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Total Synthesis of Leucascandrolide A

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Presented by

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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"

Angew. Chem. Int. Ed. **2002**, *41*, 4098–4101; *Angew. Chem.* **2002**, *41*, 4272–4275.

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.
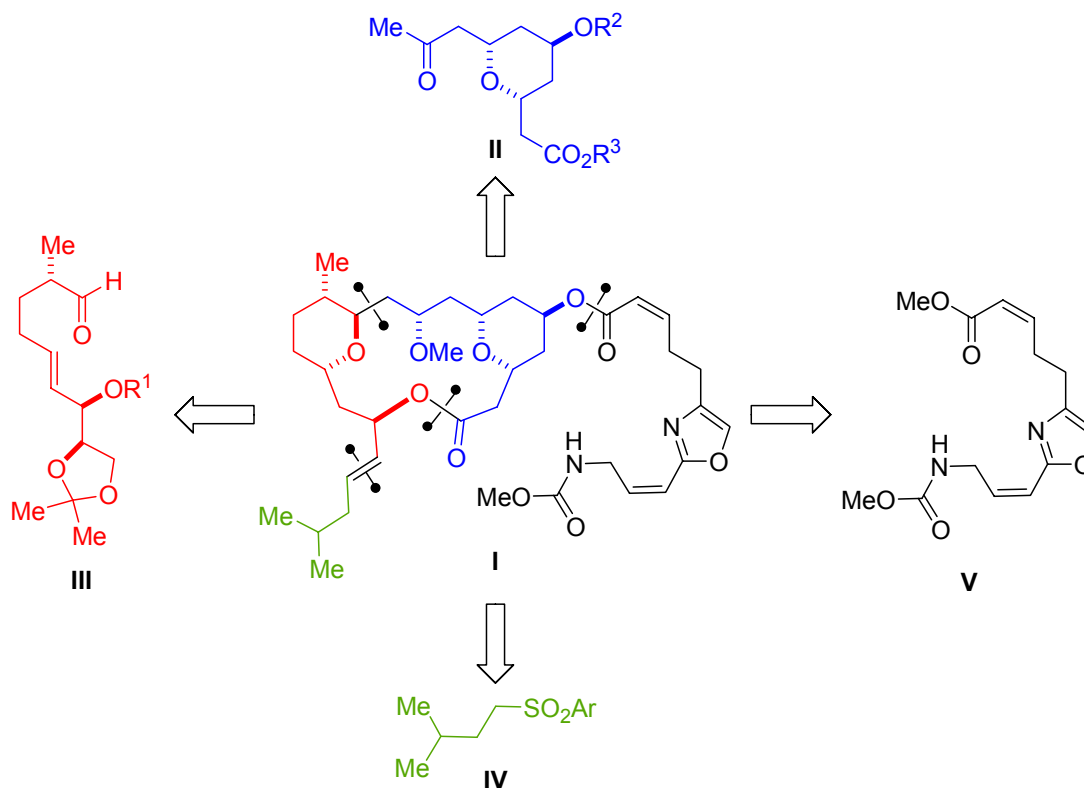
Scheme I. Retrosynthetic Analysis and Key Intermediates.

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.
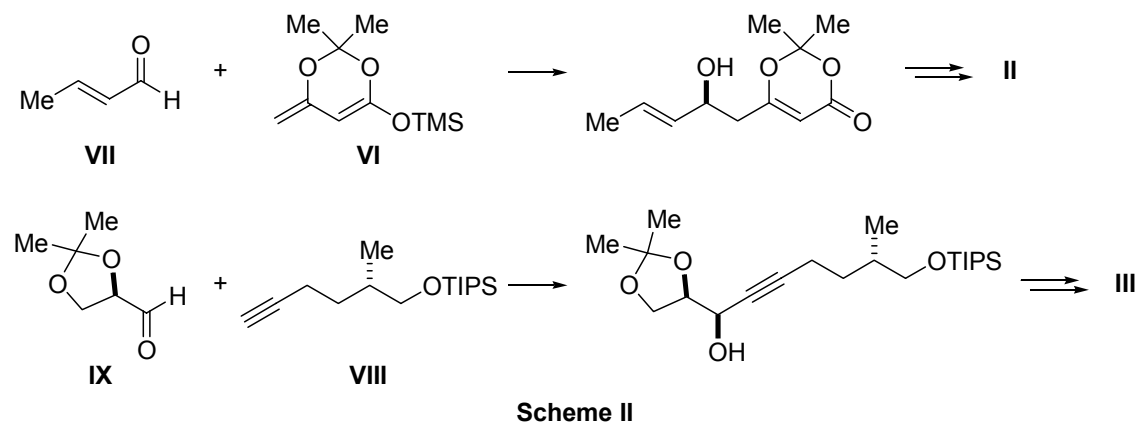
Scheme II

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.

Scheme III
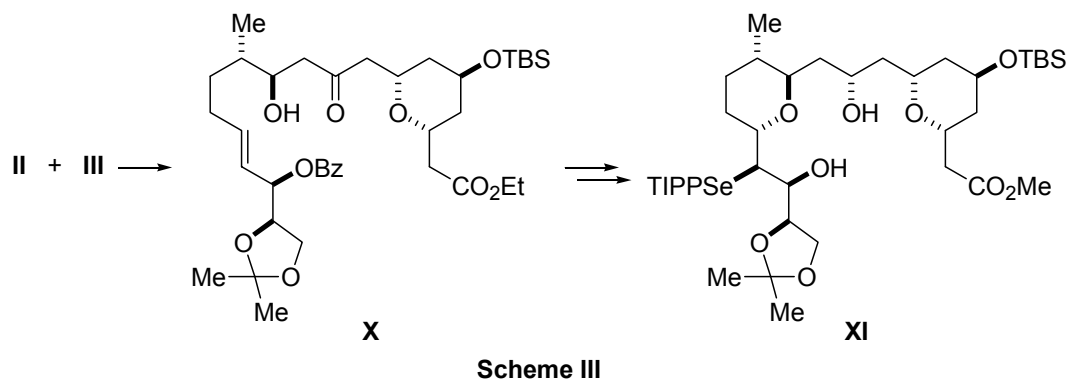
Seco acid **XII** showed pronounced recalcitrance towards macrolactonization under standard Yamaguchi conditions. The use of DMF as solvent, breaking up putative intramolecular hydrogen bonds involving the C9 hydroxy group, was found to be beneficial to the cyclization, leading to the desired macrocycle **XIII** in good yield. Introduction of the C17 and C5 side chains completed the synthesis of target compound **I** (Scheme IV).
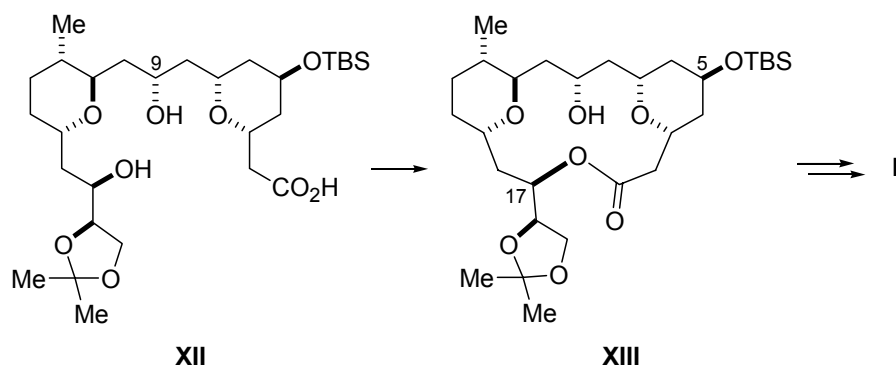
Scheme IV

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

Leucascandrolide A (**I**), ein neuartiges polyoxygeniertes Makrolid (Schema I), wurde 1996 von *Pietra* und Mitarbeitern aus dem Kalkschwamm *Leucascandra caveolata* isoliert. Trotz intensiver Bemühungen konnten keine weiteren Mengen des Naturstoffes bei späteren Tauchgängen gefunden werden.

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.
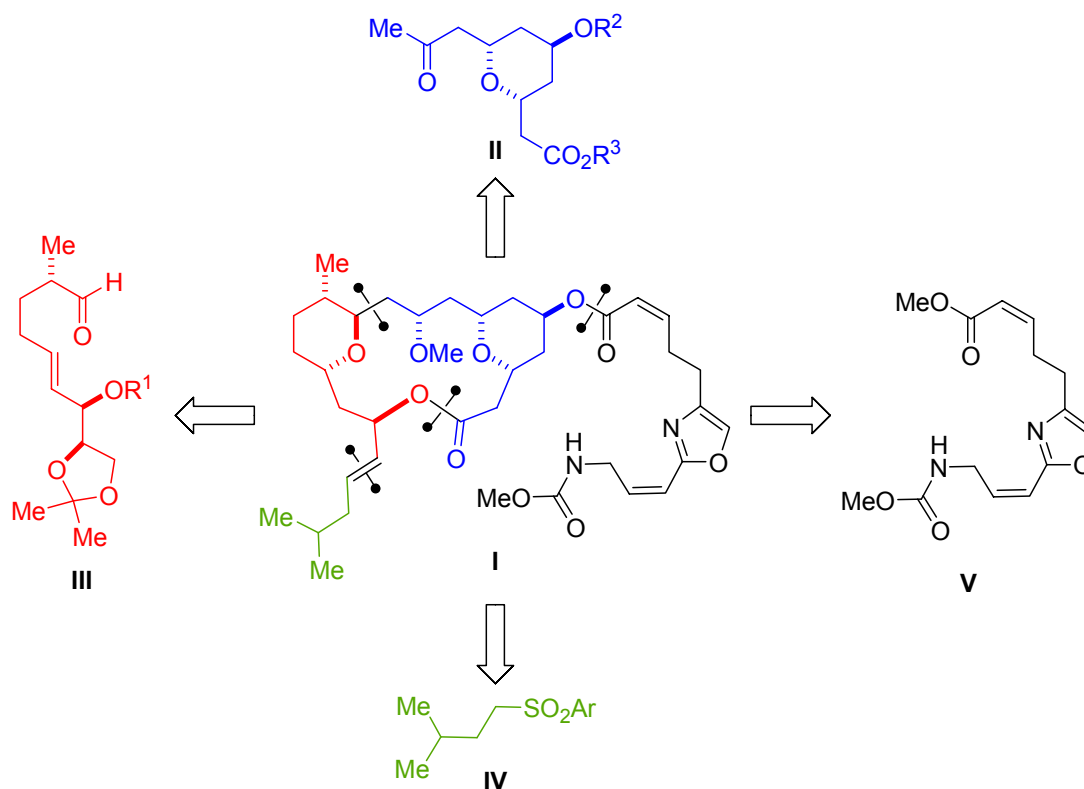
Schema I. Synthesestrategie und wichtige Zwischenprodukte.

Die beiden Bausteine **II** und **III** wurden als wichtige Zwischenprodukte identifiziert und mit Hilfe von uns entwickelter Methoden hergestellt (Schema II): Methylketon **II** konnte in nur sieben Schritten mittels Kupfer(I)-katalysierter asymmetrischer Addition des Dienolats **VI** an Crotonaldehyd (**VII**) erhalten werden; Aldehyd **III** wurde durch Addition des Zink(II) Acetylids von Alkin **VIII** an Aldehyd **IX** synthetisiert.
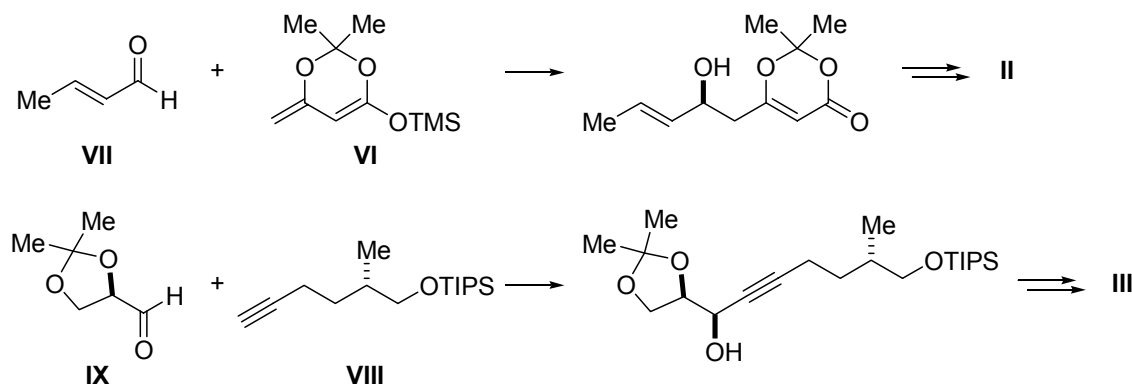
Schema II

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.
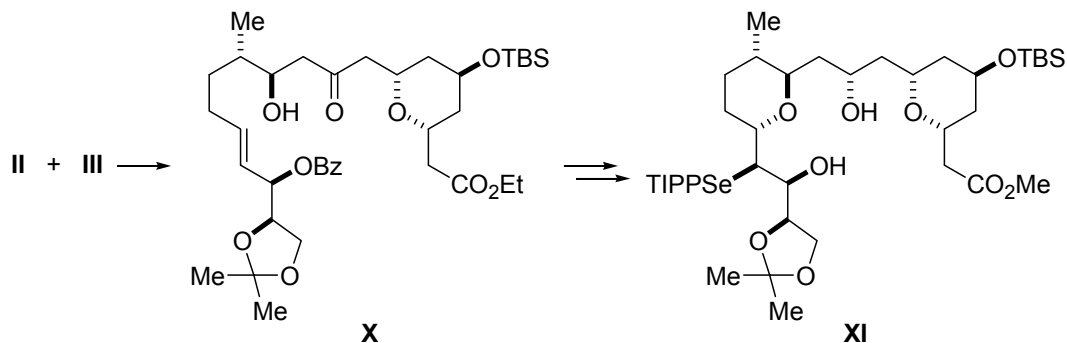
Schema III

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).
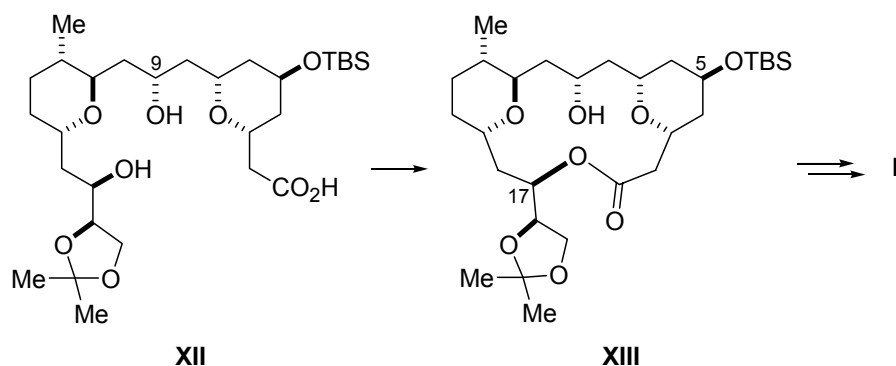
Schema IV

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

$[\alpha]^T_D$	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

CSA	10-camphorsulfonic acid
Cy	cyclohexyl
δ	NMR chemical shift in ppm downfield from a standard
d	day, doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	diethylaminosulfur trifluoride
dba	(*E,E*)-dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL–H	diisobutylaluminum hydride
DIPA	*N,N*-diisopropyl amine
DIPCl	*B*-chloro-diisopinocampheyl borane
DIPT	diisopropyl tartrate
DMAP	4-*N,N*-dimethylamino pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethyl formamide
DMP	*Dess–Martin* periodinane
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
ee	enantiomeric excess
EI	electron impact ionization
eq	equatorial
Eq.	equation
equiv	equivalent

Et	ethyl
eV	electronvolt
g	gram
h	hour
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOBt	1-hydroxy benzotriazole
HPLC	high-pressure liquid chromatography
HR	high resolution
Hz	hertz (s^{-1})
IC_{50}	concentration that is infective in 50% of test subjects
imid	imidazole
Ipc	isopinocampheyl
J	coupling constant
kcal	kilocalorie
KHMDS	potassium 1,1,1,3,3,3-hexamethyldisilazide
λ	wavelength
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
LHMDS	lithium 1,1,1,3,3,3-hexamethyldisilazide
L-Selectride	lithium tri-*sec*-butylborohydride
m	multiplet
m	meta
M	molarity (moles·l^{-1})
MALDI	matrix-assisted laser desorption ionization
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl

mg	milligram
MHz	megahertz
min	minute
ml	milliliter
μl	microliter
mmol	millimole
μmol	micromole
mol%	mole per cent
mp	melting point
M.S.	molecular sieves
MS	mass spectrometry
MTPA	2-methoxy-2-phenyl-2-(trifluoromethyl) acetic acid
NMM	*N*-methyl morpholine
NMO	*N*-methyl morpholine *N*-oxide
Nu	nucleophile
o	*ortho*
Oxone	potassium peroxymonosulfate $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
p	*para*
PCC	pyridinium chlorochromate
PG	protective group
Ph	phenyl
PKS	polyketide synthetase
PMB	4-methoxybenzyl
ppm	parts per million
PPTS	pyridinium 4-toluenesulfonate
Pr	propyl
Proton Sponge	*N,N,N',N'*-tetramethyl-1,8-naphtalene-diamine

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

THF	tetrahydrofuran
THP	tetrahydropyran
TIPP	2,4,6-triisopropylphenyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
(*R*)-Tol-BINAP	(*R*)-2,2'-bis(di-*p*-tolyl-phosphino)-1,1'-binaphthyl
Ts	4-methylphenyl sulfonyl
(*S*,*S*)-TsDPEN	(1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine
TPAP	tetra-*n*-propylammonium perruthenate
vs	versus

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-β-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

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(1) Collie, N; Myers, W. S. *J. Chem. Soc.* **1893**, 329–337.

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).

Erythromycin (**1**)

Tetracycline (**2**)

Laulimalide (**3**)

Epothilone B (**4**)

FK506 (**5**)

Rapamycin (**6**)

Amphotericin B (**7**)
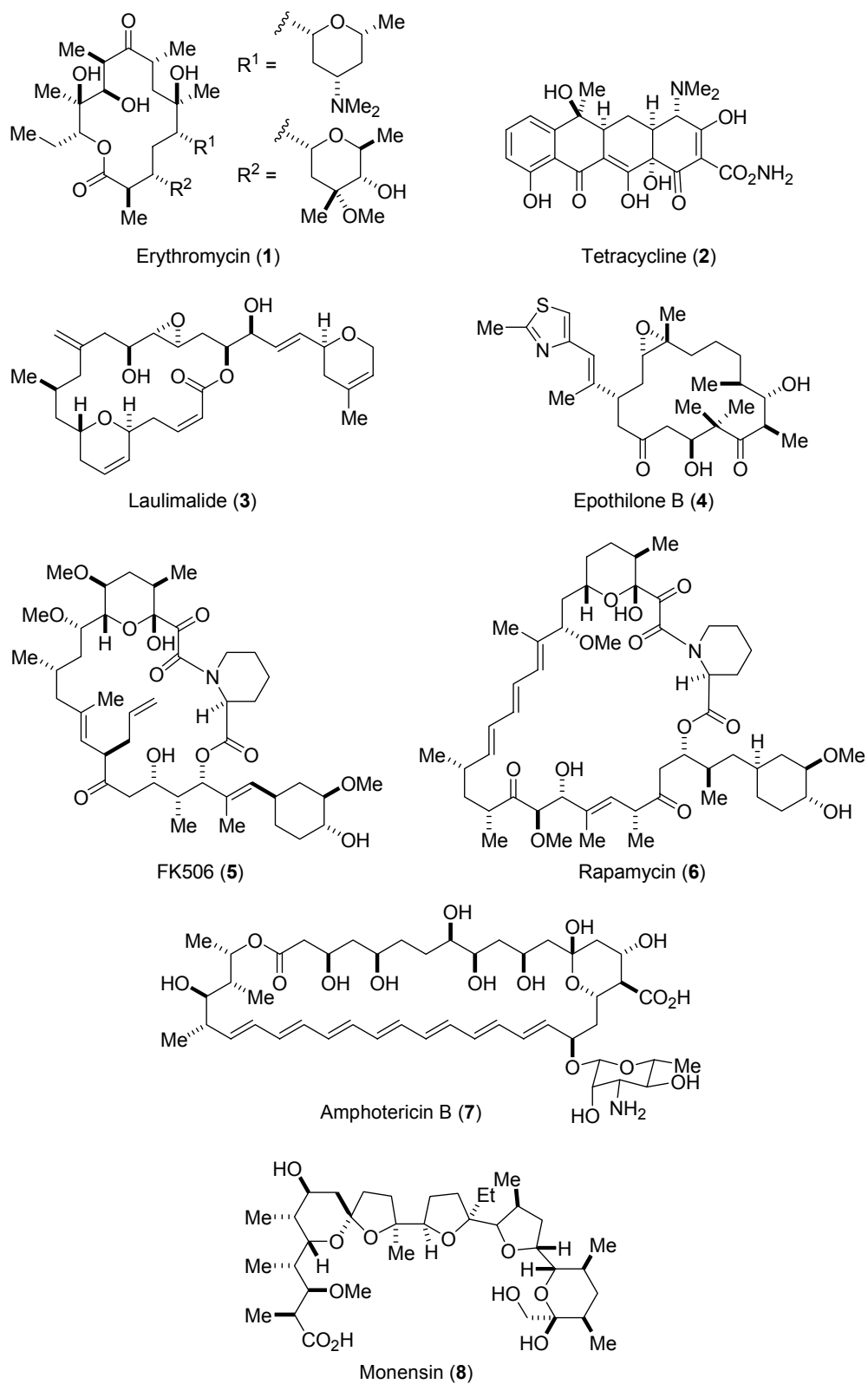
Monensin (**8**)

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).[2] 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.

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(2) The biosynthesis of polyketides has been extensively reviewed: (a) Staunton, J.; Wilkinson, B. In *Topics in Current Chemistry*, 1998; Vol. 195, pp 49–92; (b) Rawlings, B. J. *Nat. Prod. Rep.* **1997**, *14*, 523–556; (c) Simpson, T. J. *Nat. Prod. Rep.* **1991**, *8*, 573–602.
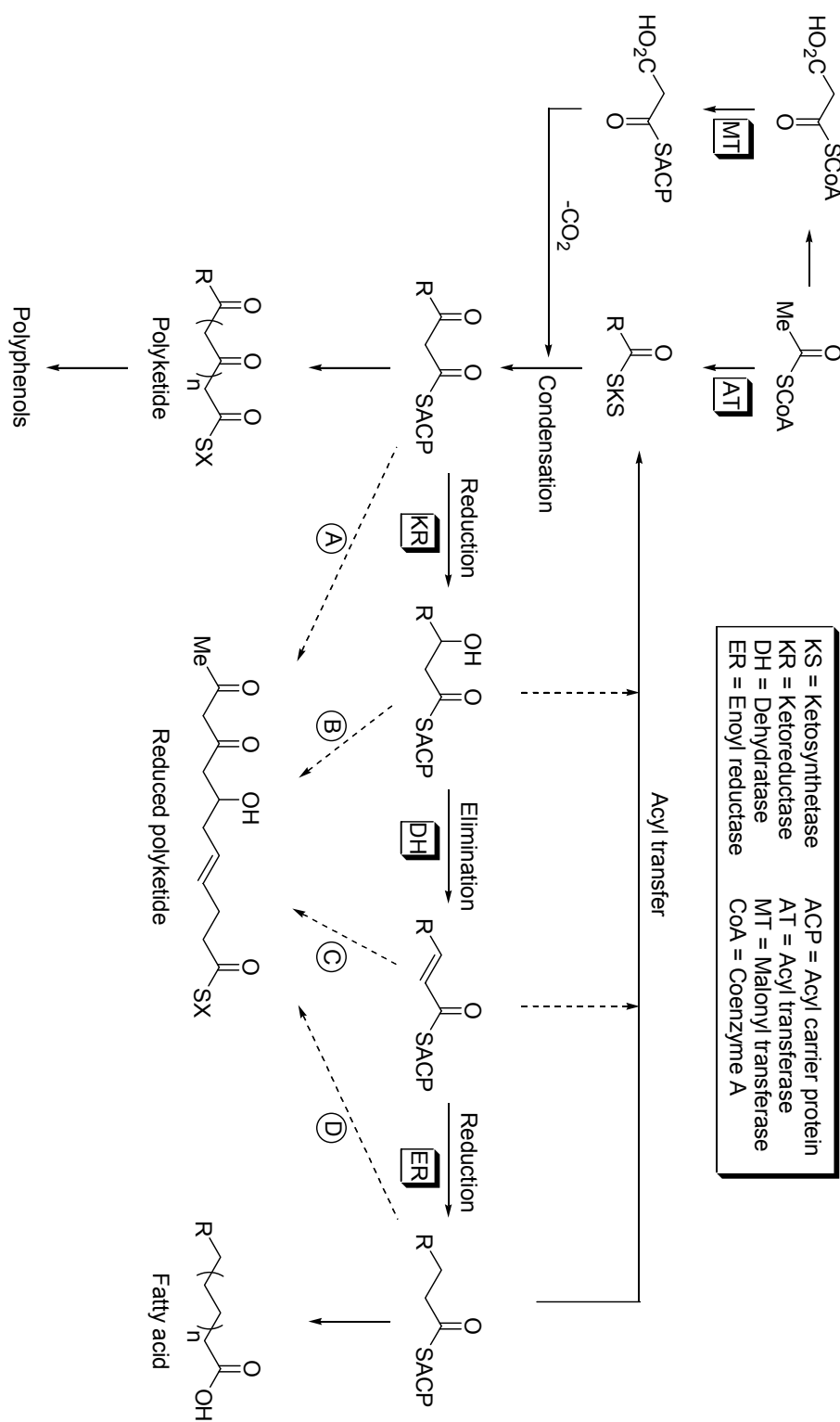
Figure 2. The assembly of fatty acids, polyketides, and reduced polyketides.

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).
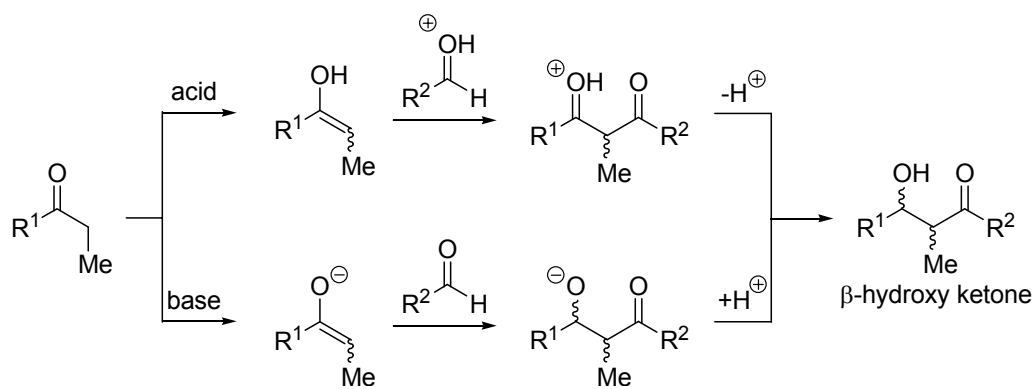
Scheme 1

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 π-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[6] giving *syn* products and (E)-enolates *anti* products via *Zimmerman–Traxler* transition states (Scheme 2).[7,8] Thus, the enolization step is of prime importance in this type of

(3) Mukaiyama, T. *Tetrahedron* **1999**, *55*, 8609–8670.

(4) For reviews on substrate-controlled aldol additions, see: (a) Franklin, A. S.; Paterson, I. *Cont. Org. Synthesis* **1994**, *1*, 317–338; (b) Heathcock, C. H.; Kim, B. M.; Williams, S. F.; Masamune, S.; Paterson, I.; Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon, Oxford, 1991, Vol. 2; (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D. Ed.; Academic Press: New York, 1984; Vol. 3, pp 111–212; (d) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095–1120.

(5) Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, *20*, 1665–1668.

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

(7) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

additions, and reaction conditions leading selectively to one or the other have been developed.[9]
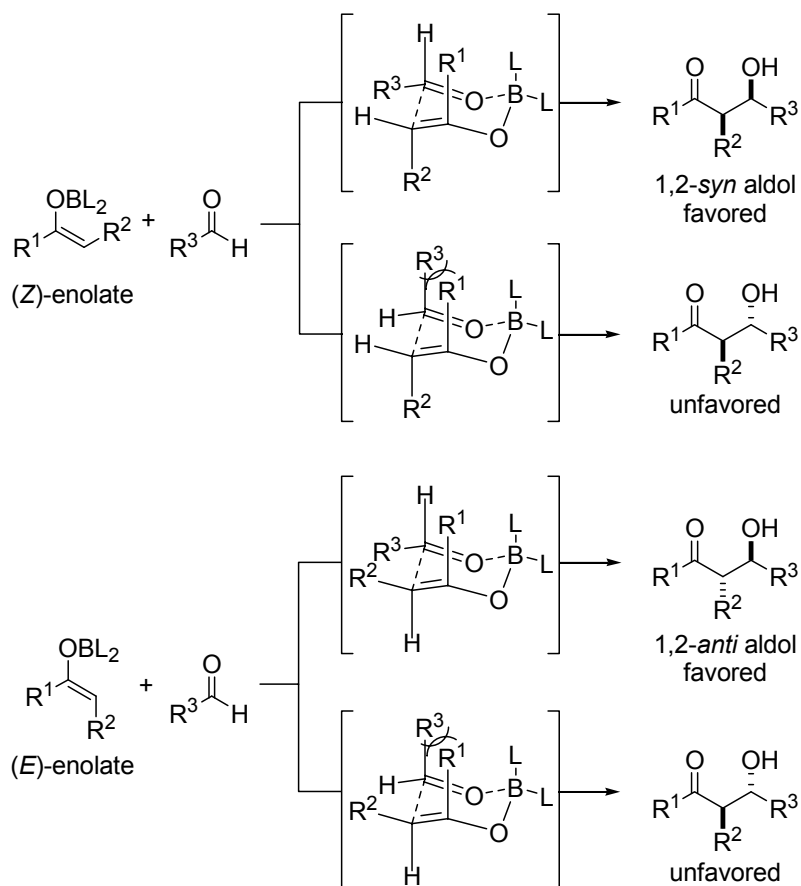
Scheme 2

The chiral-auxiliary approach, leading to enantiomerically enriched aldol adducts, was pioneered by *Evans* and co-workers.[10,11] The high predictability of the

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(8) The *like/unlike* nomenclature introduced by *Seebach* and *Prelog* is frequently used to refer to relative configurations (*l* or *u*) or relative topicities (*lk* or *ul*): Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654–660.

(9) (*E*)-enolates are formed by reaction with Cy$_2$BCl and Et$_3$N, while the use of Bu$_2$BOTf and *Hünig*'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.

sense of induction and the ability to access both *syn-* and *anti-*aldol products are two of the reasons for the widespread application of these oxazolidinone-based auxiliaries in total synthesis (Scheme 3).[12,13]
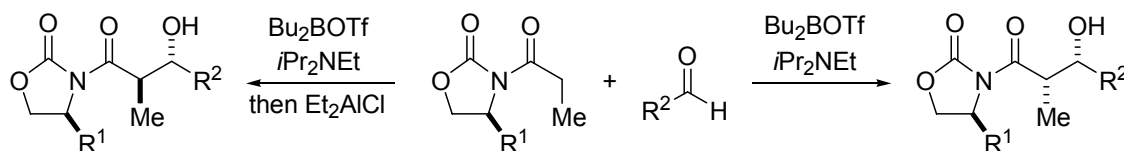
Scheme 3

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).[14]

(11) Initial, groundbreaking work in the area of chiral auxiliaries was reported by *Meyers*. For leading references, see: (a) Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032–3033; (b) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567–576; (c) Meyers, A. I.; Knaus, G. *J. Am. Chem. Soc.* **1974**, *96*, 6508–6510; (d) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873.

(12) *anti-*Aldol products are accessed through (*Z*)-enolates by complexation of the aldehyde with a *Lewis* acid, diverting the reaction from a cyclic transition state: Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747–5750.

(13) Other chiral auxiliaries have been reported for aldol reactions: *syn* aldols: (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894–902; (b) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883–7884; *anti* aldols: (c) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527–2528; (d) Abiko, A.; Liu, J. F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586–2587.

(14) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868; (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127–2142.
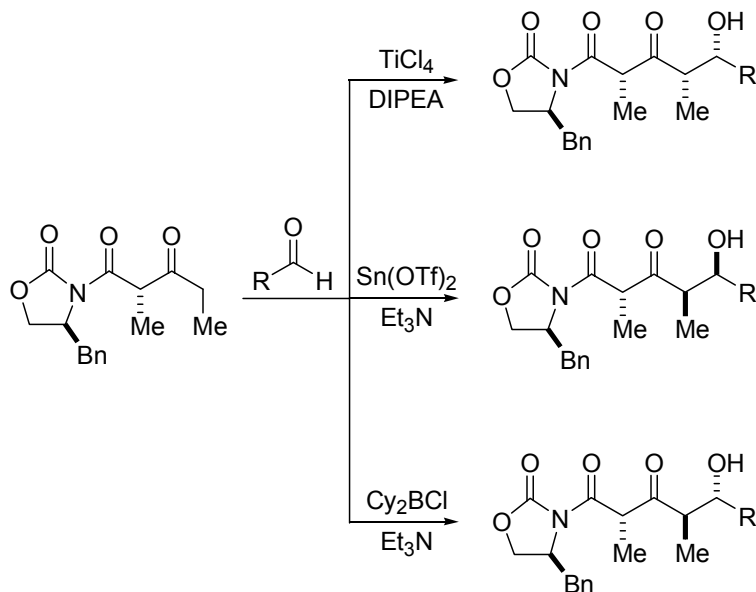
Scheme 4

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

(15) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391–2393.

(16) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909–912.

(17) Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237–12254.
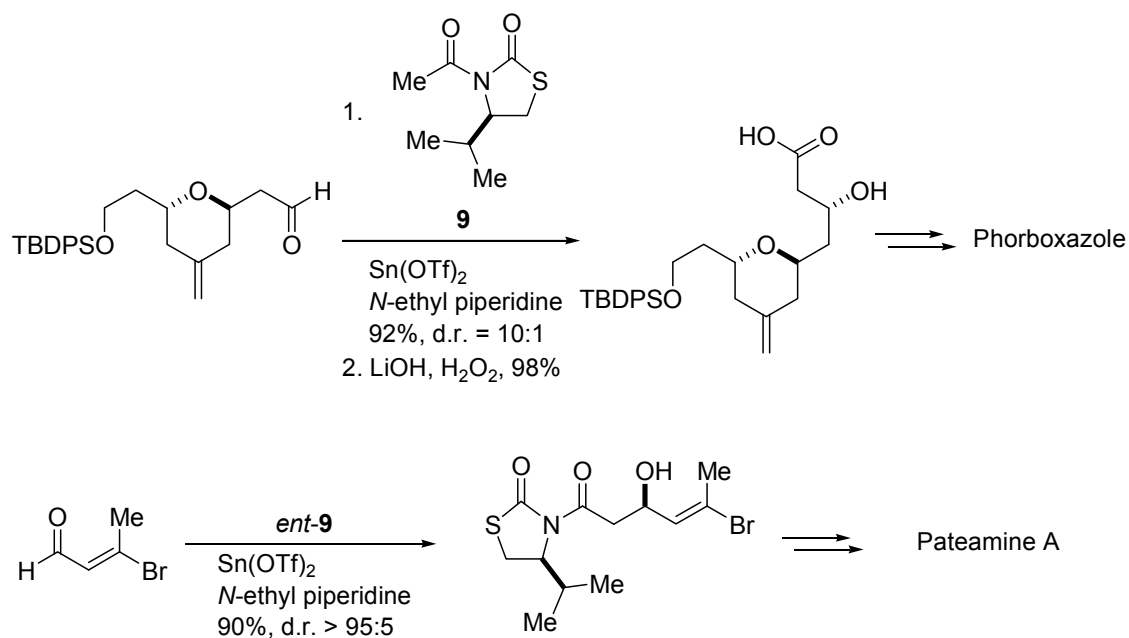
Scheme 5

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.[18] Some of the chiral reagents developed for this purpose are outlined in Figure 3.

Figure 3. Chiral boron reagents used in aldol chemistry.

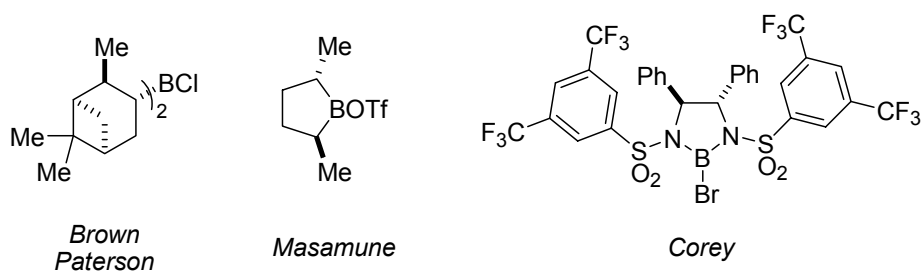(18) Chiral ligands on other metals have also been reported: titanium: (a) Duthaler, R. O.; Herold, P.; Wylerhelfer, S.; Riediker, M. *Helv. Chim. Acta* **1990**, *73*, 659–673; (b) Oertle, K.; Beyeler, H.; Duthaler, R. O.; Lottenbach, W.; Riediker, M.; Steiner, E. *Helv. Chim. Acta* **1990**, *73*, 353–358; tin: (c) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1983**, 297–298.

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.
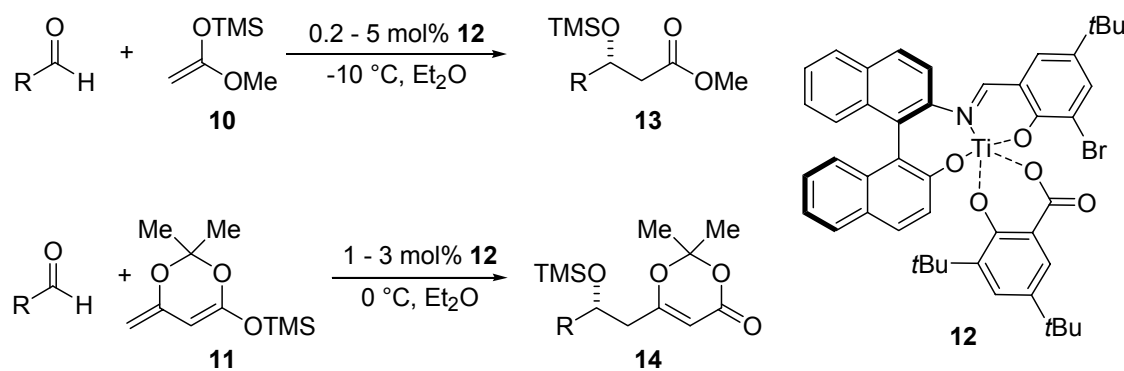
Scheme 6

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]

(19) Carreira, E. M. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; John Wiley & Sons: New York, 2000; pp 513–542.

(20) (a) Carreira, E. M.; Singer, R. A.; Lee, W. S. *J. Am. Chem. Soc.* **1994**, *116*, 8837–8838; (b) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360–12361.

(21) Rychnovsky, S. D.; Khire, U. R.; Yang, G. *J. Am. Chem. Soc.* **1997**, *119*, 2058–2059.
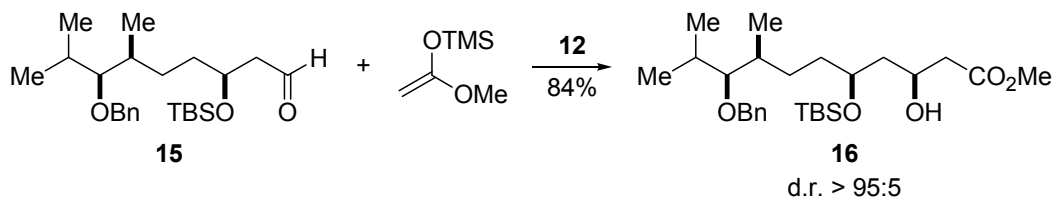
Scheme 7

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, benzyloxyacetaldeyhde (**21**), and glyoxylates undergo aldol reaction with a large variety of nucleophiles—acetate- and propionate-derived silyl ketene acetals, thioacetals and dienolate **22**—to give aldol adducts in high yields and excellent levels of optical purity.
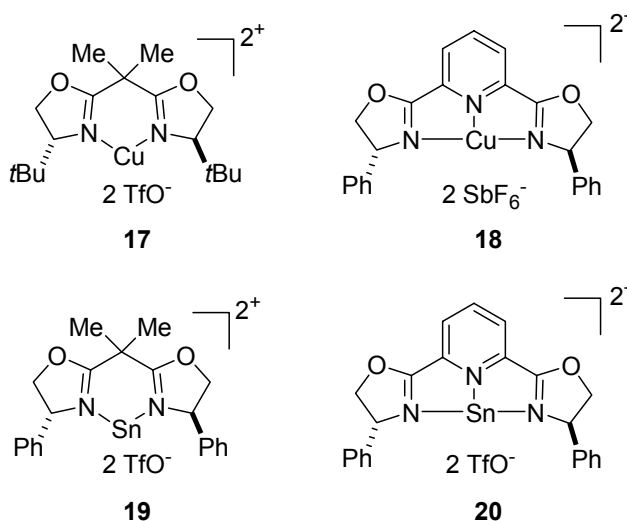
Scheme 8

(22) For other applications in total synthesis, see: (a) Kim, Y.; Singer, R. A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1261–1263; (b) Li, K. W.; Wu, J.; Xing, W. N.; Simon, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 7237–7238; Myers, A. G.; Hogan, P. C.; Hurd, A. R.; Goldberg, S. D. *Angew. Chem. Int. Ed.* **2002**, *41*, 1062–1067.

These catalytic systems were successfully applied by *Evans* to the total syntheses of phorboxazole B[23] and bryostatin 2[24] (Scheme 9).
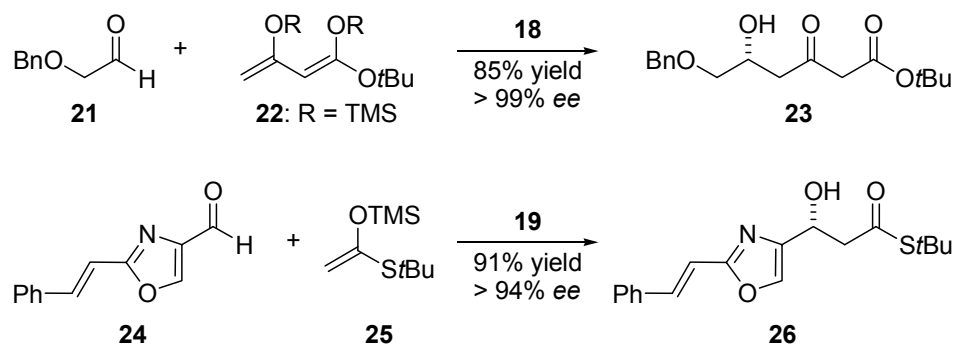
Scheme 9

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.[25]

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(23) (a) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033–10046; (b) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 2533–2536; (c) Evans, D. A.; Fitch, D. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2536–2540.

(24) (a) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540–7552; (b) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2354–2359.

(25) Several excellent accounts of this work are available: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley–VCH: Weinheim, 2000; pp 299–401; (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley–VCH: Weinheim, 2000; pp 403–490.
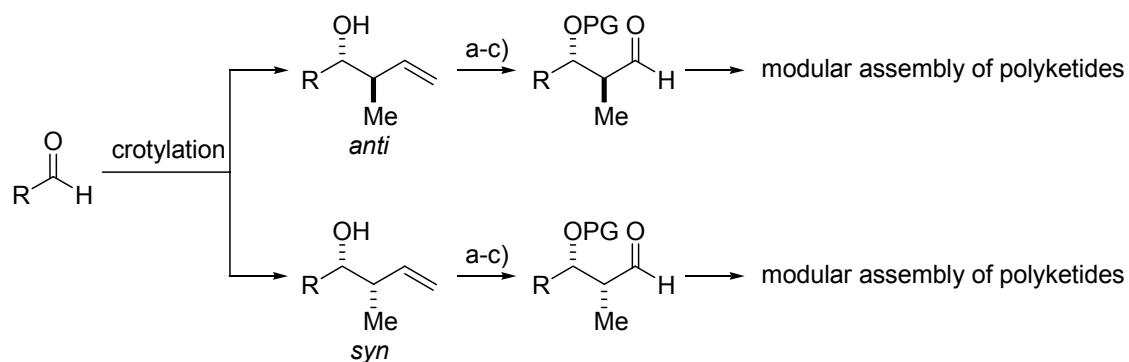
Scheme 10. (a) protection; (b) dihydroxylation; (c) glycol cleavage.

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.[26]

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 trialkoxysilanes, trialkylstannanes (thermally promoted reaction) and allylaluminum

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(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 → 28** or **29 → 30**) faster than metallotropic rearrangement (**27 ⇆ 29**), thus resulting in efficient translation of stereochemical information (Scheme 11).[27]
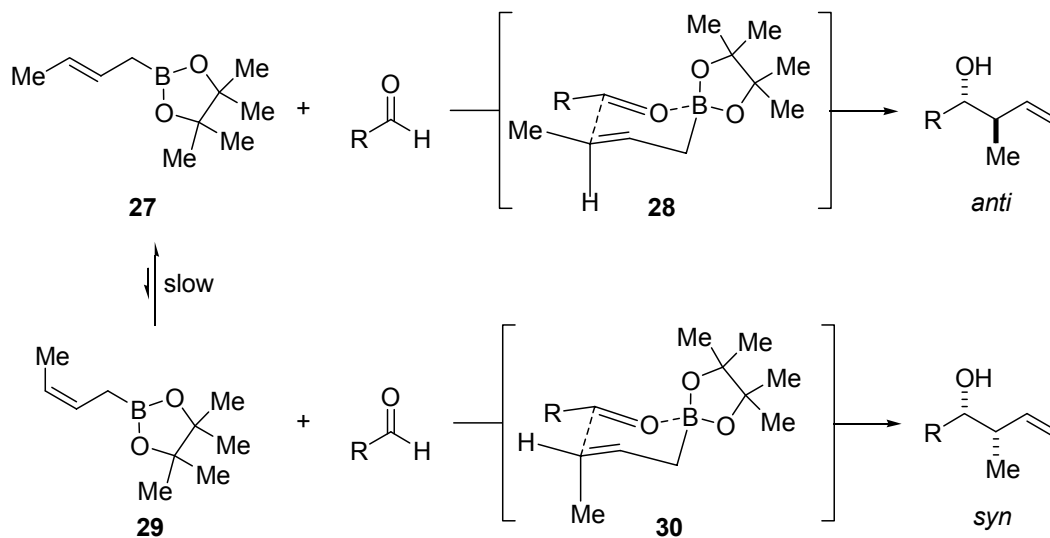
Scheme 11

Type III crotylmetal reagents—including crotylchromium, crotyltitanium and crotylzirconium reagents—undergo metallotropic rearrangement (**32 ⇆ 35**) faster than allylation with aldehydes (**32 → 33** or **35 → 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.
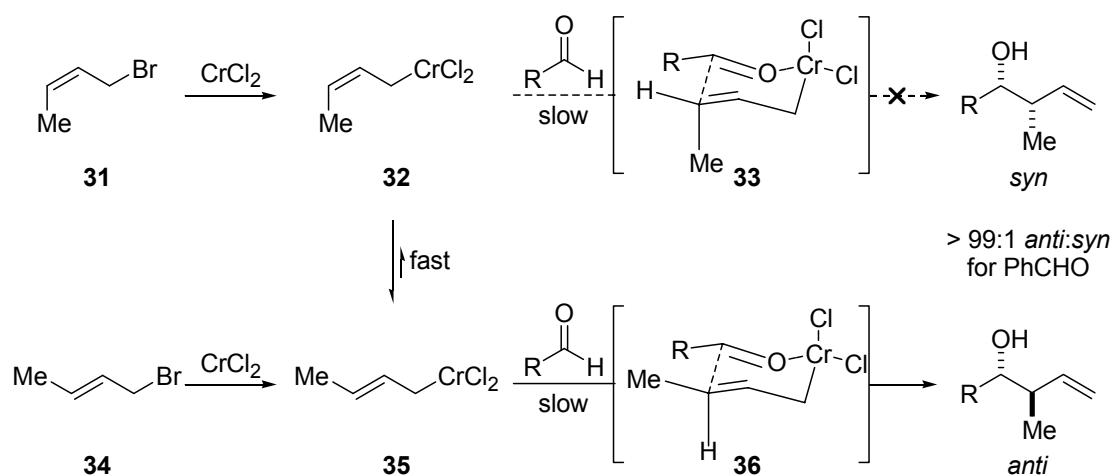
Scheme 12

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*[28] (pinene-derived reagent **37**), *Hoffmann*[29] (pinacol-derived **38**) and *Roush*[30] (tartrate-derived **39**) which had the greatest impact on polyketide synthesis (Figure 4).

(28) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093.

(29) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123–130.

(30) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186–8190.
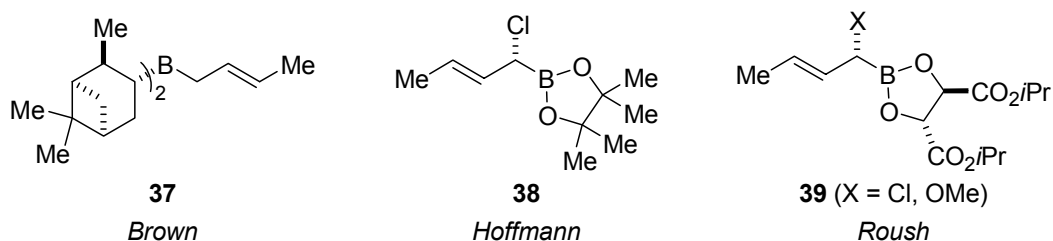
Figure 4. Chiral allylation reagents.

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 SmI$_2$, but oxidative cleavage with ozone has also been documented.[32]
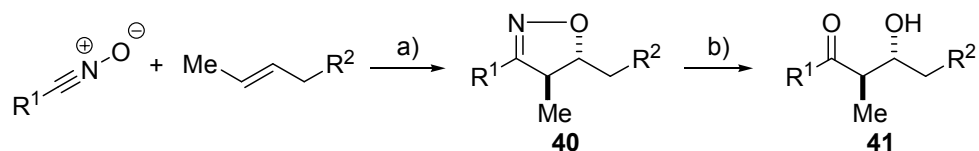
Scheme 13. (a) nitrile-oxide cycloadditions; (b) N–O bond reduction.

(31) (a) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024–4026; (b) Torssell, K.; Zeuthen, O. *Acta Chem. Scand. Ser. B* **1978**, *32*, 118–124.

(32) (a) Ra–Ni: Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474–3478; (b) Mo(CO)$_6$: McGarvey, G. J.; Mathys, J. A.; Wilson, K. J. *J. Org. Chem.* **1996**, *61*, 5704–5705; (c) SmI$_2$: Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587–1590; (d) ozone: Jäger, V.; Grund, H.; Buss, V.; Schwab, W.; Müller, I.; Schohe, R.; Franz, R.; Ehrler, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039–1054.

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**.[33] 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.
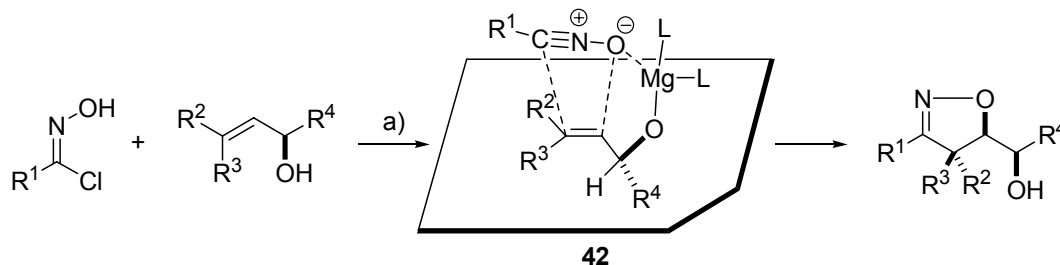
Scheme 14. (a) *i*PrOH (3.3 equiv), EtMgBr (3.0 equiv), CH_2Cl_2, 0 °C → RT.

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.[34] Based on the combination of reiterative *Diels–Alder* cycloadditions and stereoselective reactions, a general strategy was devised which gives access to skipped polyols.

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(33) (a) Kanemasa, S.; Kobayashi, S.; Nishiuchi, M.; Yamamoto, H.; Wada, E. *Tetrahedron Lett.* **1991**, *32*, 6367–6370; (b) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 2082–2085; (c) for an application to polyketide synthesis, see: Bode, J. W.; Carreira, E. M. *J. Org. Chem*. **2001**, *66*, 6410–6424; (d) Muri, D.; Carreira, E. M. *unpublished results*.

(34) (a) Myles, D. C.; Danishefsky, S. J. *Pure Appl. Chem.* **1989**, *61*, 1235–1242; (b) Danishefsky, S. J. *Aldrichim. Acta* **1986**, *19*, 59–69.

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).
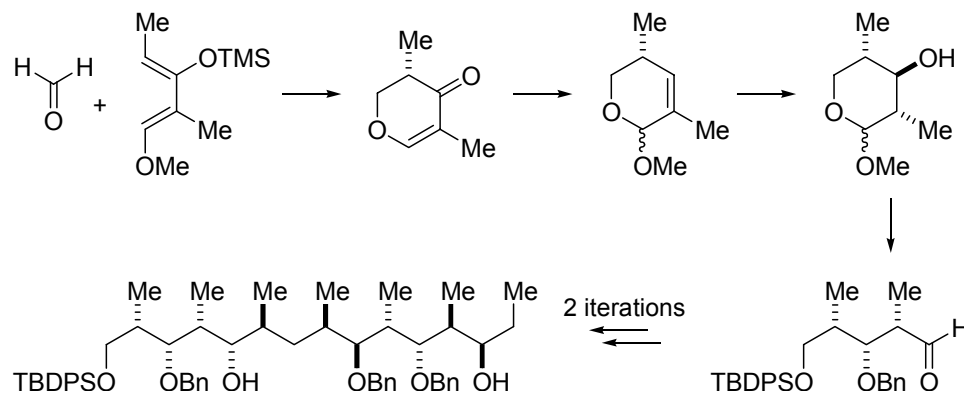
Scheme 15

1.2. Isolation of Leucascandrolide A

Leucascandrolide A[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[36], along with another, smaller macrolide, leucascandrolide B (**44**)[37] (Figure 5).

(35) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51–60.

(36) Borojevic, R; Klautau, M. *Zoosystema*, **2000**, *22*, 187–201.

(37) (a) D'Ambrosio, M.; Tato, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347–353; (b) D'Ambrosio, M.; Tato, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 1135.
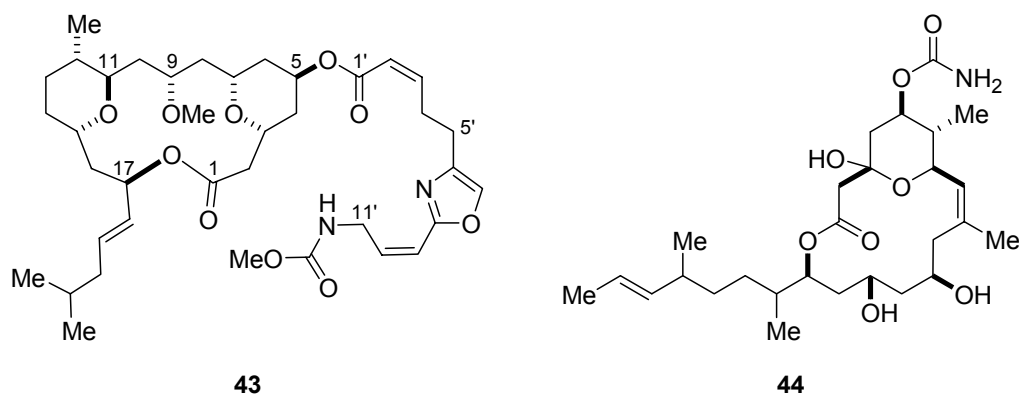
Figure 5. Structures of leucascandrolide A (**43**) and B (**44**).

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 CH_2Cl_2, flash chromatography (eluting with MeOH) and further purification by HPLC (eluting with MeOH/H_2O 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.
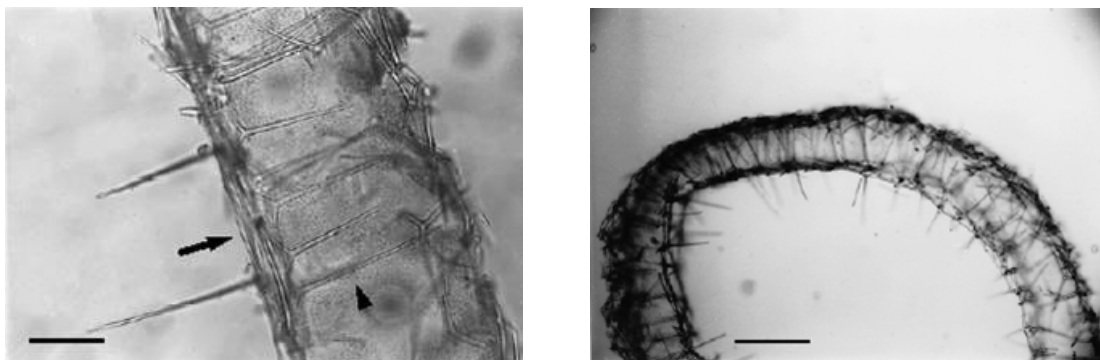
Figure 6. Left: *Leucascandra caveolata n. gen. n. sp.* Transverse section. Scale bar: 30 µm. Right: *Leucascandra caveolata n. gen. n. sp.* Transverse section through the sponge wall. Scale bar: 80 µm.[38]

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.[39] 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. *Zoosystema*, **2000**, *22*, 187–201.

(39) *Leucascandra caveolata*'s main symbiont, the cyanobacterium *Aphanocapsa feldmanni*, widely occurs in calcareous sponges, none of which, except *Leucascandra caveolata*, are known to produce macrolides.

few calcareas, like *Leucetta*[40] and *Clathrina*[41], 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*, *Phytophtora 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

(40) (a) Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1987**, *28*, 3003–3006; (b) Carmely, S.; Ilan, M.; Kashman, Y. *Tetrahedron* **1989**, *45*, 2193–2200; (c) Akee, R. K.; Carroll, T. R.; Yoshida, W. Y.; Scheuer, P. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1990**, *55*, 1944–1946; (d) Chan, G. W.; Mong, S.; Hemling, M. E.; Freyer, A. J.; Offen, P. H.; Debrosse, C. W.; Sarau, H. M.; Westley, J. W. *J. Nat. Prod.* **1993**, *56*, 116–121; (e) Carroll, A. R.; Bowden, B. F.; Coll, J. C. *Aust. J. Chem.* **1993**, *46*, 1229–1234; (f) He, H. Y.; Faulkner, D. J.; Lee, A. Y.; Clardy, J. *J. Org. Chem.* **1992**, *57*, 2176–2178; (g) Alvi, K. A.; Peters, B. M.; Hunter, L. M.; Crews, P. *Tetrahedron* **1993**, *49*, 329–336.

(41) (a) Ciminiello, P.; Fattorusso, E.; Magno, S.; Mangoni, A. *Tetrahedron* **1989**, *45*, 3873–3878; (b) Ciminiello, P.; Fattorusso, E.; Mangoni, A.; Diblasio, B.; Pavone, V. *Tetrahedron* **1990**, *46*, 4387–4392.

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

1.4. Structure

The composition $C_{38}H_{56}N_2O_{10}$ 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,[42] the macrolide moiety was freed from the oxazole side chain at C5 by treatment of **43** with Na_2CO_3 in methanol, giving alcohol **45** and methyl ester **46** (Scheme 16).[43] Scattered $\Delta\delta = \delta(S) - \delta(R)$ data was obtained from the C5-MTPA esters of **45** and thus precluded a reliable interpretation.[44] 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

(42) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543.

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

(44) The observed deviation from the typical *Mosher* trend is not unexpected for a sterically hindered axial hydroxyl group: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

for clear and unambiguous assignment of the (5*R*)-configuration in natural leucascandrolide A.
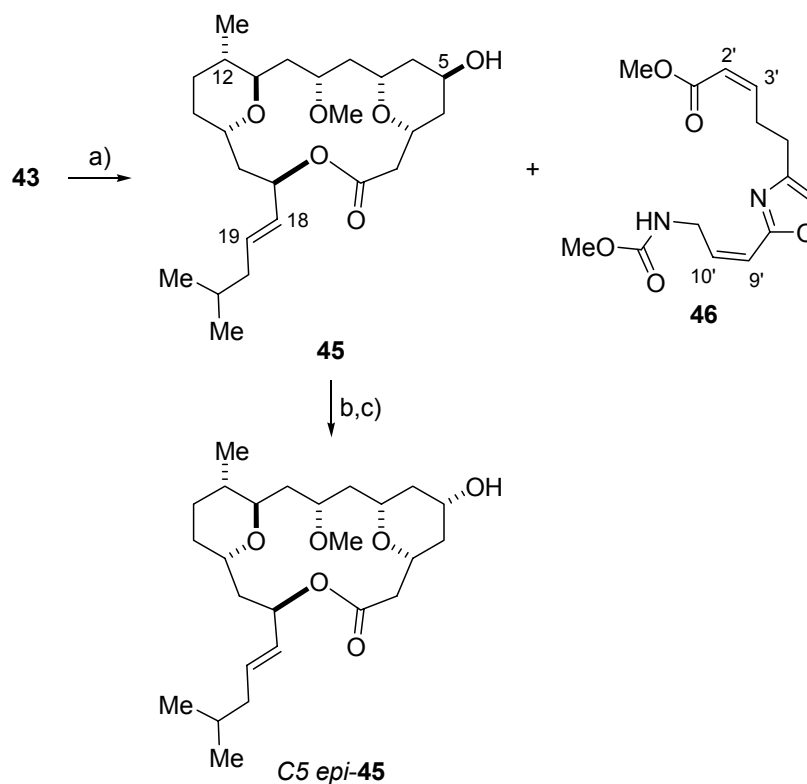
Scheme 16. (a) Na$_2$CO$_3$, MeOH, RT, 2 d, 77%; (b) PCC, CH$_2$Cl$_2$, RT, 2 h, 70%; (c) NaBH$_4$, EtOH, RT, 1 h, 86%.

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.
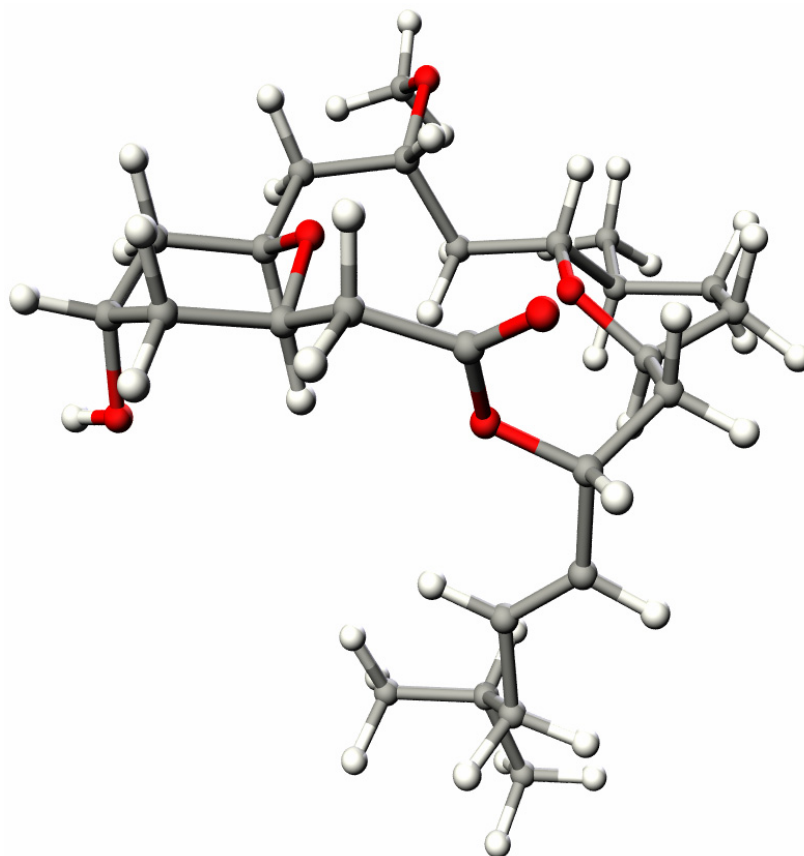
Figure 7. Energy-minimized structure of **45** (generated by semi-empirical calculations at the PM3 level).

Several important conclusions concerning the preferred conformation of the macrolide moiety **45** can be drawn from the energy-minimized structure represented in Figure 7:[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.

(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,[46] 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.[47]

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*,[48] which confirmed the relative and absolute configuration originally assigned by *Pietra*. A total synthesis by *Kozmin*[49] and *Paterson*[50] as well as formal syntheses by *Rychnovsky*[51] and *Wipf*[52]

(46) A recent example for erroneous structure assignment by modern spectroscopic means which was revealed by total synthesis is represented by the diazonamides: (a) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4765–4770; (b) Ritter, T.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 2489–2495.

(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.

(48) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894–12895.

(49) (a) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670–13671; (b) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755–758.

(50) Paterson, I.; Tudge, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 343–347.

were also documented. Additional interesting studies by *Crimmins*,[53] *Hoffmann*,[54] *O'Doherty*,[55] and *Panek*[56] as well as unpublished studies by *Williams*[57] 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:[48] 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,[58] followed by rhodium(I)-catalyzed formylation of the organomercurial species **49** (Scheme 17).[59] The *syn* selectivities observed in these reactions are usually very high.

(51) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421.

(52) (a) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066–2067; (b) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2001**, *66*, 3242–3245.

(53) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 597–599.

(54) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 177–180.

(55) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049–1052.

(56) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812-6815.

(57) Personal communication.

(58) (a) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 3197–3199; (b) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 403–405.

(59) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 3205–3208.

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*-*t*BuC$_6$H$_4$)$_3$, 0.5 equiv DABCO, 800 psi CO/H$_2$, 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*-*t*BuC$_6$H$_4$)$_3$, 0.5 equiv DABCO, 800 psi 1:1 CO/H$_2$, EtOAc, 50 °C, 62%; (c) (–)-Ipc$_2$B((*E*)-crotyl), BF$_3$·Et$_2$O, THF, −78 °C;

NaOH, H_2O_2, 67% (d.r. > 10:1); (d) 2 mol% Rh(acac)(CO)$_2$, 8 mol% PPh$_3$, 400 psi 1:1 CO/H$_2$, THF, 50 °C, 89% (d.r. > 10:1); (e) Ac$_2$O, DMAP, pyr., CH$_2$Cl$_2$; (f) allyl–TMS, Ti(O–iPr)$_2$Cl$_2$, CH$_2$Cl$_2$, –78 °C (d.r. > 10:1); (g) TBAF, THF, 62% over 3 steps; (h) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, –78 °C to –40 °C; (i) allyl-(–)-Ipc$_2$B, Et$_2$O, –78 °C → RT; NaOH, H$_2$O$_2$, 75% over 2 steps (d.r. > 10:1); (j) TBDPSCl, imid, DMF, 99%; (k) AcOH, H$_2$O, 40 °C, 98%; (l) 10 mol% PdCl$_2$, 4 equiv CuCl$_2$, 1 atm CO, MeOH/PhCN (1:1), 75% (d.r. > 10:1); (m) Me$_3$OBF$_4$, Proton Sponge, 4 Å M.S., CH$_2$Cl$_2$, 96%; (n) O$_3$, CH$_2$Cl$_2$, –78 °C; PPh$_3$, RT, 93%; (o) 4-methyl-1-pentyne, Cy$_2$BH, Et$_2$Zn, N,N-di-n-butyl amino ethanol, Ti(O–iPr)$_4$, toluene, –40 °C → –20 °C, 45% (d.r. = 3:1); (p) TMSOK, Et$_2$O; (q) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, 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]
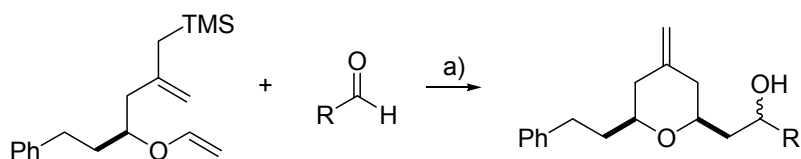
Scheme 19. a) CSA, CH$_2$Cl$_2$, 0 °C.

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).
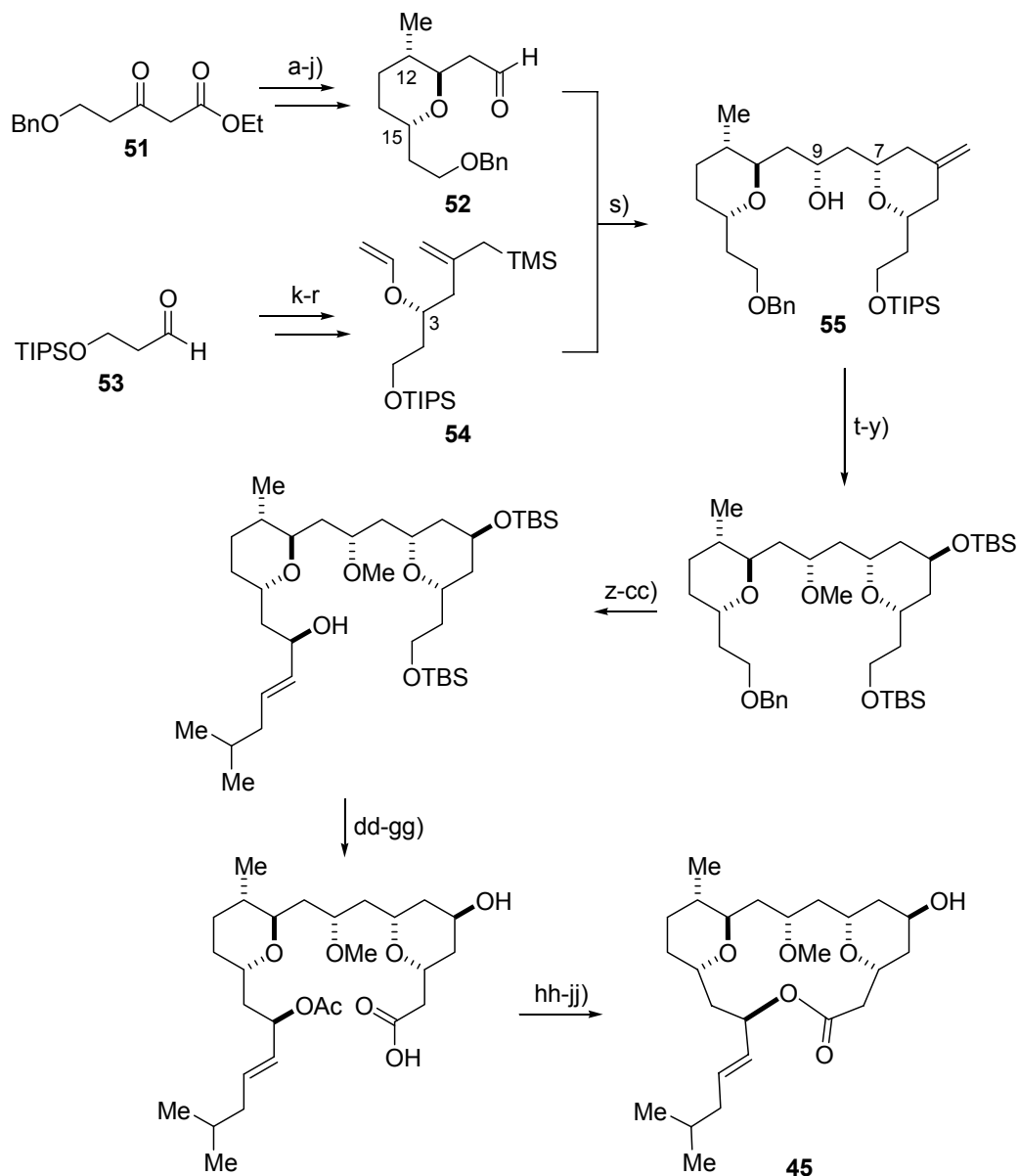
Scheme 20. (a) [(*R*)-BINAP]-RuCl(C$_6$H$_6$), 80 atm H$_2$, EtOH, 96% (*ee* > 94%); (b) TBSCl, imid, DMF, 86%; (c) DIBAL–H, THF, –25 °C, 88%; (d) PPh$_3$, I$_2$, imid, CH$_2$Cl$_2$, 100%; (e) LDA, (–)-pseudoephedrine propionamide, LiCl, THF, –78 °C, 98% (d.r. > 20:1); (f) 1.0 M aq. H$_2$SO$_4$, dioxane, 95 °C, 77%; (g) DIBAL–H, CH$_2$Cl$_2$,

–78 °C; (h) Ac_2O, DMAP, pyr., 95% over 2 steps; (i) allyl–TMS, $BF_3 \cdot Et_2O$, CH_2Cl_2, –78 °C, 97% (d.r. > 20:1); (j) O_3, CH_2Cl_2, –78 °C; PPh_3, 95%; (k) N_2CHCO_2Et, $SnCl_2$, CH_2Cl_2, 72%; (l) [(*S*)-BINAP]–$RuCl(C_6H_6)$, 4 atm H_2, EtOH, 10 °C, 51%, (*ee* > 95%); (m) TMSCl, Et_3N, CH_2Cl_2, 91%; (n) $CeCl_3$, $TMSCH_2MgCl$, THF/Et_2O, –78 °C → RT; then SiO_2, CH_2Cl_2, 87%; (o) $ClCH_2COCl$, pyr., CH_2Cl_2, 95%; (p) DIBAL–H, CH_2Cl_2, –78 °C; (q) Ac_2O, DMAP, pyr., 95% over 2 steps; (r) Li^0, NH_3, THF, –78 °C, 65%; (s) $BF_3 \cdot Et_2O$, 2,6-di-*tert*-butyl-4-methyl pyridine, CH_2Cl_2, –78 °C; then $NaBH_4$, EtOH, 78% (d.r. = 5.5:1); (t) Me_3OBF_4, Proton Sponge, 4 Å M.S., CH_2Cl_2, 79%; (u) OsO_4, NMO; (v) $NaIO_4$, 80%; (w) L-Selectride, THF, –90 °C → –60 °C, 82%; (x) TBAF, THF, 92%; (y) TBSOTf, 2,6-lutidine, CH_2Cl_2, 89%; (z) H_2, $Pd(OH)_2$, EtOAc, 96%; (aa) *Swern* oxidation, 94%; (bb) Me_2AlCl, $Me_3SnC≡C\,CH_2CHMe_2$, $PhCH_3$, –78 °C, 80% (d.r. = 3.5:1); (cc) Red-Al, Et_2O, 60%; (dd) Ac_2O, DMAP, pyr., CH_2Cl_2, 89%; (ee) neutral Al_2O_3, hexane, 96%; (ff) *Swern* oxidation, 97%; (gg) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 71%; (hh) K_2CO_3, MeOH; (ii) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, PhH, RT, 56% over 2 steps; (jj) HF·pyr., THF, 96%.

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**.[60]
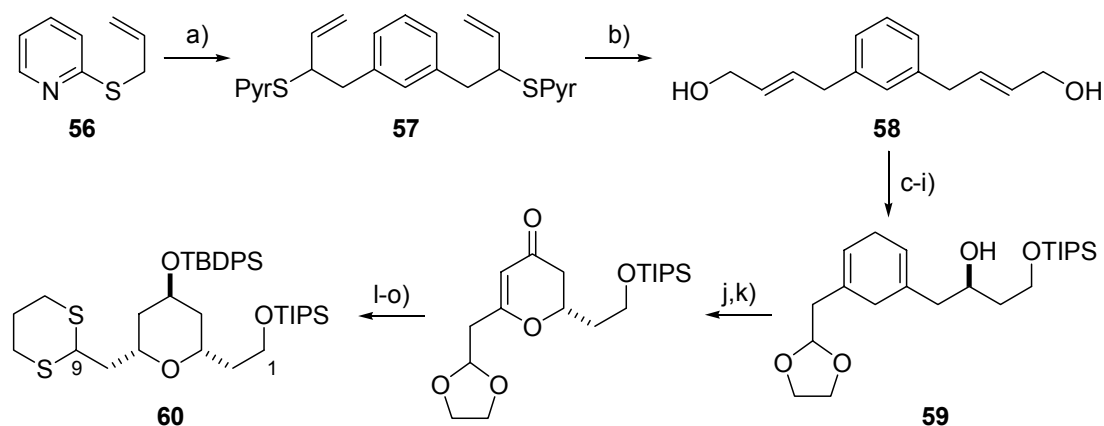
Scheme 21. (a) *n*BuLi, THF, –78 °C; *m*-(CH$_2$Br)$_2$C$_6$H$_4$, 78%; (b) *m*CPBA, MeOH, Et$_2$NH, 81%; (c) NaH, THF, TBSCl, 73% based on rec. SM; (d) (–)-DIPT, Ti(*i*PrO)$_4$, TBHP, 86%; (e) Red-Al, THF, –15 °C, 96%; (f) TIPSCl, imid, CH$_2$Cl$_2$, 91%; (g) O$_3$, CH$_2$Cl$_2$, –78 °C; PPh$_3$; (h) (CH$_2$OH)$_2$, TsOH, PhH, reflux, 62% over 2 steps; (i) Li^0, NH$_3$, THF, –50 °C; EtCMe$_2$OH, 89%; (j) O$_3$, EtOAc, –78 °C; H$_2$, Pd(OH)$_2$; (k) TsOH, PhH, reflux, 43% over 2 steps; (l) H$_2$, Pd/C, EtOAc, 71%; (m) L-Selectride, THF, –78 °C, 79%; (n) TBDPSCl, imid, DMAP, DMF, 83%; (o) CH$_2$(CH$_2$SH)$_2$, TiCl$_4$, CH$_2$Cl$_2$, 64%.

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.

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(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.
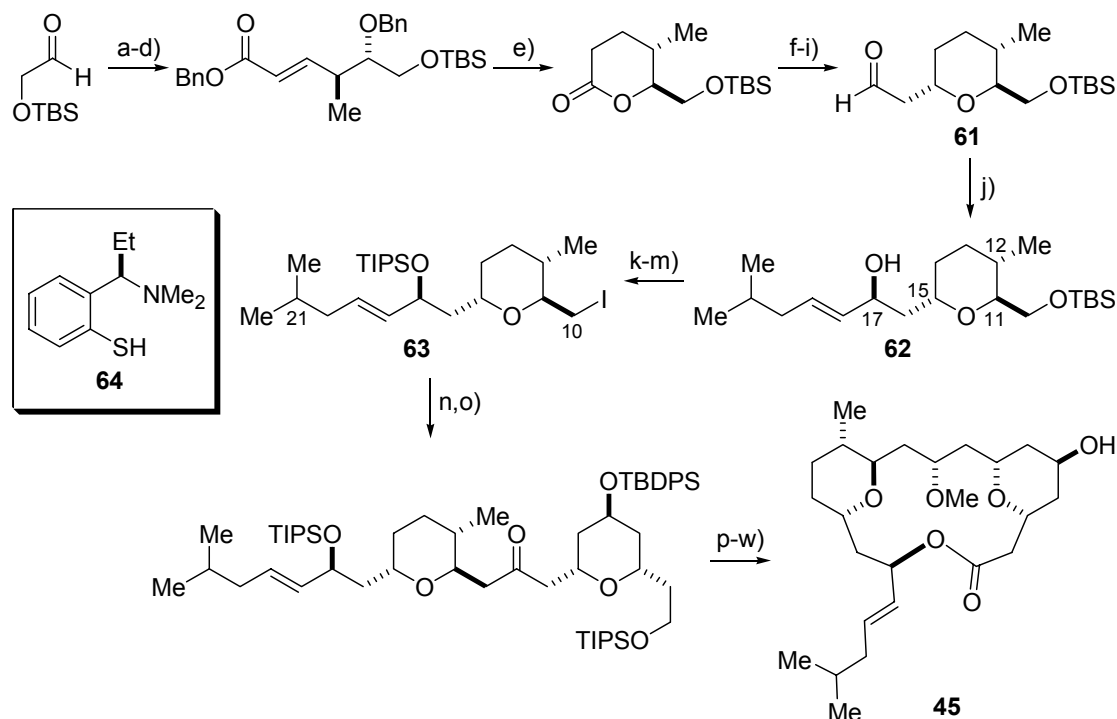
Scheme 22. (a) (–)-Ipc$_2$B((E)-crotyl), THF, Et$_2$O, –78 °C; NaOH, H$_2$O$_2$, 55%; (b) tBuLi, THF, –78 °C; BnBr, HMPA, 86%; (c) O$_3$, CH$_2$Cl$_2$, –78 °C; PPh$_3$, 74%; (d) Ph$_3$PCHCO$_2$Bn, CH$_2$Cl$_2$, 63%; (e) H$_2$, Pd/C, EtOAc, 87%; (f) DIBAL–H, PhCH$_3$, –78 °C; (g) Ac$_2$O, pyr., 87% over 2 steps; (h) allyl–TMS, BF$_3$·Et$_2$O, CH$_2$Cl$_2$, –78 °C, 80%; (i) O$_3$, CH$_2$Cl$_2$, –78 °C; PPh$_3$, 86%; (j) 4-methyl pentyne, Cp$_2$Zr(H)Cl, CH$_2$Cl$_2$; Me$_2$Zn, PhCH$_3$, **64** (25 mol%), –30 °C, 62%; (k) TIPSCl, imid, DMAP, DMF, 76%; (l) EtOH, PPTS, 82%; (m) PPh$_3$, I$_2$, imid, 87%; (n) tBuLi, THF/HMPA; **60**, 74%; (o) PhI(O$_2$CCF$_3$)$_2$, THF/MeOH/H$_2$O, 61%; (p) L-Selectride, THF, –78 °C, 98%; (q) MeOTf, 2,6-di-*tert*-butyl-4-methyl pyridine, CH$_2$Cl$_2$, 93%; (r) EtOH, TsOH, 71%; (s) DMP, CH$_2$Cl$_2$; (t) NaClO$_2$, 2-methyl-2-butene, tBuOH, THF, H$_2$O, 94% over 2 steps; (u) 1.0 M aq. HCl, THF, 78%; (v) PPh$_3$, DIAD, THF, 0 °C, 58%; (w) TBAF, THF, 78%.

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.[49b] 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).
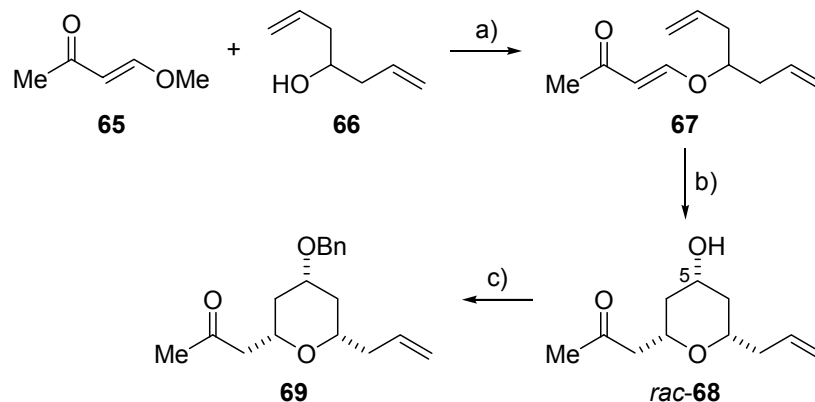
Scheme 23. (a) PPTS, toluene, 92%; (b) TFA, 5 °C; LiOH, THF/H$_2$O, 77%; (c) BnOC(NH)CCl$_3$, TfOH (cat.), 71%.

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.
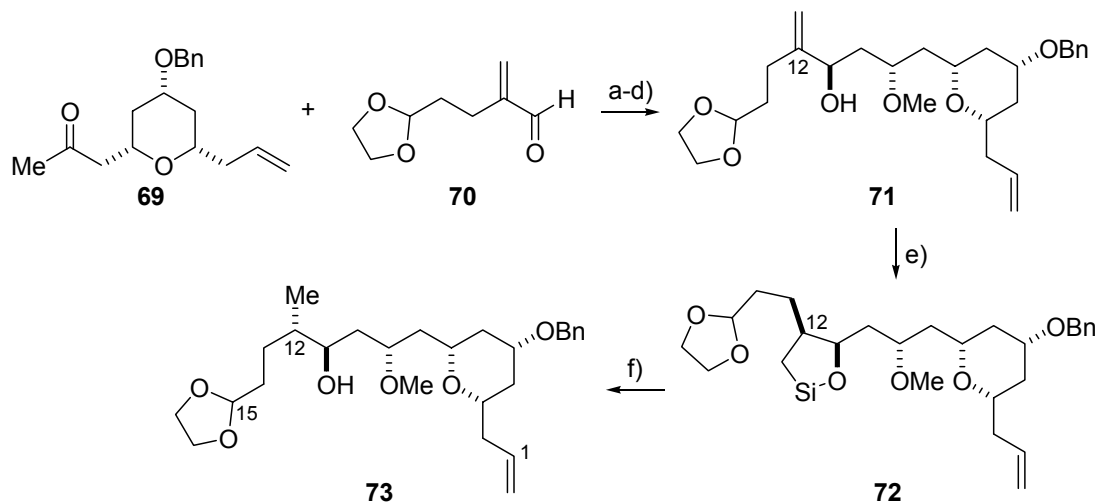
Scheme 24. (a) Cy$_2$BCl, Et$_3$N, −78 °C, 74%; (b) SmI$_2$ (30 mol%), CH$_3$CHO, THF, −5 °C, 92%; (c) MeOTf, 2,6-di-*tert*-butyl pyridine, 71%; (d) LiAlH$_4$, Et$_2$O, −78 °C, 86%; (e) (Me$_2$HSi)$_2$NH, H$_2$PtCl$_6$, 50 °C; (f) TBAF, DMF, 70 °C, 54% over 2 steps (d.r. = 87:13).

Recently, the total synthesis of leucascandrolide A in ten steps from intermediate **73** was reported (Scheme 25).[49a] 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]

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(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.
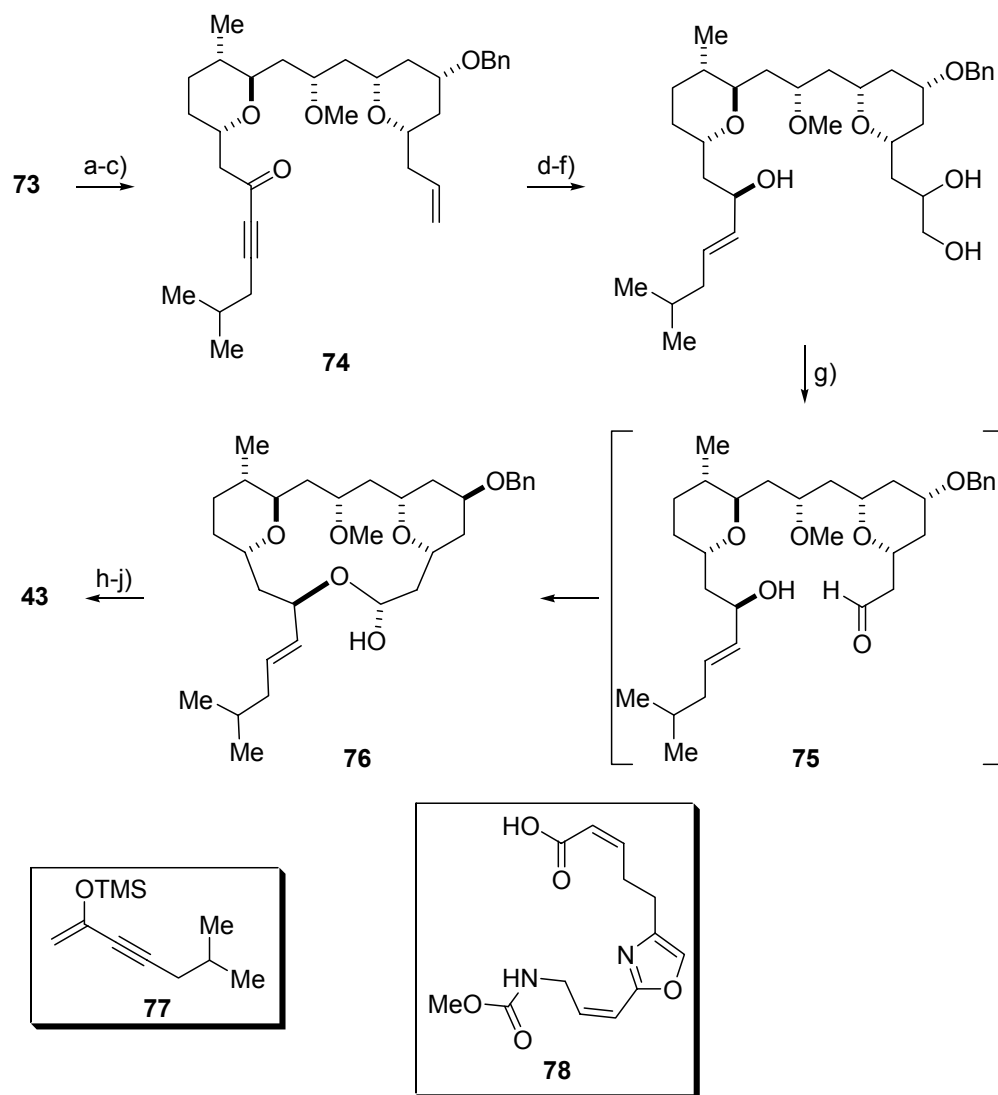
Scheme 25. (a) THF/H$_2$O, H$_2$SO$_4$; (b) Ac$_2$O, pyr., 83% over 2 steps; (c) **77**, ZnCl$_2$, CH$_2$Cl$_2$, 80%; (d) L-Selectride, THF, −78 °C, 65% (d.r. = 2:1); (e) OsO$_4$ (cat.), NMO, *t*BuOH/H$_2$O, 77%; (f) Red-Al, Et$_2$O, 20 °C, 18 h, 78%; (g) Pb(OAc)$_4$, EtOAc; then 18 h at 20 °C, 92%; (h) PCC, CH$_2$Cl$_2$, 85%; (i) DDQ, CH$_2$Cl$_2$, pH 7, 99%; (j) **78**, DIAD, PPh$_3$, PhH, 20 °C, 78%.

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]
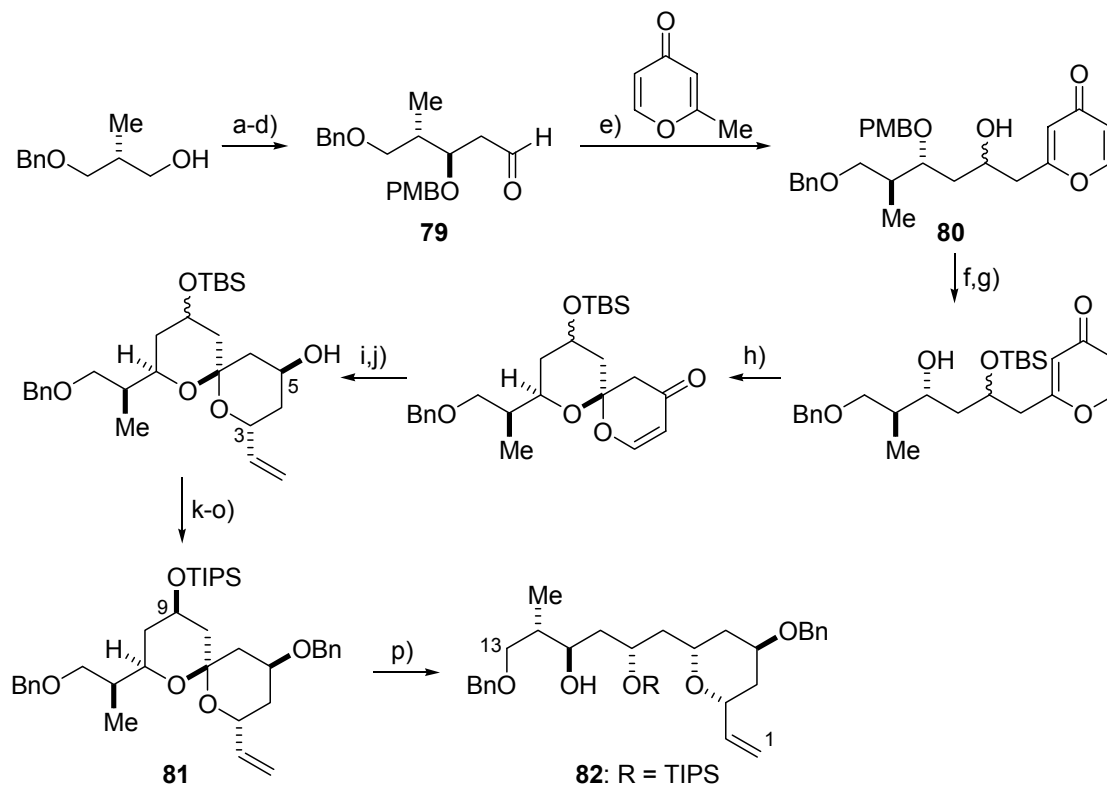
Scheme 26. (a) *Swern* oxidation; (b) allyl–TMS, SnCl$_4$, CH$_2$Cl$_2$, 83% over 2 steps (d.r. = 89:11); (c) PMBCl, NaH, DMF; (d) OsO$_4$, NaIO$_4$, THF, H$_2$O, 73% over 2 steps; (e) LHMDS, THF, −78 °C, 84%; (f) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0 °C, 90%; (g) DDQ, 78%; (h) TFA, C$_6$H$_6$, 80%; (i) CH$_2$=CHMgBr, [CuIP*n*Bu$_3$]$_4$, THF, 78%; (j) L-Selectride, THF, 76%; (k) KH, BnBr, THF, 98%; (l) 5% HF, CH$_3$CN; (m) *Jones* oxidation, 86% over 2 steps; (n) SmI$_2$, *i*PrOH, THF, 84%; (o) TIPSCl, imid, CH$_2$Cl$_2$; (p) Et$_3$SiH, AlCl$_3$, CH$_2$Cl$_2$, −78 °C, 73%.

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.[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

(62) (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1995; (b) Hendrickson, J. B. *Accounts Chem. Res.* **1986**, *19*, 274–281.

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.

(63) For dead ends and detours in synthesis, see: Sierra, M. A.; de la Torre, M. C. *Angew. Chem. Int. Ed.* **2000**, *39*, 1538–1559.

Scheme 27

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 a 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.

Scheme 28

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.
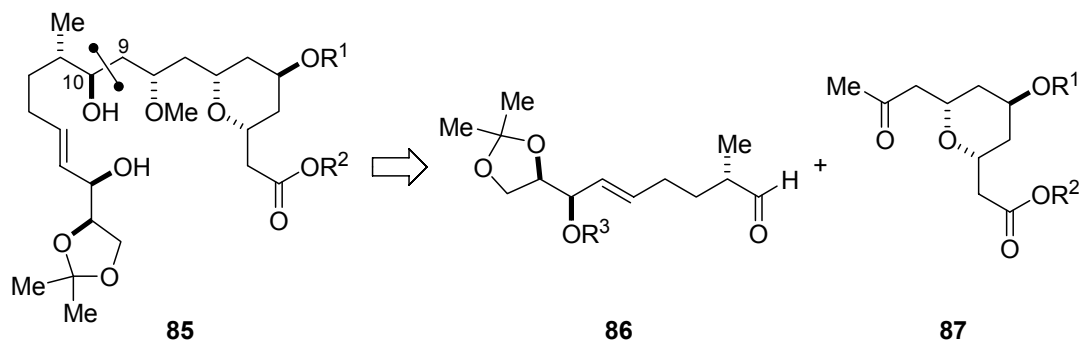
Unraveling of the 2,6-*cis*-disubstituted tetrahydropyran ring in **83** could be achieved by various ways: Displacement of a C15 sulfonate by an incoming C11 hydroxyl group would proceed with inversion of configuration at C15 and would thus be a viable approach, requiring prior incorporation of the 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.
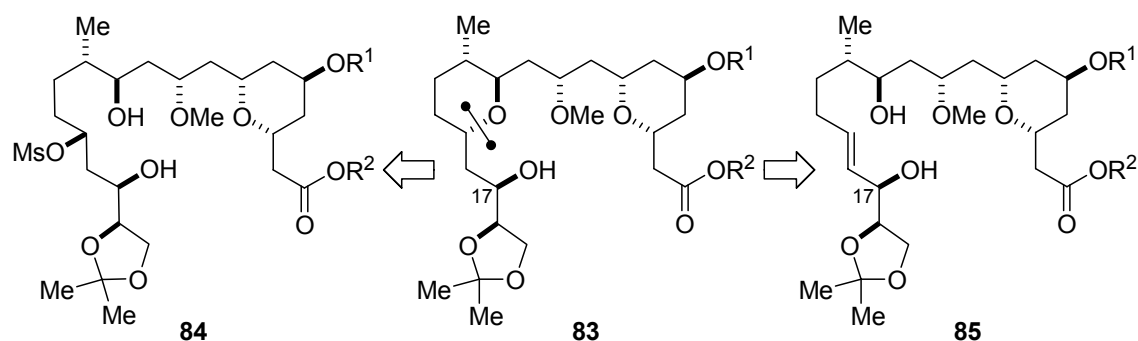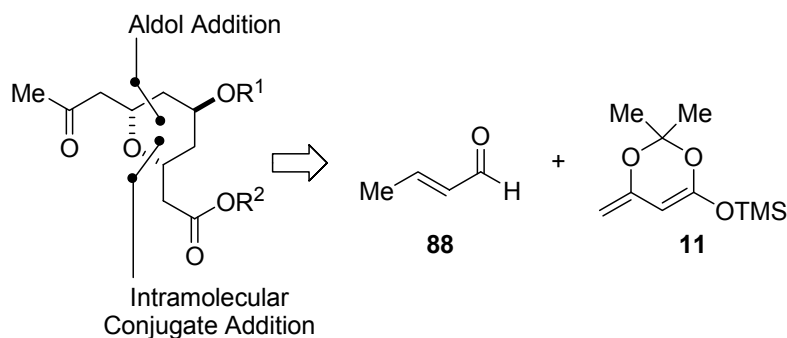

Scheme 29

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.

Scheme 30

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 trimethylsilyl dienolate **11** by a catalytic, asymmetric aldol addition (Scheme 31).
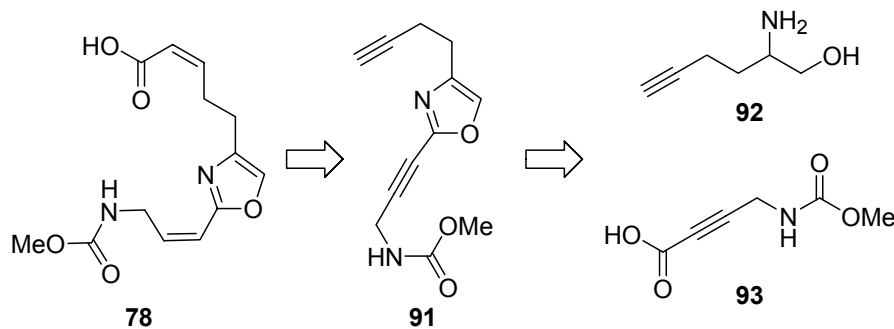

Scheme 31

Aldehyde **86** would be accessed from a propargylic alcohol prepared by addition of alkyne **90** to (*R*)-isopropylidene glyceraldehyde (**89**) (Scheme 32).
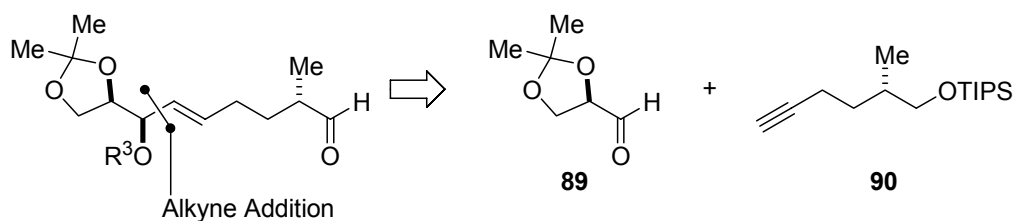
Scheme 32

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**.
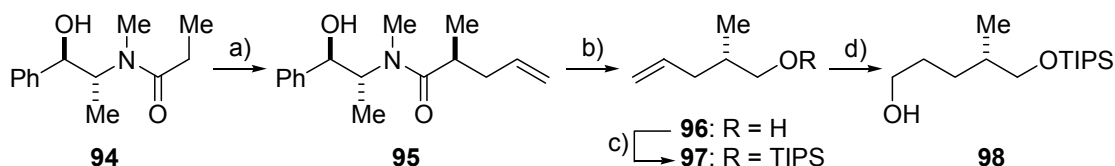

Scheme 33

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 C_α; (*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   Results and Discussion

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]

Scheme 34. (a) LDA, LiCl, allyl iodide, THF, −78 °C → 0 °C, 2 h; (b) LDA, NH₃·BH₃, THF, RT, 2 h; (c) TIPSCl, imid, DMAP, RT, 1 h; (d) 9-BBN, THF, RT, 6 h, 75% over 4 steps.

Asymmetric alkylation of **94** with allyl iodide, using the conditions reported by *Myers*, was followed by BH₃·NH₃-mediated reduction of amide **95** to alcohol **96**.[65] Protection of the primary hydroxyl group as TIPS ether under standard conditions

(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.

(65) (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362; (b) Myers, A. G.; Gleason, J. L.; Yoon, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 8488–8489.

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.[66] 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).[67] On large scale, however, the use of *Ohira* reagent[68] (**100**) using the protocol developed by *Bestmann* and *Roth*[69] was the method of choice because of its ease of execution, giving alkyne **90** in 87% yield over two steps (Scheme 35).[70]
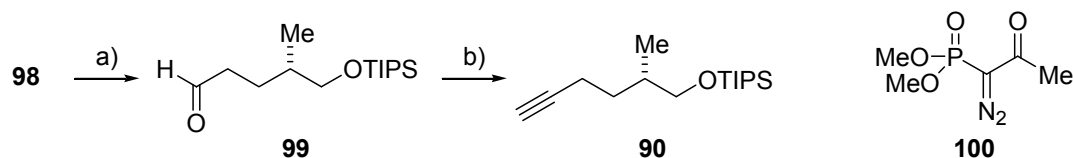
Scheme 35. (a) bleach, TEMPO (2 mol%), KBr (10 mol%), CH$_2$Cl$_2$, pH 8.6 buffer, 0 °C, 15 min; (b) **100**, K$_2$CO$_3$, MeOH, 16 h, RT, 87% over 2 steps.

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

(66) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562; (b) for a review on the use of stable nitroxyl radicals for the oxidation of alcohols, see: De Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H. *Synthesis* **1996**, 1153–1174.

(67) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107–108.

(68) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564.

(69) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.

(70) For other methods of conversion of aldehydes to terminal alkynes, see: (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772; (b) Wang, Z.; Campagna, S.; Yang, K. H.; Xu, G. Y.; Pierce, M. E.; Fortunak, J. M.; Confalone, P. N. *J. Org. Chem.* **2000**, *65*, 1889–1891.

nitrones and aldehydes.[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 $Zn(OTf)_2$, Et_3N and *N*-methyl ephedrine (**103**)[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).[73]
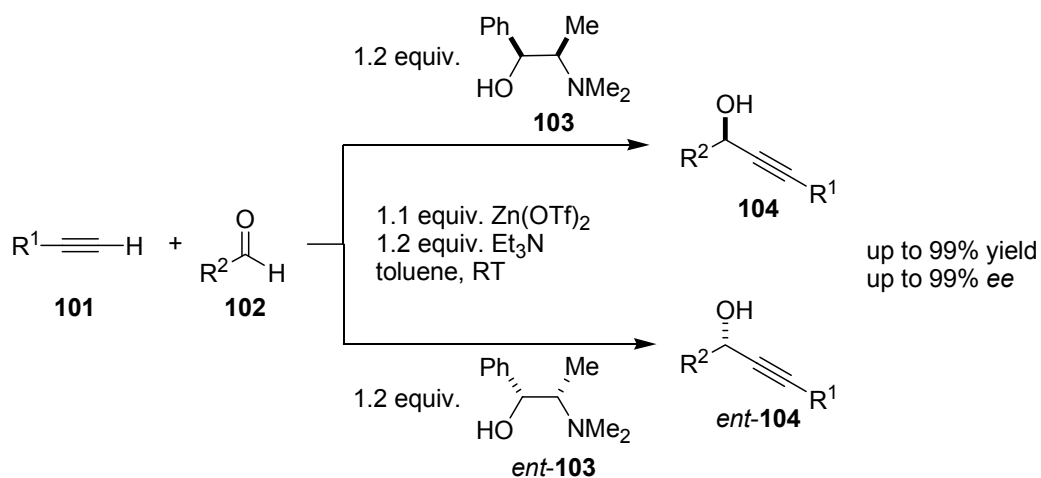
Scheme 36

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

(71) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245–11246; (b) Fässler R., Ph.D. thesis, ETH Zürich, 2002.

(72) Importantly, both enantiomers of *N*-methyl ephedrine are commercially available.

(73) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807; (b) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373–381; for related processes, see: (c) Boyall, D.; Lopez, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233–4236; (d) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017–3020; (e) Anand, N. K.; Carreira, E.M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688; (f) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245–11246.

| Entry	Aldehyde	Alkyne	Yield (%)	*ee* (%)
1	Ph	Ph(CH$_2$)$_2$	52	96
2	PhCH=CH	Ph(CH$_2$)$_2$	39	80
3	*i*Pr	Ph(CH$_2$)$_2$	90	99
4	*t*Bu	Ph(CH$_2$)$_2$	84	99
5	Cy	Ph(CH$_2$)$_2$	99	96
6	Me$_3$CCH$_2$	Ph(CH$_2$)$_2$	72	99

Table 1

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

(74) Boyall, D.; Lopez, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233–4236.

(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.
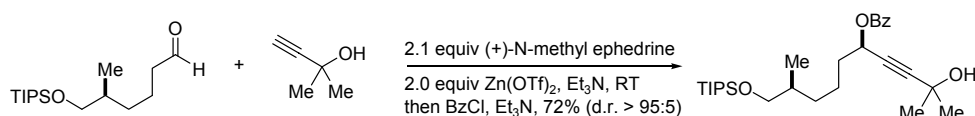
component was expected not to strongly bias the stereoinduction because of the remoteness of the stereogenic center, the situation was less clear as far as the aldehyde was concerned. Of additional importance was the question whether (*R*)-isopropylidene glyceraldehyde (**89**) would be compatible with the reaction conditions. Thus, the use of this capricious aldehyde would constitute a notable and useful extension of the method.

The zinc alkynilide of **90**, prepared in situ by reaction of **90** with $Zn(OTf)_2$ (1.1 equiv), (–)-*N*-methyl ephedrine (1.1 equiv) and Et_3N (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.
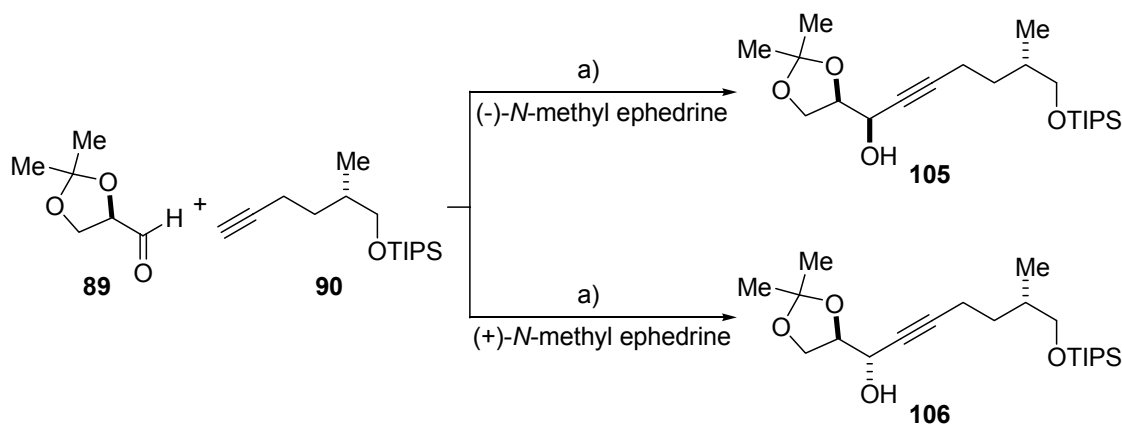

Scheme 37. (a) $Zn(OTf)_2$, Et_3N, toluene, then **89**, RT, 48 h.

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

(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.[77] The lack of diastereoselectivity observed with the corresponding lithium alkynilide underscores the significance of these results.[78]

The sense of stereochemical induction was confirmed by *Ley* oxidation[79] of **105** to the corresponding ketone **107** (TPAP, NMO, 4 Å M.S., CH$_2$Cl$_2$, 75%) and subsequent asymmetric hydrogenation to **105** using *Noyori's* catalyst **108**.[80]
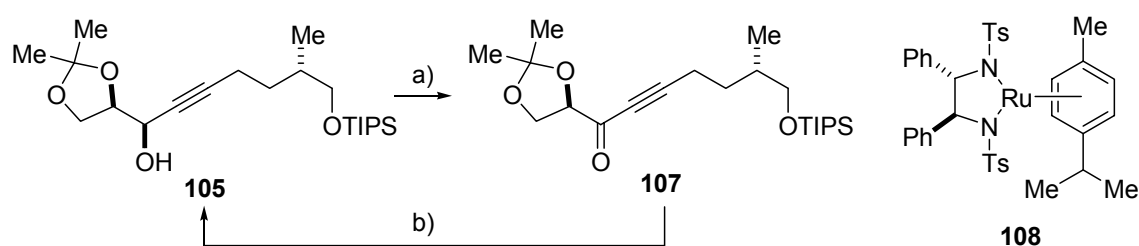
Scheme 38. (a) TPAP, NMO, 4 Å M.S., CH$_2$Cl$_2$, 75%; (b) **108**, *i*PrOH, RT.

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 (*Z*)-isomers are conveniently obtained under mild conditions by hydrogenation of carbon–carbon triple bonds, methods for their selective conversion to (*E*)-olefins are scarce and often not tolerant of a wide variety of functional groups.

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(77) A similar result was obtained with (2*S*)-2-(*tert*-butyldimethylsilyloxy)-propanal: El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017–3020.

(78) (a) Additions of lithium acetylides to this aldehyde are known to be fairly nonselective: Kang, S. H.; Kim, W. J. *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. *Chem. Rev.* **1999**, *99*, 1191–1223.

(79) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.

(80) The reaction was stopped before full conversion.

The most widely used methods include dissolving metal reductions (Na/NH$_3$), low-valent chromium salts and hydroalumination reagents.[81] An intriguing hydrogenation catalyst was reported by *Bayer* and co-worker:[82] 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.[83] 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.[84]

(81) Na/NH$_3$: (a) Smith M. In *Reduction: Techniques and Applications in Organic Synthesis*; Augustine, R. L., Ed.; Dekker: New York, 1968; (b) Birch, A. J.; Subba Rao, G. S. R. in *Advances in Organic Chemistry, Methods and Results*; Taylor, E. C., Ed.; Wiley: New York, 1972; Cr(II): (c) Castro, C. E.; Stephens, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 4358–4363; (d) Smith, A. B., III; Levenberg, P. A.; Suits, J. Z. *Synthesis* **1986**, 184–189.

(82) Bayer, E.; Schumann, W. *J. Chem. Soc. Chem. Commun.* **1986**, 949–952.

(83) (a) Ziegler, K.; Bond, A. C.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1947**, *69*, 1199–1203; (b) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245–4247.

(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 Et$_2$O. 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.
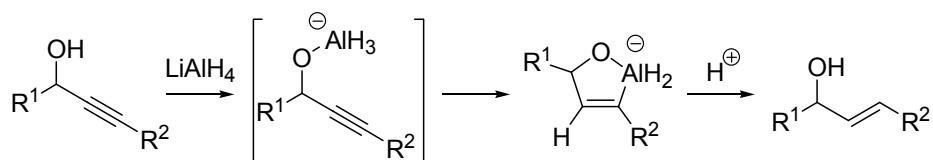
Scheme 39

Reduction of propargylic alcohol **105** to the corresponding (*E*)-allylic alcohol using LiAlH$_4$ in THF was followed by benzoylation under standard conditions (BzCl, Et$_3$N, CH$_2$Cl$_2$) to give benzoate **109** in 90% over two steps (Scheme 40). No trace of (*Z*)-isomer **110** could be detected by ^{1}H NMR spectroscopy.

Deprotection of the triisopropylsilyl ether[85] in **109** with TBAF (96%) and subsequent *Ley* oxidation[79] (TPAP, NMO, 4 Å M.S., CH$_2$Cl$_2$) 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 C$_\alpha$ was observed.
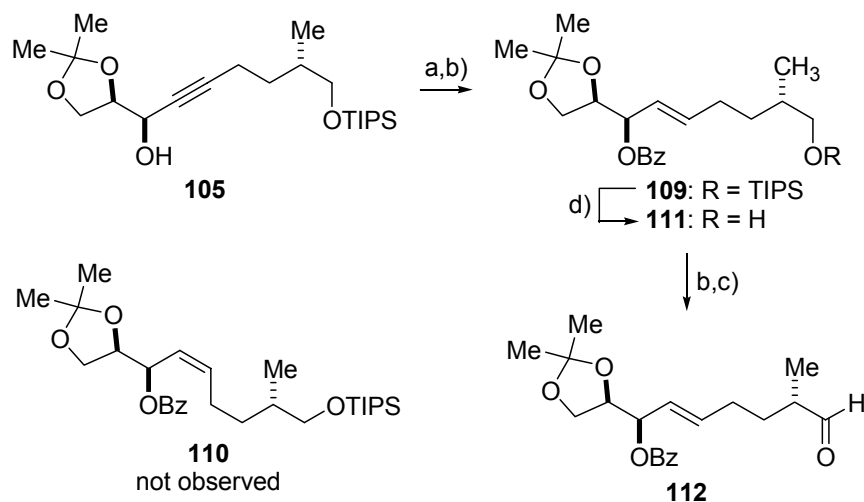
Scheme 40. (a) LiAlH$_4$, THF, RT, 5 h; (b) BzCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, RT, 15 h, 90% over 2 steps; (c) TBAF, THF, 0 °C → RT, 24 h, 96%; (d) 4 Å M.S., NMO, CH$_2$Cl$_2$, then TPAP, RT, 30 min, 87%.

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(85) For an excellent review on silyl-ether deprotection, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031–1069.

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 $nBu_4NPh_3SiF_2$ (TBAT) in THF at room temperature.[87]
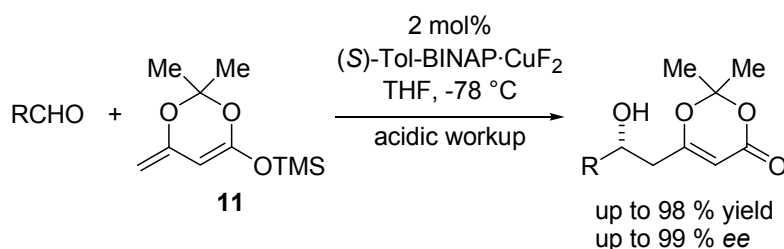
Scheme 41

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(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*. $nBu_4NPh_3SiF_2$ 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 α,β-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).
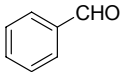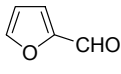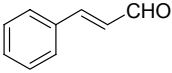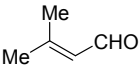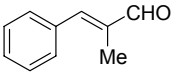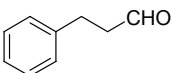
Entry	Aldehyde	Yield (%)	*ee* (%)
1	CHO (benzaldehyde)	92	94
2	CHO (furaldehyde)	91	94
3	CHO (cinnamaldehyde)	83	85
4	Me Me CHO	81	83
5	CHO Me	74	65
6	CHO	< 10	84

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**.

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(88) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **1998**, *37*, 3124–3126.

(89) The reduction of copper(II) to copper(I) by ketone-derived enol silanes has previously been reported: Kobayashi, Y.; Taguchi, T.; Morikawa, T.; Tokuno, E.; Sekiguchi, S. *Chem. Pharm. Bull.* **1980**, *28*, 262–267.
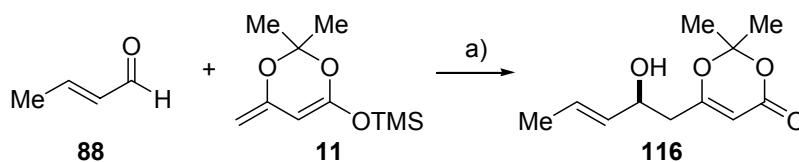
Scheme 42
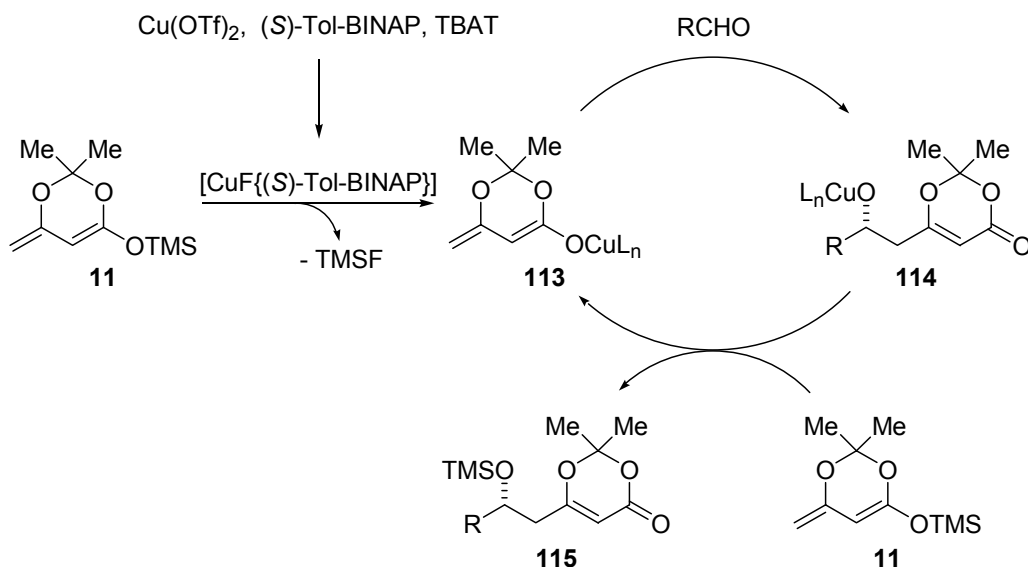
This process is highly efficient for the rapid access to enantiopure δ-hydroxy-β-keto esters and has proven successful in two synthetic applications.[90]

In the context of our leucascandrolide 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**[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).

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(90) For synthetic applications, see: (a) Krüger, J.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 7013–7016; (b) Snider, B. B.; Song, F. B. *Org. Lett.* **2001**, *3*, 1817–1820.

(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*.

Scheme 43. (a) (*R*)-Tol-BINAP (2.1 mol%), Cu(OTf)$_2$ (2.0 mol%), *n*Bu$_4$NPh$_3$SiF$_2$ (4.0 mol%), THF, –78 °C, then **11** and **88**, 4 h, then TFA, 44%.

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).
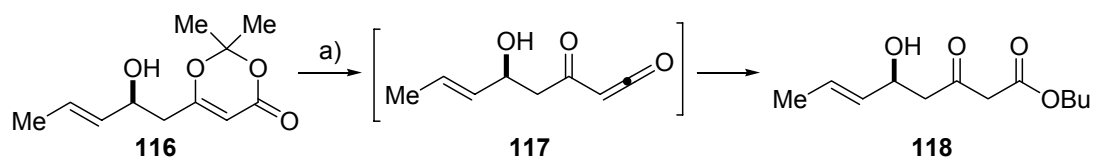

Scheme 44. (a) *n*BuOH, reflux, 1 h, 78%.

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(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**.

(93) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431–2435.

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* (NaBH$_4$, Et$_3$B, MeOH, THF).[94] The observed selectivity can be rationalized by chelation-controlled 1,3-induction: the intermediate chair-like transition state, where R^1 and R^2, 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).[95]
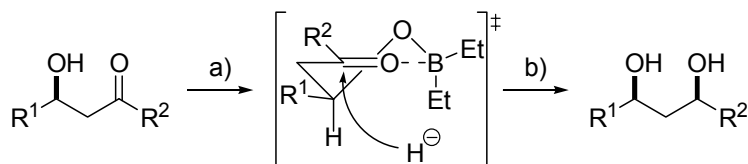
Scheme 45. (a) Et$_3$B, MeOH, THF, 0 °C; (b) NaBH$_4$, THF, –78 °C.

Subsequent protection of the diol as bis-O-triethylsilyl ethers (TESCl, imid, DMAP, DMF, RT)[96] yielded **119** as a single diastereomer and semireduction of the *n*-butyl 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*[97]

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(94) (a) Chen, K. M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923–1926; (b) Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158.

(95) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190–5192.

(96) Corey, E. J.; Venkates. A *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

(97) (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186; (b) *Eschenmoser* first recognized that a tertiary amine and a lithium salt may be used instead of strong alkoxide or amide bases for the generation of enolates in aprotic media: Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710–734.

conditions (DBU, LiCl, CH₃CN, RT) and deprotection of the silyl ethers with TBAF in THF led to diol **121** (80% over two steps) (Scheme 46).
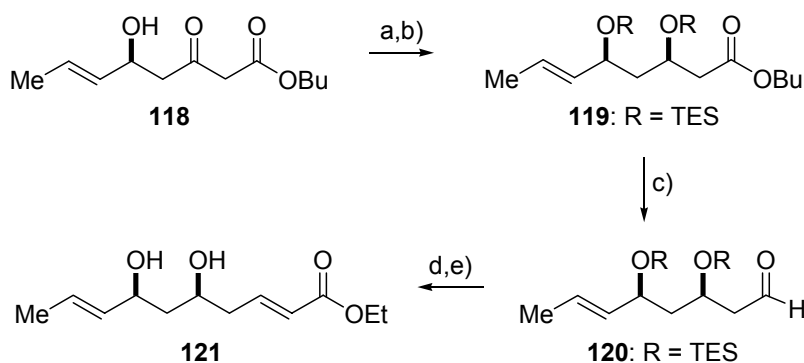
Scheme 46. (a) Et₃B, MeOH, THF, −78 °C, then **118** followed by NaBH₄, 5 h; (b) TESCl, imid, DMAP, DMF, RT, 12 h; (c) DIBAL–H, toluene, −78 °C, 30 min, 92% over 3 steps (d.r. > 95:5); (d) DBU, LiCl, (EtO)₂P(O)CH₂CO₂Et, CH₃CN, RT, 2 h; (e) TBAF, THF, RT, 2 h, 80% over 2 steps.
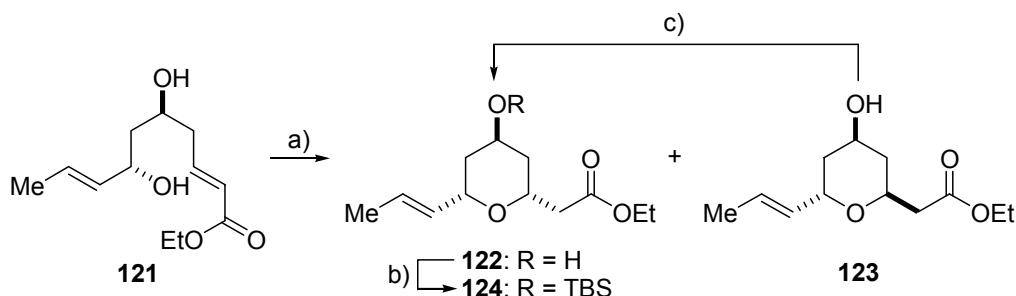
3.2.3. Tetrahydropyran Formation

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 *t*BuOK in THF at 0 °C produced the desired cyclic compound **122** in 63% yield and 10:1 diastereoselectivity (Scheme 47).[98] 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] This

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(98) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446–2453.

(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*-butyldimethylsilyl ether (TBSCl, imid, DMAP, DMF) gave **124** in 96% yield.[96]

Scheme 47. (a) *t*BuOK (10 mol%), THF, 0 °C, 63% (d.r. = 10:1); (b) TBSCl, imid, DMAP, DMF, RT, 20 h, 96%; c) *t*BuOK (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 K_2CO_3/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.

(101) Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, M. *J. Am. Chem. Soc.* **1982**, *104*, 3635–3643.

interactions between the C2 and C6 substituents.[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.[103]
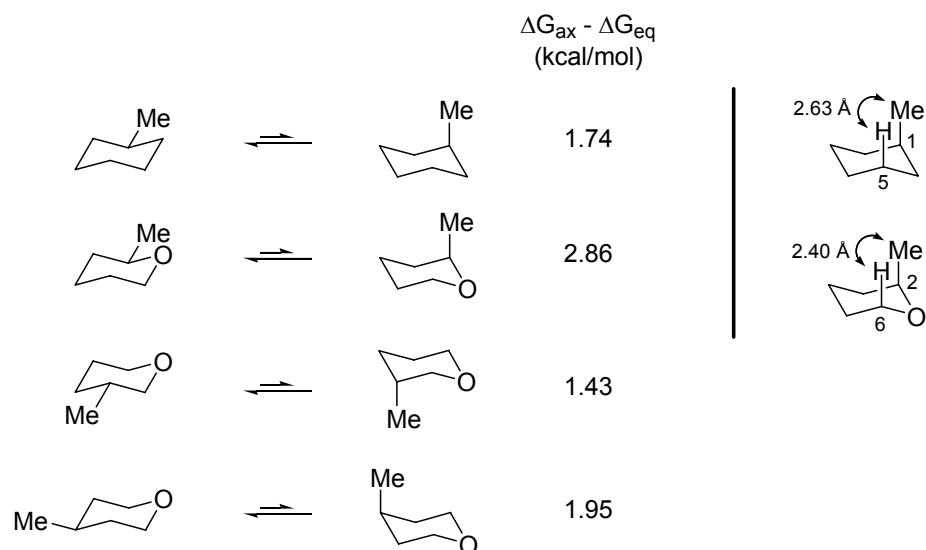

Figure 8. Free energies of methyl-substituted tetrahydropyrans.

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

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(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. *Acta Chem. Scand. Ser. A* **1979**, *33*, 225–233.

(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.[104]

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 (TBSCl, imid, DMAP, RT, DMF) afforded **126** in 77% yield from keto ester **118**.[96] Two-carbon chain extension was achieved by semireduction of the lactone to the corresponding lactol **127** (DIBAL–H, toluene, –78 °C) and subsequent *Horner–Wadsworth–Emmons* olefination:[105] when lactol **127** was added to a mixture of triethylphosphonoacetate and sodium hydride in THF at –78 °C, clean tetrahydropyran formation (72% yield) was observed upon warming to ambient temperature, albeit as a 2:1 diastereomeric mixture of *cis* and *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.[106] Indeed, upon treatment with catalytic amounts

(104) (a) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; (b) Trost, B. M. *Science* **1991**, *254*, 1471–1477.

(105) Lactol **127** was obtained as a mixture of diastereomers at C3.

(106) Schneider, H. J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866–3873.

of *t*BuOK (10 mol%), the mixture cleanly equilibrated to the thermodynamically more stable isomer **124** (d.r. = 9:1).
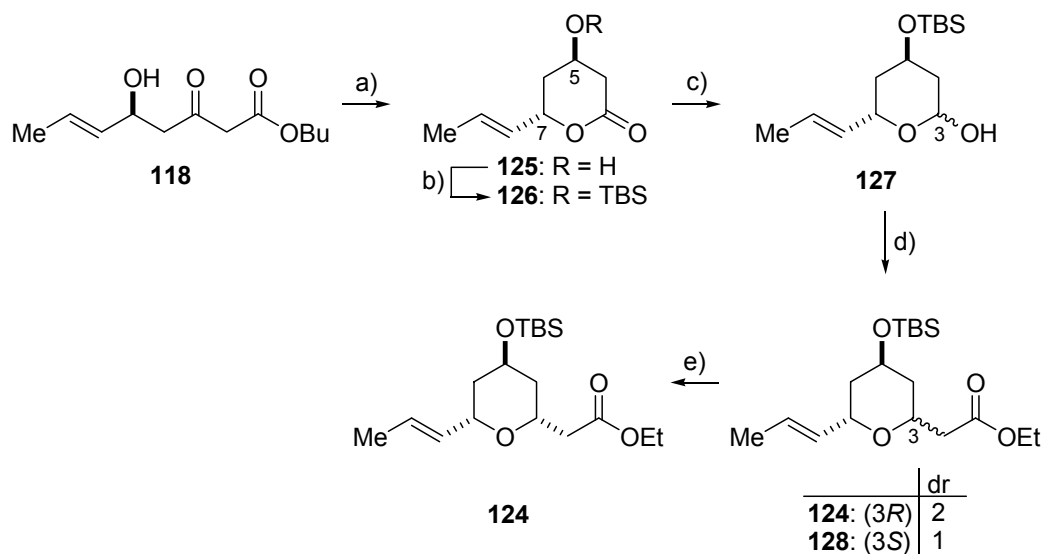

Scheme 48. (a) (i) Et₃B, MeOH, THF, –78 °C, then **118** followed by NaBH₄, 5 h; (ii) PPTS, PhH, reflux, 90 min; (b) TBSCl, imid, DMAP, DMF, RT, 2 h, 77% over 2 steps; (c) DIBAL–H, toluene, –78 °C, 1 h; (d) (EtO)₂P(O)CH₂CO₂Et, NaH, THF, –78 °C → RT, 72% over 2 steps; (e) *t*BuOK (10 mol%), THF, 0 °C, 4 h, 90% (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

applied to the synthesis of acetaldehyde by $PdCl_2$-catalyzed oxidation of ethylene (Scheme 49).[107]
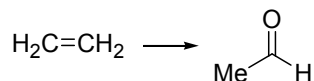
Scheme 49. $PdCl_2$, $CuCl_2$, H_2O, O_2.

While oxidation of monosubstituted double bonds is well documented and leads to the selective formation of methyl ketones,[108] 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.[109] Indeed, for these compounds, oxidation takes place at the alkenic carbon atom furthest away from the neighboring alkoxy or acyloxy group.[110]

When applied to our substrate, methyl ketone **129** was obtained in good yield (86%) and complete regioselectivity upon treatment of olefin **124** with $PdCl_2$ (0.2 equiv), CuCl (1.2 equiv) and oxygen (air) in a DMF/H_2O 7:1 mixture for two days.

(107) Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Ruttinger, R.; Kojer, H. *Angew. Chem. Int. Ed. Engl.* **1959**, *71*, 176–182.

(108) Tsuji, J.; Shimizu, I.; Kobayashi, Y. *Isr. J. Chem.* **1984**, *24*, 153–156.

(109) Tsuji, J.; Nagashima, H.; Hori, K. *Tetrahedron Lett.* **1982**, *23*, 2679–2682.

(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.
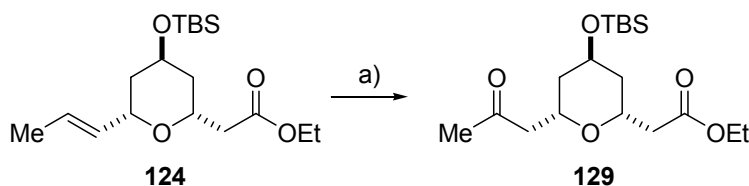
Scheme 50. (a) PdCl$_2$ (20 mol%), CuCl (1.2 equiv), air, DMF/H$_2$O 7:1, RT, 48 h, 86%.

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}.
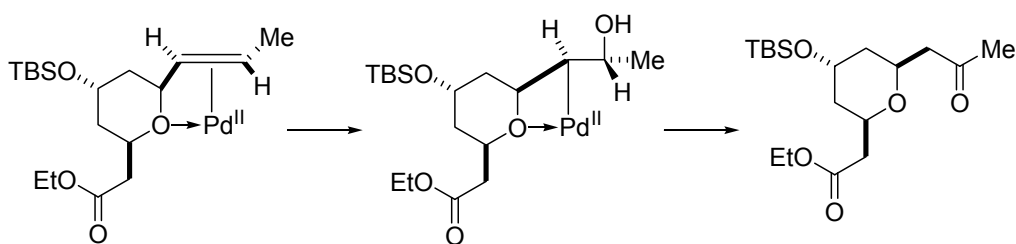
Scheme 51

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.[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:

i. The inherent chirality of the electrophilic component: The presence of the C12 stereogenic center may result in the preferred formation of the (11*S*)-stereocenter by *Felkin–Anh* control (Figure 9).[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.
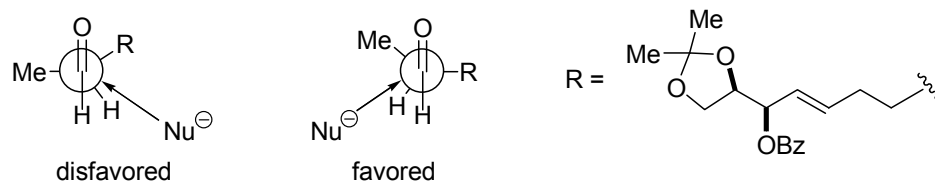

**Figure 9**. Preferred approach of the nucleophile according to the Felkin–Anh model.

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*[113] and *Evans*[114] that boron enolates derived

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

(112) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199–2204; (b) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205–2208; (c) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155–158.

(113) (a) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581–8584; (b) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585–8588; (c) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187–1191.

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).
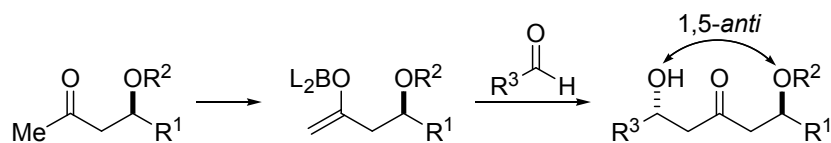
Scheme 52

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 (11*R*)-stereocenter in a matched fashion.

Enolization of methyl ketone **129** with (–)-DIPCl in conjunction with triethylamine in Et_2O 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).

(114) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788–789.

(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 nBu$_2$BOTf and DIPEA instead, the same β-hydroxy ketone **130** was isolated as a single isomer in 80% yield.[114b,116]
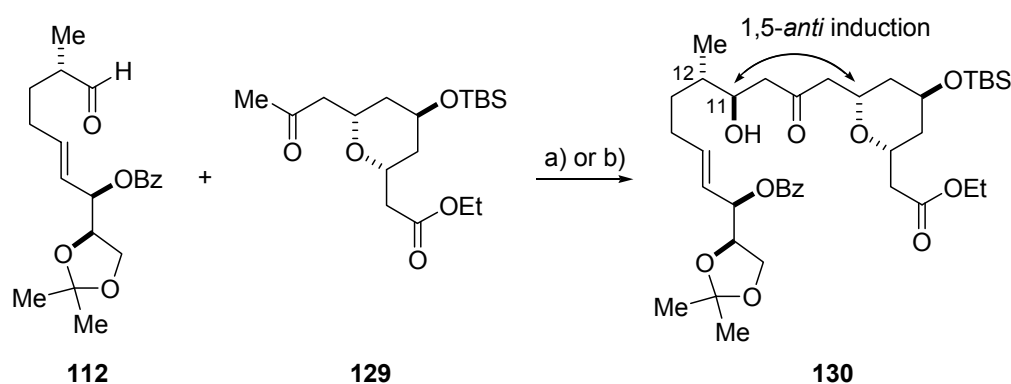
Scheme 53. (a) **129**, nBu$_2$BOTf, EtiPr$_2$N, Et$_2$O, −78 °C, then **112**, 5 h, 80% (d.r. > 95:5); (b) **129**, (−)-DIPCl, Et$_3$N, Et$_2$O, −78 °C, then **112**, 24 h, 81% (d.r. > 95:5).

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-*anti* relationship was deemed dispensable.

At present, the origin of the high levels of 1,5-*anti* induction obtained with these boron enolates is unclear.[113]

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(116) *Kozmin* reported a similar fragment coupling using Cy$_2$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 monoester **131** would have allowed for full differentiation of all hydroxy groups, and thus selective methylation of the C9 alcohol (Scheme 54).[117]
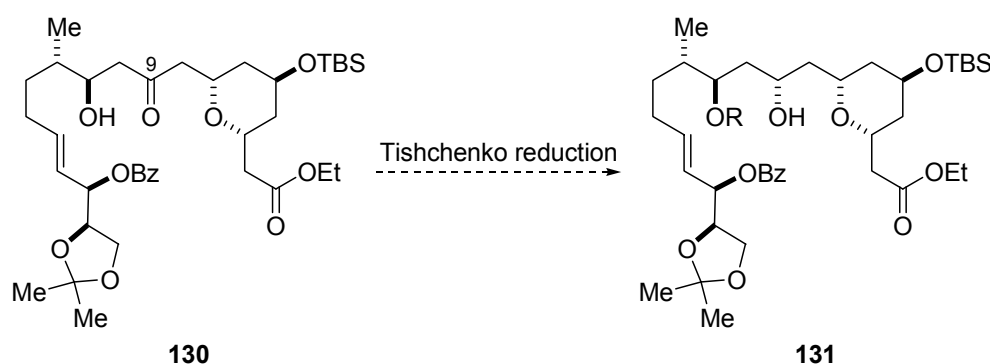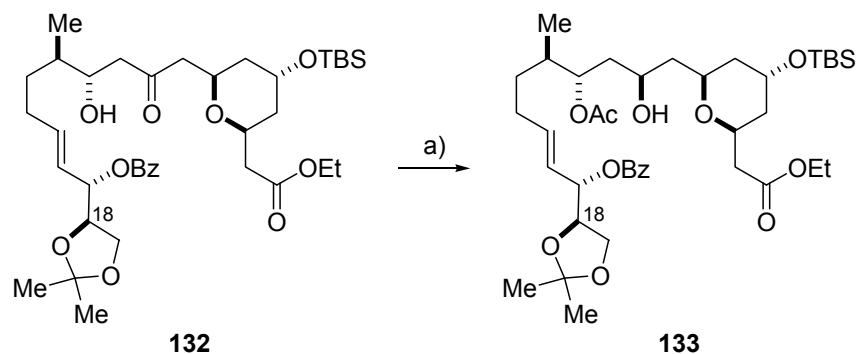

Scheme 54

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]

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(117) (a) Tishchenko, V. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 355; (b) a samarium diiodide catalyzed *Tishchenko* reduction has been reported: Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.

(118) THF solutions (0.10 M) of SmI$_2$ were prepared prior to use from Sm^0 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, SmI$_2$ (10–30 mol%), THF, –78 °C, > 85%.

Upon addition of SmI$_2$ to a THF solution of a hydroxy ketone and R^{1}CHO, the deep blue hue of Sm^{II} quickly fades to give rise to the yellow color of Sm^{III}, 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.
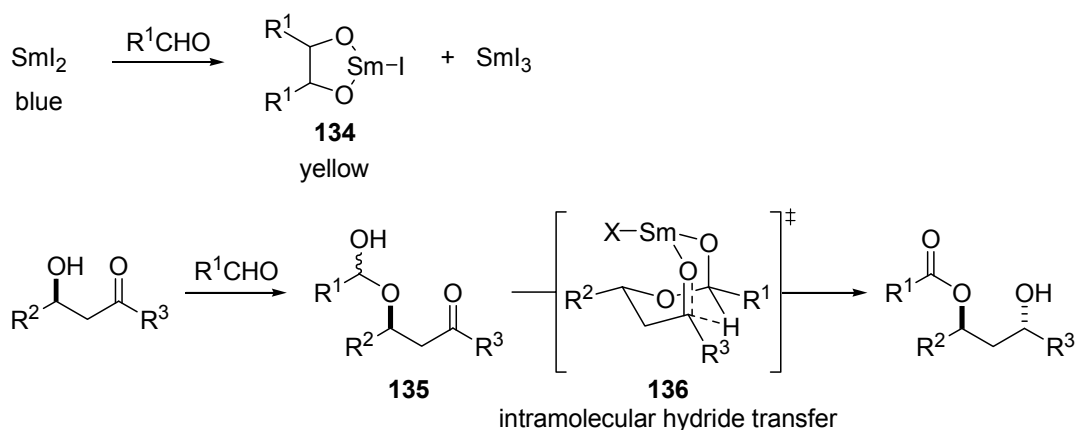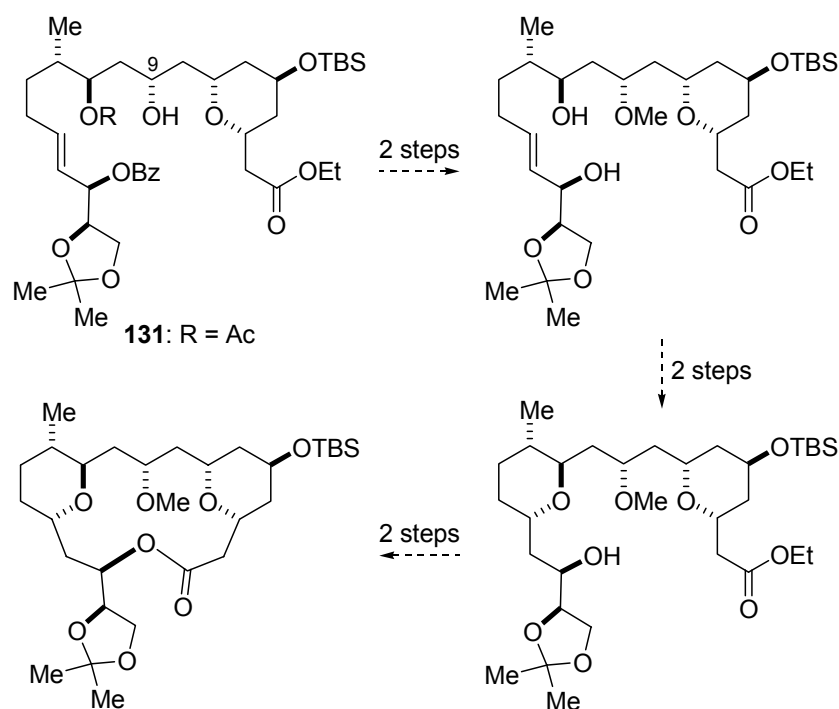

Scheme 56

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**.

Scheme 57

(119) Gillespie, K. M.; Munslow, I. J.; Scott, P. *Tetrahedron Lett.* **1999**, *40*, 9371–9374.

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.[120] 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.[121]

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 ^{1}H NMR) (Scheme 58).[122] Deprotection of the C17 benzoate with concomitant transesterification to the C1 methyl ester was achieved with K_2CO_3 in MeOH, yielding triol **138** in 92% yield.

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(120) (a) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761–3770; (b) Anwar, S.; Davis, A. P. *J. Chem. Soc. Chem. Commun.* **1986**, 831–832; (c) see also ref. 122.

(121) Several ring-size selective macrolactonizations on highly functionalized substrates have been reported. For examples, see: (a) Evans, D. A.; Fitch, D. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2536–2540; (b) White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593–8595; (c) Scheufler, F.; Maier, M. E. *Synlett* **2001**, 1221–1224; (d) Kuhnert, S. M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643–646.

(122) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.
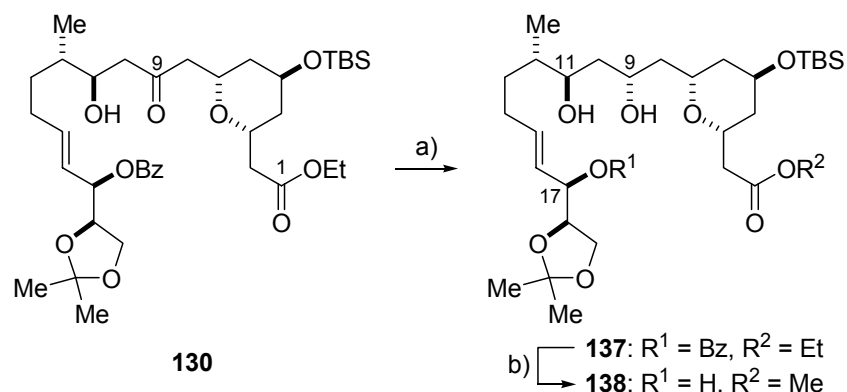
Scheme 58. (a) $Me_4NBH(OAc)_3$, AcOH, CH_3CN, −40 °C, 48 h, 97%; (b) K_2CO_3, MeOH, RT, 40 h, 92%.

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 R^2 and OAc in **140**, destabilizing the system to a greater extent than the interactions between HO^+ and OAc found in **139**.
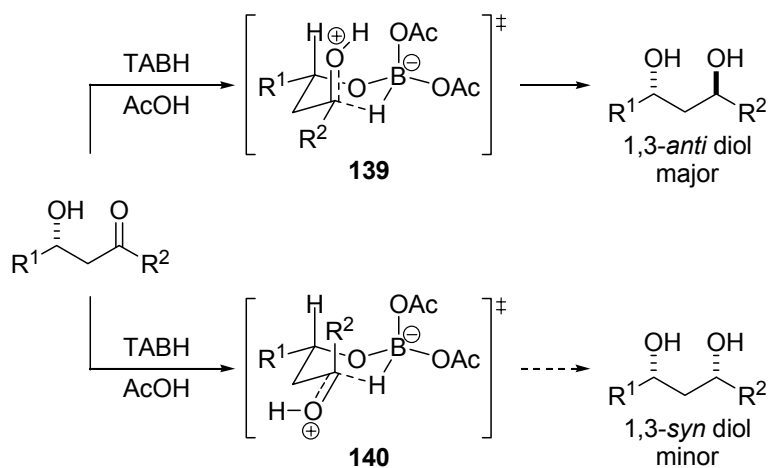
Scheme 59

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^+, Hg^{2+}, PhS^+ and $PhSe^+$.[123]
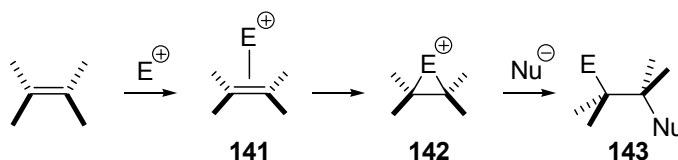
Scheme 60

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).

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(123) For reviews on electrophile-mediated cyclizations onto carbon–carbon multiple bonds, see: (a) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33–62; (b) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 63–115.
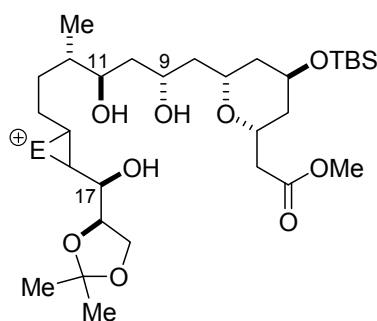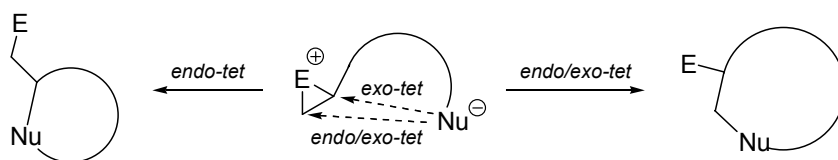
Figure 10. Potential intramolecular nucleophiles.

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).[124]

Scheme 61. Possible modes of attack of a tethered nucleophile onto an onium ion.

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).

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[124] (a) For rules on ring-closure, see: Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734–736; (b) the concept of hybrid *endo/exo-tet* cyclizations has been introduced by *Warren*: McIntyre, S.; Warren, S. *Tetrahedron Lett.* **1990**, *31*, 3457–3460.
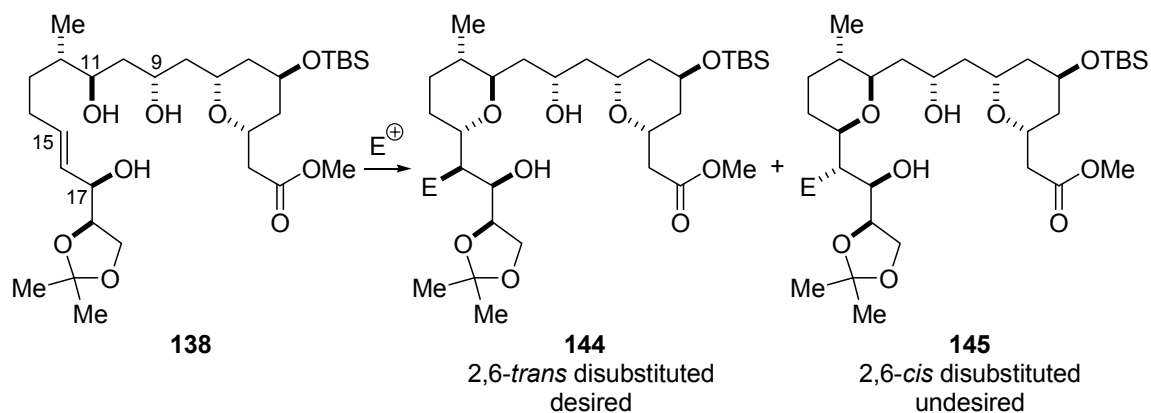
Scheme 62

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.[125] This reaction has been successfully applied to the synthesis of the rutamycin spiroketal skeleton by *Evans* and co-workers (Scheme 63).[126]
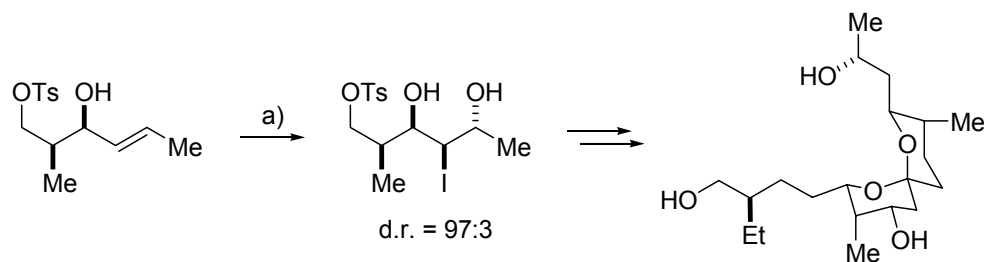
Scheme 63. I_2, THF/H_2O, KH_2PO_4.

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

(125) Chamberlin, A. R.; Mulholland, R. L. *Tetrahedron* **1984**, *40*, 2297–2302.

(126) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260–6268.

directing groups.[127] 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**.
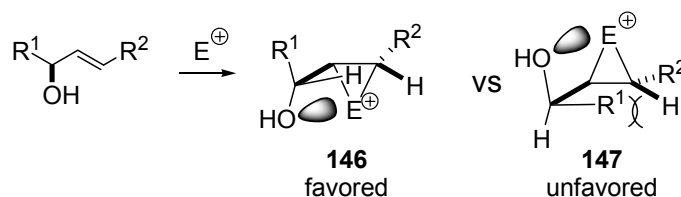
Scheme 64

With this information in hand, cyclization via iodonium ions was investigated first. While I_2-mediated reactions proved to be extremely slow and nonselective (1:1 diastereomeric mixture of **148** and **149**),[128] iodine-monobromide has been reported by *Smith* to give enhanced addition rates, allowing for low-temperature cyclizations of homoallylic carbonates with superior diastereoselectivities.[129] Indeed, the use of IBr led to significantly accelerated additions, albeit unchanged stereoinduction (Scheme **65**).

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(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.

(129) (a) Duan, J. J.-W.; Smith, A. B., III *J. Org. Chem.* **1993**, *58*, 3703–3711; (b) Duan, J. J.-W.; Sprengeler, P. A.; Smith, A. B., III *Tetrahedron Lett.* **1992**, *33*, 6439–6442.
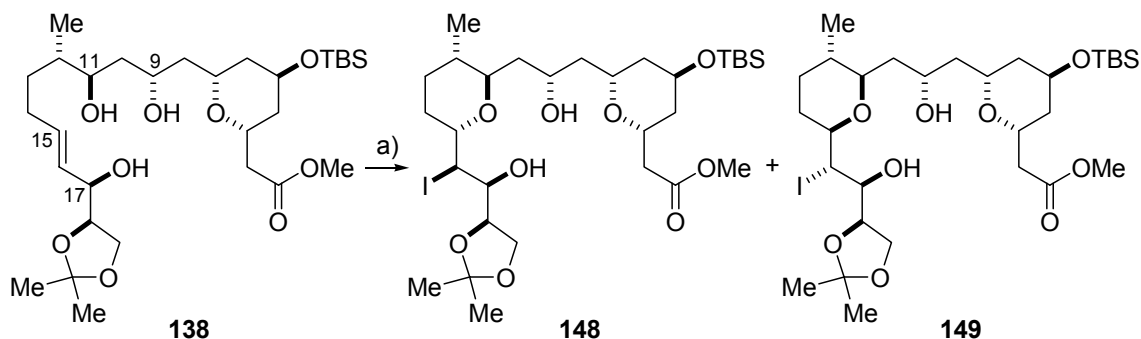
Scheme 65. (a) 2,6-di-*tert*-butyl-4-methyl pyridine, IBr, toluene, −78 °C, 2 h, 50% (d.r. = 1:1).

Typical reaction conditions involved the slow addition over 1 h of a toluene solution of IBr (2.0 equiv, 1.0 M in CH_2Cl_2) to a toluene solution of allylic alcohol **138** and 2,6-di-*tert*-butyl-4-methyl pyridine (2.5 equiv) at −78 °C.[130] After workup with 2.0 M aqueous $Na_2S_2O_3$, 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 K_2CO_3 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

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(130) The use of additional base was necessary to avoid deprotection of the C5 silyl ether.

epoxide **151**, characteristic for *cis* epoxides.[131] **150**, obtained from **148**, displays a coupling constant of $^3J_{\text{H-H}} = 2.16$ Hz, typical for *trans* epoxides.[132]

expected: $^3J_{cis} = 4.5$ Hz
found: $^3J_{cis} = 4.36$ Hz

$^3J_{cis} = 4.36$ Hz (300 MHz)

expected: $^3J_{trans} = 2.2$ Hz
found: $^3J_{trans} = 2.16$ Hz

$^3J_{trans} = 2.16$ Hz (500 MHz)
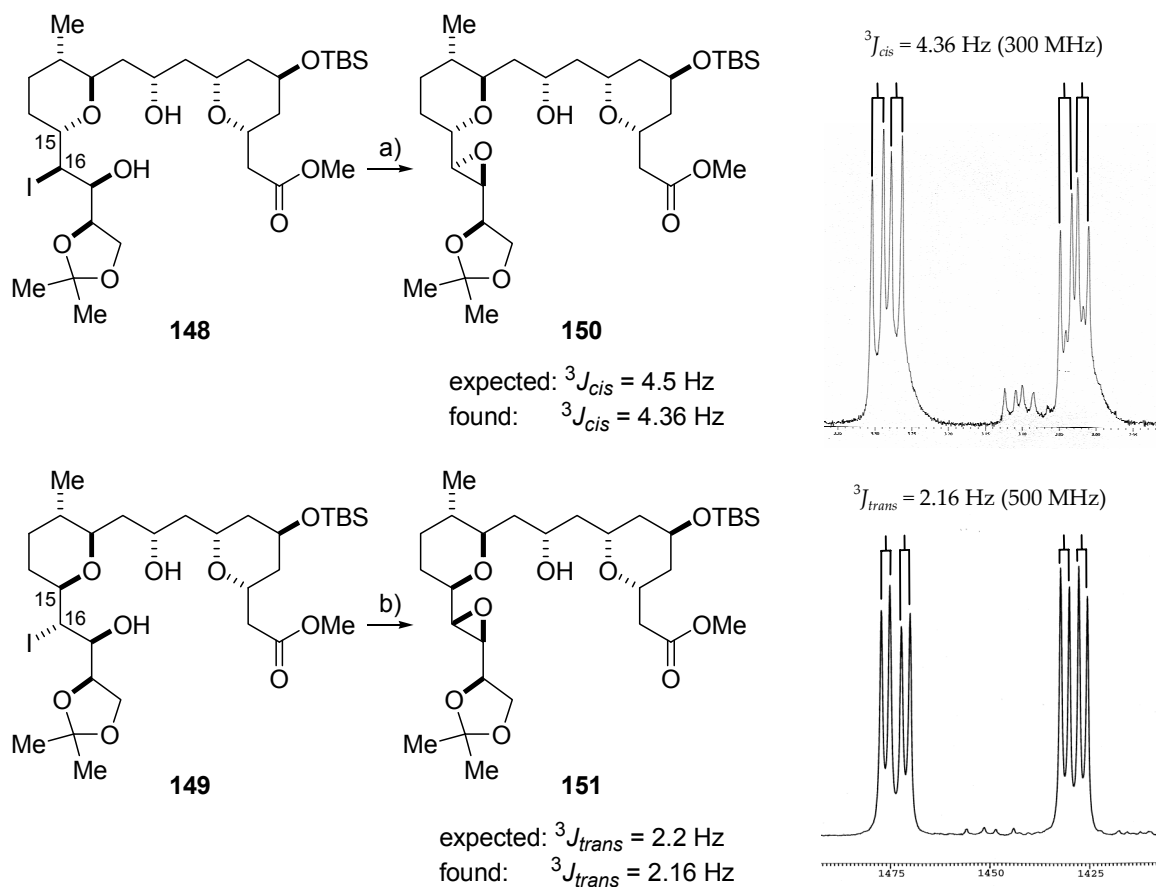
Scheme 66: (a) K$_2$CO$_3$, MeOH, RT, 15 h, 57%; (b) K$_2$CO$_3$, MeOH, RT, 15 h, 69%.

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

(131) Pretsch, E.; Bühlmann, P.; Affolter, C. *Structure Determination of Organic Compounds: Tables of Spectral Data*; Springer: Berlin, 2000.

(132) For a related *trans* epoxide with similar ^3J 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).[133]

Encouraged by this result, we turned our attention to bulkier, substituted phenylselenyl reagents. In this respect, 2,4,6-triisopropylphenylselenyl bromide (TIPPSeBr) (**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.[134]
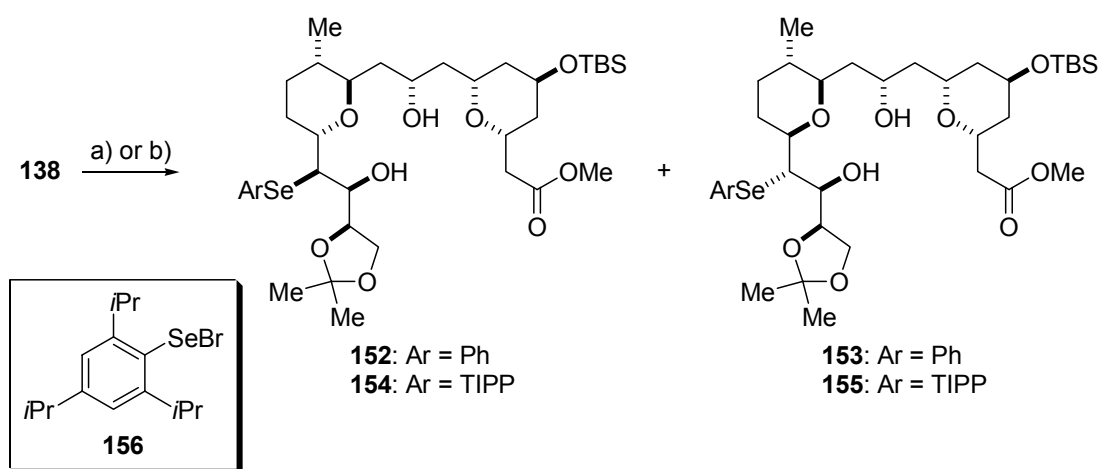
Scheme 67. (a) 2,6-di-*tert*-butyl-4-methyl pyridine, CH$_2$Cl$_2$, –78 °C, followed by slow addition (over 1 h) of PhSeCl, 1 h, 78% (d.r. = 75:25 **152**:**153**); (b) 2,6-di-*tert*-butyl-4-methyl pyridine, CH$_2$Cl$_2$, –78 °C, followed by slow addition (1 h) of **156**, 4 h, 74% (d.r. = 88:12 **154**:**155**).

Formation of the intermediate seleniranium ion seemed to be much slower as compared to phenylselenyl chloride.[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

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

(134) Lipshutz, B. H.; Gross, T. *J. Org. Chem.* **1995**, *60*, 3572–3573.

(135) The terms seleniranium and selenenium ions are both used in the literature to refer to selenium onium 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 CH_2Cl_2 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 Br_2.
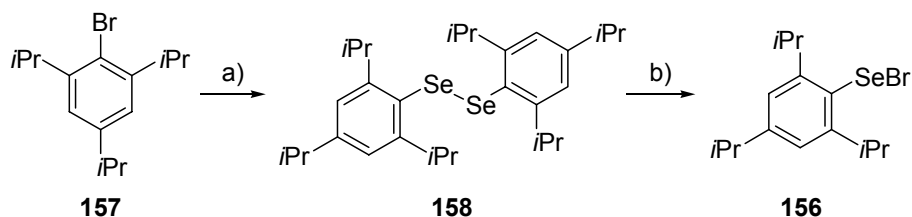
Scheme 68: (a) *t*BuLi, THF, –78 °C, then Se, –78 °C → RT, 50%; (b) Br_2, CH_2Cl_2, –78 °C to RT.

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]

(136) Dumont, W. W.; Martens, A.; Pohl, S.; Saak, W. *Inorg. Chem.* **1990**, *29*, 4847–4848.

(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 metals[139] (Li^0, Na^0, Cr^{II} and Sm^{II} among others), metal hydrides[140] ($NaBH_4$, LAH, $LiHBEt_3$, R_3SnH) and catalytic hydrogenation[141].

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 nBu$_3$SnH in combination with AIBN as radical initiator in refluxing, deoxygenated benzene, giving **159** in excellent yields (97%) (Scheme 69).

148: X = I
154: X = TIPPSe

159
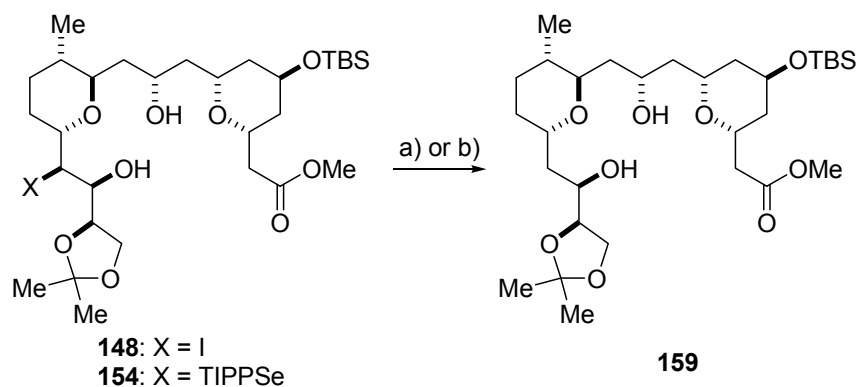
Scheme 69. (a) nBu$_3$SnH, AIBN, PhH, reflux, 1 h, 97% for X = I; (b) **160**, AIBN, hexane, reflux, 2 h, 85% for X = I, 80% for X = TIPPSe.

(139) (a) Li^0/tBuOH: Gassman, P. G.; Pape, P. G. *J. Org. Chem.* **1964**, *29*, 160–163; (b) Na^0/tBuOH: Gassman, P. G.; Aue, D. H.; Patton, D. S. *J. Am. Chem. Soc.* **1968**, *90*, 7271–7276; (d) Cr^{II}: Hanson, J. R. *Synthesis* **1974**, 1–8; (e) Sm^{II}/HMPA: Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485–1486.

(140) (a) NaBH$_4$: Bell, H. M.; Vanderslice, C. W.; Spehar, A. *J. Org. Chem.* **1969**, *34*, 3923–3926; (b) LiHBEt$_3$: Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1–12; (c) Neumann, W. P. *Synthesis* **1987**, 665–683.

(141) For a discussion, see: Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985.

However, purification problems[142] associated with organotin reagents prompted us to investigate modern, alternative methods, which are not based on organotin reagents.[143,144] 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· 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]
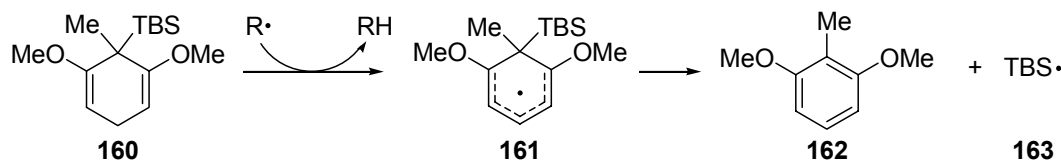
Scheme 70

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.

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(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.

(143) For a review on tin-hydride substitutes in reductive radical-chain reactions, see: Studer, A.; Amrein, S. *Synthesis* **2002**, 835–849.

(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.

(145) Prof. *Armido Studer* is gratefully acknowledged for a generous gift of **160**. See: Studer, A.; Amrein, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 3080–3082.

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]
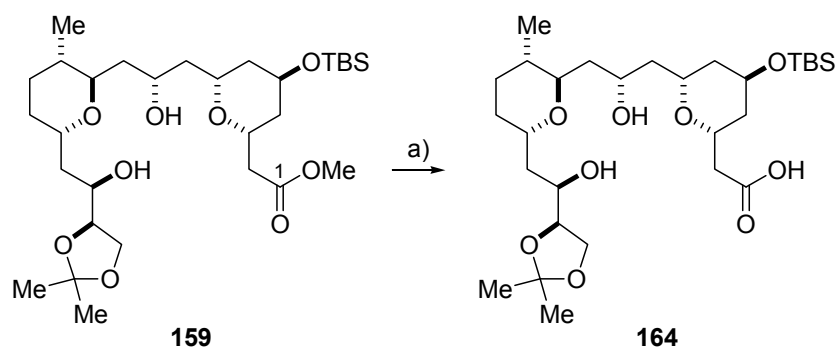
Scheme 71. (a) TMSOK, Et$_2$O, RT, 24 h.

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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(146) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831–5834.

(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.
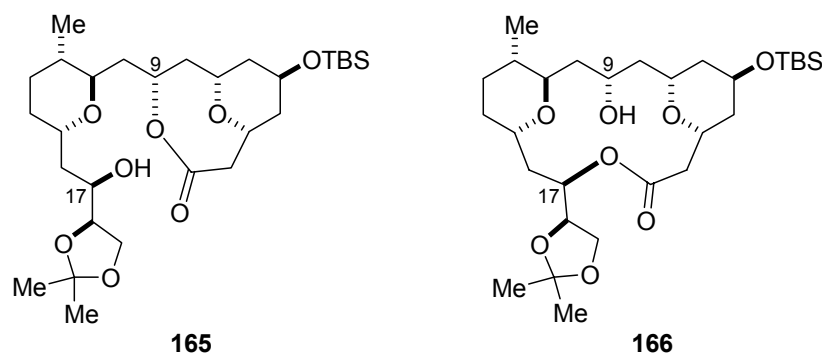
Figure 11. Structure of the potentially formed lactones.

Although formation of **165** is theoretically possible, the thermodynamic bias was expected to be considerably in favor of the larger macrocycle **166**.[148] 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.
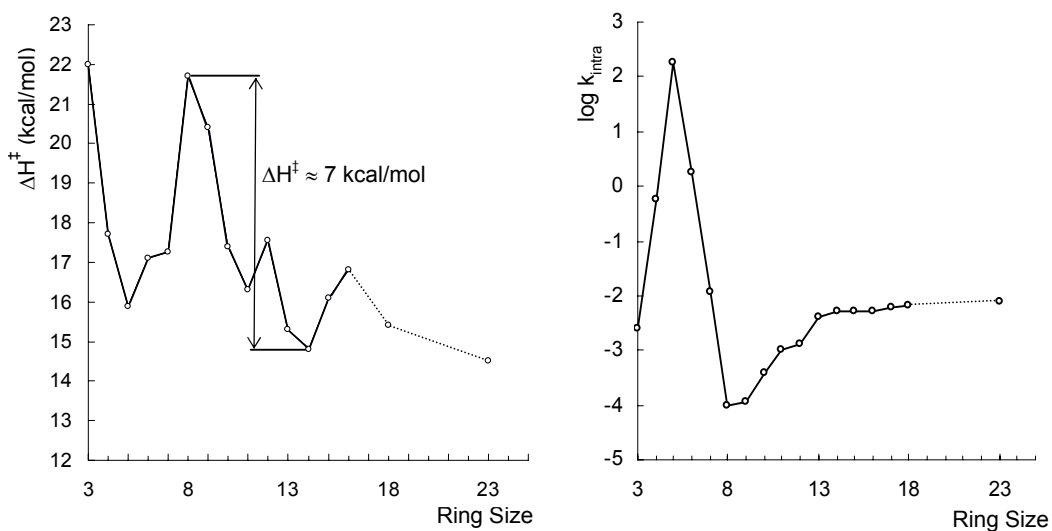
Figure 12. $\Delta H^{\ddagger}$ for the formation of lactones (left); Reactivity profile for lactone formation (right).[148]

(148) For a general discussion on energetics of lactonization, see: (a) Mandolini, L. *J. Am. Chem. Soc.* **1978**, *100*, 550–554; (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102.

Semi-empiric calculations of the cationic acyl-DMAP adduct derived from seco acid **164** suggest that eight-membered ring formation is disfavored by almost 5 kcal/mol (Figure 14).[149] 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.[150]
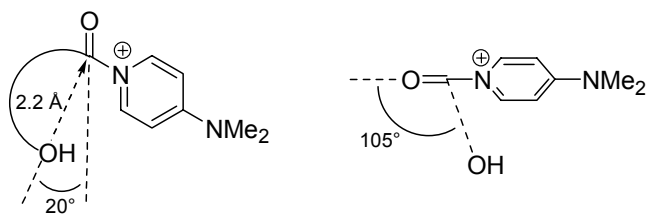
Figure 13. Geometrical constraints for lactonization.

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(149) Semi-empiric calculations were performed at the PM3 level using PC Spartan Pro® for Windows.

(150) (a) Bürgi, H. B.; Dunitz, J. D. *Accounts Chem. Res.* **1983**, *16*, 153–161; (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563–1572.

14-membered "assembly"

E	-273.73 kcal·mol^{-1}
rel. E	0.0 kcal·mol^{-1}

8-membered "assembly"

E	-268.87 kcal·mol^{-1}
rel. E	4.86 kcal·mol^{-1}
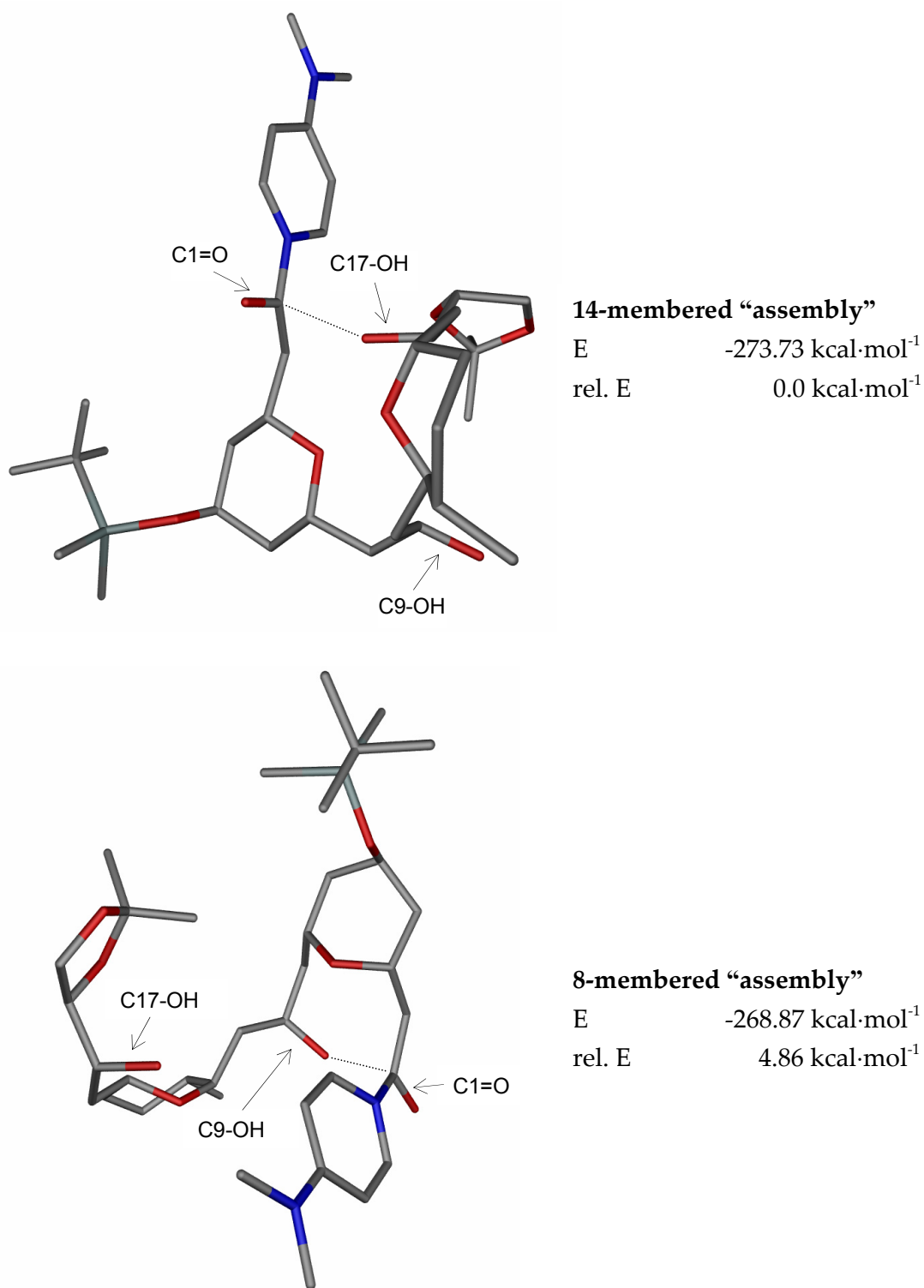
Figure 14. Energy-minimized reactive conformations (PM3) of lactonization pathways for the cationic acyl-DMAP adduct derived from **164**.

Because of these theoretical considerations and earlier success in our laboratory with model compound **167**, the macrolactonization step was tackled with some confidence.[151] Indeed, under typical *Yamaguchi* conditions (formation of the mixed anhydride by treatment with $2,4,6\text{-}Cl_3(C_6H_2)COCl/Et_3N$, followed by DMAP-promoted cyclization), seco acid **167** cleanly afforded macrolactone **168** in 80% yield (Scheme 72).[152]
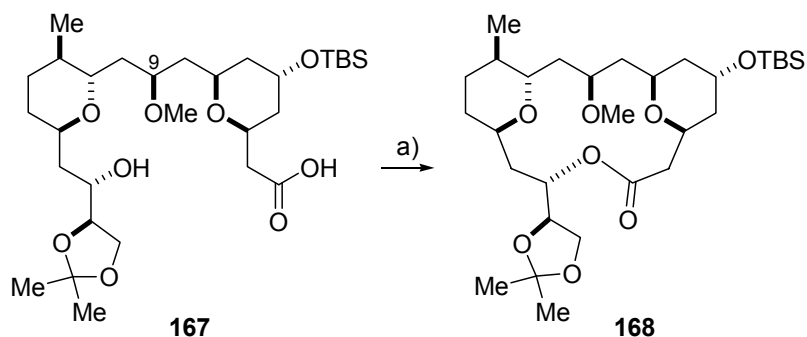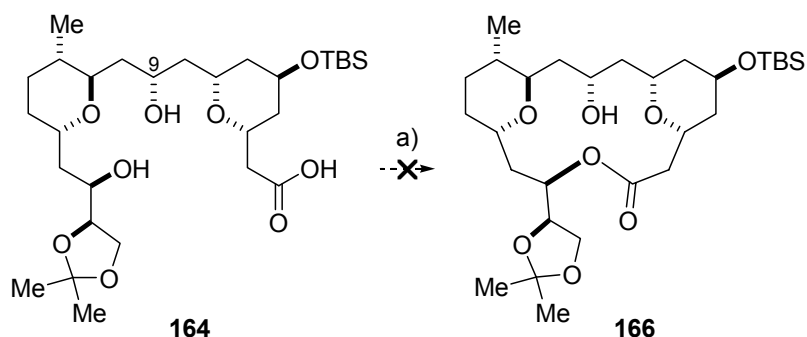
Scheme 72. (a) $2,4,6\text{-}Cl_3(C_6H_2)COCl$, Et_3N, THF, RT, 1 h; then addition to DMAP in THF, 80%.

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(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

(153) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Auyeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H. J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Babu, T. V. R.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N. C. *J. Am. Chem. Soc.* **1981**, *103*, 3213–3215.

(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.
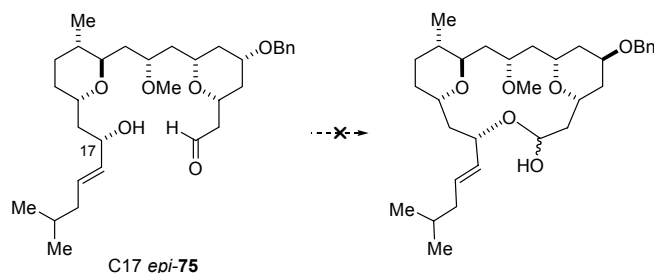
arrangement may lock the molecule in a conformation which is unfavorable for ring-closure: molecular-mechanics calculation showed that, in the preferred conformation of the macrocyclic structure **45**, the C9 methyl ether resides peripherally, a disposition which is not compatible with the postulated array, wherein the C9 hydroxy group is supposedly between the tetrahydropyran rings (Figure 15).[155]
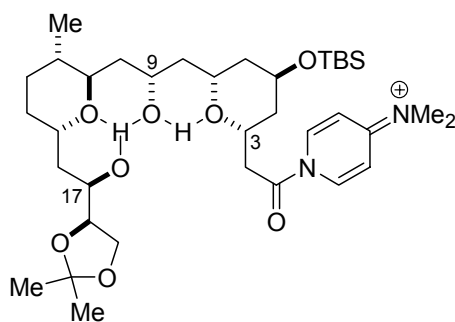
Figure 15. Postulated hydrogen-bonded array of the prelactonization complex derived from seco acid **164** and DMAP.

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 ($2.4 \cdot 10^{-3}$ M in THF/DMF) to a solution of DMAP (10 equiv; $1.5 \cdot 10^{-2}$ M in DMF) over 3 h (Scheme 15).[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.

(156) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(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 Me_3OBF_4 in combination with Proton Sponge (**170**) and 4 Å molecular sieves, using the improved conditions reported by *Ireland* (Scheme 73).[158]
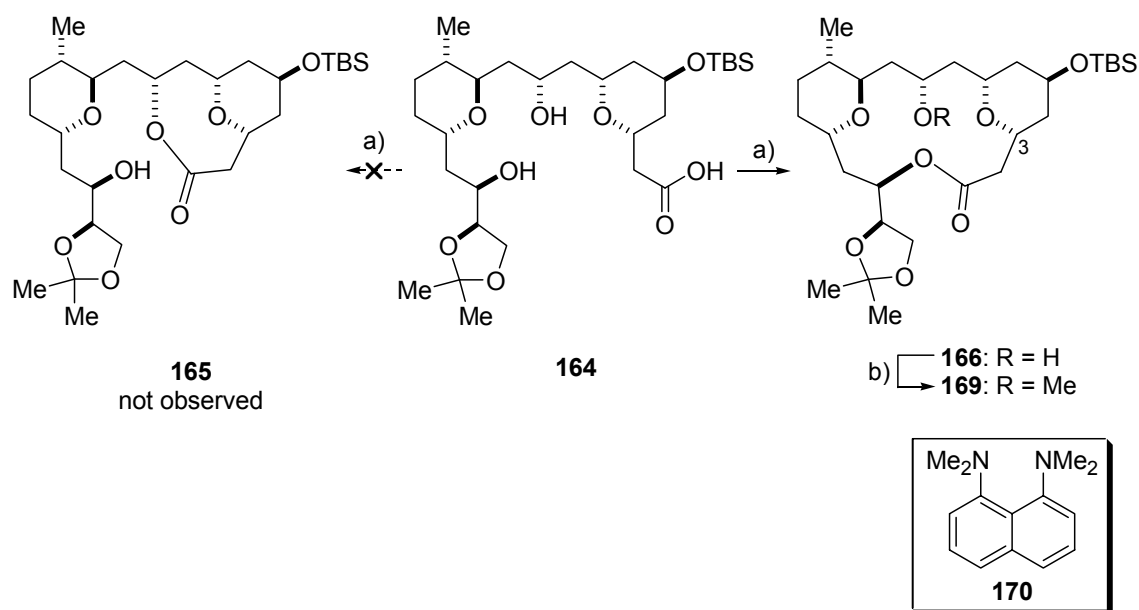
Scheme 73. (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, RT, 1 h, then dilution with DMF and slow addition (3 h) to DMAP in DMF, RT, 2 h; (b) Me_3OBF_4, Proton Sponge (**170**), 4 Å M.S., RT, 30 min, 49% over 3 steps.

(158) (a) Ireland, R. E.; Liu, L. B.; Roper, T. D.; Gleason, J. L. *Tetrahedron* **1997**, *53*, 13257–13284; (b) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *Tetrahedron Lett.* **1994**, *35*, 7171–7172.

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/H_2O 2:1:1 (Scheme 74).[159] These mild acidic conditions were found to leave the C5 silyl ether untouched.
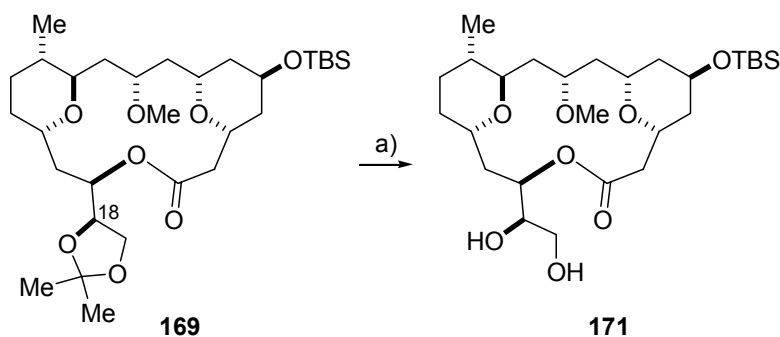
Scheme 74. (a) AcOH/THF/H_2O 2:1:1, 45 °C, 5 h, 80%.

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

(159) (a) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4672–4685; (b) other methods used for the deprotection of acetonides have been reported: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Second Edition; John Wiley & Sons: New York, 1991.

modifications, is perhaps the most versatile and widely used method for this purpose.[160] Since the original report by *Marc Julia*,[160a] involving a three-step reaction sequence, the protocol has been simplified by *Lythgoe*[160b,c], *Sylvestre Julia*[160d,e] and *Kocieński*[160f,g], leading to the development of a less capricious one-step variation. While the use of benzothiazolyl sulfones shows considerable limitations,[161] 1-phenyl-1*H*-tetrazol-5-yl sulfones extensively studied and reported by *Kocieński* circumvent these problems.[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_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 ^{1}H NMR.

(160) (a) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833–4836; (b) Kocieński, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1045–1050; (c) Kocieński, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc. Perkin Trans. 1* **1978**, 829–834; (d) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175–1178; (e) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856–878; (f) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26–28; (g) Kocieński, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365–366.

(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.
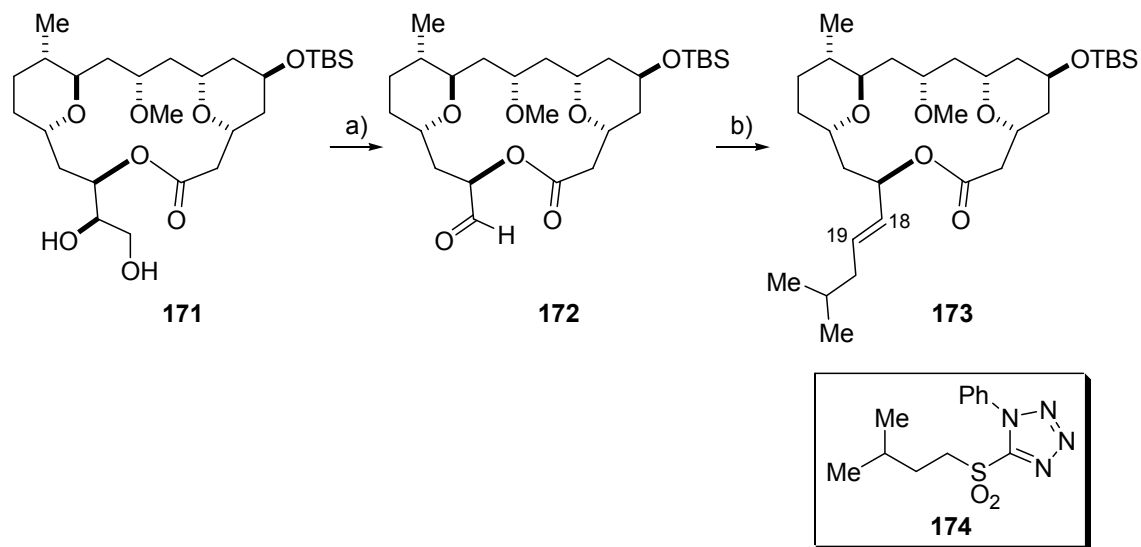
Scheme 75. (a) Pb(OAc)$_4$, EtOAc, 0 °C, 15 min; (b) **174**, KHMDS, DME, −78 °C → −55 °C, 2 h; added to **172**, DME, −78 °C → −55 °C, 2 h, then 0 °C, 3 h, 73% over 2 steps.

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).
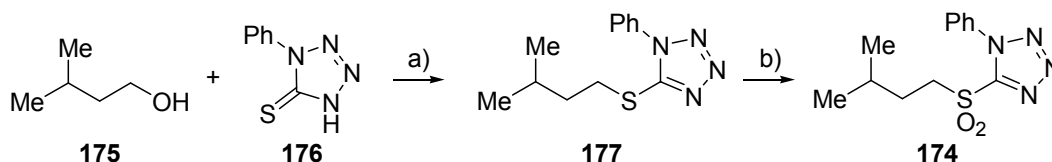
Scheme 76. (a) PPh$_3$, DEAD, THF, RT, 16 h, 86%; (b) Oxone, MeOH, H$_2$O, RT → 50 °C, 21 h, 90%.

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 (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$, IR, HRMS) to the material obtained from degradation of the natural

product by *Pietra* and to the material previously synthesized by *Leighton* and *Rychnovsky*.[162]
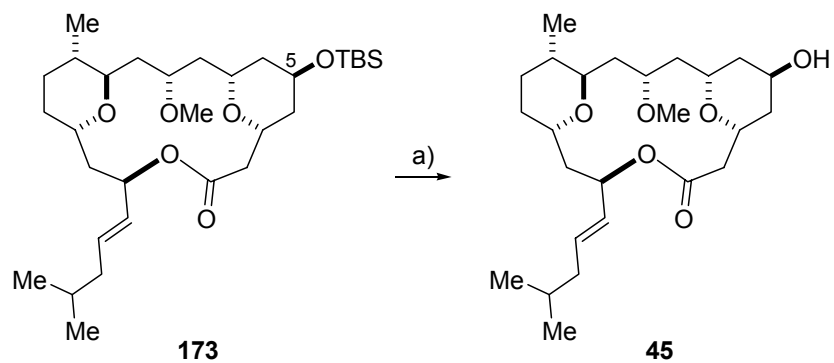
Scheme 77. (a) TBAF, THF, 0 °C → RT, 7 h, 98%.

(162) See ref. 35, 48, 51 for details.

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).[163] Two different syntheses are proposed, one of them leading to methyl ester **46**, the other one to aldehyde **178**.
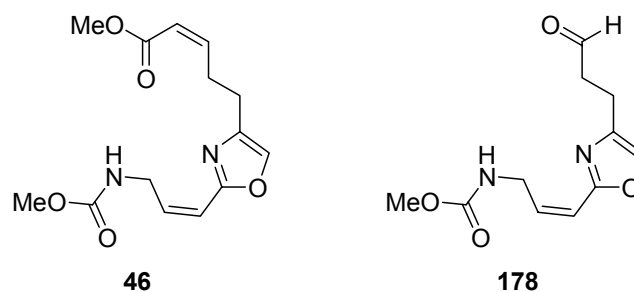
Figure 16. Structures of the synthesized side chains.

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.[164]

Alkylation of diethyl acetamidomalonate (**179**) with tosylate **180** gave known compound **181** in poor yield (28%) (Scheme 78).[165] Subsequent decarboxylation using

(163) Treatment of natural leucascandrolide A with Na_2CO_3 in MeOH gave the macrolide moiety **45** (77% yield) and the methyl ester side chain **46**. See ref. 35 for details.

(164) (a) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604–3606; (b) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558–559.

(165) Van Hest, J. C. M.; Kiick, K. L.; Tirrell, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 1282–1288.

the method developed by *Krapcho* (LiCl, DMSO, 120 °C, 83%) afforded ester **182**,[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.
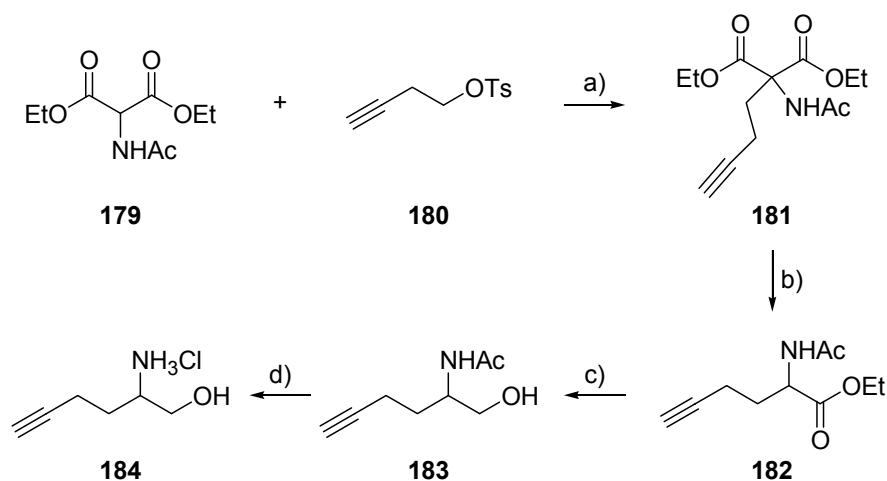
Scheme 78. (a) **179**, *t*BuOK, THF, reflux, 2 h, then **180**, reflux, 2 d, 47%; (b) LiCl, DMSO, 120 °C, 4 h, 83%; (c) LiBH$_4$, MeOH, THF, RT, 1 h, 91%; (d) 1.0 M aq. HCl, MeOH, reflux, 2 h, quant.

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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(166) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, *8*, 215–217.
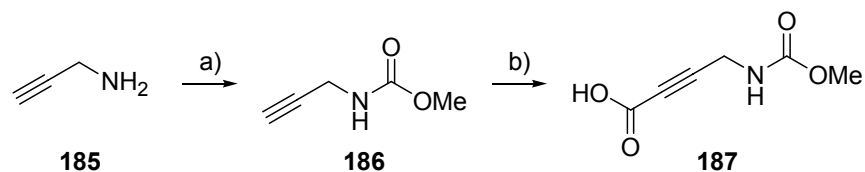
Scheme 79. (a) ClCO$_2$Me, Et$_3$N, CH$_2$Cl$_2$, RT, 3 h, 80%; (b) LHMDS, THF, –78 °C, then CO$_2$, –78 °C, 2 h, 80%.

PyBrop-mediated peptide coupling of acid **187** and hydrochloride **184** afforded the highly unstable hydroxy amide **188**,[167] which was immediately oxidized to the corresponding, unstable aldehyde **189** with *Dess–Martin* periodinane (Scheme 80).[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**.
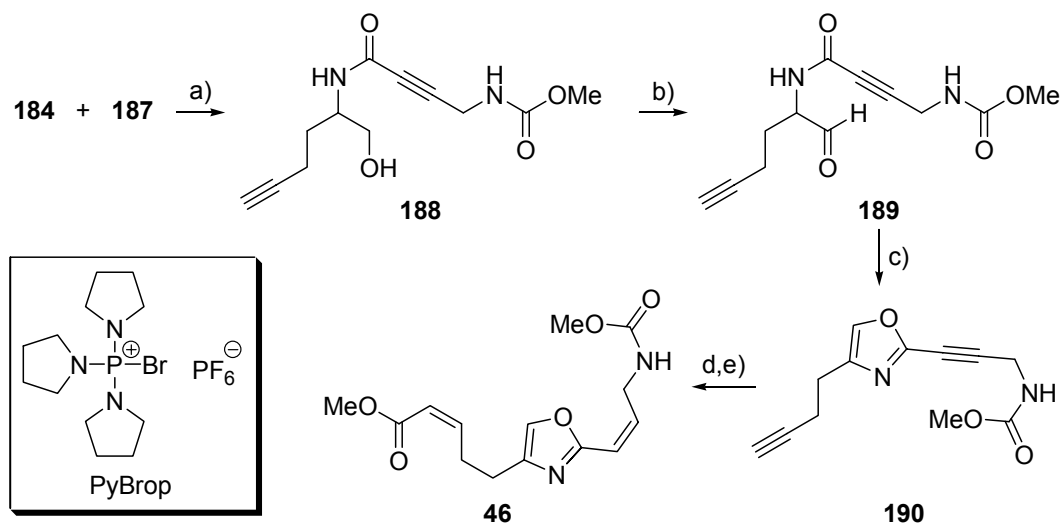
Scheme 80. (a) PyBrop, DIPEA, CH$_2$Cl$_2$, RT; (b) DMP, CH$_2$Cl$_2$, RT; (c) 2,6-di-*tert*-butyl-4-methyl pyridine, PPh$_3$, (CBrCl$_2$)$_2$, CH$_2$Cl$_2$, then DBU, RT, 25% from **187**; (d) PdCl$_2$, CuCl$_2$, NaOAc, CO (1 atm), MeOH, RT, 3 h; (e) H$_2$ (1 atm), Pd/BaSO$_4$, quinoline, MeOH, RT, 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.

(168) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156; (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

Further elaboration towards **46** was planned by methoxycarbonylation or carboxylation of the terminal acetylene in **190**. However, deprotonation with LHMDS, LDA or *n*BuLi followed by trapping with methylchloroformate or CO_2 proved unsuccessful, leading in all cases to a complex mixture of unidentified products. As an alternative, the palladium-mediated carbonylation[169] ($PdCl_2$, $CuCl_2$, CO, AcONa, MeOH) provided the desired methyl ester. After partial hydrogenation using $Pd/BaSO_4$ 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[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).[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 $BrCCl_3$ employing the one-pot protocol recently disclosed by *Wipf* and *Williams*.[172]

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(169) Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 849–850.

(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.

(171) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446–456.

(172) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168.
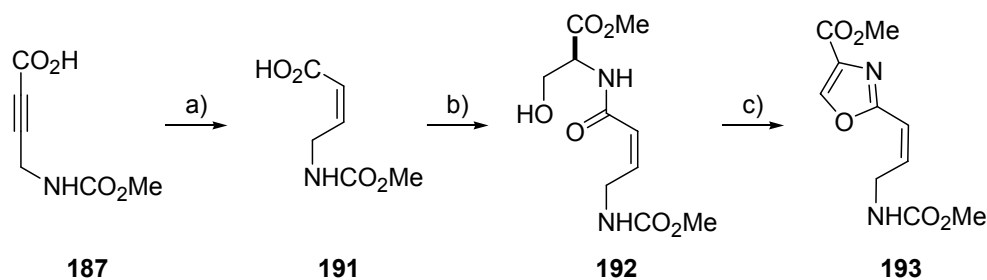
Scheme 81. (a) *Lindlar*'s catalyst, quinoline, 1 atm H$_2$, EtOAc; (b) *i*BuOCOCl, NMM, L-Ser-OMe·HCl, THF, 35% (over 2 steps); (c) DAST, CH$_2$Cl$_2$, –20 °C; BrCCl$_3$, DBU, 0 °C, 60%.

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 (CBr$_4$, PPh$_3$, CH$_3$CN).[173] Two-carbon chain extension could be realized by *Stille* coupling[174] with tributylvinyltin, catalyzed by Pd$_2$(dba)$_3$ and tri(2-furyl)phosphine[175], 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 H$_2$O$_2$. The desired aldehyde **178** was obtained in 63% yield (over 2 steps) by oxidation under *Swern* conditions ((COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$).[176]

(173) Hayashi, H.; Nakanish.K; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749–8757.

(174) (a) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–523; (b) Mitchell, T. N. *Synthesis* **1992**, 803–815.

(175) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

(176) (a) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482; (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
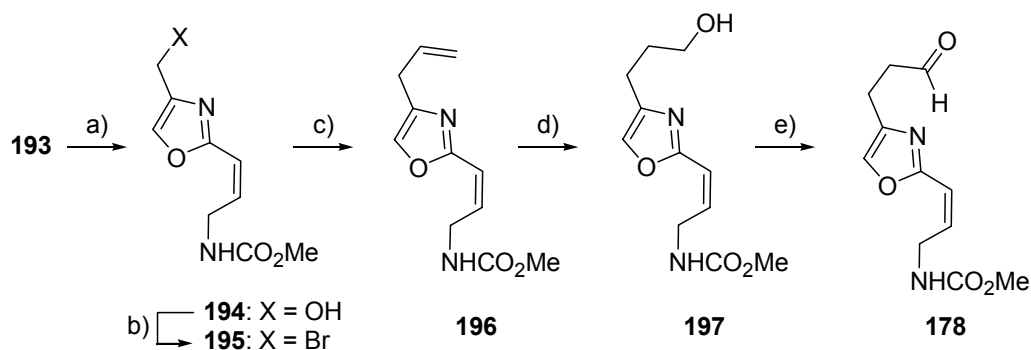
Scheme 82. (a) DIBAL–H, THF, 0 °C, 57%; (b) CBr$_4$, PPh$_3$, 2,6-lutidine, CH$_3$CN, 76%; (c) nBu$_3$SnCH=CH$_2$, Pd$_2$dba$_3$, tri(2-furyl)phosphine, THF, reflux, 63%; (d) 9-BBN, THF, H$_2$O$_2$; (e) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, –78 °C to 0 °C, 63% over 2 steps.

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)phosphono acetic acid (**198**), employing EDCI·HCl and HOBt·H$_2$O 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).
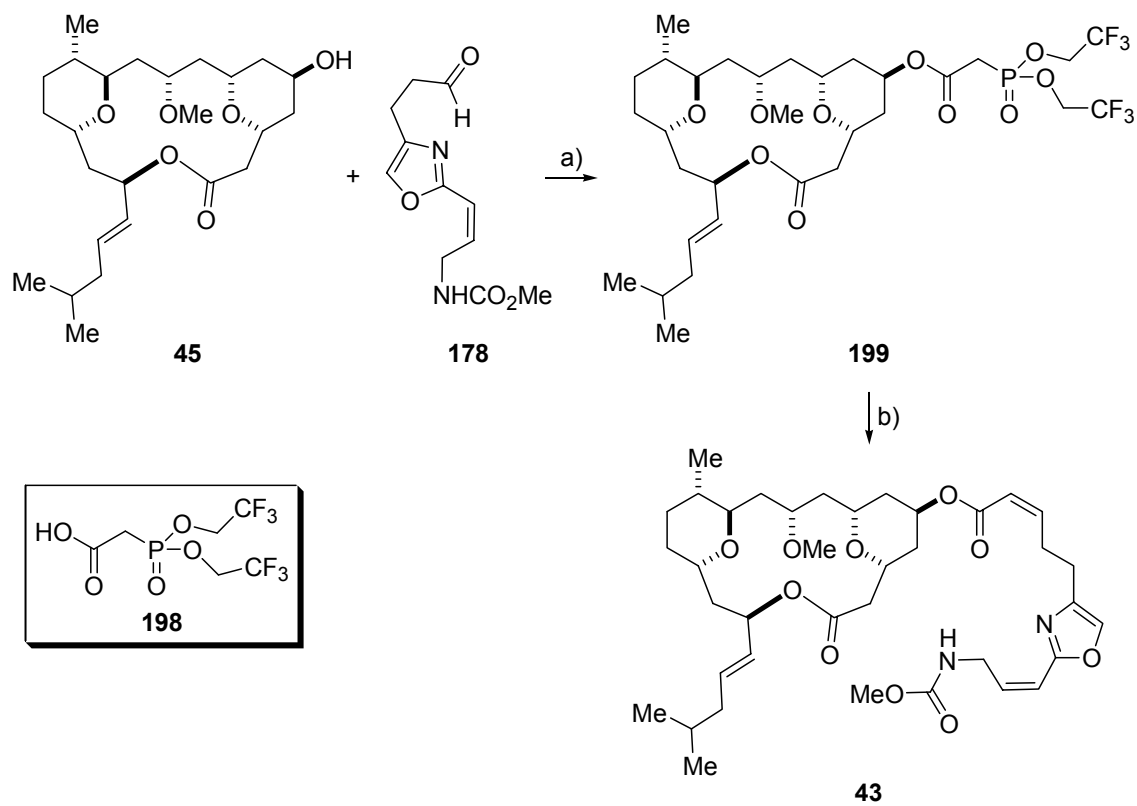
Scheme 83. (a) **45**, HOBt·H₂O, EDCI·HCl, CH₂Cl₂, RT, 15 min; (b) 18C6·CH₃CN, KHMDS, THF, −78 °C, 1 h, then **178**, THF, −100 °C, 2 h, 10% (*Z:E* = 5:1).

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 macrocyle.

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　Experimental Section

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 (H_2O content < 30 ppm, *Karl–Fischer* titration).[177] 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 (*n*Bu₃SnH), 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-

(177) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

methyl pyridine was flashed over activated, acidic alumina.[178] Potassium hydride (commercially available as a dispersion in mineral oil) was purified according to the procedure reported by *Brown*.[179] *n*-Butyl lithium was titrated with *s*BuOH/phenanthroline.[180] KHMDS solutions were titrated according to a literature procedure.[181] All other commercially available reagents were used without further purification. Tetra-*n*-propyl ammonium perruthenate,[182] (1-diazo-2-oxo-propyl)-phosphonic acid dimethyl ester,[183] tetra-*n*-butylammonium triphenyl difluorosilicate,[87a] (*R*)-1,2-isopropylidene glyceraldehyde,[76] 2,4,6-triisopropyl-phenylselenium bromide,[134] and *Dess–Martin* periodinane[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_{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.[185] Concentration under reduced pressure was performed by rotary

(178) Anderson, A. G.; Stang, P. J. *Organic Syntheses* **1981**, *60*, 34–40.

(179) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913–3918.

(180) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.

(181) Ireland, R. E.; Meissner, R. S. *J. Org. Chem.* **1991**, *56*, 4566–4568.

(182) Bailey, A. J.; Griffith, W. P.; Mostafa, S. I.; Sherwood, P. A. *Inorg. Chem.* **1993**, *32*, 268–271.

(183) Callant, P.; Dhaenens, L.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 155–161.

(184) (a) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538; (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549–7552.

(185) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

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: $[\alpha]^T_D$, 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 (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26) and benzene (δ 7.15) for ^{1}H, and chloroform (δ 77.0) and benzene (δ 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.

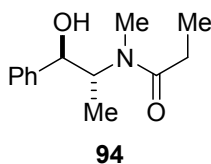Buffers were prepared according to the following procedures:

pH 7 phosphate buffer: KH_2PO_4 (6.8 g), NaOH (1.16 g), H_2O (1000 ml)

pH 8.6 carbonate buffer: $NaHCO_3$ (42 g), Na_2CO_3 (0.53 g), H_2O (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**

94

N-**((1R,2R)-2-Hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-propionamide** (**94**). To a solution of (1*R*,2*R*)-(–)-pseudoephedrine (50.0 g, 302 mmol, 1.00 equiv) in CH_2Cl_2 (540 ml) at room temperature was added Et_3N (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 $NaHCO_3$ (400 ml), 1.0 M aqueous HCl (2 × 400 ml) and brine (400 ml). The organic layer was dried over anhydrous Na_2SO_4 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.

^{1}H NMR (300 MHz, C_6D_6) δ 7.45–6.95 (m, 5 H), 4.83 (br s, 1 H), 4.51 (t, 1 H, *J* = 7.2 Hz), 4.20–4.00 (m, 2 H), 3.75–3.60 (m, 1 H), 2.77 (s, 3 H), 2.40 (m, 2 H), 2.06 (s, 3 H), 1.73 (m, 2 H), 1.22 (t, 3 H, *J* = 7.3 Hz), 1.10–0.90 (m, 6 H), 0.53 (d, 3 H, *J* = 6.7 Hz).

These spectral characteristics were identical to those previously reported.[186]

OH Me Me
|
Ph⠀⠀N
⠀⠀⠀⠀⠀
Me O

95
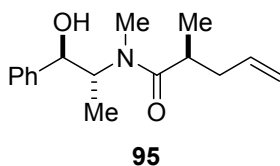
(2*S*)-2-Methyl-pent-4-enoic acid ((1*R*,2*R*)-2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide (95). To an ice-cooled suspension of flame-dried lithium chloride (17.3 g, 407 mmol, 6.00 equiv) in THF (80 ml) was added *i*Pr$_2$NH (21.5 ml, 152 mmol, 2.25 equiv) followed by *n*BuLi (2.28 M in hexane, 62.0 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.

(186) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

¹H NMR (200 MHz, CDCl₃) δ 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
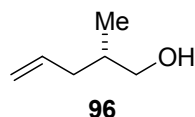
(2*S*)-2-Methyl-pent-4-en-1-ol (96). To a solution of *i*Pr₂NH (20.1 ml, 142 mmol, 4.20 equiv) in THF (100 ml) at 0 °C was added *n*BuLi (2.28 M in hexane, 59.5 ml, 136 mmol, 4.00 equiv) and the resulting yellow solution was warmed to room temperature for 10 min before being recooled to 0 °C. Ammonia-borane 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 Na₂SO₄, 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 Na₂SO₄, filtered, and concentrated under reduced pressure (40 °C at 180 mbar) to give (2*S*)-methyl-pent-4-en-1-ol (**96**) which was used without further purification.

¹H NMR (200 MHz, CDCl₃) δ 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]

97

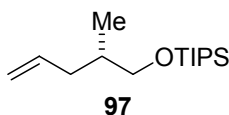**(2*S*)-Triisopropyl-(2-methyl-pent-4-enyloxy)-silane** (**97**). To a solution of alcohol **96** (3.39 g, 33.9 mmol, 1.00 equiv) in dry DMF (20 ml) at 0 °C was added imidazole (5.80 g, 84.7 mmol, 2.50 equiv) followed by TIPSCl (8.60 ml, 40.7 mmol, 1.20 equiv) and DMAP (414 mg, 3.39 mmol, 10.0 mol%). The cloudy mixture was stirred for 1 h at room temperature and then poured onto H₂O (30 ml). The layers were separated and the aqueous phase was extracted with pentane (3 × 50 ml). The combined organic solutions were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give silyl ether **97** which was used without further purification.

¹H NMR (300 MHz, CDCl₃) δ 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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(187) Lin, N.-H.; Overmann, L. E.; Rabinowity, M. H.; Robinson, L. A.; Sharp, J. M.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062.

98
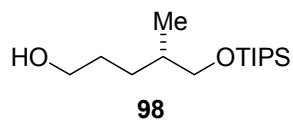
(4*S*)-4-Methyl-5-triisopropylsilanyloxy-pentan-1-ol (**98**). To olefin **97** (8.92 g, 34.8 mmol, 1.00 equiv) in THF (280 ml) was added 9-BBN (0.50 M in THF, 0.14 l, 70 mmol, 2.0 equiv) over 20 min. The clear, colorless solution was stirred for 6 h at ambient temperature and then cooled to 0 °C, whereupon 2.0 M aqueous NaOH (70 ml) and aqueous H_2O_2 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 Na_2SO_4, 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, $CDCl_3$) 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).

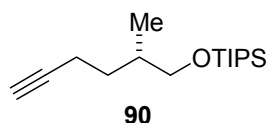These spectral characteristics were identical to those previously reported.[33c]

90

(2*S*)-Triisopropyl-(2-methyl-hex-5-ynyloxy)-silane (**90**). To a solution of alcohol **98** (7.15 g, 26.0 mmol, 1.00 equiv) in CH_2Cl_2 (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 CH_2Cl_2 (3 × 150 ml). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, 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 K_2CO_3 (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 $NaHCO_3$. The aqueous layer was extracted with hexane (3 × 200 ml), washed with brine, dried over anhydrous Na_2SO_4, 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: $[\alpha]^{22}_D$ (*c* 0.96, $CHCl_3$) = –0.2°.

¹H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{13}H_{25}OSi$ [M–C_3H_7]$^+$, 225.1675; found, 225.1665.
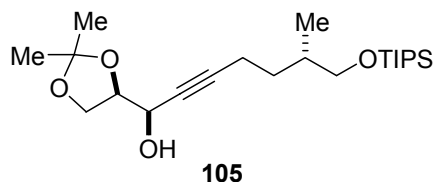
(1R,6S)-1-((4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-6-methyl-7-triisopropyl-silanyloxy-hept-2-yn-1-ol (105). $Zn(OTf)_2$ (2.23 g, 6.14 mmol, 1.10 equiv) and (–)-*N*-methyl ephedrine (1.10 g, 6.14 mmol, 1.10 equiv) were suspended in anhydrous toluene (15 ml) and purged with N_2 for 15 min. Et_3N (0.940 ml, 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 NH_4Cl (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 Na_2SO_4, 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 ^{1}H NMR by integration of the signals at 4.28 and 4.48 ppm, respectively) as a clear, colorless oil.

R$_f$ = 0.52 (hexane/EtOAc 2:1).

Optical Rotation: $[\alpha]^{27}_D$ (*c* 1.00, $CHCl_3$) = +12.4°.

^{1}H NMR (300 MHz, $CDCl_3$) 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$_3$) δ 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) ν 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.
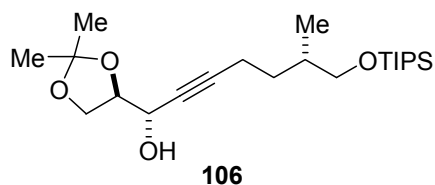
(1*S*,6*S*)-1-((4*R*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-6-methyl-7-triisopropyl-silanyloxy-hept-2-yn-1-ol (106).

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

^{1}H NMR (300 MHz, CDCl$_3$) δ 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).
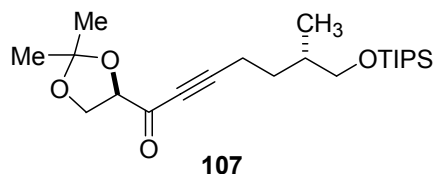
(6S)-1-((4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-6-methyl-7-triisopropyl-silanyloxy-hept-2-yn-1-one (107). A mixture of propargylic alcohol **105** (170 mg, 0.488 mmol, 1.00 equiv), 4 Å molecular sieves (250 mg) and NMO (86.0 mg, 0.732 mmol, 1.50 equiv) in anhydrous CH_2Cl_2 (1 ml) was stirred at room temperature 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 $C_{22}H_{40}O_4SiNa$ [M+Na]$^+$, 419.2594; found, 419.2591.
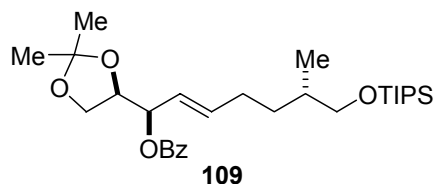
109

(1*R*,6*S*)-Benzoic acid 1-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-6-methyl-7-triisopropylsilanyloxy-hept-2-enyl 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 LiAlH$_4$ (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 CH$_2$Cl$_2$ (40 ml) were added successively Et$_3$N (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 NaHCO$_3$ (40 ml). The aqueous layer was extracted with diethyl ether (3 × 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 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]^{22}$_D$ (*c* 1.00, CHCl$_3$) = +10.4°.

¹H NMR (300 MHz, CDCl₃) δ 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).

¹³C NMR (75 MHz, CDCl₃) δ 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) ν 2942, 2866, 1723, 1462, 1452, 1381, 1370, 1315, 1269, 1215, 1155, 1110, 1070, 1026, 972, 882, 851, 794, 711, 682 cm⁻¹.

Anal. Calcd for $C_{29}H_{48}O_5Si$: C, 69.00; H, 9.58. Found: C, 69.17; H, 9.43.

HRMS (MALDI) calcd for $C_{29}H_{48}O_5SiNa$ [M+Na]⁺, 527.3169; found, 527.3164.

111
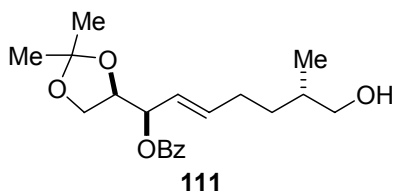
(1*R*,6*S*)-Benzoic acid 1-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-7-hydroxy-6-methyl-hept-2-enyl ester (111). To an ice-cooled solution of silyl ether **109** (1.87 g, 3.70 mmol, 1.00 equiv) in dry THF (40 ml) was added TBAF (1.0 M in THF, 4.1 ml, 4.1 mmol, 1.1 equiv). The solution was stirred at 0 °C for 12 h, then at ambient temperature for another 12 h. Saturated, aqueous NaHCO₃ (40 ml) was added and 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 2:1) gave alcohol **111** (1.24 g, 96% yield) as clear, colorless oil.

R$_f$ = 0.68 (hexane/EtOAc 1:1).

Optical Rotation: $[\alpha]^{22}_D$ (*c* 0.98, CHCl$_3$) = +15.6°.

^{1}H NMR (300 MHz, CDCl$_3$) δ 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).

^{13}C NMR (75 MHz, CDCl$_3$) δ 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.

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

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

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

112
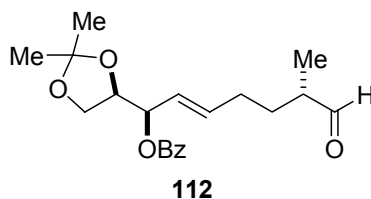
(1*R*,6*S*)-Benzoic acid 1-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-6-methyl-7-oxo-hept-2-enyl ester (**112**). To a solution of alcohol **111** (700 mg, 2.01 mmol, 1.00 equiv) in anhydrous CH$_2$Cl$_2$ were added 4 Å molecular sieves (1.00 g) and NMO (353 mg,

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 (hexane/EtOAc 2:1).

Optical Rotation: $[\alpha]^{25}_D$ (*c* 1.03, CHCl$_3$) = +29.3°.

^{1}H NMR (300 MHz, C$_6$D$_6$) δ 9.19 (d, 1 H, *J* = 1.6 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 Hz), 5.44 (ddt, 1 H, *J* = 15.4, 7.6, 1.4 Hz), 4.17 (ddd, 1 H, *J* = 6.2, 6.2, 6.2 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 Hz).

^{13}C NMR (75 MHz, CDCl$_3$) δ 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) ν 2985, 2934, 1720, 1452, 1372, 1315, 1269, 1215, 1177, 1156, 1112, 1069, 1026, 972, 849, 713 cm^{-1}.

Anal. Calcd for C$_{20}$H$_{26}$O$_5$: C, 69.34; H, 7.56. Found: C, 69.29; H, 7.60.

HRMS (MALDI) calcd for C$_{20}$H$_{26}$O$_5$Na [M+Na]$^+$, 369.1678; found, 369.1672.

5.2.1.2. Synthesis of Methyl Ketone **129**

11
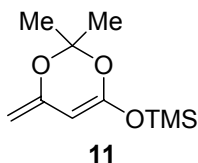
(2,2-Dimethyl-6-methylene-6*H*-[1,3]dioxin-4-yloxy)-trimethyl-silane (**11**).[188] To a solution of *i*Pr$_2$NH (6.70 ml, 48.0 mmol, 1.09 equiv) in anhydrous THF (30 ml) at 0 °C was added *n*BuLi (1.32 M in hexane, 36.4 ml, 48.0 mmol, 1.09 equiv) over 15 min. The clear, colorless solution was stirred 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}H NMR (300 MHz, CDCl$_3$) δ 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}C NMR (75 MHz, CDCl$_3$) δ 153.1, 151.5, 102.3, 84.9, 76.5, 24.5, 0.3.

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(188) The experimental conditions reported herein lead to improved yields compared to the conditions reported in ref. 20b.

116
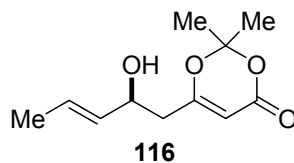
6-((2S,3E)-2-Hydroxy-pent-3-enyl)-2,2-dimethyl-[1,3]dioxin-4-one   (**116**).   A

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 nBu$_4$NPh$_3$SiF$_2$ (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 NaHCO$_3$. 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

Na$_2$SO$_4$, 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.

R$_f$ = 0.17 (hexane/Et$_2$O 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]

118
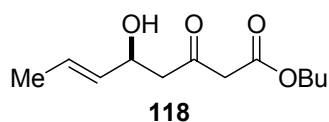
(5*S*,6*E*)-5-Hydroxy-3-oxo-oct-6-enoic acid butyl ester (**118**). Dioxenone **116** (4.70 g, 22.1 mmol, 1.00 equiv) was dissolved in anhydrous 1-butanol (1000 ml) and the resulting solution was degassed by passing an argon stream through for 1 h. After heating to reflux for 1 h, the solution was allowed 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$_f$ = 0.33 (hexane/EtOAc 2:1).

Optical Rotation: [α]^{38}$_D$ (*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).

¹³C NMR (75 MHz, CDCl₃) δ 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) ν 3446, 2962, 2937, 2876, 1742, 1715, 1651, 1454, 1410, 1384, 1317, 1274, 1152, 1062, 1035, 967 cm⁻¹.

Anal. Calcd for $C_{12}H_{20}O_4Si$: C, 63.14; H, 8.83. Found: C, 62.98; H, 8.73.

HRMS (MALDI) calcd for $C_{12}H_{20}O_4Na$ [M+Na]⁺, 251.1259; found, 251.1254.

119
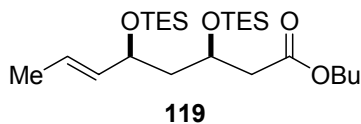
(3R,5S,6E)-3,5-Bis-triethylsilanyloxy-oct-6-enoic acid butyl ester (119). To a solution of MeOH (22.5 ml) in THF (110 ml) was added triethylborane (1.0 M in THF, 18 ml, 18 mmol, 1.1 equiv) dropwise under ice cooling. After stirring for 1 h at ambient temperature, the solution was cooled to –78 °C and 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 NaBH₄ (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 NH₄Cl (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 × 150 ml). The combined organic extracts were washed with brine (200 ml), dried over anhydrous Na₂SO₄ and filtered. Concentration under reduced pressure gave a colorless oil which was azeotroped with MeOH (3 × 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 H_2O (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 Na_2SO_4, filtered, and concentrated under reduced pressure to afford bis-silyl ether **119** as a single diastereoisomer (d.r. > 95:5 by ^{1}H NMR spectroscopy). A small amount was purified by flash chromatography (hexane/EtOAc 19:1) for characterization purposes.

R$_f$ = 0.53 (hexane/EtOAc 9:1).

Optical Rotation: $[\alpha]^{22}_D$ (*c* 1.1, $CHCl_3$) = −13.0°.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (dq, 1 H, *J* = 15.3, 6.3 Hz), 5.38 (ddq, 1 H, *J* = 15.3, 7.2, 1.4 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 Hz), 2.41 (dd, 1 H, *J* = 14.7, 7.4 Hz), 1.80–1.68 (m, 1 H), 1.65 (dd, 3 H, *J* = 6.3, 1.2 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).

^{13}C NMR (75 MHz, $CDCl_3$) δ 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) ν 2959, 2914, 2877, 1739, 1459, 1415, 1379, 1312, 1240, 1167, 1085, 1005, 967, 742 cm^{-1}.

HRMS (MALDI) calcd for $C_{24}H_{50}O_4Si_2Na$ [M+Na]$^+$, 481.3145; found, 481.3143.

120
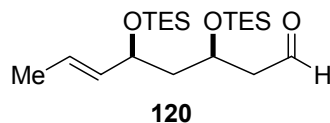
(3*R*,5*S*,6*E*)-3,5-Bis-triethylsilanyloxy-oct-6-enal (**120**). To the unpurified ester **119** (16.2 mmol, 1.00 equiv) in toluene (140 ml) at –78 °C was added DIBAL–H (1.5 M in toluene, 13 ml, 19 mmol, 1.2 equiv) dropwise over 20 min. The solution was stirred at –78 °C for 30 min. Excess reducing 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 Na_2SO_4, 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 (hexane/EtOAc 9:1).

Optical Rotation: $[\alpha]^{22}_D$ (*c* 0.28, CHCl$_3$) = –3.2°.

^{1}H NMR (300 MHz, CDCl$_3$) δ 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 (ddd, 1 H, *J* = 15.7, 4.7, 2.0 Hz), 2.51 (ddd, 1 H, *J* = 15.7, 6.6, 3.0 Hz), 1.84 (ddd, 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}C NMR (75 MHz, CDCl$_3$) δ 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 $C_{20}H_{42}O_3Na$ [M+Na]$^+$, 409.2570; found, 409.2565.

121
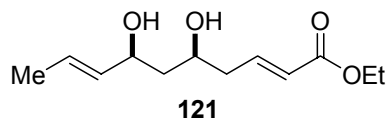
(2*E*,5*S*,7*S*,8*E*)-5,7-Dihydroxy-deca-2,8-dienoic acid ethyl ester (**121**). To a suspension of flame-dried lithium chloride (560 mg, 13.0 mmol, 1.20 equiv) in dry acetonitrile (100 ml) was added triethylphosphonoacetate (2.62 ml, 13.0 mmol, 1.20 equiv) and DBU (1.63 ml, 10.9 mmol, 1.00 equiv). A solution of aldehyde **120** (4.20 g, 10.9 mmol, 1.00 equiv) in CH$_3$CN (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 KH$_2$PO$_4$ (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 Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford the intermediate ester (R_f = 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 NaHCO$_3$. 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 Na$_2$SO$_4$, 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 (hexane/EtOAc 1:1).

**Optical Rotation**: $[\alpha]^{29}_D$ (*c* 1.06, CHCl$_3$) = –12.2°.

¹H NMR (300 MHz, CDCl$_3$) δ 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).

¹³C NMR (75 MHz, CDCl$_3$) δ 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) ν 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.

HRMS (MALDI) calcd for C$_{12}$H$_{20}$O$_4$Na [M+Na]$^+$, 251.1259; found, 251.1252.

122
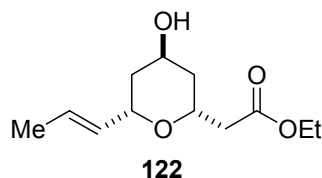
[(2*R*,4*S*,6*S*)-4-Hydroxy-6-((*E*)-propenyl)-tetrahydro-pyran-2-yl]-acetic acid ethyl ester (122). To an ice-cooled solution of diol **121** (1.80 g, 8.10 mmol, 1.00 equiv) in THF (160 ml) was added *t*BuOK (91.0 mg, 0.810 mmol, 10.0 mol%) in one portion. After stirring at 0 °C for 30 min, the reaction 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_2SO_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, CHCl$_3$) = –4.3°.

^{1}H NMR (300 MHz, CDCl$_3$) δ 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$_3$) δ 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) ν 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 $C_{12}H_{20}O_4Na$ [M+Na]$^+$, 251.1259; found, 251.1254.

124
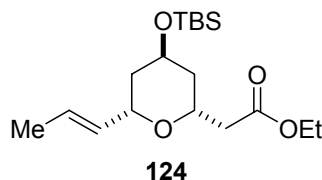
[(2*R*,4*S*,6*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-((*E*)-propenyl)-tetrahydro-pyran-2-yl]-acetic acid ethyl ester (124).

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, H_2O (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 Na_2SO_4, 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 Na_2SO_4, 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 H_2O (10 ml) and extracted with diethyl ether (3 × 10 ml). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, 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 *t*BuOK (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 Na_2SO_4, 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: $[\alpha]^{22}_D$ (*c* 1.05, $CHCl_3$) = −1.4°.

^{1}H NMR (300 MHz, $CDCl_3$) 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).

^{13}C NMR (75 MHz, $CDCl_3$) 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, 1472, 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.

126
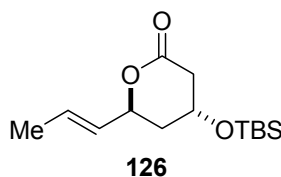
(4*R*,6*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-(*E*)-propenyl-tetrahydro-pyran-2-one (**126**). To a solution of MeOH (8 ml) in THF (40 ml) was added triethylborane (1.0 M in THF, 4.4 ml, 4.4 mmol, 1.1 equiv) dropwise under ice cooling. After stirring for 1 h at ambient temperature, the solution 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 Na_2SO_4, 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), TBSCl (731 mg, 4.85 mmol, 1.20 equiv) and DMAP (50.0 mg, 0.404 mmol, 10.0 mol%). After stirring for 2 h, H_2O (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 Na_2SO_4, 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.

R$_f$ = 0.66 (hexane/EtOAc 2:1).

Optical Rotation: $[\alpha]^{21}_D$ (*c* 0.985, $CHCl_3$) = +25.0°.

^{1}H NMR (300 MHz, $CDCl_3$) 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).

^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{10}H_{17}O_3Si$ $[M–C_4H_9]^+$, 213.0947; found, 213.0939.

OTBS

Me ... O ... OEt

129
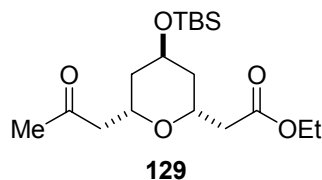
[(2R,4R,6S)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-(2-oxo-propyl)-tetrahydro-pyran-2-yl]-acetic acid ethyl ester (129). To a solution of olefin **124** (1.61 g, 4.70 mmol, 1.00 equiv) in DMF/H_2O 7:1 (64 ml) was added $PdCl_2$ (170 mg, 0.900 mmol, 20.0 mol%) and CuCl (560 mg, 5.60 mmol, 1.20 equiv). 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 H_2O (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 Na_2SO_4, 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 (hexane/EtOAc 4:1).

Optical Rotation: $[\alpha]^{26}_D$ (*c* 0.99, $CHCl_3$) = –0.2°.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30–4.20 (m, 2 H), 4.19–4.15 (m, 1 H), 4.11 (q, 2 H, *J* = 7.1 Hz), 2.56 (dd, 1 H, *J* = 14.9, 8.5 Hz), 2.45 (dd, 1 H, *J* = 14.8, 8.2 Hz), 2.35 (dd, 1 H, *J* = 14.9, 4.7 Hz), 2.32 (dd, 1 H, *J* = 14.8, 5.4 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 Hz), 0.9 (s, 9 H), 0.05 (s, 6 H).
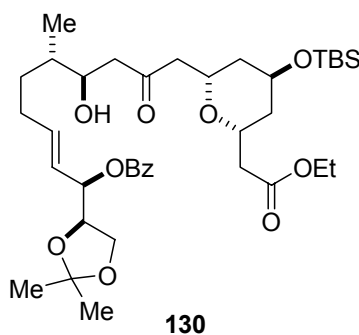
^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 171.0, 68.8, 64.5, 60.3, 50.0, 41.4, 38.8, 38.5, 30.5, 30.4, 25.7, 18.0, 14.1, –5.0.

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 $C_{18}H_{34}O_5Si$: C, 60.30; H, 9.56. Found: C, 60.34; H, 9.50.

HRMS (MALDI) calcd for $C_{18}H_{34}O_5SiNa$ [M+Na]$^+$, 381.2073; found, 381.2068.

5.2.1.3. On the Way to the Macrocycle

130

{(2R,4R,6S)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-[(4R,5S,8E,10R)-10-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-4,10-dihydroxy-5-methyl-2-oxo-dec-8-enyl]-tetra-hydro-pyran-2-yl}-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 Et_3N (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 H_2O_2 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 Na_2SO_4, 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 *Hünig*'s base (19 μl, 0.11 mmol, 1.5 equiv). The solution was cooled to –78 °C and nBu$_2$BOTf (1.0 M in CH$_2$Cl$_2$, 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% H$_2$O$_2$/MeOH 1:2 (0.3 ml) and stirred at room temperature for 12 h. The mixture was diluted with H$_2$O (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 Na$_2$SO$_4$, 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 ^{1}H NMR spectroscopy).

R$_f$ = 0.30 (hexane/EtOAc 2:1).

Optical Rotation: $[\alpha]^{22}_{\text{D}}$ (*c* 1.12, CHCl$_3$) = +16.0°.

^{1}H NMR (500 MHz, C$_6$D$_6$) 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 Hz), 5.87 (t, 1 H, *J* = 7.33 Hz), 5.65 (ddt, 1 H, *J* = 15.5, 7.6, 1.5 Hz), 4.56–4.49 (m, 2 H), 4.32 (ddd, 1 H, *J* = 6.4, 6.4, 6.4 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 Hz), 2.54 (dd, 1 H, *J* = 15.1, 7.8 Hz), 2.50 (dd, 1 H, *J* = 15.0, 8.0 Hz), 2.45 (dd, 1 H, *J* = 17.0, 9.7 Hz), 2.36 (dd, 1 H, *J* = 17.0, 2.5 Hz), 2,27 (dd, 1 H, *J* = 15.1, 5.48 Hz), 2.16 (dd, 1 H, *J* = 15.0, 4.9 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$_3$) δ 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) ν 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.
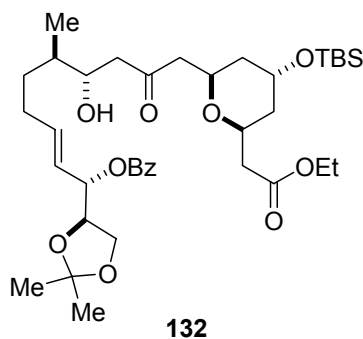
{(2*S*,4*S*,6*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-[(4*S*,5*R*,8*E*,10*S*)-10-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-4,10-dihydroxy-5-methyl-2-oxo-dec-8-enyl]-tetra-hydro-pyran-2-yl}-acetic acid methyl ester (132).

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

^{1}H NMR (300 MHz, CDCl$_3$) δ 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).
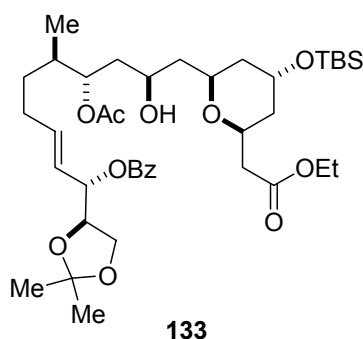
(1*S*,2*E*,6*R*,7*S*,9*R*)-Benzoic acid 7-acetoxy-10-[(2*S*,4*S*,6*S*)-4-(*tert*-butyl-dimethyl-silanyloxy)-6-ethoxycarbonylmethyl-tetrahydro-pyran-2-yl]-1-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-9-hydroxy-6-methyl-dec-2-enyl ester (133). To a solution of hydroxy ketone **132** (480 mg, 0.681 mmol, 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 SmI$_2$ (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 NaHCO$_3$ (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 Na$_2$SO$_4$, 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.

R$_f$ = 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).

137
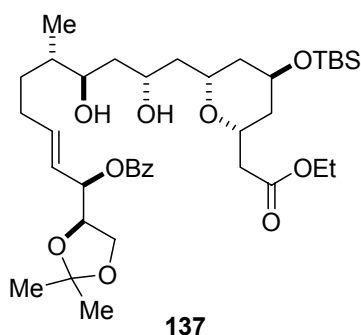
(1*R*,2*E*,6*S*,7*R*,9*R*)-Benzoic acid 10-[(2*R*,4*R*,6*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-6-ethoxycarbonylmethyl-tetrahydro-pyran-2-yl]-1-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-7,9-dihydroxy-6-methyl-dec-2-enyl ester (137). A solution of tetramethylammonium triacetoxyborohydride (1.36 g, 5.18 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**: $[\alpha]^{27}_D$ (*c* 1.07, CHCl$_3$) = +3.8°.

^{1}H NMR (500 MHz, C$_6$D$_6$) δ 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$_3$) δ 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) ν 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.

138
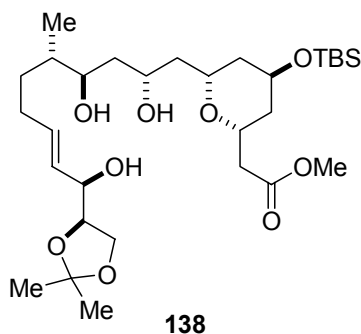
{(2*R*,4*R*,6*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-[(2*R*,4*R*,5*S*,8*E*,10*R*)-10-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2,4,10-trihydroxy-5-methyl-dec-8-enyl]-tetrahydro-pyran-2-yl}-acetic acid methyl ester (138). To a solution of benzoate **137** (400 mg, 0.566 mmol, 1.00 equiv) in anhydrous 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 CH_2Cl_2 (20 ml) and washed with 1.0 M aqueous HCl (20 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 20 ml). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, 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°.

¹H NMR (500 MHz, C$_6$D$_6$) 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$_3$) δ 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) ν 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.
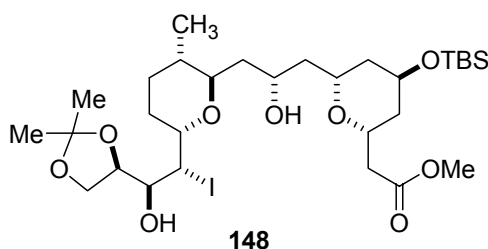
[(2*R*,4*R*,6*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-((2*S*)-3-{(2*R*,3*S*,6*S*)-6-[(1*S*,2*S*)-2-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-hydroxy-1-iodo-ethyl]-3-methyl-tetra-hydro-pyran-2-yl}-2-hydroxy-propyl)-tetrahydro-pyran-2-yl]-acetic acid methyl ester (148). To a solution of allylic alcohol **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 × 50 ml). The combined organic solutions were washed with brine, dried

over anhydrous Na_2SO_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).
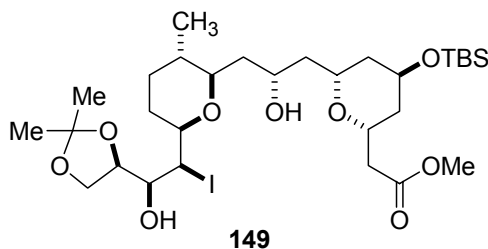
R$_f$ = 0.32 (hexane/EtOAc 1:1).

Optical Rotation: $[\alpha]^{27}_D$ (*c* 0.61, $CHCl_3$) = +10.0°.

^{1}H NMR (500 MHz, C_6D_6) δ 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, $CDCl_3$) δ 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) ν 3497, 2929, 2859, 1742, 1460, 1438, 1370, 1253, 1216, 1160, 1060, 1039, 1003, 838, 772 cm^{-1}.

HRMS (MALDI) calcd for $C_{30}H_{55}IO_9SiNa$ [M+Na]$^+$, 737.2558; found, 737.2550.

[(2*R*,4*R*,6*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-((2*S*)-3-{(2*R*,3*S*,6*R*)-6-[(1*R*,2*S*)-2-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-hydroxy-1-iodo-ethyl]-3-methyl-tetra-hydro-pyran-2-yl}-2-hydroxy-propyl)-tetrahydro-pyran-2-yl]-acetic acid methyl ester (149).

R$_f$ =0.24 (hexane/EtOAc 1:1).

Optical Rotation: $[\alpha]^{24}_D$ (*c* 0.94, CHCl$_3$) = +17.7°.

¹H NMR (500 MHz, C$_6$D$_6$) 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.
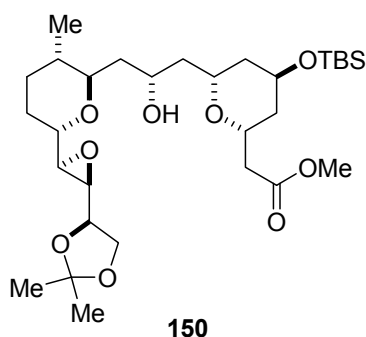
[(2R,4R,6R)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-((2S)-3-{(2R,3S,6S)-6-[(2S,3S)-3-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-oxiranyl]-3-methyl-tetrahydro-pyran-2-yl}-2-hydroxy-propyl)-tetrahydro-pyran-2-yl]-acetic acid methyl ester (150). To a solution of iodoalcohol **148** (5.0 mg, 7.0 µmol, 1.0 equiv) in MeOH (1 ml) at room temperature was added K_2CO_3 (4.8 mg, 35 µmol, 5.0 equiv) in one portion. The solution was stirred at ambient temperature for 15 h, diluted with CH_2Cl_2 (5 ml) and washed with pH 7 phosphate buffer (5 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 ml). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, 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).

^{1}H NMR (300 MHz, CDCl$_3$) 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).
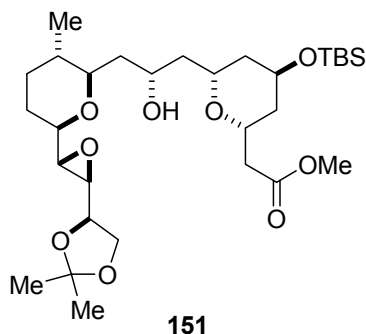
[(2R,4R,6R)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-((2S)-3-{(2R,3S,6R)-6-[(2R,3S)-3-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-oxiranyl]-3-methyl-tetrahydro-pyran-2-yl}-2-hydroxy-propyl)-tetrahydro-pyran-2-yl]-acetic acid methyl ester (151). To a solution of iodoalcohol **149** (25.0 mg, 35.0 μmol, 1.00 equiv) in MeOH (2 ml) at room temperature was added K_2CO_3 (24.0 mg, 175 μmol, 5.00 equiv) in one portion. The solution was stirred at ambient temperature for 15 h, diluted with CH_2Cl_2 (5 ml) and washed with pH 7 phosphate buffer (5 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 ml). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, 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.

R$_f$ =0.19 (hexane/EtOAc 1:1).

Optical Rotation: $[\alpha]^{23}_D$ (*c* 0.60, CHCl$_3$) = +15.9°.

^{1}H NMR (500 MHz, C$_6$D$_6$) 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_6D_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 $C_{30}H_{54}O_9SiNa$ [M+Na]$^+$, 609.3434; found, 609.3429.
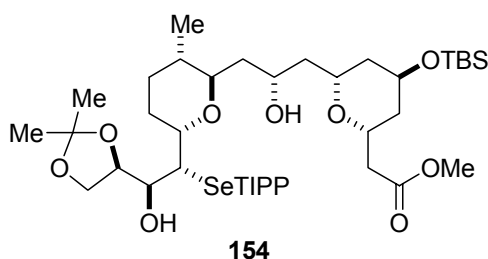
[(2*R*,4*R*,6*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-((2*S*)-3-{(2*R*,3*S*,6*S*)-6-[(1*R*,2*S*)-2-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-hydroxy-1-(2,4,6-triisopropyl-phenyl-selanyl)-ethyl]-3-methyl-tetrahydro-pyran-2-yl}-2-hydroxy-propyl)-tetrahydro-pyran-2-yl]-acetic acid methyl ester (154). To a solution of (TIPPSe)$_2$ (20.1 mg, 35.7 µmol, 2.10 equiv) in dry CH_2Cl_2 (0.3 ml) was added bromine (0.113 M in CH_2Cl_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_2Cl_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 $NaHCO_3$ (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 Na_2SO_4, 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 ^{1}H NMR spectroscopy by integration of the signals at 3.45 and 3.48 ppm, respectively).

R$_f$ = 0.29 (hexane/EtOAc 3:1).

Optical Rotation: $[\alpha]^{23}_D$ (*c* 0.5, $CHCl_3$) = –1.6°.

^{1}H NMR (500 MHz, C_6D_6) δ 7.09 (s, 2 H), 4.93 (q, 1 H, *J* = 6.7 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 Hz), 2.47 (dd, 1 H, *J* = 15.0, 7.5 Hz), 2.17 (dd, 1 H, *J* = 15.0, 5.8 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 (d, 3 H, *J* = 6.4 Hz), 0.00 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 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) ν 2957, 2928, 2870, 1742, 1462, 1436, 1382, 1362, 1309, 1253, 1213, 1159, 1098, 1062, 1038, 1002, 913, 875, 837, 803, 774, 742 cm^{-1}.

HRMS (MALDI) calcd for $C_{45}H_{78}O_9SeSiNa$ [M+Na]$^+$, 893.4477; found, 893.4464.

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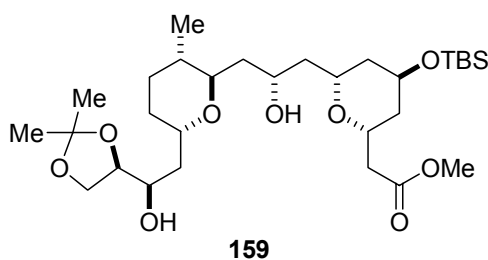
[(2*R*,4*R*,6*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-((2*S*)-3-{(2*R*,3*S*,6*S*)-6-[(2*R*)-2-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-hydroxy-ethyl]-3-methyl-tetrahydro-pyran-2-yl}-2-hydroxy-propyl)-tetrahydro-pyran-2-yl]-acetic acid methyl ester (159).

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.
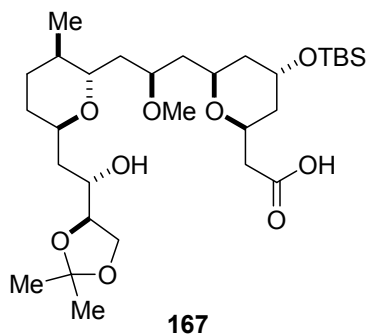
R$_f$ = 0.38 (hexane/EtOAc 1:1).

Optical Rotation: $[\alpha]^{22}_D$ (c 0.72, CHCl$_3$) = +23.5°.

^{1}H 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).

^{13}C 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$_9$SiNa [M+Na]$^+$, 611.3591; found, 611.3601.

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[(2*S*,4*S*,6*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-((2*R*)-3-{(2*S*,3*R*,6*R*)-6-[(2*S*)-2-((4*R*)-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$_6$D$_6$) δ 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$_9$SiNa [M+Na]$^+$, 611.3591; found, 611.3586.
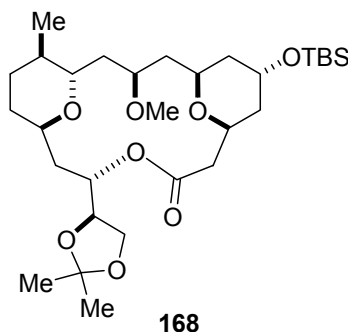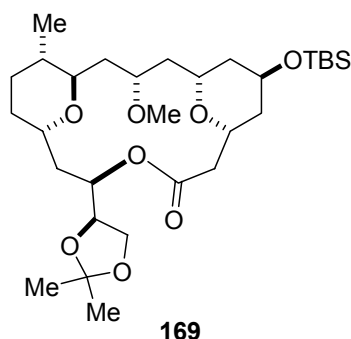
(1*S*,3*R*,5*S*,7*S*,9*S*,13*S*,15*R*,18*R*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-13-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-3-methoxy-18-methyl-12,19,20-trioxa-tricyclo [13.3.1.1^{5,9}]icosan-11-one (**168**). To an ice-cooled solution of acid **167** (4.5 mg, 7.6 µmol, 1.0 equiv) in THF (0.8 ml) was added Et$_3$N (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/Et$_2$O 1:1 as eluant). The filtrate was concentrated under reduced pressure. Purification by flash chromatography (hexane/Et$_2$O 1:1) afforded lactone **168** (3.5 mg, 80% yield) as a clear, colorless oil.

R$_f$ = 0.40 (hexane/EtOAc 2:1).

^{1}H NMR (300 MHz, C$_6$D$_6$) δ 5.44–5.38 (m, 1 H), 4.74 (dt, 1 H, *J* = 6.8, 2.5 Hz), 4.34–4.22 (m, 1 H), 4.16 (d, 1 H, *J* = 11.2 Hz), 3.96–3.71 (m, 5 H), 3.67 (dd, 1 H, *J* = 8.7, 6.2 Hz), 3.42 (s, 3 H), 2.49 (t, 1 H, *J* = 13.0 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).

HRMS (MALDI) calcd for C$_{30}$H$_{54}$O$_8$SiNa [M+Na]$^+$, 593.3485; found, 593.3486.

169

(1*R*,3*S*,5*R*,7*R*,9*R*,13*R*,15*S*,18*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-13-((4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-3-methoxy-18-methyl-12,19,20-trioxa-tricyclo [13.3.1.1^{5,9}]icosan-11-one (169). 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 NaHSO$_4$ (4 ml). The aqueous layer was extracted with CH$_2$Cl$_2$ (6 × 4 ml), dried over anhydrous Na$_2$SO$_4$, 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 Et$_3$N (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 CH_2Cl_2 (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 H_2O (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 Na_2SO_4, 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**).

R_f = 0.34 (hexane/EtOAc 2:1).

Optical Rotation: $[\alpha]^{28}_D$ (*c* 0.21, $CHCl_3$) = +58.7°.

¹H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{30}H_{54}O_8SiNa$ [M+Na]⁺, 593.3486; found, 593.3491.

5.2.1.4. Completion of the Macrolide Moiety **45**

171
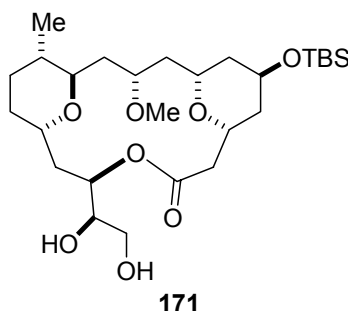
(1*R*,3*S*,5*R*,7*R*,9*R*,13*R*,15*S*,18*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-13-((1*R*)-1,2-dihydroxy-ethyl)-3-methoxy-18-methyl-12,19,20-trioxa-tricyclo[13.3.1.1^{5,9}]icosan-11-one (171). A solution of acetonide **169** (4.0 mg, 7.0 µmol, 1.0 equiv) in AcOH/THF/H$_2$O 2:1:1 (1 ml) was heated to 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 NaHCO$_3$ (10 ml). The aqueous phase was extracted with CH$_2$Cl$_2$ (5 × 5 ml) and the combined organic solutions were washed with brine, dried over anhydrous Na$_2$SO$_4$, 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 (EtOAc).

Optical Rotation: [α]^{25}$_D$ (*c* 0.15, CHCl$_3$) = +42.9°.

^{1}H NMR (300 MHz, CDCl$_3$) δ 5.26–5.18 (m, 1 H), 4.22 (t, 1 H, *J* = 2.4 Hz), 4.19–4.08 (m, 1 H), 3.85 (dd, 1 H, *J* = 10.5, 0.6 Hz), 3.80–3.71 (m, 2 H), 3.62–3.43 (m, 4 H), 3.35 (s, 3 H), 2.68 (t, 1 H, *J* = 6.6 Hz), 2.58 (dd, 1 H, *J* = 12.0, 3.6 Hz), 2.44–2.31 (m, 2 H), 2.26–2.22 (m, 1 H), 2.02–1.80 (m, 3 H), 1.72–1.23 (m, 11 H), 1.15 (d, 3 H, *J* = 7.1 Hz), 0.91 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 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.

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

HRMS (MALDI) calcd for C$_{27}$H$_{50}$O$_8$SiNa [M+Na]$^+$, 553.3172; found, 553.3167.
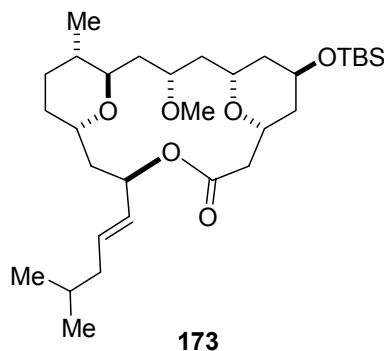
(1*R*,3*S*,5*R*,7*R*,9*R*,13*R*,15*S*,18*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-3-methoxy-18-methyl-13-((1*E*)-4-methyl-pent-1-enyl)-12,19,20-trioxa-tricyclo[13.3.1.1^{5,9}]icosan-11-one (**173**). To an ice-cooled solution of diol **171** (6.5 mg, 12 μmol, 1.0 equiv) in ethyl acetate (1 ml) was added Pb(OAc)$_4$ (8.0 mg, 18 μmol, 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 × 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 H_2O (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 Na_2SO_4 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.

R$_f$ = 0.24 (CH_2Cl_2/EtOAc 9:1).

Optical Rotation: $[\alpha]^{28}_D$ (*c* 0.225, $CHCl_3$) = +60.9°.

¹H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{31}H_{56}O_6SiNa$ [M+Na]⁺, 575.3744; found, 575.3752.

177
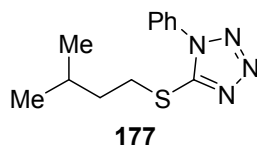
5-(3-Methyl-butylsulfanyl)-1-phenyl-1*H*-tetrazole (**177**). To a mixture of 3-methyl-butan-1-ol (**175**) (270 μl, 2.50 mmol, 1.00 equiv), triphenylphosphine (720 mg, 2.75 mmol, 1.10 equiv) and 2-phenyl-2*H*-tetrazole-5-thiol (**176**) (490 mg, 2.75 mmol, 1.10 equiv) in anhydrous THF (30 ml) was added 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-1*H*-tetrazole (**177**) (532 mg, 86% yield) as a colorless oil.
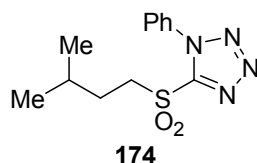
R$_f$ = 0.56 (hexane/EtOAc 2:1).

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 $C_{12}H_{17}N_4S$ [M+H]$^+$, 249.1174; found, 249.1161.

174

5-(3-Methyl-butane-1-sulfonyl)-1-phenyl-1*H*-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_2O. The layers were separated and the aqueous phase extracted with diethyl ether (3×50 ml). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_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).

¹H NMR (300 MHz, $CDCl_3$) δ 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).

¹³C NMR (75 MHz, $CDCl_3$) δ 153.3, 132.9, 131.3, 129.6, 125.0, 54.5, 30.2, 27.3, 22.1.

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

HRMS (MALDI) calcd for $C_{12}H_{16}N_4O_2SNa$ [M+Na]$^+$, 303.0892; found, 303.0892.
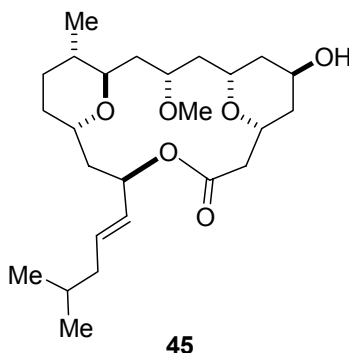
(1R,3S,5S,7R,9R,13R,15S,18S)-7-Hydroxy-3-methoxy-18-methyl-13-((1E)-4-methyl-pent-1-enyl)-12,19,20-trioxa-tricyclo[13.3.1.1^{5,9}]icosan-11-one (**45**). To a solution of silyl ether **173** (4.5 mg, 8.1 µmol, 1.0 equiv) in anhydrous THF (0.5 ml) was added TBAF (1.0 M in THF, 41 µl, 41 µmol, 5.0 equiv) 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 NH$_4$Cl (2 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (4 × 5 ml), washed with brine, dried over anhydrous Na$_2$SO$_4$ 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.

R$_f$ = 0.16 (hexane/EtOAc 1:1).

Optical Rotation: [α]^{22}$_D$ (*c* 0.175, EtO H) = +32.3°.

^{1}H NMR (500 MHz, C$_5$D$_5$N) δ 6.39 (d, 1 H, *J* = 3.4 Hz), 5.81 (ddt, 1 H, *J* = 14.9, 7.2, 0.8 Hz), 5.77 (dd, 1 H, *J* = 11.0, 6.9 Hz), 5.58 (ddt, 1 H, *J* = 15.4, 6.9, 1.3 Hz), 4.67 (dddd, 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),
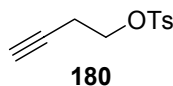
1.11 (d, 2 H, *J* = 7.1 Hz), 1.15–1.05 (m, 2 H), 0.82 (d, 3 H, *J* = 6.6 Hz), 0.81 (d, 3 H, *J* = 6.6 Hz).

^{13}C NMR (75 MHz, C_5D_5N) δ 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.

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

**HRMS** (MALDI) calcd for $C_{25}H_{42}O_6Na$ [M+Na]$^+$, 461.2879; found, 491.2889.

5.2.2. Synthesis of Methyl Ester 46

180

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 × 300 ml), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the known tosylate **180** which was used without further purification.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.80 (d, 2 H, *J* = 7.8 Hz), 7.39 (d, 2 H, *J* = 7.8 Hz), 4.10 (t, 2 H, *J* = 6.8 Hz), 2.56 (t, 2 H, *J* = 6.8 Hz), 2.45 (s, 3 H), 1.98 (s, 1 H).

These spectral characteristics were identical to those reported previously.[189]


181
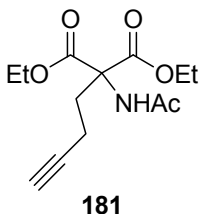
2-Acetylamino-2-but-3-ynyl-malonic acid diethyl ester (**181**). To a solution of diethyl acetamidomalonate (**179**) (10.0 g, 46.0 mmol, 1.00 equiv) in THF (70 ml) was added *t*BuOK (5.68 g, 50.6 mmol, 1.10 equiv) under vigorous stirring. The suspension was stirred for 2 h at 60 °C. Tosylate **180** 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_2SO_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.

¹H NMR (300 MHz, $CDCl_3$) δ 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.[189]

(189) Van Hest, J. C. M.; Kiick, K. L.; Tirrell, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 1282–1288.
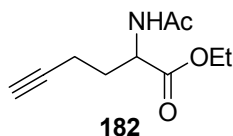
2-Acetylamino-hex-5-ynoic acid ethyl ester (**182**). To a solution of malonate **181** (5.25 g, 19.5 mmol, 1.00 equiv) in DMSO (15 ml) was added LiCl (2.07 g, 48.8 mmol, 2.50 equiv). The mixture was heated to 120 °C for 10 h. After cooling to room temperature, the solution was diluted with H_2O (100 ml) and extracted with diethyl ether (5 × 25 ml). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc) afforded ester **182** (3.20 g, 83% yield) as a colorless oil.
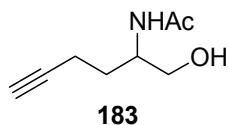
R_f = 0.50 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (br s, 1 H), 4.97–4.60 (m, 1 H), 4.18 (q, 2 H, J = 6.5 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 Hz), 1.94–1.84 (m, 1 H), 1.27 (t, 3 H, J = 6.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.0, 82.8, 69.3, 61.5, 51.6, 31.0, 23.0, 15.0, 14.2.

IR (thin film) ν 3290, 3069, 2983, 2938, 2119, 1739, 1658, 1548, 1446, 1375, 1298, 1213, 1191, 1134, 1095, 1027, 861 cm^{-1}.

HRMS (MALDI) calcd for $C_{10}H_{16}NO_3$ [M+H]$^+$, 198.1130; found, 198.1124.

183

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 $LiBH_4$ (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.
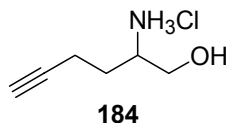
R_f = 0.30 (EtOAc/MeOH 92:8).

¹H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_8H_{13}NO_2$ [M]⁺, 155.0946; found, 155.0941.

184

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 (CH$_2$Cl$_2$/MeOH/NH$_4$OH conc. 75:22:3).

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

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

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


186
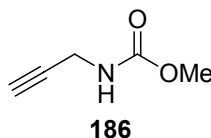
Prop-2-ynyl-carbamic acid methyl ester (**186**). To an ice-cooled solution of propargyl amine (**185**) (3.00 g, 54.5 mmol, 1.00 equiv) and Et$_3$N (8.04 ml, 57.2 mmol, 1.05 equiv) in CH$_2$Cl$_2$ (60 ml) was added methylchloroformate (4.40 ml, 57.2 mmol, 1.05 equiv) dropwise over 10 min. The solution 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$_2$Cl$_2$ (3 × 100 ml). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, 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 (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]

187
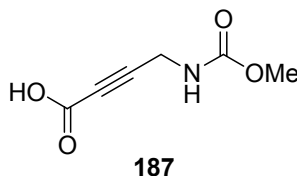
4-Methoxycarbonylamino-but-2-ynoic acid (**187**). To an ice-cooled solution of HMDS (2.45 ml, 11.8 mmol, 2.05 equiv) in dry THF (120 ml) was added *n*BuLi (2.28 M in hexane, 5.16 ml, 11.8 mmol, 2.05 equiv) dropwise over 20 min. The solution was stirred at ambient temperature for 10 min. After cooling 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. CO_2 (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 $NaHCO_3$ (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 $NaHCO_3$ (50 ml) and washed with CH_2Cl_2 (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 Na_2SO_4, filtered, and concentrated under reduced pressure, giving known acid **187** (720 mg, 80% yield) as brownish oil.

R$_f$ = 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]

190
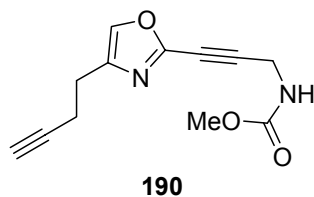
[3-(4-But-3-ynyl-oxazol-2-yl)-prop-2-ynyl]-carbamic acid methyl ester (**190**). A mixture of acid **187** (25.0 mg, 0.159 mmol, 1.00 equiv), hydrochloride **184** (28.1 mg, 0.188 mmol, 1.18 equiv), and DIPEA (82 µl, 0.48 mmol, 3.0 equiv) in CH$_2$Cl$_2$ was cooled to –10 °C. PyBrop (103 mg, 0.223 mmol, 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 (EtOAc/hexane 1:2).

¹H NMR (300 MHz, CDCl$_3$) δ 7.46 (s, 1 H), 4.96 (br s, 1 H), 4.23 (d, 2 H, J = 5.6 Hz), 3.71 (s, 3 H), 2.75 (t, 2 H, J = 6.7 Hz), 2.53 (dt, 2 H, J = 6.7, 2.4 Hz), 1.96 (t, 1 H, J = 2.4 Hz).

¹³C NMR (75 MHz, CDCl$_3$) δ 156.2, 145.4, 139.9, 135.5, 87.9, 82.8, 71.2, 69.1, 52.5, 31.2, 25.5, 17.7.

IR (thin film) ν 3259, 3128, 3053, 2926, 1715, 1590, 1548, 1531, 1464, 1436, 1415, 1344, 1283, 1270, 1198, 1147, 1100, 1040, 1020, 990, 926, 877, 803 cm^{-1}.

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

46
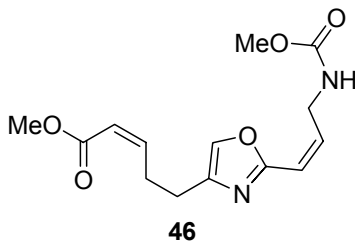
(2Z)-5-[2-((1Z)-3-Methoxycarbonylamino-propenyl)-oxazol-4-yl]-pent-2-enoic acid methyl ester (46). PdCl$_2$ (0.40 mg, 2.1 µmol, 10 mol%), CuCl$_2$ (5.8 mg, 43 µmol, 2.0 equiv) and AcONa (3.5 mg, 43 µmol, 2.0 equiv) were suspended in MeOH (0.5 ml) and stirred at room temperature for 5 min, giving a frog-green 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_2O (5 ml) and extracted with EtOAc (3×5 ml). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_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 (EtOAc/CH$_2$Cl$_2$ 1:4).

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

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

5.2.3. Synthesis of Aldehyde 178

192
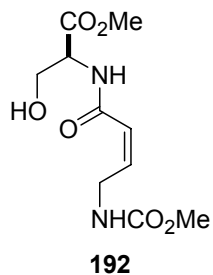
3-Hydroxy-2-((2Z)-4-methoxycarbonylamino-but-2-enoylamino)-propionic acid methyl ester (192). To a solution of acid **187** (2.36 g, 15.0 mmol, 1.00 equiv) in EtOAc (190 ml) at room temperature was added *Lindlar*'s catalyst (500 mg) and quinoline (1.80 ml, 15.0 mmol, 1.00 equiv). The mixture was stirred for 30 min and a balloon filled with hydrogen was fitted to the flask. The reaction was monitored by ^{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 × 100 ml) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, giving enoic acid **191** (R_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 $NaHCO_3$ (100 ml) was added and the aqueous layer was extracted with EtOAc (5 × 100 ml). The combined organic solutions were dried over

anhydrous Na_2SO_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 (EtOAc).

^{1}H NMR (300 MHz, CD$_3$OD) δ 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]
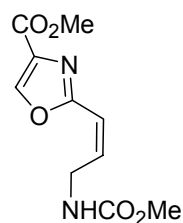
193

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).

^{1}H NMR (300 MHz, CD$_3$OD) 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).

^{13}C NMR (75 MHz, CD$_3$OD) 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.

194

[(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_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc) afforded alcohol **194** (248 mg, 57% yield) as a white solid.

mp = 123 °C.

R_f = 0.34 (EtOAc).

^{1}H NMR (300 MHz, CD_3OD) δ 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_3OD) δ 161.5, 159.1, 142.8, 138.9, 136.2, 115.4, 56.9, 52.2, 40.7.

IR (thin film) ν 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 $C_9H_{12}N_2O_4Na$ $[M+Na]^+$, 235.0694; found, 235.0687.

195

[(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_3CN were added successively triphenylphosphine (606 mg, 2.31 mmol, 2.00 equiv), 2,6-lutidine (69 μl, 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 NaHCO$_3$. The aqueous phase was extracted with diethyl ether (3×50 ml) and the combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, 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.
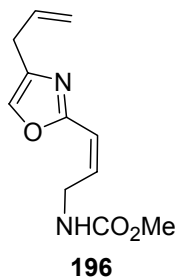
R$_f$ = 0.38 (hexane/EtOAc 1:1).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.61 (s, 1 H), 6.31 (dt, 1 H, $J = 11.8$, 1.8 Hz), 6.22–6.10 (m, 1 H), 5.41 (br s, 1 H), 4.38 (s, 2 H), 4.34 (t, 2 H, $J = 5.6$ Hz), 3.69 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 160.4, 157.0, 138.4, 137.9, 135.6, 115.8, 52.2, 39.6, 22.9.

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

HRMS (MALDI) calcd for C$_9$H$_{12}$BrN$_2$O$_3$Na [M+H]$^+$, 275.0031; found, 275.0026.

196

[(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 Pd$_2$(dba)$_3$·CHCl$_3$ (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*-butylvinyltin (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 (hexane/EtOAc 1:1).

¹H NMR (300 MHz, CDCl₃) δ 7.34 (s, 1 H), 6.30 (dt, 1 H, J = 11.8, 1.9 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 Hz), 3.68 (s, 3 H), 3.34–3.28 (m, 2 H).

¹³C NMR (75 MHz, CDCl₃) δ 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) ν 3335, 3080, 2952, 1713, 1643, 1588, 1537, 1520, 1463, 1433, 1260, 1194, 1169, 1148, 1103, 997, 953, 921 cm⁻¹.

HRMS (MALDI) calcd for $C_{11}H_{15}N_2O_3$ [M+H]⁺, 223.1082; found, 223.1077.

178
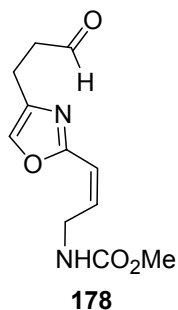
{(2Z)-3-[4-(3-Oxo-propyl)-oxazol-2-yl]-allyl}-carbamic acid methyl ester (178). To a solution of alkene **196** (120 mg, 0.540 mmol, 1.00 equiv) in dry THF (2 ml) was added at room temperature 9-BBN (0.50 M in THF, 1.2 ml, 0.59 mmol, 1.1 equiv). The solution was stirred for 2 h, whereupon EtOH (0.60 ml), 6.0 M aqueous NaOH (0.22 ml), and H₂O₂ 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 H_2O. 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 Na_2SO_4 and concentrated under reduced pressure. Filtration over a short pad of silica gel (eluting with EtOAc) afforded intermediate alcohol **197** ($\mathbf{R}_f$ = 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 CH_2Cl_2 (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 CH_2Cl_2 (1 ml + 2×1 ml rinse) was added dropwise. After 20 min, Et_3N (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 CH_2Cl_2 (5 ml) and quenched with saturated, aqueous NH_4Cl (10 ml). Following extraction with CH_2Cl_2 (4×20 ml), the combined organic layers were washed with saturated, aqueous NH_4Cl (3×20 ml), H_2O (20 ml), and brine (20 ml). The organic layer was dried over anhydrous Na_2SO_4, 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.

$\mathbf{R}_f$ = 0.50 (EtOAc).

¹H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{11}H_{15}N_2O_4$ [M+H]⁺, 239.1031; found, 239.1026.

5.2.4. Completion of the Total Synthesis

43
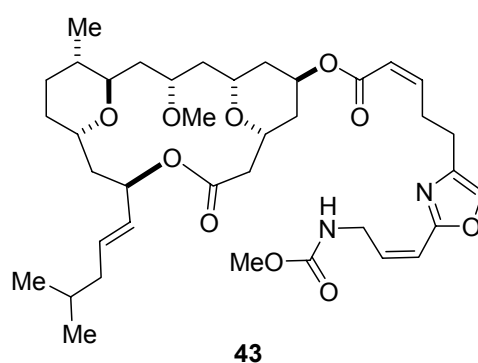
(1*R*,3*R*,5*R*,7*R*,9*R*,13*R*,15*S*,18*S*)-3-Methoxy-18-methyl-13-[(1*E*)-4-methylpent-1-enyl]-11-oxo-12,19,20-trioxatricyclo[13.3.1.1⁵·⁹]icos-7-yl (2*Z*)-5-{2-{(1*Z*)-3-[(methoxy-carbonyl)amino]prop-1-enyl}oxazole-4-yl}pent-2-enoate; Leucascandrolide A (43).
To a solution of alcohol **45** (3.3 mg, 7.5 μmol, 1.0 equiv) and acid **198** (4.6 mg, 15 μmol, 2.0 equiv) in CH_2Cl_2 (1 ml) was added HOBt·H_2O (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 NH_4Cl (2 ml). The aqueous layer was extracted with diethyl ether (4 × 3 ml). The combined organic layers were dried over anhydrous Na_2SO_4, 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 (hexane/EtOAc 1:1).

^{1}H NMR (300 MHz, CDCl$_3$) δ 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).

HRMS (MALDI) calcd for $C_{38}H_{56}N_2O_{10}$ [M+H]$^+$, 723.3832; 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