THE THIOPYRAN ROUTE TO POLYPROPIONATES: SEQUENTIAL
ENANTIOTOPIC GROUP SELECTIVE ENOLIZATION OF *MESO* 1,9-DIKETONES.

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by

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ABSTRACT

Meso 1,9-diketones (six to seven stereocenters) are readily obtained by stepwise or simultaneous two-directional aldol reactions of tetrahydro-4*H*-thiopyran-4-one with a thiopyran-derived aldehyde. Enantioselective enolizations of these diketones with the lithium amide from (*R,R*)-bis(1-phenylethyl)amine **I** occur with simultaneous kinetic resolution to give the mono-TMS enol ethers in >90% yields based on recovered starting material (BORSM) and >90% ee. The developed methodology was applied in synthetic studies towards the asymmetric synthesis of denticulatin A.

intramolecular
ketalization

denticulatin A (10-*S*)

meso

meso

ent-**230**

TMSCl

>90% yield (BORSM)
>90% ee

+

meso

synthetic studies
towards denticulatin A

ACKNOWLEDGMENTS

Dedicated to the memory and inspiration
of my beloved sister,

Shelly Olive Gillis

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LIST OF ABBREVIATIONS

α	observed optical rotation in degrees
$[\alpha]_D$	specific rotation (expressed without units; the actual units, (deg·mL)/(g·dm), are understood)
Ac	acetyl
anhyd	anhydrous
ap	apparent (spectral)
aq	aqueous
Ar	aryl
atm	atmosphere(s)
Bn, Bzl	benzyl
bp	boiling point
br	broad (spectral)
Bu, *n*-Bu	normal (primary) butyl
t-Bu	*tert*-butyl
Bz	benzoyl (not benzyl)
°C	degrees Celsius
calcd	calculated
Chx	cyclohexyl
CI	chemical ionization; configuration interaction
CLA	chiral lithium amide

cm^{-1}	wavenumber(s)
concd	concentrated
COSY	correlation spectroscopy
m-CPBA	*meta*-chloroperoxybenzoic acid
CSA	camphorsulfonic acid
δ	chemical shift in parts per million downfield from tetramethylsilane
d	day(s); doublet (spectral); deci
d	density
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
dil	dilute
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DRIFT	diffuse reflectance infrared Fourier transform spectroscopy
ee	enantiomeric excess
eq	equation
equiv	equivalents

er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
FCC	flash column chromatography
g	gram(s); prefix to NMR abbreviation denoting gradient-selected (e.g., gCOSY, gHSQC)
GC	gas chromatography
h	hour(s)
hfc	3-(heptafluoropropylhydroxy-methylene)camphorate
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoric triamide (hexamethylphosphoramide)
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
IR	infrared
J	coupling constant (in NMR spectrometry)
k	kilo
K	kelvin(s) (absolute temperature)
L	liter(s)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane, lithium bis(trimethylsilyl) amide

lit.	literature (abbreviation used with period)
LRMS	low-resolution mass spectrometry
μ	micro
m	multiplet (spectral); meter(s); milli
M	molar (moles per liter); mega
M^+	parent molecular ion
max	maximum
Me	methyl
MEM	(2-methoxyethoxy)methyl
MHz	megahertz
min	minute(s); minimum
mM	millimolar (millimoles per liter)
mol	mole(s); molecular (as in mol wt)
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
MTPA	2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid
MTPACl	2-methoxy-2-(trifluoromethyl)-2-phenylacetyl chloride
MW, mol wt	molecular weight
m/z	mass-to-charge ratio
N	normal (equivalents per liter)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
obsd	observed
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMA	phosphomolybdic acid
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
PTLC	preparative thin layer chromatography
PTSA	*para*-toluenesulfonic acid
q	quartet (spectral)
rel	relative
rt	room temperature
s	singlet (spectral); second(s)
t	triplet (spectral)
TBDMS, TBS	*tert*-butyldimethylsilyl
TBDPS, TPS	*tert*-butyldiphenylsilyl
temp	temperature

TES	triethylsilyl; triethylsilane
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAE	2,2,2-trifluoro-1-(9-anthryl)ethanol
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	N,N,N',N'-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl; tetramethylsilane
TOF	time-of-flight
Tr	triphenylmethyl (trityl)
UV	ultraviolet
vis	visible
vol	volume
v/v	volume per unit volume (volume-to-volume ratio)
wt	weight
w/w	weight per unit weight (weight-to-weight ratio)

CHAPTER 1
1. INTRODUCTION

1.1. Marine polypropionate natural products

Polyketide-derived natural products represent a large class of biologically active compounds that have found many applications.[1, 2] They are synthesized by bacteria, fungi and plants by polyketide synthase (PKS) enzymes through decarboxylative condensation of simple coenzyme A activated esters (Scheme 1.1.). The polyketides

ACP = acyl carrier protien
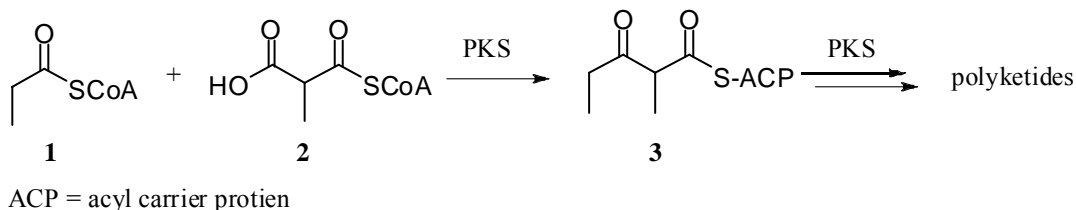
Scheme 1.1.

possess very diverse structures which can be divided into subgroups: fatty acids, polypropionates and aromatic polyketides. Polypropionates can be further classified into three groups: polyether antibiotics, macrolides and spiroketals (Figure 1.1.). Some of the
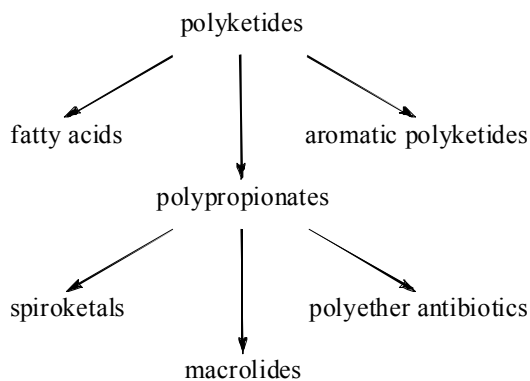
Figure 1.1. Classification of polyketides.

most biologically active compounds are the polypropionates and as a result, their study has been a very active area of research. While investigations of terrestrial derived polypropionates have received much attention, the understanding of marine polypropionates and their biosynthetic processes is in its infancy.[3] Indeed, some very interesting compounds possess numerous biological activities. For example, (−)-discodermolide,[4] isolated from the sponge *Discodermia dissoluta* is found to be a potent microtubule-stabilizing agent. The mode of action, similar to that of taxol, arrests cells at the G_2/M phase of the cell cycle. This antimitotic action is also shared with other marine polypropionate compounds such as peloruside A[5] and dictyostatin[6] (Figure 1.2.).

(−)-discodermolide **4**

dictyostatin **5**

peloruside A **6**

Taxol (paclitaxel) **7**
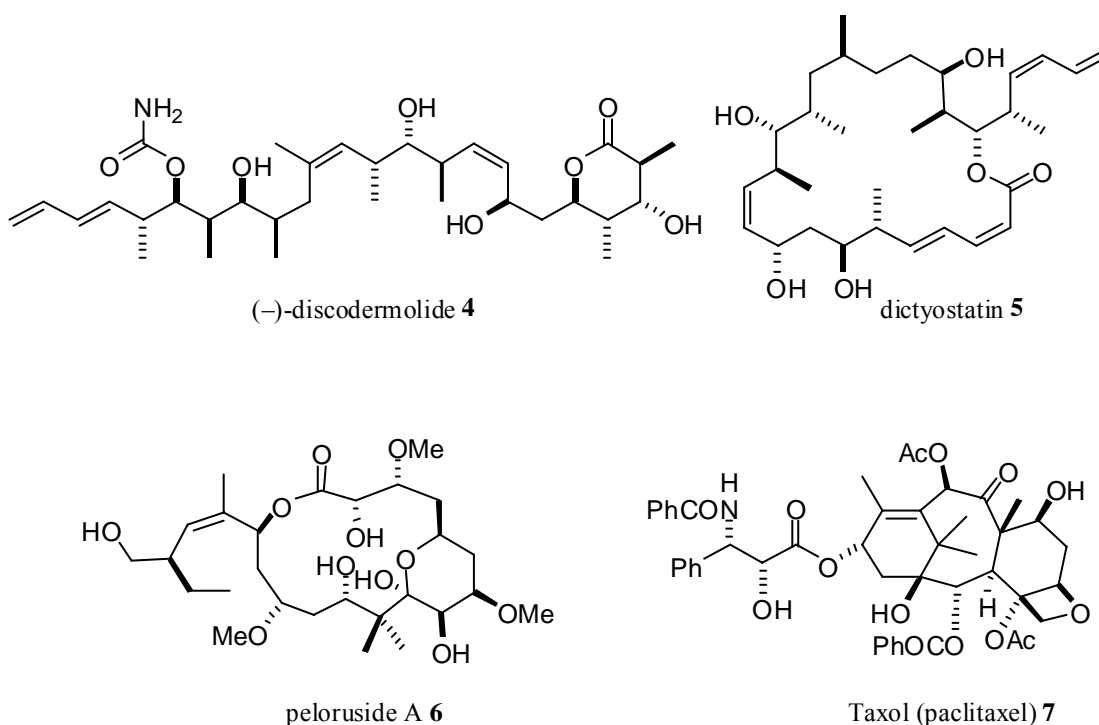
Figure 1.2. Biologically active natural products.

The most important source of marine polypropionate compounds are the Mollusca.[3] While a few isolated compounds have no apparent biological activities, many are important for therapies against respiratory infections, Legionnaires disease and for

infections in patients sensitive to penicillin antibiotics. They show cytotoxic antibiotic, antifungal and antiviral properties. The structural diversity of compounds isolated from Mollusca presents some intriguing questions with respect to their biosynthetic pathways (Figure 1.3.). By what means are these complex molecules assembled? Are they

caloudrin B **8**

denticulatin A (10-*S*)-**9**
denticulatin B (10-*R*)-**10**

auripyrone A **11** R =

auripyrone B **12** R =
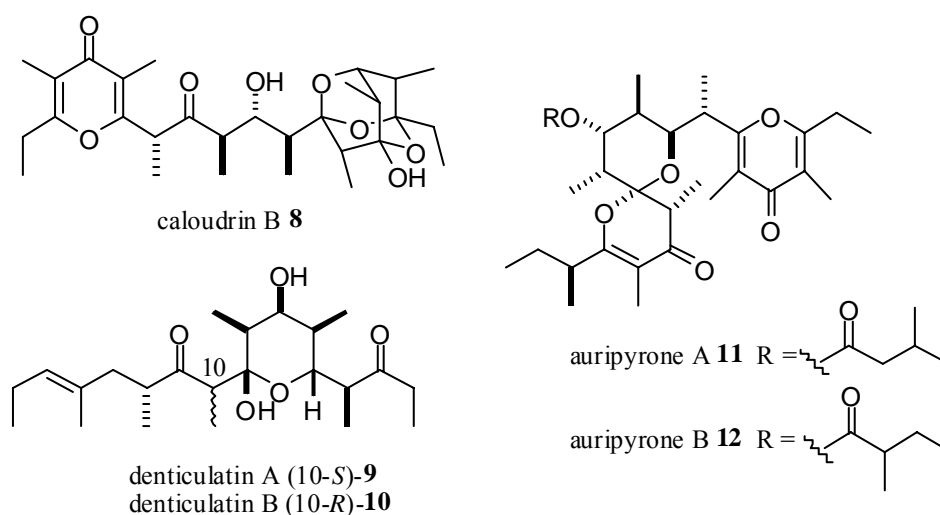
Figure 1.3. Mollusca polypropionate natural products.

synthesized by the same PKS system as for terrestrial organisms? In fact, it has been noted that some marine polypropionates are artifacts of isolation and the actual 'active' compound may be some other precursor.[3] The pharmaceutical potential of Mollusca polypropionates are unlikely to be realized until a more complete understanding of their chemical properties and biosynthetic pathway emerges.

1.2. The denticulatins

1.2.1. Isolation, structure determination and biosynthesis

In 1983, Faulkner and co-workers isolated two polypropionate metabolites from an air-breathing marine mollusk *Siphonaria denticulata* that displayed ichthyotoxic activity

towards goldfish.[7]   Perhaps one of the simplest marine polypropionates, the structural
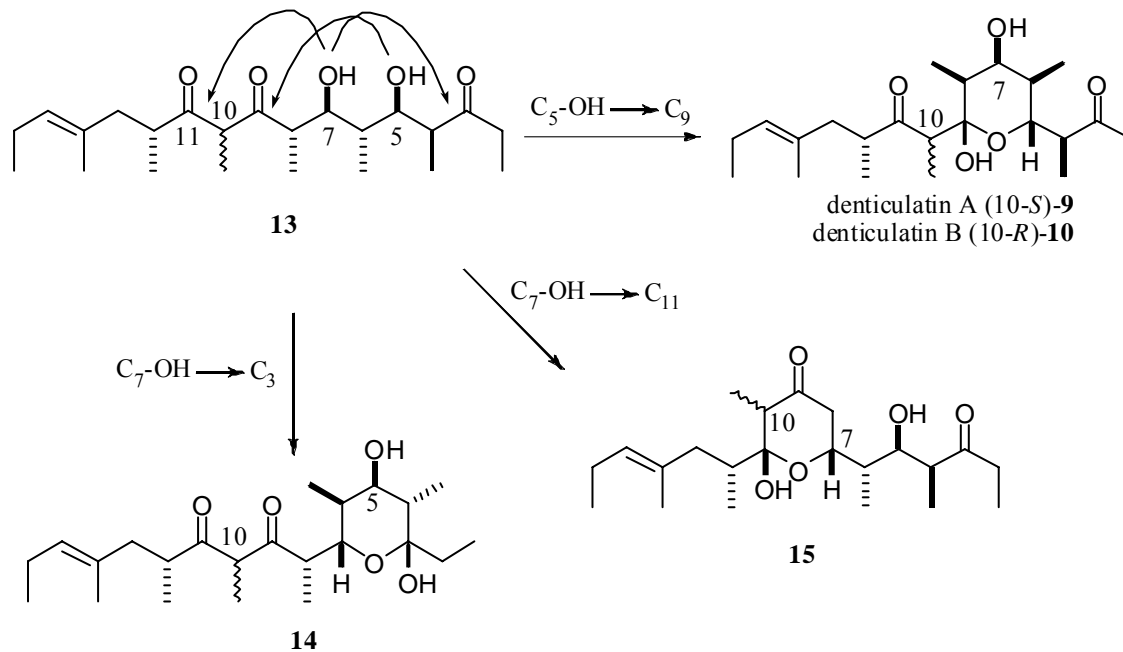
Scheme 1.2.

elucidation of denticulatin A **9** and denticulatin B **10** (Figure 1.3. and Scheme 1.2.) were

determined by a combination of NMR and X-ray analysis.   The denticulatins exist

predominantly as hemiketals formed by addition of C_5-OH onto C_9-carbonyl to give a

pyran ring with all carbon substituents in equatorial positions and hydroxyl groups in

axial positions.   The events leading to the formation of the hemiketal is an interesting

issue.   Perhaps a C_9 monoketone undergoes cyclization followed by oxidation at C_3 and

C_{11}.   There are three modes of cyclization available for triketone **13** (Scheme 1.2.).   If the

cyclization were to be driven solely by steric contributions, compound **15** would be

formed as all carbon substituents are equatorial.   However, because of hydrogen-bonding

between the axial hydroxyl groups, the thermodynamically favored cyclization mode is

C_5-OH onto C_9-carbonyl.

The denticulatins were the first marine polypropionates for which investigations confirmed the operation of a polypropionate biosynthesis rather than an acetate-methionine route (Scheme 1.3.).[3,8] This was accomplished by feeding and injection

denticulatin A (10-*S*)-**9**
denticulatin B (10-*R*)-**10**
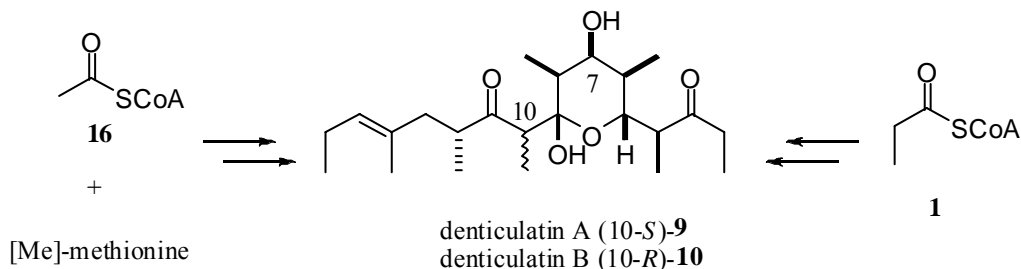
Scheme 1.3.

experiments using ^{14}C labeled propionate and acetate. From theses studies, the first three cycles of a biosynthetic pathway to denticulatin A have been proposed (Scheme 1.4.).[3]

KS = ketosynthase   DH = dehydratase
KR = ketoreductase ER = enoyl reductase

denticulatin A (10-*S*)-**9**
denticulatin B (10-*R*)-**10**
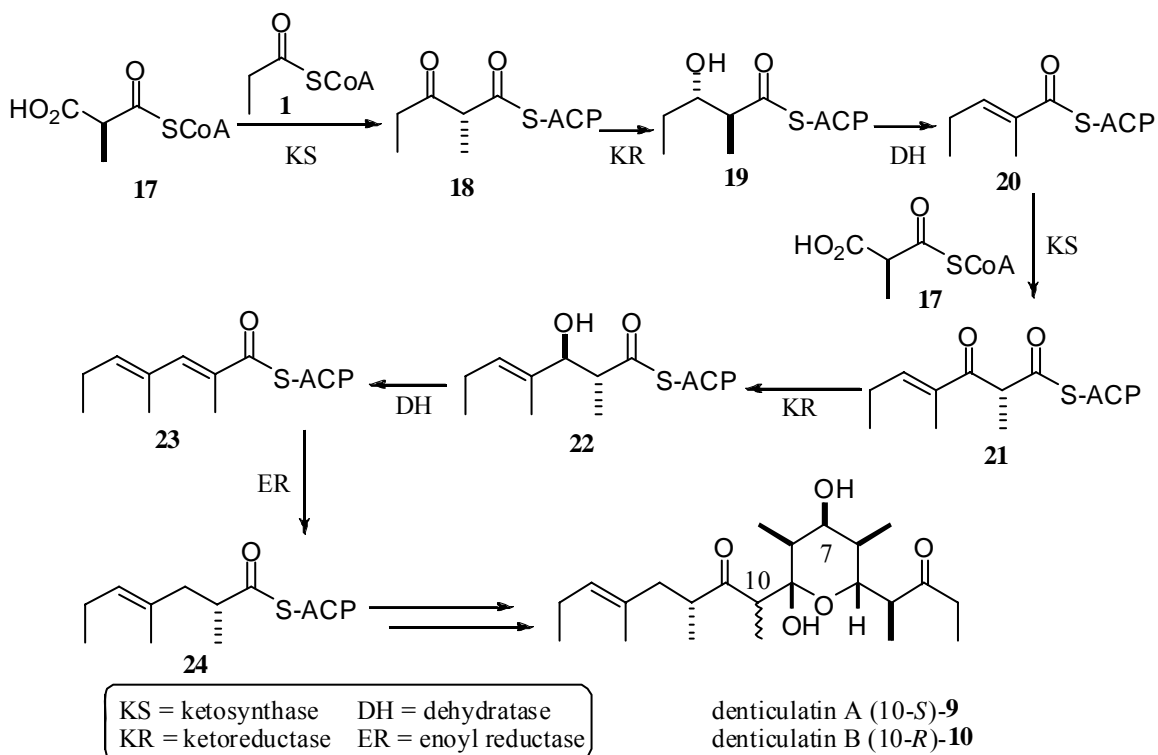
Scheme 1.4.

Despite these impressive results, further insights will only be available if additional material is available. As for many natural products, quantities obtained from natural sources are typically small (*i.e.* 0.12 mg/animal for denticulatin A)[7] and chemical synthesis plays a major role in both biosynthetic studies and also for the application of such materials for medicinal and/or agrochemical uses.

1.2.2. Synthetic studies and total syntheses

As part of a study to derivatize denticulatin A, Davies-Coleman and co-workers subjected the metabolite to the Sharpless AD-mix dihydroxylation reagent and rather than the expected diol, they obtained funiculatin A (Scheme 1.5.).[9, 10] This observation was

denticulatin A (10-*S*)-**9**   funiculatin A (10-*S*)-**25**
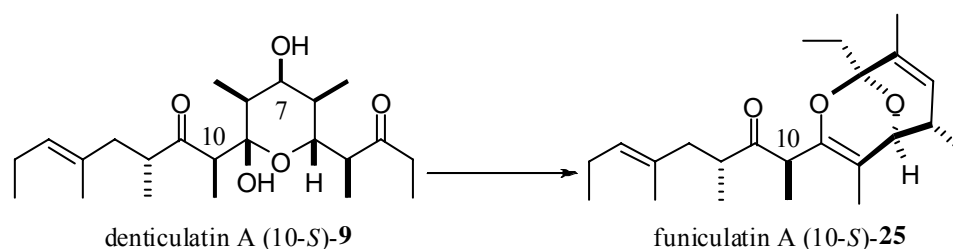
Scheme 1.5.

speculated to have resulted from the presence of K_2CO_3 in the reaction mixture. In fact, subjection of denticulatin A to K_2CO_3 alone furnished several polypropionate products. The susceptibility of denticulatin A and other marine polypropionates to skeletal rearrangements under mild conditions suggest that the isolated compounds may represent non-enzymatic cyclization products (*i.e.* kinetic or thermodynamic) of unstable acyclic natural products.

In order to further investigate the chemical properties of the denticulatins and other marine polypropionates, total synthesis plays a significant role because of the limited bio-availability of such materials. There have been four total syntheses of the denticulatins,[11] the first being denticulatin B by Ziegler and co-workers in 1990[12]. Since then, there have

been three other elegant syntheses by the Hoffmann,[13, 14] Paterson,[15, 16] and Oppolzer[17, 18] groups.

1.2.2.1. Ziegler's synthesis

The basic strategy employed by Ziegler and co-workers involved the preparation of *p*-methoxyacetophenylidene protected triketone **26**[i] that, after mild deprotection, spontaneously cyclized to the denticulatins.[12] The triketone **26** was prepared from an aldol reaction of ketone **27** and keto aldehyde **28** followed by oxidation (Scheme 1.6.).

denticulatin A (10-*S*)-**9**
denticulatin B (10-*R*)-**10**

3-methyl-γ-butyrolactone route
to polypropionates

Enders' RAMP hydrazone alkylation
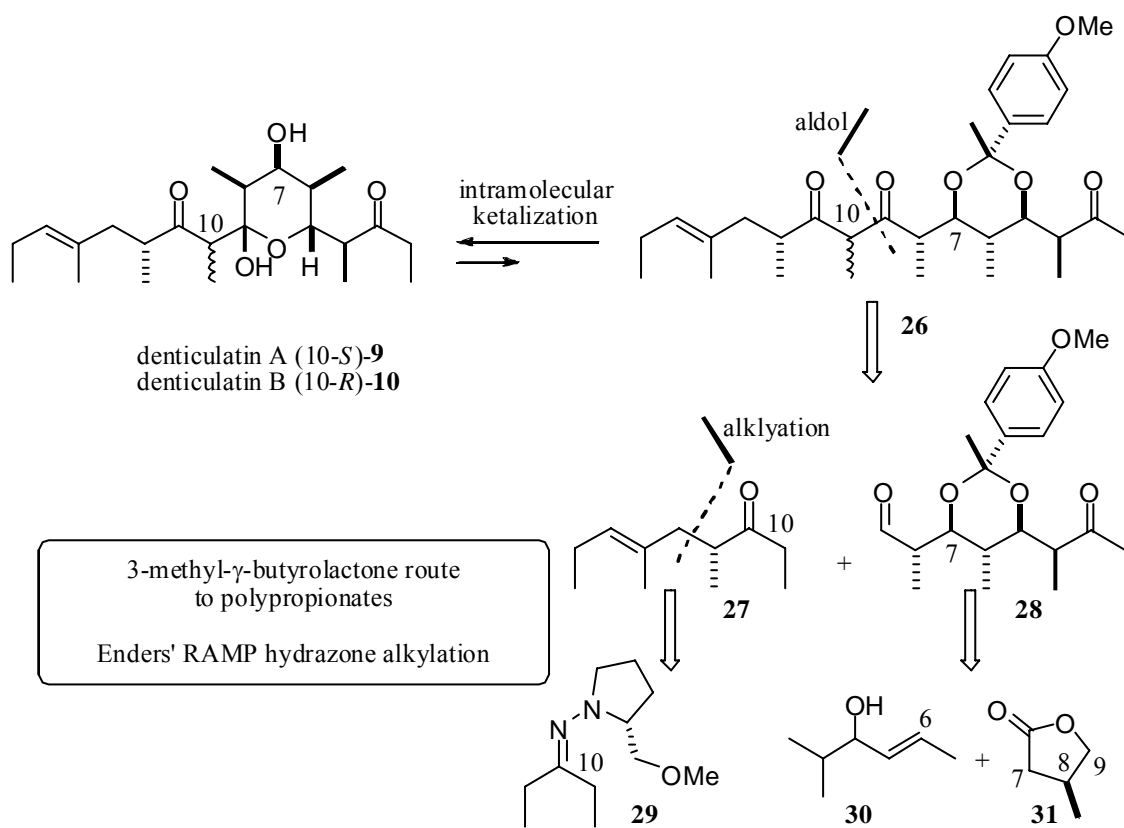
Scheme 1.6.

Access to keto aldehyde **28** was achieved by two enolate Ireland-Claisen protocols using both enantiomers of (*E*)-allylic alcohol **30** and (*S*)-3-methyl-γ-butyrolactone **31**. This method was described earlier by Ziegler and co-workers as a general approach for the

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[i] An acetonide protecting group proved to be resistant to hydrolytic conditions.

asymmetric synthesis of polypropionates.[19, 20] The synthesis of keto aldehyde **28** began with an Ireland-Claisen rearrangement of the diethyl orthoester **35**[ii] (Scheme 1.7.) and (*R*)-allylic alcohol **30**[iii] to give lactone **36** which was subjected to a Criegee oxidation sequence to provide acetonide **37** in 81% yield over 5 steps (Scheme 1.7.). Acetonide **37**
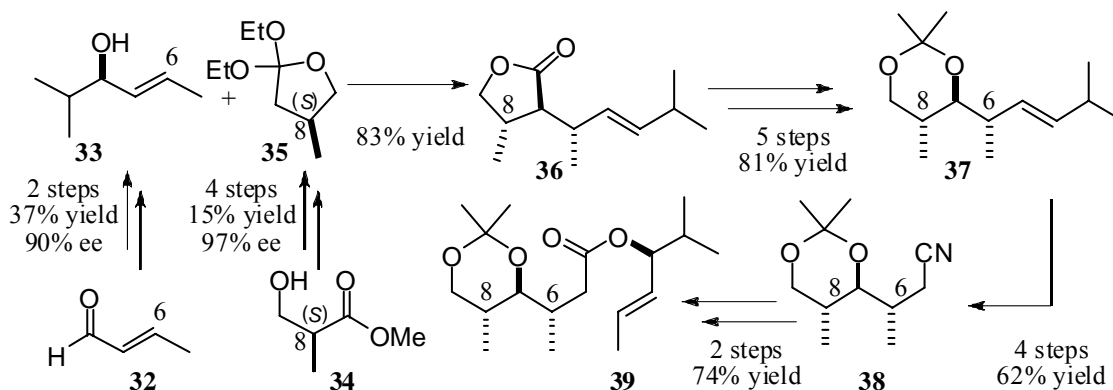
Scheme 1.7.

was subjected to ozonolysis, LAH reduction, tosylation, and cyanide substitution to provide cyano acetonide **38** in 62% yield over 4 steps. Cyano acetonide **38** was then carefully hydrolyzed and esterified with (*S*)-allylic alcohol **30**[iii] to give ester **39** in 74% overall 2 steps. Enol silylation of ester **39** by treatment with LDA/TBSCl gave (*E*)-*O*-silylketene acetonide that underwent an Ireland-Claisen rearrangement to give, after dilute acid hydrolysis, hydroxy lactone **41** in 84% yield over 2 steps (Scheme 1.8.).
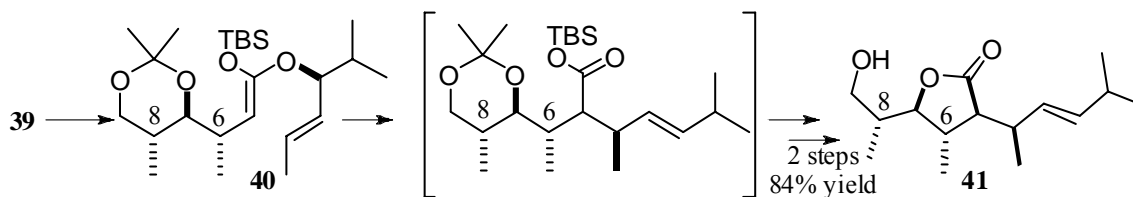
Scheme 1.8.

[ii] Prepared from commercially available (*S*)-3-hydroxy-2-methylpropionate in 3 steps in 19% yield and 97% ee.

[iii] Prepared from commercially available crotonaldehyde *via* Grignard addition of diisopropylmagnesium chloride and subsequent kinetic resolution by Sharpless epoxidation.

Protection of hydroxy lactone **41** as the TBDPS ether was followed by the Criegee sequence[iv] to give diol **42** in 73% yield over 5 steps (Scheme 1.9.). Protection of diol **42**
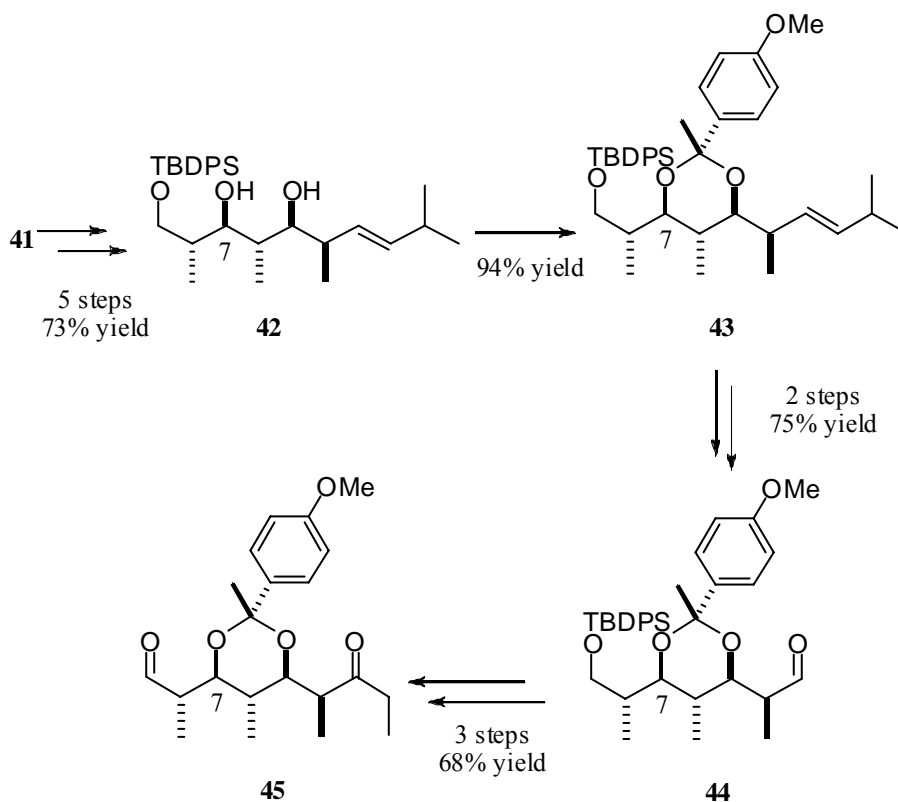
Scheme 1.9.

using the dimethyl ketal of *p-* methoxyacetophenone gave **43** as single diastereomer in 94% yield. Ozonolysis of **43** followed by a reductive work-up and Swern oxidation gave aldehyde **44** that reacted with ethylmagnesium bromide, followed by hydrolysis of the TBDPS protecting group and a double Swern oxidation to give the desired keto aldehyde **45** in 68% yield over 3 steps. Ziegler and co-workers elegantly applied their 3-methyl-γ-butyrolactone strategy for the preparation of keto aldehyde **45**. Despite the rather lengthy synthesis, the approach provided keto aldehyde **45** in 1% yield over a total of 29 steps. This was truly an amazing accomplishment, reflecting an average yield per step of 86%.

[iv] DIBAL-H replaced LAH in the Criegee sequence.

The other component required for the aldol reaction was ketone **27**. This was easily prepared by alkylation of the RAMP[v] hydrazone of 3-pentanone with allylic bromide **47**[vi] to provide ketone **27** in 56% yield and 89% ee over 2 steps (Scheme 1.10.). With
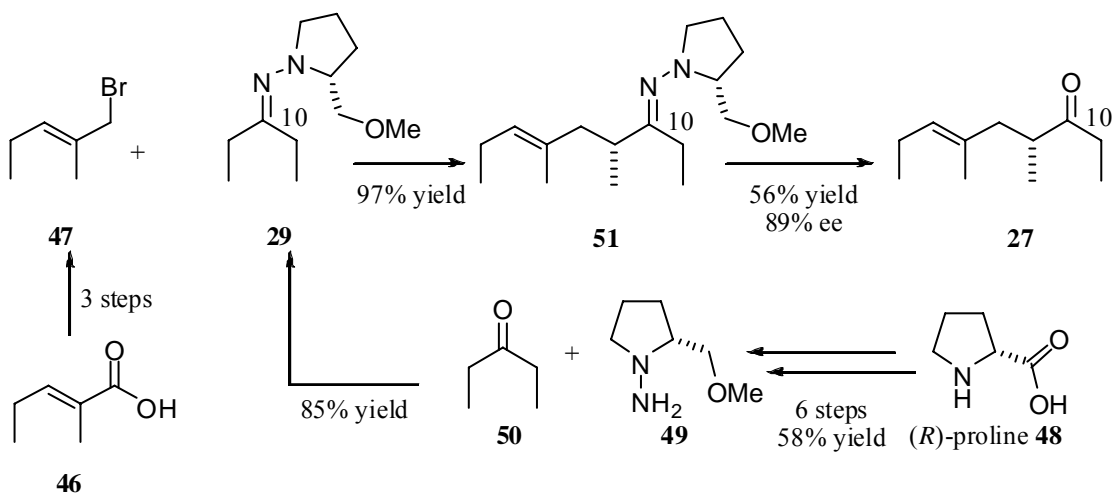
Scheme 1.10.

ketone **27** and keto aldehyde **45** available, Ziegler and co-workers generated the lithium enolate of ketone **27** using LDA and subsequently added keto aldehyde **45** which gave a mixture of three of the four possible aldol products in a ratio of 1.0:3.6:2.1 with a combined yield of 86% (Scheme 1.11.). Swern oxidation of this mixture gave a 2.7:1.0 mixture of triketone (10-*S*)-**53** and triketone (10-*R*)-**54**, respectively, in a combined yield of 81%. Careful fractionation of these triketones gave enriched samples that were separately subjected to mild deprotection using 5% oxalic acid in aqueous THF. Denticulatin A **9** and denticulatin B **10** were isolated as a mixture that reflected the starting ratios of triketones (Scheme 1.11. and Table 1.1.). The data in Table 1.1.

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[v] Prepared from commercially available (*R*)-proline in 6 steps in 58% yield. RAMP is also commercially available, albeit *ca.* $20,000/mol.

[vi] Yield for the preparation of allylic bromide **47** is not reported, however the cited procedure for (*E*)-2-methyl-2-butenyl bromide from tiglic acid occurs in 3 steps in 50% yield.
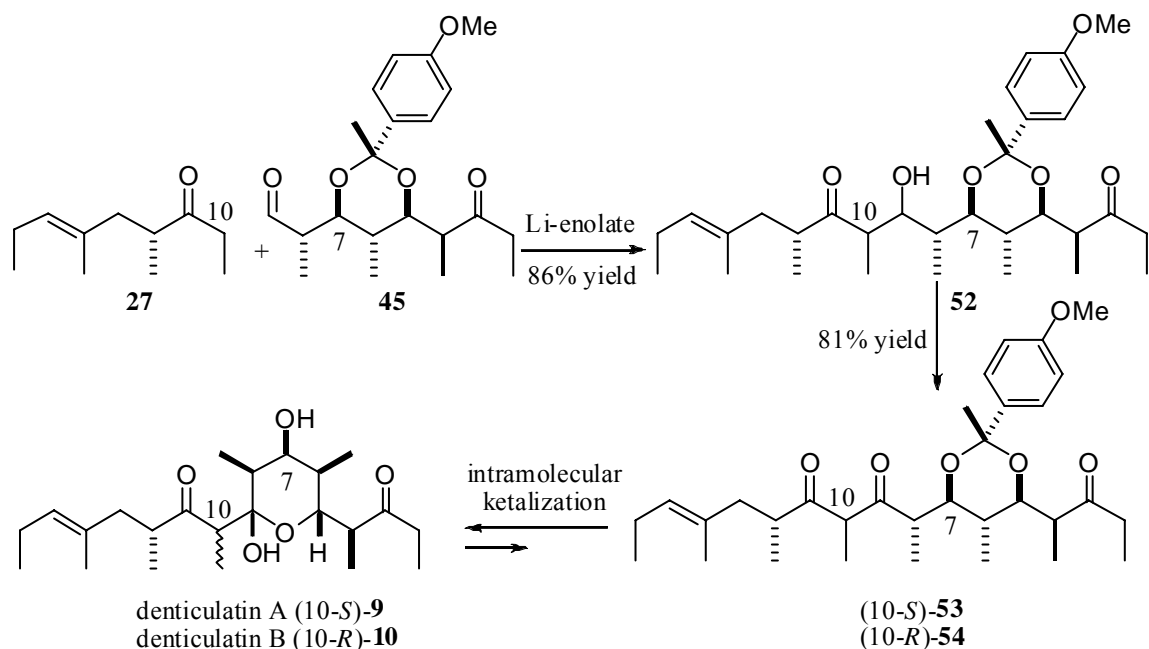
Scheme 1.11.

Table 1.1. Deprotection of triketones.

enriched triketones (10-S)-**53**:(10-R)-**53**	denticulatins (10-S)-**9**:(10-R)-**10** (% yield)	recovered triketones (10-S)-**53**:(10-R)-**54** (% yield)
4.6:1.0	6.0:1.0 (33)	2.9:1.0 (54)
1.0:4.7	1.0:8.0 (45)	1.0:1.5 (40)

indicated that the triketones do not completely isomerize prior to hydrolysis and cyclization. These results were obtained when the deprotection was allowed to progress to only *ca.* 50% conversion. Further conversion lead to significant amounts of dehydration products. To summarize, Ziegler and co-workers synthesized enriched samples of denticulatin A and denticulatin B in 0.3% and 0.4% yield, respectively over a longest linear sequence of 32 steps starting from (*S*)-3-hydroxy-2-methylpropionate. A remarkable synthesis, this reflects an average yield per step of 83%.

1.2.2.2. Hoffmann's synthesis

In 1991, Hoffmann and co-workers published the second total synthesis of the denticulatins.[13, 14] Similar to Ziegler's synthesis, Hoffman and co-workers prepared a protected triketone from an aldol reaction of ketone **27** with aldehyde **56** followed by deprotection and oxidation (Scheme 1.12.). A significant improvement was achieved as aldehyde **56** was obtained in 8% yield over 12 steps (Zeigler and co-workers prepared keto aldehyde **45** in 1% yield over 29 steps) by a route involving three crotylboration reactions (Scheme 1.12. and Scheme 1.13.). The synthesis of aldehyde **56** began with the

denticulatin A (10-*S*)-**9**
denticulatin B (10-*R*)-**10**

crotylboration route
to polypropionates

Ireland-Claisen rearrangement

crotylboronates   +
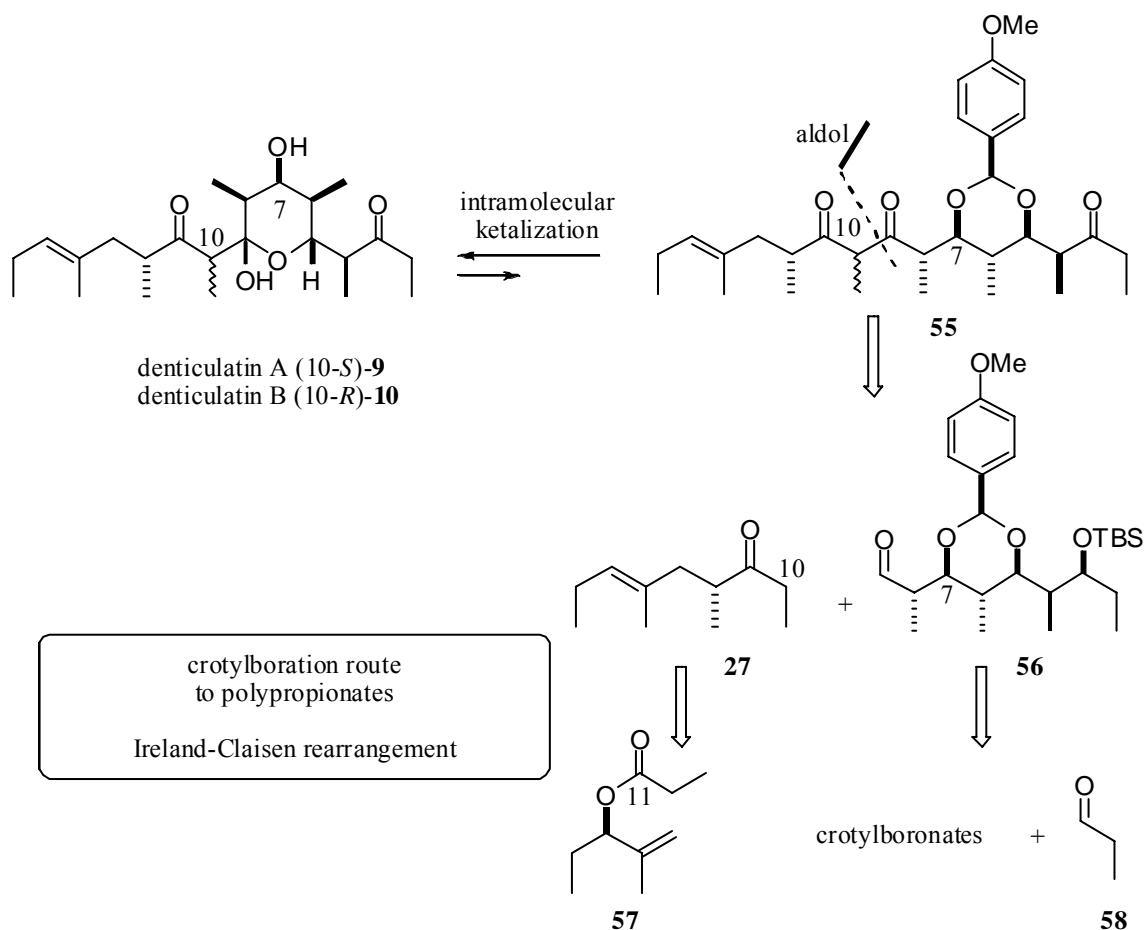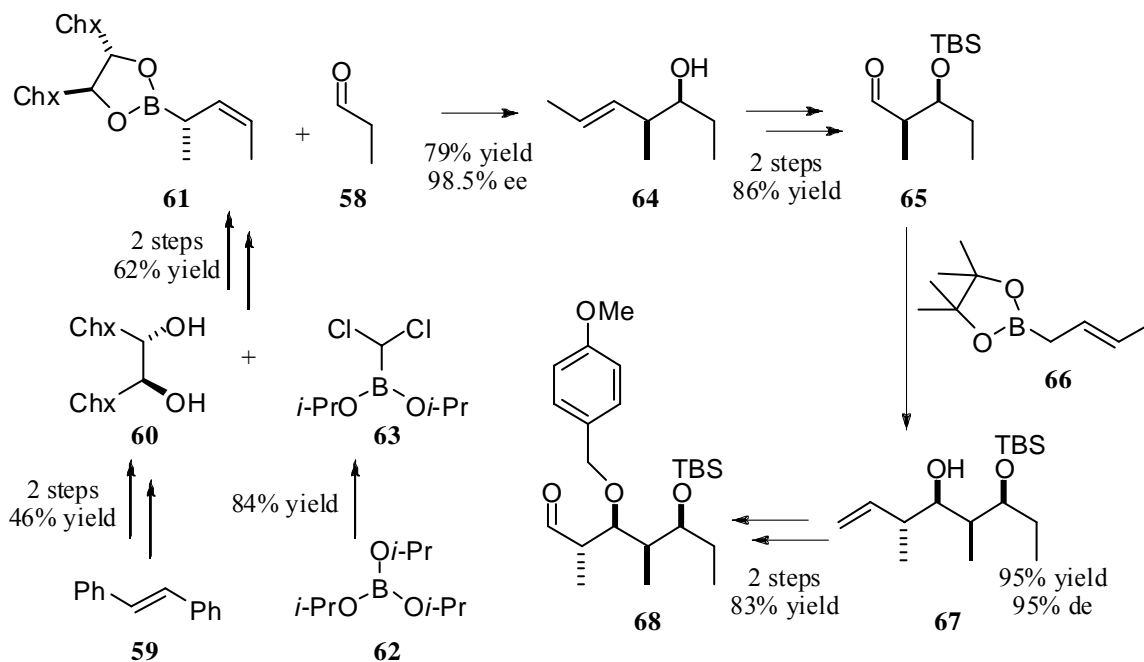
Scheme 1.12.

Scheme 1.13.

addition of **61** to propionaldehyde **58** to give alcohol **64** in 79% yield and 98.5% ee. TBS

protection of **64** followed by ozonolysis provided aldehyde **65** that was used in a second

crotylboration reaction using **66**[vii] to give **67** in 95% yield and 95% de. Sequential

protection and ozonolysis of **67** furnished aldehyde **68** in 83% yield. Chain extension of

68 to aldehyde **56** required an alternative approach as the high 1,3-*anti*

diastereoselectivity found for aldehyde **68** had to be reversed to give the desired 1,3-*syn*

relative configuration. To this end, Hoffmann and co-workers developed α-substituted

crotylboronate **69**[viii] for the crotylboration of aldehyde **68** to give a 3:1 mixture of

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[vii] Prepared from commercially available pinacol and triisopropoxyborane in 4 steps in 38% yield.
[viii] Prepared from commercially available pinacol and (*S*)-butyn-2-ol in 4 steps in 48% yield.
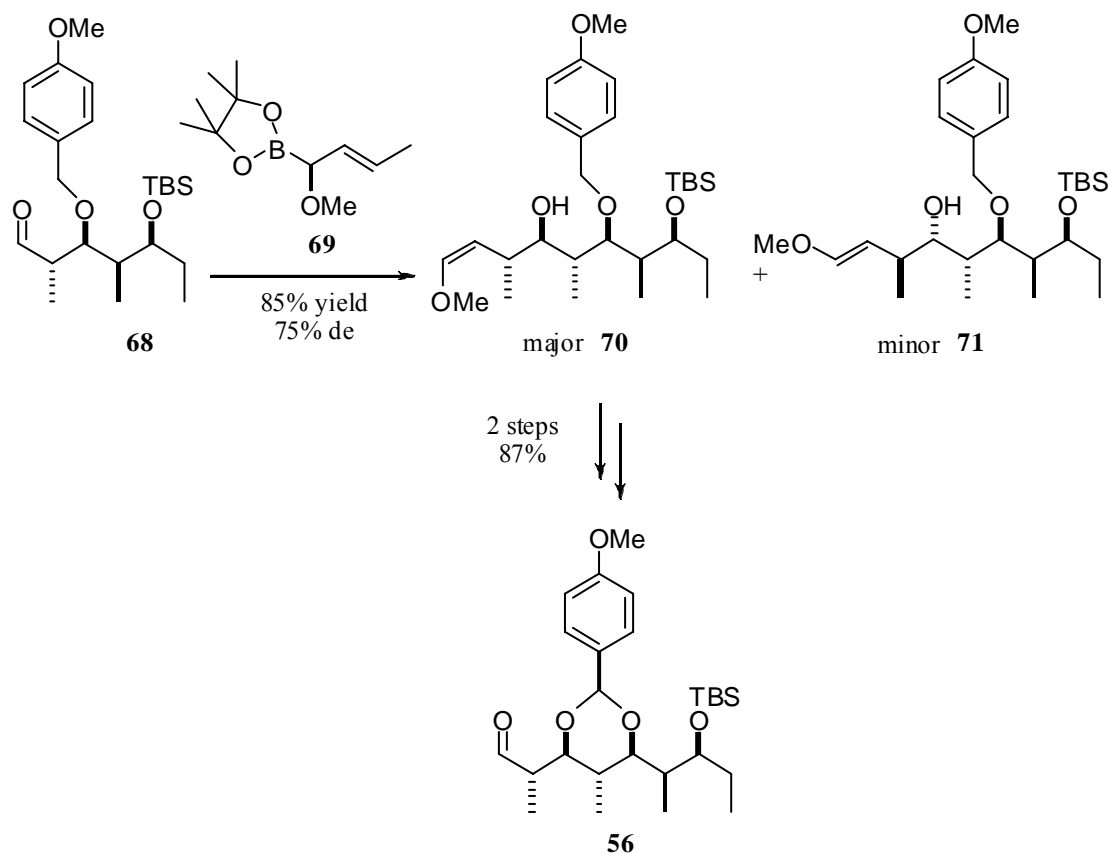
Scheme 1.14.

homoallylic alcohols **70** and **71** in a combined yield of 85% (Scheme 1.14.). DDQ

oxidation of the desired **70** followed by ozonolysis furnished aldehyde **56** in 8% yield

over a total of 12 steps. The remaining fragment required for the final aldol coupling,

ketone **27**, was prepared from racemic alcohol **72**[ix] by an Ireland-Claisen rearrangement
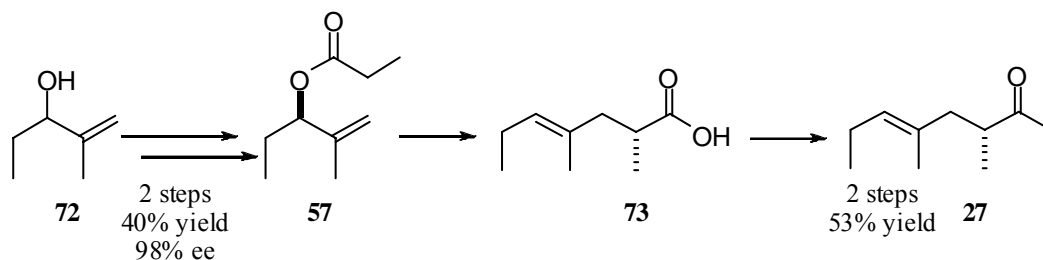
Scheme 1.15.

[ix] Prepared by kinetic resolution of commercially available (±)-2-methyl-1-penten-3-ol *via* Sharpless epoxidation.

via the (*E*)-enolate of ester **57** to provide acid **73** that was directly converted into the desired ketone **27** in 53% yield over 2 steps (Scheme 1.15.). The boron-mediated aldol reaction of ketone **27** with aldehyde **56** furnished two adducts **74** and **75** in 88% combined yield in 75% de (Scheme 1.16.). As is clearly evident from the structures,
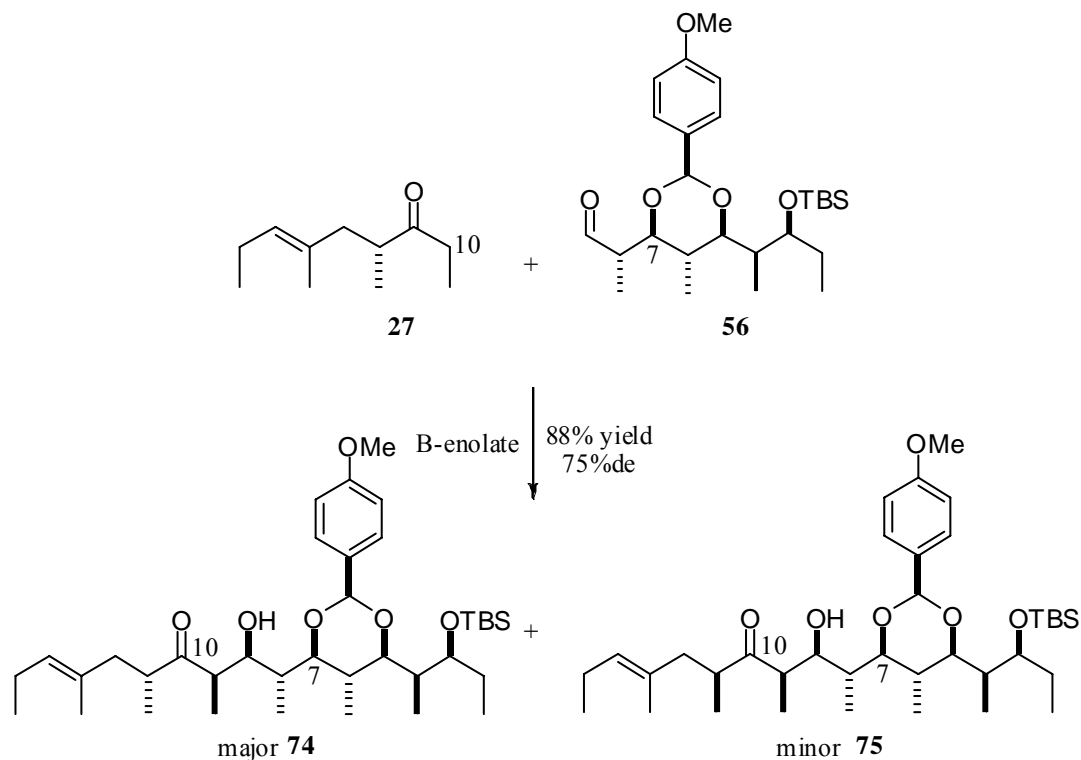
Scheme 1.16.

the two diastereomers arise from the two different enantiomers of ketone **27**. Hoffmann and co-workers speculated that compounds **74** and **75** likely resulted from the reduced enantiopurity of ketone **27**. It has been noted that ketone **27** has a high propensity to racemize upon storage or distillation. Removal of the TBS protecting group in **74** proved to be very troublesome and the diol **76** was obtained in variable yields (20-85%) even after considerable experimentation. The variability was suggested to be a result of the high lability of the *p*-methoxybenzylidene acetal. Collins oxidation of diol **76** provided

the desired triketones (10-*S*)-**77** and (10-*R*)-**78** as a 1:1 mixture with a combined yield of

61% (Scheme 1.17.). Despite the hardship Hoffmann *et al.* had in preparing the desired
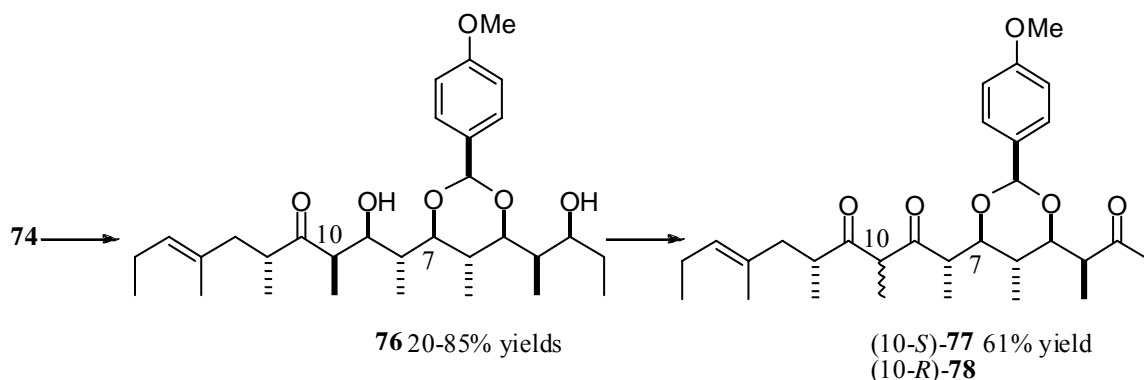
Scheme 1.17.

triketones, further difficulties were faced as deprotection could not be achieved under

numerous conditions without obtaining mainly elimination products. Instead of changing

the *p*-methoxybenzylidene acetal protecting group, Hoffmann and co-workers questioned

if it were possible to synthesize hemiketal **79** resulting from the C_7-OH addition onto C_3-

carbonyl of diol **80** and whether this compound will spontaneously isomerize to the

denticulatins (Scheme 1.18.). Aldehyde **82** was prepared from **81** in 88% yield over 3

steps (Scheme 1.19.). Addition of (*E*)-crotylboronate **69** to aldehyde **82** gave, after

cyclization, **83** and **84** as a 4:1 mixture, respectively in 75% yield. Ozonolysis of **83**

furnished second generation aldehyde **85** (Scheme 1.20.) in 85% yield which was used in
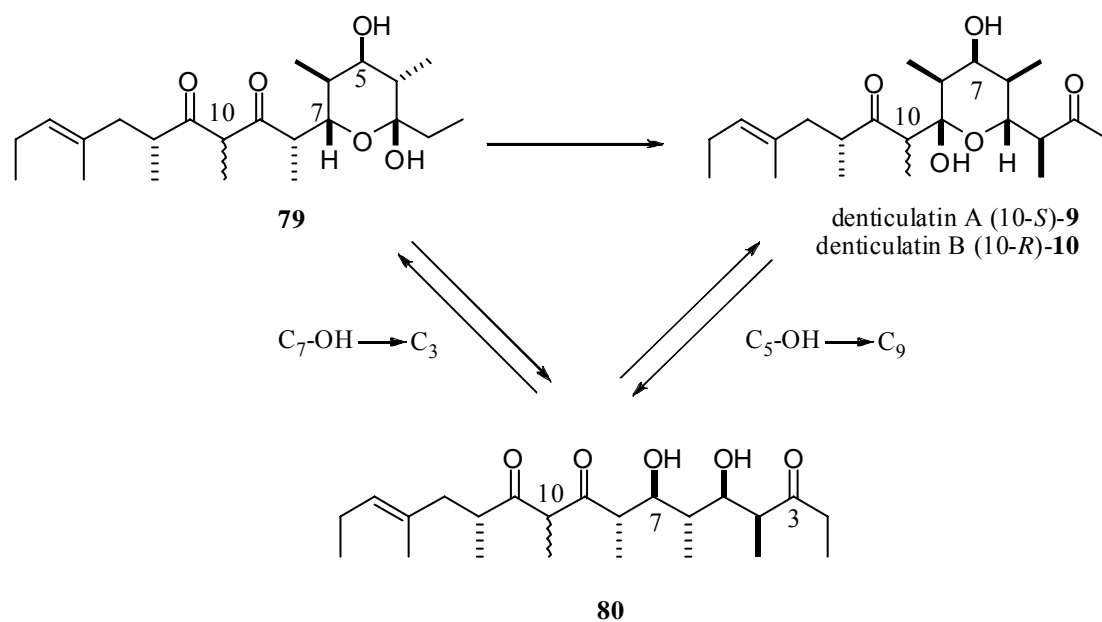
Scheme 1.18.
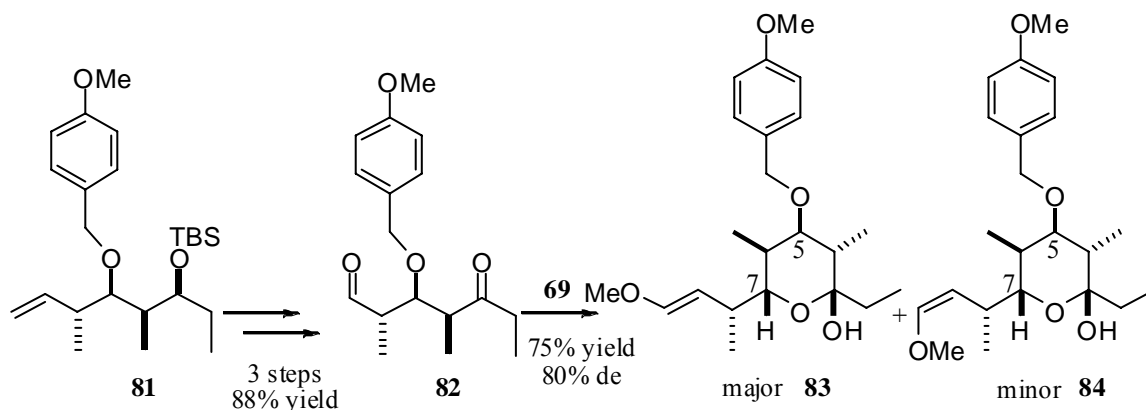
Scheme 1.19.

a boron-mediated aldol reaction with ketone **27** to provide two aldol adducts **86** and **87** in 89% combined yield and 78% de (Scheme 1.20.). Dess-Martin oxidation of **86** furnished diketone **88** in 85% yield. At this stage, only the deprotection of the *p*-methoxybenzyl ether protecting group was required to facilitate isomerization to the denticulatins. Again, attempted deprotection of **88** under numerous conditions failed or resulted in decomposition. After considerable experimentation, deprotection of **88** was achieved by using lithium in ammonia on the corresponding dianion preformed using LDA.

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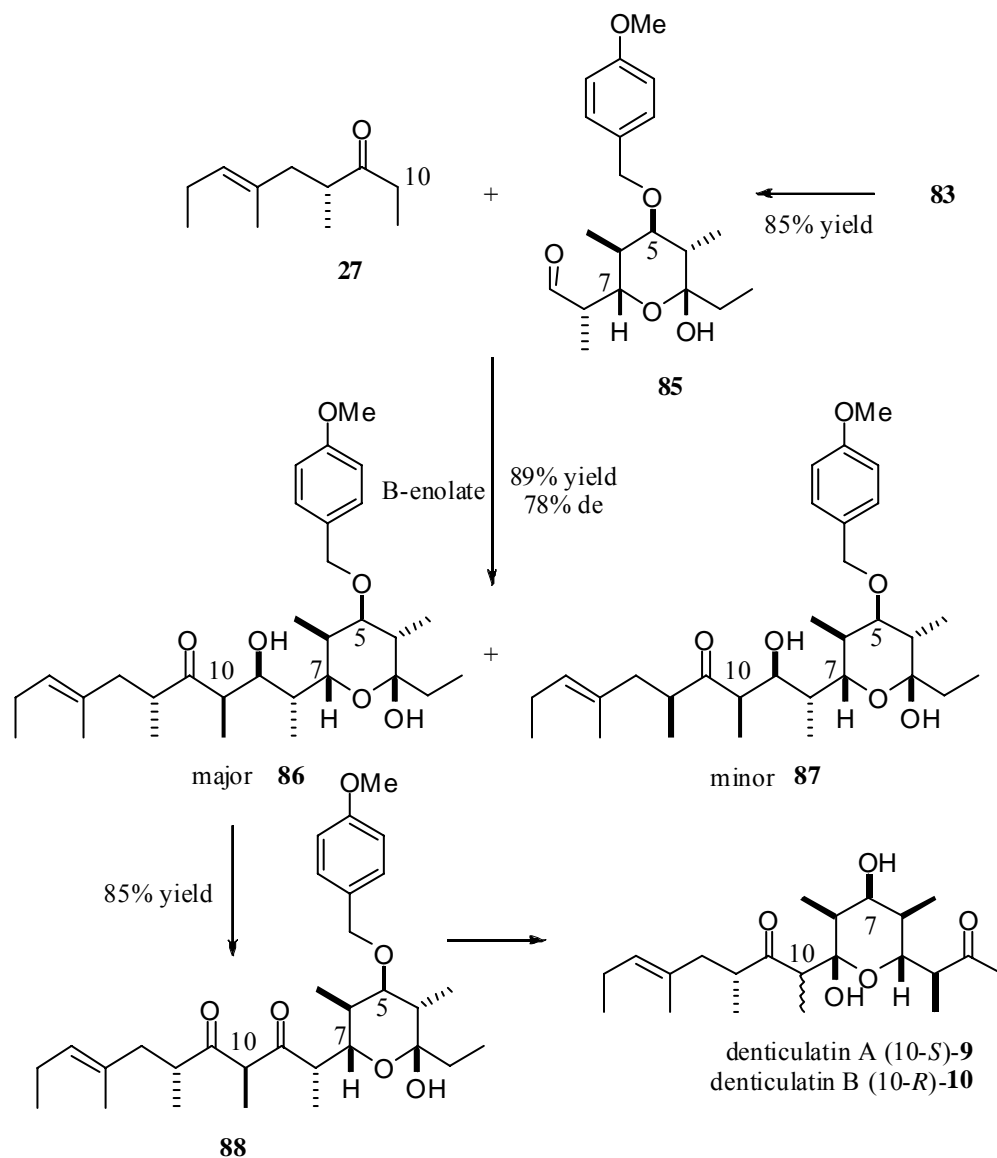
Scheme 1.20.

This process furnished a 1.5:1.0 mixture of denticulatin A and denticulatin B, respectively in 58% combined yield. To summarize, Hoffmann and co-workers synthesized denticulatin A and denticulatin B as a mixture in 2% overall yield over a longest linear sequence of 17 steps starting from *trans*-stilbene (average yield per step of 80%).

1.2.2.3. Paterson's synthesis

In 1992, Paterson and Perkins presented an alternative route for the synthesis of denticulatin B by exploiting boron- and titanium-mediated aldol couplings (Scheme 1.21.).[15, 16] As with the previous syntheses, a protected triketone **89** was prepared. In this
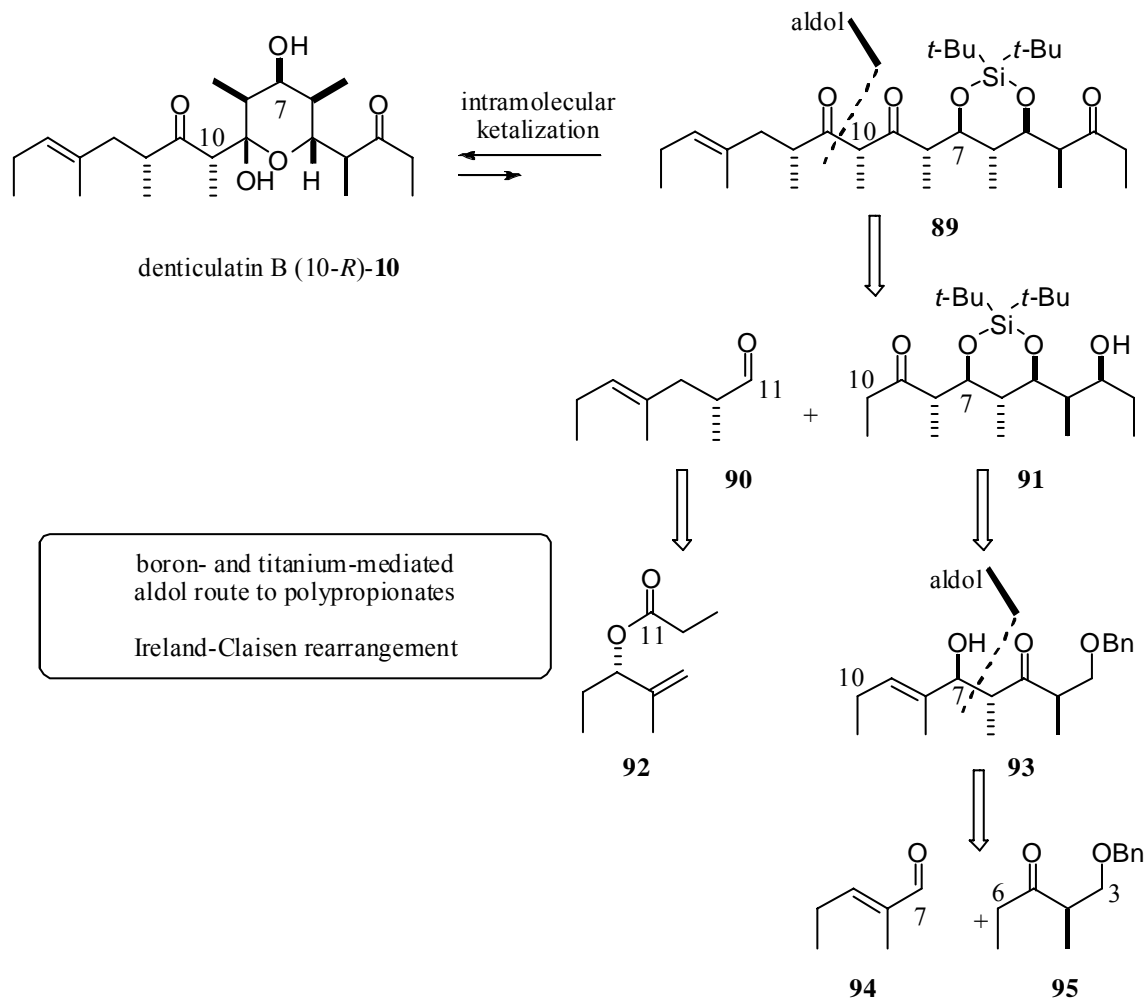
Scheme 1.21.

case, a di-*tert*-butylsilylene protected triketone was prepared with the expectation that deprotection could be effected under mild HF·pyridine deprotection. The synthesis began with a boron-mediated aldol reaction of ketone **97**[x] with aldehyde **96** followed by *in situ*

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[x] Prepared from commercially available (*R*)-methyl 3-hydroxy-2-methylpropionate in 3 steps in 59% yield and 97% ee.

LiBH$_4$ reduction to furnish the diol **98** in 81% yield (Scheme 1.22.).[xi] Sequential

protection and hydroboration of **98** provided **99** in 77% yield in 2 steps (Scheme 1.22.).
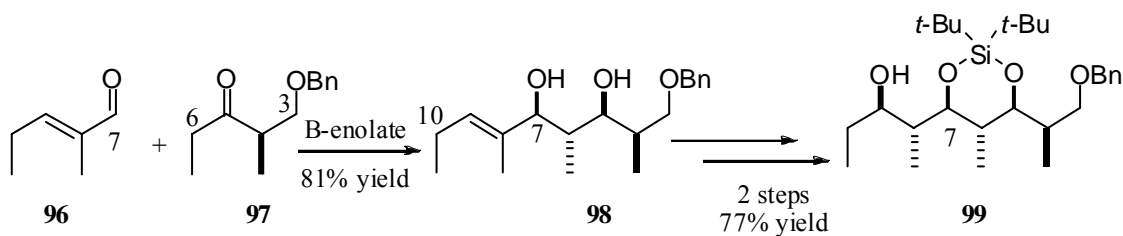
Scheme 1.22.

Conversion of **99** to required ketol **101** was achieved by debenzylation, oxidation, and

ethylmagnesium bromide addition in 70% yield over 3 steps (Scheme 1.23.). With ketol
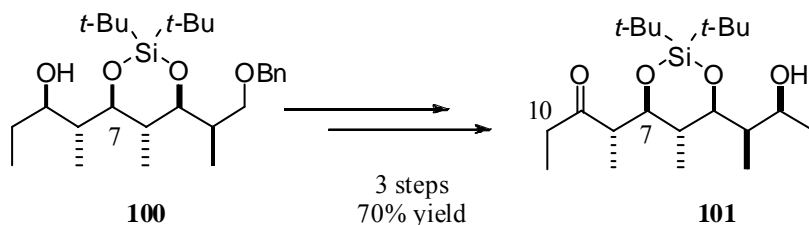
Scheme 1.23.

101 available, aldehyde **90** was prepared from alcohol **102**[ix] by an Ireland-Claisen

rearrangement of the (Z)-O-silylketene of ester *ent*-**57** followed by LAH reduction and

subsequent PCC oxidation of the resulting alcohol to give aldehyde **90** in 42% yield and

80% ee over 3 steps (Scheme 1.24.). The titanium-mediated aldol reaction of ketone **101**

Scheme 1.24.

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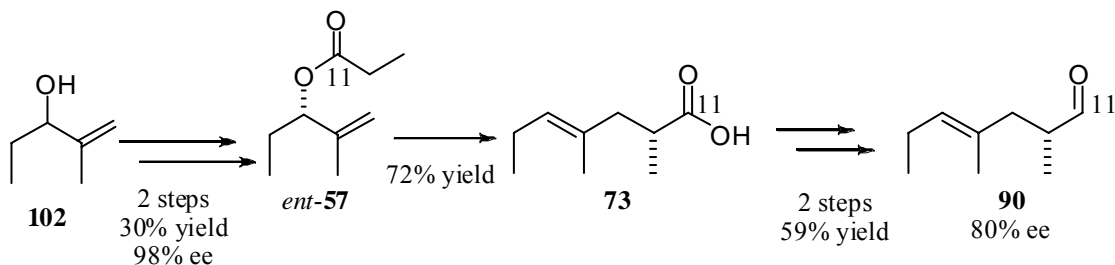
with aldehyde **90** provided two aldol adducts, **103** and **104** in 90% yield and 83% de

(Scheme 1.25.). The minor aldol adduct **104** results from reaction of the minor
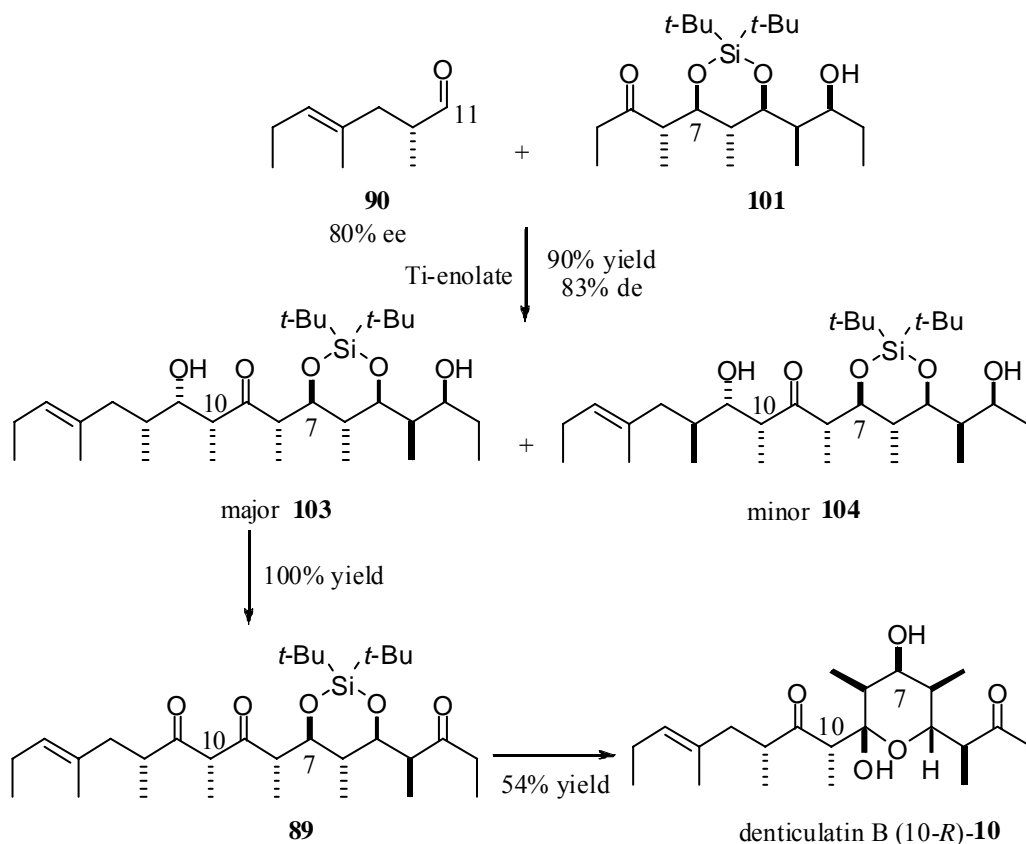
Scheme 1.25.

enantiomer of aldehyde **90** (80% ee). Double Swern oxidation of **103** and subsequent

silyl deprotection using buffered HF·pyridine afforded pure denticulatin B in 54% yield.

Paterson and Perkins were also able to equilibrate triketone **89** using SiO_2 or Et_3N (*i.e.*

C_{10} epimerization). Silyl deprotection of the resulting mixture of C-10 epimers using

buffered HF·pyridine provided a 1:2 mixture of denticulatin A and denticulatin B,

respectively with a combined yield of 78%. To summarize, Paterson and Perkins

achieved the first stereoselective synthesis of denticulatin B in 10% yield over a longest

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linear sequence of 12 steps starting from (*R*)-methyl 3-hydroxy-2-methylpropionate. A

synthesis that reflects an average yield per step of 82%.

1.2.2.4. Oppolzer's synthesis

The first stereoselective synthesis of denticulatin A was achieved by Oppolzer and

co-workers in 1995.[17, 18] Denticulatin B was also prepared from a common intermediate

en route to denticulatin A (Scheme 1.26.). As seen in the stereoselective synthesis of

denticulatin A (10-*S*)-**9**
denticulatin B (10-*R*)-**10**

Scheme 1.26.

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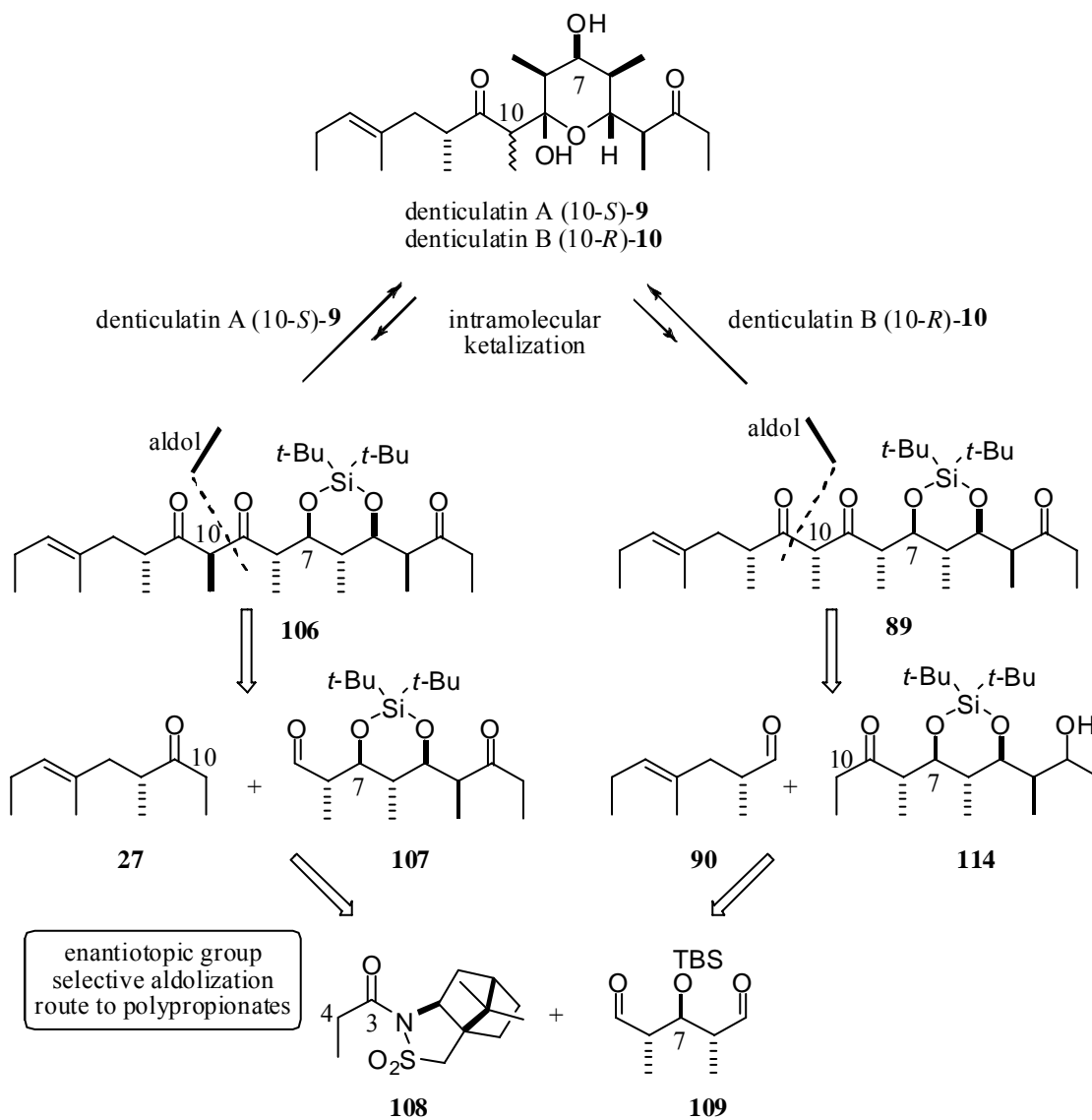
denticulatin B by Paterson and Perkins, Oppolzer *et al.* selected the di-*tert*-butylsilylene triketones **89** and **106** for the synthesis of the denticulatins (Scheme 1.26.). Triketones **89** and **106** were envisioned to arise *via* titanium-mediated aldol couplings (after oxidation) of ketol **114** with aldehyde **90** and ketone **27** with aldehyde **107**. The required aldol components were prepared from *meso* dialdehyde **109**[xii] and chiral *N*-propionylsultam **108**[xiii]. Boron-mediated aldol reaction of chiral *N*-propionylsultam **108** with *meso*
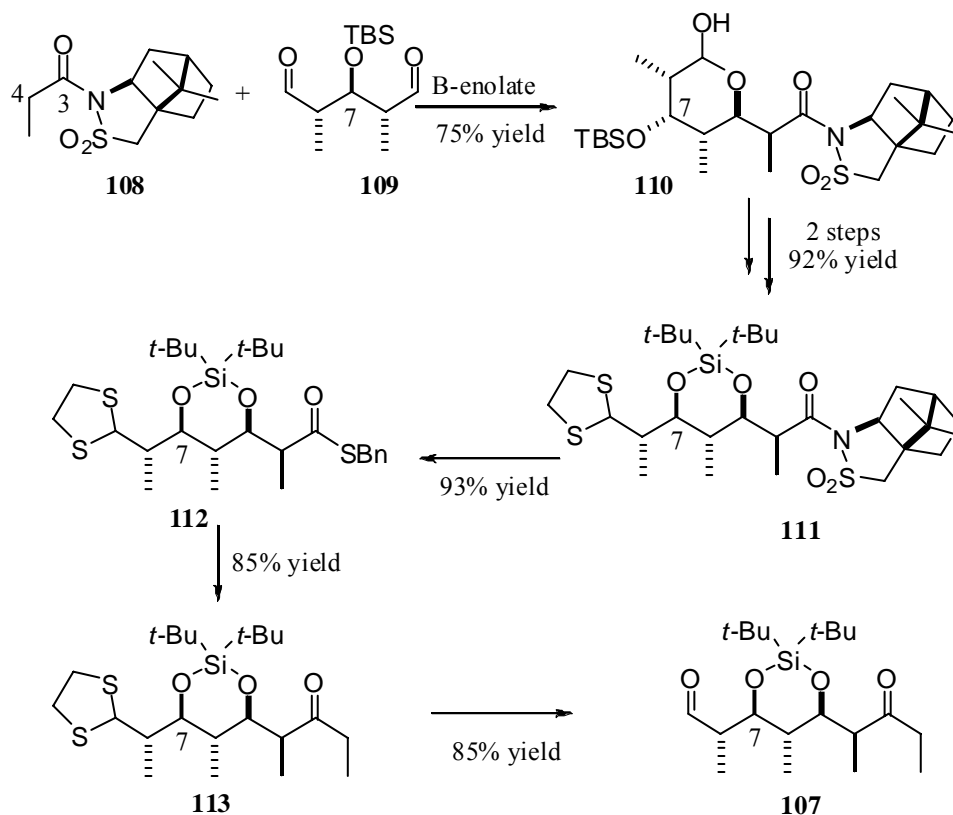
Scheme 1.27.

dialdehyde **109** provided aldol adduct **110** as a cyclized lactol in 75% yield. Simultaneous silyl deprotection and ethanedithiol trapping was achieved in the presence of ZnI$_2$ to give a diol that was subsequently protected to give di-*tert*-butylsilylene dithiolane **111** in 92% yield over 2 steps (Scheme 1.27.). Removal of the chiral auxiliary

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[xii] Prepared from commercially available 2,4-dimethyl-1,4-pentadiene-3-ol in 3 steps in 63% yield.
[xiii] Prepared from commercially available (−)-camphorsulfonic acid in 5 steps in 67% yield.

was best performed using the ate-complex derived from AlMe$_3$ and lithium benzylthiolate which furnished benzyl thioester **112** in 93% yield. Ethylmagnesium bromide addition to **112** followed by dithiolane deprotection using buffered mercury perchlorate provided the desired aldehyde **107** in 72% yield over 2 steps. Access to ketone **27** commenced with alkylation of chiral *N*-propionylsultam **108** with allylic bromide **47**[vi] *via* the sodium enolate to give **115** in 69% yield (Scheme 1.28.). Removal of the chiral auxiliary and ethylmagnesium bromide addition to resulting benzyl thioester
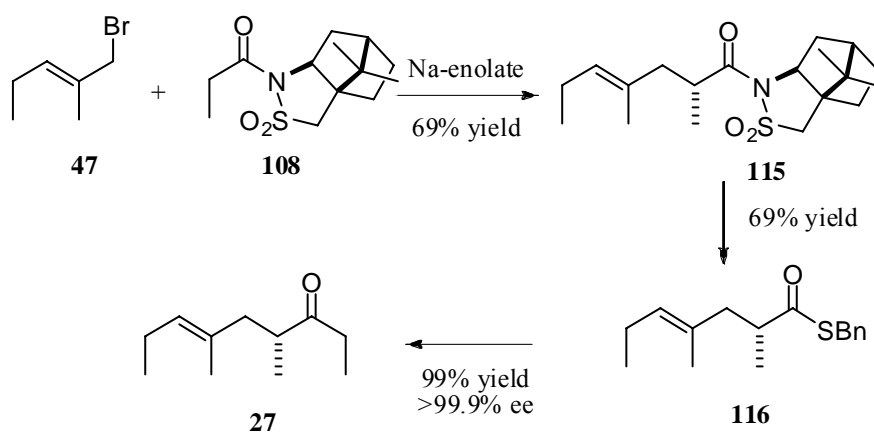
Scheme 1.28.

116 provided ketone **27** in 99% yield and 99.9% ee. Titanium-mediated aldol reaction of ketone **27** with aldehyde **107** provided aldol adducts **117** and **118** in 61% combined yield and 90% de (Scheme 1.29.). Minor aldol adduct **118** was oxidized using Dess-Martin periodinane[xiv] to give triketone **89** that was reported by Paterson and Perkins in their synthesis of denticulatin B. Swern oxidation of the major aldol adduct **117** furnished triketone **106** that was deprotected using buffered HF·pyridine to give denticulatin A and denticulatin B as a 20:1 mixture respectively, in 89% yield (Scheme 1.29.). This

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[xiv] Swern oxidation was unsuccessful.
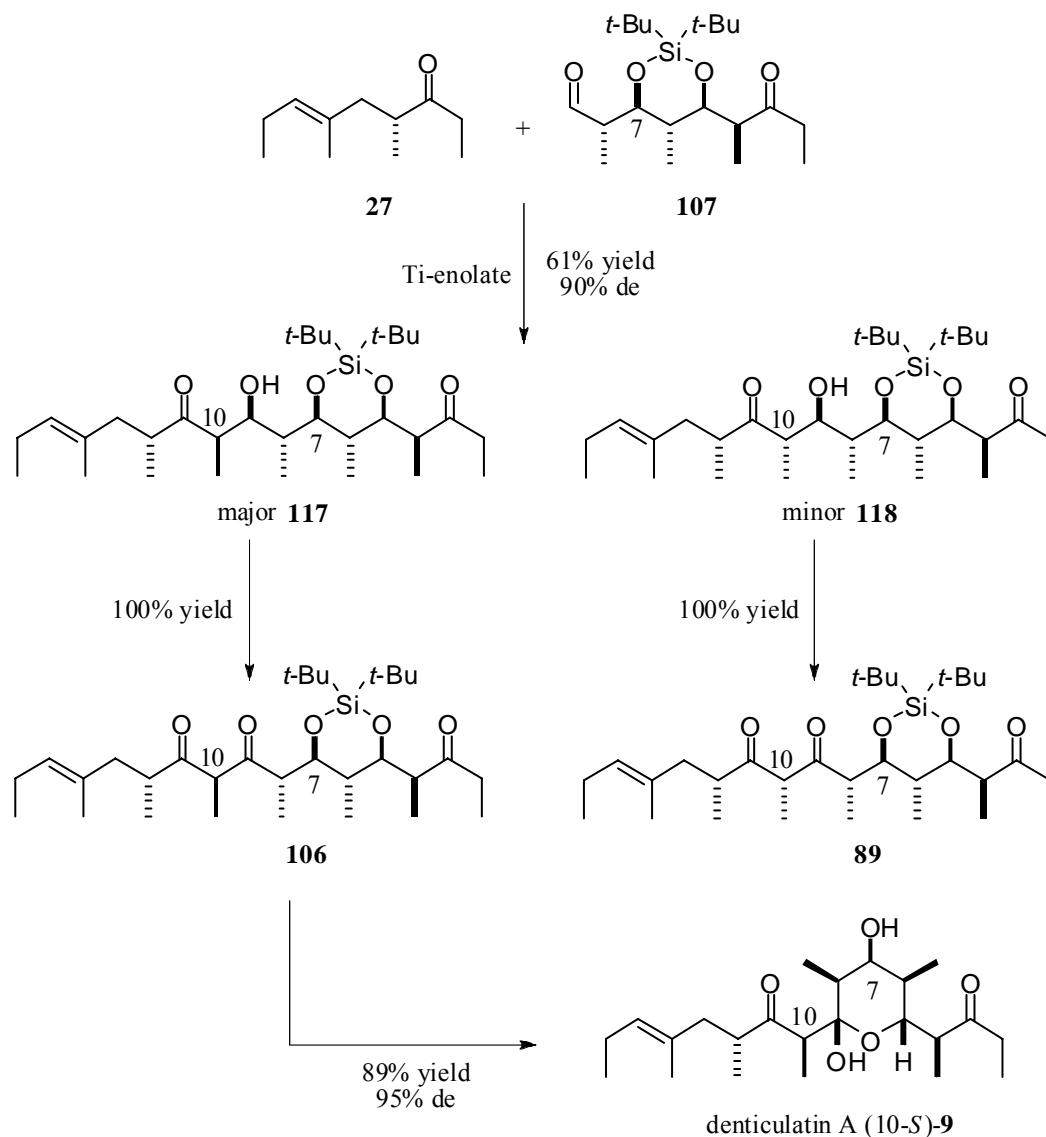
Scheme 1.29

represents the first stereoselective synthesis of denticulatin A that was accomplished in 14 steps and 14% overall yield (average yield per step of 87%).

Oppolzer and co-workers also applied their methodology for the synthesis of denticulatin B *via* aldol coupling of ketol **114** and aldehyde **90** that was similarly achieved by Paterson and Perkins (Scheme 1.21. and Scheme 1.26.). Preparation of aldehyde **90** was achieved by reduction of **115** with lithium triethylborohydride followed by oxidation of **120** with PCC to give the desired aldehyde in 82% yield over 2 steps and

>99.9% ee (Scheme 1.30.). Access to the desired ketol was obtained by a sequence of

reactions that first involved dithiolane deprotection of **111** using buffered mercury
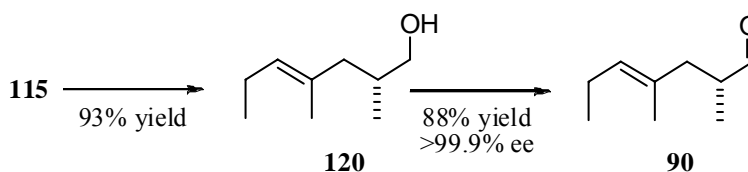
Scheme 1.30.

perchlorate which provided aldehyde **121** in 92% yield. Ethylmagnesium bromide

addition to aldehyde **121** provided a 2:1 mixture of alcohols **122** in 95% yield (Scheme

1.31.). Lithium triethylborohydride reduction of this mixture followed by Dess-Martin
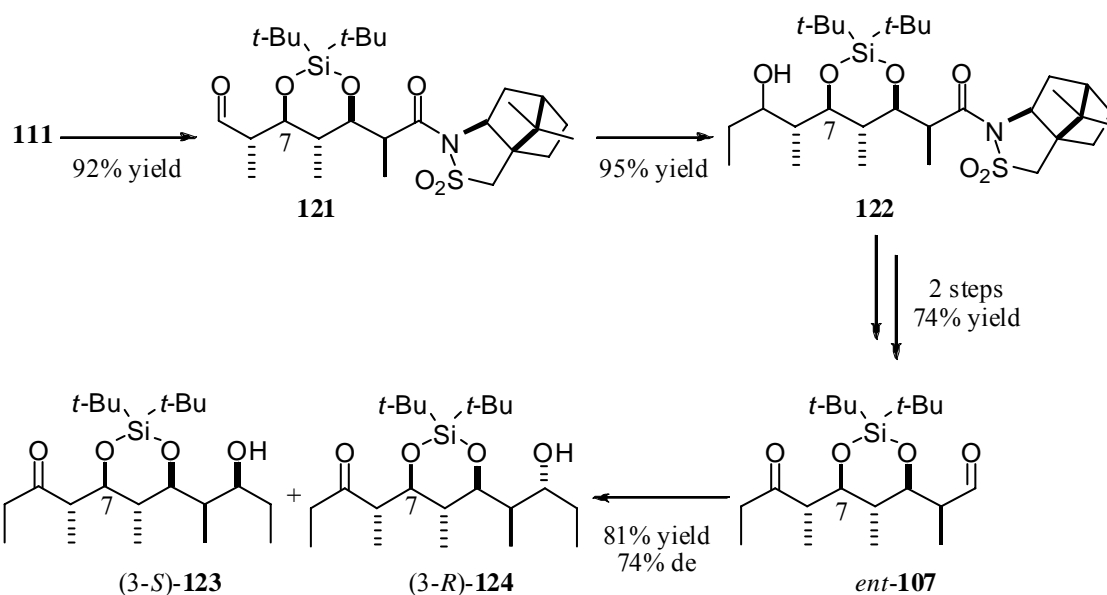
Scheme 1.31.

oxidation furnished keto aldehyde *ent*-**107** in 74% yield over 2 steps. Ethylmagnesium

bromide addition to aldehyde *ent*-**107** provided ketols (3-*S*)-**123** (60% yield) and (3-*R*)-

124 (21% yield). Titanium-mediated aldol coupling of aldehyde **90** and ketol (3-*S*)-**123**

provided aldol adduct **125** in 89% yield. Similarly, titanium-mediated aldol coupling of

aldehyde **90** and ketol (3-*R*)-**124** provided aldol adduct **126** in 71% yield (Scheme 1.33.).

Swern oxidation of **125** or **126** furnished desired triketone **89** in quantitative yield that was deprotected using buffered HF·pyridine to give pure denticulatin B in 78% yield (Scheme 1.32.). To summarize, Oppolzer and co-workers achieved an improved
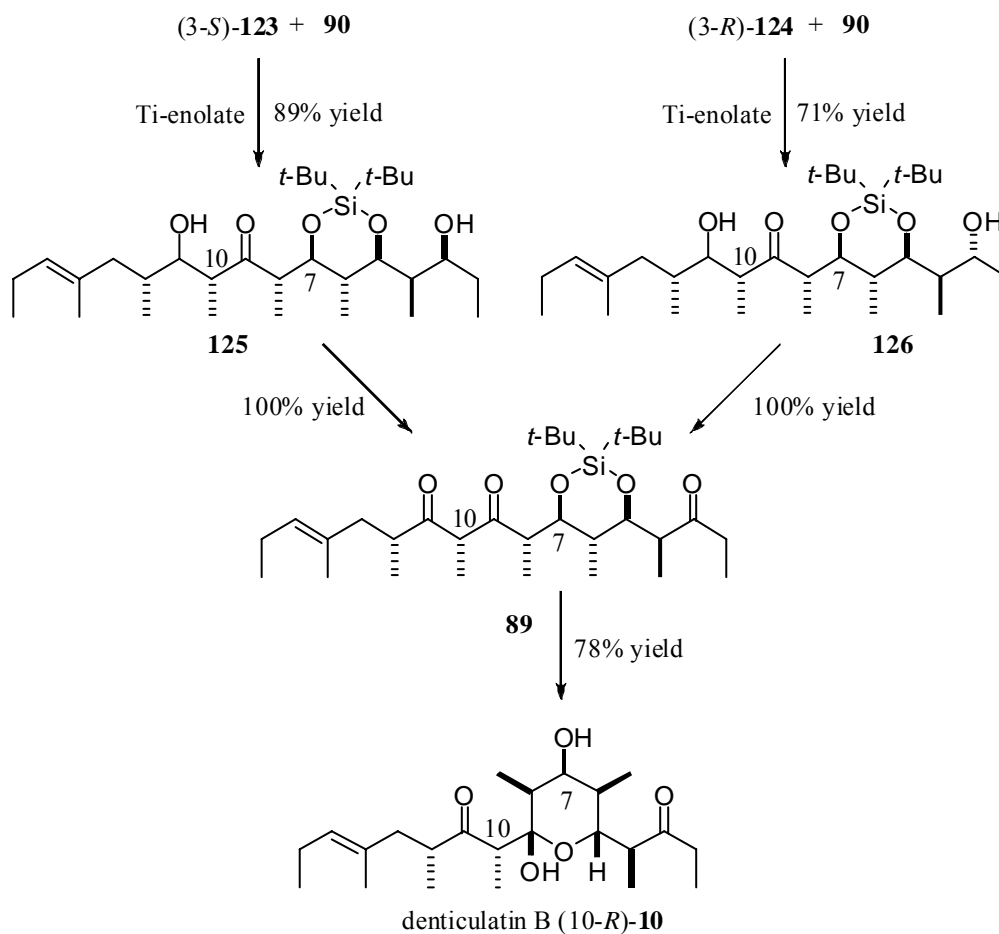
Scheme 1.32.

stereoselective synthesis of denticulatin B in 12% yield over a total of 16 steps (average yield per step of 87%).

1.2.3. Comparative analysis of syntheses

All total syntheses of the denticulatins exploited aldol related chemistry to effect fragment coupling. All routes rely on acyclic precursor A (Scheme 1.33.) as the penultimate intermediate. This precursor was assembled by substrate-controlled aldol reactions of **27** and B for denticulatin A or C and **90** for denticulatin B
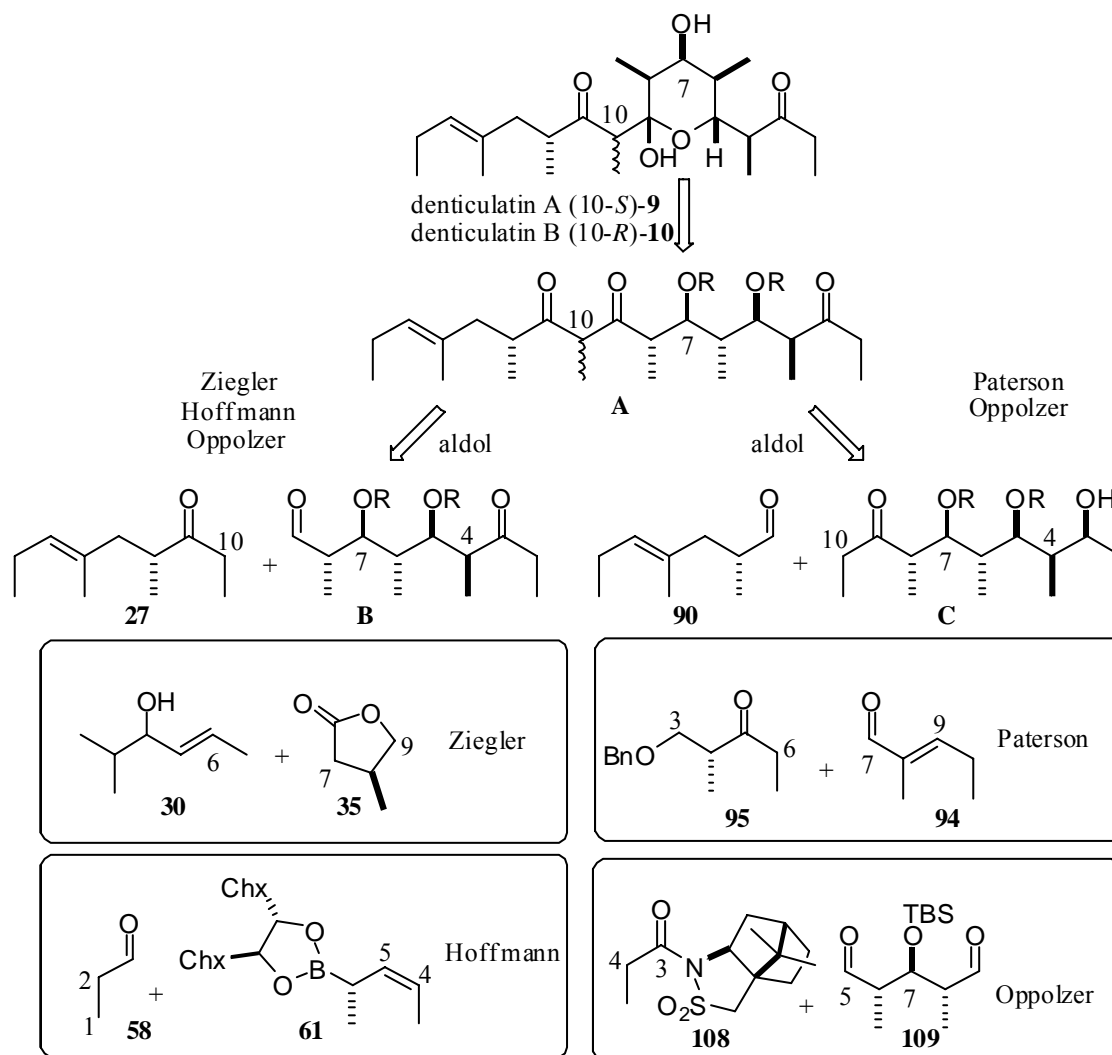
Scheme 1.33.

(Scheme 1.33. and Table 1.2.). Each research group applied their own methodologies for the synthesis of the required aldol coupling partners. Ziegler and co-workers used enolate Ireland-Claisen protocols involving both enantiomers of **30** and (*S*)-3-methyl-γ-butyrolactone **35** to arrive at B. Hoffmann and co-workers implemented several crotylboration maneuvers to prepare an equivalent of aldehyde B. Paterson and Perkins synthesized ketol C from a boron-mediated aldol reaction of ketone **95** and aldehyde **94**. Lastly, Oppolzer applied an enantiotopic group selective aldolization route for the preparation of both B and C. While the syntheses overlap to some extent, the route of

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Oppolzer and co-workers' is noteworthy in that it was adaptable for the synthesis of denticulatin A or denticulatin B.

Table 1.2. Total syntheses of the denticulatins.

	denticulatin		% yield[a]	number of steps[b]	longest linear sequence	average yield per step[c]
	A:B	B				
Ziegler	6:1	-	0.3	46	32[d]	83
Ziegler	1:8	-	0.4	46	32[d]	83
Hoffmann	1.5:1	-	2	26	17[e]	80
Paterson	-	pure	10	17	12[f]	82
Oppolzer	20:1	-	14	23	14[g]	87
Oppolzer	-	pure	12[h]	21	16[g]	87

[a] Yields calculated based on commercially available starting materials over the longest linear sequence.
[b] Total number of synthetic manipulations including preparation of starting materials and reagents.
[c] Calculated based on the longest linear sequence. [d] Based on (S)-3-hydroxy-2-methylpropionate. [e] Based on *trans*-stilbene. [f] Based on (R)-methyl 3-hydroxy-2-methylpropionate. [g] Based on (−)-camphorsulfonic acid. [h] 18% yield when combined with material deriving from (3-R)-**124**.

1.3. Total synthesis of polypropionate natural products

Polypropionate natural products are characterized by structure with alternating methyl groups and oxygen functionalities (alcohol, ketone and/or carboxyl) along a contiguous carbon chain (Figure 1.4.). Among the approximately 5000-10,000 known

R = O, H/OH, H/H
n = 0, 1, 2,...integer
* = stereogenic center
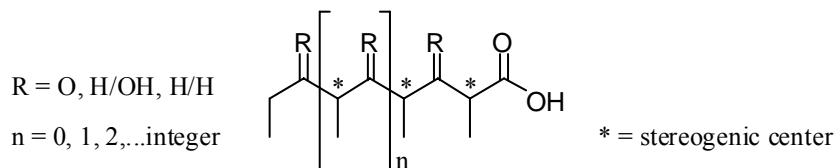
Figure 1.4. Generalized structure of polypropionate natural products.

polypropionates, only 1% of them possess biological activity. Despite this rather low value, it surprisingly represents five times the average for natural products.[21] The considerable interest in polypropionate natural products is due to their biological applications and stereochemical complexity.[22-26] For more than three decades, synthetic chemists have made significant contributions to the development and advancement of asymmetric synthetic methodologies.[21, 27, 28] The inherent challenge for the synthesis of

polypropionates derives from the long sequence of stereocenters. For example, a dipropionate can have up to four different stereoisomers, a tripropionate (16), a tetrapropionate (64), a pentapropionate (256), a hexapropionate (1024) and a heptapropionate (4096) (Figure 1.5.). In some cases, the relative and/or absolute
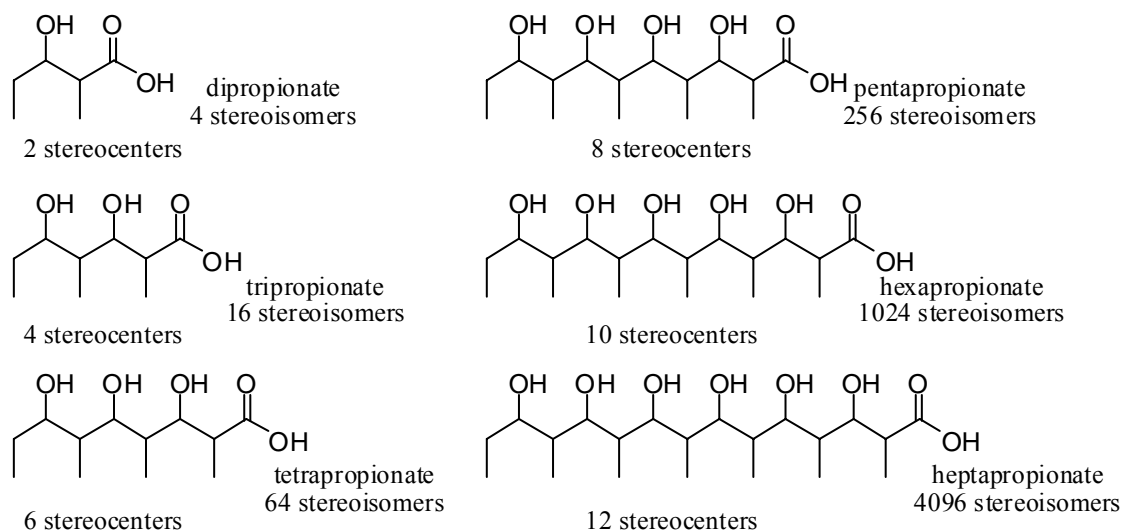
Figure 1.5. Possible stereoisomers for polypropionates.

configurations of isolated polypropionates are not known and to resolve this problem, the synthesis of all stereoisomers is required.[29, 30] In 1987, Hoffmann introduced the term 'stereotriad' for the analysis of sequences possessing three consecutive stereocenters (Figure 1.6.).[28] Coupling of chiral (non-racemic) stereotriad fragments allows the
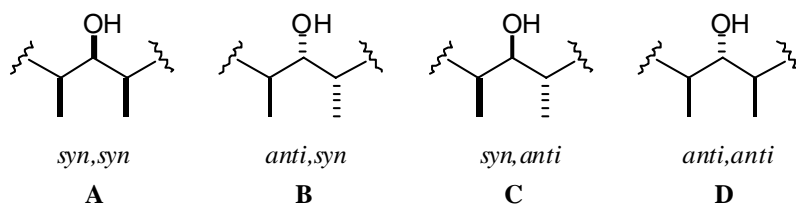
Figure 1.6. Stereotriads A-D.

construction of more elaborate polypropionate structures.[31-36] However, this union is complicated by double stereodifferentation and introduces a major obstacle to be overcome in any total synthesis.[28, 37-45] As a result, numerous reactions have been

developed for the synthesis of polypropionate structures. For example, aldol,[31, 46-63] crotylation,[42, 45, 64-69] Diels-Alder,[70-76] Wittig,[77] Tischtschenko,[78] alkylation,[79-84] propargylation-reductive coupling,[85, 86] acetalization,[87] hydroformylation,[88] formate reduction,[89] allyltitanation[58, 78, 90, 91] and allenylstannylation[92] reactions have found numerous applications in polypropionate syntheses. Other approaches involving cyclopropane,[93] oxabicylic,[70, 94-96] 1,3-polyol,[97, 98] acyl halide[99] and γ-lactone[19, 20, 100] intermediates have also proved to be very convenient methods for the synthesis of polypropionate compounds. Despite the plethora of approaches available, the asymmetric synthesis of polypropionate compounds continues to be a synthetic challenge because very few methods can be generally applied for the preparation of the numerous polypropionate motifs found in various natural products (Figure 1.6.).[xv]

In Nature, polypropionates are assembled by polyketide synthase (PKS) enzymes through an iterative decarboxylative condensation of methylmalonyl CoA to a growing polyketide chain generating (up to) two stereocenters per iteration. The first PKS elucidated was for the erythromycin antibiotics (Figure 1.7.) isolated from *Streptomyces*

erythromycin A, R = OH **128**
erythromycin B, R = H **129**   6-deoxyerythronolide B **127**

Figure 1.7. *Streptomyces erythreus* **macrolides.**

[xv] Considering both enantiomeric series of stereotriads **A-D**, there are 8 possible stereoisomers.

erythreus.[26]   In fact, the intermediate 6-deoxyerythronolide B **127**,[101] isolated from

blocked mutants of *Streptomyces erythreus* proved to be instrumental for this objective.

The erythromycin polyketide synthase consists of 7 enzymes and is a so-called type I[xvi]

polyketide synthase.[102]   In an iterative fashion, 6-deoxyerythronolide B **127**, is

biosynthesized from one molecule of propionyl CoA **1** and six molecules of

methylmalonyl CoA **2** (Scheme 1.34.). The PKS possesses six modules that consist of

several enzymes (AT, KS and ACP) along with additional enzymes involved with

functional group manipulations.   The first step of chain elongation involves

decarboxylative condensation of ACP bound methyl malonic acid **139** with KS bound

propionate **138** (Scheme 1.35.). Subsequent acyl transfer of the newly formed ACP

bound polypropionate and preparation of the second ACP bound methyl malonic acid **139**

[xvi] There are three types of PKS: Type I, consist of multifunctional enzymes that are organized into modules which are responsible for the catalysis of one cycle of polyketide chain elongation. Type II, consist of dissociable multienzyme complexes. Type III, consists of dissociable homodimeric enzymes.
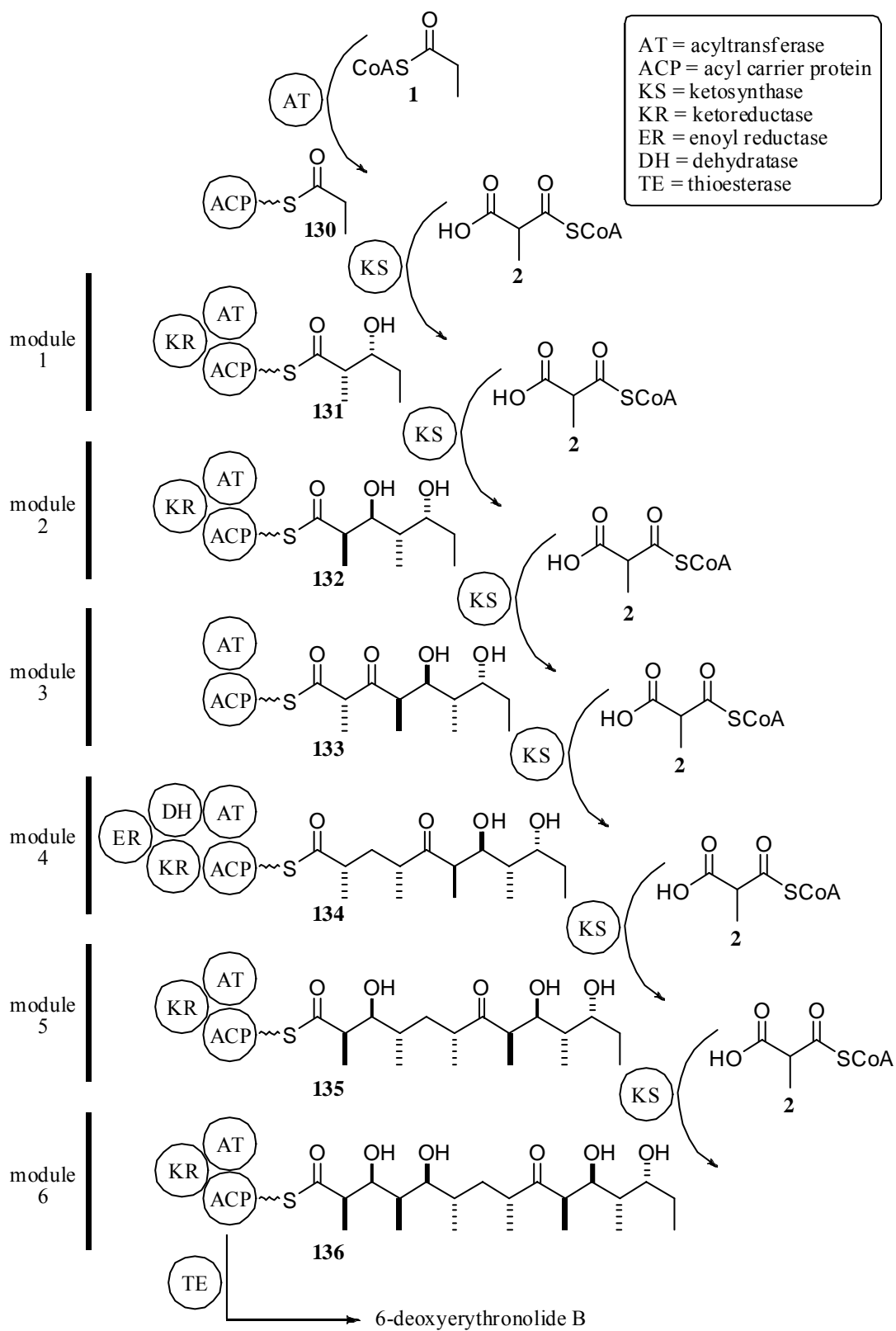
Scheme 1.34.
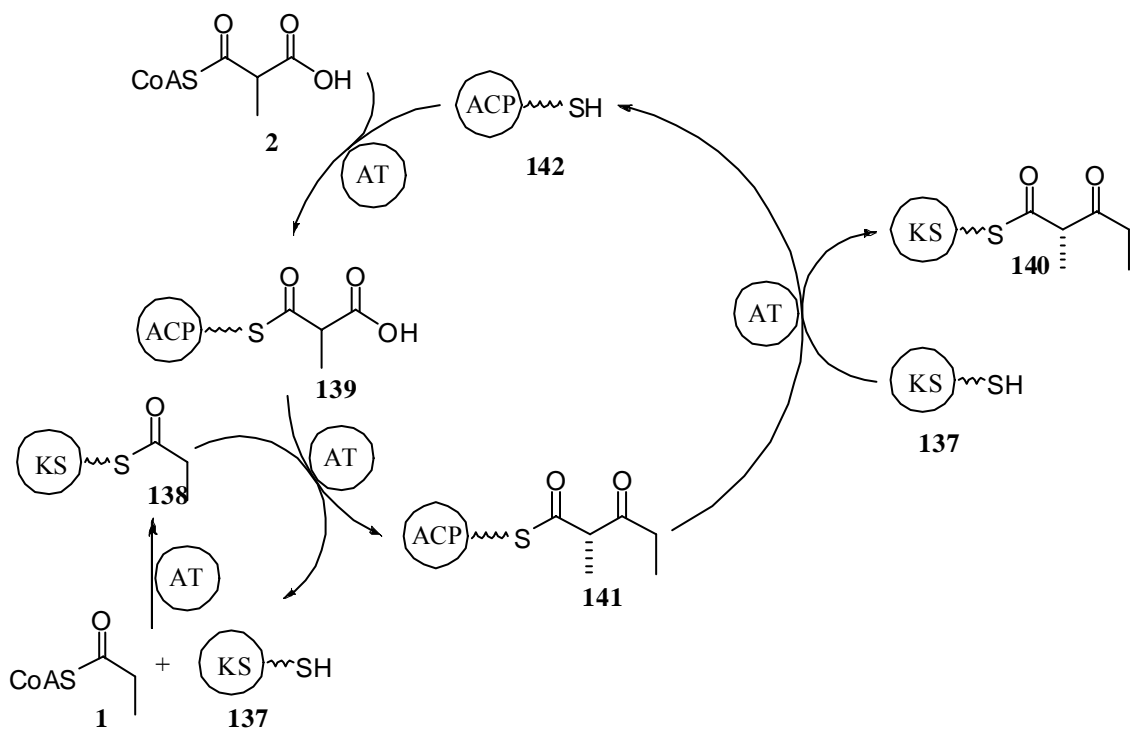
Scheme 1.35.

sets the stage for a second iteration in as few as two steps. Reiteration of this process with the growing KS bound polypropionates and intervening functional group manipulations produces 6-deoxyerythronolide B in only 6 carbon-carbon bond forming reactions.

Polypropionate natural products and their related compounds have benefited humans on several different levels and their significance cannot be overstated. Convenient, flexible and efficient methods are still required for the synthesis of polypropionate compounds. Despite the numerous synthetic approaches for polypropionate synthesis, very few have been applied in an iterative[xvii] fashion that attempts to mimic the elegant approach displayed in Nature.

[xvii] Defined in this context where a particular reaction or sequence of reactions were iterated 3 or more times.

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1.3.1. Iterative strategies for polypropionate synthesis

Many of the iterative strategies developed to date involve the reaction of chiral (non-racemic) or achiral aldehydes with chiral (non-racemic) or achiral reagents generating (up to) two new stereocenters for each step. For an iterative strategy, the aldehyde must be prepared from the product resulting from the chain elongating step (Scheme 1.36.). There are two major obstacles for an iterative strategy: 1) the number of
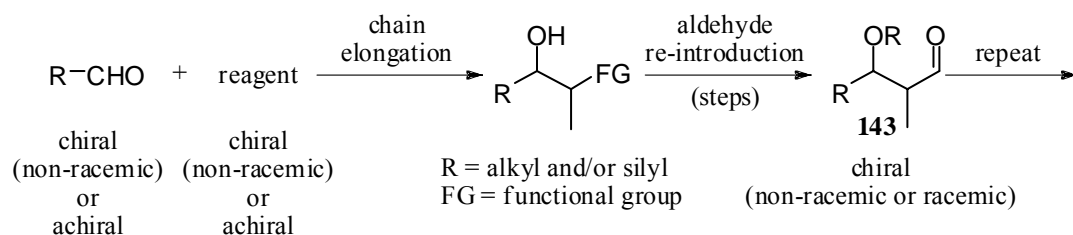
Scheme 1.36.

synthetic manipulations required for aldehyde re-introduction[xviii] and 2) the enantio- and diastereoselectivities of the chain elongation steps. In Nature, as few as two steps are performed for each iteration and the enantio- and diastereoselectivities are controlled by enzymes (Scheme 1.34. and Scheme 1.35.). As was discussed earlier (Figure 1.5.) the number of possible stereoisomers increases exponentially with the number of stereogenic centers. Often, the major challenge faced by synthetic chemists involves establishing the desired configurations of the polypropionate compound. Over the past 15 years, several iterative strategies have emerged and have found various applications for the synthesis of polypropionate compounds. The following examples are presented to provide a representation of iterative approaches. All of the examples have shown the capacity to control the stereochemical outcome of different reactions by exploiting substrate- and/or reagent-control.

[xviii] That is, the efficiency of preparing the required aldehyde for the next iteration.

In 1990, Danishefsky and Myles disclosed a Lewis acid catalyzed diene aldehyde cyclocondensation (LACDAC) reaction that was applied in an iterative fashion for the synthesis of racemic 6-deoxyerythronolide B (Scheme 1.37.).[75] The strategy exploited
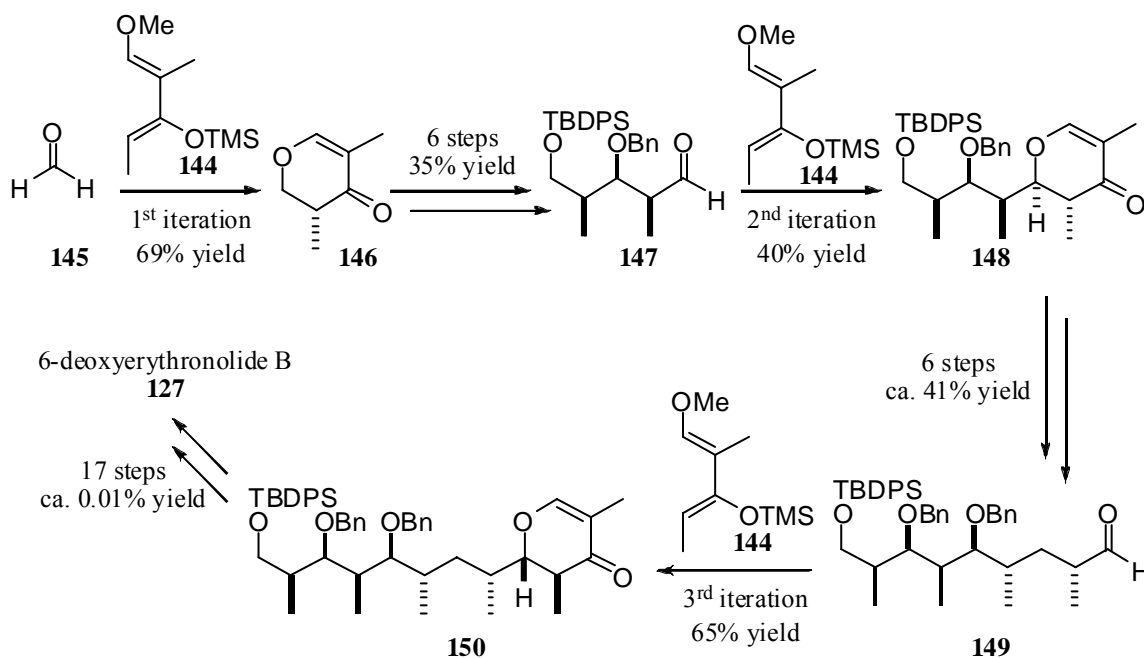
Scheme 1.37.

substrate-controlled Diels-Alder reactions of diene **144** with various aldehydes in the presence of different Lewis acids (e.g. $ZnCl_2$ or $BF_3 \cdot OEt_2$) to produce dihydropyrones. Processing the dihydropyrones into their corresponding aldehydes (6 steps) permitted iteration of the sequence. Although the approach was iterative, a major limitation was the 6 steps (*ca.* 35-41% yields) required before the next iteration.

In a related synthesis, Hoffmann and co-workers presented an impressive asymmetric synthesis of (9-*S*)-dihydroerythronolide A **160** (Scheme 1.38.).[64] The strategy employed four reagent-controlled crotylboration reactions utilizing chiral (non-racemic) crotylboronates and chiral (non-racemic) aldehydes where, after the first iteration, only 2 steps were required to prepare for iterative chain elongation.
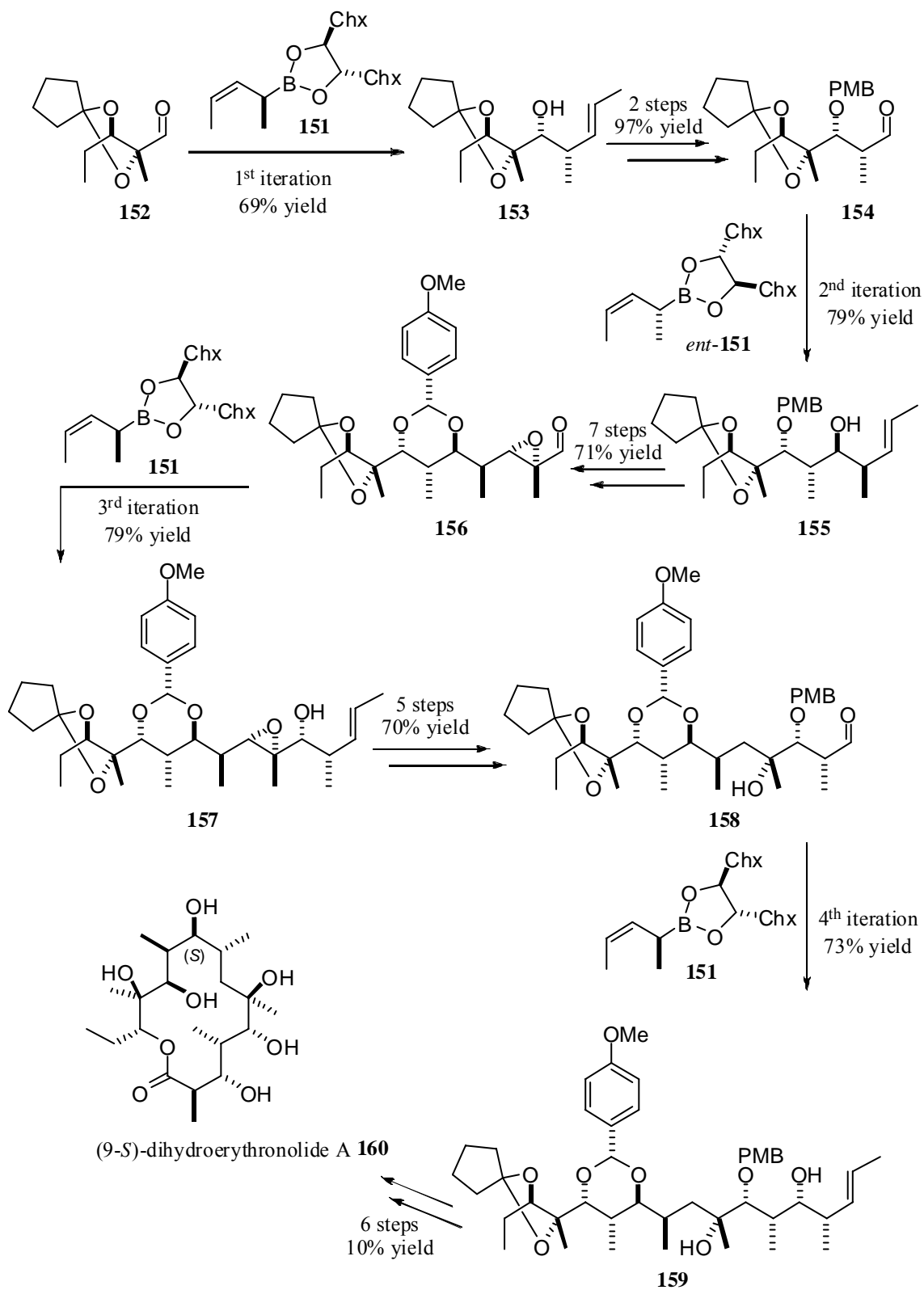
Scheme 1.38.

A more general approach was developed by Hanessian and co-workers that utilized Wittig methodology. The basis of the approach involved substrate-controlled methyl cuprate additions to protected chiral (non-racemic) γ-alkoxy-α,β-unsaturated esters followed by a Davis α-hydroxylation to complete the installation of a propionate fragment (Scheme 1.39.).[77] Iteration was achieved by a three step sequence that provided
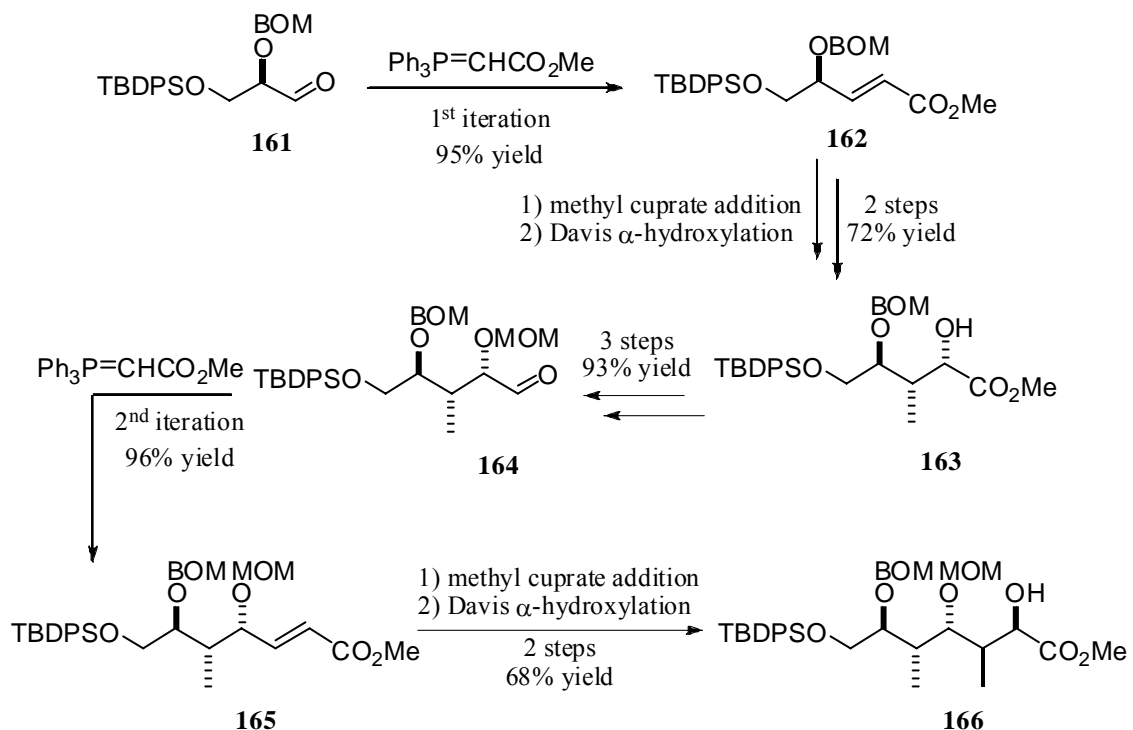
Scheme 1.39.

the next aldehyde to be used for chain elongation. Unlike the previous examples, this approach sequentially installed the desired stereocenters after chain elongation. As a result of the inherent stereochemical outcome of the conjugate addition and subsequent hydroxylation and in combination with an optional Mitsunobu inversion, stereotriads **B-D** (Figure 1.6.) can be obtained by this method. Although stereotriad **A** (Figure 1.6.) is not accessible by this approach, it could be obtained by an oxidation-reduction sequence.

In 1999, Paterson and Scott reported a boron-mediated aldol reaction strategy for the synthesis of polypropionate compounds. The strategy exploited substrate-controlled aldol reactions of preformed chiral (non-racemic) (*E*)-enol borinate **167** (or *ent*-**167**) with various aldehydes (Scheme 1.40.).[46, 63] The sequence was made iterable by a 4 step protocol that provided the desired aldehydes for subsequent iterations. Similarly, during the synthesis of oleandolide, Paterson and co-workers also demonstrated reagent-controlled boron-mediated aldol reactions of chiral (non-racemic) (*Z*)-enol borinates **170** and **173** derived from (*S*)-ketone **95** and (−)-Ipc$_2$BOTf/*i*-Pr$_2$EtN or (+)-Ipc$_2$BOTf/*i*-Pr$_2$EtN with aldehydes **171** or **173**, respectively (Scheme 1.41.)[103]. By application of the appropriate reaction conditions, Paterson and co-workers demonstrated that a diverse library of polypropionate compounds could be accessed with different relative and/or absolute configurations.
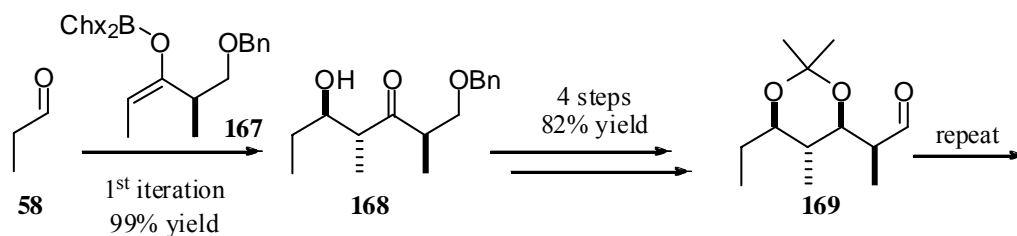
Scheme 1.40.
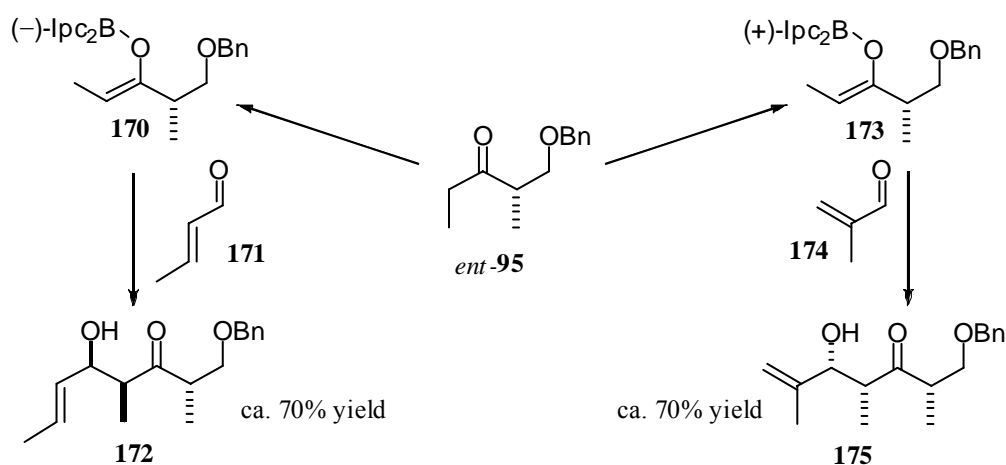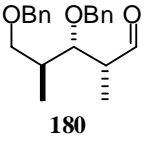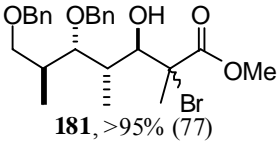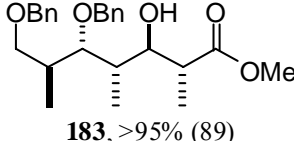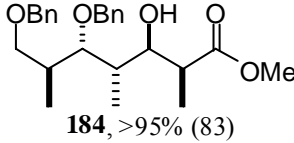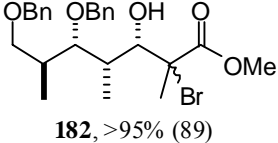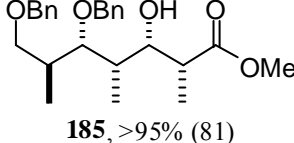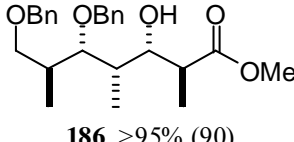
Scheme 1.41.

Guindon and co-workers also exploited an aldol-type process that permitted access to all stereotriads **A-D** (Figure 1.6.).[53, 55, 104] The basis of the methodology involved Lewis acid-mediated (AlMe$_3$, Bu$_2$BOTf, BF$_3$·OEt$_2$ or (*i*-PrO)TiCl$_3$) substrate-controlled Mukaiyama aldol reactions[105] of different chiral (non-racemic) aldehydes with tetrasubstituted enoxysilane **177** in tandem with a Lewis acid-mediated (Bu$_2$BOTf or AlMe$_3$) stereoselective hydrogen transfer using Bu$_3$SnH. Subjecting the resulting β-hydroxy ester **179** to a 3 step sequence allowed the strategy to be reiterated (Scheme 1.42. and Table 1.3.).
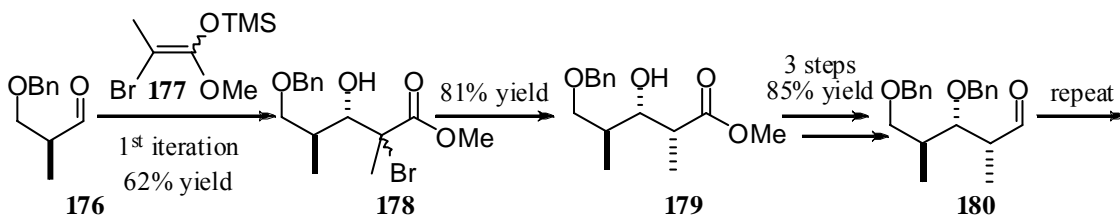
Scheme 1.42.

Table 1.3. **Diastereoselective Mukaiyama aldol and stereoselective hydrogen transfer processes.**

aldehyde	Lewis acid	% de (% yield)	Lewis acid	% de (% yield)
180	$(i\text{-PrO})\text{TiCl}_3$ **177**	**181**, >95% (77)	$\dfrac{\text{Bu}_2\text{BOTf}}{\text{Bu}_3\text{SnH}}$	**183**, >95% (89)
			$\dfrac{\text{AlMe}_3}{\text{Bu}_3\text{SnH}}$	**184**, >95% (83)
	$\text{BF}_3\cdot\text{OEt}_2$ **177**	**182**, >95% (89)	$\dfrac{\text{AlMe}_3}{\text{Bu}_3\text{SnH}}$	**185**, >95% (81)
			$\dfrac{\text{Bu}_2\text{BOTf}}{\text{Bu}_3\text{SnH}}$	**186**, >95% (90)

Similarly, by application of titanium-mediated aldol reactions, Crimmins and Slade reported a thiazolidinethione chiral auxiliary approach that was used for the formal synthesis of 6-deoxyerythronolide B (Scheme 1.43.).[54] The sequence was iterated five times during a 23 step synthesis. This was an excellent example where a chiral auxiliary was used for an iterative approach to a polypropionate natural product.

Scheme 1.43.

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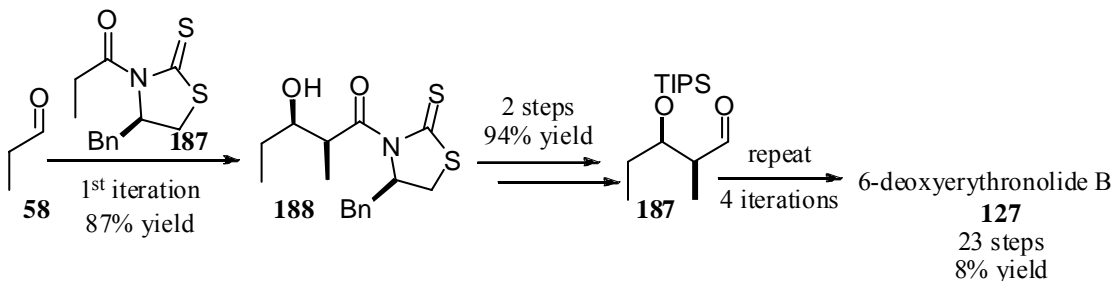
Lastly, Nelson and co-workers reported an asymmetric catalytic approach employing a [2+2] cycloaddition reaction of ketene **191** (derived from propionyl chloride) with achiral aldehyde **190** in the presence of 10 mol % of chiral (non-racemic) **192** for the total synthesis of (−)-pironetin (Scheme 1.44.).[99] Nelson and co-workers also
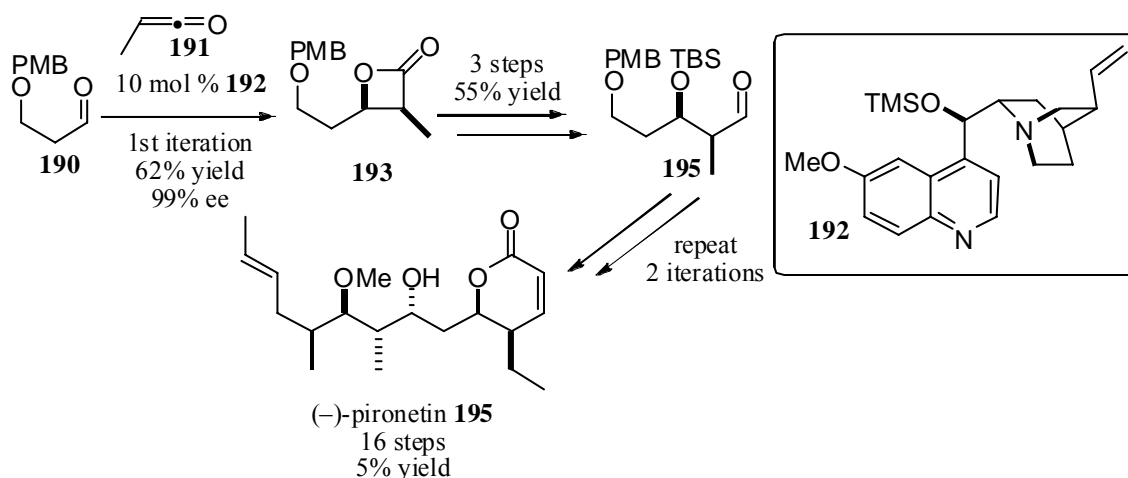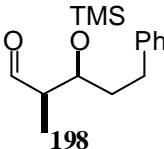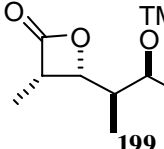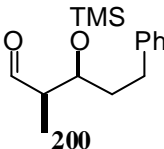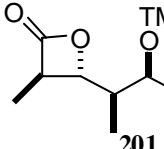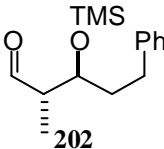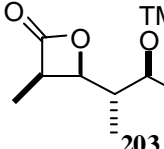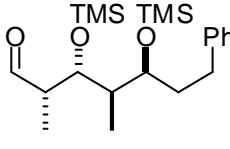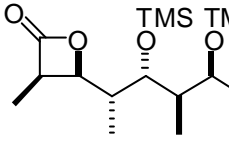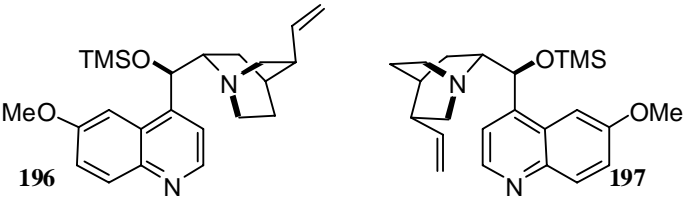
Scheme 1.44.

demonstrated that the same approach could be applied to chiral (non-racemic) aldehydes (Table 1.4.). In these cases, the authors suggested that the diastereoselectivities of the reactions were enhanced by double stereodifferentiation.[xix] By employing either diastereomer of quinine derived catalysts (**196** and **197**, β-lactones (**199-205**) were selectively obtained in good yields and in high diastereomeric excess.

[xix] Although Nelson and co-workers referred to this as double stereodifferentiation, these were actually diastereoselective reactions since catalyst **196** and **197** are diastereomers (not enantiomers).

Table 1.4. Acyl halide-aldehyde cyclocondensation of chiral (non-racemic) aldehydes.

catalyst	aldehyde	β-lactone	% de (% yield)
196	**198**	**199**	≥95 (83)
197	**200**	**201**	≥91 (81)
196	**202**	**203**	≥95 (81)
197	**204**	**205**	≥95 (83)
	196 / **197**		

Overcoming the challenges inherent to the synthesis of polypropionate compounds during the last three decades has greatly contributed to the development of 'asymmetric synthesis' (*i.e.* acyclic control). Although the aforementioned approaches presented very interesting and unique features that were exploited for the synthesis of various polypropionate compounds, many strategies required access to expensive[xx] chiral (non-racemic) starting materials and/or reagents. As a result, there is a continuous demand for

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[xx] Either in terms of cost and/or effort required for preparation.

effective protocols that are both highly efficient and cost-effective with controllable access to chiral (non-racemic) polypropionate compounds.

1.3.2. Thiopyran route to polypropionates

Among all the strategies used for the synthesis of polypropionate compounds, the aldol reaction has found numerous applications and has been successfully applied for the total syntheses of many polypropionate natural products.[105-110] While the occurrence of acylic aldol reactions are frequently encountered, cyclic variants are less common. In particular, thiopyran-derived compounds are useful templates to facilitate access to polypropionate synthetic targets.[111-115] An attractive strategy for polypropionate synthesis involves aldol reactions of tetrahydro-4*H*-thiopyran-4-one derivatives followed by desulfurization.[112, 116]

During the last decade, extensive exploration of this approach was conducted by Ward and co-workers.[116-124] Efforts to effect rapid access to stereochemically diverse tetrapropionate and hexapropionate synthons[xxi] *via* iterative two-directional and simultaneous aldol reactions of tetrahydro-4*H*-thiopyran-4-one derivatives with 1,4-dioxa-8-thispiro[4.5]-decane-6-carboxaldehyde **207** or *meso/dl* 1,4-dioxa-8-thiaspiro[4.5]decane-6-10-dicarboxaldehyde **208**, respectively were investigated (Scheme 1.45.). The challenge of selectively preparing hexapropionate **214** is revealed when considering the 512 possible diastereomers (*i.e.* 1024 possible stereoisomers).

[xxi] Defined as a structural unit within a molecule which is related to a possible synthetic operation.

iterative two-directional homologation   simultaneous two-directional homologation
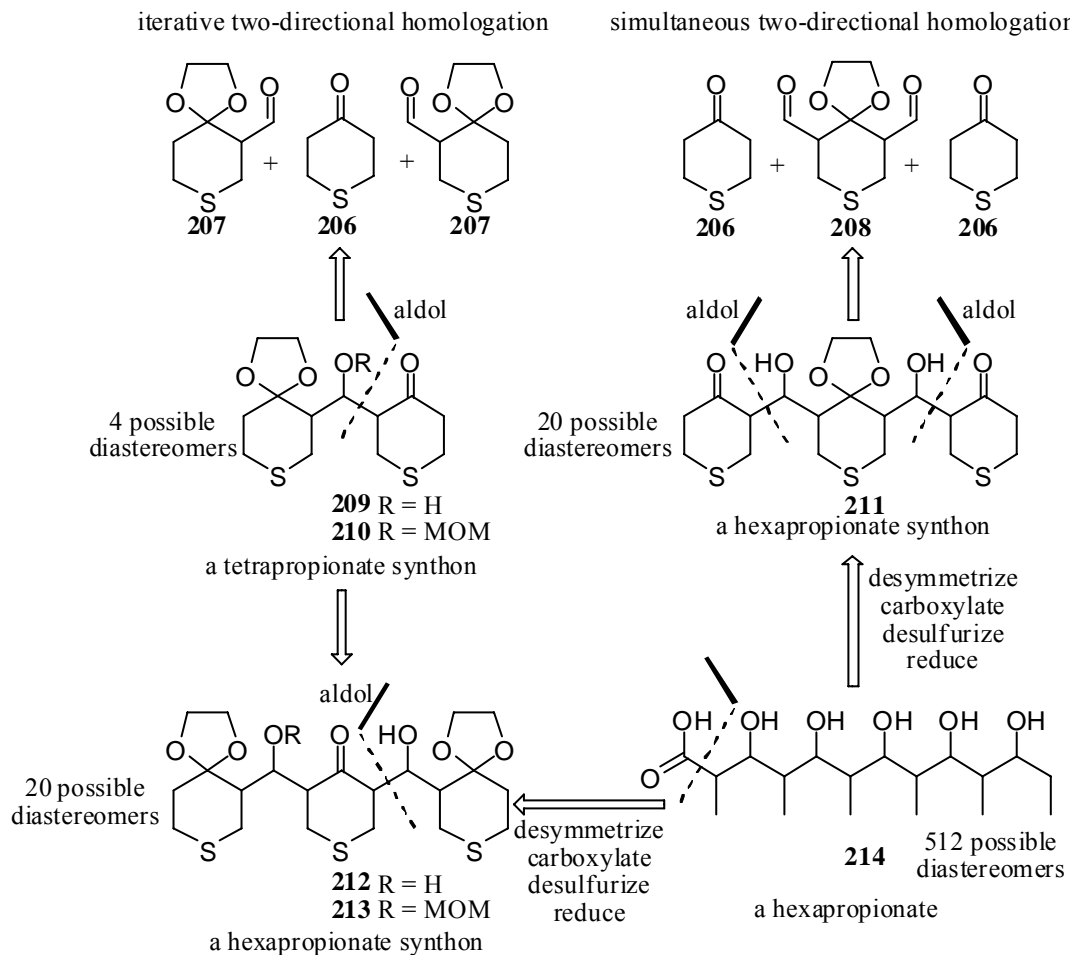
Scheme 1.45.

Disconnection of the carboxyl group of hexapropionate **214**, functional group manipulations and adjustments of oxidation states provides bisaldol adducts **212** and **213**, where the number of possible diastereomers is reduced (by design) to only 20. For example, bisaldol adduct **211a** was obtained by simultaneous two-directional boron-mediated aldol coupling of thiopyranone **206** and *meso* dialdehyde **215** (Scheme 1.46.). Moreover, 11 of the 20 possible bisaldol adducts were obtained by iterative two-directional aldol couplings of thiopyranone **206** (or silyl enol ether **218**) and aldehyde **207** (Schemes 1.47-1.51).

Scheme 1.46.

Scheme 1.47.

(±)-**209as** R = H

Ti-enolate
(±)-**207**

meso **212a** 82% yield

(−)-**210as** R = MOM
(±)-**210as** R = MOM

Ti-enolate
(*S*)-**207**
(±)-**207**

(−)-**213a** 70% yield
(±)-**213a** 34% yield

(−)-**210as** R = MOM
(±)-**210as** R = MOM

Ti-enolate
(*R*)-**207**
(±)-**207**

(−)-**213b** 55% yield
(±)-**213b** 32% yield

Scheme 1.48.

(+)-**209ss** R = H
(±)-**209ss** R = H
(±)-**210ss** R = MOM

Ti-enolate
(±)-**207**

(+)-**212b** 51% yield
(±)-**212b** 53% yield

Ti-enolate
(±)-**207**

(±)-**213c** 27% yield

(±)-**213d** 25% yield
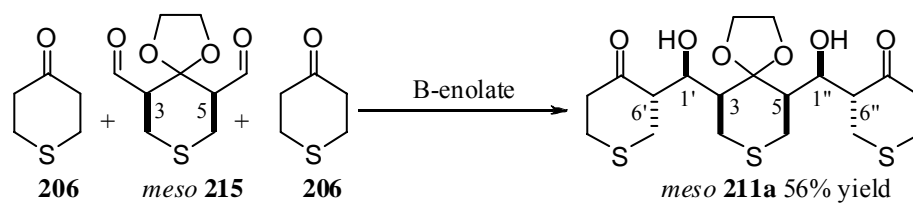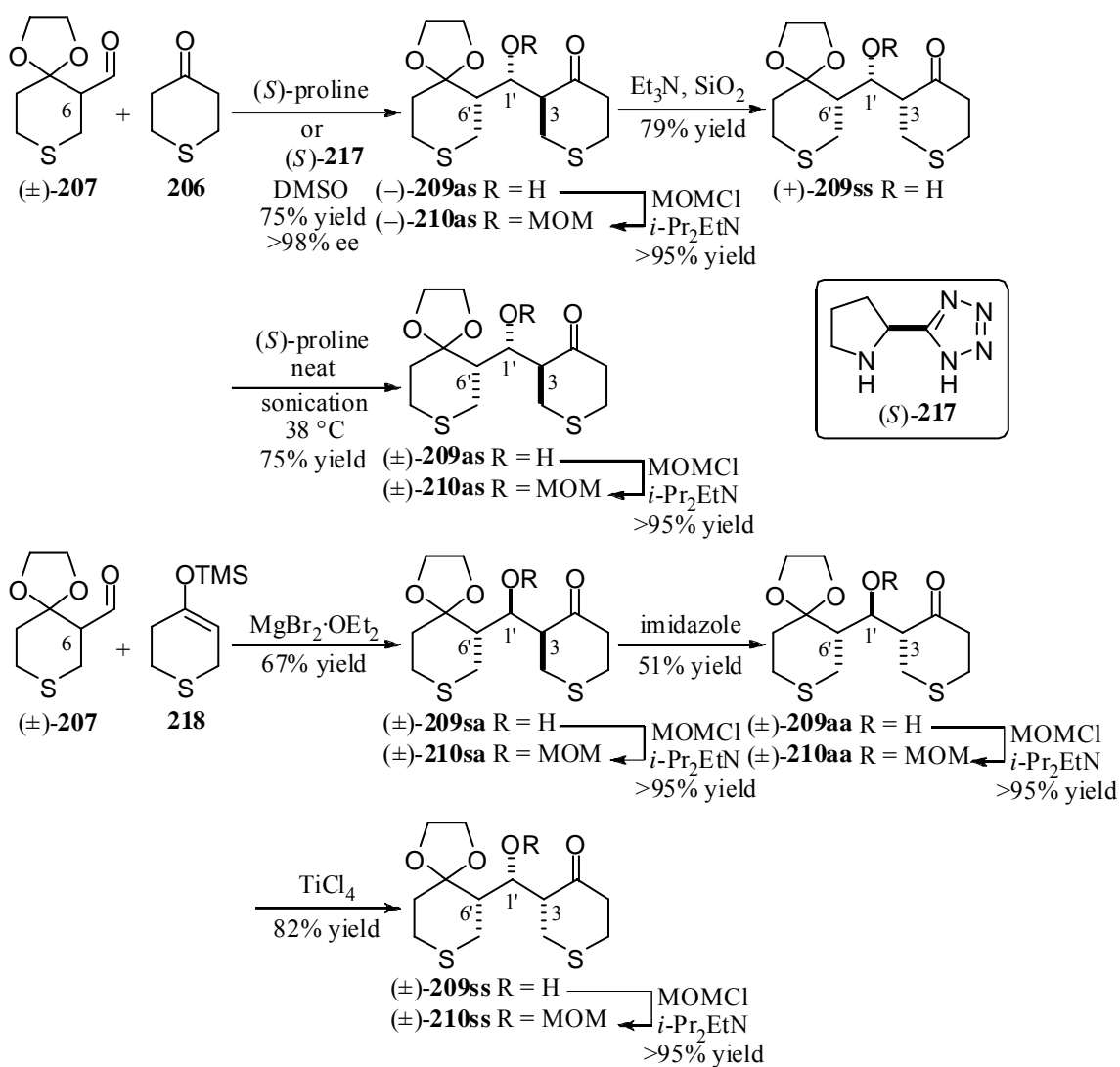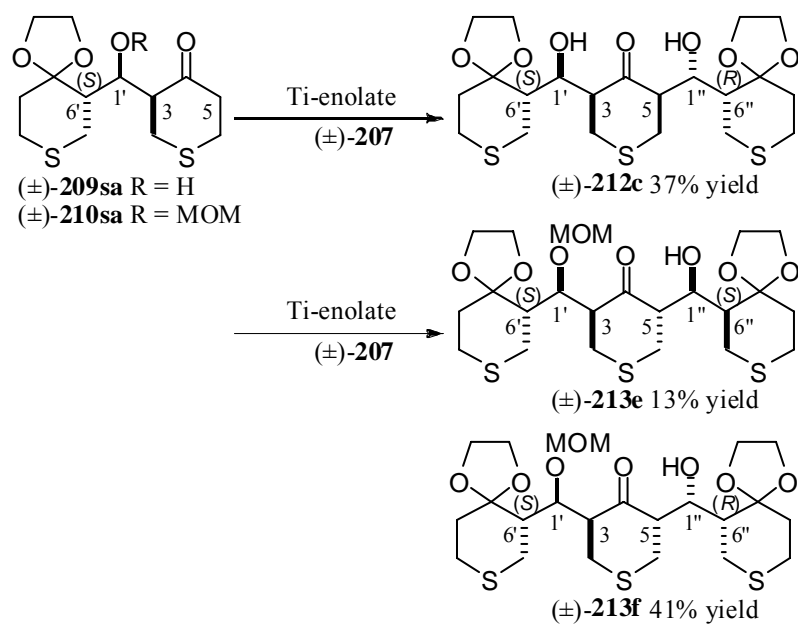
Scheme 1.49.
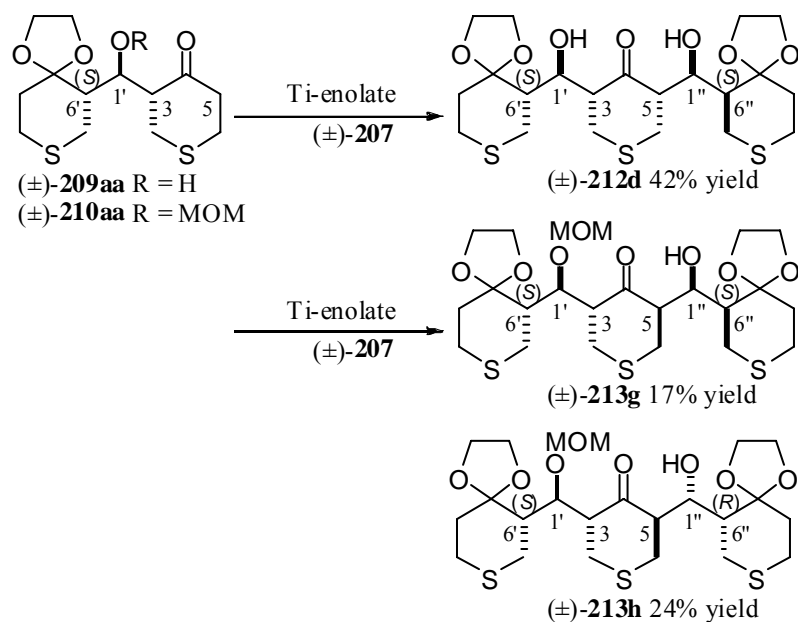
Scheme 1.50.

Scheme 1.51.

Perhaps the most impressive (or unique) result was the aldol coupling of (±)-**209as** with (±)-**207** that provided *meso* bisaldol adduct **212a** in 82% yield (Scheme 1.48.). A remarkable outcome considering that such a union could produce eight diastereoisomers (four each from the *like* and *unlike* combinations of the reactant enantiomers where the

like combination refers to the same absolute configurations at C-6′ of (±)-**209as** and C-6 of (±)-**207**, while *unlike* refers to the opposite absolute configurations at C-6′ of (±)-**209as** and C-6 of (±)-**207**).[xxii] The aldol couplings of (±)-**209** or (±)-**210** with (±)-**207** offers the opportunity to exploit double stereodifferentiation (DS)[37-45, 125, 126] and Ward *et al.* elegantly demonstrated that reactions of β-hydroxy ketones (e.g. (±)-**207**) with (±)-**209** occurred with high DS and high MKE[xxiii], while reactions of β-alkoxy ketones (e.g. (±)-**207**) with (±)-**210** occurred with low DS and low MKE. For example, reaction of (±)-**209as** and (±)-**207** gave *meso* bisaldol adduct **212a** in 82% yield (Scheme 1.48.) which resulted from a combination of reactants where the absolute configurations at C-6′ of (±)-**209as** and C-6 of (±)-**207** are *unlike*. This aldol coupling occurred with high DS and MKE and the *unlike* reaction is remarkably diastereoselective. Alternatively, reaction of (±)-**210as** and (±)-**207** furnished two bisaldol adducts (±)-**213a** and (±)-**213b** in 34% and 32% yield, respectively (Scheme 1.48.). Examination of bisaldol adducts (±)-**213a** and (±)-**213b** reveal that (±)-**213a** resulted from a *like* reaction while (±)-**213b** resulted from an *unlike* reaction. This aldol coupling occurred with low DS and MKE (*ca.* 1.1); however, both the *like* and *unlike* reactions are remarkably diastereoselective (only one product from each *like* and *unlike* reactions). Despite the low DS and MKE, such a result offered the opportunity to exploit double stereodifferentiation for the synthesis of bisaldol adducts (−)-**213a** and (−)-**213b** by employing chiral (non-racemic) starting materials. Indeed, Ward and co-workers were successful in selectively

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[xxii] The combination of reactant enantiomers that leads to product **212** (or **213**) is conveniently characterized by comparing the configurations at C-6′ and C-6″ of bisaldol adduct **212** (or **213**).

[xxiii] Mutual kinetic enantioselection (or resolution) is the reaction between two chiral racemic compounds that produce chiral racemic product(s) and can be evaluated by the sum of the products resulting from a *like* combination of starting materials divided by the sum of the products resulting from an *unlike* combination of starting materials.

synthesizing bisaldol adducts (–)-**213a** and (–)-**213b** by reaction of (–)-**209as** with (*S*)-**207** and (*R*)-**207** in 70% and 55% yield, respectively. The diastereoselectivities for the aldol couplings of **209** and **210** were rationalized by cyclic titanium-enolates **219** and **220**
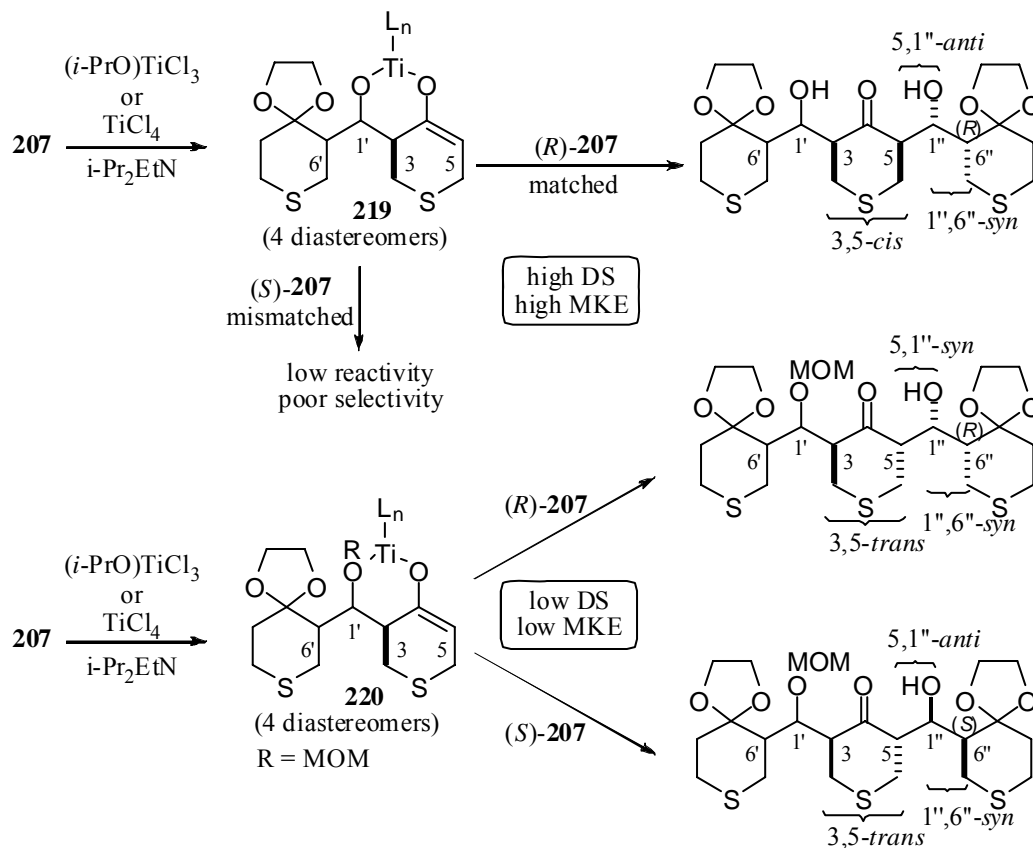
Scheme 1.52.

(Scheme 1.52.) and considering three stereocontrol elements; the enolate and aldehyde diastereoface selectivities and the aldol relative topicity.[122] Aldol couplings of β-hydroxy ketones (**209**) occurred with substantial MKE and gave a major (or sole) product that resulted from: 1) Felkin diastereoface addition of **207** to give 1″,6″-*syn* relative configuration; 2) addition of enolate **219** to give 3,5-*cis* relative configuration; and 3) 5,1″-*anti* aldol relative topicity. Aldol couplings of β-alkoxy ketones (**210**) occurred with low MKE that gave two products from reactions that have the same diastereoface

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selectivity of enolate **220** (3,5-*trans*) and aldehyde **207** (1″,6″-*syn*) but differ in the aldol relative topicity (5,1″-*anti vs.* 5,1″-*syn*). The effects of DS and MKE were attenuated using β-alkoxy ketones (**210**) and provided access to different bisaldol adducts. By extension to the other diastereomers of **209** and **210** (Schemes 1.48-1.51.), Ward and co-workers demonstrated that 11 of the 20 possible bisaldol diastereomers can be produced in 2-3 steps which should serve as a source of stereochemically diverse hexapropionate synthons for polypropionate synthesis.

1.4. Conclusions

The development of methodologies for the total synthesis of polypropionate natural products embodies a very active area of research. Many different strategies have been developed; however, new methodologies applying more efficient and cost effective strategies are required. In particular, general methods that provide controlled access to any given stereoisomer. Equally important is the development of protecting group chemistry that enables efficient functional group manipulations of substrates that are compatible with other functional groups and/or reagents.

1.5. Objectives of this thesis

An advantage of the thiopyran template (*i.e.* thiopyran route to polypropionates) is the possibility of desymmetrization of *meso* (and chiral) diastereomers of bisaldol adducts **221** by extension of the well-established enantioselective enolization of six-membered cyclic ketones (Scheme 1.53.).[127, 128] Enantiotopic group selective processes

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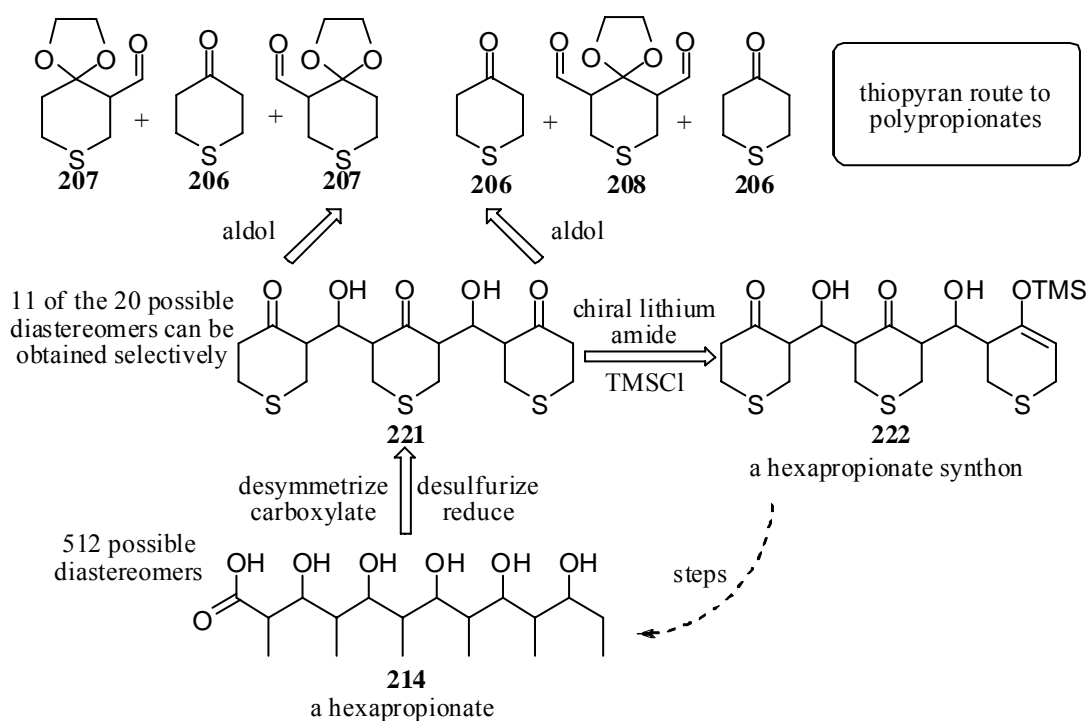
Scheme 1.53.

where the two enantiotopic groups can sequentially react are very powerful methods to obtain highly enantiomerically enriched products in good to excellent yields.[129] The requirements of this approach are: 1) ease of access to C_s (or C_i) symmetric starting materials, 2) a group selective reaction with at least modest group selectivity ($E > 6:1$) and 3) ease of recycling bis-reacted material. Ketone enolization is an ideal reaction for these processes because it is both synthetically useful and easily reversible. Reversibility of enantiotopic group selective processes are especially important to improve the efficiency and efficacy of processes with modest enantioselectivities. Enantiotopic group selective enolization of *meso* diketones was unknown until this work; however, examples of kinetic resolution and enantioselective desymmetrization of chiral and achiral C_s (or C_i) symmetric ketones by enolborination[127] or by enolization with chiral lithium amides[130-137] are known (Scheme 1.54.). Kinetic resolution and enantioselective desymmetrization are
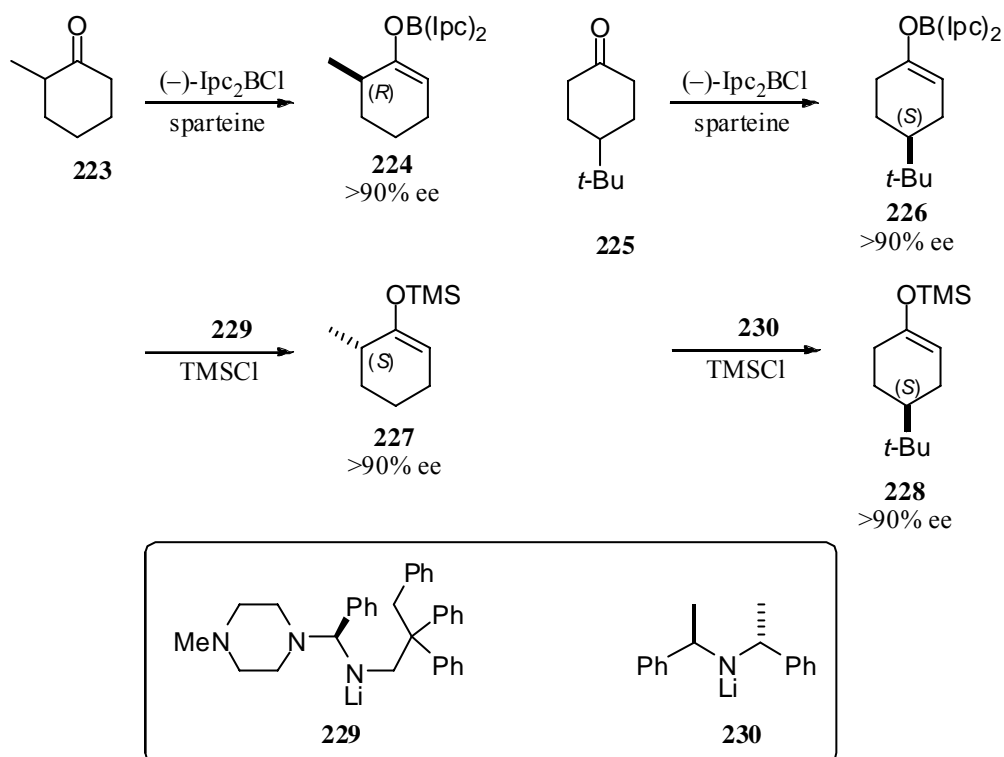
Scheme 1.54.

equivalent to an enantiotopic group selective reaction; groups on enantiomeric substrates are enantiotopic by external comparison, while groups on C_s (or C_i) symmetric substrates are enantiotopic by internal comparison.[138] The requirement to apply an enantioselective enolborination or enolization demands access to suitably protected *meso* diketones. Ward and co-workers established a synthetic route to a *meso* 1,9-diketone **233** (Scheme 1.55.) however, they were unable to effect enantioselective enolborination; unreacted **233** was recovered after treatment with (–)-Ipc$_2$BCl and sparteine.[121] Alternatively,
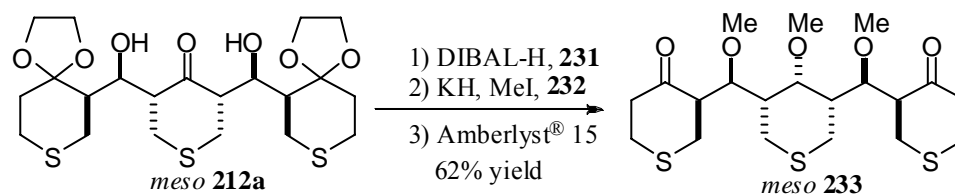
Scheme 1.55.

enantioselective enolization of *meso* **233** could be achieved by reaction with chiral

lithium amide (CLA) **230** and TMSCl. . The research objectives in this thesis were:
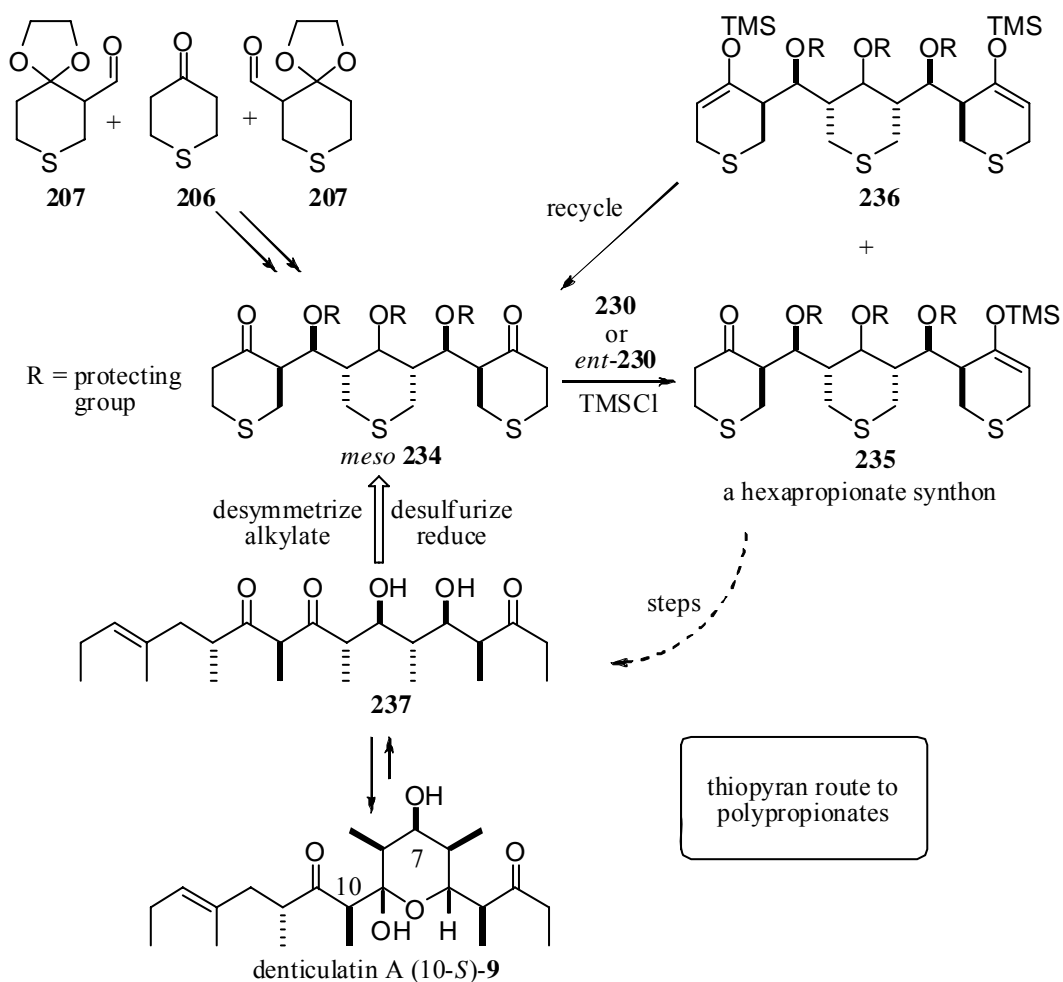
Scheme 1.56.

1) establishment of an efficient process (*i.e.* including recycling) for the enantioselective

enolization of *meso* 1,9-diktone **233**, 2) determination of the absolute configuration of the

resulting mono-silyl enol ether, 3) desulfurization of a hexapropionate synthon and 4)

application of the developed methodology (*i.e.* thiopyran route to polypropionates) for

the asymmetric synthesis of (−)-denticulatin A (Scheme 1.56.)

CHAPTER 2
2. RESULTS AND DISCUSSION

2.1. Enantioselective desymmetrization

During the last several decades, there has been increasing interest in the preparation

of enantiomerically pure compounds because of their biological and agricultural roles.

There are three fundamentally different approaches for the preparation of

enantiomerically pure compounds: 1) the use of enantiopure starting materials provided

by Nature (*i.e.* the chiral pool), 2) separation of enantiomers by chemical or physical

means (*i.e.* resolution) and 3) preparation from achiral starting materials using chiral

reagents or chiral catalysts (*i.e.* 'asymmetric synthesis').[139] The asymmetric synthesis of

enantiomerically pure compounds from C_s (or C_i) symmetric or *meso* starting materials

(*i.e.* enantioselective desymmetrization) is proving to be a powerful synthetic tool.[140] In

order to effect such transformations, chiral reagents or chiral catalysts are required to

differentiate enantiotopic faces or groups present in the reactant.[141] While many of the

methods developed involve enantiotopic face selective reactions, non-enzymatic[142]

examples involving group selective reactions are less common.

2.1.1. Sequential enantiotopic group selective desymmetrization

Enantiotopic group selective reactions can be classified into two types: 1) external

group selective processes (*i.e.* kinetic resolution) and 2) internal group selective

processes (*i.e.* enantiotopic group selective desymmetrization).[143] An interesting feature

of processes where the enantiotopic groups can react sequentially is the coupling of an

enantiotopic group selective desymmetrization (*i.e.* 'asymmetric synthesis') with a kinetic

resolution to produce products with enhanced levels of enantiopurity (Scheme 2.1.).[121, 129, 144-146] One of the earliest examples of a sequential enantiotopic group (SEG)
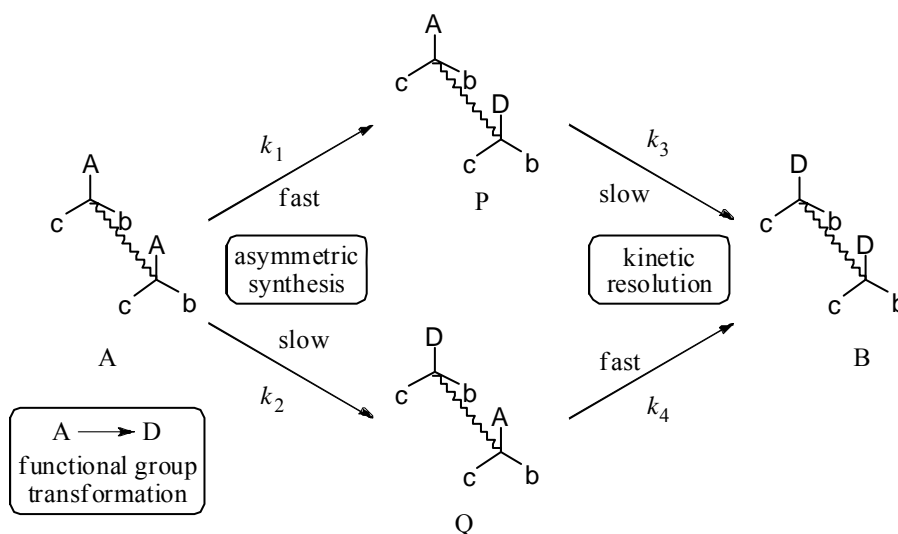
Scheme 2.1.

selective desymmetrization was reported by Sugimoto and co-workers where they demonstrated oxidation of achiral aromatic sulfides with NaIO$_4$ and H$_2$O$_2$ in the presence of bovine serum albumin (Scheme 2.2.).[147] More recently, Nelson and co-workers

Scheme 2.2.
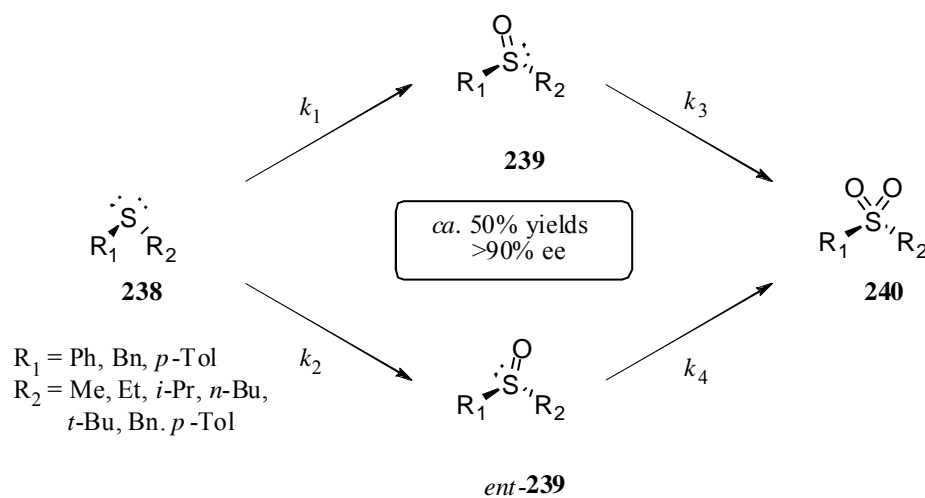
achieved a catalytic desymmetrization of C_i symmetric bis-epoxide **242** by enantiogroup selective epoxide hydrolysis using Jacobsen's chiral salen catalyst **241** during their work

towards the synthesis of an advanced intermediate for the total synthesis of hemibrevetoxin B (Scheme 2.3.).[148, 149] Other examples involving catalytic benzoylation
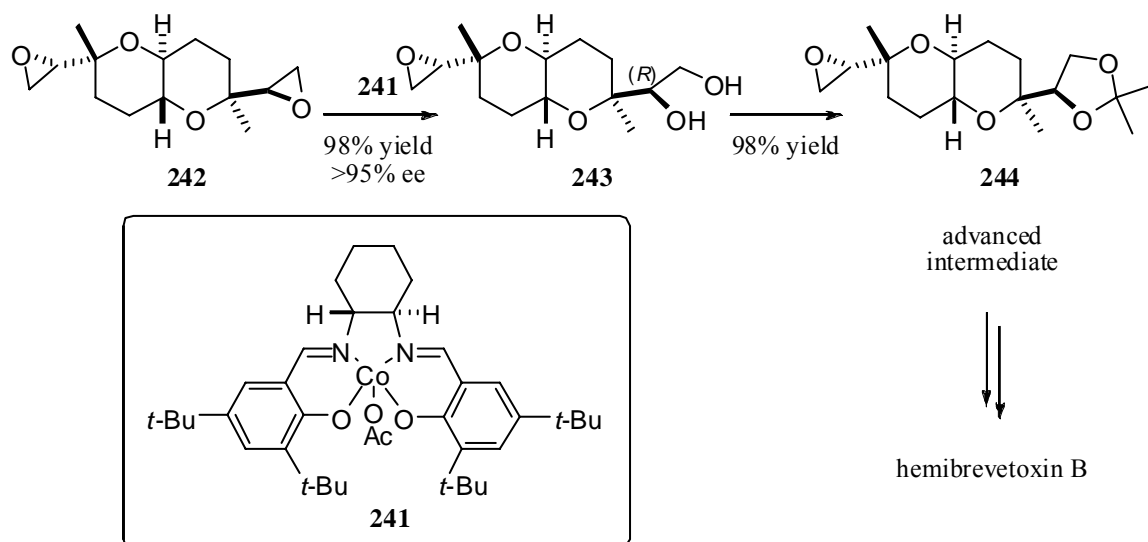
Scheme 2.3.

and silylation of cyclic *meso* diols have also recently appeared (Scheme 2.4.).[150, 151]
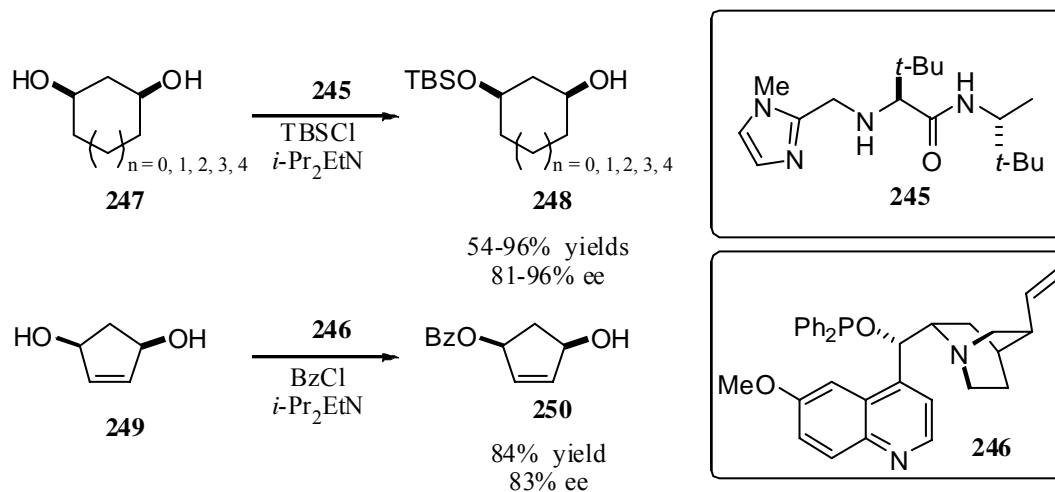
Scheme 2.4.

While these recent examples illustrated the benefits of coupling an enantiotopic group selective desymmetrization with a kinetic resolution, convenient and cost effective

methods for the preparation of stereochemically complex and multifunctional substrates are still unknown.

The requirements for any successful SEG selective desymmetrization necessitate the ease of access to C_s (or C_i) symmetric starting materials and a group selective reaction with at least a modest group selectivity ($s > 6:1$). Furthermore, a group selective reaction where the bis-reacted material can be easily recycled is especially important for those reactions that proceed with modest selectivity. The benefits of SEG selective desymmetrizations are readily illustrated using the well-known theoretical framework for such processes. Figure 2.1. illustrates the calculated[129] results for a hypothetical process (Scheme 2.1.) where the enantiotopic group selectivity ($s = k_1/k_2$) is 6. The yield of products (P+Q) rises and then decreases as the yield of B increases. However, the enantiopurity of the intermediate product (P+Q) continuously increases with conversion to reach any arbitrarily high ratio of P/Q. In this case, the maximum yield of desymmetrized product (P+Q) is 66% with 87% ee (P/Q = 14). In principle, higher levels of enantiopurities can be reached with an appropriate sacrifice in yield. For this example, the same reaction at higher conversion provides 50% yield of desymmetrized product that is 97% ee. The exploitation of the ee enhancement feature of SEG selective desymmetrizations can be successfully achieved with reactions possessing only modest group selectivity; provided the bis-reacted material can be efficiently recycled.
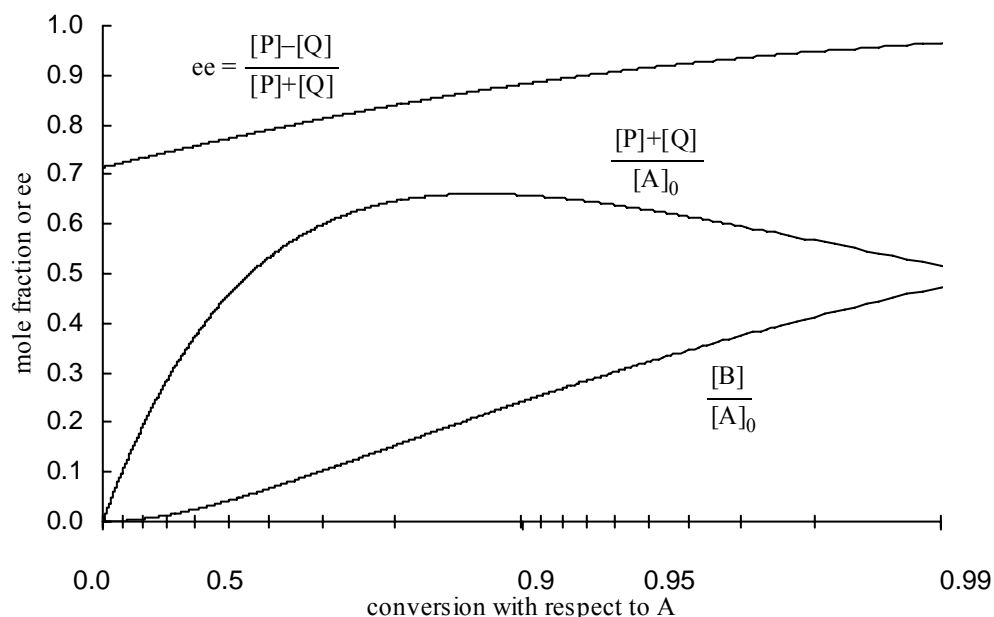
Figure 2.1. Calculated mole fractions of products and ee produced in a hypothetical reaction with an enantiotopic group selectivity ($s = k_1/k_2$) of 6.

(*i.e.*, assuming $k_1 = k_4$; $k_2 = k_3$).

2.1.2. Chiral lithium amides

In 1980, Whitesell and Felman reported the first example of an enantioselective deprotonation of a cyclic *meso* epoxide to give allylic alcohol **252** using chiral lithium amides (CLA) (Scheme 2.5.).[152] The preferred mechanism involves an initial coordination of the CLA followed by a *syn* β-elimination of the enantiotopic *pseudo*-axial protons (*i.e.* external comparison) of the two enantiomeric conformers **252** and *ent*-**252**. Since this initial report, the enantioselective deprotonation of achiral C_s symmetric substrates has resulted in the development of methodologies for the synthesis of a wide range of natural products and other optically active materials.[128] For example, the enantioselective enolization of achiral C_s symmetric cyclic ketones has developed into a
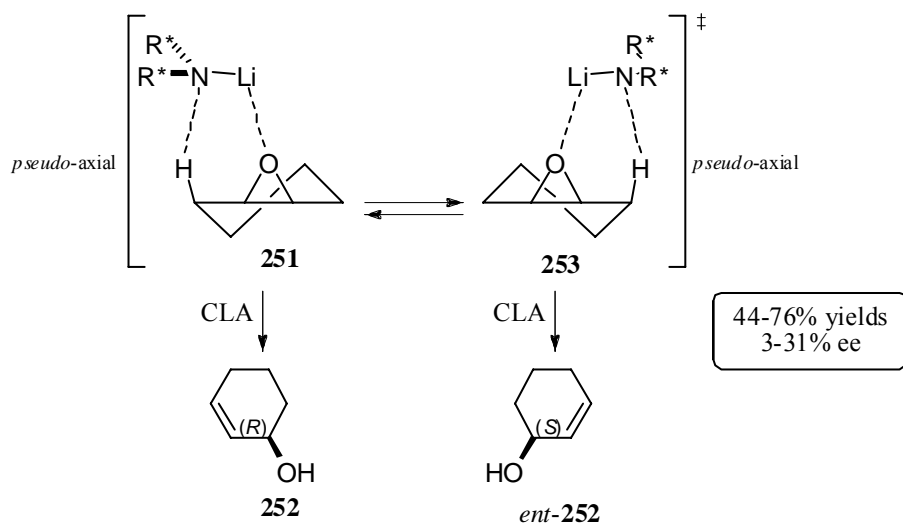
Scheme 2.5.

very powerful strategy for several applications to natural product synthesis.[137, 153-157] For conformationally locked cyclohexanones, there is a stereoelectronic preference for the removal of the axial protons (Scheme 2.6.).[128] The effect of adding lithium chloride was
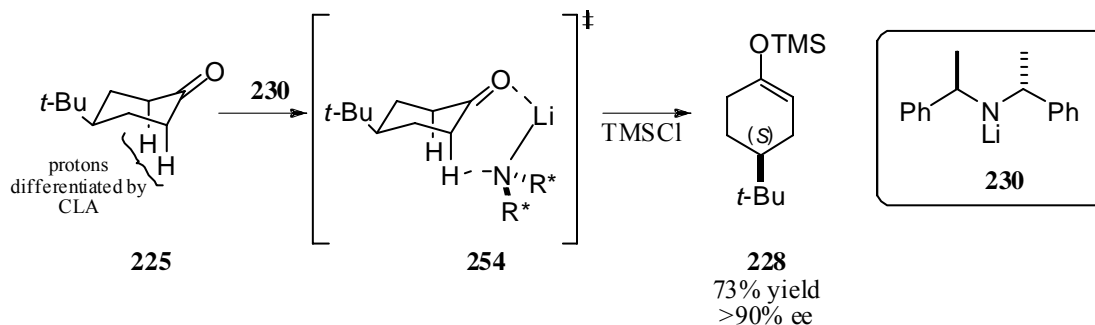
Scheme 2.6.

shown to enhance the levels of enantioselectivities and is believed to occur through reaction of a different aggregated form of the chiral lithium amides (Figure 2.2.). In general, optimal levels of enantioselectivities were observed *via* internal quench conditions (lithium chloride pre-mixed with chiral lithium amide during addition to a

solution of ketone and TMSCl)[158-161] where the mixed dimer **256** is implicated for the more enantioselective processes.
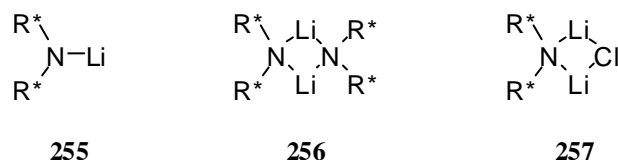
Figure 2.2. Aggregate solution structures of chiral lithium amides.

While chiral lithium amides were successfully used for the enantioselective enolizations of various achiral C_s symmetric ketones,[128] kinetic resolution of chiral ketones are much less frequent. Koga and co-workers demonstrated kinetic resolution of 2-substituted cyclohexanones and established protocols to provide enantioenriched ketones in good yields and enantiopurities (Scheme 2.7.).[135] Although enantioselective

	R_1	R_2	R_3
a	t-Bu	H	H
b	Ph	H	H
c	i-Pr	H	H
d	Me	H	H
e	Me	t-Bu	H (*cis*)
f	i-Pr	H	Me (*trans*)
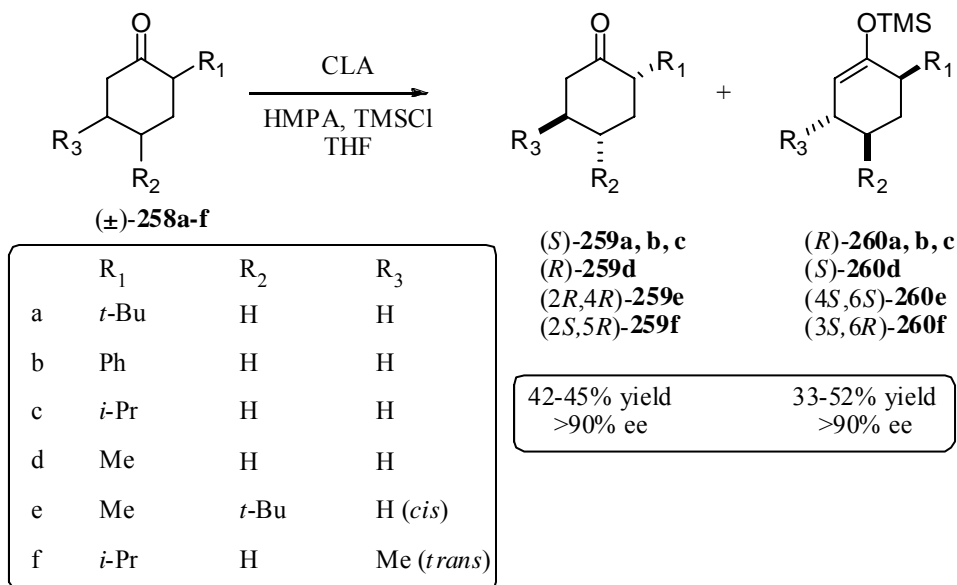
Scheme 2.7.

enolization of achiral C_s symmetric and racemic ketones is well-established, there are no examples of enantioselective enolization of achiral *meso* diketones, where two

independently activated enantiotopic axial hydrogens can react sequentially and thereby exploit the ee enhancement feature of a SEG selective enolization.

2.1.3. Model study

With the requisite access to a *meso* 1,9-diketone **233** established (Scheme 1.55., Section 1.4.), the synthetic potential of a sequential enantiotopic group selective enolization using a chiral lithium amide can be investigated (Scheme 2.8.). While there are more than twenty chiral lithium amides available,[128] chiral lithium amide **230** (or *ent-***230**) was chosen because the precursor amine is commercially available and has been successfully used in numerous enantioselective enolizations of C_s symmetric ketones.

Scheme 2.8.

62
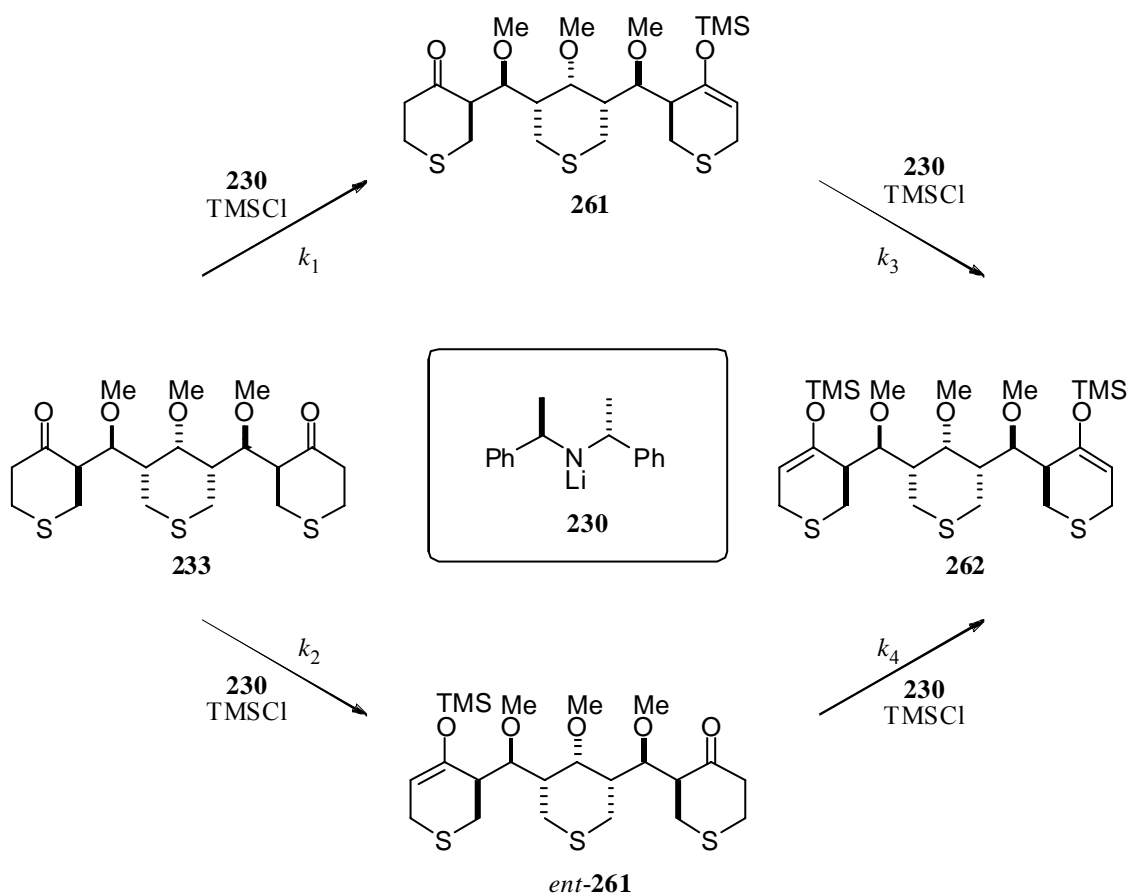
2.1.3.1. Synthesis of *meso* 1,9-diketone 233

While the established procedure for the preparation of *meso* **212a** was sufficient to carry out this study, several key improvements were accomplished during the course of this work. For example, *meso* bisaldol adduct **212a** was previously prepared by aldol coupling of (±)-**207** with the lithium enolate of **206** generated by reaction of **218** with methyllithium, followed by a second aldol coupling of the resulting aldol adduct (±)-**209as** with (±)-**207** (Scheme 2.9.). The two-step sequence provided *meso* bisaldol adduct **212a** in 42% yield; an impressive result considering that six stereocenters are formed in
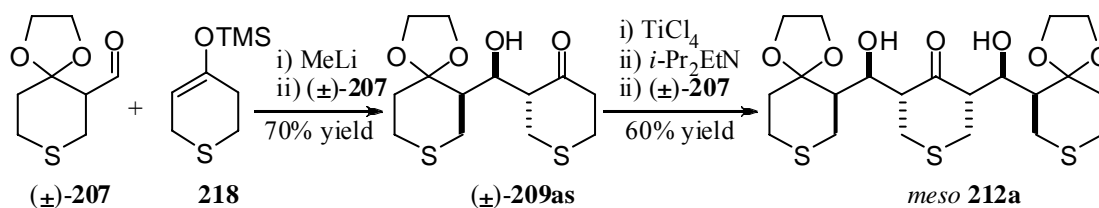
Scheme 2.9.

only two reactions. The required aldehyde (±)-**207** was prepared following a modified[xxiv] Swern oxidation[162, 163] of alcohol (±)-**263** (Scheme 2.10.);[118] however, the yield often varied (*ca.* 10-80%) and was especially problematic on larger scales (*i.e.* 5-20 g). The addition of dimethyl sulfide was believed to reduce chlorination (*i.e. via* chloride exchange) of cyclic sulfide (±)-**264** or Swern activated (±)-**266** and attenuate the formation of decomposition products[xxv] (Scheme 2.10.). While this method was amenable up to *ca.* 1 g scale, yields at higher scales varied and could be extremely poor at 10 g of (±)-**263** (*i.e.* <30% yield of aldehyde (±)-**207** with no recovered

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[xxiv] Addition of 1.0-2.0 equiv of dimethyl sulfide with (±)-**263** during addition to Swern reagent.
[xxv] The significant challenge to optimize this reaction was the absence of any appreciable amounts of decomposition product(s) in the crude material after work-up. This implies that they are water-soluble or volatile materials and as a result the only measurement for optimization was the crude mass recovery.
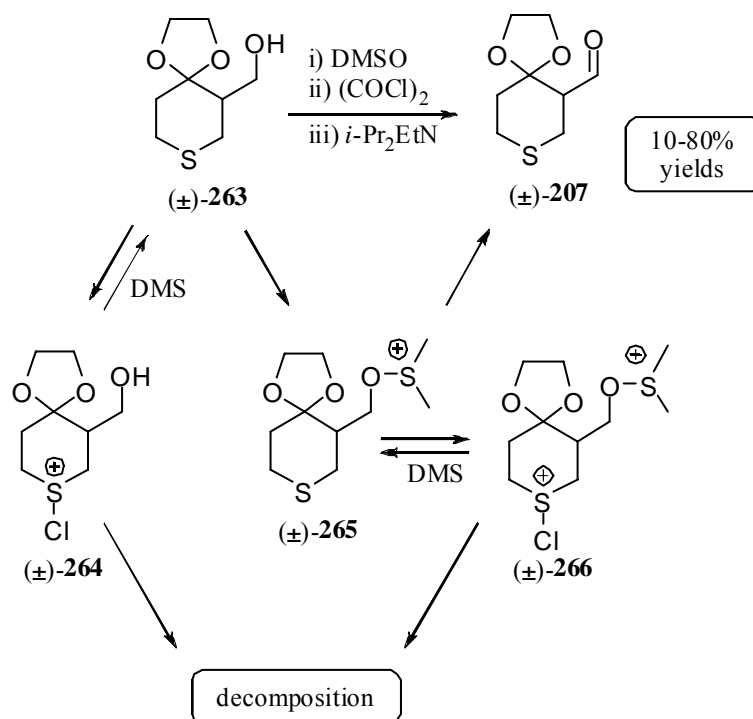
Scheme 2.10.

starting material). After considerable experimentation,[xxvi] it was discovered that replacing dimethyl sulfide with 1 equiv of i-Pr$_2$EtN during the addition of the aldehyde to the Swern reagent consistently provided a 85-89% yield of aldehyde (±)-**207**, accompanied with 3-5% yield of recovered alcohol (±)-**263** on 1-25 g scales This result suggests that the decomposition products result from the presence of HCl during the Swern activation of alcohol (±)-**263** (Scheme 2.11.). Surprisingly, the presence of i-Pr$_2$EtN does not destroy the Swern reagent. This implies that the rate of Swern activation of alcohol (±)-**263** is faster than destruction of Swern reagent. Thus, this example represents a very mild procedure for oxidation of sensitive compounds. It would be interesting to see whether this modification would benefit other difficult oxidations.[164]

[xxvi] Reaction optimizations were performed on *ca.* 1 g of (±)-**263**.
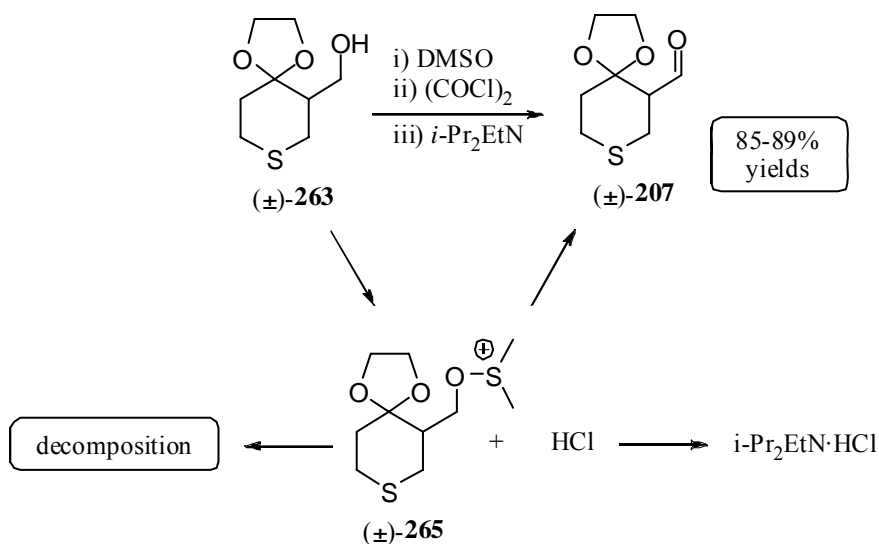
Scheme 2.11.

With access to a scaleable and convenient method for the preparation of aldehyde (±)-**207**, the first aldol reaction was investigated. Ward and co-workers recently demonstrated the enantioselective synthesis of chiral (non-racemic) aldol adduct (−)-**209as** by (S)-proline (or **217**) catalyzed direct aldol reaction of ketone **206** with aldehyde (±)-**207** that occurred with dynamic kinetic resolution (Scheme 2.12).[111, 120] Similarly,
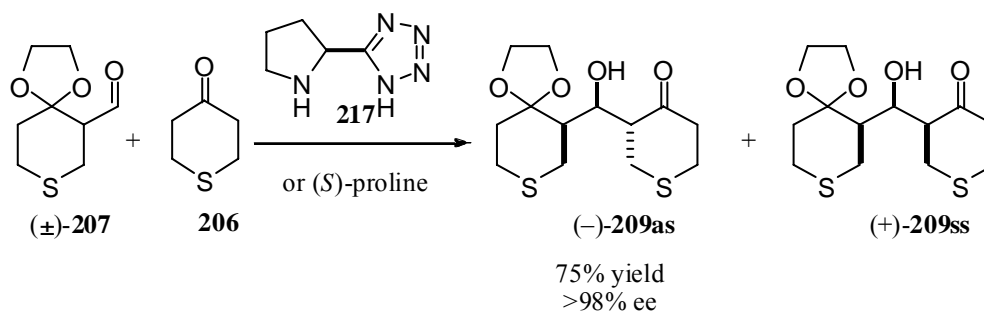
Scheme 2.12.

the synthesis of (±)-**209as** can be prepared from **206** and (±)-**207** using *rac*-proline.[xxvii] Interestingly, the synthesis of aldol adduct (±)-**209as** can be prepared *via* proline

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[xxvii] Investigations done concurrently and in collaboration with Dr. Vishal Jheengut.

catalyzed aldol reaction under solvent-free conditions facilitated by sonication and/or

acid additives. Solvent-free aldol reactions of **206** and (±)-**207** were investigated by

varying the amount of added water, time, temperature and under sonication with *rac*-

proline (Table 2.1.). While aldol reactions of **206** and (±)-**207** at room temperature or 38

°C did not provide any significant amounts of aldol adducts (entries 1 and 2), under

sonication aldol adducts were observed (entries 5 and 8). The presence of water has been

reported[165, 166] to have a beneficial affect for enantio- and diastereoselectivities for proline

catalyzed reactions; however, excess water appears to completely inhibit the reaction at

22 °C and 38 °C under sonication (entries 6 and 7). In light of these results, the amount

of water was reduced to 2 equiv which resulted in high conversion and high

diastereoselectivity of aldol adduct (±)-**209as** (entry 8).

Table 2.1. *Rac*-proline catalyzed aldol reaction of 206 with (±)-207.

entry[a]	**206** (equiv)	H_2O (equiv)	sonication time (d)	total time (d)	temp (°C)	conversion[b] (%)	de[c] (%)
1	1.5	5	0	2	22	0	
2	1.5	5	0	1	38	5	>95
4	1.5	5	2	4	22	0	0
5	1.5	5	1	2	38	42	90
6	1.5	10	2	4	22	0	
7	1.5	10	1	1	38	0	
8	**1.5**	**2**	**3**	**3**	**38**	**94**	**93**

[a] Reactions with (±)-**207** (*ca.* 0.5 mmol) and (*S*)-proline (0.5 equiv). [b] Conversion with respect to (±)-**207**.
[c] Calculated from the ratio of **209as**:**209ss** by ^{1}H NMR analysis of crude reaction mixture.

Interestingly , aldol reaction of **206** with (±)-**207** using (*S*)-proline (Table 2.2.) according

to the optimized conditions for *rac*-proline (entry 8, Table 2.1.) furnished nearly racemic

aldol adduct (±)-**209as**. At this point, it was decided that further optimizations would be

Table 2.2. (*S*)-proline catalyzed aldol reaction of 206 with (±)-207.

entry[a]	**206** (equiv)	H_2O (equiv)	sonication time (d)	total time (d)	temp (°C)	conversion[b] (%)	de[c]	ee[d] (%)
1	1.5	0	0	7	22	0		
2	1.5	0	2	2	22	0		
4	1.5	0	3	3	38	86	86	13
5	3	0	3	3	38	96	83	6
6	6	0	3	3	38	96	92	
7	**1.5**	**1**	**3**	**3**	**38**	**92**	**93**	**11**
8	1.5	2	3	3	38	90	88	13
9	3	2	3	3	38	93	89	
10	6	2	3	3	38	88	92	
11	1.5	4	3	3	38	75	90	17
12	3	4	3	3	38	78	88	
13	6	4	3	3	38	83	90	
14	1.5	8	3	3	38	44	>95	
15	1.5	2	1	1	38	34	>95	
16	1.5	2	1	2	22	42	>95	
17	1.5	2	1	4	22	65	>95	

[a] Reactions with (±)-**207** (*ca.* 0.5 mmol) and (*S*)-proline (0.5 equiv). [b] Conversion with respect to (±)-**207**. [c] Calculated from the ratio of **209as**:**209ss** by ^{1}H NMR analysis of crude reaction mixture. [d] ee was calculated assuming a linear correlation of optical purity and enantiomeric excess; $[\alpha]_D$ (max) for (−)-**209as** = −47 at ambient temperature (*ca.* 23 °C), *c* = 1.0, $CHCl_3$.

conducted using (*S*)-proline as this would offer a more economical[xxviii] approach for the preparation of aldol adduct (±)-**209**. Additional optimizations involving varying the amount of ketone, water, time and temperature under sonication gave results essentially identical to those obtained with *rac*-proline (entry 7, Table 2.2. vs. entry 8, Table 2.1.). The low enantiopurity along with the high diastereoselectivity was intriguing and prompted a time-course study to investigate any conversion dependency of the enantioselectivity (Table 2.3.). Indeed, higher enantiopurities of (−)-**209as** were higher at low conversion which suggests a possible kinetic resolution mechanism.[167-169] The presence of water clearly enhances the enantiopurity of the aldol adduct, while the diastereoselectivities obtained with 1-4 equiv of water were quite similar.

[xxviii] (*S*)-proline is *ca.* 40× cheaper than its racemate.

Table 2.3. Time course study of (*S*)-proline catalyzed aldol reaction of 206 with (±)-207.

entry[a]	H_2O (equiv)	sonication time (d)	total time (d)	temp (°C)	conversion[b] (%)	de[c] (%)	ee[d] (%)
1	0	0.5	0.5	38	43	87	21
2	0	2	2	38	86	86	13
3	1	0.5	0.5	38	27	>95	55
4	1	1.5	1.5	38	50	>95	47
5	1	3	3	38	92	93	11
6	2	0.5	0.5	38	23	>95	64
7	2	3	3	38	90	88	13
8	4	0.5	0.5	38	13	>95	77
9	4	2	2	38	57	92	43
10	4	3	3	38	75	90	17

[a] Reactions with (±)-**207** (*ca.* 0.5 mmol), **206** (1.5 equiv) and (*S*)-proline (0.5 equiv). [b] Conversion with respect to **207**. [c] Calculated from the ratio of **209as**:**209ss** by ^{1}H NMR analysis of crude reaction mixture. [d] ee was calculated assuming a linear correlation of optical purity and enantiomeric excess; $[\alpha]_D$ (max) for (−)-**209as** = −47 at ambient temperature (*ca.* 23 °C), *c* = 1.0, CHCl$_3$.

This result suggests that aldehyde (±)-**207** does not readily isomerize under solvent free conditions compared to the aldol reaction. Addition of bases to the reaction mixture dramatically reduced the diastereoselectivities with no effect on enantiopurities (entries 1 and 2, Table 2.4.). For example, the addition of imidazole resulted in an equilibrium ratio for **209as**:**209ss** of 1:1.5, with both aldol adducts in low enantiopurity (entry 2). However, the addition acetic acid facilitated the aldol reaction without the requirement of sonication at room temperature or 38 °C (entry 4). Adapting the reaction conditions in entry 4 (Table 2.4.), nearly racemic **209as** (<20% ee) was obtained in 90% yield on gram scale. This procedure has several advantages over the previously reported lithium-enolate procedure.[118] It is simple and cost effective and the requirements of low temperatures and inert atmosphere are avoided. Lastly, the aldol adduct (±)-**209as** can be obtained by simple trituration of the crude reaction mixture allowing the procedure to be easily performed on multigram scales.

Table 2.4. (*S*)-proline catalyzed aldol reaction of 206 with (±)-207 with acid or base additives.[a]

entry[a]	additive (equiv)	sonication time (d)	total time (d)	temp (°C)	conversion[b] (%)	de[c] (%)	$[\alpha]_D$[d]
1	Bu₃N (1.0)	3	3	38	79	69	−7
2	imidazole (1.0)	3	3	38	83[e]		−7[f]
3	AcOH (0.3)		2	22	56	>95	−12
4	**AcOH (0.3)**		**2**	**38**	**98**	**>95**	**−9**

[a] Reactions with (±)-**207** (*ca.* 0.5 mmol), **206** (1.5 equiv), water (2.0 equiv) and (*S*)-proline (0.5 equiv). [b] Conversion with respect to (±)-**207**. [c] Calculated from the ratio of **209as**:**209ss** by ¹H NMR analysis of crude reaction mixture. [d] At ambient temperature (*ca.* 23 °C); *c* = 1.0, CHCl₃; $[\alpha]_D$ (max) for (−)-**209as** = −47. [e] Equilibrium ratio for **209as**:**209ss** (1:1.5). [f] $[\alpha]_D$ +8 for (+)-**209ss**; $[\alpha]_D$ for *ent*-**209ss** of 90% ee: $[\alpha]_D$ −48, *c* = 1.3, CHCl₃).[119]

The second aldol coupling of (±)-**209as** with (±)-**207** was accomplished according to the reported titanium-enolate method using *i*-Pr₂EtN/TiCl₄.[117] While this procedure furnished *meso* bisaldol adduct **212a** (Scheme 2.9.) in 40-60% yields, further improvements were attained using *i*-Pr₂EtN/(*i*-OPr)TiCl₃[170] that provided yields of 78-85% on multigram scales (Scheme 2.13.). As noted earlier (Section 1.3.2.), this is an
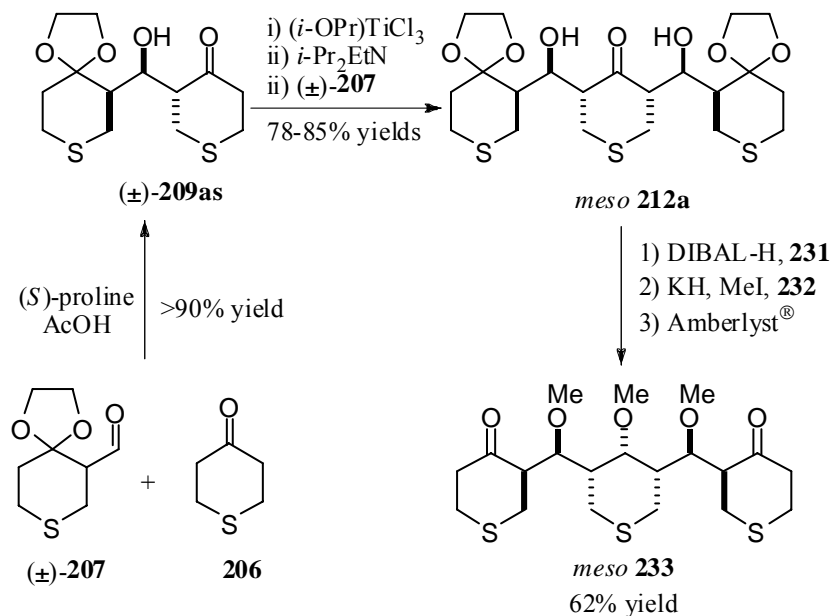
Scheme 2.13.

impressive (perhaps unique) result whereby the coupling of two racemic reactants furnished a *meso* product. Finally, the synthesis of the desired *meso* diketone for the SEG enolization study was achieved by a reduction, protection and deprotection sequence on *meso* bisaldol adduct **212a** that furnished *meso* 1,9-diketone **233** (Scheme 2.13.). This synthetic route provided the rapid assembly of stereochemically complex hexapropionate synthons (*i.e. meso* bisaldol adduct **212a** and *meso* 1,9-diketone **233**; 6-7 stereocenters) on multigram scale and should be applicable to a number of synthetic endeavors.

2.1.3.2. Sequential enantiotopic group selective enolization of *meso* 1,9-diketone 233

Enantioselective enolization of *meso* 1,9-diketone **233** was successfully achieved by deprotonation with **230** (Scheme 2.14.).[121] The yield and ee of **261** are dependent on
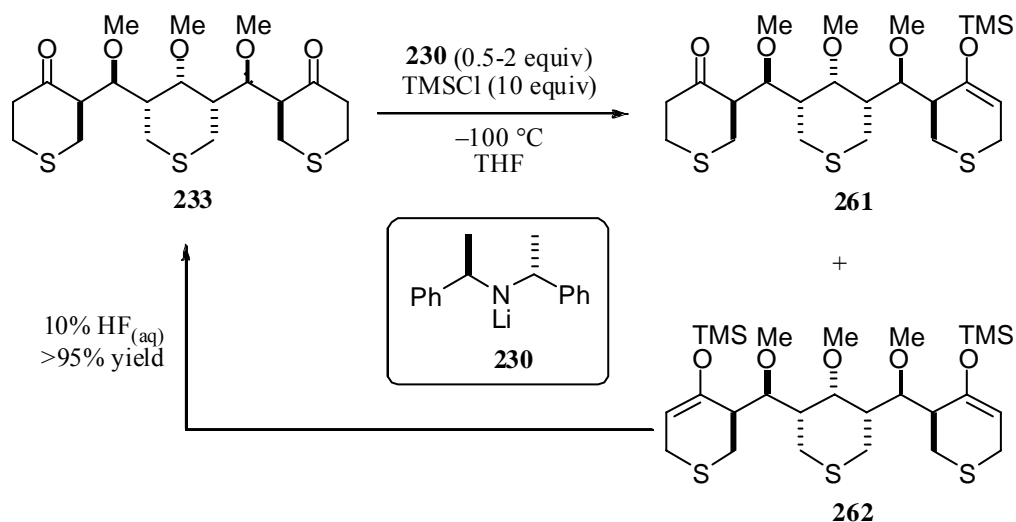
Scheme 2.14.

the reaction enantioselectivity and conversion.[129] The reaction of **233** with **230** was analyzed at various conversions by rapid cannulation of a THF solution of **230** (0.5-2 equiv) at −78 °C to a THF solution of **230** (0.2-0.3 mmol) and TMSCl (10 equiv) at −100

70

°C (Table 2.5.). Under these optimized conditions,[xxix] **261** was obtained in 78% yield with >98% ee. Using similar conditions, reactions using **230** were more selective than those using **230**·LiCl[159, 161, 171] (entries 2 and 6). The expected feature of ee enhancement with increased conversion is evident (entries 1-3; 4, 6 and 8). At low conversions, the er of **261** should approximate the enantiotopic group selectivity for the reaction.[129] Reactions using small amounts of **230** or **230**·LiCl (entries 1 and 4) performed poorly,

Table 2.5. Enantioselective enolization of 233 with 230/TMSCl.

entry[a]	230 (# equiv)	^{1}H NMR ratio[b] 233:261:262	isolated yields (%)		
			233	261 (%ee)[c]	262
1	0.5[d]	71:26:3	70	22 (86)	3
2	1.0[d]	16:69:12	20	61 (90)	12
3	1.4[d]	2:74:24		73 (92)	
4	0.5	86:14:0	78	15 (81)	
5	1.2	52:46:10			
6	1.3	26:67:8	25	61 (94)	8
7	1.4	14:76:9			
8	**1.5**	**4:80:15**		**78 (98)**	
9	1.7	0:62:38		58 (>98)	34

[a] A THF solution of **230** or **230**·LiCl was rapidly cannulated (*ca.* 30 sec) to a THF solution of **233** (0.2-1.5 mmol) and TMSCl (10 equiv) at −100 °C. [b] Crude products after work-up. [c] Determined by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$/CF$_3$CO$_2$Ag. [d] Using **230**·LiCl.

giving **261** in low ee accompanied by an amount of **262** that far exceeded expectations. That is, the product distributions in entries 1 and 4 are similar to a nonselective reaction (*e.g.* using LDA as base). By contrast, a reaction with an enantiotopic group selectivity of 9:1 would not be expected to give 3% of the bis-product until *ca.* 50% conversion.[129]

[xxix] Reactions conducted at −78 °C were very capricious and much less enantioselective. Slow addition of **230** was less enantioselective. External quench (*i.e.* addition of TMSCl after addition of **230**) gave considerably lower conversions.

In order to establish the reaction selectivity,[xxx] the experimental data was compared to those calculated for an idealized group selective process at various enantiotopic group selectivities (s) and mole fractions (χ) according to the equations 2.1.-2.4.[129]

$$\chi_{261} = \chi_{233}^{1/s+1} - \chi_{233} \qquad \text{(eq 2.1.)}$$

$$\chi_{ent\text{-}261} = \chi_{233}^{s/s+1} - \chi_{233} \qquad \text{(eq 2.2.)}$$

$$\chi_{262} = 1 - \chi_{233} - \chi_{261} - \chi_{ent\text{-}261} \qquad \text{(eq 2.3.)}$$

$$ee = (\chi_{261} - \chi_{ent\text{-}261})/(\chi_{261} + \chi_{ent\text{-}261}) \qquad \text{(eq 2.4.)}$$

The observed product distributions (**261** and **262**) and ee of **261** formed in the reaction of **233** with **230** correspond closely with those predicted from a model reaction with an enantioselectivity of *ca.* 17:1 (Figure 2.4.). Although an enantioselectivity of 17:1 is

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[xxx] Assuming the enantiotopic carbonyl groups underwent enolization independently (*i.e.* Scheme 2.8., $s = k_1/k_2$; $k_1 = k_4$, $k_2 = k_3$).
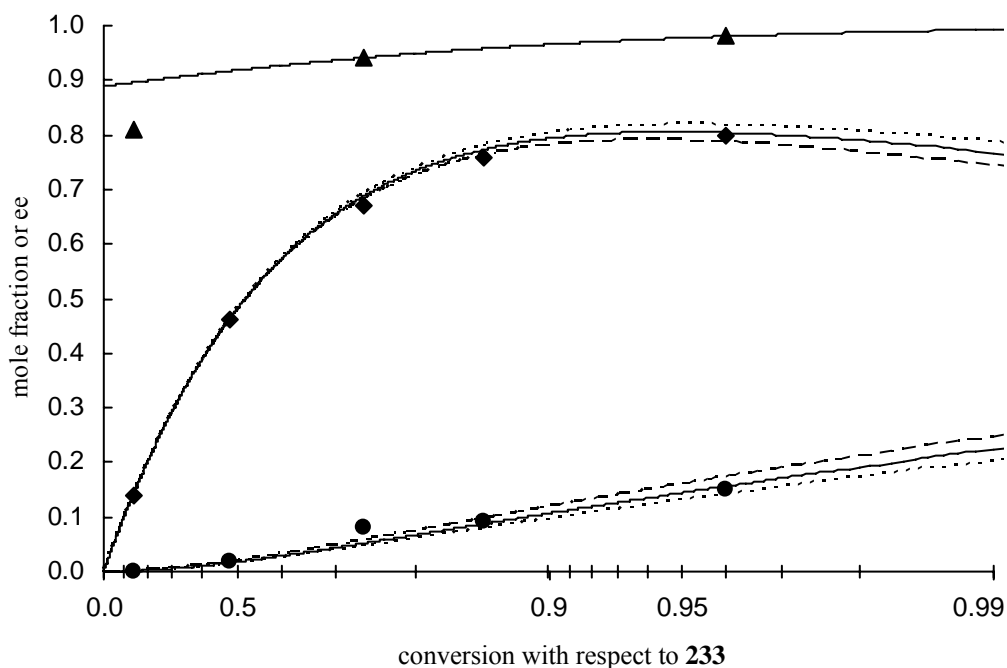
Figure 2.4. Calculated and observed mole fractions of 261 (◆) and 262 (●) and ee of 261 (▲) produced in the reaction of 233 with 230/TMSCl as a function of conversion of 233.

(*i.e.*, assuming $s = 19$ (---), $s = 17$ (—) and $s = 15$ (– –)).

lower than that observed for deprotonation of C_s symmetric cyclohexanones under similar conditions,[128] **261** is easily obtained with greater enantiopurity because of the ee enhancement feature of SEG desymmetrizing reactions. The lower selectivity may result because the initial coordination of lithium amide to ketone is an enantioselective step for *meso* 1,9-diketone **233** (k_{on}) (Scheme 2.15.) but not for C_s symmetrical ketone **268** (Scheme 2.16.).[xxxi] If the enantioselectivity for the coordination step is lower than that for the deprotonation step (as expected), then dissociation (k_{off}) of the complex must be much faster than deprotonation to prevent attenuation of the overall enantioselectivity.

[xxxi] The only enantioselective step for C_s symmetrical ketones is the deprotonation of the axial α-hydrogen.
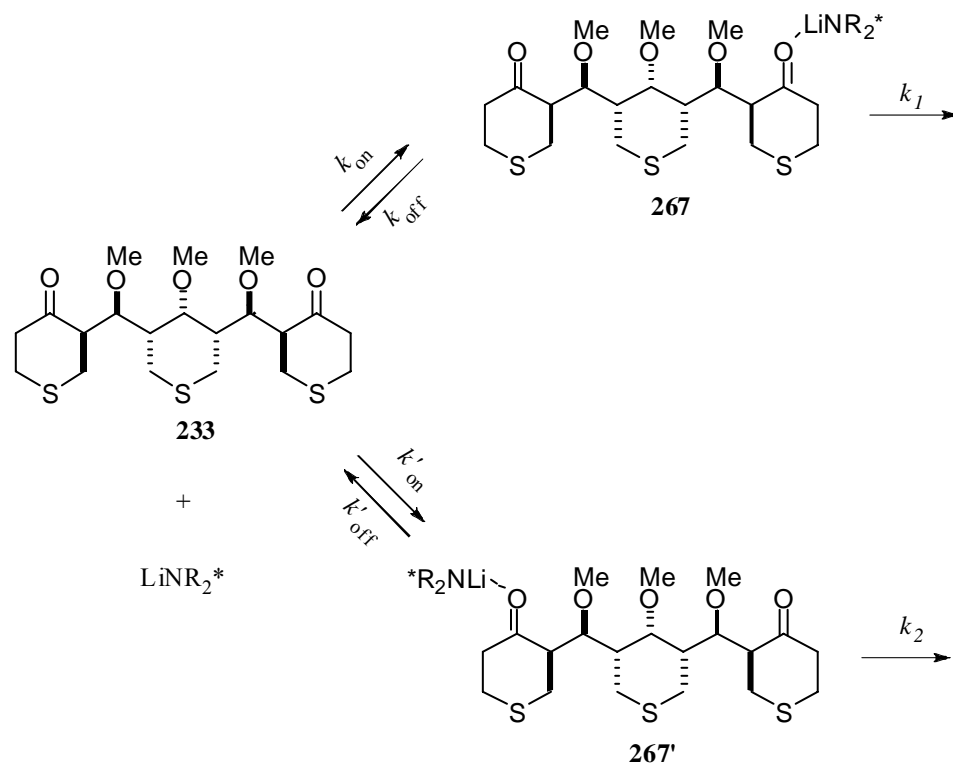
Scheme 2.15.
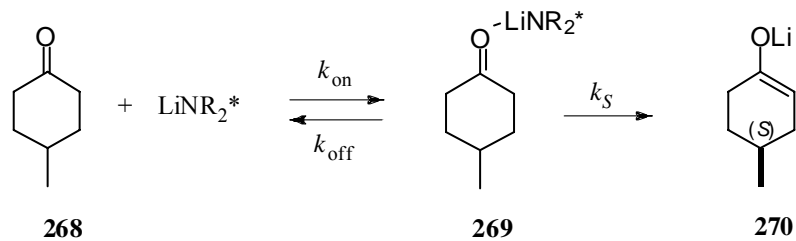
Scheme 2.16.

Reactions of **233** with **230** under the optimized conditions gave the corresponding mono-silyl enol ether **261** in good yields and with excellent enantiopurities. This process is extremely efficient (>90% yield based on recovered diketone **233**) as bis-silyl enol ether **262** is easily recycled to diketone **233** on treatment with $HF_{(aq)}$ (>95% yield) (Scheme 2.14.).

2.1.3.4. Determination of absolute configuration

The absolute configuration of **261** was determined by ^{1}H NMR analysis of the (*R*)-

and (*S*)-*O*-acetylmandelate esters **272** and **273** of the derived alcohol **271** (Scheme 2.17

1) L-Selectride®

2) DCC/DMAP
(*R*)-OAM or (*S*)-OAM

271 R = H, 82% yield
272 R = (*R*)-OAM, 64% yield
273 R = (S)-OAM, 44% yield
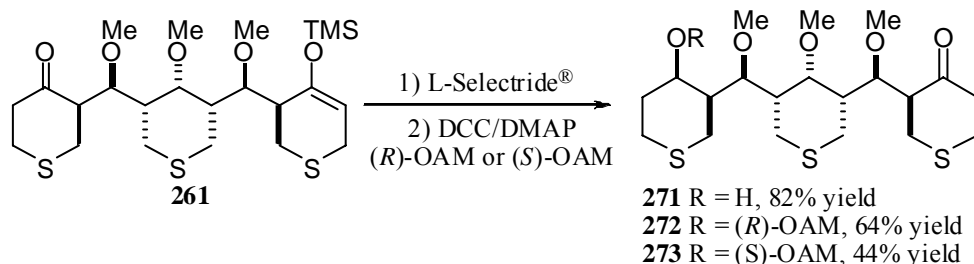
Scheme 2.17.

Table 2.6. ^{1}H NMR chemical shifts for 272 and 273.[a]

proton	δ for **273**	δ for **272**	Δδ (**273–272**)
HC-5" (α)	1.77	1.89	−0.12
HC-5" (β)	2.03	2.36	−0.33
HC-4"	5.08	4.97	+0.11
HC-3"	2.23	2.13	+0.10
HC-1"	2.90	2.16	+0.74
HC-5	1.77	1.44	+0.33
HC-4	3.96	3.71	+0.25
HC-3	1.77	1.61	+0.16
HC-3'	2.71	2.68	+0.03
HC-1'	4.00	3.95	+0.05
H₃COC-1"	3.41	2.94	+0.47
H₃COC-4	3.45	3.32	+0.13
H₃COC-1'	3.31	3.29	+0.02

[a] In cases where assignment of δ_H was difficult because of overlapping signals in the ^{1}H NMR, HSQC cross peaks were used to assign the δ_H value.

and Table 2.6.).[172]   The 3",4"-*cis* relative configurations for **271**, **272** and **273** were

assigned based on the appearance of HC-4" as a broad singlet (all *J*'s <3 Hz) in the ^{1}H

NMR spectra. The NMR assignments for **272** and **273** (Table 2.6.) were based on chemical shifts and multiplicity were confirmed by 1D and/or 2D heteronuclear correlation experiments (i.e. gsCOSY, gsHSQC and/or gsHMBC). Accordingly, the signs of the observed $\Delta\delta$'s indicated that the absolute configuration at C-4" was (R) when using chiral lithium amide **230** (Figure 2.5.).[172] The formation of **261** involves
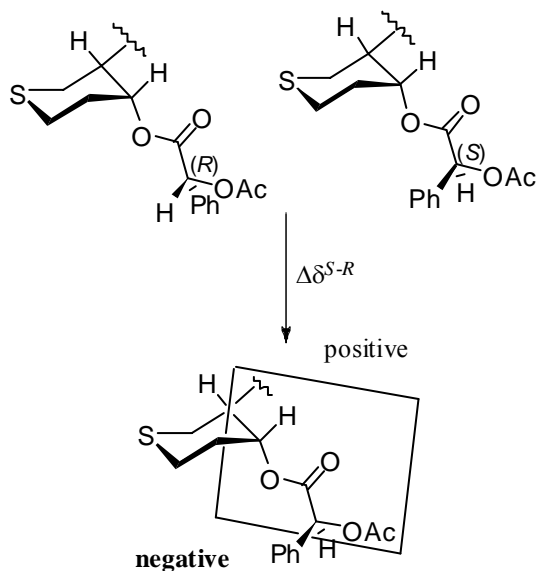
Figure 2.5. Model for establishing the absolute configuration of 261.

preferential abstraction of the axial pro-(S)-hydrogen from the α-methylene group from **233** as expected considering the known[173] enantioselectivity for deprotonation of C_s symmetrical cyclohexanones with **230** (Scheme 2.18.).
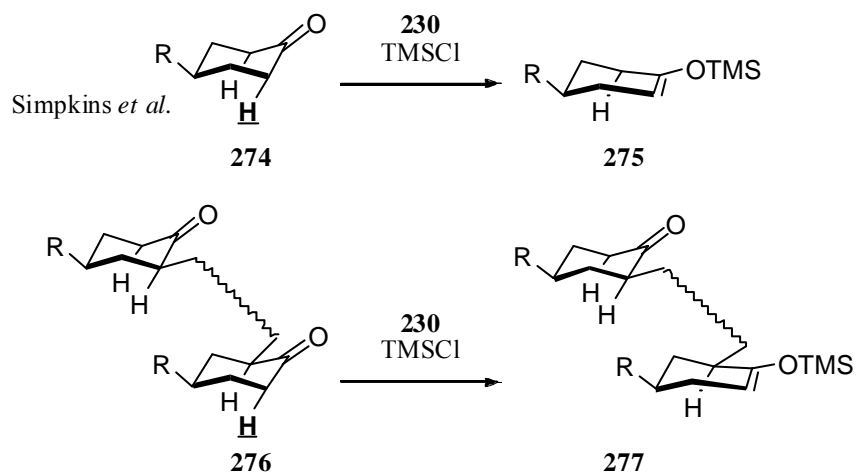
Scheme 2.18.

2.1.3.5. Desulfurization of hexapropionate synthon 271

With access to an enantiomerically enriched hexapropionate synthon (*i.e.* ketol **271**), demonstration of the thiopyran route to polypropionates was accomplished by desulfurization of ketol **271** using Raney Ni (Scheme 2.19.). Oxidation of acyclic ketol **278** gave *meso* **279**, indicating that desulfurization had occurred without loss of stereochemical integrity.
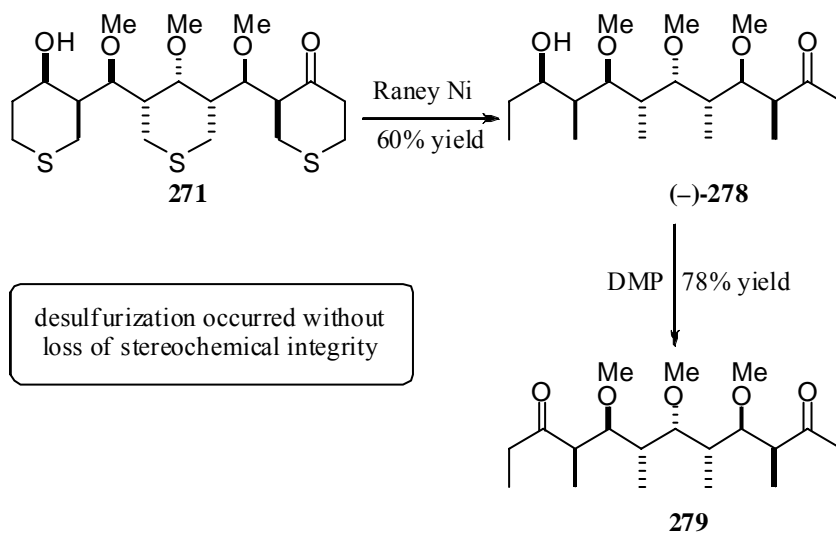
Scheme 2.19.

In summary, enantiotopic group selective enolization of *meso* 1,9-diketone **233** occurs with simultaneous kinetic resolution to give mono-silyl enol ether **261** with enhanced enantiopurity and in excellent overall yield. The thiopyran route to polypropionates can be applied for the asymmetric synthesis of stereochemically complex natural products. For example, by strategically synthesizing a suitably protected *meso* 1,9-diketone from readily available *meso* bisaldol adduct **212a**, application of a SEG selective enolization followed by desulfurization permits access to enantioenriched hexapropionate synthons that could be used for the synthesis 6-deoxyerythronolide B
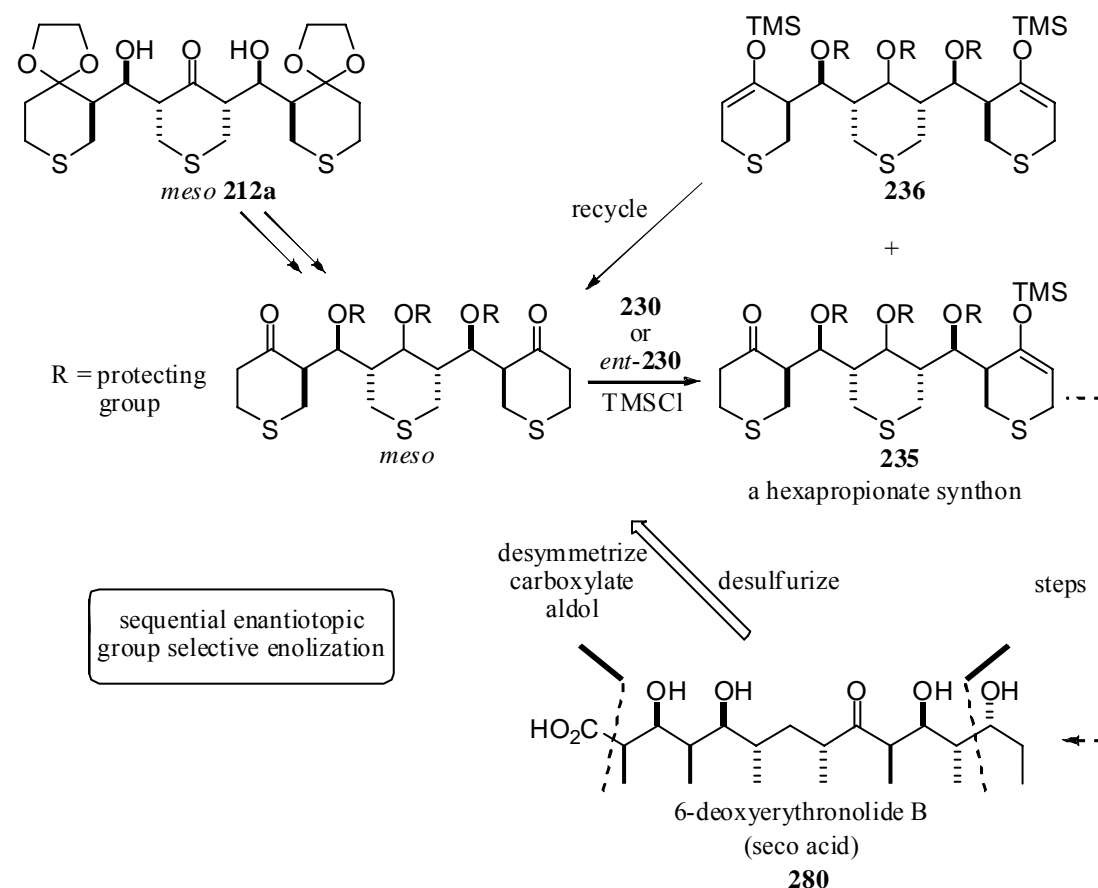
Scheme 2.20.

(Scheme 2.20.)[31, 54, 174]. In fact, *meso* 1,9-diketone **281** was prepared and desymmetrized as above to obtain **282**, an intermediate towards 6-deoxyerythronolide B (Scheme

78

2.21.).[xxxii] Extending the same principle to 1,9-diketones derived from chiral (non-racemic) bisaldol **212e** permits an opportunity for application of a sequential
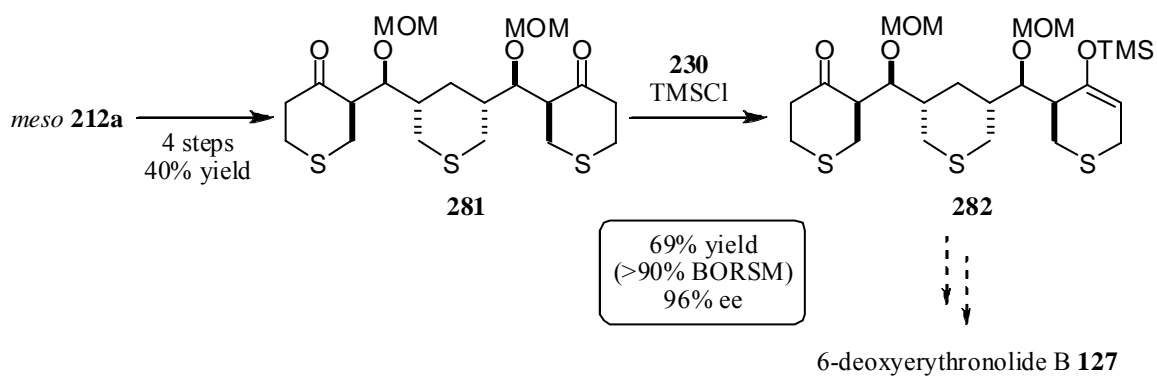
Scheme 2.21.

diastereoselective group selective enolization that would allow access to additional polypropionate natural products (Scheme 2.22.). Indeed, demonstration of this approach was established by the reaction of 1,9-diketone **287** with **230** and TMSCl (Scheme 2.23.).[xxxiii] The thiopyran route to polypropionates offers the opportunity to access tetra- and hexapropionate synthons for the asymmetric synthesis of various targets. Enantio- and/or diastereoselective enolization of *meso* 1,9-diketones provides access to enantioenriched materials that can accommodate many synthetic endeavors.

[xxxii] Work done by Dr. Mohammed A. Rasheed.
[xxxiii] Work done by Mr. Garrison Beye.
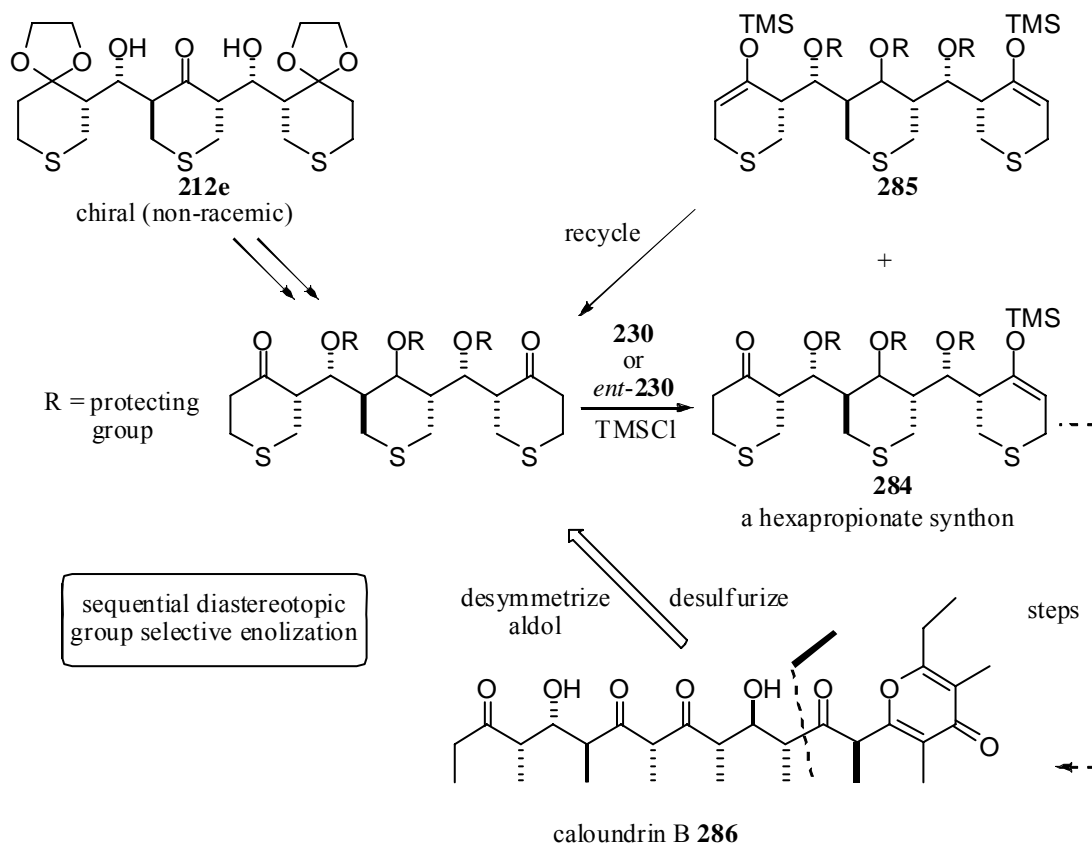
Scheme 2.22.
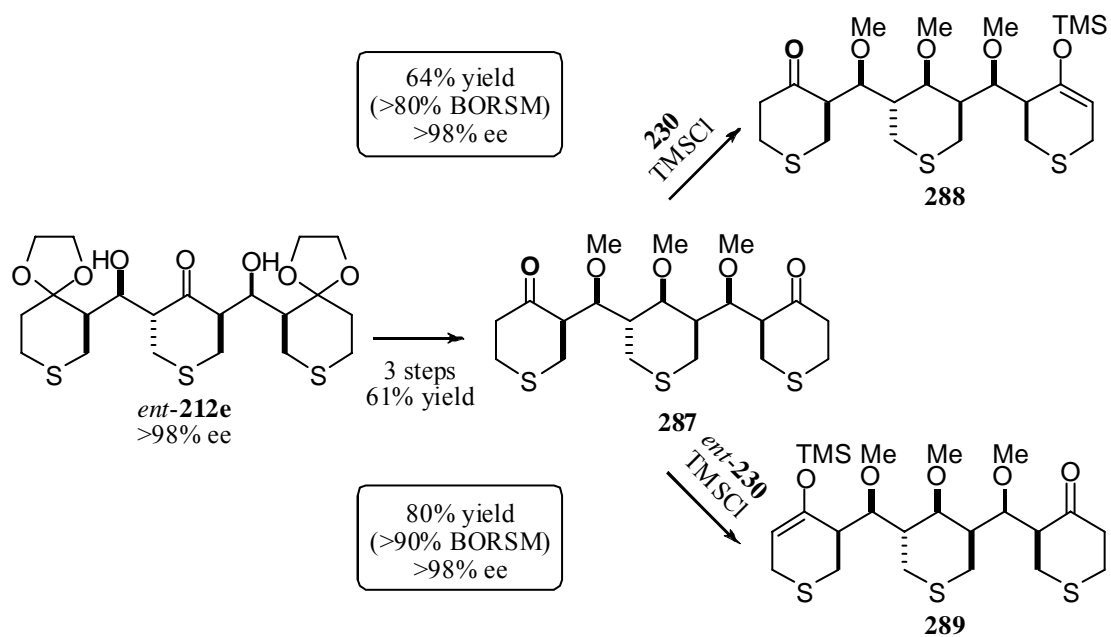
Scheme 2.23.

2.2. Synthetic studies towards the asymmetric synthesis of (−)-denticulatin A

The denticulatins (Section 1.2.1.) represent an ideal polypropionate natural product that could be synthesized *via* the thiopyran route (Scheme 2.24.). The previous syntheses involved fragment coupling of chiral (non-racemic) fragments where an aldol reaction found several successful applications. While Ziegler and Hoffman had problematic

denticulatin A (10-*S*)-**9**
denticulatin B (10-*R*)-**10**

290
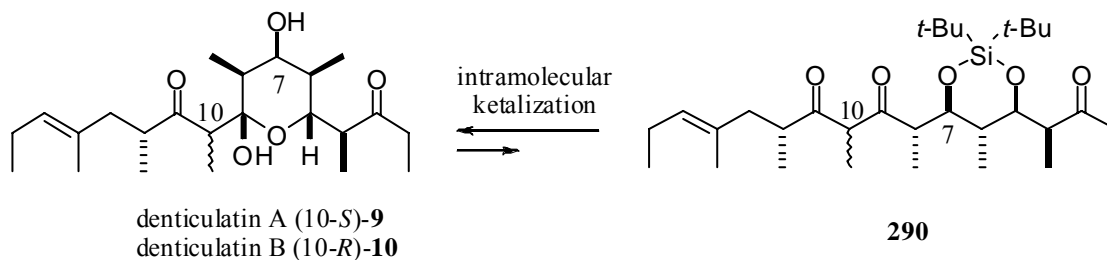
Scheme 2.24.

deprotection of hydroxyl protecting groups towards the end of their syntheses, Paterson and Oppolzer were successful with the deprotection and subsequent cyclization of di-*tert*-butylsilylene triketone **290** for their syntheses of the denticulatins. As a result, triketone **290** emerges as an ideal target for application of the thiopyran route and it was decided to evoke the recently developed sequential enantiotopic group selective enolization to gain access to a hexapropionate synthon that would demonstrate the thiopyran route as a viable approach.

2.2.1. Synthetic plan

It was envisioned that triketone **290** could be prepared *via* an alkylation-desulfurization-oxidation strategy employing a suitably protected ketone **292** (Scheme 2.25.). The required 10,12-*trans* relative configuration would be controlled by the corresponding fixed *trans* enolate of ketone **292**, while access to ketone **292** would result from an enantioselective enolization of *meso* 1,9-diketone **294** using *ent*-**230**. The required relative configuration at C-7 would be controlled by a stereoselective reduction

of readily available *meso* bisaldol **212a**. While there is some flexibility for hydroxyl protecting groups, this approach demands access to a substrate where the cyclic di-*tert*-butylsilylene protecting group can be installed at C_5-OH and C_7-OH. The required diol could be obtained from the protected *meso* trihydroxydiketone **294** with orthogonal R_1 and R_2 protecting groups. After a desymmetrization and alkylation followed by a reduction and R_1 deprotection sequence, a 5,9,11-triol would result that allows isolation of the C_5-OH group; for example, acetonide formation on the 9,11-diol. Subsequent removal of the R_2 protecting group at C-7 would reveal a 5,7-diol and allow installation of the desired silylene protecting group.
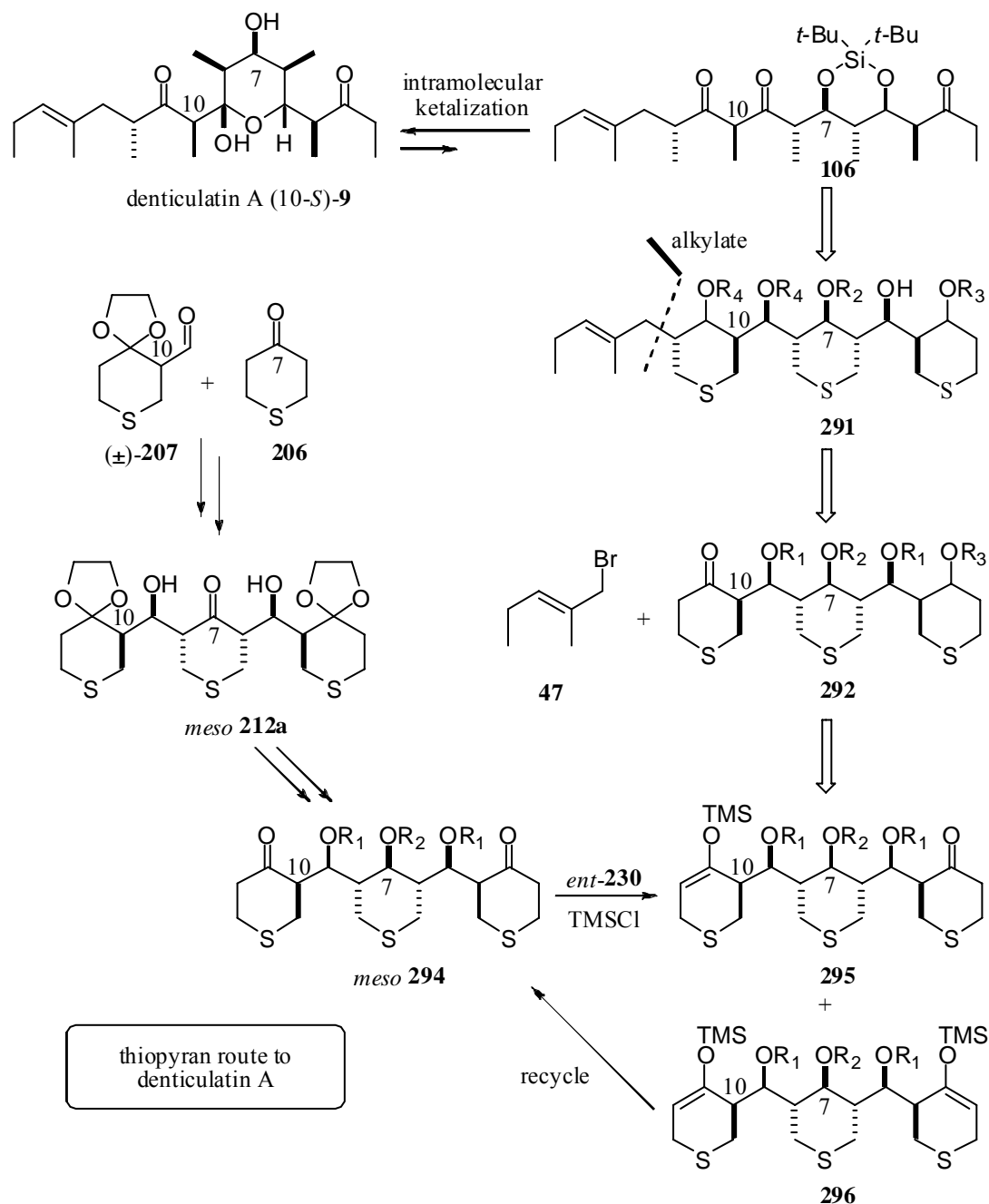
Scheme 2.25.

2.2.1.1. Synthesis of *meso* 1,9-diketones

Two conceptually different approaches were attempted for the synthesis of *meso* 1,9-diketone **294**. The first approach involved the initial reduction of *meso* **212a** using Et$_2$BOMe/NaBH$_4$ that gave the desired all *syn* triol in 70% yield as a single diastereomer

(Scheme 2.26.). The relative configuration of **297** was unambiguously established by X-ray crystallography (Figure 2.6.).[xxxiv] The next step involved exposure of *syn* triol **297** to

meso **212a**

i) Et$_2$BOMe
ii) NaBH$_4$

70% yield

297
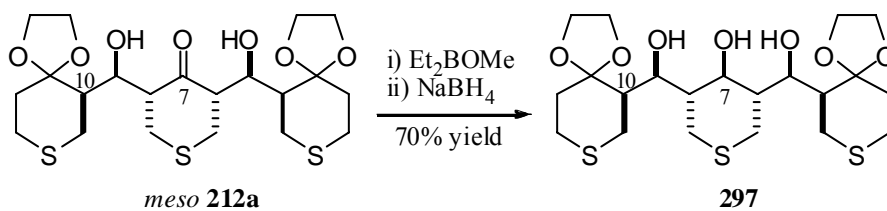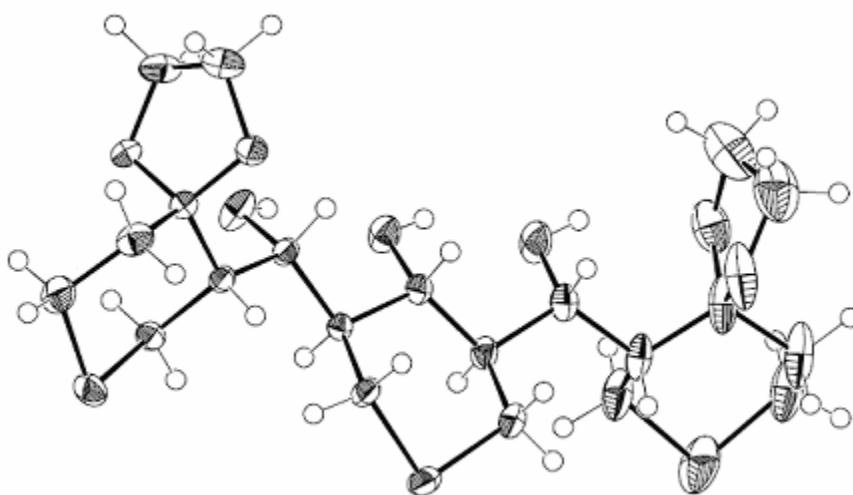
Scheme 2.26.

Figure 2.6. ORTEP diagram of *syn* triol 297.

FeCl$_3$·SiO$_2$[175, 176] in acetone at room temperature for 2 hours that furnished acetonide **298** in 74% yield (Scheme 2.27.). Ketal deprotection of **298** using identical conditions but

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[xxxiv] The numbering system according to the denticulatins (Scheme 2.24.) will be used in this section.
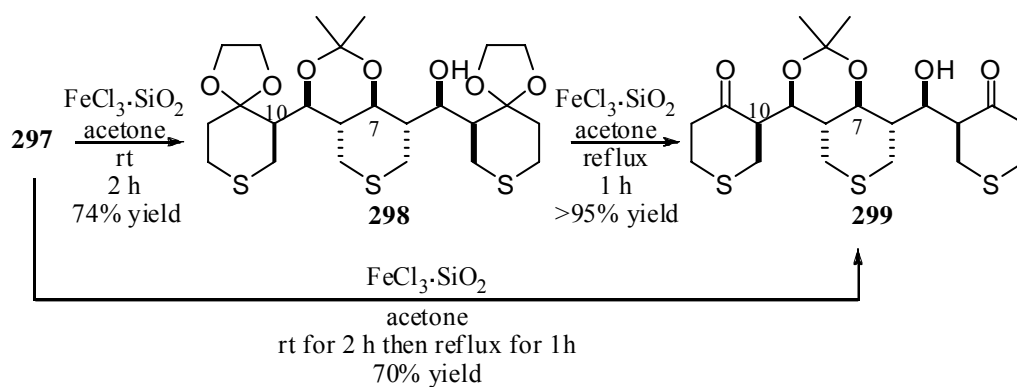
Scheme 2.27.

under reflux for 1 hour provided **299** in >95% yield. This transformation was simplified

as **299** can be obtained in a one-pot sequence from *syn* triol **297** in 70% yield (Scheme

2.27.). At this stage, it was necessary to establish conditions that would remove the

acetonide of **299**. Successful deprotection of the acetonide in **299** would enable the

differentiation of the C_5-OH/C_9-OH from the C_7-OH by internal acetal formation

(Scheme 2.28.).[111] However, attempted deprotection of acetonide **299** under various
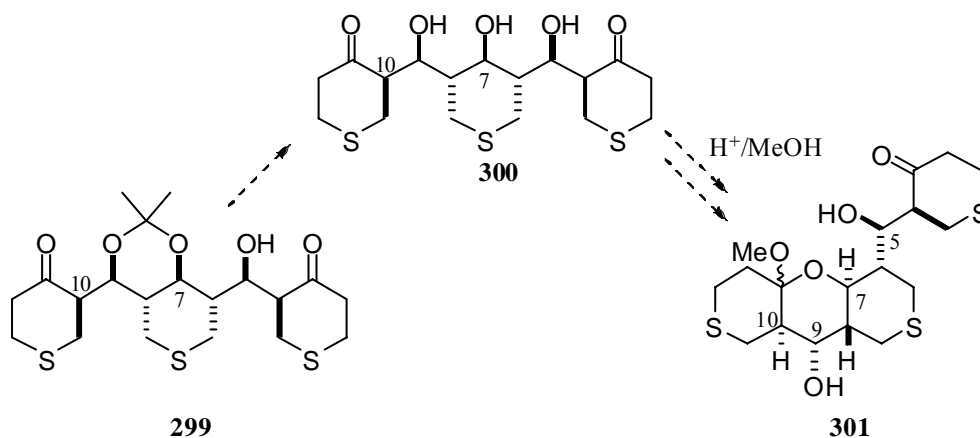
Scheme 2.28.

conditions *(e.g.* H$^+$/THF$_{(aq)}$ or H$^+$/MeOH) failed to yield the desired product and this

approach was eventually abandoned. Alternatively, regioselective protection of *syn* triol

297 by reaction with MOMCl and *i*-Pr$_2$EtN in the presence of *n*-Bu$_4$NI for 2 days

provided *meso* bis-MOM alcohol **303** in 70% yield; however, allowing the reaction to

extend to 3 days furnished **302**[xxxv] in 74 % yield (Scheme 2.29.). Subsequent benzylation

of *meso* bis-MOM alcohol **303** using KH/BnBr gave **304** in 93% yield.
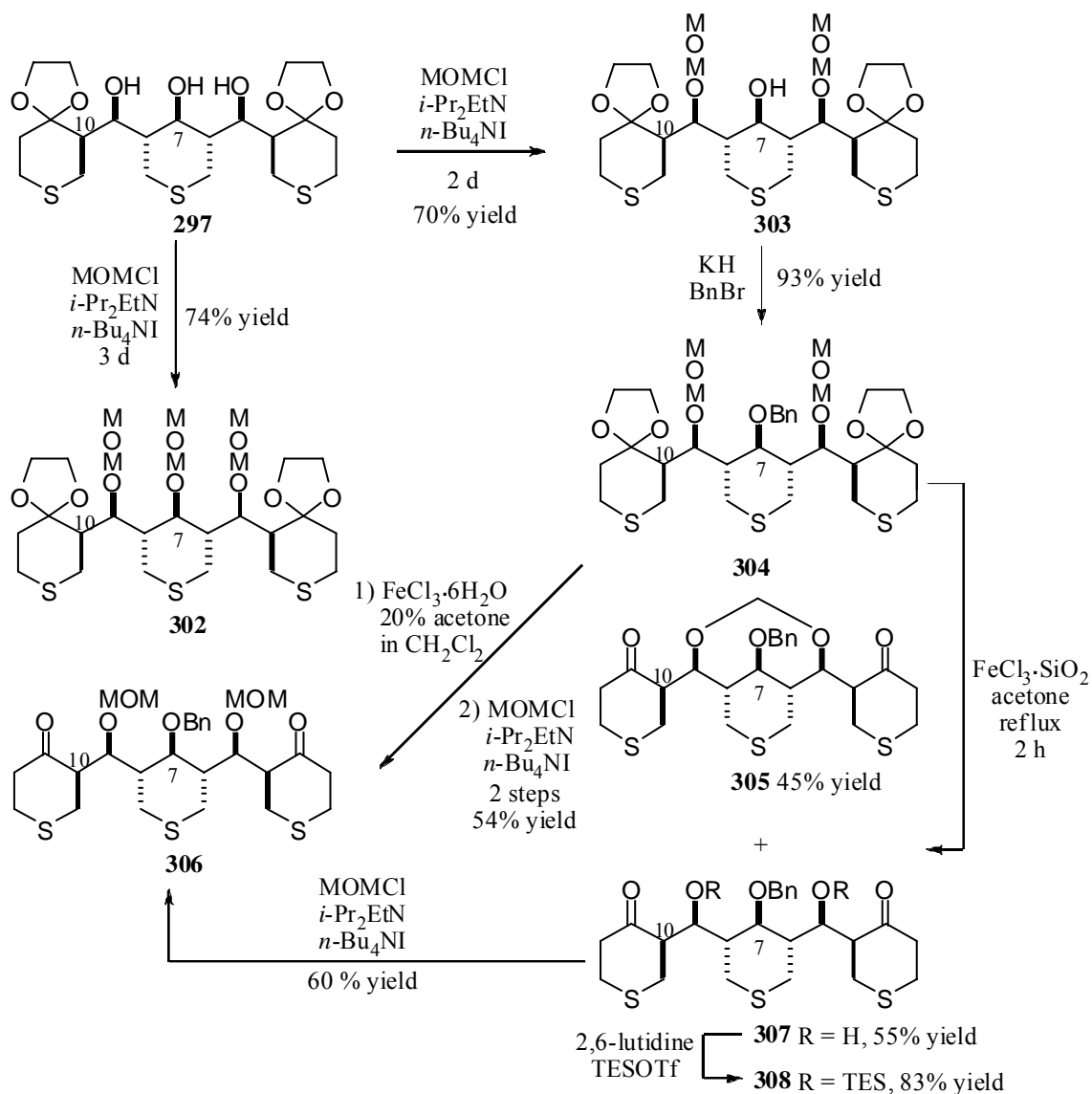
Scheme 2.29.

The next step required ketal deprotection of **304** to provide a protected *meso* 1,9-diketone

for the enantioselective enolization. This was accomplished by subjection of **304** to

FeCl$_3$·6H$_2$O[175] in 20% acetone in dichloromethane for 4 hours that resulted in a mixture

of MOM protected and hydroxy diketones that upon re-installation of the MOM groups

---

[xxxv] Attempts to recycle tris-MOM **302** failed to provide *syn* triol **297**.

provided **306** in 54 % yield (Scheme 2.29.). Alternatively, reaction of **304** with

FeCl$_3$·SiO$_2$[176] in acetone at reflux furnished diol diketone **307** in 55% yield that upon

MOM protection provided the desired *meso* bis-MOM diketone **306** in 60% yield.

Interestingly, this reaction also produced the methylidene acetal **305** in 45% yield.

Although **305** was an unexpected product for this reaction, there is an example where the

formation of a methylidene acetal resulted from the deprotection of a MOM protected

substrate using similar conditions.[175] Presumably, **305** resulted from the cyclization of a

free hydroxyl onto the oxonium ion intermediate resulting from hydrolysis of the second

MOM group (Scheme 2.30.). Although both **305** and **306** could potentially be used for
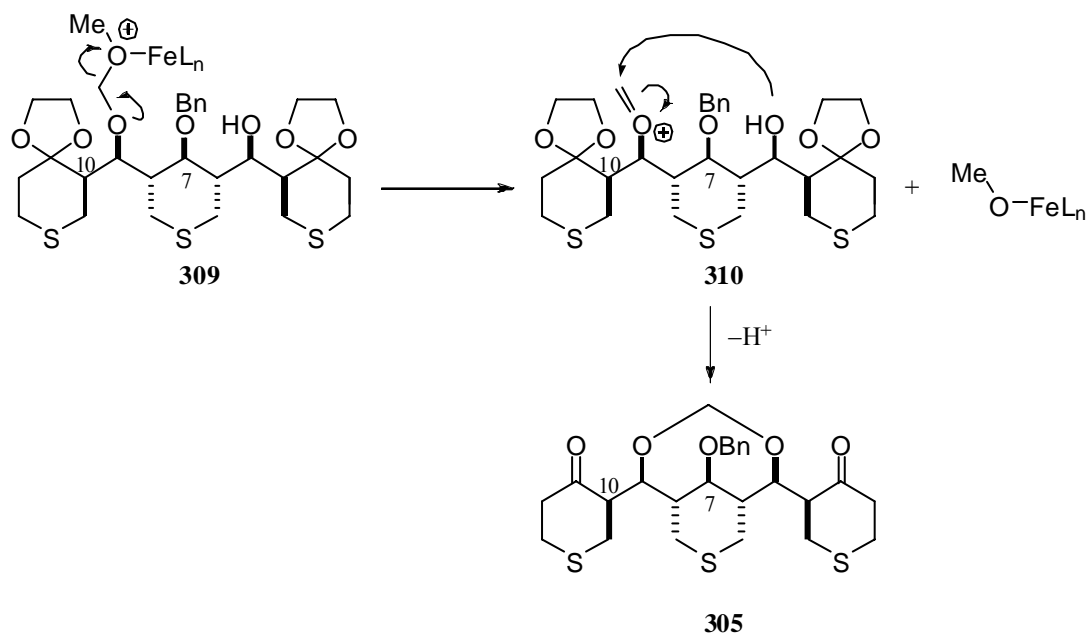
Scheme 2.30.

the enantioselective enolization, they were insufficiently soluble in numerous organic

solvents, including THF. The low solubility likely contributes to the poor yields for the

preparation of *meso* 1,9-diketone **306** (Scheme 2.29.). As an alternative, exposure of diol

diketone **307** to TESOTf and 2,6-lutidine provided *meso* bis-silyl 1,9-diketone **308** in

83% yield (Scheme 2.29.) that proved to be soluble in THF and represents a suitably

protected substrate for subjection to an enantioselective enolization. In light of this

result, access to diol diketone **307** was slightly modified as *syn* triol **297** was allowed to

react with TMSCl and *i*-Pr$_2$EtN for 2 days that furnished *meso* bis-silyl alcohol **312** in

85% and *meso* mono-silyl diol **311** in 15% (Scheme 2.31.). Fortunately, recycling of **297**
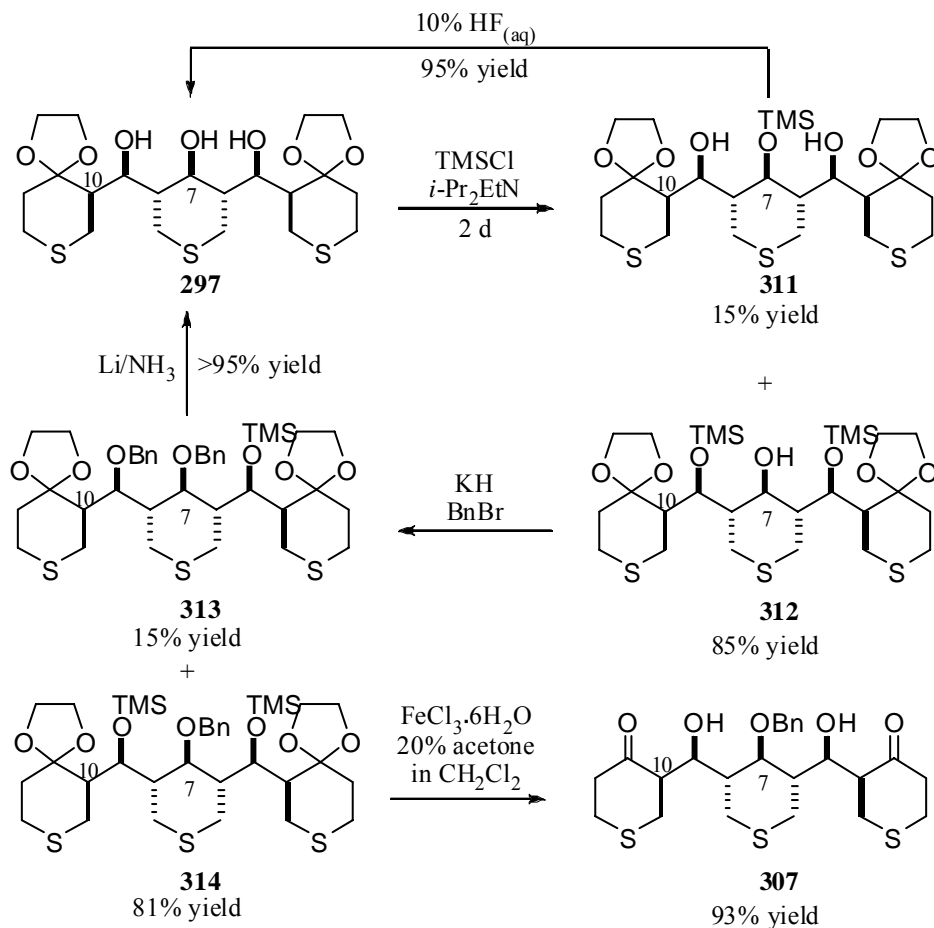
Scheme 2.31.

was efficiently achieved by treatment of **311** with HF$_{(aq)}$ that gave *syn* triol **297** in near

quantitative yield. Benzylation of **312** using KH/BnBr furnished **314** in 81% yield and

bis-benzylated **313** in 15% yield; the latter was recycled to *syn* triol **297** under Birch

conditions (*e.g.* Li/NH$_3$) in quantitative yield. This protocol for the synthesis of **314** is

very efficient as both by-products resulting from silylation and benzylation (*i.e.* **311** and **313**) are quantitatively converted back to starting *syn* triol **297**. The overall yield of **314** is 94% based on recovered starting *syn* triol **297** over a total of four steps (average yield per step >98%). A one-pot silyl and ketal deprotection of **314** using $FeCl_3 \cdot 6H_2O$ provided diol diketone **307** in 93% yield that was converted to the bis-TES ether **308** by treatment with 2,6-lutidine and TESOTf (Scheme 2.29.).[xxxvi]

2.2.1.2. Sequential enantiotopic group selective enolization of *meso* 1,9-diketone 308

Enantioselective enolization of *meso* 1,9-diketone **308** was successfully achieved by deprotonation with *ent*-**230** (Scheme 2.32.). Again, the yield and ee of **315**[xxxvii] were
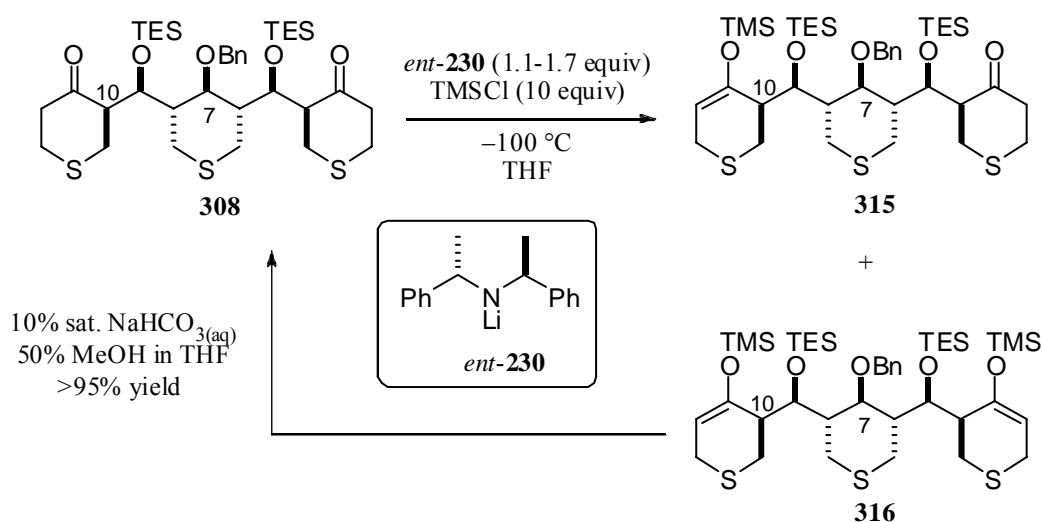
Scheme 2.32.

dependent on the reaction enantioselectivity and conversion.[129] Modelling of the product distributions and ee's of **315** at various conversions in the reaction of **308** with *ent*-**230** in the presence of TMSCl suggests a reaction enantioselectivity of *ca.* 8:1 using conditions

---

[xxxvi] In principle, with access to diol diketone **307** many different protecting groups could have been used. The triethylsilyl protecting group was chosen with the expectation of higher solubility in organic solvents. In fact, the initial trimethylsilyl protecting group was chosen by design as its hydrolysis during ketal deprotection of **314** was anticipated.

[xxxvii] The absolute configuration of **315** is based on analogy as determined for **261** with **230**.

identical to those that gave a 17:1 enantioselectivity with *meso* 1,9-diketone **233** (Table

2.7. and Figure 2.7.). While this lower enantioselectivity is intriguing,[xxxviii] it again

Table 2.7. Enantioselective enolization of 308 with *ent*-230/TMSCl.

entry[a]	**308** (# equiv)	^{1}H NMR ratio[b] **308:315:316**	isolated yields (%)		
			308	**315** (%ee)[c]	**316**
1	1.5	71:26:3			
2	1.7	43:49:8			
3	1.7	26:56:18			
4	1.1	18:61:21	23	59 (92)	14
5	1.4	16:62:22	24	59 (92)	19
6	**1.5**	**9:66:23**	**9**	**66 (93)**	**17**
7	1.3	6:44:50	11	44 (94)	35
8[d]	1.4	20:59:21			
9[e]	1.5	18:64:18	29	52 (82)	20
10[f]	1.4	7:48:45			

[a] A THF solution of *ent*-**230** or *ent*-**230**·LiCl was rapidly cannulated (*ca.* 30 sec) to a THF solution of **308** (0.2-1.5 mmol) and TMSCl (10 equiv) at −100 °C. [b] Crude products after work-up. [c] Determined by ^{1}H NMR analysis of the corresponding Mosher's esters of ketol **323**. [d] Slow addition of *ent*-**230** (*ca.* 5 min). [e] Using *ent*-**230**·LiCl. [f] External quench (*i.e.* addition of *ent*-**230** followed by TMSCl).

highlights the benefits of the ee enhancement feature of the SEG desymmetrizing

reaction. Efforts to increase the enantioselectivity (entries 8 and 10) by either slow

addition of *ent*-**230** or by external quench gave no substantial improvements. Under

similar conditions, reactions using *ent*-**230** were more selective than those using *ent*-

230·LiCl (entry 9 vs. entry 6). As was seen for *meso* 1,9-diketone **233** (Section 2.1.3.2.),

unexpectedly large amounts of bis-product **316** were also observed at low conversions

(entries 1 and 2). Although the enantioselectivity of the enolization of **308** is somewhat

lower than that observed from the *meso* 1,9-diketone **233**, mono-silyl enol ether **315** was

obtained with satisfactory yield and ee. This process is very efficient (>90% yield based

---

[xxxviii] The exact role of the triethylsilyl group is unclear; however, it is likely that the lack of coordination sites is important (*i.e.* MOM vs. TES).

on recovered diketone **308**) as bis-silyl enol ether **316** can be easily recycled to diketone **308** by treatment with 10% sat. aqueous NaHCO$_3$ in 50% methanol in THF.
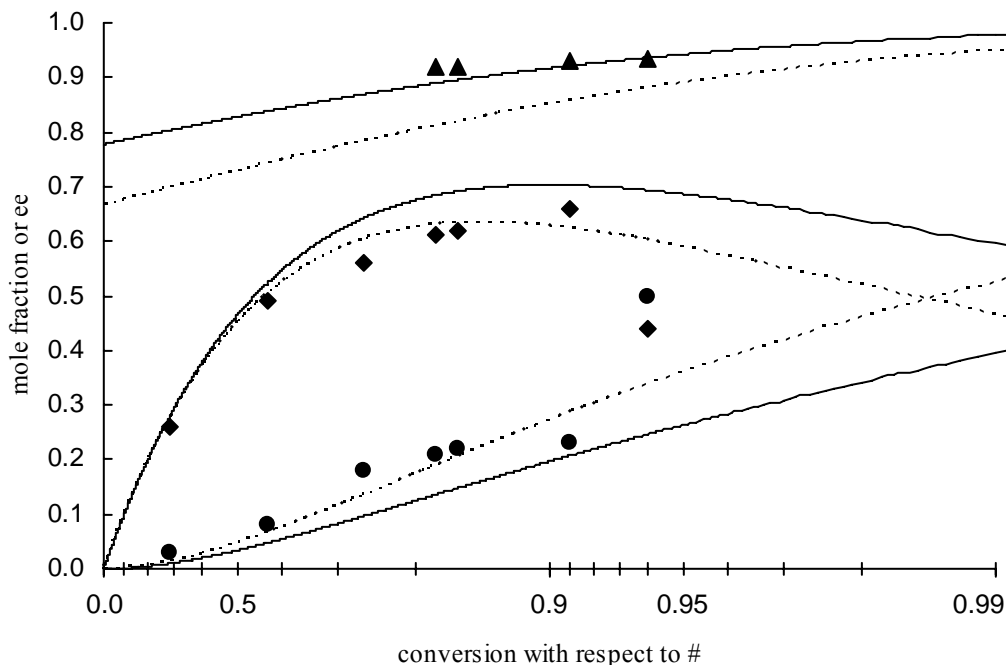
Figure 2.7. Calculated and observed mole fractions of 315 (♦) and 316 (●) and ee of 316 (▲) produced in the reaction of 308 with 230/TMSCl as a function of conversion of 308.

(*i.e.*, assuming *s* = 8 (——) and *s* = 5 (---)).

2.2.1.3. Alkylation and desulfurization

With access to the protected desymmetrized hexapropionate synthon **315**, establishing reaction conditions for addition of the 2-methyl-2-pentyl group and for desulfurization were required (Scheme 2.25.). To ascertain the viability of these processes, model substrates **210sa** and **317sa** were chosen for study (Scheme 2.33.).[xxxix] In both cases, *C*-alkylation of the Li-enolates derived by treatment with *t*-BuLi at −78 °C followed by addition of (2*E*)-1-bromo-2-methyl-2-pentene and HMPA occurred to give

---

[xxxix] **209sa** aldol adduct was chosen since it has the identical stereochemical array as compared to **315**.

ca. 20:1 mixtures of diastereomeric *C*-alkylated products. These alkylations of **210sa** and

317sa were very efficient as the yields based on recovered starting materials were >95%

in both cases. Equally important, the double bonds in **318sa** and **319sa** survived the
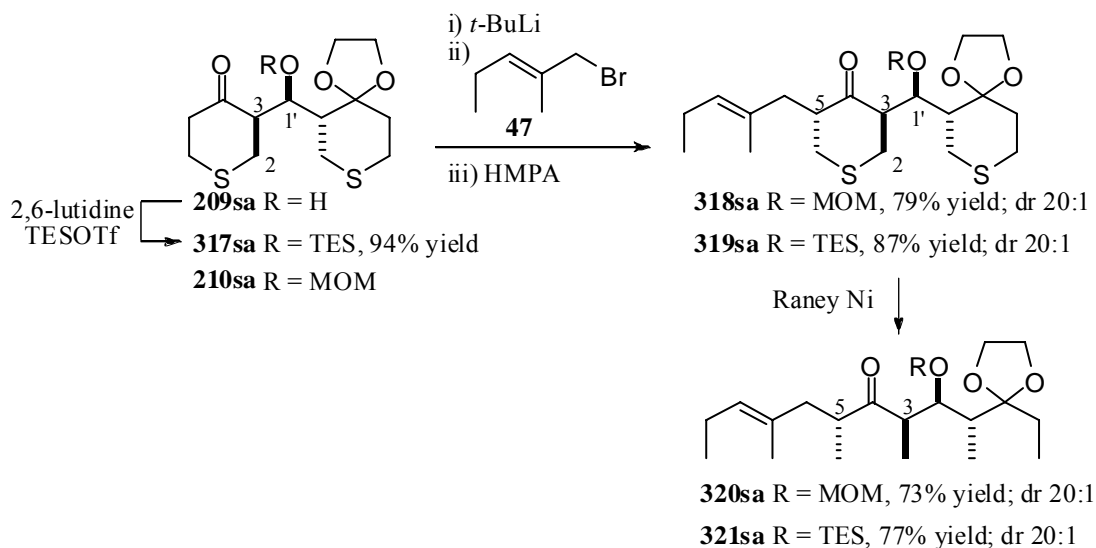
Scheme 2.33.

subsequent Raney Ni desulfurizations to give the desired **320sa** and **321sa**, respectively,

in good overall yields (Scheme 2.33.)..   Analysis of the proton coupling constants

observed in the NMR spectra of **318sa** and **319sa** (*i.e.* $J_{HC-1'-HC-3}$, $J_{HeqC-2-HC-3}$ and $J_{HaxC-2-HC-3}$

$_3$) and observations of positive NOE's between H$_2$CC-5 and HC-3 reveal that, in each

case, the major diastereomer has the desired 3,5-*trans* relative configuration (Figure 2.8.).
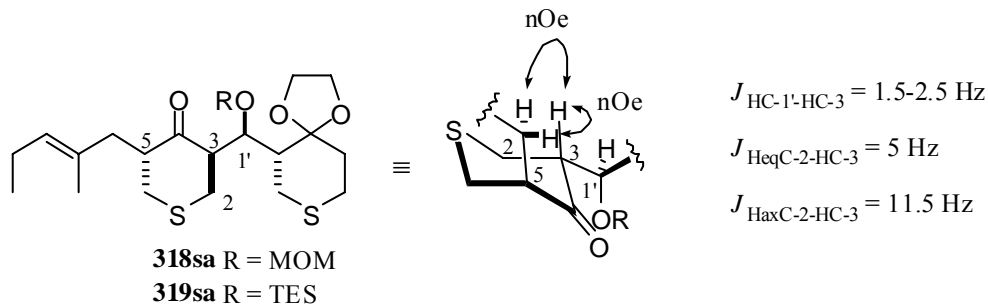
Figure 2.8. Structure determination of 318sa and 319sa.

Processing of silyl enol ether **315** required several synthetic manipulations to arrive

at a suitably protected substrate for *C*-alkylation (Scheme 2.34.). Reduction of **315** using
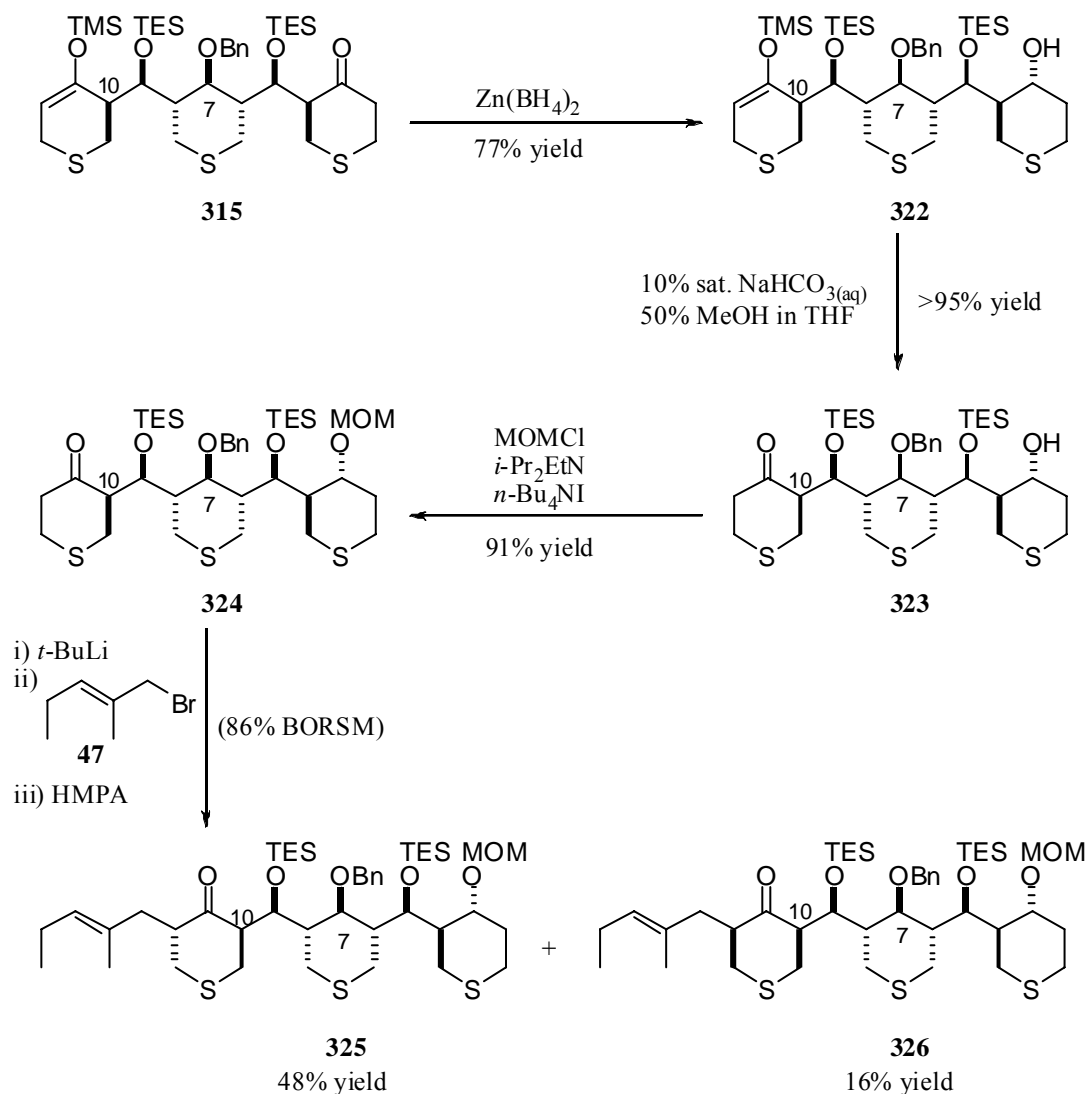
Scheme 2.34.

Zn(BH$_4$)$_2$ gave an 8:1   mixture of diastereomeric alcohols that upon fractionation

provided **322** in 77% yield. The 3,4-*trans* relative configuration for **322** was assigned

based on the appearance of HC-3 as a ddd (*i.e.* $J = 4$, 10, 10 Hz) in the ^{1}H NMR spectra

(Figure 2.9.). Hydrolysis of silyl enol ether in **322** gave ketol **323** in near quantitative

yield that was subsequently protected as the MOM ether to give **324** in 91% yield.

Subjecting ketone **324** to the *C*-alkylation conditions that were developed using model
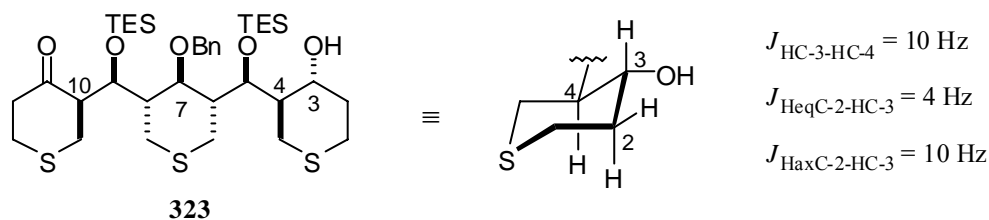
Figure 2.9. Structure determination of 322.

substrates **210sa** and **317sa** (Scheme 2.33.) resulted in very low conversions (*ca.* 5-10%);

however, with efficient recovery of ketone **324**. Fortunately, by using excess *t*-BuLi (*i.e.*

10 equiv) a 3:1 mixture of diastereomeric *C*-alkylated products **325** and **326**[xl] was

obtained. Fractionation of this crude mixture gave **325** and **326** in 48% and 16% yields,

respectively, along with 25% of recovered ketone **324** (86% yield based on recovered

ketone **324**). Efforts to improve the diastereoselectivity of the alkyation by employing

either LDA or NaHMDS resulted in low conversion, isomerization and/or elimination

products. While the yield of this reaction was only modest, it was thought sufficient to

move forward.

Reduction of **325** using NaBH₃CN furnished alcohol **327** as the only diastereomer

in 79% yield (Scheme 2.35). Interestingly, the TES group in a 1,3-relationship to the

alcohol in **327** was selectively deprotected by brief exposure to TBAF to give diol **328** in

95% yield. Acetylation of diol **328** using Ac₂O and DMAP furnished diacetate **329a** in

88% yield. Considering all four possible diastereomers of **329** that could result from *C*-

alkylation and reduction, only one diastereomer matches the expected and observed

vicinal H-H coupling constants for diacetate **329a**, which confirms the 10,12-*trans*

[xl] The major diastereomer **325** was assumed to be 10,12-*trans* but was later verified by analysis of the vicinal proton coupling constants of diacetate **329a** (Figure 2.10.).

relative configuration resulting from *C*-alkylation and the 10,11-*trans* relative

configuration from the reduction of **325** (Figure 2.10.). Desulfurization of diacetate **329a**

using Raney Ni provided partly desulfurized **330**, which after re-subjection to Raney Ni
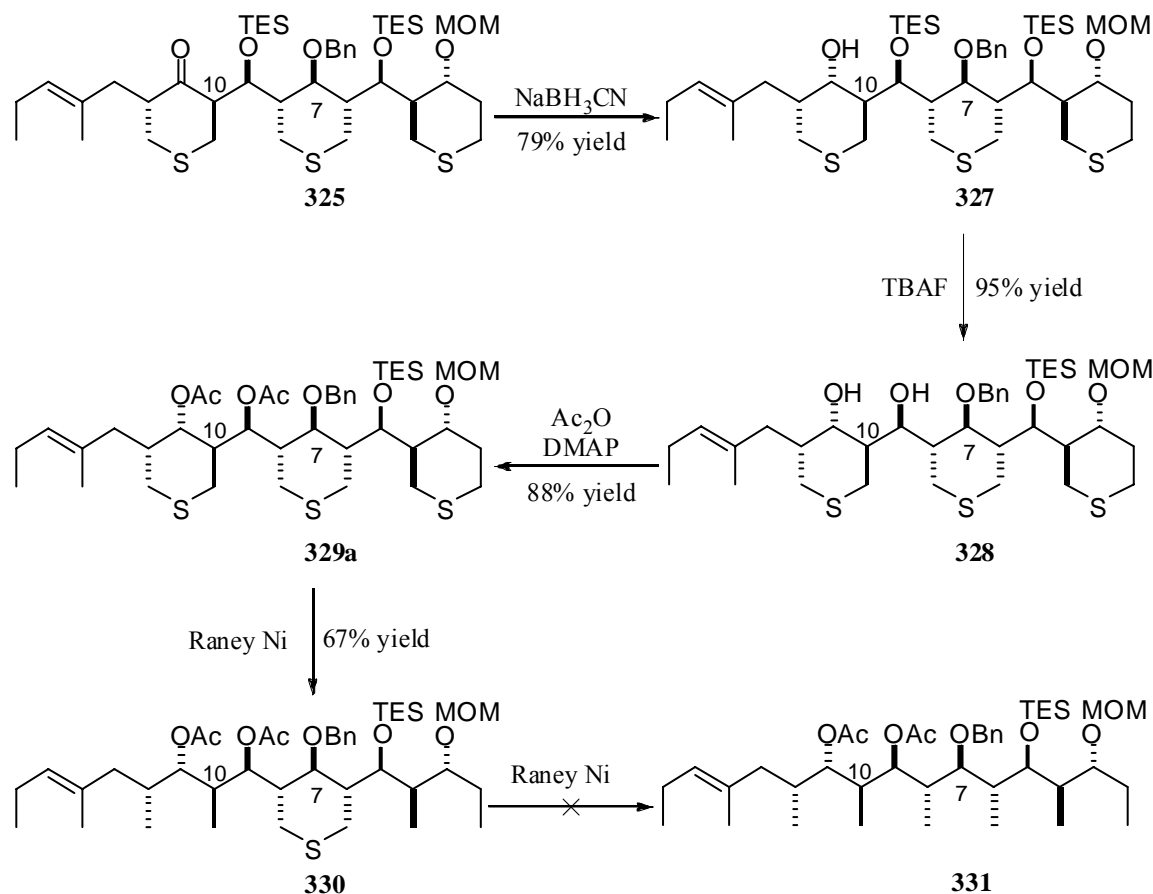
Scheme 2.35.

resulted in a mixture of compounds where the double bond was reduced and/or the benzyl

protecting group was lost. As a result, this was not a viable approach to the denticulatins.

The alternative approach of desulfurization before *C*-alkylation introduces the challenge

of controlling the stereoselectivity of the desired *C*-alkylation. During the syntheses of

(−)-discodermolide **4** (or *ent*-**4**), several researchers[177-184] proposed a chelation controlled

alkylation (as opposed to an A-strain controlled alkylation) of chiral (*Z*)-*O*-enolates as a

method for introducing the 16,18-*cis* relative configuration (Figure 2.11.). However, the

major products from alkylation of (*Z*)-*O*-enolates formed using lithium or sodium hexamethyldisilazide bases had *trans* relative configuration. (Scheme 2.36.). After extensive experimentation, only Myles and co-workers were able to effect a chelation-controlled alkylation of **344** that provided a 6:1 diastereomeric mixture of **346**.
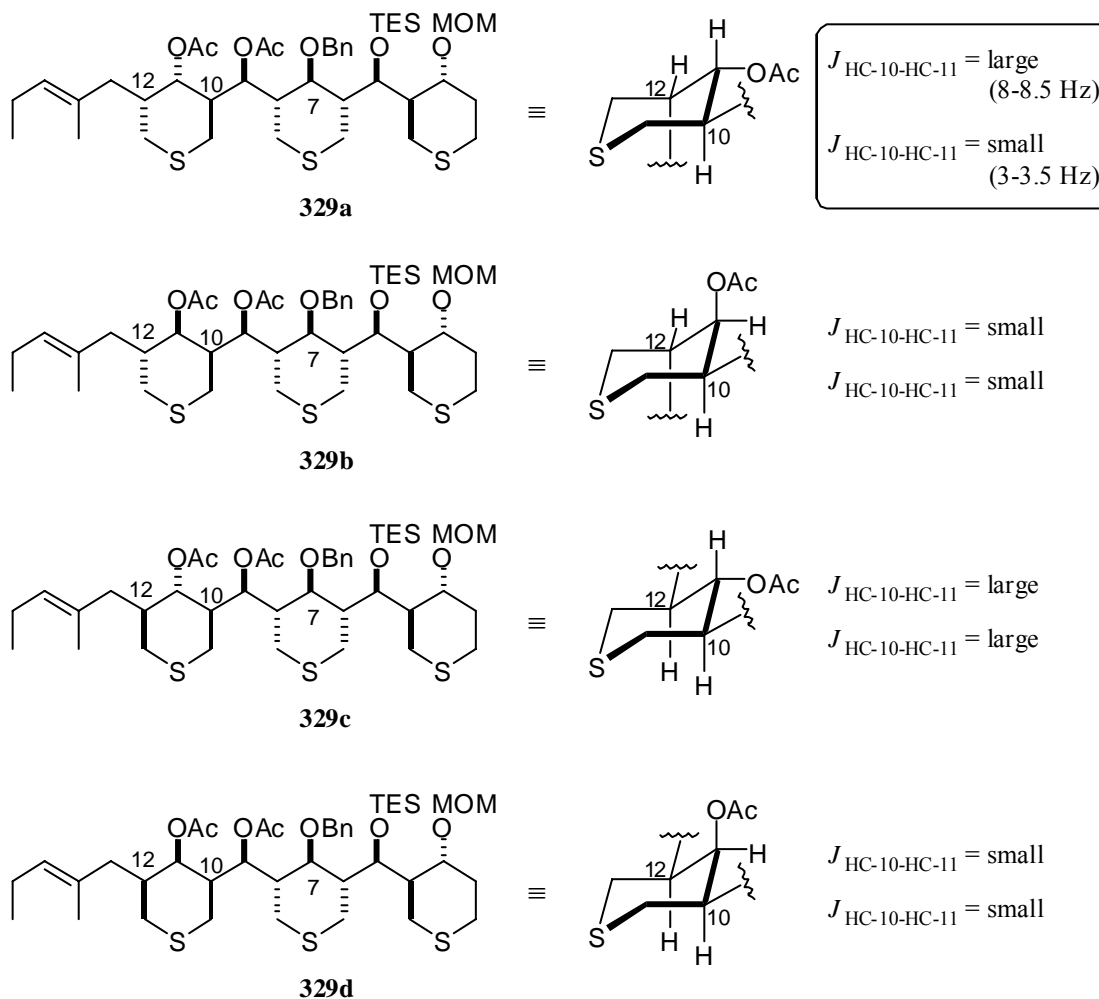
Figure 2.10. Structure determination of 329a.
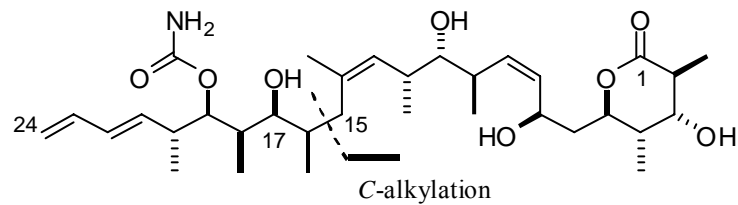
C-alkylation

(−)-discodermolide **4**

chelation control

332　　**333**　　**334**　*cis*

A-strain control

335　　**336**　　**337**　*trans*
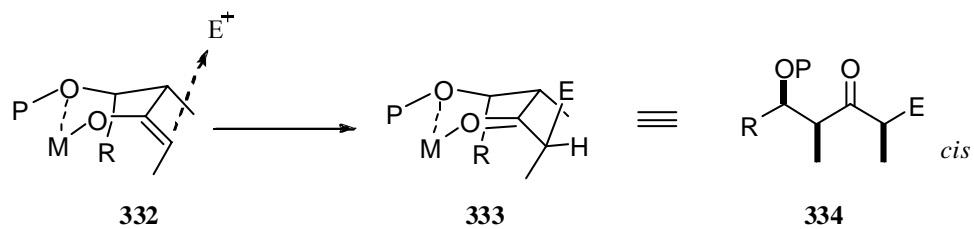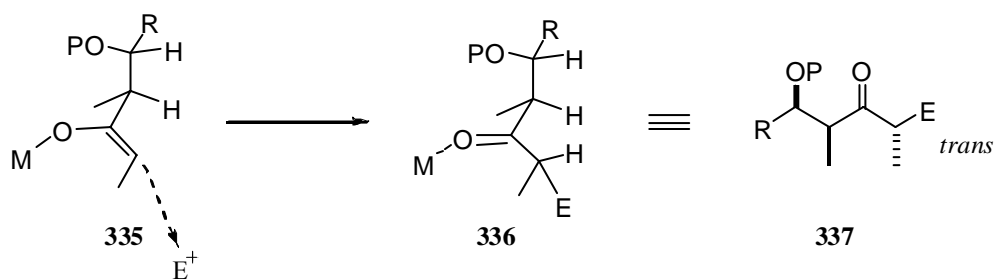
Figure 2.11. Syntheses of (−)-discodermolide 4.
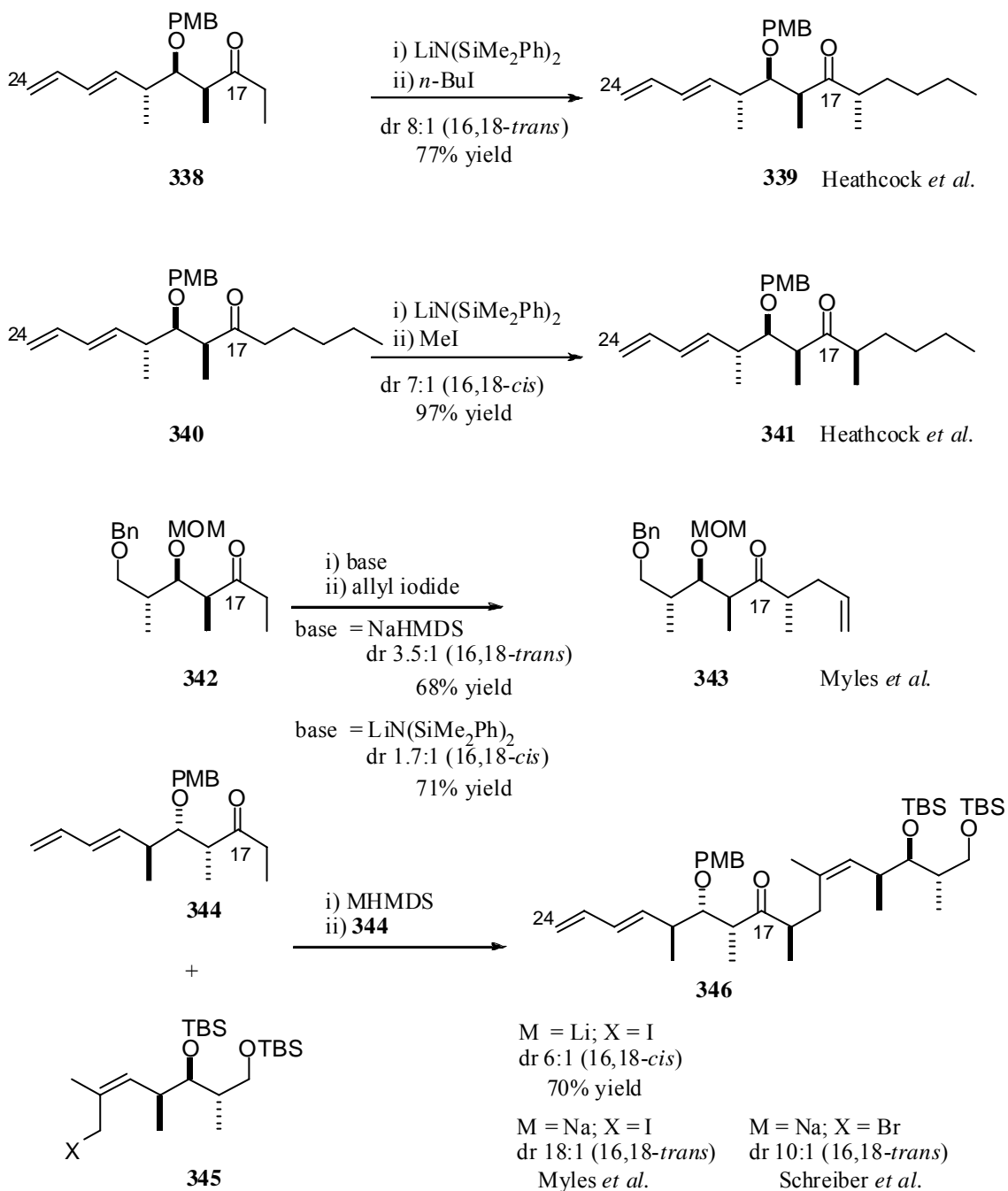
Scheme 2.36.

These findings suggest that the desired 10,12-*trans* relative configuration could be obtained by *C*-alkylation of the acylic version of ketone **324** with allyl bromide **47**. Desulfurization of ketone **324** furnished the desired **347** in 70% yield (Scheme 2.37.). *C*-alkylation of ketone **347** was achieved by exposure of **347** to excess NaHMDS (10 equiv)

followed by addition of allyl bromide **47** and TMEDA at −78 °C to give **349** in 65% yield

(>90% based on recovered ketone **347**) with a dr of 4.6:1 (Scheme 2.37.). To verify that

the presence of excess NaHMDS does not erode the dr during the reaction, *C*-alkylated

349 (dr 4.6:1) was subjected to identical reaction conditions. *C*-alkylated **349** with the

same originating diastereomeric ratio of 4.6:1 was recovered quantitatively.
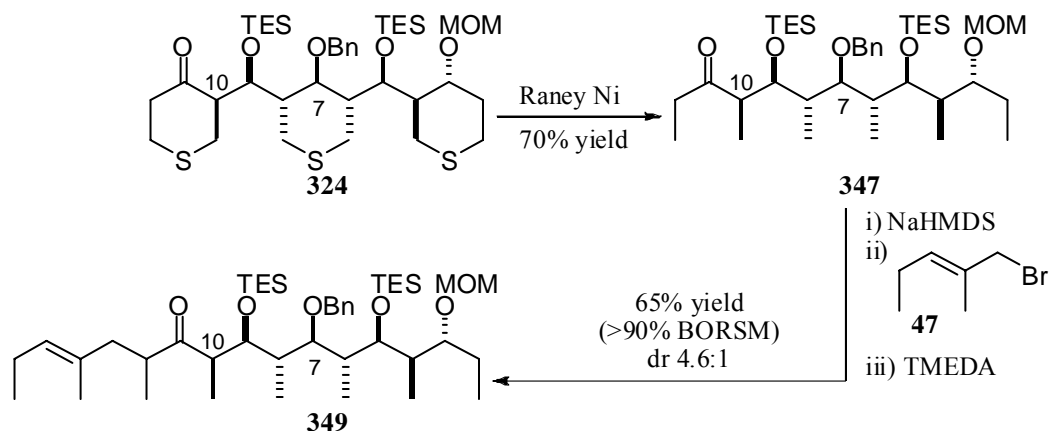
Scheme 2.37.

At this stage, the relative configuration at C-10 and C-12 in **349** was unknown,

although the literature precedent (Scheme 2.36.)[177-184] supported the desired 10,12-*trans*

relative configuration. It was decided to advance towards triketone **106** with an enriched

mixture of *C*-alkylated **349** with the anticipation that isolation of the major diastereomer

and determination of the relative configuration could be achieved at a later stage in the

synthesis.

2.2.1.4. Synthesis towards triketone 106

The initial step toward triketone **106** involved silyl deprotection of *C*-alkylated **349**

(dr 4.6:1) by treatment with 0.1% HF to furnish diol **350** (4.6:1) in 93% yield (Scheme

2.38.). Subsequent reduction of **350** (dr 4.6:1) using $Et_2BOMe/NaBH_4$ resulted in a

diastereomeric mixture of triols **351** (dr 6:1:1) in 93% yield. Acetonide protection of the

1,3-diol in **351** (dr 6:1:1) by reaction with 2,2-dimethoxypropane and PTSA provided

alcohol **352** (dr 6:1:1) in 93% yield. Analysis of the ^{13}C NMR spectrum of **352** (dr 6:1:1)

revealed the diagnostic acetonide methyl chemical shifts for a 1,3-*syn* acetonide (*i.e.* 30.8

ppm and 20.3 ppm) for the major dastereomer.[185] Hydrogenolysis of **352** (dr 6:1:1) by

treatment with Li/NH$_3$ furnished diol **353** (dr 6:1:1) in 91% yield that was protected with

the required di-*tert*-butylsilylene group by treatment with 2,6-lutidine and *t*-Bu$_2$Si(OTf)$_2$

for 7 h that gave partially protected **354** (dr 6:1:1) in 77% yield. Interestingly, partially

protected **354** (dr 6:1:1) cyclized on brief treatment with aqueous TFA in THF (15 min)

to give **355** (dr 6:1:1) in 75% yield. The structures of **354** and **355** were comfirmed by

extensive spectroscopic studies. Of particular note was an XH type IR frequency (3492

cm^{-1}) for **354** suggesting the presence of hydroxyl group(s). Indeed, this was further

supported by deutrium chemical exchange which also assisted in establishing the location

of the silyl group *via* HSQC and HMBC ^{1}H-^{13}C NMR correlation experiments (*i.e.*

correlation of <u>H</u>OC-5/<u>C</u>-5). Cyclized **355** did not posses any XH type IR frequencies and

was also supported by the presence of a HRMS ([M+H]$^+$) molecular ion.
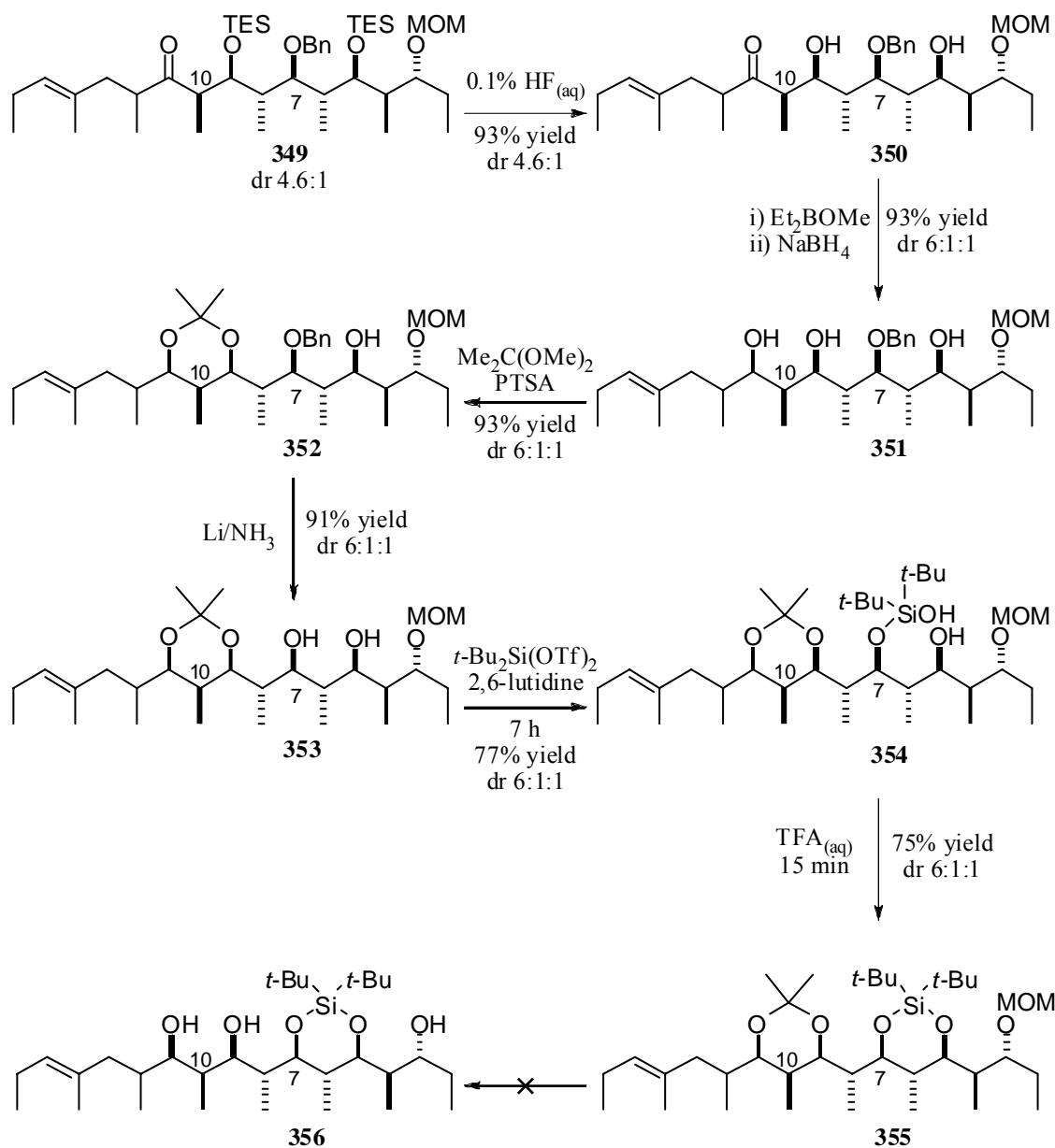
Scheme 2.38.

The next step required the removal of the acetonide and MOM protecting groups. Unfortunately, this transformation could not be effected under various conditions (*e.g.* TFA$_{(aq)}$/THF, TiCl$_4$/PhSH, TiCl$_4$/1,3-propanedithiol, FeCl$_3$·6H$_2$O). Attempted deprotection of **355** (dr 6:1:1) using TiCl$_4$/PhSH, TiCl$_4$/1,3-propanedithiol or FeCl$_3$·6H$_2$O resulted with the loss of the double bond while aqueous TFA in THF resulted with *ca.*

1.5:1 mixture of compounds that did not possess the expected chemicals shifts for the proposed triol **356**. In light of these results, **355** did not offer any obvious solution to access the desired triol **356**. While this concluded the synthetic studies, the strategy to assemble complex polypropionate structures by implementation of the thiopyran route was clearly demonstrated.

At this point it was decided to focus on establishing the 10,12 relative configuration for the *C*-alkylation of **347** using allylic bromide **47**. Conformational analysis[xli] of representative structures **358** and **359** for **355** revealed one dominant[xlii] conformer for each diastereomer (Figure 2.12.). After extensive NOE studies, only one correlation was

358   **359**
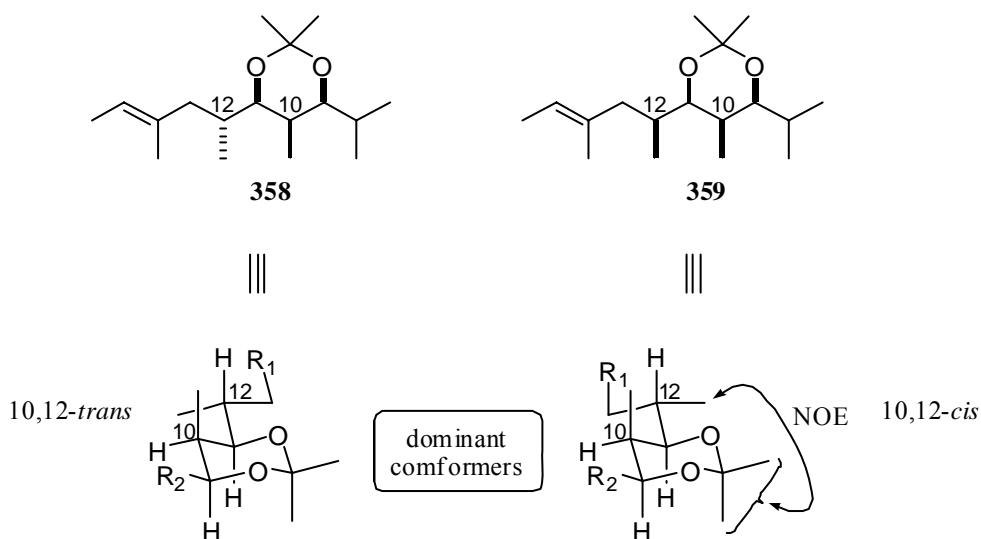
Figure 2.12. Attempted determination of the relative configuration of *C*-alkylation products.

clearly identified between the acetonide methyls and the H_3CC-12 (Figure 2.12.). Unfortunately, there was no obvious NOE between either the H_3CC-10 and HC-12 or HC-10 and H_2C-13. Literature examples[177-184] suggest that under the reaction conditions used for the *C*-alkylation of **347**, a 10,12-*trans* products would result; however, these

findings are suggestive for a 10,12-*cis* C-alkylation. One plausible rationale is that the use of excess NaHMDS promotes a chelation controlled mechanism rather than an A-strain controlled mechanism (Figure 2.11.). Ultimately, there is insufficient data to conclusively confirm the relative configuration and it is cautioned to form any conclusions.

2.3. Conclusions

Until this work, there have been no reports of a sequential enantiotopic group selective enolization of *meso* diketones. One of the significant challenges for this investigation was providing rapid access to the required starting materials. The thiopyran route to polypropionates provided a strategy that involved two aldol couplings of racemic substrates and allowed access to *meso* bisaldol adduct **212a** which was used for the establishment of a method for desymmetrization of *meso* diketones (Scheme 2.39.). Processing of **212a** gave a suitably protected *meso* diketone **233** which was desymmetrized using **230** to give access to enantioenriched (−)-**261** with high yields (>90% BORSM) and ee's (>95%). Reduction and desulfurization of (−)-**261** gave hexapropionate synthon (−)-**278** which established the thiopyran route to polypropionates and concluded the SEG selective enolization model study.

Application of the thiopyran route to polypropionates was realized by extension of the developed methodology for synthetic studies toward denticulatin A (Scheme 2.40.). During this work, several interesting features were elucidated. Processing of *meso* bis-aldol adduct **212a** to diol diketone **307** provided a rapid and diverse approach to various protected diketones. Enantioselective enolization of bis-TES diketone **308** using *ent*-**230** furnished mono-silyl enol ether **315** that was processed to ketone **347**. *C*-alkylation of

347 gave **349** in good yield (65%; >90% BORSM) and was derivatized to fully protected

355 over 7 steps in 27% yield.
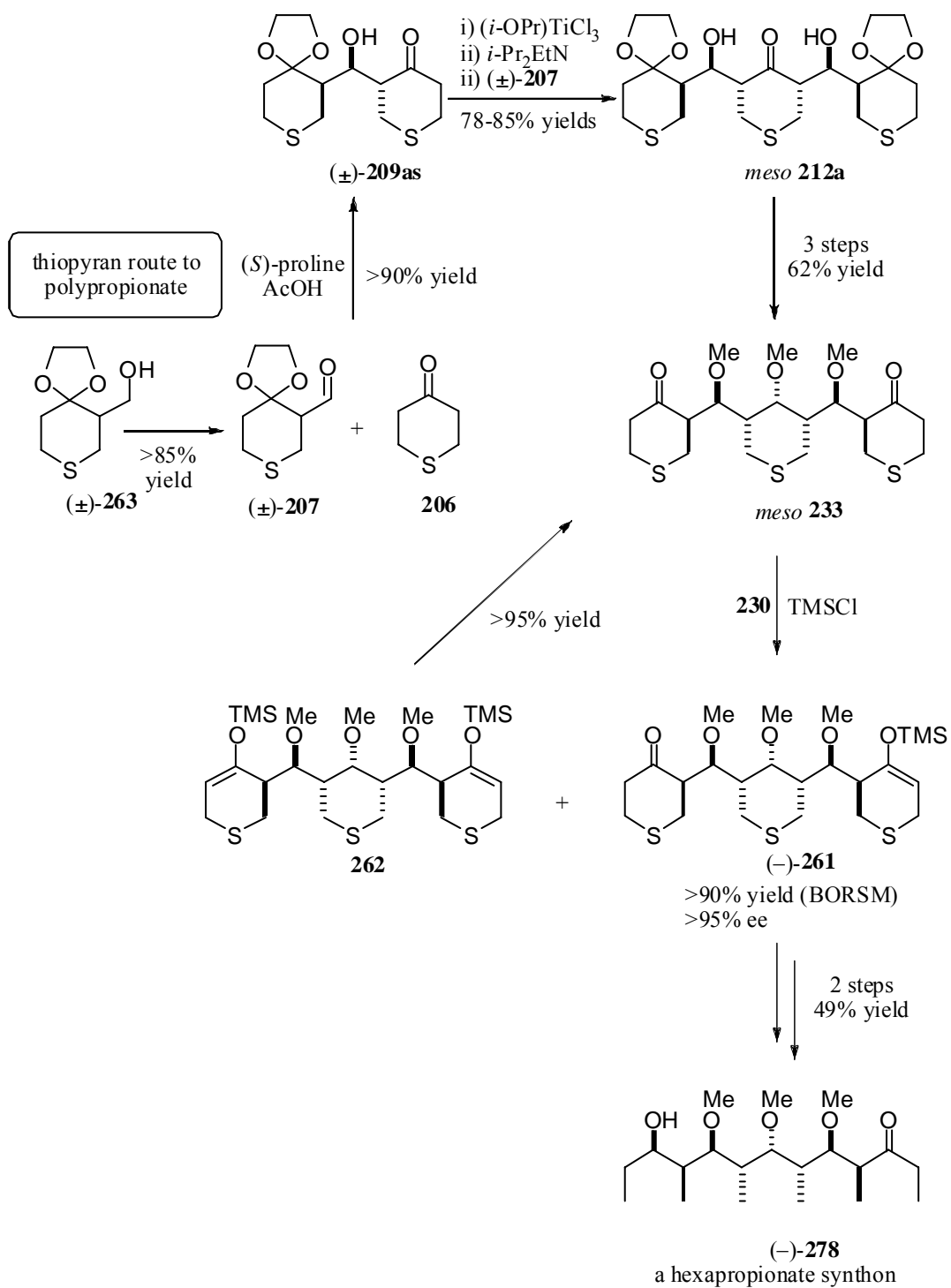
Scheme 2.39.
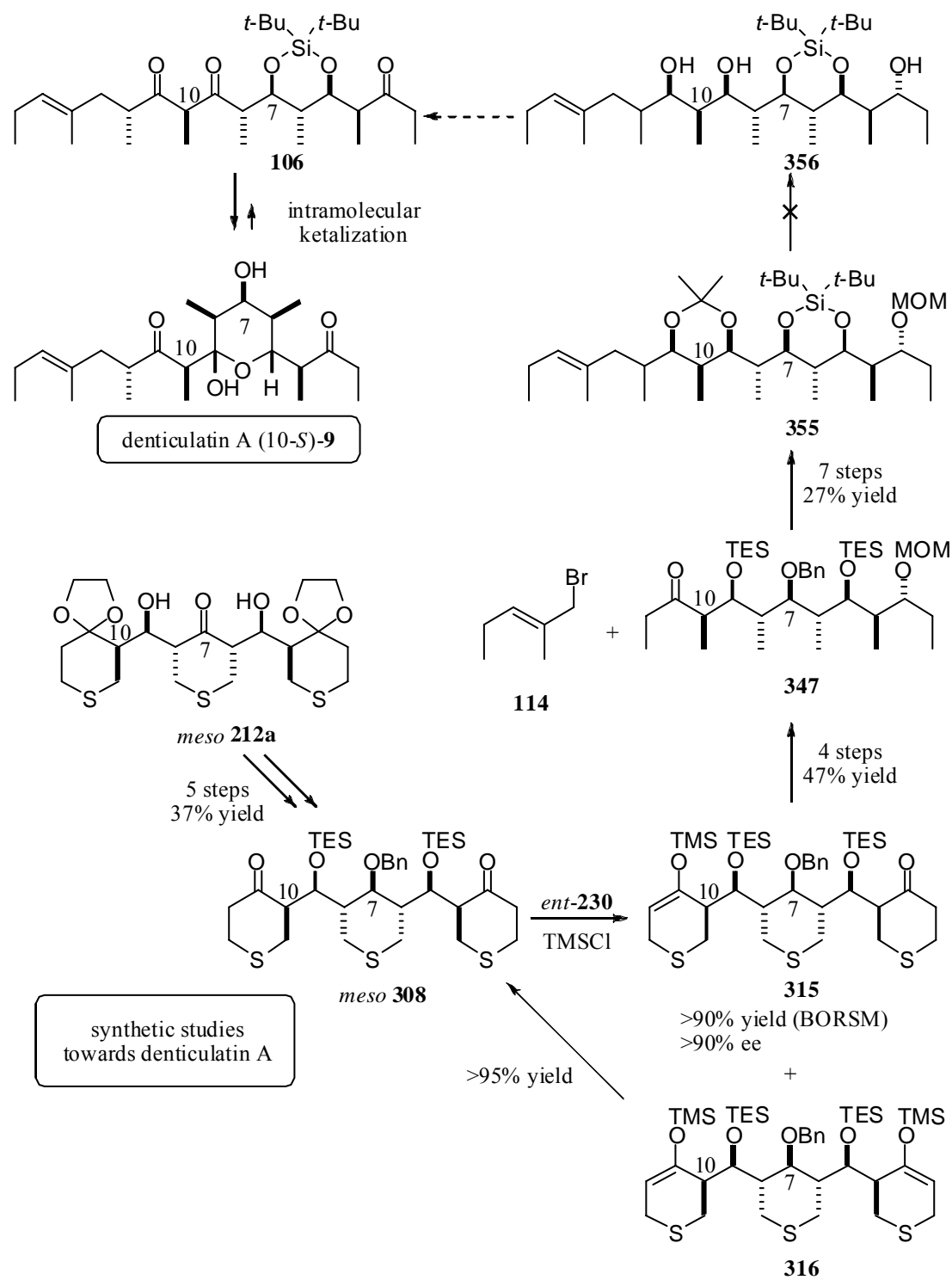
Scheme 2.40.

CHAPTER 3
3. EXPERIMENTAL

3.1. General methods

All solvents were distilled prior to use. Et$_3$N, *i*-Pr$_2$EtN, *i*-Pr$_2$NH and TiCl$_4$ were distilled from CaH$_2$ (Et$_3$N and *i*-Pr$_2$EtN were then stored over KOH). TMEDA was distilled over KOH and then stored over KOH. TMSCl was distilled from Bu$_3$N or CaH$_2$. *n*-BuLi, *t*-BuLi and NaHMDS were routinely titrated[186-188] using BHT with fluorene as the indicator.[xliii] Anhydrous solvents were distilled under argon atmosphere as follows: THF and ether from benzophenone sodium ketyl; CH$_2$Cl$_2$ and toluene from CaH$_2$; MeOH from Mg(OMe)$_2$. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven or flamed dried round-bottom flask capped with a rubber septum, and attached *via* a needle and connecting tubing to an argon manifold equipped with mercury bubbler (*ca.* 5 mm positive pressure of argon). Low temperature baths were ice/water (0 °C), CO$_{2(s)}$/acetonitrile (−30 - −50 °C), CO$_{2(s)}$/acetone (−78 °C) and liquid nitrogen/ether (−100 °C). Reaction temperatures refer to that of the bath unless otherwise noted.

PTLC was carried out on glass plates (20×20 cm) precoated (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 (5%) containing a trace of ceric sulfate in aqueous sulfuric acid

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[xliii] BHT (*ca.* 100 mg, 0.45 mmol) and fluorene (*ca.* 10 mg) were dissolved in THF (2 mL) and cooled to 0 °C under Ar. The organolithium or sodium hexamethyldisilazide was then added dropwise *via* syringe until an orange end-point persisted.

(5% v/v), followed by charring on a hot plate. Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Unless otherwise noted, all reported compounds were homogeneous by TLC and by NMR.

FCC was performed according to Still *et al.*[189] with Merck Silica Gel 60 (40-63 µm). All mixed solvent eluents are reported as v/v solutions.

3.2. Spectral data

HRMS and LRMS were obtained on an API QSTAR® Pulsar Hybrid LC/MS/MS system and/or a VG 70E double focusing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI at 50 eV with ammonia as the reagent gas; only partial data are reported. IR spectra were recorded on a Bio-Rad Fourier transform interferometer using a diffuse reflectance cell (DRIFT);[190] only diagnostic and/or intense peaks are reported. Specific rotations ($[\alpha]_D$) measurements were determined on a DigiPol 781-T6U automatic polarimeter and reported as the average of 5 measurements with an acceptable STD (*i.e.* < 0.003° for α < 20°). NMR spectra were obtained on an Avance NMR spectrometer equipped with a 5 mm TXI (inverse triple resonance), BBI (inverse broadband) and/or BBO (observe broadband) probe. Spectra were measured in $CDCl_3$ or C_6D_6 solutions 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.

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Couplings constants (*J*) are reported to the nearest 0.5 Hz. The ^{1}H NMR assignments[191-193] were made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling,[194] gCOSY,[191, 193, 195] and/or gNOESY[191, 193, 196-199] experiments. The ^{13}C NMR assignments[191-193] were made on the basis of chemical shift and multiplicity (*i.e.*, s = C, d = CH, t = CH$_2$, q = CH$_3$) as determined by ^{13}C-DEPT-135[191, 193, 200] and/or *J*-modulation[193, 201] and/or gHSQC[191, 193, 202] experiments and were confirmed, where necessary, by gHMBC.[191, 203]

3.3. Materials

The preparations of the following compounds were described previously: **206**[118, 124], **218**[118, 124], **263**[118], **210sa**[118], W-2 Raney Ni,[204] DMP,[205] MOMCl,[206-210] (*E*)-1-bromo-2-methylpent-2-ene **47**[18, 211] and both (*R*)- and (*S*)-*O*-acetylmandelic acid[212, 213]. (+)-(*R*,*R*)-bis(1-phenylethyl)amine **230** and *ent*-**230** and their corresponding hydrochloride salts are commercially available. Both **230**·HCl and *ent*-**230**·HCl were also prepared according to the published procedures.[214, 215] The $[\alpha]_D$ value reported for *ent*-**230**·HCl varies widely (−71.8, *c* 4, EtOH;[215] −84.1, *c* 3, EtOH[214]) and appears to be sensitive to solvent, concentration and temperature. Samples of *ent*-**230**·HCl were routinely obtained with $[\alpha]_D^{24\text{-}25}$ −68 to −70 (*c* 3.0-4.0, EtOH). These samples were determined to be >99% ee by ^{1}H NMR in the presence of (+)-(*R*)-TFAE as a chiral solvating agent. All other reagents were commercially available and unless otherwise noted, were used as received.

3.4. Experimental procedures and spectral data

207
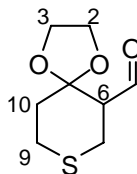
1,4-Dioxa-8-thiaspiro[4.5]decane-6-carbaldehyde

DMSO (20.9 mL, 23.0 g, 0.29 mol) was added dropwise *via* syringe to a stirred solution of oxalyl chloride (12.8 mL, 19.0 g, 0.15 mol) in CH$_2$Cl$_2$ (560 mL) at −78 °C under argon. After 10 min at −78 °C, a solution of **263** (26.54 g, 0.14 mol) and *i*-Pr$_2$EtN (24.4 mL, 18.1 g, 0.14 mol) in CH$_2$Cl$_2$ (*ca.* 1 M, 140 mL) was added dropwise over 10 min *via* syringe to the reaction mixture. After 5 min, *i*-Pr$_2$EtN (53.7 mL, 39.8 g, 0.31 mol) was added and the reaction mixture was allowed to warm to *ca.* 0 °C over 30 min. The mixture was transferred to a separatory funnel containing ice-cold aqueous 1 N HCl and was extracted with CH$_2$Cl$_2$ (3×). The combined organic layers were washed with sat. aqueous NaHCO$_3$, dried over Na$_2$SO$_4$ and concentrated to give crude **207** (24.8 g). Fractionation of the residue by FCC (10-50% ethyl acetate in hexane) gave recovered **263** (0.86 g, 3%) and aldehyde **207** (22.2 g, 85%).

Spectral data for **207** were in accord with that previously reported.[118]
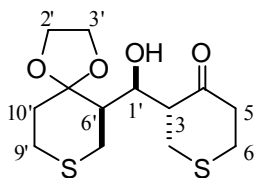
209as

(*R*)-3-((*S*)-Hydroxy((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one

A mixture of ketone **206** (4.33 g, 37.2 mmol), aldehyde **207** (3.84 g, 20.4 mmol), (*S*)-proline (1.22 g, 10.6 mmol) and acetic acid (0.36 mL, 6.38 mmol) was stirred at 38 °C. After 2 days, the brownish solid reaction mixture was dissolved in dichloromethane, passed through a pad of silica, concentrated and triturated with 5% ethyl acetate in hexanes to give aldol adduct **209as** as a white solid (4.66 g, 75%) ($[\alpha]_D^{25}$ −9; *c* 1.0, CHCl$_3$).

Spectral data for **209as** were in accord with that previously reported.[118]
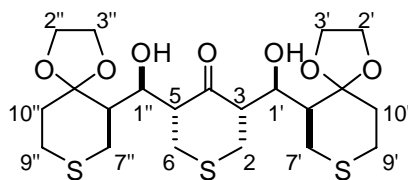
212a

(3*R*,5*S*)-3-((*S*)-Hydroxy((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-5-((*R*)-hydroxy((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one

(*i*-PrO)TiCl$_3$ (*ca.* 0.5 M solution in CH$_2$Cl$_2$, 21.5 mL, 10.7 mmol)[216] was added dropwise *via* syringe to a stirred solution of the ketone **209as** (2.97 g, 9.76 mmol) in CH$_2$Cl$_2$ (100 mL) at −78 °C under argon. After 5 min, *i*-Pr$_2$EtN (1.79 mL, 1.32 g, 10.2 mmol) was added dropwise *via* syringe to the reaction mixture at −78 °C. After 1 h, **207** (3.67 g, 19.5 mmol) was added and the mixture was stirred at −78 °C for 2 h and then *i*-Pr$_2$EtN (2.55 mL, 1.89 g, 14.6 mmol) was added dropwise *via* syringe to the reaction mixture at −78 °C and the mixture was stirred for an additional 2 h. The reaction was quenched by addition of saturated aqueous NH$_4$Cl and quickly worked up by dilution with water and extraction with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Fractionation of the residue by FCC gave recovered **207** (2.03 g, 55%) and *meso* bisaldol adduct **212a** (3.96 g, 82%) as a white solid (mp 166-167 °C).

Spectral data for **212a** were in accord with that previously reported.[117, 122]
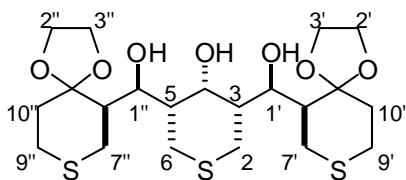
231

(3*S*,4*s*,5*R*)-3-((*S*)-Hydroxy((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-5-((*R*)-hydroxy((S)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)tetrahydro-2*H*-thiopyran-4-ol

DIBAL-H (1.5 M in toluene; 7.0 mL, 10.6 mmol) was added dropwise *via* syringe to a solution of bisaldol **212a** (1.04 g, 2.11 mmol) in THF (30 mL) at −78 °C under Ar. After 3 h, excess DIBAL-H was quenched by dropwise addition of methanol (*ca.* 1 mL) and the resulting mixture was warmed to room temperature over 15-30 min. A sat. aqueous solution of sodium potassium tartrate (30 mL) was slowly added (caution: exothermic) to the well-stirred solution. After 30 min, the mixture was diluted with water and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4 and concentrated to give crude triol **231** (1.04 g) which was an 8:1 mixture of diastereomers by ^{1}H NMR. Fractionation of the crude by FCC (75-100% ethyl acetate in hexane) gave the titled triol **231** (890 mg, 86%) as a white solid (mp 109-110 °C).

IR (DRIFT) ν_{max}: 3438, 2901, 1415, 1254, 1049 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 4.69 (1H, br s, HC-4), 4.13 (2H, dd, *J* = 2, 7.5 Hz, HC-1', HC-1"), 4.10-3.92 (8H, m, H$_2$C-2', H$_2$C-3', H$_2$C-2", H$_2$C-3"), 3.50 (1H, s, HOC-4), 3.40-3.16 (2H, br s, HOC-1', HOC-1"), 3.08-2.94 (4H, m, HC-2, HC-6, HC-7', HC-7"), 2.85-2.71 (4H, m, HC-7', HC-7", HC-9', HC-9"), 2.61 (2H, dddd, *J* = 1, 3.5, 5, 13 Hz,

HC-9', HC-9"), 2.18-2.09 (4H, m, HC-2, HC-6, HC-10', HC-10"), 2.07 (2H, ddd, $J = 3, 3,$ 10.5 Hz, HC-6', HC-6"), 1.87 (2H, dddd, $J = 2, 3.5, 7.5, 12$ Hz, HC-3, HC-5), 1.75 (2H, ddd, $J = 3.5, 11.5, 14.5$ Hz, HC-10', HC-10").

^{13}**C NMR** (125 MHz, CDCl$_3$): δ 110.2 (s ×2, C-5', C-5"), 70.6 (d ×2, C-1', C-1"), 64.8 (t ×2, C-2', C-2" or C-3', C-3"), 64.7 (d, C-4), 64.5 (t ×2, C-2', C-2" or C-3', C-3"), 47.2 (d ×2, C-6', C-6"), 46.2 (d ×2, C-3, C-5), 36.0 (t ×2, C-10', C-10"), 26.8 (t ×2, C-7', C-7" or C-9', C-9"), 26.7 (t ×2, C-7', C-7" or C-9', C-9"), 24.9 (t ×2, C-2, C-6).

LRMS (EI), *m/z* (relative intensity): 494 ([M]$^+$, 85), 414 (72), 317 (80), 255 (96), 226 (60).

HRMS *m/z* calcd. for C$_{21}$H$_{34}$O$_7$S$_3$: 494.1467; found: 494.1469.

Anal. Calcd. for C$_{21}$H$_{34}$O$_7$S$_3$: C, 50.99; H, 6.93. Found: C, 50.12; H, 7.01.
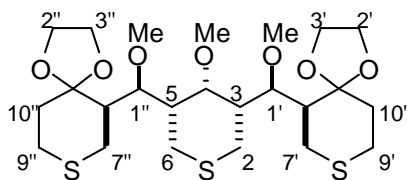
232

(3*S*,4*s*,5*R*)-4-Methoxy-3-((*S*)-hydroxy((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-5-((*R*)-hydroxy((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)tetrahydro-2*H*-thiopyran

A solution of the triol **231** (913 mg, 1.85 mmol) in THF (5 mL, plus a 5 mL wash) was added dropwise *via* syringe to a stirred suspension of oil free KH (prepared by washing 2 g of a 30% w/v suspension in oil with hexane under Ar; *ca.* 15 mmol) in THF (150 mL) at 0 °C under Ar. The resulting mixture was warmed to room temperature over 1 h and iodomethane (2.3 mL, 37 mmol) was added. After 8 h, the mixture was cooled to 0 °C and methanol (0.75 mL) was added dropwise *via* syringe (caution: H_2 evolution). The mixture was diluted with H_2O and extracted with CH_2Cl_2 (3×) and the combined organic layers were dried over Na_2SO_4, concentrated and fractionated by FCC (50% ethyl acetate in hexane) to give the titled **232** (897 mg, 91%).

IR (DRIFT) v_{max}: 2917, 2827, 1446, 1314, 1260, 1087 cm^{-1}.

¹H NMR (500 MHz, CDCl₃): δ 4.17 (1H, br s, HC-4), 4.09-3.92 (8H, m, H₂C-2', H₂C-3', H₂C-2", H₂C-3"), 3.46 (3H, s, H₃COC-4), 3.38 (6H, s, H₃COC-1', H₃COC-1"), 3.23 (2H, dd, *J* = 2, 9 Hz, HC-1', HC-1"), 2.92-2.79 (6H, m, HC-2, HC-6, HC-7', HC-7", HC-9', HC-9"), 2.63 (2H, ddd, *J* = 3, 3, 14 Hz, HC-7', HC-7"), 2.51 (2H, dddd, *J* = 3.5, 3.5, 6, 13.5 Hz, HC-9', HC-9"), 2.26 (2H, dd, *J* = 2, 13.5 Hz, HC-2, HC-6), 2.21 (2H, ddd, *J* = 3,

3, 11.5 Hz, HC-6', HC-6"), 2.12 (2H, ddd, J = 3.5, 3.5, 13.5 Hz, HC-10', HC-10"), 1.75-

1.66 (4H, m, HC-3, HC-5, HC-10', HC-10").

^{13}C NMR (125 MHz, CDCl$_3$): 108.7 (s ×2, C-5', C-5"), 78.3 (d ×2, C-1', C-1"), 74.6 (d,

C-4), 64.8 (t ×2, C-2', C-2" or C-3', C-3"), 64.7 (t ×2, C-2', C-2" or C-3', C-3"), 60.4 (q,

CH$_3$OC-4), 59.1 (q ×2, CH$_3$OC-1', CH$_3$OC-1"), 50.5 (d ×2, C-3, C-3 or C-6', C-6"), 50.4

(d ×2, C-3, C-3 or C-6', C-6"), 36.6 (t ×2, C-10', C-10"), 27.6 (t ×2), 26.8 (t ×2), 25.1 (t

×2).

LRMS (EI), *m/z* (relative intensity): 536 ([M]$^+$, 8), 504 (3), 472 (4), 345 (18), 203 (50),

132 (24), 99 (100), 71 (87).

HRMS *m/z* calcd. for C$_{24}$H$_{40}$O$_7$S$_3$: 536.1936; found: 536.1924.

Anal. Calcd. for C$_{24}$H$_{40}$O$_7$S$_3$: C, 53.70; H, 7.51. Found: C, 53.61; H, 7.21.
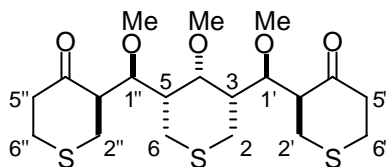
233

(3*R*,3'*S*)-3,3'-((1*S*,1'*R*)-((3*R*,4*s*,5*S*)-4-Methoxytetrahydro-2*H*-thiopyran-3,5-diyl)bis(methoxymethylene))bis(dihydro-2*H*-thiopyran-4(3*H*)-one)

Amberlyst$^®$ 15 (1.6 g) was added to a well-stirred solution of bis-ketal **232** (779 mg, 1.41 mmol) in acetone (60 mL) and the resulting suspension was heated under refluxed for 4 h. After cooling to room temperature, CH_2Cl_2 (15 mL) and solid $NaHCO_3$ (excess) were added. The mixture was filtered and the combined filtrate and washings were concentrated and fractionated by FCC (5-25% ethyl acetate in hexane) to give the titled diketone **233** (530 mg, 81%) as a white solid (mp 214-215 °C).

From bis-silyl enol ether **262**

10% vol aqueous HF (0.5 mL) was added dropwise to a stirred solution of bis-silyl enol ether **262** (54 mg, 0.091 mmol) in THF (5 mL) at room temperature. After 30 min, sat. aqueous $NaHCO_3$ was slowly added (caution: effervescence) and the resulting mixture was diluted with EtOAc and washed sequentially with sat. aqueous $NaHCO_3$ (3×), brine, dried over Na_2SO_4 and concentrated to give crude diketone **233**. Recrystallization of the crude from ethyl acetate gave the titled diketone **233** (39 mg, 95%).

IR (DRIFT) ν_{max}: 2922, 2838, 1702, 1432, 1331, 1218 cm^{-1}.

¹H NMR (500 MHz, CDCl₃): δ 4.07 (1H, br s, HC-4), 4.01 (1H, dd, *J* = 1.5, 9 Hz, HC-1', HC-1"), 3.48 (3H, s, CH₃OC-4), 3.30 (6H, s, CH₃OC-1', CH₃OC-1"), 3.04-2.76 (12H, m), 2.75-2.62 (4H, m, HC-5', HC-5", HC-3', HC-3"), 1.98 (2H, dd, *J* = 2, 13 Hz, HC-2, HC-6), 1.73 (2H, br ddd, *J* = 2, 9, 13 Hz, HC-3, HC-5).

¹³C NMR (125 MHz, CDCl₃): δ 208.6 (s ×2, C-4', C-4"), 77.1 (d ×2, C-1',C-1"), 74.0 (d, C-4), 61.5 (q, CH₃OC-4), 59.3 (q ×2, CH₃OC-1', CH₃OC-1"), 54.7 (d ×2, C-3', C-3"), 48.0 (d ×2, C-3, C-5), 43.9 (t ×2, C-5', C-5"), 29.1 (t ×2, C-2', C-2" or C-6', C-6"), 28.7 (t ×2, C-2', C-2" or C-6', C-6"), 24.5 (t ×2, C-2, C-6).

LRMS (EI), *m/z* (relative intensity): 448 ([M]⁺, 7), 301 (11), 197 (9), 159 (14).

HRMS *m/z* calcd. for C₂₀H₃₂O₅S₃: 448.1412; found: 448.1399.

Anal. Calcd. for C₂₀H₃₂O₅S₃: C, 53.54; H, 7.19. Found: C, 53.95; H, 6.75.
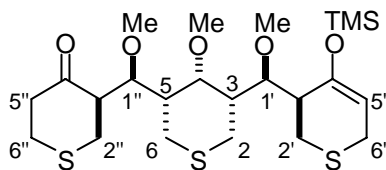
(−)-**261**

(*R*)-3-((*S*)-Methoxy((3*S*,4*R*,5*R*)-4-methoxy-5-((*R*)-methoxy((*S*)-4-(trimethylsilyloxy)-3,6-dihydro-2*H*-thiopyran-3-yl)methyl)tetrahydro-2*H*-thiopyran-3-yl)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one

A solution of *n*-BuLi in hexanes (2.1 M; 0.16 mL, 0.33 mmol) was added dropwise *via* syringe to a solution of (*R*,*R*)-bis(1-phenylethyl)amine (0.075 mL, 74 mg, 0.33 mmol) in THF (6 mL) at −78 °C under Ar. After stirring for 30 min at −78 °C the resulting pink solution was quickly transferred *via* cannula (*ca.* 15-30 sec.) into a well-stirred solution of diketone **233** (92 mg, 0.205 mmol) and TMSCl (0.22 mL, 223 mg, 2.05 mmol) in THF (10 mL) at −100 °C under Ar. After 15 min, the reaction was quenched by addition of acetone (0.5 mL) followed by Et₃N (0.5 mL) and sat. aqueous NaHCO₃. The resulting cold mixture was diluted with ethyl acetate and washed sequentially with 1% w/v aqueous citric acid (4×), sat. aqueous NaHCO₃, brine, dried over Na₂SO₄, concentrated and fractionated by FCC (10-20% ethyl acetate in hexane) to give the bis-silyl enol ether **262** (13 mg, 11%), recovered diketone **233** (15 mg, 16%) and the titled mono-silyl enol ether (−)-**261** (75 mg, 71%) ($[\alpha]_D^{25}$ −1.0; *c* 5.9, C₆H₆; >96% ee by ¹H NMR as shown in Appendix A).

IR (DRIFT) ν_{max}: 2928, 2832, 1702, 1666, 1420, 1187 cm^{-1}.

^{1}**H NMR** (500 MHz, CDCl$_3$): δ 5.14 (1H, ddd, J = 2, 2, 6.5 Hz, HC-5'), 4.10 (1H, br s, HC-4), 4.01 (1H, dd, J = 2, 9 Hz, HC-1"), 3.84 (1H, dd, J = 1, 10 Hz, HC-1'), 3.51 (3H, s, H$_3$COC-4), 3.44 (3H, s, H$_3$COC-1'), 3.38 (1H, ddd, J = 3, 3, 16.5 Hz, HC-6'), 3.31 (3H, s, H$_3$COC-1"), 3.06-2.64 (11H, m), 2.60 (1H, ddd, J = 1.5, 5.5, 14 Hz, HC-2'), 2.36 (1H, br s, HC-3'), 2.05 (1H, dd, J = 2.5, 16.5 Hz, HC-2, HC-6), 1.99 (1H, dd, J = 2.5, 13 Hz, HC-2, HC-6), 1.74 (2H, m, HC-3, HC-5), 0.21 (9H, s, (H$_3$C)$_3$SiOC-4').

^{13}**C NMR** (125 MHz, CDCl$_3$): δ 208.8 (s, C-4"), 152.8 (s, C-4'), 104.1 (d, C-5'), 78.1 (d, C-1'), 77.3 (d, C-1"), 74.3 (d, C-4), 61.1 (q, CH$_3$OC-4), 59.3 (q, CH$_3$OC-1"), 58.9 (q, CH$_3$OC-1'), 54.7 (d, C-3"), 47.7 (d, C-3 or C-5), 47.5 (d, C-3 or C-5), 43.9 (t, C-5"), 42.0 (d, C-3'), 29.1 (t, C-2" or C-6"), 28.8 (t, C-2" or C-6"), 25.4 (t, C-2' or C-6'), 25.4 (t, C-2' or C-6'), 24.5 (t, C-2 or C-6), 24.3 (t, C-2 or C-6), 0.5 (q, (CH$_3$)$_3$SiOC-4').

LRMS (CI, NH$_3$), m/z (relative intensity): 538 ([M+18]$^+$, 13), 521 ([M+7]$^+$, 20), 489 (68), 464 (32), 457 (42), 447 (39), 415 (49), 333 (41), 301 (60), 227 (100).

HRMS m/z calcd. for C$_{23}$H$_{40}$O$_5$S$_3$Si: 520.1807 (527.1967 for M+Li); found: 527.1956 (FAB, LiBr/NBA).

Anal. Calcd. for C$_{23}$H$_{40}$O$_5$S$_3$Si: C, 53.04; H, 7.74. Found: C, 53.42; H, 7.65.
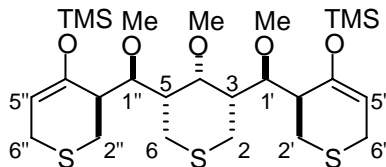
262

((*S*)-3-((*R*)-Methoxy((3*R*,4*s*,5*S*)-4-methoxy-5-((*S*)-methoxy((*R*)-4-(trimethylsilyloxy)-3,6-dihydro-2*H*-thiopyran-3-yl)methyl)tetrahydro-2*H*-thiopyran-3-yl)methyl)-3,6-dihydro-2*H*-thiopyran-4-yloxy)trimethylsilane

IR (DRIFT) ν_{max}: 2922, 2839, 1660, 1420, 1241, 1086 cm^{-1}.

^{1}**H NMR** (500 MHz, CDCl$_3$): δ 5.15 (2H, ddd, *J* = 2, 6.5, 6.5 Hz, HC-5, HC-5"), 4.13 (1H, br s, HC-4), 3.84 (2H, dd, *J* = 1, 10 Hz, HC-1', HC-1"), 3.55 (3H, s, H$_3$COC-4), 3.44 (6H, s, H$_3$COC-4', H$_3$COC-4"), 3.39 (2H, ddd, *J* = 3, 3, 16.5 Hz, HC-6', HC-6"), 3.00 (2H, dd, *J* = 10, 14 Hz, HC-2', HC-2"), 2.91 (2H, ddd, *J* = 1.5, 6.5, 16.5 Hz, HC-6', HC-6"), 2.76 (2H, dd, *J* = 12.5, 12.5 Hz, HC-2, HC-6), 2.61 (2H, ddd, *J* = 1.5, 5.5, 14 Hz, HC-2', HC-2"), 2.37 (2H, br s, HC-3', HC-3"), 2.06 (2H, dd, *J* = 3, 12.5 Hz, HC-2, HC-6), 1.75 (2H, br ddd, *J* = 3, 10, 12.5 Hz, HC-3, HC-5), 0.22 (18H, s, (H$_3$C)$_3$SiOC-4', (H$_3$C)$_3$SiOC-4").

^{13}**C NMR** (125 MHz, CDCl$_3$): δ 152.9 (s ×2, C-4, C-4"), 104.1 (s ×2, C-5', C-5"), 78.3 (d ×2, C-1', C-1"), 74.5 (d, C-4), 61.5 (q, CH$_3$OC-4), 59.0 (q ×2, CH$_3$OC-1', CH$_3$OC-1"), 47.3 (d ×2, C-3, C-5), 42.0 (d ×2, C-3', C-3"), 25.5 (t ×2, C-2', C-2" or C-6', C-6"), 25.5 (t ×2, C-2', C-2" or C-6', C-6"), 24.4 (t ×2, C-2, C-6), 0.5 (q ×6, (CH$_3$)$_3$SiOC-4', (CH$_3$)$_3$SiOC-4").

LRMS (CI, NH$_3$), *m/z* (relative intensity): 593 ([M+1]$^+$, 11), 561 (28), 405 (11), 373 (13), 227 (100), 185 (18), 90 (35), 71 (31).

HRMS *m/z* calcd. for C$_{26}$H$_{48}$O$_5$S$_3$Si$_2$: 592.2202 (599.2363 for M+Li); found: 592.2139 (FAB, LiBr/NBA).

Anal. Calcd. for C$_{26}$H$_{48}$O$_5$S$_3$Si$_2$: C, 52.66; H, 8.16. Found: C, 52.90; H, 8.12.
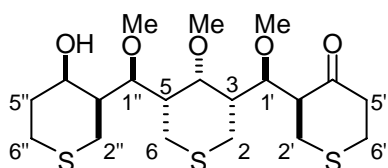
(−)-**271**

(*S*)-3-((*R*)-((3*R*,4*S*,5*R*)-5-((*R*)-((3*S*,4*R*)-4-Hydroxytetrahydro-2*H*-thiopyran-3-yl)(methoxy)methyl)-4-methoxytetrahydro-2*H*-thiopyran-3-yl)(methoxy)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one

L-Selectride$^®$ (0.8 M in THF; 0.83 mL, 0.7 mmol) was added dropwise to a stirred solution of mono-silyl enol ether (−)-**261** (138 mg, 0.265 mmol) in THF (13 mL) at −78 °C. After 30 min, the reaction was quenched by dropwise addition of MeOH (0.5 mL) and the resulting mixture was warmed to 0 °C over 10 min. Phosphate buffer (0.1 M in water, pH 7; 2.0 mL) and aqueous H$_2$O$_2$ (30% w/v; 0.5 mL) were added. After vigorous stirring for 10 min, the mixture was diluted with ice-cold aqueous Na$_2$SO$_3$ (2% w/v; 50 mL) and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, concentrated and fractionated by FCC (10-50% ethyl acetate in CH$_2$Cl$_2$) to give the titled ketol (−)-**271** (97mg, 82%) ([α]$_D^{24}$ −40; *c* 0.8, CH$_2$Cl$_2$).

IR (DRIFT) ν_{max}: 3430, 2928, 2832, 1696, 1420 cm^{-1}.

^{1}**H NMR** (500 MHz, CDCl$_3$): δ 4.09 (1H, br s, HC-4"), 4.05 (1H, br d, J = 9.5 Hz, HC-1'), 3.96 (1H, br s, HC-4), 3.53 (3H, s, H$_3$COC-4), 3.49 (3H, s, H$_3$COC-1"), 3.32 (1H, dd, J = 3.5, 7.5 Hz, HC-1"), 3.30 (3H, s, H$_3$COC-1'), 3.17 (1H, br dd, J = 13.5, 13.5 Hz, HC-6"), 3.09 (1H, br dd, J = 13, 13 Hz, HC-2"), 3.04-2.79 (7H, m), 2.75-2.64 (2H, m, HC-3', HC-5'), 2.29 (1H, br d, J = 13 Hz, HC-2"), 2.24 (1H, br d, J = 13.5 Hz, HC-6"), 2.20-2.10 (2H, m, HC-6, HC-5"), 2.08-1.93 (4H, m, HC-2,HC-3",HC-3,HO-4"), 1.86 (1H, br ddd, J = 3.5, 13, 13 Hz, HC-3"), 1.77 (1H, br dd, J = 9.5, 10 Hz, HC-3).

^{13}**C NMR** (125 MHz, CDCl$_3$): δ 208.52 (s, C-4'), 87.23 (d, C-1"), 76.86 (d, C-1'), 74.34 (d, C-4), 69.60 (d, C-4"), 60.55 (q, CH$_3$OC-4), 59.57 (q, CH$_3$OC-1"), 59.24 (q, CH$_3$OC-1'), 54.74 (d, C-3'), 48.54 (d, C-3), 47.62 (d, C-5), 45.06 (d, C-3"), 43.83 (t, C-5'), 35.39 (t, C-5"), 29.10 (t, C-2' or C-6'), 28.66 (t, C-2' or C-6'), 24.65 (t, C-2 or C-6), 24.49 (t, C-2 or C-6), 22.33 (t, C-2" or C-6"), 22.09 (t, C-2" or C-6").

LRMS (EI), m/z (relative intensity): 450 ([M]$^{+}$, 74), 386 (35), 301 (100), 232 (54), 159 (63).

HRMS m/z calcd. for C$_{20}$H$_{34}$O$_5$S$_3$: 450.1568; found: 450.1571.
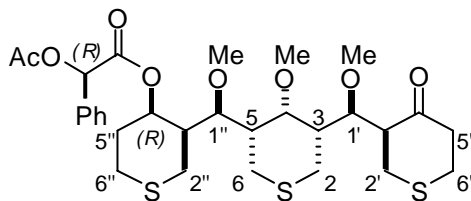
272

(R)-((3S,4R)-3-((R)-Methoxy((3R,4S,5R)-4-methoxy-5-((R)-methoxy((S)-4-oxotetrahydro-2H-thiopyran-3-yl)methyl)tetrahydro-2H-thiopyran-3-yl)methyl)tetrahydro-2H-thiopyran-4-yl)-2-acetoxy-2-phenylacetate

DCC (11 mg, 0.054 mmol) was added to a stirred solution of ketol (−)-**271** (8 mg, 0.02 mmol), (R)-OAM (10 mg, 0.054 mmol) and DMAP (*ca.* 1 mg) in CH$_2$Cl$_2$ (2 mL) at 0 °C under Ar. After 30 min, the reaction was diluted with ethyl acetate (2 mL) and filtered through Celite®. The combined filtrate and washings were washed sequentially with 10% w/v aqueous citric acid (3×), sat. aqueous NaHCO$_3$ and brine (1× 20 mL), dried over Na$_2$SO$_4$, concentrated, and fractionated by PTLC (50% ethyl acetate in hexane) to give crude **272** that was refractionated by PTLC (1% CH$_3$OH in CH$_2$Cl$_2$) to give the titled compound **272** (7 mg, 64%) containing *ca.* 10% (by ^{1}H NMR) of the diastereoisomeric ester from the (S)-acid.

IR (DRIFT) ν_{max}: 2934, 2827, 1738, 1696, 1432 cm^{-1}.

[1]**H NMR** (500 MHz, CDCl$_3$): 7.56-7.35 (5H, m, Ph), 5.91 (1H, s, HCPhCO$_2$C-4"), 4.97 (1H, dd, *J* = 2, 2.5 Hz, HC-4"), 3.95 (1H, dd, *J* = 2, 9 Hz, HC-1'), 3.71 (1H, dd, *J* = 1.5, 1.5 Hz, HC-4), 3.32 (3H, s, H$_3$COC-4), 3.29 (3H, s, H$_3$COC-1'), 3.03-2.57 (13H, m), 2.94 (3H, s, H$_3$COC-1"), 2.41-2.30 (2H, m, HC-6", HC-5"), 2.22 (3H, s, H$_3$CCO$_2$CHPhCO$_2$C-4"), 2.16 (1H, dd, *J* = 4, 8 Hz, HC-1"), 2.13 (1H, dddd, *J* = 2, 4, 8, 9 Hz, HC-3"), 1.94

(1H, dd, J = 3, 13 Hz, HC-2), 1.89 (1H, dddd, J = 2.5, 4, 14.5, 14.5 Hz, HC-5"), 1.61 (1H, dddd, J = 1.5, 3, 9, 12 Hz, HC-3), 1.49 (1H, dd, J = 10, 12 Hz, HC-6), 1.44 (1H, dddd, J = 1.5, 4, 4, 12 Hz, HC-5).

^{13}C NMR (125 MHz, CDCl$_3$): 208.8 (s, C-4'), 170.7 (s, CO$_2$CHPhCO$_2$C-4"), 168.3 (s, CO$_2$C-4"), 134.2 (s, Ph), 129.8 (d, Ph), 129.3 (d ×2, Ph), 128.1 (d ×2, Ph), 84.7 (d, C-1"), 77.2 (d, C-1'), 74.8 (d, CHPhCO$_2$C-4"), 74.1 (d, C-4), 70.7 (d, C-4"), 61.1 (q, CH$_3$OC-1"), 60.0 (q, CH$_3$OC-1'), 59.6 (q, CH$_3$OC-4), 54.7 (d, C-3'), 48.5 (d, C-3), 47.5 (d, C-5), 45.2 (d, C-3"), 43.9 (t, C-5'), 32.1 (t, C-5"), 29.1 (t, C-2' or C-6'), 28.9 (t, C-2' or C-6'), 25.6 (t, C-6), 24.8 (t, C-2 or C-2"), 24.8 (t, C-2 or C-2"), 22.4 (t, C-6"), 20.9 (q, CH$_3$CO$_2$CHPhCO$_2$C-4").

LRMS (EI), m/z (relative intensity): 626 ([M]$^+$, 3), 562 (3), 479 (3), 407 (2), 337 (33), 224 (40), 143 (100), 108 (37), 71 (54).

HRMS m/z calcd. for C$_{30}$H$_{42}$O$_8$S$_3$: 626.2042; found: 626.2040.
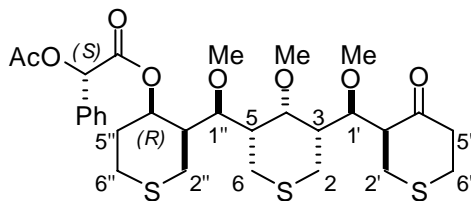
273

(S)-((3S,4R)-3-((R)-Methoxy((3R,4S,5R)-4-methoxy-5-((R)-methoxy((S)-4-oxotetrahydro-2H-thiopyran-3-yl)methyl)tetrahydro-2H-thiopyran-3-yl)methyl)tetrahydro-2H-thiopyran-4-yl)-2-acetoxy-2-phenylacetate

DCC (7 mg, 0.03 mmol) was added to a stirred solution of ketol (−)-**271** (5 mg, 0.01 mmol), (S)-OAM (6 mg, 0.03) and DMAP (*ca.* 0.5 mg) in CH_2Cl_2 (2 mL) at 0 °C. After 30 min, the reaction was diluted with ethyl acetate (2 mL) and filtered through Celite®. The combined filtrate and washings were washed sequentially with 10% w/v aqueous citric acid (3×), sat. aqueous $NaHCO_3$ and brine (1× 20 mL), dried over Na_2SO_4, concentrated, and fractionated by PTLC (50% ethyl acetate in hexane) to give crude **273** that was refractionated by PTLC (1% CH_3OH in CH_2Cl_2) to give the titled compound **273** (3 mg, 44%) containing *ca.* 10% (by ^{1}H NMR) of the diastereoisomeric ester from the (R)-acid.

IR (DRIFT) ν_{max}: 2928, 1744, 1696, 1432, 1373, 1169 cm^{-1}.

[1]**H NMR** (500 MHz, $CDCl_3$): δ 7.56-7.36 (5H, m, Ph), 5.95 (1H, s, HCPhCO$_2$C-4″), 5.08 (1H, br s, HC-4″), 4.00 (1H, dd, *J* = 1.5, 9 Hz, HC-1′), 3.96 (1H, br s, HC-4), 3.45 (3H, s, H$_3$COC-4), 3.41 (3H, s, H$_3$COC-1″), 3.31 (3H, s, H$_3$COC-1′), 3.04-2.80 (9H, m), 2.75-2.66 (2H, m, HC-3′, HC-5′), 2.51 (1H, br d, *J* = 13.5 Hz, HC-2 or HC-6), 2.26-2.19 (5H,

m, H$_3$CCO$_2$CHPhCO$_2$C-4", HC-3",HC-2" or HC-6"), 2.12-1.95 (3H, m), 2.03 (1H, m,

HC-5"), 1.82-1.72 (3H, m, HC-3, HC-5, HC-5").

^{13}**C NMR** (125 MHz, CDCl$_3$): δ 208.8 (s, C-4'), 170.5 (s, CO$_2$CHPhCO$_2$C-4"), 168.4 (s,

CO$_2$C-4"), 133.9 (s, Ph), 129.7 (d, Ph), 129.2 (d ×2, Ph), 127.6 (d ×2, Ph), 84.6 (d, C-1"),

77.1 (d, C-1'), 74.9 (d, CHPhCO$_2$C-4"), 74.0 (d, C-4), 71.6 (d, C-4"), 60.5 (q, CH$_3$OC-4),

60.3 (q, CH$_3$OC-1"), 59.4 (q, CH$_3$OC-1'), 54.7 (d, C-3'), 48.6 (d, C-3 or C-5), 48.2 (d, C-3

or C-5), 45.2 (d, C-3"), 43.9 (t, C-5'), 32.1 (t, C-5"), 29.1 (t, C-2' or C-6'), 28.8 (t, C-2' or

C-6'), 25.1 (t), 24.8 (t), 24.7 (t), 22.3 (t, C-2" or C-6"), 20.9 (q, CH$_3$CO$_2$CHPhCO$_2$C-4").

LRMS (EI), *m/z* (relative intensity): 626 ([M]$^+$, 2), 337 (36), 143 (100), 107 (12), 97

(15), 71 (39).

HRMS *m/z* calcd. for C$_{30}$H$_{42}$O$_8$S$_3$: 626.2042; found: 626.2046.
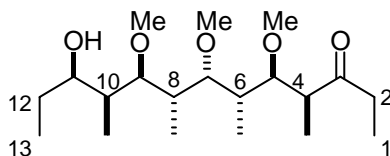
(−)-**278**

(4*S*,5*R*,6*R*,7*S*,8*R*,9*R*,10*S*,11*R*)-11-Hydroxy-5,7,9-trimethoxy-4,6,8,10-tetramethyltridecan-3-one

Sodium acetate buffer (1.0 M in water, pH 5.2; 1.5 mL), sodium hypophosphite monohydrate (1 M in water; 1.5 mL) and Raney Ni (W-2) (*ca.* 1 mL settled volume; added as a suspension in ethanol) were sequentially added to a well-stirred solution of a ketol (−)-**271** (31 mg, 0.069 mmol) in ethanol (2 mL) and THF (2 mL). The resultant mixture was heated under reflux and additional Raney Ni was added every 2 h. After 8 h, the reaction mixture was filtered through a pad of Celite® and the filter cake was rinsed sequentially with hot methanol (2× 20 mL), CH_2Cl_2 (2× 20 mL) and acetone (2× 20 mL). The combined filtrate and washings were concentrated and the residue was taken up in dichloromethane and washed with water, dried over Na_2SO_4, concentrated and fractionated by FCC (10-20% ethyl acetate in hexane) to give the titled ketol (−)-**278** (15 mg, 60%) ($[\alpha]_D^{27}$ −9; *c* 0.7, CH_3OH).

IR (DRIFT) ν_{max}: 3436, 2926, 2835, 1703, 1654, 1354 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 3.65-3.57 (2H, m, HC-5, HC-11), 3.50-3.46 (4H, m, HC-7, H₃COC-7), 3.43 (3H, s, H₃COC-9), 3.31 (3H, s, H₃COC-5), 3.21 (1H, dd, *J* = 3, 6.5 Hz, HC-9), 3.11-2.90 (1H, br s, HOC-11), 2.70-2.41 (3H, m, HC-4, H₂C-2), 1.98 (1H,

ddq, *J* = 6.5, 6.5, 7 Hz, HC-8), 1.75-1.65 (2H, m, HC-6, HC-10), 1.60-1.37 (2H, m, H_2C-12), 1.11 (3H, d, *J* = 7 Hz, H_3CC-4), 1.08 (3H, dd, *J* = 7.5, 7.5 Hz, H_3C-1), 0.98 (3H, d, *J* = 7 Hz, H_3CC-8), 0.93 (3H, t, *J* = 7.5 Hz, H_3C-13), 0.92 (3H, t, *J* = 7 Hz, H_3CC-6 or H_3CC-10), 0.89 (3H, t, *J* = 7 Hz, H_3CC-6 or H_3CC-10).

^{13}C NMR (125 MHz, CDCl$_3$): δ 214.4 (s, C-3), 87.2 (d, C-9), 83.9 (d, C-5), 81.1 (d, C-7), 77.7 (d, C-11), 61.1 (q, H_3COC-7), 59.7 (q, H_3COC-5), 58.6 (q, H_3COC-9), 48.4 (d, C-4), 40.3 (d, C-6), 39.9 (d, C-8), 37.9 (d, C-10), 34.5 (t, C-2), 27.7 (t, C-12), 11.6 (q), 11.0 (q), 10.8 (q), 9.9 (q), 8.2 (q), 7.6 (q).

LRMS (CI, NH$_3$), *m/z* (relative intensity): 361 ([M+1]$^+$, 77), 329 (73), 297 (50), 239 (313), 201 (76), 169 (100), 73 (65).

Me Me Me

$$\underset{\underset{13}{12}}{O} \quad \underset{10}{\overset{O}{|}} \quad \underset{8}{\overset{O}{|}} \quad \underset{6}{\overset{O}{|}} \quad \underset{4}{\overset{O}{|}} \quad \underset{\underset{1}{2}}{O}$$
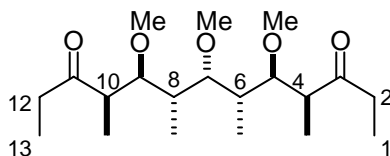
279

(4*R*,5*S*,6*S*,7*s*,8*R*,9*R*,10*S*)-5,7,9-Trimethoxy-4,6,8,10-tetramethyltridecane-3,11-dione

DMP (55 mg, 0.125 mmol) was added to a stirred solution of ketol (−)-**278** (9 mg, 0.025 mmol) in water-saturated CH$_2$Cl$_2$ (0.5 mL). After 30 min, the mixture was diluted with ether and washed sequentially with a 1:1 mixture of 10% w/v aqueous Na$_2$S$_2$O$_3$ and sat. aqueous NaHCO$_3$, respectively, water and brine (20 mL). The aqueous washings were extracted with ether and the combined organic layers were dried over Na$_2$SO$_4$, concentrated and fractionated by PTLC (20% ethyl acetate in hexane) to give the titled diketone **279** (7 mg, 75%).

IR (DRIFT) ν_{max}: 2622, 1714, 1660, 1457, 1373, 1092 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 3.56-3.48 (3H, m, HC-5, HC-7, HC-9), 3.43 (3H, s, H$_3$COC-7), 3.32 (6H, s, H$_3$COC-5, H$_3$COC-9), 2.72-2.45 (6H, m, H$_2$C-2, HC-4, HC-10, H$_2$C-12), 1.64 (2H, ddq, *J* = 4, 7, 7 Hz, HC-6, HC-8), 1.11 (6H, d, *J* = 7 Hz, H$_3$CC-4, H$_3$CC-10), 1.07 (6H, dd, *J* = 7.5, 7.5 Hz, H$_3$C-1, H$_2$C-13), 0.91 (6H, d, *J* = 7 Hz, H$_3$CC-6, H$_3$CC-8).

^{13}C NMR (125 MHz, CDCl$_3$): δ 214.46 (s ×2, C-3, C-11), 84.05 (d ×2, C-5, C-9), 79.73 (d, C-7), 60.51 (q, H$_3$COC-7), 59.84 (q ×2, H$_3$COC-5, H$_3$COC-9), 48.43 (d ×2, C-4, C-

10), 41.78 (q ×2, C-6, C-8), 34.59 (t ×2, C-2, C-12), 11.65 (q ×2, CH$_3$C-4, CH$_3$C-10), 10.78 (t ×2, C-1, C-13), 8.11 (q ×2, CH$_3$C-6, CH$_3$C-8).

LRMS (CI, NH$_3$), *m/z* (relative intensity): 359 ([M+1]$^+$, 8), 327 (40), 295 (38), 201 (39), 169 (100), 129 (30), 57 (32).
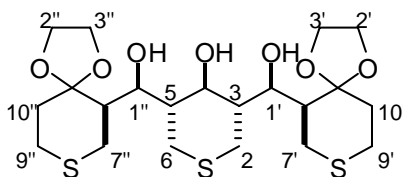
297

(3S,4r,5R)-3-((S)-Hydroxy((R)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-5-((R)-hydroxy((S)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)tetrahydro-2H-thiopyran-4-ol

Et$_2$BOMe (1.00 mL, 761 mg, 7.61 mmol) was added to a stirred solution of bisaldol **212a** (3.12 g, 6.33 mmol) in MeOH (20 mL) and THF (80 mL) at −78 °C under argon. After 30 min, NaBH$_4$ (1.92 g, 50.6 mmol) was added. After 30 min, the reaction mixture was diluted with 3 M aqueous NaOH (40 mL) and warmed to room temperature over 1 h. The mixture was diluted with brine and extracted with CH$_2$Cl$_2$ (3×). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. To this residue was added 3 M aqueous NaOH (20 mL) and THF (20 mL) and after vigorous stirring for 24 h at room temperature, the mixture was diluted with brine and extracted with CH$_2$Cl$_2$ (3×). The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (50-100% ethyl acetate in CH$_2$Cl$_2$) to give the titled triol **297** (2.20 g, 70%).

From mono-silyl diol **311**:

10% vol aqueous HF (1.5 mL) was added dropwise to a stirred solution of mono-silyl diol **311** (146 mg, 0.258 mmol) in THF (15 mL) at room temperature. After 30 min, sat. aqueous $NaHCO_3$ was slowly added (caution: effervescence) and the resulting mixture was diluted with EtOAc and washed sequentially with sat. aqueous $NaHCO_3$ (3×), brine, dried over Na_2SO_4, concentrated and fractionated by FCC (50-100% ethyl acetate in CH_2Cl_2) to give the titled triol **297** (113 mg, 95%).

From mono-silyl bis-benzyl bis-ketal **313**:

Anhydrous NH_3 (*ca.* 10 mL) was condensed to a solution of **313** (310 mg, 0.628 mmol) in THF (10 mL) at −78 °C under Ar. Lithium (2-3 2 mm^3 pieces) were added over 5-10 min until a blue color persisted. After 30 min, methanol (*ca.* 5 mL) was added dropwise followed by sat. aqueous NH_4Cl (*ca.* 5 mL). The mixture was warmed to room temperature over 2 h and diluted with sat. aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3×), dried over Na_2SO_4, concentrated and fractionated by PTLC (50-100% ethyl acetate in CH_2Cl_2) to give the titled triol **297** (209 mg, >95%).

IR (DRIFT) ν_{max}: 3412, 2906, 1429, 1173, 1042, 912 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.61 (1H, s, HOC-4), 4.17 (2H, d, *J* = 8 Hz, HC-1', HC-1"), 4.13 (2H, s, HOC-1', HOC-1"), 4.11-3.90 (8H, m, H_2C-2', H_2C-3', $H_2C-2"$, $H_2C-3"$),

3.74 (1H, dd, J = 9.5, 9.5 Hz, HC-4), 3.07 (2H, dd, J = 12, 14 Hz, HC-7', HC-7"), 2.86 (2H, ddd, J = 2, 13, 13 Hz, HC-9', HC-9"), 2.66 (2H, br d, J = 14 Hz, HC-7', HC-7"), 2.51 (4H, m, HC-2, HC-6, HC-9', HC-9"), 2.34 (2H, dd, J = 12, 12 Hz, HC-2, HC-6), 2.14 (2H, ddd, J = 3, 3, 13 Hz, HC-10', HC-10"), 2.08 (2H, dd, J = 2.5, 12 Hz, HC-6', HC-6"), 1.98 (2H, dddd, J = 3.5, 9, 9, 11.5 Hz, HC-3, HC-5), 1.74 (2H, ddd, J = 3.5, 13, 13 Hz, HC-10', HC-10").

^{13}**C NMR** (125 MHz, CDCl$_3$): δ 110.1 (s ×2, C-5', C-5"), 77.5 (d, C-4), 73.4 (d ×2, C-1', C-1"), 65.0 (t ×2, C-2', C-2" or C-3', C-3"), 64.6 (t ×2, C-2', C-2" or C-3', C-3"), 48.1 (d ×2, C-3, C-5), 47.9 (d ×2, C-6', C-6"), 37.1 (t ×2, C-10', C-10"), 29.8 (t ×2, C-2, C-6), 26.8 (t ×2, C-9', C-9"), 26.4 (t ×2, C-7', C-7").

LRMS (EI), *m/z* (relative intensity): 494 ([M]$^+$, 2), 477 (2), 433 (3), 414 (6), 273 (11), 159 (11), 99 (100).

HRMS *m/z* calcd. for C$_{21}$H$_{34}$O$_7$S$_3$: 494.1467; found: 494.1484.
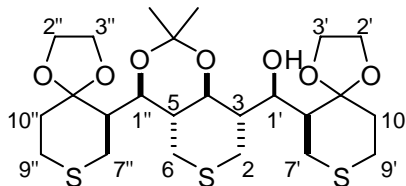
298

(*R*)-((4S,4aS,8S,8aS)-2,2-Dimethyl-4-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)hexahydrothiopyrano[4,3-d][1,3]dioxin-8-yl)((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methanol

A suspension of $FeCl_3 \cdot SiO_2$[176] (3 mg) and triol **297** (10 mg, 0.02 mmol) in acetone (1 mL) was stirred at room temperature for 2 h. The reaction mixture was filtered through SiO_2 and was rinsed with ethyl acetate, concentrated and fractionated by PTLC (50% ethyl acetate in hexane) to obtain the titled **298** (8 mg, 74%).

IR (DRIFT) ν_{max}: 3498, 2627, 1706, 1431, 1388, 1248, 1043, 888 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 4.10-3.81 (10H, m), 3.69 (1H, dd, *J* = 10, 10 Hz, HC-4), 3.26 (1H, m, HOC-1'), 3.03 (2H, ddd, *J* = 13.5, 13.5, 13.5 Hz), 2.91 (1H, dd, *J* = 13, 13 Hz, HC-10' or HC-10"), 2.81 (1H, dd, *J* = 12, 12 Hz, HC-10' or HC-10"), 2.72-2.54 (5H, m), 2.47 (2H, dd, *J* = 12.5, 12.5 Hz), 2.29 (1H, dd, *J* = 12.5, 12.5 Hz, HC-3 or HC-5), 2.16-1.99 (5H, m), 1.84 (1H, dd, *J* = 10.5, 10.5 Hz, HC-3 or HC-5), 1.74 (2H, dd, *J* = 11.5, 11.5 Hz, HC-10', HC-10"), 1.45 (3H, s, H$_3$CCO-1"), 1.34 (3H, s, H$_3$CCO-1").

^{13}C NMR (125 MHz, CDCl$_3$): δ 109.6 (s, C-5' or C-5"), 109.1 (s, C-5' or C-5"), 98.3 (s, COC-1"), 75.8 (d, C-4), 71.4 (d, C-1' or C-1"), 69.0 (d, C-1' or C-1"), 65.1 (t, C-2' or C-2" or C-3' or C-3"), 65.0 (t ×2, C-2' or C-2" or C-3' or C-3"), 64.8 (t, C-2' or C-2" or C-3' or

C-3"), 48.3 (d, C-3' or C-5" or C-6' or C-6"), 48.2 (d, C-3' or C-5" or C-6' or C-6"), 47.5

(d, C-3' or C-5" or C-6' or C-6"), 44.1 (d, C-3 or C-5), 38.5 (t, C-10' or C-10"), 36.8 (t, C-

10' or C-10"), 30.5 (t), 30.2 (q, CH_3COC-1"), 28.2 (t), 27.5 (t), 27.0 (t), 26.8 (t ×2), 19.4

(q, CH_3COC-1").

LRMS (EI), *m/z* (relative intensity): 534 ([M]$^+$, 11), 414 (11), 199 (11), 159 (28), 99

(100).

HRMS *m/z* calcd. for $C_{24}H_{38}O_7S_3$: 534.1780; found: 534.1781.
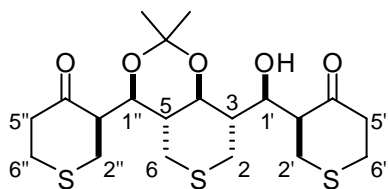
299

(*S*)-3-((*R*)-((4*S*,4a*S*,8*S*,8a*S*)-2,2-Dimethyl-4-((*R*)-4-oxotetrahydro-2*H*-thiopyran-3-yl)hexahydrothiopyrano[4,3-d][1,3]dioxin-8-yl)(hydroxy)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one

A suspension of FeCl$_3$·SiO$_2$[176] (10 mg) and triol **297** (50 mg, 0.10 mmol) in acetone

(5 mL) was stirred at room temperature for 2 h and then refluxed for 1 h. The reaction

mixture was cooled to room temperature, filtered through SiO$_2$, rinsed with ethyl acetate,

concentrated and fractionated by FCC (20-40% ethyl acetate in hexane) to obtain the

titled **299** (35 mg, 70%).

IR (DRIFT) ν_{max}: 3484, 2918, 1709, 1417, 1382, 1203, 1066, 900 cm^{-1}.

¹H NMR (500 MHz, CDCl₃): δ 4.40 (1H, dd, J = 2.5, 2.5 Hz, HC-1''), 4.16 (1H, dd, J = 6, 6 Hz, HC-1'), 3.77 (1H, dd, J = 9.5, 9.5 Hz, HC-4), 3.46 (1H, d, J = 4 Hz, HOC-1'), 3.20-2.20 (18H, m), 1.99 (1H, dddd, J = 3.5, 6, 9.5, 13 Hz, HC-3), 1.90 (1H, dddd, J = 3.5, 10.5, 10.5, 10.5 Hz, HC-5), 1.54 (3H, s, H₃CCOC-1''), 1.35 (3H, s, H₃CCOC-1'').

¹³C NMR (125 MHz, CDCl₃): δ 209.5 (s, C-4'), 207.4 (s, C-4''), 99.4 (s, COC-1''), 77.7 (d, C-4), 73.5 (d, C-1'), 69.7 (d, C-1''), 56.7 (d, C-3'), 53.3 (d, C-3''), 46.5 (d, C-3), 44.2 (t, C-5' or C-5''), 43.7 (t, C-5' or C-5''), 43.3 (d, C-5), 30.1 (t), 29.9 (t), 29.9 (q, CH₃COC-1''), 29.6 (t, C-2), 28.4 (t), 28.2 (t, C-6), 27.5 (t), 19.7 (q, CH₃COC-1'').

LRMS (EI), m/z (relative intensity): 446 ([M]⁺, 15), 370 (91), 225 (10), 152 (35), 114 (32).

HRMS m/z calcd. for $C_{20}H_{30}O_5S_3$: 446.1255; found: 446.1260.
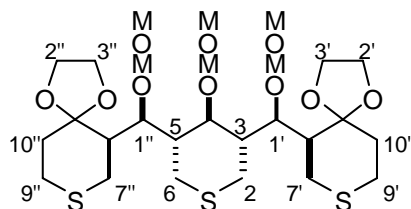
302

(3S,4r,5R)-4-Methoxymethoxy-3-((S)-(methoxymethoxy)((R)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-5-((R)-(methoxymethoxy)((S)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)tetrahydro-2H-thiopyran

i-Pr$_2$EtN (0.094 mL, 69 mg, 0.54 mmol) was added to a stirred solution of triol **297** (20 mg, 0.04 mmol) and *n*-Bu$_4$NI (44 mg, 0.12 mmol) in CH$_2$Cl$_2$ (0.4 mL) at room temperature under Ar. After 2 min, MOMCl (0.028 mL, 29 mg, 0.361 mmol) was added and the reaction was stirred vigorously for 3 d. The mixture was diluted with 1% w/v aqueous citric acid and extracted with CH$_2$Cl$_2$ (3×). The combined organic layers were washed with sat. aqueous NaHCO$_3$, dried over Na$_2$SO$_4$ and concentrated. The residue was dissolved with CH$_2$Cl$_2$, filtered through a short silica pad (50% ethyl acetate in hexane then 100% ethyl acetate) and concentrated to give the titled **302** (25 mg, 95%).

IR (DRIFT) v_{max}: 2917, 1412, 1264, 1146, 1022, 923 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 4.77 (2H, s, H$_2$COC-4), 4.64 (4H, ap dd, *J* = 6.5, 6.5 Hz, H$_2$COC-1', H$_2$COC-1"), 4.08 (2H, dd, *J* = 3, 3 Hz, HC-1', HC-1"), 4.05-3.90 (8H, m, H$_2$C-2', H$_2$C-3', H$_2$C-2", H$_2$C-3"), 3.60 (1H, dd, *J* = 9, 9 Hz, HC-4), 3.39 (6H, s, H$_3$CO ×2), 3.38 (3H, s, H$_3$CO), 2.94-2.63 (8H, m), 2.55-2.42 (4H, m, HC-2, HC-6, HC-9', HC-9"), 2.32-2.20 (4H, m, HC-3, HC-5, HC-6', HC-6"), 2.12 (2H, ddd, *J* = 3.5, 3.5, 13.5 Hz, HC-10', HC-10"), 1.71 (2H, ddd, *J* = 3.5, 13, 13 Hz, HC-10', HC-10").

¹³C NMR (125 MHz, CDCl₃): δ 109.2 (s ×2, C5', C5"), 97.0 (t ×2, CH₂OC-1", CH₂OC-1'), 96.8 (t, CH₂OC-4), 77.0 (d, C-4), 76.2 (d ×2, C-1', C-1"), 64.7 (t ×2, C-2', C-2" or C-3', C-3"), 64.6 (t ×2, C-2', C-2" or C-3', C-3"), 56.3 (q, CH₃O), 56.1 (q ×2, CH₃O), 50.3 (d ×2, C-3, C-5), 48.6 (d ×2, C-6', C-6"), 36.7 (t ×2, C-10', C-10"), 29.1 (t ×2, C-7', C-7"), 27.7 (t ×2, C-2, C-6), 26.9 (t ×2, C-9', C-9").

LRMS (EI), *m/z* (relative intensity): 626 ([M]⁺, 2), 549 (11), 487 (6), 361 (6), 199 (12), 159 (15).

HRMS *m/z* calcd. for C₂₇H₄₆O₁₀S₃: 626.2253; found: 626.2258.
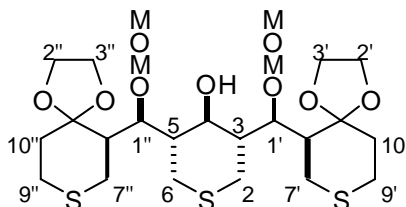
303

(3*S*,4*r*,5*R*)-3-((*S*)-(Methoxymethoxy)((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-5-((*R*)-(methoxymethoxy)((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)tetrahydro-2*H*-thiopyran-4-ol

i-Pr₂EtN (10.5 mL, 7.79 g, 60.1 mmol) was added to a stirred solution of triol **297** (2.20 g, 4.45 mmol) and *n*-Bu₄NI (4.9 g, 13 mmol) in CH₂Cl₂ (75 mL) at room temperature under Ar. After 2 min, MOMCl (3.00 mL, 3.18 g, 40.0 mmol) was added and the reaction was stirred vigorously for 2 d. The mixture was diluted with ethyl acetate and washed with 1% w/v aqueous citric acid (3×). The combined organic layers

were washed with sat. aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated and fractionated by MPC (15% acetone in hexane) to give the titled **303** (1.82 g, 70%).

IR (DRIFT) ν_{max}: 3498, 2916, 1466, 1426, 1260, 1099, 913 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 4.68 (2H, d, J = 7 Hz, H$_2$COC-1', H$_2$COC-1"), 4.56 (2H, d, J = 7 Hz, H$_2$COC-1', H$_2$COC-1"), 4.10 (2H, br s, HC-1', HC-1"), 4.09-3.90 (8H, m, H$_2$C-2', H$_2$C-3', H$_2$C-2", H$_2$C-3"), 3.58 (1H, d, J = 3.5 Hz, HOC-4), 3.43-3.30 (7H, m, HC-4, H$_3$CO ×2), 2.85-2.76 (4H, m, HC-7', HC-7", HC-9', HC-9"), 2.69 (2H, br d, J = 13.5 Hz, HC-2, HC-6), 2.62 (2H, br d, J = 14 Hz, HC-7', HC-7"), 2.53-2.43 (4H, m, HC-2, HC-6, HC-9', HC-9"), 2.26 (2H, br d, J = 11 Hz, HC-6', HC-6"), 2.15-2.06 (4H, m, HC-3, HC-5, HC-10', HC-10"), 1.73 (2H, ddd, J = 3.5, 13.5, 13.5 Hz, HC-10', HC-10").

^{13}C NMR (125 MHz, CDCl$_3$): δ 109.6 (s ×2, C-5', C-5"), 96.3 (t ×2, CH$_2$OC-1', CH$_2$OC-1"), 73.2 (d ×2, C-1', C-1"), 69.7 (d, C-4), 64.9 (t ×2, C-2', C-2" or C-3', C-3"), 64.7 (t ×2, C-2', C-2" or C-3', C-3"), 56.1 (q ×2, CH$_3$O), 52.5 (d ×2, C-3, C-5), 48.0 (d ×2, C-6', C-6"), 36.6 (t ×2, C-10',C-10"), 29.1 (t ×2, C-7', C-7"), 28.3 (t ×2, C-2, C-6), 26.8 (t ×2, C-9', C-9").

LRMS (EI), m/z (relative intensity): 582 ([M]$^+$, 2), 488 (7), 458 (14), 269 (2), 159 (14), 133 (27), 131 (65), 99 (100), 67 (10).

HRMS m/z calcd. for $C_{25}H_{42}O_9S_3$: 582.1991; found: 582.2013.
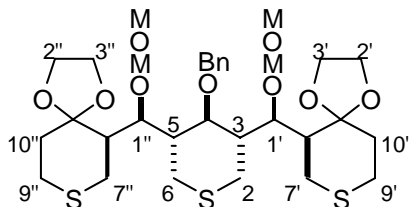
304

(3S,4r,5R)-4-(Benzyloxy)-3-((S)-(methoxymethoxy)((R)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-5-((R)-(methoxymethoxy)((S)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)tetrahydro-2H-thiopyran

A solution of alcohol **303** (1.77 g, 3.04 mmol) in THF (10 mL, plus 2× 10 mL washings) was added dropwise *via* syringe to a stirred suspension of 30% w/v KH in oil (*ca.* 30 mmol) in THF (15 mL) at 0 °C under Ar. The resulting mixture was warmed to room temperature over 1 h and benzylbromide (0.80 mL, 1.14 g, 6.7 mmol) was added. After 1 h, the mixture was cooled to 0 °C and methanol (2 mL) was added dropwise *via* syringe (caution: H$_2$ evolution). The mixture was diluted with H$_2$O and extracted with CH$_2$Cl$_2$ (3×) and the combined organic layers were dried over Na$_2$SO$_4$, concentrated and fractionated by FCC (5-20% acetone in hexane) to give the titled product **304** (1.90 g, 93%).

IR (DRIFT) v_{max}: 2919, 1432, 1336, 1253, 1217, 1145, 1091 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.51-7.18 (5H, m, Ph), 4.70 (2H, d, *J* = 6.5 Hz, H$_2$COC-1', H$_2$COC-1"), 4.68 (2H, s, H$_2$COC-4), 4.63 (2H, d, *J* = 6.5 Hz, H$_2$COC-1', H$_2$COC-1"), 4.15 (2H, s, HC-1', HC-1"), 4.00-3.79 (6H, m, H$_2$C-2', H$_2$C-3', H$_2$C-2", H$_2$C-3"), 3.68-3.60 (3H, m, H$_2$C-2', H$_2$C-3', H$_2$C-2", H$_2$C-3", HC-4), 3.43 (6H, s, H$_3$CO ×2), 2.87 (2H, dd, *J* = 12.5, 12.5 Hz, HC-7', HC-7"), 2.85-2.75 (4H, m, HC-2, HC-6, HC-9', HC-9"),

2.63 (2H, br d, J = 14.5 Hz, HC-7', HC-7"), 2.59 (2H, dd, J = 12.5, 12.5 Hz, HC-2, HC-6), 2.54-2.45 (4H, m, HC-3, HC-5, HC-9', HC-9"), 2.30 (2H, br d, J = 11 Hz, HC-6', HC-6"), 2.10 (2H, br d, J = 13 Hz, HC-10', HC-10"), 1.72 (2H, ddd, J = 3, 13, 13 Hz, HC-10', HC-10").

^{13}C NMR (125 MHz, CDCl$_3$): δ 139.8 (s, Ph), 128.3 (d ×2, Ph), 127.4 (d ×2, Ph), 127.1 (d, Ph), 109.1 (s ×2, C-5, C-5"), 97.2 (t ×2, CH$_2$OC-1', CH$_2$OC-1"), 75.2 (d, C-4), 74.9 (d ×2, C-1', C-1"), 66.7 (t, CH$_2$OC-4), 64.59 (t ×2, C-2', C-2" or C-3', C-3"), 64.58 (t ×2, C-2', C-2" or C-3', C-3"), 56.0 (q ×2, CH$_3$O), 49.4 (d ×2, C-3, C-5), 48.2 (d ×2, C-6', C-6"), 36.7 (t ×2, C-10', C-10"), 29.2 (t ×2, C-7', C-7"), 28.4 (t ×2, C-2, C-6), 26.9 (t ×2, C-9', C-9").

LRMS (EI), *m/z* (relative intensity): 672 ([M]$^+$, 1), 578 (9), 489 (12), 233 (12), 159 (9), 99 (100).

HRMS *m/z* calcd. for C$_{32}$H$_{48}$O$_9$S$_3$: 672.2460; found: 672.2441.
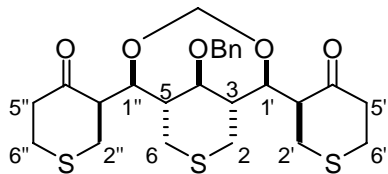
305

(3R,3'S)-3,3'-((1R,2R,6S,7S,11r)-11-(Benzyloxy)-3,5-dioxa-9-thiabicyclo[5.3.1]undecane-2,6-diyl)bis(dihydro-2H-thiopyran-4(3H)-one)

A stirred suspension of FeCl$_3$·SiO$_2$[176] (1 g) and bis-MOM ketal **304** (100 mg, 0.15 mmol) in acetone (20 mL) was heated under reflux for 2 h. The reaction mixture was cooled to room temperature and filtered. The combined filtrate and washings (20% methanol in CH$_2$Cl$_2$) were concentrated and the residue was dissolved in CH$_2$Cl$_2$, washed with sat. aqueous NaHCO$_3$, dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (5-30% acetone in hexane) to obtain diketone **307** (41 mg, 55%) and the titled diketone **305** (34 mg, 45%).

IR (DRIFT) v_{max}: 2916, 1706, 1427, 1274, 1129, 1020, 754 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.30-7.09 (5H, m, Ph), 5.46 (1H, d, J = 8 Hz, H$_2$COC-1', H$_2$COC-1"), 5.28 (2H, dd, J = 2, 11 Hz, HC-1', HC-1"), 5.16 (1H, d, J = 8 Hz, H$_2$COC-1', H$_2$COC-1"), 4.25 (2H, s, H$_2$COC-4), 4.19 (1H, dd, J = 3.5, 3.5 Hz, HC-4), 3.27 (2H, dd, J = 3, 14.5 Hz, HC-2, HC-6), 2.98 (2H, dd, J = 11, 14 Hz, HC-2', HC-2"), 2.51 (2H, ddd, J = 2.5, 4.5, 14 Hz, HC-2', HC-2"), 2.45-2.29 (6H, m), 2.22-2.09 (4H, m), 1.95 (2H, br dd, J = 2.5, 11 Hz, HC-3, HC-5), 1.53 (2H, d, J = 14 Hz, HC-2, HC-6).

¹³C NMR (125 MHz, C₆D₆): δ 205.9 (s ×2, C-4', C-4"), 139.4 (s, Ph), 128.3 (d ×2, Ph), 127.8 (d ×2, Ph), 127.7 (d, Ph), 100.8 (t, CH₂OC-1', CH₂OC-1"), 76.4 (d ×2, C-1', C-1"), 74.3 (d, C-4), 72.1 (t, CH₂OC-4), 56.9 (d ×2, C-3', C-3"), 44.3 (d ×2, C-5', C-5"), 37.0 (d ×2, C-3, C-5), 26.3 (t ×2, C-6', C-6"), 29.0 (t ×2, C-2', C-2"), 25.6 (t ×2, C-2, C-6).

LRMS (EI), *m/z* (relative intensity): 508 ([M]⁺, 6), 399 (2), 384 (2), 226 (8), 91 (100), 67 (31).

HRMS *m/z* calcd. for C₂₅H₃₂O₅S₃: 508.1412; found: 508.1411.
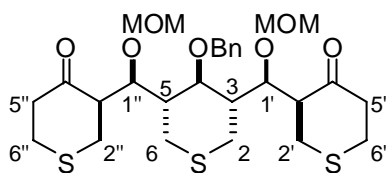
306

(3*R*,3'*S*)-3,3'-((1*S*,1'*R*)-((3*R*,4*r*,5*S*)-4-(Benzyloxy)tetrahydro-2*H*-thiopyran-3,5-diyl)bis((methoxymethoxy)methylene))bis(dihydro-2*H*-thiopyran-4(3*H*)-one)

FeCl₃·6H₂O (600 mg, 2.22 mmol) was added to a well-stirred solution of bis-MOM ketal **304** (100 mg, 0.15 mmol) in 20% acetone in CH₂Cl₂ (10 mL). After 4 h, the mixture was diluted with ethyl acetate and washed with 1% w/v aqueous citric acid (3×). The combined organic layers were washed with sat. aqueous NaHCO₃, dried over Na₂SO₄ and concentrated to give crude diketones (87 mg) which was a mixture (*ca.* 1:1) of MOM protected and MOM deprotected diketones by ¹H NMR. The crude was subjected to MOM protection by addition of *i*-Pr₂EtN (0.37 mL, 0.27 g, 2.12 mmol) and *n*-Bu₄NI (129 mg, 0.35 mmol) in CH₂Cl₂ (4 mL) at room temperature under Ar. After 2

min, MOMCl (0.08 mL, 85 mg, 1.1 mmol) was added and the reaction was stirred vigorously for 1 d. The mixture was diluted with ethyl acetate and washed with 1% w/v aqueous citric acid (3×). The combined organic layers were washed with sat. aqueous NaHCO$_3$, dried over Na$_2$SO$_4$, concentrated, and recrystallized from benzene to give the titled diketone **306** (47 mg, 54%).

IR (DRIFT) ν_{max}: 2910, 1693, 1420, 1103, 1033, 919 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.49-7.28 (5H, m, Ph), 4.80 (2H, d, J = 6.5 Hz, H$_2$COC-1', H$_2$COC-1"), 4.72 (2H, d, J = 6.5 Hz, H$_2$OC-1', H$_2$COC-1"), 4.60 (2H, s, H$_2$COC-4), 4.51 (2H, dd, J = 2.5, 7.5 Hz, HC-1', HC-1"), 3.43 (6H, s, H$_3$CO ×2), 3.29 (1H, dd, J = 10, 10 Hz, HC-4), 3.08 (2H, ddd, J = 4, 8, 8 Hz, HC-3', HC-3"), 3.03-2.91 (4H, m, H$_2$C-2', H$_2$C-2"), 2.89-2.84 (4H, m, H$_2$C-6', H$_2$C-6"), 2.80 (2H, br d, J = 13 Hz, HC-2, HC-6), 2.78-2.71 (2H, m, HC-5', HC-5"), 2.63 (2H, dd, J = 12, 12 Hz, HC-2, HC-6), 2.59-2.52 (2H, m, HC-5', HC-5"), 2.41 (2H, dddd, J = 2.5, 2.5, 10.5, 10.5 Hz, HC-3, HC-5).

^{13}C NMR (125 MHz, CDCl$_3$): δ 209.8 (s ×2, C-5', C-5"), 138.1 (s, Ph), 128.8 (d ×2, Ph), 128.6 (d ×2, Ph), 128.0 (d, Ph), 95.5 (t ×2, CH$_2$OC-1', CH$_2$OC-1"), 77.1 (d, C-4), 76.5 (d ×2, C-1', C-1"), 67.9 (t, CH$_2$OC-4), 56.3 (q ×2, CH$_3$O), 55.7 (d ×2, C-3', C-3"), 48.7 (d ×2, C-3, C-5), 44.3 (d ×2, C-5', C-5"), 33.6 (t ×2, C-2', C-2"), 31.3 (t ×2, C-6', C-6"), 29.6 (t ×2, C-2, C-6).

LRMS (EI), *m/z* (relative intensity): 584 ([M]⁺, 10), 553 (48), 490 (92), 353 (76), 351 (48), 289 (14), 281 (28), 265 (43), 215 (100).

HRMS *m/z* calcd. for $C_{28}H_{40}O_7S_3$: 584.1936; found: 584.1942.
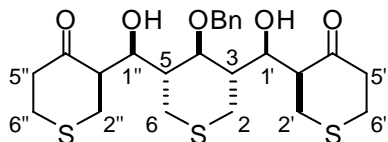
307

(3*R*,3'*S*)-3,3'-((1*S*,1'*R*)-((3*R*,4*s*,5*S*)-4-(Benzyloxy)tetrahydro-2*H*-thiopyran-3,5-diyl)bis(hydroxymethylene))bis(dihydro-2*H*-thiopyran-4(3*H*)-one)

$FeCl_3 \cdot 6H_2O$ (10.30 g, 38.11 mmol) was added to a well-stirred solution of bis-TMS ketal **314** (1.72 g, 2.36 mmol) in 20% acetone in CH_2Cl_2 (170 mL). After 12 h, the mixture was diluted with 1% w/v aqueous citric acid and extracted with CH_2Cl_2 (4×). The combined organic layers were washed with sat. aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (30% acetone in hexane) to obtain the titled diketone **307** (0.95 g, 81%).

From bis-MOM ketal **304**:

A stirred suspension of $FeCl_3 \cdot SiO_2$[176] (1 g) and bis-MOM ketal **304** (100 mg, 0.15 mmol) in acetone (20 mL) was heated under reflux for 2 h. The reaction mixture was cooled to room temperature and filtered. The combined filtrate and washings (20% methanol in CH_2Cl_2) were concentrated and the residue was dissolved in CH_2Cl_2, washed

with sat. aqueous NaHCO$_3$, dried over Na$_2$SO$_4$, concentrated and fractionated by FCC (5-30% acetone in hexane) to obtain diketone **305** (34 mg, 45%) and the titled diketone **307** (41 mg, 55%).

IR (DRIFT) ν_{max}: 3474, 2916, 1699, 1610, 1458, 1109, 817 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.35-7.06 (5H, m, Ph), 4.87 (2H, d, J = 9.5 Hz, HC-1', HC-1"), 4.41 (2H, s, H$_2$COC-4), 4.21 (1H, dd, J = 4, 4 Hz, HC-4), 3.53 (2H, br s, HOC-1', HOC-1"), 3.01 (2H, dd, J = 3, 14 Hz, HC-2, HC-6), 2.89 (2H, dd, J = 11.5, 13.5 Hz, HC-2', HC-2"), 2.61 (2H, ddd, J = 3, 4.5, 11.5 Hz, HC-3', HC-3"), 2.49 (2H, ddd, J = 2.5, 4.5, 13.5 Hz, HC-2', HC-2"), 2.42 (2H, ddd, J = 4, 11.5, 15 Hz, HC-6', HC-6"), 2.32 (2H, ddd, J = 3.5, 3.5, 13 Hz, HC-5', HC-5"), 2.22-2.08 (4H, m, HC-5', HC-5", HC-6', HC-6"), 2.05 (2H, dddd, J = 3, 4, 4.5, 9.5 Hz, HC-3, HC-5), 1.86 (2H, dd, J = 4.5, 14 Hz, HC-2, HC-6).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 210.2 (s ×2, C-3', C-3"), 139.6 (s, Ph), 129.0 (d ×2, Ph), 128.7 (d ×2, Ph), 128.2 (d, Ph), 74.8 (d, C-4), 71.8 (t, CH$_2$OC-4), 69.3 (d ×2, C-1', C-1"), 55.7 (d ×2, C-3', C-3"), 44.9 (t ×2, C-5', C-5"), 40.9 (d ×2, C-3, C-5), 30.2 (t ×2, C-6', C-6"), 29.6 (t ×2, C-2', C-2"), 25.9 (t ×2, C-2, C-2).

HRMS m/z calcd. for C$_{24}$H$_{32}$O$_5$S$_3$: 496.1412 (519.1304 for M+Na); found: 519.1328 (TOF, CH$_3$OH).
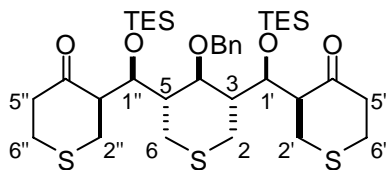
308

(3*R*,3'*S*)-3,3'-((1*S*,1'*R*)-((3*R*,4*r*,5*S*)-4-(Benzyloxy)tetrahydro-2H-thiopyran-3,5-diyl)bis((triethylsilyloxy)methylene))bis(dihydro-2*H*-thiopyran-4(3*H*)-one)

2,6-Lutidine (2.21 mL, 2.04 g, 19.1 mmol) was added to a stirred solution of diketone **307** (0.95 g, 1.91 mmol) in CH₂Cl₂ (95 mL) at 0 °C under Ar. After 2 min, TESOTf (2.15 mL, 2.28 g, 9.53 mmol) was added and the reaction was stirred vigorously for 15 min. Methanol (2 mL) was added and the mixture was diluted with ethyl acetate and washed with 1% w/v aqueous citric acid (3×). The combined organic layers were washed with sat. aqueous NaHCO₃, dried over Na₂SO₄, concentrated, and fractionated by FCC (30% ether in hexane) to give bis-silyl diketone **308** (1.11 g, 83%).

From bis-silyl enol ether **316**:

Aqueous sat. NaHCO₃ (0.2 mL) was added dropwise to a stirred solution of bis-silyl enol ether **316** (19 mg, 0.02 mmol) in methanol (1 mL) and THF (1 mL) at room temperature. After 1 h, the reaction was diluted with water and extracted with CH₂Cl₂ (3×). The combined organic extracts were dried over Na₂SO₄, concentrated and fractionated by PTLC (50% ether in hexane) to give the titled bis-silyl diketone **308** (15 mg, >95%).

IR (DRIFT) ν_{max}: 2948, 1703, 1142, 1245, 1084, 763 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.84-7.03 (5H, m, Ph), 4.85 (2H, br s, HC-1', HC-1"), 4.74 (2H, br s, H$_2$COC-4), 3.52 (1H, dd, J = 10, 10 Hz, HC-4), 3.27 (2H, br s, HC-3', HC-3"), 3.00 (2H, br d, J = 13 Hz, HC-2', HC-2"), 2.94 (2H, br d, J = 13 Hz, HC-2, HC-6), 2.81 (2H, dd, J = 13, 13 Hz, HC-2', HC-2"), 2.54 (2H, dd, J = 12.5, 12.5 Hz, HC-2, HC-6), 2.47-2.35 (4H, m, HC-3, HC-5, HC-6', HC-6"), 2.33 (2H, ddd, J = 4.5, 4.5, 13 Hz, HC-5', HC-5"), 2.23 (2H, dddd, J = 2.5, 5, 5, 13 Hz, HC-6', HC-6"), 2.13 (2H, ddd, J = 5, 13, 13 Hz, HC-5', HC-5"), 0.96 (18H, m, (H$_3$CC)$_3$Si, ×2), 0.62 (12H, m, (H$_2$C)$_3$Si, ×2).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 209.1 (s ×2, C-4', C-4"), 138.8 (s, Ph), 129.4 (d ×2, Ph), 129.2 (d ×2, Ph), 128.7 (d, Ph), 78.6 (d, C-4), 71.7 (t, CH$_2$OC-4), 71.3 (d ×2, C-1', C-1"), 57.1 (d ×2, C-3', C-3"), 53.4 (d ×2, C-3, C-5), 45.1 (t ×2, C-5', C-5"), 33.9 (t ×2, C-2', C-2"), 31.2 (t ×2, C-2, C-6), 31.0 (t ×2, C-6', C-6"), 7.7 (t ×6, (CH$_2$)Si), 6.0 (q ×6, (CH$_3$C)Si).

LRMS (EI), m/z (relative intensity): 724 ([M]$^+$, 1), 589 (8), 457 (12), 259 (32), 171 (65), 91 (100).

HRMS m/z calcd. for C$_{36}$H$_{60}$O$_5$S$_3$Si$_2$: 724.3141; found: 724.3142.
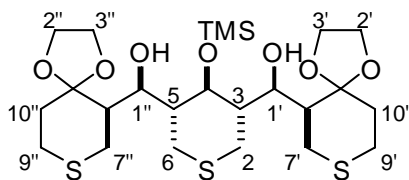
311

(*R*)-((3*S*,4*s*,5*R*)-5-((*S*)-Hydroxy((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-4-(trimethylsilyloxy)tetrahydro-2*H*-thiopyran-3-yl)((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methanol

IR (DRIFT) ν_{max}: 3462, 3341, 2954, 1616, 1420, 1331, 1147, 1052 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 4.90 (2H, d, *J* = 11 Hz, HC-1', HC-1"), 4.72 (1H, dd, *J* = 3, 3 Hz, HC-4), 4.00 (2H, s, HOC-1', HOC-1"), 3.74-3.27 (8H, m, H$_2$C-2', H$_2$C-3', H$_2$C-2", H$_2$C-3"), 3.31-3.23 (4H, m, HC-7', HC-7", HC-2, HC-6), 2.77 (2H, ddd, *J* = 3, 13, 13 Hz, HC-9', HC-9"), 2.68 (2H, ddd, *J* = 3, 3, 14 Hz, HC-7', HC-7"), 2.21 (2H, ddd, *J* = 3.5, 6, 13 Hz, HC-9', HC-9"), 2.10-2.01 (4H, m, HC-2, HC-6, HC-6', HC-6"), 1.86-1.77 (4H, m, HC-3, HC-5, HC-10', HC-10"), 1.69 (2H, ddd, *J* = 3.5, 13, 13 Hz, HC-10', HC-10"), 0.12 (9H, s, (H$_3$C)$_3$Si).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 110.8 (s ×2, C-5', C-5"), 67.8 (d ×2, C-1', C-1"), 65.9 (d, C-4), 65.5 (t ×2, C-2', C-2" or C-3', C-3"), 64.9 (t ×2, C-2', C-2" or C-3', C-3"), 49.6 (d ×2, C-6', C-6"), 44.6 (d ×2, C-3, C-5), 38.1 (t ×2, C-10', C-10"), 27.2 (t ×2, C-9', C-9"), 26.5 (t ×2, C-7', C-7"), 25.9 (t ×2, C-2, C-6), 0.3 (q ×3, (CH$_3$)Si).

LRMS (EI), *m/z* (relative intensity): 566 ([M]$^+$, 4), 476 (11), 373 (1), 287 (2), 199 (4), 189 (18), 159 (11), 99 (100), 73 (43).

HRMS *m/z* calcd. for $C_{24}H_{42}O_7S_3Si$: 566.1862; found: 566.1856.

LRMS (EI), *m/z* (relative intensity): 341 ([M−29]$^+$, 3), 279 (3), 145 (6), 143 (3), 101 (100), 69 (10), 57 (11).

HRMS *m/z* calcd. for $C_{21}H_{38}O_5$: 370.2719 (341.2328 for M−C_2H_5); found: 341.2316.
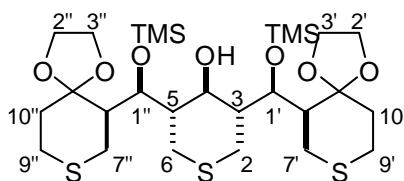
312

(3R,4r,5S)-3-((R)-((S)-1,4-Dioxa-8-thiaspiro[4.5]decan-6-yl)(trimethylsilyloxy)methyl)-5-((S)-((R)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)(trimethylsilyloxy)methyl)tetrahydro-2H-thiopyran-4-ol

i-Pr$_2$EtN (6.23 mL, 4.65 g, 36.0 mmol) was added to a stirred solution of triol **297** (1.78 g, 3.60 mmol) in CH$_2$Cl$_2$ (180 mL) at room temperature under Ar. After 2 min, TMSCl (2.28 mL, 1.95 g, 17.9 mmol) was added and the reaction was stirred vigorously for 2 d. The mixture was diluted with ethyl acetate and washed with 1% w/v aqueous citric acid (3×). The combined organic layers were washed with sat. aqueous NaHCO$_3$, dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give mono-silyl diol **311** (0.32 g, 15%) and the titled bis-TMS alcohol **312** (1.97 g, 85%).

IR (DRIFT) ν_{max}: 3493, 2916, 1724, 1426, 1242, 1039, 887 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 4.33 (2H, dd, J = 3, 3 Hz, HC-1', HC-1"), 3.65 (1H, ddd, J = 4, 9.5, 9.5 Hz, HC-4), 3.56 (1H, d, J = 4 Hz, HOC-4), 3.52-3.20 (8H, m, H$_2$C-2', H$_2$C-3', H$_2$C-2", H$_2$C-3"), 3.03 (2H, dd, J = 11, 14 Hz, HC-7', HC-7"), 2.84 (2H, ddd, J = 3, 3, 14 Hz, HC-7', HC-7"), 2.76 (2H, br d, J = 13 Hz, HC-2, HC-6), 2.67 (2H, ddd, J = 3, 13, 13 Hz, HC-9', HC-9"), 2.53 (2H, ddd, J = 3.5, 3.5, 11 Hz, HC-6', HC-6"), 2.46 (2H, dd, J = 12.5, 12.5 Hz, HC-2, HC-6), 2.38 (2H, dddd, J = 2.5, 2.5, 10, 12 Hz, HC-3, HC-5), 2.22 (2H, ddd, J = 4, 4, 13.5 Hz, HC-9', HC-9"), 1.71 (2H, ddd, J = 4, 4, 13.5 Hz, HC-10', HC-10"), 1.57 (2H, ddd, J = 3.5, 13, 13 Hz, HC-10', HC-10"), 0.16 (18H, s, (H$_3$C)$_3$Si ×2).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 110.4 (s ×2, C-5', C-5"), 70.3 (d ×2, C-1', C-1"), 70.2 (d, C-4), 64.1 (t ×2, C-2', C-2" or C-3', C-3"), 64.0 (t ×2, C-2', C-2" or C-3', C-3"), 54.9 (d ×2, C-3, C-5), 48.3 (d ×2, C-6', C-6"), 36.2 (t ×2, C-10', C-10"), 29.5 (t ×2, C-7', C-7"), 29.1 (t ×2, C-2, C-6), 26.7 (t ×2, C-9', C-9"), 0.5 (q ×6, (CH$_3$)Si).

LRMS (EI), m/z (relative intensity): 638 ([M]$^+$, 1), 533 (10), 489 (1), 377 (1), 261 (50), 132 (30), 129 (100), 75 (12).

HRMS m/z calcd. for C$_{27}$H$_{50}$O$_7$S$_3$Si$_2$: 638.2257; found: 638.2242.
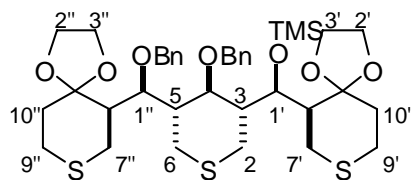
313

((R)-((3R,4R,5S)-4-(Benzyloxy)-5-((S)-benzyloxy((R)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)tetrahydro-2H-thiopyran-3-yl)((S)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methoxy)trimethylsilane

IR (DRIFT) ν_{max}: 2912, 1495, 1305, 1153, 948 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.49-7.00 (10H, m, Ph), 4.97 (2H, ap dd, J = 12.5, 12.5 Hz, H$_2$COC-4), 4.64 (1H, d, J = 11 Hz, H$_2$COC-1"), 4.50 (1H, d, J = 11 Hz, H$_2$COC-1"), 4.34 (1H, br s), 4.23 (1H, d, J = 5 Hz, HC-1'), 4.01 (1H, dd, J = 3.5, 3.5 Hz, HC-1"), 3.90 (1H, dd, J = 8, 8 Hz, HC-4), 3.55-3.25 (7H, m, H$_2$C-2', H$_2$C-3', H$_2$C-2", H$_2$C-3"), 3.22 (1H, dd, J = 10.5, 13.5 Hz, HC-6), 2.99 (1H, dd, J = 10, 13.5 Hz), 2.89-2.5 (12H, m), 2.28 (2H, m, H$_2$C-9' or H$_2$C-9"), 1.79 (1H, ddd, J = 3, 3, 13.5 Hz, H$_2$C-10' or H$_2$C-10"), 1.74 (1H, ddd, J = 3, 6, 13.5 Hz, H$_2$C-10' or H$_2$C-10"), 1.69-1.58 (1H, m, H$_2$C-10' or H$_2$C-10"), 1.52 (1H, ddd, J = 3.5, 11, 13.5 Hz, H$_2$C-10' or H$_2$C-10"), 0.20 (9H, s, (H$_3$C)$_3$Si).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 140.8 (s, Ph), 139.9 (s, Ph), 128.91 (d, Ph), 128.87 (d, Ph), 128.7 (d, Ph), 128.0 (d, Ph), 127.8 (d, Ph), 127.4 (d, Ph), 127.3 (d, Ph), 127.2 (d, Ph), 110.2 (s, C-5'), 109.9 (s, C-5"), 78.8 (d, C-1"), 77.8 (d, C-4), 74.5 (t, CH$_2$OC-1"), 73.3 (d, C-1'), 70.6 (t, CH$_2$OC-4), 65.3 (t, C-2', C-2" or C-3', C-3"), 64.7 (t, C-2', C-2" or C-3', C-3"), 64.5 (t, C-2', C-2" or C-3', C-3"), 64.3 (t, C-2', C-2" or C-3', C-3"), 52.7 (d, C-3), 50.5

(d, C-5), 50.0 (d, C-6″), 49.2 (d, C-6′), 36.9 (t, C-10′ or C-10″), 36.4 (t, C-10′ or C-10″),

30.1 (t ×3), 29.6 (t, C-6), 27.3 (t), 27.1 (t), 1.2 (q ×3, (CH$_3$)Si).

LRMS (EI), *m/z* (relative intensity): 746 ([M]$^+$, 15), 656 (35), 549 (72), 459 (42), 261

(36), 99 (100).

HRMS *m/z* calcd. for C$_{38}$H$_{54}$O$_7$S$_3$Si: 746.2801; found: 746.2823.
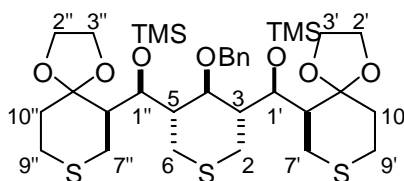
314

((S)-((3S,4r,5R)-5-((R)-((S)-1,4-Dioxa-8-thiaspiro[4.5]decan-6-yl)(trimethylsilyloxy)methyl)-4-(benzyloxy)tetrahydro-2H-thiopyran-3-yl)((R)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methoxy)trimethylsilane

A solution of alcohol **312** (552 mg, 0.864 mmol) in THF (10 mL, plus 2× 5 mL

washings) was added dropwise *via* syringe to a stirred suspension of 30% w/v KH in oil

(*ca.* 2 mmol) in THF (10 mL) at 0 °C under Ar. The resulting mixture was warmed to

room temperature over 1 h and benzylbromide (1.03 mL, 1.47 g, 8.64 mmol) was added.

After 8-12 h, the mixture was cooled to 0 °C and 2-propanol (2 mL) was added dropwise

via syringe (caution: H$_2$ evolution). The mixture was diluted with aqueous phosphate

buffer (0.1 M, pH 7; 2.0 mL) and extracted with CH$_2$Cl$_2$ (3×) and the combined organic

layers were dried over Na$_2$SO$_4$, concentrated and fractionated by FCC (5-10% ethyl

acetate in hexane) to give bis-benzyl mono-silyl **313** (97 mg, 15%) and the titled bis-silyl **314** (512 mg, 81%).

IR (DRIFT) ν_{max}: 2947, 1415, 1254, 1099, 895 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.58-7.09 (5H, m, Ph), 5.11 (2H, s, H$_2$COC-4), 4.17 (2H, br d, J = 4.5 Hz, HC-1', HC-1"), 3.79 (1H, dd, J = 8.5, 8.5 Hz, HC-4), 3.55-3.24 (8H, m, H$_2$C-2', H$_2$C-3', H$_2$C-2", H$_2$C-3"), 2.95 (2H, dd, J = 10, 13.5 Hz, HC-7', HC-7"), 2.83 (2H, br d, J = 14 Hz, HC-9', HC-9"), 2.80-2.63 (8H, m), 2.58 (2H, ddd, J = 2.5, 10.5, 13 Hz, HC-6', HC-6"), 2.33 (2H, br d, J = 14 Hz, HC-9', HC-9"), 1.75 (2H, ddd, J = 3, 6, 13.5 Hz, HC-10', HC-10"), 1.57 (2H, ddd, J = 3, 10.5, 13.5 Hz, HC-10', HC-10"), 0.20 (18H, s, (H$_3$C)$_3$Si ×2).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 140.7 (s, Ph), 128.9 (d ×2, Ph), 127.5 (d ×2, Ph), 127.2 (d, Ph), 110.2 (s ×2, C-5', C-5"), 71.5 (d ×3, C-1', C-1", C-4), 64.4 (t ×2, C-2', C-2" or C-3', C-3"), 64.3 (t ×3, C-2', C-2" or C-3', C-3", CH$_2$OC-4), 53.3 (d ×2, C-3, C-5), 49.4 (d ×2, C-6', C-6"), 36.3 (t ×2, C-10', C-10"), 30.1 (t ×4), 27.1 (t ×2, C-9', C-9"), 1.3 (q ×6, (CH$_3$)Si)

LRMS (EI), *m/z* (relative intensity): 728 ([M]$^+$, 1), 548 (7), 261 (72), 99 (100), 73 (71), 55 (3)

HRMS *m/z* calcd. for $C_{34}H_{56}O_7S_3Si_2$: 728.2727 (751.2618 for M+Na); found: 728.2733; 751.2640 (ESI, CH_3OH).
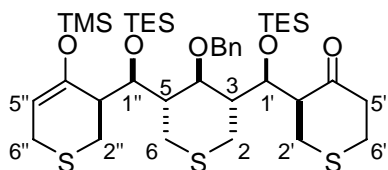
315

(S)-3-((R)-((3R,4R,5S)-4-(Benzyloxy)-5-((S)-(triethylsilyloxy)((R)-4-(trimethylsilyloxy)-3,6-dihydro-2H-thiopyran-3-yl)methyl)tetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)dihydro-2H-thiopyran-4(3H)-one

A solution of *n*-BuLi in hexanes (2.2 M; 0.086 mL, 0.19 mmol) was added dropwise *via* syringe to a solution of (S,S)-bis(1-phenylethyl)amine (0.044 mL, 43 mg, 0.19 mmol) in THF (5 mL) at −78 °C under Ar. After stirring for 30 min at −78 °C the resulting pink solution was quickly transferred *via* cannula (*ca.* 15-30 sec.) into a well-stirred solution of diketone **308** (92 mg, 0.127 mmol) and TMSCl (0.16 mL, 138 mg, 1.27 mmol) in THF (13 mL) at −100 °C under Ar. After 15 min, the reaction was quenched by addition of acetone (0.5 mL) followed by Et_3N (0.5 mL) and sat. aqueous $NaHCO_3$. The resulting cold mixture was diluted with ethyl acetate and washed sequentially with 1% w/v aqueous citric acid (4×), sat. aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (5-30% ether in hexane) to give the bis-silyl enol ether **316** (19 mg, 17%), recovered diketone **308** (8 mg, 8%) and the titled mono-silyl enol ether **315** (67 mg, 66%) ($[\alpha]_D^{23}$ −21; *c* 4.0, C_6H_6; >90% ee by ^1H NMR analysis of Mosher's ester **360** and/or **361**).

IR (DRIFT) ν_{max}: 2953, 1712, 1660, 1497, 1377, 1156, 1070 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.88-7.09 (5H, m, Ph), 5.30 (1H, br s, HC-1'), 4.95 (1H, br d, J = 8 Hz, HC-1"), 4.90 (1H, dd, J = 4, 4 Hz, HC-5"), 4.83 (1H, d, J = 9.5 Hz, H$_2$COC-4), 4.48 (1H, d, J = 9.5 Hz, H$_2$COC-4), 3.65 (1H, dd, J = 10, 10 Hz, HC-4), 3.27 (1H, br dd, J = 12.5, 12.5 Hz), 3.18 (1H, dd, J = 3, 13 Hz), 3.13-2.87 (6H, m), 2.67-2.21 (10H, m), 1.01 (9H, m, (H$_3$CC)$_3$Si), 0.99 (9H, m, (H$_3$CC)$_3$Si), 0.79 (6H, m, (H$_2$C)$_3$Si), 0.69 (6H, m, (H$_2$C)$_3$Si), 0.19 (9H, s, (H$_3$C)$_3$SiOC-4").

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 207.3 (s, C-4'), 152.1 (s, C-4"), 139.5 (s, Ph), 129.4 (d, Ph), 128.9 (d, Ph), 128.7 (d, Ph), 128.4 (d, Ph), 128.2 (d, Ph), 107.1 (d, C-5"), 77.8 (d, C-4), 74.2 (t, CH$_2$OC-4), 73.5 (d, C-1' or C-1"), 73.4 (d, C-1' or C-1"), 56.3 (d ×3, t), 45.1 (t), 43.9 (d), 33.1 (t), 30.4 (t), 29.5 (t), 28.9 (t), 25.1 (t), 7.68 (t ×3, (CH$_2$)$_3$Si), 7.62 (t ×3, (CH$_2$)Si), 6.2 (q ×3, (CH$_3$C)Si), 5.8 (q ×3, (CH$_3$C)Si), 0.8 (q ×3, (CH$_3$)SiOC-4").

HRMS *m/z* calcd. for C$_{39}$H$_{68}$O$_5$S$_3$Si$_3$: 796.3537 (819.3428 for M+Na); found: 819.3416 (ESI, CH$_3$OH).
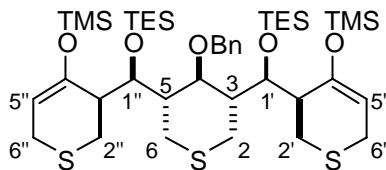
316

((*S*)-((3*S*,4*r*,5*R*)-4-(Benzyloxy)-5-((*R*)-(triethylsilyloxy)((*S*)-4-(trimethylsilyloxy)-3,6-dihydro-2*H*-thiopyran-3-yl)methyl)tetrahydro-2*H*-thiopyran-3-yl)((*R*)-4-(trimethylsilyloxy)-3,6-dihydro-2*H*-thiopyran-3-yl)methoxy)triethylsilane

IR (DRIFT) ν_{max}: 2955, 1660, 1458, 1413, 1156, 1095, 873 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.65-7.10 (5H, m, Ph), 5.02 (2H, dd, *J* = 4.5, 4.5 Hz, HC-5', HC-5"), 4.94 (4H, m, HC-1', HC-1", H$_2$COC-4), 3.92 (1H, dd, *J* = 10, 10 Hz, HC-4), 3.18 (2H, dd, *J* = 6.5, 13.5 Hz, HC-2', HC-2"), 3.09-3.03 (4H, m, H$_2$C-2, H$_2$C-6), 3.00 (2H, dd, *J* = 3.5, 17 Hz, HC-6', HC-6"), 2.86 (2H, dd, *J* = 5, 17 Hz, HC-6', HC-6"), 2.75 (2H, dd, *J* = 4.5, 13.5 Hz, HC-2', HC-2"), 2.71-2.64 (4H, m, HC-3', HC-3", HC-3, HC-5), 1.02 (18H, m, (H$_3$CC)$_3$Si, ×2), 0.72 (12H, m, (H$_2$C)$_3$Si, ×2), 0.11 (18H, s, (H$_3$C)$_3$SiOC-4', (H$_3$C)$_3$SiOC-4").

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 152.3 (s ×2, C-4', C-4"), 140.1 (s, Ph), 128.8 (d ×2, Ph), 128.7 (d ×2, Ph), 127.7 (d, Ph), 106.5 (d ×2, C-5', C-5"), 78.0 (d, C-4), 72.5 (d ×2, C-1', C-1"), 71.8 (t, CH$_2$OC-4), 54.3 (d ×2, C-3, C-5), 44.6 (d ×2, C-3', C-3"), 29.4 (t ×2, C-2, C-6), 28.7 (t ×2, C-2', C-2"), 25.4 (t ×2, C,6', C-6"), 7.7 (q ×6, (CH$_3$C)Si), 6.1 (t ×6, (CH$_2$)Si), 0.7 (q ×6, (CH$_3$)SiOC-4").

HRMS *m/z* calcd. for $C_{42}H_{76}O_5S_3Si_4$: 868.3932 (891.3824 for M+Na); found: 891.3857 (ESI, CH_3OH).
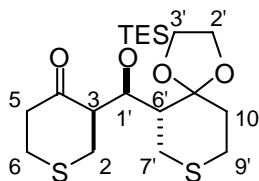
317sa

(*R*)-3-((*R*)-((*R*)-1,4-Dioxa-8-thiaspiro[4.5]decan-6-yl)(triethylsilyloxy)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one

2,6-Lutidine (0.43 mL, 0.40 g, 3.69 mmol) was added to a stirred solution of ketone **209sa** (255 mg, 0.84 mmol) in CH_2Cl_2 (20 mL) at 0 °C under Ar. After 2 min, TESOTf (0.42 mL, 0.49 g, 1.84 mmol) was added and the reaction was stirred vigorously for 15 min. Methanol (2 mL) was added and the mixture was diluted with ethyl acetate and washed with 1% w/v aqueous citric acid (3×). The combined organic layers were washed with sat. aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated and fractionated by FCC (30% ethyl acetate in hexane) to give silyl ketone **317sa** (331 mg, 94%).

IR (DRIFT) ν_{max}: 2942, 1715, 1429, 1221, 1072, 745 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ 5.43 (1H, dd, *J* = 2.5, 2.5 Hz, HC-1'), 3.60-3.32 (2H, m, H_2C-2' or H_2C-3'), 3.28 (1H, ddd, *J* = 2.5, 5, 11.5 Hz, HC-3), 3.20-3.08 (2H, m, H_2C-2' or H_2C-3'), 3.01-2.83 (4H, m, H_2C-2, H_2C-7), 2.70 (1H, ddd, *J* = 3.5, 13, 13 Hz, HC-9'), 2.57 (1H, br dd, *J* = 10, 11 Hz, HC-6), 2.48-2.41 (2H, m, HC-5, HC-6'), 2.36-2.26 (2H,

m, HC-5, HC-6), 2.13 (1H, ddd, J = 3.5, 3.5, 13.5 Hz, HC-9'), 1.69-1.56 (2H, m, H$_2$C-10'), 1.01 (9H, m, (H$_3$CC)$_3$Si), 0.69 (6H, m, (H$_2$C)$_3$Si).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 207.4 (s, C-4), 108.7 (s, C-5'), 65.4 (d, C-1'), 64.5 (t, C-2' or C-3'), 64.2 (t, C-2' or C-3'), 56.6 (d, C-3), 54.9 (d, C-6'), 44.8 (t, C-5), 37.8 (t, C-10'), 32.4 (t, C-2), 30.2 (t, C-6), 27.7 (t, C-7'), 27.4 (t, C-9'), 7.6 (q ×3, (CH$_3$C)Si), 5.7 (t ×3, (CH$_2$)Si).

LRMS (EI), *m/z* (relative intensity):   418 ([M]$^+$, 2), 389 (35), 333 (9), 286 (15), 229 (100), 171 (64), 99 (98).

HRMS *m/z* calcd. for C$_{19}$H$_{34}$O$_4$S$_2$Si: 418.1668; found: 418.1660.
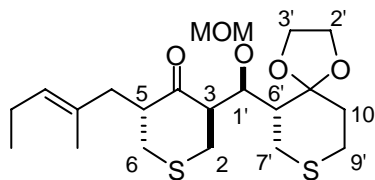
318sa

(3*R*,5*R*)-3-((*R*)-(Methoxymethoxy)((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-5-((*E*)-2-methylpent-2-enyl)dihydro-2*H*-thiopyran-4(3*H*)-one

t-BuLi (1.7 M in pentane; 0.19 mL, 0.32 mmol) was added dropwise *via* syringe to a solution of ketone **210sa** (100 mg, 0.29 mmol) in THF (6 mL) at −30 °C under Ar. After 30 min, allyl bromide (0.10 mL, 140 mg, 0.85 mmol) and HMPA (0.15 mL, 155 mg, 0.86 mmol) were added sequentially. After 2 h, the mixture was diluted with sat. aqueous NH$_4$Cl and extracted with CH$_2$Cl$_2$ (3×). The combined organic layers were dried over Na$_2$SO$_4$, concentrated and fractionated by FCC (10-50% ethyl acetate in hexane) to give recovered **210sa** (20 mg, 20%) and the titled *C*-alkylated **318sa** (98 mg, 79%; dr 20:1).

IR (DRIFT) v_{max}: 2961, 1701, 1414, 1169, 1103, 1038, 888 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 5.28 (1H, br dd, *J* = 7, 7 Hz, HC=C), 5.10 (1H, dd, *J* = 3, 3 Hz, HC-1'), 4.67 (1H, d, *J* = 6.5 Hz, H$_2$COC-1'), 4.51 (1H, d, *J* = 6.5 Hz, H$_2$COC-1'), 3.59 (1H, m, H$_2$C-2' or H$_2$C-3'), 3.47 (1H, ddd, *J* = 2.5, 5, 11.5 Hz, HC-3), 3.44-3.37 (2H, m, H$_2$C-2' or H$_2$C-3'), 3.18 (1H, m, H$_2$C-2' or H$_2$C-3'), 3.14 (3H, s, H$_3$CO), 3.17 (1H, dd, *J* = 11.5, 13.5 Hz, HC-2), 2.97 (1H, dd, *J* = 12.5, 12.5 Hz, HC-7'), 2.87-2.70 (5H, m), 2.68 (1H, ddd, *J* = 3, 3, 12 Hz, HC-6'), 2.56 (1H, dd, *J* = 10, 13.5 Hz, H$_2$CC-5), 2.46 (1H,

ddd, J = 2, 5, 13 Hz, HC-6), 2.37 (1H, dd, J = 4, 13.5 Hz, H$_2$CC-5), 2.17 (1H, dddd, J =

2,5, 4, 4, 13.5 Hz, HC-9'), 1.94-1.84 (2H, m, H$_2$CCH=C), 1.72-1.59 (2H, m, HC-10'),

1.42 (3H, s, H$_3$CC=C), 0.87 (3H, t, J = 7.5 Hz, H$_3$CCCH=C).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 211.0 (s, C-4), 131.2 (s, C=CH), 130.6 (d, CH=C), 109.5

(s, C-5'), 98.1 (t, CH$_2$OC-1'), 73.6 (d, C-1'), 64.7 (t, C-2' or C-3'), 64.3 (t, C-2' or C-3'),

56.0 (q, CH$_3$O), 53.8 (d, C-3), 52.0 (d, C-6'), 49.0 (d, C-5), 40.8 (t, CH$_2$C-5), 37.9 (t, C-

10'), 32.5 (t, C-6), 31.0 (t, C-2), 29.1 (t, C-7'), 27.4 (t, C-9'), 21.9 (t, CH$_2$CH=C), 15.9 (q,

CH$_3$C=C), 14.7 (q, CH$_3$CCH=C).

LRMS (EI), m/z (relative intensity): 430 ([M]$^+$, 4), 368 (9), 199 (6), 159 (11) 132 (74).

HRMS m/z calcd. for C$_{21}$H$_{34}$O$_5$S$_2$: 430.1848; found: 430.1833.
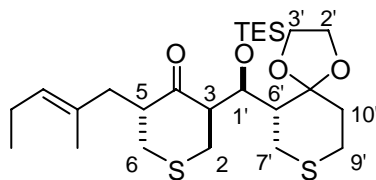
319sa

(3*R*,5*R*)-3-((*R*)-((*R*)-1,4-Dioxa-8-thiaspiro[4.5]decan-6-yl)(triethylsilyloxy)methyl)-5-((*E*)-2-methylpent-2-enyl)dihydro-2*H*-thiopyran-4(3*H*)-one

t-BuLi (1.7 M in pentane; 0.06 mL, 0.10 mmol) was added dropwise *via* syringe to a solution of ketone **317sa** (38 mg, 0.09 mmol) in THF (2 mL) at −30 °C under Ar. After 30 min, allyl bromide (0.030 mL, 42 mg, 0.26 mmol) and HMPA (0.050 mL, 52 mg, 0.27 mmol) were added sequentially. After 2h, the mixture was diluted with sat. aqueous NH$_4$Cl and extracted with CH$_2$Cl$_2$ (3×). The combined organic layers were dried over Na$_2$SO$_4$, concentrated and fractionated by FCC (10-50% ethyl acetate in hexane) to give recovered **317sa** (5 mg, 13%) and the titled *C*-alkylated **319sa** (40 mg, 87%; dr 20:1).

IR (DRIFT) ν_{max}: 2960, 1703, 1417, 1167, 1054, 739 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 5.24 (1H, dd, *J* = 7, 7 Hz, HC=C), 5.05 (1H, dd, *J* = 2, 2 Hz, HC-1'), 3.99-3.73 (4H, m, H$_2$C-2', H$_2$C-3'), 3.24 (1H, ddd, *J* = 1.5, 5, 11.5 Hz, HC-3), 3.02-2.70 (7H, m), 2.58 (1H, ddd, *J* = 2, 5, 13 Hz, HC-2), 2.51 (1H, dd, *J* = 11, 13.5 Hz, H$_2$CC-5), 2.44 (1H, dddd, *J* = 3.5, 3.5, 3.5, 13.5 Hz, HC-10'), 2.21-2.12 (2H, m), 2.05-1.93 (3H, m), 1.66 (1H, ddd, *J* = 3.5, 13.5, 13.5 Hz, HC-10'), 1.54 (3H, s, H$_3$CC=C), 0.95-0.89 (12H, m, (H$_3$CC)$_3$Si, H$_3$CCC=C), 0.58 (6H, m, (H$_2$C)$_3$Si).

¹³C NMR (125 MHz, CDCl₃): δ 212.1 (s, C-4), 130.8 (d, CH=C), 130.3 (s, CCH₃CH₂C-5), 108.9 (s, C-5'), 65.4 (d, C-1'), 64.6 (t, C-2' or C-3'), 64.2 (t, C-2' or C-3'), 54.3 (d, C-6'), 53.2 (d, C-3), 48.5 (d, C-5), 40.2 (t, CH₂C-5), 37.4 (t, C-10'), 31.5 (t, C-2), 30.1 (t, C-6), 27.4 (t, C-7'), 27.0 (t, C-9'), 21.5 (t, CH₂CH=C), 15.7 (q, CH₃C=C), 14.4 (q, CH₃CCH=C), 7.1 (q ×3, (CH₃C)Si), 5.1 (t ×3, (CH₂)Si).

LRMS (EI), *m/z* (relative intensity): 500 ([M]⁺, 10), 471 (20), 368 (20), 310 (31), 245 (57), 171 (50), 98 (100).

HRMS *m/z* calcd. for C₂₅H₄₄O₄S₂Si: 500.2450; found: 500.2402.
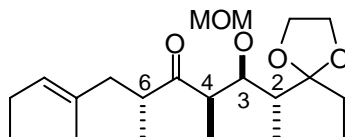
320sa

(2R,3R,4R,6R,E)-2-(2-Ethyl-1,3-dioxolan-2-yl)-3-(methoxymethoxy)-4,6,8-trimethylundec-8-en-5-one

Raney Ni (W-2) (*ca.* 1 mL settled volume; added as a suspension in ethanol) was added to a well-stirred solution of a ketone **318sa** (35 mg, 0.081 mmol) in methanol (10 mL). The resultant mixture was heated under reflux and additional Raney Ni was added every 2 h. After 4 h, the reaction mixture was filtered through a pad of Celite® and the filter cake was rinsed sequentially with hot methanol (2× 20 mL), CH₂Cl₂ (2× 20 mL) and acetone (2× 20 mL). The combined filtrate and washings were concentrated and the residue was taken up in dichloromethane and washed with water, dried over Na₂SO₄,

concentrated and fractionated by PTLC (20% ethyl acetate in hexane) to give the titled **320sa** (22 mg, 73%).

IR (DRIFT) ν_{max}: 2955, 1707, 1464, 1324, 1157, 1032, 811 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 5.22 (1H, dd, J = 7, 7 Hz, HC-9), 4.75 (1H, d, J = 6.5 Hz, H$_2$COC-3), 4.61 (1H, d, J = 6.5 Hz, H$_2$COC-3), 4.45 (1H, br s, HC-3), 3.56-3.40 (4H, m, H$_2$CO ×2), 3.31 (1H, dq, J = 3, 7 Hz, HC-2), 3.22 (3H, s, H$_3$CO), 2.95 (1H, m, HC-6), 2.55-2.43 (2H, m), 2.01-1.89 (2H, m), 1.78-1.60 (2H, m, H$_2$CC-1), 1.54 (3H, s, H$_3$CC=C), 1.31 (3H, d, J = 7 Hz, H$_3$CC-4), 1.78 (3H, d, J = 7 Hz, H$_3$CC-2 or H$_3$CC-6), 1.56 (3H, d, J = 7 Hz, H$_3$CC-2 or H$_3$CC-6), 1.00 (3H, t, J = 7.5 Hz, H$_3$CCC-1), 0.91 (3H, t, J = 7.5 Hz, H$_3$C-11).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 215.2 (s, C-5), 129.8 (d, CH=C), 128.7 (s, C-8), 113.4 (s, CC-2), 97.5 (t, CH$_2$OC-3), 76.5 (d, C-3), 65.9 (t, CH$_2$O), 65.0 (t, CH$_2$O), 56.0 (q, CH$_3$O), 47.7 (d), 44.4 (t, C-7), 43.7 (d), 43.0 (d), 29.5 (t, CH$_2$C-1), 22.0 (t, C-10), 16.9 (q), 16.2 (q), 14.8 (q), 12.9 (q), 10.7 (q), 8.6 (q).

TES

O   O   O   O

6   4   2

3
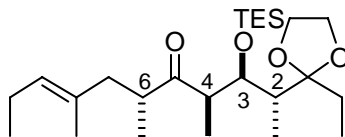
321sa

(2*R*,3*R*,4*R*,6*R*,*E*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4,6,8-trimethyl-3-(triethylsilyloxy)undec-8-en-5-one

Raney Ni (W-2) (*ca.* 1 mL settled volume; added as a suspension in ethanol) was added to a well-stirred solution of ketone **319sa** (15 mg, 0.03 mmol) in methanol (10 mL). The resultant mixture was heated under reflux. After 1 h, the reaction mixture was filtered through a pad of Celite® and the filter cake was rinsed sequentially with hot methanol (2× 20 mL), CH$_2$Cl$_2$ (2× 20 mL) and acetone (2× 20 mL). The combined filtrate and washings were concentrated and the residue was taken up in dichloromethane and washed with water, dried over Na$_2$SO$_4$, concentrated, and fractionated by PTLC (20% ether in hexane) to give the titled **321sa** (10 mg, 77%).

IR (DRIFT) ν_{max}: 2955, 1706, 1452, 1053, 989, 723 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 5.25 (1H, dd, *J* = 7, 7 Hz, HC-9), 4.76 (1H, dd, *J* = 3, 3 Hz, HC-3), 3.61-3.39 (5H, m), 3.32 (1H, dq, *J* = 3.5, 7 Hz, HC-4), 2.86 (1H, ddd, *J* = 6.5, 6.5, 8 Hz), 2.57 (1H, dd, *J* = 6.5, 13.5 Hz), 2.33 (1H, dq, *J* = 3, 7 Hz, HC-2), 2.01-1.91 (2H, m), 1.72-1.57 (2H, m), 1.54 (3H, s, H$_3$CC-8), 1.28 (3H, d), 1.20 (3H, d), 1.12-1.05 (12H, m), 0.99-0.91 (6H, m, (H$_2$C)$_3$Si), 0.79 (3H, d), 0.78 (3H, d).

¹³**C NMR** (125 MHz, C_6D_6): δ 215.0 (s, C-5), 132.3 (d, CH=C), 129.3 (s, C=C), 113.1

(s, C-1), 69.5 (d, C-3), 65.3 (t, CH_2O), 64.4 (t, CH_2O), 47.0 (d), 46.2 (t, CH_2C-6), 43.3

(d), 42.5 (d), 28.9 (t, CH_2C-1), 21.5 (t, C-10), 16.6 (q), 15.6 (q), 14.3 (q), 13.1 (q), 9.6

(q), 8.2 (q), 7.2 (q ×3, $(CH_3)Si$), 5.5 (t ×3, $(CH_2)Si$).

LRMS (EI), *m/z* (relative intensity): 411 ([M−29]$^+$, 3), 215 (22), 163 (15), 101 (100).

HRMS *m/z* calcd. for $C_{25}H_{48}O_4Si$: 440.3322 (411.2931 for M−C_2H_5; 463.3219 for

M+Na); found: 411.2932 (EI); 463.3209 (ESI, CH_3OH).
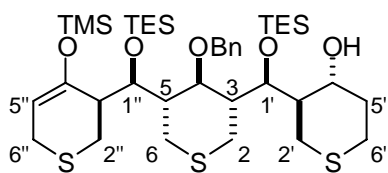
322

(3R,4R)-3-((S)-((3R,4S,5S)-4-(Benzyloxy)-5-((S)-(triethylsilyloxy)((R)-4-(trimethylsilyloxy)-3,6-dihydro-2H-thiopyran-3-yl)methyl)tetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2H-thiopyran-4-ol

Zn(BH$_4$)$_2$ (0.1 M in ether; 3.5 mL, 0.35 mmol) was added dropwise *via* syringe to a

solution of mono-silyl enol ether **315** (187 mg, 0.23 mmol) in THF (24 mL) at room

temperature under Ar. After 1 d, excess Zn(BH$_4$)$_2$ was quenched by dropwise addition of

1% w/v aqueous citric acid (*ca.* 2 mL) at 0 °C and the resulting mixture was diluted with

ethyl acetate, washed sequentially with sat. aqueous NaHCO$_3$ and brine, dried over

Na$_2$SO$_4$, and concentrated to give crude alcohol **322** (264 mg) that was a 8-10:1 mixture

of diastereomers by ^{1}H NMR. Fractionation of the crude by FCC (5-10% ether in hexane) gave the titled alcohol **322** (196 mg, 77%).

IR (DRIFT) ν_{max}: 3433, 2896, 1669, 1257, 1076, 741 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.79-7.06 (5H, m, Ph), 5.11-4.8 (5H, m, HC-1', HC-1", HC-5", H$_2$COC-4), 3.90 (1H, dd, J = 10, 10 Hz, HC-4), 3.27 (1H, br s, HC-4'), 3.17 (1H, dd, J = 2.5, 13 Hz), 3.13-3.00 (4H, m), 2.82-2.55 (6H, m), 2.50 (1H, br dd, J = 10, 10 Hz), 2.44-2.33 (2H, m), 2.24 (1H, br d, J = 13.5 Hz), 1.95 (1H, m), 1.76 (1H, m), 1.69-1.50 (2H, m), 1.02 (18H, m, (H$_3$CC)$_3$Si ×2), 0.78-0.59 (12H, m, (H$_2$C)$_3$Si ×2), 0.23 (9H, s, (H$_3$C)$_3$SiOC-4").

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 151.8 (s, C-4"), 140.3 (s, Ph), 128.8 (d ×2, Ph), 128.71 (d, Ph), 128.69 (d, Ph), 128.0 (d, Ph), 106.9 (d, C-5"), 77.4 (d, C-4), 72.8 (d, C-1'), 72.5 (d, C-4'), 71.5 (d, C-1"), 68.9 (t, CH$_2$OC-4), 56.3 (d ×2), 48.6 (d), 43.9 (d), 39.5 (t), 30.1 (t), 29.2 (t), 28.8 (t), 28.4 (t), 28.3 (t), 25.1 (t), 7.7 (q ×6, (CH$_3$C)Si), 6.5 (t ×3, (CH$_2$)Si), 5.9 (t ×3, (CH$_2$)Si), 0.9 (q ×3, (CH$_3$)SiOC-4").

LRMS (EI), m/z (relative intensity): 798 ([M]$^+$, 1), 617 (13), 575 (40), 331 (60), 171 (94), 115 (87).

HRMS m/z calcd. for C$_{39}$H$_{70}$O$_5$S$_3$Si$_3$: 798.3693 (821.3585 for M+Na); found: 798.3668 (EI); 821.3610 (ESI, CH$_3$OH).
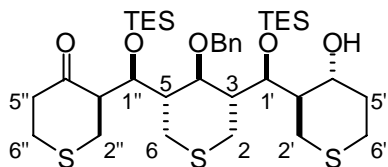
323

(R)-3-((S)-((3S,4S,5R)-4-(Benzyloxy)-5-((S)-((3R,4R)-4-hydroxytetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)dihydro-2H-thiopyran-4(3H)-one

Aqueous sat. $NaHCO_3$ (2 mL) was added dropwise to a stirred solution of mono-silyl enol ether **322** (196 mg, 0.25 mmol) in methanol (10 mL) and THF (10 mL) at room temperature. After 2 h, the reaction was diluted with water and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over Na_2SO_4, concentrated and fractionated by FCC (30% ether in hexane) to give the titled ketol **323** (172 mg, >95%).

IR (DRIFT) ν_{max}: 3474, 2953, 1708, 1379, 1238, 886 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ 7.74-7.08 (5H, m, Ph), 4.94 (1H, d, J = 10 Hz, H$_2$COC-4), 4.91 (1H, br s, HC-1'), 4.85 (1H, br s, HC-1"), 4.75 (1H, d, J = 10 Hz, H$_2$COC-4), 3.60 (1H, dd, J = 10, 10 Hz, HC-4), 3.31 (1H, ddd, J = 4, 10, 10 Hz, HC-4'), 3.05 (1H, m, HC-3"), 2.99-2.80 (5H, m), 2.77-2.64 (2H, m, H$_2$C-7'), 2.59-2.04 (10H, m), 1.98 (1H, br dd, J = 9.5, 9.5 Hz, HC-3'), 1.88 (1H, ddd, J = 4, 4, 13 Hz, HC-5'), 1.62 (1H, ddd, J = 4, 13, 13 Hz, HC-5'), 1.02-0.94 (18H, m, (H$_3$CC)$_3$Si ×2), 0.69-0.58 (12H, m, (H$_2$C)$_3$Si ×2).

^{13}C NMR (125 MHz, C_6D_6): δ 209.7 (s, C-4"), 139.1 (s, Ph), 129.1 (d, Ph), 128.8 (d, Ph), 128.6 (d, Ph), 128.4 (d, Ph), 128.2 (d, Ph), 77.7 (d, C-4), 71.6 (d, C-4'), 70.7 (d, C-

1"), 69.6 (d, C-1'), 69.4 (t, CH$_2$OC-4), 56.5 (d, C-3"), 53.3 (d, C-3 or C-5), 51.9 (d, C-3 or

C-5), 48.8 (d, C-3'), 44.7 (t, C-5"), 38.9 (t, C-5'), 33.7 (t, C-2"), 31.0 (t, C-6"), 30.5 (t, C-2

or C-6), 30.3 (t, C-2 or C-6), 29.7 (t, C-2'), 28.1 (t, C-6'), 7.70 (q ×3, (CH$_3$C)$_3$Si), 7.65 (q

×3, (CH$_3$C)$_3$Si), 6.1 (t ×3, (CH$_2$)$_3$Si), 6.0 (t ×3, (CH$_2$)$_3$Si).

LRMS (EI), *m/z* (relative intensity): 726 ([M]$^+$, 46), 565 (37), 459 (27), 243 (28), 171

(100), 91 (61).

HRMS *m/z* calcd. for C$_{36}$H$_{62}$O$_5$S$_3$Si$_2$: 726.3298; found: 726.3304.
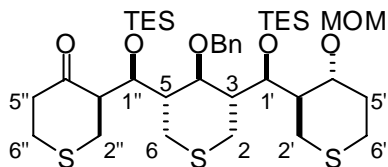
324

**(*R*)-3-((*S*)-((3*S*,4*S*,5*R*)-4-(Benzyloxy)-5-((*S*)-((3*R*,4*R*)-4-
(methoxymethoxy)tetrahydro-2*H*-thiopyran-3-
yl)(triethylsilyloxy)methyl)tetrahydro-2*H*-thiopyran-3-
yl)(triethylsilyloxy)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one**

i-Pr$_2$EtN (0.85 mL, 0.63 g, 4.9 mmol) was added to a stirred solution of ketol **323**

(178 mg, 0.24 mmol) and *n*-Bu$_4$NI (90 mg, 0.24 mmol) in CH$_2$Cl$_2$ (12 mL) at room

temperature under Ar. After 2 min, MOMCl (0.19 mL, 0.20 g, 2.5 mmol) was added and

the reaction was stirred vigorously for 4 d. The mixture was diluted with ethyl acetate

and washed with 1% w/v aqueous citric acid (3×). The combined organic layers were

washed with sat. aqueous NaHCO$_3$, dried over Na$_2$SO$_4$, concentrated and fractionated by

FCC (30% ether in hexane) to give the titled **324** (172 mg, 91%).

IR (DRIFT) ν_{max}: 2940, 1701, 1451, 1235, 1064 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.59-7.02 (5H, m, Ph), 5.02 (1H, d, J = 11 Hz, H$_2$COC-4), 4.81-4.71 (2H, m, HC-1', HC-1''), 4.74 (1H, d, J = 11 Hz, H$_2$COC-4), 4.35 (1H, d, J = 7 Hz, H$_2$COC-4'), 4.24 (1H, d, J = 7 Hz, H$_2$COC-4'), 3.52 (1H, dd, J = 9, 9 Hz, HC-4), 3.42 (1H, dddd, J = 1.5, 3.5, 8.5, 8.5 Hz, HC-4'), 2.92 (3H, s, H$_3$CO), 2.92-2.63 (6H, m), 2.56-2.01 (13H, m), 1.65 (1H, dddd, J = 3, 9, 9, 13 Hz, HC-5'), 1.00-0.90 (18H, m, (H$_3$CC)$_3$Si ×2), 0.68-0.54 (12H, m, (H$_2$C)$_3$Si ×2).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ 208.9 (s, C-4''), 139.7 (s, Ph), 128.4 (d, Ph), 128.2 (d, Ph), 128.1 (d, Ph), 127.7 (d, Ph), 127.5 (d, Ph), 96.8 (t, CH$_2$OC-4'), 78.4 (d, C-4), 78.8 (d, C-4'), 71.3 (t, CH$_2$OC-4), 70.65 (d, C-1' or C-1''), 70.62 (d, C-1' or C-1''), 57.0, 56.0, 53.8, 53.0, 46.1, 45.0, 37.0, 33.2, 30.7, 29.1, 27.4, 26.9, 26.8, 7.8 (q ×3, (CH$_3$C)Si), 7.7 (q ×3, (CH$_3$C)Si), 6.2 (t ×3, (CH$_2$)Si), 6.1 (t ×3, (CH$_2$)Si).

LRMS (EI), m/z (relative intensity): 770 ([M]$^+$, 1), 609 (6), 243 (22), 171 (35), 91 (100).

HRMS m/z calcd. for C$_{38}$H$_{66}$O$_6$S$_3$Si$_2$: 770.3560 (793.3452 for M+Na); found: 770.3560 (EI); 793.3438 (ESI, CH$_3$OH).
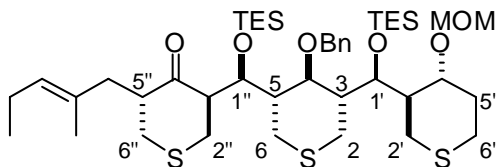
325

(3R,5R)-3-((S)-((3S,4S,5R)-4-(Benzyloxy)-5-((S)-((3R,4R)-4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)-5-((E)-2-methylpent-2-enyl)dihydro-2H-thiopyran-4(3H)-one

t-BuLi (1.5 M in pentane; 1.2 mL, 1.8 mmol) was added dropwise *via* syringe to a solution of ketone **324** (138 mg, 0.18 mmol) in THF (9 mL) at −50 °C under Ar. After 2 min, allyl bromide (0.42 mL, 584 mg, 3.58 mmol) and HMPA (0.62 mL, 640 mg, 3.6 mmol) were added sequentially. After 2 h, the mixture was diluted with ethyl acetate and washed with aqueous phosphate buffer (0.1 M, pH 7; 3× 40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 and applied to a bed of silica and eluted with 50% CH_2Cl_2 in hexane followed by ether. The ether eluate was were concentrated to give crude *C*-alkylated products that was a 2:1 mixture of diastereomers by ^{1}H NMR. Fractionation of the crude by PTLC (CH_2Cl_2) gave recovered **324** (30 mg, 22%), minor *C*-alkylated product **326** (25 mg, 16%) and the titled *C*-alkylated product **325** (73 mg, 48%).

IR (DRIFT) ν_{max}: 2958, 1702, 1451, 1241, 1097, 1020, 727 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ 7.66-7.09 (5H, m, Ph), 5.24 (1H, dd, *J* = 6.5, 6.5 Hz, HC=C), 5.11 (1H, d, *J* = 10.5 Hz, H₂COC-4), 4.94-4.68 (2H, m), 4.44 (1H, d, *J* = 7 Hz, H₂COC-4'), 4.31 (1H, d, *J* = 7 Hz, H₂COC-4'), 3.61 (1H, dd, *J* = 9.5, 9.5 Hz), 3.46 (1H,

dd, J = 9.5, 9.5 Hz), 3.40 (1H, br s), 2.98 (3H, s, H_3CO), 2.97-2.78 (6H, m), 2.76-2.68 (2H, m), 2.64-2.40 (5H, m), 2.37-2.16 (7H, m), 1.96 (2H, m, $H_2CCH=C$), 1.72 (1H, m), 1.41 (3H, s, $H_3CC=C$), 1.07-0.98 (18H, m, $(H_3CC)_3Si$ ×2), 0.95 (3H, t, J = 7.5 Hz, $H_3CCCH=C$), 0.74-0.61 (12H, m, $(H_2C)_3Si$ ×2).

^{13}**C NMR** (125 MHz, C_6D_6): δ 211.9 (s, C-4"), 139.8 (s, C=CH), 131.3 (s, Ph), 130.4 (d, CH=C), 128.9 (d ×2, Ph), 128.7 (d, Ph), 128.1 (d, Ph), 128.0 (d, Ph), 96.9 (t, CH_2OC-4'), 78.4 (d ×3), 71.1 (d, t), 55.5 (q, CH_3O), 54.0, 53.7, 50.4, 46.4 (×4), 40.6, 34.4, 33.0, 31.3, 29.2, 27.0, 22.0 (t, $CH_2CH=C$), 16.0 (q, $CH_3C=C$), 14.9 (q, $CH_3CCH=C$), 7.79 (q ×3, $(CH_3C)Si$), 7.77 (q ×3, $(CH_3C)Si$), 6.19 (t ×3, $(CH_2)Si$), 6.17 (t ×3, $(CH_2)Si$).

HRMS *m/z* calcd. for $C_{44}H_{76}O_6S_3Si_2$: 852.4343 (875.4234 for M+Na); found: 875.4240 (ESI, CH_3OH).
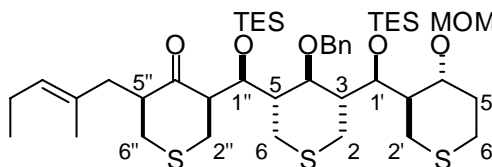
326

(3R,5S)-3-((S)-((3S,4S,5R)-4-(Benzyloxy)-5-((S)-((3R,4R)-4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)-5-((E)-2-methylpent-2-enyl)dihydro-2H-thiopyran-4(3H)-one

IR (DRIFT) ν_{max}: 2958, 1702, 1455, 1135, 1101, 739 cm^{-1}.

¹H NMR (500 MHz, C₆D₆): δ 7.63-7.06 (5H, m, Ph), 5.15 (1H, d, *J* = 10.5 Hz), 5.04 (1H, dd, *J* = 6.5, 6.5 Hz, HC=C″), 4.90-4.56 (2H, m), 4.38 (1H, d, *J* = 6 Hz), 4.25 (1H, d, *J* = 6 Hz), 3.66 (1H, dd, *J* = 9, 9 Hz), 3.46 (2H, br s), 3.12 (1H, d, *J* = 13 Hz), 2.98-2.90 (2H, m), 2.95 (3H, s, H₃CO), 2.88-2.06 (16, m), 1.94-1.77 (3H, m), 1.66 (1H, m), 1.31 (3H, m, H3CC=C), 1.08-0.99 (18H, m, (H₃CC)₃Si ×2), 0.89 (3H, t, *J* = 7.5 Hz, H₃CCCH=C), 0.75-0.57 (12H, m, (H₂C)₃Si ×2).

¹³C NMR (125 MHz, C₆D₆): δ 211.1 (s, C-4″), 139.8 (s, Ph), 131.7 (s, C=CH), 129.6 (d, CH=C), 128.9 (d ×2, Ph), 128.7 (d, Ph), 128.01 (d, Ph), 128.96 (d, Ph), 95.8 (t, CH₂OC-4′), 78.6 (d), 72.1 (d, t), 58.6 (d ×2), 55.4 (q, CH₃O), 52.8, 46.2 (×2), 39.4, 37.4, 35.5, 31.7 (×3), 29.0 (×3), 26.8, 21.9 (t, CH₂CH=C), 16.8 (q, CH₃C=C), 14.9 (q, CH₃CCH=C), 7.8 (q ×6, (CH₃C)Si), 6.2 (t ×3, (CH₂)Si), 6.1 (t ×3, (CH₂)Si).

LRMS (EI), *m/z* (relative intensity): 852 ([M]⁺, 1), 720 (1), 691 (2), 341 (6), 115 (38), 91 (100), 87 (30).

HRMS *m/z* calcd. for C₄₄H₇₆O₆S₃Si₂: 852.4343; found: 852.4379.
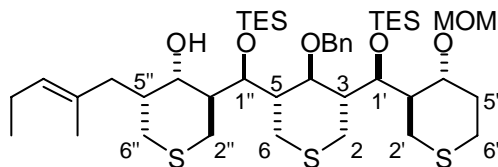
327

(3S,4S,5R)-3-((R)-((3S,4R,5R)-4-(Benzyloxy)-5-((S)-((3R,4R)-4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)-5-((E)-2-methylpent-2-enyl)tetrahydro-2H-thiopyran-4-ol

NaBH₃CN (70 mg, 1.1 mmol) was added to a solution of ketone **325** (47 mg, 0.055 mmol) and citric acid (116 mg, 0.55 mmol) in ethanol (3 mL) and THF (3 mL) at 0 °C under Ar. After 4-8 h, excess NaBH₃CN was quenched by dropwise addition of sat. aqueous NaHCO₃ (*ca.* 2 mL) at 0 °C and the resulting mixture was diluted with water and extracted with CH₂Cl₂ (3×), dried over Na₂SO₄, concentrated and fractionated by PTLC (CH₂Cl₂) to give the titled alcohol **327** (37 mg, 79%).

IR (DRIFT) ν_{max}: 3495, 2952, 1463, 1412, 1073, 728 cm⁻¹.

¹H NMR (500 MHz, C₆D₆): δ 7.65-6.96 (5H, m, Ph), 5.31 (1H, dd, J = 6.5, 6.5 Hz, HC=C), 5.09 (2H, br s), 4.75 (1H, br s), 4.63 (1H, br s), 4.31 (1H, br s), 4.15 (1H, br s), 3.90 (1H, br s), 3.71 (1H, dd, J = 9, 9 Hz), 3.56 (1H, br s), 2.96 (3H, s, H₃CO), 2.91-2.14 (19H, m), 2.13-1.98 (3H, m), 1.85 (1H, br s), 1.68 (1H, m), 1.60 (3H, s, H₃CC=C), 1.16-0.95 (21H, m), 0.83-0.65 (12H, m, (H₂C)₃Si ×2).

LRMS (EI), m/z (relative intensity): 854 ([M]⁺, 8), 693 (25), 571 (11), 325 (52), 243 (80), 171 (76), 91 (100).

173

HRMS *m/z* calcd. for $C_{44}H_{78}O_6S_3Si_2$: 854.4499; found: 854.4499.
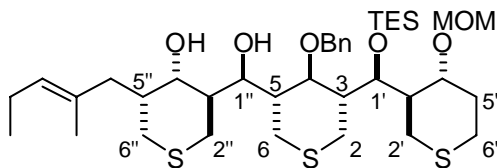
328

(3S,4S,5R)-3-((R)-((3R,4R,5R)-4-(Benzyloxy)-5-((S)-((3R,4R)-4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2H-thiopyran-3-yl)(hydroxy)methyl)-5-((E)-2-methylpent-2-enyl)tetrahydro-2H-thiopyran-4-ol

TBAF (55 mg, 0.21 mmol) was added to a solution of alcohol **327** (18 mg, 0.021 mmol) in CH_2Cl_2 (2 mL) at room temperature under Ar. After 15 min, the mixture was diluted with ethyl acetate and washed sequentially with 1% w/v aqueous citric acid, sat. aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (50% ethyl acetate in hexane) to give the titled diol **328** (16 mg, >95%).

^{1}H NMR (500 MHz, C_6D_6): δ 7.46-6.95 (5H, m, Ph), 5.50 (1H, br s, HOC-1" or HOC-4"), 5.36 (1H, dd, *J* = 6, 6 Hz), 4.84 (1H, d, *J* = 11 Hz), 4.71 (1H, br s), 6.68 (1H, d, *J* = 11 Hz), 4.36 (1H, d, *J* = 7 Hz), 4.24 (1H, d, *J* = 7 Hz), 4.17 (1H, br s), 3.82 (1H, br d, *J* = 6 Hz), 3.60 (1H, dd, *J* = 8.5, 8.5 Hz), 3.51 (br s), 3.25 (br s, HOC-1" or HOC-4"), 2.97 (3H, s, H_3CO), 2.94 (1H, br s), 2.83 (1H, br d, *J* = 11.5 Hz), 2.78-2.30 (10H, m), 2.29-1.93 (9H, m), 1.72 (2H, m), 1.56 (3H, s, $H_3CC=C$), 1.04 (9H, m, $(H_3CC)_3Si$), 0.95 (3H, t, *J* = 7 Hz, $H_3CCCH=C$), 0.71 (6H, m, $(H_2C)_3Si$).
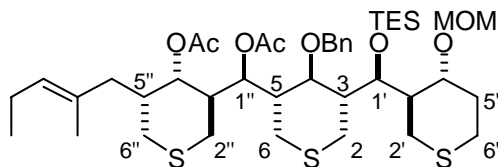
329a

(3*S*,4*S*,5*R*)-3-((*S*)-Acetoxy((3*S*,4*R*,5*R*)-4-(benzyloxy)-5-((*S*)-((3*R*,4*R*)-4-(methoxymethoxy)tetrahydro-2*H*-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2*H*-thiopyran-3-yl)methyl)-5-((*E*)-2-methylpent-2-enyl)tetrahydro-2*H*-thiopyran-4-yl acetate

Ac$_2$O (0.020 mL, 22 mg, 0.22 mmol) was added to a solution of diol **328** (16 mg, 0.02 mmol) and DMAP (50 mg, 0.42 mmol) in CH$_2$Cl$_2$ (2 mL) at room temperature under Ar. After 15 min, the mixture was diluted with ethyl acetate and washed sequentially with 1% w/v aqueous citric acid (3×), sat. aqueous NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, concentrated, and fractionated by PTLC (5% ether in CH$_2$Cl$_2$) to give **329a** (15 mg, 88%).

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.57-7.07 (5H, m, Ph), 5.79 (1H, dd, *J* = 3, 8 Hz), 5.28 (1H, dd, *J* = 7, 7 Hz), 4.94 (1H, dd, *J* = 3.5, 8.5 Hz), 4.78 (1H, br s), 4.71 (1H, d, *J* = 11 Hz), 4.62 (1H, d, *J* = 11 Hz), 4.53 (1H, d, *J* = 6.5 Hz), 4.47 (1H, d, *J* = 6.5 Hz), 3.54 (1H, br d), 3.43 (1H, br dd), 3.07 (3H, s, H$_3$CO), 2.95 (2H, m), 2.87-2.70 (2H, m), 2.68-2.17 (16H, m), 1.98-1.85 (3H, m), 1.95 (3H, s, H$_3$CCO), 1.84 (3H, s, H$_3$CCO), 1.39 (3H, s, H$_3$CC=C), 1.02 (9H, m, (H$_3$CC)$_3$Si), 0.90 (3H, t, *J* = 7 Hz, H$_3$CCCH=C), 0.68 (6H, m, (H$_2$C)$_3$Si).
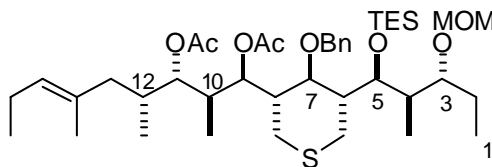
330

(1R,2S,3S,4R,E)-1-((3S,4R,5R)-4-(Benzyloxy)-5-((5R,6R,7S)-5,9,9-triethyl-6-methyl-2,4,8-trioxa-9-silaundecan-7-yl)tetrahydro-2H-thiopyran-3-yl)-2,4,6-trimethylnon-6-ene-1,3-diyl diacetate

Raney Ni (W-2) (*ca.* 1 mL settled volume; added as a suspension in ethanol) was added to a well-stirred solution of **329a** (10 mg, 0.01 mmol) in ethanol (10 mL). The resultant mixture was heated under reflux and additional Raney Ni was added every 2 h. After 8 h, the reaction mixture was filtered through a pad of Celite® and the filter cake was rinsed sequentially with hot methanol (2× 20 mL), CH$_2$Cl$_2$ (2× 20 mL) and acetone (2× 20 mL). The combined filtrate and washings were concentrated and the residue was taken up in dichloromethane and washed with water, dried over Na$_2$SO$_4$, concentrated and fractionated by PTLC (10% ethyl acetate in hexane) to give **330** (6 mg, 67%).

IR (DRIFT) v_{max}: 2906, 1729, 1451, 1366, 1246, 1030, 740 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.55-7.03 (5H, m, Ph), 5.63 (1H, br d, *J* = 9 Hz, HC-9), 5.29 (1H, dd, *J* = 7, 7 Hz, HC-15), 5.06 (1H, dd, *J* = 3, 9 Hz, HC-11), 4.76-4.53 (4H, m), 4.42 (1H, br s, HC-5), 3.57 (1H, dd, *J* = 4.5, 10.5 Hz, HC-7), 3.48 (1H, ddd, *J* = 3, 6, 6 Hz, HC-3), 3.16-3.13 (1H, m), 3.15 (3H, s, H$_3$CO), 3.03 (1H, dd, *J* = 2, 13.5 Hz), 2.76 (1H, dd, *J* = 12.5, 12.5 Hz), 2.65-2.50 (2H, m), 2.41-2.20 (4H, m), 2.11-1.95 (3H, m),

1.93 (3H, s), 1.83-1.79 (1H, m), 1.81 (3H, s), 1.79-1.68 (1H, m), 1.60 (1H, m), 1.55 (3H, s, H$_3$CC-14), 1.12-0.88 (24H, m), 0.77-0.63 (6H, (H$_2$C)$_3$Si).
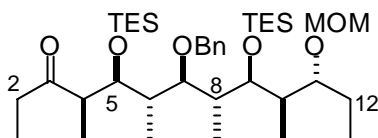
347

(4*R*,5*S*,6*S*,7*S*,8*R*,9*S*,10*R*,11*R*)-7-(Benzyloxy)-11-(methoxymethoxy)-4,6,8,10-tetramethyl-5,9-bis(triethylsilyloxy)tridecan-3-one

Raney Ni (W-2) (*ca.* 1 mL settled volume; added as a suspension in ethanol) was added to a well-stirred solution of a ketone **324** (31 mg, 0.04 mmol) in ethanol (10 mL). The resultant mixture was heated under reflux for 1 h. The reaction solution was filtered through a pad of Celite® and the remaining Raney Ni was sequentially extracted with refluxing (*ca.* 10 min) ethanol (1× 10 mL) and 50% acetone in CH$_2$Cl$_2$ (3× 10 mL). The combined filtrate and washings were concentrated and fractionated by PTLC (30% ether in hexane) to give the titled ketone **347** (19 mg, 70%) ([α]$_D^{22}$ −1.0; *c* 1, C$_6$H$_6$).

IR (DRIFT) ν_{max}: 2886, 1708, 1378, 1343, 1303, 1214, 970 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.48-7.05 (5H, m, Ph), 4.77 (2H, ap dd, *J* = 11.5, 11.5 Hz, H$_2$COC-7), 4.66 (1H, br dd, *J* = 4.5, 4.5 Hz, HC-5), 4.61 (1H, d, *J* = 7 Hz, HCOC-11), 4.48 (1H, d, *J* = 7 Hz, HCOC-11), 4.38 (1H, br s, HC-7), 3.51-3.46 (2H, m, HC-9, HC-11), 3.18 (3H, s, H$_3$CO), 3.08-2.99 (1H, m, HC-4), 2.40-2.32 (1H, m, HC-10), 2.29-2.14

(4H, m, H$_2$C-2, HC-6, HC-8), 1.81-1.70 (1H, m, HC-12), 1.63-1.52 (1H, m, HC-12), 1.26-0.95 (36H, m), 0.82-0.68 (12H, m, (H$_2$C)$_3$Si ×2).

^{13}**C NMR** (125 MHz, C$_6$D$_6$): δ 212.8 (s, C-3), 140.2 (s, Ph), 128.8 (d, Ph), 128.7 (d, Ph), 128.3 (d, Ph), 127.8 (d, Ph), 127.7 (d, Ph), 96.7 (t, CH$_2$O), 84.5 (d, C-9), 82.9 (d, C-11), 74.5 (t, CH$_2$OC-7), 73.0 (d, C-5), 72.7 (d, C-7), 55.8 (q, CH$_3$O), 49.8 (d, C-4), 43.7 (d, C-8), 42.5 (d, C-6), 37.9 (d, C-10), 34.8 (t, C-2), 23.6 (t, C-12), 14.6 (q), 13.9 (q), 13.4 (q), 11.1 (q), 9.4 (q), 8.3 (q), 7.82 (q ×3, (CH$_3$C)Si), 7.77 (q ×3, (CH$_3$C)Si), 6.4 (t ×3, (CH$_2$)Si), 6.3 (t ×3, (CH$_2$)Si).

LRMS (CI, NH$_3$), m/z (relative intensity): 698 ([M+18]$^+$, 100), 573 (21), 441 (26), 377 (28), 132 (54).

HRMS *m/z* calcd. for C$_{38}$H$_{72}$O$_6$Si$_2$: 680.4867 (651.4476 for M−C$_2$H$_5$; 698.5211 for M+NH$_4$); found: 651.4475 (EI); 698.5212 (CI, NH$_3$).
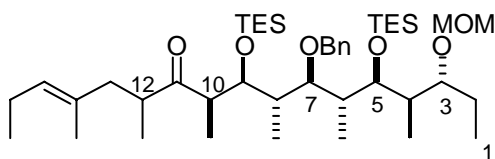
349

(8R,9S,10S,11S,12R,13S,14R,15R,E)-11-(benzyloxy)-15-(methoxymethoxy)-4,6,8,10,12,14-hexamethyl-9,13-bis(triethylsilyloxy)heptadec-3-en-7-one

NaHMDS (1.0 M in THF; 0.51 mL, 0.51 mmol) was added dropwise *via* syringe to a solution of ketone **347** (35 mg, 0.051 mmol) in THF (5 mL) at −78 °C under Ar. After

30 min, TMEDA (0.080 mL, 59 mg, 0.51 mmol) was added and after stirring for 5 min allyl bromide **47** (0.12 mL, 20 mg, 1.0 mmol) was added. After 3 h, the mixture was quenched with acetone (0.2 mL) and warmed to 0 °C over 15 min. Phosphate buffer (0.1 M, pH 7) was added and the mixture was diluted with ethyl acetate. The organic layer was washed with phosphate buffer (0.1 M, pH 7; 3×), dried over Na_2SO_4 and concentrated to give starting material and crude alkylated products which were a 4:1 mixture of diastereomers by ^{1}H NMR. Fractionation on the crude by PTLC (5% ether in hexanes) gave recovered **347** (10 mg, 29%) and *C*-alkylated products **349** as a mixture of diastereomers (25 mg, 65%; dr 4.6:1).

IR (DRIFT) ν_{max}: 2946, 2880, 1708, 1456, 1366, 1229, 721 cm^{-1}.

[1]**H NMR** (500 MHz, C_6D_6): δ (for major diastereomer) 7.49-7.03 (5H, m, Ph), 5.20 (1H, dd, *J* = 7, 7 Hz, HC-15), 4.84-4.67 (3H, m, HC-9, H_2COC-7), 4.65 (1H, d, *J* = 7 Hz, HCOC-3), 4.53-4.47 (1H, m, HC-5), 4.51 (1H, d, *J* = 7 Hz, HCOC-3), 3.52 (1H, dd, *J* = 5, 8 Hz, HC-7), 3.51-3.46 (1H, m, HC-3), 3.20-3.16 (1H, m, HC-10), 3.19 (3H, s, H_3CO), 2.93-2.78 (1H, m, HC-12), 2.45 (1H, dd, *J* = 4.5, 13.5 Hz, HC-13), 2.30 (1H, br dd, *J* = 7, 7 Hz, HC-4), 2.28 (2H, m, HC-6, HC-8), 1.99 (1H, dd, *J* = 10, 13.5 Hz, HC-13), 1.98-1.91 (2H, m, HC-16), 1.86-1.76 (1H, m, HC-2), 1.65-1.52 (1H, m, HC-2), 1.47 (3H, s, H_3CC-14), 1.26 (3H, d, *J* = 7 Hz, H_3CC-10), 1.21 (3H, d, *J* = 7 Hz, H_3CC-6 or H_3CC-8), 1.19 (3H, d, *J* = 7 Hz, H_3CC-6 or H_3CC-8), 1.15-1.07 (27H, m), 1.05 (3H, d, *J* = 7 Hz, H_3CC-12), 1.00 (3H, t, *J* = 7.5 Hz, H_3C-1), 0.92 (3H, t, *J* = 7.5 Hz, H_3C-17), 0.76 (6H, m, $(H_2C)_3Si$).

¹³**C NMR** (125 MHz, C$_6$D$_6$): δ (for major diastereomer) 215.3 (s, C-11), 140.3 (s, Ph), 132.1 (s, C-14), 129.9 (d, C-15), 128.8 (d, Ph), 128.7 (d ×2, Ph), 127.8 (d, Ph), 127.6 (d, Ph), 96.9 (t, CH$_2$O), 83.8 (d, C-7), 83.4 (d, C-3), 73.6 (t, CH$_2$OC-7), 72.1 (d, C-5), 71.6 (d, C-9), 55.8 (q, CH$_3$O), 48.5 (d, C-10), 44.4 (d, C-6 or C-8), 44.2 (t, C-13), 42.8 (d, C-6 or C-8), 41.9 (d, C-12), 37.6 (d, C-4), 23.8 (t, C-2), 22.0 (t, C-16), 16.0 (q, C-1), 15.9 (q, CH$_3$C-14), 14.8 (q, C-17), 13.9 (q, CH$_3$C-6 or CH$_3$C-8), 13.3 (q, CH$_3$C-6 or CH$_3$C-8), 12.4 (q, CH$_3$C-10), 10.9 (q, CH$_3$C-12), 9.4 (q, CH$_3$C-4), 7.9 (q ×3, (CH$_3$C)Si), 7.8 (q ×3, (CH$_3$C)Si), 6.4 (t ×6, (CH$_2$)Si).

LRMS (EI), *m/z* (relative intensity): 734 ([M−29]$^+$, 1), 201 (12), 271 (12), 115 (26).

HRMS *m/z* calcd. for C$_{44}$H$_{82}$O$_6$Si$_2$: 762.5650 (733.5259 for M−C$_2$H$_5$); found: 733.5259.
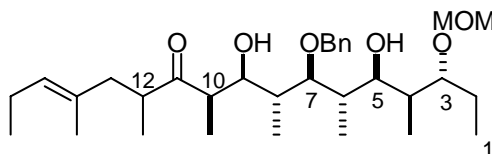
350

(8*R*,9*S*,10*R*,11*S*,12*S*,13*S*,14*S*,15*R*,*E*)-11-(Benzyloxy)-9,13-dihydroxy-15-(methoxymethoxy)-4,6,8,10,12,14-hexamethylheptadec-3-en-7-one

10% vol aqueous HF (0.01 mL) was added dropwise to a stirred solution of **349** (22 mg, 0.030 mmol; dr 4.6:1) in acetonitrile (10 mL) at 0 °C. After 30 min, the reaction was diluted with sat. aqueous NaHCO$_3$ and extracted with ethyl acetate (3×). The combined

organic extracts were dried over Na_2SO_4, concentrated and fractionated by PTLC (50% ethyl acetate in hexane) to give the titled diols **350** (14 mg, 93%; dr 4.6:1).

IR (DRIFT) ν_{max}: 3496, 2981, 2868, 1701, 1450, 1307, 954 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ (for major diastereomer) 7.35-7.02 (5H, m, Ph), 5.19 (1H, dd, J = 7, 7 Hz, HC-15), 4.60 (1H, ap d, J = 6.5 Hz), 4.56 (1H, ap d, J = 6.5 Hz), 4.52-4.43 (2H, m), 4.23-4.11 (2H, m), 4.03 (1H, dd, J = 5, 5 Hz), 3.92 (1H, d, J = 1.5 Hz), 3.83 (1H, d, J = 1.5 Hz), 3.66 (1H, q, J = 5.5 Hz), 3.19 (3H, s, H_3CO), 2.87 (1H, q, J = 7 Hz), 2.66 (1H, dq, J = 3, 7 Hz), 2.49 (1H, dd, J = 6.5, 13.5 Hz), 2.31-2.19 (2H, m), 2.05-1.88 (3H, m), 1.85-1.60 (2H, m), 1.55 (1H, dq, J = 1.5, 7 Hz), 1.48 (3H, s, H_3CC-14), 1.15 (3H, d, J = 7 Hz), 1.01 (3H, d, J = 7 Hz), 0.98 (3H, d, J = 7 Hz), 0.96-0.87 (12H, m).

^{13}C NMR (125 MHz, C_6D_6): δ (for major diastereomer) 218.0 (s, C-11), 139.2 (s, Ph), 132.3 (s, C-14), 129.9 (d, C-15), 129.0 (d, Ph), 128.7 (d ×4, Ph), 97.4 (t, CH_2OC-3), 86.4 (d), 82.8 (d), 73.8 (t, CH_2O), 73.2 (d), 72.0 (d), 55.9 (q, CH_3O), 48.1 (d), 44.2 (t, C-13), 42.9 (d), 39.3 (d), 39.0 (d), 37.7 (d), 25.5 (t), 22.0 (t), 17.2 (q), 16.2 (q), 14.82 (q), 14.78 (q), 14.2 (q), 9.8 (q), 9.4 (q), 8.9 (q).

LRMS (EI), m/z (relative intensity): 534 ([M]$^+$, 13), 326 (58), 286 (1), 275 (100).

HRMS m/z calcd. for $C_{32}H_{54}O_6$: 534.3920; found: 534.3943.
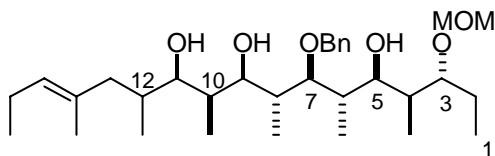
351

(3*R*,4*S*,5*S*,6*S*,7*R*,8*R*,9*R*,10*S*,11*R*,*E*)-7-(benzyloxy)-3-(methoxymethoxy)-4,6,8,10,12,14-hexamethylheptadec-14-ene-5,9,11-triol

Et$_2$BOMe (0.010 mL, 10 mg, 0.10 mmol) was added to a stirred solution of **350** (14 mg, 0.03 mmol; dr 4.6:1) in MeOH (1 mL) and THF (4 mL) at −78 °C under argon. After 30 min, NaBH$_4$ (11 g, 0.30 mmol) was added. After 2 h at −78°C, the reaction mixture was warmed to 0 °C for 30 min (caution: effervescence) and then diluted with 3 M aqueous NaOH (5 mL) and warmed to room temperature over 2 h. The mixture was diluted with brine and extracted with CH$_2$Cl$_2$ (3×). The combined organic layers were dried over Na$_2$SO$_4$, concentrated and fractionated by PTLC (50% ethyl acetate in hexanes) to give the titled triols **351** as a mixture of three diastereomers (13 mg, 93%; dr 6:1:1).

IR (DRIFT) ν_{max}: 3454, 2962, 1450, 1381, 1089, 969 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ (for major diastereomer) 7.39-6.95 (5H, m, Ph), 5.38-5.19 (1H, m, HC-15), 5.07-4.79 (1H, br s), 4.55-4.30 (4H, m), 4.11 (1H, d, *J* = 10 Hz), 3.95 (1H, dd, *J* = 3.5, 6 Hz), 3.90 (1H, br d, *J* = 9.5 Hz), 3.70 (1H, dd, *J* = 2.5, 7.5 Hz), 3.60 (1H, br s), 3.43-3.31 (1H, m), 3.06 (3H, s, H$_3$CO), 2.39-2.18 (2H, m), 2.15-1.90 (5H, m), 1.79 (1H, dd, *J* = 10, 13 Hz), 1.75-1.64 (2H, m), 1.58 (3H, s, H$_3$CC-14), 1.56-1.46 (2H,

m), 1.24 (3H, d, J = 6.5 Hz), 1.18 (3H, d, J = 7 Hz), 1.03-0.84 (12H, m), 0.78 (3H, t, J = 7.5 Hz).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ (for major diastereomer) 138.9 (s, Ph), 133.8 (s, C-14), 129.8 (d), 128.8 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.1 (d), 97.3 (t, CH$_2$OC-3), 87.3 (d), 84.1 (d), 81.7 (d), 80.3 (d), 74.0 (t, CH$_2$OC-7), 71.3 (d), 55.9 (q, CH$_3$OCH$_2$OC-3), 44.9 (t, C-13), 39.9 (d), 39.1 (d), 37.2 (d), 36.2 (d), 34.5 (d), 25.7 (t), 21.9 (t), 16.4 (q), 16.1 (q), 15.9 (q), 15.0 (q), 13.3 (q), 10.2 (q), 9.8 (q), 5.9 (q).

LRMS (EI), m/z (relative intensity): 536 ([M]$^+$, 2), 414 (1), 241 (6), 91 (100).

HRMS m/z calcd. for C$_{32}$H$_{56}$O$_6$: 536.4077; found: 536.4074.
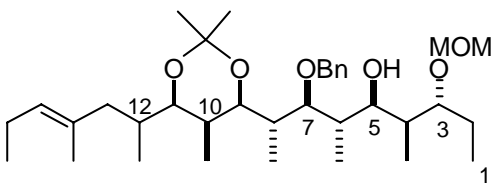
352

(2S,3S,4S,5S,6S,7R)-3-(Benzyloxy)-7-(methoxymethoxy)-4,6-dimethyl-2-((4S,5S,6R)-2,2,5-trimethyl-6-((E)-4-methylhept-4-en-2-yl)-1,3-dioxan-4-yl)nonan-5-ol

PTSA (*ca.* 0.5 mg) was added to a stirred solution of triols **351** (13 mg, 0.024 mmol; dr 6:1:1) and 2,2-dimethoxypropane (0.2 mL) in CH$_2$Cl$_2$ (4 mL) at room temperature under Ar. After 10 min, the reaction quenched by addition of sat. aqueous NaHCO$_3$ (*ca.* 1 mL). The mixture was diluted with sat. aqueous NaHCO$_3$ and extracted

with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated and fractionated by PTLC (20% ethyl acetate in hexanes) to give the titled alcohols **352** (13 mg, 93%; dr 6:1:1).

IR (DRIFT) ν_{max}: 3504, 2963, 1454, 1200, 1040 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ (for major diastereomer) 7.40-6.98 (5H, m, Ph), 5.25 (1H, dd, J = 7, 7 Hz, HC-15), 4.89 (1H, d, J = 6.5 Hz, HCOC-3), 4.77 (1H, d, J = 6.5 Hz, HCOC-3), 4.55 (1H, d, J = 11 Hz, HCOC-7), 4.46 (1H, d, J = 11 Hz, HCOC-7), 4.20 (1H, ddd, J = 1.5, 1.5, 9.5 Hz, HC-5), 4.16 (1H, s, HOC-5), 3.96-3.89 (1H, m, HC-3), 3.87 (1H, dd, J = 2, 10 Hz, HC-9), 3.62 (1H, dd, J = 2, 7.5 Hz, HC-7), 3.32 (3H, s, H_3CO), 3.27 (1H, dd, J = 2, 9.5 Hz, HC-11), 2.42 (1H, ddd, J = 7, 7, 9 Hz, HC-6), 2.19 (1H, ddd, J = 2, 7, 9.5 Hz, HC-8), 2.12-1.80 (6H, m), 1.66-1.29 (5H, m), 1.54 (3H, s, H_3CCOC-9), 1.51 (3H, s, H_3CC-14), 1.32 (3H, s, H_3CCOC-9), 1.07-0.96 (4H, m), 1.04 (3H, d, J = 7 Hz), 1.02 (3H, d, J = 7 Hz, H_3CC-12), 0.99 (3H, d, J = 7 Hz), 0.93 (3H, d, J = 7 Hz, H_3CC-8), 0.85 (3H, d, J = 7 Hz, H_3CC-6).

^{13}C NMR (125 MHz, C_6D_6): δ (for major diastereomer) 139.1 (s, Ph), 133.0 (s, C-14), 129.24 (d, C-15), 129.23 (d, Ph), 129.1 (d, Ph), 128.7 (d, Ph), 128.6 (d, Ph), 128.4 (s, Ph), 99.3 (t, COC-9), 97.7 (d, CH_2OC-3), 89.0 (d, C-7), 81.3 (d, C-3), 79.5 (t, C-11), 74.85 (d, CH_2OC-7), 78.81 (d, C-9), 73.1 (q, C-5), 55.9 (t, CH_3OCH_2OC-3), 42.3 (t, C-13), 39.0 (d, C-6), 38.5 (d), 38.1 (d, C-8), 32.9 (d), 31.5 (q), 30.7 (t, CH_3COC-9), 25.3 (t, C-2), 22.0

(q, C-16), 20.0 (q, CH$_3$COC-9), 16.5 (q), 15.94 (q), 15.86 (q, CH$_3$C=C), 15.0 (q), 13.0 (q), 9.4 (q), 9.0 (q), 5.3 (q).

LRMS (EI), *m/z* (relative intensity): 561 ([M−15]$^+$, 1), 91 (100), 181 (20), 69 (26).

HRMS *m/z* calcd. for C$_{35}$H$_{60}$O$_6$: 576.4390 (561.4155 for M−CH$_3$); found: 561.4152.
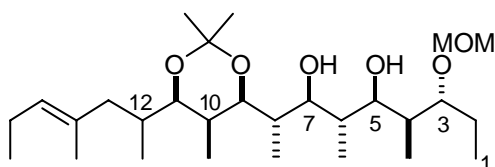
353

(2*S*,3*S*,4*S*,5*R*,6*S*,7*R*)-7-(Methoxymethoxy)-4,6-dimethyl-2-((4*S*,5*S*,6*S*)-2,2,5-trimethyl-6-((*R*,*E*)-4-methylhept-4-en-2-yl)-1,3-dioxan-4-yl)nonane-3,5-diol

Anhydrous NH$_3$ (*ca.* 5 mL) was condensed onto a solution of **352** (13 mg, 0.02 mmol; dr 6:1:1) in THF (5 mL) at −78 °C under Ar. Lithium (2-3 2 mm^3 pieces) were added over 5-10 min until a blue color persisted. After 30 min, methanol (*ca.* 0.5 mL) was added and the mixture was warmed to room temperature over 2 h and diluted with sat. aqueous NH$_4$Cl. The mixture was extracted with CH$_2$Cl$_2$ (3×), dried over Na$_2$SO$_4$, concentrated and fractionated by PTLC (20% ethyl acetate in hexane) to give a mixture of three diastereomeric diols **353** (10 mg, 91%; dr 6:1:1).

IR (DRIFT) ν_{max}: 3454, 2962, 1265, 1200, 1178, 1012 cm^{-1}.

¹H NMR (500 MHz, C₆D₆): δ (for major diastereomer) 5.24 (1H, dd, *J* = 7, 7 Hz, HC-15), 4.34-4.30 (1H, m), 4.32 (1H, d, *J* = 6.5 Hz), 4.27 (1H, d, *J* = 6.5 Hz), 4.19 (1H, d, *J* = 10 Hz), 4.14-3.90 (2H, br s), 3.79 (1H, dd, *J* = 3, 7.5 Hz), 3.36 (1H, br d, *J* = 6.5 Hz), 3.32 (1H, ddd, *J* = 6, 6, 6 Hz), 3.04 (3H, s, H₃CO), 2.44-2.34 (1H, m), 2.34-2.25 (1H, m), 2.15-1.96 (3H, m), 1.88 (1H, br s), 1.81 (1H, m), 1.66-1.22 (15H, m), 1.14 (3H, d, *J* = 7 Hz), 1.07 (3H, d, *J* = 6.5 Hz), 1.05-1.01 (6H, m), 0.98 (2H, t, *J* = 7.5 Hz), 0.95 (3H, d, *J* = 6.5 Hz), 0.75 (2H, t, *J* = 7.5 Hz).

¹³C NMR (125 MHz, C₆D₆): δ (for major diastereomer) 133.1 (s, C-14), 129.1 (d, C-15), 99.0 (s, COC-9), 97.4 (t, CH₂OC-3), 84.8 (d), 83.3 (d), 79.8 (d), 76.0 (d), 753.6 (d), 56.0 (q, CH₃OCH₂OC-3), 42.3 (t, C-13), 39.6 (d), 37.6 (d), 37.5 (d), 33.0 (d), 31.7 (d), 30.8 (q, CH₃COC-9), 25.9 (t, C-2), 22.0 (t, C-16), 20.3 (q, CH₃COC-9), 16.5 (q), 15.9 (q), 15.1 (q), 15.0 (q), 14.8 (q), 10.9 (q), 10.0 (q), 5.6 (q).

LRMS (EI), *m/z* (relative intensity): 486 ([M]⁺, 1), 341 (2), 239 (11), 69 (100).

HRMS *m/z* calcd. for C₂₈H₅₄O₆: 486.3920; found: 486.3960.
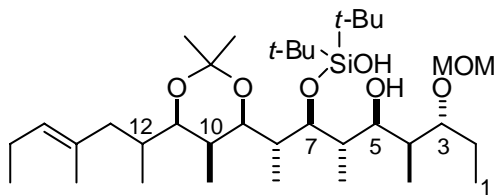
354

(5*R*,6*S*,7*S*,8*S*,9*S*)-11-*tert*-Butyl-5-ethyl-6,8,12,12-tetramethyl-9-((1*R*)-1-((4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-((*E*)-4-methylhept-4-en-2-yl)-1,3-dioxan-4-yl)ethyl)-2,4,10-trioxa-11-silatridecane-5,11-diol

2,6-Lutidine (0.02 mL, 18 mg, 0.17 mmol) was added to a stirred solution of diols **353** (10 mg, 0.02 mmol; dr 6:1:1) in CH_2Cl_2 (2 mL) at rt under Ar. After 2 min, *t*-Bu$_2$(OTf)$_2$ (0.020 mL, 27 mg, 0.060 mmol) was added and the reaction was stirred vigorously for 7 h. Methanol (0.2 mL) was added and the mixture was diluted with ethyl acetate and washed with 1% w/v aqueous citric acid (3×). The combined organic layers were washed with sat. aqueous NaHCO$_3$, dried over Na$_2$SO$_4$, concentrated and fractionated by PTLC (20% ethyl acetate in hexane) to give **354** as a mixture of diastereomers (10 mg, 77%; dr 6:1:1).

IR (DRIFT) ν_{max}: 3492, 2964, 1470, 1352, 1180 cm^{-1}.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ (for major diastereomer) 5.25 (1H, dd, *J* = 7, 7 Hz, HC-15), 4.91 (1H, d, *J* = 6 Hz, HCOC-3), 4.79 (1H, d, *J* = 6 Hz, HCOC-3), 4.58 (1H, dd, *J* = 1.5, 7 Hz), 4.35 (1H, d, *J* = 9 Hz), 4.21 (1H, s), 4.10 (1H, s), 3.91 (1H, ddd, *J* = 4.5, 4.5, 8.5 Hz), 3.59 (1H, dd, *J* = 1.5, 11 Hz), 3.31 (3H, s, H$_3$CO), 3.18 (1H, dd, *J* = 1.5, 9.5 Hz), 2.46-2.35 (1H, m), 2.19-2.10 (1H, m), 2.07-1.89 (5H, m), 1.88-1.76 (1H, m), 1.69-1.59 (1H, m), 1.49 (3H, s, H$_3$CC-14), 1.48-1.37 (1H, m), 1.47 (3H, s, H$_3$CCOC-9), 1.27-1.18

(18H, m), 1.11 (3H, s), 1.09-1.03 (6H, m), 1.00 (3H, d, J = 6.5 Hz), 0.99-0.93 (9H, m),

0.88 (3H, d, J = 7 Hz).

^{13}**C NMR** (125 MHz, C$_6$D$_6$): δ (for major diastereomer) 132.9 (s, C-14), 129.4 (d, C-15),

99.7 (s, COC-9), 98.5 (t, CH$_2$O), 82.1 (d), 79.4 (d), 78.9 (d), 76.4 (d), 72.6 (d), 55.9 (q,

CH$_3$O), 43.9 (d), 42.3 (t, C-13), 38.3 (d), 38.2 (d), 32.8 (d), 31.5 (d), 30.4 (q, CH$_3$COC-

9), 28.5 (q ×3), 28.3 (q ×3), 25.7 (t, C-2), 22.1 (s), 22.0 (t, C-16), 20.8 (s), 20.1 (q,

CH$_3$COC-9), 16.6 (q), 16.0 (q), 15.8 (q, CH$_3$C-14), 15.0 (q), 9.7 (q), 9.5 (q), 9.0 (q), 4.9

(q).

LRMS (EI), m/z (relative intensity): 629 ([M−15]$^+$, 1), 479 (10), 181 (69), 95 (37), 69

(100).

HRMS m/z calcd. for C$_{36}$H$_{72}$O$_7$Si: 644.5047 (629.4813 for M−CH$_3$); found: 629.4186.
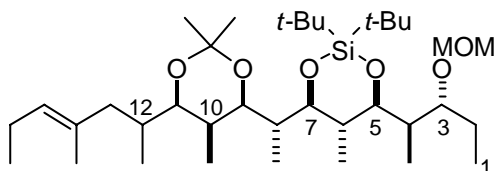
355

**(4S,5S,6R)-2,2-Di-*tert*-butyl-4-((2R,3R)-3-(methoxymethoxy)pentan-2-yl)-5-methyl-
6-((1R)-1-((4R,5S,6R)-2,2,5-trimethyl-6-((E)-4-methylhept-4-en-2-yl)-1,3-dioxan-4-
yl)ethyl)-1,3,2-dioxasilinane**

TFA (0.5 mL) was added dropwise to a stirred solution of diols **354** (21 mg, 0.03

mmol; dr 6:1:1) in THF (0.5 mL) and water (0.5 mL) at rt. After 15 min, ethyl acetate

was added and the reaction was washed with sat. aqueous NaHCO$_3$ (3×), brine, dried

over Na_2SO_4, concentrated, and fractionated by PTLC (10% ether in hexane) to give **355** as a mixture of diastereomers (15 mg, 75%; dr 6:1:1).

IR (DRIFT) ν_{max}: 2964, 1468, 1200, 1101, 923 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ (for major diastereomer) 5.21 (1H, dd, J = 6.5, 6.5 Hz, HC-15), 4.92 (1H, d, J = 6.5 Hz, HCOC-3), 4.77 (1H, d, J = 6.5 Hz, HCOC-3), 4.23 (1H, dd, J = 1.5, 4.5 Hz, HC-5 or HC-9), 4.21 (1H, dd, J = 1.5, 4.5 Hz, HC-5 or HC-9), 3.90 (1H, dd, J = 1.5, 9.5 Hz, HC-7), 3.82 (1H, ddd, J = 4.5, 4.5, 8.5 Hz, HC-3), 3.41 (1H, dd, J = 1.5, 9.5 Hz, HC-11), 3.30 (3H, s, H_3CO), 2.39-2.26 (1H, m, HC-6), 2.18-1.95 (6H, m), 1.94-1.82 (1H, m, HC-12), 1.66-1.53 (1H, m, HC-2), 1.53-1.45 (1H, m, HC-10), 1.50 (6H, s ×2, H_3CCOC-9, H_3CC-14), 1.49 (3H, s, H_3CCOC-9), 1.35 (1H, dd, J = 1.5, 12 Hz, HC-13), 1.20 (9H, s ×3), 1.19 (9H, s ×3), 1.07 (3H, t, J = 7.5 Hz, H_3C-1), 1.03 (3H, d, J = 6.5 Hz, H_3CC-12), 1.02-0.98 (6H, m), 0.99-0.95 (6H, m), 0.90 (3H, d, J = 6.5 Hz, H_3CC-6).

^{13}C NMR (125 MHz, C_6D_6): δ (for major diastereomer) 133.0 (s, C=CH), 129.2 (d, CH=C), 99.8 (s, COC-9), 98.5 (t, CH_2O), 85.0 (d, C-7), 82.2 (d, C-3), 81.1 (d, C-5 or C-9), 79.7 (d, C-11), 73.2 (d, C-5 or C-9), 55.8 (q, CH_3O), 42.2 (t, C-13), 40.1 (d, C-6), 38.7 (d), 37.6 (d), 32.9 (d, C-12), 31.8 (d), 30.8 (q, CH_3COC-9), 28.6 (q ×3, CH_3CSi), 28.5 (q ×3, CH_3CSi), 25.4 (t, C-2), 23.9 (s, CSi), 22.0 (t, C-16), 21.1 (q, CH_3COC-9), 20.9 (s, CSi), 16.5 (q), 15.9 (d), 15.2 (q), 15.0 (q), 13.3 (q, CH_3C-6), 9.3 (q), 8.6 (q, CH_3C-1), 5.5 (q, CH_3C-12).

HRMS *m/z* calcd. for $C_{36}H_{70}O_6Si$: 626.4942 (627.5020 for M+H); found: 627.5027 (CI, NH$_3$).
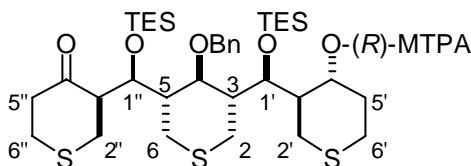
360

(*R*)-((3*R*,4*R*)-3-((*S*)-((3*R*,4*S*,5*S*)-4-(Benzyloxy)-5-((*S*)-((*R*)-4-oxotetrahydro-2*H*-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2*H*-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2*H*-thiopyran-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

Oxalyl chloride (0.015 mL, 22 mg, 0.17 mmol) was added to a solution of (*R*)-(+)-MTPA (8 mg, 0.03 mmol) and DMF (0.003 mL, 3 mg, 0.04 mmol) in hexane (1 mL) at room temperature. A white precipitate formed immediately.   After 1 h the mixture was filtered and concentrated. A solution of ketol **323** (3 mg, 0.004 mmol), Et$_3$N (0.010 mL, 7 mg, 0.07 mL) and DMAP (*ca.* 1 mg) in CH$_2$Cl$_2$ (1 mL) was added to the residue. After 1 h, excess reagent was quenched with methanol (0.5 mL) and the mixture was diluted with ethyl acetate and washed sequentially with 1% w/v aqueous citric acid (3×), sat. aqueous NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated to give crude Mosher's ester which was a 11:1 mixture of diastereomers by ^{1}H NMR. Fractionation on the crude by PTLC (15% ether in hexane) gave a mixture of Mosher's esters **360** (4 mg, >95%) which was a 11:1 mixture of diastereomers by ^{1}H NMR.

¹H NMR (500 MHz, C₆D₆): δ (for major diastereomer) 7.65 (10H, m, Ph), 5.45 (1H, br s), 5.06-4.91 (2H, m), 4.79 (1H, d, *J* = 10.5 Hz), 4.41 (1H, d, *J* = 8 Hz), 3.75 (1H, dd, *J* = 9.5, 9.5 Hz, HC-4), 3.27 (3H, s, H₃CO), 3.02 (1H, dd, *J* = 3, 14 Hz), 2.96 (1H, br d, *J* = 12.5 Hz), 2.94-2.25 (14H, m), 2.36-2.26 (1H, m), 1.79 (1H, br d, *J* = 13 Hz), 1.72-1.62 (1H, m), 1.61-1.52 (1H, m), 1.08-0.93 (18H, m, (H₃CC)₃Si ×2), 0.83-0.58 (12H, m, (H₂C)₃Si ×2).
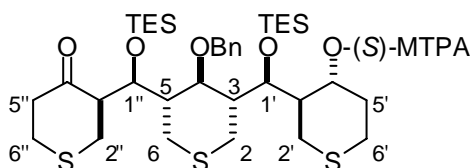
361

(*S*)-((3*R*,4*R*)-3-((*S*)-((3*R*,4*S*,5*S*)-4-(Benzyloxy)-5-((*S*)-((*R*)-4-oxotetrahydro-2*H*-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2*H*-thiopyran-3-yl)(triethylsilyloxy)methyl)tetrahydro-2*H*-thiopyran-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

Oxalyl chloride (0.015 mL, 22 mg, 0.17 mmol) was added to a solution of (*R*)-(+)-MTPA (8 mg, 0.03 mmol) and DMF (0.003 mL, 3 mg, 0.04 mmol) in hexane (1 mL) at room temperature. A white precipitate formed immediately. After 1 h the mixture was filtered and concentrated. A solution of ketol **323** (4 mg, 0.006 mmol), Et₃N (0.010 mL, 7 mg, 0.07 mL) and DMAP (*ca.* 1 mg) in CH₂Cl₂ (1 mL) was added to the residue. After 1 h, excess reagent was quenched with methanol (0.5 mL) and the mixture was diluted with ethyl acetate and washed sequentially with 1% w/v aqueous citric acid (3×), sat. aqueous NaHCO₃ and brine, dried over Na₂SO₄, and concentrated to give crude Mosher's ester that was a 11:1 mixture of diastereomers by ¹H NMR. Fractionation on the crude

by PTLC (15% ether in hexane) gave a mixture of Mosher's esters **361** (4 mg, >95%) which was a 11:1 mixture of diastereomers by ^{1}H NMR.

^{1}H NMR (500 MHz, C_6D_6): (for major diastereomer) δ 7.71-6.96 (10H, m, Ph), 5.35 (1H, br s), 5.07-4.93 (2H, m), 4.79 (1H, d, J = 10.5 Hz), 4.33 (1H, d, J = 7.5 Hz), 3.79 (1H, dd, J = 9.5, 9.5 Hz, HC-4), 3.32 (3H, s, H_3CO), 3.06-2.22 (17H, m), 1.98-1.80 (2H, m), 1.63 (1H, m), 1.07-0.92 (18H, m, $(H_3CC)_3Si \times 2$), 0.80-0.58 (12H, m, $(H_2C)_3Si \times 2$).

APPENDIX A

Determination of enantiomeric purity

230·HCl

A solution of NaOH in D_2O (1.1 M 0.05 mL, 0.055 mmol) was added to a solution

of **230**·HCl (6.5 mg, 0.025 mmol) and (+)-(*R*)-TFAE (55 mg, 0.20 mmol) in $CDCl_3$ (0.4

mL) in a 5 mm NMR tube. After shaking the sample, the ^{1}H NMR spectrum (500 MHz)

was obtained. To verify separation, the chemical shift of the minor enantiomer was

established by adding a solution of *ent*-**230**·HCl (ca. 2 mg) in $CDCl_3$ (ca 0.05 mL) to the

above NMR tube and then reacquiring the NMR spectrum (Figure A.1.).
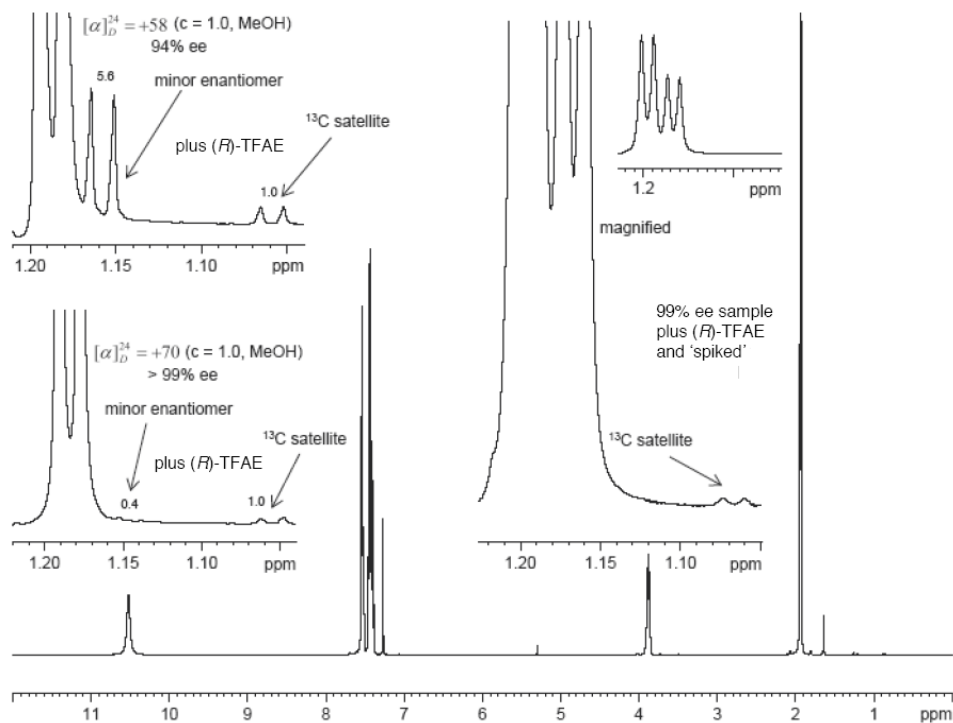
Figure A.1. Determination of enantiomeric purity of 230·HCl.

Mono-silyl enol ether (–)-261

A stock solution of (+)-Eu(hfc)₃ (0.1 M) and AgO₂CCF₃ (0.1 M) in CDCl₃ was prepared. The above solution of shift reagent (0.025 mL) was added to a solution of **261** (6 mg, 0.01 mmol) in CDCl₃ (0.4 mL) in a 5 mm NMR tube. After shaking the sample, the ¹H NMR spectrum (500 MHz) was obtained. To verify separation, the chemical shift of the minor enantiomer was established by adding a solution of *ent*-**261** (obtained by enolization of *meso* **233** using *ent*-**230**) (ca. 2 mg) in CDCl₃ (ca. 0.05 μL) to the above NMR tube and then reacquiring the NMR spectrum (Figure A.2.).
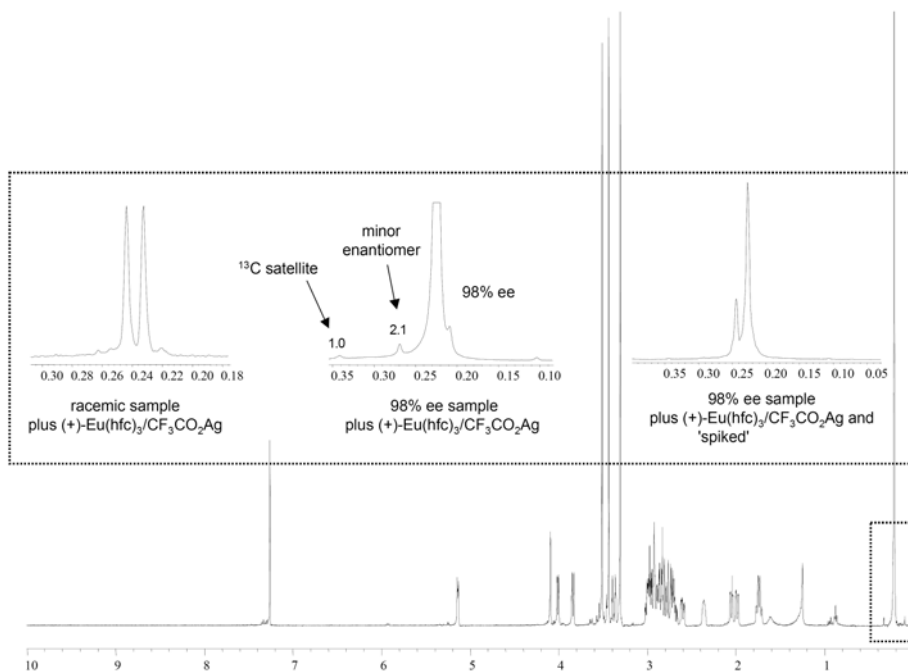
Figure A.2. Determination of enantiomeric purity of 261.

Mono-silyl enol ether (–)-315

Enantiomeric purity of mono-silyl enol ether **315** was determined by analysis of the ¹H NMR spectra of the diastereomeric Mosher's esters resulting from the reaction of ketol **323** and (*R*)-MTPCl and (*S*)-MTPCl. Both Mosher's esters **360** and **361**, respectively, were prepared to verify peak identities (Figure A.3.).

194
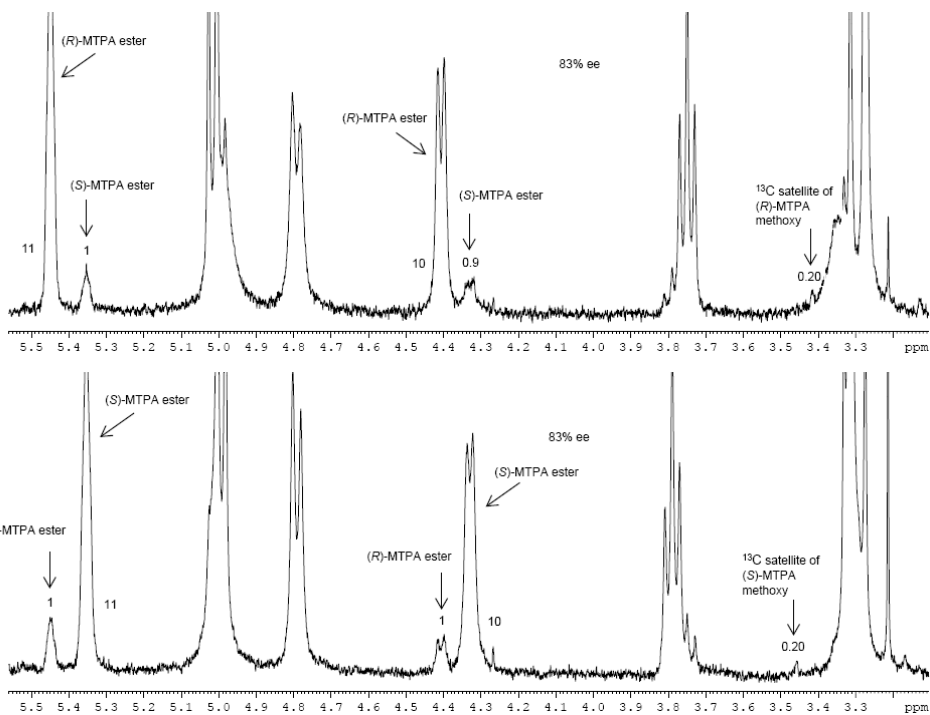
Figure A.3. Determination of enantiomeric purity of 315 (83% ee).
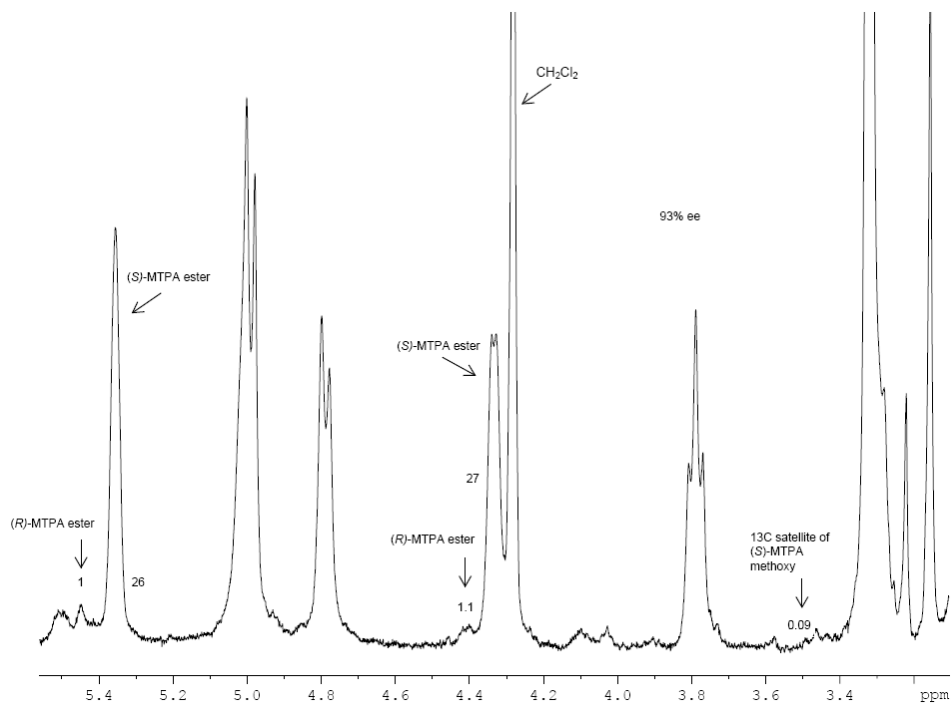
Figure A.4. Determination of enantiomeric purity of 315 (93% ee).

APPENDIX B

X-ray crystallographic data

ORTEP diagram of bis-silyl enol ether 262
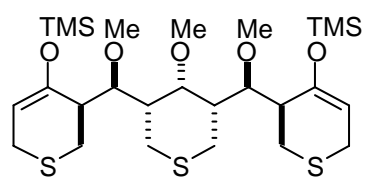
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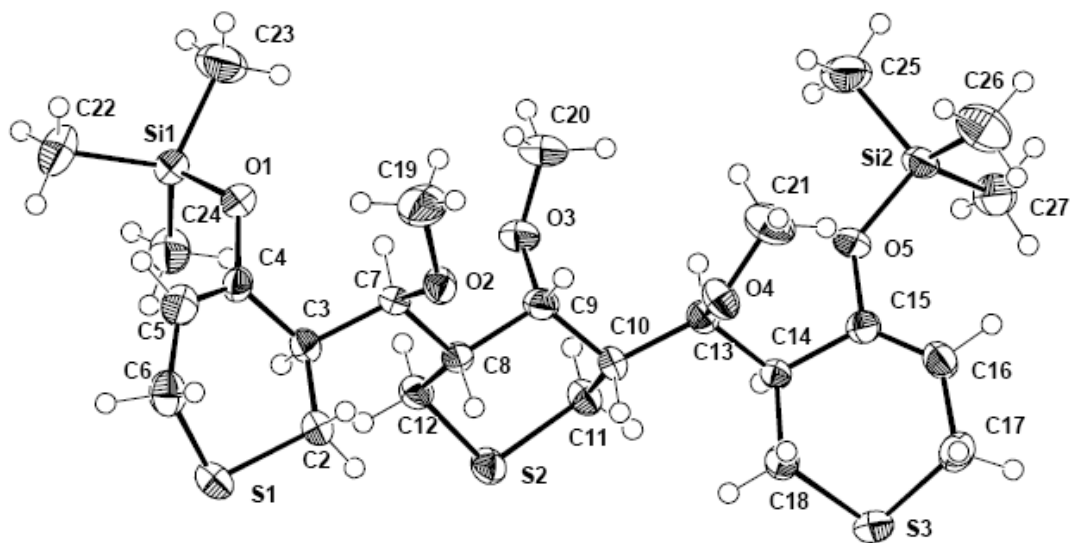
ORTEP diagram of *syn* triol 297
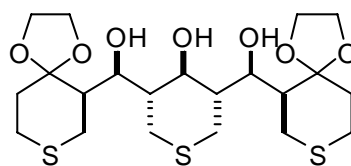
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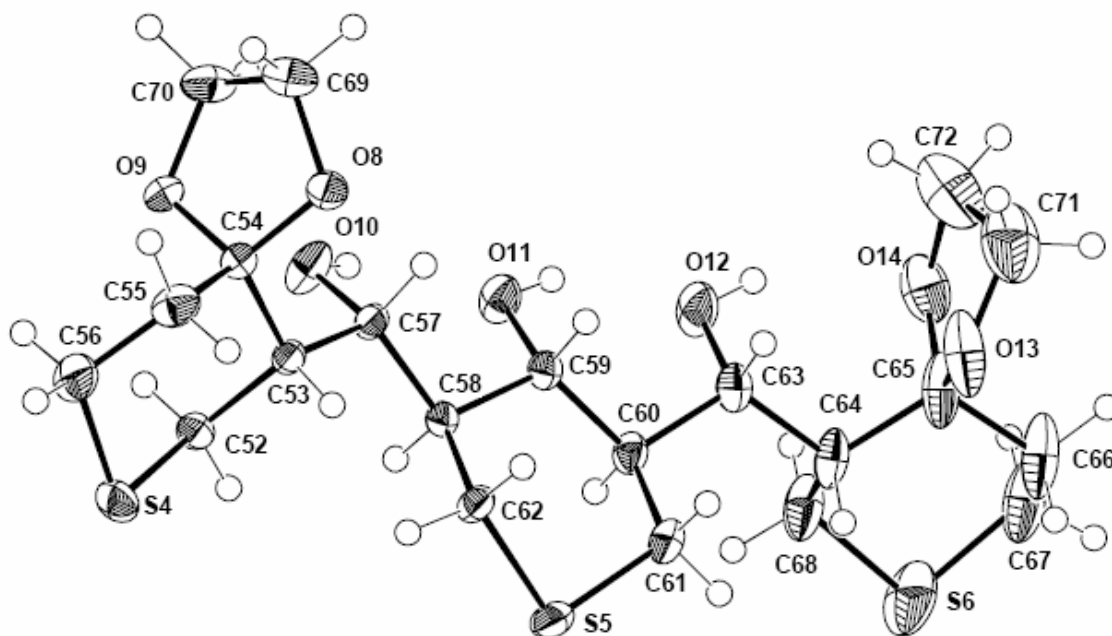
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PAPERS   Asymmetric Synthesis of Hexapropionate Synthons by
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                   Dale E. Ward, H. Martin Gillis, Olukayode T. Akinnusi, M. Abdul
                   Rasheed, K. Saravanan and Pradip K. Sasmal (*Org. Lett.* **2006**, 8,
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                   Simple and Efficient Procedures for the Preparation of Methyl
                   Tetrahydro-4-oxo-2*H*-thiopyran-3-carboxylate, Tetrahydro-4*H*-
                   thiopyran-4-one and 3,6-Dihydro-4-trimethylsilyloxy-2*H*-
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                   Thiopyran Route to Polypropionates: Exploiting and Overcoming
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                   H. Martin Gillis and Vishal Jheengut (*J. Org. Chem.* **2007**, *72,
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PRESENTATIONS   Asymmetric Synthesis of Hexapropionate Synthons by
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