THE TOTAL SYNTHESIS OF DOLABRIFEROL C VIA ONE-POT ENANTIOSELECTIVE BISALDOL REACTIONS

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By

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My Parents
(Manohar Diddi & Kalavathi Diddi)

and

All My Teachers (Gurus)

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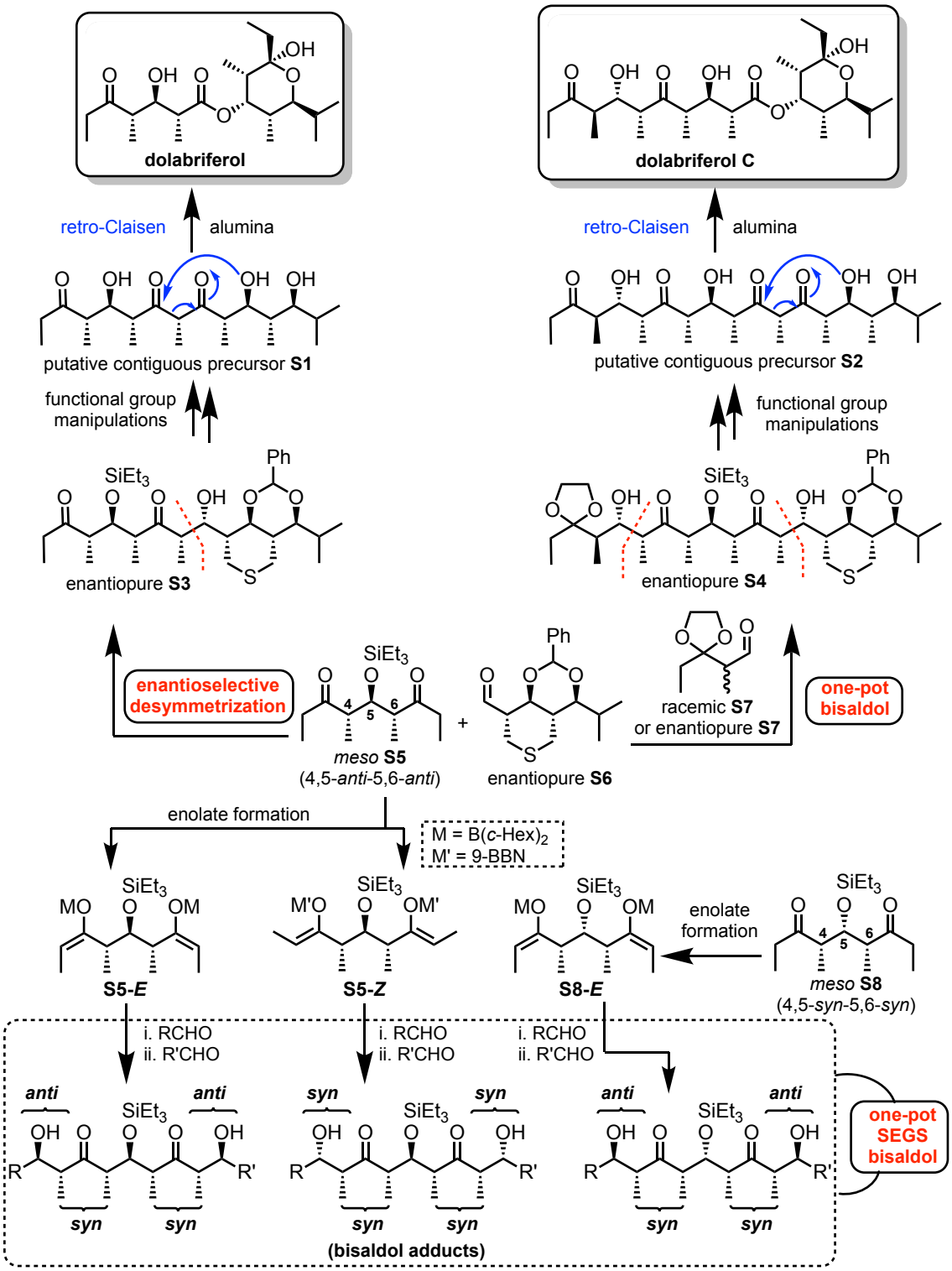
ABSTRACT

Dolabriferol C is a member of a small family of marine natural products known as *non-contiguous* polypropionates that are esters of a polypropionate carboxylic acid with a polypropionate alcohol. The origin of these so-called 'natural products' is uncertain, but they are often hypothesized to arise from a retro-Claisen fragmentation of a hemiacetal formed from a 5-hydroxy-1,3-dione embedded in a *contiguous* polypropionate chain (e.g., **S1** and **S2**). To test that conjecture, these putative precursors have been targeted for total synthesis to allow exploration of their properties, especially the tendency to rearrange into the *non-contiguous* 'natural products'. In previous work, the Ward group produced experimental evidence for the proposed origin of *non-contiguous* polypropionates baconipyrone A, baconipyrone C, and dolabriferol by total synthesis from their putative contiguous precursors via a retro-Claisen approach.

Towards the synthesis of **S2**, the putative *contiguous* precursor of dolabriferol C, a new strategy was contemplated and examined the potential of bisenolates of *meso* 1,5-diketones **S5** and **S8**, previously unknown entities. The research presented herein describes the development and application of one-pot sequential enantiotopic group selective (SEGS) aldol reactions as a powerful strategy for highly convergent polypropionate synthesis. Both (*E,E*)- and (*Z,Z*)-bisenol borinates (e.g., **S5-*E***, **S5-*Z***, **S8-*E***) were prepared stereoselectively from *meso* 1,5-diketones **S5** and **S8**, and were successfully used in enantioselective desymmetrization and SEGS bisaldol reactions to synthesize several *meso*, racemic, and enantiopure polypropionate motifs with high diastereoselectivities.

The putative *contiguous* precursor **S2** was prepared via a highly stereoselective bisaldol reaction of a *meso* 1,5-diketone **S5** with two different chiral aldehydes **S6** (enantiopure) and **S7** (racemic or enantiopure) that generates the full carbon skeleton **S4** (enantiopure) and sets the

absolute configuration of eight stereocenters in a one-pot process. Brief exposure of the precursor **S2** to neutral alumina cleanly produced dolabriferol C via a remarkably chemoselective retro-Claisen reaction thereby establishing this natural product as a plausible isolation artifact. This is the first total synthesis of dolabriferol C (and its contiguous precursor **S2**) and was achieved in 7 steps with 13.6% overall yield from the known aldehyde **S6**. Using this strategy, an improved synthesis of dolabriferol was also achieved in 5 steps with 34% overall yield from **S6**.


dolabriferol
dolabriferol C
retro-Claisen
alumina
putative contiguous precursor S1
putative contiguous precursor S2
functional group manipulations
enantiopure S3
enantiopure S4
enantioselective desymmetrization
meso S5
(4,5-anti-5,6-anti)
enantiopure S6
racemic S7
or enantiopure S7
one-pot bisaldol
enolate formation
M = B(c-Hex)2
M' = 9-BBN
S5-E
S5-Z
S8-E
meso S8
(4,5-syn-5,6-syn)
i. RCHO
ii. R'CHO
anti
syn
(bisaldol adducts)
one-pot SEGS bisaldol

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LIST OF ABBREVIATIONS

α	observed optical rotation in degrees
$[\alpha]_D$	specific rotation at the sodium D line (expressed without units; implied actual units are: (deg·mL)/(g·dm))
Å	angstrom, 10^{-10} m
Ac	acetyl ($CH_3C(O)$-)
AcOH	acetic acid
ap	apparent (NMR signal)
Ar	aryl (as a substituent or fragment)
atm	atmosphere(s) (as a measure of pressure)
aq	aqueous
9-BBN	borabicyclo[3.3.1]non-9-yl
Bn	benzyl ($-CH_2Ph$)
BOM	benzyloxymethyl ($-CH_2OCH_2Ph$)
BORSM	based on recovered starting material (referring to the yield of a reaction product)
bp	boiling point
br	broad (description of a spectral signal)
BSA	bis(trimethylsilyl)acetamide
n-BuLi	*n*-butyllithium
t-Bu	*tert*-butyl (also abbreviated ^{t}Bu)
t-BuOH	*tert*-butyl alcohol (also abbreviated ^{t}BuOH)
Bz	benzoyl ($PhC(O)$-)

°C	degrees Celsius (temperature)
calcd	calculated
CI	chemical ionization (in mass spectrometry)
cm	centimeter(s)
^{13}C NMR	carbon 13 nuclear magnetic resonance
COSY	correlation spectroscopy
m-CPBA	3-chloroperoxybenzoic acid (also abbreviated MCPBA)
c-Hex	cyclohexyl
δ	NMR chemical shift in parts per million downfield from TMS
d	day(s); doublet (spectral signal)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEPT	distortionless enhancement by polarization transfer (an NMR technique)
DIBAL-H	diisobutylaluminium hydride
dil	dilute
DIPA	*N*,*N*-diisopropylamine
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomer ratio
DRIFT	diffuse reflectance Fourier transform infrared
DYKAT	dynamic kinetic asymmetric transformation

E and *Z*	configurational descriptors for alkenes. *E* denotes that the substituents of highest CIP (Cahn-Ingold-Prelog) priority at each end of the double bond are on opposite sides. If the pertinent substituents are on the same side, the descriptor is *Z*
ee	enantiomer excess (the composition of a sample composed of *R* and *S* enantiomers can be expressed as: ee = [*R*]−[*S*]/[*R*]+[*S*]. This expression describes the excess of one enantiomer over the other and that of enantiomeric purity of a sample, where [*R*]>[*S*])
EGS	enantiotopic group selective
EI	electron impact
ent	enantiomer of
epi	epimer of
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
FCC	flash column chromatography
FTIR	Fourier transform infrared
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond correlation (a 2D NMR experiment)

HMDS	hexamethyldisilazane, bis(trimethylsilyl)amide
^{1}H NMR	proton nuclear magnetic resonance
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation (a 2D NMR experiment)
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant (in NMR spectroscopy)
KR	kinetic resolution
LDA	lithium diisopropylamide
like	the reflection-invariant *relative topicity* of approach of reactants is defined as *like* if the corresponding descriptor pairs are *Re, Re* or *R, Re*. The duality of diastereomorphic relationships based on combination of two stereogenic atoms and their descriptor pairs with the same first letters (e.g., *Re, Re* or *R, R*) denoted as *like*.
lit.	literature value (abbreviation used with period)
M	molar (moles per litre)
M^+	parent molecular ion
m	multiplet (spectral)
Me	methyl
MHz	megahertz
min	minute(s)
MKE	mutual kinetic enantioselection

mol	mole(s)
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
MW	molecular weight
m/z	mass-to-charge ratio
ν	wavenumber
NaOMe	sodium methoxide
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid plot
Pd/C	palladium on charcoal
Ph	phenyl
Ph_3P	triphenylphosphine
PhSH	thiophenol
Piv	pivaloyl
PMA	phosphomolybdic acid
PMB	p-methoxybenzyl or p-methoxyphenylmethyl
ppm	part(s) per million
PPTS	pyridinium para-toluenesulfonate
^{i}Pr	*iso*-propyl
Pr	propyl
PTLC	preparative thin layer chromatography
Py	pyridine

q	quartet (spectral)
quant	quantitative
R	alkyl substituent
rac	a prefix to denote racemic
R_f	retention factor (in chromatography)
rel	relative
ROESY	rotating frame nuclear Overhauser enhancement spectroscopy
R and *S*	absolute stereochemical configuration descriptors in the CIP (Cahn-Ingold-Prelog) system
rt	room temperature
s	singlet (spectral); second(s)
sat	saturated
SEGS	sequential enantiotopic group selective
S_N2	bimolecular nucleophilic substitution
t	triplet (spectral)
TAS-F	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylamonium fluoride
TBDMS	*tert*-butyldimethylsilyl (also abbreviated TBS)
TES	triethylsilyl
temp.	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl (para-toluenesulfonyl [*p*-$CH_3C_6H_4SO_2$-])
p-TsOH	*p*-toluenesulfonic acid (also abbreviated PTSA)
UV	ultraviolet
v/v	volume per unit volume (volume-to-volume ratio)
wt	weight

1. INTRODUCTION

1.1. Polypropionates

Polypropionates are one of the most important classes of secondary metabolites isolated from plants, fungi, bacteria and sponges.[1] The characteristic structural motif of polypropionates is a hydrocarbon chain with alternating methyl and hydroxy (or oxo) substituents (Figure 1-1).

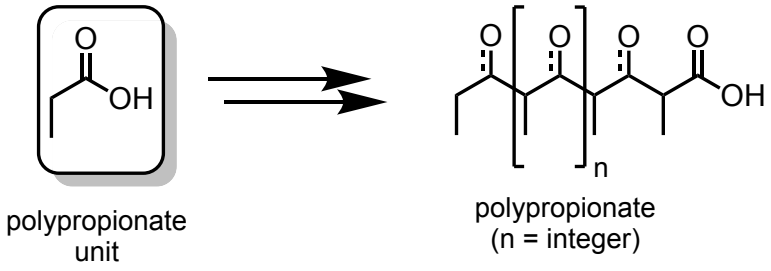
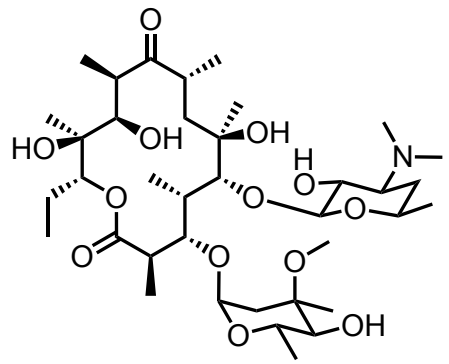
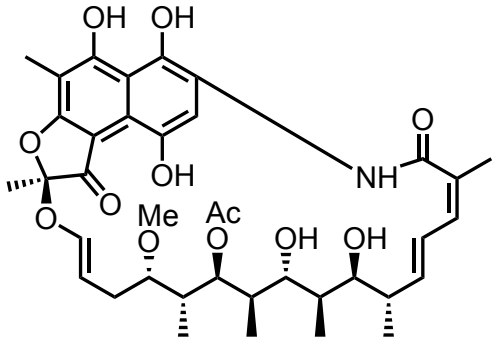


Figure 1-1: Structure of polypropionate.

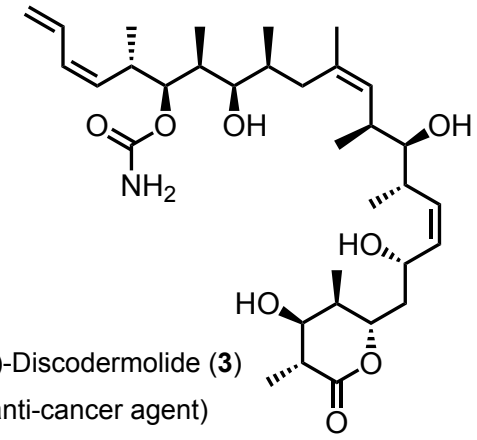
Several polypropionate natural products exhibit various biological activities and are widely used in drug development for human health (Figure 1-2). Because of their wide range of biological activities and structural complexity, polypropionates have attracted the attention of many synthetic chemists and several synthetic strategies have been developed.



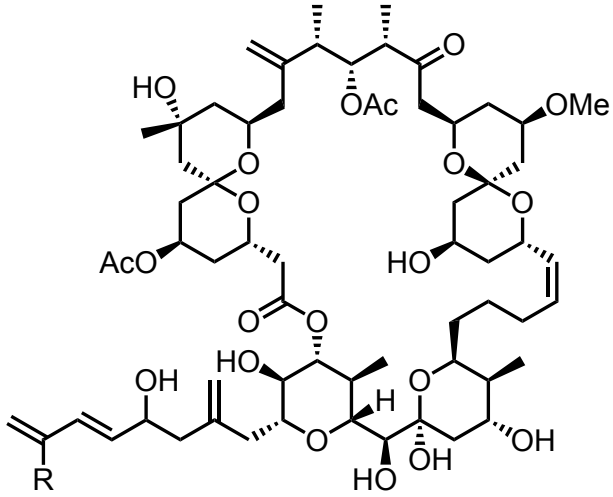
erythromycin A (**1**)
(antibiotic)



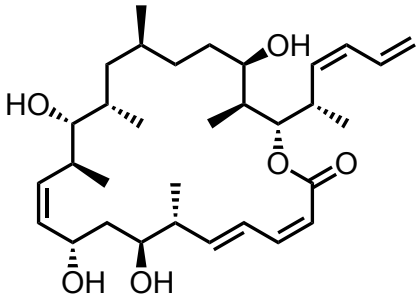
Rifamycin SV (**2**)
(antibiotic)



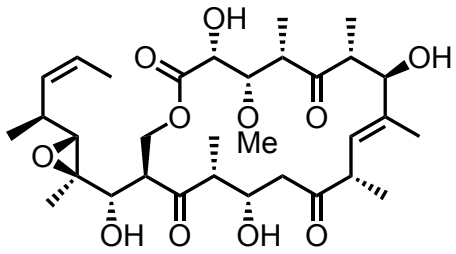
(+)-Discodermolide (**3**)
(anti-cancer agent)



spongistatin 1 (**4**), R = Cl
spongistatin 2 (**5**), R = H
(anti-tumor activity)



(—)-Dictyostatin (**6**)
(anti-cancer agent)

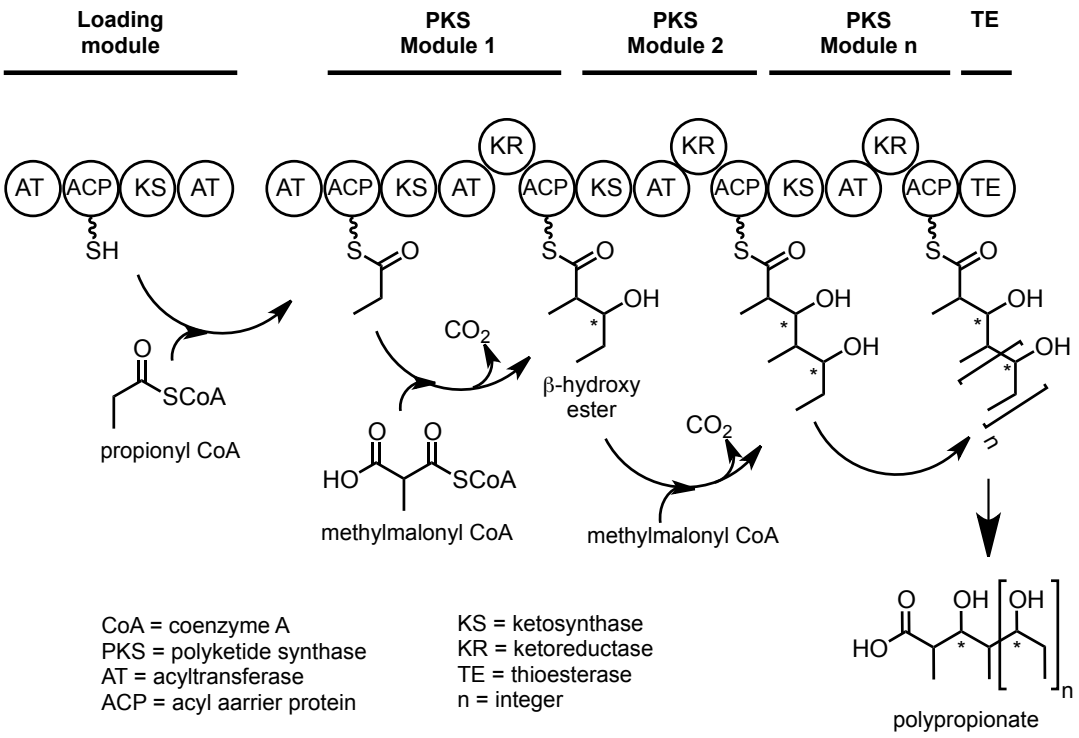


(+)-Tedanolide (**7**)
(anti-tumor activity)

Figure 1-2: Polypropionates as potent drugs and drug leads.

1.1.1. Biosynthesis of polypropionates

The biosynthesis of polypropionates proceeds via iterative coupling of propionate units by polyketide synthase (PKS) enzymes. These multi-modular enzymes complete multistep biosynthetic sequences by passing the substrate from the active site of one module to that of the next module in a coordinated fashion. In general, the process begins with a stereoselective decarboxylative addition of methyl malonyl CoA catalyzed by the first ketosynthase (KS) module to give the corresponding β-ketoester intermediate (Scheme 1-1); however, the next module often is a ketoreductase (KR) that effects stereoselective reduction of the ketoester intermediate to give β-hydroxy ester before the next homologation of the chain. This process repeats with each homologation of the chain and the process is terminated by thioesterase (TE) module to provide polypropionate that have alternating methyl and hydroxy subunits.[1–3] However, these linear polypropionates may not be the final products and can undergo further modification by enzyme catalyzed or spontaneous rearrangements, cyclizations, and elimination reactions to form new products.



Scheme 1-1: Biosynthetic pathway for polypropionate synthesis (adapted from ref. 1).

1.2. Non-Contiguous Polypropionates

1.2.1. Structure and isolation

Non-contiguous polypropionates are esters of a polypropionate carboxylic acid with a polypropionate alcohol and consequently have a non-contiguous carbon chain. To date, all members of this small family of polypropionates have been isolated from marine mollusks (Figure 1-3).

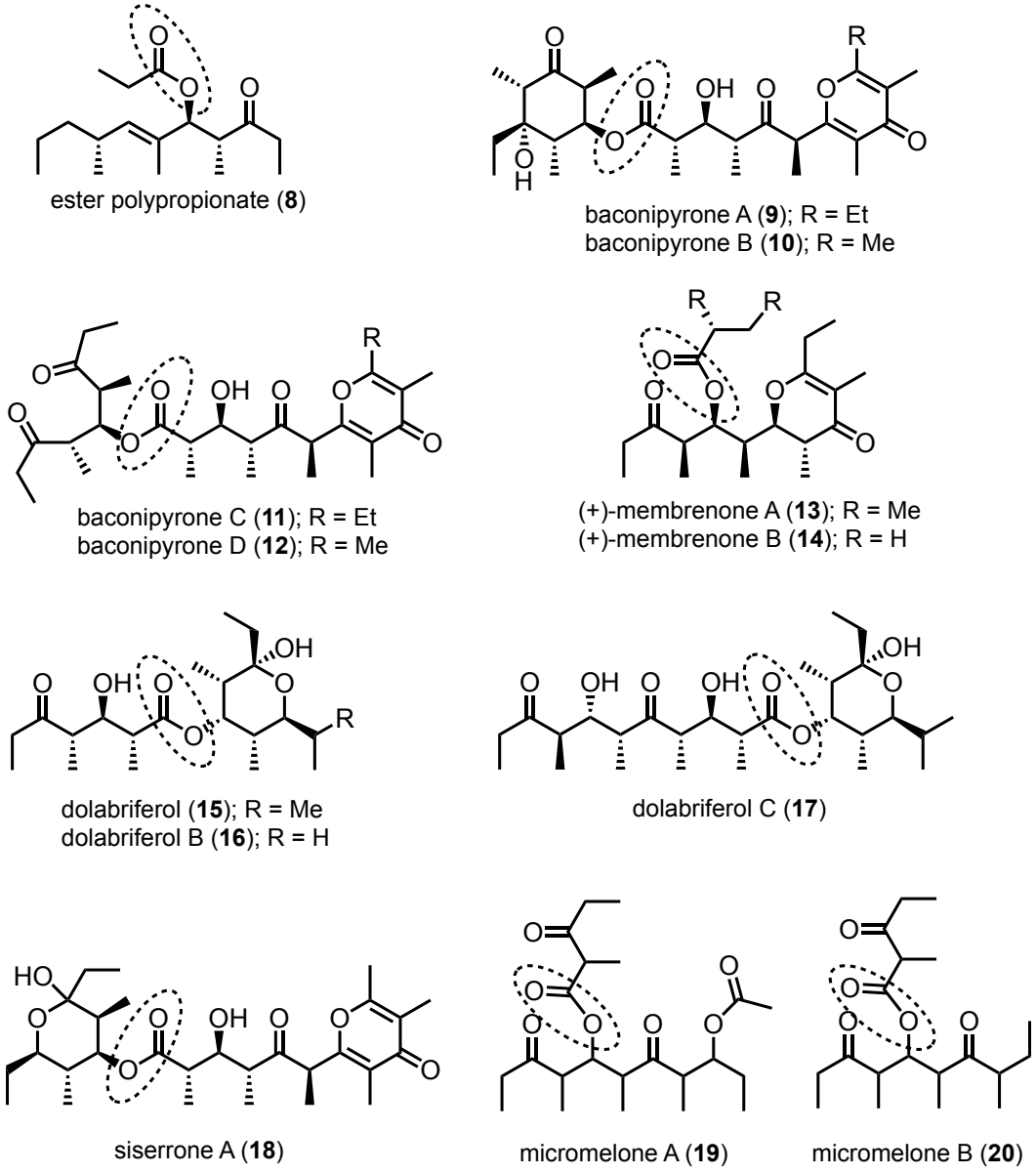


Figure 1-3: Isolated non-contiguous polypropionates.

The first non-contiguous polypropionate **8** was isolated along with the hemiacetal isomer **8a** from *Siphonaria australis* collected near Auckland, New Zealand (Figure 1-4).[4] Spectral data analysis allowed assignment of the relative configuration at C-7, C-8, C-10 and C-11 in **8a**; however, the relative configuration at C-4 and absolute configuration of either **8** or **8a** was not determined.

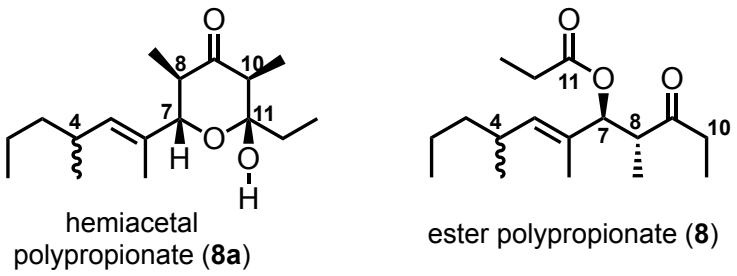
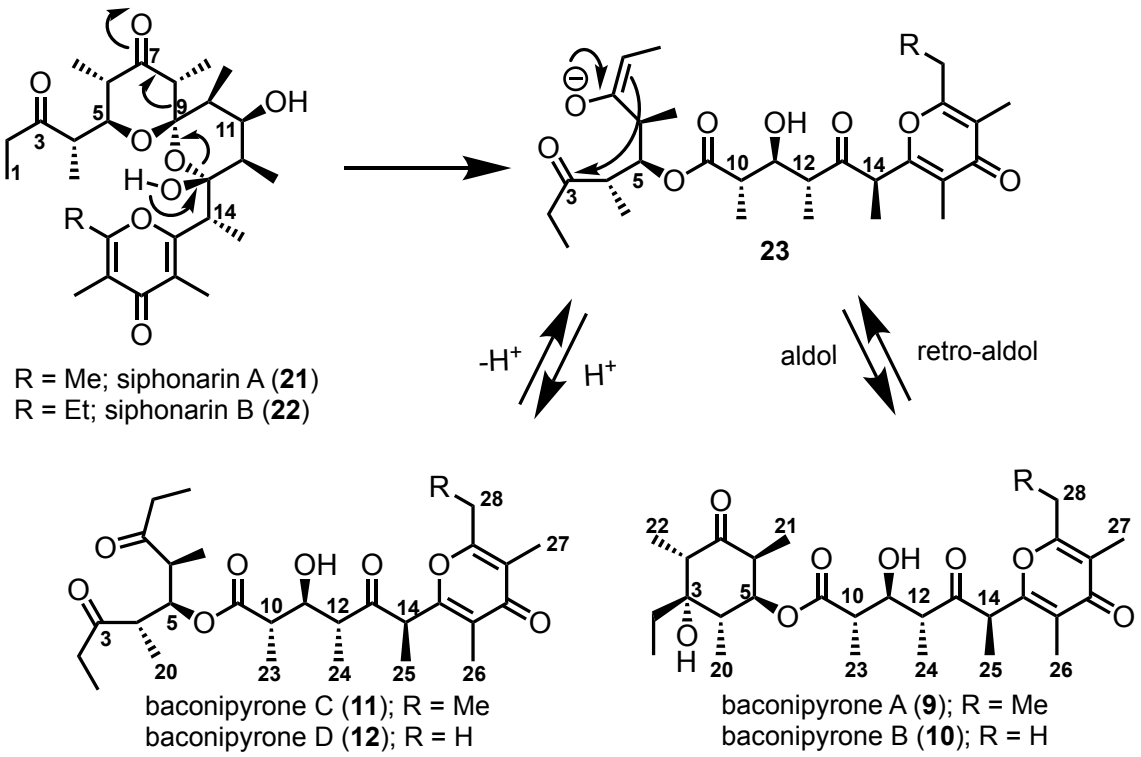


Figure 1-4: Structures of **8** and **8a**.

Faulkner et al. isolated baconipyrones A-D (**9**-**12**) along with the known[5] siphonarin A (**21**) from *Siphonaria baconi* collected near Melbourne, Australia (Scheme 1-2). The structure of baconipyrone B (**10**) was established by X-ray crystallography, while the structures of other baconipyrones were established by comparing their spectral data with the known **10**. The spectral data of baconipyrone A (**9**) were quite similar to those of **10** and differed only by the signals due to the presence of a methyl vs. an ethyl group at C-28. The relative configuration at C-4, C-6, C-10, C-11, C-12 and C-14 in **10** are identical to those of siphonarin A (**21**). Baconipyrones A-D (**9**-**12**) all contain a polypropionate ester chain and highly substituted γ-pyrone ring system. In the structures of **9** and **10**, the polypropionate carboxylic acid fragment was connected through an ester link to a highly substituted β-hydroxy cyclohexanone, whereas in **11** and **12**, the same fragment was connected to an acyclic 1,5-diketone. Baconipyrones **9** and **10** are interrelated with **11** and **12**, respectively, by means of an aldol-retro aldol pathway (Scheme 1-2).



Scheme 1-2: Relationship of baconipyrones (A-D) with siphonarins A and B.

Membrenones A-C (**13**, **14** and **24**) (Figure 1-5) were isolated from the skin of *Pleurobranchus membranaceus*, a Mediterranean mollusc species collected by SCUBA divers in the bay of Pozzuoli, and the structures were reported by Ciavatta et al. in 1993.[6] The three structures have a common polysubstituted γ-dihydropyrone core. Membrenone A (**13**) and membrenone B (**14**) have non-contiguous carbon-chains (esters of simple carboxylic acids), whereas, membrenone C (**24**) has a contiguous carbon-chain. The relative configuration at C-6 and C-7 of membrenones was established on the basis of the $^{3}J_{H6\text{-}H7}$ coupling constant values and by comparison with model compounds. The C-8, C-9 and C-10 relative configuration and the absolute configuration of the membrenones could not be determined.

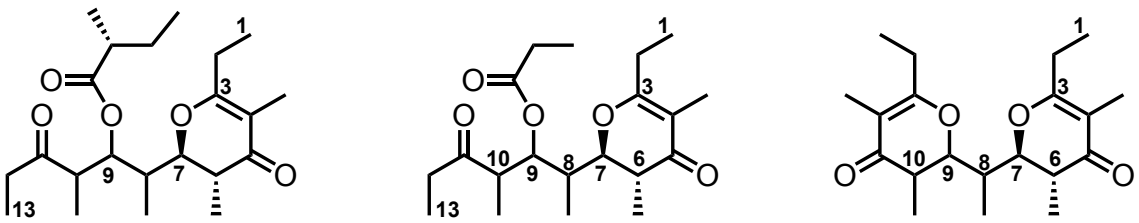


Figure 1-5: Structures of membrenones A-C.

Dolabriferol (**15**) was isolated from the anaspidean mollusc *Dolabrifera dolabrifera* collected in Cuba by SCUBA divers, and its structure was reported by Gavagnin and co-workers in 1996.[7] Dolabriferol (**15**) consists of a highly substituted 4-hydroxyoxane connected to a β-hydroxy-5-oxo carboxylic acid via an ester linkage (Figure 1-6). The structure of **15** was elucidated by NMR studies and the relative configuration was confirmed by X-ray crystallography. In 2012, Rodríguez et al. reported dolabriferol B (**16**) and dolabriferol C (**17**) along with the known **15** isolated from *Dolabrifera dolabrifera* collected in Puerto Rico.[8] The structure of **16** differs from **15** by having an ethyl group at C-18 instead of isopropyl group. The relative configuration of the cyclic hemiacetal in **16** was established by ^{1}H NMR coupling constant values and by NOE correlations. Because the spectral data and optical rotation values of **16** are in close agreement with those of **15**, all the relative configuration of **16** were assumed to be same as in **15**. This assumption was further supported by obtaining the common acid fragment **25** from degradation of **15** and **16**. The spectral data of dolabriferol C (**17**) were quite similar to those of **15**. The relative configuration of **17** was determined unambiguously from X-ray crystallographic analysis. The absolute configuration of **17** was assumed to be same as in **15** based on their similar spectral data and similar optical rotation values with the same sign.

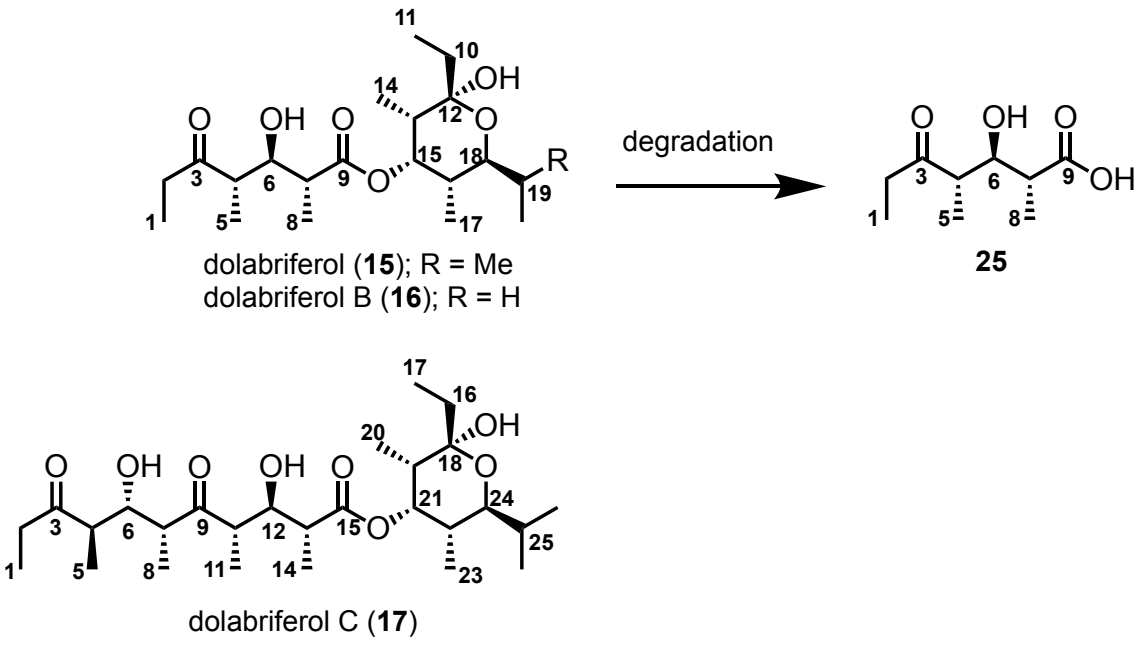


Figure 1-6: Structures of dolabriferols; degradation of **15** and **16** to the common acid fragment **25**.

Siserrone A (**18**) was isolated along with the known[5] dihydrosiphonarins A and B from *Siphonaria serrata* and its structure was reported by Davies-Coleman in 2000 (Figure 1-7).[9] The structure of **18** is comprised of a γ-pyrone polypropionate carboxylic acid connected to a hydroxy-substituted cyclic hemiacetal via an ester link. With the exception of C-7, the relative configuration of cyclic hemiacetal in **18** was determined by ^{1}H NMR coupling constant values and by ROESY correlations, while the relative configuration of the acyclic chain was established by chemical degradation studies. A 4:1 diastereomeric mixture of carboxylic acids was obtained from degradation of **18**. After esterification of the acid mixture, the major ester **26** was isolated, and its spectral data was consistent with those of the known acid **27**[10] suggesting the relative configuration of the acyclic chain in **26** and hence in **18** were identical with that of **27**.

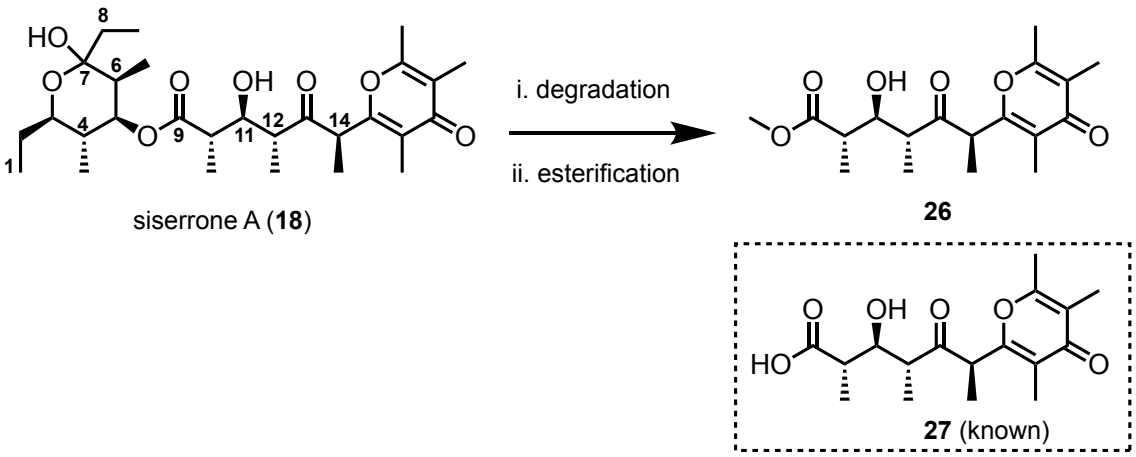


Figure 1-7: Degradation of siserrone A followed by esterification to ester **26**.

Micromelones A (**19**) and B (**20**) were isolated from *Micromelo undata* collected from the intertidal zone along the north coast of Tenerife (Figure 1-8). Structures of **19** and **20** were determined by NMR data analysis and MS fragmentation. However, the relative and absolute configurations of either **19** or **20** were not established due to their rapid decomposition.

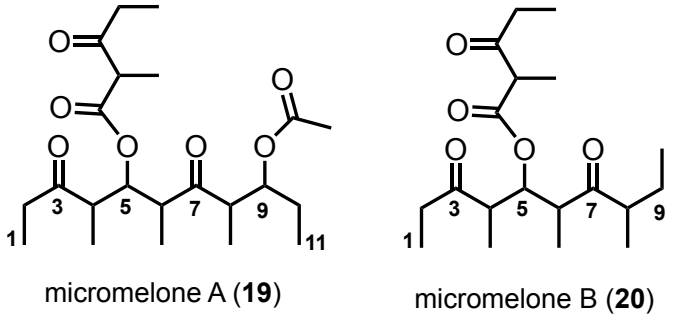
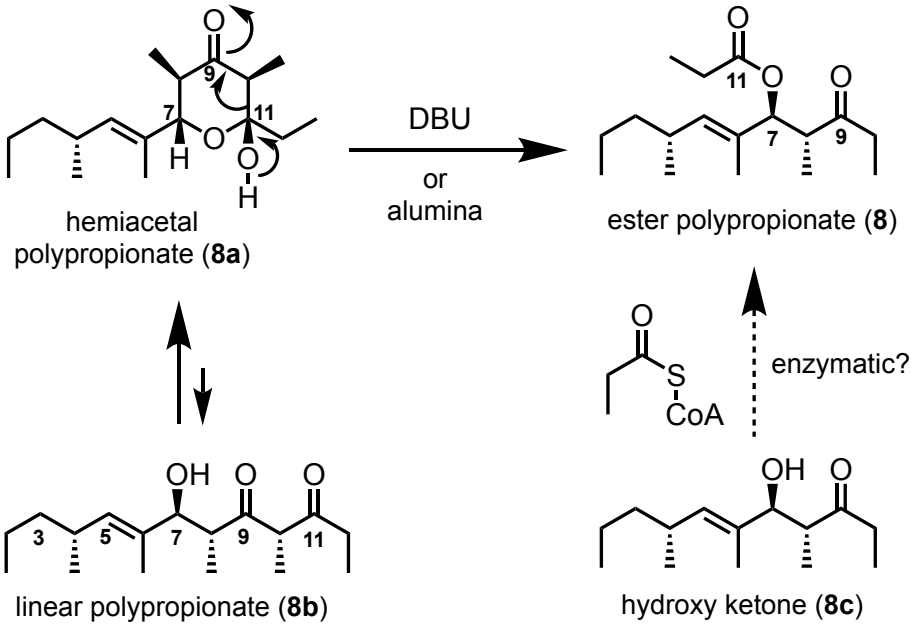


Figure 1-8: Structures of micromelones A and B.

1.2.2. Biosynthetic hypothesis on the origin of non-contiguous polypropionates

Compounds **8** and **8a** have the same chemical formula and are related by a rearrangement pathway (Scheme 1-3). Indeed, it was hypothesized that the ester link in non-contiguous **8** was formed from a retro-Claisen rearrangement of the contiguous **8a** generated by ring-chain tautomerism of the 5-hydroxy-1,3-dione **8b**. This hypothesis was supported by the retro-Claisen

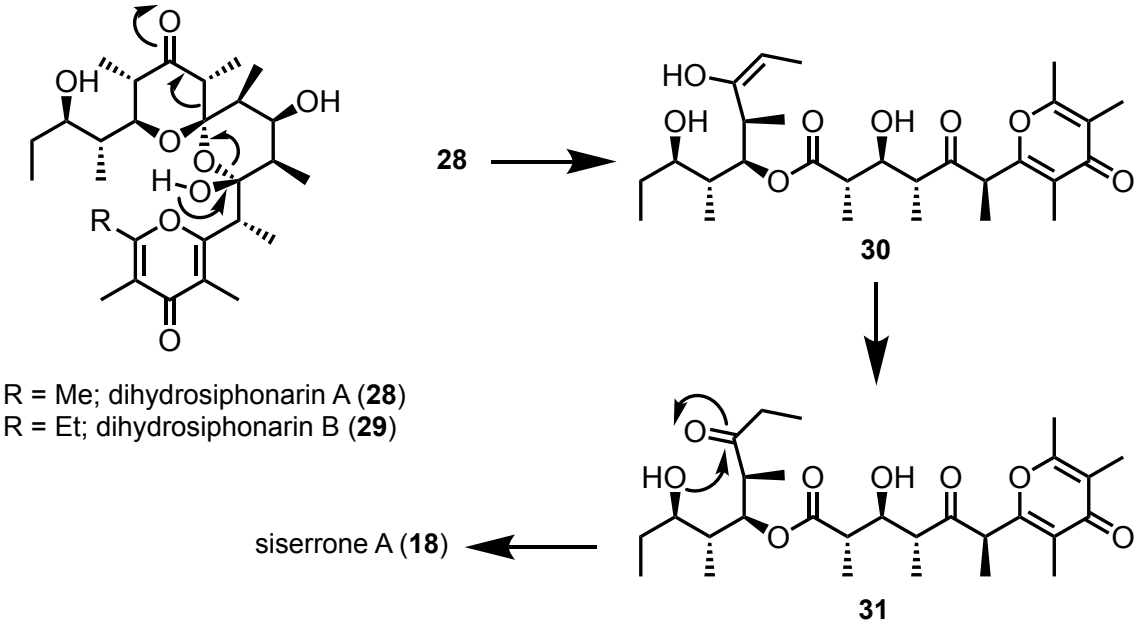
rearrangement of **8a** to **8** in presence of DBU[4,11] or basic alumina.[12] Although the in vitro transformation of **8a** to **8** is evidence for the proposed retro-Claisen rearrangement, an enzymatic propionylation of β-hydroxy ketone **8c** to **8** cannot be ruled out.



Scheme 1-3: Transformation of contiguous **8a** to non-contiguous **8** via a retro-Claisen rearrangement.

Faulkner et al. proposed a biosynthetic hypothesis that links baconipyrones A-D (**9-12**) with siphonarins A-B (**21, 22**) as shown in Scheme 1-2. The proposed mechanism suggests baconipyrones **9**, **11** could be derived from siphonarin A (**21**), whereas **10**, **12** could be derived from siphonarin B (**22**) (Scheme 1-4).[13] Furthermore, baconipyrones and siphonarins have identical absolute configurations at related centers. A careful extraction of the same mollusk *Siphonaria baconi* by Davies-Coleman revealed the presence of siphonarins but no baconipyrones were detected.[9] Similarly, preliminary extraction of *Siphonaria serrata* yielded the known[5] dihydrosiphonarin A (**28**) and dihydrosiphonarin B (**29**) as major components along with minor siserrone A (**18**). Surprisingly, latter extractions from the same species collected from the same collection site produced **18**, but no dihydrosiphonarins were observed. Because the appearance of

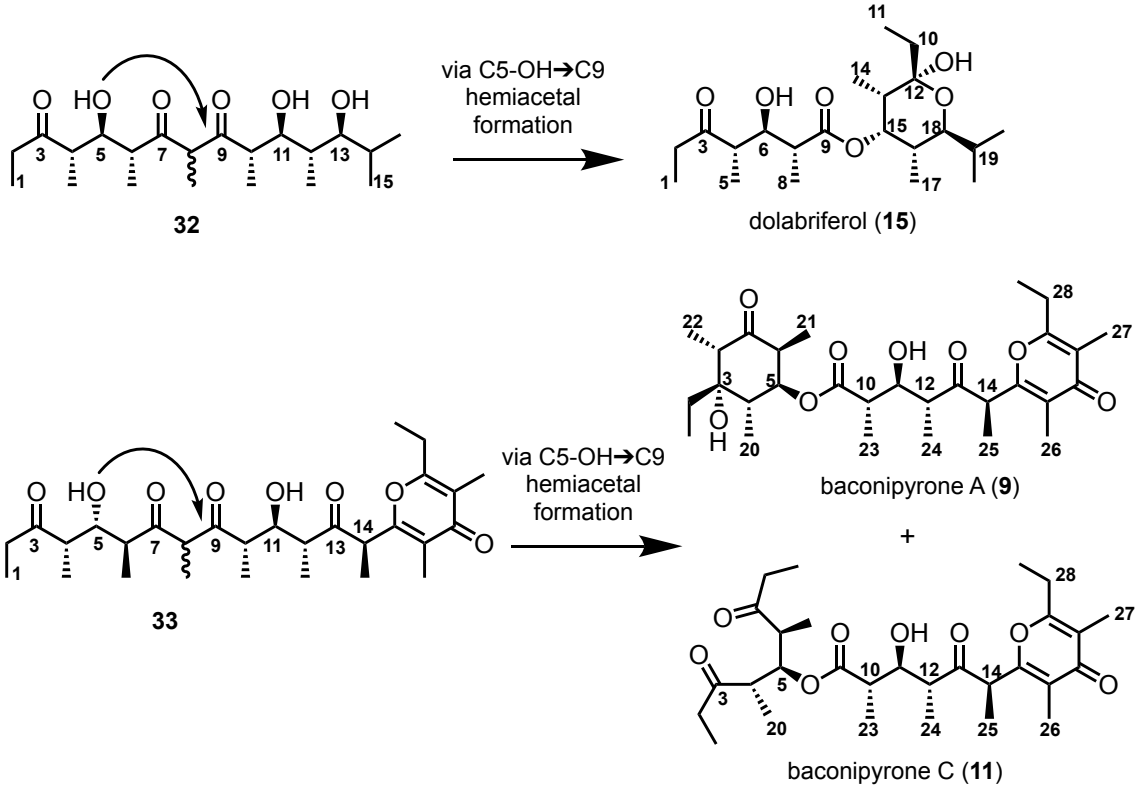
baconipyrones and siserrone varied with extraction procedures, the natural product status of these polypropionate esters was viewed with suspicion. Furthermore, it was hypothesized that the non-contiguous polypropionate **18** could be formed from contiguous precursor **28** during isolation via a plausible rearrangement pathway as shown in Scheme 1-4.



Scheme 1-4: A plausible rearrangement pathway of dihydrosiphonarin A (**28**) to siserrone A (**18**).

Gavagnin also hypothesized that the non-contiguous natural product **15** could be obtained from its isomeric hemiacetal precursor **32** (C5-OH➔C9-carbonyl) via a retro-Claisen rearrangement pathway (Scheme 1-5).[7] Towards the synthesis of dolabriferol (**15**), Perkins[14] and Goodman[15] independently generated non-contiguous polypropionates (hydroxy protected) from their isomeric C13-hydroxy protected contiguous polypropionates (e.g., **32**) via a DBU induced retro-Claisen rearrangement. Although, these approaches support the proposed retro-Claisen rearrangement pathway to form a non-contiguous carbon chain, the presence of protecting groups prevents other competitive cyclizations or rearrangements. Ward et al. successfully synthesized contiguous polypropionate precursors (e.g., **32** and **33**) and transformed them into the isomeric

non-contiguous polypropionate "natural products" (e.g., **15**, **9** and **11**, respectively) via a regioselective retro-Claisen rearrangement under mild conditions (Scheme 1-5).[16,17] Ward's synthetic approaches provide the first experimental evidence that supports the proposed hypothesis on the origin of non-contiguous polypropionates **9**, **11** and **15**. Based on all the above observations and experimental evidence, it can be concluded that non-contiguous polypropionates are most likely generated from their isomeric contiguous polypropionates during isolation, but not from enzymatic reactions in biological systems.



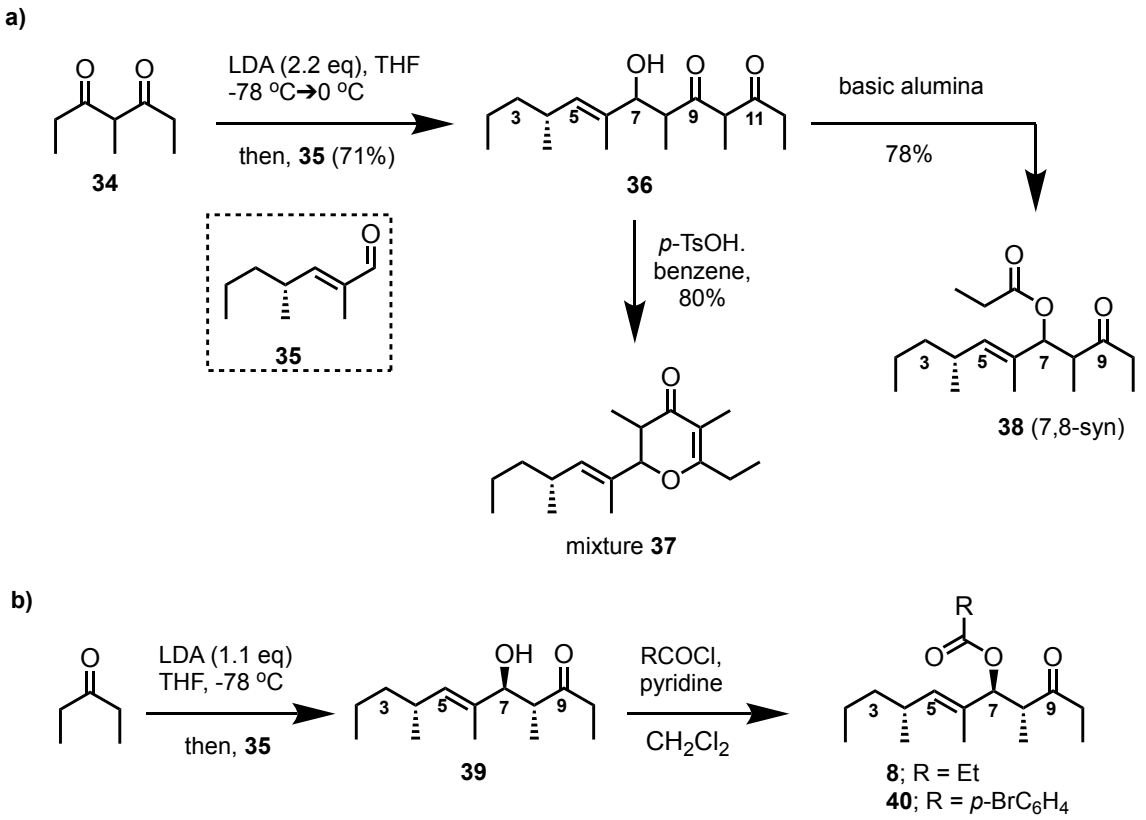
Scheme 1-5: Proposed retro-Claisen rearrangement of putative contiguous precursors to non-contiguous natural products.

1.2.3. Total synthesis and synthetic studies on non-contiguous polypropionates (by other groups)

Several research groups have published synthetic studies on non-contiguous polypropionates; however, only a few of these so-called natural products have been synthesized to date.

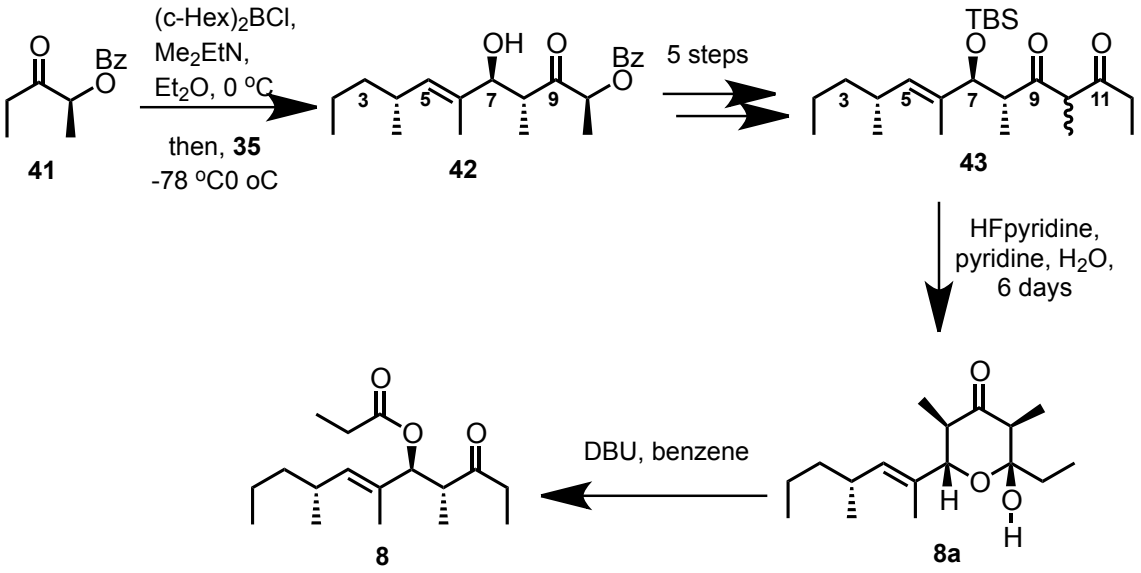
1.2.3.1. Total synthesis of polypropionate ester 8

In 1992, Albizati et.al., reported the relative and absolute configuration of polypropionate ester **8** by achieving its synthesis (Scheme 1-6).[12] Aldol reaction of dione **34** with enantiopure aldehyde **35** produced the hydroxy dione **36** as a mixture of stereoisomers (major adduct has 7,8-*syn* relative configuration) (Scheme 1-6a). The adduct **36** was readily dehydrated (under basic or acidic or buffered conditions) to give **37** as a mixture of diastereomers. Interestingly, flash chromatography of **36** produced the ester **38** via retro-Claisen rearrangement of the corresponding hemiacetal. However, the relative configuration at C7-C8 in **38** was determined as *syn*, which is not identical to the natural product **8** (7,8-*anti*). Alternatively, an aldol reaction of Li-enolate of 3-pentanone with aldehyde **35** produced the adduct **39** that was converted to the corresponding esters **8** and **40** (Scheme 1-6b). The absolute configuration of natural and synthetic products was assigned as shown in **8** by using the exciton chirality method on **40**. Because **8** was obtained from **8a**, the absolute configuration of **8a** was assigned on the basis of **8**.



Scheme 1-6: Albizati's synthesis of ester polypropionate **8**.

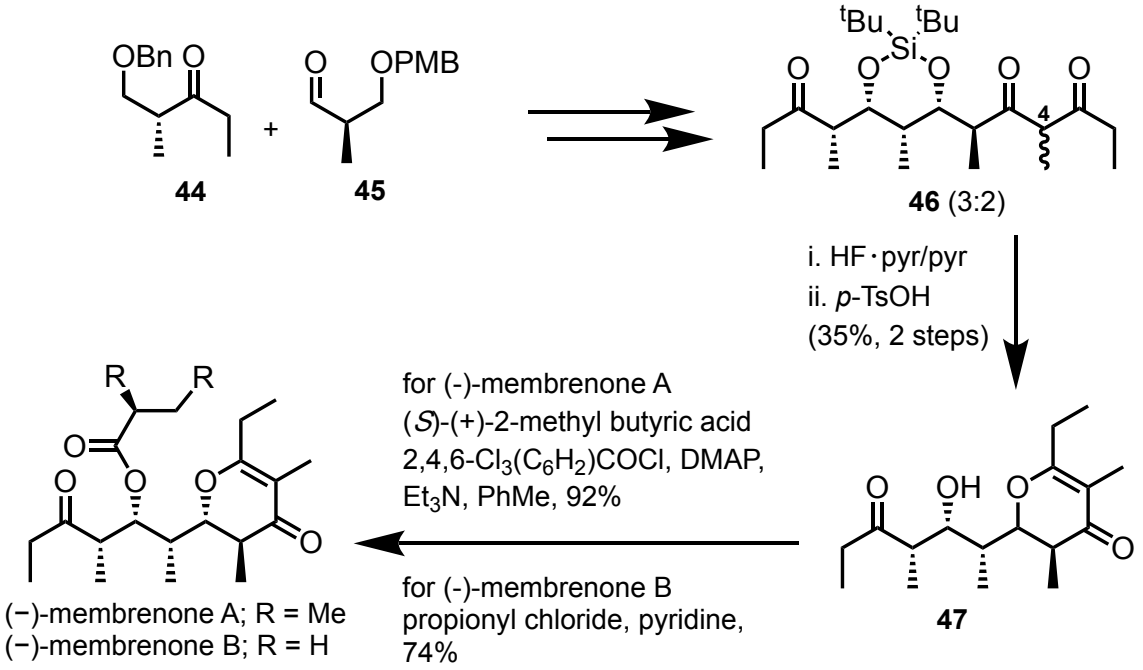
Lister and Perkins reported a stereocontrolled synthesis of hemiacetal **8a** and its transformation to polypropionate ester **8** via retro-Claisen rearrangement, thereby establishing the absolute and relative configurations of both natural products (Scheme 1-7).[11] A substrate-controlled aldol reaction of Paterson's ketone **41** (enantiopure) with aldehyde **35** (enantiopure) generated the adduct **42** (enantiopure) with the desired 7,8-*anti* relative configuration. Subsequent functional group manipulations and chain elongation produced the adduct **43** with an epimerizable stereocenter at C-10 as a mixture of keto-enol tautomers. Treatment of **43** with buffered pyridinium hydrofluoride and catalytic amount of water for six days produced the thermodynamically stable hemiacetal **8a**. Applying the known[4] DBU conditions on **8a** generated the ester **8** via retro-Claisen rearrangement.



Scheme 1-7: Perkins' synthesis of ester polypropionate **8**.

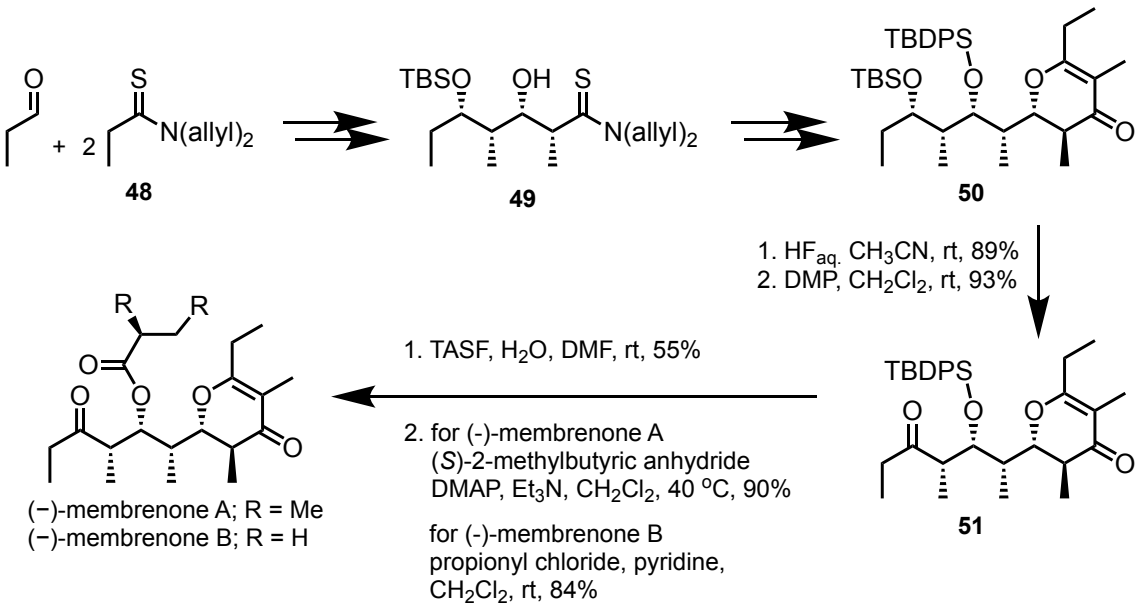
1.2.3.2.Total synthesis of membrenone A and B

Several research groups accomplished the total syntheses of (−)-membrenones A and B (unnatural enantiomers). Perkins et al. achieved the total syntheses of (−)-membrenones A and B via an esterification approach. Using Paterson's ketone **44** and aldehyde **45**, trione **46** was prepared as a 3:2 mixture (C4-epimers) of diastereomers (Scheme 1-8).[18] Treatment of this trione mixture **46** with HF·pyridine and pyridine, and then with *p*-TsOH accomplished desilylation, cyclization and dehydration to give the γ-dihydropyrone **47**. Final acylations of the hydroxy group in γ-dihydropyrone **47** with (*S*)-(+)-2-methyl butyric acid (using modified Yonemitsu-Yamaguchi esterification conditions[19,20]) and propionyl chloride furnished (−)-membrenone A and (−)-membrenone B, respectively.



Scheme 1-8: Perkins' synthesis of (−)-membrenones A and B.

Shibasaki et al. synthesized (−)-membrenones A and B via an esterification approach starting from thiopropionamide **48** using an iterative aldol coupling strategy (Scheme 1-9).[21] Thiopropionamide **48** was converted to hydroxy-thiopropionamide **49** that was further transformed to γ-dihydropyrone **50** with the desired stereochemical configurations. The γ-dihydropyrone **50** upon silyl removal and oxidation produced the keto-pyrone **51**. Final TBDPS removal with TASF, followed by acylations with (*S*)-2-methylbutyric anhydride and propionyl chloride afforded (−)-membrenone A and (−)-membrenone B, respectively.



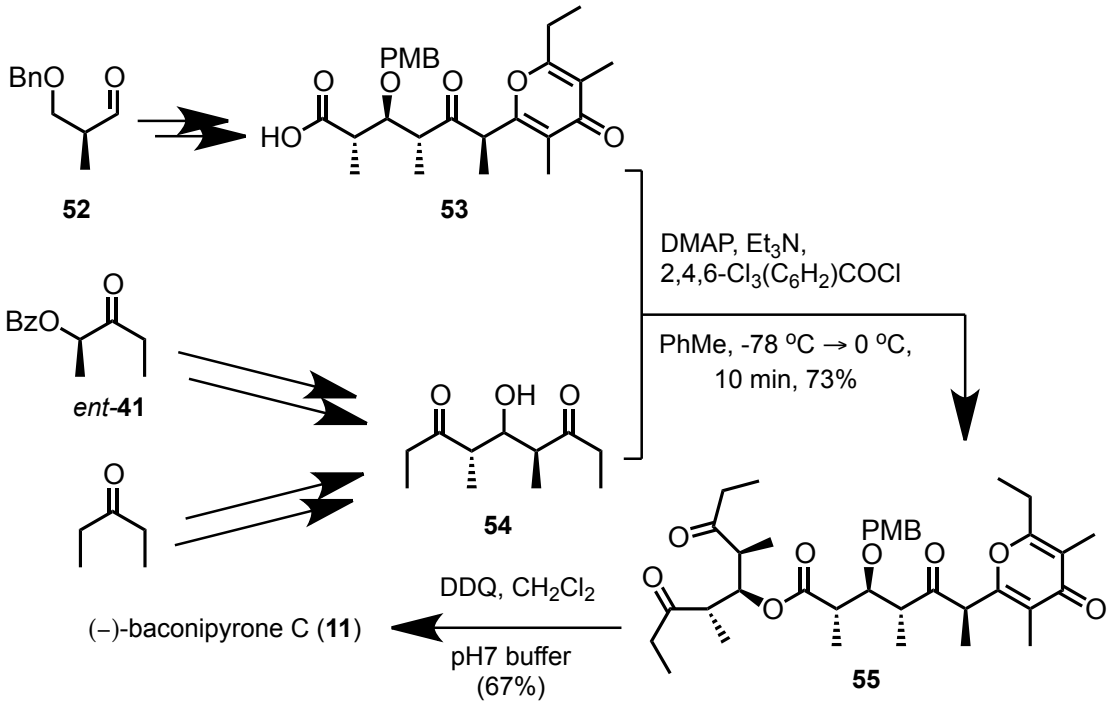
Scheme 1-9: Shibasaki's synthesis of (−)-membrenones A and B.

1.2.3.3.Total synthesis of baconipyrone C

Among the four total syntheses of baconipyrone C, three of them (Paterson, Hoveyda and Yadav) followed an identical approach to make the key ester link in the natural product by coupling the corresponding carboxylic acid with alcohol. Ward et al. established a retro-Claisen approach towards the synthesis of baconipyrone C from its putative contiguous precursor (for detailed discussion refer to the section **1.2.4**)

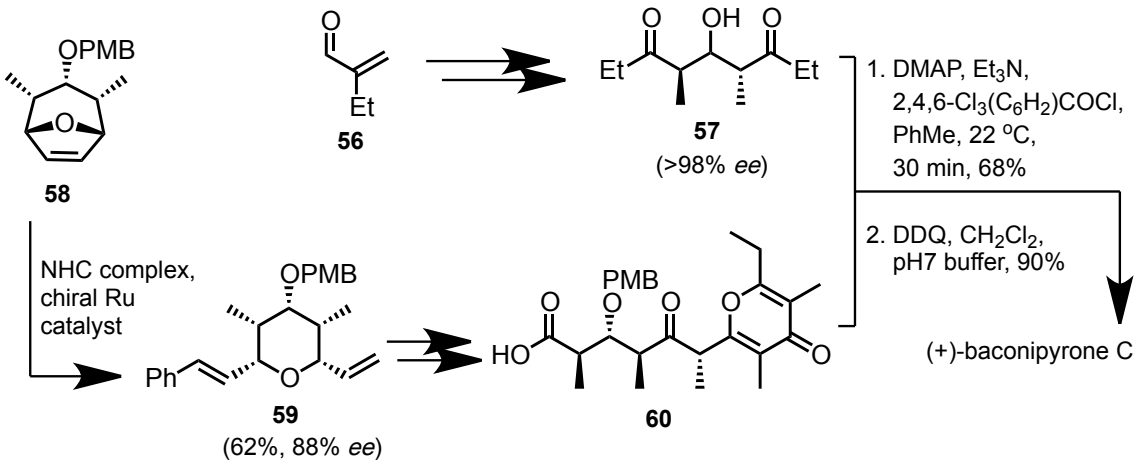
The first total synthesis of (−)-baconipyrone C (**11**) was achieved by Paterson et al. via coupling of alcohol fragment **54** with acid fragment **53** (Scheme 1-10).[22] The acid fragment **53** was prepared from **52** via iterative aldol couplings. The alcohol fragment **54** was prepared from enantiopure ketone *ent*-**41** or from 3-pentanone. After several attempts at the challenging esterification between alcohol **54** and acid **53**, the corresponding ester was generated as an inseparable mixture of diastereomers resulting from epimerization of the acid fragment **53**. However, after modifications of Yonemitsu-Yamaguchi protocol,[19,20] the epimerization was minimized to give the PMB protected baconipyrone C **55** (73%) that underwent oxidative PMB

deprotection with DDQ to give (−)-baconipyrone C (**11**) (67%). This total synthesis was achieved in 17 steps with 13.9% overall yield from **52**.



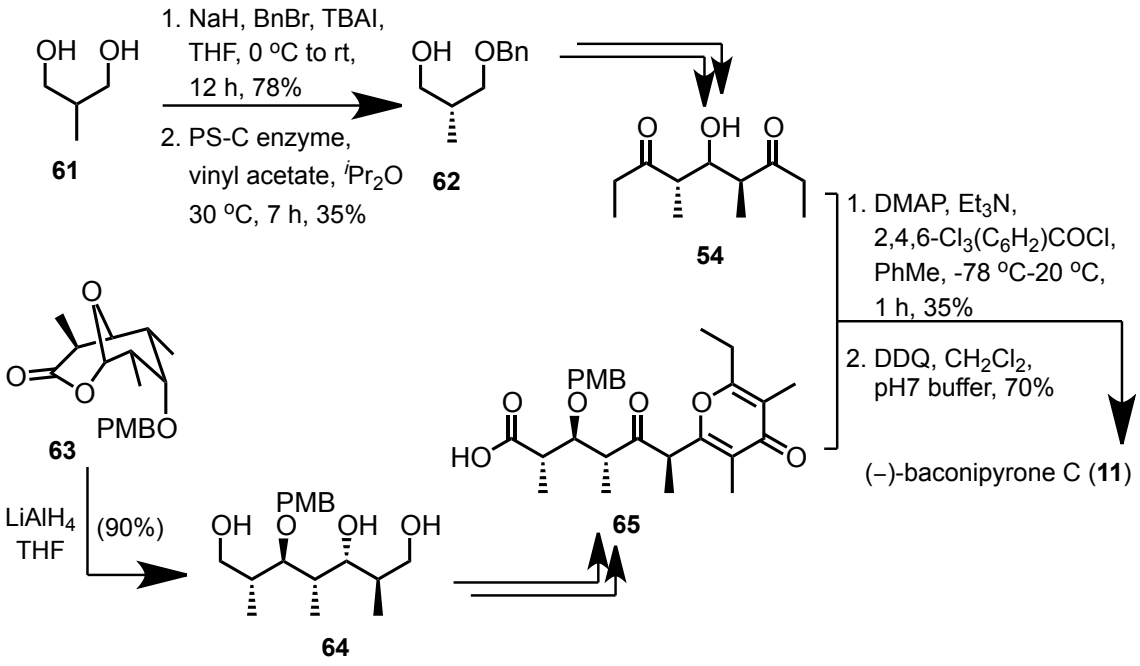
Scheme 1-10: Paterson's synthesis of (−)-baconipyrone C.

Hoveyda et al. used an NHC-catalyzed asymmetric ring opening metathesis (AROM) and asymmetric allylic alkylation (AAA) to achieve the total synthesis of *ent*-baconipyrone C (the unnatural enantiomer) via coupling of alcohol fragment **57** with acid fragment **60** (Scheme 1-11).[23] The desired hydroxy diketone **57** was prepared from aldehyde **56**. The acid fragment **60** was synthesized starting from the oxabicycle **58** via Ru-catalyzed asymmetric ring opening metathesis (AROM) to give highly substituted pyran **59** with 88% *ee*. The pyran **59** was converted to acid **60** that was treated with alcohol **57** under modified Yonemitsu-Yamaguchi esterification conditions as Paterson reported,[22] followed by oxidative removal of PMB group with DDQ afforded the *ent*-baconipyrone C.



Scheme 1-11: Hoveyda's synthesis of (+)-baconipyrone C.

In 2009, Yadav et al. reported a total synthesis of (−)-baconipyrone C by coupling alcohol **54** with acid **65** (Scheme 1-12).[24] Using an enzymatic strategy, the racemic monobenzyl ether of diol **61** was resolved to give the single enantiomer **62** (35%). After chain elongation and functional group manipulations, alcohol **62** was converted to hydroxy diketone **54**. The γ-pyrone acid **65** was prepared from lactone **63**. Final esterification was achieved by treating acid **65** with alcohol **54** under the modified Yonemitsu-Yamaguchi protocol as previously reported by Paterson et al.,[22] followed by oxidative removal of the PMB ether with DDQ afforded the (−)-baconipyrone C (**11**).



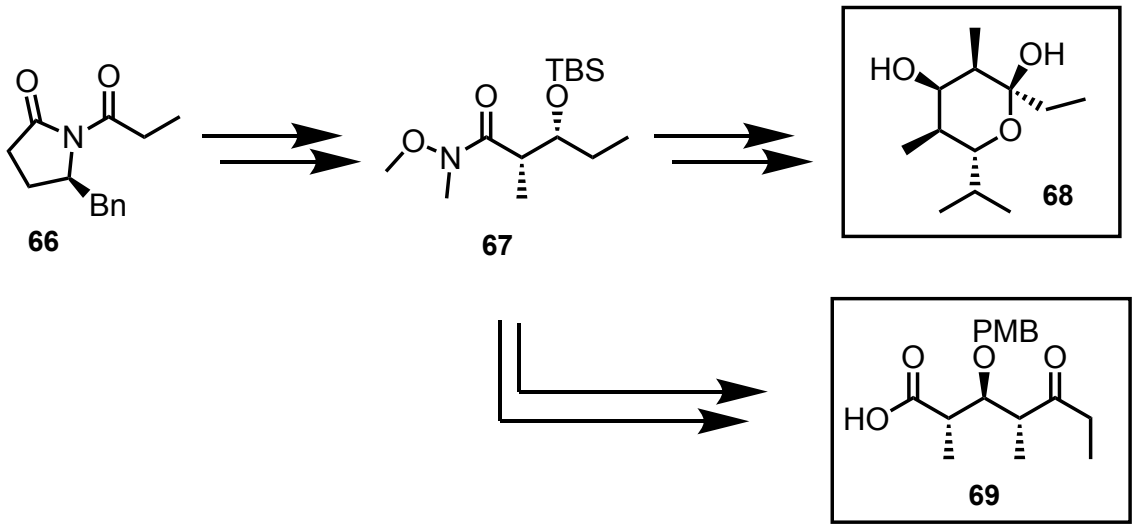
Scheme 1-12: Yadav's synthesis of (−)-baconipyrone C.

1.2.3.4.Towards the total synthesis of dolabriferol

Several research groups worked towards the total synthesis of dolabriferol. Dias et al.[25] and Chênevert et al.[26,27] prepared the corresponding carboxylic acid and alcohol coupling fragments to make the ester link in **15**; however, no coupling of these fragments was reported. Perkins et al.[14] and Toste et al.[28] were able to generate an ester precursor (a non-contiguous carbon chain) to **15**; however, they were unsuccessful in final deprotection to obtain the natural product **15**. The first total synthesis of **15** was achieved by Vogel et al. in 2010 by coupling of the corresponding acid and alcohol.[29] Later, Goodman et al.[15] and Ward et al.[17] accomplished the total synthesis of **15** via a retro-Claisen approach. Very recently, Pabbaraja et al.[30] synthesized **15** via an esterification approach from the corresponding acid and alcohol (similar to Vogel's approach).

Dias approach:

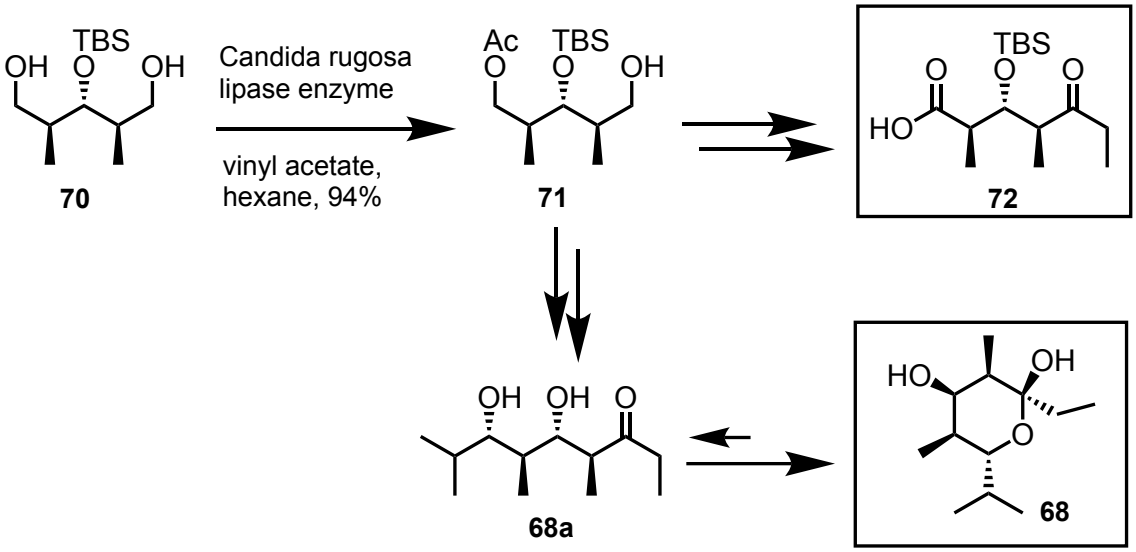
Dias et al. proposed a convergent synthesis of dolabriferol (**15**) via the coupling of the two fragments: keto acid **69** and hemiacetal **68** (Scheme 1-13).[25] Both of these fragments were synthesized from a common enantiopure Weinreb amide **67** that was prepared from the known Evans acyloxazolidinone **66**. Although the two coupling fragments **68** and **69** were synthesized, no esterification to obtain **15** was reported.



Scheme 1-13: Dias synthetic route to alcohol **68** and acid **69**.

Chênevert approach:

Towards the synthesis of dolabriferol (**15**), Chênevert synthesized the two coupling fragments: alcohol **68** and acid **72**, starting from an enzyme mediated desymmetrization of *meso* diol **70** to give the corresponding monoester **71** in excellent yield (94%) with high enantiopurity (97% *ee*) (Scheme 1-14).[26,27] To achieve high enantiopurity, addition of molecular sieves to the medium was essential to trap the byproduct acetaldehyde. The monoester **71** was converted to the desired acid and alcohol fragments **72** and **68**, respectively. However, Chênevert et al. never reported the coupling of **68** and **72** towards synthesis of **15**.

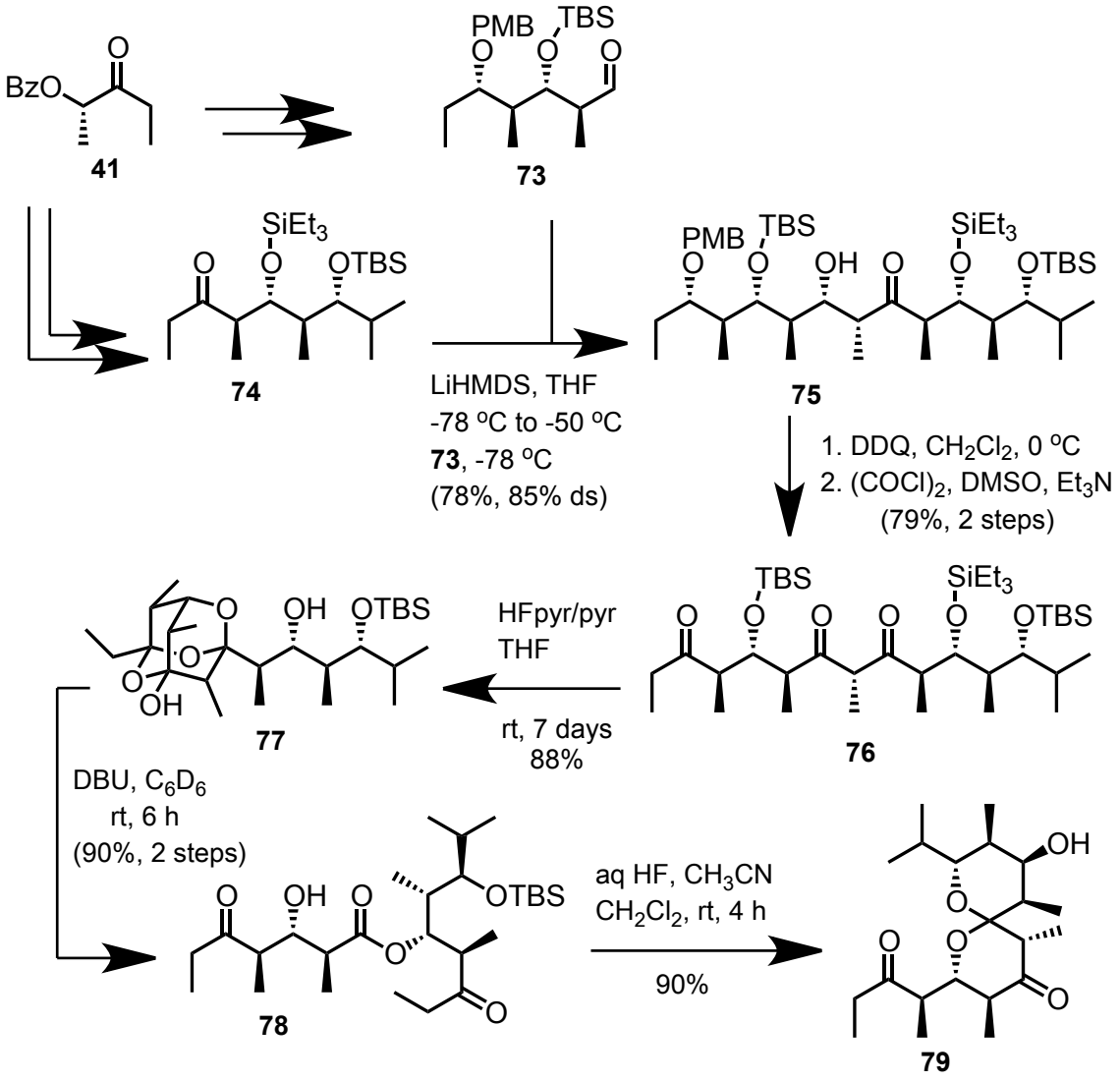


Scheme 1-14: Chênevert synthetic route to alcohol **68** and acid **72**.

Perkins approach:

Lister and Perkins synthesized the desired ester **78** (a non-contiguous carbon chain), a precursor to dolabriferol (**15**), using a retro-Claisen approach; however, they were unsuccessful in transforming **78** to **15** under variety of conditions (Scheme 1-15). Both coupling fragments aldehyde **73** and ketone **74** were synthesized from a common enantioenriched ketone **41**. Having these coupling fragments, the Li-enolate of **74** was generated and treated with aldehyde **73** to give the adduct **75** as a separable mixture of diastereomers (6:1 *dr*). PMB deprotection of **75**, followed by oxidation of the free hydroxy groups gave the trione **76**. Desilylation of **76** using HF·pyridine and pyridine in THF led to a trioxaadamantane **77** that was acid sensitive and decomposed upon exposure to $CDCl_3$. Alternatively, a reaction of **77** with DBU facilitated a retro-Claisen rearrangement to give the desired ester **78**. The final steps to obtain **15** require removal of TBS group from **78** and formation of a cyclic hemiacetal. Attempted removal of TBS group, led to elimination of a hydroxy group (to form an enone) under a variety of desilylation conditions, except in a reaction with aq $HF/CH_3CN/CH_2Cl_2$, where the spiroketal **79** was obtained instead of

15. Despite the challenges to obtain **15** from **78**, this approach demonstrated a base induced retro-Claisen rearrangement of the linear precursor **77** to form the desired ester link in **78**.

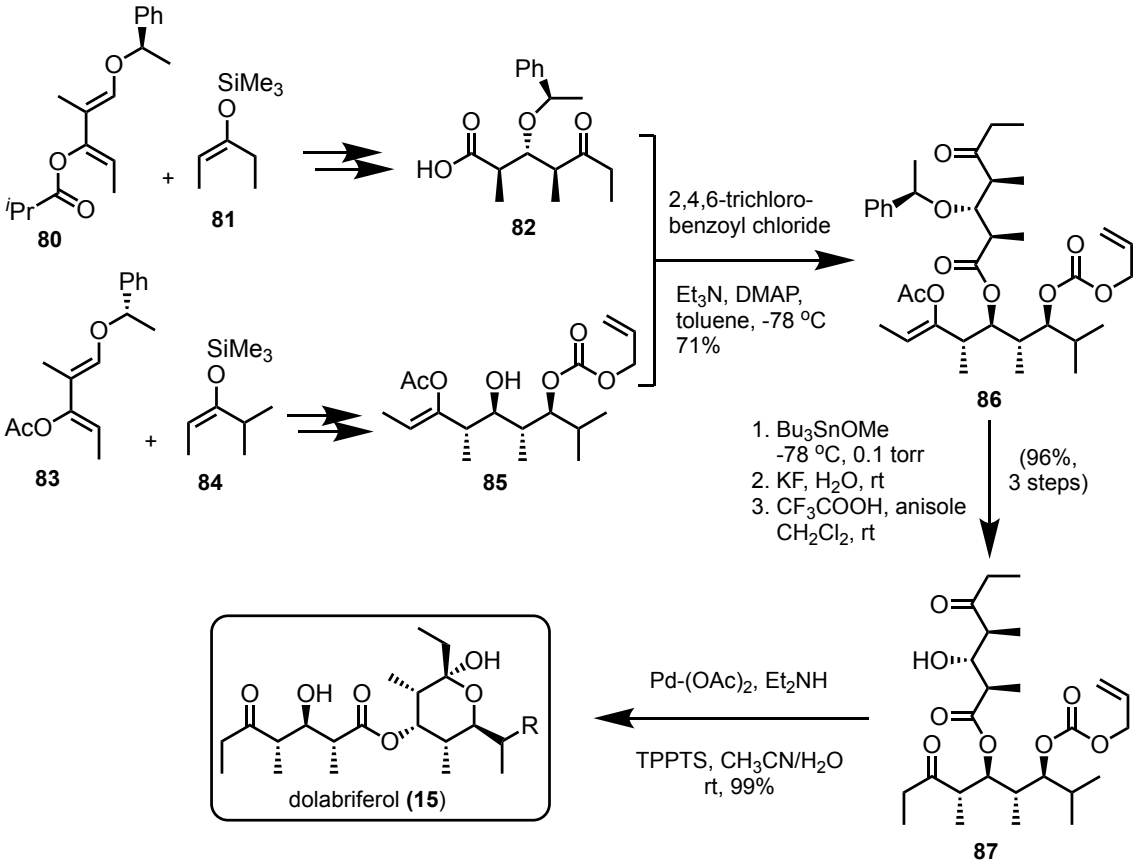


Scheme 1-15: Perkins approach to dolabriferol.

Vogel approach:

Vogel and co-workers achieved the first total synthesis of dolabriferol (**15**) and established its absolute configuration (Scheme 1-16).[29] The key ester link in **15** was established by direct

esterification of acid **82** with acyclic alcohol **85**.[i] Both these coupling partners **82** and **85** were synthesized from a common SO_2-induced oxyallylation cascade reaction. Esterification of acid **82** with alcohol **85** (less hindered than the cyclic alcohol **68**) using modified Yonemitsu-Yamaguchi esterification protocol[22] provided **86** as a 9:1 mixture of diastereomers. Selective removal of acetyl group in **86**, followed by cleavage of phenylethyl ether resulted in the formation of the precursor **87**. Final alloc deprotection (easier than the silyl deprotection as in Perkins approach) generated the free alcohol that underwent hemiacetal formation to give **15**. Using an identical approach, a stereoisomer of **15** was also synthesized.



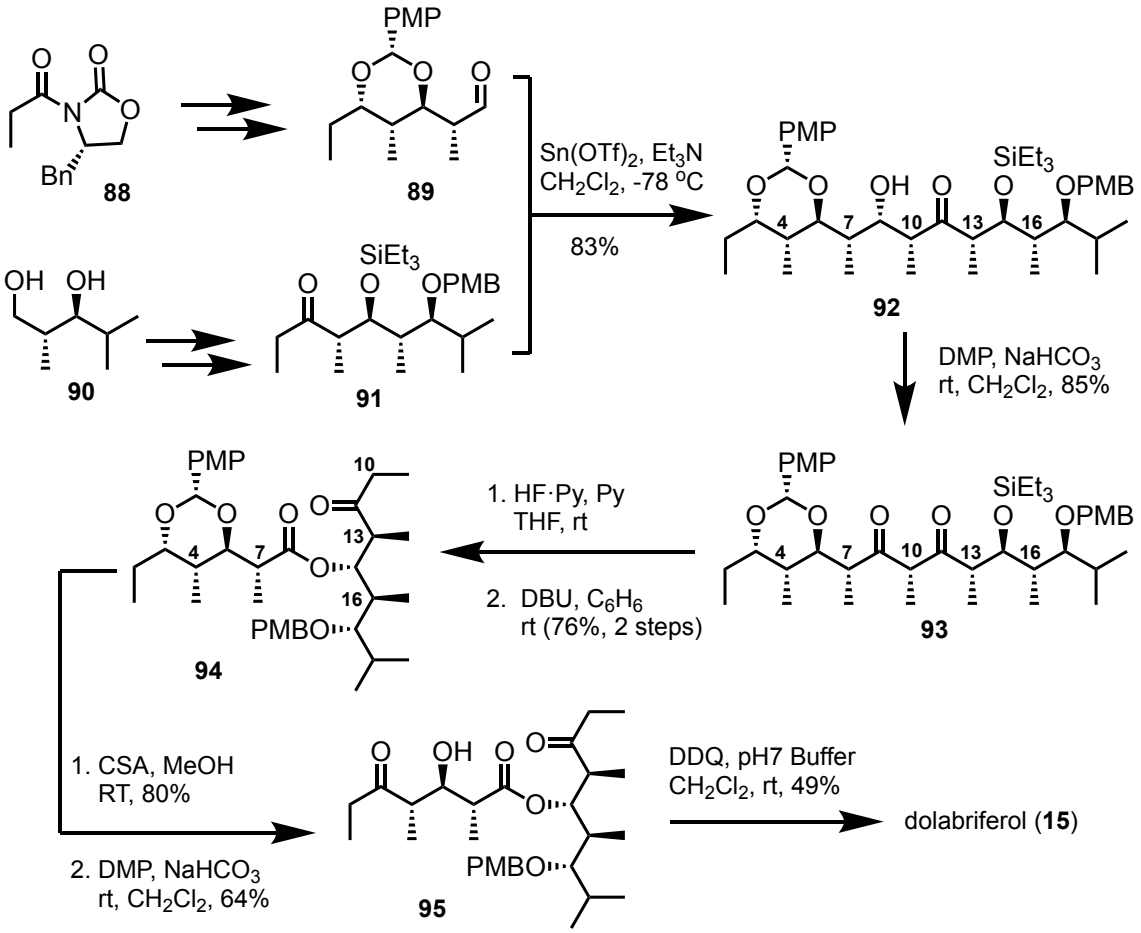
Scheme 1-16: Vogel approach to dolabriferol.

[i] Direct esterification of the acid **82** with the known cyclic alcohol **68** failed to give the corresponding ester.

Goodman approach:

Goodman et al. achieved the total synthesis of dolabriferol (**15**) via a retro-Claisen approach from the PMB-protected contiguous precursor **95** (Scheme 1-17).[15] The full carbon skeleton **92** required for **15** was prepared by a stereoselective aldol coupling of ketone **91** with aldehyde **89**. The aldehyde **89** was prepared from Evans oxazolidinone **88** and the ketone **91** was prepared from the diol **90** that was generated from a one-pot L-proline catalyzed aldol reaction of propanal with isobutyraldehyde and $NaBH_4$ reduction as reported by MacMillan[31].

Coupling aldehyde **89** with the Sn-enolate of ketone **91** afforded the adduct **92** with good diastereoselectivity (12.6:1, *dr*) (Scheme 1-17). Oxidation of the free hydroxy group in **92** produced the stable diastereomer **93** with no evidence of epimerization at C-10. Removal of the silyl ether in **93** with HF·pyridine and pyridine in THF, followed by DBU induced retro-Claisen rearrangement furnished the adduct **94** (a non-contiguous carbon chain) with the desired ester link. Removal of the PMP acetal in **94**, followed by oxidation of the terminal hydroxy group with DMP afforded **95**. The final oxidative removal of PMB protecting group in **95** with DDQ allowed hemiacetal formation to give **15**. This total synthesis was accomplished in 15 steps with 4% overall yield from propanal. Although this synthesis demonstrated a retro-Claisen rearrangement of the precursor **93** to form dolabriferol (**15**), the PMB and PMP-acetal protection groups in **93** blocked possible competing retro-Claisen reactions.

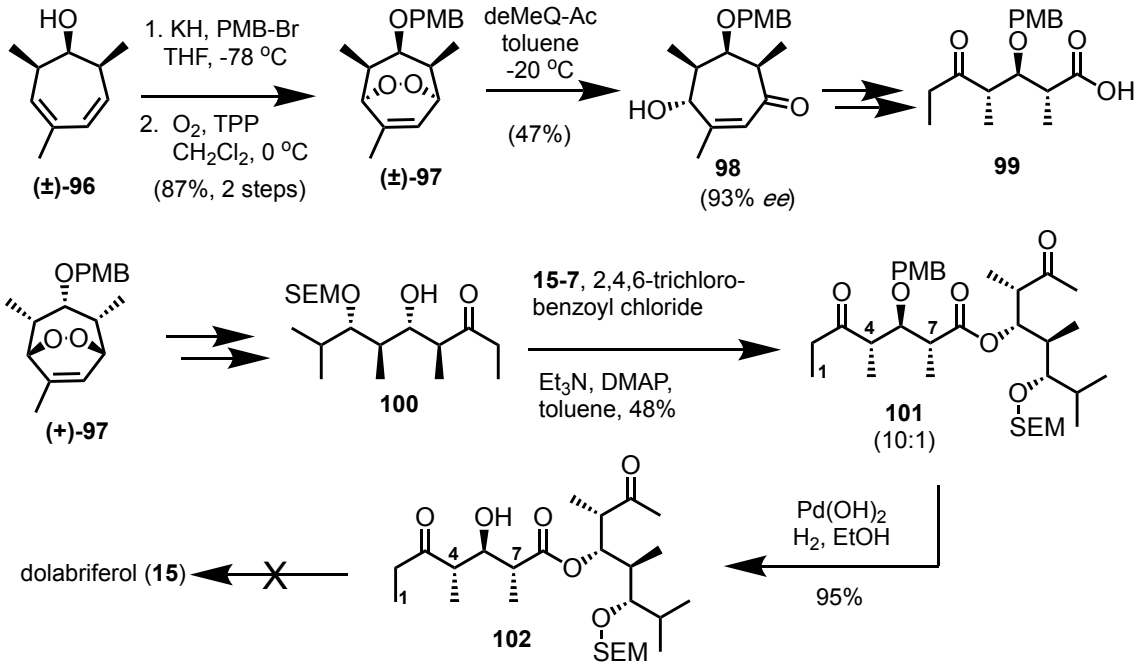


Scheme 1-17: Goodman approach to dolabriferol.

Toste approach:

Toste et al. used a novel Kornblum-DeLaMare enantiomeric resolution to generate the two coupling fragments **99** and **100** for dolabriferol (**15**) from a common precursor **(±)-96** (Scheme 1-18).[28] Although, Toste and co-workers achieved the synthesis of the non-contiguous precursor **102**, final deprotection was unsuccessful to obtain the natural product **15**. Towards the synthesis of **15**, Toste et al. chose racemic peroxide **(±)-97** as a precursor that originated from a [4+2] addition of singlet oxygen to the PMB derivative of diene **(±)-96**. Under optimized Kornblum-DeLaMare enantiomeric resolution the racemic peroxide **(±)-97** provided the enone **98** (93% *ee*) that was converted to the desired carboxylic acid **99**.

Enantiomer **(+)-97** was converted to the desired alcohol **100** (Scheme 1-18). Coupling of acid **99** with alcohol **100** was attempted using Yamaguchi esterification conditions;[19] however, during esterification, racemization at C-4 stereocenter was observed resulting an inseparable mixture of diastereomers **101** (10:1). This 10:1 mixture was separated after removal of the PMB group from **101** to obtain alcohol **102** as a single diastereomer. Final removal of SEM-ether from **102** led to either elimination or no reaction under variety of conditions. Alternatively, TES, TBS and BOM variants were synthesized, but none of them afforded the natural product **15**. Although Toste et al. were unsuccessful to obtain **15**, their method generated enantiopure non-contiguous precursor **102**.

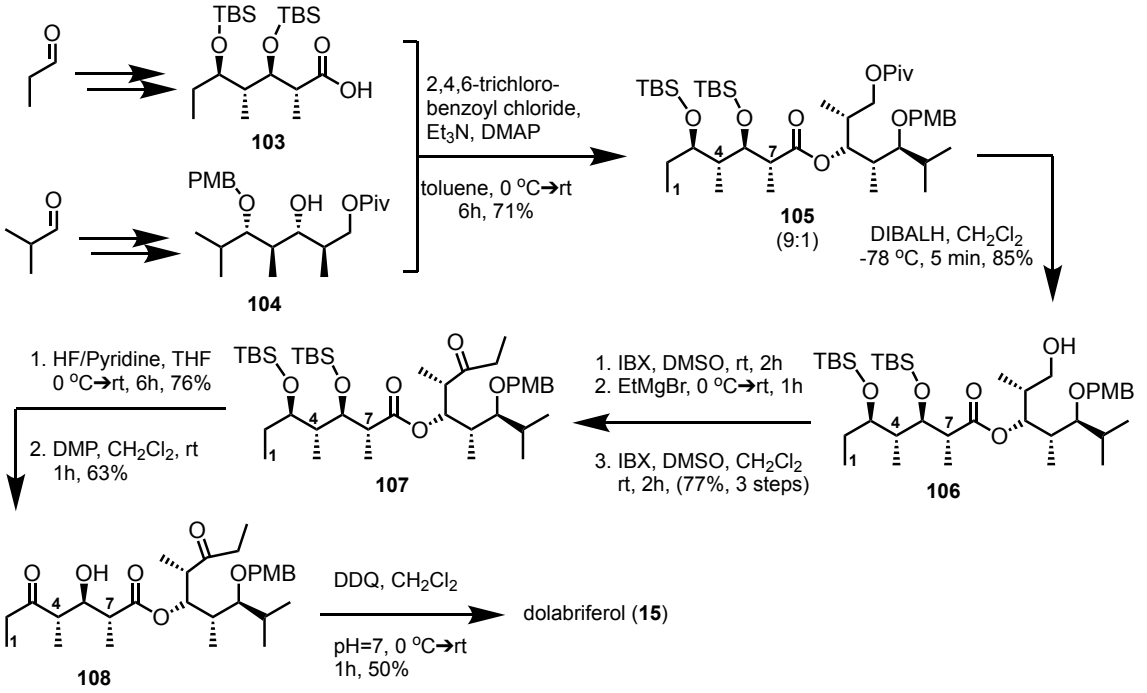


Scheme 1-18: Toste approach to dolabriferol.

Pabbaraja approach:

Pabbaraja et al. reported the total synthesis of dolabriferol (**15**) in 2018 via esterification of acid **103** with alcohol **104** (Scheme 1-19).[30] Acid **103** and alcohol **104** were prepared starting

from propanal and isobutyraldehyde, respectively.[ii] After several attempts, coupling of acid **103** with alcohol **104** was achieved under Yamaguchi esterification conditions[19] affording the ester **105** as an inseparable mixture of diastereomers (9:1, *dr*). The pivaloyl group was removed by treating **105** with DIBALH to give alcohol **106**. Subjecting alcohol **106** to a series of oxidation-Grignard-oxidation reactions produced ketone **107**. Silyl ether removal in **107** followed by selective oxidation of the least hindered alcohol with DMP afforded the known[15] precursor **108**. Oxidative removal of PMB group in **108** with DDQ facilitated the hemiacetal formation to give **15**. This total synthesis was accomplished in 17 steps (LLS) from commercially available propanal with 3% overall yield.



Scheme 1-19: Pabbaraja approach to dolabriferol.

From all the above synthetic approaches towards dolabriferol (**15**), it is clear that coupling of the corresponding carboxylic acid with alcohol and the choice of protecting group (and

[ii] Initially, an analogous alcohol was prepared as TBS-ether, but this alcohol with TBS group did not couple with acid **103** under variety of esterification conditions.

deprotection conditions) at the late stage of the synthesis were crucial to achieve the natural product **15**.

1.2.4. Total synthesis of non-contiguous polypropionates (by Ward group)

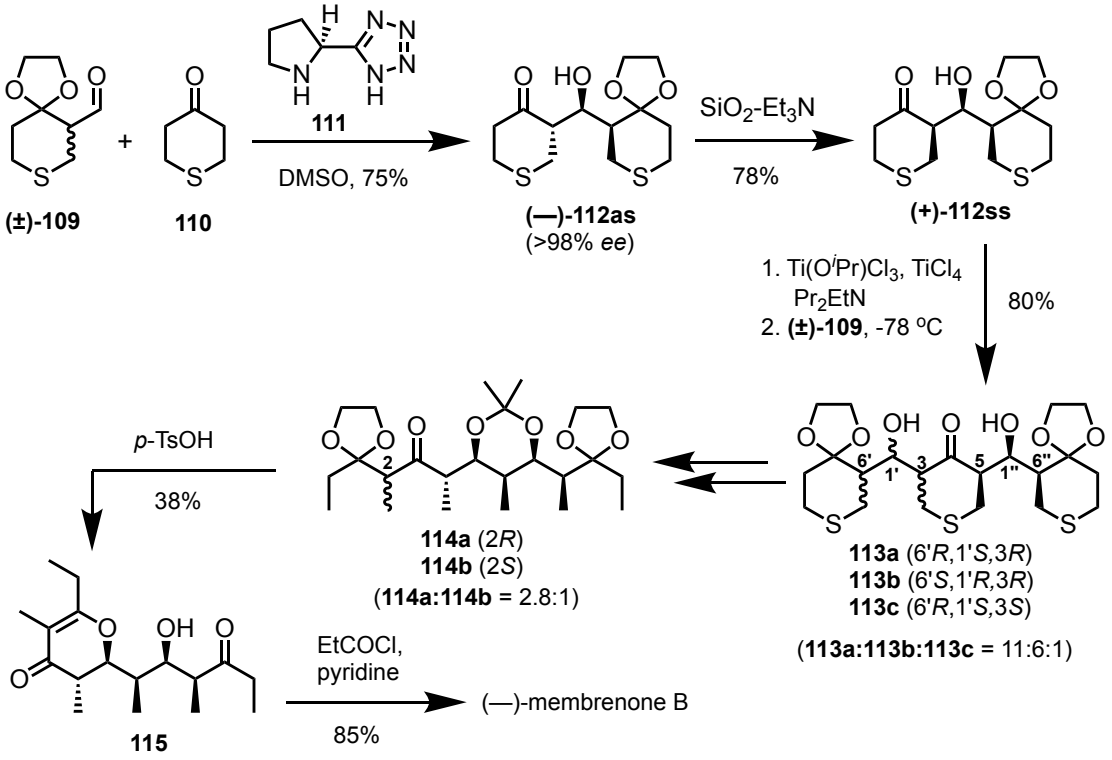
The Ward group has synthesized several polypropionates by developing the thiopyran route to polypropionates (TR2P) and the acyclic thiopyran route to polypropionates (ATR2P) strategies. Among thirteen non-contiguous polypropionates, Ward and co-workers have synthesized (−)-membrenone B, baconipyrone A, baconipyrone C, dolabriferol, and dolabriferol C, to date.[iii] The TR2P and the ATR2P are attractive strategies for the rapid assembly of hexapropionate synthons from simple and readily available precursors (for detailed discussion of these strategies, please refer to section **1.3**).

1.2.4.1. Total synthesis of (−)-membrenone B

Ward et al. synthesized (−)-membrenone B, the unnatural enantiomer, using dynamic kinetic resolution (DKR) and kinetic resolution (KR) strategy to access enantiopure hexapropionates **114a** and **114b** from racemic and achiral materials (Scheme 1-20).[32] In a previous study, the tetrapropionate (−)-**112as** was prepared in good yield (75%)[iv] with high enantiopurity (>98% *ee*) via a tetrazole derivative **111** catalyzed aldol reaction of (±)-**109** with **110**, which proceeds with dynamic kinetic resolution (DKR).[33] The *anti,syn*-diastereomer **112as** was isomerized to the desired *syn,syn*-diastereomer **112ss** using the known[34] isomerization conditions. A reaction of the Ti-enolate of enantiopure ketone (+)-**112ss** with racemic aldehyde (±)-**109** that

[iii] The synthetic route to (−)-membrenone B also constitutes a formal synthesis of (−)-membrenone A.
[iv] Although yields were improved further (up to 85%) at lower reaction concentrations, a large excess of **110** (6-12 equiv) was required.

proceeds with kinetic resolution gave the enantiopure adducts **113a, 113b, 113c** as 11:6:1 mixture of diastereomers, respectively. This mixture was converted to **114a, 114b** as a 2.8:1 mixture of diastereomers, respectively. Brief exposure of the mixture **114a:114b** (2.8:1) to *p*-TsOH in CH_2Cl_2 gave the known[18] γ-dihydropyrone **115** via cyclization and elimination. The γ-dihydropyrone **115** serves as a common precursor for the synthesis of (−)-membrenones A and B. Thus, final acylation of **115** with propanoyl chloride in the presence of pyridine gave (−)-membrenone B. Because the synthesis of (−)-membrenone A is known from the common precursor **115**, this route also constitutes a formal synthesis of (−)-membrenone A.

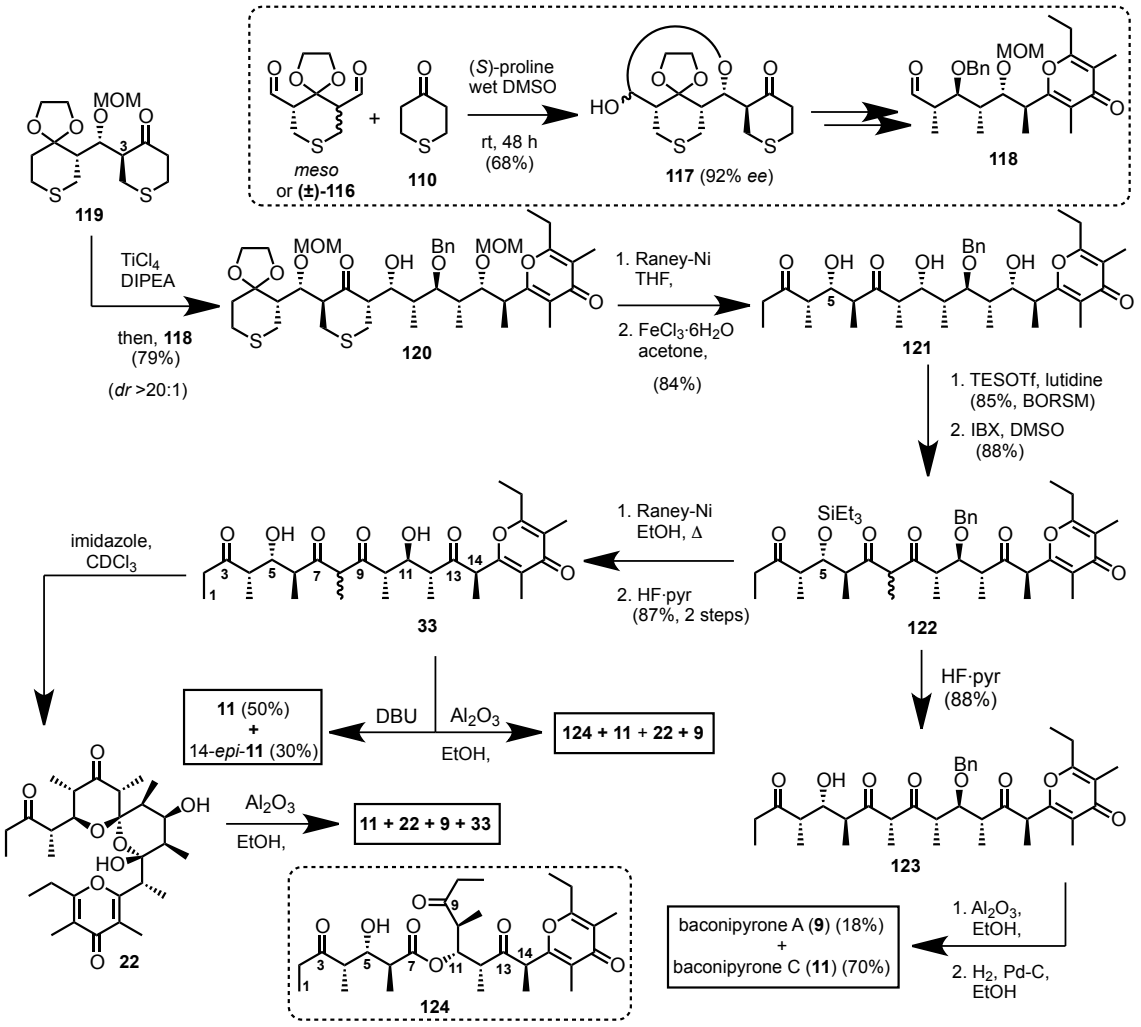


Scheme 1-20: Ward approach to (−)-membrenone B (adapted from ref. 32).

1.2.4.2. Total synthesis of baconipyrone A and baconipyrone C via their putative common precursor (a retro-Claisen approach)

Ward et al. accomplished a "biomimetic" synthesis of complex non-contiguous polypropionates baconipyrone A (**9**) and baconipyrone C (**11**) from their common putative contiguous precursor **123** via a retro-Claisen rearrangement (Scheme 1-21). The known tetrapropionate **117** was prepared from a proline catalyzed aldol reaction of **110** with a mixture of *meso* and racemic aldehyde **116** that proceeds with enantiotopic group selectivity with dynamic kinetic and thermodynamic resolution.[35] Tetrapropionate **117** was converted to aldehyde **118** that was used in aldol reaction with the Ti-enolate of the known ketone **119**[33,35] to give the adduct **120** as a single diastereomer. The high stereoselectivity under these conditions was governed and predicted by the known diastereoface selectivities of ketone **119** (reaction occurs selectively from the *trans* face of the C-3 substituent)[36,37] and aldehyde **118** (addition is highly Felkin-selective)[38]. Desulfurization of **120** with Raney nickel, followed by a simultaneous $FeCl_3$-mediated acetal hydrolysis[39,40] and MOM-deprotection resulted the triol **121**. Selective protection of the C-5 hydroxy group in **121** as triethylsilyl (TES) ether,[v] followed by IBX oxidation produced the tetraone **122** as a mixture of keto-enol tautomers. Sequential removal of benzyl and silyl ethers in **122** afforded the desired precursor **33** as a complex mixture of ring-chain and keto-enol tautomers.

[v] The triol **121** was regenerated from the corresponding undesired bis TES-protected adduct by deprotection and was recycled to **122**.



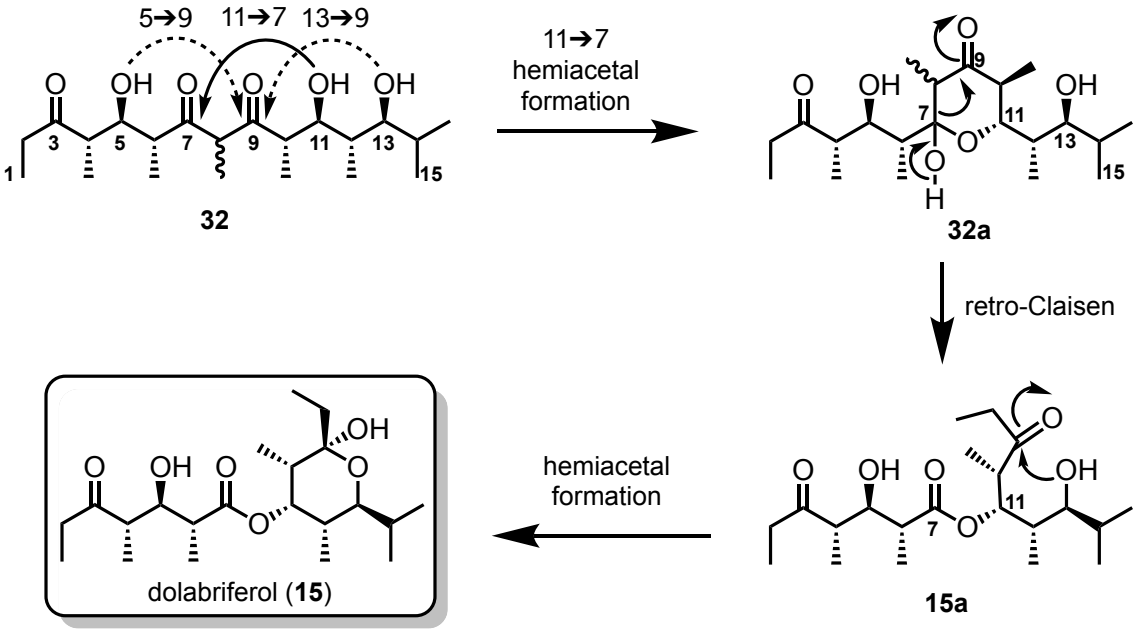
Scheme 1-21: Ward retro-Claisen approach to baconipyrones A and C (adapted from ref. 16).

The isomerization or rearrangement of **33** was examined under various conditions (Scheme 1-21). On treatment with imidazole in $CDCl_3$ for 24 h, **33** isomerized to the thermodynamically more stable siphonarin B (**22**) (ca. 70%); while treatment of **33** with DBU in C_6D_6 for 1 h induced a retro-Claisen rearrangement (via a hemiacetal generated from C5-OH to C9-C=O) to give a 2:1 mixture of baconipyrone C (**11**) and 14-*epi*-**11**, respectively. Alternatively, subjecting the precursor **33** to neutral alumina in refluxing ethanol for 1 h (a similar condition for retro-Claisen rearrangement was reported by Albizati[12]) provided a 10:7:5:3 mixture of **124** (undesired retro-Claisen adduct formed via a hemiacetal generated from C11-OH to C7-C=O), **11**, **22** and **9**,

respectively. Under the same neutral alumina conditions, **22** produced 3:2.3:1:1 mixture of **11**, **22**, **9** and **33**, respectively. Surprisingly, **123** (obtained from TES-ether removal of **122**) was stable under the identical neutral alumina conditions; however, using basic alumina produced a 4:1 mixture of retro-Claisen adducts that, after hydrogenolysis of the benzyl ether, gave **9** (18%) and **11** (70%). These results suggest that the in situ generated enolate of **11** or its benzyl ether (generated by retro-Claisen rearrangement of precursor **33** or **123**) underwent a stereoselective intramolecular aldol coupling with the proximal ketone to give **9** or its benzyl ether. These results demonstrate that baconipyrones A (**9**) and C (**11**) are plausible isolation artifacts and suggest that they were more likely generated from **22** than directly from **33**, a plausible biosynthetic product.

1.2.4.3. Total synthesis of dolabriferol from the putative contiguous precursor (a retro-Claisen approach)

Similar to the baconipyrone syntheses,[16] Ward et al. intended to synthesize the putative contiguous precursor **32** and examine its propensity to undergo a selective retro-Claisen rearrangement to give dolabriferol (**15**) (Scheme 1-22). According to Goodman's calculations,[41] the formation of 13→9 hemiacetal is more favorable among the three possible hemiacetals in precursor **32**; however, only the 11→7 hemiacetal can lead to **15**.

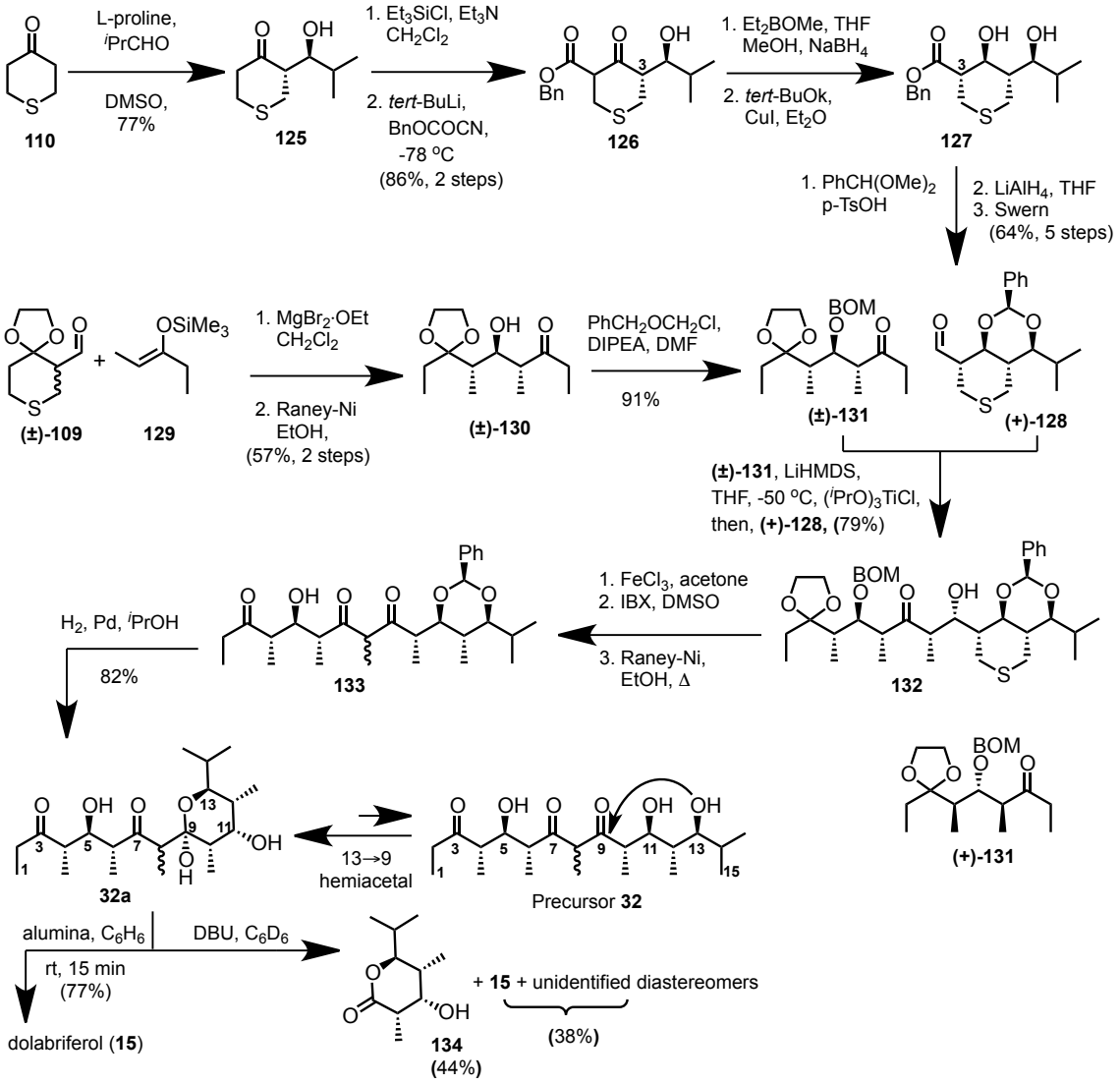


Scheme 1-22: Regioselective retro-Claisen rearrangement of **32** to **15**.

The synthesis was initiated from a proline catalyzed enantioselective aldol reaction of **110** with isobutyraldehyde to produce **125** as the only product with good enantioselectivity (92% *ee*) (Scheme 1-23). Silyl protection of the hydroxy group in **125**, followed by reaction of the corresponding Li enolate with BnO_2CCN provided the β-ketoester **126**. Hydroxy-directed stereoselective reduction of **126**, generated a 1:1 mixture of 1,3-*syn* diols **127** and 3-*epi*-**127**. However, the mixture was successfully isomerized to the single diastereomer (3*S*)-**127** in presence of *tert*-BuOK and CuI. Protection of the diol (3*S*)-**127** as benzylidene acetal followed by reduction of ester gave the corresponding alcohol that was oxidized to the desired aldehyde (+)-**128**. Mukaiyama aldol reaction of (±)-**109** with **129** (4:1 *dr*), followed by desulfurization gave the hydroxy ketone (±)-**130** that was converted to the corresponding BOM derivative (±)-**131**. Aldol reaction of Ti-enolate of (±)-**131** with aldehyde (+)-**128** (7:1 *dr*) that proceeds with kinetic

resolution gave the adduct **132** along with (+)-**131**.[vi] The 8,9-*syn*-9,10-*syn* relative configuration in **132** was expected based on known diastereoselectivities from similar substrates and reaction conditions.[42,43] $FeCl_3$ catalyzed acetal hydrolysis of **132**, oxidation of the C9-hydroxy group with IBX, and simultaneous desulfurization and hydrogenolysis of BOM group gave **133** as a 10:10:1 mixture of two keto and enol tautomeric forms, respectively. Hydrogenolysis of the benzylidene acetal in **133** with freshly prepared Pd black (excess) in ^{i}PrOH under H_2 atmosphere (4 bar) cleanly produced the precursor **32** that exists predominantly as a 1.5:1 mixture of hemiacetals **32** ((9S), 13→9; epimeric at C-8) consistent with Goodman's calculations. Treatment of **32** with DBU in benzene produced a 3:6:1 mixture of **15** and two unidentified diastereomers, respectively (38%), and the known lactone **134** (ca. 44%), among others. The formation of **15** and **134** indicates that the retro-Claisen fragmentation occurred at C7-C8 bond in 11→7 hemiacetal and at C8-C9 bond in 13→9 or 5→9 hemiacetal, respectively. Treatment of **32** with neutral alumina in benzene (known conditions[12,16]) furnished **15** in good yield. Formation of **15** and absence of **134** indicates a regioselective retro-Claisen rearrangement occurred at C7-C8 bond in the 11→7 hemiacetal of the precursor, where the hemiacetal equilibration (between 11→7 and 13→9 hemiacetals) is rapid.

[vi] Recovery of **(+)-131** (ca. 20% *ee*) confirming the preferential reaction of **(+)-128** with enantiomer **(-)-131** has occurred.

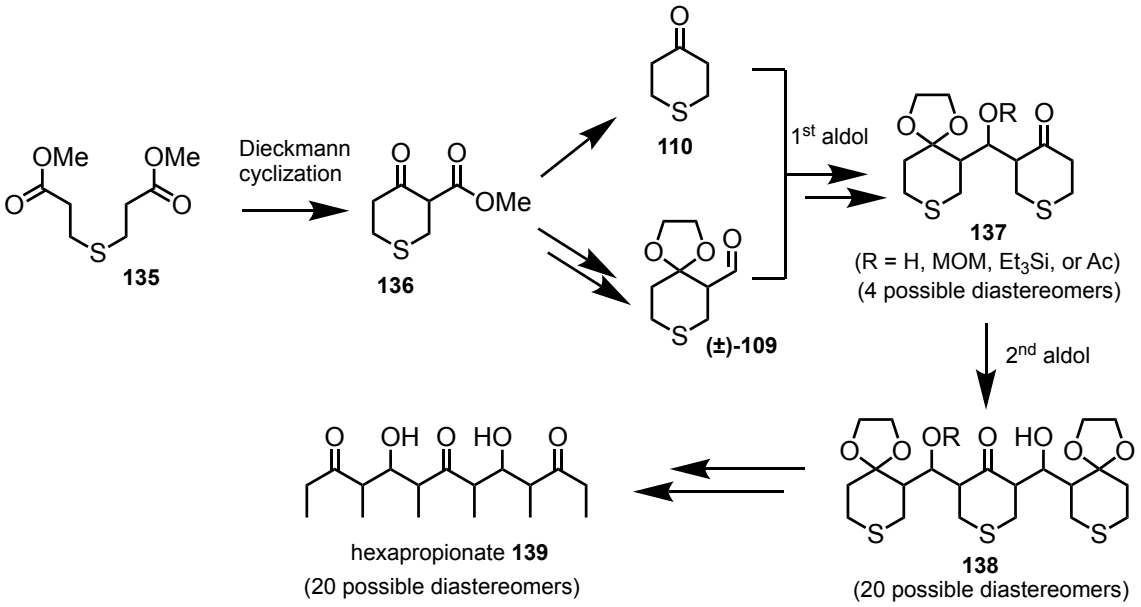


Scheme 1-23: Ward's retro-Claisen approach to dolabriferol (adapted from ref. 17).

The Ward group established synthetic routes to obtain the putative contiguous precursors (plausible biosynthetic products) and showed their rearrangements to produce the 'non-contiguous natural products' baconipyrone A, baconipyrone C and dolabriferol. These results provided experimental evidence in support of the earlier hypothesis on the origin of non-contiguous polypropionates and demonstrated that the so-called non-contiguous natural products are plausible isolation artifacts.

1.3. Ward Group Synthetic Strategy Towards Polypropionates

The Ward group has developed efficient strategies (e.g., the thiopyran route to polypropionates-TR2P and the acyclic thiopyran route to polypropionates-ATR2P) using stereoselective aldol reactions to access racemic and enantiopure polypropionates from simple chiral or achiral substrates.[42,44] The TR2P is well-established and has been an active research theme in the Ward group to access tetrapropionate motifs **137** and hexapropionate motifs **138** selectively from readily available starting materials (Scheme 1-24). Tetrahydro-4*H*-thiopyran-4-one (**110**) and β-ketoester **136** are the most common starting materials for the preparation of the thiopyran motifs. Ward et al. developed an efficient method to prepare **110** and **136** conveniently on large scales (50-700 g) without chromatography.[45] The TR2P strategy has several advantages including simple preparation methods, versatile reaction chemistry and relative ease of removal of sulphur from the products.



Scheme 1-24: The thiopyran route to polypropionates (TR2P).

The four possible monoaldol diastereomers (tetrapropionate synthons) **137** (Scheme 1-24) can be selectively produced from aldol reactions of ketone **110** with aldehyde **(±)-109** by varying

the reaction conditions.[43,46] The diastereomers **137** can be prepared in enantiopure form by using proline (or a derivative) to achieve enantioselective aldol or retro-aldol reactions.[33,35] Aldol reactions of **137** with aldehyde **(±)-109** give the bisaldol adducts **138** (20 possible diastereomers with R = H).[36,37] The hexapropionate synthons **138** can be transformed into various polypropionate motifs using a variety of reactions (e.g., desulfurization, reductions, desymmetrization).

The diastereoselectivities in a kinetically controlled aldol reaction of two chiral coupling partners (ketone and aldehyde) can be qualitatively predicted and rationalized by application of the multiplicativity rule.[37,47–49] In this approach, the stereoselectivity is factorized into three stereocontrol elements:[32,44,50] (1) *The relative topicity* (***R***, also known as *simple diastereoselectivity*); (2) *The diastereoface selectivity for the chiral ketone enol(ate)* (***E***); and (3) *The diastereoface selectivity for the chiral aldehyde* (***A***). In general, an aldol reaction of a simple ethyl ketone with an aldehyde can produce adducts with up to two new stereogenic centers (i.e., up to four stereoisomers can be formed) (Scheme 1-25a). For any given adduct diastereomer resulting from a kinetically controlled aldol reaction of an enolate derivative with an aldehyde, inspection of the adduct's structure reveals which face of the enolate (*re* or *si*) has added to which face of the aldehyde (*re* or *si*) and thereby the senses of the three stereocontrol elements involved.

(1) *The relative topicity* (***R***, also known as *simple diastereoselectivity*): The relative topicity of a reaction leading to a specific adduct is assigned according to whether that adduct was formed by addition of "*like*" (*re-re* and *si-si*) verses "*unlike*" (*re-si* and *si-re*) faces[51] (Scheme 1-25a).[vii] More commonly, the relative topicity is designated by the relative configuration of the newly formed two stereocenters (i.e., *syn* or *anti*). When a reaction

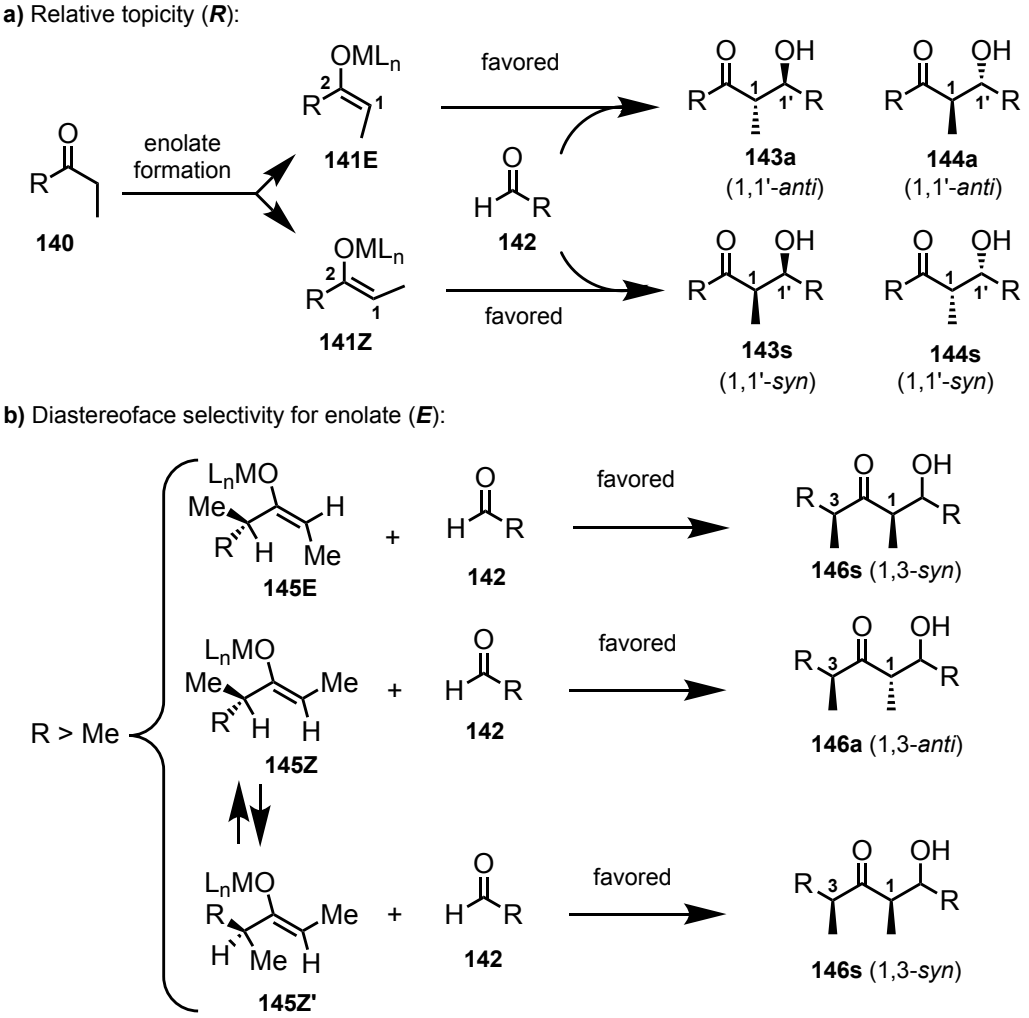
[vii] "The *like* and *unlike* descriptors specify the relationship between the absolute configurations of the reactant enantiomers" (see ref. 30).

leads to more than one diastereomer, the preferred relative topicity (and the extent of preference) of the reaction is the greater of the mole fractions (ratio of the mole fractions) of products formed with "*like*" verses "*unlike*" relative topicity. In most aldol reactions, the preferred relative topicity is strongly correlated to the geometry of the enolate; i.e., (*E*) and (*Z*)- enolates produce 1,1′-*anti* (e.g., **143a**, **144a**) and 1,1′-*syn* (e.g., **143s**, **144s**) adducts, respectively. This outcome can be explained via "closed" (a six-membered chair-like conformation) transition-states.

(2) *The diastereoface selectivity for the chiral ketone enol(ate)* (***E***): A chiral enolate will have two diastereotopic faces (*re* and *si*), and these faces can be differentiated by their relationship with an existing stereocenter in the enolate- "*like*" (*R-re, S-si*) versus "*unlike*" (*S-re, R-si*). The two faces will have different reactivity and, for any adduct, the reacting face is revealed by the structure of that adduct. The diastereoface selectivity (and the extent of the selectivity) of the reaction is the greater of the mole fractions (ratio of the mole fractions) of adducts formed by addition to the "*like*" verses "*unlike*" diastereofaces. More commonly, the diastereoface selectivity for addition to the enolate is designated by relative configuration of the newly formed stereocenter in the adduct to a preexisting stereocenter in the starting ketone (i.e., *syn* or *anti*) (Scheme 1-25b). An important factor that contributes to this diastereoselectivity is the preferred torsion angle of the C-C bond between an α-stereocenter and the enolate (i.e., H−C*−C=C torsion) and this torsion angle will be strongly influenced by allylic 1,3-strain.

(3) *The diastereoface selectivity for the chiral aldehyde* (***A***): The chiral aldehyde will have two diastereotopic faces (*re* and *si*), and these faces can be differentiated by their relationship with an existing stereocenter in the aldehyde- "*like*" (*R-re, S-si*) versus "*unlike*" (*S-re, R-*

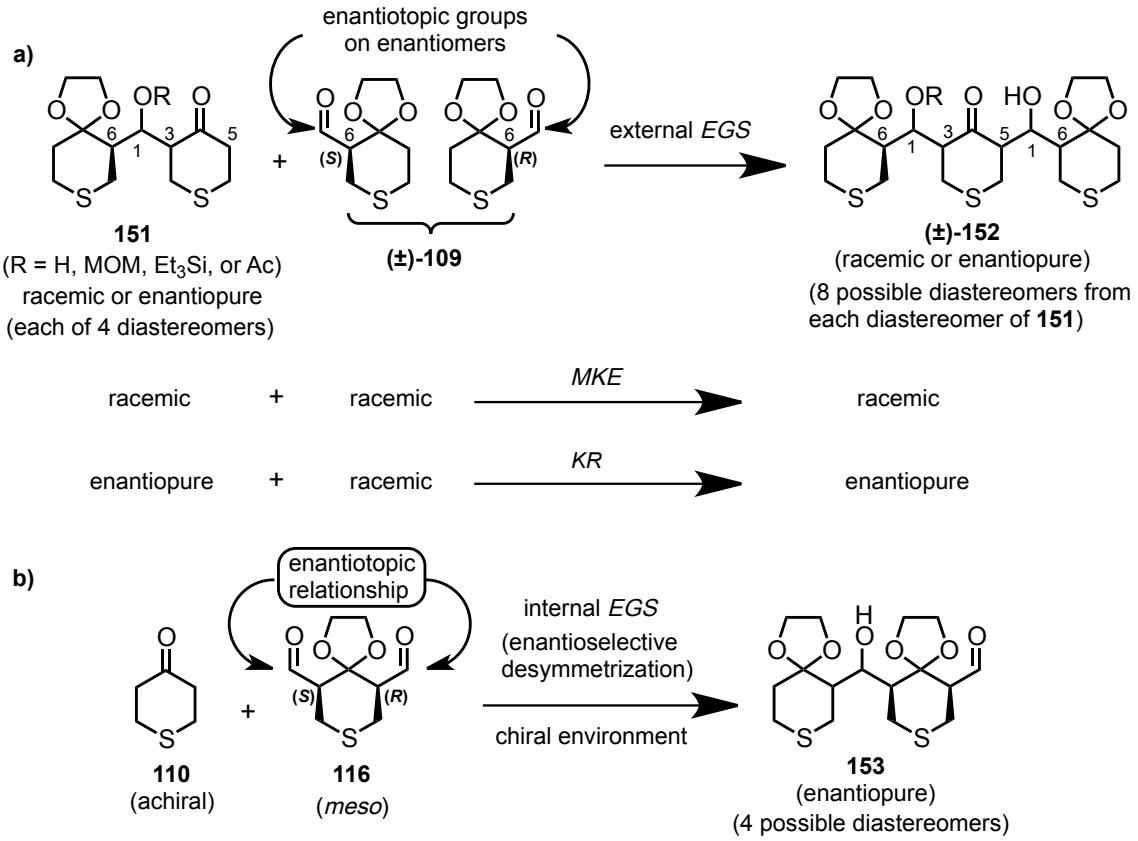
si). The two faces will have different reactivity and, for any adduct, the reacting face is revealed by the structure of that adduct. The diastereoface selectivity (and the extent of the selectivity) of the reaction is the greater of the mole fractions (ratio of the mole fractions) of adduct formed by addition to the "*like*" verses "*unlike*" diastereofaces. More commonly, the diastereoface selectivity for addition to the aldehyde is designated by relative configuration of the newly formed stereocenter in the adduct to the preexisting stereocenter in the starting aldehyde (i.e., *syn* or *anti*) (Scheme 1-25c). The diastereoselectivities are usually predicted (depending on the nature of the C-2 substituent) using the Felkin-Anh[52–54] (in absence of chelating effects), Cram-Chelate[55–57] (in presence of chelating effects) or Cornforth-Evans[58–60] (in presence of polar substituent at C-2) transition-state models.



Scheme 1-25: Favored stereoselectivities in aldol reactions influenced by stereocontrol elements.

1.3.1. Enantiotopic group selective (EGS) aldol reactions

In enantiotopic group selective (EGS) aldol reactions, enantiotopic groups are differentiated in a chiral environment (i.e., with a chiral reagent or catalyst or reactant). The enantiotopic groups must have substantially different reactivities (e.g., >10:1) in this chiral environment for an EGS reaction to have synthetic utility. Enantiotopic group selective aldol reactions are categorized into two types: i) external enantiotopic group selective aldol reactions (e.g., mutual kinetic enantioselection (MKE) and kinetic resolution (KR)); ii) internal enantiotopic group selective aldol reactions (e.g., enantioselective desymmetrization) (Scheme 1-26).



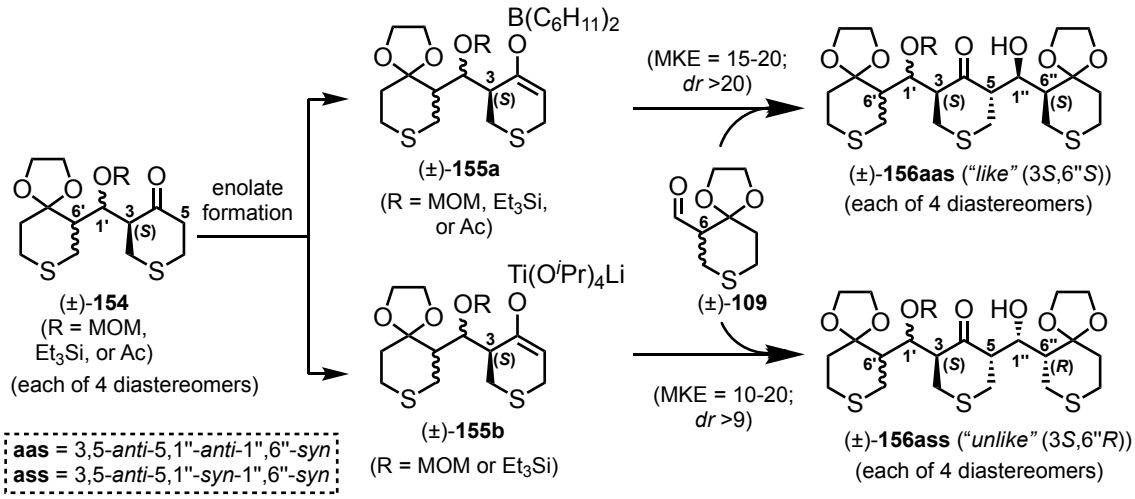
Scheme 1-26: External and internal EGS aldol reactions.

1.3.1.1.External enantiotopic group selective (external EGS) aldol reactions

In external EGS aldol reactions, the enantiotopic groups are associated with different molecules (i.e., enantiomers) and have different reactivity in a chiral environment.

Aldol reactions proceeding with mutual kinetic enantioselection (MKE):

In a kinetically controlled aldol coupling of racemic reactants, there are four possible reactions, two each from *like* and *unlike* combinations of reactant enantiomers. The ratio of *like* and *unlike* adducts is equal to the ratio of rate constants for the *like* and *unlike* reactions (k_{like}/k_{unlike}) and a measure of mutual kinetic enantioselection (MKE);[61,62] i.e., the kinetic preference of one enantiomer of racemic reactant to react with one enantiomer of the other racemic reactant. Aldol reactions of each diastereomer of (±)-**154** with (±)-**109** can produce up to eight diastereomeric adducts (racemic), four each from the "*like*" and the "*unlike*" combinations[51] of the reactant enantiomers (Scheme 1-27). Under established reaction conditions, the boron enolate (±)-**155a** favored the "*like*" reaction to give (±)-**156aas** (i.e., 3*S*,6″*S* and 3*R*,6″*R*), whereas the titanium "ate" enolate (±)-**155b** favored the "*unlike*" reaction to give (±)-**156ass** (i.e., 3*S*,6″*R* and 3*R*,6″*S*).[37] MKE for each of these reactions was determined by the ratio of *like* and *unlike* adducts (observed MKE for reactions with boron enolate (±)-**155a** is 15-20:1 and for reactions with titanium "ate" enolate (±)-**155b** is 10-20:1).



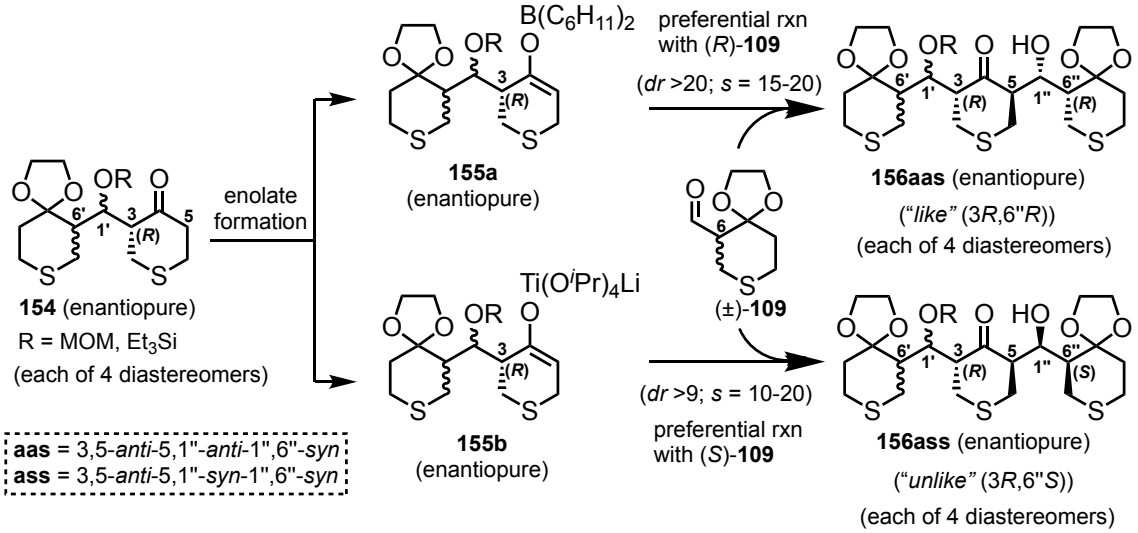
Scheme 1-27: Aldol reactions proceeding with MKE (NOTE: only one enantiomer is depicted for each racemic compound).

Aldol reactions proceeding with kinetic resolution (KR):

Synthesis of polypropionate natural products typically demands non-racemic (or enantiopure) intermediates. Synthesis of enantiomerically pure compounds is generally achieved by: (i) diastereoselective transformation of enantiomerically pure reactants (chiral pool), (ii) separation of enantiomers by chemical or physical methods (resolution), (iii) enantioselective transformation of achiral compounds (asymmetric synthesis). Coupling of two enantioenriched reactants is a well-known strategy to obtain non-racemic products; however, it requires preparation of both reactants in enantiomerically pure form. Alternatively, enantioselective transformation of racemic reactants to non-racemic (enantioenriched) adducts requires a method where enantiotopic faces or groups in the reactants are differentiated. For instance, an aldol reaction that proceeds with kinetic resolution (KR)[63] can discriminate the enantiomers of a racemic reactant with an enantiopure reactant. In an aldol coupling of an enantiopure reactant with a racemic reactant, there are two possible reactions, the coupling of *like* or *unlike* enantiomers. Under these conditions, the ratio of rate constants for the *like* and *unlike* reactions (k_{like}/k_{unlike}) is a measure of kinetic resolution

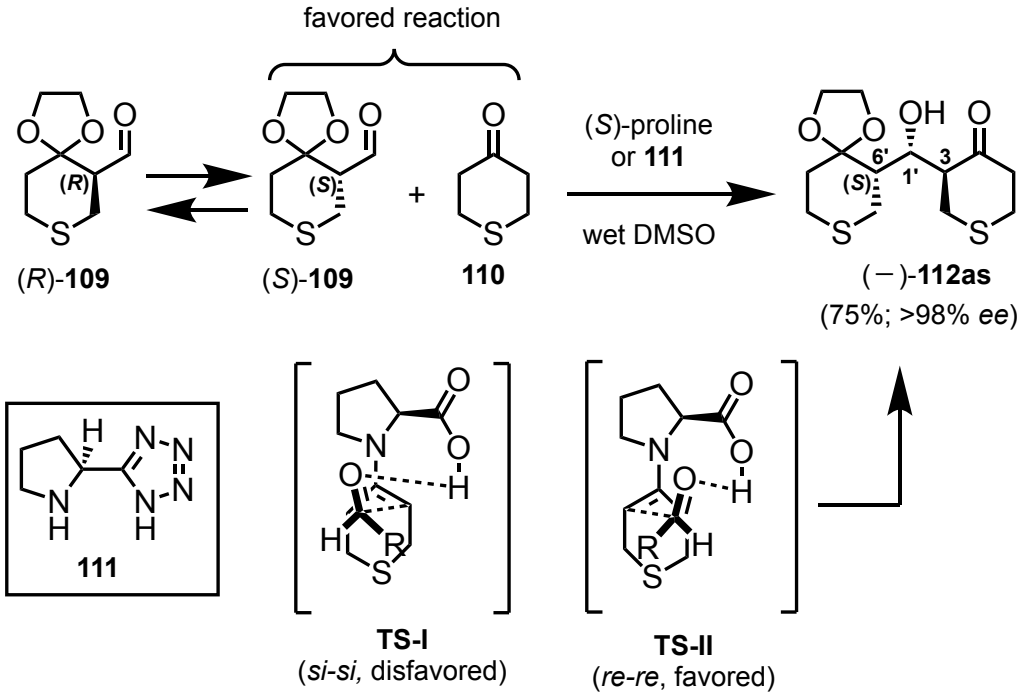
(KR); i.e., kinetic preference of the enantiopure reactant to preferentially react with one enantiomer of racemic reactant. This strategy is convenient because it requires preparation of only one reactant in enantiomerically pure form.

Aldol reactions of each diastereomer of enantiopure ketone (−)-**154** with racemic aldehyde (±)-**109** can produce up to eight diastereomeric adducts (enantiopure), four each from the "*like*" and the "*unlike*" combinations of the reactant enantiomers (Scheme 1-28). Aldol reactions of (−)-**154** with (±)-**109** proceeded with KR to give the corresponding enantiopure adducts **156aas** and **156ass** in good yields with high enantio- and diastereo selectivities (Scheme 1-28).[37] In these reactions, the boron enolate **155a** favored the "*like*" reaction to give the adduct **156aas** (i.e., 3*R*,6″*R*); whereas, titanium "ate" enolate **155b** favored the "*unlike*" reaction to give the adduct **156ass** (i.e., 3*R*,6″*S*). The kinetic resolution selectivity (*s*) for each of these reactions should be identical to the MKE in analogous reactions with (±)-**154** (i.e., 15-20:1 for reactions of the boron enolate and 10-20:1 for reactions with titanium "ate" enolate).



Scheme 1-28: Kinetic resolution (KR) in synthesis of polypropionate motifs.

Ward et al. reported a (*S*)-proline or the tetrazole derivative **111** catalyzed aldol reaction of (±)-**109** with **110** that proceeded with dynamic kinetic resolution (DKR)[64] to give the adduct (−)-**112as** with high enantio- and diastereoselectivities (Scheme 1-29).[33,35]



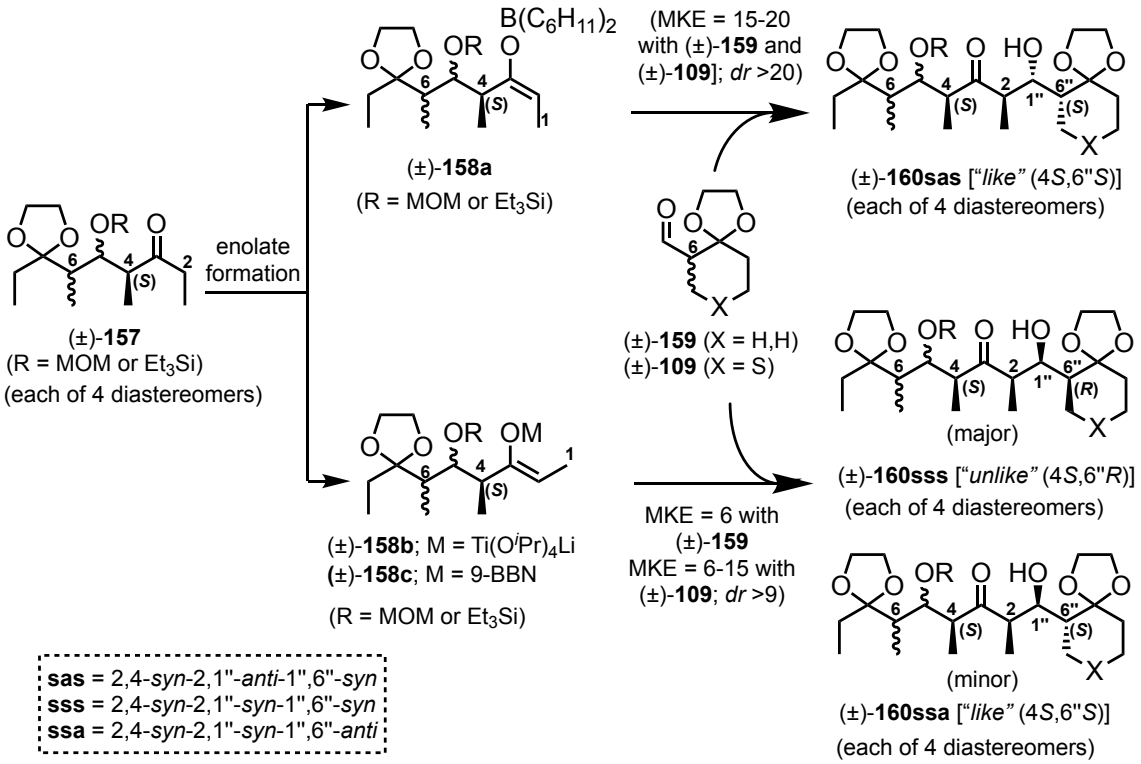
Scheme 1-29: (*S*)-proline catalyzed dynamic kinetic resolution (DKR) of (±)-**109** with **110**.

As shown in the **TS-II**, this result is explained by the preferential addition of the more accessible *re*-face of the β-carbon in the *anti*-oriented enamine to the *re*-face of the aldehyde (*S*)-**109** (Felkin addition) with *like* relative topicity preferred by the "closed" transition state (Scheme 1-29). The absolute configuration of the proline catalyst, the strong preference for Felkin diastereoface selectivity in addition to the aldehyde (±)-**109**, and the "closed" transition state are the key factors that govern the stereoselectivity of the reaction. It was concluded that the reaction proceeds with dynamic kinetic resolution based on the following observations: (i) (−)-**112as** was re-isolated in >85% yield with >90% *ee* after subjecting it to the identical reaction conditions (i.e., (*R*)- or (*S*)-proline, wet DMSO, 48 h); (ii) (±)-**109** was recovered from the reaction; (ii) (*S*)-**109**

was shown[65] to racemize under the reaction conditions. These results indicate that the isomerization of the aldehyde (±)-**109** is much faster than the aldol reaction.

Acyclic thiopyran route to polypropionates (ATR2P):

Similar to the thiopyran route to polypropionates (TR2P), extensive research on stereoselective aldol reactions for the acyclic thiopyran route to polypropionates (ATR2P) has been done in the Ward group.[66] Aldol reactions of each diastereomer of ketone (±)-**157** with aldehydes (±)-**109**, (±)-**159** proceeded with moderate to good MKE to give the adducts (±)-**160sas**, (±)-**160sss** and (±)-**16-ssa** (Scheme 1-30). Reactions of (*E*)-boron enolate (±)-**158a** with aldehydes (±)-**109**, (±)-**159** are more selective (MKE = 15-20; *dr* >20) than the corresponding (*Z*)-titanium "ate" and (*Z*)-boron enolates (±)-**158b**, (±)-**158c** (MKE = 6-15; *dr* >9), respectively. However, much lower stereoselectivities were obtained in reactions of (*Z*)-enolates (±)-**158b**, (±)-**158c** with acyclic aldehyde (±)-**159** compare to reactions with cyclic aldehyde (±)-**109**. The obtained results indicate that the minor adduct (±)-**160ssa** (1″,6″-*anti*) results from non-Felkin addition of the (*Z*)-enolates (±)-**158b**, (±)-**158c** to aldehyde (±)-**159**. By adapting these established conditions, KR was achieved using the corresponding enantiopure ketones in the ATR2P.

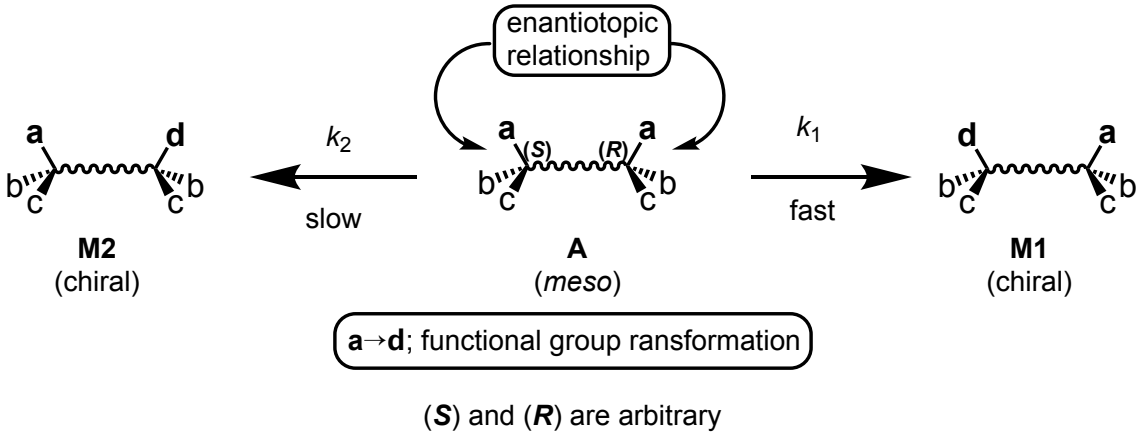


Scheme 1-30: External EGS aldol reactions in ATR2P (NOTE: only one enantiomer is depicted for each racemic compound).

1.3.1.2. Internal enantiotopic group selective (internal EGS) aldol reactions

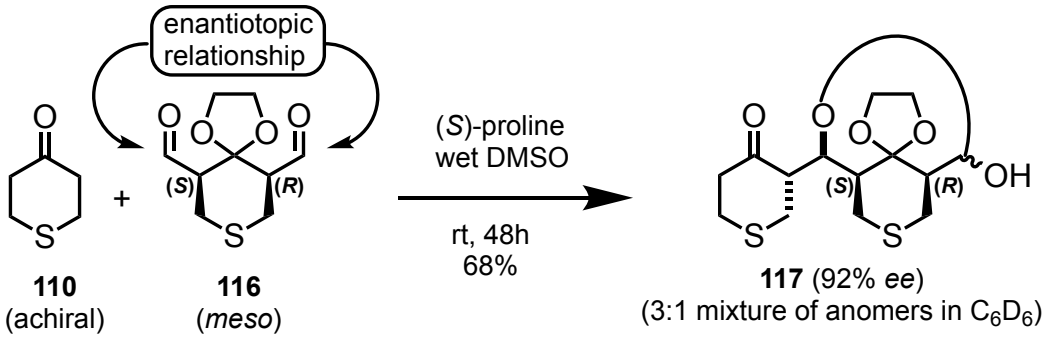
Enantioselective desymmetrization:

The desymmetrization of *meso*-bifunctional compounds by an enantiotopic group selective reaction is a powerful strategy for asymmetric synthesis ("*meso* trick"[67]).[68–70] In enantioselective desymmetrization, enantiotopic groups in a *meso* substrate have different reactivities in a chiral environment. For instance, the *meso* substrate **A** has two enantiotopic groups that can react with different rate constants in a chiral environment to produce chiral products **M1** and **M2** in unequal amounts (i.e., **M1**/**M2** = k_1/k_2) (Scheme 1-31).



Scheme 1-31: Enantioselective desymmetrization (internal EGS) of *meso* substrate A where ligand "a" is replaced by ligand "d" and the *R* group react faster than the *S* group (i.e., $k_R > k_S$).

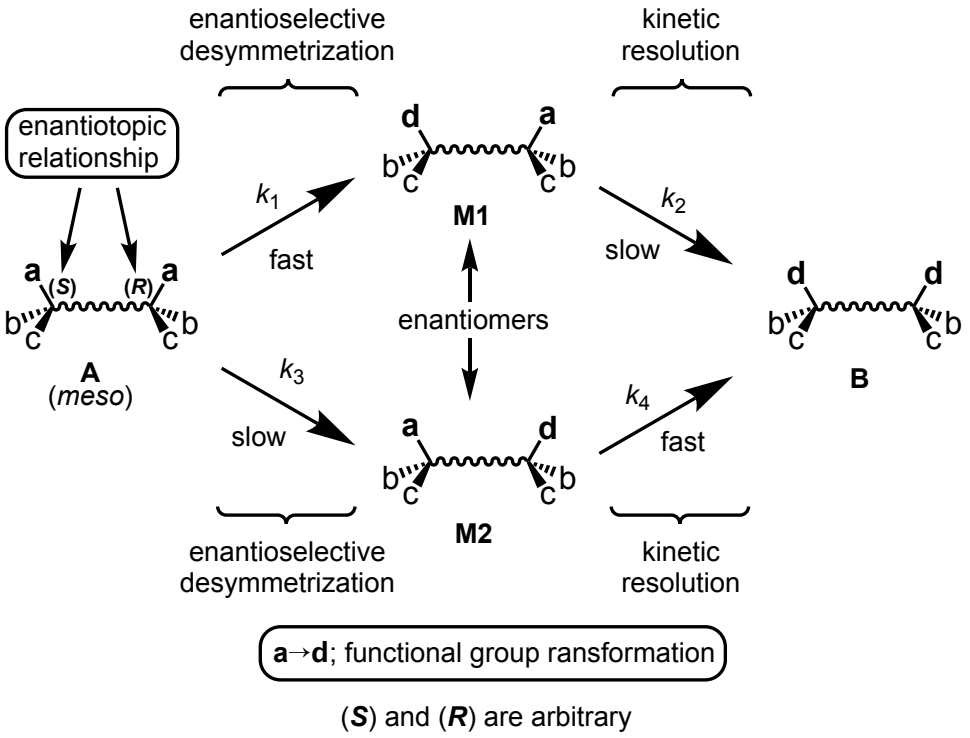
The (*S*)-proline catalyzed enantioselective desymmetrization (internal EGS aldol) of *meso* dialdehyde **116** with **110** gave the mono-aldol adduct **117** with high enantio- and diastereoselectivities (Scheme 1-32).[35] The selective formation of **117** (92% *ee*) from *meso*-**116** confirms that preferential aldol reaction of **110** (*re*-face of the corresponding enamine) occurred with the *re*-face of the (α*S*)-aldehyde group of *meso*-**116**. The high enantiotopic group selectivity results from the strong preference for Felkin additions to the aldehyde combined with the high propensity for addition to the aldehyde *re*-face imposed by the (*S*) proline catalyst. This remarkable process simultaneously sets the absolute configurations of four stereogenic centers in **117** with excellent enantio- and diastereo selectivities.



Scheme 1-32: (*S*)-proline catalyzed enantioselective desymmetrization (internal EGS aldol) of *meso*-dialdehyde **116**.

1.3.2. Sequential enantiotopic group selective (SEGS) reactions

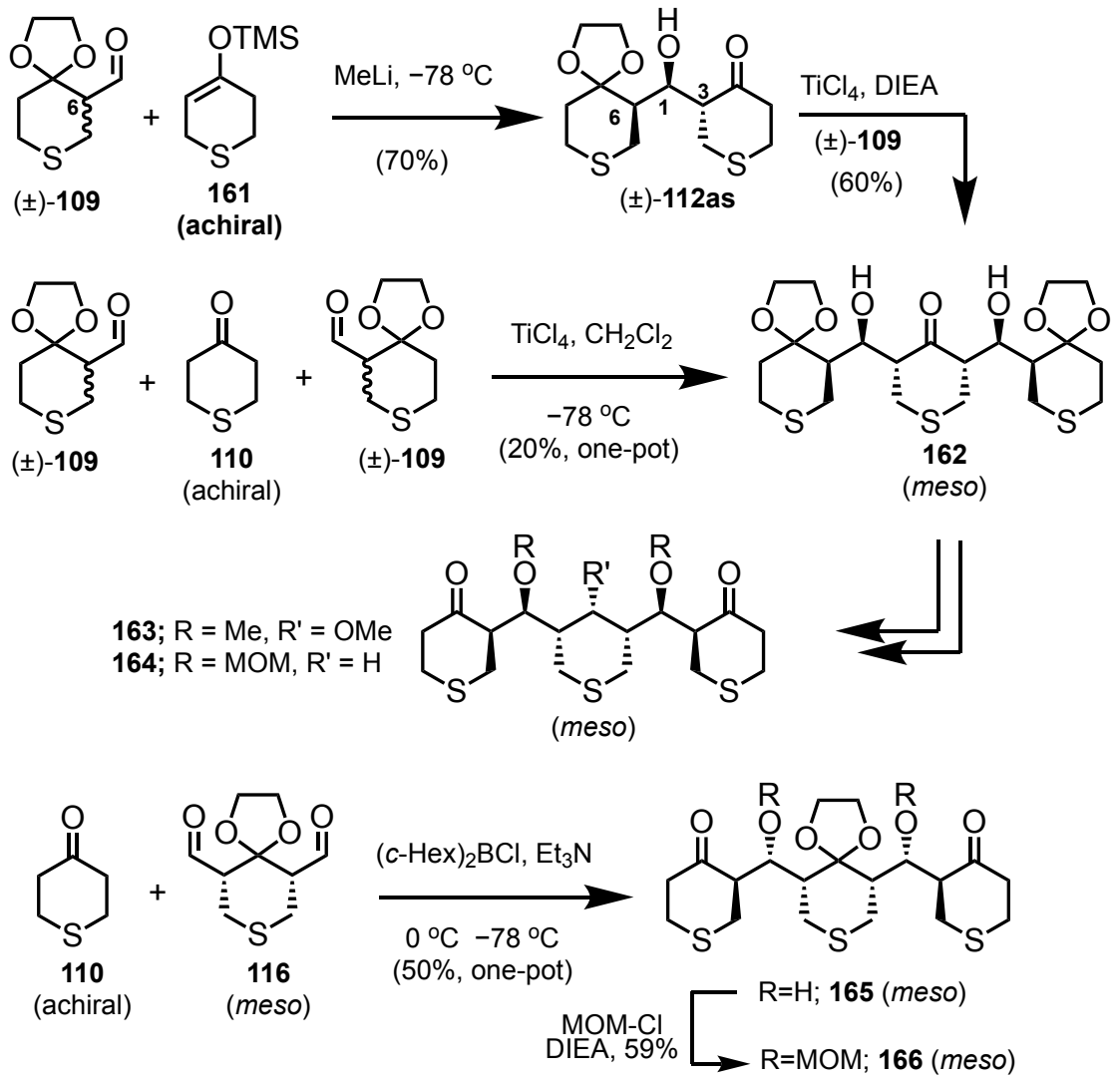
The use of EGS reactions to achieve asymmetric synthesis is particularly effective if the enantiotopic groups can react sequentially, thereby coupling an asymmetric synthesis with a kinetic resolution and producing products with high enantio- and diastereomeric purity, even from reactions of moderate group selectivity (Scheme 1-33).[69–72] In a sequential enantiotopic group selective (SEGS) reaction, the products of the initial EGS reaction (**M1**, **M2**) are enantiomers that have reactive enantiotopic groups (external comparison) capable of a second EGS reaction, in this case a kinetic resolution. If the enantiotopic group selectivity of the 1st (enantioselective desymmetrization) and 2nd (kinetic resolution) EGS reactions favors the same enantiotopic group, the kinetic resolution increases the enantiopurity of **M** (i.e., [**M1**]/[**M2**]), but reduces the yield (i.e., [**M1**]+[**M2**]) as the conversion increases (*ee* enhancement feature).



Scheme 1-33: Sequential enantiotopic group selective (SEGS) reactions of *meso* substrate A ("*meso*" trick).

1.3.2.1. Preparation of meso 1,9-diketones from one-pot bisaldol reactions

The ease of access to C_s (or C_i) symmetric starting materials is one of the primary challenges to the use of sequential enantiotopic group selective (SEGS) reactions. Ward et al. established synthetic routes to *meso* 1,9-diketones **163**, **164** and **166** (Scheme 1-34).[73,74] A highly stereoselective synthesis of the *meso* bisaldol **162** was achieved in two steps from readily available starting materials (±)-**109** and **161**; alternatively, the same *meso* bisaldol **162** was obtained from a Ti(IV)-mediated one-pot sequential bisaldol reactions of **110** with (±)-**109**, albeit with much lower diastereoselectivity.[73] Similarly, a one-pot two directional aldol reaction of *meso* **116** with **110** via the boron enolate gave the *meso* bisaldol adduct **165** (50%). The adducts **162** and **165** were converted to the corresponding *meso* 1,9-diketones **163**, **164** and **166** to investigate enantioselective desymmetrization by SEGS reactions.

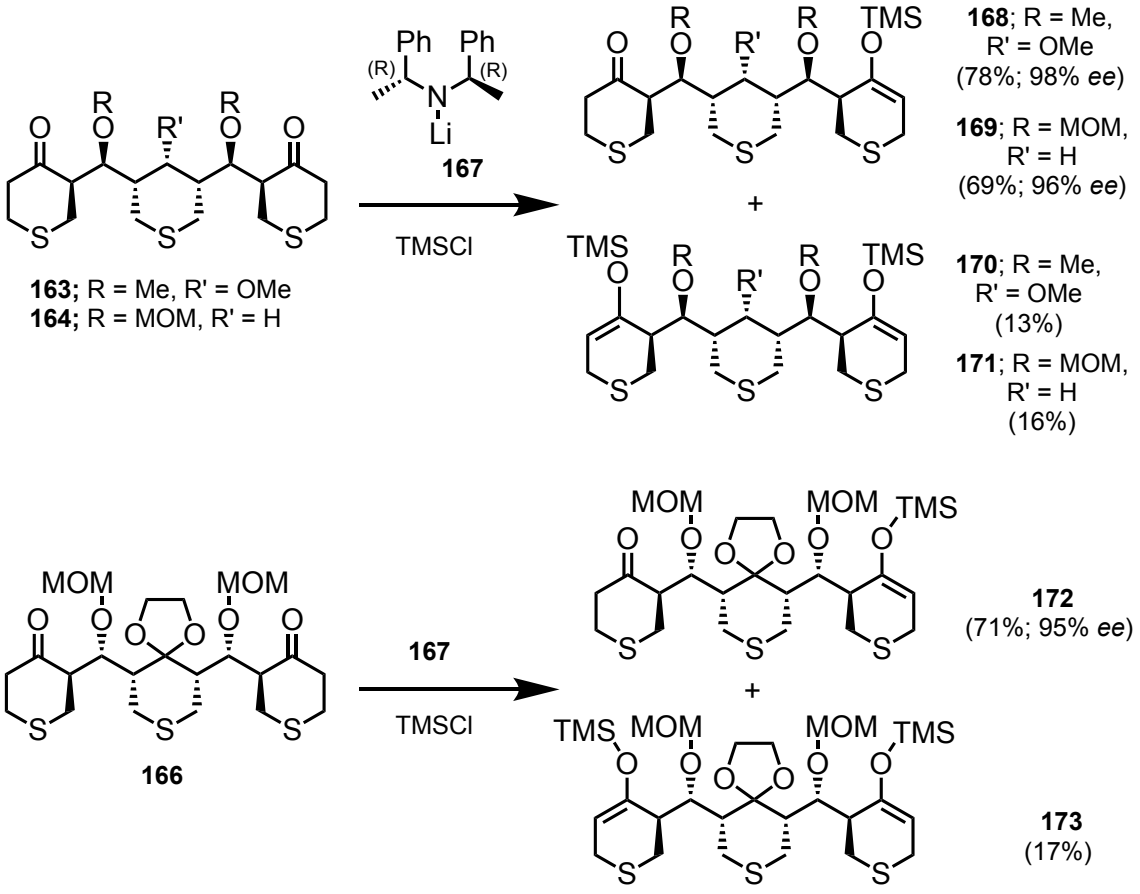


Scheme 1-34: Preparation of *meso* 1,9-diketones from one-pot bisaldol reactions.

1.3.2.2. Sequential enantiotopic group selective (SEGS) enolizations of meso 1,9-diketones

Having the *meso* diketones **163**, **164** and **166** in hand, Ward et al. investigated their enantioselective desymmetrization and SEGS enolizations towards the synthesis of non-racemic (−)-denticulatin A.[74,75] Enantioselective enolborination of *meso* **163** under the known[76] conditions ((−)-Ipc_2BCl and sparteine conditions used for kinetic resolution of 2-methylcyclohexanone) gave the unreacted **163** (Scheme 1-35). Alternatively, enantioselective enolization of *meso* 1,9-diketones **163**, **164** and **166** was successfully achieved by deprotonation with chiral lithium amide

167, followed by trapping the corresponding enolate with TMSCl. As expected,[72] the enantiopurity of mono-enol ethers (**168**, **169** and **172**) increased with increasing conversion due to kinetic resolution (*ee* enhancement feature) of these mono-enol ethers to form *meso* bis-enol ethers (**170**, **171** and **173**) in the second reaction. This method is very efficient to obtain products with high enantiopurity and high yields (>90%), because the starting diketones **163**, **164** and **166** were easily obtained from the bis-enol ethers **170**, **171** and **173**, respectively, upon treatment with aqueous HF.



Scheme 1-35: Enantioselective (SEGS) enolization of *meso* 1,9-diketones.

1.4. Conclusions

In most synthetic approaches to obtain non-contiguous polypropionates, the key ester link was established via coupling of the corresponding polypropionate carboxylic acid with a

polypropionate alcohol. In those approaches, several research groups were unsuccessful to achieve non-contiguous natural products due to difficulties in coupling of hindered alcohol with carboxylic acid or removing protecting groups at late stages of the synthesis. In a few approaches (Perkin, Goodman and Ward), non-contiguous polypropionates were synthesized via a retro-Claisen rearrangement of the corresponding contiguous precursors (with or without protecting groups); in particular, Ward et al. successfully synthesized the putative contiguous precursors **33** and **133** (without protecting groups) and transformed them into the non-contiguous natural products **9**, **11** and **15**, respectively, via retro-Claisen rearrangement, thereby providing experimental evidence for the proposed origin of non-contiguous natural products and demonstrating that these so-called natural products are plausible isolation artifacts.

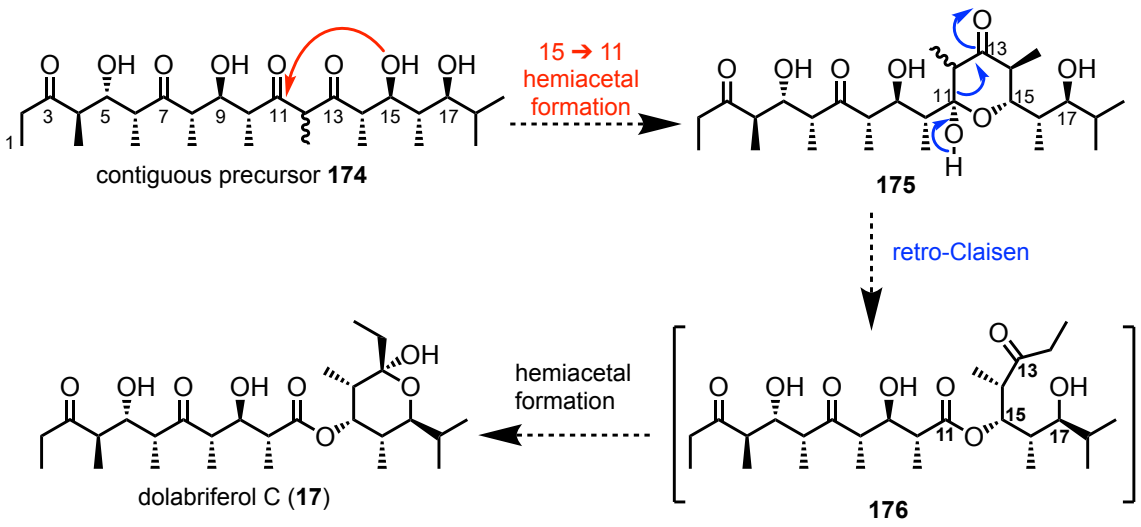
Ward et al. established enantiotopic group selective (EGS) aldol reactions (proceeding with MKE or KR or enantioselective desymmetrization) using the thiopyran route to polypropionates (TR2P) and the acyclic thiopyran route to polypropionates (ATR2P) themes to access various polypropionates with high enantio- and diastereoselectivites from readily available starting materials.

2. RESULTS AND DISCUSSION

2.1. Research Objectives

Dolabriferol C (**17**) (Scheme 2-1) is a "non-contiguous polypropionate". The 'natural product' status of **17** and other non-contiguous polypropionates are viewed with suspicion because they are speculated to arise from retro-Claisen fragmentation of a contiguous biosynthetically derived polypropionate, possibly as isolation artifacts.[1,8,9] Similar to Ward's syntheses of baconipyrone C (**11**) and dolabriferol (**15**), this research project was designed to test this hypothesis on the origin of dolabriferol C. The main research objectives were:

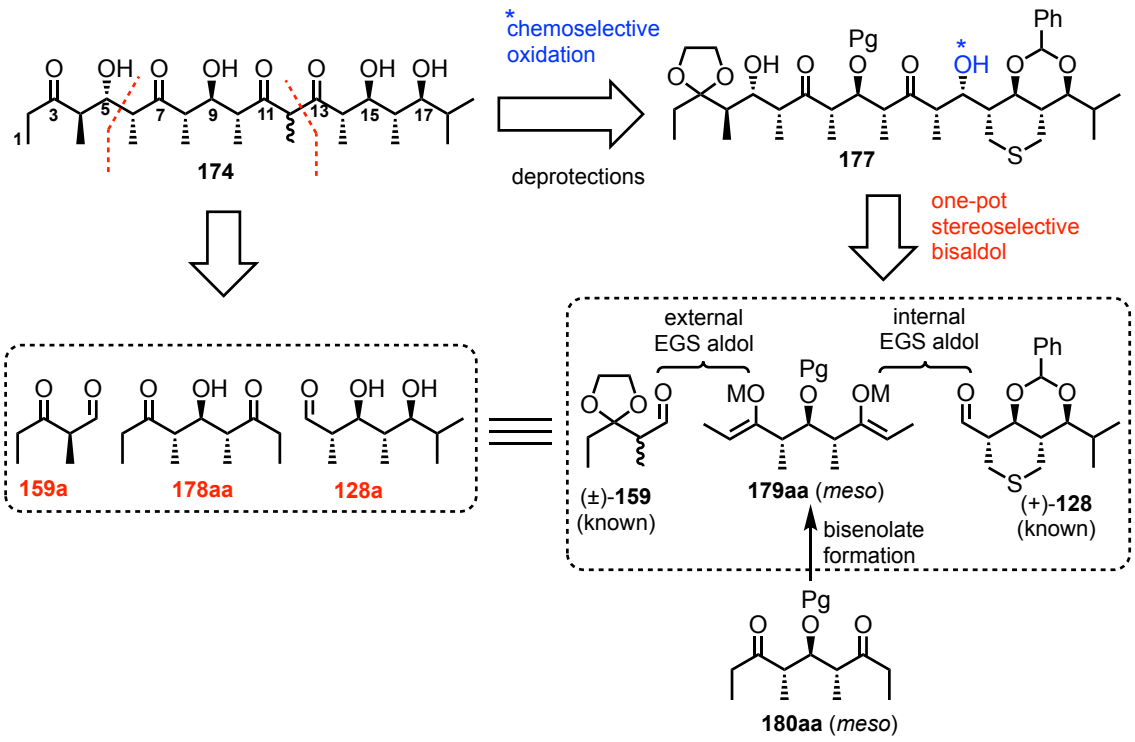
1. To test whether the putative contiguous precursor **174** can be transformed in vitro into the "natural product" **17** via the proposed chemoselective retro-Claisen rearrangement (Scheme 2-1).
2. To develop a new synthetic strategy (one-pot sequential enantiotopic group selective (SEGS) bisaldol reactions of *meso* bisenolates) for convergent enantioselective synthesis of the contiguous precursor **174** (Scheme 2-2).



Scheme 2-1: Proposed retro-Claisen rearrangement of precursor **174** to the natural product **17**.

2.2. Retrosynthetic Analysis

The synthesis of **174** presents a significant challenge, as this molecule has eleven stereocenters on a nineteen-carbon chain. Because the natural product **17** exists as a single enantiomer, all the relative and absolute configurations must be controlled in synthesis of precursor **174**. Retrosynthetic analysis of precursor **174** suggested the well-established TR2P and ATR2P could be used to develop a highly convergent approach to this target molecule from readily available starting materials (Scheme 2-2).

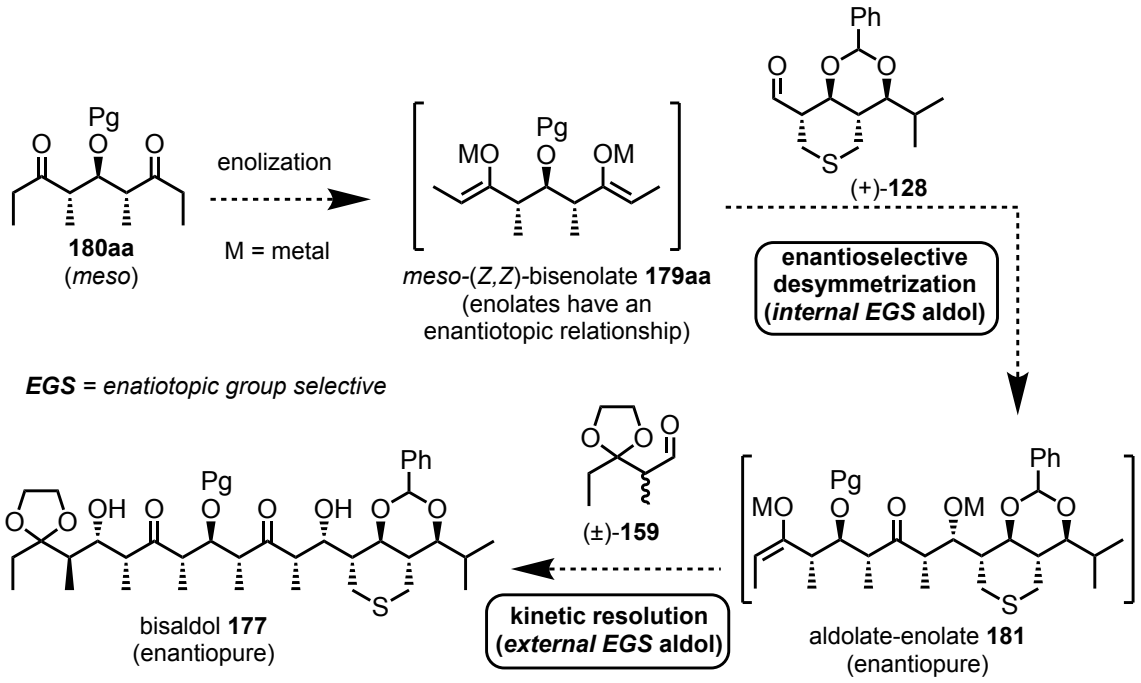


Scheme 2-2: Retrosynthesis of the putative precursor **174**.

Disconnection of the C5-C6 and C12-C13 bonds of the target molecule **174** leads to two aldehydes (**159a, 128a**) and a diketone (**178aa**) (Scheme 2-2). These fragments can be coupled together to construct the full carbon skeleton of precursor **174** via two consecutive stereoselective aldol reactions. However, these synthons can't be used directly in aldol reactions because they have free hydroxy groups. Equivalent reagents for **159a**, and **128a** are the proposed chiral aldehydes (±)-**159**[42] and (+)-**128,**[17] respectively, both known in the Ward group; whereas bisenolate **179aa** can be generated from the *meso* diketone **180aa**[77].

In considering the coupling of fragments (±)-**159**, (+)-**128**, and **180aa**, a one-pot stereoselective bisaldol strategy was contemplated (Scheme 2-3). In this proposed strategy, the *meso* bisenolate **179aa** would undergo sequential directed aldol reactions with two different aldehydes, first with enantioenriched aldehyde (+)-**128** via enantioselective desymmetrization and

then with racemic aldehyde **(±)-159** via kinetic resolution to obtain the enantioenriched bisaldol product **177** in a one-pot process.



Scheme 2-3: One-pot sequential enantiotopic group selective (SEGS) bisaldol reactions of *meso* **180aa** with (+)-**128** and (±)-**159**.

The proposed one-pot SEGS bisaldol strategy (Scheme 2-3) to couple **180aa**, (+)-**128** and (±)-**159** is clearly not trivial; to achieve this strategy there are three major problems to resolve: i) *how to generate bisenolates of 1,5-diketones **180aa**?* ii) *how to control stereoselectivity in the formation of meso bisenolates **179aa**?* iii) *how to control stereoselectivity in the sequential aldol reactions?* Although suitable ways to handle these challenges were unknown, the extensive research from the Ward group provided some guidance to solve these problems.

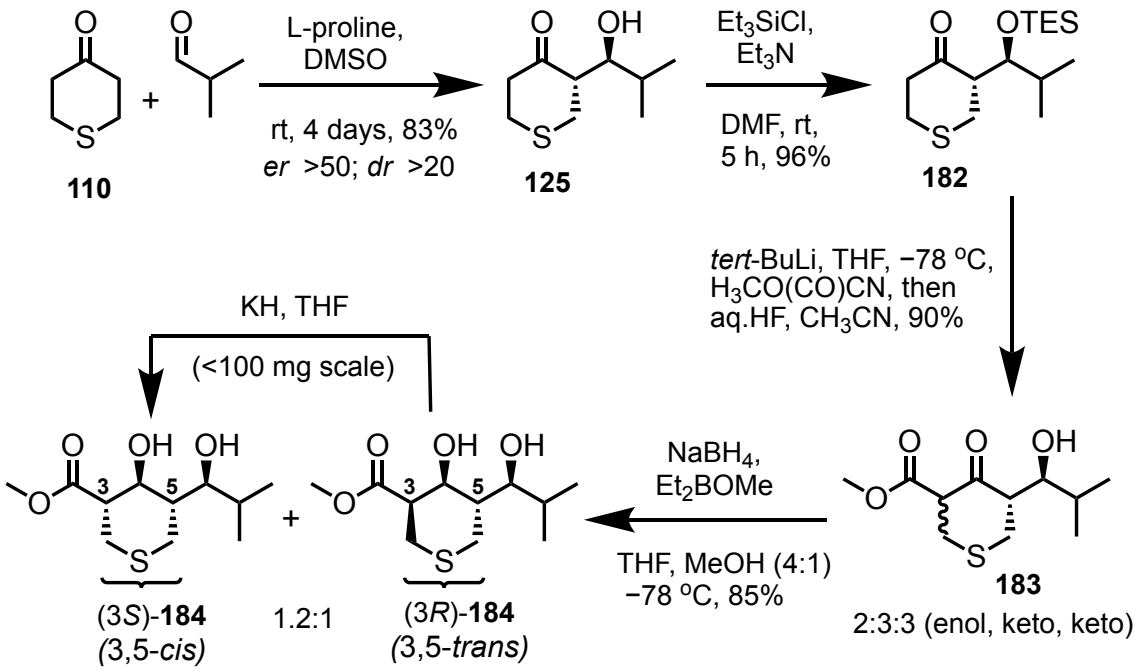
The Ward group has developed a powerful strategy for stereoselective synthesis of complex polypropionates which involves the iterative aldol coupling of dipropionate fragments with kinetic resolution[63] (in TR2P and ATR2P) thereby generating three stereocenters in each coupling step.[35,37,78–80] The results from these well-established methods suggested that the desired

stereoselectivities for the proposed one-pot bisaldol strategy were feasible. Because the two enolates in *meso* **179aa** have an enantiotopic relationship, they can be differentiated in an aldol reaction with (+)-**128** via enantioselective desymmetrization[68] (or internal enantiotopic group selectivity; *internal EGS*) (Scheme 2-3). Coupling of the resulting enantioenriched aldolate-enolate **181** with racemic aldehyde (±)-**159** is expected to proceed with kinetic resolution (or external enantiotopic group selectivity; *external EGS*) to obtain enantioenriched bisaldol product **177** in a one-pot process. Chemoselective oxidation of the C13-hydroxy group in **177** followed by global deprotection would lead to the desired putative contiguous precursor **174** as shown Scheme 2-2. The proposed starting materials *meso* diketone **180aa** and chiral aldehydes (+)-**128** and (±)-**159** were prepared from readily available inexpensive starting materials.

2.3. Preparation of the Starting Materials

2.3.1. Preparation of the 'eastern' aldehyde (+)-128

Preparation of enantioenriched aldehyde **(+)-128** was initiated with the known[81] L-proline catalyzed aldol reaction of **110** with isobutyraldehyde that provided adduct **125** with high enantio- and diastereoselectivities (Scheme 2-4). Treatment of the adduct **125** with Et_3SiCl and Et_3N gave **182** in excellent yield. Reaction of **182** with *tert*-BuLi gave the corresponding Li-enolate that was trapped with Mander's reagent which, after an aqueous HF workup (to remove the triethylsilyl protecting group), afforded β-keto ester **183** as a 2:3:3 mixture of enol and two keto tautomers, respectively.



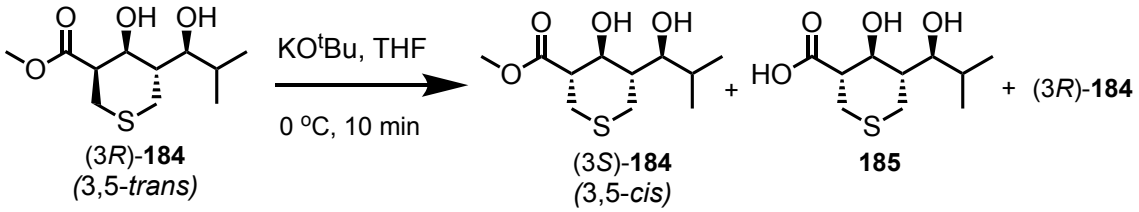
Scheme 2-4: Towards the synthesis of aldehyde (+)-**128**.

Hydroxy directed 1,3-*syn*-selective reduction[82] of β-hydroxyketone **183** (keto-enol mixture) generated a separable 1.2:1 mixture of *syn* diols (3*S*)-**184** (3,5-*cis*) and (3*R*)-**184** (3,5-*trans*), respectively (Scheme 2-4). Among these two diols, diastereomer (3*S*)-**184** (3,5-*cis*) has the relative and absolute configuration corresponding to the desired aldehyde (+)-**128**. Rather than discarding (3*R*)-**184** (3,5-*trans*) and losing half of the material in the process, isomerization at C-3 of (3*R*)-**184** (or a derivative thereof) was considered. Toward that end, Pramod Jadhav (a previous member of the Ward group) attempted alkylation of the hydroxy groups of (3*R*)-**184** by treatment with benzyl bromide in presence of KH. Surprisingly, a clean isomerization of (3*R*)-**184** to (3*S*)-**184** occurred, instead of the anticipated alkylation. This serendipitous observation provided a great opportunity to improve the yield of the desired (3*S*)-**184**. Thano Karagiannis (another former Ward group member) studied the isomerization reaction extensively. Although good yields were obtained in small scale reactions (<100 mg), larger scale attempts gave

incomplete isomerization and lower material recovery. Despite examining numerous variations in the reaction conditions, a reliable and scalable procedure was not identified.

2.3.1.1. Isomerization study

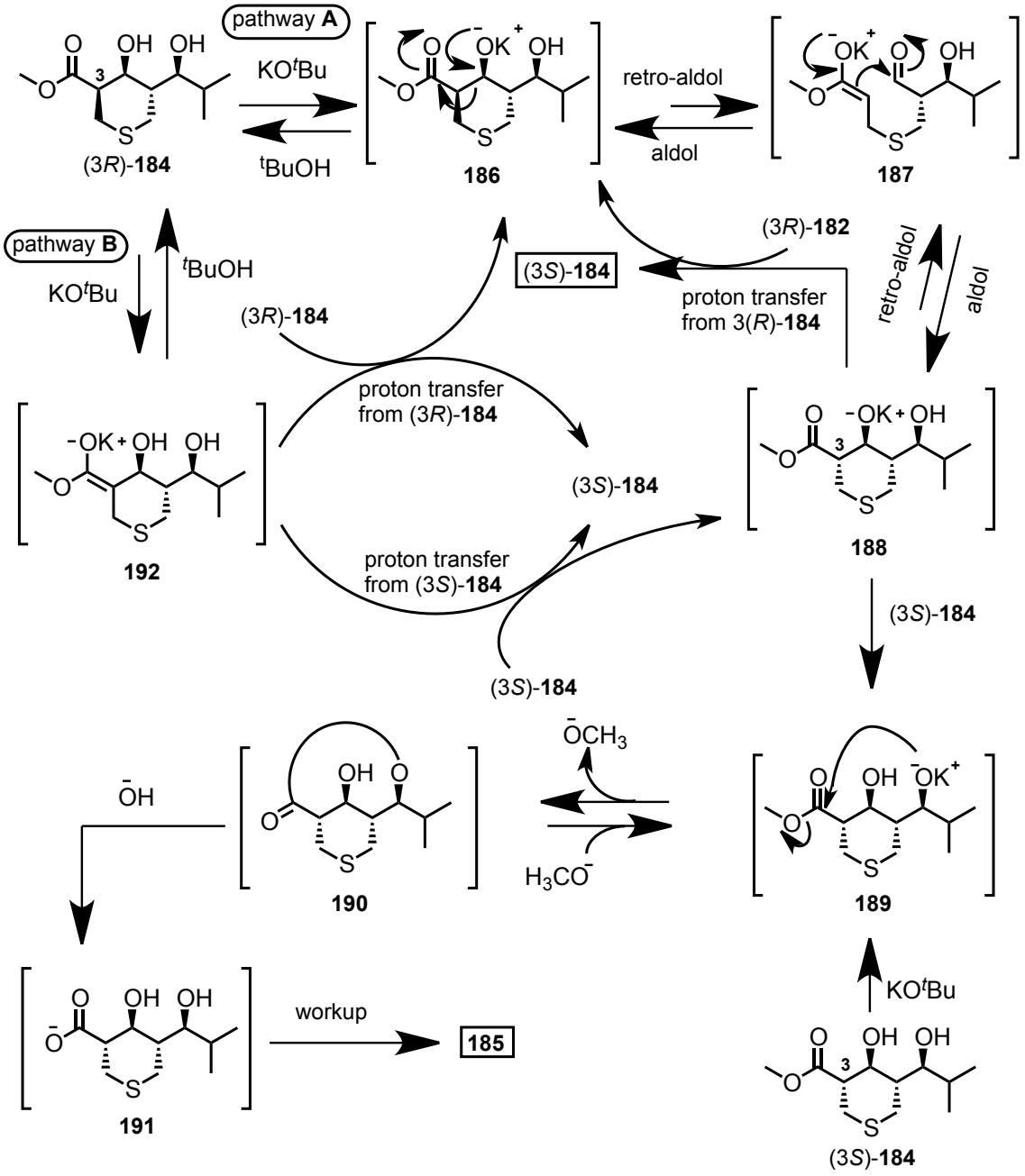
I investigated the isomerization reaction of (3*R*)-**184** to (3*S*)-**184** using KO^{t}Bu that initially provided poor and non-reproducible yields of the desired product (<50%) (Scheme 2-5). After extensive experimentation, formation of the corresponding carboxylic acid **185** (in variable amounts) was identified as an important side reaction.



Scheme 2-5: Isomerization of (3*R*)-**184** to (3*S*)-**184** with KO^{t}Bu.

Presumably, the isomerization occurs via a retro-aldol pathway (**A**) as proposed in Scheme 2-6. Deprotonation of (3*R*)-**184** at the C3 hydroxy group leads to alkoxide **186**, which upon retro-aldol generates enolate **187**, which then can undergo a stereoselective (or reversible) aldol reaction to give the thermodynamically more stable **188**. A similar deprotonation of (3*S*)-**184** would also lead to **188**; however, it is also possible that deprotonation is diastereomer selective in favor of (3*R*)-**184**. Proton transfer from (3*R*)-**184** to **188** would make the process catalytic in base.

On the other hand, alkoxide **189** can be formed by an intramolecular proton transfer in **188** or direct deprotonation of (3*S*)-**184**. Alkoxide **189** can lactonize to generate **190**. This lactonization reaction would be reversible; however, in presence of hydroxide ions lactone **190** would be irreversibly transformed to the carboxylate **191**. Apparently, the presence of carboxylate ion **191** impedes the isomerization pathway resulting in incomplete conversion, low yields, and poor reproducibility.

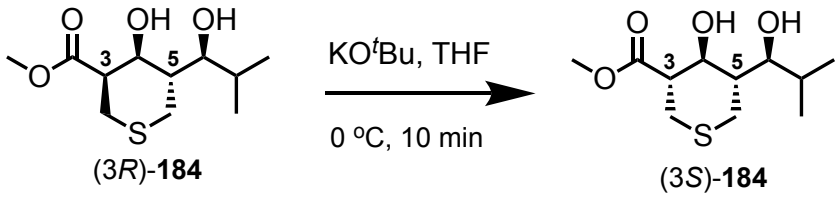


Scheme 2-6: Plausible mechanism for the isomerization of (3*R*)-**184** to (3*S*)-**184** and hydrolysis to carboxylic acid **185**.

In order to improve the isomerization reaction, it was essential to prevent the formation of lactone **190** or the hydrolysis pathway to the carboxylate ion **191**. After examination of various reaction conditions, it was observed that addition of CuI improved the isomerization reaction

yields (Table 2-1, entries 2, 4 and 5). Using 2 equivalents of KO^{t}Bu and 20 mol% of CuI, the isomerization reaction yields were reproducible even on larger scales. These results suggest that CuI has an important role in suppressing the formation of **190** or its hydrolysis. Interestingly, addition of excess CuI (1 equiv) diminished the isomerization yields (entry 6). Presumably, CuI traps hydroxide ions as CuOH that impedes the hydrolysis of lactone **190** to carboxylate **191**, and (or) produced the Cu (I) alkoxide from **189** that is less prone to lactonize. In any event, the presence of the optimal amount of CuI is highly beneficial to the reaction.

Table 2-1: Isomerization of (3*R*)-**184** to (3*S*)-**184** with KO^{t}Bu in presence of CuI.



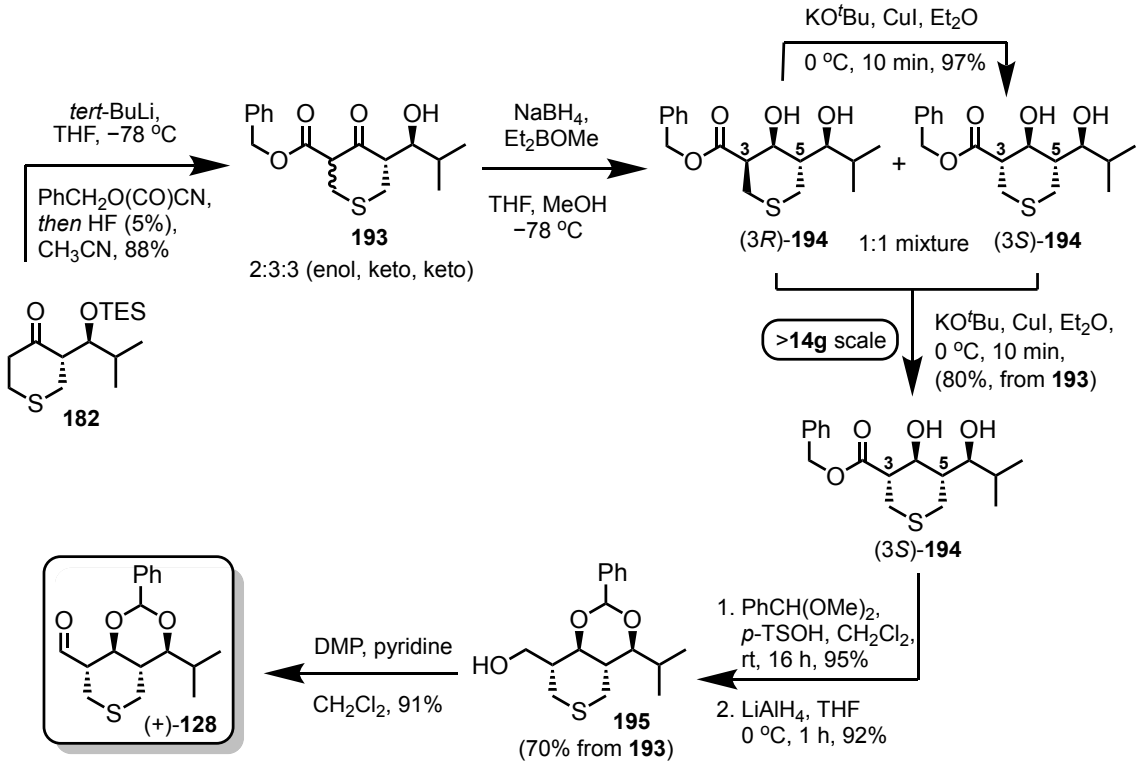
(3*R*)-**184** (3*S*)-**184**

entry	KO^{t}Bu (equiv)	CuI (equiv)	(3*S*)-**184** (% yield)[a]
1	1	0	31
2	1	0.1	38
3	2	0	42
4	2	0.1	66
5	2	0.2	75
6	2	1	39

[a] Isolated yields.

To improve synthetic efficiency, the crude mixture of (3*R*)-**184** and (3*S*)-**184** (obtained from reduction of **183**; Scheme 2-4) was subjected to the established isomerization conditions (2 equiv of KO^{t}Bu and 20 mol% of CuI). Interestingly, isomerization of the mixture gave the desired (3*S*)-**184** in low yield (61%) with increased amount of acid **185** compared to the isomerization of (3*R*)-**184** alone.

It was hypothesized that replacing the methyl ester in compound **183** (Scheme 2-4) with a more hindered benzyl ester would further impede the lactonization pathway. Accordingly, the benzyl analogue of Mander's reagent (benzyl cyanoformate[83]) was prepared and used for the carboxylation of **182** to obtain benzyl ester **193** in 88% yield as a 2:3:3 mixture of enol and two keto tautomers, respectively (Scheme 2-7). Hydroxy-directed *syn*-selective reduction of ketone **193** (keto-enol mixture) generated a separable 1:1 mixture of diols (3*R*)-**194** (3,5-*trans*) and (3*S*)-**194** (3,5-*cis*). After extensive experimentation, the mixture of diols (3*R*)-**194** and (3*S*)-**194** was successfully isomerized to the desired diol (3*S*)-**194** (85%) by treatment with KO^{t}Bu (2 equiv) and CuI (20 mol%). The isomerization yield was further improved (97%) by changing the reaction solvent from THF to Et_2O. This method allowed direct isomerization of the crude mixture of (3*R*)-**194** and (3*S*)-**194** (i.e., the crude product obtained from *syn*-selective reduction of **193**) to the desired product (3*S*)-**194** on large scale (14 g) in excellent yield (80% over two steps). Remarkably, under these optimized conditions, isomerization was completed in 10 minutes at 0 ^oC even on large scale. Hence, these reaction conditions are reliable, scalable, and reproducible to prepare the desired 3,5-*cis* diastereomer (3*S*)-**194**.



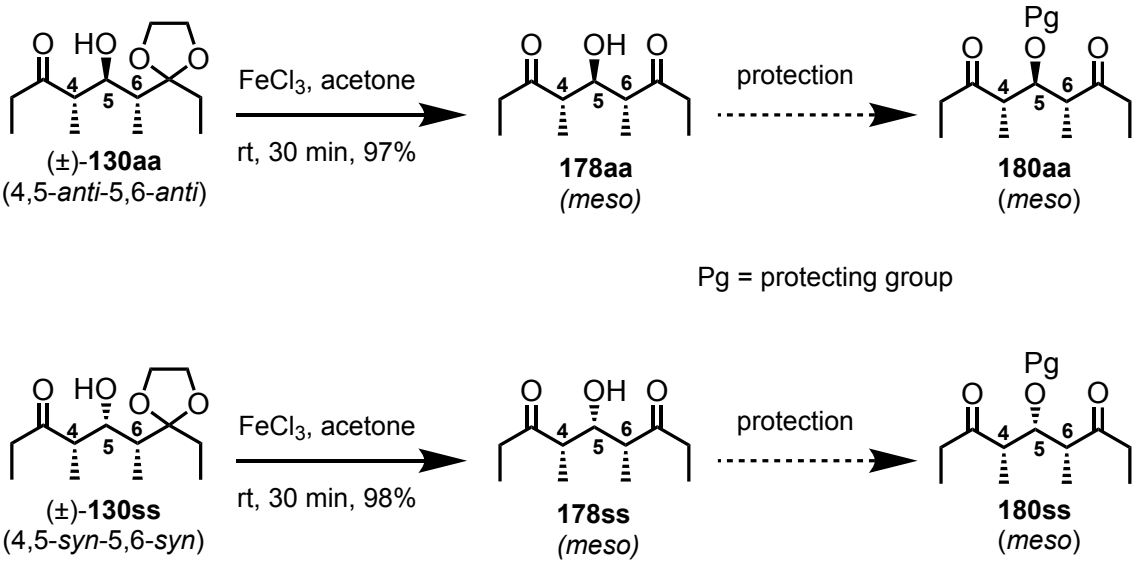
Scheme 2-7: Preparation of aldehyde (+)-**128** via an improved isomerization to (3*S*)-**194**.

The diol (3*S*)-**194**, without purification, upon treatment with $PhCH(OMe)_2$ in presence of a catalytic amount of *p*TsOH · H_2O gave the corresponding benzylidene acetal which was subjected to $LiAlH_4$ reduction to give the desired alcohol **195** in 70% yield over 4 steps (from **193**) (Scheme 2-7). Oxidation of **195** with DMP[84–87] gave the desired aldehyde (+)-**128** in high yield (91%). It is noteworthy that only two chromatographic purifications were required to prepare aldehyde (+)-**128** from **110** (over 8 steps).

2.3.2. Preparation of *meso*-1,5-diketones

The two *meso* 1,5-diketones **180aa** (4,5-*anti*-5,6-*anti*) and **180ss** (4,5-*syn*-5,6-*syn*) were considered as possible substrates for stereoselective synthesis of *meso* bisenolates (Scheme 2-8).

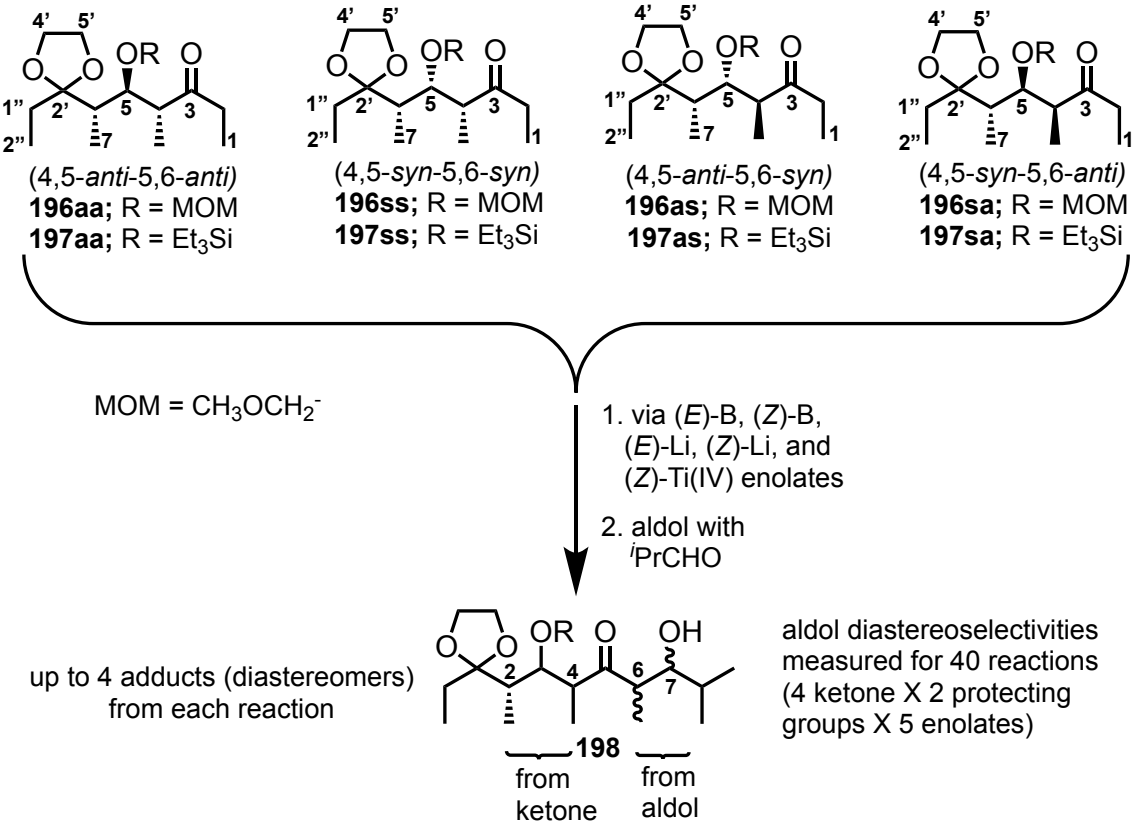
$FeCl_3$ catalyzed removal of the ketal protecting group in the known ketones **130aa**[42] and **130ss**[42] produced *meso* 1,5-diketones **178aa** and **178ss**, respectively, in excellent yields.



Scheme 2-8: Preparation of *meso* 1,5-diketones **178aa** and **178ss**.

2.4. Preparation of *Meso* Bisenolates

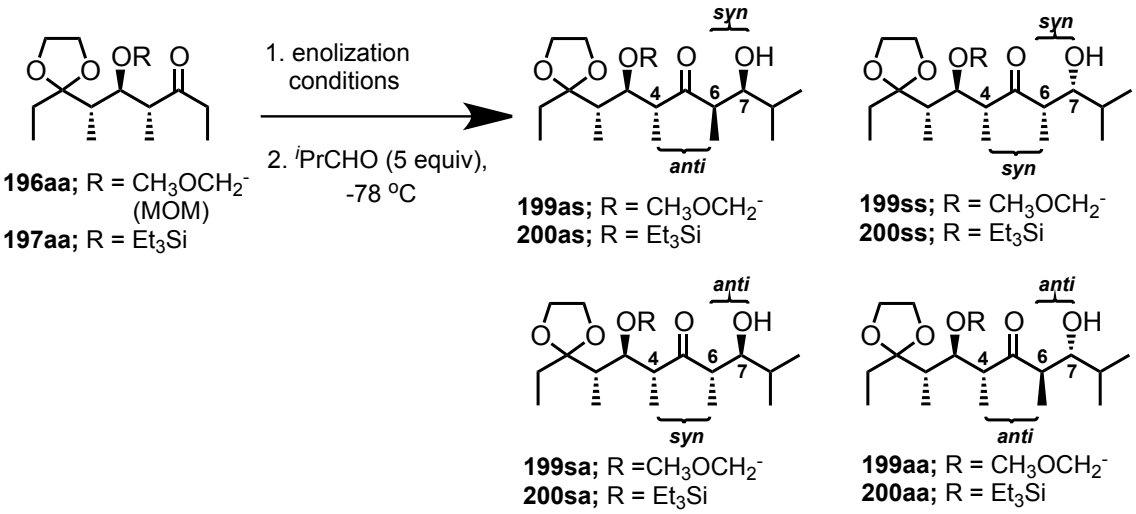
The hydroxy groups in diketones **178aa** and **178ss** (Scheme 2-8) require protection before proceeding to the stereoselective synthesis of *meso* bisenolates. Although, various protecting groups are available to install on **178aa** and **178ss**, the choice of protecting group was mainly guided by the Ward group study on 'the effect of the protecting group on the diastereoselectivities of aldol reactions of chiral ethyl ketones'.[42] In this study, the CH_3OCH_2- (MOM) and Et_3Si- (TES) protected ketones (**196** and **197**) were used to generate Li and B-enolates (both *E*- and *Z*) and (*Z*)-Ti(IV) enolates that were treated with isobutyraldehyde to obtain aldol adducts (diastereomers) in different ratios (Scheme 2-9). The diastereoselectivities of these reactions were greatly influenced by the enolate geometry, the nature of the metal, the protecting group, and the relative configuration of the ketone.



Scheme 2-9: Known aldol reactions of ketones **196** and **197** with isobutyraldehyde.

Ketones **196ss** or **197ss** (*syn,syn*) and **196aa** or **197aa** (*anti,anti*) were of particular interest because they share the same relative configurations as **180ss** (*syn,syn*) and **180aa** (*anti,anti*), respectively. The results for reactions of Li and B-enolates of **196aa** and **197aa** with isobutyraldehyde are summarized in Table 2-2.

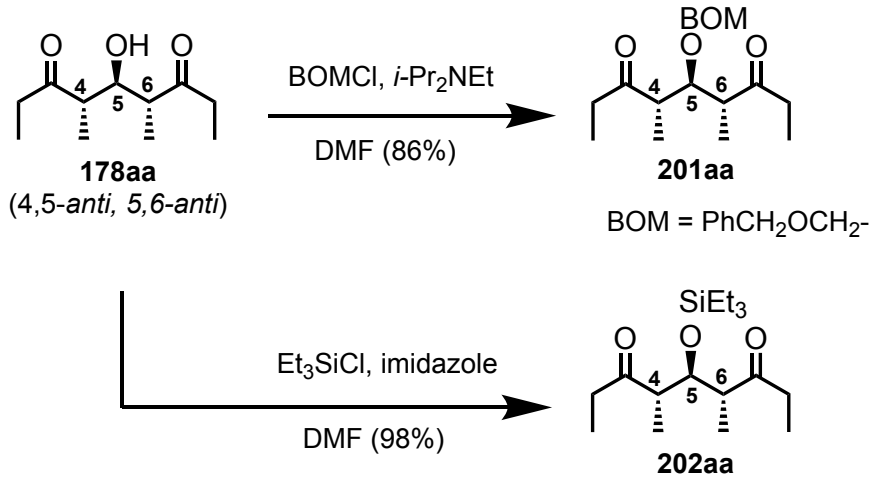
Table 2-2: Diastereoselectivities in aldol reactions of **196aa** (MOM) and **197aa** (Et_3Si) with isobutyraldehyde.[42]



entry	ketone (protecting group)	enolization conditions (enolate geometry & type)	aldol adducts (ratio; convn)[a]
1	**196aa** (CH_3OCH_2-)	$(Me_3Si)_2N$-Li, (1.1 equiv), THF, −50 °C, ((*Z*)-Li)	**199as, 199ss** (*dr* 8:1; 95%)
2	**197aa** (Et_3Si)	$(Me_3Si)_2N$-Li, (1.1 equiv), THF, −50 °C, ((*Z*)-Li)	**200as, 200ss** (*dr* 2.7:1; 90%)
3	**196aa** (CH_3OCH_2-)	9-BBNOTf (1.6 equiv), Et_3N (1.9 equiv), Et_2O, −78 °C, ((*Z*)-B)	**199ss** (*dr* > 19:1; 95%)
4	**197aa** (Et_3Si)	9-BBNOTf (1.6 equiv), Et_3N (1.9 equiv), Et_2O, −50 °C, ((*Z*)-B)	**200ss, 200as** (*dr* 2:1; 70%)
5	**196aa** (CH_3OCH_2-)	*c*-Hex_2BCl (2 equiv), Et_3N (2.4 equiv), Et_2O, −78 °C, ((*E*)-B)	**199sa, 199aa** (*dr* 6:1; 90%)
6	**197aa** (Et_3Si)	*c*-Hex_2BCl (2 equiv), Et_3N (2.4 equiv), Et_2O, 0 °C, ((*E*)-B)	**200sa** (*dr* > 19:1; 70%)

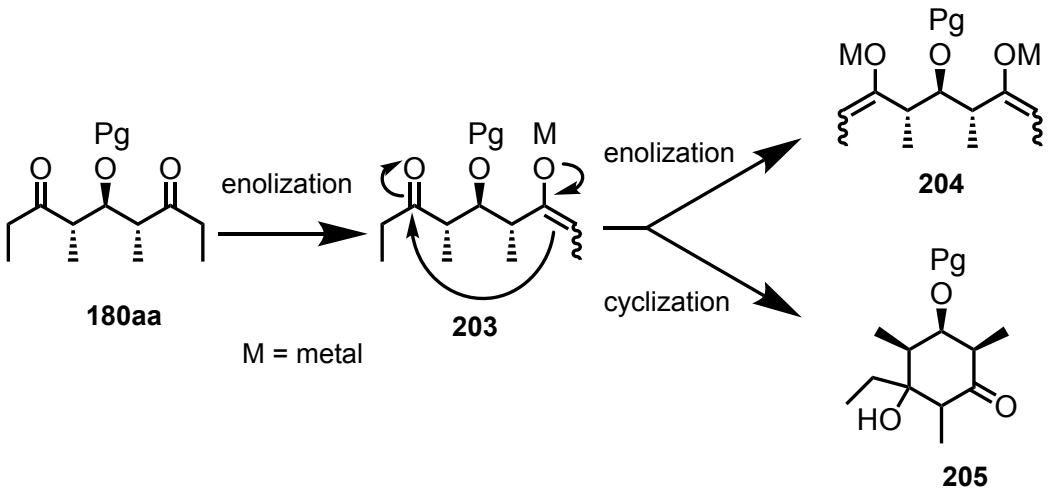
[a] Obtained from ^1H NMR data of crude reaction mixture unless otherwise indicated.

According to the above study, aldol diastereoselectivities from the (*Z*)-Li and (*Z*)-B-enolates of the methoxymethyl (MOM) protected ketone **196aa** were much higher than those from the Et_3Si-protected ketone **197aa**; conversely, the (*E*)-B-enolate of **197aa** (Et_3Si) gave higher diastereoselectivites than the MOM analogue **196aa** (Table 2-2). Thus, the benzyloxymethyl (BOM; a synthetically more versatile analogue of MOM) and Et_3Si-derivatives of **178aa** were prepared to generate *meso* bisenolates (Scheme 2-10).



Scheme 2-10: Preparation of BOM and Et_3Si-protected *meso* 1,5-diketones (**201aa**, **202aa**).

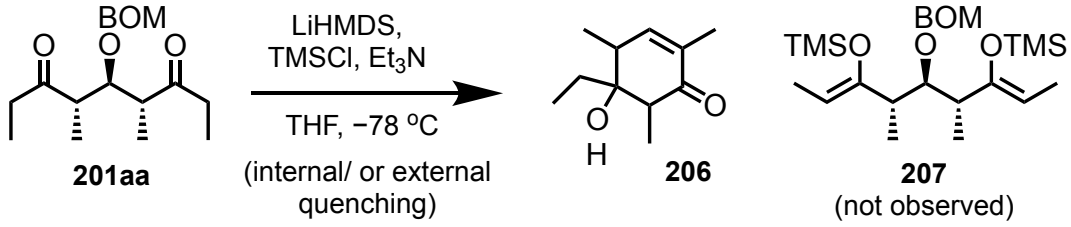
As indicated, stereoselective preparation of *meso* bisenolate **179aa** from **180aa** is an essential requirement to achieve the proposed SEGS bisaldol strategy (Scheme 2-3). Nevertheless, no literature method was available to prepare bisenolates until this work. Hence, to explore the proposed strategy, the initial goal was to develop a method to prepare *meso* bisenolates stereoselectively. Because the two keto groups in *meso* diketone **180aa** are at 1,5 relationship, a challenge in achieving bisenolate formation is overcoming the potentially facile cyclization of the intermediate enolate-ketone **203** (Scheme 2-11).



Scheme 2-11: Potential competitive reactions (enolization vs. cyclization) from monoenolate **203**.

2.4.1. Attempts to generate *meso*-(*Z,Z*)-bisenolate from 201aa

Reaction of *meso* diketone **201aa** with LiHMDS and TMSCl/Et_3N[88] (with both internal and external quenching) was attempted in an effort to produce the corresponding disilyl (*Z,Z*)-bisenol ether derivative **207** (Scheme 2-12). Interestingly, only the cyclization-elimination product **206** was observed. The formation of **206** is presumably due to an intramolecular aldol addition of the mono Li-enolate of **201aa** to the proximal ketone as previously shown for **203** (Scheme 2-11). This result suggests that the cyclization pathway is faster than the silyl enol formation under these conditions.



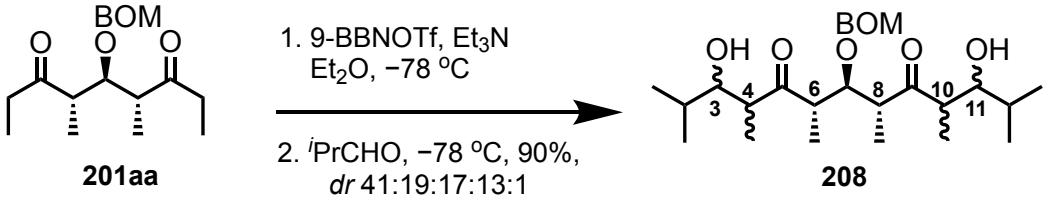
Scheme 2-12: Attempts to generate *meso*-(*Z,Z*)-Li-bisenolate from **201aa**.

Collum et al. developed a rapid enolization of acyclic ketones using LiHMDS or LDA in Et_3N-toluene.[89] In this research, it was observed that formation of enolate from 2-methylcyclohexanone was >100 times faster in Et_3N-toluene than in THF. The use of Et_3N-toluene system not only enhanced the rate of enolization, but also influenced the *E/Z* diastereoselectivities and enolate reactivity. Inspired by this work, it was anticipated that using LiHMDS or LDA in Et_3N-toluene might generate the desired bisenolate from **201aa** if the rate of enolization of the corresponding intermediate enolate-ketone was faster than the rate of its cyclization. Accordingly, *meso* diketone **201aa** was subjected to enolization conditions using Collum's procedure both with LiHMDS and LDA in presence of TMSCl and Et_3N (internal and external quenching). Disappointingly, only the cyclized product **206** was observed. Using an alternative silyl enol ether preparation method via soft enolization with TMSOTf and Et_3N[90] did not yield fruitful results.

Next, generation of the (*Z,Z*)-bisenol borinate of **201aa** by soft enolization was attempted adapting the reaction conditions from a previous study in the Ward group.[42] Accordingly, **201aa** was treated with 9-BBNOTf and Et_3N under the conditions previously established for **196aa**, followed by addition of isobutyraldehyde (10 equiv) to give a 41:19:17:13:1 mixture (by ^1H NMR) of bisaldol diastereomers **208** (90%) (Scheme 2-13).[viii] After careful analysis of the ^{13}C NMR spectrum of the mixture **208** (particularly the diagnostic signals for the ^{i}Pr methyl groups;[42] ca. 15 and 20 ppm = *anti*, two at ca. 20 ppm = *syn*), it was concluded that both *syn* and *anti*-aldols were present suggesting that both (*E*) and (*Z*)-enolates were generated.[ix] Although this reaction afforded poor diastereoselectivity, formation of the bisaldol adducts in excellent yield confirmed

[viii] ^1H NMR of the mixture **208** confirmed the presence of five bisaldols; however, it was difficult to interpret the bisaldols as chiral or achiral diastereomers.
[ix] Detailed analysis of the data obtained from various *syn* and *anti*-aldol adducts are discussed in the structure determination section.

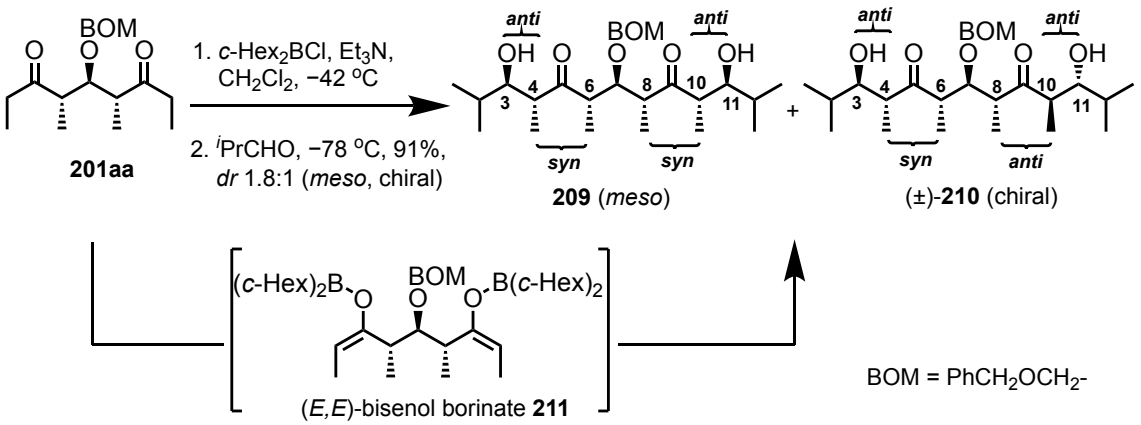
that the bisenolate was generated efficiently. Remarkably, no cyclization product was detected under these soft enolization conditions.



Scheme 2-13: Preparation of (*Z,Z*)-bisenolates and bisaldols from *meso* **201aa**.

Alternatively, attempting to generate the (*E,E*)-bisenol borinate, **201aa** was treated with *c*-Hex_2BCl and Et_3N followed by addition of isobutyraldehyde to give a 1.8:1 mixture of bisaldol adducts **209** (*meso*) and **210** (chiral), respectively (Scheme 2-14). Both adducts were found to have 3,4-*anti*-10,11-*anti* relative configuration with the *meso* bisaldol **209** having 4,6-*syn*-8,10-*syn* and the chiral-bisaldol **210** having 4,6-*syn*-8,10-*anti* relative configurations by analysis of their ^{13}C NMR data.[x] In keeping with the convention that has been used previously for the minor aldol products, the 3,4,6 relative configuration should be 'normal' and the 8,10,11 configuration 'abnormal'. That is, the minor isomer should be 8,10-*anti*-10,11-*anti*. This result confirms that the (*E,E*)-bisenol borinate **211** was formed stereoselectively under these conditions. The 8,10-*anti* relative configuration in chiral-bisaldol **210** (as opposed to 8,10-*syn* in **209**) presumably results from poor diastereoface selectivity in aldol addition to the enolate. Notably, low diastereoselectivity was observed in the known reaction of the (*E*)-enol borinate of ketone **196aa** (MOM) with isobutyraldehyde (Table 2-2, entry 5).

[x] Structures of **209** and **210** are discussed in detail in the structure determination section.



Scheme 2-14: Preparation of (*E,E*)-bisenolates and bisaldols from *meso* **201aa**.

Because, the (*E,E*)-bisenol borinate **211** was formed stereoselectively (confirmed by the *anti* aldol products) from **201aa** and the adducts were obtained with 1.8:1 diastereoselectivity (Scheme 2-14), further exploration of this chemistry was initiated. In an effort to improve diastereoselectivities in reactions with the (*E,E*)-bisenol borinate (e.g., **211**), the Et_3Si-protected analogue **202aa** was prepared (Scheme 2-10) in excellent yields using the known[42] procedure. The choice of silyl protecting group (TES) was based on the observation that the (*E*)-enol borinate of Et_3Si (TES) protected ketone **197aa** gives much higher diastereoselectivity (*dr* >19:1; Table 2-2, entry 6) in aldol reaction with isobutyraldehyde than the corresponding methoxymethyl (MOM) protected analogue **196aa** (*dr* = 6:1; Table 2-2, entry 5).

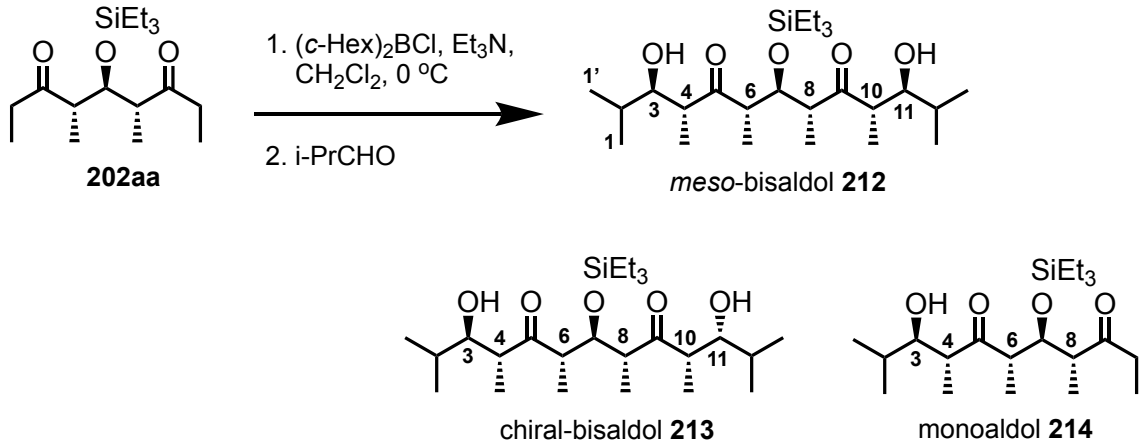
2.5. Preparation of *Meso* Bis-*Anti*-Aldol Adducts

2.5.1. Preparation of *meso* bis-*anti*-aldols from diketone 202aa (4,5-*anti*-5,6-*anti*)

Compared to methoxymethyl (MOM) protected β-hydroxy ketones, the Et_3Si protected analogues require higher temperatures, longer reaction times and higher concentrations to generate enol borinates by soft enolization.[42] The reaction of *meso* diketone **202aa** with *c*-Hex_2BCl and Et_3N at 0 °C followed by addition of isobutyraldehyde was studied extensively

(Table 2-3). As the enolization time and concentration were increased, conversion to bisaldol **212** was improved significantly (entries 1-3). After 3 h of enolization at higher concentration (0.18 M), 3 h of aldol reaction at −78 °C produced 63% of **212** as the only bisaldol detected (by ^{1}H NMR) (entry 3). At this stage, it was not clear whether enolization was incomplete or the aldol reaction was not proceeding to completion at lower temperatures (−78 °C). By increasing the aldol reaction temperature after 3 h, from −78 °C to room temperature, conversion was improved significantly (79%); however, the reaction produced a 9:1 mixture of *meso*- (**212**) and chiral- (**213**) bisaldols, respectively (entry 4). Diminished diastereoselectivities are presumably due to lower stereoselectivity at room temperature. After increasing stoichiometry of *c*-Hex$_2$BCl to 4 equivalents, conversion was dramatically improved to 93% with 9:1 mixture of bisaldols (entry 5). Further improvements in diastereoselectivities (*dr* >19:1) were obtained after aldol reaction was performed at lower temperature for longer time (−78 °C for 24 h, entry 6).

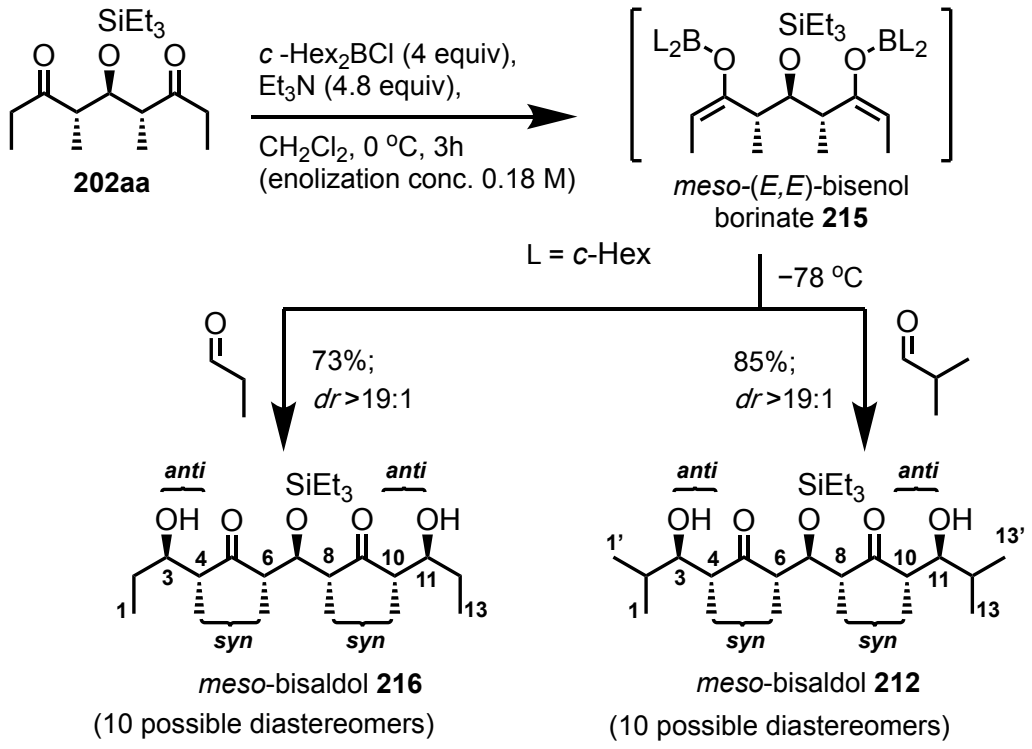
Table 2-3: Formation of (*E,E*)-bisenol borinate and bisaldols from *meso* diketone **202aa**.



entry	*c*-Hex$_2$BCl (equiv)	enolization conditions (conc.)[a]	aldol conditions	products (mole fraction)[b]		
				212 (213)	214	202aa
1	3	0 °C, 1 h (0.14 M)	−78 °C, 3 h	0.36	0.53	0.11
2	3	0 °C, 1.5 h (0.14 M)	−78 °C, 3 h	0.48	0.41	0.11
3	3	0 °C, 3 h (0.18 M)	−78 °C, 3 h	0.63	0.29	0.8
4	3	0 °C, 3 h (0.18 M)	−78 °C, 3 h, rt, 0.5 h	0.71 (0.08)	0.11	0.10
5	4	0 °C, 3 h (0.18 M)	−78 °C, 3 h, rt, 0.5 h	0.84 (0.09)	0.05	0.02
6	4	0 °C, 3 h (0.18 M)	−78 °C, 24 h	0.87 (0.04)	0.06	0.03

[a] Reaction concentration with respect to **202aa**. [b] From ^{1}HNMR data of crude reaction mixture unless otherwise indicated.

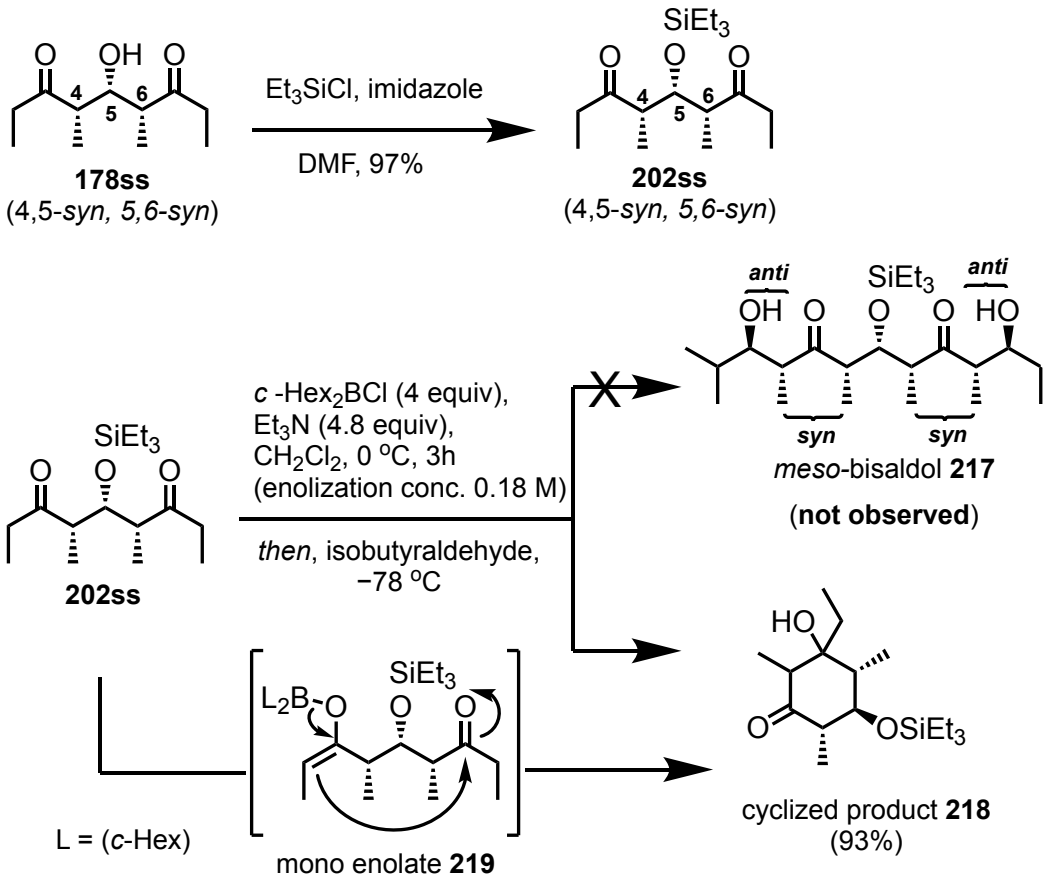
Using the above optimized reaction conditions, stereoselective enolization and aldol reactions of *meso* diketone **202aa** with isobutyraldehyde and propanal gave *meso* bisaldols **212** (85%; *dr* >19:1) and **216** (73%; *dr* >19:1), respectively (Scheme 2-15). These results confirmed that the *meso* (*E,E*)-bisenolate **215** was generated stereoselectively and the corresponding aldol reactions were highly diastereoselective (obtained 1 of 10 possible diastereomers exclusively) generating *meso* bisaldol adducts in excellent yields.



Scheme 15: Stereoselective synthesis of *meso* bisenolate **215** and bisaldols **212** and **216** from *meso* diketone **202aa**.

2.5.2. Preparation of *meso* bis-*anti*-aldols from *meso* diketone 202ss

To extend the scope of bisenolate and bisaldol chemistry, *meso* diketone **202ss** (4,5-*syn*-5,6-*syn*) was prepared from **178ss** using the standard procedure (Scheme 2-16). A reaction of **202ss** with *c*-Hex_2BCl and Et_3N, followed by addition of isobutyraldehyde, under the identical conditions used for **202aa** (Scheme 2-15) gave the unanticipated cyclized product **218** instead of the expected *meso* bisaldol adduct **217**.

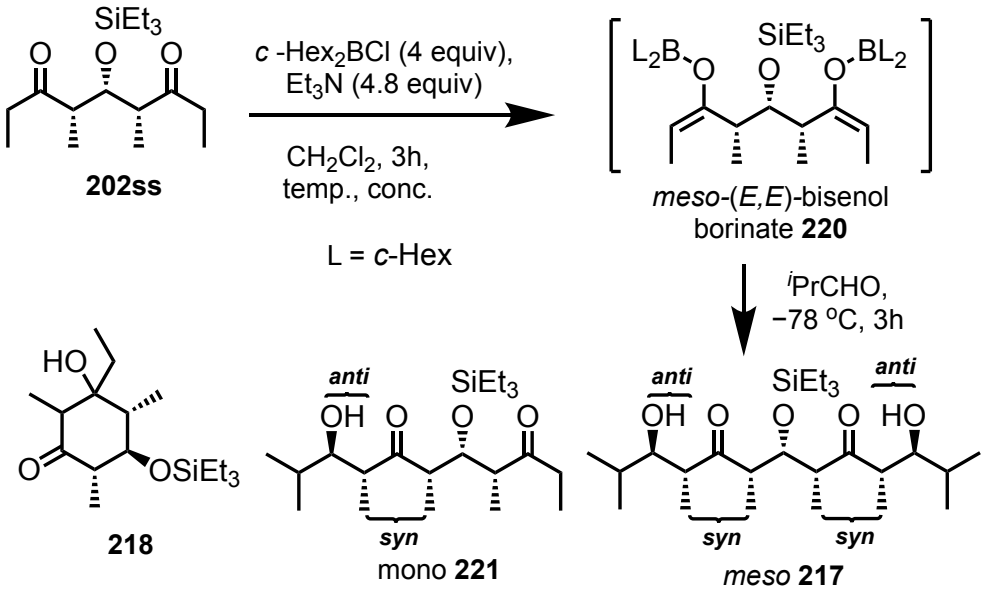


Scheme 2-16: Cyclization of *meso* diketone **202ss** to **218**.

Although monoenolate **219** can undergo further enolization to generate bisenolate, a competitive cyclization reaction (faster than enolization) is favored to give **218** (Scheme 2-16). Because cyclization occurs via an intramolecular reaction, the rate of cyclization does not depend on the reaction concentration; in contrast, enolization occurs via an intermolecular reaction, so the rate of enolization depends on reaction concentration, temperature and stoichiometry. Thus, by altering these reaction parameters, it should be possible to manipulate the difference in rates of enolization and cyclization. It was presumed that increasing reaction concentration would enhance the rate of bisenolate formation and decreasing the enolization temperature would slow down the undesired cyclization (reducing temperature might increase the difference in rates ($\Delta G^{\ddagger}$) of competitive reactions). To that end, reaction of **202ss** with *c*-Hex_2BCl and Et_3N was examined at

various concentrations and temperatures, followed by addition of isobutyraldehyde (Table 2-4). As anticipated, a significant amount of *meso* bisaldol **217** was observed when the enolization temperature was decreased from 0 °C to –42 °C confirming that (*E,E*)-bisenol borinate was formed under these reaction conditions (entry 2).[xi] Next, by increasing reaction concentration from 0.18M to 0.64M,[xii] the conversion to **217** was improved further (entry 3). Under optimized reaction conditions, treatment of **202ss** with *c*-Hex_2BCl and Et_3N (at −78 °C, 0.64M), followed by addition of isobutyraldehyde furnished the anticipated **217** in high yield (82%) with excellent diastereoselectivity (*dr* >19:1) (entry 4).

Table 2-4: Diastereoselective synthesis of *meso* bisaldol **217** from *meso* diketone **202ss**.



[xi] Lowering temperature will slow cyclization because it will reduce the concentration of the conformer leading to cyclization; and may also "relatively" assist the enolization by favoring the necessary $R_2C{=}O\text{-}BL_2Cl$ complex that leads to enolization.

[xii] Most of the solvent (hexane) comes from the borane reagent and was removed under reduced pressure before proceeding to the enolization.

entry	enolization temp., conc.[a]	products (mole fraction) [b]			
		217	221	202ss	218
1	0 °C, 0.18 M	------	------	0.03	0.97
2	−42 °C, 0.18 M	0.41	0.15	0.02	0.42
3	−42 °C, 0.64 M	0.86	0.02	0.02	0.1
4	−78 °C, 0.64 M	0.91	0.05	0.04	------

[a] Reaction concentration with respect to **202ss**. [b] From ^{1}H NMR data of crude reaction mixture unless otherwise indicated.

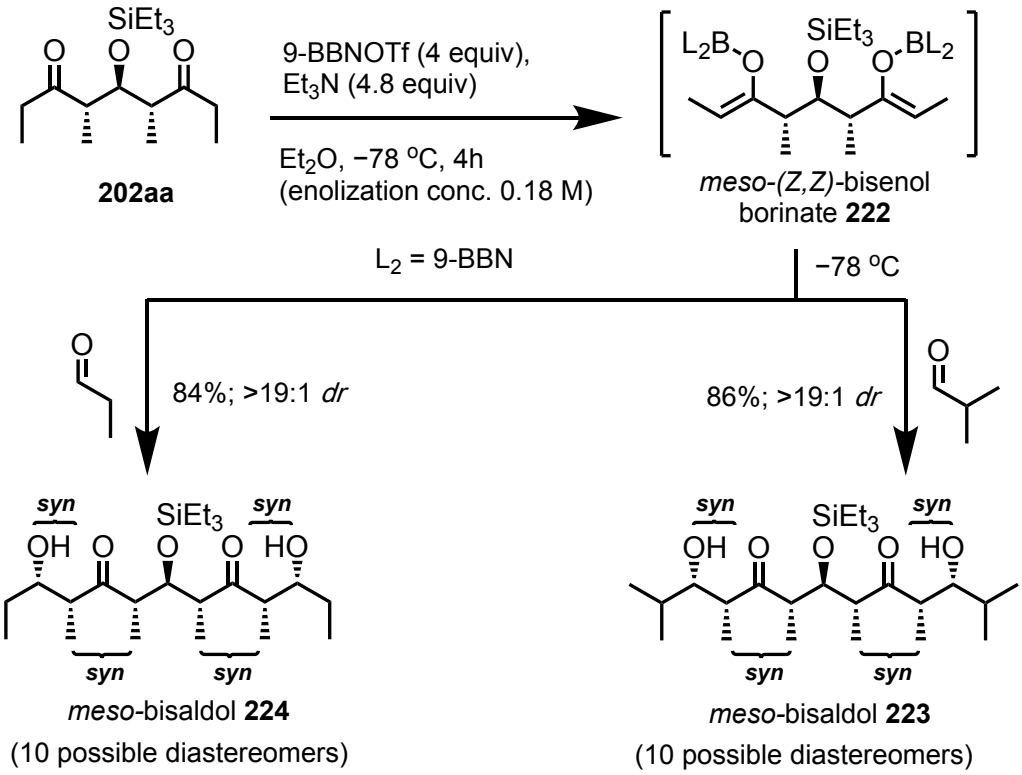
In summary, stereoselective preparations of *meso* (*E,E*)-bisenol borinates were achieved from both *meso* diketones **202aa** and **202ss**, and the corresponding aldol reactions of these bisenolates were highly diastereoselective to give *meso* bis-*anti*-aldols. However, it is clear that *syn*-aldol adducts are required to prepare the target precursor **174** from the proposed SEGS aldol strategy. Towards that goal, research was focused on stereoselective synthesis of (*Z,Z*)-bisenolates in hope of generating the desired *syn*-aldol adducts with high diastereoselectivites.

2.6. Preparation of *Meso* Bis-*Syn*-Aldol Adducts

2.6.1. Preparation of *meso* bis-*syn*-aldols from 202aa

Previous attempts to prepare the *meso*-(*Z,Z*)-bisenolate from the BOM protected ketone **201aa** confirmed the formation of bisenolates (Scheme 2-13); however, a mixture of adducts was obtained with poor diastereoselectivities. Alternatively, Et_3Si protecting group on diketone **178aa** was considered with hopes of improving the diastereoselectivities in bisaldol reactions. Although aldol additions of the (*Z*)-enol borinate of the related TES protected ketone **197aa** to isobutyraldehyde gave low diastereoselectivities (*dr* 2:1, Table 2-2, entry 4), diketone **202aa** was

chosen to attempt bisaldol reaction. Accordingly, **202aa** was treated with 9-BBNOTf, Et_3N, under conditions analogous to those used for **197aa**, followed by addition of achiral aldehydes as shown in Scheme 2-17. Remarkably, under these conditions, *meso* bisaldols **223** (86%; *dr* >19:1) and **224** (84%; *dr* >19:1) were obtained in excellent yields and diastereoselectivities. Formation of the *meso*-bis-*syn*-aldols **223** and **224** confirmed that the *meso*-(*Z,Z*)-bisenol borinate **222** was generated stereoselectively and the corresponding aldol reactions were highly diastereoselective. The much higher diastereoface selectivities observed for aldol additions to the *meso*-(*Z,Z*)-bisenolates of **202aa** compared with those to the known (*Z*)-enolate of **197aa** suggest that the ketal group plays an important role.



Scheme 2-17: Stereoselective synthesis of *meso*-(*Z,Z*)-bisenol borinate **222** and *meso* bisaldols **223**, **224** from *meso* diketone **202aa**.

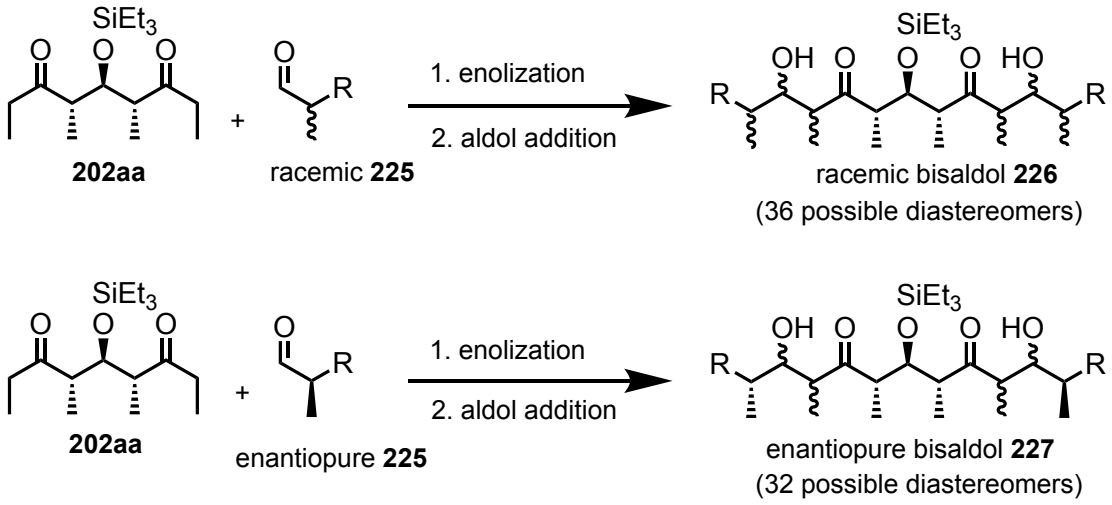
In summary, all the obtained results from both *meso* diketones **202aa** and **202ss** confirmed that the enolization reactions were highly stereoselective to generate both *meso*-(*E,E*)- and (*Z,Z*)-

bisenol borinates with *c*-Hex_2BCl and 9-BBNOTf respectively, and subsequent aldol reactions were highly diastereoselective to obtain *meso* bisaldols exclusively. However, all the above reactions were examined only with simple achiral aldehydes. Towards the synthesis of the putative precursor **174** and to develop the proposed SEGS bisaldol strategy, further bisaldol reactions were investigated with chiral aldehydes using the optimized conditions for bisenolate formation.

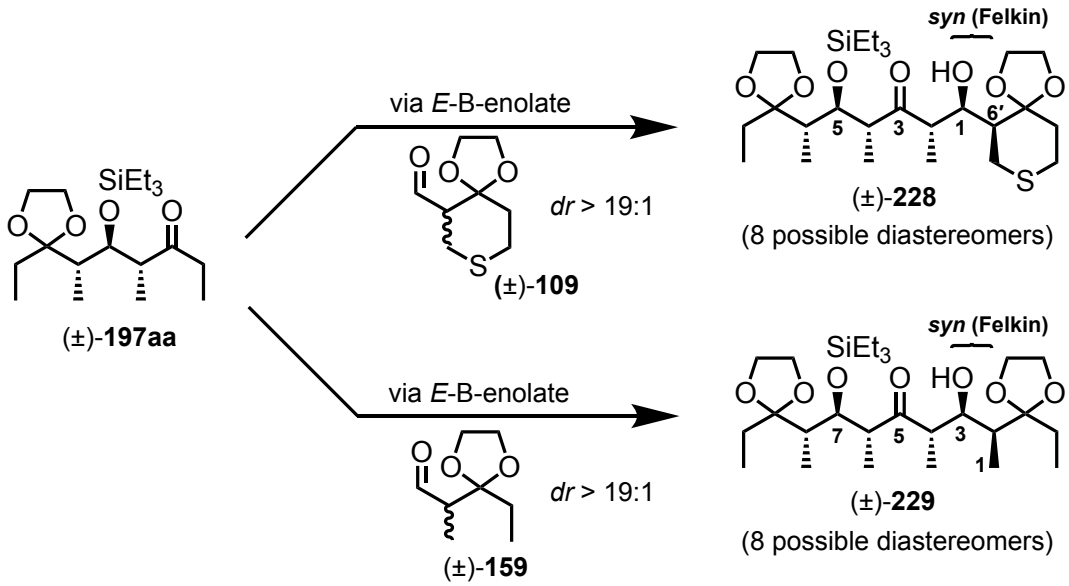
2.7. Bisaldol Reactions with Chiral Aldehydes

Aldol reactions of bisenolates of **202aa** with racemic and enantiopure aldehydes are more complicated and can generate up to 36 and 32 possible diastereomers, respectively (Scheme 2-18a). Thus, selective formation of the desired aldol adduct will be more challenging in such cases. Importantly, addition of (*E*)-enol borinates of ethyl ketones to chiral aldehydes (±)-**109** and (±)-**159** are known[42] to proceed with high Felkin diastereoface selectivity in the Ward group (Scheme 2-18b).[66] These reactions are not only diastereoselective, but also proceed with high mutual kinetic enantioselection (MKE); i.e., each enantiomer of ketone (±)-**197aa** preferentially reacts with one enantiomer of racemic aldehydes (±)-**109** or (±)-**159**.

a) possible diastereomers from aldol reactions of **202aa** with chiral aldehydes



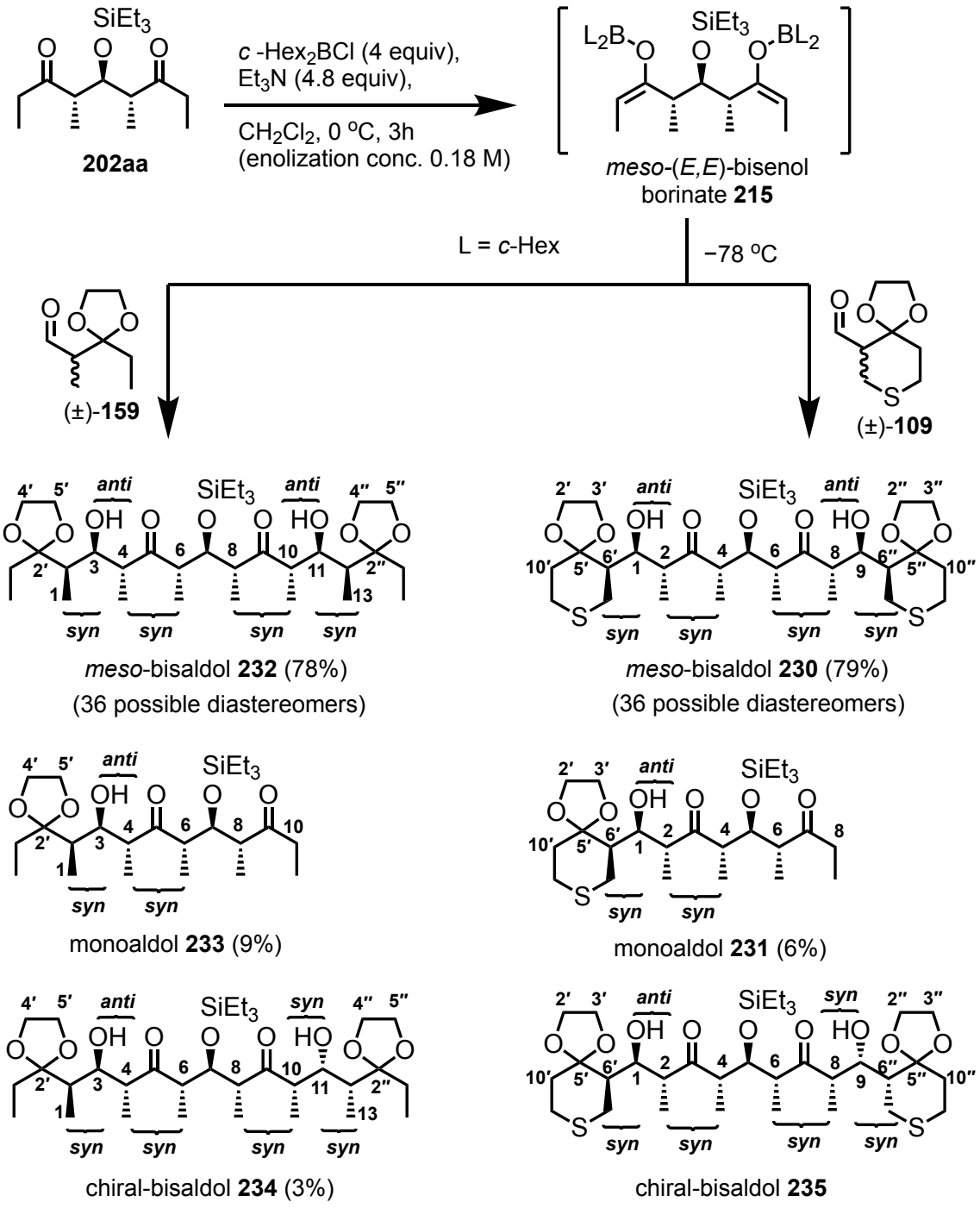
b) diastereoselectivities with the known aldehydes (±)-**109** and (±)-**159**



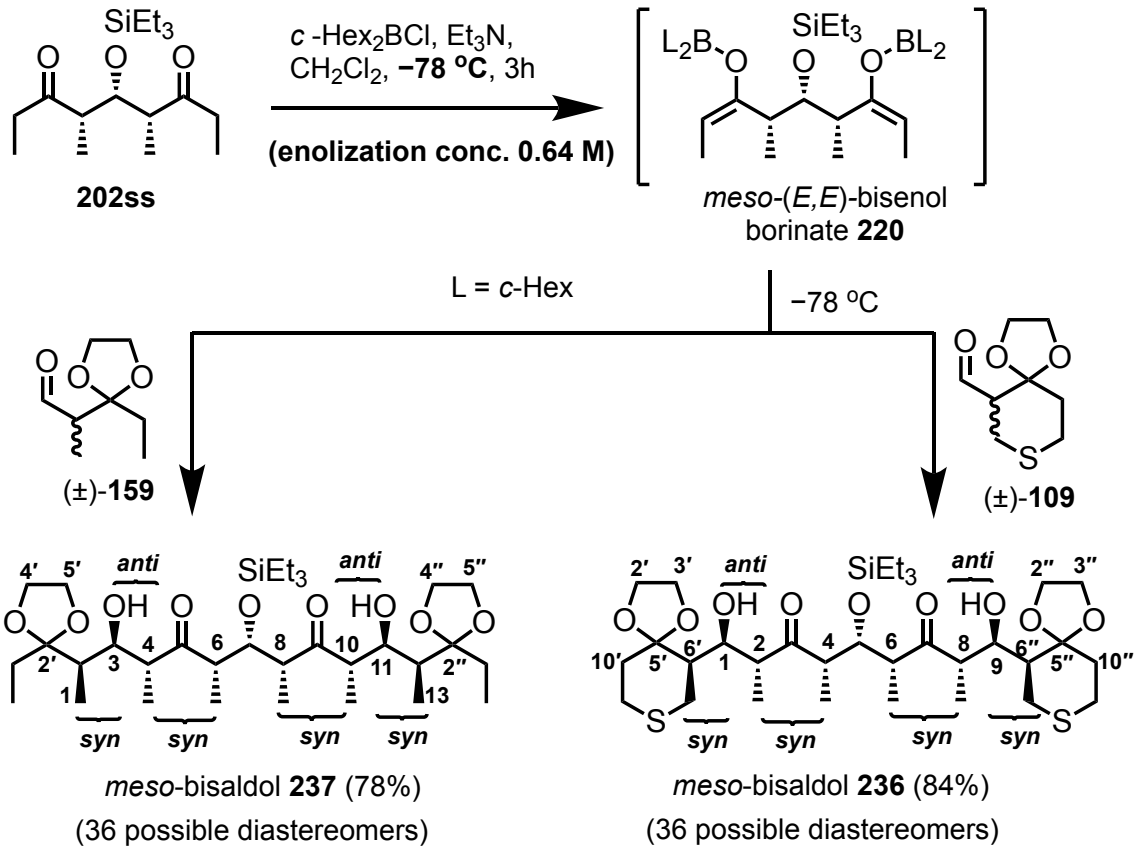
Scheme 2-18: a) Possible diastereomers from aldol reactions of **202aa** with chiral aldehydes; b) Diastereoselectivities from the known aldol reactions of **197aa** (via (*E*)-enol borinate) with chiral aldehydes.

2.7.1. Reactions of (*E,E*)-bisenol borinates of 202aa and 202ss with chiral aldehydes

Under optimized conditions, reactions of *meso*-(*E,E*)-bisenol borinate of **202aa** with chiral aldehydes (±)-**109** and (±)-**159** furnished the *meso* bisaldols **230** and **232**, respectively, in good yields and with excellent diastereoselectivities (Scheme 2-19). These results confirmed that additions of (*E*)-enol borinates of **215** to the aldehydes (±)-**109** and (±)-**159** proceeded with high Felkin diastereoface selectivities as was anticipated according to the known results from Scheme 2-18. Similarly, under optimized conditions, reaction of *meso*-(*E,E*)-bisenol borinate of **202ss** with chiral aldehydes (±)-**109** and (±)-**159** furnished the anticipated *meso* bisaldols **236** and **237**, respectively, in good yields and with high diastereoselectivities (Scheme 2-20).



Scheme 2-19: Reactions of *meso*-(*E,E*)-bisenol borinate of **202aa** with chiral aldehydes (±)-**109** and (±)-**159**.

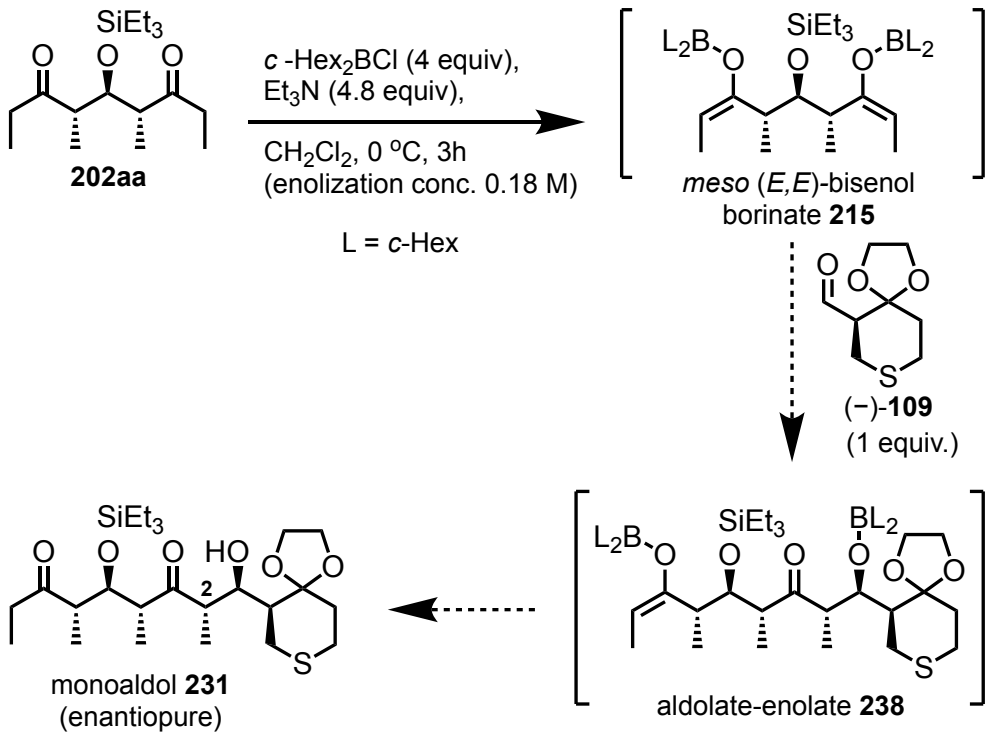


Scheme 2-20: Reactions of *meso*-(*E,E*)-bisenol borinate of **202ss** with chiral aldehydes (±)-**109** and (±)-**159**.

Formation of *meso* bisaldols **230**, **232**, **236** and **237** with excellent diastereoselectivities and mutual kinetic enantioselections (MKEs) confirmed that these reactions are highly enantiotopic group selective (EGS) (Schemes 2-19 & 2-20). The two enolates in *meso* bisenolates **215** and **235** have an enantiotopic relationship and each enolate will have two diastereotopic faces; each enantiotopic enolate (in **215**, **235)** must preferentially react with the *matched* enantiomer (kinetic preference) of racemic aldehydes **(±)-109, (±)-159** to provide the *meso* bisaldols **230**, **232**, **236** and **237**. The selective formation of these *meso* bisaldols (with high MKE) demonstrates that with the proper choice of protecting group and enolate type, it should be possible to achieve enantioselective desymmetrization (or internal EGS) by reaction with an enantiopure aldehyde to obtain monoaldol adducts with high enantio- and diastereoselectivities.

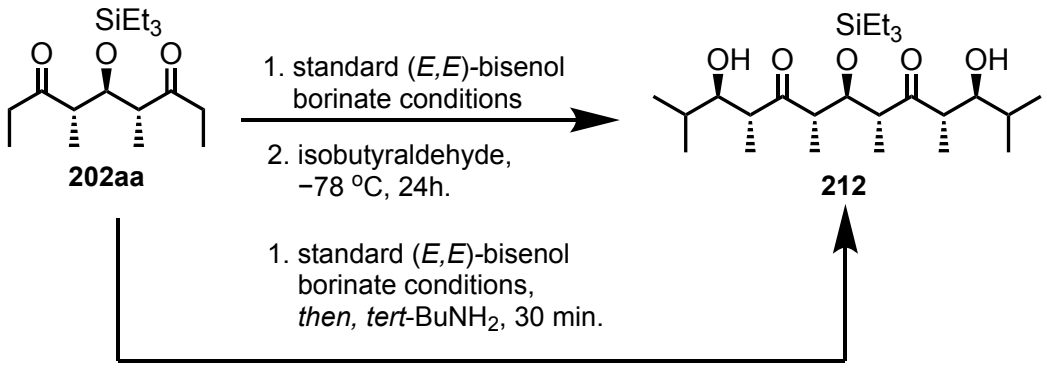
2.7.2. Enantioselective desymmetrization

Enantioselective desymmetrization[68] of *meso* bifunctional compounds is a powerful strategy to obtain enantioenriched products in asymmetric synthesis.[74] Because high diastereo- and enantiotopic group selectivities were observed in reactions of *meso* (*E,E*)-bisenol borinates of **202aa** and **202ss** with racemic aldehyde **(±)-109** (Schemes 2-19 & 2-20), it was predicted that the corresponding enantiopure aldehyde **(−)-109**[65] would preferentially react with one enolate (*matched*) of **202aa** via enantioselective desymmetrization (internal EGS) (Scheme 2-21). However, for efficient enantioselective desymmetrization of the *meso* bisenolate, the amount of enantiopure aldehyde needs to be carefully controlled (e.g., one equivalent) to maximize conversion and to avoid further reactions (i.e., *mismatched* reactions) with the enolate in **238**. This normally straightforward requirement is complicated by the stoichiometry of the boron reagent. Only two equivalents of borane reagent are needed to prepare bisenolates of *meso*-1,5-diketones; however, four equivalents of borane reagent were required to obtain bisenolates efficiently under optimized conditions. Thus, the excess (2 equiv) of borane reagent in the reaction mixture could potentially react with and consume the enantioenriched aldehyde (−)-**109**. To overcome this problem, the stoichiometry of aldehyde could be increased to 3 equivalents; however, the relative rates of the reactions of the aldehyde with enolate and borylating agent are unknown. This approach might be effective if the rate of borylation of the aldehyde is much faster than aldol; however, this process would not be practical if only because of the 'expense' of the enantiopure aldehyde. Given these difficulties, other possible alternatives for consuming the excess borane reagent before addition of aldehyde were considered. The method to consume excess reagent should be selective and should not interfere with any of the other components (e.g., enolates, aldolates, aldehyde) in the reaction mixture.



Scheme 2-21: Proposed enantioselective desymmetrization of *meso* bisenolate **215** with enantiopure aldehyde (−)-**109**.

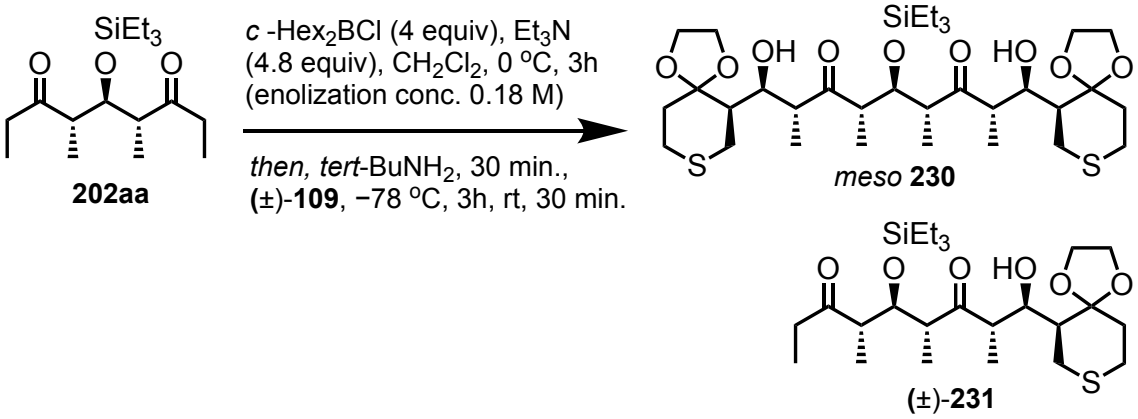
Cragg et al. described a method to prepare aminoboranes from reaction of arylchloroboranes with *tert*-butylamine.[91] It was found that the reactivity of aminoboranes is much lower than that of arylchloroboranes. Encouraged by this research, it was anticipated that *tert*-butylamine could react with and consume excess boron reagent in the proposed aldol reactions. To test this approach and to determine the effect of *tert*-butylamine (if any) in aldol reactions, *meso* (*E,E*)-bisenol borinate of **202aa** was prepared under the optimized conditions and was treated with *tert*-butylamine followed by addition of isobutyraldehyde (excess) (Scheme 2-22). Aldol reactions with and without *tert*-butylamine produced the known *meso* bisaldol **212** with >95% conversion confirming that *tert*-butylamine did not interfere with aldol reactions.



Scheme 2-22: Aldol reaction of **202aa** with isobutyraldehyde in presence and in absence of *tert*-butylamine.

Secondly, to determine if *tert*-butylamine could prevent borylation of the aldehyde, aldol reactions of *meso* **202aa** with (±)-**109** (2 equiv) were examined with different amounts of *tert*-butylamine (Table 2-5). Increasing the amount of *tert*-butylamine from 0-3 equiv (with respect to ketone), improved conversion to aldol adducts accordingly (entries 1-4). These results suggest that the *tert*-butylamine reacted with excess borane reagent presumably to form the corresponding aminoborane, which apparently has no impact on enolate, aldehyde, or aldols; as a result, aldol conversion was improved.

Table 2-5: Effect of *tert*-butylamine in aldol reactions with excess borane reagent *c*-Hex_2BCl.



entry	*tert*-butylamine (equiv to 202aa)	(±)-109 (equiv)	conversion to aldols (%)[a]
1	0	2	69
2	1	2	76
3	2	2	81
4	3	2	86
5	4	2	88
6	0	4	96

[a] Determined from ^{1}H NMR data of crude reaction unless otherwise indicated.

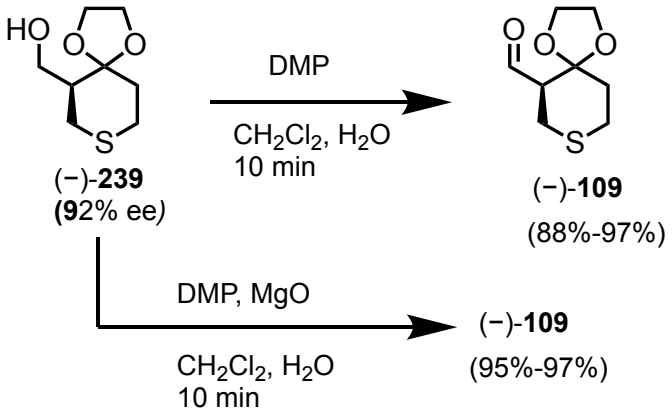
The above results (from Table 2-5) suggest that *tert*-butylamine is a suitable additive to consume excess borane reagent before addition of enantiopure aldehyde to *meso* bisenolate for enantioselective desymmetrization reactions. The known and readily available enantioenriched aldehyde (−)-**109**[65] was considered for enantiotopic group selective aldol reactions.

2.7.2.1. Preparation of enantioenriched aldehyde (−)-109

The Ward group has previously reported the preparation of enantioenriched aldehyde (−)-**109** via oxidation of the corresponding alcohol (−)-**239** using the Dess-Martin periodinane (DMP) (Scheme 2-23).[65] This method is advantageous because the pure aldehyde is obtained after a simple aqueous work up in >90% yield and with negligible change in enantiopurity compared to the starting alcohol. However, the aldehyde (−)-**109** is known to racemize on standing and long-term storage is not prudent. The amount of aldehyde to be used in EGS aldol reaction is crucial and must be carefully controlled. A possible solution to control the amount of (−)-**109** would be to oxidize a known amount of the stable alcohol (−)-**239** and then directly use the resulting aldehyde product in the enantioselective desymmetrization reaction. However, this approach must be robust and give reproducible yields.[65] Over multiple experiments, it was observed that the DMP oxidation of (−)-**239** was very sensitive to the reaction time and the quality of DMP. Overoxidation (i.e., sulfide oxidation to the corresponding sulfoxide or sulfone) was observed

when the reaction time exceeded 10 minutes. Although overoxidation was negligible at shorter reaction times, the oxidation of (−)-**239** was incomplete under these conditions. Running the reaction until the disappearance of (−)-**239** (TLC monitoring, ca. 15 min) resulted in variable amounts of overoxidation products. Although the byproducts were removed by the aqueous work up, the yield of (−)-**109** varied from 88-97%.

Based on the supposition that sulfide oxidation by DMP might be catalyzed by the acetic acid byproduct from the alcohol oxidation,[92,93] MgO was introduced as an insoluble base that might trap the acetic acid. After optimization of these conditions, the alcohol (−)-**239** was oxidized to (−)-**109** in reproducibly high yields (95% to 97%) over multiple experiments on various scales.[xiii]



Scheme 2-23: An improved preparative method of aldehyde (−)-**109** from alcohol (−)-**239**.

2.7.2.2. Enantioselective desymmetrization of meso-(E,E)-bisenol borinate 215

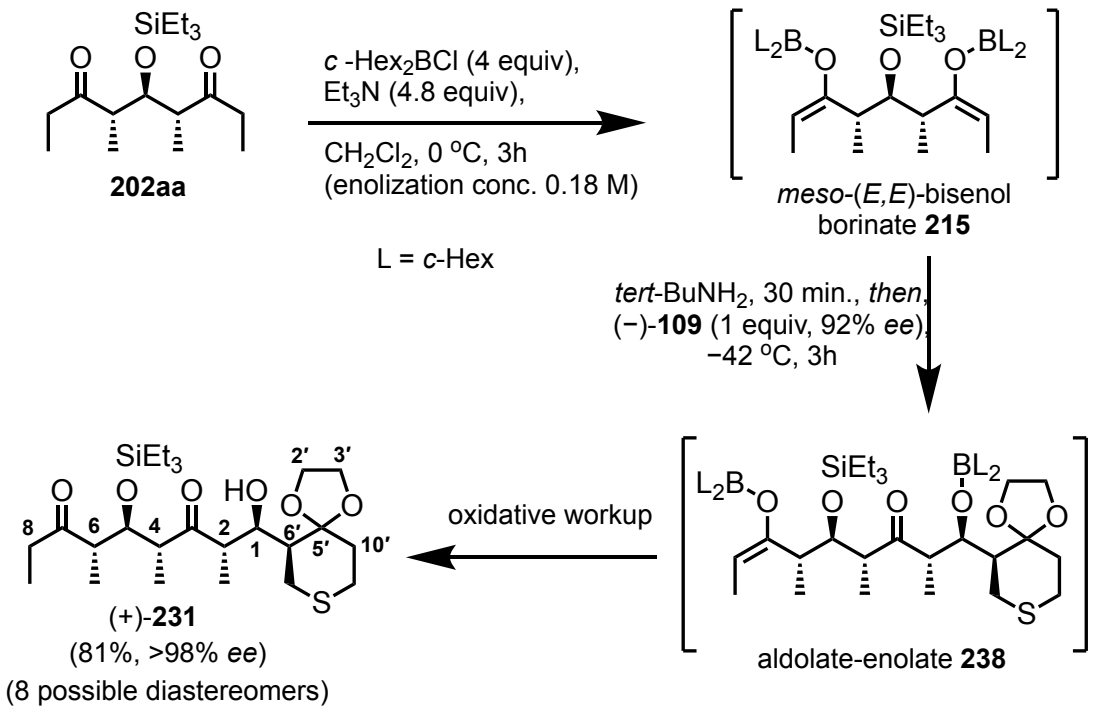
A reaction of *meso*-(*E,E*)-bisenol borinate **215** with *tert*-butylamine at 0 °C, followed by addition of one equivalent of enantioenriched aldehyde (−)-**109**[xiv] at −78 °C, furnished the

[xiii] Quality of DMP is very important to obtain reproducible results; freshly prepared and recrystallized DMP was used for these oxidations.

[xiv] Prepared from one equivalent of the alcohol (−)-**239** as previously described and used immediately without any purification.

enantioenriched monoaldol adduct (+)-**231**, albeit in moderate yields (69%) (Scheme 2-24). Enantioselective desymmetrization yields were improved (81%) by increasing aldol reaction temperature to −42 ºC. The adduct (+)-**231** has 1,6′-*syn*-1,2-*anti*-2,4-*syn* relative configuration as expected from the previously described aldol reactions with racemic aldehydes. Although the enantiopurity of (−)-**109** was 92% *ee* (assumed from 92% *ee* of the precursor alcohol (−)-**239**; Scheme 2-23), the monoaldol (+)-**231** was generated with enhanced enantiopurity (*ee* >98%, by HPLC). This amplification of the product *ee* is an advantage of enantioselective desymmetrization reactions and results from consumption of the minor aldehyde enantiomer (+)-**109** by preferential reaction (i.e., kinetic preference, *matched*) with enolate **238** generating the known *meso* bisaldol **230**.

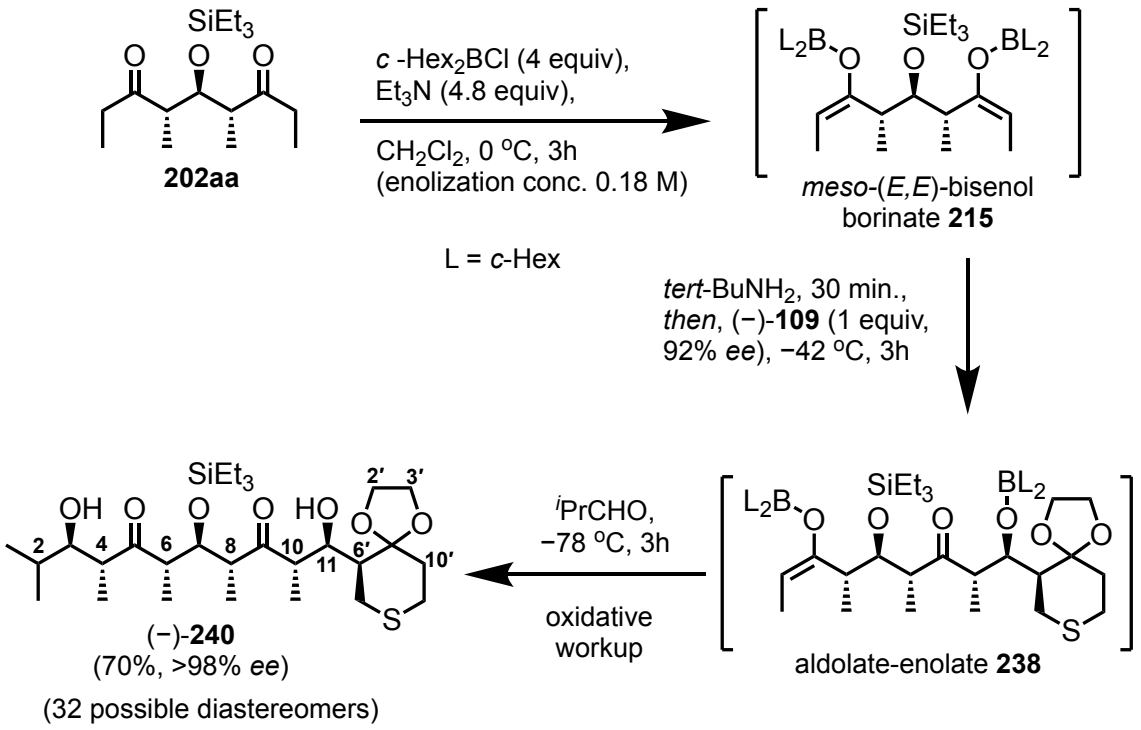
In summary, enantioselective desymmetrization of a simple *meso* diketone **202aa** with enantioenriched aldehyde (−)-**109** produced the aldol adduct (+)-**231** with high enantio- and diastereoselectivity. Extrapolating from this result, it should be possible to obtain even more complex enantioenriched bisaldol adducts if the intermediate aldolate-enolate **238** can selectively react with different aldehydes (chiral or achiral) in a second aldol reaction.



Scheme 2-24: Enantioselective desymmetrization of *meso*-(*E,E*)-bisenol borinate **215** with enantioenriched (92% *ee*) aldehyde (−)-**109**.

2.7.3. One-pot sequential enantiotopic group selective (SEGS) bisaldol reactions of *meso*-(*E,E*)-bisenol borinate 215

Towards developing a one-pot SEGS bisaldol strategy, the initial plan was to test stability and reactivity of the intermediate enolate **238** (Scheme 2-24) by trapping it with a simple achiral aldehyde (e.g., isobutyraldehyde) in the second aldol reaction. To that end, the aldolate-enolate **238**, generated as described above, was treated with isobutyraldehyde resulting in the formation of enantioenriched bisaldol product (−)-**240** (32 possible diastereomers) in good yields with high enantio- and diastereoselectivities (Scheme 2-25).

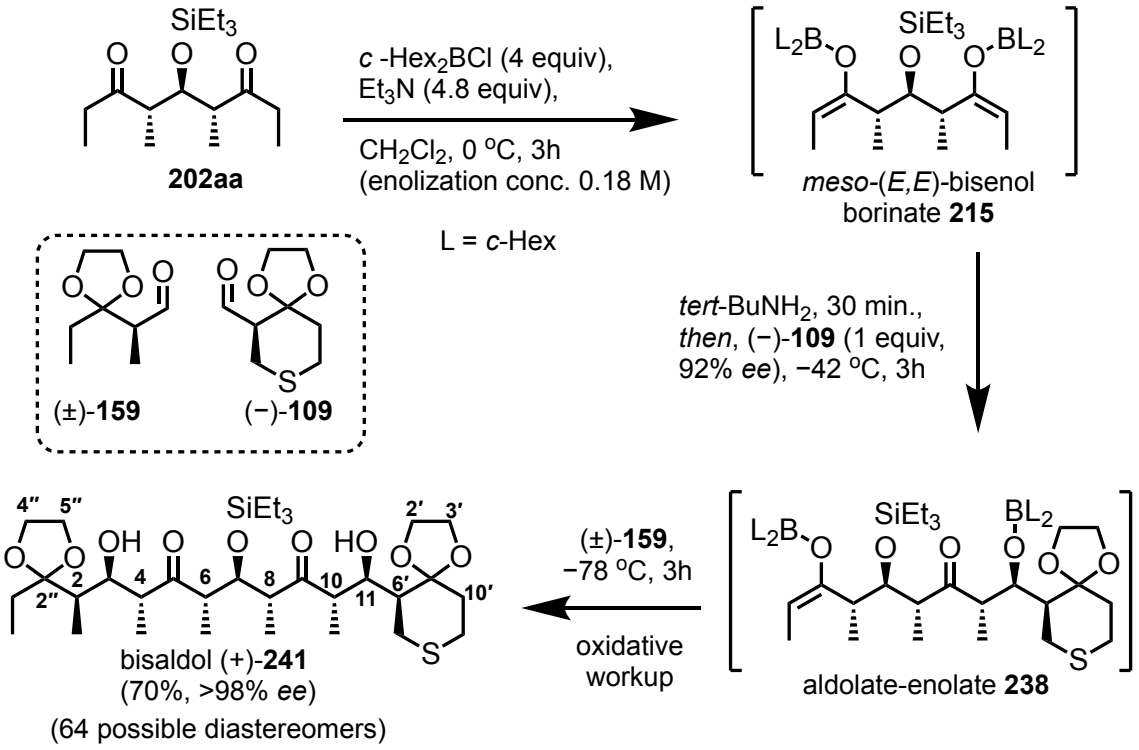


Scheme 2-25: One-pot enantioselective bisaldol reaction of *meso*-(*E,E*)-bisenol borinate **215** with (−)-**10**9 and isobutyraldehyde.

The Ward group has done extensive research to design stereoselective aldol reactions that proceed with kinetic resolution (KR); several polypropionates have been synthesized by exploiting racemic reactants with enantiopure reactants using this strategy. Adapting this strategy, it should be possible to achieve kinetic resolution (*external EGS*) by trapping the enantiopure intermediate **238** (>98% *ee*) with a racemic aldehyde in a second aldol reaction. For an efficient kinetic resolution, the two enantiomers of the racemic aldehyde must react with enantiomerically pure enolate with substantially different rate constants to produce an aldol product with high diastereoselectivity.

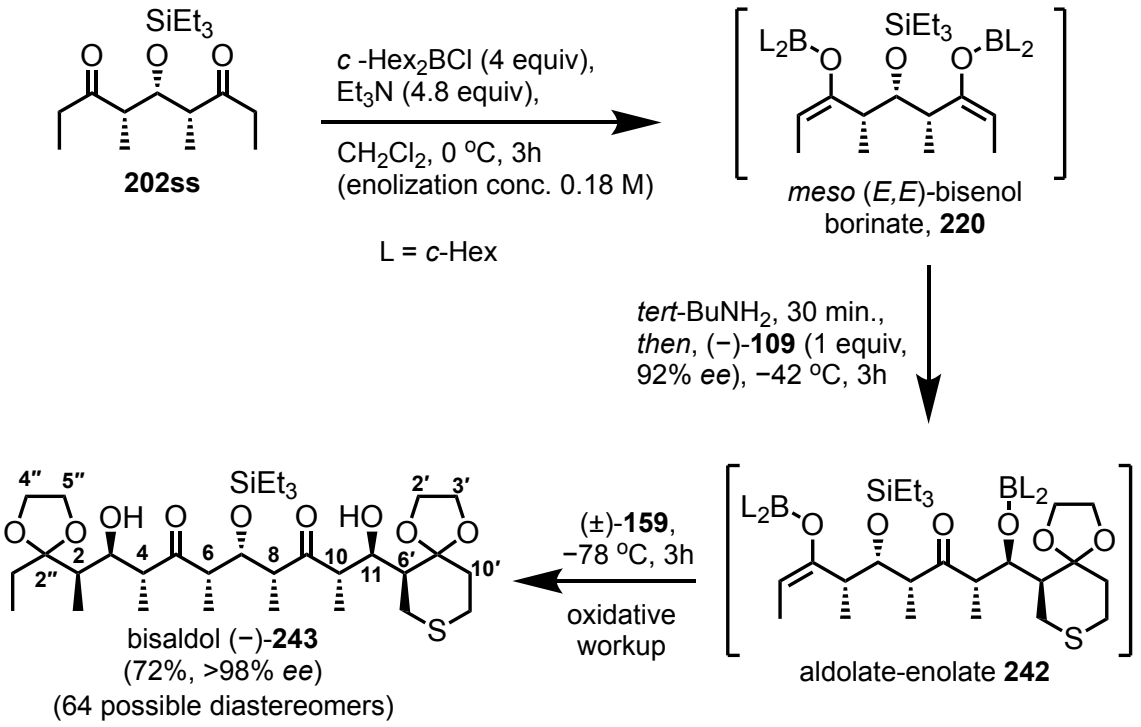
In order to achieve kinetic resolution with high enantioselectivity a suitable racemic aldehyde must be used for aldol reaction with intermediate **238**. Because the aldehyde (±)-**159** is known to react with *meso* bisenolate **215** with a high level of mutual kinetic enantioselection

(MKE), it was a logical candidate for this reaction. Accordingly, the aldolate-enolate **238**, generated as described previously, was treated with racemic aldehyde (±)-**159** to afford the enantioenriched bisaldol product (+)-**241** (64 possible diastereomers) in good yields and with excellent diastereo- and enantioselectivities (*dr* >19:1; *ee* >98%, HPLC) (Scheme 2-26).



Scheme 2-26: One-pot SEGS bisaldol reactions of *meso*-(*E,E*)-bisenol borinate **215** with (−)-**109** and (±)-**159**.

In an analogous manner, addition of aldehyde (±)-**159** to the aldolate-enolate **242**, prepared from *meso* diketone **202ss** as previously described, afforded enantioenriched bisaldol product (−)-**243** (64 possible diastereomers) in good yield and with excellent diastereo- and enantioselectivities (Scheme 2-27).



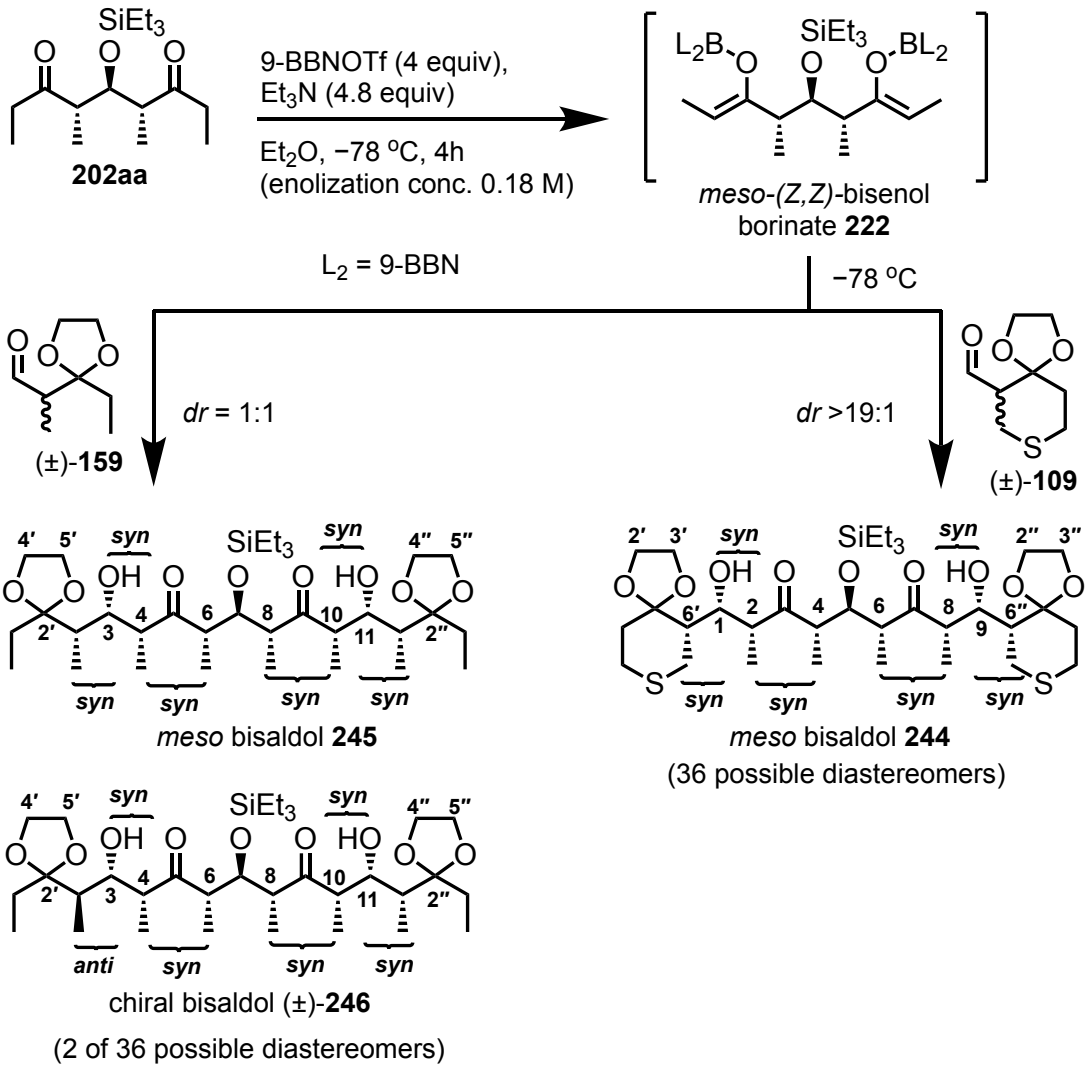
Scheme 2-27: One-pot SEGS bisaldol reaction of *meso*-(*E,E*)-bisenol borinate **220** with (−)-**109** and (±)-**159**.

In summary, *meso* diketones **202aa** and **202ss** underwent sequential directed aldol reactions first with enantioenriched aldehyde (−)-**109** via enantioselective desymmetrization (*internal EGS*) and then with racemic aldehyde (±)-**159** via kinetic resolution (*external EGS*) to give the enantioenriched bisaldol adducts (+)-**241** and (−)-**243**, respectively, and sets the absolute configurations of eight stereocenters (C2 to C11) in a one-pot process (Schemes 2-26 & 2-27). This powerful SEGS bisaldol strategy demonstrates that simple *meso* diketones can be converted to a variety of complex enantiopure bisaldol products that are potential intermediates in polypropionate syntheses. The next objective was to apply this developed SEGS bisaldol strategy to the total synthesis of dolabriferol C (**17**). However, so far this strategy was applied to *meso*-(*E,E*)-bisenol borinate to obtain *anti*-aldol products. To achieve the synthetic target **174** (Scheme 2-2), stereoselective preparation of *syn*-bisaldol adducts is required. Thus, the SEGS bisaldol

strategy was further explored with *meso*-(*Z,Z*)-bisenolates to obtain *syn*-bisaldol products selectively.

2.7.4. Reactions of *meso*-(*Z,Z*)-bisenol borinate 222 with chiral aldehydes

The reaction of *meso*-(*Z,Z*)-bisenol borinate **222** with (±)-**109** under the previously established conditions produced the *meso* bisaldol adduct **244** in excellent yield (80%) and with high diastereoselectivity (*dr* >19:1) (Scheme 2-28). However, under the identical conditions, reaction of **222** with (±)-**159** produced a 1:1 mixture of *meso* bisaldol **245** and chiral bisaldol (±)-**246**. Both **245** and (±)-**246** have 3,4-*syn*-4,6-*syn*-8,10-*syn*-10,11-*syn*-11,12-*syn* relative configurations, with the *meso* **245** having 2,3-*syn* and the chiral (±)-**246** having 2,3-*anti* relative configurations, respectively. This result proves that the mutual kinetic enantioselection (MKE) in reaction of (*Z*)-enol borinate **222** with (±)-**159** is considerably lower than in reaction with (±)-**109**. Additions of (*Z*)-enolates to chiral 2-methyl aldehydes are known to proceed with lower Felkin (2,3-*syn*) diastereoselectivity compared to similar additions of (*E*)-enolates.[94,95] It is also known in the Ward group that addition of (*Z*)-enolates of several ketones related to (±)-**159** produced a mixture of aldols with both 2,3-*syn* (Felkin) and 2,3-*anti* (non-Felkin) relative configurations.[66]



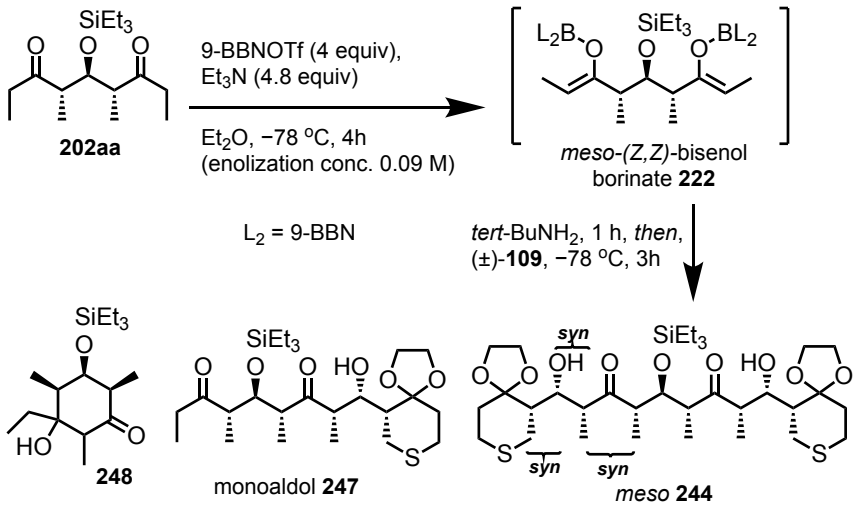
Scheme 2-28: Reactions of *meso*-(*Z,Z*)-bisenol borinate **222** with chiral aldehydes.

2.7.4.1. Effect of tert-butylamine on aldol reactions of meso-(Z,Z)-bisenol borinate 222

Reactions of *meso*-(*Z,Z*)-bisenol borinate **222** with racemic aldehyde (±)-**109** in presence of *tert*-butylamine at various temperatures were investigated, and the results are presented in the Table 2-6. With exception of the control experiment (with no additive, entry 1), poor conversions were observed in experiments with *tert*-butylamine (entries 2-5). In contrast to the previously described use of *tert*-butylamine to consume *c*-Hex_2BCl reagent (Table 2-5), increasing reaction

temperature did not improve conversion (Table 2-6, entries 4-6). The cyclized product **248**[xv] was observed in presence of *tert*-butylamine at 0 °C.

Table 2-6: Effect of *tert*-butylamine on bisaldol reactions of *meso*-(*Z,Z*)-bisenol borinate **222**.



entry	*tert*-butylamine (3 equiv) conditions	(±)-109 equiv	products (mole fraction)[a]			
			244	**247**	**202aa**	**248**
1	none	4	0.94	0.03	0.03	-------
2	−78 °C, 1 h	4	0.44	0.43	0.13	-------
3	−78 °C, 1 h	2	0.36	0.44	0.2	-------
4	−42 °C, 1 h	2	0.3	0.44	0.25	-------
5	0 °C, 1 h	2	0.23	0.18	0.24	0.36
6	none, 0 °C, 1 h	4	0.96	0.2	0.2	-------

[a] Determined from ^{1}H NMR data of crude reaction unless otherwise indicated.

The stability of the *meso*-(*Z,Z*)-bisenol borinate **222** at higher temperature was tested by warming the reaction mixture to 0 °C for 1 h before addition of aldehyde (Table 2-6, entry 6). The

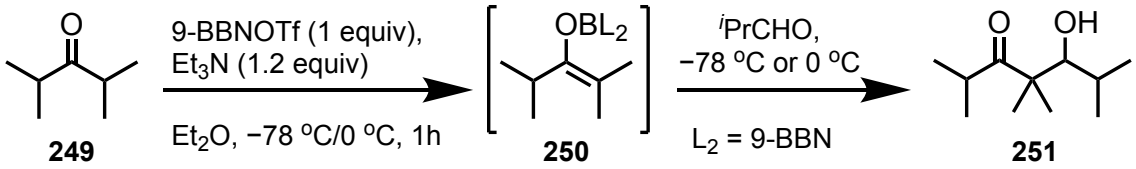
[xv] Structure of **248** was tentatively assigned based on ^{1}H NMR data analysis.

result of this reaction was quite similar to the standard reaction with aldehyde (±)-**109** (entry 1) confirming the stability of *meso*-(*Z,Z*)-bisenol borinate **222** at 0 °C was not the reason for poor conversion or cyclization. From the above observations, it was concluded that the poor conversions were due to reaction of *tert*-butylamine with the *meso*-(*Z,Z*)-bisenol borinate **222**. Thus, *tert*-butylamine was not effective in consuming excess 9-BBNOTf.

2.7.4.2. A suitable additive to consume 9-BBNOTf

As an alternative, 2,4-dimethyl-3-pentanone (**249**) was selected to react with and consume the excess 9-BBNOTf by formation of the corresponding enol borinate (Table 2-7). Initial experiments aimed to establish conditions to prepare the enolate from ketone **249** with 9-BBNOTf and test the reactivity of the generated enolate in aldol reactions. Accordingly, a reaction of ketone **249** with 9-BBNOTf and Et_3N at −78 °C, followed by addition of isobutyraldehyde gave no aldol adduct suggesting either no enolate was generated at −78 °C, or no aldol reaction occurred. However, an otherwise identical experiment where the enolization temperature was increased to 0 °C produced the expected aldol product **251**[96] in reasonable yield (64%) (entry 2). Thereafter, aldol conversion with respect to 9-BBNOTf was examined with various stoichiometries of ketone **249**. Increasing the amount of ketone **249** improved aldol conversion significantly (entries 3-6). The obtained results from this optimization study suggested that the reaction of ketone **249** (4 equiv) with 9-BBNOTf (1 equiv) at 0 °C for 1 h is a suitable condition to generate the enolate **250** in over 95% yield (entry 6). On the other hand, using optimized enolization conditions, aldol reaction at −78 °C produced only 18% of the adduct **251** suggesting the enolate **250** is much less reactive (at −78 °C) to couple with isobutyraldehyde compare to the *meso*-(*Z,Z*)-bisenol borinate **222** (entry 8). A large difference in reactivity is required for preferential reaction of *meso*-(*Z,Z*)-bisenol borinate **222** with aldehyde to occur in presence of enolborinate **250**.

Table 2-7: Enolization and aldol conditions for 2,4-dimethyl-3-pentanone (**249**).

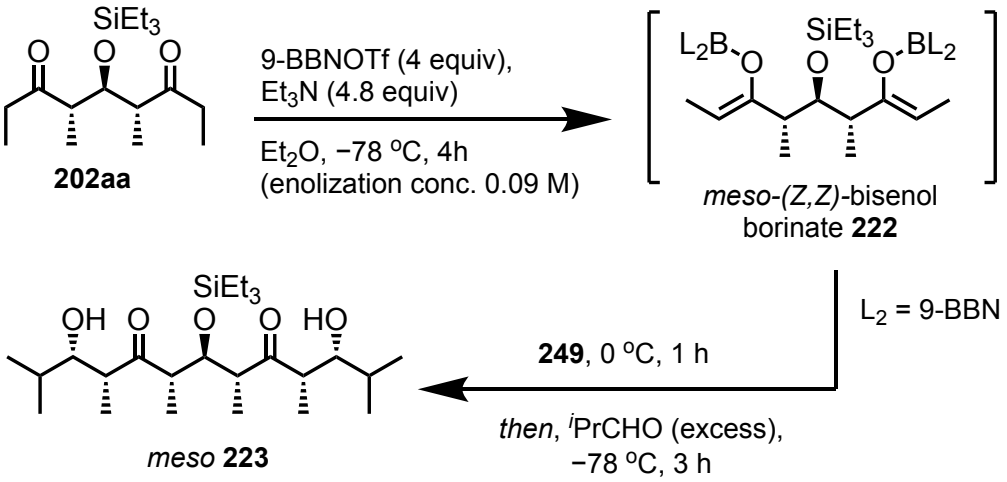


entry	ketone 249 equivalents	enolization conditions	aldol conditions	conversion (%)[a]
1	1	−78 °C, 1 h	−78 °C, 1 h, then 0 °C, 0.5 h	---------
2	1	0 °C, 1 h	−78 °C, 1 h, then 0 °C, 0.5 h	64
3	2	0 °C, 1 h	0 °C, 0.5 h	90
4	2	0 °C, 1.5 h	0 °C, 0.5 h	93
5	3	0 °C, 1 h	0 °C, 0.5 h	95
6	4	0 °C, 1 h	0 °C, 0.5 h	97
7	4	0 °C, 1 h	−78 °C, 3 h	18

[a] Conversion measured from ^{1}H NMR data of crude reaction.

The above investigation confirms that excess 9-BBNOTf must be consumed at 0 °C. Although the previous study confirmed the stability of *meso*-(*Z,Z*)-bisenol borinate **222** at 0 °C (Table 2-6, entry 6), it was not clear how this enolate behaves at 0 °C in presence of ketone **249**. The stability of *meso*-(*Z,Z*)-bisenol borinate **222** was tested by warming the enolization reaction to 0 °C for 1 h in presence of **249**, followed by addition of isobutyraldehyde at −78 °C using standard conditions to produce the known bisaldol **223** in excellent yield (Table 2-8, entry 1). From these results, ketone **249** was identified as a promising additive to consume excess 9-BBNOTf prior to enantioselective desymmetrization.

Table 2-8: Stability of *meso* (*Z,Z*)-bisenol borinate **222** at 0 °C in presence of ketone **249**.



entry	249 (equivalents)	enolization conditions	aldol conditions	conversion (%)[a]
1	8	−78 °C, 4 h, then 0 °C 1 h with **249**	−78 °C, 3 h	96
2	none	−78 °C, 4 h, then 0 °C 1 h	−78 °C, 3 h	97
3	none	−78 °C, 4 h	−78 °C, 3 h	96

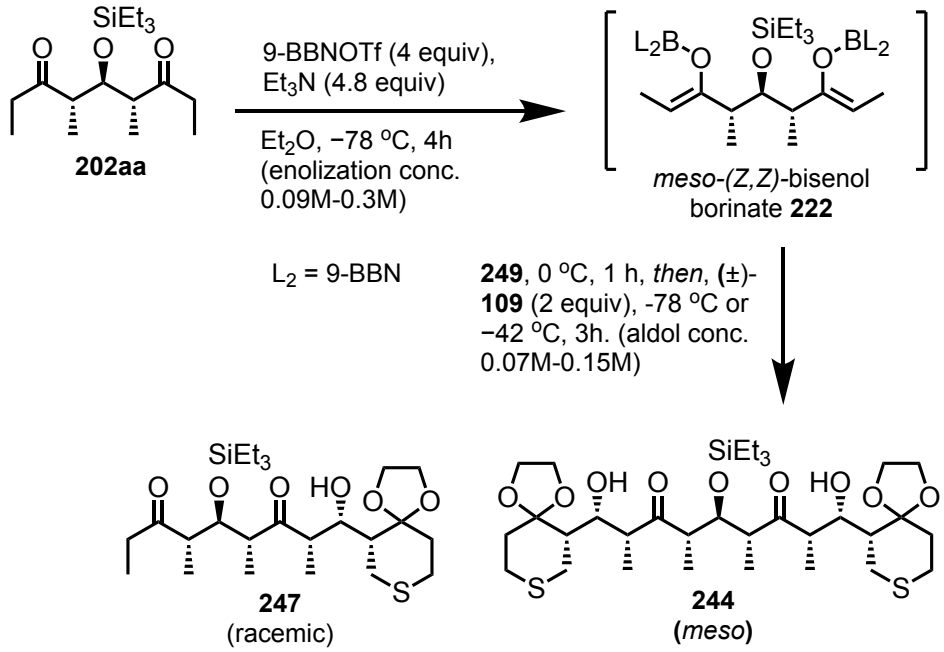
[a] Conversion measured from ^{1}H NMR data of crude reaction.

Although excellent conversions were obtained from reactions of bisenolate **222** with isobutyraldehyde in presence of **249**, the aldehyde was used in excess (10 equiv) to drive the aldol reaction (Table 2-8). However, in enantioselective desymmetrization the amount of enantiopure aldehyde must be limited to one equivalent (with respect to diketone **202aa**) to avoid undesired reactions. Reducing the amount of aldehyde to one equivalent would decrease the rate of aldol reaction at lower temperatures. Thus, the conversion of aldehyde in reactions of bisenolate **222** with a limited amount of (±)-**109** (2 equiv) was determined in presence of ketone **249** (Table 2-9).

A reaction of bisenolate **222** with aldehyde (±)-**109** in presence of ketone **249** under the conditions previously established to consume 9-BBNOTf (0 °C for 1h), produced the bisaldol **244**

(62%) in low yield (Table 2-9, entry 2). Increasing the aldol reaction temperature to 0 °C, improved conversion to **244** (78%) (entry 5). However, higher temperatures (0 °C) are not convenient for enantioselective desymmetrization because controlling undesired reactions and stereoselectivities might be challenging. To overcome this issue, increasing the reaction concentration while maintaining a lower temperature was considered. Accordingly, the reaction concentration (with respect to ketone **202aa**) was increased from 0.07 M to 0.15 M by removing the solvent from 9-BBNOTf[xvi] followed by enolization and aldol reactions at −78 °C gave **244** (76% conversion) (entry 6). Under optimized conditions, increasing aldol reaction temperature from −78 °C to −42 °C at 0.15 M concentration, improved conversion to **244** (88%) (entry 7). On the other hand, aldol reaction in absence of **249** led to poor conversion (entry 4) confirming the 9-BBNOTf must be consumed before addition of aldehyde.

Table 2-9: Aldol reaction of diketone **202aa** with 2 equiv of (±)-**109** in presence of ketone **249**.



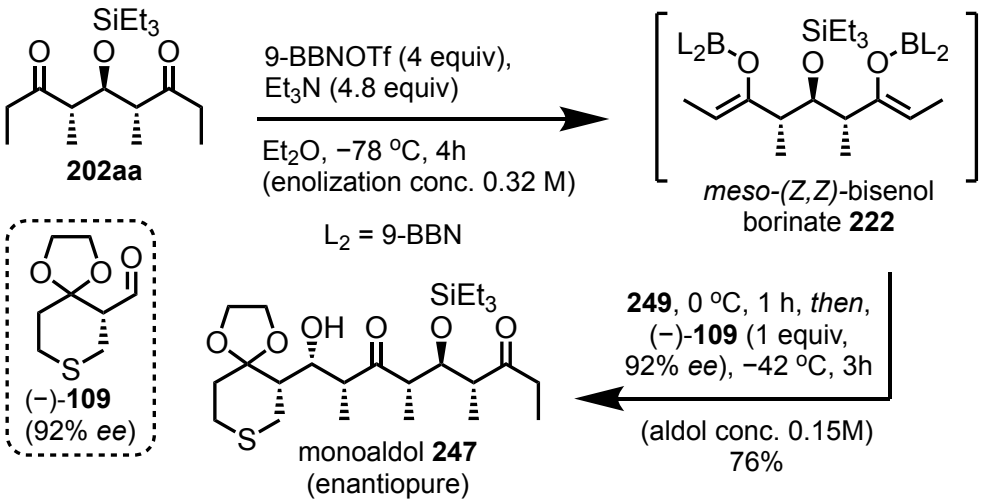
[xvi] Half of the solvent in the reaction mixture comes from 9-BBNOTf as this reagent concentration is 0.5 M in hexanes.

entry	ketone 249 conditions (8 equiv to 202aa)	aldol conditions	products (mole fraction)			Conversion of (±)-109 (%)
			244	247	202aa	
1	0 °C, 0.5 h	−78 °C, 3 h	0.55	0.38	0.07	74
2	0 °C, 1 h	−78 °C, 3 h	0.62	0.29	0.09	77
3	0 °C, 1.5 h	−78 °C, 3 h	0.67	0.26	0.06	80
4	none	−78 °C, 3 h	0.13	0.57	0.3	42
5	0 °C, 1 h	−78 °C, 3 h, 0 °C, 0.5 h	0.78	0.18	0.04	87
6[a]	0 °C, 1 h	−78 °C, 3 h	0.76	0.19	0.05	86
7[a]	0 °C, 1 h	−42 °C, 3 h	0.88	0.06	0.06	93

[a] enolization and aldol reactions performed at 0.32 M and 0.15 M concentrations (with respect to ketone **202aa**), respectively.

2.7.4.3. Enantioselective desymmetrization of meso-(Z,Z)-bisenol borinate 222 with aldehyde (−)-109

Having established conditions to consume excess 9-BBNOTf, enantiotopic group selective aldol reactions with *meso*-(*Z,Z*)-bisenol borinate **222** were explored. Gratifyingly, enantioselective desymmetrization of **222** with aldehyde (−)-**109** afforded enantioenriched monoaldol **247** in good yield with excellent diastereo- and enantioselectivities (76%; *dr* >19:1; *ee* >98%) (Scheme 2-29).

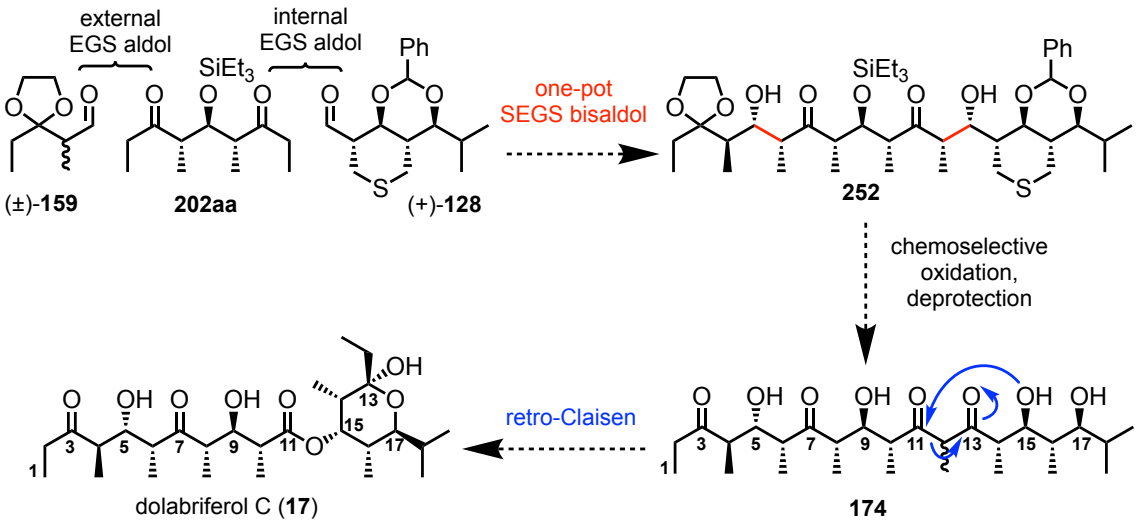


Scheme 2-29: Enantioselective desymmetrization of *meso*-(*Z,Z*)-bisenol borinate **222** with enantioenriched aldehyde (−)-**247**.

In summary, three *meso* bisenolates (**215**, **220** and **222**) were prepared stereoselectively from two different *meso* diketones (**202aa**, **202ss**) and were used in sequential aldol reactions with chiral and achiral aldehydes to obtain bisaldol adducts with high enantio- and diastereoselectivities. The established enantioselective desymmetrization of *meso* bisenolates and the one-pot SEGS bisaldol strategy allows access to various enantioenriched monoaldol and bisaldol adducts, respectively, in a very robust way. Application of these strategies in synthesis of polypropionate natural products is an opportunity to demonstrate their scope and advantages.

2.8. Total Synthesis of Dolabriferol C

As indicated, the main objective of this research was to test whether the putative contiguous precursor **174** could be transformed to dolabriferol C (**17**) via a spontaneous retro-Claisen rearrangement (Scheme 2-30). Towards this objective, the initial synthetic target was the putative contiguous precursor **174** that can be synthesized from the established one-pot SEGS bisaldol strategy using *meso* diketone **202aa** and aldehydes (+)-**128** and (±)-**159**.



Scheme 2-30: Proposed synthesis of dolabriferol C (**17**) via the SEGS bisaldol strategy.

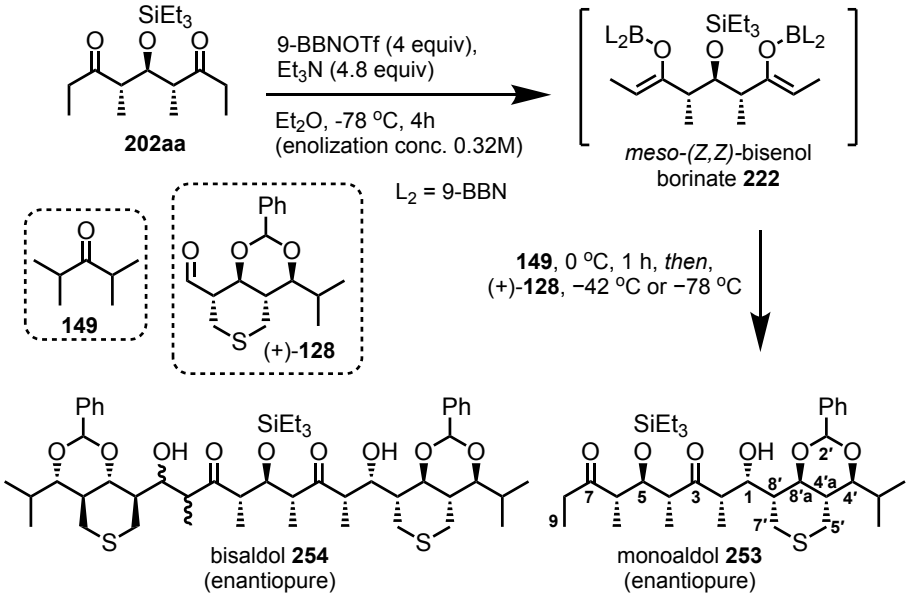
2.8.1. Enantioselective desymmetrization of *meso*-(*Z,Z*)-bisenol borinate 222 with 'eastern' aldehyde (+)-128

Towards the synthesis of the putative precursor **174**, enantioselective desymmetrization of *meso*-(*Z,Z*)-bisenol borinate **222** with aldehyde (+)-**128**[17], under the previously optimized conditions, produced the anticipated monoaldol **253**, albeit in low yield (33%) (Table 2-10, entry 1). Due to poor solubility of the aldehyde (+)-**128** in diethyl ether (in contrast to the aldehyde (−)-**109**), additional solvent was required to make a solution for addition to the bisenolate (reaction concentration was 0.08 M with respect to diketone **202aa**). The poor conversion was presumably due to the lower rate of aldol reaction with lower concentration and (or) precipitation of the aldehyde (+)-**128** in diethylether at −42 °C. To improve conversion, the reaction was investigated under various conditions (Table 2-10). Gratifyingly, the aldehyde (+)-**128** is highly soluble in THF and addition of a THF solution of (+)-**128** to the bisenolate (reaction concentration was 0.16M with respect to **202aa**) at −42 °C markedly improved the yield (69%) of **253** (entry 2);

however, undesired homo-bisaldol **254**[xvii] was observed in significant amounts (10%). A slight improvement in ratio of **253** to **254** (from 7:1 to 10:1) was observed when the reaction was performed at −78 °C (entry 3).

Because, the aldol conversion improved significantly in THF, the enolization solvent was switched from Et_2O to THF; surprisingly, only starting ketone **202aa** was recovered (Table 2-10, entry 4; presumably an irreversible reaction of 9-BBNOTf with THF occurred). Next, keeping the aldol temperature at −78 °C and using a slight excess of (+)-**128** (1.2 equivalents) improved the aldol conversion to 87% with an 8:1 mixture of **253** and **254**, respectively (entry 5). Under optimized conditions, reaction of **222** with 1.1 equivalents of (+)-**128** at −78 °C, for 16 h improved the conversion to 88% with a 10:1 mixture of **253** (72% isolated yield) and **254**, respectively (entry 6).

Table 2-10: Enantioselective desymmetrization of meso (Z,Z)-bisenol borinate **222** with 'eastern' aldehyde (+)-**128**.



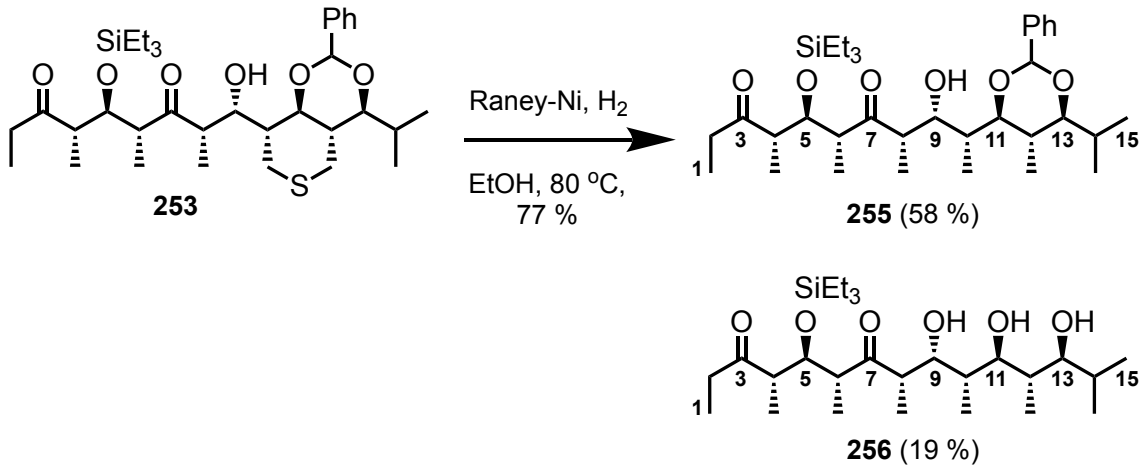
[xvii] Structure of **254** was tentatively assigned based on ^1H NMR data.

entry	(+)-128 (equiv)	aldol conditions[a]	products (mole fraction)		
			254	253	202aa
1	1	−42 °C, 3 h, Et_2O	--------	0.33	0.67
2	1	−42 °C, 3 h, THF	0.1	0.69	0.21
3	1	−78 °C, 3 h, THF	0.06	0.6	0.34
4[b]	1	−78 °C, 3 h, THF	-------	-------	1
5	1.2	−78 °C, 3 h, THF	0.08	0.7	0.22
6	1.1	−78 °C, 16 h, THF	0.08	0.8[c]	0.12

[a]The solvent refers to the solution of aldehyde added to the bisenolate; reaction concentrations (with respect to **202aa**) were 0.08 M (Et2O) and 0.16 M (THF). [b]Enolization performed in THF. [c]72% isolated yield.

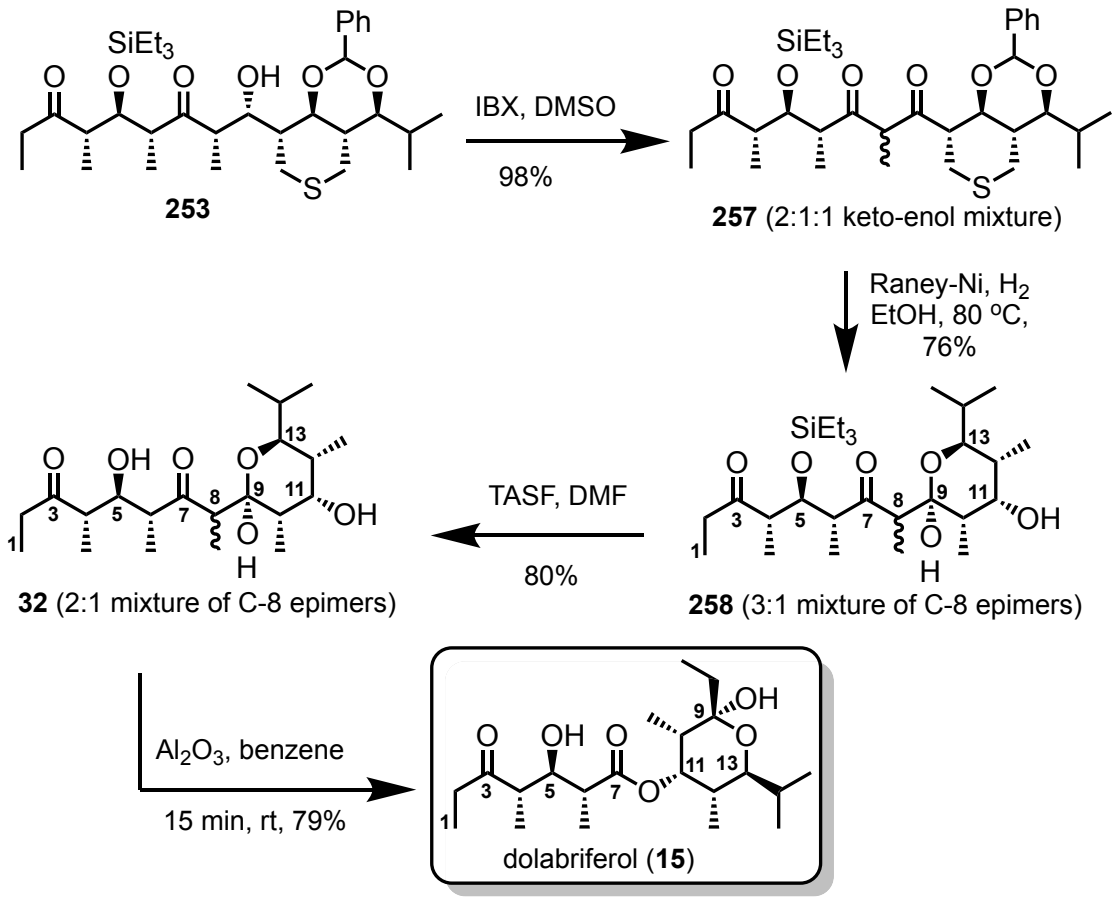
2.8.2. An improved synthesis of dolabriferol

The monoaldol **253** (Table 2-10) is a potential intermediate for the synthesis of dolabriferol (**15**). Thus, an improved synthesis of **15** from **253** was proposed by adapting and streamlining the previous synthetic route.[17] A reaction of monoaldol **253** with Raney-Ni in EtOH gave the desired **255** in moderate yield (58%) and surprisingly, **256** was also obtained in a significant amount (19%) (Scheme 2-31). Compound **256** is a possible advanced intermediate for synthesis of the putative precursor **32**; however, selective oxidation at C9 would be more challenging as two additional free hydroxy groups (at C-11 and C-13) are present in **256**.



Scheme 2-31: Hydrogenolysis of **253** with Raney Ni.

To avoid the challenging chemoselective oxidation of **256** (Scheme 2-31), reordering of synthetic sequence was considered. Accordingly, IBX mediated oxidation of **253** furnished the desired trione **257** in excellent yield (98%) (Scheme 2-32). As anticipated, under optimized reaction conditions, treatment of **257** with Raney-Ni resulted in both desulfurization and benzylidene acetal hydrogenolysis to produce the desired **258** (76%) predominantly in one hemiacetal form (13➔9) as a 3:1 mixture of C-8 epimers. TASF mediated silyl ether deprotection of **258** gave the known contiguous precursor **32** in good yield (80%) as a 2:1 mixture of C-8 epimers. The spectral data for the contiguous precursor **32** fully matched those previously reported by Ward et al.[17] Treating **32** with neutral alumina according to the known reaction conditions cleanly produced dolabriferol (**15**) in excellent yield (79%).



Scheme 2-32: Synthesis of dolabriferol (**15**) from monoaldol **253**.

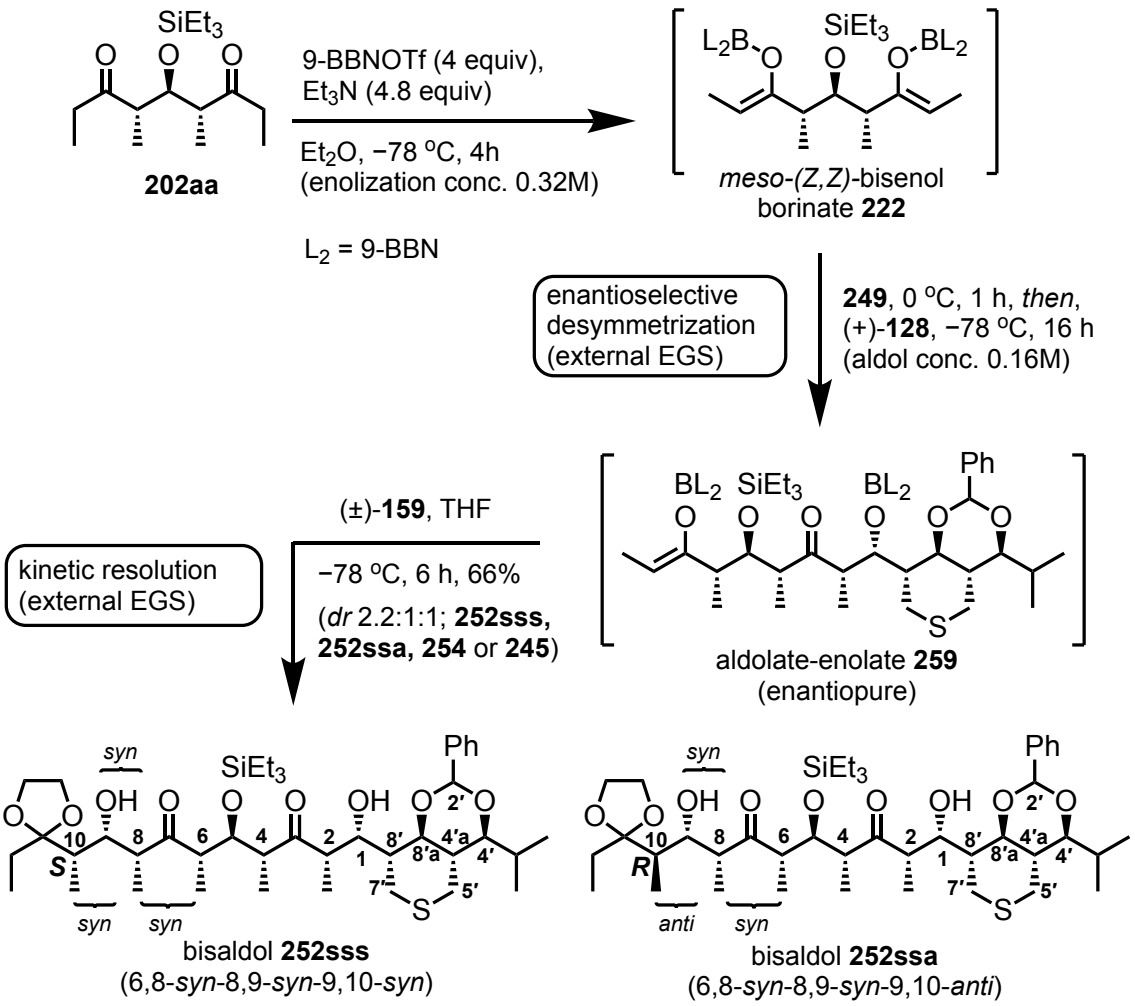
In summary, total synthesis of dolabriferol (**15**) was achieved via enantioselective desymmetrization (or internal EGS aldol reaction) of *meso* diketone **202aa** with aldehyde (+)-**128**. This improved synthesis was accomplished in 5 steps with 34% overall yield from the known aldehyde (+)-**128**.[xviii].

[xviii] Previous total synthesis was achieved in 6 steps with 34% overall yield from (+)-128.[17]

2.8.3. One-pot SEGS bisaldol reactions of *meso*-(*Z*,*Z*)-bisenol borinate 222 with aldehydes (+)-128 and (±)-159

Towards the synthesis of dolabriferol C (**17**), a one-pot SEGS bisaldol reaction was initiated to construct the full carbon skeleton for the putative precursor **174** as proposed in Scheme 2-30. The aldolate-enolate **259**, generated as described previously (Table 2-10), was treated with racemic aldehyde (±)-**159** (kinetic resolution) to afford a 2.2:1:1 mixture of enantioenriched bisaldols **252sss** (10*S*), **252ssa** (10*R*) and homo-bisaldols **245** or **254**, respectively (Scheme 2-33). As expected, addition of the (*Z*)-enol borinate **222** to aldehyde (±)-**159** proceeded with lower Felkin (2,3-*syn*) diastereoselectivity (see Scheme 2-28) compared to the corresponding (*E*)-enol borinate **215** (see Scheme 2-19). However, the minor bisaldol **252ssa** has the desired carbon skeleton and stereochemical arrangement (9,10-*anti*; C10 with '*R*' configuration) for synthesis of the putative precursor **174**. The desired 10*R* absolute configuration and improved diastereoselectivity in preparation of the adduct **252ssa** should result by addition of the (*R*)-**159** to the (*Z*)-enol borinate **222**. Because no literature method was available to prepare enantiopure aldehyde (*R*)-**159**;[xix] an enantioselective synthesis of (*R*)-**159** was considered.

[xix] Recently, Leighton et al. reported preparation of the aldehyde (*R*)-**159** in 53% yield with 81% *ee*.[97]



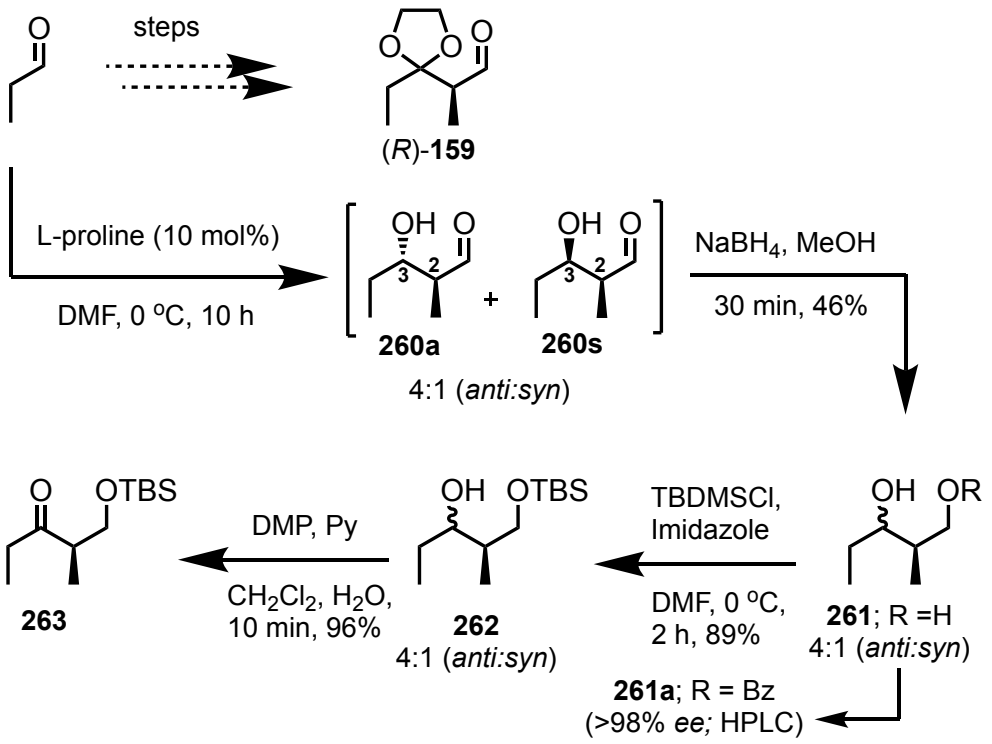
Scheme 2-33: One-pot SEGS bisaldol reactions of **202aa** with (+)-**128** and (±)-**159**.

2.8.4. Preparation of enantiopure acyclic aldehyde (+)-(*R*)-159

Synthesis of enantiopure aldehyde (+)-(*R*)-**159**[97] was initiated with L-proline catalyzed enantioselective self-aldol reaction of propanal using MacMillan's procedure[31] (Scheme 2-34). According to the MacMillan's method, aldol adducts **260a** (*anti*) and **260s** (*syn*) were obtained in 4:1 ratio, respectively. Although the structure of **260a** is proven (2*S*,3*S* absolute configuration), the absolute configuration of the minor (*syn*) diastereomer **260s** was unknown.[31,98] The absolute configuration at C2 of minor diastereomer **260s** (*syn*) is very important to know. If **260a** and **260s**

have the same configuration at C2 then they can be converted into (+)-(*R*)-**159** without separation (note that the C3 stereocenter is lost in that process). However, if the diastereomers have different configurations at C2, then they must be separated before proceeding to (*R*)-(+)-**159**.

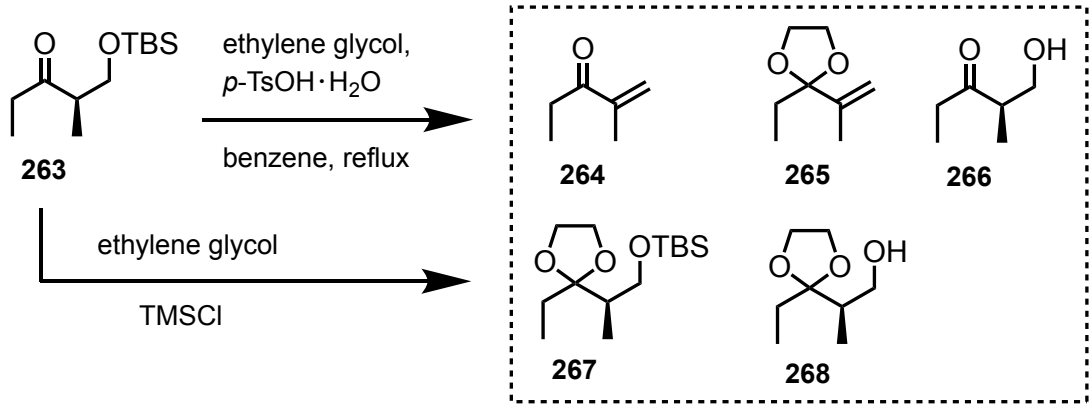
Using MacMillan's procedure, L-proline catalyzed enantioselective aldol reaction of propanal gave no pure aldol adduct, but a complex mixture of oligomers was observed. To prevent oligomerization in the aldol reaction, Cordova et al. converted the aldol adducts to the corresponding diols with $NaBH_4$ before isolation.[99] Using Cordova's procedure, one-pot aldol and reduction of propanal gave the diols **261**[100–108] as a 4:1 mixture of *anti* and *syn* diastereomers, respectively, in 46% yield (Scheme 2-34). The enantiopurity of the diol mixture (each >98% *ee*) was determined by HPLC after conversion to the corresponding monobenzoyl esters **261a**.[105–107] The so obtained **261a** with high enantioenrichement (each >98% *ee*) suggesting that the 4:1 mixture of **260a** and **260s** diastereomers, respectively was enantiomerically pure. Selective silylation of the primary alcohol in diol **261** generated the TBS protected alcohol **262**[103,109] that upon DMP oxidation produced the known ketone **263**[104,110,111] ($[\alpha]_D$ –36, *c* 1.2, $CHCl_3$; lit.[112] (for the *S* enantiomer) $[\alpha]_D$ +43.70, *c* 1.0, $CHCl_3$) in excellent yield (85% over two steps). The spectral data and optical rotation values of **263** was closely matched (with opposite sign) with those of the known (*S*)-**263** clearly establishing that the absolute configuration of **263** is "*R*" and that of **260s** is 2*S*,3*R*.



Scheme 2-34: Towards the synthesis of enantiopure aldehyde (+)-(*R*)-**159**.

Ketal protection of the ketone, TBS removal and oxidation of the resulting primary alcohol are required to convert (*R*)-**263** to the desired aldehyde (+)-(*R*)-**159**. Accordingly, a reaction of ketone (*R*)-**263** with ethylene glycol under standard ketalization conditions (*p*-TsOH · H_2O, benzene, Dean-Stark reflux) produced mixture of desired ketal products **267** and **268** along with undesired ketal and elimination products (**264**, **265** and **266**) (Scheme 2-35).[xx] An alternative ketalization method[104] using TMSCl did not improve the result.

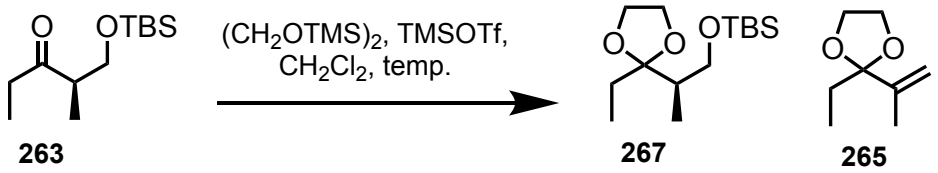
[xx] Structures were assigned tentatively based on ^{1}H NMR data.



Scheme 2-35: Ketal protection of **263** towards the synthesis of (+)-(*R*)-**159**.

Noyori et al. converted various ketones to the corresponding ketals under aprotic conditions using 1,2-bis(trimethylsiloxy)ethane and catalytic amount of TMSOTf at lower temperature (e.g., −78 °C).[113] Encouraged by this method, ketalization of **263** was examined using Noyori method (Table 2-11). Only 6% conversion to the desired ketal product **267** was observed under Noyori conditions (−78 °C, 4 h) (entry 1). Although increasing reaction temperature doubled the conversion (12%), undesired alkene **265** obtained as the major product (51%) (entry 2). Increasing reaction temperature (−78 °C to 0 °C), improved the yield of **267** significantly (52%) but formation of the undesired **265** was not completely suppressed (entries 3 and 4).

Table 2-11: Noyori ketalization with ketone **263**.

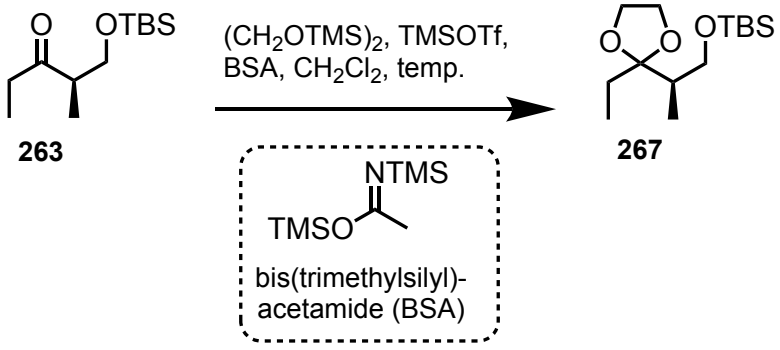


entry	ketalization conditions	products (% yield)[a]	
		267	**265**
1	−78 °C, 4 h	6	-------
2	−78 °C, 5 min, *then* rt, 4 h	12	51
3	−78 °C, 5 min, *then* 0 °C, 4 h	52	16
4	−78 °C, 5 min, *then* 0 °C, 4 h, rt, 30 min.	44	23

[a]Determined from ^{1}H NMR data using trichloroethylene as an internal standard, unless otherwise indicated.

The undesired elimination reaction was presumably catalyzed by small amounts of triflic acid that was generated from TMSOTf in the reaction mixture. To remove the triflic acid (TfOH), bis(trimethylsilyl)acetamide (BSA) was introduced in the reaction mixture as a silylating agent to convert TfOH to TMSOTf. Addition of one equivalent of BSA to the ketalization reaction did not give any product; most likely BSA silylated the ketone **263** to the corresponding silyl enol ether (Table 2-12, entry 1). Decreasing the amount of BSA (10 mol%) drastically improved yields (>90%) (entries 2 and 3). Under the modified Noyori conditions (at −20 °C, 2 h), ketone **263** was successfully converted to the desired ketal **267** in excellent yield (96%) (entry 3).

Table 2-12: Ketalization of **263** using modified Noyori conditions in presence of BSA.

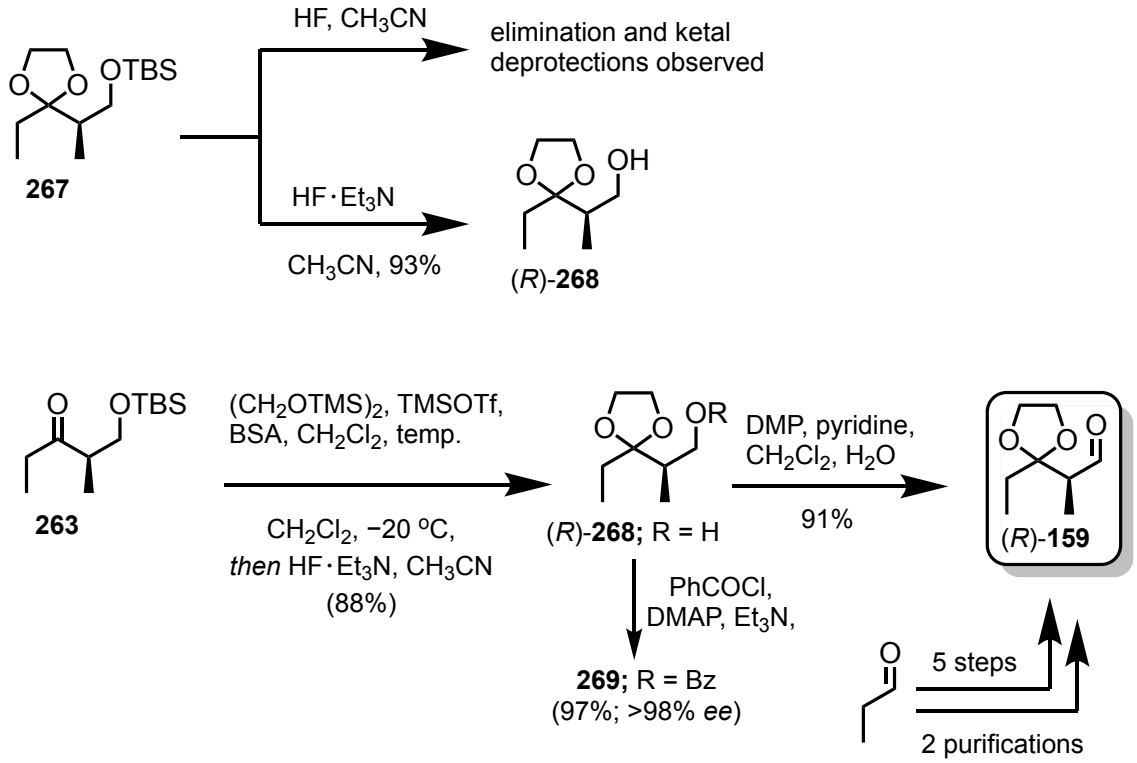


entry	BSA equivalents	ketalization conditions	products (% yield)[a]	
			267	265
1[b]	1	−42 °C, 4 h, −20 °C, 30 min	-------	-------
2	0.1	−42 °C, 4 h, −20 °C, 30 min	93	-------
3	0.1	−20 °C, 2 h	96	-------

[a]Determined from ^{1}H NMR data using trichloroethylene as an internal standard, unless otherwise indicated.
[b]>90% of ketone **263** was recovered in reaction with 1 equivalent of BSA.

Removal of the TBS group in **267** with 10% aqueous hydrofluoric acid in acetonitrile led to elimination and ketal deprotected products (Scheme 2-36). Alternatively, treating **267** with HF·Et_3N cleanly produced the desired alcohol (*R*)-**268** in excellent yield (93%). In further improvements, both Noyori ketalization and TBS deprotection of ketone **263** were achieved in a one-pot process to give (*R*)-**268** in excellent yield (88%). The enantiopurity of (*R*)-**268** (97% *ee*) was determined by HPLC after conversion to the corresponding benzoate ester **269**. Alcohol (*R*)-**268** was successfully oxidized to the desired aldehyde (*R*)-**159** in good yield (91%) using DMP. It is noteworthy that only two chromatographic purifications were required to prepare enantiopure aldehyde (*R*)-**159** starting from commercially available propanal.[xxi] Aldehyde (*R*)-**159** was not stable and racemized upon storage. Consequently, (*R*)-**268** was treated with DMP and, following an aqueous work up, the resulting aldehyde (*R*)-**159** was used without purification in one-pot stereoselective bisaldol reactions.

[xxi] ketone **263** and alcohol **268** were purified.

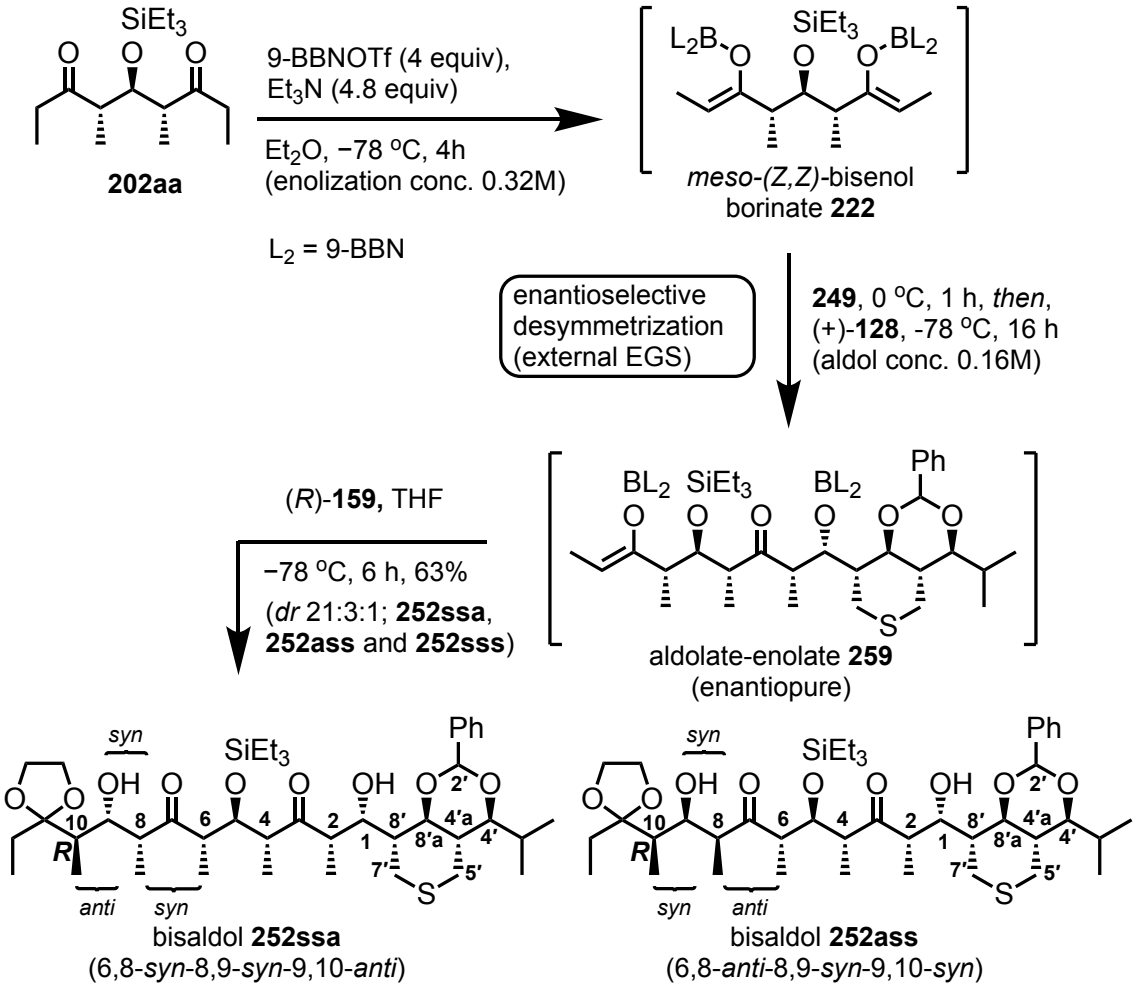


Scheme 2-36: Preparation of enantiopure aldehyde (+)-(*R*)-**159**.

2.8.5. One-pot stereoselective bisaldol reactions of *meso*-(*Z,Z*)-bisenol borinate 222 with aldehydes (+)-128 and (*R*)-(+)-159

Under optimized conditions, an aldol reaction of freshly prepared aldehyde **(*R*)-(+)-159** with the intermediate aldolate-enolate **259**, generated as described previously, gave a 21:3:1 mixture of bisaldol adducts **252ssa**, **252ass** (tentative), and **252sss**, respectively, in 63% yield (Scheme 2-37). Although the minor adduct **252ass** (from a mismatched reaction of **259** with (+)-(*R*)-**159**) was not fully characterized, careful analysis of 1D and 2D NMR spectral data of the mixture suggested the adduct **252ass** has 6,8-*anti*-8,9-*syn*-9,10-*syn* relative configuration. The presence of **252sss** arises from reaction of **259** with (*S*)-enantiomer of aldehyde **159** suggesting that (+)-(*R*)-**159** was not enantiopure; presumably, (+)-(*R*)-**159** underwent partial racemization

(ca. 24:1, *R*:*S*) during its preparation. The above 21:3:1 mixture was carried forward in the synthesis of precursor **174** without any further purification. A small sample of the mixture was fractionated twice by PTLC to obtain pure (ca. 95%) **252ssa**. Overall, by replacing the racemic **159** with enantioenriched (+)-(*R*)-**159** in reaction with the enolate **259**, the yield of **252ssa** was improved (63% of 21:3:1 mixture; i.e., ca. 53% of **252ssa**) in this one-pot stereoselective bisaldol reaction.



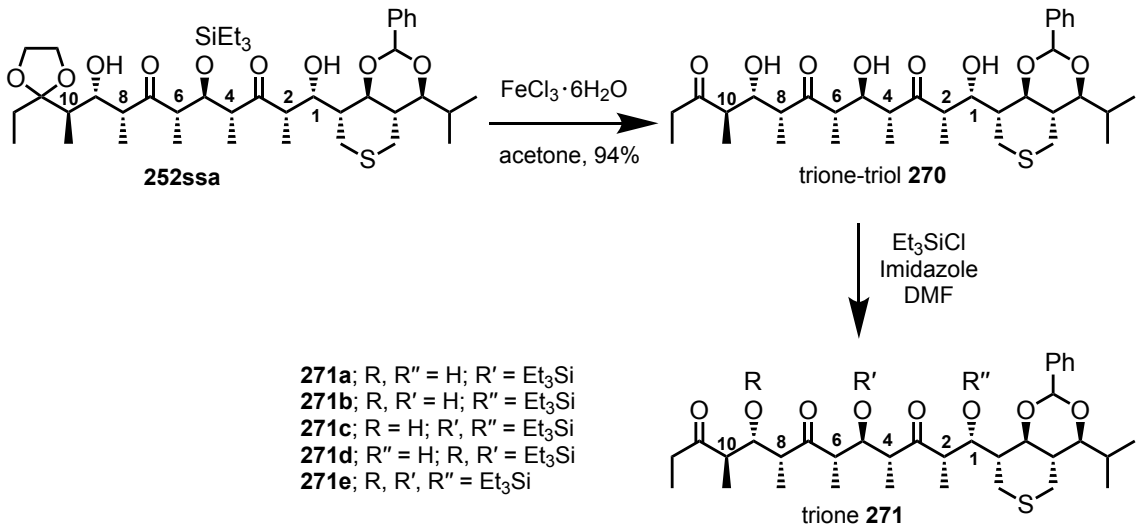
Scheme 2-37: One-pot stereoselective bisaldol reactions of **202aa** with (+)-**128** and (*R*)-**159**.

2.8.6. Synthesis of the putative contiguous precursor 174

The bisaldol **252ssa** (Scheme 2-37) has the desired carbon skeleton and stereochemical configuration for the synthesis of putative precursor **174**. The adduct **252ssa** was subjected to $FeCl_3{\cdot}6H_2O$ in acetone to remove the ketal group at C2″ (Scheme 2-38). Both ketal (at C2″) and Et_3Si group (at C5) were removed under these conditions to give undesired trione-triol **270**, which presented a significant challenge for selective oxidation at C1. Before attempting selective oxidation at C1, it was advisable to assess the relative reactivity of three hydroxy groups at C9, C5 and C1. Toward that end, silylation of the trione-triol **270** was considered in hope to recover the **252ssa** after desilylation of the corresponding undesired silylated products. If the C1-OH was more reactive than other two OH's, then **270** would be suitable for selective oxidation at C1; however, if the C5-OH and C9-OH groups were more reactive than the C1-OH, then it might be possible to silylate the C5-OH and C9-OH groups before proceeding to oxidation of the C1-OH.

Accordingly, reaction of trione-triol **270** with one equivalent of Et_3SiCl and imidazole gave the silylated products **271a** (34%) and **271b** (13%) along with recovered **270** (44%), suggesting the C5-OH is the most reactive among three hydroxy groups (Scheme 2-38). Using two equivalents of Et_3SiCl, produced 1.8:1.6:1.1:1 mixture of Et_3Si protected products **271e, 271d, 271c** and **271a**, respectively.[xxii] The bis-Et_3Si protected product **271d** (at C5 and C9) (29%) is the desired compound for oxidation at C1. The trione-triol **270** was regenerated after treating all the undesired mixture of Et_3Si protected products **271e, 271c** and **271a** with $FeCl_3{\cdot}6H_2O$. Although successful, this silyl protection-deprotection cycle was a laborious process to obtain **271d** in reasonable yield (e.g., >70%) from **270**. Thus, an alternative route that included a selective oxidation at C1 of bisaldol **252ssa** was considered.

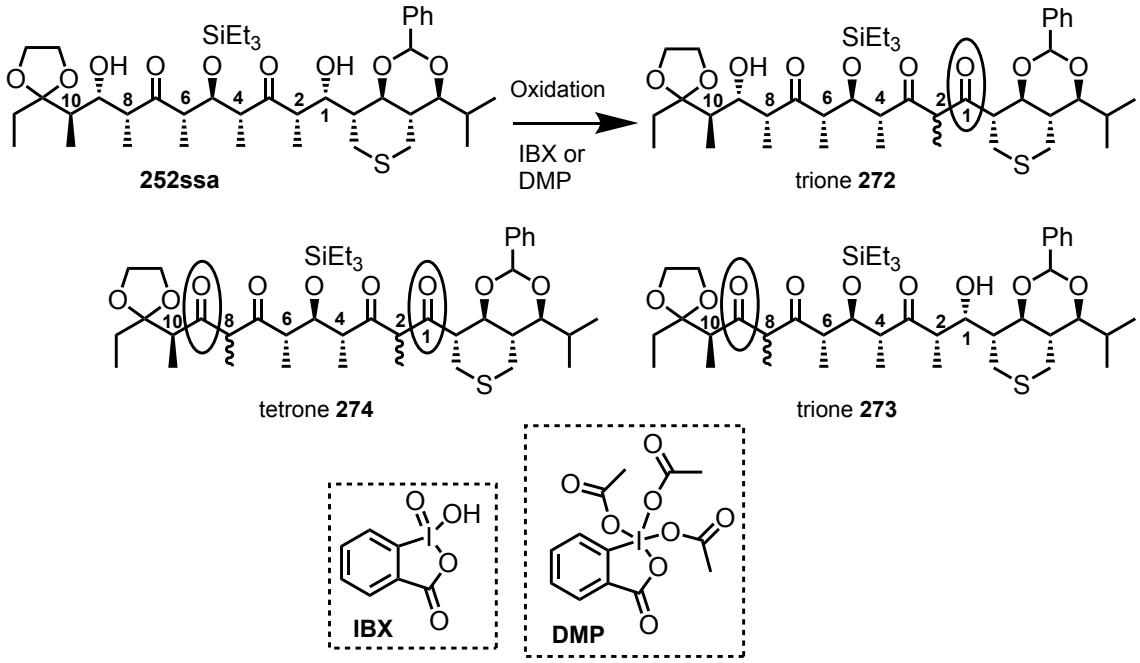
[xxii] Structures of all the silylated products were tentatively assigned by NMR data.



Scheme 2-38: Ketal and Et_3Si- deprotections of **252ssa**; selective silylation of trione-triol **270**.

Oxidation of **252ssa** with IBX in DMSO (Table 2-13, entry 1) generated a mixture of trione and tetrone products, suggesting that oxidation of the hydroxy groups at C1 and C9 was not selective under these conditions. Interestingly, DMP oxidation of **252ssa** gave the desired product **272** in low yield (33%) (entry 2). The three acetoxy groups on iodine makes DMP sterically bulkier than IBX. Based on this result, it was hypothesized that if the chemoselectivity of oxidation of **252ssa** was improved with DMP compared to IBX, then increasing the steric bulkiness on DMP could improve selectivity further. Dess-Martin reported addition of a small amount of alcohols or water improved reactivity of DMP by replacing one of the acetoxy groups with an electron donating group (e.g., -OH, -OR).[84] Thus, DMP was treated with *tert*-butanol to generate bulkier and more reactive oxidant than DMP,[84,114] before addition of **252ssa**. As hoped, under these conditions a chemoselective oxidation of the C1-OH group in **252ssa** proceeded to give the desired trione **272** (76% by ^{1}H NMR; 68% isolated yield) as a 1:2:5 mixture of enol and two keto tautomers, respectively (entry 4).

Table 2-13: Chemoselective oxidation of **252ssa**.

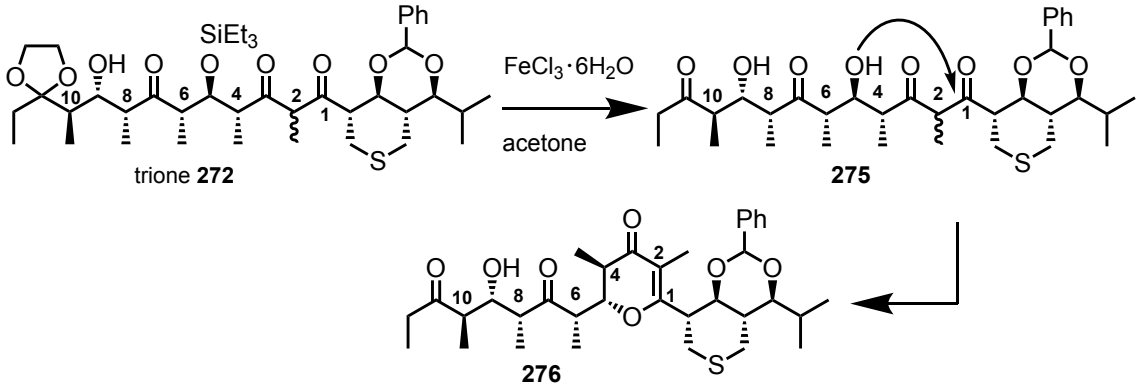


entry	oxidation conditions	products (mole fractions)[a]			
		272	**273**	**274**	**252ssa**
1	IBX, DMSO, 16 h	0.14	0.1	0.23	0.53
2	DMP[b], pyridine, CH_2Cl_2, 0 °C, 20 min	0.33	0.05	0.11	0.51
3	DMP[b], pyridine, CH_2Cl_2, *t*-BuOH, 0 °C, 20 min	0.39	------	0.06	0.55
4	DMP[c], pyridine, CH_2Cl_2, *t*-BuOH, 0 °C, 60 min	0.76[d]	------	0.18	0.06

[a]Determined from ^{1}H NMR spectra, unless otherwise indicated. [b]1.2 equivalents of DMP was used. [c]1.5 equivalents of DMP was used. [d]68% isolated yield.

The remaining steps to obtain the putative precursor **174** were deprotections of **272**. Treatment of trione **272** with $FeCl_3 \cdot 6H_2O$ gave the desired tetrone **275** along with the undesired

elimination product **279**[xxiii] (Scheme 2-39). The enone **276** presumably resulted from $FeCl_3 \cdot 6H_2O$ catalyzed hemiacetal formation (C5-OH➔C1-carbonyl) from tetrone **275**, followed by dehydration. After considerable experimentation, addition of $FeCl_3 \cdot 6H_2O$ at 0 °C and quenching the reaction with saturated $NaHCO_3$ solution, suppressed the undesired elimination reaction and produced the desired product **275** in excellent yield (91%) as a 1:1:2 mixture of enol and two keto tautomers, respectively.

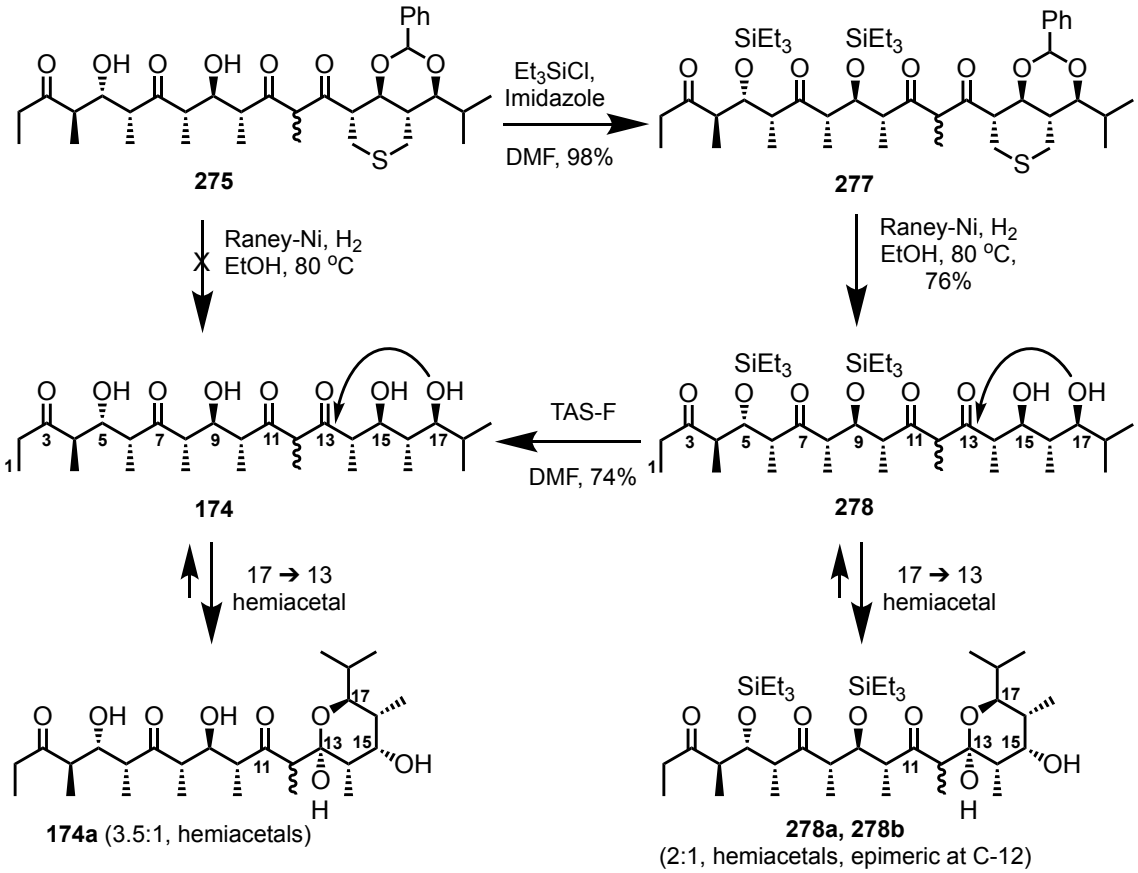


Scheme 2-39: Ketal and Et_3Si- deprotections of trione **272** with $FeCl_3 \cdot 6H_2O$.

The remaining steps for the synthesis of putative precursor **174** from **275** were removal of the benzylidene protecting group and desulfurization (Scheme 2-40). A reaction of **275** with Raney-Ni under hydrogen atmosphere (previously established conditions desulfurization and benzylidene hydrogenolysis) gave a complex mixture with low mass recovery. An alternative bis-silyl protected derivative **277** was prepared in excellent yield (98%) and was subjected to the identical hydrogenation conditions (Raney Ni, H_2) to give the desired product **278** (71%) as a 2:1 mixture of hemiacetals (epimeric at C12). Final Et_3Si-deprotections from **278** with TAS-F

[xxiii] Structure was assigned tentatively based on NMR data.

produced the putative precursor **174** in good yield (74%). The precursor **174** predominantly existed as 3.5:1 mixture of hemiacetals in C_6D_6 solution.

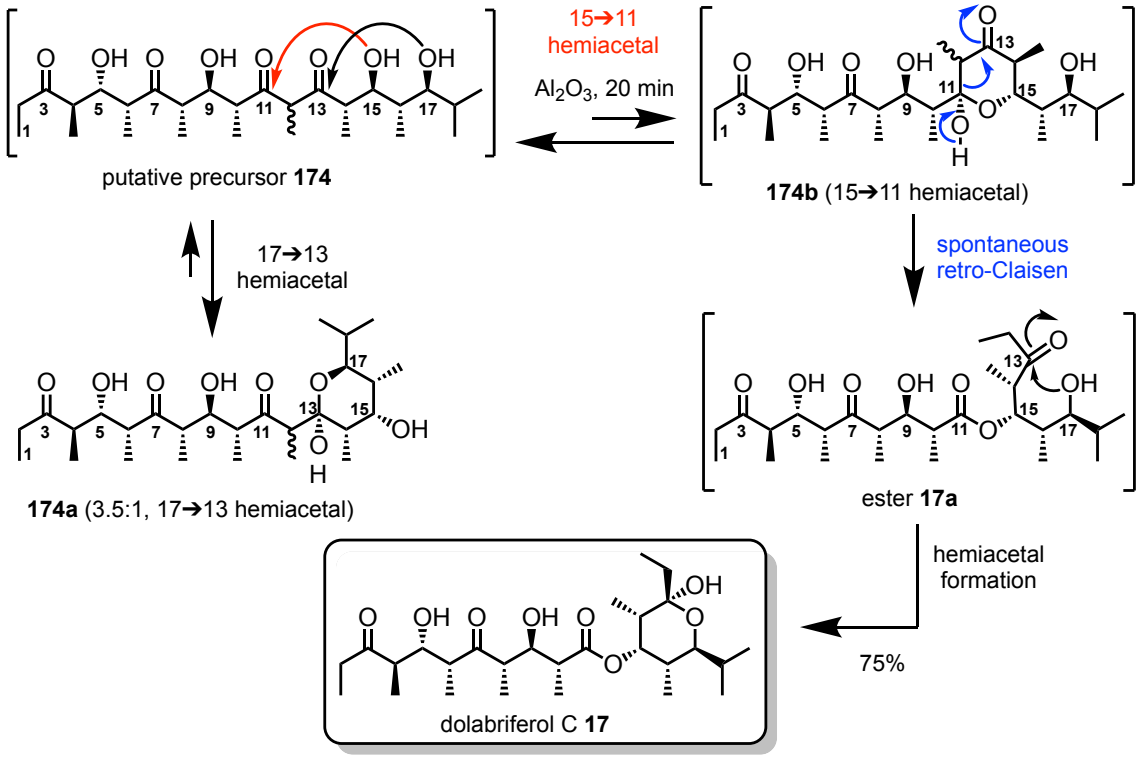


Scheme 2-40: Synthesis of putative precursor **174** from tetrone **275**.

2.8.7. Regioselective retro-Claisen rearrangement of the putative precursor 174 to dolabriferol C

Having the putative precursor **174a** in hand, the main objective of this research (i.e., retro-Claisen rearrangement of **174** to dolabriferol C) and the final transformation in this synthesis was tested (Scheme 2-41). Based on previous results from the dolabriferol synthesis,[17] it was known that DBU induced retro-Claisen rearrangement of the putative precursor **32** occurred non-regioselectively. However, neutral alumina conditions were superior to transform the putative

precursor **32** to dolabriferol via a highly regioselective retro-Claisen rearrangement. Thus, following these known conditions, a solution of the precursor **174a** in benzene was applied to a column of neutral alumina, and after 20 minutes was eluted with ethyl acetate to afford dolabriferol C (**17)** in good yield (75%). The spectroscopic data (MS, ^{1}H and ^{13}C NMR) for the synthetic dolabriferol C ($[\alpha]_D$ –38 (*c* 0.5, $CHCl_3$) fully matched with those reported by Rodriguez et al ($[\alpha]_D$ –45.2 (*c* 0.7, $CHCl_3$) (Tables 2-14 and 2-15).[8] This highly regioselective rearrangement clearly demonstrates that the putative contiguous precursor **174** can undergo retro-Claisen rearrangement under mild conditions during isolation to give the non-contiguous natural product, dolabriferol C (**17**).



Scheme 2-41: Regioselective retro-Claisen rearrangement of the putative precursor **174** to dolabriferol C (**17**).

Table 2-14: ^{1}H NMR ($CDCl_3$) comparison of synthetic and natural dolabriferol C (**17**)

synthetic		assignment	natural	
δ_H (500 MHz)	**multiplicity (*J*'s in Hz)**		**δ_H (500 MHz)**	**multiplicity (*J*'s in Hz)**
5.24	dd (2.5, 2.5)	HC-21	5.24	dd (2.8, 2.6)
4.19	ddd (5, 7, 7)	HC-6	4.19	dt (7, 5.2)
4.06	d (11.5)	HOC-12	4.04	br d (11.4)
4.00	d (1.5)	HOC-18	3.97	br s
3.68	dd (2, 10.5)	HC-24	3.68	dd (2.3, 10.6)
3.64	ddd (3, 10, 11.5)	HC-12	3.64	ddd (3.0, 10.0, 11.4)
3.25	d (7)	HOC-6	3.25	br d (7.0)
3.05	dq (10, 7)	HC-10	3.05	dq (10.0, 6.9)
2.88	dq (5, 7)	HC-7	2.88	dq (6.9, 5.2)
2.85	dq (7, 7)	HC-4	2.85	dq (7.3, 5.2)
2.77	dq (3, 7)	HC-13	2.78	dq (7.2, 3.0)
2.60-2.50	m	H_2C-2	2.55	m
1.92	ddq (1.5, 2.5, 7)	HC-19	1.92	dq (7.1, 2.8)
1.79	dqq (2, 7, 7)	HC-25	1.80	dsp (6.8, 2.3)
1.78-1.65	m	HC-22, H_2C-16	1.76 (HC-22)	ddd (10.6, 6.9, 2.6)
			1.72 (HC-16)	m
1.37	d (7)	H_3C-14	1.37	d (7.2)
1.10	d (7)	H_3C-8, H_3C-5	1.10 (H_3C-8)	d (6.9)
			1.09 (H_3C-5)	d (7.3)
1.06	d (7)	H_3C-20	1.06	d (7.1)
1.01	ap d (7)	H_3C-26	1.01	d (6.8)
1.00	t (7)	H_3C-1	1.00	t (7.3)
0.97	t (7)	H_3C-17	0.97	t (7.4)
0.84	d (7)	H_3C-27		
0.78	d (7)	H_3C-23	0.78	d (6.9)

Table 2-15: ^{13}C NMR ($CDCl_3$) comparison of synthetic and natural dolabriferol C (**17**)

synthetic δ_C (125 MHz)	assignment	natural δ_C (125 MHz)
218.3	C-3	218.2
216.6	C-9	216.6
173.8	C-15	173.8
98.4	C-18	98.4
76.8	C-12	76.8
76.6	C-21	76.6
72.4	C-24	72.4
72.0	C-6	72
50.4	C-7	50.3
49.8	C-10	49.8
47.0	C-4	47
43.2	C-13	43.2
39.2	C-19	39.2
36.7	C-22	36.7
36.6	C-2	36.6
32.7	C-16	32.8
27.9	C-25	27.9
20.2	C-26	20.2
16.3	C-14	16.3
14.4	C-11	14.3
14.3	C-5	14.2
14.0	C-27	14
13.1	C-20	13.1
12.9	C-23	12.9
9.3	C-8	9.3
7.3	C-1	7.3
7.2	C-17	7.2

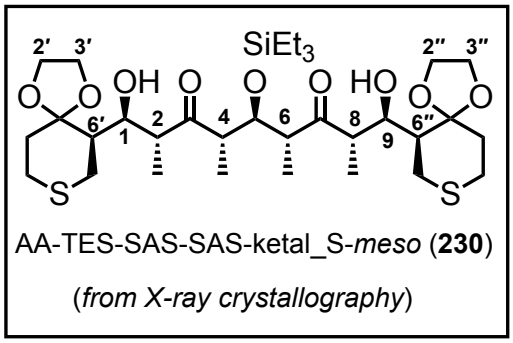
2.9. Structure Determination

This structure determination section is divided into five main parts: 1) assignment by X-ray crystallography; 2) assignment by chemical correlation (e.g., desulfurization) to the known compounds; 3) assignment by NMR analysis of derivatives (e.g., reduction and acetonide formation); 4) assignment based on comparison of NMR data with a database; v) assignment by analogy.

2.9.1. Assignment by X-ray crystallography

***Meso* bisaldol 230:**

The structure of *meso* bisaldol **230** was confirmed unambiguously by X-ray crystallography (Figure 2-1).



AA-TES-SAS-SAS-ketal_S-*meso* (**230**)

(*from X-ray crystallography*)

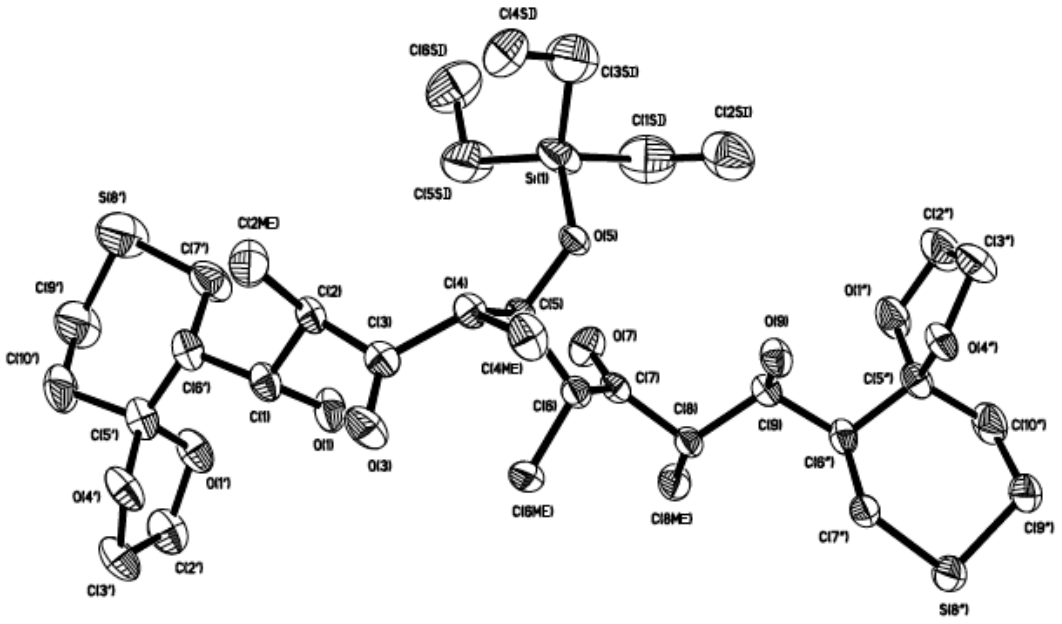
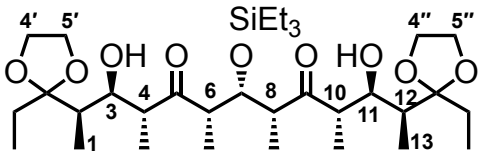


Figure 2-1: Ellipsoid plot of **230**.

***Meso* bisaldol 237:**

The structure of *meso* bisaldol **237** was confirmed unambiguously by X-ray crystallography (Figure 2-2).



SS-TES-SAS-SAS-ketal-*meso* (**237**)

(*from X-ray crystallography*)

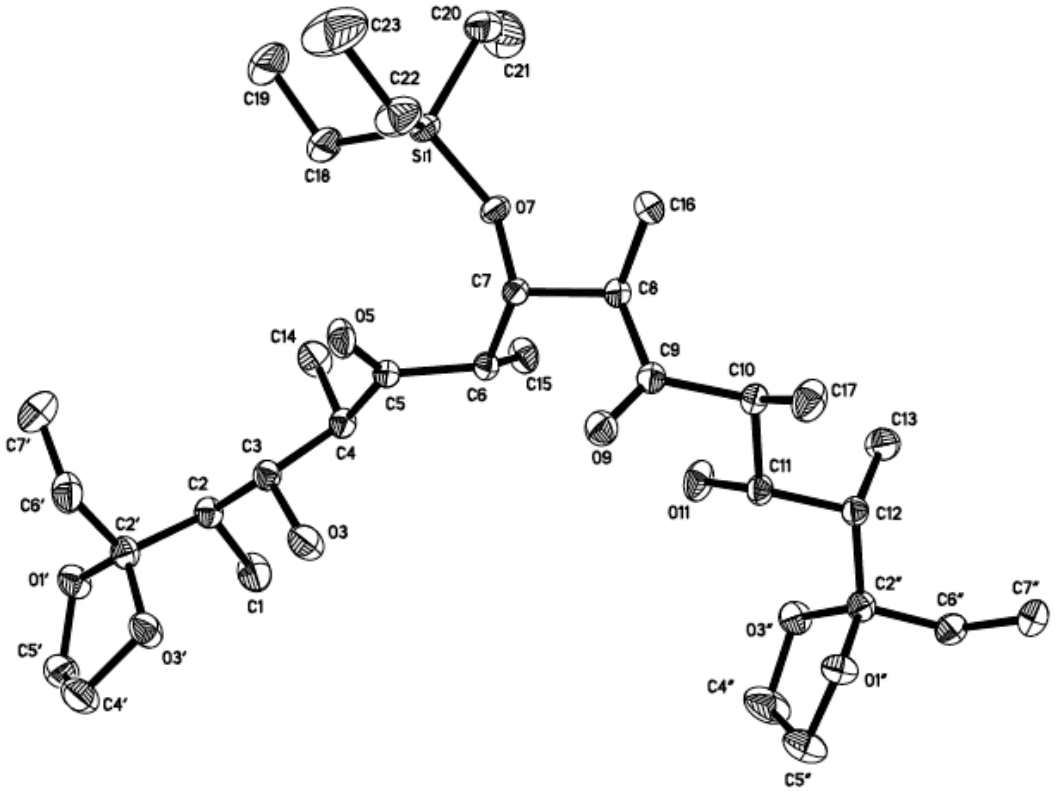
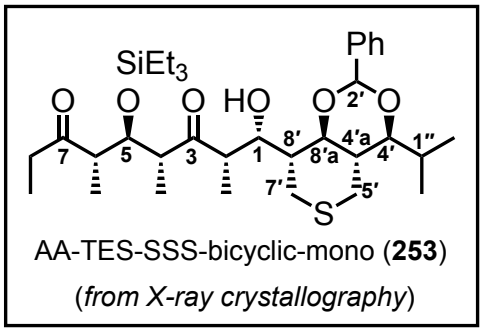


Figure2-2: Ellipsoid plot of **237**.

Monoaldol 253:

The structure of **monoaldol 253** was confirmed unambiguously by X-ray crystallography (Figure 2-3).



AA-TES-SSS-bicyclic-mono (**253**)

(*from X-ray crystallography*)

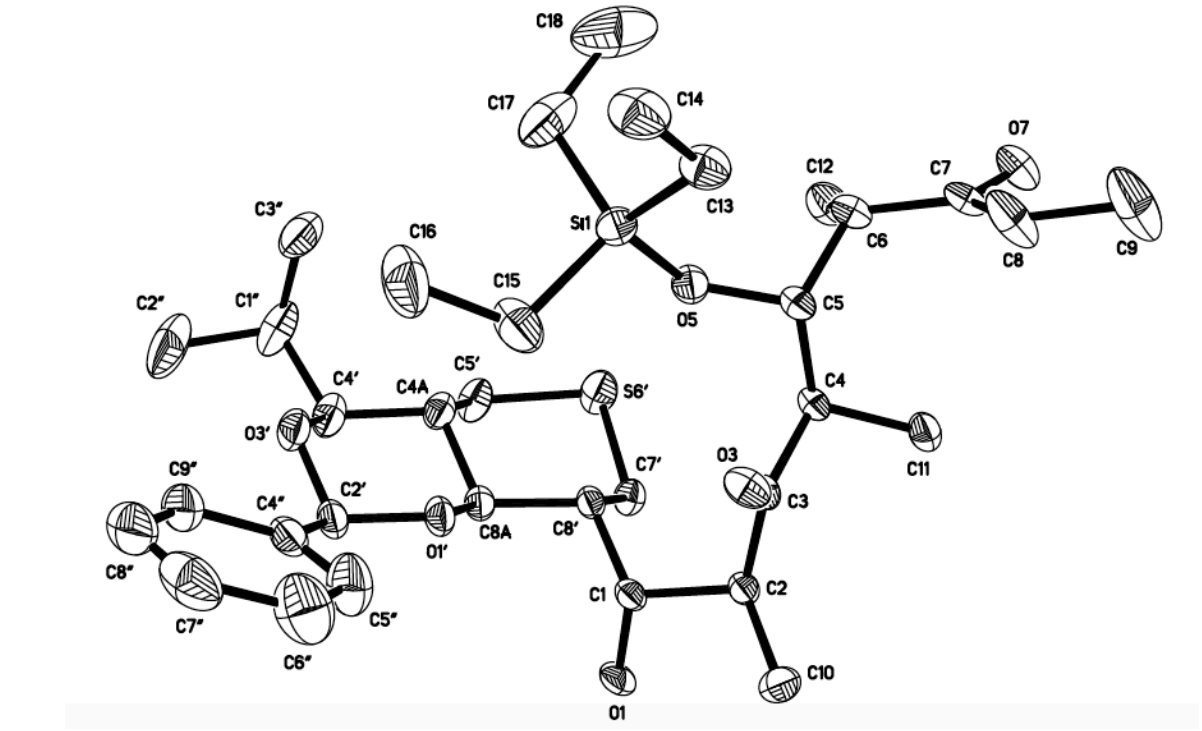


Figure 2-3: Ellipsoid plot of **253**.

2.9.2. Assignment by correlation to known compounds

***Meso* bisaldol 232:**

The structure of **10** was established by its correlation to the known **230** via desulfurization (Figure 2-4).

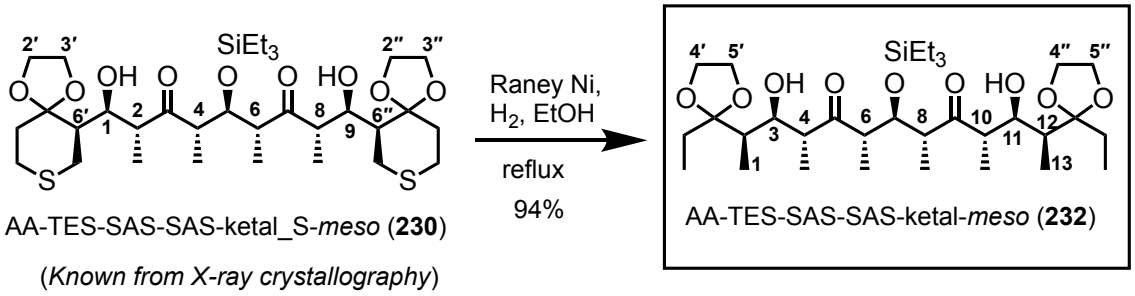


Figure 2-4: Desulfurization of the known **230** to **232**.

***Meso* bisaldol 236:**

The structure of **236** was established by its correlation to the known **237** via desulfurization (Figure 2-5).

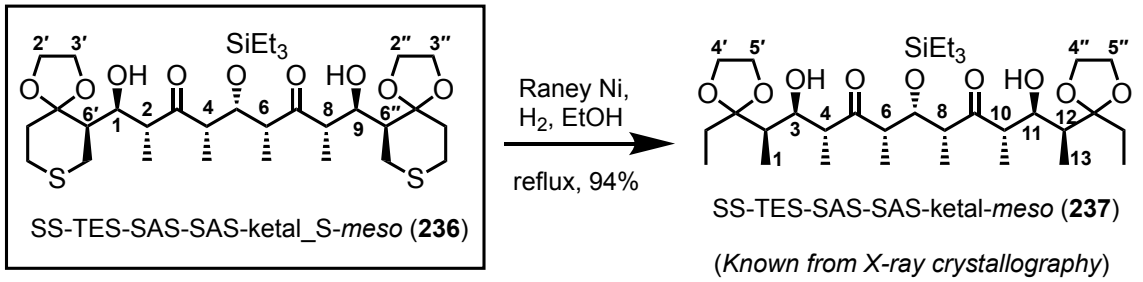


Figure 2-5: Desulfurization of **236** to the known **237**.

***Meso* bisaldol 241:**

The structure of **241** was established by its correlation to the known **232** via desulfurization (Figure 2-6).

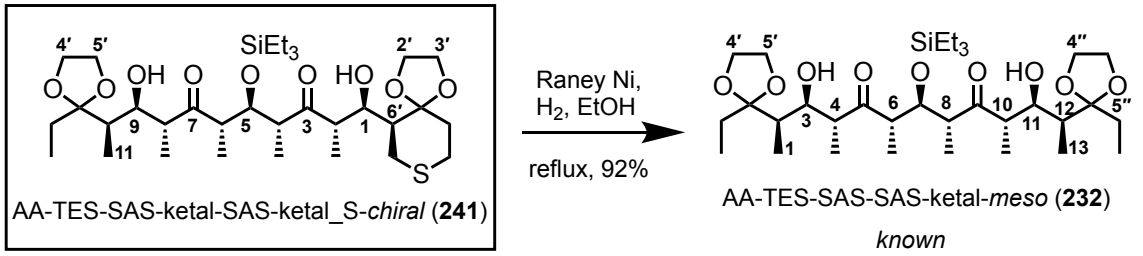


Figure 2-6: Desulfurization of **241** to the known **232**.

***Meso* bisaldol 243:**

The structure of **243** was established by its correlation to the known **237** via desulfurization (Figure 2-7).

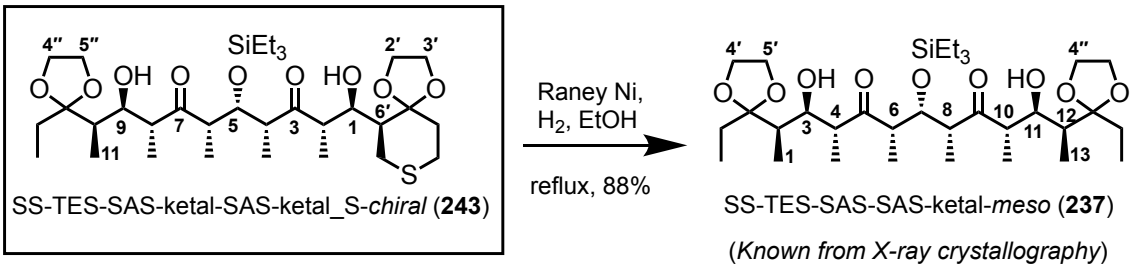


Figure 2-7: Desulfurization of **243** to the known **237**.

2.9.3. Assignment via NMR analysis of derivatives

General procedure for assignment of NMR spectra of bisacetonides 280a and 282a:

Analysis of the ^{1}H and ^{13}C NMR data for acetonides **280a** and **282a** allowed assignment of each ^{1}H and ^{13}C signal and enabled assignment of the relative configurations of **280a** and **282a** and thus, of the precursor bisaldols **212** and **223**. No attempt was made to distinguish between diastereotopic protons or carbons.

Two-dimensional HH COSY data allowed assignment of all the hydrogens in the spin system spanning from $(H_3C)_2CH$-HC6‴ to HC4$(H_3C)_2$. The COSY correlation of the HO- proton to HC-3 allowed the correct alignment of this otherwise symmetrical spin system. The attached carbons were assigned by analysis of a two-dimensional $^{1}J_{CH}$ correlation spectrum (e.g., gHSQC). The quaternary carbons C2′ and C2‴ are easily distinguished by their chemical shifts (ca. 110 ppm) and were assigned by reference to the appropriate $^{3}J_{CH}$ correlations (i.e., $^{3}J_{C2'''\text{-}HC6'''}$, $^{3}J_{C2'''\text{-}HC4'''}$, $^{3}J_{C2'\text{-}HC6'}$ and $^{3}J_{C2'\text{-}HC4'}$) observed in the HMBC spectrum as shown in Figure 2-8. The methyl groups attached to C2′ and C2″ were identified based on $^{2}J_{H\text{-}C}$ correlations in the HMBC spectrum.

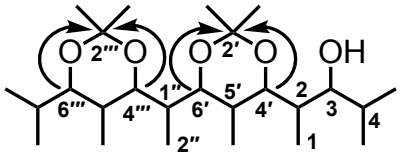


Figure 2-8: Key HMBC correlations (H→C) in chiral bis-acetonides **280a** and **282a**.

The 1,3-relative configuration of acetonides of *syn*- and *anti*-1,3 diols can be readily determined using ^{13}C chemical shifts of acetal carbon (e.g., C2′ of **1b**) and acetal methyl groups.[115] In general, the acetal carbon (C2′) of the '*syn*-1,3 acetonides' appears at <99.5 ppm (98-99.5 ppm) and the acetal methyls are near 19 and 30 ppm ($\Delta\boldsymbol{\delta}_C$ = >9 ppm); while the '*anti*-1,3 acetonides' have the acetal carbon (C2′) at >100.5 ppm (100.5-102 ppm) and the acetal methyls at around 23 and 25 ppm ($\Delta\boldsymbol{\delta}_C$ = <5 ppm).

Assignment of the relative configuration of *Meso* bisaldol 212:

The bisaldol **212** is symmetric (C_s) as indicated by the presence of 12 signals in the ^{13}C NMR spectrum (Figure 2-9). Hydroxy-directed 1,3-*syn* selective reduction of **212** afforded the *meso* tetrol **279** (70% isolated yield) that upon treatment with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in acetone, was converted to a separable mixture of acetonides **280a** (33%), **280b** (21%) and **280c** (25%). The number of carbon resonances in the respective ^{13}C NMR spectra indicated that **280b** and **280c** are symmetric and **280a** is asymmetric. Analysis of the NMR data for **280a** (derived from a *meso* tetrol) allowed assignment of its relative configuration thereby establishing the relative configuration of the precursor **212**.

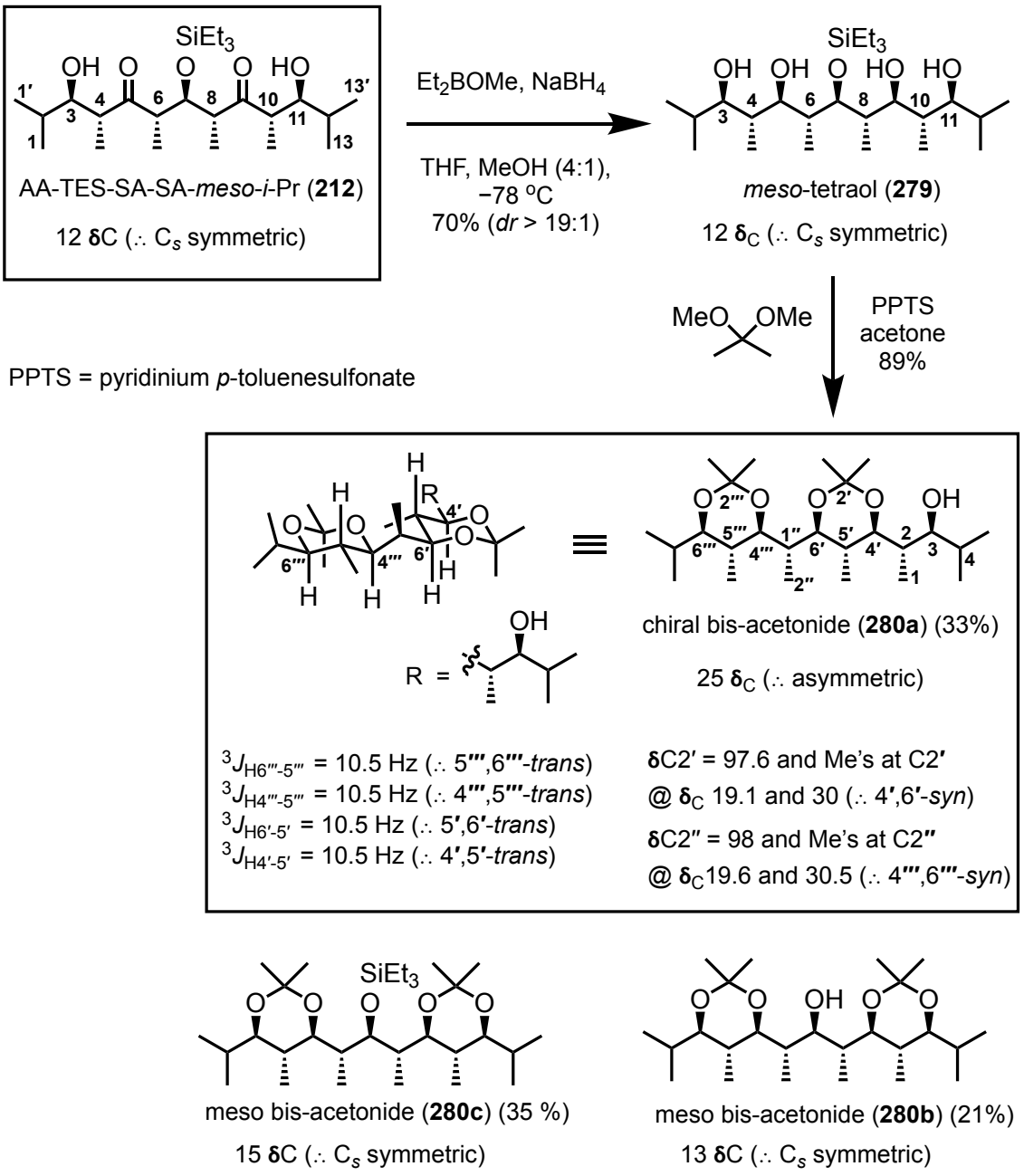


Figure 2-9: Structure determination of **212** via conversion to the acetonide **280a**.

The C4‴-C6‴ and C4′-C6′ relative configurations of the bis-acetonide **280a** were assigned based on the ^{13}C NMR chemical shifts of C2′ (97.6 ppm → 4′,6′-*syn*), C2‴ (98.0 ppm → 4‴,6‴-*syn*), the C2′-Me's (19.1 ppm and 30.0 ppm → 4′,6′-*syn*) and the C2‴-Me's (19.6 ppm and 30.5 ppm → 4‴,6‴-*syn*) (Figure 2-9). The relative configurations at C6‴-C5‴, C4‴-C5‴, C6′-C5′ and

C5′-C4′ of bis-acetonide **280a** were assigned based on the ^{1}H NMR coupling constants: $^{3}J_{H5'''\text{-}H6'''}$ (10.5 Hz), $^{3}J_{H4'''\text{-}H5'''}$ (10.5 Hz), $^{3}J_{H5'\text{-}H6'}$ (10.5 Hz) and $^{3}J_{H4'\text{-}H5'}$ (10.5 Hz). These large *J*-values clearly indicate that the coupled hydrogens are in trans diaxial relationships (i.e., *anti*-relation) establishing a 5‴,6‴-*anti*-4‴,5‴-*anti*-5′,6′-*anti*-4′,5′-*anti* relative configuration. Because **279** is *meso* (as are **280b** and **280c**) the C3-C6‴, C2-C5‴, C4′-C4‴, and C5′-C1″ relative configurations in **280a** must be *syn*. Thus, the relative configurations of **280a** is 2,3-*anti*-2,4′-*anti*-4′,5′-*anti*-5′,6′-*anti*-6′,1″-*anti*-1″,4‴-*anti*-4‴,5‴-*anti*-5‴,6‴-*anti* and that of **212** is 3,4-*anti*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*syn*-10,11-*anti*.

Assignment of the relative configuration of *Meso* bisaldol 223:

The bisaldol **223** is symmetric (C_s) as indicated by the presence of 12 resonances in the ^{13}C NMR spectrum (Figure 2-10). Hydroxy-directed 1,3-*syn* selective reduction of **223** afforded the *meso* tetrol **281** (89% isolated yield) that, upon treatment with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in acetone, was converted to a separable mixture of acetonides **282a** (38%), **282b** (40%) and **282c** (9%). The numbers of carbon resonances in the respective ^{13}C NMR spectra indicated that the **282b**, **282c** are symmetric (C_s) and **282a** is asymmetric. Analysis of the NMR data for **282a** (derived from a *meso* tetraol) allowed assignment of its relative configuration thereby establishing the relative configuration of the precursor **223**.

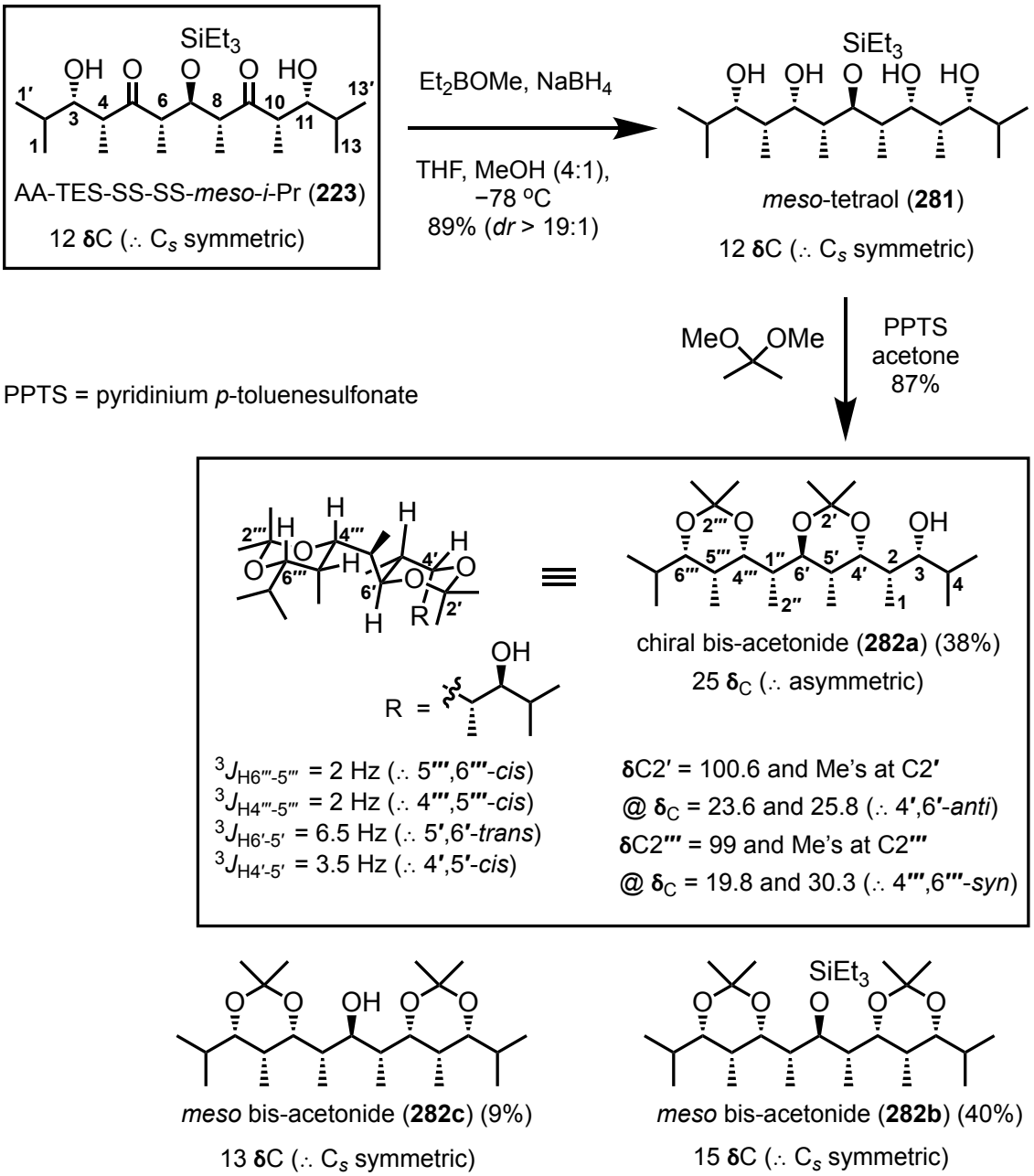


Figure 2-10: Structure determination of **223** via conversion to the acetonide **282a**.

The C4‴-C6‴ and at C4′-C6′ relative configurations of bis-acetonide **282a** were assigned based on the ^{13}C NMR chemical shifts of C2′ (100.6 ppm → 4′,6′-*anti*), C2‴ (99.0 ppm → 4‴,6‴-*syn*), the C2′-Me's (23.6 ppm and 25.8 ppm → 4′,6′-*anti*), and the C2‴-Me's (19.8 ppm and 30.3 ppm → 4‴,6‴-*syn*) (Figure 2-10). The relative configurations at C6‴-C5‴, C4‴-C5‴,

C6′-C5′ and C5′-C4′ of bis-acetonide **282a** were assigned based on the ^{1}H NMR coupling constants of $^{3}J_{H5'''\text{-}H6'''}$ (2 Hz), $^{3}J_{H4'''\text{-}H5'''}$ (2 Hz), $^{3}J_{H5'\text{-}H6'}$ (6.5 Hz) and $^{3}J_{H4'\text{-}H5'}$ (3.5 Hz). These *J*-values suggest a 5′′′,6′′′-*syn*-4′′′,5′′′-*syn*-5′,6′-*anti*-4′,5′-*syn* relative configuration. Because **281** is *meso* (as are **282b** and **282c**) the C3-C6′′′, C2-C5′′′, C4′-C4′′′, and C5′-C1′′ relative configurations in **282a** must be *syn*. Thus, the relative configuration of **282a** is 2,3-*syn*-2,4′-*syn*-4′,5′-*syn*-5′,6′-*anti*-6′,1′′-*anti*-1′′,4′′′-*syn*-4′′′,5′′′-*syn*-5′′′,6′′′-*syn* and that of **223** is 3,4-*syn*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*syn*-10,11-*syn*.

2.9.4. Assignment based on comparison of NMR data with a database

In addition to the confirmed structures established in the previous sections, a large number of aldol adducts with the general structure **GS1** have been established in previous work within the Ward group (Figure 2-11).[42,66] The NMR data for these adducts of known structure generates a database that reveals consistent correlations of certain NMR data with the underlying relative configurations. Thus, comparison of the NMR data of an 'unknown' isomer with the database can provide evidence for the assignment of the relative configuration of the 'unknown'.

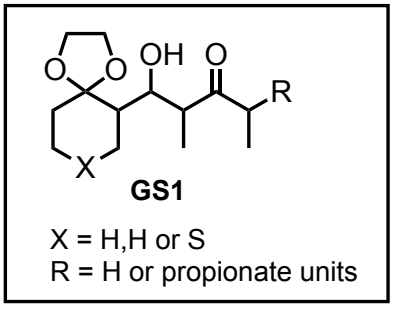


Figure 2-11: General aldol adduct structure **GS1**.

Mono aldol 231:

Procedure for assignment of NMR spectra:

The ^{1}H NMR spectra of **231** can be divided in to six distinct 'spin systems' via analysis of the two-dimensional HH COSY spectrum (Figure 2-13). The Et_3Si, H_2C8-H_3C9, and H_2C2'-H_2C3' proton spin systems are unique and were readily assigned in the COSY spectrum; the ^{13}C chemical shifts of attached carbon atoms were identified based on the relevant $^{1}J_{CH}$ correlations observed in the HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in these spin systems.

The proton signal for HC-1 was readily identified by the $^{3}J_{HH}$ correlation to the OH proton and two adjacent methine groups (i.e., HC-6′ and HC-2) (Figure 2-13). By analysis of the HH COSY spectrum and using the assigned HC-1 as an 'anchor' all the hydrogens in the spin system (i.e, HC-7′, HC-6′, HC-1, HC-2 and H_3CC-2) were assigned. With the aid of these assigned protons, the chemical shifts of the attached carbons were assigned by analysis of a two-dimensional $^{1}J_{CH}$ correlation spectrum (e.g., gHSQC). Among the carbonyl carbons, C3 is readily distinguished by $^{2}J_{CH}$ and $^{3}J_{CH}$ correlations (e.g., HMBC) to the HC-2 and CH_3C-2, respectively (Figure 2-12). The HC-4 and CH_3C-4 were assigned by $^{2}J_{CH}$ and $^{3}J_{CH}$ correlations to C3, respectively, observed in the HMBC spectrum. By analysis of the HH COSY spectrum and using the assigned HC-4 as an 'anchor' all the hydrogens in the spin system (i.e., H_3CC-4, HC-5, HC-6 and H_3CC-6) were assigned. Although the assignment of C7 can be inferred after the assignment of the other carbonyl C3, the $^{2}J_{C7\text{-}HC6}$ and $^{3}J_{C7\text{-}CH3C6}$ correlations observed in the HMBC spectrum is additional evidence to support this assignment. Among the methylene protons, H_2C-8 is unique and was assigned using chemical shift and multiplicity; this assignment was further supported by $^{2}J_{C7\text{-}HC8}$ and $^{3}J_{C7\text{-}HC9}$ correlations, observed in the HMBC spectrum. The methylene carbon C-9′ was assigned based on

$^{3}J_{C9\text{-}HC7'}$ correlation, observed in the HMBC spectrum. The H_2C-9′ protons were assigned by analysis of $^{1}J_{CH}$ correlation spectrum (gHSQC) and also based on a long-range W-coupling ($^{4}J_{H9'\text{-}7'}$; 1 Hz) with the assigned HC-7′; thus H_2C-10′ was assigned by $^{3}J_{H9'\text{-}H10'}$ correlation observed in the COSY spectrum. The quaternary carbon C5′ is unique and was readily distinguished in the ^{13}C NMR spectrum on the basis of the chemical shift ($\boldsymbol{\delta}_C$ C5′ = 110.4)

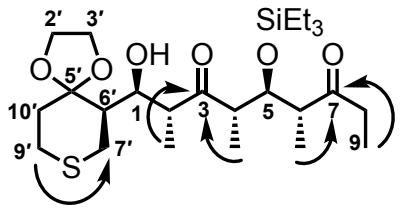


Figure 2-12: Key HMBC correlations (H→C) in monoaldol **231**.

Assignment of the relative configuration of 231:

NMR analysis of the known[3] four diastereomers of **283** revealed consistent trends that allowed assignment of the relative configurations in **231** (Figure 2-13 & Table 2-16). The 6′,1-*syn* diastereomers (i.e., **283as** and **283ss**) consistently had lower $^{3}J_{H6'\text{-}H1}$ (2-3 Hz) and ^{13}C chemical shifts for C7′ ($\boldsymbol{\delta}_C$ 26-26.9) and higher $^{3}J_{H1\text{-}H2}$ (7.5-9 Hz) values compared to those of the 6′,1-*anti* diastereomers (**283aa** and **283sa**). Similarly, the 1,2-*anti* diastereomers (**283as** and **283aa**) consistently had higher ^{13}C chemical shifts for C1 ($\boldsymbol{\delta}_C$ 71.8-74.6) and CH_3C-2 ($\boldsymbol{\delta}_C$ 13.9-14.2) compared to those of the 1,2-*syn* diastereomers (**283ss** and **283sa**). The diastereomer **283sa** can be easily distinguishable by its characteristic lower ^{13}C chemical shift for CH_3C-2 ($\boldsymbol{\delta}_C$ 8.1) compared to the other three diastereomers ($\boldsymbol{\delta}_C$ 13.3-14.2).

The ^{1}H and ^{13}C NMR data of the known *meso* bisaldol **230** closely matches those of **283as** suggesting the trends from database are consistent and are applicable to the assignment of the relative configurations in similar structures (Figure 2-13 & Table 2-16). The mono aldol **231** was obtained from an incomplete reaction of (*E,E*)-bisenol borinate **215** with aldehyde **109** suggesting the adduct **231** has the same relative configuration as **230** (arising from complete reaction of **215** with **109**). The ^{1}H and ^{13}C NMR data for **231** were compared with those of the known adducts **230** and **283as** to assign the relative configurations in **231**. The coupling constants $^{3}J_{H6'\text{-}H1}$ (1 Hz; 6′,1-*syn*), $^{3}J_{H1\text{-}H2}$ (9.5 Hz; 1,2-*anti*), the ^{13}C chemical shifts of C7′ ($\boldsymbol{\delta}_C$ 25.8; 6′,1-*syn*), CH_3C-2 ($\boldsymbol{\delta}_C$ 14.1; 1,2-*anti*) and the ^{1}H chemical shift of H_3CC-2 ($\boldsymbol{\delta}_H$ 0.96; 6′,1-*syn*) for **231** are consistent with those of the known adducts **230** and **283as** suggesting the relative configuration of **231** is 1,2-*anti*-6′,1-*syn*. The C2-C4 relative configuration in **231** was assumed as 2,4-*syn* by analogy to the known adduct **230** as both the aldols (**231** and **230**) are obtained from reaction of (*E,E*)-bis enolborinate **215** with aldehyde **109**. The relative configurations of C4-C5 and C5-C6 should be unchanged from the starting diketone **202aa** and were already confirmed as 4,5-*anti*-5,6-*anti* from the X-ray structure of **230**. Thus, the relative configuration of **231** was assigned as 6′,1-*syn*-1,2-*anti*-2,4-*syn*-4,5-*anti*-5,6-*anti*.

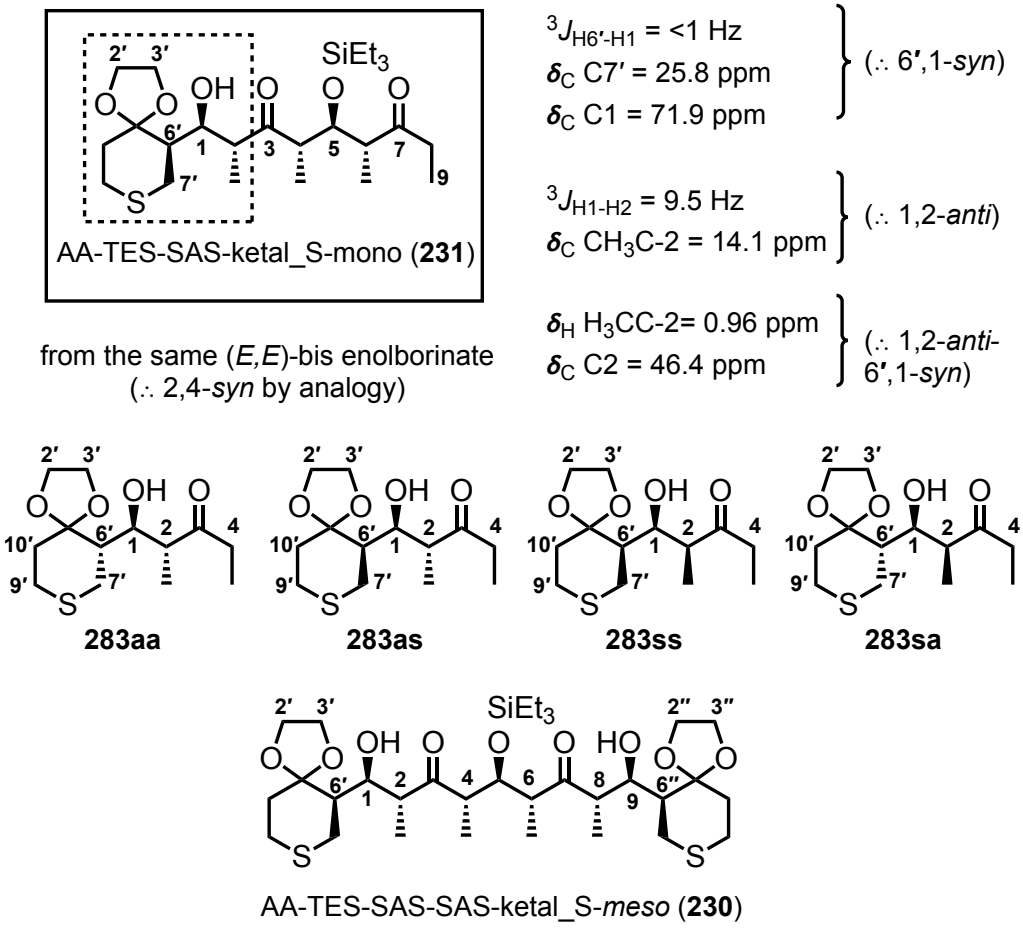


Figure 2-13: Assignment of the relative configuration of **231** by NMR comparison with the known compounds.

Table 2-16: Comparison of the selected NMR data of **231** with those of the known **230** and **283**.

adduct	$^3J_{H6'-H1}$ (Hz)	$^3J_{H1-H2}$ (Hz)	δ_H CH_3C-2	δ_C C-6′	δ_C C-7′	δ_C C-1	δ_C C-2	δ_C CH_3C-2
283aa	7	4.5	1.21	46.5	30.0	74.6	49.4	14.2
283ss	3	7.5	1.19	47.3	26.9	69.4	49.7	13.3
283sa	8.5	2	1.10	46.2	29.4	70.9	48.0	8.1
283as	2	9	0.97	46.3	26.0	71.8	47.9	13.9
230	<1	9.5	0.96	46.6	25.8	71.7	47.2	14.1
231	1	9.5	0.96	46.5	25.8	71.9	46.4	14.1

Mono aldol 233:

The ^{1}H NMR spectra of **233** can be divided in to six distinct 'spin systems' via analysis of the two-dimensional HH COSY spectrum (Figure 2-15). The Et_3Si, H_2C10-H_3C11, and H_2CC2'-H_3CCC2' proton spin systems are unique and were readily assigned in the COSY spectrum; the ^{13}C chemical shifts of the attached carbon atoms were identified based on the relevant $^{1}J_{CH}$ correlations observed in the HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in these spin systems.

The proton signal for HC-3 was readily identified by the $^{3}J_{HH}$ correlation to the OH proton and two adjacent methine groups (i.e., HC-2 and HC-4) (Figure 2-15). By analysis of the HH COSY spectrum and using the assigned HC-3 as an 'anchor' all the hydrogens in the spin system (i.e, HC-1, HC-2, HC-4 and H_3CC-4) were assigned. With the aid of these assigned protons, the chemical shifts of the attached carbons were assigned by analysis of a two-dimensional $^{1}J_{CH}$ correlation spectrum (e.g., gHSQC). Among the carbonyl carbons, C5 is readily distinguished by $^{2}J_{C5\text{-}HC4}$ and $^{3}J_{C5\text{-}H3CC4}$ correlations observed in the HMBC spectrum (Figure 2-14). The HC-6 and CH_3C-6 were assigned by $^{2}J_{C5\text{-}HC6}$ and $^{3}J_{C5\text{-}H3CC6}$ correlations, respectively, observed in the HMBC spectrum. By analysis of the HH COSY spectrum and using the assigned HC-6 as an 'anchor' all the hydrogens in the spin system (i.e., H_3CC-6, HC-7, HC-8 and H_3CC-8) were assigned. Although the assignment of C9 can be inferred after the assignment of the other carbonyl C5, the $^{2}J_{C9\text{-}HC8}$ and $^{3}J_{C9\text{-}CH3C8}$ correlations observed in HMBC spectrum is additional evidence to support this assignment. The quaternary carbon C2′ is unique and was readily distinguished in ^{13}C NMR spectrum on the basis of the chemical shift ($\boldsymbol{\delta}_C$ C2′ = 114.7). Among the methylene protons, H_2C-10 was assigned by $^{2}J_{C9\text{-}HC10}$ and $^{3}J_{C9\text{-}HC11}$ correlations; H_2CC2' was assigned by $^{2}J_{C2'\text{-}H2CC2'}$ and $^{3}J_{C2'\text{-}H3CCC2'}$ correlations observed in the HMBC spectrum.

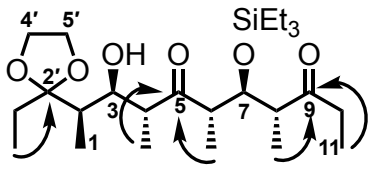


Figure 2-14: Key HMBC correlations (H→C) in monoaldol **233**.

Assignment of the relative configuration of 233:

NMR analysis of the known[42] four diastereomers of **130** revealed consistent trends that allowed assignment of the relative configurations in **233** (Figure 2-15 & Table 2-17). The 2,3-*syn* diastereomers (i.e., **130as** and **130ss**) consistently had lower $^{3}J_{H2\text{-}H3}$ (1 Hz), ^{1}H chemical shift of H_3CC-4 ($\boldsymbol{\delta}_H$ 0.94-1.24), ^{13}C chemical shift of C1 ($\boldsymbol{\delta}_C$ 6.9-7.4), C2 ($\boldsymbol{\delta}_C$ 38.5-39.9) and higher $^{3}J_{H3\text{-}H4}$ (9-9.5 Hz), ^{13}C chemical shift of CH_2C-2′ ($\boldsymbol{\delta}_C$ 28.1-28.2), CH_3CC-2′ ($\boldsymbol{\delta}_C$ 8.2-8.3) values compared to those of the 2,3-*anti* diastereomers (**130aa** and **130sa**). Similarly, the 3,4-*anti* diastereomers (**130aa** and **130as**) consistently had higher ^{13}C chemical shift of C3 ($\boldsymbol{\delta}_C$ 73.4-76.1) compared to those of the 3,4-*syn* diastereomers (**130ss** and **130sa**). The diastereomer **130sa** can be easily distinguishable by its characteristic lower ^{13}C chemical shift of CH_3C-2 ($\boldsymbol{\delta}_C$ 8.0) compared to the other three diastereomers ($\boldsymbol{\delta}_C$ 13.7-14.9).

The ^{1}H and the ^{13}C NMR data of the known *meso* bisaldol **232** closely matches those of **130as** suggesting the trends from database are consistent and are applicable to the assignment of the relative configurations in similar structures (Figure 2-15 & Table 2-17). The mono aldol **233** was obtained from an incomplete reaction of (*E,E*)-bis enolborinate **215** with aldehyde **159** suggesting the adduct **233** has the same C4-C6 relative configuration as **232** (arising from complete reaction of **215** with **159**). The coupling constants $^{3}J_{H2\text{-}H3}$ (<1 Hz; 2,3-*syn*) and $^{3}J_{H3\text{-}H4}$ (10 Hz; 3,4-*anti*), the ^{13}C chemical shifts of C1 ($\boldsymbol{\delta}_C$ 6.6; 2,3-*syn*), C2 ($\boldsymbol{\delta}_C$ 38.4; 2,3-*syn*), CH_2C-2′ ($\boldsymbol{\delta}_C$ 28.3; 2,3-*syn*), CH_3CC-2′ ($\boldsymbol{\delta}_C$ 8.3; 2,3-*syn*) and the ^{1}H chemical shifts of H_3CC-4 ($\boldsymbol{\delta}_H$ 0.91; 2,3-*syn*) of **233**

are consistent with those of the known adducts **232** and **130as** suggesting the relative configuration of **233** is 2,3-*syn*-3,4-*anti*. The C4-C6 relative configuration in **233** was assumed as 4,6-*syn* by analogy to the known adduct **232** as both the aldols (**232** and **233**) are obtained from reaction of (*E,E*)-bis enolborinate **215** with aldehyde **159**. The relative configurations of C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known structure of **232**. Thus, the relative configuration of **233** was assigned as 2,3-*syn*-3,4-*anti*-4,6-*syn*-6,7-*anti*-7,8-*anti*.

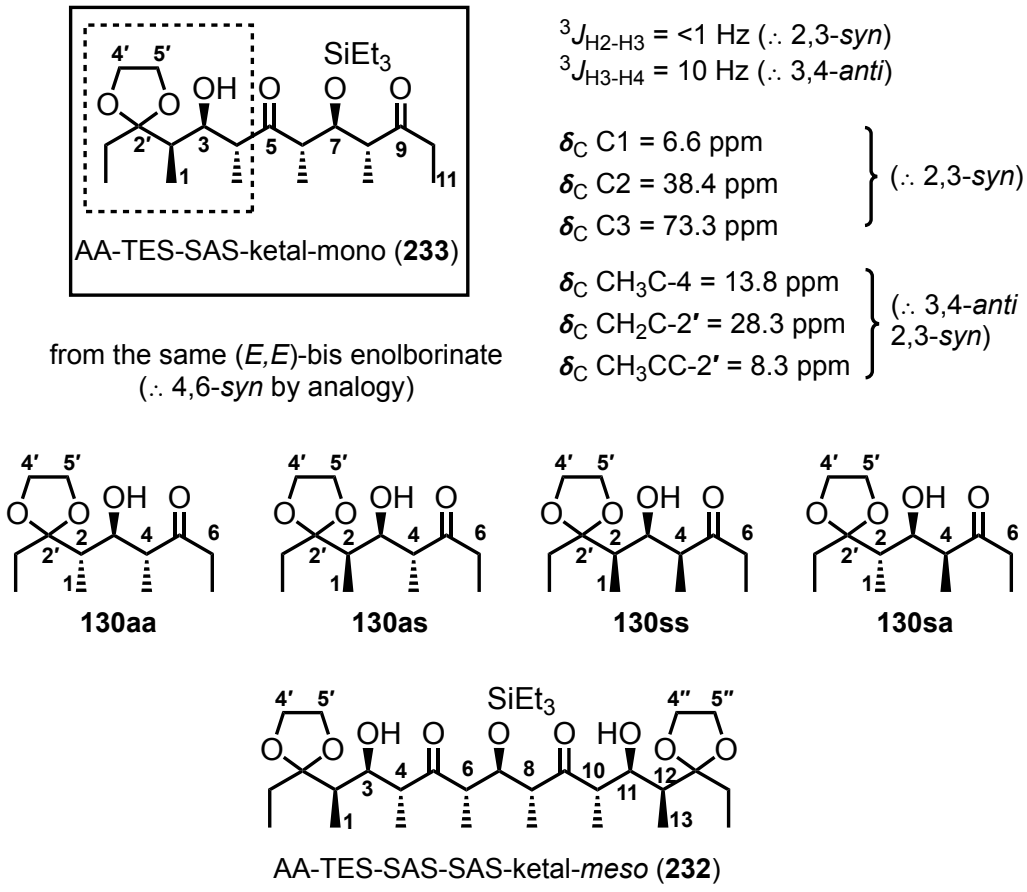


Figure 2-15: Assignment of the relative configuration of **233** by NMR comparison with the known compounds.

Table 2-17: Comparison of the selected NMR data of **233** with those of the known **232** and **130**.

adduct	$^3J_{H2\text{-}H3}$ (Hz)	$^3J_{H3\text{-}H4}$ (Hz)	δH CH_3C-4	δ_C C-1	δ_C C-2	δ_C C-3	δ_C C-4	δ_C CH_3C-4	δ_C CH_2C-2′	δ_C CH_3C C-2′
130aa	8.5	3.5	1.24	13.1	42.0	76.1	49.7	14.5	26.0	7.1
130ss	1	9	1.21	7.4	39.9	71.6	50.2	14.9	28.1	8.2
130sa	9.5	2.5	1.06	12.8	41.4	73.0	49.1	8.0	25.7	7.0
130as	<1	9.5	0.94	6.9	38.5	73.4	48.7	13.7	28.2	8.3
232	<1	9.5	0.91	6.7	38.8	73.1	48.0	13.8	28.2	8.2
233	<1	10	0.91	6.6	38.4	73.3	47.1	13.8	28.3	8.3

Mono aldol 214:

Procedure for assignment of NMR spectra:

The ^{1}H NMR spectra of **214** can be divided in to four distinct 'spin systems' from analysis of its two-dimensional HH COSY NMR spectrum (Figure 2-17). The Et_3Si and H_2C10-H_3C11 proton spin systems are unique and were readily assigned in the COSY spectrum; the ^{13}C chemical shifts of attached carbon atoms were identified based on the relevant $^1J_{CH}$ correlations observed in the HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in these spin systems.

The proton signal for HC-3 is readily differentiated by the $^3J_{HH}$ correlation to the OH group and two adjacent methine groups (i.e., HC-2 and HC-4) (Figure 2-17). By analysis of the HH COSY spectrum and using the assigned HC-3 as an 'anchor' all the hydrogens in the spin system (i.e, HC-1, HC-1′, HC-2, HC-4 and H_3CC-4) were assigned. With the aid of these assigned protons, the attached carbons were assigned by analysis of the two-dimensional $^1J_{CH}$ correlation spectrum (gHSQC). Among the carbonyl carbons, C5 is readily distinguishable by $^2J_{C5\text{-}HC4}$ and $^3J_{C5\text{-}CH3C4}$

correlations observed in the HMBC spectrum (Figure 2-16). The HC-6 and H_3CC-6 were assigned from $^2J_{C5\text{-}HC6}$ and $^3J_{C5\text{-}CH3C6}$ correlations, respectively, observed in the HMBC spectrum. By analysis of the HH COSY spectrum and using the assigned HC-6 as an 'anchor' all the hydrogens in the spin system (i.e, H_3CC-6, HC-7, HC-8 and H_3CC-8) were assigned. Although the assignment of C9 can be inferred after the assignment of the other carbonyl at C5, the $^2J_{C9\text{-}HC8}$ and $^3J_{C9\text{-}CH3C8}$ correlations observed in HMBC spectrum is additional evidence to support this assignment. The methylene protons H_2C-10 are unique and were assigned using ^{1}H chemical shift and multiplicity and this assignment was further supported by $^2J_{C9\text{-}HC10}$ correlations observed in the HMBC spectrum.

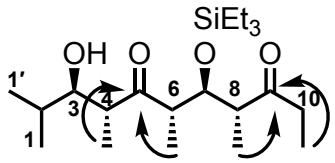


Figure 2-16: Key HMBC correlations (H→C) in monoaldol **214**.

Assignment of the relative configuration of 214:

NMR analysis of the known[42] 13 diastereomers of **200** revealed consistent trends that allowed assignment of relative configurations in **214** (Figure 2-17, Table 2-18). Comparison of the coupling constants ($^3J_{H2\text{-}H3}$, $^3J_{H3\text{-}H4}$), ^{13}C chemical shifts ($\boldsymbol{\delta}_C$ CH_3C-4), differences in ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ (C1, C1′), $\Delta\boldsymbol{\delta}_C$ (C2, C4) and $\Delta\boldsymbol{\delta}_C$ (C3, CH_3C-4)] values between 13 diastereomers of **200**, **212** and **214** allowed assignment of the relative configuration at C3-C4 and C4-C6 in **214**. The 3,4-*anti* diastereomers (**200aa** and **200sa**) consistently had lower $^3J_{H2\text{-}H3}$ (3.9-5 Hz), $\Delta\boldsymbol{\delta}_C$ [C3, CH_3C-4] (63.6-64.6 ppm) and higher $^3J_{H3\text{-}H4}$ (7-7.9 Hz), $\Delta\boldsymbol{\delta}_C$ [C1, C1′] (4.2-5.3 ppm), $\Delta\boldsymbol{\delta}_C$ [C2, C4] (17.8-19.7 ppm), $\boldsymbol{\delta}_C$ CH_3C-4 (14.3 ppm) values compared to those of the 3,4-*syn* diastereomers (**200as** and **200ss**). Similarly, the relative configurations at C4-C6 was also assigned by comparing

the ^{13}C NMR data of the 4,6-*syn* diastereomers with those of the corresponding 4,6-*anti* diastereomers (i.e., **ss** vs. **as** and **sa** vs. **aa**). The 4,6-*syn* diastereomers consistently had higher $\Delta\boldsymbol{\delta}_C$ [C1, C1′], $\Delta\boldsymbol{\delta}_C$ [C2, C4] and lower $\Delta\boldsymbol{\delta}_C$ (C3, CH_3C-4) values compared to those of the corresponding 4,6-*anti* diastereomers (Table 2-18).

The ^1H and ^{13}C NMR data of the known *meso* bisaldol **212** closely matches those of **200as** suggesting the trends from data base are consistent and are applicable to the assignment of the relative configurations of similar structures (Table 2-18). The mono aldol **214** was obtained from an incomplete reaction of (*E,E*)-bis enolborinate **215** with ^{i}PrCHO suggesting the adduct **214** has same C4-C6 relative configuration as *meso* bisaldol **212** (arising from complete reaction of **215** with ^{i}PrCHO) (Figure 2-17). The ^1H and ^{13}C NMR data for **214** were compared with those of the known adducts **212** and **200sa**. The coupling constants $^3J_{H2\text{-}H3}$ (3.5 Hz) and $^3J_{H3\text{-}H4}$ (8 Hz), the ^{13}C chemical shift of CH_3C-4 ($\boldsymbol{\delta}_C$ 14.0) and the difference in ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C1, C1′] = 5.7; $\Delta\boldsymbol{\delta}_C$ [C2, C4] = 19.5; $\Delta\boldsymbol{\delta}_C$ [C3, CH_3C-4] = 64.3) for **214** are consistent with the observed trends from the database and with those of the known adducts **212** and **200sa** suggesting the relative configuration of **214** is 3,4-*anti*-4,6-*syn* (Table 2-18). The relative configurations of C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known **212**. Thus, the relative configuration of **214** was assigned as 3,4-*anti*-4,6-*syn*-6,7-*anti*-7,8-*anti*.

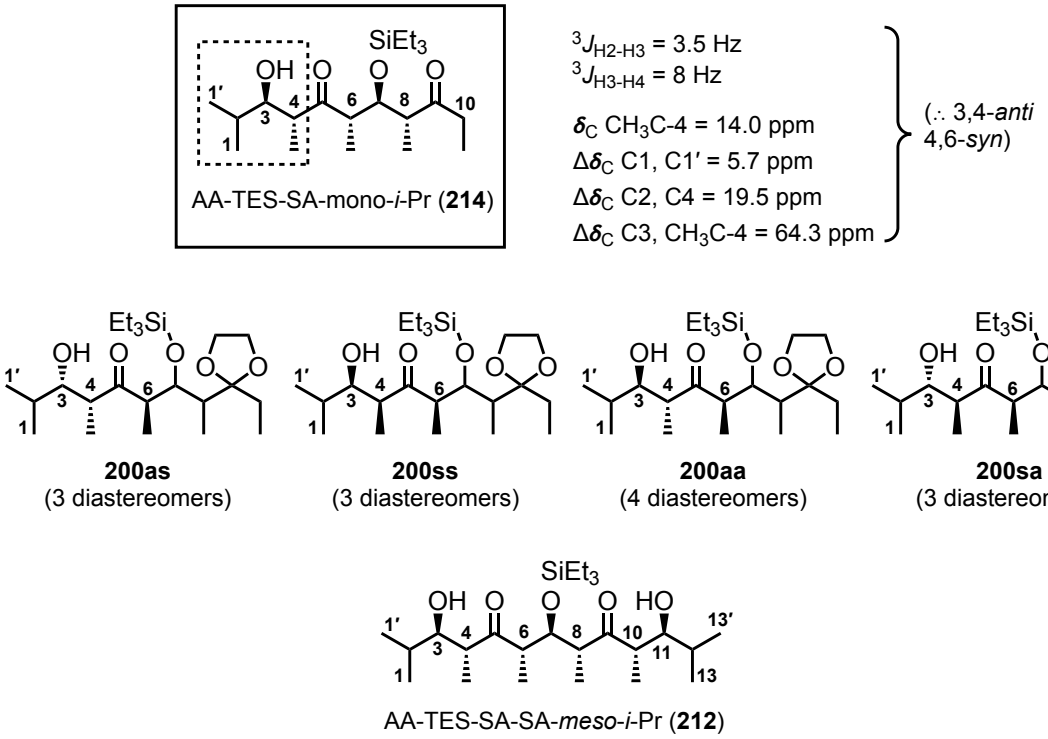


Figure 2-17: Assignment of the relative configuration of **214** by NMR comparison with the known compounds.

Table 2-18: Comparison of the selected NMR data of **214** with those of the known **212** and **200**.

adduct	$^3J_{H2\text{-}H3}$ (Hz)	$^3J_{H3\text{-}H4}$ (Hz)	$\Delta\delta_C$ (C1,C1′)	$\Delta\delta_C$ (C2,C4)	$\Delta\delta_C$ (C3,CH_3C-4)	δ_C CH_3C-4
200as	8.8	1.9	0.6	15.8	68.2	8.5
200ss	9.4	1.4	1.0	16.7	67.1	9.0
200aa	5	7	4.2	17.8	64.6	14.3
200sa	3.9	7.9	5.3	19.7	63.6	14.3
212	3.5	7	5.6	19.3	64.0	14.2
214	3.5	8	5.7	19.5	64.3	14.0

***Meso*-bisaldol 217:**

The adduct **217** is C_s-symmetric as indicated by the presence of 12 resonances in the ^{13}C NMR spectrum (Figure 2-18). NMR spectra of **217** was assigned by following the identical procedure used for **214**.

Assignment of the relative configuration of 217:

Similar to the assignment of **214**, comparison of the coupling constants ($^3J_{H2\text{-}H3}$, $^3J_{H3\text{-}H4}$), ^{13}C chemical shifts ($\boldsymbol{\delta}_C$ CH_3C-4), difference in ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C1, C1′, $\Delta\boldsymbol{\delta}_C$ [C2, C4] and $\Delta\boldsymbol{\delta}_C$ [C3, CH_3C-4]) values between the known 13 diastereomers of **200**, **212** and **217** allowed assignment of the relative configuration at C3-C4 and C4-C6 in **217** (for detailed discussion, refer to the assignment of **214**) (Figure 2-17). The bisaldol **217** was obtained from the identical reaction conditions (i.e., from (*E,E*)-bis enolborinate **215** with ^{i}PrCHO) as **212**, suggesting the adduct **217** has same C4-C6 relative configuration as **212**. The coupling constants $^3J_{H2\text{-}H3}$ (4.0 Hz) and $^3J_{H3\text{-}H4}$ (7.0 Hz), the ^{13}C chemical shift of CH_3C-4 ($\boldsymbol{\delta}_C$ 14.5), and the difference in the ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C1, C1′] = 5.0; $\Delta\boldsymbol{\delta}_C$ [C2, C4] = 18.7; $\Delta\boldsymbol{\delta}_C$ [C3, CH_3C-4] = 64.0) for **217** are consistent with the observed trends from the database and with those of the known adducts **212** and **200sa** suggesting the relative configuration of **217** is 3,4-*anti*-4,6-*syn* (Table 2-19). The relative configurations of C6-C7 and C7-C8 should be unchanged from the starting diketone **202ss** and were already confirmed as 6,7-*syn*-7,8-*syn* from the known **237**. Because **217** is *meso*, the C3-C11, C4-C10 and C6-C8 relative configurations in **217** must be *syn*. Thus, the relative configuration of **217** was assigned as 3,4-*anti*-4,6-*syn*-6,7-*syn*-7,8-*syn*-8,10-*syn*-10,11-*anti*.

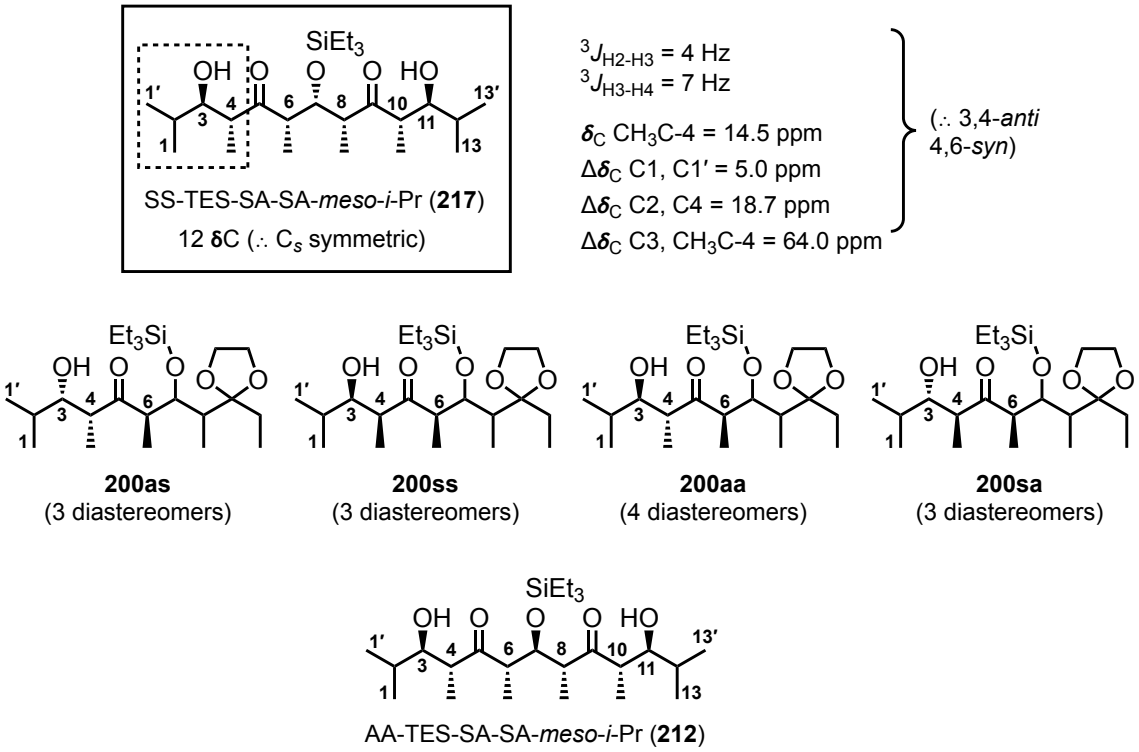


Figure 2-18: Assignment of the relative configuration of **217** by NMR comparison with the known compounds.

Table 2-19: Comparison of the selected NMR data of **217** with those of the known **212** and **200**.

adduct	$^3J_{H2\text{-}H3}$ (Hz)	$^3J_{H3\text{-}H4}$ (Hz)	$\Delta\delta_C$ (C1,C1′)	$\Delta\delta_C$ (C2,C4)	$\Delta\delta_C$ (C3,CH_3C-4)	δ_C CH_3C-4
200as	8.8	1.9	0.6	15.8	68.2	8.5
200ss	9.4	1.4	1.0	16.7	67.1	9.0
200aa	5	7	4.2	17.8	64.6	14.3
200sa	3.9	7.9	5.3	19.7	63.6	14.3
212	3.5	7	5.6	19.3	64.0	14.2
217	4.0	7	5.0	18.7	64.0	14.5

Chiral-bisaldol 213:

The bisaldol **213** is asymmetric as indicated by the presence of 21 resonances in the ^{13}C NMR spectrum. The ^1H NMR spectra of **213** can be divided in to four distinct 'spin systems' from

analysis of its two-dimensional HH COSY NMR spectrum. The Et_3Si proton spin system is unique and was readily assigned in the COSY spectrum; the ^{13}C chemical shifts of attached carbon atoms were identified based on the relevant $^1J_{CH}$ correlations observed in the HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in this spin system.

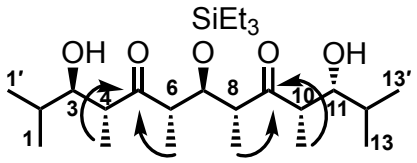


Figure 2-19: Key HMBC correlations (H→C) in bisaldol **213**.

Comparison of the NMR data for the known 13 diastereomers of **200**, **212** and **213** allowed assignment of the structure of **213** (Figure 2-20). To simplify the assignment, each spin system was analyzed and compared individually with the known compounds. The carbinol proton signals for "spin systems" 'A' and 'B' (i.e., HC-3 and HC-11) are readily differentiated by the $^3J_{HH}$ correlations to the OH protons and two adjacent methine groups (i.e., HC-2, HC-4 and HC-10, HC-12). By analysis of the HH COSY spectrum and using the assigned HC-3 and HC-11 as 'anchors' all the hydrogens in the spin systems A and B (i.e, HC-1, HC-1′, HC-2, HC-4, H_3CC-4 and H_3CC-10, HC-10, HC-12, HC-13′, HC-13) were assigned. The coupling constants $^3J_{H2\text{-}H3}$ (3.5 Hz) and $^3J_{H3\text{-}H4}$ (7 Hz), the ^{13}C chemical shift of CH_3C-4 ($\boldsymbol{\delta}_C$ 14.2), and the differences in the ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C1, C1′] = 5.6; $\Delta\boldsymbol{\delta}_C$ [C2, C4] = 19.4; $\Delta\boldsymbol{\delta}_C$ [C3, CH_3C-4] = 63.9) for the "spin system-A" of **213** closely match those of the known adducts **212** and **200sa** suggesting that the relative configuration of the "spin system-A" in **213** is 3,4-*anti*-4,6-*syn* (Table 2-20). Similarly, the coupling constants $^3J_{H11\text{-}H12}$ (9.5 Hz) and $^3J_{H10\text{-}H11}$ (1.5 Hz), the ^{13}C chemical shift of CH_3C-10 ($\boldsymbol{\delta}_C$ 9.2), and the differences in ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C13, C13′] = 1.0; $\Delta\boldsymbol{\delta}_C$ [C10, C12] = 16.7; $\Delta\boldsymbol{\delta}_C$ [C11, CH_3C-10] = 66.7) for "spin system-B" of **213** closely match those of the known

adducts **223** and **200ss** suggesting the relative configuration of the "spin system-B" in **213** is 8,10-*syn*-10,11-*syn* (Table 2-21). By analysis of the HMBC spectrum, the $^{2}J_{C5\text{-}HC4}$, $^{3}J_{C5\text{-}CH3C4}$, $^{2}J_{C9\text{-}HC10}$ and $^{3}J_{C9\text{-}CH3C10}$ correlations allowed assignment of the carbonyls at C5 and C9. Knowing the chemical shifts for C5 and C9, the HC-6, H_3CC-6 and HC-8, H_3CC-8 protons were assigned from the $^{2}J_{C5\text{-}HC6}$, $^{3}J_{C5\text{-}CH3C6}$ and the $^{2}J_{C9\text{-}HC8}$, $^{3}J_{C9\text{-}CH3C8}$ correlations, respectively, observed in the HMBC spectrum (Figure 2-19). By analysis of the HH COSY spectrum and using the assigned HC-6 and HC-8 as 'anchors' all the hydrogens in the spin system (i.e, H_3CC-6, HC-7 and H_3CC-8) were assigned. The relative configurations at C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known **212**. Thus, the relative configuration of **213** was assigned as 3,4-*anti*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*syn*-10,11-*syn*.

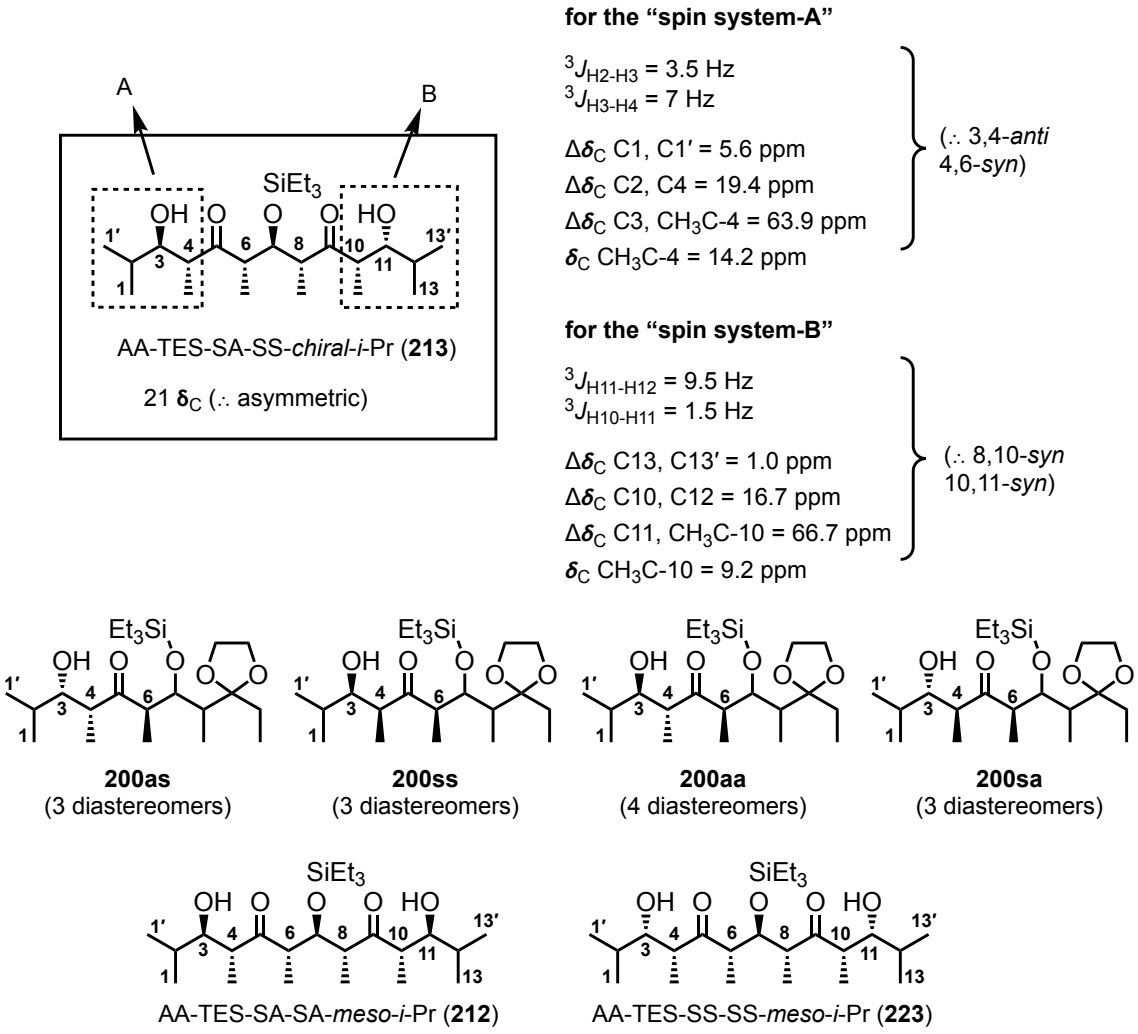


Figure 2-20: Structure assignment of **213** by NMR comparison with the known compounds.

Table 2-20: Comparison of the selected NMR data of "spin system-A" in **213** with those of the known **212** and **200**.

adduct	$^3J_{H2-H3}$ (Hz)	$^3J_{H3-H4}$ (Hz)	Δδ_C (C1,C1′)	Δδ_C (C2,C4)	Δδ_C (C3,CH_3C-4)	δ_C CH_3C-4
200as	8.8	1.9	0.6	15.8	68.2	8.5
200ss	9.4	1.4	1.0	16.7	67.1	9.0
200aa	5	7	4.2	17.8	64.6	14.3
200sa	3.9	7.9	5.3	19.7	63.6	14.3
212	3.5	7	5.6	19.3	64.0	14.2
213	3.5	7	5.6	19.4	63.9	14.2

Table 2-21: Comparison of the selected NMR data of "spin system-B" in **213** with those of the known **223** and **200**.

adduct	$^3J_{H2\text{-}H3}$ (Hz) ($^3J_{H11\text{-}H12}$)	$^3J_{H3\text{-}H4}$ (Hz) ($J_{H10\text{-}H11}$)	$\delta_{C1} - \delta_{C1'}$ ($\delta_{C13} - \delta_{C13'}$)	$\delta_{C2} - \delta_{C4}$ ($\delta_{C10} - \delta_{C12}$)	$\delta_{C3} - \delta_{CH3C4}$ ($\delta_{C11} - \delta_{CH3C10}$)	δ_C CH_3C-4 (δ_C CH_3C-10)
200as	8.8	1.9	0.6	15.8	68.2	8.5
200aa	5	7	4.2	17.8	64.6	14.3
200sa	3.9	7.9	5.3	19.7	63.6	14.3
200ss	9.4	1.4	1.0	16.7	67.1	9.0
223	9.5	1.5	1.0	16.7	66.7	9.2
213	(9.5)	(1.5)	(1.0)	(16.7)	(66.7)	(9.2)

***Meso*-bisaldol 209:**

The adduct **209** is C_s-symmetric as indicated by the presence of 12 resonances in the ^{13}C NMR spectrum (Figure 2-21). NMR spectra of **209** was assigned by following the identical procedure used for **214**.

Assignment of the relative configuration of 209:

Similar to the assignment of **214** and **217**, comparison of the coupling constants ($^3J_{H2\text{-}H3}$, $^3J_{H3\text{-}H4}$), ^{13}C chemical shifts (δ_C CH_3C-4), difference in ^{13}C chemical shifts ($\Delta\delta_C$ [C1, C1′, $\Delta\delta_C$ [C2, C4] and $\Delta\delta_C$ [C3, CH_3C-4]) values between the known 16 diastereomers of **199**, **212** and **209** allowed assignment of the relative configuration at C3-C4 and C4-C6 in **209** (for detailed discussion, refer to the assignment of **214**) (Figure 2-21). The bisaldol **209** was obtained from similar reaction conditions as **212** (i.e., from (*E,E*)-bis enolborinate **215** with ^{i}PrCHO), suggesting the adduct **209** has same C4-C6 relative configuration as **212**. The coupling constants $^3J_{H2\text{-}H3}$ (4.0 Hz) and $^3J_{H3\text{-}H4}$ (7.5 Hz), the ^{13}C chemical shift of CH_3C-4 (δ_C 14.4), and the difference in the ^{13}C chemical shifts ($\Delta\delta_C$ [C1, C1′] = 5.0; $\Delta\delta_C$ [C2, C4] = 19.4; $\Delta\delta_C$ [C3, CH_3C-4] = 63.9) for **209** are

consistent with the observed trends from the database and with those of the known adducts **212** and **199sa** suggesting the relative configuration of **209** is 3,4-*anti*-4,6-*syn* (Table 2-22). The relative configurations of C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known **212**. Because **209** is *meso*, the C3-C11, C4-C10 and C6-C8 relative configurations in **209** must be *syn*. Thus, the relative configuration of **209** was assigned as 3,4-*anti*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*syn*-10,11-*anti*.

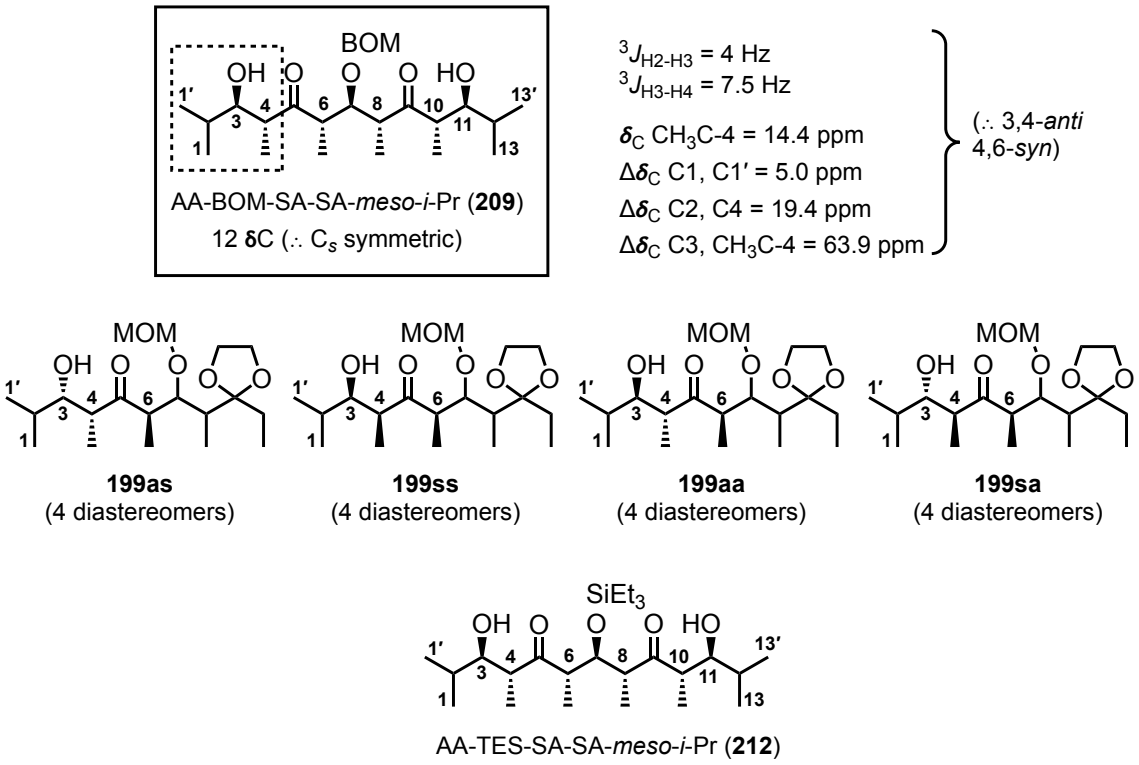


Figure 2-21: Assignment of the relative configuration of **209** by NMR comparison with the known compounds.

Table 2-22: Comparison of the selected NMR data of **209** with those of the known **212** and **199**.

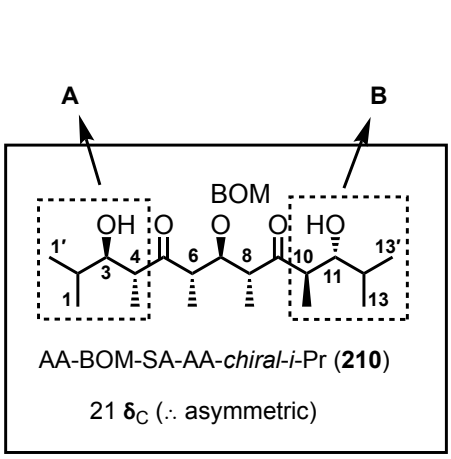
adduct	$^3J_{H2\text{-}H3\ (Hz)}$	$^3J_{H3\text{-}H4\ (Hz)}$	$\Delta\boldsymbol{\delta}_C$ (C1,C1′)	$\Delta\boldsymbol{\delta}_C$ (C2,C4)	$\Delta\boldsymbol{\delta}_C$ (C3,CH_3C-4)	$\boldsymbol{\delta}_C$ CH_3C-4
199as	8.9	2.1	0.53	16.3	68.3	8.5
199ss	9.4	1.4	1.0	17.0	67.3	8.6
199aa	4.7	6.9	4.6	18.3	64.5	14.0
199sa	3.5	8.4	5.6	20.7	63.0	14.2
212	3.5	7	5.6	19.3	64.0	14.2
209	4.0	7.5	5.0	19.4	63.9	14.4

Chiral bisaldol 210:

The bisaldol **210** is asymmetric as indicated by the presence of 21 resonances in the ^{13}C NMR spectrum. The ^1H NMR spectra of **210** can be divided in to four distinct 'spin systems' from analysis of its two-dimensional HH COSY NMR spectrum. The BOM-proton spin system is unique and was readily assigned in the COSY spectrum; the ^{13}C chemical shifts of attached carbon atoms were identified based on the relevant $^1J_{CH}$ correlations observed in the HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in this spin system.

Comparison of the NMR data for the known 16 diastereomers of **199**, **212** and **210** allowed assignment of the structure of **219** (Figure 2-22). To simplify the assignment, each spin system was analyzed and compared individually with the known compounds. The carbinol proton signals for "spin systems" 'A' and 'B' (i.e., HC-3 and HC-11) are readily differentiated by the $^3J_{HH}$ correlations to the OH protons and two adjacent methine groups (i.e., HC-2, HC-4 and HC-10, HC-12). By analysis of the HH COSY spectrum and using the assigned HC-3 and HC-11 as 'anchors' all the hydrogens in the spin systems A and B (i.e, HC-1, HC-1′, HC-2, HC-4, H_3CC-4 and H_3CC-10, HC-10, HC-12, HC-13′, HC-13) were assigned. The coupling constants $^3J_{H2\text{-}H3}$ (4 Hz) and $^3J_{H3\text{-}H4}$ (5 Hz), the ^{13}C chemical shift of CH_3C-4 ($\boldsymbol{\delta}_C$ 14.4), and the differences in the ^{13}C

chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C1, C1′] = 5.1; $\Delta\boldsymbol{\delta}_C$ [C2, C4] = 19.4; $\Delta\boldsymbol{\delta}_C$ [C3, CH_3C-4] = 64.0) for the "spin system-A" of **210** closely match those of the known adducts **212**, **199sa** and **209** suggesting that the relative configuration of the "spin system-A" in **210** is 3,4-*anti*-4,6-*syn* (Table 2-23). Similarly, the coupling constants $^3J_{H11\text{-}H12}$ (4 Hz) and $^3J_{H10\text{-}H11}$ (4.5 Hz), the ^{13}C chemical shift of CH_3C-10 ($\boldsymbol{\delta}_C$ 14.1), and the differences in ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C13, C13′] = 4.9; $\Delta\boldsymbol{\delta}_C$ [C10, C12] = 18.0; $\Delta\boldsymbol{\delta}_C$ [C11, CH_3C-10] = 64.6) for "spin system-B" of **210** closely match those of the known adduct **199aa** suggesting the relative configuration of the "spin system-B" in **210** is 8,10-*syn*-10,11-*syn* (Table 2-24). By analysis of the HH COSY spectrum and using the assigned HC-6 and HC-8 as 'anchors' all the hydrogens in the spin system (i.e, H_3CC-6, HC-7 and H_3CC-8) were assigned. The relative configurations at C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known **212**. Thus, the relative configuration of **210** was assigned as 3,4-*anti*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*anti*-10,11-*anti*.



for the "spin system-A"

$^3J_{H2\text{-}H3}$ = 4 Hz
$^3J_{H3\text{-}H4}$ = 5 Hz

$\Delta\delta_C$ C1, C1′ = 5.1 ppm
$\Delta\delta_C$ C2, C4 = 19.4 ppm
$\Delta\delta_C$ C3, CH_3C-4 = 64.0 ppm
δ_C CH_3C-4 = 14.4 ppm

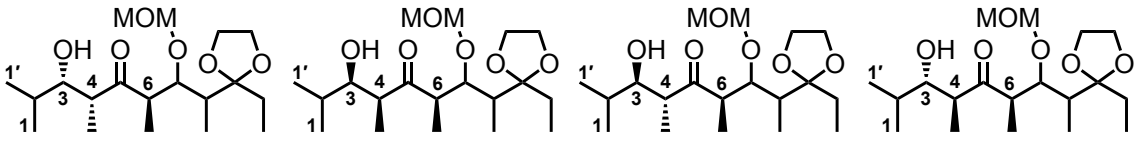
(∴ 3,4-*anti* 4,6-*syn*)

for the "spin system-B"

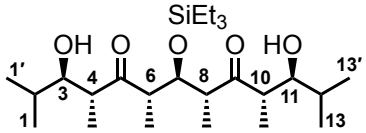
$^3J_{H11\text{-}H12}$ = 4 Hz
$^3J_{H10\text{-}H11}$ = 4.5 Hz

$\Delta\delta_C$ C13, C13′ = 4.9 ppm
$\Delta\delta_C$ C10, C12 = 18.0 ppm
$\Delta\delta_C$ C11, CH_3C-10 = 64.6 ppm
δ_C CH_3C-10 = 14.1 ppm

(∴ 8,10-*anti* 10,11-*anti*)



199as (4 diastereomers) **199ss** (4 diastereomers) **199aa** (4 diastereomers) **199sa** (4 diastereomers)



AA-TES-SA-SA-*meso-i*-Pr (**212**)

Figure 2-22: Structure assignment of **210** by NMR comparison with the known compounds.

Table 2-23: Comparison of the selected NMR data of "spin system-A" in **210** with those of the known **212** and **199**.

adduct	$^3J_{H2\text{-}H3\ (Hz)}$	$^3J_{H3\text{-}H4\ (Hz)}$	$\Delta\delta_C$ (C1,C1′)	$\Delta\delta_C$ (C2,C4)	$\Delta\delta_C$ (C3,CH_3C-4)	δ_C CH_3C-4
199as	8.9	2.1	0.53	16.3	68.3	8.5
199ss	9.4	1.4	1.0	17.0	67.3	8.6
199aa	4.7	6.9	4.6	18.3	64.5	14.0
199sa	3.5	8.4	5.6	20.7	63.0	14.2
212	3.5	7	5.6	19.3	64.0	14.2
209	4.0	7.5	5.0	19.4	63.9	14.4
210	4.0	5.0	5.1	19.4	64.0	14.4

Table 2-24: Comparison of the selected NMR data of "spin system-B" in **210** with those of the known **199**.

adduct	$^3J_{H2\text{-}H3\ (Hz)}$	$^3J_{H3\text{-}H4\ (Hz)}$	$\Delta\delta_C$ (C1,C1′)	$\Delta\delta_C$ (C2,C4)	$\Delta\delta_C$ (C3,CH_3C-4)	δ_C CH_3C-4
199as	8.9	2.1	0.53	16.3	68.3	8.5
199ss	9.4	1.4	1.0	17.0	67.3	8.6
199sa	3.5	8.4	5.6	20.7	63.0	14.2
199aa	4.7	6.9	4.6	18.3	64.5	14.0
210	4.0	4.5	4.9	18.0	64.6	14.1

Chiral-bisaldol 240:

The bisaldol **20** is asymmetric as indicated by the presence of 25 resonances in the ^{13}C NMR spectrum. The ^1H NMR spectra of **240** can be divided in to four distinct 'spin systems' from analysis of its two-dimensional HH COSY NMR spectrum. The Et_3Si and H_2C2'-H_2C3' proton spin systems are unique and were readily assigned in the COSY spectrum; the ^{13}C chemical shifts of attached carbon atoms were identified based on the relevant $^1J_{CH}$ correlations observed in the

HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in this spin system.

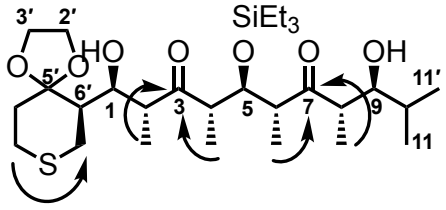


Figure 2-23: Key HMBC correlations (H→C) in bisaldol **240**.

Comparison of the NMR data of the database (diastereomers of **200** and **283**), **212**, **230** and **240** allowed assignment of the structure of **240** (Figure 2-24, Tables 2-25 and 2-26). To simplify the assignment, each spin system was analyzed and compared individually with the known compounds. The carbinol proton signals for "spin systems" 'A' and 'B' (i.e., HC-1 and HC-9) are readily differentiated by the $^{3}J_{HH}$ correlations to the OH protons and two adjacent methine groups (i.e., HC-2, HC-6′ and HC-8, HC-10). By analysis of the HH COSY spectrum and using the assigned HC-1 and HC-9 as 'anchors' all the hydrogens in the spin systems A and B (i.e, HC-6′, HC-7′, HC-2, H_3CC-2 and HC-8, HC-10, H_3CC-8, HC-11, HC-11′) were assigned. The coupling constants $^{3}J_{H6'\text{-}H1}$ (<1 Hz) and $^{3}J_{H1\text{-}H2}$ (9.5 Hz), the ^{13}C chemical shifts of C6′ ($\boldsymbol{\delta}_C$ = 46.4 ppm), , C7′ ($\boldsymbol{\delta}_C$ = 25.8 ppm), C1 ($\boldsymbol{\delta}_C$ = 71.7 ppm), C2 ($\boldsymbol{\delta}_C$ = 46.6 ppm), CH_3C-2 ($\boldsymbol{\delta}_C$ = 14.3 ppm), the ^{1}H chemical shift of CH_3C-2 ($\boldsymbol{\delta}_H$ = 0.96 ppm) for the "spin system-A" of **240** closely match those of the known adducts **230** and **283as** suggesting that the relative configuration of the "spin system-A" in **240** is 1,6′-*syn*-1,2-*anti* (Table 2-25). Similarly, the coupling constants $^{3}J_{H9\text{-}H10}$ (3.0 Hz) and $^{3}J_{H8\text{-}H9}$ (8.5 Hz), the ^{13}C chemical shift of CH_3C-8 ($_C$ 13.6), and the differences in the ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C11, C11′] = 5.95; $\Delta\boldsymbol{\delta}_C$ [C8, C10] = 20.4; $\Delta\boldsymbol{\delta}_C$ [C9, CH_3C-8] = 64.8) for the "spin system-B" of **240** closely match those of the known adducts **212** and **200sa** suggesting that the

relative configuration of the "spin system-B" in **240** is 6,8-*syn*-8,9-*anti* (Table 2-26). By analysis of the HMBC spectrum, the $^{2}J_{C3\text{-}HC2}$, $^{3}J_{C3\text{-}CH3C2}$, $^{2}J_{C7\text{-}HC8}$ and $^{3}J_{C7\text{-}CH3C8}$ correlations allowed assignment of the carbonyls at C3 and C7 (Figure 2-23). Knowing the chemical shifts for C3 and C7, the HC-4, H_3CC-4 and HC-6, H_3CC-6 were assigned from the $^{2}J_{C3\text{-}HC4}$, $^{3}J_{C3\text{-}CH3C4}$ and the $^{2}J_{C7\text{-}HC6}$, $^{3}J_{C7\text{-}CH3C6}$ correlations, respectively, observed in the HMBC spectrum. By analysis of the HH COSY spectrum and using the assigned HC-4 and HC-6 as 'anchors' all the hydrogens in the spin system (i.e, H_3CC-4, HC-5 and H_3CC-6) were assigned. The methylene carbon C-9′ was assigned based on $^{3}J_{C9\text{-}HC7'}$ correlation, observed in the HMBC spectrum. The H_2C-9′ protons were assigned by analysis of $^{1}J_{CH}$ correlation spectrum (gHSQC); thus H_2C-10′ was assigned by $^{3}J_{H9'\text{-}H10'}$ correlation observed in the COSY spectrum. The quaternary carbon C5′ is unique and was readily distinguished in the ^{13}C NMR spectrum on the basis of the chemical shift ($\boldsymbol{\delta}_C$ C5′ = 110.3). The relative configuration at C2-C4 was assigned as 2,4-*syn* based on analogy. The relative configurations at C4-C5 and C5-C6 should be unchanged from the starting diketone **215** and were already confirmed as 4,5-*anti*-5,6-*anti* from the known **212** and **230**. Thus, the relative configuration of **240** was assigned as 1,6′-*syn*-1,2-*anti*-2,4-*syn*-4,5-*anti*-5,6-*anti*-6,8-*syn*-8,9-*anti*.

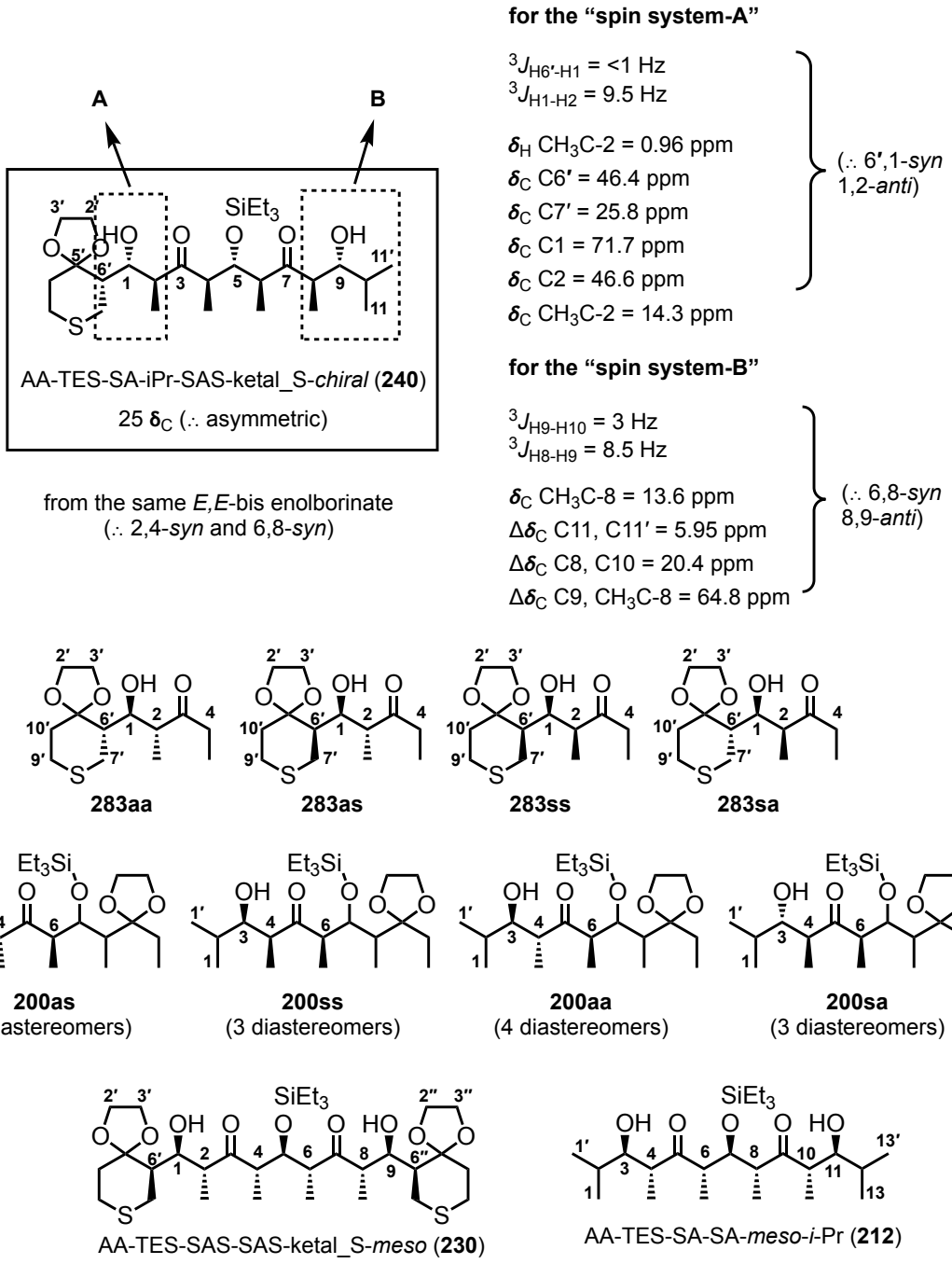


Figure 2-24: Assignment of the relative configuration of **240** by NMR comparison with the known compounds.

Table 2-25: Comparison of the selected NMR data of "spin system-A" in **240** with those of the known **230** and **283**.

adduct	$^3J_{H6'\text{-}H1}$ (Hz)	$^3J_{H1\text{-}H2}$ (Hz)	δ_H CH_3C-2	δ_C C-6′	δ_C C-7′	δ_C C-1	δ_C C-2	δ_C CH_3C-2
283aa	7	4.5	1.21	46.5	30.0	74.6	49.4	14.2
283ss	3	7.5	1.19	47.3	26.9	69.4	49.7	13.3
283sa	8.5	2	1.10	46.2	29.4	70.9	48.0	8.1
283as	2	9	0.97	46.3	26.0	71.8	47.9	13.9
230	<1	9.5	0.96	46.6	25.8	71.7	47.2	14.1
240	<1	9.5	0.96	46.4	25.8	71.7	46.6	14.3

Table 2-26: Comparison of the selected NMR data of "spin system-B" in **240** with those of the known **212** and **200**.

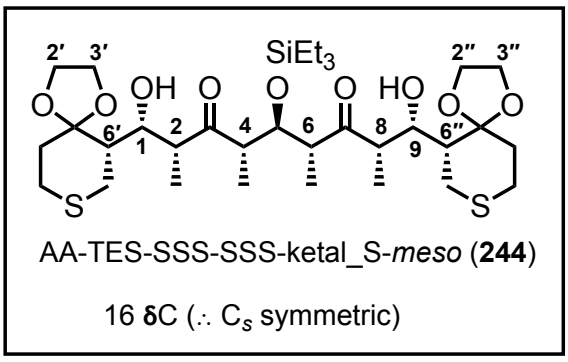
adduct	$^3J_{H2\text{-}H3}$ (Hz) ($^3J_{H9\text{-}H10}$)	$^3J_{H3\text{-}H4}$ (Hz) ($^3J_{H8\text{-}H9}$)	$\delta_{C1}-\delta_{C1'}$ ($\delta_{C11}-\delta_{C11'}$)	$\delta_{C2}-\delta_{C4}$ ($\delta_{C8}-\delta_{C10}$)	$\delta_{C3}-\delta_{CH3C4}$ ($\delta_{C9}-\delta_{CH3C8}$)	δ_C CH_3C-4 (δ_C CH_3C-8)
200as	8.8	1.9	0.6	15.8	68.2	8.5
200ss	9.4	1.4	1.0	16.7	67.1	9.0
200aa	5	7	4.2	17.8	64.6	14.3
200sa	3.9	7.9	5.3	19.7	63.6	14.3
212	3.5	7	5.6	19.3	64.0	14.2
240	(3.0)	(8.5)	(5.95)	(20.4)	(64.8)	(13.6)

***Meso* bisaldol 244:**

The bisaldol **244** is C_s-symmetric as indicated by the presence of only 16 resonances in the ^{13}C NMR spectrum (Figure 2-25). NMR spectra of **244** was assigned by following the identical procedure used for **231**.

Assignment of the relative configuration of 244:

Similar to the assignment of **231**, comparison of the coupling constants $^{3}J_{H6'\text{-}H1}$, $^{3}J_{H1\text{-}H2}$, ^{13}C chemical shifts of C1, CH_3C-2 and ^{1}H chemical shifts of H_3CC-2 values of the known adducts (**283**) and **244** allowed assignment of the relative configuration at C6′-C1 and C1-C2 in **244** (for the detailed discussion, refer to the assignment of **231**) (Figure 2-25, Table 2-27). The coupling constants $^{3}J_{H6'\text{-}H1}$ (3.5 Hz) and $^{3}J_{H1\text{-}H2}$ (4.5 Hz), the ^{13}C chemical shifts of C1 ($\boldsymbol{\delta}_C$ 67.9), CH_3C-2 ($\boldsymbol{\delta}_C$ 11.5), C6′ ($\boldsymbol{\delta}_C$ 46.8) and the ^{1}H chemical shift of H_3CC-2 ($\boldsymbol{\delta}_H$ 1.18) for **244** are consistent with those of the known adducts **283ss** suggesting the relative configuration of **244** is 1,2-*syn*-6′,1-*syn* (Table 2-27). The C2-C4 relative configuration is assumed as '2,4-*syn'* by analogy to the known adduct **223** as both the aldols (**223** and **244**) are obtained from (*Z,Z*)-bis enolborinate **222** reaction conditions. The relative configurations of C4-C5 and C5-C6 should be unchanged from the starting diketone **212** and were already confirmed as 4,5-*anti*-5,6-*anti* from the known structure of **223**. Because **244** is *meso*, the C6′-C6″, C1-C9, C2-C8 and C4-C6 relative configurations in **244** must be *syn*. Thus, the relative configuration of **244** was assigned as 6′,1-*syn*-1,2-*anti*-2,4-*syn*-4,5-*anti*-5,6-*anti*-6,8-*syn*-8,9-*syn*-9,6″-*syn*.

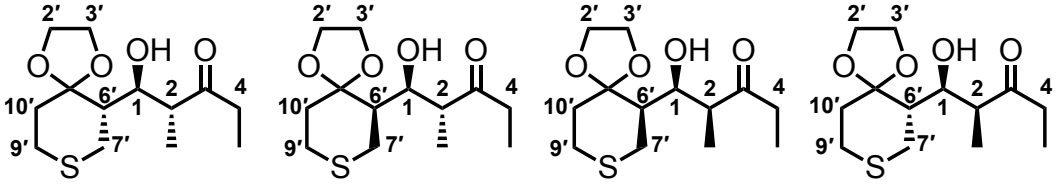


from the same (*Z,Z*)-bis enolborinate
(∴ 2,4-*syn*)

$^3J_{H6'-H1}$ = 3.5 Hz
δ_C C1 = 67.9 ppm
} (∴ 6′,1-*syn*)

$^3J_{H1-H2}$ = 4.5 Hz
δ_C CH_3C-2 = 11.5 ppm
} (∴ 1,2-*syn*)

δ_H H_3CC-2= 1.18 ppm
δ_C C6′ = 46.8 ppm
δ_C C1 = 67.9 ppm
δ_C C7′ = 28.1 ppm
} (∴ 1,2-*anti*-6′,1-*syn*)



283aa **283as** **283ss** **283sa**

Figure 2-25: Assignment of the relative configuration of **244** by NMR comparison with the known compounds.

Table 2-27: Comparison of the selected NMR data of **244** with those of the known adducts **283**.

adduct	$^3J_{H6'-H1}$ (Hz)	$^3J_{H1-H2}$ (Hz)	δ_H CH_3C-2	δ_C C-6′	δ_C C-7′	δ_C C-1	δ_C C-2	δ_C CH_3C-2
283aa	7	4.5	1.21	46.5	30.0	74.6	49.4	14.2
283sa	8.5	2	1.10	46.2	29.4	70.9	48.0	8.1
283as	2	9	0.97	46.3	26.0	71.8	47.9	13.9
283ss	3	7.5	1.19	47.3	26.9	69.4	49.7	13.3
244	3.5	4.5	1.18	46.8	28.1	67.9	49.0	11.5

Monoaldol 247:

NMR spectra of **247** was assigned by following the identical procedure used for **231**.

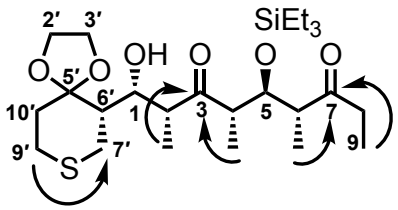


Figure 2-26: Key HMBC correlations (H→C) in monoaldol **247**.

Assignment of the relative configuration of 247:

NMR analysis of the known[3] four diastereomers of **283** revealed consistent trends that allowed assignment of the relative configuration of **247** (Figure 2-27 & Table 2-28). The 6′,1-*syn* diastereomers (i.e., **283as** and **283ss**) consistently had lower $^{3}J_{H6'\text{-}H1}$ (2-3 Hz) and ^{13}C chemical shifts for C7′ ($\boldsymbol{\delta}_C$ 26-26.9) and higher $^{3}J_{H1\text{-}H2}$ (7.5-9 Hz) values compared to those of the 6′,1-*anti* diastereomers (**283aa** and **283sa**). Similarly, the 1,2-*anti* diastereomers (**283as** and **283aa**) consistently had higher ^{13}C chemical shifts for C1 ($\boldsymbol{\delta}_C$ 71.8-74.6) and CH_3C-2 ($\boldsymbol{\delta}_C$ 13.9-14.2) compared to those of the 1,2-*syn* diastereomers (**283ss** and **283sa**). The diastereomer **283sa** can be easily distinguishable by its characteristic lower ^{13}C chemical shift for CH_3C-2 ($\boldsymbol{\delta}_C$ 8.1) compared to the other three diastereomers ($\boldsymbol{\delta}_C$ 13.3-14.2).

The ^{1}H and ^{13}C NMR data of the *meso*-bisaldol **244** closely matches those of **283ss** suggesting the trends from database are consistent and are applicable to the assignment of the relative configurations in similar structures (Figure 2-27 & Table 2-28). The mono aldol **247** was obtained from an incomplete reaction of (*Z,Z*)-bis enolborinate **222** with aldehyde **109** suggesting the adduct **247** has the same relative configuration as **244** (arising from complete reaction of **222** with **109**). The ^{1}H and ^{13}C NMR data for **247** were compared with those of the known adducts **244** and **283ss** to assign the relative configuration of **247**. The coupling constants $^{3}J_{H6'\text{-}H1}$ (5 Hz; 6′,1-*syn*), $^{3}J_{H1\text{-}H2}$ (4.5 Hz; 1,2-*anti*), the ^{13}C chemical shifts of C7′ ($\boldsymbol{\delta}_C$ 28; 6′,1-*syn*), CH_3C-2 ($\boldsymbol{\delta}_C$ 11.9; 1,2-*syn*) and the ^{1}H chemical shift of H_3CC-2 ($\boldsymbol{\delta}_H$ 1.17; 6′,1-*syn*) for **247** are consistent with those

of the known adducts **244** and **283ss** suggesting the relative configuration of **247** is 1,2-*syn*-6′,1-*syn*. The C2-C4 relative configuration in **247** was assumed as 2,4-*syn* by analogy to the known adduct **244** as both the aldols (**244** and **247**) are obtained from reaction of (*Z,Z*)-bis enolborinate **222** with aldehyde **109**. The relative configurations of C4-C5 and C5-C6 should be unchanged from the starting diketone **202aa** and were already confirmed as 4,5-*anti*-5,6-*anti* from the X-ray structure of **230**. Thus, the relative configuration of **247** was assigned as 6′,1-*syn*,-1,2-*syn*-2,4-*syn*-4,5-*anti*-5,6-*anti*.

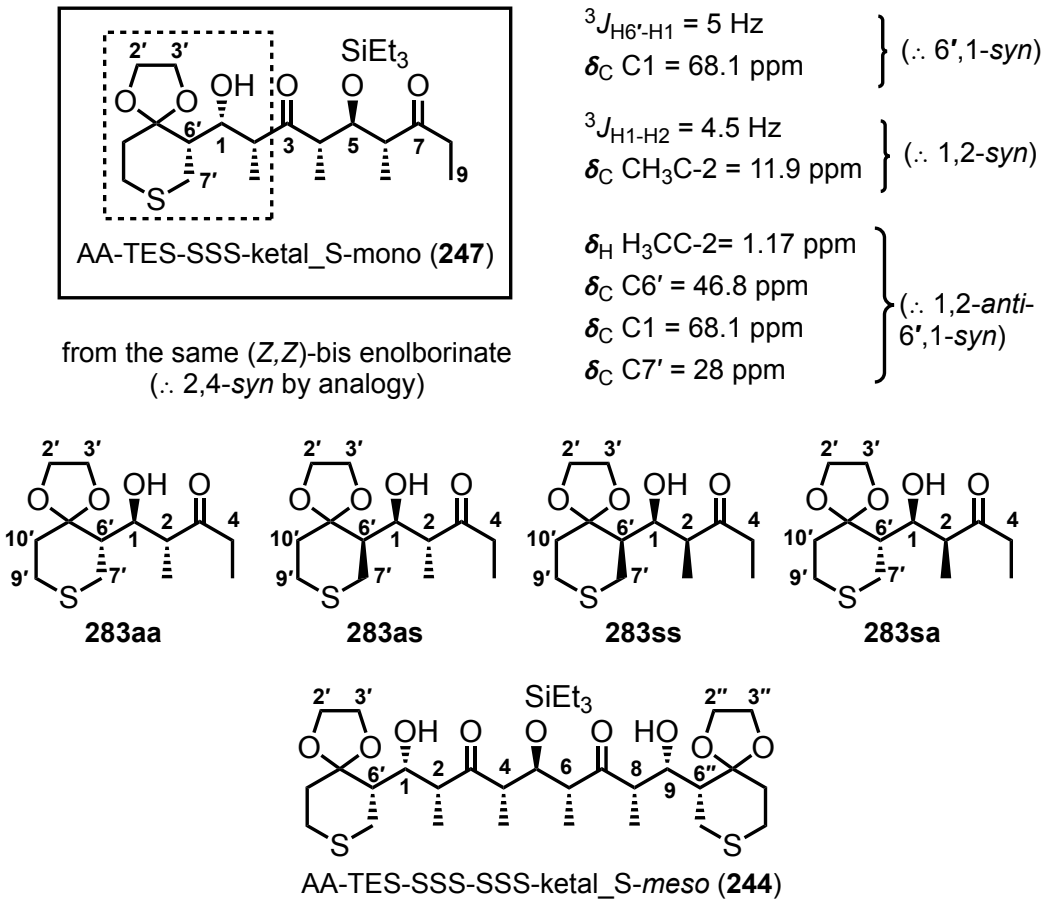


Figure 2-27: Assignment of the relative configuration of **247** by NMR comparison with the known compounds.

Table 2-28: Comparison of the selected NMR data of **247** with those of the known adducts **244** and **283**.

adduct	$^3J_{H6'-H1}$ (Hz)	$^3J_{H1-H2}$ (Hz)	δ_H CH_3C-2	δ_C C-6′	δ_C C-7′	δ_C C-1	δ_C C-2	δ_C CH_3C-2
283aa	7	4.5	1.21	46.5	30.0	74.6	49.4	14.2
283sa	8.5	2	1.10	46.2	29.4	70.9	48.0	8.1
283as	2	9	0.97	46.3	26.0	71.8	47.9	13.9
283ss	3	7.5	1.19	47.3	26.9	69.4	49.7	13.3
244	3.5	4.5	1.18	46.8	28.1	67.9	49.0	11.5
247	5	4.5	1.17	46.8	28	68.1	48.1	11.9

***Meso* bisaldol 245:**

The adduct **245** is C_s-symmetric as indicated by the presence of 16 resonances in the ^{13}C NMR spectrum (Figure 2-28). NMR spectra of **245** was assigned by following the identical procedure used for **233**.

Assignment of the relative configuration of 245:

Similar to the assignment of **233**, comparison of the coupling constants $^3J_{H2-H3}$, $^3J_{H3-H4}$, ^{13}C chemical shifts of C1, C2, C3, CH_3C-2′, CH_3CC-2′ and ^1H chemical shifts of H_3CC-4 values for the known adducts **130** and **245** allowed assignment of the relative configuration at C2-C3 and C3-C4 in **245** (for the detailed discussion, refer to the assignment of **233**) (Figure 2-28, Table 2-29). The coupling constants $^3J_{H2-H3}$ (3 Hz), $^3J_{H3-H4}$ (7 Hz), ^{13}C chemical shifts of C1 (δ_C 9.0), C2 (δ_C 40.4), C3 (δ_C 70.5), CH_3C-4 (δ_C 13.6), CH_2C-2′ (δ_C 27.5) and CH_3CC-2′ (δ_C 7.9) and ^1H chemical shifts of H_3CC-4 (δ_H 1.23) are consistent with those of the known adduct **130ss** suggesting the C2-C3 and C3-C4 relative configurations are 2,3-*syn*-3,4-*syn*. The C4-C6 relative configuration in **245** was assumed as 4,6-*syn* by analogy to the known adduct **223** as both the

aldols (**223** and **245**) were obtained from (*Z,Z*)-bis enolborinate **222** reaction conditions. The relative configurations at C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known structure of **223**. Because **245** is *meso*, the C2-C12, C3-C11, C4-C10 and C6-C8 relative configurations in **245** must be *syn*. Thus, the relative configuration of **245** was assigned as 2,3-*syn*-3,4-*syn*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*syn*-10,11-*syn*-11,12-*syn*.

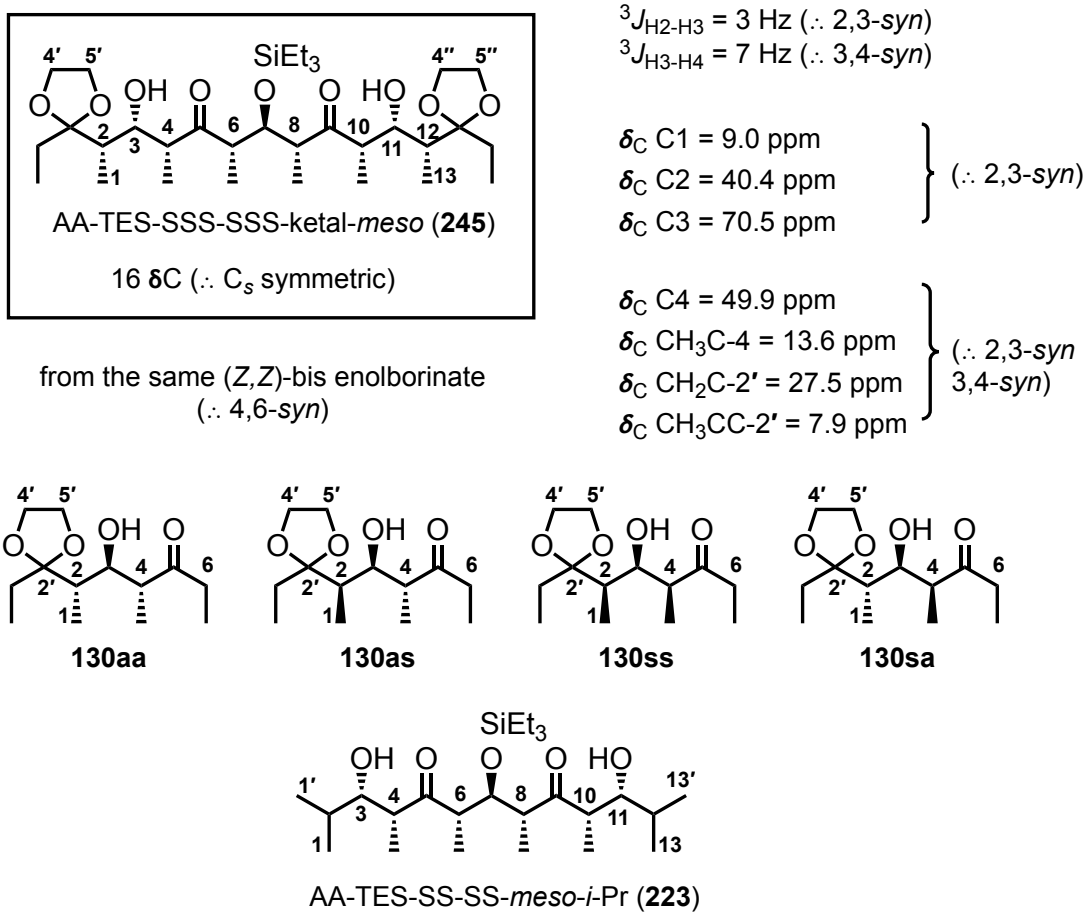


Figure 2-28: Assignment of the relative configuration of **245** by NMR comparison with the known compounds.

Table 2-29: Comparison of the selected NMR data of **245** with those of the known adducts **130**.

adduct	$^3J_{H2\text{-}H3}$ (Hz)	$^3J_{H3\text{-}H4}$ (Hz)	δH CH_3C-4	δ_C C-1	δ_C C-2	δ_C C-3	δ_C C-4	δ_C CH_3C-4	δ_C CH_2C-2′	δ_C CH_3C C-2′
130aa	8.5	3.5	1.24	13.1	42.0	76.1	49.7	14.5	26.0	7.1
130sa	9.5	2.5	1.06	12.8	41.4	73.0	49.1	8.0	25.7	7.0
130as	<1	9.5	0.94	6.9	38.5	73.4	48.7	13.7	28.2	8.3
130ss	1	9	1.21	7.4	39.9	71.6	50.2	14.9	28.1	8.2
245	3	7	1.23	9.0	40.4	70.5	49.9	13.6	27.5	7.9

A complementary correlation between **244** and **245** was obtained via desulfurization confirming both **244** and **245** have the same relative configuration (Figure 2-29).

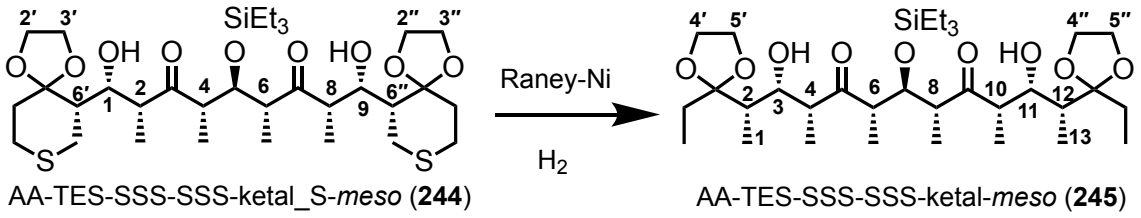


Figure 2-29: Desulfurization of **244** to **245**.

Chiral-bisaldol 234:

The bisaldol **234** is asymmetric as indicated by the presence of 29 resonances in the ^{13}C NMR spectrum (Figure 2-31). The ^1H NMR spectra of **234** can be divided in to eight distinct 'spin systems' from analysis of its two-dimensional HH COSY NMR spectrum. The Et_3Si proton spin system is unique and was readily assigned in the COSY spectrum; the ^{13}C chemical shifts of attached carbon atoms were identified based on the relevant $^1J_{CH}$ correlations observed in the HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in this spin system.

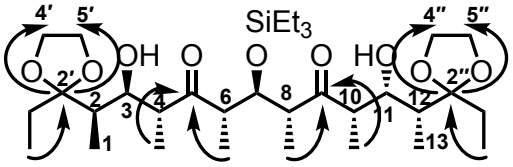
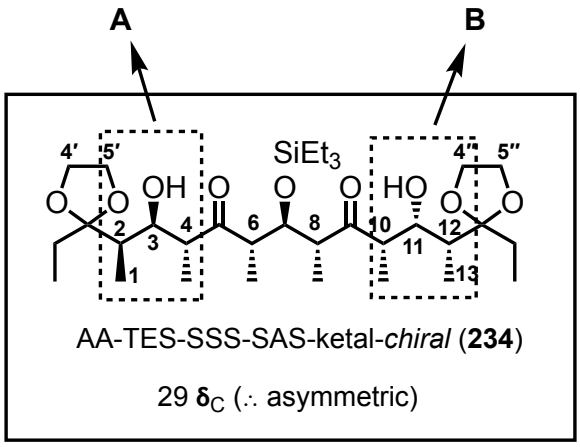


Figure 2-30: Key HMBC correlations (H→C) in bisaldol **234**.

Comparison of the NMR data for the known **130**, **232, 245** and **234** allowed assignment of the structure of **234** (Figure 2-31, Tables 2-30 and 2-31). To simplify the assignment, each spin system was analyzed and compared individually with the known compounds. The carbinol proton signals for "spin systems" 'A' and 'B' (i.e., HC-3 and HC-11) are readily differentiated by the $^{3}J_{HH}$ correlations to the OH protons and two adjacent methine groups (i.e., HC-2, HC-4 and HC-10, HC-12). By analysis of the HH COSY spectrum and using the assigned HC-3 and HC-11 as 'anchors' all the hydrogens in the spin systems A and B (i.e, HC-1, HC-2, HC-4, H_3CC-4 and H_3CC-10, HC-10, HC-12, HC-13) were assigned. The coupling constants $^{3}J_{H2\text{-}H3}$ (<1 Hz) and $^{3}J_{H3\text{-}H4}$ (10 Hz), the ^{13}C chemical shifts of C1 (δ_C 6.6), C2 (δ_C 38.7), C3 (δ_C 72.9), C4 (δ_C 48.4), CH_3C-4 (δ_C 13.8), CH_2C-2′ (δ_C 28.2), CH_3CC-2′ (δ_C 8.3) and the ^{1}H chemical shift of CH_3C-4 (δ_H 0.93) for the "spin system-A" of **234** closely match those of the known adducts **232** and **130as** suggesting that the relative configuration of the "spin system-A" in **234** is 2,3-*syn*-3,4-*anti*-4,6-*syn* (Table 2-30). Similarly, the coupling constants $^{3}J_{H11\text{-}H12}$ (3.0 Hz) and $^{3}J_{H10\text{-}H11}$ (7.0 Hz), the ^{13}C chemical shifts of C13 (δ_C 9.0), C12 (δ_C 40.6), C11 (δ_C 70.6), C10 (δ_C 49.8), CH_3C-10 (δ_C 13.5), CH_2C-2″ (δ_C 27.6), CH_3CC-2″ (δ_C 7.9) and the ^{1}H chemical shift of CH_3C-10 (δ_H 1.22) for "spin system-B" of **234** closely match those of the known adducts **245** and **130ss** suggesting the relative configuration of the "spin system-B" in **234** is 8,10-*syn*-10,11-*syn*-11,12-*syn* (Table 2-31). By analysis of the HMBC spectrum, the $^{2}J_{C5\text{-}HC4}$, $^{3}J_{C5\text{-}CH3C4}$, $^{2}J_{C9\text{-}HC10}$ and $^{3}J_{C9\text{-}CH3C10}$ correlations allowed assignment of the carbonyls at C5 and C9 (Figure 2-30). Knowing the chemical shifts for

C5 and C9, the HC-6, H_3CC-6 and HC-8, H_3CC-8 were assigned from the $^{2}J_{C5\text{-}HC6}$, $^{3}J_{C5\text{-}CH3C6}$ and the $^{2}J_{C9\text{-}HC8}$, $^{3}J_{C9\text{-}CH3C8}$ correlations, respectively, observed in the HMBC spectrum. By analysis of the HH COSY spectrum and using the assigned HC-6 and HC-8 as 'anchors' all the hydrogens in the spin system (i.e, H_3CC-6, HC-7 and H_3CC-8) were assigned. The quaternary carbons C2′ and C2″ are unique and were readily distinguished in the ^{13}C NMR spectrum on the basis of the chemical shifts ($\boldsymbol{\delta}_C$ 114.7, 114.5) and were assigned by the $^{3}J_{C2'\text{-}HC1}$ and the $^{3}J_{C2''\text{-}HC13}$ correlations, observed in the HMBC spectrum. The HC-4′/HC-5′ and HC-4″/HC-5″ protons are unique and were assigned by the $^{3}J_{C2'\text{-}HC4'/5'}$ and the $^{3}J_{C2''\text{-}HC4''/5''}$ correlations, observed in the HMBC spectrum. The ethyl protons CH_3CH_2-C2′ and CH_3CH_2-C2″ were assigned from the $^{2}J_{C2'\text{-}H2CC2'}$, $^{3}J_{C2'\text{-}H3CCC2'}$ and $^{2}J_{C2''\text{-}H2CC2''}$, $^{3}J_{C2''\text{-}H3CCC2''}$ correlations, respectively, observed in the HMBC spectrum. The relative configurations at C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known **232**. Thus, the relative configuration of **234** was assigned as 2,3-*syn*-3,4-*anti*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*syn*-10,11-*syn*-11,12-*syn*.



for the "spin system-A"

$^3J_{H2\text{-}H3}$ = <1 Hz (∴ 2,3-*syn*)
$^3J_{H3\text{-}H4}$ = 10 Hz (∴ 3,4-*anti*)

δ_H CH_3C-4 = 0.93 ppm
δ_C C1 = 6.6 ppm
δ_C C2 = 38.7 ppm
δ_C C3 = 72.9 ppm
δ_C CH_2C-2′ = 28.2 ppm
δ_C CH_3CC-2′ = 8.3 ppm
} (∴ 2,3-*syn*)

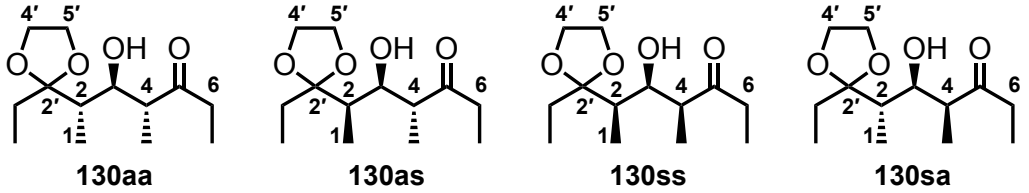
δ_C C4 = 48.4 ppm
δ_C CH_3C-4 = 13.8 ppm
} (∴ 3,4-*anti* and 2,3-*syn*)

for the "spin system-B"

$^3J_{H11\text{-}H12}$ = 3 Hz
$^3J_{H10\text{-}H11}$ = 7 Hz
} (∴11,12-*syn*)

δ_H CH_3C-10 = 1.22 ppm
δ_C C10 = 49.8 ppm
δ_C CH_3C-10 = 13.5 ppm
δ_C C13 = 9.0 ppm
δ_C C12 = 40.6 ppm
δ_C C11 = 70.6 ppm
δ_C CH_2C-2″ = 27.6 ppm
δ_C CH_3CC-2″ = 7.9 ppm
} (∴ 10,11-*syn* 11,12-*syn*)

from the same (*E,E*)-bis enolborinate conditions (∴ 4,6-*syn* and 8,10-*syn*)



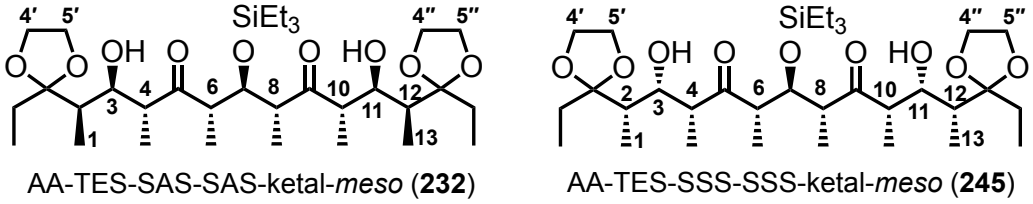


Figure 2-31: Structure assignment of **234** by NMR comparison with the known compounds.

Table 2-30: Comparison of the selected NMR data of "spin system-A" in **234** with those of the known **232** and **130**.

adduct	$^3J_{H2\text{-}H3}$ (Hz)	$^3J_{H3\text{-}H4}$ (Hz)	δH CH_3C-4	δ_C C-1	δ_C C-2	δ_C C-3	δ_C C-4	δ_C CH_3C-4	δ_C CH_2C-2′	δ_C CH_3C C-2′
130aa	8.5	3.5	1.24	13.1	42.0	76.1	49.7	14.5	26.0	7.1
130sa	9.5	2.5	1.06	12.8	41.4	73.0	49.1	8.0	25.7	7.0
130ss	1	9	1.21	7.4	39.9	71.6	50.2	14.9	28.1	8.2
130as	<1	9.5	0.94	6.9	38.5	73.4	48.7	13.7	28.2	8.3
232	<1	9.5	0.91	6.7	38.8	73.1	48.0	13.8	28.2	8.2
234	<1	10	0.93	6.6	38.7	72.9	48.4	13.8	28.2	8.3

Table 2-31: Comparison of the selected NMR data of "spin system-B" in **234** with those of the known **245** and **130**.

adduct	$^3J_{H2\text{-}H3}$ (Hz)	$^3J_{H3\text{-}H4}$ (Hz)	δH CH_3C-4	δ_C C-1	δ_C C-2	δ_C C-3	δ_C C-4	δ_C CH_3C-4	δ_C CH_2C-2′	δ_C CH_3C C-2′
130aa	8.5	3.5	1.24	13.1	42.0	76.1	49.7	14.5	26.0	7.1
130sa	9.5	2.5	1.06	12.8	41.4	73.0	49.1	8.0	25.7	7.0
130as	<1	9.5	0.94	6.9	38.5	73.4	48.7	13.7	28.2	8.3
130ss	1	9	1.21	7.4	39.9	71.6	50.2	14.9	28.1	8.2
245	3	7	1.23	9.0	40.4	70.5	49.9	13.6	27.5	7.9
234	3	7	1.22	9.0	40.6	70.6	49.8	13.5	27.6	7.9

Chiral-bisaldol 246:

The bisaldol **246** is asymmetric as indicated by the presence of 29 resonances in the ^{13}C NMR spectrum. The ^1H NMR spectra of **246** can be divided in to eight distinct 'spin systems' from analysis of its two-dimensional HH COSY NMR spectrum. The Et_3Si proton spin system is unique and was readily assigned in the COSY spectrum; the ^{13}C chemical shifts of attached carbon

atoms were identified based on the relevant $^{1}J_{CH}$ correlations observed in the HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in this spin system.

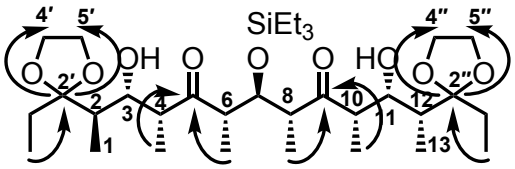
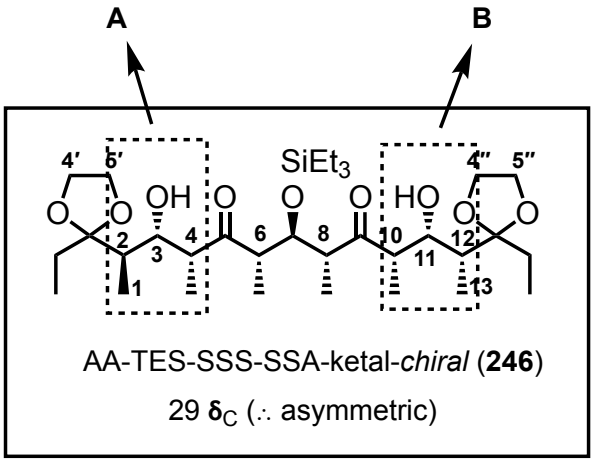


Figure 2-32: Key HMBC correlations (H→C) in bisaldol **246**.

Comparison of the NMR data between the known **130**, **245** and **246** allowed assignment of the structure of **246** (Figure 2-33). To simplify the assignment, each spin system was analyzed and compared individually with the known compounds. The carbinol proton signals for "spin systems" 'A' and 'B' (i.e., HC-3 and HC-11) are readily differentiated by the $^{3}J_{HH}$ correlation to the OH protons and two adjacent methine groups (i.e., HC-2, HC-4 and HC-10, HC-12). By analysis of the HH COSY spectrum and using the assigned HC-3 and HC-11 as 'anchors' all the hydrogens in the spin systems A and B (i.e, HC-1, HC-2, HC-4, H_3CC-4 and H_3CC-10, HC-10, HC-12, HC-13) were assigned. The coupling constants $^{3}J_{H2\text{-}H3}$ (9.5 Hz) and $^{3}J_{H3\text{-}H4}$ (<1 Hz), the ^{13}C chemical shifts of C1 ($\boldsymbol{\delta}_C$ 12.8), C2 ($\boldsymbol{\delta}_C$ 41.5), C3 ($\boldsymbol{\delta}_C$ 72.1), C4 ($\boldsymbol{\delta}_C$ 49.2), CH_3C-4 ($\boldsymbol{\delta}_C$ 8.1; '*key signal'*), CH_2C-2′ ($\boldsymbol{\delta}_C$ 25.9), CH_3CC-2′ ($\boldsymbol{\delta}_C$ 7.0) and the ^{1}H chemical shift of CH_3C-4 ($\boldsymbol{\delta}_H$ 1.15) for the "spin system-A" of **246** closely match those of the known adduct **130sa** suggesting that the relative configuration of the "spin system-A" in **246** is 2,3-*anti*-3,4-*syn*-4,6-*syn* (Table 2-32). Similarly, the coupling constant $^{3}J_{H10\text{-}H11}$ (7.0 Hz), the ^{13}C chemical shifts of C13 ($\boldsymbol{\delta}_C$ 8.7), C12 ($\boldsymbol{\delta}_C$ 40.1), C11 ($\boldsymbol{\delta}_C$ 70.8), C10 ($\boldsymbol{\delta}_C$ 48.5), CH_3C-10 ($\boldsymbol{\delta}_C$ 14.4), CH_2C-2″ ($\boldsymbol{\delta}_C$ 27.6), CH_3CC-2″ ($\boldsymbol{\delta}_C$ 7.9) and the ^{1}H chemical shift of CH_3C-10 ($\boldsymbol{\delta}_H$ 1.22) for "spin system-B" of **246** closely match those of the known adducts **245** and **130ss** suggesting the relative configuration of the "spin system-B" in **246** is 8,10-*syn*-10,11-*syn*-11,12-*syn* (Table 2-33). By analysis of the HMBC spectrum, the $^{2}J_{C5\text{-}HC4}$,

$^{3}J_{C5\text{-}CH3C4}$, $^{2}J_{C9\text{-}HC10}$ and $^{3}J_{C9\text{-}CH3C10}$ correlations allowed assignment of the carbonyls at C5 and C9 (Figure 2-32). Knowing the chemical shifts for C5 and C9, the HC-6, H_3CC-6 and HC-8, H_3CC-8 protons were assigned from the $^{2}J_{C5\text{-}HC6}$, $^{3}J_{C5\text{-}CH3C6}$ and the $^{2}J_{C9\text{-}HC8}$, $^{3}J_{C9\text{-}CH3C8}$ correlations, respectively, observed in the HMBC spectrum. By analysis of the HH COSY spectrum and using the assigned HC-6 and HC-8 as 'anchors' all the hydrogens in the spin system (i.e, H_3CC-6, HC-7 and H_3CC-8) were assigned. The quaternary carbons C2′ and C2″ are unique and were readily distinguished in the ^{13}C NMR spectrum on the basis of the chemical shifts ($\boldsymbol{\delta}_C$ 114.9, 114.5) and were assigned by the $^{3}J_{C2'\text{-}HC1}$ and the $^{3}J_{C2''\text{-}HC13}$ correlations, observed in the HMBC spectrum. The HC-4′/HC-5′ and HC-4″/HC-5″ protons are unique and were assigned by the $^{3}J_{C2'\text{-}HC4'/5'}$ and the $^{3}J_{C2''\text{-}H4C''/5''}$ correlations, observed in the HMBC spectrum. The ethyl protons H_2CC-2′-H_3CCC-2′ and H_2CC-2″- H_3CCC-2″ were assigned by $^{2}J_{C2'\text{-}H2CC2'}$, $^{3}J_{C2'\text{-}H3CCC2'}$ and $^{2}J_{C2''\text{-}H2CC2''}$, $^{3}J_{C2''\text{-}H3CCC2''}$ correlations, respectively, observed in the HMBC spectrum. The relative configurations at C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known **245**. Thus, the relative configuration of **246** was assigned as 2,3-*anti*-3,4-*syn*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*syn*-10,11-*syn*-11,12-*syn*.



for the "spin system-A"

$^3J_{H2\text{-}H3}$ = 9.5 Hz (∴ 2,3-*anti*)
$^3J_{H3\text{-}H4}$ = <1 Hz (∴ 3,4-*syn*)

δ_H CH_3C-4 = 1.15 ppm
δ_C C1 = 12.8 ppm
δ_C C2 = 41.5 ppm
δ_C C3 = 72.1 ppm
δ_C CH_2C-2′ = 25.9 ppm
} (∴ 2,3-*anti*)

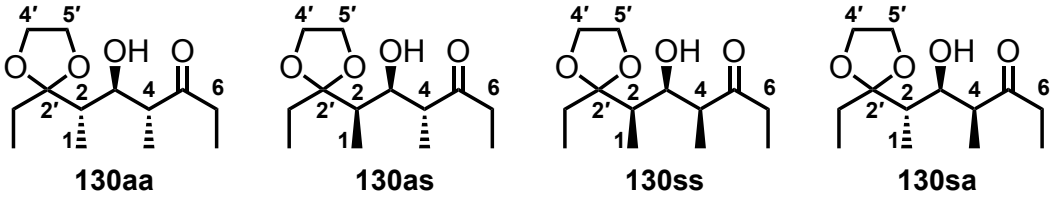
δ_C CH_3CC-2′ = 7.0 ppm

δ_C C4 = 49.2 ppm
δ_C CH_3C-4 = 8.1 ppm
} (∴ 3,4-*syn* 2,3-*anti*)

for the "spin system-B"

$^3J_{H10\text{-}H11}$ = 7 Hz
δ_H CH_3C-10 = 1.22 ppm
δ_C C10 = 48.5 ppm
δ_C CH_3C-10 = 14.4 ppm
δ_C C13 = 8.7 ppm
δ_C C12 = 40.7 ppm
δ_C C11 = 70.8 ppm
δ_C CH_2C-2″ = 27.6 ppm
δ_C CH_3CC-2″ = 7.9 ppm
} (∴ 10,11-*syn* 11,12-*syn*)

from the same (*Z,Z*)-bis enolborinate conditions (∴ 4,6-*syn* and 8,10-*syn*)



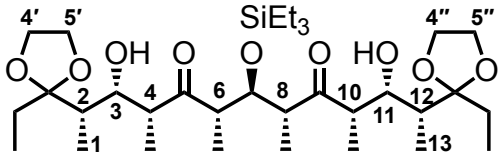


Figure 2-33: Structure assignment of **246** by NMR comparison with the known compounds.

Table 2-32: Comparison of the selected NMR data of "spin system-A" in **246** with those of the known **245** and **130**.

adduct	$^3J_{H2\text{-}H3}$ (Hz)	$^3J_{H3\text{-}H4}$ (Hz)	δH CH_3C-4	δ_C C-1	δ_C C-2	δ_C C-3	δ_C C-4	δ_C CH_3C-4	δ_C CH_2C-2′	δ_C CH_3C C-2′
130ss	1	9	1.21	7.4	39.9	71.6	50.2	14.9	28.1	8.2
130as	<1	9.5	0.94	6.9	38.5	73.4	48.7	13.7	28.2	8.3
130aa	8.5	3.5	1.24	13.1	42.0	76.1	49.7	14.5	26.0	7.1
130sa	9.5	2.5	1.06	12.8	41.4	73.0	49.1	8.0	25.7	7.0
245	3	7	1.23	9.0	40.4	70.5	49.9	13.6	27.5	7.9
246	9.5	<1	1.15	12.8	41.5	72.1	49.2	8.1	25.9	7.0

Table 2-33: Comparison of the selected NMR data of "spin system-B" in **246** with those of the known **245** and **130**.

adduct	$^3J_{H3\text{-}H4}$ ($^3J_{H12\text{-}H13}$) (Hz)	δH CH_3C-4 (δ_H CH_3C-10)	δ_C C-1 (δ_C C-13)	δ_C C-2 (δ_C C-12)	δ_C C-3 (δ_C C-11)	δ_C C-4 (δ_C C-10)	δ_C CH_3C-4 (δ_C CH_3C-10)	δ_C CH_2C-2′ (δ_C CH_2C-2″)	δ_C CH_3CC-2′ (δ_C CH_3CC-2″)
130aa	3.5	1.24	13.1	42.0	76.1	49.7	14.5	26.0	7.1
130sa	2.5	1.06	12.8	41.4	73.0	49.1	8.0	25.7	7.0
130as	9.5	0.94	6.9	38.5	73.4	48.7	13.7	28.2	8.3
130ss	9	1.21	7.4	39.9	71.6	50.2	14.9	28.1	8.2
245	7	1.23	9.0	40.4	70.5	49.9	13.6	27.5	7.9
246	(7)	(1.22)	(8.7)	(40.1)	(70.8)	(48.5)	(14.4)	(27.6)	(7.9)

Chiral bisaldol 252ssa:

Procedure for assignment of NMR spectra:

The bisaldol **252ssa** is asymmetric as indicated by the presence of 36 resonances in the ^{13}C NMR spectrum (Figure 2-35). The ^1H NMR spectra of **252ssa** can be divided in to eight distinct

'spin systems' from analysis of its two-dimensional HH COSY NMR spectrum. The Et_3Si, HC-4″-HC-5″, HC-2′ and -Ph proton spin systems are unique and were readily assigned in the COSY spectrum and by chemical shifts; the ^{13}C chemical shifts of attached carbon atoms were identified based on the relevant $^1J_{CH}$ correlations observed in the HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in these spin systems.

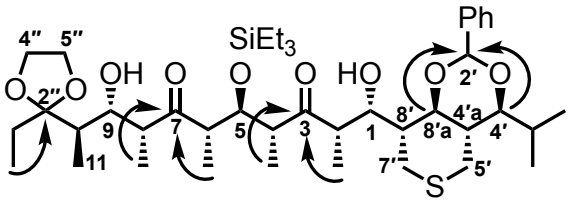
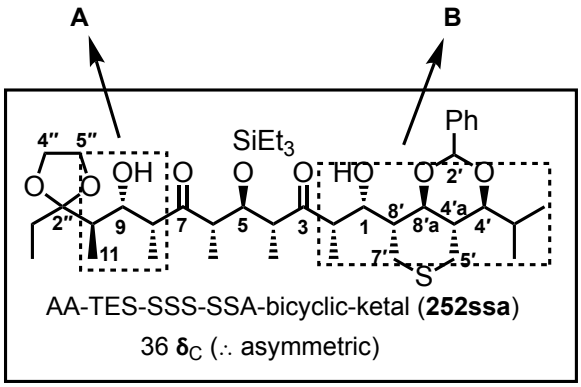


Figure 2-34: Key HMBC correlations (H→C) in bisaldol **252ssa**.

The C4-C5, C5-C6, C6-C8, C8-C9 and C9-C10 relative configurations in **252ssa** were unambiguously confirmed by achieving the total synthesis of dolabriferol C (relative configuration of dolabriferol C known as 4,5-*anti*-5,6-*anti*-6,8-*syn*-8,9-*syn*-9,10-*anti*) from **252ssa** (Figure 2-35). The stereocenter at C1 and the absolute configuration at C2 were lost due to oxidation of the hydroxy group at C1 to the keto group in the process of the synthesis of dolabriferol C; as a result, the C1-C8′, C1-C2 and C2-C4 relative configurations cannot be established from dolabriferol C. However, comparison of the NMR data between the known **130**, **253**, **234** and **252ssa** allowed assignment of the structure of **252ssa** (Figure 2-35). To simplify the assignment, each spin system was analyzed and compared individually with the known compounds. The carbinol proton signals for "spin systems" 'A' and 'B' (i.e., HC-1 and HC-9) are readily differentiated by the $^3J_{HH}$ correlation to the OH protons and two adjacent methine groups (i.e., HC-8′, HC-2 and HC-8, HC-10). By analysis of the HH COSY spectrum and using the assigned HC-1 and HC-9 as 'anchors' all the hydrogens in the spin systems A and B (i.e, HC-8, H_3CC-8, HC-10, HC-11 and HC-2, H_3CC-2, HC-8′, HC-7′, HC-8′a, HC-4′a, HC-5′, HC-4′, HCC-4′, H_3CCC-4′) were assigned. The

coupling constants $^{3}J_{H8\text{-}H9}$ (<1 Hz) and $^{3}J_{H9\text{-}H10}$ (10 Hz), the ^{13}C chemical shifts of C11 ($\boldsymbol{\delta}_C$ 12.8), C10 ($\boldsymbol{\delta}_C$ 41.4), C9 ($\boldsymbol{\delta}_C$ 72.3), C8 ($\boldsymbol{\delta}_C$ 48.1), CH_3C-8 ($\boldsymbol{\delta}_C$ 8.35; '*key signal'*), CH_2C-2″ ($\boldsymbol{\delta}_C$ 25.95), CH_3CC-2″ ($\boldsymbol{\delta}_C$ 7.1) and the ^{1}H chemical shift of CH_3C-8 ($\boldsymbol{\delta}_H$ 1.11) for the "spin system-A" of **252ssa** closely match those of the known adducts **130sa** and **234** suggesting that the relative configuration of the "spin system-A" in **252ssa** is 6,8-*syn*-8,9-*syn*-9,10-*anti* (Table 2-34). The bisaldol **252ssa** was obtained from a complete reaction of (*Z,Z*)-bis enolborinate **222** with aldehydes **128** and **159** suggesting the "spin system-B" in **252ssa** has the same relative configuration as **253** (arising from an incomplete reaction of **222** with **128**). The coupling constants $^{3}J_{H1\text{-}H2}$ (3.0 Hz) and $^{3}J_{H1\text{-}H8'}$ (5.5 Hz), the ^{13}C chemical shifts of C1 ($\boldsymbol{\delta}_C$ 69.9), C2 ($\boldsymbol{\delta}_C$ 49.6), CH_3C-2 ($\boldsymbol{\delta}_C$ 11.1), C8′ ($\boldsymbol{\delta}_C$ 46.3), C7′ ($\boldsymbol{\delta}_C$ 28.5) for "spin system-B" of **252ssa** closely match those of the known adduct **253** suggesting the relative configuration of the "spin system-B" in **252ssa** is 1,2-*syn*-1,8′-*syn*-2,4-*syn* (Table 2-35). By analysis of the HMBC spectrum, the $^{2}J_{C3\text{-}HC2}$, $^{3}J_{C3\text{-}CH3C2}$, $^{2}J_{C7\text{-}HC8}$ and $^{3}J_{C7\text{-}CH3C8}$ correlations allowed assignment of the carbonyls at C3 and C7 (Figure 2-34). Knowing the chemical shifts of C3 and C7, the HC-4, H_3CC-4 and HC-6, H_3CC-6 were assigned from the $^{2}J_{C3\text{-}HC4}$, $^{3}J_{C3\text{-}CH3C4}$ and the $^{2}J_{C7\text{-}HC6}$, $^{3}J_{C7\text{-}CH3C6}$ correlations, respectively, observed in the HMBC spectrum. By analysis of the HH COSY spectrum and using the assigned HC-4 and HC-6 as 'anchors' all the hydrogens in the spin system (i.e, H_3CC-4, HC-5 and H_3CC-6) were assigned. The H_2CC-2″-H_3CCC-2″ proton spin system was assigned by $^{2}J_{C2''\text{-}H2CC2''}$, $^{3}J_{C2''\text{-}H3CCC2''}$ correlations, observed in the HMBC spectrum. The relative configurations at C4-C5 and C5-C6 should be unchanged from the starting diketone **202aa** and were already confirmed as 4,5-*anti*-5,6-*anti* from the known **253**. Thus, the relative configuration of **252ssa** was assigned as 1,8′-*syn*-1,2-*syn*-2,4-*syn*-4,5-*anti*-5,6-*anti*-6,8-*syn*-8,9-*syn*-9,10-*anti*.



for the "spin system-A"

$^3J_{H9\text{-}H10}$ = 9.5 Hz (∴ 9,10-*anti*)
$^3J_{H8\text{-}H9}$ = <1 Hz (∴ 8,9-*syn*)

δ_H CH_3C-8 = 8.35 ppm
δ_C C11 = 12.8 ppm
δ_C C10 = 41.4 ppm
δ_C C9 = 72.3 ppm
δ_C CH_2C-2″ = 25.95 ppm
} (∴ 9,10-*anti*)

δ_C CH_3CC-2″ = 7.1 ppm

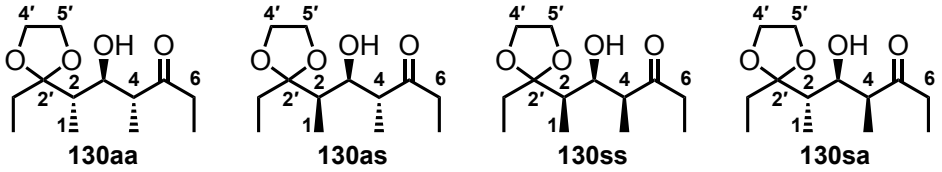
δ_C C8 = 49.2 ppm
δ_C CH_3C-8 = 8.1 ppm
} (∴ 8,9-*syn* 9,10-*anti*)

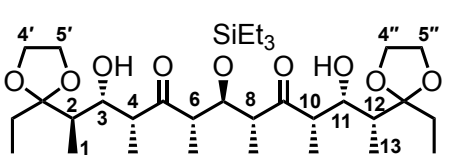
for the "spin system-B"

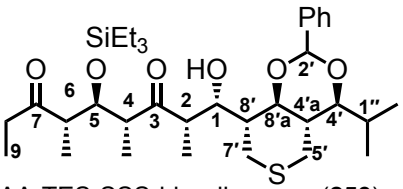
$^3J_{H1\text{-}H2}$ = 3 Hz (∴ 1,2-*syn*)
$^3J_{H1\text{-}H8'}$ = 5.5 Hz (∴ 1,8′-*syn*)

δ_C C-1 = 69.9 ppm
δ_C C-2 = 49.6 ppm
δ_C CH_3C-2 = 11.1 ppm
δ_C C-8′ = 46.3 ppm
δ_C C-7′ = 28.5 ppm
} (∴1,2-*syn* 1,8′-*syn*)

from the same (*Z,Z*)-bis enolborinate conditions (∴ 2,4-*syn* and 6,8-*syn*)




AA-TES-SSS-SSA-ketal-*chiral* (**234**)


AA-TES-SSS-bicyclic-mono (**253**)

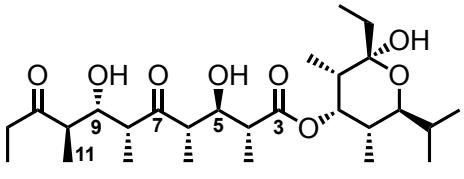

dolabriferol C (**17**)

Figure 2-35: Structure assignment of **252ssa** by NMR comparison with the known compounds.

Table 2-34: Comparison of the selected NMR data of "spin system-A" in **252ssa** with those of the known **234** and **130**.

adduct	$^3J_{H2\text{-}H3}$ (Hz) ($^3J_{H9\text{-}H10}$)	$^3J_{H3\text{-}H4}$ (Hz) ($^3J_{H8\text{-}H9}$)	δH CH_3C-4 (δ_H H_3CC-8)	δ_C C-1 (δ_C C-11)	δ_C C-2 (δ_C C-10)	δ_C C-3 (δ_C C-9)	δ_C C-4 (δ_C C-8)	δ_C CH_3C-4 (δ_C CH_3C-8)	δ_C CH_2C-2′ (CH_2C-2″)	δ_C CH_3C-2′ (CH_3C-2″)
130aa	8.5	3.5	1.24	13.1	42.0	76.1	49.7	14.5	26.0	7.1
130as	<1	9.5	0.94	6.9	38.5	73.4	48.7	13.7	28.2	8.3
130ss	1	9	1.21	7.4	39.9	71.6	50.2	14.9	28.1	8.2
130sa	9.5	2.5	1.06	12.8	41.4	73.0	49.1	8.0	25.7	7.0
234	9.5	<1	1.15	12.8	41.5	72.1	49.2	8.1	25.9	7.0
252ssa	(10)	(<1)	(1.11)	(12.8)	(41.4)	(72.3)	(48.1)	(8.35)	(25.95)	(7.1)

Table 2-35: Comparison of the selected NMR data of "spin system-B" in **252ssa** with those of the known **253**.

Adduct	$^3J_{H1\text{-}H2}$ (Hz)	$^3J_{H1\text{-}H8'}$ (Hz)	δ_C C-1	δ_C C-2	δ_C CH_3C-2	δ_C C-8′	δ_C C-7′
253	3.5	5.5	70.1	50.1	10.9	46.2	28.6
252ssa	3	5.5	69.9	49.6	11.1	46.3	28.5

Chiral bisaldol 252sss:

The bisaldol **252sss** is asymmetric as indicated by the presence of 36 resonances in the ^{13}C NMR spectrum (Figure 2-37). NMR spectra of **252sss** was assigned by following the identical procedure used for **252ssa**.

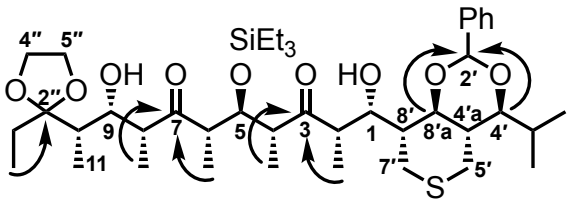
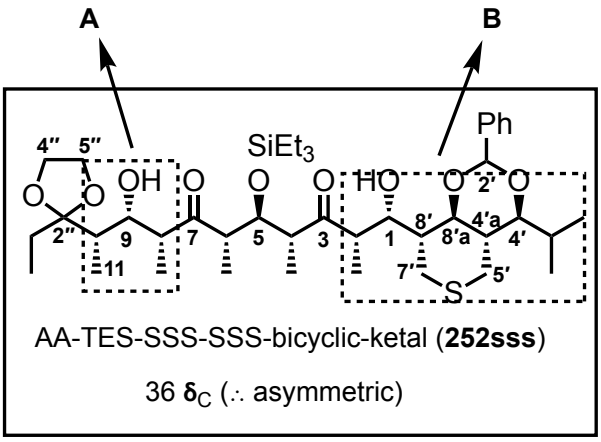


Figure 2-36: Key HMBC correlations (H→C) in bisaldol **252sss**.

Assignment of the relative configuration of 252sss:

The coupling constants $^{3}J_{H8\text{-}H9}$ (8 Hz) and $^{3}J_{H9\text{-}H10}$ (2.5 Hz), the ^{13}C chemical shifts of C11 ($\boldsymbol{\delta}_C$ 12.8), C10 ($\boldsymbol{\delta}_C$ 39.94), C9 ($\boldsymbol{\delta}_C$ 70.9), C8 ($\boldsymbol{\delta}_C$ 48.5), CH_3C-8 ($\boldsymbol{\delta}_C$ 14.7), CH_2C-2″ ($\boldsymbol{\delta}_C$ 27.7), CH_3CC-2″ ($\boldsymbol{\delta}_C$ 7.9) and the ^{1}H chemical shift of CH_3C-8 ($\boldsymbol{\delta}_H$ 1.21) for the "spin system-A" of **252sss** closely match those of the known adducts **130ss** and **245** suggesting that the relative configuration of the "spin system-A" in **252sss** is 6,8-*syn*-8,9-*syn*-9,10-*syn* (Figure 2-37, Table 2-36). The bisaldol **252sss** was obtained from a complete reaction of (*Z,Z*)-bis enolborinate **222** with aldehydes **128** and **159** suggesting the "spin system-B" in **252sss** has the same relative configuration as **253** (arising from an incomplete reaction of **222** with **128**). The coupling constants $^{3}J_{H1\text{-}H2}$ (3.0 Hz) and $^{3}J_{H1\text{-}H8'}$ (6.0 Hz), the ^{13}C chemical shifts of C1 ($\boldsymbol{\delta}_C$ 70.3), C2 ($\boldsymbol{\delta}_C$ 50.9), CH_3C-2 ($\boldsymbol{\delta}_C$ 10.4), C8′ ($\boldsymbol{\delta}_C$ 46.0), C7′ ($\boldsymbol{\delta}_C$ 28.9) for "spin system-B" of **252sss** closely match those of the known adduct **253** suggesting the relative configuration of the "spin system-B" in **252sss** is 1,2-*syn*-1,8′-*syn*-2,4-*syn* (Table 2-37). The relative configurations at C4-C5 and C5-C6 should be unchanged from the starting diketone **202aa** and were already confirmed as 4,5-*anti*-5,6-*anti* from the known **253**. Thus, the relative configuration of **252sss** was assigned as 1,8′-*syn*-1,2-*syn*-2,4-*syn*-4,5-*anti*-5,6-*anti*-6,8-*syn*-8,9-*syn*-9,10-*syn*.



for the "spin system-A"

$^3J_{H9\text{-}H10}$ = 2.5 Hz (∴ 9,10-*syn*
$^3J_{H8\text{-}H9}$ = 8 Hz (∴ 8,9-*syn* 9,10-*syn*)

δ_H CH_3C-8 = 14.7 ppm
δ_C C11 = 8.5 ppm
δ_C C10 = 39.9 ppm
δ_C C9 = 70.9 ppm
δ_C CH_2C-2″ = 27.7 ppm
δ_C CH_3CC-2″ = 7.9 ppm
} (∴ 9,10-*syn*)

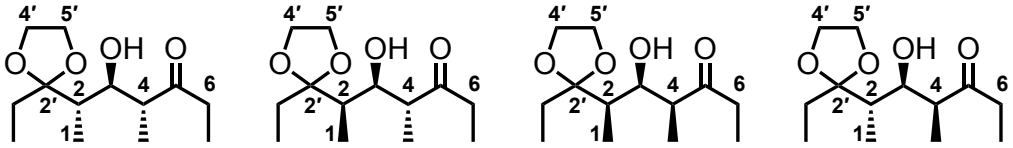
δ_C C8 = 48.5 ppm
δ_C CH_3C-8 = 14.7 ppm
} (∴ 8,9-*syn* 9,10-*syn*)

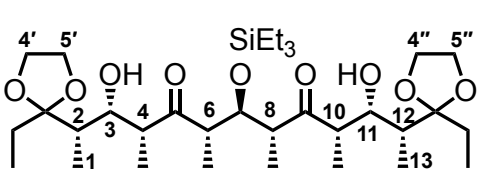
for the "spin system-B"

$^3J_{H1\text{-}H2}$ = 3 Hz (∴ 1,2-*syn*)
$^3J_{H1\text{-}H8'}$ = 6 Hz (∴ 1,8′-*syn*)

δ_C C-1 = 70.3 ppm
δ_C C-2 = 50.9 ppm
δ_C CH_3C-2 = 10.4 ppm
δ_C C-8′ = 46.0 ppm
δ_C C-7′ = 28.9 ppm
} (∴1,2-*syn* 1,8′-*syn*)

from the same (*Z,Z*)-bis enolborinate conditions (∴ 2,4-*syn* and 6,8-*syn*)





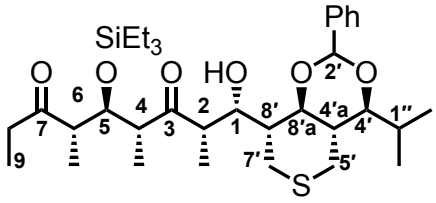


Figure 2-37: Structure assignment of **252sss** by NMR comparison with the known compounds.

Table 2-36: Comparison of the selected NMR data of "spin system-A" in **252sss** with those of the known **245** and **130**.

adduct	$^3J_{H2\text{-}H3}$ (Hz) ($^3J_{H9\text{-}H10}$)	$^3J_{H3\text{-}H4}$ (Hz) ($^3J_{H8\text{-}H9}$)	δH CH_3C-4 (δ_H H_3CC-8)	δ_C C-1 (δ_C C-11)	δ_C C-2 (δ_C C-10)	δ_C C-3 (δ_C C-9)	δ_C C-4 (δ_C C-8)	δ_C CH_3C-4 (δ_C CH_3C-8)	δ_C CH_2C-2′ (CH_2C-2″)	δ_C CH_3C-2′ (CH_3C-2″)
130aa	8.5	3.5	1.24	13.1	42.0	76.1	49.7	14.5	26.0	7.1
130sa	9.5	2.5	1.06	12.8	41.4	73.0	49.1	8.0	25.7	7.0
130as	<1	9.5	0.94	6.9	38.5	73.4	48.7	13.7	28.2	8.3
130ss	1	9	1.21	7.4	39.9	71.6	50.2	14.9	28.1	8.2
245	3	7	1.23	9.0	40.4	70.5	49.9	13.6	27.5	7.9
252sss	(2.5)	(8)	(1.21)	(12.8)	(39.94)	(70.9)	(48.5)	(14.7)	(27.7)	(7.9)

Table 2-37: Comparison of the selected NMR data of "spin system-B" in **252sss** with those of the known **253**.

Adduct	$^3J_{H1\text{-}H2}$ (Hz)	$^3J_{H1\text{-}H8'}$ (Hz)	δ_C C-1	δ_C C-2	δ_C CH_3C-2	δ_C C-8′	δ_C C-7′
253	3.5	5.5	70.1	50.1	10.9	46.2	28.6
252sss	3	6	70.3	50.9	10.4	46.0	28.9

2.9.5. Assignment by analogy

***Meso* bisaldol 216:**

Procedure for assignment of NMR spectra:

The bisaldol **216** is C_s-symmetric as indicated by the presence of 11 resonances in the ^{13}C NMR spectrum (Figure 2-38). The ^1H NMR spectra of **216** can be divided in to three distinct 'spin systems' from analysis of its two-dimensional HH COSY NMR spectrum. The Et_3Si, H_2C2-H_3C1/H_2C12-H_3C13 proton spin systems and C5/C9 carbonyls are unique and were readily

assigned in the COSY and ^{13}C NMR spectrum, respectively; the ^{13}C chemical shifts of attached carbon atoms were identified based on the relevant $^{1}J_{CH}$ correlations observed in the HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in these spin systems.

The proton signals for HC-3 and HC-11 are readily differentiated by the $^{3}J_{HH}$ correlation to the OH protons and two adjacent groups (i.e., H_2C-2, HC-4 and H_2C-12, HC-10) (Figure 2-38, Table 2-38). By analysis of the HH COSY spectrum and using the assigned HC-3 and HC-11 as 'anchors' all the hydrogens in the spin system (i.e., HC-1, HC-2, HC-4, H_3CC-4 and HC-10, H_3CC-10, HC-12, HC-13) were assigned. With the aid of these assigned protons, the attached carbons were assigned by analysis of the two-dimensional $^{1}J_{CH}$ correlation spectrum (gHSQC). Among the methine protons in the remaining spin system, the HC-7 has unique ^{1}H chemical shift ($\boldsymbol{\delta}_H$ 4.59) and multiplicity (t) that allowed assignment of all the protons in the spin system (i.e., HC-6, H_3CC-6, HC-7, HC-8 and H_3CC-8) by $^{3}J_{HH}$ correlations observed in the HH COSY spectrum.

Assignment of the relative configuration of 216:

The relative configurations of **216** was determined by analogy to the known **212** and by comparing ^{1}H and ^{13}C NMR data of **216** with those of the known **212** and **200** (Figure 2-38, Table 2-38). Based on the established structures so far, it is clear that both (*E,E*) and (*Z,Z*)-bis enolborinates **215** and **222**, respectively, followed a trend and produced adducts with a common relative configuration (i.e., 4,6-*syn* or 8,10-*syn*) under identical conditions. Similarly, (*E,E*)-**215** produced adducts with 3,4-*anti* relative configurations, while (*Z,Z*)-**222** produced adducts with 3,4-*syn* relative configurations irrespective of type of aldehydes. Based on this trend and analogy, the relative configuration of **216** was assumed as 3,4-*anti*-4,6-*syn*-8,10-*syn*-10,11-*anti*. This

assignment was further supported by comparing ^{1}H and ^{13}C NMR data of **216** with those of the known **212** and **200**. The coupling constant $^{3}J_{H3\text{-}H4}$ (J = 7.5 Hz), the ^{13}C chemical shift of CH_3C-4 (δ_C 14.4) and the difference in ^{13}C chemical shifts ($\Delta\delta_C$ [C3, CH_3C-4] = 61.0) for **216** are consistent with the observed trend from the database and with those of the known adducts **212** and **200sa** suggesting the relative configuration of **216** is 3,4-*anti*-4,6-*syn* (Table 2-38). The relative configurations of C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known **212**. Because **216** is *meso*, the C3-C11, C4-C10 and C6-C8 relative configurations in **216** must be *syn*. Thus, the relative configuration of **216** was assigned as 3,4-*anti*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*syn*-10,11-*anti*.

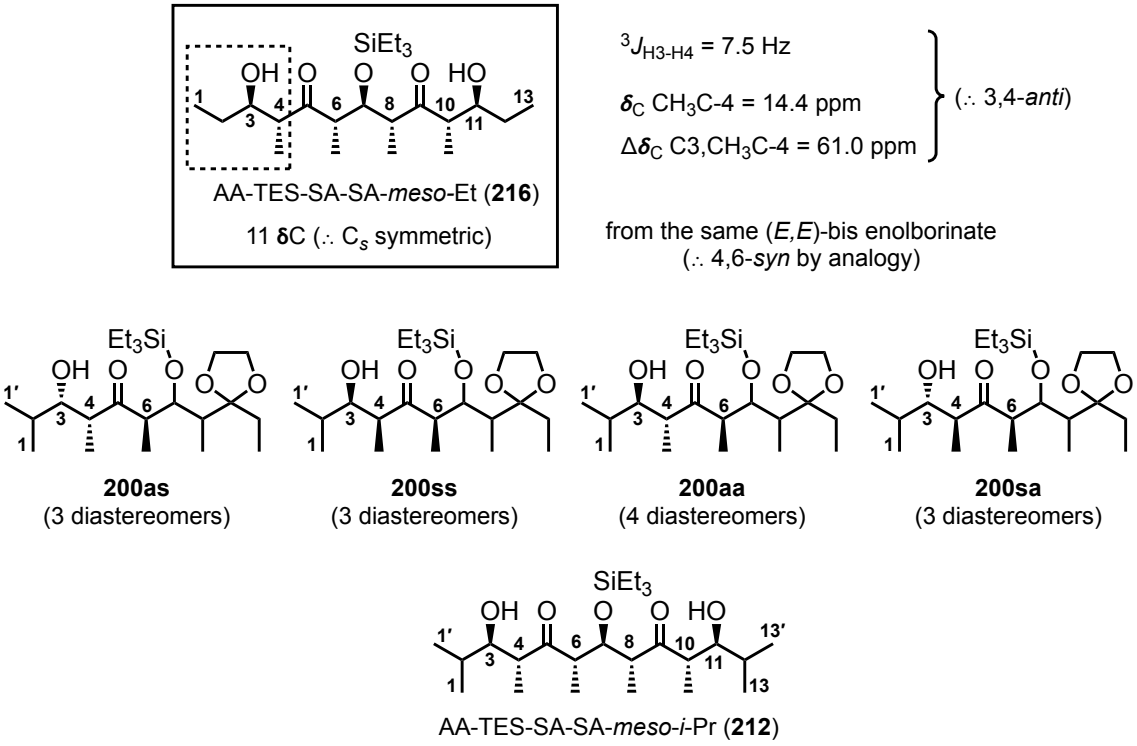


Figure 2-38: Assignment of the relative configuration of **216** by NMR comparison with the known compounds.

Table 2-38: Comparison of the selected NMR data of **216** with those of the known **212** and **200**.

adduct	$^{3}J_{H2\text{-}H3\ (Hz)}$	$^{3}J_{H3\text{-}H4\ (Hz)}$	$\Delta\boldsymbol{\delta}_C$ (C3,CH_3C-4)	$\boldsymbol{\delta}_C$ CH_3C-4
200as	8.8	1.9	68.2	8.5
200ss	9.4	1.4	67.1	9.0
200aa	5	7	64.6	14.3
200sa	3.9	7.9	63.6	14.3
212	3.5	7	64.0	14.2
216	αH=3.5; βH=7.5	7.5	61.0	14.4

Mono aldol 216a:

Procedure for assignment of NMR spectra:

The ^{1}H NMR spectra of **216a** can be divided in to four distinct 'spin systems' from analysis of its two-dimensional HH COSY NMR spectrum (Figure 2-40). The Et_3Si and H_2C10-H_3C11 proton spin systems are unique and were readily assigned in the COSY spectrum; the ^{13}C chemical shifts of attached carbon atoms were identified based on the relevant $^{1}J_{CH}$ correlations observed in the HSQC spectrum. No attempt was made to distinguish between diastereotopic protons or carbons in these spin systems.

The proton signals for HC-3 is readily differentiated by the $^{3}J_{HH}$ correlation to the OH protons and two adjacent groups (i.e., H_2C-2, HC-4) (Figure 2-40). By analysis of the HH COSY spectrum and using the assigned HC-3 as an 'anchor' all the hydrogens in the spin system (i.e, HC-1, HC-2, HC-4, H_3CC-4) were assigned. With the aid of these assigned protons, the attached carbons were assigned by analysis of the two-dimensional $^{1}J_{CH}$ correlation spectrum (gHSQC). Among the carbonyl carbons, C5 is readily distinguishable by $^{2}J_{C5\text{-}HC4}$ and $^{3}J_{C5\text{-}CH3C4}$ correlations observed in the HMBC spectrum (Figure 2-39). The HC-6 and H_3CC-6 were assigned from $^{2}J_{C5\text{-}HC6}$ and $^{3}J_{C5\text{-}CH3C6}$ correlations, respectively, observed in the HMBC spectrum. By analysis of the

HH COSY spectrum and using the assigned HC-6 as an 'anchor' all the hydrogens in the spin system (i.e, H_3CC-6, HC-7, HC-8 and H_3CC-8) were assigned. Although the assignment of C9 can be inferred after the assignment of the other carbonyl C5, the $^2J_{C9\text{-}HC8}$ and $^3J_{C9\text{-}CH3C8}$ correlations observed in the HMBC spectrum is additional evidence to support this assignment. The methylene protons H_2C-10 are unique and were assigned using ^1H chemical shift and multiplicity; this assignment was further supported by $^2J_{C9\text{-}HC10}$ correlations observed in the HMBC spectrum.

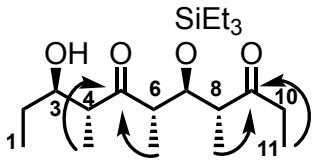


Figure 2-39: Key HMBC correlations (H→C) in mono aldol **216a**.

Assignment of the relative configuration of 216a:

The mono aldol **216a** was obtained from an incomplete reaction of (*E,E*)-bis enolborinate **215** with propanal suggesting **216a** has same relative configuration as *meso* bisaldol **216** (arising from complete reaction of **215** with propanal) (Figure 2-40, Table 2-39). Similar to **216**, the relative configuration of **216a** was determined by analogy to the known **212** and by comparing ^1H and ^{13}C NMR data of **216a** with those of the known adducts **212** and **200**. The coupling constant $^3J_{H3\text{-}H4}$ (J = 7.5 Hz), ^{13}C chemical shift of CH_3C-4 ($\boldsymbol{\delta}_C$ 14.4) and the difference in ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C3, CH_3C-4] = 61.4) values of **216a** are consistent with the observed trend from the database and with those of the known adducts **212** and **200sa** suggesting the relative configuration of **216a** is 3,4-*anti*-4,6-*syn* (Table 2-39). The relative configurations of C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known **212**. Thus, the relative configuration of **216a** was assigned as 3,4-*anti*-4,6-*syn*-6,7-*anti*-7,8-*anti*.

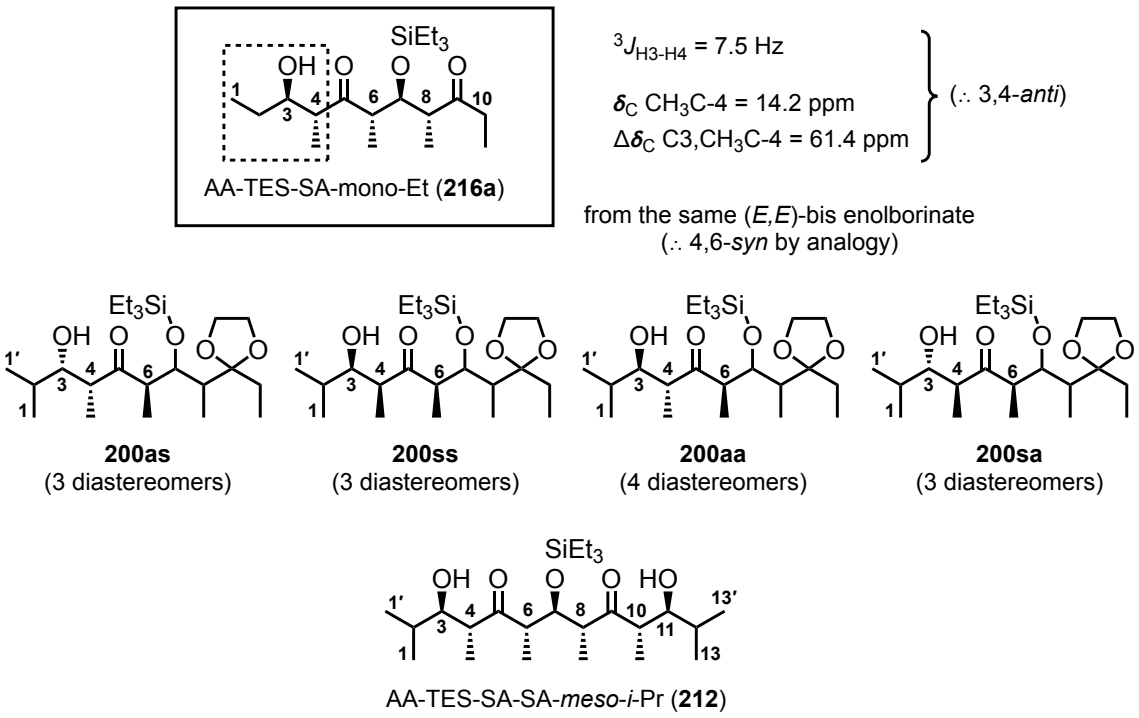


Figure 2-40: Assignment of the relative configuration of **216a** by NMR comparison with the known compounds.

Table 2-39: Comparison of the selected NMR data of **216a** with those of the known **212** and **200**.

adduct	$^3J_{H2\text{-}H3\ (Hz)}$	$^3J_{H3\text{-}H4\ (Hz)}$	$\Delta\delta_C$ (C3,CH_3C-4)	δ_C CH_3C-4
200as	8.8	1.9	68.2	8.5
200ss	9.4	1.4	67.1	9.0
200aa	5	7	64.6	14.3
200sa	3.9	7.9	63.6	14.3
212	3.5	7	64.0	14.2
216a	αH=3.0; βH= 7.5	7.5	61.4	14.4

***Meso* bisaldol 224:**

The bisaldol **224** is C_s-symmetric as indicated by the presence of 11 resonances in the ^{13}C NMR spectrum (Figure 2-41). NMR spectra of **224** was assigned by following the identical procedure used for **216**.

Similar to **216**, the relative configuration of **224** was determined by analogy the known **223** and by comparing ^{1}H and ^{13}C NMR data of **224** with those of the known adducts **223** and **200** (Figure 2-41, Table 2-40). The coupling constant $^{3}J_{H3\text{-}H4}$ (J = 2.0 Hz), ^{13}C chemical shift of CH_3C-4 ($\boldsymbol{\delta}_C$ 9.4) and the difference in ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C3, CH_3C-4] = 62.6) for **224** are consistent with the observed trend from the database and with those of the known adducts **223** and **200ss** suggesting the relative configuration of **224** is 3,4-*syn*-4,6-*syn*. The relative configurations of C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known **223**. Because **224** is *meso* the C3-C11, C4-C10 and C6-C8 relative configurations in **224** must be *syn*. Thus, the relative configuration of **224** was assigned as 3,4-*syn*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*syn*-10,11-*syn*.

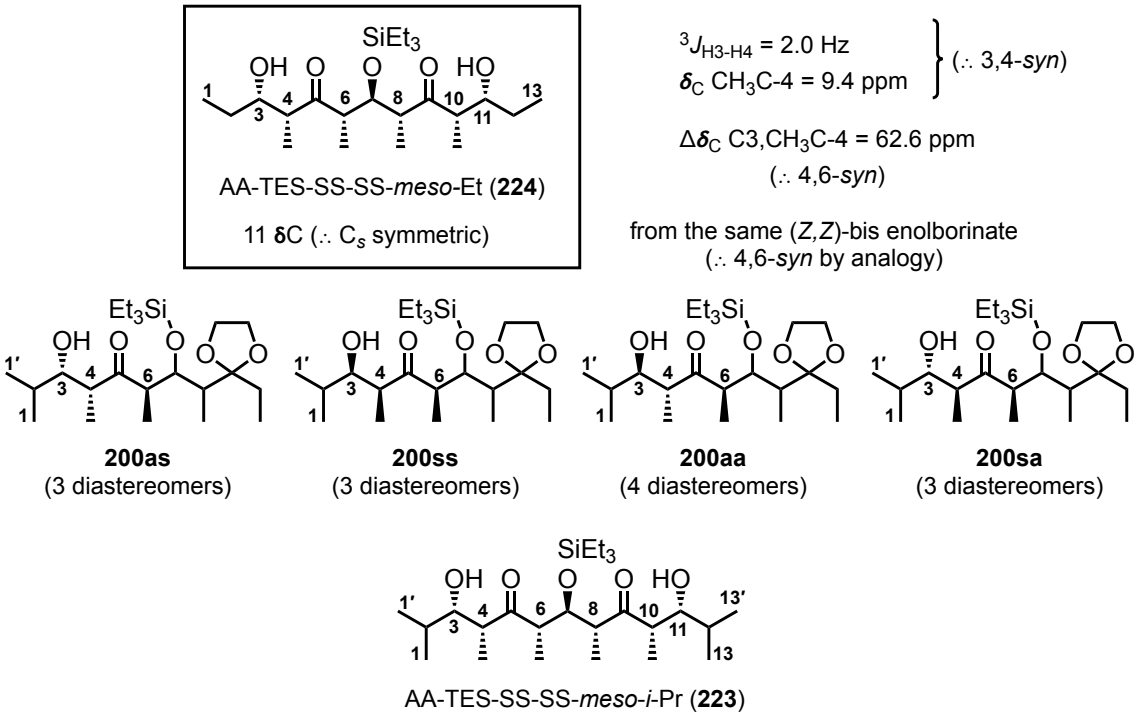


Figure 2-41: Assignment of the relative configuration of **224** by NMR comparison with the known compounds.

Table 2-40: Comparison of the selected NMR data of **224** with those of the known **223** and **200**.

adduct	$^3J_{H2\text{-}H3\ (Hz)}$	$^3J_{H3\text{-}H4\ (Hz)}$	$\Delta\boldsymbol{\delta}_C$ (C3,CH_3C-4)	$\boldsymbol{\delta}_C$ CH_3C-4
200aa	5.0	7.0	64.6	14.3
200sa	3.9	7.9	63.6	14.3
200as	8.8	1.9	68.2	8.5
200ss	9.4	1.4	67.1	9.0
223	9.5	1.5	66.7	9.2
224	αH=5.0; βH=7.5	2.0	62.6	9.4

Chiral-bisaldol 216b:

The bisaldol **216b** is asymmetric as indicated by the presence of 19 resonances in the ^{13}C NMR spectrum (Figure 2-43). NMR spectra of **216b** was assigned by following the identical procedure used for **213**.

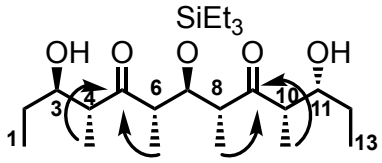


Figure 2-42: Key HMBC correlations (H→C) in bisaldol **216b**.

Comparison of the NMR data between the known 13 diastereomers of **200**, **212**, **216**, **224** and **216b** allowed assignment of the structure of **216b** (Figure 2-43, Tables 2-41 and 2-42). The coupling constant $^{3}J_{H3\text{-}H4}$ (7.5 Hz), the ^{13}C chemical shift of CH_3C-4 ($\boldsymbol{\delta}_C$ 14.4), and the differences in the ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C3, CH_3C-4] = 61.0) for the "spin system-A" of **216b** closely match those of the known adducts **200sa**, **212** and **216** suggesting that the relative configuration of the "spin system-A" in **216b** is 3,4-*anti*-4,6-*syn* (Table 2-41). Similarly, the coupling constants $^{3}J_{H10\text{-}H11}$ (2.0 Hz), the ^{13}C chemical shift of CH_3C-10 ($\boldsymbol{\delta}_C$ 9.5), and the differences in ^{13}C chemical shifts ($\Delta\boldsymbol{\delta}_C$ [C11, CH_3C-10] = 62.5) for "spin system-B" of **216b** closely match those of the known adducts **200ss**, **223** and **224** suggesting the relative configuration of the "spin system-B" in **216b** is 8,10-*syn*-10,11-*syn* (Table 2-42). The relative configurations at C6-C7 and C7-C8 should be unchanged from the starting diketone **202aa** and were already confirmed as 6,7-*anti*-7,8-*anti* from the known **212** and **223**. Thus, the relative configuration of **216b** was assigned as 3,4-*anti*-4,6-*syn*-6,7-*anti*-7,8-*anti*-8,10-*syn*-10,11-*syn*.

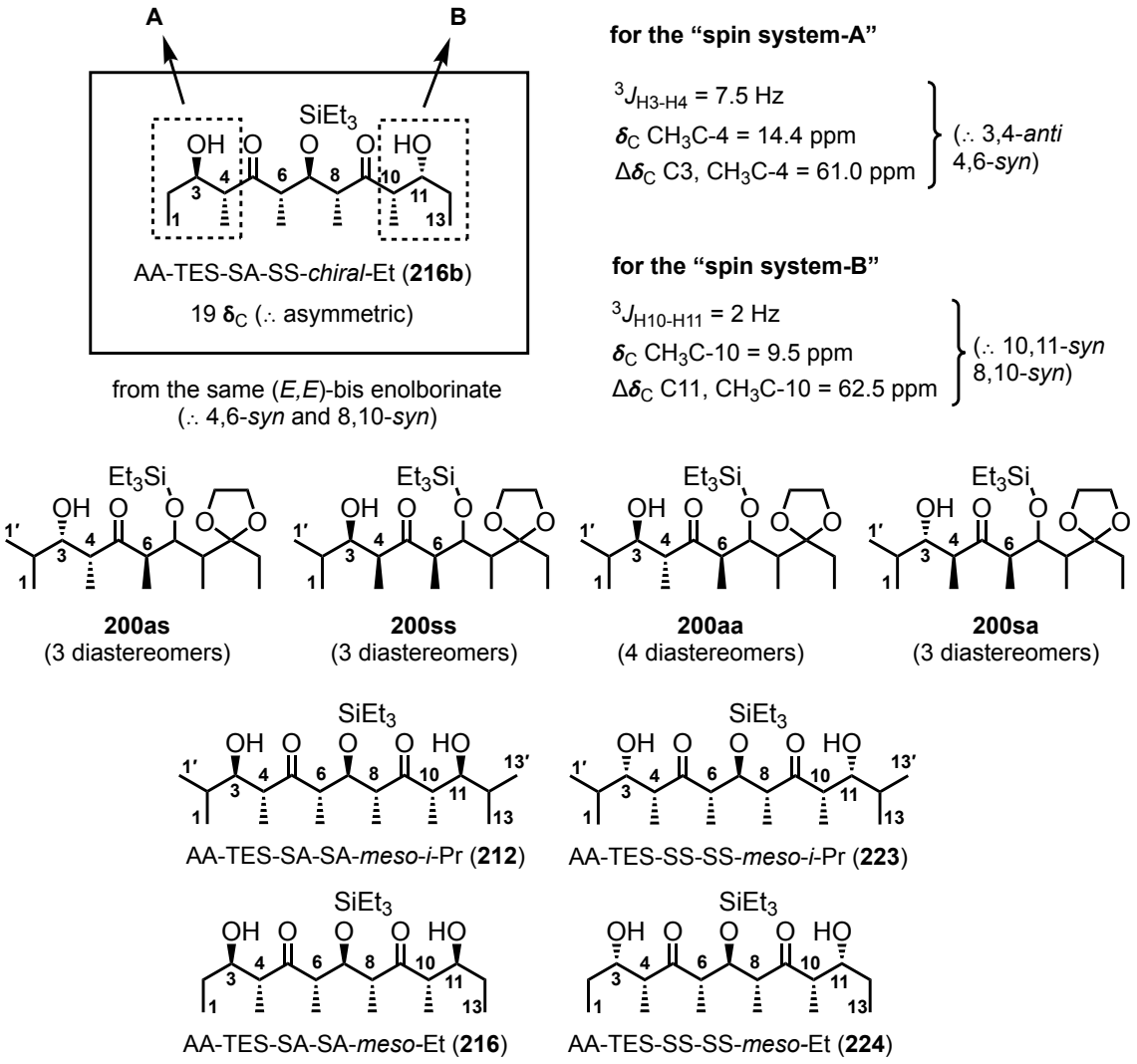


Figure 2-43: Assignment of the relative configuration of **216b** by NMR comparison with the known compounds.

Table 2-41: Comparison of the selected NMR data of the "spin system-A" in **216b** with those of the known **200**, **212**, and **216**.

adduct	$^3J_{H2\text{-}H3\ (Hz)}$	$^3J_{H3\text{-}H4\ (Hz)}$	$\Delta\boldsymbol{\delta}_C$ (C3,CH_3C-4)	$\boldsymbol{\delta}_C$ CH_3C-4
200ss	9.4	1.4	67.1	9.0
200as	8.8	1.9	68.2	8.5
200aa	5	7	64.6	14.3
200sa	3.9	7.9	63.6	14.3
212	3.5	7	64.0	14.2
216	αH=3.5; βH=7.5	7.5	61.0	14.4
216b	αH=3.0; βH=7.5	7.5	61.0	14.4

Table 2-42: Comparison of the selected NMR data of the "spin system-B" in **216b** with those of the known **200**, **223**, and **224**.

adduct	$^3J_{H2\text{-}H3\ (Hz)}$	$^3J_{H3\text{-}H4\ (Hz)}$	$\Delta\boldsymbol{\delta}_C$ (C3,CH_3C-4)	$\boldsymbol{\delta}_C$ CH_3C-4
200aa	5.0	7.0	64.6	14.3
200as	8.8	1.9	68.2	8.5
200sa	3.9	7.9	63.6	14.3
200ss	9.4	1.4	67.1	9.0
223	9.5	1.5	66.7	9.2
224	αH=5.0; βH=7.5	2.0	62.6	9.4
216b	αH=6.5; βH=7.5 ($^3J_{H11\text{-}H12}$)	2.0 ($^3J_{H10\text{-}H11}$)	62.5 (C11,CH_3C-10)	9.5 (CH_3C-10)

3. SUMMARY AND CONCLUSIONS

Although several research groups attempted synthesis of non-contiguous natural products via esterification approach or retro-Claisen rearrangement approach, only the Ward group accomplished syntheses of complex natural products baconipyrone A, baconipyrone C, dolabriferol and dolabriferol C from their putative contiguous precursors. Regioselective retro-Claisen rearrangements of the precursors to these natural products under mild conditions (on exposure to neutral alumina) provide the first experimental evidence that support the proposed hypothesis on the origin of the so-called non-contiguous natural products and suggests these products are isolation artifacts.

For the highly convergent total synthesis of **174**, the putative contiguous precursor of dolabriferol C, a powerful sequential enantiotopic group selective (SEGS) bisaldol strategy was established. For the first time, stereoselective syntheses of *meso* bisenolates (*E,E* and *Z,Z*) **215**, **222** and **220** were achieved from *meso* diketones **202aa** and **202ss**, respectively and were successfully used in stereoselective aldol reactions. Several mono and bisaldols (*meso*, racemic and enantioenriched) were prepared by establishing internal and external EGS aldol reactions using *meso* diketones **202aa** and **202ss**. SEGS bisaldol reaction of *meso* diketones **202aa** and **202ss** with aldehyde (−)-**109** (via enantioselective desymmetrization) and then with aldehyde (±)-**159** (via kinetic resolution) generated the enantioenriched bisaldols (+)-**241** and (−)-**243**, respectively, and sets the absolute configuration of eight stereocenters in a one-pot process. This remarkable process is the first example where eight stereocenters (absolute configurations) were generated from a coupling of *meso*, racemic and enantioenriched reactants in a one-pot process. Using this strategy, the desired bisaldol **252ssa** that has the full carbon skeleton of the precursor **174** was prepared. An alternative stereoselective bisaldol reaction of diketone **202aa** with enantioenriched

aldehydes (−)-**109** and (+)-**159** gave the desired bisaldol **252ssa** with improved yield and diastereoselectivity. This strategy allowed access to the natural products dolabriferol (**15**) and dolabriferol C (**17**) from monoaldol **253** and bisaldol **252ssa**, respectively.

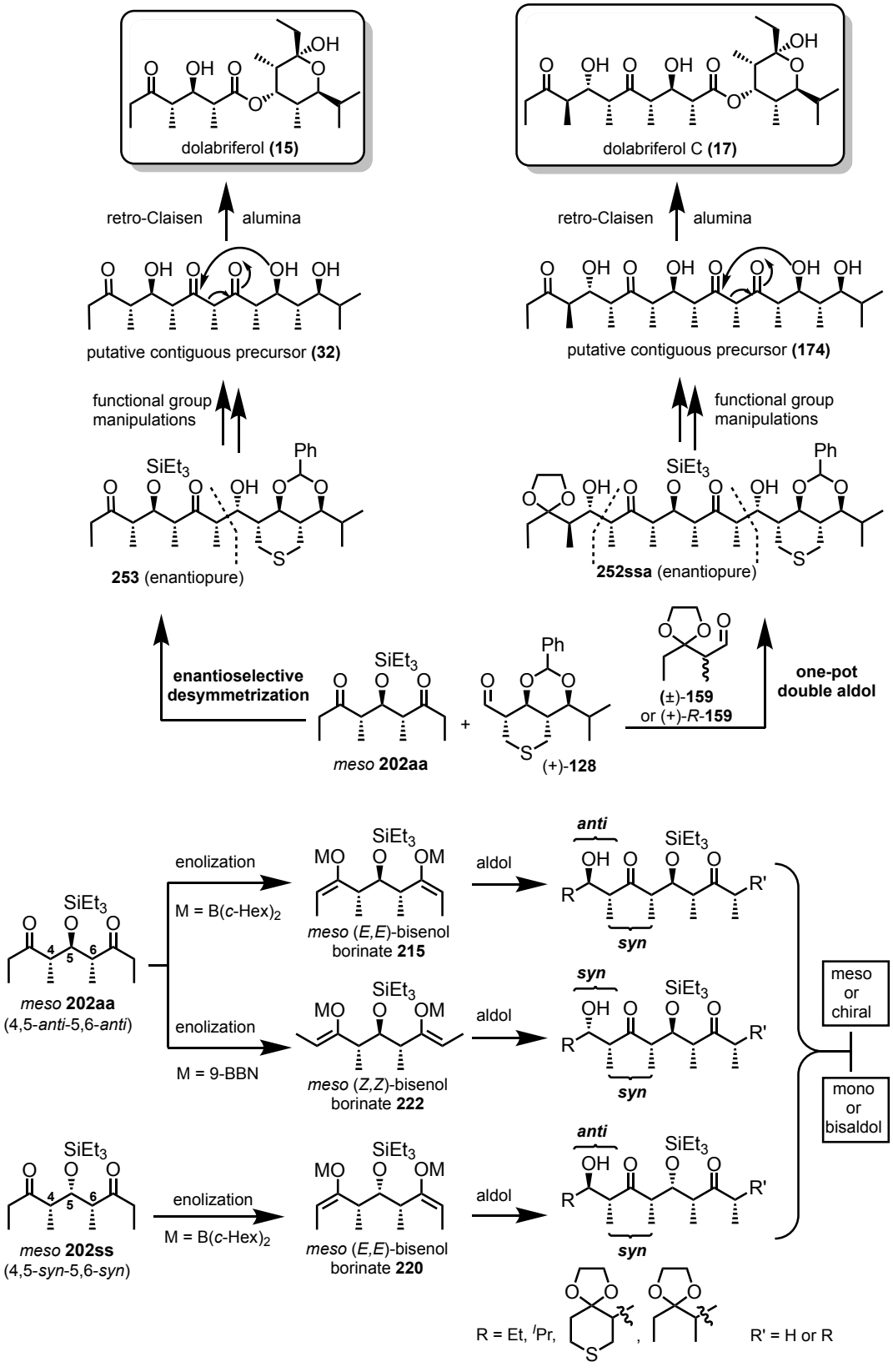


Figure 2-44: Summary of the research.

4. EXPERIMENTAL

4.1. General Methods

Anhydrous solvents were distilled under argon atmosphere as follows: tetrahydrofuran (THF) from benzophenone sodium ketyl; CH_2Cl_2 from CaH_2; MeOH from $Mg(OMe)_2$; acetonitrile (CH_3CN) from CaH_2 and stored over 4 Å molecular sieves; DMSO from CaH_2 under reduced pressure; DMF over P_2O_5 and stored over 4 Å molecular sieves. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum and attached via a needle and connecting tubing to a mercury bubbler under argon atmosphere. Low temperature baths were ice/water (0 °C), CO_2(s)/acetonitrile (−42 °C) and CO_2(s)/acetone (−78 °C). Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Evacuation at ca. 0.1 torr with a vacuum pump generally followed rotary evaporation.

Preparative TLC was carried out on glass plates (20x20 cm) pre-coated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (PMA) solution [PMA (40 g), $Ce(SO_4)_2$ (10 g) and H_2SO_4 (50 mL) and diluted to 1 L with water] followed by charring on a hot plate. Flash column chromatography (FCC) was performed according to Still et al.[116] with Merck Silica Gel 60 (40-63 mm). All mixed solvent eluents are reported as v/v solutions. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR spectroscopy.

4.2. Spectral Data

High resolution mass spectra (HRMS) were obtained on a JEOL AccuTOF 4G GCv Mass spectrometer using field desorption (FD) ionization or a QSTAR XL MS/MS Mass spectrometer using electrospray ionization (ESI) method; only partial data are reported. Alternatively, HRMS was obtained on a LC-MS/MS time-of-flight high resolution spectrometer with electrospray ionization (ESI) from methanol solution. Infrared spectra were recorded on a Bio-Rad FTS-40 Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported.

The NMR solvent $CDCl_3$ was passed through small plug of basic alumina prior to use. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ or C_6D_6 solution at 500 MHz for ^1H and 125 MHz for ^{13}C. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^1H NMR) served as the internal standard: $CDCl_3$ (7.26 δ_H, 77.23 δ_C); C_6D_6 (7.16 δ_H, 128.39 δ_C). The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. Coupling constants are reported to the nearest 0.5 Hz (consistent with the digital resolution of ca. 0.2 Hz/pt). The NMR assignments were made on the basis of chemical shifts, coupling constants (*J*) and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or two-dimensional correlation experiments (gCOSY, gHSQC, gHMBC).[117] The multiplicity of ^{13}C NMR signals refers to the number of H's attached (i.e., s = C, d = CH, t = CH_2, q = CH_3) and was determined by gHSQC.

Specific rotations ($[\alpha]_D$) are the average of five determinations at ambient temperature on a Rudolph Digipol 781 polarimeter using a 1 mL, 10 dm cell; the units are 10^{-1} deg cm^2 g^{-1} and

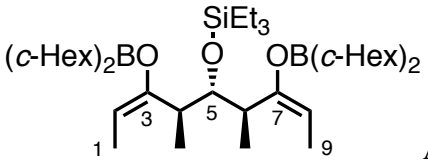
the concentrations (*c*) are reported in g/100 mL. The values reported are rounded to reflect the accuracy of the measured concentrations (the major source of error). HPLC analyses were carried out using a normal phase Agilent Technologies 1200 series liquid chromatograph using chiralpak® IB column or chiralpak® IC column (column size: 150 x 2.1 mm (L x I.D.); particle size: 5 um), eluted with 1% or 2% isopropanol in hexanes.

4.3. Materials

The following compounds and reagents were prepared as described previously: **109**,[78] **110**,[45] **(+)-128**,[17] **130aa**,[42] **130ss**,[42] **159**,[42] W-2 Raney® nickel,[118] IBX,[119] DMP (from IBX),[120] benzyl cyanoformate,[83] *c*-Hex_2BCl.[121] *n*-Butylithium and *t*-Butylithium were titrated using diphenyl acetic acid as the titrant and indicator. Et_3N, *i*-Pr_2NEt and *i*-Pr_2NH were distilled from CaH_2 under argon and stored over KOH. All other reagents were commercially available and, unless otherwise noted, were used as received.

4.4. Experimental Procedures and Characterization Data

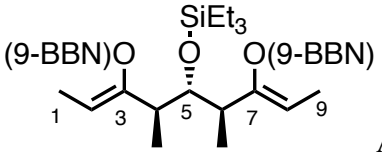
4.4.1. Compounds synthesized from methodology project



AA-TES-(*E,E*)-bisborinate (**215**)

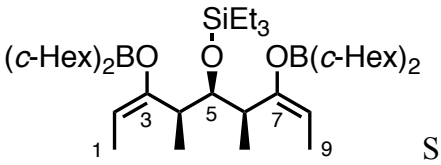
General procedure for aldol reactions of 202aa via its (2*E*,7*E*)-dien-3,7-yl bis(dicyclohexylborinate). *c*-Hex_2BCl (1.0 M in hexane; 4 equiv) was added via syringe to a stirring solution of Et_3N (5 equiv) and **202aa** (0.65 M in CH_2Cl_2; 1 equiv) at 0 °C under argon.

After 3 h, the mixture was cooled to –78 °C and the aldehyde was added. After the indicated aldol reaction time and temperature, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 6 mL/mmol of boron), MeOH (6 mL/mmol of boron), and 30% aq H_2O_2 (3 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath and after vigorous stirring for 15 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^1H NMR and then fractionated.



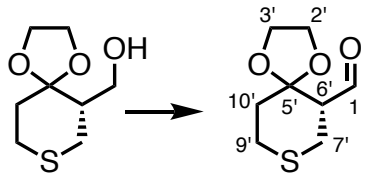
AA-TES-(*Z*,*Z*)-bisborinate (**222**)

General procedure for aldol reactions of 202aa via its (2*Z*,7*Z*)-2,7-dien-3,7-diyl bis(9-borabicyclo[3.3.1]nonan-9-ylborinate). 9-BBNOTf (0.5 M in hexane; 0.50 mL, 0.25 mmol) was added via syringe to a stirred solution of **202aa** (20 mg, 0.064 mmol) and Et_3N (0.044 mL, 31 mg, 0.31 mmol) in Et_2O (0.2 mL) at –78 °C under argon. After 4 h, aldehyde (4-10 equiv) was added. After 3 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 0.5 mL), 30% aq H_2O_2 (0.5 mL), and MeOH (0.5 mL) with vigorous stirring. The reaction vessel was transferred to an ice bath and after vigorous stirring for 15 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^1H NMR and then fractionated.



SS-TES-(*E*,*E*)-bisborinate (**220**)

General procedure for aldol reactions of 202ss via its (2*E*,7*E*)-dien-3,7-yl bis(dicyclohexylborinate). *c*-Hex_2BCl (1.0 M in hexane; 4 equiv) was added via syringe to a clean dry Schlenk tube containing a magnetic stir bar, and the hexane was removed under reduced pressure. A solution of Et_3N (5 equiv) and **202ss** (20 mg, 0.064 mmol) in CH_2Cl_2 (0.10 mL) was added via syringe to the neat borane reagent with stirring at –78 °C under argon. After 3 h, the aldehyde was added. After the indicated aldol reaction time and temperature, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 6 mL/mmol of boron), MeOH (6 mL/mmol of boron), and 30% aq H_2O_2 (3 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath and after vigorous stirring for 15 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^1H NMR and then fractionated.

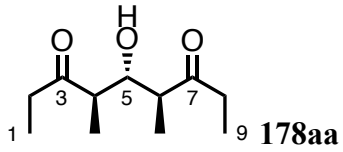


(–)-**109**

(*S*)-(–)-1,4-dioxa-8-thiaspiro[4.5]decan-6-carbaldehyde ((–)-109)

A solution of (–)-(*S*)-**239**[65] ($[\alpha]_D$ = –25 (*c* 1.0, $CHCl_3$); er >50:1 (HPLC); 10-15 mg, 0.052-0.079 mmol) in water-saturated CH_2Cl_2 (0.1 M) was added to a stirring suspension of MgO (10 equiv) and Dess-Martin periodinane (DMP) (1.5 equiv) in water-saturated CH_2Cl_2 (0.15 M in DMP). After 10 min, Et_2O (ca. 2× the volume of CH_2Cl_2) was added and a white precipitate formed. A solution made up of saturated $NaHCO_3$ (0.8 mL) and $Na_2S_2O_3$ (0.2 g) diluted to 2 mL with water was added to the stirring reaction mixture resulting in two layers. The aqueous phase was extracted with Et_2O and the combined organic layers were dried over Na_2SO_4 and concentrated to give the

title compound as pale yellow oil (>95%) that was immediately used in the aldol reaction. An analogous reaction of (±)-**239** (32 mg, 0.17 mmol) gave a (±)-**109** (31 mg, 97%) whose ^{1}H NMR spectrum indicated >95% purity.



178aa

(4*R*,5*r*,6*S*)-5-Hydroxy-4,6-dimethylnonane-3,7-dione (178aa)

Anhydrous $FeCl_3$ (147 mg, 0.91 mmol) was added to a stirring solution of **130aa** (1.1 g, 4.5 mmol) in acetone (40 mL). After 30 min, most of the acetone was removed under reduced pressure and the remaining mixture was taken up in CH_2Cl_2 and transferred to a separatory funnel. The mixture was washed sequentially with saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give the title compound (870 mg, 97%).

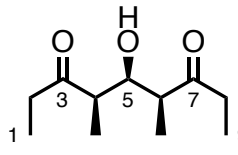
colorless oil, TLC R_f = 0.3 (30% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3487, 1710, 1698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (1H, dt, *J* = 9, 6 Hz, HC-5), 3.60 (1H, d, *J* = 9 Hz, HO), 2.70 (2H, dq, *J* = 6, 7 Hz, HC-4 & HC-6), 2.52 (2H, dq, *J* = 18.5, 7.5 Hz, HC-2 & HC-8), 2.43 (2H, dq, *J* = 18.5, 7.5 Hz, HC-2 & HC-8), 1.09 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-6), 0.98 (6H, t, *J* = 7.5 Hz, H_3C-1 & H_3C-9).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2 (s ×2, C-3 & C-7), 77.0 (d, C-5), 48.4 (d ×2, C-4 & C-6), 36.3 (t ×2, C-2 & C-8), 14.7 (q ×2, CH_3C-4 & CH_3C-6), 7.5 (q ×2, C-1 & C-9).

HRMS *m/z* calcd for $C_{11}H_{20}O_3$+Na^+ 223.1305, found 223.1297 (ESI).



178ss

(4*R*,5*s*,6*S*)-5-Hydroxy-4,6-dimethylnonane-3,7-dione (178ss)

$FeCl_3$ (25 mg, 0.15 mmol) was added to a stirring solution of **130ss** (180 mg, 0.74 mmol) in acetone (8 mL). After 30 min, the reaction mixture was concentrated under reduced pressure and the residue was taken up in CH_2Cl_2 and then washed sequentially with saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to give the title compound as colorless oil (143 mg, 97%).

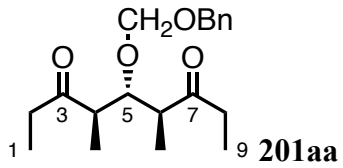
pale yellow liquid, TLC R_f = 0.40 (35% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3509, 1702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (1H, dt, *J* = 2.5, 5.5 Hz, HC-5), 3.14 (1H, d, *J* = 2.5 Hz, HO), 2.66 (2H, dq, *J* = 5.5, 7 Hz, HC-4 & HC-6), 2.55 (2H, dq, *J* = 18, 7 Hz, HC-2 & HC-8), 2.43 (2H, dq, *J* = 18, 7 Hz, HC-2 & HC-8), 1.16 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-6), 1.04 (6H, t, *J* = 7 Hz, H_3C-1 & H_3C-9).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.7 (s ×2, C-3 & C-7), 71.4 (d, C-5), 48.0 (d ×2, C-4 & C-6), 35.3 (t ×2, C-2 & C-8), 12.3 (q ×2, H_3CC-4 & H_3CC-6), 7.8 (q ×2, C-1 & C-9).

HRMS *m/z* calcd for $C_{11}H_{20}O_3$+Na^+ 223.1304, found 223.1316 (ESI).



201aa

(4*R*,5*r*,6*S*)-5-((Benzyloxy)methoxy)-4,6-dimethylnonane-3,7-dione (201aa)

$PhCH_2OCH_2Cl$ (BOM-Cl) (ca. 80% (w/w), mainly contaminated with BnCl and Bn_2O; 145 mg, ca. 0.74 mmol of BOM-Cl) was added to a stirring solution of **178aa** (126 mg, 0.63 mmol) and *i*Pr_2EtN (0.28 mL, 204 mg, 1.6 mmol) in DMF (3 mL) at room temperature under argon. After 20 h, *i*Pr_2EtN and $PhCH_2OCH_2Cl$ (same amounts as above) were added. After 5 h (reaction complete by TLC analysis), the reaction was quenched by addition of methanol (1.5 mL). After 1 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NH_4Cl, water and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (15% ethyl acetate in hexane) to give the title compound (173 mg, 86%).

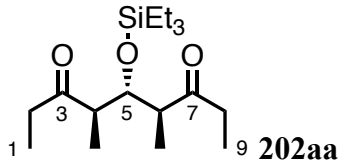
colorless oil, TLC R_f = 0.3 (15% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (5H, m, Ph), 4.70 (2H, s, H_2CO2), 4.53 (2H, s, H_2CPh), 4.22 (1H, t, *J* = 6.5 Hz, HC-5), 2.91 (2H, dq, *J* = 6.5, 7 Hz, HC-4 & HC-6), 2.52 (4H, ap q, *J* = 7 Hz, H_2C-2 & H_2C-8), 1.03 (6H, t, *J* = 7 Hz, H_3C-1 & H_3C-9), 1.02 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-6).

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1 (s ×2, C-3 & C-7), 137.7 (s, Ph), 128.6 (d ×2, Ph), 128.98 (d ×2, Ph), 127.96 (d, Ph), 95.6 (t, OCH_2O), 81.5 (d, C-5), 70.3 (t, CH_2Ph), 48.8 (d ×2, C-4 & C-6), 35.9 (d ×2, C-2 & C-8), 12.2 (q ×2, CH_3C-4 & CH_3C-6), 7.8 (q ×2, C-1 & C-9).

HRMS *m/z* calcd for $C_{19}H_{28}O_4$ 320.1988, found 320.1990 (FD).



202aa

(4*R*,5*r*,6*S*)-4,6-Dimethyl-5-((triethylsilyl)oxy)nonane-3,7-dione (202aa)

Imidazole (196 mg, 2.87 mmol) and Et_3SiCl (0.41 ml, 371 mg, 2.46 mmol) were sequentially added to a stirring solution of **178aa** (410 mg, 2.05 mmol) at room temperature. After 45 min, the reaction mixture was diluted with Et_2O and washed sequentially with aq citric acid (0.2 M) and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (5% ethyl acetate in hexane) gave the title compound (612 mg, 95%).

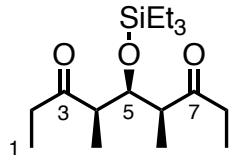
colorless oil, TLC R_f = 0.5 (5% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 1715 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (1H, t, *J* = 6 Hz, HC-5), 2.68 (2H, dq, *J* = 6, 7 Hz, HC-4 & HC-6), 2.49 (4H, ap q, *J* = 7 Hz, HC-2 & HC-8), 1.02 (6H, t, *J* = 7 Hz, H_3C-1 & H_3C-9), 0.98 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-6), 0.92 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.57 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3 (s ×2, C-3 & C-7), 75.7 (d, C-5), 50.9 (d ×2, C-4 & C-6), 36.1 (d ×2, C-2 & C-8), 12.4 (q ×2, CH_3C-4 & CH_3C-6), 7.7 (q ×2, C-1 & C-9), 7.1 (q ×3, CH_3CSi), 5.2 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{17}H_{34}O_3Si+Na^+$ 337.2169, found 337.2155 (ESI).



202ss

(4*R*,5*s*,6*S*)-4,6-Dimethyl-5-((triethylsilyl)oxy)nonane-3,7-dione (202ss)

Imidazole (92 mg, 1.4 mmol) and Et_3SiCl (0.19 mL, 170 mg, 0.75 mmol) were sequentially added to a stirring solution of **178ss** (150 mg, 0.75 mmol) in DMF (2.0 mL) at 0 °C under argon. The ice bath was removed and the mixture was allowed to warm to ambient temperature. After 3 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NH_4Cl and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (5% ethyl acetate in hexane) to afford the titled compound (229 mg, 97%).

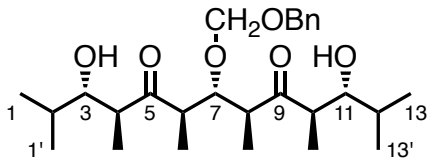
colorless liquid, TLC R_f = 0.32 (5% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 1709 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (1H, t, *J* = 5.5 Hz, HC-5), 2.63 (2H, dq, *J* = 5.5, 7 Hz, HC-4 & HC-6), 2.56 (2H, dq, *J* = 18, 7 Hz, HC-2 & HC-8), 2.46 (2H, dq, *J* = 18, 7 Hz, HC-2 & HC-8), 1.024 (6H, t, *J* = 7 Hz, H_3C-1 & H_3C-9), 1.017 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-6), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.60 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.8 (s ×2, C-5 & C-7), 73.7 (d, C-5), 50.6 (d ×2, C-4 & C-6), 35.8 (t ×2, C-2 & C-8), 13.0 (q ×2, CH_3C-4 & CH_3C-6), 7.8 (q ×2, C-1 & C-9), 7.2 (q ×3, CH_3CSi), 5.4 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{17}H_{34}O_3Si+Na^+$ 337.2169, found 337.2166 (ESI).



209

(3*S*,4*S*,6*R*,7*r*,8*S*,10*R*,11*R*)-7-((Benzyloxy)methoxy)-3,11-dihydroxy-2,4,6,8,10,12-hexamethyltridecane-5,9-dione (209)

c-Hex_2BCl (1.0 M in hexane; 0.19 mL, 0.19 mmol) was added to a stirring solution of **201aa** (20 mg, 0.063 mmol) and Et_3N (0.032 mL, 0.14 g, 0.23 mmol) in CH_2Cl_2 (0.2 mL) at –42 °C under argon. After 3 h, the mixture was cooled to –78 °C and *i*PrCHO (0.57 mL, 45 mg, 0.63 mmol) was added. After 3 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 0.3 mL), MeOH (0.5 mL), and 30% aq H_2O_2 (0.3 mL) with vigorous stirring. The reaction vessel was transferred to an ice bath and after vigorous stirring for 15 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose 1H NMR spectrum indicated the presence of a 1.8:1 mixture of **209** and **210**, respectively. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave **210** (9.5 mg; ca. 85% pure) and the title compound (16 mg, 55%).

colorless viscous oil, TLC R_f = 0.35 (20% ethyl acetate in hexane).

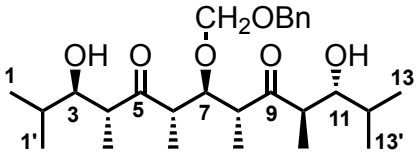
IR (DRIFT) ν_{max} 3501, 1707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (5H, m, Ph), 4.75 (2H, s, H_2CO2), 4.57 (2H, s, H_2CPh), 4.34 (1H, t, *J* = 6 Hz, HC-7), 3.48 (2H, ddd, *J* = 4, 5.5, 8 Hz, HC-3 & HC-11), 3.22 (2H, dq, *J* = 6, 7 Hz, HC-6, HC-8), 2.93 (2H, dq, *J* = 8, 7 Hz, HC-4 & HC-10), 2.63 (2H, d, *J* = 5.5 Hz, HO ×2), 1.76 (2H, dqq, *J* = 4, 7, 7 Hz, HC-2 & HC-12), 1.06 (6H, d, *J* = 7 Hz, H_3CC-6 & H_3CC-8),

1.02 (6H, d, J = 7 Hz, H_3CC-4 & H_3CC-10), 0.96 (6H, d, J = 7 Hz, H_3C-1 & H_3C-13), 0.89 (6H, d, J = 7 Hz, H_3C-1' & H_3C-13').

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.7 (s ×2, C-5 & C-9), 137.6 (s, Ph), 128.7 (d ×2, Ph), 128.1 (d ×2, Ph), 128.0 (d, Ph), 96.2 (t, OCH_2O), 81.5 (d, C-7), 78.3 (d ×2, C-3 & C-11), 70.5 (t, CH_2Ph), 49.3 (d ×2, C-4 & C-10), 49.0 (d ×2, C-6 & C-8), 29.9 (d ×2, C-2 & C-12), 20.3 (q ×2, CH_3-1 & CH_3-13), 15.3 (q ×2, CH_3-1' & CH_3-13'), 14.4 (q ×2, CH_3C-4 & CH_3C-10), 12.2 (q ×2, CH_3C-6 & CH_3C-8).

HRMS *m/z* calcd for $C_{27}H_{44}O_6$+Na^+ 487.3030, found 487.3009 (ESI).



210

(3*R*,4*R*,6*S*,7*R*,8*R*,10*R*,11*R*)-7-((Benzyloxy)methoxy)-3,11-dihydroxy-2,4,6,8,10,12-hexamethyltridecane-5,9-dione (210)

For procedure, see the preparation of **209**.

colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

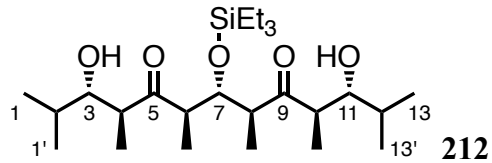
IR (DRIFT) ν_{max} 3553, 1707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.28 (5H, m, Ph), 4.75 (1H, d, J = 7 Hz, HCO_2), 4.73 (1H, d, J = 7 Hz, HCO_2), 4.58 (1H, d, J = 11.5 Hz, CHPh), 4.55 (1H, d, J = 11.5 Hz, CHPh), 4.30 (1H, dd, J = 6, 6.5 Hz, HC-7), 3.49 (1H, ddd, J = 4, 5.5, 8 Hz, HC-3), 3.45 (1H, ddd, J = 4, 7, 7.5 Hz, HC-11), 3.20 (1H, dq, J = 6.5, 7 Hz, HC-6*), 3.18 (1H, dq, J = 6, 7 Hz, HC-8*), 2.94 (1H, dq, J =

8, 7 Hz, HC-4), 2.93 (1H, dq, *J* = 7.5, 7 Hz, HC-10), 2.67 (1H, d, *J* = 5.5 Hz, HOC-3), 2.25 (1H, d, *J* = 7 Hz, HOC-11), 1.77 (1H, dqq, *J* = 4, 7, 7 Hz, HC-12), 1.72 (1H, dqq, *J* = 4, 7, 7 Hz, HC-2), 1.07 (3H, d, *J* = 7 Hz, H_3CC-8), 1.06 (3H, d, *J* = 7 Hz, H_3CC-4), 1.04 (3H, d, *J* = 7 Hz, H_3CC-6), 1.02 (3H, d, *J* = 7 Hz, H_3CC-10), 0.97 (3H, d, *J* = 7 Hz, H_3C-13), 0.93 (3H, d, *J* = 7 Hz, H_3C-1), 0.90 (3H, d, *J* = 7 Hz, H_3C-13), 0.84 (3H, d, *J* = 7 Hz, H_3C-1) (* assignments may be reversed).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.9 (s, C-5), 217.1 (s, C-9), 137.7 (s, Ph), 128.7 (d ×2, Ph), 128.1 (d ×2, Ph), 128.0 (d, Ph), 95.9 (t, OCH_2O), 80.6 (d, C-7), 78.7 (d, C-11), 78.4 (d, C-3), 70.5 (d, CH_2Ph), 50.2 (d, C-8*), 49.3 (d, C-4), 48.9 (d, C-6*), 48.2 (d, C-10), 30.2 (d, C-12), 29.9 (d, C-2), 20.3 (q, C-1'), 20.2 (q, C-13), 15.3 (q, C-13'), 15.2 (q, C-1), 14.4 (q, CH_3C-4), 14.1 (q, CH_3C-10), 12.6 (q, CH_3C-6), 11.6 (q, CH_3C-8) (* assignments may be reversed).

HRMS *m/z* calcd for $C_{27}H_{44}O_6$+Na^+ 487.3030, found 487.3023 (ESI).



212

(3*S*,4*S*,6*R*,7*r*,8*S*,10*R*,11*R*)-3,11-Dihydroxy-2,4,6,8,10,12-hexamethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (212)

*i*PrCHO (0.175 mL, 138 mg, 1.9 mmol) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (60 mg, 0.19 mmol) according to the general procedure, at –78 °C under Ar. After 24 h, the reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 85:7:5:3 mixture of **212**, **214**, **213**, and **202aa**, respectively. Fractionation of the crude product by FCC

(20% ethyl acetate in hexane) gave **213** (3.5 mg, 4%), **214** (4.5 mg, 6%), and the title compound (71 mg, 81%).

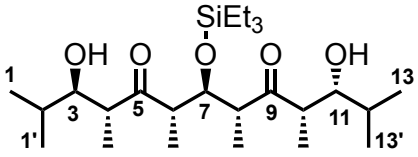
colorless viscous oil, TLC R_f = 0.3 (15% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3470, 1716 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (1H, t, *J* = 6 Hz, HC-7), 3.48 (2H, ddd, *J* = 3.5, 5, 8 Hz, HC-3 & C-11), 3.03 (2H, dq, *J* = 6, 7 Hz, HC-6 & HC-8), 2.90 (2H, dq, *J* = 8, 7 Hz, HC-4 & HC-10), 2.75 (2H, d, *J* = 5 Hz, HO ×2), 1.77 (2H, dqq, *J* = 3.5, 6.5, 7 Hz, HC-2 & HC-12), 1.01 (12H, ap d, *J* = 7 Hz, H_3CC-4 & H_3CC-6, H_3CC-8 & H_3CC-10), 0.98 (6H, d, *J* = 6.5 Hz, H_3C-1 & H_3C-13), 0.96 (9H, t, *J* = 8 Hz, H_3CCCSi ×3), 0.89 (6H, d, *J* = 7 Hz, H_3C-1' & H_3C-13'), 0.63 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3 (s ×2, C-5 & C-9), 78.2 (d ×2, C-3 & C-11), 74.0 (d , C-7), 51.3 (d ×2, C-6 & C-8), 48.9 (d ×2, C-4 & C-10), 29.7 (d ×2, C-2 & C-12), 20.3 (q ×2, C-1 & C-13), 14.8 (q ×2, C-1' & C-13'), 14.2 (q ×2, CH_3C-4 & CH_3C-10), 11.6 (q ×2, CH_3C-6 & CH_3C-8), 7.0 (q ×3, CH_2Si), 5.1 (t ×3, CH_3CSI).

HRMS *m/z* calcd for $C_{25}H_{50}O_5Si+Na^+$ 481.3305, found 481.3319 (ESI).



213

(3*R*,4*R*,6*S*,7*R*,8*R*,10*S*,11*R*)-*rel*-3,11-Dihydroxy-2,4,6,8,10,12-hexamethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (213)

*i*PrCHO (0.116 mL, 92 mg, 1.3 mmol) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (40 mg, 0.13 mmol) according to the general procedure, at –78 °C under Ar. After 3 h, the reaction vessel was removed from the cool bath. After 30 min, the reaction vessel was transferred to an ice bath and the reaction was quenched and processed as described in the general procedure. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave **212** (45 mg, 77%) and the title compound (5 mg, 9%).

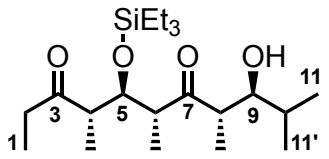
colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3517, 1699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (1H, t, *J* = 6 Hz, HC-7), 3.50 (1H, ddd, *J* = 3.5, 5, 8 Hz, HC-3), 3.50 (1H, ddd, *J* = 1.5, 2, 9 Hz, HC-11), 3.23 (1H, d, *J* = 2 Hz, HOC-11), 3.03 (1H, dq, *J* = 6, 7 Hz, HC-6), 3.00 (1H, dq, *J* = 6, 7 Hz, HC-8), 2.90 (1H, dq, *J* = 8, 7 Hz, HC-4), 2.88 (1H, dq, *J* = 1.5, 7.5 Hz, HC-10), 2.62 (1H, d, *J* = 5 Hz, HOC-3), 1.78 (1H, dqq, *J* = 3.5, 7, 7 Hz, HC-2), 1.67 (1H, dqq, *J* = 9, 7, 7 Hz, HC-12), 1.13 (3H, d, *J* = 7.5 Hz, H_3CC-10), 1.04 (3H, d, *J* = 7 Hz, H_3C-13), 1.02 (3H, d, *J* = 7 Hz, H_3CC-4), 1.01 (6H, br d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 0.99 (3H, d, *J* = 7 Hz, H_3C-1), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.90 (3H, d, *J* = 7 Hz, H_3C-1'), 0.84 (3H, d, *J* = 7 Hz, H_3C-13'), 0.62 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.6 (s, C-9), 217.2 (s, C-5), 78.1 (d, C-3), 75.9 (d, C-11), 75.0 (d, C-7), 51.1 (d, C-6), 49.5 (d, C-8), 49.1 (d, C-4), 47.2 (d, C-10), 30.5 (d, C-12), 29.7 (d, C-2), 20.3 (q, C-1), 19.9 (q, C-13), 18.9 (q, C-13'), 14.8 (q, C-1'), 14.2 (q, CH_3C-4), 12.1 (q, CH_3C-8), 11.9 (q, CH_3C-6), 9.2 (q, CH_3C-10), 7.1 (q ×3, CH_3CSi), 5.2 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{25}H_{50}O_5Si+Na^+$ 481.3319, found 481.3322 (ESI).



214

(4*S*,5*R*,6*R*,8*S*,9*S*)-*rel*-9-Hydroxy-4,6,8,10-tetramethyl-5-((triethylsilyl)oxy)undecane-3,7-dione (214)

For preparation, see the preparation of **212**. Characterization data.

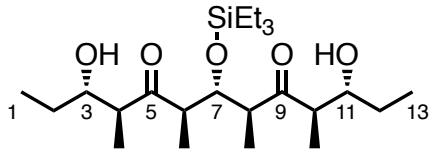
colorless viscous oil, TLC R_f = 0.5 (15% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3544, 1714 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (1H, dd, *J* = 6, 6 Hz, HC-5), 3.48 (1H, ddd, *J* = 3.5, 4.5, 8 Hz, HC-9), 3.00 (1H, dq, *J* = 6, 7 Hz, HC-6), 2.87 (1H, dq, *J* = 8, 7 Hz, HC-8), 2.76 (1H, dq, *J* = 6, 7 Hz, HC-4), 2.75 (1H, d, *J* = 4.5 Hz, HO), 2.57-2.45 (2H, m, H_2C-2), 1.78 (1H, dqq, *J* = 3.5, 7, 7 Hz, HC-10), 1.05 (3H, d, *J* = 7 Hz, CH_3C-4), 1.04 (3H, t, *J* = 7.5 Hz, H_3C-1), 1.01 (3H, d, *J* = 7 Hz, H_3CC-8), 0.99 (3H, d, *J* = 7 Hz, H_3C-11), 0.95 (3H, d, *J* = 7 Hz, H_3CC-6), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.90 (3H, d, *J* = 7 Hz, H_3C-11'), 0.62 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.0 (s, C-7), 212.6 (s, C-3), 78.3 (d, C-9), 75.2 (d, C-5), 51.4 (d, C-4), 50.8 (d, C-6), 49.2 (d, C-8), 35.8 (t, C-2), 29.7 (d, C-10), 20.4 (q, C-11), 14.7 (q, C-11'), 14.0 (q, CH_3C-8), 12.5 (q, CH_3C-6), 11.4 (q, CH_3C-4), 7.8 (q, C-1), 7.1 (q ×3, CH_3CSi), 5.1 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{21}H_{42}O_4Si+Na^+$ 409.2745, found 409.2753 (ESI).



216

(3*S*,4*S*,6*R*,7*r*,8*S*,10*R*,11*R*)-3,11-Dihydroxy-4,6,8,10-tetramethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (216)

EtCHO (0.140 mL, 111 mg, 1.9 mmol) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (60 mg, 0.19 mmol) according to the general procedure, at –78 °C under Ar. After 24 h, the reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 82:5:3:4:1 mixture of **216**, **216b**, 10-*epi*-**216b**, **216a**, and **202aa**, respectively. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave a 1.6:1 mixture of **216b**, 10-*epi*-**216b** (5 mg, 6%), **216a** (5 mg, 7%), and the title compound (60 mg, 73%).

colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

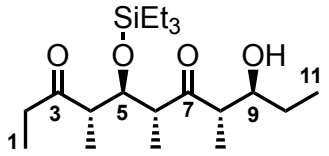
IR (DRIFT) ν_{max} 3459, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (1H, t, *J* = 6 Hz, HC-7), 3.58 (2H, dddd, *J* = 3, 5, 7.5, 7.5 Hz, HC-3 & HC-11), 3.02 (2H, dq, *J* = 6, 7 Hz, HC-6 & HC-8), 2.93 (2H, d, *J* = 5 Hz, HO ×2), 2.79 (2H, dq, *J* = 7.5, 7 Hz, HC-4 & HC-10), 1.60 (2H, ddq, *J* = 3,14, 7.5 Hz, HC-2 & HC-12), 1.41 (2H, ddq, *J* = 7.5,14, 7.5 Hz, HC-2 & HC-12), 1.06 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-10), 1.01 (6H, d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 0.98 (6H, t, *J* = 7.5 Hz, H_3C-1 & H_3C-13), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.64 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.0 (s ×2, C-5 & C-9), 75.4 (d ×2, C-3 & C-11), 74.3 (d , C-7), 51.1 (d ×2, C-6 & C-8), 50.9 (d ×2, C-4 & C-10), 27.4 (t ×2, C-2 & C-12), 14.4 (q ×2, CH_3C-4 &

CH_3C-10), 11.7 (q ×2, CH_3C-6 & CH_3C-8), 9.8 (q ×2, C-1 & C-11), 7.0 (q ×3, CH_3CSi), 5.1 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{23}H_{46}O_5Si+Na^+$ 453.3006, found 453.3014 (ESI).



216a

(4*S*,5*R*,6*R*,8*S*,9*S*)-*rel*-9-Hydroxy-4,6,8-trimethyl-5-((triethylsilyl)oxy)undecane-3,7-dione (216a)

For preparation, see the preparation of **216**.

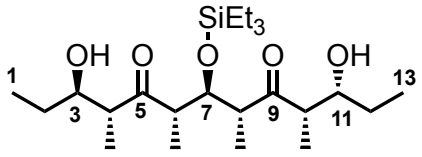
colorless oil, TLC R_f = 0.3 (15 % ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3523, 1713 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (1H, dd, *J* = 6, 6 Hz, HC-5), 3.58 (1H, dddd, *J* = 3, 4.5 8, 8 Hz, HC-9), 3.00 (1H, dq, *J* = 6, 7.0 Hz, HC-6), 2.94 (1H, d, *J* = 4.5 Hz, HO), 2.78 (1H, dq, *J* = 8, 7 Hz, HC-8), 2.75 (1H, dq, *J* = 6, 7 Hz, HC-4), 2.58-2.45 (2H, m, H_2C-2), 1.61 (1H, ddq, *J* = 3, 14, 7.5 Hz, HC-10), 1.42 (1H, ddq, *J* = 8, 14, 7.5 Hz, HC-10), 1.05 (3H, d, *J* = 7 Hz, H_3CC-8), 1.04 (3H, d, *J* = 7 Hz, H_3CC-4), 1.04 (3H, t, *J* = 7.5 Hz, H_3C-1), 0.98 (3H, t, *J* = 7.5 Hz, H_3C-11), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.94 (3H, d, *J* = 7 Hz, H_3CC-6), 0.62 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.8 (s, C-7), 212.6 (s, C-3), 75.6 (d, C-9), 75.2 (d, C-5), 51.4 (d, C-4), 51.0 (d, C-8), 50.7 (d, C-6), 35.8 (t, C-2), 27.4 (t, C-10), 14.2 (q, CH_3C-8), 12.5 (q, CH_3C-6), 11.4 (q, CH_3C-4), 9.7 (q, C-11), 7.8 (q, C-1), 7.0 (q ×3, CH_3CSi), 5.1 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{20}H_{40}O_4Si+Na^+$ 395.2588, found 395.2589 (ESI).



216b

(3*R*,4*R*,6*S*,7*R*,8*R*,10*S*,11*R*)-*rel*-3,11-Dihydroxy-4,6,8,10-tetramethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (216b)

EtCHO (0.091 mL, 74 mg, 1.3 mmol) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (40 mg, 0.13 mmol) according to the general procedure, at –78 °C under Ar. After 3 h, the reaction vessel was removed from the cool bath. After 30 min, the reaction vessel was transferred to an ice bath and the reaction was quenched and processed as described in the general procedure. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave **216** (27 mg, 49%) and the title compound as a 3:1 mixture with 10-*epi*-**216b** (tentatively identified) (7 mg, 13%).

colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

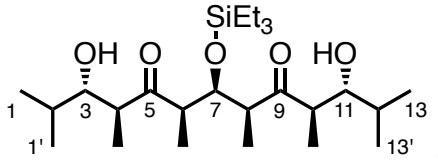
IR (DRIFT) ν_{max} 3472, 1701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (1H, dd, *J* = 6, 6.5 Hz, HC-7), 3.86 (1H, ddd, *J* = 6.5, 7, 8 Hz, HC-11), 3.60 (1H, dddd, *J* = 3, 5, 7.5, 7.5 Hz, HC-3), 3.09 (1H, br s, HOC-11), 3.00 (1H, dq, *J* =

6, 7 Hz, HC-6 or HC-8), 2.99 (1H, dq, *J* = 6, 7 Hz, HC-8 or HC-6), 2.85-2.75 (2H, m, HOC-3 & HC-4), 2.72 (1H, br q, *J* = 7 Hz, HC-10), 1.68-1.50 (2H, m, HC-2 & HC-12), 1.48-1.30 (2H, m, HC-2 & HC-12), 1.13 (3H, d, *J* = 7 Hz, H_3CC-10), 1.07 (3H, d, *J* = 7 Hz, H_3CC-4), 1.00 (6H, br d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 0.98 (3H, t, *J* = 7 Hz, H_3C-1), 0.97 (3H, t, *J* = 7 Hz, H_3C-13), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.67-0.58 (6H, m, H_2CSi ×3), δ (for minor isomer; partial data) 4.54 (1H, dd, *J* = 5.5, 6.5 Hz, HC-7), 2.47 (1H, d, *J* = 6 Hz, HO).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3 (s, C-9), 217.0 (s, C-5), 75.4 (d, C-3), 75.0 (d, C-7), 72.0 (d, C-11), 51.0 (d, C-4 or C-6), 50.8 (d, C-6 or C-4), 49.5 (d, C-8 or C-10), 49.3 (d, C-10 or C-8), 27.4 (t, C-2), 26.7 (t, C-12), 14.4 (q, CH_3C-4), 12.0 (q, CH_3C-8 or CH_3C-6), 11.7 (q, CH_3C-6 or CH_3C-8), 10.7 (q, C-13), 9.8 (q, C-1), 9.5 (q, CH_3C-10), 7.0 (q ×3, CH_3CSi), 5.2 (t ×3, CH_2Si), δ (for minor isomer) 217.5, 216.5, 75.5, 75.4, 73.7, 52.0, 50.9, 50.8, 49.9, 27.7, 27.4, 14.4, 14.0, 12.0, 11.3, 9.9, 9.8, 7.0, 5.2.

HRMS *m/z* calcd for $C_{23}H_{46}O_5Si+Na^+$ 453.3006, found 453.3018 (ESI).



217

(3*S*,4*S*,6*R*,7*s*,8*S*,10*R*,11*R*)-3,11-Dihydroxy-2,4,6,8,10,12-hexamethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (217)

*i*PrCHO (0.060 mL, 47 mg, 0.64 mmol) was added via syringe to a stirring solution of the (*E*,*E*)-**220** prepared from **202ss** (20 mg, 0.064 mmol) according to the general procedure, at –78 °C under Ar. After 24 h, the reaction was quenched and processed as described in the general

procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 85:7:5:3 mixture of **217**, **221**, 11-*epi*-**217** (tentatively identified), and **202aa**, respectively. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave the title compound (24 mg, 82%).

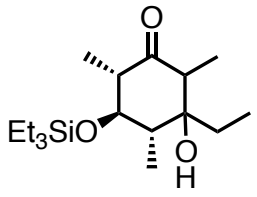
colorless viscous oil, TLC R_f = 0.4 (15% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3487, 1704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (1H, t, *J* = 5.5 Hz, HC-7), 3.49 (2H, ddd, *J* = 4, 6, 8 Hz, HC-3 & HC-11), 2.91 (2H, dq, *J* = 8, 7 Hz, HC-4 & HC-10), 2.86 (2H, dq, *J* = 5.5, 7 Hz, HC-6 & HC-8), 2.51 (2H, d, *J* = 6 Hz, HO ×2), 1.75 (2H, dqq, *J* = 4, 7, 7 Hz, HC-2 & HC-12), 1.10 (6H, d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 1.03 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-10), 0.97 (6H, d, *J* = 7 Hz, H_3C-1 & H_3C-13), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.89 (6H, d, *J* = 7 Hz, H_3C-1', H_3C-13'), 0.65 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.8 (s ×2, C-5 & C-9), 78.5 (d ×2, C-3 & C-11), 72.0 (d, C-7), 51.5 (d ×2, C-6 & C-8), 48.7 (d ×2, C-4 & C-10), 30.0 (d ×2, C-2 & C-12), 20.3 (q ×2, C-1 & C-13), 15.2 (q ×2, C-1' & C-13'), 14.5 (q ×2, CH_3C-4 & CH_3C-10), 12.9 (q ×2, CH_3C-6 & CH_3C-8), 7.3 (q ×3, CH_3CSi), 5.4 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{25}H_{50}O_5Si+Na^+$ 481.3320, found 481.3339 (ESI).



218

(4*R*,5*R*,6*S*)-*rel*-3-Ethyl-3-hydroxy-2,4,6-trimethyl-5-((triethylsilyl)oxy)cyclohexanone (218)

c-Hex_2BCl (1M in hexane; 0.25 mL, 0.25 mmol) was added via syringe to a stirring solution of **202ss** (20 mg, 0.064 mmol) and triethylamine (0.043 mL, 31 mg, 0.31 mmol) in CH_2Cl_2 (0.1 mL) at 0 °C under argon. After 3 h, the mixture was cooled to –78 °C and a solution of *i*PrCHO (0.60 mL, 47 mg, 0.64 mmol) was added via syringe. After 3 h, the reaction was quenched with sequential addition of phosphate buffer (pH 7, 0.5 mL), 30% aq H_2O_2 (0.5 mL), and MeOH (0.5 mL) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 20 min, the mixture was diluted with sat. $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (15% ethyl acetate in hexane) to give the title compound as a single diastereomer (19 mg, 95%).

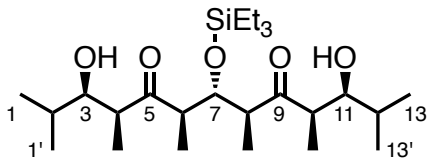
white waxy solid, TLC R_f = 0.3 (15% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3518, 1699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.49 (1H, t, *J* = 9.5 Hz, HC-5), 2.64 (1H, dq, *J* = 9.5, 6.5 Hz, HC-6), 2.49 (1H, q, *J* = 7.5 Hz, HC-2), 1.96 (1H, dq, *J* = 9.5, 7 Hz, HC-4), 1.72 (1H, dq, *J* = 15, 7.5 Hz, HC-1'), 1.48 (1H, dq, *J* = 15, 7.5 Hz, HC-1'), 1.34 (1H, s, OH), 1.12 (3H, d, *J* = 7.5 Hz, H_3CC-2), 1.10 (3H, d, *J* = 6.5 Hz, H_3CC-6), 1.06 (3H, d, *J* = 6.5 Hz, H_3CC-4), 0.98 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.85 (3H, t, *J* = 7.5 Hz, H_3C-2'), 0.67 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.8 (s, C-1), 79.5 (d, C-5), 77.1 (d, C-3), 52.8 (d, C-2), 49.1 (d, C-6), 42.7 (d, C-4), 29.2 (t, C-1'), 14.7 (q, H_3CC-2), 11.8 (q, H_3CC-6), 11.0 (q, H_3CC-4), 7.3 (q ×3, H_3CCSi), 6.5 (q, C-2'), 5.9 (t ×3, H_2CSi).

HRMS *m/z* calcd for $C_{17}H_{34}O_3Si+Na^+$ 337.2169, found 337.2168 (ESI).



223

(3*R*,4*S*,6*R*,7*r*,8*S*,10R,11S)-3,11-Dihydroxy-2,4,6,8,10,12-hexamethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (223)

Reaction of the (*Z*,*Z*)-**222**, prepared from **202aa** (20 mg, 0.064 mmol), with *i*-PrCHO (0.058 mL, 46 mg, 0.64 mmol) according to the general procedure gave a crude product whose ^{1}H NMR spectrum suggested the presence of a 50:1.5:1 mixture of **223**, monoaldol, and **202aa**, respectively. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave the title compound (25 mg, 86%).

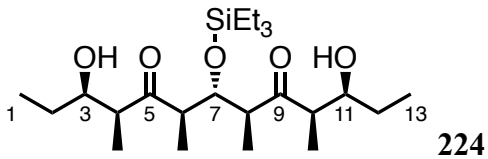
colorless viscous oil, TLC R_f = 0.3 (15% ethylacetate in hexanes).

IR (DRIFT) ν_{max} 3513, 1699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (1H, t, *J* = 6 Hz, HC-7), 3.50 (2H, ddd, *J* = 1.5. 2, 9.5 Hz, HC-3 & HC-11), 3.21 (2H, d, *J* = 2 Hz, HO ×2), 2.97 (2H, dq, *J* = 6, 7 Hz, HC-6 & HC-8), 2.87 (2H, dq, *J* = 1.5, 7.5 Hz, HC-4 & HC-10), 1.66 (2H, dqq, *J* = 9.5, 6.5, 7 Hz, HC-2 & HC-12), 1.13 (6H, d, *J* = 7.5 Hz, H_3CC-4 & H_3CC-10), 1.04 (6H, d, *J* = 6.5 Hz, H_3C-1 & H_3C-13), 0.99 (6H, d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.84 (6H, d, *J* = 7 Hz, H_3C-1' & H_3C-13'), 0.59 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.5 (s ×2, C-5 & C-9), 75.9 (d ×2, C-3 & C-11), 75.8 (d, C-7), 49.5 (d ×2, C-6 & C-8), 47.1 (d ×2, C-4 & C-10), 30.4 (d ×2, C-2 & C-12), 19.9 (q ×2, C-1 & C-13), 18.9 (q ×2, C-1' & C-13'), 12.0 (q ×2, CH_3C-6 & CH_3C-8), 9.2 (q ×2, CH_3C-4 & CH_3C-10), 7.1 (q ×3, CH_3CSi), 5.2 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{25}H_{50}O_5Si+Na^+$ 481.3320, found 481.3304 (ESI).



224

(3*R*,4*S*,6*R*,7*r*,8*S*,10*R*,11*S*)-3,11-Dihydroxy-4,6,8,10-tetramethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (224)

Reaction of the (*Z*,*Z*)-**222**, prepared from **202aa** (20 mg, 0.064 mmol), with propanal (0.046 mL, 38 mg, 0.64 mmol) according to the general procedure gave a crude product whose ^{1}H NMR spectrum suggested the presence of a 25:1.3:1 mixture of **224**, monoaldol, and **202aa**, respectively. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave the title compound (23 mg, 84%).

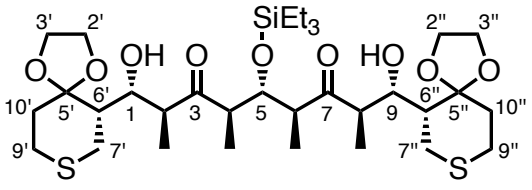
colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3487, 1699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (1H, t, *J* = 6 Hz, HC-7), 3.85 (2H, dddd, *J* = 2, 2, 5.5, 8 Hz, HC-3 & HC-11), 3.08 (2H, d, *J* = 2 Hz, HO), 2.95 (2H, dq, *J* = 6, 7 Hz, HC-6 & HC-8), 2.70 (2H, dq, *J* = 2, 7.5 Hz, HC-4 & HC-10), 1.56 (2H, ddq, *J* = 8, 14, 7.5 Hz, HC-2 & HC-12), 1.34 (2H, ddq, *J* = 5.5, 14, 7.5 Hz, HC-2 & HC-12), 1.12 (6H, d, *J* = 7.5 Hz, H_3CC-4 & H_3CC-10), 0.97 (6H, d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 0.94 (6H, t, *J* = 7.5 Hz, H_3C-1 & H_3C-13), 0.94 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.58 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3 (s ×2, C-5 & C-9), 75.6 (d, C-7), 72.0 (d ×2, C-3 & C-11), 49.4 (d ×2, C-6 & C-8), 49.2 (d ×2, C-4 & C-10), 26.7 (t ×2, C-2 & C-12), 11.8 (q ×2, CH_3C-6 & CH_3C-8), 10.7 (q ×2, C-1 & C-13), 9.4 (q ×2, CH_3C-4 & CH_3C-10), 7.0 (q ×3, CH_3CSi), 5.2 (t ×3, CH_2Si).

HRMS *m/z* calcd for C23H46O5Si+Na^+ 453.3007, found 453.3009 (ESI).



230

(1*R*,2*S*,4*R*,5*r*,6*S*,8*R*,9*S*)-1,9-dihydroxy-2,4,6,8-tetramethyl-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-9-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)nonane-3,7-dione (230)

A solution of (±)-**109** (96 mg, 0.51 mmol) in CH_2Cl_2 (0.20 mL) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (40 mg, 0.13 mmol) according to the general procedure, at –78 °C under Ar. After 24 h, the reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 82:12:3:3 mixture of **230**, **231**, **230a** (tentative), and **235**, respectively. Fractionation of the crude product by FCC (40% ethyl acetate in hexane) gave recovered (±)-**109** (37 mg, 38%), **231** (4.5 mg, 6%), and the title compound (69 mg, 79%).

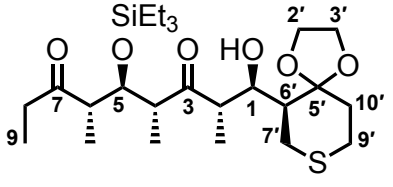
colorless viscous oil, TLC R_f = 0.3 (40% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3525, 2879 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (1H, t, *J* = 6 Hz, HC-5), 4.23 (2H, br d, *J* = 9.5 Hz, HC-1 & HC-9), 4.08-3.9 (8H, m, H_2CO ×4), 3.08 (2H, dd, *J* = 12, 13.5 Hz, HC-7' & HC-7''), 3.03 (2H, s, HO ×2), 2.93-2.85 (6H, m, HC-2 & HC-4 & HC-6, HC-8 & HC-9' & HC-9''), 2.64 (2H, br d, *J* = 14 Hz, HC-1'), 2.56 (2H, br d, *J* = 13.5 Hz, HC-7' & HC-7''), 2.50 (2H, br d, *J* = 14 Hz, HC-9' & HC-9''), 2.12 (2H, br d, *J* = 14 Hz, HC-10' & HC-10''), 2.02 (2H, br d, *J* = 11.5 Hz, HC-6' & HC-6''), 1.72 (2H, dd, *J* = 3, 12.5, 14 Hz, HC-10' & HC-10''), 1.07 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-6), 0.96 (6H, d, *J* = 7 Hz, H_3CC-2 & H_3CC-8), 0.94 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.63 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2 (s ×2, C-3 & C-7), 110.3 (s ×2, C-5' & C-5''), 73.9 (d , C-5), 71.7 (d ×2, C-1 & C-9), 64.9 (t ×2, C-2' & C-2''), 64.4 (t ×2, C-3' & C-3''), 51.7 (d ×2, C-4 & C-6), 47.2 (d ×2, C-2 & C-8), 46.6 (d ×2, C-6' & C-6''), 36.9 (t ×2, C-10' & C-10''), 26.7 (t ×2, C-9' & C-9''), 25.8 (t ×2, C-7' & C-7''), 14.1 (q ×2, CH_3C-2 & CH_3C-8), 12.3 (q ×2, CH_3C-4 & CH_3C-6), 7.2 (q ×3, CH_3CSi), 5.3 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{33}H_{58}O_9S_2Si+Na^+$ 713.3183, found 713.3189 (ESI).



(±)-**231**

(1*R*,2*S*,4*R*,5*R*,6*S*)-*rel*-1-Hydroxy-2,4,6-trimethyl-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)nonane-3,7-dione ((±)-231)

A solution of (±)-**109** (11 mg, 0.059 mmol) in CH_2Cl_2 (0.080 mL) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (21 mg, 0.067 mmol) according to the

general procedure, at –78 °C under Ar. After 3 h, the reaction vessel was removed from the cooling bath. After 30 min, the reaction vessel was transferred to an ice bath and the reaction was quenched and processed as described in the general procedure. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) to give recovered **202aa** (4 mg, 19%), **230** (10 mg, 50%), and a fraction containing (±)-**231**; fractionation of the latter by PTLC (20% ethyl acetate in toluene) gave the title compound (13 mg, 44%).

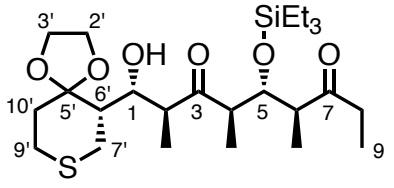
colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3526, 1715 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (1H, dd, *J* = 4, 8 Hz, HC-5), 4.27 (1H, ddd, *J* = 1, 1.5, 9.5 Hz, HC-1), 4.09-3.90 (4H, m, H_2C-2' & H_2C-3'), 3.07 (1H, dd, *J* = 12, 14 Hz, HC-7'), 3.01 (1H, d, *J* = 1.5 Hz, HO), 2.95 (1H, dq, *J* = 9.5, 7 Hz, HC-2), 2.83 (1H, dt, *J* = 2.5, 13, 13 Hz, HC-9'), 2.78 (1H, dq, *J* = 4, 7 Hz, HC-4), 2.75 (1H, dq, *J* = 8, 7 Hz, HC-6), 2.57 (1H, ddd, *J* = 2, 3.5, 14 Hz, HC-7'), 2.55-2.39 (2H, m, HC-8 & HC-9'), 2.43 (1H, dq, *J* = 18.5, 7 Hz, HC-8), 2.14 (1H, ddd, *J* = 2.5, 4, 13.5 Hz, HC-10'), 2.03 (1H, ddd, *J* = 1, 3.5, 12 Hz, HC-6'), 1.72 (1H, dt, *J* = 4, 13, 13.5 Hz, HC-10'), 1.14 (3H, d, *J* = 7 Hz, H_3CC-4), 1.01 (3H, t, *J* = 7 Hz, H_3C-9), 0.96 (6H, br d, *J* = 7 Hz, H_3CC-2 & H_3CC-6), 0.93 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.59 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2 (s, C-3), 213.9 (s, C-7), 110.4 (s, C-5'), 75.1 (d, C-5), 71.9 (d, C-1), 64.9 (t, C-2'), 64.4 (t, C-3'), 51.7 (d, C-4), 50.6 (d, C-6), 46.46 (d, C-2 or C-6'), 46.42 (d, C-2 or C-6'), 36.7 (t, C-10'), 36.5 (t, C-8), 26.7 (t, C-9'), 25.8 (t, C-7'), 14.1 (q, CH_3C-2), 13.4 (q, CH_3C-6), 12.0 (q, CH_3C-4), 7.6 (q, C-9), 7.1 (q ×3, CH_3CSi), 5.2 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{25}H_{46}O_6SSi+Na^+$ 525.2676, found 525.2690 (ESI).

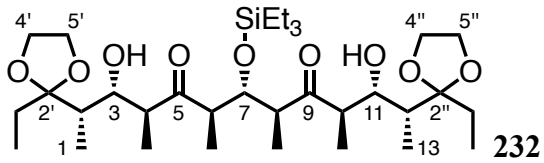


(+)-**231**

(1*R*,2*S*,4*R*,5*R*,6*S*)-(+)-1-Hydroxy-2,4,6-trimethyl-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)nonane-3,7-dione ((+)-231)

t-$BuNH_2$ (0.020 mL, 14 mg, 0.19 mmol) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (20 mg, 0.064 mmol) according to the general procedure, at 0 °C under Ar. After 30 min, the mixture was cooled to –50 °C and a solution of (–)-(*S*)-**109**, prepared from (–)-(*S*)-**139** (92% ee; 11 mg, 0.058 mmol) as described above, in CH_2Cl_2 (0.10 mL) was added via syringe. After 3 h, the reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 87:10:2:1 mixture of **(+)-231**, **202aa**, **230a**, and (–)-(*S*)-**109**, respectively. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave recovered **202aa** (1.5 mg, 8%), and the title compound (26 mg, 81%) ($[\alpha]_D$ +71 (*c* 1.0, $CHCl_3$); er > 50:1 by HPLC). ^{1}H and ^{13}C NMR data closely matched those reported above for (±)-**231**.

colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).



232

(2*S*,3*R*,4*S*,6*R*,7*r*,8*S*,10*R*,11*S*,12*R*)-2,12-Bis(2-ethyl-1,3-dioxolan-2-yl)-3,11-dihydroxy-4,6,8,10-tetramethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (232)

From **230**. A suspension of Raney nickel (W2; 0.3 mL settled volume) in EtOH (1 mL) was added to **230** (21 mg, 0.030 mmol), and the mixture was heated under reflux with vigorous stirring. After 2.5 h (reaction was complete by TLC analysis), the mixture was decanted, and the solid was suspended in EtOH (2 mL) and heated under reflux with vigorous stirring for several min. This washing procedure was repeated with ethyl acetate, and acetone. The combined organic layers were filtered through Celite® and concentrated to get the crude product. The crude was dissolved in 30% ethyl acetate in hexane and passed through a short plug of silica gel washing with 30% ethyl acetate in hexane. The combined filtrate and washings were concentrated to give the title compound (18 mg, 94%); spectral data were consistent with those reported below. From (±)-**241**. A suspension of Raney Ni (W2; 0.3 mL settled volume) in EtOH (0.8 mL) was added to (±)-**241** (17 mg, 0.026 mmol) and the mixture was heated under reflux with vigorous stirring. After 3 h (reaction was complete by TLC analysis), the mixture was processed as described above to give the title compound (15 mg, 92%); spectral data were consistent with those reported below. From **202aa**. A solution of (±)-**159** (121 mg, 0.76 mmol) in CH_2Cl_2 (0.30 mL) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (60 mg, 0.19 mmol) according to the general procedure, at –78 °C under Ar. After 24 h, the reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 81:11:3:5 mixture of **232**, **233**, **234**, and **202aa**, respectively. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave **233** (8 mg, 9%), a 2.3:1 mixture of **234** and **232**, respectively (6 mg, 5%), and the title compound (93 mg, 77%).

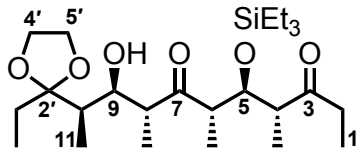
colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3529, 1712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (1H, t, *J* = 5.5 Hz, HC-7), 4.03 (2H, br d, *J* = 9.5 Hz, HC-3 & HC-9), 3.97-3.94 (8H, m, H_2CO ×4), 3.07 (2H, br s, HO ×2), 2.95-2.84 (4H, m, HC-4 & HC-6), 1.96 (2H, br q, *J* = 7 Hz, HC-2 & HC-12), 1.78-1.64 (4H, m, H_2CC-2' & H_2CC-2''), 1.07 (6H, d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.94 (6H, d, *J* = 7 Hz, H_3C-1 & H_3C-13), 0.91 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-10), 0.87 (6H, t, *J* = 7.5 Hz, H_3CCC-2' & H_3CCC-2''), 0.66 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.6 (s ×2, C-5 & C-9), 114.7 (s ×2, C-2' & C-2''), 73.9 (d, C-7), 73.1 (d ×2, C-3 & C-11), 65.8 (t ×2, C-4' & C-4''), 64.9 (t ×2, C-5', & C-5''), 51.8 (d ×2, C-6 & C-8), 48.0 (d ×2, C-4 & C-10), 38.8 (d ×2, C-2 & C-12), 28.2 (t ×2, CH_2C-2' & CH_2C-2''), 13.8 (q ×2, CH_3C-4 & CH_3C-10), 12.1 (q ×2, CH_3C-6 & CH_3C-8), 8.2 (q ×2, CH_3CC-2' & CH_3CC-2''), 7.2 (q ×3, CH_3CSi), 6.6 (q ×2, C-1 & C-13), 5.3 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{33}H_{62}O_9Si+Na^+$ 653.4055, found 653.4029 (ESI).



233

(4*R*,5*S*,6*S*,8*R*,9*S*,10*R*)-*rel*-10-(2-ethyl-1,3-dioxolan-2-yl)-9-hydroxy-4,6,8-trimethyl-5-((triethylsilyl)oxy)undecane-3,7-dione (233)

For preparation, see the preparation of **232**.

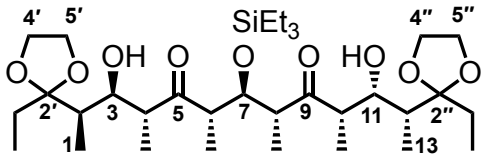
colorless viscous oil, TLC R_f = 0.4 (20% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3530, 1716 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (1H, dd, *J* = 4, 8 Hz, HC-5), 4.07 (1H, br d, *J* = 10 Hz, HC-9), 4.0-3.93 (4H, m, H_2C-4' & H_2C-5'), 3.05 (1H, d, *J* = 1 Hz, HO), 2.93 (1H, dq, *J* = 10, 7 Hz, HC-8), 2.80 (1H, dq, *J* = 4, 7 Hz, HC-6), 2.77 (1H, dq, *J* = 8, 7 Hz, HC-4), 2.53 (1H, dq, *J* = 18.5, 7 Hz, HC-2), 2.44 (1H, dq, *J* = 18.5, 7 Hz, HC-2), 1.98 (1H, br q, *J* = 7 Hz, HC-10), 1.77-1.65 (2H, m, H_2CC-2'), 1.16 (3H, d, *J* = 7 Hz, H_3CC-6), 1.01 (3H, t, *J* = 7 Hz, H_3C-1), 0.97 (3H, d, *J* = 7 Hz, H_3CC-4), 0.95 (3H, d, *J* = 7 Hz, H_3C-11), 0.94 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.91 (3H, d, *J* = 7 Hz, H_3CC-8), 0.88 (3H, t, *J* = 7.5 Hz, H_3CCC-2'), 0.61 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.5 (s, C-7), 213.9 (s, C-3), 114.7 (s, C-2'), 75.1 (d, C-5), 73.3 (d, C-9), 65.8 (t, C-4'), 64.9 (t, C-5'), 51.8 (d, C-6), 50.6 (d, C-4), 47.1 (d, C-8), 38.4 (d, C-10), 36.4 (t, C-2), 28.3 (t, CH_2C-2'), 13.8 (q, CH_3C-8), 13.3 (q, CH_3C-4), 12.0 (q, CH_3C-6), 8.3 (q, CH_3CC-2'), 7.6 (q, C-1), 7.1 (q ×3, CH_3CSi), 6.6 (q, C-11), 5.2 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{25}H_{48}O_6Si+Na^+$ 495.3112, found 495.3108 (ESI).



234

(2*R*,3*S*,4*R*,6*S*,7*S*,8*R*,10*S*,11*S*,12*R*)-*rel*-2,12-Bis(2-ethyl-1,3-dioxolan-2-yl)-3,11-dihydroxy-4,6,8,10-tetramethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (234)

Fractionation of a 2.3:1 mixture of **234** and **232**, respectively (6 mg) (see preparation of **232**), by PTLC (20% Et_2O in hexane) gave the title compound as an ca. 7:1 mixture with 10-*epi*-**234** (tentatively identified) (3 mg, 2.5% from **202aa**).

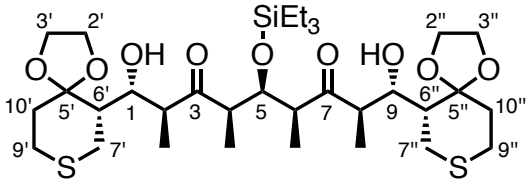
colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3532, 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.51 (1H, dd, *J* = 5.5, 5.5 Hz, HC-7), 4.11 (1H, ddd, *J* = 1, 3, 7 Hz, HC-11), 4.06 (1H, br d, *J* = 10 Hz, HC-3), 4.00-3.94 (8H, m, H_2CO ×4), 3.16 (1H, d, *J* = 1 Hz, HOC-11), 3.07 (1H, d, *J* = 1.5 Hz, HOC-3), 2.98-2.89 (3H, m, HC-6 & HC-8 & HC-10), 2.86 (1H, dq, *J* = 10, 7 Hz, HC-4), 1.97 (1H, br q, *J* = 7 Hz, HC-2), 1.88 (1H, dq, *J* = 3, 7 Hz, HC-12), 1.77-1.62 (4H, m, H_2CC-2' & H_2CC-2''), 1.22 (3H, d, *J* = 7 Hz, H_3CC-10), 1.04 (6H, br d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 0.99 (3H, d, *J* = 7 Hz, H_3C-13), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.95 (3H, d, *J* = 7 Hz, H_3C-1), 0.92 (3H, d, *J* = 7 Hz, H_3CC-4), 0.88 (3H, t, *J* = 7.5 Hz, H_3CCC-2'), 0.86 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.63 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR δ 216.2 (s, C-9 or C-5), 216.0 (s, C-5 or C-9), 114.7 (s, C-2' or C-2''), 114.6 (s, C-2 or C-2'), 73.9 (d, C-7), 72.9 (d, C-3), 70.6 (d, C-11), 65.8 (t, CH_2O), 65.5 (t, CH_2O), 65.1 (t, CH_2O), 64.9 (t, CH_2O), 51.5 (d, C-6), 50.0 (d, C-8 or C-10), 49.8 (d, C-10 or C-8), 48.5 (d, C-4), 40.6 (d, C-12), 38.7 (d, C-2), 28.2 (t, CH_2C-2'), 27.6 (t, CH_2C-2''), 13.8 (q, CH_3C-4), 13.5 (q, CH_3C-10), 12.2 (q, CH_3C-6 or CH_3C-8), 12.0 (q, CH_3C-6 or CH_3C-8), 9.0 (q, C-13), 8.3 (q, CH_3CC-2'), 7.9 (q, CH_3CC-2''), 7.2 (q ×3, CH_3CSi), 6.6 (q, C-1), 5.3 (t ×3, CH_2Si), minor, 216.7, 215.2, 114.8, 73.7, 73.2, 73.0, 65.7, 64.9, 53.4, 51.0, 48.4, 47.9, 38.8, 38.4, 28.3, 28.2, 13.8, 13.2, 12.3, 10.7, 8.4, 8.2, 7.2, 6.73, 6.68, 5.3.

HRMS *m/z* calcd for $C_{33}H_{62}O_9Si+Na^+$ 653.4055, found 653.4054 (ESI).



236

(1*R*,2*S*,4*R*,5*s*,6*S*,8*R*,9*S*)-1,9-Dihydroxy-2,4,6,8-tetramethyl-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-9-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)nonane-3,7-dione (236)

A solution of (±)-**109** (48 mg, 0.26 mmol) in CH_2Cl_2 (0.10 mL) was added via syringe to a stirring solution of the (*E,E*)-**220**, prepared from **202ss** (20 mg, 0.064 mmol) according to the general procedure, at –78 °C under Ar. After 24 h, the reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 82:12:3:3 mixture of **236**, monoaldol, 5-*epi*-**235** (tentative), and **202ss**, respectively. Fractionation of the crude product by FCC (30% ethyl acetate in hexane) gave recovered (±)-**109** (15 mg, 31%), **236** δ (4.5 mg, 6%), and the title compound (37 mg, 84%).

colorless viscous oil, TLC R_f = 0.3 (40% ethyl acetate in hexane).

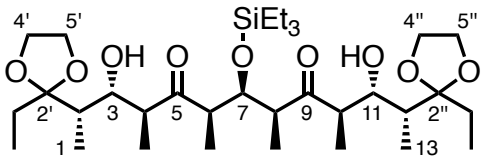
IR (DRIFT) ν_{max} 3520, 1709 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (2H, br d, *J* = 9.5 Hz, HC-1 & HC-9), 4.07-3.9 (8H, m, CH_2O ×4), 3.04 (2H, dd, *J* = 12, 14 Hz, HC-7' & HC-7), 2.95 (2H, d, *J* = 2.5 Hz, HO ×2), 2.93 (2H, dq, *J* = 9, 7 Hz, HC-2 & HC-8), 2.86-2.78 (4H, m, HC-4 & HC-6 & HC-9' & HC-9"), 2.62 (2H, ddd, *J* = 2, 3.5, 14 Hz, HC-7' & HC-7"), 2.51 (2H, dddd, *J* = 2, 3.5, 4, 13.5 Hz, HC-9' & HC-9"), 2.14 (2H, ddd, *J* = 2.5, 4, 13.5 Hz, HC-10' & HC-10"), 2.00 (2H, br d, *J* = 12 Hz, HC-6' & HC-6"), 1.72 (2H, ddd, *J* = 3.5, 13, 13.5 Hz, HC-10' & HC-10"), 1.09 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-6), 0.95 (6H, d, *J* = 7 Hz, H_3CC-2 & H_3CC-8), 0.93 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.63 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.8 (s ×2, C-3 & C-7), 110.3 (s ×2, C-5' & C-5"), 71.9 (d ×2, C-1 & C-9), 70.8 (d, C-5), 64.9 (t ×2, C-2' & C-2"), 64.4 (t ×2, C-3' & C-3"), 51.7 (d ×2, C-4 & C-

6), 47.0 (d ×2, C-2 & C-8), 46.5 (d ×2, C-6' & C-6"), 36.7 (t ×2, C-10' & C-10"), 26.7 (t ×2, C-9' & C-9"), 26.0 (t ×2, C-7' & C-7"), 14.2 (q ×2, CH_3C-2 & HC3C-8), 12.2 (q ×2, CH_3C-4 & CH_3C-6), 7.3 (q ×3, CH_3CSi), 5.5 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{33}H_{58}O_9S2Si$ 690.3292, found 690.3281 (FD).



237

(2*S*,3*R*,4*S*,6*R*,7*s*,8*S*,10*R*,11*S*,12*R*)-2,12-Bis(2-ethyl-1,3-dioxolan-2-yl)-3,11-dihydroxy-4,6,8,10-tetramethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (237)

From **236**. A suspension of Raney nickel (W2; 0.2 mL settled volume) in EtOH (1 mL) was added to **236** (13.5 mg, 0.020 mmol), and the mixture was heated under reflux with vigorous stirring. After 3 h (reaction was complete by TLC analysis), the mixture was decanted, and the solid was suspended in EtOH (2 mL) and heated under reflux with vigorous stirring for several min and then decanted. This washing procedure was repeated with ethyl acetate, and acetone (×2). The combined organic layers were filtered through Celite®, concentrated to get the crude product. The crude was dissolved in 30% ethyl acetate in hexanes, passed through a short silica gel pad and the combined organic layers were concentrated to give the title compound (11.6 mg, 94%). Spectral data were consistent with those reported below. From **202ss**. A solution of (±)-**159** (48 mg, 0.26 mmol) in CH_2Cl_2 (0.10 mL) was added via syringe to a stirring solution of the (*E*,*E*)-**220**, prepared from **202aa** (20 mg, 0.064 mmol) according to the general procedure, at –78 °C under Ar. After 24 h, the reaction was quenched and processed as described in the general procedure to

give the crude product whose ^{1}H NMR spectrum suggested the presence of a 100:4:3:5 mixture of **237**, monoaldol 7-*epi*-**234**, and **202ss**, respectively. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave the title compound (31 mg, 78%).

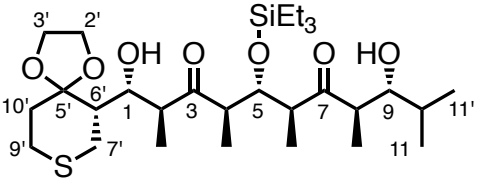
colorless viscous oil, TLC R_f = 0.5 (30% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3530, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (1H, t, *J* = 5 Hz, HC-7), 4.05 (2H, dd, *J* = 1, 9.5 Hz, HC-3 & HC-11), 3.99-3.92 (8H, m, H_2CO ×4), 2.97 (2H, br s, HO ×2), 2.92-2.85 (4H, m, HC-4 & HC-10 & HC-6 & HC-8), 1.94 (2H, dq, *J* = 1, 7 Hz, HC-2, HC-12), 1.76-1.63 (4H, m, H_2CC-2' & H_2CC-2"), 1.09 (6H, d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 0.93 (6H, d, *J* = 7 Hz, H_3C-1 & H_3C-13), 0.92 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.89 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-10), 0.86 (6H, t, *J* = 7.5 Hz, H_3CCC-2' & H_3CCC-2"), 0.63 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.2 (s ×2, C-5 & C-9), 114.7 (s ×2, C-2' & C-2"), 73.2 (d ×2, C-3 & C-11), 70.9 (d, C-7), 65.7 (t ×2, C-4' & C-4"), 64.9 (t ×2, C-5' & C-5"), 51.7 (d ×2, C-6 & C-8), 47.7 (d ×2, C-4 & C-10), 38.6 (d ×2, C-2 & C-12), 28.2 (t ×2, CH_2C-2' & CH_2C-2"), 14.0 (q ×2, CH_3C-4 & CH_3C-10), 12.1 (q ×2, CH_3C-6 & CH_3C-8), 8.3 (q ×2, CH_3CC-2' & CH_3CC-2"), 7.3 (q ×3, CH_3CSi), 6.7 (q ×2, C-1 & C-13), 5.4 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{33}H_{62}O_9Si+Na^+$ 653.4055, found 653.4035 (ESI).



(–)-**240**

(1*R*,2*S*,4*R*,5*R*,6*S*,8*R*,9*R*)-(–)-1,9-dihydroxy-2,4,6,8,10-Pentamethyl-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)undecane-3,7-dione ((–)-240)

t-$BuNH_2$ (0.020 mL, 14 mg, 0.19 mmol) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (20 mg, 0.064 mmol) according to the general procedure, at 0 °C under Ar. After 30 min, the mixture was cooled to –42 °C and a solution of (–)-(*S*)-**109**, prepared from (–)-(*S*)-**139** (92% ee; 11 mg, 0.058 mmol) as described above, in CH_2Cl_2 (0.10 mL) was added via syringe. After 3 h, *i*PrCHO (0.060 mL, 46 mg, 0.64 mmol) was added via syringe. After 3 h, reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 50:7:5:4 mixture of (–)-**240**, **212**, **231**, and **202aa**, respectively. Fractionation of the crude product by PTLC (20% ethyl acetate in hexane; 3 developments) gave the title compound (26 mg, 71%); $[\alpha]_D$ –41 (*c* 1.0, $CHCl_3$) (enantiomers not separable by HPLC; er assumed to be >50:1 based on the results for (+)-**231** and (+)-**241**).

colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

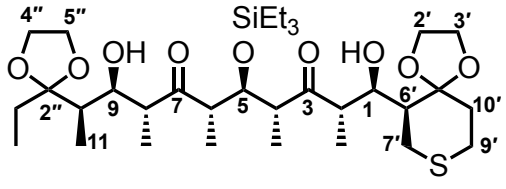
IR (DRIFT) ν_{max} 3519, 1712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (1H, dd, *J* = 3.5, 8.5 Hz, HC-5), 4.29 (1H, br d, *J* = 9.5 Hz, HC-1), 4.09-3.91 (4H, m, H_2C-2' & H_2C-3'), 3.43 (1H, dd, *J* = 3, 8.5 Hz, HC-9), 3.13-3.06 (3H, m, HO & HC-6 & HC-7'), 3.02 (1H, br s, HO), 2.98 (1H, dq, *J* = 9.5, 7 Hz, HC-2), 2.87-2.80 (3H, m, HC-4 & HC-8 & HC-9'), 2.57 (1H, ddd, *J* = 2, 3, 14 Hz, HC-7'), 2.51 (1H, ap dq, *J* = 3, 3, 3.5, 13.5 Hz, HC-9'), 2.15 (1H, ddd, *J* = 3, 3.5, 14 Hz, HC-10'), 2.02 (1H, br dd, *J* = 2, 12 Hz, HC-6'), 1.78 (1H, dqq, *J* = 3, 7, 7 Hz, HC-10), 1.72 (1H, ddd, *J* = 3.5, 13, 13.5 Hz, HC-10'), 1.17 (3H, d, *J* = 7 Hz, H_3CC-4), 0.99 (3H, d, *J* = 7 Hz, H_3C-11), 0.98 (3H, d, *J* = 7 Hz, H_3CC-8), 0.96 (3H, d,

J = 7 Hz, H_3CC-2), 0.95 (9H, t, J = 8 Hz, H_3CCSi ×3), 0.88 (6H, ap d, J = 6.5 Hz, H_3C-11' & H_3CC-6,), 0.63 (6H, q, J = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.5 (s, C-7), 215.0 (s, C-3), 110.3 (s, C-5'), 78.4 (d, C-9), 73.7 (d, C-5), 71.5 (d, C-1), 64.9 (t, C-2'), 64.3 (t, C-3'), 52.5 (d, C-4), 51.0 (d, C-6), 49.9 (d, C-8), 46.6 (d, C-2), 46.4 (d, C-6'), 36.6 (t, C-10'), 29.5 (d, C-10), 26.7 (t, C-9'), 25.8 (t, C-7'), 20.4 (q, C-11), 14.4 (q, C-11), 14.3 (q, CH_3C-2), 13.6 (q, CH_3C-8), 13.0 (q, CH_3C-6), 10.4 (q, CH_3C-4), 7.1 (q ×3, HC3CSi), 5.1 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{29}H_{54}O_7SSi+Na^+$ 597.3252, found 597.3238 (ESI).



(±)-**241**

(1*R*,2*S*,4*R*,5*R*,6*S*,8*R*,9*S*,10*R*)-*rel*-10-(2-Ethyl-1,3-dioxolan-2-yl)-1,9-dihydroxy-2,4,6,8-tetramethyl-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)undecane-3,7-dione ((±)-241)

A solution of (±)-**109** (11 mg, 0.059 mmol) in CH_2Cl_2 (0.10 mL) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (21 mg, 0.067 mmol) according to the general procedure, at −78 °C under Ar. After 6 h, a solution of (±)-**159** (43 mg, 0.27 mmol) in CH_2Cl_2 (0.10 mL) was added After 14 h, the reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of an ca. 3:1.5:1:1:1:1:1 mixture of (±)-**241**, **231**, **232**, **230**, **233**, and **202aa**, respectively. Fractionation of the crude product by FCC (30% ethyl acetate in hexane) gave a 1.8:1 mixture of

231 and **232**, respectively (8 mg), **230** (3.5 mg, 8.5%), **233** (4 mg; ca. 80% pure), **202aa** (2 mg, 10%), and the title compound (14.5 mg, 33%).

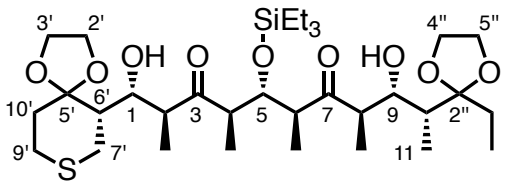
colorless viscous oil, TLC R_f = 0.4 (40% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3524, 1712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (1H, ap t, *J* = 5.5 Hz, HC-5), 4.24 (1H, br d, *J* = 9.5 Hz, HC-1), 4.09-3.90 (8H, m, H_2CO ×4), 4.05-4.02 (1H, m, HC-9), 3.07 (1H, dd, *J* = 12, 14 Hz, HC-7'), 3.06 (1H, d, *J* = 1 Hz, HOC-9), 3.05 (1H, d, *J* = 1.5 Hz, HOC-1), 2.94-2.81 (4H, m, HC-2 & HC-4 & HC-6 & HC-8), 2.84 (1H, ddd, *J* = 2.5, 13, 13.5 Hz, HC-9'), 2.58 (1H, ddd, *J* = 2.5, 3, 14 Hz, HC-7'), 2.50 (1H, dddd, *J* = 2.5, 3.5, 4, 13.5 Hz, HC-9'), 2.13 (1H, ddd, *J* = 2.5, 4, 13.5 Hz, HC-10'), 2.02 (1H, ddd, *J* = 1, 3, 12 Hz, HC-6'), 1.96 (1H, dq, *J* = 1, 7 Hz, HC-10), 1.77-1.60 (3H, m, HC-10' & H_2CC-2''), 1.077 (3H, d, *J* = 7 Hz, H_3CC-4 or H_3CC-6), 1.074 (3H, d, *J* = 7 Hz, H_3CC-4 or H_3CC-6), 0.97 (3H, d, *J* = 7 Hz, H_3CC-2), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.94 (3H, d, *J* = 7 Hz, H_3C-11), 0.91 (3H, d, *J* = 7 Hz, H_3CC-8), 0.87 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.65 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.5 (s, C-7), 216.3 (s, C-3), 114.7 (s, C-2''), 110.3 (s, C-5'), 73.9 (d, C-5), 73.1 (d, C-9), 71.7 (d, C-1), 65.8 (t, CH_2O), 64.9 (t ×2, CH_2O), 64.5 (t, CH_2O), 51.8 (d, C-6 or C-4), 51.7 (d, C-4 or C-6), 48.0 (d, C-8), 47.3 (d, C-2), 46.6 (d, C-6'), 38.7 (d, C-10), 36.9 (t, C-10'), 28.2 (t, H_2CC-2''), 26.7 (t, C-9'), 25.9 (t, C-7'), 14.1 (q, CH_3C-2), 13.8 (q, CH_3C-8), 12.3 (q, CH_3C-4 or CH_3C-6), 12.2 (q, CH_3C-6 or CH_3C-4), 8.3 (q, CH_3CC-2''), 7.2 (q ×3, CH_3CSi), 6.6 (q, C-10), 5.3 (q ×3, CH_2Si).

HRMS *m/z* calcd for $C_{33}H_{60}O_9SSi$ 660.3727, found 660.3722 (FD).

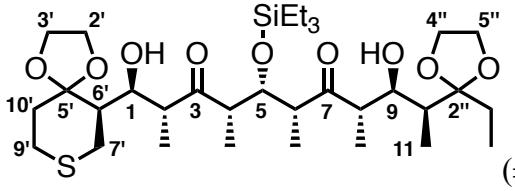


(+)-**241**

(1*R*,2*S*,4*R*,5*R*,6*S*,8*R*,9*S*,10*R*)-(+)-10-(2-Ethyl-1,3-dioxolan-2-yl)-1,9-dihydroxy-2,4,6,8-tetramethyl-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)undecane-3,7-dione ((+)-241)

t-$BuNH_2$ (0.020 mL, 14 mg, 0.19 mmol) was added via syringe to a stirring solution of the (*E*,*E*)-**215**, prepared from **202aa** (20 mg, 0.064 mmol) according to the general procedure, at 0 °C under Ar. After 30 min, the mixture was cooled to –50 °C and a solution of (–)-(*S*)-**109**, prepared from (–)-(*S*)-**139** (92% ee; 11 mg, 0.058 mmol) as described above, in CH_2Cl_2 (0.10 mL) was added via syringe. After 3 h, a solution of (±)-**159** (30 mg, 0.19 mmol) CH_2Cl_2 (0.10 mL) was added via syringe. After 3 h, reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 78:10:7:3:2 mixture of (+)-**241**, **231**, **232**, **233**, and **202aa**, respectively. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave the title compound (29 mg, 70%); $[\alpha]_D$ +6.2 (*c* 1.0, $CHCl_3$) (er > 50:1 by HPLC). ^{1}H and ^{13}C NMR data closely matched those reported above for (±)-**241**.

colorless viscous oil, TLC R_f = 0.4 (40% ethyl acetate in hexane).



(±)-**243**

(1*S*,2*R*,4*S*,5*R*,6*R*,8*S*,9*R*,10*S*)-*rel*-10-(2-Ethyl-1,3-dioxolan-2-yl)-1,9-dihydroxy-2,4,6,8-tetramethyl-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)undecane-3,7-dione ((±)-243)

t-$BuNH_2$ (0.020 mL, 14 mg, 0.19 mmol) was added via syringe to a stirring solution of the (*E*,*E*)-**220**, prepared from **202ss** (20 mg, 0.064 mmol) according to the general procedure, at –78 °C under Ar. The reaction vessel was transferred to an ice-bath and stirring continued for 30 min. The mixture was cooled to –42 °C and a solution of (±)-**109** (13 mg, 0.070 mmol) in CH_2Cl_2 (0.10 mL) was added via syringe with stirring. After 3 h, a solution of (±)-**159** (30 mg, 0.19 mmol) CH_2Cl_2 (0.10 mL) was added via syringe. After 3 h, reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 50:19:6:15:10 mixture of **243**, **236**, **237**, monoaldol, and **202aa**, respectively. Fractionation of the crude product by FCC (30% ethyl acetate in hexane) gave the title compound (19 mg, 46%).

colorless viscous oil, TLC R_f = 0.3 (30% ethyl acetate in hexane).

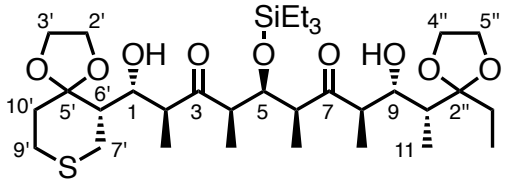
IR (DRIFT) ν_{max} 3525, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (1H, dd, *J* = 4.5, 6 Hz, HC-5), 4.25 (1H, br d, *J* = 9.5 Hz, HC-1), 4.07-3.90 (8H, m, H_2CO ×4), 4.03 (1H, d, *J* = 10 Hz, HC-9), 3.05 (1H, dd, *J* = 12, 14 Hz, HC-7'), 2.98 (2H, br s, HO), 2.96 (1H, dq, *J* = 9.5, 7 Hz, HC-2), 2.90-2.79 (4H, m, HC-4 & HC-6 & HC-8 & HC-9'), 2.63 (1H, ddd, *J* = 2, 3, 14 Hz, HC-7'), 2.50 (1H, dddd, *J* = 2, 3.5, 4, 13.5 Hz, HC-

9'), 2.12 (1H, ddd, *J* = 2.5, 4, 13.5 Hz, HC-10'), 2.00 (1H, ddd, *J* = 1.5, 3, 12 Hz, HC-6'), 1.95 (1H, br q, *J* = 7 Hz, HC-10), 1.75-1.66 (3H, m, HC-10' & H_2C-2''), 1.10 (3H, d, *J* = 7 Hz, H_3CC-6), 1.08 (3H, d, *J* = 7 Hz, H_3CC-4), 0.95 (3H, d, *J* = 7 Hz, H_3CC-2), 0.94 (3H, d, *J* = 7 Hz, H_3C-11), 0.93 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.89 (3H, d, *J* = 7 Hz, H_3CC-8), 0.87 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.63 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3 (s, C-7), 216.8 (s, C-3), 114.7 (s, C-2''), 110.3 (s, C-5'), 73.5 (d, C-9), 71.7 (d, C-1), 70.8 (d, C-5), 65.8 (t, CH_2O), 65.0 (t, CH_2O), 64.9 (t, CH_2O), 64.4 (t, CH_2O), 52.1 (d, C-6), 51.4 (d, C-4), 47.8 (d, C-8), 46.7 (d, C-2), 46.6 (d, C-6'), 38.5 (d, C-10), 36.7 (t, C-10'), 28.3 (t, CH_2C-2''), 26.7 (t, C-9'), 26.1 (t, C-7'), 14.3 (q, CH_3C-2), 13.9 (q, CH_3C-8), 12.7 (q, CH_3C-6), 11.5 (q, CH_3C-4), 8.3 (q, CH_3CC-2''), 7.4 (q ×3, CH_3CSi), 6.6 (q, C-11), 5.5 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{33}H_{60}O_9SSi+Na^+$ 683.3620, found 683.3597 (ESI).



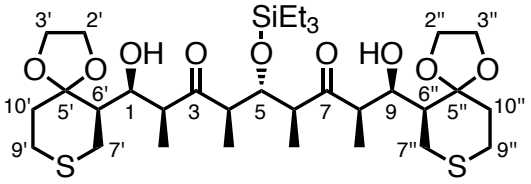
(–)-**243**

(1*R*,2*S*,4*R*,5*S*,6*S*,8*R*,9*S*,10*R*)-(–)-10-(2-Ethyl-1,3-dioxolan-2-yl)-1,9-dihydroxy-2,4,6,8-tetramethyl-1-((S)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)undecane-3,7-dione ((–)-243)

Following the same procedure described for the preparation of (±)-**243** but using (–)-(*S*)-**109** (prepared from (–)-(*S*)-**139** (92% ee; 12 mg, 0.063 mmol) as described above) instead of (±)-**109** gave a crude product whose ^{1}H NMR spectrum suggested the presence of a 70:12:8:10 mixture

of (–)-**243**, **232**, and **202aa**, respectively. Fractionation of the crude product by FCC (30% ethyl acetate in hexane) gave **232** (5 mg, 12%) and the title compound (29 mg, 70%); $[\alpha]_D$ –15 (*c* 0.60, $CHCl_3$) (er > 40:1 by HPLC). ^1H and ^{13}C NMR data closely matched those reported above for (±)-**243**.

colorless viscous oil, TLC R_f = 0.3 (30% ethyl acetate in hexane).



244

(1*S*,2*S*,4*R*,5*r*,6*S*,8*R*,9*R*)-1,9-dihydroxy-2,4,6,8-tetramethyl-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-9-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)nonane-3,7-dione (244)

Reaction of the (*Z*,*Z*)-**222**, prepared from **202aa** (20 mg, 0.064 mmol), with a solution of (±)-**109** (50 mg, 0.26 mmol) in Et_2O (0.1 mL) according to the general procedure gave a crude product whose ^1H NMR spectrum suggested the presence of a 33:2:1 mixture of **244**, **247**, and **202aa**, respectively. Fractionation of the crude product by FCC (30% ethyl acetate in hexane) afforded (±)-**109** (18 mg, 36%) and the title compound (34 mg, 78%).

colorless viscous oil, TLC R_f = 0.3 (35% ethylacetate in hexanes).

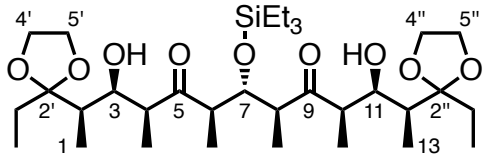
IR (DRIFT) ν_{max} 3513, 1696 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.44 (1H, t, *J* = 6 Hz, HC-5), 4.37 (2H, ddd, *J* = 1.5, 4, 6 Hz, HC-1, HC-9), 4.04-3.94 (8H, m, H_2CO ×4), 3.23 (2H, d, *J* = 2 Hz, HO ×2), 3.1 (2H, dq, *J* = 4, 7 Hz,

HC-2 & HC-8), 2.97-2.87 (6H, m, HC-4 & HC-6 & H_2C-7' & H_2C-7"), 2.70 (2H, ddd, *J* = 3, 9.5, 13.5 Hz, HC-9'), 2.63 (2H, br ddd, *J* = 3.5, 6.5, 13,5 Hz, HC-9"), 2.03 (2H, ddd, *J* = 3.5, 6.5, 13.5 Hz, HC-10'), 1.98 (2H, ddd, *J* = 3.5, 6, 8.5 Hz, HC-6' & HC-6"), 1.71 (2H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-10"), 1.19 (6H, d, *J* = 7 Hz, H_3CC-2 & H_3CC-8), 0.98 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-6), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.62 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1 (s ×2, C-3 & C-7), 109.5 (s ×2, C-5' & C-5"), 74.4 (d, C-5), 67.9 (d ×2, C-1 & C-9), 64.6 (t ×2, C-2' & C-2"), 64.3 (t ×2, C-3' & C-3"), 49.6 (d ×2, C-4 & C-6), 49.0 (d ×2, C-2 & C-8), 46.8 (d ×2, C-6' & C-6"), 35.3 (t ×2, C-10' & C-10"), 28.1 (t ×2, C-7' & C-7"), 26.7 (t ×2, C-9' & C-9"), 11.7 (q ×2, CH_3C-4 & CH_3C-6), 11.5 (q ×2, CH_3C-2 & CH_3C-8), 7.1 (q ×3, CH_3CSi), 5.1 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{33}H_{58}O_9S_2Si$+Na 713.3184, found 713.3176 (ESI).



245

(2*R*,3*S*,4*S*,6*R*,7*r*,8*S*,10*R*,11*R*,12*S*)-2,12-Bis(2-ethyl-1,3-dioxolan-2-yl)-3,11-dihydroxy-4,6,8,10-tetramethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (245)

From **202aa**. Reaction of the (*Z*,*Z*)-**222**, prepared from **202aa** (20 mg, 0.064 mmol), with a solution of (±)-**159** (43 mg, 0.26 mmol) in Et_2O (0.1 mL) according to the general procedure gave a crude product whose ^{1}H NMR spectrum suggested the presence of a 9:9:1 mixture of a **245**, **246**, and an unidentified product (possibly a mono aldol), respectively. Fractionation of the crude product by FCC (30% ethyl acetate in hexane) gave an inseparable 1:1 mixture the title compound

and **245** (29 mg, 73%). The NMR signals for **246** in the 1:1 mixture could be readily assigned because a pure sample of **245** was available (see below). From **244**. A suspension of Raney nickel (W2; 0.1 mL settled volume) in EtOH (2 mL) was added to **244** (15 mg, 0.022 mmol), and the mixture was heated under reflux with vigorous stirring under a H_2 atmosphere (balloon). After 2 h (reaction was complete by TLC analysis), the mixture was decanted, and the solid was suspended in EtOH (2 mL) and heated under reflux with vigorous stirring for several min. This washing procedure was repeated with ethyl acetate, and acetone. The combined organic layers were filtered through Celite® and concentrated to get the crude product. The crude was dissolved in 30% ethyl acetate in hexane and passed through a short plug of silica gel washing with 30% ethyl acetate in hexane. The combined filtrate and washings were concentrated to give the title compound (13 mg, 92%)..

colorless viscous oil, TLC R_f = 0.3 (30% ethyl acetate in hexane).

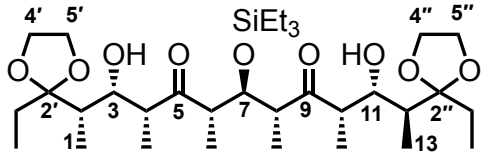
IR (DRIFT) ν_{max} 3524, 1703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (1H, t, *J* = 5.5 Hz, HC-7), 4.11 (2H, dd, *J* = 2.5, 7 Hz, HC-3, HC-11), 4.02-3.93 (8H, m, H_2CO ×4), 3.17 (2H, br s, HO ×2), 2.93 (2H, dq, *J* = 5.5, 7 Hz, HC-6 & HC-8), 2.90 (2H, dq, *J* = 7, 7 Hz, HC-4 & HC-10), 1.87 (2H, dq, *J* = 3, 7 Hz, HC-2 & HC-12), 1.75-1.60 (4H, m, H_2CC-2' & H_2CC-2"), 1.23 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-10), 0.99 (6H, br d, *J* = 7 Hz, H_3C-1 & H_3C-13, H_3CC-6 & H_3CC-8), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.86 (6H, t, *J* = 7.5 Hz, H_3CCC-2' & H_3CCC-2"), 0.61 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8 (s, C-5 & C-9), 114.5 (s, C-2' & C-2"), 73.9 (d, C-7), 70.4 (d, C-3 & C-11), 65.4 (t, C-4' & C-4"), 65.1 (t, C-5' & C-5"), 49.9 (d, C-4, & C-10), 49.8 (d, C-6 & C-8), 40.5 (d, C-2 & 12), 27.5 (t, CH_2C-2' & CH_2C-2"), 13.5 (q, CH_3C-4 & CH_3C-10), 12.0 (q,

CH_3C-6 & CH_3C-8), 9.0 (q, C-1 & C-13), 7.8 (q, CH_3CC-2' & CH_3CC-2''), 7.1 (q ×3, CH_3CSi), 5.2 (t ×3, CH_2Si).

HRMS *m/z* calcd for C33H62O9Si+Na^+ 653.4055, found 653.4064 (ESI).



246

(2*S*,3*R*,4*R*,6*S*,7*S*,8*R*,10*S*,11*S*,12*S*)-*rel*-2,12-Bis(2-ethyl-1,3-dioxolan-2-yl)-3,11-dihydroxy-4,6,8,10-tetramethyl-7-((triethylsilyl)oxy)tridecane-5,9-dione (246)

NMR data from a 1:1 mixture with **245** (see preparation of **245**).

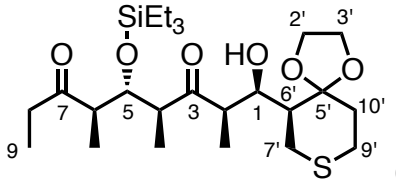
colorless viscous oil, TLC R_f = 0.3 (30% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3514, 1702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (1H, dd, *J* = 3, 8.5 Hz, HC-7), 4.12-4.09 (2H, m, HOC-11, HC-3), 4.06 (1H, br d, *J* = 9.5 Hz, HC-11), 4.03-3.92 (8H, m, H_2CO ×4), 3.50 (1H, d, *J* = 0.5 Hz, HOC-3), 3.08 (1H, dq, *J* = 8, 7 Hz, HC-8), 3.03 (1H, dq, *J* = 7, 7 Hz, HC-4), 2.95-2.87 (1H, m, HC-6), 2.48 (1H, br q, *J* = 7 Hz, HC-10), 1.91-1.84 (1H, m, HC-2), 1.81 (1H, dq, *J* = 4, 7 Hz, HC-12), 1.76-1.60 (4H, m, H_2CC-2', H_2CC-2''), 1.22 (3H, d, *J* = 7 Hz, H_3CC-4), 1.15 (3H, d, *J* = 7 Hz, H_3CC-10), 1.12 (3H, d, *J* = 7 Hz, H_3CC-6), 0.98 (3H, d, *J* = 7 Hz, H_3C-1), 0.93 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.88 (3H, t, *J* = 7.5 Hz, H_3CC-2''), 0.87 (3H, d, *J* = 7 Hz, H_3C-13), 0.86 (3H, d, *J* = 7 Hz, H_3CC-8), 0.86 (3H, t, *J* = 7.5 Hz, H_3CC-2'), 0.59 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.72 (s, C-5 or C-9), 215.65 (s, C-9 or C-5), 114.9 (s, C-2''), 114.5 (s, C-2'), 74.8 (d, C-7), 72.1 (d, C-11), 70.8 (d, C-3), 65.47 (t, C-4''), 65.44 (t, C-4'), 65.06 (t, C-5'), 65.04 (t, C-5''), 51.0 (d, C-6), 49.2 (d, C-10), 48.5 (d, C-4), 47.0 (d, C-8), 41.5 (d, C-12), 40.1 (d, C-2), 27.6 (t, CH_2C-2'), 25.9 (t, CH_2C-2''), 14.4 (q, CH_3C-4), 13.4 (q, CH_3C-8), 12.8 (q, C-13), 10.8 (q, CH_3C-6), 8.7 (q, C-1), 8.1 (q, CH_3C-10), 7.9 (q, CH_3CC-2'), 7.1 (q ×3, CH_3CSi), 7.0 (q, CH_3CC-2''), 5.2 (t ×3, CH_2Si).

HRMS *m/z* calcd for C33H62O9Si+Na 653.4055, found 653.4061 (ESI).



(+)-**247**

(1*R*,2*R*,4*S*,5*S*,6*R*)-(+)-1-Hydroxy-2,4,6-trimethyl-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)nonane-3,7-dione ((+)-247)

2,4-Dimethyl-3-pentanone (0.072 ml, 58.5 mg, 0.51 mmol) was added was added via syringe to a stirring solution of the (*Z*,*Z*)-**222**, prepared from **202aa** (20 mg, 0.064 mmol) according to the general procedure, at 0 °C under Ar. After 1 h, the mixture was cooled to –78 °C and a solution of (–)-(*S*)-**109**, prepared from (–)-(*S*)-**139** (92% ee; 12 mg, 0.064 mmol) as described above, in Et_2O (0.20 mL) was added via syringe. After 3 h, the reaction was quenched and processed as described in the general procedure to give the crude product whose ^{1}H NMR spectrum suggested the presence of a 81:14:5 mixture of (+)-**247**, **202aa**, and 6′-*epi*-**244** (tentative), respectively. Fractionation of the crude product by PTLC (30% ethyl acetate in hexane) gave the title compound (24 mg, 76%); $[\alpha]_D$ +14 (*c* 1.1, $CHCl_3$).

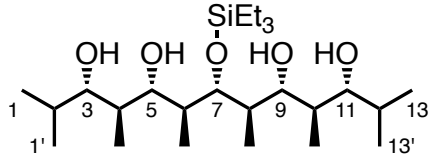
colorless viscous oil, TLC R_f = 0.4 (30% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3515, 1714 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (1H, dd, *J* = 4.5, 7.5 Hz, HC-5), 4.33 (1H, br t, *J* = 5 Hz, HC-1), 4.07-3.93 (4H, m, H_2C-2', H_2C-3'), 3.29 (1H, br s, HO), 3.16 (1H, dq, *J* = 4.5, 7 Hz, HC-2), 2.94 (1H, dd, *J* = 9, 14 Hz, HC-7'), 2.90-2.83 (2H, m, HC-7', HC-4), 2.75 (1H, dq, *J* = 7.5, 7 Hz, HC-6), 2.70 (1H, ddd, *J* = 3, 10, 13.5 Hz, HC-9'), 2.64-2.58 (1H, m, HC-9'), 2.53-2.44 (2H, m, H_2C-8), 2.04 (1H, ddd, *J* = 3, 6.5, 13.5 Hz, HC-10'), 1.97 (1H, ddd, *J* = 3.5, 5.5, 9 Hz, HC-6'), 1.70 (1H, ddd, *J* = 3.5, 10, 13.5 Hz, HC-10'), 1.17 (3H, d, *J* = 7 Hz, H_3CC-2), 1.03 (3H, d, *J* = 7 Hz, H_3CC-4), 1.01 (3H, d, *J* = 7 Hz, H_3C-9), 0.93 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.90 (3H, d, *J* = 7 Hz, H_3CC-6), 0.59 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4 (s, C-3), 213.4 (s, C-7), 109.5 (s, C-5'), 75.1 (d, C-5), 68.1 (d, C-1), 64.6 (t, C-2'), 64.3 (t, C-3'), 50.3 (d, C-6), 50.2 (d, C-4), 48.1 (d, C-2), 46.8 (d, C-6'), 36.7 (d, C-8), 35.3 (t, C-10'), 28.0 (t, C-7'), 26.7 (t, C-9'), 12.6 (q, H_3CC-6), 11.9 (q, H_3CC-2), 11.1 (q, H_3CC-4), 7.6 (q, H_3C-9), 7.1 (q ×3, H_3CCSi), 5.1 (t ×3, H_2CSi).

HRMS *m/z* calcd for $C_{25}H_{46}O_6SSi+Na^+$ 525.2677, found 525.2684 (ESI).



279

(3*S*,4*S*,5*S*,6*S*,7*s*,8*R*,9*R*,10*R*,11*R*)-*rel*-2,4,6,8,10,12-Hexamethyl-7-((triethylsilyl)oxy)tridecane-3,5,9,11-tetraol (279)

Et_2BOMe (25 μL, 22 mg, 0.22 mmol) was added to a stirring solution of **212** (30 mg, 0.072 mmol) in THF (0.60 mL) at −78 °C under argon. The mixture was removed from the cooling bath, and the Et_2BOMe slowly dissolved. After 1 h, the mixture was cooled to −78 °C, and MeOH (0.15 mL) and $NaBH_4$ (22 mg, 0.58 mmol) were added. After 2 h, the mixture was allowed to slowly warm to ambient temperature. After 12 h, hexane (0.2 mL), and aq phosphate buffer (pH 7; 1 mL) were added. The mixture was cooled to 0 °C and 30% aq H_2O_2 (1 mL) was added with vigorous stirring. After 1 h, the mixture was allowed to warm to ambient temperature. After 2 h, the mixture was diluted with dichloromethane and washed sequentially with saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (30% ethyl acetate in hexanes) to afford the title compound (21 mg, 70%) as a single diastereomer.

white amorphous solid, TLC R_f = 0.3 (30% ethyl acetate in hexane).

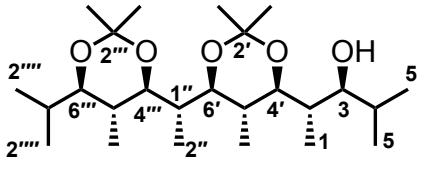
IR (DRIFT) ν_{max} 3370 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ 4.40-4.25 (2H, br s, HO ×2), 4.31 (1H, t, *J* = 4 Hz, HC-7), 3.59 (2H, dd, *J* = 3.5, 8.5 Hz, HC-5 & HC-9), 3.52 (2H, dd, *J* = 3.5, 8 Hz, HC-3 & HC-11), 3.29-3.14 (2H, br s, HO ×2), 2.44 (2H, ddq, *J* = 4, 8.5, 7 Hz, HC-6 & HC-8), 1.92 (2H, ddq, *J* = 3.5, 3.5, 7 Hz, HC-4 & HC-10), 1.78 (2H, dqq, *J* = 3.5, 6.5, 6.5 Hz, HC-2 & HC-12), 1.14 (6H, d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 1.02 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 1.01 (6H, d, *J* = 6.5 Hz, H_3C-1 & H_3C-13), 0.97 (6H, d, *J* = 6.5 Hz, H_3C-1' & H_3C-13'), 0.94 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-10), 0.67 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, C_6D_6) δ 81.0 (d ×2, C-5 & C-9), 80.3 (d ×2, C-3 & C-11), 80.1 (d, C-7), 43.2 (d ×2, C-6 & C-8), 38.4 (d ×2, C-4 & C-10), 31.2 (d ×2, C-2 & C-12), 21.0 (q ×2, C-1 & C-

13), 18.1 (q ×2, CH_3C-4 & CH_3C-10), 16.0 (q ×2, CH_3C-6 & CH_3C-8), 15.6 (q ×2, C-1' & C-13'), 7.5 (q ×3, CH_3CSi), 5.8 (q ×3, CH_2Si).

HRMS *m/z* calcd for $C_{25}H_{54}O_5Si+Na^+$ 485.3633, found 485.3629 (ESI).



280a

(2*S*,3*S*)-*rel*-2-{(4*S*,5*S*,6*S*)-6-[(*R*)-1-((4*R*,5*R*,6*R*)-6-Isopropyl-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-4-methylpentan-3-ol (280a)

2,2-dimethoxypropane (0.21 mL, 0.18 g, 1.7 mmol) was added to a stirring solution of **279** (8 mg, 0.02 mmol) in acetone (0.3 mL) at room temperature. After 3 h, the reaction mixture was diluted with dichloromethane and washed sequentially with saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (5% ethyl acetate in hexane) to give **280c** (the *meso* bisacetonide of **279**; 3.3 mg, 35%; ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.6, 78.4, 76.1, 72.7, 44.3, 35.5, 30.3, 28.1, 20.5, 19.7, 14.6, 12.7, 12.6, 7.3, 5.8) and **280b** (the TES-deprotected derivative of **280c**;1.3 mg, 21%; ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.0, 79.8, 78.6, 77.6, 37.2, 34.0, 30.4, 28.3, 20.4, 19.3, 17.9, 14.6, 12.3) along with the title compound (2 mg, 33%).

colorless viscous oil, TLC R_f = 0.5 (5% ethyl acetate in hexane).

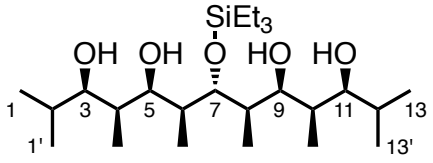
IR (DRIFT) ν_{max} 3550 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56 (1H, dd, *J* = 3.5, 10.5 Hz, HC-6'), 3.52 (1H, dd, *J* = 3, 10 Hz, HC-4'''), 3.47 (1H, dd, *J* = 1.5, 10.5 Hz, HC-4'), 3.36 (1H, ddd, *J* = 3.5, 4, 7.5 Hz, HC-3), 3.28 (1H,

dd, *J* = 2, 10 Hz, HC-6'''), 3.21 (1H, d, *J* = 4 Hz, HO), 2.02 (1H, ddq, *J* = 3, 3.5, 7.5 Hz, HC-1''), 1.98 (1H, ddq, *J* = 10.5, 10.5, 6.5 Hz, HC-5'), 1.92 (1H, ddq, *J* = 1.5, 7.5, 7 Hz, HC-2), 1.89 (1H, dqq, *J* = 2, 7, 7 Hz, HCC-6'''), 1.81 (1H, dqq, *J* = 4.5, 6.5, 7 Hz, HC-4), 1.57 (1H, ddq, *J* = 10, 10, 6.5 Hz, HC-5'''), 1.40 (3H, s, H_3CC-2'), 1.361 (3H, s, H_3CC-2' or H_3CC-2'''), 1.360 (3H, s, H_3CC-2' or H_3CC-2'''), 1.30 (3H, s, H_3CC-2'''), 1.01 (3H, d, *J* = 7.5 Hz, H_3C-2''), 0.99 (3H, d, *J* = 7 Hz, H_3C-5), 0.98 (3H, d, *J* = 7 Hz, H_3C-1), 0.93 (3H, d, *J* = 7 Hz, H_3CCC-6'''), 0.91 (3H, d, *J* = 6.5 Hz, H_3C-5), 0.84 (3H, d, *J* = 6.5 Hz, H_3CC-5'), 0.83 (3H, d, *J* = 7 Hz, H_3CCC-6'''), 0.74 (3H, d, *J* = 6.5 Hz, H_3CC-5''').

^{13}C NMR (125 MHz, $CDCl_3$) δ 98.0 (s, C-2'''), 97.6 (s, C-2'), 81.1 (d, C-4'), 79.8 (d, C-3), 78.3 (d, C-6'''), 75.9 (d, C-6'), 75.7 (d, C-4'''), 40.8 (d, C-1''), 36.5 (d, C-2), 34.8 (d, C-5'), 33.0 (d, C-5'''), 31.0 (d, C-4), 30.5 (q, CH_3C-2'), 30.3 (q, CH_3C-2'''), 28.3 (d, CHC-6'''), 20.7 (q, C-5), 20.4 (q, H_3CCC-6'''), 19.6 (q, H_3CC-2'''), 19.1 (q, H_3CC-2'), 18.8 (q, C-1), 16.1 (q, C-5), 14.6 (q, H_3CCC-6'''), 14.1 (q, C-2''), 13.4 (q, H_3CC-5'), 12.5 (q, H_3CC-5''').

HRMS *m/z* calcd for $C_{25}H_{48}O_5$+Na^+ 451.3394, found 451.3389 (ESI).



281

(3*R*,4*S*,5*R*,6*S*,7*s*,8*R*,9*S*,10*R*,11*S*)-2,4,6,8,10,12-Hexamethyl-7-((triethylsilyl)oxy)tridecane-3,5,9,11-tetraol (281)

Et_2BOMe (14 μL, 12 mg, 0.12 mmol) was added to a stirring solution of **223** (18 mg, 0.040 mmol) in THF (0.40 mL) at −78 °C under argon. The mixture was removed from the cooling bath,

and the Et_2BOMe slowly dissolved. After 1 h, the mixture was cooled to −78 °C, and MeOH (0.1 mL) and $NaBH_4$ (12 mg, 0.31 mmol) were added. After 3 h, the mixture was allowed to slowly warm to ambient temperature. After 1 h, ethyl acetate (0.5 mL), and aq NaOH (0.1 M; 0.5 mL) were added. The mixture was cooled to 0 °C and 30% aq H_2O_2 (0.5 mL) was added with vigorous stirring. After 1 h, the mixture was allowed to warm to ambient temperature. After 3 h, the mixture was diluted with dichloromethane and washed sequentially with saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (30% ethyl acetate in hexanes) to afford the title compound (16 mg, 89%) as a single diastereomer.

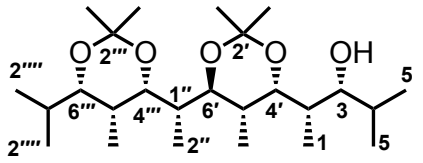
colorless viscous oil, TLC R_f = 0.3 (40% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3393 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (2H, dd, *J* = 2, 6.5 Hz, HC-5 & HC-9), 3.82 (1H, t, *J* = 4.5 Hz, HC-7), 3.28 (2H, br s, HO ×2), 3.21 (2H, dd, *J* = 1, 9.5 Hz, HC-3 & HC-11), 2.18 (2H, br s, HO ×2), 2.0 (2H, ddq, *J* = 2, 4.5, 7 Hz, HC-6 & HC-8), 1.71 (2H, ddq, *J* = 2, 6.5, 7 Hz, HC-4 & HC-10), 1.69 (2H, dqq, *J* = 9.5, 6.5, 6.5 Hz, HC-2 & HC-12), 1.04 (6H, d, *J* = 7 Hz, H_3CC-6 & H_3CC-8), 1.01 (6H, d, *J* = 6.5 Hz, H_3C-1 & H_3C-13), 0.99 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.97 (6H, d, *J* = 7 Hz, H_3CC-4 & H_3CC-10), 0.83 (6H, d, *J* = 6.5 Hz, H_3C-1' & H_3C-13'), 0.69 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 81.9 (d, C-7), 80.0 (d, C-3 & C-11), 75.0 (d, C-5 & C-9), 38.6 (d, C-4 & C-10), 38.4 (d, C-6 & C-8), 31.6 (d, C-2 & C-12), 20.1 (q, C-1 & C-13), 19.3 (q, C-1' & C-13'), 11.4 (q, CH_3C-6 & CH_3C-8), 7.6 (q, CH_3C-4 & CH_3C-10), 7.2 (q ×3, CH_3CSi), 5.4 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{25}H_{54}O_5Si+Na^+$ 485.3633, found 485.3643 (ESI).



282a

(2*S*,3*R*)-2-((4*R*,5*S*,6*S*)-6-((*R*)-1-((4*S*,5*R*,6*S*)-6-Isopropyl-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-4-methylpentan-3-ol (282a)

For procedure, see the preparation of **282b**.

colorless viscous oil, TLC R_f = 0.3 (5% ethyl acetate in hexane).

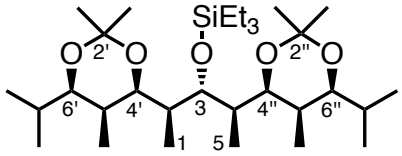
IR (DRIFT) ν_{max} 3480 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (1H, dd, *J* = 3.5, 10 Hz, HC-4'), 3.66 (1H, dd, *J* = 2, 8 Hz, HC-4'''), 3.27-3.23 (2H, m, HC-6', HC-6'''), 3.16 (1H, ddd, *J* = 1.5, 6.5, 8 Hz, HC-3), 2.01 (1H, ddq, *J* = 3.5, 6.5, 6.5 Hz, HC-5'), 1.87 (1H, ddq, *J* = 6, 8, 7 Hz, HC-1''), 1.83 (1H, ddq, *J* = 1.5, 10, 6.5 Hz, HC-2), 1.73-1.63 (3H, m, HC-4, HC-5''', HC-1''''), 1.39 (3H, s, H_3CC-2'''), 1.37 (3H, s, H_3CC-2'''), 1.34 (3H, s, H_3CC-2'), 1.30 (3H, s, H_3CC-2'), 1.25-1.23 (1H, d, *J* = 6.5 Hz, HO), 1.03 (3H, d, *J* = 6.5 Hz, H_3C-5), 0.96 (3H, d, *J* = 7 Hz, H_3C-2''), 0.93 (3H, d, *J* = 6.5 Hz, H_3C-2''''), 0.91 (3H, d, *J* = 6.5 Hz, H_3C-1), 0.89 (3H, d, *J* = 6.5 Hz, H_3CC-5'), 0.86 (3H, d, *J* = 7 Hz, H_3CC-5'''), 0.84 (3H, d, *J* = 6.5 Hz, H_3C-5), 0.79 (3H, d, *J* = 6.5 Hz, H_3C-2'''').

^{13}C NMR (125 MHz, $CDCl_3$) δ 100.6 (s, C-2'), 99.0 (s, C-2'''), 80.0 (d, C-6'''), 77.0 (d, C-3), 76.4 (d, C-6'), 75.4 (d, C-4'''), 71.8 (d, C-4'), 39.8 (d, C-1''), 34.5 (d, C-2), 34.3 (d, C-5'), 33.3 (d, C-5'''), 32.2 (d, C-4), 30.3 (q, H_3CC-2'''), 29.4 (d, C-1''''), 25.8 (q, H_3CC-2'), 23.6 (q, H_3CC-2'), 20.3 (q,

C-5), 20.1 (q, C-2""), 19.8 (q, H_3CC-2"'), 19.0 (q, C-5), 17.6 (q, C-2""), 13.8 (q, H_3CC-5'), 11.2 (q, C-2"), 8.4 (q, C-1), 5.8 (q, H_3CC-5"').

HRMS *m/z* calcd for $C_{25}H_{48}O_5$+Na^+ 451.3394, found 451.3404 (ESI).



282b

Triethyl(((2*S*,3*s*,4*R*)-2-((4*R*,5*S*,6*R*)-6-isopropyl-2,2,5-trimethyl-1,3-dioxan-4-yl)-4-((4*S*,5*R*,6*S*)-6-isopropyl-2,2,5-trimethyl-1,3-dioxan-4-yl)pentan-3-yl)oxy)silane (282b)

2,2-dimethoxypropane (0.21 mL, 0.18 g, 1.7 mmol) was added to a stirring solution of **282b** (12 mg, 0.026 mmol) in CH_2Cl_2 (0.2 mL) at room temperature. After 40 h, the reaction mixture was diluted with CH_2Cl_2 and washed sequentially with saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (5% ethyl acetate in hexane) to give **282c** (1 mg, 9%), **282a** (4.2 mg, 38%), and the title compound (5.5 mg, 40%).

colorless viscous oil, TLC R_f = 0.7 (5% ethyl acetate in hexane).

IR (DRIFT) ν_{max} cm^{-1}.

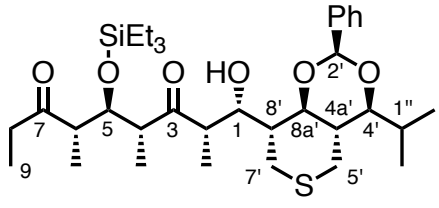
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (2H, dd, *J* = 2, 6.5 Hz, HC-4' & HC-4"), 3.54 (1H, t, *J* = 4 Hz, HC-3), 3.26 (2H, dd, *J* = 2, 9.5 Hz, HC-6' & HC-6"), 1.77 (2H, ddq, *J* = 4, 6.5, 7 Hz, HC-2 & HC-4), 1.65 (2H, dqq, *J* = 9.5, 6.5, 6.5 Hz, HCC-6' & HCC-6"), 1.56 (2H, ddq, *J* = 2, 2, 7 Hz, HC-5' & HC-5"), 1.37 (12H, ap s, (H_3C)2C-2' & (H_3C)2CC-2"), 0.98 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.932 (6H, d, *J* = 6.5 Hz, H_3CCC-6' & H_3CCC-6'), 0.930 (6H, d, *J* = 7 Hz, H_3C-1 & H_3C-5), 0.88 (6H,

d, J = 7 Hz, H_3CC-5' & H_3CC-5"), 0.79 (6H, d, J = 7 Hz, H_3CCC-6' & H_3CCC-6'), 0.63 (6H, q, J = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 99.0 (s, C-2' & C-2"), 80.0 (d, C-6' & C-6"), 77.9 (d, C-3), 73.8 (d, C-4' & C-4"), 39.8 (d, C-2 & C-4), 33.6 (d, C-5' & C-5"), 30.2 (q, H_3CC-2' & H_3CC-2"), 29.4 (d, CHC-6' & CHC-6"), 20.1 (q, H_3CCC-6' & H_3CCC-6"), 19.9 (q, H_3CC-2' & H_3CC-2"), 17.6 (q, H_3CCC-6' & H_3CCC-6'), 13.8 (q, C-1 & C-5), 7.3 (q ×3, H_3CCSi), 5.7 (q, H_3CC-5' & H_3CC-5"), 5.5 (t ×3, H_2CSi).

HRMS *m/z* calcd for $C_{31}H_{62}O_5Si+Na^+$ 565.4264, found 565.4264 (ESI).

4.4.2. Compounds synthesized from total synthesis project



253

(1*S*,2*S*,4*R*,5*R*,6*S*)-1-Hydroxy-1-((2*S*,4*S*,4a*S*,8*R*,8a*R*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6-trimethyl-5-((triethylsilyl)oxy)nonane-3,7-dione (253)

9-BBNOTf (0.5 M in hexane; 5.3 mL, 2.6 mmol) was added via syringe to a clean dry Schlenk tube and the hexane was removed under reduced pressure. A solution of **202aa** (207 mg, 0.66 mmol) and Et_3N (0.44 mL, 0.32 g, 3.2 mmol) in Et_2O (2.0 mL) was added to the neat borane reagent at –78 °C under argon with stirring. After 4 h, the reaction mixture was warmed to 0 °C and 2,4-dimethyl-3-pentanone (0.75 mL, 0.60 g, 5.3 mmol) was added (to quench the excess 9-

BBN-OTf). After 1 h, the mixture was cooled to −78 °C and a solution of (+)-**128** (223 mg, 0.73 mmol) in THF (2 mL) was added via syringe. After 16 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 4 mL), 30% aq H_2O_2 (4 mL), and MeOH (4 mL) with vigorous stirring. The reaction vessel was transferred to an ice bath and after vigorous stirring for 20 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 9:1.3:1 mixture of **253**, **202aa**, and an unidentified adduct (presumably a bisaldol), respectively. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave the title compound (294 mg, 72%); $[\alpha]_D$ –42 (*c* 1.1, C_6H_6).

colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

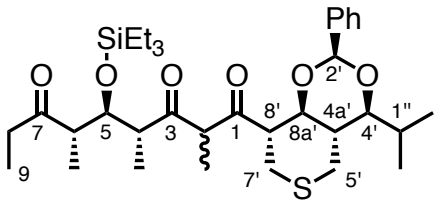
IR (DRIFT) ν_{max} 3509, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.43 (2H, m, Ph), 7.38-7.31 (3H, m, Ph), 5.53 (1H, s, HC-2'), 4.36 (1H, dd, *J* = 5.5, 7 Hz, HC-5), 4.17 (1H, ddd, *J* = 3, 3.5, 6 Hz, HC-1), 3.50 (1H, ap t, *J* = 9.5 Hz, HC-8'a), 3.39 (1H, dd, *J* = 2, 10 Hz, HC-4'), 3.06 (1H, dq, *J* = 3.5, 7 Hz, HC-2), 2.92 (1H, ddd, *J* = 2.5, 3, 14 Hz, HC-7'), 2.88 (1H, d, *J* = 3.5 Hz, HO), 2.80 (1H, dq, *J* = 7, 7 Hz, HC-4), 2.68 (1H, dd, *J* = 11, 14 Hz, HC-7'), 2.65 (1H, dq, *J* = 5.5, 7 Hz, HC-6), 2.55-2.40 (3H, m, HC-5', H_2C-8), 2.31 (1H, dd, *J* = 12, 13 Hz, HC-5'), 2.11-2.02 (2H, m, HC-8', HC-4'a), 1.94 (1H, dqq, *J* = 2, 7, 7 Hz, HC-1''), 1.16 (3H, d, *J* = 7 Hz, H_3CC-2), 1.05 (3H, d, *J* = 7 Hz, H_3CC-1''), 1.02 (3H, t, *J* = 7 Hz, H_3C-9), 0.97 (3H, d, *J* = 7 Hz, H_3CC-1''), 0.95 (3H, d, *J* = 7 Hz, H_3CC-6), 0.91 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.83 (3H, d, *J* = 7 Hz, H_3CC-4), 0.55 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.0 (s, C-3), 212.4 (s, C-7), 138.9 (s, Ph), 128.8 (d, Ph), 128.3 (d ×2, Ph), 126.3 (d ×2, Ph), 101.1 (d, C-2'), 84.0 (d, C-4'), 82.3 (d, C-8'a), 75.2 (d, C-5), 70.1 (d,

C-1), 51.6 (d, C-6), 50.1 (d, C-2), 49.0 (d, C-4), 46.2 (d, C-8'), 43.8 (d, C-4'a), 35.6 (t, C-8), 28.6 (t, C-7'), 28.4 (d, C-1"), 27.5 (t, C-5'), 20.2 (q, CH_3C-1"), 15.0 (q, CH_3C-1"), 12.9 (q, CH_3C-4), 11.2 (q, CH_3C-6), 10.9 (q, CH_3C-2), 7.8 (q, C-9), 7.1 (q, CH_3CSi ×3), 5.2 (t, CH_2Si ×3).

HRMS *m/z* calcd for $C_{34}H_{56}O_6SSi+Na^+$ 643.3459, found 643.3437 (ESI).



257

4*R*,5*R*,6*S*)-1-((2*S*,4*S*,4a*S*,8*R*,8a*R*)-4-Isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6-trimethyl-5-((triethylsilyl)oxy)nonane-1,3,7-trione (257)

To a stirring solution of **253** (120 mg, 0.19 mmol) in DMSO (2 mL) was added IBX (82 mg, 0.29 mmol). After 20 h, the mixture was diluted with saturated aq $NaHCO_3$ and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (15% ethyl acetate in hexane) to afford the title compound as a 1:2:1 mixture of an enol and two keto tautomers, respectively (117 mg, 98%); $[\alpha]_D$ +50 (*c* 1.0, C_6H_6)..

colorless viscous oil, TLC R_f = 0.5 (15% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 2959, 2878, 1716 cm^{-1}.

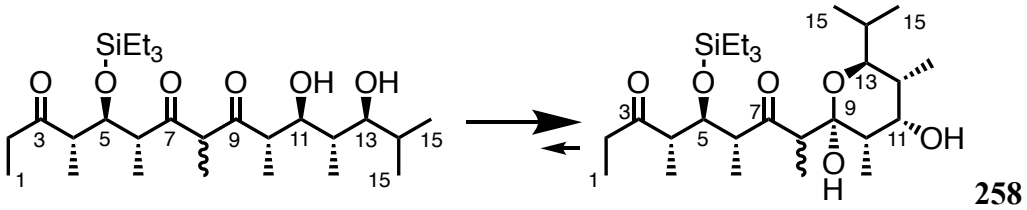
^{1}H NMR (500 MHz, C_6D_6) δ (* enol tautomer; † major keto tautomer; ‡ minor keto tautomer) 17.80 (0.25H, s, *HO), 7.59-7.47 (2H, m, Ph), 7.28-7.02 (3H, m, Ph), 5.47 (0.25H, s, ‡HC-2'), 5.31 (0.25H, s, *HC-2'), 5.29 (0.5H, s, †HC-2'), 4.43 (0.25H, dd, *J* = 4.5, 8 Hz, *HC-5), 4.37 (0.5H, ap t, *J* = 6 Hz, †HC-5), 4.34 (0.25H, dd, *J* = 4.5, 7 Hz, ‡HC-5), 3.98 (0.5H, q, *J* = 7 Hz, †H_3C-2), 3.82

(0.25H, ap t, J = 10 Hz, ‡HC-8'a), 3.78 (0.25H, q, J = 7 Hz, ‡H_3C-2), 3.64 (0.25H, ap t, J = 10 Hz, *HC-8'a), 3.60 (0.5H, ap t, J = 10 Hz, †HC-8'a), 3.35-3.20 (1H, m, H-8'), 3.07 (0.25H, dd, J = 11.5, 13.5 Hz, ‡HC-7'), 3.04 (0.25H, dq, J = 7, 7 Hz, *HC-4), 3.02 (0.25H, dd, J = 2, 10 Hz, ‡HC-4'), 2.99-2.89 (1.5H, m, †‡HC-7', *†HC-4'), 2.80 (0.25H, dd, J = 11.5, 13.5 Hz, *HC-7'), 2.71 (0.25H, dq, J = 4.5, 7 Hz, ‡HC-4), 2.68-2.55 (1.25H, m, J = 7 Hz, †HC-4, *†HC-6), 2.52 (0.25H, ddd, J = 2.5, 2.5, 13.5 Hz, *HC-7'), 2.37-1.96 (4.25H, m, H_2C-8, HC-4'a, HC-5', ‡HC-7'), 1.91-1.79 (1H, m, HC-5'), 1.72 (0.75H, s, *H_3CC-2), 1.55-1.41 (1H,, J = m Hz, HC-1''), 1.30 (1.5H, d, J = 7 Hz, †H_3CC-2), 1.20 (0.75H, d, J = 7 Hz, ‡H_3CC-2), 1.05 (0.75H, d, J = 7 Hz, *H_3CC-4), 1.04 (0.75H, d, J = 7 Hz, *H_3CC-6), 1.03-0.93 (7.5H, m, H_3C-9, H_3CC-1'', †‡H_3CC-6), 0.99 (2.25H, t, J = 8 Hz, *$(H_3CC)_3Si$ or ‡$(H_3CC)_3Si$), 0.97 (4.5H, t, J = 8 Hz, †$(H_3CC)_3Si$), 0.91 (2.25H, t, J = 8 Hz, *$(H_3CC)_3Si$ or ‡$(H_3CC)_3Si$), 0.89 (0.75H, d, J = 7 Hz, ‡H_3CC-6), 0.87 (1.5H, ap d, J = 7 Hz, *‡H_3CC-2''), 0.86 (1.5H, d, J = 7 Hz, †H_3CC-2''), 0.85 (1.5H, d, J = 7 Hz, †H_3CC-4), 0.80 (0.75H, d, J = 7 Hz, ‡H_3CC-4), 0.69-0.50 (6H, m, $(H_2C)_3Si$).

^{13}C NMR (125 MHz, C_6D_6) δ (* enol tautomer; † major keto tautomer; ‡ minor keto tautomer) 211.9 (s, ‡C-7), 211.26 (s, *C-7), 211.24 (s, †C-7), 210.8 (s, †C-3), 209.2 (s, ‡C-1 or ‡C-3), 209.1 (s, ‡C-1 or ‡C-3), 208.3 (s, †C-1), 196.7 (s, *C-3), 193.1 (s, *C-1), 139.8 (s, *Ph or ‡Ph), 139.5 (s, †Ph), 139.4 (s, *Ph or ‡Ph), 129.4 (d, *Ph or ‡Ph), 129.2 (d, †Ph), 129.1 (d, *Ph or ‡Ph), 128.68 (d ×2, †Ph), 128.67 (d ×2, *Ph or ‡Ph), 128.55 (d ×2, *Ph or ‡Ph), 127.2 (d ×2, *Ph or ‡Ph), 127.0 (d ×2, *Ph or ‡Ph), 126.6 (d ×2, †Ph), 106.2 (s, *C-2), 102.1 (d, *C-2'), 101.6 (d, ‡C-2'), 101.2 (d, †C-2'), 83.84 (d, ‡C-4'), 83.83 (d, †C-4'), 83.79 (d, *C-4'), 83.5 (d, †C-8'a), 82.6 (d, *C-8'a), 81.3 (d, ‡C-8'a), 76.7 (d, ‡C-5), 76.2 (d, †C-5), 75.9 (d, *C-5), 62.1 (d, †C-2), 60.6 (d, ‡C-2), 56.1 (d, †C-8'), 53.7 (d, ‡C-8'), 51.7 (d, †C-6), 51.14 (d, ‡C-6 or *C-6), 51.11 (d, ‡C-6 or *C-6), 50.5 (d, †C-4), 49.6 (d, ‡C-4), 48.9 (d, *C-8'), 44.23 (d, *C-4), 44.15 (d, ‡C-4'a), 43.8 (d, †C-4'a), 43.7 (d, *C-4'a), 36.4

(t, ‡C-8 or *C-8), 36.1 (t, †C-8), 35.6 (t, ‡C-8 or *C-8), 31.0 (t, *C-7' or ‡C-7'), 30.9 (t, *C-7' or ‡C-7'), 30.8 (t, †C-7'), 28.6 (d, ‡C-1" or *C-1"), 28.5 (d ×2, †C-1" & ‡C-1" or *C-1"), 27.57 (t, *C-5' or ‡C-5'), 27.54 (t, *C-5' or ‡C-5'), 27.51 (t, ‡C-5'), 20.37 (q, *CH_3C-1" or ‡CH_3C-1"), 20.36 (q, *CH_3C-1" or ‡CH_3C-1"), 20.34 (q, †CH_3C-1"), 15.20 (q, *CH_3C-1" or ‡CH_3C-1"), 15.17 (q, †CH_3C-1"), 15.16 (q, *CH_3C-1" or ‡CH_3C-1"), 13.8 (q, *CH_3C-6), 13.7 (q, †CH_3C-4), 13.5 (q, *CH_3C-4 or ‡CH_3C-6), 13.4 (q, *CH_3C-4 or ‡CH_3C-6), 13.2 (q, ‡CH_3C-2), 12.5 (q, *CH_3C-4), 12.41 (q, †CH_3C-6), 12.37 (q, †CH_3C-2), 12.3 (q, *CH_3C-2), 8.2 (q, *C-9 or ‡C-9), 8.1 (q, †C-9), 8.0 (q, *C-9 or ‡C-9), 7.7 (q ×2, †$(CH_3C)_3$Si and *$(CH_3C)_3$Si or ‡$(CH_3C)_3$Si), 7.6 (q, *$(CH_3C)_3$Si or ‡$(CH_3C)_3$Si), 5.75 (t, †CH_2Si), 5.72 (t, *$(CH_2)_3$Si or ‡$(CH_2)_3$Si), 5.70 (t, *$(CH_2)_3$Si or ‡$(CH_2)_3$Si).

HRMS *m/z* calcd for $C_{34}H_{54}O_6SSi+Na^+$ 641.3303, found 641.3288 (ESI).



258

(4*S*,5*R*,6*R*,10*S*,11*S*,12*S*,13*S*)-11,13-Dihydroxy-4,6,8,10,12,14-hexamethyl-5-((triethylsilyl)oxy)pentadecane-3,7,9-trione (258)

A suspension of Raney nickel (W2; 0.5 mL settled volume) in EtOH (5 mL) was added to **257** (62 mg, 0.10 mmol), and the mixture was heated under reflux with vigorous stirring under H_2 atmosphere (balloon). After 2 h (reaction was complete by TLC analysis), the mixture was decanted, and the solid was suspended in EtOH (4 mL) and heated under reflux with vigorous stirring for several min. This washing procedure was repeated with ethyl acetate and with acetone. The combined organic layers were filtered through Celite®, concentrated and fractionated by FCC

(20% ethyl acetate in hexane) to give the title compound (38 mg, 76%) that was predominantly a 3:1 mixture of two hemiacetal forms (HOC-13 → O=C-9; epimeric at C-8) in C_6D_6 solution; $[\alpha]_D$ –48 (*c* 1.0, C_6H_6).

colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexane).

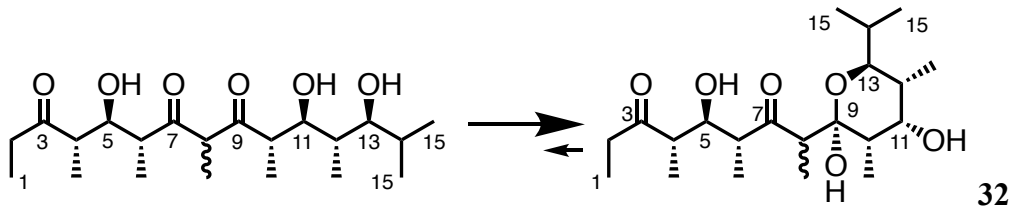
IR (DRIFT) ν_{max} 3407, 1705 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ (* denotes signals for the minor hemiacetal) 5.43 (0.75H, s, HOC-9), 5.03 (0.25H, s, *HOC-9), 4.66 (0.75H, dd, *J* = 6, 6.5 Hz, HC-5), 4.38 (0.25H, dd, *J* = 6, 6.5 Hz, *HC-5), 3.68 (0.25H, dd, *J* = 2.5, 10.5 Hz, *HC-13), 3.61 (0.75H, dq, *J* = 7, 7 Hz, HC-6), 3.56 (0.75H, dq, *J* = 2, 10.5 Hz, HC-13), 3.22 (0.25H, dq, *J* = 7, 7 Hz, *HC-6), 3.20 (0.75H, q, *J* = 7 Hz, HC-8), 3.15 (0.25H, br s, *HC-11), 3.12 (0.75H, br s, HC-11), 3.08 (0.25H, q, *J* = 7 Hz, *HC-8), 2.73 (0.75H, dq, *J* = 6.5, 7 Hz, HC-4), 2.69 (0.25H, dq, *J* = 6, 7 Hz, *HC-4), 2.41-2.11 (3H, t, *J* = 8 Hz, H_2C-2, *H_2C-2, HOC-13, *HOC-13), 1.75-1.57 (1H, m, HC-14, *HC-14), 1.53 (0.25H, dq, *J* = 2.5, 7 Hz, *HC-10), 1.48 (0.75H, d, *J* = 7 Hz, *H_3CC-8), 1.44 (0.75H, dq, *J* = 2.5, 7 Hz, HC-10), 1.30-1.21 (1H, m, HC-12, *HC-12), 1.23 (0.75H, d, *J* = 7 Hz, *H_3CC-10), 1.20 (2.25H, d, *J* = 7 Hz, H_3CC-6), 1.18 (2.25H, d, *J* = 7 Hz, H_3CC-8), 1.14 (0.75H, d, *J* = 7 Hz, *H_3CC-6), 1.11 (3H, ap d, *J* = 7 Hz, H_3C-15, *H_3C-15), 1.08 (0.75H, d, *J* = 7 Hz, *H_3CC-4), 1.06 (6.75H, t, *J* = 8 Hz, $(H_3CC)_3Si$), 1.04-0.98 (9.75H, m, H_3C-1, *H_3C-1, H_3CC-4, H_3CC-10, *$(H_3CC)_3Si$), 0.89 (2.25H, d, *J* = 7 Hz, H_3C-15), 0.87 (0.75H, d, *J* = 7 Hz, *H_3C-15), 0.79-0.69 (4.5H, m, $(H_2C)_3Si$), 0.70 (0.75H, d, *J* = 7 Hz, *H_3CC-12), 0.69 (1.5H, ap q, *J* = 8 Hz, *$(H_2C)_3Si$), 0.62 (2.25H, d, *J* = 7 Hz, H_3CC-12).

^{13}C NMR (125 MHz, C_6D_6) δ (* denotes signals for the minor hemiacetal) 216.6 (s, *C-7), 212.3 (s, C-7), 211.9 (s, C-3), 211.5 (s, *C-3), 101.8 (s, C-9), 101.5 (s, *C-9), 77.4 (d, *C-5), 77.1 (d,

*C-11), 77.0 (d, C-11), 76.4 (d, C-5), 72.7 (d, *C-13), 72.4 (d, C-13), 54.4 (d, *C-8), 52.7 (d, C-6), 52.4 (d, C-8), 51.9 (d, *C-4), 51.2 (d, C-4), 47.9 (d, *C-6), 41.8 (d, *C-10), 39.1 (d, C-10), 38.2 (d, *C-12), 37.8 (d, C-12), 36.6 (t, C-2), 36.0 (t, *C-2), 28.9 (d, C-14), 28.8 (d, *C-14), 21.1 (q, C-15), 21.0 (q, *C-15), 15.2 (q, *C-15), 15.0 (q, *CH_3C-6), 14.70 (q, C-15), 14.67 (q, *CH_3C-10), 13.8 (q ×2, CH_3C-12, *CH_3C-12), 13.7 (q, CH_3C-10), 13.1 (q, *CH_3C-4), 12.7 (q, CH_3C-8), 12.3 (q, CH_3C-4), 11.9 (q, CH_3C-6), 11.1 (q, *CH_3C-8), 8.1 (q ×2, C-1, *C-1), 7.6 (q ×2, $(CH_3C)_3Si$ *$(CH_3C)_3Si$), 5.81 (t, $(CH_2)_3Si$), 5.77 (t, *$(CH_2)3Si$).

HRMS *m/z* calcd for $C_{27}H_{52}O_6Si+Na^+$ 523.3425, found 523.3437 (ESI).



32

(4*S*,5*R*,6*R*,10*S*,11*S*,12*S*,13*S*)-5,11,13-Trihydroxy-4,6,8,10,12,14-hexamethylpentadecane-3,7,9-trione (32)

Tris(dimethylamino)sulfonium Difluorotrimethylsilicate (TASF, 15 mg, 0.054 mmol) was added to a stirring solution of **258** (18 mg, 0.036 mmol) in DMF (0.2 ml). After 30 min, the reaction was quenched by sequential addition of saturated aq $NaHCO_3$ and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and fractionated first by FCC (40% ethyl acetate in hexane) and then by PTLC (40% ethyl acetate in hexane) gave the title compound (11 mg, 80%) that was predominantly a 1.8:1 mixture of two hemiacetal forms (HOC-13 → O=C-9; epimeric at C-8) in C_6D_6 solution. Specific rotation and NMR data for **32** closely match those

previously reported ($[\alpha]_D$ –36 (*c* 1.1, C_6H_6), lit. –30 (*c* 0.5, C_6H_6); $\Delta\delta_H \leq 0.02$ for H-C, ≤ 0.2 for H-O; $\Delta\delta_C \leq 0.2$).[17]

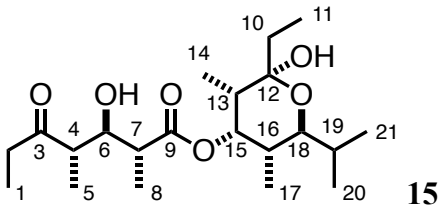
colorless oil, TLC $R_f = 0.3$ (40% ethyl acetate in hexane).

^{1}H NMR (500 MHz, C_6D_6) δ (* denotes signals for the minor hemiacetal) 5.57 (0.7H, s, HOC-9), 5.08 (0.4H, s, *HOC-9), 3.85-3.70 (2H, m, HC-5, *HC-5, HOC-5, *HOC-5), 3.66 (0.4H, dd, *J* = 2, 11 Hz, *HC-13), 3.58 (0.7H, dd, *J* = 2, 11 Hz, HC-13), 3.37 (0.7H, dq, *J* = 7, 7 Hz, HC-6), 3.15 (0.4H, ddd, *J* = 2.5, 2.5, 7 Hz, *HC-11), 3.13-3.01 (2H, m, *HC-6, HC-8, *HC-8, HC-11), 2.54 (0.4H, dq, *J* = 4.5, 7 Hz, *HC-4), 2.51 (0.7H, dq, *J* = 4.5, 7 Hz, HC-4), 2.37 (0.4H, d, *J* = 7 Hz, *HOC-11), 2.29 (0.7H, d, *J* = 7.5 Hz, HOC-11), 2.23 (0.4H, dq, *J* = 18.5, 7 Hz, *HC-2), 2.17-2.03 (1.7H, m, *HC-2, H_2C-2), 1.73-1.63 (1H, m, HC-14, *HC-14), 1.51 (0.4H, dq, *J* = 2.5, 7 Hz, HC-10*), 1.36 (0.7H, dq, *J* = 2.5, 7 Hz, HC-10), 1.31 (0.4H, ddq, *J* = 2.5, 11, 7 Hz, *HC-12), 1.25 (1.2H, d, *J* = 7 Hz, *H_3CC-8), 1.21 (0.7H, ddq, *J* = 2.5, 11, 7 Hz, HC-12), 1.16 (1.2H, d, *J* = 7 Hz, *H_3CC-10), 1.14 (2H, d, *J* = 7 Hz, H_3CC-8), 1.111 (2H, d, *J* = 7 Hz, H_3CC-6 or H_3CC-15), 1.107 (2H, d, *J* = 7 Hz, H_3CC-6 or H_3CC-15), 1.07 (1.2H, d, *J* = 7 Hz, *H_3CC-15), 1.02 (1.2H, d, *J* = 7 Hz, *H_3CC-4), 1.00 (1.2H, d, *J* = 7 Hz, *H_3CC-6), 0.98 (1.2H, t, *J* = 7 Hz, *H_3C-1), 0.96 (4H, ap d, *J* = 7 Hz, H_3CC-4, H_3CC-10), 0.93 (2H, t, *J* = 7 Hz, H_3C-1), 0.87 (2H, d, *J* = 7 Hz, H_3C-15), 0.85 (1.2H, d, *J* = 7 Hz, *H_3C-15), 0.71 (1.2H, d, *J* = 7 Hz, *H_3CC-12), 0.65 (2H, d, *J* = 7 Hz, H_3CC-12).

^{13}C NMR (125 MHz, C_6D_6) δ (* denotes signals for the minor hemiacetal) 218.5* (s, C-7), 217.4 (s, C-7), 215.6 (s, C-3), 215.2* (s, C-3), 102.4 (s, C-9), 101.8* (s, C-9), 78.8 (d, C-5), 78.0* (d, C-5), 77.2* (d, C-11), 76.7 (d, C-11), 72.7* (d, C-13), 72.6 (d, C-13), 54.6* (d, C-8), 54.3 (d, C-8), 49.6 (d, C-6), 49.0* (d, C-6), 48.31* (d, C-4), 48.29 (d, C-4), 41.5* (d, C-10), 39.1 (d, C-10), 38.2*

(d, C-12), 37.8 (d, C-12), 36.5 (t, C-2), 36.0* (t, C-2), 28.9 (d, C-14), 28.7* (d, C-14), 21.2 (q, C-15), 21.0* (q, C-15), 15.4* (q, H_3CC-6), 15.3 (q, H_3CC-6), 15.15 (q, H_3CC-4), 15.10* (q, H_3CC-4), 14.9* (q, H_3CC-15), 14.84 (q, H_3CC-15), 14.76* (q, H_3CC-10), 14.0 (q, H_3CC-12), 13.9* (q, H_3CC-12), 13.7 (q, H_3C-C10), 12.5 (q, H_3CC-8), 11.8* (q, H_3CC-8), 7.95* (q, C-1), 7.93 (q, C-1).

HRMS *m/z* calcd for $C_{21}H_{38}O_6$+Na^+ 409.2561, found 409.2574 (ESI).



15

Dolabriferol **(15)**

Following the published procedure,[17] a solution of **32** (5.6 mg, 0.015 mmol) in benzene (0.2 mL) was applied to a small column of neutral alumina (Brockmann I; ca. 5 cm in a Pasteur pipette). After 30 min, the column was eluted with ethyl acetate and the eluent was concentrated and fractionated by PTLC (40% ethyl acetate in hexane) to give dolabriferol (**15**) (4.4 mg, 79%). Specific rotation and NMR data for **15** closely match those previously reported ($[\alpha]_D$ –27 (*c* 0.44, $CHCl_3$), lit. –29.4 (*c* 0.7, $CHCl_3$); $\Delta\delta_H \leq 0.01$ for H-C, ≤ 0.03 for H-O; $\Delta\delta_C \leq 0.1$).[7]

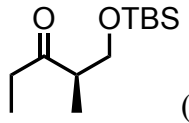
white solid, TLC R_f = 0.5 (40% ethylacetate in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (1H, dd, *J* = 2.5, 2.5 Hz), 3.76 (1H, ddd, *J* = 5, 8, 8 Hz), 3.62 (1H, d, *J* = 8 Hz), 3.61 (1H, dd, *J* = 2, 10.5 Hz), 3.46 (1H, s), 2.78 (1H, dq, *J* = 7, 7 Hz), 2.74 (1H, dq, *J* = 5, 7 Hz), 2.58 (1H, dq, *J* = 18, 7 Hz), 2.46 (1H, dq, *J* = 18, 7 Hz), 1.91 (1H, dq, *J* = 3, 7 Hz), 1.81 (1H, dqq, *J* = 2, 7, 7 Hz), 1.77 (1H, ddq, *J* = 2.5, 10.5, 7 Hz), 1.65 (1H, dq, *J* = 14.5, 7.5

Hz), 1.59 (1H, dq, J = 14.5, 7.5 Hz), 1.33 (3H, d, J = 7 Hz), 1.15 (3H, d, J = 7 Hz), 1.04 (3H, t, J = 7 Hz), 1.01 (3H, d, J = 7 Hz), 1.00 (3H, d, J = 7 Hz), 0.91 (3H, t, J = 7.5 Hz), 0.83 (3H, d, J = 7 Hz), 0.78 (3H, d, J = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 173.9, 98.7, 77.1, 75.9, 72.5, 49.6, 43.9, 39.6, 36.6, 36.2, 32.7, 28.2, 20.5, 15.8, 14.6, 14.2, 13.2, 13.0, 7.7, 7.5.

HRMS *m/z* calcd for $C_{21}H_{38}O_6$+Na^+ 409.2561, found 409.2571.



(*R*)-**263**

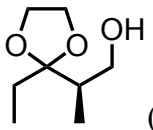
(*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2-methylpentane-3-one ((*R*)-263)

Following the known procedures,[31,99] propanal (4.80 g, 82.6 mmol) was added to a stirring suspension of L-proline (476 mg, 4.14 mmol) in dry dimethylformamide (36 mL) at 4 °C. After 10 h, MeOH (6.7 mL, 5.3 g, 0.17 mol) and $NaBH_4$ (6.2 g, 16 mmol) were added and the reaction mixture was allowed warmed to ambient temperature over 30 minutes. The mixture was cooled to 0 °C, and reaction was quenched by slow addition of water (20 mL) and 30% H_2O_2 (18.5 mL, 0.166 mol) with vigorous stirring. After 30 min, the mixture was diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and re-concentrated from toluene (several times) to obtain the crude diol (2.59 g) as a 4:1 mixture of **260a** (*anti*), **260s** (*syn*) diastereomers, that was used in the next step without further purification. A small sample of this mixture was converted to the corresponding mono benzoate ester **261a**;[106–108] HPLC analysis of **261a** indicated >98% ee (for each diastereomer).

TBSCl (2.91g, 19.3 mmol) and imidazole (1.77g, 26 mmol) were added to a stirring solution of the crude diol (2.59 g, 21.9 mmol) in dry dimethylformamide (22 mL) at 0 °C under

argon. After 2 h, the mixture was diluted with a 30% Et_2O in hexane solution and washed sequentially with 0.2 M aq citric acid and brine, dried over Na_2SO_4, concentrated and reconcentrated from toluene (several times) to give the crude TBS alcohol **262** (4.32 g) that was used in the next step without further purification.

A solution of the crude TBS alcohol **262** (4.32 g, 18.6 mmol) and pyridine (4.5 mL, 4.40 g, 56 mmol) in wet CH_2Cl_2 (20 mL; saturated with water) was added to a stirring solution of DMP (12.1 g, 28.5 mmol) in wet CH_2Cl_2 (170 mL; saturated with water) under argon. After 10 min, the reaction was quenched by addition of a 1:1 mixture (v/v) of 10% aq $Na_2S_2O_3$ and saturated aq $NaHCO_3$. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, concentrated, and fractionated by FCC (5% ethyl acetate in hexane) to give the title compound (4.2 g; 44% from propanal) as a colorless liquid. NMR data for (*R*)-**263** closely matched those previously reported.[104,112] ($[\alpha]_D$ –36, *c* 1.2, $CHCl_3$; lit.[112] (for the *S* enantiomer) $[\alpha]_D$ +43.70, *c* 1.0, $CHCl_3$).



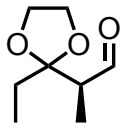
(*R*)-**268**

(*R*)-2-(2-ethyl-1,3-dioxalane-2-yl)propan-1-ol (268)

1,2-Bis(trimethylsiloxy)ethane (8.0 mL, 8.6 g, 32 mmol), bis(trimethylsilyl)acetamide (0.20 mL, 0.17 g, 0.82 mmol), and TMSOTf (0.42 mL, 0.52 g, 2.3 mmol) were sequentially added to a stirring solution of **263** (1.80 g, 7.82 mmol) in dry CH_2Cl_2 (13 mL) at –20 °C under argon. After 2 h, a solution of Et_3N (3.3 mL, 2.4 g, 24 mmol) in CH_2Cl_2 (20 mL) and saturated aq $NaHCO_3$ was were added to the reaction mixture with vigorous stirring. The organic layer was washed with

water, dried over Na_2SO_4, and concentrated to give the crude product (8.7 g) that was used in the next step without further purification.

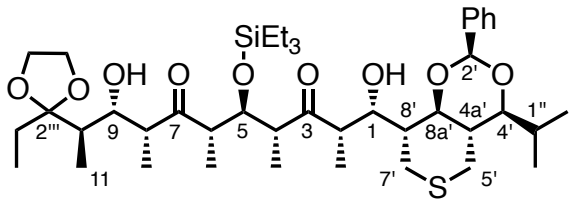
Et_3N (16.3 mL, 11.9 g, 120 mmol) and 7.7% aq HF (31 mL, 0.12 mol) were sequentially added to a stirring solution of the above crude product (8.7 g) in acetonitrile (26 mL) at 0 °C. The cooling bath was removed and stirring continued at room temperature for 3 h. The reaction mixture was cooled to 0 °C and saturated aq $NaHCO_3$ was added. The mixture was diluted with EtOAc and the organic layer was separated and washed with brine, dried over Na_2SO_4, concentrated, and fractionated by FCC to give the title compound (1.08 g, 86% from **263**) as a colorless oil ($[\alpha]^{25}$ +38, *c* 1.3, $CHCl_3$). NMR data for (*R*)-**268** closely matched those previously reported.[78] The enantiopurity of (*R*)-**268** (97% ee) was determined by HPLC of the corresponding benzoate ester as described by Leighton et al.[97]



(+)-*R*-**159**

(*R*)-2-(2-ethyl-1,3-dioxalane-2-yl)propanal (159)

A solution of (*R*)-**268** (342 mg, 2.14 mmol), pyridine (0.52 mL, 511 mg, 6.45 mmol) in water-saturated CH_2Cl_2 (10.0 mL) was added to a stirring suspension of Dess-Martin periodinane (DMP) (1.36 g, 3.21 mmol) in water-saturated CH_2Cl_2 (10.0 mL). After 10 min, Et_2O (40 mL) was added and a white precipitate formed. A solution made up of saturated $NaHCO_3$ (12.6 mL) and $Na_2S_2O_3$ (3.3 g) diluted to 20 mL with water was added to the stirring reaction mixture resulting in two layers. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with H_2O, brine, dried over Na_2SO_4 and concentrated to give the title compound (311 mg) as colourless oil that was immediately used in the aldol reaction.



252ssa

(1*S*,2*S*,4*R*,5*R*,6*S*,8*R*,9*R*,10*R*)-10-(2-Ethyl-1,3-dioxolan-2-yl)-1,9-dihydroxy-1-((2*S*,4*S*,4a*S*,8*R*,8a*R*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6,8-tetramethyl-5-((triethylsilyl)oxy)undecane-3,7-dione (252ssa)

As described above for the preparation of **253**, the (*Z*,*Z*)-dienyl bis(9-borabicyclo[3.3.1]nonan-9-ylborinate) of **202aa** (221 mg, 0.71 mmol) was prepared by reaction with 9-BBNOTf (4 equiv) and Et_3N (5 equiv) in Et_2O at –78 °C for 4 h, followed by addition of 2,4-dimethyl-3-pentanone (8 equiv) and reaction at 0 °C for 1 h (to quench the excess 9-BBN-OTf). The stirring mixture was cooled to –78 °C and a solution of (+)-**128** (238 mg, 0.78 mmol) in THF (2.0 mL) was added via syringe. After 16 h, a solution of (*R*)-(+)-**159** (311 mg, 1.97 mmol) in Et_2O (2 mL) was added. After 6 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7, 4 ml), 30% aq H_2O_2 (4 ml), and MeOH (4 ml) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 20 min, the mixture was diluted with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product as pale yellow oil whose ^1H NMR spectrum indicated the presence of a 4:1 mixture of **252ssa** and homobisaldols (i.e., double addition of (+)-**128** or (+)-**159** to **222**), respectively. Fractionation of the crude product by FCC (30% ethyl acetate in hexane) and then a second FCC (20% acetone in hexane) gave an ca. 84:12:4 mixture of **252ssa**, **252ass** (tentative), and **252sss**, respectively (345 mg, 63%; ca. 53% of **252ssa**).

A small sample of the mixture was fractioned twice by PTLC (20% Et_2O in toluene, developed twice) to give the title compound (ca. 95% pure); $[\alpha]_D$ +14 (*c* 0.4, $CHCl_3$).

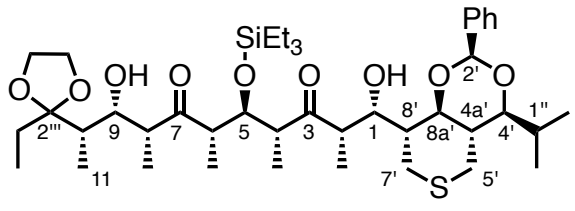
pale yellow viscous oil, TLC R_f = 0.3 (30% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3540, 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.44 (2H, m, Ph), 7.37-7.30 (3H, m, Ph), 5.54 (1H, s, HC-2'), 4.39 (1H, dd, *J* = 6, 6 Hz, HC-5), 4.22 (1H, ddd, *J* = 3, 3, 5 Hz, HC-1), 4.18 (1H, s, HOC-9), 4.03 (1H, br d, *J* = 10 Hz, HC-9), 4.02-3.95 (4H, m, H_2CO ×2), 3.51 (1H, dd, *J* = 9.5, 9.5 Hz, HC-8'a), 3.39 (1H, dd, *J* = 2, 10 Hz, HC-4'), 3.07 (1H, dq, *J* = 3, 7 Hz, HC-2), 2.98 (1H, d, *J* = 3 Hz, HOC-1), 2.97 (1H, dq, *J* = 6, 7 Hz, HC-6), 2.92-2.88 (1H, m, HC-7'), 2.85 (1H, dq, *J* = 6, 7 Hz, HC-4), 2.70 (1H, dd, *J* = 11, 14 Hz, HC-7'), 2.63-2.57 (1H, m, HC-8), 2.53-2.47 (1H, m, HC-5'), 2.31 (1H, dd, *J* = 12, 13.5 Hz, HC-5'), 2.11-2.03 (2H, m, HC-4'a, HC-8'), 1.94 (1H, dqq, *J* = 2, 7, 7 Hz, HC-1''), 1.85 (1H, dq, *J* = 9.5, 7 Hz, HC-10), 1.83-1.69 (2H, m, H_2CC-2'''), 1.17 (3H, d, *J* = 7 Hz, H_3CC-2), 1.11 (3H, d, *J* = 7 Hz, H_3CC-8), 1.05 (3H, d, *J* = 7 Hz, H_3CC-1''), 0.97 (3H, d, *J* = 7 Hz, H_3CC-1''), 0.94 (3H, d, *J* = 7 Hz, H_3CC-6), 0.92-0.88 (9H, m, H_3CC-4, H_3C-11, H_3CCC-2'''), 0.90 (9H, t, *J* = 8 Hz, $(H_3CC)_3Si$), 0.54 (6H, ap q, *J* = 8 Hz, $(H_2C)_3Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.1 (s, C-3), 214.6 (s, C-7), 138.9 (s, Ph), 128.8 (d, Ph), 128.3 (d ×2, Ph), 126.3 (d ×2, Ph), 114.8 (s, C-2'''), 101.1 (d, C-2'), 84.0 (d, C-4'), 82.1 (d, C-8'a), 74.9 (d, C-5), 72.3 (d, C-9), 69.9 (d, C-1), 65.4 (t, CH_2O), 65.1 (t, CH_2O), 49.6 (d, C-2), 49.2 (d, C-4), 48.4 (d, C-6), 48.1 (d, C-8), 46.3 (d, C-8'), 43.7 (d, C-4'a), 41.4 (d, C-10), 28.5 (t, C-7'), 28.4 (d, C-1''), 27.5 (t, C-5'), 26.0 (t, CH_2C-2'''), 20.2 (q, CH_3C-1''), 15.0 (q, CH_3C-1''), 12.8 (q ×2, CH_3C-4 & C-11), 12.1 (q, CH_3C-6), 11.1 (q, CH_3C-2), 8.4 (q, CH_3C-8), 7.2 (q, $(CH_3C)_3Si$), 7.1 (q, CH_3CC-2'''), 5.2 (t, $(CH_2)_3Si$).

HRMS *m/z* calcd for $C_{42}H_{70}O_9SiS+Na^+$ 801.4402, found 801.4405 (ESI).



252sss

(1*S*,2*S*,4*R*,5*R*,6*S*,8*R*,9*R*,10*S*)-10-(2-Ethyl-1,3-dioxolan-2-yl)-1,9-dihydroxy-1-((2*S*,4*S*,4a*S*,8*R*,8a*R*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6,8-tetramethyl-5-((triethylsilyl)oxy)undecane-3,7-dione (252sss)

As described above for the preparation of **253**, the (*Z*,*Z*)-dienyl bis(9-borabicyclo[3.3.1]nonan-9-ylborinate) of **202aa** (20 mg, 0.064 mmol) was prepared by reaction with 9-BBNOTf (4 equiv) and Et_3N (5 equiv) in Et_2O at –78 °C for 4 h, followed by addition of 2,4-dimethyl-3-pentanone (8 equiv) and reaction at 0 °C for 1 h (to quench the excess 9-BBN-OTf). The stirring mixture was cooled to –78 °C and a solution of (+)-**128** (24 mg, 0.08 mmol) in THF (0.2 mL) was added via syringe. After 12 h, a solution of (±)-**159** (31 mg, 0.19 mmol) in Et_2O (0.2 mL) was added. After 6 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7, 0.5 ml), 30% aq H_2O_2 (0.5 ml), and MeOH (0.5 ml) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 20 min, the reaction mixture was diluted with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product as pale yellow oil whose ^1H NMR spectrum indicated the presence of a 2.2:1:1 mixture of **252sss**, **252ssa**, and homobisaldols (i.e., double addition of (+)-**128** or (±)-**159** to **222**), respectively. Fractionation of the crude product by FCC (30% ethyl acetate in hexane) and then by PTLC (10% acetone in

hexane) gave a 1:1.1 mixture of **252sss** and **252ssa** (17 mg, 34%; ^{13}C NMR signals of the major component match those of a authentic sample; see below), respectively, and the title compound as an 8:1 mixture with **252ssa** (17 mg, ca. 90% pure, ca. 30%); $[\alpha]_D$ +9.0 (*c* 1.4, $CHCl_3$).

colorless viscous oil, TLC R_f = 0.3 (30% ethyl acetate in hexane).

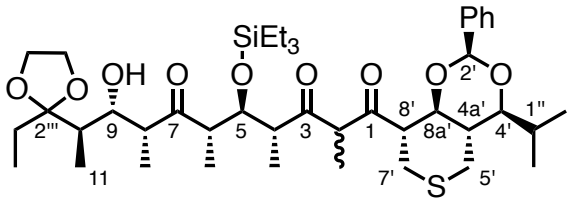
IR (DRIFT) ν_{max} 3536, 1712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.44 (2H, m, Ph), 7.37-7.32 (3H, m, Ph), 5.53 (1H, s, HC-2'), 4.42 (1H, dd, *J* = 3, 8.5 Hz, HC-5), 4.17 (1H, dd, *J* = 3, 6 Hz, HC-1), 4.10 (1H, dd, *J* = 2.5, 8 Hz, HC-9), 4.02-3.93 (4H, m, H_2CO ×2), 3.49 (1H, dd, *J* = 9 Hz, HC-8'a), 3.39 (1H, dd, *J* = 2, 10 Hz, HC-4'), 3.22 (1H, br s, HO), 3.07 (1H, dq, *J* = 3, 7 Hz, HC-2), 3.00 (1H, dq, *J* = 8, 7 Hz, HC-8), 2.97 (1H, br d, *J* = 14 Hz, HC-7'), 2.85 (1H, dq, *J* = 8.5, 7 Hz, HC-4), 2.82 (1H, dq, *J* = 3, 7 Hz, HC-6), 2.64 (1H, dd, *J* = 11.5, 14 Hz, HC-7'), 2.50 (1H, br d, *J* = 13.5 Hz, HC-5'), 2.31 (1H, dd, *J* = 12, 13.5 Hz, HC-5'), 2.13-2.03 (2H, m, HC-8', HC-4'a), 1.95 (1H, dqq, *J* = 2, 7, 7 Hz, HC-1"), 1.85 (1H, dq, *J* = 2.5, 7 Hz, HC-10), 1.72-1.64 (2H, m, H_2CC-2'"), 1.21 (3H, d, *J* = 7 Hz, H_3CC-8), 1.14 (3H, d, *J* = 7 Hz, H_3CC-2), 1.05 (3H, d, *J* = 7 Hz, H_3CC-1"), 1.04 (3H, d, *J* = 7 Hz, H_3CC-6), 0.97 (6H, ap d, *J* = 7 Hz, H_3CC-1", H_3C-11), 0.91 (9H, t, *J* = 8 Hz, $(H_3CC)_3Si$), 0.85 (3H, t, *J* = 7.5 Hz, H_3CCC-2'"), 0.75 (3H, d, *J* = 7 Hz, H_3CC-4), 0.55 (6H, ap q, *J* = 8 Hz, $(H_2C)_3Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.9 (s, C-3), 215.1 (s, C-7), 138.9 (s, Ph), 128.9 (d, Ph), 128.3 (d ×2, Ph), 126.3 (d ×2, Ph), 114.5 (s, C-2'"), 101.1 (d, C-2'), 84.0 (d, C-4'), 82.5 (d, C-8'a), 73.7 (d, C-5), 70.9 (d, C-9), 70.3 (d, C-1), 65.5 (t, CH_2O), 65.0 (t, CH_2O), 51.5 (d, C-6), 50.9 (d, C-2), 48.54 (d, C-4), 48.47 (d, C-8), 46.0 (d, C-8'), 43.8 (d, C-4'a), 39.9 (d, C-10), 28.9 (t, C-7'), 28.5 (d, C-1"), 27.7 (t, CH_2C-2'"), 27.6 (t, C-5'), 20.2 (q, CH_3C-1"), 15.0 (q, CH_3C-1"), 14.7 (q, CH_3C-8),

13.5 (q, CH_3C-4), 10.4 (q, CH_3C-2), 9.8 (q, CH_3C-6), 8.5 (q, C-11), 7.9 (q, CH_3CC-2'''), 7.1 (q, $(CH_3C)_3Si$), 5.2 (t, $(CH_2)_3Si$).

HRMS *m/z* calcd for $C_{42}H_{70}O_9SiS+Na^+$ 801.4402, found 801.4391 (ESI).



272

(4*R*,5*R*,6*S*,8*R*,9*R*,10*R*)-10-(2-Ethyl-1,3-dioxolan-2-yl)-9-hydroxy-1-((2*S*,4*S*,4a*S*,8*S*,8a*S*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6,8-tetramethyl-5-((triethylsilyl)oxy)undecane-1,3,7-trione (272)

A solution of Dess-Martin periodinane (DMP; 133 mg, 0.31 mmol) and *tert*-butylalcohol (23 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) was stirred for 10 min at room temperature and then cooled to 0 °C. A solution of the above 84:12:4 mixture of **252ssa**, **252ass**, and **252sss**, respectively (162 mg, 0.21 mmol), and pyridine (0.05 mL, 50 mg, 0.64 mmol) in CH_2Cl_2 (2 mL) was added to the above stirring solution. After 1 h, the reaction was quenched by sequential addition of Et_2O (12 mL) and a 1:1 mixture (v/v) of saturated aq $NaHCO_3$ and 10% aq $Na_2S_2O_3$ (12 mL) with vigorous stirring. The two layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the crude product, whose ^1H NMR spectrum indicated the presence of a 12:3:1 mixture of **272**, the corresponding tetrone (tentatively identified), and **252ssa**, respectively. Fractionation of the crude product by FCC (15% ethyl acetate in hexane) provided the title compound (110 mg, 81% based

on **252ssa**; 43% from (+)-**128**) that was a 1:2:5 mixture of enol and two keto tautomers, respectively, in C_6D_6 solution; $[\alpha]_D$ +54 (*c* 1.0, C_6H_6).

colorless viscous oil, TLC R_f = 0.3 (15% ethyl acetate in hexane).

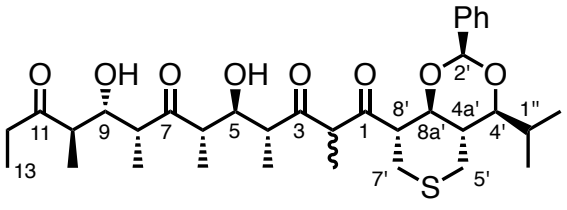
IR (DRIFT) ν_{max} 3488, 1700 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ (* enol tautomer; † major keto tautomer; ‡ minor keto tautomer) 17.86 (0.15H, s, HO-enol), 7.60-7.48 (2H, m, Ph), 7.33-7.07 (3H, m, Ph), 5.45 (0.15H, s, *HC-2'), 5.32 (0.25H, s, ‡HC-2'), 5.31 (0.6H, s, †HC-2'), 4.60 (0.6H, dd, *J* = 5.5, 6 Hz, †HC-5), 4.60-4.57 (0.15H, m, *HC-5), 4.51 (0.25H, dd, *J* = 4.5, 8 Hz, ‡HC-5), 4.34-4.26 (2H, m, HOC-9, HC-9), 4.09 (0.6H, q, *J* = 7 Hz, †HC-2), 3.88 (0.25H, q, *J* = 7 Hz, ‡HC-2), 3.67 (0.15H, ap t, *J* = 10 Hz, *HC-8'a), 3.62 (0.25H, ap t, *J* = 10 Hz, ‡HC-8'a), 3.62 (0.6H, ap t, *J* = 10 Hz, †HC-8'a), 3.40-3.20 (6H, m, *J* = 7 Hz, H_2CO ×2, HC-6, HC-8'), 3.10-2.77 (3.6H, m, HC-4, HC-4', †H_2C-7', ‡HC-7', *HC-7'), 2.72 (0.15H, br q, *J* = 7 Hz, *HC-8), 2.65 (0.6H, br q, †HC-8), 2.61-2.54 (0.5H, m, ‡HC-7', ‡HC-8), 3.25 (0.15H, ddd, *J* = 2.5, 2.5, 13.5 Hz, *HC-7'), 2.15-2.81 (4H, m, HC-4'a, H_2C-5', HC-10), 1.80 (0.45H, s, *H_3CC-2), 1.75-1.44 (3H, m, HC-1", H_2CC-2'"), 1.35 (1.8H, d, *J* = 7 Hz, †H_3CC-2), 1.33 (0.75H, d, *J* = 7 Hz, ‡H_3CC-8), 1.31 (1.8H, d, *J* = 7 Hz, †H_3CC-8), 1.30 (0.45H, d, *J* = 7 Hz, *H_3CC-8), 1.25 (0.75H, d, *J* = 7 Hz, ‡H_3CC-2), 1.23 (0.45H, d, *J* = 7 Hz, *H_3CC-6), 1.12 (2.55H, ap d, *J* = 7 Hz, †H_3CC-6, ‡H_3CC-6), 1.07-0.92 (15H, m, H_3CC-4, H_3CC-1", $(H_3CC)_3Si$), 0.90-0.81 (9H, m, H_3CC-10, H_3CC-1", H_3CCC-2'"), 0.75-0.62 (6H, m, $(H_2C)_3Si$).

^{13}C NMR (125 MHz, C_6D_6) δ (* enol tautomer; † major keto tautomer; ‡ minor keto tautomer) 215.0 (s, ‡C-7), 214.2 (s, *C-7), 213.7 (s, †C-7), 209.9 (s, †C-3), 209.24 (s, ‡C-1 or ‡C-3), 209.16 (s, ‡C-1 or ‡C-3), 208.3 (s, †C-1), 196.4 (s, *C-3), 193.3 (s, *C-1), 139.7 (s, *Ph), 139.5 (s, †Ph), 139.4 (s, ‡Ph), 129.3 (d, ‡Ph), 129.2 (d ×2, ‡Ph), 129.1 (d, *Ph), 128.9 (d, †Ph), 128.66 (d ×2, †Ph),

128.64 (d ×2, *Ph), 127.2 (d ×2, ‡Ph), 126.9 (d ×2, *Ph), 126.6 (d ×2, †Ph), 115.22 (d, ‡C-2'''), 115.17 (t, †C-2'''), 115.13 (d, *C-2'''), 106.35 (s, *C-2), 102.0 (d, ‡C-2'), 101.4 (d, *C-2'), 101.3 (d, †C-2'), 83.9 (d ×2, †C-4' & ‡C-4'), 83.8 (d, *C-4'), 83.3 (d, †C-8'a), 82.6 (d, ‡C-8'a), 81.4 (d, *C-8'a), 77.1 (d, ‡C-5), 76.1 (d, †C-5), 75.9 (d, *C-5), 73.42 (d, ‡C-9), 73.38 (d, *C-9), 73.2 (d, †C-9), 65.4 (t, CH_2O), 65.1 (t, CH_2O), 62.2 (d, †C-2), 60.5 (d, ‡C-2), 55.8 (d, †C-8'), 53.6 (d, ‡C-8'), 51.0 (d, †C-4), 50.1 (d, ‡C-4), 49.5 (d, ‡C-8), 49.2 (d, †C-8), 49.0 (d, *C-8 or *C-8'), 48.9 (d, *C-8 or *C-8'), 48.3 (d, †C-6), 47.9 (d, *C-6), 47.6 (d, ‡C-6), 44.6 (d, *C-4 or *C-4'a), 44.2 (d, *C-4 or *C-4'a), 43.8 (d, †C-4'a), 43.7 (d, ‡C-4'a), 42.08 (d, *C-10), 42.05 (d, ‡C-10), 42.02 (d, †C-10), 31.1 (d, ‡C-7'), 30.9 (d, †C-7'), 30.5 (d, *C-7'), 28.7 (d, *C-1''), 28.6 (d ×2, †C-1'' & ‡C-1''), 27.6 (d ×2, ‡C-5' & *C-5'), 27.5 (d, †C-5'), 26.6 (d, *CH_2C-2'''), 26.4 (d, †CH_2C-2'''), 26.3 (d, ‡CH_2C-2'''), 20.3 (q, CH_3C-1''), 15.8 (q, CH_3C-1''), 14.1 (q, ‡CH_3C-6), 13.6 (q ×2, †CH_3C-4 & *CH_3C-4 or *CH_3C-6), 13.53 (q, *CH_3C-4 or *CH_3C-6), 13.46 (q ×2, ‡CH_3C-2 & ‡CH_3C-4), 13.3 (q, †CH_3C-6), 13.0 (q ×2, †CH_3C-10 & ‡CH_3C-10), 12.9 (q, *CH_3C-10), 12.5 (q, †CH_2C-2), 12.4 (q, *CH_3C-2), 8.9 (q, *CH_3C-8), 8.8 (q, †CH_3C-8), 8.6 (q, ‡CH_3C-8), 7.71 (q, ‡$(CH_3C)_3Si$), 7.69 (q, †$(CH_3C)_3Si$), 7.6 (q, *$(CH_3C)_3Si$), 7.55 (q, *CH_3CC-2'''), 7.48 (q, †CH_3CC-2'''), 7.43 (q, ‡CH_3CC-2'''), 5.83 (t, †$(H_2C)_3Si$), 5.81 (t, ‡$(H_2C)_3Si$), 8.79 (t, *$(H_2C)_3Si$).

HRMS *m/z* calcd for $C_{42}H_{68}O_9SiS+Na^+$ 799.4246, found 799.4263 (ESI).



275

(4*R*,5*R*,6*S*,8*R*,9*S*,10*R*)-5,9-Dihydroxy-1-((2*S*,4*S*,4a*S*,8*S*,8a*S*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6,8,10-pentamethyltridecane-1,3,7,11-tetraone (275)

$FeCl_3 \cdot 6H_2O$ (4.7 mg, 0.018 mmol) was added to a stirring solution of **272** (68 mg, 0.088 mmol) in acetone (2.5 mL) at 0 °C. The reaction vessel was removed from the ice bath and allowed to warm to ambient temperature with stirring. After 30 min, the reaction was quenched by sequential addition of saturated aq $NaHCO_3$ and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and fractionate by FCC (30% ethyl acetate in hexane) to give the title compound (49 mg, 91%) that was a 1:2:1 mixture of enol and two keto tautomers, respectively, in C_6D_6 solution; $[\alpha]_D$ +59 (*c* 1.0, C_6H_6).

colorless viscous oil, TLC R_f = 0.3 (30% ethyl acetate in hexane).

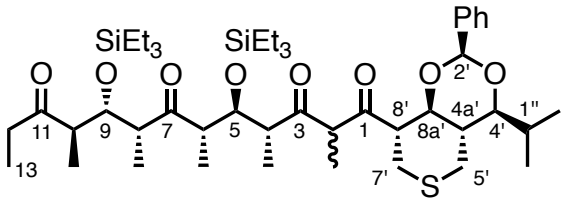
IR (DRIFT) ν_{max} 3483, 1712 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ (for major keto tautomer) 7.41-7.37 (2H, m, Ph), 7.13-7.08 (2H, m, Ph), 7.07-7.02 (1H, m, Ph), 5.18 (1H, s, HC-2'), 4.45 (1H, dd, *J* = 4, 8 Hz, HC-9), 4.07-4.02 (1H, m, HO), 3.54-3.50 (1H, m, HC-5), 3.50 (1H, q, *J* = 7 Hz, HC-2), 3.43 (1H, dd, *J* = 9.5, 10 Hz, HC-8'a), 3.36 (1H, dq, *J* = 10, 6.5 Hz, HC-6), 2.96 (1H, ddd, *J* = 3, 10, 11.5 Hz, HC-8'), 2.90 (1H, dd, *J* = 2, 9.5 Hz, HC-4'), 2.82 (1H, dq, *J* = 3, 7 Hz, HC-8), 2.78 (1H, dd, *J* = 11.5, 13.5 Hz, HC-7'), 2.73 (1H, dq, *J* = 8, 7 Hz, HC-10), 2.48 (1H, dq, *J* = 18, 7 Hz, HC-12), 2.45-2.40 (1H, dq, *J* = 2.5, 7.5 Hz, HC-4), 2.23 (1H, dq, *J* = 18, 7 Hz, HC-12), 2.11 (1H, br d, *J* = 13.5 Hz, HC-7'), 2.09-1.99 (2H, m, HC-5', HC-4'a), 1.83 (1H, dd, *J* = 12.5, 14 Hz, HC-5'), 1.51-1.44 (1H, m, HC-1''), 1.16 (3H, d, *J* = 7 Hz, H_3CC-8), 1.07-1.02 (6H, m, H_3C-13, H_3CC-6), 0.91 (3H, d, *J* = 7 Hz, H_3CC-1''),

0.90 (3H, d, *J* = 7 Hz, H_3CC-1"), 0.88 (3H, d, *J* = 7 Hz, H_3CC-2), 0.86 (3H, d, *J* = 7 Hz, H_3CC-10), 0.51 (3H, d, *J* = 7.5 Hz, H_3CC-4), δ (for minor keto tautomer; partial data) 3.85 (1H, q, *J* = 7 Hz, HC-2), 1.19 (3H, d, *J* = 7 Hz, H_3CC-2), δ (for enol tautomer; partial data) 17.4 (1H, br s, enol HO), 1.52 (3H, s, H_3CC-2).

^{13}C NMR (125 MHz, C_6D_6) δ (for major keto tautomer) 217.8 (s, C-7), 214.8 (s, C-11), 213.15 (s, C-3), 210.8 (s, C-1), 138.9 (s, Ph), 130.0 (d, Ph), 129.0 (d ×2, Ph), 127.3 (d ×2, Ph), 102.7 (d, C-2'), 83.9 (d, C-8'a), 83.8 (d, C-4'), 79.1 (d, C-5), 73.7 (d, C-9), 60.2 (d, C-2), 54.8 (d, C-8'), 51.0 (d, C-8), 49.0 (d, C-6), 48.0 (d, C-10), 46.4 (d, C-4), 43.7 (d, C-4'a), 36.7 (t, C-12), 30.3 (t, C-7'), 28.5 (d, C-1"), 27.5 (t, C-5'), 20.2 (q, CH_3C-1"), 15.3 (q, CH_3C-6), 15.1 (q, CH_3C-1"), 14.9 (q, CH_3C-4), 14.3 (q, CH_3C-10), 11.5 (q, CH_3C-2), 9.7 (q, CH_3C-8), 8.0 (q, C-13), δ (for minor keto tautomer; partial data), 213.11 (s, C-3), 208.1 (s, C-1), 61.9 (d, C-2), 56.1 (d, C-8'), 12.6 (q, CH_3C-2), δ (for enol tautomer; partial data) 200.6 (s, C-3), 192.5 (s, C-1), 106.6 (s, C-2), 48.7 (d, C-8'), 39.5 (d, C-4), 12.2 (q, CH_3C-2).

HRMS *m/z* calcd for $C_{34}H_{50}O_8S+Na^+$ 641.3119, found 641.3126 (ESI).



277

(4*R*,5*R*,6*S*,8*R*,9*S*,10*R*)-5,9-Dihydroxy-1-((2*S*,4*S*,4a*S*,8*S*,8a*S*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6,8,10-pentamethyl-5,9-bis((triethylsilyl)oxy)tridecane-1,3,7,11-tetraone (277)

Imidazole (21 mg, 0.297 mmol) and Et_3SiCl (0.034 ml, 30 mg, 0.199 mmol) were sequentially added to a stirring solution of **275** (41 mg, 0.066 mmol) in dry DMF (1 mL) at 0 °C. The reaction mixture was removed from the ice-bath and allowed to warm to ambient temperature with stirring. After 2 h (reaction was complete by TLC analysis), the mixture was diluted with Et_2O and washed sequentially with aq citric acid (0.2 M) and brine, dried over Na_2SO_4, and concentrated to give the crude product. Fractionation of the crude product by FCC (10% ethyl acetate in hexane) gave the title compound (55 mg, 98%) that was an ca. 2:5:1 mixture of enol and two keto tautomers, respectively, in C_6D_6 solution; $[\alpha]_D$ +18 (*c* 1.0, C_6H_6).

colorless viscous oil, TLC R_f = 0.3 (10% ethyl acetate in hexane).

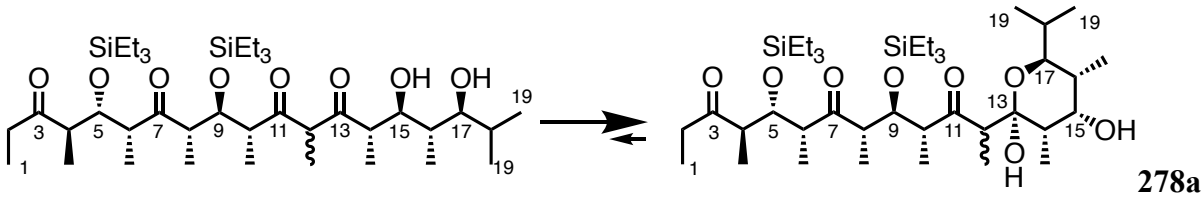
IR (DRIFT) ν_{max} 1720 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ (for major keto tautomer) 7.50-7.46 (2H, m, Ph), 7.19-716 (2H, m, Ph), 7.09 (1H, br t, *J* = 7.5 Hz, Ph), 5.29 (1H, br s, HC-2'), 4.62 (1H, dd, *J* = 3, 7.5 Hz, HC-9), 4.49 (1H, ap t, *J* = 6 Hz, HC-5), 4.02 (1H, q, *J* = 7 Hz, HC-2), 3.60 (1H, dd, *J* = 9.5, 10 Hz, HC-8'a), 3.23 (1H, ddd, *J* = 3, 10, 11.5 Hz, HC-8'), 3.02 (1H, dd, *J* = 11.5, 14 Hz, HC-7'), 2.97-2.90 (3H, m, HC-6, HC-4', HC-7'), 2.77 (1H, dq, *J* = 3, 7 Hz, HC-8), 2.73 (1H, dq, *J* = 7, 6.5 Hz, HC-4), 2.61 (1H, dq, *J* = 7.5, 7 Hz, HC-10), 2.4-2.15 (2H, m, HC-12), 2.08-1.98 (2H, m, HC-5', HC-4'a), 1.84 (1H, dd, *J* = 12.5, 13.5 Hz, HC-5'), 1.54-1.44 (1H, m, HC-1''), 1.32 (3H, d, *J* = 7 Hz, H_3CC-2), 1.17 (3H, d, *J* = 7 Hz, H_3CC-8), 1.08-1.03 (15H, m, H_3C-13, $(H_3CC)_3Si$, H_3CC-6), 0.98 (9H, t, *J* = 8 Hz, $(H_3CC)_3Si$), 0.95 (3H, d, *J* = 7 Hz, H_3CC-1''), 0.92 (3H, d, *J* = 6.5 Hz, H_3CC-4), 0.91 (3H, d, *J* = 7 Hz, H_3CC-10), 0.85 (3H, d, *J* = 7 Hz, H_3CC-1''), 0.80-0.74 (6H, m, $(H_2C)_3Si$), 0.71-0.65 (6H, m, $(H_2C)_3Si$), δ (for minor keto tautomer; partial data) 5.31 (1H, br s, HC-2'), 3.76 (1H, q, *J* = 7 Hz, HC-2), 3.64 (1H, dd, *J* = 9.5, 10 Hz, HC-8'a), 1.19 (3H, d, *J* = 7 Hz, H_3CC-2), δ (for enol tautomer; partial data) 17.78 (1H, br s, HO), 5.46 (1H, br s, HC-2'), 4.56 (1H, dd, *J* = 3.5, 7.5

Hz, HC-9), 4.54 (1H, dd, *J* = 3, 8 Hz, HC-5), 3.85 (1H, dd, *J* = 9.5, 10 Hz, HC-8'a), 1.76 (3H, s, H_3CC-2).

^{13}C NMR (125 MHz, C_6D_6) δ (for major keto tautomer) 213.0 (s, C-7), 212.25 (s, C-11), 210.6 (s, C-3), 208.3 (s, C-1), 139.5 (s, Ph), 129.2 (d, Ph), 128.7 (d ×2, Ph), 126.6 (d ×2, Ph), 101.3 (d, C-2'), 83.9 (d, C-4'), 83.5 (d, C-8'a), 76.3 (d, C-5), 73.54 (d, C-9), 62.2 (d, C-2), 56.1 (d, C-8'), 51.0 (d, C-4 or C-10), 50.5 (d, C-4 or C-10), 49.8 (d, C-6), 48.53 (d, C-8), 43.9 (d, C-4'a), 37.1 (t, C-12), 30.8 (t, C-7'), 28.6 (d, C-1''), 27.5 (t, C-5'), 20.3 (q, CH_3C-1''), 15.2 (q, CH_3C-1''), 14.0 (q, CH_3C-4 or CH_3C-10), 13.8 (q, CH_3C-4 or CH_3C-10), 12.6 (q, CH_3C-6), 12.4 (q, CH_3C-2), 11.6 (q, CH_3C-8), 8.0 (q, C-13), 7.8 (q, $(CH_3C)_3Si$), 7.7 (q, $(CH_3C)_3Si$), 6.0 (t, $(CH_2)_3Si$), 5.9 (t, $(CH_2)_3Si$), δ (for minor keto tautomer; partial data) 213.20 (s, C-7), 212.29 (s, C-11), 209.1 (s, C-3), 209.0 (s, C-1), 102.1 (d, C-2'), 82.6 (d, C-8'a), 76.5 (d, C-5), 73.47 (d, C-9), 60.8 (d, C-2), δ (for enol tautomer; partial data) 213.22 (s, C-7), 212.15 (s, C-11), 196.7 (s, C-3), 193.2 (s, C-1), 106.1 (s, C-2), 101.6 (d, C-2'), 81.3 (d, C-8'a), 76.0 (d, C-5), 74.0 (d, C-9), 12.3 (q, CH_3C-2).

HRMS *m/z* calcd for $C_{46}H_{78}O_8Si_2S+Na^+$ 869.4848, found 869.4869 (ESI).



278a

(4*R*,5*S*,6*R*,8*S*,9*R*,10*R*,14*S*,15*S*,16*S*,17*S*)-15,17-Dihydroxy-4,6,8,10,12,14,16,18-octamethyl-5,9-bis((triethylsilyl)oxy)nonadecane-3,7,11,13-tetraone (278a)

A suspension of Raney nickel (W2; 0.3 mL settled volume) in EtOH (2 mL) was added to **277** (32 mg, 0.038 mmol), and the mixture was heated under reflux with vigorous stirring under

H_2 atmosphere. After 2 h (reaction was complete by TLC analysis), the mixture was decanted, and the solid was suspended in EtOH (4 mL) and heated under reflux with vigorous stirring for several min. This washing procedure was repeated with ethyl acetate and acetone. The combined organic layers were filtered through Celite, and concentrated to obtain the crude product (12 mg) as a 2:1 mixture of hemiacetal diastereomers (HOC-17 → O=C-13; epimeric at C-12) **278a** and **278b**, respectively, by ^{1}H NMR in C_6D_6 solution. The crude product was fractionated by PTLC (15% ethyl acetate in hexane) to give **278b** as a 6:1 mixture with **278a** (6 mg, 23%) and **278a** (13 mg, 48%); $[\alpha]_D$ –27 (*c* 1.0, C_6H_6).

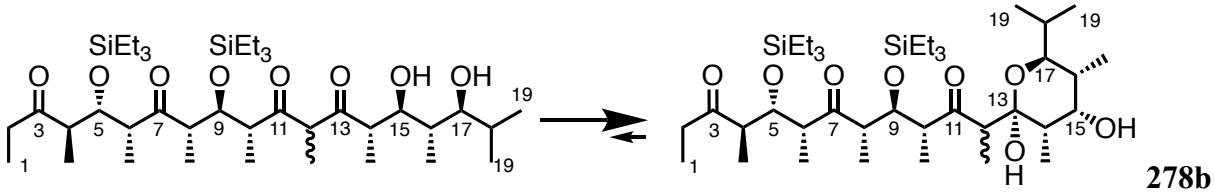
colorless viscous oil, TLC R_f = 0.5 (20% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3417, 1712 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ 5.38 (1H, s, HOC-13), 4.76 (1H, dd, *J* = 5.5, 7 Hz, HC-9), 4.70 (1H, dd, *J* = 2.5, 8 Hz, HC-5), 3.67 (1H, dq, *J* = 5.5, 7 Hz, HC-10), 3.54 (1H, dd, *J* = 2, 10.5 Hz, HC-17), 3.22 (1H, q, *J* = 7 Hz, HC-12), 3.15 (1H, dq, *J* = 7, 7 Hz, HC-8), 3.06 (1H, br s, HC-15), 3.72 (1H, dq, *J* = 2.5, 7.5 Hz, HC-6), 2.61 (1H, dq, *J* = 8, 7 Hz, HC-4), 2.35 (1H, dq, *J* = 18.5, 7 Hz, HC-2), 2.22 (1H, dq, *J* = 18.5, 7 Hz, HC-2), 1.81 (1H, br d, *J* = 5 Hz, HOC-15), 1.65 (1H, dqq, *J* = 2, 7, 7 Hz, HC-18), 1.41 (1H, dq, *J* = 2.5, 7 Hz, HC-14), 1.28 (3H, d, *J* = 7 Hz, H_3CC-10), 1.24-1.19 (1H, m, HC-16), 1.18 (3H, d, *J* = 7 Hz, H_3CC-12), 1.17 (3H, d, *J* = 7.5 Hz, H_3CC-6), 1.13 (3H, d, *J* = 7 Hz, H_3CC-8), 1.12 (3H, d, *J* = 7 Hz, H_3C-19), 1.10 (9H, t, *J* = 8 Hz, $(H_3CC)_3Si$), 1.06 (9H, t, *J* = 8 Hz, $(H_3CC)_3Si$), 1.06 (3H, t, *J* = 7 Hz, H_3C-1), 0.97 (3H, d, *J* = 7 Hz, H_3CC-14), 0.888 (3H, d, *J* = 7 Hz, H_3CC-4), 0.886 (3H, d, *J* = 7 Hz, H_3C-19), 0.81 (12H, ap q, *J* = 8 Hz, $(H_2C)_3Si$ × 2), 0.58 (3H, d, *J* = 7 Hz, H_3CC-16).

^{13}C NMR (125 MHz, C_6D_6) δ 213.3 (s, C-7), 212.4 (s, C-3), 212.0 (s, C-11), 101.7 (s, C-13), 77.0 (d, C-15), 76.4 (d, C-9), 73.5 (d, C-5), 72.4 (d, C-17), 52.8 (d, C-10), 52.1 (d, C-12), 50.8 (d, C-4), 49.1 (d, C-6), 48.8 (d, C-8), 39.1 (d, C-14), 37.7 (d, C-16), 37.3 (t, C-2), 28.8 (d, C-18), 21.0 (q, C-19), 14.7 (q, C-19), 14.2 (q, CH_3C-4), 13.7 (q, CH_3C-16), 13.6 (q, CH_3C-14), 12.9 (q, CH_3C-8), 12.8 (q, CH_3C-12), 12.0 (q, CH_3C-10), 10.9 (q, CH_3C-6), 8.0 (q, C-1), 7.8 (q, $(CH_3C)_3Si$), 7.7 (q, $(CH_3C)_3Si$), 6.0 (t, $(CH_2)3Si$), 5.9 (t, $(CH_2)_3Si$).

HRMS *m/z* calcd for $C_{39}H_{76}O_8Si2+Na^+$ 751.4971, found 751.4978 (ESI).



278b

(4*R*,5*S*,6*R*,8*S*,9*R*,10*R*,14*S*,15*S*,16*S*,17*S*)-15,17-Dihydroxy-4,6,8,10,12,14,16,18-octamethyl-5,9-bis((triethylsilyl)oxy)nonadecane-3,7,11,13-tetraone (278b)

A 6:1 mixture of diastereomers. For preparation, see **278a**.

colorless viscous oil, TLC R_f = 0.4 (20% ethyl acetate in hexane).

$[\alpha]_D$ –18 (*c* 0.6, C_6H_6).

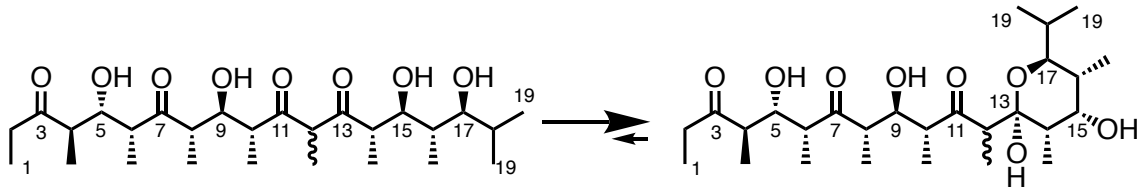
IR (DRIFT) ν_{max} 1716 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ (for the major diastereomer of the 6:1 mixture) 4.92 (1H, s, HOC-13), 4.67 (1H, dd, *J* = 2.5, 8 Hz, HC-5), 4.57 (1H, dd, *J* = 5.5, 6.5 Hz, HC-9), 3.66 (1H, dd, *J* = 2, 11 Hz, HC-17), 3.32 (1H, dq, *J* = 5.5, 7 Hz, HC-10), 3.13-3.07 (3H, m, HC-8, HC-12, HC-15), 2.79 (1H, dq, *J* = 2.5, 7.5 Hz, HC-6), 2.61 (1H, dq, *J* = 8, 7 Hz, HC-4), 2.35 (1H, dq, *J* = 18.5, 7

Hz, HC-2), 2.21 (1H, dq, *J* = 18.5, 7 Hz, HC-2), 1.93 (1H, d, *J* = 6 Hz, HOC-15), 1.69 (1H, dqq, *J* = 2.5, 7, 7 Hz, HC-18), 1.53 (1H, dq, *J* = 2.5, 7 Hz, HC-14), 1.50 (3H, d, *J* = 7 Hz, H_3CC-12), 1.28-1.22 (1H, m, HC-16), 1.228 (3H, d, *J* = 7 Hz, H_3CC-8), 1.223 (3H, d, *J* = 7.5 Hz, H_3CC-6), 1.20 (6H, ap d, *J* = 7 Hz, H_3CC-10, H_3CC-14), 1.12 (3H, d, *J* = 7 Hz, H_3C-19), 1.09 (3H, t, *J* = 7 Hz, H_3C-1), 1.07 (9H, t, *J* = 8 Hz, $(H_3CC)_3Si$), 1.06 (9H, t, *J* = 8 Hz, $(H_3CC)_3Si$), 0.90 (3H, d, *J* = 7 Hz, H_3CC-4), 0.87 (3H, d, *J* = 7 Hz, H_3C-19), 0.84-0.72 (12H, m, $(H_2C)_3Si \times 2$), 0.65 (3H, d, *J* = 7 Hz, H_3CC-16).

^{13}C NMR (125 MHz, C_6D_6) δ (for the major diastereomer of the 6:1 mixture) 216.2 (s, C-11), 213.0 (s, C-7), 212.3 (s, C-3), 101.4 (s, C-13), 77.1 (d, C-15), 77.0 (d, C-9), 73.6 (d, C-5), 72.3 (d, C-17), 54.6 (d, C-12), 51.0 (d, C-4), 49.9 (d, C-8), 48.3 (d, C-6), 47.9 (d, C-10), 41.5 (d, C-14), 38.1 (d, C-16), 37.3 (t, C-2), 28.8 (d, C-18), 21.1 (q, C-19), 15.1 (q, CH_3C-10), 15.0 (q, C-19), 14.6 (q, CH_3C-14), 14.1 (q, CH_3C-4), 13.7 (q, CH_3C-16), 13.0 (q, CH_3C-8), 11.4 (q, CH_3C-6), 11.0 (q, CH_3C-12), 8.0 (q, C-1), 7.8 (q, $(CH_3C)_3Si$), 7.6 (q, $(CH_3C)_3Si$), 6.0 (t, $(CH_2)_3Si$), 5.9 (t, $(CH_2)_3Si$).

HRMS *m/z* calcd for $C_{39}H_{76}O_8Si2+Na^+$ 751.4971, found 751.4942 (ESI).



174

(4*R*,5*S*,6*R*,8*S*,9*R*,10*R*,14*S*,15*S*,16*S*,17*S*)-5,9,15,17-Tetrahydroxy-4,6,8,10,12,14,16,18-octamethylnonadecane-3,7,11,13-tetraone (174)

To a stirring solution of **278** (a 2:1 mixture of C-12 epimers; 14 mg, 0.020 mmol) in DMF (0.2 ml) was added tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF; 22 mg, 0.08 mmol). After 1 h, the reaction was quenched by the sequential addition of saturated aq $NaHCO_3$ and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the crude product whose ^1H NMR spectrum (C_6D_6) indicated the presence of a 1:1 mixture of hemiacetals. Fractionation of the crude product by FCC (40% ethyl acetate in hexane), followed by PTLC gave the title compound (7 mg, 74%) that was predominantly a 3.5:1 mixture of hemiacetal diastereomers (HOC-17 → O=C-13; epimeric at C-12) by ^1H NMR in C_6D_6 solution; $[\alpha]_D$ –25 (*c* 0.7, C_6H_6).

colorless waxy solid, TLC R_f = 0.3 (40% ethylacetate in hexanes).

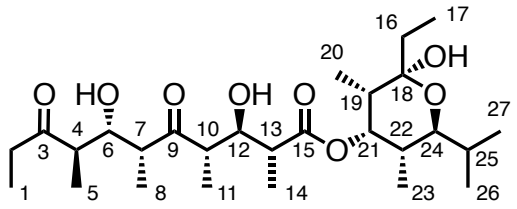
IR (DRIFT) ν_{max} 3394, 1708 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ (for the major diastereomer) 5.83 (1H, s, HOC-13), 4.41 (1H, ddd, *J* = 3, 4.5, 8 Hz, HC-5), 4.02 (1H, br d, *J* = 9 Hz, HOC-9), 3.85 (1H, ddd, *J* = 4.5, 8.5, 9 Hz, HC-9), 3.66 (1H, br d, *J* = 4.5 Hz, HOC-5), 3.61 (1H, dd, *J* = 2, 11 Hz, HC-17), 3.26 (1H, dq, *J* = 4.5, 7 Hz, HC-10), 3.15-3.11 (1H, m, HC-15), 3.00 (1H, dq, *J* = 8.5, 7 Hz, HC-8), 2.96 (1H, q, *J* = 7 Hz, HC-12), 2.71-2.65 (2H, m, HC-4, HC-6), 2.48 (1H, dq, *J* = 18.5, 7 Hz, HC-2), 2.45 (1H, br dd, *J* = 5.5 Hz, HOC-15), 2.20 (1H, dq, *J* = 18.5, 7 Hz, HC-2), 1.67 (1H, dqq, *J* = 2, 7, 7 Hz, HC-18), 1.31 (1H, dq, *J* = 2.5, 7 Hz, HC-14), 1.23-1.18 (1H, m, HC-16), 1.15 (3H, d, *J* = 7 Hz, H_3CC-10), 1.12 (3H, d, *J* = 7 Hz, H_3CC-6), 1.08 (3H, d, *J* = 7 Hz, H_3C-19), 1.05 (3H, d, *J* = 7 Hz, H_3CC-12), 1.02 (3H, t, *J* = 7 Hz, H_3C-1), 0.99 (3H, d, *J* = 7 Hz, H_3CC-8), 0.94 (3H, d, *J* = 7 Hz, H_3CC-14), 0.86 (3H, d, *J* = 7 Hz, H_3C-19), 0.84 (3H, d, *J* = 7 Hz, H_3CC-4), 0.68 (3H, d, *J* = 7 Hz, H_3CC-16), δ (for the minor diastereomer; partial data) 5.53 (1H, s, HOC-13), 4.38 (1H, ddd, *J* = 4, 4, 8

Hz, HC-5), 3.97 (1H, br d, J = 6.5 Hz, HOC-9), 3.76 (1H, ddd, J = 4.5, 6.5, 8.5 Hz, HC-9), 3.70 (1H, dd, J = 2, 11 Hz, HC-17), 3.24-3.21 (1H, m, HC-15), 3.07 (1H, q, J = 7 Hz, HC-12), 2.87 (1H, br d, J = 6 Hz, HOC-15), 1.52 (1H, dq, J = 2.5, 7 Hz, HC-14), 1.21 (3H, d, J = 7 Hz, H_3CC-12).

^{13}C NMR (125 MHz, C_6D_6) δ (for the major diastereomer) 218.0 (s, C-11), 217.6 (s, C-7), 215.2 (s, C-3), 102.6 (s, C-13), 79.3 (s, C-9), 76.7 (d, C-15), 73.6 (d, C-5), 72.7 (d, C-17), 52.9 (d, C-12), 50.4 (d, C-6), 48.6 (d, C-8), 48.2 (d, C-10), 47.9 (d, C-4), 39.0 (d, C-14), 37.7 (d, C-16), 37.2 (t, C-2), 28.8 (d, C-18), 21.1 (q, C-19), 15.3 (q, CH_3C-10), 15.2 (q, H_3CC-8), 14.7 (q, C-19), 14.2 (q, CH_3C-4), 13.9 (q, CH_3C-16), 13.5 (q, CH_3C-14), 12.7 (q, CH_3C-12), 9.3 (q, CH_3C-6), 8.0 (q, C-1), δ (for minor diastereomer; partial data) 219.9 (s, C-11), 216.9 (s, C-7), 214.6 (s, C-3), 102.1 (s, C-13), 79.0 (d, C-9), 77.7 (d, C-15), 73.8 (d, C-5), 54.6 (d, C-12), 50.1 (d, C-6), 48.8 (d, C-8), 40.7 (d, C-14), 37.9 (d, C-16), 28.7 (d, C-18), 12.1 (q, CH_3C-12).

HRMS *m/z* calcd for $C_{27}H_{48}O_8$+Na^+ 523.3241, found 523.3225.



17

dolabriferol C **(17)**

A solution of **174** (6 mg, 0.012 mmol) in benzene (0.2 mL) was applied to a small column of neutral alumina (Brockmann I; ca. 5 cm in a Pasteur pipette). After 20 min, the column was eluted with ethyl acetate and the eluent was concentrated and fractionated by PTLC (30% ethyl acetate in hexane) to give dolabriferol C (**17**; 4.5 mg, 75%); $[\alpha]_D$ –38 (*c* 0.5, $CHCl_3$).

White solid, TLC R_f = 0.3 (30% ethyl acetate in hexane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (1H, dd, *J* = 2.5, 2.5 Hz, HC-21), 4.19 (1H, ddd, *J* = 5, 7, 7 Hz, HC-6), 4.06 (1H, d, *J* = 11.5 Hz, HOC-12), 4.00 (1H, d, *J* = 1.5 Hz, HOC-18), 3.68 (1H, dd, *J* = 2, 10.5 Hz, HC-24), 3.64 (1H, ddd, *J* = 3, 10, 11.5 Hz, HC-12), 3.25 (1H, d, *J* = 7 Hz, HOC-6), 3.05 (1H, dq, *J* = 10, 7 Hz, HC-10), 2.88 (1H, dq, *J* = 5, 7 Hz, HC-7), 2.85 (1H, dq, *J* = 7, 7 Hz, HC-4), 2.77 (1H, dq, *J* = 3, 7 Hz, HC-13), 2.60-2.50 (2H, m, H_2C-2), 1.92 (1H, ddq, *J* = 1.5, 2.5, 7 Hz, HC-19), 1.79 (1H, dqq, *J* = 2, 7, 7 Hz, HC-25), 1.78-1.65 (3H, m, HC-22, H_2C-16), 1.37 (3H, d, *J* = 7 Hz, H_3C-14), 1.10 (6H, ap d, *J* = 7 Hz, H_3C-8, H_3C-5), 1.06 (3H, d, *J* = 7 Hz, H_3C-20), 1.01 (6H, ap d, *J* = 7 Hz, H_3C-11, H_3C-26), 1.00 (3H, t, *J* = 7 Hz, H_3C-1), 0.97 (3H, t, *J* = 7 Hz, H_3C-17), 0.84 (3H, d, *J* = 7 Hz, H_3C-27), 0.78 (3H, d, *J* = 7 Hz, H_3C-23).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3 (s, C-3), 216.6 (s, C-9), 173.8 (s, C-15), 98.4 (s, C-18), 76.8 (d, C-12), 76.6 (d, C-21), 72.4 (d, C-24), 72.0 (d, C-6), 50.4 (d, C-7), 49.8 (d, C-10), 47.0 (d, C-4), 43.2 (d, C-13), 39.2 (d, C-19), 36.7 (d, C-22), 36.6 (d, C-2), 32.7 (t, C-16), 27.9 (d, C-25), 20.2 (q, C-26), 16.3 (q, C-14), 14.4 (q, C-11), 14.3 (q, C-5), 14.0 (q, C-27), 13.1 (q, C-20), 12.9 (q, C-23), 9.3 (q, C-8), 7.3 (q, C-1), 7.2 (q, C-17).

HRMS *m/z* calcd for $C_{27}H_{48}O_8$+Na^+ 523.3241, found 523.3235 (ESI).

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