MAX-PLANCK-INSTITUT FÜR KOHLENFORSCHUNG

technische universität dortmund

# Totalsynthese von Limaol

**Dissertation**

Zur Erlangung des akademischen Grades eines
Doktors der Naturwissenschaften
(Dr. rer. nat.)
Der Fakultät für Chemie und Chemische Biologie
der Technischen Universität Dortmund

vorgelegt von
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Mülheim an der Ruhr, Mai 2022

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1. Berichterstatter: Prof. Dr. Alois Fürstner
2. Berichterstatter: Prof. Dr. Norbert Krause

Die vorliegende Arbeit entstand unter der Anleitung von Prof. Dr. Alois Fürstner in der Zeit von November 2018 bis Mai 2022 am Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. Teile dieser Arbeit wurden bereits veröffentlicht:

Hess, S. N.; Mo, X.; Wirtz, C.; Fürstner, A. Total Synthesis of Limaol. *J. Am. Chem. Soc.* **2021**, *143* (6), 2464-2469.

Die praktischen Arbeiten erfolgten zum Teil in Zusammenarbeit mit Dr. Xiaobin Mo und Tristano Martini. Die beschriebenen Ergebnisse bilden eine vollständige Darstellung dieser gemeinsamen Arbeiten. Die von diesen Mitarbeitern alleinverantwortlich erzielten Ergebnisse wurden als solche an entsprechender Stelle gekennzeichnet.

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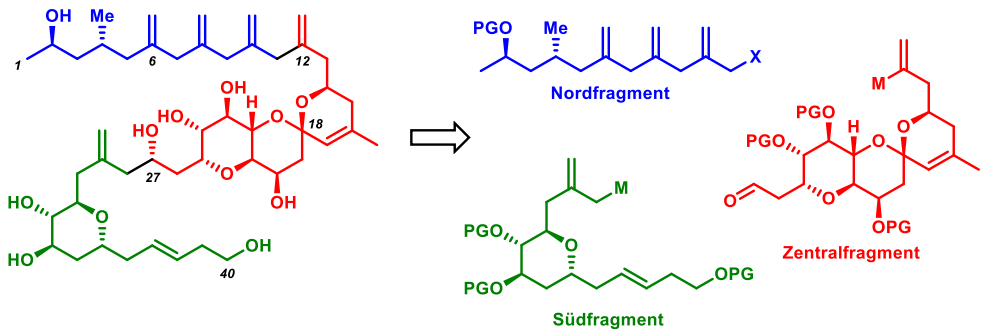
Abschließend möchte ich meinen Eltern, meinem Bruder, und meinen vielen guten Freunden in Augsburg und Umgebung für ihre tatkräftige Unterstützung herzlichst danken.

**Inhalt:**

Die Totalsynthese ist eine Kerndisziplin der organischen Chemie. Sie ermöglicht eine gründliche Prüfung synthetischer Methoden und dient gleichzeitig als Quelle für neue Transformationen. Darüber hinaus ermöglicht sie einen vereinfachten Zugang zu größeren Mengen an spärlich verfügbaren, bioaktiven Naturstoffen und beschleunigt so Innovationen in Biologie und Medizin.

Dinoflagellate bilden eine besonders vielfältige Gruppe von Meeresorganismen, sowohl morphologisch als auch biochemisch. Diese Algen produzieren komplexe Polyketide wie die Brevetoxine, die Amphidinolide und die Okadasäure. Limaol fügte sich 2017 in die Reihe dieser interessanten Moleküle ein, als es aus dem benthischen Dinoflagellaten *Prorocentrum lima* isoliert wurde. Es ist ein C40-Polyketid mit auffälligen Strukturmerkmalen wie vier nicht-konjugierten *exo*-Methylengruppen im nördlichen Teil und einem chiralen Spiroketalkern.

Die in dieser Dissertation vorgestellte Arbeit beschreibt die Synthese von Limaol. Aufgrund der Größe des Zielmoleküls wurde ein fragmentbasierter Ansatz gewählt. Retrosynthetisch wurde das Molekül in drei Bausteine von ungefähr gleicher Komplexität aufgeteilt, was eine konvergente Synthese ermöglichte. Das nördliche Fragment sollte durch eine Allyl-Alkenyl-Kreuzkupplung zwischen dem nördlichen Trien-Allylelektrophil und einem Alkenyl-Nukleophil, das den Rest des Zielmoleküls bildet, eingeführt werden. Das zentrale und das südliche Fragment würden durch eine asymmetrische Allylierung vereinigt, wobei gleichzeitig die Stereochemie an C27 gesetzt wird.




Das nördliche Fragment wurde ausgehend von einem 1,4-Dien-haltigen Allylelektrophil, das über eine Baylis–Hillman-Reaktion synthetisiert wurde, in einem bidirektionalem Ansatz aufgebaut. Das Elektrophil wurde an ein Alkenylzink-Nukleophil gekoppelt, das in mehreren Schritten von Propylenoxid abgeleitet wurde, um das gewünschte nicht-konjugierte Trien zu erhalten. Die Umwandlung eines primären Silylethers in ein Acetat vervollständigte die Konstruktion des Nordfragments für die geplante finale Allyl-Alkenyl-Kreuzkupplung.

Die Synthese des zentralen Teils begann mit $\alpha$-D-Glucopyranosylpentaacetat, das durch selektive Allylierung, Standard-Schutzgruppenmodifikationen, asymmetrische Propargylierung und Sonogashira-Kreuzkupplung mit einem von Epichlorhydrin abgeleiteten Keton-tragenden

Alkenyliodid zu einem Enin verarbeitet wurde. Eine Gold-katalysierte Spiroketalisierung und Lemieux–Johnson-Oxidation eines terminalen Olefins lieferten das tricyclische, zentrale Aldehydfragment.

Der südliche Teil wurde aus Tri-*O*-acetyl-D-glucal hergestellt, das in ein Allyl-2-desoxy-C-glucosid umgewandelt wurde. Eine Kettenverlängerung durch Olefin-Kreuzmetathese und Blei-vermittelte oxidative Dehydroxymethylierung ergab das anomere Acetat, das nach selektiver Allylierung das Allylchlorid-tragende 2,6-*trans*-Tetrahydropyran lieferte. Die nukleophile Substitution mit Tributylstannyl-Lithium ergab das entsprechende Allylstannan.

Die Lewis-Säure-vermittelte Allylierung des Zentralfragment-Aldehyds mit dem südlichen Allylstannan verlief entgegen der nach dem Cram-Chelat-Modell erwarteten Stereoselektivität. Die Stereochemie an C27 wurde *a posteriori* durch Mitsunobu-Inversion korrigiert. Das Keton-Verbindungsstück wurde zunächst in das Alkenyltriflat und dann in das Alkenylstannan umgewandelt, das unter milden Bedingungen eine Stille-Kreuzkupplung mit dem nördlichen Allylacetat durchlief. Die globale Entschützung des resultierenden nicht-konjugierten Tetraens ergab Limaol in einer Gesamtausbeute von 1,5% über 20 Schritte der längsten linearen Sequenz, ausgehend von $\alpha$-D-Glucopyranosylpentaacetat. Insgesamt wurden auf diese Weise 3,3 mg Limaol hergestellt.

In dem Bestreben, die Materialausbeute für biologische Tests zu erhöhen, wurde eine Synthese der zweiten Generation entwickelt. Die größten Engpässe des ersten Ansatzes waren auf die ungünstige Sterik des Zentralfragments zurückzuführen. Ein Wechsel der Schutzgruppen sollte die Stereoselektivität der allylativen Fragmentkopplung umkehren sowie die wenig ergiebige Alkenylstannanbildung und die träge globale Entschützung verbessern. In die Syntheseroute des Zentralfragments wurden daher zwei Umschützungsschritte aufgenommen. Darüber hinaus konnte das nördliche Fragment auf effizientere Weise hergestellt werden, indem käufliches 4,6-Dimethyl-2-pyron durch asymmetrische Hydrierung, Ringöffnung des Lactons und Silylierung in ein bekanntes Zwischenprodukt der nördlichen Fragmentsynthese konvertiert wurde.

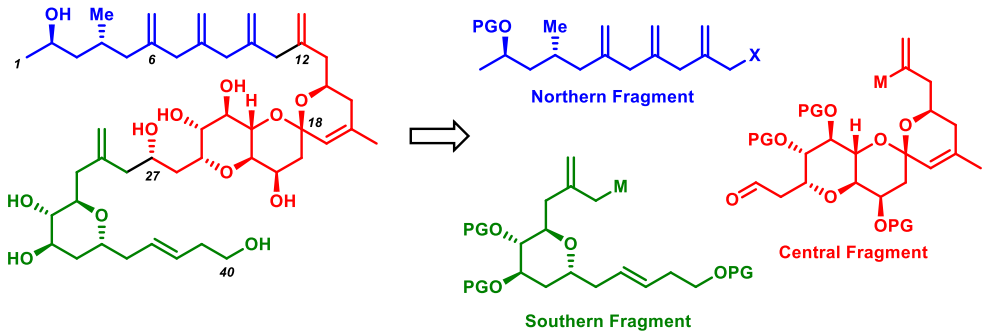
Die Fragmentkopplung zwischen dem Zentralfragment-Aldehyd und dem Südfragment-Allylstannan konnte nun mit der gewünschten Stereoselektivität durchgeführt werden, wodurch die Mitsunobu-Inversion vermieden wurde. Darüber hinaus konnte das Alkenylstannan nun aus dem entsprechenden terminalen Alkin gewonnen werden, was die Selektivität und Ausbeute erheblich verbesserte. Nach der finalen Fragmentvereinigung durch eine Stille-Kreuzkupplung ergab die Deacetylierung und darauffolgende Desilylierung Limaol in insgesamt 7,0% Ausbeute über 19 Schritte in längster linearer Sequenz ausgehend von $\alpha$-D-Glucopyranosylpentaacetat. Dies bedeutet eine Vervierfachung der Ausbeute gegenüber dem Ansatz der ersten Generation. Darüber hinaus erwies sich die überarbeitete Route als skalierbar und lieferte 277 mg Limaol in einem Durchgang.

**Abstract:**

The total synthesis of natural products is among the core disciplines of organic chemistry. It enables thorough scrutiny of synthetic methods and simultaneously functions as a rich source for new transformations itself. Additionally, it allows for improved access to scantily available bioactive compounds of natural origin, accelerating innovation in both biology and medicine.

Dinoflagellates form an especially diverse group of marine organisms, morphologically as well as biochemically. These algae produce complex polyketides such as the brevetoxins, the amphidinolides, and okadaic acid. Limaol joined the ranks of these interesting molecules in 2017, when it was isolated from the benthic marine dinoflagellate *Prorocentrum lima*. It is a C40-polyketide with striking structural features such as an array of four skipped *exo*-methylene groups in its northern section and a chiral spiroketal core.

The work presented in this thesis describes the total synthesis of limaol. Due to the size of the target, a fragment-based approach was chosen. Retrosynthetically, the molecule was split into three building blocks of approximately equal complexity, allowing for a convergent synthesis. The northern fragment would be introduced by an allyl-alkenyl cross-coupling between the northern triene allyl electrophile and an alkenyl nucleophile comprising the rest of the target molecule. The central and southern fragments would be united by an asymmetric allylation, concomitantly setting the stereochemistry at C27.




In a forward sense, the northern fragment was assembled in a two-directional approach, starting from a 1,4-diene-containing allyl electrophile synthesized *via* a Baylis–Hillman reaction. It was coupled to an alkenylzinc nucleophile derived in several steps from propylene oxide to give the desired all-skipped triene. Conversion of the terminus to the allyl acetate completed the construction of the electrophile for the envisioned final allyl-alkenyl cross-coupling.

The synthesis of the central section commenced from $\alpha$-D-glucopyranosyl pentaacetate, which was elaborated by selective allylation, standard protecting group modifications, asymmetric propargylation, and Sonogashira cross-coupling with an epichlorohydrin-derived alkenyl iodide into an enyne. Gold-catalyzed spiroketalization and Lemieux–Johnson oxidation of a terminal olefin furnished the tricyclic central fragment ketoaldehyde.

The southern section was prepared from tri-*O*-acetyl-D-glucal, which was converted to the allyl 2-deoxy-C-glucoside. Chain elongation by olefin cross-metathesis and lead-mediated dehydroxy-methylative cleavage gave the anomeric acetate, which after selective allylation furnished the 2,6-*trans*-tetrahydropyran bearing an allyl chloride. Nucleophilic substitution with tributylstannyl lithium gave the corresponding allyl stannane nucleophile.

Lewis acid-mediated allylation of the central fragment aldehyde with the southern fragment allyl stannane proceeded with the inverse of the stereoselectivity that was expected according to the Cram-chelate model. The stereochemistry on C27 was corrected *a posteriori* by Mitsunobu inversion. The ketone "tether" was converted first to the alkenyltriflate and then to the alkenylstannane, which underwent Stille cross-coupling with the northern allyl acetate under mild conditions to afford the all-skipped tetraene. Global deprotection gave limaol in a total yield of 1.5% over 20 steps in longest linear sequence starting from $\alpha$-D-glucopyranosyl pentaacetate. Overall, 3.3 mg of limaol were prepared using this route.

In an effort to increase the material output for biological testing, a second-generation synthesis was devised. The main bottlenecks of the first-generation approach seemed to be the result of unfavorable sterics of the central fragment. A change in protecting groups was projected to alleviate problems such as the undesired selectivity of the allylative fragment coupling, the low-yielding alkenylstannane formation, and the sluggish global deprotection. The central fragment synthesis was thus changed to incorporate acetate protecting groups by simply including de- and reprotection steps in the route. In addition, the northern fragment could be prepared in a more efficient fashion by asymmetric hydrogenation of commercial 4,6-dimethyl-2-pyrone, ring opening of the resulting lactone, and silylation to give a known intermediate of the first-generation northern fragment synthesis.

The allylative fragment coupling between the central fragment aldehyde and the southern fragment allyl stannane could now be performed with the desired stereoselectivity, obviating the Mitsunobu inversion. Moreover, alkenylstannane formation now commenced from the corresponding terminal alkyne, improving selectivity and yield significantly. After fragment union by Stille allyl-alkenyl cross-coupling, a two-step deacetylation and desilylation gave limaol in a total of 7.0% yield over 19 steps in longest linear sequence starting from $\alpha$-D-glucopyranosyl pentaacetate. This signifies a fourfold increase in yield over the first-generation approach. The revised route also proved scalable, providing 277 mg of limaol in one pass.

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# Total Synthesis of Limaol

# Table of Contents

# Abbreviations

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AD | asymmetric dihydroxylation |
| aq. | aqueous |
| Ar | aryl |
| BAIB | bis-(acetoxy)iodobenzene |
| BBN | 9-borabicyclo(3.3.1)nonane |
| b.p. | boiling point |
| Bn | benzyl |
| brsm | based on recovered starting material |
| Bu | butyl |
| Bz | benzoyl |
| calcd. | calculated |
| cat. | catalytic |
| conc. | concentrated |
| CSA | camphorsulfonic acid |
| Cy | cyclohexyl |
| d | doublet |
| dr | diastereoisomeric ratio |
| dba | dibenzylideneacetone |
| DCC | *N*,*N*′-dicyclohexylcarbodiimide |
| DCE | 1,2-dichloroethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAD | diethyl azodicarboxylate |
| $(DHQD)_2PHAL$ | hydroquinidine-1,4-phthalazinediyl diether |
| $(DHQD)_2PYR$ | hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether |
| DIBAL-H | diisobutylaluminium hydride |
| DMAc | *N*,*N*-dimethylacetamide |
| DMAP | *N*,*N*-dimethyl-4-aminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| *ee* | enantiomeric excess |
| *epi* | epimeric |
| equiv. | equivalent(s) |

| | |
|---|---|
| Et | ethyl |
| exp. | experimental |
| g | gram(s) |
| GC | gas chromatography |
| h | hour(s) |
| hep | heptett |
| HFIP | hexafluoroisopropanol |
| HMDS | hexamethyldisilazane |
| HPLC | high-performance liquid chromatography |
| HRMS | high-resolution mass spectrometry |
| *i* | *iso* (branched) |
| IR | infrared spectroscopy |
| *J* | coupling constant |
| KHMDS | potassium hexamethyldisilazide |
| L | liter(s) |
| LDA | lithium diisopropylamide |
| LiDBB | lithium 4,4’-di-*tert*-butylbiphenylide |
| LiHMDS | lithium hexamethyldisilazide |
| LLS | longest linear sequence |
| M | molar |
| Me | methyl |
| MeO-BIBOP | 3,3'-di-*tert*-butyl-4,4'-dimethoxy-2,2',3,3'-tetrahydro-2,2'-bibenzo[d][1,3]oxaphosphole |
| Mes | mesityl |
| mg | milligram(s) |
| min | minute(s) |
| mL | milliliter(s) |
| m.p. | melting point |
| Ms | methanesulfonyl |
| MS | mass spectrometry |
| MS | molecular sieves |
| μg | microgram(s) |
| μL | microliter(s) |
| *n* | *normal* (linear) |
| n.d. | not determined |
| NCS | *N*-chloro succinimide |
| NHC | *N*-heterocyclic carbene |

| | |
|---|---|
| NHK | Nozaki–Hiyama–Kishi |
| NIS | *N*-iodo succinimide |
| NMP | *N*-methyl-2-pyrrolidinone |
| NMR | nuclear magnetic resonance |
| 4-$NO_2$-Bz | 4-nitrobenzoyl |
| NOE | nuclear Overhauser effect |
| NOESY | nuclear Overhauser effect spectroscopy |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| PIDA | phenyliodonium diacetate |
| pin | pinacol |
| PG | protecting group |
| PMB | *para*-methoxybenzyl |
| PMP | *para*-methoxyphenyl |
| ppm | parts per million |
| PPTS | pyridinium *para*-toluenesulfonate |
| Pr | propyl |
| PTSA | *para*-toluenesulfonic acid |
| Py | pyridine |
| q | quartet |
| quant. | quantitative |
| rr | regioisomeric ratio |
| *rac* | racemic |
| RT | room temperature |
| s | singlet |
| SAR | structure-activity relationship |
| SKP | spiroketal-based diphosphine ligand |
| SM | starting material |
| sat. | saturated |
| t | triplet |
| *t* | *tert* (branched) |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBS | *tert*-butyldimethylsilyl |
| TBDPS | *tert*-butyldiphenylsilyl |
| TC | thiophene-2-carboxylate |
| TEMPO | (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl |
| TES | triethylsilyl |

| | |
|---|---|
| Tf | trifluoromethanesulfonyl |
| THF | tetrahydrofuran |
| TIPS | tri-*iso*-propylsilyl |
| TLC | thin-layer chromatography |
| TMS | trimethylsilyl |
| TMP | 2,2,6,6-tetramethylpiperidine |
| TS | transition state |
| Ts | toluenesulfonyl |
| UV | ultraviolet |

# 1 Introduction

## 1.1 Total Synthesis and Its Role in Organic Chemistry

The field of natural product synthesis emerged in 1828 when Friedrich Wöhler famously synthesized urea from silver cyanate and ammonium chloride, proving that naturally occuring molecules could be recreated in a laboratory.[1] Since then, this branch of organic chemistry has undergone profound changes. Most notably, two pioneers of organic chemistry, the Nobel laureates R. B. Woodward and E. J. Corey, have each elevated total synthesis to new heights.

Some important milestones in the total synthesis of natural products are shown in Figure 1.1. Fischer's synthesis of D-glucose[2] and Robinson's tropinone synthesis[3] both marked significant early contributions. Shortly thereafter, Woodward revolutionized organic chemistry as a whole with his ingenious syntheses of, among many others, quinine and strychnine.[4] Finally, Corey transformed modern total synthesis into an exact science with the introduction of retrosynthetic analysis, as well as his many impressive contributions to the field, of which the synthesis of ginkgolide B should be highlighted here.[5]

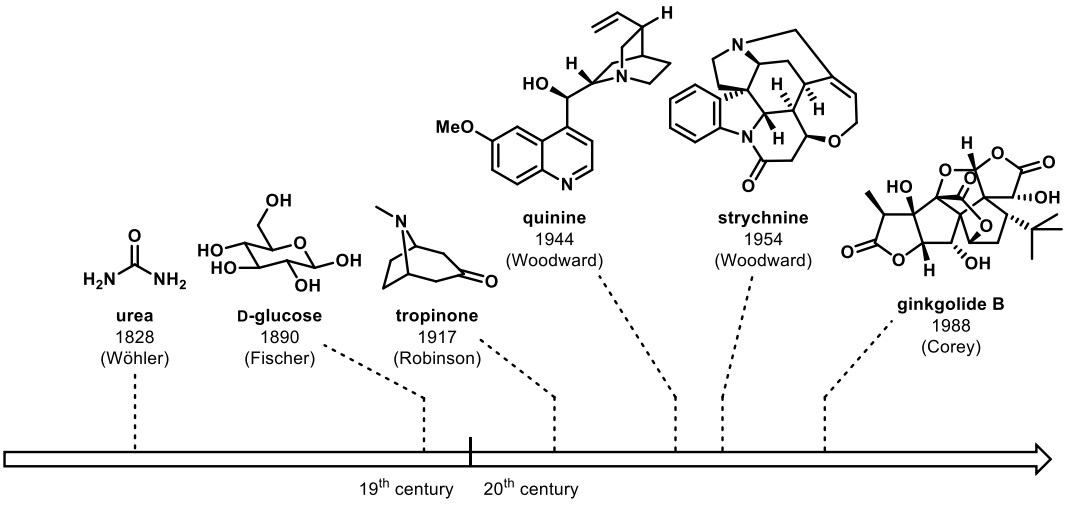



**Figure 1.1.** Selected milestones of natural product synthesis in the 19th and 20th century.

Even today, total synthesis is far from matured, as synthetic chemists shift their focus from feasibility to scalability.[6] Nevertheless, it has been a matter of extensive debate whether the field is still at the forefront of research or if it lost its role as an engine for innovation.[7]

Why do chemists do total synthesis? Historically, the synthesis of complex organic molecules has been used both as a benchmark for synthetic methodology, as well as a productive source of novel synthetic methods itself. A famous example of the latter is Yoshito Kishi's co-development of the Nozaki–Hiyama–Kishi reaction, where an unmet synthetic need was identified during the synthesis of palytoxin. Requiring facile access to allylic alcohols under

mild conditions, Kishi and co-workers filled the gap by discovering the catalytic effect of nickel(II) salts on the chromium(II)-mediated coupling of alkenyl iodides with aldehydes.[8] As an example of the reverse, Krische and co-workers have demonstrated the usefulness of their transfer hydrogenative allylation in the total syntheses of swinholide A and leiodermatolide A, using complex polyketide synthesis to show the value of synthetic methods developed in their laboratory.[9]

Apart from the rapid acceleration of method development driven by total synthesis, a deepened understanding of the electronic structure and reactivity of organic molecules often goes hand in hand with attempts to synthesize them. For example, Woodward and Eschenmoser's synthesis of vitamin $B_{12}$ inspired the development of the Woodward–Hoffman rules, allowing chemists to use orbital theory to predict reactivity.[10] In a similar vein, there is no more rigorous way of structure elucidation than simply making the molecule in question. Even though modern analytical methods grant an unprecedented level of precision, mistakes in the structure assignment of natural products are still commonplace.[11]

In light of the intriguing biological properties of many naturally occuring molecules, it has become more important for modern total synthesis to provide access to molecules in sufficient quantitites for biological assays and SAR studies.[6] In turn, synthetic chemists are required to consider the scalability and robustness of their syntheses, further increasing the complexity of the task at hand. Thus, even though there is a vast array of synthetic methods and the toolbox is more refined than ever, the synthesis of a complex molecule is still not an easy undertaking. A core feature of any total synthesis is the troubleshooting and creative problem solving that goes into it, not to mention the many roadblocks the researcher has to overcome to complete it.[12] In my opinion, the wide variety of reactions and analytical methods that the student comes in contact with while meandering through a synthetic route makes natural product synthesis one of the most thorough trainings an organic chemist can attain.

Finally, a certain aesthetic appeal of total synthesis cannot be denied. In this aspect, the construction of molecules has been likened to architecture.[13] In both endeavours, practitioners build useful and sometimes inherently beautiful structures, albeit on entirely different scales. However, while architecture can certainly be appreciated by people outside of the field, the same cannot be said for total synthesis. The "beauty" chemists see in a synthesis most likely parallels the "beauty" mathematicians and physicists observe in certain formulas. In both cases, beauty lies in the eye of the beholder.

But even outside aesthetics, mentioned above are still more than enough reasons to engage in total synthesis. Since the days of Wöhler, the field has changed radically, and it is my hope that it is dynamic enough to adapt further, ensuring its place as a core discipline of organic chemistry far into the future.

## 1.2 Dinoflagellates and Their Secondary Metabolites

Dinoflagellates (from ancient Greek *dinos* – "whirling" – and Latin *flagellum* – "whip") are a superclass of eukaryotes and form one of the largest groups of algae, occuring in both marine and freshwater environments.[14] Some species cause harmful algal blooms known as "red tides" and are associated with shellfish poisoning.[15] The majority of dinoflagellates are photoautotrophic, while others rely on mixotrophy, heterotrophy, or even parasitic/symbiotic behaviour to feed. Morphology among the approximately 2000 living species of dinoflagellates is surprisingly diverse, with some species being unicellular, some being colonial, and some even being multicellular.[16] A unifying feature among all dinoflagellates are their two dissimilar flagella (hence their name) arising from the ventral cell side, referred to as *dinokont* flagellation. Some dinoflagellate species (e.g. *Prorocentrum*) posess what is called a *desmokont* flagellation, where the two flagella are inserted apically instead.[17] Most dinoflagellates are also encased in a cell covering called *emphiesma*. In some species, this covering is akin to plates of armor called *theca*, whereas other, unarmored dinoflagellates are referred to as *athecate*.[18]

Apart from their interesting biology, dinoflagellates are also highly diverse in their biochemistry.[19] In total, over 30,000 structurally diverse marine natural products have been identified to date, a major source of which are dinoflagellates.[20] The numerous species of dinoflagellates produce some of the most complex polyketides, e.g. okadaic acid (**1**),[21] brevetoxin B (**2**),[22] goniodomin A (**3**),[23] and amphidinolide C (**4**).[24] The latter three compounds are shown in Figure 1.2. Biosynthetically, these secondary metabolites are assembled by a group of enzymes called the polyketide synthase in a process similar to fatty acid synthesis. The polyketide chain is usually initiated with acetyl-CoA and then extended by a series of Claisen condensations with acetate units in the form of malonyl-CoA. While in fatty acid synthesis, each acetate is fully reduced via ketoreduction, dehydration, and enoyl reduction to afford the alkane, in polyketide synthesis some or all of these steps are omitted, leading to functional diversity in the form of carbonyl groups, hydroxyl groups, and double bonds.[25] In addition, building blocks other than acetates, e.g. propionates, butyrates, or even amino acids are occasionally incorporated into the chain. A unique feature of polyketide synthesis in dinoflagellates are the modifications made to the carbon chain after its assembly, e.g. carbon deletion, β-alkylation, and $\alpha$-alkylation of the acetate units. During construction of the polyketide chain, intramolecular ether formation can also take place, leading to unique polyether moieties as seen for example in brevetoxin B or the gargantuan maitotoxin.[26] Finally, chain release is proposed to be accomplished by a thioesterase and can lead to lactone formation, sometimes affording large macrocyclic rings.[25]

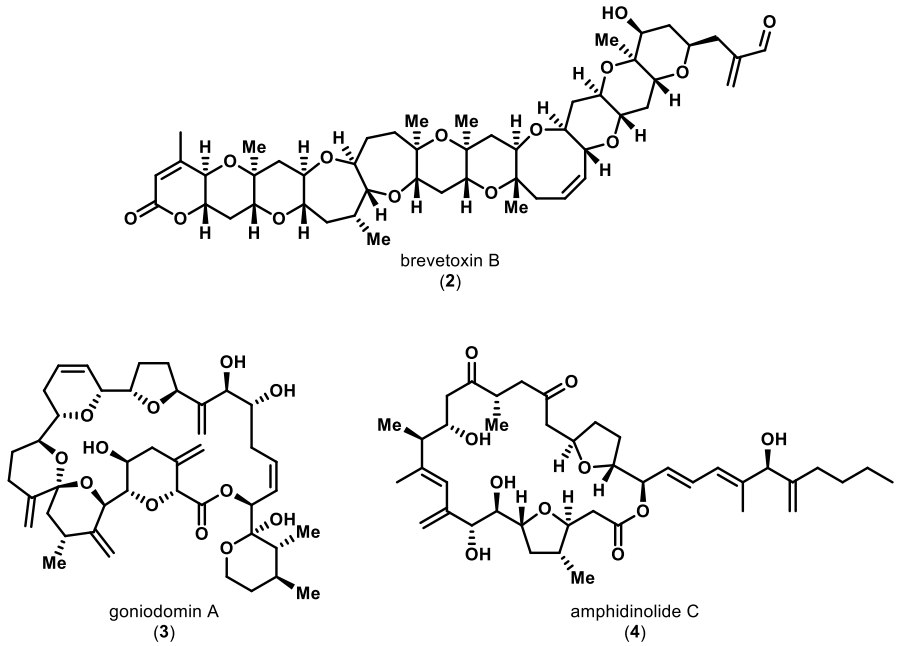



**Figure 1.2.** Selected polyketides found in dinoflagellates.

Many of the dinoflagellates' diverse and structurally interesting secondary metabolites also exhibit intriguing bioactivities. Some dinoflagellates produce toxins that find their way into humans *via* contaminated shellfish and, depending on the ingested compound, lead to a variety of distinct pathologies, e.g. diarrhetic, paralytic, or neurotoxic shellfish poisoning.[19] A prominent example of a toxin implicated in ciguatera, a form of seafood poisoning, is maitotoxin.[27] It is unique in the natural product realm due to its colossal size, with a molecular weight of over 3,000 g·mol$^{-1}$. In addition, it acts as a highly potent $Ca^{2+}$-channel agonist and exhibits a lethality against mice of $LD_{50}$ = 50 ng·kg$^{-1}$, making it one of most toxic non-peptidic compounds known to man.[28] Despite their harmful effects, however, some polyketides from dinoflagellates have proven to be of use in medical research. A number of patent applications in recent years show a surge of interest in pharmaceutical utilization of biotoxins produced by dinoflagellates.[29]

## 1.3 Okadaic Acid

One of the most notable examples of a medically relevant polyketide isolated from dinoflagellates is okadaic acid (**1**, Figure 1.3). It was first isolated from the sponges *Halichondria okadai* and *Halichondria melanodocia*, and its structure was elucidated in 1981. In preliminary biological studies, it was found to be cytotoxic.[21] Okadaic acid is mainly produced by dinoflagellates of the genus *Prorocentrum* and *Dynophysis*, and it accumulates in shellfish, inducing diarrhetic shellfish poisoning when contaminated seafood is consumed.[30]

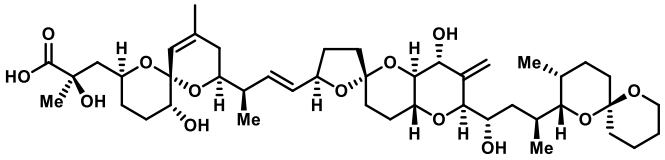


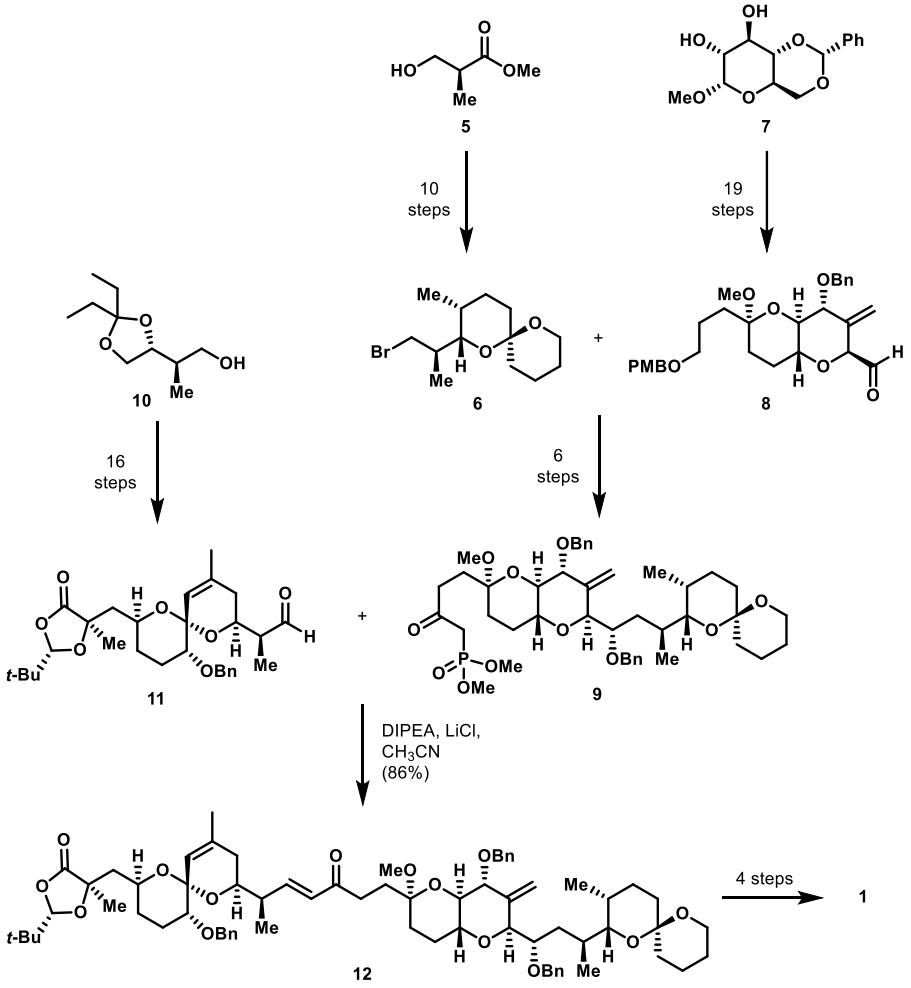
**Figure 1.3.** Structure of okadaic acid (**1**).

Okadaic acid has demonstrated a wide range of interesting biological properties, which have been extensively reviewed.[29-30] It principally acts as a selective serine/threonine phosphatase type 2A (PP2A) inhibitor, causing alterations of protein phosphorylation states and eventually leading to the collapse of cellular regulatory processes. This property makes it a useful tool in pharmacology to study phosphatase inhibition in cellular signaling. It is unclear whether its toxic effects stem exclusively from its PP2A inhibitory activity or if other cellular targets play a role.[31] Apart from its cytotoxicity, okadaic acid has been found to be neurotoxic, carcinogenic, genotoxic, and potentially immunotoxic.[30]

Due to its intriguing biological properties, compelling structural features, and scarcity from natural sources, okadaic acid has been a popular target for total synthesis. Isobe and co-workers presented the first total synthesis of okadaic acid in a series of papers in 1986 and 1987,[32] with Forsyth and co-workers and Ley and co-workers following in 1998.[33] Forsyth and co-workers also continued to improve on their synthesis, publishing a gold-catalysis-based formal synthesis in 2010.[34] Forsyth's landmark synthesis from 1998 is briefly summarized in Scheme 1.1.

Starting from (*S*)-Roche ester (**5**), the alkyl bromide **6** was prepared in 10 steps. The D-glucose derivative **7** was converted to the fused bicyclic compound **8** over a total of 19 steps. **6** underwent halogen-lithium exchange and was added into aldehyde **8** to give a mixture of diastereoisomeric alcohols in a ratio of 2.5:1, where the undesired isomer preponderated and was recycled using an oxidation/diastereoselective reduction sequence. The desired diastereoisomer was taken forward for five steps to give phosphonate **9**, completing one of the fragments. Synthesis of the other fragment commenced from compound **10**, which was converted to the aldehyde **11** in a total of 16 steps. **9** and **11** were unified *via* a Horner–

Wadsworth–Emmons olefination, giving enone **12** in 86% yield. After asymmetric reduction of the ketone, ketalization, saponification, and global debenzylation, okadaic acid was obtained in a total of 56 steps and in 30 steps in longest linear sequence starting from **7**. The route was projected to be amenable to minor modifications and could therefore in theory provide analogues of okadaic acid for studies of the mechanism of phosphatase inhibition.




**Scheme 1.1.** Summary of Forsyth and co-workers' total synthesis of okadaic acid (**1**).

Interest in polyketides produced by dinoflagellates remains high and the field of total synthesis can help alleviate the scarcity of many of these intriguing natural products. Ideally, synthetic studies of dinoflagellate-derived metabolites can further elucidate their rich and fascinating biological properties and even open up avenues for new medical and scientific applications.

## 1.4 Limaol

In 2017, in an effort to isolate bioactive polyketides from the benthic marine dinoflagellate *Prorocentrum lima*, Rho and co-workers harvested the biomass from 400 L of cell culture and subjected it to solvent extraction with methanol. Cytotoxicity-guided fractionation and repeated chromatographic purification led to the isolation of limaol (**13**, Figure 1.4), a previously unknown polyol, along with literature-known derivatives of both okadaic acid and dinophysistoxin-1.[35]

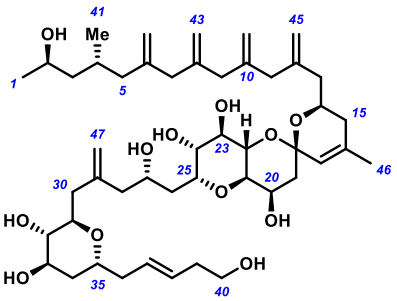



**Figure 1.4.** Structure of limaol (**13**).

The structure and absolute configuration of the molecule were elucidated using a combination of different analytical techniques. The molecular formula was determined to be $C_{47}H_{74}O_{12}$ by high-resolution mass spectrometry, indicating a total of 11 degrees of unsaturation in the compound. IR spectroscopy revealed the presence of hydroxy groups and olefins. NMR spectroscopy was then performed to unveil the structural details of limaol. $^{13}C$ and HSQC NMR spectra showed 47 signals, splitting up into three methyl, 20 methylenic, 17 methinic, one ketal, and six quaternary carbons. Of the 20 methylene signals, five corresponded to *exo*-methylene groups. Together with two internal olefins, seven of the 11 degrees of unsaturation were therefore accounted for by double bonds, suggesting the presence of four rings in the molecule. A thorough 2D-NMR investigation using DQF-COSY, TOCSY, HMBC, HECADE, and ROESY spectra as well as coupling constant-based configuration analysis allowed elucidation of the connectivity of limaol. The absolute configuration was determined by Mosher's ester analysis, during which six of the eight hydroxy groups (all of them except C-20 and C-23) were esterified using (*R*)/(*S*)-MTPA-Cl and the differences in proton chemical shifts were evaluated. In consequence, the structure of limaol was established to be the one shown in Figure 1.4. This impressive work by Rho and co-workers is a testament to the power of the analytical techniques available to chemists nowadays.

Among this linear C40-polyketide's most striking structural features are the array of four skipped *exo*-methylene groups in its northern section and the chiral spiroketal moiety in its central section. To the best of our knowldedge, the 1,3,5,7-tetra(methylene)heptane subunit is

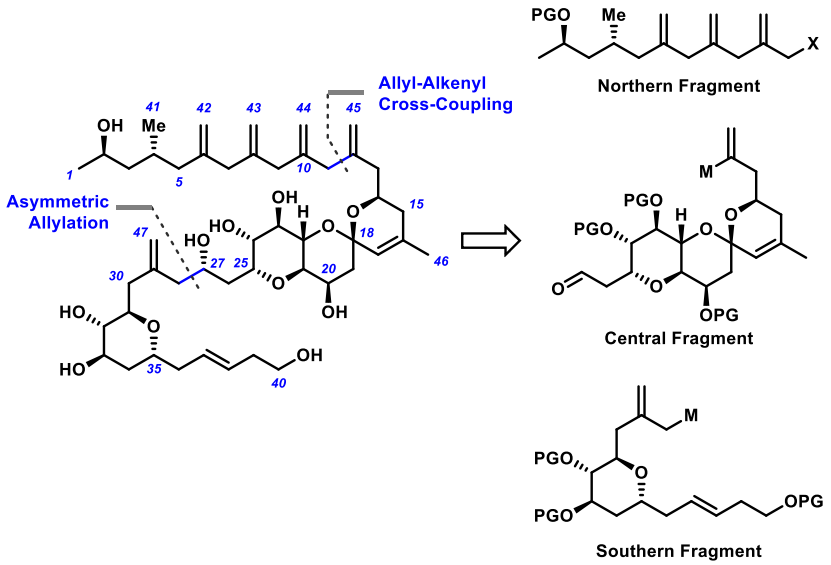
unprecedented in natural product space. Despite its intriguing structure, limaol only showed limited biological activity in preliminary studies performed by Rho and co-workers: In an *in vitro* assay, it exhibited moderate cytotoxicity against the three cancer cell lines HepG2 ($IC_{50}$ = 3.7 μM), HCT-116 ($IC_{50}$ = 7.3 μM), and Neuro2a ($IC_{50}$ = 9.6 μM). Especially when drawing a comparison to okadaic acid, the cytotoxicity of limaol is significantly lower: The $IC_{50}$ values for okadaic acid against the same three cancer cell lines were found to be 0.54 μM, 0.67 μM, and 0.85 μM, respectively.[35]

Limaol was chosen as a target for our synthetic efforts mainly due to its unique structure. With a total of 15 stereogenic centers, seven carbon-carbon double bonds, as well as four pyran ring systems of varying degrees of saturation, limaol poses a tempting challenge. Furthermore, Rho and co-workers could only isolate 1.6 mg of limaol from 400 L of cell culture, significantly limiting their ability to conduct thorough biological studies aside from cytotoxicity assays. Ideally, our synthetic efforts would allow for the production of ample amounts of this interesting polyketide to facilitate elucidation of its bioactivity.

# 2 First-Generation Synthesis of Limaol

## 2.1 Retrosynthetic Analysis

Due to the considerable size and complexity of the synthetic target, a convergent fragment-based approach was deemed most viable. The total synthesis was envisioned to involve the unification of three fragments, which were named "northern", "central", and "southern" fragment according to their position in the target molecule as depicted in Scheme 2.1. In addition, a global protection strategy employing silyl groups was desired in order to prevent harshly acidic, basic, oxidative, or reductive conditions during final deprotection of the target molecule. Mild conditions were considered crucial due to the presumed sensitivity of the four skipped *exo*-methylene groups in the northern section of **13**.

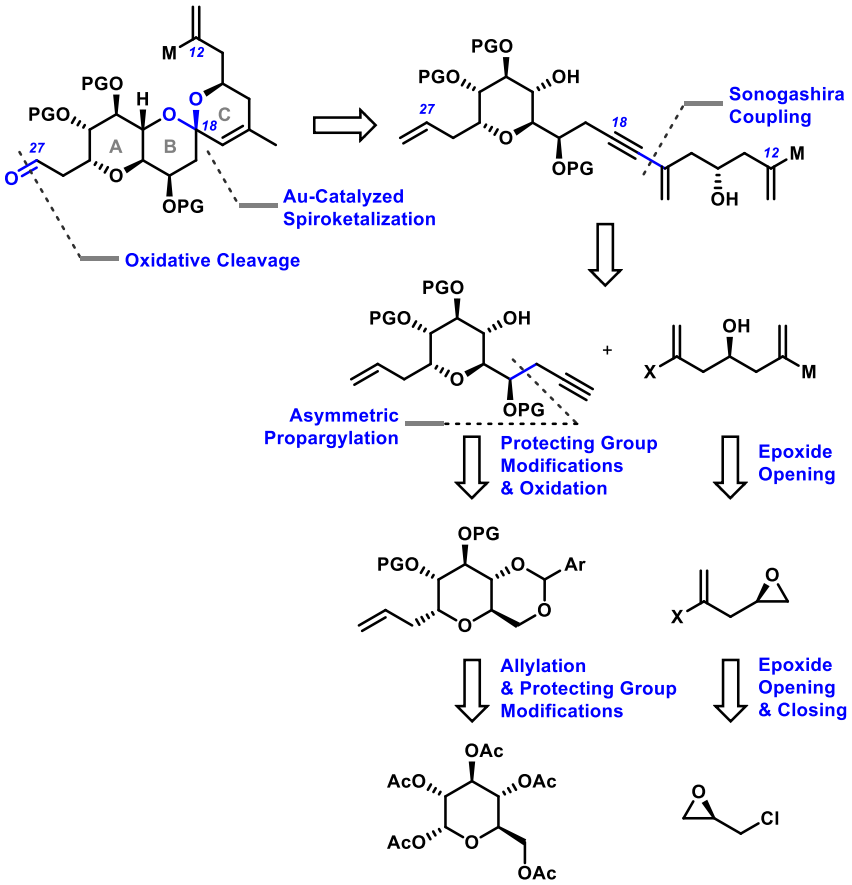



**Scheme 2.1.** Retrosynthetic disconnection of limaol.

The southern and the central fragment were to be connected *via* an asymmetric allylation of the aldehyde on the central fragment, which would simultaneously set the homoallylic alcohol stereocenter at C27. The combined central and southern fragment were envisioned to be unified with the northern triene by a transition metal-catalyzed allyl-alkenyl cross-coupling. Both asymmetric allylations of aldehydes and allyl-alkenyl cross-couplings are reliable reactions, offering a plethora of possibilities to effect these transformations.[36] Thus, the nucleophiles in both reactions were intentionally left undefined until optimization would reveal the appropiate conditions. Although fragment mergers are notoriously challenging, our considerations made us optimistic to be able to achieve these couplings with relative ease.

In another key disconnection, the spiroketal moiety of the central fragment was considered an ideal opportunity to demonstrate the strength of π-acid catalysis, allowing the masked C18-

carbonyl group to be encoded as a triple bond and enabling the concomitant construction of rings B and C (Scheme 2.2). The unsaturation in the C-ring would be incorporated into the cyclization precursor as an *exo*-methylene group, which upon treatment with a carbophilic π-acid catalyst should give the thermodynamically favored internal double bond. The corresponding enyne could be accessed by Sonogashira cross-coupling of a sugar-derived terminal alkyne and an alcohol-bearing alkenyl halide. The alkyne fragment was envisioned to emerge by asymmetric propargylation of an aldehyde, which itself would be accessed by selective protecting group modification and oxidation of a fully protected and C1-allylated D-glucose derivative. Evidently, this intermediate could be easily obtained from inexpensive α-D-glucopyranosyl pentaacetate. The alkenyl halide fragment was proposed to emanate from a functionalized oxirane *via* epoxide opening. This modular approach would allow facile introduction of the alkenyl metal group (or equivalent synthons) on said fragment, ensuring access to a broad range of nucleophiles for the key coupling of the northern to the central fragment. The epoxide itself was suggested to be prepared from commercially available (*R*)-epichlorohydrin by epoxide opening and subsequent reclosing of the ring. In the case of both Sonogashira coupling partners, the alkenyl halide and the terminal alkyne, most of the required stereogenic centers are already present in the starting materials.

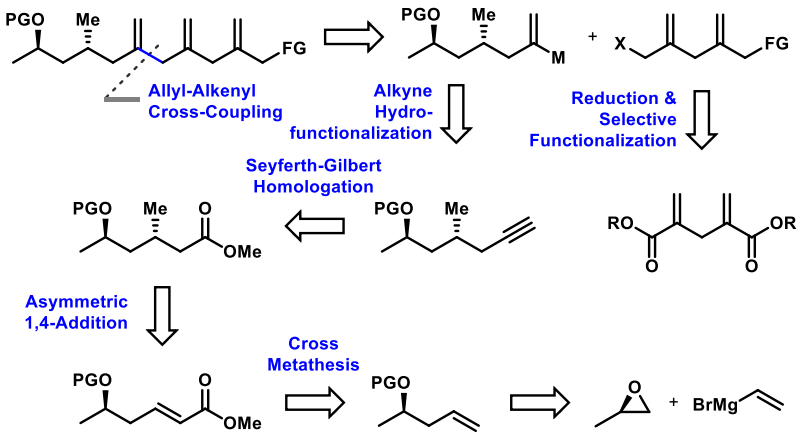



**Scheme 2.2.** Retrosynthetic disconnections of the central fragment.

The retrosynthetic analyses for the northern and southern fragment were performed entirely by Dr. Xiaobin Mo. The following represents a summary of his considerations regarding the disconnections for both fragments.

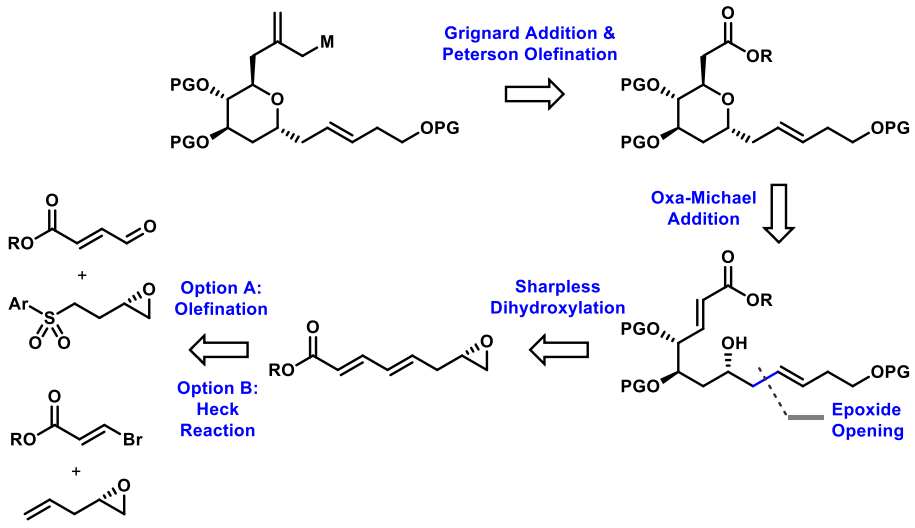
For the northern section, a bidirectional approach was chosen. The skipped triene moiety was envisioned to be formed in a similar fashion as the final tetraene (Scheme 2.3). Allyl-alkenyl cross-couplings starting from a diene-containing allyl halide using highly nucleophilic alkenyl metal species, such as alkenyl zinc or alkenyl tin, would ensure C–C bond formation under mild conditions and secure stability of the resulting skipped tetraene. The first alkenyl metal building block could be derived by hydrofunctionalization of an alkyne, which itself can be formed by reduction and subsequent Seyferth–Gilbert homologation of an ester. The ester moiety would in turn be vital for the installation of the C4-stereocenter by an asymmetric 1,4-addition into the analogous $\alpha,\beta$-unsaturated ester. This disubstituted olefin could be derived from the corresponding terminal homoallylic alcohol by ruthenium-catalyzed cross metathesis with methyl acrylate. Finally, the starting alcohol would be obtained by epoxide opening of commercially available (*R*)-propylene oxide with vinylmagnesium bromide. The allyl halide-bearing diene fragment was proposed to be acquired by reduction and selective mono-

functionalization of the corresponding literature-known diester, which is the product of a Baylis–Hillman reaction.[37]



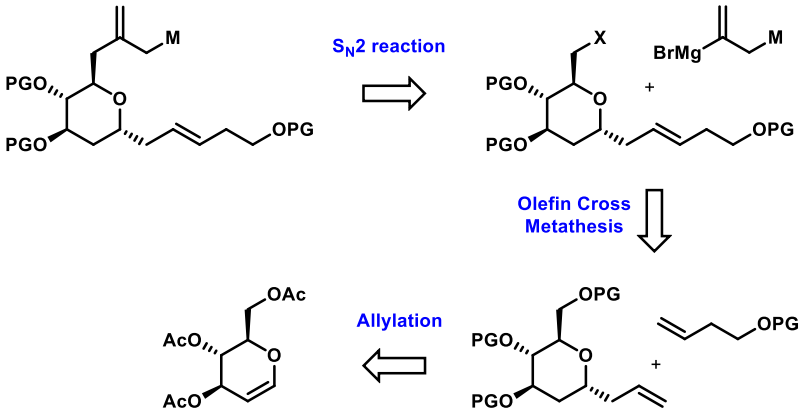

**Scheme 2.3.** Retrosynthetic disconnections of the northern fragment.

Lastly, two synthetic approaches were devised for the southern fragment. The first approach was based on an *oxa*-Michael cyclization, which would give access to the ornate tetrahydropyran ring system (Scheme 2.4). The resulting ester would allow formation of the desired allylmetal species by double Grignard addition with $TMSCH_2MgCl$ and subsequent Peterson olefination. The starting material for the *oxa*-Michael reaction was envisioned to be obtained by an epoxide opening and Sharpless' asymmetric dihydroxylation of an α,β,γ,δ-unsaturated ester. This diene could be accessed in two ways: Either by an olefination reaction (such as a Julia–Kocienski olefination) of an aldehyde with an arylsulfone or by a Heck reaction of 3-bromoacrylate with a homoallylic epoxide.




**Scheme 2.4.** *Oxa*-Michael-based retrosynthetic analysis of the southern fragment.

Due to unforeseen difficulties in the *oxa*-Michael reaction (see Section 2.4.1), a second retrosynthetic analysis was later conducted (Scheme 2.5). In this approach, a chiral pool strategy was employed, since *de novo* formation of the tetrahydropyran ring proved challenging. Retrosynthetically, the desired allylmetal fragment could be accessed *via* a copper-catalyzed nucleophilic substitution on a primary alkyl electrophile by an alkenylmagnesium species already bearing the preinstalled allylmetal species. The leaving group on the electrophile would be installed by modification of a selectively unmasked primary alcohol. Formation of the olefinic side chain could be achieved by olefin cross metathesis starting from an allylated 2-deoxy-D-glucose derivative. This sugar building block can in turn be easily accessed from inexpensive tri-*O*-acetyl-D-glucal by selective allylation on C1.



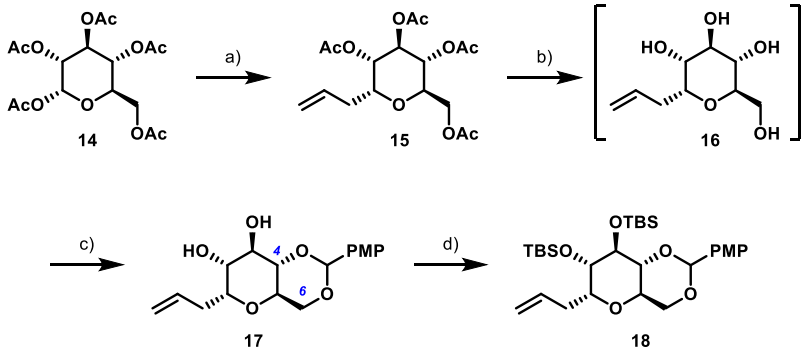

**Scheme 2.5.** Chiral pool-based retrosynthetic analysis of the southern fragment.

## 2.2 Synthesis of the Central Fragment

### 2.2.1 Synthesis of the Glucose-Derived Aldehyde

As outlined above, the synthesis of the central fragment commenced from α-D-glucopyranosyl pentaacetate (**14**). The initial allylation using an excess of allyltrimethylsilane and boron trifluoride etherate is literature-known and proceeds with high α-selectivity.[38] The large excess of Lewis acid and the polar solvent acetonitrile are presumed to favor formation of the open oxonium ion from the starting sugar, despite the possibility of anchimeric assistance by the neighboring group at C2.[38a] Nucleophilic attack of the allylsilane then preferentially occurs from the axial trajectory, giving 56% yield of the pure α-anomer **15** after column chromatography and recrystallization (Scheme 2.6).

The acetate groups were subsequently removed under Zemplén conditions by treatment with a catalytic amount sodium methoxide in methanol, affording the deprotected C-allylated D-glucose derivative **16**. Due to the high polarity of this compound, purification was postponed and the crude deacetylated product was directly subjected to the next step. Treatment of **16** with *p*-anisaldehyde-dimethylacetal and a catalytic amount of *p*-toluenesulfonic acid selectively gave the six-membered cyclic acetal **17** under participation of the C4 and C6 alcohols. The acetalization was plagued by incomplete conversion of the starting material in several attempts, likely due to the presence of nascent methanol in the reaction mixture. Effective removal of methanol was achieved by increasing the reaction temperature to 85 °C and running the reaction under reduced pressure (250 mbar). Conversion was thereby driven to completion, affording 90% yield of the desired acetal **17** over two steps.

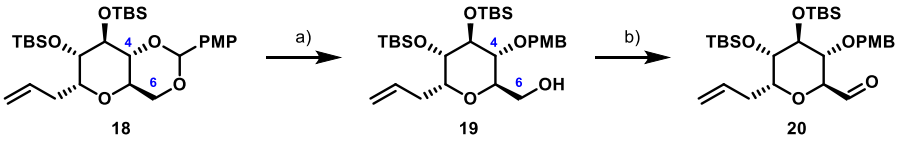



**Scheme 2.6.** Synthesis of the fully protected sugar derivative **18**. Conditions: a) Allyltrimethylsilane, $BF_3$·$OEt_2$, MeCN, 80 °C, 56% (single diastereoisomer after recryst.); b) NaOMe, MeOH, RT; c) *p*-Anisaldehyde-dimethylacetal, *p*-TsOH, DMF, 85 °C, 250 mbar, 90% over two steps; d) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −40 °C, 91%.

The remaining two free alcohols in **17** were protected with the global silyl protecting group strategy in mind (*vide supra*). *tert*-Butyldimethylsilyl (TBS) groups were selected due to

their comparatively facile removal and their resilience against mildly acidic and harshly basic conditions.[39] The best results were achieved using TBSOTf as the silylating reagent and 2,6-lutidine as the base in dichloromethane. In contrast, TBSCl and imidazole in DMF exhibited sluggish reactivity, as the alcohols to be protected were sterically hindered. Another crucial factor for a quick and high-yielding transformation was the choice of reaction temperature: The optimal temperature was found to be −40 °C, at which the desired fully protected sugar derivative **18** was obtained in 91% yield. When running the reaction at 0 °C, only 53% yield was isolated. This decrease in yield is most likely a consequence of the Lewis acidic nature of TBSOTf (and Lewis acidic impurities in the reagent), which can effect the decomposition of the acid-labile PMP acetal at sufficiently high temperatures. Conversely, maintaining the reaction solution at −78 °C effectively brings conversion to a halt.

Reductive acetal opening of sugar derivative **18** using DIBAL-H selectively liberated the C6 alcohol and left the *p*-methoxybenzyl group on the C4 alcohol intact (Scheme 2.7).[40] This transformation occurred in quantitative yield and with excellent selectivity to afford the monodeprotected sugar derivative **19**. The temperature again had to be carefully controlled, as warming above 0 °C resulted in decreased yields. The regioselectivity can be rationalized as follows: The ability of DIBAL-H to open benzylidene acetals stems from its Lewis acidity, which allows it to form donor-acceptor complexes with ethers, ketals, and acetals.[41] Coordination of aluminum occurs at the sterically less encumbered O6 oxygen of the benzylidene acetal, simultaneously making the acetal carbon susceptible to nucleophilic hydride attack. Hydride delivery then presumably ensues *via* an $S_Ni$ mechanism (in analogy to alane),[42] furnishing the benzyl-protected O4 oxygen and aluminum-bound O6 oxygen. After work-up and removal of aluminum salts, the free C6 alcohol remains. The resulting primary alcohol **19** was then subjected to Swern oxidation conditions to reproducibly give the desired aldehyde **20** in 93% yield without any detectable epimerization occurring at the $\alpha$-position.

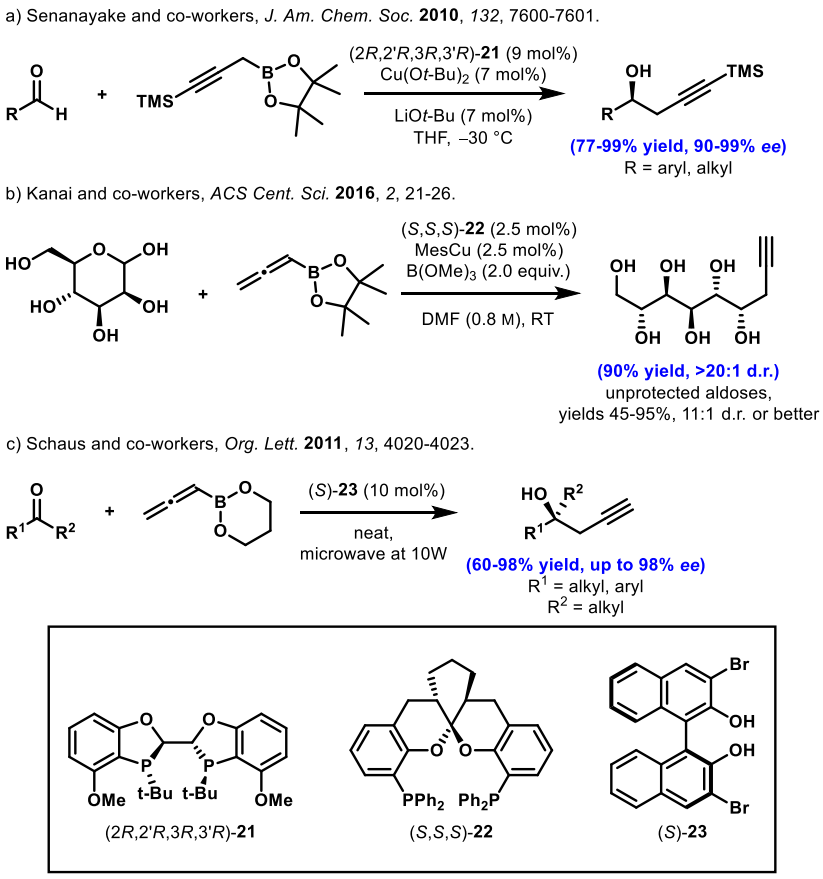



**Scheme 2.7.** Synthesis of the aldehyde **20**. Conditions: a) DIBAL-H, $CH_2Cl_2$, −78 °C to 0 °C, quant.; b) $(COCl)_2$, DMSO, *then* $NEt_3$, $CH_2Cl_2$, −78 °C, 93%.

### 2.2.2 Asymmetric Propargylation

With compound **20** in hand, methods for the asymmetric propargylation of the aldehyde were investigated. Several review articles on this topic are available.[43] Three especially noteworthy asymmetric propargylations are shown in Scheme 2.8: A copper-catalyzed propargylation of aromatic and aliphatic aldehydes using a propargyl borolane developed by Senanayake and co-

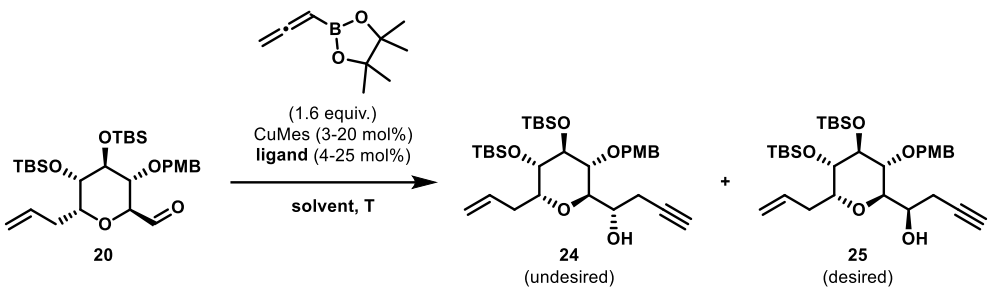
workers,[44] a direct propargylation of unprotected aldoses reported by Kanai and co-workers,[45] and a BINOL-catalyzed propargylation of ketones using allenyl boronates established by Schaus and co-workers.[46]

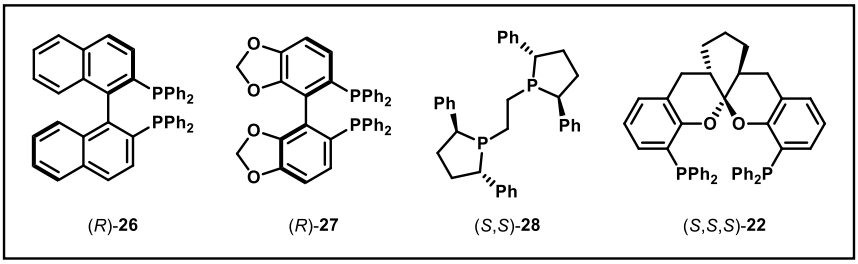



**Scheme 2.8.** Selected literature precedents for asymmetric propargylation of aldehydes and ketones.[44-46]

All three of the methods shown in Scheme 2.8 were considered viable options for the propargylation of aldehyde **20**. Since the (2*R*,2′*R*,3*R*,3′*R*)-MeO-BIBOP ligand (**21**) is not commercially available and its synthesis is lengthy,[47] Kanai's propargylation using (*S*,*S*,*S*)-Ph-SKP (**22**) as ligand was instead attempted first (Table 2.1). Importantly, the trimethyl borate used in Kanai's method functions preeminently as an activating agent by ensuring that the aldose starting material adopts its reactive open-ring aldehyde form.[45] Since in the case of **20** the aldehyde functionality is already present, the additive was omitted.

**Table 2.1.** Screening of solvents, ligands, and temperature for the asymmetric propargylation of aldehyde **20** based on Kanai's method.



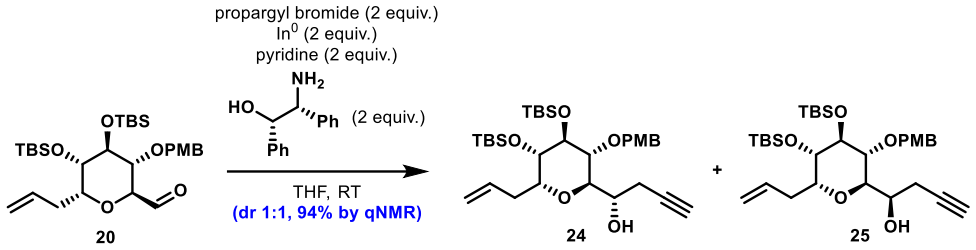




| Entry | Solvent | Ligand | T/°C | dr (by $^1$H NMR) 24 : 25 |
|---|---|---|---|---|
| 1 | DMF | (*R*)-**26** | RT | 1.0 : 1.0 |
| 2 | DMF | (*R*)-**26** | −55 | 2.6 : 1.0 |
| 3 | THF | (*R*)-**26** | −78 | 2.7 : 1.0 |
| **4** | **DMF** | **(*S*)-26** | **−55** | **1.0 : 1.3** |
| 5 | DMF | (*S*)-**27** | −40 | 1.3 : 1.0 |
| 6 | DMF | (*S*,*S*)-**28** | −40 | Decomposition |
| 7 | DMF | (*S*,*S*,*S*)-**22** | −55 | 2.1 : 1.0 |
| 8 | DMF | (*R*,*R*,*R*)-**22** | −55 | 2.5 : 1.0 |

Our first foray into copper-catalyzed asymmetric propargylation was met with low diastereoselectivities, giving almost equimolar mixtures of the homopropargylic alcohol isomers **24** and **25**. Mosher ester analysis was utilized to elucidate the absolute configuration of each of the diastereoisomers.[48] The most promising dr obtained was 1.3:1.0 in favor of the desired diastereoisomer **25** (entry 4). In almost all other cases, the undesired diastereoisomer **24** preponderated. It became apparent that Kanai's method was not able to exert sufficient catalyst control regardless of solvent, ligand, and reaction temperature employed.

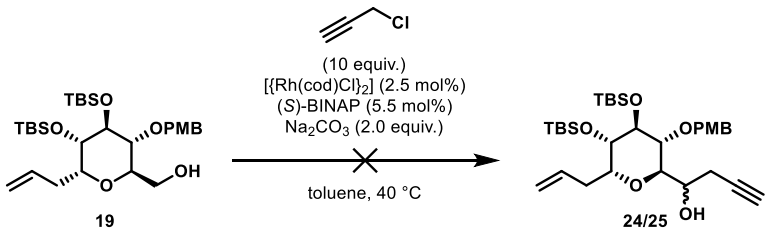
Haddad *et al*. have developed an indium-mediated asymmetric propargylation using chiral 2-amino-1,2-diphenylethanol as stochiometric ligand.[49] The reaction proceeds under Barbier conditions with indium metal and propargyl bromide as the pronucleophile. When this

system was applied to the propargylation of aldehyde **20**, the homopropargylic alcohol was observed in a yield of 94% by $^1$H NMR, but as a 1:1 mixture of diastereoisomers (Scheme 2.9). Evidently, the chiral additive was not able to induce diastereoselectivity in this case.



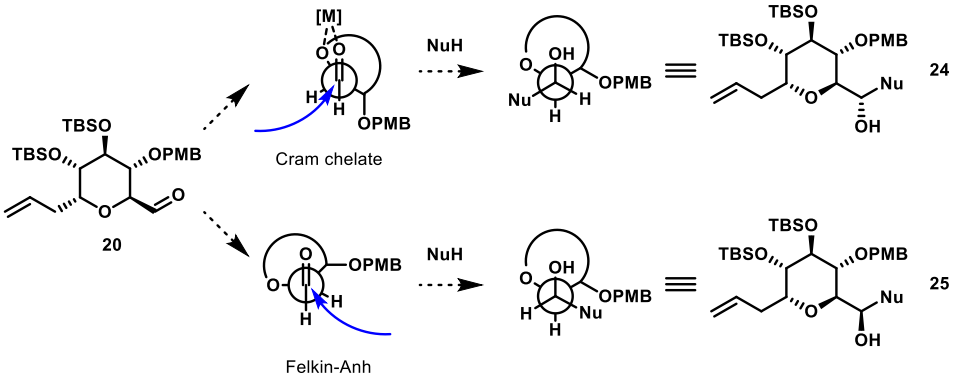

**Scheme 2.9.** Indium-mediated asymmetric propargylation of aldehyde **20** according to a method developed by Haddad *et al*.[49]

Krische and co-workers have reported a rhodium-catalyzed transfer hydrogenation which converts primary alcohols into homopropargylic alcohols.[50] The transformation requires a large excess of propargyl chloride and only exhibits moderate levels of enantio- and diastereoselectivity. Nevertheless, the method was applied to the propargylation of alcohol **19** under the assumption that substrate control would deliver the desired product in a synthetically useful dr. However, no conversion of the starting material was observed (Scheme 2.10).




**Scheme 2.10.** Attempted rhodium-catalyzed asymmetric propargylation developed by Krische and co-workers.[50]

The stereochemical situation in aldehyde **20** was reconsidered in an attempt to rationalize the selectivity issues in the methods thus far examined. In Scheme 2.11, the two common stereochemical models for nucleophilic addition into carbonyls are illustrated. In the case of aldehyde **20**, the Cram chelate conformation induced by coordination of oxophilic metal cations (e.g. $Mg^{2+}$ or $Zn^{2+}$) would afford the undesired diastereoisomer **24**. In contrast, the Felkin–Anh model, which places the sterically most demanding or most electron-withdrawing $\alpha$-substituent at a 90° angle to the carbonyl C–O bond, would result in generation of the desired diastereoisomer **25**. Hence, the desired diastereoselectivity is most likely to be achieved by preventing formation of the Cram chelate, specifically by ensuring the absence of any polyvalent metal cations.

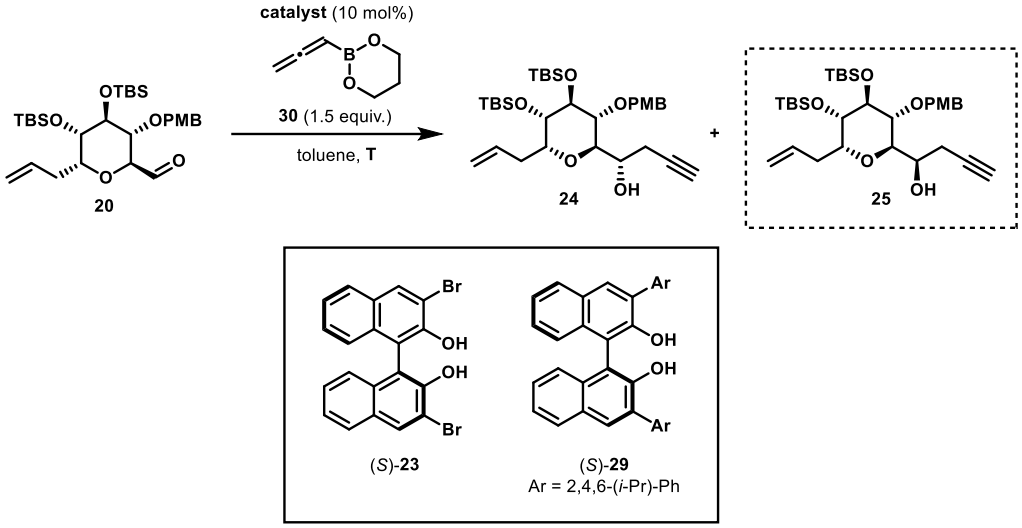



**Scheme 2.11.** Stereochemical models for formation of the homopropargylic alcohols **24** and **25** by propargylation of the aldehyde **20**.

The BINOL-catalyzed asymmetric propargylation developed by Schaus and co-workers (briefly summarized in Scheme 2.8) meets this requirement.[46] We were especially confident in this method since it had already been successfully applied to the total synthesis of leiodermatolide in our laboratory.[51] A screening of reaction conditions is shown in Table 2.2. Following Schaus' procedure, the first experiments (entries 1-3) were conducted using microwave irradiation, (*S*)-3,3′-dibromo-1,1′-bi-2-naphthol (**23**) as catalyst, and elevated temperatures. A sterically more demanding BINOL-derivative (**29**) was also evaluated in hopes of increasing diastereoselectivity. However, no improvement in dr was observed and the yield decreased significantly (entry 4). In contrast to the original findings, ambient temperatures proved optimal in terms of selectivity and yield. At room temperature without microwave irradiation, selectivity was enhanced to a dr of 7:1 in favor of the desired alcohol **25** (entries 5 & 6), but lowering the reaction temperature further did not increase selectivity (entry 7). The question arose whether the system exhibits an intrinsic bias towards one of the two diastereoisomers. By omitting the catalyst entirely, a 3:1 mixture of **25** and **24** in a combined yield of 95% was obtained (entry 8). This clearly demonstrates an inherent preference of the allenyl boronate for attack from the *Si* face of the aldehyde in congruence with the Felkin–Anh model. Using (*R*)-**23** instead of its enantiomer surprisingly led to another substantial increase in diastereoselectivity, giving a 31:1 mixture in favor of **25** and a total yield of 74% (entry 9). This result stands in contrast to Schaus' original observations, where (*R*)-**23** preferentially afforded the *Re* face adducts.[46] However, comparability might be limited due to different carbonyl components: Substrate **20** is an aldehyde, while Schaus and co-workers describe the propargylation of ketones in their report.

The yield of this reaction could be further improved to 96% of pure **25** after separation of the diastereoisomers. This additional gain was achieved using a newly synthesized batch of allenyl dioxaborinane **30**, indicating that the quality of this reagent is critical for the outcome of the reaction.

**Table 2.2.** Screening of catalysts and temperature for the asymmetric propargylation of aldehyde **20** based on Schaus' method.




| Entry | Catalyst | T/°C | dr (by HPLC) 24 : 25 | Combined yield (by qNMR) |
|---|---|---|---|---|
| 1 | (*S*)-**23** | 120 (MW) | 1.0 : 1.6 | 67% |
| 2 | (*S*)-**23** | 65 (MW) | 1.0 : 2.0 | 69% |
| 3 | (*S*)-**23** | 30 (MW) | 1.0 : 4.6 | 92% |
| 4 | (*S*)-**29** | 30 (MW) | 1.0 : 2.9 | 35% |
| 5 | (*S*)-**23** | RT | 1.0 : 6.5 | 78% |
| 6 | (*S*)-**23** | RT | 1.0 : 6.8 | 82%[a] |
| 7 | (*S*)-**23** | 0 | 1.0 : 4.8 | 83% |
| 8 | - | RT | 1.0 : 3.2 | 95% |
| 9 | (*R*)-**23** | RT | 1.0 : 31 | 74% |
| **10**[b] | **(*R*)-23** | **RT** | **n.d.**[c] | **96%**[d] |

[a] Combined isolated yield. [b] Reaction was performed with freshly prepared **30**. [c] Reaction mixture was directly purified and dr was therefore not determined. [d] Isolated yield of pure **25**.

In summary, the asymmetric propargylation of aldehyde **20** was accomplished in excellent yield to afford homopropargylic alcohol **25** as a single diastereoisomer.

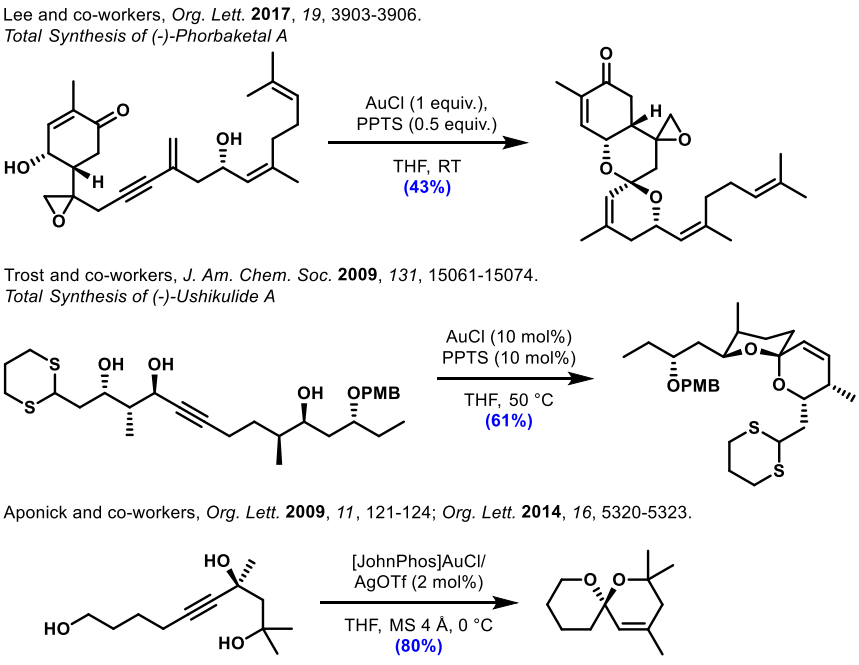
### 2.2.3 Preliminary Spiroketalization Studies

With access to ample quantities of homopropargylic alcohol **25**, the π-acid-catalyzed spiroketalization was promptly investigated. Our group has a long-standing history in research concerning gold π-acid catalysis, so evaluating this noble metal for the activation of the triple bond seemed appropiate.[52]

Due to their ability to transform simple starting materials into products of significantly increased complexity,[53] gold complexes have found numerous applications in total synthesis.[54] In particular, their capacity to induce the formation of spiroketals from acetylenic diols has been the subject of continuous research.[55]

Selected examples of applications relevant to this work are shown in Scheme 2.12. The synthesis of (−)-phorbaketal A by Lee and co-workers features the spiroketalization and accompanying double bond isomerization of a diol-containing enyne using stochiometric gold(I) chloride and PPTS as an additive.[56] Intriguingly, the resulting spirocycle bears resemblance to the central section of limaol due to its unsaturation, as well as the vinylic methyl group. Likewise, Trost and co-workers utilized a gold-catalyzed and PPTS-co-catalyzed spiroketalization in their synthesis of (−)-ushikulide A.[57] The resulting spirocycle also comprises an unsaturation, which is produced by accompanying dehydration of the propargylic alcohol during cyclization. Aponick and co-workers have likewise reported on methods for the gold-catalyzed synthesis of olefin-containing spirocycles.[58] The authors transform monopropargylic triols into the unsaturated target compounds once more by spiroketalization and concomitant dehydration. Importantly, the stereoinformation encoded in the triol strongly affects the productivity of the reaction.[58b]

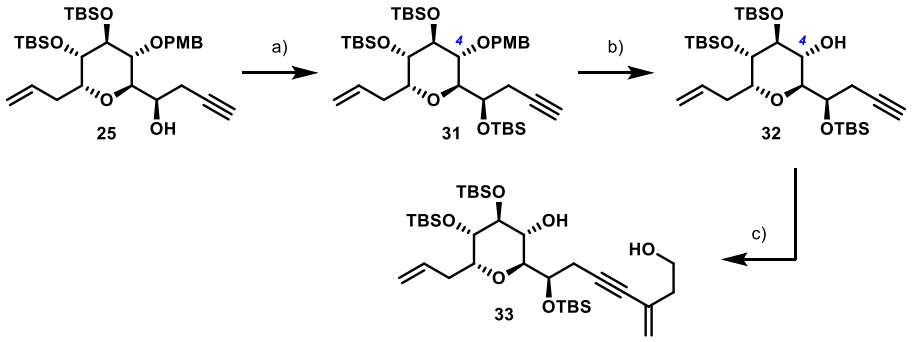
After evaluation of the literature precedence, the approach used in the synthesis of (−)-phorbaketal was deemed most suitable for our efforts. Instead of having to stereoselectively produce a monopropargylic triol, an enyne was considered the more accessible synthetic target.




**Scheme 2.12.** Selected literature precedents for gold(I)-catalyzed spiroketalizations.[56-58]

Before spending time and resources on the synthesis of the fully functionalized spirocyclization precursor, a model system was devised to probe the reactivity of the enyne. The synthesis commenced with two simple protecting group modifications of propargylic alcohol **25** (Scheme 2.13). First, protection of the free hydroxyl group afforded TBS ether **31**, then liberation of the PMB-protected C4-alcohol by treatment with DDQ furnished compound **32**. Both transformations proceeded in quantitative yield.

Alkyne **32** represents an essential building block in the synthesis of the central fragment. It can be diversified into a library of enyne-bearing cyclization precursors by means of Sonogashira cross-coupling with alkenyl halides. The generality and robustness of Sonogashira couplings would potentially allow the introduction of fully functionalized alkenyl fragments at a this stage of the synthesis.[59] However, in order to gain first insights into the spiroketalization, simple 3-iodobut-3-en-1-ol was initially chosen as the reaction partner. It smoothly underwent cross-coupling under palladium and copper co-catalysis to afford the enyne **33** in 73% yield.

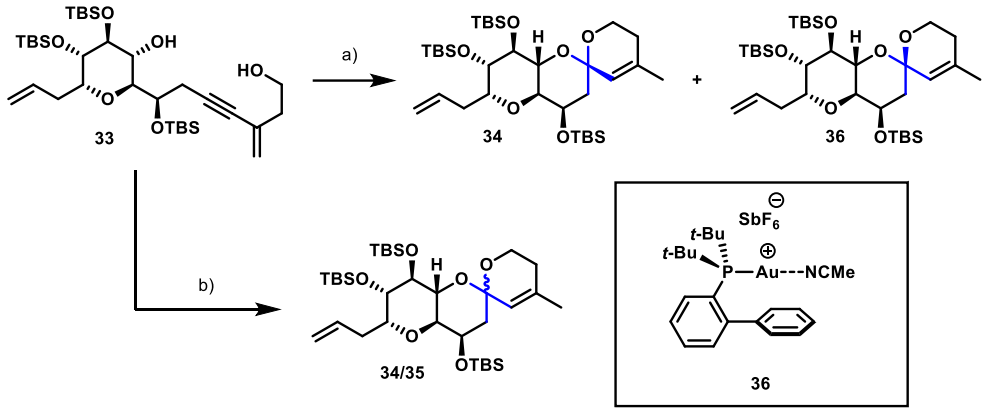



**Scheme 2.13.** Synthesis of the spirocyclization precursor **33**. Conditions: a) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, quant.; b) DDQ, $CH_2Cl_2$, 0 °C to RT, quant.; c) 3-iodobut-3-en-1-ol, $Pd(PPh_3)_4$ (10 mol%), CuI (40 mol%), DIPEA, toluene, RT, 73%.

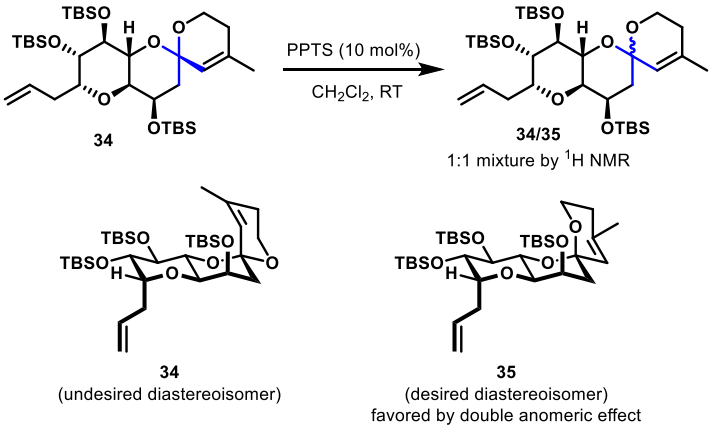
The model cyclization precursor **33** was promptly subjected to a mixture of neutral gold complex chloro-(trimethylphosphine)gold(I), PPTS as an acid co-catalyst, and silver tetrafluoroborate as a halide scavenger to produce the cationic gold(I) species *in situ* (Scheme 2.14). Gratifyingly, the desired cyclization occurred to give two diastereomers in a ratio of 3:1 in a combined yield of 66%. After separation, it became apparent that the undesired isomer **34** preponderated, while the desired diastereoisomer **35** could only be obtained in 13% yield. Changing the catalyst to the air-stable cationic gold complex **36** did not effect any shift in diastereoselectivity.

This disappointing revelation called for the design of a backup strategy: If production of the desired diastereoisomer in the spirocyclization fails, recycling of the undesired diastereoisomer would be necessary. To test whether the two isomers can be interconverted, pure **35** was treated with catalytic amounts of PPTS (Scheme 2.15). $^1$H NMR analysis of the resulting mixture showed a 1:1 ratio of diastereoisomers, confirming the dynamic nature of the

spiroketal moiety and that, despite the double anomeric effect present in its structure, **35** does not seem to be thermodynamically favored over **34**.




**Scheme 2.14.** Spirocyclization of model enyne **33**. Conditions: a) $Au(PMe_3)_3Cl$ (10 mol%), PPTS (10 mol%), $AgBF_4$ (20 mol%), THF, 0 °C to RT, 50% (**34**), 16% (**35**); b) **36** (10 mol%), PPTS (10 mol%), $CH_2Cl_2$, 0 °C, yield not determined, dr 3:1 by $^1H$ NMR.




**Scheme 2.15.** Interconversion of the diastereoisomers **34** and **35** and their respective structures.

In this model study, the spiroketalization was proven to take place with accompanying double bond isomerization to afford the desired internal olefin. In addition, the resulting diastereoisomers can be interconverted under acidic conditions, allowing recycling of the undesired isomer. This encouraged us to move forward with the synthesis of the fully functionalized cyclization substrate.

### 2.2.4 Synthesis of the Sonogashira Cross-Coupling Partner

At this point our synthetic effort had arrived at a crossroad: With alkyne **32** in hand, it was necessary to establish the exact nature of the Sonogashira coupling partner. Its general structure, as seen in Scheme 2.16, would incorporate a chiral alcohol, an alkenyl halide to allow

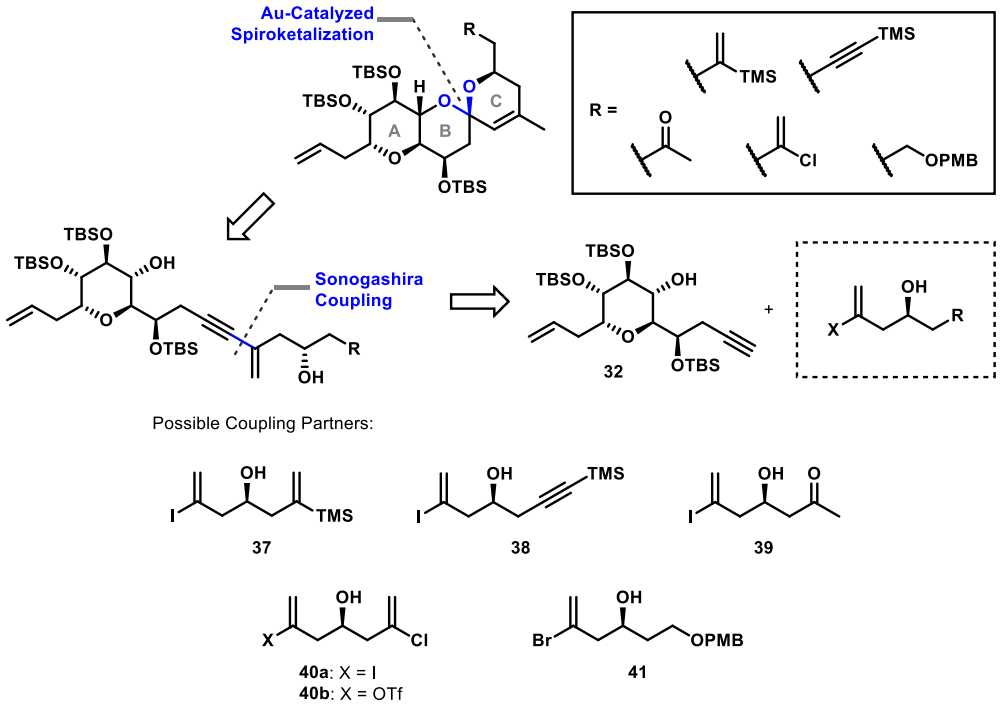
coupling to the alkyne **32**, and finally an alkenyl metal nucleophile, or ideally a less sensitive functionality that could be easily unmasked to provide said nucleophile.

Several possibilities were considered and are listed in Scheme 2.16 in non-chronological order: The alkenyl silane **37** was regarded as an ideal coupling partner. While the alkenyl silane moiety itself would likely not engage in the anticipated coupling to the northern fragment, it was expected to undergo conversion into an alkenyl halide *via* halodesilylation. Several methods are known to effect this transformation[60] and the iododesilylation of alkenyl silanes has also found application in numerous total syntheses.[38b, 61]

The TMS-capped alkyne **38** was likewise deemed a suitable candidate. After removal of the silyl protecting group, the resulting terminal alkyne could be elaborated into an alkenyl nucleophile *via* hydrofunctionalization. A large range of these alkyne derivatizations are well documented. Hydrometalation in general,[62] hydrostannation,[63] hydro- and metalloboration,[64] and dimetalation[65] of alkynes have all been extensively reviewed. On the other hand, the direct hydrohalogenation of alkynes is rather underexplored. While the addition of hydrogen halides to alkynes is considered textbook knowledge, the synthetic applicability of this transformation is limited due to the harshly acidic conditions required. Some more modern methods exist for the hydroiodination of alkynes, however, most rely on the generation of HI *in situ* or on haloboration using highly reactive haloboranes and subsequent protodeboration.[66] A notable exception to this trend is a Ni-catalyzed $\alpha$-selective hydroalumination/iodination sequence developed by Gao and Hoveyda.[67]

The β-hydroxy ketone **39** was considered a riskier alternative to **37** and **38**, since the unprotected ketone was presumed to be rather sensitive. It was unclear whether it would emerge unscathed from the Sonogashira coupling and the acidic conditions of the subsequent gold-catalyzed spiroketalization. In addition, introduction of a second carbonyl group would complicate the coupling of the southern to the central fragment: Since this unification was planned to occur *via* allylation of an aldehyde, conditions would have to be identified that prevent competing allylation of the ketone. Should the ketone remain intact during these transformations, deprotonation and subsequent triflation could convert the functionality into an alkenyl triflate, which in turn can be elaborated into an alkenylstannane.[68]

Compound **40** was another solution to the synthetic problem at hand. The alkenyl iodide or triflate are exptected to be magnitudes more reactive towards Sonogashira coupling than the alkenyl chloride, dispelling any doubts about chemoselectivity. After cyclization, the chloride could be treated with LiDBB to induce lithium-halogen exchange.[69] Subsequent transmetalation of the lithium species to tin or zinc would allow for a palladium-catalyzed cross-coupling to the northern allyl electrophile.




**Scheme 2.16.** Sonogashira coupling partners and the resulting final central fragments under consideration.

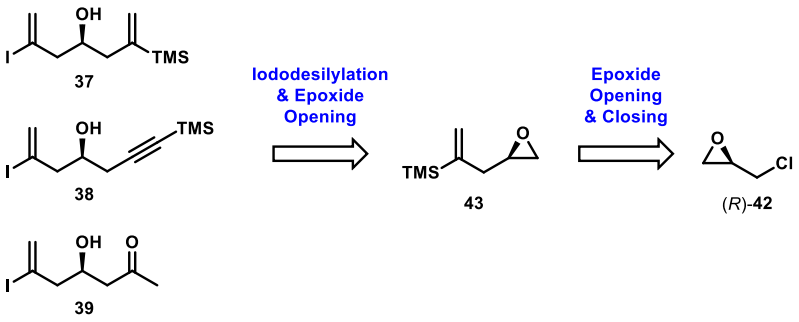
The final option under consideration was the literature-known monoprotected diol **41**.[70] After coupling and cyclization, the northern section of the central fragment would comprise an orthogonally protected primary alcohol. After deprotection, this functional group could be converted into an alkyne by an oxidation/Seyferth–Gilbert homologation sequence. Although the protected alcohol is projected to be less susceptible to unwanted side reactions, its transformation into the desired alkenyl nucleophile is also significantly more laborious in terms of step-count.

### 2.2.4.1 Synthesis of Alkenyl Silane, Alkyne, and Ketone Partners

The synthesis of **37**, **38**, and **39** was envisioned to start from inexpensive (*R*)-epichlorohydrin ((*R*)-**42**, see Scheme 2.17). Both enantiomers are commercially available. Copper-catalyzed epoxide opening and subsequent base-mediated ring closing would furnish the literature-known intermediate **43**.[71] Iododesilylation and another epoxide opening would grant access to the desired chiral building blocks.

In a forward sense, the first step of the synthesis proceeded well (Scheme 2.18). Addition of the Grignard reagent **44** (prepared from bromide **45**) to (*R*)-epichlorohydrin with catalytic amounts of CuCN selectively resulted in epoxide opening at the less hindered site and afforded the alcohol **46** in quantitative yield.[72] The following epoxide closing proved more challenging than anticipated. Treatment of chlorohydrin **46** with potassium carbonate in methanol gave the desired product, but isolation was complicated by the volatility of the target epoxide **43**. The

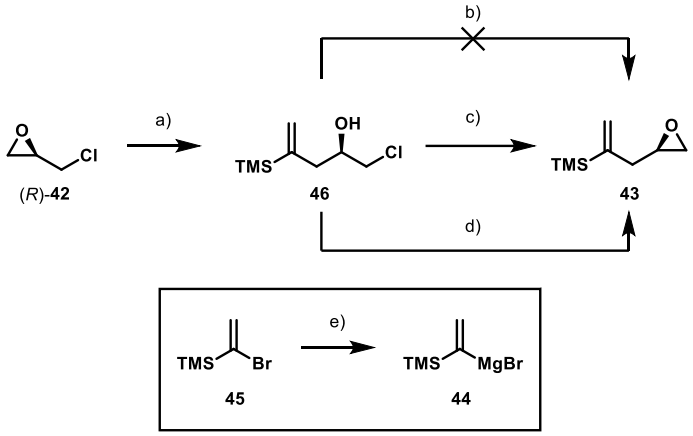
solvent could not be fully separated from the desired product. Since residual methanol was expected to be deleterious for subsequent transformations, an alternative epoxide closing was sought out.




**Scheme 2.17.** Retrosynthetic analysis of alkenyl silane **37**, alkyne **38**, and ketone **39**.

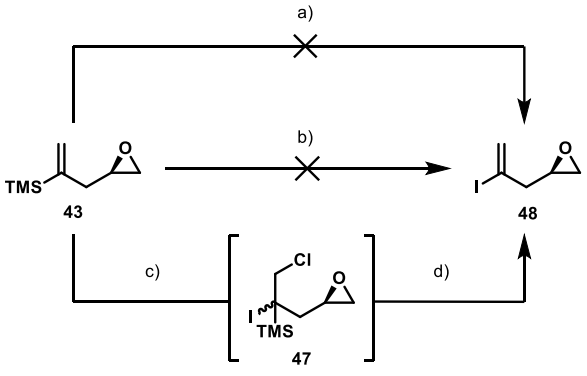
To minimize the presence of methanol in the reaction mixture, a defined amount of potassium methoxide was produced *in situ* by reacting one equivalent of methanol with one equivalent of the strong base KHMDS in THF at low temperatures. The resulting fine suspension of potassium methoxide in THF was then treated with halohydrin **46**, affording the desired epoxide **43** in quantitative yield. Although this method proved efficient, some THF remained in the product. Ultimately, this was of little concern, since the following steps were performed in THF as the reaction solvent as well.

Later along the synthesis of limaol, a final modification was made to the epoxide closing procedure: To avoid presence of any residual solvents in the product, highly volatile diethyl ether was chosen as the reaction medium. To our delight, adding alcohol **46** to a suspension of powdered sodium hydroxide in diethyl ether provided **43** in quantitative yield and high purity after filtration and removal of the solvent *in vacuo*.




**Scheme 2.18.** Synthesis of the epoxide-bearing alkenyl silane **43**. Conditions: a) **44**, CuCN (10 mol%), THF, −50 to −20 °C, quant.; b) $K_2CO_3$, MeOH, RT; c) KHMDS, MeOH, THF, −78 °C to RT, quant.; d) NaOH, $Et_2O$, RT, quant.; e) Mg turnings, 1,2-dibromoethane (5 drops), THF, RT, quant.

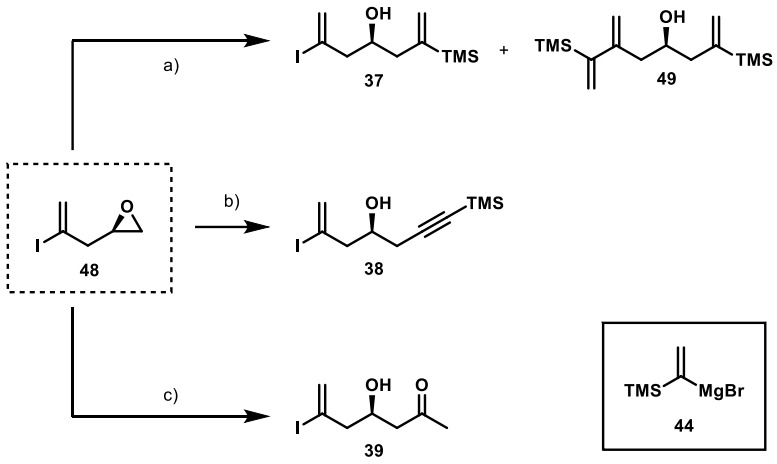
With reliable access to the epoxide **43** secured, conditions for the iododesilylation of the alkenyl silane were evaluated (Scheme 2.19). The research groups of Zakarian and Vilarrasa have found hexafluoroisopropanol (HFIP) to be effective for iododesilylations.[60a, 60b] However, in the case of **43**, HFIP as the solvent and NIS as the $I^+$-source resulted in an intractable mixture. Similarly, treatment of **43** with iodine in $CH_2Cl_2$ also led to a complex mixture of products. The desired product was not observed in either case. In light of these results, a two-step protocol using a modified procedure by Miller and co-workers was attempted instead:[60c, 60d] Addition of iodine monochloride gave the temperature-sensitive dihalide **47**, which was subjected to a quick work-up to remove traces of ICl, and then treated with TBAF to induce the elimination of TMSCl. This efficient series of transformations afforded alkenyl iodide **48** in 79% yield over both steps. The volatile product had to be handled with extreme care, as prolonged application of vacuum led to a significantly diminished yield.




**Scheme 2.19.** Preparation of the alkenyl iodide **48**. Conditions: a) NIS, HFIP, 0 °C; b) $I_2$, $CH_2Cl_2$, RT; c) ICl, $CH_2Cl_2$, −78 °C; d) TBAF, THF/$Et_2O$, 0 °C, 79% over two steps.

The bifunctional building block **48** allowed for another bifurcation in the synthetic route. It could either be directly cross-coupled to alkyne **32**, or functionalized further *via* conventional epoxide opening as shown before. With the goal of a more convergent synthesis in mind, the second option was favored (Scheme 2.20). Treatment of the epoxide **48** with Grignard reagent **44** under copper catalysis furnished the silane **37** in 62% yield. Undesired triene **49** was also isolated in 26% yield and is presumably the product of an Ullmann-type coupling between the Grignard reagent **44** and the vinyl iodide moiety of **37**.

Similarly, the TMS-capped alkyne **38** was obtained in excellent yield by Lewis acid-mediated epoxide opening of **48** using lithiated TMS-acetylene as the nucleophile. In the same vein, β-hydroxy ketone **39** could be accessed by employing *in situ* generated 1-ethoxyvinyllithium as the nucleophilic partner. Subsequent acidic hydrolysis of the ethyl enol ether primarily formed **39** in 63% yield over two steps.



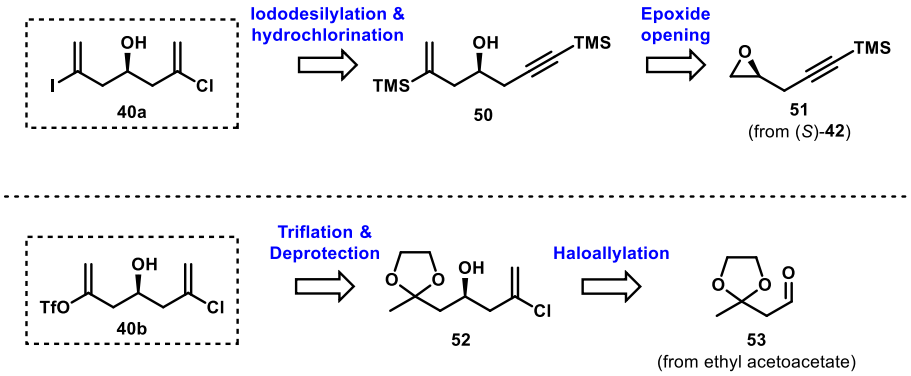

**Scheme 2.20.** Synthesis of the Sonogashira coupling partners **37**, **38**, and **39**. Conditions: a) **44**, CuI (10 mol%), THF, −40 to 0 °C, 62% (**37**), 26% (**49**); b) TMS-acetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C, 94%; c) i) ethyl vinyl ether, *t*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; ii) aq. HCl (0.1 M), THF/$H_2O$, RT, 63% over two steps.

### 2.2.4.2 Attempted Synthesis of an Alkenyl Chloride Partner

The alkenyl chloride **40** was not easily accessible from the bifunctional building block **48**, since the required nucleophile (1-chlorovinyl)lithium is not accessible in a synthetically useful way. Although a report by Köbrich and Flory on chlorosubstituted vinyllithium compounds describes the desired nucleophile, it is noted to be extremely temperature sensitive. If allowed to warm above −110 °C, it rapidly undergoes a Fritsch–Buttenberg–Wiechell rearrangement or an intermolecular base-induced β-elimination to afford lithiated acetylene.[73] Nonetheless, an attempt was undertaken to produce the nucleophile by treatment of 1,2-dichloroethane with two equivalents of *n*-butyllithium and react it with epoxide **48** under Lewis acid-mediation at

−110 °C. No conversion of the starting epoxide was observed, most likely due to the highly cryogenic reaction conditions.

Thus, two alternative retrosyntheses of **40** were devised (Scheme 2.21). Both the alkenyl iodide **40a** and the alkenyl triflate **40b** were considered viable coupling partners. The dihalide **40a** was envisioned to be accessible by iododesilylation of the corresponding alkenyl silane, which in turn could be synthesized from the enyne **50** by hydrochlorination. This compound could be traced back to epoxide **51**, which could again be derived from (*S*)-epichlorohydrin ((*S*)-**42**) in a literature-known epoxide opening/closing sequence.[74] The alkenyl triflate **40b** can be obtained by deprotection and triflation of ketal **52**, which in turn could be accessed by an asymmetric 2-haloallylation developed by Kishi and co-workers[75] using the literature-known aldehyde **53** derived from ethyl acetoacetate as starting material.[76]

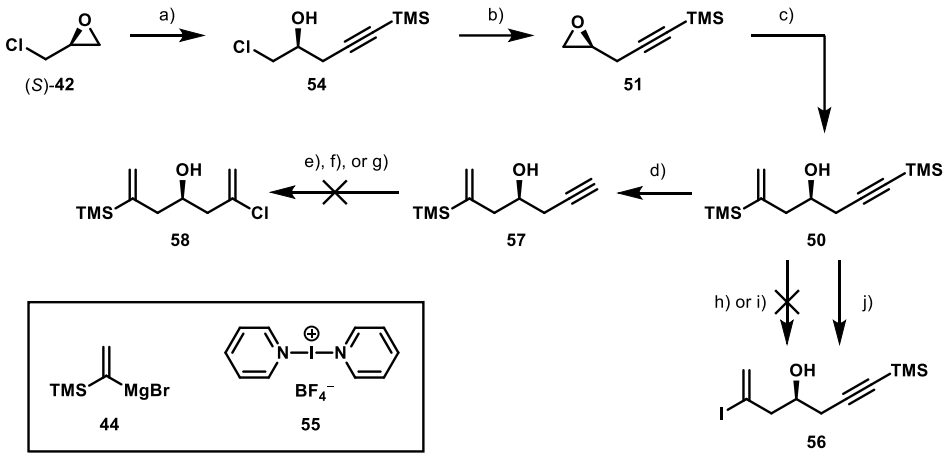



**Scheme 2.21.** Retrosynthetic analyses of alkenyl chlorides **40a** and **40b**.

The synthesis of dihalide **40a** commenced with the Lewis acid-mediated epoxide opening of (*S*)-epichlorohydrin ((*S*)-**42**) and base-mediated ring closing to give epoxide **51**.[74] Subsequent copper-catalyzed epoxide opening using Grignard reagent **44** produced the enyne **50** in 90% yield (Scheme 2.22). At this point, the question arose which halide functionality to install first. Since the alkenyl chloride was presumed to be more stable than the iodide, pursuing the hydrochlorination of the alkyne was prioritized. Nonetheless, some iododesilylations were tested on enyne **50** to give first insights into the suitability of this substrate. Utilizing NIS in acetonitrile or NIS with stochiometric amounts of silver carbonate in HFIP both led to decomposition of the starting material. Only Barluenga's reagent (**55**) in HFIP gave the desired alkenyl iodide **56** in moderate yield.[60b]

In order to prepare the enyne **50** for hydrochlorination, the TMS-cap was removed by treatment with potassium carbonate in methanol to provide the terminal alkyne **57** in 90% yield. The deprotected alkyne was then subjected to a ruthenium-catalyzed hydrochlorination developed by Dérien and co-workers.[77] Disappointingly, this method only resulted in decomposition of the starting material. Hydroalumination using Hoveyda's method[67] or an

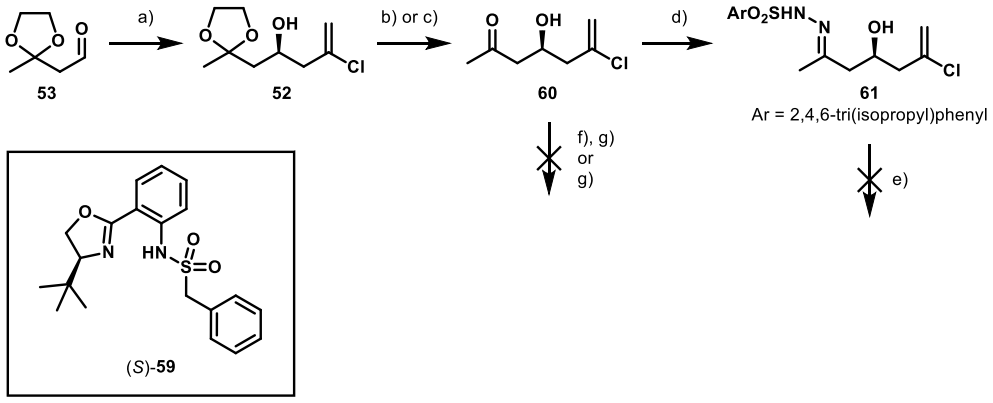
alcohol-directed hydrozirconation using Schwartz' reagent[78] and subsequent quenching of the alkenylmetal species with NCS were also unsuccessful, affording the protodemetalated alkene as the only detectable product in both cases. The desired chloroalkene **58** was not observed.




**Scheme 2.22.** Attempted synthesis of dihalide **40a**. Conditions: a) TMS-acetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C to RT, 98%; b) NaOH, $Et_2O$, RT, 80%; c) **44**, CuI (10 mol%), THF, −50 to −20 °C, 90%; d) $K_2CO_3$, MeOH, RT, 90%; e) Cp*RuCl(cod) (2.5 mol%), $PPh_3$ (2.5 mol%), HCl in $Et_2O$, DCE, RT; f) Ni(dppp)$Cl_2$ (3 mol%), DIBAL-H, *then* NCS, THF, 0 °C to RT; g) $Cp_2ZrHCl$, $CH_2Cl_2$, *then* NCS, THF, RT; h) NIS, MeCN, 0 °C; i) NIS, $Ag_2CO_3$, HFIP, 0 °C; j) Barluenga's reagent (**55**), HFIP, RT, 42%.

Since the dihalide **40a** proved challenging to synthesize, we directed our attention towards the triflate **40b**. To this end, literature-known aldehyde **53** was prepared from ethyl acetoacetate in three steps.[76] Kishi's chromium-catalyzed 2-haloallyation using the PHOX-type ligand (*S*)-**59** gave the desired homoallylic alcohol **52** in 92% yield and 92% *ee* on a 1.5 mmol-scale (Scheme 2.23). Upon scale-up to 5.0 mmol, the yield and enantiomeric excess decreased to 43% and 86% *ee*, respectively. However, enough material was obtained to investigate downstream transformations. Deprotection of the ketal unveiled β-hydroxy ketone **60** either by treatment with PPTS as an acid catalyst at elevated temperatures or, in a milder variant, using catalytic indium(III) triflate at ambient temperature.[79] However, attempts to convert the ketone moiety into an alkenyl electrophile through either a Shapiro reaction (*via* hydrazone **61**) or Barton's vinyl iodide synthesis failed.[80] Even prior silyl protection of the free alcohol did not alleviate the problems faced in subsequent transformations: Neither triflation of the ketone nor another attempt at Barton's vinyl iodide synthesis led to any desired product.

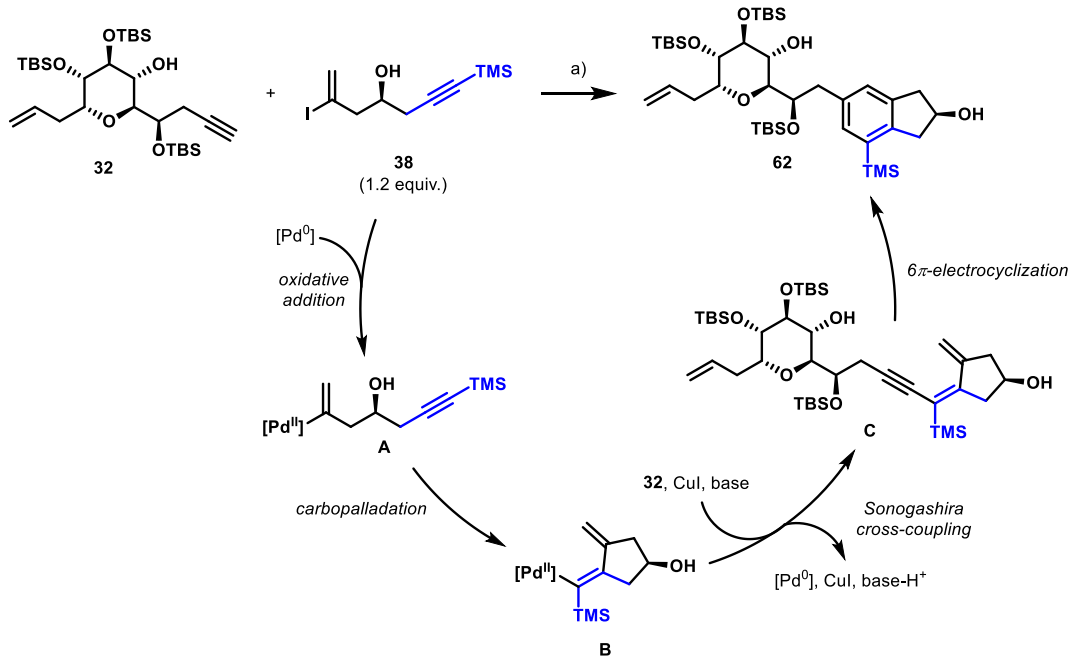
Due to repeated failure to access the bifunctional building block **40**, synthetic efforts towards this fragment were suspended. Instead, downstream chemistry with coupling partners **37**, **38**, **39**, and **41** was explored.




**Scheme 2.23.** Attempted synthesis of the alkenyl triflate **40b**. Conditions: a) $CrCl_3$·3 THF (10 mol%), **59** (11 mol%), $NEt_3$ (20 mol%), Mn, *then* 3-bromo-2-chloropropene, 2,6-lutidine, *then* **68**, TMSCl, *then* TBAF, THF, RT to 0 °C, 92%, 92% *ee* on 1.5 mmol-scale, 43%, 86% *ee* on 5.0 mmol-scale; b) PPTS (30 mol%), acetone, reflux, 71%; c) $In(OTf)_3$ (0.8 mol%), acetone, RT, 88%; d) trisylhydrazine, $Et_2O$, RT, 72%; e) *n*-BuLi, TMEDA, *then* NIS, 0 °C to RT; f) TESOTf, 2,6-lutidine, $CH_2Cl_2$, –78 °C; g) hydrazine monohydrate, EtOH, 70 °C, *then* $NEt_3$, $I_2$, $CH_2Cl_2$/THF, 0 °C.

### 2.2.5 Assembly of the Enyne and Gold-Catalyzed Spiroketalization

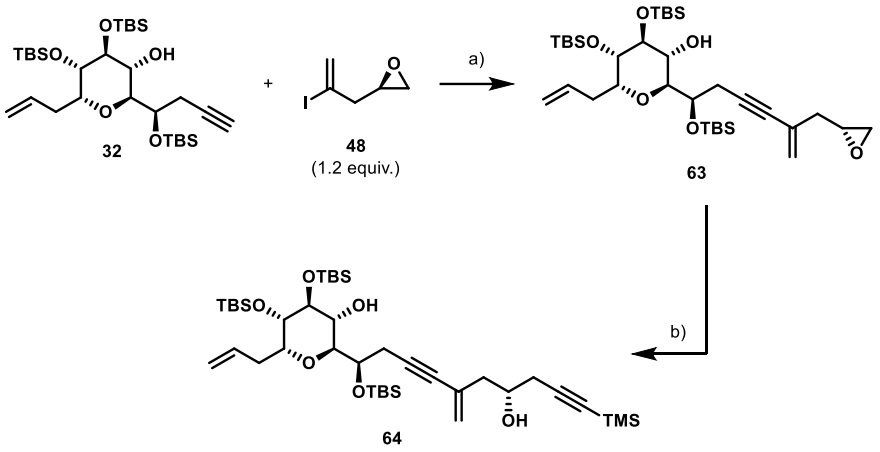
The Sonogashira cross-coupling between alkenyl halides and terminal alkynes is a robust and popular method of forging conjugated enynes.[59] The first cross-coupling en route to the desired enyne was attempted with alkyne-bearing alkenyl iodide **38** and alkyne **32**. To our surprise, instead of the conjugated enyne, the arene **62** was isolated as the sole product in 27% yield (Scheme 2.24). This intriguing result can best be explained as follows: After oxidative addition of palladium(0) into the alkenyl iodide to give palladium(II) complex **A**, intramolecular carbopalladation onto the alkyne takes place, giving the cyclized complex **B**. A copper acetylide formed from alkyne **32** then undergoes transmetalation onto the palladium(II) species and, after reductive elimination in accordance with the standard Sonogashira cross-coupling mechanism, palladium(0) and dienyne **C** are produced. This dienyne is primed for a 6π-electrocyclization to afford the observed benzene derivative **62**. Although this reaction is interesting from a mechanistic perspective, it was of little synthetic use for our efforts towards the desired conjugated enyne. To prevent the intramolecular carbopalladation from taking place, a detour in the synthetic route was necessary.



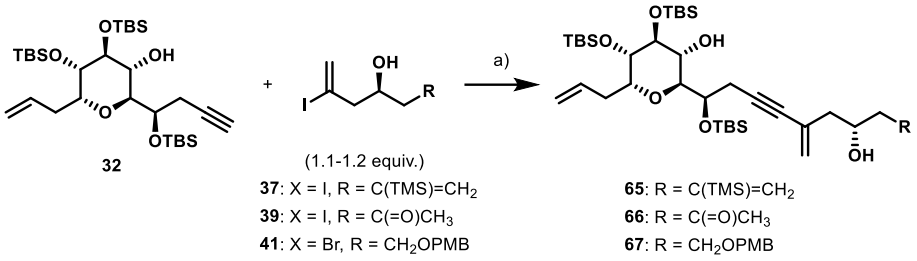

**Scheme 2.24.** Attempted Sonogashira cross-coupling between alkyne **32** and alkenyl iodide **38** and proposed mechanism for the formation of **62**. Conditions: a) $Pd(PPh_3)_4$ (10 mol%), CuI (20 mol%), $HNEt_2$, THF, RT, 27%.

Rather than coupling the alkenyl iodide **38** directly, its precursor **48** was instead used in hopes of a subsequent epoxide opening allowing access to the desired enyne. Sonogashira cross-coupling afforded the epoxide-bearing enyne **63** in 99% yield after brief optimization of the reaction conditions (Scheme 2.25). The optimal solvent was found to be pure diisopropylamine instead of mixtures of toluene, THF, DMF and DIPEA. Instead of employing $Pd(PPh_3)_4$ as the palladium source, $Pd_2(dba)_3$ and two equivalents of triphenylphosphine per equivalent of palladium(0) ensured a faster and higher yielding reaction. Since the active catalyst in the Sonogashira coupling is di-ligated $Pd(0)L_2$, the presence of more than two equivalents of ligand slows down the reaction due to competitive ligand coordination.[59a] With access to **63**, opening of the epoxide under Lewis-acid-mediated conditions with lithium TMS-acetylide as the nucleophile gave the desired alkyne-bearing enyne **64** in excellent yield over two steps.

Using the optimized Sonogashira cross-coupling conditions, alkenyl iodides **37** and **39** and the alkenyl bromide **41** were united with alkyne **32** to give the enynes **65**, **66**, and **67**, respectively, in excellent yields (Scheme 2.26).

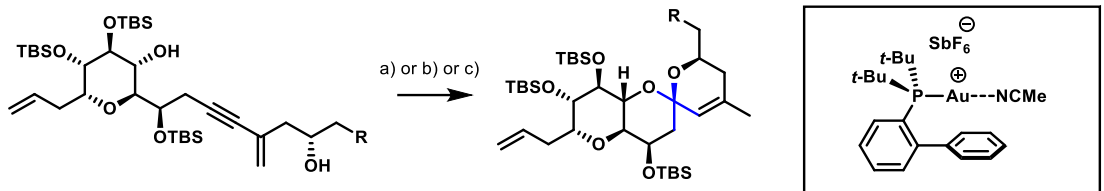



**Scheme 2.25.** Synthesis of the alkyne-bearing enyne **64**. Conditions: a) $Pd_2(dba)_3$ (5 mol%), $PPh_3$ (20 mol%), CuI (15 mol%), HN(*i*-Pr)$_2$, RT, 99%; b) TMS-acetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C, 97%.




**Scheme 2.26.** Synthesis of the enynes **65**, **66**, and **67**. Conditions: a) $Pd_2(dba)_3$ (5 mol%), $PPh_3$ (20 mol%), CuI (15 mol%), HN(*i*-Pr)$_2$, RT, 96% (**65**), 93% (**66**), 68% (**67**).

With the fully substituted enynes in hand, the gold-catalyzed spiroketalization could be further investigated. Again using the air-stable cationic gold complex **36** and PPTS as an acid co-catalyst, the alkyne-bearing enyne **64** was efficiently cyclized, giving a single diastereoisomer of the spiroketal **68** in 68% yield (Scheme 2.27, conditions a). Comparison of the $^1$H NMR spectrum of compound **68** with the spectra of diastereoisomers **34** and **35** indicated that exclusively the desired diastereoisomer had formed (Figure 2.1): The characteristic shift of the olefinic proton on the unsaturated spiroketal moiety was nearly identical for compounds **68** and **35** at 5.18 ppm but significantly downfield-shifted for compound **34** at 6.36 ppm. The notable disparity between these two values bears witness to the drastically different chemical environments above and below the plane of the central *trans*-decaline system of limaol.




**64**: R = C≡CTMS
**65**: R = C(TMS)=$CH_2$
**66**: R = C(=O)$CH_3$
**67**: R = $CH_2$OPMB

**68**: R = C≡CTMS
**69**: R = C(TMS)=$CH_2$
**70**: R = C(=O)$CH_3$
**71**: R = $CH_2$OPMB
**72**: R = C≡CH

**36**

**Scheme 2.27.** Spiroketalization of enynes **64**, **65**, **66**, and **67**. Conditions: a) **36** (10 mol%), PPTS (10 mol%), $CH_2Cl_2$, 0 °C to RT, 76% (**68**), 74% (**69**), 65-78% (**70**); b) **36** (5.0 mol%), 2,6-di-*tert*-butylpyridine, $CH_2Cl_2$, RT, *then* AcOH, RT, 89% (**69**), 87% (**71**); c) **36** (10 mol%), 2,6-di-*tert*-butylpyridine, DCE, 100 °C, microwave, *then* AcOH, RT, 61% (**72**).

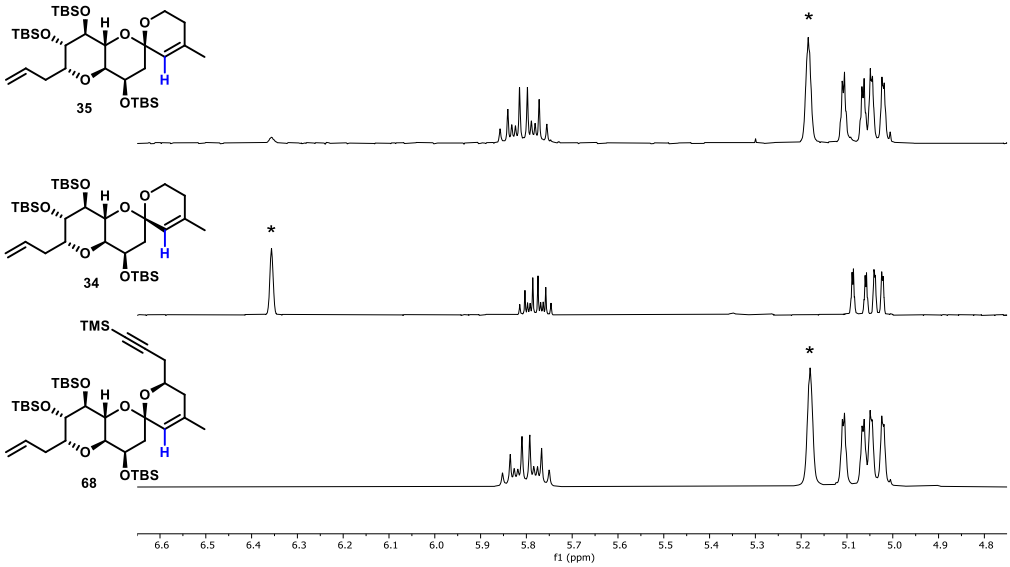
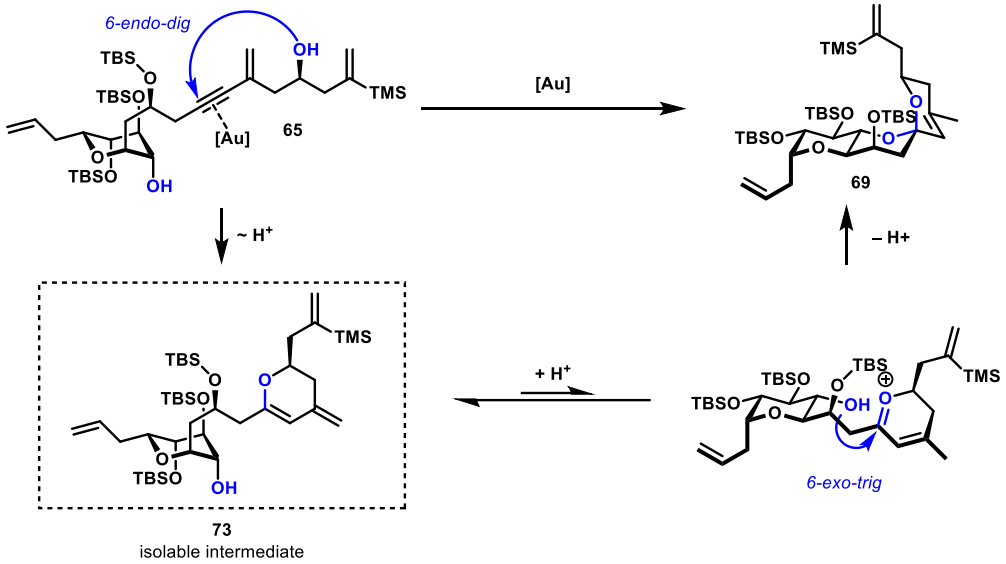



**Figure 2.1.** Comparison of the olefinic range (4.8-6.6 ppm) of the $^1$H NMR spectra of compounds **36**, **35**, and **68**. The peaks marked with asterisks correspond to the respective protons marked in blue.

The excellent diastereoselectivity is likely a product of the aforementioned double anomeric effect present in the desired natural diastereoisomer. For all central fragments, this selectivity was retained and only a single diastereoisomer was formed in good yields: Using PPTS as a co-catalyst, alkenyl silane **69** was formed in 74% yield and ketone **70** in 65-78% yield depending on the reaction scale. In all reactions, partial deprotection of the silyl ethers due to the acidity of the utilized reagents was also observed. In an effort to improve the yields by preventing the transient formation of $HSbF_6$ by protonation of the non-coordinating counterion of complex **36**, buffered conditions using 2,6-di-*tert*-butylpyridine as a stochiometric base were employed (Scheme 2.27, conditions b). Zhdanko and Maier observed that this additive allowed for the isolation of the intermediate enol ethers in gold-catalyzed ketalizations.[81] In congruence

with this observation, the dienol ether **73** could be isolated from the reaction of enyne **65** and identified *via* NMR spectroscopy, indicating that the first cyclization occurs by nucleophilic attack of the exocyclic alcohol on the triple bond in a 6-*endo-dig* fashion (Scheme 2.28). Importantly, the preferred conformation of the saturated pyran ring present in enyne **65** and dienol ether **73** is surmised to be the one where the TBS ethers on the ring are in axial position. The propensity of these bulky protecting groups to adapt the axial conformation is discussed later in the context of the synthesis of the southern fragment (see Section 2.4.1). $^{1}$H NMR experiments indicate that both ring conformers interchange rapidly, as for propargyl alcohol **32** the $^{3}J_{HH}$ coupling constants between the protons geminal to the TBS ethers average to ~6 Hz. Exposure of **73** to acetic acid then induced the second cyclization after ring inversion, furnishing the desired spiroketal **69**. Using these conditions, silane-bearing spiroketal **69** and benzyl ether-bearing spiroketal **71** were prepared in 89% and 87% yield, respectively.




**Scheme 2.28.** Proposed mechanism of the gold-catalyzed spiroketalization of enyne **65** using gold complex **36** and stochiometric 2,6-di-*tert*-butylpyridine, followed by treatment with acetic acid.

When the buffered conditions were applied to alkyne-bearing enyne **64**, the starting material was only partially consumed at room temperature. An explanation for this sluggish reactivity might be the aurophilicity of the second alkyne moiety, which binds the gold catalyst and prevents productive turnover. Switching to high-boiling DCE as solvent and subjecting the mixture to forcing conditions at 100 °C in a microwave reactor achieved full conversion of the starting material (Scheme 2.27, conditions c). Upon concentration and treatment of the residue with acetic acid, the spiroketal **72** bearing a terminal alkyne could be isolated in 61% yield. Although this would obviate a separate alkyne desilylation step, it was significantly less efficient than the acid co-catalyzed variant with 76% yield of silyl-capped **68**.

In summary, effective approaches to all cyclized central fragments were developed, paving the way for the next step of the synthesis: Selective oxidative cleavage of the terminal alkene present in **68**, **69**, **70**, and **72** to unveil the aldehyde required for coupling of the southern fragment.

### 2.2.6 Oxidative Cleavage of the Terminal Olefin

At this point in our efforts, the PMB ether-bearing central fragment **71** was disregarded due to the large number of steps required to transform the PMB ether to an alkenyl nucleophile of any sort. Thus, only compounds **68**, **69**, **70** and **72** were examined further. To prepare these fragments for coupling to the southern section of limaol, the terminal olefin present in each of the compounds had to be selectively converted to an aldehyde in the presence of additional unsaturation (Figure 2.2).

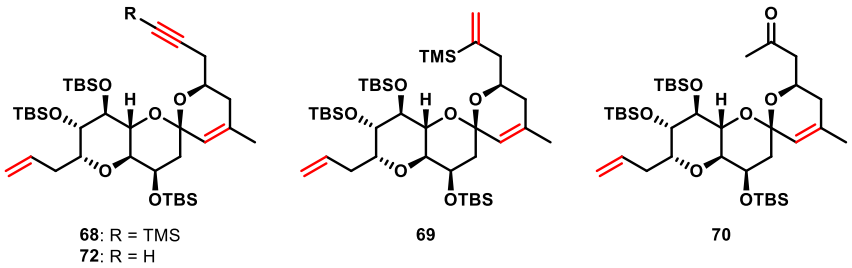
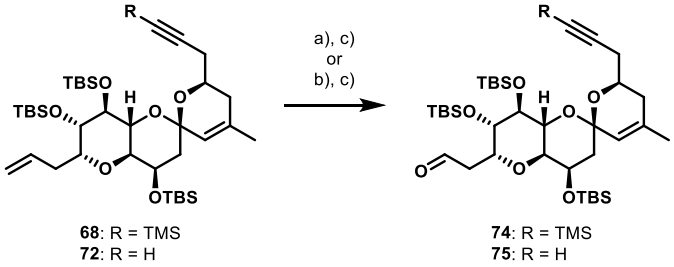



**Figure 2.2.** Unsaturation present in the four central fragments **68**, **69**, **70**, and **72**.

Ozonolysis of the TMS-alkyne-bearing central fragment **68** was low-yielding due to partial decomposition of the starting material. Attempts to attenuate the reactivity of ozone by addition of pyridine[82] or by titration of a solution of the substrate with a saturated solution of ozone[83] were to no avail.[84] Oxidative cleavage under modified Lemieux–Johnson conditions on the other hand led only to sluggish conversion of the starting material and formation of various side products.[85] The same observations proved true for the terminal alkyne-bearing central fragment **72**. It became apparent that a more selective method for the oxidation of terminal alkenes was required.

Sharpless' asymmetric dihydroxylation (AD) has been used to differentiate sterically distinct olefins.[86] Specifically, Negishi and co-workers have employed AD and subsequent treatment of the diol with sodium periodate to effect the oxidative cleavage of a terminal olefin in the presence of a trisubstituted one.[87] In the case of fragments **68** and **72**, this method proved especially valuable (Scheme 2.29). Brief optimization of the ligand showed that for TMS-capped alkyne **68**, standard AD-mix β gave essentially quantitative conversion to an inconsequential mixture of diastereoisomeric diols, which after workup could be subjected to sodium periodate on silica to give the aldehyde **74** in 97% yield. Interestingly, AD-mix α gave no conversion of the starting material, indicating a matched/mismatched case for this system. Ligand optimization

for the AD of terminal alkyne **72** revealed that $(DHQD)_2Pyr$ was most suitable. In addition, the catalyst and ligand loading had to be increased significantly over standard conditions to ensure full conversion of the starting material to the desired diol. Upon periodate-mediated cleavage, the aldehyde **75** could be isolated in 85% yield, giving rapid access to both aldehydes in good yields.




**68**: R = TMS
**72**: R = H

**74**: R = TMS
**75**: R = H

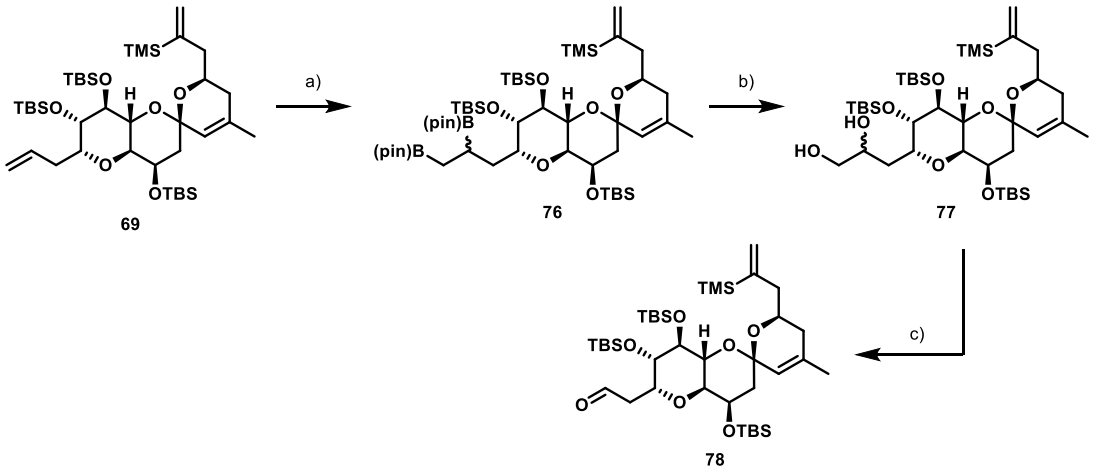
**Scheme 2.29.** Oxdiative cleavage of the terminal olefin in alkyne-bearing fragments **68** and **72**. Conditions: a) AD-mix β, $MeSO_2NH_2$, *t*-BuOH/$H_2O$ 1:1, RT; b) $K_2OsO_4 \cdot 2\ H_2O$ (10 mol%), $(DHQD)_2Pyr$ (25 mol%), $K_2CO_3$, $K_3[Fe(CN)_6]$, $MeSO_2NH_2$, *t*-BuOH/$H_2O$ 1:1, RT; c) $NaIO_4$ on silica, $CH_2Cl_2$, RT, 97% over two steps (a,c) for **74**, 85% over two steps (b,c) for **75**.

For the alkenyl silane-bearing central fragment **69**, neither ozonolysis, Lemieux–Johnson conditions, nor the two-step sequence employing AD and periodate cleavage were productive. Each of these attempts only led to decomposition of the starting material. Thus, a highly selective method for the functionalization of terminal olefins had to be exploited. Inspired by the asymmetric platinum-catalyzed diboration developed by Morken and co-workers, we turned our attention to diboration as the method of choice.[88] The racemic variant pioneered by Miyaura and co-workers exhibits high selectivity for monosubstituted olefins.[89] Using $Pt(dba)_3$ as the catalyst, the terminal olefin present in **69** could be diborated to give an inconsequential mixture of diastereomers of **76** in excellent yield (Scheme 2.30). This compound could be purified by standard flash chromatography using silica and the boron moieties were subsequently oxidized to give the diol **77**. Utilizing mild sodium perborate was paramount to ensure high yields, since use of the standard oxidant hydrogen peroxide led to decomposition. The diol **77** could be cleaved as described above to afford the aldehyde **78** in 87% yield over three steps.

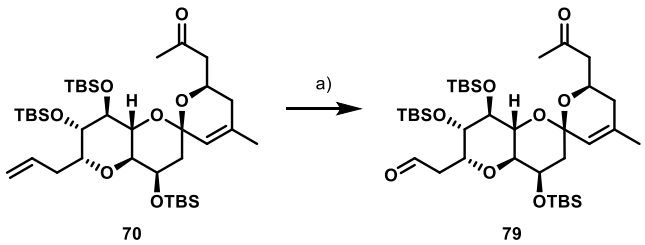
For ketone-bearing central fragment **70**, ozonolysis again failed to produce the desired aldehyde. However, modified Lemieux–Johnson conditions using 2,6-lutidine as an additive effected selective cleavage of the terminal olefin to give aldehyde **79** in one step and in excellent yield (Scheme 2.31).

All four central fragments were efficiently converted to the corresponding aldehydes, which allowed for a first foray into the fragment coupling between the southern and the central fragments *via* an allylation approach (*vide infra*). In summary, aldehyde **74** was prepared in 28%

yield over 15 steps, **75** in 20% over 15 steps, **78** in 30% over 14 steps, and **79** in 27% over 12 steps in linear sequence.




**Scheme 2.30.** Diboration-oxidation sequence to provide aldehyde **78** from fragment **69**. Conditions: a) $Pt(dba)_3$ (3.0 mol%), $B_2(pin)_2$, toluene, RT, 93%; b) $NaBO_3 \cdot H_2O$, THF/$H_2O$ 1:1, 0 °C to RT, 94%; c) $NaIO_4$ on silica, $CH_2Cl_2$, RT, quant.



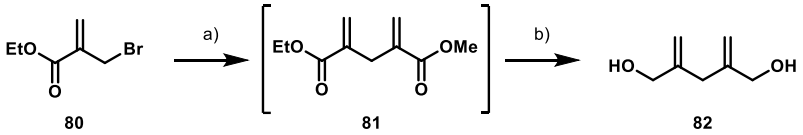

**Scheme 2.31.** Lemieux–Johnson approach to ketoaldehyde **79** from ketone **70**. Conditions: a) $OsO_4$ (10 mol%), 2,6-lutidine, $NaIO_4$, 1,4-dioxane/$H_2O$ 3:1, RT, 87-93%.

## 2.3 Synthesis of the Northern Fragment

The first-generation synthesis of the northern fragment was performed by Dr. Xiaobin Mo. This chapter represents a summary of his results.

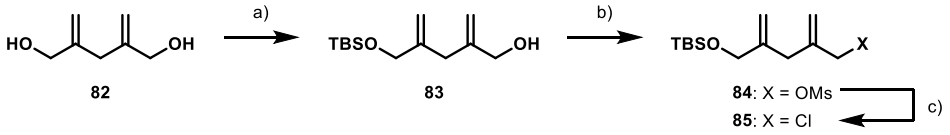
### 2.3.1 Synthesis of the Allyl Electrophile

The preparation of the diene-containing allyl electrophile commenced from allyl bromide **80**, which was subjected to a Baylis–Hillman reaction with methyl acrylate to give the diester **81** (Scheme 2.32).[37] This compound was found to be unstable and partially decomposed upon purification by silica flash chromatography. To circumvent this, methyl acrylate was instead removed *in vacuo* and the residue was directly subjected to reduction using DIBAL-H to give the desired skipped diene-containing diol **82** in 57% yield over two steps.




**Scheme 2.32.** Synthesis of the skipped diene **82** *via* a Baylis–Hillman reaction. Conditions: a) DABCO, methyl acrylate, RT; b) DIBAL-H, THF, RT, 57% over two steps.

The diol was selectively mono-protected using TBSCl and sodium hydride to afford the alcohol **83** in 87% yield (Scheme 2.33). The remaining free hydroxy group was converted to the mesylate to give the electrophile **84** in 88% yield. This allyl mesylate was chlorinated by treatment with lithium chloride and gentle heating to quantitatively produce the allyl chloride **85**. In summary, the diene electrophile **85** was prepared in 43% yield over five steps.



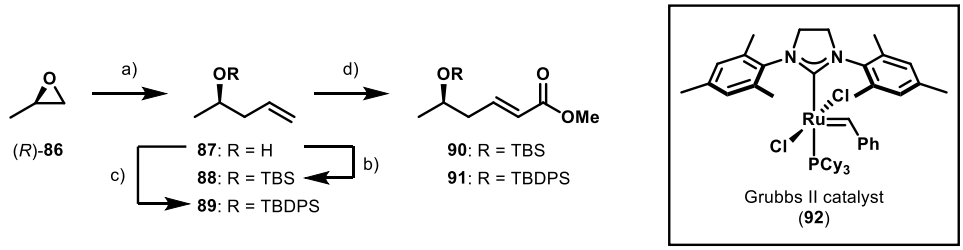

**Scheme 2.33.** Preparation of the skipped diene-containing allyl electrophiles **84** and **85**. Conditions: a) NaH, TBSCl, THF, 0 °C to RT, 87%; b) MsCl, $NEt_3$, THF, RT, 88%; c) LiCl, THF, 40 °C, 98%.

### 2.3.2 Synthesis of the Alkenyl Nucleophile

The preparation of the alkenyl nucleophile began from (*R*)-propylene oxide ((*R*)-**86**), which underwent copper-catalyzed epoxide opening with vinylmagnesium bromide to give the homoallylic alcohol **87** (Scheme 2.34). Competitive bromohydrin formation caused the desired product to form only in moderate yield. Subsequent protection of the free alcohol to afford either the TBS ether **88** or TBDPS ether **89** proceeded in excellent yield. Some intermediates bearing the TBS group were found to be volatile later along the synthetic route, while the

TBDPS-containing compounds were easier to handle. However, initially both silyl ethers were taken forward, since concerns about the ease of removal of the TBDPS group led us to first prioritize the synthesis of the alkenyl nucleophile bearing the TBS group.

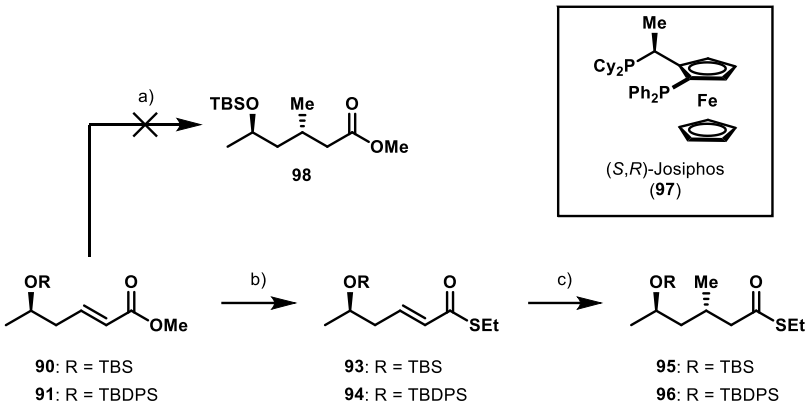
In order to construct the α,β-unsaturated esters **90** and **91**, an olefin cross-metathesis between olefins **88** or **89**, both "type I" olefins, and methyl acrylate, a "type II" olefin, was executed.[90] Using Grubbs II catalyst (**92**) provided the desired products in excellent yields on up to 9.3 mmol-scale with a catalyst loading of 1.0 mol%, underscoring the efficiency of this reaction.



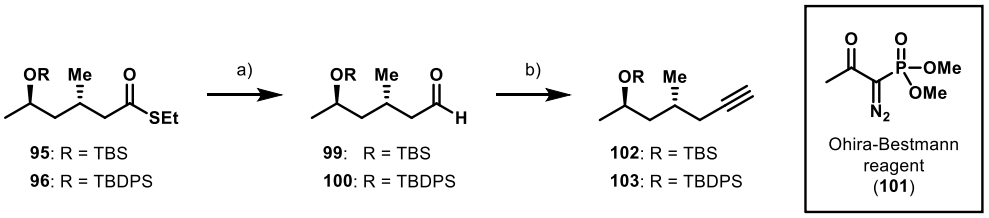

**Scheme 2.34.** Synthesis of the α,β-unsaturated esters **90** and **91**. Conditions: a) CuI (17 mol%), vinylmagnesium bromide, THF, −78 °C to 0 °C, 38%; b) TBSCl, imidazole, DMF, RT, 87%; c) TBDPSCl, imidazole, DMF, RT, 90%; d) **92** (1-5 mol%), methyl acrylate, $CH_2Cl_2$, reflux, 78% (**90**), 86% (**91**).

With the Michael acceptors **90** and **91** in hand, the diastereoselective 1,4-addition of a methyl nucleophile could be explored. Initial attempts using a method developed by Loh and co-workers failed, resulting exclusively in 1,2-addition of the methyl Grignard reagent and the formation of additional side products (Scheme 2.35).[91] This observation was attributed to the steric encumbrance of the substrates, the generally poor Michael acceptor capabilities of α,β-unsaturated esters, and the comparatively low nucleophilicity of methylmagnesium bromide. In order to increase the reactivity of the system, both esters **90** and **91** were converted to the corresponding thioesters **93** and **94** in good yields. The reduced electron delocalization in the thioester moiety of these compounds results in decreased electron density in the double bond, thereby facilitating conjugate addition. Utilizing a method developed by Feringa and co-workers, asymmetric 1,4-addition of methylmagnesium bromide was achieved with high diastereoselectivity and in excellent yields to give access to the saturated thioesters **95** and **96**.[92] This reaction also proved scalable: It was performed on a 8.6 mmol-scale with substrate **94** using a copper catalyst loading of 2.0 mol% and 2.4 mol% of ligand **97**.

The thioesters underwent palladium-catalyzed Fukuyama reduction using triethylsilane as the reductant to provide the aldehydes **99** and **100** in 73% and 85% yield, respectively (Scheme 2.36).[93] Treatment of the aldehydes with Ohira–Bestmann reagent (**101**) effected chain elongation to the alkynes **102** and **103** in 65% and 94% yield, respectively.[94] Throughout this sequence, the yields for the TBS-protected compounds were lower as a result of their volatility.



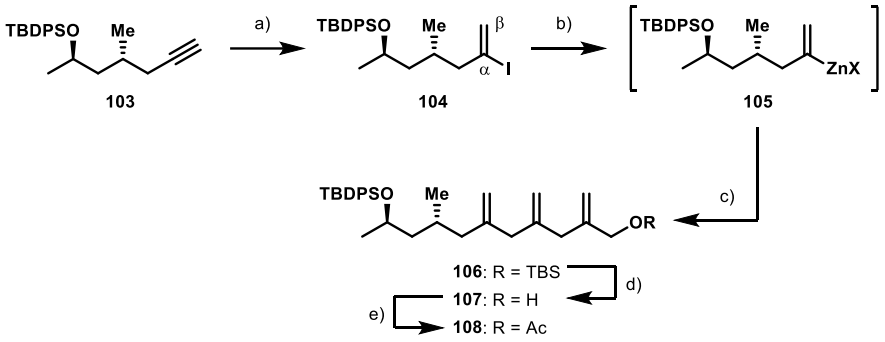

**Scheme 2.35.** Synthesis of the methylated thioesters **95** and **96**. Conditions: a) CuI (2 mol%), (*S*)-Tol-BINAP (3 mol%), MeMgBr, THF, −20 °C, *tert*-butyl methyl ether; b) $AlCl_3$, TMS-SEt, THF, reflux, 73-79% for **93**, 86-96% for **94**; c) CuBr·$SMe_2$ (2.0-5.0 mol%), **97** (2.4-6.0 mol%), MeMgBr, −78 °C, *tert*-butyl methyl ether, 87%, dr 10:1 (**95**), 90%, dr 20:1 (**96**).




**Scheme 2.36.** Synthesis of the alkynes **102** and **103**. Conditions: a) Pd/C (5 mol%), $Et_3SiH$, $CH_2Cl_2$, RT, 73% (**99**), 85% for (**100**); b) **101**, $K_2CO_3$, MeOH, RT, 65% (**102**), 94% (**103**).

To convert **102** and **103** into alkenyl nucleophiles in readiness for allyl-alkenyl cross-coupling, hydrofunctionalizations of the terminal alkynes in the Markovnikov-sense had to be conducted. Although an $\alpha$-selective hydrostannation was briefly considered, this approach was disregarded due to apparent regioselectivity problems described in the literature.[63b] Instead, a two-step approach to the corresponding alkenyl zinc species *via* the alkenyl iodide was pursued. Several methods to effect $\alpha$-selective hydroiodination were examined: Kamiya and co-workers developed a synthesis of internal alkenyl iodides from alkynes through the addition of hydrogen iodide generated *in situ*.[95] The strongly acidic conditions, however, proved incompatible with silyl ether-bearing **102** and **103**. Gao and Hoveyda's nickel-catalyzed $\alpha$-selective hydroalumination and subsequent quenching of the alkenylmetal species with NIS provided access to the desired alkenyl iodides in 72-79% yield and moderate regioselectivity.[67] However, the TBS-protected alkenyl iodide resulting from this reaction contained inseparable impurities, hampering its use in later reactions. Thus, all further transformations were only conducted with the more easily purified TBDPS-protected analog **103**. A higher-yielding alternative was found in the iodoboration of terminal alkynes established by Suzuki and co-workers.[66d] Treating TBDPS-containing alkyne **103** with *B*-iodo-9-BBN and subsequent

protodeboration using acetic acid gave the desired alkenyl iodide **104** in 96% yield and with high regioselectivity (Scheme 2.37).




**Scheme 2.37.** Completion of the synthesis of the northern fragment **108**. Conditions: a) *B*-Iodo-9-BBN, hexanes, RT, *then* AcOH, RT, 98% over two steps, $\alpha/\beta$ > 20:1; b) *t*-BuLi, −78 °C, $Et_2O$, *then* $ZnBr_2$, THF, −78 °C to RT, 96%; c) **85**, $Pd(PPh_3)_4$ (5 mol%), DMF, RT; d) TBAF, THF, 0 °C to RT, 82% over two steps; e) $Ac_2O$, pyridine, DMAP (10 mol%), $CH_2Cl_2$, RT, 96%.

Several metalation protocols were tested on the alkenyl iodide **104**. Either halogen-lithium-exchange using *tert*-butyllithium or halogen-magnesium-exchange using isopropylmagnesium chloride and subsequent transmetalation to zinc, by addition of zinc chloride, provided the desired alkenylzinc **105**.[96] The yields of the metalation step were determined by iodometric titration, showing that the lithiation approach was most productive with 96% yield of **105**.[97] In comparison, direct insertion of metallic zinc in presence of lithium chloride gave the desired alkenylmetal species in only 51% yield.[98]

In order to examine the fragment unification of nucleophile **105** and allyl electrophile **85**, a model alkenyl zinc nucleophile derived from 2-iodohept-1-ene was subjected to a range of coupling conditions with **85**. Catalytic amounts of copper(I) cyanide to induce a $S_N2'$ reaction or use of catalytic $CoBr_2$ in accordance with a procedure developed by Knochel and co-workers both provided the desired model triene in good yields.[99] The best outcome was achieved with classical Negishi cross-coupling conditions employing $Pd(PPh_3)_4$ as the catalyst. This reaction afforded the model triene in quantitative yield. Applying the same conditions to the coupling between **105** and **85** gave the triene **106**, which was inseparable from apolar impurities present in the crude reaction mixture. Thus, TBAF-mediated deprotection of the primary TBS ether facilitated purification and gave the allylic alcohol **107** in 82% yield over two steps.

The resulting free alcohol was then converted to a stable and storable allyl acetate using acetic anhydride, pyridine, and catalytic DMAP. The reaction proceeded smoothly to give the completed allyl electrophile **108** in 96% yield. In summary, **108** was prepared in 12% yield, 12 steps in longest linear sequence, and a total of 17 steps.

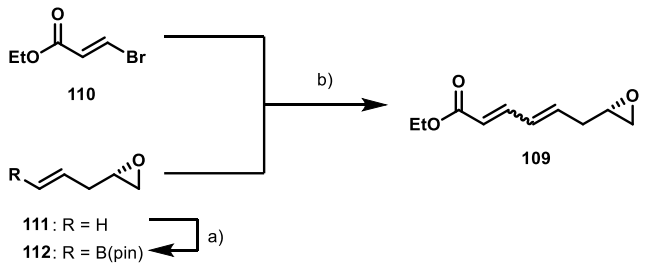
## 2.4 Synthesis of the Southern Fragment

The first-generation synthesis of the southern fragment was mainly performed by Dr. Xiaobin Mo. This chapter represents a summary of his results.

### 2.4.1 The *Oxa*-Michael Approach

#### 2.4.1.1 Synthesis of the Epoxide-Containing *E*,*E*-Diene

Synthetic studies towards the southern fragment began with investigation of cross-coupling conditions to afford the required epoxide-containing *E*,*E*-diene **109** (Scheme 2.38). Bromopropenoate **110** was conveniently prepared in two steps from propiolic acid closely following a literature procedure.[100] Olefinic coupling partner **111** could be synthesized starting from (*S*)-epichlorohydrin ((*S*)-**42**) as described by Kumar and co-worker.[101] Heck cross-coupling conditions to assemble building blocks **110** and **111** failed to afford the desired diene **109**. Alternatively, a Suzuki cross-coupling was envisioned between the boronic acid ester **112** and bromide **110**. However, the preparation of **112** by cross-metathesis using Grubbs II catalyst (**92**) proved to be problematic and did not allow for enough material throughput to attempt downstream chemistry. Due to these issues, the cross-coupling approach was abandoned.

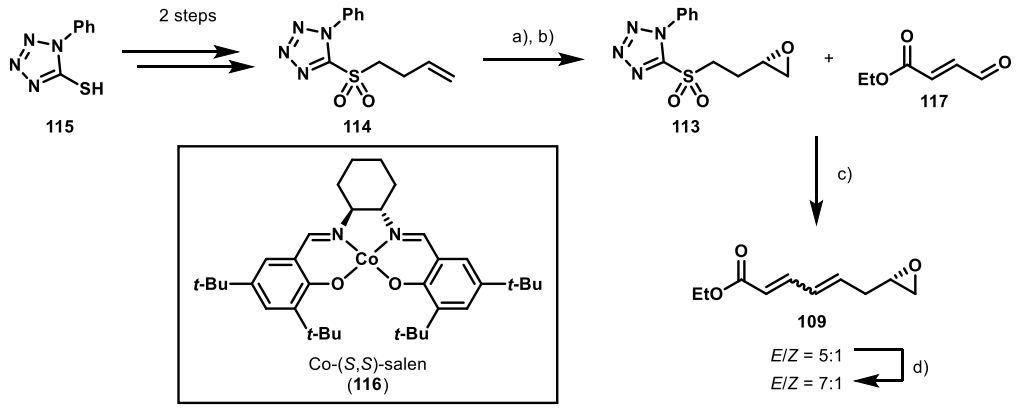



**Scheme 2.38.** Cross-coupling approach to *E*,*E*-diene **109**. Conditions: a) **92** (2.0 mol%), vinylboronic acid pinacol ester, $CH_2Cl_2$, reflux, 17%; b) $Pd(OAc)_2$ (10 mol%), $Ag_2CO_3$, DMF, 50 °C, 33%, *E*/*Z* 10:1.

Focus was instead shifted to a Julia–Kocienski olefination strategy, necessitating the synthesis of enantiomerically pure sulfone **113** (Scheme 2.39). This was achieved by epoxidation of literature-known olefin **114** (obtained in two steps from commercial **115**)[102] using *m*-CPBA. The resulting racemic epoxide **113** was subjected to two cycles of hydrolytic kinetic resolution employing Jacobsen's cobalt-salen catalyst **116** to obtain the enantioentriched material with 93% *ee*.[103] Alternative routes to **113** *via* Sharpless' asymmetric dihydroxylation or Morken's asymmetric diboration and oxidation followed by ring closing of the diol to the epoxide had failed.[86, 88a]

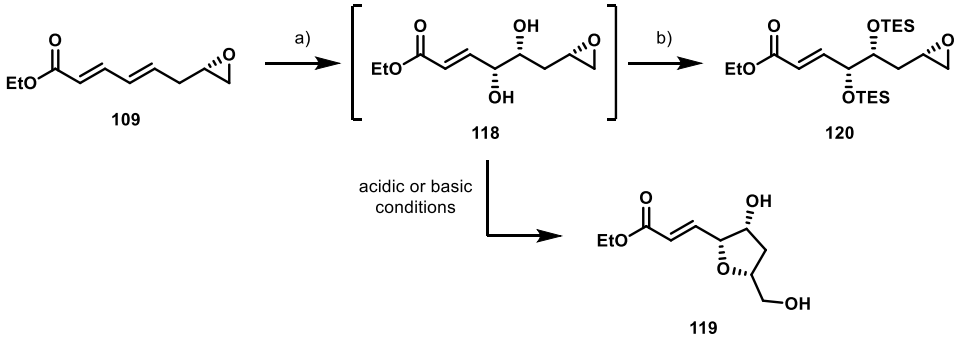
The Julia–Kocienski olefination of commercially available aldehyde **117** with sulfone **113** proceeded smoothly using KHMDS as base and DME as the solvent at −60 °C to afford the desired diene **109** in 97% yield, but moderate stereoselectivity, with an *E*/*Z* ratio of 5:1.[104] An

attempt to improve the isomer ratio by treatment with thiol radicals led to significant loss of material and only a slight increase of the *E*/*Z* ratio to give 54% yield of an *E*/*Z* = 7:1 mixture.[105]




**Scheme 2.39.** Julia–Kocienski olefination approach to diene **109**. Conditions: a) *m*-CPBA, $NaHCO_3$, $CH_2Cl_2$, RT, 91%; b) **116** (0.5 mol%), acetic acid (10 mol%), $H_2O$, THF, RT, 35%, 93% *ee* after two cycles; c) KHMDS, DME, −60 °C, 97%, *E*/*Z* 5:1; d) PhSSPh, benzene, white light, 54%, *E*/*Z* 7:1.

Dihydroxylation in the γ,δ-position of the diene **109** was carried out following a procedure developed by Sharpless and co-workers (Scheme 2.40).[106] The resulting diol **118** was highly unstable, since it could undergo an intramolecular epoxide opening to form the tetrahydrofuran **119**. This instability also thwarted all attempts to protect the diol as the disilyl ether **120** in meaningful yields, as significant decomposition occurred *via* this pathway. It became apparent that the terminal epoxide would have to be revealed at a later stage, preferably after installation of the diol.

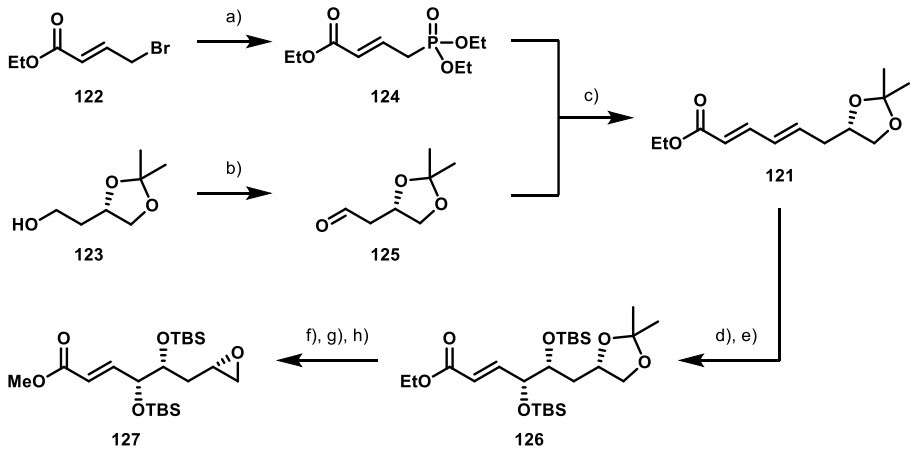



**Scheme 2.40.** Synthesis of protected diol **120** from diene **109**. Conditions: a) $K_2OsO_4 \cdot 2\ H_2O$ (3.0 mol%), $(DHQD)_2PHAL$ (15 mol%), $K_2CO_3$, $K_3[Fe(CN)_6]$, $MeSO_2NH_2$, *t*-BuOH/$H_2O$ 1:1, 0 °C, 63-67%, rr 9:1, dr 18:1; b) TESCl, imidazole, DMF, 0 °C, 34% over two steps.

### 2.4.1.2 Synthesis of the Acetonide-Containing *E*,*E*-Diene and Attempted *oxa*-Michael Cyclization

An acetonide-protected diol was deemed an appropiate alternative to the terminal epoxide, as this moiety could later be deprotected and cyclized to give the desired oxirane. To this end,

acetonide **121** was prepared from commercially available starting materials **122** and **123** by way of the phosphonate **124** and the aldehyde **125** (Scheme 2.41). These two building blocks were combined by a Horner–Wadsworth–Emmons olefination to give the desired diene **121** in 50% yield and in an *E*/*Z* ratio of 7:1.[107] Sharpless dihydroxylation afforded the diol, albeit with a lower regioselectivity than in the case of epoxide-bearing diene **109**. This was likely a result of the larger steric hindrance engendered by the bulky acetonide group present in **121**. The diol was promptly protected to give the isomerically pure disilyl ether **126** in 35% yield over two steps. A sequence of Lewis acid-mediated acetonide cleavage,[108] selective tosylation of the primary alcohol, and treatment with base delivered the terminal epoxide **127** with concomitant transesterification.

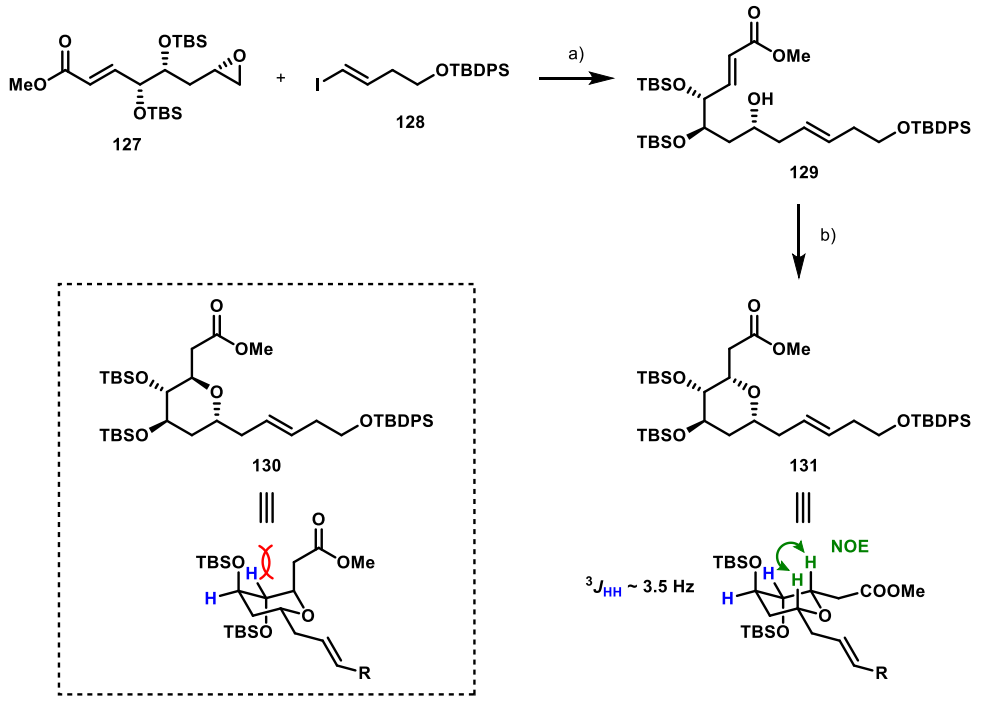



**Scheme 2.41.** Synthesis of the TBS-protected epoxide **127**. Conditions: a) $P(OEt)_3$, neat, 80 °C; b) PCC, $CH_2Cl_2$, RT; c) LiHMDS, THF, −78 °C to RT, 50%, *E*/*Z* 7:1; d) $K_2OsO_4 \cdot 2\ H_2O$ (3.0 mol%), $(DHQD)_2PHAL$ (15 mol%), $K_2CO_3$, $K_3[Fe(CN)_6]$, $MeSO_2NH_2$, *t*-BuOH/$H_2O$ 1:1, 0 °C, rr 3:1, dr 16:1; e) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, RT, 35% over two steps, single isomer; f) $BF_3 \cdot OEt_2$, 1,3-propanedithiol, $CH_2Cl_2$, RT, 50-75%; g) TsCl, $NEt_3$, DMAP, $CH_2Cl_2$, RT; h) $K_2CO_3$, MeOH, RT, 66% over two steps.

Epoxide opening of the oxirane **127** turned out to be challenging, since competitive halohydrin formation would occur as soon as halide salts were present in the reaction mixture. This precluded the use of catalytic amounts of copper halide salts in combination with either Grignard reagents or organozinc species. Alkenyllithiums in conjunction with $BF_3 \cdot OEt_2$ again only led to halohydrin formation or decomposition of the starting material. The key to limit the presence of halides salts in the reaction was to execute lithium-halogen exchange of literature-known iodide **128**[109] with *n*-butyllithium and transmetalate to copper using stochiometric lithium 2-thienylcyanocuprate (Scheme 2.42).[110] This gave the desired homoallylic alcohol **129** in 58% yield.

With access to compound **129**, the proposed *oxa*-Michael cyclization to afford the target 2,6-*trans*-tetrahydropyran **130** could be examined. In general, 2,6-*trans*-tetrahydropyrans are

considered the kinetic products of *oxa*-Michael cyclizations, while 2,6-*cis*-tetrahydropyrans correspond to the thermodynamic products.[111] As such, treatment with a strong base at low temperatures should allow selective formation of the desired tetrahydropyran **130**. Following a procedure by Brewitz *et al.*, **129** was treated with potassium *tert*-butoxide at −10 °C.[112] Surprisingly, only minimal conversion was observed, and the sole product was the undesired *cis*-isomer **131**, which was isolated in 10% yield. The rest of the starting material did not undergo reaction, and lowering the temperature further prevented any reaction from occurring at all.




**Scheme 2.42.** Synthesis of the homoallylic alcohol **129**, attempted *oxa*-Michael cyclization, and NMR-based conformational analysis of cyclization product **131**. Conditions: a) *n*-Butyllithium, lithium 2-thienylcyanocuprate, *then* $BF_3{\cdot}OEt_2$, **127**, $Et_2O$, −78 °C, 58%; b) *t*-BuOK (5 mol%), THF, −10 °C, 10%.

The 2,6-*cis* relationship on **131** was proven by observation of a NOE signal between the two axially positioned protons (Scheme 2.42). $^1$H NMR studies additionally showed that the two TBS ethers were in an axial disposition, as indicated by the small equatorial-equatorial $^3J_{HH}$ coupling constant of 3.5 Hz of the two protons geminal to the ethers. The tendency of silyl ethers to adapt an axial conformation in these systems is well documented in the context of "superarmed" glycosyl donors.[113] This might explain the reluctancy of **129** to undergo an *oxa*-Michael reaction and afford the desired 2,6-*trans* product **130**, since steric repulsion between the axial silyl ether and the ester group would strongly disfavor its formation. In an effort to force the vicinal diols into an equatorial conformation, an attempt to tether the two alcohols together using a cyclic silyl protecting group was undertaken. However, treating the intermediate

dihydroxylation product of diene **121** with *t*-$Bu_2SiOTf_2$ and 2,6-lutidine only led to decomposition of the starting material.

Due to the difficulties encountered in the key *oxa*-Michael reaction, an alternative retrosynthesis was devised (see Section 2.1). The desired 2,6-*trans* tetrahydropyran was envisioned to be formed at the earliest possible stage, and then functionalized further to give the southern section in readiness for fragment assembly.

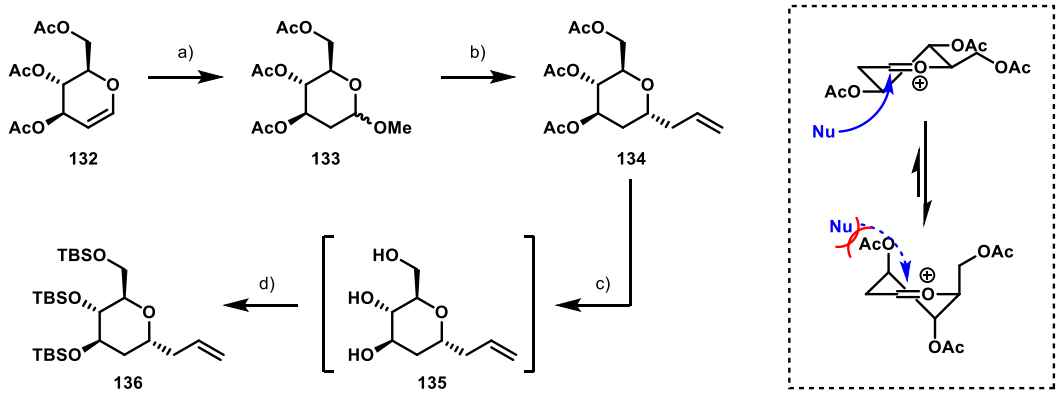
### 2.4.2 The Chiral-Pool Approach

#### 2.4.2.1 Derivatization of D-Glucal and Attempted Nucleophilic Substitution

An ideal precursor for the alternative synthesis was found in tri-*O*-acetyl-D-glucal (**132**), where three of the four stereocenters on the final tetrahydropyran ring are already present. In reference to the "chiral pool", a designation for the entirety of naturally abundant and inexpensive chiral molecules, this strategy was labelled the chiral-pool approach.

The installation of the fourth stereocenter was achieved using a two-step allylation procedure developed by Ghosh and co-workers (Scheme 2.1).[114] Lewis acid-mediated addition of methanol to glucal **132** afforded an anomeric mixture of the methyl 2-deoxyglycoside **133** in 52% yield. Lewis acid-catalyzed addition of allyltrimethylsilane selectively gave the allylated C-glycoside **134** in 57% yield in an $\alpha/\beta$ ratio of 10:1. The diastereoselectivity was in congruence with the expected outcome according to Woerpel and co-workers.[115] Nucleophilic attack on the half-chair oxocarbenium ion preferentially occurs from the face which prevents formation of a twist-boat transition state and instead leads to a chair transition state. Of the two possible conformations the oxocarbenium ion can adopt, the $^3H_4$ conformer is presumed to be lower in energy.[115b] However, developing 1,3-diaxial interactions between the incoming nucleophile and the axial substituents disfavor addition from the stereoelectronically preferred face of the half-chair. The favorable outcome thus reflects a Curtin–Hammett situation, where the desired 2,6-*trans*-substituted tetrahydropyran arises from addition to the stereoelectronically preferred face of the thermodynamically less stable $^4H_3$ conformer.

The triacetylated compound **134** was completely deprotected by treatment with catalytic potassium carbonate in methanol. After neutralization and removal of methanol, the crude material was subjected to TBSOTf and 2,6-lutidine at room temperature to give the trisilylated sugar derivative **136** in 95% over both steps.



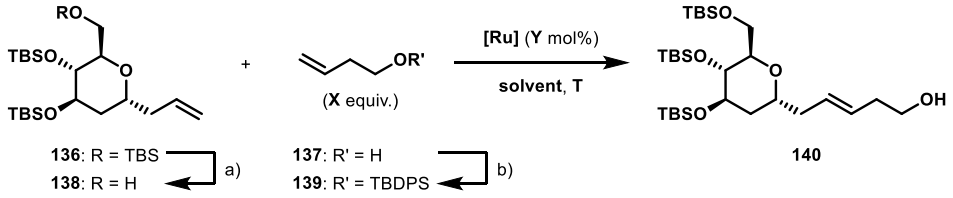

**Scheme 2.43.** Synthesis of the persilylated sugar derivative **136**. Conditions: a) $CeCl_3 \cdot 7\,H_2O$, NaI, MeOH, MeCN, reflux, 52%; b) TMSOTf, allyltrimethylsilane, MeCN, RT, 57%, dr > 10:1; c) $K_2CO_3$ (20 mol%), MeOH, RT; d) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, RT, 95% over two steps.

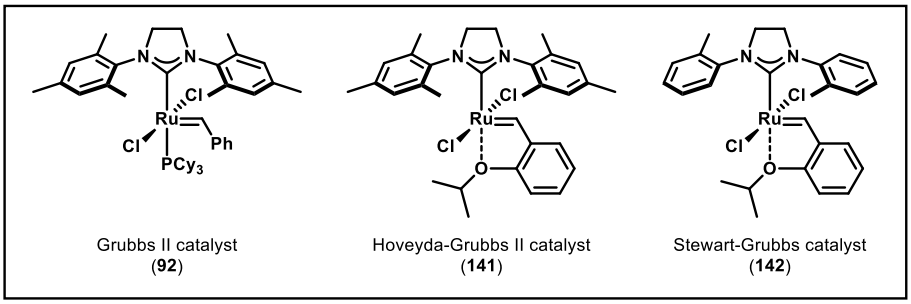
Polysilyl ether **136** was the precursor for a key step of the southern fragment synthesis: the olefin cross-metathesis with 3-buten-1-ol (**137**) or a protected derivative thereof. Both olefins in this reaction are terminal and thus considered "type I" olefins, making this transformation far from trivial due to facile homo-dimerization of the starting materials.[90] The choice of catalyst and protecting groups proved to be vital (Table 2.3). In order to test all sensible protecting group patterns, the most accessible silyl ether of **136** was selectively cleaved to give the primary alcohol **138** and 3-buten-1-ol (**137**) was protected to give TBDPS ether **139**.

As a starting point, the differentially protected coupling partners were subjected to Grubbs II catalyst (**92**) in refluxing dichloromethane. Importantly, the butenols **137** and **139** had to be used in large excess to drive the reaction equilibrium towards the desired product. Interestingly, only the cross-metathesis using fully protected glucal derivative **136** and ten equivalents of unprotected 3-buten-1-ol (**137**) gave the desired cross-product **140**. Any other combination of protecting groups led to complex mixtures and purification difficulties due to the similar polarities of the dimers and the product (entries 1-3). Of all catalysts screened, the sterically least encumbered Stewart–Grubbs catalyst (**142**) performed best (entries 4-6).[116] Over the course of these experiments, the facile homodimerization of 3-buten-1-ol was also frequently observed, while no dimer formation of the bulkier sugar derivative **136** was detected. It was surmised that the sterically more accessible Stewart–Grubbs catalyst (**142**) could, in contrast to Grubbs II (**92**) and Hoveyda–Grubbs II (**141**), productively engage with the dimer of 3-buten-1-ol, allowing for progression of the reaction. Increasing the catalyst loading from 2.0 mol% to 10 mol% further improved the yield and selectivity (entry 7), while variation of the temperature led to diminished yields (entries 8 and 9). Finally, the catalyst loading and the amount of 3-buten-1-ol could be reduced to 5.0 mol% and 5.0 equivalents respectively without negatively impacting the reaction outcome (entry 10). On a 1.2 mmol-scale using these conditions, the

desired *E*-isomer of **140** could be isolated in 75% yield. The undesired *Z*-isomer was also formed in 7% yield, corresponding to an *E*/*Z*-ratio of 10:1.

**Table 2.3.** Exploration of the olefin cross-metathesis for the synthesis of the southern fragment. Reactions were run on a 0.1 mmol-scale of the limiting reagent. Conditions: a) HF·pyridine, THF, RT, 75%; b) TBDPSCl, imidazole, $CH_2Cl_2$, RT, 99%.



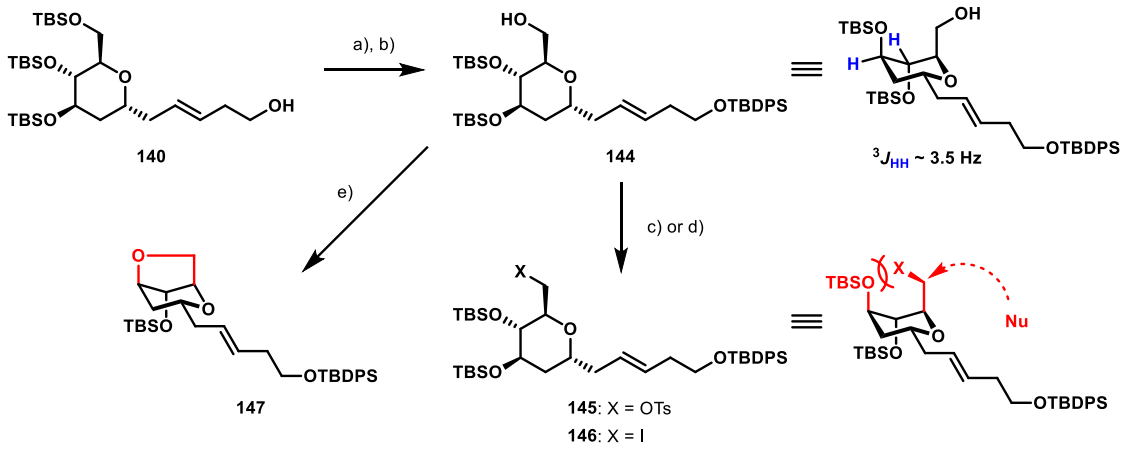

| Entry | R | R′ | X | [Ru] | Y | solvent | T/°C | Yield[a] | *E*/*Z*[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | TBS | H | 10 | **92** | 2.0 | $CH_2Cl_2$ | 40 | 17% | ND |
| 2 | H | TBDPS | 10 | **92** | 2.0 | $CH_2Cl_2$ | 40 | - | - |
| 3 | TBS | TBDPS | 10 | **92** | 2.0 | $CH_2Cl_2$ | 40 | - | - |
| 4 | TBS | H | 10 | **92** | 10 | $CH_2Cl_2$ | 40 | 42% | 9:1 |
| 5 | TBS | H | 10 | **141** | 2.0 | $CH_2Cl_2$ | 40 | 31% | ND |
| 6 | TBS | H | 10 | **142** | 2.0 | $CH_2Cl_2$ | 40 | 63% | 5:1 |
| 7 | TBS | H | 10 | **142** | 10 | $CH_2Cl_2$ | 40 | 72% | 9:1 |
| 8 | TBS | H | 10 | **142** | 2.0 | $CH_2Cl_2$ | 20 | 46% | 7:1 |
| 9[c] | TBS | H | 10 | **142** | 10 | 1,2-DCE | 80 | 27% | 3:1 |
| **10** | **TBS** | **H** | **10** | **142** | **5.0** | **$CH_2Cl_2$** | **40** | **71%** | **10:1** |

[a] Isolated yield of both alkene isomers. [b] The ratio was determined by GC-MS analysis of the reaction mixture. [c] Reaction was run in 1,2-DCE along with 10 mol% of benzoquinone.

With reliable and scalable access to **140** secured, some protecting group modifications were necessary (Scheme 2.44). Treatment of the primary alcohol with TBDPSCl gave the fully protected silyl ether **143**, which was subjected to catalytic amounts of CSA in a methanol/dichloromethane mixture to achieve cleavage of the primary TBS ether. Selectivity

was ensured by the relative insensitivity of TBDPS ethers towards acidic conditions,[39] allowing the resulting primary alcohol **144** to be obtained in 77% yield.

In order to allow nucleophilic substitution on the site of the primary alcohol, the hydroxyl group was converted to a series of leaving groups. Tosylate **145** and iodide **146** were each obtained in good yields, while the attempt to access the corresponding triflate failed. In this case, the nucleofuge was too reactive, preventing its isolation. Instead, upon warming the reaction mixture to above −78 °C, cyclization occurred to give the bridged compound **147**. Treatment of **145** and **146** with an array of nucleophiles induced no reaction in most experiments. Neither lithium acetylides, nor alkenyl Grignard reagents with catalytic amounts of copper(I) salts, nor cyanide salts led to any satisfactory conversion. Instead, the same cyclized intermediate **147** was observed upon prolonged heating of the reaction mixtures. The reason for this peculiar reactivity is of steric nature: As manifested once again by the $^3J_{HH}$ coupling constant of 3.5 Hz between the protons geminal to the TBS ethers, both of the bulky silyl groups of **144** occupy the axial position. Thus, for an $S_N2$ reaction with an external nucleophile to occur, the leaving group would have to reside above the ring, where it clashes with one of the silyl groups. Evidently, this precludes any nucleophilic substitution from taking place on this position. In the face of these results, an alternative plan for the installation of the allyl nucleophile moiety had to be devised.



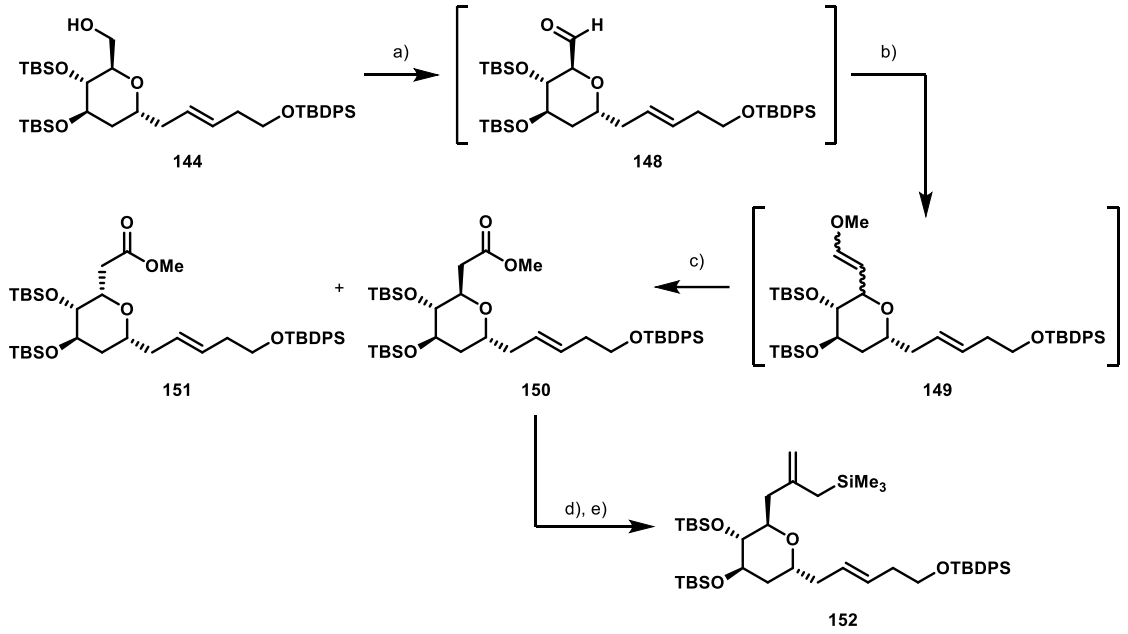

**Scheme 2.44.** Synthesis of alcohol-bearing sugar derivative **144** and attempted nucleophilic substitution on the position of the primary alcohol. Conditions: a) TBDPSCl, imidazole, $CH_2Cl_2$, RT, 99%; b) (*R*)-(−)-CSA, MeOH/$CH_2Cl_2$ 1:1, −20 °C, 77%; c) TsCl, pyridine, $CH_2Cl_2$, RT, 70%; d) $I_2$, $PPh_3$, imidazole, toluene, 60 °C, 85%; e) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, −78 °C, yield not determined.

### 2.4.2.2 Wittig Olefination-Strategy Towards the Allylsilane Nucleophile

In an effort to effect homologation of the carbon chain on compound **144**, a more conventional approach using Wittig olefination methodology was designed (Scheme 2.45). Following close literature precedent, the compound **144** was oxidized under Swern conditions to afford

sensitive aldehyde **148**, which was directly subjected to a Wittig olefination to give the homologated methyl enol ether **149** as a mixture of isomers.[38b] Under the basic conditions of the Wittig reaction, epimerization of the aldehyde had taken place. In addition, both the *E*- and *Z*-isomers of the enol ether had formed. This intractable mixture of isomers was directly treated with PCC to achieve oxidation to the methyl ester. The aforementioned epimerization had taken its toll on the material throughput: After separation by flash column chromatography, 47% yield of the desired 2,6-*trans*-tetrahydropyran **150** and 46% of the 2,6-*cis*-tetrahydropyran **151** could be isolated. Following a literature procedure, the former compound was reacted with two equivalents of $TMSCH_2MgCl$ to afford an intermediate tertiary alcohol, which after silica-induced Peterson olefination gave the desired allylsilane **152**.[117]

The main drawback of this approach is the configurational instability of aldehyde **148**, which results in the loss of almost half of the material. Nevertheless, allylsilane **152** could be prepared in 5% yield over twelve steps and in sufficient amounts to allow for a first examination of the fragment coupling between the central and southern fragments (*vide infra*).

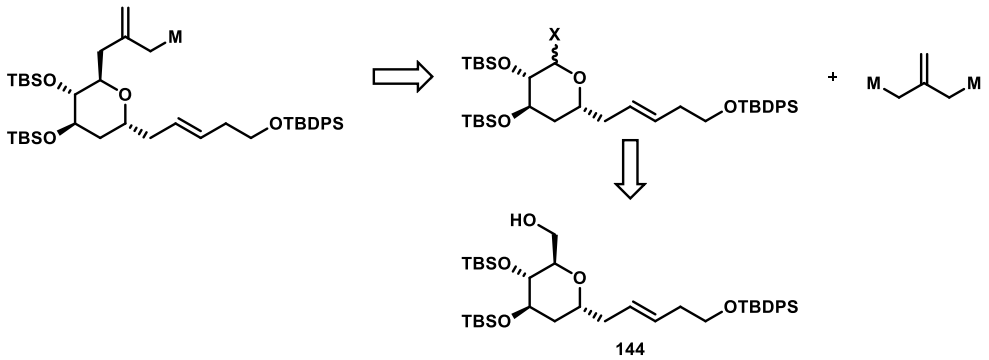



**Scheme 2.45.** Synthesis of the allylsilane **152**. Conditions: a) $(COCl)_2$, DMSO, DIPEA, $CH_2Cl_2$, −78 °C to RT, 89%; b) $(MeOCH_2PPh_3)Cl$, *t*-BuOK, THF, 0 °C, *then* **148**, −78 °C to RT, 90%, mixture of isomers; c) PCC, $CH_2Cl_2$, 47% *trans*-isomer (**150**) + 46% *cis*-isomer (**151**) over two steps; d) $CeCl_3$, $ClMgCH_2TMS$, THF, −78 °C to RT; e) silica, $CH_2Cl_2$, 83% over two steps.

### 2.4.2.3 Lead-Mediated One-Carbon-Excision Strategy Towards the Allystannane Nucleophile

Extensive studies on the lead-mediated dehydroxymethylative acetoxylation of β-hydroxy ethers were conducted by Tristano Martini. Detailed information on this transformation can be found in his Master's thesis. This section represents a summary of his results.[118]

Since the previous Wittig-olefination approach had proven to be relatively low-yielding, a more efficient route to allyl nucleophile **152**, or an equivalent thereof, was sought out. Another retrosynthetic analysis was conducted towards this end (Scheme 2.46). It was proposed that an allylmetal nucleophile of type **152** could also be formed by allylation of a glycosyl donor with a double allylmetal nucleophile. The stereoselectivity in this case would again be in accordance with stereochemical models developed by Woerpel and co-workers (see Section 2.4.2.1).[115] This hypothetical glycosyl donor, however, would have to be produced from the primary alcohol **144** by excision of one carbon atom.



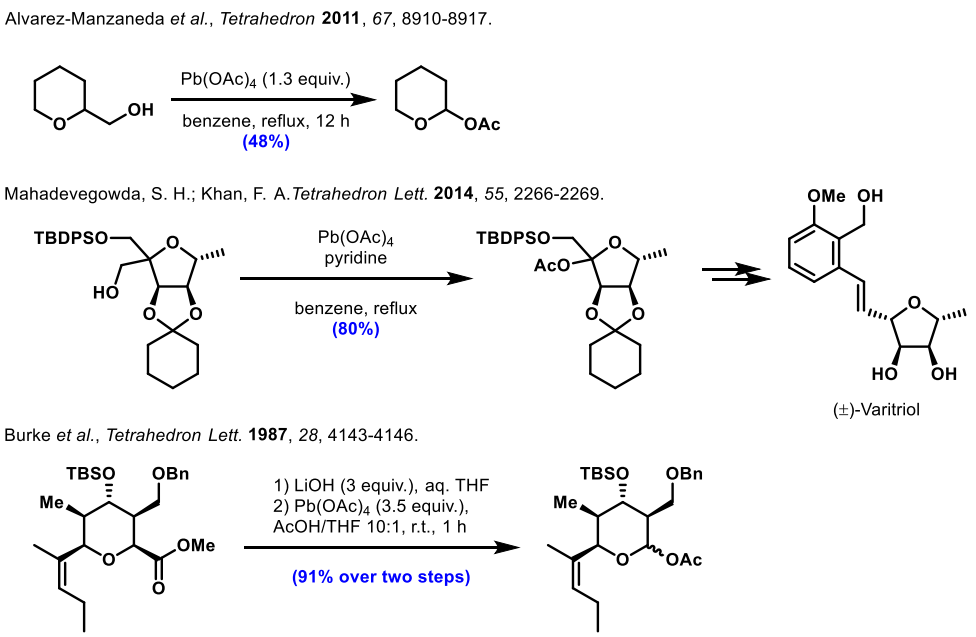

**Scheme 2.46.** Revised retrosynthetic analysis of the southern fragment allyl nucleophile.

Although this transformation was considered to be challenging, some examples of a one-carbon excision on sugar derivatives exist in the literature (Scheme 2.47).[119] The closest example is a study by Alvarez-Manzaneda *et al*., in which the researchers subjected cyclic β-hydroxy ethers to stochiometric lead(IV) acetate in refluxing benzene to afford the $\alpha$-acetoxy ether by formal expulsion of formaldehyde.[119a] Mahadevegowda et al. employed similar conditions to effect dehydroxymethylation en route to their synthesis of varitriol.[119b] On the other hand, several examples exist of a decarboxylative oxidation of cyclic ethers bearing a carboxylic acid,[120] one being a decarboxylative acetoxylation applied by Burke *et al*. in their synthetic studies towards erythronolides A and B.[119c] The expulsion of carbon dioxide is a driving force for C–C-bond cleavage, making this transformation more facile than the cleavage of β-hydroxy ethers.

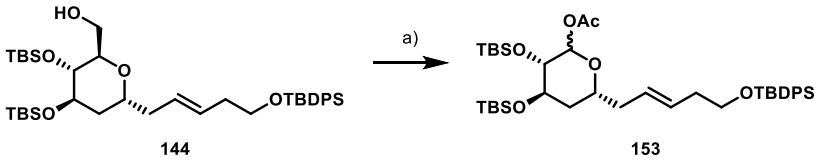
In an initial attempt to cleave the hydroxymethyl group on primary alcohol **144**, Burke's conditions were used (Scheme 2.48).[119c] To our delight, the starting material was converted to a mixture of anomeric acetoxy acetals **153** in 61% yield. However, a number of unidentified side products also arose. Still, this promising result prompted us to investigate the generality of the reaction and its mechanism.

Mechanistically, this transformation likely proceeds with the intermediacy of alkoxy radicals, as shown for the oxidative cleavage of model substrate **154** to pyranyl acetate **155** (Scheme 2.49).[121] Lead(IV) acetate is assumed to reversibly form lead alkoxides of type **A** with

free alcohols. The Pb–O-bond in these compounds is labile towards homolytic cleavage, induced by either photolysis or heating to 70-80 °C. What results is a lead(III) acetate metalloradical and the alkoxy radical **B**. After loss of formaldehyde through β-fragmentation, a stabilized α-alkoxy radical of type **C** is formed. This radical is then oxidized, presumably by lead(III) still present in the reaction mixture, affording lead(II) acetate and the oxocarbenium ion **D**, which promptly undergoes nucleophilic addition of acetate anions to give the α-acetoxy ether as a mixture of anomers.



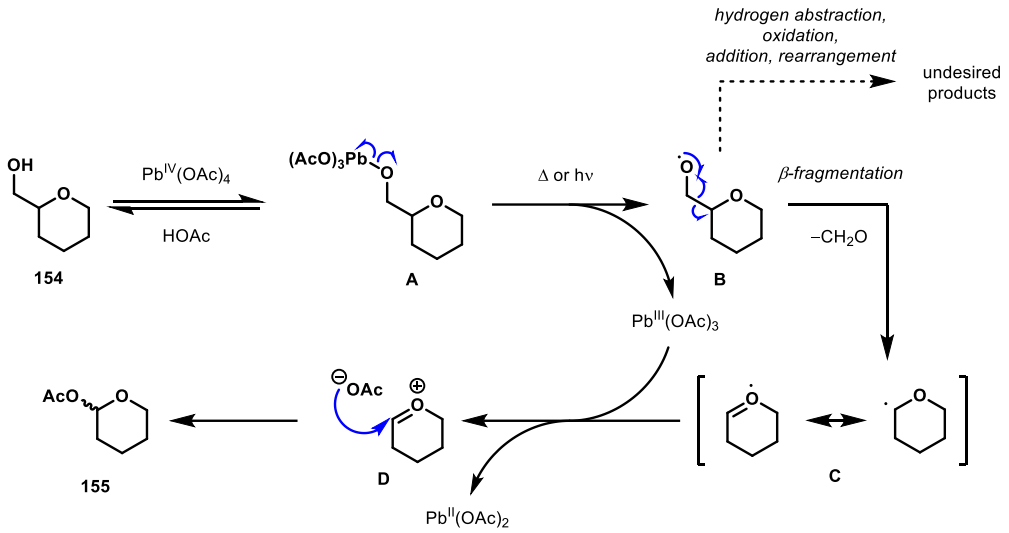

**Scheme 2.47.** Selected literature examples of lead tetraacetate-mediated one-carbon excisions on sugar-like compounds.[119]




**Scheme 2.48.** Lead-mediated one-carbon excision to form α-acetoxy ether **153**. Conditions: a) $Pb(OAc)_4$, THF/AcOH 10:1, RT, 61%.

The high reactivity of alkoxy radicals also explains the emergence of numerous side products. Brun and Waegell describe a variety of reactions which these intermediates can undergo, such as intra- and intermolecular hydrogen abstraction, oxidation, β-fragmentation, intra- and intermolecular additions, and rearrangements.[121a] In line with these possible pathways, one of the isolated side products of the reaction was tetrahydrofuran-2-yl acetate, likely stemming from intermolecular hydrogen abstraction from the solvent, subsequent oxidation of the resulting radical, and addition of acetate into the oxocarbenium ion.

Furthermore, intramolecular hydrogen abstraction was also often observed in sugar-derived substrates bearing protecting groups other than silyl groups. In the case of glycal substrates, intramolecular addition was also detected, where cyclization through radical attack on the double bond took place.[118]

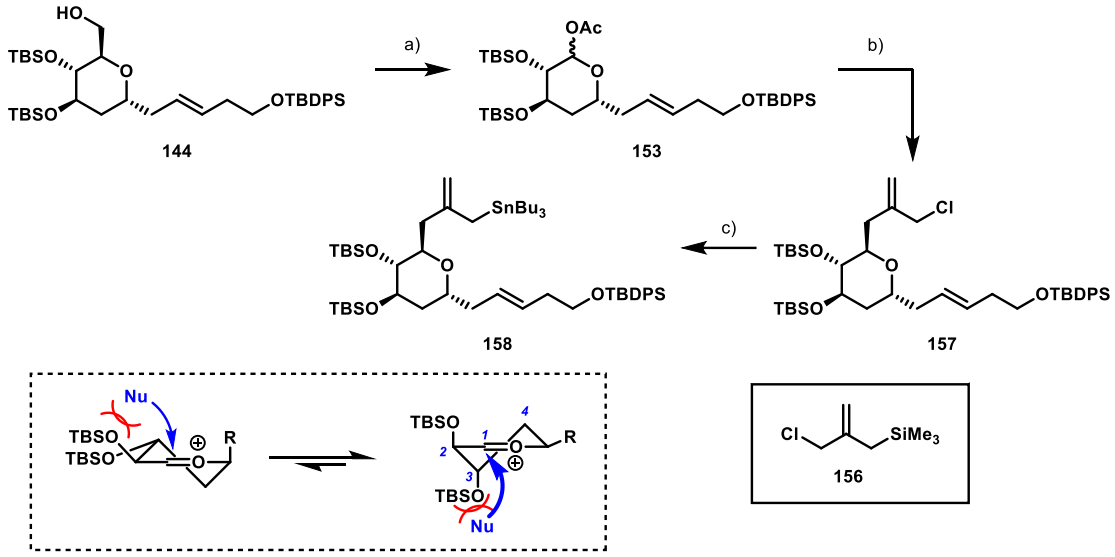



**Scheme 2.49.** Mechanism of the lead(IV)-mediated cleavage of β-hydroxy ethers.

The electronic activation engendered by silyl ethers seems to be necessary to favor the β-fragmentation pathway over unproductive reaction channels. Since the rate of fragmentation depends on the stability of the resulting radical,[122] this observation can be ascribed to the stabilization of the intermediate $\alpha$-alkoxy radical by the silyl ethers in axial disposition, allowing for stronger orbital overlap between the SOMO and the σ-orbital of the C–O-bond. This effect has been described in sugar chemistry in the context of "superarmed" glycosyl donors, where the same stabilizing factor facilitates oxocarbenium ion formation.[123] The limited substrate scope of the lead-mediated fragmentation reaction comes as a consequence of this electronic requirement, since it precludes the use of any protecting groups other than silyl.[118]

However, based on the mechanism, some improvements of the reaction in the context of our synthetic efforts were possible. Since intermolecular hydrogen abstraction occurred in tetrahydrofuran, dichloromethane was found to be the solvent of choice. In addition, the reaction could be accelerated significantly under photolytic conditions through induction of Pb–O-bond cleavage. Both of these improvements led to a more reproducible, higher-yielding transformation and allowed for a reduction of the excess of lead(IV) acetate from 3.5 equivalents to 2.0 equivalents (Scheme 2.50). The anomeric acetal **153** was obtained in 72% yield with these updated conditions. The glycosyl donor could then be allylated using allylsilane **156** and stochiometric Lewis acid to afford the allyl chloride **157** in 83% yield and a dr of 5:1 in favor of the desired 2,6-*trans*-tetrahydropyran. Selectivity was steered by several stereoelectronic

factors.[115] The $^4H_3$ conformer of the half-chair oxocarbenium ion is likely lower in energy than the $^3H_4$ conformer, since orbital overlap between the bonding σ(C2–O)-orbital and the empty π*-orbital of the oxocarbenium ion is maximal in the $^4H_3$ conformer. In the case of the $^3H_4$ conformer, steric repulsion between the pseudoequatorial TBS ether on C2 and the incoming nucleophile also disfavors formation of the 2,6-*cis*-product. Nucleophilic attack from the stereoelectronically preferred face of the thermodynamically more stable conformer thus gives the desired product in spite of developing 1,3-diaxial interactions. Since both possible trajectories of attack are hindered by the steric bulk of the TBS ethers, selectivity likely stems mainly from the thermodynamic preference for the $^4H_3$ conformer.




**Scheme 2.50.** Synthesis of the allylstannane **158** *via* a photochemical lead(IV)-mediated dehydroxymethylative acetoxylation. Conditions: a) $Pb(OAc)_4$, irradiation with UV-A light (365 nm), $CH_2Cl_2$, RT to reflux, 72%; b) **156**, $SnCl_4$, $CH_2Cl_2$, −78 °C, 83%, dr 5:1; c) $Bu_3SnLi$, THF, −78 °C, 91%, dr 5:1.

The allyl chloride **157** was easily converted to the corresponding allylstannane **158** by treatment with tributylstannyl lithium, which can be conveniently generated by addition of *n*-butyllithium to hexabutylditin.[124] Since the diastereoisomers of **157** could not be separated by standard flash chromatography, the mixture was carried forward. Thus, stannane **158** was also obtained as a 5:1 mixture of diastereoisomers in 91% yield.

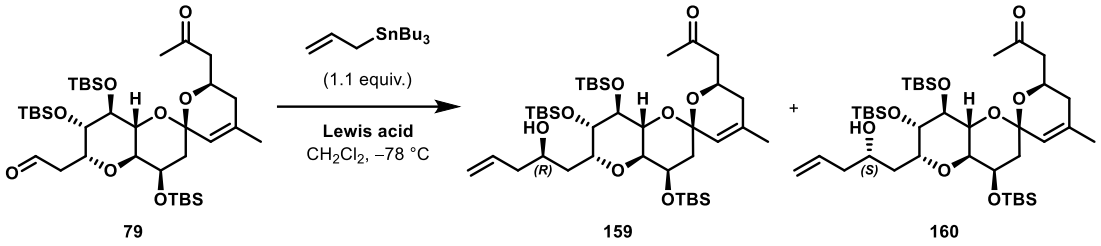
This concludes the synthesis of the southern fragment. In summary, the final allyl stannane **158** could be synthesized in 7% yield over ten steps. In addition to its shorter and higher-yielding synthetic route compared to the allylsilane **152**, the stannane was also expected to be more reactive. With these two different allyl nucleophiles in hand, the fragment coupling between the southern and central fragments could be examined.

## 2.5 Assembly of the Southern and Central Fragments

### 2.5.1 Attempts to Override Substrate Control by Asymmetric Allylation

In order to test the viability of asymmetric allylation of the aldehyde-bearing central fragments **74**, **75**, **78**, and **79**, they were first reacted with simple allyl nucleophiles. Initially, ketoaldehyde **79** was treated with allyltributylstannane and a series of Lewis acid promotors to afford the diastereoisomeric homoallylic alcohols (Table 2.4). Of the three Lewis acids screened, magnesium bromide gave the highest diastereoselectivity and isolated yield (entry 1). The dominant diastereoisomer **159** was identified to be the undesired (*R*)-configured product by Mosher's ester analysis.[48] Use of tin tetrachloride and boron trifluoride both gave roughly 1:1 mixtures of the diastereoisomers **159** and **160** (entries 2 & 4). When an excess of a strong Lewis acid was used, decomposition of the starting material ensued (entry 3).

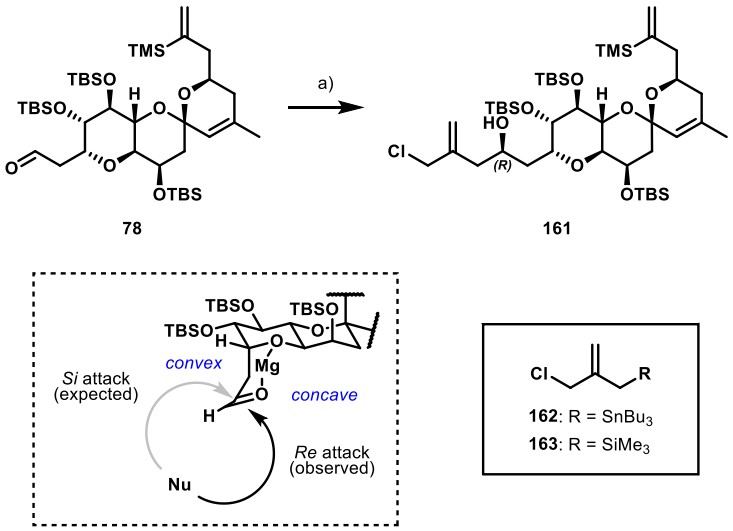
**Table 2.4.** Screening of Lewis acid promotors in the allylation of **79**.




79 159 160

| Entry | Lewis acid | dr 159:160 | Yield |
|---|---|---|---|
| 1 | $MgBr_2 \cdot OEt_2$ (5 equiv.) | 14:1 | 76% |
| 2 | $SnCl_4$ (1 equiv.) | 3:4 | 28% (NMR) |
| 3 | $SnCl_4$ (2 equiv.) | - | Decomposition |
| 4 | $BF_3 \cdot OEt_2$ (1 equiv.) | 1:1 | 56% (NMR) |

These results came as a surprise, since chelating Lewis acids were predicted to predominantly give the desired diastereoisomer **160** according to the Cram-chelate model (Scheme 2.51).[125] This peculiar substrate bias was not limited to ketoaldehyde **79**, but was also observed when reacting aldehyde **78** and the allyl stannane **162**. Employing an excess of magnesium bromide resulted in exclusive formation of the undesired (*R*)-diastereoisomer **161** in 80% yield. When the less nucleophilic allylsilane **163** was employed instead, a significantly lowered yield of the allylation product was isolated, confirming that a sufficiently reactive allyl nucleophile had to be used to ensure complete conversion before decomposition of the aldehyde set in.

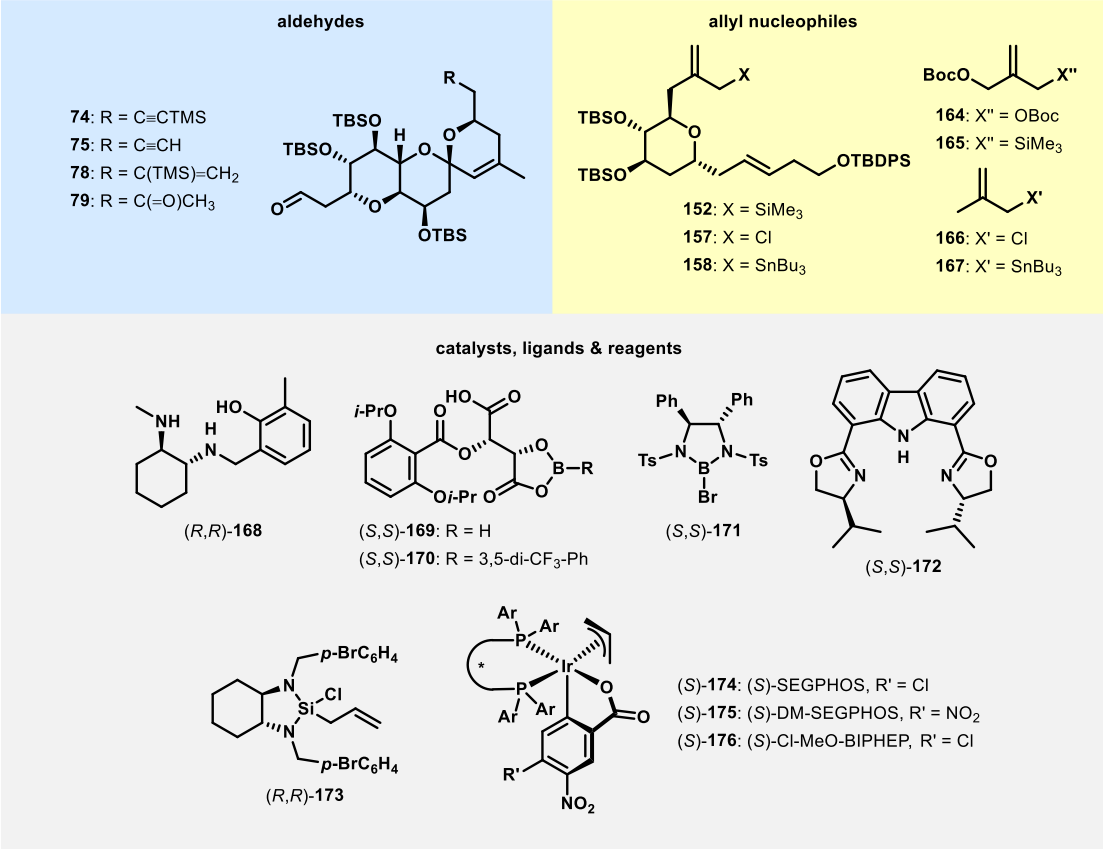



**Scheme 2.51.** Expected and observed outcome of allylation of **78** *via* the Cram-chelate. Conditions: a) $MgBr_2 \cdot OEt_2$, $CH_2Cl_2$, −78 °C, for R = $SnBu_3$: 80%, single diastereoisomer, for R = $SiMe_3$: 18%, single diastereoisomer.

Since the inherent substrate bias of the central fragment aldehydes forbade the use of achiral Lewis acid promotors, we turned our attention to the plethora of known catalyst- and reagent-controlled asymmetric allylations in hopes of overriding substrate control.[36b-d] An overview of the various conditions investigated is given in Table 2.5.

Most employed methods led either to no reaction or decomposition of the sensitive aldehyde starting material. However, in select cases, the substrate bias could be overriden. First experiments using Krische's transfer hydrogenation/allylation were conducted using the simple allyl carbonates **164** and **165**.[126] When the aldehyde **74** bearing a TMS-capped alkyne was used, the reaction with the symmetric dicarbonate **164** gave the desired diastereoisomer in 61% yield (entry 1). When the bifunctional allyl nucleophile **165** or the aldehyde **75** bearing a terminal alkyne were used, no desired reaction occurred (entries 2 & 3). Krische's method worked well on ketoaldehyde **79** using a series of Ir-catalysts (**174**, **175**, and **176**) and simple allyl nucleophiles such as methallyl chloride (**166**) and dicarbonate **164** (entries 9, 10, 12, and 13). However, upon increasing the complexity of the allyl nucleophile in hopes of introducing the entire southern sector as the chloride **157** in one operation, the method failed to give any reaction (entry 14). The recalcitrance of allyl chloride **157** to take part in allylation was ascribed to the Lewis basic moieties in the molecule, which can inhibit reactivity by blocking coordination sites on the iridium catalyst as soon as the allylmetal complex is formed.

**Table 2.5.** Attempted reagent- and catalyst-controlled asymmetric allylations.




| Entry | Aldehyde | Nu[a] | Conditions | Result |
|---|---|---|---|---|
| 1 | **74** | **164** | (*S*)-**175** (5 mol%), $K_3PO_4$, *i*-PrOH, 1,2-DME, 70 °C | 61%[b] |
| 2 | **74** | **165** | (*S*)-**175** (5 mol%), $K_3PO_4$, *i*-PrOH, THF, 70 °C | Reduction[c] |
| 3 | **75** | **164** | (*S*)-**175** (5 mol%), $K_3PO_4$, *i*-PrOH, 1,2-DME, 70 °C | No reaction |
| 4 | **75** | **173** | $CH_2Cl_2$, −10 °C | 53%[b] |
| 5 | **78** | **152** | (*S*,*S*)-**170**, EtCN, −78 °C to RT | No reaction |
| 6 | **79** | **167** | (*S*,*S*)-**170**, EtCN, −78 °C to RT | No reaction |
| 7 | **79** | **158** | (*S*,*S*)-**169**, TFAA, EtCN, −78 °C to RT | No reaction |
| 8 | **79** | **167** | $Ti(O\textit{i}\text{-}Pr)_4$, (*S*)-BINOL, *i*-PrSBEt$_2$, $CH_2Cl_2$, −78 °C to RT | No reaction |
| 9 | **79** | **164** | (*S*)-**175** (5 mol%), $Cs_2CO_3$, *i*-PrOH, 1,2-DME, 70 °C | 53%[b] |
| 10 | **79** | **166** | (*S*)-**174** (15 mol%), $K_3PO_4$, *i*-PrOH, THF, 60 °C | 61%[b] |
| 11 | **79** | **166** | CuBr (25 mol%), $NEt_3$, $HSiCl_3$, 2,6-di-*tert*-butylpyridine, *then* $Bu_4NBr$, DBU, (*R*,*R*)-**168**, $CH_2Cl_2$, −78 °C to −10 °C | Decomposition |
| 12 | **79** | **164** | (*S*)-**175** (5 mol%), $K_3PO_4$, *i*-PrOH, 1,2-DME, 70 °C | 70%[b] |
| 13 | **79** | **166** | (*S*)-**176** (12 mol%), $K_3PO_4$, *i*-PrOH, THF, 60 °C | 71%[b] |
| 14 | **79** | **157** | (*S*)-**176** (12 mol%), $K_3PO_4$, *i*-PrOH, THF, 60 °C | No reaction |
| 15 | **79** | **167** | (*S*,*S*)-**171**, $CH_2Cl_2$, RT, *then* add **79**, −78 °C to RT | No reaction |
| 16 | **79** | **158** | (*S*,*S*)-**171**, $CH_2Cl_2$, RT, *then* add **79**, −78 °C to RT | No reaction |
| 17 | **79** | **157** | $CrCl_2$ (15 mol%), (*S*,*S*)-**172** (30 mol%), PcCo (0.5 mol%), $ZrCp_2Cl_2$, proton sponge, Mn, LiCl, THF, RT | No reaction |

[a] Between 1.1 and 2.0 equivalents of the nucleophile were used. [b] Isolated yield of the desired diastereoisomer.

[c] Reduction of the aldehyde to the primary alcohol.

Leighton and co-workers have developed an Lewis base-mediated asymmetric allylation employing strained silacycles.[127] The commercially available allylsilane (*R*,*R*)-**173** was first tested to probe reactivity of this system towards the aldehyde **75**. Selective allylation of the aldehyde took place, and the desired diastereoisomer could be isolated in 53% yield (entry 4). For more complex allyl donors, a modified procedure employing diamine **168** was established and later used in the total synthesis of Spongistatin 1.[127a, 127d]

The protocol starts from an allyl chloride, which is converted to the allyltrichlorosilane using copper(I) bromide and trichlorosilane. In one pot, the diamine ligand (*R*,*R*)-**168** is then added to form the reactive allylating species. This method was applied to simple methallyl chloride (**166**) first, and the ketoaldehyde **79** was treated with the so derived allylsilane. To our dismay, the aldehyde did not withstand the conditions, and only decomposition was observed (entry 11).

Another more conventional approach to asymmetric allylation is through the use of chiral Lewis acids. Two commonly employed systems in this category are Hisashi Yamamoto's chiral (acyloxy)borane complexes **169** and **170** as well as Keck's BINOL-derived titanium(IV)-complexes.[128] Both were tested for the allylation of aldehydes **78** and **79** with a variety of allyl nucleophiles, but in all cases no conversion was observed (entries 5-8). Even warming to ambient temperature and addition of *i*-PrSSiMe$_3$ as a promotor did not provoke any reaction.[129] A similar titanium-based protocol developed by Gauthier and Carreira was also attempted with complex allylsilane **152** and aldehyde **78**, but was likewise not able to elicit a reaction.[130]

An additional asymmetric allylation under consideration was developed by Williams and co-workers and was based on 1,2-diphenyl-1,2-ethylenediamine as a chiral controller.[131] The method had already been used to great effect in our group.[132] In this protocol, a chiral diamine is treated with boron tribromide to give the chiral boron species **171**. This compound reacts with an allylstannane to give the boron-based allylation reagent after transmetallation over night at ambient temperature. However, neither simple methallylstannane (**167**) nor the stannane-bearing southern fragment **158** underwent any reaction with ketoaldehyde **79** after transmetallation to boron, once again demonstrating the reluctance of the central fragment aldehydes to undergo mismatched asymmetric allylation (entries 15 & 16).

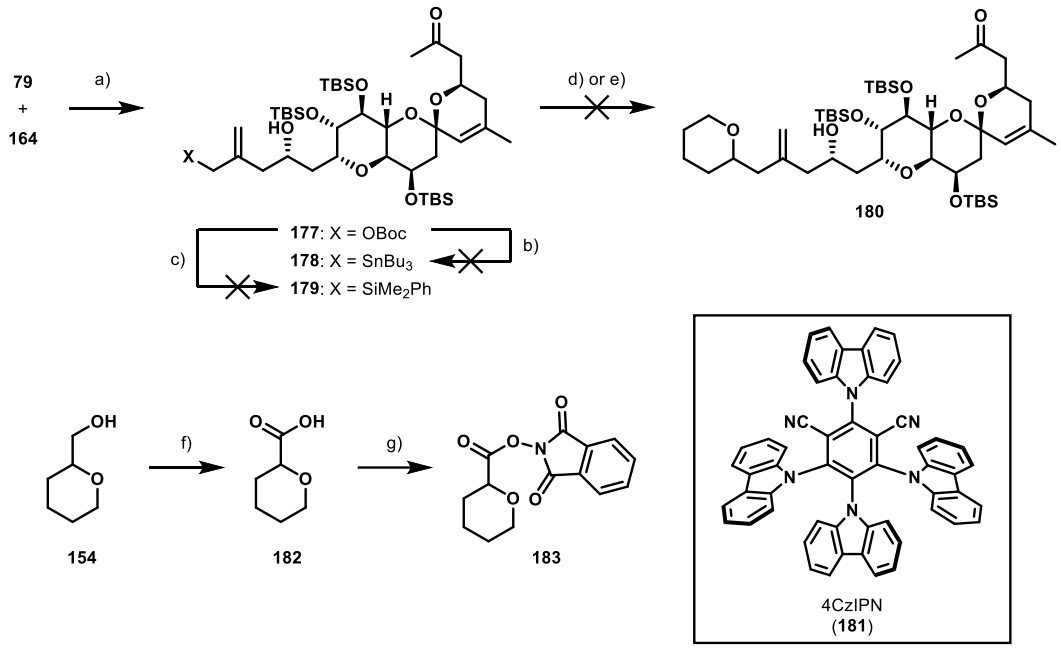
The final conditions probed in this series of experiments were based on the asymmetric Nozaki–Hiyama–Kishi reaction.[43c, 43d] NHK reactions are rendered catalytic in chromium by addition of manganese as stochiometric reductant, which allowed for the development of catalytic asymmetric variants of the reaction.[133] One such embodiment was developed by Kishi and co-workers and employs the chiral bis(oxazoline) ligand **172** to effect asymmetric allylation of aldehydes.[75, 134] However, the conditions reported by Kishi were not able to coax aldehyde **79** and allyl chloride **157** to undergo coupling and no reaction was observed at all (entry 17). In the

face of these discouraging results, alternative disconnections to achieve fragment union were briefly examined.

### 2.5.2 Alternative Disconnections Between the Southern and Central Fragments

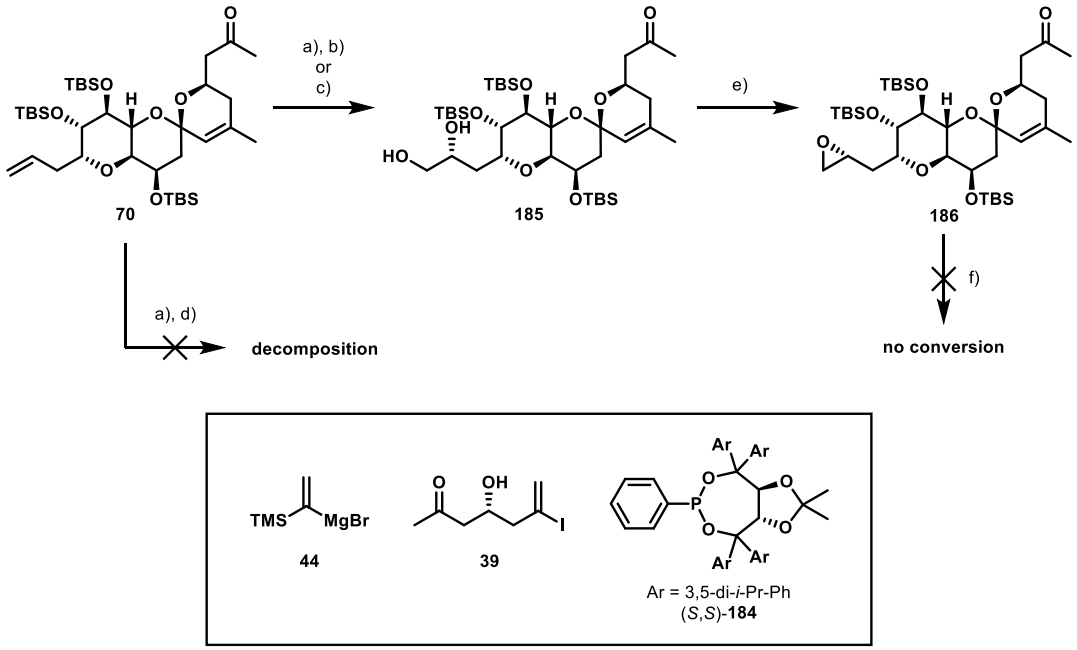
So far in the synthesis, the only methods capable of installing the desired (*S*)-stereochemistry at C27 correctly were the Krische allylation and the Leighton allylation. Both protocols, however, failed once the complexity of the allyl fragment was increased. Nevertheless, in an effort to allow coupling of the rest of the southern fragment, it was attempted to further functionalize the product **177** of the Krische allylation in a bidirectional manner (Scheme 2.52).

Initially, the allyl carbonate moiety of **177** was planned to be transformed to allylstannane **178** or allylsilane **179** by way of a Stille cross-coupling or a copper-mediated nucleophilic substitution using a silylmetal nucleophile, respectively.[135] Both approaches failed, either decomposing the starting material or giving no conversion at all. Tunge and Cartwright developed a decarboxylative coupling of carboxylic acids with π-electrophiles such as allyl carbonates, which was also attempted.[136] In this method, a palladium catalyst forms a π-allyl complex by oxidative addition into the π-electrophile, and photoredox catalyst **181** effects decarboxylative formation of an alkyl radical from the carboxylic acid. These two components are expected to couple *via* a Pd(0)-Pd(II)-Pd(III)-Pd(I) catalytic cycle. Employing the model carboxylic acid **182** (prepared in one step from commercial **154**) and the allyl carbonate **177**, the palladium/photoredox dual catalytic conditions were not able to induce any conversion to desired coupling product **180**. Similarly, Weix and co-workers presented a decarboxylative cross-electrophile coupling of NHPI esters with aryl iodides.[137] Although aryl electrophiles are not directly comparable to allyl electrophiles, this method was nevertheless tested using NHPI ester **183** and allyl carbonate **177**. Again, no reaction was observed.




**Scheme 2.52.** Attempted functionalizations of allyl carbonate **177**. Conditions: a) (*S*)-**175** (5 mol%), $K_3PO_4$, *i*-PrOH, 1,2-DME, 70 °C, 70%; b) $Bu_3SnSnBu_3$, $Pd(PPh_3)_4$ (10 mol%), DMF, 60 °C, decomposition; c) $Me_2PhSiCl$, Li metal, CuI, THF, 0 °C, no conversion; d) $Pd(OAc)_2$ (20 mol%), BINAP (22 mol%), **181** (3.2 mol%), $Na_2CO_3$, **182**, MeCN, blue LED, RT, no conversion; e) $NiBr_2$·diglyme (10 mol%), 4,4′-di-*t*-Bu-bipyridine (10 mol%), **183**, Zn, DMAc, RT, no conversion; f) TEMPO (30 mol%), PIDA, $H_2O$, MeCN, RT, 95%; g) *N*-Hydroxyphthalimide, DCC, DMAP (5 mol%), $CH_2Cl_2$, RT, 85%.

Due to the reluctance of carbonate **177** to undergo any productive transformation, the southern-central disconnection was again reconsidered: The synthesis of the desired homoallylic alcohol could in theory also be effected by an epoxide opening. The stereochemistry of the terminal epoxide would be conserved, transferring the problem of setting the stereocenter to formation of the epoxide. Two methods of constructing the epoxide were evaluated (Scheme 2.53): Morken's asymmetric diboration using chiral phosphine **184** as ligand on platinum followed by oxidation of the diboronic acid ester to the diol, or direct dihydroxylation using Sharpless' method.[86, 88] Starting from central fragment **70**, both methods were able to produce the desired diol **185** in good yields, but only moderate diastereoselectivity. By treatment with sodium hydride and trisylimidazole, the diol was closed to the corresponding epoxide **186** in 68% yield under preservation of the diastereoisomer ratio. Epoxide opening could not be achieved using copper catalysis and model Grignard reagents, marking the end of this attempt. Instead, the intermediate 1,2-bis(boronate) resulting from Morken's diboration was examined further. The primary boronate of this sensitive species can be directly subjected to Suzuki cross-coupling conditions, leaving the secondary boronate untouched. The coupling protocol developed by Morken and co-workers was tested using alkenyl iodide **39** as a model electrophile, however, no reaction was observed.

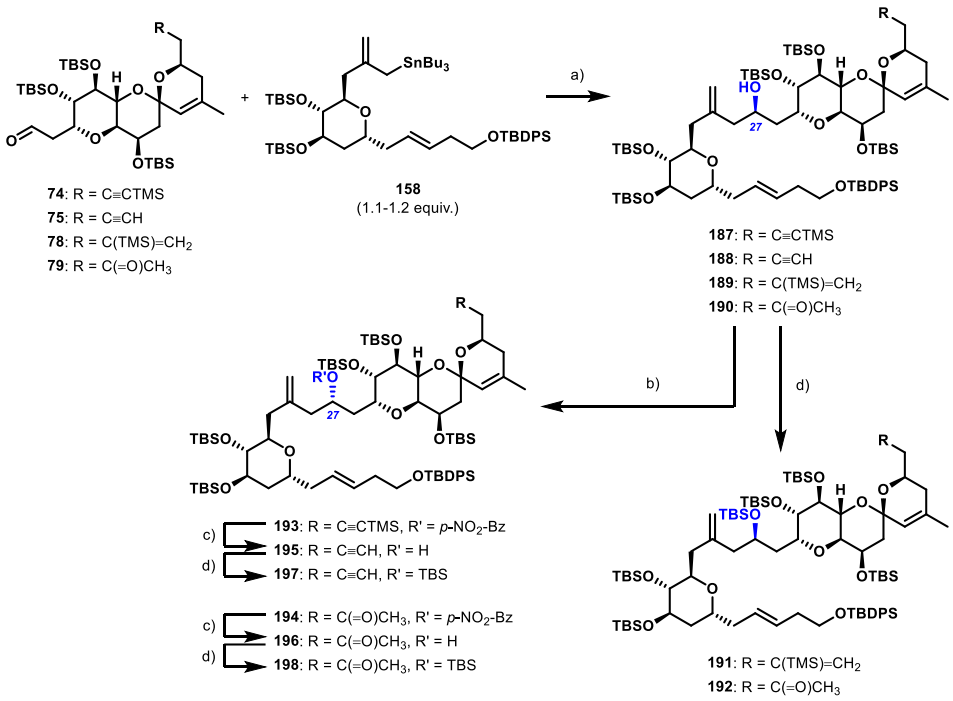



**Scheme 2.53.** Attempted Suzuki coupling and epoxide opening to effect fragment coupling. Conditions: a) $Pt(dba)_3$ (10 mol%), (*S,S*)-**184** (12 mol%), $B_2(pin)_2$, THF, 60 °C; b) $NaBO_3 \cdot 6\ H_2O$, THF/$H_2O$, 0 °C to RT, 71% over two steps, dr 5:1; c) $K_2OsO_4 \cdot 2\ H_2O$ (10 mol%), $(DHQD)_2PHAL$ or $(DHQD)_2PYR$ (25 mol%), $K_2CO_3$, $K_3[Fe(CN)_6]$, $MeSO_2NH_2$, *t*-BuOH/$H_2O$ 1:1, 0 °C to RT, for $(DHQD)_2PHAL$: 99%, dr 1.5:1, for $(DHQD)_2PYR$: 99%, dr 3.0:1; d) $Pd(OAc)_2$ (10 mol%), RuPhos (11 mol%), **39**, KOH, $Ag_2O$, THF/$H_2O$, 70 °C; e) NaH, trisylimidazole, THF, 0 °C to RT, 68%, dr 1.5:1; f) vinylmagnesium bromide or **44**, CuI (30 mol%), THF, −50 °C to −20 °C.

### 2.5.3 Mitsunobu Inversion Strategy

Since all efforts to set the C27 stereocenter correctly had failed, a different approach had to be pursued. Instead, the stereochemistry would have to be corrected *a posteriori*. For secondary alcohols in general, this can be accomplished either by oxidation to a ketone followed by stereoselective reduction, or an inversion of the stereocenter by a Mitsunobu reaction.[138] Since a ketone was also present in the case of the coupling product of central fragment **79**, the latter approach was deemed most viable.

Thus, fragment assembly was effected by substrate-controlled asymmetric allylation of the aldehydes **74**, **75**, **78**, and **79** using achiral Lewis-acid promotor $MgBr_2 \cdot OEt_2$ and the allylstannane **158** (Scheme 2.54). The corresponding homoallylic alcohols **187**, **188**, **189**, and **190** were isolated as single diastereoisomers in moderate to good yields. The terminal alkenylsilane- and ketone-bearing coupling products **189** and **190** were TBS-protected to give fully silylated **191** and **192**, which were used as model compounds for a foray into the introduction of the northern fragment (see Section 2.6).




**Scheme 2.54.** Allylative fragment coupling between the southern and central fragments and Mitsunobu inversion on C27. Conditions: a) $MgBr_2 \cdot OEt_2$ (5.0 equiv.), $CH_2Cl_2$, −78 °C, 70% (**187**), 44% (**188**), 91% (**189**), 88% (**190**); b) $PPh_3$, DEAD, 4-nitrobenzoic acid, toluene, 0 °C to RT, 69% (**193**), 67% (**194**); c) NaOH, MeOH/THF, RT, 92% (**195**), 91% (**196**); d) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C, 94% (**197**), 87% (**198**), 83% (**191**), 84% (**192**).

The TMS-capped alkyne- and ketone-bearing coupling products **187** and **190** were subjected to Mitsunobu conditions using an excess of triphenylphosphine, diethyl azodicarboxylate, and 4-nitrobenzoic acid as the carboxylic acid component. The latter reagent is commonly used due to the clear correlation between the $pK_a$ of the acid component and the yield of Mitsunobu reactions.[139] The benzoic acid esters **193** and **194** were obtained in yields of 69% and 67%, respectively, and were saponified to give the homoallylic alcohols **195** and **196** both in good yields. In the case of the TMS-capped alkyne **193**, concomitant deprotection of the alkyne was achieved under the basic conditions. The inversion of the alcohol stereocenters was confirmed by Mosher's ester analysis at this stage (see Section 6). After protection as silyl ethers, fully protected precursors of limaol **197** and **198** were obtained in 12% and 13% yield over 19 and 16 steps in longest linear sequence, respectively.

## 2.6 Assembly of the Northern and Central Fragments

According to our retrosynthetic analysis of limaol, the central fragment would have to be converted into an alkenyl metal nucleophile in readiness for palladium-catalyzed cross-coupling with the allyl electrophile **108**. Three functional groups on the central fragment were evaluated for their ability to unveil an alkenyl metal species in an advanced stage of the total synthesis: an alkenylsilane (**191**), an alkyne (**197**), and a ketone (**198**).

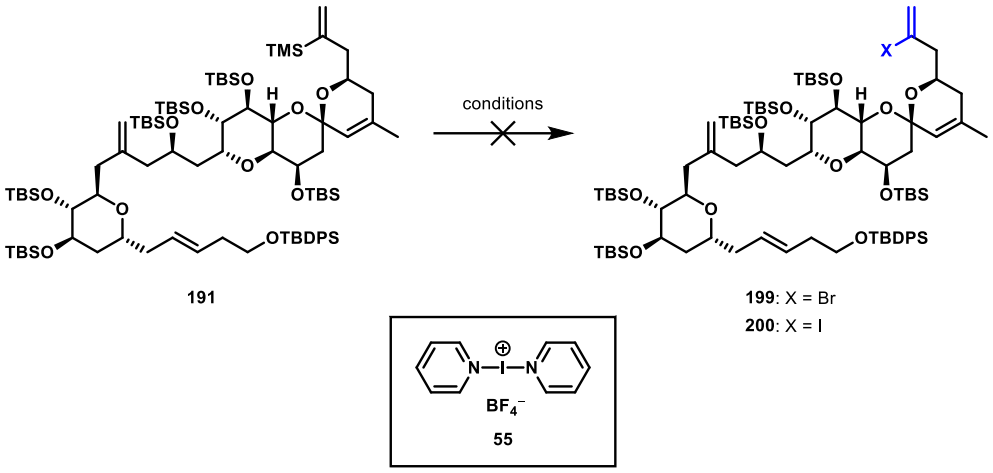
### 2.6.1 Halodesilylation Approach

Typically, alkenylsilanes such as the one present in **191** have two major functions in organic synthesis. First, and most importantly, they serve as placeholders for alkenyl halides or ketones through halodesilylation or Fleming–Tamao oxidation, or, alternatively, they can directly act as a metal nucleophile in a Hiyama or Hiyama–Denmark cross-coupling.[140] The latter often requires specialized silanes or derivatives thereof, harshly basic conditions, or fluoride anions to form pentavalent fluorosilicates, facilitating transmetalation onto palladium. These requirements precluded the use of **191** in direct cross-coupling methods. Instead, electrophilic substitution of the alkenylsilane was examined. Specifically, halodesilylation was considered most valuable, since the resulting alkenyl halides **199** and **200** can be converted into metal nucleophiles by Miyaura borylation, zinc insertion, or Stille cross-coupling with ditin species among others.[141]

A series of halodesilylation experiments were conducted on the alkenylsilane-bearing C27-epimer **191** (Table 2.6). Zakarian and co-workers have found hexafluoroisopropanol to facilitate iododesilylation reactions significantly.[60a] Due to the insolubility of apolar **191** in HFIP, dichloromethane was added as co-solvent when testing Zakarian's conditions. Silver carbonate was used to sequester iodide impurities present in NIS and thereby prevent unwanted side reactions.[60b] However, decomposition was observed (entry 1), and adding 2,6-lutidine in hopes of attenuating the acidity of the reaction medium was also to no avail (entry 2). Kishi and co-workers developed a mild and efficient NIS-mediated iododesilylation in mixtures of acetonitrile and chloroacetonitrile.[60f] Again due to its low polarity, **191** proved only to be soluble in homologous propionitrile. No conversion of the starting material was detected (entry 3). The same was true when alkenylsilane **191** was subjected to Barluenga's reagent (**55**) in different solvent mixtures (entries 5 & 6).[142] Addition of molecular iodine to a solution of **191** expectedly led to decomposition (entry 4). Bromine and iodine monochloride are both capable of adding across double bonds. In the case of alkenylsilanes, subsequent treatment with base leads to elimination of either the silyl bromide or the silyl chloride, respectively, and the alkenyl halide is formed.[60d, 60e] This approach also failed in the case of silane **191**, either leaving the starting material untouched (entry 7) or decomposing it entirely (entries 8 & 9).

Given the results outlined above, investigation of the halodesilylation was discontinued. Since Fleming–Tamao oxidation would eventually give ketone **198** and this compound could be prepared more efficiently by a different strategy, the alkenylsilane route in its entirety was abandoned. The likely reasons for the failure of this route are briefly discussed in Section 3.1.

**Table 2.6.** Attempted halodesilylation of alkenylsilane **191**.



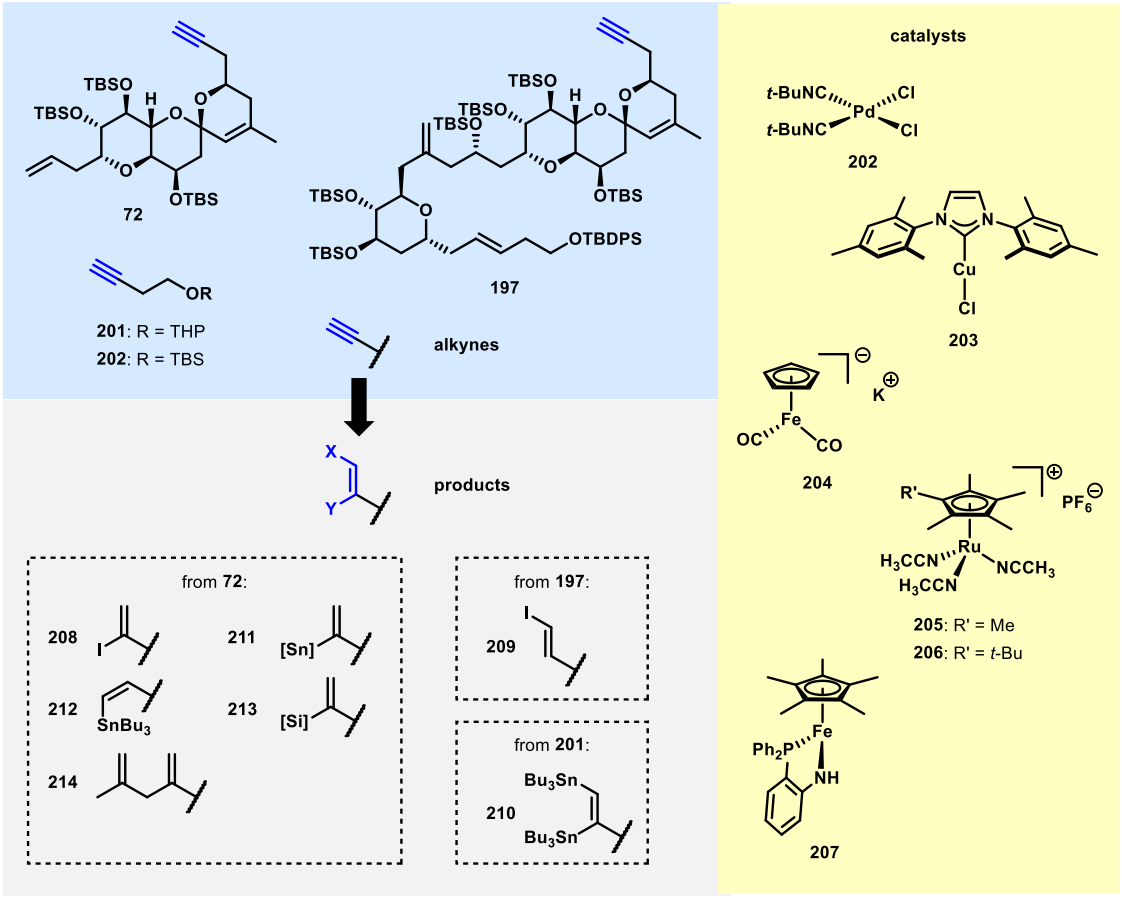

| Entry | Reagents | Solvent | T/°C | Result |
|---|---|---|---|---|
| 1 | NIS (1.2 equiv.), $Ag_2CO_3$ | HFIP/$CH_2Cl_2$ 1:1 | 0 | decomposition |
| 2 | NIS (1.2 equiv.), $Ag_2CO_3$, 2,6-lutidine | HFIP/$CH_2Cl_2$ 1:1 | 0 | decomposition |
| 3 | NIS (1.2 equiv.) | EtCN or $ClCH_2CN$ | RT | no conversion |
| 4 | $I_2$ (2.0 equiv.) | $CH_2Cl_2$ | RT | decomposition |
| 5 | **55** (1.2 equiv.) | HFIP/$CH_2Cl_2$ 1:1 | RT | no conversion |
| 6 | **55** (1.2 equiv.) | EtCN | RT | no conversion |
| 7 | $Br_2$ (1.1 equiv.), *then* KOMe (1.1 equiv.)[a] | $CH_2Cl_2$ | −78 to −20 | no conversion |
| 8 | $Br_2$ (1.1 equiv.), *then* NaOMe (3.0 equiv.)[b] | $CH_2Cl_2$ | −78 to −20 | decomposition |
| 9 | ICl (1.1 equiv.), *then* NaOMe (3.0 equiv.)[b] | $CH_2Cl_2$ | −78 to −20 | decomposition |

[a] In THF. [b] In MeOH.

### 2.6.2 Alkyne Hydrofunctionalization Approach

Terminal alkynes are convenient and versatile synthetic handles in organic chemistry. Through hydrometalation,[62-64] hydration,[143] or bis-metalation,[65] a number of complex functional group patterns can be installed in a straightforward way by electrophilic activation of triple bonds. Shown in Table 2.7 are a series of attempted functionalizations of **197** as well as model compounds **72**, **201**, and **202**. The goal of these experiments was to afford an alkenylmetal nucleophile in readiness for fragment coupling with allyl acetate **108**.

**Table 2.7.** Attempted hydro- and difunctionalizations of alkynes **72**, **197**, **201**, and **202**.




| Entry | Alkyne | Conditions | Result |
|---|---|---|---|
| 1 | **72** | $B_2(pin)_2$, CuCl, KOAc, P(*t*-Bu)$_3$, DMF, RT | No reaction |
| 2 | **72** | $Ni(dppp)Cl_2$ (10 mol%), DIBAL-H, THF, −78 °C to RT, *then* NIS, THF, RT | **208**, 87%[a,b] |
| 3 | **197** | $Ni(dppp)Cl_2$ (10 mol%), DIBAL-H, THF, −78 °C to RT, *then* NIS, THF, RT | **209**, 25% |
| 4 | **201** | **202** (10 mol%), $Bu_3SnSnBu_3$, THF, RT | **210**, 78% |
| 5 | **72** | **202** (10 mol%), $Bu_3SnSnBu_3$, THF, RT | No reaction |
| 6 | **72** | $Bu_3SnAlEt_2$, CuCN (50 mol%), THF, −30 °C | **211**, 77%[b] |
| 7 | **72** | $(Bu_3Sn)_2CuCNLi_2$, MeOH, THF, −78 °C | No reaction |
| 8 | **72** | **203** (12 mol%), **204** (8 mol%), $Bu_3SnH$, THF, −10 °C | No reaction |
| 9 | **72** | **205**, $[Cp^*RuCl]_4$, or **206** (20 mol%), $Bu_3SnH$ *or* $Me_3SnH$, $CH_2Cl_2$, RT | **211**, 48%[b] |
| 10 | **72** | **205** (20 mol%), $(EtO)_3SiH$, $Me_2BnSiH$, $Me_2(EtO)SiH$, $Me_2PhSiH$, or 1-methylsiletane, $CH_2Cl_2$, RT | **213**, 72-99% |
| 11 | **72** | Methallyl bromide, $In^0$, THF, RT, sonication | **214**, 64% |
| 12 | **202** | Methallyl bromide, $NiBr_2$·diglyme (10 mol%), 4,4′-di-*t*-bu-2,2′-dipyridyl (12 mol%), BINAP (15 mol%), $Cs_2CO_3$, $Me(EtO)_2SiH$, DMAc, RT | 31%[c] |
| 13 | **72** | **207** (12 mol%), $Bu_3SnH$, toluene, RT | **212**, 63% |

[a] Contains unknown impurity. [b] Reproducibility issues. [c] By $^1$H-NMR; major product is an unidentified conjugated diene.

Miyaura and co-workers developed a borylcupration of terminal alkynes, which affords the $\alpha$-borylated product after protodecupration in moderate to good selectivity.[144] When this

method was applied to compound **72**, no reaction was observed (entry 1). Steric shielding of the alkyne is surmised to obstruct the approach of the bulky borylcopper species, thereby preventing any interaction.

Hoveyda's $\alpha$-selective hydroalumination and subsequent treatment with NIS in one pot gave the desired 1,1-disubstituted alkenyl iodide **208** from model alkyne **72** (entry 2).[67] The resulting product, however, contained an inseparable and unidentified contaminant. In addition, the reaction was plagued by reproducibility issues, giving strongly varying degrees of conversion and inconsistent isolated yields. Applying the same conditions on the complex substrate **197** resulted in an unexpected outcome: Exclusively the 1,2-disubstituted alkenyl iodide **209** was isolated by HPLC as the major product from a mixture of several species (entry 3). The strong substrate bias was capable of overriding catalyst control in this case, giving the undesired β-hydroalumination product.

Distannation and subsequent protodestannation of the more accessible stannyl residue to give the 1,1-disubstituted alkenylstannane was also evaluated. Mancuso and Lautens developed a palladium-catalyzed procedure for the bis(stannylation) of terminal alkynes.[145] Using palladium complex **202**, the model alkyne **201** was succesfully distannylated to give distannane **210** in 78% yield (entry 4). Selective protodestannation could also be effected by treatment with citric acid, giving the $\alpha$-alkenylstannane in 47% yield. However, when applying Lautens' method to the more complex alkyne **72**, no conversion was observed (entry 5).

An additional dimetalation approach, namely stannylcupration, was examined. As for borylcupration, dimetalation and subsequent protodecupration should selectively afford the 1,1-disubstituted alkenylstannane after work-up.[146] When treating alkyne **72** with an *in situ* generated stannylaluminate and substochiometric amounts of copper(I) cyanide, up to 77% yield of the desired alkenylstannane **211** were obtained (entry 6). To our dismay, these results proved to be highly variable and even irreproducible, giving low conversion regardless of the amount of tin reagent or copper source employed. Surprisingly, using the stannylcopper reagent $(Bu_3Sn)_2CuCNLi_2$ gave no conversion at all, despite this species likely being the reactive intermediate of the previously employed conditions (entry 7).

Of special interest to our synthetic efforts were direct $\alpha$-selective hydrostannations, which would also give 1,1-disubstituted alkenylstannanes suitable for Stille cross-coupling. Several catalysts are known to effect hydrostannation.[63] Three different catalytic methods were examined: Cheng and Mankad developed a heterobimetallic system employing the catalysts **203** and **204** which is capable of accomplishing regioselective hydrostannation by cooperative Sn–H bond activation.[147] However, no reaction occurred with alkyne **72** (entry 8). This is likely due to the sensitivity of the system towards the steric environment of the alkyne. For example, the authors observed low reactivity and even reversed selectivity in the case of 3,3-dimethylbut-1-yne. A ruthenium-catalyzed method for *trans*-hydrostannation was developed by Fürstner and

co-workers and mainly applied to internal alkynes using catalysts such as **205** and **206**.[148] In the instance of terminal alkynes, the system exhibits good $\alpha$-selectivity. Care has to be taken regarding the order of addition: Adding a solution of the substrate and tributyltin hydride to a solution of the catalyst is vital to prevent catalyst decomposition and/or unproductive ruthenium vinylidene formation.[149] In the case of alkyne **72**, this reaction again faced reproducibility issues, regardless of which catalyst was employed (entry 9). Up to 48% yield of the stannane **211** were obtained, but strongly varying amounts of conversion and inconsistent yields led us to abandon this system. Recently, Wang and co-workers disclosed an iron-catalyzed regiodivergent hydrostannation, which is capable of selectively furnishing the $\alpha$-alkenylstannane when using catalyst **207**.[150] Preparation of **207** proved to be challenging, and the iron complex could only be prepared in an impure form. When subjecting alkyne **72** to this catalyst and tributyltin hydride, β-(*Z*)-alkenylstannane **212** was isolated in 63% yield (entry 13). Intriguingly, Wang and co-workers do not describe the formation of (*Z*)-alkenes in their report. Whether this surprising observation was a result of impurities present in our batch of **207** or the steric environment of **72** could not be determined.

At the turn of the century, Trost and co-workers pioneered the ruthenium-catalyzed *trans*-hydrosilylation of alkynes.[62, 151] This reaction smoothly provided a series of corresponding alkenylsilanes of the type **213** from alkyne **72**. Depending on the silane, yields between 72% and 99% were obtained (entry 10). However, as can be deduced from the failed halodesilylation described previously, these alkenylsilanes were reluctant to undergo any further transformation. Neither Hiyama–Denmark coupling, nor halodesilylation, nor Fleming–Tamao oxidation conditions could provide desilylated products in useful yields. Thus, this approach also had to be abandoned.

Allylindium reagents prepared under Barbier conditions by mixing indium metal and allyl halides have the ability to directly carbometalate terminal alkynes in a Markovnikov sense.[152] We pursued to harness this property for a direct fragment coupling between an allyl electrophile and the alkyne **197**. To test the viability of this plan, alkyne **72** was subjected to an excess of methallyl bromide and metallic indium under sonication conditions. Indeed, the methallylated product **214** could be isolated in 64% yield (entry 11). The rest of the starting alkyne was left untouched, despite employing 8 equivalents of allyl halide. Since the envisioned fragment coupling would require a complex allyl donor similar to allyl acetate **108**, using a large excess of the allyl partner was deemed too costly. It was later attempted to lower the amount of allyl halide needed for full conversion of the alkyne (see Section 3.2).

Finally, a nickel-catalyzed Markovnikov hydroallylation of alkynes developed by Fu and co-workers was examined.[153] Reacting methallyl bromide and model alkyne **202** gave a complex mixture of products. By quantitative $^1$H NMR, the major product was determined to be a conjugated diene in around 31% yield (entry 12). This result can be traced back to the

formation of nickel hydride species in the reaction mixture, which have the ability to effect alkene isomerization. Non-thermodynamic unsaturated systems such as 1,3-dienes are therefore not compatible with these conditions.

The results described above once again led to a reconsideration of our synthetic strategy: Neither alkenylsilane **191** nor terminal alkyne **197** turned out to be suitable alkenylmetal nucleophile precursors. Accordingly, we turned our attention to ketone **198**.

### 2.6.3 Ketone Triflation/Stannation Approach

Methyl ketones can be elaborated into a variety of alkenyl electrophiles through an intermediate hydrazone by Shapiro reaction or Barton's alkenyl iodide synthesis.[80a, 154] This approach is plagued by regioselectivity issues if two enolizable positions are present in the ketone. A more selective approach proceeds *via* "kinetic" enolization of the methyl ketone to ensure 1,1-disubstitution on the alkene and trapping of the enolate with a triflate source.[155] The resulting alkenyl triflate can be transformed into an alkenylmetal nucleophile by copper-mediated stannylation or Miyaura borylation.[156] An alkenylstannane was selected as the preferred target over an alkenylboronic acid ester, as the latter requires the presence of base to undergo transmetalation, while Stille cross-couplings can be conducted under comparatively mild, nearly neutral conditions. Due to the presumed sensitivity of the skipped tetraene in limaol, strongly basic conditions were to be avoided and thus Suzuki couplings were disregarded.

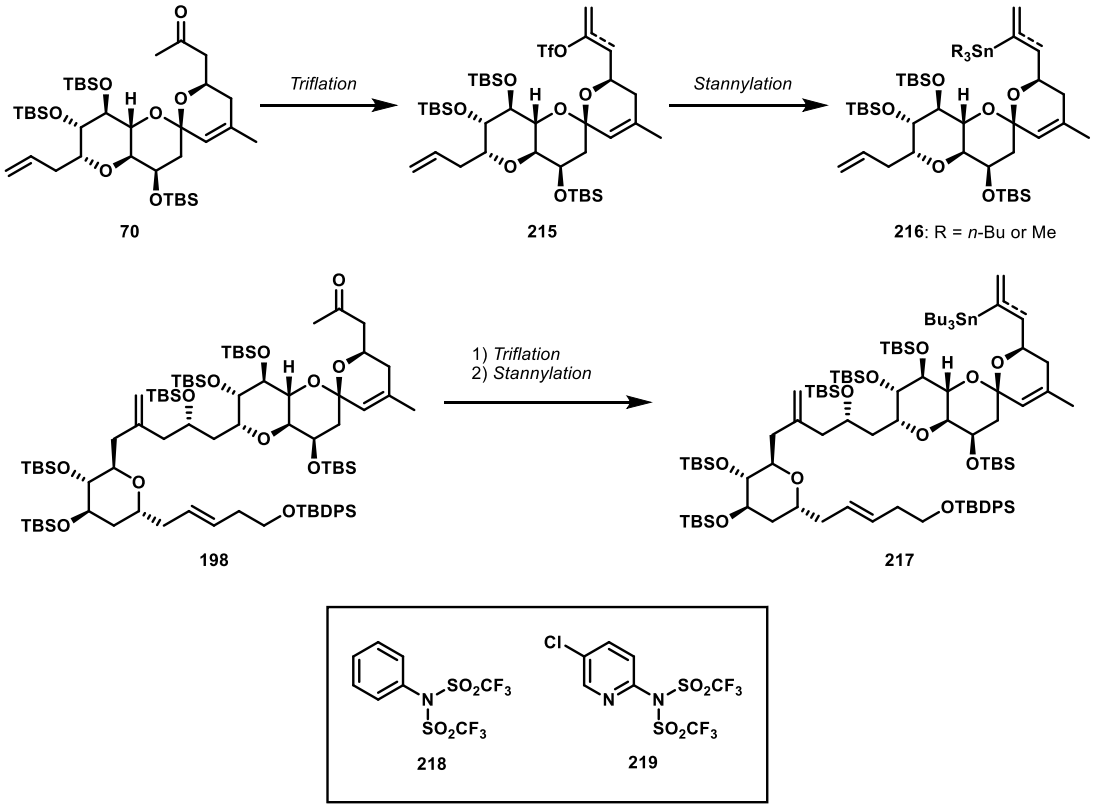
Direct conversion of the methyl ketone to the alkenylstannane was first attempted by addition of tributylstannyl lithium and elimination of the resulting tertiary alcohol *via* mesylation and treatment with base.[157] This approach gave an intractable mixture of products and was therefore not pursued further.

Instead of the direct conversion, a two-step triflation/stannation sequence was then evaluated in a series of experiments (Table 2.8). A first attempt to isolate the alkenyl triflate **215** formed from ketone **70** by deprotonation with KHMDS and treatment with **218** was undertaken (entry 1). The triflate **215** slowly decomposed at ambient temperature, compelling us to develop a one-pot procedure to minimize the lifetime of this sensitive intermediate. To directly convert the alkenyl triflate into the corresponding stannane, two possible transformations were examined: A Stille-type cross-coupling with a ditin reagent (entry 2),[158] or a direct stannylation using a stannylcuprate (entry 3).[68] The latter approach gave slightly better yields, affording alkenylstannane **216** in 87% yield and a 4:1 ratio of inseparable double bond isomers. The major isomer was the desired 1,1-disubstituted olefin derived from deprotonation of the methyl ketone at the more accessible position. To improve upon the ratio of olefin isomers, several strong and sterically hindered bases were tested. LiHMDS was examined due to lithium's strong oxophilicity, ensuring the formation of a more configurationally stable lithium enolate. Some lithium enolates are in fact so stable that complete triflation using **218** requires several

hours at 0 °C, which may in turn cause enolate equilibration to occur. To circumvent this issue, more reactive Comin's reagent (**219**) was used when employing LiHMDS as the base (entry 4).[159] However, **219** was not compatible with the one-pot stannylation conditions, leading instead to decomposition of the starting material.

After investigating a series of standard amide bases, we arrived at the rather unconventional base trityl potassium.[160] Upon treatment of ketone **70** with this base, triflation with **218**, and stannylation in a one-pot procedure, 80% yield of the desired 1,1-disubstituted alkenylstannane **216** were isolated (entry 5). This promising result was promptly transferred to the more complex ketone **198**. In a similar fashion as for **70**, a series of bases (KHMDS, LDA, LiTMP, and trityl potassium) were evaluated. Surprisingly, the isomer ratios in all cases were not as favorable as for model ketone **70**, although the ketone region of both **70** and **198** is highly conserved. KHMDS and LDA gave ratios of 2:1 and 1:1, respectively (entries 6 & 7), while treatment with LiTMP decomposed the starting material (entry 8). Again, trityl potassium proved to be the best option, as the desired alkenylstannane **217** was obtained as a 3:1 mixture of *exo*/*endo* regioisomers in 63% combined yield (entry 9). The olefin isomers were not separable at this stage, so the following fragment coupling step had to be attempted with the mixture of isomers.

**Table 2.8.** Triflation/stannation sequence on model ketone **70** and on ketone **198**.




| Entry | Ketone | Triflation[a] | Stannylation | Result |
|---|---|---|---|---|
| 1 | **70** | KHMDS, *then* **218** | - | 27%, 4:1 rr (**215**)[b] |
| 2 | **70** | KHMDS, *then* **218** | $Me_3SnSnMe_3$, $Pd_2(dba)_3$ (15 mol%), P(2-furyl)$_3$ (60 mol%), LiCl, THF, RT | 77%, 4:1 rr (**216**) |
| 3 | **70** | KHMDS, *then* **218** | $(Bu_3Sn)_2CuCNLi_2$, THF, −60 °C to −25 °C | 87%, 4:1 rr (**216**) |
| 4 | **70** | LiHMDS, *then* **219** | $(Bu_3Sn)_2CuCNLi_2$, THF, −60 °C to −25 °C | Decomposition |
| 5 | **70** | $Ph_3CK$, *then* **218** | $(Bu_3Sn)_2CuCNLi_2$, THF, −60 °C to −25 °C | 80%, single regioisomer (**216**) |
| 6 | **198** | KHMDS, *then* **218** | $(Bu_3Sn)_2CuCNLi_2$, THF, −60 °C to −25 °C | 73%, 2:1 rr (**217**) |
| 7 | **198** | LDA, *then* **218** | $(Bu_3Sn)_2CuCNLi_2$, THF, −60 °C to −25 °C | 70%, 1:1 rr (**217**) |
| 8 | **198** | LiTMP, *then* **218** | $(Bu_3Sn)_2CuCNLi_2$, THF, −60 °C to −25 °C | Decomposition |
| 9 | **198** | $Ph_3CK$, *then* **218** | $(Bu_3Sn)_2CuCNLi_2$, THF, −60 °C to −25 °C | 63%, 3:1 rr (**217**) |

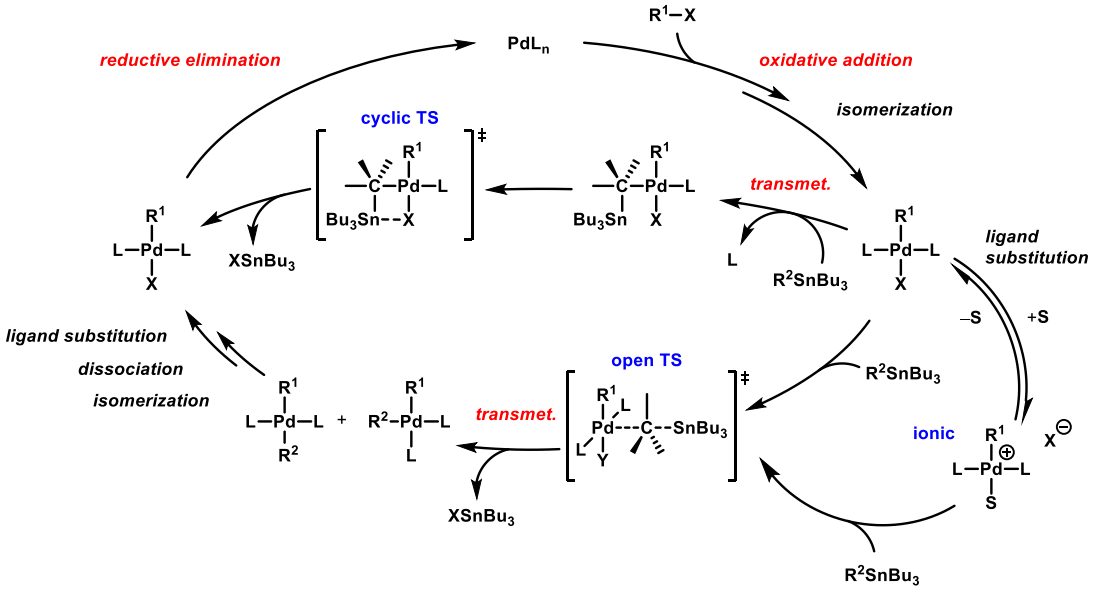
[a] General procedure: A solution of the base (1.1-3.0 equiv.) was added to a solution of ketone at −78 °C. After 2 h, a solution of the triflation reagent (2.0-2.5 equiv.) was added at −78 °C and the solution was kept at this temperature for 1 h. [b] Product slowly decomposes at room temperature.

### 2.6.4 π-Allyl Stille Cross-Coupling

Stille cross-couplings have been thoroughly reviewed and are among the most popular methods for fragment assembly in total synthesis due to their reliability and mild reaction

conditions.[36a, 161] In order to merge alkenylstannane **217** and the allyl acetate **108**, the mechanism of π-allyl Stille cross-couplings was reviewed more closely.

A detailed account of the mechanism of the Stille reaction has been disclosed by Espinet and Echavarren.[161b, 162] The catalytic cycle shown in Scheme 2.55 is adapted from their work. Of all elememtary steps shown in the cycle, especially the transmetalation is notoriously slow and typically rate-limiting. It has therefore been the target of many improvements. For example, the use of electron-deficient ligands such as P(2-furyl)$_3$ and AsPh$_3$ pioneered by Farina and co-workers aims to facilitate ligand dissociation and thereby allow for more rapid coordination of the tin nucleophile and subsequent transmetalation.[163] In addition, copper(I) additives have been proven to significantly increase the coupling rate and ensure improved selectivity for *ipso*- over *cine*-substitution for hindered alkenylstannanes.[164] The presumed role of copper is two-fold: For one, it acts a ligand scavenger for catalysts of type [Pd(0)L$_4$], sequestering superfluous ligand and thereby ensuring that free coordination sites on palladium are open for transmetalation. Secondly, the tin nucleophile can transmetalate onto copper in polar reaction media, affording the more nucleophilic organocopper species and thereby further facilitating transmetalation onto palladium.[162] Since the copper-tin exchange is reversible, methods for *in situ* removal of the tin byproducts have proven valuable. For example, Baldwin and co-workers established the synergic effect of copper(I) salts with a fluoride source such as CsF, which effects precipitation of insoluble Bu$_3$SnF, thereby ensuring quantitative transmetalation to copper.[165] As an added challenge for the coupling of allyl electrophiles, reductive elimination can become the rate-limiting step in these special cases due to the relatively slow formation of C(sp$^2$)–C(sp$^3$)-bonds compared to C(sp$^2$)–C(sp$^2$)-bonds.[166]

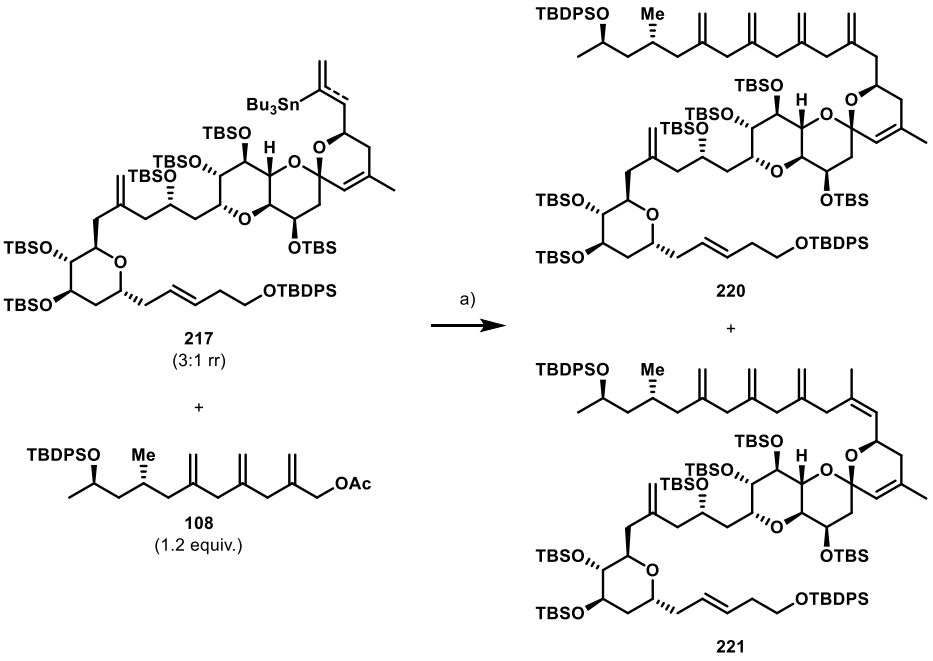



**Scheme 2.55.** Catalytic cycle of the Stille reaction adapted from Espinet and co-workers.[161b]

With these findings in mind, we proceeded to evaluate a series of experimental conditions for the cross-coupling of stannane **217** with allyl acetate **108**. Stille and co-workers had reported the palladium-catalyzed cross-coupling of allyl halides with alkenylstannanes.[167] However, due to the presumed sensitivity of the halide analog of triene **108**, this method was disregarded, and instead, a method developed by Hegedus and co-workers employing allyl acetates was examined. Addition of an excess of LiCl and catalytic amounts of $Pd_2(dba)_3$ *without* added ligand were necessary for these electrophiles to undergo reaction.[168] This "ligand-less" approach is enabled by the stability of the π-allylpalladium(II) complex resulting from oxidative addition of Pd(0) into the allyl electrophile. Importantly, phosphine ligands shut down the reaction in this case. The addition of LiCl effects ligand exchange, replacing an acetate on palladium for a chloride. The resulting complex undergoes transmetalation with the stannane nucleophile more easily due to its increased electrophilicity. In their total synthesis of azaspiracid-1, Nicolaou and co-workers had successfully effected a fragment coupling of an alkenylstannane and an allyl acetate using $Pd_2(dba)_3$, LiCl, $AsPh_3$, and Hünig's base to limit protodestannation caused by adventitious water.[169] In another protocol developed by Fürstner and co-workers, using catalytic $Pd(PPh_3)_4$, CuTC, and tetrabutylammonium diphenylphosphonate as a tin scavenger in DMF achieved the coupling of complex starting materials at ambient temperature and under fluoride-free conditions.[170]

In the first series of experiments, the latter method was tested with addition of LiCl, since this additive proved vital for the coupling of allyl acetates according to Hegedus and co-workers. However, low conversion was observed and only intractable mixtures of olefin isomers were isolated from these attempts. Next, Nicolaou's protocol was employed, but again, only mixtures of products were obtained. Importantly, all experiments conducted at this point exhibited extremely slow consumption of the alkenylstannane. Since addition of copper did not seem to significantly accelerate the reaction, it was presumed that reductive elimination and not transmetalation was the rate-limiting step. In an effort to alleviate this, $Pd[P(t\text{-}Bu)_3]_2$ was employed as a catalyst. The wide cone-angle of the bulky phosphines should be able to expedite reductive elimination by decreasing the distance between the organic residues on the palladium complex.[161b] In this case, however, no reaction was observed. With a similar rationale in mind, the bulky and electron-deficient ligand JackiePhos was briefly tested with $Pd_2(dba)_3$ as the palladium source, but the starting materials again remained untouched. After extensive experimentation, the reason for the failure of our first attempts became apparent: When using CuTC and tetrabutylammonium diphenylphosphonate, the addition of LiCl led the reaction mixture to become highly heterogeneous and slowed down conversion significantly. Upon omission of LiCl, the transformation proceeded to completion within 14 h. Furthermore, due to the low polarity of the starting materials, addition of THF was necessary to keep them in

solution. The Stille coupling afforded the skipped tetraene **220** in 60% yield after separation of the internal double bond isomer **221** (Scheme 2.56).




**Scheme 2.56.** Final fragment assembly *via* Stille cross-coupling. Conditions: a) $Pd(PPh_3)_4$ (10 mol%), $[NBu_4][Ph_2P(=O)O]$, CuTC, DMF/THF (1:1), 60% (**220**), 13% (**221**).

Triflation, stannation, and Stille coupling converted ketone **198** into fully protected limaol (**220**) in 38% yield over three steps. Taking the entire synthesis into account, this precursor was synthesized in 4.5% yield over 19 steps in longest linear sequence. With the carbon skeleton of limaol now in place, achieving global deprotection was the final goal.

## 2.7 Completion of the Synthesis

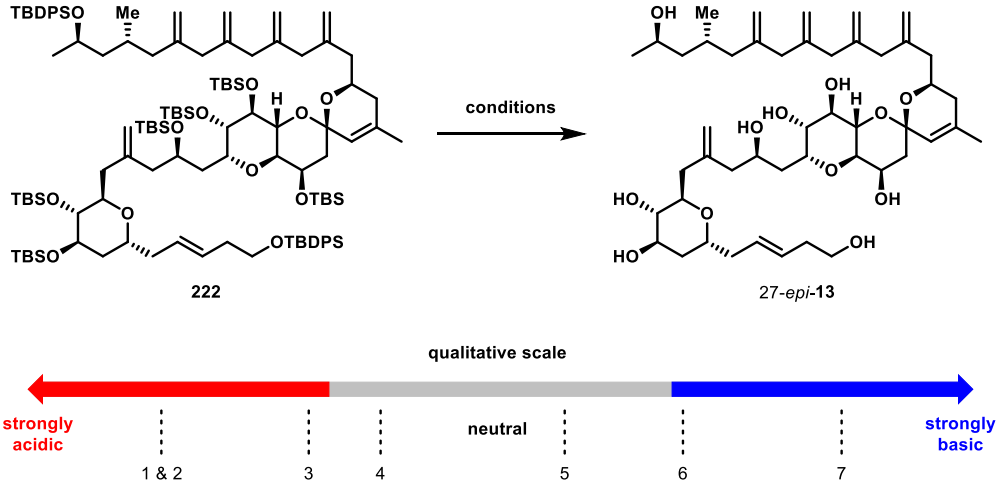
### 2.7.1 Global Deprotection

A wide variety of methods for the cleavage of silyl ethers are known.[39, 171] Some of the more functional-group-tolerant and mild protocols were tested in a series of experiments (Table 2.9). The deprotection studies were conducted on the C-27 epimer of **220**, compound **222**, which was obtained from ketone **192** by conversion to the corresponding alkenylstannane and Stille cross-coupling with **108** as described above.

Due to the polarity of the desired product, all reactions were monitored by HPLC analysis. Acidic conditions (entries 1 & 2) were not well tolerated, leading to a complex mixture of products.[172] With a p$K_a$ of 3.1 in MeCN, aqueous HF is considerably more acidic than pyridinium cations (p$K_a$ = 5.0 in water) or acetic acid (p$K_a$ = 4.8 in water). The latter has been used to buffer the basicity of TBAF in deprotections of sensitive substrates.[173] In our hands, this system, as well as the unbuffered variant, only led to incomplete conversion (entries 3 & 7). Roush and co-workers introduced TAS-F as a mild desilylating reagent in the context of natural product synthesis.[174] In addition, in Roush's total synthesis of (−)-bafilomycin A, TAS-F was used in conjunction with water to further attenuate the basicity of the reagent.[175] Both of these protocols again only led to incomplete deprotection of **222** (entries 5 & 6). The only method capable of producing the desired octaol 27-*epi*-**13** was the treatment of the silyl ether with a large excess of HF–pyridine in a 1:3 volume ratio with pyridine. The addition of pyridine in this amount ensured that the most acidic species in solution was a pyridinium cation. After 10 d at ambient temperature, the starting material and most of the intermediate deprotection products had been consumed according to HPLC analysis of the reaction mixture. After isolation by preparative HPLC, 27-*epi*-**13** was isolated in 37% yield.

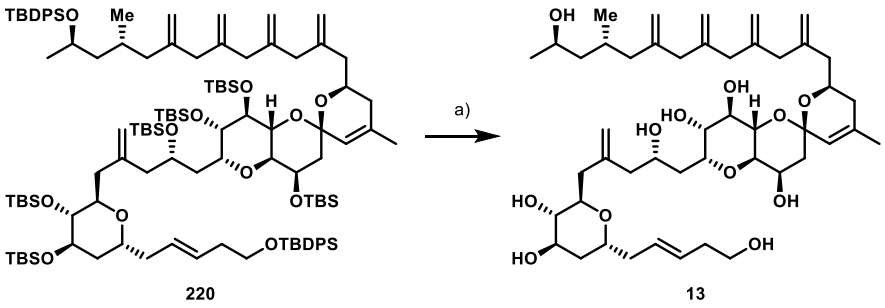
With these results in mind, the deprotection of **220** was undertaken using the same conditions. After treatment with HF–pyridine in pyridine and THF for 11 d, **13** could be isolated from the reaction mixture in 32% yield (Scheme 2.57). In summary, **13** could be synthesized in 1.5% yield and in 20 steps in longest linear sequence starting from $\alpha$-D-glucopyranosyl pentaacetate.

**Table 2.9.** Qualitative comparison of deprotection conditions for the cleavage of silyl ethers.




| Entry | Conditions[a] | Result |
|---|---|---|
| 1 | Aq. HF, MeCN, RT | Decomposition |
| 2 | HF·pyr, THF, RT | Decomposition |
| 3 | TBAF/AcOH (1.0:1.1), THF, RT | Incomplete conversion |
| 4 | HF–pyridine/pyridine (v/v 1:3), THF, RT, 10 d | 37% (27-*epi*-**13**) |
| 5 | TASF/$H_2O$ (1:1), DMF, RT | Incomplete conversion |
| 6 | TASF, DMF, RT | Incomplete conversion |
| 7 | TBAF, THF, RT | Incomplete conversion |

[a] In every case, a large excess of reagents was employed (10-20 equiv.).




**Scheme 2.57.** Deprotection of silyl ether **220** to give synthetic limaol (**13**). Conditions: a) HF–pyridine/pyridine (v/v 1:3), THF, RT, 11 d, 32%.

### 2.7.2 Comparison of the Synthetic Material to Authentic Limaol

Both the $^{13}C$ NMR and $^{1}H$ NMR data of the synthetic material were in good agreement with the those of natural limaol (see Section 6).[35] A graphical comparison of the $^{13}C$ NMR spectra is given in Figure 2.3.

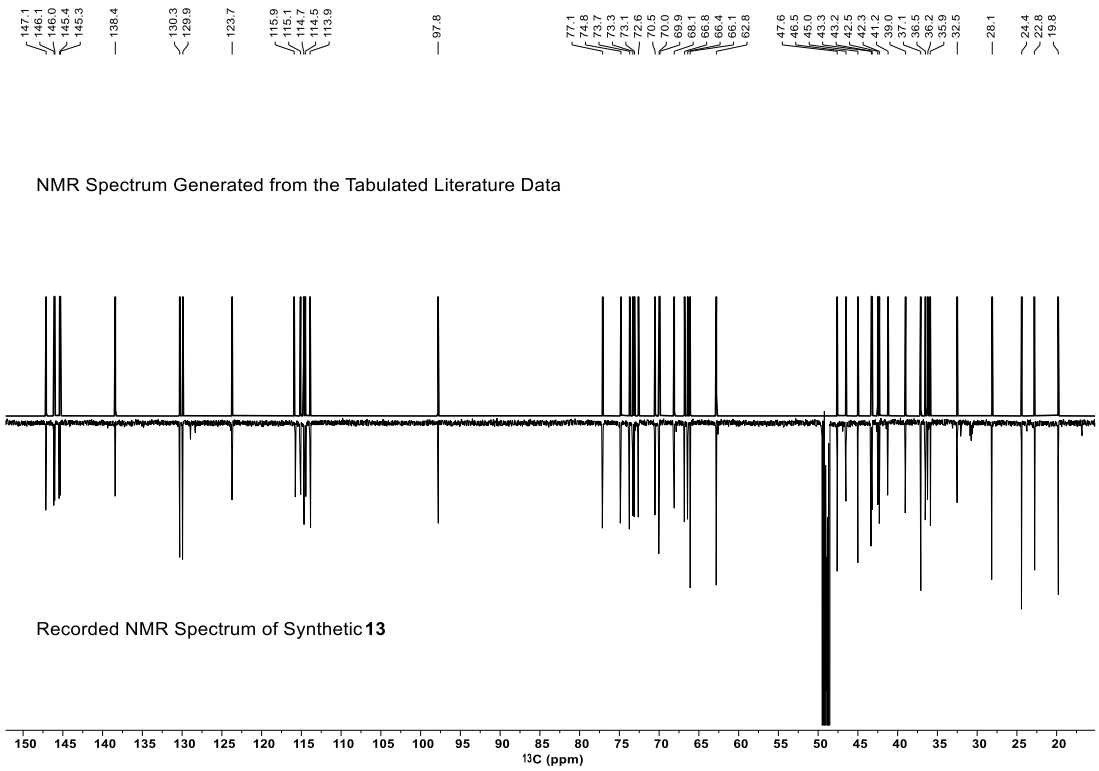



**Figure 2.3.** Visual comparison of the $^{13}C$ data of authentic limaol (**13**) with those of synthetic **13**.

During the deprotection studies, 27-*epi*-**13** had also been synthesized as shown above. Comparison of the $^{13}C$ NMR data showed a clear disparity in the chemical shifts clustered around carbon C27 (Figure 2.4).

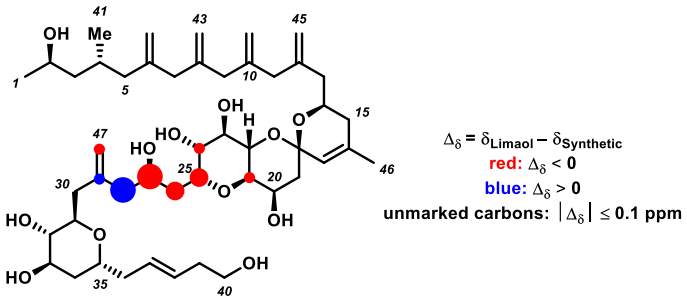



**Figure 2.4.** Visual comparison of deviations in $^{13}C$ shifts between 27-*epi*-**13** and **13**. The absolute value of deviations is denoted by the size of the colored spheres (0.3 ppm deviation for the smallest spheres and 1.9 ppm for the largest spheres).

# 3 Second-Generation Synthesis of Limaol

## 3.1 Identification of Bottlenecks of the First-Generation Synthesis

After completion of the synthesis of **13**, some questions remained to be answered. The peculiar stereochemical bias of the central fragment aldehydes as well as the recalcitrance of alkenylsilane **191** and alkyne **197** to undergo any synthetically productive reaction could so far not be explained. Elucidation of these unexpected reactivities might open up avenues to revise the synthetic sequence and solve some of the issues encountered in the first-generation synthesis. Ideally, a more scalable and higher-yielding second-generation synthesis would result, allowing access to sufficient quantities of **13** for biological studies.

In order to develop an improved route, the bottlenecks of the prior synthesis were identified (Figure 3.1). The coupling of the southern fragment to the central fragment aldehyde affords exlusively the undesired diastereoisomer of the allylic alcohol, although stereochemical models such as the Cram-chelate would suggest otherwise. To repair the stereochemistry *a posteriori*, a Mitsunobu inversion was required (Bottleneck "A"). The formation of the alkenylstannane necessary for the subsequent π-allyl Stille cross-coupling occurs with unsatisfactory regioselectivity, demanding tedious separation of double bond isomers after coupling and providing low yields of the target tetraene (Bottleneck "B"). Finally, the global deprotection is the step with the lowest yield in the entire sequence. The cleavage of the eight silyl ethers is sluggish, and requires a fine balancing of reaction conditions. Nevertheless, only one third of the theoretically possible amount of product was isolated, indicating a significant loss of valuable material at this very late stage (Bottleneck "C").

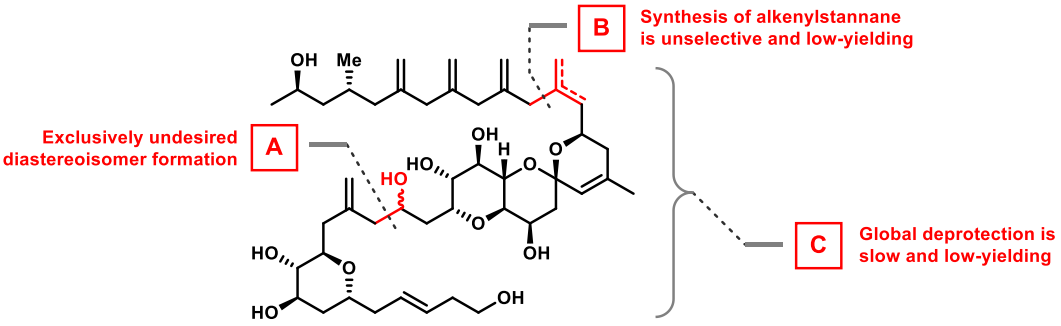


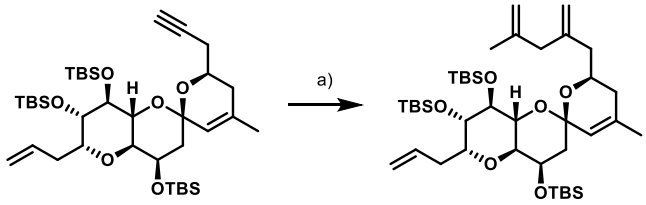

**Figure 3.1.** Bottlenecks of the first-generation synthesis of limaol.

In the following sections, each bottleneck will be addressed. Since the coupling between the northern and central fragment was considered to allow the most room for improvement, it was investigated first.

## 3.2 Revised Assembly of the Northern and Central Fragments *via* Indium-Mediated Alkyne Allylation

### 3.2.1 Starting point

During the efforts to functionalize alkyne **197**, a rather underexplored transformation was tested in an attempt to directly allylate the terminal alkyne. Using indium metal and allyl halides under Barbier conditions, terminal alkynes can be directly allylated in a Markovnikov-sense.[152] Klaps *et al*. employed ultrasonication to facilitate generation of the active allylindium species and a large excess of allyl halide (8.0 equiv.) to ensure full conversion of the terminal alkyne.[152c] Upon testing these conditions on alkyne **72** with methallyl bromide, 1,4-diene **214** was obtained in 64% yield (Scheme 3.1). The entirety of the remaining starting material (36%) could be reisolated, indicating a clean, but incomplete transformation.




72 214

**Scheme 3.1.** Allylindation of alkyne **72**. Conditions: a) Methallyl bromide (8.0 equiv.), $In^0$ (1.5 equiv.), THF, RT, sonication, 64% (quant. brsm).

Considering this result, two questions arose: Could the same transformation be driven to full conversion with just a stochiometric quantity of allyl halide? And secondly, could more complex allyl donors than methallyl bromide be used? In order to answer them, the literature on organoindium compounds was consulted.

### 3.2.2 Indium-Mediated Allylations in Organic Synthesis

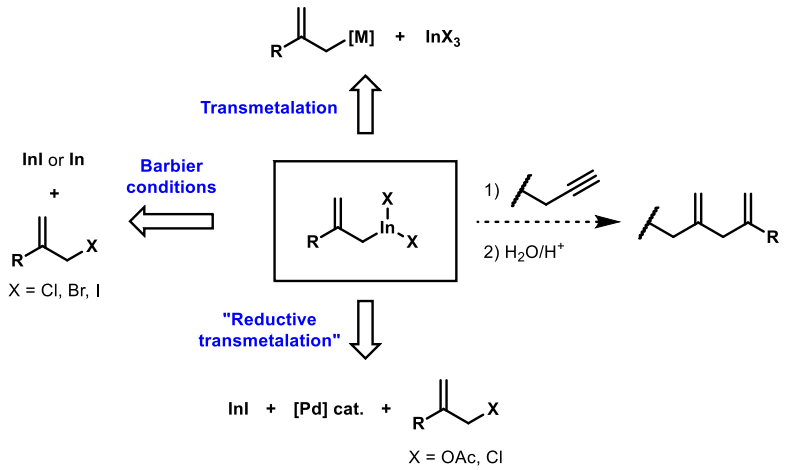
Several reviews on indium and its role in organic synthesis have been published. The reactivity of indium can be classified into two major categories: (i) It can function as a π-acid to effect electrophilic activation of unsaturated carbon-carbon bonds,[176] and (ii) organoindium species are highly nucleophilic, allowing attack on a variety of electrophiles such as carbonyls and alkynes.[152d, 177]

The latter reactivity is predominantly utilized in indium-mediated allylations under Barbier conditions.[178] Surprisingly, the exact nature of the nucleophilic intermediates in these allylation reactions remains unclear. Araki *et al*. have initially proposed the nucleophile to be an "indium-sesquihalide" of the type $(allyl)_3In_2Br_3$, based on the optimal stochiometry between allyl halide, indium metal, and electrophile being 3:2:1 and on $^1H$ NMR experiments showing

two distinct sets of allylic proton signals in a ratio of 1:2.[178c, 178d] However, later studies found the structure of the reactive intermediate to be far more complex. Koszinowski found several aggregated and charged or neutral species containing varying amounts of In(III), halide anions, and allyl residues to be in equilibrium.[179] In a later review by Bowyer *et al.*, the conclusion was drawn that there are two species mainly present: monoallylindium dibromide and diallylindium bromide.[180] Baba and co-workers confirmed by X-ray crystallography that the two intermediates exist at least in solid state.[181] In solution, a dynamic equilibrium between these two compounds and a variety of aggregated states is likely. The blurred nature of the allylindium intermediates significantly hampers the quest to synthesize a defined indium-containing allylation reagent (*vide infra*).

### 3.2.3 Allylindation of Alkynes for Complex Fragment Couplings

Three general pathways towards nucleophilic allylindium species were examined in our efforts (Scheme 3.2). Firstly, mixing either indium metal or indium monoiodide and an allyl halide should produce an allylindium(III) halide capable of addition to an alkyne *in situ* (Barbier conditions).[152] Transmetalation of an allylmetal nucleophile such as allylstannanes or allylmagnesium bromides onto an indium(III) halide is likely to also allow access to the same desired species.[182] Finally, Araki *et al*. have developed a "reductive transmetalation" approach towards allylindium(III) reagents, where allyl electrophiles are reacted with a palladium catalyst to form π-allylpalladium(II) complexes. These complexes presumably undergo indium(I) iodide-mediated reduction back to palladium(0) and the allylindium(III) halide product.[183] All three synthetic methods were evaluated in an effort to obtain a defined allylindium(III) reagent with the capability to react with alkynes in a stochiometric fashion, e.g. without requiring an excess of the allyl donor.




**Scheme 3.2.** Pathways towards nucleophilic allylindium species.

To summarize an extensive series of experiments, it was not possible to effect the quantitative allylation of a model alkyne using only one equivalent of methallyl halides and applying the methods described above. Araki's protocol gave no conversion of the alkyne at all, while Barbier conditions or transmetalation only ever resulted in partial conversion (Figure 3.2). There was a clear correlation between the amount of methallyl halide added and the achieved conversion. In all cases, a minimum of 1.6 equivalents of allyl halide were necessary for full consumption of the alkyne. Attempts to employ defined methallylindium chlorides synthesized from the corresponding Grignard reagents and indium(III) chloride only led to atypically low conversion of the alkyne of <10%.[182d] Increasing the nucleophilicity of the allylindium reagent by converting it into the anionic indate or boosting the π-acidity of indium(III) by halide abstraction were also to no avail.[184]

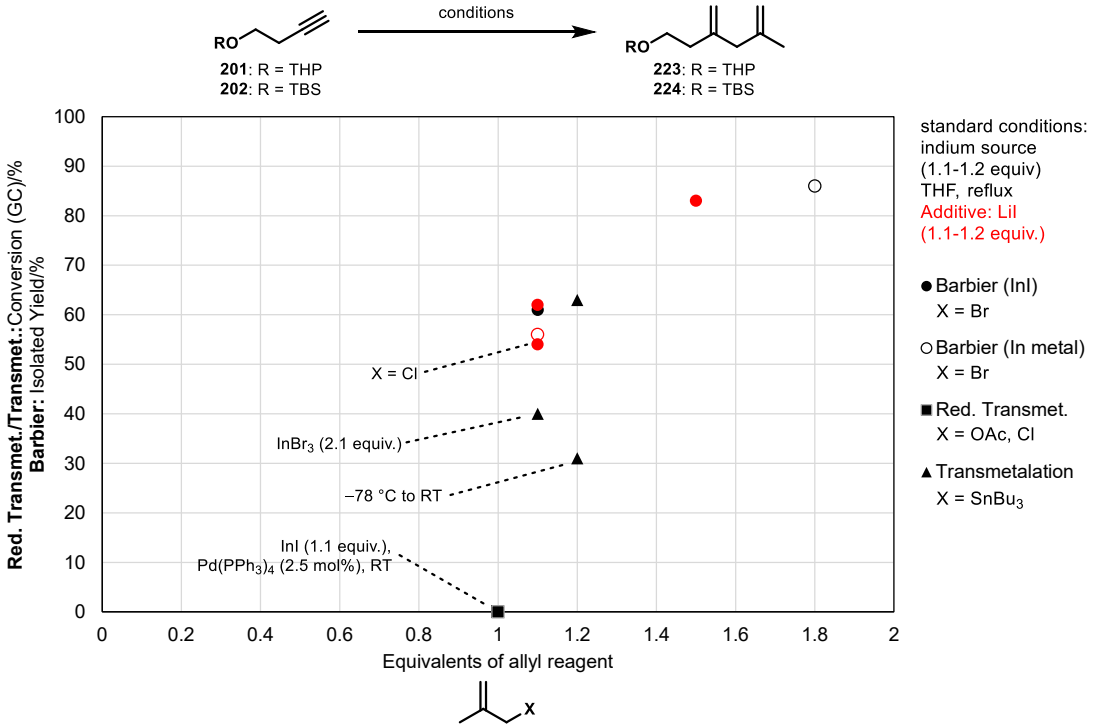
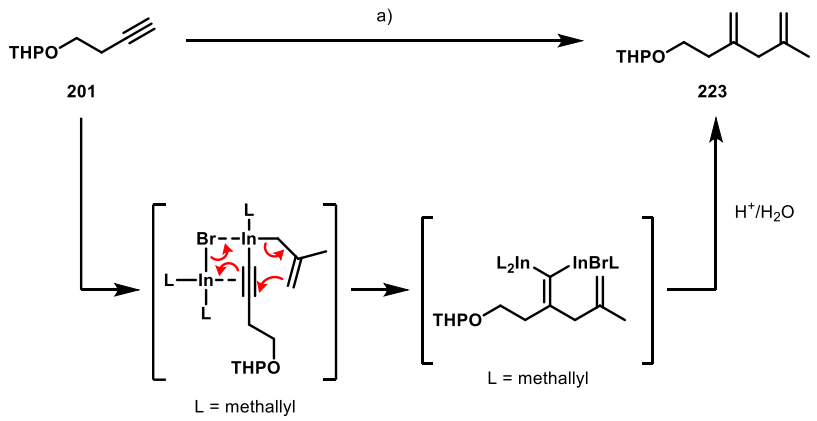



**Figure 3.2.** Graphical summary of allylindation experiments.

Since at least one of the allyl residues on indium seems to remain on the metal as a tightly bound ligand, the idea of using sacrificial ligands was explored next. In an initial series of experiments, electron-deficient methyl 2-(bromomethyl)acrylate and benzyl bromide were used. While the first was presumed to form less electron-rich and therefore less nucleophilic allylindium(III) complexes, the latter was chosen due to the experimentally demonstrated slower reaction rate of benzylindium(III) over allylindium(III) reagents in the carboindation of alkynes.[152a] In all cases, incomplete conversion of the model alkyne **201** was observed, regardless of the added amount of sacrificial halide.

Cyclopentadienylindium(I) was also briefly explored as a reductant for methallyl bromide, since it was envisioned to give allylindium(III) complexes with a Cp ligand attached.[185] A complex mixture of products was obtained, which can likely be attributed to the strong reducing power of CpIn. The use of more classical ligands such as triphenylphosphine or pyridine as additives in standard allylindation reactions led to no improvement of conversion. Attempts to synthesize a series of defined heteroleptic allylindium(III) reagents *in situ* from indium(III) chloride by sequential addition of a variety of Grignard reagents and alkali metal alkoxides, were also not fruitful. Of the four allylindium(III) species prepared in this way, none was able to fully consume one equivalent of model alkyne **201**.

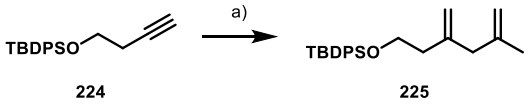
A crucial insight into the mechanism of the allylmetalation of alkynes was provided by Takai and co-workers in their study of amine-accelerated allylgallation.[186] According to the authors, a vital step of allylgallation is the deprotonation of the terminal alkyne to form a gallium acetylide. This intermediate rearranges under π-acid mediation, giving the carbogallated product. The described mechanism is likely also operative in allylindation (Scheme 3.3). When testing Takai's conditions with stochiometric DIPEA as an additive, the allylindation of alkyne **201** proceeded smoothly at ambient temperature to give the 1,4-diene **223** in quantitative yield according to $^1$H NMR. However, an excess of methallyl bromide and indium metal still had to be employed. Yet, it was clearly demonstrated that DIPEA has an accelerating effect on the reaction, likely due to facilitation of alkyne deprotonation.



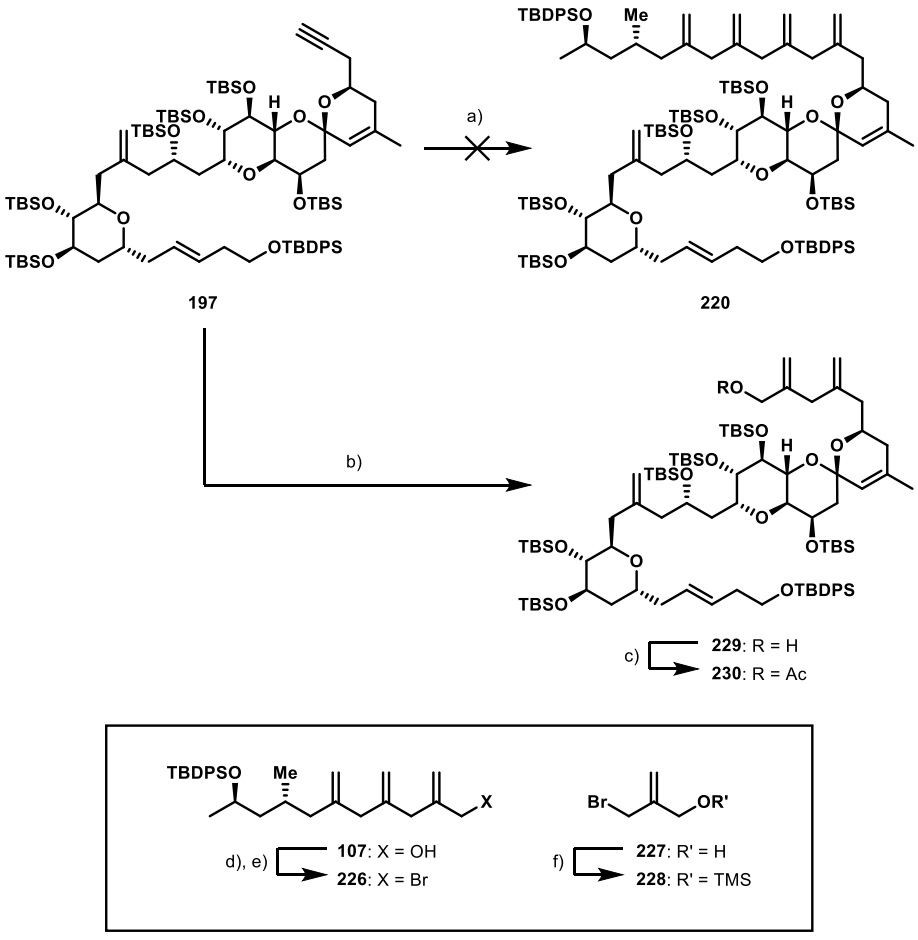

**Scheme 3.3.** Amine-accelerated allylindation and its proposed mechanism (adapted from Takai and co-workers).[186] Conditions: a) Methallyl bromide (3.0 equiv.), $In^0$ (2.0 equiv.), DIPEA (1.0 equiv.), THF, RT, 2.5 h, quant. (by $^1$H NMR).

This result also indicates why an excess of allylindium(III) reagent has to be employed: Some of the organometallic species is presumably consumed in a simple deprotonation reaction. As Takai and co-workers suggest, stochiometric deprotonation of the terminal alkyne before addition of the allylindium(III) reagent should ensure an improved allylindation and allow for a reduction in equivalents of allyl halide.[186] This hypothesis was tested on model

alkyne **224**, which smoothly underwent deprotonation using ethylmagnesium bromide and subsequent allylindation to give diene **225** in 82% yield after treatment with a methallylindium(III) bromide solution (Scheme 3.4). Importantly, the organoindium species was prepared from only 1.2 equivalents of allyl halide.




**Scheme 3.4.** Allylindation of alkynylmagnesium bromides. Conditions: a) EtMgBr (1.1 equiv.), THF, 0 °C to 50 °C, *then* add prestirred solution of methallyl bromide (1.2 equiv.), $In^0$ (1.0 equiv.), THF, RT, 82%.



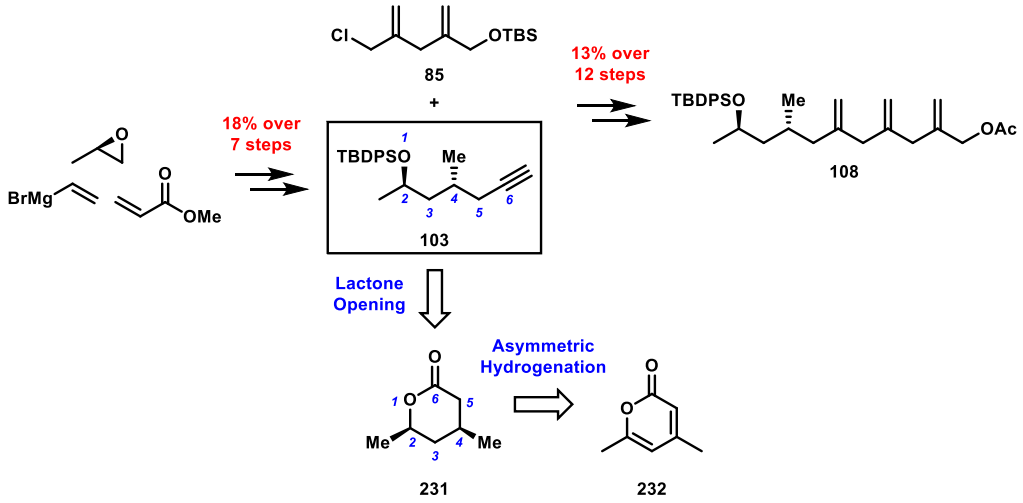

**Scheme 3.5.** Allylindation in fragment coupling reactions. Conditions: a) *i*-PrMgBr, THF, RT, *then* add prestirred solution of **226** (2.0 equiv.), $In^0$, TMSCl, 1,2-dibromoethane, THF, RT to 100 °C, *then* 1 M HCl (aq.), THF, RT, low conversion; b) *i*-PrMgBr, THF, RT, *then* add prestirred solution of **228** (6.0 equiv.), $In^0$, TMSCl, 1,2-dibromoethane, THF, RT to 100 °C, *then* 1 M HCl (aq.), THF, RT, 58%; c) $Ac_2O$, pyridine, DMAP, $CH_2Cl_2$, 0 °C to RT, quant.; d) MsCl, $NEt_3$, THF, 0 °C to RT; e) LiBr, THF, RT, 97% over two steps; f) TMSCl, $NEt_3$, $CH_2Cl_2$, 0 °C, 70%.

With these results in hand, the allylindation was tested on significantly more complex systems (Scheme 3.5). After conversion of the northern fragment alcohol **107** to the corresponding allyl bromide **226**, two equivalents of this halide were used in an attempted indium-mediated fragment coupling with alkyne **197** in its deprotonated form. However, even forcing conditions such as heating to 100 °C in a pressure vessel could not effect full conversion of the alkyne. Instead, an inseparable mixture of starting material and some presumed product (<20%) was isolated. Complex allyl donors seem not to be compatible with the allylindation, so a simpler allyl bromide was devised. Literature-known **227**[187] was silylated to give compound **228**. Six equivalents of this simple allyl bromide were employed in the allylindation reaction with alkyne **197**. The large excess of allyl donor and the forcing conditions ensured full consumption of the starting material. Thus, the complex diene **229** could be isolated in a moderate 58% yield after aqueous work-up. The free alcohol was acetylated to afford the electrophile **230** in readiness for cross-coupling to achieve completion of the northern section of limaol. The required alkenylmetal nucleophile would have to be a "shortened" equivalent of the prior northern fragment, necessitating a revision of the northern fragment synthesis.

## 3.3 Revised Northern Fragment Synthesis

### 3.3.1 Revised Retrosynthetic Analysis

To improve the synthesis of the northern fragment, its retrosynthetic analysis was briefly reconsidered (Scheme 3.6). The target allyl acetate **108** was obtained in 13% yield over 12 steps by iodination of **103** and merger of the building block with allyl chloride **85** through Negishi cross-coupling. While diene **85** is synthesized efficiently in 43% yield over five steps, the alkyne **103** was accessed in 18% yield over seven steps. Material throughput is therefore significantly hampered by the rather lengthy synthesis of **103**. Alternatively, this compound was envisioned to be formed by reductive opening of lactone **231** to form an acetylenic alcohol directly.[188] The stereoinformation on the required lactone could be installed by asymmetric hydrogenation of the commercially available 2-pyrone **232**.[189]

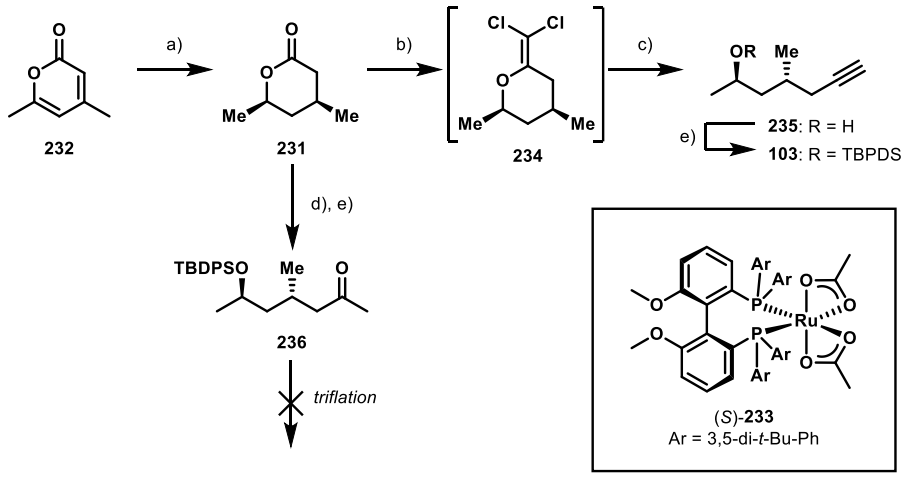



**Scheme 3.6.** First-generation synthesis of the northern fragment and proposed new retrosynthesis.

### 3.3.2 Second-Generation Northern Fragment Synthesis

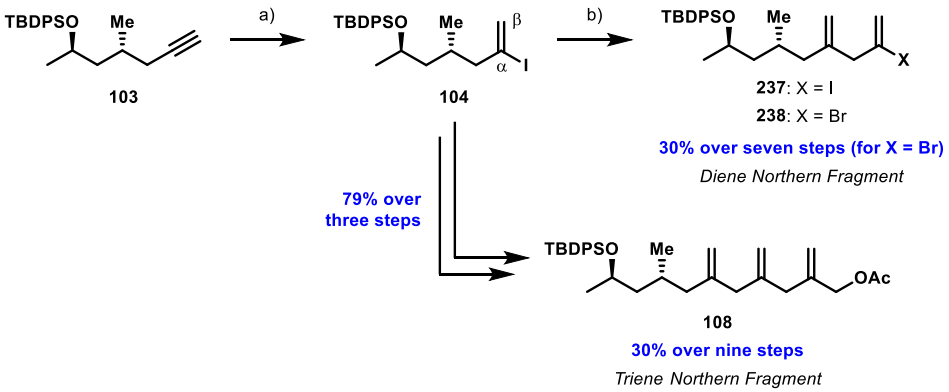
Schmid and co-workers have developed a ruthenium catalyst capable of effecting the asymmetric hydrogenation of 2-pyrones in high diastereo- and enantioselectivities.[189] After its facile preparation, the catalyst (*S*)-**233** was promptly employed to hydrogenate 2-pyrone **232** under 60 bar of $H_2$ at 60 °C to afford the saturated lactone **232**, with high selectivity and yields between 68-79% (Scheme 3.7). Next, a procedure by Yadav and co-workers was followed to effect dichloro-olefination of the lactone carbonyl, and subsequent reductive ring opening of **234**, to give the terminal alkyne **235** in 56% yield over two steps. The resulting material was volatile, and was thus quickly silylated, giving the known TBDPS-ether **103** in a total of 39% yield over four steps. This was a significant improvement over the first-generation approach, cutting three steps and doubling the total yield.

An alternative approach was briefly attempted, where lactone **231** was treated with methyl lithium to effect ring opening, followed by silylation to give methyl ketone **236**. Attempts to convert this ketone to the corresponding "kinetic" enol triflate (an analogue to alkenyl iodide **104**) were however not fruitful, leading us to abandon this approach.




**Scheme 3.7.** Improved synthesis of the alkyne **103**. Conditions: a) (*S*)-**233** (0.2 mol%), $H_2$ (60 bar), *i*-PrOH, 60 °C, 3 mmol-scale: 79%, 93:7 *cis*/*trans*, 97% *ee*, 9 mmol-scale: 68%, 95:5 *cis*/*trans*, 98% *ee*; b) $CCl_4$, $PPh_3$, THF, reflux; c) $Li^0$, THF, reflux, 56% over two steps; d) MeLi, THF, −78 °C; e) TBDPSCl, imidazole, DMF, RT, 88% (**103**), 61% over two steps (**236**).

With access to ample amounts of alkyne **103** secured, further modifications to the route could be made. Most importantly, a modified, diene-containing northern fragment in readiness for coupling to allyl acetate **230** had to be prepared. After iodination of **103**, an iodine-magnesium exchange was carried out on resulting alkenyl iodide **104** at low temperatures by treatment with a trialkylmagnesate (Scheme 3.8).[190] Subsequent transmetalation to copper allowed smooth nucleophilic attack on 2-haloallyl bromides to give the corresponding 1,4-dienes decorated with either an iodide (**237**) or bromide (**238**). The latter could be accessed in a higher yield of 77%, giving the "shortened" northern fragment **238** in a total 30% yield over seven steps in longest linear sequence.

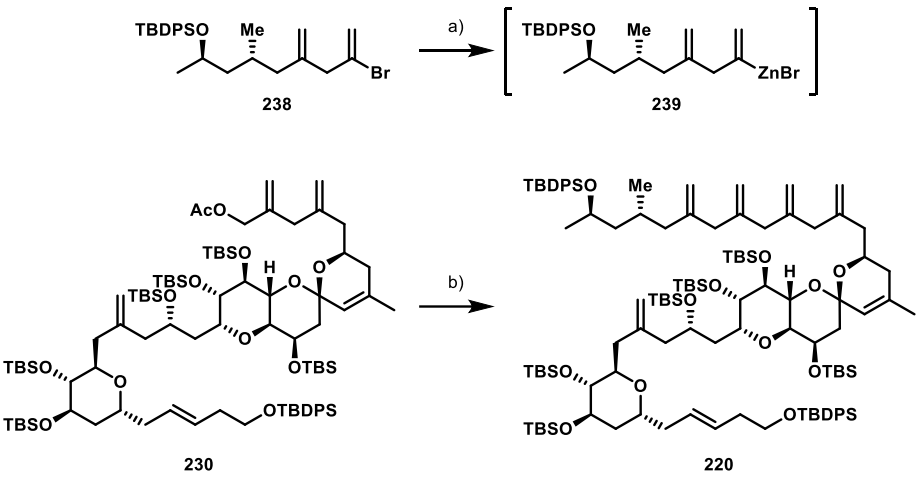



**Scheme 3.8.** Completion of the synthesis of the northern fragments **238** and **108**. Conditions: a) *B*-Iodo-9-BBN, hexanes, RT, *then* AcOH, RT, 98% over two steps, α:β > 20:1; b) *n*-BuLi, *i*-PrMgBr, 0 °C, THF, *then* **104**, CuCN·2 LiCl, THF, −78 °C, *then* 2-bromoallyl bromide *or* 2-iodoallyl bromide, THF, −78 °C to 0 °C, 37% (X = I), 77% (X = Br).

Alternatively, the alkenyl iodide **104** could be subjected to the previously described route towards the triene-containing allyl acetate **108**, giving the final product in 30% yield over a total of nine steps in longest linear sequence. In the first-generation approach, **108** could only be prepared in 13% yield over 12 steps, clearly demonstrating the significant improvement made to the northern fragment synthesis.

### 3.3.3 Negishi Cross-Coupling of the Diene-Containing Northern Fragment

In order to complete the total synthesis of limaol using the indium-mediated allylation developed in Section 3.2, the tetraene **220** had to be accessed from allyl acetate **230**. To achieve this, alkenyl bromide **238** was converted to organozinc species **239**, which underwent Negishi cross-coupling with allyl acetate **230** (Scheme 3.9). The isolated yield of **220** was moderate, at 36%, and was not further optimized.




**Scheme 3.9.** Negishi cross-coupling towards tetraene **220**. Conditions: a) *t*-BuLi, −78 °C, $Et_2O$, *then* $ZnBr_2$, THF, −78 °C to RT, yield not determined; b) **239**, $Pd(PPh_3)_4$ (20 mol%), DMF, RT, 36%.

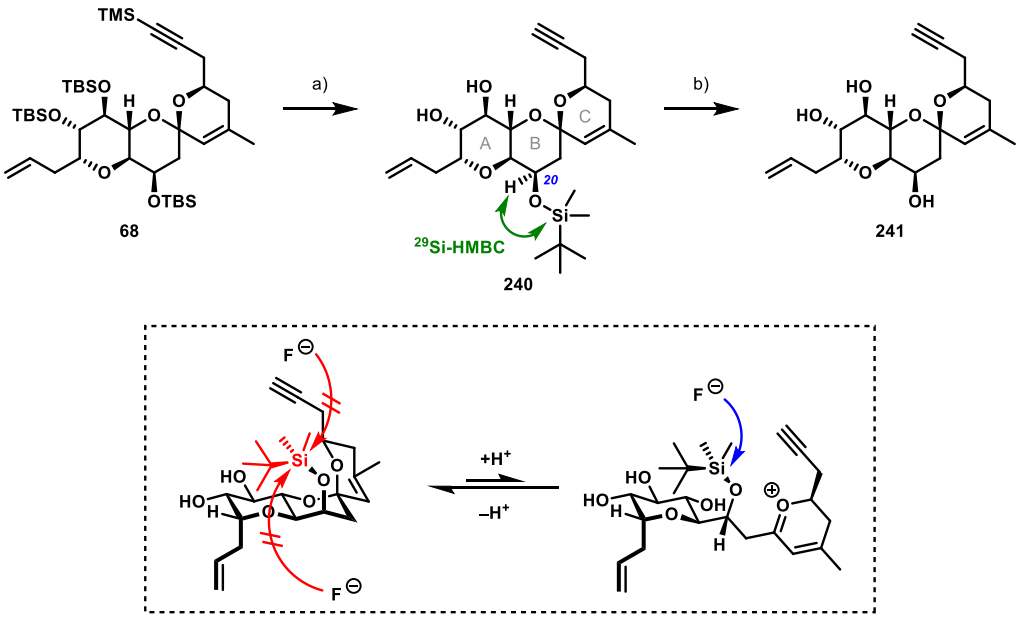
In total, the tetraene **220** could be accessed in 2% yield over 21 steps in longest linear sequence using the route described above. This was no improvement over the first-generation approach, where the same intermediate could be obtained in 5% over 19 steps. The inefficient allylindation and the low-yielding Negishi cross-coupling made the newly developed pathway far less productive than the previous route. It became clear that in order to significantly improve the first-generation synthesis, a more fundamental revision of our synthetic efforts would be required.

## 3.4 Revised Protecting Group Strategy

### 3.4.1 Deprotection Studies & Implications for the Synthesis

In an effort to identify the reason for the low yields obtained in the final global deprotection step, a model study on the central fragment **68** was performed (Scheme 3.10). Treatment of **68** with TBAF exclusively gave the monosilylated compound **240**. $^{29}$Si-HMBC revealed the remaining TBS group to be positioned on the axial alcohol on C20. Intriguingly, this persistent silyl ether was only cleaved by treatment with HF–pyridine, which had already been proven to work reliably in the global deprotection. Fully deprotected **241** was obtained in 28% yield, also indicating that significant decomposition of the material had set in under these conditions. These findings led us to assume the silyl ether on C20 to be the root cause of the problematic global deprotection.

The reason for this silyl ether's persistence can be inferred from consideration of its steric environment. Due to the axial disposition of the alcohol on C20, the silyl ether is in direct vicinity to ring C, which itself is also perpendicular to the *trans*-decaline system of the central fragment. The three-dimensional structure of **240** forms a steric envelope around the silyl ether, preventing nucleophilic attack on silicon. The spiroketal is presumed to be in equilibrium with its open form under the reaction conditions, allowing for an attack trajectory for fluoride anions. For this, the acidity of the reaction mixture is vital, since it allows pyran ring B to open. Incidentally, the spiroketal is also closed under similar conditions. In both cases, the acidic species is a pyridinium cation, further validating this hypothesis (see Section 2.2.5).




**Scheme 3.10.** Deprotection of alkyne **68** and mechanistic hypothesis for the final deprotection. Conditions: a) TBAF, THF, 0 °C to RT, 96%; b) HF–pyridine, THF, RT, 2 d, 28%.

The results above demonstrate that the silyl ethers exert too much steric hindrance to be effectively cleaved in this system. The simplest solution for this conundrum was to exchange the protecting groups for less sterically demanding alternatives.

An additional motivation for a revised protection strategy was also found in the counterintuitive stereochemical outcome of the allylative southern-central fragment coupling and the reluctance of the northern "tether" moieties to undergo functionalization. The suspicion arose that these two issues are also intimately connected to the overbearing protecting groups (Figure 3.3). It was surmised that in the case of the assembly of the southern and central fragments, the silyl groups in equatorial position (on C23 & C24) block the *Si* face of the aldehyde, preventing formation of the desired diastereoisomer. In the case of the northern "tether" functionalities, e.g. the terminal alkyne of **197**, the steric shielding exerted by the persistent TBS group on C20 might also inhibit any addition to the alkyne.

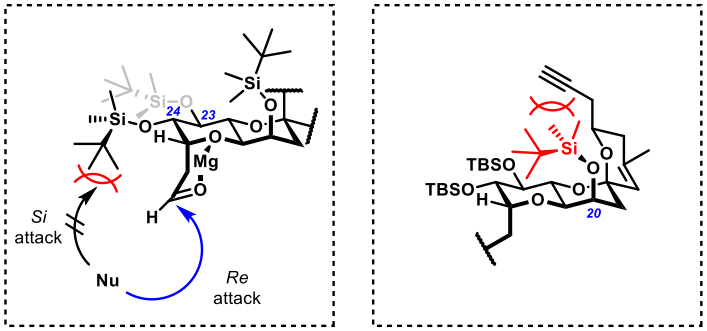
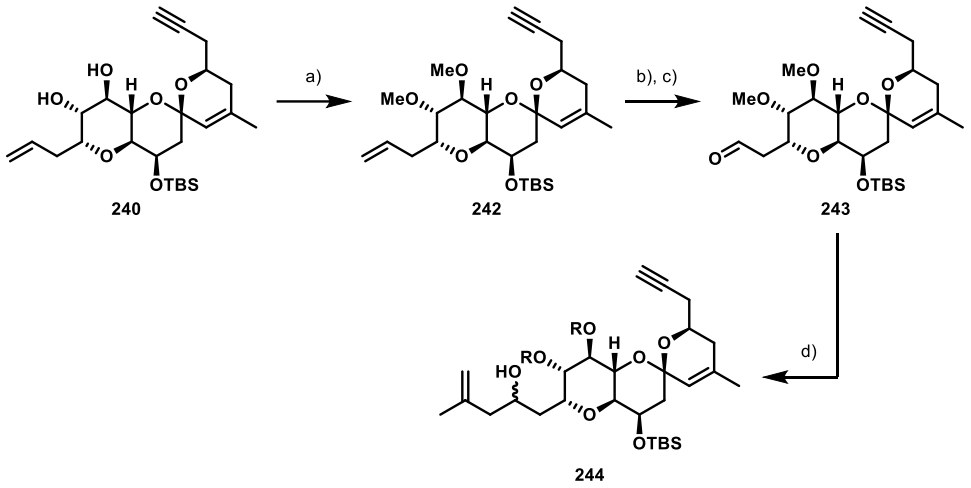



**Figure 3.3.** Influence of steric bulk on the outcomes of the southern-central fragment allylation (left) and the functionalization of the northern "tether" alkyne (right).

To test the first part of this hypothesis, partially desilylated **240** was converted to the bis(ether) **242** (Scheme 3.11). Methyl groups were chosen due to their small size. The terminal olefin was cleaved using the established Sharpless' ADH/periodate cleavage protocol, affording the aldehyde **243** in good yield. Finally, treatment of the electrophile with methallylstannane and the chelating Lewis acid $MgBr_2 \cdot OEt_2$ gave a 1:1 mixture of diastereoisomers (**244**) in 77% yield. The significant reduction of the substrate bias confirmed the hypothesis that the protecting groups on C23 and C24 were responsible for the unexpected stereocontrol seen in the first-generation synthesis. This result also revealed the opportunity to once again attempt a catalyst- or reagent-controlled allylation, since the formerly strong substrate bias could now likely be overriden.

These insights formed the foundation for the design of a second-generation synthesis based on a revised choice of protecting groups. This time, steric factors surrounding the central fragment and their impact on the synthesis would be taken into account. An alkyne was chosen as the tether moiety to the northern fragment, as we surmised an $\alpha$-selective hydrometalation to be possible in the absence of the previously mentioned steric shielding.




**Scheme 3.11.** Model study examining the role of the C23 and C24 protecting groups in the diastereoselectivity of aldehyde allylation. Conditions: a) NaH, MeI, THF, 0 °C to RT, 95%; b) AD-mix β, $MeSO_2NH_2$, *t*-BuOH/$H_2O$ 1:1, RT; c) $NaIO_4$ on silica, $CH_2Cl_2$, RT, 83% over two steps; d) Methallylstannane, $MgBr_2 \cdot OEt_2$, $CH_2Cl_2$, −78 °C, 77%, dr 1:1.

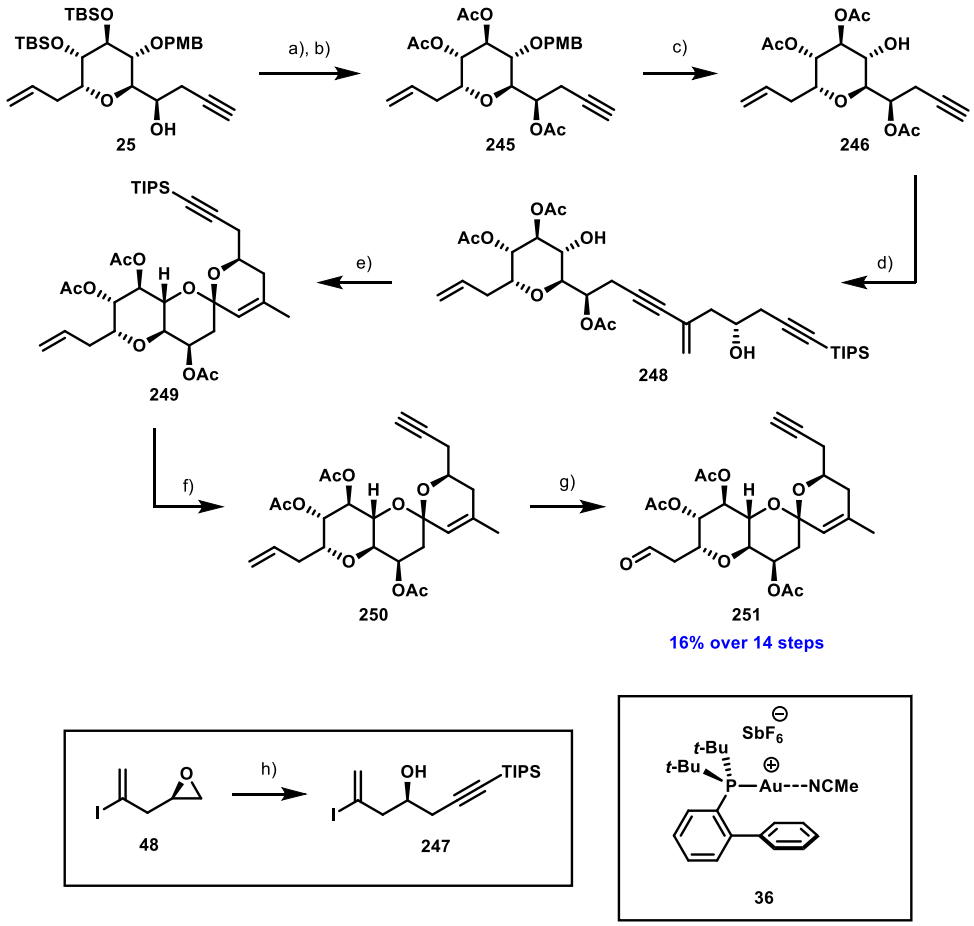
### 3.4.2 Revised Central Fragment Synthesis

Since the first-generation synthesis of the central fragment was well optimized, the decision was made to simply conduct a reprotection on an advanced intermediate. Thereby, most of the route could be preserved, ensuring rapid access to a redesigned central fragment.

The homopropargylic alcohol **25** was chosen as the entry point for our efforts, since the pivotal diastereoselective propargylation of aldehyde **20** presumably depends on the exact nature of the substrate. Changes to **20** would likely incur selectivity issues and necessitate reoptimization of the propargylation. Thus, **25** was selected to be reprotected, removing all TBS groups and replacing them with less sterically demanding alternatives. Several options for protecting groups were considered: Benzyl groups were disregarded, since their hydrogenolytic removal was anticipiated to be challenging in the presence of numerous olefins. Slightly less bulky silyl groups such as TES were regarded not to be distinct enough from TBS in terms of sterics, and were therefore also not chosen. Finally, esters, specifically benzoates and acetates, were evaluated. Since the goal was to accumulate the minimal amount of steric demand on the central fragment, the smaller acetates were selected.[39] These deliberations led to the synthesis shown in Scheme 3.12.

Treatment of **25** with TBAF and subsequent peracetylation gave the triacetate **245** in 89% yield over two steps. Cleavage of the PMB ether proceeded smoothly to give the alcohol **246** in 95% yield. Starting from the previously prepared epoxide-bearing alkenyl iodide **48**, the Sonogashira coupling partner **247** was synthesized in quantitative yield using a $BF_3$-mediated epoxide opening as shown before. Importantly, the alkyne of **247** was chosen to carry a TIPS group instead of TMS. The Sonogashira coupling between **246** and **247** afforded the enyne **248**

in 80% yield. Incidentally, in the previous iteration, direct Sonogashira coupling had failed on the similar substrates **32** and **38** due to competitive carbopalladation. This was suppressed in part through steric shielding of the appended alkyne enforced by the larger TIPS group. Next, gold-catalyzed spiroketalization was effected by treatment with catalytic amounts of **36** and PPTS to give the spirocycle **249** as a single diastereoisomer in 79% yield. As an additional advantage of the reduced steric bulk in the system, the catalyst loading of **36** and PPTS could be reduced from 10 mol% in the previous approach to 2.0 mol% without negatively influencing reaction rate or yield. Attempted desilylation of the alkyne by treatment of **249** with TBAF led to partial acetate cleavage, so less basic conditions were required. Deprotection was achieved by treatment with silver(I) fluoride to afford compound **250** in 90% yield.[191] Finally, Lemieux–Johnson conditions accomplished olefin cleavage to give the aldehyde **251** in 79% yield.[85]

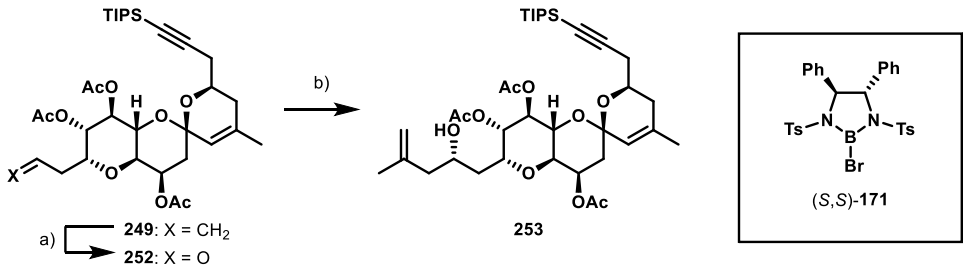



**Scheme 3.12.** Synthesis of the acetate-bearing central fragment **251**. Conditions: a) TBAF, THF, 0 °C to RT; b) $Ac_2O$, pyridine, DMAP (5 mol%), $CH_2Cl_2$, RT, 89% over two steps; c) DDQ, $CH_2Cl_2/H_2O$ (10:1), 0 °C to RT, 95%; d) **247** (1.1 equiv.), $Pd(PPh_3)_2Cl_2$ (5.0 mol%), CuI (20 mol%), $HN(i\text{-}Pr)_2$, RT, 80%; e) **36** (2.0 mol%), PPTS (2.0 mol%), $CH_2Cl_2$, RT, 79%; f) AgF, MeCN, RT, 90%; g) $OsO_4$ (0.5 mol%), 2,6-lutidine, $NaIO_4$, 1,4-dioxane/$H_2O$ (3:1), RT, 79%; h) *n*-BuLi, $HC{\equiv}CSi(i\text{-}Pr)_3$, $BF_3{\cdot}OEt_2$, THF, −78 °C, quant.

In total, the revised central fragment **251** was synthesized in 16% yield over 14 steps in longest linear sequence starting from α-D-glucopyranosyl pentaacetate. Compared to the established central fragment aldehyde **79**, which was obtained in 27% yield over 12 steps in longest linear sequence, this was no improvement. However, the possibility to circumvent the bottlenecks of the first approach further downstream in the synthesis was projected to increase the total yield substantially.

### 3.4.3 Diastereoselective Assembly of the Southern and Central Fragments

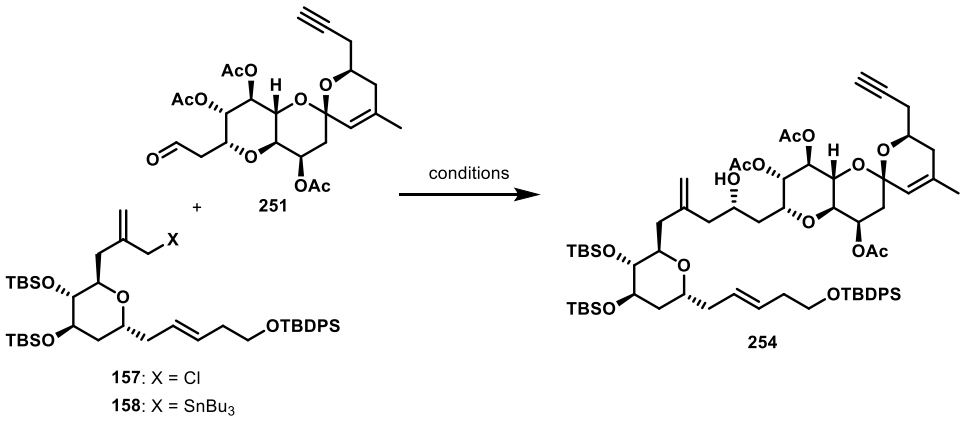
In order to test the viability of the asymmetric allylation on the modified central fragment, a model study was first conducted (Scheme 3.13). To this end, TIPS-protected central fragment **249** was subjected to Lemieux–Johnson conditions to produce aldehyde **252**, which was allylated using methallyltributylstannane and chiral auxiliary (*S*,*S*)-**171** in accordance with the procedure developed by Williams and co-workers.[131] The resulting homoallylic alcohol **253** was obtained in a dr of 7.5:1 in favor of the desired diastereoisomer and a combined yield of 81%. The absolute configuration was confirmed by Mosher's ester analysis.[48] This once again confirmed our suspicions about the steering effect of the TBS-groups on the previous central fragments.

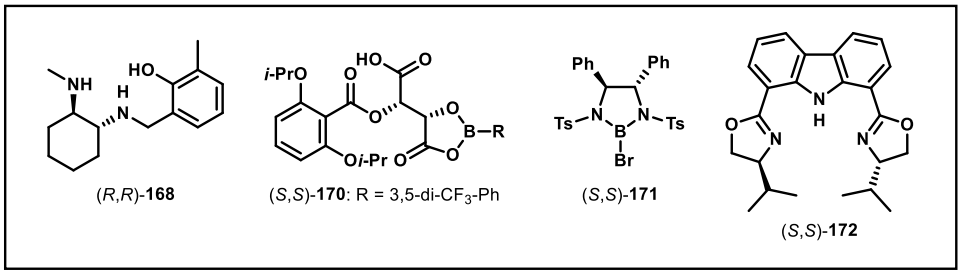



**Scheme 3.13.** Test of asymmetric allylation on the modified central fragment. Conditions: a) $OsO_4$ (2.0 mol%), 2,6-lutidine, $NaIO_4$, 1,4-dioxane/$H_2O$ 3:1, RT, 99%; b) Methallyltributylstannane, (*S*,*S*)-**171**, $CH_2Cl_2$, RT, *then* add **252**, −78 °C to RT, 81%, dr 7.5:1.0.

With the model study corroborating our hypothesis and the aldehyde **251** in hand, the southern fragment could be attached. Using either the allyl chloride **157** or the allylstannane **158**, some of the methods for asymmetric allylation described in Section 2.5.1 were reconsidered (Table 3.1).

**Table 3.1.** Diastereoselective allylative fragment coupling of **158** and **251**.




| Entry | Nu | Conditions | Result[a] |
|---|---|---|---|
| 1 | **157** (1.2 equiv.) | CuBr (25 mol%), $NEt_3$, $HSiCl_3$, 2,6-di-*tert*-butylpyridine, *then* $Bu_4NBr$, DBU, (*R*,*R*)-**168**, $CH_2Cl_2$, −78 °C to −10 °C | 48% |
| 2 | **158** (1.2 equiv.) | $Ti(OiPr)_4$, (*S*)-BINOL, $CH_2Cl_2$, −78 °C to RT | No reaction |
| 3 | **158** (1.2 equiv.) | (*S*,*S*)-**170**, TFAA, EtCN, −78 °C to RT | No reaction |
| 4 | **157** (1.1 equiv.) | $CrCl_2$ (15 mol%), (*S*,*S*)-**172** (30 mol%), PcCo (0.5 mol%), $ZrCp_2Cl_2$, proton sponge, Mn, LiCl, THF, RT | 38%[b] |
| 5 | **158** (1.2 equiv.) | (*S*,*S*)-**171**, $CH_2Cl_2$, RT, *then* add **251**, −78 °C to RT | 64% |
| 6 | **158** (1.5 equiv.) | (*S*,*S*)-**171**, $CH_2Cl_2$, RT, *then* add **251**, −78 °C to RT | 84%[c] |

[a] Isolated yield of the desired diastereoisomer. [b] Impure. [c] The undesired isomer **255** was isolated in 16% yield (dr 5:1).

Leighton's method was evaluated first.[127] Here, an *in situ* generated allyltrichlorosilane is reacted with the Lewis base (*R*,*R*)-**168** to form a chiral allylsilane capable of asymmetrically allylating an aldehyde. Using chloride **157** and aldehyde **251**, the desired diastereoisomer of coupled product **254** was obtained in 48% yield (entry 1). Only minor amounts of the undesired diastereoisomer were detected.

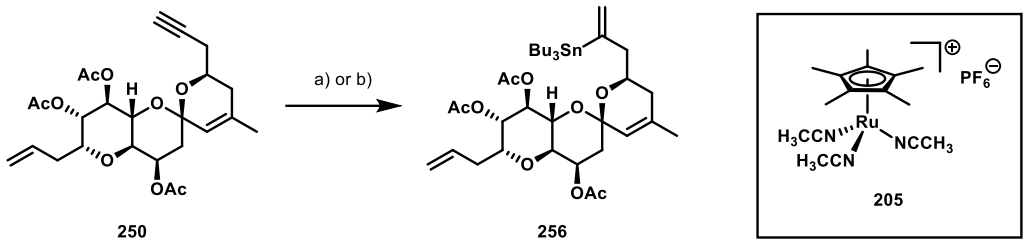
The use of chiral Lewis acids such as Hisashi Yamamoto's chiral (acyloxy)borane complexes (*S*,*S*)-**170** or Keck's chiral titanium(IV)-complexes failed to elicit any reaction when using stannane **158** and aldehyde **251** as the substrates (entries 2 & 3).[128] Similarly, attempts to employ an asymmetric Nozaki–Hiyama–Kishi reaction were of limited success. [43c, 43d, 75, 134] Using allyl chloride **157** as the nucleophile gave only 38% yield of the desired alcohol **254**, albeit contaminated with inseparable impurities of unknown structure (entry 4).

Finally, the asymmetric allylation developed by Williams and co-workers based on 1,2-diphenyl-1,2-ethylenediamine as a chiral controller was evaluated once again.[131] Conversion was not complete, but the protocol smoothly provided a yield of 64% of the desired product **254** when employing 1.2 equivalents of the stannane **158** (entry 5). Upon scaling the reaction up and increasing the amount of stannane to 1.5 equivalents, the homoallylic alcohol **254** could be produced in 84% yield on a 0.9 mmol-scale (entry 6). In addition, the undesired diastereoisomer **255** was also isolated in 16% yield, signifying a dr of 5:1. The configuration of the minor diastereoisomer was confirmed by Mosher's ester analysis.[48]

In total, this allowed **254** to be synthesized in a yield of 13% over 15 steps in longest linear sequence. One of the primary bottlenecks of the first-generation synthesis, the Mitsunobu inversion, could be circumvented entirely. This reconfirmed our suspicions about the disruptive effect of the TBS groups on the entire total synthesis.

### 3.4.4 Revised Assembly of the Northern and Central Fragments

In order to test the stability of the acetate protecting groups towards hydrometalation conditions, central fragment **250** was used as a model compound. Two sets of conditions were examined: Fürstner and co-workers' *trans*-hydrostannation[148] and stannylcupration followed by protodecupration (Scheme 3.14).[146]

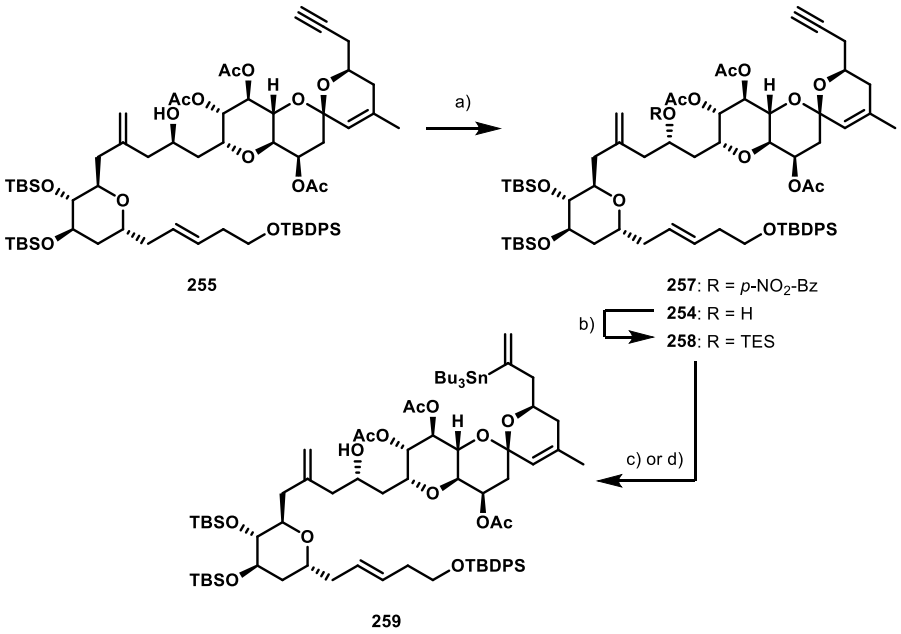



**Scheme 3.14.** Hydrostannation of model compound **250**. Conditions: a) **205** (20 mol%), $Bu_3SnH$, $CH_2Cl_2$, RT, 79%; b) $(Bu_3Sn)_2CuCNLi_2$, THF, −78 °C, 40% + 30% mono-deacetylated product.

Adding a solution of $Bu_3SnH$ and **250** to a solution of catalyst **205** cleanly gave the desired 1,1-disubstituted alkenylstannane **256** in 79% yield. When treating the alkyne **250** with the stannylcuprate $(Bu_3Sn)_2CuCNLi_2$, **256** could be isolated in only 40% yield. Partial deacetylation of the product had occurred, as the mono-deacetylated material could also be obtained in 30% yield. Contrary to the common literature procedures,[146a] no proton source was added before addition of the alkyne. Thus, nucleophilic species such as $Bu_3SnLi$ were still present, resulting in partial deprotection. Both protocols led to sufficient amounts of selectively stannylated product, making us confident to test them on more complex alkyne **254**.

Before the hydrofunctionalization was attempted, the undesired diastereoisomer **255** obtained previously was subjected to a Mitsunobu inversion to increase the material

throughput (Scheme 3.15). This gave the benzoate-protected compound **257** in 53% yield. Since it was unclear if the stannation methods described above tolerated free hydroxy groups in the substrate, the alcohol in **254** was silylated to give TES-protected derivative **258** in 93% yield. First, the ruthenium-catalyzed hydrostannation was attempted on all three alkynes **254**, **257**, and **258**.



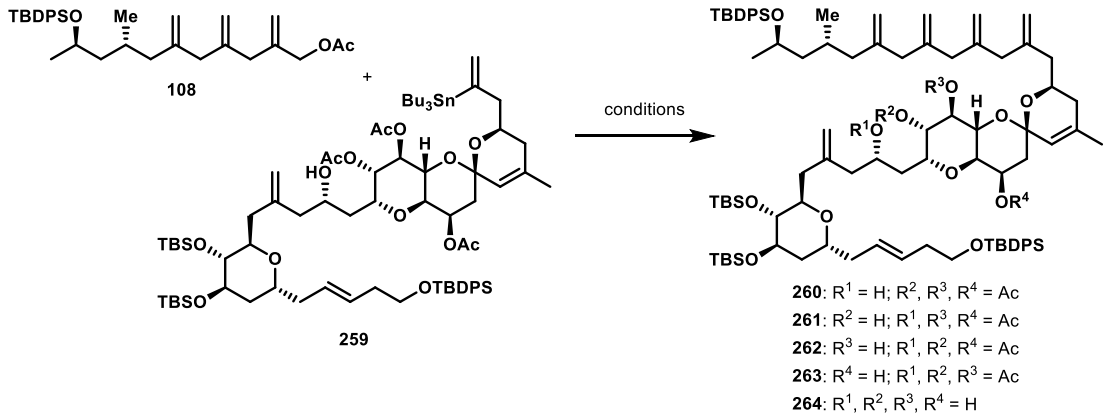

**Scheme 3.15.** Hydrostannation of **254** and its derivatives. Conditions: a) $PPh_3$, 4-nitrobenzoic acid, DEAD, toluene, 0 °C to RT, 53% (**257**); b) TESOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C, 93%; c) **205** (20 mol%), $Bu_3SnH$, $CH_2Cl_2$, RT, for **254**: 40% + 23% reisolated SM, for **257**: 48% reisolated SM, for **258**: decomposition; d) $(Bu_3Sn)_2CuCNLi_2$, MeOH, THF, −78 °C, for **254**: 80%.

For unprotected **254**, the desired 1,1-disubstituted alkenylstannane **259** was isolated in 40% yield and 23% of the starting material was recovered. For both protected compounds, **257** and **258**, significant decomposition was observed. In the case of nitroaryl-containing **257**, the incompatibility probably stems from reduction of the nitro-group by intermediate ruthenium hydrides. For silyl ether **258**, the reason is not as obvious. Most likely, the presence of adventitious water induced catalyst decomposition, forming highly acidic $HPF_6$ in the process.

The alternative method, stannylcupration, proceeded smoothly with unprotected **254**, giving the alkenylstannane **259** in 80% yield. It was crucial to include methanol in the reaction mixture before addition of the alkyne to quench residual stannyllithium, but leaving the stannylcuprate intact. In addition, the presence of methanol effects protodecupration of the nascent alkenylcuprate, thereby preventing reversal of the reaction to give back the alkyne and ensuring the desired "kinetic" regioselectivity.[146a]

With a generous supply of stannane **259** secured, the π-allyl Stille cross-coupling with allyl acetate **108** was investigated next (Table 3.2). No attempts to protect the free alcohol were undertaken, since the Stille reaction is generally known to tolerate hydroxyl groups.[36a, 161] The previously employed protocol by Fürstner and co-workers was tested first.[170] To our dismay, protodestannation was a significant side reaction, and formed the major component of the isolated product mixture. The amount of desired coupling product detected by $^1$H NMR constituted a yield of only 20% (entry 1). Next, Hegedus' method was assessed.[168] The reaction proceeded well, and the starting materials were consumed after heating over night. However, an intractable mixture of the four possible acetyl-shift regioisomers **260**, **261**, **262**, and **263** was obtained, albeit in a good yield of 76% (entry 2).

**Table 3.2.** π-Allyl Stille cross-coupling of **259** with **108**.




| Entry | Conditions | Yield |
|---|---|---|
| 1 | **108** (1.1 equiv.), $Pd(PPh_3)_4$ (10 mol%), $[NBu_4][Ph_2P(=O)O]$, CuTC, DMF, RT | 20% (**260**)[a] |
| 2 | **108** (1.0 equiv.), $Pd_2(dba)_3$ (5.0 mol%), LiCl, DMF, 60 °C | 76%[b] |
| 3 | **108** (1.1 equiv.), $Pd(PPh_3)_4$ (10 mol%), CuCl, LiCl, DMSO, 40 °C | 77% (**260**) |
| 4 | **108** (1.1 equiv.), $Pd_2(dba)_3$ (5.0 mol%), LiCl, DIPEA, NMP, 60 °C, *then* $Ba(OH)_2$, MeOH, RT | 55% (**264**) |
| 5 | **108** (1.1 equiv.), $Pd_2(dba)_3$ (5.0 mol%), LiCl, DMF, 60 °C, *then* NaOH, THF/MeOH/$H_2O$, RT | 70% (**264**) |

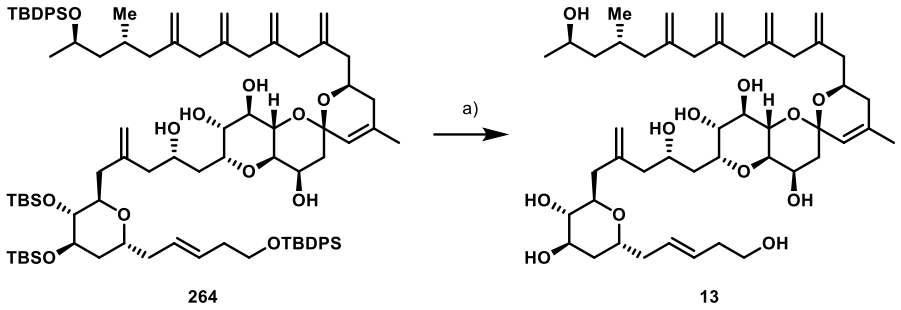
[a] Contaminated with protodestannation byproduct. [b] Inseparable mixture of **260**, **261**, **262**, and **263**.

Corey and co-workers' cross-coupling protocol employing an excess of copper(I) chloride was examined last.[164c] The unification of stannane **259** and allyl acetate **108** gave the desired tetraene **260** as a single regioisomer in 77% yield (entry 3). However, the reaction suffered from preparative issues, such as a difficult-to-stir and inhomogeneous reaction mixture and troublesome phase separation during work-up. In addition, formation of a polar product was observed by TLC during the reactions, raising concerns of diminished yields upon scale-up. Due to these problems and because the total yields did not differ significantly, Hegedus' protocol was prioritized.

Since the next step following the cross-coupling would be a two-step deprotection anyway, the acetyl-shifted regioisomer mixture resulting from the Stille reaction was subjected to deprotection immediately after work-up. Treatment with barium hydroxide gave fully deacetylated **264** in 55% yield over two steps (entry 4). The combined yield of the coupling/deprotection sequence could be increased by using Hegedus' standard coupling method followed simply by treatment with NaOH in THF/MeOH/$H_2O$. This protocol allowed the isolation of the desired tetraol **264** in 70% yield over two steps on a 24 μmol-scale (entry 5). The transformation proved amenable to scale-up, giving 70% yield (521 mg) of **264** on a 0.49 mmol-scale.

### 3.4.5 Simplified Global Deprotection

With the structure of limaol fully established in compound **264**, global desilylation of the four remaining silyl ethers was attempted next. Since the tetraene moiety had proven to be insensitive towards basic conditions in the deacetylation, simple treatment with TBAF was considered the most obvious option. Upon addition of a large excess of TBAF to a solution of **264** and stirring over night, limaol (**13**) could be isolated by standard flash column chromatography in a yield of 99% (Scheme 3.16).




**Scheme 3.16.** Global desilylation of **264**. Conditions: a) TBAF·3 $H_2O$, THF, 0 °C to RT, 99%.

In total, the second-generation synthetic sequence comprises 45 steps, providing 7.0% yield of the final product starting from α-D-glucopyranosyl pentaacetate over 19 steps in longest linear sequence. Using this route, 277 mg of limaol have been prepared in a single campaign.

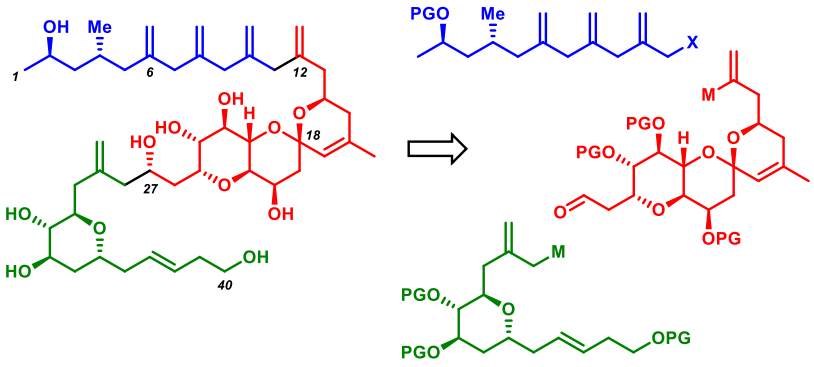
The strength of the second-generation approach was clearly proven by circumventing all three bottlenecks of the first-generation synthesis. Simply exchanging the silyl protecting groups on the central fragment allowed for: (i) an efficient asymmetric allylative fragment coupling between the southern and central fragments, delivering the desired diastereoisomer directly; (ii) a facile hydrofunctionalization of the alkyne "tether"-moiety, enabling high-yielding and selective access to an alkenyl nucleophile in readiness for allyl-alkenyl Stille cross-coupling; and (iii) a rapid, two-step global deprotection procedure that provides the target compound in excellent yields and in a scalable manner.

# 4 Conclusion & Summary

## 4.1 Summary of the First-Generation Synthesis

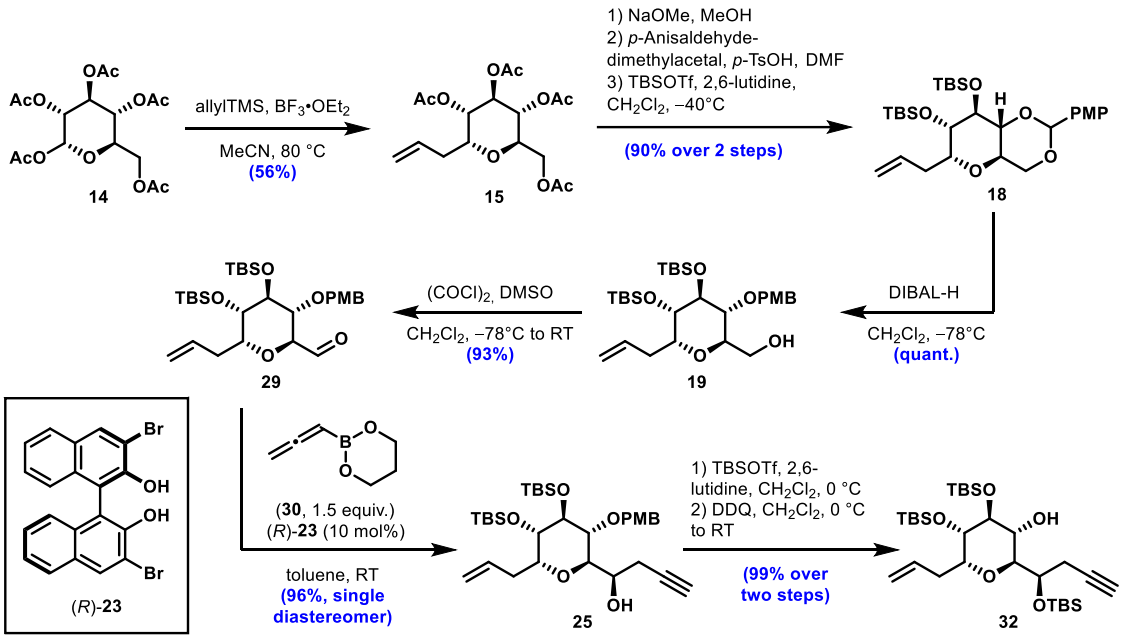
Limaol is a linear C40-polyketide first isolated from the benthic marine dinoflagellate *Prorocentrum lima* in 2017. Among its most striking structural features are the array of four skipped *exo*-methylene groups in its northern section and the chiral spiroketal moiety in its central region. It comprises a total of 15 stereogenic centers, seven carbon-carbon double bonds as well as four pyran ring systems of varying degrees of saturation, making it a formidable synthetic target.

Retrosynthetically, limaol was traced back to three fragments of approximately equal size and complexity, allowing for a convergent synthesis of the final compound (Scheme 4.1). The northern fragment would contain a skipped triene-motif, and was to be unified with the rest of the molecule *via* an allyl-alkenyl cross-coupling. The central fragment comprises the required alkenyl nucleophile as well as the spirocyclic core. Alcohol C27 of limaol was recognized as an attachment point for the southern and central fragments and would allow for assembly by asymmetric allylation, concomitantly installing the homoallylic alcohol stereocenter at C27.



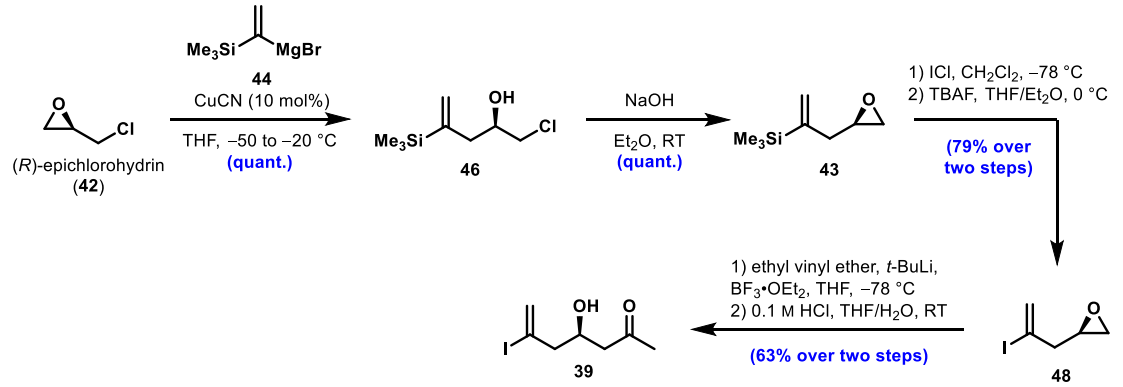

**Scheme 4.1.** Retrosynthetic analysis of limaol.

In a forward sense, the central fragment synthesis commenced from $\alpha$-D-glucopyranosyl pentaacetate (**14**), which was diastereoselectively allylated and subjected to protecting group modifications to give the benzylidene acetal **18** (Scheme 4.2). Selective acetal opening and Swern oxidation of the unveiled primary alcohol gave aldehyde **20**, which was asymmetrically propargylated using allenylboronate **30** and catalytic (*R*)-3,3′-dibromo-BINOL (**23**) to afford homopropargylic alcohol **25** as a single diastereoisomer in excellent yield. Further protecting group modifications gave the silyl ether **32**, the alkyne component for a projected Sonogashira cross-coupling.




**Scheme 4.2.** Synthesis of the alkyne **32**.

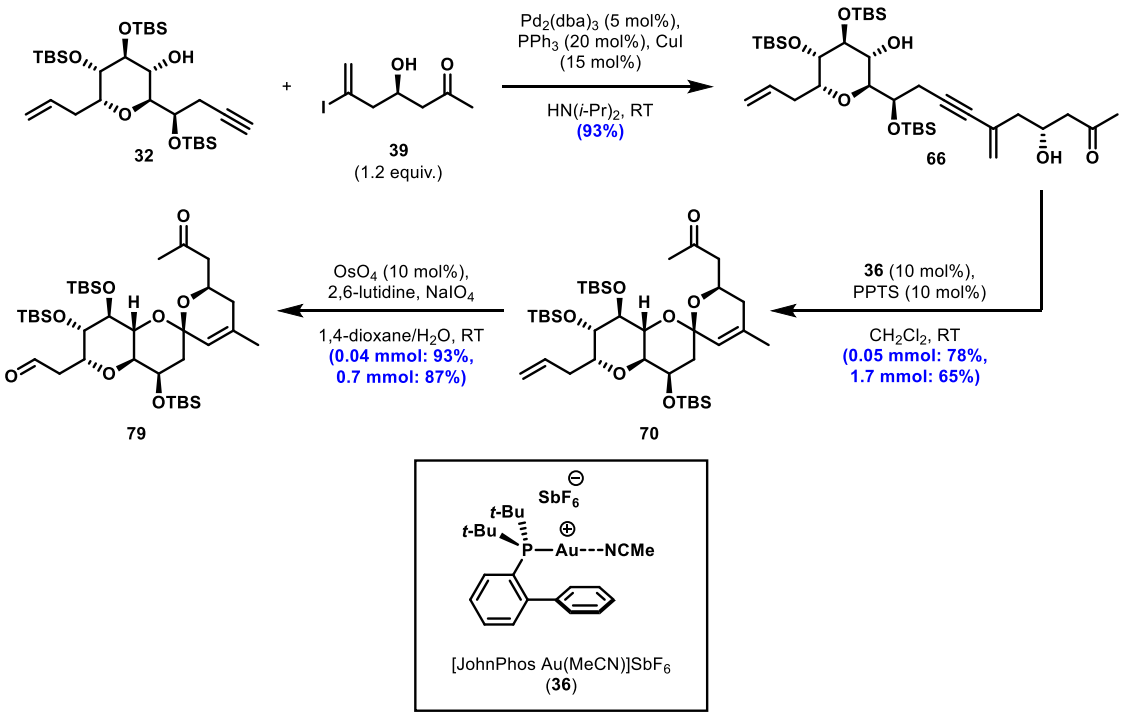
To allow for variation of the alkenyl nucleophile moiety that would function as a "tether" towards the northern fragment, a series of alkenyl iodides were synthesized as shown in Scheme 4.3. Copper-catalyzed epoxide opening of (*R*)-epichlorohydrin (**42**) with Grignard reagent **44** gave chlorohydrin **46**, which was treated with base to give the epoxide **43**. A two-step iododesilylation afforded the alkenyl iodide **48**, which could be transformed into β-hydroxy ketone **39** by boron trifluoride-mediated epoxide opening.




**Scheme 4.3.** Synthesis of the Sonogashira cross-coupling partner.

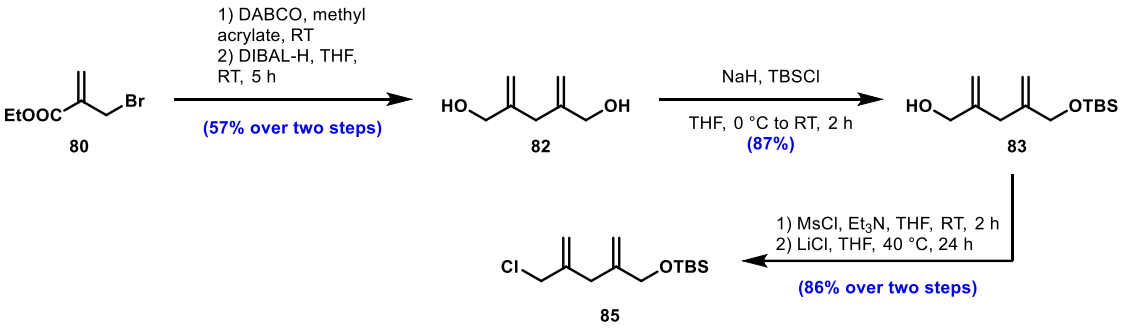
The Sonogashira cross coupling of alkenyl iodide **39** with alkyne **32** proceeded smoothly to afford the enyne **66**, which was subjected to gold catalyst **36** to give the spirocyclic compound **70** (Scheme 4.4). Oxidative cleavage of the terminal olefin present in **70** lead to ketoaldehyde **79**, completing the synthesis of the central fragment. Two additional central fragments bearing an

alkyne and an alkenyl silane instead of a methyl ketone as "tether"-moiety were synthesized analogously, however, they ultimately could not be productively transformed into limaol and were therefore not pursued further.



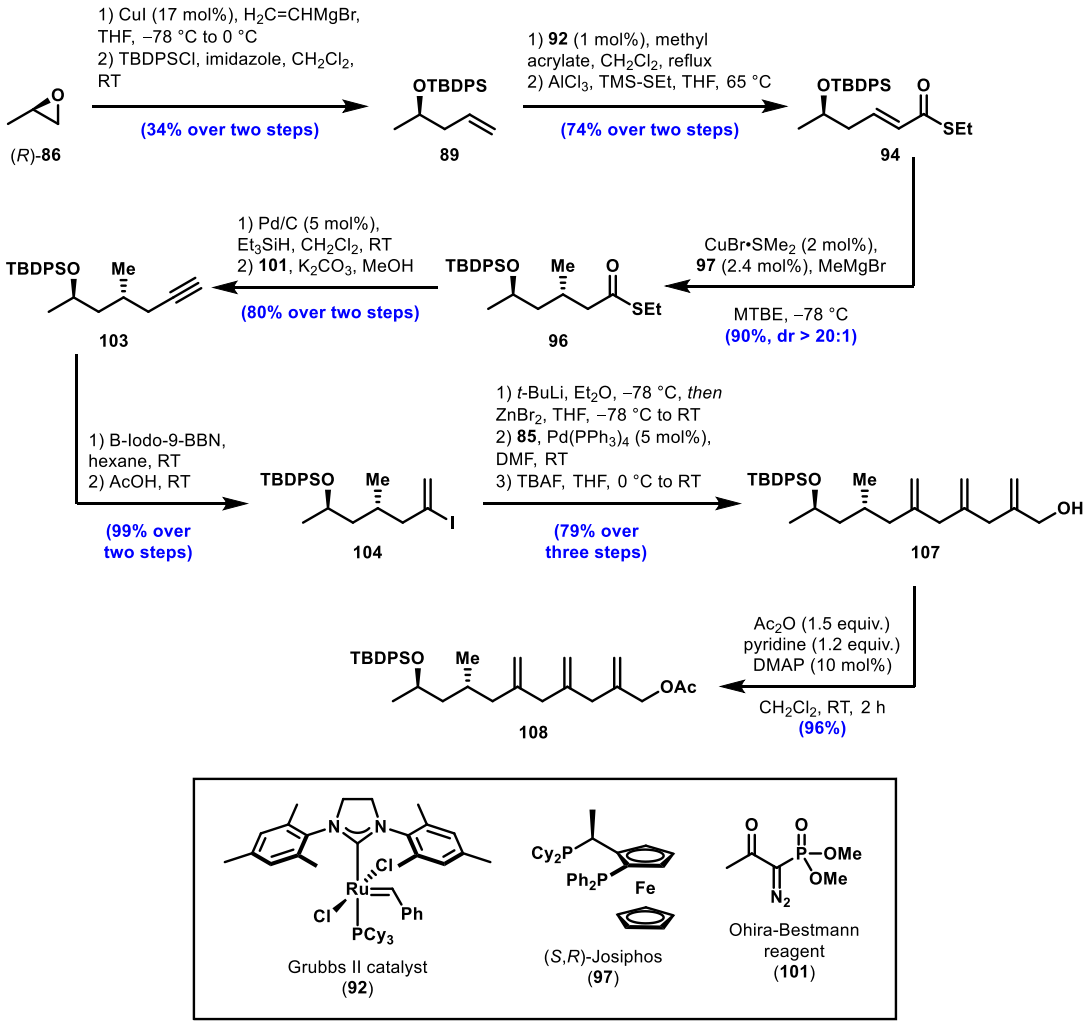

**Scheme 4.4.** Completion of the central fragment synthesis.

For the northern fragment synthesis, the latent symmetry found in this section was exploited. The bifunctional diene building block **85** was envisioned to allow stepwise allyl-alkenyl cross-couplings to forge the final tetraene. A Baylis–Hillman reaction between methyl acrylate and allyl bromide **80** followed by exhaustive reduction of the diester gave skipped diene **82** (Scheme 4.5). Selective monosilylation, mesylation of the remaining free alcohol, and nucleophilic substitution of the mesylate with lithium chloride gave the allyl electrophile **85** in readiness for chain elongation *via* palladium-catalyzed cross-coupling.



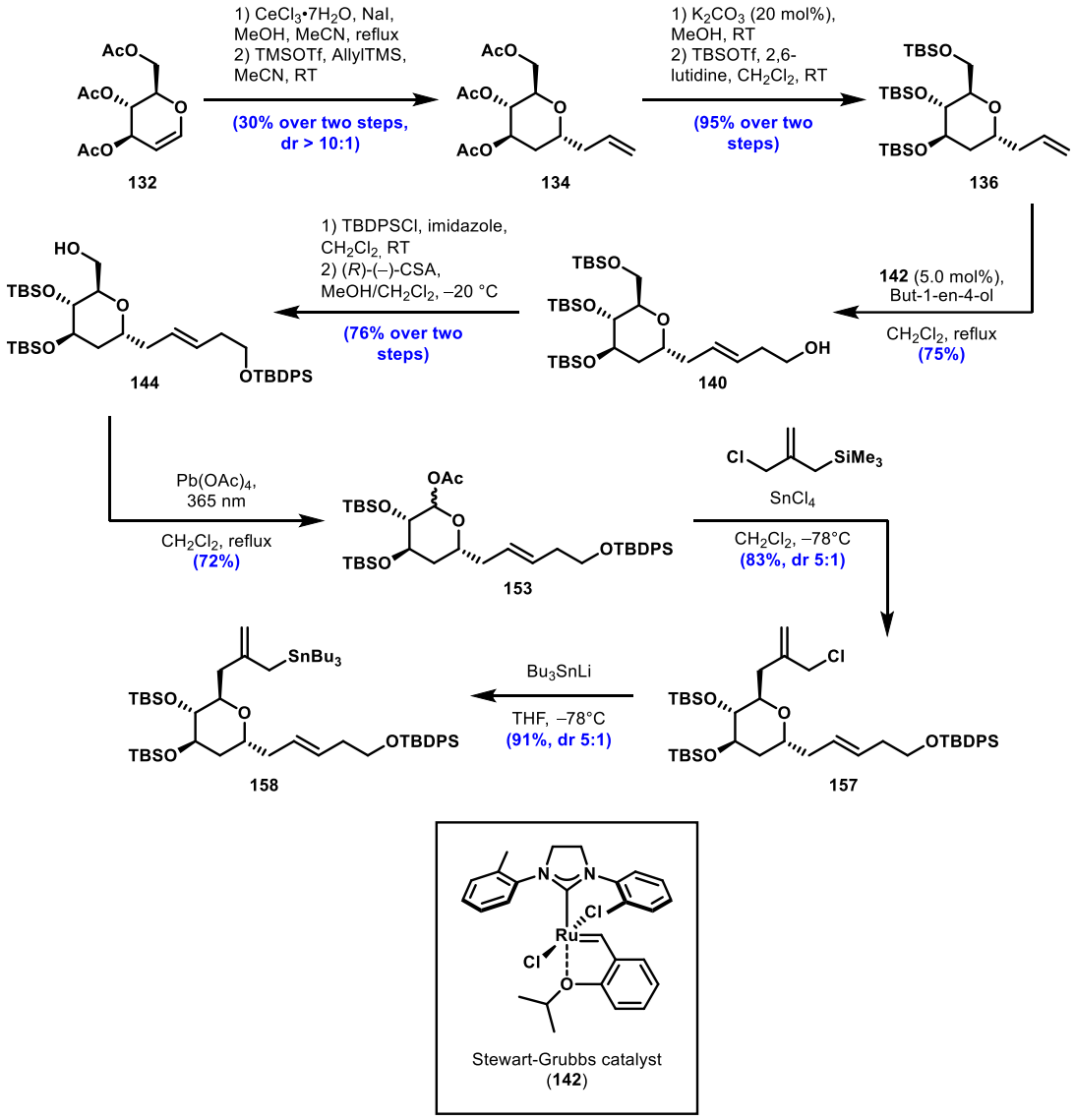

**Scheme 4.5.** Synthesis of the skipped diene.

The corresponding alkenyl nucleophile was prepared from (*R*)-propylene oxide (**86**) by copper-catalyzed epoxide opening and silylation to reduce the volatility of the resulting homoallylic alcohol **89** (Scheme 4.6). Ruthenium-catalyzed olefin cross-metathesis with methyl acrylate gave an enoate, which was transesterified to give thioester **94** and then subjected to copper-catalyzed asymmetric 1,4-addition of methylmagnesium bromide to afford the methylated compound **96**. Fukuyama reduction converted the thioester to the aldehyde, which was homologated using Ohira–Bestmann reagent (**101**) to give the terminal alkyne **103**. Addition of *B*-iodo-9-BBN and subsequent protodeboration selectively provided the $\alpha$-alkenyl iodide **104**, which was converted to an alkenyl zinc species by lithiation and transmetalation and underwent Negishi cross-coupling with allyl electrophile **85** to forge the desired skipped triene. To facilitate purification, the primary silyl ether was cleaved to give the free allylic alcohol **107**. Acetylation completed the northern fragment synthesis to provide allyl electrophile **108** in readiness for the final allyl-alkenyl cross-coupling.



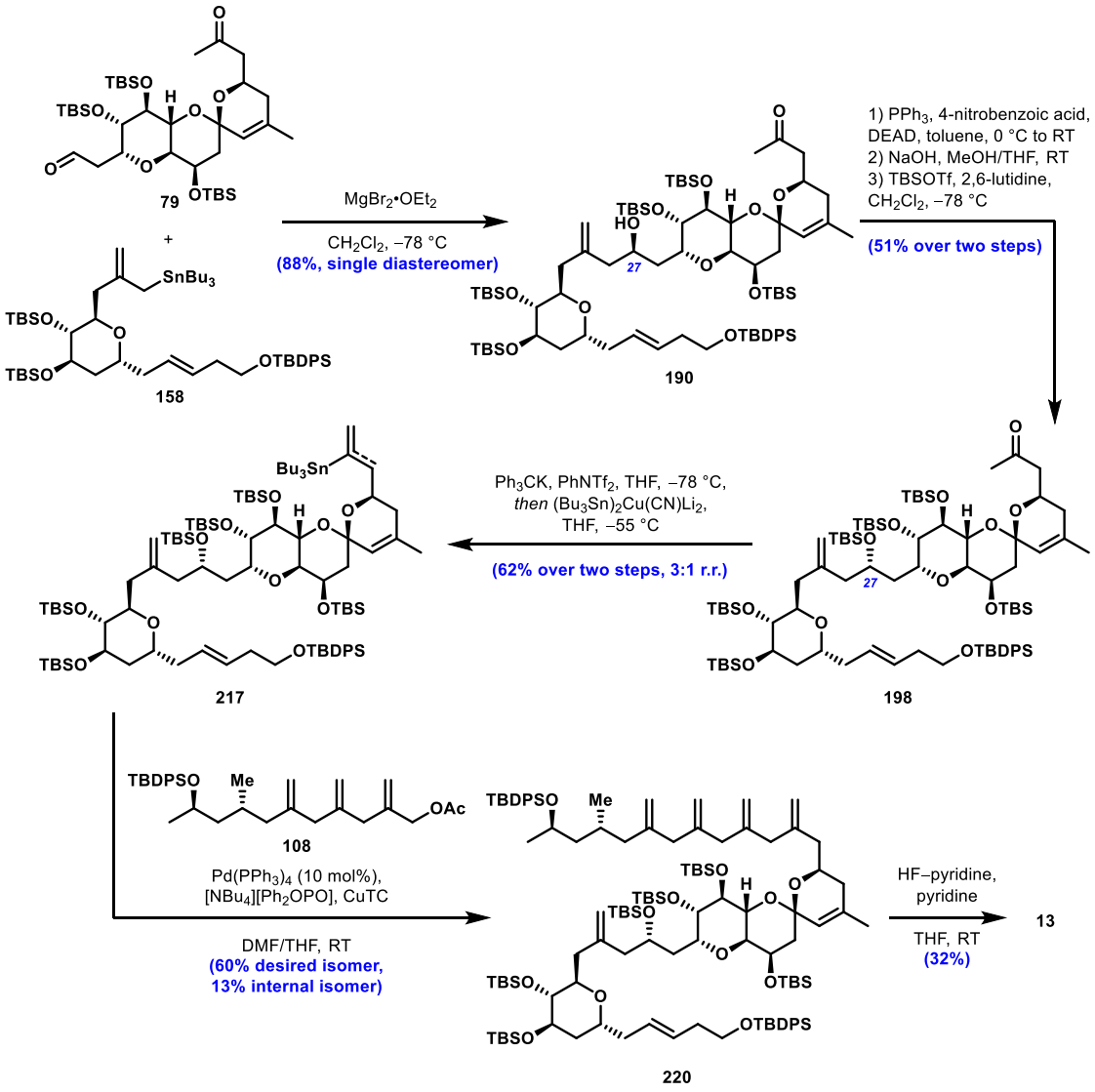

**Scheme 4.6.** Completion of the northern fragment synthesis.

The synthesis of the final building block started from tri-*O*-acetyl-D-glucal (**132**), which was converted first to the corresponding 2-deoxyglucoside and then allylated to give the 2,6-*trans*-disubstituted tetrahydropyran **134** in a dr of > 10:1. Protecting group exchange provided silyl ether **136**, which underwent olefin cross-metathesis between two "type I" olefins to afford the chain elongated primary alcohol **140**. An excess of the coupling partner buten-1-en-4-ol had to be employed to ensure full conversion of the valuable sugar derivative. Further protecting group modifications unveiled the other primary alcohol, priming it for lead tetraacetate-mediated dehydroxymethylative oxidation to give the anomeric acetate **153**. Sakurai allylation again favored the 2,6-*trans*-adduct to afford the allyl chloride **157** in a dr of 5:1, which underwent nucleophilic substitution with tributylstannyl lithium to give the allylstannane **158** in preparation for allylative fragment coupling with aldehyde **79**.




**Scheme 4.7.** Synthesis of the southern fragment.

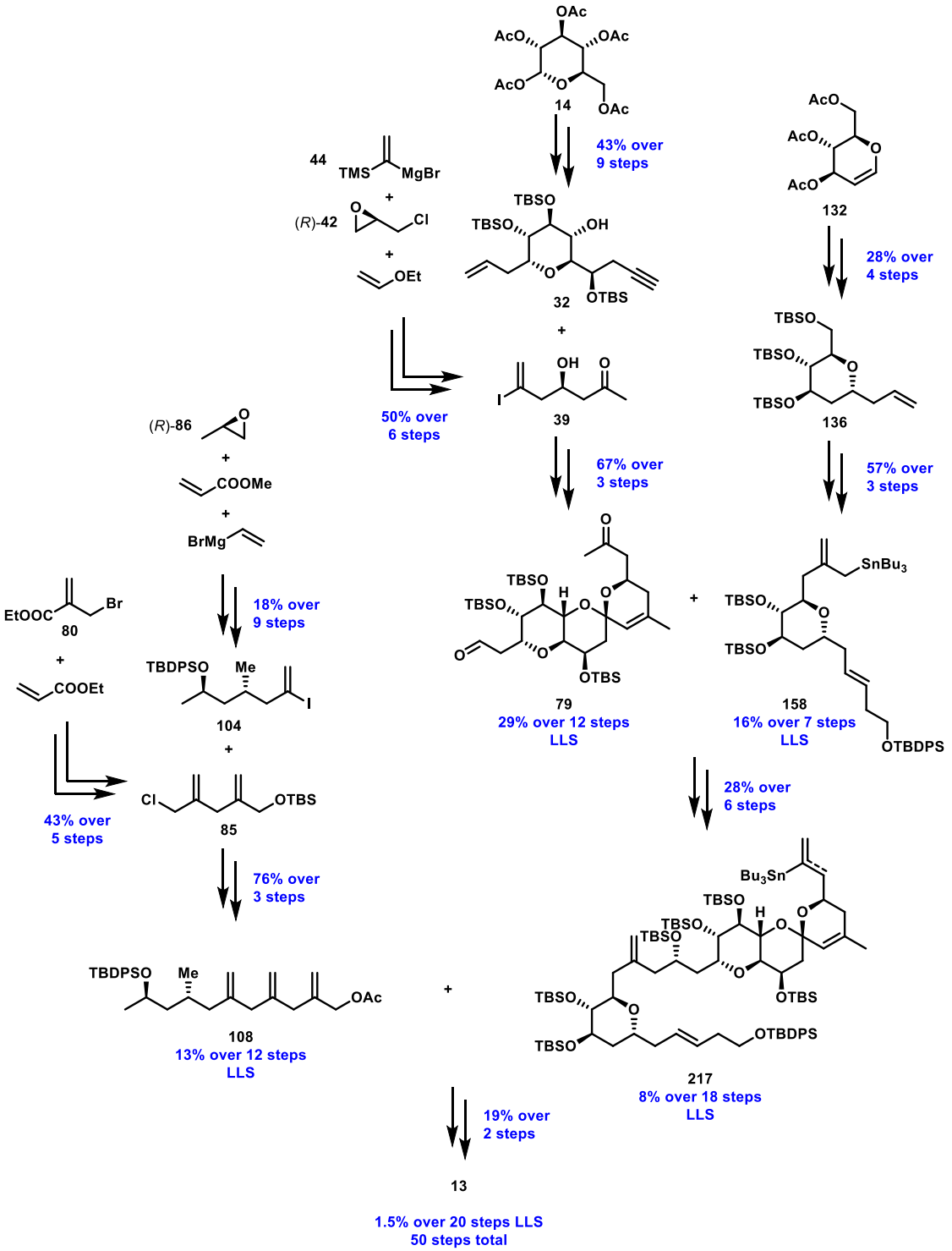
Coupling of the southern and central fragment was achieved by treatment with chelating Lewis acid $MgBr_2 \cdot OEt_2$, giving a single diastereoisomer of the homoallylic alcohol **190** in 88% yield. Unexpectedly, exclusively the undesired diastereoisomer was obtained, necessitating inversion of the newly formed alcohol by Mitsunobu reaction and saponification of the resulting 4-nitrobenzoate to correct the stereochemistry at C27. Silylation afforded the fully protected ketone **198**, which was elaborated into the alkenylstannane **217** in a two-step sequence *via* triflation and stannylcuprate-mediated stannylation. Stille cross-coupling between the alkenylstannane and allyl acetate **108** gave the desired skipped tetraene **220**, which was globally deprotected using pyridine-buffered HF–pyridine to afford limaol (**13**).




**Scheme 4.8.** Completion of the total synthesis of limaol.

An overview of the first-generation synthesis of limaol is given in Scheme 4.9. The synthetic sequence comprises a total of 50 steps. Our approach was proven to be highly

convergent: The longest linear sequence consists of 20 steps with an average yield of 81%, giving the natural product **13** in a yield of 1.5% starting from $\alpha$-D-glucopyranosyl pentaacetate. In total, 3.3 mg of limaol were prepared using this route.




**Scheme 4.9.** Summarized first-generation synthesis of limaol.

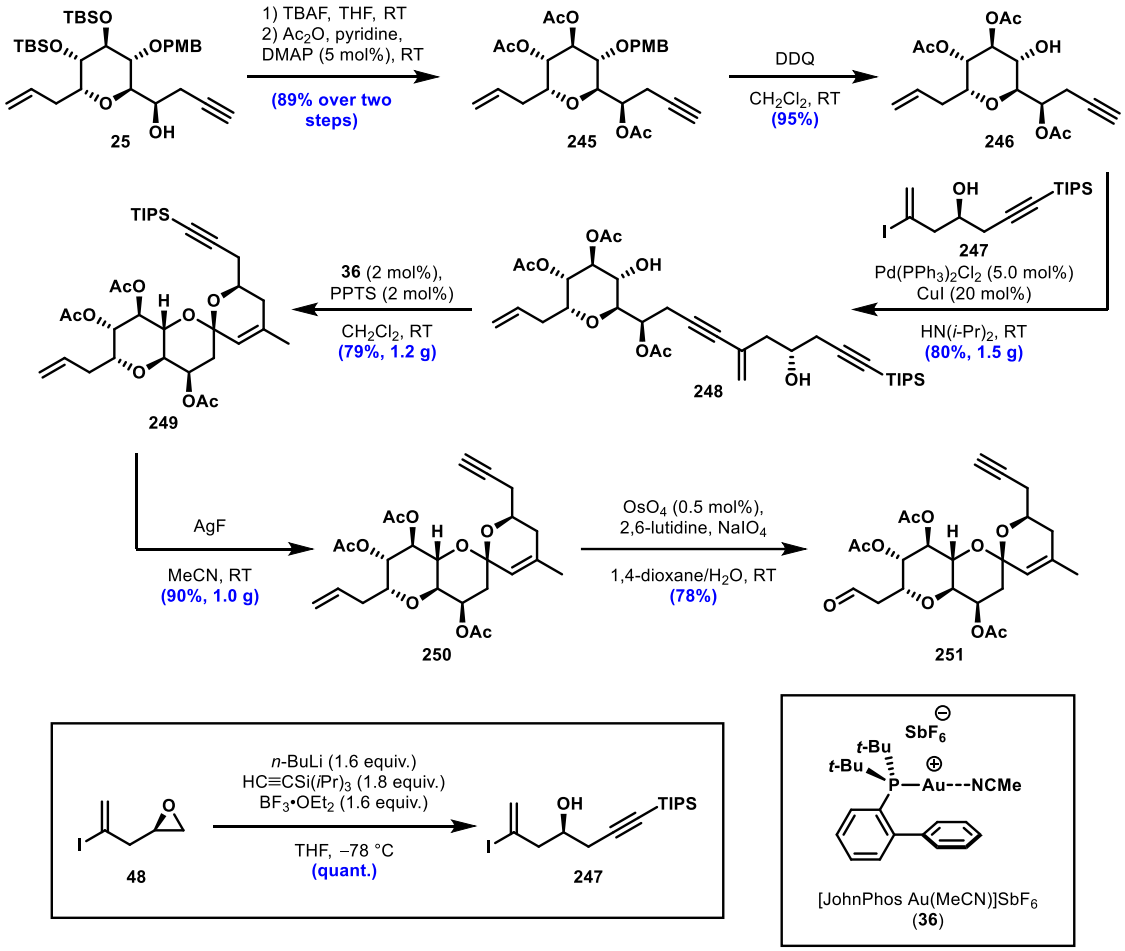
## 4.2 Summary of the Second-Generation Synthesis

During our synthetic efforts, three major bottlenecks of the first-generation approach were identified: (i) The allylative unification of the southern and central fragments was predicted to proceed in accordance with the Cram-chelate model, but exclusively formed the opposite diastereoisomer, requiring an elaborate correction of the stereochemistry on C27; (ii) The preparation of the alkenylstannane from the methyl ketone functioning as "tether" to the northern fragment proceeded with poor selectivity. This, in turn, caused a diminished yield for the fragment assembly *via* allyl-alkenyl cross-coupling, since an undesired double bond isomer had to be separated; (iii) The global deprotection suffered from extremely slow conversion to the target and low yields due to extended reaction times.

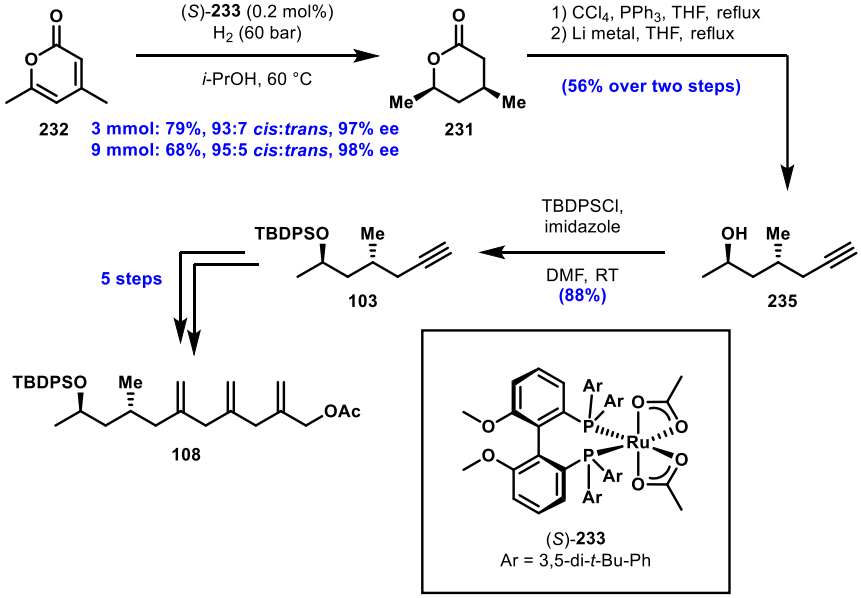
The common reason behind all of these shortcomings was identified to be the choice of protecting groups: The silyl ethers on the central fragment exert an enormous amount of steric hindrance, shielding it from attack by most external reagents. This explains the contraintuitive trajectory of attack during the allylative fragment coupling as well as the sluggish global deprotection. The peculiar selectivity issues observed during functionalization of the methyl ketone "tether" could also arise from the exuberant steric hindrance surrounding this functional group. Changing the protecting groups from silyl ethers to a smaller alternative such as acetates was projected to help overcome these challenges.

The modified central fragment synthesis commenced from previously described homopropargylic alcohol **25**, which was completely desilylated and subsequently peracetylated to give the triacetate **245** (Scheme 4.10). PMB ether cleavage afforded alcohol **246**, which smoothly underwent Sonogashira cross-coupling with alkenyl iodide **247** (easily prepared from known compound **48** by epoxide opening) to access the enyne **248**. Gold-catalyzed spiroketalization gave the tricyclic system **249**, which was subjected to silver(I) fluoride to effect desilylation of the alkyne. The monosubstituted olefin of the resulting terminal alkyne **250** was selectively cleaved under Lemieux–Johnson conditions to afford the aldehyde **251**, completing the revised central fragment synthesis.

In order to also improve upon the synthesis of the northern triene fragment, the preparation of the alkyne **103** was reconsidered. This building block could be derived from the 2-pyrone **232** by asymmetric hydrogenation, dichloroolefination, and reductive ring opening to provide access to the acetylenic alcohol **235** directly (Scheme 4.11). After silylation, the desired alkyne **103** was obtained in a total of four steps instead of seven. The following transformations were identical to the first-generation effort, ultimately giving the triene acetate **108** in nine steps in longest linear sequence and an improved total yield of 30% starting from inexpensive 4,6-dimethyl-2-pyrone.

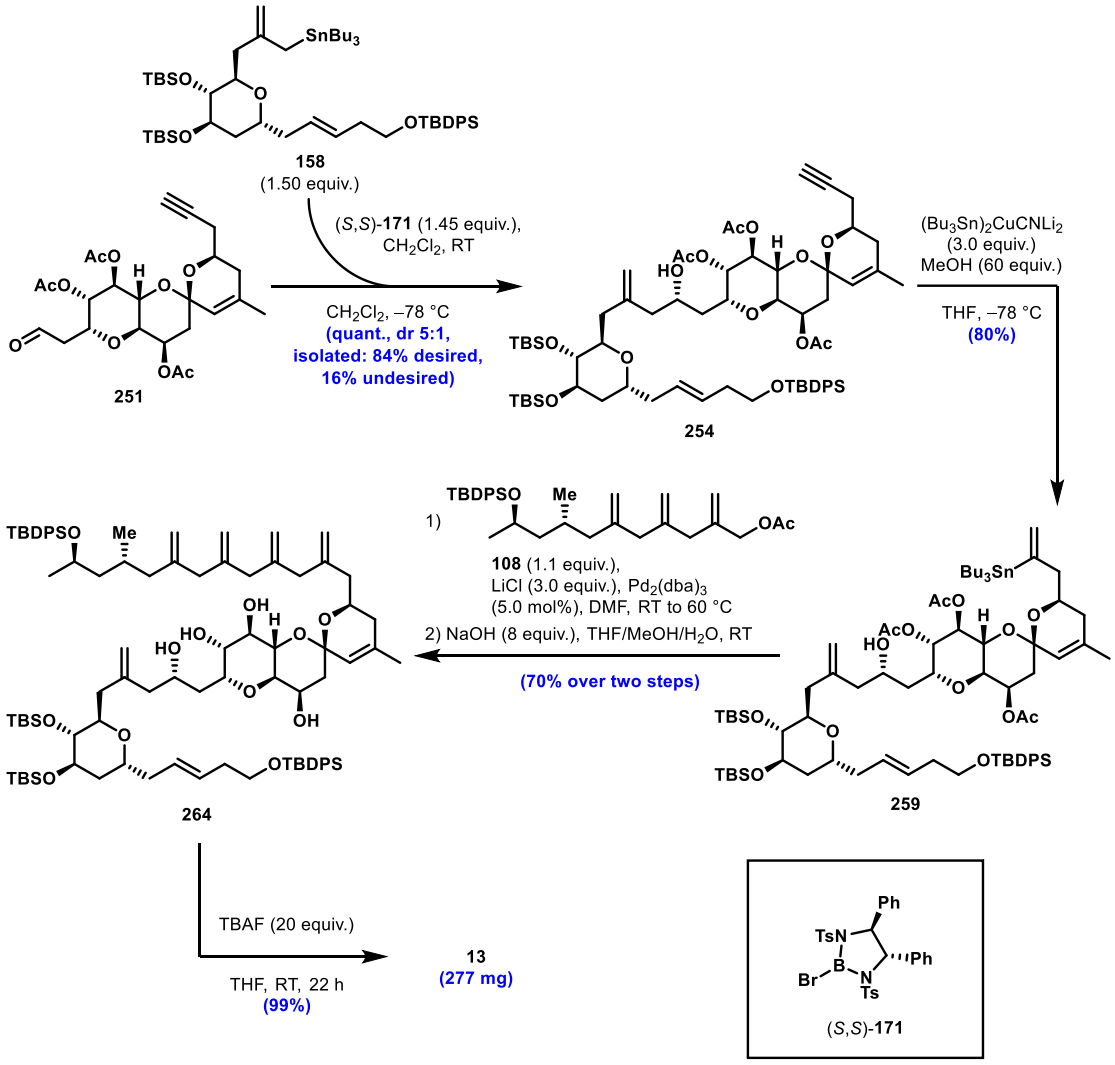



**Scheme 4.10.** Second-generation central fragment synthesis.




**Scheme 4.11.** Improved synthesis of northern fragment triene.

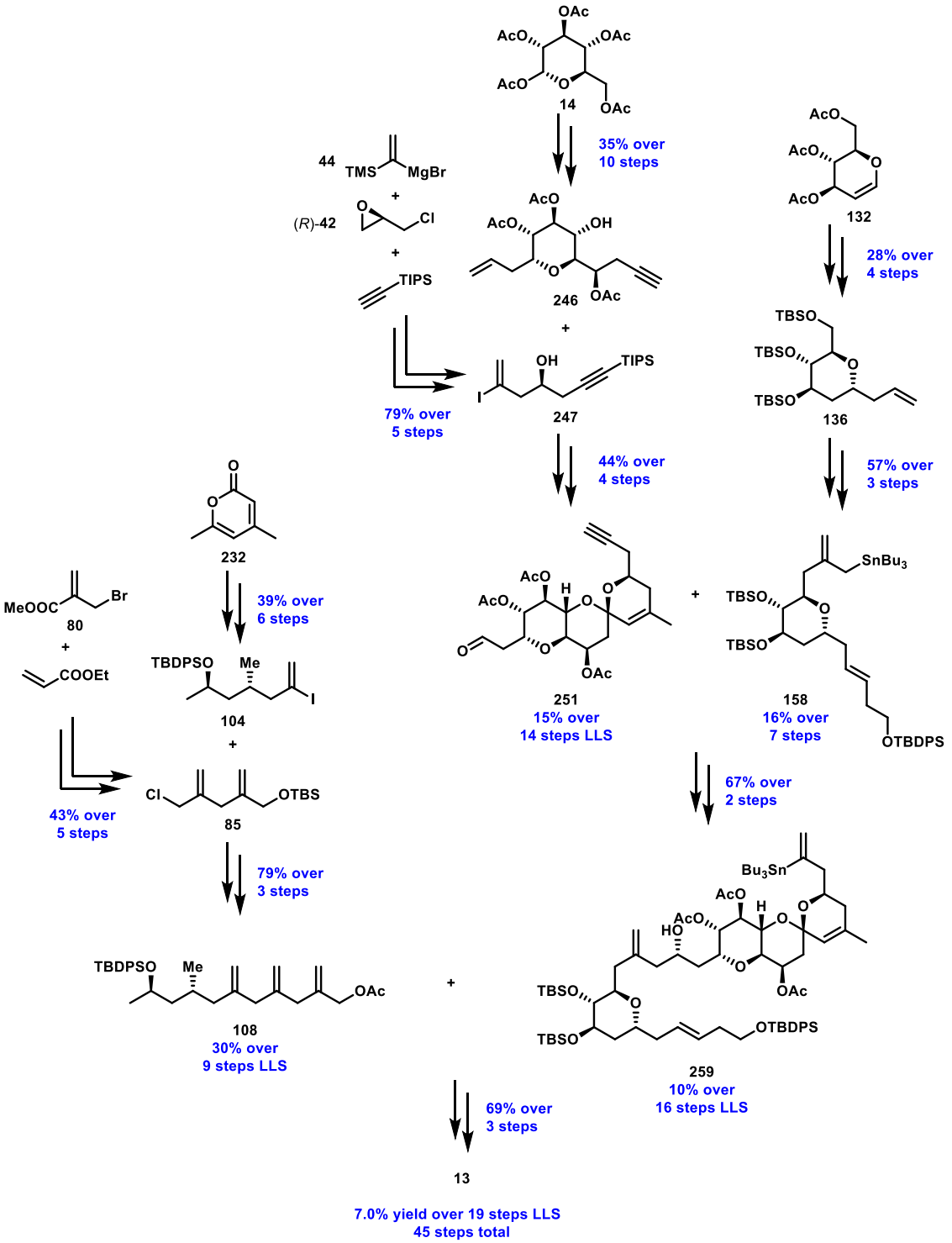
The completion of the second-generation synthesis was concisely achieved in five steps, including the assembly of all three fragments and a two-step global deprotection (Scheme 4.12). Allyl stannane **158** was converted *in situ* to the corresponding chiral allyl boron reagent, which was coupled to aldehyde **251** in excellent yield and good selectivity to directly provide the desired homoallylic alcohol diastereoisomer **254**. Upon stannylcupration of the alkyne "tether" to give alkenylstannane **259** after aqueous work-up, Stille cross-coupling with triene **108** under ligand-free conditions and subsequent deacetylation gave the partially protected natural product precursor **264**. Global desilylation afforded limaol (**13**) in a scalable manner with several hundred miligrams of the target molecule being produced in a single campaign.




**Scheme 4.12.** Completion of the second-generation synthesis of limaol.

The revised approach to limaol is summarized in Scheme 4.13. In total, the new route comprises 45 steps, five less than the previous approach. In longest linear sequence starting from $\alpha$-D-glucopyranosyl pentaacetate, the step count has been reduced by one, from 20 to 19,

and the overall yield has increased significantly, from 1.5% in the first-generation synthesis to 7.0% in the updated route. Our new approach also proved to be substantially more scalable, providing 277 mg of **13** in a single pass, compared to 3.3 mg total output in the first synthesis.




**Scheme 4.13.** Summarized second-generation synthesis of limaol.

# 5 Outlook

Since a scalable approach to limaol (**13**) has now been established, more thorough biological studies can be conducted. Due to some common structual elements that limaol shares with okadaic acid (**1**), as well as their similar biochemical origins, a comparable bioactivity seems at least somewhat likely. For this reason, investigation of limaol's phosphatase inihibition activity should be a good starting point when gauging its biological properties. However, additional bioactivity can not be excluded, so a broader array of assays should be considered.

If limaol exhibits bioactivity of interest, further optimizations of its synthesis may become necessary. Although the primary bottlenecks of the first-generation approach have been adressed, some limitations still persist. One issue plaguing the second-generation route is the need to perform two separate global deprotections, one for the acetate groups and one for the silyl groups. Streamlining the protecting group strategy to ideally only use acetates or other base-sensitive groups should allow for a further reduction in the number of steps. In addition, the synthesis of the central fragment strongly relies on the use of silyl groups in its initial phase, e.g. to allow for an orthogonal reductive benzylidene acetal opening. These bulky groups likely also play an important role in steering the stereochemical outcome of the pivotal aldehyde propargylation. Ideally, a revised approach would utilize the fact that the central fragment synthesis commences from peracetylated D-glucose, and would leave most of the preinstalled protecting groups intact throughout the route. The same argument can be made for the southern fragment, which is prepared from peracetylated D-glucal. Again, finding a way to keep most of the preinstalled acetates untouched would greatly reduce the amount of unproductive protection/deprotection steps, leading to a more streamlined synthesis. Due to the modular nature of our approach, the idea of synthesizing analogs of limaol and testing individual building blocks for bioactivity seems reasonable.

These considerations, however, should strongly depend on the results of any biological studies performed on limaol. If no significant bioactivity is observed, further expansion of our synthetic efforts towards this target would seem of little value. However, due to the complexity of the molecule in question, it seems unlikely that marine organisms such as *Prorocentrum lima* would produce it without it having some biochemical effect on itself or its environment. Intuitively, if limaol were only "dead weight", evolutionary pressure would presumably lead to the shutdown of its biosynthetic pathway and the enzymes involved in it. In light of this, a biological evaluation of limaol is of immediate interest.

# 6 Experimental Section

## 6.1 General Information

All reactions were carried out under argon in glassware flame-dried under vacuum. The solvents were purified by distillation over the indicated drying agents and were transferred under Ar: THF, $Et_2O$ (Mg/anthracene); hexanes, toluene (Na/K); $NEt_3$, diisopropylamine, diisopropylethylamine, 2,6-lutidine, pyridine, *tert*-butyl methyl ether, $CH_2Cl_2$, NMP, DMPU ($CaH_2$); MeOH (Mg, stored over 3 Å molecular sieves); DMF, 1,4-dioxane, and MeCN were dried by an adsorption solvent purification system based on molecular sieves.

Thin layer chromatography (TLC): Macherey-Nagel precoated plates (POLYGRAM®SIL/UV254); Flash chromatography: Merck silica gel 60 (40-63 μm or 15-40 μm – referred to as "fine silica") with pre-distilled or HPLC grade solvents.

NMR: Spectra were recorded on Bruker AV 400, AV VIII 500, or AV VIII 600 cryo spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$ at 7.26 and 77.16 ppm for $^1H$ and $^{13}C$ NMR spectroscopy, respectively; $CD_2Cl_2$ at 5.32 and 53.84 ppm for $^1H$ and $^{13}C$ NMR spectroscopy, respectively; $C_6D_6$ at 7.16 and 128.06 ppm for $^1H$ and $^{13}C$ NMR spectroscopy, respectively; $CD_3OD$ at 4.87 and 3.31 ppm for $^1H$ NMR and 49.00 ppm for $^{13}C$ NMR spectroscopy, respectively). $^1H$ NMR data are reported as δ (ppm) (s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet or unresolved, br = broad signal, app = appearing as; coupling constant(s) (*J*) in Hz; integration). $^{13}C$ NMR spectra were recorded with broadband $^1H$ decoupling. $^{119}Sn$ NMR spectra were recorded using $Me_4Sn$ as external standard.

IR: Spectrum One (Perkin-Elmer) spectrometer, wavenumbers ($\tilde{\nu}$) in $cm^{-1}$.

MS (EI): Finnigan MAT 8200 (70 eV), ESIMS: ESQ 3000 (Bruker), accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or MAT 95 (Finnigan).

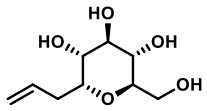
Unless stated otherwise, all commercially available compounds (ABCR, Acros, Aldrich, Apollo Scientific, Strem, TCI) were used as received. $CuBr{\cdot}SMe_2$ was recrystallized from dimethyl sulfide and stored under argon before use. *t*-BuOK was sublimated and stored under argon. $(MeOCH_2PPh_3)Cl$ was dried under high vacuum at 50 °C overnight and stored under argon before use. The following reagents and compounds were prepared according to the cited literature procedures: 2-Allenyl-1,3,2-dioxaborinane (**30**),[46] tetrabutylammonium diphenylphosphinate,[192] trityl potassium.[160b, 160c]

## 6.2 First-Generation Synthesis of Limaol

### 6.2.1 Synthesis of the Central Fragment

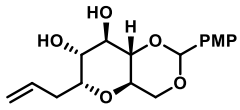
#### 6.2.1.1 Synthesis of the Homopropargylic Alcohol

**(2*R*,3*R*,4*R*,5*S*,6*R*)-2-Allyl-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (16).**



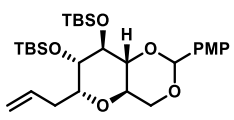
The compound was prepared according to a procedure previously described by our group.[38b] **$^1$H NMR** ($CD_3OD$, 400 MHz): δ 5.88 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.12 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.04 (ddt, *J* = 10.2, 2.2, 1.1 Hz, 1H), 3.95 (ddd, *J* = 10.5, 5.6, 4.3 Hz, 1H), 3.74 (dd, *J* = 11.8, 2.5 Hz, 1H), 3.64 (dd, *J* = 11.7, 5.2 Hz, 1H), 3.60 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.53 (dd, *J* = 9.5, 8.4 Hz, 1H), 3.45 (ddd, *J* = 9.6, 5.3, 2.6 Hz, 1H), 3.28 (dd, *J* = 9.6, 8.4 Hz, 1H), 2.53 – 2.36 (m, 2H); **$^{13}$C NMR** ($CD_3OD$, 101 MHz): δ 136.6, 116.9, 77.1, 75.1, 74.4, 72.9, 72.2, 62.9, 30.5.

**Compound 17.**



Anisaldehyde dimethyl acetal (3.80 mL, 22.3 mmol) and camphorsulfonic acid (432 mg, 1.86 mmol) were added to a stirred solution of **16** (3.80 g, 18.6 mmol) in anhydrous DMF (30 mL). The mixture was stirred at 85 °C under reduced pressure (250 mbar) for 3 h. The reaction was quenched with triethylamine (1.0 mL) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc 2:3 to 0:1) to give the title compound (5.39 g, 90%) as a pale yellow solid. $[\alpha]_D^{20}$ = +56.6 (c = 1.22, $CHCl_3$); **m.p.** 193.0-193.5 °C; **$^1$H NMR** ($CD_3OD$, 400 MHz): δ 7.42 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.84 (dddd, *J* = 16.8, 10.2, 7.5, 6.4 Hz, 1H), 5.51 (s, 1H), 5.15 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.07 (ddt, *J* = 10.1, 2.2, 1.2 Hz, 1H), 4.11 (dd, *J* = 9.6, 4.3 Hz, 1H), 4.02 (ddd, *J* = 10.4, 6.3, 3.8 Hz, 1H), 3.79 (s, 3H), 3.77 – 3.70 (m, 2H), 3.65 (t, *J* = 9.8 Hz, 1H), 3.59 (td, *J* = 9.8, 9.4, 4.3 Hz, 1H), 3.46 – 3.36 (m, 1H), 2.61 – 2.43 (m, 2H); **$^{13}$C NMR** ($CD_3OD$, 101 MHz): δ 161.6, 136.3, 131.5, 128.8, 117.0, 114.3, 103.0, 83.6, 78.2, 73.7, 72.2, 70.3, 64.8, 55.7, 30.8; **IR** (film, $cm^{-1}$): 3504, 3314, 2915, 1614, 1519, 1385, 1250, 1129, 1108, 1072, 1034, 1020, 973, 926, 829, 616, 599; **HRMS** (ESI) for $C_{17}H_{22}O_6Na$ [M+Na]$^+$: calcd. 345.1309; found 345.1310.

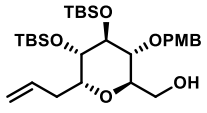
**Compound 18.**



2,6-Lutidine (7.78 mL, 66.8 mmol) and TBSOTf (9.59 mL, 41.8 mmol) were added to a solution of compound **17** (5.39 g, 16.7 mmol) in $CH_2Cl_2$ (90 mL) at −40 °C. After stirring at this temperature for 2 h, the reaction was quenched at −40 °C with saturated aqueous sodium bicarbonate (100 mL) and the mixture was allowed to reach room temperature over 30 min. The aqueous phase was extracted with EtOAc (3 × 60 mL), the combined organic fractions were dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 20:1) to give

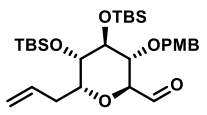
the title compound (8.37 g, 91%) as a colorless oil. $[\alpha]_D^{20}$ = +21.7 (c = 0.93, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz,): δ 7.39 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.80 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.39 (s, 1H), 5.15 (dq, *J* = 17.2, 1.3 Hz, 1H), 5.12 – 5.08 (m, 1H), 4.20 (dd, *J* = 9.6, 4.3 Hz, 1H), 3.97 (td, *J* = 7.5, 5.0 Hz, 1H), 3.85 – 3.57 (m, 7H), 3.39 (dd, *J* = 9.4, 8.3 Hz, 1H), 2.50 (t, *J* = 7.4 Hz, 2H), 0.92 (s, 9H), 0.82 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 160.1, 134.9, 130.1, 127.8, 117.1, 113.6, 102.2, 83.5, 72.9, 69.8, 63.7, 55.4, 30.4, 26.3, 26.2, 26.0, 25.9, 18.4, 18.2, −3.4, −3.9, −4.0, −4.3; **IR** (film, $cm^{-1}$): 2954, 2930, 2895, 2857, 1519, 1251, 1171, 1080, 1035, 1003, 858, 837, 777; **HRMS** (ESI) for $C_{29}H_{50}O_6Si_2Na$ [M+Na]$^+$: calcd. 573.3038; found 573.3042.

**Compound 19.**




A solution of DIBAL-H (1.0 M in $CH_2Cl_2$, 6.6 mL, 6.6 mmol) was added dropwise to a solution of acetal **18** (1.2 g, 2.2 mmol) in $CH_2Cl_2$ (10 mL) at −78 °C. After stirring at −78 °C for 2 h, the mixture was allowed to warm to 0 °C and maintained at this temperature for 14 h. The reaction was carefully quenched with water (1 mL), and the mixture was diluted with EtOAc (30 mL) and warmed to room temperature. Saturated aqueous sodium potassium tartrate (20 mL) was added and the biphasic mixture was vigorously stirred for 8 h. The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic fractions were dried over anhydrous $Na_2SO_4$, filtered and the solvent was evaporated. The residue was purified by flash chromatography (hexanes/EtOAc 4:1) to give the title compound (1.2 g, quant.) as a colorless oil. $[\alpha]_D^{20}$ = +41.8 (c = 1.09, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.81 (ddt, *J* = 17.2, 10.2, 6.8 Hz, 1H), 5.16 – 5.06 (m, 2H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 3.90 (dt, *J* = 10.5, 3.8 Hz, 1H), 3.84 – 3.69 (m, 6H), 3.64 – 3.55 (m, 2H), 3.24 (t, *J* = 6.9, 6.1 Hz, 1H), 2.51 – 2.41 (m, 1H), 2.36 – 2.28 (m, 1H), 1.89 (t, *J* = 5.9 Hz, 1H), 0.92 (s, 18H), 0.91 (s, 12H), 0.12 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 159.2, 135.1, 130.3, 129.2, 117.1, 113.8, 78.1, 73.2, 73.2, 73.1, 73.0, 73.0, 61.9, 55.3, 31.8, 26.2, 26.1, 18.3, 18.0, −3.6, −3.7, −4.2, −4.5; **IR** (film, $cm^{-1}$): 3498, 2954, 2930, 2893, 2857, 1613, 1514, 1472, 1250, 1088, 837, 776, 686; **HRMS** (ESI) for $C_{29}H_{52}O_6Si_2Na$ [M+Na]$^+$: calcd. 575.3195; found 575.3195.

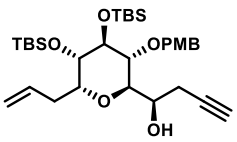
**Aldehyde 20.**




DMSO (4.32 mL, 60.8 mmol) was added dropwise to a stirred solution of oxalyl chloride (2.61 mL, 30.4 mmol) in $CH_2Cl_2$ (130 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 10 min before a solution of alcohol **19** (8.40 g, 15.2 mmol) in $CH_2Cl_2$ (15.0 mL, rinse 2 × 2.5 mL) was added dropwise. After stirring for another 20 min at −78 °C, triethylamine (21.2 mL, 152 mmol) was slowly added at this temperature over the course of 5 min. After an additional 5 min at −78 °C, the mixture was

allowed to warm to room temperature and stirring was continued for 30 min. The reaction was quenched with water (150 mL) and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with brine (150 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 12:1) to afford the title compound (7.76 g, 93%) as a pale yellow oil. $[\alpha]_D^{20}$ = +40.1 (c = 1.12, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.74 (s, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.94 (ddt, *J* = 17.2, 10.2, 6.8 Hz, 1H), 5.17 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.10 (ddt, *J* = 10.3, 2.1, 1.2 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.43 (d, *J* = 12.2 Hz, 1H), 4.32 (d, *J* = 0.8 Hz, 1H), 4.09 (ddd, *J* = 8.5, 5.0, 1.6 Hz, 1H), 3.84 (t, *J* = 3.2 Hz, 1H), 3.81 (s, 3H), 3.59 (ddd, *J* = 2.8, 1.5, 1.0 Hz, 1H), 3.36 – 3.34 (m, 1H), 2.57 (dddt, *J* = 14.9, 8.2, 6.4, 1.5 Hz, 1H), 2.21 (dddt, *J* = 14.8, 6.6, 5.0, 1.4 Hz, 1H), 0.93 (s, 9H), 0.78 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), −0.04 (s, 3H), −0.13 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 200.8, 159.5, 135.2, 130.0, 129.9, 117.0, 114.0, 80.0, 74.4, 71.3, 71.2, 70.1, 69.0, 55.5, 35.8, 26.1, 25.7, 18.5, 18.0, −3.9, −4.5, −5.0, −5.1; **IR** (film, $cm^{-1}$): 2952, 2929, 2857, 1733, 1513, 1250, 1139, 1087, 1038, 835, 775; **HRMS** (ESI) for $C_{29}H_{50}O_6Si_2Na$ $[M+Na]^{+\cdot}$ calcd. 573.3038; found 573.3042.

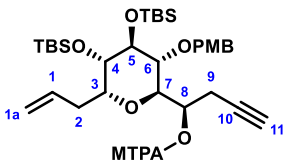
**Compound 25.**




2-Allenyl-1,3,2-dioxaborinane (**30**, 0.13 mL, 1.4 mmol) and (*R*)-(+)-3,3'-dibromo-1,1'-bi-2-naphthol ((*S*)-**23**, 42 mg, 0.093 mmol) were added to a solution of aldehyde **20** (0.51 g, 0.93 mmol) in toluene (2 mL). The mixture was stirred at room temperature for 15 h. The reaction mixture was adsorbed on silica and the product purified by flash chromatography (fine silica, hexanes/EtOAc 10:1) to give the title compound as a colorless oil (0.53 g, 96%, single diastereoisomer by $^1$H NMR). $[\alpha]_D^{20}$ = +22.6 (c = 0.94, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.86 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.17 – 5.04 (m, 2H), 4.57 – 4.49 (m, 2H), 4.10 – 4.02 (m, 1H), 3.88 (dd, *J* = 4.2, 3.0 Hz, 1H), 3.86 – 3.73 (m, 5H), 3.56 – 3.51 (m, 2H), 2.57 – 2.35 (m, 4H), 2.13 (dddd, *J* = 14.4, 7.1, 3.3, 2.0 Hz, 1H), 2.00 (t, *J* = 2.6 Hz, 1H), 0.91 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 159.4, 135.6, 130.2, 129.8, 117.1, 113.9, 81.2, 74.6, 72.0, 72.0, 71.7, 71.6, 70.7, 69.5, 55.4, 34.8, 26.1, 26.0, 24.0, 18.4, 18.0, −3.8, −4.2, −4.6, −4.6; **IR** (film, $cm^{-1}$): 3505, 2953, 2930, 2857, 1514, 1472, 1250, 1089, 1038, 915, 835, 775, 635; **HRMS** (ESI) for $C_{32}H_{54}O_6Si_2Na$ $[M+Na]^{+\cdot}$ calcd. 613.3351; found 613.3354.

The absolute configuration was determined by Mosher ester analysis:

**Preparation of the (*S*)-and (*R*)-MTPA esters (265) of alcohol 25.**[48]




(*R*)-(−)-MTPA-Cl (7.3 mg, 29 μmol) was added to a stirred solution of **25** (8.5 mg, 14 μmol) and pyridine (3.6 μL, 45 μmol) in $CH_2Cl_2$

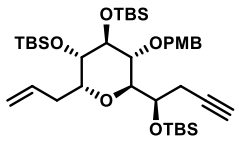
(0.3 mL). After stirring for 16 h at room temperature, the reaction was quenched with $H_2O$ (1 mL) and the mixture was diluted with *tert*-butyl methyl ether (3 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (2 × 3 mL) and the combined organic fractions were dried over anhydrous $Na_2SO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexanes/EtOAc 15:1) to give the desired (*S*)-MTPA ester (*S*)-**265** (8.1 mg, 70%) as a pale yellow oil. **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 7.64 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.48 – 7.34 (m, 3H), 7.29 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.75 (ddt, *J* = 17.2, 10.8, 6.9 Hz, 1H), 5.70 (q, *J* = 6.0 Hz, 1H), 5.10 – 5.05 (m, 1H), 5.01 – 4.97 (m, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 11.3 Hz, 1H), 4.16 (t, *J* = 5.6 Hz, 1H), 4.00 (ddd, *J* = 8.3, 5.9, 2.8 Hz, 1H), 3.85 (t, *J* = 4.1 Hz, 1H), 3.80 (s, 3H), 3.53 (dd, *J* = 4.6, 2.8 Hz, 1H), 3.42 (d, *J* = 1.3 Hz, 3H), 3.23 – 3.20 (m, 1H), 2.50 (ddd, *J* = 16.9, 5.9, 2.7 Hz, 1H), 2.43 (ddd, *J* = 16.9, 6.5, 2.7 Hz, 1H), 2.35 (dt, *J* = 14.7, 7.3 Hz, 1H), 2.29 (dd, *J* = 14.0, 7.1 Hz, 1H), 1.87 (t, *J* = 2.6 Hz, 1H), 0.92 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H), −0.01 (s, 3H).

The (*R*)-MTPA ester (*R*)-**265** was prepared analogously using (*S*)-(+)-MTPA-Cl as the reagent. **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 7.67 – 7.63 (m, 2H), 7.40 – 7.38 (m, 3H), 7.31 – 7.27 (m, 2H), 6.91 – 6.86 (m, 2H), 5.76 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.56 (td, *J* = 6.5, 3.8 Hz, 1H), 5.08 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.00 (dq, *J* = 10.2, 2.2, 1.1 Hz, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.27 (d, *J* = 11.0 Hz, 1H), 4.09 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.89 (ddd, *J* = 8.8, 5.1, 3.3 Hz, 1H), 3.81 (s, 3H), 3.80 – 3.78 (m, 1H), 3.60 – 3.57 (m, 3H), 3.46 (dd, *J* = 5.4, 3.4 Hz, 1H), 3.10 (dd, *J* = 7.6, 4.4 Hz, 1H), 2.67 – 2.61 (m, 2H), 2.35 (dt, *J* = 15.6, 7.7 Hz, 1H), 2.30 – 2.21 (m, 1H), 2.00 (t, *J* = 2.7 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.00 (s, 3H).

**Table 6.1.** Analysis of the Mosher esters **265** according to Hoye and co-workers;[48] arbitrary numbering scheme as shown in the insert.

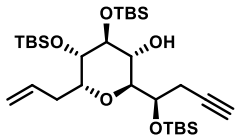
| Atom number | 25 δ [ppm] | (*S*)-265 δ [ppm] | (*R*)-265 δ [ppm] | Δδ [ppm] |
|---|---|---|---|---|
| 11 | 2.00 | 1.87 | 2.00 | −0.13 |
| 9' | 2.40 | 2.43 | 2.64 | −0.21 |
| 9'' | 2.52 | 2.50 | 2.64 | −0.14 |
| 8 | 3.88 | 5.70 | 5.56 | +0.14 |
| 7a | 3.83 | 4.16 | 4.09 | +0.07 |
| 6 | 2.53 | 3.21 | 3.10 | +0.11 |
| 5 | 3.77 | 3.85 | 3.79 | +0.06 |
| 4 | 3.53 | 3.53 | 3.46 | +0.07 |
| 3 | 4.06 | 4.00 | 3.89 | +0.11 |
| 2' | 2.47 | 2.35 | 2.35 | ±0.00 |
| 2'' | 2.13 | 2.26 | 2.26 | ±0.00 |

**Compound 31.**




*tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.46 mL, 2.0 mmol) was added dropwise to a solution of alcohol **25** (0.98 g, 1.7 mmol) and 2,6-lutidine (0.39 mL, 3.3 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C and the mixture was stirred at 0 °C for 30 min. The reaction was quenched at 0 °C with saturated aqueous $NH_4Cl$ (15 mL) and the mixture was diluted with *tert*-butyl methyl ether (20 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$, and filtered. The solvent was evaporated and the residue was purified by flash chromatography (hexanes/EtOAc 30:1) to give the title compound (1.2 g, 99%) as a colorless oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +39.2 (c = 1.03, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.86 (dddd, *J* = 16.6, 10.2, 7.5, 6.3 Hz, 1H), 5.17 – 5.02 (m, 2H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.05 (ddd, *J* = 6.9, 6.0, 2.7 Hz, 1H), 3.90 – 3.79 (m, 6H), 3.60 (dd, *J* = 5.7, 3.7 Hz, 1H), 3.51 (dd, *J* = 8.2, 4.4 Hz, 1H), 2.50 – 2.40 (m, 2H), 2.35 (ddd, *J* = 16.9, 6.9, 2.7 Hz, 1H), 2.23 (dddd, *J* = 14.7, 7.5, 3.3, 2.1 Hz, 1H), 1.92 (t, *J* = 2.6 Hz, 1H), 0.90 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.09 (s, 18H), 0.08 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 159.0, 135.6, 130.9, 128.7, 116.7, 113.7, 82.9, 79.3, 74.4, 74.0, 73.5, 72.9, 72.3, 72.2, 69.8, 55.4, 33.0, 26.2, 26.2, 26.1, 24.1, 18.4, 18.3, 18.1, −3.5, −3.6, −4.0, −4.1, −4.5, −4.5; **IR** (film, $cm^{-1}$): 2953, 2929, 2895, 2857, 1515, 1472, 1250, 1094, 1040, 1004, 836, 776, 672, 637; **HRMS** (ESI) for $C_{38}H_{68}O_6Si_3Na$ $[M+Na]^{+}$ calcd. 727.4216; found 727.4213.

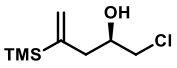
**Compound 32.**




Water (3.0 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.52 g, 2.3 mmol) were added to a solution of **31** (1.2 g, 1.6 mmol) in $CH_2Cl_2$ (30 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature before it was diluted with water (20 mL) and extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic fractions were washed with water (20 mL) and brine (20 mL), dried over anhydrous $Na_2SO_4$, and filtered. The solvent was evaporated and the crude product purified by flash chromatography (hexanes/*tert*-butyl methyl ether 50:1) to yield the title compound (0.95 g, 99%) as a colorless oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +20.8 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.84 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.19 – 5.04 (m, 2H), 4.14 (dt, *J* = 8.5, 4.4 Hz, 1H), 3.89 – 3.76 (m, 2H), 3.69 (dd, *J* = 8.1, 5.5 Hz, 1H), 3.61 (q, *J* = 5.7 Hz, 1H), 3.58 – 3.52 (m, 1H), 3.40 (d, *J* = 6.5 Hz, 1H), 2.59 – 2.38 (m, 3H), 2.29 – 2.19 (m, 1H), 1.97 (t, *J* = 2.6 Hz, 1H), 0.92 (s, 9H), 0.90 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 135.1, 117.3, 81.2, 73.2, 72.9, 72.6, 72.1, 71.7, 70.6, 27.1, 26.2, 26.1, 25.9, 24.6, 18.3, 18.3, 18.2, −3.7, −3.9, −3.9, −4.0, −4.2, −4.5; **IR** (film, $cm^{-1}$): 3505, 2954, 2930, 2896, 2858, 1472, 1254, 1096, 1033, 1005, 914, 836, 776, 680, 638; **HRMS** (ESI) for $C_{30}H_{60}O_5Si_3Na$ $[M+Na]^{+}$ calcd. 607.3641; found 607.3644.

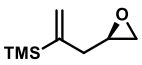
### 6.2.1.2 Synthesis of the Sonogashira Coupling Partner

**(*R*)-1-Chloro-4-(trimethylsilyl)pent-4-en-2-ol (46).**




A two-necked flask equipped with a reflux condenser was charged with Mg turnings (0.46 g, 19 mmol) and THF (4 mL). The suspension was stirred at reflux temperature for 1 min before 1,2-dibromoethane (16 μL, 0.19 mmol) was added and stirring was continued for 5 min. (1-Bromovinyl)trimethylsilane (0.70 mL, 4.5 mmol) was then added dropwise over 15 min at such a rate as to maintain gentle reflux but avoid strong foaming. Once the addition was complete, the mixture was stirred for 1 h at room temperature. The resulting solution of the Grignard reagent was transferred into a separate two-necked jacketed Schlenk vessel *via* cannula. Complete transfer was ensured by washing the flask with THF (2 × 2 mL). The solution was cooled to −50 °C and copper(I) cyanide (34 mg, 0.38 mmol) and (*R*)-(−)-epichlorohydrin ((*R*)-**42**, 0.30 mL, 3.8 mmol) were successively added at this temperature. The resulting mixture was warmed to −20 °C and stirring was continued at this temperature for 2 h. The solution gradually turned red and then brown during this time. Saturated aqueous $NH_4Cl$ (15 mL) and *tert*-butyl methyl ether (15 mL) were added and the mixture was warmed to room temperature over 10 min, giving a biphasic mixture. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic fractions were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by bulb-to-bulb distillation to give the desired chlorohydrin (0.73 g, 99%) as a colorless oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −0.9 (c = 1.16, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.71 (dt, *J* = 2.7, 1.4 Hz, 1H), 5.52 (dt, *J* = 2.8, 0.8 Hz, 1H), 3.92 (dddt, *J* = 7.9, 6.3, 5.5, 4.0 Hz, 1H), 3.62 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.52 (dd, *J* = 11.0, 6.3 Hz, 1H), 2.49 (dddd, *J* = 14.0, 5.6, 1.4, 0.7 Hz, 1H), 2.36 (dddd, *J* = 13.9, 7.9, 1.3, 0.8 Hz, 1H), 2.15 (d, *J* = 4.0 Hz, 1H), 0.12 (s, 9H).; **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 148.2, 128.4, 70.1, 49.7, 41.5, −1.3; **IR** (film, $cm^{-1}$): 3411, 2956, 1429, 1249, 1049, 934, 837, 758, 692, 658; **HRMS** (ESI) for $C_8H_{17}ClOSiNa$ $[M+Na]^{+}$ calcd. 215.0629; found 215.0629.

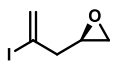
**(*R*)-Trimethyl(3-(oxiran-2-yl)prop-1-en-2-yl)silane (43).**




Freshly powdered sodium hydroxide (0.23 g, 5.7 mmol) was added to a solution of chlorohydrin **46** (0.73 g, 3.8 mmol) in $Et_2O$ (8 mL). The suspension was stirred for 27 h at room temperature before the mixture was filtered and the residue was washed with $Et_2O$ (3 × 2 mL). The combined filtrates were dried over anhydrous $Na_2SO_4$ and concentrated by distilling the solvent off at atmospheric pressure (bath temperature ≤ 40 °C). The residue was purified by bulb-to-bulb distillation to afford the desired epoxide (0.59 g, 99%) as a colorless liquid. The spectral data and specific rotation were in good agreement with those reported in the literature.[71] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −4.1 (c = 0.96, $CHCl_3$), literature: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{18}}$ = −6.0 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.73 (dt, *J* = 2.9, 1.5 Hz, 1H), 5.45 (dt, *J* = 2.8, 1.0 Hz, 1H), 3.00 (tdd, *J* = 5.7, 3.9, 2.7 Hz, 1H), 2.79 (ddd, *J* = 5.1, 3.9, 0.7 Hz, 1H), 2.50 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.46 – 2.38 (m,

1H), 2.29 (ddt, *J* = 15.1, 5.5, 1.3 Hz, 1H), 0.11 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 148.1, 126.6, 51.9, 47.4, 39.0, −1.6; **IR** (film, $cm^{-1}$): 2956, 1402, 1248, 1042, 930, 905, 833, 756, 691, 654; **HRMS** (CI) for $C_8H_{17}OSi$ $[M+H]^{+\cdot}$ calcd. 157.1049; found 157.1047.

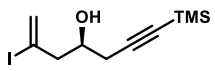
**(*R*)-2-(2-Iodoallyl)oxirane (48).**



A solution of iodine monochloride (1.3 mL, 25 mmol) in $CH_2Cl_2$ (20 mL) was added dropwise to a solution of alkenylsilane **43** (3.6 g, 23 mmol) in $CH_2Cl_2$ (100 mL) at −78 °C. After maintaining the solution at −78 °C for 30 min, saturated aqueous $Na_2S_2O_3$ (100 mL) was added and the mixture was vigorously stirred until the yellow color had disappeared. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL) and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuum (bath temperature ≤ 30 °C).

The residue was taken up in $Et_2O$/THF (4:1, 100 mL) and solid tetrabutylammonium fluoride trihydrate (8.7 g, 28 mmol) was added at 0 °C. The reaction was stirred at 0 °C for 1 h and quenched with saturated aqueous $NaHCO_3$ (100 mL). The mixture was diluted with pentane (150 mL) and the aqueous phase was extracted with pentane (3 × 100 mL). The combined organic fractions were washed with saturated aqueous $NH_4Cl$ (100 mL) and brine (100 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated by distilling the solvent off at atmospheric pressure (bath temperature 45 °C). The residue was purified by flash chromatography (pentane/$Et_2O$ 10:1) and the combined fractions were carefully concentrated at atmospheric pressure (bath temperature 45 °C). The residue was purified by bulb-to-bulb distillation ($1.0 \times 10^{-3}$ mbar, receiving flask cooled to −78 °C) to give the desired alkenyl iodide (3.8 g, 79%) as a pale yellow oil. $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = −11.9 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 6.20 (q, *J* = 1.5 Hz, 1H), 5.88 – 5.82 (m, 1H), 3.14 (dddd, *J* = 5.9, 5.2, 3.9, 2.6 Hz, 1H), 2.85 (ddd, *J* = 4.7, 3.9, 0.6 Hz, 1H), 2.81 – 2.70 (m, 1H), 2.70 – 2.60 (m, 1H), 2.62 (dd, *J* = 4.9, 2.7 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 128.1, 103.8, 51.3, 48.2, 46.9; **IR** (film, $cm^{-1}$): 3050, 2992, 2922, 1618, 1404, 1257, 1135, 1116, 969, 896, 835, 799, 760, 616, 545, 492; **HRMS** (GC-EI) for $C_5H_7OI$ $[M^{\bullet+}]$: calcd. 209.9536; found 209.9534.

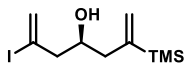
**(*S*)-2-Iodo-6-(trimethylsilyl)hepta-1,6-dien-4-ol (38).**




*n*-Butyllithium (0.48 mL, 1.6 M in hexanes, 0.76 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (0.12 mL, 0.86 mmol) in anhydrous THF (4 mL) at −78 °C. The resulting solution was stirred at this temperature for 20 min. Boron trifluoride etherate (94 μL, 0.76 mmol) was added dropwise at −78 °C. After stirring at −78 °C for 5 min, a solution of epoxide **48** (0.11 g, 0.48 mmol) in THF (0.5 mL, 2 × 0.2 mL washes) was added *via* cannula at −78 °C. After 1 h of stirring at this temperature, the reaction was quenched by adding brine (5 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 5 mL) and the combined organic layers were dried over anhydrous

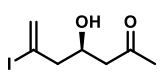
$Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 8:1) to give the title compound (0.14 mg, 94%) as a colorless oil. $[\alpha]_D^{20}$ = −13.1 (c = 1.06, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 6.19 (q, *J* = 1.3 Hz, 1H), 5.85 (d, *J* = 1.4 Hz, 1H), 4.04 (dddt, *J* = 7.9, 6.1, 5.4, 4.8 Hz, 1H), 2.69 (dddd, *J* = 14.3, 4.7, 1.4, 0.5 Hz, 1H), 2.58 (ddd, *J* = 14.4, 7.9, 1.1 Hz, 1H), 2.52 (dd, *J* = 16.9, 5.4 Hz, 1H), 2.45 (dd, *J* = 16.8, 6.1 Hz, 1H), 2.03 (d, *J* = 4.9 Hz, 1H), 0.17 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 129.0, 106.4, 102.3, 88.5, 68.4, 51.6, 27.6, 0.2; **IR** (film, $cm^{-1}$): 3395, 2958, 2176, 1617, 1420, 1249, 1189, 1119, 1055, 1027, 899, 842, 760, 698, 647, 512; **HRMS** (GC-EI) for $C_{10}H_{17}OISi$ $[M]^+$: calcd. 308.0088; found 308.0086.

**(*S*)-2-Iodo-6-(trimethylsilyl)hept-1-en-6-yn-4-ol (37).**




1,2-Dibromoethane (20 μL, 0.23 mmol) was added to a suspension of magnesium (46 mg, 1.9 mmol) in THF (3 mL). The mixture was stirred at room temperature for 5 min and then (1-bromovinyl)trimethylsilane (0.15 mL, 0.95 mmol) was added dropwise over 5 min, so as to maintain the mixture at gentle reflux. The resulting mixture was filtered under argon and the filtrate was cooled to −40 °C. Copper(I) iodide (9.1 mg, 48 μmol) was added and the mixture was stirred at this temperature for 30 min. A solution of epoxide **48** (0.10 g, 0.48 mmol) in THF (0.5 mL, 2 × 0.2 mL washes) was added over 10 min at −40 °C. The reaction mixture was warmed to 0 °C over 14 h. The reaction was quenched by adding saturated aq. $NH_4Cl$ (8 mL), the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 8 mL), and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc 10:1) to give the title compound as a colorless oil (92 mg, 62%). $[\alpha]_D^{20}$ = +0.7 (c = 1.06, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 6.17 (q, *J* = 1.3 Hz, 1H), 5.84 (d, *J* = 1.4 Hz, 1H), 5.70 (dt, *J* = 2.8, 1.3 Hz, 1H), 5.52 (dt, *J* = 2.9, 0.7 Hz, 1H), 3.97 (dtq, *J* = 9.4, 5.0, 2.2 Hz, 1H), 2.60 – 2.49 (m, 2H), 2.45 (dddd, *J* = 13.7, 4.3, 1.5, 0.7 Hz, 1H), 2.26 (ddt, *J* = 13.7, 8.9, 0.9 Hz, 1H), 1.82 (d, *J* = 2.4 Hz, 1H), 0.14 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 149.0, 128.5, 128.4, 107.7, 68.2, 52.5, 43.7, –1.1; **IR** (film, $cm^{-1}$): 3428, 2954, 2906, 1616, 1406, 1351, 1283, 1248, 1208, 1161, 1110, 1046, 930, 896, 837, 758, 691, 660, 561, 518, 485; **HRMS** (ESI) for $C_{10}H_{19}OISiNa$ $[M+Na]^+$: calcd. 333.0142; found 333.0146.

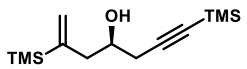
**(*S*)-4-Hydroxy-6-iodohept-6-en-2-one (39).**




*tert*-Butyllithium (1.9 M solution in pentane, 5.5 mL, 10 mmol) was added dropwise to a solution of ethyl vinyl ether (1.5 mL, 16 mmol) in THF (12 mL) at −78 °C. The resulting mixture was allowed to slowly warm to 5 °C over 40 min (programmed cryostat) and then recooled to −78 °C. This solution of the lithium species (−78 °C) was added dropwise *via* cannula to a stirred solution of boron trifluoride etherate (1.3 mL, 10 mmol) in THF (20 mL) at −78 °C. A solution of epoxide **48** (0.73 g, 3.5 mmol) in THF (4 mL, 2 x 2 mL

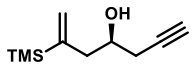
washes) was added quickly *via* cannula at −78 °C. After 30 min of stirring at this temperature, the reaction was quenched at −78 °C by addition of saturated aqueous $NaHCO_3$ (30 mL) and the resulting mixture was warmed to room temperature. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL). The combined organic fractions were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and evaporated. The residue was taken up in THF (8 mL) and aqueous HCl (2 mL, 0.1 M) and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic fractions were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexanes/EtOAc 3:2) to give the title compound as pale yellow oil (0.56 g, 63% over two steps). $[\alpha]_D^{20}$ = −18.4 (c = 0.92, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 6.17 (q, *J* = 1.3 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 4.39 – 4.28 (m, 1H), 3.01 (d, *J* = 3.8 Hz, 1H), 2.72 – 2.54 (m, 3H), 2.47 (ddd, *J* = 14.4, 5.5, 1.3 Hz, 1H), 2.20 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 209.2, 128.8, 106.3, 66.5, 51.5, 48.5, 30.9; **IR** (film, $cm^{-1}$): 3416, 2929, 1708, 1617, 1419, 1359, 1295, 1261, 1190, 1164, 1119, 1078, 901, 870, 551, 515, 421; **HRMS** (GC-CI) for $C_7H_{12}O_2I$ $[M+H]^+$: calcd. 254.9877; found 254.9874.

**(*S*)-2,7-Bis(trimethylsilyl)hept-1-en-6-yn-4-ol (50).**



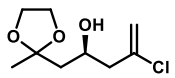

1,2-Dibromoethane (73 µL, 0.84 mmol) was added to a suspension of magnesium (819 mg, 33.7 mmol) in THF (60 mL). The mixture was stirred at room temperature for 5 min and then (1-bromovinyl)trimethylsilane (1.95 mL, 12.6 mmol) was added dropwise over 5 min, so as to maintain the mixture at gentle reflux. The resulting mixture was filtered under argon and the filtrate was cooled to −50 °C. Copper(I) iodide (160 mg, 0.843 mmol) was added and the mixture was stirred at this temperature for 30 min. A solution of epoxide **51**[74] (1.30 g, 8.43 mmol) in THF (15 mL, 2 × 2.5 mL washes) was added over 10 min at −50 °C. The reaction mixture was warmed to −20 °C over 14 h. The reaction was quenched by adding saturated aq. $NH_4Cl$ (100 mL), the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 100 mL), and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 12:1) to give the title compound as a colorless oil (1.93 g, 90%). $[\alpha]_D^{20}$ = −5.5 (c = 1.10, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.69 (dt, *J* = 2.8, 1.3 Hz, 1H), 5.50 (dt, *J* = 3.0, 0.7 Hz, 1H), 3.90 – 3.73 (m, 1H), 2.61 (dddd, *J* = 13.8, 4.5, 1.5, 0.6 Hz, 1H), 2.47 (dd, *J* = 16.7, 5.8 Hz, 1H), 2.40 (dd, *J* = 16.7, 6.3 Hz, 1H), 2.26 (ddt, *J* = 13.8, 8.6, 1.0 Hz, 1H), 1.97 (d, *J* = 3.7 Hz, 1H), 0.16 (s, 9H), 0.12 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 149.1, 128.1, 103.3, 87.8, 68.6, 43.6, 28.3, 0.2, –1.2; **IR** (film, $cm^{-1}$): 3421, 2957, 2176, 1421, 1249, 1026, 931, 839, 759, 694, 647, 426; **HRMS** (ESI) for $C_{13}H_{26}OSi_2Na$ $[M+Na]^+$: calcd. 277.1414; found 277.1412.

**(*S*)-2-(Trimethylsilyl)hept-1-en-6-yn-4-ol (57).**




Potassium carbonate (180 mg, 1.30 mmol) was added to a solution of enyne **50** (111 mg, 0.434 mmol) in MeOH (2 mL). The mixture was stirred at room temperature for 2 h before the solvent was evaporated and the residue was taken up in saturated aq. $NH_4Cl$ (4 mL), water (2 mL), and *tert*-butyl methyl ether (5 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 5 mL), and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 5:1) to give the title compound as a colorless oil (71.0 mg, 90%). $[\alpha]_D^{20}$ = −2.2 (c = 1.30, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.70 (dt, *J* = 2.8, 1.3 Hz, 1H), 5.51 (dt, *J* = 2.9, 0.8 Hz, 1H), 3.85 (qdd, *J* = 8.7, 5.3, 3.2 Hz, 1H), 2.56 (dddd, *J* = 13.8, 4.7, 1.4, 0.7 Hz, 1H), 2.41 (dd, *J* = 2.6, 1.1 Hz, 1H), 2.39 (dd, *J* = 2.7, 1.3 Hz, 1H), 2.30 (ddt, *J* = 13.8, 8.5, 1.0 Hz, 1H), 2.07 (t, *J* = 2.7 Hz, 1H), 2.00 (dd, *J* = 3.7, 1.5 Hz, 1H), 0.12 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 148.9, 128.3, 80.9, 70.9, 68.4, 43.6, 26.8, –1.2; **IR** (film, $cm^{-1}$): 3311, 2955, 1421, 1249, 1050, 931, 837, 758, 691, 637; **HRMS** (ESI) for $C_{10}H_{18}OSiNa$ $[M+Na]^+$: calcd. 205.1019; found 205.1020.

**(*R*)-4-Chloro-1-(2-methyl-1,3-dioxolan-2-yl)pent-4-en-2-ol (52).**




$NEt_3$ (83 µL, 0.60 mmol) was added to a suspension of the ligand (*S*)-**59**[75a] (118 mg, 0.317 mmol), $CrCl_3$·3 THF (113 mg, 0.301 mmol), Mn (496 mg, 9.02 mmol) in THF (13 mL) and the reaction mixture was stirred vigorously for 1.5 h. 2,6-lutidine (0.774 mL, 6.65 mmol) and 3-bromo-2-chloropropene (1.03 mL, 7.91 mmol) were added. After stirring for 10 min at RT, the mixture was cooled to 0 °C and stirred for 10 min. A solution of aldehyde **53**[76] (206 mg, 1.58 mmol) in THF (2.0 mL) and TMSCl (1.15 mL, 9.02 mmol) were added at 0 °C. The reaction mixture was stirred for 16 h at this temperature and then diluted with *tert*-butyl methyl ether (20 mL). The suspension was filtered through a silica plug and washed with *tert*-butyl methyl ether (20 mL). The combined filtrates were concentrated, the residue was taken up in THF (5 mL) and the resulting solution was added to a solution of TBAF trihydrate (549 mg, 1.74 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL), and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated. Purification by flash chromatography (hexanes/EtOAc 3:1) afforded the title compound as a colorless oil (300 mg, 92%). Purity was determined to be 92% by GC-MS analysis (Figure 6.1) and the *ee* was found to be 92% by GC-MS analysis using a chiral stationary phase (Figure 6.2). $[\alpha]_D^{20}$ = −5.4 (c = 1.24, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.26 (d, *J* = 1.2 Hz, 1H), 5.24 (q, *J* = 1.0 Hz, 1H), 4.24 (ddddd, *J* = 9.4, 7.6, 5.6, 1.9, 1.1 Hz, 1H), 4.05 – 3.98 (m, 4H), 3.61 (s, 1H), 2.57 (ddd, *J* = 14.4, 7.4, 0.9 Hz, 1H), 2.38 (ddt, *J* = 14.3, 5.5, 0.9 Hz, 1H), 1.91 (dd, *J* = 14.6, 1.9 Hz, 1H), 1.79 (dd, *J* = 14.6,

9.9 Hz, 1H), 1.38 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 139.3, 114.8, 110.3, 65.5, 64.9, 64.5, 47.0, 44.2, 24.3; **IR** (film, $cm^{-1}$): 3500, 2984, 2952, 2889, 1637, 1417, 1379, 1256, 1216, 1160, 1105, 1052, 948, 886, 837, 819, 641, 542; **HRMS** (ESI) for $C_9H_{15}ClO_3Na$ $[M+Na]^+$: calcd. 229.0602; found 229.0603.

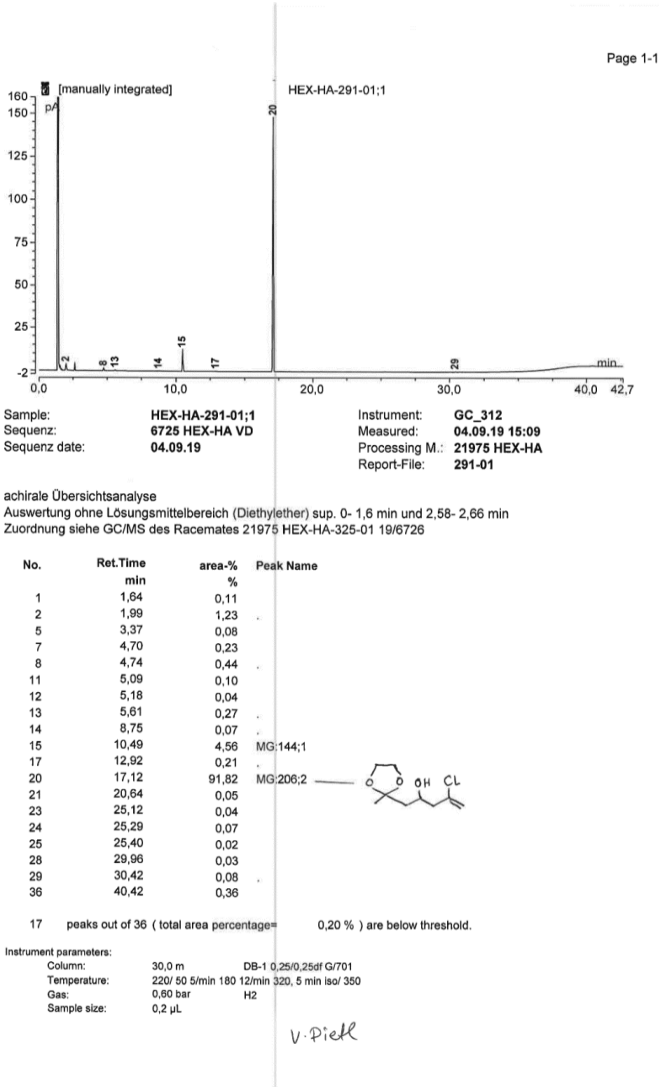



**Figure 6.1.** GC-MS analysis of **52** using an achiral stationary phase.

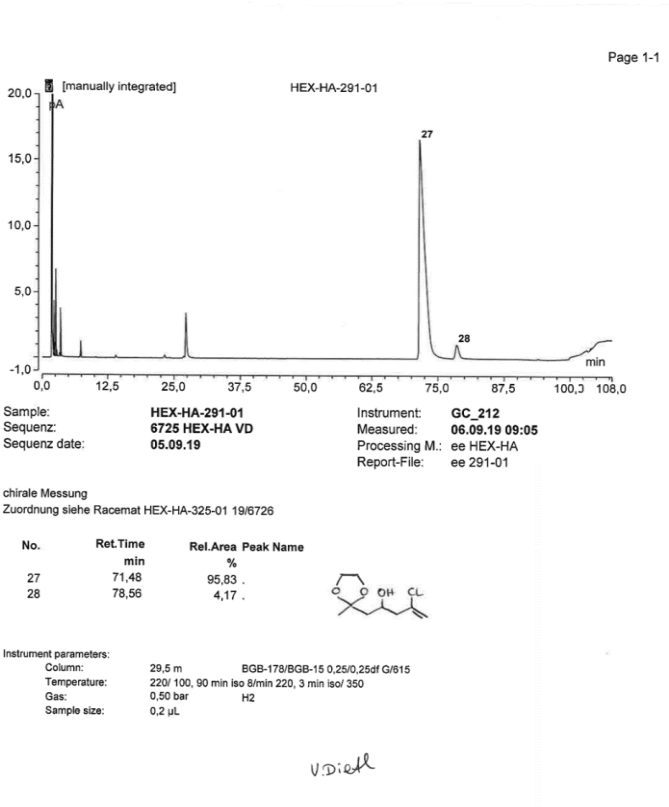
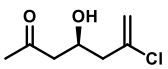



**Figure 6.2.** GC-MS analysis of **52** using a chiral stationary phase.

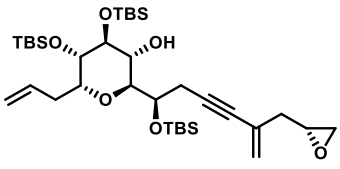
**(*S*)-2-(Trimethylsilyl)hept-1-en-6-yn-4-ol (60).**



$In(OTf)_3$ (1.1 mg, 1.9 µmol) was added to a solution of ketal **52** (50 mg, 0.24 mmol) in acetone (2.5 mL). The mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was purified by flash chromatography (hexanes/$Et_2O$ 2:1) to give the title compound as a colorless oil (35 mg, 88%). $[\alpha]_D^{20}$ = +29.8 (c = 1.09, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.28 (d, *J* = 1.2 Hz, 1H), 5.26 (q, *J* = 1.1 Hz, 1H), 4.38 (dddd, *J* = 8.7, 7.6, 5.6, 3.1 Hz, 1H), 2.70 (dd, *J* = 17.7, 3.1 Hz, 1H), 2.64 – 2.54 (m, 2H), 2.42 (ddd, *J* = 14.3, 5.6, 1.0 Hz, 1H), 2.20 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 209.3, 138.7, 115.4, 65.2, 48.8, 45.9, 30.9; **IR** (film, $cm^{-1}$): 3453, 2920, 1709, 1636, 1421, 1361, 1167, 1134, 1085, 983, 889, 644, 553, 495, 462, 416; **HRMS** (ESI) for $C_7H_{11}ClO_2Na$ $[M+Na]^+$: calcd. 185.0340; found 185.0340.

### 6.2.1.3 Completion of the Central Fragment Synthesis

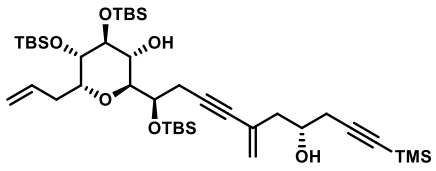
**Compound 63.**



Copper(I) iodide (62 mg, 0.33 mmol) was added to a solution of alkyne **32** (0.95 g, 1.6 mmol) in degassed diisopropylamine (10 mL). The mixture was stirred at room temperature for 10 min. A solution of alkenyl iodide **48** (0.41 g, 2.0 mmol) in

diisopropylamine (2 mL, 2 × 2 mL wash) was added, followed by triphenylphosphine (86 mg, 0.33 mmol) and tris(dibenzylideneacetone)dipalladium(0) (75 mg, 82 μmol). The resulting mixture was stirred for 1 h at room temperature before the reaction was quenched at 0 °C by addition of saturated aqueous $NH_4Cl$ (30 mL). The mixture was diluted with *tert*-butyl methyl ether (30 mL) and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL) once room temperature had been reached. The combined organic extracts were washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 50:1 to 20:1) to afford the desired enyne as a colorless oil (1.1 g, 97%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +44.1 (c = 1.10, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.85 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.37 – 5.33 (m, 1H), 5.27 (d, *J* = 1.5 Hz, 1H), 5.16 – 5.06 (m, 2H), 4.16 (dt, *J* = 8.4, 4.5 Hz, 1H), 3.83 – 3.76 (m, 2H), 3.68 – 3.58 (m, 2H), 3.56 (dd, *J* = 6.2, 3.4 Hz, 1H), 3.41 (d, *J* = 6.1 Hz, 1H), 3.13 (tdd, *J* = 5.7, 3.9, 2.6 Hz, 1H), 2.80 (ddd, *J* = 4.7, 3.9, 0.6 Hz, 1H), 2.67 (dd, *J* = 17.2, 4.3 Hz, 1H), 2.61 – 2.53 (m, 2H), 2.50 – 2.37 (m, 2H), 2.25 (ddd, *J* = 14.6, 5.8, 1.2 Hz, 2H), 0.92 (s, 9H), 0.90 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), 0.13 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 135.1, 127.4, 122.3, 117.2, 87.7, 82.7, 76.6, 73.3, 72.9, 72.6, 72.5, 71.7, 50.9, 47.2, 40.6, 26.2, 26.2, 25.9, 25.4, 18.3, 18.3, 18.2, −3.7, −3.9, −3.9, −4.0, −4.2, −4.5; **IR** (film, $cm^{-1}$): 3517, 2953, 2929, 2896, 2857, 1472, 1254, 1125, 1096, 1037, 1005, 903, 836, 812, 777, 681; **HRMS** (ESI) for $C_{35}H_{66}O_6Si_3Na$ $[M+Na]^{+}$ calcd. 689.4059; found 689.4062.

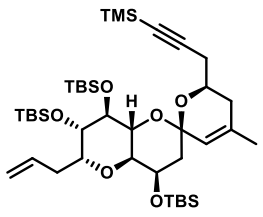
**Compound 64.**




*n*-Butyllithium (1.6 M in hexanes, 2.2 mL, 3.5 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (0.53 mL, 3.8 mmol) in anhydrous THF (25 mL) at −78 °C. The resulting solution was stirred at this temperature for 20 min. Boron trifluoride etherate (0.43 mL, 3.5 mmol) was added dropwise at −78 °C. After stirring at −78 °C for 5 min, a solution of epoxide **63** (1.1 g, 1.6 mmol) in THF (2.0 mL, 2 × 1.5 mL wash) was added *via* cannula at −78 °C. After 1 h of stirring at this temperature, the reaction was quenched by adding brine (30 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL) and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 20:1) to give the title compound as a colorless oil (1.2 g, 97%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +28.9 (c = 1.16, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.84 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1H), 5.36 (d, *J* = 2.0 Hz, 1H), 5.31 – 5.23 (m, 1H), 5.14 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.13 – 5.05 (m, 1H), 4.13 (dt, *J* = 8.4, 4.4 Hz, 1H), 4.02 (d, *J* = 8.1 Hz, 1H), 3.84 – 3.75 (m, 2H), 3.70 – 3.51 (m, 3H), 3.41 (d, *J* = 5.8 Hz, 1H), 2.65 (dd, *J* = 17.3, 4.2 Hz, 1H), 2.57 (dd, *J* = 17.3, 4.6 Hz, 1H), 2.54 – 2.37 (m, 4H), 2.34 (ddd, *J* = 13.7, 7.6, 0.9 Hz, 1H), 2.31 – 2.20 (m, 2H), 0.92 (s, 9H), 0.90 (s, 9H), 0.90 (s, 9H), 0.16 (s, 12H), 0.13 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 135.1, 128.1, 123.3,

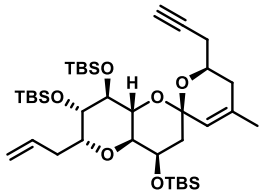
117.3, 103.1, 88.1, 87.7, 82.4, 76.3, 73.4, 73.2, 72.7, 72.6, 72.0, 68.3, 44.3, 32.5, 28.0, 26.3, 26.2, 25.9, 25.5, 18.4, 18.3, 18.2, 0.3, –3.7, –3.9, –3.9, –3.9, –4.2, –4.4; **IR** (film, $cm^{-1}$): 3518, 2954, 2930, 2897, 2858, 2177, 1472, 1251, 1125, 1096, 1029, 1005, 913, 837, 777, 681; **HRMS** (ESI) for $C_{40}H_{76}O_6Si_4Na$ $[M+Na]^{+}$ calcd. 787.4611; found 787.4620.

**Compound 68.**




(Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**36**, 77 mg, 0.10 mmol) and pyridinium *p*-toluenesulfonate (25 mg, 0.10 mmol) were added to a solution of enyne **64** (0.96 g, 1.2 mmol) in $CH_2Cl_2$ (12 mL). The mixture was stirred at room temperature for 1.5 h before the reaction was quenched with triethylamine (1.0 mL). Saturated aqueous $NH_4Cl$ (20 mL) and *tert*-butyl methyl ether (30 mL) were added and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic fractions were washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 80:1) to give the title compound (0.71 g, 74%) as a pale yellow oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +26.9 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.18 (s, 1H), 5.09 (dd, *J* = 17.2, 1.9 Hz, 1H), 5.03 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.12 (tdd, *J* = 8.8, 6.8, 4.2 Hz, 1H), 3.99 (q, *J* = 3.0 Hz, 1H), 3.92 – 3.78 (m, 2H), 3.68 – 3.55 (m, 2H), 3.29 (dd, *J* = 10.1, 2.8 Hz, 1H), 2.59 (dd, *J* = 16.6, 4.9 Hz, 1H), 2.47 – 2.39 (m, 2H), 2.30 (dd, *J* = 16.6, 9.0 Hz, 1H), 1.98 (dd, *J* = 17.2, 4.0 Hz, 1H), 1.93 – 1.88 (m, 1H), 1.84 (dd, *J* = 14.2, 3.0 Hz, 1H), 1.71 (s, 3H), 1.67 (dd, *J* = 14.3, 3.3 Hz, 1H), 0.91 (s, 9H), 0.91 (s, 9H), 0.87 (s, 9H), 0.15 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.05 (s, 6H), 0.01 (s, 3H), −0.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 135.7, 124.4, 116.2, 103.8, 95.4, 86.1, 76.3, 74.2, 73.2, 70.3, 68.7, 66.7, 65.7, 42.3, 34.3, 29.6, 27.1, 26.6, 26.4, 26.0, 22.9, 18.5, 18.4, 18.3, 0.3, −3.4, −3.6, −4.2, −4.2, −5.2; **IR** (film, $cm^{-1}$): 2955, 2928, 2887, 2856, 2183, 1473, 1463, 1383, 1361, 1250, 1204, 1130, 1091, 1037, 1005, 968, 912, 858, 837, 775, 674; **HRMS** (ESI) for $C_{40}H_{76}O_6Si_4Na$ $[M+Na]^{+}$ calcd. 787.4611; found 787.4624.

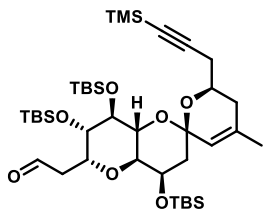
**Compound 72.**




2,6-Di-*tert*-butylpyridine (53 μL, 0.24 mmol) and (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**36**, 4.5 mg, 5.9 μmol) were added to a solution of enyne **64** (90 mg, 0.12 mmol) in 1,2-DCE (5.0 mL) in a microwave vial at room temperature. The vial was sealed and the mixture was stirred at 100 °C under microwave irradiation for 15 min. After cooling to ambient temperature, the mixture was filtered over a silica plug and washed with *tert*-butyl methyl ether. The combined filtrates were concentrated.

The residue was taken up in acetic acid (2.0 mL) and the mixture was stirred at room temperature for 14 h, then diluted with *tert*-butyl methyl ether (10 mL) and cooled to 0 °C. Saturated aq. $NaHCO_3$ (5 mL) was added slowly and additional solid $NaHCO_3$ was added until no more gas evolution was observed. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 5 mL) and the combined organic fractions were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 80:1) to give the title compound as a pale yellow oil (50 mg, 61%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +38.9 (c = 0.90, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.19 (q, *J* = 1.6 Hz, 1H), 5.09 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.04 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 4.15 (tt, *J* = 8.5, 5.5 Hz, 1H), 4.00 (q, *J* = 3.0 Hz, 1H), 3.88 (td, *J* = 7.0, 2.1 Hz, 2H), 3.67 – 3.57 (m, 2H), 3.30 (dd, *J* = 10.1, 2.8 Hz, 1H), 2.51 (ddd, *J* = 16.5, 5.1, 2.7 Hz, 1H), 2.46 – 2.38 (m, 2H), 2.29 (ddd, *J* = 16.5, 8.3, 2.7 Hz, 1H), 2.02 – 1.91 (m, 3H), 1.86 (dd, *J* = 14.2, 2.9 Hz, 1H), 1.74 – 1.64 (m, 4H), 0.91 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 135.8, 124.4, 116.2, 95.4, 81.2, 76.3, 74.3, 73.0, 70.3, 69.9, 68.7, 66.7, 65.5, 42.2, 34.1, 29.7, 26.5, 26.4, 26.0, 25.4, 22.8, 18.5, 18.4, 18.3, 1.2, −3.5, −3.5, −3.6, −4.2, −4.2, −5.2; **IR** (film, $cm^{-1}$): 3315, 2928, 2856, 1472, 1383, 1361, 1252, 1204, 1088, 1037, 1005, 969, 912, 859, 834, 774, 672, 636, 463; **HRMS** (ESI) for $C_{37}H_{69}O_6Si_3$ $[M+H]^+$: calcd. 693.4397; found 693.4392.

**Compound 74.**

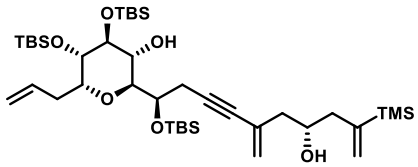



***Dihydroxylation***: AD-mix β (1.08 g) and $MeSO_2NH_2$ (73.5 mg, 0.772 mmol) were added sequentially to a pre-stirred solution of **68** (591 mg, 0.772 mmol) in *tert*-butanol/water (7 mL, *v*/*v* 1:1). The mixture was stirred at room temperature for 24 h. The reaction was quenched with saturated aq. $Na_2S_2O_3$ (7 mL) and diluted with EtOAc (7 mL). The biphasic mixture was stirred until it turned colorless (ca. 5 min), then the aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic layers were washed with saturated aq. NaOH (2.0 M, 15 mL) and brine (15 mL), dried over $Na_2SO_4$ and concentrated. The residue was filtered over a silica plug and the silica gel was washed with EtOAc (3 × 5 mL). The filtrate was concentrated to give the diol, which was used in the next step without further purification.

***Oxidative cleavage of the diol***: Sodium periodate on silica (1.94 g, 17 wt. %, 1.54 mmol) was added to a solution of the diol (prepared as above) in $CH_2Cl_2$ (8 mL) at room temperature. The mixture was stirred at this temperature for 3 h, then filtered through a cotton plug, and the silica gel was washed with *tert*-butyl methyl ether (3 × 5 mL). The filtrate was concentrated to afford the title compound as a colorless oil (574 mg, 97% over two steps). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{22}}$ = +9.6 (c = 1.26, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.76 – 9.73 (m, 1H), 5.15 (p, *J* = 1.2 Hz, 1H), 4.52 (ddd, *J* = 10.5, 5.1, 3.8 Hz, 1H), 4.10 (dddd, *J* = 10.6, 8.8, 4.9, 3.9 Hz, 1H), 3.95 (q, *J* = 3.0 Hz, 1H), 3.86 (dd, *J*

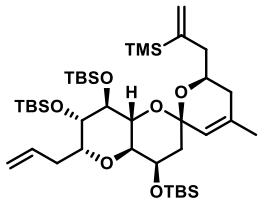
= 10.1, 8.3 Hz, 1H), 3.66 (dd, *J* = 8.2, 5.1 Hz, 1H), 3.55 (t, *J* = 8.2 Hz, 1H), 3.30 (dd, *J* = 10.1, 2.8 Hz, 1H), 2.85 – 2.67 (m, 2H), 2.57 (dd, *J* = 16.7, 4.9 Hz, 1H), 2.30 (dd, *J* = 16.6, 8.9 Hz, 1H), 1.97 (dd, *J* = 17.2, 3.9 Hz, 1H), 1.90 (ddd, *J* = 10.7, 2.4, 1.2 Hz, 1H), 1.83 (dd, *J* = 14.3, 3.0 Hz, 1H), 1.70 (s, 3H), 1.65 (dd, *J* = 14.3, 3.2 Hz, 1H), 0.90 (s, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.15 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.04 (s, 6H), −0.01 (s, 3H), −0.03 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 201.5, 135.8, 124.2, 103.7, 95.4, 86.1, 73.5, 73.2, 72.0, 71.0, 68.4, 66.4, 65.9, 42.2, 41.2, 34.3, 27.0, 26.6, 26.4, 25.9, 22.8, 18.4, 18.3, 18.2, 0.3, −3.4, −3.5, −3.6, −4.2, −4.3, −5.1; **IR** (film, $cm^{-1}$): 2955, 2929, 2888, 2857, 1732, 1473, 1463, 1383, 1361, 1250, 1204, 1124, 1094, 1040, 1007, 982, 965, 838, 776, 673; **HRMS** (ESI) for $C_{39}H_{74}O_7Si_4Na$ $[M+Na]^+$: calcd. 789.4404; found 789.4404.

**Compound 65.**




Copper(I) iodide (23 mg, 0.12 mmol) was added to a solution of alkyne **32** (0.48 g, 0.81 mmol) in degassed diisopropylamine (6 mL). The mixture was stirred at room temperature for 10 min. A solution of alkenyl iodide **37** (0.27 g, 0.87 mmol) in diisopropylamine (1 mL, 2 × 1 mL wash) was added, followed by triphenylphosphine (43 mg, 0.16 mmol) and tris(dibenzylideneacetone)dipalladium(0) (37 mg, 41 μmol). The mixture was stirred for 1 h at room temperature before the reaction mixture was quenched at 0 °C by addition of saturated aqueous $NH_4Cl$ (20 mL). The mixture was diluted with *tert*-butyl methyl ether (20 mL), allowed to warm to room temperature, and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 15:1) to afford the title compound as a colorless oil (0.60 g, 96%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +28.2 (c = 1.24, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.83 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.69 (dd, *J* = 2.9, 1.4 Hz, 1H), 5.48 (d, *J* = 3.0 Hz, 1H), 5.35 (d, *J* = 2.1 Hz, 1H), 5.29 – 5.21 (m, 1H), 5.12 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.11 – 5.03 (m, 1H), 4.19 – 4.10 (m, 1H), 3.98 (tt, *J* = 8.7, 5.0 Hz, 1H), 3.84 – 3.74 (m, 2H), 3.62 (dt, *J* = 8.7, 5.8 Hz, 2H), 3.55 (dd, *J* = 6.3, 3.5 Hz, 1H), 3.37 (d, *J* = 5.7 Hz, 1H), 2.66 (dd, *J* = 17.3, 4.3 Hz, 1H), 2.55 (dd, *J* = 17.2, 4.9 Hz, 1H), 2.48 – 2.35 (m, 2H), 2.36 – 2.18 (m, 4H), 1.96 (d, *J* = 2.5 Hz, 1H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.15 (s, 3H), 0.13 (d, *J* = 1.4 Hz, 9H), 0.11 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 149.3, 135.1, 128.8, 127.7, 122.9, 117.2, 87.9, 82.7, 77.4, 76.6, 73.3, 73.1, 72.6, 71.8, 68.3, 45.2, 43.9, 32.6, 26.3, 26.2, 25.9, 25.4, 18.3, 18.2, 18.2, −1.2, −3.7, −3.9, −3.9, −4.0, −4.2, −4.4; **IR** (film, $cm^{-1}$): 3517, 2953, 2929, 2857, 1472, 1250, 1096, 835, 777, 682; **HRMS** (ESI) for $C_{40}H_{78}O_6Si_4Na$ $[M+Na]^+$: calcd. 789.4768; found 789.4777.

**Compound 69.**

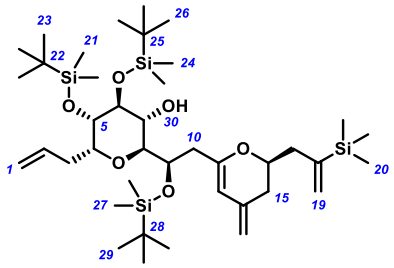



2,6-Di-*tert*-butylpyridine (0.13 mL, 0.59 mmol) and (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**36**, 22 mg, 28 μmol) were added to a solution of enyne **65** (0.43 g, 0.56 mmol) in $CH_2Cl_2$ (5.5 mL) at 0 °C. The mixture was stirred at 0 °C for 5 h and then directly filtered through Celite. The filtrate was concentrated to afford the corresponding enol ether contaminated with residual pyridine base.

The residue was taken up in acetic acid (5.5 mL) and the mixture was stirred at room temperature for 30 min, then diluted with *tert*-butyl methyl ether (20 mL) and cooled to 0 °C. Saturated aq. $NaHCO_3$ (10 mL) was added slowly and additional solid $NaHCO_3$ was added until no more gas evolution was observed. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 8 mL) and the combined organic fractions were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 100:1) to give the title compound as a pale yellow oil (0.38 g, 89%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +44.9 (c = 1.12, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.82 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.77 – 5.71 (m, 1H), 5.42 (dd, *J* = 3.0, 1.3 Hz, 1H), 5.18 (p, *J* = 1.3 Hz, 1H), 5.09 (dd, *J* = 17.3, 1.8 Hz, 1H), 5.08 – 5.00 (m, 1H), 4.15 (ddt, *J* = 10.4, 8.8, 4.5 Hz, 1H), 4.01 (q, *J* = 3.0 Hz, 1H), 3.95 – 3.82 (m, 2H), 3.67 (t, *J* = 8.4 Hz, 1H), 3.61 (dd, *J* = 8.5, 4.9 Hz, 1H), 3.28 (dd, *J* = 10.0, 2.9 Hz, 1H), 2.54 (ddt, *J* = 15.3, 5.0, 1.8 Hz, 1H), 2.47 – 2.38 (m, 2H), 2.16 (dd, *J* = 15.2, 8.3 Hz, 1H), 1.91 – 1.69 (m, 4H), 1.72 – 1.63 (m, 5H), 0.92 (s, 9H), 0.89 (s, 8H), 0.88 (s, 7H), 0.11 (s, 3H), 0.09 (s, 12H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 4H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 148.2, 135.9, 135.6, 125.7, 124.4, 116.2, 95.0, 76.5, 74.2, 73.4, 70.7, 68.7, 66.8, 66.1, 42.5, 40.9, 34.9, 29.8, 26.5, 26.4, 26.1, 22.9, 18.7, 18.6, 18.4, −1.6, −3.5, −3.5, −3.7, −4.1, −4.3, −5.1; **IR** (film, $cm^{-1}$): 2953, 2928, 2857, 1472, 1250, 1205, 1090, 1038, 968, 836, 776, 671; **HRMS** (ESI) for $C_{40}H_{79}O_6Si_4$ $[M+H]^+$: calcd. 767.4948; found 767.4952.

**Note**: The structure of the intermediate enol ether **73** was elucidated by NMR spectroscopy using $^1$H, $^{13}$C, COSY, HSQC, HMBC, and NOESY experiments (Table 6.2).

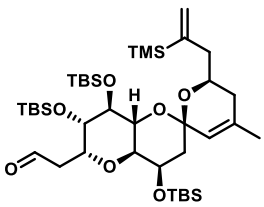
**Table 6.2.** Detailed NMR data of **73**; numbering scheme as shown in the insert.




| atom number | **$^1$H NMR** ($CDCl_3$, 500 MHz) | | | **$^{13}$C NMR** ($CDCl_3$, 126 MHz) | |
|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **δ** [ppm] | **HMBC** |
| 1-*cis* | 5.06 | 1.9 (1-*trans*), 10.3 (2) | 2 | 116.9 | |
| 1-*trans* | 5.1 | 17.2 (2), 1.9 (1-*cis*) | 2 | | |
| 2 | 5.82 | 17.2 (1-*trans*), 10.3 (1-*cis*) | 1-*cis*, 1-*trans*, 3', 3'' | 135.1 | 3', 3'' |
| 3' | 2.38 | - | 2, 4 | 32.4 | 1-*cis*, 1-*trans* |
| 3'' | 2.26 | - | 2, 4 | | |
| 4 | 3.83 | 9.8, 4.0, 4.0 | 3', 3'', 5 | 72.7 | 5 |
| 5 | 3.55 | 5.8 (6) | 4, 6 | 72.4 | 3', 6 |
| 6 | 3.79 | 5.8 (5), 6.0 (7) | 5, 7 | 73.3 | 5, 7 |
| 7 | 3.62 | 6.0 (8), 6.0 (30), 6.0 (6) | 6, 8, 30 | 71 | 5, 6, 8 |
| 8 | 3.56 | 6.0 (7) | 7, 9 | 78 | 7, 9, 10 |
| 9 | 4.35 | - | 8, 10', 10'' | 70.7 | 8, 10'' |
| 10' | 2.56 | - | 9 | 39.5 | 8, 12 |
| 10'' | 2.21 | - | 9 | | |
| 11 | - | - | - | 154.3 | 10', 10'', 12 |
| 12 | 5.32 | - | - | 104 | 10'', 14', 14'' |
| 13 | - | - | - | 137.9 | 15', 15'' |
| 14' | 4.61 | - | 14'' | 105 | 12 |
| 14'' | 4.41 | - | 14' | | |
| 15' | 2.38 | - | 16 | 34.5 | 12, 14', 14'', 17', 17'' |
| 15'' | 2.18 | - | 16 | | |
| 16 | 4.06 | - | 15', 15'', 17', 17'' | 75.3 | 15', 15'', 17', 17'' |
| 17' | 2.57 | - | 16 | 41.3 | - |
| 17'' | 2.35 | - | 16 | | |
| 18 | - | - | - | 147.8 | 17', 17'', 19', 19'', 20, 20', 20'' |
| 19' | 5.65 | - | 19'' | 127.5 | 17', 17'' |
| 19'' | 5.45 | - | 19' | | |
| 20 | 0.1 | - | - | –1.38 | 18 |
| 21, 24, 27 | 0.06 – 0.14 | - | - | –4.66 – –3.71 | - |

| atom number | **$^1$H NMR** ($CDCl_3$, 500 MHz) | | | **$^{13}$C NMR** ($CDCl_3$, 126 MHz) | |
|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **δ** [ppm] | **HMBC** |
| 22, 25, 28 | - | - | - | 18.1 – 18.2 | - |
| 23, 26, 29 | 0.86 – 0.93 | - | - | 25.9 – 26.1 | - |
| 30 | 3.07 | 6.0 (7) | 7 | - | - |

**Compound 78.**

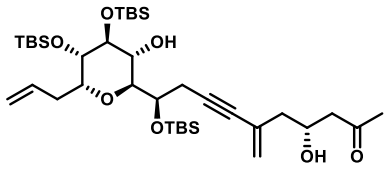



***Diboration***: A solution of **69** (60 mg, 78 μmol) in toluene (0.2 mL) was added to a pre-stirred solution of tris(dibenzylideneacetone)-platinum(0) (2.1 mg, 2.3 μmol) and bis(pinacolato)diboron (24 mg, 93 μmol) in toluene (0.3 mL). The mixture was stirred at room temperature for 3 h and then concentrated. The residue was directly purified by flash chromatography (hexanes/EtOAc 20:1) to give an inconsequential mixture of diastereoisomers of the diborated product **76** as a pale yellow oil (73 mg, 92%, dr 1.9:1.0 by $^1$H NMR).

***Oxidation of the diboronate***: Sodium perborate monohydrate (46 mg, 0.23 mmol) was added to a solution of the diboronate (39 mg, 38 μmol, prepared as above) in THF/water (0.4 mL, 3:1 *v*/*v*) in one portion at 0 °C. The resulting white slurry was stirred at room temperature for 14 h. The mixture was concentrated and the residue directly purified by flash chromatography (hexanes/EtOAc 2:1) to give an inconsequential mixture of diastereoisomers of the diol **77** as a colorless oil (30 mg, 96%, dr 1.9:1 by $^1$H NMR).

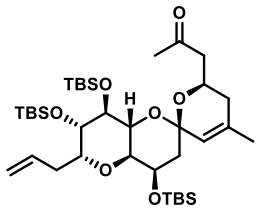
***Oxidative cleavage of the diol***:[193] Sodium periodate on silica (49 mg, 14% *w*/*w*, 32 μmol) was added to a solution of the diol (13 mg, 16 μmol, prepared as above) in $CH_2Cl_2$ (0.3 mL) at room temperature. The mixture was stirred at this temperature for 3 h, then filtered through a cotton plug, and the silica gel was washed with *tert*-butyl methyl ether (3 × 1 mL). The filtrate was concentrated to afford the title compound as a colorless oil (12 mg, 97%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +31.2 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.75 (dd, *J* = 3.8, 1.4 Hz, 1H), 5.72 (dq, *J* = 3.1, 1.4 Hz, 1H), 5.44 – 5.39 (m, 1H), 5.15 (dt, *J* = 2.5, 1.3 Hz, 1H), 4.54 (dt, *J* = 10.2, 4.4 Hz, 1H), 4.13 (ddt, *J* = 10.4, 8.8, 4.4 Hz, 1H), 3.97 (q, *J* = 3.0 Hz, 1H), 3.89 (dd, *J* = 10.0, 8.1 Hz, 1H), 3.71 – 3.56 (m, 2H), 3.30 (dd, *J* = 10.0, 2.9 Hz, 1H), 2.85 – 2.66 (m, 2H), 2.53 (ddt, *J* = 15.3, 4.9, 1.8 Hz, 1H), 2.15 (dd, *J* = 15.3, 8.3 Hz, 1H), 1.90 – 1.73 (m, 3H), 1.69 – 1.60 (m, 4H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.09 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), −0.00 (s, 3H), −0.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 201.6, 148.2, 135.8, 125.6, 124.2, 95.1, 73.6, 73.4, 72.1, 71.4, 68.3, 66.5, 66.2, 42.5, 41.4, 40.9, 34.9, 26.5, 26.4, 26.0, 22.9, 18.7, 18.5, 18.3, −1.6, −3.5, −3.6, −3.7, −4.2, −4.3, −5.0; **IR** (film, $cm^{-1}$): 2954, 2928, 2856, 1732, 1472, 1379, 1250, 1205, 1094, 1041, 1007, 967, 836, 776, 671; **HRMS** (ESI) for $C_{39}H_{76}O_7Si_4Na$ $[M+Na]^+$: calcd. 791.4560; found 791.4554.

**Compound 66.**




Copper(I) iodide (57 mg, 0.30 mmol) was added to a solution of alkyne **32** (1.2 g, 2.0 mmol) in degassed diisopropylamine (10 mL). The mixture was stirred at room temperature for 10 min. A solution of alkenyl iodide **39** (0.55 g, 2.2 mmol) in diisopropylamine (2 mL, 2 × 2 mL wash) was added, followed by triphenylphosphine (0.11 g, 0.40 mmol) and tris(dibenzylideneacetone)dipalladium(0) (91 mg, 0.10 mmol). The resulting mixture was stirred for 4 h at room temperature before the reaction was quenched at 0 °C by addition of saturated aqueous $NH_4Cl$ (30 mL). The mixture was diluted with *tert*-butyl methyl ether (30 mL), allowed to warm to room temperature, and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc 5:1) to afford the desired enyne (1.3 g, 93%) as a colorless oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +21.9 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.85 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.35 (d, *J* = 2.0 Hz, 1H), 5.26 – 5.23 (m, 1H), 5.18 – 5.07 (m, 2H), 4.32 (tdt, *J* = 7.1, 6.1, 3.5 Hz, 1H), 4.14 (dt, *J* = 8.2, 4.3 Hz, 1H), 3.87 – 3.74 (m, 2H), 3.68 – 3.57 (m, 2H), 3.56 (dd, *J* = 6.3, 3.5 Hz, 1H), 3.42 (d, *J* = 6.1 Hz, 1H), 3.03 (d, *J* = 3.8 Hz, 1H), 2.72 – 2.51 (m, 4H), 2.49 – 2.33 (m, 2H), 2.30 – 2.20 (m, 2H), 2.18 (s, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), 0.13 (s, 6H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 209.4, 135.1, 128.1, 123.2, 117.3, 88.0, 82.5, 73.3, 73.1, 72.6, 72.4, 71.8, 66.4, 49.2, 44.5, 32.6, 30.9, 26.3, 26.2, 25.9, 25.4, 18.4, 18.3, 18.2, −3.7, −3.9, −3.9, −4.0, −4.2, −4.4; **IR** (film, $cm^{-1}$): 3523, 2953, 2930, 2896, 2857, 1712, 1472, 1410, 1389, 1361, 1254, 1125, 1096, 1035, 1005, 937, 902, 860, 837, 777, 680; **HRMS** (ESI) for $C_{37}H_{70}O_7Si_3Na$ $[M+Na]^+$: calcd. 733.4322; found 733.4320.

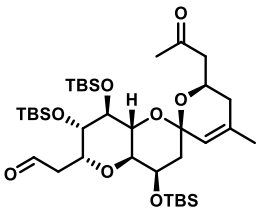
**Compound 70.**




(Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**36**, 3.8 mg, 4.9 μmol) and pyridinium *p*-toluenesulfonate (1.2 mg, 4.9 μmol) were added to a solution of enyne **66** (35 mg, 49 μmol) in $CH_2Cl_2$ (0.5 mL). The mixture was stirred at room temperature for 2 h and then quenched with triethylamine (0.1 mL). Saturated aqueous $NH_4Cl$ (2 mL) and *tert*-butyl methyl ether (2 mL) were added and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 2 mL). The combined organic fractions were washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 30:1) to give the title compound (27 mg, 78%) as a pale yellow oil. The reaction was repeated on a 1.7 mmol-scale to afford the desired product in 65% yield (730 mg). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +51.1 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.17 (p, *J* = 1.2 Hz, 1H), 5.14 –

4.99 (m, 2H), 4.34 (dtd, *J* = 10.5, 6.4, 4.0 Hz, 1H), 4.01 (q, *J* = 3.0 Hz, 1H), 3.95 – 3.79 (m, 2H), 3.69 – 3.56 (m, 2H), 3.30 (dd, *J* = 10.1, 2.8 Hz, 1H), 2.74 (dd, *J* = 16.0, 6.1 Hz, 1H), 2.52 (dd, *J* = 16.1, 6.8 Hz, 1H), 2.42 (ddt, *J* = 8.3, 6.8, 1.5 Hz, 2H), 2.23 (s, 3H), 1.96 – 1.76 (m, 3H), 1.74 – 1.65 (m, 4H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 207.2, 135.7, 135.5, 124.4, 116.3, 95.2, 76.3, 74.3, 73.2, 70.3, 68.8, 66.8, 64.0, 50.2, 42.5, 34.8, 30.9, 29.7, 26.4, 26.1, 22.8, 18.6, 18.4, 18.3, −3.5, −3.5, −3.6, −4.2, −4.2, −5.1; **IR** (film, $cm^{-1}$): 2953, 2928, 2887, 2856, 1720, 1472, 1463, 1387, 1361, 1252, 1204, 1156, 1130, 1089, 1060, 1039, 1005, 971, 913, 858, 835, 807, 776, 672; **HRMS** (ESI) for $C_{37}H_{70}O_7Si_3Na$ [M+Na]$^+$: calcd. 733.4322; found 733.4320.

**Compound 79.**

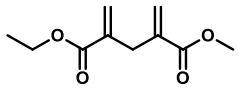



2,6-Lutidine (0.16 mL, 1.4 mmol), osmium tetroxide (51 μL, 4% in water, 70 μmol) and sodium periodate (0.60 g, 2.8 mmol) were sequentially added to a stirred solution of spiroketal **70** (0.50 g, 0.70 mmol) in 1,4-dioxane/$H_2O$ (3:1, 12 mL) at room temperature. The resulting mixture was stirred at room temperature for 20 h before the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NH_4Cl$ (10 mL) and brine (10 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (pentane/*tert*-butyl methyl ether 20:1 to 15:1) to afford the aldehyde (0.43 g, 87%) as a pale yellow oil.[85] When performed on a 0.04 mmol-scale, the desired product was obtained in 93% yield. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +35.9 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.75 (dd, *J* = 3.8, 1.4 Hz, 1H), 5.15 (s, 1H), 4.53 (dt, *J* = 9.9, 4.3 Hz, 1H), 4.32 (dp, *J* = 10.5, 3.9, 3.3 Hz, 1H), 3.97 (d, *J* = 3.0 Hz, 1H), 3.87 (dd, *J* = 10.1, 8.1 Hz, 1H), 3.71 – 3.51 (m, 2H), 3.32 (dd, *J* = 10.1, 2.8 Hz, 1H), 2.86 – 2.66 (m, 3H), 2.51 (dd, *J* = 16.2, 6.9 Hz, 1H), 2.21 (s, 3H), 1.97 – 1.76 (m, 3H), 1.74 – 1.63 (m, 4H), 0.91 (s, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.05 (s, 6H), 0.00 (s, 3H), −0.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 206.9, 201.4, 135.6, 124.2, 95.2, 73.6, 73.2, 71.9, 71.0, 68.4, 66.5, 64.1, 50.1, 42.4, 41.3, 34.8, 30.9, 26.4, 26.0, 22.7, 18.6, 18.3, 18.3, −3.5, −3.6, −3.6, −4.2, −4.3, −5.0; **IR** (film, $cm^{-1}$): 2954, 2929, 2888, 2856, 1729, 1472, 1463, 1387, 1361, 1252, 1204, 1157, 1130, 1093, 1042, 1006, 979, 959, 836, 807, 776, 671; **HRMS** (ESI) for $C_{36}H_{68}O_8Si_3Na$ [M+Na]$^+$: calcd. 735.4114; found 735.4112.

### 6.2.2 Synthesis of the Northern Fragment

#### 6.2.2.1 Synthesis of the Diene Fragment

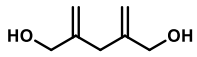
**1-Ethyl 5-methyl 2,4-dimethylenepentanedioate (81).**[37]



A solution of DABCO (897 mg, 8.00 mmol) in methyl acrylate (4 mL) was slowly added to methyl 2-(bromomethyl)prop-2-enoate (**80**, 772 mg, 4.00 mmol), leading to the formation of a white precipitate. The resulting suspension was stirred at room temperature for 7 d. The reaction mixture was diluted with *tert*-butyl methyl ether (30 mL) and washed successively with aq. HCl (2 M) and water. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc 15:1) to provide the desired product (557 mg, 70%). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 6.25 (m, 2H), 5.60 (app q, *J* = 1.3 Hz, 1H), 5.58 (app q, *J* = 1.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.35 – 3.29 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 166.9, 166.4, 137.8, 137.6, 126.7, 126.5, 60.6, 51.8, 33.6, 14.0; **IR** (film, $cm^{-1}$): 2984, 2954, 1700, 1632, 1438, 1211, 1137, 951; **HRMS** (EI) for $C_{10}H_{14}O_4$ $[M+H]^{+\cdot}$ calcd. 198.0887; found 198.0884.

**Note**: Compound **81** is rather unstable upon contact with silica; therefore the yield after flash chromatography is variable. It is therefore recommended to skip the purification and reduce the crude material with DIBAL-H as described below.

**2,4-Dimethylenepentane-1,5-diol (82).**

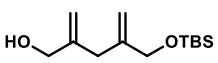


A solution of DABCO (1.80 g, 16.0 mmol) in methyl acrylate (8 mL) was slowly added to methyl 2-(bromomethyl)prop-2-enoate (**80**, 1.54 g, 8.00 mmol), leading to the formation of a white precipitate. The resulting suspension was stirred at room temperature for 7 d before the mixture was diluted with *tert*-butyl methyl ether (50 mL) and washed successively with aq. HCl (2 M) and water. The organic layer was dried over anhydrous $Na_2SO_4$. *tert*-Butyl methyl ether was carefully removed under vacuum (300 mbar) at 25 °C. Next, the pressure was gradually reduced and excess methyl acrylate was distilled off at 80 mbar at 25 °C (an aliquot of the crude was examined by $^1$H NMR to ensure that most of the methyl acrylate had been removed).

A solution of DIBAL-H (40 mL, 1.0 M in THF, 40 mmol) was slowly added to a solution of the residue in THF (60 mL) at 0 °C. The cooling bath was removed and the mixture was stirred for 5 h. The reaction was quenched at 0 °C with Rochelle's salt solution (20 mL) and the resulting mixture was vigorously stirred overnight before the aqueous layer was extracted with EtOAc (6 × 30 mL). It was essential to use EtOAc and the extraction must be performed repeatedly to recover the diol from the aqueous phase. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography

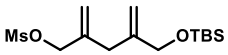
(hexanes/EtOAc 1:2) to give the title compound as a colorless oil (581 mg, 57%). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.13 (d, *J* = 1.5 Hz, 2H), 4.98 – 4.97 (m, 2H), 4.09 (d, *J* = 4.2 Hz, 4H), 2.90 (s, 2H), 1.64 (t, *J* = 5.0 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 146.3, 112.5, 65.7, 37.4; **IR** (film, $cm^{-1}$): 3300, 3088, 2917, 2858, 1646, 1433, 1261, 1055, 1021, 899; **HRMS** (ESI) for $C_7H_{12}O_2Na$ [M+Na]$^+$: calcd. 151.0729; found 151.0730.

**4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methylenepent-4-en-1-ol (83).**



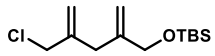

A solution of diol **82** (760 mg, 5.93 mmol) in THF (5 mL) was added dropwise at 0 °C to a suspension of NaH (157 mg, 6.52 mmol) in THF (15 mL). The resulting mixture was stirred for 45 min at ambient temperature before *tert*-butylchlorodimethylsilane (983 mg, 6.52 mmol) was added in one batch and stirring was continued for an additional 2 h. The reaction was carefully quenched with $H_2O$ and the resulting mixture extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried with $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 9:1 to 4:1) to provide the title compound as a colorless oil (1.25 g, 87 % yield). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.14 (d, *J* = 1.8 Hz, 1H), 5.11 (d, *J* = 1.5 Hz, 1H), 4.94 (d, *J* = 1.3 Hz, 1H), 4.92 (d, *J* = 1.9 Hz, 1H), 4.07 (d, *J* = 6.2 Hz, 2H), 4.06 (s, 2 H), 2.83 (s, 2H), 1.64 (t, *J* = 6.2 Hz, 1H), 0.91 (s, 9H), 0.07 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 146.4, 145.9, 111.9, 111.5, 65.7, 37.2, 26.1, 18.5, −5.2; **IR** (film, $cm^{-1}$): 3329, 3079, 2929, 2857, 1648, 1472, 1255, 1109, 836; **HRMS** (ESI) for $C_{13}H_{26}O_2SiNa$ [M+Na]$^+$: calcd. 265.1594; found 265.1594.

**4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methylenepent-4-en-1-yl methanesulfonate (84).**




MsCl (344 mg, 3.00 mmol) was added dropwise to a solution of the allylic alcohol **83** (364 mg, 1.50 mmol) and triethylamine (455 mg, 4.50 mmol) in $CH_2Cl_2$ (6 mL) at 0 °C. The cooling bath was removed after 15 min and stirring was continued for 2 h. Water (10 mL) was added to quench the reaction. The resulting mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), and the combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, and concentrated. The residue was subjected to flash chromatography (hexanes/EtOAc 10:1) to give the title compound as pale yellow oil (421 mg, 88%). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.29 – 5.26 (m, 1H), 5.19 (d, *J* = 1.7 Hz, 1H), 5.16 – 5.14 (m, 1H), 4.92 (d, *J* = 1.5 Hz, 1H), 4.64 (s, 2H), 4.04 (s, 2H), 3.01 (s, 3H), 2.87 (s, 2H), 0.91 (s, 9H), 0.06 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 144.8, 139.6, 117.6, 112.1, 71.5, 65.3, 38.0, 36.8, 26.0, 18.5, −5.3; **IR** (film, $cm^{-1}$): 2955, 2857, 1649, 1463, 1359, 1176, 1109, 836; **HRMS** (ESI) for $C_{14}H_{28}O_4SSiNa$[M+Na]$^+$: calcd. 343.1370; found 343.1370.

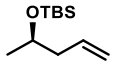
***tert*-Butyl((4-(chloromethyl)-2-methylenepent-4-en-1-yl)oxy)dimethyl-silane (85).**




Anhydrous LiCl (30 mg, 0.70 mmol) was added to a solution of mesylate **84** (75 mg, 0.23 mmol) in THF (0.8 mL). The reaction mixture was stirred at 40 °C for 24 h, causing the formation of a white suspension. After reaching ambient temperature, the reaction was quenched with brine (2 mL) and the resulting mixture was extracted with *tert*-butyl methyl ether (3 × 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated to afford the desired allyl chloride (59 mg, 98%) as a colorless oil, which was used without further purification. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.21 (s, 1H), 5.18 (d, *J* = 1.8 Hz, 1H), 5.03 (d, *J* = 1.3 Hz, 1H), 4.93 (d, *J* = 1.8 Hz, 1H), 4.04 (s, 2H), 4.03 (d, *J* = 0.9 Hz, 2H), 2.92 (s, 2H), 0.91 (s, 9H), 0.06 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 145.1, 142.8, 116.7, 111.8, 65.3, 47.5, 37.1, 26.1, 18.5, −5.2; **IR** (film, $cm^{-1}$): 2955, 2929, 2857, 1645, 1463, 1256, 1109, 836; **HRMS** (ESI) for $C_{13}H_{25}OClSiNa$ $[M+Na]^+$: calcd. 283.1255; found 283.1258.

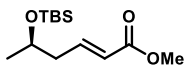
### 6.2.2.2 Synthesis of the Alkenyl Iodide

**(*R*)-*tert*-Butyldimethyl(pent-4-en-2-yloxy)silane (88).**[194]




Imidazole (809 mg, 11.9 mmol) and *tert*-butylchlorodimethylsilane (1.79 g, 11.9 mmol) were sequentially added to a solution of (*R*)-pent-4-en-2-ol (**72**, 854 mg, 9.90 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C. The cooling bath was removed and the mixture was stirred for 2 h, before the reaction was quenched with saturated aq. $NH_4Cl$ (20 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 × 15 mL) and the combined organic layers were washed with water (20 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (pentane/EtOAc 20:1) to give the title compound as a colorless liquid (1.72 g, 87%). $[\boldsymbol{\alpha}]_D^{20}$ = −4.8 (c = 1.20, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.81 (ddt, *J* = 17.4, 10.3, 7.2 Hz, 1H), 5.07 – 5.02 (m, 1H), 5.00 (m, 1H), 3.84 (app h, *J* = 6.1 Hz, 1H), 2.18 (m, 2H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 135.8, 116.7, 68.6, 44.4, 26.0, 23.6, 18.3, −4.4; **IR** (film, $cm^{-1}$): 2958, 2858, 1643, 1463, 1254, 1128, 1089, 833; **HRMS** (ESI) for $C_{11}H_{25}OSi$ $[M+H]^+$: calcd. 201.1669; found 201.1670.

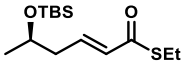
**Methyl (*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)hex-2-enoate (90).**[195]




Compound **88** (200 mg, 1.00 mmol) was dissolved in $CH_2Cl_2$ (7.0 ml) and the resulting solution was degassed for fifteen minutes by bubbling Ar through it, at which point there was only a total volume of ≈3.5 mL left. Freshly distilled methyl acrylate (215 mg, 2.50 mmol) was added, followed by Grubbs II catalyst (42 mg, 50 μmol). The resulting mixture was stirred at reflux temperature for 20 h. After full consumption of the starting material, stirring was continued under air for 1 h to destroy the catalyst. The dark brown solution was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc 20:1 to 10:1) to give the title compound as a colorless syrup (200 mg, 77%). $[\boldsymbol{\alpha}]_D^{20}$

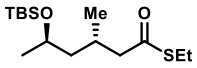
= −5.4 (c = 1.17, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 6.96 (dt, *J* = 15.4, 7.5 Hz, 1H), 5.84 (dt, *J* = 15.7, 1.4 Hz, 1H), 3.93 (app h, *J* = 6.1 Hz, 1H), 3.73 (s, 3H), 2.49 – 2.06 (m, 2H), 1.15 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 167.0, 146.5, 122.9, 67.8, 51.6, 42.6, 26.0, 23.9, 18.2, −4.4, −4.7; **IR** (film, $cm^{-1}$): 2954, 2857, 1727, 1660, 1436, 1321, 1257, 1171, 835; **HRMS** (ESI) for $C_{13}H_{26}O_3SiNa$ [M+Na]$^+$: calcd. 281.1543; found 281.1544.

***S*-Ethyl (*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)hex-2-enethioate (93).**




$Me_3SiSEt$ (269 mg, 2.00 mmol) and $AlCl_3$ (160 mg, 1.20 mmol) were added to a solution of enoate **90** (258 mg, 1.00 mmol) in THF (4.0 mL). The resulting mixture was stirred at reflux temperature for 3 h before the reaction was carefully quenched at room temperature with aqueous phosphate buffer solution (pH 7). The mixture was extracted with *tert*-butyl methyl ether (3 × 10 mL) and the combined organic layers were washed with water (10 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 10:1) to afford the title compound as a pale yellow liquid (210 mg, 73%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −11.9 (c = 0.64, $CHCl_3$); **$^1$H NMR** ($C_6D_6$, 400 MHz): δ 6.98 (dt, *J* = 15.2, 7.5 Hz, 1H), 6.10 (dt, *J* = 15.5, 1.4 Hz, 1H), 3.56 (m, 1H), 2.79 (q, *J* = 7.4 Hz, 2H), 2.07 – 1.75 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.95 (s, 9H), 0.92 (d, *J* = 6.1 Hz, 3H), 0.03 (s, 3H), −0.01 (s, 3H); **$^{13}$C NMR** ($C_6D_6$, 100 MHz): 188.5, 141.7, 130.7, 67.4, 42.0, 25.7, 23.6, 22.9, 17.8, 14.7, −4.8, −5.0; **IR** (film, $cm^{-1}$): 2957, 2929, 2857, 1637, 1638, 1462, 1361, 1255, 1129, 1004, 833; **HRMS** (ESI) for $C_{14}H_{28}O_2SSiNa$ [M+Na]$^+$: calcd. 311.1472; found 311.1474.

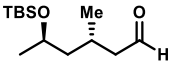
***S*-Ethyl (3*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-methylhexanethioate (95).**




$CuBr{\cdot}SMe_2$ (2.0 mg, 10 μmol) and (*S*,*R*)-Josiphos ((*S*,*R*)-**97**, 7.1 mg, 12 μmol) were added to *tert*-butyl methyl ether (1.6 mL) and the mixture was stirred at room temperature for 30 min to form a clear solution. The mixture was cooled to −75 °C before methyl magnesium bromide (3.0 M solution in $Et_2O$, 0.24 mL, 0.72 mmol) was added dropwise. After stirring for another 10 min, a solution of thioester **93** (58 mg, 20 μmol) in *tert*-butyl methyl ether (0.4 mL) was added *via* a syringe pump over the course of 1.5 h. Once the addition was complete, stirring was continued at −75 °C for 18 h. The reaction mixture was quenched with MeOH at −75 °C and the mixture was warmed to room temperature. Saturated aq. $NH_4Cl$ solution (5.0 mL) was then added, the phases were separated and the aqueous layer extracted with *tert*-butyl methyl ether (3 × 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 100:1) to afford the title compound as a colorless liquid (49 mg, 82%, dr 9:1 by $^1$H NMR). **Note**: For the absolute configuration of the compound, please reference the analogous compound carrying TBDPS as the protecting group. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −13.5 (c = 0.52, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 3.94 – 3.79 (m, 1H), 2.87 (q, *J* = 7.4 Hz, 2H), 2.52 (dd, *J* = 14.3, 5.9 Hz, 1H), 2.36 (dd, *J*

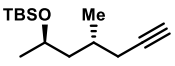
= 14.3, 8.2 Hz, 1H), 2.26 – 2.14 (m, 1H), 1.49 (ddd, *J* = 13.4, 8.5, 4.8 Hz, 1H), 1.24 (t, *J* = 7.4 Hz, 3H), 1.18 (ddd, *J* = 13.4, 8.8, 4.2 Hz, 1H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 199.0, 77.3, 66.2, 51.9, 46.7, 27.8, 25.9, 24.4, 23.3, 19.5, 18.1, 14.8, −4.1, −4.8; **IR** (film, $cm^{-1}$): 2958, 2929, 2857, 1690, 1461, 1373, 1255, 1311, 1004, 834; **HRMS** (ESI) for $C_{15}H_{32}O_2SSiNa$ $[M+Na]^+$: calcd. 327.1783; found 327.1785.

**(3*S*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-methylhexanal (99).**[93]



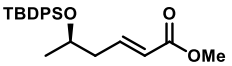

A solution of the thioester **95** (31 mg, 0.10 mmol) in $CH_2Cl_2$ (0.1 mL) was added to a stirred suspension of Pd-C (10% *w*/*w*, 5.3 mg, 5.0 μmol) in $CH_2Cl_2$ (0.1 mL) at room temperature, followed by $Et_3SiH$ (35 mg, 0.30 mmol). After stirring for 30 min, the mixture was filtered through a pad of Celite which was carefully rinsed with $CH_2Cl_2$ (10 mL). The combined filtrates were concentrated under reduced pressure (200-300 mbar, 25 °C) and the residue was purified by flash chromatography (hexanes/EtOAc 100:1 to 20:1) to afford the title compound as a colorless liquid (18 mg, 73%). $[\alpha]_D^{20}$ = −26.7 (c = 0.35, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.74 (t, *J* = 2.4 Hz, 1H), 3.95 – 3.81 (m, 1H), 2.43 – 2.33 (m, 1H), 2.28 – 2.15 (m, 2H), 1.48 (ddd, *J* = 13.5, 8.9, 4.2 Hz, 1H), 1.27 – 1.17 (m, 1H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 203.2, 66.3, 51.8, 47.1, 26.0, 25.0, 24.6, 19.9, 18.2, −3.9, −4.6; **IR** (film, $cm^{-1}$): 2957, 2929, 2857, 2710, 1721, 1463, 1373, 1255, 1069, 834; **HRMS** (CI) for $C_{13}H_{29}O_2Si$ $[M+H]^+$: calcd. 245.1939; found 245.1935.

***tert*-Butyldimethyl(((2*R*,4*R*)-4-methylhept-6-yn-2-yl)oxy)silane (102).**[94a]



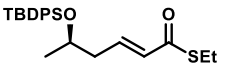

$K_2CO_3$ (84 mg, 0.61 mmol) was added a solution of aldehyde **99** (15 mg, 0.061 mmol) in MeOH (0.6 mL), followed by the addition of the Bestmann-Ohira reagent (14 mg, 0.074 mmol) in one portion. The mixture was stirred at room temperature for 16 h before the reaction was quenched with water (3 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated (300 mbar, 35 °C). Purification of the residue by flash chromatography (hexanes/*tert*-butyl methyl ether 100:1) afforded the product as a colorless liquid (9.6 mg, 66%). $[\alpha]_D^{20}$ = −14.6 (c = 0.43, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 3.95 – 3.78 (m, 1H), 2.18 (ddd, *J* = 16.7, 5.6, 2.6 Hz, 1H), 2.08 (ddd, *J* = 16.6, 6.7, 2.7 Hz, 1H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.90 – 1.77 (m, 1H), 1.62 – 1.54 (m, 1H), 1.26 – 1.17 (m, 1H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 83.34, 69.3, 66.6, 46.2, 29.0, 26.5, 26.1, 24.6, 19.4, 18.2, −4.0, −4.6; **IR** (film, $cm^{-1}$): 3314, 2957, 2929, 2857, 1462, 1373, 1254, 1132, 1062, 834; **HRMS** (ESI) for $C_{14}H_{29}OSi$ $[M+H]^+$: calcd. 241.1982; found 241.1983.

**Methyl (*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)hex-2-enoate (91).**



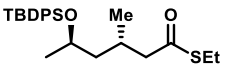

Compound **89**[196] (325 mg, 1.00 mmol) was dissolved in $CH_2Cl_2$ (7.0 ml) and the resulting solution was degassed for fifteen minutes by bubbling Ar through it, at which point there was only a total volume of ≈3.5 mL left. Freshly distilled methyl acrylate (215 mg, 2.50 mmol) was added, followed by Grubbs II catalyst (8.5 mg, 10 μmol). The resulting mixture was stirred at reflux temperature for 20 h. After full consumption of the starting material, stirring was continued under air for 1 h to destroy the catalyst. The dark brown solution was concentrated and the residue was purified by flash chromatography (hexanes/EtOAc 20:1 to 10:1) to give the title compound as a colorless syrup (383 mg, 86%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +35.1 (c = 0.27, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.71 – 7.61 (m, 4H), 7.49 – 7.30 (m, 6H), 6.92 (dt, *J* = 15.3, 7.5 Hz, 1H), 5.76 (dt, *J* = 15.7, 1.4 Hz, 1H), 3.96 (app h, *J* = 6.1 Hz, 1H), 3.72 (s, 3H), 2.41 – 2.20 (m, 2H), 1.09 (d, *J* = 6.1 Hz, 3H), 1.05 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 167.0, 146.0, 136.0, 136.0, 134.5, 134.1, 129.8, 129.7, 127.7, 127.7, 123.2, 68.6, 51.5, 42.3, 27.1, 23.3, 19.4; **IR** (film, $cm^{-1}$): 2932, 2858, 1725, 1659, 1428, 1270, 1110, 702; **HRMS** (ESI) for $C_{23}H_{30}O_3SiNa$ $[M+Na]^+$: calcd. 405.1856; found 405.1856.

***S*-Ethyl (*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)hex-2-enethioate (94).**




$Me_3SiSEt$ (263 mg, 1.76 mmol) and $AlCl_3$ (141 mg, 1.06 mmol) were added to a solution of enoate **91** (337 mg, 0.880 mmol) in THF (4.0 mL). The resulting mixture was stirred at reflux temperature for 3 h before the reaction was carefully quenched at room temperature with aqueous phosphate buffer solution (pH 7). The mixture was extracted with *tert*-butyl methyl ether (3 × 10 mL) and the combined organic layers were washed with water (10 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 20:1) to afford the title compound as a colorless liquid (313 mg, 86%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +52.5 (c = 0.56, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.64 (m, 4H), 7.46 – 7.34 (m, 6H), 6.85 (dt, *J* = 15.2, 7.5 Hz, 1H), 6.03 (dt, *J* = 15.5, 1.4 Hz, 1H), 3.97 (h, *J* = 6.0 Hz, 1H), 2.94 (q, *J* = 7.4 Hz, 2H), 2.37 – 2.10 (m, 2H), 1.28 (t, *J* = 7.4 Hz, 3H), 1.09 (d, *J* = 6.1 Hz, 3H), 1.05 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 190.0, 141.6, 135.9, 135.8, 134.3, 133.9, 130.8, 129.7, 129.6, 127.6, 127.5, 68.5, 42.1, 27.0, 23.3, 23.1, 19.2, 14.8; **IR** (film, $cm^{-1}$): 3070, 2964, 2857, 1670, 1634, 1427, 1377, 1262, 1109, 991; **HRMS** (ESI) for $C_{24}H_{32}O_2SSiNa$ $[M+Na]^+$: calcd. 435.1785; found 435.1783.

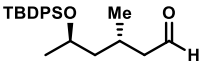
***S*-Ethyl (3*S*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhexanethioate (96).**




CuBr·$SMe_2$ (36 mg, 0.17 mmol) and (*S*,*R*)-Josiphos ((*S*,*R*)-**97**, 0.12 g, 0.21 mmol) were added to *tert*-butyl methyl ether (69 mL) and the mixture was stirred at room temperature for 30 min to form a clear solution. The mixture was cooled to −75 °C before methyl magnesium bromide (3.0 M solution in $Et_2O$, 5.20 mL, 15.6 mmol) was

added dropwise. After stirring for another 10 min, a solution of thioester **94** (3.56 g, 8.62 mmol) in *tert*-butyl methyl ether (17.2 mL) was added *via* syringe pump over 2 h. Once the addition was complete, stirring was continued at −75 °C for 18 h. The reaction was quenched with MeOH at −75 °C and the mixture was warmed to room temperature. Saturated aq. $NH_4Cl$ solution (50 mL) was then added, the phases were separated and the aqueous layer extracted with *tert*-butyl methyl ether (3 × 50 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 100:1) to afford the title compound as a colorless liquid (3.34 g, 90%, dr > 20:1 by $^1$H NMR). $[\alpha]_D^{20}$ = 13.2 (c = 0.53, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.72 – 7.65 (m, 4H), 7.46 – 7.33 (m, 6H), 3.85 (app dq, *J* = 12.2, 6.1 Hz, 1H), 2.85 (q, *J* = 7.4 Hz, 2H), 2.40 – 2.26 (m, 1H), 2.25 – 2.10 (m, 2H), 1.61 – 1.47 (m, 1H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.21 – 1.12 (m, 1H), 1.06 (m, 12H), 0.78 (d, *J* = 6.3 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 199.0, 136.0, 134.9, 134.2, 129.6, 129.4, 127.6, 127.4, 67.4, 51.6, 46.7, 27.8, 27.1, 24.0, 23.2, 19.6, 19.3, 14.8; **IR** (film, cm$^{-1}$): 3070, 2963, 2931, 2857, 1689, 1428, 1110, 702; **HRMS** (ESI) for $C_{25}H_{36}O_2SSiNa$ [M+Na]$^+$: calcd. 451.2098; found 451.2098.

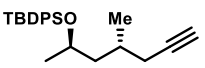
**(3*S*,5*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-3-methylhexanal (100).**[93]




A solution of compound **96** (3.34 g, 7.80 mmol) in $CH_2Cl_2$ (8 mL) was added to a stirred suspension of Pd-C (10% *w*/*w*, 0.41 g, 0.39 mmol) in $CH_2Cl_2$ (8 mL) at room temperature, followed by $Et_3SiH$ (2.72 g, 23.4 mmol). After stirring for 30 min, the mixture was filtered through a pad of Celite which was carefully rinsed with $CH_2Cl_2$ (100 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 100:1 to 20:1) to afford the title compound as a colorless liquid (2.45 g, 85%). $[\alpha]_D^{20}$ = +5.4 (c = 0.24, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.64 – 9.61 (m, 1H), 7.73 – 7.63 (m, 4H), 7.45 – 7.32 (m, 6H), 3.86 (app dq, *J* = 12.2, 6.1 Hz, 1H), 2.28 – 2.13 (m, 2H), 2.14 – 2.00 (m, 1H), 1.60 – 1.45 (m, 1H), 1.23 (ddd, *J* = 13.5, 8.2, 4.7 Hz, 1H), 1.08 (d, *J* = 6.1 Hz, 3H), 1.05 (s, 9H), 0.78 (d, *J* = 6.6 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 203.0, 136.1, 136.1, 134.8, 134.3, 129.8, 129.6, 127.7, 127.6, 67.6, 51.4, 47.2, 27.2, 25.0, 24.2, 20.1, 19.4; **IR** (film, cm$^{-1}$): 3071, 2930, 2857, 2712, 1725, 1462, 1427, 1109, 822; **HRMS** (ESI) for $C_{23}H_{32}O_2SiNa$ [M+Na]$^+$: calcd. 391.2064; found 391.2061.

**Note**: Comparison of the recorded data of **96** with the data of this aldehyde as reported by Nelson and co-workers confirmed the relative and absolute stereochemistry.[197]

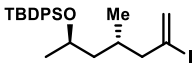
***tert*-Butyl(((2*R*,4*R*)-4-methylhept-6-yn-2-yl)oxy)diphenylsilane (103).**




$K_2CO_3$ (9.19 g, 66.5 mmol) was added a solution of aldehyde **100** (2.45 g, 6.65 mmol) in MeOH (66 mL), followed by addition of the Bestmann–Ohira reagent **101** (1.53 g, 7.98 mmol) in one portion. The mixture was stirred at room temperature for 16 h before the reaction was quenched with water (30 mL). The aqueous phase was extracted

with *tert*-butyl methyl ether (3 × 50 mL), and the combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated. Purification of the residue by flash chromatography (hexanes/*tert*-butyl methyl ether 100:1) afforded the product as colorless liquid (2.27 g, 94%). $[\alpha]_D^{20}$ = +13.0 (c = 0.68, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.73 – 7.65 (m, 4H), 7.47 – 7.32 (m, 6H), 3.89 (app h, *J* = 5.9 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.99 – 1.90 (m, 2H), 1.85 (app dq, *J* = 14.4, 6.5 Hz, 1H), 1.69 (app dt, *J* = 13.4, 6.5 Hz, 1H), 1.30 – 1.17 (m, 1H), 1.06 (m, 12H), 0.84 (d, *J* = 6.6 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 136.1, 135.1, 134.4, 129.7, 129.5, 127.7, 127.5, 83.3, 69.3, 67.8, 46.3, 29.0, 27.2, 26.3, 24.2, 19.5; **IR** (film, $cm^{-1}$): 3309, 3071, 2930, 2858, 1461, 1427, 1375, 1109, 1061, 702; **HRMS** (ESI) for $C_{24}H_{32}OSiNa$ $[M+Na]^+$: calcd. 387.2115; found 387.2111.

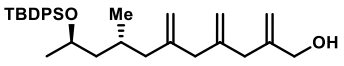
***tert*-Butyl(((2*R*,4*S*)-6-iodo-4-methylhept-6-en-2-yl)oxy)diphenylsilane (104).**




*B*-Iodo-9-BBN (0.32 mL, 1.0 M in hexane, 0.32 mmol) was added over the course of 1 h to a stirred solution of alkyne **103** (91 mg, 0.25 mmol) in anhydrous hexane (2.5 mL) at 0 °C. Once the addition was complete, stirring was continued at room temperature for 16 h. At this point, AcOH (56 mg, 0.93 mmol) was added and the mixture stirred for another 1 h. The reaction was then quenched with aq. $NaS_2O_3$ (1 M) and $NaHCO_3$ until the mixture was colorless and showed a pH = 7. The aqueous layer was separated and extracted with *tert*-butyl methyl ether (3 × 10 mL), and the combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/$NEt_3$ 100:1) to give the title compound as a colorless liquid (121 mg, 99%). **Note**: It was critical to ensure that the silica was neutralized. $[\alpha]_D^{20}$ = +19.8 (c = 0.30, $CHCl_3$); **$^1$H NMR** ($C_6D_6$, 400 MHz): δ 7.88 – 7.76 (m, 4H), 7.27 – 7.20 (m, 6H), 5.64 (d, *J* = 1.2 Hz, 1H), 5.58 – 5.52 (s, 1H), 3.99 – 3.89 (m, 1H), 2.19 – 2.00 (m, 2H), 1.78 (dd, *J* = 14.3, 7.7 Hz, 1H), 1.57 (ddd, *J* = 13.1, 8.1, 4.7 Hz, 1H), 1.23 (s, 9H), 1.08 (d, *J* = 6.1 Hz, 3H), 0.97 (ddd, *J* = 13.4, 8.8, 4.5 Hz, 1H), 0.66 (d, *J* = 6.5 Hz, 3H); **$^{13}$C NMR** ($C_6D_6$, 100 MHz): δ 136.4, 135.3, 134.6, 130.0, 129.9, 126.5, 112.3, 67.8, 53.1, 46.5, 29.1, 27.5, 24.5, 19.6, 18.7; **IR** (film, $cm^{-1}$): 3070, 2962, 2929, 2857, 1616, 1427, 1110, 509; **HRMS** (ESI) for $C_{24}H_{33}OISiNa$ $[M+Na]^+$: calcd. 515.1238; found 515.1245.

### 6.2.2.3 Completion of the Northern Fragment Synthesis

**Compound 107.**



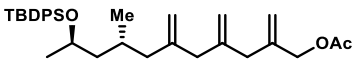

***Preparation of the Organozinc Compound Derived from Iodide 86***: *tert*-Butyllithium (1.31 mL, 1.7 M in pentane, 2.23 mmol) was added dropwise over 20 min to a solution of iodide **104** (524 mg, 1.06 mmol) in $Et_2O$ (1.6 mL) at –78 °C and the resulting solution was stirred at this temperature for 30 min. A solution of zinc bromide (2.16 mL, 0.5 M in THF, 1.08 mmol) was added dropwise

at –78 °C. After 15 min at –78 °C, the cooling bath was removed and the solution was warmed to ambient temperature over 30 min.

***Negishi Cross-Coupling Reaction/Deprotection***: A flame-dried Schlenk tube was charged with allyl chloride **85** (265 mg, 1.01 mmol) and DMF (2.7 mL). This solution was then degassed by purging with Ar for 15 min. $Pd(PPh_3)_4$ (61 mg, 53 μmol) was added followed by the solution of the organozinc reagent (prepared as above). The mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated $NH_4Cl$ (10 mL) solution and the resulting mixture was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated.

TBAF solution (1 M in THF, 1.17 mL, 1.17 mmol) was added to a solution of the crude material in THF (2.0 mL) at 0 °C. The cooling bath was removed and the mixture was stirred for 2.5 h, before the reaction was quenched with saturated aq. $NH_4Cl$ solution (5 mL). The aqueous phase extracted with *tert*-butyl methyl ether (3 × 5 mL) and the combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was subjected to flash chromatography (hexanes/*tert*-butyl methyl ether 6:1) to give the title compound as a colorless liquid (416 mg, 82% over two steps). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −4.8 (c = 0.45, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.72 – 7.65 (m, 4H), 7.44 – 7.32 (m, 6H), 5.12 (s, 1H), 4.91 (s, 1H), 4.87 (s, 1H), 4.84 (s, 1H), 4.77 (s, 1H), 4.76 (s, 1H), 4.03 (s, 2H), 3.90 (app dq, *J* = 12.1, 6.0 Hz, 1H), 2.75 (s, 2H), 2.66 (s, 2H), 1.89 – 1.76 (m, 2H), 1.65 (m, 1H), 1.57 (ddd, *J* = 12.6, 8.0, 4.5 Hz, 1H), 1.04 (d, *J* = 2.2 Hz, 13H), 0.69 (d, *J* = 6.4 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 146.3, 145.6, 144.6, 136.0, 135.9, 135.0, 134.3, 129.5, 129.4, 127.5, 127.3, 113.8, 113.1, 111.8, 67.7, 65.4, 47.3, 43.6, 42.5, 39.5, 27.1, 27.0, 24.3, 19.5, 19.3; **IR** (film, $cm^{-1}$): 3330, 3071, 2962, 2928, 2857, 1638, 1428, 1375, 1110, 1060, 897; **HRMS** (ESI) for $C_{31}H_{44}O_2SiNa$ $[M+Na]^+$: calcd. 499.3003; found 499.3008.

**(8*R*,10*R*)-10-((*tert*-Butyldiphenylsilyl)oxy)-8-methyl-2,4,6-trimethyleneundecyl acetate (108).**



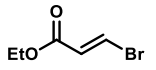

Pyridine (30 μL, 0.37 mmol), acetic anhydride (44 μL, 0.47 mmol), and DMAP (3.8 mg, 31 μmol) were sequentially added to a stirred solution of alcohol **107** (0.15 g, 0.31 mmol) in $CH_2Cl_2$ (4 mL) at 0 °C. The cooling bath was removed and the mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous $NH_4Cl$ solution (4 mL) and the mixture diluted with *tert*-butyl methyl ether (8 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 4 mL). The combined organic fractions were washed with brine (4 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 20:1) to give the title compound as a colorless oil (0.15 g, 96%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −5.2 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 (ddd, *J* = 8.2, 6.8, 1.6 Hz, 4H), 7.47 – 7.32 (m, 6H), 5.12 (s, 1H), 5.02 – 4.95 (m, 1H), 4.86 (s, 2H), 4.79 – 4.73 (m, 2H), 4.49 (s, 2H), 3.90 (dqd, *J* = 8.1, 6.1, 4.6 Hz, 1H), 2.75 (s, 2H), 2.66 (s, 2H), 2.08 (s, 3H), 1.91 – 1.76 (m, 2H),

1.72 – 1.50 (m, 2H), 1.10 – 1.07 (m, 1H), 1.05 (s, 9H), 1.04 (d, *J* = 6.1 Hz, 3H), 0.69 (d, *J* = 6.2 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 170.8, 145.6, 143.9, 141.5, 136.1, 136.1, 135.1, 134.5, 129.6, 129.5, 127.6, 127.5, 114.6, 114.3, 113.2, 67.8, 66.3, 47.4, 43.8, 42.6, 39.7, 27.2, 27.1, 24.4, 21.1, 19.6, 19.5; **IR** (film, $cm^{-1}$): 3072, 2962, 2929, 2858, 1744, 1638, 1472, 1459, 1428, 1374, 1227, 1155, 1129, 1110, 1058, 1027, 996, 951, 899, 822, 741, 728, 703, 685, 612, 500; **HRMS** (ESI) for $C_{33}H_{46}O_3SiNa$ $[M+Na]^+$: calcd. 541.3108; found 541.3112.

### 6.2.3 Synthesis of the Southern Fragment

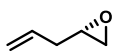
#### 6.2.3.1 Oxa-Michael Approach

**Ethyl (*E*)-3-bromoacrylate (110).**



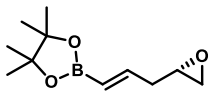
The compound was prepared following a procedure by Heck and co-workers.[100] **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.59 (d, *J* = 13.9 Hz, 1H), 6.52 (d, *J* = 13.9 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 164.3, 129.0, 126.7, 61.1, 14.3; **IR** (film, $cm^{-1}$): 3081, 2983, 2906, 1718, 1605, 1446, 1367, 1298, 1229, 1151, 1032, 940; **HRMS** (EI) for $C_5H_7O_2Br$ $[M]^+$: calcd. 177.9630; found 177.9628.

**(*S*)-2-Allyloxirane (111).**



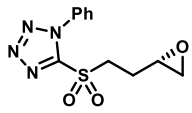
The compound was prepared following a procedure by Kumar and co-workers.[101] **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.83 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 5.17 (d, *J* = 17.2 Hz, 1H), 5.11 (d, *J* = 10.3 Hz, 1H), 3.06 – 2.90 (m, 1H), 2.77 (app t, *J* = 4.5 Hz, 1H), 2.52 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.33 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 133.1, 117.7, 51.4, 46.7, 36.7.

**(*S*,*E*)-4,4,5,5-Tetramethyl-2-(3-(oxiran-2-yl)prop-1-en-1-yl)-1,3,2-dioxaborolane (112).**



This compound was prepared according to a procedure by Nagorny and co-workers.[198] Grubbs II catalyst (8.5 mg, 0.01 mmol) was added to a solution of epoxide **93** (42 mg, 0.50 mmol) and vinyl boronic acid pinacol ester (154 mg, 1.00 mmol) in $CH_2Cl_2$ (2.5 mL). The resulting mixture was stirred at reflux temperature for 24 h. Stirring was continued in air for 30 min at room temperature to destroy most of the catalyst. The dark brown solution was the concentrated and the residue was subjected to flash chromatography (hexanes/EtOAc 10:1) to afford the title compound as a light brown liquid (17.8 mg, 17%). $[\alpha]_D^{20}$ = +9.4 (c = 0.82, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 6.61 (dt, *J* = 18.1, 6.4 Hz, 1H), 5.58 (dt, *J* = 18.0, 1.6 Hz, 1H), 3.01 (tdd, *J* = 5.6, 3.9, 2.7 Hz, 1H), 2.80 – 2.69 (m, 1H), 2.53 – 2.41 (m, 2H), 2.32 (dtd, *J* = 15.4, 6.0, 1.6 Hz, 1H), 1.26 (s, 12H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 148.1, 122.5, 83.4, 50.9, 46.9, 38.7, 24.9; **IR** (film, $cm^{-1}$): 2978, 2927, 1639, 1359, 1391, 1359, 1323, 1143, 971, 848; **$^{11}$B NMR** ($CDCl_3$, 128 MHz) δ 29.51; **HRMS** (ESI) for $C_{11}H_{19}O_3BNa$ $[M+Na]^+$: calcd. 233.1319; found 233.1320.

**(*S*)-5-((2-(oxiran-2-yl)ethyl)sulfonyl)-1-phenyl-1*H*-tetrazole ((*S*)-113).**

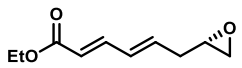


***Epoxidation***: *m*-Chloroperbenzoic acid (2.85 g, 12.7 mmol, 77%) and $NaHCO_3$ (1.07 g, 12.7 mmol) were sequentially added to a solution of olefin **114**[102] (2.24 g, 8.94 mmol) in $CH_2Cl_2$ (55 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 24 h. The reaction mixture was diluted with $CH_2Cl_2$ (50 mL) and the reaction was quenched with aq. $Na_2S_2O_3$ solution (1.0 M, 30 mL) at 0 °C.

The organic layer was washed with aq. $Na_2CO_3$ solution (1.0 M, 30 mL), water (30 mL), and brine (30 mL). The solvent was evaporated and the residue was purified by flash chromatography (hexanes/EtOAc 2:1 to 1:1) to give the racemic epoxide **113** (2.17 g, 91%).

***Kinetic Resolution of* 113**:[103] AcOH (25 mg, 0.42 mmol) was added to a solution of (1*S*,2*S*)-(+)-1,2-cyclohexanediamino-N,N'-bis(3,5-di-*tert*-butylsalicylidene)cobalt(II) (24 mg, 0.039 mmol) in toluene (0.5 mL) under air. The resulting mixture was stirred under air for 30 min, during which time the reaction mixture turned from dark orange to brown. This solution was concentrated to provide a brown solid. A solution of epoxide **113** (2.17 g, 7.74 mmol) in THF (5 mL) was added to the residue. Water (77 mg, 4.3 mmol) was added to the mixture at 0 °C. After 24 h at room temperature, three times more of the catalyst, prepared as previously, was added to the reaction mixture. The reaction was stirred for another 24 h. The volatiles were removed and the residue was purified by flash chromatography (hexanes/EtOAc 1:1) to afford the enantioenriched title compound (1.13 g, 52%, 57% *ee*). A second kinetic resolution was performed under the same conditions to increase the enantiomeric excess and give the title compound as a colorless oil (766 mg, 68%, 92% *ee*). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −13.0 (c = 0.67, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.77 – 7.46 (m, 5H), 3.89 (ddd, *J* = 8.2, 6.7, 1.2 Hz, 2H), 3.11 (dtd, *J* = 6.7, 4.0, 2.6 Hz, 1H), 2.84 (dd, *J* = 4.6, 4.0 Hz, 1H), 2.59 (dd, *J* = 4.7, 2.6 Hz, 1H), 2.50 – 2.24 (m, 1H), 2.17 – 1.88 (m, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 153.4, 133.1, 131.7, 129.9, 125.2, 52.9, 49.8, 47.3, 25.8; **IR** (film, $cm^{-1}$): 3067, 2995, 2927, 1595, 1498, 1412, 1346, 1153, 765; **HRMS** (ESI) for $C_{11}H_{12}O_3N_4SNa$ $[M+Na]^+$: calcd. 303.0522; found 303.0524.

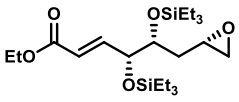
**Ethyl (2*E*,4*E*)-6-((*S*)-oxiran-2-yl)hexa-2,4-dienoate (109).**



KHMDS (44 mg, 0.22 mmol) in DME (1.0 mL) was added to a solution of (*S*)-**113** (56 mg, 0.20 mmol) in DME (1.0 mL) at −60 °C. The reaction mixture was allowed to stir at the same temperature for 30 min before the addition of the ethyl *trans*-4-oxo-2-butenoate (**116**, 38 mg, 0.30 mmol). The resulting mixture was kept stirring for 3 h at −60 °C and for 16 h at room temperature. At this point, water (5.0 mL) and *tert*-butyl methyl ether (5.0 mL) were added and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 5.0 mL). The combined organic layers were washed with brine (5.0 mL), dried over $Na_2SO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (hexanes/*tert*-butyl methyl ether 20:1 to 10 :1) to afford the product as a mixture of *E*/*Z* isomers (35 mg, 97%, *E*/*Z* 2.2:1 by $^1$H NMR). A second chromatographic purification was performed to isolate pure *E*-**109**.[104] Analytical data of the *E* isomer: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −12.6 (c = 0.61, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.30 – 7.19 (m, 1H), 6.29 (dd, *J* = 15.3, 10.9 Hz, 1H), 6.15 – 6.04 (m, 1H), 5.84 (d, *J* = 15.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.07 – 2.95 (m, 1H), 2.84 – 2.72 (m, 1H), 2.52 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.48 – 2.22 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 167.2, 144.2, 137.5,

131.0, 120.9, 60.5, 50.9, 46.7, 35.7, 14.4; **IR** (film, $cm^{-1}$): 2983, 2932, 1708, 1644, 1619, 1478, 1259, 1246, 1136, 1001, 838; **HRMS** (ESI) for $C_{10}H_{14}O_3Na$ $[M+Na]^+$: calcd. 205.0835; found 205.0837.

**Ethyl (4*R*,5*R*,*E*)-6-((*S*)-oxiran-2-yl)-4,5-bis((triethylsilyl)oxy)hex-2-enoate (120).**

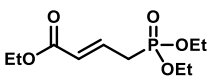


***Dihydroxylation of the diene***: $OsO_4$ (4.6 mg, 0.013 mmol), $(DHQD)_2PHAL$ (48 mg, 0.062 mmol), $K_3Fe(CN)_6$ (407 mg, 1.23 mmol), $K_2CO_3$ (171 mg, 1.23 mmol), and $MeSO_2NH_2$ (39 mg, 0.41 mmol) were added to a mixture of *t*-BuOH and $H_2O$ (4.2 mL, 1:1 *v*/*v*) at 0 °C and the mixture was stirred at this temperature for 15 min. The diene **109** (75 mg, 0.41 mmol) was added and the mixture was stirred for 10 h at 0 °C. The reaction was quenched with saturated aq. $Na_2S_2O_3$ solution (5.0 mL) and the aqeuous phase was extracted with EtOAc (8 × 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was dried under high vacuum and used directly in the next step, assuming full conversion and containing 1.0 equivalent of the $MeSO_2NH_2$.[106]

**Note**: The desired product was not stable under strongly acidic and basic conditions. Therefore, it was not possible to remove the $MeSO_2NH_2$ by washing with aq. KOH (1.0 M). The diol also decomposed slowly upon contact with silica. According to the $^1H$ NMR analysis of the crude residue, the product was obtained in a regioselectivity of 9:1 and dr of 18:1.

***Double protection of the diol***: Imidazole (17 mg, 0.25 mmol) and TESCl (19 mg, 0.13 mmol) were added to a solution of the diol (0.05 mmol, crude mixture from the dihydroxylation with 1.0 equivalent of $MeSO_2NH_2$) in DMF (0.25 mL) at 0 °C. The mixture was stirred for 6 h at 0 °C before the reaction was quenched with saturated aq. $NH_4Cl$ (5.0 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 5.0 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexans/EtOAc 50:1 to 20:1) to give the title compound as a colorless liquid (7.5 mg, 34%). $[\alpha]_D^{20}$ = +58.8 (c = 0.55, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.11 (dd, *J* = 15.7, 3.5 Hz, 1H), 6.06 (dd, *J* = 15.7, 2.0 Hz, 1H), 4.38 (ddd, *J* = 5.3, 3.5, 2.0 Hz, 1H), 4.20 (m, 2H), 3.90 (dt, *J* = 7.2, 5.1 Hz, 1H), 3.02 (tdd, *J* = 6.1, 3.9, 2.7 Hz, 1H), 2.74 – 2.67 (m, 1H), 2.39 (dd, *J* = 5.1, 2.7 Hz, 1H), 1.70 – 1.54 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.65 (q, *J* = 8.0 Hz, 6H), 0.62 (q, *J* = 8.0 Hz, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 166.6, 147.3, 121.8, 74.5, 73.5, 60.5, 50.5, 47.3, 35.7, 14.4, 7.0, 7.0, 5.1, 4.9; **IR** (film, $cm^{-1}$): 2956, 2912, 2878, 1722, 1658, 1460, 1413, 1366, 1267, 1109, 1006, 728; **HRMS** (ESI) for $C_{22}H_{44}O_5Si_2Na$ $[M+Na]^+$: calcd. 467.2620; found 467.2620.

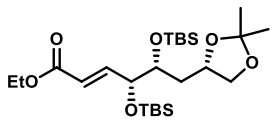
**Ethyl (*E*)-4-(diethoxyphosphoryl)but-2-enoate (124).**



The compound was prepared as described by Ley and coworkers.[107a] **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 6.87 (dt, *J* = 15.7, 7.9 Hz, 1H), 5.96 (dt, *J* = 15.6, 1.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.12 (qd, *J* = 7.1, 2.2 Hz, 4H), 2.74 (dd, *J* = 7.9, 1.4 Hz, 2H), 1.32 (t,

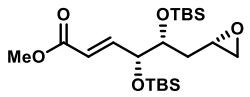
*J* = 7.1 Hz, 6H), 1.28 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 165.8, 137.6 (d, *J* = 11.1 Hz), 126.0 (d, *J* = 13.8 Hz), 62.5, 62.4, 60.6, 30.8 (d, *J* = 138.8 Hz), 16.6, 16.5, 14.4.

**Ethyl (4*R*,5*R*,*E*)-4,5-bis((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-hex-2-enoate (126).**



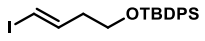
The compound was prepared by a similar dihydroxylation and double protection sequence as compound **120** in 35% yield over two steps.[106] $[\alpha]_D^{20}$ = +63.0 (c = 0.55, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.10 (dd, *J* = 15.7, 3.3 Hz, 1H), 6.04 (dd, *J* = 15.7, 2.0 Hz, 1H), 4.33 (ddd, *J* = 5.2, 3.3, 2.1 Hz, 1H), 4.20 (qt, *J* = 7.1, 3.8 Hz, 3H), 4.02 (dd, *J* = 7.8, 5.9 Hz, 1H), 3.71 (app dt, *J* = 7.8, 4.5 Hz, 1H), 3.43 (app t, *J* = 7.7 Hz, 1H), 1.75 (ddd, *J* = 13.9, 7.3, 4.2 Hz, 1H), 1.68 – 1.58 (m, 1H), 1.38 (s, 3H), 1.32 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 166.6, 147.2, 121.8, 108.7, 74.4, 73.8, 72.7, 69.8, 60.5, 36.3, 27.1, 26.0, 25.9, 25.9, 18.3, 18.1, 14.4, −4.2, −4.7, −4.7, −4.8; **IR** (film, $cm^{-1}$): 2984, 2955, 2931, 2887, 2858, 1723, 1658, 1472, 1368, 1296, 1257, 1161, 1108, 1069, 834, 776; **HRMS** (ESI) for $C_{25}H_{50}O_6Si_2Na$ $[M+Na]^+$: calcd. 525.3038; found 525.3043.

**Methyl (4*R*,5*R*,*E*)-4,5-bis((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-oxiran-2-yl)hex-2-enoate (127).**



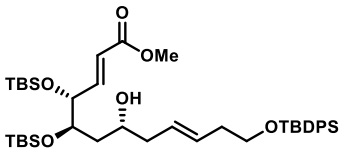
The compound was prepared by a similar dihydroxylation and double protection sequence as compound **126**, followed by deproctection of the acetonide and eventually epoxide formation.[199] $[\alpha]_D^{20}$ = +121.0 (c = 0.42, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.12 (dd, *J* = 15.7, 3.3 Hz, 1H), 6.06 (dd, *J* = 15.7, 2.1 Hz, 1H), 4.35 (ddd, *J* = 5.2, 3.3, 2.1 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.75 (s, 3H), 2.99 (tdd, *J* = 6.1, 3.9, 2.7 Hz, 1H), 2.72 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.38 (dd, *J* = 5.1, 2.7 Hz, 1H), 1.61 (t, *J* = 6.1 Hz, 2H), 0.92 (s, 9H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 167.0, 147.4, 121.4, 74.4, 73.5, 51.7, 50.6, 47.2, 35.5, 25.9, 18.3, 18.1, 1.2, −4.3, −4.7, −4.2, −4.8; **IR** (film, $cm^{-1}$): 2954, 2950, 2887, 2858, 1727, 1659, 1472, 1435, 1300, 1259, 1109, 836, 777; **HRMS** (ESI) for $C_{21}H_{42}O_5Si_2Na$ $[M+Na]^+$: calcd. 453.2463; found 453.2464.

**(*E*)-*tert*-Butyl((4-iodobut-3-en-1-yl)oxy)diphenylsilane (128).**



The compound was prepared as described by Roush and co-workers.[109] **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.60 (m, 4H), 7.46 – 7.34 (m, 6H), 6.53 (dt, *J* = 14.5, 7.3 Hz, 1H), 6.06 (dt, *J* = 14.4, 1.3 Hz, 1H), 3.69 (t, *J* = 6.3 Hz, 2H), 2.28 (qd, *J* = 6.3, 1.3 Hz, 2H), 1.05 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 143.5, 135.7, 133.8, 129.8, 127.8, 62.5, 39.3, 27.0, 19.3.

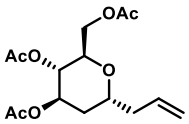
**Compound 129.**




*n*-Butyllithium (11 μL, 1.6 M in hexane, 0.018 mmol) was added to a solution of alkenyl iodide **128** (7.9 mg, 0.018 mmol) in $Et_2O$ (0.1 mL) at −78 °C. The resulting mixture was stirred for 1 h at −78 °C. A solution of lithium 2-thienylcyanocuprate (80 μL, 0.25 M in THF, 20 μmol) was added dropwise and the mixture was stirred for 30 min at −78 °C. A solution of $BF_3{\cdot}OEt_2$ (20 μL, 0.8 M in $Et_2O$, 0.016 mmol) was added and the reaction mixture was stirred for 20 min before a solution of the epoxide **127** (4.5 mg, 0.01 mmol) in $Et_2O$ (1.0 mL) was introduced at −78 °C. The reaction mixture stirred at the same temperature for 1 h before the reaction was quenched with a mixture of saturated aq. $NH_4Cl$ (0.9 mL) and 30% aq. $NH_4OH$ (0.1 mL) at 0 °C. The biphasic mixture was vigorously stirred for another 2 h at room temperature before diluting with $Et_2O$ (2.0 mL). The aqueous phases was extracted with $Et_2O$ (3 × 2.0 mL) and the combined organic layers were washed with brine (2.0 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 40:1 to 20:1) to afford the title compound (4.4 mg, 58%).[110] **Note**: The desired product had very similar polarity to the halohydrin side product. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +30.2 (c = 0.20, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.72 – 7.59 (m, 4H), 7.47 – 7.30 (m, 6H), 7.09 (dd, *J* = 15.7, 3.3 Hz, 1H), 6.05 (dd, *J* = 15.7, 2.0 Hz, 1H), 5.59 – 5.29 (m, 2H), 4.33 (ddd, *J* = 5.1, 3.3, 2.1 Hz, 1H), 3.87 (dt, *J* = 8.9, 4.0 Hz, 1H), 3.74 (s, 3H), 3.70 (m, 1H), 3.66 (t, *J* = 6.7 Hz, 2H), 2.27 (app q, *J* = 6.5 Hz, 2H), 2.16 – 2.01 (m, 2H), 1.76 (dt, *J* = 14.4, 4.0 Hz, 1H), 1.43 – 1.31 (m, 1H), 1.04 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.12 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 166.9, 147.2, 135.7, 134.2, 130.4, 129.7, 128.2, 127.7, 121.6, 74.6, 74.2, 70.1, 63.9, 51.7, 40.7, 37.8, 36.3, 27.0, 26.0, 25.9, 19.4, 18.2, 18.0, −3.9, −4.6, −4.7, −4.7; **IR** (film, $cm^{-1}$): 3557, 2954, 2930, 2857, 1728, 1659, 1472, 1429, 1259, 1166, 836, 777; **HRMS** (ESI) for $C_{41}H_{68}O_6Si_3Na$ $[M+Na]^+$: calcd. 763.4216; found 763.4218.

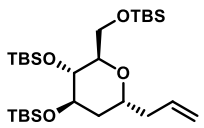
### 6.2.3.2 Chiral-Pool Approach

**(2*R*,3*S*,4*R*,6*R*)-2-(Acetoxymethyl)-6-allyltetrahydro-2H-pyran-3,4-diyl diacetate (134).**




Prepared according to the cited literature procedure.[114] **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.77 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.17 – 5.07 (m, 3H), 4.87 (t, *J* = 7.3 Hz, 1H), 4.37 (dd, *J* = 12.0, 6.3 Hz, 1H), 4.14 – 4.01 (m, 2H), 3.90 (td, *J* = 6.7, 3.3 Hz, 1H), 2.57 – 2.45 (m, 1H), 2.34 – 2.24 (m, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.99 (dt, *J* = 13.6, 4.8 Hz, 1H), 1.85 (ddd, *J* = 13.7, 8.9, 4.9 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 170.9, 170.2, 169.9, 133.9, 117.8, 70.8, 70.0, 68.8, 62.3, 36.8, 32.2, 21.2, 21.0, 21.0.

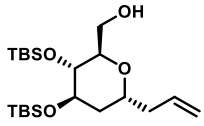
**(((2*R*,3*R*,4*R*,6*R*)-6-Allyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-3,4-diyl)bis-(oxy))bis(*tert*-butyldimethylsilane) (136).**




$K_2CO_3$ (165 mg, 1.19 mmol) was added to a solution of triacetate **134** (3.75 g, 11.9 mmol) in methanol (12 mL) at room temperature. After 1 h, the yellow solution was filtered through a silica plug rinsing with 10% MeOH/EtOAc. The combined filtrates were concentrated and the crude material was dried in high vacuum overnight to remove any residual methanol.

TBSOTf (12.4 mL, 53.6 mmol) was slowly added to a solution of the crude triol and 2,6-lutidine (8.35 mL, 71.7 mmol) in $CH_2Cl_2$ (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 h before the reaction was quenched with saturated aq. $NH_4Cl$ solution (100 mL) and the aqueous phase extracted with *tert*-butyl methyl ether (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was subjected to flash chromatography (hexanes/*tert*-butyl methyl ether 200:1 to 100:1) to furnish the title compound as a pale yellow liquid (6.01 g, 95% over two steps). $[\alpha]_D^{20}$ = +8.8 (c = 0.58, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.82 (ddt, *J* = 17.2, 10.2, 6.9 Hz, 1H), 5.08 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.05 – 5.00 (m, 1H), 3.89 (d, *J* = 7.0 Hz, 2H), 3.87 – 3.82 (m, 1H), 3.80 (d, *J* = 3.4 Hz, 1H), 3.74 (t, *J* = 7.0 Hz, 1H), 3.58 (d, *J* = 3.5 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.15 (app dt, *J* = 14.1, 6.5 Hz, 1H), 1.82 (ddd, *J* = 13.5, 11.0, 2.6 Hz, 1H), 1.38 (d, *J* = 13.4 Hz, 1H), 0.89 (s, 27H), 0.05 (m, 18H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 135.2, 116.7, 80.3, 69.9, 68.3, 65.2, 61.8, 40.4, 33.8, 26.1, 26.0, 26.0, 18.4, 18.2, 18.1, −4.5, −4.6, −4.8, −5.1, −5.1; **IR** (film, $cm^{-1}$): 2953, 2929, 2885, 2857, 1643, 1472, 1361, 1253, 1087, 669; **HRMS** (ESI) for $C_{27}H_{58}O_4Si_3Na$ $[M+Na]^+$: calcd. 553.3535; found 553.3539.

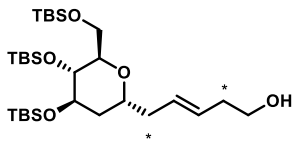
**((2*R*,3*R*,4*R*,6*R*)-6-Allyl-3,4-bis((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)methanol (138).**



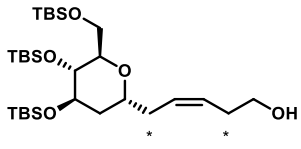

A solution of HF–pyridine (1.5 mL) in THF/pyridine (2.5:1 *v*/*v*, 16 mL) was slowly added to a solution of **136** (0.44 g, 0.82 mmol) in THF (19 mL) in a plastic vial at 0 °C. After stirring the mixture for 5 h at room temperature, the reaction was quenched with saturated aq. $Na_2CO_3$ solution (50 mL) and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 20:1) to afford the title compound as a colorless oil (258 mg, 75%). $[\alpha]_D^{20}$ = +1.4 (c = 0.82, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.82 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.17 – 4.99 (m, 2H), 4.12 (dd, *J* = 11.6, 9.2 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.83 – 3.66 (m, 2H), 3.47 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.38 – 3.24 (m, 1H), 2.35 (app dt, *J* = 14.0, 6.9 Hz, 1H), 2.18 (app dt, *J* = 14.2, 7.1 Hz, 1H), 1.87 (ddd, *J* = 13.1, 10.0, 2.8 Hz, 1H), 1.45 (ddd, *J* = 13.5, 4.4, 2.7 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.06 (t, *J* = 1.5 Hz, 12H); **$^{13}$C NMR** ($CDCl_3$,

100 MHz): δ 134.8, 117.3, 79.4, 69.8, 69.7, 65.4, 60.9, 39.7, 34.2, 26.0, 26.0, 18.2, 18.2, −4.4, −4.5, −4.6, −4.7; **IR** (film, $cm^{-1}$): 3459, 3080, 2954, 2929, 2888, 2858, 1643, 1472, 1389, 1361, 1317, 1255, 1097, 836; **HRMS** (ESI) for $C_{21}H_{44}O_4Si_2Na$ $[M+Na]^+$: calcd. 437.2670; found 439.2673.

**(*E*)-5-((2*R*,4*R*,5*R*,6*R*)-4,5-Bis((*tert*-butyldimethylsilyl)oxy)-6-(((*tert*-butyldimethylsilyl)oxy)-methyl) tetrahydro-2*H*-pyran-2-yl)pent-3-en-1-ol (140).**




A solution of compound **136** (0.65 g, 1.2 mmol) and 3-buten-1-ol (0.44 g, 6.1 mmol) in $CH_2Cl_2$ (11 mL) was purged with argon for 15 min. A solution of complex **142** (35 mg, 61 μmol) in $CH_2Cl_2$ (1.0 mL) was added and the resulting mixture was stirred at reflux temperature for 5 h. Stirring was continued in air for 30 min at room temperature to destroy most of the catalyst. Volatile materials were evaporated and the crude product was subjected to flash chromatography (hexanes/*tert*-butyl methyl ether 20:1 to 10:1) to give *E*-**140** as a colorless liquid (0.53 g, 75%). A second fraction contained the undesired *Z*-isomer (50 mg, 7%). Analytical and spectral data of the major isomer *E*-**140**: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +3.2 (c = 0.72, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.62 – 5.53 (m, 1H), 5.50 – 5.41 (m, 1H), 3.90 – 3.87 (m, 2H), 3.84 – 3.77 (m, 2H), 3.73 (t, *J* = 6.9 Hz, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 3.57 (d, *J* = 3.5 Hz, 1H), 2.27 (p, *J* = 5.8, 5.3 Hz, 3H), 2.14 (dt, *J* = 13.4, 6.2 Hz, 1H), 1.82 (ddd, *J* = 13.5, 11.0, 2.6 Hz, 1H), 1.35 (d, *J* = 13.4 Hz, 1H), 0.89 (s, 27H), 0.07 – 0.01 (m, 18H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 130.2, 128.3, 80.3, 69.8, 68.3, 65.3, 62.1, 61.8, 39.2, 36.2, 33.8, 26.1, 26.0, 26.0, 18.5, 18.2, 18.1, −4.5, −4.6, −4.8, −5.1, −5.1; **IR** (film, $cm^{-1}$): 3421, 2954, 2929, 2857, 1463, 1361, 1255, 1090, 835; **HRMS** (ESI) for $C_{29}H_{62}O_5Si_3Na$ $[M+Na]^+$: calcd. 597.3797; found 597.3801.




Analytical and spectral data of the minor isomer *Z*-**140**: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +1.7 (c = 0.71, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.60 (dt, *J* = 10.9, 7.2 Hz, 1H), 5.48 (dt, *J* = 10.9, 7.5 Hz, 1H), 3.89 – 3.78 (m, 4H), 3.73 (t, *J* = 7.0 Hz, 1H), 3.68 – 3.61 (m, 2H), 3.57 (d, *J* = 3.4 Hz, 1H), 2.42 – 2.28 (m, 3H), 2.22 – 2.09 (m, 1H), 1.86 (ddd, *J* = 13.6, 11.3, 2.6 Hz, 1H), 1.35 (d, *J* = 13.3 Hz, 1H), 0.89 (m, 27H), 0.05 (m, 18H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 129.1, 127.6, 80.3, 69.8, 68.1, 65.1, 62.2, 61.6, 34.0, 31.1, 26.1, 26.0, 26.0, 18.4, 18.2, 18.1, −4.6, −4.6, −4.6, −4.8, −5.1, −5.1; **IR** (film, $cm^{-1}$): 3418, 2953, 2929, 2886, 2857, 1472, 1389, 1361, 1089, 775; **HRMS** (ESI) for $C_{29}H_{62}O_5Si_3Na$ $[M+Na]^+$: calcd. 597.3797; found 597.3740.

**Note**: The configuration of the double bond was assigned based on the $^{13}$C NMR shifts of the carbon signals vicinal to the alkenes: the $CH_2$ groups (as labeled with stars) adjacent to *E*-alkenes are more deshielded (Figure 6.3).

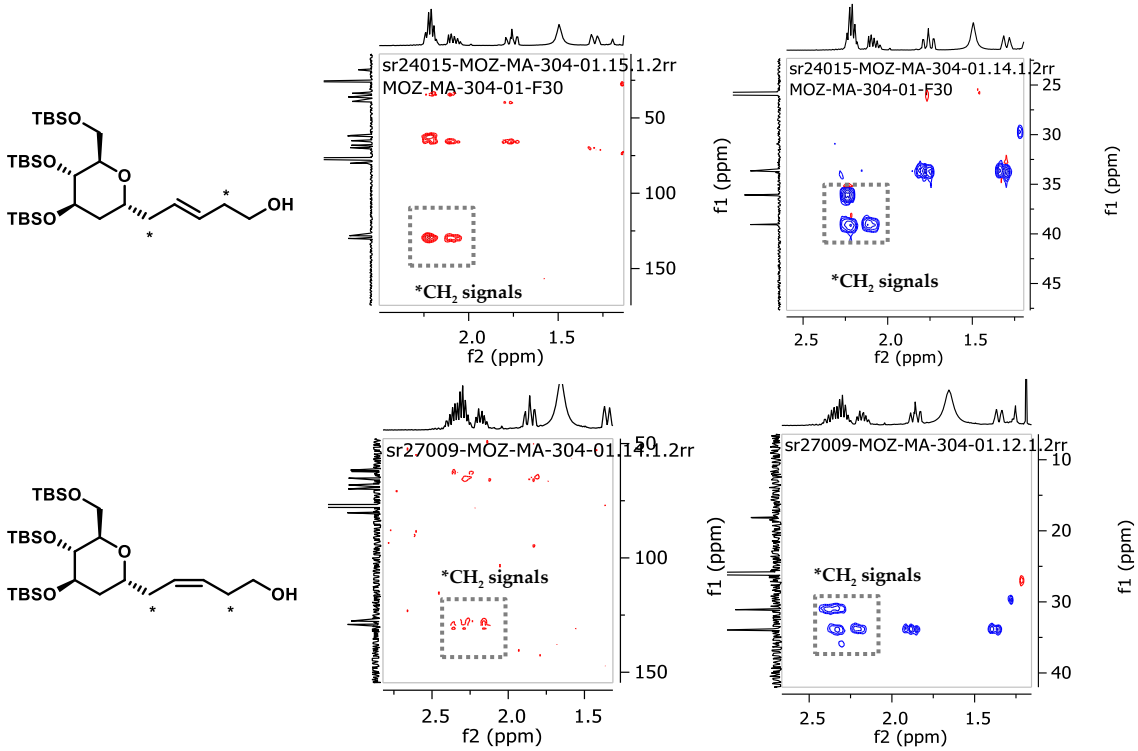
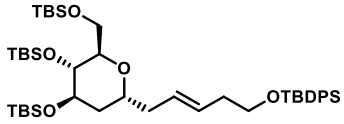


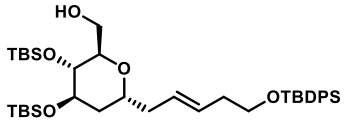

**Figure 6.3.** Determination of the *E*/*Z* isomers of **140** based on $^{13}$C NMR data.

**Compound 143.**



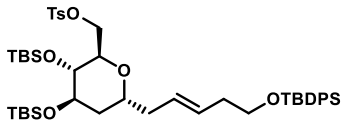

Imidazole (85 mg, 1.3 mmol) was added to a solution of the homoallylic alcohol **140** (0.36 g, 0.63 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C. After 5 min, TBDPSCl (0.19 g, 0.69 mmol) was added in one portion. The cooling bath was removed and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aq. $NH_4Cl$ solution (10 mL), the aqueous phase was extracted with $CH_2Cl_2$ (3 × 15 mL), and the combined organic layers were washed with water (20 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 100:1) to afford the title compound as a colorless liquid (507 mg, 99%). $[\alpha]_D^{20}$ = +5.0 (c = 1.10, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.63 (m, 4H), 7.43 – 7.32 (m, 6H), 5.46 (t, *J* = 3.7 Hz, 2H), 3.88 (d, *J* = 6.9 Hz, 2H), 3.81 – 3.70 (m, 3H), 3.66 (t, *J* = 6.9 Hz, 2H), 3.56 (d, *J* = 3.3 Hz, 1H), 2.31 – 2.19 (m, 3H), 2.07 (app dt, *J* = 14.0, 6.2 Hz, 1H), 1.78 (ddd, *J* = 13.4, 11.0, 2.5 Hz, 1H), 1.35 (d, *J* = 13.6 Hz, 1H), 1.04 (s, 9H), 0.89 (s, 18H), 0.87 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 135.7, 134.2, 129.7, 128.9, 128.5, 127.7, 80.2, 69.9, 68.4, 65.5, 64.2, 61.8, 39.3, 36.3, 33.7, 27.0, 26.1, 26.0, 26.0, 19.4, 18.4, 18.2, 18.1, −4.5, −4.6, −4.6, −4.8, −5.1, −5.1; **IR** (film, cm$^{-1}$): 3072, 2954, 2929, 2857, 1472, 1361, 1254, 1087, 938; **HRMS** (ESI) for $C_{45}H_{80}O_5Si_4Na$ $[M+Na]^+$: calcd. 835.4975; found 835.4979.

**((2*R*,3*R*,4*R*,6*R*)-3,4-Bis((*tert*-butyldimethylsilyl)oxy)-6-((*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-pent-2-en-1-yl)tetrahydro-2*H*-pyran-2-yl)methanol (144).**



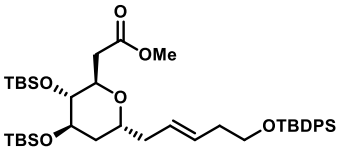

(*R*)-Camphor-10-sulfonic acid (18 mg, 0.077 mmol) was added to a solution of **143** (0.63 g, 0.77 mmol) in a solvent mixture of MeOH/$CH_2Cl_2$ (1:1 *v*/*v*, 7.6 mL) at −20 °C. The mixture was stirred at this temperature for 18 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layers were washed with water (20 mL), dried over $Na_2SO_4$, filtered and concentrated. The crude material was subjected to flash chromatography (hexanes/*tert*-butyl methyl ether 20:1 to 10:1) to afford the title compound as a colorless liquid (0.42 g, 77%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +1.3 (c = 0.56, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.68 – 7.64 (m, 4H), 7.44 – 7.34 (m, 6H), 5.55 – 5.39 (m, 2H), 4.09 (dd, *J* = 11.5, 9.1 Hz, 1H), 3.87 (app q, *J* = 9.2 Hz, 1H), 3.81 – 3.71 (m, 2H), 3.66 (t, *J* = 6.8 Hz, 2H), 3.46 (dd, *J* = 11.6, 3.3 Hz, 1H), 3.38 – 3.30 (m, 1H), 2.27 (app q, *J* = 6.6 Hz, 3H), 2.11 (dt, *J* = 13.3, 6.4 Hz, 1H), 1.83 (ddd, *J* = 12.8, 9.8, 2.8 Hz, 1H), 1.47 – 1.36 (m, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 135.7, 134.2, 129.7, 129.6, 128.1, 127.7, 79.2, 70.0, 69.7, 65.9, 64.1, 61.0, 38.5, 36.3, 34.2, 27.0, 26.0, 26.0, 19.4, 18.2, 18.2, −4.4, −4.4, −4.6; IR (film, cm$^{-1}$): 3469, 3071, 2954, 2929, 2893, 2857, 1472, 1428, 1255, 1038, 835; HRMS (ESI) for $C_{39}H_{66}O_5Si_3Na$ [M+Na]$^+$: calcd. 721.4110; found 721.4116.

**Compound 145.**




Pyridine (69 mg, 0.87 mmol), DMAP (3.4 mg, 0.028 mmol) and TsCl (43 mg, 0.22 mmol) were added to a solution of **144** (39 mg, 0.056 mmol) in $CH_2Cl_2$ (0.5 mL) at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature overnight. The reaction was quenched wtih saturated aq. $NH_4Cl$ (5 mL) and the aqeuous phase was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with water (10 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexane/*tert*-butyl methyl ether 20:1 to 10:1) to afford the title compound (33 mg, 69%).[200] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +8.9 (c = 0.33, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.79 (m, 2H), 7.66 (m, 4H), 7.39 (m, 6H), 7.29 (m, 2H), 5.47 – 5.37 (m, 1H), 5.34 – 5.24 (m, 1H), 4.52 (dd, *J* = 10.7, 9.0 Hz, 1H), 4.03 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.91 (dd, *J* = 8.9, 3.6 Hz, 1H), 3.70 (d, *J* = 3.1 Hz, 1H), 3.65 (t, *J* = 7.0 Hz, 1H), 3.47 (dt, *J* = 13.7, 6.2 Hz, 1H), 3.33 (d, *J* = 3.6 Hz, 1H), 2.40 (s, 3H), 2.26 (app q, *J* = 6.8 Hz, 2H), 2.04 (m, 2H), 1.72 (ddd, *J* = 13.6, 11.3, 2.4 Hz, 1H), 1.26 (d, *J* = 8.1 Hz, 1H), 1.04 (s, 9H), 0.86 (s, 9H), 0.82 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H), −0.04 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 144.7, 135.7, 134.2, 133.4, 129.9, 129.7, 129.3, 128.2, 127.8, 127.7, 76.7, 69.1, 68.6, 67.6, 64.6, 64.1, 38.9, 36.3, 32.9, 27.0, 25.9, 25.9, 21.8, 19.4, 18.1, 18.0, –4.7, –4.8, –4.8, –4.9; **IR** (film, cm$^{-1}$): 3071, 2998, 2853, 2929, 2893, 2857, 1599, 1472, 1428, 1362, 1256, 1178, 1069, 976, 833; **HRMS** (ESI) for $C_{46}H_{72}O_7Si_3SNa$ [M+Na]$^+$: calcd. 875.4199; found 875.4204.

**Compound *trans*-150.**




***Oxidation of the primary alcohol* 144 *to the aldehyde***: DMSO (34 mg, 0.44 mmol) was added to a solution of oxalyl chloride (28 mg, 0.22 mmol) in $CH_2Cl_2$ (1.0 mL) at –78 °C. The resulting mixture was stirred for 5 min at –78 °C, before a solution of **144** (70 mg, 0.10 mmol) in $CH_2Cl_2$ (0.5 mL) was introduced slowly. The mixture was stirred for 20 min at –78 °C. DIPEA (129 mg, 1.00 mmol) was added to the mixture at –78 °C over a period of 5 min. The reaction mixture was stirred at –78 °C for 5 min, then allowed to warm to room temperature over 30 min. The reaction was quenched with water (5 mL) and phosphate buffer (200 mM, pH = 7, 10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL) and the combined organic layers were washed with water (10 mL), dried over $Na_2SO_4$, filtered and concentrated.

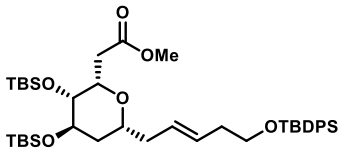
**Note**: The product can be used directly in the next step after drying under vacuum. However, purification by flash chromatography (hexanes/tert-butyl methyl ether 100:1) was performed in this case to provide the aldehyde (70 mg). $^1$H NMR analysis showed no racemization of the aldehyde.[38b]

***Wittig reaction***: A solution of freshly sublimed *t*-BuOK (0.80 mL, 0.25 M in THF, 0.20 mmol) was added to a suspension of $(MeOCH_2PPh_3)Cl$ (69 mg, 0.20 mmol, dried overnight under high vacuum at 50 °C) in THF (0.2 mL) at –78 °C. The resulting mixture was allowed to warm to 0 °C and stirred for 30 min before cooling to –78 °C again. The suspension turned dark red at 0 °C and deep orange at –78 °C. A solution of the aldehyde (prepared as above, 70 mg, 0.10 mmol) in THF (0.5 mL) was added slowly at –78 °C. The mixture was stirred at the same temperature for 1 h before warming to room temperature. After 3 h at room temperature, the reaction was quenched by addition of saturated aq. $NH_4Cl$ (5 mL) and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 100:1) to provide the methyl enol ether as a mixture of *E*/*Z* isomers (65 mg, 89%), which was used directly in the next step.

***Oxidation of the methyl enol ether***: PCC (39 mg, 0.18 mmol) was added to a solution of the methyl enol ether (prepared as above, 65 mg, 0.09 mmol) in $CH_2Cl_2$ (3 mL) at room temperature. After 6 h at room temperature, Celite was added to the reaction and the mixture was stirred for 10 min. The suspension was filtered through a pad of silica gel with $CH_2Cl_2$ as eluent. The combined filtrates were concentrated and the residue was purified by flash chromatography (fine silica, hexanes/EtOAc 100:1) to afford the 2,6-*trans* product as a colorless liquid (31 mg, 47%).[38b] $[\alpha]_D^{20}$ = +10.0 (c = 0.59, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.62 (m, 4H), 7.44 – 7.33 (m, 6H), 5.43 (m, 2H), 4.16 (t, *J* = 7.3 Hz, 1H), 3.82 (d, *J* = 2.7 Hz, 1H), 3.76 – 3.69 (m, 1H), 3.65 (m, 5H), 3.34 (d, *J* = 3.5 Hz, 1H), 2.59 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.43 (dd, *J* = 15.6, 6.3 Hz, 1H), 2.30

– 2.15 (m, 3H), 2.07 – 1.96 (m, 1H), 1.66 (ddd, *J* = 13.6, 11.7, 2.3 Hz, 1H), 1.35 (d, *J* = 13.6 Hz, 1H), 1.04 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 172.3, 135.7, 134.2, 129.6, 128.7, 128.4, 127.7, 71.5, 71.4, 70.4, 69.1, 64.2, 51.6, 39.2, 37.0, 36.3, 33.6, 27.0, 26.0, 25.9, 19.4, 18.2, 18.1, –4.4, –4.6, –4.7; **IR** (film, $cm^{-1}$): 3071, 2953, 2929, 2893, 2857, 1741, 1658, 1590, 1472, 1255, 1069, 835; **HRMS** (ESI) for $C_{41}H_{68}O_6Si_3Na$ $[M+Na]^+$: calcd. 763.4216; found 763.4216.

**Compound *cis*-150.**




From the above procedure, the 2,6-*cis* product was also isolated as a colorless liquid (30.9 mg, 46%). $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = –2.1 (c = 2.31, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.62 (m, 4H), 7.45 – 7.31 (m, 6H), 5.44 (app q, *J* = 5.3 Hz, 2H), 4.14 (t, *J* = 7.5 Hz, 1H), 3.87 – 3.75 (m, 2H), 3.65 (m, 5H), 3.42 (s, 1H), 2.97 – 2.76 (m, 2H), 2.32 – 2.15 (m, 3H), 2.07 (dt, *J* = 13.1, 5.9 Hz, 1H), 1.79 (ddd, *J* = 13.4, 10.6, 2.8 Hz, 1H), 1.38 (d, *J* = 13.6 Hz, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 172.4, 135.7, 134.2, 129.7, 128.9, 128.4, 127.7, 75.1, 70.4, 70.1, 65.3, 64.2, 51.6, 38.9, 36.3, 36.1, 33.9, 27.0, 26.0, 25.9, 19.4, 18.1, –4.5, –4.6, –4.7, –4.7; **IR** (film, $cm^{-1}$): 3072, 2952, 2929, 2894, 2857, 1739, 1590, 1463, 1428, 1255, 1069, 834; **HRMS** (ESI) for $C_{41}H_{68}O_6Si_3Na$ $[M+Na]^+$: calcd. 763.4216; found 763.4217.

The 2,6-*trans* and the 2,6-*cis* isomers were identified by nOe analysis. In the 2,6-*trans* configuration, no nOe signal was observed while a signal was detected in the 2,6-*cis* configuration (Figure 6.4).

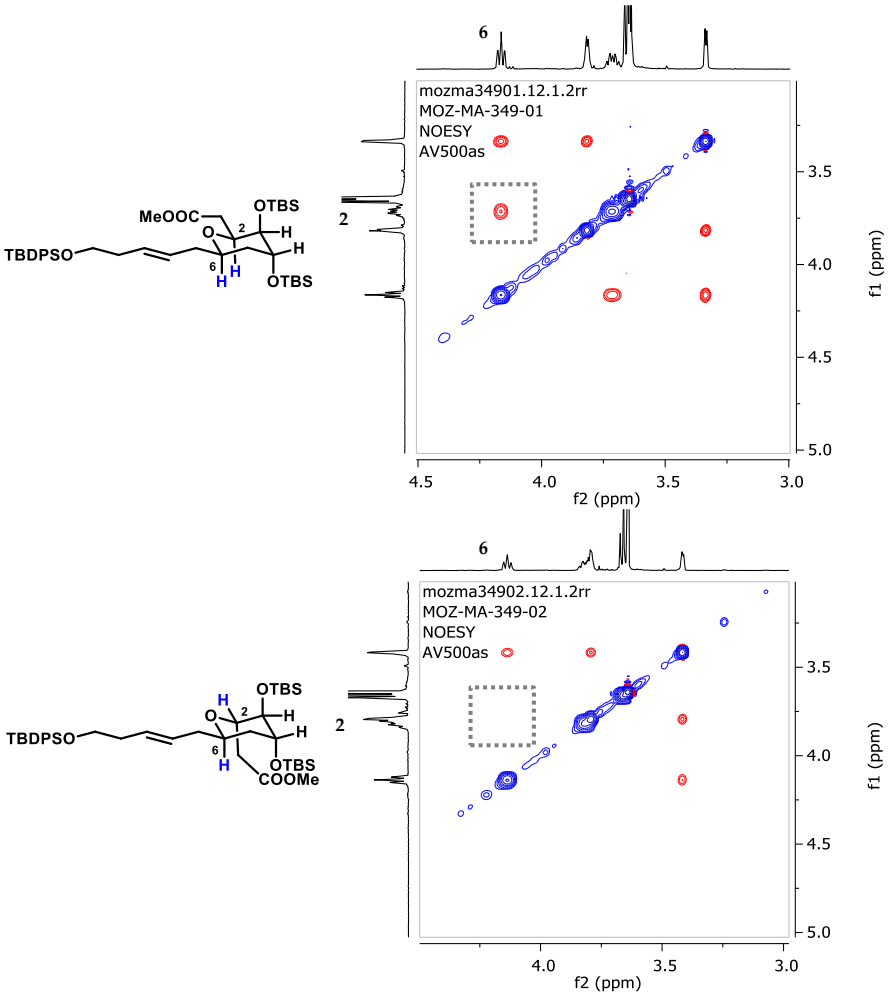
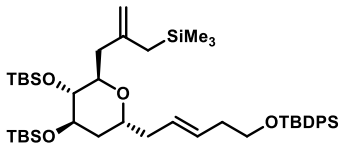



**Figure 6.4.** Determination of the 2,6-*trans* and the 2,6-*cis* configuration of compound **132**.

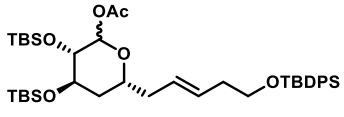
**Compound 152.**




THF (1.2 mL) was added to anhydrous $CeCl_3$ (63.8 mg, 0.26 mmol, dried overnight under high vaccum at 140 °C). The suspension was vigorously stirred at room temperature for 2 h and then subjected to sonication for 1 h. The suspension was stirred at room temperature for another 30 min before cooling to −78 °C. A solution of the Grignard reagent $TMSCH_2MgCl$ (0.26 mL, 1.0 M in $Et_2O$, 0.26 mmol) was added dropwise and the resulting mixture was stirred for 30 min at −78 °C. A solution of *trans*-**150** (32 mg, 0.043 mmol) in THF (0.6 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 2 h. The cooling bath was removed and the mixture was stirred over night at room temperature. The reaction was quenched with saturated aq. $NH_4Cl$ (2.0 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with water (10 mL), dried over $Na_2SO_4$, filtered and concentrated.

The residue was taken up in $CH_2Cl_2$ (5 mL) and silica (500 mg) was added. The reaction mixture was stirred for 5 h at room temperature, then filtered and the filtrate was concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 200:1 to 100:1) to afford the title compound (29 mg, 83%).[117b] **Note**: The compound is not stable under acidic conditions. $[\alpha]_D^{20}$ = +8.4 (c = 0.23, $C_6H_6$); **$^1$H NMR** ($C_6D_6$, 400 MHz): δ 7.83 – 7.74 (m, 4H), 7.25 (dd, *J* = 6.5, 2.7 Hz, 6H), 5.69 – 5.57 (m, 1H), 5.51 – 5.38 (m, 1H), 5.00 (d, *J* = 2.2 Hz, 1H), 4.78 (d, *J* = 2.1 Hz, 1H), 4.22 – 4.14 (m, 1H), 4.08 (app q, *J* = 8.6 Hz, 1H), 4.01 (d, *J* = 3.4 Hz, 1H), 3.72 (t, *J* = 7.0 Hz, 2H), 3.66 – 3.60 (m, 1H), 2.88 (dd, *J* = 14.4, 8.8 Hz, 1H), 2.62 (dd, *J* = 14.1, 5.6 Hz, 1H), 2.49 – 2.31 (m, 3H), 2.19 (m, 1H), 2.02 (ddd, *J* = 13.3, 10.4, 2.9 Hz, 1H), 1.76 (d, *J* = 13.6 Hz, 1H), 1.69 (d, *J* = 13.5 Hz, 1H), 1.51 (d, *J* = 13.4 Hz, 1H), 1.19 (s, 9H), 1.01 (s, 9H), 0.97 (s, 9H), 0.14 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H), 0.09 (s, 9H), 0.05 (s, 3H); **$^{13}$C NMR** ($C_6D_6$, 100 MHz): δ 145.9, 136.1, 134.5, 129.9, 129.2, 128.9, 110.0, 77.5, 72.0, 71.1, 65.1, 64.5, 39.8, 39.5, 36.7, 34.8, 27.2, 26.8, 26.1, 19.5, 18.4, 18.3, –1.1, –4.3, –4.4, –4.7; **IR** (film, $cm^{-1}$): 3072, 2954, 2929, 2894, 2857, 1631, 1472, 1427, 1361, 1250, 1087, 835; **HRMS** (ESI) for $C_{45}H_{78}O_4Si_4Na$ [M+Na]$^+$: calcd. 817.4869; found 817.4867.

**(3*S*,4*R*,6*R*)-3,4-Bis((*tert*-butyldimethylsilyl)oxy)-6-((*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-2-en-1-yl)tetrahydro-2H-pyran-2-yl acetate (153).**

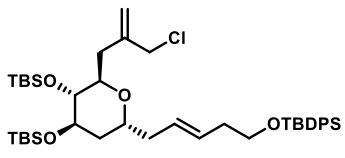



***Non-photochemical conditions***: Lead(IV) acetate (1.6 g, 3.6 mmol) was added in one portion to a solution of alcohol **144** (0.71 g, 1.0 mmol) in THF (10 mL) at room temperature. After stirring for 4.5 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL) and the mixture was diluted with *tert*-butyl methyl ether (20 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 5 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 20:1) to give the title compound as an inconsequential mixture of diastereoisomers (0.45 g, 61%).

***Photochemical conditions***: Lead(IV) acetate (2.55 g, 5.18 mmol) was added in one portion to a solution of alcohol **144** (1.81 g, 2.59 mmol) in $CH_2Cl_2$ (100 mL) at room temperature. The mixture was irradiated using a circular arrangement of 8 UV-A lamps (Philips Fluorescent lamps TUV PL-S 9W/2P, λ = 340-380 nm, at 6 cm distance from the reaction vessel) in an aluminum box. The temperature in the apparatus rose to 45 °C over the course of 45 min. The light source was turned off and the mixture was allowed to cool to ambient temperature. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (80 mL) and the mixture was diluted with *tert*-butyl methyl ether (150 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 50 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (80 mL) and brine (80 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 20:1) to give

the title compound as an inconsequential mixture of diastereoisomers (1.35 g, 72%). $[\alpha]_D^{20}$ = +12.9 (c = 1.33, $CHCl_3$). Spectral data of the major diastereoisomer: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.64 (m, 4H), 7.46 – 7.33 (m, 6H), 5.79 (d, *J* = 1.4 Hz, 1H), 5.55 – 5.37 (m, 2H), 4.23 – 4.08 (m, 1H), 3.79 (q, *J* = 3.3 Hz, 1H), 3.66 (t, *J* = 6.9 Hz, 2H), 3.53 – 3.41 (m, 1H), 2.37 – 2.21 (m, 3H), 2.18 – 2.07 (m, 1H), 2.04 (s, 3H), 1.81 (ddd, *J* = 13.9, 11.5, 2.6 Hz, 1H), 1.46 – 1.39 (m, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 170.1, 135.7, 134.2, 129.7, 129.5, 127.7, 127.7, 96.0, 68.6, 68.4, 65.8, 64.1, 38.7, 36.3, 33.0, 27.0, 25.9, 25.8, 21.5, 19.4, 18.1, −4.7, −4.7, −4.8, −4.9; **IR** (film, $cm^{-1}$): 2954, 2929, 2857, 1734, 1472, 1428, 1362, 1254, 1166, 1107, 1008, 939, 836, 777, 739, 702, 614, 505; **HRMS** (ESI) for $C_{40}H_{66}O_6Si_3Na$ $[M+Na]^+$: calcd. 749.4059; found 749.4047.

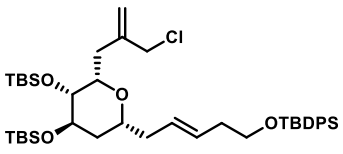
**Compound 157.**




Tin (IV) chloride (1.0 M in $CH_2Cl_2$, 0.92 mL, 0.92 mmol) was added dropwise with a graduated glass pipette to a solution of compound **153** (0.45 g, 0.61 mmol) and 2-(chloromethyl)allyl-trimethylsilane (**156**, 0.22 mL, 1.2 mmol) in $CH_2Cl_2$ (6 mL) at −78 °C. Once the addition was complete, stirring was continued at this temperature for 1.5 h. The reaction was quenched by addition of triethylamine (0.5 mL) at −78 °C before the mixture was allowed to reach room temperature. Saturated aqueous $NH_4Cl$ (10 mL) and *tert*-butyl methyl ether (10 mL) were added, followed by addition of water until all solid materials had been dissolved. The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 50:1) to give the title compound as a colorless oil (0.39 g, 83%, dr ≈ 5:1 by $^1$H NMR).

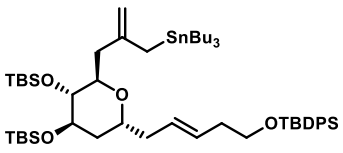
Analytically pure samples of both diastereomers were obtained by preparative HPLC (column: 250 mm MultoKrom Si 3 μm, 4.6 mm i.D.; gradient: 1.0 mL/min, *n*-heptane/*i*-PrOH = 99.9:0.1; $R_t$ (minor) = 6.89 min; $R_t$ (major) = 7.57 min). Analytical and spectral data of the major 2,6-*trans* diastereoisomer: $[\alpha]_D^{20}$ = +6.1 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.67 (dd, *J* = 7.9, 1.7 Hz, 4H), 7.44 – 7.35 (m, 6H), 5.52 – 5.34 (m, 2H), 5.09 (d, *J* = 1.5 Hz, 1H), 4.96 (d, *J* = 1.3 Hz, 1H), 4.12 – 4.02 (m, 2H), 3.88 – 3.78 (m, 3H), 3.65 (t, *J* = 7.1 Hz, 2H), 3.35 (ddd, *J* = 3.9, 2.0, 0.8 Hz, 1H), 3.02 (ddd, *J* = 15.0, 11.0, 1.0 Hz, 1H), 2.38 – 2.14 (m, 4H), 2.11 – 1.95 (m, 1H), 1.78 (ddd, *J* = 13.4, 10.4, 2.8 Hz, 1H), 1.44 – 1.35 (m, 1H), 1.05 (s, 9H), 0.90 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H), 0.06 (s, 3H), 0.04 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 143.7, 135.7, 134.2, 129.7, 128.8, 128.6, 127.7, 116.4, 71.7, 70.2, 64.9, 64.1, 48.3, 38.9, 36.2, 34.2, 33.7, 27.0, 26.0, 26.0, 19.4, 18.2, 18.1, 14.8, −4.5, −4.5, −4.7; **IR** (film, $cm^{-1}$): 2954, 2929, 2894, 2857, 1472, 1428, 1361, 1256, 1091, 1006, 970,

835, 776, 740, 702, 613, 505; **HRMS** (ESI) for $C_{42}H_{69}O_4Si_3ClNa$ $[M+Na]^+$: calcd. 779.4084; found 779.4085.




Spectral data of the minor 2,6-*cis* diastereoisomer: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.64 (m, 4H), 7.45 – 7.34 (m, 6H), 5.51 – 5.37 (m, 2H), 5.23 – 5.13 (m, 1H), 4.99 (d, *J* = 1.3 Hz, 1H), 4.18 – 4.03 (m, 2H), 3.92 – 3.78 (m, 3H), 3.65 (td, *J* = 6.9, 0.9 Hz, 2H), 3.37 (ddd, *J* = 3.6, 1.8, 0.8 Hz, 1H), 3.07 (ddd, *J* = 15.0, 10.9, 0.9 Hz, 1H), 2.39 – 2.25 (m, 3H), 2.23 – 2.06 (m, 2H), 1.79 (ddd, *J* = 13.4, 10.6, 2.7 Hz, 1H), 1.39 (dt, *J* = 13.5, 3.0 Hz, 1H), 1.04 (s, 9H), 0.90 (s, 18H), 0.07 (s, 6H), 0.06 (s, 3H), 0.05 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 143.7, 135.7, 134.1, 129.7, 127.7, 127.6, 127.4, 116.4, 77.3, 71.5, 70.2, 64.6, 63.7, 48.4, 34.2, 33.7, 33.6, 31.2, 29.9, 27.0, 26.1, 26.0, 19.3, 18.3, 18.1, −4.5, −4.7.

**Compound 158.**



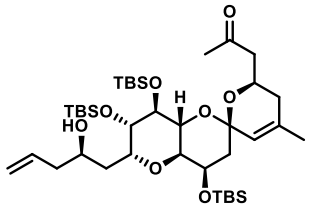

*n*-Butyllithium (1.6 M in hexanes, 0.96 mL, 1.5 mmol) was added to a solution of bis(tributyltin) (0.83 mL, 1.6 mmol) in THF (1.5 mL) at −20 °C. The mixture was stirred at this temperature for 15 min to give a clear solution of tributylstannyllithium.[124]

This solution was added dropwise to a solution of allyl chloride **157** (0.39 g, 0.51 mmol, d.r. = 5:1) in THF (3.5 mL) at −78 °C. The mixture was stirred at this temperature for 20 min. The reaction was quenched at −78 °C with water (5 mL), before the mixture was warmed to room temperature. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 5 mL) and the combined organic fractions were washed with brine (5 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether/triethylamine 200:1:2) to give the title compound as a colorless oil (0.47 g, 91%, dr ≈ 5:1 by $^1$H NMR). An analytically pure sample was obtained by reacting isomerically pure **157** under the same conditions; it analyzed as follows: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +7.5 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.67 (dd, *J* = 7.8, 1.7 Hz, 4H), 7.45 – 7.32 (m, 6H), 5.50 – 5.42 (m, 2H), 4.56 (d, *J* = 2.2 Hz, 1H), 4.48 (d, *J* = 2.2 Hz, 1H), 3.88 – 3.78 (m, 3H), 3.66 (t, *J* = 6.9 Hz, 2H), 3.41 (dd, *J* = 3.7, 1.6 Hz, 1H), 2.57 (dd, *J* = 14.0, 8.7 Hz, 1H), 2.34 – 2.16 (m, 4H), 2.11 – 2.02 (m, 1H), 1.88 – 1.73 (m, 3H), 1.59 – 1.38 (m, 6H), 1.41 – 1.36 (m, 1H), 1.30 (dq, *J* = 14.3, 7.2 Hz, 6H), 1.05 (s, 9H), 0.95 – 0.72 (m, 33H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 147.5, 135.7, 134.2, 129.6, 128.8, 128.6, 127.7, 107.4, 77.5, 71.2, 70.4, 64.5, 64.2, 39.2, 39.1, 36.3, 34.0, 29.3, 27.5, 27.0, 26.1, 26.0, 19.4, 18.8, 18.2, 18.2, 13.9, 9.6, −4.4, −4.5, −4.6, −4.7; **$^{119}$Sn NMR** ($CDCl_3$, 149 MHz): δ −16.3; **IR** (film, $cm^{-1}$): 2955, 2928, 2857, 1471, 1463, 1428, 1378, 1361, 1255, 1091, 1006, 973, 939, 835, 775, 738, 702, 688, 672, 666, 614, 505; **HRMS** (ESI) for $C_{54}H_{97}O_4Si_3Sn$ $[M+H]^+$: calcd. 1013.5711; found 1013.5729.

### 6.2.4 Fragment Assembly and Completion of the Total Synthesis

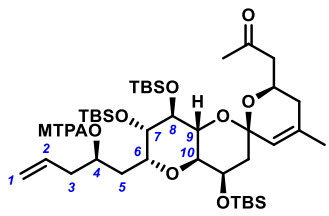
#### 6.2.4.1 Ketone Route

**Model Compound 159.**




Solid magnesium bromide diethyl etherate (14 mg, 53 μmol) was added in one portion to a solution of aldehyde **79** (7.6 mg, 11 μmol) and allyltributylstannane (3.5 μL, 11 μmol) in $CH_2Cl_2$ (0.3 mL) at −78 °C and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by addition of triethylamine (0.1 mL) at −78 °C before the mixture was warmed to room temperature and diluted with *tert*-butyl methyl ether (1 mL) and saturated aqueous $NH_4Cl$ (1 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (3 x 1 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$ and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc 15:1) to give the title compound as a colorless oil (6.1 mg, 76%, dr = 14:1 by $^1$H NMR). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.84 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.15 (dd, *J* = 2.6, 1.6 Hz, 2H), 5.14 – 5.05 (m, 1H), 4.34 (dddd, *J* = 10.9, 7.0, 5.9, 3.8 Hz, 1H), 4.16 – 4.06 (m, 1H), 4.01 (q, *J* = 3.0 Hz, 1H), 3.87 (dd, *J* = 10.1, 8.0 Hz, 1H), 3.88 – 3.80 (m, 1H), 3.66 – 3.52 (m, 2H), 3.49 (dd, *J* = 10.1, 2.8 Hz, 1H), 3.39 (d, *J* = 1.1 Hz, 1H), 2.75 (dd, *J* = 16.2, 6.0 Hz, 1H), 2.52 (dd, *J* = 16.2, 7.0 Hz, 1H), 2.36 – 2.20 (m, 2H), 2.21 (s, 3H), 1.98 – 1.75 (m, 5H), 1.75 – 1.67 (m, 1H), 1.68 (s, 3H), 0.89 (s, 18H), 0.88 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 206.9, 135.7, 134.9, 124.2, 117.6, 95.2, 78.4, 73.9, 72.9, 72.8, 71.1, 68.4, 66.6, 64.1, 50.1, 42.5, 42.0, 34.8, 30.8, 30.4, 26.4, 26.4, 26.0, 22.7, 18.5, 18.3, 18.3, −3.5, −3.6, −3.7, −4.3, −4.3, −4.8.

**Preparation of the (*S*)- and (*R*)-MTPA esters (266) of alcohol 159.**




(*R*)-(−)-MTPA-Cl (2.0 mg, 7.9 μmol) and DMAP (0.1 mg, 0.8 μmol) were added to a stirred solution of **159** (3.0 mg, 4.0 μmol) and pyridine (1.0 μL, 12 μmol) in $CH_2Cl_2$ (0.2 mL) at room temperature. After stirring for 16 h at room temperature, the reaction was quenched with $H_2O$ (1 mL) and the mixture was diluted with *tert*-butyl methyl ether (2 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (2 × 2 mL). The combined organic fractions were dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 15:1) to give (*S*)-**266** (3.8 mg, 3.9 μmol, 98%) as a pale yellow oil. **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 7.58 – 7.51 (m, 2H), 7.45 – 7.34 (m, 3H), 5.76 (dddd, *J* = 16.5, 10.2, 7.8, 6.0 Hz, 1H), 5.29 – 5.23 (m, 1H), 5.22 (dt, *J* = 2.3, 1.1 Hz, 1H), 5.12 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.10 (d, *J* = 10.2 Hz, 1H), 4.34 (ddd, *J* = 10.5, 6.4, 4.1 Hz, 1H), 4.10 (q, *J* = 3.0 Hz, 1H), 3.93 (dt, *J* = 12.2, 4.0 Hz, 1H), 3.82 (dd, *J* =

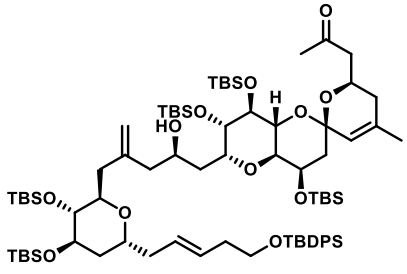
9.9, 7.5 Hz, 1H), 3.64 – 3.57 (m, 2H), 3.55 (d, *J* = 1.2 Hz, 3H), 3.40 (dd, *J* = 10.1, 2.9 Hz, 1H), 2.74 (dd, *J* = 16.1, 6.1 Hz, 1H), 2.60 – 2.55 (m, 1H), 2.51 (dd, *J* = 16.1, 6.7 Hz, 1H), 2.42 – 2.29 (m, 1H), 2.23 (s, 3H), 2.15 – 2.04 (m, 1H), 1.96 – 1.79 (m, 3H), 1.79 – 1.71 (m, 2H), 1.69 (s, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H), 0.03 (s, 9H), 0.02 (s, 3H).

(*R*)-**266** was prepared analogously using (*S*)-(+)-MTPA-Cl. **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 7.61 – 7.50 (m, 2H), 7.47 – 7.31 (m, 3H), 5.62 (ddt, *J* = 16.6, 10.2, 7.2, 7.0 Hz, 1H), 5.27 – 5.18 (m, 1H), 5.22 – 5.16 (m, 1H), 5.02 (dd, *J* = 17.2, 1.7 Hz, 1H), 4.99 (dt, *J* = 10.0, 1.4 Hz, 1H), 4.33 (dtd, *J* = 10.5, 6.5, 3.9 Hz, 1H), 4.08 (q, *J* = 3.0 Hz, 1H), 3.97 (dt, *J* = 12.1, 4.0 Hz, 1H), 3.84 (dd, *J* = 10.1, 7.4 Hz, 1H), 3.67 – 3.56 (m, 2H), 3.56 (d, *J* = 1.2 Hz, 3H), 3.40 (dd, *J* = 10.4, 3.5 Hz, 1H), 2.74 (dd, *J* = 16.1, 6.1 Hz, 1H), 2.51 (dd, *J* = 16.1, 6.8 Hz, 1H), 2.48 (s, 1H), 2.38 – 2.25 (m, 1H), 2.22 (s, 3H), 2.23 – 2.11 (m, 1H), 1.96 – 1.76 (m, 4H), 1.72 (dd, *J* = 14.4, 3.4 Hz, 1H), 1.68 (s, 3H), 0.90 (s, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

**Table 6.3.** Analysis of the Mosher esters **266** according to Hoye and co-workers;[48] arbitrary numbering scheme as shown in the insert.

| Atom number | **159** δ [ppm] | (*S*)-**266** δ [ppm] | (*R*)-**266** δ [ppm] | Δδ [ppm] |
|---|---|---|---|---|
| 1-*cis* | 5.1 | 5.1 | 5.02 | +0.08 |
| 1-*trans* | 5.13 | 5.12 | 4.99 | +0.13 |
| 2 | 5.84 | 5.76 | 5.62 | +0.14 |
| 3' | 2.27 | 2.57 | 2.48 | +0.09 |
| 3'' | 2.27 | 2.34 | 2.31 | +0.03 |
| 4 | 3.84 | 5.25 | 5.23 | +0.02 |
| 5' | 1.85 | 2.09 | 2.17 | −0.08 |
| 5'' | 1.85 | 1.74 | 1.86 | −0.12 |
| 6 | 4.11 | 3.93 | 3.97 | −0.04 |
| 7 | 3.59 | 3.59 | 3.62 | −0.03 |
| 8 | 3.87 | 3.82 | 3.84 | −0.02 |
| 9 | 3.59 | 3.59 | 3.62 | −0.03 |
| 10 | 3.49 | 3.4 | 3.4 | ±0.00 |

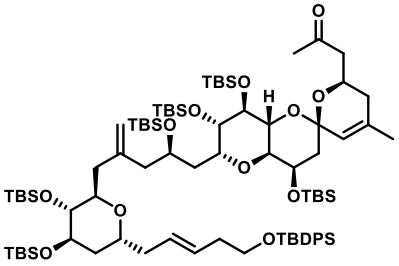
**Compound 190.**




Solid magnesium bromide diethyl etherate (574 mg, 2.22 mmol) was added in one portion to a solution of aldehyde **79** (317 mg, 0.445 mmol) and allyl stannane **158** (540 mg, 0.533 mmol, dr 5:1) in $CH_2Cl_2$ (12 mL) at −78 °C. The resulting mixture was stirred at this temperature for 3 h before the reaction was quenched at −78 °C with

triethylamine (0.5 mL). The mixture was warmed to room temperature and diluted with *tert*-butyl methyl ether (20 mL) and saturated aqueous $NH_4Cl$ (20 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 20 mL). The organic phase was dried over anhydrous $Na_2SO_4$ and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc 15:1) to give the title compound as a colorless oil (561 mg, 88%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +22.1 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.70 – 7.63 (m, 4H), 7.48 – 7.32 (m, 6H), 5.53 – 5.33 (m, 2H), 5.15 (s, 1H), 4.90 (s, 2H), 4.35 (dtd, *J* = 10.5, 6.5, 3.9 Hz, 1H), 4.14 – 4.02 (m, 1H), 4.00 (q, *J* = 3.0 Hz, 1H), 3.94 (dt, *J* = 9.7, 5.0 Hz, 1H), 3.90 – 3.74 (m, 4H), 3.65 (td, *J* = 8.5, 7.7, 5.5 Hz, 3H), 3.56 (dd, *J* = 8.7, 5.2 Hz, 1H), 3.49 (dd, *J* = 10.1, 2.7 Hz, 1H), 3.42 (s, 1H), 3.36 (dd, *J* = 3.9, 2.7 Hz, 1H), 2.81 – 2.60 (m, 2H), 2.52 (dd, *J* = 16.2, 6.9 Hz, 1H), 2.37 (dd, *J* = 14.3, 4.9 Hz, 1H), 2.33 – 2.15 (m, 7H), 2.14 – 2.03 (m, 1H), 1.98 – 1.69 (m, 7H), 1.70 – 1.65 (m, 3H), 1.46 – 1.36 (m, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.89 (s, 27H), 0.88 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.05 (s, 15H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 207.0, 144.0, 135.7, 135.5, 134.2, 129.7, 128.9, 128.5, 127.7, 124.2, 114.9, 95.1, 77.7, 76.3, 73.9, 72.8, 71.9, 71.0, 70.6, 70.5, 68.4, 66.6, 65.5, 64.1, 64.0, 50.2, 43.4, 42.5, 38.5, 37.2, 36.3, 34.8, 34.2, 30.8, 27.0, 26.6, 26.5, 26.4, 26.4, 26.1, 26.0, 22.7, 19.4, 18.5, 18.4, 18.3, 18.2, 18.2, −3.5, −3.6, −3.6, −4.0, −4.2, −4.3, −4.3, −4.3, −4.4, −4.7, −4.7, −4.8; **IR** (film, $cm^{-1}$): 2953, 2929, 2893, 2857, 1719, 1472, 1463, 1428, 1388, 1361, 1253, 1205, 1091, 1040, 1007, 961, 836, 776, 738, 703, 688, 672, 667, 613, 506; **HRMS** (ESI) for $C_{78}H_{138}O_{12}Si_6Na$ $[M+Na]^+$: calcd. 1457.8696; found 1457.8698.

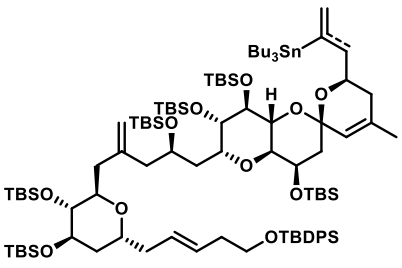
**Compound 192.**




A solution of TBSOTf (1.0 M in $CH_2Cl_2$, 0.29 mL, 0.29 mmol) was added dropwise to a solution of alcohol **190** (0.38 g, 0.27 mmol) and 2,6-lutidine (93 µL, 0.80 mmol) in $CH_2Cl_2$ (2.5 mL) at −78 °C using a glas pipette. Stirring was continued at −78 °C for 6 h before the reaction was quenched with saturated aqueous $NH_4Cl$ (3 mL). The mixture was warmed to room temperature and stirred until all solids had dissolved. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 3 mL). The combined organic fractions were washed with brine (3 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 25:1) to give the title compound as a colorless syrup (0.35 g, 84%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +27.1 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.70 – 7.63 (m, 4H), 7.45 – 7.32 (m, 6H), 5.48 – 5.41 (m, 2H), 5.16 (s, 1H), 4.87 (s, 1H), 4.85 (s, 1H), 4.35 (dtd, *J* = 10.5, 6.4, 4.0 Hz, 1H), 4.02 (q, *J* = 3.0 Hz, 1H), 3.95 – 3.71 (m, 6H), 3.65 (dd, *J* = 7.5, 6.3 Hz, 3H), 3.54 (dd, *J* = 7.9, 4.9 Hz, 1H), 3.42 (dd, *J* = 3.6, 1.6 Hz, 1H), 3.36 (d, *J* = 10.0 Hz, 1H), 2.74 (dd, *J* = 15.9, 6.0 Hz, 1H), 2.72 – 2.63 (m, 1H), 2.51 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.41 (dd, *J* = 14.3, 6.0 Hz, 1H), 2.23 (s, 7H), 2.08 (dd, *J* = 13.5, 7.8 Hz, 2H), 1.96 – 1.69 (m, 6H), 1.68 (s, 3H), 1.65 (dd, *J*

= 14.5, 3.6 Hz, 1H), 1.37 (dt, *J* = 13.7, 2.8 Hz, 1H), 1.04 (s, 9H), 0.90 (s, 9H), 0.90 (s, 9H), 0.89 – 0.88 (m, 36H), 0.10 (s, 3H), 0.06 – 0.02 (m, 27H), 0.02 (s, 3H), 0.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 207.2, 144.2, 144.1, 135.7, 135.4, 134.2, 134.2, 129.7, 128.8, 128.6, 127.7, 124.5, 115.1, 95.2, 74.2, 73.3, 70.9, 70.8, 70.3, 69.6, 68.9, 66.9, 64.4, 64.2, 64.1, 50.2, 42.8, 42.6, 39.1, 37.6, 36.3, 34.9, 33.9, 30.8, 27.0, 26.5, 26.5, 26.2, 26.0, 26.0, 22.7, 19.4, 19.3, 18.6, 18.4, 18.2, 18.2, 18.1, −3.5, −3.6, −3.7, −3.9, −4.1, −4.3, −4.3, −4.4, −4.5, −4.8, −4.9; **IR** (film, $cm^{-1}$): 2954, 2929, 2894, 2857, 1721, 1472, 1463, 1428, 1388, 1361, 1253, 1205, 1093, 1041, 1006, 963, 835, 809, 775, 738, 702, 671, 666, 505; **HRMS** (ESI) for $C_{84}H_{152}O_{12}Si_7Na$ [M+Na]$^+$: calcd. 1571.9561; found 1571.9561.

**Compound 267.**

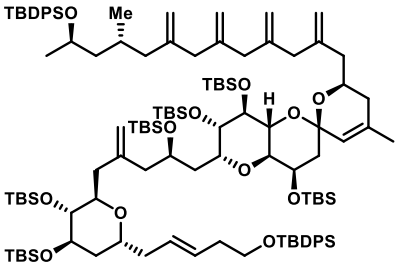



*n*-Butyllithium (1.6 M in hexanes, 0.15 mL, 0.24 mmol) was added to a solution of hexabutylditin (0.13 mL, 0.25 mmol) in THF (1.8 mL) at −20 °C. The mixture was stirred at this temperature for 15 min to give a pale yellow solution of tributylstannyllithium. This solution was cooled to −78 °C and solid copper(I) cyanide (11 mg, 0.12 mmol) was added in one portion. The mixture was allowed to warm to −55 °C and stirred at this temperature for 15 min to give a green-yellow solution of the bis(tributylstannyl) cuprate reagent.[68, 124]

In a separate flask, trityl potassium (0.20 M in 1,2-dimethoxyethane, 0.90 mL, 0.18 mmol) was added dropwise to a stirred solution of ketone **192** (62 mg, 0.040 mmol) and bis(trifluoromethanesulfonyl)aniline (29 mg, 0.080 mmol) in THF (3.0 mL) at −78 °C until the red color of the trityl anion persisted. Stirring was continued at −78 °C for 15 min and the resulting solution of the alkenyl triflate was transferred *via* cannula into the cooled (−55 °C) stannylcuprate solution. The mixture was kept at −55 °C for 15 min before the reaction was quenched with saturated aqueous $NH_4Cl$ (6 mL). The mixture was diluted with *tert*-butyl methyl ether (6 mL) and then warmed to room temperature. Stirring was continued until all solids had dissolved. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 6 mL) and the combined organic fractions were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/toluene 2:1 + 1% $NEt_3$) to give the title compound and its internal double bond isomer as an inseperable mixture (4:1, 57 mg, 77%). Analytical and spectral data of the mixture of double bond isomers: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +27.9 (c = 1.02, $CHCl_3$); **$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ 7.72 – 7.60 (m, 4H), 7.51 – 7.34 (m, 6H), 5.85 (d, *J* = 2.0 Hz, 1H), 5.64 (dd, *J* = 6.7, 1.9 Hz; *resolved signal of minor isomer*), 5.55 – 5.40 (m, 2H), 5.26 (s, 1H), 5.19 (q, *J* = 1.2 Hz, 1H), 4.87 (d, *J* = 4.8 Hz, 2H), 4.16 (ddt, *J* = 12.7, 8.7, 4.4 Hz, 1H), 4.05 (q, *J* = 3.0 Hz, 1H), 4.02 – 3.78 (m, 5H), 3.78 – 3.64 (m, 4H), 3.60 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.45 (dd, *J* = 3.6, 1.5 Hz, 1H), 3.42 – 3.33 (m, 1H), 2.79 – 2.64 (m, 1H), 2.46 (dd, *J* = 14.3, 6.2 Hz, 1H), 2.38 – 2.24 (m, 4H), 2.19 (ddt, *J* = 11.1, 5.3, 2.5 Hz, 1H), 2.08 (dt, *J* = 14.6, 7.5 Hz, 2H), 2.01 –

1.70 (m, 7H), 1.72 – 1.61 (m, 3H), 1.60 – 1.40 (m, 7H), 1.34 (dq, *J* = 14.4, 7.2 Hz, 6H), 1.28 (s, 3H), 1.05 (s, 9H), 0.95 – 0.87 (m, 69H), 0.14 – 0.11 (m, 3H), 0.11 – 0.09 (m, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 – 0.05 (m, 16H), 0.04 (s, 3H), 0.03 (s, 3H); **$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ 150.9, 144.9, 144.7, 142.5, 136.0, 135.8, 134.5, 134.5, 130.0, 129.2, 128.9, 128.0, 127.1, 124.9, 114.9, 95.4, 77.0, 74.6, 74.0, 71.5, 71.2, 70.6, 70.0, 69.2, 67.2, 66.7, 64.6, 46.4, 43.1, 39.5, 38.1, 36.6, 35.2, 34.2, 32.4, 31.5, 30.2, 29.8, 29.7, 29.6, 29.5, 27.9, 27.1, 26.8, 26.7, 26.6, 26.3, 26.2, 26.1, 26.1, 23.2, 22.9, 20.7, 19.5, 18.9, 18.8, 18.7, 18.5, 18.4, 18.3, 14.0, 9.9, 9.4, −3.3, −3.5, −3.6, −3.7, −4.0, −4.1, −4.2, −4.3, −4.4, −4.5, −4.7, −4.8; **$^{119}$Sn NMR** ($CD_2Cl_2$, 149 MHz): δ −40.6 (minor), −44.2 (major); **IR** (film, $cm^{-1}$): 2956, 2928, 2857, 1489, 1466, 1446, 1361, 1288, 1247, 1215, 1184, 1157, 1086, 1037, 1007, 974, 962, 941, 922, 897, 856, 834, 814, 788, 753, 702, 664, 507; **HRMS** (ESI) for $C_{96}H_{178}O_{11}Si_7SnNa$ $[M+Na]^+$: calcd. 1846.0668; found 1846.0677.

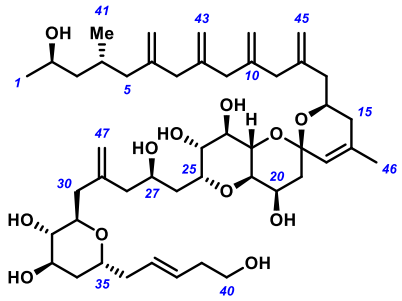
**Compound 222.**




A degassed solution of stannane **267** (10 mg, 5.5 μmol, 4:1 mixture of isomers) and allylic acetate **108** (3.4 mg, 6.6 μmol) in NMP (0.3 mL) was added to a Schlenk tube containing flame-dried tetrabutylammonium diphenylphosphinate (10 mg, 22 μmol). Copper-thiophene carboxylate complex (CuTC, 3.1 mg, 16 μmol) was then introduced followed by $Pd(PPh_3)_4$ (1.3 mg, 1.1 μmol). The reaction mixture was stirred for 2 h at ambient temperature before the reaction mixture was quenched with aqueous saturated $NH_4Cl$ (1 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 1 mL), the combined organic layers were washed with brine (1 mL), dried over anhydrous $Na_2SO_4$, filtered, and evaporated. The residue was purified twice by flash chromatography (fine silica, hexanes/toluene 3:2) to afford the fully protected polyol **222** as a colorless oil (single isomer, 8.4 mg, 77%). $[\alpha]_D^{20}$ = +9.8 (c = 0.98, $CH_2Cl_2$); **$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ 7.75 – 7.61 (m, 8H), 7.48 – 7.32 (m, 12H), 5.46 (t, *J* = 3.9 Hz, 2H), 5.19 (q, *J* = 1.6 Hz, 1H), 4.97 (dd, *J* = 3.7, 2.1 Hz, 2H), 4.90 – 4.82 (m, 6H), 4.77 (s, 1H), 4.75 (s, 1H), 4.16 (tt, *J* = 8.1, 5.9 Hz, 1H), 4.04 (q, *J* = 3.0 Hz, 1H), 3.98 – 3.79 (m, 6H), 3.76 – 3.69 (m, 2H), 3.67 (t, *J* = 6.9 Hz, 2H), 3.58 (dd, *J* = 8.5, 5.1 Hz, 1H), 2.74 (s, 2H), 2.66 (s, 5H), 2.41 (ddd, *J* = 16.5, 14.3, 5.8 Hz, 2H), 2.33 – 2.23 (m, 3H), 2.22 – 2.13 (m, 1H), 2.05 (dt, *J* = 14.5, 8.3 Hz, 3H), 2.00 – 1.48 (m, 17H), 1.38 (dt, *J* = 13.6, 2.7 Hz, 1H), 1.04 (s, 9H), 1.04 (s, 9H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (s, 36H), 0.70 (d, *J* = 6.3 Hz, 3H), 0.11 (s, 3H), 0.09 – 0.03 (m, 33H), 0.02 (s, 3H); **$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ 146.3, 145.4, 145.1, 144.7, 143.9, 136.4, 136.3, 136.0, 135.9, 135.5, 134.8, 134.5, 129.9, 129.9, 129.8, 129.1, 128.9, 128.0, 127.9, 127.7, 124.8, 114.9, 114.6, 114.0, 113.9, 113.2, 95.4, 77.0, 74.4, 73.6, 71.6, 71.1, 70.6, 70.0, 68.8, 68.2, 67.2, 65.7, 64.5, 64.5, 47.7, 44.1, 43.9, 43.2, 42.8, 41.9, 41.6, 39.5, 38.0, 36.6, 35.2, 34.2, 27.4, 27.3, 27.1, 26.7, 26.6, 26.2, 26.1, 26.1, 26.1, 24.4, 22.8, 19.8, 19.6, 19.5, 18.9, 18.7, 18.5, 18.4, 18.3, 18.3, 1.2, −3.3, −3.6, −3.6, −3.8, −4.0,

−4.1, −4.2, −4.3, −4.5, −4.5, −4.8, −4.8; **IR** (film, $cm^{-1}$): 3072, 2954, 2928, 2894, 2857, 1640, 1472, 1462, 1428, 1379, 1361, 1253, 1206, 1095, 1038, 1007, 965, 896, 835, 775, 739, 702, 686, 613, 505; **HRMS** (ESI) for $C_{115}H_{194}O_{12}Si_8Na$ [M+Na]$^+$: calcd. 2014.2617; found 2014.2636.

**27-*epi*-13.**




Water (9.4 μL, 0.52 mmol) and TASF (48 mg, 0.17 mmol) were added to a solution of silyl ether **222** (14 mg, 7.2 μmol) in DMF/THF (1:1, 0.4 mL) at room temperature. After 24 h, additional TASF (48 mg, 0.17 mmol) was introduced and stirring continued for another 24 h. The reaction was quenched with pH 7.4 phosphate buffer (1 mL) and the aqueous phase was extracted with EtOAc (5 × 1 mL). The combined organic fractions were washed with brine (1 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was taken up in pyridine/THF (3:1 *v*/*v*, 0.4 mL) and HF–pyridine complex (0.1 mL) was added at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature for 11 d. The reaction was quenched by dropwise addition of pH 7.4 phosphate buffer (1 mL) and the aqueous phase was extracted with EtOAc (5 × 1 mL). The combined organic fractions were washed with brine (1 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by preparative HPLC (column: YMC-Actus ODS-A, S-5 μm, 150 mm length, 20.0 mm ID; gradient: 20.0 mL/min, MeCN/$H_2O$ 50:50 for 10 min, then 100:0 for 50 min; $R_t$ = 6.65 min) to afford 27-*epi*-**13** as a colorless oil (2.2 mg, 37%). **Analytical HPLC:** column: YMC ODS-A, S-5 μm, 150 mm length, 4.6 mm ID; gradient: 1.0 mL/min, MeCN/$H_2O$ 50:50 for 10 min, then 100:0 for 20 min; $R_t$ = 8.76 min; **$^1$H NMR** ($CD_3OD$, 600 MHz): δ 5.56 – 5.49 (m, 1H), 5.49 – 5.43 (m, 1H), 5.30 (p, *J* = 1.3 Hz, 1H), 5.01 (t, *J* = 1.5 Hz, 1H), 4.96 (d, *J* = 2.2 Hz, 1H), 4.93 – 4.86 (m, 7H), 4.82 – 4.80 (m, 1H), 4.80 (q, *J* = 1.2 Hz, 1H), 4.25 (ddt, *J* = 10.7, 9.5, 3.8 Hz, 1H), 4.13 (ddd, *J* = 10.1, 5.6, 4.7 Hz, 1H), 3.99 (q, *J* = 3.1 Hz, 1H), 3.97 – 3.88 (m, 2H), 3.82 (dqd, *J* = 12.4, 6.1, 3.9 Hz, 1H), 3.74 (ddd, *J* = 10.7, 8.1, 4.7 Hz, 1H), 3.69 – 3.58 (m, 4H), 3.54 (t, *J* = 6.8 Hz, 2H), 3.41 (m, 1H), 3.04 – 2.98 (m, 2H), 2.88 (d, *J* = 14.7 Hz, 1H), 2.77 – 2.66 (m, 6H), 2.45 (ddd, *J* = 14.5, 8.3, 6.4 Hz, 1H), 2.39 (dd, *J* = 14.2, 3.9 Hz, 1H), 2.29 (dd, *J* = 13.8, 4.1 Hz, 1H), 2.27 – 2.19 (m, 4H), 2.14 (dd, *J* = 14.5, 9.4 Hz, 2H), 2.00 – 1.79 (m, 8H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.63 (ddd, *J* = 13.1, 10.8, 5.6 Hz, 1H), 1.46 (ddd, *J* = 13.7, 9.1, 4.3 Hz, 1H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.07 (ddd, *J* = 13.4, 9.1, 3.9 Hz, 1H), 0.87 (d, *J* = 6.3 Hz, 3H); **$^{13}$C NMR** ($CD_3OD$, 151 MHz): δ 147.1, 146.1, 146.0, 145.3, 145.1, 138.3, 130.2, 130.0, 123.8, 115.7, 115.1, 114.9, 114.7, 113.9, 97.8, 77.1, 76.1, 73.7, 73.4, 73.3, 72.6, 70.8, 70.0, 69.9, 68.3, 68.0, 66.8, 66.1, 62.8, 47.6, 45.0, 44.8, 43.3, 43.2, 42.5, 42.3, 41.2, 38.9, 37.1, 36.5, 36.2, 35.8, 33.7, 28.2, 24.4, 22.8, 19.8; **HRMS** (ESI) for $C_{47}H_{74}O_{12}Na$ [M+Na]$^+$: calcd. 853.5072; found 853.5073.

**Table 6.4.** NMR data of 27-*epi*-**13**; numbering scheme as shown in the insert.

| atom number | **$^1$H NMR** ($CDCl_3$, 500 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 126 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 1 | 1.14 | 6.2 | 2 | 3a | 24.4 | 3ab |
| 2 | 3.82 | 12.4, 6.1, 3.9 | 1, 3a, 3b | 3b, 41 | 66.1 | 1, 3ab |
| 3a | 1.46 | 13.7, 9.1, 4.3 | 2, 3b, 4 | 1 | 47.6 | 1, 5ab, 41 |
| 3b | 1.07 | 13.4, 9.1, 3.9 | 2, 3a, 4 | 2, 41 | | |
| 4 | 1.87 | - | 3a, 3b, 41 | - | 28.2 | 3ab, 5ab, 41 |
| 5a | 1.98 | - | 42' | 42' | 45 | 3ab, 7, 41, 42', 42'' |
| 5b | 1.82 | - | 42' | 41, 42' | | |
| 6 | - | - | - | - | 147.1 | 5ab, 7, 42', 42'' |
| 7 | 2.73 | - | 42', 42'', 43', 43'' | 42'' | 43.4 | 9, 5ab, 42', 42'', 43', 43'' |
| 8 | - | - | - | - | 146.1 | 7, 9, 43', 43'' |
| 9 | 2.7 | - | 43', 43'', 44', 44'' | 44', 44'' | 42.3 | 7, 11ab, 43', 43'', 44', 44'' |
| 10 | - | - | - | - | 146 | 9, 11ab, 44', 44'' |
| 11a | 3.01 | 14.7 | 11b, 44', 45', 45'' | 13a, 14, 44', 44'', 45'' | 43.2 | 9, 13ab, 44', 44'', 45', 45'' |
| 11b | 2.88 | 14.7 | 11a, 44', 44'', 45'' | 44', 44'', 45'' | | |
| 12 | - | - | - | - | 145.3 | 11ab, 13ab, 45' |
| 13a | 2.29 | 13.8, 4.1 | 13b, 14, 45' | 11a | 42.5 | 11ab, 45', 45'' |
| 13b | 2.22 | - | 13a, 14, 45' | 45' | | |
| 14 | 4.25 | 10.7, 9.5, 3.8, 3.8 | 13ab, 15ab | 11a, 22, 44', 45' | 66.8 | 13ab |
| 15a | 1.93 | - | 14, 15b, 17, 46 | 46 | 36.2 | 13ab, 17, 46 |
| 15b | 1.84 | - | 14, 15a, 17, 46 | 46 | | |
| 16 | - | - | - | - | 138.3 | 15ab, 46 |
| 17 | 5.3 | 1.3 | 15ab, 19a, 46 | 19b, 46 | 123.8 | 15ab, 19b, 46 |
| 18 | - | - | - | - | 97.8 | 17, 19ab, 20 |
| 19a | 1.94 | - | 17, 19b, 20 | 20 | 41.2 | 20 |
| 19b | 1.89 | - | 19a, 20 | 17, 20, 21 | | |
| 20 | 3.99 | 3.1 | 19ab, 21 | 19ab, 21 | 68 | 19a, 22 |
| 21 | 3.41 | - | 20, 22 | 19b, 20, 26a, 27 | 70.8 | 19a, 20, 22, 25 |
| 22 | 3.66 | - | 21, 23 | 14 | 69.9 | 20, 21, 23 |
| 23 | 3.66 | - | 22, 24 | 26a | 72.6 | 21, 22, 24, 25 |
| 24 | 3.62 | - | 23, 25 | 25 | 73.4 | 23, 25 |
| 25 | 4.13 | 10.1, 5.6, 4.7 | 24, 26ab | 24, 27, 28a | 76.1 | 26ab |
| 26a | 1.89 | - | 25, 26b, 27 | 21, 23 | 33.7 | 24, 25, 28b |

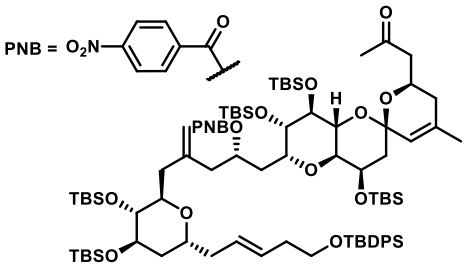
| atom number | $^1$H NMR ($CDCl_3$, 500 MHz) | | | | $^{13}$C NMR ($CDCl_3$, 126 MHz) | |
|---|---|---|---|---|---|---|
| | δ [ppm] | *J* [Hz] | COSY | NOESY | δ [ppm] | HMBC |
| 26b | 1.84 | - | 25, 26a, 27 | - | | |
| 27 | 3.94 | - | 26ab, 28ab | 21, 25, 28a, 30a, 31, 47'' | 68.3 | 25, 26ab, 28a |
| 28a | 2.39 | 14.2, 3.9 | 27, 28b, 47', 47'' | 25, 27, 31, 47'' | 44.8 | 30b, 47', 47'' |
| 28b | 2.14 | - | 27, 28a, 47', 47'' | 47'' | | |
| 29 | - | - | - | - | 145.1 | 28ab, 30ab, 47' |
| 30a | 2.69 | - | 30b, 31, 47', 47'' | 27, 32, 47' | 38.9 | 28b, 32, 47', 47'' |
| 30b | 2.14 | 14.5, 9.4 | 30a, 31, 47', 47'' | 32, 47' | | |
| 31 | 3.6 | - | 30ab, 32 | 27, 28a, 33, 36ab, 47' | 73.8 | 30ab, 32, 35 |
| 32 | 3 | 8.3, 8.3 | 31, 33 | 30ab, 34b | 77.1 | 30b, 33, 34ab |
| 33 | 3.74 | 10.7, 8.1, 4.7 | 32, 34ab | 31, 34a, 36ab | 70 | 32, 34ab, 35 |
| 34a | 1.9 | - | 33, 34b, 35 | 33 | 36.5 | 36a |
| 34b | 1.63 | 13.1, 10.8, 5.6 | 33, 34a, 35 | 32, 35 | | |
| 35 | 3.91 | - | 34ab, 36ab | 34b, 37 | 73.3 | 34b, 36ab |
| 36a | 2.45 | 14.5, 8.3, 6.4 | 35, 36b, 37 | 31, 33, 37 | 35.8 | 34b, 37, 38 |
| 36b | 2.24 | - | 35, 36a, 37 | 31, 33, 37 | | |
| 37 | 5.47 | - | 36ab, 38 | 35, 36ab | 130 | 36ab, 39 |
| 38 | 5.52 | - | 37, 39 | 39, 40 | 130.2 | 36ab, 39, 40 |
| 39 | 2.22 | - | 38, 40 | 38 | 37.1 | 37, 38, 40 |
| 40 | 3.54 | 6.8 | 39 | 38 | 62.8 | 38, 39 |
| 41 | 0.87 | 6.3 | 4 | 2, 3b, 5b, 42' | 19.8 | 3ab, 5ab |
| 42' | 4.81 | - | 5ab, 7, 42'' | 5ab, 41 | 113.9 | 5ab, 7 |
| 42'' | 4.8 | 1.2 | 7, 42' | 7 | | |
| 43' | 4.9 | - | 7, 9, 43'' | - | 114.7 | 7, 9 |
| 43'' | 4.88 | - | 7, 9, 43' | - | | |
| 44' | 5.01 | 1.5 | 9, 11ab, 44'' | 9, 11ab, 14 | 115.1 | 9, 11ab |
| 44'' | 4.88 | - | 9, 11b, 44' | 9, 11ab | | |
| 45' | 4.96 | 2.2 | 11a, 13ab, 45'' | 13b, 14 | 115.8 | 11ab, 13ab |
| 45'' | 4.91 | - | 11ab, 45' | 11ab | | |
| 46 | 1.71 | 1.3 | 15ab, 17 | 15ab, 17 | 22.8 | 15b, 17 |
| 47' | 4.91 | - | 28ab, 30ab, 47'' | 30ab, 31 | 114.9 | 28ab, 30a |
| 47'' | 4.88 | - | 28ab, 30ab, 47' | 27, 28ab | | |

**Table 6.5.** Comparison of $^{13}C$ NMR shifts of synthetic polyol 27-*epi*-**13** with authentic Limaol;[35] color code: $|\Delta\delta| \leq 0.1$ ppm; $|\Delta\delta| > 0.1$ ppm.

| Atom number | Limaol (13) δ [ppm] | 27-*epi*-13 δ [ppm] | Δδ [ppm] |
|---|---|---|---|
| 1 | 24.4 | 24.4 | ±0.0 |
| 2 | 66.1 | 66.1 | ±0.0 |
| 3 | 47.6 | 47.6 | ±0.0 |
| 4 | 28.1 | 28.2 | −0.1 |
| 5 | 45.0 | 45.0 | ±0.0 |
| 6 | 147.1 | 147.1 | ±0.0 |
| 7 | 43.3 | 43.4 | −0.1 |
| 8 | 146.1 | 146.1 | ±0.0 |
| 9 | 42.3 | 42.3 | ±0.0 |
| 10 | 146.0 | 146.0 | ±0.0 |
| 11 | 43.2 | 43.2 | ±0.0 |
| 12 | 145.3 | 145.3 | ±0.0 |
| 13 | 42.5 | 42.5 | ±0.0 |
| 14 | 66.8 | 66.8 | ±0.0 |
| 15 | 36.2 | 36.2 | ±0.0 |
| 16 | 138.4 | 138.3 | +0.1 |
| 17 | 123.7 | 123.8 | −0.1 |
| 18 | 97.8 | 97.8 | ±0.0 |
| 19 | 41.2 | 41.2 | ±0.0 |
| 20 | 68.1 | 68.0 | +0.1 |
| 21 | 70.5 | 70.8 | −0.3 |
| 22 | 69.9 | 69.9 | ±0.0 |
| 23 | 72.6 | 72.6 | ±0.0 |
| 24 | 73.1 | 73.4 | −0.3 |
| 25 | 74.8 | 76.1 | −1.3 |
| 26 | 32.5 | 33.7 | −1.2 |
| 27 | 66.4 | 68.3 | −1.9 |
| 28 | 46.5 | 44.8 | +1.7 |
| 29 | 145.4 | 145.1 | +0.3 |
| 30 | 39.0 | 38.9 | +0.1 |
| 31 | 73.7 | 73.8 | −0.1 |
| 32 | 77.1 | 77.1 | ±0.0 |
| 33 | 70.0 | 70.0 | ±0.0 |
| 34 | 36.5 | 36.5 | ±0.0 |
| 35 | 73.3 | 73.3 | ±0.0 |

| Atom number | Limaol (13) δ [ppm] | 27-*epi*-13 δ [ppm] | Δδ [ppm] |
|---|---|---|---|
| 36 | 35.9 | 35.8 | +0.1 |
| 37 | 129.9 | 130.0 | −0.1 |
| 38 | 130.3 | 130.2 | +0.1 |
| 39 | 37.1 | 37.1 | ±0.0 |
| 40 | 62.8 | 62.8 | ±0.0 |
| 41 | 19.8 | 19.8 | ±0.0 |
| 42 | 113.9 | 113.9 | ±0.0 |
| 43 | 114.7 | 114.7 | ±0.0 |
| 44 | 115.1 | 115.1 | ±0.0 |
| 45 | 115.9 | 115.8 | +0.1 |
| 46 | 22.8 | 22.8 | ±0.0 |
| 47 | 114.5 | 114.9 | −0.4 |

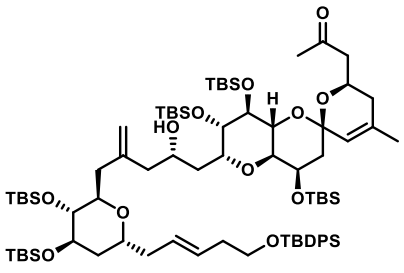
**Compound 194.**




Diethyl azodicarboxylate (888 µL, 40% in toluene, 1.95 mmol) was added dropwise to a solution of alcohol **190** (560 mg, 0.390 mmol), triphenylphosphine (516 mg, 1.95 mmol), and 4-nitrobenzoic acid (293 mg, 1.75 mmol) in toluene (4.0 mL) at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (5 mL). The mixture was diluted with *tert*-butyl methyl ether (10 mL), the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL), and the combined organic fractions were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 25:1) to give the title compound as a colorless oil (417 mg, 67%). $[\alpha]_D^{20}$ = +24.6 (c = 0.98, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.32 – 8.20 (m, 2H), 8.18 – 8.09 (m, 2H), 7.70 – 7.64 (m, 4H), 7.45 – 7.32 (m, 6H), 5.51 – 5.33 (m, 2H), 5.22 – 5.12 (m, 1H), 4.85 (dd, *J* = 9.0, 1.8 Hz, 2H), 4.34 (dtd, *J* = 10.4, 6.3, 3.8 Hz, 1H), 4.00 (dq, *J* = 7.4, 4.4, 3.6 Hz, 2H), 3.92 – 3.76 (m, 5H), 3.65 (t, *J* = 7.0 Hz, 2H), 3.60 (dd, *J* = 5.5, 1.9 Hz, 2H), 3.38 (dd, *J* = 3.7, 1.8 Hz, 1H), 3.21 (dd, *J* = 10.2, 2.7 Hz, 1H), 2.83 (dd, *J* = 14.5, 9.7 Hz, 1H), 2.73 (dd, *J* = 16.1, 6.1 Hz, 1H), 2.59 – 2.45 (m, 2H), 2.42 – 2.34 (m, 2H), 2.30 – 2.14 (m, 6H), 2.10 – 1.99 (m, 3H), 1.97 – 1.71 (m, 4H), 1.69 – 1.61 (m, 5H), 1.37 (dt, *J* = 13.6, 3.0 Hz, 1H), 1.04 (s, 9H), 0.92 (s, 9H), 0.90 (s, 9H), 0.88 (s, 18H), 0.84 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.07 (s, 9H), 0.04 (s, 3H), 0.03 (s, 6H), −0.01 (s, 3H), −0.08 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 207.0, 163.8, 150.5, 143.1, 136.2, 135.7, 135.6, 134.2, 134.2, 130.7, 129.7, 128.7, 128.5, 127.7, 124.2, 123.5, 115.6, 95.1, 76.7, 73.9, 73.0, 71.1,

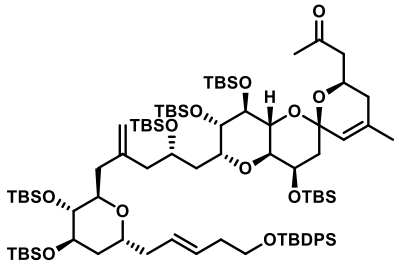
70.9, 70.8, 70.3, 68.6, 66.7, 64.7, 64.1, 64.0, 62.1, 50.1, 42.5, 41.4, 38.9, 36.5, 36.3, 34.8, 34.0, 30.8, 27.0, 26.5, 26.4, 26.0, 26.0, 26.0, 22.7, 19.3, 18.5, 18.3, 18.3, 18.2, 18.1, 14.4, −3.5, −3.6, −3.6, −4.2, −4.4, −4.4, −4.6, −4.8, −5.2; **IR** (film, $cm^{-1}$): 2953, 2929, 2889, 2857, 1726, 1531, 1472, 1463, 1428, 1388, 1360, 1349, 1273, 1254, 1205, 1156, 1095, 1044, 1006, 978, 836, 776, 720, 703, 506; **HRMS** (ESI) for $C_{85}H_{141}NO_{15}Si_6Na$ $[M+Na]^+$: calcd. 1606.8809; found 1606.8799.

**Compound 196.**



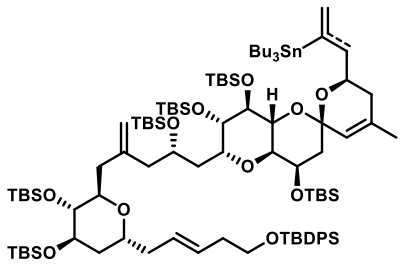

Powdered NaOH (13 mg, 0.33 mmol) was added in one portion to a solution of *p*-nitrobenzoate ester **194** (75 mg, 0.047 mmol) in MeOH/THF (3:1, 2 mL) at room temperature. After stirring for 14 h at this temperature, the reaction was quenched with saturated aqueous $NH_4Cl$ (3 mL) and the mixture was diluted with *tert*-butyl methyl ether (4 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 4 mL). The combined organic fractions were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 20:1) to give the title compound as a colorless oil (62 mg, 91%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +15.5 (c = 1.03, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.71 – 7.63 (m, 4H), 7.46 – 7.33 (m, 6H), 5.53 – 5.35 (m, 2H), 5.17 (s, 1H), 4.93 (s, 1H), 4.90 (s, 1H), 4.35 (dtd, *J* = 10.5, 6.5, 4.0 Hz, 1H), 4.23 – 4.14 (m, 1H), 4.01 (q, *J* = 3.0 Hz, 1H), 3.84 (ddd, *J* = 21.0, 9.2, 5.7 Hz, 5H), 3.70 – 3.56 (m, 4H), 3.38 (dd, *J* = 3.8, 2.2 Hz, 1H), 3.32 (dd, *J* = 10.0, 2.8 Hz, 1H), 2.74 (dd, *J* = 16.1, 6.1 Hz, 1H), 2.72 – 2.64 (m, 1H), 2.52 (dd, *J* = 16.1, 6.7 Hz, 1H), 2.41 (dd, *J* = 14.4, 5.5 Hz, 1H), 2.34 – 2.13 (m, 9H), 2.09 (dt, *J* = 13.2, 6.6 Hz, 1H), 1.98 – 1.62 (m, 10H), 1.40 (ddd, *J* = 13.5, 4.4, 2.5 Hz, 1H), 1.05 (s, 9H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 207.1, 144.5, 135.7, 135.5, 134.2, 130.9, 129.7, 129.0, 128.4, 127.7, 124.4, 123.7, 114.7, 95.2, 77.0, 74.2, 73.5, 73.1, 71.3, 70.8, 70.4, 68.9, 66.9, 66.8, 65.1, 64.1, 64.0, 50.2, 44.6, 42.5, 38.8, 37.4, 36.3, 34.9, 34.0, 32.7, 30.8, 27.0, 26.5, 26.4, 26.0, 22.7, 19.3, 18.6, 18.4, 18.3, 18.2, 18.1, 1.2, −3.5, −3.6, −3.7, −4.1, −4.1, −4.3, −4.4, −4.7, −4.9; **IR** (film, $cm^{-1}$): 2954, 2929, 2887, 2857, 1718, 1472, 1463, 1428, 1388, 1361, 1254, 1204, 1089, 1006, 961, 939, 835, 808, 775, 741, 702, 688, 671, 667, 613, 505, 489, 459, 446, 433, 421; **HRMS** (ESI) for $C_{78}H_{138}O_{12}Si_6Na$ $[M+Na]^+$: calcd. 1457.8696; found 1457.8706.

**Compound 198.**




TBSOTf (11 μL, 0.047 mmol) was added dropwise to a solution of alcohol **196** (62 mg, 0.043 mmol) and 2,6-lutidine (15 μL, 0.13 mmol) in $CH_2Cl_2$ (0.4 mL) at −78 °C. The mixture was stirred at this temperature for 1 h before the reaction was quenched with saturated aqueous $NH_4Cl$ (2 mL). The mixture was warmed to room temperature and stirring was continued until all solids had dissolved. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 2 mL). The combined organic fractions were washed with brine (2 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 25:1) to give the title compound (56 mg, 84%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.9 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.65 (m, 4H), 7.46 – 7.34 (m, 6H), 5.52 – 5.37 (m, 2H), 5.15 (s, 1H), 4.83 (s, 1H), 4.80 (s, 1H), 4.36 (dtd, *J* = 10.5, 6.5, 3.8 Hz, 1H), 4.09 (dt, *J* = 10.7, 2.8 Hz, 1H), 3.98 (q, *J* = 3.0 Hz, 1H), 3.92 (p, *J* = 5.1, 4.5 Hz, 1H), 3.80 (td, *J* = 6.8, 5.9, 2.6 Hz, 4H), 3.66 (t, *J* = 7.0 Hz, 2H), 3.63 – 3.55 (m, 2H), 3.38 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.22 – 3.10 (m, 1H), 2.76 (dd, *J* = 16.0, 5.9 Hz, 1H), 2.72 – 2.66 (m, 1H), 2.51 (dd, *J* = 16.1, 6.8 Hz, 1H), 2.39 – 2.19 (m, 8H), 2.19 – 2.02 (m, 2H), 1.95 – 1.72 (m, 5H), 1.67 (s, 3H), 1.65 – 1.54 (m, 2H), 1.39 (dt, *J* = 13.8, 2.9 Hz, 1H), 1.05 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.90 (s, 18H), 0.88 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H), 0.06 (s, 9H), 0.05 (s, 12H), 0.03 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 207.2, 144.1, 135.7, 135.3, 134.2, 129.7, 128.8, 128.6, 127.7, 124.5, 114.2, 95.0, 76.6, 73.9, 73.1, 71.2, 70.5, 70.4, 68.8, 67.2, 67.0, 64.6, 64.2, 64.0, 50.3, 44.6, 42.7, 39.0, 37.8, 36.3, 34.9, 33.9, 30.8, 27.0, 26.6, 26.5, 26.2, 26.1, 26.0, 22.7, 19.4, 18.6, 18.4, 18.4, 18.2, 18.1, 1.2, −3.3, −3.4, −3.6, −3.9, −4.1, −4.2, −4.3, −4.4, −4.5, −4.7, −4.9; **IR** (film, $cm^{-1}$): 2954, 2929, 2887, 2857, 1720, 1472, 1463, 1428, 1388, 1361, 1253, 1204, 1086, 1060, 1006, 973, 939, 835, 808, 775, 739, 702, 686, 613, 505, 488, 467; **HRMS** (ESI) for $C_{84}H_{152}O_{12}Si_7Na$ $[M+Na]^+$: calcd. 1571.9561; found 1571.9569.

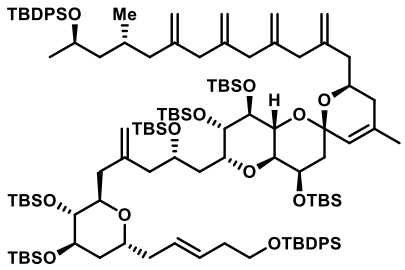
**Compound 217.**




*n*-Butyllithium (1.6 M in hexanes, 0.19 mL, 0.31 mmol) was added to a solution of hexabutylditin (0.16 mL, 0.32 mmol) in THF (2.0 mL) at −20 °C. The mixture was stirred at −20 °C for 15 min to give a pale yellow solution of tributylstannyllithium. The solution was cooled to −78 °C and solid copper(I) cyanide (14 mg, 0.15 mmol) was added in one portion. The mixture was allowed to reach −55 °C and stirring was continued at this temperature for 15 min to give a green-yellow solution of the bis(tributylstannyl) cuprate reagent.[68, 124]

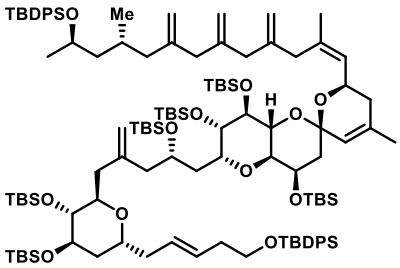
In a separate flask, a solution of trityl potassium (0.20 M in 1,2-dimethoxyethane, 1.2 mL, 0.23 mmol) was added dropwise to a stirred solution of ketone **198** (80 mg, 0.052 mmol) and bis(trifluoromethanesulfonyl)aniline (37 mg, 0.10 mmol) in THF (3.5 mL) at −78 °C until the red color of the trityl anion persisted. The resulting mixture was stirred at this temperature for 15 min to give a solution of the alkenyl triflate, which was transferred *via* cannula into the flask containing the cooled (−55 °C) stannylcuprate solution. Stirring was continued at −55 °C for 15 min before the reaction was quenched with saturated aqueous $NH_4Cl$ (8 mL). The mixture was diluted with *tert*-butyl methyl ether (8 mL) and warmed to room temperature. Stirring was continued until all solids had dissolved. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 8 mL) and the combined organic fractions were washed with brine (15 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/$CH_2Cl_2$ 4:1 + 1% $NEt_3$) to give the desired alkenyl stannane **217** and its internal double bond isomer as an inseperable mixture (3:1, 58 mg, 62%). Analytical and spectral data of the mixture of double bond isomers: $[\alpha]_D^{20}$ = +23.2 (c = 0.93, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.70 – 7.64 (m, 4H), 7.47 – 7.32 (m, 6H), 5.84 (s, 1H), 5.63 – 5.55 (m, *resolved signal of the minor isomer*), 5.50 – 5.36 (m, 2H), 5.23 (s, 1H), 5.16 (s, 1H), 4.84 (s, 1H), 4.80 (s, 1H), 4.22 – 4.02 (m, 2H), 4.03 – 3.77 (m, 6H), 3.74 – 3.57 (m, 4H), 3.38 (s, 1H), 3.14 (t, *J* = 9.9 Hz, 1H), 2.72 (dt, *J* = 14.8, 7.2 Hz, 2H), 2.41 – 2.17 (m, 6H), 2.11 (ddd, *J* = 17.6, 13.8, 8.1 Hz, 2H), 2.00 – 1.71 (m, 7H), 1.72 – 1.64 (m, 3H), 1.63 – 1.23 (m, 19H), 1.05 (s, 9H), 0.94 – 0.86 (m, 63H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 – 0.02 (m, 30H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 150.4, 144.2, 142.2, 135.7, 135.3, 134.2, 129.7, 128.7, 128.6, 127.7, 127.2, 124.6, 114.3, 94.9, 76.5, 73.9, 73.4, 73.3, 73.0, 71.2, 71.1, 71.0, 70.9, 70.4, 68.8, 67.3, 67.2, 66.9, 66.4, 64.5, 64.2, 46.1, 44.6, 42.9, 39.1, 37.7, 36.3, 35.0, 34.9, 33.9, 29.3, 27.6, 27.5, 27.0, 26.7, 26.6, 26.2, 26.0, 22.9, 22.8, 20.5, 19.4, 18.7, 18.6, 18.5, 18.5, 18.4, 18.4, 18.2, 18.1, 13.9, 9.7, 9.2, −3.3, −3.4, −3.4, −3.5, −3.5, −3.6, −3.9, −4.2, −4.2, −4.3, −4.3, −4.4, −4.4, −4.5, −4.7, −4.8; **$^{119}$Sn NMR** ($CDCl_3$, 149 MHz): −40.7 (minor isomer), −44.4 (major isomer); **IR** (film, $cm^{-1}$): 2955, 2928, 2896, 2857, 1472, 1463, 1428, 1378, 1361, 1253, 1205, 1088, 1060, 1006, 971, 939, 861, 836, 811, 775, 738, 702, 671, 666, 506; **HRMS** (ESI) for $C_{96}H_{178}O_{11}Si_7SnNa$ $[M+Na]^+$: calcd. 1846.0668; found 1846.0692.

**Compound 220.**




A degassed solution of stannane **217** (0.11 g, 0.060 mmol, 3:1 mixture of isomers) and allylic acetate **108** (31 mg, 0.060 mmol) in DMF/THF (1:1, 0.6 mL) was added to a Schlenk tube containing flame-dried tetrabutylammonium diphenylphosphinate (0.11 g, 0.24 mmol). Copper-thiophene carboxylate complex (CuTC, 35 mg, 0.18 mmol) was then introduced, followed by $Pd(PPh_3)_4$ (7.0 mg, 6.0 μmol). The mixture was stirred for 2 h

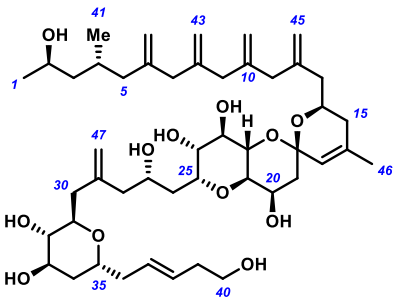
at ambient temperature before the reaction was quenched with aqueous saturated $NH_4Cl$ (2 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 2 mL), the combined organic layers were washed with brine (2 mL), dried over anhydrous $Na_2SO_4$, and evaporated *in vacuo*. The residue was purified twice by flash chromatography (first column: fine silica, hexanes/acetone 90:1; second column: fine silica, hexanes/toluene, 3:2) to afford **220** (72 mg, 60%) and the internal double bond isomer **221** (16 mg, 13%) as a colorless oil each. Analytical and spectral data of the desired isomer **220**: $[\alpha]_D^{20}$ = +8.9 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.73 – 7.64 (m, 8H), 7.45 – 7.32 (m, 12H), 5.51 – 5.37 (m, 2H), 5.16 (s, 1H), 4.97 (s, 2H), 4.88 – 4.73 (m, 8H), 4.18 – 4.12 (m, 1H), 4.11 – 4.04 (m, 1H), 3.97 (q, *J* = 3.0 Hz, 1H), 3.90 (ddd, *J* = 7.8, 6.0, 4.7 Hz, 2H), 3.84 – 3.78 (m, 4H), 3.66 (t, *J* = 7.0 Hz, 2H), 3.63 – 3.60 (m, 2H), 3.37 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.11 (d, *J* = 10.0 Hz, 1H), 2.76 – 2.68 (m, 4H), 2.65 (s, 3H), 2.44 – 2.18 (m, 6H), 2.17 – 1.98 (m, 3H), 1.94 – 1.71 (m, 7H), 1.66 (s, 4H), 1.64 – 1.53 (m, 5H), 1.42 – 1.35 (m, 1H), 1.05 (s, 8H), 1.05 (s, 9H), 0.91 (s, 9H), 0.89 (s, 18H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.70 (d, *J* = 6.2 Hz, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 – 0.01 (m, 33H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 145.9, 145.0, 144.7, 144.2, 143.5, 136.1, 136.1, 135.7, 135.6, 135.2, 134.5, 134.2, 129.7, 129.6, 129.5, 128.7, 128.6, 127.7, 127.6, 127.5, 124.6, 114.5, 114.3, 113.9, 113.8, 113.1, 94.9, 76.5, 73.9, 73.2, 71.2, 70.9, 70.4, 68.5, 67.8, 67.3, 66.9, 65.3, 64.6, 64.2, 47.5, 44.6, 43.9, 43.7, 42.7, 41.7, 41.4, 39.0, 37.7, 36.3, 34.9, 33.9, 27.2, 27.1, 27.1, 27.0, 26.6, 26.6, 26.2, 26.1, 26.0, 24.4, 22.9, 19.7, 19.5, 19.4, 18.7, 18.5, 18.4, 18.2, 18.1, −3.3, −3.7, −3.9, −4.2, −4.2, −4.3, −4.4, −4.4, −4.5, −4.7, −4.8; **IR** (film, $cm^{-1}$): 3072, 2954, 2928, 2894, 2857, 1641, 1472, 1463, 1428, 1379, 1361, 1253, 1205, 1090, 1060, 1006, 970, 939, 895, 836, 775, 739, 702, 686, 672, 666, 612, 506; **HRMS** (ESI) for $C_{115}H_{194}O_{12}Si_8Na$ $[M+Na]^+$: calcd. 2014.2617; found 2014.2636.




Spectral data of the double bond isomer **221**: **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 7.70 (ddt, *J* = 9.5, 6.7, 1.5 Hz, 4H), 7.69 – 7.64 (m, 4H), 7.45 – 7.38 (m, 4H), 7.40 – 7.33 (m, 9H), 5.49 – 5.38 (m, 2H), 5.25 (dq, *J* = 7.6, 1.2 Hz, 1H), 5.17 (q, *J* = 2.5, 1.3 Hz, 1H), 4.86 – 4.82 (m, 4H), 4.82 (d, *J* = 2.1 Hz, 1H), 4.80 – 4.78 (m, 1H), 4.78 (d, *J* = 2.2 Hz, 1H), 4.75 (d, *J* = 2.4 Hz, 1H), 4.69 (ddd, *J* = 11.3, 7.7, 3.9 Hz, 1H), 4.07 (ddd, *J* = 12.2, 5.4, 2.1 Hz, 1H), 3.96 (q, *J* = 3.0 Hz, 1H), 3.94 – 3.88 (m, 2H), 3.86 (t, *J* = 9.3 Hz, 1H), 3.84 – 3.78 (m, 4H), 3.66 (t, *J* = 7.0 Hz, 2H), 3.63 (t, *J* = 8.7 Hz, 1H), 3.59 (dd, *J* = 9.1, 5.3 Hz, 1H), 3.37 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.12 (d, *J* = 9.7 Hz, 1H), 2.72 (dd, *J* = 15.4, 10.0 Hz, 1H), 2.68 (d, *J* = 15.0 Hz, 1H), 2.65 (s, 2H), 2.64 (s, 2H), 2.60 (d, *J* = 14.5 Hz, 1H), 2.32 (dd, *J* = 14.1, 4.2 Hz, 1H), 2.30 – 2.19 (m, 4H), 2.13 (dd, *J* = 13.9, 9.1 Hz, 1H), 2.10 – 2.04 (m, 1H), 1.93 (ddm, *J* = 17.1, 10.9 Hz, 1H), 1.90 – 1.80 (m, 5H), 1.79 – 1.71 (m, 3H), 1.71 – 1.64 (m, 7H), 1.62 – 1.55 (m, 6H), 1.38 (dt, *J* = 13.9, 2.9 Hz, 1H), 1.05 (d, *J* = 2.0 Hz, 19H), 1.03 (d, *J* = 6.1 Hz, 4H), 0.70 (d, *J* = 6.1 Hz, 3H), 0.09 – 0.01 (m, 37H); **$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ 145.7,

144.9, 144.8, 144.0, 136.0, 135.9, 135.7, 135.6, 135.4, 135.0, 134.3, 134.0, 129.5, 129.5, 129.3, 129.1, 128.6, 128.4, 127.6, 127.5, 127.3, 124.4, 114.1, 113.8, 113.3, 112.9, 94.6, 77.2, 77.0, 76.8, 76.4, 76.4, 73.7, 73.0, 73.0, 71.0, 70.8, 70.2, 68.3, 67.7, 67.1, 66.7, 64.4, 64.1, 64.0, 47.2, 45.9, 44.5, 43.7, 42.5, 42.4, 41.7, 38.9, 37.5, 36.1, 35.1, 33.8, 31.9, 29.7, 29.7, 29.7, 29.6, 29.4, 27.1, 27.0, 27.0, 26.9, 26.9, 26.4, 26.0, 25.9, 25.8, 24.3, 22.7, 22.7, 22.7, 19.6, 19.6, 19.3, 19.2, 18.6, 18.3, 18.2, 18.0, 18.0, 16.8, 14.1, −3.6, −3.8, −4.1, −4.3, −4.4, −4.5, −4.5, −4.6, −4.7, −4.9, −5.0.

**Limaol (13).**




Silyl ether **220** (25 mg, 13 µmol) was dissolved in pyridine/THF (3:1, 0.8 mL) and HF–pyridine complex (0.2 mL) was added at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature for 11 d. The reaction was quenched by dropwise addition of pH 7.4 phosphate buffer (2 mL) and the aqueous phase was extracted with EtOAc (5 × 2 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by preparative HPLC (column: YMC-Actus ODS-A, S-5 µm, 150 mm length, 20.0 mm ID; gradient: 20.0 mL/min, MeCN/$H_2O$ 50:50 for 10 min, then 100:0 for 50 min; $R_t$ = 6.59 min) to afford Limaol as a colorless oil (3.3 mg, 32%). $[\alpha]_D^{20}$ = +40 (c = 0.1, MeOH); literature: $[\alpha]_D^{20}$ = +63 (c = 0.1, MeOH);[35] **Analytical HPLC:** column: YMC ODS-A, S-5 µm, 150 mm length, 4.6 mm ID; gradient: 1.0 mL/min, MeCN/$H_2O$ 50:50 for 10 min, then 100:0 for 20 min; $R_t$ = 9.04 min; **$^1$H NMR** ($CD_3OD$, 600 MHz): 5.58 – 5.44 (m, 2H), 5.29 (dq, *J* = 2.6, 1.4 Hz, 1H), 5.02 – 4.99 (m, 1H), 4.96 (d, *J* = 2.2 Hz, 1H), 4.92 – 4.90 (m, 3H), 4.89 – 4.87 (m, 2H), 4.86 (d, *J* = 2.0 Hz, 1H), 4.81 (d, *J* = 2.4 Hz, 1H), 4.80 (q, *J* = 1.2 Hz, 1H), 4.28 – 4.20 (m, 2H), 3.95 (q, *J* = 3.1 Hz, 1H), 3.96 – 3.88 (m, 2H), 3.82 (dqd, *J* = 9.0, 6.2, 3.9 Hz, 1H), 3.73 (ddd, *J* = 10.8, 8.2, 4.7 Hz, 1H), 3.66 (dd, *J* = 10.3, 9.0 Hz, 1H), 3.65 (dd, *J* = 9.3, 6.3 Hz, 1H), 3.60 (d, *J* = 9.1 Hz, 1H), 3.60 – 3.57 (m, 1H), 3.55 (t, *J* = 6.8 Hz, 2H), 3.26 (dd, *J* = 10.2, 2.9 Hz, 1H), 3.01 (d, *J* = 14.7 Hz, 1H), 2.98 (t, *J* = 8.4 Hz, 1H), 2.88 (d, *J* = 14.6 Hz, 1H), 2.73 (d, *J* = 2.3 Hz, 2H), 2.70 (s, 2H), 2.61 (d, *J* = 14.8 Hz, 1H), 2.50 – 2.42 (m, 1H), 2.36 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.32 – 2.18 (m, 6H), 2.12 (dd, *J* = 15.1, 9.7 Hz, 1H), 2.01 – 1.78 (m, 9H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.68 – 1.58 (m, 2H), 1.46 (ddd, *J* = 13.7, 9.1, 4.3 Hz, 1H), 1.14 (d, *J* = 6.1 Hz, 3H), 1.07 (ddd, *J* = 13.9, 9.1, 3.9 Hz, 1H), 0.87 (d, *J* = 6.4 Hz, 3H); **$^{13}$C NMR** ($CD_3OD$, 151 MHz): δ 147.1, 146.1, 146.0, 145.5, 145.3, 138.4, 130.3, 129.9, 123.7, 115.8, 115.1, 114.7, 114.4, 113.8, 97.8, 77.1, 74.9, 73.7, 73.3, 73.1, 72.6, 70.5, 70.0, 70.0, 68.1, 66.8, 66.4, 66.1, 62.8, 47.6, 46.5, 45.0, 43.3, 43.2, 42.5, 42.3, 41.3, 39.1, 37.1, 36.5, 36.2, 35.9, 32.5, 28.2, 24.4, 22.8, 19.8; **IR** (film, $cm^{-1}$): 3383, 2924, 2856, 1638, 1430, 1379, 1176, 1069, 996, 967, 895; **HRMS** (ESI) for $C_{47}H_{74}O_{12}Na$ $[M+Na]^+$: calcd. 853.5072; found 853.5075.

**Table 6.6.** NMR data of synthetic limaol (**13**); numbering scheme as shown in the insert.

| atom number | **$^1$H NMR** ($CDCl_3$, 500 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 126 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 1 | 1.14 | 6.1 | 2 | 2, 3ab | 24.4 | 3ab |
| 2 | 3.82 | 9.0, 6.2, 3.9 | 1, 3ab | 1, 3b, 41 | 66.1 | 1, 3ab |
| 3a | 1.46 | 13.7, 9.1, 4.3 | 2, 3b, 4, 41 | 1, 4, 5ab, 7, 41 | 47.6 | 1, 5ab, 41 |
| 3b | 1.07 | 13.9, 9.1, 3.9 | 2, 3a, 4, 41 | 1, 2, 4, 5ab, 41 | | |
| 4 | 1.87 | - | 3ab, 5b, 41 | 3ab, 7, 41, 42' | 28.2 | 3ab, 5ab, 41 |
| 5a | 1.98 | 13.3, 5.8 | 5b, 41, 42' | 3ab, 7, 42' | 45.0 | 3ab, 7, 41, 42', 42'' |
| 5b | 1.82 | 13.2, 8.2 | 4, 5a, 41, 42' | 3ab, 7, 41, 42' | | |
| 6 | - | - | - | - | 147.1 | 5ab, 7, 42', 42'' |
| 7 | 2.73 | - | 42', 42'', 43' | 3a, 4, 5ab, 41, 42'', 43' | 43.4 | 5ab, 9, 42', 42'', 43', 43'' |
| 8 | - | - | - | - | 146.1 | 7, 9, 43', 43'' |
| 9 | 2.70 | - | 43', 43'', 44', 44'' | 11a, 13a, 44'' | 42.3 | 7, 11ab, 43', 43'', 44', 44'' |
| 10 | - | - | - | - | 146.0 | 9, 11ab, 44', 44'' |
| 11a | 3.01 | 14.7 | 11b, 44', 45', 45'' | 9, 44', 45'' | 43.2 | 9, 13ab, 44', 44'', 45', 45'' |
| 11b | 2.88 | 14.6 | 11a, 44', 44'', 45'' | 44', 45'' | | |
| 12 | - | - | - | - | 145.3 | 11ab, 13ab, 14, 45', 45'' |
| 13a | 2.29 | 14.0, 3.8 | 13b, 14, 45' | 9, 15b, 45' | 42.5 | 11ab, 45', 45'' |
| 13b | 2.21 | - | 13a, 14, 45' | 45' | | |
| 14 | 4.24 | - | 13ab, 15ab | - | 66.8 | 13ab, 15a |
| 15a | 1.93 | - | 14, 15b, 17, 46 | - | 36.2 | 13ab, 17, 46 |
| 15b | 1.84 | - | 14, 15a, 46 | 13a | | |
| 16 | - | - | - | - | 138.4 | 15ab, 46 |
| 17 | 5.29 | - | 15ab, 19a, 46 | 19ab | 123.7 | 15ab, 46 |
| 18 | - | - | - | - | 97.8 | 17, 19ab, 20, 22 |
| 19a | 1.94 | - | 17, 20 | 17 | 41.3 | 20 |
| 19b | 1.86 | - | 20 | 17 | | |
| 20 | 3.95 | 3.1 | 19ab, 21 | 21 | 68.1 | 19a, 22 |
| 21 | 3.26 | 10.2, 2.9 | 20, 22 | 20, 26a | 70.5 | 19a, 20, 22, 25 |
| 22 | 3.66 | 10.3, 9.0 | 21 | - | 70.0 | 20, 21, 23 |
| 23 | 3.59 | 9.1 | 24 | - | 72.6 | 21, 22, 25 |
| 24 | 3.64 | 9.3, 6.3 | 23, 25 | - | 73.1 | 23, 25 |
| 25 | 4.25 | - | 24, 26ab | - | 74.9 | 24, 26a |

| atom number | $^1$H NMR ($CDCl_3$, 500 MHz) | | | | $^{13}$C NMR ($CDCl_3$, 126 MHz) | |
|---|---|---|---|---|---|---|
| | δ [ppm] | *J* [Hz] | COSY | NOESY | δ [ppm] | HMBC |
| 26a | 1.88 | - | 25, 26b, 27 | 21 | 32.5 | 22, 28ab |
| 26b | 1.62 | - | 25, 26a, 27 | - | | |
| 27 | 3.92 | - | 26ab, 28ab | 47'' | 66.4 | 26b, 28ab |
| 28a | 2.36 | 13.7, 6.5 | 27, 28b, 47'' | 30a | 46.5 | 30ab, 47', 47'' |
| 28b | 2.23 | - | 27, 28a, 47'' | 47'' | | |
| 29 | - | - | - | - | 145.5 | 28ab, 30ab, 31, 47', 47'' |
| 30a | 2.61 | 14.8 | 30b, 31, 47', 47'' | 28a, 31, 32, 47' | 39.1 | 28ab, 32, 47', 47'' |
| 30b | 2.12 | 15.1, 9.7 | 30a, 31, 47' | 32, 47' | | |
| 31 | 3.59 | - | 30ab, 32 | 30a, 36ab, 47' | 73.8 | 30ab, 32, 35 |
| 32 | 2.98 | 8.4 | 31, 33 | 30ab, 34b | 77.1 | 30b, 31, 33, 34ab |
| 33 | 3.73 | 10.8, 8.2, 4.7 | 32, 34ab | 36ab | 70.0 | 32, 34ab |
| 34a | 1.92 | - | 33, 34b, 35 | 36ab | 36.5 | 32, 35, 36ab |
| 34b | 1.63 | - | 33, 34a, 35 | 32 | | |
| 35 | 3.92 | - | 34ab, 36ab | 36a, 37 | 73.3 | 34b, 36ab, 37 |
| 36a | 2.46 | - | 35, 36b, 37 | 31, 33, 34a, 35 | 35.9 | 34b, 35, 37, 38 |
| 36b | 2.25 | - | 35, 36a, 37 | 31, 33, 34a | | |
| 37 | 5.48 | - | 36ab, 38 | 35 | 139.9 | 35, 36ab, 38 |
| 38 | 5.54 | - | 37, 39 | 39, 40 | 130.3 | 36ab, 37, 40 |
| 39 | 2.23 | - | 38, 40 | 38, 40 | 37.1 | 37, 38, 40 |
| 40 | 3.55 | 6.8 | 39 | 38, 39 | 62.8 | 38, 39 |
| 41 | 0.87 | 6.4 | 3ab, 4, 5ab | 2, 3ab, 4, 5b, 7, 42', 42'' | 19.8 | 3ab, 5ab |
| 42' | 4.81 | 2.4 | 5ab, 7 | 4, 5ab, 41 | 113.8 | 5ab, 7 |
| 42'' | 4.80 | 1.2 | 7 | 7, 41 | | |
| 43' | 4.90 | - | 7, 9 | 7 | 114.7 | 7, 9 |
| 43'' | 4.88 | - | 9 | - | | |
| 44' | 5.01 | - | 9, 11ab, 44'' | 11ab | 115.1 | 9, 11ab |
| 44'' | 4.88 | - | 9, 11b, 44' | 9 | | |
| 45' | 4.96 | 2.2 | 11a, 13ab, 45'' | 13ab | 115.8 | 11ab, 13ab |
| 45'' | 4.91 | - | 11ab, 45' | 11ab | | |
| 46 | 1.71 | 1.2 | 15ab, 17 | - | 22.8 | 15b, 17 |
| 47' | 4.91 | - | 30ab, 47'' | 30ab, 31 | 114.4 | 28ab, 30ab |
| 47'' | 4.86 | 2 | 28ab, 30a, 47' | 27, 28b | | |

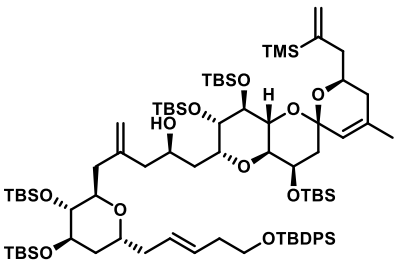
**Table 6.7.** Comparison of $^{13}C$ NMR data of synthetic **13** with authentic Limaol.[35]

| Atom number | Limaol (13) δ [ppm] | Synthetic 13 δ [ppm] | Δδ [ppm] |
|---|---|---|---|
| 1 | 24.4 | 24.4 | ±0.0 |
| 2 | 66.1 | 66.1 | ±0.0 |
| 3 | 47.6 | 47.6 | ±0.0 |
| 4 | 28.1 | 28.2 | −0.1 |
| 5 | 45.0 | 45.0 | ±0.0 |
| 6 | 147.1 | 147.1 | ±0.0 |
| 7 | 43.3 | 43.3 | ±0.0 |
| 8 | 146.1 | 146.1 | ±0.0 |
| 9 | 42.3 | 42.3 | ±0.0 |
| 10 | 146.0 | 146.0 | ±0.0 |
| 11 | 43.2 | 43.2 | ±0.0 |
| 12 | 145.3 | 145.3 | ±0.0 |
| 13 | 42.5 | 42.5 | ±0.0 |
| 14 | 66.8 | 66.8 | ±0.0 |
| 15 | 36.2 | 36.2 | ±0.0 |
| 16 | 138.4 | 138.4 | ±0.0 |
| 17 | 123.7 | 123.7 | ±0.0 |
| 18 | 97.8 | 97.8 | ±0.0 |
| 19 | 41.2 | 41.2 | ±0.0 |
| 20 | 68.1 | 68.1 | ±0.0 |
| 21 | 70.5 | 70.5 | ±0.0 |
| 22 | 69.9 | 70 | −0.1 |
| 23 | 72.6 | 72.6 | ±0.0 |
| 24 | 73.1 | 73.1 | ±0.0 |
| 25 | 74.8 | 74.9 | −0.1 |
| 26 | 32.5 | 32.5 | ±0.0 |
| 27 | 66.4 | 66.4 | ±0.0 |
| 28 | 46.5 | 46.5 | ±0.0 |
| 29 | 145.4 | 145.5 | −0.1 |
| 30 | 39.0 | 39.1 | −0.1 |
| 31 | 73.7 | 73.7 | ±0.0 |
| 32 | 77.1 | 77.1 | ±0.0 |
| 33 | 70.0 | 70.0 | ±0.0 |
| 34 | 36.5 | 36.5 | ±0.0 |
| 35 | 73.3 | 73.3 | ±0.0 |

| Atom number | Limaol (13) δ [ppm] | Synthetic 13 δ [ppm] | Δδ [ppm] |
|---|---|---|---|
| 36 | 35.9 | 35.9 | ±0.0 |
| 37 | 129.9 | 129.9 | ±0.0 |
| 38 | 130.3 | 130.3 | ±0.0 |
| 39 | 37.1 | 37.1 | ±0.0 |
| 40 | 62.8 | 62.8 | ±0.0 |
| 41 | 19.8 | 19.8 | ±0.0 |
| 42 | 113.9 | 113.8 | +0.1 |
| 43 | 114.7 | 114.7 | ±0.0 |
| 44 | 115.1 | 115.1 | ±0.0 |
| 45 | 115.9 | 115.8 | +0.1 |
| 46 | 22.8 | 22.8 | ±0.0 |
| 47 | 114.5 | 114.4 | +0.1 |

### 6.2.4.2 Alkenyl Silane Route

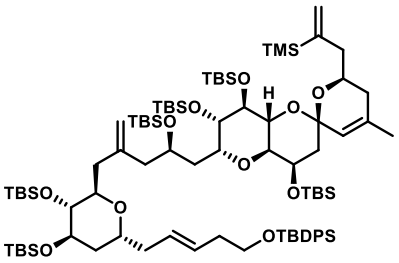
**Compound 189.**




Solid magnesium bromide diethyl etherate (23 mg, 89 μmol) was added in one portion to a solution of aldehyde **78** (14 mg, 18 μmol) and allyl stannane **158** (22 mg, 21 μmol, dr 5:1) in $CH_2Cl_2$ (0.3 mL) at −78 °C. The resulting mixture was stirred at this temperature for 3 h before the reaction was quenched at −78 °C with triethylamine (0.5 mL). The mixture was warmed to room temperature and diluted with *tert*-butyl methyl ether (5 mL) and saturated aqueous $NH_4Cl$ (5 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 5 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$ and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc 25:1 to 20:1) to give the title compound as a colorless oil (24 mg, 91%). $[\alpha]_D^{23}$ = +16.5 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.66 (dt, *J* = 6.6, 1.7 Hz, 4H), 7.46 – 7.32 (m, 6H), 5.80 – 5.68 (m, 1H), 5.50 – 5.34 (m, 3H), 5.16 (dd, *J* = 2.6, 1.4 Hz, 1H), 4.90 (s, 2H), 4.11 (ddq, *J* = 23.5, 9.5, 4.4 Hz, 2H), 4.00 (d, *J* = 3.0 Hz, 1H), 3.98 – 3.90 (m, 1H), 3.89 (dd, *J* = 9.9, 8.5 Hz, 1H), 3.80 (m, 3H), 3.66 (td, *J* = 7.8, 7.0, 5.3 Hz, 3H), 3.57 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.46 (dd, *J* = 10.0, 2.6 Hz, 2H), 3.40 – 3.33 (m, 1H), 2.69 (dd, *J* = 14.4, 9.7 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.38 (dd, *J* = 14.4, 4.9 Hz, 1H), 2.34 – 2.02 (m, 7H), 1.81 (tdd, *J* = 21.0, 8.8, 2.8 Hz, 5H), 1.69 (d, *J* = 3.3 Hz, 1H), 1.66 (s, 3H), 1.47 – 1.35 (m, 1H), 1.04 (s, 9H), 0.97 – 0.93 (m, 1H), 0.91 – 0.86 (m, 45H), 0.10 (s, 3H), 0.09 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H), 0.06 – 0.03 (m, 12H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 148.2, 144.0, 135.7, 134.2, 129.7, 128.9, 128.5, 127.7, 125.7, 124.3, 114.9, 95.0, 78.0, 76.3, 73.9, 73.0, 71.8,

71.4, 70.7, 70.5, 68.3, 66.6, 66.1, 65.5, 64.2, 43.5, 42.5, 41.0, 38.5, 37.2, 36.3, 34.9, 34.2, 31.0, 29.9, 27.0, 26.5, 26.5, 26.1, 26.0, 22.9, 19.4, 18.7, 18.5, 18.3, 18.2, 18.2, −1.6, −3.5, −3.6, −3.8, −4.2, −4.2, −4.3, −4.3, −4.3, −4.6, −4.8; **IR** (film, $cm^{-1}$): 2953, 2928, 2857, 1472, 1428, 1388, 1361, 1251, 1205, 1090, 1006, 967, 835, 775, 738, 702, 613, 505; **HRMS** (ESI) for $C_{81}H_{146}O_{11}Si_7Na$ $[M+Na]^+$: calcd. 1513.9142; found 1513.9131.

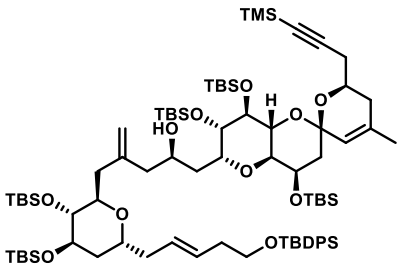
**Compound 191.**




A solution of TBSOTf (0.1 M in $CH_2Cl_2$, 0.17 mL, 17 μmol) was added dropwise to a solution of alcohol **189** (24 mg, 16 μmol) and 2,6-lutidine (5.6 μL, 48 μmol) in $CH_2Cl_2$ (0.2 mL) at 0 °C using a glas pipette. Stirring was continued at 0 °C for 30 min before the reaction was quenched with saturated aqueous $NH_4Cl$ (3 mL) and the mixture was warmed to room temperature. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 3 mL). The combined organic fractions were washed with brine (3 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 80:1) to give the title compound as a colorless oil (22 mg, 83%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +22.4 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.71 – 7.63 (m, 4H), 7.46 – 7.32 (m, 6H), 5.75 – 5.70 (m, 1H), 5.48 – 5.41 (m, 2H), 5.41 (dd, *J* = 3.0, 1.2 Hz, 1H), 5.17 (dt, *J* = 2.4, 1.3 Hz, 1H), 4.88 (d, *J* = 2.0 Hz, 1H), 4.84 (d, *J* = 2.0 Hz, 1H), 4.13 (ddt, *J* = 10.8, 7.1, 4.7 Hz, 1H), 4.02 (q, *J* = 3.0 Hz, 1H), 3.96 – 3.61 (m, 9H), 3.55 (dd, *J* = 8.2, 5.0 Hz, 1H), 3.42 (dd, *J* = 3.5, 1.6 Hz, 1H), 3.33 (d, *J* = 9.7 Hz, 1H), 2.69 (dd, *J* = 14.1, 8.5 Hz, 1H), 2.60 – 2.49 (m, 1H), 2.41 (dd, *J* = 14.2, 6.0 Hz, 1H), 2.33 – 2.01 (m, 7H), 1.97 – 1.82 (m, 2H), 1.76 (ddd, *J* = 20.0, 10.4, 5.5 Hz, 4H), 1.66 (d, *J* = 1.4 Hz, 3H), 1.62 (dd, *J* = 14.2, 3.3 Hz, 1H), 1.42 – 1.33 (m, 1H), 1.04 (s, 9H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88 – 0.88 (m, 27H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H), 0.03 (s, 6H), 0.03 (s, 6H), 0.02 (s, 3H), 0.00 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 148.3, 144.1, 135.7, 135.6, 134.2, 129.6, 128.8, 128.7, 127.7, 125.7, 124.5, 115.1, 95.0, 74.2, 73.4, 71.3, 70.9, 70.3, 69.6, 68.7, 66.8, 66.1, 64.4, 64.2, 42.8, 42.7, 41.2, 39.1, 37.6, 36.3, 34.9, 33.9, 29.9, 27.0, 26.5, 26.5, 26.2, 26.0, 22.9, 19.4, 18.8, 18.5, 18.3, 18.2, 18.1, 1.2, −1.5, −3.4, −3.7, −3.7, −3.8, −4.1, −4.2, −4.3, −4.5, −4.8, −4.9; **IR** (film, $cm^{-1}$): 2954, 2929, 2857, 1472, 1428, 1388, 1361, 1252, 1205, 1095, 1007, 968, 836, 775, 736, 702, 506, 441; **HRMS** (ESI) for $C_{87}H_{160}O_{11}Si_8Na$ $[M+Na]^+$: calcd. 1628.0007; found 1627.9994.

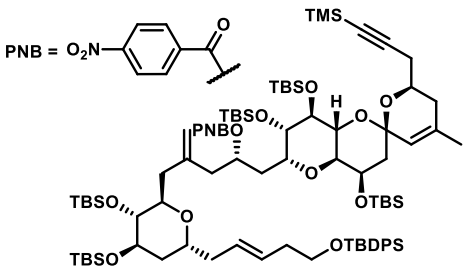
### 6.2.4.3 Alkyne Route

**Compound 187.**




Solid magnesium bromide diethyl etherate (966 mg, 3.74 mmol) was added in one portion to a solution of aldehyde **74** (574 mg, 0.748 mmol) and allyl stannane **158** (956 mg, 0.944 mmol, dr 5:1) in $CH_2Cl_2$ (21 mL) at −78 °C. The resulting mixture was stirred at this temperature for 4.5 h before the reaction was quenched with triethylamine (2.0 mL). The mixture was warmed to room temperature and diluted with *tert*-butyl methyl ether (40 mL) and saturated aqueous $NH_4Cl$ (40 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 30 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$ and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc 20:1) to give the title compound as a colorless oil (781 mg, 70%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +11.7 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.70 – 7.64 (m, 4H), 7.45 – 7.34 (m, 6H), 5.43 (dd, *J* = 5.6 Hz, 2H), 5.16 (s, 1H), 4.90 (s, 2H), 4.18 – 4.04 (m, 2H), 3.98 (q, *J* = 3.0 Hz, 1H), 3.94 (t, *J* = 5.6 Hz, 1H), 3.89 – 3.74 (m, 4H), 3.65 (t, *J* = 7.0 Hz, 2H), 3.61 – 3.54 (m, 2H), 3.52 – 3.45 (m, 2H), 3.36 (dd, *J* = 4.0, 2.6 Hz, 1H), 2.68 (dd, *J* = 14.4, 9.7 Hz, 1H), 2.59 (dd, *J* = 16.6, 4.9 Hz, 1H), 2.38 (dd, *J* = 14.4, 4.9 Hz, 1H), 2.35 – 2.16 (m, 6H), 2.09 (dt, *J* = 13.1, 6.5 Hz, 1H), 2.01 – 1.74 (m, 6H), 1.71 (s, 3H), 1.70 – 1.65 (m, 1H), 1.41 (ddd, *J* = 13.3, 4.9, 2.6 Hz, 1H), 1.04 (s, 9H), 0.91 (s, 9H), 0.89 (s, 27H), 0.88 (s, 9H), 0.15 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H), 0.05 (s, 15H), 0.03 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 144.0, 135.8, 135.7, 134.2, 129.7, 128.9, 128.5, 127.7, 124.3, 114.9, 103.8, 95.3, 86.1, 77.9, 76.3, 73.8, 72.9, 71.9, 71.0, 70.7, 70.5, 68.4, 66.5, 65.9, 65.5, 64.1, 43.5, 42.3, 38.5, 37.2, 36.3, 34.3, 34.2, 27.0, 26.6, 26.4, 26.1, 25.9, 22.8, 19.4, 18.4, 18.3, 18.3, 18.2, 18.2, 0.3, −3.4, −3.5, −3.6, −4.2, −4.2, −4.3, −4.3, −4.7, −4.9; **IR** (film, cm$^{-1}$): 2954, 2929, 2891, 2857, 1472, 1463, 1428, 1387, 1361, 1251, 1205, 1091, 1037, 1007, 965, 837, 775, 738, 702, 505; **HRMS** (ESI) for $C_{81}H_{144}O_{11}Si_7Na$ [M+Na]$^+$: calcd. 1511.8986; found 1511.9005.

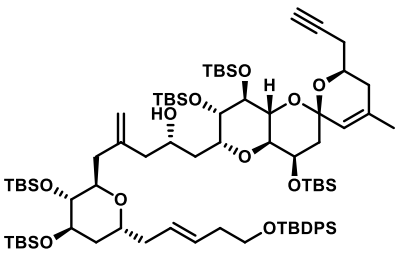
**Compound 193.**




Diethyl azodicarboxylate (398 µL, 2.45 mmol) was added dropwise to a solution of alcohol **187** (730 mg, 0.490 mmol), triphenylphosphine (649 mg, 2.45 mmol), and 4-nitrobenzoic acid (368 mg, 2.20 mmol) in toluene (5.0 mL) at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (8 mL). The mixture was diluted with *tert*-butyl methyl ether (10 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL), and the combined organic fractions were washed with

brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (fine silica, hexanes/EtOAc 40:1 to 35:1) to give the desired benzoate ester as a colorless oil (552 mg, 69%). $[\alpha]_D^{20}$ = +17.3 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.26 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 9.1 Hz, 2H), 7.70 – 7.63 (m, 4H), 7.46 – 7.32 (m, 6H), 5.50 – 5.33 (m, 3H), 5.17 (s, 1H), 4.85 (s, 1H), 4.83 (s, 1H), 4.11 (ddt, *J* = 10.6, 8.9, 4.4 Hz, 1H), 4.04 – 3.93 (m, 2H), 3.87 (dd, *J* = 9.6, 4.9 Hz, 1H), 3.84 – 3.74 (m, 3H), 3.65 (t, *J* = 7.0 Hz, 2H), 3.63 – 3.53 (m, 2H), 3.38 (dd, *J* = 3.7, 1.9 Hz, 1H), 3.19 (dd, *J* = 10.1, 2.6 Hz, 1H), 2.82 (dd, *J* = 14.5, 9.7 Hz, 1H), 2.55 (td, *J* = 16.4, 5.5 Hz, 2H), 2.43 – 2.13 (m, 6H), 2.11 – 1.97 (m, 3H), 1.98 – 1.70 (m, 4H), 1.71 (s, 3H), 1.61 (dd, *J* = 14.2, 3.2 Hz, 1H), 1.36 (dt, *J* = 13.7, 3.1 Hz, 1H), 1.04 (s, 9H), 0.93 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.82 (s, 9H), 0.14 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.06 (s, 6H), 0.04 (s, 3H), 0.03 (s, 6H), −0.03 (s, 3H), −0.10 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 163.8, 150.5, 143.1, 136.3, 135.8, 135.7, 134.2, 134.2, 130.7, 129.7, 128.7, 128.6, 127.7, 124.3, 123.5, 115.6, 103.7, 95.3, 86.1, 76.7, 73.8, 73.1, 72.9, 71.2, 70.8, 70.7, 70.3, 68.5, 66.5, 65.8, 64.7, 64.2, 42.3, 41.5, 38.9, 36.5, 36.3, 34.3, 34.0, 27.1, 27.0, 26.6, 26.5, 26.0, 26.0, 25.9, 22.8, 19.4, 18.4, 18.3, 18.3, 18.2, 18.1, 0.3, −3.3, −3.5, −3.5, −4.1, −4.2, −4.4, −4.4, −4.5, −4.8, −5.3; **IR** (film, $cm^{-1}$): 2954, 2929, 2893, 2857, 1728, 1531, 1472, 1462, 1427, 1384, 1360, 1348, 1272, 1252, 1205, 1094, 1043, 1007, 983, 965, 837, 776, 738, 720, 702, 506; **HRMS** (ESI) for $C_{88}H_{147}NO_{14}Si_7Na$ $[M+Na]^+$: calcd. 1660.9099; found 1660.9107.

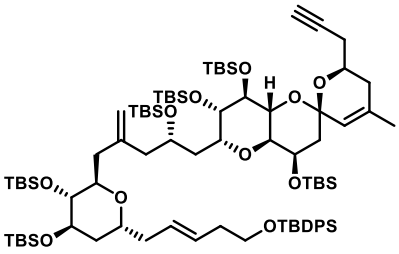
**Compound 195.**




Powdered NaOH (90.2 mg, 2.25 mmol) was added in one portion to a solution of *p*-nitrobenzoate ester **193** (528 mg, 0.322 mmol) in MeOH/THF (3:1, 10 mL) at room temperature. After stirring for 20 h at this temperature, the reaction was quenched with saturated aqueous $NH_4Cl$ (20 mL) and the mixture was diluted with *tert*-butyl methyl ether (20 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL). The combined organic fractions were washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 25:1) to give the title compound as a colorless oil (422 mg, 92%). $[\alpha]_D^{20}$ = +24.6 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.64 (m, 4H), 7.44 – 7.34 (m, 6H), 5.52 – 5.36 (m, 2H), 5.18 (d, *J* = 1.7 Hz, 1H), 4.93 (s, 1H), 4.89 (s, 1H), 4.24 – 4.11 (m, 2H), 4.00 (q, *J* = 3.0 Hz, 1H), 3.94 – 3.76 (m, 5H), 3.65 (t, *J* = 6.9 Hz, 2H), 3.62 – 3.57 (m, 2H), 3.38 (dd, *J* = 3.9, 2.2 Hz, 1H), 3.32 (dd, *J* = 10.1, 2.7 Hz, 1H), 2.68 (dd, *J* = 14.4, 9.1 Hz, 1H), 2.51 (ddd, *J* = 16.5, 5.2, 2.7 Hz, 1H), 2.41 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.36 – 2.14 (m, 7H), 2.08 (dt, *J* = 13.2, 6.5 Hz, 1H), 2.00 – 1.91 (m, 3H), 1.86 (dd, *J* = 14.1, 2.8 Hz, 2H), 1.82 – 1.63 (m, 6H), 1.40 (ddd, *J* = 13.5, 4.3, 2.5 Hz, 1H), 1.04 (s, 9H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (s, 27H), 0.12 (s, 3H), 0.10 (s, 3H), 0.05 (s, 6H), 0.05 (s, 9H), 0.03 (s, 6H), 0.01

(s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 144.5, 135.7, 134.2, 129.7, 129.0, 128.5, 127.7, 124.4, 114.7, 95.4, 81.2, 77.0, 74.2, 73.5, 73.0, 71.4, 70.9, 70.4, 69.9, 68.8, 66.9, 66.7, 65.6, 65.2, 64.1, 44.6, 42.3, 38.8, 37.4, 36.3, 34.1, 34.0, 29.9, 27.1, 27.0, 26.5, 26.5, 26.1, 26.0, 25.4, 22.8, 19.4, 18.4, 18.3, 18.3, 18.2, 18.2, −3.5, −3.6, −3.6, −4.1, −4.3, −4.4, −4.7, −5.0; **IR** (film, $cm^{-1}$): 2953, 2928, 2889, 2857, 1472, 1462, 1428, 1385, 1361, 1253, 1205, 1091, 1040, 1007, 968, 939, 860, 836, 775, 738, 702, 688, 672, 613, 506; **HRMS** (ESI) for $C_{78}H_{136}O_{11}Si_6Na$ [M+Na]$^+$: calcd. 1439.8591; found 1439.8600.

**Compound 197.**

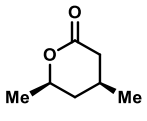



TBSOTf (73.7 μL, 0.321 mmol) was added dropwise to a solution of alcohol **195** (414 mg, 0.292 mmol) and 2,6-lutidine (102 μL, 0.876 mmol) in $CH_2Cl_2$ (3.3 mL) at 0 °C. The mixture was stirred at this temperature for 40 min before the reaction was quenched at 0 °C with saturated aqueous $NH_4Cl$ (10 mL). The mixture was warmed to room temperature and stirring was continued until all solids had dissolved. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 8 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 80:1) to give the title compound as a colorless oil (421 mg, 94%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +25.4 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.71 – 7.63 (m, 4H), 7.46 – 7.33 (m, 6H), 5.44 (td, *J* = 5.0, 3.2 Hz, 2H), 5.17 (d, *J* = 1.6 Hz, 1H), 4.84 (s, 1H), 4.80 (s, 1H), 4.22 – 4.11 (m, 1H), 4.09 (ddd, *J* = 12.2, 5.2, 2.1 Hz, 1H), 3.97 (q, *J* = 3.0 Hz, 1H), 3.97 – 3.87 (m, 1H), 3.88 – 3.76 (m, 4H), 3.66 (t, *J* = 7.0 Hz, 2H), 3.65 – 3.52 (m, 2H), 3.38 (dd, *J* = 3.7, 1.8 Hz, 1H), 3.14 (d, *J* = 9.9 Hz, 1H), 2.70 (dd, *J* = 14.2, 9.3 Hz, 1H), 2.52 (ddd, *J* = 16.5, 5.1, 2.7 Hz, 1H), 2.37 – 2.17 (m, 6H), 2.10 (ddd, *J* = 24.8, 13.6, 7.5 Hz, 2H), 2.00 – 1.91 (m, 3H), 1.92 – 1.81 (m, 2H), 1.77 (ddd, *J* = 13.3, 10.4, 2.7 Hz, 1H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.64 – 1.56 (m, 2H), 1.39 (dt, *J* = 13.9, 2.7 Hz, 1H), 1.05 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.90 (s, 27H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 144.1, 135.7, 135.6, 134.2, 129.7, 128.8, 128.6, 127.7, 124.5, 114.2, 95.3, 81.2, 76.6, 73.9, 73.0, 71.2, 70.6, 70.4, 69.9, 68.7, 67.1, 66.9, 65.5, 64.6, 64.2, 44.7, 42.5, 39.0, 37.8, 36.3, 34.1, 34.0, 27.1, 27.0, 26.7, 26.6, 26.2, 26.0, 26.0, 25.5, 22.8, 19.4, 18.5, 18.3, 18.2, 18.1, −3.3, −3.3, −3.6, −3.9, −4.1, −4.2, −4.3, −4.4, −4.5, −4.7, −4.9; **IR** (film, $cm^{-1}$): 2954, 2929, 2887, 2857, 1472, 1463, 1428, 1386, 1361, 1253, 1205, 1090, 1006, 971, 940, 860, 836, 775, 738, 702, 506; **HRMS** (ESI) for $C_{84}H_{151}O_{11}Si_7Na$ [M+Na]$^+$: calcd. 1531.9636; found 1531.9647.

## 6.3 Second-Generation Synthesis of Limaol

### 6.3.1 Revised Synthesis of the Northern Fragment

**(4*S*,6*R*)-4,6-Dimethyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (231).**



The compound was prepared according to a procedure by Schmid and co-workers. A freshly prepared solution of tetrafluoroboric acid (0.04 M in EtOH, 5.50 mL, 0.220 mmol) was added to a solution of [Ru((*S*)-MeO-BIPHEP)$(OAc)_2$][201] ((*S*)-**233**, 27.5 mg, 22.0 μmol) in EtOH (12.5 mL) and the mixture was stirred at room temperature for 2 h. A solution of 4,6-dimethyl-2-pyrone (**232**, 1.37 g, 11.0 mmol) in EtOH (5.0 mL, 2 × 2.5 mL washes) was added to an oven-dried 150 mL-autoclave under argon equipped with a glass insert and a stirring bar. The catalyst solution (18.0 mL total volume) was added and complete transfer was ensured with EtOH washes (2 × 4.0 mL). The autoclave was closed, pressurized with 60 bar of $H_2$, and heated to 60 °C for 23 h. After cooling to room temperature, the residual gas was released and the mixture was concentrated. The residue was purified by flash chromatography (fine silica, hexanes/*tert*-butyl methyl ether 1:1) to give the title compound as a colorless oil (961 mg, 68%). The spectral data and specific rotation were in good agreement with the reported values.[189b] Purity and dr after flash chromatography were determined by GC-MS analysis to be 93% and 18:1, respectively (Figure 6.5). According to GC-MS analysis using a chiral stationary phase, the *ee* of the major diastereoisomer was determined to be 98% (Figure 6.6). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +7.6 (c = 0.63, MeOH), literature: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +6.6 (c = 0.56, MeOH); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.41 (dqd, *J* = 11.6, 6.3, 2.9 Hz, 1H), 2.67 (dd, *J* = 11.8, 1.9 Hz, 1H), 2.12 – 1.96 (m, 2H), 1.97 – 1.87 (m, 1H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.30 – 1.13 (m, 1H), 1.03 (d, *J* = 6.3 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 171.6, 77.4, 39.0, 38.0, 27.0, 22.0, 21.8.

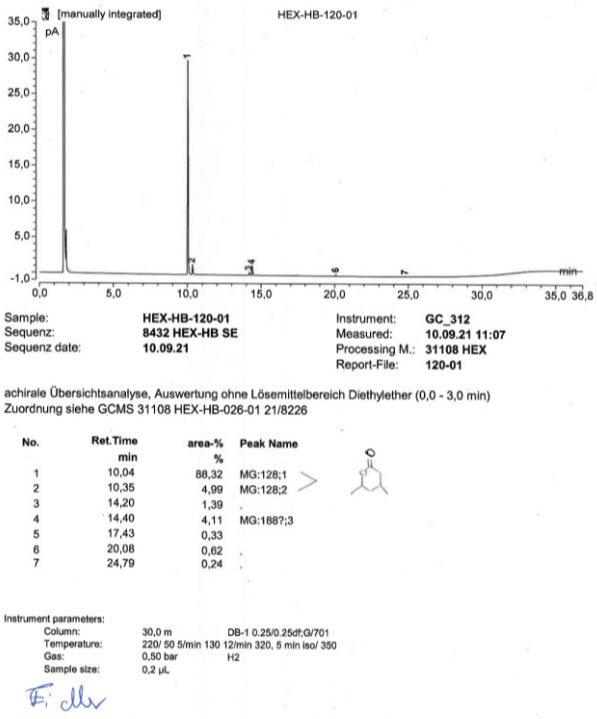



**Figure 6.5.** GC-MS analysis of **231** using an achiral stationary phase.

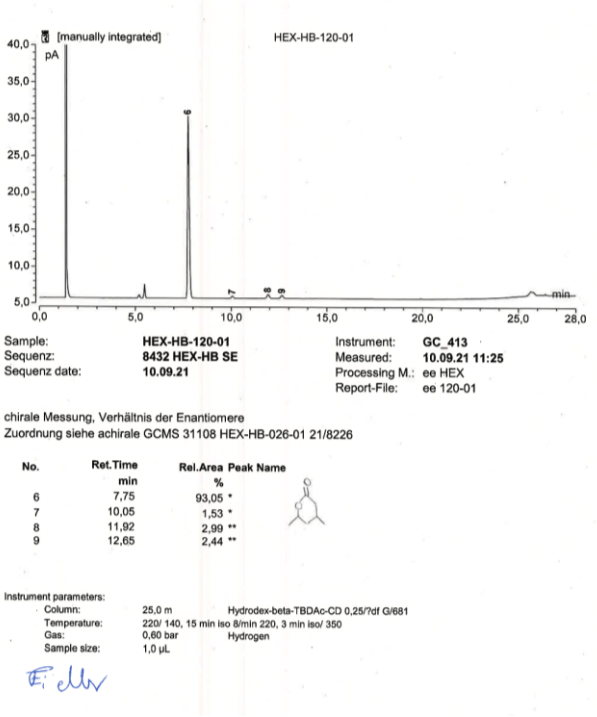
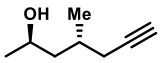



**Figure 6.6.** GC-MS analysis of **231** using a chiral stationary phase.

**(2*R*,4*R*)-4-Methylhept-6-yn-2-ol (235).**[188]

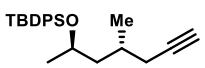



A solution of $CCl_4$ (17.3 mL, 180 mmol) in THF (24 mL) was added dropwise over the course of 4 h to a refluxing solution of lactone **231** (961 mg, 7.49 mmol) and triphenylphosphine (7.86 g, 30.0 mmol) in THF (96 mL). Once the addition was complete, the mixture was allowed to cool to ambient temperature. Water (60 mL) was added, the phases were separated, and the aqueous layer extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic phases were washed with saturated aq. $NaHCO_3$ (20 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure to a total volume of ca. 10 mL. Pentane (50 mL) was added under vigorous stirring, the precipitate was filtered off, and the filtrate again reduced to a total volume of ca. 10 mL. This cycle of precipitation/evaporation was repeated three times before all volatile materials were evaporated and the solid residue subjected to flash chromatography (pentane/$Et_2O$, 98:2) to furnish the dichloroolefin **234** as a colorless syrup (1.10 g, 75%). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 3.77 (dqd, *J* = 11.3, 6.2, 2.1 Hz, 1H), 2.81 (ddd, *J* = 14.3, 4.0, 1.9 Hz, 1H), 1.79 – 1.68 (m, 2H), 1.61 (dd, *J* = 14.3, 11.9 Hz, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 1.12 (dt, *J* = 13.7, 12.2 Hz, 1H), 1.00 (d, *J* = 6.2 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 150.2, 104.2, 76.8, 40.8, 33.8, 29.2, 22.0, 21.8.

A solution of compound **234** in THF (15 mL) was added to a suspension of lithium sand (236 mg, 33.7 mmol) in THF (30 mL) at room temperature. The reaction mixture was stirred at reflux temperature for 3 h before being allowed to cool to room temperature. The reaction was quenched with MeOH (3 mL) followed by aq. $NH_4CI$ (30 mL), and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over $Na_2SO_4$, and concentrated. The residue was purified by flash chromatography (pentane/$Et_2O$ 2:1) to afford the title compound as colorless liquid (531 mg, 75%, 56% over two steps). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 3.90 (qt, *J* = 10.1, 4.8 Hz, 1H), 2.25 – 2.08 (m, 2H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.91 (dqd, *J* = 9.0, 6.4, 5.0 Hz, 1H), 1.59 (ddd, *J* = 14.1, 9.1, 5.0 Hz, 1H), 1.30 (ddd, *J* = 13.9, 9.0, 3.8 Hz, 1H), 1.26 – 1.23 (m, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 83.2, 69.6, 66.1, 45.6, 29.3, 26.5, 24.6, 19.3.

**Note**: This compound was directly used in the next step due to its volatility.

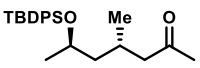
***tert*-Butyl(((2*R*,4*R*)-4-methylhept-6-yn-2-yl)oxy)diphenylsilane (103).**




Imidazole (539 mg, 7.92 mmol) and TBDPSCl (1.55 mL, 5.94 mmol) were added to a solution of alcohol **235** (500 mg, 3.96 mmol) in DMF (10 mL) at room temperature. The mixture was stirred at room temperature for 18 h before the reaction was quenched with saturated aq. $NH_4Cl$ (20 mL). The resulting mixture was extracted with *tert*-butyl methyl ether (3 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 100:1) to afford the title compound as

colorless liquid (1.28 g, 88%). The spectral data and specific rotation matched the recorded data of the previously synthesized material.

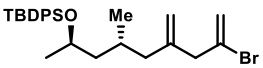
**(4*S*,6*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4-methylheptan-2-one (236).**




Methyl lithium (1.88 M in $Et_2O$, 3.23 mL, 6.08 mmol) was added dropwise to a solution of lactone **231** (742 mg, 5.79 mmol) in THF (15 mL) at –78 °C. The mixture was stirred at –78 °C for 1 h. The reaction was quenched with water (15 mL) at –78 °C and the biphasic mixture was warmed to room temperature. The aqueous layer was extracted with $Et_2O$ (3 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried over $Na_2SO_4$ and concentrated. Due to the volatility of the resulting alcohol, this residue was directly subjected to the protection step.

Imidazole (0.788 g, 11.6 mmol) and TBDPSCl (2.26 mL, 8.68 mmol) were added to a solution of the residue (prepared as above) in DMF (15 mL) at room temperature. The mixture was stirred at this temperature for 18 h. Saturated aq. $NH_4CI$ (20 mL) and *tert*-butyl methyl ether (20 mL) were added, and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic phases were washed with brine (30 mL), dried over $Na_2SO_4$, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 20:1) to afford the title compound as colorless liquid (1.35 g, 61% over two steps). $[\alpha]_D^{20}$ = +2.0 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.73 – 7.65 (m, 4H), 7.46 – 7.34 (m, 6H), 3.83 (dqd, *J* = 7.4, 6.1, 5.0 Hz, 1H), 2.21 – 2.04 (m, 3H), 2.03 (s, 3H), 1.49 (ddd, *J* = 13.7, 7.4, 5.3 Hz, 1H), 1.19 (ddd, *J* = 13.7, 7.8, 5.1 Hz, 1H), 1.07 (d, *J* = 6.1 Hz, 3H), 1.05 (s, 9H), 0.73 (d, *J* = 6.5 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 209.0, 136.1, 134.9, 134.4, 129.7, 129.6, 127.7, 127.5, 67.7, 51.7, 47.2, 30.2, 27.2, 26.2, 24.2, 20.1, 19.4.; **IR** (film, $cm^{-1}$): 2962, 2931, 2895, 2857, 1716, 1471, 1461, 1427, 1373, 1361, 1158, 1110, 1065, 1030, 996, 822, 741, 727, 703, 685, 612, 507; **HRMS** (ESI) for $C_{24}H_{34}O_2SiNa$ $[M+Na]^+$: calcd. 405.2220; found 405.2226.

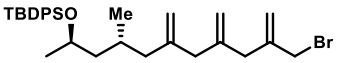
**(((2*R*,4*R*)-8-Bromo-4-methyl-6-methylenenon-8-en-2-yl)oxy)(*tert*-butyl)diphenylsilane (238).**




*n*-Butyllithium (1.6 M in hexanes, 0.73 mL, 1.2 mmol) was added dropwise to a solution of *i*-PrMgBr (2.4 M in 2-Me-THF, 0.26 mL, 0.63 mmol) in THF (4.0 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. After cooling to −78 °C, a solution of vinyl iodide **104** (241 mg, 0.488 mmol) in THF (1.0 mL + 2 × 0.5 mL rinse) was added and the mixture was stirred for 2 h at −78 °C. A solution of CuCN·2LiCl (1.0 M in THF, 0.54 mL, 0.54 mmol) was added at −78 °C and the resulting solution was stirred at this temperature for 15 min. 2,3-Dibromopropene (0.17 mL, 1.7 mmol) was added at −78 °C. The solution was warmed to 0 °C and stirred for 5 h at this temperature, before saturated aq. $NH_4Cl$ (10 mL) was added. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered, and

concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 100:1) to afford the title compound as a colorless oil (183 mg, 77%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +0.5 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 (tt, *J* = 7.5, 1.6 Hz, 4H), 7.46 – 7.33 (m, 6H), 5.57 (q, *J* = 1.3 Hz, 1H), 5.47 (d, *J* = 1.5 Hz, 1H), 4.91 (d, *J* = 1.5 Hz, 1H), 4.87 (d, *J* = 1.7 Hz, 1H), 3.91 (dqd, *J* = 8.2, 6.1, 4.3 Hz, 1H), 3.05 (s, 2H), 1.93 – 1.86 (m, 1H), 1.81 (dddd, *J* = 14.0, 9.9, 7.2, 4.9 Hz, 1H), 1.73 (ddd, *J* = 13.1, 7.9, 1.0 Hz, 1H), 1.58 (ddd, *J* = 13.8, 8.2, 4.4 Hz, 1H), 1.11 – 1.02 (m, 13H), 0.69 (d, *J* = 6.3 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 143.5, 136.1, 136.1, 135.1, 134.5, 132.0, 129.7, 129.5, 127.7, 127.5, 118.6, 114.8, 67.7, 48.1, 47.3, 43.5, 27.2, 27.1, 24.5, 19.6, 19.5; **IR** (film, $cm^{-1}$): 3071, 3049, 2963, 2929, 2896, 2857, 1626, 1472, 1461, 1427, 1375, 1190, 1154, 1128, 1110, 1061, 1027, 1007, 997, 974, 953, 890, 822, 740, 728, 702, 685, 612, 510, 499, 434; **HRMS** (ESI) for $C_{27}H_{37}BrOSiNa$ $[M+Na]^+$: calcd. 507.1689; found 507.1694.

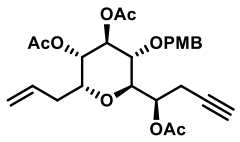
**Compound 226.**




Triethylamine (29 μL, 0.21 mmol) and methanesulfonyl chloride (11 μL, 0.14 mmol) were added sequentially to a stirred solution of alcohol **107** (50 mg, 0.10 mmol) in THF (1.0 mL) at 0 °C. After stirring for 1 h at room temperature, a solution of lithium bromide (36 mg, 0.42 mmol) in THF (0.5 mL) was added. The mixture was stirred for 15 h at room temperature. Saturated aq. $NH_4Cl$ solution (4 mL) and *tert*-butyl methyl ether (5 mL) were added and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 4 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated to afford the title compound as a colorless oil (55 mg, 97%), which was used without further purification. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −6.7 (c = 1.03, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 (ddd, *J* = 8.1, 6.7, 1.6 Hz, 4H), 7.45 – 7.33 (m, 6H), 5.26 – 5.23 (m, 1H), 4.99 (q, *J* = 1.3 Hz, 1H), 4.92 – 4.89 (m, 1H), 4.89 – 4.87 (m, 1H), 4.77 (d, *J* = 1.5 Hz, 2H), 3.93 (d, *J* = 0.8 Hz, 2H), 3.92 – 3.85 (m, 1H), 2.89 (s, 2H), 2.63 (s, 2H), 1.88 – 1.76 (m, 2H), 1.69 – 1.61 (m, 1H), 1.61 – 1.54 (m, 1H), 1.11 – 1.05 (m, 1H), 1.04 (s, 9H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.69 (d, *J* = 6.3 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 145.5, 143.9, 143.3, 136.1, 136.1, 135.1, 134.5, 129.6, 129.5, 127.6, 127.5, 117.6, 114.7, 113.4, 67.8, 47.4, 43.8, 42.5, 39.8, 36.0, 27.2, 27.1, 24.4, 19.7, 19.5; **IR** (film, $cm^{-1}$): 3072, 2962, 2928, 2857, 1637, 1472, 1461, 1427, 1375, 1260, 1211, 1154, 1105, 1059, 1025, 949, 900, 820, 799, 762, 739, 727, 701, 684, 666, 611, 504, 487; **HRMS** (ESI) for $C_{31}H_{43}OSiBrNa$ $[M+Na]^+$: calcd. 561.2159; found 561.2160.

### 6.3.2 Revised Synthesis of the Central Fragment

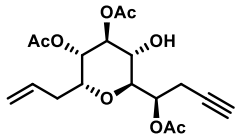
**Compound 245.**




TBAF (22.6 mL, 1.0 M in THF, 22.6 mmol) was added to a solution of **25** (6.08 g, 10.3 mmol) in THF (80 mL) at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature for 2 h. Water (80 mL) and EtOAc (80 mL) were added and the aqueous phase was extracted with EtOAc (3 × 40 mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$, and filtered. The solvent was evaporated and the residue was taken up in $CH_2Cl_2$ (50 mL).

Pyridine (6.66 mL, 82.3 mmol), acetic anhydride (5.83 mL, 61.7 mmol), and DMAP (62.8 mg, 0.514 mmol) were added sequentially and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (50 mL) and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic fractions were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, and filtered. After vacuum evaporation of the solvent the crude product was purified by flash chromatography (hexanes/EtOAc 3:1) to afford the title compound (4.46 g, 89%) as a colorless oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +40.7 (c = 0.95, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.77 (ddt, *J* = 17.1, 10.3, 7.0 Hz, 1H), 5.33 (dt, *J* = 17.4, 6.3 Hz, 2H), 5.16 – 5.06 (m, 2H), 4.88 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.59 (q, *J* = 11.2 Hz, 2H), 4.02 (dt, *J* = 9.5, 4.5 Hz, 1H), 3.88 (t, *J* = 6.0 Hz, 1H), 3.79 (s, 3H), 3.52 (t, *J* = 6.2 Hz, 1H), 2.57 – 2.45 (m, 3H), 2.32 – 2.21 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 1.97 (t, *J* = 2.8 Hz, 1H), 1.95 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 170.3, 170.0, 169.9, 159.6, 133.4, 129.9, 129.5, 118.2, 114.1, 79.8, 73.4, 73.0, 72.7, 70.8, 70.6, 70.1, 69.7, 69.6, 55.4, 32.6, 21.2, 21.0, 20.9, 20.3; **IR** (film, $cm^{-1}$): 3279, 2937, 1743, 1613, 1514, 1430, 1370, 1303, 1230, 1175, 1096, 1034, 920, 823, 671, 665, 640, 603, 519, 483, 459; **HRMS** (ESI) for $C_{26}H_{32}O_9Na$ $[M+Na]^+$: calcd. 511.1939; found 511.1941.

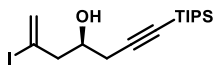
**Compound 246.**




Water (9.0 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.90 g, 12.8 mmol) were sequentially added to a solution of **245** (4.46 g, 9.14 mmol) in $CH_2Cl_2$ (90 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature, diluted with water (60 mL) and extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with water (60 mL) and brine (60 mL), dried over anhydrous $Na_2SO_4$, and filtered. The solvent was evaporated and the crude product purified by flash chromatography (hexanes/EtOAc 3:2) to yield the title compound (3.18 g, 95%) as a colorless oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +59.9 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.74 (dddd, *J* = 16.7, 10.2, 7.4, 6.3 Hz, 1H), 5.31 (dt, *J* = 7.0, 5.3 Hz, 1H), 5.19 – 5.07 (m, 3H), 4.97 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.13 (dt, *J* = 10.6, 4.7 Hz, 1H), 3.84 (dd, *J* = 8.1, 5.1 Hz, 1H), 3.71 (dd, *J* = 7.4 Hz, 1H), 2.91 – 2.85 (m, 1H), 2.66 (ddd, *J* = 17.1, 5.5, 2.7 Hz, 1H), 2.55 (ddd, *J* =

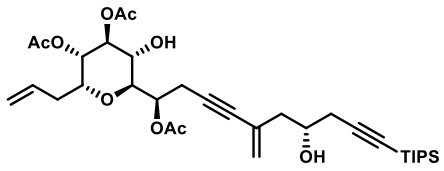
17.1, 6.9, 2.7 Hz, 1H), 2.51 – 2.42 (m, 1H), 2.33 – 2.21 (m, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.98 (t, *J* = 2.7 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 171.3, 170.3, 169.9, 133.3, 118.0, 79.7, 72.9, 72.7, 71.6, 70.7, 70.6, 70.0, 69.6, 31.5, 21.1, 21.0, 20.9, 20.0; **IR** (film, $cm^{-1}$): 3483, 3290, 2932, 1741, 1643, 1430, 1370, 1230, 1149, 1097, 1072, 1033, 995, 918, 671, 637, 604, 554, 535, 497, 473, 446, 424; **HRMS** (ESI) for $C_{18}H_{24}O_8Na$ [M+Na]$^+$: calcd. 391.1363; found 391.1366.

**(*S*)-2-Iodo-7-(triisopropylsilyl)hept-1-en-6-yn-4-ol (247).**




*n*-Butyllithium (8.09 mL, 1.6 M in hexanes, 13.0 mmol) was added dropwise to a stirred solution of (triisopropylsilyl)acetylene (3.27 mL, 14.6 mmol) in anhydrous THF (60 mL) at −78 °C. The resulting solution was stirred at this temperature for 20 min. Boron trifluoride etherate (1.60 mL, 13.0 mmol) was added dropwise at −78 °C. After stirring at −78 °C for 5 min, a solution of epoxide **48** (1.70 g, 8.09 mmol) in THF (2.0 mL, 2 × 1.5 mL washes) was added *via* cannula at −78 °C. After 1 h of stirring at this temperature, the reaction was quenched by adding brine (60 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 50 mL) and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 12:1) to give the title compound (3.13 g, 98%) as a colorless oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −13.2 (c = 0.96, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 6.18 (q, *J* = 1.3 Hz, 1H), 5.85 (d, *J* = 1.4 Hz, 1H), 4.05 (dp, *J* = 8.0, 5.4 Hz, 1H), 2.75 (ddd, *J* = 14.3, 4.7, 1.3 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.57 – 2.45 (m, 2H), 2.03 (d, *J* = 5.2 Hz, 1H), 1.07 (d, *J* = 3.2 Hz, 21H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 128.9, 106.5, 103.7, 84.6, 68.5, 51.6, 27.6, 18.8, 11.4; **IR** (film, $cm^{-1}$): 3394, 2942, 2892, 2864, 2172, 1617, 1462, 1421, 1383, 1188, 1117, 1072, 1057, 1025, 995, 898, 883, 677, 663, 641, 596, 581, 509, 490, 457, 444, 409; **HRMS** (ESI) for $C_{16}H_{29}OISiNa$ [M+Na]$^+$: calcd. 415.0925; found 415.0926.

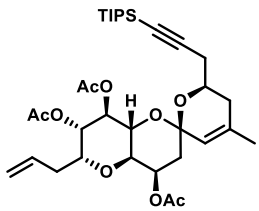
**Compound 248.**




Copper(I) iodide (110 mg, 0.580 mmol) was added to a solution of alkyne **246** (1.07 g, 2.90 mmol) in degassed diisopropylamine (3 mL). The mixture was stirred at room temperature for 10 min. A solution of alkenyl iodide **247** (1.25 g, 3.19 mmol) in diisopropylamine (1 mL, 2 × 0.5 mL wash) was added, followed by bis(triphenylphosphine)palladium(II) chloride (102 mg, 0.145 mmol). The mixture was stirred for 1.5 h at room temperature, before the reaction was quenched at 0 °C by addition of saturated aqueous $NH_4Cl$ (25 mL). The mixture was diluted with EtOAc (25 mL), allowed to warm to room temperature, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous $Na_2SO_4$, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 3:2) to afford

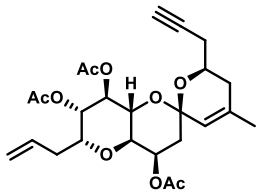
the desired enyne (1.47 g, 80%) as a pale yellow oil. $[\alpha]_D^{20}$ = +33.9 (c = 0.94, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.76 (dddd, *J* = 16.6, 10.2, 7.4, 6.3 Hz, 1H), 5.38 (d, *J* = 1.9 Hz, 1H), 5.33 (td, *J* = 6.5, 4.1 Hz, 1H), 5.31 – 5.25 (m, 1H), 5.21 – 5.04 (m, 3H), 5.01 (dd, *J* = 8.8, 5.3 Hz, 1H), 4.17 (dt, *J* = 10.7, 4.8 Hz, 1H), 4.07 – 3.96 (m, 1H), 3.89 – 3.76 (m, 2H), 3.11 (d, *J* = 5.7 Hz, 1H), 2.83 (dd, *J* = 17.1, 6.7 Hz, 1H), 2.64 (dd, *J* = 17.1, 6.3 Hz, 1H), 2.58 – 2.42 (m, 4H), 2.43 – 2.32 (m, 2H), 2.28 (dddt, *J* = 15.1, 6.0, 4.4, 1.4 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.13 – 0.99 (m, 21H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 13C NMR (101 MHz, CDCl3) δ 171.2, 170.2, 169.9, 133.3, 127.7, 123.9, 118.1, 104.2, 86.3, 84.1, 82.8, 73.0, 72.9, 71.8, 70.8, 70.2, 69.5, 69.0, 43.8, 31.4, 28.1, 21.2, 21.0, 20.9, 20.7, 18.8, 11.4; **IR** (film, $cm^{-1}$): 3458, 2943, 2865, 2171, 1745, 1464, 1430, 1369, 1230, 1163, 1073, 1031, 995, 916, 884, 676, 605, 526, 478, 447; **HRMS** (ESI) for $C_{34}H_{52}O_9SiNa$ [M+Na]$^+$: calcd. 655.3273; found 655.3274.

**Compound 249.**




(Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**36**, 36.0 mg, 46.5 μmol) and pyridinium p-toluenesulfonate (11.7 mg, 46.5 μmol) were added to a solution of enyne **248** (1.47 g, 2.33 mmol) in $CH_2Cl_2$ (23 mL). The mixture was stirred at room temperature for 20 min and the reaction quenched with triethylamine (1.0 mL). Saturated aqueous $NH_4Cl$ (30 mL) and EtOAc (40 mL) were added. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic fractions were washed with brine (40 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 5:1) to give the title compound (1.16 g, 79%) as a colorless oil. $[\alpha]_D^{20}$ = +19.3 (c = 1.07, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.74 (dddd, *J* = 17.5, 10.2, 7.4, 6.1 Hz, 1H), 5.30 (t, *J* = 9.8 Hz, 1H), 5.21 (d, *J* = 1.6 Hz, 1H), 5.17 – 5.06 (m, 3H), 5.03 (q, *J* = 3.1 Hz, 1H), 4.33 – 4.18 (m, 2H), 3.89 (ddt, *J* = 9.1, 7.8, 5.3 Hz, 1H), 3.53 (dd, *J* = 10.2, 3.1 Hz, 1H), 2.74 – 2.51 (m, 2H), 2.49 – 2.34 (m, 2H), 2.26 (dd, *J* = 15.3, 3.0 Hz, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 – 1.93 (m, 2H), 1.74 (dd, *J* = 15.2, 3.2 Hz, 1H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.11 – 0.97 (m, 21H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 171.0, 170.5, 170.0, 137.4, 133.5, 122.7, 117.7, 104.4, 95.5, 82.5, 73.3, 71.1, 70.7, 67.9, 67.8, 66.8, 66.7, 37.9, 34.4, 30.6, 27.0, 22.9, 21.5, 21.0, 20.9, 18.7, 11.4; **IR** (film, $cm^{-1}$): 2942, 2865, 2175, 1750, 1463, 1432, 1369, 1223, 1161, 1120, 1101, 1067, 1034, 995, 965, 917, 883, 847, 757, 677, 664, 603, 459, 422; **HRMS** (ESI) for $C_{34}H_{52}O_9SiNa$ [M+Na]$^+$: calcd. 655.3273; found 655.3274.

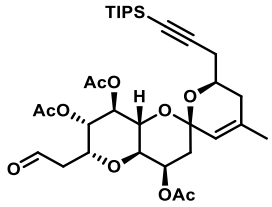
**Compound 250.**




Silver(I) fluoride (432 mg, 3.41 mmol) was added to a solution of spiroketal **249** (1.44 g, 2.27 mmol) in acetonitrile (23 mL). The mixture was stirred at room temperature for 19 h. Saturated aqueous $NH_4Cl$

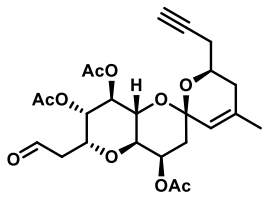
(20 mL) was added and the biphasic mixture was vigorously stirred for 90 min. EtOAc (40 mL) was added and the suspension was filtered through Celite. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic fractions were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 7:3) to give the title compound (975 mg, 90%) as a pale yellow foam. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +32.5 (c = 1.03, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.75 (dddd, *J* = 17.4, 10.2, 7.4, 6.2 Hz, 1H), 5.30 (t, *J* = 9.8 Hz, 1H), 5.23 (dt, *J* = 2.6, 1.3 Hz, 1H), 5.17 – 5.07 (m, 3H), 5.03 (q, *J* = 3.1 Hz, 1H), 4.35 (t, *J* = 10.0 Hz, 1H), 4.25 (ddd, *J* = 10.7, 5.9, 4.5 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.54 (dd, *J* = 10.3, 3.1 Hz, 1H), 2.64 – 2.52 (m, 1H), 2.49 – 2.33 (m, 3H), 2.28 (dd, *J* = 15.3, 3.0 Hz, 1H), 2.10 (s, 3H), 2.06 (s, 3H), 2.05 – 2.01 (m, 4H), 1.93 (ddd, *J* = 10.3, 2.4, 1.2 Hz, 1H), 1.86 (dd, *J* = 17.1, 4.0 Hz, 1H), 1.75 (dd, *J* = 15.2, 3.2 Hz, 1H), 1.70 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 171.1, 170.5, 170.1, 137.4, 133.5, 122.9, 117.7, 95.6, 80.8, 73.2, 71.3, 70.5, 70.0, 67.9, 67.8, 66.9, 66.7, 37.9, 34.4, 30.6, 25.2, 22.8, 21.5, 21.1, 20.9; **IR** (film, $cm^{-1}$): 3279, 2933, 1737, 1681, 1643, 1431, 1370, 1223, 1119, 1101, 1066, 1034, 994, 966, 907, 864, 756, 666, 645, 605, 521, 466, 424; **HRMS** (ESI) for $C_{25}H_{32}O_9Na$ $[M+Na]^+$: calcd. 499.1939; found 499.1940.

**Compound 252.**




2,6-Lutidine (3.7 μL, 32 μmol), osmium tetroxide (1.7 μL, 4% in water, 0.32 μmol) and sodium periodate (14 mg, 63 μmol) were sequentially added to a stirred solution of spiroketal **249** (10 mg, 16 μmol) in 1,4-dioxane/$H_2O$ (3:1, 0.16 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h before the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (2 mL), and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with saturated aqueous $NH_4Cl$ (3 mL) and brine (3 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 3:2) to afford the desired aldehyde (9.9 mg, 99%) as a colorless oil. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.73 (dd, *J* = 2.5, 1.5 Hz, 1H), 5.28 – 5.16 (m, 3H), 5.05 (q, *J* = 3.1 Hz, 1H), 4.90 – 4.80 (m, 1H), 4.35 – 4.20 (m, 1H), 3.89 (ddt, *J* = 11.2, 8.0, 5.5 Hz, 1H), 3.52 (dd, *J* = 10.3, 3.0 Hz, 1H), 2.93 – 2.77 (m, 2H), 2.62 (dd, *J* = 16.6, 5.3 Hz, 1H), 2.45 (dd, *J* = 16.6, 7.7 Hz, 1H), 2.24 (dd, *J* = 15.3, 3.0 Hz, 1H), 2.08 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.99 – 1.93 (m, 2H), 1.76 (dd, *J* = 15.3, 3.2 Hz, 1H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.16 – 0.95 (m, 21H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 198.3, 170.8, 170.4, 169.8, 137.5, 122.6, 104.4, 95.5, 82.6, 70.5, 70.1, 69.1, 69.0, 67.4, 66.8, 66.4, 41.7, 38.0, 34.4, 26.9, 22.9, 21.4, 21.0, 20.8, 18.8, 11.4.

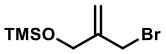
**Compound 251.**



2,6-Lutidine (379 μL, 3.26 mmol), osmium tetroxide (50.0 μL, 4% in water, 8.14 μmol) and sodium periodate (1.39 g, 6.51 mmol) were sequentially added to a stirred solution of spiroketal **250** (776 mg, 1.63 mmol) in 1,4-dioxane/$H_2O$ (3:1, 16 mL) at room temperature. The resulting mixture was stirred at room temperature for 21 h before the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with saturated aqueous $NH_4Cl$ (30 mL) and brine (30 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 1:1 to 1:2) to afford the desired aldehyde (612 mg, 79%) as a white foam. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +13.3 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.72 (dd, *J* = 2.4, 1.5 Hz, 1H), 5.26 – 5.13 (m, 3H), 5.05 (q, *J* = 3.1 Hz, 1H), 4.85 (dt, *J* = 7.8, 6.1 Hz, 1H), 4.38 (dd, *J* = 10.3, 9.4 Hz, 1H), 3.89 (dddd, *J* = 10.7, 6.9, 5.8, 3.8 Hz, 1H), 3.52 (dd, *J* = 10.3, 3.1 Hz, 1H), 2.93 – 2.77 (m, 2H), 2.49 – 2.34 (m, 2H), 2.25 (dd, *J* = 15.3, 3.0 Hz, 1H), 2.10 (s, 3H), 2.06 (s, 3H), 2.04 (d, *J* = 2.8 Hz, 1H), 2.01 (s, 3H), 1.94 – 1.91 (m, 1H), 1.90 – 1.83 (m, 1H), 1.76 (dd, *J* = 15.3, 3.3 Hz, 1H), 1.70 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 198.3, 170.9, 170.4, 169.9, 137.5, 122.7, 95.6, 80.8, 70.3 (two overlapping signals), 70.0, 69.1, 68.8, 67.5, 66.8, 66.4, 41.7, 37.9, 34.4, 25.2, 22.8, 21.4, 21.0, 20.8; **IR** (film, $cm^{-1}$): 3281, 2917, 1732, 1428, 1371, 1235, 1161, 1118, 1103, 1066, 1035, 994, 965, 904, 851, 756, 666, 648, 603, 521, 494, 466, 426; **HRMS** (ESI) for $C_{24}H_{30}O_{10}Na$ $[M+Na]^+$: calcd. 501.1731; found 501.1730.

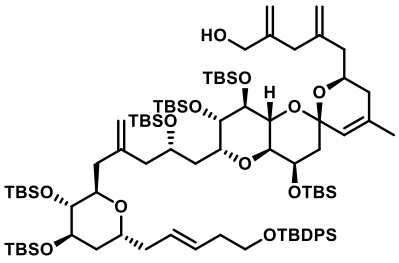
### 6.3.3 Completion of the Synthesis by the Indium-Mediated Hydroallylation Path

**((2-(Bromomethyl)allyl)oxy)trimethylsilane (228).**




Triethylamine (4.01 mL, 28.7 mmol) and trimethylsilyl chloride (2.26 mL, 17.2 mmol) were added to a solution of 2-(bromomethyl)prop-2-en-1-ol[187] (**227**, 2.17 g, 14.4 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h, then warmed to room temperature. Saturated aq. $NH_4Cl$ (40 mL) was added and the aqueous phase was extracted with $Et_2O$ (3 × 20 mL). The combined organic fractions were washed with brine (40 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by bulb-to-bulb distillation to give the title compound as an inseperable mixture (4:1, 2.80 g) of the allyl bromide (2.33 g, 73%) and the allyl chloride (467 mg, 18%). Spectral data of the major component: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.27 (q, *J* = 1.0 Hz, 1H), 5.23 (q, *J* = 1.4 Hz, 1H), 4.24 (t, *J* = 1.3 Hz, 2H), 4.02 (d, *J* = 0.8 Hz, 2H), 0.15 (s, 9H).

**Compound 229.**

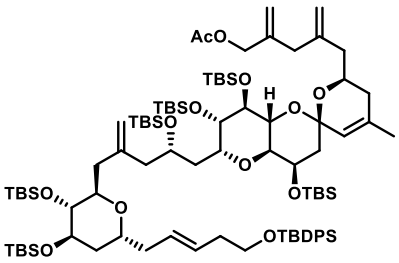



***Preparation of the allylindium reagent***: 1,2-Dibromoethane (1.7 μL, 20 μmol) and trimethylsilyl chloride (1.3 μL, 9.8 μmol) were added to a suspension of indium powder (18 mg, 0.16 mmol) in THF (30 μL) at room temperature. The mixture was briefly heated with a heatgun to activate the indium powder. A solution of bromide **228** (26 mg, 0.12 mmol) in THF (0.2 mL) was added and argon was blown over the mixture to reduce its total volume (~50 μL). The mixture was stirred at 40 °C for 24 h. After cooling to room temperature, the supernatant was separated from the residual indium powder to give a solution of the allylindium reagent.

***Carbometalation of the alkyne***: *i*-PrMgBr (9.0 μL, 2.4 M in 2-Me-THF, 22 μmol) was added to a solution of alkyne **197** (30 mg, 20 μmol) in THF (20 μL) in a pressure Schlenk tube. The mixture was stirred at room temperature for 1.5 h. The allylindium reagent solution was added and the resulting mixture was heated to 100 °C for 18 h. After cooling to room temperature, aq. HCl (1 M, 1 mL) was added and the biphasic mixture was vigorously stirred for 1 h at room temperature. *tert*-Butyl methyl ether (2 mL) was added, the layers were separated, and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 2 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 15:1) to give the title compound as a colorless oil (18 mg, 58%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +17.7 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.70 – 7.64 (m, 4H), 7.45 – 7.33 (m, 6H), 5.53 – 5.35 (m, 2H), 5.22 – 5.10 (m, 2H), 5.02 (dd, *J* = 1.9, 1.0 Hz, 1H), 4.99 – 4.94 (m, 1H), 4.87 (d, *J* = 1.7 Hz, 1H), 4.83 (d, *J* = 1.9 Hz, 1H), 4.79 (d, *J* = 1.9 Hz, 1H), 4.18 – 4.11 (m, 1H), 4.09 – 4.04 (m, 3H), 3.97 (dd, *J* = 3.0 Hz, 1H), 3.95

– 3.87 (m, 1H), 3.86 – 3.75 (m, 4H), 3.66 (t, *J* = 7.1 Hz, 3H), 3.62 (d, *J* = 2.3 Hz, 1H), 3.37 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.14 – 3.08 (m, 1H), 2.85 (s, 2H), 2.71 (dd, *J* = 14.2, 9.3 Hz, 1H), 2.47 – 2.01 (m, 9H), 1.91 – 1.70 (m, 5H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.65 – 1.58 (m, 3H), 1.38 (dt, *J* = 13.6, 2.8 Hz, 1H), 1.05 (s, 9H), 0.92 (s, 9H), 0.89 (s, 18H), 0.88 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 – 0.06 (m, 9H), 0.05 – 0.04 (m, 12H), 0.04 – 0.02 (m, 9H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 146.6, 144.2, 143.8, 135.7, 135.5, 134.2, 129.7, 128.8, 128.6, 127.7, 124.6, 114.3, 113.7, 112.3, 95.0, 76.5, 73.8, 73.3, 71.1, 70.9, 70.4, 68.5, 67.3, 66.9, 65.6, 65.5, 64.6, 64.2, 44.6, 42.6, 42.0, 41.3, 39.0, 37.7, 36.3, 35.0, 33.9, 27.0, 26.6, 26.1, 26.1, 26.0, 22.8, 19.4, 18.8, 18.6, 18.4, 18.2, 18.1, −3.3, −3.4, −3.7, −3.9, −4.2, −4.3, −4.4, −4.4, −4.6, −4.8, −4.8; **IR** (film, cm$^{-1}$): 2953, 2928, 2887, 2856, 1472, 1463, 1428, 1380, 1361, 1253, 1205, 1086, 1059, 1006, 967, 939, 896, 835, 811, 775, 739, 702, 686, 669, 613, 506; **HRMS** (ESI) for $C_{88}H_{158}O_{12}Si_7Na$ [M+Na]$^+$: calcd. 1626.0031; found 1626.0031.

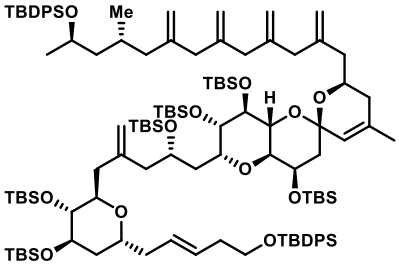
**Compound 230.**




Pyridine (4.6 μL, 57 μmol), acetic anhydride (3.2 μL, 34 μmol) and DMAP (1.4 mg, 11 μmol) were added sequentially to a solution of alcohol **229** (18 mg, 11 μmol) in $CH_2Cl_2$ (0.1 mL) at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature for 18 h. Saturated aq. $NH_4Cl$ (2 mL) and *tert*-butyl methyl ether (2 mL) were added and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 2 mL). The combined organic fractions were washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 30:1) to give the title compound as a colorless oil (19 mg, quant.). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +14.3 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.64 (m, 4H), 7.45 – 7.33 (m, 6H), 5.43 (td, *J* = 5.1, 3.4 Hz, 2H), 5.16 (s, 1H), 5.13 (d, *J* = 1.6 Hz, 1H), 5.10 (s, 1H), 4.99 (s, 1H), 4.86 (s, 1H), 4.83 (s, 1H), 4.79 (s, 1H), 4.49 (s, 2H), 4.14 (qd, *J* = 6.4, 5.7, 3.6 Hz, 1H), 4.08 (ddd, *J* = 12.4, 4.8, 2.0 Hz, 1H), 3.97 (q, *J* = 3.0 Hz, 1H), 3.95 – 3.87 (m, 1H), 3.86 – 3.75 (m, 4H), 3.65 (t, *J* = 7.0 Hz, 2H), 3.63 – 3.56 (m, 2H), 3.37 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.11 (d, *J* = 9.7 Hz, 1H), 2.84 (s, 2H), 2.71 (dd, *J* = 14.2, 9.3 Hz, 1H), 2.45 – 2.18 (m, 6H), 2.16 – 2.02 (m, 6H), 1.93 – 1.69 (m, 5H), 1.66 (s, 3H), 1.60 (dd, *J* = 14.2, 3.4 Hz, 2H), 1.41 – 1.35 (m, 1H), 1.05 (s, 9H), 0.91 (s, 9H), 0.89 (s, 18H), 0.88 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H), 0.06 – 0.04 (m, 15H), 0.03 – 0.02 (m, 9H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 170.8, 144.2, 142.7, 141.5, 135.7, 135.5, 134.2, 129.7, 128.7, 128.6, 127.7, 124.6, 115.0, 114.3, 114.1, 95.0, 76.5, 73.9, 73.2, 71.2, 70.9, 70.4, 68.5, 67.3, 66.9, 66.2, 65.4, 64.6, 64.2, 44.6, 42.6, 41.8, 39.0, 37.7, 36.3, 34.9, 33.9, 27.0, 26.6, 26.1, 26.1, 26.0, 22.8, 21.1, 19.4, 18.7, 18.5, 18.4, 18.2, 18.1, −3.3, −3.7, −3.9, −4.2, −4.2, −4.3, −4.4, −4.4, −4.5, −4.7, −4.8; **IR** (film, cm$^{-1}$): 2954, 2929, 2886, 2857, 1747, 1472, 1463, 1428, 1378, 1361, 1252, 1087, 1059, 1006, 968, 939, 896,

835, 812, 775, 739, 702, 672, 613, 506; **HRMS** (ESI) for $C_{90}H_{160}O_{13}Si_7Na$ $[M+Na]^+$: calcd. 1668.0136; found 1668.0142.

**Compound 220.**

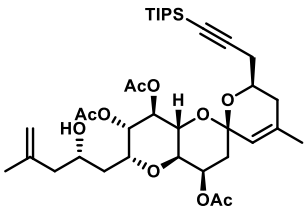



***Preparation of the Organozinc Compound Derived from Bromide* 238**: *tert*-Butyllithium (93 μL, 0.17 M in pentane, 16 μmol) was added dropwise to a solution of bromide **238** (4.0 mg, 7.6 μmol) in diethyl ether (0.1 mL) at –78 °C. The resulting solution was stirred at this temperature for 30 min before a solution of zinc bromide (0.5 M in THF, 15 μL, 7.6 μmol) was added dropwise at –78 °C. After stirring had been continued for 15 min at this temperature, the solution was allowed to warm to room temperature over 30 min.

***Negishi cross-coupling reaction***: $Pd(PPh_3)_4$ (1.5 mg, 1.3 μmol) and the solution of the organozinc reagent were added sequentially to a degassed solution of the allyl acetate **230** (10 mg, 6.3 μmol) in DMF (0.1 mL) at room temperature. Stirring was continued for 24 h at room temperature, saturated $NH_4Cl$ (3 mL) solution was added and the resulting mixture was extracted with *tert*-butyl methyl ether (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 80:1) to give the title compound as a colorless oil (4.5 mg, 36%). The analytical and spectral data matched the recorded data of the previously synthesized material.

### 6.3.4 Completion of the Synthesis Using a Revised Protecting Group Strategy

**Model Compound 253.**

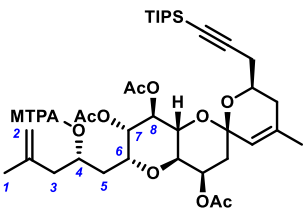



Boron tribromide (1.0 M in $CH_2Cl_2$, 31 μL, 31 μmol) was added at 0 °C to a solution of (*S*,*S*)-1,2-diphenyl-1,2-ethylenediamine bis(toluenesulfonamide)[202] (16 mg, 31 μmol) in $CH_2Cl_2$ (0.3 mL). The mixture was stirred for 10 min at 0 °C and for 1 h at ambient temperature before all volatile materials were removed in high vacuum.

Methallyltributylstannane (7.2 μL, 31 μmol) was added dropwise at 0 °C to a solution of the residue in $CH_2Cl_2$ (0.3 mL). After stirring for 17 h at ambient temperature, the mixture was cooled to −78 °C and a solution of aldehyde **252** (9.9 mg, 16 μmol) in $CH_2Cl_2$ (0.2 mL) was added dropwise over 5 min. The mixture was stirred for 2 h before the reaction was quenched with aq. pH 7.4 phosphate buffer (2 mL). Water (2 mL) was introduced and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (4 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash

chromatography (toluene/EtOAc, 3:1) to give the title compound as a colorless oil (8.7 mg, 81%, dr 7.5:1 by $^1$H NMR). Spectral data of the major diastereoisomer: **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.28 – 5.15 (m, 3H), 5.07 (q, *J* = 3.0 Hz, 1H), 4.90 (t, *J* = 1.8 Hz, 1H), 4.80 (dd, *J* = 2.1, 1.1 Hz, 1H), 4.49 (ddd, *J* = 11.8, 5.4, 2.8 Hz, 1H), 4.27 (dd, *J* = 10.6, 9.1 Hz, 1H), 3.89 (dtd, *J* = 10.4, 7.8, 5.1 Hz, 2H), 3.52 (dd, *J* = 10.2, 3.0 Hz, 1H), 2.63 (dd, *J* = 16.7, 5.1 Hz, 1H), 2.44 (dd, *J* = 16.6, 8.0 Hz, 1H), 2.26 (dd, *J* = 15.3, 3.0 Hz, 1H), 2.21 (d, *J* = 6.2 Hz, 2H), 2.08 (s, 3H), 2.04 (s, 6H), 1.99 – 1.92 (m, 2H), 1.86 (d, *J* = 3.6 Hz, 1H), 1.79 – 1.73 (m, 4H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.67 – 1.59 (m, 2H), 1.10 – 1.00 (m, 21H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 171.0, 170.5, 169.9, 142.3, 137.5, 122.7, 114.0, 104.4, 95.5, 82.6, 71.0, 70.8, 70.6, 68.3, 67.8, 66.8, 66.7, 64.7, 46.5, 38.0, 34.4, 31.9, 28.0, 27.0, 27.0, 22.9, 22.7, 21.5, 21.0, 21.0, 18.8, 17.7, 13.7, 11.4.

**Preparation of the (*S*)- and (*R*)-MTPA esters (268) of alcohol 253.**




(*R*)-(−)-MTPA-Cl (3.1 mg, 12 μmol) and DMAP (0.15 mg, 1.2 μmol) were added to a stirred solution of **253** (4.3 mg, 6.2 μmol) and pyridine (1.6 μL, 19 μmol) in $CH_2Cl_2$ (0.2 mL) at room temperature. Stirring was continued for 16 h before the reaction was quenched with $H_2O$ (1 mL) and the mixture was diluted with EtOAc (2 mL). The aqueous phase was extracted with EtOAc (2 × 2 mL). The combined organic fractions were dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 4:1) to give (*S*)-**268** (4.8 mg, 85%) as a pale yellow oil. **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 7.48 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.43 – 7.36 (m, 3H), 5.26 (dddd, *J* = 9.1, 7.6, 5.9, 3.0 Hz, 1H), 5.24 – 5.20 (m, 1H), 5.17 (dd, *J* = 10.0, 9.3 Hz, 1H), 5.13 (dd, *J* = 9.9, 5.9 Hz, 1H), 5.03 (q, *J* = 3.0 Hz, 1H), 4.82 (q, *J* = 1.6 Hz, 1H), 4.74 (dq, *J* = 2.0, 1.0 Hz, 1H), 4.24 (dd, *J* = 10.2, 9.3 Hz, 1H), 4.18 (ddd, *J* = 11.8, 5.8, 2.5 Hz, 1H), 3.87 (ddt, *J* = 10.0, 7.9, 5.0 Hz, 1H), 3.49 (d, *J* = 1.1 Hz, 3H), 3.46 (dd, *J* = 10.2, 3.1 Hz, 1H), 2.62 (dd, *J* = 16.6, 5.3 Hz, 1H), 2.50 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.44 (dd, *J* = 16.6, 7.8 Hz, 1H), 2.28 (dd, *J* = 15.3, 3.0 Hz, 1H), 2.22 (ddd, *J* = 13.7, 7.7, 0.9 Hz, 1H), 2.13 (ddd, *J* = 15.1, 11.7, 2.9 Hz, 1H), 2.08 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 2.00 – 1.94 (m, 2H), 1.82 (ddd, *J* = 15.6, 9.2, 2.5 Hz, 1H), 1.74 (dt, *J* = 1.9, 1.0 Hz, 3H), 1.71 (t, *J* = 2.4 Hz, 1H), 1.71 – 1.69 (m, 3H), 1.10 – 0.99 (m, 21H).

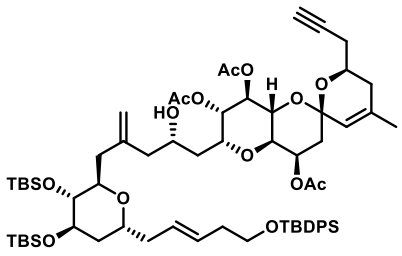
(*R*)-**268** was prepared analogously using (*S*)-(+)-MTPA-Cl. **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 7.50 (dt, *J* = 6.8, 1.6 Hz, 2H), 7.43 – 7.34 (m, 3H), 5.32 (dddd, *J* = 9.1, 7.6, 6.1, 2.8 Hz, 1H), 5.22 – 5.18 (m, 1H), 5.12 (dd, *J* = 9.9, 9.2 Hz, 1H), 5.08 (dd, *J* = 9.9, 5.8 Hz, 1H), 5.03 (q, *J* = 3.0 Hz, 1H), 4.88 (p, *J* = 1.5 Hz, 1H), 4.80 (dq, *J* = 2.0, 1.1 Hz, 1H), 4.22 (dd, *J* = 10.2, 9.3 Hz, 1H), 3.98 (ddd, *J* = 11.8, 5.8, 2.4 Hz, 1H), 3.87 (ddt, *J* = 9.8, 8.1, 4.8 Hz, 1H), 3.52 (q, *J* = 1.1 Hz, 3H), 3.41 (dd, *J* = 10.2, 3.0 Hz, 1H), 2.63 (dd, *J* = 16.6, 5.1 Hz, 1H), 2.55 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.44 (dd, *J* = 16.6, 8.1 Hz, 1H), 2.32 (ddd, *J* = 13.8, 7.7, 1.1 Hz, 1H), 2.26 (dd, *J* = 15.3, 3.0 Hz, 1H), 2.09 (s, 3H), 2.08 (d, *J* = 1.4

Hz, 1H), 2.02 (s, 3H), 1.98 (s, 3H), 1.97 – 1.95 (m, 2H), 1.83 – 1.79 (m, 1H), 1.78 (d, *J* = 0.7 Hz, 3H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.69 – 1.66 (m, 1H), 1.10 – 0.99 (m, 21H).

**Table 6.8.** Analysis of the Mosher esters **268** according to Hoye and co-workers;[48] arbitrary numbering scheme as shown in the insert.

| Atom number | (*S*)-268 δ [ppm] | (*R*)-268 δ [ppm] | Δδ [ppm] |
|---|---|---|---|
| 1 | 1.74 | 1.78 | −0.04 |
| 2a | 4.82 | 4.88 | −0.06 |
| 2b | 4.74 | 4.80 | −0.06 |
| 3a | 2.5 | 2.55 | −0.05 |
| 3b | 2.22 | 2.32 | −0.10 |
| 4 | 5.26 | 5.32 | −0.06 |
| 5a | 2.13 | 2.08 | +0.05 |
| 5b | 1.82 | 1.80 | +0.02 |
| 6 | 4.18 | 3.98 | +0.20 |
| 7 | 5.13 | 5.08 | +0.05 |
| 8 | 5.17 | 5.12 | +0.05 |

**Compound 254.**

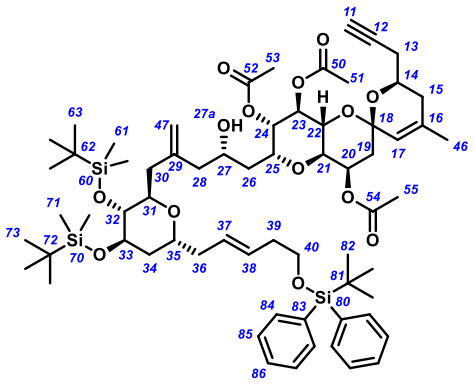



Boron tribromide (1.0 M in $CH_2Cl_2$, 1.26 mL, 1.26 mmol) was added to a solution of (*S*,*S*)-1,2-diphenyl-1,2-ethylene-diamine bis(toluenesulfonamide)[202] ((*S*,*S*)-**171**, 654 mg, 1.26 mmol) in $CH_2Cl_2$ (12 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C and for 1 h at ambient temperature before all volatile materials were removed in high vacuum.

A solution of allyl stannane **158** (1.32 g, 1.30 mmol) in $CH_2Cl_2$ (3.0 mL) was added dropwise at 0 °C to a solution of the residue in $CH_2Cl_2$ (10 mL). After stirring for 17 h at ambient temperature, the mixture was cooled to −78 °C and a solution of aldehyde **251** (415 mg, 0.867 mmol) in $CH_2Cl_2$ (2.0 mL) was added dropwise over 5 min. The mixture was stirred for 3 h before the reaction was quenched with aq. pH 7.4 phosphate buffer (15 mL). Water (15 mL) was introduced and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was suspended in $Et_2O$ (5 mL) and the colorless solid was filtered off to recover the chiral diamine ligand. The residue was purified by flash chromatography (fine silica, hexanes/EtOAc, 3:1) to give the title compound as a colorless oil (877 mg, 84%). A second fraction contained the undesired diastereoisomer **255** (163 mg, 16%). Analytical and spectral data of the major diastereoisomer: $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = +19.6 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ

7.70 – 7.63 (m, 4H), 7.44 – 7.34 (m, 6H), 5.52 – 5.34 (m, 2H), 5.26 – 5.19 (m, 2H), 5.15 (dd, *J* = 9.8, 5.8 Hz, 1H), 5.05 (q, *J* = 3.0 Hz, 1H), 4.96 (d, *J* = 1.8 Hz, 1H), 4.92 – 4.87 (m, 1H), 4.49 (ddd, *J* = 11.7, 5.7, 2.6 Hz, 1H), 4.38 (t, *J* = 9.8 Hz, 1H), 3.95 – 3.74 (m, 5H), 3.65 (t, *J* = 6.9 Hz, 2H), 3.53 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.37 (dd, *J* = 3.8, 2.3 Hz, 1H), 2.67 (dd, *J* = 14.3, 9.1 Hz, 1H), 2.42 (tddt, *J* = 16.8, 12.5, 8.6, 4.3 Hz, 3H), 2.32 – 2.14 (m, 7H), 2.10 (s, 4H), 2.06 (s, 3H), 2.03 (s, 3H), 2.00 – 1.83 (m, 3H), 1.77 (ddd, *J* = 12.7, 8.5, 2.9 Hz, 2H), 1.69 (s, 3H), 1.67 – 1.56 (m, 2H), 1.46 – 1.36 (m, 1H), 1.04 (s, 9H), 0.94 – 0.85 (m, 18H), 0.05 (s, 3H), 0.04 (s, 6H), 0.02 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 171.0, 170.4, 170.0, 144.0, 137.4, 135.7, 134.2, 129.7, 129.2, 128.2, 127.8, 127.7, 122.9, 115.4, 95.6, 80.8, 77.1, 71.2, 70.9, 70.8, 70.7, 70.3, 70.1, 68.4, 67.9, 66.8, 66.7, 65.3, 64.1, 44.8, 38.7, 37.9, 37.6, 36.2, 34.4, 33.9, 32.1, 28.0, 27.0, 26.0, 25.2, 22.8, 21.5, 21.1, 21.0, 19.3, 18.2, 18.1, 17.7, 13.7, −4.3, −4.4, −4.4, −4.7; **IR** (film, $cm^{-1}$): 2954, 2929, 2895, 2857, 1753, 1471, 1462, 1428, 1380, 1366, 1239, 1160, 1094, 1069, 1036, 1006, 967, 836, 776, 742, 704, 613, 505, 489; **HRMS** (ESI) for $C_{66}H_{100}O_{14}Si_3Na$ $[M+Na]^+$: calcd. 1223.6313; found 1223.6305.

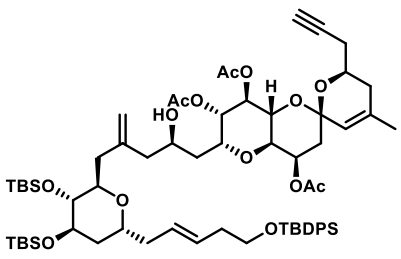
**Table 6.9.** Detailed NMR data of **254**; numbering scheme as shown in the insert.



| atom number | **$^1$H NMR** ($CDCl_3$, 600 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 151 MHz)/ **$^{29}$Si NMR** ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 11 | 2.05 | 2.6 | 13a, 13b | - | 69.9 | 13a, 13b |
| 12 | - | - | - | - | 80.6 | 11, 13a, 13b, 14 |
| 13a | 2.46 | 16.6, 6.8, 2.6 | 11, 13b, 14 | - | 25.1 | 11, 14, 15a |
| 13b | 2.39 | 16.6, 5.8, 2.7 | 11, 13a, 14 | - | | |
| 14 | 3.91 | 10.5, 6.4, 3.5 | 13a, 13b, 15a, 15b | 22 | 66.5 | 13a, 13b, 15a, 15b |
| 15a | 1.95 | - | 14, 15b, 17 | 46 | 34.2 | 13a, 13b, 17, 46 |
| 15b | 1.87 | 17.0, 3.7 | 14, 15a, 17 | 46 | | |
| 16 | - | - | - | - | 137.2 | 15a, 15b, 46 |
| 17 | 5.22 | - | 15a, 15b, 46 | 19a, 19b, 46 | 122.7 | 15a, 15b, 19b, 46 |
| 18 | - | - | - | - | 95.4 | 14, 17, 19a, 19b, 20, 22 |

| atom number | **$^{1}$H NMR** ($CDCl_3$, 600 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 151 MHz)/ **$^{29}$Si NMR** ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 19a | 2.29 | 15.3, 3.0 | 19b, 20 | 17, 20 | 37.7 | 17 |
| 19b | 1.76 | 15.3, 3.1 | 19a, 20 | 17, 20, 21, 23 | | |
| 22 | 4.38 | 9.9 | 21, 23 | 14, 24 | 66.7 | 20, 21, 23, 24 |
| 23 | 5.22 | 9.7 | 22, 24 | 19b, 21, 26b | 70.6 | 21, 22, 24, 25 |
| 24 | 5.15 | 9.8, 5.9 | 23, 25 | 22, 25 | 70.6 | 23, 25, 26a |
| 25 | 4.50 | 11.7, 5.9, 2.6 | 24, 26a, 26b | 24, 26b, 27, 27a | 70.7 | 23, 24, 26a |
| 26a | 1.94 | 14.9, 11.4, 7.4 | 25, 26b, 27 | 21 | 32.0 | 24, 25, 28a, 28b |
| 26b | 1.61 | - | 25, 26a, 27 | 23, 25, 27 | | |
| 27 | 3.87 | - | 26a, 26b, 28a, 28b | 25, 26b, 28a, 28b, 47'' | 65.2 | 25, 26b, 28a, 28b |
| 27a | 2.26 | - | - | 25, 47'' | - | - |
| 28a | 2.27 | - | 27, 28b, 47'' | 27, 31, 47'' | 44.6 | 26b, 30a, 30b, 47', 47'' |
| 28b | 2.16 | 13.9, 9.1 | 27, 28a, 47'' | 27, 47'' | | |
| 29 | - | - | - | - | 143.8 | 28a, 28b, 30a, 30b, 31, 47', 47'' |
| 30a | 2.67 | 14.3, 9.2 | 30b, 31, 47' | 31, 35, 47' | 37.5 | 28a, 28b, 31, 32, 47', 47'' |
| 30b | 2.41 | 14.7, 4.4 | 30a, 31, 47', 47'' | 31, 32, 47' | | |
| 31 | 3.78 | 10.9, 4.7, 2.2 | 30a, 30b, 32 | 28a, 30a, 30b, 32, 47'' | 76.9 | 30a, 30b, 33, 35 |
| 32 | 3.37 | 3.5, 2.3 | 31, 33, 34b | 30b, 31, 33, 47', 61, 61' | 71.1 | 30a, 30b, 31, 33, 34b |
| 33 | 3.80 | 3.9 | 32, 34a, 34b | 32, 34a, 34b | 70.1 | 32, 34a, 34b |
| 34a | 1.77 | - | 33, 34b, 35 | 33 | 33.7 | 32, 36a, 36b |
| 34b | 1.40 | 13.5 | 32, 33, 34a, 35 | 33 | | |
| 35 | 3.83 | - | 34a, 34b, 36a, 36b | 30a, 36a, 36b, 37 | 65.2 | 31, 33, 34a, 36a, 36b, 37 |
| 36a | 2.22 | - | 35, 36b, 37 | 35 | 38.5 | 35, 37, 38 |
| 36b | 2.08 | - | 35, 36a, 37 | 35 | | |
| 37 | 5.40 | 15.4, 7.2, 6.2, 1.0 | 36a, 36b, 38 | 35 | 128.0 | 35, 36a, 36b, 38, 39 |
| 38 | 5.46 | 15.1, 6.5 | 37, 39 | 40 | 129.1 | 36a, 36b, 37, 39, 40 |
| 39 | 2.26 | - | 38, 40 | - | 36.1 | 37, 38, 40 |
| 40 | 3.65 | - | 39 | 38 | 64.0 | 38, 39 |
| 46 | 1.70 | - | 17 | 15a, 15b, 17 | 22.7 | 15b |
| 47' | 4.96 | 1.8 | 30a, 30b, 47'' | 30a, 30b, 31, 32 | 115.3 | 28a, 28b, 30a, 30b |
| 47'' | 4.89 | 2.0 | 28a, 28b, 30b, 47' | 27, 27a, 28a, 28b | | |

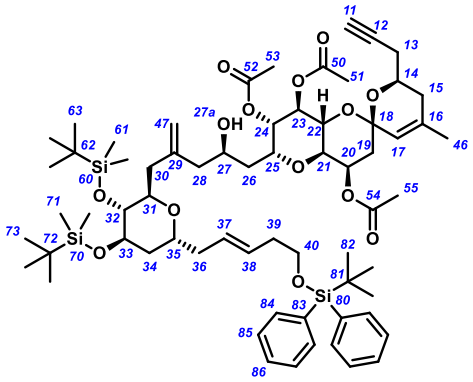
| atom number | **$^1$H NMR** ($CDCl_3$, 600 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 151 MHz)/ **$^{29}$Si NMR** ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 50 | - | - | - | - | 170.3 | 23, 51 |
| 51 | 2.06 | - | - | - | 20.9 | - |
| 52 | - | - | - | - | 169.8 | 24, 53 |
| 53 | 2.03 | - | - | - | 20.8 | - |
| 54 | - | - | - | - | 170.9 | 20, 55 |
| 55 | 2.10 | - | - | - | 21.3 | - |
| 60 | - | - | - | - | 18.4 | 32, 61, 61′ |
| 61 | 0.04 | - | - | 32 | −4.4 | 61′ |
| 61′ | 0.04 | - | - | 32 | −4.6 | 61 |
| 62 | - | - | - | - | 18.0 | 61, 61′, 63 |
| 63 | 0.89 | - | - | - | 25.9 | 63 |
| 70 | - | - | - | - | 18.5 | 33, 71, 71′ |
| 71 | 0.05 | - | - | - | −4.5 | 71′ |
| 71′ | 0.02 | - | - | - | −4.9 | 71 |
| 72 | - | - | - | - | 18.0 | 71, 71′, 73 |
| 73 | 0.88 | - | - | - | 25.6 | 73 |
| 80 | - | - | - | - | −4.8 | 40, 82, 84 |
| 81 | - | - | - | - | 19.2 | 82 |
| 82 | 1.04 | - | - | - | 26.8 | 82 |
| 83 | - | - | - | - | 134.0 | 84, 85 |
| 83′ | - | - | - | - | 134.0 | 84′, 85′ |
| 84 | 7.66 | - | 85 | - | 135.5 | 84,86 |
| 84′ | 7.66 | - | 85′ | - | 135.5 | 84′, 86′ |
| 85 | 7.37 | - | 84, 86 | - | 127.6 | 84, 85 |
| 85′ | 7.37 | - | 84′, 86′ | - | 127.6 | 84′, 85′ |
| 86 | 7.40 | - | 85 | - | 129.5 | 84 |
| 86' | 7.40 | - | 85′ | - | 129.5 | 84′ |




Analytical and spectral data of the minor diastereoisomer **255**: $[\alpha]_D^{20}$ = +12.1 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.69 – 7.63 (m, 4H), 7.45 – 7.33 (m, 6H), 5.52 – 5.33 (m, 2H), 5.26 (t, *J* = 9.7 Hz, 1H), 5.23 – 5.20 (m, 1H), 5.13 – 5.01 (m, 2H), 4.92 (s, 1H), 4.89 (s, 1H), 4.46 – 4.27 (m, 2H), 3.95 – 3.86 (m, 2H), 3.80 (dt, *J* = 7.1, 3.1 Hz, 3H), 3.75 (dd, *J* = 10.3, 3.0 Hz, 1H), 3.65 (t, *J* = 6.9 Hz, 2H), 3.32 (dd, *J* = 3.9, 2.2 Hz, 1H), 2.87 – 2.77 (m, 2H), 2.42

(qdd, *J* = 16.6, 6.3, 2.7 Hz, 2H), 2.33 – 2.11 (m, 7H), 2.09 (s, 3H), 2.06 (s, 3H), 2.05 – 2.04 (m, 2H), 2.03 (s, 3H), 2.00 – 1.83 (m, 3H), 1.81 – 1.72 (m, 2H), 1.70 (s, 3H), 1.67 – 1.62 (m, 1H), 1.39 (dt, *J* = 14.0, 3.1 Hz, 1H), 1.04 (s, 9H), 0.92 – 0.85 (m, 18H), 0.07 – 0.03 (m, 9H), 0.02 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 171.0, 170.4, 170.0, 143.8, 137.3, 135.7, 134.2, 129.7, 129.0, 128.4, 127.7, 123.0, 115.3, 95.5, 80.9, 76.4, 73.4, 71.8, 71.2, 70.6, 70.3, 70.0, 68.7, 68.4, 67.7, 66.8, 66.7, 65.2, 64.1, 43.4, 38.6, 37.9, 36.9, 36.2, 34.4, 34.1, 32.1, 27.0, 26.1, 26.0, 26.0, 25.9, 25.3, 22.8, 21.5, 21.1, 20.9, 19.4, 18.2, 18.1, −4.4, −4.4, −4.6, −4.7; **IR** (film, $cm^{-1}$): 2953, 2929, 2894, 2857, 1751, 1472, 1428, 1380, 1366, 1238, 1094, 1068, 1036, 1006, 967, 836, 776, 741, 704, 506; **HRMS** (ESI) for $C_{66}H_{100}O_{14}Si_3Na$ $[M+Na]^+$: calcd. 1223.6313; found 1223.6314.

**Table 6.10.** Detailed NMR data of **255**; numbering scheme as shown in the insert.

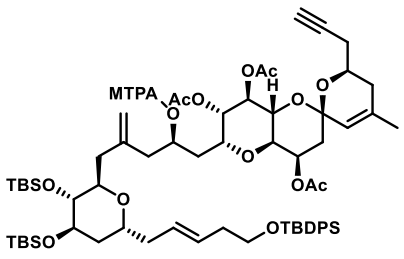


| atom number | **$^1$H NMR** ($CDCl_3$, 600 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 151 MHz)/ **$^{29}$Si NMR** ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 11 | 2.05 | 2.6 | 13a, 13b | - | 69.9 | 13a, 13b |
| 12 | - | - | - | - | 80.7 | 11, 13a, 13b, 14 |
| 13a | 2.45 | 16.7, 6.9, 2.6 | 11, 13b, 14 | - | 25.1 | 11, 14, 15a |
| 13b | 2.39 | 16.6, 5.8, 2.6 | 11, 13a, 14 | - | | |
| 14 | 3.90 | - | 13a, 13b, 15a, 15b | - | 66.5 | 13a, 13b, 15a, 15b |
| 15a | 1.95 | - | 14, 15b, 17 | 46 | 34.2 | 13a, 13b, 17, 46 |
| 15b | 1.87 | 17.2, 3.6 | 14, 15a, 17 | 46 | | |
| 16 | - | - | - | - | 137.1 | 15a, 15b, 46 |
| 17 | 5.22 | - | 15a, 15b, 46 | 19a, 19b | 122.8 | 15a, 15b, 19b, 46 |
| 18 | - | - | - | - | 95.4 | 14, 17, 19a, 19b, 20, 22 |
| 19a | 2.26 | 15.3, 3.0 | 20 | 17, 20 | 37.7 | 17 |
| 19b | 1.77 | 15.4, 3.2 | 20 | 17, 20, 21, 23 | | |
| 20 | 5.04 | 3.0 | 19a, 19b, 21 | 19a, 19b, 21 | 67.6 | 19a, 21, 22 |
| 21 | 3.75 | 10.3, 3.0 | 20, 22 | 19b, 20, 23, 26a | 68.2 | 19a, 20, 23, 25 |

| atom number | $^{1}$H NMR ($CDCl_3$, 600 MHz) | | | | $^{13}$C NMR ($CDCl_3$, 151 MHz)/ $^{29}$Si NMR ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | δ [ppm] | *J* [Hz] | COSY | NOESY | δ [ppm] | HMBC |
| 22 | 4.36 | 10.0 | 21, 23 | - | 66.6 | 20, 21, 23, 24 |
| 23 | 5.26 | 9.7 | 22, 24 | 19b, 21, 26b | 70.4 | 21, 22, 24, 25 |
| 24 | 5.07 | 9.8, 5.9 | 23, 25 | 25 | 71.0 | 23, 25, 26a |
| 25 | 4.35 | - | 24, 26a, 26b | 24, 26b, 27, 28a | 73.2 | 23, 24, 26a, 27, 31 |
| 26a | 2.02 | 14.9, 11.4, 7.4 | 25, 26b, 27 | 21 | 31.9 | 24, 25, 27a |
| 26b | 1.67 | - | 25, 26a, 27 | 23, 25, 27 | | |
| 27 | 3.90 | - | 26a, 26b, 28a, 28b | 25, 26b, 27a, 47'' | 68.5 | 25, 26a, 26b, 28a, 28b |
| 27a | 2.84 | - | - | 27 | - | - |
| 28a | 2.28 | - | 27, 47'' | 25, 31, 47'' | 43.2 | 30a, 47', 47'' |
| 28b | 2.13 | 14.2, 9.3 | 27 | 47'' | | |
| 29 | - | - | - | - | 143.6 | 28a, 28b, 30a, 30b, 31, 47', 47'' |
| 30a | 2.82 | 14.6, 10.6 | 30b, 31 | 31, 32, 35, 47' | | 31, 32, 47', 47'' |
| 30b | 2.22 | 14.7, 4.4 | 30a, 31, 47' | 31, 47' | | |
| 31 | 3.82 | 10.9, 4.7, 2.2 | 30a, 30b, 32 | 28a, 30a, 30b, 32, 47' | 76.2 | 30a, 30b, 33, 35 |
| 32 | 3.33 | 3.9, 2.3 | 31, 33 | 30a, 31, 33, 47', 61, 61' | 71.6 | 30a, 30b, 31, 33, 34b |
| 33 | 3.79 | 3.9 | 32 | 32, 34a, 34b | 70.1 | 31, 32, 34b, 35 |
| 34a | 1.76 | - | 34b | 33 | 33.9 | 32, 36a, 36b |
| 34b | 1.39 | - | 34a | 33 | | |
| 35 | 3.81 | - | - | 30a, 36a, 36b, 37 | 65.0 | 31, 33, 34a, 36a, 36b, 37 |
| 36a | 2.19 | - | 36b, 37 | 35 | 38.4 | 35, 37, 38 |
| 36b | 2.06 | - | 36a, 37 | 35 | | |
| 37 | 5.39 | - | 36a, 36b, 38 | 35 | 128.2 | 35, 36a, 36b, 38, 39 |
| 38 | 5.44 | - | 37, 39 | 40 | 128.9 | 36a, 36b, 37, 39, 40 |
| 39 | 2.26 | - | 38, 40 | - | 36.1 | 37, 38, 40 |
| 40 | 3.65 | - | 39 | 38 | 64.0 | 38, 39 |
| 46 | 1.70 | - | 17 | 15a, 15b | 22.7 | 17 |
| 47' | 4.92 | - | 30b | 30a, 30b, 31, 32 | 115.1 | 28a, 28b, 30a, 30b |
| 47'' | 4.89 | - | 28a | 27, 28a, 28b | | |
| 50 | - | - | - | - | 170.2 | 23, 51 |
| 51 | 2.06 | - | - | - | 20.9 | - |
| 52 | - | - | - | - | 169.8 | 24, 53 |

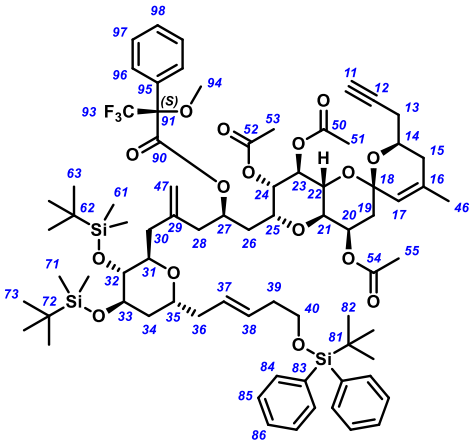
| atom number | $^1$H NMR ($CDCl_3$, 600 MHz) | | | | $^{13}$C NMR ($CDCl_3$, 151 MHz)/ $^{29}$Si NMR ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | δ [ppm] | *J* [Hz] | COSY | NOESY | δ [ppm] | HMBC |
| 53 | 2.03 | - | - | - | 20.8 | - |
| 54 | - | - | - | - | 170.8 | 20, 55 |
| 55 | 2.09 | - | - | - | 21.3 | - |
| 60 | - | - | - | - | 18.3 | 32, 61, 61', 63 |
| 61 | 0.04 | - | - | - | −4.5 | 61' |
| 61' | 0.04 | - | - | - | −4.6 | 61 |
| 62 | - | - | - | - | 18.1 | 61, 61', 63 |
| 63 | 0.88 | - | - | - | 25.9 | 63 |
| 70 | - | - | - | - | 18.5 | 33, 71, 71', 73 |
| 71 | 0.05 | - | - | - | −4.6 | 71' |
| 71' | 0.02 | - | - | - | −4.9 | 71 |
| 72 | - | - | - | - | 25.8 | 73 |
| 73 | 0.88 | - | - | - | 25.8 | 73 |
| 80 | - | - | - | - | −4.8 | 40, 82, 84, 84', 85, 85' |
| 81 | - | - | - | - | 19.2 | 82 |
| 82 | 1.04 | - | - | - | 26.8 | 82 |
| 83 | - | - | - | - | 134.0 | 84, 84', 85, 85' |
| 83' | - | - | - | - | 134.0 | - |
| 84 | 7.66 | - | 85 | - | 135.5 | 84, 86 |
| 84' | 7.66 | - | 85' | - | 135.5 | 84', 86' |
| 85 | - | - | - | - | 127.6 | 85 |
| 85' | - | - | - | - | 127.6 | 85' |

**Preparation of the (*S*)- and (*R*)-MTPA esters (269) of alcohol 255.**




(*R*)-(−)-MTPA-Cl (4.2 mg, 17 μmol) and DMAP (0.20 mg, 1.7 μmol) were added to a stirred solution of **255** (10 mg, 8.3 μmol) and pyridine (2.1 μL, 26 μmol) in $CH_2Cl_2$ (0.2 mL) at room temperature. Stirring was continued for 16 h before the reaction was quenched with $H_2O$ (1 mL) and the mixture was diluted with EtOAc (2 mL). The aqueous phase was extracted with EtOAc (2 × 2 mL). The combined organic fractions were dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 4:1) to give (*S*)-**269** (9.3 mg, 79%) as a pale yellow oil. For NMR data, see Table 6.11.

**Table 6.11.** NMR data of (*S*)-**269**; numbering scheme as shown in the insert.



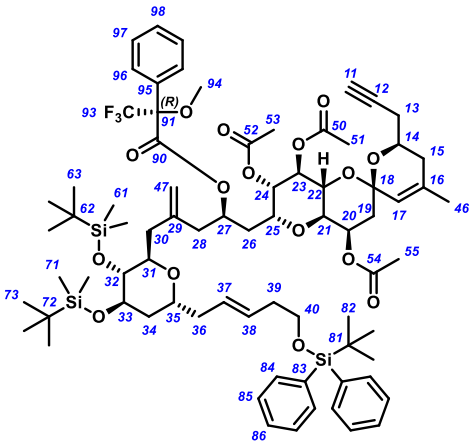
| atom number | $^{1}$**H NMR** ($CDCl_3$, 600 MHz) | | | | $^{13}$**C NMR** ($CDCl_3$, 151 MHz)/ $^{29}$**Si NMR** ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 11 | 2.05 | 2.6 | 13a, 13b | 22 | 69.9 | 13a, 13b |
| 12 | - | - | - | - | 80.7 | 11, 13a, 13b, 14 |
| 13a | 2.45 | 16.7, 6.8, 2.8 | 11, 13b, 14 | - | 25.1 | 11, 14, 15a |
| 13b | 2.39 | 16.7, 5.9, 2.7 | 11, 13a, 14 | - | | |
| 14 | 3.91 | 10.8, 6.9, 5.9, 3.6 | 13a, 13b, 15a, 15b | - | 66.5 | 13a, 13b, 15a |
| 15a | 1.95 | - | 14, 15b, 17 | - | 34.2 | 13a, 13b, 17, 46 |
| 15b | 1.88 | 17.5, 3.6 | 14, 15a, 17 | - | | |
| 16 | - | - | - | - | 137.2 | 15a, 15b, 46 |
| 17 | 5.25 | - | 15a, 15b, 46 | - | 122.8 | 15b, 46 |
| 18 | - | - | - | - | 95.5 | 14, 17, 19a, 19b, 20, 22 |
| 19a | 2.30 | 15.3, 3.1 | 19b, 20 | - | 37.7 | 17 |
| 19b | 1.78 | 15.3, 3.1 | 19a, 20 | - | | |
| 20 | 5.10 | 3.1 | 19a, 19b, 21 | 19b, 21 | 67.9 | 19a, 21, 22 |
| 21 | 3.72 | 10.3, 3.0 | 20, 22 | 19b, 20, 23, 26a | 68.4 | 19a, 20, 22, 23, 25 |
| 22 | 4.36 | 10.0 | 21, 23 | 11, 24, 55 | 66.6 | 21, 23, 24 |
| 23 | 5.19 | 9.6 | 22, 24 | 21 | 70.4 | 22, 24, 25, 51 |
| 24 | 5.09 | 9.7, 5.9 | 23, 25 | 22 | 70.6 | 23, 25, 53 |
| 25 | 4.16 | 11.1, 5.9, 3.5 | 24, 26a, 26b | - | 70.8 | 24, 26a, 27 |
| 26a | 2.17 | - | 25, 26b, 27 | 21 | 29.4 | 24, 27, 28 |
| 26b | 1.83 | - | 25, 26a, 27 | - | | |
| 27 | 5.34 | - | 26a, 26b, 28 | 47'' | 72.7 | 25, 26a, 28 |
| 28 | 2.41 | - | 27, 47'' | 31, 47'' | 39.0 | 26a, 27, 30a, 30b, 47', 47'' |

| atom number | **$^{1}$H NMR** ($CDCl_3$, 600 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 151 MHz)/ **$^{29}$Si NMR** ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 29 | - | - | - | - | 142.0 | 27, 28, 30a, 30b, 31, 47', 47'' |
| 30a | 2.76 | 14.6, 9.9 | 30b, 31, 47' | 47' | 36.7 | 28, 31, 47', 47'' |
| 30b | 2.28 | - | 30a, 31, 47' | 32 | | |
| 31 | 3.74 | - | 30a, 30b, 32 | 28, 32, 47' | 76.4 | 30a, 30b, 33 |
| 32 | 3.33 | 3.9, 2.0 | 31, 33 | 30b, 31, 47' | 71.2 | 30a, 31, 34b |
| 33 | 3.79 | - | 32, 34a, 34b | 34a, 34b | 70.1 | 31, 32, 34b |
| 34a | 1.75 | 13.4, 10.4, 2.9 | 33, 34b, 35 | 33 | 33.7 | 34a, 34b |
| 34b | 1.38 | 14.4 | 33, 34a, 35 | 33 | | |
| 35 | 3.79 | - | 34a, 34b, 36a, 36b | - | 64.7 | 31, 34a, 36a, 36b, 37 |
| 36a | 2.17 | - | 35, 36b, 37 | - | 38.6 | 37, 38 |
| 36b | 2.05 | - | 35, 36a, 37 | - | | |
| 37 | 5.39 | - | 36a, 36b, 38 | - | 128.3 | 35, 36a, 36b, 39 |
| 38 | 5.43 | - | 37, 39 | - | 128.7 | 36a, 36b, 39, 40 |
| 39 | 2.25 | - | 38, 40 | - | 36.1 | 37, 38, 40 |
| 40 | 3.64 | 7.0 | 39 | - | 64.0 | 38, 39 |
| 46 | 1.70 | - | 17 | - | 22.7 | 15b, 17 |
| 47' | 4.89 | - | 30a, 30b | 30a, 31, 32 | 115.7 | 28, 30a, 30b |
| 47'' | 4.83 | - | 28 | 27, 28 | | |
| 50 | - | - | - | - | 170.2 | 23, 51 |
| 51 | 2.06 | - | - | - | 20.9 | - |
| 52 | - | - | - | - | 169.7 | 24, 53 |
| 53 | 2.01 | - | - | - | 20.7 | - |
| 54 | - | - | - | - | 170.7 | 55 |
| 55 | 2.08 | - | - | 22 | 21.3 | - |
| 61 | 0.01, 0.02, 0.03, 0.04 | - | - | - | −4.92, −4.68, −4.66, −4.61 | - |
| 61' | 0.01, 0.02, 0.03, 0.04 | - | - | - | −4.92, −4.68, −4.66, −4.61 | - |
| 62 | - | - | - | - | 17.94, 17.99 | - |
| 63 | 0.88, 0.88 | - | - | - | 25.83, 25.85 | - |
| 71 | 0.01, 0.02, 0.03, 0.04 | - | - | - | −4.92, −4.68, −4.66, −4.61 | - |
| 71' | 0.01, 0.02, 0.03, 0.04 | - | - | - | −4.92, −4.68, −4.66, −4.61 | - |
| 72 | - | - | - | - | 17.94, 17.99 | - |

| atom number | $^{1}$H NMR ($CDCl_3$, 600 MHz) | | | | $^{13}$C NMR ($CDCl_3$, 151 MHz)/ $^{29}$Si NMR ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | δ [ppm] | *J* [Hz] | COSY | NOESY | δ [ppm] | HMBC |
| 73 | 0.88, 0.88 | - | - | - | 25.83, 25.85 | - |
| 81 | - | - | - | - | 19.2 | 82 |
| 82 | 1.04 | - | - | - | 26.8 | 82 |
| 83 | - | - | - | - | 134.02, 134.03 | 84, 85 |
| 83' | - | - | - | - | 134.02, 134.03 | 84', 85' |
| 84 | 7.66 | - | 85 | - | 135.6 | 84, 86 |
| 84' | 7.66 | - | 85' | - | 135.6 | 84', 86' |
| 85 | 7.37 | - | 84 | - | 127.6 | 85 |
| 85' | 7.37 | - | 84' | - | 127.6 | 85' |
| 86 | 7.41 | - | - | - | 129.5 | 84 |
| 86' | 7.41 | - | - | - | 129.5 | 84' |
| 90 | - | - | - | - | 166.2 | 27 |
| 91 | - | - | - | - | 84.9 | 94, 96 |
| 92 | - | - | - | - | 122.7 | - |
| 94 | 3.42 | 1.30 | - | - | 55.9 | - |
| 95 | | | Signals not found | | | |
| 96 | 7.41 | - | - | - | Signal not found | |
| 97 | | | Signals not found | | | |
| 98 | | | Signals not found | | | |

(*R*)-**269** was prepared analogously using (*S*)-(+)-MTPA-Cl. For NMR data, see Table 6.12.

**Table 6.12.** NMR data of (*R*)-**269**; numbering scheme as shown in the insert.

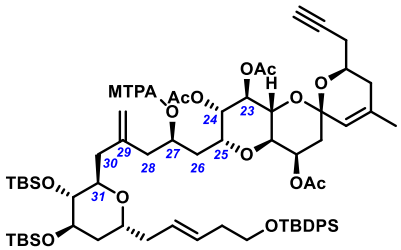


| atom number | **$^{1}$H NMR** ($CDCl_3$, 600 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 151 MHz)/ **$^{29}$Si NMR** ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 11 | 2.05 | 2.6 | 13a, 13b | 22 | 69.9 | 13a, 13b |
| 12 | - | - | - | - | 80.7 | 11, 13a, 13b, 14 |
| 13a | 2.45 | 16.5, 6.8, 2.6 | 11, 13b, 14 | - | 25.1 | 11, 14, 15a |
| 13b | 2.39 | 16.7, 5.8, 2.7 | 11, 13a, 14 | - | | |
| 14 | 3.89 | - | 13a, 13b, 15a, 15b | - | 66.5 | 13a, 13b, 15a |
| 15a | 1.94 | - | 14, 15b, 17 | - | 34.2 | 13a, 13b, 17, 46 |
| 15b | 1.87 | 17.2, 3.6 | 14, 15a, 17 | - | | |
| 16 | - | - | - | - | 137.2 | 15a, 15b, 46 |
| 17 | 5.24 | | 15a, 15b, 46 | - | 122.8 | 15b, 46 |
| 18 | - | - | - | - | 95.5 | 14, 17, 19a, 19b, 20, 22 |
| 19a | 2.28 | - | 19b, 20 | - | 37.6 | 17 |
| 19b | 1.76 | - | 19a, 20 | 20, 21 | | |
| 20 | 5.07 | 3.1 | 19a, 19b, 21 | 19b, 21 | 67.8 | 19a, 21, 22 |
| 21 | 3.68 | 10.3, 3.0 | 20, 22 | 19b, 20, 23, 26a | 68.4 | 19a, 20, 22, 23, 25 |
| 22 | 4.37 | 9.9 | 21, 23 | 11, 24, 55 | 66.6 | 21, 23, 24 |
| 23 | 5.20 | 9.7 | 22, 24 | 21 | 70.4 | 22, 24, 25, 51 |
| 24 | 5.12 | 9.8, 5.8 | 23, 25 | 22 | 70.6 | 23, 25, 53 |
| 25 | 4.22 | 10.7, 5.9, 3.6 | 24, 26a, 26b | - | 70.8 | 24, 26a, 27 |
| 26a | 2.20 | - | 25, 26b, 27 | 21 | 29.7 | 24, 27, 28 |
| 26b | 1.93 | - | 25, 26a, 27 | - | | |
| 27 | 5.30 | - | 26a, 26b, 28 | 47'' | 72.8 | 25, 26a, 28 |
| 28 | 2.35 | - | 27, 47'' | 31, 47'' | 38.9 | 26a, 27, 30a, 30b, 47', 47'' |
| 29 | - | - | - | - | 141.6 | 27, 28, 30a, 30b, 31, 47', 47'' |
| 30a | 2.66 | 14.6, 9.7 | 30b, 31, 47' | 47' | 36.7 | 28, 31, 47', 47'' |
| 30b | 2.25 | - | 30a, 31, 47' | 32 | | |
| 31 | 3.71 | - | 30a, 30b, 32 | 28, 32, 47' | 76.4 | 30a, 30b |
| 32 | 3.32 | 3.6, 1.7 | 31, 33 | 30b, 31, 47' | 71.0 | 30a, 31, 34b |
| 33 | 3.77 | - | 32, 34a, 34b | 34a, 34b | 70.1 | 31, 32, 34b |
| 34a | 1.73 | - | 33, 34b, 35 | 33 | 33.7 | 32, 36a, 36b |
| 34b | 1.36 | 14.4, 2.4, 4.4 | 33, 34a, 35 | 33 | | |
| 35 | 3.75 | - | 34a, 34b, 36a, 36b | - | 64.6 | 31, 34a, 36a, 36b, 37 |
| 36a | 2.16 | - | 35, 36b, 37 | - | 38.7 | 37, 38 |

| atom number | **$^{1}$H NMR** ($CDCl_3$, 600 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 151 MHz)/ **$^{29}$Si NMR** ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 36b | 2.04 | - | 35, 36a, 37 | - | | |
| 37 | 5.38 | - | 36a, 36b, 38 | - | 128.3 | 36a, 36b, 39 |
| 38 | 5.43 | - | 37, 39 | - | 128.7 | 36a, 36b, 39, 40 |
| 39 | 2.25 | - | 38, 40 | - | 36.1 | 37, 38, 40 |
| 40 | 3.64 | 7.0 | 39 | - | 64.0 | 38, 39 |
| 46 | 1.70 | - | 17 | - | 22.7 | 15b, 17 |
| 47' | 4.76 | - | 30a, 30b | 30a, 31, 32 | 115.6 | 28, 30a, 30b |
| 47'' | 4.71 | - | 28 | 27, 28 | | |
| 50 | - | - | - | - | 170.2 | 23, 51 |
| 51 | 2.06 | - | - | - | 20.9 | - |
| 52 | - | - | - | - | 169.7 | 24, 53 |
| 53 | 2.03 | - | - | - | 20.7 | - |
| 54 | - | - | - | - | 170.7 | 55 |
| 55 | 2.09 | - | - | 22 | 21.3 | - |
| 61 | 0.02, 0.03, 0.04 | - | - | - | −4.93, −4.70, −4.66, −4.62 | - |
| 61' | 0.02, 0.03, 0.04 | - | - | - | −4.93, −4.70, −4.66, −4.62 | - |
| 62 | - | - | - | - | 17.95, 17.99 | - |
| 63 | 0.88, 0.88 | - | - | - | 25.83, 25.84 | - |
| 71 | 0.02, 0.03, 0.04 | - | - | - | −4.93, −4.70, −4.66, −4.62 | - |
| 71' | 0.02, 0.03, 0.04 | - | - | - | −4.93, −4.70, −4.66, −4.62 | - |
| 72 | - | - | - | - | 17.95, 17.99 | - |
| 73 | 0.88, 0.88 | - | - | - | 25.83, 25.84 | - |
| 81 | - | - | - | - | 19.2 | 82 |
| 82 | 1.04 | - | - | - | 26.8 | 82 |
| 83 | - | - | - | - | 134.0 | 84, 85 |
| 83' | - | - | - | - | 134.0 | 84', 85' |
| 84 | 7.66 | - | 85 | - | 135.6 | 84, 86 |
| 84' | 7.66 | - | 85' | - | 135.6 | 84', 86' |
| 85 | 7.37 | - | 84 | - | 127.6 | 85 |
| 85' | 7.37 | - | 84' | - | 127.6 | 85' |
| 86 | 7.41 | - | - | - | 129.5 | 84 |
| 86' | 7.41 | - | - | - | 129.5 | 84' |
| 90 | - | - | - | - | 166.1 | 27 |

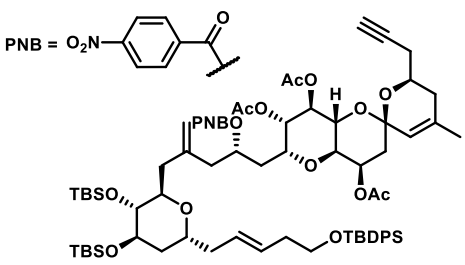
| atom number | $^{1}$H NMR ($CDCl_3$, 600 MHz) | | | | $^{13}$C NMR ($CDCl_3$, 151 MHz)/ $^{29}$Si NMR ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | δ [ppm] | *J* [Hz] | COSY | NOESY | δ [ppm] | HMBC |
| 91 | - | - | - | - | 84.9 | 94, 96 |
| 92 | - | - | - | - | 122.7 | - |
| 94 | 3.42 | 1.3 | - | - | 55.9 | - |
| 95 | | | Signals not found | | | |
| 96 | 7.41 | - | - | - | - | - |
| 97 | | | Signals not found | | | |
| 98 | | | Signals not found | | | |

**Table 6.13.** Analysis of the Mosher esters **269** according to Hoye and co-workers;[48] arbitrary numbering scheme as shown in the insert.




| Atom number | (*S*)-268 δ [ppm] | (*R*)-268 δ [ppm] | Δδ [ppm] |
|---|---|---|---|
| 31 | 3.74 | 3.71 | +0.03 |
| 30a | 2.76 | 2.66 | +0.10 |
| 30b | 2.28 | 2.25 | +0.03 |
| 28 | 2.41 | 2.35 | +0.06 |
| 27 | 5.34 | 5.30 | +0.04 |
| 26a | 2.17 | 2.20 | −0.03 |
| 26b | 1.83 | 1.93 | −0.10 |
| 25 | 4.16 | 4.22 | −0.06 |
| 24 | 5.09 | 5.12 | −0.03 |
| 23 | 5.19 | 5.20 | −0.01 |

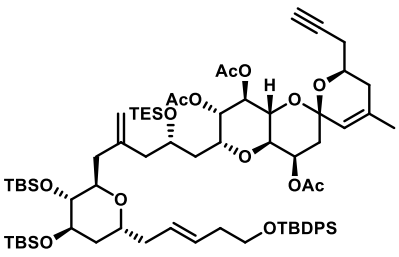
**Compound 257.**




Diethyl azodicarboxylate (40% in toluene, 258 µL, 0.566 mmol) was added dropwise to a solution of alcohol **255** (136 mg, 0.113 mmol), triphenylphosphine (150 mg, 0.566 mmol), and 4-nitrobenzoic acid (86.0 mg, 0.509 mmol) in toluene (1.1 mL) at 0 °C.

The cooling bath was removed and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (4 mL) and the mixture was diluted with *tert*-butyl methyl ether (4 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 4 mL), and the combined organic fractions were washed with brine (5 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (fine silica, hexanes/EtOAc 4:1) to give the title compound as a colorless oil (80.5 mg, 53%). $[\alpha]_D^{20}$ = +13.3 (c = 0.98, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.26 (d, *J* = 8.9 Hz, 2H), 8.10 (d, *J* = 8.9 Hz, 2H), 7.66 (ddd, *J* = 6.8, 3.0, 1.1 Hz, 4H), 7.46 – 7.33 (m, 6H), 5.50 – 5.34 (m, 2H), 5.33 – 5.26 (m, 1H), 5.24 – 5.17 (m, 2H), 5.06 (dd, *J* = 9.9, 6.0 Hz, 1H), 4.94 (q, *J* = 3.0 Hz, 1H), 4.88 (s, 1H), 4.84 (s, 1H), 4.42 – 4.30 (m, 2H), 3.93 – 3.83 (m, 2H), 3.80 (q, *J* = 3.5 Hz, 2H), 3.64 (q, *J* = 7.0 Hz, 2H), 3.48 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.38 (dd, *J* = 3.8, 1.9 Hz, 1H), 2.82 (dd, *J* = 14.6, 9.8 Hz, 1H), 2.59 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.51 – 2.32 (m, 4H), 2.30 – 2.15 (m, 4H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 – 2.00 (m, 3H), 1.95 – 1.82 (m, 3H), 1.76 (ddd, *J* = 13.3, 10.4, 2.8 Hz, 1H), 1.71 – 1.63 (m, 4H), 1.42 – 1.35 (m, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 170.8, 170.3, 169.9, 164.0, 150.6, 142.8, 137.4, 135.9, 135.7, 134.2, 130.7, 129.6, 128.9, 128.5, 127.7, 123.6, 122.8, 115.9, 95.6, 80.8, 76.7, 71.2, 71.1, 70.7, 70.4, 70.4, 70.3, 70.0, 68.5, 67.8, 66.7, 66.7, 64.8, 64.1, 40.6, 38.8, 37.9, 36.5, 36.2, 34.4, 33.9, 28.6, 27.0, 26.0, 25.8, 25.2, 22.8, 21.4, 21.1, 21.0, 19.3, 18.2, 18.1, −4.4, −4.5, −4.5, −4.7; **IR** (film, $cm^{-1}$): 2954, 2930, 2894, 2857, 1740, 1530, 1472, 1428, 1364, 1350, 1272, 1235, 1102, 1068, 1038, 1012, 967, 872, 836, 776, 720, 705, 507; **HRMS** (ESI) for $C_{73}H_{103}NO_{17}Si_3Na$ $[M+Na]^+$: calcd. 1372.6426; found 1372.6423.

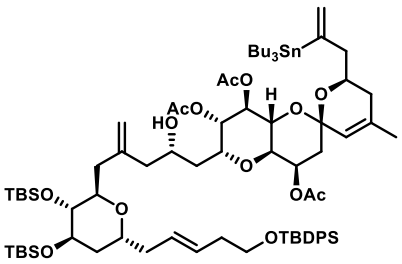
**Compound 258.**




TESOTf (30.0 μL, 0.133 mmol) was added dropwise to a solution of alcohol **254** (145 mg, 0.121 mmol) and 2,6-lutidine (42.2 μL, 0.362 mmol) in $CH_2Cl_2$ (1.2 mL) at −78 °C. The mixture was stirred at −78 °C for 2 h before the reaction was quenched with saturated aqueous $NH_4Cl$ (5 mL) at 0 °C. The mixture was warmed to room temperature and stirring was continued until all solids had dissolved. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 5 mL). The combined organic fractions were washed with brine (8 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 5:1) to give the title compound as a colorless oil (147 mg, 93%). $[\alpha]_D^{20}$ = +23.8 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.70 – 7.62 (m, 4H), 7.46 – 7.32 (m, 6H), 5.54 – 5.35 (m, 2H), 5.22 (s, 1H), 5.17 (d, *J* = 9.5 Hz, 1H), 5.11 (dd, *J* = 10.0, 6.0 Hz, 1H), 5.04 (d, *J* = 3.0 Hz, 1H), 4.87 (d, *J* = 1.8 Hz, 1H), 4.80 (s, 1H), 4.39 – 4.25 (m, 2H), 3.89 (dqd, *J* = 12.5, 6.1, 3.3 Hz, 2H), 3.85 – 3.73 (m, 3H), 3.66 (t, *J* = 7.0 Hz, 2H), 3.46 – 3.34 (m, 2H), 2.65 (dd, *J* =

14.2, 9.0 Hz, 1H), 2.54 – 2.10 (m, 10H), 2.10 (s, 3H), 2.05 (s, 4H), 2.03 (s, 4H), 2.00 – 1.82 (m, 2H), 1.77 (ddd, *J* = 13.3, 10.3, 2.8 Hz, 1H), 1.75 – 1.66 (m, 4H), 1.48 – 1.35 (m, 2H), 1.04 (s, 9H), 0.94 – 0.90 (m, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.57 (q, *J* = 7.8 Hz, 6H), 0.06 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 171.0, 170.4, 170.1, 143.8, 137.3, 135.7, 134.2, 129.6, 128.9, 128.5, 127.7, 123.0, 114.8, 95.5, 80.8, 76.6, 71.1, 70.9, 70.7, 70.5, 70.4, 70.0, 67.8, 67.5, 67.2, 67.1, 66.7, 64.8, 64.2, 44.4, 38.9, 38.1, 37.9, 36.3, 34.4, 33.9, 31.7, 27.0, 26.0, 26.0, 25.2, 22.8, 21.4, 21.1, 21.0, 19.3, 18.2, 7.0, 5.2, −4.3, −4.4, −4.5, −4.7; **IR** (film, $cm^{-1}$): 2954, 2930, 2884, 2857, 1753, 1472, 1428, 1380, 1365, 1237, 1158, 1091, 1038, 1005, 967, 898, 836, 776, 741, 704, 669, 614, 506; **HRMS** (ESI) for $C_{72}H_{114}O_{14}Si_4Na$ [M+Na]$^+$: calcd. 1337.7178; found 1337.7173.

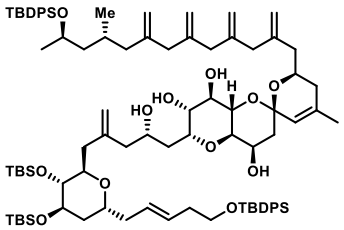
**Compound 259.**




*n*-Butyllithium (1.6 M in hexanes, 2.39 mL, 3.83 mmol) was added to a solution of hexabutylditin (2.03 mL, 4.02 mmol) in THF (7.0 mL) at −20 °C. The mixture was stirred at this temperature for 15 min to give a pale yellow solution of tributylstannyllithium. This solution was cooled to −40 °C and solid copper(I) cyanide (171 mg, 1.91 mmol) was added in one portion. The mixture was cooled to −78 °C over 30 min. Methanol (1.55 mL, 38.3 mmol) and a solution of **254** (766 mg, 0.638 mmol) in THF (1.0 mL, 2 × 1.0 mL washes) were added sequentially at this temperature and the orange mixture was stirred at −78 °C for 2 h. The mixture was warmed to room temperature and sat. aq. $NH_4Cl$ (15 mL), water (5 mL), and EtOAc (20 mL) were added. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/18% EtOAc + 1% $NEt_3$) to give the title compound as a colorless oil (762 mg, 80%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +22.7 (c = 1.00, $CH_2Cl_2$); **$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ 7.67 (dt, *J* = 6.4, 1.7 Hz, 4H), 7.48 – 7.32 (m, 6H), 5.93 – 5.82 (m, 1H), 5.55 – 5.36 (m, 2H), 5.30 (dd, *J* = 2.7, 1.3 Hz, 1H), 5.27 – 5.18 (m, 2H), 5.09 – 5.01 (m, 2H), 4.96 (d, *J* = 1.9 Hz, 1H), 4.89 (d, *J* = 1.9 Hz, 1H), 4.48 (ddd, *J* = 11.7, 6.0, 2.6 Hz, 1H), 4.25 (t, *J* = 9.9 Hz, 1H), 3.95 (ddt, *J* = 9.8, 8.5, 4.9 Hz, 1H), 3.88 – 3.75 (m, 4H), 3.68 (t, *J* = 6.9 Hz, 2H), 3.51 (dd, *J* = 10.1, 3.1 Hz, 1H), 3.40 (dd, *J* = 3.7, 2.0 Hz, 1H), 2.76 (dd, *J* = 14.4, 9.4 Hz, 1H), 2.69 (dd, *J* = 14.8, 5.5 Hz, 1H), 2.41 – 2.14 (m, 8H), 2.10 (dd, *J* = 14.3, 7.6 Hz, 1H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 – 1.91 (m, 1H), 1.85 – 1.78 (m, 3H), 1.75 (td, *J* = 6.6, 2.9 Hz, 1H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.62 – 1.47 (m, 7H), 1.45 – 1.39 (m, 1H), 1.39 – 1.26 (m, 7H), 1.04 (s, 9H), 0.96 – 0.87 (m, 33H), 0.09 – 0.06 (m, 9H), 0.04 (s, 3H); **$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ 170.9, 170.6, 170.0, 150.6, 144.6, 138.2, 135.9, 134.5, 129.9, 129.3, 128.8, 128.0, 127.6, 122.9, 115.3, 95.6, 77.4, 71.6, 71.3, 71.0, 70.7, 70.6, 68.7, 68.1, 67.1, 65.5, 65.2, 64.5, 46.6, 45.1, 39.1, 38.5, 37.7, 36.5, 35.2, 34.2, 32.4, 29.5, 27.8, 27.8, 27.0, 26.1, 26.1, 23.0, 21.5, 21.2, 21.0, 19.5, 18.4, 18.3, 13.9, 9.9, 9.7, −4.4, −4.4, −4.5, −4.7; **$^{119}$Sn NMR** ($CD_2Cl_2$,

149 MHz): δ −43.6; **IR** (film, $cm^{-1}$): 2954, 2928, 2856, 1754, 1471, 1463, 1428, 1378, 1364, 1236, 1090, 1070, 1006, 964, 939, 919, 836, 776, 740, 703, 688, 671, 613, 505; **HRMS** (ESI) for $C_{78}H_{128}O_{14}Si_3SnNa$ $[M+Na]^+$: calcd. 1515.7526; found 1515.7518.

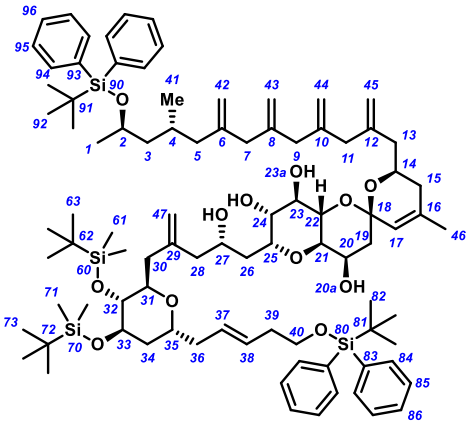
**Compound 264.**




Tris(dibenzylideneacetone)dipalladium(0) (22.3 mg, 24.3 μmol) was added to a degassed solution of stannane **259** (726 mg, 0.486 mmol), acetate **108** (278 mg, 0.535 mmol), and lithium chloride (61.9 mg, 1.46 mmol) in DMF (1.0 mL) at room temperature. The solution was stirred at 60 °C for 20 h before the reaction was quenched with water (4 mL) and pH 7.4 phosphate buffer (2 mL) at room temperature. The aqueous phase was extracted with EtOAc (3 × 8 mL) and the combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated to give a mixture of acetate regioisomers.

The residue was taken up in THF (6.0 mL). MeOH (2.0 mL) and aq. NaOH (2.0 M, 2.0 mL, 4.0 mmol) were added to the solution and the mixture was stirred for 3 h at room temperature. The reaction was quenched with sat. aq. $NH_4Cl$ (10 mL) and water (5 mL). The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (fine silica, hexanes/EtOAc 7:3) to give the title compound as a colorless oil (521 mg, 70% over two steps). $[\alpha]_D^{20}$ = +38.7 (c = 1.00, $CHCl_3$); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.72 – 7.64 (m, 8H), 7.44 – 7.32 (m, 12H), 5.42 (qt, *J* = 15.4, 6.4 Hz, 2H), 5.26 (s, 1H), 4.99 (s, 1H), 4.98 (s, 1H), 4.96 – 4.94 (m, 1H), 4.93 (d, *J* = 2.0 Hz, 1H), 4.90 (d, *J* = 1.9 Hz, 1H), 4.85 (s, 1H), 4.83 (s, 2H), 4.76 (d, *J* = 2.2 Hz, 1H), 4.74 (d, *J* = 2.3 Hz, 1H), 4.37 (q, *J* = 5.9 Hz, 1H), 4.16 (ddt, *J* = 10.7, 8.7, 4.2 Hz, 1H), 4.01 (dq, *J* = 9.8, 3.0 Hz, 1H), 3.96 – 3.71 (m, 9H), 3.70 – 3.60 (m, 3H), 3.35 (dd, *J* = 3.8, 2.3 Hz, 1H), 3.29 (dt, *J* = 6.5, 2.8 Hz, 1H), 2.93 (d, *J* = 14.8 Hz, 1H), 2.83 (d, *J* = 14.8 Hz, 1H), 2.77 (dd, *J* = 14.4, 10.0 Hz, 1H), 2.68 – 2.57 (m, 5H), 2.37 – 2.15 (m, 8H), 2.12 – 2.02 (m, 2H), 2.00 – 1.89 (m, 2H), 1.87 – 1.53 (m, 12H), 1.47 – 1.37 (m, 1H), 1.09 – 0.99 (m, 22H), 0.94 – 0.86 (m, 18H), 0.69 (d, *J* = 6.1 Hz, 3H), 0.18 – −0.03 (m, 12H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 145.8, 144.7, 144.6, 143.9, 143.3, 137.8, 136.1, 136.1, 135.7, 135.2, 134.5, 134.2, 129.7, 129.6, 129.5, 129.3, 128.2, 127.7, 127.6, 127.5, 122.4, 116.0, 114.4, 114.1, 113.1, 96.7, 75.0, 72.5, 72.0, 71.5, 70.4, 70.3, 68.3, 68.1, 67.8, 66.9, 65.8, 65.5, 64.1, 47.4, 45.0, 43.7, 42.6, 42.1, 41.4, 41.4, 40.3, 38.6, 37.6, 36.2, 35.4, 35.2, 34.0, 27.2, 27.1, 27.0, 26.0, 24.4, 23.0, 19.7, 19.5, 19.3, 18.2, 18.1, −4.3, −4.3, −4.4, −4.7; **IR** (film, $cm^{-1}$): 3456, 3072, 2954, 2929, 2896, 2857, 1638, 1472, 1462, 1428, 1379, 1361, 1255, 1177, 1109, 1090, 998, 958, 940, 895, 835, 776, 740, 702, 612, 505, 446, 420; **HRMS** (ESI) for $C_{91}H_{138}O_{12}Si_4Na$ $[M+Na]^+$: calcd. 1557.9158; found 1557.9150.

**Table 6.14.** Detailed NMR data of **264**; numbering scheme as shown in the insert.



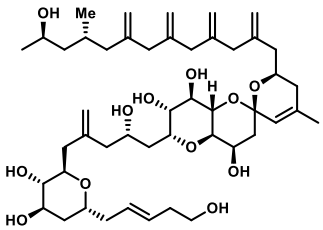
| atom number | $^{1}$H NMR ($CDCl_3$, 600 MHz) | | | | $^{13}$C NMR ($CDCl_3$, 151 MHz)/ $^{29}$Si NMR ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | δ [ppm] | *J* [Hz] | COSY | NOESY | δ [ppm] | HMBC |
| 1 | 1.03 | 6.1 | 2 | - | 24.2 | 3b |
| 2 | 3.89 | - | 1, 3a, 3b | 41 | 67.7 | 1, 3a, 3b |
| 3a | 1.06 | - | 2, 3b, 4 | - | 47.3 | 1, 2, 4, 5a, 5b, 41 |
| 3b | 1.57 | 13.0, 8.0, 4.4 | 2, 3a, 4 | - | | |
| 4 | 1.82 | - | 3a, 3b, 5a, 5b, 41 | - | 27.0 | 2 |
| 5a | 1.64 | - | 4, 5b, 42'' | 7, 42'', 43 | 43.6 | 3a, 3b, 4, 7, 42', 42'' |
| 5b | 1.82 | - | 4, 5a, 42'' | 7, 42'', 43 | | |
| 6 | - | - | - | - | 145.7 | 5a, 5b, 7, 41, 42', 42'', 43 |
| 7 | 2.63 | - | 42', 43 | 5a, 5b, 42', 43 | 42.5 | 5a, 5b, 9, 42', 42'', 43 |
| 8 | - | - | - | - | 144.6 | 7, 9, 42', 42'', 43, 44', 44'' |
| 9 | 2.63 | - | 43, 44', 44'' | 11a, 11b, 44'' | 41.3 | 7, 43, 44', 44'' |
| 10 | - | - | - | - | 144.4 | 9, 11a, 11b, 43, 44', 44'', 45', 45'' |
| 11a | 2.83 | 14.6 | 11b, 44', 44'', 45'' | 9, 13b, 14, 22, 44', 45', 45'' | 42.0 | 9, 13a, 13b, 44', 44'', 45', 45'' |
| 11b | 2.93 | 14.7 | 11a, 44', 45'' | 9, 13b, 14, 22, 44' | | |
| 12 | - | - | - | - | 143.1 | 11a, 11b, 13a, 13b, 14, 45', 45'' |
| 13a | 2.21 | - | 13b, 14, 45' | 44', 45' | 41.2 | 11a, 11b, 15b, 45', 45'' |
| 13b | 2.25 | - | 13a, 14, 45' | 11a, 11b, 44', 45' | | |
| 14 | 4.15 | - | 13a, 13b, 15a, 15b | 11a, 11b, 22, 44', 45' | 65.6 | 13a, 13b, 15b, 45', 45'' |
| 15a | 1.82 | 17.6, 3.6 | 14, 15b | - | 35.3 | 13a, 13b, 17, 46 |
| 15b | 1.93 | 17.1, 10.9 | 14, 15a, 17, 46 | - | | |

| atom number | **$^{1}$H NMR** ($CDCl_3$, 600 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 151 MHz)/ **$^{29}$Si NMR** ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 16 | - | - | - | - | 137.7 | 15a, 15b, 46 |
| 17 | 5.26 | - | 15b, 46 | 19a, 46 | 122.3 | 15a, 15b, 46 |
| 18 | - | - | - | - | 96.6 | 17, 19a, 19b, 20 |
| 19a | 1.81 | 15.5, 3.1 | 19b, 20 | 17, 20a, 21 | 40.2 | 17, 20a |
| 19b | 2.06 | 14.6, 3.3 | 19a, 20 | 20, 20a | | |
| 20 | 4.01 | 9.4, 3.1 | 19a, 19b, 20a, 21 | 19b, 21 | 66.7 | 19b, 20a, 22 |
| 20a | 3.68 | 10.5 | 20 | 19a, 19b, 45', 45'' | - | - |
| 21 | 3.29 | 6.6, 2.8 | 20, 22 | 19a, 20, 26a, 26b | 70.3 | 19b, 20, 22, 23, 25 |
| 22 | 3.74 | - | 21, 23 | 11a, 11b, 14, 23a, 45', 45'' | 68.1 | 20, 21, 23, 23a |
| 23 | 3.74 | - | 22, 23a, 24 | 23a, 25 | 72.3 | 21, 22, 23a, 24, 25 |
| 23a | 2.57 | - | 23 | 22, 23 | - | - |
| 24 | 3.77 | - | 23, 25 | 25 | 71.9 | 22, 23, 23a, 25, 26a, 26b |
| 25 | 4.37 | 6.1 | 24, 26a, 26b | 23, 24, 27 | 74.8 | 24, 26a, 26b |
| 26a | 1.79 | - | 25, 26b, 27 | 21 | 35.1 | 24, 25, 28a, 28b |
| 26b | 1.96 | - | 25, 26a, 27 | 21 | | |
| 27 | 3.90 | - | 26a, 26b, 28a, 28b | 25, 28b, 30b, 47'' | 67.9 | 25, 26a, 26b, 28a, 28b, 47', 47'' |
| 28a | 2.19 | - | 27, 28b, 47'' | 47'' | 44.9 | 26a, 26b, 30a, 30b, 47', 47'' |
| 28b | 2.30 | - | 27, 28a, 47'' | 27, 47'' | | |
| 29 | - | - | - | - | 143.7 | 28a, 28b, 30a, 30b, 31, 47', 47'' |
| 30a | 2.33 | 14.3, 5.0 | 30b, 31, 47' | 32, 47' | 37.5 | 28a, 28b, 31, 47', 47'' |
| 30b | 2.76 | 14.3, 10.0 | 30a, 31, 47' | 27, 32, 35, 47' | | |
| 31 | 3.80 | - | 30a, 30b, 32 | 36a, 47' | 77.2 | 30a, 30b, 33 |
| 32 | 3.35 | 3.7, 2.5 | 31, 33 | 30a, 30b, 47' | 71.4 | 30a, 30b, 31, 34a |
| 33 | 3.79 | 3.8 | 32, 34a, 34b | 31, 70 | 70.1 | 31, 32, 34a, 35 |
| 34a | 1.40 | 13.4, 4.6, 2.7 | 33, 34b, 35 | - | 33.9 | 32, 36a, 36b |
| 34b | 1.77 | 13.1, 9.9, 2.8 | 33, 34a, 35 | - | | |
| 35 | 3.83 | 9.2, 6.5, 2.4 | 34a, 34b, 36a, 36b | 30b, 36a, 37, 47' | 65.3 | 31, 34b, 36a, 36b, 37 |
| 36a | 2.07 | 13.8, 7.0 | 35, 36b, 37, 38 | 31, 35, 38 | 38.5 | 34b, 37, 38 |
| 36b | 2.20 | 13.3, 6.5 | 35, 36a, 37, 38 | 38 | | |
| 37 | 5.38 | 15.4, 6.8, 1.2 | 36a, 36b, 38, 39 | 35 | 128.1 | 36a, 36b, 38, 39 |
| 38 | 5.45 | 15.4, 6.7, 1.2 | 36a, 36b, 37, 39 | 36a, 36b, 40 | 129.2 | 36a, 36b, 37, 39, 40 |

| atom number | **$^{1}$H NMR** ($CDCl_3$, 600 MHz) | | | | **$^{13}$C NMR** ($CDCl_3$, 151 MHz)/ **$^{29}$Si NMR** ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | **δ** [ppm] | ***J*** [Hz] | **COSY** | **NOESY** | **δ** [ppm] | **HMBC** |
| 39 | 2.26 | 6.9 | 37, 38, 40 | - | 36.1 | 37, 38, 40 |
| 40 | 3.65 | 6.9 | 39 | 38 | 63.9 | 38, 39 |
| 41 | 0.68 | 6.2 | 4 | 2, 42'' | 19.6 | 3b, 4, 5a, 5b |
| 42' | 4.76 | 2.4 | 7, 42'' | 7 | 112.9 | 5a, 5b, 7 |
| 42'' | 4.74 | 2.3 | 5a, 5b, 42' | 5a, 5b, 41 | | |
| 43 | 4.83 | - | 7, 9 | 5a, 5b, 7 | 113.9 | 7, 9 |
| 44' | 4.92 | - | 9, 11a, 11b, 44'' | 11a, 11b, 13a, 13b, 14 | 114.2 | 9, 11a, 11b |
| 44'' | 4.84 | - | 9, 11a, 44' | 9 | | |
| 45' | 4.98 | 1.8 | 13a, 13b, 45'' | 11a, 13a, 13b, 14, 20a, 22 | 115.9 | 11a, 11b, 13a, 13b |
| 45'' | 4.97 | 1.9 | 11a, 11b, 45' | 11a, 20a, 22 | | |
| 46 | 1.72 | - | 15b, 17 | 17 | 22.8 | 15a, 17 |
| 47' | 4.95 | - | 30a, 30b, 47'' | 30a, 30b, 31, 32, 35 | 115.9 | 28a, 28b, 30a, 30b |
| 47'' | 4.90 | - | 28a, 28b, 47' | 27, 28a, 28b | | |
| 60 | - | - | - | - | 18.5 | 32, 61, 61', 63 |
| 61 | 0.05 | - | - | - | −4.5 | 61' |
| 61' | 0.04 | - | - | - | −4.6 | 61 |
| 62 | - | - | - | - | 17.98, 18.05 | 61, 61', 63 |
| 63 | 0.89 | - | - | - | 25.86, 25.87 | 63 |
| 70 | - | - | - | - | 18.6 | 33, 71, 71', 73 |
| 71 | 0.05 | - | - | - | −4.5 | 71' |
| 71' | 0.03 | - | - | - | −4.9 | 71 |
| 72 | - | - | - | - | 17.98, 18.05 | 71, 71', 73 |
| 73 | 0.88 | - | - | - | 25.86, 25.87 | 73 |
| 80 | - | - | - | - | −4.7 | 40, 82, 84, 84' |
| 81 | - | - | - | - | 19.2 | 82 |
| 82 | 1.04 | - | - | - | 26.9 | 82 |
| 83 | - | - | - | - | 134.0 | 84, 85 |
| 83' | - | - | - | - | 134.0 | 84', 85' |
| 84 | 7.66 | - | - | - | 135.6 | 84, 86 |
| 84' | 7.66 | - | - | - | 135.6 | 84', 86' |
| 85 | 7.37 | - | - | - | 127.6 | 84, 85 |
| 85' | 7.37 | - | - | - | 127.6 | 84', 85' |
| 86 | 7.41 | - | - | - | 129.5 | 84 |

| atom number | $^{1}$H NMR ($CDCl_3$, 600 MHz) | | | | $^{13}$C NMR ($CDCl_3$, 151 MHz)/ $^{29}$Si NMR ($CDCl_3$, 119 MHz) | |
|---|---|---|---|---|---|---|
| | δ [ppm] | *J* [Hz] | COSY | NOESY | δ [ppm] | HMBC |
| 86' | 7.41 | - | - | - | 129.5 | 84' |
| 90 | - | - | - | - | -6.9 | 2, 92, 94, 94' |
| 91 | - | - | - | - | 19.3 | 92 |
| 92 | 1.05 | - | - | - | 27.1 | 92 |
| 93 | - | - | - | - | 134.3 | 94, 95 |
| 93' | - | - | - | - | 135.0 | 94', 95' |
| 94 | 7.70 | - | - | - | 135.9 | 94, 96 |
| 94' | 7.68 | - | - | - | 136.0 | 94', 96' |
| 95 | 7.36 | - | - | - | 127.5 | 94, 95 |
| 95' | 7.36 | - | - | - | 127.3 | 94', 95' |
| 96 | 7.41 | - | - | - | 129.5 | 94 |
| 96' | 7.41 | - | - | - | 129.3 | 94' |

**Limaol (13).**




A solution of silyl ether **264** (521 mg, 0.339 mmol) in THF (1.0 mL, 2 × 0.5 mL wash) was added to a solution of TBAF trihydrate (2.14 g, 6.78 mmol) in THF (5.0 mL) at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature for 22 h. The reaction was quenched with pH 7.4 phosphate buffer (10 mL) and the aqueous phase was extracted with EtOAc (5 × 8 mL). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (EtOAc/8% MeOH) to give the title compound as a white foam (278 mg, 99%). The analytical and spectral data matched the data previously obtained.

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