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)tetrahydro-2H-pyran-3-yl)-4-((4-methoxybenzyl)oxy)butan-1-ol



Chemical Formula: $C_{28}H_{47}IO_5Si$

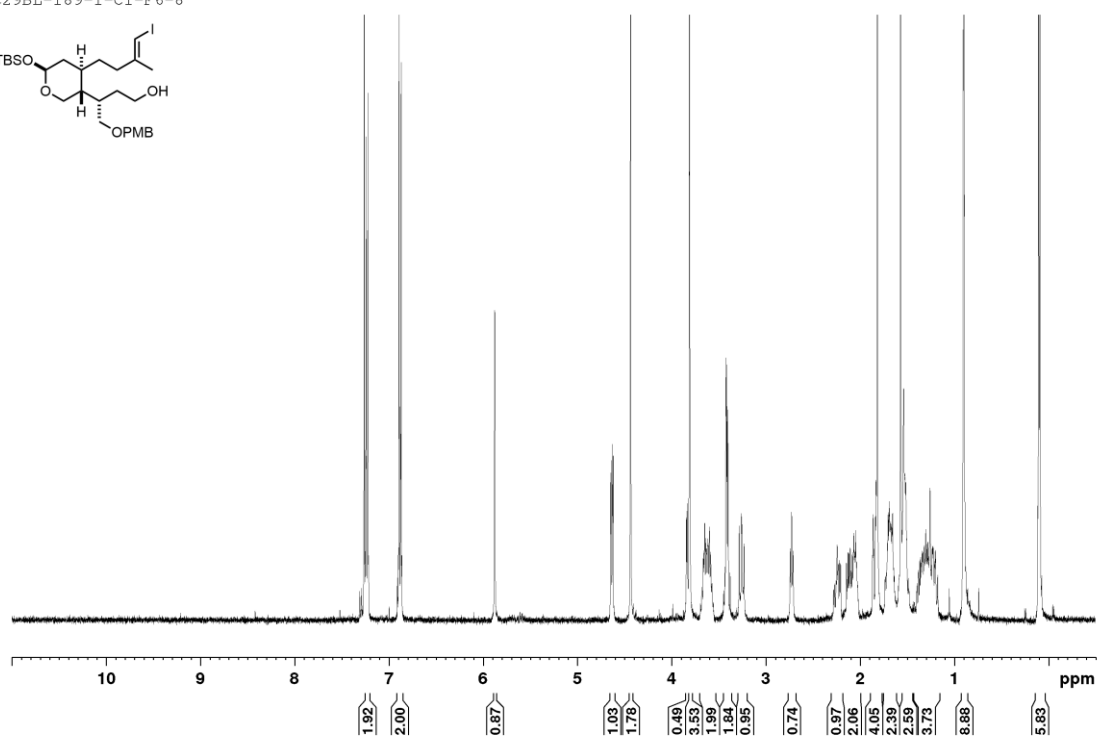
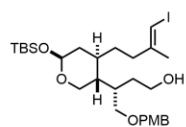
Exact Mass: 618.2237

Molecular Weight: 618.6598

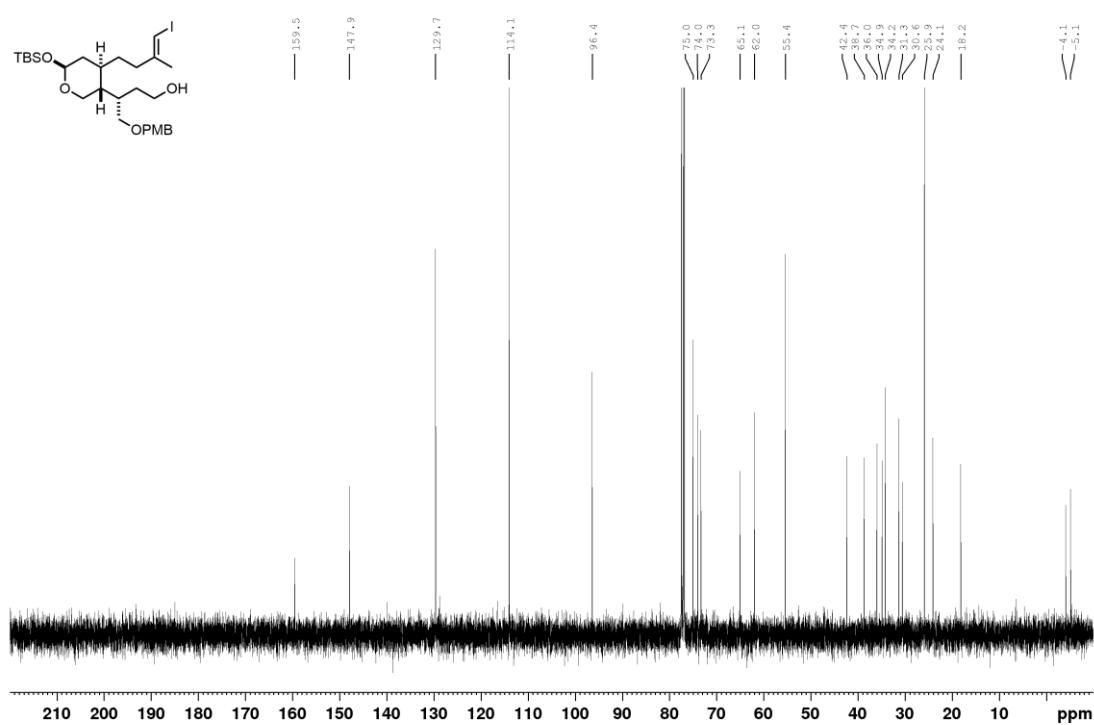
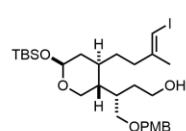
315 (14.5 mg, 24.1 μ mol, 1 eq., twice coevaporated with benzene) was dissolved in THF (0.1 mL) and cooled to 0 °C. A solution of 9-BBN in THF (23.3 mg, 2 mL, 0.0955 M) was prepared in a dry volumetric flask. An aliquot of this solution (0.62 mL, 60.4 μ mol, 2.5 eq.) was added to the SM. After 4 min, the clear solution was put into a water bath and stirred at for 24 h, with almost no visible conversion, additional 9-BBN (2.5 equiv.) was added. After further 8 h, a thir dportio of 9-BBN (2.5 equiv.) was added. After a total of 22 h, the mixture was cooled to 0 °C and quenched by dropwise addition of MeOH (78 μ L, 80 eq.), NaOH (3 M, 24 μ L, 3 eq.) and H₂O₂ (30 %, 20.5 μ L, 2.9 eq). The mixture was then stirred for 55 min at ambient temperature, followed by 1 h 40 min at 45 °C. It was evaporated to dryness and purified by two rounds of FC (1:3 EtOAc:hexanes) to give the title compound (6.7 mg, 45%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.26-7.21 (m, 2H), 6.92-6.85 (m, 2H), 5.88 (d, J = 1.0 Hz, 1H), 4.63 (dd, J = 8.5, 2.4 Hz, 1H), 4.43 (s, 2H), 3.85-3.79 (m, 1H), 3.81 (s, 3H), 3.70-3.54 (m, 2H), 3.45-3.36 (m, 2H), 3.25 (dd, J = 11.5, 9.8 Hz, 1H), 2.72 (t, J = 5.9 Hz, 1H, OH), 2.29-2.19 (m, 1H), 2.15-2.00 (m, 2H), 1.88-1.79 (m, 1H), 1.81 (d, J = 0.9 Hz, 3H), 1.74-1.62 (m, 2H), 1.55-1.46 (m, 2H), 1.40-1.16 (3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 159.5, 147.9, 129.7, 114.1, 96.4, 75.0, 74.0, 73.3, 65.1, 62.0, 55.4, 42.4, 38.7, 36.0, 34.9, 34.2, 31.3, 30.6, 25.9, 24.1, 18.2, -4.1, -5.1; **Rf-value:** 0.27 (EtOAc:hexanes 1:3)

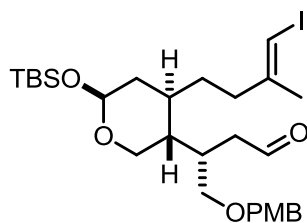
C29BL-189-1-C1-F6-8



C29BL-189-1-C1-F6-8



320 (S)-3-((3R,4R,6S)-6-((tert-butyldimethylsilyl)oxy)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)tetrahydro-2H-pyran-3-yl)-4-((4-methoxybenzyl)oxy)butanal



Chemical Formula: $C_{28}H_{45}IO_5Si$

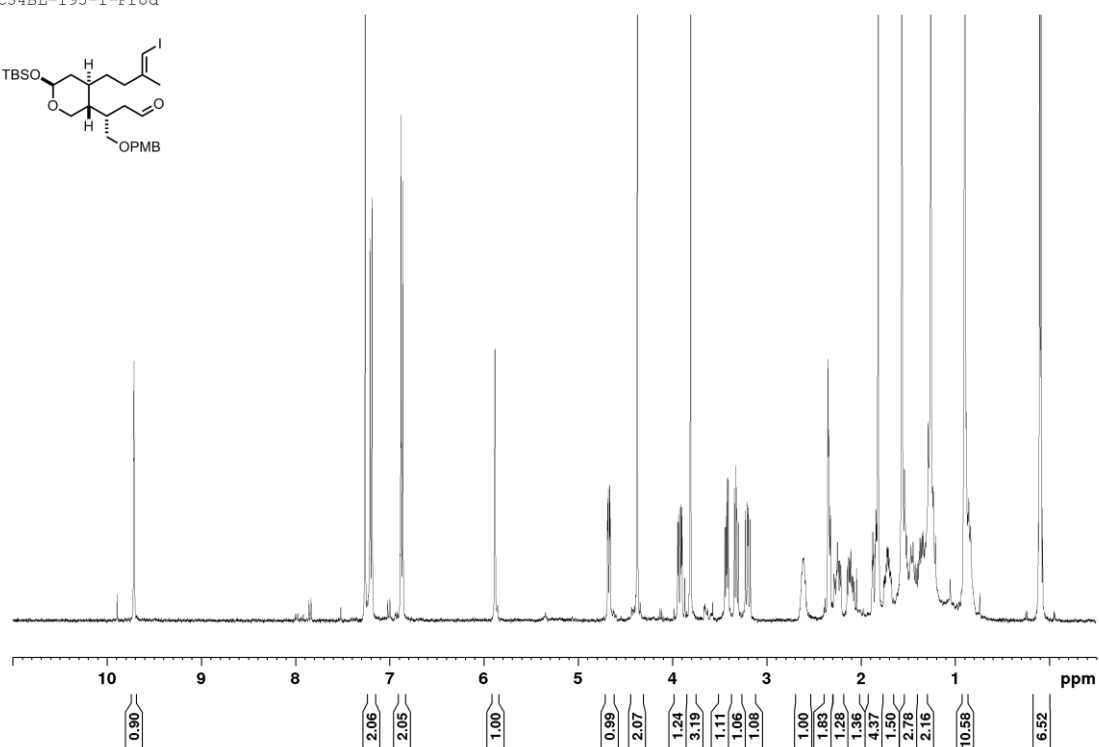
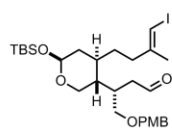
Exact Mass: 616.2081

Molecular Weight: 616.6439

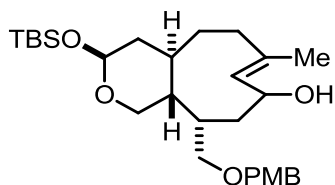
A batch of **316** (6.7 mg) was dissolved in CH_2Cl_2 (0.5 mL). Added was pyridine (0.009 mL, 10 eq.) and Dess-Martin periodinane (5 mg, 1 eq.). Over time more DMP (7.2 mg+5.2 mg+4.1 mg+11.5 mg+9.3 mg+20.5 mg) and more pyridine (0.01 mL+0.02 mL+0.02 mL) and CH_2Cl_2 (0.2 mL) was added in variable intervals of 30 min to 1 h 40 min. Total amount of Dess-Martin used: 62.5 mg and total reaction time: 5 h 45 min. Total amount of Dess-Martin used: 62.5 mg. Quenched by addition of $NaHCO_3$ (1 mL, sat., aq.) and Na_2SO_3 (1 mL, sat., aq.) and diluted with Et_2O (5 mL). Stirred vigorously for 40 minutes until both layers were clear, separated and extracted with Et_2O (2x5 mL). Washed with $NaHCO_3$ (1 mL, sat., aq.), NH_4Cl (1 mL, sat., aq.), brine (1 mL) and dried over $MgSO_4$. The solvent was removed to give the crude product. A second batch of f **316** (2 mg) was dissolved in CH_2Cl_2 (0.3 mL). Pyridine (0.02 mL, 80 eq.) was added, followed by Dess-Martin periodinane (26.3 mg, 20 eq.). After 3 h, more than 75 % conversion was judged by TLC and CH_2Cl_2 (0.5 mL) was added. After a total of 15 h, it was quenched by addition of $NaHCO_3$ (0.46 mL, sat., aq.) and Na_2SO_3 (0.46 mL, sat., aq.) and diluted with Et_2O (5 mL). Stirred vigorously for 45 minutes until both layers were clear, separated and extracted with Et_2O (2x5 mL). Washed with $NaHCO_3$ (0.46 mL, sat., aq.), NH_4Cl (0.46 mL, sat., aq.), brine (0.46 mL) and dried over $MgSO_4$. The solvent was removed, the crude product was combined with the crude from above and purified by FC (EtOAc:hexanes 1:4) to give the title compound (4.4 mg, 66% overall).

1H NMR: ($CDCl_3$, 400 MHz) δ = 9.71 (t, J = 1.8 Hz, 1H), 7.23-7.17 (m, 2H), 6.90-6.84 (m, 2H), 5.88 (s, 1H), 4.67 (dd, J = 7.9, 2.5 Hz, 1H), 4.37 (s, 2H), 3.92 (dd, J = 11.8, 3.9 Hz, 1H), 3.81 (s, 3H), 3.42 (dd, J = 9.3, 5.5 Hz, 1H), 3.32 (dd, J = 9.1, 7.1 Hz, 1H), 3.20 (dd, J = 11.8, 9.1 Hz, 1H), 2.66-2.56 (m, 1H), 2.39-2.30 (m, 2H), 2.30-2.20 (m, 1H), 2.18-2.03 (m, 1H), 1.88-1.80 (m, 1H), 1.81 (d, J = 0.7 Hz, 3H), 1.77-1.66 (m, 1H), 1.54-1.40 (m, 2H), 1.40-1.30 (m, 2H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **Rf-value:** 0.47 (EtOAc:hexanes 1:3), 0.37 (EtOAc:hexanes 1:4)

C34BL-195-1-Prod



321 (3S,4aR,11S,11aR,E)-3-((tert-butyldimethylsilyl)oxy)-11-(((4-methoxybenzyl)oxy)methyl)-7-methyl-1,3,4,4a,5,6,9,10,11,11a-decahydrocyclonona[c]pyran-9-ol



Chemical Formula: $C_{28}H_{46}O_5Si$

Exact Mass: 490.3115

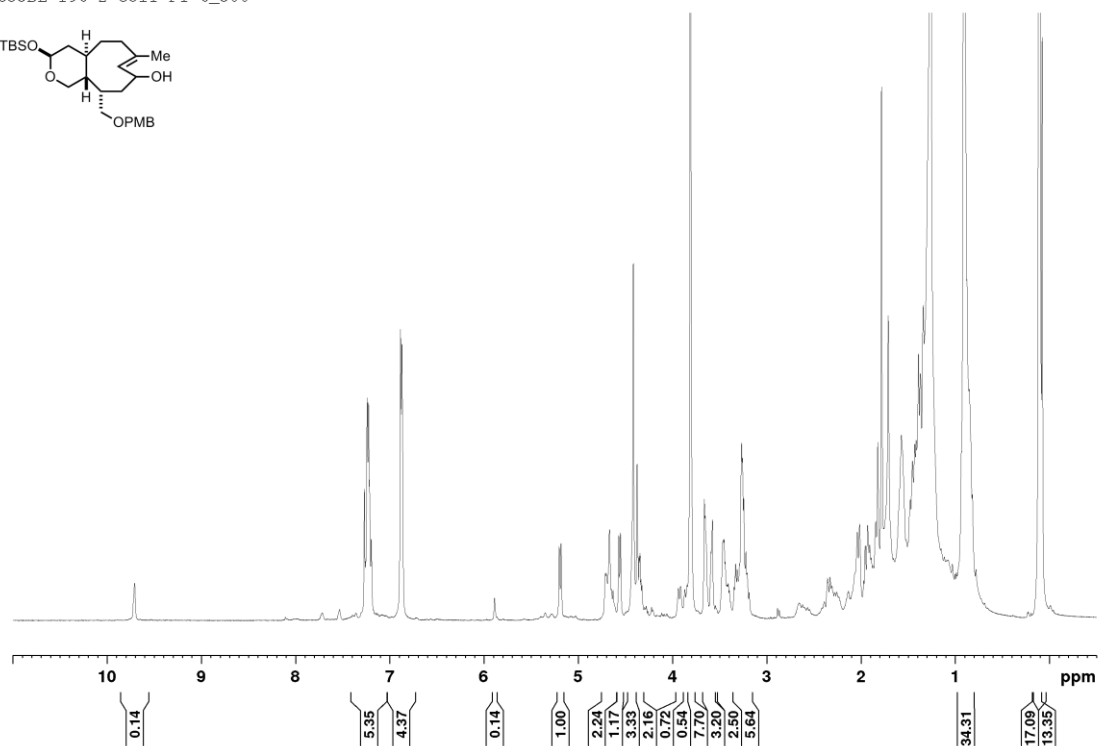
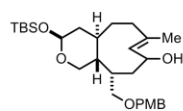
Molecular Weight: 490.7473

DMSO out of a fresh bottle was degassed by freeze and thaw (3 cycles). $NiCl_2$ (0.1 mg, 0.3 μ mol, 0.06 eq.) and $CrCl_2$ (20.0 mg, 165 μ mol, 36.2 eq.) were weighed in a glove box into a flame dried flask. **320** (2.8 mg, 4.5 μ mol, 1 eq.) was coevaporated with benzene and placed under an atmosphere of argon. It was transferred to the solid metal salts with DMSO (3.9 mL + 0.39 mL rinsing). The solution turned slight green, then turquoise and quickly black. It was stirring for 23 h at 50 °C. The reaction was diluted with saturated aqueous NH_4Cl (4.25 mL), and extracted with EtOAc (3x105 mL). The combined extracts were washed with H_2O (2x2.2 mL) and saturated brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purified by FC (1:1 EtOAc:hexanes) gave the title compound (1.4 mg, 64%, purity is low).

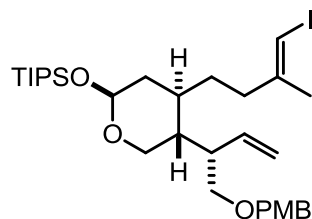
1H NMR: ($CDCl_3$, 400 MHz) δ = only some diagnostic signals could be identified by comparison with 323: vinyl proton 5.19 (d, J = 9.8 Hz, 1H, C7), anomeric proton 4.56 (d, J = 9.0 Hz, 1H, C17);

HRMS (ESI-TOF): calc. for $[M+Na]^+$: 513.3007, found 513.3013 (no signs of the dimer were found); **Rf-value:** 0.57 (EtOAc:hexanes 1:1)

C35BL-196-2-coll-F1-6_500



317 (((2S,4R,5R)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)-5-((S)-1-((4-methoxybenzyl)oxy)but-3-en-2-yl)tetrahydro-2H-pyran-2-yl)oxy)triisopropylsilane



Chemical Formula: C₃₁H₅₁IO₄Si

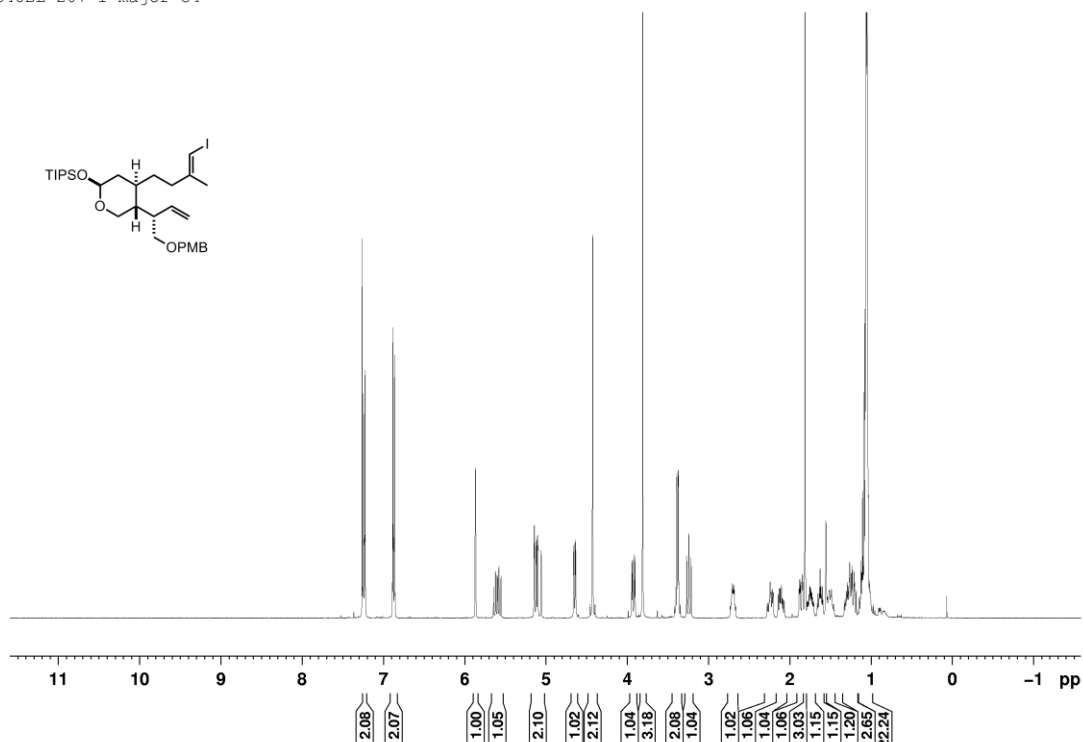
Exact Mass: 642.2601

Molecular Weight: 642.7242

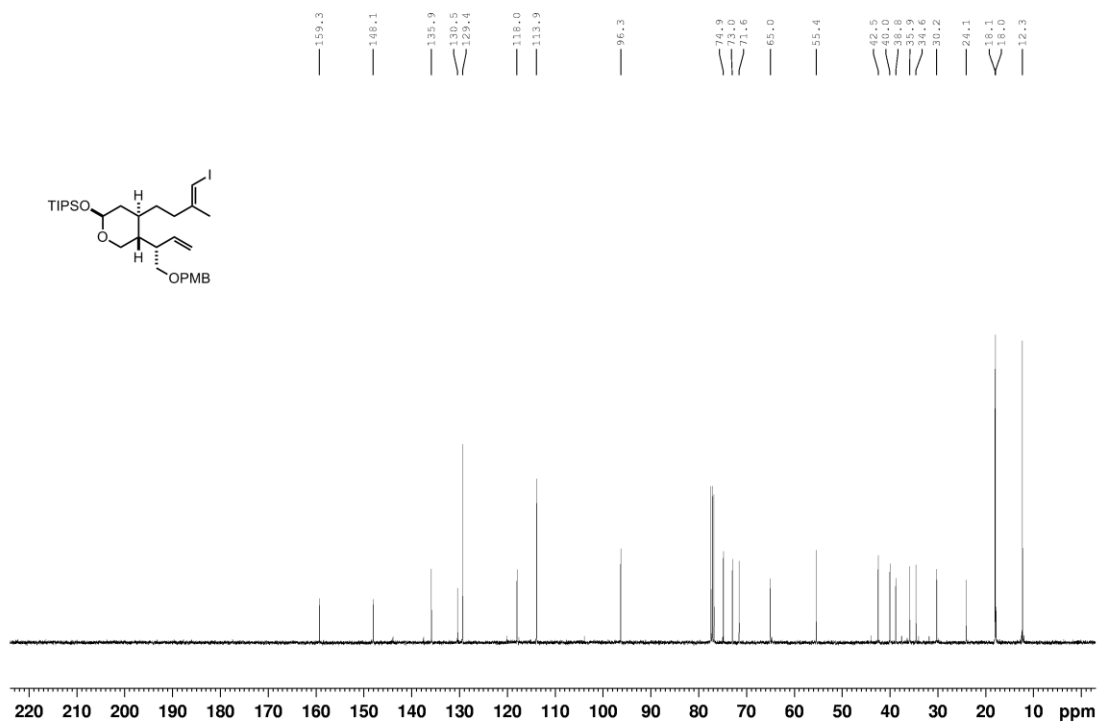
314 (151.1 mg, 0.311 mmol, 1 eq.) was dissolved in DMF (0.62 mL) and added was imidazole (28.8 mg, 0.404 mmol, 1.3 eq.) and DMAP (9.7 mg, 0.26 eq.) followed by TIPSCI (84 μ L, 0.373 mmol, 1.2 eq.). The solution was stirred for 4 h and additional imidazole (17.3 mg, 0.8 eq.) and TIPSCI (40 μ L, 0.6 eq.) were added. After a total of 22 h, the mixture was diluted with Et₂O (10 mL) and washed sequentially with 1 mL of each 10 % citric acid, water, sat. aq. NaHCO₃ and brine. Each of the aqueous phase was backextracted with one portion of Et₂O (10 mL). The two organic phases were combined, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by four rounds of FC (Et₂O:hexanes 1:15 to 1:10; again with Et₂O:hexanes 1:15 to neat Et₂O, a third time with Et₂O:hexanes 1:15 and finally Et₂O:hexanes 1:20) to give the title compound (130.9 mg, 66%). The other isomer was partly decomposed and discarded.

¹H NMR: (CDCl₃, 400 MHz) δ = 7.26-7.21 (m, 2H), 6.90-6.86 (m, 2H), 5.87 (d, J = 1.0 Hz, 1H), 5.60 (dt, J = 17.1, 9.8 Hz, 1H), 5.13 (dd, J = 10.4, 1.8 Hz, 1H), 5.08 (dd, J = 17.2, 1.6 Hz, 1H), 4.64 (dd, J = 8.6, 2.3 Hz, 1H), 4.42 (apparent t, higher order, apparent J = 12.1 Hz, 2H), 3.92 (dd, J = 11.5, 4.1 Hz, 1H), 3.81 (s, 3H), 3.38 (quartet like, higher order, 2H), 3.24 (dd, J = 10.7, 11.2 Hz, 1H), 2.75-2.65 (m, 1H), 2.29-2.19 (m, 1H), 2.16-2.06 (m, 1H), 1.86 (ddd, J = 12.9, 3.8, 2.4 Hz, 1H), 1.81 (d, J = 0.9 Hz, 3H), 1.80-1.69 (m, 1H), 1.67-1.58 (tt, J = 10.3, 3.9 Hz, 1H), 1.55-1.44 (m, 1H), 1.34-1.17 (m, 2H), 1.15-1.98 (m, 21H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 159.3, 148.1, 135.9, 130.5, 129.4, 118.0, 113.9, 96.3, 74.9, 73.0, 71.6, 65.0, 55.4, 42.5, 40.0, 38.8, 35.9, 34.6, 30.2, 24.1, 18.1, 18.0, 12.3; **HRMS (MALDI/ESI):** calc. for [M+Na]⁺: 665.2494, found 665.2494, calc. for [M+K]⁺: 681.2233, found 681.2234; **IR (neat):** 2941, 2893, 2864, 1613, 1513, 1462, 1390, 1361, 1301, 1247, 1169, 1126, 1065, 1037, 1012, 994, 919, 882, 819, 769, 681, 664; **[α]_D²⁰** = -35.94 \pm 0.16° (c = 0.92, CHCl₃); **Rf-value:** 0.41 (EtOAc:hexanes 1:10)

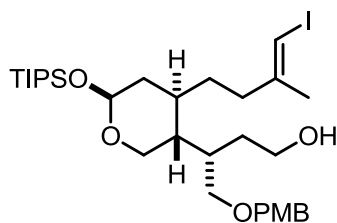
C48BL-207-1-major-C4



C48BL-207-1-major-C4



318 (S)-3-((3R,4R,6S)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)-6-((triisopropylsilyl)oxy)tetrahydro-2H-pyran-3-yl)-4-((4-methoxybenzyl)oxy)butan-1-ol



Chemical Formula: C₃₁H₅₃IO₅Si

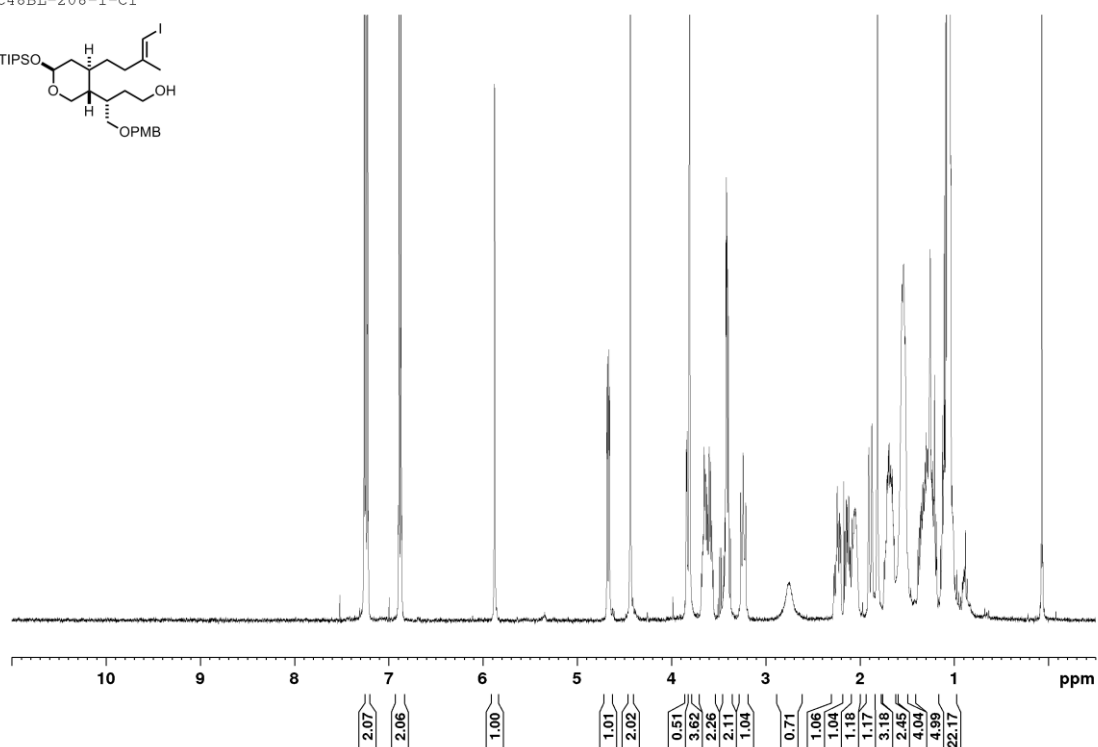
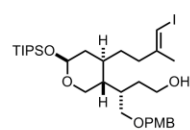
Exact Mass: 660.2707

Molecular Weight: 660.7395

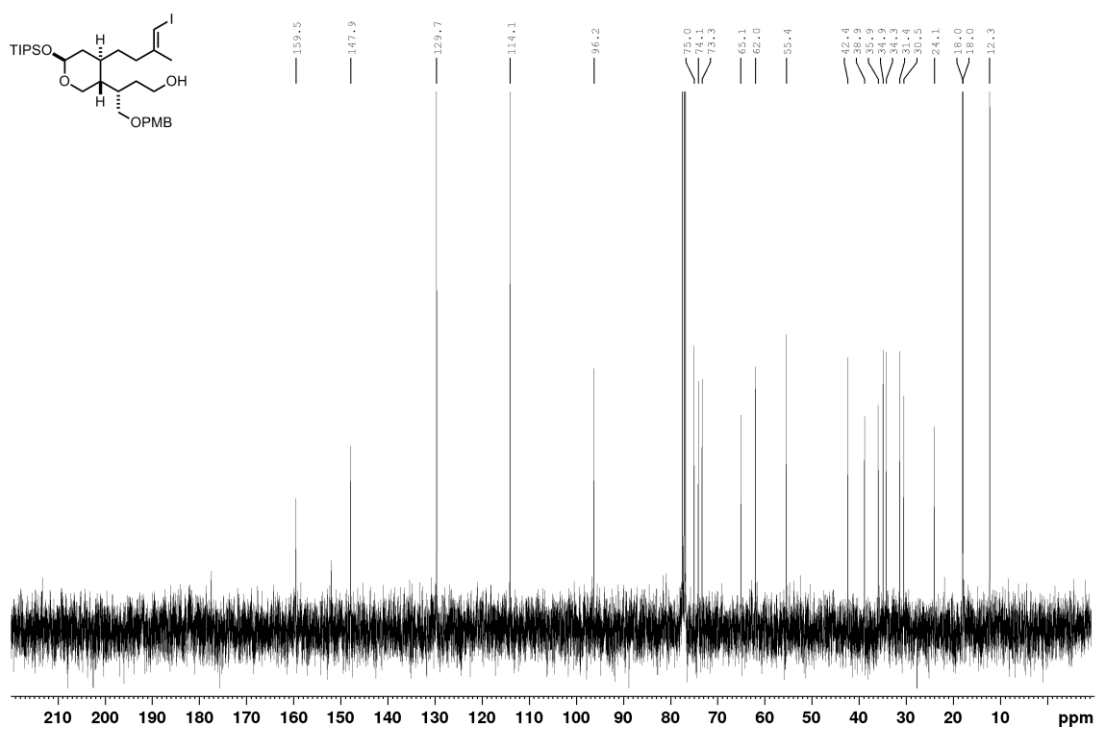
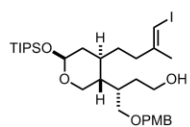
317 (64.7 mg, 10.1 μ mol, 1 eq., twice coevaporated with benzene) was weighed in a microwave vial equipped with a stir bar, put under an atmosphere of Argon and closed. It was cooled to 0 °C. A solution of 9-BBN in THF (35.5 mg, 98 %, 1 mL, 0.285 M) was prepared in a dry volumetric flask. An aliquot of this solution (0.71 mL, 2 eq.) was added to the SM and immediately after the addition, the cooling was removed and the cloudy solution was let to warm to ambient temperature. After 3 h 15 min, the mixture was quenched with NaOH (3 M, 68 μ L, 2 eq.) and MeOH (0.33 mL, 80 eq.) in a water bath at ambient temperature. After 30 min, added was dropwise and carefully H₂O₂ (30 %, 62 μ L, 6 eq.). The mixture was stirred at ambient temperature for 25 min and afterwards was left to stand at 45 °C for 30 min. It was then evaporated to dryness, diluted with H₂O (1 mL) and extracted with Et₂O (4x5 mL) and washed with brine (1 mL). Dried over MgSO₄ and evaporated to dryness. Purified by flash chromatography (EtOAc:hexanes 1:5 to 1:4) to give the title compound as a clear, colorless oil (49.1 mg, 74%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.26-7.21 (m, 2H), 6.91-6.85 (m, 2H), 5.88 (d, J = 0.9 Hz, 1H), 4.67 (dd, J = 2.3, 8.5 Hz, 1H), 4.44 (s, 2H), 3.86-3.78 (m, 1H), 3.81 (m, 3H), 2.75 (s, br, 1H, OH), 2.29-2.19 (m, 1H), 2.18-2.09 (m, 1H), 2.09-2.00 (m, 1H), 1.89 (d, J = 13.1 Hz, 1H), 1.82 (d, J = 0.9 Hz, 3H), 1.76-1.62 (m, 2H), 1.60-1.49 (m, 2H), 1.40-1.16 (m, 2H), 1.16-1.00 (m, 21H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 159.5, 147.9, 129.7, 114.1, 96.2, 75.0, 74.1, 73.3, 65.1, 62.0, 55.4, 42.4, 38.9, 35.9, 34.9, 34.3, 31.4, 30.5, 24.1, 18.0, 18.0, 12.3; **HRMS (ESI-TOF):** calc. for [M+Na]⁺: 683.2599, found 683.2600; **IR (neat):** 3421, 2940, 2864, 1612, 1513, 1462, 1390, 1362, 1301, 1248, 1202, 1169, 1134, 1059, 1038, 1013, 997, 921, 882, 817, 757, 682, 662, 580; **[α]_D²⁰** = -20.4 ° (c = 0.365, CH₂Cl₂); **Rf-value:** 0.56 (EtOAc:hexanes 1:1)

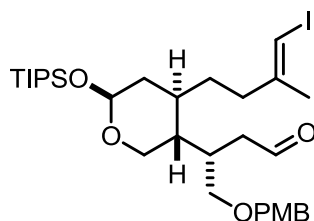
C48BL-208-1-C1



C49BL-208-1-old



322 (S)-3-((3R,4R,6S)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)-6-((triisopropylsilyl)oxy)tetrahydro-2H-pyran-3-yl)-4-((4-methoxybenzyl)oxy)butanal



Chemical Formula: $C_{31}H_{51}IO_5Si$

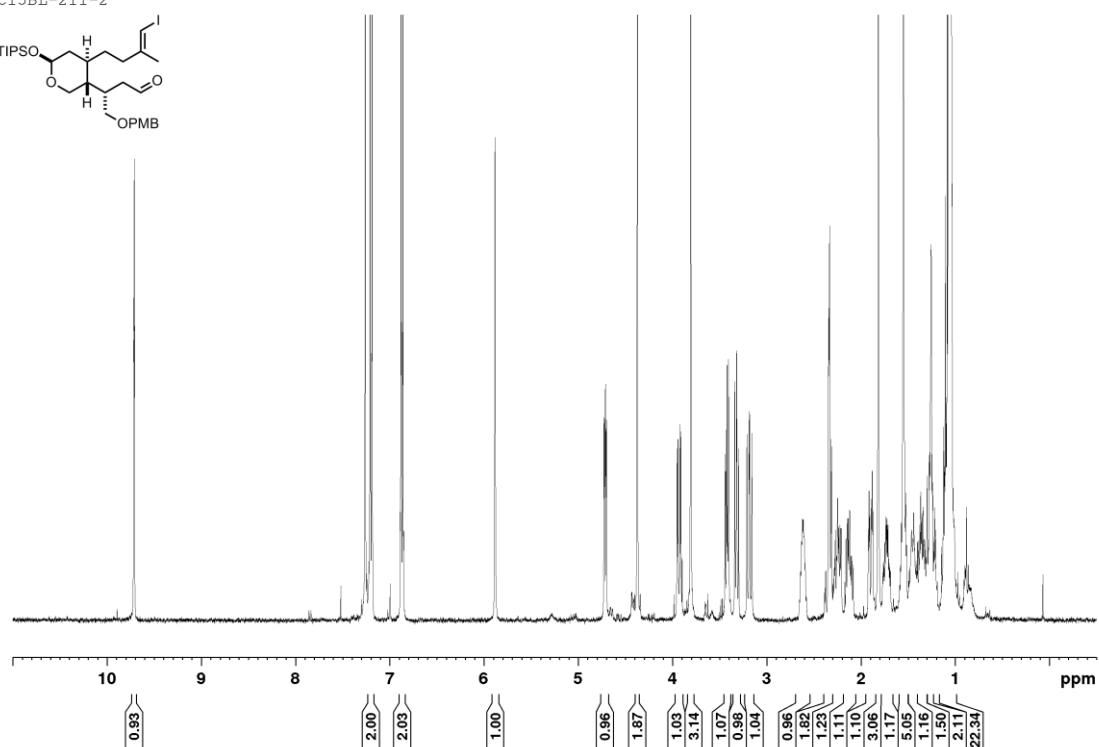
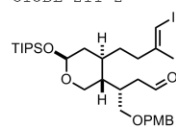
Exact Mass: 658.2550

Molecular Weight: 658.7236

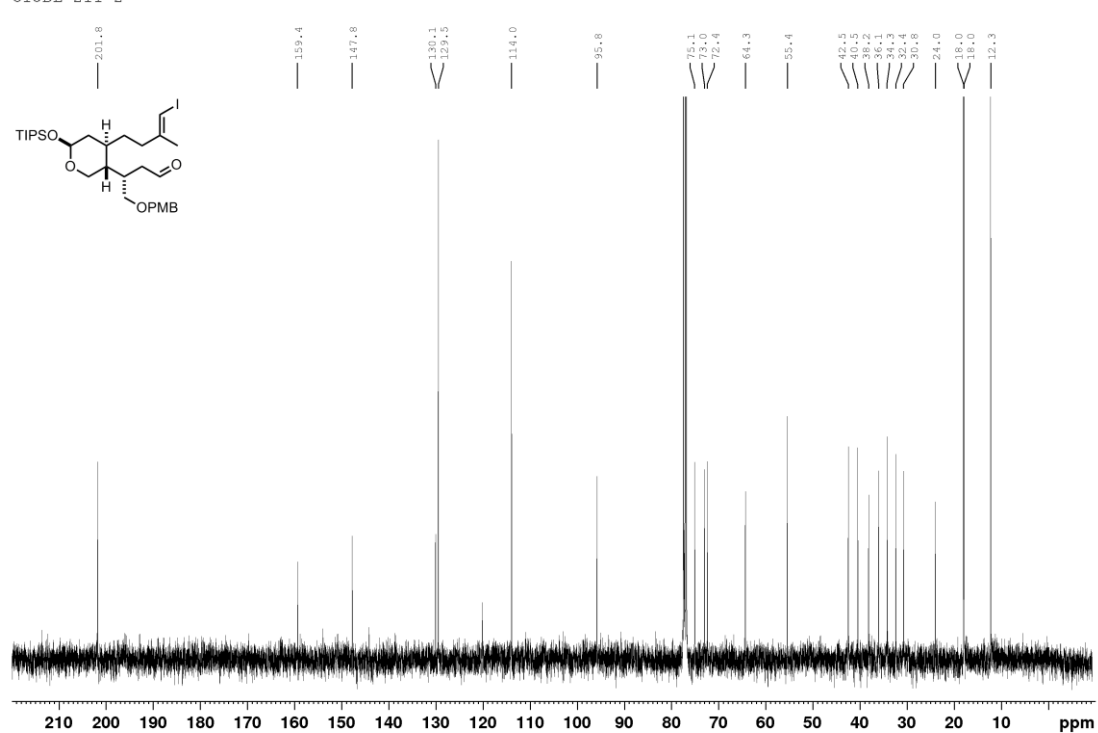
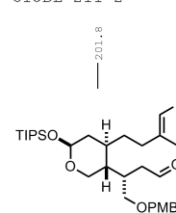
318 (49.1 mg) was dissolved in CH_2Cl_2 (3 mL). Pyridine (0.06 mL) and *t*-BuOH (21 μ L, 0.223 mmol, 3 eq.) was added, followed by Dess-Martin periodinane (95.1 mg). After 70 min, reaction was complete to more than 95 % as judged by TLC and it was quenched by addition of $NaHCO_3$ (1.5 mL, aq., sat) and Na_2SO_3 (1.5 mL, aq., sat) and stirred for 2 h. Extracted with Et_2O (2x10 mL and 1x5 mL), combined and washed subsequently with $NaHCO_3$ (1.5 mL, aq., sat), brine (1.5 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product was purified by FC ($EtOAc$:hexanes 1:15 to 1:10) to give the title compound as a clear, colorless oil (38.2 mg, 78%).

1H NMR: ($CDCl_3$, 400 MHz) δ = 9.71 (dd, J = 2.5, 1.5 Hz, 1H), 7.24-7.17 (m, 2H), 6.90-6.84 (m, 2H), 5.88 (d, J = 1.1 Hz, 1H), 4.71 (dd, J = 2.5, 8.0 Hz, 1H), 4.37 (s, 2H), 3.93 (dd, J = 11.8, 4.0 Hz, 1H), 3.81 (m, 3H), 3.42 (dd, J = 9.1, 5.4 Hz, 1H), 3.32 (dd, J = 9.1, 7.2 Hz, 1H), 3.18 (dd, J = 11.7, 9.4 Hz, 1H), 2.66-2.57 (m, 1H), 2.40-2.30 (m, 2H), 2.30-2.19 (m, 1H), 2.19-2.05 (m, 1H), 1.90 (ddd, J = 13.0, 3.6, 2.8 Hz, 1H), 1.82 (d, J = 0.9 Hz, 3H), 1.78-1.67 (m, 1H), 1.60-1.50 (m, 1H), 1.50-1.40 (m, 1H), 1.40-1.30 (m, 1H), 1.30-1.23 (m, 1H), 1.17-0.97 (m, 21H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 201.8, 159.4, 147.8, 130.1, 129.5, 114.0, 95.8, 75.1, 73.0, 72.4, 64.3, 55.4, 42.5, 40.5, 38.2, 36.1, 34.3, 32.4, 30.8, 24.0, 18.0, 18.0, 12.3; **HRMS (ESI-TOF):** calc. for $[M+Na]^+$: 681.2443, found 681.2444; **IR (neat):** 2941, 2892, 2863, 2724, 2361, 2337, 1724, 1613, 1586, 1512, 1462, 1391, 1364, 1301, 1246, 1203, 1170, 1134, 1104, 1063, 1035, 1013, 994, 943, 919, 883, 820, 772, 760, 731, 681, 667, 605, 574, 542, 516, 509; **$[\alpha]^{20}_D$** = -19.5 $^\circ$ (c = 0.764, CH_2Cl_2); **Rf-value:** 0. ($EtOAc$:hexanes 1:1)

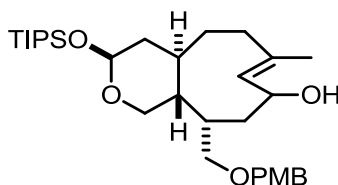
C15BL-211-2



C15BL-211-2



323 (3S,4aR,11S,11aR,E)-11-(((4-methoxybenzyl)oxy)methyl)-7-methyl-3-((triisopropylsilyl)oxy)-1,3,4,4a,5,6,9,10,11,11a-decahydrocyclonona[c]pyran-9-ol



Chemical Formula: $C_{31}H_{52}O_5Si$

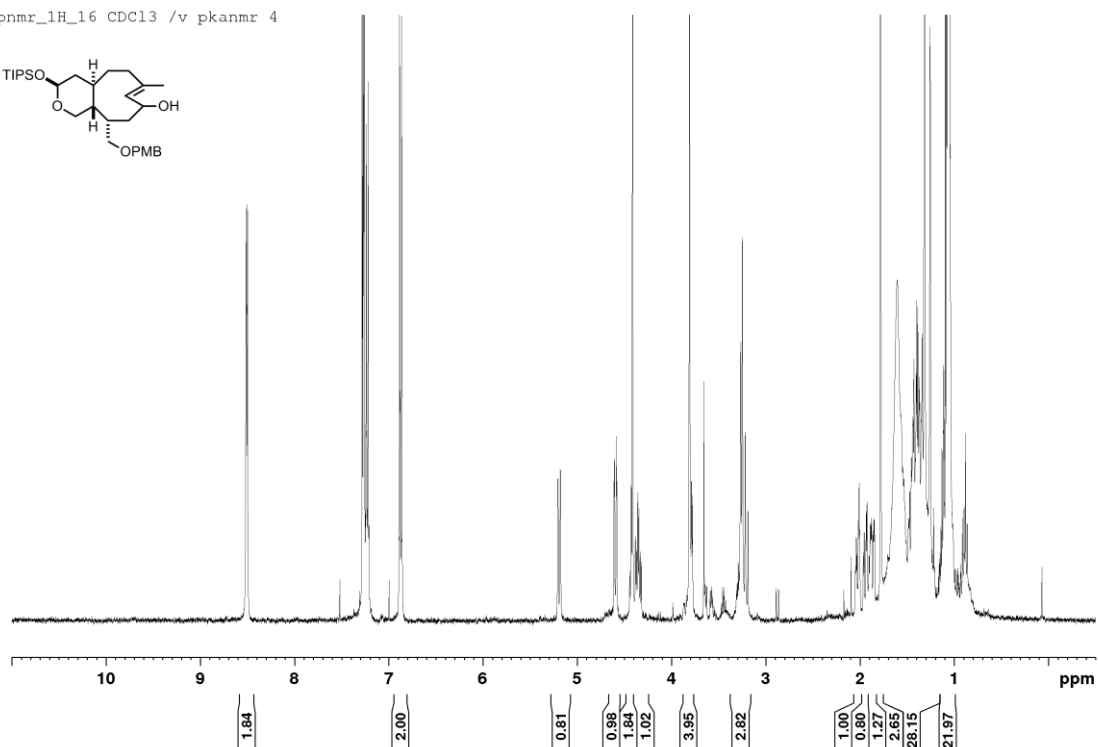
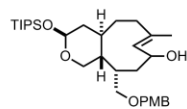
Exact Mass: 532.3584

Molecular Weight: 532.8271

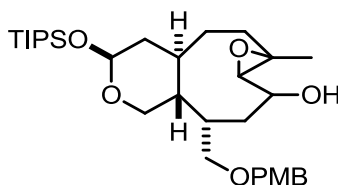
DMSO out of a fresh bottle was degassed by freeze and thaw in a flame-dried Schlenk tube. $NiCl_2$ (0.5 mg) and $CrCl_2$ (127.9 mg) were weighed in a glove box into a flame dried flask and afterwards suspended in DMSO (4 mL). The recovered material **323** (38 mg before first round) was coevaporated with benzene and put under an atmosphere of argon. It was transferred to the solid metal salts with DMSO (2 mL and rinsed with 2x2 mL). The solution turned strong green, and was stirred for 5 d at 50 °C, upon which the color did not change. The reaction was quenched with a solution of Na_2EDTA (40 mL, 0.1 M, Titriplex III), the black solution was diluted with Et_2O (25 mL) and stirred for 2 h until upon which it turned a purple black color. Brine (40 mL) was added, phases were separated and the aqueous phase was extracted with Et_2O (4x25 mL). The combined extracts were washed first with Na_2EDTA (20 mL, 0.1 M, Titriplex III) and then with brine (20 mL). Dried over $MgSO_4$ and concentrated *in vacuo*. Purified by FC (1:10 EtOAc:hexanes to 1:3) gave the title compound as a slightly yellow, viscous oil contaminated with residual 4-*t*-Bu-py (17.8 mg, effective content 14.4 mg, 47%).

1H NMR: ($CDCl_3$, 400 MHz) δ = 7.26-7.20 (m, 2H), 6.90-6.85 (m, 2H), 5.19 (d, J = 10.0 Hz, 1H), 4.59 (dd, J = 9.1, 1.9 Hz, 1H), 4.45-4.40 (m, 2H), 4.35 (td, J = 10.3, 4.4 Hz, 1H), 3.88-3.77 (m, 1H), 3.81 (s, 3H), 3.32-3.16 (m, 3H), 2.02 (ddd, J = 11.8, 3.7, 2.7 Hz, 1H), 1.94 (dd, J = 11.9, 3.6 Hz, 1H), 1.87 (dd, J = 12.8, 1.9 Hz, 1H), 1.78 (s, 3H), 1.76-1.15 (m, 12H) 1.15-0.99 (m, 21H); **Rf-value:** 0.59 (EtOAc:hexanes 1:1)

pnmr_1H_16 CDCl3 /v pkanmr 4



324 (3aR,5S,7aR,8S)-8-(((4-methoxybenzyl)oxy)methyl)-1a-methyl-5-(((triisopropylsilyl)oxy)dodecahydrooxireno[2',3':5,6]cyclonona[1,2-c]pyran-10-ol



Chemical Formula: $C_{31}H_{52}O_6Si$

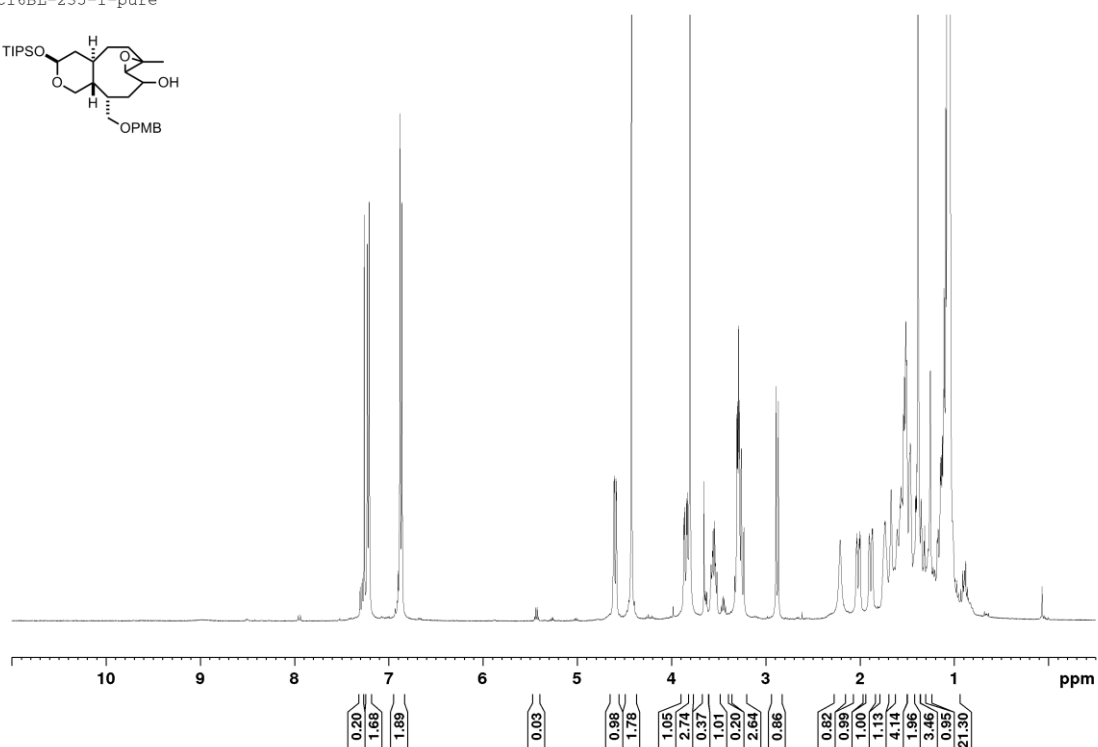
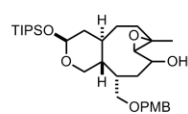
Exact Mass: 548.3533

Molecular Weight: 548.8265

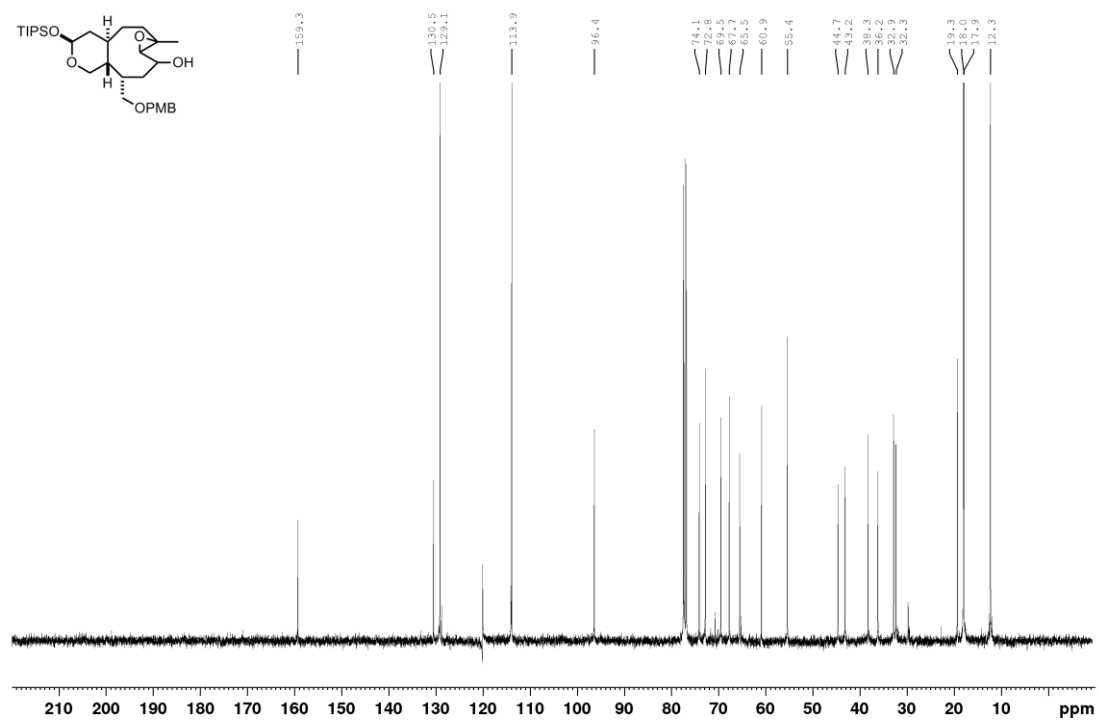
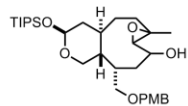
m-CPBA used for this reaction had been purified^[356] 2 month prior and was stored in a plastic centrifuge vial in the freezer. To a solution of **323** (14.4 mg, 27.0 μ mol, 1 eq.) and anhydrous Na_2HPO_4 (15.3 mg, 0.108 mmol, 3.6 eq.) in CH_2Cl_2 (0.9 mL) at 0 °C was added *m*-CPBA (13.8 mg, 0.014 mmol, 3 eq.) in one portion. The mixture was stirred at this temperature for 70 min, diluted with CH_2Cl_2 (10 mL) and quenched with $Na_2S_2O_3$ (3.5 mL, aq., sat.) and $NaHCO_3$ (3.5 mL, aq., sat.). It was stirred for 30 min and after separation of the phases, it was extracted with CH_2Cl_2 (2x5 mL). It was washed with $NaHCO_3$ (3.5 mL, aq., sat.), dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. Purified by FC (Et_2O /hexanes 7:3) gave the title compound as a clear, colorless oil (12.3 mg, 83% by mass, contains some impurity, corrected yield around 65%).

1H NMR: ($CDCl_3$, 400 MHz) δ = 7.25-7.18 (m, 2H), 6.94-6.84 (m, 2H), 4.60 (dd, J = 9.2, 1.9 Hz, 1H), 4.42 (s, 2H), 3.90-3.82 (m, 1H), 3.80 (s, 3H), 3.60-3.50 (m, 1H), 3.36-3.20 (m, 3H), 2.88 (d, J = 9.5 Hz, 1H), 2.21 (s, br, 1H, OH), 2.02 (ddd, J = 12.7, 4.2, 2.0 Hz, 1H), 1.88 (ddd, J = 12.7, 3.5, 1.8 Hz, 1H), 1.79-1.70 (m, 1H), 1.63-1.50 (m, 4H), 1.50-1.42 (m, 2H), 1.42-1.36 (m, 3H), 1.36-1.31 (m, 1H), 1.24-0.94 (m, 22H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 159.3, 130.5, 129.1, 128.8, 120.1, 114.1, 113.9, 96.4, 74.1, 72.8, 70.7, 69.5, 67.7, 65.5, 60.9, 55.4, 44.7, 43.2, 38.3, 36.2, 32.9 (2 signals), 32.3, 19.3, 18.0, 17.9, 12.3; **Rf-value:** 0.10 (Et_2O :hexanes 1:1), 0.53 (Et_2O), 0.41 ($EtOAc$:hexanes 1:1)

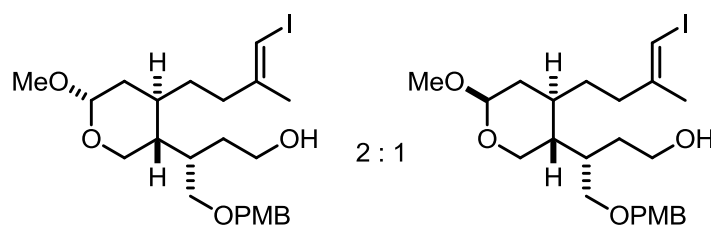
C16BL-235-1-pure



C16BL-235-1-pure



326 (S)-3-((3R,4R,6S)- and (S)-3-((3R,4R,6R)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)-6-methoxytetrahydro-2H-pyran-3-yl)-4-((4-methoxybenzyl)oxy)butan-1-ol



Chemical Formula: $C_{23}H_{35}IO_5$

Exact Mass: 518.1529

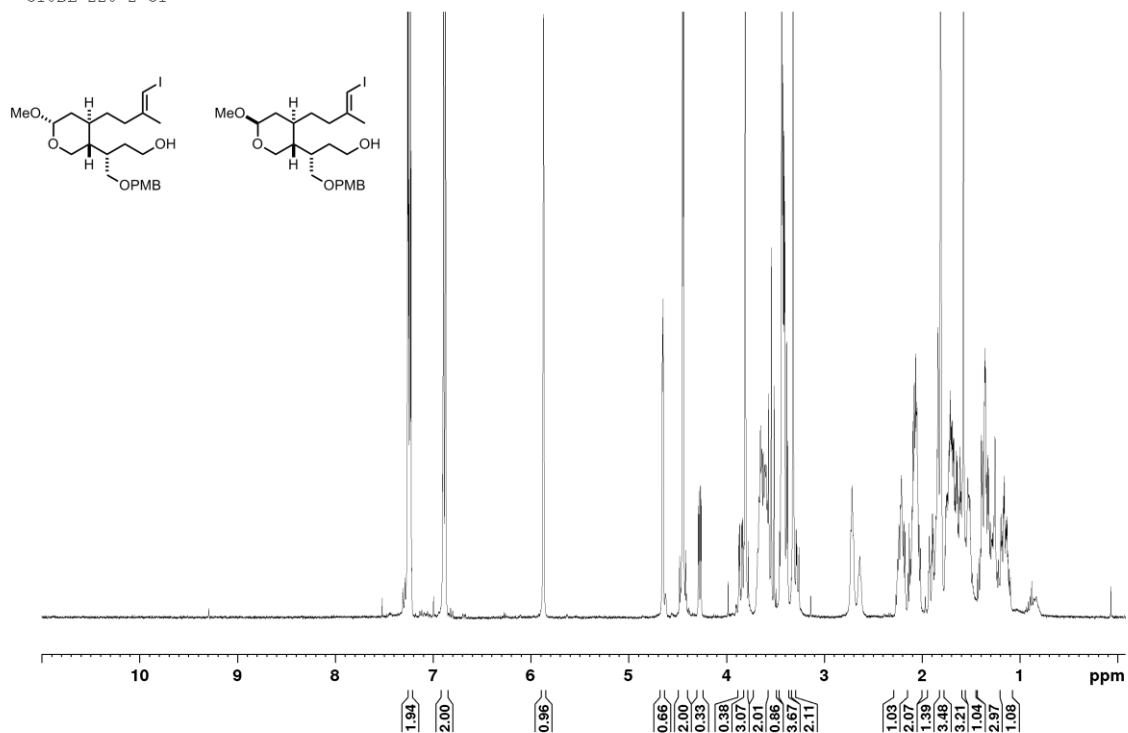
Molecular Weight: 518.4255

313 (20.6 mg, 42.5 μ mol, 1 eq., not dried prior to reactio) was weighed in a microwave vial equipped with a stir bar, put under an atmosphere of argon and closed. It was cooled to -78 °C. A solution of 9-BBN in THF (32.8 mg, 98 %, 1 mL, 0.243 M) was prepared in a volumetric flask. An aliquot of this solution (0.47 mL, 3 eq.) was added to **313**. Immediately after the addition, the cooling was removed and the cloudy solution was let to warm to ambient temperature upon which it turned clear. After 4 h, the mixture was quenched with MeOH (0.13 mL, 80 eq.) in a water bath at ambient temperature. After 35 min, added was dropwise, NaOH (3 M, 41 μ L, 3 eq.) and H₂O₂ (30 %, 35 μ L, 8.4 eq.) which led to vigorous bubbling. After the quench, neither **313**, **314** nor the desired **327** were observed in the mixture. The mixture was stirred for 30 min, transferred into a pear shaped flask using Et₂O and 1 mL water. It was stirred at 45 °C at the rotary evaporator (no vacuum) for 30 min and then evaporated to dryness. Diluted with 30 mL EtOAc and washed with brine (2x5 mL), dried over MgSO₄ and evaporated to dryness. Purified by flash chromatography (EtOAc:hexanes 1:1 to 3:1) to give the title compound as clear colorless oil (17.3 mg, 79%)

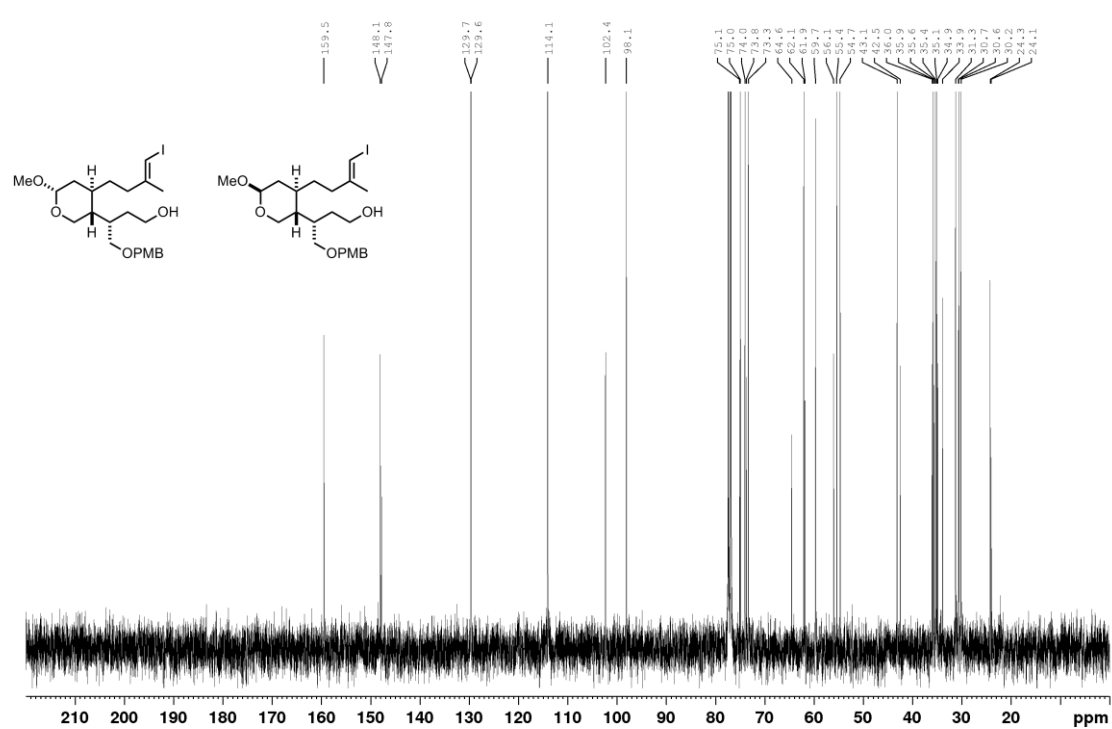
¹H NMR: (CDCl₃, 400 MHz) δ = 7.26-7.22 (m, 2H), 6.91-6.86 (m, 2H), 5.87 (m, s-like, 1H), 4.65 (dd, J = 2.2, 1.1 Hz, 0.65H), 4.48-4.41 (m, 2H), 4.27 (dd, J = 8.6, 2.6 Hz, 0.35H), 4.85 (dd, J = 11.8, 3.5 Hz, 0.35H), 3.81 (s, 3H), 3.71-3.55 (m, 2H), 3.54 (t, J = 11.2 Hz, 0.86H), 3.46-3.36 (m, 2.77H), 3.44 (s, 0.9 H), 3.32 (s, 2H), 2.28-2.16 (m, 1H), 2.15-2.00 (m, 2H), 1.95-1.78 (m, 1.87H), 1.81 (d, J = 0.9 Hz, 3H), 1.78-1.59 (m, 3.2H), 1.56-1.45 (m, 1H), 1.44-1.20 (m, 3H), 1.20-1.08 (m, 1H); ¹³C NMR: (CDCl₃, 100 MHz) δ = 159.5, 148.1, 147.8, 129.7, 129.6, 114.1, 102.4, 98.1, 75.1, 75.0, 74.0, 73.8, 73.3, 64.6, 62.1, 61.9, 59.7, 56.1, 55.4, 54.7, 43.1, 42.5, 36.0, 35.9, 35.6, 35.4, 35.1, 34.9, 33.9, 31.3, 30.7, 30.6, 30.2, 24.3, 24.1; HRMS (ESI-TOF): calc. for [M+NH₄]⁺: 536.1867, found 536.1869; IR (neat): 3438, 3363, 2924, 2858, 1612, 1585, 1513, 1459, 1442, 1390, 1375, 1360, 1301, 1246, 1210, 1173, 1127, 1081, 1047, 955, 928, 894, 820, 773, 758,

734, 723, 666, 647, 636, 624, 598, 577; $[\alpha]^{20}_{\text{D}} = +10.06^{\circ}$ (c = 0.885, CHCl_3); **Rf-value:** 0.51 and 0.45 (EtOAc:hexanes 3:1), anomers were not separated

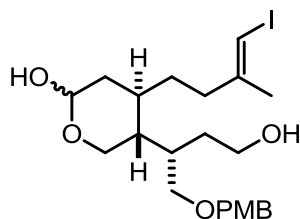
C10BL-220-2-C1



C10BL-220-2-C1



327 (4R,5R)-5-((S)-4-hydroxy-1-((4-methoxybenzyl)oxy)butan-2-yl)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)tetrahydro-2H-pyran-2-ol



Chemical Formula: C₂₂H₃₃IO₅

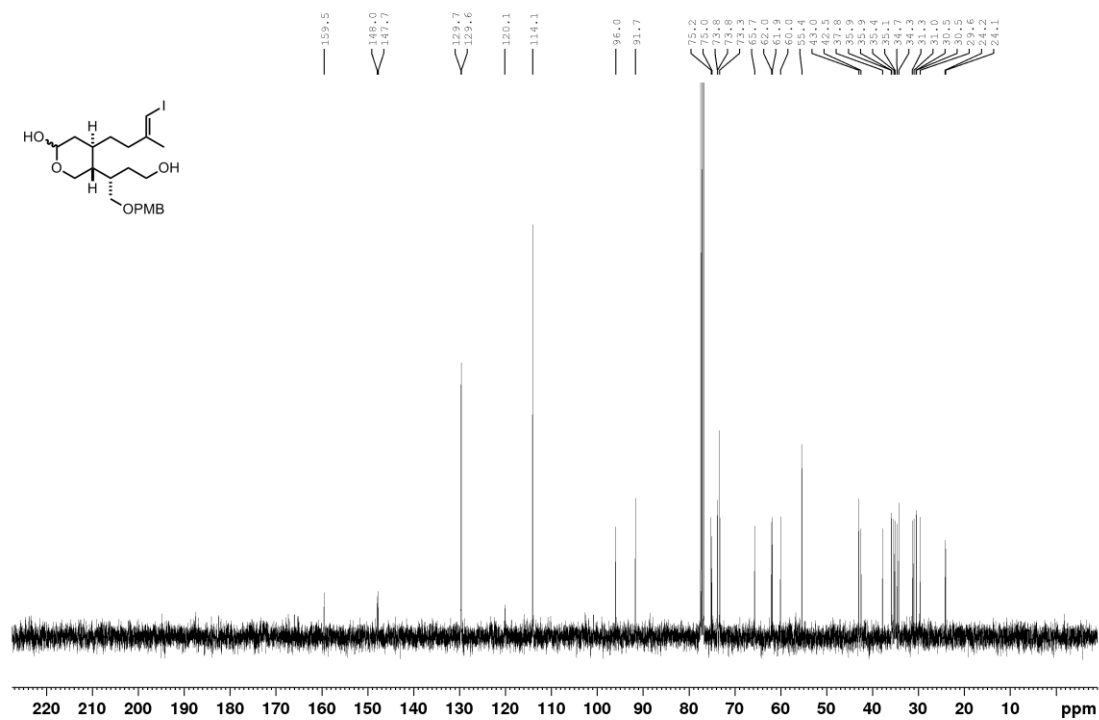
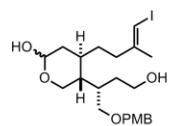
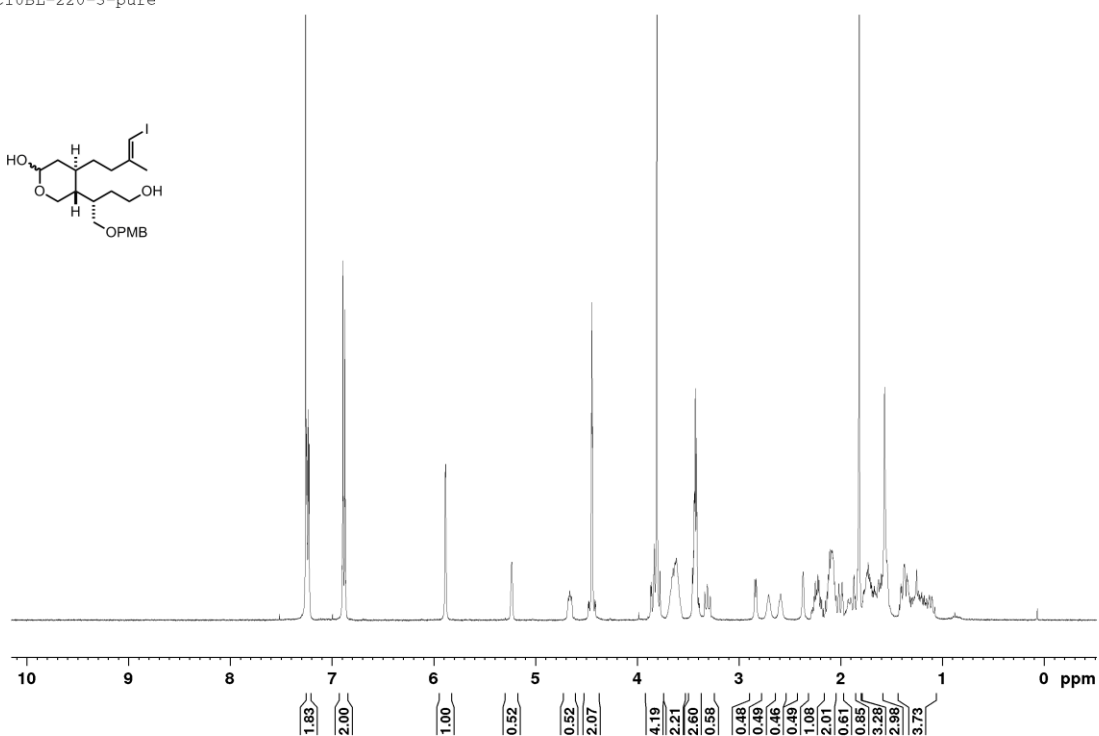
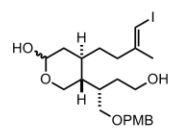
Exact Mass: 504.1373

Molecular Weight: 504.3989

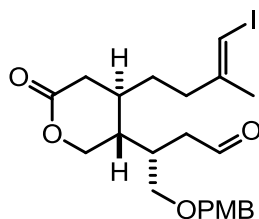
313 (4.87 g, 10.04 mmol, coevaporated with benzene twice) was dissolved in THF (60 mL) and cooled to -78 °C. 9-BBN (2.82 g, 2.25 eq.) was weighed in a glove box and dissolved in THF (20 mL). It was added to the SM and rinsed with THF (2x10 mL). After 2 h 30 min, the SM was gone, after further 20 min, the mixture was warmed to 0 °C. NaOH (7.5 mL, aq., 3 M, 2.25 eq.) was added quickly, which caused some foaming, followed by addition of MeOH (23 mL, technical grade). The cooling bath was removed and the mixture was stirred for 30 min, then cooled again to 0 °C and added was dropwise and slowly H₂O₂ (30 %, 6.8 mL, 6.6 eq.) which led to vigorous bubbling. After the quench, mainly the desired product and cyclooctanediol were observed by TLC. The mixture was stirred at ambient temperature for 30 min, then rotated in the rotary evaporator bath at 45 °C for 30 min without vacuum. It was evaporated to dryness, giving a white foam, dissolved in 35 mL water and extracted with Et₂O (2x140 mL). The combine organic phases were washed with water (21 mL), then brine (21 mL), dried over MgSO₄ and evaporated to dryness. The crude material was purified by two rounds of flash chromatography (15:85 Et₂O/EtOAc) to give the title compound as a clear slightly yellow oil (4.122 g, 81%)

¹H NMR: (CDCl₃, 400 MHz) δ = 7.27-7.22 (m, 2 H), 6.92-6.85 (m, 2H), 5.89 (dd, *J* = 2.1, 1.0 Hz, 1H), 5.23 (s, br, 0.5 H), 4.70-4.63 (m, 0.5 H), 4.49-4.42 (m, higher order spin system, 2H), 3.98-3.74 (m, 2x0.5H), 3.81 (s, 3H), 3.72-3.55 (m, br, 2H), 3.48-3.38 (m, 2.5H), 3.35-3.27 (m, 0.5H), 2.84 (d, *J* = 5.8 Hz, 0.5H, OH), 2.71 (s, br, 0.5H, OH), 2.59 (s, br, 0.5H, OH), 2.37 (s, br, 0.5H, OH), 2.30-2.16 (m, 1H), 2.17-2.03 (m, 2H), 2.02 (t, *J* = 2.4 Hz, 0.25H), 1.99 (t, *J* = 2.8 Hz, 0.25H), 1.97-1.80 (m, 1H), 1.92 (s, 3H), 1.79-1.50 (m, 3.25H), 1.44-1.06 (m, 3.75H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 159.5, 148.0, 147.7, 129.7, 129.6, 120.1, 114.1, 96.0, 91.7, 75.2, 75.0, 73.8, 73.8, 73.3, 65.7, 62.0, 61.9, 60.0, 55.4, 43.0, 42.5, 37.8, 35.9, 35.9, 35.4, 35.1, 34.7, 34.3, 31.3, 31.0, 30.5, 30.5, 29.6, 24.2, 24.1; **HRMS (ESI-TOF):** calc. for [M+Na]⁺: 527.1265, found 527.1266

IR (neat): 3436, 3374, 2923, 2855, 2036, 1612, 1586, 1513, 1457, 1442, 1361, 1302, 1247, 1209, 1173, 1115, 1083, 1052, 1034, 1018, 895, 818, 776, 757, 730, 705, 664, 630, 624, 583, 570; $[\alpha]_D^{20} = -2.72 \pm 0.38^\circ$ (c = 0.715, CHCl₃); **Rf-value:** 0.31. (EtOAc neat)



9 (S)-3-((3R,4R)-4-((E)-4-iodo-3-methylbut-3-en-1-yl)-6-oxotetrahydro-2H-pyran-3-yl)-4-((4-methoxybenzyl)oxy)butanal



Chemical Formula: C₂₂H₂₉IO₅

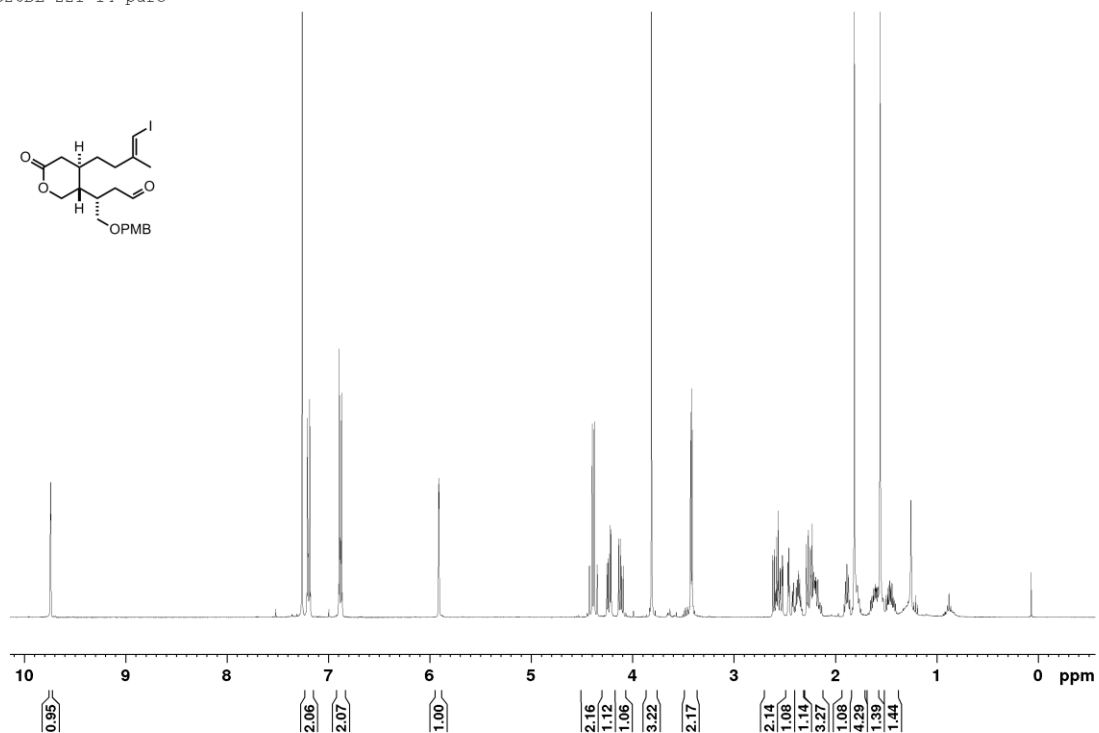
Exact Mass: 500.1060

Molecular Weight: 500.3671

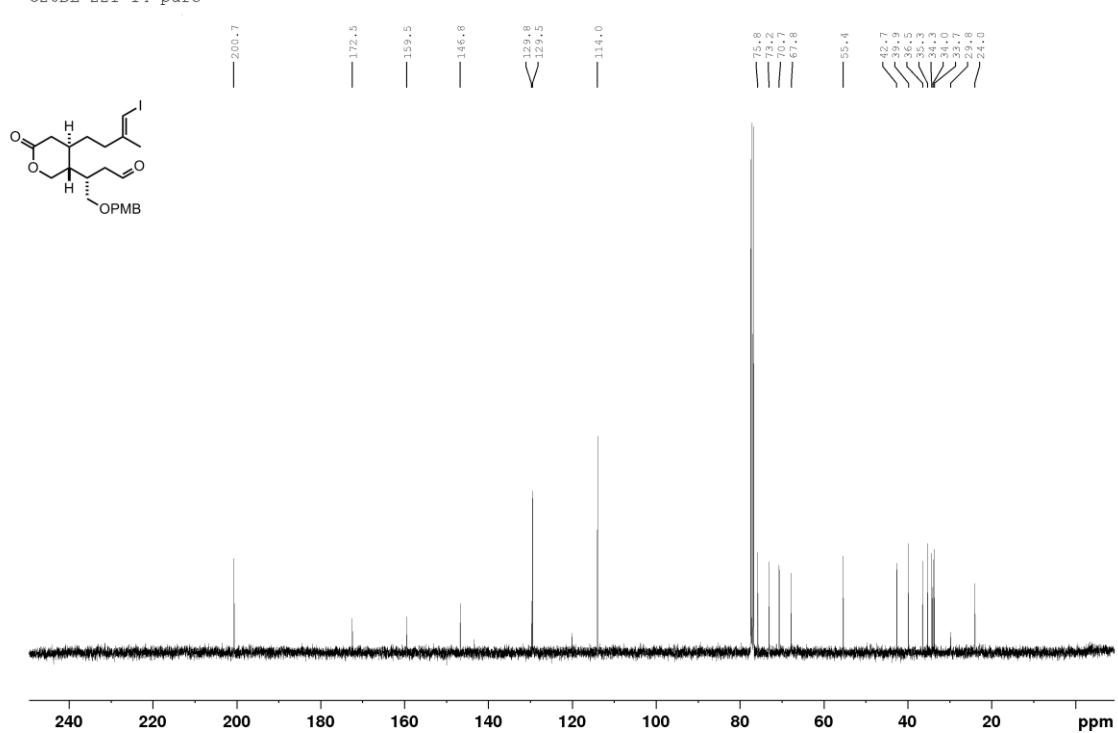
327 (703 mg, 1.38 mmol, 1 eq.) was dissolved in CH₂Cl₂ (15 mL). To this solution was added NMO (821 mg, 6.94 mmol, 5 eq.), followed by powdered 4 Å molecular sieves (965 mg). The wall of the flask were rinsed down with CH₂Cl₂ (2 mL) and the mixture was stirred for 10 min, then TPAP (49 mg) was added in one portion. The solution turned yellow immediately and yellow-black within 5 min. The outside of the flask warmed to around 30 °C. After 15 min, the solution was diluted with hexanes (5 mL) and directly transferred onto the column. FC (only 2 cm height x 5 cm Ø silica gel, 30 mL fractions; EtOAc:hexanes 1:1) removed an apolar impurity (fraction 2) and gave the title compound in fractions 3-12, which was evaporated to a viscous, slightly yellow oil (475 mg, 68%).

¹H NMR: (CDCl₃, 400 MHz) δ = 9.74 (dd, *J* = 1.9, 1.0 Hz, 1H), 7.22-7.17 (m, 2H), 6.91-6.85 (m, 2H), 5.91 (dd, *J* = 2.1, 1.0 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.23 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.11 (dd, *J* = 12.0, 6.6 Hz, 1H), 3.81 (s, 3H), 3.42 (d, *J* = 3.4 Hz, 2H), 2.59 (dd, *J* = 15.6, 6.5 Hz, 1H), 2.55 (ddd, *J* = 17.2, 9.0, 2.0 Hz, 1H), 2.44 (ddd, *J* = 17.2, 4.0, 0.9 Hz, 1H), 2.41-2.31 (m, 1H), 2.30-2.12 (m, 2H), 2.26 (dd, *J* = 15.6, 7.5 Hz, 1H), 1.93-1.85 (m, 1H), 1.84-1.71 (m, 1H), 1.81 (d, *J* = 1.0 Hz, 3H), 1.66-1.52 (m, 1H), 1.51-1.40 (m, 1H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 200.7, 172.5, 159.5, 146.8, 129.8, 129.5, 114.0, 75.8, 73.2, 70.7, 67.8, 55.4, 42.7, 39.9, 36.5, 35.3, 34.3, 34.0, 33.7, 24.0; **HRMS (MALDI-TOF):** calc. for [M+Na]⁺: 523.0952, found 523.0950; **IR (neat):** 3060, 2920, 2855, 2729, 2358, 1744, 1721, 1612, 1585, 1513, 1455, 1441, 1410, 1376, 1362, 1301, 1246, 1174, 1141, 1081, 1031, 930, 820, 774, 760, 710, 666, 569; **[α]_D²⁰** = -12.50° (*c* = 0.64, CH₂Cl₂); **Rf-value:** 0.54 (EtOAc:MePh 1:1)

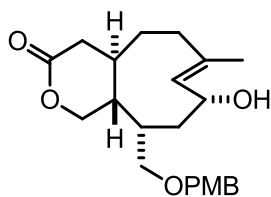
C26BL-221-14-pure



C26BL-221-14-pure



10 (4aR,9R,11S,11aR,E)-9-hydroxy-11-(((4-methoxybenzyl)oxy)methyl)-7-methyl-4,4a,5,6,9,10,11,11a-octahydrocyclonona[c]pyran-3(1H)-one



Chemical Formula: C₂₂H₃₀O₅

Exact Mass: 374.2093

Molecular Weight: 374.4706

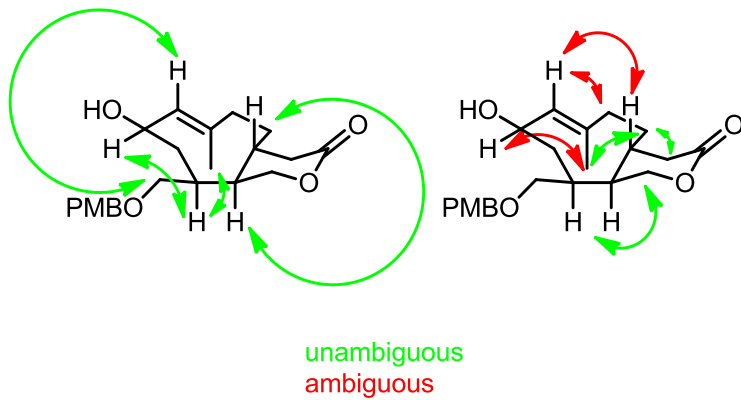
NiCl₂ (6.9 mg, 57 μmol, 0.06 eq.) and CrCl₂ (870 mg, 7.12 mmol, 7.5 eq.) were weighed in a glove box into a flame dried flask, taken out of the box and suspended in DMSO (24 mL, fresh bottle), which gave a black suspension. This had to be vigorously stirred so as to break up any lumps and to allow for good conversion. **9** (475 mg, 0.949 mmol, 1 eq.) was coevaporated with benzene (5 mL) and put under an atmosphere of argon. It was transferred to the suspended metal salts quickly dropwise in DMSO (14.5 mL and rinsed with 2x4.5 mL). The solution was stirred for 14 h. The reaction mixture was quenched by quick transfer into an ice cold mixture of Na₂EDTA (70 mL, 0.2 M, pH adjusted to 8), rinsed with Na₂EDTA (2x10 mL) and diluted with brine (385 mL). The reaction flask was rinsed with several portions of EtOAc (100 mL total). The purple mixture was stirred at ambient temperature for 1 h (color must change from green to purple or black), phases were separated and the aqueous phase was extracted with EtOAc (3x100 mL). The combined extracts were washed with first Na₂EDTA (20 mL, 0.2 M, pH adjusted to 8, saturated with solid NaCl), then brine (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purified by several times by FC (4:6 acetone:hexanes) to give the title compound as a white foam (252 mg, 71%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.25-7.19 (m, 2H), 6.90-6.85 (m, 2H), 6.33 (s, *J* = 7.3 Hz, 1H), 4.71 (d, br, *J* = 3.1 Hz, 1H), 4.43 (triplet like, higher order, apparent *J* = 11.9 Hz, 2H), 4.01 (dd, *J* = 11.3, 6.9 Hz, 1H), 3.95 (t, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.71 (t, *J* = 9.6 Hz, 1H), 3.64 (dd, *J* = 14.5, 5.9 Hz, 1H), 2.77 (dd, *J* = 9.7, 5.8 Hz, 1H), 2.18 (dd, *J* = 14.6, 4.4 Hz, 1H), 2.14-2.05 (m, 3H), 1.92-1.81 (m, 3H), 1.79-1.69 (m, 1H), 1.64 (s, 3H), 1.64-1.57 (m, 1H), 1.55-1.45 (m, 2H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 174.2, 159.5, 133.2, 129.9, 129.6, 128.9, 114.1, 73.3, 71.5, 71.3, 68.8, 55.4, 44.0, 39.9, 39.4, 38.1, 37.4, 35.5, 31.4, 17.8; **HRMS (ESI-TOF):** calc. for [M+Na]⁺: 397.1985, found 397.1981; **IR (neat):** 3485, 3456, 2923, 2856, 2363, 2359, 2343, 2327, 1745, 1612, 1585, 1513, 1440, 1385, 1366, 1330, 1301, 1248, 1172, 1151, 1084, 1033, 946, 850, 820,

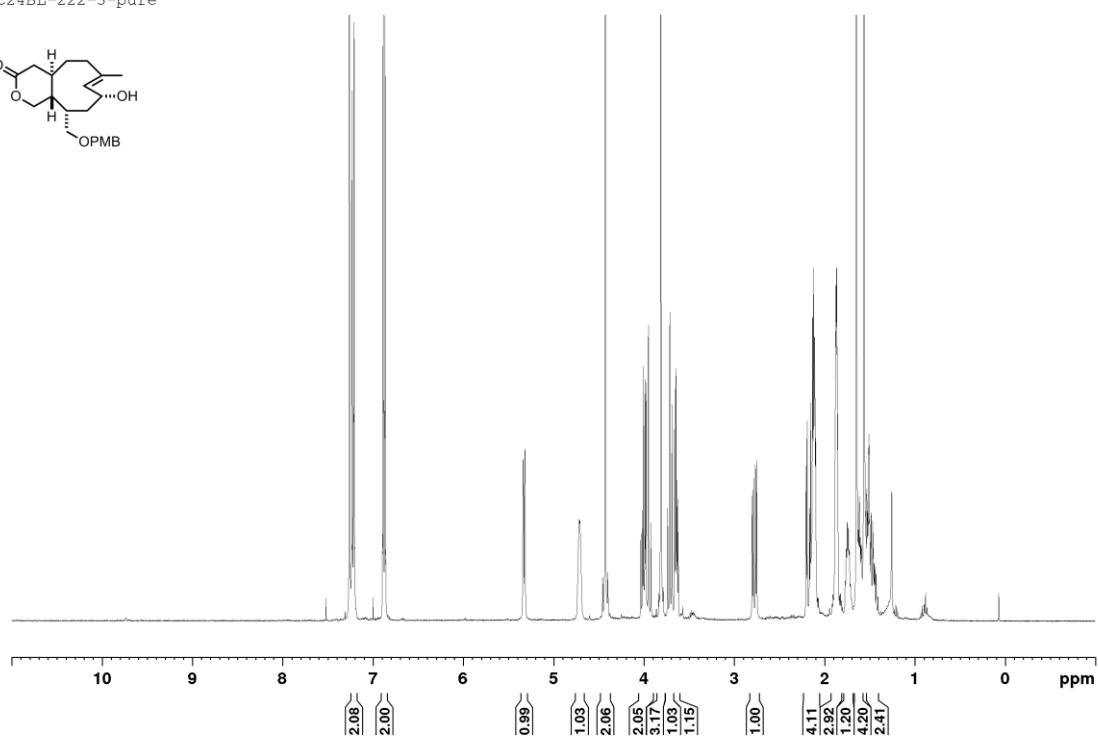
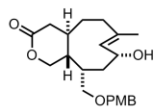
614, 575; $[\alpha]^{20}_D = +32.24^\circ$ ($c = 1.25$, CH_2Cl_2); **m.p.:** 123-139 °C (no decomposition, recrystallized from 1,2-difluorobenzene); **Rf-value:** 0.46 (EtOAc:hexanes 3:1)

key NOE signals

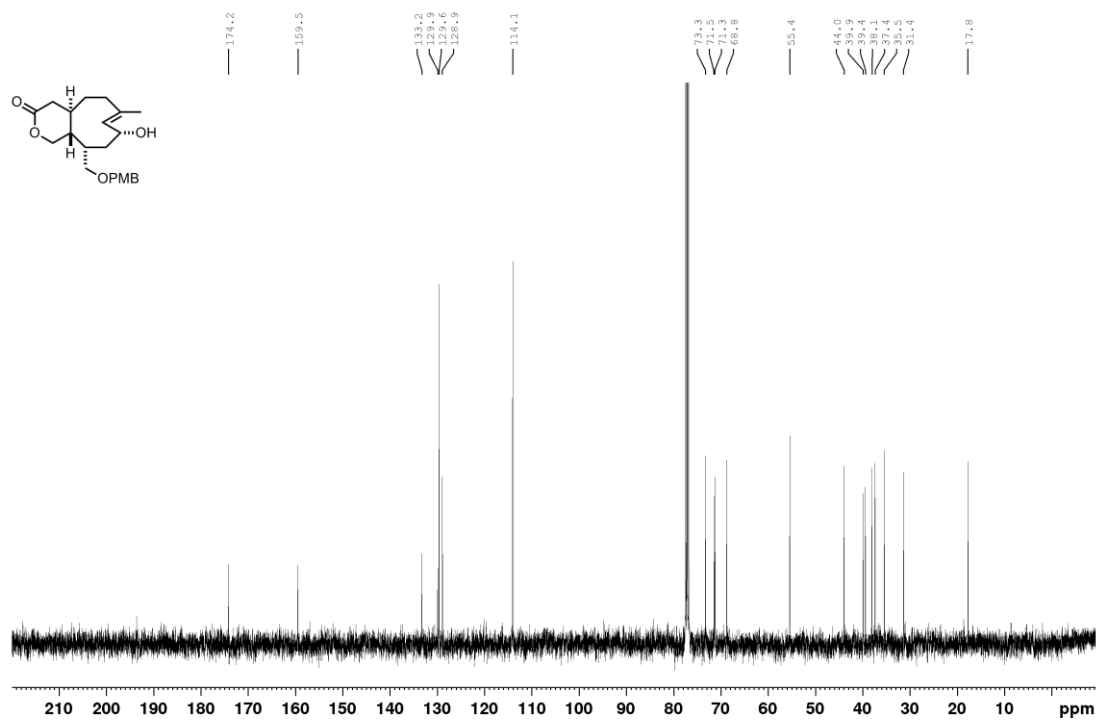
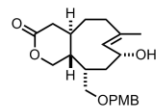
other NOE signals



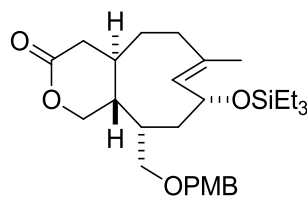
C24BL-222-3-pure



C24BL-222-3-pure



331 (4aR,9R,11S,11aR,E)-11-(((4-methoxybenzyl)oxy)methyl)-7-methyl-9-((triethylsilyl)oxy)-4,4a,5,6,9,10,11,11a-octahydrocyclonona[c]pyran-3(1H)-one



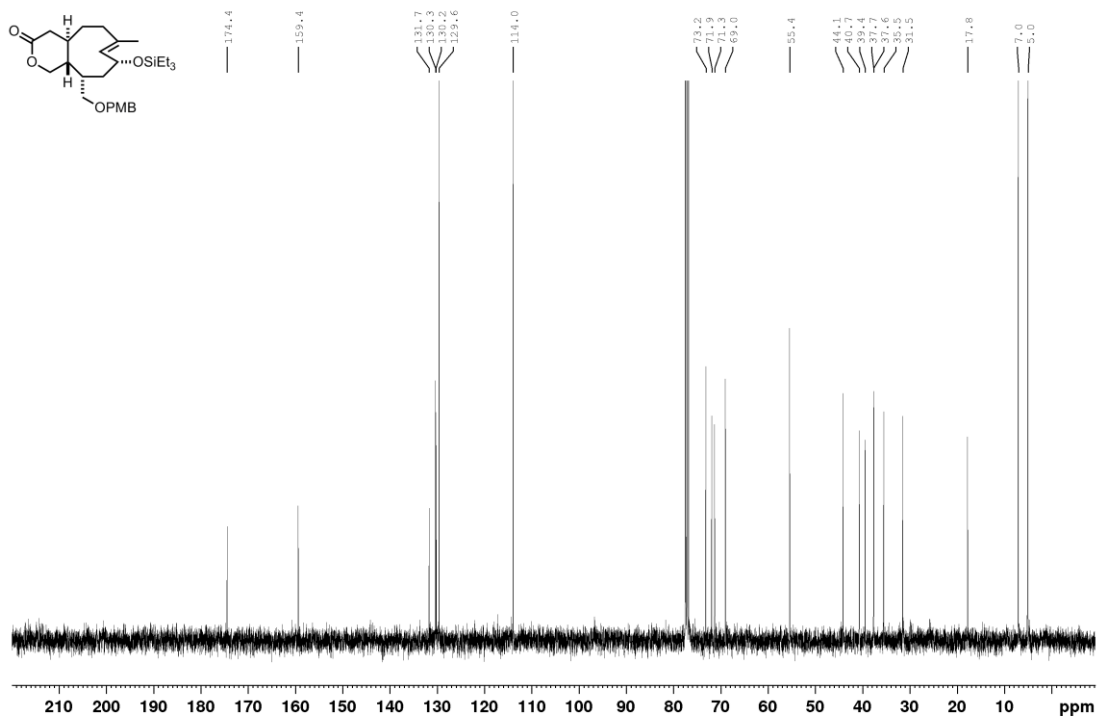
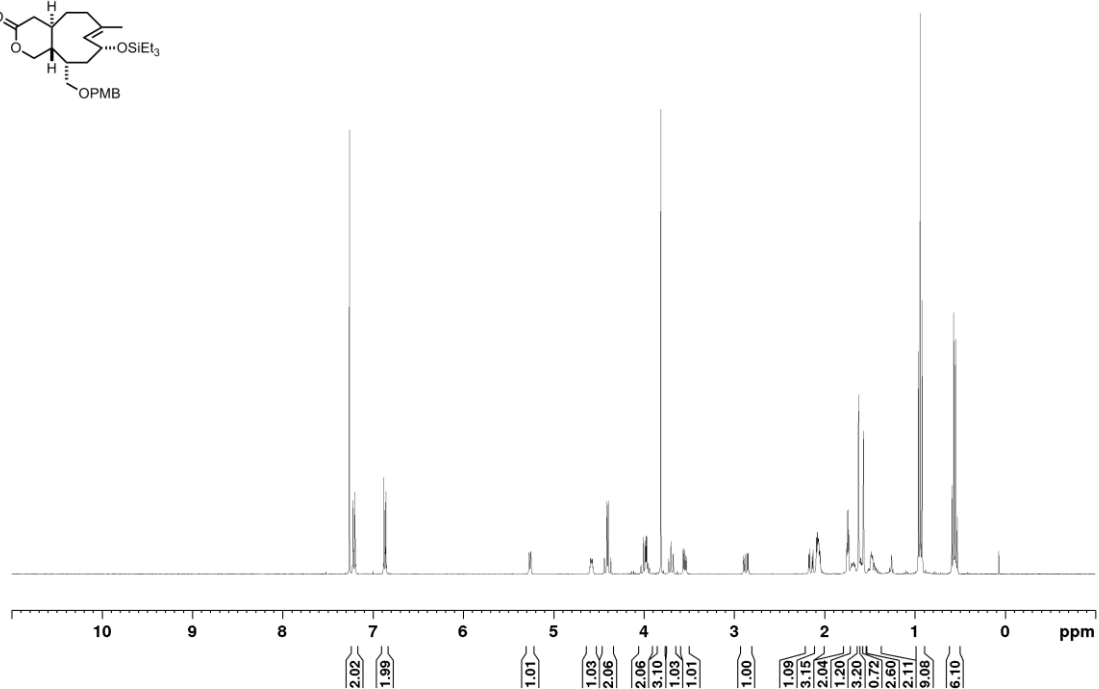
Chemical Formula: $C_{28}H_{44}O_5Si$

Exact Mass: 488.2958

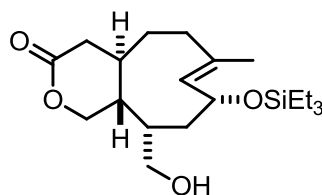
Molecular Weight: 488.7315

10 (221.3 mg, 0.591 mmol, 1 eq.) was dissolved in CH_2Cl_2 (1.4 mL) and added was imidazole (182 mg, 2.67 mmol, 4.5 eq.), followed by addition of TES chloride (0.13 mL, 0.768 mmol, 1.3 eq.). The reaction mixture quickly turned cloudy and was stirred for 4 h. It was diluted with water (15 mL) and extracted with Et_2O (3x7 mL). The combined organic phases were washed sequentially with NH_4Cl (1 mL, sat., aq.), $NaHCO_3$ (1 mL, sat., aq.) and brine (1 mL). The solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by FC (EtOAc:Hexanes 1:10 to 3:17 to 1:5 to 1:4) to give the pure title compound as a clear colorless oil (245 mg, 85%).

1H NMR: ($CDCl_3$, 400 MHz) δ = 7.24-7.18 (m, 2H), 6.89-6.84 (m, 2H), 6.33 (s, J = 7.3 Hz, 1H), 5.26 (dd, J = 7.3, 1.0 Hz, 1H), 4.58 (m, 1H), 4.43 (apparent dd, higher order, apparent J = 16.9, 11.3 Hz, 2H), 4.04-3.93 (m, 2H), 3.81 (s, 3H), 3.70 (t, J = 10.3 Hz, 1H), 3.55 (dd, J = 10.1, 4.7 Hz, 1H), 2.87 (dd, J = 5.9, 14.8 Hz, 1H), 2.15 (dd, J = 14.7, 4.3 Hz, 1H), 2.11-2.01 (m, 3H), 1.74 (t, J = 4.0, 2H), 1.72-1.64 (m, 1H), 1.62 (s, 3H), 1.62-1.57 (m, 1H), 1.53-1.38 (m, 2H), 0.94 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.9 Hz, 6H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 174.4, 159.4, 131.7, 130.3, 130.2, 129.6, 114.0, 73.2, 71.9, 71.3, 69.0, 55.4, 44.1, 40.7, 39.4, 37.7, 37.6, 35.5, 31.5, 17.8, 7.0, 5.0; **HRMS (MALDI-TOF):** calc. for $[M+Na]^+$: 511.2850, found 511.2849; **IR (neat):** 2951, 2911, 2874, 2365, 2337, 1750, 1673, 1611, 1586, 1513, 1456, 1415, 1380, 1329, 1301, 1246, 1170, 1149, 1082, 1053 1008, 975, 883, 852, 822, 793, 769, 730 671, 612; **$[\alpha]^{20}_D$** = +12.50° (c = 0.96, CH_2Cl_2); **Rf-value:** 0. (EtOAc:hexanes 1:1)



332 (4aR,9R,11S,11aR,E)-11-(hydroxymethyl)-7-methyl-9-((triethylsilyl)oxy)-4,4a,5,6,9,10,11,11a-octahydrocyclonona[c]pyran-3(1H)-one



Chemical Formula: C₂₀H₃₆O₄Si

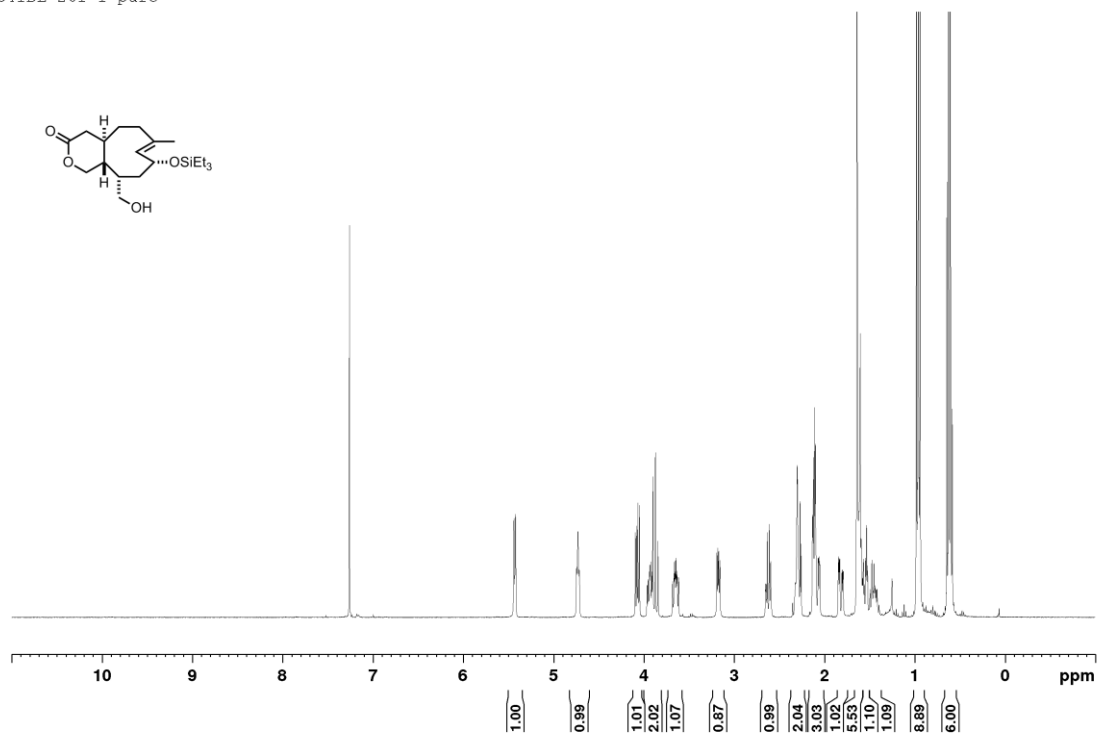
Exact Mass: 368.2383

Molecular Weight: 368.5829

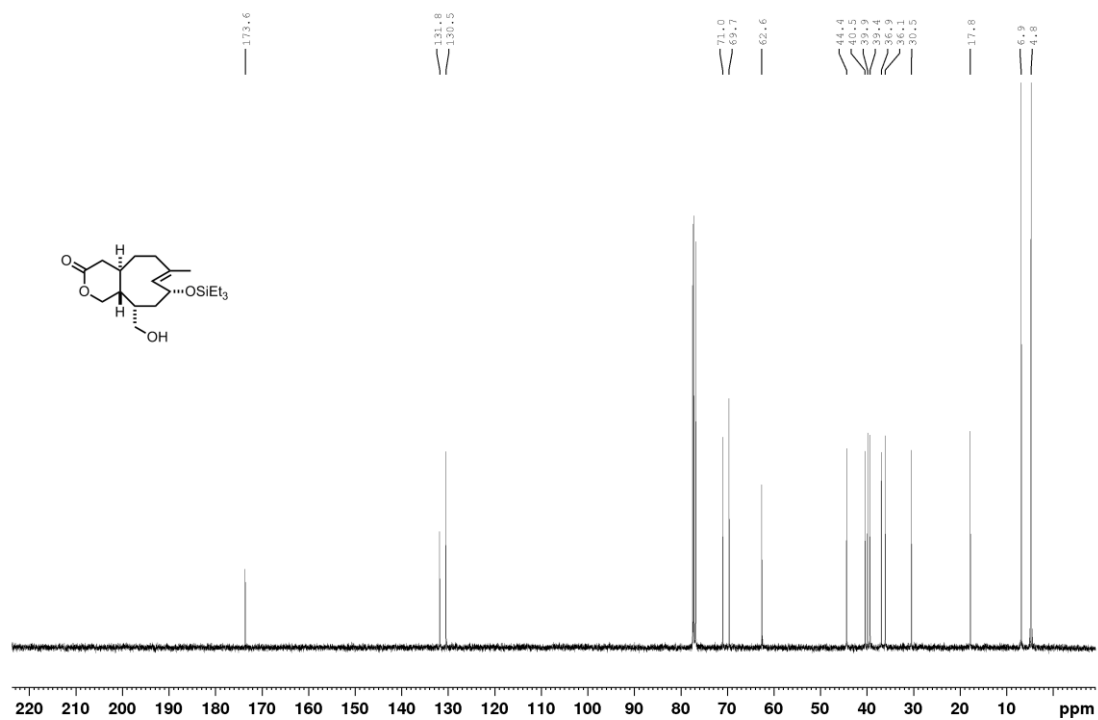
To a stirred solution of **331** (245 mg, 0.501 mmol) in a vigorously stirred mixture of CH₂Cl₂ (17 mL) and phosphate buffer (0.85 mL, pH 7, 0.5 M) at 0 °C was added DDQ (214 mg, 0.295 mmol, 1.9 eq.) in 4 approx. equal portions in intervals of 4 min. Immediately after the last portion, the ice bath was replaced by a water bath. After 1 h, still around 10-15% of SM was left by TLC and another portion of DDQ (27 mg, 0.24 eq.) was added. Stirring was continued for another 45 min, the reaction mixture was diluted with CH₂Cl₂ (50 mL) and quenched with sat. aq. NaHCO₃ (13 mL). The organic phase was separated and the aqueous solution was extracted with CH₂Cl₂ (25 mL). The resulting emulsified suspension was filtered through paper to allow for separation of the phases. The solids were rinsed with CH₂Cl₂ (25 mL), which was used to extract the aqueous phase again. The combined organic extracts were washed with sat. aq. NaHCO₃ (2x5 mL), dried over MgSO₄, diluted with MePh (10 mL) and evaporated to 10 mL. The crude solution was directly loaded onto a column and purified by FC (EtOAc:Hexanes 4:6) to give the title compound as a clear slightly yellow oil (171.7 mg, 93%).

¹H NMR: (CDCl₃, 400 MHz) δ = 5.43 (d, *J* = 6.7 Hz, 1H), 4.73 (t, *J* = 5.6 Hz, 1H), 4.07 (dd, *J* = 11.6, 6.6 Hz, 1H), 3.97-3.89 (m, 1H), 3.87 (t, *J* = 11.3 Hz, 1H), 3.69-3.60 (m, 1H), 3.17 (dd, *J* = 8.9, 4.8 Hz, 1H, OH), 2.67-2.57 (m, 1H), 2.36-2.24 (m, 2H), 2.15-2.04 (m, 3H), 1.82 (ddd, *J* = 2.1, 5.0, 15.1 Hz, 1H), 1.64 (s, 3H), 1.64-1.58 (m, 2H), 1.58-1.51 (m, 1H), 1.51-1.38 (m, 1H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.96 (q, *J* = 8.0 Hz, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 173.6, 131.8, 130.5, 71.0, 69.7, 62.6, 44.4, 40.5, 39.9, 39.4, 36.9, 36.1, 30.5, 17.8, 6.9, 4.8; **HRMS (ESI-TOF):** calc. for [M+Na]⁺: 391.2275, found 391.2278; **IR (neat):** 3463, 2952, 2914, 2876, 1745, 1453, 1437, 1381, 1331, 1300, 1247, 1167, 1079, 1039, 1006, 917, 854, 823, 792, 767, 729, 676, 633; **[α]_D²⁰** = +19.90 ° (*c* = 2.0, CH₂Cl₂); **Rf-value:** 0.40 (EtOAc:hexanes 3:1)

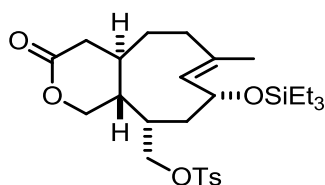
C41BL-261-1-pure



C41BL-261-1-pure



11 (4aR,9R,11aR,E)-7-methyl-11-methylene-9-((triethylsilyl)oxy)-4,4a,5,6,9,10,11,11a-octahydrocyclonona[c]pyran-3(1H)-one



Chemical Formula: C₂₇H₄₂O₆SSi

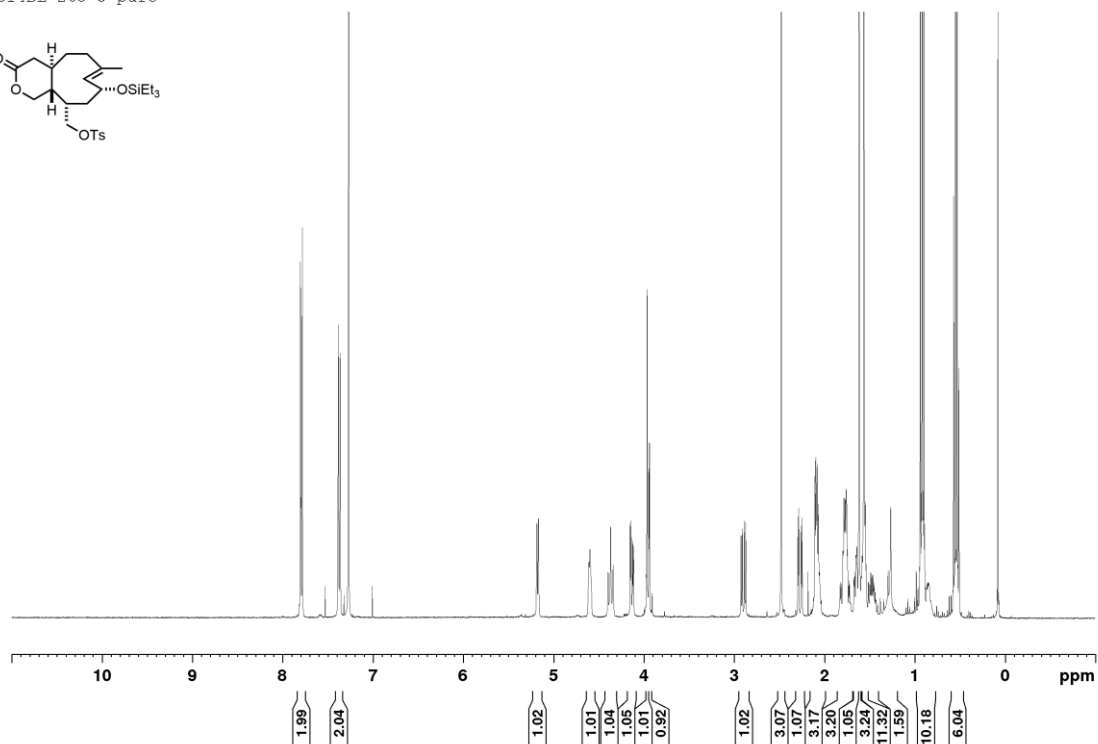
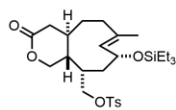
Exact Mass: 522.2471

Molecular Weight: 522.7693

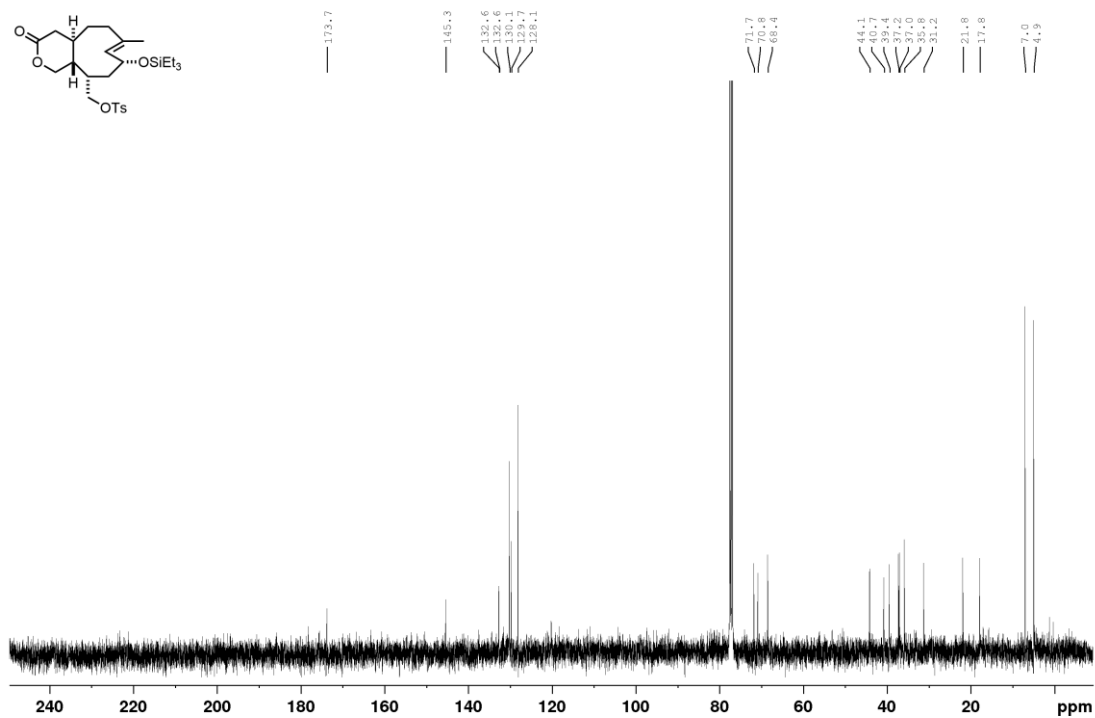
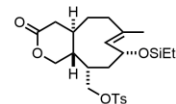
332 (171.7 mg, 466 μ mol) was dissolved in CH₂Cl₂ (1.6 mL). DMAP (30 mg, 0.53 eq.) was added, followed by Et₃N (0.39 mL, 6.0 eq.) and TsCl (266 mg, 3.0 eq.) at ambient temperature. The mixture turned light brown within 1 h and dark brown within 2 h. It was stirred for a total of 20 h and the reaction mixture was quenched with sat. aq. NH₄Cl (10 mL). The mixture was extracted with CH₂Cl₂ (3x10 mL) and the combined organic extract were washed with sat. NH₄Cl (2x5 mL) and sat. NaHCO₃ (5 mL) and finally brine (5 mL), dried over MgSO₄, diluted with MePh (10 mL) and concentrated to 10 mL. FC (EtOAc:hexanes 1:3) gave the title compound as a slightly yellow, viscous oil (217 mg, 89%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.82-7.76 (m, 2H), 7.40-7.35 (m, 2H), 5.18 (d, J = 6.8 Hz, 1H), 4.60 (m, br, 1H), 4.37 (t, br, J = 11.0 Hz, 1H), 4.13 (dd, J = 10.6, 4.2 Hz, 1H), 3.96 (s, 1H), 3.94 (d, J = 3.0 Hz, 1H), 2.90 (dd, J = 14.9, 5.9 Hz, 1H), 2.48 (s, 3H), 2.27 (dd, J = 14.9, 3.5 Hz, 1H), 2.15-2.03 (m, 3H), 1.85-1.70 (m, 3H), 1.68-1.61 (m, 1H), 1.61 (s, 3H), 1.59-1.52 (m, 2H), 0.92 (t, J = 7.9 Hz, 9H) 0.54 (q, J = 7.9 Hz, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 173.7, 145.3, 132.6, 132.6, 130.1, 129.7, 128.1, 71.7, 70.8, 68.4, 44.1, 40.7, 39.4, 37.2, 37.0, 35.8, 31.2, 21.8, 17.8, 7.0, 4.9; **HRMS (MALDI):** calc. for [M+Na]⁺: 545.2364, found 545.2363; **IR (neat):** 2951, 2932, 2914, 2876, 1752, 1598, 1454, 1436, 1414, 1361, 1303, 1246, 1236, 1175, 1151, 1118, 1079, 1052, 1011, 951, 890, 857, 821, 790, 765, 729; **[α]_D²⁰** = +36.46° (c=0.65, CH₂Cl₂); **Rf-value:** 0.62 (EtOAc:hexanes 3:1), 0.42 (EtOAc:hexanes 1:1)

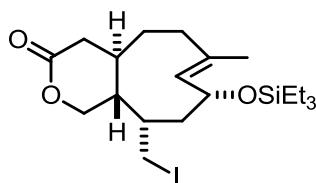
C14BL-263-5-pure



C14BL-263-5-pure



333 (4aR,9R,11S,11aR,E)-11-(iodomethyl)-7-methyl-9-((triethylsilyl)oxy)-4,4a,5,6,9,10,11,11a-octahydrocyclonona[c]pyran-3(1H)-one

Chemical Formula: C₂₀H₃₅IO₃Si

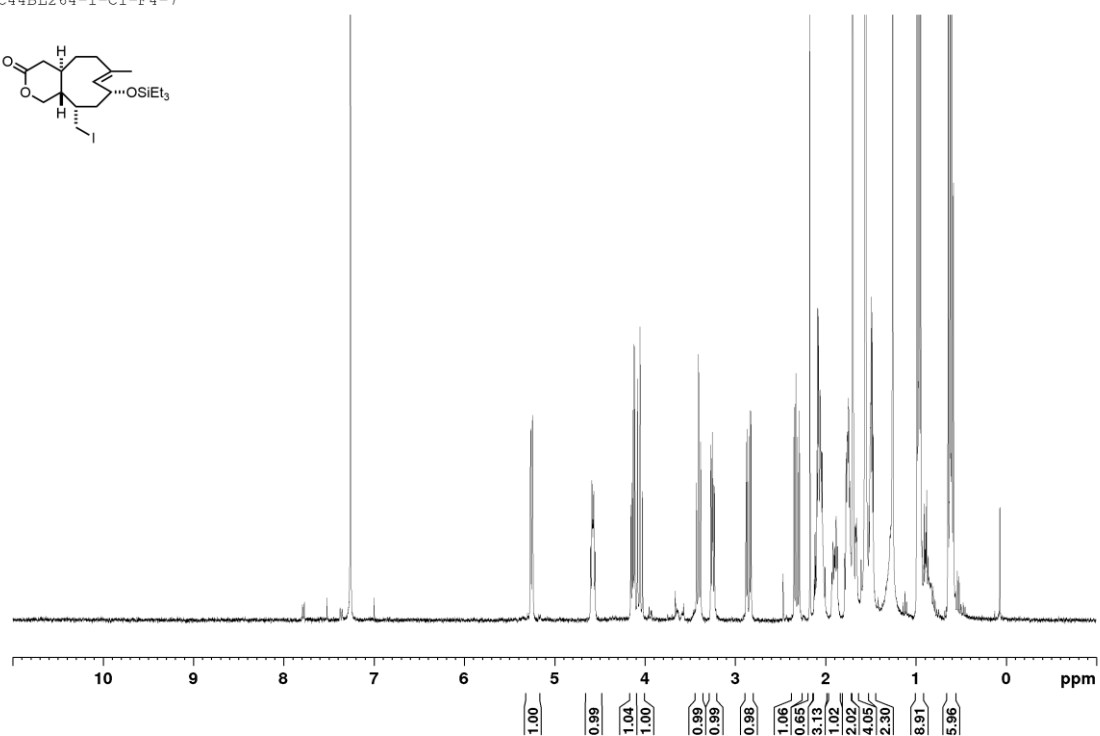
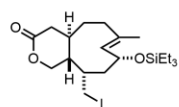
Exact Mass: 478.1400

Molecular Weight: 478.4801

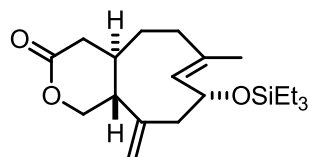
Tosylate **11** (5 mg) was dissolved on acetone (1 mL). Sodium iodide (55.4 mg) and copper powder (0.4 mg) were added. The solution was stirred for 17 h with only trace of conversion. Additional sodium iodide (195 mg) was added and stirring was continued for 4 h without much change. The mixture was warmed to 50 °C and stirred for 4 h. Silica gel (500 mg) was added and the mixture was evaporated to dryness. The silica was loaded onto a column and purified by FC (EtOAc:hexanes 1:3 to 1:1) to the title compound as a clear, colorless oil (2.7 mg, 59%).

¹H NMR: (CDCl₃, 400 MHz) δ = 5.25 (d, J = 8.3 Hz, 1H), 4.61-4.53 (m, 1H), 4.13 (dd, J = 11.6, 6.1 Hz, 1H), 4.05 (t, J = 11.3 Hz, 1H), 3.40 (t, J = 9.3 Hz, 1H), 3.25 (dd, J = 9.7, 6.1 Hz, 1H), 2.85 (dd, J = 16.2, 6.0 Hz, 1H), 2.32 (dd, J = 16.2, 7.6 Hz, 1H), 2.13-1.99 (m, 3H), 1.94-1.84 (m, 1H), 1.80-1.71 (m, 2H), 1.70 (s, 3H), 1.71-1.64 (m, 1H), 1.53-1.45 (m, 2H), 0.96 (t, J = 8.0 Hz, 9H), 0.61 (q, J = 7.9 Hz, 6H); **Rf-value:** 0.40 (EtOAc:hexanes 1:3)

C44BL264-1-C1-F4-7



12 (4aR,9R,11aR,E)-7-methyl-11-methylene-9-((triethylsilyl)oxy)-4,4a,5,6,9,10,11,11a-octahydrocyclonona[c]pyran-3(1H)-one



Chemical Formula: $C_{20}H_{34}O_3Si$

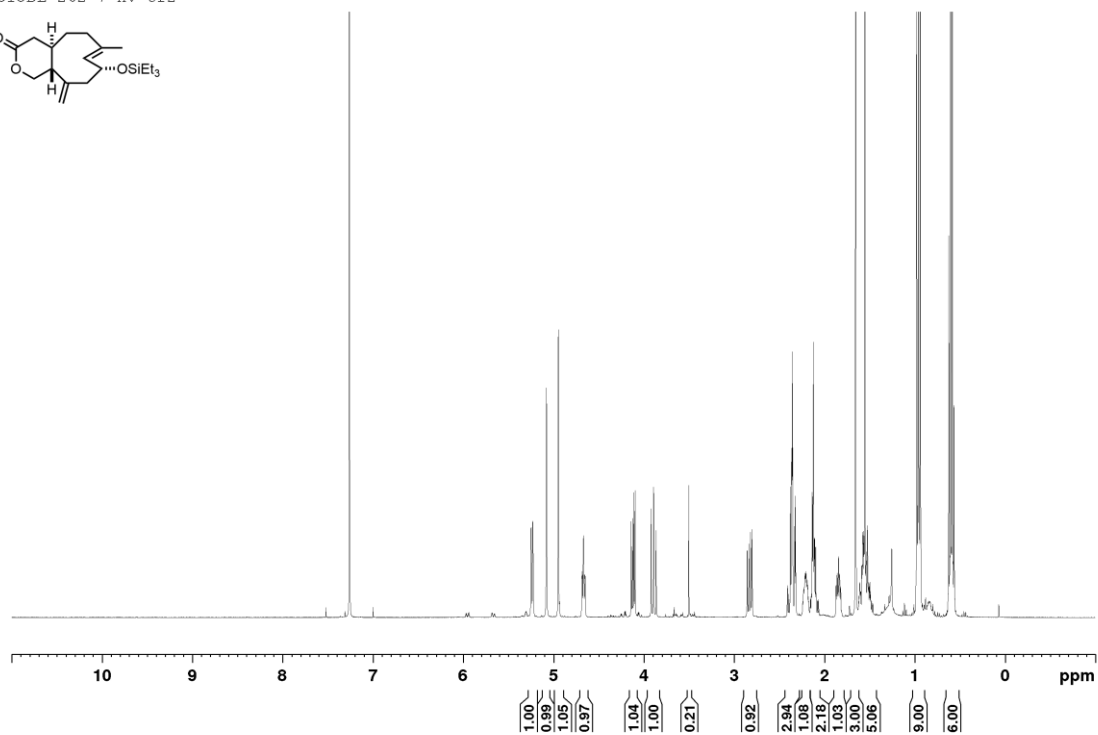
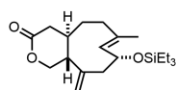
Exact Mass: 350.2277

Molecular Weight: 350.5677

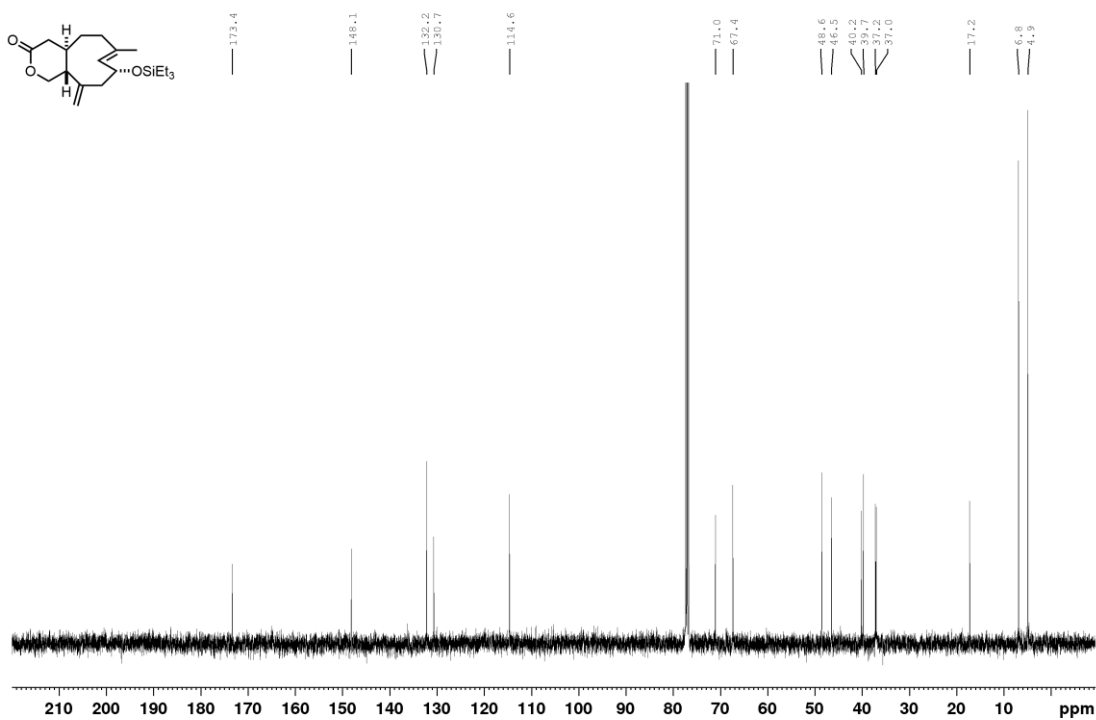
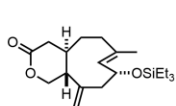
NaI (295 mg, 1.97 mmol, 5 eq.) was flame dried in a pear-shaped flask. Added was recently (within 7 d) distilled DBU (0.18 mL, 1.2 mmol, 3 eq.), immediately followed by 11 (205.8 mg, 0.394 mmol, azeotropically dried with benzene just prior to reaction) in DME (3 mL+2x0.9 mL rinsing). The solution turned yellow for a moment, then colorless. It was stirred in a 90 °C oil bath upon which quickly a beige precipitate formed. After 2 h, the walls sticking with some solid which were washed down with DME (0.5 mL) and reaction was continued for an additional 1 h. The mixture was quickly cooled with a water bath and quenched by addition of, $Na_2S_2O_3$ (0.5 mL, aq., sat.). H_2O (5 mL) was added to dissolve all the precipitates and the mixture was extracted with EtOAc (100 mL + 2x25 mL). The combined organic phases were washed with NH_4Cl (5 mL, aq., sat.), $NaHCO_3$ (5 mL, aq., sat.), brine (5 mL), dried over $MgSO_4$ and evaporated to around 10 mL. MePh (1 mL) was added and the solution was evaporated to around 1 mL. The crude solution was directly loaded onto a column and purified by FC (EtOAc:hexanes 1:3 to 6:4) to give the title compound as a slightly yellow solid (107.9 mg, 78%).

1H NMR: ($CDCl_3$, 400 MHz) δ = 5.24 (d, J = 3.4 Hz, 1H), 5.08 (s, 1H), 4.95 (s, 1H), 4.70-4.64 (m, 1H), 4.12 5.18 (dd, J = 11.7, 5.9 Hz, 1H), 3.89 5.18 (dd, J = 11.4, 10.7 Hz, 1H), 2.83 5.18 (dd, J = 14.7, 7.0 Hz, 1H), 2.42-2.30 (m, 3H), 2.26-2.16 (m, 1H), 2.16-2.05 (m, 2H), 1.89-1.80 (m, 1H), 1.65 (s, 3H), 1.63-1.45 (m, 2H), 0.96 (t, J = 7.9 Hz, 9H) 0.59 (q, J = 7.9 Hz, 6H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 173.4, 148.1, 132.2, 130.7, 114.6, 71.0, 67.4, 48.6, 46.5, 40.2, 39.7, 37.2, 37.0, 17.2, 6.8, 4.9; **HRMS (MALDI):** calc. for $[M+Na]^+$: 373.2169, found 373.2169; **IR (neat):** 3075, 2954, 2915, 2876, 2851, 1748, 1733, 1673, 1639, 1457, 1434, 1414, 1383, 1331, 1308, 1268, 1242, 1175, 1159, 1141, 1068, 1053, 1027, 1004, 966, 901, 893, 854, 844, 830, 800, 790, 768, 725, 672, 622, 604; **$[\alpha]^{20}_D$** = +31.89° (c = 0.53, CH_2Cl_2); **Rf-value:** 0.69 (EtOAc:hexanes 3:1)

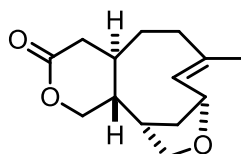
C13BL-262-7-HV-tr2



C13BL-262-7-HV-tr2



334 (4aR,9R,12S,12aR,E)-7-methyl-1,4,4a,5,6,11,12,12a-octahydro-9,12-methanopyrano[3,4-d]oxecin-3(9H)-one

Chemical Formula: C₁₄H₂₀O₃

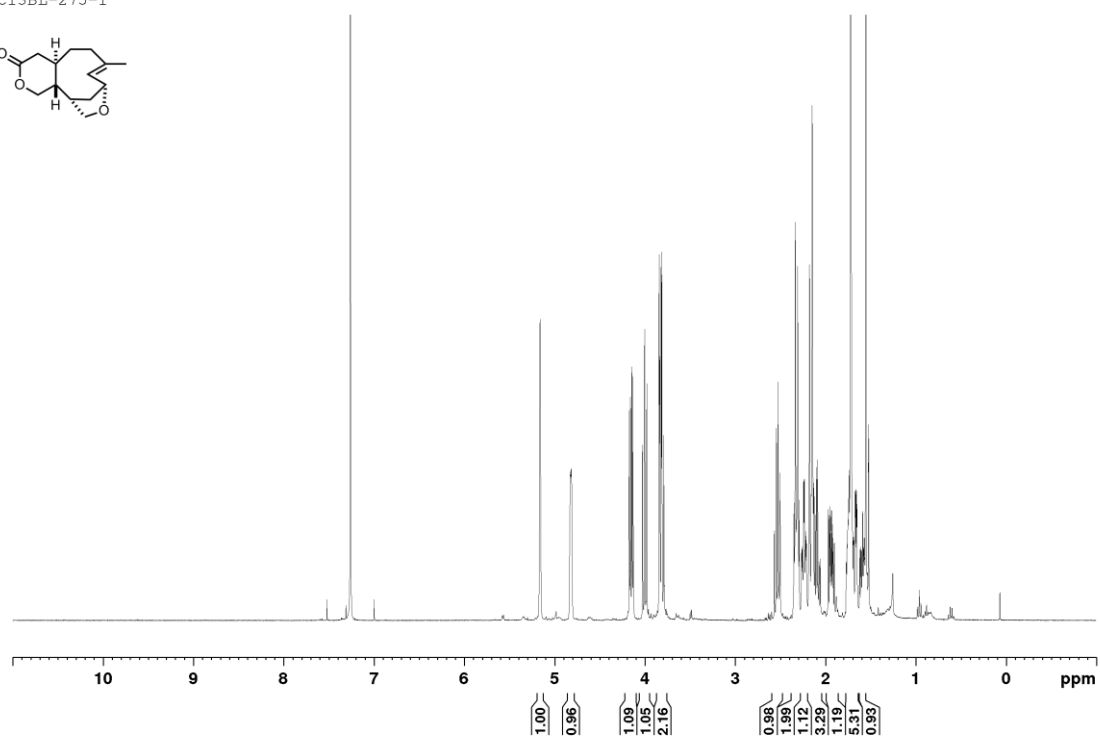
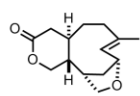
Exact Mass: 236.1412

Molecular Weight: 236.3068

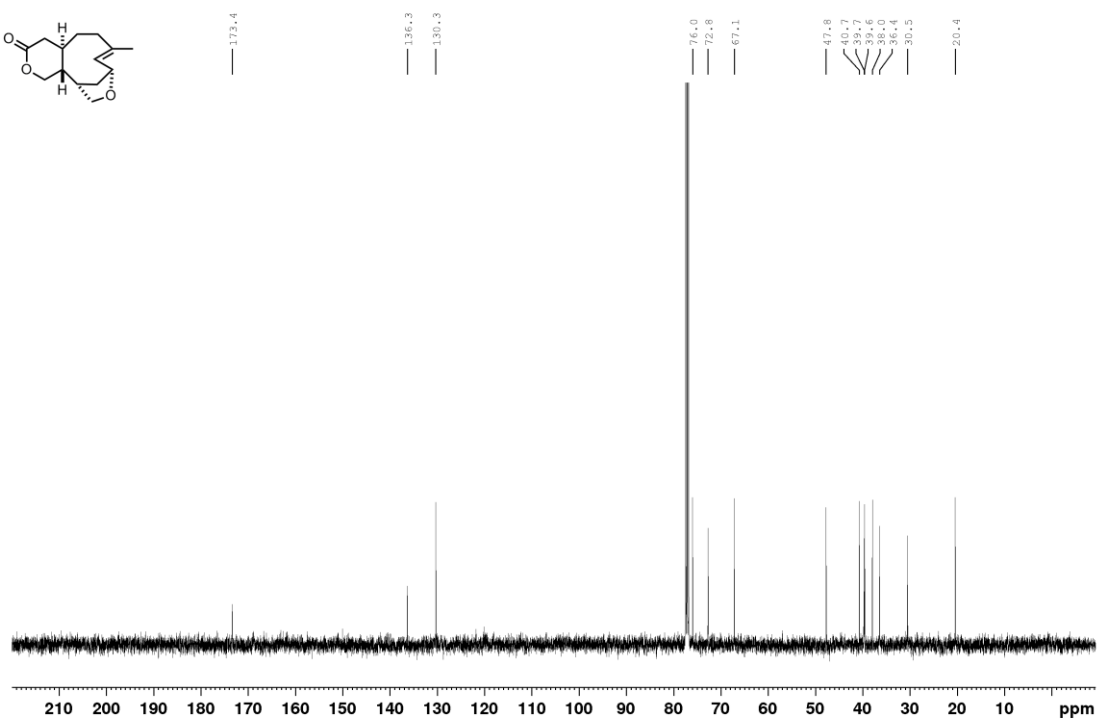
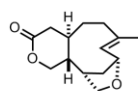
This compound was obtained according to the procedure used for the synthesis 11, but slightly decomposed **332** (66% purity) was used. The material was purified by FC (EtOAc:Hexanes 1:1 to 6:4) and obtain as a white solid.

¹H NMR: (CDCl₃, 400 MHz) δ = 5.16 (s, 1H), 4.82 (d, J = 4.2 Hz, 1H), 4.15 (q, J = 11.5, 5.3 Hz, 1H), 4.00 (t, J = 9.2 Hz, 1H), 3.86-3.77 (m, 2H), 2.53 (dd, J = 16.5, 8.9 Hz, 1H), 2.36-2.28 (m, 2H), 2.24 (td, J = 8.7, 3.0 Hz, 1H), 2.20-2.04 (m, 3H), 1.98-1.89 (m, 1H), 1.78-1.64 (m, 2H), 1.72 (t, J = 1.5 Hz, 3H), 1.63-1.55 (m, 1H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 173.4, 136.3, 130.3, 76.0, 72.8, 67.1, 47.8, 40.7, 39.7, 39.6, 38.0, 36.4, 30.5, 20.4; **HRMS (MALDI):** calc. for [M+Na]⁺: 259.1305, found 259.1305; **IR (neat):** 2933, 1746, 1483, 1438, 1387, 1327, 1311, 1272, 1260, 1244, 1194, 1150, 1115, 1084, 1051, 1052, 1026, 1003, 969, 961, 896, 886, 876, 852, 823, 797, 770, 742, 692, 610; **[α]_D²⁰** = -54.79 ° (c = 0.73, CH₂Cl₂); **Rf-value:** 0.28 (EtOAc:hexanes 3:1)

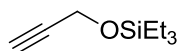
C13BL-275-1



C13BL-275-1



336 triethyl(prop-2-yn-1-yloxy)silane

Chemical Formula: C₉H₁₈OSi

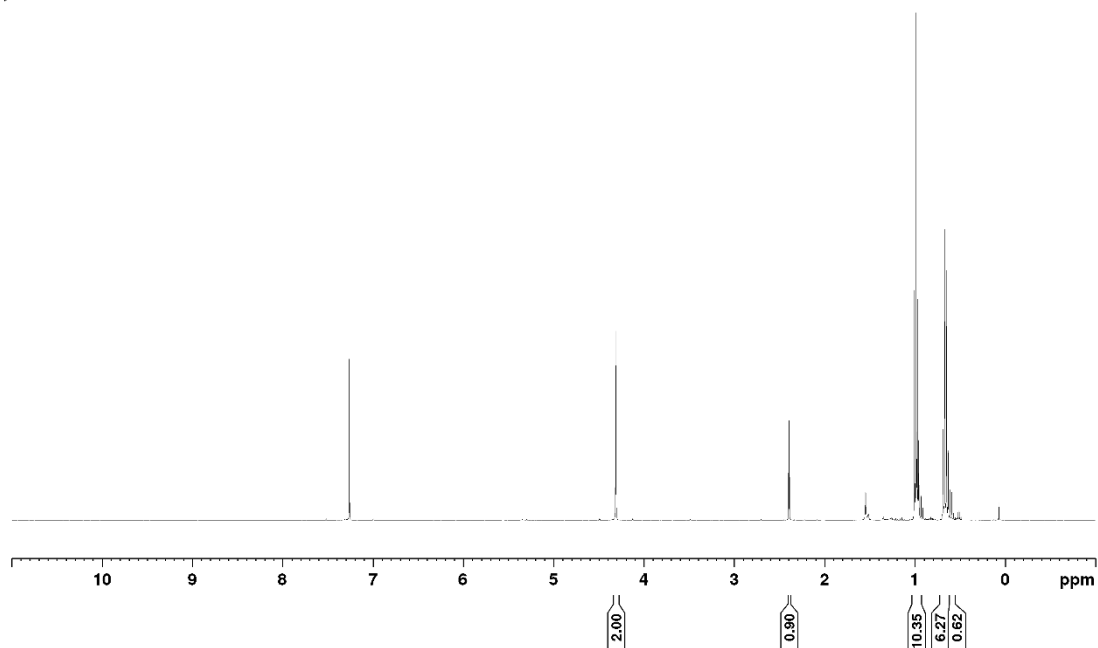
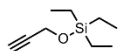
Exact Mass: 170.1127

Molecular Weight: 170.3241

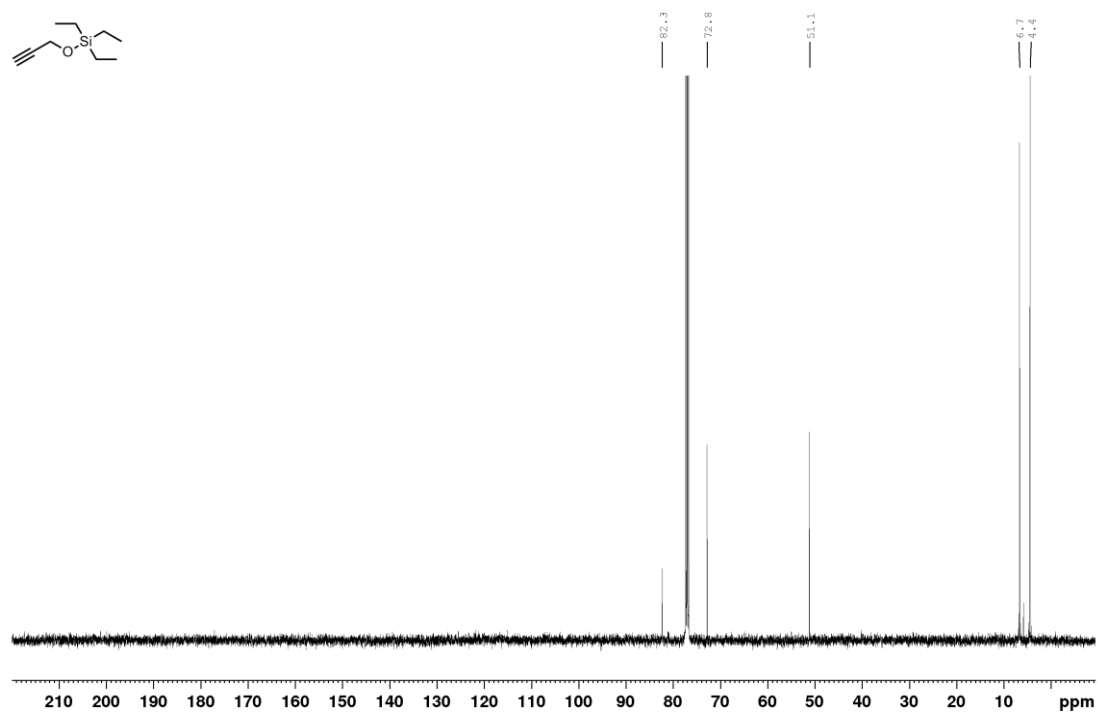
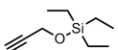
To a suspension of imidazole (22.5 g, 330 mmol, 3.7 eq.) in dichloromethane (48 mL) at 0 °C was added propargyl alcohol (5.2 mL, 89 mmol, 1 eq.) followed by TES chloride (16.5 mL, 98 mmol, 1.1 eq.) dropwise and quickly. The reaction mixture immediately turned cloudy and was stirred at 0 °C for 5 min, then 2 min in an ambient temperature water bath. TLC already indicated completion. The mixture was diluted with Et₂O (300 mL), washed sequentially with NH₄Cl (4x40 mL, sat., aq., whereby 18 mL H₂O was added to the first wash to dissolve precipitates, 6 mL in the following washes), NH₄Cl (40 mL, sat., aq.), NaHCO₃ (3x40 mL, sat., aq.) and brine (40 mL). The solution was dried over MgSO₄, filtered, and concentrated under reduced pressure. The clear, slightly yellow crude product (15.5 g, purity around 88%) was directly used for the next step.

¹H NMR: (CDCl₃, 400 MHz) δ = 4.31 (d, *J* = 2.4 Hz, 2H), 2.39 (t, *J* = 2.4 Hz, 1H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.66 (q, *J* = 8.0 Hz, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 82.3, 72.8, 51.1, 6.7, 4.4; **HRMS (ESI-TOF):** calc. for [M]⁺: 170.1121, found 170.1128; **Rf-value:** 0.65 (EtOAc:hexanes 1:10)

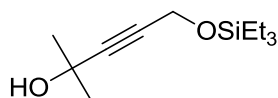
C38BL-255-1-cr2



C38BL-255-1-cr2/3



337 2-methyl-5-((triethylsilyl)oxy)pent-3-yn-2-ol

Chemical Formula: C₁₂H₂₄O₂Si

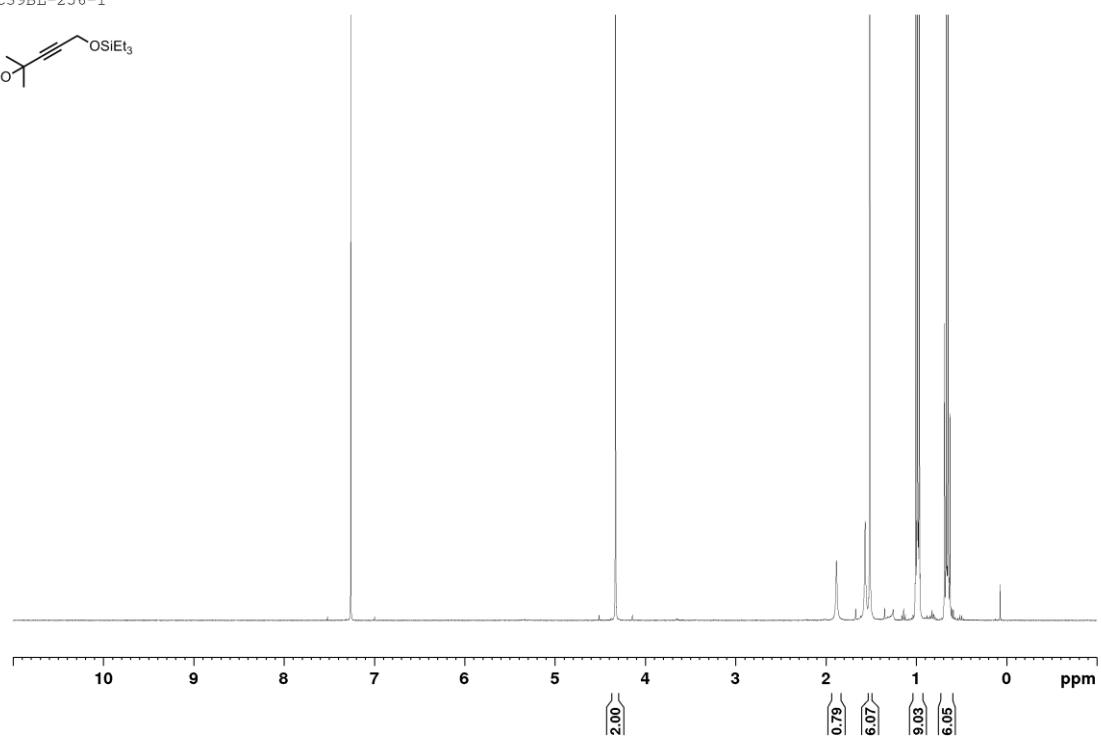
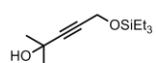
Exact Mass: 228.1546

Molecular Weight: 228.4033

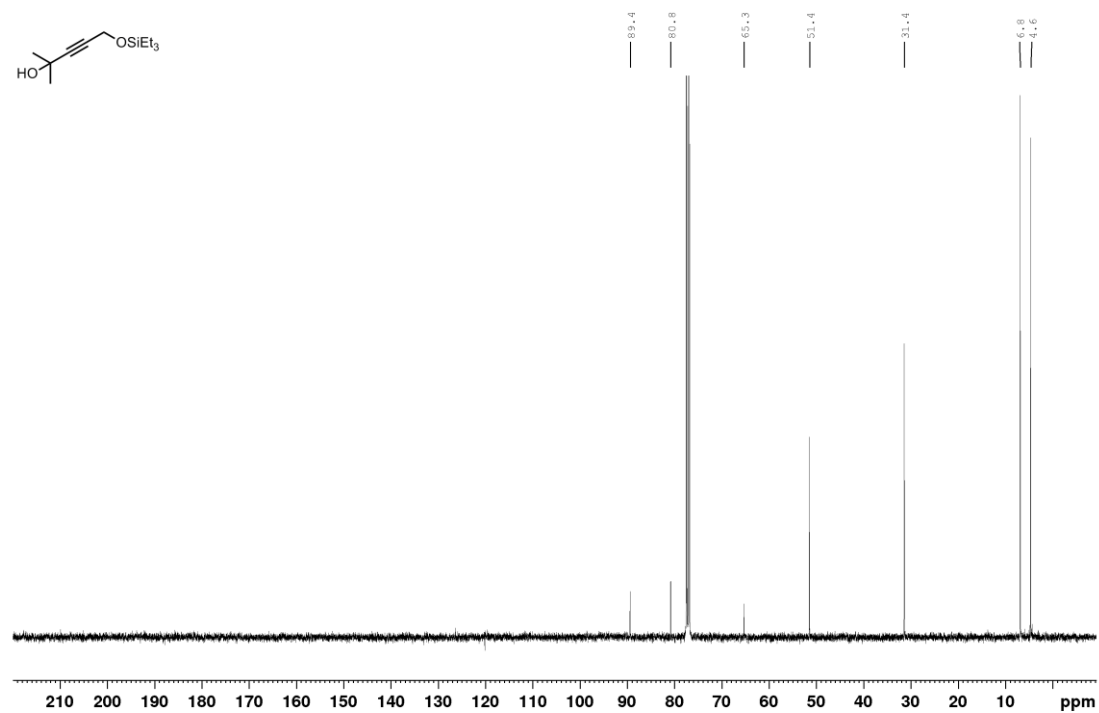
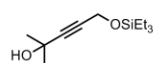
To a solution of crude propargyl silyl ether **336** (15.00 g) in THF (125 mL) under argon at -20 °C was added in a slow stream *n*-BuLi (60.5 mL, 1.6 M in hexane, 1.1 eq.). After 12 min, acetone (9.7 mL, 1.5 eq.) was added dropwise over 4 min. The solution was stirred for 1 h 40 min during which it warmed to around 10 °C, then the reaction was quenched by addition of a solution of sat. aq. NH₄Cl (82 mL) while being vigorously stirred, and letting the temperature raise to ambient temperature in a water bath. The resulting suspension was diluted with Et₂O (150 mL) and water until all precipitates had dissolved and the phases were separated. The aqueous phase was extracted with Et₂O (4x100 mL), the combined organic layers were washed with brine (50 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the crude product was purified by two rounds of FC (Et₂O:hexanes 1:3 to 1:1 and again with Et₂O:hexanes 1:4 to 7:13) to give the pure title compound as a slightly yellow oil (16.62 g, purity 93%, 78% yield).

¹H NMR: (CDCl₃, 400 MHz) δ = 4.33 (s, 2H), 1.88 (s, br, 1H, OH), 1.51 (s, 6H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.65 (q, *J* = 7.9 Hz, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 89.4, 80.8, 65.3, 51.4, 31.4, 6.8, 4.6; **HRMS (EI):** calc. for [M-CH₃]⁺ = 213.1305, found 213.1308; calc. for [M-C₂H₅]⁺ = 199.1149, found 199.1145; **IR (neat):** 3387, 2955, 2912, 2877, 1459, 1413, 1367, 1236, 1167, 1092, 1034, 1004, 949, 855, 805, 728, 675, 617; **Rf-value:** 0.27 (EtOAc:hexanes 1:5)

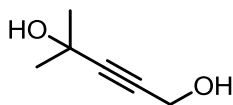
C39BL-256-1



C39BL-256-1



338 4-methylpent-2-yne-1,4-diol

Chemical Formula: C₆H₁₀O₂

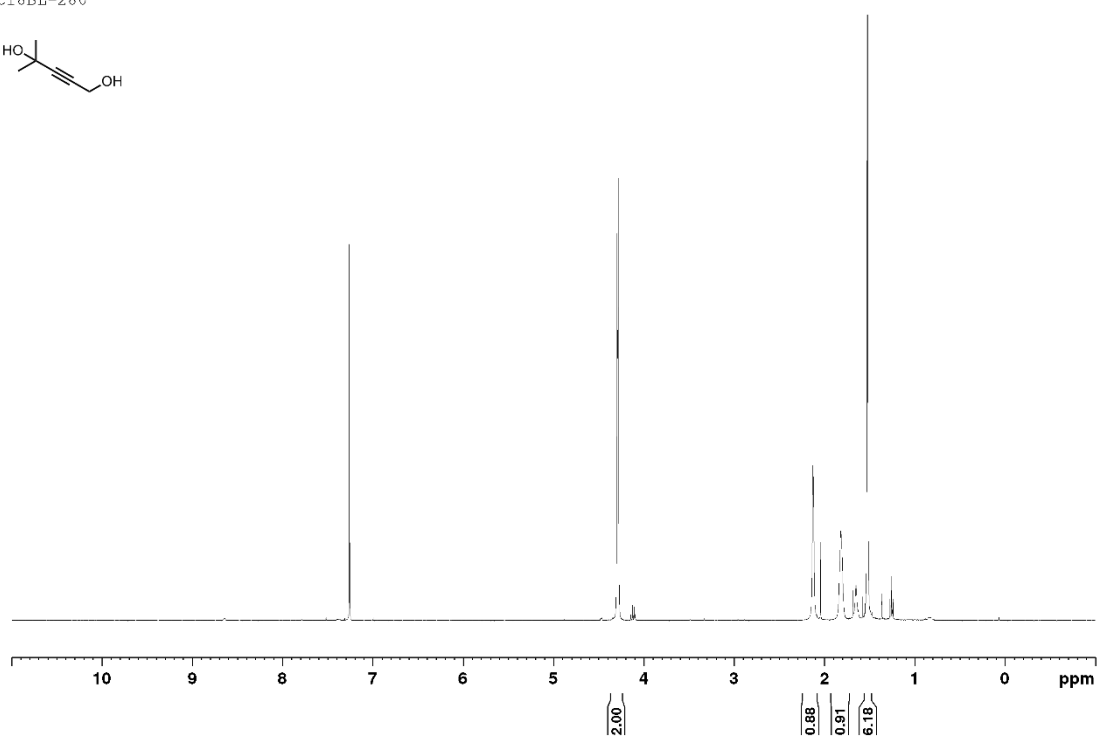
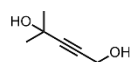
Exact Mass: 114.0681

Molecular Weight: 114.1424

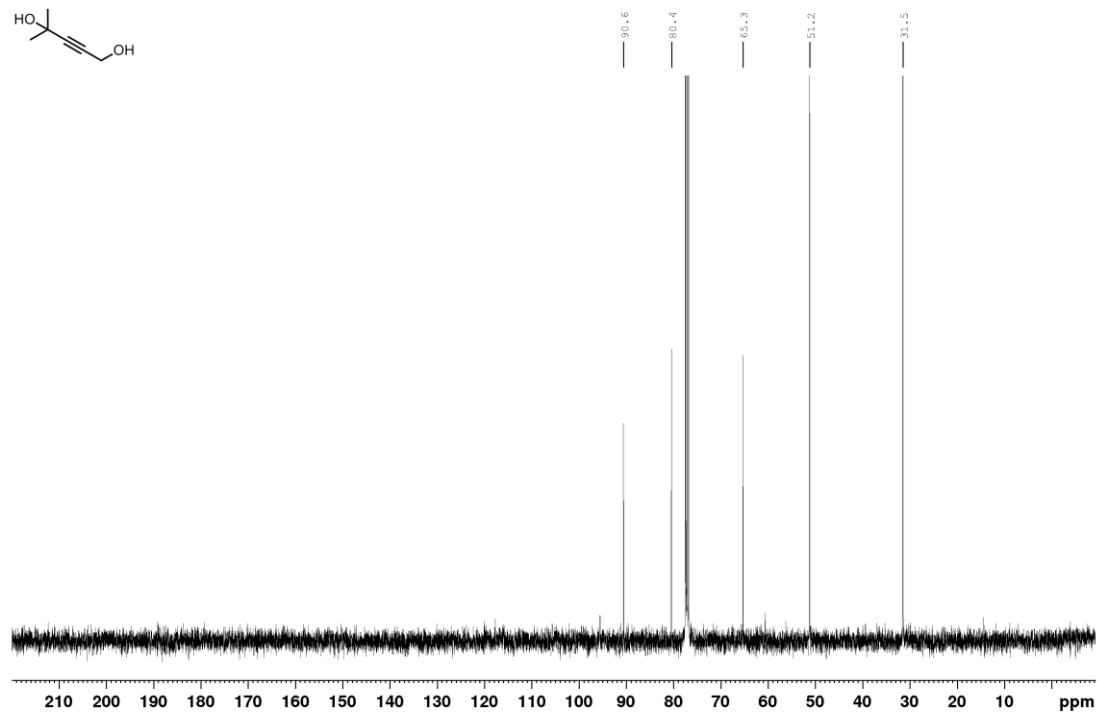
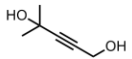
To a solution of **337** (2.00 g, 8.75 mmol, 1 eq.) in MeOH/THF (87.5 mL, 2:1) at ambient temperature was added PPTS (1.10 g, 4.37 mmol, 0.5 eq.). The reaction mixture was stirred at ambient temperature for 12 min and was quenched by addition of NaHCO₃ (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. FC (EtOAc:hexane 2:1) gave the known title compound as colorless oil (852 mg, 85 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 4.29 (d, J = 4.9 Hz, 2H), 2.13 (s, br, 1H), 1.82 (s, br, 1H), 1.52 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 90.6, 80.4, 65.3, 51.2, 31.5.

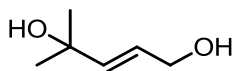
C18BL-280



C18BL-280



339 (E)-4-methylpent-2-ene-1,4-diol

Chemical Formula: C₆H₁₂O₂

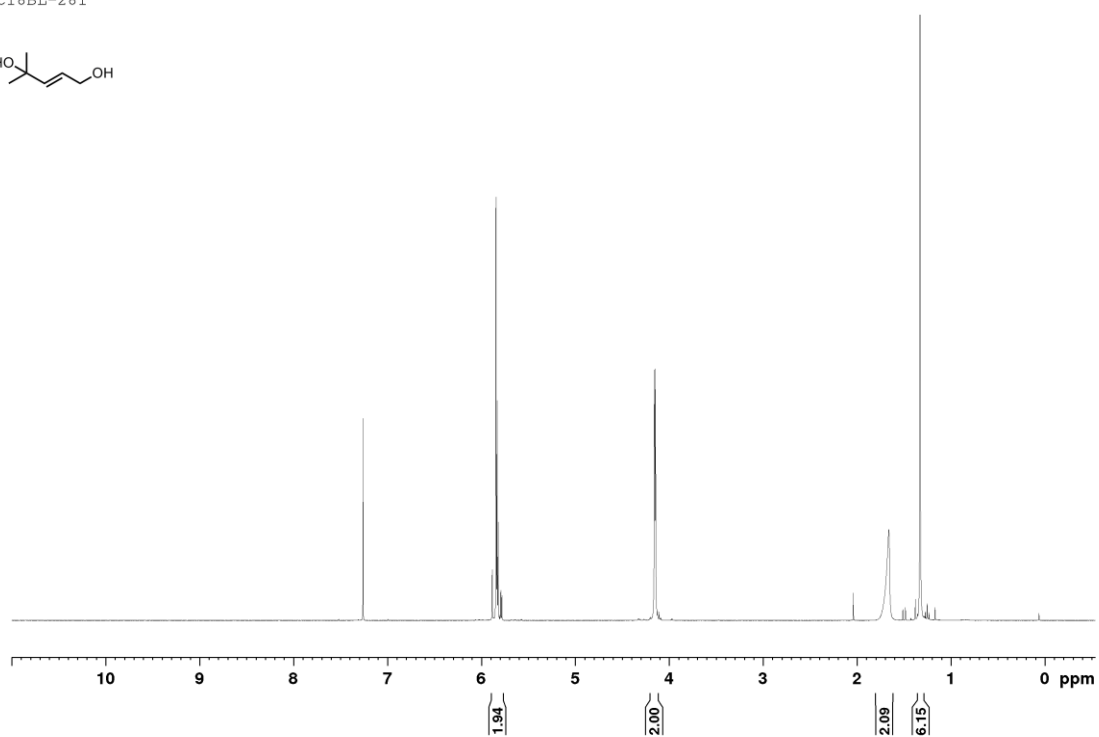
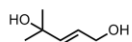
Exact Mass: 116.0837

Molecular Weight: 116.1583

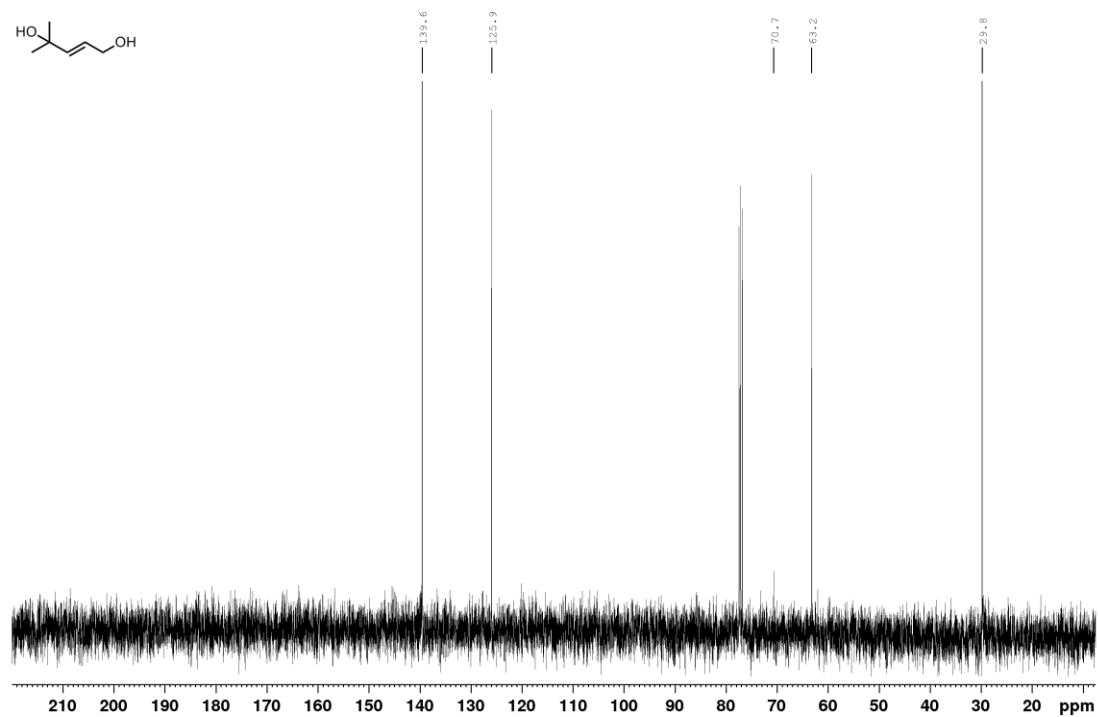
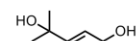
A solution of **338** (0.845 g, 7.40 mmol) in THF (48 mL) was cooled to 0 °C and LiAlH₄ (12.33 mL, 2.4 M in THF, 29.6 mmol, 4 eq.) was added dropwise over 15 min. After complete addition, the mixture was allowed to warm to ambient temperature over 45 min (complete conversion by TLC). The reaction mixture was cooled again to 0 °C and quenched by the addition of EtOAc. Rochelle's salt solution (aq., sat.) was added and the reaction mixture was stirred at ambient temperature for 1 h. The layers were separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄ and concentrated under reduced pressure. FC (EtOAc:hexanes 3:1) gave the known title compound as colorless oil (632 mg, 73 %, single isomer).

¹H NMR: (CDCl₃, 400 MHz) δ = 5.86 (d, *J* = 15.6 Hz, 1H), 5.81 (dd, *J* = 15.6, 4.6 Hz, 1H), 4.15 (d, *J* = 4.1 Hz, 2H), 1.66 (s, br, 2OH), 1.29 (s, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 139.6, 125.9, 70.7, 63.2, 29.8; **Rf-value:** 0.07 (EtOAc:hexanes 1:1), 0.15 (EtOAc:hexanes 3:1)

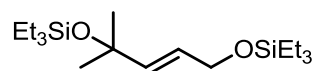
C18BL-281



C18BL-281



340 (E)-3,3,10,10-tetraethyl-5,5-dimethyl-4,9-dioxo-3,10-disiladodec-6-ene

Chemical Formula: C₁₈H₄₀O₂Si₂

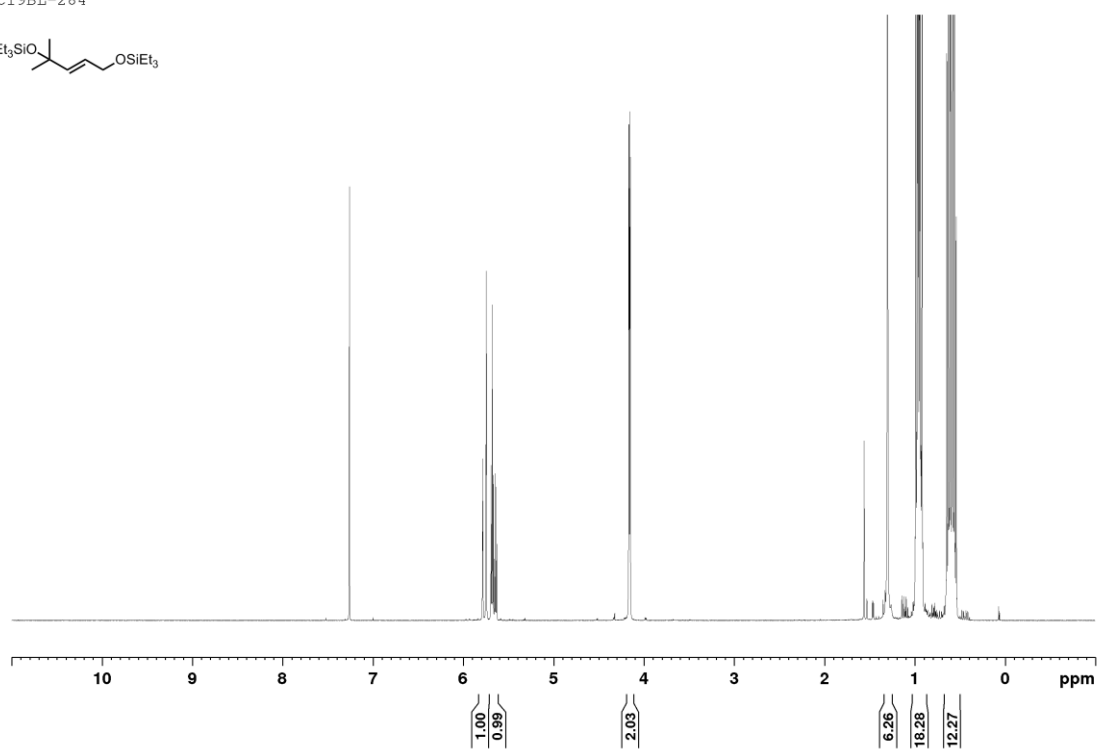
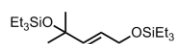
Exact Mass: 344.2567

Molecular Weight: 344.6800

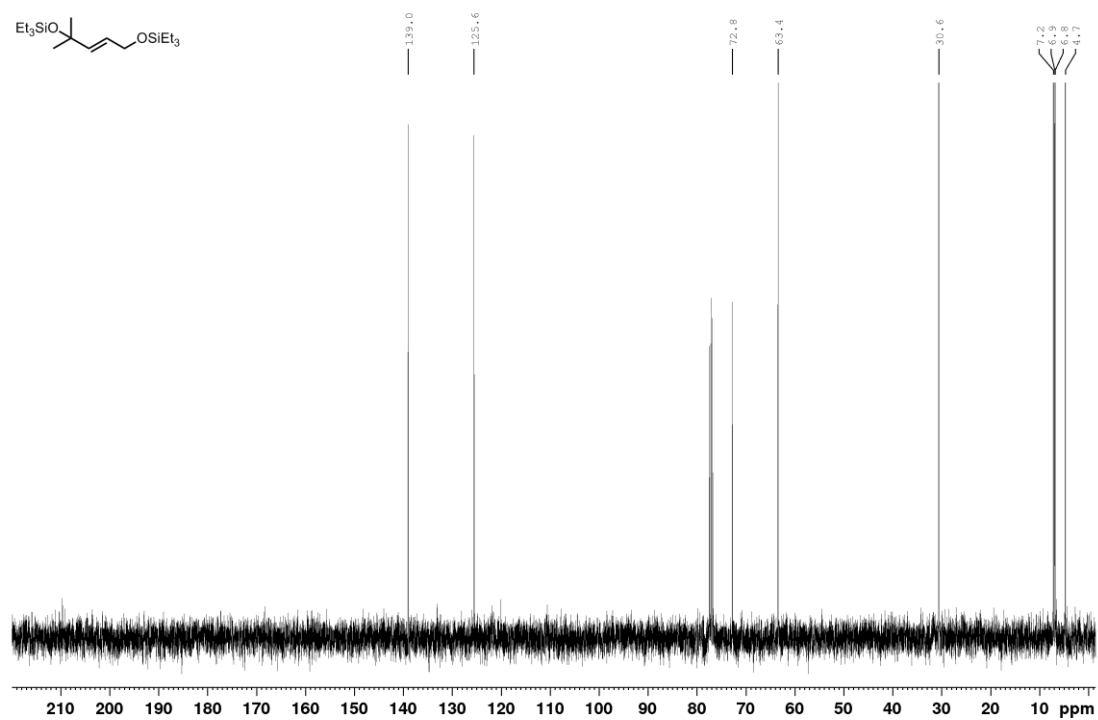
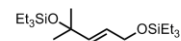
To a solution of **339** (0.100 g, 0.86 mmol, 1 eq.) in CH₂Cl₂ (4.0 ml) at ambient temperature, were added imidazole (0.269 g, 3.96 mmol, 4.6 eq.), DMAP (21 mg, 0.17 mmol, 0.2 eq.) and neat TESCl (0.43 mL, 2.6 mmol, 3.0 eq.). The solution turned from colorless to a white emulsion within minutes. The reaction mixture was stirred at ambient temperature for 1 h 20 min and was diluted with hexanes. It was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. FC (EtOAc:hexane 1:20) gave the title compound as colorless oil (286 mg, 96 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 5.76 (dt, J = 15.5, 1.3 Hz, 1H), 5.66 (dt, J = 15.5, 5.0 Hz, 1H), 1.30 (s, 6H), 0.97 (t, J = 7.9 Hz, 9H), 0.94 (t, J = 7.9 Hz, 9H), 0.61 (q, J = 7.9 Hz, 6H), 0.57 (q, J = 7.9 Hz, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 139.0, 125.6, 72.8, 63.4, 30.6, 7.2, 6.9, 6.8, 4.7; **HRMS (EI):** calc. for [M-C₂H₅]⁺: 315.2170, found 315.2180; **IR (neat):** 2954, 2911, 2877, 1460, 1415, 1377, 1236, 1172, 1149, 1124, 1110, 1040, 1008, 970, 849, 776, 722, 671; **Rf-value:** 0.91 (EtOAc:hexanes 1:10)

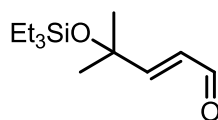
C19BL-284



C19BL-284



13 (E)-4-methyl-4-((triethylsilyl)oxy)pent-2-enal

Chemical Formula: C₁₂H₂₄O₂Si

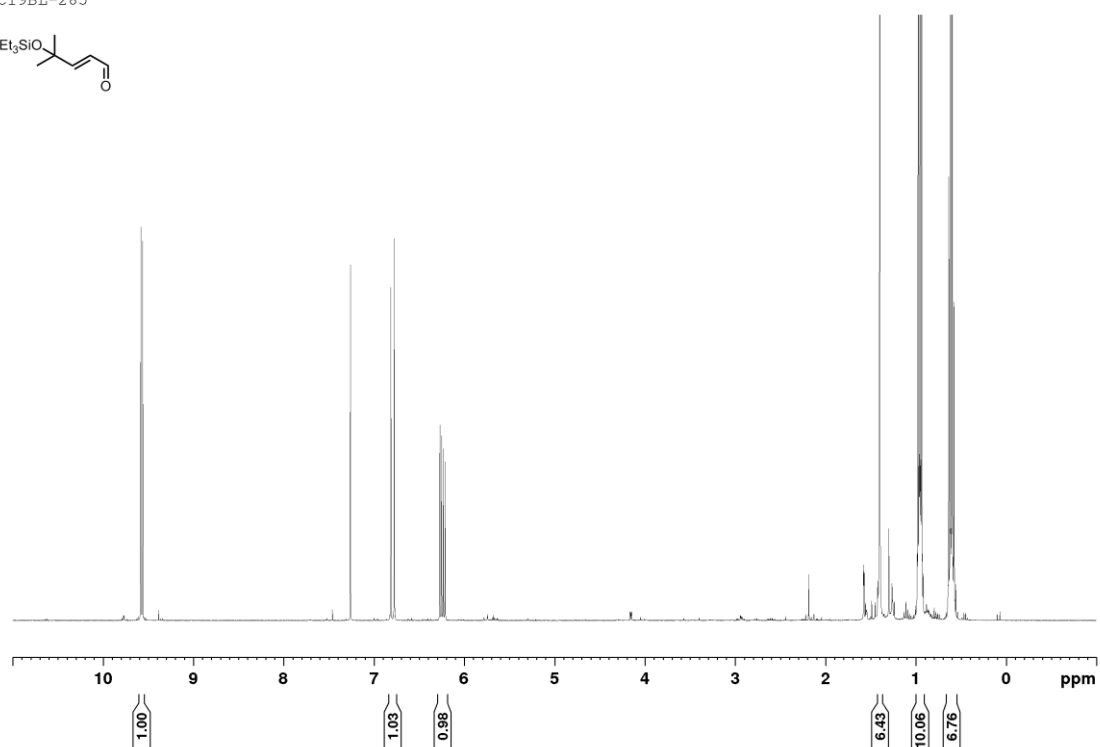
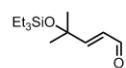
Exact Mass: 228.1546

Molecular Weight: 228.4033

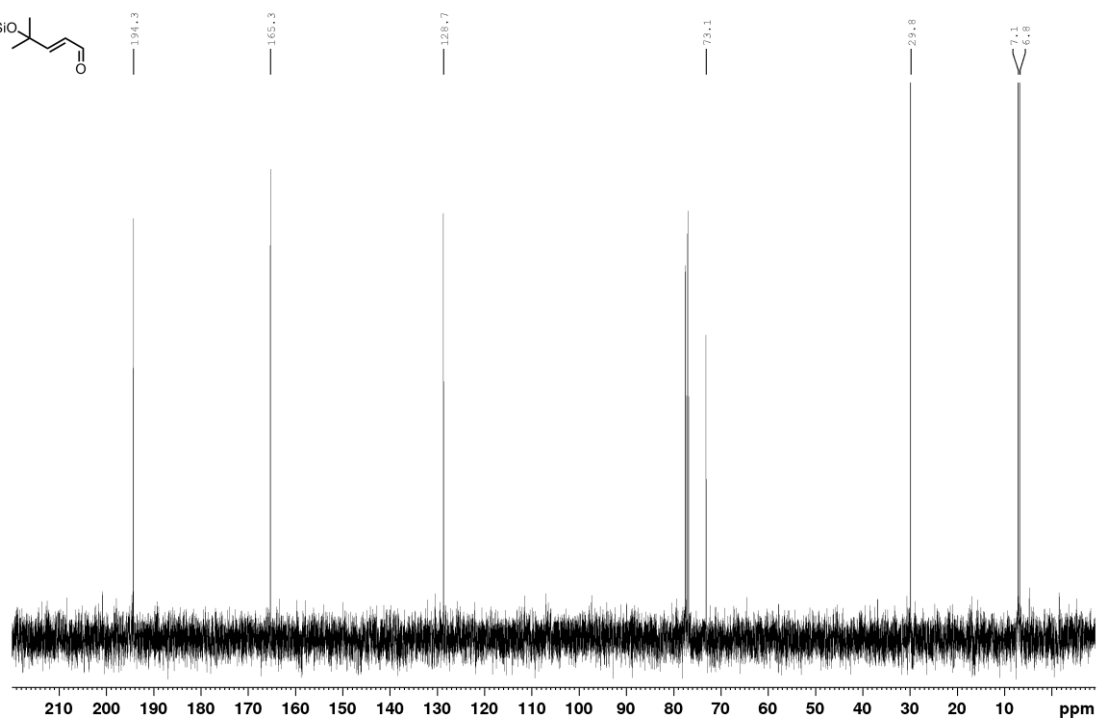
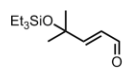
To a solution of (COCl)₂ (0.11 ml, 1.3 mmol, 4.4 eq.) in CH₂Cl₂ (2.0 mL) at -78 °C was added DMSO (0.21 ml, 2.9 mmol, 10 eq.) dropwise. The mixture was stirred for 15 min and a solution of **340** (100 mg, 0.29 mmol, 1.0 eq.) in CH₂Cl₂ (0.9 mL) was added dropwise. After 1 h, Et₃N (0.81 ml, 5.8 mmol, 20 eq.) was carefully added, and the reaction was stirred at -78 °C for 10 min. It was allowed to reach ambient temperature and diluted with water. The two phases were separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. FC (EtOAc:hexanes 1:10) gave the title compound as colorless (46.6 mg, 70 %).

¹H NMR: (CDCl₃, 400 MHz) δ = 9.57 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 15.5 Hz, 1H), 6.24 (dd, *J* = 15.5, 8.0 Hz, 1H), 1.40 (s, 6H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.9 Hz, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 194.3, 165.3, 128.7, 73.1, 29.8, 7.1, 6.8; **HRMS (EI):** calc. for [M-CH₃]⁺: 213.1305, found 213.1306; **IR (neat):** 2956, 2912, 2878, 1692, 1460, 1415, 1380, 1362, 1239, 1163, 1110, 1042, 1007, 974, 883, 722, 674, 593, 559; **Rf-value:** 0.80 (EtOAc:hexanes 1:3).

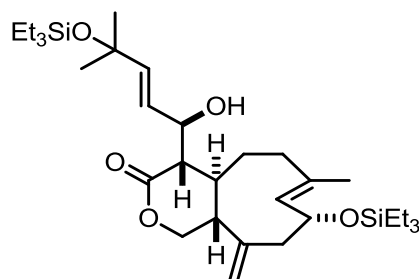
C19BL-285



C19BL-285



341 (4*S*,4*aS*,9*R*,11*aR*,*E*)-4-((*R*,*E*)-1-hydroxy-4-methyl-4-((triethylsilyl)oxy)pent-2-en-1-yl)-7-methyl-11-methylene-9-((triethylsilyl)oxy)-4,4*a*,5,6,9,10,11,11*a*-octahydrocyclonona[*c*]pyran-3(1*H*)-one



Chemical Formula: C₃₂H₅₈O₅Si₂

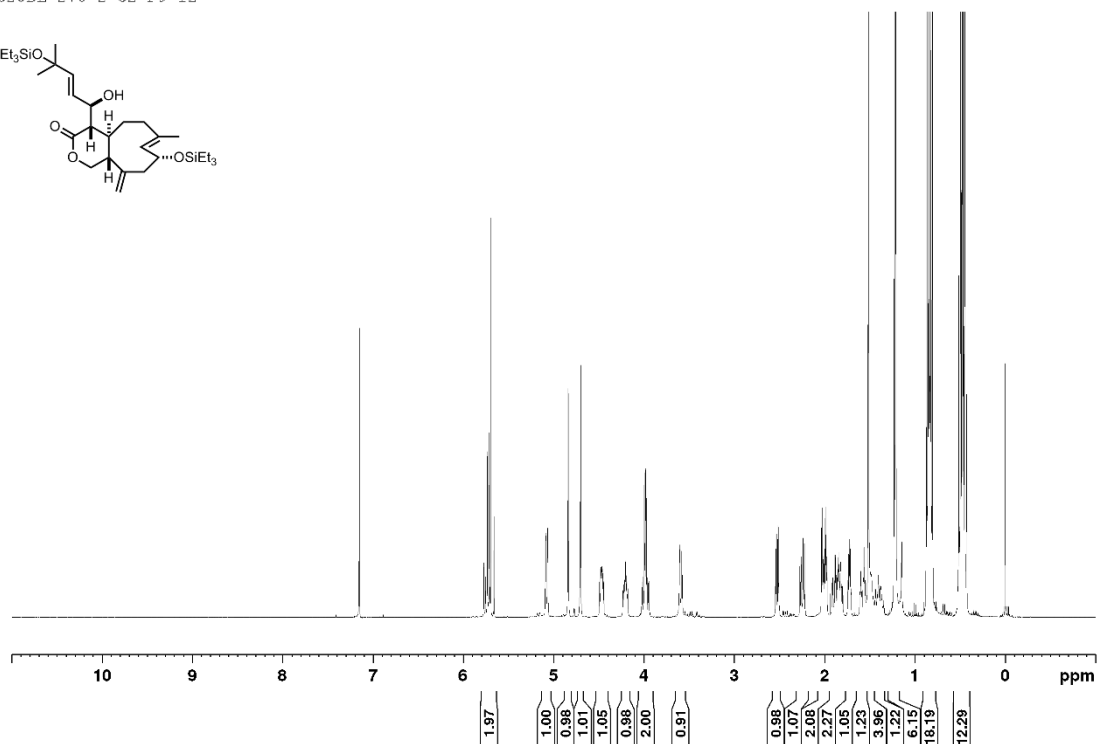
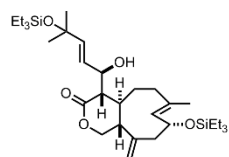
Exact Mass: 578.3823

Molecular Weight: 578.9709

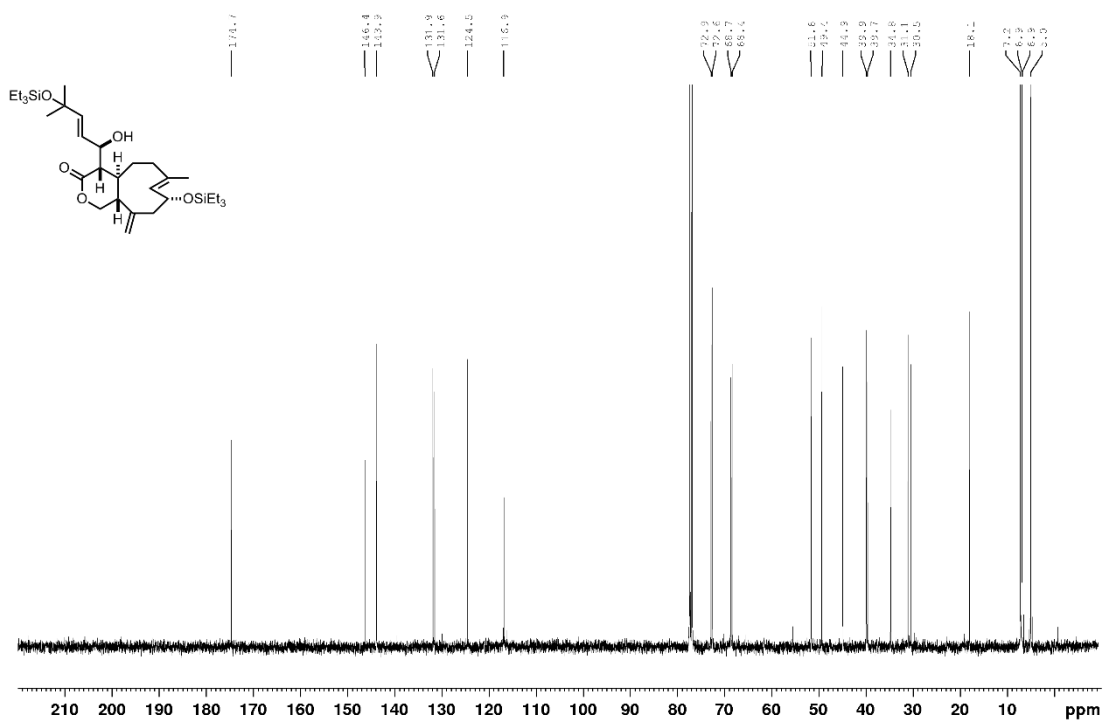
A stock solution of LiHMDS in THF (41.8 mg in 1 mL, 0.25 M) was prepared. An aliquot of this solution (0.66 mL, 2.9 eq.) was transferred to a flame-dried flask, that had been pre-cooled to -78 °C with a dry-ice/acetone bath. A solution of lactone **12** (20 mg, 0.057 μmol, 1 eq.) was slowly added in THF (0.15+2x0.15 mL rinsing). The mixture was stirred for 1 h before a solution of aldehyde **13** (19.1 mg, 0.084 mmol, 1.47 eq) was added dropwise in THF (0.3 mL+2x0.15 mL rinsing). The reaction mixture was stirred for 2 h at -78 °C and then allowed to warm to -10 °C. Conversion did not increase during warming. The reaction was quenched with NH₄Cl (2 mL, sat., aq.) and extracted with Et₂O (3x10 mL). The combined organic extracts were washed with NH₄Cl (2 mL, sat., aq.), brine (2 mL), dried over MgSO₄ and evaporated to dryness. The residue was purified by FC (EtOAc:hexanes 1:5 to 1:3) to recover some starting **12** (8.4 mg, 42%) and give the title compound as a slightly yellow oil (9.7 mg, 29%).

¹H NMR: (CDCl₃, 400 MHz) δ = 5.85 (dd, *J* = 15.4, 7.0 Hz, 1H), 5.78 (d, *J* = 15.4 Hz, 1H), 5.18 (d, *J* = 8.2 Hz, 1H), 4.95 (s, 1H), 4.81 (s, 1H), 4.61-4.54 (m, 1H), 4.35-4.27 (m, 1H), 4.14-4.03 (m, 2H), 3.70 (d, br, *J* = 9.9 Hz, 1H), 2.63 (dd, *J* = 10.0, 3.8 Hz, 1H), 2.36 (dd, *J* = 13.1, 6.0 Hz, 1H), 2.16-2.07 (m, 2H), 2.06-1.85 (m, 2H), 1.88-1.79 (m, 1H), 1.77-1.65 (m, 1H), 1.62 (s, 3H), 1.59-1.44 (m, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 0.94 (dd, *J* = 16.1, 8.0 Hz, 18H), 0.59 (dd, *J* = 15.8, 7.9 Hz, 6H), 0.56 (dd, *J* = 15.9, 7.9 Hz, 6H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 174.7, 146.4, 143.9, 131.9, 131.6, 124.5, 116.9, 72.9, 72.6, 68.7, 68.4, 51.6, 49.4, 44.9, 39.9, 39.7, 34.8, 31.1, 30.5, 18.1, 7.2, 6.9, 6.9, 5.0; **HRMS (ESI):** calc. for [M+Na]⁺: 601.3715, found 601.3713; **IR (neat):** 2950, 2880, 1721, 1458, 1407, 1318, 1233, 1161, 1048, 1008, 873, 822, 729; **[α]_D²⁰** = -44.13 ° (c = 0.92, CH₂Cl₂); **Rf-value:** 0.40 (EtOAc:hexanes 1:3)

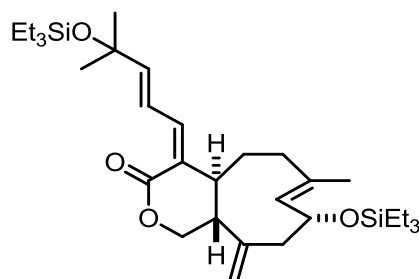
C28BL-278-2-C2-F9-12



C28BL-278-2-C2-F9-12



342 (4Z,4aS,7E,9R,11aR)-7-methyl-4-((E)-4-methyl-4-((triethylsilyl)oxy)pent-2-en-1-ylidene)-11-methylene-9-((triethylsilyl)oxy)-4,4a,5,6,9,10,11,11a-octahydrocyclonona[c]pyran-3(1H)-one



Chemical Formula: $C_{32}H_{56}O_4Si_2$

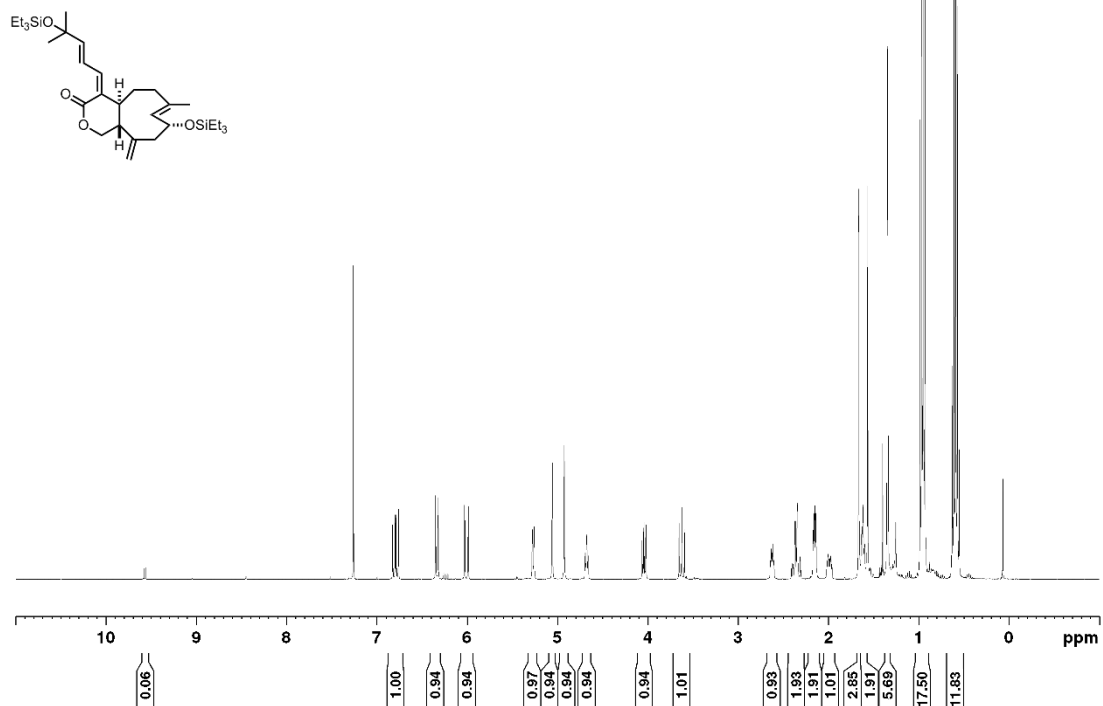
Exact Mass: 560.3717

Molecular Weight: 560.9556

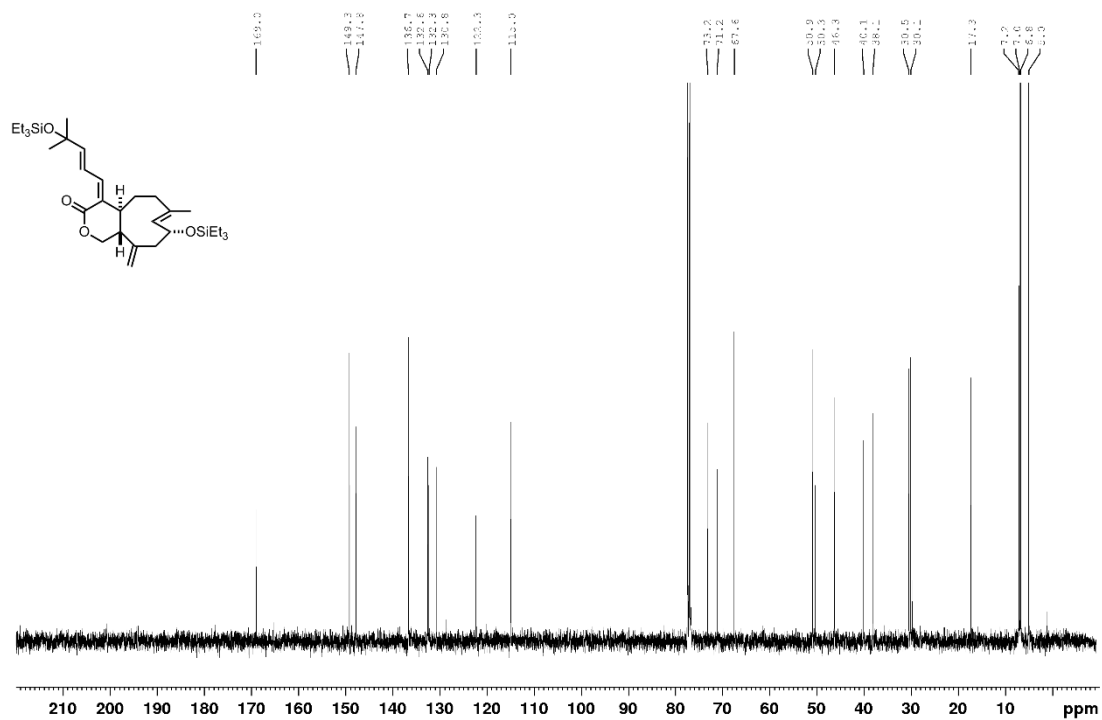
341 (5.4 mg) was dissolved in MePh (0.5 mL). Added was EDC (10 μ L, 5.85 eq., free amine) and a catalytic amount of $CuCl_2$. The mixture was stirred for 26 min at 80 $^{\circ}C$, upon which all the SM had already disappeared. It was let to cool in a water bath, diluted with H_2O (1 mL) and extracted with Et_2O (3x10 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by FC (Et_2O :hexanes 1:9) to give the title compound as a slightly yellow oil (4 mg, 76 %)

1H NMR: ($CDCl_3$, 400 MHz) δ = 6.79 (dd, J = 15.5, 11.1 Hz, 1H), 6.33 (d, J = 11.1 Hz, 1H), 6.01 (d, J = 15.5 Hz, 1H), 5.27 (d, J = 7.4 Hz, 1H), 5.06 (s, 1H), 4.92 (s, 1H), 4.68 (t, J = 6.5 Hz, 1H), 4.04 (dd, J = 11.4, 5.8 Hz, 1H), 3.62 (dd, J = 12.1, 11.6 Hz, 1H), 2.62 (dt, J = 8.6, 3.6 Hz, 1H), 2.38 (dd, J = 13.3, 5.9 Hz, 1H), 2.33 (dd, J = 13.3, 1.6 Hz, 1H), 2.15 (dd, J = 7.6, 5.0 Hz, 2H), 1.99 (dt, J = 12.1, 4.8 Hz, 1H), 1.66 (s, 3H), 1.65-1.58 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H), 0.95 (d, J = 14.8, 7.8 Hz, 18H), 0.60 (dd, J = 15.4, 7.7 Hz, 6H), 0.58 (dd, J = 15.6, 7.7 Hz, 6H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 169.0, 149.3, 147.8, 136.7, 132.6, 132.3, 130.8, 122.3, 115.0, 73.2, 71.2, 67.6, 50.9, 50.3, 46.3, 40.1, 38.1, 30.5, 30.1, 17.3, 7.2, 7.0, 6.8, 5.0; **HRMS (ESI):** calc. for $[M+Na]^+$: 583.3609, found 583.3599; **IR (neat):** 2950, 2880, 1738, 1642, 1458, 1382, 1238, 1156, 1121, 1024, 888, 730; **$[\alpha]^{20}_D$** = -10.00 $^{\circ}$ (c = 0.63, CH_2Cl_2); **Rf-value:** 0.70 ($EtOAc$:hexanes 1:3), 0.46 (Et_2O :hexanes 1:5), 0.25 (Et_2O :hexanes 1:10)

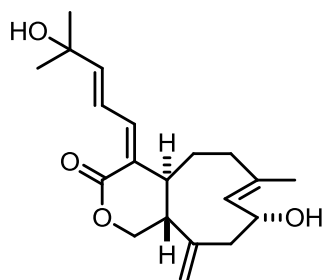
X29BL-286-3-C1



X29BL-286-3-C1



1 isoxeniolide A

Chemical Formula: C₂₀H₂₈O₄

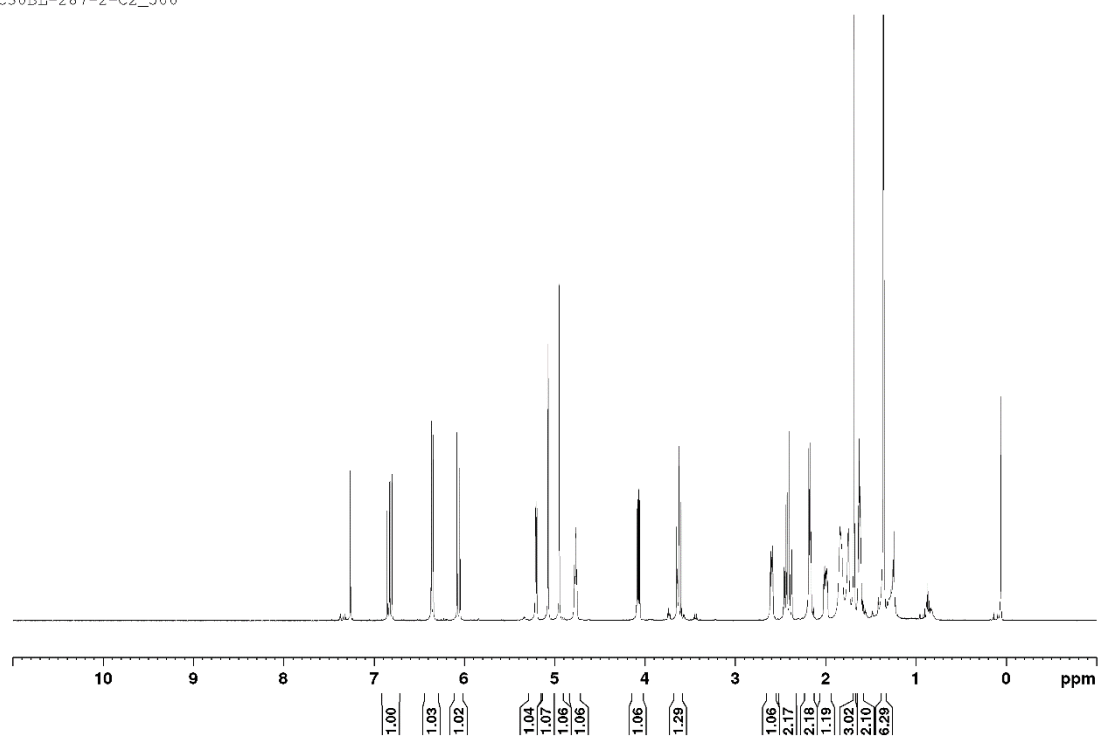
Exact Mass: 332.1988

Molecular Weight: 332.4339

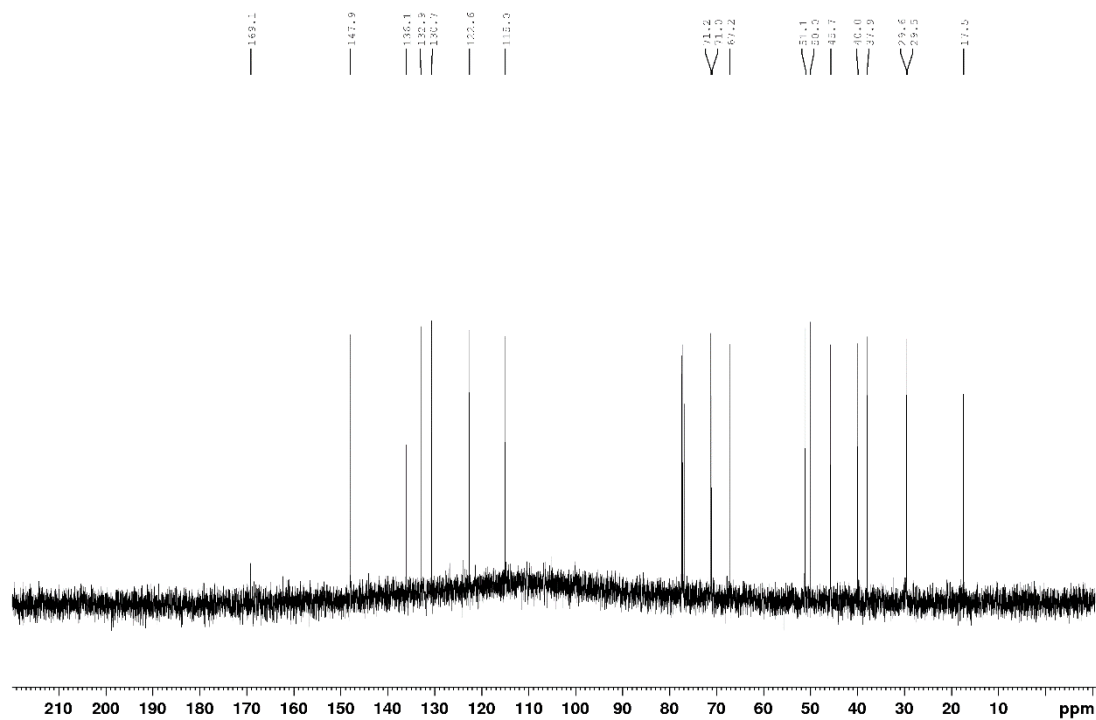
342 (4 mg, 7.1 μ mol, 1 eq.) was dissolved in THF (0.7 mL) and cooled to 0 °C. Added was Et₃N•3HF (0.01 mL, 64 μ mol, 27 eq. fluoride). After stirring the mixture for 20 min at 0 °C, it was warmed to ambient temperature in a water bath. It was stirred for 2 d, quenched with KHCO₃ (1 mL, sat., aq.) and stirred for 20 min. The mixture was extracted with EtOAc (3x10 mL), the combined organic extracts were washed with KHCO₃ (0.5 mL, sat., aq.), brine (1 mL) and dried over MgSO₄. The solvent was removed *in vacuo* and the crude material was purified by FC (acetone:hexanes 3:7) to give the title compound as a yellow solid (3.85 mg, 103 %).

¹H NMR: (CDCl₃, 500 MHz) δ = 6.83 (dd, J = 15.5, 11.1 Hz, 1H), 6.36 (d, J = 11.0 Hz, 1H), 6.06 (d, J = 15.5 Hz, 1H), 5.21 (d, J = 7.3 Hz, 1H), 5.07 (s, 1H), 4.95 (s, 1H), 4.77 (t, J = 6.8 Hz, 1H), 4.07 (dd, J = 11.4, 5.9 Hz, 1H), 3.62 (t, J = 12.0 Hz, 1H), 2.63-2.57 (m, 1H), 2.44 (dd, J = 13.7, 6.1 Hz, 1H), 2.39 (d, J = 13.8 Hz, 1H), 2.23-2.13 (m, 2H), 2.03-1.97 (m, 1H), 1.68 (s, 3H), 1.66-1.58 (m, 2H), 1.67 (2s, 6H); **¹³C NMR:** (CDCl₃, 125 MHz) δ = 169.1, 147.9 (2 signals), 136.1, 132.9, 130.7, 122.6, 115.0, 71.2, 71.0, 67.2, 51.1, 50.0, 45.7, 40.0, 37.9, 29.6, 29.5, 17.5; **HRMS (MALDI):** calc. for [M+Na]⁺: 355.1880, found 355.1880, calc. for [M+K]⁺: 371.1619, found 371.1620; **IR (neat):** 3494, 2924, 1703, 1389, 1272, 1160, 1024, 979, 904, 849, 734, 612, 538; **[α]²⁰_D** = +19.22° (c = 0.385, MeOH); **Rf-value:** 0.10 (acetone:hexanes 3:7), 0.26 (acetone:hexanes 4:6).

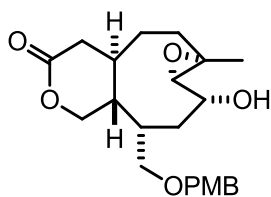
C30BL-287-2-C2_500



C30BL-287-2-C2_500



347 (1a*S*,3a*R*,7a*R*,8*S*,10*R*,10a*S*)-10-hydroxy-8-(((4-methoxybenzyl)oxy)methyl)-1a-methyldecahydrooxireno[2',3':5,6]cyclonona[1,2-*c*]pyran-5(1a*H*)-one



Chemical Formula: C₂₂H₃₀O₆

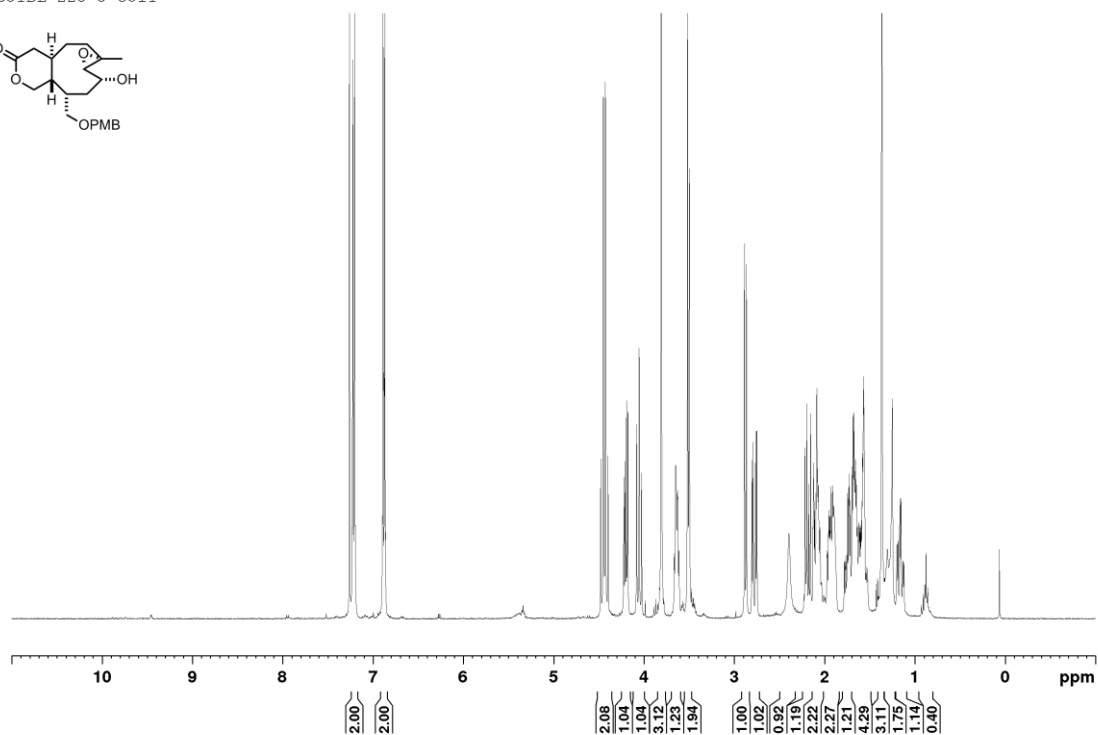
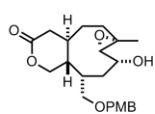
Exact Mass: 390.2042

Molecular Weight: 390.4700

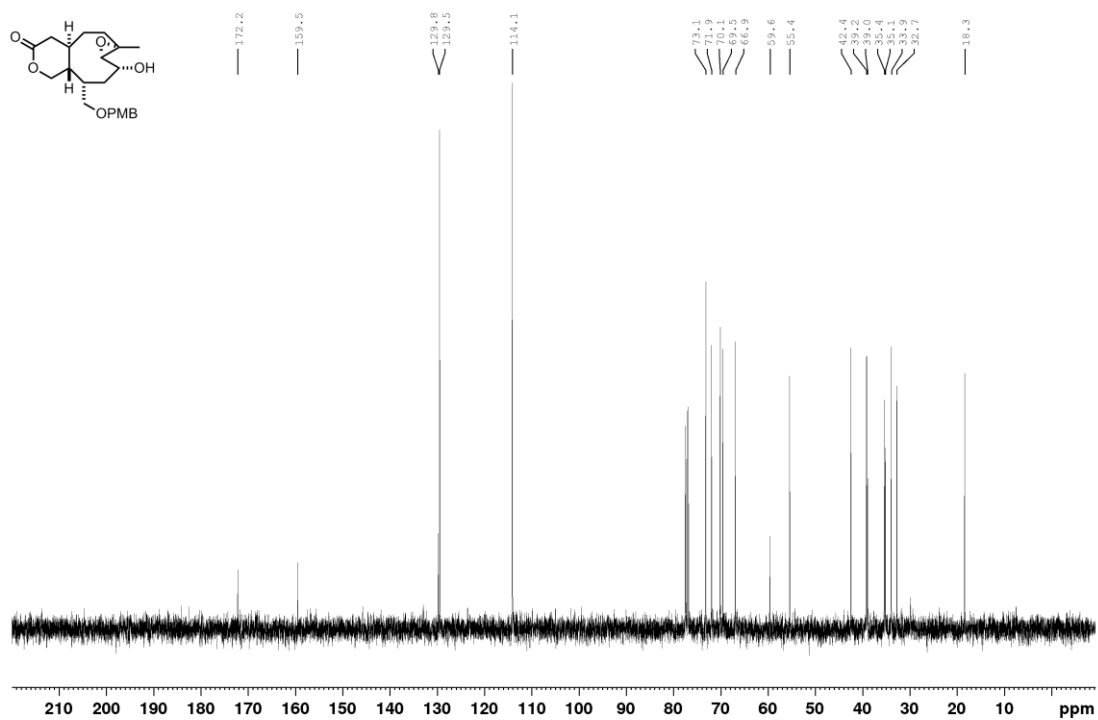
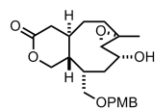
m-CPBA used for this reaction had been purified^[356] 6 month prior and was stored in a plastic centrifuge vial in the freezer. To a solution of **10** (15.4 mg, 41.1 μmol, 1 eq.) and anhydrous Na₂HPO₄ (13.2 mg, 92.5 μmol, 2.25 eq.) in CH₂Cl₂ (2.0 mL) at 0 °C was added *m*-CPBA (10.4 mg, 61.6 μmol, 1.5 eq.) in one portion. The mixture was stirred at this temperature for 17 min, diluted with EtOAc (10 mL) and quenched with Na₂S₂O₃ (2.7 mL, aq., sat.) and NaHCO₃ (2.6 mL, aq., sat.). It was stirred for 30 min and after separation of the phases, extracted with EtOAc (2x10 mL). The combined organic phases were washed first with NaHCO₃ (2.6 mL, aq., sat.), then brine (2 mL), dried over anhydrous MgSO₄, and evaporated *in vacuo*. Purified by FC (EtOAc:hexanes 8:1) to give the title compound as a clear, colorless oil (15.8 mg, 98%).

¹H NMR: (CDCl₃, 400 MHz) δ = 7.25-7.18 (m, 2H), 6.92-6.84 (m, 2H), 4.44 (dd, *J* = 11.6, 20.6 Hz, 2H), 4.20 (q, *J* = 5.8 Hz, 1H), 4.05 (t, *J* = 11.12 Hz, 1H), 3.81 (s, 3H), 3.68-3.60 (m, 1H), 3.51 (d, br, *J* = 7.4 Hz, 2H), 2.88 (d, *J* = 8.7 Hz, 1H), 2.78 (dd, *J* = 5.6, 16.1 Hz, 1H), 2.39 (s, br, 1H, OH), 2.19 (dd, *J* = 8.0, 16.2 Hz, 1H), 2.14-2.02 (m, 2H), 1.99-1.85 (m, 2H), 1.80-1.50 (m, 4H), 1.37 (s, 3H), 1.16 (td, *J* = 13.0, 4.8 Hz, 1H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 172.2, 159.5, 129.8, 129.5, 114.1, 73.1, 71.9, 70.1, 69.5, 66.9, 59.6, 55.4, 42.4, 39.2, 39.0, 35.4, 35.1, 33.9, 32.7, 18.3; **HRMS (ESI-TOF):** calc. for [M+Na]⁺, 413.1935 found 413.1934; **IR (neat):** 3430, 2927, 2861, 1731, 1611, 1586, 1513, 1457, 1388, 1364, 1335, 1302, 1245, 1174, 1081, 1060, 1032, 931, 815, 752, 712, 662; **[α]_D²⁰ = +40.38 °** (c = 0.78, CH₂Cl₂); **Rf-value:** 0.26 (EtOAc:hexanes 3:1)

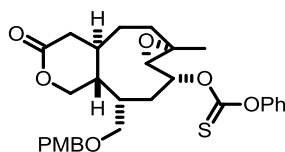
C31BL-223-3-col1



C31BL-223-3-col1/4



348 O-((1a*S*,3a*R*,7a*R*,8*S*,10*R*,10a*S*)-8-(((4-methoxybenzyl)oxy)methyl)-1a-methyl-5-oxododecahydrooxireno[2',3':5,6]cyclonona[1,2-*c*]pyran-10-yl) O-phenyl carbonothioate



Chemical Formula: C₂₉H₃₄O₇S

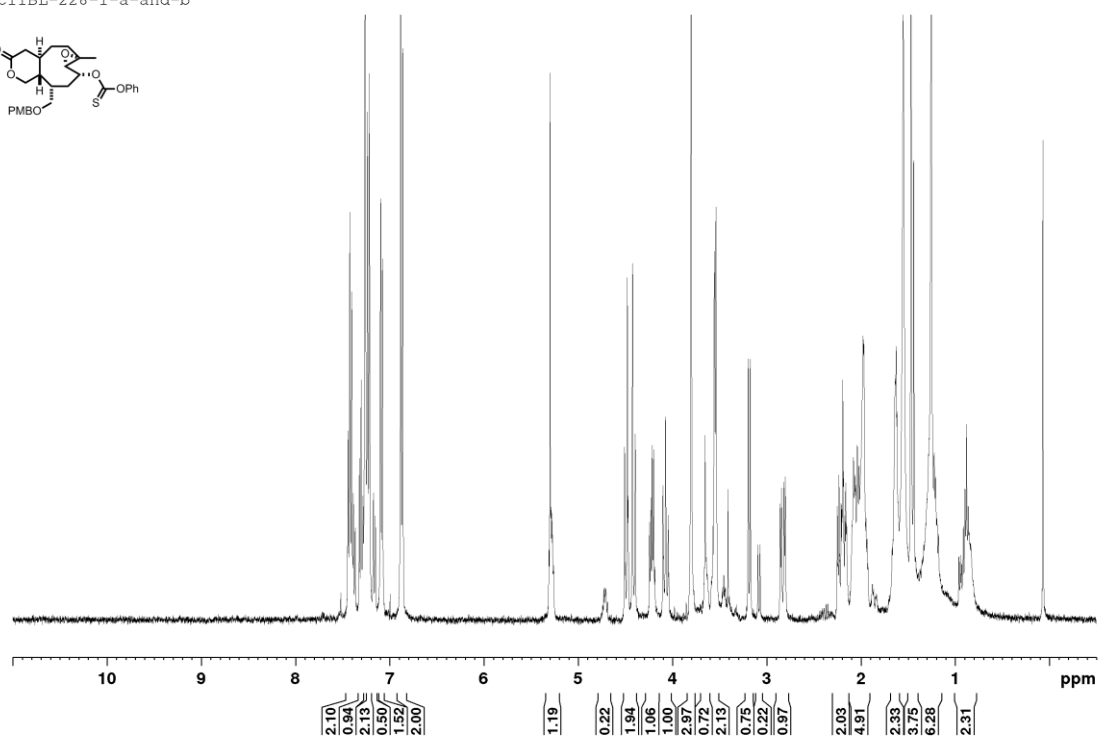
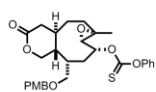
Exact Mass: 526.2025

Molecular Weight: 526.6411

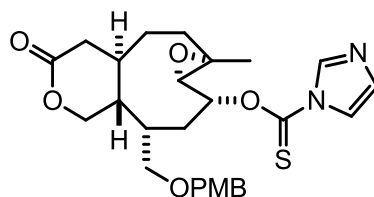
347 (3.9 mg, 10 μ mol, 1 eq.) was dissolved pyridine (0.1 mL) and added was O-Phenyl chlorothionoformate (5.2 mg, 3 eq.). The mixture quickly turned strong yellow and a precipitate formed. CH₂Cl₂ (0.2 mL) was used to rinse down the walls of the flask. The mixture was stirred for 14 h, evaporated and directly purified by FC (EtOAc:hexanes 3:1 to 1:1 to neat EtOAc) to give the title compound as a yellow solid (3.1 mg, 59%). The ¹H NMR signals 3.18 and 3.08 indicate that the compound might have partly isomerized or decomposed.

¹H NMR: (CDCl₃, 400 MHz) δ = 7.47-7.34 (m, 2H), 7.34-7.27 (m, 1H), 7.25-7.20 (m, 2H), 7.19-7.14 (m, 0.5H), 7.12-7.06 (m, 1.5H), 5.32-5.25 (m, 1H), 4.52-4.38 (m, 2H), 4.21 (quintet, J = 5.6 Hz, 1H), 4.07 (t, J = 11.1 Hz, 1H), 3.80 (s, 3H), 3.60-3.51 (m, 2H), 3.18 (d, J = 8.8 Hz, 0.75H), 3.08 (d, J = 8.8 Hz, 0.25H), 2.83 (dd, J = 15.9, 5.4 Hz, 1H), 2.30-2.12 (m, 2H), 2.12-2.91 (m, 5H), 1.69-1.60 (m, 2H), 1.50-1.39 (m, 4H); **Rf-value:** 0.52 (EtOAc:hexanes 3:1)

C11BL-228-1-a-and-b



17 O-((1aS,3aR,7aR,8S,10R,10aS)-8-(((4-methoxybenzyl)oxy)methyl)-1a-methyl-5-oxododecahydrooxireno[2',3':5,6]cyclonona[1,2-c]pyran-10-yl) 1H-imidazole-1-carbothioate



Chemical Formula: $C_{26}H_{32}N_2O_6S$

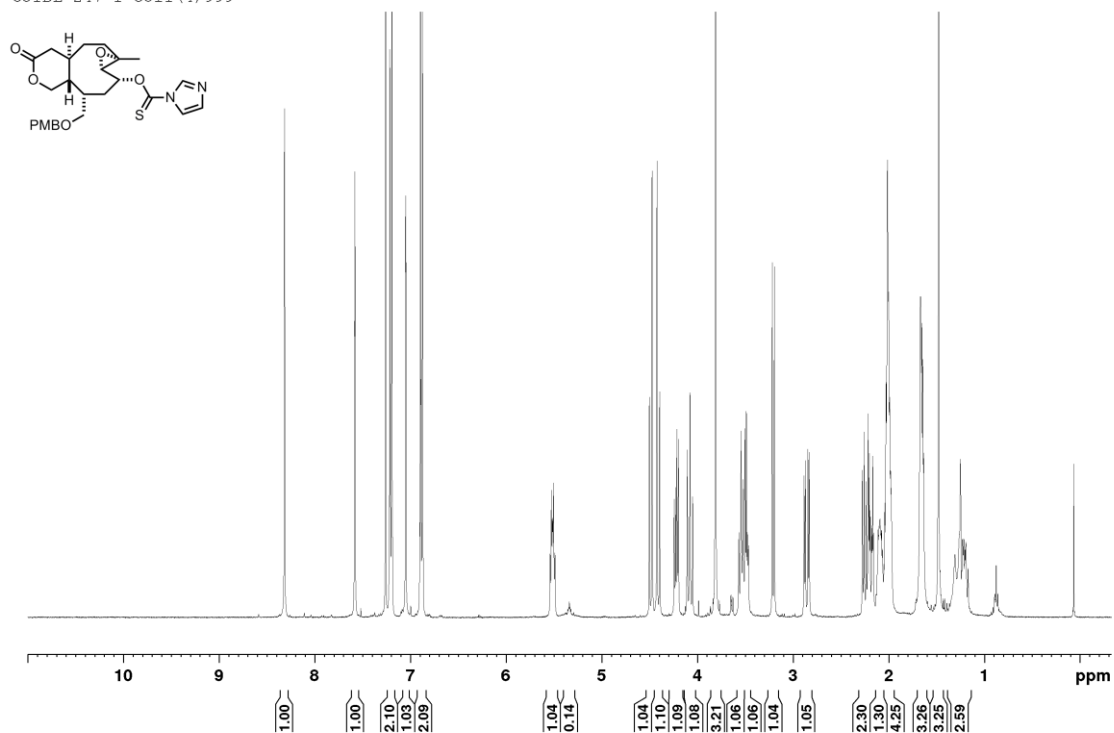
Exact Mass: 500.1981

Molecular Weight: 500.6071

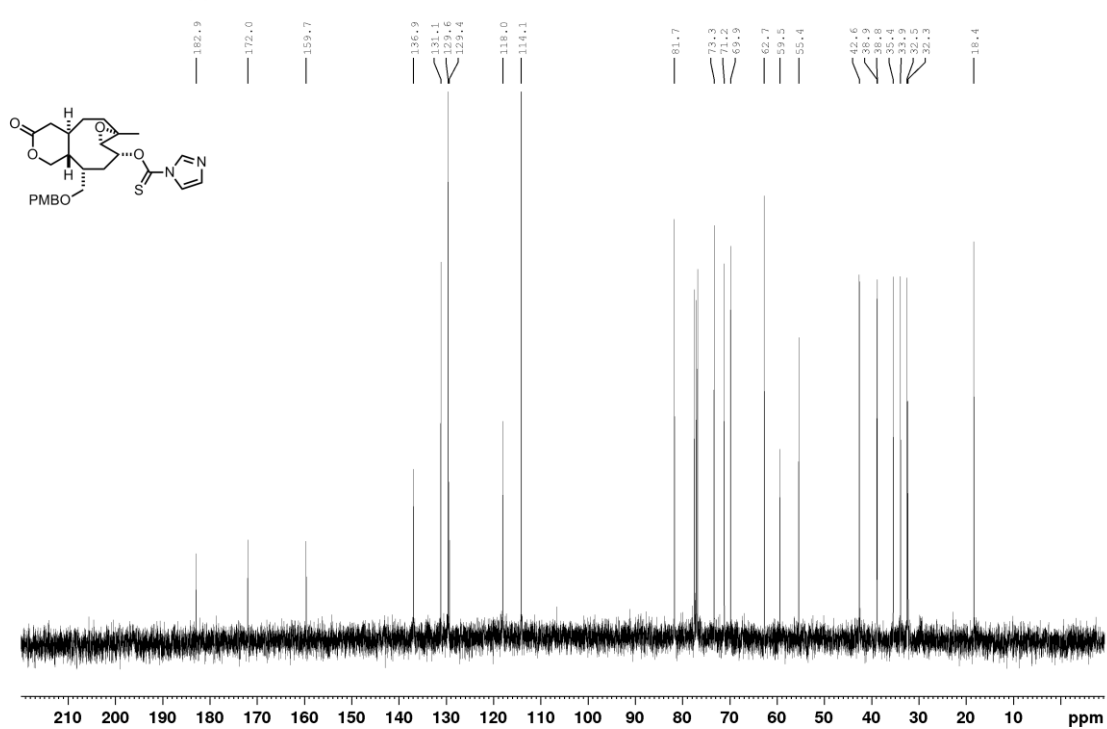
347 (15.6 mg, 40 μ mol, 1 eq.) was dissolved in CH_2Cl_2 (0.4 mL) in an HPCL vial and DMAP (3 mg, 20 μ mol, 0.5 eq.) was added. Solid thiocarbonyldiimidazole (21.2 mg, 0.12 mmol, 3 eq.) was added and the mixture was stirred at ambient temperature for 13 h. The yellow solution was evaporated to dryness and directly purified by FC (EtOAc:hexanes 6:4 to 3:1) to give the title compound as a colorless oil (17.4 mg, 88%).

1H NMR: ($CDCl_3$, 400 MHz) δ = 8.32 (t, J = 0.9 Hz, 1H), 7.58 (t, J = 1.4 Hz, 1H), 2.24-2.17 (m, 2H), 7.05 (q, J = 0.8 Hz, 1H), 6.91-6.56 (m, 2H), 5.55-5.48 (m, 1H), 4.45 (apparent dd, higher order, apparent J = 32.0, 11.5 Hz, 2H), 4.22 (dd, J = 11.7, 6.1 Hz, 1H), 4.07 (t, J = 11.1 Hz, 1H), 3.81 (s, 3H), 3.54 (t, J = 9.0 Hz, 1H), 3.51-3.45 (m, dd-like 1H), 3.21 (d, J = 8.9 Hz, 1H), 2.86 (dd, J = 15.9, 5.6 Hz, 1H), 2.24 (dd, J = 16.0, 7.4 Hz, 1H), 2.18 (dt, J = 13.4, 3.5 Hz, 1H), 2.14-2.05 (m, 1H), 2.05-1.95 (m, 4H), 1.70-1.60 (m, 2H), 1.48 (s, 3H), 1.38-1.14 (m, 2H); **^{13}C NMR:** ($CDCl_3$, 100 MHz) δ = 182.9, 172.0, 159.7, 136.9, 131.1, 129.6, 129.4, 118.0, 114.1, 81.7, 73.3, 71.2, 69.9, 62.7, 59.5, 55.4, 42.6, 38.9, 38.8, 35.4, 33.9, 32.5, 32.3, 18.4; **HRMS (ESI-TOF):** calc. for $[M+Na]^+$: 523.1873, found 523.1872; **IR (neat):** 2923, 2855, 2358, 2331, 1742, 1669, 1611, 1512, 1465, 1386, 1327, 1283, 1228, 1173, 1084, 1028, 973, 816, 749, 655; **$[\alpha]^{20}_D$** = -2.61° (c = 1.19, $CHCl_3$); **Rf-value:** 0.31 (EtOAc:hexanes 3:1)

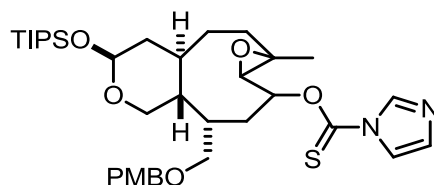
C31BL-247-1-coll\4/999



C31BL-247-1-coll\4/999



16 O-((3aR,5S,7aR,8S)-8-(((4-methoxybenzyl)oxy)methyl)-1a-methyl-5-((triisopropylsilyl)oxy)dodecahydrooxireno[2',3':5,6]cyclonona[1,2-c]pyran-10-yl) 1H-imidazole-1-carbothioate



Chemical Formula: $C_{35}H_{54}N_2O_6SSi$

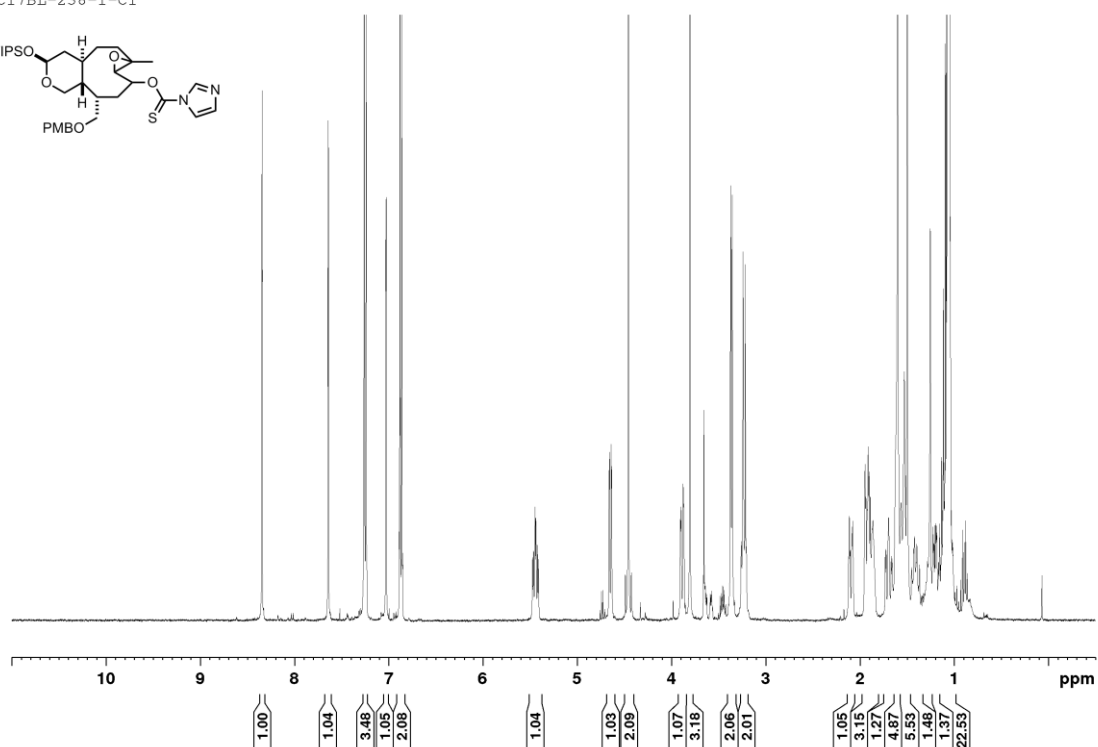
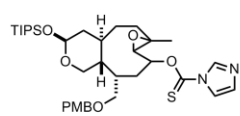
Exact Mass: 658.3472

Molecular Weight: 658.9636

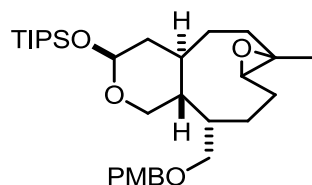
324 (6 mg, 10.0 μ mol, 1 eq.) was dissolved in CH_2Cl_2 (0.11 mL) in an HPCL vial and DMAP (6 mg, 0.43 eq.) was added. Solid thiocarbonyldiimidazole (5.8 mg, 3 eq.) was added and the mixture was stirred at ambient temperature overnight. It was evaporated to dryness and directly purified by FC (Et_2O /hexanes 6:4) to give the title compound as a yellow solid (6 mg, 83%).

1H NMR: ($CDCl_3$, 400 MHz) δ = 8.34 (t, J = 0.9 Hz, 1H), 7.64 (t, J = 1.4 Hz, 1H), 7.28-7.23 (m, 2H), 7.03 (q, J = 0.8 Hz, 1H), 6.90-6.84 (m, 2H), 5.44 (td, J = 10.6, 3.7 Hz, 1H), 4.65 (dd, J = 9.0, 1.9 Hz, 1H), 4.46 (s, 2H), 3.87 (dd, J = 11.5, 3.0 Hz, 1H), 3.80 (s, 3H), 3.36 (d, J = 7.1 Hz, 2H), 3.27-3.19 (m, 2H), 2.14-2.06 (m, 1H), 1.98-1.81 (m, 3H), 1.75-1.64 (m, 1H), 1.64-1.57 (m, 2H), 1.57-1.47 (m, 5H), 1.47-1.34 (m, 1H), 1.24-1.15 (m, 1H), 1.15-0.98 (m, 21H); **Rf-value:** 0.49 ($EtOAc$:hexanes 1:1), 0.16 (Et_2O :hexanes 6:4)

C17BL-238-1-C1



350 Triisopropyl(((3aR,5S,7aR,8S)-8-(((4-methoxybenzyl)oxy)methyl)-1a-methyldodecahydrooxireno[2',3':5,6]cyclonona[1,2-c]pyran-5-yl)oxy)silane



Chemical Formula: $C_{31}H_{52}O_5Si$

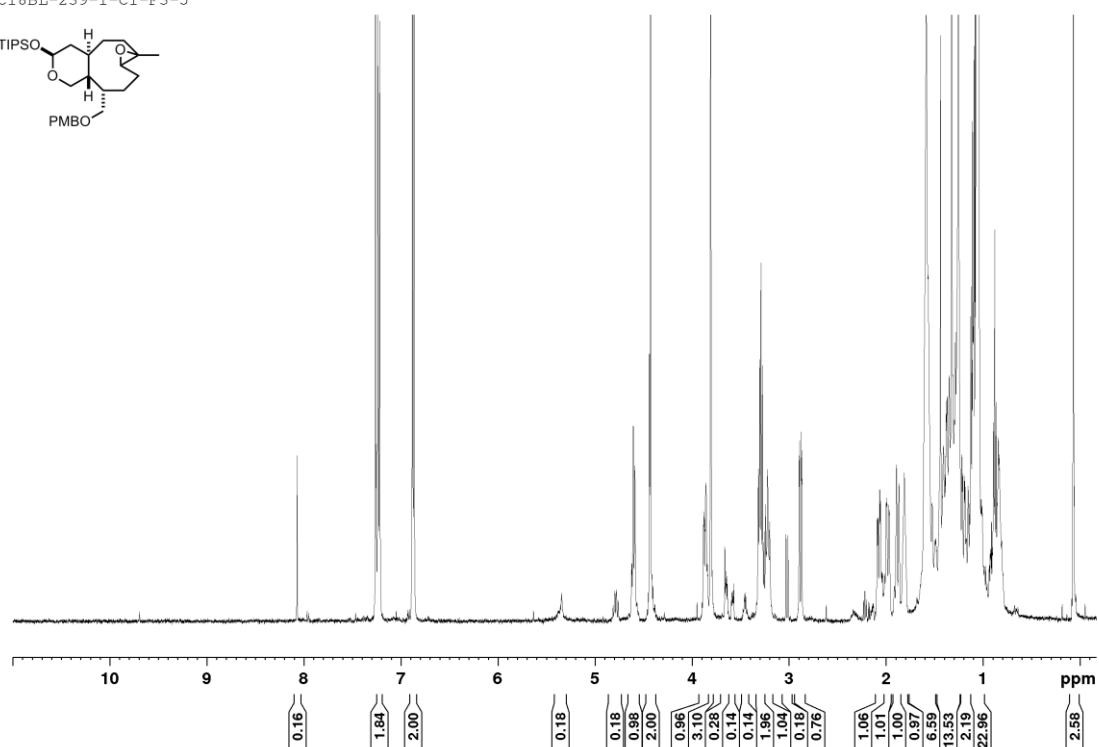
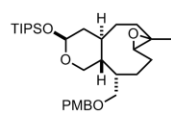
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Molecular Weight: 532.8271

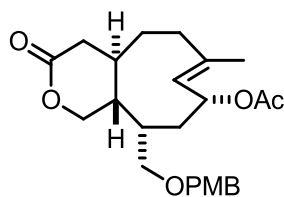
16 (3 mg, 4.6 μ mol, 1 eq.) was put under an atmosphere of argon and dissolved in benzene (0.25 mL). Neat Bu_3SnH (2.6 μ L, 2.2 eq.) was added, followed by Et_3B (10 μ L, 2.2 eq., 1 M in hexanes, Aldrich). The mixture was stirred for 2 h 30 min. The reaction was quenched with $NaHCO_3$ (1 mL, aq., sat.) and extracted with Et_2O (3*5 mL). the combine dorganic phases were washed with brine (1 mL), dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. Purified by FC (1:1 Et_2O :hexanes to neat Et_2O to neat $EtOAc$) gave the title compound as a clear colorless oil (2 mg, 82 %).

1H NMR: ($CDCl_3$, 500 MHz) δ = 7.25-7.20 (m, 2H), 6.90-6.85 (m, 2H), 4.64-4.55 (m, 1H), 4.47-4.37 (m, 2H), 3.90-3.83 (m, 1H), 3.81 (s, 3H), 3.34-3.25 (m, 2H), 3.25-3.17 (m, 1H), 3.02 (d, J = 10.1 Hz, 0.2 H), 2.88 (dd, J = 11.4, 2.2 Hz, 0.8 H), 2.11-2.02 (m, 1H), 2.02-1.95 (m, 1H), 1.93-1.85 (m, 1H), 1.23-1.13 (m, 2H), 1.13-0.95 (m, 21H) The signals in the middle of the aliphatic region 1.85-1.23 could not be interpreted due to impurities and too many signals; **Rf-value:** 0.75 ($EtOAc$:hexanes 1:1).

C18BL-239-1-C1-F3-5



18 (4aR,9R,11S,11aR,E)-11-(((4-methoxybenzyl)oxy)methyl)-7-methyl-3-oxo-1,3,4,4a,5,6,9,10,11,11a-decahydrocyclonona[c]pyran-9-yl acetate



Chemical Formula: C₂₄H₃₂O₆

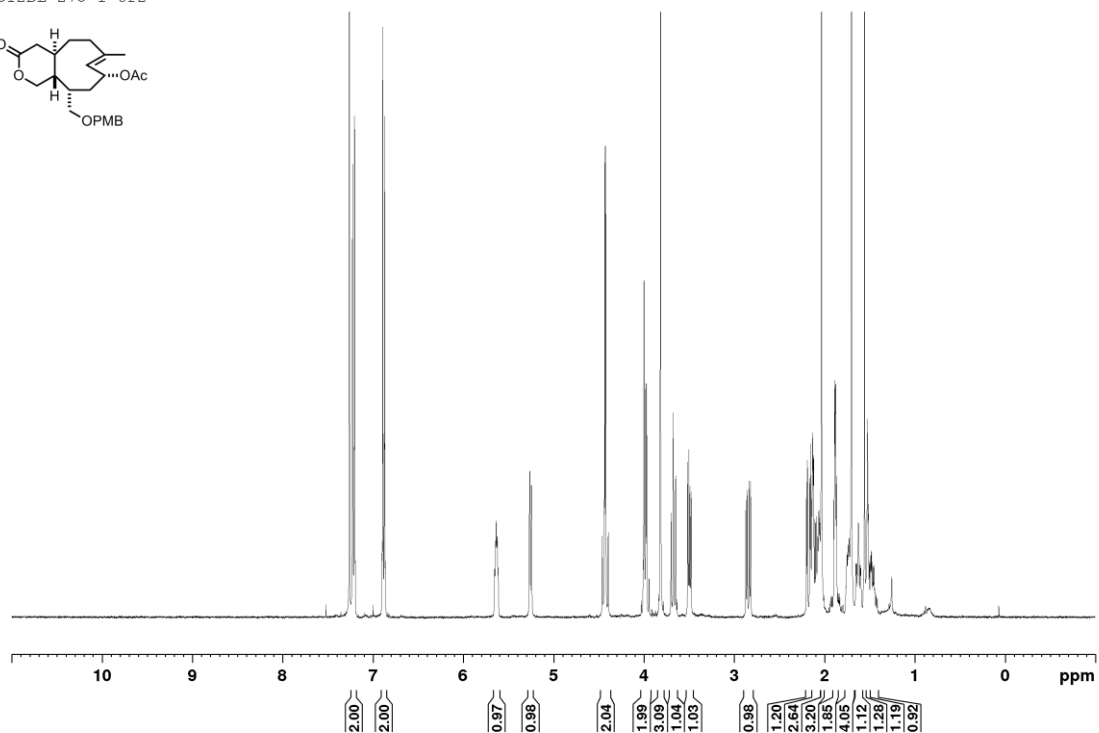
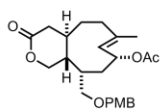
Exact Mass: 416.2199

Molecular Weight: 416.5073

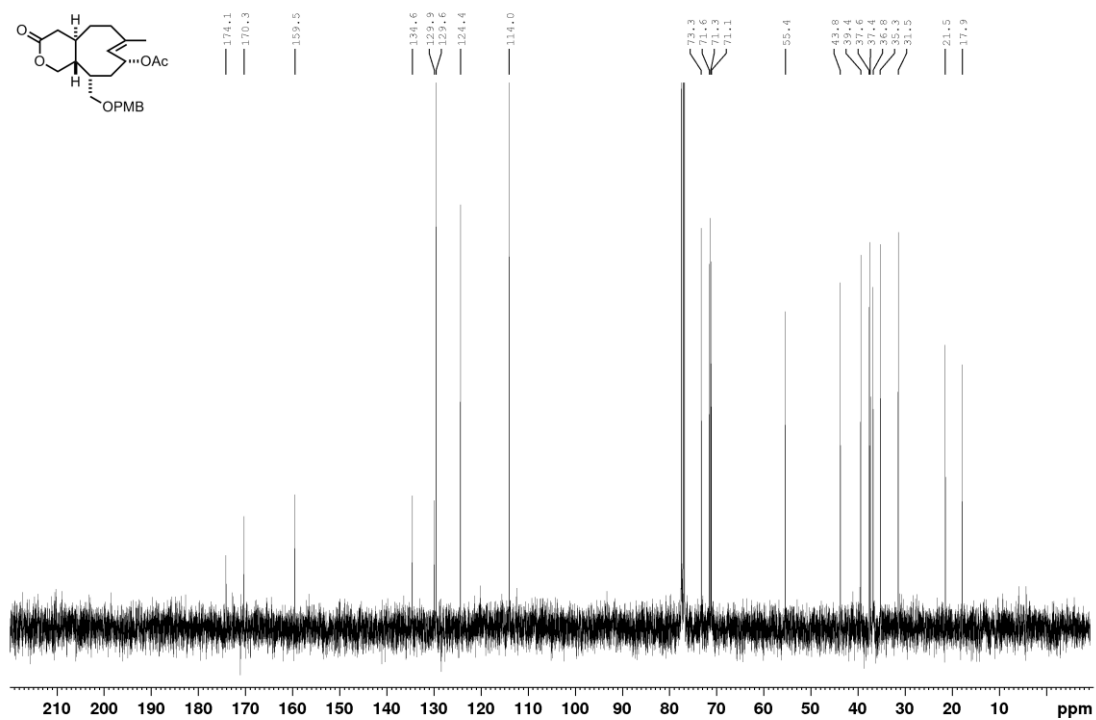
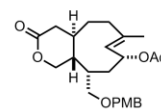
Allylic alcohol **10** (50.3 mg, 134 μ L, 1 eq.) was dissolved in CH₂Cl₂ (1.4 mL) and cooled to -15 °C in an ice bath. DMAP (12.6 mg, 0.77 eq.) was added, followed by Et₃N (0.06 mL, 3.2 eq.) and acetic anhydride (0.03 mL, 2.36 eq.). The mixture was left to warm to 11 °C over 1.5 h (around 80% conversion by TLC) and to ambient temperature overnight. It was stirred for a total of 14 h, transferred into a vigorously stirred solution of saturated aqueous sodium hydrogen carbonate (1 mL) and the reaction vessel was rinsed with CH₂Cl₂ (10 mL). After stirring for 30 min, no more bubbling was observable. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic solution was washed with N₄HCl (1 mL), brine (1 mL), dried over MgSO₄ and evaporated to dryness. The residue was purified by FC (silica gel, EtOAc:hexanes 1:3 to 9:11) to deliver the clean title compound (48.6 mg, 87%) as a clear colorless oil.

¹H NMR: (CDCl₃, 400 MHz) δ = 7.24-7.19 (m, 2H), 6.91-6.85 (m, 2H), 5.66-5.60 (m, 1H), 5.25 (d, J = 7.5 Hz, 1H), 4.43 (higher order spins system, dd-like, 2H), 4.03-3.93 (m, 2H), 3.81 (s, 3H), 3.67 (t, J = 10.1 Hz, 1H), 3.49 (dd, J = 9.7, 5.0 Hz, 1H), 2.84 (dd, J = 14.7, 5.9 Hz, 1H), 2.17 (dd, J = 14.7, 4.0 Hz, 1H), 2.15-2.04 (m, 3H), 2.03 (s, 3H), 1.91-1.85 (m, 2H), 1.78-1.70 (m, 1H), 1.70 (s, 3H), 1.66-1.58 (m, 1H), 1.54-1.40 (m, 2H); **¹³C NMR:** (CDCl₃, 100 MHz) δ = 174.1, 170.3, 159.5, 134.6, 129.9, 129.6, 124.4, 114.0, 73.3, 71.6, 71.3, 71.1, 55.4, 43.8, 39.4, 37.6, 37.4, 36.8, 35.3, 31.5, 21.5, 17.9; **HRMS (ESI-TOF):** calc. for [M+Na]⁺: 439.2091, found 439.2092; **IR (neat):** 2928, 2858, 1730, 1612, 1512, 1437, 1369, 1330, 1300, 1241, 1171, 1151, 1082, 1028, 962, 917, 855, 818, 730; **[α]_D²⁰** = +6.35 ° (c = 0.63, CH₂Cl₂); **Rf-value:** 0.28 (EtOAc:hexanes 1:1), 0.22 (EtOAc:hexanes 2:3)

C12BL-273-1-tr2



C12BL-273-1-tr2



6 Bibliography

*“This paper will no doubt be found interesting
by those who take an interest in it”*

John Dalton

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