Total Synthesis of Leucascandrolide A

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Presented by

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Zürich, 2003
Acknowledgments

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I would also like to express my gratitude to the rest of the Carreira group for useful discussions and support, in particular Claudia Dörfler and Franziska Peyer, who managed to solve all administrative problems very efficiently.

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I will always be indebted to Anne, Brian, Christiane, Dieter, Gabi, Jeff, and Tobias for their friendship. I have fond memories of the past four years. I will never forget the long-distance run from St-Gallen to Zürich with Christiane (8h15’), the mountain hikes with Tobias and Dieter, my skiing lessons with Gabi, the evenings at Corazón and the nights at Nelson (as well as the headaches in the morning).

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Mr. Emile “Tokyo” Gérard, by his enthusiasm and energy, inspired in me the desire to study organic chemistry.

To my sister Nadia and my brother Philippe, I am grateful for their persistence in cheering me up when I needed it the most and for convincing me to carry on.

To my parents, I am indebted for their love and generous financial support throughout the many years of my studies, as well as for their seemingly weird motivational techniques (“Du wärts spéider beim Gilbert Neel verkafen”) at an earlier time in my life.

Finally, I would like to thank Corinne for the good time we had together. Your support was invaluable to me and I would not have achieved this without your help and advice.
Wir können nicht immer kontrollieren, was uns passiert.
Aber wir können kontrollieren, was wir über das denken, was passiert.
Und was wir darüber denken, ist unser "Leben" in jedem einzelnen Moment.

—Norman G. Shidie
List of Publications

Alec Fettes, Erick M. Carreira
“Total Synthesis of Leucascandrolide A”

Alec Fettes, Erick M. Carreira
“Leucascandrolide A: Synthesis and Related Studies”
manuscript in preparation.

Alec Fettes, Christiane Meyers, Erick M. Carreira
“Catalytic Asymmetric Aldol Reactions”
Org. Reactions, manuscript in preparation.
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Abstract

Leucascandrolide A (I), a polyoxygenated marine macrolide of a new genus (Scheme I), was isolated in 1996 by Pietra and co-workers from the calcareous sponge *Leucascandra caveolata*. Despite intensive efforts, subsequent expeditions failed to provide additional quantities of I.

The biological profile of I is characterized by strong cytotoxic activity against human cancer cell lines as well as powerful inhibition of *Candida albicans*.

This thesis describes the total synthesis of leucascandrolide A. The synthesis planning, outlined in Scheme I, relies on the use of asymmetric synthetic methods recently developed in our laboratories and was chosen for reasons of flexibility and convergency.

Scheme I. Retrosynthetic Analysis and Key Intermediates.
Two building blocks II and III were identified as key intermediates and readily synthesized using methods developed in our group (Scheme II): Methyl ketone II was accessed in seven steps using a copper(I)-catalyzed asymmetric aldol addition of dienolate VI to crotonaldehyde (VII). Aldehyde III was conveniently synthesized by addition of alkyne VIII to (R)-isopropylidene glyceraldehyde (IX), using the protocol recently reported for the generation of zinc acetylides under mild conditions.

Coupling of II and III by 1,5-anti-selective boron-aldol reaction led to hydroxy ketone X containing all the carbon atoms of the leucascandrolide A core (Scheme III). Further functionalization required the development of an intramolecular, electrophile-mediated cyclization of a 6-hydroxy alkene to a 2,6-trans-disubstituted tetrahydropyran ring, leading to bis-pyran XI. This transformation was carried out in a highly diastereoselective manner using 2,4,6-triisopropylphenylselenyl bromide.
Seco acid **XII** showed pronounced recalcitrance towards macrolactonization under standard Yamaguchi conditions. The use of DMF as solvent, breaking up putative intramolecular hydrogen bonds involving the C9 hydroxy group, was found to be beneficial to the cyclization, leading to the desired macrocycle **XIII** in good yield. Introduction of the C17 and C5 side chains completed the synthesis of target compound **I** (Scheme IV).

![Scheme IV](image)

In the course of our synthetic studies, we had the opportunity to develop and apply new reaction methodology in the context of complex natural product synthesis. Highlights of the approach include the highly enantioselective dienolate addition to crotonaldehyde, the diastereoselective alkyne addition to a notoriously unstable aldehyde as well as other modern methods for asymmetric bond construction. The described synthesis of leucascandrolide A proceeds in twenty-one synthetic steps (longest linear sequence) and 3.5% overall yield.
Zusammenfassung


Beeindruckende zytotoxische Aktivität gegenüber menschlichen Krebszelllinien sowie Inhibition von *Candida albicans* kennzeichnen diesen Naturstoff.

Die vorliegende Arbeit beschreibt die Totalsynthese von Leucascandrolide A. Unsere Syntheseplanung beruht auf der Anwendung moderner asymmetrischer Methoden, welche kürzlich in unserem Arbeitskreis entwickelt wurden, und zeichnet sich durch Flexibilität und Konvergenz aus.

*Schema I. Synthesestrategie und wichtige Zwischenprodukte.*

Die Kupplung beider Fragmente II und III durch eine 1,5-anti-selektive Bor-Aldol-Reaktion lieferte β-Hydroxyketon X (Schema III), welches bereits alle C-Atome des Leucascandrolide A Makrolids enthält. Der zweite Tetrahydropyran-Ring konnte durch eine 2,4,6-Triisopropylphenylselenylbromid-vermittelte Zyklisierung eines 6-Hydroxyalkens eingeführt werden, wobei das bis-Pyran XI stereoselektiv erhalten wurde.
Makrolaktonisierung der Secosäure XII unter Standard-Yamaguchi-Bedingungen führte nicht zum gewünschten Makrolid XIII. Es stellte sich heraus, dass die Verwendung von DMF als Lösungsmittel, welches vermeintliche intramolekulare Wasserstoffbrücken aufzubrechen vermag, die Zyklisierung ermöglichte und in guten Ausbeuten zu XIII führte. Einführung der C5 und C17 Seitenketten vervollständigten die Synthese des Zielmoleküls I (Schema IV).

Schema IV

Unsere synthetischen Studien haben die Entwicklung und Anwendung neuer Methoden im Rahmen einer komplexen Naturstoffsynthese ermöglicht. Als Höhepunkte unserer Vorgehensweise sind die enantioselektive Dienolat Addition an Crotonaldehyd, die diastereoselektive Alkynilid Addition an einen notorisch instabilen Aldehyd sowie die Anwendung moderner stereoselektiver Methoden besonders erwähnenswert. Die beschriebene Synthese von Leucascandrolide A gelang in einundzwanzig Schritten und 3.5% Gesamtausbeute.
List of Abbreviations, Acronyms, and Symbols

[α]_D^T  specific rotation at temperature T at the sodium D line
Å  angstrom
Ac  acetyl
acac  acetylacetonyl
ACP  acyl carrier protein
AIBN  2,2'-azoisobutyronitrile
anal.  analytical
aq.  aqueous
atm  atmosphere
ax  axial
9-BBN  9-borabicyclo[3.3.1]nonane
Bn  benzyl
bp  boiling point
br  broadened
Bu  butyl
Bz  benzoyl
c  concentration
° C  degree centigrade
calcd  calculated
cat.  catalytic
cm⁻¹  reciprocal centimeters
CoA  coenzyme A
conc.  concentrated
Cp  cyclopentadienyl
18C6  18-crown-6
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>CSA</td>
<td>10-camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>δ</td>
<td>NMR chemical shift in ppm downfield from a standard</td>
</tr>
<tr>
<td>d</td>
<td>day, doublet</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DAST</td>
<td>diethylaminosulfur trifluoride</td>
</tr>
<tr>
<td>dba</td>
<td>(E,E)-dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL–H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIPA</td>
<td>N,N-diisopropyl amine</td>
</tr>
<tr>
<td>DIPC1</td>
<td>B-chloro-diisopinocampheyl borane</td>
</tr>
<tr>
<td>DIPT</td>
<td>diisopropyl tartrate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-N,N-dimethylamino pyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethyl formamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess–Martin periodinane</td>
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<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>EDCI</td>
<td>1-(3-dimethylaminopropyl)-3-ethylcarbodiimide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact ionization</td>
</tr>
<tr>
<td>eq</td>
<td>equatorial</td>
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<tr>
<td>Eq.</td>
<td>equation</td>
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<td>equiv</td>
<td>equivalent</td>
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<td>Definition</td>
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<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>eV</td>
<td>electronvolt</td>
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<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HMDS</td>
<td>1,1,1,3,3,3-hexamethyldisilazane</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HOBT</td>
<td>1-hydroxy benzotriazole</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-pressure liquid chromatography</td>
</tr>
<tr>
<td>HR</td>
<td>high resolution</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz (s⁻¹)</td>
</tr>
<tr>
<td>IC₅₀</td>
<td>concentration that is infective in 50% of test subjects</td>
</tr>
<tr>
<td>imid</td>
<td>imidazole</td>
</tr>
<tr>
<td>IpC</td>
<td>isopinocampheyl</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>kcal</td>
<td>kilocalorie</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium 1,1,1,3,3,3-hexamethyldisilazide</td>
</tr>
<tr>
<td>λ</td>
<td>wavelength</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropyl amide</td>
</tr>
<tr>
<td>LHMDS</td>
<td>lithium 1,1,1,3,3,3-hexamethyldisilazide</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>lithium tri-sec-butylborohydride</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>m</td>
<td>molarity (moles·l⁻¹)</td>
</tr>
<tr>
<td>MALDI</td>
<td>matrix-assisted laser desorption ionization</td>
</tr>
<tr>
<td>mCPBA</td>
<td>3-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>ml</td>
<td>milliliter</td>
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<tr>
<td>µl</td>
<td>microliter</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>µmol</td>
<td>micromole</td>
</tr>
<tr>
<td>mol%</td>
<td>mole per cent</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>M.S.</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
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<tr>
<td>MTPA</td>
<td>2-methoxy-2-phenyl-2-(trifluoromethyl) acetic acid</td>
</tr>
<tr>
<td>NMM</td>
<td>N-methyl morpholine</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methyl morpholine N-oxide</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>Oxone</td>
<td>potassium peroxymonosulfate 2KHSO$_5$·KHSO$_4$·K$_2$SO$_4$</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PG</td>
<td>protective group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PKS</td>
<td>polyketide synthetase</td>
</tr>
<tr>
<td>PMB</td>
<td>4-methoxybenzyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium 4-toluenesulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>Proton Sponge</td>
<td>$N,N,N',N'$-tetramethyl-1,8-naphtalene-diamine</td>
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psi pounds per square inch
PyBrop bromotri(pyrrolidino)phosphonium hexafluorophosphate
Pyr 2-pyridyl
pyr. pyridine
q quartet
quant. quantitative
Ra–Ni Raney–Nickel
rec. recovered
Red-Al sodium bis(2-methoxyethoxy)aluminum hydride
R_f retention factor
RT room temperature
s second, singlet
sat. saturated
Ser serine
SM starting material
t triplet
T temperature
TABH tetra-n-butylammonium triacetoxyborohydride
TBAF tetra-n-butylammonium fluoride
TBAT tetra-n-butylammonium triphenyldifluorosilicate
TBDPS tert-butyldiphenylsilyl
TBHP tert-butylhydroperoxide
TBS tert-butyldimethylsilyl
TEMPO 2,2,6,6-tetramethylpiperidine 1-oxyl radical
TES triethylsilyl
Tf trifluoromethanesulfonyl
TFA trifluoroacetic acid
List of Abbreviations, Acronyms, and Symbols

<table>
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<tr>
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<th>Full Form</th>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TIPP</td>
<td>2,4,6-triisopropylphenyl</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>(R)-Tol-BINAP</td>
<td>(R)-2,2’-bis(di-p-tolyl-phosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>Ts</td>
<td>4-methylphenyl sulfonyl</td>
</tr>
<tr>
<td>(S,S)-TsDPEN</td>
<td>(1S,2S)-N-p-toluenesulfonyl-1,2-diphenylethylene diamine</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetra-n-propylammonium perruthenate</td>
</tr>
<tr>
<td>vs</td>
<td>versus</td>
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</tbody>
</table>
If you understand, things are just as they are;

if you do not understand, things are just as they are.

—Zen proverb
1

Introduction

1.1. Polyketide Synthesis

1.1.1. General Aspects

More than one hundred years ago, Collie first hypothesized that certain classes of aromatic natural products might be derived from simple two-carbon “CH$_2$–CO” building blocks by way of linear poly-$\beta$-keto intermediates that could undergo cyclization by carbonyl-condensation reactions:\(^1\) “This condensation of diacetylacetone and of its allied compounds are of considerable interest, as it enables us to trace, step by step, the simple manner in which the gradual building-up of the most complicated molecules is effected... and although at the present time we are almost entirely ignorant of the methods by which most of these processes are effected, still we can, with a considerable amount of certainty, guess at a solution of part of the problem.... Polymerisation and condensation are probably the two chief types of change which are instrumental in forming many of the multitudinous natural compounds.” This proposal was remarkable in that it contained an intrinsically mechanistic hypothesis at a time when chemical mechanisms were

---

hardly perceived. Only decades later was Collie’s concept validated by means of modern spectroscopic techniques and isotope-labeling experiments.

The term polyketide was coined to refer to natural products containing multiple carbonyl and/or hydroxyl groups, each separated by a methylene spacer unit. Polyketides are generally nonessential molecules that are synthesized as secondary metabolites following the onset of stationary phase in the life-cycle of an organism. Equally diverse as their structural properties is their biological activity: many polyketides are valuable therapeutic agents, including numerous antibiotics (e.g. erythromycin (1), tetracycline (2)), anticancer agents (e.g. laulimalide (3), epothilone B (4)), immunosuppressants (e.g. FK506 (5), rapamycin (6)), antiparasitic agents (e.g. avermectin, nemadectin), antifungals (e.g. amphotericin (7)), cardiovascular agents (e.g. lavostatin, compactin), and veterinary products (e.g. monensin (8), tylosin) (Figure 1).
Figure 1. Some representative polyketide-derived natural products.
1.1.2. Biosynthesis

A myriad polyketides have been isolated, displaying huge structural diversity. By the late 1980’s, it was evident that the biosynthesis of aromatic and reduced polyketides bears a close mechanistic resemblance to the well-understood formation of fatty acids. Despite the wide variety of stereochemical and oxidation-state permutations represented in these molecules, they all share their common origin from highly functionalized carbon chains whose assemblage is controlled by multi-enzyme systems, the polyketide synthetases (PKSs). These enzymes catalyze the modular chain extension (two carbons at a time) by repetitious Claisen condensations between acetyl–SACP and malonyl–SACP, to afford β-keto esters, as shown in Figure 2. Each condensation is followed by oxidation-state adjustment before subsequent reiteration of the cycle: keto reduction, dehydration, and enoyl reduction. In contrast to the biosynthesis of fatty acids, the whole reductive cycle need not be passed, allowing for a highly selective and controlled assembly of polyketide intermediates with a sheer endless number of possible combinations along the growing chain. Virtually every imaginable array of relative configuration may be produced by the action of polyketide synthetases. As can be seen from Figure 2, the elimination step can be entirely omitted, reducing the cycle to condensation followed by keto reduction, giving rise to a regular array of 1,3-polyols (pathway B). The chain-extender unit is malonyl–SACP for the synthesis of fatty acids and aromatic polyketides, but varies for reduced polyketides: incorporation of propionate or butyrate residues (from methylmalonyl–CoA or ethylmalonyl–CoA chain extenders) produces methyl or ethyl side chains in the polyketide product.

Figure 2. The assembly of fatty acids, polyketides, and reduced polyketides.
1.1.3. Synthetic Approaches

The inherent stereochemical complexity present in polyketides has captured the imagination of organic chemists. Their stereocontrolled, asymmetric total synthesis has stimulated the development of a host of new reactions and concepts for C–C bond construction in the context of acyclic stereocontrol. A succinct survey of the most general carbon–carbon bond-forming methods is appropriate to place our own efforts in context. They include: (i) aldol additions; (ii) allylation- and crotylation reactions; (iii) nitrile-oxide cycloadditions; (iv) Hetero-Diels–Alder reactions.

1.1.3.1. Aldol Additions

The acid- or base-promoted attack of an enol or enolate onto a carbonyl is one of the most widely used chemical reactions (Scheme 1).

The aldol addition has been developed into one of the most powerful and versatile methods in modern carbonyl chemistry for the regio-, stereo-, and enantioselective construction of carbon–carbon bonds in acyclic systems. This progress had tremendous impact on the synthesis of complex, polyoxygenated...
molecules, in particular polyketides, which are considered the quintessential aldol products.\(^3\)

Of paramount interest is the application of aldol methodology to the synthesis of enantiopure, skipped hydroxylation patterns. The required \(\pi\)-face bias can be imparted either from substrate control, reagent control, or a combination of both.

Extensive studies on substrate-directed aldol reactions have been reported by Evans, Heathcock, Masamune, and Paterson among others.\(^4\) Substrate-controlled induction in aldol additions may originate from a chiral aldehyde, from a chiral ketone or both. Several variables can be tuned to lead to the desired stereochemical outcome, hence showing great flexibility for the synthetic planning: enolate geometry, enolate metal, ligands on the metal.

The use of boron enolates in aldol chemistry, discovered by Masamune\(^5\) and popularized by Paterson and Evans, has proven to be enormously versatile and was used with great success in polyketide synthesis. The relative configuration of the aldol adduct is determined by the geometry of the enolate component, \((Z)\)-enolates giving \(\text{syn}\) products and \((E)\)-enolates \(\text{anti}\) products via Zimmerman–Traxler transition states (Scheme 2).\(^7,8\) Thus, the enolization step is of prime importance in this type of

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(6) To simplify discussion, \((Z)\)- and \((E)\)-enolates are assigned whereby the oxygen-metal substituent is designated a higher priority than \(R^1\).

additions, and reaction conditions leading selectively to one or the other have been developed. The chiral- auxiliary approach, leading to enantiomerically enriched aldol adducts, was pioneered by Evans and co-workers. The high predictability of the


(9) (E)-enolates are formed by reaction with Cy₂BCl and Et₃N, while the use of Bu₂BOTf and Hüng's base leads to the formation of (Z)-enolates: Cowden, C. J.; Paterson, I. Org. React. 1997, 51, 1–200.

(10) The use of these auxiliaries has been extensively studied and reviewed: Evans, D. A.; Nelson, J. V.; Taber, T. In Topics in Stereochemistry; John Wiley & Sons: New York, 1982; 1–115.

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {\includegraphics[width=0.8\textwidth]{scheme3.png}};

\end{tikzpicture}
\end{center}

\textbf{Scheme 3}

The stereochemical outcome of these reactions has been shown to be crucially dependent on the enolization conditions: indeed, different diastereomers are accessible from the same auxiliary, depending on the metal involved and the reaction conditions (Scheme 4).\footnote{\textit{anti}-Aldol products are accessed through (Z)-enolates by complexation of the aldehyde with a \textit{Lewis} acid, diverting the reaction from a cyclic transition state: Walker, M. A.; Heathcock, C. H. \textit{J. Org. Chem.} \textbf{1991}, \textit{56}, 5747–5750.}

\begin{itemize}
\end{itemize}
The tin-mediated acetate aldol reported by Nagao,\textsuperscript{(15)} frequently applied when other systems fail to give high selectivities (especially with unsubstituted enolates), was used in Smith’s synthetic studies on phorboxazole\textsuperscript{(16)} and the pateamine A synthesis by Romo and Liu\textsuperscript{(17)} (Scheme 5).


Chiral reagents have gained increased attention to control the stereoinduction in aldol additions. It is clear that, as far as stoichiometric variations are concerned, boron is the most widely used metal for attaching chiral ligands in aldol chemistry. Some of the chiral reagents developed for this purpose are outlined in Figure 3.

The ubiquity of catalytic, asymmetric aldol reactions makes a comprehensive discussion impractical. Excellent reviews on this topic have appeared and only the two most versatile and widely used catalysts, independently developed by Carreira and Evans, will be briefly discussed.19

Carreira and co-workers reported the catalytic, enantioselective aldol addition of methyl acetate derived trimethylsilyl ketene acetal 10 and dienolate 11 to a variety of aliphatic, α,β-unsaturated, and aromatic aldehydes, using as little as 0.2 mol% of chiral Ti(IV) catalyst 12 (Scheme 6).20 Aldol adducts 13 and 14 are consistently obtained in excellent yields and enantioselectivities.

\[
\begin{align*}
\text{R}^+\text{H} + \text{OMe} \text{OTMS} & \xrightarrow{0.2 - 5 \text{ mol\% } 12} \text{TMSO} \text{R}^+\text{H} \text{OMe} \\
\text{R}^+\text{H} + \text{Me} \text{Me} \text{Me} \text{OTMS} & \xrightarrow{1 - 3 \text{ mol\% } 12} \text{TMSO} \text{R}^+\text{H} \text{Me} \text{Me}
\end{align*}
\]

Scheme 6

The utility and efficiency of this process in diastereoselective additions was demonstrated by Rychnovsky, using highly functionalized aldehyde 15 to give β-hydroxy ester 16 in the context of the roflamycoin synthesis, as outlined in Scheme 7.21,22

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Another catalytic, asymmetric Mukaiyama aldol was developed by Evans and co-workers, using chiral copper- or tin-based bis-oxazoline catalysts (17–20) (Scheme 8). These reactions are noteworthy in that they allow the use of unusual electrophiles: pyruvate, benzyloxyacetaldehyde (21), and glyoxylates undergo aldol reaction with a large variety of nucleophiles—acetate- and propionate-derived silyl ketene acetics, thioacetals and dienolate 22—to give aldol adducts in high yields and excellent levels of optical purity.

These catalytic systems were successfully applied by Evans to the total syntheses of phorboxazole B\textsuperscript{23} and bryostatin 2\textsuperscript{24} (Scheme 9).

\[
\begin{align*}
\text{BnO} & \text{O} \quad 21 \\
\text{H} & \quad 22: R = \text{TMS} \\
\text{18} & \quad 85\% \text{ yield} \\
& \quad > 99\% \text{ ee} \\
\text{BnO} & \quad \text{O} \\
\text{H} & \quad 23 \\
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{O} \quad 24 \\
\text{Ph} & \quad \text{O} \\
\text{H} & \quad 25 \\
\text{19} & \quad 91\% \text{ yield} \\
& \quad > 94\% \text{ ee} \\
\text{N} & \quad \text{O} \\
\text{Ph} & \quad \text{O} \\
& \quad \text{StBu} \\
& \quad 26
\end{align*}
\]

Scheme 9

1.1.3.2. Crotylation and Allylation Reactions

Allylation and crotylation reactions have been extensively used for the stereocontrolled assembly of polyketides (Scheme 10). Due to the explosive development of this field over the last decades, a detailed description would go beyond the scope of this introduction and thus, only a general overview will be provided.\textsuperscript{25}

\begin{itemize}
\end{itemize}
The allylmetal to aldehyde additions have proven to be extremely successful for the construction of adjacent stereocenters. The reasons for the success of this method are manifold: (i) the high degree of enantio- and diastereoinduction; (ii) the ability to access different stereodyads and -triads; (iii) the inherent versatility of the obtained products towards further functionalization; (iv) the possibility to adapt the reactivity of the intervening species by careful selection of the involved metal.

One of the most intriguing features of these reactions is the dramatic relationship between the configuration of the product and the geometry of the starting alkene, dividing them into three mechanistically distinct classes: (i) additions wherein the syn/anti ratio of the formed products is reflected by the Z/E ratio of the starting olefinic bond (Type I) (ii) additions leading predominantly to syn products independent of the double bond configuration (Type II) (iii) additions leading to the preferential formation of anti products independent of the double bond geometry (Type III).

Type I allylmetal reagents include crotylboronates, crotyltrihalo- and trialkoxyisilanes, trialkylstannanes (thermally promoted reaction) and allylaluminum.

(26) Additions with aluminum, boron, chromium, indium, lithium, magnesium, samarium, silicon, tin, titanium, zinc and zirconium (among others) have been documented; see ref. 25.
species. They react through cyclic, six-membered transition states and undergo allylation reactions with aldehydes (27 $\rightarrow$ 28 or 29 $\rightarrow$ 30) faster than metallotropic rearrangement (27 $\rightleftharpoons$ 29), thus resulting in efficient translation of stereochemical information (Scheme 11).^{27}

Scheme 11

Type III crotylmetal reagents—including crotylchromium, crotyltitanium and crotylzirconium reagents—undergo metallotropic rearrangement (32 $\rightleftharpoons$ 35) faster than allylation with aldehydes (32 $\rightarrow$ 33 or 35 $\rightarrow$ 36). As for type I reagents, transition states involve closed, six-membered structures. In the case of crotylchromium reagents, the selectivity for the anti product is usually very high, independent of the geometry of the allylic bromide used (31 or 34) (Scheme 12).

(27) Indeed, some of these allylmetal reagents are configurationally stable and can be stored over extended periods of time.
Type II reagents include allyltrialkylsilanes and allyltrialkylstannanes and react with aldehydes through opened transition states, wherein an external Lewis acid is present to activate the aldehyde towards electrophilic attack.

Among the various metals encountered in these reactions, boron has found the most widespread application in the modular assembly of polyketides. Although the corresponding substrate-directed allylations and crotylations have been used with substantial success, it is the development of chiral reagents mainly by Brown\textsuperscript{28} (pinene-derived reagent 37), Hoffmann\textsuperscript{29} (pinacol-derived 38) and Roush\textsuperscript{30} (tartrate-derived 39) which had the greatest impact on polyketide synthesis (Figure 4).


1.1.3.3. Nitrile-Oxide Cycloadditions

Extensive efforts have been spent on the identification of novel methods to access aldol-like products in a straightforward and stereoselective manner. Although aldol additions and crotylations still remain the most widely used approaches, a number of innovative alternatives have emerged.

A conceptually different pathway was proposed by Curran and Torssell:31 the products of nitrile-oxide cycloadditions, isoxazolines 40, can be considered aldol surrogates and converted to β-hydroxy ketones 41 by N–O bond cleavage (Scheme 13). A variety of reagents have been reported for this type of cleavage, including mostly reductants like Ra–Ni, Mo(CO)₆ and SmI₂, but oxidative cleavage with ozone has also been documented.32

![Figure 4. Chiral allylation reagents.](image)

**Scheme 13.** (a) nitrile-oxide cycloadditions; (b) N–O bond reduction.


This intriguing concept found application in the total synthesis of polypropionate-derived natural product after the discovery by Kanemasa and development by Carreira of a general protocol for the stereocontrolled synthesis of isoxazolines: the hydroxyl-directed, magnesium(II)-mediated nitrile-oxide cycloadditions to chiral allylic alcohols (Scheme 14), proceeding via putative transition state 42. The high degree of regio- and stereocontrol observed in this reaction provided a viable entry to the synthesis of all possible diastereomers found in polypropionates and polyacetates.

![Scheme 14](image)

**Scheme 14.** (a) iPrOH (3.3 equiv), EtMgBr (3.0 equiv), CH₂Cl₂, 0 °C → RT.

1.1.3.4. Hetero-Diels–Alder Cycloadditions

A novel approach towards the assembly of polyketide-derived structures was forged by Danishefsky and co-workers in the context of their 6-deoxyerythronolide B synthesis. Based on the combination of reiterative Diels–Alder cycloadditions and stereoselective reactions, a general strategy was devised which gives access to skipped polyols.


The emphasis is on elaborating, by Diels–Alder reaction, branched pyranose rings, which are used as template for further functionality development and allow repetitive chain elongation by conversion of the C1 anomeric carbon into an aldehyde (Scheme 15).

1.2. Isolation of Leucascandrolide A

Leucascandrolide A\textsuperscript{(35)} (43), a doubly O-bridged macrolide of a new genus, was isolated in 1996 by Pietra and co-workers from a calcareous sponge, *Leucascandra caveolata* Borojevic and Klautau\textsuperscript{(36)}, along with another, smaller macrolide, leucascandrolide B (44)\textsuperscript{(37)} (Figure 5).

The sponge was collected by scuba diving during two expeditions along the Passe de Nakéty, eastern coast of New Caledonia, at depths of 20 to 40 meters: in September 1989 (3 kg of fresh weight, 200 g of freeze-dried weight) and in July 1992 (40 g of freeze-dried weight). When alive, the sponge was constituted of an arborescent brownish mass of tubules (5 × 5 to 25 × 25 cm overall dimensions) and turned to white when immersed in ethanol (Figure 6). After extraction with CH₂Cl₂, flash chromatography (eluting with MeOH) and further purification by HPLC (eluting with MeOH/H₂O 9:1), 70 mg of pure leucascandrolide A were obtained.

The sponge was regularly encountered at the location described above. However, in April 1995, only a few, quite small specimens could be found: since this kind of sponges are opportunistic and their life-cycle is limited to a few years, disappearance of *Leucascandra caveolata* possibly results from a major ecological change.
The fact that samples of *Leucascandra caveolata* collected in 1994 did not contain any trace of 43 or 44 suggests a microbial origin of these two macrolides. Their profound structural differences may be best rationalized by an assembly of different microbes. The occurrence in great abundance of 43 and 44 in the sample harvested in 1989 could be explained by the presence of extensive dead and thus possibly extensively colonized sponge. Therefore, these putative microbes appear opportunistic rather than symbiotic, explaining why they may or may not be found in different sponge samples, and why the structure of these macrolides are so unusual for calcareous sponges.

### 1.3. Biological Activity

The relatively small number of calcareous sponges found in nature have attracted the organic chemists much less than the widely spread demosponges. Only

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(38) These pictures are taken from: Borojevic, R; Klautau, M. *Zoosystena*, 2000, 22, 187–201.

(39) *Leucascandra caveolata*’s main symbiont, the cyanobacterium *Aphanocapsa feldmannii*, widely occurs in calcareous sponges, none of which, except *Leucascandra caveolata*, are known to produce macrolides.
few calcareas, like *Leucetta* and *Clathrina*, were systematically examined and all the metabolites found showed only scarce bioactivity. These metabolites were limited to 2-aminoimidazoles that incorporate one or two benzyl-substituted moieties. Leucascandrolide A is not only the first powerfully bioactive metabolite isolated from a calcareous sponge, but also the first macrolide ever found in calcareas.

The raw extracts from the sponge were strongly antimicrobial, toxic, and cytotoxic. Both the lipophilic and aqueous extracts from freeze-dried *Leucascandra caveolata* inhibit phytopathogenic fungi *Fusarium oxysporum*, *Helminthosporium sativum*, *Phytophthora hevea*, *Botrytis cinerea* and *Pyricularia oryzae* as well as animal pathogenic yeast *Candida albicans*. Furthermore, the lipophilic extracts proved strongly cytotoxic to both KB throat epithelial cancer cell lines (IC$_{50}$ 0.05 µg/ml for pure 43) and P388 murine leukemia cell lines (IC$_{50}$ 0.25 µg/ml for pure 43), while aqueous extracts were only KB active. In contrast to leucascandrolide A, leucascandrolide B shows only marginal cytotoxicity on tumor cell lines (IC$_{50}$ 5 µg/ml on KB cells and > 10 µg/ml on P388 cells) and no activity on *Candida albicans*.

It is well-worth noting that the macrolide moiety is essential to the cytotoxic activity, while the oxazole side chain contributes to the antifungal properties of

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leucascandrolide A. Indeed, the macrolide part 45 shows cytotoxic activity towards KB cells comparable to that of 43.

1.4. Structure

The composition C_{38}H_{56}N_{2}O_{10} was deduced from HR-EI-MS and 1D $^{13}$C NMR spectra and DEPT data: a total of thirty-eight $^{13}$C signals were found, which indicated the presence of one trisubstituted and three disubstituted olefinic double bonds, seven O-bound CH groups, two methoxy groups, twelve CH$_2$ groups, two C$_{sp}^3$H groups and three C-bound methyl groups, besides four signals at $\delta$(C) > 158 ppm. Detailed structural assignments were made possible by HMQC, HMBC, DQ-COSY and ROESY experiments.

In order to establish the absolute configuration by Mosher-ester analysis, the macrolide moiety was freed from the oxazole side chain at C5 by treatment of 43 with Na$_2$CO$_3$ in methanol, giving alcohol 45 and methyl ester 46 (Scheme 16). Scattered $\Delta\delta = \delta(S) - \delta(R)$ data was obtained from the C5-MTPA esters of 45 and thus precluded a reliable interpretation. A solution was found by converting alcohol 45 into its C5 epimer using a two-step reaction sequence: oxidation with PCC afforded the corresponding ketone and subsequent reduction with NaBH$_4$ gave C5 epi-45 with the hydroxyl group in equatorial position. Mosher-Ester analysis of C5 epi-45 allowed

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(43) Throughout the text, the atom numbering introduced by Pietra and co-workers will be used; see ref. 35.

for clear and unambiguous assignment of the (5R)-configuration in natural leucascandrolide A.

Scheme 16. (a) Na₂CO₃, MeOH, RT, 2 d, 77%; (b) PCC, CH₂Cl₂, RT, 2 h, 70%; (c) NaBH₄, EtOH, RT, 1 h, 86%.

Leucascandrolide A displays several distinctive architectural features: The structure is characterized by extensive 1,3-dioxygenation, a single methyl branching (at C12), an (E)-olefinic bond (C18–C19) and a peculiar side chain bearing a 2,4-disubstituted oxazole and two (Z)-olefinic bonds (C2′–C3′ and C9′–C10′). Its nucleus consists of an eighteen-membered macrolactone which encompasses two trisubstituted tetrahydropyran rings whose endocyclic oxygens are directed towards the interior of the macrolide.
Figure 7. Energy-minimized structure of 45 (generated by semi-empirical calculations at the PM3 level).

Several important conclusions concerning the preferred conformation of the macroclide moiety 45 can be drawn from the energy-minimized structure represented in Figure 7:\textsuperscript{45} (i) the 2,6-cis-disubstituted tetrahydropyran ring possesses a chair conformation with both C3 and C7 substituents in equatorial and the C5 hydroxy group in axial positions; (ii) the 2,6-trans-disubstituted tetrahydropyran ring adopts a twist-boat conformation with all three alkyl substituents oriented pseudo-equatorially; (iii) the C9 methoxy ether resides peripherally, outside of the confines of the macrocyclic structure.

\textsuperscript{45} Calculations (semi-empirical) were performed at the PM3 level using PC Spartan Pro for Windows.
1.5. Syntheses of Leucascandrolide A

1.5.1. Introduction

The total synthesis of natural products has constituted, over the past century, an important area of organic chemistry. Not only does it represent the ultimate way to confirm a proposed structure, but it also allows access to substances which are not isolable from nature in amounts significant enough for full biological testing and, in some cases, for their commercial use as drugs.

After the isolation of leucascandrolide A in 1996 by Pietra and co-workers, numerous synthetic groups have embarked on programs aiming at its total synthesis. The reasons for this considerable interest are manifold: the lack of availability from natural sources, the exceptional bioactivity as well as the aesthetically appealing and challenging architecture render leucascandrolide A an ideal target for total synthesis. Accordingly, considerable efforts have been made by several research groups, culminating in the pioneering total synthesis reported by Leighton, which confirmed the relative and absolute configuration originally assigned by Pietra. A total synthesis by Kozmin and Paterson as well as formal syntheses by Rychnovsky and Wipf.


(47) In the case of discodermolide, full biological testing was possible only after sufficient quantities of material were made accessible by total synthesis: Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621–12622.


were also documented. Additional interesting studies by Crimmins, Hoffmann, O’Doherty, and Panek as well as unpublished studies by Williams underline the importance and appeal of this natural product.

Among these studies, remarkable strategies, approaches and chemical curiosities can be found, and the most interesting findings and key steps will be shortly described and critically evaluated in the next paragraphs.

1.5.2. A Carbonylation Approach by Leighton

A carbonylation-based approach was used by Leighton and co-workers to assemble the leucascandrolide A macrolide: protected 1,3-syn-diol 50 is prepared from homoallylic alcohol 47 and ketone 48 by Yb(OTf)₃-catalyzed oxymercuration of the derived hemiacetal, followed by rhodium(I)-catalyzed formylation of the organomercurial species 49 (Scheme 17). The syn selectivities observed in these reactions are usually very high.

(57) Personal communication.
Scheme 17: (a) 5 mol% Yb(OTf)₃, HgCl(OAc), 0 °C → RT; (b) 4 mol% Rh(acac)(CO)₂, 4 mol% P(O–o-tBuC₆H₄)₃, 0.5 equiv DABCO, 800 psi CO/H₂, EtOAc, 50 °C.

As depicted in Scheme 18, a total of three carbonylation reactions were used, and their combination with either crotylation or allylsilylation methodology allowed for the straightforward construction of the polyacetate portion of leucascandrolide A by well-established methods with moderate to good diastereoselectivities.

Scheme 18. (a) HgCl(OAc), acetone, 5 mol% Yb(OTf)₃, 0 °C → RT, 76%; (b) 4 mol% Rh(acac)(CO)₂, 4 mol% P(O–o-tBuC₆H₄)₃, 0.5 equiv DABCO, 800 psi 1:1 CO/H₂, EtOAc, 50 °C, 62%; (c) (−)-Ipc₂B((E)-crotyl), BF₃·Et₂O, THF, −78 °C;
NaOH, H₂O₂, 67% (d.r. > 10:1); (d) 2 mol% Rh(acac)(CO)₂, 8 mol% PPh₃, 400 psi 1:1 CO/H₂, THF, 50 °C, 89% (d.r. > 10:1); (e) Ac₂O, DMAP, pyr., CH₂Cl₂; (f) allyl-TMS, Ti(O–iPr)₂Cl₂, CH₂Cl₂, −78 °C (d.r. > 10:1); (g) TBAF, THF, 62% over 3 steps; (h) (COCl)₂, DMSO, Et₂N, CH₂Cl₂, −78 °C to −40 °C; (i) allyl-(-)-Ipc₂B, Et₂O, −78 °C → RT; NaOH, H₂O₂, 75% over 2 steps (d.r. > 10:1); (j) TBDPSCl, imid, DMF, 99%; (k) AcOH, H₂O, 40 °C, 98%; (l) 10 mol% PdCl₂, 4 equiv CuCl₂, 1 atm CO, MeOH/PhCN (1:1), 75% (d.r. > 10:1); (m) Me₂OB₉₄, Proton Sponge, 4 Å M.S., CH₂Cl₂, 96%; (n) O₃, CH₂Cl₂, −78 °C; PPh₃, RT, 93%; (o) 4-methyl-1-pentyn, Cy₂BH, Et₂Zn, N,N-di-n-butyl amino ethanol, Ti(O–iPr)₄, toluene, −40 °C → −20 °C, 45% (d.r. = 3:1); (p) TMSOK, Et₂O; (q) 2,4,6-trichlorobenzoyl chloride, Et₂N, DMAP, PhH, 76%; (r) TBAF, THF, 77%.

The synthesis by Leighton highlights the utility of carbonylation chemistry for the synthesis of complex polyketide-derived natural products. Despite its highly linear character, it proceeds in only twenty steps (longest linear sequence) and 1.2% overall yield.

1.5.3. The Rychnovsky Strategy

The strategy followed by the Rychnovsky group utilized the development of a Mukaiyama aldol–Prins cyclization cascade (Scheme 19).⁵¹

\[
\text{Ph} \quad \text{O} \quad \text{O} \quad \text{R} \\
\text{Ph} \quad \text{O} \quad \text{OH} \quad \text{R}
\]

Scheme 19. a) CSA, CH₂Cl₂, 0 °C.

In order to prepare the requisite building blocks, the strategy makes use of asymmetric hydrogenation reactions to establish the C3 and C15 stereocenters (Scheme 20). The challenging introduction of the stereogenic C12 center is achieved by asymmetric enolate alkylation.

The full potential of this approach was demonstrated by the highly convergent coupling of aldehyde 52 (prepared in ten steps from keto ester 51) and enol ether 54.
(prepared in eight steps from aldehyde 53) with simultaneous formation of two C–C bonds and installation of the C7 and C9 stereogenic centers. The relatively high diastereomeric ratio (5.5:1) obtained in the key step is noteworthy, given the limited stereoinduction observed in closely related model studies (1.1:1 to 1.8:1).

Scheme 20. (a) \([R]-\text{BiINAP}\)-RuCl\((C_6H_6)\), 80 atm \(H_2\), EtOH, 96% \((ee > 94\%); (b) \text{TBSCI}, \text{imid}, \text{DMF}, 86\%; (c) \text{DIBAL–H}, \text{THF}, –25 °C, 88\%; (d) \text{PPh}_3, I_2, \text{imid}, \text{CH}_2\text{Cl}_2, 100\%; (e) \text{LDA}, (–)-\text{pseudoephedrine propionamide}, \text{LiCl}, \text{THF}, –78 °C, 98\% (d.r. > 20:1); (f) 1.0 m aq. \text{H}_2\text{SO}_4, \text{dioxane}, 95 °C, 77\%; (g) \text{DIBAL–H}, \text{CH}_2\text{Cl}_2,
Despite the successful implementation of this elegant key step, the elaboration of the coupling product 55 towards the fully functionalized macrolide 45 is rendered awkward by the plethora of functional-group interconversions and oxidation-state adjustments. The synthesis proceeds in twenty-eight steps (longest linear sequence) and 0.77% overall yield.

1.5.4. The Formal Synthesis by Wipf

The highly convergent synthesis proposed by Wipf and co-workers envisions formation of the C9–C10 bond by uniting a C9 dithiane and a C10 iodide.52a

This work is highlighted by a bidirectional synthesis of the C1–C9 portion of leucascandrolide A: allyl sulfide 56 was converted into bis-sulfide 57, followed by double Evans–Mislow rearrangement to furnish achiral diol 58 (Scheme 21). The meta-disubstituted arene served as precursor for a 1,3-dicarbonyl compound,
revealed by Birch reduction followed by ozonolysis of the resulting 1,4-cyclohexadiene 59.\cite{60}

\[
\begin{align*}
\text{a)} & \quad \text{nBuLi, THF, } -78 \, ^\circ\text{C}; \quad m-(\text{CH}_2\text{Br})_2\text{C}_6\text{H}_4, \quad 78\%; \\
\text{b)} & \quad \text{mCPBA, MeOH, Et}_3\text{NH}, \quad 81\%; \\
\text{c)} & \quad \text{NaH, THF, TBSCI, } 73\% \text{ based on rec. SM}; \\
\text{d)} & \quad \text{(-)-DIPT, Ti(PrO)_4, TBHP, } 86\%; \\
\text{e)} & \quad \text{Red-Al, THF, } -15 \, ^\circ\text{C}, \quad 96\%; \\
\text{f)} & \quad \text{TIPSCI, imid, CH}_2\text{Cl}_2, \quad 91\%; \\
\text{g)} & \quad \text{O}_3, \quad \text{CH}_2\text{Cl}_2, \quad -78 \, ^\circ\text{C}; \quad \text{PPh}_3; \\
\text{h)} & \quad \text{(CH}_2\text{O})_2\text{H}, \quad \text{TsOH, PhH, reflux, } 62\% \text{ over 2 steps}; \\
\text{i)} & \quad \text{Li^0, NH}_3, \quad \text{THF, } -50 \, ^\circ\text{C}; \quad \text{EtCMe}_2\text{OH}, \quad 89\%; \\
\text{j)} & \quad \text{O}_3, \quad \text{EtOAc, } -78 \, ^\circ\text{C}; \quad \text{H}_2, \quad \text{Pd(OH)}_2; \\
\text{k)} & \quad \text{TsOH, PhH, reflux, } 43\% \text{ over 2 steps}; \\
\text{l)} & \quad \text{H}_2, \quad \text{Pd/C, EtOAc, } 71\%; \\
\text{m)} & \quad \text{L-Selectride, THF, } -78 \, ^\circ\text{C}, \quad 79\%; \\
\text{n)} & \quad \text{TBDPSCI, imid, DMAP, DMF, } 83\%; \\
\text{o)} & \quad \text{CH}_2(\text{CH}_2\text{SH})_2, \quad \text{TiCl}_4, \quad \text{CH}_2\text{Cl}_2, \quad 64\%.
\end{align*}
\]

The synthesis of iodide 63 is based on asymmetric crotylation and allylsilylation chemistry to efficiently install the C11, C12 and C15 stereocenters (Scheme 22). An unexpected stereochemical outcome at C17 was observed in the conversion of aldehyde 61 into alcohol 62 by reagent- and substrate-controlled vinylzinc addition. The newly formed stereogenic center was shown to possess (S)-configuration and not the desired (R)-configuration. In order to account for this surprising stereochemical induction, the macrolactonization needed carried out under Mitsunobu conditions to give lactone 45 with concomitant inversion of the C17 center.

\(\text{(60)}\) The use of substituted arenes as a masked form of diketones has been reported by Evans and co-workers in the course of their total synthesis of bryostatin 2, see ref. 24a.
This synthesis proceeds in twenty-five steps (longest linear sequence) and an overall yield of 0.24%.

1.5.5. Total Synthesis by Kozmin

In 2001, Kozmin reported the synthesis of a racemic C1–C15 fragment of leucascandrolide A. Formation of the 2,6-cis-disubstituted tetrahydropyran ring
was achieved by intramolecular Prins cyclization of 67, leading, however, to an equatorial C5 hydroxyl group in 68. Although methyl ketone 69 is accessed only as a racemate, its expedient synthesis in only three steps from commercially available heptadienol 66 and known 4-methoxy-3-butenone (65) is noteworthy (Scheme 23).

Coupling of methyl ketone 69 with aldehyde 70 and further elaboration of the product led to key intermediate 71 (Scheme 24). Diastereoselective, platinum-mediated hydrosilylation of 71 gave silacycle 72, which, following protodesilylation, afforded the targeted C1–C15 fragment 73.

The salient and most distinctive feature of this synthesis is, with no doubt, the stereoselective introduction of the C12 methyl group by platinum-catalyzed hydrosilylation. While other groups have introduced this methyl group by asymmetric auxiliary-mediated enolate alkylation or crotylation (vide supra), this route constitutes an elegant alternative to the ‘classical’ pathways. The devised strategy permits ready access to highly functionalized fragment 103 in an amazing nine steps.
Scheme 24. (a) Cy₂BCl, Et₃N, -78 °C, 74%; (b) Sml₂ (30 mol%), CH₃CHO, THF, -5 °C, 92%; (c) MeOTf, 2,6-di-tert-butyl pyridine, 71%; (d) LiAlH₄, Et₂O, -78 °C, 86%; (e) (Me₂HSi)₂NH, H₂PtCl₆, 50 °C; (f) TBAF, DMF, 70 °C, 54% over 2 steps (d.r. = 87:13).

Recently, the total synthesis of leucascandrolide A in ten steps from intermediate 73 was reported (Scheme 25). Particularly noteworthy is the spontaneous macrolactolization of intermediate hydroxy aldehyde 75, which is further oxidized to the corresponding lactone with PCC. Coupling of the oxazole side chain under Mitsunobu conditions, with inversion of configuration at C5, completes the total synthesis of leucascandrolide A (43).

With only nineteen steps, this synthesis by Kozmin is shortest (1.8% overall yield). However, the major drawbacks of this approach are twofold: (i) the synthesis of leucascandrolide A in racemic form; (ii) and the associated, fairly nonselective reduction of ketone 74 to the corresponding secondary alcohol.⁶¹

(61) A reagent-controlled, asymmetric reduction would have been a viable alternative to L-Selectride for an enantiomerically pure ketone 74, but is precluded for racemic mixtures.
1.5.6. Synthesis of the C1–C13 Fragment by Crimmins

The synthesis of a C1–C13 fragment of leucascandrolide A has been reported by Crimmins and co-workers using a metalated-pyrone addition to β-alkoxy aldehyde 79 to construct the key spiroketal intermediate 80 (Scheme 26). 53
The rigid, bicyclic template allows for the stereocontrolled introduction of the C5 and C9 stereocenters by ketone reduction and of the C3 center by conjugate cuprate addition. The stereo- and regioselective cleavage of the anomeric spirocenter in 81 efficiently leads to the desired 2,6-cis-disubstituted tetrahydropyran ring 82.
1.6. Conclusion

A large number of methods have emerged which allow access to the myriad polyketides found in nature. Their combination with well-established methods for further stereocontrolled functionalization enables the synthesis of virtually all naturally occurring and imaginable arrays of stereocenters. Nonetheless, in spite of the remarkable intellectual and experimental foundations of organic chemistry, great difficulties still beset the total synthesis of complex molecules and creativity is required to reach these targets.

The fascination emanating from leucascandrolide A becomes manifest in the increasing number of published reports: no less than five syntheses have been documented in the last two years, and a couple of research groups are close to reaching this goal. The importance of this natural product as measure of the state-of-the-art in synthetic organic chemistry is witnessed by the tremendous efforts spent by the chemical community on its synthesis and the number of innovative routes devised.
2. Synthetic Planning

2.1. Introduction

When we started our work on leucascandrolide A, none of the aforementioned syntheses had been published, leaving us ample freedom in the identification of an appropriate and innovative route.

The requirements for a route are manifold:

- The value of convergency is well-known in the synthesis of highly functionalized natural products, and we obviously hoped to make our synthesis as convergent as possible.\(^\text{(62)}\)

- Furthermore, the synthetic plan should be flexible enough to circumvent obstacles which would undoubtedly arise along the way. Aware of the innumerable unexpected failures and dead ends encountered previously in the

total synthesis of highly functionalized natural products, the significance of flexibility cannot be overstated.63

- The synthesis should be amenable to the facile and straightforward preparation of analogues. The potentially attractive elements for alteration should be introduced as late as possible.

- Last but not least, total synthesis is the ideal proving ground for the application of newly developed methods to multifunctional substrates, and these results may be of great value to explore the limitations of existing systems. Finally, the chosen target molecule, with its structural features, and the methods sought to be applied should harmonize in order to allow for a concise synthesis, avoiding the excessive use of functional-group interconversions and protective-group manipulations.

2.2. Retrosynthetic Analysis

The obvious disconnection at the C1’–O ester bond led us to envision the introduction of the oxazole-bearing side chain as ultimate step. Coupling of macrolide moiety 45 obtained by Pietra from degradation and side chain 78 was thought to be achieved by esterification (Scheme 27).

The macrolide moiety 45, containing all the stereogenic centers of leucascandrolide A, represents the major synthetic challenge.

In view of chemoselectivity problems associated with the C18–C19 double bond and prospective analogue synthesis, we planned to introduce the C17 side chain by trans-selective olefination at a late stage, the requisite aldehyde being masked as a 1,3-dioxolane throughout the synthesis (Scheme 28).

The macrocyclization reaction, planned by lactonization of an ω-hydroxy acid, was believed to be facilitated by the presence of both tetrahydropyran rings because of reduced degrees of freedom as compared to a linear substrate.

One of the major structural characteristics of leucascandrolide A is the presence of two trisubstituted tetrahydropyran rings. The 2,6-cis substitution of the C11–C15 heterocyclic ring requires a different strategy from that employed for the assembly of the 2,6-trans-disubstituted C3–C7 tetrahydropyran. Our initial thoughts focused on
ring-closure by C–O bond formation for both of them. However the reaction conditions needed to be adapted to the different substitution patterns.

Unraveling of the 2,6-cis-disubstituted tetrahydropyran ring in 83 could be achieved by various ways: Displacement of a C15 sulfonate by an incoming C11 hydroxyl group would proceed with inversion of configuration at C15 and would thus be a viable approach, requiring prior incorporation of the C15 stereocenter (84 → 83). Yet this idea was let down in its fledgling stages because of potential problems associated with chemoselective sulfonylation and the identification of a more tempting strategy, requiring the elaboration of a stereochemically less complex precursor: electrophile-mediated intramolecular cyclization onto a carbon–carbon double bond (85 → 83). In this regard, the presence of the C17 hydroxyl group was speculated to facilitate the stereochemical course of the reaction. While the advantages of this approach over the sulfonate-displacement strategy are obvious, electrophile-mediated cyclizations leading to the selective formation of 2,6-trans-substituted tetrahydropyrans are unprecedented.

Further simplification of cyclization precursor through a diastereoselective methyl ketone aldol transform at C9–C10 would reduce the synthetic challenge to the preparation of two key intermediates of comparable size and roughly equal stereochemical complexity (Scheme 30): aldehyde 86 and methyl ketone 87, which
are readily amenable to asymmetric synthesis by methods recently developed in our group.

In contrast to the aforementioned tetrahydropyran ring, the 2,6-cis-disubstituted tetrahydropyran found in methyl ketone 87 may be formed by intramolecular conjugate addition of a tethered oxyanion, if the reaction conditions were appropriately tuned as to give the thermodynamic product. The requisite hydroxy ester was believed to be accessible from crotonaldehyde (88) and trimethylsilyldienolate 11 by a catalytic, asymmetric aldol addition (Scheme 31).

Aldehyde 86 would be accessed from a propargylic alcohol prepared by addition of alkyne 90 to (R)-isopropylidene glyceraldehyde (89) (Scheme 32).
Our retrosynthetic analysis of the C5 oxazole side chain 78 is outlined in Scheme 33. Given the inherent instability and reactivity of both (Z)-alkenes, our approach envisioned their unraveling from the corresponding alkynes as the last step. Formation of the 2,4-disubstituted oxazole 91 was planned by cyclodehydration of a β-aldehyde amide, prepared from amino alcohol 92 and acid 93.

2.3. Conclusion

The devised route would allow assembly of the macrolide moiety of leucascandrolide A in a straightforward, convergent manner. Key issues to be addressed include (i) the diastereoselective addition of alkyne 90 to the inherently unstable aldehyde 89 bearing a heteroatom at Cα; (ii) the diastereoselective coupling of methyl ketone 87 and aldehyde 86; (iii) the development of a trans-selective tetrahydropyran synthesis from a 6-hydroxy alkene; (iv) macrolactonization; (v) coupling of the C5 and C17 side chains to the macrolide.
3.1. Synthesis of the Aldehyde Fragment

The synthesis of leucascandrolide A commenced with the preparation of known alcohol 98 from (1R,2R)-(−)-pseudoephedrine propionamide 94 by a high-yielding four-step reaction sequence reported by Bode and Carreira in the course of their total syntheses of epothilone natural products (Scheme 34).64

Asymmetric alkylation of 94 with allyl iodide, using the conditions reported by Myers, was followed by BH$_3$·NH$_3$-mediated reduction of amide 95 to alcohol 96.65 Protection of the primary hydroxyl group as TIPS ether under standard conditions

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(64) (a) Bode, J. W.; Carreira, E. M. J. Am. Chem. Soc. 2001, 123, 3611–3612; (b) see ref. 33c; (c) Fräfel N., Diploma Thesis, ETH Zürich, 2000.

and hydroboration of the monosubstituted double bond in 97 with 9-BBN gave the desired compound 98 in 75% yield over four steps.

Oxidation of the alcohol in 98 to the corresponding aldehyde 99 was conveniently achieved with the biphasic NaClO/TEMPO/KBr system. Conversion to the terminal alkyne 90 could be carried out by various methods. Addition of lithiated trimethylsilyl diazomethane was found to give the best yields (90% over two steps). On large scale, however, the use of Ohira reagent (100) using the protocol developed by Bestmann and Roth was the method of choice because of its ease of execution, giving alkyne 90 in 87% yield over two steps (Scheme 35).

![Scheme 35](attachment:Scheme35.png)

Scheme 35. (a) bleach, TEMPO (2 mol%), KBr (10 mol%), CH₂Cl₂, pH 8.6 buffer, 0 °C, 15 min; (b) 100, K₂CO₃, MeOH, 16 h, RT, 87% over 2 steps.

3.1.1. Asymmetric Alkyne Additions to Aldehydes

Just prior to the beginning of our leucascandrolide A endeavor, Douglas E. Frantz, a co-worker in the Carreira group, developed a procedure for the mild generation of zinc acetylides and their addition to various electrophiles, in particular

nitrones and aldehydes.\textsuperscript{71} In collaboration with Roger Fässler, a general protocol for the asymmetric addition of in situ-generated zinc alkynilides to aldehydes was elaborated. Treatment of terminal alkynes 101 with Zn(OTf)\textsubscript{2}, Et\textsubscript{3}N and N-methyl ephedrine (103)\textsuperscript{72} at ambient temperature in toluene followed by addition of aldehydes 102 resulted in the clean and highly enantioselective formation of propargylic alcohol 104 in high yields (Scheme 36).\textsuperscript{73}

\begin{center}
\textbf{Scheme 36}
\end{center}

This first generation procedure gave excellent asymmetric induction for aromatic (entry 1), $\alpha,\beta$-unsaturated (entry 2), $\alpha$-branched (entries 3–5) and highly hindered aldehydes (entry 6) (Table 1).

\begin{flushleft}
\end{flushleft}

\begin{flushleft}
\textsuperscript{(72)} Importantly, both enantiomers of N-methyl ephedrine are commercially available.
\end{flushleft}

\begin{flushleft}
\end{flushleft}
Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Alkyne</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph(CH₂)₂</td>
<td>52</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>PhCH=CH</td>
<td>Ph(CH₂)₂</td>
<td>39</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>iPr</td>
<td>Ph(CH₂)₂</td>
<td>90</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>tBu</td>
<td>Ph(CH₂)₂</td>
<td>84</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>Cy</td>
<td>Ph(CH₂)₂</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>Me₃CCH₂</td>
<td>Ph(CH₂)₂</td>
<td>72</td>
<td>99</td>
</tr>
</tbody>
</table>

A more general procedure, consisting in slow addition of the aldehyde to a solution of the zinc alkynilide, was discovered and optimized by Fernando López and expands the scope of the reaction to aldehydes more prone to enolization.⁷⁴

The total synthesis of leucascandrolide A provided the opportunity to investigate whether zinc-acetylide additions can be carried out with highly functionalized aldehydes on preparatively useful scale. Especially the use of chiral aldehydes and/or alkynes as substrates, leading to the formation of diastereomeric propargylic alcohols, was left unexplored by previous work and thus seemed particularly alluring.⁷⁵

As pointed out earlier in the retrosynthetic analysis (vide supra), we wished to use (R)-isopropylidene glyceraldehyde as electrophile and an optically active alkyne as nucleophile. While the “chiral information” contained in the nucleophilic

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(⁷⁵) The addition of a chiral aldehyde possessing a remote stereocenter to 3-methyl-butyn-3-ol was reported by Carreira and Bode in the recently published epothilone A synthesis. See ref. 33c for details.
component was expected not to strongly bias the stereoinduction because of the remoteness of the stereogenic center, the situation was less clear as far as the aldehyde was concerned. Of additional importance was the question whether (R)-isopropylidene glyceraldehyde (89) would be compatible with the reaction conditions. Thus, the use of this capricious aldehyde would constitute a notable and useful extension of the method.

The zinc alkylnilide of 90, prepared in situ by reaction of 90 with Zn(OTf)$_2$ (1.1 equiv), (−)-N-methyl ephedrine (1.1 equiv) and Et$_3$N (1.2 equiv), cleanly added to 89 to give propargylic alcohol 105 in 75% yield and 94:6 diastereoselectivity, favoring the syn configuration (Scheme 37).$^{76}$ In sharp contrast to the second-generation procedure, best results were obtained when the aldehyde was added in one portion.

![Scheme 37.](image)

In contrast, when (+)-N-methyl ephedrine was used instead, under otherwise identical conditions, product 106, displaying an anti configuration, was obtained as a

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(76) (R)-isopropylidene glyceraldehyde (89) was prepared in 2 steps from D-mannitol and carefully distilled immediately prior to use. The yield of the addition reaction was shown to be highly dependent on the quality of the aldehyde: Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. J. Org. Chem. 1991, 56, 4056–4058.
sole product, indicating that reagent control is dominant in this addition.\textsuperscript{77} The lack of diastereoselectivity observed with the corresponding lithium alkynilide underscores the significance of these results.\textsuperscript{78}

The sense of stereochemical induction was confirmed by \textit{Ley} oxidation\textsuperscript{79} of 105 to the corresponding ketone 107 (TPAP, NMO, 4 Å M.S., CH\textsubscript{2}Cl\textsubscript{2}, 75%) and subsequent asymmetric hydrogenation to 105 using \textit{Noyori’s} catalyst 108.\textsuperscript{80}

\begin{center}
\textbf{Scheme 38.} (a) TPAP, NMO, 4 Å M.S., CH\textsubscript{2}Cl\textsubscript{2}, 75%; (b) 108, iPrOH, RT.
\end{center}

\textbf{3.1.2. Reduction of Propargylic Alcohols}

Next, we turned our attention to the reduction of propargylic alcohol 105 to the corresponding allylic alcohol. While (\textit{Z})-isomers are conveniently obtained under mild conditions by hydrogenation of carbon–carbon triple bonds, methods for their selective conversion to (\textit{E})-olefins are scarce and often not tolerant of a wide variety of functional groups.


\textsuperscript{(78)} (a) Additions of lithium acetylides to this aldehyde are known to be fairly nonselective: Kang, S. H.; Kim, W. J. \textit{Tetrahedron Lett.} 1989, 30, 5915–5918; (b) for an overview on the addition of lithium, magnesium and zinc nucleophiles to isopropylidene glyceraldehyde, see: Mengel, A.; Reiser, O. \textit{Chem. Rev.} 1999, 99, 1191–1223.


\textsuperscript{(80)} The reaction was stopped before full conversion.
The most widely used methods include dissolving metal reductions (Na/NH₃), low-valent chromium salts and hydroalumination reagents. An intriguing hydrogenation catalyst was reported by Bayer and co-worker: palladium on poly(ethylenimine) support, when bound to benzonitrile, was shown to reduce 2-pentyne to (E)-2-pentene selectively. However, in our hands and with our substrate, this catalyst proved futile.

Hydroalumination of alkenes and alkynes at high temperature and high pressure has been known for a long time. A pronounced positive effect on the ease of reduction is observed when a neighboring hydroxyl group is present because of the formation of intermediate alkoxy hydridoaluminate, facilitating intramolecular hydride delivery (Scheme 39) and allowing for reduction at ambient temperature and atmospheric pressure. These reactions appear to be quite sensitive to solvent effects and THF was found to be the solvent of choice for the selective formation of (E)-olefins.

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(84) A pronounced inverse correlation between the Lewis basicity of the solvent and the extent of cis reduction was observed: (E)-olefins are obtained in THF and E/Z mixtures in Et₂O. For a possible rationale, see: (a) Grant, B.; Djerassi, C. J. Org. Chem. 1974, 39, 968–970; (b) Blunt, J. W.; Hartshorn, M. P.; Munro, M. H. G.; Soong, L. T.; Thompson, R. S.; Vaughan, J. J. Chem. Soc. Chem. Commun. 1980, 820–821.
Reduction of propargylic alcohol 105 to the corresponding (E)-allylic alcohol using LiAlH₄ in THF was followed by benzylation under standard conditions (BzCl, Et₃N, CH₂Cl₂) to give benzoate 109 in 90% over two steps (Scheme 40). No trace of (Z)-isomer 110 could be detected by ¹H NMR spectroscopy.

Deprotection of the triisopropylsilyl ether 85 in 109 with TBAF (96%) and subsequent Ley oxidation⁷⁹ (TPAP, NMO, 4 Å M.S., CH₂Cl₂) of the resulting alcohol 111 furnished the targeted aldehyde 112 in 87% yield. We were pleased to find that under these mild oxidation conditions, no epimerization at Cα was observed.

3.1.3. Conclusion

The preparation of 112 concluded the synthesis of the aldehyde fragment. Noteworthy is the use of the alkyne addition to (R)-isopropylidene glyceraldehyde, which was essential to the elaboration of propargylic alcohol 105 in multi-gram quantities and high stereoselectivity. Aldehyde 112 is obtained in seven steps and 49% overall yield from the known alcohol 98.

3.2. Synthesis of the Methyl Ketone Fragment

3.2.1. Copper(I)-Catalyzed Asymmetric Aldol Additions

The asymmetric dienolate addition to aldehydes catalyzed by a copper(I) fluoride complex was discovered by Jochen Krüger, a postdoctoral fellow in the Carreira group (Scheme 41).86 The catalyst is easily prepared in situ by premixing Cu(OTf)$_2$, Tol-BINAP and $n$Bu$_4$NPh$_3$SiF$_2$ (TBAT) in THF at room temperature.87

![Scheme 41](image)

(86) (a) Krüger, J.; Carreira, E. M. J. Am. Chem. Soc. 1998, 120, 837–838; furthermore, a titanium-catalyzed aldol addition of dienolate 11 has been reported: see ref. 20b and 22a for details.

(87) The use of TBAT as anhydrous fluoride source has been reported and extensively used by DeShong. $n$Bu$_3$NPh$_3$SiF$_2$ is conveniently prepared in two steps from triphenylsilanol, aqueous hydrofluoric acid and TBAF: (a) Pilcher, A. S.; Ammon, H. L.; DeShong, P. J. Am. Chem. Soc. 1995, 117, 5166–5167; (b) Handy, C. J.; Lam, Y. F.; DeShong, P. J. Org. Chem. 2000, 65, 3542–3543.)
High yields and excellent levels of asymmetric induction for a variety of aromatic (entries 1 and 2) and $\alpha,\beta$-unsaturated aldehydes (entries 3–5) have been reported. Although the enantioselectivities observed for additions to aliphatic aldehydes are equally good (entry 6), the yields diminish considerably (< 40%) (Table 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
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<td>94</td>
</tr>
<tr>
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<td><img src="image6" alt="Aldehyde" /></td>
<td>&lt; 10</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 2

Mechanistically, this addition process is different from the vast majority of Mukaiyama aldol additions in that it proceeds by nucleophilic activation via chiral metalloenolate 113. The proposed catalytic cycle is depicted in Scheme 42.88,89 Generation of 113 is followed by the addition process, giving rise to copper aldolate 114. The catalytic cycle is completed by regeneration of metalloenolate 113 by metal–silicon exchange with 11 and associated formation of the aldol adduct 115.


This process is highly efficient for the rapid access to enantiopure $\delta$-hydroxy-$\beta$-keto esters and has proven successful in two synthetic applications.\(^\text{90}\)

In the context of our leucasandrolide A synthesis, we wished to apply asymmetric dienolate additions to aldehydes to further demonstrate the efficiency of the process and the versatility of the obtained products towards subsequent functionality development. In this view, the synthesis of the methyl-ketone fragment commenced with the enantioselective addition of TMS-dienolate 11\(^\text{91}\) to crotonaldehyde (88) using the previously described (R)-Tol-BINAP copper(I) fluoride complex, prepared in situ from (R)-Tol-BINAP, copper(II) triflate and \(n\)Bu\(_4\)NPh\(_3\)SiF\(_2\) (Scheme 43).

---


\(^{91}\) 11 is readily prepared from commercially available 2,2,6-trimethyl-[1,3]dioxin-4-one by treatment with LDA and subsequent enolate quenching with TMSCl: see Experimental Part.
This reaction can be conducted on multi-gram scale, utilizing as little as 2 mol% of catalyst.\(^{(92)}\) Dioxenone 116 was obtained with high degrees of enantioselectivity (91% ee as determined by HPLC), albeit relatively low yield (44%). The C=O addition reactions to crotonaldehyde are typically executed only with some difficulty, because of the susceptibility of the aldehyde towards polymerization; thus, formation of product 116 in high levels of enantioselectivity is noteworthy.

Conversion of 116 to keto ester 118 (78%) was achieved by thermal retro-Diels–Alder reaction leading to acetone extrusion and trapping of the intermediate ketene 117 with 1-butanol (used as solvent) (Scheme 44).\(^{(93)}\) The choice of the solvent was motivated by the relatively high temperatures needed for ketene formation (at least 110 °C; bp (\(n\)BuOH) = 118 °C).

\[(\text{116}) \xrightarrow{\text{a)}} (\text{118})\]

\[\text{Me} \xrightarrow{\text{O}} \text{O} \xrightarrow{\text{Me}} \text{Me} \xrightarrow{\text{OH}} \text{Me} \xrightarrow{\text{O}} \text{Me} \xrightarrow{\text{OH}} \text{OH} \xrightarrow{\text{O}} \text{OBu}\]

\[\text{116} \xrightarrow{\text{a)}} \text{117} \xrightarrow{\text{Me}} \text{118}\]

\[\text{116} \xrightarrow{\text{a)}} \text{117} \xrightarrow{\text{Me}} \text{118}\]

\[\text{Me} \xrightarrow{\text{O}} \text{O} \xrightarrow{\text{Me}} \text{Me} \xrightarrow{\text{OH}} \text{Me} \xrightarrow{\text{O}} \text{Me} \xrightarrow{\text{OH}} \text{OH} \xrightarrow{\text{O}} \text{OBu}\]

(92) The reaction run with as much as 140 mmol of TMS-dienolate 11 without deterioration of the optical purity of the aldol adduct 116.

3.2.2. Initial Approach to the Tetrahydropyran Ring

In a first approach, conversion of keto ester 118 to the corresponding syn diol was achieved by stereoselective ketone reduction using the method developed by Prasad (NaBH₄, Et₃B, MeOH, THF). The observed selectivity can be rationalized by chelation-controlled 1,3-induction: the intermediate chair-like transition state, where R¹ and R², as the large substituents, occupy equatorial positions, is proposed. Intermolecular hydride delivery occurs axially to give the syn diol as the preferred product (Scheme 45). 

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
R^1 & \quad \text{R}^2 \\
\text{a)} & \quad \text{b)}
\end{align*}
\]

\textbf{Scheme 45.} (a) Et₃B, MeOH, THF, 0 °C; (b) NaBH₄, THF, –78 °C.

Subsequent protection of the diol as bis-O-triethylsilyl ethers (TESCl, imid, DMAP, DMF, RT) yielded 119 as a single diastereomer and semireduction of the n-buty1 ester with DIBAL–H in toluene at –78 °C gave aldehyde 120 in 92% over three steps from 118. Olefination with triethylphosphonoacetate under Roush–Masamune. 

---

conditions (DBU, LiCl, CH$_3$CN, RT) and deprotection of the silyl ethers with TBAF in THF led to diol 121 (80% over two steps) (Scheme 46).

**Scheme 46.** (a) Et$_3$B, MeOH, THF, –78 °C, then 118 followed by NaBH$_4$, 5 h; (b) TESCl, imid, DMAP, DMF, RT, 12 h; (c) DIBAL-H, toluene, –78 °C, 30 min, 92% over 3 steps (d.r. > 95:5); (d) DBU, LiCl, (EtO)$_2$P(O)CH$_2$CO$_2$Et, CH$_3$CN, RT, 2 h; (e) TBAF, THF, RT, 2 h, 80% over 2 steps.

3.2.3. Tetrahydropyran Formation

The structural architecture of leucascandrolide A required the stereoselective formation of a tetrahydropyran ring possessing a 2,6-cis configuration. We sought to achieve 6-exo-trig cyclization by conjugate addition of an oxyanion to the tethered acrylate moiety. In this respect, treatment of diol 121 with catalytic amounts of tBuOK in THF at 0 °C produced the desired cyclic compound 122 in 63% yield and 10:1 diastereoselectivity (Scheme 47). When the undesired isomer 123 was resubmitted to identical reaction conditions, isomerization to 122 took place, showing that the reaction proceeds under thermodynamic control. Interconversion probably takes place by a retro-Michael/Michael elimination/addition sequence.


(99) The term Michael addition is generally used to refer to the conjugate addition of C-nucleophiles. In the present thesis, it will be used for O-nucleophiles as well.
would suggest that, under these conditions, the olefin geometry does not play a crucial role in these cyclizations.100

Protection of the secondary hydroxy group as tert-butylidimethylsilyl ether (TBSCI, imid, DMAP, DMF) gave 124 in 96% yield.96

![Chemical structure](image)

**Scheme 47.** (a) tBuOK (10 mol%), THF, 0 °C, 63% (d.r. = 10:1); (b) TBSCI, imid, DMAP, DMF, RT, 20 h, 96%; c) tBuOK (10 mol%), THF, 0 °C.

While there is a large amount of information available on the conformation of substituted cyclohexane rings, the corresponding data for tetrahydropyrans is scarce. Free-energy profiles for various monosubstituted tetrahydropyrans have been deduced from NMR studies by Eliel and co-workers.101 The A-value of the methyl substituent in 2-methyltetrahydropyran has been estimated to 2.86 kcal/mol, exceeding the corresponding value of methylcyclohexane (1.74 kcal/mol) by more than 1 kcal/mol (Figure 8). While this significant difference cannot be attributed to the C–O–C and C–C–C bond angles, it is rationalized by the shortness of the C–O bond (1.42 Å for C–O vs 1.54 Å for C–C), leading to increased 1,3-diaxial steric

(100) Similar cyclizations were reported by Banwell using K₂CO₃/MeOH. In this case, it was found that the olefin geometry is important for the stereochemical outcome of the reaction: Banwell, M. G.; Bissett, B. D.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. Aust. J. Chem. 1998, 51, 9–18.

interactions between the C2 and C6 substituents.\textsuperscript{102} Despite the expected substituent dependency of A-values, this value for 2-methyltetrahydropyran remains a valuable reference point for the prediction of thermodynamically controlled cyclizations.\textsuperscript{103}

\begin{center}
\begin{tabular}{|c|c|}
\hline
\textbf{Me} & 1.74 \\
\hline
\textbf{Me} & 2.86 \\
\hline
\textbf{Me} & 1.43 \\
\hline
\textbf{Me} & 1.95 \\
\hline
\end{tabular}
\end{center}

\textbf{Figure 8}. Free energies of methyl-substituted tetrahydropyrans.

3.2.4. Optimized Route towards Tetrahydropyran 124

Although the reaction pathway described previously (Sections 3.2.2 and 3.2.3) allowed quick and high-yielding access to the desired compound 124, the reaction sequence from keto ester 118 to 124 was rendered awkward by protective-group manipulations and thus further refinement and shortening was highly desirable. An

\textsuperscript{102} The molecular structure of gaseous THP has been studied. Indeed, the C–O–C (111.5°) bond angle in THP and the C–C–C (110.9°) bond angle in cyclohexane are nearly identical: Breed, H. E.; Gundersen, G.; Seip, R. \textit{Acta Chem. Scand. Ser. A} \textbf{1979}, \textit{33}, 225–233.

\textsuperscript{103} The A-value of the 4-hydroxyl group in the tetrahydropyran series is comparable to the corresponding A-value in the cyclohexane series (0.6–0.8 kcal/mol).
alternative, more “atom-economical” route, which does not require unnecessary protection and deprotection steps, was thus developed.\(^\text{(104)}\)

\textit{Syn} reduction of keto ester 118, using the same method as in the first-generation synthesis, was followed by acidic workup: prolonged exposure of the reaction mixture to aqueous hydrochloric acid (1.0 M) led to partial formation of six-membered lactone 125 (Scheme 48). The lactonization, allowing for differentiation of the C5 and C7 hydroxyl functionalities, was rendered complete by treatment with catalytic amounts of PPTS in benzene. Protection of the secondary alcohol as tert-butyldimethylsilyl ether (TBSCI, imid, DMAP, RT, DMF) afforded 126 in 77\% yield from keto ester 118.\(^\text{(96)}\) Two-carbon chain extension was achieved by semireduction of the lactone to the corresponding lactol 127 (DIBAL–H, toluene, \(-78\, ^\circ\text{C}\)) and subsequent \textit{Horner–Wadsworth–Emmons} olefination:\(^\text{(105)}\) when lactol 127 was added to a mixture of triethylphosphonoacetate and sodium hydride in THF at \(-78\, ^\circ\text{C}\), clean tetrahydropyran formation (72\% yield) was observed upon warming to ambient temperature, albeit as a 2:1 diastereomeric mixture of \textit{cis} and \textit{trans} oxanes 124 and 128, favoring the thermodynamic product 124. The use of potassium hydride as base did not lead to any improvement in selectivity. However, we were confident that we would be able to ensure diastereoselectivities similar to those obtained in the first-generation synthesis, given the fact that equilibration is possible under basic conditions (vide supra) and that A-values of hydroxy groups and the corresponding O-silyl ethers are nearly identical.\(^\text{(106)}\) Indeed, upon treatment with catalytic amounts

\begin{itemize}
\item \textsuperscript{(105)} Lactol 127 was obtained as a mixture of diastereomers at C3.
\end{itemize}
of $t$BuOK (10 mol%), the mixture cleanly equilibrated to the thermodynamically more stable isomer 124 (d.r. = 9:1).

Not only is this modified reaction sequence two steps shorter than the initially reported route, but the overall yield from aldol adduct 116 to 124 is also improved (39% vs 35%).

3.2.5. The Wacker Oxidation

Completion of this fragment only required, as ultimate functional-group interconversion, the oxidation of the disubstituted olefinic bond in 124 to the methyl ketone. Our initial efforts were focused on achieving this transformation by a straightforward hydroboration/oxidation sequence. However, problems associated with low conversion in the hydroboration step prompted us to investigate other methods. A one-step alternative is the Wacker oxidation, which was originally

\[ \text{Scheme 48.} \]
applied to the synthesis of acetaldehyde by PdCl₂-catalyzed oxidation of ethylene (Scheme 49).  

\[ \text{H}_2\text{C} = \text{CH}_2 \xrightarrow{\text{PdCl}_2, \text{CuCl}_2, \text{H}_2\text{O}, \text{O}_2} \text{Me} \text{H} \]

**Scheme 49.** PdCl₂, CuCl₂, H₂O, O₂.

While oxidation of monosubstituted double bonds is well documented and leads to the selective formation of methyl ketones, little has been reported on the Wacker oxidation of internal 1,2-disubstituted alkenes. These tend to react more slowly and mixtures of isomeric ketones are generally obtained. Thus, in spite of the great synthetic utility of this process, this reaction has found only limited application in the synthesis of complex molecules.

An exception is observed for allylic and homoallylic ethers and esters. Indeed, for these compounds, oxidation takes place at the alkenic carbon atom furthest away from the neighboring alkoxy or acyloxy group.

When applied to our substrate, methyl ketone 129 was obtained in good yield (86%) and complete regioselectivity upon treatment of olefin 124 with PdCl₂ (0.2 equiv), CuCl (1.2 equiv) and oxygen (air) in a DMF/H₂O 7:1 mixture for two days.


(110) In these cases, yields generally tend to be rather low. For a related example, see: Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* 1986, 108, 3474–3480.
The regioselectivity may be explained by a nonsymmetrical bonding of the palladium to the olefinic bond, caused by coordination to the tetrahydropyranyl oxygen atom, resulting in attack of H$_2$O at the remote olefinic terminus (Scheme 51). β-Hydride elimination then leads to the desired methyl ketone 129 with concomitant generation of a Pd$^0$ species which is reoxidized to Pd$^{II}$ by Cu$^{II}$.

3.2.6. Conclusion

The delineated synthetic pathway highlights the utility of dienolate additions to aldehydes for the construction of 1,3-polyol fragments. An exceptionally regioselective and high-yielding Wacker oxidation leads to the requisite methyl ketone 129. It is well-worth noting that this advanced intermediate possesses one of the tetrahydropyran rings found in the natural product with attendant stereocenters and, importantly, is accessed in seven steps and 34% overall yield from known compound 116.
3.3. On the Way to the Macrocycle

3.3.1. Fragment Coupling

With multi-gram quantities of both key fragments 112 and 129 in hand, we were poised to explore their coupling by aldol addition.\(^\text{111}\) Control of the C11 stereocenter was the crucial issue to be addressed and the required π-face selectivity was believed to be accessible by different means:

\(\text{i.} \) The inherent chirality of the electrophilic component: The presence of the C12 stereogenic center may result in the preferred formation of the (11S)-stereocenter by Felkin–Anh control (Figure 9).\(^\text{112}\) However, the π-face bias imparted by this control element was expected to be not high enough to give synthetically useful levels of stereoinduction.

\[
\begin{align*}
\text{disfavored} & \quad \text{Nu} \quad \text{Nu} \\
\text{favored} & \quad \text{Nu} \quad \text{Nu}
\end{align*}
\]

**Figure 9.** Preferred approach of the nucleophile according to the Felkin–Anh model.

\(\text{ii.} \) The inherent chirality of the nucleophilic component: The stereoinduction may originate from the substituent in β-position of the methyl ketone. Indeed, it was independently shown by Paterson\(^\text{113}\) and Evans\(^\text{114}\) that boron enolates derived

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(111) For an excellent review of asymmetric aldol reactions using boron enolates, see ref. 9.


from methyl ketones bearing a β-alkoxy or β-silyloxy substituent add to aldehydes in a highly stereoselective manner to give β-hydroxy ketones displaying a 1,5-anti relationship between the β-alkoxy (or β-silyloxy) substituent and the hydroxy group on the newly formed stereogenic center (Scheme 52).

![Scheme 52]

### iii.

A reagent-controlled induction would certainly be a viable alternative. A number of chiral boron reagents have been reported for asymmetric aldol additions (see paragraph 1.1.3.1).

In a first approach, the desire to move forward in order to explore the upcoming key steps prompted us to combine all three elements. To this end, we examined the use of DIPCl reported by Paterson,\(^{113}\) giving triple asymmetric induction.\(^{115}\) The two dominant stereocontrol elements—chiral β-alkoxy ketone 129 and the chiral boron reagent—were expected to operate synergistically to lead selectively to the requisite (11R)-stereocenter in a matched fashion.

Enolization of methyl ketone 129 with (−)-DIPCl in conjunction with triethylamine in Et₂O at 0 °C led to the clean formation of the corresponding boron enolate, which was allowed to react with aldehyde 112 at −78 °C for 24 h (Scheme 53).

---


\(^{(115)}\) There are only few examples of triply stereodifferentiating aldol reactions. For an example, see: Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. Tetrahedron Lett. 1989, 30, 7357–7360.
The desired product 130 was isolated as a single diastereomer (d.r. > 95:5 by \(^1\)H NMR) in 81% yield after hydrolytic workup.

It turned out that similar degrees of stereoinduction were obtained with achiral boron reagents (double stereoinduction). Indeed, when enolization was performed with \(n\)Bu\(_2\)BOTf and DIPEA instead, the same \(\beta\)-hydroxy ketone 130 was isolated as a single isomer in 80% yield.\(^{114b,116}\)

\[
\begin{align*}
\text{Me} & \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{OBz} \\
\text{O} \\
\text{Me} \\
\text{Me}
\end{array} \\
\text{Me} & \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{OTBS} \\
\text{O} \\
\text{OEt} \\
\text{O}
\end{array} \\
\text{Me} & \quad \begin{array}{c}
\text{H} \\
\text{O}
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
\text{112} & \quad \begin{array}{c}
\text{O} \\
\text{OBz} \\
\text{O} \\
\text{Me}
\end{array} \\
\text{129} & \quad \begin{array}{c}
\text{Me} \\
\text{Me}
\end{array} \\
\text{130} & \quad \begin{array}{c}
\text{Me} \\
\text{1,5-anti induction}
\end{array}
\]
\]

Scheme 53. (a) 129, \(n\)Bu\(_2\)BOTf, Et\(_2\)Pr\(_2\)N, Et\(_2\)O, \(-78^\circ\text{C}\), then 112, 5 h, 80\% (d.r. > 95:5); (b) 129, (−)-DIPCl, Et\(_3\)N, Et\(_2\)O, \(-78^\circ\text{C}\), then 112, 24 h, 81\% (d.r. > 95:5).

A proof of the sense of stereoinduction was not easy to achieve at this point: the lack of crystallinity prohibited analysis by X-ray crystallography and no straightforward chemical transformation which allowed for the unambiguous assignment was identified at the time. However, trusting the precedence reported for similar reactions, further demonstration of the 1,5-\textit{anti} relationship was deemed dispensable.

At present, the origin of the high levels of 1,5-\textit{anti} induction obtained with these boron enolates is unclear.\(^{113}\)

(116) Kozmin reported a similar fragment coupling using Cy\(_3\)BCl in combination with Et\(_3\)N. See ref 49b for details.
3.3.2. The Ketone Reduction Problem—A Dead End?

Further elaboration of the aldol product was planned by stereoselective reduction of the C9 ketone. Tishchenko reduction of aldol adduct 130 would have been ideal, since the resulting 1,3-anti-diol monooester 131 would have allowed for full differentiation of all hydroxy groups, and thus selective methylation of the C9 alcohol (Scheme 54).\(^{117}\)

![Scheme 54](image)

Earlier studies had shown the feasibility of such an approach: model compound 132, the C18 epimer of ent-130, was consistently reduced to diol monoacetate 133 in excellent yields using acetaldehyde, according to the procedure reported by Evans for samarium-catalyzed Tishchenko reductions (> 85%) (Scheme 55).\(^{118}\)

---


(118) THF solutions (0.10 M) of SmI\(_2\) were prepared prior to use from Sm\(^{3+}\) and freshly washed diiodoethane by standard procedures: (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698; (b) also see ref. 117b.
Scheme 55. (a) MeCHO, SmI₂ (10-30 mol%), THF, -78 °C, > 85%.

Upon addition of SmI₂ to a THF solution of a hydroxy ketone and R¹CHO, the deep blue hue of Sm² quickly fades to give rise to the yellow color of Sm³, indicating the formation of the samarium(III) pinacolate 134, the supposedly active catalyst. In contrast to the Prasad reduction giving a 1,3-syn diol by intermolecular hydride transfer (see paragraph 3.2.2), the observed anti stereoselectivity can be rationalized by formation of intermediate hemiacetal 135 and subsequent intramolecular hydride delivery via cyclic transition state 136 as shown in Scheme 56.

Scheme 56

To our surprise, 130 proved resistant under identical reaction conditions, and the desired product 131 could not be isolated (130 ⇄ 131).
Recently, Scott has reported on the use of Sc(OTf)$_3$ as a catalyst for stereoselective Tishchenko reduction of β-hydroxy ketones.$^{119}$ Nevertheless, this protocol did not lead to any improvement.

### 3.3.3. Revision of the Proposed Route

Thwarted by the unfeasibility of the Tishchenko reduction on this advanced intermediate, our synthetic planning needed some adjustment and we sought for an alternative strategy. The originally proposed route would have allowed access to the requisite macrocycle in only six steps from reduction product $^{131}$ by the synthetic pathway outlined in Scheme 57. Key to this expeditious elaboration was the full differentiation of all alcohol functionalities present in the “Tishchenko product” $^{131}$.

![Diagram of the proposed route and differentiation](image-url)

Scheme 57

---

The reduction of the C9 ketone was a high-priority step and alternative pathways from β-hydroxy ketones to 1,3-anti diols have been reported, leaving, however, the resulting hydroxy groups undifferentiated. Selective protection of any of the resulting alcohol functionalities was believed unpredictable.

A potential solution to this problem was identified, which avoided the speculative and excessive use of protective-group manipulations: we hypothesized that hydroxy-group protection was not essential for the successful execution of the upcoming steps and that differentiation of the secondary alcohols at C9, C11, and C17 should be possible by electrophile-mediated etherification and ring-size selective macrolactonization.

3.3.4. Implementation of the Revised Strategy

Reduction of the β-hydroxy ketone 130 using tetramethylammonium triacetoxyborohydride, as reported by Evans, cleanly afforded the desired diol 137 in 97% yield and complete diastereoselectivity (> 95:5 by 1H NMR) (Scheme 58). Deprotection of the C17 benzoate with concomitant transesterification to the C1 methyl ester was achieved with K₂CO₃ in MeOH, yielding triol 138 in 92% yield.

---


As in the *Tishchenko* reduction, the stereocontrol in this reaction arises from intramolecular hydride delivery, as depicted in Scheme 59. The use of excess acetic acid was found indispensable to activate the ketone towards electrophilic attack. Both competing six-membered cyclic transition states 139 and 140 involve a chair-like arrangement and intramolecular hydride delivery is possible for both of them. The preferential formation of the *anti* diol can be attributed to unfavorable 1,3-diaxial interactions between R₂ and OAc in 140, destabilizing the system to a greater extent than the interactions between HO⁺ and OAc found in 139.

Scheme 58. (a) Me₃NBH(OAc)₃, AcOH, CH₃CN, –40 °C, 48 h, 97%; (b) K₂CO₃, MeOH, RT, 40 h, 92%.

Scheme 59
3.3.5. Formation of the Second Tetrahydropyran

With triol 138 in hand, the stage was set for the formation of the second tetrahydropyran ring found in leucascandrolide A. We sought to achieve this transformation by electrophile-mediated, hydroxyl-directed, intramolecular cyclization of the C11 alcohol onto the C15–C16 (E)-olefinic bond. These reactions are known to proceed by a three-step mechanism (Scheme 60): (i) formation of π-complex 141, (ii) followed by generation of intermediate onium ion 142 (iii) and subsequent anti attack of a nucleophile, leading to product 143 with two newly formed stereogenic centers. Commonly used electrophiles that induce such cyclizations are Br⁺, I⁺, Hg²⁺, PhS⁺ and PhSe⁺.123

![Scheme 60](image)

In our case, the control of three key issues was essential to the successful execution of the reaction:

i. **Diastereoselectivity**: The attack of an electrophile onto either diastereotopic face of an unsymmetrical disubstituted alkene leads to diastereomeric onium ions.

ii. **Chemoselectivity**: The onium ion formed in the first step may react with different tethered O-nucleophiles. Indeed, three unprotected secondary hydroxy groups (at C9, C11, and C17) are present and their relative reactivity is expected to depend on the ring size of the formed ether (Figure 10).

---

iii. **Regioselectivity:** In principle, two modes of attack are conceivable. Cyclization may occur either by *exo-tet* or by hybrid *endo/exo-tet* attack of the nucleophile (Scheme 61).

![Scheme 61](image)

Despite the potential formation of twelve different isomers by intramolecular cyclization, we were confident that only two of these would require special consideration. Indeed, chemo- and regioselectivity issues can be ruled out as the formation of six-membered rings is known to be both kinetically and thermodynamically favored as compared to three-, four-, seven-, eight- and nine-membered rings. This reduces the problem to the stereoselective formation of the intermediate onium ion, which undergoes opening by the incoming C11 hydroxyl group and potentially leads to two diastereomeric tetrahydropyrans 144 and 145 (Scheme 62).

---

The intermolecular variant of this reaction is well known with allylic alcohols: 1,3-anti diols are obtained as major products if water is used as nucleophile.\textsuperscript{(125)} This reaction has been successfully applied to the synthesis of the rutamycin spiroketal skeleton by Evans and co-workers (Scheme 63).\textsuperscript{(126)}

In a seminal study by Chamberlin and Hehre, the intramolecular case has been studied, mostly for the generation of five-membered ring systems, using a tethered carboxylate or alcohol as nucleophile and various oxygen- or nitrogen-based


directing groups. In this work, the diastereoselectivity was rationalized by the preferential formation of intermediate onium ion 146 (Scheme 64). Indeed, although stabilizing interactions between the developing positive charge and one of the oxygen lone pairs can be invoked for both transitions states 146 and 147, unfavorable non-bonding 1,5-interactions should disfavor 147.

![Scheme 64](image)

With this information in hand, cyclization via iodonium ions was investigated first. While I₂-mediated reactions proved to be extremely slow and nonselective (1:1 diastereomeric mixture of 148 and 149), iodine-monobromide has been reported by Smith to give enhanced addition rates, allowing for low-temperature cyclizations of homoallylic carbonates with superior diastereoselectivities. Indeed, the use of IBr led to significantly accelerated additions, albeit unchanged stereoinduction (Scheme 65).

(127) Three types of substrates have been studied: (i) directing group on the tether, (ii) directing group in the tether, (iii) independent directing group. For a detailed analysis, see: Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. J. Am. Chem. Soc. 1987, 109, 672–677 and references therein.

(128) The reaction was quenched before full conversion after 2 days at ambient temperature.

Typical reaction conditions involved the slow addition over 1 h of a toluene solution of IBr (2.0 equiv, 1.0 M in CH₂Cl₂) to a toluene solution of allylic alcohol 138 and 2,6-di-tert-butyl-4-methyl pyridine (2.5 equiv) at −78 °C. After workup with 2.0 M aqueous Na₂S₂O₅, a 1:1 diastereomeric mixture of 148 and 149 was isolated in 50% yield (74% based on recovered 138). To our delight, separation was easily performed by column chromatography on silica gel. All attempts to improve yield and/or selectivity failed with iodine electrophiles.

In order to determine the relative configuration, iodides 148 and 149 were converted into the corresponding epoxides 150 and 151, respectively, by treatment with K₂CO₃ in methanol, with inversion of configuration at C16 (Scheme 66). Unambiguous stereochemical assignment of the relative configuration at C15 and C16 was made possible by comparison of the coupling constants of the vicinal epoxide protons. Iodide 149 was shown to possess the requisite 2,6-trans-disubstituted tetrahydropyran ring, given a coupling constant of ³J_H–H = 4.36 Hz for

(130) The use of additional base was necessary to avoid deprotection of the C5 silyl ether.
epoxide 151, characteristic for cis epoxides.\textsuperscript{131} 150, obtained from 148, displays a coupling constant of $^{3}J_{H-H} = 2.16$ Hz, typical for trans epoxides.\textsuperscript{132}

![Diagram of chemical structures and coupling constants](image)

**Scheme 66:** (a) K$_2$CO$_3$, MeOH, RT, 15 h, 57%; (b) K$_2$CO$_3$, MeOH, RT, 15 h, 69%.

The use of selenium-electrophiles led to a major advance in our efforts to optimize yield and diastereoselectivity: phenylselenyl chloride gave a promising


\textsuperscript{132} For a related trans epoxide with similar $^{3}J$ coupling constant, see: Vidal, J. P.; Escale, R.; Girard, J. P.; Rossi, J. C.; Chantraine, J. M.; Aumelas, A. J. Org. Chem. 1992, 57, 5857–5860.
75:25 selectivity of 152:153 (78% yield), favoring the required 2,6-trans-disubstituted tetrahydropyran (Scheme 67). \(^\text{133}\)

Encouraged by this result, we turned our attention to bulkier, substituted phenylselenyl reagents. In this respect, 2,4,6-triisopropylphenylselenyl bromide (TIPPS\(_{\text{SeBr}}\)) (156) has been reported by Lipshutz to give improved selectivities in electrophile-mediated hybrid 6-endo-tet/5-exo-tet cyclizations of homoallylic alcohols to tetrahydrofurans as compared to phenylselenyl chloride. \(^\text{134}\)

Formation of the intermediate seleniranium ion seemed to be much slower as compared to phenylselenyl chloride. \(^\text{135}\) When applied to our system, the use of 156 turned out to give the best results, leading to selenides 154:155 in 74% yield and a

\[\text{Scheme 67. (a) 2,6-di-\text{tert}-butyl-4-methyl pyridine, CH}_2\text{Cl}_2, -78 ^\circ\text{C}, \text{followed by slow addition (over 1 h) of PhSeCl, 1 h, 78\% (d.r. = 75:25 152:153); (b) 2,6-di-\text{tert}-\text{butyl-4-methyl pyridine, CH}_2\text{Cl}_2, -78 ^\circ\text{C}, \text{followed by slow addition (1 h) of 156, 4 h, 74\% (d.r. = 88:12 154:155).}\]

(133) The diastereomeric ratio was determined by \(^1\text{H}\) NMR. The assignment was possible only after reductive removal of the phenylselenyl moiety by comparison with 159 obtained from iodide 148.


(135) The terms seleniranium and selenenium ions are both used in the literature to refer to seleniumonium ions.
diastereomeric ratio of 88:12 (Scheme 67). A typical reaction procedure consists in the slow addition (over 1 h) of a solution of selenyl bromide 156 (4.0 equiv) to a solution of triol 138 and 2,6-di-tert-butyl-4-methyl pyridine (5.0 equiv) in CH₂Cl₂ at –78 °C.\(^{133}\)

While not commercially available, this reagent is conveniently prepared in two steps from 1-bromo-2,4,6-triisopropylbenzene (157) (Scheme 68): lithium–halogen exchange, achieved upon treatment with \(t\)BuLi, and subsequent addition of selenium powder gives air stable, orange needles of diselenide 158.\(^{136}\) Selenyl bromide 156 is then prepared in situ at –78 °C by dropwise addition of Br₂.

![Scheme 68](image)

**Scheme 68:** (a) \(t\)BuLi, THF, –78 °C, then Se, –78 °C → RT, 50%; (b) Br₂, CH₂Cl₂, –78 °C to RT.

To the best of our knowledge, the stereoselective formation of 2,6-\(trans\)-disubstituted tetrahydropyrans by intramolecular trapping of a bulky seleniranium ion by a hydroxyl group is unprecedented.\(^{137}\) The directing effect of the free hydroxy group at C17 could not be ascertained in the course of our studies.\(^{138}\)

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(137) One example has been reported with phenylselenyl chloride: Kühnert, S. M.; Maier, M. E. *Org. Lett.* 2002, 4, 643–646.

(138) An interesting direction for further study would be the examination of the influence of the C17 protective group on the stereoinduction of the electrophile-mediated cyclization.
3.3.6. Reductive Removal of the Electrophilic Component

Reductive deiodination or deselenation can be achieved by a variety of reagents, including low-valent metals² (Li⁰, Na⁰, Cr°° and Sm°° among others), metal hydrides (NaBH₄, LAH, LiHBEt₃, R₃SnH) and catalytic hydrogenation.³

Because of chemoselectivity issues, reduction with aluminum- or borohydrides was not envisioned. One of the most widely used reagents for this purpose is tributyltin hydride, leading to the desired product by radical-chain reduction. Deiodination of 148 was achieved using nBu₃SnH in combination with AIBN as radical initiator in refluxing, deoxygenated benzene, giving 159 in excellent yields (97%) (Scheme 69).

Scheme 69. (a) nBu₃SnH, AIBN, PhH, reflux, 1 h, 97% for X = I; (b) AIBN, hexane, reflux, 2 h, 85% for X = I, 80% for X = TIPPSe.


However, purification problems associated with organotin reagents prompted us to investigate modern, alternative methods, which are not based on organotin reagents. In this respect, the silylated cyclohexadiene $160$, recently reported by Studer for tin-free radical reductions, is perhaps one of the most promising systems.

Upon reaction with $160$, an alkyl radical $R\cdot$ is reduced to $RH$ with concomitant formation of cyclohexadienyl radical $161$. Aromatization then leads to $162$ and silyl radical $163$, which is able to propagate the radical chain by halogen abstraction. It was shown that, in our case, $159$ was obtained in an operationally much simpler way, not requiring the use of deoxygenated solvents and giving only easily removable by-products, albeit in slightly decreased yield of 85%.145

![Scheme 70](image)

Upon treatment with $160$ and catalytic amounts of AIBN in refluxing hexane, selenide $154$ could be converted to the desired reduced product $159$ in 80% yield.

(142) Organotin halides and unreacted hydrides are highly soluble in apolar organic solvents and are not easily removed by column chromatography on silica gel. Several procedures for their efficient removal have been developed: Berge, J. M.; Roberts, S. M. *Synthesis* 1979, 471–472.


(144) Another drawback of organotin reagents is their high toxicity, which renders their application on large scale problematic: Boyer, I. J. *Toxicology* 1989, 55, 253–298.

3.3.7. Macrolactonization

In preparation for the macrocyclization reaction, hydrolysis of the C1 methyl ester in 159 to seco acid 164 was required. Initial attempts with LiOH and NaOH turned out to be low yielding. The use of potassium trimethylsilanolate proceeded without incident and cleanly gave the desired acid 164, which was used without further purification in the cyclization step (Scheme 71).146

![Diagram](image)

**Scheme 71.** (a) TMSOK, Et2O, RT, 24 h.

The failure of the Evans–Tishchenko reduction at an earlier point in the synthesis (see sections 3.3.2 and 3.3.3) still left unresolved a hydroxy-group-differentiation problem (both secondary hydroxy groups at C9 and C17), which we planned to work out by chemoselective macrolactonization. Formation of two isomeric lactones, namely eight-membered lactone 165 and fourteen-membered lactone 166, is conceivable (Figure 11).147

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(147) The enantioselective synthesis of alkyl-substituted, eight-membered lactones by Claisen rearrangement has been reported by *Holmes*: Harrison, J. R.; Holmes, A. B.; Collins, I. *Synlett* **1999**, 972–974.
Although formation of 165 is theoretically possible, the thermodynamic bias was expected to be considerably in favor of the larger macrocycle 166. Indeed, as can be seen from Figure 12, the rate of lactonization of ω-bromoalkanoate ions reaches a nadir for eight-membered rings, whereas formation of the larger macrocycle is expected to be faster by several orders of magnitude.

![Figure 11. Structure of the potentially formed lactones.](image1)

![Figure 12. ΔH‡ for the formation of lactones (left); Reactivity profile for lactone formation (right).](image2)

Semi-empiric calculations of the cationic acyl-DMA adduct derived from seco acid 164 suggest that eight-membered ring formation is disfavored by almost 5 kcal/mol (Figure 14). For these calculations, a Bürgi–Dunitz approach of the incoming hydroxyl group on the activated carbonyl center was mimicked by imposing certain constraints on the system, as can be seen from Figure 13.

![Figure 13. Geometrical constraints for lactonization.](image)

(149) Semi-empiric calculations were performed at the PM3 level using PC Spartan Pro® for Windows.
Figure 14. Energy-minimized reactive conformations (PM3) of lactonization pathways for the cationic acyl-DMAP adduct derived from 164.
Because of these theoretical considerations and earlier success in our laboratory with model compound 167, the macrolactonization step was tackled with some confidence. Indeed, under typical Yamaguchi conditions (formation of the mixed anhydride by treatment with 2,4,6-Cl₃(C₆H₂)COCl/Et₃N, followed by DMAP-promoted cyclization), seco acid 167 cleanly afforded macrolactone 168 in 80% yield (Scheme 72).

(151) Seco acid 167 was prepared from alcohol 133 by O-methylation of the C9 hydroxy group, followed by a reaction pathway similar to that described for the conversion of diol 137 to seco acid 164. It is the C18 epimer of ent-164, incorporating a C9 methyl ether.

(152) Leighton, Kozmin and Rychnovsky have reported related Yamaguchi macrolactonization reactions with substrates incorporating a C9 methyl ether, giving macrocycles in good yields. See ref. 48, 49a, 51 for details.
To our disappointment, acid 164 proved recalcitrant to cyclization when submitted to otherwise identical reaction conditions and no traces of lactone 166 could be isolated. Various solvents typically used in this type of reaction were screened (benzene, toluene, xylene, THF). However, these studies were frustrated by the unexpected inertness of 164 towards ring-closure, leading to the exclusive formation of oligomeric products, in spite of slow addition (up to 24 h) and high dilutions (10^{-3} M).

This difference in reactivity between acid 164 and model compound 167 may be ascribed to various factors: indeed, subtle stereochemical modifications have been shown in the past to critically influence macrocyclization reactions and to decide their success or failure. \(^{(153,154)}\) We hypothesized that this resistance towards cyclization was attributable to the presence of the C9 hydroxy group in 164, compared to the C9 methyl ether in model compound 167, leading to a hydrogen-bonded network. This


(154) In the course of their synthetic studies on Leucascandrolide A, Kozmin and co-workers observed that aldehyde 75 underwent clean cyclization to macrolactol 76 (see Section 1.5.5), while the corresponding C17 epimer did not cyclize. For details, see ref. 49a.
arrangement may lock the molecule in a conformation which is unfavorable for ring-closure: molecular-mechanics calculation showed that, in the preferred conformation of the macrocyclic structure 45, the C9 methyl ether resides peripherally, a disposition which is not compatible with the postulated array, wherein the C9 hydroxy group is supposedly between the tetrahydropyran rings (Figure 15).\(^\text{155}\)

![Figure 15. Postulated hydrogen-bonded array of the prelactonization complex derived from seco acid 164 and DMAP.](image)

If our hypothesis was correct, a polar solvent, able to break up hydrogen bonds, should be beneficial to the outcome of the reaction. Most gratifyingly, the use of DMF led to the formation of the desired macrocyclic structure 166. The procedure employed involved addition of the mixed anhydride (2.4·10\(^{-3}\) M in THF/DMF) to a solution of DMAP (10 equiv; 1.5·10\(^{-2}\) M in DMF) over 3 h (Scheme 15).\(^\text{156,157}\) No trace of the eight-membered macrocycle 165 could be detected by \(^1\)H NMR. Although the

\(^{155}\) (a) See Section 1.4 for details; (b) Pietra and co-workers performed molecular-mechanics calculations, based on MMX force field, using PCMOD 4.0 for Windows. For details, see ref. 35.


\(^{157}\) We were worried that the increased polarity of the solvent may lead to epimerization at C3 by retro-Michael/Michael reaction. However, no epimerization of this stereogenic center was observed as judged by \(^1\)H NMR.
exact nature of non-bonding interactions is not known with certainty, the successful implementation of the proposed solution gives strong evidence for our assumption.

O-Methylation of the C9 alcohol gave 169 in 49% yield from methyl ester 159 upon treatment with Me₃OBF₄ in combination with Proton Sponge (170) and 4 Å molecular sieves, using the improved conditions reported by Ireland (Scheme 73).¹⁵⁸

![Scheme 73](image)

**Scheme 73.** (a) 2,4,6-trichlorobenzoyl chloride, Et₃N, RT, 1 h, then dilution with DMF and slow addition (3 h) to DMAP in DMF, RT, 2 h; (b) Me₃OBF₄, Proton Sponge (170), 4 Å M.S., RT, 30 min, 49% over 3 steps.

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3.4. Completion of the Macrolide Moiety

The completion of the leucascandrolide A macrolide required the introduction of the C17 side chain, which was planned by (E)-selective olefination of a C18 aldehyde. Unmasking of the 1,2-diol protected as isopropylidene acetal was achieved in 80% yield by careful hydrolysis of the isopropylidene ketal in 169 by heating to 45 °C in AcOH/THF/H₂O 2:1:1 (Scheme 74).¹⁵⁹ These mild acidic conditions were found to leave the C5 silyl ether untouched.

\[
\text{Me} \quad \text{OTBS} \\
\text{O} \quad \text{OMe} \\
\text{O} \quad \text{O} \\
\text{Me} \quad \text{Me}
\]

\[
\text{Me} \quad \text{OTBS} \\
\text{O} \quad \text{OMe} \\
\text{O} \quad \text{OH} \\
\text{HO}
\]

**Scheme 74.** (a) AcOH/THF/H₂O 2:1:1, 45 °C, 5 h, 80%.

3.4.1. Introduction of the C17 Side Chain

Subsequent glycol cleavage of the resulting 1,2-diol 171 with Pb(OAc)₄ in EtOAc at 0 °C resulted in the formation of aldehyde 172, which was used without further purification and taken immediately to the olefination step (Scheme 75).

Among the various procedures reported for aldehyde olefination, those which selectively lead to (E)-alkenes are few. The Julia olefination, with its numerous

modifications, is perhaps the most versatile and widely used method for this purpose.\textsuperscript{160} Since the original report by Marc Julia,\textsuperscript{160a} involving a three-step reaction sequence, the protocol has been simplified by Lythgoe\textsuperscript{160b,c}, Sylvestre Julia\textsuperscript{160d,e} and Kocieński\textsuperscript{160f,g}, leading to the development of a less capricious one-step variation.

While the use of benzothiazoyl sulfones shows considerable limitations,\textsuperscript{161} 1-phenyl-1H-tetrazol-5-yl sulfones extensively studied and reported by Kocieński circumvent these problems.\textsuperscript{160f}

Introduction of the C17 side chain, leading to 173, was achieved using the one-pot Kocieński modification of the Julia–Lythgoe olefination with sulfone 174 (Scheme 75). Upon treatment with freshly prepared KHMDS (1.0 M in DME), sulfone 174 undergoes rapid deprotonation, giving a canary-yellow solution of the potassiated sulfone. Addition of aldehyde 172 at –78 °C, followed by stirring for 2 h at –55 °C and 3 h at 0 °C, led to clean SO\textsubscript{2} extrusion. The product with the desired disubstituted C18–C19 olefinic bond of (E)-configuration was formed exclusively in 73% over two steps. No trace of the (Z)-isomer could be detected by \textsuperscript{1}H NMR.


(161) High stereoselectivities are obtained only for the synthesis of some conjugated dienes and the metallated sulfone has been shown to be prone to self-condensation even at low temperature.
Preparation of 174 in two steps from commercially available 3-methyl-1-butanol (175) was achieved by Mitsunobu reaction with 1-phenyl-2-tetrazoline-5-thione (176) followed by oxidation of sulfide 177 with Oxone (Scheme 76).

3.4.2. Completion of the Leucascandrolide A Macrolide

Completion of the formal synthesis required, as the final step, the cleavage of the C5 tert-butyldimethylsilyl ether (Scheme 77). Deprotection of 173 with excess TBAF in THF proceeded smoothly and provided the leucascandrolide A macrolide 45 in 98% yield. This synthetic material proved identical in all respects (1H NMR, 13C NMR, [α]D, IR, HRMS) to the material obtained from degradation of the natural
product by Pietra and to the material previously synthesized by Leighton and Rychnovsky.\textsuperscript{162}

\[ \text{Scheme 77. (a) TBAF, THF, } 0 \, ^\circ \text{C} \to RT, 7 \text{ h, } 98\%. \]
3.5. Synthesis of the Oxazole Side Chain

In order to complete our synthetic studies on leucascandrolide A, the synthesis of the peculiar oxazole-containing side chain was tackled and its subsequent coupling to the macrolide moiety was investigated (Figure 16). Two different syntheses are proposed, one of them leading to methyl ester 46, the other one to aldehyde 178.

![Figure 16. Structures of the synthesized side chains.](image)

3.5.1. Synthesis of Methyl Ester 46

Given the reactivity of both (Z)-alkenes, our approach envisioned their unraveling from the corresponding alkynes as the ultimate step. Formation of the 2,4-disubstituted oxazole was planned by a three-stage oxidation/cyclodehydration reaction sequence of a β-hydroxy amide using Wipf’s improved protocol.\(^\text{164}\)

Alkylation of diethyl acetamidomalonate (179) with tosylate 180 gave known compound 181 in poor yield (28%) (Scheme 78).\(^\text{165}\) Subsequent decarboxylation using

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(163) Treatment of natural leucascandrolide A with Na\(_2\)CO\(_3\) in MeOH gave the macrolide moiety 45 (77% yield) and the methyl ester side chain 46. See ref. 35 for details.


the method developed by Krapcho (LiCl, DMSO, 120 °C, 83%) afforded ester 182\(^\text{166}\) which was chemoselectively reduced to alcohol 183 with LiBH\(_4\) in 89% yield. Deprotection of the \(N\)-acetyl was best achieved under acidic conditions (1.0 M aq. HCl/THF 1:1, reflux), giving, after lyophilization, hydrochloride 184 in quantitative yield.

![Chemical structure](image)

**Scheme 78.** (a) 179, \(t\)BuOK, THF, reflux, 2 h, then 180, reflux, 2 d, 47%; (b) LiCl, DMSO, 120 °C, 4 h, 83%; (c) LiBH\(_4\), MeOH, THF, RT, 1 h, 91%; (d) 1.0 M aq. HCl, MeOH, reflux, 2 h, quant.

The synthesis of acid 187 began with propargyl amine (185) by treatment with methyl chloroformate to give carbamate 186 (Scheme 79). Carboxylation of the alkyne in 186 was best achieved by double deprotonation with LHMDS and subsequent quenching of the dianion with CO\(_2\), to afford ynoic acid 187 upon acidic workup.

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PyBrop-mediated peptide coupling of acid 187 and hydrochloride 184 afforded the highly unstable hydroxy amide 188,\(^\text{(167)}\) which was immediately oxidized to the corresponding, unstable aldehyde 189 with Dess–Martin periodinane (Scheme 80).\(^\text{(168)}\) Treatment of 189 with (CBrCl\(_2\))\(_2\), PPh\(_3\) and 2,6-di-tert-butyl-4-methyl pyridine followed by DBU afforded the desired oxazole 190 in 25% yield from 187.

\(\text{Scheme 79. (a) ClCO}_2\text{Me, Et}_3\text{N, CH}_2\text{Cl}_2, \text{RT, 3 h, 80%; (b) LHMDS, THF, –78 °C, then CO}_2, \text{–78 °C, 2 h, 80%.} \)

\(\text{Scheme 80. (a) PyBrop, DIPEA, CH}_2\text{Cl}_2, \text{RT; (b) DMP, CH}_2\text{Cl}_2, \text{RT; (c) 2,6-di-tert-butyl-4-methyl pyridine, PPh}_3, \text{(CBrCl}_2)_2, \text{CH}_2\text{Cl}_2, \text{then DBU, RT, 25% from 187; (d) PdCl}_2, \text{CuCl}_2, \text{NaOAc, CO (1 atm), MeOH, RT, 3 h; (e) H}_2 (1 \text{ atm}), \text{Pd/BaSO}_4, \text{quinoline, MeOH, RT, 21% over 2 steps.} \)

\(^{(167)}\) Exposure to aqueous media led to extensive product decomposition. For a closely related amide which was shown to readily rearrange to an amino ester derivative upon storage, see ref. 52.

Further elaboration towards 46 was planned by methoxycarbonylation or carboxylation of the terminal acetylene in 190. However, deprotonation with LHMDS, LDA or nBuLi followed by trapping with methylchloroformate or CO₂ proved unsuccessful, leading in all cases to a complex mixture of unidentified products. As an alternative, the palladium-mediated carbonylation\(^\text{169}\) (PdCl₂, CuCl₂, CO, AcONa, MeOH) provided the desired methyl ester. After partial hydrogenation using Pd/BaSO₄ poisoned with quinoline as catalyst, the desired side chain 46 was obtained in 21% unoptimized yield over two steps.

3.5.2. Synthesis of Aldehyde 178\(^\text{170}\)

The synthesis of aldehyde 178 initially followed a similar route to that described for methyl ester 46 in the previous section. Semireduction of ynoic acid 187 to (Z)-enoic acid 191 was realized by hydrogenation employing Lindlar’s catalyst, the reaction being carefully monitored by \(^1\)H NMR to avoid overreduction (Scheme 81).\(^\text{171}\) Peptide coupling of 191 with l-serine methyl ester hydrochloride mediated by isobutyl chloroformate gave access to amide 192 in 35% yield over two steps. Conversion to the requisite 2,4-disubstituted oxazole 193 could be achieved by formal cyclodehydration upon treatment with DAST, DBU and BrCCl₃ employing the one-pot protocol recently disclosed by Wipf and Williams.\(^\text{172}\)


\(^{(170)}\) The proposed route to aldehyde 178 as well as its coupling to the macrolide moiety 45 was developed by Leighton and co-workers in the course of their studies on leucascandrolide A and adopted for the completion of our total synthesis. See ref. 48.


Reduction of the methyl ester in 193 to the corresponding alcohol 194 with DIBAL–H (57%) in THF at 0 °C was followed by formation of the corresponding bromide 195 by standard methods (CBr₄, PPh₃, CH₃CN).¹⁷³ Two-carbon chain extension could be realized by Stille coupling with tributylvinyltin, catalyzed by Pd₂(dba)₃ and tri(2-furyl)phosphine, and afforded allyl oxazole 196 in 63% yield. 9-BBN-mediated, chemoselective hydroboration of the monosubstituted alkene smoothly afforded alcohol 197 upon oxidative workup with H₂O₂. The desired aldehyde 178 was obtained in 63% yield (over 2 steps) by oxidation under Swern conditions ((COCl)₂, DMSO, Et₃N, CH₂Cl₂).¹⁷⁶


3.6. Completion of the Total Synthesis

Coupling of the C5 side chain to the macrolide moiety 45 was tackled with the small amounts of 45 at our disposition. Not wanting to run the risk at losing this valuable material, implementation of this last step was accomplished by a known procedure. The only total synthesis reported at the time relied on a two-step sequence involving esterification followed by a (Z)-selective olefination with aldehyde 178 instead of the seemingly straightforward esterification with 46.48

Esterification of the C5 alcohol in 45 with bis(2,2,2-trifluoroethyl)phosphonoacetic acid (198), employing EDCI·HCl and HOBt·H2O gave intermediate phosphonoacetate 199, which was used without further purification. Horner–Wadsworth–Emmons olefination using the conditions developed by Still and Gennari (KHMDS, 18-crown-6, THF, –100 °C) afforded fully synthetic leucascandrolide A (43) in 10% yield (from 45) as a 5:1 mixture of inseparable Z/E isomers (Scheme 83).
Scheme 83. (a) 45, HOBt·H₂O, EDCI·HCl, CH₂Cl₂, RT, 15 min; (b) 18C6·CH₃CN, KHMDS, THF, –78 °C, 1 h, then 178, THF, –100 °C, 2 h, 10% (Z:E = 5:1).
4 Conclusion

When we embarked on the program aiming at the total synthesis of leucascandrolide A, the novelty of some projected key steps rendered the feasibility of our strategy uncertain. We were delighted to find that, in spite of numerous drawbacks, the project could be successfully completed. A number of routes were abandoned, either because of dead-ends or because of the identification of more enticing strategies.

With its eight stereogenic centers, leucascandrolide A represents a demanding target. The synthetic challenges encountered include (i) the access to enantiomerically enriched building blocs, (ii) the stereoselective formation of both trisubstituted tetrahydropyran rings, (iii) the macrocyclization reaction, (iv) the differentiation of alcohol functionalities, and (v) the stereoselective introduction of three carbon–carbon double bonds.

As originally intended, this project constituted an ideal opportunity to apply newly developed methods for asymmetric C–C-bond formation. In this respect, the enantioselective dienolate addition to aldehydes, catalyzed by a copper fluoride complex, as well as the addition of in situ-generated zinc acetylides to aldehydes, both developed in the Carreira group, were successfully applied to the synthesis of aldehyde 112 and methyl ketone 129.
The salient and most distinctive feature of our approach is the stereoselective formation of the 2,6-trans-substituted tetrahydropyran ring by 2,4,6-triisopropylphenylselenyl bromide-mediated cyclization of a 6-hydroxy alkene onto an olefinic bond. To the best of our knowledge, the use of this reagent is unprecedented for the formation of six-membered heterocycles. In all other syntheses of leucascandrolide A, this structural element was introduced by C-glycosidation.

Furthermore, the efficiency of tin-free radical reduction using the silylated cyclohexadiene 160 recently reported by Studer was demonstrated, for the first time, on a highly functionalized substrate.

Interesting observations were made in the context of the macrolactonization reaction. Indeed, the importance of the C9 methyl ether was established by showing the recalcitrance of seco acid 164, incorporating a C9 hydroxy group, towards cyclization, a consequence of a putative, intramolecular hydrogen-bonded network. It was found that the use of DMF, a hydrogen bond breaking solvent, resulted in the formation of the desired macrocycle.

Unexpectedly, leucascandrolide A has become, over the past three years, one of the ‘hot molecules’ in synthetic organic chemistry, which is manifest in the large number of research groups working on its synthesis and underlines the synthetic challenges encountered.

To assess the results of our own efforts, comparison to the work reported by others is important, and, in this regard, two easily tangible criteria are the number of synthetic steps and the overall yield. Our synthesis of the macrolide moiety 45 proceeds in only nineteen steps (longest linear sequence) and 3.5% overall yield, compared to routes by Leighton (18 steps, 2.2%), Rychnovsky (28 steps, 0.77%), Wipf (25 steps, 0.24%), and Kozmin (18 steps, 2.3%).
We have developed a highly efficient and concise total synthesis of leucascandrolide A. Our approach relies on the extensive use of modern stereoselective methods.
5.1. General Methods

All non-aqueous reactions were carried out using oven-dried (90 °C) or flame-dried glassware under a positive pressure of dry nitrogen unless otherwise noted.

Tetrahydrofuran, diethyl ether, toluene, acetonitrile, and methylene chloride were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H₂O content < 30 ppm, Karl–Fischer titration). Benzene and 1,2-dimethoxyethane were distilled from sodium/benzophenone ketyl under an atmosphere of dry nitrogen. Methanol was distilled from magnesium turnings and iodine under an atmosphere of dry nitrogen. Triethylamine, diisopropylamine, and pyridine were distilled from KOH under an atmosphere of dry nitrogen. Trimethylchlorosilane was distilled from calcium hydride. Triethylchlorosilane, diethylisopropylamine (Hünig’s base), tri- n-butyltin hydride (nBu₃SnH), 2,4,6-trichlorobenzoyl chloride (Yamaguchi reagent), 2,2,6-trimethyl-[1,3]dioxin-4-one, 1,1,1,3,3,3-hexamethyldisilazane, and crotonaldehyde were distilled prior to use. 4-N,N-dimethylamino pyridine was recrystallized from toluene. 2,6-di-tert-butyl-4-

methyl pyridine was flashed over activated, acidic alumina. Potassium hydride (commercially available as a dispersion in mineral oil) was purified according to the procedure reported by Brown.\textsuperscript{179} n-Butyl lithium was titrated with sBuOH/phenanthroline.\textsuperscript{180} KHMDS solutions were titrated according to a literature procedure.\textsuperscript{181} All other commercially available reagents were used without further purification. Tetra-\textit{n}-propyl ammonium perruthenate,\textsuperscript{182} (1-diazo-2-oxo-propyl)phosphonic acid dimethyl ester,\textsuperscript{183} tetra-\textit{n}-butylammonium triphenyl difluorosilicate,\textsuperscript{87a} (R)-1,2-isopropylidene glyceraldehyde,\textsuperscript{76} 2,4,6-triisopropylphenylselenium bromide,\textsuperscript{134} and Dess–Martin periodinane\textsuperscript{184} were prepared according to literature procedures.

Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using Merck Silica Gel 60 F\textsubscript{254} plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate or potassium permanganate stain.

Chromatographic purification of products (flash chromatography) was performed on E. Merck Silica Gel 60 (230–400 mesh) using a forced flow of eluant at 0.3–0.5 bar.\textsuperscript{185} Concentration under reduced pressure was performed by rotary

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evaporation at 40 °C at the appropriate pressure, unless otherwise stated. Purified compounds were further dried for 12–72 h under high vacuum (0.01–0.05 Torr). Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

**Melting points**: measured on a Büchi 510 apparatus. All melting points were measured in open capillaries and are uncorrected.

**Optical rotations**: Optical rotations were measured on a Jasco DIP-1000 polarimeter operating at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]_D^\text{T}$, concentration (g/100 ml), and solvent.

**NMR spectra**: NMR spectra were recorded either on a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz for $^1$H and $^{13}$C acquisitions, respectively, or on a Bruker DRX500 spectrometer operating at 500 MHz and 125 MHz for $^1$H and $^{13}$C acquisitions, respectively. Chemical shifts ($\delta$) are reported in ppm with the solvent resonance as the internal standard relative to chloroform ($\delta$ 7.26) and benzene ($\delta$ 7.15) for $^1$H, and chloroform ($\delta$ 77.0) and benzene ($\delta$ 128.0) for $^{13}$C. All $^{13}$C spectra were measured with complete proton decoupling. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz.

**IR spectra**: recorded on a PerkinElmer Spectrum RXI FT-IR spectrophotometer. Absorptions are given in wavenumbers (cm$^{-1}$).

**Mass spectra**: recorded by the MS service at ETH Zürich. EI-MS ($m/z$): VG-TRIBRID spectrometer. MALDI-MS ($m/z$): IonSpec Ultima Fourier Transform Mass Spectrometer.

**Elemental analyses**: performed at the Mikrolabor der ETH Zürich.
**High-performance liquid chromatography:** performed on a Merck Hitachi (Interface D-7000, UV-Detector L-7400, Pump L-7100). The detector wavelength was fixed at $\lambda = 254$ nm. All chromatograms were taken at ambient temperature.

**Chemical names:** generated with AutoNom 2.02 (Beilstein Informationssysteme GmbH) and modified where appropriate.

Buffers were prepared according to the following procedures:

- **pH 7 phosphate buffer:** $\text{KH}_2\text{PO}_4$ (6.8 g), NaOH (1.16 g), H$_2$O (1000 ml)
- **pH 8.6 carbonate buffer:** NaHCO$_3$ (42 g), Na$_2$CO$_3$ (0.53 g), H$_2$O (1000 ml)
5.2. Experimental Procedures and Characterization Data

5.2.1. Synthesis of the Macrolide Moiety 45

5.2.1.1. Synthesis of Aldehyde 112

\[ \text{N-((1R,2R)-2-Hydroxy-1-methyl-2-phenyl-ethyl)-N-methyl-propionamide (94).} \]

To a solution of (1R,2R)-(−)-pseudoephedrine (50.0 g, 302 mmol, 1.00 equiv) in CH₂Cl₂ (540 ml) at room temperature was added Et₃N (46.2 ml, 340 mmol, 1.10 equiv) and propionic anhydride (57.6 ml, 320 mmol, 1.07 equiv) in 1 ml portions over 10 min. After stirring for 20 min, the mixture was washed with saturated, aqueous NaHCO₃ (400 ml), 1.0 M aqueous HCl (2 × 400 ml) and brine (400 ml). The organic layer was dried over anhydrous Na₂SO₄ and filtered. Concentration under reduced pressure gave a white solid which was dried under vacuum for 12 h. This solid was dissolved in refluxing toluene (280 ml), placed in a water bath at 80 °C and allowed to slowly cool to ambient temperature. Further cooling to −18 °C overnight followed by filtration and drying afforded known propionamide 94 (58.4 g, 88%) as white crystals.

\[ ^1H \text{ NMR } (300 \text{ MHz, } C₆D₆) \delta 7.45–6.95 \text{ (m, 5 H), } 4.83 \text{ (br s, 1 H), } 4.51 \text{ (t, 1 H, } J = 7.2 \text{ Hz), } 4.20–4.00 \text{ (m, 2 H), } 3.75–3.60 \text{ (m, 1 H), } 2.77 \text{ (s, 3 H), } 2.40 \text{ (m, 2 H), } 2.06 \text{ (s, 3 H), } 1.73 \text{ (m, 2 H), } 1.22 \text{ (t, 3 H, } J = 7.3 \text{ Hz), } 1.10–0.90 \text{ (m, 6 H), } 0.53 \text{ (d, 3 H, } J = 6.7 \text{ Hz).} \]
These spectral characteristics were identical to those previously reported.\textsuperscript{186}

\[
\text{Ph} \quad \text{N} \quad \text{Me} \quad \text{Me} \quad \text{OH} \quad \text{Me} \quad \text{Me} \\
\text{95}
\]

(2S)-2-Methyl-pent-4-enoic acid ((1R,2R)-2-hydroxy-1-methyl-2-phenyl-ethyl)-methylamide (95). To an ice-cooled suspension of flame-dried lithium chloride (17.3 g, 407 mmol, 6.00 equiv) in THF (80 ml) was added \(i\)Pr\(_2\)NH (21.5 ml, 152 mmol, 2.25 equiv) followed by \(n\)BuLi (2.28 M in hexane, 62.0 ml, 141 mmol, 2.08 equiv). The yellow slurry was stirred for 15 min at 0 °C, 20 min at room temperature and then cooled to −78 °C. A solution of amide 94 (15.0 g, 67.8 mmol, 1.00 equiv) in THF (200 ml) was added via cannula over 30 min and the solution was vigorously stirred for 45 min. After 15 min at 0 °C, 15 min at room temperature, and recooling to −78 °C, allyl iodide (17.0 g, 102 mmol, 1.50 equiv) was added neat and the reaction mixture was stirred for 1 h at −78 °C and an additional 60 min at 0 °C. The reaction mixture was quenched by the addition of saturated, aqueous NH\(_4\)Cl (150 ml) and saturated, aqueous Na\(_2\)S\(_2\)O\(_3\) (10 ml). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 150 ml). The combined organic solutions were washed with brine (100 ml), dried over anhydrous Na\(_2\)SO\(_4\), and filtered. Concentration under reduced pressure provided known 95 (17.7 g, 99%) as a thick oil, which was used without further purification.

\(^1\text{H NMR}\) (200 MHz, CDCl\(_3\)) \(\delta 7.38–7.27\) (m, 5 H), 5.79–5.66 (m, 1 H), 5.01–4.99 (m, 2 H), 4.64–4.60 (m, 1 H), 4.50–4.39 (m, 1 H), 2.88 (s, 3 H), 2.71 (q, 1 H, \(J = 6.6\) Hz), 2.42–2.34 (m, 1 H), 2.17–2.06 (m, 1 H), 1.16–1.03 (m, 6 H).

These spectral characteristics were identical to those previously reported.\(^{186}\)

\(96\)

\((2S)-2\text{-Methyl-pent-4-en-1-ol (96)}\). To a solution of \(i\text{Pr}_2\text{NH}\) (20.1 ml, 142 mmol, 4.20 equiv) in THF (100 ml) at 0 °C was added \(n\text{BuLi}\) (2.28 M in hexane, 59.5 ml, 136 mmol, 4.00 equiv) and the resulting yellow solution was warmed to room temperature for 10 min before being recooled to 0 °C. Ammonia-borane complex (90% purity, 4.9 g, 0.14 mmol, 4.2 equiv) was added as a solid in portions to give a white slurry which was stirred at ambient temperature for 1 h. Amide 95 (8.85 g, 33.9 mmol, 1.00 equiv) was added to the reaction mixture at 0 °C and stirring was continued at room temperature for 2 h. The mixture was cooled to 0 °C, carefully quenched by the portionwise addition of 2.0 M aqueous HCl (200 ml) and extracted with diethyl ether (3 × 250 ml). The combined organic solutions were washed with 1.5 M aqueous HCl (200 ml) and brine (200 ml), dried over anhydrous Na\(_2\text{SO}_4\), filtered, and concentrated under reduced pressure (40 °C at 400 mbar) to give a THF solution of alcohol 96. This solution was poured onto 1.0 M aqueous KOH (200 ml) and stirred for 1 h at room temperature. After acidification with 1.0 M aqueous HCl (200 ml), the mixture was extracted with diethyl ether (3 × 200 ml). The combined organic solutions were washed with brine (200 ml), dried over anhydrous Na\(_2\text{SO}_4\), filtered, and concentrated under reduced pressure (40 °C at 180 mbar) to give (2S)-methyl-pent-4-en-1-ol (96) which was used without further purification.
1H NMR (200 MHz, CDCl\textsubscript{3}) \(\delta\) 5.84 (ddt, 1 H, \(J = 17.0, 10.4, 7.1\) Hz), 5.23–5.00 (m, 2 H), 3.51 (dd, 2 H, \(J = 5.8, 4.2\) Hz), 2.24–2.13 (m, 1 H), 2.04–1.93 (m, 1 H), 1.81–1.71 (m, 1 H), 1.31 (br s, 1 H), 0.95 (d, 3 H, \(J = 6.6\) Hz).

These spectral characteristics were identical to those previously reported.\(^{187}\)

(2S)-Triisopropyl-(2-methyl-pent-4-enyloxy)-silane (97). To a solution of alcohol 96 (3.39 g, 33.9 mmol, 1.00 equiv) in dry DMF (20 ml) at 0 °C was added imidazole (5.80 g, 84.7 mmol, 2.50 equiv) followed by TIPSCl (8.60 ml, 40.7 mmol, 1.20 equiv) and DMAP (414 mg, 3.39 mmol, 10.0 mol%). The cloudy mixture was stirred for 1 h at room temperature and then poured onto H\textsubscript{2}O (30 ml). The layers were separated and the aqueous phase was extracted with pentane (3 \(\times\) 50 ml). The combined organic solutions were washed with brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated under reduced pressure to give silyl ether 97 which was used without further purification.

1H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 5.81 (ddt, 1 H, \(J = 17.1, 10.0, 6.9\) Hz), 5.04–4.97 (m, 2 H), 3.56–3.47 (m, 2 H), 2.28–2.19 (m, 1 H), 1.92–1.83 (m, 1 H), 1.75–1.64 (m, 1 H), 1.12–0.96 (m, 21 H), 0.89 (d, 3 H, \(J = 6.9\) Hz).

These spectral characteristics were identical to those previously reported.\(^{64a}\)

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(4S)-4-Methyl-5-triisopropylsilanyloxy-pentan-1-ol (98). To olefin 97 (8.92 g, 34.8 mmol, 1.00 equiv) in THF (280 ml) was added 9-BBN (0.50 M in THF, 0.14 l, 70 mmol, 2.0 equiv) over 20 min. The clear, colorless solution was stirred for 6 h at ambient temperature and then cooled to 0 °C, whereupon 2.0 M aqueous NaOH (70 ml) and aqueous H₂O₂ 30% (70 ml) were added successively. The resulting mixture was stirred for 1 h at 0 °C and for 10 h at room temperature. Following extraction with diethyl ether (2 × 200 ml), the combined organic solutions were washed with brine (200 ml), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 10:1) provided alcohol 98 (7.15 g, 75% over 3 steps) as a clear, colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 3.64 (t, 2 H, J = 6.5 Hz), 3.54 (dd, 1 H, J = 9.7, 6.2 Hz), 3.49 (dd, 1 H, J = 9.7, 6.2 Hz), 1.71–1.40 (m, 4 H), 1.21–1.00 (m, 22 H), 0.91 (d, 3 H, J = 6.8 Hz).

These spectral characteristics were identical to those previously reported.³³c

(2S)-Triisopropyl-(2-methyl-hex-5-ynyloxy)-silane (90). To a solution of alcohol 98 (7.15 g, 26.0 mmol, 1.00 equiv) in CH₂Cl₂ (150 ml) were added TEMPO (78.0 mg, 0.520 mmol, 2.00 mol%) and KBr (310 mg, 2.60 mmol, 10.0 mol%) at room temperature, and the resulting solution was cooled to 0 °C. Aqueous sodium hypochlorite (13%, 30 ml, 52 mmol, 2.0 equiv) in pH 8.6 phosphate buffer (110 ml)
was added portionwise and the biphasic solution vigorously stirred at 0 °C for 15 min. The reaction was quenched with MeOH (10 ml), the layers were separated, and the aqueous solution was extracted with CH₂Cl₂ (3 × 150 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give aldehyde 99 as a clear liquid which was used without further purification.

To a solution of aldehyde 99 in MeOH (300 ml) were added K₂CO₃ (7.20 g, 54.0 mmol, 2.00 equiv) and Ohira reagent (100) (6.50 g, 33.8 mmol, 1.30 equiv). The cloudy mixture was stirred at ambient temperature for 16 h before being diluted with hexane (300 ml) and washed with saturated, aqueous NaHCO₃. The aqueous layer was extracted with hexane (3 × 200 ml), washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford alkyne 90 (6.13 g, 87% yield over two steps).

R_f = 0.26 (hexane).

**Optical Rotation:** [α]_{22}^{D} (c 0.96, CHCl₃) = −0.2°.

**1H NMR** (300 MHz, CDCl₃) δ 3.54–3.47 (m, 2 H), 2.32–2.11 (m, 2 H), 1.90 (t, 1 H, J = 2.8 Hz), 1.82–1.62 (m, 2 H), 1.40–1.26 (m, 1 H), 1.10–1.00 (m, 21 H), 0.89 (d, 3 H, J = 6.5 Hz).

**13C NMR** (75 MHz, CDCl₃) δ 84.6, 68.1, 68.0, 35.0, 32.1, 18.0, 16.4, 16.2, 12.0.

**IR** (thin film) ν 2944, 2867, 2120, 1463, 1389, 1367, 1246, 1149, 1102, 1070, 1048, 1014, 996, 918, 882, 791, 681, 630 cm⁻¹.

**HRMS** (EI) calcd for C₁₃H₂₅OSi [M–C₅H₅]⁺, 225.1675; found, 225.1665.
(1R,6S)-1-((4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-6-methyl-7-triisopropylsilanyloxy-hept-2-yn-1-ol (105). Zn(OTf)₂ (2.23 g, 6.14 mmol, 1.10 equiv) and (−)-N-methyl ephedrine (1.10 g, 6.14 mmol, 1.10 equiv) were suspended in anhydrous toluene (15 ml) and purged with N₂ for 15 min. Et₃N (0.940 ml, 6.70 mmol, 1.20 equiv) was added in one portion and the white slurry was stirred at ambient temperature for 3 h. Alkyne 90 (1.50 g, 5.59 mmol, 1.00 equiv) was added, followed, after 30 min, by freshly distilled (R)-1,2-isopropylidene glyceraldehyde (89) (1.16 g, 8.94 mmol, 1.60 equiv) (in one portion). The cloudy mixture was stirred at room temperature for 48 h and then quenched with saturated, aqueous NH₄Cl (50 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 200 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by gradient flash chromatography (hexane/EtOAc 9:1 → 4:1) provided propargylic alcohol 105 (1.66 g, 75% yield, d.r. = 94:6 by 1H NMR by integration of the signals at 4.28 and 4.48 ppm, respectively) as a clear, colorless oil.

Rᵥ = 0.52 (hexane/EtOAc 2:1).

Optical Rotation: [α]²⁷°₀ (c 1.00, CHCl₃) = +12.4°.

¹H NMR (300 MHz, CDCl₃) δ 4.31–4.25 (m, 1 H), 4.17–4.05 (m, 2 H), 3.89–3.83 (m, 1 H), 3.51 (d, 2 H, J = 5.6 Hz), 2.29–2.20 (m, 2 H), 1.76–1.63 (m, 2 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 1.36–1.22 (m, 1 H), 1.09–1.03 (m, 21 H), 0.90 (d, 3 H, J = 6.7 Hz).
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 110.4, 87.4, 79.3, 77.0, 68.1, 66.3, 64.7, 35.1, 32.0, 26.9, 25.3, 18.0, 16.5, 16.4, 12.0.

IR (thin film) $\nu$ 3448, 2943, 2892, 2866, 2231, 1463, 1382, 1255, 1215, 1152, 1101, 1071, 918, 882, 855, 798, 682, 659 cm$^{-1}$.

Anal. Calcd for C$_{22}$H$_{42}$O$_4$Si: C, 66.28; H, 10.62. Found: C, 66.09; H, 10.74.

HRMS (MALDI) calcd for C$_{22}$H$_{42}$O$_4$SiNa $[M+Na]^+$, 421.2750; found, 421.2745.

\[\text{Me} \quad \text{OTIPS} \quad \text{O} \quad \text{OH} \quad 106\]

(15,6S)-1-((4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-6-methyl-7-triisopropylsilanyloxy-hept-2-yln-1-ol (106).

$R_f = 0.50$ (hexane/EtOAc 2:1).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.51–4.45 (m, 1 H), 4.24–4.18 (m, 1 H), 4.10–4.01 (m, 2 H), 3.51 (d, 2 H, $J = 5.6$ Hz), 2.31–2.20 (m, 2 H), 2.16 (d, 1 H, $J = 3.7$ Hz), 1.79–1.63 (m, 2 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 1.36–1.24 (m, 1 H), 1.12–1.00 (m, 21 H), 0.90 (d, 3 H, $J = 6.3$ Hz).
(6S)-1-((4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-6-methyl-7-triisopropyl-silanyloxy-hept-2-yn-1-one (107). A mixture of propargylic alcohol 105 (170 mg, 0.488 mmol, 1.00 equiv), 4 Å molecular sieves (250 mg) and NMO (86.0 mg, 0.732 mmol, 1.50 equiv) in anhydrous CH$_2$Cl$_2$ (1 ml) was stirred at room temperature for 30 min. TPAP (8.5 mg, 24 µmol, 5.0 mol%) was added in one portion and the resulting dark-green suspension was stirred at ambient temperature for 1 h. The reaction mixture was filtered over silica gel (hexane/EtOAc 2:1) and concentrated under reduced pressure. Purification by flash chromatography afforded ketone 107 (127 mg, 75% yield) as a clear, colorless oil.

$R_f = 0.54$ (hexane/EtOAc 2:1).

**Optical Rotation**: $[\alpha]^{22}_D$ (c, CHCl$_3$) = +4.8°.

$^1$H NMR (300 MHz, CDCl$_3$) δ 4.51 (dd, 1 H, $J = 7.4, 5.1$ Hz), 4.22 (dd, 1 H, $J = 8.8, 7.4$ Hz), 4.13 (dd, 1 H, $J = 8.8, 5.1$ Hz), 3.56 (dd, 1 H, $J = 9.7, 5.2$ Hz), 3.49 (dd, 1 H, $J = 9.7, 5.7$ Hz), 2.56–2.37 (m, 2 H), 1.86–1.66 (m, 2 H), 1.50 (s, 3 H), 1.47–1.40 (m, 1 H), 1.40 (s, 3 H), 1.13–0.99 (m, 21 H), 0.91 (d, 3 H, $J = 6.6$ Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 186.4, 111.6, 99.8, 81.0, 78.8, 77.5, 77.0, 76.6, 68.0, 66.8, 35.2, 31.4, 26.2, 25.6, 18.2, 17.2, 16.4, 12.1.

**IR** (thin film) ν 2944, 2892, 2867, 2212, 1675, 1464, 1382, 1373, 1256, 1216, 1150, 1102, 1069, 1014, 996, 919, 883, 845, 795, 682, 668 cm$^{-1}$.

**HRMS** (MALDI) calcd for C$_{22}$H$_{40}$O$_4$SiNa [M+Na]$^+$, 419.2594; found, 419.2591.
(1R,6S)-Benzoic acid 1-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-6-methyl-7-triisopropylsilanyloxy-hept-2-ynyl ester (109). To a solution of propargylic alcohol 105 (1.65 g, 4.14 mmol, 1.00 equiv) in anhydrous THF (40 ml) at ambient temperature was added LiAlH₄ (785 mg, 20.7 mmol, 5.00 equiv) and the suspension was stirred for 5 h. The reaction was quenched by the careful addition of ethyl acetate (15 ml). Sodium sulfate decahydrate was added and the suspension stirred vigorously for 12 h at room temperature. The remaining solids were filtered off and the filtrate was concentrated under reduced pressure. The resulting colorless oil was used without further purification.

To a solution of the unpurified alcohol in dry CH₂Cl₂ (40 ml) were added successively Et₃N (1.12 ml, 8.00 mmol, 2.00 equiv), benzoyl chloride (0.930 ml, 8.00 mmol, 2.00 equiv) and DMAP (97.0 mg, 0.800 mmol, 20.0 mol%) at 0 °C. The solution was stirred at room temperature for 15 h before being quenched with saturated, aqueous NaHCO₃ (40 ml). The aqueous layer was extracted with diethyl ether (3 × 50 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1) afforded benzoate 109 (1.89 g, 90% yield over two steps) as a clear, colorless oil.

R_f = 0.26 (hexane/EtOAc 9:1).

Optical Rotation: [α]_D^{22} (c 1.00, CHCl₃) = +10.4°.
\textbf{Experimental Section}

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.10–8.04 (m, 2 H), 7.59–7.52 (m, 1 H), 7.47–7.40 (m, 2 H), 6.00–5.83 (m, 1 H), 5.60–5.45 (m, 2 H), 4.36–4.28 (m, 1 H), 4.04 (dd, 1 H, $J=8.6, 6.6$ Hz), 3.83 (dd, 1 H, $J=8.6, 6.0$ Hz), 3.54–3.43 (m, 2 H), 2.15–1.98 (m, 2 H), 1.64–1.49 (m, 2 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 1.25–1.00 (m, 22 H), 0.88 (d, 3 H, $J=6.6$ Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.7, 137.8, 132.9, 130.4, 129.8, 128.3, 123.7, 110.0, 76.8, 75.7, 68.3, 65.8, 35.6, 32.3, 29.9, 26.5, 25.5, 18.0, 16.6, 12.0.

IR (thin film) $\nu$ 2942, 2866, 1723, 1462, 1452, 1381, 1370, 1315, 1269, 1215, 1155, 1110, 1070, 1026, 972, 882, 851, 794, 711, 682 cm$^{-1}$.

\textbf{Anal. Calcd} for C$_{29}$H$_{48}$O$_5$Si: C, 69.00; H, 9.58. Found: C, 69.17; H, 9.43.

\textbf{HRMS} (MALDI) calcd for C$_{29}$H$_{48}$O$_5$SiNa $[\text{M+Na}]^{+}$, 527.3169; found, 527.3164.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{111}};
\node at (-1.5,1.5) {$\text{Me}$};
\node at (-1.5,0.5) {$\text{Me}$};
\node at (1.5,1.5) {$\text{OH}$};
\node at (1.5,0.5) {$\text{OBz}$};
\end{tikzpicture}
\end{center}

(1R,6S)-Benzoic acid 1-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-7-hydroxy-6-methyl-hept-2-enyl ester (111). To an ice-cooled solution of silyl ether 109 (1.87 g, 3.70 mmol, 1.00 equiv) in dry THF (40 ml) was added TBAF (1.0 M in THF, 4.1 ml, 4.1 mmol, 1.1 equiv). The solution was stirred at 0 °C for 12 h, then at ambient temperature for another 12 h. Saturated, aqueous NaHCO$_3$ (40 ml) was added and the aqueous layer was extracted with diethyl ether (3 $\times$ 50 ml). The combined organic solutions were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and
concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 2:1) gave alcohol \textbf{111} (1.24 g, 96% yield) as clear, colorless oil.

\[ R_f = 0.68 \text{ (hexane/EtOAc 1:1)}. \]

\textbf{Optical Rotation:} \([\alpha]^{22}_D (c 0.98, \text{CHCl}_3) = +15.6^\circ.\]

\textbf{1H NMR} (300 MHz, CDCl$_3$) \(\delta\) 8.09–8.04 (m, 2 H), 7.60–7.52 (m, 1 H), 7.48–7.40 (m, 2 H), 6.00–5.86 (m, 1 H), 5.57–5.47 (m, 2 H), 4.33 (ddd, 1 H, \(J = 6.1, 6.1, 6.0\) Hz), 4.05 (dd, 1 H, \(J = 8.6, 6.1\) Hz), 3.82 (dd, 1 H, \(J = 8.6, 6.0\) Hz), 3.51–3.37 (m, 2 H), 2.22–1.98 (m, 2 H), 1.67–1.47 (m, 2 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 1.29–1.13 (m, 1 H), 0.90 (d, 3 H, \(J = 6.6\) Hz).

\textbf{13C NMR} (75 MHz, CDCl$_3$) \(\delta\) 165.7, 137.3, 133.0, 130.3, 129.7, 128.4, 124.1, 110.1, 76.8, 75.6, 68.0, 65.8, 35.3, 32.1, 29.8, 26.5, 25.4, 16.5.

\textbf{IR} (thin film) \(\nu\) 3436, 2985, 2930, 1720, 1452, 1371, 1316, 1270, 1215, 1177, 1156, 1112, 1069, 1026, 974, 848 cm\(^{-1}\).

\textbf{Anal. Calcd} for C$_{20}$H$_{28}$O$_5$: C, 68.94; H, 8.10. Found: C, 69.11; H, 8.11.

\textbf{HRMS} (MALDI) calcd for C$_{20}$H$_{28}$O$_5$Na [M+Na]$^+$, 371.1835; found, 371.1829.

\begin{center}
\begin{tikzpicture}
  \node (111) at (0,0) {\includegraphics[width=0.5\textwidth]{111.png}};
\end{tikzpicture}
\end{center}

\textbf{(1R,6S)-Benzoic acid 1-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-6-methyl-7-oxohept-2-enyl ester (112)}. To a solution of alcohol \textbf{111} (700 mg, 2.01 mmol, 1.00 equiv) in anhydrous CH$_2$Cl$_2$ were added 4 Å molecular sieves (1.00 g) and NMO (353 mg,
3.00 mmol, 1.50 equiv). The mixture was stirred at ambient temperature for 30 min, whereupon TPAP (35.0 mg, 0.100 mmol, 5.00 mol%) was added in one portion. The resulting dark-green mixture was stirred at ambient temperature for 10 min. The reaction mixture was filtered over silica gel using hexane/EtOAc 1:1 as eluant and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 2:1) provided aldehyde 112 (600 mg, 87% yield) as a clear, colorless oil.

\[ R_f = 0.54 \text{ (hexane/EtOAc 2:1).} \]

**Optical Rotation:** \([\alpha]_D^{25}\) (c 1.03, CHCl₃) = +29.3°.

**1H NMR** (300 MHz, C₆D₆) \(\delta 9.19 \text{ (d, 1 H, } J = 1.6 \text{ Hz), 8.26–8.20 (m, 2 H), 7.12–7.00 (m, 3 H), 5.75–5.68 (m, 1 H), 5.65 (dd, 1 H, } J = 6.7, 6.6 \text{ Hz), 5.44 (ddt, 1 H, } J = 15.4, 7.6, 1.4 \text{ Hz), 4.17 (dddd, 1 H, } J = 6.2, 6.2, 6.2 \text{ Hz), 3.80–3.71 (m, 2 H), 1.82–1.64 (m, 3 H), 1.48 (s, 3 H), 1.44–1.31 (m, 1 H), 1.29 (s, 3 H), 1.04–0.96 (m, 1 H), 0.66 (d, 3 H, } J = 7.0 \text{ Hz).} \)

**13C NMR** (75 MHz, CDCl₃) \(\delta 204.6, 165.6, 135.9, 133.0, 130.2, 129.7, 128.4, 125.1, 110.0, 76.7, 75.2, 65.7, 45.6, 29.6, 29.4, 26.4, 25.4, 13.2. \)

**IR** (thin film) \(\nu 2985, 2934, 1720, 1452, 1372, 1315, 1269, 1215, 1177, 1156, 1112, 1069, 1026, 972, 849, 713 \text{ cm}^{-1}. \)


**HRMS** (MALDI) calcd for C₂₀H₂₆O₅Na [M+Na]⁺, 369.1678; found, 369.1672.
5.2.1.2. Synthesis of Methyl Ketone

(2,2-Dimethyl-6-methylene-6H-[1,3]dioxin-4-yloxy)-trimethyl-silane (11).\textsuperscript{188} To a solution of $\text{iPr}_2\text{NH}$ (6.70 ml, 48.0 mmol, 1.09 equiv) in anhydrous THF (30 ml) at 0 °C was added $\text{nBuLi}$ (1.32 M in hexane, 36.4 ml, 48.0 mmol, 1.09 equiv) over 15 min. The clear, colorless solution was stirred at 0 °C for 20 min and then cooled to –78 °C. 2,2,6-Trimethyl-[1,3]dioxin-4-one (5.70 ml, 44.0 mmol, 1.00 equiv) was added neat over 10 min and the resulting yellowish solution was stirred at –78 °C for 60 min. TMSCl (6.60 ml, 52.0 mmol, 1.18 equiv) was added via cannula over 15 min and the reaction mixture stirred for an additional 30 min at –78 °C. The thick, orange suspension was allowed to warm to ambient temperature over 90 min and was then filtered over anhydrous Na$_2$SO$_4$ under argon. The filter cake was rinsed twice with each 7 ml dry pentane and the clear, orange filtrate was concentrated under reduced pressure (80 mbar). The remaining red oil was distilled (the oil-bath temperature must not exceed 70 °C in order to avoid product decomposition) under reduced pressure (0.5 mbar, 40 °C) to give 11 (8.20 g, 87% yield) as a colorless liquid, which can be stored at –18 °C under argon for extended periods of time.

$^1\text{H NMR}$ (300 MHz, CDCl$_3$) $\delta$ 4.64 (s, 1 H), 4.07 (s, 1 H), 3.87 (s, 1 H), 1.54 (s, 6 H), 0.26 (s, 9 H).

$^{13}\text{C NMR}$ (75 MHz, CDCl$_3$) $\delta$ 153.1, 151.5, 102.3, 84.9, 76.5, 24.5, 0.3.

(188) The experimental conditions reported herein lead to improved yields compared to the conditions reported in ref. 20b.
6-((25,3E)-2-Hydroxy-pent-3-enyl)-2,2-dimethyl-[1,3]dioxin-4-one (116). A mixture of (R)-Tol-BINAP (671 mg, 1.07 mmol, 2.10 mol%) and Cu(OTf)₂ (371 mg, 1.03 mmol, 2.00 mol%) in anhydrous THF (250 ml) was stirred at ambient temperature for 15 min, giving a clear, initially dark-green solution which slowly turned canary yellow. A solution of nBu₄NPh₃SiF₂ (1.11 g, 2.05 mmol, 4.00 mol%) in THF (5 ml) was added at room temperature and stirring was continued for another 10 min. After cooling the mixture to −78 °C, a solution of TMS-dienolate 11 (11.0 g, 51.3 mmol, 1.00 equiv) in THF (5 ml) was added dropwise, followed by slow addition of freshly distilled crotonaldehyde (8.44 ml, 103 mmol, 2.00 equiv). The resulting dark-red solution was stirred at −78 °C for 4 h. TFA (10.0 ml, 128 mmol, 2.50 equiv) was added and the cooling bath removed. The solution was allowed to reach room temperature, during which time the desilylation process was monitored by TLC. Upon completion, the solution was diluted with diethyl ether (250 ml) and adjusted to pH 7 by the careful addition of saturated, aqueous NaHCO₃. The layers were separated, the aqueous phase was extracted with diethyl ether (3 × 300 ml) and the combined organic solutions were washed with brine (300 ml), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 3:1) provided aldol adduct 116 (4.79 g, 44% yield) as a clear, colorless oil.

Rₛ = 0.17 (hexane/Et₂O 1:3).
**1H NMR** (300 MHz, CDCl₃) δ 5.75 (ddq, 1 H, J = 15.3, 6.5, 1.0 Hz), 5.50 (ddq, 1 H, J = 15.3, 7.0, 1.6 Hz), 5.31 (t, 1 H, J = 0.6 Hz), 4.42–4.31 (m, 1 H), 2.47 (ddd, 1 H, J = 14.5, 7.4, 0.6 Hz), 2.41 (ddd, 1 H, J = 14.5, 5.8, 0.6 Hz), 1.73–1.67 (m, 9 H).

**HPLC:** Chiralcel OD column. hexane/2-propanol 95:5, flow rate 0.9 ml/min, minor enantiomer 15.7, major enantiomer 17.1. The enantiomers were obtained in a ratio of 94.1:4.5 (91% ee).

These spectral characteristics were identical to those previously reported.⁸⁶a

![Structure](image)

(5S,6E)-5-Hydroxy-3-oxo-oct-6-enoic acid butyl ester (118). Dioxenone 116 (4.70 g, 22.1 mmol, 1.00 equiv) was dissolved in anhydrous 1-butanol (1000 ml) and the resulting solution was degassed by passing an argon stream through for 1 h. After heating to reflux for 1 h, the solution was allowed to cool to room temperature and was concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 4:1) gave hydroxy ester 118 (3.95 g, 78% yield) as pale, yellow oil.

R<sub>f</sub> = 0.33 (hexane/EtOAc 2:1).

**Optical Rotation:** [α]<sup>38</sup> <sub>D</sub> (c 0.97, CHCl₃) = −17.2°.

**1H NMR** (300 MHz, CDCl₃) δ 5.74 (ddq, 1 H, J = 15.3, 6.5, 1.1 Hz), 5.49 (ddq, 1 H, J = 15.3, 6.6, 1.6 Hz), 4.59–4.49 (m, 1 H), 4.14 (t, 2 H, J = 6.7 Hz), 3.48 (s, 2 H), 2.76 (d, 2 H, J = 6.1 Hz), 2.61 (d, 1 H, J = 3.6 Hz), 1.71–1.67 (m, 3 H), 1.66–1.57 (m, 2 H), 1.44–1.31 (m, 2 H), 0.93 (t, 3 H, J = 7.3 Hz).
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 202.9, 167.1, 132.5, 131.9, 68.4, 65.3, 49.9, 49.7, 30.4, 19.0, 17.6, 13.6.

IR (thin film) \(\nu\) 3446, 2962, 2937, 2876, 1742, 1715, 1651, 1454, 1410, 1384, 1317, 1274, 1152, 1062, 1035, 967 cm\(^{-1}\).

**Anal. Calcd** for C\(_{12}\)H\(_{20}\)O\(_4\)Si: C, 63.14; H, 8.83. Found: C, 62.98; H, 8.73.

**HRMS** (MALDI) calcd for C\(_{12}\)H\(_{20}\)O\(_4\)Na [M+Na]\(^+\), 251.1259; found, 251.1254.

![Diagram](image-url)

(3R,5S,6E)-3,5-Bis-triethylsilanyloxy-oct-6-enoic acid butyl ester (119). To a solution of MeOH (22.5 ml) in THF (110 ml) was added triethylborane (1.0 M in THF, 18 ml, 18 mmol, 1.1 equiv) dropwise under ice cooling. After stirring for 1 h at ambient temperature, the solution was cooled to –78 °C and keto ester 118 (3.70 g, 16.2 mmol, 1.00 equiv) in THF (15 ml) was added via cannula. Stirring was continued for 20 min at –78 °C before NaBH\(_4\) (3.68 g, 97.2 mmol, 6.00 equiv) was added in one portion. After 5 h at –78 °C, the excess reducing agent was quenched by the careful addition of saturated, aqueous NH\(_4\)Cl (10 ml). The solution was warmed to ambient temperature, diluted with diethyl ether (150 ml), and acidified to pH 1 using 1.0 M aqueous HCl. The layers were separated and the aqueous phase was extracted with diethyl ether (3 \(\times\) 150 ml). The combined organic extracts were washed with brine (200 ml), dried over anhydrous Na\(_2\)SO\(_4\) and filtered. Concentration under reduced pressure gave a colorless oil which was azeotroped with MeOH (3 \(\times\) 100 ml) to give the intermediate diol which was used without further purification.
To the unpurified diol in dry DMF (16 ml) was added imidazole (5.50 g, 81.0 mmol, 5.00 equiv) followed by TESCl (6.80 ml, 40.5 mmol, 2.50 equiv) and DMAP (197 mg, 1.62 mmol, 0.100 equiv). The mixture was stirred at ambient temperature for 12 h and then poured onto H₂O (30 ml). The layers were separated and the aqueous phase was extracted with pentane (3 × 100 ml). The combined organic solutions were washed with brine (100 ml), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford bis-silyl ether 119 as a single diastereoisomer (d.r. > 95:5 by ¹H NMR spectroscopy). A small amount was purified by flash chromatography (hexane/EtOAc 19:1) for characterization purposes. 

\[ R_f = 0.53 \text{ (hexane/EtOAc 9:1).} \]

**Optical Rotation:** \([\alpha]^{22}_D \text{ (c 1.1, CHCl}_3) = -13.0^\circ.\]

**¹H NMR** (300 MHz, CDCl₃) \(\delta\) 5.55 (dq, 1 H, \(J = 15.3, \ 6.3 \text{ Hz}\)), 5.38 (ddq, 1 H, \(J = 15.3, \ 7.2, \ 1.4 \text{ Hz}\)), 4.25–4.05 (m, 2 H), 4.10–3.95 (m, 2 H), 2.51 (dd, 1 H, \(J = 14.7, \ 5.2 \text{ Hz}\)), 2.41 (dd, 1 H, \(J = 14.7, \ 7.4 \text{ Hz}\)), 1.80–1.68 (m, 1 H), 1.65 (dd, 3 H, \(J = 6.3, \ 1.2 \text{ Hz}\)), 1.63–1.53 (m, 3 H), 1.41–1.24 (m, 2 H), 0.95–0.86 (m, 21 H), 0.60–0.49 (m, 12 H).

**¹³C NMR** (75 MHz, CDCl₃) \(\delta\) 171.9, 134.5, 126.2, 70.9, 66.9, 64.4, 46.5, 43.2, 30.8, 19.3, 17.7, 13.9, 7.0, 6.9, 5.2.

**IR** (thin film) \(\nu\) 2959, 2914, 2877, 1739, 1459, 1415, 1379, 1312, 1240, 1167, 1085, 1005, 967, 742 cm⁻¹.

**HRMS** (MALDI) calcd for C₂₄H₅₀O₄Si₂Na [M+Na]⁺, 481.3145; found, 481.3143.
(3R,5S,6E)-3,5-Bis-triethylsilanyloxy-oct-6-enal (120). To the unpurified ester 119 (16.2 mmol, 1.00 equiv) in toluene (140 ml) at –78 °C was added DIBAL–H (1.5 M in toluene, 13 ml, 19 mmol, 1.2 equiv) dropwise over 20 min. The solution was stirred at –78 °C for 30 min. Excess reducing agent was carefully quenched with MeOH (2 ml). The solution was diluted with diethyl ether (150 ml) and allowed to warm to room temperature. Saturated, aqueous sodium potassium tartrate (200 ml) was added and the solution was vigorously stirred at ambient temperature for 12 h. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 200 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1) afforded aldehyde 120 (5.76 g, 92% yield over 3 steps) as a clear, colorless oil.

\[ R_f = 0.46 \text{ (hexane/EtOAc 9:1).} \]

**Optical Rotation:** \([\alpha]^{22}_D (c 0.28, \text{CHCl}_3) = -3.2^\circ.\]

\(^1\text{H NMR}\) (300 MHz, CDCl₃) \(\delta 9.8\) (dd, 1 H, \(J = 3.0, 2.0\) Hz), 5.58 (ddq, 1 H, \(J = 15.3, 6.3, 0.6\) Hz), 5.41 (ddq, 1 H, \(J = 15.3, 7.2, 1.2\) Hz), 4.36–4.27 (m, 1 H), 4.19–4.10 (m, 1 H), 2.63 (dd, 1 H, \(J = 15.7, 4.7, 2.0\) Hz), 2.51 (dd, 1 H, \(J = 15.7, 6.6, 3.0\) Hz), 1.84 (dd, 1 H, \(J = 13.7, 7.2, 1.9\) Hz), 1.68 (dd, 3 H, \(J = 6.3, 1.1\) Hz), 1.66–1.60 (m, 1 H), 0.97–0.90 (m, 18 H), 0.63–0.51 (m, 12 H).

\(^{13}\text{C NMR}\) (75 MHz, CDCl₃) \(\delta 202.4, 134.2, 126.2, 70.7, 65.4, 50.9, 46.3, 17.6, 6.9, 6.8, 5.0.\)
IR (thin film) ν 2955, 2914, 2877, 1728, 1458, 1415, 1373, 1220, 1083, 1005, 967, 772, 743, 668 cm⁻¹.

HRMS (MALDI) calcd for C₂₀H₄₂O₃Na [M+Na]+, 409.2570; found, 409.2565.

(2E,5S,7S,8E)-5,7-Dihydroxy-deca-2,8-dienoic acid ethyl ester (121). To a suspension of flame-dried lithium chloride (560 mg, 13.0 mmol, 1.20 equiv) in dry acetonitrile (100 ml) was added triethylphosphonoacetate (2.62 ml, 13.0 mmol, 1.20 equiv) and DBU (1.63 ml, 10.9 mmol, 1.00 equiv). A solution of aldehyde 120 (4.20 g, 10.9 mmol, 1.00 equiv) in CH₃CN (20 ml) was added via cannula and the cloudy mixture was stirred at ambient temperature for 2 h. The reaction was quenched with 1.0 M aqueous KH₂PO₄ (100 ml). The layers were separated and the aqueous phase was extracted with pentane (3 × 100 ml). The combined pentane layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the intermediate ester (Rᶠ = 0.46 (hexane/EtOAc 9:1)), which was used without further purification.

To the unpurified bis-triethylsilyl ether in THF (100 ml) was added dropwise at 0 °C a solution of TBAF (1.0 M in THF, 27 ml, 27 mmol, 2.5 equiv). After stirring at room temperature for 2 h, the dark-red solution was quenched with saturated, aqueous NaHCO₃. The layers were separated, the aqueous phase was extracted with diethyl ether (3 × 200 ml) and the combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure.
Flash chromatography (hexane/EtOAc 1:1) afforded diol 121 (1.97 g, 80% yield over two steps) as a clear, colorless oil.

\[ R_f = 0.31 \text{ (hexane/EtOAc 1:1).} \]

**Optical Rotation:** \( [\alpha]_{29}^\text{D} \text{ (c 1.06, CHCl}_3\text{) = }-12.2^\circ. \)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.97 (dt, 1 H, \( J = 15.4, 7.4 \) Hz), 5.90 (dt, 1 H, \( J = 15.7, 1.5 \) Hz), 5.70 (ddq, 1 H, \( J = 15.3, 6.4, 0.9 \) Hz), 5.50 (ddq, 1 H, \( J = 15.3, 7.0, 1.2 \) Hz), 4.37–4.29 (m, 1 H), 4.19 (q, 2 H, \( J = 7.1 \) Hz), 4.09–3.98 (m, 1 H), 3.35 (br s, 1 H), 2.45–2.32 (m, 2 H), 2.26 (br s, 1 H), 1.72–1.68 (m, 3 H), 1.66–1.60 (m, 2 H), 1.28 (t, 3 H, \( J = 7.1 \) Hz).

\(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 166.4, 144.9, 133.5, 127.0, 123.9, 73.6, 70.8, 60.4, 42.7, 40.6, 17.6, 14.2.

IR (thin film) \( \nu \) 3395, 2979, 2939, 1719, 1655, 1446, 1370, 1319, 1271, 1194, 1164, 1095, 1044, 969, 924, 852 cm\(^{-1}\).

**Anal. Calcd** for C\(_{12}\)H\(_{20}\)O\(_4\): C, 63.14; H, 8.83. Found: C, 63.11; H, 8.88.


![Diagram of compound 122](image)

\([2R,4S,6S]-4\text{-Hydroxy-6-((E)-propenyl)-tetrahydro-pyran-2-yl}-acetic\text{ acid ethyl ester (122).} \]

To an ice-cooled solution of diol 121 (1.80 g, 8.10 mmol, 1.00 equiv) in THF (160 ml) was added tBuOK (91.0 mg, 0.810 mmol, 10.0 mol%) in one portion. After stirring at 0 °C for 30 min, the reaction was quenched with pH 7 phosphate
buffer. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 200 ml). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 3:2) provided tetrahydropyran 122 (1.13 g, 63% yield) as a clear, colorless oil (d.r. = 10:1 by $^1$H NMR spectroscopy by integration of the signals at 2.39 and 2.81 ppm, respectively).

$R_f = 0.43$ (hexane/EtOAc 1:1).

**Optical Rotation:** $[\alpha]_{38}^{D} (c 1.02, \text{CHCl}_3) = -4.3^\circ$.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.69 (ddq, 1 H, $J = 15.4, 6.2, 1.6$ Hz), 5.45 (ddq, 1 H, $J = 15.4, 6.5, 1.1$ Hz), 4.34–4.22 (m, 3 H), 4.14 (q, 2 H, $J = 7.1$ Hz), 2.59 (dd, 1 H, $J = 15.2, 7.0$ Hz), 2.38 (dd, 1 H, $J = 15.2, 6.4$ Hz), 1.78–1.46 (m, 4 H), 1.68 (ddd, 3 H, $J = 6.5, 1.0, 1.5$ Hz), 1.25 (t, 3 H, $J = 7.1$ Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.4, 131.8, 127.0, 72.3, 68.3, 64.1, 60.4, 41.3, 38.0, 37.9, 17.8, 14.1.

**IR (thin film)** $\nu$ 3453, 2978, 2918, 1737, 1376, 1344, 1300, 1197, 1165, 1070, 1045, 968, 930 cm$^{-1}$.

**Anal. Calcd** for C$_{12}$H$_{20}$O$_4$: C, 63.14; H, 8.83. Found: C, 63.17; H, 8.76.

**HRMS (MALDI)** calcd for C$_{12}$H$_{20}$O$_4$Na $[\text{M+Na}]^+$, 251.1259; found, 251.1254.
[(2R,4S,6S)-4-(tert-Butyl-dimethyl-silanyloxy)-6-((E)-propenyl)-tetrahydro-pyran-2-yl]-acetic acid ethyl ester (124).

**Method A**: from alcohol 122: To a solution of alcohol 122 (1.12 g, 4.90 mmol, 1.00 equiv) in anhydrous DMF (5 ml) at ambient temperature were added successively imidazole (1.33 g, 19.6 mmol, 4.00 equiv), TBSCl (1.48 g, 9.80 mmol, 2.00 equiv) and DMAP (60.0 mg, 0.490 mmol, 10.0 mol%). After stirring for 20 h, H2O (50 ml) was added and the aqueous phase was extracted with pentane (3 × 100 ml). The combined organic solutions were washed with brine, dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1) gave 124 (1.61 g, 96% yield) as colorless oil.

**Method B**: from lactone 126: To a solution of lactone 126 (100 mg, 0.370 mmol, 1.00 equiv) in dry toluene (3 ml) was added DIBAL–H (1.5 M in toluene, 0.27 ml, 0.41 mmol, 1.1 equiv) dropwise over 5 min. The mixture was stirred at –78 °C for 60 min and then quenched by the careful addition of MeOH (1 ml). Saturated, aqueous sodium potassium tartrate (10 ml) was added and the resulting biphasic mixture was vigorously stirred at room temperature for 12 h. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic solutions were washed with brine, dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. Lactol 127 was used without further purification.

Triethylphosphonoacetate (124 mg, 0.560 mmol, 1.50 equiv) was added dropwise to an ice-cooled suspension of NaH (95% purity, 14 mg, 0.56 mmol, 1.5 equiv) in dry
THF (1 ml). The suspension was stirred at room temperature until a clear solution was obtained (20 min). A solution of lactol 127 in THF (1 ml) was added dropwise over 10 min at –78 °C and the resulting solution was allowed to warm to room temperature. Stirring was maintained for 20 h. The mixture was diluted with H₂O (10 ml) and extracted with diethyl ether (3 × 10 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a diastereomeric mixture of 124 and 128. The unpurified oil was dissolved in THF (2 ml) and tBuOK (41.0 mg, 37.0 µmol, 0.100 equiv) was added at 0 °C in one portion. After stirring at 0 °C for 30 min, the reaction was quenched with pH 7 phosphate buffer. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 200 ml). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1) gave 124 (82 mg, 65% yield from lactone 126, d.r. = 9:1) as colorless oil.

R_f = 0.34 (hexane/EtOAc 9:1).

**Optical Rotation:** [α]_22^D (c 1.05, CHCl₃) = –1.4°.

**^1H NMR** (300 MHz, CDCl₃) δ 5.66 (ddq, 1 H, J = 15.4, 6.4, 1.1 Hz), 5.46 (ddq, 1 H, J = 15.4, 6.2, 1.5 Hz), 4.31–4.21 (m, 2 H), 4.21–4.16 (m, 1 H), 4.13 (q, 2 H, J = 7.1 Hz), 2.59 (dd, 1 H, J = 14.9, 6.9 Hz), 2.35 (dd, 1 H, J = 14.9, 6.6 Hz), 1.69–1.66 (m, 3 H), 1.65–1.38 (m, 4 H), 1.25 (t, 3 H, J = 7.1 Hz), 0.9 (s, 9 H), 0.05 (s, 6 H).

**^13C NMR** (75 MHz, CDCl₃) δ 171.2, 132.1, 126.8, 72.3, 68.5, 64.7, 60.3, 41.6, 39.0, 38.6, 25.8, 18.0, 17.8, 14.2, –4.9.
IR (thin film) ν 2954, 2928, 2857, 1740, 1346, 1298, 1254, 1194, 1163, 1049, 965, 940, 837 cm\(^{-1}\).

**Anal. Calcd** for C\(_{18}\)H\(_{34}\)O\(_4\)Si: C, 63.11; H, 10.00. Found: C, 63.26; H, 9.90.

(4R,6S)-4-(tert-Butyl-dimethyl-silanyloxy)-6-(E)-propenyl-tetrahydro-pyran-2-one (126). To a solution of MeOH (8 ml) in THF (40 ml) was added triethylborane (1.0 M in THF, 4.4 ml, 4.4 mmol, 1.1 equiv) dropwise under ice cooling. After stirring for 1 h at ambient temperature, the solution was cooled to −78 °C and keto ester 118 (922 mg, 4.04 mmol, 1.00 equiv) in THF (4 ml) was added via cannula. Stirring was continued for 20 min at −78 °C before NaBH\(_4\) (916 mg, 24.2 mmol, 6.00 equiv) was added in one portion. After 5 h at −78 °C, the excess reducing agent was quenched by the careful addition of saturated, aqueous NH\(_4\)Cl (3 ml). The solution was warmed to ambient temperature, diluted with diethyl ether (30 ml), and acidified to pH 1 using 1.0 M aqueous HCl. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 30 ml). The combined organic extracts were washed with brine (50 ml), dried over anhydrous Na\(_2\)SO\(_4\) and filtered. Concentration under reduced pressure gave a colorless oil which was azeotroped with MeOH (3 × 30 ml) and dissolved in dry benzene (80 ml). PPTS (100 mg, 0.444 mmol, 0.110 equiv) was added and the solution was refluxed for 90 min. After cooling to ambient temperature, the reaction mixture was washed with saturated, aqueous NaHCO\(_3\) (50 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 50 ml). The combined organic solutions were washed with brine, dried
over anhydrous Na₂SO₄ filtered, and concentrated under reduced pressure, giving intermediate alcohol 125 which was used without further purification.

To a solution of unpurified alcohol 125 in anhydrous DMF (5 ml) at ambient temperature were added successively imidazole (688 mg, 10.1 mmol, 2.50 equiv), TBSCI (731 mg, 4.85 mmol, 1.20 equiv) and DMAP (50.0 mg, 0.404 mmol, 10.0 mol%). After stirring for 2 h, H₂O (25 ml) was added and the aqueous phase was extracted with pentane (3 × 100 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄ filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 4:1) gave 126 (838 g, 77% yield from keto ester 118) as colorless oil.

Rₛ = 0.66 (hexane/EtOAc 2:1).

**Optical Rotation**: [α]²¹ D (c 0.985, CHCl₃) = +25.0°.

**¹H NMR** (300 MHz, CDCl₃) δ 5.87–5.74 (m, 1 H), 5.58–5.47 (m, 1 H), 5.14–5.04 (m, 1 H), 4.33–4.25 (m, 1 H), 2.66–2.50 (m, 2 H), 1.93–1.68 (m, 5 H), 0.88 (s, 9 H), 0.01 (s, 3 H), 0.01 (s, 3 H).

**¹³C NMR** (75 MHz, CDCl₃) δ 169.8, 129.5, 129.0, 76.5, 63.5, 39.3, 36.9, 25.8, 18.1, 17.8, –4.7, –4.8.

**IR** (thin film) ν 2956, 2931, 1745, 1732, 1472, 1440, 1381, 1348, 1253, 1234, 1161, 1079, 1040, 1006, 966, 927, 838, 809, 778 cm⁻¹.

**HRMS** (EI) calcd for C₁₀H₁₇O₃Si [M–C₄H₉]⁺, 213.0947; found, 213.0939.
[(2R,4R,6S)-4-(tert-Butyl-dimethyl-silanyloxy)-6-(2-oxo-propyl)-tetrahydro-
pyran-2-yl]-acetic acid ethyl ester (129). To a solution of olefin 124 (1.61 g,
4.70 mmol, 1.00 equiv) in DMF/H₂O 7:1 (64 ml) was added PdCl₂ (170 mg,
0.900 mmol, 20.0 mol%) and CuCl (560 mg, 5.60 mmol, 1.20 equiv). The reaction
mixture was stirred at room temperature for 48 h and air was bubbled through the
solution during this time via a Pasteur pipette. The solution was diluted with H₂O
(100 ml), the layers were separated and the aqueous phase was extracted with diethyl
ether (5 × 150 ml). The combined diethyl ether layers were washed with brine, dried
over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure.
Purification by flash chromatography (hexane/EtOAc 4:1) provided methyl ketone
129 (1.46 g, 86% yield) as a clear, colorless oil.

\[ R_f = 0.42 \text{ (hexane/EtOAc 4:1)}. \]

**Optical Rotation:** \[ [\alpha]^{26}_D (c 0.99, CHCl₃) = -0.2^\circ. \]

**¹H NMR** (300 MHz, CDCl₃) δ 4.30–4.20 (m, 2 H), 4.19–4.15 (m, 1 H), 4.11 (q, 2 H,
\(J = 7.1 \text{ Hz})\), 2.56 (dd, 1 H, \(J = 14.9, 8.5 \text{ Hz})\), 2.45 (dd, 1 H, \(J = 14.8, 8.2 \text{ Hz})\), 2.35 (dd, 1 H,
\(J = 14.9, 4.7 \text{ Hz})\), 2.32 (dd, 1 H, \(J = 14.8, 5.4 \text{ Hz})\), 2.16 (s, 3 H), 1.66–1.52 (m, 2 H),
1.46–1.32 (m, 2 H), 1.24 (t, 3 H, \(J = 7.1 \text{ Hz})\), 0.9 (s, 9 H), 0.05 (s, 6 H).

**¹³C NMR** (75 MHz, CDCl₃) δ 207.4, 171.0, 68.8, 64.5, 60.3, 50.0, 41.4, 38.8, 38.5,
30.5, 30.4, 25.7, 18.0, 14.1, −5.0.

**IR** (thin film) ν 2954, 2929, 2857, 1738, 1717, 1472, 1418, 1385, 1360, 1281, 1254,
1178, 1157, 1097, 1061, 1039, 942, 887, 836 cm⁻¹.
Anal. Calcd for C₁₈H₃₄O₅Si: C, 60.30; H, 9.56. Found: C, 60.34; H, 9.50.

HRMS (MALDI) calcd for C₁₈H₃₄O₅SiNa [M+Na]^+; 381.2073; found, 381.2068.

5.2.1.3. On the Way to the Macrocycle

{\((2R,4R,6S)-4-(\text{tert-Butyl-dimethyl-silanyloxy})-6-[(4R,5S,8E,10R)-10-(\text{4R})-2,2-\text{dimethyl-[1,3]dioxolan-4-yl})-4,10\text{-dihydroxy-5-methyl-2-oxo-dec-8-eyl}]-\text{tetra-hydro-pyran-2-yl}]-\text{acetic acid methyl ester} (130).

Method A: To an ice-cooled solution of (–)-B-chloro-diisopinocampheyl borane (667 mg, 2.08 mmol, 1.60 equiv) and Et₃N (330 µl, 2.35 mmol, 1.81 equiv) in anhydrous diethyl ether (14 ml) was added methyl ketone 129 (466 mg, 1.30 mmol, 1.00 equiv) in diethyl ether (1 ml) via cannula (2 × 1 ml rinse). The white slurry was stirred at 0 °C for 3 h, and then cooled to −78 °C. Aldehyde 112 (540 mg, 1.56 mmol, 1.20 equiv) in diethyl ether (1 ml) was added dropwise via cannula (2 × 1 ml rinse) and stirred at −78 °C for 24 h. The reaction was quenched by the addition of MeOH (10 ml), pH 7 phosphate buffer (10 ml) and aqueous H₂O₂ 30% (5 ml) and stirred at room temperature for 12 h. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 50 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under
reduced pressure. The obtained oil was purified by flash chromatography (hexanes/EtOAc 3:1) to give aldol adduct 130 (741 mg, 81% yield) as a colourless oil and as a single diastereoisomer (d.r. > 95:5).

**Method B**: To a solution of methyl ketone 129 (25.8 mg, 72.2 µmol, 1.00 equiv) in dry ether (1 ml) was added Hüning’s base (19 µl, 0.11 mmol, 1.5 equiv). The solution was cooled to −78 °C and nBu₂BOTf (1.0 M in CH₂Cl₂, 0.11 ml, 0.11 mmol, 1.5 equiv) was added dropwise. The resulting white slurry was stirred at −78 °C for 30 min, whereupon aldehyde 112 (30.0 mg, 86.6 µmol, 1.20 equiv) in diethyl ether (0.7 ml) was added slowly over 5 min. The mixture was stirred at −78 °C for 5 h, whereupon MeOH (0.6 ml) and pH 7 phosphate buffer (0.1 ml) were added. The resulting solution was placed at 0 °C followed by the addition of 30% H₂O₂/MeOH 1:2 (0.3 ml) and stirred at room temperature for 12 h. The mixture was diluted with H₂O (5 ml) and the aqueous phase was extracted with diethyl ether (3 × 5 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The obtained oil was purified by flash chromatography (hexane/EtOAc 3:1) to give aldol adduct 130 (40.6 mg, 80% yield) as a colorless oil and as a single diastereoisomer (d.r. > 95:5 by ¹H NMR spectroscopy).

\[ R_f = 0.30 \text{ (hexane/EtOAc 2:1).} \]

**Optical Rotation**: \([\alpha]^{22}_D\) (c 1.12, CHCl₃) = +16.0°.

¹H NMR (500 MHz, C₆D₆) δ 8.34–8.30 (m, 2 H), 7.25–7.11 (m, 3 H), 5.97 (ddt, 1 H, \( J = 15.4,\ 6.7,\ 1.2 \text{ Hz})\), 5.87 (t, 1 H, \( J = 7.33 \text{ Hz})\), 5.65 (ddt, 1 H, \( J = 15.5,\ 7.6,\ 1.5 \text{ Hz})\), 4.56–4.49 (m, 2 H), 4.32 (ddd, 1 H, \( J = 6.4,\ 6.4,\ 6.4 \text{ Hz})\), 4.10–4.04 (m, 2 H), 4.00–3.94 (m, 2 H), 3.91–3.88 (m, 2 H), 3.17 (d, 1 H, \( J = 3.4 \text{ Hz})\), 2.54 (dd, 1 H, \( J = 15.1,\ 7.8 \text{ Hz})\), 2.50 (dd, 1 H, \( J = 15.0,\ 8.0 \text{ Hz})\), 2.45 (dd, 1 H, \( J = 17.0,\ 9.7 \text{ Hz})\), 2.36 (dd, 1 H, \( J = 17.0,\ 2.5 \text{ Hz})\), 2.27 (dd, 1 H, \( J = 15.1,\ 5.48 \text{ Hz})\), 2.16 (dd, 1 H, \( J = 15.0,\ 4.9 \text{ Hz})\), 2.13–2.06
(m, 1 H), 1.98–1.89 (m, 1 H), 1.70–1.60 (m, 1 H), 1.59–1.48 (m, 3 H), 1.58 (d, 3 H, $J = 0.3$ Hz), 1.39 (d, 3 H, $J = 0.5$ Hz), 1.30–1.21 (m, 3 H), 1.08 (t, 3 H, $J = 7.1$ Hz), 1.05 (s, 9 H), 0.91 (d, 3 H, $J = 6.8$ Hz), 0.12 (s, 3 H), 0.11 (s, 3 H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 210.9, 171.0, 165.7, 137.3, 133.0, 130.4, 129.8, 128.3, 124.1, 110.0, 76.8, 75.6, 71.1, 68.9, 68.8, 65.8, 64.5, 60.4, 49.7, 47.0, 41.3, 38.8, 38.5, 37.6, 31.2, 30.0, 26.5, 25.8, 25.5, 18.1, 15.0, 14.2, –4.9.

IR (thin film) $\nu$ 3518, 2930, 2857, 1722, 1602, 1585, 1472, 1452, 1371, 1315, 1269, 1159, 1111, 1069, 972, 942, 837, 806, 775, 714 cm$^{-1}$.

Anal. Calcd for C$_{38}$H$_{60}$O$_{10}$Si: C, 64.7; H, 8.58. Found: C, 64.92; H, 8.38.

HRMS (MALDI) calcd for C$_{38}$H$_{60}$O$_{10}$SiNa [M+Na]$^+$, 727.3853; found, 727.3748.

{2S,4S,6R}-4-(tert-Butyl-dimethyl-silanyloxy)-6-[(4S,5R,8E,10S)-10-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-4,10-dihydroxy-5-methyl-2-oxo-dec-8-enyl]-tetrahydro-pyran-2-yl-acetic acid methyl ester (132).

$R_f = 0.16$ (hexane/EtOAc 4:1).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.12–8.04 (m, 2 H), 7.61–7.52 (m, 1 H), 7.48–7.41 (m, 2 H), 5.84–5.80 (m, 1 H), 5.60–5.48 (m, 2 H), 4.35–4.20 (m, 2 H), 4.19–4.05 (m, 5 H),
3.96 (dd, 1 H, J = 8.7, 5.9 Hz), 3.90–3.82 (m, 1 H), 2.64–2.26 (m, 6 H), 2.24–2.10 (m, 1 H), 1.80–1.28 (m, 15 H), 1.24 (t, 2 H, J = 6.9 Hz), 0.91–0.86 (m, 12 H), 0.05 (s, 6 H).

To a solution of hydroxy ketone 132 (480 mg, 0.681 mmol, 1.00 equiv) in degassed THF (2 ml) (degassed by repeated freeze-pump-thaw cycles) was added acetaldehyde (0.200 ml, 3.40 mmol, 5.00 equiv). The solution was cooled to -10 °C, whereupon SmI₂ (0.10 M in THF, 2.0 ml, 0.20 mmol, 30 mol%) was added dropwise over 10 min. The yellow solution was stirred for 4 h at -10 °C. The solution was diluted with diethyl ether (5 ml) and washed with saturated, aqueous NaHCO₃ (5 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 5 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 4:1) afforded diol monoacetate 133 (434 mg, 85% yield) as a clear, colorless oil.

Rᵣ = 0.22 (hexane/EtOAc 2:1).
1H NMR (300 MHz, CDCl₃) δ 8.10–8.05 (m, 2 H), 7.59–7.51 (m, 1 H), 7.46–7.40 (m, 2 H), 5.84 (ddt, 1 H, J = 14.9, 6.2, 1.2 Hz), 5.60–5.46 (m, 2 H), 5.12–5.00 (m, 1 H), 4.34–3.90 (m, 8 H), 3.82–3.66 (m, 2 H), 2.45 (dd, 1 H, J = 14.9, 8.7 Hz), 2.32 (dd, 1 H, J = 14.9, 5.0 Hz), 2.20–2.09 (m, 1 H), 2.03 (s, 3 H), 1.80–1.68 (m, 1 H), 1.62–1.30 (m, 16 H), 1.21 (t, 3 H, J = 6.9 Hz), 1.19–1.10 (m, 1 H), 0.88 (s, 9 H), 0.84 (d, 3 H, J = 6.9 Hz), 0.03 (s, 3 H), 0.02 (s, 3 H).

(1R,2E,6S,7R,9R)-Benzoic acid 10-[(2R,4R,6R)-4-(tert-butyl-dimethyl-silanyloxy)-6-ethoxycarbonylmethyl-tetrahydro-pyran-2-yl]-1-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-7,9-dihydroxy-6-methyl-dec-2-enyl ester (137). A solution of tetramethylammonium triacetoxyborohydride (1.36 g, 5.18 mmol, 5.00 equiv) in acetonitrile/acetic acid 1:1 (5 ml) was stirred for 20 min at room temperature and then added dropwise over 10 min to a solution of aldol adduct 130 (730 mg, 1.03 mmol, 1.00 equiv) in dry acetonitrile (10 ml) at –40 °C. After 48 h at –40 °C and 1 h at 0 °C, the reaction was quenched by the addition of saturated, aqueous sodium potassium tartrate (10 ml) and stirred at 0 °C for 4 h. The aqueous layer was extracted with ethyl acetate (3 × 50 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 2:1), followed by azeotropic
drying with benzene provided 1,3-anti diol 137 (544 mg, 97% yield) as a single diastereoisomer (d.r. > 95:5 by $^1$H NMR spectroscopy).

$R_f = 0.28$ (hexane/EtOAc 2:1).

**Optical Rotation:** $[\alpha]^2_7D (c 1.07, CHCl_3) = +3.8^\circ$.

$^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 8.25–8.21 (m, 2 H), 7.12–7.01 (m, 3 H), 5.91 (dt, 1 H, $J = 15.4, 6.8$ Hz), 5.79 (dd, 1 H, $J = 7.4$, 6.9 Hz), 5.56 (dd, 1 H, $J = 15.4, 7.5$ Hz), 4.40–4.35 (m, 1 H), 4.24–4.10 (m, 4 H), 4.02–3.95 (m, 2 H), 3.86–3.77 (m, 2 H), 3.79–3.77 (m, 2 H), 3.35 (d, 1 H, $J = 3.0$ Hz), 2.25 (dd, 1 H, $J = 15.0$, 8.8 Hz), 2.09 (dd, 1 H, $J = 15.0$, 4.4 Hz), 2.12–2.05 (m, 1 H), 1.96–1.89 (m, 1 H), 1.76–1.69 (m, 2 H), 1.64–1.53 (m, 2 H), 1.49 (s, 3 H), 1.42–1.36 (m, 2 H), 1.30 (s, 3 H), 1.32–1.22 (m, 2 H), 1.20–1.10 (m, 3 H), 0.99 (t, 3 H, $J = 7.1$ Hz), 0.94 (s, 9 H), 0.87 (d, 3 H, $J = 6.8$), 0.01 (s, 6 H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.2, 165.6, 137.6, 132.9, 130.4, 129.7, 128.3, 123.8, 110.0, 76.8, 75.6, 73.7, 72.2, 70.7, 68.8, 65.8, 64.3, 60.7, 41.9, 41.1, 39.5, 38.7, 38.2, 31.4, 30.1, 26.5, 25.8, 25.4, 18.0, 15.0, 14.2, 14.1, –4.9.

**IR** (thin film) $\nu$ 3468, 2930, 2858, 1721, 1368, 1311, 1269, 1160, 1109, 1068, 1038, 837, 774, 712 cm$^{-1}$.

**Anal. Calcd** for C$_{38}$H$_{62}$O$_{10}$Si: C, 64.56; H, 8.84. Found: C, 64.34; H, 9.08.

**HRMS** (MALDI) calcd for C$_{38}$H$_{62}$O$_{10}$SiNa [M+Na]$^+$, 729.4010; found, 729.4021.
To a solution of benzoate 137 (400 mg, 0.566 mmol, 1.00 equiv) in anhydrous methanol (6 ml) was added solid potassium carbonate (391 mg, 2.83 mmol, 5.00 equiv) in one portion. The solution was stirred at ambient temperature for 40 h before being diluted with CH₂Cl₂ (20 ml) and washed with 1.0 M aqueous HCl (20 ml). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (4 × 20 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 2:3) followed by azeotropic drying with benzene provided triol 138 (305 mg, 92% yield) as a clear, colorless oil.

\[ R_f = 0.37 \] (hexane/EtOAc 1:2).

**Optical Rotation:** \([\alpha]^{23}_D (c 1.05, CHCl_3) = +0.4^\circ\).

\[^1H\text{ NMR}\] (500 MHz, C₆D₆) δ 5.73 (ddt, 1 H, \(J = 15.5, 6.3, 1.0\) Hz), 5.46 (ddt, 1 H, \(J = 15.4, 6.6, 1.4\) Hz), 4.37–4.32 (m, 1 H), 4.19 (br s, 1 H), 4.14–4.09 (m, 2 H), 3.97–3.88 (m, 3 H), 3.82 (t, 1 H, \(J = 2.7\) Hz), 3.74–3.68 (m, 2 H), 3.38 (s, 3 H), 3.31 (br s, 1 H), 2.25 (dd, 1 H, \(J = 15.0, 8.9\) Hz), 2.19 (br s, 1 H), 2.18–2.10 (m, 1 H), 2.05 (dd, 1 H, \(J = 15.0, 4.3\) Hz), 2.02–1.94 (m, 1 H), 1.80–1.71 (m, 2 H), 1.69–1.58 (m, 2 H), 1.45–1.40 (m, 1 H),
1.38 (d, 3 H, $J = 0.5$ Hz), 1.38–1.27 (m, 6 H), 1.19–1.08 (m, 3 H), 0.94 (s, 9 H), 0.92 (d, 3 H, $J = 6.8$ Hz), 0.00 (s, 6 H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.7, 135.4, 127.7, 109.7, 79.0, 74.3, 73.6, 72.1, 70.5, 68.7, 65.9, 64.3, 51.8, 41.2, 40.8, 39.4, 38.8, 38.7, 38.1, 31.6, 30.0, 26.8, 25.8, 25.3, 18.0, 15.0, –4.9.

IR (thin film) $\nu$ 3468, 2929, 2858, 1741, 1462, 1439, 1377, 1254, 1207, 1160, 1064, 1033, 837, 774 cm$^{-1}$.

Anal. Calcd for C$_{30}$H$_{56}$O$_9$Si: C, 61.19; H, 9.59. Found: C, 61.01; H, 9.64.

HRMS (MALDI) calcd for C$_{30}$H$_{56}$O$_9$SiNa [M+Na]$^+$, 611.3591; found, 611.3586.

![Chemical structure](image)

[(2R,4R,6R)-4-((tert-Butyl-dimethyl-silanyloxy)-6-((2S)-3-((2R,3S,6S)-6-[(1S,2S)-2-(4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-hydroxy-1-iodo-ethyl]-3-methyl-tetrahydro-pyran-2-yl)-2-hydroxy-propyl)-tetrahydro-pyran-2-yl]-acetic acid methyl ester (148). To a solution of allylic alcohol 138 (345 mg, 0.586 mmol, 1.00 equiv) and 2,6-di-tert-butyl-4-methyl pyridine (300 mg, 1.46 mmol, 2.50 equiv) in dry toluene (60 ml) at –78 °C was added dropwise over 60 min a solution of iodine monobromide (1.0 M in CH$_2$Cl$_2$, 1.2 ml, 1.2 mmol, 2.0 equiv) in anhydrous toluene (10 ml). After 2 h at –78 °C, the reaction was quenched by addition of 2.0 M aqueous sodium thiosulfate (20 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 50 ml). The combined organic solutions were washed with brine, dried
over anhydrous Na$_2$SO$_4$ filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 2:1) afforded iodide 148 (103 mg, 25% yield, 37% based on recovered starting material, d.r. = 50:50).

\[ R_f = 0.32 \text{ (hexane/EtOAc 1:1).} \]

**Optical Rotation:** $[\alpha]^{27}_D \ (c \ 0.61, \text{CHCl}_3) = +10.0^\circ$.

$^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 4.48–4.44 (m, 1 H), 4.38 (ddd, 1 H, $J = 6.7, 6.7, 6.6$ Hz), 4.34–4.28 (m, 3 H), 4.13 (tt, 1 H, $J = 11.0, \ 2.0$ Hz), 3.92 (dd, 1 H, $J = 8.2, \ 6.2$ Hz), 3.86–3.82 (m, 3 H), 3.78–3.76 (br s, 1 H), 3.62–3.58 (m, 1 H), 3.45 (s, 3 H), 3.37 (br s, 1 H), 2.41 (dd, 1 H, $J = 15.3, \ 7.9$ Hz), 2.14 (dd, 1 H, $J = 15.3, \ 5.2$ Hz), 2.14–2.09 (m, 1 H), 1.87–1.81 (m, 1 H), 1.65–1.54 (m, 2 H), 1.52 (s, 3 H), 1.45–1.32 (m, 4 H), 1.35 (s, 3 H), 1.26–1.04 (m, 5 H), 0.94 (s, 9 H), 0.79 (d, 3 H, $J = 6.7$ Hz), 0.00 (s, 3 H), –0.01 (s, 3 H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.4, 109.7, 80.8, 73.5, 72.7, 72.6, 70.0, 68.4, 67.8, 66.2, 64.4, 51.8, 43.2, 40.8, 40.7, 39.5, 38.6, 34.4, 27.4, 26.7, 26.6, 25.8, 25.8, 25.7, 18.1, 18.0, –4.9.

**IR** (thin film) $\nu$ 3497, 2929, 2859, 1742, 1460, 1438, 1370, 1253, 1216, 1160, 1060, 1039, 1003, 838, 772 cm$^{-1}$.

**HRMS** (MALDI) calcd for C$_{30}$H$_{55}$IO$_9$SiNa [M+Na]$^+$, 737.2558; found, 737.2550.

R_f=0.24 (hexane/EtOAc 1:1).

**Optical Rotation:** [α]_D^{24} (c 0.94, CHCl_3) = +17.7°.

**¹H NMR** (500 MHz, C_6D_6) δ 4.67 (dt, 1 H, J = 6.7, 3.1 Hz), 4.43 (dd, 1 H, J = 7.3, 6.6 Hz), 4.39–4.34 (m, 1 H), 4.30 (t, 1 H, J = 9.5 Hz), 4.20 (t, 1 H, J = 10.3 Hz), 3.93–3.84 (m, 3 H), 3.71 (dt, 1 H, J = 7.4, 2.9 Hz), 3.49–3.44 (m, 1 H), 3.43 (s, 3 H), 3.37–3.33 (m, 1 H), 3.10 (d, 1 H, J = 7.3 Hz), 2.35 (dd, 1 H, J = 15.0, 8.3 Hz), 2.12 (dd, 1 H, J = 15.0, 5.0 Hz), 1.99–1.96 (m, 1 H), 1.83–1.78 (m, 1 H), 1.68–1.61 (m, 1 H), 1.56–1.50 (m, 1 H), 1.49–0.95 (m, 16 H), 0.94 (s, 9 H), 0.69 (d, 3 H, J = 6.6 Hz), 0.01 (s, 6 H).

**¹³C NMR** (75 MHz, CDCl_3) δ 171.6, 109.5, 80.5, 77.8, 73.0, 72.0, 68.5, 67.8, 66.5, 64.5, 64.4, 51.8, 43.3, 42.0, 41.0, 40.6, 39.5, 38.6, 35.0, 32.4, 30.9, 26.4, 25.8, 25.2, 18.1, 17.6, –4.8, –4.9.

**IR** (thin film) ν 3502, 2952, 2856, 1742, 1462, 1437, 1381, 1253, 1206, 1160, 1063, 1006, 838, 807, 774, 733 cm⁻¹.

**HRMS** (MALDI) calcd for C_{30}H_{55}IO_{9}SiNa [M+Na]^+, 737.2558; found, 737.2555.
[(2R,4R,6R)-4-(tert-Butyl-dimethyl-silanyloxy)-6-((2S)-3-((2R,3S,6S)-6-[((2S,3S)-3-(4R)-2,2-dimethyl-[1,3]dioxolan-4-yl]-oxiranyl)-3-methyl-tetrahydro-pyran-2-yl)-2-hydroxy-propyl)-tetrahydro-pyran-2-yl]-acetic acid methyl ester (150). To a solution of iodoalcohol 148 (5.0 mg, 7.0 µmol, 1.0 equiv) in MeOH (1 ml) at room temperature was added K₂CO₃ (4.8 mg, 35 µmol, 5.0 equiv) in one portion. The solution was stirred at ambient temperature for 15 h, diluted with CH₂Cl₂ (5 ml) and washed with pH 7 phosphate buffer (5 ml). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 5 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) afforded epoxide 150 (2.3 mg, 57% yield) as a clear, colorless oil.

R_f = 0.19 (hexane/EtOAc 1:1).

^1H NMR (300 MHz, CDCl₃) δ 4.30–4.00 (m, 5 H), 3.85–3.72 (m, 3 H), 3.71–3.65 (m, 4 H), 3.29 (dd, 1 H, J = 7.8, 4.4 Hz), 3.03 (dd, 1 H, J = 6.8, 4.4 Hz), 2.47 (dd, 1 H, J = 14.9, 8.7), 2.36 (dd, 1 H, J = 5.0, 14.9), 1.80–1.30 (m, 17 H), 1.28–1.20 (m, 2 H), 0.96 (d, 3 H, J = 6.8 Hz), 0.90 (s, 9 H), 0.04 (s, 6 H).
[(2R,4R,6R)-4-(tert-Butyl-dimethyl-silanyloxy)-6-((2S)-3-((2R,3S,6R)-6-[(2R,3S)-3-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-oxiranyl]-3-methyl-tetrahydro-pyran-2-yl)2-hydroxy-propyl)-tetrahydro-pyran-2-yl]-acetic acid methyl ester (151). To a solution of iodoalcohol 149 (25.0 mg, 35.0 µmol, 1.00 equiv) in MeOH (2 ml) at room temperature was added K₂CO₃ (24.0 mg, 175 µmol, 5.00 equiv) in one portion. The solution was stirred at ambient temperature for 15 h, diluted with CH₂Cl₂ (5 ml) and washed with pH 7 phosphate buffer (5 ml). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 5 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) afforded epoxide 151 (14 mg, 69% yield) as a clear, colorless oil.

Rᵣ=0.19 (hexane/EtOAc 1:1).

**Optical Rotation:** [α]²³° (c 0.60, CHCl₃) = +15.9°.

**¹H NMR** (500 MHz, C₆D₆) δ 4.43 (t, 1 H,  J = 9.3 Hz), 4.38–4.33 (m, 1 H), 4.18 (t, 1 H,  J = 11.2 Hz), 3.86–3.83 (m, 2 H), 3.80 (dt, 1 H,  J = 6.6, 4.5 Hz), 3.70–3.64 (m, 2 H), 3.45–3.38 (m, 4 H), 3.12 (ddd, 1 H,  J = 11.4, 5.0, 2.4), 2.95 (dd, 1 H,  J = 5.0, 2.16 Hz), 2.86 (dd, 1 H,  J = 4.5, 2.16 Hz), 2.32 (dd, 1 H,  J = 14.9, 8.5 Hz), 2.11 (dd, 1 H,  J = 14.9, 4.8 Hz), 1.91 (ddd, 1 H,  J = 13.9, 9.2, 1.9 Hz), 1.70 (dt, 1 H,  J = 14.3, 9.8 Hz),
1.54–1.48 (m, 2 H), 1.45–1.12 (m, 14 H), 0.99–0.87 (m, 10 H), 0.76 (d, 3 H, J = 6.6 Hz), –0.01 (s, 3 H), –0.01 (s, 3 H).

$^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 171.0, 109.9, 80.5, 76.8, 75.7, 73.3, 68.9, 68.2, 66.2, 65.1, 57.2, 54.6, 51.4, 44.2, 41.8, 41.2, 39.8, 38.9, 35.3, 32.7, 28.5, 26.7, 26.0, 25.9, 18.3, 18.0, –4.8, –4.9.

IR (thin film) ν 3514, 2929, 2857, 1742, 1459, 1437, 1381, 1253, 1209, 1159, 1097, 1062, 1038, 838, 774 cm$^{-1}$.

HRMS (MALDI) calcd for C$_{30}$H$_{54}$O$_9$SiNa [M+Na]$^+$, 609.3434; found, 609.3429.

To a solution of (TIPPSe)$_2$ (20.1 mg, 35.7 µmol, 2.10 equiv) in dry CH$_2$Cl$_2$ (0.3 ml) was added bromine (0.113 M in CH$_2$Cl$_2$, 0.300 ml, 34.0 µmol, 2.00 equiv) at –78 °C in three portions over 2 min. The resulting yellow mixture was stirred at –78 °C for 10 min and was then allowed to warm to ambient temperature.

To a solution of allylic alcohol 138 (10.0 mg, 17.0 µmol, 1.00 equiv) and 2,6-di-tert-butyl-4-methyl pyridine (17.4 mg, 84.9 µmol, 5.00 equiv) in CH$_2$Cl$_2$ (1.8 ml) at
−78 °C was added dropwise over 60 min the solution of 2,4,6-triisopropylphenylselenyl bromide. After 2 h at −78 °C, the reaction was quenched by addition of saturated, aqueous NaHCO₃ (2 ml). The mixture was allowed to warm to ambient temperature. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 5 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 3:1) followed by azeotropic drying with benzene afforded selenide 154 (10.9 mg, 74% yield, d.r. = 88:12 by ¹H NMR spectroscopy by integration of the signals at 3.45 and 3.48 ppm, respectively).

\[ R_f = 0.29 \text{ (hexane/EtOAc 3:1)}. \]

**Optical Rotation:** \[ [\alpha]_{D}^{23} (c 0.5, \text{CHCl}_3) = -1.6^\circ. \]

**¹H NMR** (500 MHz, C₆D₆) \( \delta \): 7.09 (s, 2 H), 4.93 (q, 1 H, \( J = 6.7 \text{ Hz} \)), 4.65–4.61 (m, 1 H), 4.41–4.33 (m, 3 H), 4.20–4.09 (m, 4 H), 4.00–3.93 (m, 2 H), 3.84–3.85 (m, 1 H), 3.76–3.72 (m, 1 H), 3.55 (br s, 1 H), 3.45 (s, 3 H), 1.71 (q, 1 H, \( J = 6.9 \text{ Hz} \)), 2.47 (dd, 1 H, \( J = 15.0, 7.5 \text{ Hz} \)), 2.17 (dd, 1 H, \( J = 15.0, 5.8 \text{ Hz} \)), 2.01–1.97 (m, 1 H), 1.79–1.72 (m, 2 H), 1.68–1.60 (m, 4 H), 1.54–1.43 (m, 4 H), 1.42 (s, 3 H), 1.38–1.19 (m, 17 H), 1.18–1.16 (m, 6 H), 0.97–0.93 (m, 10 H), 0.75 (s, 3 H, \( J = 6.4 \text{ Hz} \)), 0.75 (d, 3 H, \( J = 6.4 \text{ Hz} \)), 0.00 (s, 6 H).

**¹³C NMR** (75 MHz, CDCl₃) \( \delta \): 171.1, 152.6, 149.6, 126.2, 121.8, 109.4, 76.8, 73.3, 73.2, 72.9, 72.0, 68.4, 67.9, 66.5, 64.4, 51.8, 49.5, 43.2, 41.1, 39.5, 38.7, 34.4, 34.2, 27.1, 26.8, 26.6, 25.8, 25.7, 24.9, 24.6, 24.1, 24.0, 18.3, 18.1, –4.8.

**IR** (thin film) \( \nu \): 2957, 2928, 2870, 1742, 1462, 1436, 1382, 1362, 1098, 1062, 1038, 1002, 913, 875, 837, 803, 774, 742 cm⁻¹.

**HRMS** (MALDI) calcd for C₄₅H₇₈O₉SeSiNa [M+Na⁺], 893.4477; found, 893.4464.
Method A: from iodide 148 with Bu₃SnH: To a solution of iodide 148 (70.0 mg, 98.0 µmol, 1.00 equiv) in benzene (degassed by repeated freeze-pump-thaw cycles) was added a minimal amount of AIBN and freshly distilled tributyltin hydride (0.50 M in C₆H₆, 0.22 ml, 0.11 mmol, 1.1 equiv). The clear, colorless solution was heated to reflux for 1 h and then cooled to ambient temperature. After concentration under reduced pressure, the obtained oil was diluted with hexane (10 ml) and extracted with acetonitrile (3 × 10 ml). The combined acetonitrile solutions were washed with 2.0 M aqueous sodium thiosulfate (10 ml) and with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1), followed by azeotropic drying with benzene, afforded 159 (56.0 mg, 97% yield) as a clear, colorless oil.

Method B: from iodide 148 with silylated cyclohexadiene 160: To a solution of iodide 148 (5.0 mg, 7.0 µmol, 1.0 equiv) in hexane (1 ml) was added silylated cyclohexadiene 160 (3.8 mg, 14 µmol, 2.0 equiv) and a minimal amount of AIBN. After refluxing the mixture for 2 h, TLC showed full conversion. The reaction was allowed to cool to ambient temperature and was concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1), followed by
azeotropic drying with benzene, afforded 159 (3.5 mg, 85% yield) as a clear, colorless oil.

**Method C**: from selenide 154 with silylated cyclohexadiene 160: To a solution of selenide 154 (5.4 mg, 6.2 µmol, 1.0 equiv) in hexane (1 ml) was added silylated cyclohexadiene 160 (6.6 mg, 25 µmol, 4.0 equiv) and a minimal amount of AIBN. After refluxing the mixture for 1 h, TLC showed full conversion. The reaction was allowed to cool to ambient temperature and was concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1), followed by azeotropic drying with benzene, afforded 159 (2.9 mg, 80% yield) as a clear, colorless oil.

R_f = 0.38 (hexane/EtOAc 1:1).

**Optical Rotation**: [α]_22^D (c 0.72, CHCl_3) = +23.5°.

**¹H NMR** (300 MHz, CDCl_3) δ 4.42–4.24 (m, 3 H), 4.23–4.13 (m, 1 H), 4.07–3.98 (m, 1 H), 3.97–3.71 (m, 7 H), 3.44 (s, 3 H), 2.42–2.33 (m, 2 H), 2.12 (dd, 1 H, J = 14.9, 5.0 Hz), 1.86 (ddd, 1 H, J = 13.5, 10.9, 1.7 Hz), 1.76–1.49 (m, 4 H), 1.48 (s, 3 H), 1.45–1.06 (m, 12 H), 0.94 (s, 9 H), 0.89 (d, 3 H, J = 6.8 Hz), 0.00 (s, 3 H), 0.01 (s, 3 H).

**¹³C NMR** (75 MHz, CDCl_3) δ 171.5, 109.2, 79.5, 73.3, 72.1, 68.5, 68.4, 68.2, 67.8, 66.1, 64.5, 51.7, 43.2, 40.9, 40.5, 39.5, 38.7, 35.5, 34.5, 28.5, 27.8, 26.6, 25.8, 25.5, 18.2, 18.0, −4.9.

**IR** (thin film) ν 2954, 2930, 2858, 1743, 1462, 1437, 1381, 1254, 1205, 1160, 1098, 1062, 1035, 940, 838, 807, 775, 733 cm⁻¹.

**HRMS** (MALDI) calcd for C_{30}H_{56}O_{8}SiNa [M+Na]^+, 611.3591; found, 611.3601.
[(2S,4S,6S)-4-((tert-Butyl-dimethyl-silanyloxy)-6-((2R)-3-((2S,3R,6R)-6-[(2S)-2-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-hydroxy-ethyl]-3-methyl-tetrahydro-pyran-2-yl]-2-methoxy-propyl)-tetrahydro-pyran-2-yl]-acetic acid (167).]

$R_f = 0.15$ (hexane/EtOAc 1:1).

$^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 4.48–4.35 (m, 2 H), 4.34–4.28 (m, 1 H), 4.20 (t, 1 H, $J = 6.8$ Hz), 4.00–3.83 (m, 5 H), 3.51 (t, 1 H, $J = 8.7$ Hz), 3.45 (s, 3 H), 2.33 (dd, 1 H, $J = 13.7, 11.2$ Hz), 2.12 (dd, 1 H, $J = 13.7, 3.1$ Hz), 2.10–1.96 (m, 2 H), 1.80–1.04 (m, 15 H), 0.94–0.80 (m, 14 H), 0.77 (d, 3 H, $J = 6.2$ Hz), $–0.03$ (s, 3 H), $–0.04$ (s, 3 H).

HRMS (MALDI) calcd for $C_{30}H_{56}O_{16}SiNa [M+Na]^+$, 611.3591; found, 611.3586.
(1S,3R,5S,7S,9S,13S,15R,18R)-7-(tert-Butyl-dimethyl-silyloxy)-13-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-3-methoxy-18-methyl-12,19,20-trioxa-tricyclo[13.3.1.15,9]icosan-11-one (168). To an ice-cooled solution of acid 167 (4.5 mg, 7.6 µmol, 1.0 equiv) in THF (0.8 ml) was added Et₃N (6.4 µl, 46 µmol, 6.0 equiv) followed by 2,4,6-trichlorobenzoyl chloride (6.0 µl, 38 µmol, 5.0 equiv). The mixture was stirred at 0 °C for 30 min and was then allowed to warm to room temperature, whereupon toluene (2.2 ml) was added. This solution was added over 3 h by syringe pump to a solution of DMAP (9.3 mg, 76 µmol, 10 equiv) in toluene (5 ml). Upon completion, stirring was maintained for an additional 2 h. The mixture was concentrated to dryness and filtered over silica gel (using hexane/Et₂O 1:1 as eluant). The filtrate was concentrated under reduced pressure. Purification by flash chromatography (hexane/Et₂O 1:1) afforded lactone 168 (3.5 mg, 80% yield) as a clear, colorless oil.

\[ R_f = 0.40 \text{ (hexane/EtOAc 2:1).} \]

\[ ^1H\text{ NMR} \ (300 \text{ MHz, } C_6D_6) \delta \ 5.44–5.38 \text{ (m, 1 H), 4.74 \ (dt, 1 H, } J = 6.8, \ 2.5 \text{ Hz), 4.34–4.22 \ (m, 1 H), 4.16 \ (d, 1 H, } J = 11.2 \text{ Hz), 3.96–3.71 \ (m, 5 H), 3.67 \ (dd, 1 H, } J = 8.7, \ 6.2 \text{ Hz), 3.42 \ (s, 3 H), 2.49 \ (t, 1 H, } J = 13.0 \text{ Hz), 2.34–2.01 \ (m, 4 H), 1.92–1.77 \ (m, 2 H), 1.51–0.84 \ (m, 28 H), –0.02 \ (s, 6 H).} \]

\[ \text{HRMS (MALDI) calcd for } C_{30}H_{54}O_8SiNa [M+Na]^+, 593.3485; \text{ found, 593.3486.} \]
To a solution of methyl ester 159 (10.0 mg, 17.0 µmol, 1.00 equiv) in dry diethyl ether (0.5 ml) was added potassium trimethylsilanolate (4.4 mg, 34 µmol, 2.0 equiv) in one portion. The slightly yellowish solution was stirred at room temperature for 24 h and then quenched by the addition of 0.10 M aqueous NaHSO₄ (4 ml). The aqueous layer was extracted with CH₂Cl₂ (6 × 4 ml), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give seco acid 164 which was azeotroped to dryness with benzene (2 × 3 ml) and used without further purification.

To a solution of unpurified seco acid 164 in anhydrous THF (2.2 ml) at ambient temperature were added sequentially Et₃N (14 µl, 0.10 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (14 µl, 85 µmol, 5.0 equiv). The solution was stirred at room temperature for 60 min, diluted with anhydrous DMF (5 ml) and then added dropwise over 3 h by syringe pump to a solution of DMAP (21.0 mg, 170 µmol, 10.0 equiv) in dry DMF (11 ml). After the end of the addition, the cloudy solution was stirred for an additional 2 h. The solvent was evaporated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) afforded macrolactone 166 as a clear, colorless oil ($R_f = 0.27$ (hexane/EtOAc 1:1)) which was used without further purification.
To a solution of the unpurified macrolactone 166 (3.5 mg, 6.3 µmol, 1.0 equiv) in anhydrous CH₂Cl₂ (1 ml) were added sequentially at ambient temperature 4 Å molecular sieves (30 mg), Proton Sponge (170) (13.5 mg, 63.0 µmol, 10.0 equiv) and trimethyloxonium tetrafluoroborate (8.4 mg, 57 µmol, 9.0 equiv). After stirring at ambient temperature for 30 min, the reaction was quenched by adding H₂O (2 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic solutions were washed with saturated, aqueous copper sulfate (2 × 3 ml) and brine. The diethyl ether solution was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The obtained product was purified by flash chromatography (hexane/EtOAc 2:1) to give 169 (3.4 mg, 49% yield over 3 steps from methyl ester 159).

Rₙ = 0.34 (hexane/EtOAc 2:1).

Optical Rotation: [α]²⁸°D (c 0.21, CHCl₃) = +58.7°.

¹H NMR (300 MHz, CDCl₃) δ 5.25 (ddd, 1 H, J = 11.1, 1.8, 1.2 Hz), 4.31 (dt, 1 H, J = 6.5, 3.4 Hz), 4.24–4.19 (m, 1 H), 4.18–4.06 (m, 1 H), 3.95–3.82 (m, 3 H), 3.81–3.70 (m, 1 H), 3.56–3.44 (m, 2 H), 3.35 (s, 3 H), 2.51 (dd, 1 H, J = 12.4, 4.0 Hz), 2.43–2.27 (m, 2 H), 1.98–1.80 (m, 3 H), 1.78–1.58 (m, 2 H), 1.54–1.24 (m, 12 H), 1.15 (d, 3 H, J = 7.1 Hz), 1.12–0.95 (m, 3 H), 0.91 (s, 9 H), 0.06 (s, 6 H).

¹³C NMR (75 MHz, CDCl₃) δ 170.2, 108.9, 77.2, 73.6, 73.5, 69.3, 69.1, 68.9, 65.3, 65.0, 62.7, 57.3, 43.0, 39.3, 39.2, 38.0, 35.7, 31.1, 27.5, 26.3, 25.9, 25.3, 24.0, 22.8, 18.2, 18.1, –4.5, –4.7.

IR (thin film) ν 2927, 2849, 1741, 1457, 1436, 1370, 1274, 1257, 1190, 1165, 1057 cm⁻¹.

HRMS (MALDI) calcd for C₃₀H₅₄O₈SiNa [M+Na]⁺, 593.3486; found, 593.3491.
5.2.1.4. Completion of the Macrolide Moiety

![Chemical Structure]

\((1R,3S,5R,7R,9R,13R,15S,18S)-7-(tert-Butyl-dimethyl-silanyloxy)-13-((1R)-1,2-dihydroxy-ethyl)-3-methoxy-18-methyl-12,19,20-trioxa-tricyclo[13.3.1.1^{5,9}]icosan-11-one\) (171). A solution of acetonide 169 (4.0 mg, 7.0 µmol, 1.0 equiv) in AcOH/THF/H₂O 2:1:1 (1 ml) was heated to 45 °C for 5 h. The solution was allowed to cool to ambient temperature and was then quenched by the careful addition of saturated, aqueous NaHCO₃ (10 ml). The aqueous phase was extracted with CH₂Cl₂ (5 × 5 ml) and the combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and then concentrated under reduced pressure. Purification by flash chromatography (EtOAc) afforded diol 171 (2.9 mg, 80% yield) as a white solid.

\[R_f = 0.39 \text{ (EtOAc).}\]

**Optical Rotation:** \([\alpha]_D^{25} (c 0.15, \text{CHCl}_3) = +42.9^\circ.\]

\[^1H\text{ NMR}\ (300 \text{ MHz, CDCl}_3) \delta 5.26–5.18 \text{ (m, 1 H)}, \ 4.22 \text{ (t, 1 H, } J = 2.4 \text{ Hz)}, \ 4.19–4.08 \text{ (m, 1 H)}, \ 3.85 \text{ (dd, 1 H, } J = 10.5, 0.6 \text{ Hz)}, \ 3.80–3.71 \text{ (m, 2 H)}, \ 3.62–3.43 \text{ (m, 4 H)}, \ 3.35 \text{ (s, 3 H)}, \ 2.68 \text{ (t, 1 H, } J = 6.6 \text{ Hz)}, \ 2.58 \text{ (dd, 1 H, } J = 12.0, 3.6 \text{ Hz)}, \ 2.44–2.31 \text{ (m, 2 H)}, \ 2.26–2.22 \text{ (m, 1 H)}, \ 2.02–1.80 \text{ (m, 3 H)}, \ 1.72–1.23 \text{ (m, 11 H)}, \ 1.15 \text{ (d, 3 H, } J = 7.1 \text{ Hz)}, \ 0.91 \text{ (s, 9 H)}, \ 0.06 \text{ (s, 6 H)}.\]
\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 172.1, 77.2, 74.2, 73.5, 73.5, 70.5, 69.4, 69.1, 64.8, 63.2, 62.8, 57.2, 42.9, 39.2, 39.1, 39.0, 35.7, 31.0, 27.4, 25.8, 23.8, 18.2, 18.1, –4.6, –4.8.

\(\text{IR (thin film)}\) \(\nu\) 3401, 2928, 2859, 1742, 1723, 1460, 1432, 1388, 1343, 1277, 1234, 1189, 1167, 1112, 1075, 1039, 881, 834, 804, 772 cm\(^{-1}\).

\(\text{HRMS (MALDI)}\) calcd for C\(_{27}\)H\(_{50}\)O\(_{8}\)SiNa [M+Na]\(^+\), 553.3172; found, 553.3167.

\((1R,3S,5R,7R,9R,13R,15S,18S)-7-(\text{tert-Butyl-dimethyl-silanyloxy})-3\text{-methoxy-18-methyl-13-}((1E)-4\text{-methy})-12,19,20\text{-trioxo-tricyclo[13.3.1.1\(5,9\)]icosan-11-one}\) (173). To an ice-cooled solution of diol 171 (6.5 mg, 12 \(\mu\)mol, 1.0 equiv) in ethyl acetate (1 ml) was added Pb(OAc)\(_4\) (8.0 mg, 18 \(\mu\)mol, 1.5 equiv) in one portion. The resulting orange solution was stirred at 0 °C for 15 min, then quickly filtered over silica gel (using diethyl ether as eluant) and concentrated under reduced pressure to give aldehyde 172 (\(R_f=0.19\) (hexane/EtOAc 4:1)) which was azeotroped to dryness with benzene (3 \(\times\) 1 ml) and used immediately without further purification.

To a suspension of freshly washed potassium hydride in anhydrous DME (4 ml) was added HMDS (1.04 ml, 5.00 mmol, 1.00 equiv) at ambient temperature over 5 min. The suspension was stirred at room temperature for 72 h, giving a clear, colorless solution of KHMDS in DME.
To a solution of sulfone 174 (90.0 mg, 320 µmol) in dry DME (0.2 ml) was added KHMDS (1.0 M in DME, 0.35 ml, 0.35 mmol) dropwise over 5 min at –78 °C to give a bright-yellow solution which was allowed to stir at –55 °C for 2 h. 8 drops of this solution were added via cannula to a solution of the unpurified aldehyde 172 in anhydrous DME (0.2 ml) at –78 °C. The resulting solution was stirred at –55 °C for 2 h and at 0 °C for 3 h. The reaction was quenched by the addition of H₂O (0.3 ml) and stirred at ambient temperature for 15 h. The solution was diluted with ether and washed with 1.0 M aqueous HCl (3 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (4 × 5 ml), washed with brine, dried over anhydrous Na₂SO₄ and filtered. Purification by flash chromatography (hexane/EtOAc 6:1) afforded olefin 173 (4.9 mg, 73% yield over 2 steps, E/Z > 95:5 by ¹H NMR spectroscopy) as a clear, colorless oil.

Rᵥ = 0.24 (CH₂Cl₂/EtOAc 9:1).

Optical Rotation: [α]₂⁰⁸ D (c 0.225, CHCl₃) = +60.9°.

¹H NMR (300 MHz, CDCl₃) δ 5.76–5.66 (m, 1 H), 5.43–5.28 (m, 2 H), 4.22 (t, 1 H, J = 2.7 Hz), 4.21–4.11 (m, 1 H), 3.92–3.85 (m, 1 H), 3.82–3.71 (m, 1 H), 3.64–3.54 (m, 1 H), 3.52 (t, 1 H, J = 10.2 Hz), 3.36 (s, 3 H), 2.48 (dd, 1 H, J = 13.2, 3.9 Hz), 2.45–2.24 (m, 2 H), 1.99–1.82 (m, 4 H), 1.76–1.25 (m, 14 H), 1.17 (d, 3 H, J = 6.9 Hz), 1.14–1.08 (m, 1 H), 1.07–0.99 (m, 1 H), 0.92 (s, 9 H), 0.85 (d, 3 H, J = 6.6 Hz), 0.06 (s, 6 H).

¹³C NMR (75 MHz, CDCl₃) δ 169.7, 131.9, 130.0, 73.6, 73.5, 70.6, 69.4, 69.2, 65.0, 63.1, 57.3, 43.3, 43.1, 41.7, 39.3, 39.2, 35.7, 30.9, 28.2, 27.2, 25.8, 24.1, 22.3, 18.3, 18.1, –4.6, –4.7.
IR (thin film) ν 2948, 2928, 2864, 1744, 1459, 1261, 1190, 1169, 1110, 1078, 962, 836, 773 cm⁻¹.

HRMS (MALDI) calcd for C₃₁H₅₆O₆SiNa [M+Na]⁺, 575.3744; found, 575.3752.

5-(3-Methyl-butylsulfanyl)-1-phenyl-1H-tetrazole (177). To a mixture of 3-methyl-butan-1-ol (175) (270 µl, 2.50 mmol, 1.00 equiv), triphenylphosphine (720 mg, 2.75 mmol, 1.10 equiv) and 2-phenyl-2H-tetrazole-5-thiol (176) (490 mg, 2.75 mmol, 1.10 equiv) in anhydrous THF (30 ml) was added dropwise, at room temperature, a solution of DEAD (430 µl, 2.75 mmol, 1.10 equiv) in THF (2 ml) over 10 min. The yellow solution was stirred at ambient temperature for 16 h and then concentrated under reduced pressure. Pentane/EtOAc 9:1 (40 ml) was added and the white precipitate filtered off over diatomaceous earth. The filtrate was concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 3:1) provided 5-(3-Methyl-butylsulfanyl)-1-phenyl-1H-tetrazole (177) (532 mg, 86% yield) as a colorless oil.

Rₛ = 0.56 (hexane/EtOAc 2:1).

¹H NMR (300 MHz, CDCl₃) δ 7.61–7.54 (m, 5 H), 3.44–3.38 (m, 2 H), 1.80–1.61 (m, 3 H), 0.96 (d, 6 H, J = 6.2 Hz).

¹³C NMR (75 MHz, CDCl₃) δ 154.7, 133.9, 130.2, 129.9, 124.0, 37.9, 31.7, 27.6, 22.3.

IR (thin film) ν 2957, 2871, 1597, 1500, 1466, 1411, 1386, 1278, 1243, 1088, 1074, 1055, 1015, 978, 914, 761, 694, 668 cm⁻¹.
HRMS (MALDI) calcd for $\text{C}_{12}\text{H}_{17}\text{N}_{4}\text{S}$ [M+H]$^+$, 249.1174; found, 249.1161.

5-(3-Methyl-butane-1-sulfonyl)-1-phenyl-1H-tetrazole (174). To a solution of sulfide 177 (532 mg, 2.14 mmol, 1.00 equiv) in methanol (20 ml) was added an aqueous solution (20 ml) of Oxone (4.00 g, 6.42 mmol, 3.00 equiv) at ambient temperature. After stirring at room temperature for 20 h and at 50 °C for 1 h, the mixture was diluted with diethyl ether (50 ml), washed with H$_2$O. The layers were separated and the aqueous phase extracted with diethyl ether ($3 \times 50$ ml). The combined organic solutions were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 4:1) provided sulfone 174 (540 mg, 90% yield) as a colorless oil.

$R_f = 0.61$ (hexane/EtOAc 2:1).

$^1\text{H NMR}$ (300 MHz, CDCl$_3$) $\delta$ 7.69–7.54 (m, 5 H), 3.74–3.68 (m, 2 H), 1.85–1.74 (m, 3 H), 0.96 (d, 6 H, $J = 6.5$ Hz).

$^{13}\text{C NMR}$ (75 MHz, CDCl$_3$) $\delta$ 153.3, 132.9, 131.3, 129.6, 125.0, 54.5, 30.2, 27.3, 22.1.

$\text{IR}$ (thin film) $\nu$ 2961, 2874, 1596, 1498, 1469, 1390, 1336, 1242, 1153, 1100, 1046, 1016, 922 cm$^{-1}$.

HRMS (MALDI) calcd for $\text{C}_{12}\text{H}_{16}\text{N}_{4}\text{O}_{2}\text{SNa}$ [M+Na]$^+$, 303.0892; found, 303.0892.
(1R,3S,5S,7R,9R,13R,15S,18S)-7-Hydroxy-3-methoxy-18-methyl-13-((1E)-4-methyl-pent-1-enyl)-12,19,20-trioxa-tricyclo[13.3.1.15,9]icosan-11-one (45). To a solution of silyl ether 173 (4.5 mg, 8.1 µmol, 1.0 equiv) in anhydrous THF (0.5 ml) was added TBAF (1.0 M in THF, 41 µl, 41 µmol, 5.0 equiv) at 0 °C. The solution was stirred at 0 °C for 45 min and at ambient temperature for 4 h. Additional TBAF (1.0 M in THF, 41 µl, 41 µmol, 5.0 equiv) was added and stirring was continued for 3 h. The reaction mixture was washed with saturated, aqueous NH₄Cl (2 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (4 × 5 ml), washed with brine, dried over anhydrous Na₂SO₄ and filtered. Purification by flash chromatography (hexane/EtOAc 1:1) provided the leucascandrolide A macrolide 45 (3.5 mg, 98% yield) as a white solid.

Rₛ = 0.16 (hexane/EtOAc 1:1).

Optical Rotation: [α]²²_D (c 0.175, EtOH) = +32.3°.

¹H NMR (500 MHz, C₅D₅N) δ 6.39 (d, 1 H, J = 3.4 Hz), 5.81 (ddt, 1 H, J = 11.0, 6.9 Hz), 5.58 (ddt, 1 H, J = 15.4, 6.9, 1.3 Hz), 4.67 (ddddd, 1 H, J = 10.6, 10.5, 3.5, 2.0 Hz), 4.46–4.45 (m, 1 H), 4.24–4.19 (m, 1 H, J = 11.6 Hz), 4.10 (br d, 1 H, J = 11.1 Hz), 3.98–3.94 (m, 1 H, J = 10.8 Hz), 3.81–3.76 (m, 1 H, J = 10.9 Hz), 3.41 (s, 3 H), 2.72 (dd, 1 H, J = 13.0, 3.7 Hz), 2.56–2.53 (m, 1 H, J = 14.3 Hz), 2.52 (dd, 1 H, J = 13.0, 11.6 Hz), 2.18–2.12 (m, 1 H), 1.97–1.21 (m, 14 H).
1.11 (d, 2 H, \( J = 7.1 \text{ Hz} \)), 1.15–1.05 (m, 2 H), 0.82 (d, 3 H, \( J = 6.6 \text{ Hz} \)), 0.81 (d, 3 H, \( J = 6.6 \text{ Hz} \)).

\(^{13}\text{C NMR} \) (75 MHz, C\(_5\)D\(_5\)N) \( \delta \) 170.0, 131.7, 131.3, 73.8, 73.7, 70.1, 69.8, 69.6, 63.7, 63.0, 56.6, 43.9, 43.3, 41.7, 39.9, 39.6, 39.4, 35.8, 31.4, 28.3, 27.4, 24.2, 22.3, 22.2, 18.4.

\( \text{IR (thin film)} \) \( \nu \) 3433, 2927, 2866, 1740, 1457, 1386, 1272, 1195, 1167, 1077, 1003, 961 cm\(^{-1}\).

\( \text{HRMS (MALDI)} \) calcd for C\(_{25}\)H\(_{42}\)O\(_6\)Na [M+Na]\(^+\), 461.2879; found, 491.2889.

5.2.2. Synthesis of Methyl Ester 46

\[ \text{Toluene-4-sulfonic acid but-3-ynyl ester (180).} \]

To an ice-cooled solution of homopropargyl alcohol (15.0 g, 210 mmol, 1.00 equiv) in pyridine (50 ml) was added tosyl chloride (39.5 g, 210 mmol, 1.00 equiv) in one portion. The solution was stirred at ambient temperature for 3 h, before being poured onto ice/conc. HCl 4:1 (150 ml). Following extraction with diethyl ether (3 \( \times \) 300 ml), the combined organic layers were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure to yield the known tosylate 180 which was used without further purification.

\(^{1}\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 7.80 (d, 2 H, \( J = 7.8 \text{ Hz} \)), 7.39 (d, 2 H, \( J = 7.8 \text{ Hz} \)), 4.10 (t, 2 H, \( J = 6.8 \text{ Hz} \)), 2.56 (t, 2 H, \( J = 6.8 \text{ Hz} \)), 2.45 (s, 3 H), 1.98 (s, 1 H).
These spectral characteristics were identical to those reported previously.\textsuperscript{189}

![Diagram of compound 181]

2-Acetylamino-2-but-3-ynyl-malonic acid diethyl ester (181). To a solution of diethyl acetamidomalonate (179) (10.0 g, 46.0 mmol, 1.00 equiv) in THF (70 ml) was added \textsuperscript{t}BuOK (5.68 g, 50.6 mmol, 1.10 equiv) under vigorous stirring. The suspension was stirred for 2 h at 60 °C. Tosylate 180 was added and the off-white suspension was stirred at reflux for 2 d. THF was removed under reduced pressure and the residual oil was acidified with 1.0 M aqueous HCl and extracted with EtOAc (3 × 100 ml). The combined organic layers were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 2:1) afforded known malonate 181 (3.49 g, 28% yield) as a colorless oil.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 6.81 (br s, 1 H), 4.33–4.17 (m, 4 H), 2.62 (t, 2 H, \( J = 7.5 \) Hz), 2.14 (dt, 2 H, \( J = 7.5, 2.5 \) Hz), 2.05 (s, 3 H), 1.93 (t, 1 H, \( J = 2.5 \) Hz), 1.27 (t, 6 H, \( J = 6.9 \) Hz).

These spectral characteristics were identical to those reported previously.\textsuperscript{189}

2-Acetylamino-hex-5-ynoic acid ethyl ester (182). To a solution of malonate 181 (5.25 g, 19.5 mmol, 1.00 equiv) in DMSO (15 ml) was added LiCl (2.07 g, 48.8 mmol, 2.50 equiv). The mixture was heated to 120 °C for 10 h. After cooling to room temperature, the solution was diluted with H₂O (100 ml) and extracted with diethyl ether (5 × 25 ml). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc) afforded ester 182 (3.20 g, 83% yield) as a colorless oil.

\[ R_f = 0.50 \text{ (EtOAc).} \]

\(^1\text{H NMR} \) (300 MHz, CDCl₃) \( \delta 6.12 \) (br s, 1 H), 4.97–4.60 (m, 1 H), 4.18 (q, 2 H, \( J = 6.5 \text{ Hz} \)), 2.28–2.20 (m, 2 H), 2.16–2.05 (m, 1 H), 2.00 (s, 3 H), 1.96 (t, 1 H, \( J = 2.5 \text{ Hz} \)), 1.94–1.84 (m, 1 H), 1.27 (t, 3 H, \( J = 6.5 \text{ Hz} \)).

\(^1\text{C NMR} \) (75 MHz, CDCl₃) \( \delta 171.8, 170.0, 82.8, 69.3, 61.5, 51.6, 31.0, 23.0, 15.0, 14.2. \)

\( \text{IR (thin film)} \) ν 3290, 3069, 2983, 2938, 2119, 1739, 1548, 1446, 1375, 1298, 1213, 1191, 1134, 1095, 1027, 861 cm\(^{-1}\).

\( \text{HRMS (MALDI)} \) calcd for C₁₀H₁₆NO₃ [M+H]⁺, 198.1130; found, 198.1124.
**N-(1-Hydroxymethyl-pent-4-ynyl)-acetamide (183).** To a solution of ester 182 (3.20 g, 16.2 mmol, 1.00 equiv) in dry THF (40 ml) at 0 °C was added LiBH₄ (0.388 g, 17.8 mmol, 1.10 equiv) portionwise over 5 min, followed by the dropwise addition of dry MeOH (1.8 ml) over 1 h. The clear solution was stirred at room temperature for 1 h, quenched with EtOAc (20 ml) and concentrated under reduced pressure. The obtained product was repeatedly diluted with methanol (5 × 15 ml) and subsequently concentrated to dryness. Purification by flash chromatography (EtOAc/MeOH 92:8) afforded alcohol 183 (2.27 g, 91% yield) as a clear, colorless oil.

R₉ = 0.30 (EtOAc/MeOH 92:8).

**¹H NMR** (300 MHz, CDCl₃) δ 5.97 (br s, 1 H), 4.08–3.97 (m, 1 H), 3.73–3.62 (m, 2 H), 2.55 (br s, 1 H), 2.29 (dt, 2 H, J = 6.8, 2.5 Hz), 2.01 (s, 3 H), 2.00 (t, 1 H, J = 2.5 Hz), 1.89–1.69 (m, 2 H).

**¹³C NMR** (75 MHz, CDCl₃) δ 171.0, 83.6, 69.0, 64.2, 51.0, 29.9, 23.3, 15.5.

**IR** (thin film) ν 3292, 2936, 1643, 1555, 1434, 1376, 1300, 1051 cm⁻¹.

**HRMS** (EI) calcd for C₈H₁₃NO₂ [M⁺], 155.0946; found, 155.0941.

**2-Amino-hex-5-yn-1-ol hydrochloride (184).** Acetamide 183 (900 mg, 5.80 mmol, 1.00 equiv) was dissolved in MeOH (45 ml) and 1.0 M aqueous HCl (45 ml) was added. The solution was refluxed for 2 h, cooled to room temperature, concentrated
under reduced pressure, and lyophilized. The fluffy white solid was used without further purification.

\[ R_f = 0.60 \text{ (CH}_2\text{Cl}_2/\text{MeOH/\text{NH}_4\text{OH conc. 75:22:3}).} \]

\( ^1\text{H NMR} \text{ (300 MHz, CDCl}_3 \text{)} \delta \ 3.79 \text{ (dd, 1 H, } J = 11.8, \ 3.6 \text{ Hz), \ 3.58 \text{ (dd, 1 H, } J = 11.8, \ 6.3 \text{ Hz),} \ 3.42–3.32 \text{ (m, 1 H),} \ 2.41–2.33 \text{ (m, 3 H),} \ 1.94–1.75 \text{ (m, 2 H).} \]

\( ^{13}\text{C NMR} \text{ (75 MHz, CDCl}_3 \text{)} \delta \ 85.7, \ 73.5, \ 63.1, \ 54.8, \ 29.9, \ 17.0. \)

\( \text{IR (thin film)} \nu \ 3326, \ 3250, \ 3133, \ 3013, \ 2960, \ 1944, \ 1618, \ 1582, \ 1495, \ 1452, \ 1440, \ 1409, \ 1384, \ 1318, \ 1269, \ 1248, \ 1209, \ 1127, \ 1099, \ 1064, \ 1033, \ 989, \ 957, \ 930 \text{ cm}^{-1}. \)

Prop-2-ynyl-carbamic acid methyl ester (186). To an ice-cooled solution of propargyl amine (185) (3.00 g, 54.5 mmol, 1.00 equiv) and Et\textsubscript{3}N (8.04 ml, 57.2 mmol, 1.05 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (60 ml) was added methylchloroformate (4.40 ml, 57.2 mmol, 1.05 equiv) dropwise over 10 min. The solution was stirred at room temperature for 2 h, whereupon 1.0 m aqueous HCl (100 ml) was added. The layers were separated and the aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 \times 100 ml). The combined organic layers were washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 2:1) afforded carbamate 186 (4.89 g, 80% yield) as a colorless oil.

\[ R_f = 0.50 \text{ (EtOAc/hexane 2:3).} \]
**1H NMR** (300 MHz, CDCl₃) δ 4.88 (br s, 1 H), 4.02–3.92 (m, 2 H), 3.70 (s, 3 H), 2.24 (t, 1 H, J = 2.5 Hz).

These spectral characteristics were identical to those reported elsewhere.⁵²b

![4-Methoxycarbonylamino-but-2-ynoic acid](image)

**4-Methoxycarbonylamino-but-2-ynoic acid (187).** To an ice-cooled solution of HMDS (2.45 ml, 11.8 mmol, 2.05 equiv) in dry THF (120 ml) was added nBuLi (2.28 M in hexane, 5.16 ml, 11.8 mmol, 2.05 equiv) dropwise over 20 min. The solution was stirred at ambient temperature for 10 min. After cooling to −78 °C, alkyne 186 (649 mg, 5.74 mmol, 1.00 equiv) in THF (10 ml) was added slowly via cannula and stirred for 1 h. CO₂ (from dry ice) was bubbled through the solution at −78 °C for 2 h. The reaction was quenched by the careful addition of saturated, aqueous NaHCO₃ (5 ml). The resulting solution was washed with 6.0 M aqueous HCl and the aqueous layer was extracted with EtOAc (3 × 100 ml). The combined organic extracts were concentrated under reduced pressure, giving a residue that was dissolved in saturated, aqueous NaHCO₃ (50 ml) and washed with CH₂Cl₂ (50 ml). The aqueous layer was acidified to pH 1 by the slow addition of concentrated HCl and extracted with EtOAc (3 × 100 ml). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure, giving known acid 187 (720 mg, 80% yield) as brownish oil.

Rᵣ = 0.40 (EtOAc/hexane/TFA 40:60:1).

**1H NMR** (300 MHz, CD₃OD) δ 4.03 (s, 2 H), 3.66 (s, 3 H).
$^{13}$C NMR (75 MHz, CD$_3$OD) δ 159.0, 155.9, 85.0, 75.5, 52.8, 31.0.

These spectral characteristics were identical to those reported elsewhere.$^{52b}$

![Chemical Structure](image)

[3-(4-But-3-ynyl-oxazol-2-yl)-prop-2-ynyl]-carbamic acid methyl ester (190). A mixture of acid 187 (25.0 mg, 0.159 mmol, 1.00 equiv), hydrochloride 184 (28.1 mg, 0.188 mmol, 1.18 equiv), and DIPEA (82 µl, 0.48 mmol, 3.0 equiv) in CH$_2$Cl$_2$ was cooled to –10 °C. PyBrop (103 mg, 0.223 mmol, 1.40 equiv) was added in one portion and the resulting solution was allowed to reach ambient temperature over 2 h and was then stirred for an additional 4 h. Concentration under reduced pressure was followed by flash chromatography (EtOAc) and gave amide 188 which was used immediately.

Dess–Martin periodinane was added in one portion to a solution of unpurified amide 188 in CH$_2$Cl$_2$ (4 ml). The solution was stirred at room temperature for 70 min, concentrated under reduced pressure and subjected to flash chromatography (EtOAc/hexane 4:1), giving aldehyde 189.

To a solution of aldehyde 189 in CH$_2$Cl$_2$ (8 ml) were added successively 2,6-di-tert-butyl-4-methyl pyridine (261 mg, 1.27 mmol, 8.00 equiv), triphenylphosphine (130 mg, 0.500 mmol, 3.14 equiv) and 1,2-dibromo-1,1,2,2-tetrachloroethane (162 mg, 0.498 mmol, 3.13 equiv). After stirring at room temperature for 16 h, DBU (211 µl, 1.42 mmol, 8.9 equiv) was added in one portion and stirring was continued for 6 h. Concentration under reduced pressure was
followed by filtration over silica gel (EtOAc/hexane 1:1). Further purification by flash chromatography (EtOAc/hexane 1:2) gave oxazole 190 (9.0 mg, 25% yield from acid 187).

\[ R_f = 0.34 \text{(EtOAc/hexane 1:2)}. \]

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \) \delta \ 7.46 \text{ (s, 1 H), 4.96 \text{ (br s, 1 H), 4.23 \text{ (d, 2 H,} J = 5.6 \text{ Hz), 3.71 \text{ (s, 3 H), 2.75 \text{ (t, 2 H,} J = 6.7 \text{ Hz), 2.53 \text{ (dt, 2 H,} J = 6.7, 2.4 \text{ Hz), 1.96 (t, 1 H,} J = 2.4 \text{ Hz).} \]

\[ ^13C \text{ NMR (75 MHz, CDCl}_3 \) \delta \ 156.2, 145.4, 139.9, 135.5, 87.9, 82.8, 71.2, 69.1, 52.5, 31.2, 25.5, 17.7. \]

\[ \text{IR (thin film) \nu = 3259, 3128, 3053, 2926, 1715, 1590, 1548, 1531, 1464, 1436, 1415,} \]

\[ 1344, 1283, 1270, 1198, 1147, 1100, 1040, 1020, 990, 926, 877, 803 \text{ cm}^{-1}. \]

\[ \text{HRMS (MALDI) calcd for C}_{12}\text{H}_{13}\text{N}_2\text{O}_3 [M+H]^+, 233.0926; found, 233.0921.} \]

(2Z)-5-[2-((1Z)-3-Methoxycarbonylamino-propenyl)-oxazol-4-yl]-pent-2-enoic acid methyl ester (46). PdCl₂ (0.40 mg, 2.1 μmol, 10 mol%), CuCl₂ (5.8 mg, 43 μmol, 2.0 equiv) and AcONa (3.5 mg, 43 μmol, 2.0 equiv) were suspended in MeOH (0.5 ml) and stirred at room temperature for 5 min, giving a frog-green mixture. Alkyne 190 (5.0 mg, 21 μmol, 1.0 equiv) was added in one portion and a balloon filled with carbon monoxide was fitted to the flask through a rubber septum. Stirring was
maintained for 3 h. The reaction mixture was diluted with H$_2$O (5 ml) and extracted with EtOAc ($3 \times 5$ ml). The combined organic solutions were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The obtained product was filtered over a short pad of silica gel (hexane/EtOAc 1:1) and used without further purification.

To a solution of intermediate methyl ester in MeOH (1 ml) at room temperature was added quinoline (0.5 µl) and Pd/BaSO$_4$ (trace amount). A rubber balloon filled with hydrogen was fitted to the flask through a rubber septum and the resulting suspension was stirred at ambient temperature for 3.5 h. After filtration over diatomaceous earth (using EtOAc as eluant), the solution was concentrated under reduced pressure and purified by flash chromatography (hexane/EtOAc 1:1), giving methyl ester 46 (1.4 mg, 21% yield over 2 steps) as a colorless oil.

$$R_f = 0.40 \text{ (EtOAc/CH}_2\text{Cl}_2 1:4).}$$

$^1\text{H NMR (300 MHz, CDCl}_3 \delta 7.38 \text{ (s, } 1 \text{ H}), 6.33–6.22 \text{ (m, } 2 \text{ H}), 6.16–6.05 \text{ (m, } 1 \text{ H}), 5.83 \text{ (dt, } 1 \text{ H, } J = 11.2, 1.6 \text{ Hz}), 5.56 \text{ (br s, } 1 \text{ H}), 4.35–4.26 \text{ (m, } 2 \text{ H}), 3.71 \text{ (s, } 3 \text{ H}), 3.68 \text{ (s, } 3 \text{ H}), 3.02 \text{ (ddt, } 2 \text{ H, } J = 7.5 \text{ Hz, } 1.5 \text{ Hz}), 2.70 \text{ (t, } 2 \text{ H, } J = 7.5 \text{ Hz).}$$

These spectral characteristics were identical to those reported elsewhere.$^{52b}$
5.2.3. Synthesis of Aldehyde 178

3-Hydroxy-2-((2Z)-4-methoxycarbonylamino-but-2-enoylamino)-propionic acid methyl ester (192). To a solution of acid 187 (2.36 g, 15.0 mmol, 1.00 equiv) in EtOAc (190 ml) at room temperature was added Lindlar’s catalyst (500 mg) and quinoline (1.80 ml, 15.0 mmol, 1.00 equiv). The mixture was stirred for 30 min and a balloon filled with hydrogen was fitted to the flask. The reaction was monitored by \textsuperscript{1}H NMR analysis of aliquots every 60 min and was complete after 6 h. The heterogeneous mixture was filtered over diatomaceous earth and the filtrate was washed with 0.50 M aqueous HCl (100 ml). The aqueous layer was extracted with EtOAc (6 \times 100 ml) and the combined organic extracts were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated under reduced pressure, giving enoic acid 191 (R\textsubscript{f} = 0.10 (EtOAc)) as a brownish oil.

To a cooled (–25 °C) solution of acid 191 in THF (100 ml) was added N-methyl morpholine (3.80 ml, 34.5 mmol, 2.30 equiv) and isobutyl chloroformate (2.46 ml, 17.3 mmol, 1.15 equiv). The mixture was stirred at –25 °C for 30 min, whereupon L-serine methyl ester hydrochloride (2.57 g, 16.5 mmol, 1.10 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Saturated, aqueous NaHCO\textsubscript{3} (100 ml) was added and the aqueous layer was extracted with EtOAc (5 \times 100 ml). The combined organic solutions were dried over
anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography afforded amide 192 (1.36 g, 35% over 2 steps) as a clear oil.

$$R_f = 0.20 \text{ (EtOAc).}$$

$^1$H NMR (300 MHz, CD$_3$OD) $\delta$ 6.08–5.94 (m, 2 H), 4.58–4.53 (m, 1 H), 4.24 (d, 2 H, $J = 6.2$ Hz), 3.89 (dd, 1 H, $J = 11.5$, 4.6 Hz), 3.80 (dd, 1 H, $J = 11.5$, 4.2 Hz), 3.74 (s, 3 H), 3.62 (s, 3 H).

These spectral characteristics were identical to those reported elsewhere.$^{48}$

2-((1Z)-3-Methoxycarbonylamino-propenyl)-oxazole-4-carboxylic acid methyl ester (193). To a solution of amide 192 (1.36 g, 5.23 mmol, 1.00 equiv) in dry CH$_2$Cl$_2$ (48 ml) at −78 °C was added DAST (0.75 ml, 5.7 mmol, 1.1 equiv) dropwise. The solution was stirred at −78 °C for 1 h and then allowed to slowly warm to −40 °C. DBU (2.81 ml, 18.8 mmol, 3.60 equiv) was added dropwise and stirring at −40 °C was continued for 30 min. After further warming to 0 °C, CBrCl$_3$ (1.86 ml, 18.8 mmol, 3.60 equiv) was added and the solution was allowed to warm to ambient temperature over 1 h. After 8 h at room temperature, the solution was quenched with saturated, aqueous NaHCO$_3$ (50 ml). The layers were separated and the aqueous phase was extracted with EtOAc (5 × 100 ml). The combined organic solutions were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) afforded a white solid
which was recrystallized from hexane/EtOAc to give oxazole 193 (750 mg, 60% yield) as white crystals.

mp = 106 °C.

R_f = 0.25 (hexane/EtOAc 1:1).

^1H NMR (300 MHz, CD_3OD) δ 8.52 (s, 1 H), 6.35 (dt, 1 H, J = 12.0, 1.8 Hz), 6.22–6.13 (m, 1 H), 4.32 (dd, 2 H, J = 6.0, 1.5 Hz), 3.89 (s, 3 H), 3.64 (s, 3 H).

^13C NMR (75 MHz, CD_3OD) δ 162.8, 162.2, 159.4, 145.3, 141.7, 134.7, 114.9, 52.4, 49.6, 40.8.

IR (thin film) ν 3351, 3156, 2956, 1724, 1715, 1652, 1564, 1532, 1463, 1399, 1342, 1322, 1276, 1202, 1143, 1118, 1004, 946, 805, 763 cm⁻¹.

HRMS (MALDI) calcd for C_{10}H_{12}N_{2}O_{5}Na [M+Na]^+, 263.0644; found, 263.0638.

![Chemical structure of 194](image)

[(2Z)-3-(4-Hydroxymethyl-oxazol-2-yl)-allyl]-carbamic acid methyl ester (194).

To an ice-cooled solution of ester 193 (495 mg, 2.06 mmol, 1.00 equiv) in dry THF (17 ml) was added DIBAL–H (1.5 M in toluene, 5.5 ml, 8.2 mmol, 4.0 equiv) dropwise over 5 min. The solution was stirred for 90 min and then quenched with saturated, aqueous sodium potassium tartrate. The biphasic mixture was vigorously stirred at room temperature for 16 h. The aqueous phase was extracted with EtOAc (5 × 20 ml)
and the combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc) afforded alcohol $194$ (248 mg, 57% yield) as a white solid.

\[ \text{mp} = 123 \, ^\circ\text{C}. \]

\[ R_f = 0.34 \, (\text{EtOAc}). \]

$^1$H NMR (300 MHz, CD$_3$OD) $\delta$ 7.77 (s, 1 H), 6.29 (dt, 1 H, $J = 11.8$, 2.0 Hz), 6.10–6.00 (m, 1 H), 4.52 (s, 2 H), 4.34–4.27 (m, 2 H), 3.64 (s, 3 H).

$^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$ 161.5, 159.1, 142.8, 138.9, 136.2, 115.4, 56.9, 52.2, 40.7.

IR (thin film) $\nu$ 3272, 3120, 3003, 2961, 1717, 1654, 1591, 1547, 1527, 1466, 1403, 1332, 1265, 1234, 1188, 1169, 1094, 1049, 1031, 993, 970, 815, 783 cm$^{-1}$.

HRMS (MALDI) calcd for C$_9$H$_{12}$N$_2$O$_4$Na [M+Na]$^+$, 235.0694; found, 235.0687.

$\text{[2Z]-3-(4-Bromomethyl-oxazol-2-yl)-allyl]-carbamic acid methyl ester (195).}$ To a solution of alcohol $194$ (245 mg, 1.15 mmol, 1.00 equiv) in dry CH$_3$CN were added successively triphenylphosphine (606 mg, 2.31 mmol, 2.00 equiv), 2,6-lutidine (69 $\mu$l, 0.58 mmol, 0.50 equiv), and carbon tetrabromide (766 mg, 2.31 mmol, 2.00 equiv). The mixture was stirred at ambient temperature for 45 min and quenched with
saturated, aqueous NaHCO₃. The aqueous phase was extracted with diethyl ether (3 × 50 ml) and the combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) afforded bromide 195 (240 mg, 76% yield) as a clear, colorless oil.

\[ R_f = 0.38 \text{ (hexane/EtOAc 1:1)}. \]

\(^1\text{H NMR}\) (300 MHz, CDCl₃) \[ \delta 7.61 \text{ (s, 1 H), 6.31 \text{ (dt, 1 H, } J = 11.8, 1.8 \text{ Hz), 6.22–6.10 \text{ (m, 1 H), 5.41 \text{ (br s, 1 H), 4.38 \text{ (s, 2 H), 4.34 \text{ (t, 2 H, } J = 5.6 \text{ Hz), 3.69 \text{ (s, 3 H).) }}] }\]

\(^{13}\text{C NMR}\) (75 MHz, CDCl₃) \[ \delta 160.4, 157.0, 138.4, 137.9, 135.6, 115.8, 52.2, 39.6, 22.9. \]

\(\text{IR}\) (thin film) \[ \nu 3280, 3119, 2958, 1716, 1655, 1590, 1548, 1527, 1466, 1404, 1332, 1264, 1188, 1169, 1093, 1049, 1031, 993, 970, 815, 783, 751 \text{ cm}^{-1}. \]

\(\text{HRMS}\) (MALDI) calcd for C₉H₁₂BrN₂O₃Na \([\text{M+H}]^+\), 275.0031; found, 275.0026.

[2Z]-3-(4-Allyl-oxazol-2-yl)-allyl]-carbamic acid methyl ester (196). To a solution of bromide 195 (240 mg, 0.880 mmol, 1.00 equiv) in degassed THF (4 ml) (by passing an argon stream through for 1 h) at room temperature was added a solution of trifurylphosphine (8.2 mg, 35 µmol, 4.0 mol%) and Pd₂(dba)₃·CHCl₃ (18.2 mg, 17.6 µmol, 2.00 mol%) in degassed THF (1 ml) (by passing an argon stream through for 1 h), followed by tri-\(n\)-butylinyltin (0.308 ml, 1.06 mmol, 1.20 equiv). The
solution was refluxed for 14 h. Concentration under reduced pressure was followed by flash chromatography (hexane/EtOAc 1:2), giving allyl oxazole 196 (124 mg, 63% yield) as a clear, colorless oil.

\[ R_f = 0.46 \text{ (hexane/EtOAc 1:1).} \]

**\(^1H\) NMR** (300 MHz, CDCl\(_3\)) \( \delta \) 7.34 (s, 1 H), 6.30 (dt, 1 H, \( J = 11.8, 1.9 \text{ Hz} \)), 6.14–6.04 (m, 1 H), 6.01–5.89 (m, 1 H), 5.52 (br s, 1 H), 5.22–5.10 (m, 2 H), 4.31 (t, 2 H, \( J = 6.2 \text{ Hz} \)), 3.68 (s, 3 H), 3.34–3.28 (m, 2 H).

**\(^13C\) NMR** (75 MHz, CDCl\(_3\)) \( \delta \) 159.9, 157.0, 140.3, 136.3, 134.0, 133.9, 116.9, 116.2, 52.0, 39.5, 30.9.

**IR** (thin film) \( \nu \) 3335, 3080, 2952, 1713, 1643, 1588, 1537, 1520, 1463, 1433, 1260, 1194, 1169, 1148, 1103, 997, 953, 921 cm\(^{-1}\).

**HRMS** (MALDI) calcd for C\(_{11}\)H\(_{15}\)N\(_2\)O\(_3\) \([\text{M+H}\]^+\), 223.1082; found, 223.1077.

\{(2Z)-3-[4-(3-Oxo-propyl)-oxazol-2-yl]-allyl\}-carbamic acid methyl ester (178).

To a solution of alkene 196 (120 mg, 0.540 mmol, 1.00 equiv) in dry THF (2 ml) was added at room temperature 9-BBN (0.50 M in THF, 1.2 ml, 0.59 mmol, 1.1 equiv). The solution was stirred for 2 h, whereupon EtOH (0.60 ml), 6.0 M aqueous NaOH (0.22 ml), and H\(_2\)O\(_2\) 30% (0.43 ml) were added. The resulting mixture was heated to
50 °C for 1 h, diluted with diethyl ether (after cooling to room temperature), and washed with H₂O. The aqueous phase was extracted with diethyl ether (3 × 20 ml) and EtOAc (3 × 20 ml). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Filtration over a short pad of silica gel (eluting with EtOAc) afforded intermediate alcohol 197 (Rₗ = 0.36 (EtOAc)) a clear, colorless oil which was used without further purification.

A solution of oxalyl chloride (137 µl, 1.62 mmol, 3.00 equiv) in CH₂Cl₂ (3 ml) was cooled to –78 °C and DMSO was added dropwise. The solution was stirred at –78 °C for 20 min. A solution of unpurified alcohol 197 in CH₂Cl₂ (1 ml + 2 × 1 ml rinse) was added dropwise. After 20 min, Et₃N (0.972 ml, 6.92 mmol, 12.8 equiv) was added. The reaction mixture was stirred at –60 °C for 1 h, and then at 0 °C for 30 min. The resulting solution was diluted with CH₂Cl₂ (5 ml) and quenched with saturated, aqueous NH₄Cl (10 ml). Following extraction with CH₂Cl₂ (4 × 20 ml), the combined organic layers were washed with saturated, aqueous NH₄Cl (3 × 20 ml), H₂O (20 ml), and brine (20 ml). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:3) afforded aldehyde 178 (80 mg, 63% over 2 steps) as a clear, colorless oil, which was used immediately.

Rₗ = 0.50 (EtOAc).

^1H NMR (300 MHz, CDCl₃) δ 9.84 (t, 1 H, J = 1.2 Hz), 7.37 (s, 1 H), 6.28 (dt, 1 H, J = 11.8, 1.2 Hz), 6.15–6.04 (m, 1 H), 5.49 (br s, 1 H), 4.30 (t, 2 H, J = 6.2), 3.68 (s, 3 H), 2.93–2.79 (m, 4 H).

^13C NMR (75 MHz, CDCl₃) δ 200.9, 159.9, 157.0, 140.1, 136.4, 133.8, 116.2, 52.2, 42.3, 39.5, 18.9.
IR (thin film) ν 3339, 3131, 2953, 2841, 2732, 1723, 1715, 1592, 1538, 1463, 1442, 1415, 1391, 1258, 1194, 1143, 1103, 1002, 948, 779 cm⁻¹.

HRMS (MALDI) calcd for C₁₁H₁₅N₂O₄ [M+H]⁺, 239.1031; found, 239.1026.

5.2.4. Completion of the Total Synthesis


To a solution of alcohol 45 (3.3 mg, 7.5 µmol, 1.0 equiv) and acid 198 (4.6 mg, 15 µmol, 2.0 equiv) in CH₂Cl₂ (1 ml) was added HOBt·H₂O (0.5 mg, 3.0 µmol, 40 mol%) and EDCI·HCl (14.7 mg, 76.7 µmol, 10.2 equiv) at room temperature. The mixture was stirred for 15 min and then filtered through a short plug of silica gel (eluting with 30 ml EtOAc). The solution was concentrated under reduced pressure and the obtained phosphonoacetate 199 was used without further purification.

To a solution of 18-crown-6 acetonitrile complex (11.7 mg, 38.4 µmol, 5.10 equiv) and phosphonoacetate 199 in THF (0.3 ml) at −78 °C was added a solution of KHMDS (0.50 M in toluene, 42 µl, 9.1 µmol, 1.2 equiv). After stirring for 1 h, the solution was further cooled to −100 °C and aldehyde 178 (3.6 mg, 15 µmol, 2.0 equiv) in THF
(0.3 ml) was added dropwise. The reaction mixture was stirred for 2 h at –100 °C and was then quenched by the addition of saturated, aqueous NH₄Cl (2 ml). The aqueous layer was extracted with diethyl ether (4 × 3 ml). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) afforded 43 (0.5 mg, 10% yield).

\[ R_f = 0.25 \text{ (hexane/EtOAc 1:1).} \]

\[^1\text{H NMR} \ (300 \text{ MHz, CDCl}_3) \delta \]

7.36 (s, 1 H), 6.38–6.26 (m, 2 H), 6.15–6.05 (m, 1 H), 5.89 (dt, 1 H, \( J = 11.5 \); 1.8 Hz), 5.76–5.64 (m, 1 H), 5.51 (br s, 1 H), 5.40–5.30 (m, 2 H), 5.28–5.23 (m, 1 H), 4.36–27 (m, 2 H), 4.08–3.96 (m, 1 H), 3.93–3.85 (d, 1 H, \( J = 11.2 \) Hz), 3.69 (s, 3 H), 3.62–3.49 (m, 3 H), 3.35 (s, 3 H), 3.10–3.00 (m, 2 H), 2.73 (t, 2 H, \( J = 7.5 \) Hz), 2.54 (dd, 1 H, \( J = 13.0 \), 3.7 Hz), 2.40–2.18 (m, 2 H), 1.92–1.10 (m, 16 H), 1.16 (d, 3 H, \( J = 6.8 \) Hz), 1.05–0.98 (m, 1 H), 0.85 (d, 6 H, \( J = 6.2 \) Hz).

\[ \text{HRMS (MALDI) calcd for } C_{38}H_{56}N_2O_{10} [M+H]^+, 723.3832; \text{ found, 723.3827.} \]

These spectral characteristics were identical to those previously reported.\(^{35}\)
Curriculum Vitae

Born June 10th 1974 in Basel, Switzerland, to Fernand Fettes and Brigitte Fettes.

1986–1993 High School diploma at Athénée de Luxembourg
1993–1994 Mechanical-Engineering studies at ETH Zürich
1994–1995 Mathematics and Physics studies (Certificat d’Etudes Scientifiques) at Centre Universitaire de Luxembourg
1995–1996 Chemistry studies (DEUG, mention sciences de la matière, option chimie) at Université Louis Pasteur Strasbourg
1996–1999 Chemistry studies (Diplôme d’Ingénieur ECPM) at Ecole de Chimie, Polymères et Matériaux de Strasbourg
  • Internship at Dow Chemical, MI, USA (2 months)
  • Internship at Novartis Pharma, Basel, CH (4 months)

Spring 1999 Diploma thesis (“Development of a Versatile, Practical Synthesis of Enantiopure, Skipped Polyols; Studies towards the Synthesis of the Polyol Subunit of Amphotericin B”) under the supervision of Christiane Meyers in the group of Prof. Erick M. Carreira at ETH Zürich

1999–2003 Ph.D. studies (“Total Synthesis of Leucascandrolide A”) under the supervision of Prof. Erick M. Carreira at ETH Zürich

During my Ph.D. thesis, I was teaching assistant and head teaching assistant for an introductory-level organic-chemistry laboratory course as well as teaching assistant for chemistry exercises and lectures.

Zürich, January 2003

Alec Fettes