

ON THE ORIGIN OF SIPHONARIID POLYPROPIONATES:
TOTAL SYNTHESIS OF CALOUNDRIN B
AND ITS ISOMERIZATION TO SIPHONARIN B

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By

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*With all my love to
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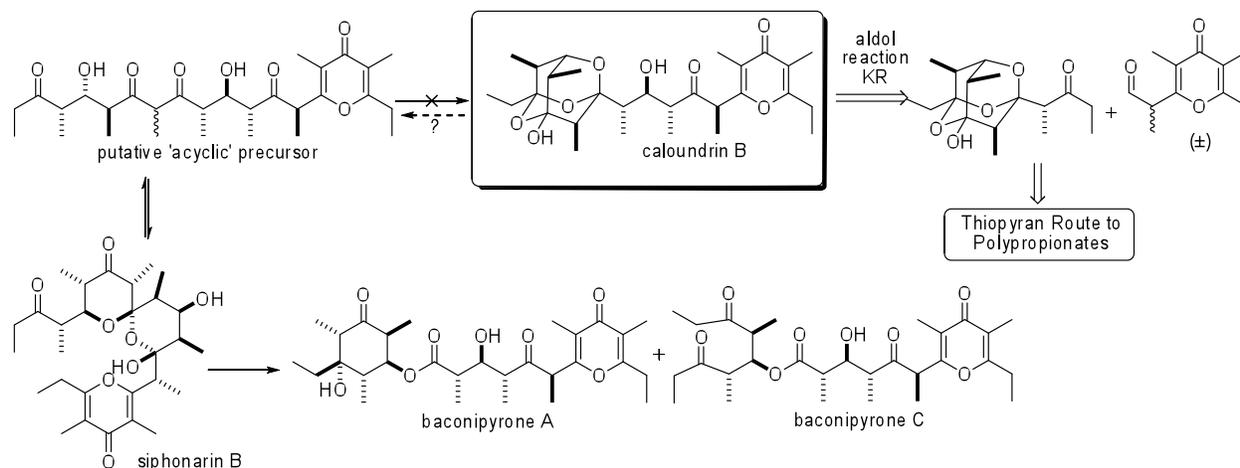
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ABSTRACT

It has been hypothesized that the polypropionates isolated from *Siphonaria zelandica*, siphonarins B, caloundrin B, baconipyrones A, and baconipyrones C, originate by non-enzymatic processes on a common 'acyclic' biosynthetic precursor. In previous work in the Ward group, the putative common precursor was synthesized and transformed into siphonarins B, baconipyrones A, and baconipyrones C. However, caloundrin B was not detected in these experiments and its origin remained as a missing piece of the puzzle. Thereafter, it was hypothesized that caloundrin B could be an unstable biosynthetic product from which the formation of the other polypropionates could be readily explained. To test that hypothesis, a new strategy to synthesize caloundrin B was proposed.



This thesis describes and analyzes the manner in which the first synthesis of *ent*-caloundrin B was achieved. The two key steps towards the target molecule involved the synthesis of the trioxadamantane motif and the assembly of the complete skeleton of *ent*-caloundrin B via a novel aldol coupling between the trioxadamantane-containing ketone and the γ -pyrone-containing aldehyde, that proceeds with kinetic resolution.

The studies toward the synthesis of caloundrin B allowed the development of new methodologies and the application of a recently disclosed protocol to design aldol reactions that proceed with kinetic resolution. During the course of those studies, a non-linear effect was identified and characterized.

After completion of the synthesis, *ent*-caloundrin B was isomerized to *ent*-siphonarin B under thermodynamic conditions, thus confirming the relative and absolute configuration of *ent*-caloundrin B. This transformation leads to the conclusion that caloundrin B is much less stable than siphonarin B; as a consequence, caloundrin B cannot be an artifact of isolation as previously proposed, but instead, it could be the biosynthetic product from which siphonarin B, baconipyronone A, and baconipyronone C are formed.

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LIST OF ABBREVIATIONS

α	observed optical rotation
$[\alpha]_D$	specific rotation (expressed without units; the actual units, (deg·mL)/(g·dm), are implied)
Ac	acetyl
AM1	Austin model 1
ap	apparent (spectral)
aq	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonyl
Bn	benzyl
BORSM	based on recovered starting material
bp	boiling point
br	broad (spectral)
^t Bu	<i>tert</i> -butyl
Bz	benzoyl
°C	degrees Celsius
calcd	calculated
CI	chemical ionization
CIF	crystallographic information file
cm	centimeter(s)
COSY	correlation spectroscopy

<i>c</i> -Hex	cyclohexyl
δ	chemical shift in parts per million
d	day(s); doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DEIPS	diethylisopropylsilyl
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DRIFT	diffuse reflectance infrared Fourier transform spectroscopy
ee	enantiomeric excess
EI	electron impact
<i>ent</i>	enantiomer of
<i>epi</i>	epimer of
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FCC	flash column chromatography

FTIR	Fourier transform infrared
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane, bis(trimethylsilyl)amide
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
IBX	2-iodoxybenzoic acid
IR	infrared
<i>J</i>	coupling constant (in NMR spectroscopy)
KR	kinetic resolution
LDA	lithium diisopropylamide
lit.	literature value (abbreviation used with period)
LRMS	low resolution mass spectrometry
M	molar (moles per litre)
M ⁺	parent molecular ion
m	multiplet (spectral)
Me	methyl
MHz	Megahertz
min	minute(s)
MKE	mutual kinetic enantioselection

mol	mole(s)
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
Ms	methanesulfonyl or mesyl
MW	molecular weight
m/z	mass-to-charge ratio
ν	wavenumber
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
ORTEP	oak ridge thermal ellipsoid plot
PCC	pyridinium chlorochromate
Pd/C	palladium on charcoal
PDC	pyridinium dichromate
Ph	phenyl
piv	pivaloyl
PMA	phosphomolybdic acid
PMB	<i>p</i> -methoxybenzyl or <i>p</i> -methoxyphenylmethyl
ppm	part(s) per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
^{<i>i</i>} Pr	<i>iso</i> -propyl
Pr	propyl

PTLC	preparative thin-layer chromatography
Py	pyridine
q	quartet (spectral)
quant	quantitative
R	alkyl substituent
<i>rac</i>	a prefix to denote racemic
Raney-Ni	Raney [®] -Nickel
R_f	retention factor (in chromatography)
rel	relative
rt	room temperature
s	singlet (spectral); second(s)
t	triplet (spectral)
TAS-F	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBDMS or TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography

TMS	trimethylsilyl
TOF	time-of-flight (in mass spectrometry)
Ts	tosyl (<i>para</i> -toluenesulfonyl [<i>p</i> -CH ₃ -C ₆ H ₄ -SO ₂])
v/v	volume per unit volume (volume-to-volume ratio)
wt	weight

1 INTRODUCTION

1.1 Polypropionates from *Siphonaria zelandica*

Marine polypropionates have been poorly studied and very little is known about their biological activity or role in the chemical ecology of the producing organisms.^{1, 2} The main difficulties are that only very small amounts of material are available by extraction of marine organisms (e.g., mollusks) and, in many cases, the isolated compounds are thought not to be genuine biosynthetic products but rather artifacts of isolation.

Marine pulmonates of the genus *Siphonaria*, also known as false limpets, are intertidal air-breathing mollusks that are a rich source of polypropionates.³ For example, the decapropionates siphonarins A (1) and B (2), baconipyrones A (4), B (5), C (6) and D (7) and caloundrin B (3), have been isolated from *Siphonaria zelandica* (Figure 1.1).⁴

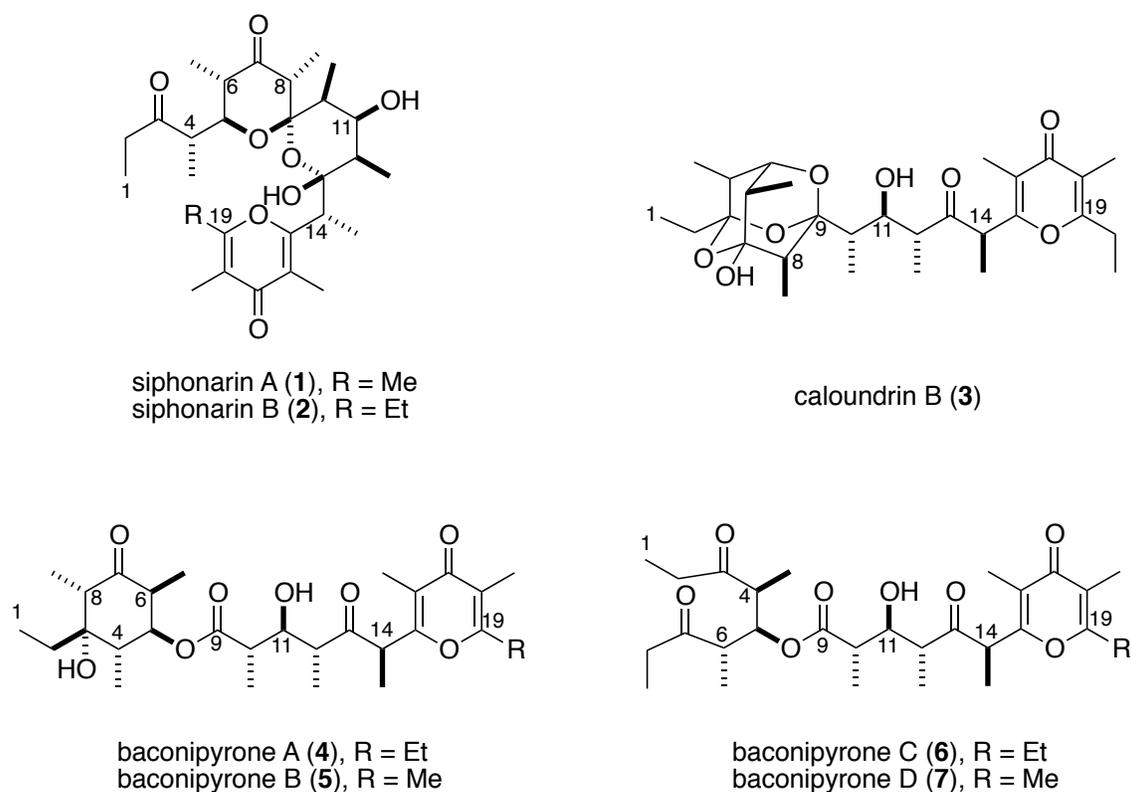


Figure 1.1 Siphonariid polypropionates isolated from *Siphonaria zelandica*.

1.1.1 Structure and isolation

In 1984, Faulkner et al. reported the isolation of siphonarin A (**1**) and siphonarin B (**2**) from *Siphonaria zelandica* collected in the intertidal zone along the coast of New South Wales, Australia, with a yield of ca. 0.05 mg of each siphonarin/animal.⁵ The structure and relative configuration of siphonarin A (**1**) was determined by spectroscopic and X-ray analysis. The homologue siphonarin B (**2**) has an ethyl rather than a methyl group at C-19 and was assigned the same relative configuration as in **1** by analogy. In 1994, Garson et al. determined the absolute configuration of **1** by X-ray analysis of its *p*-bromophenylboronate derivative.⁶ Contemporaneously, Paterson et al. were able to assign the absolute configuration of siphonarins **1** and **2** by enantioselective synthesis of the γ -pyrone acid **9**, a degradation product isolated with dihydrosiphonarin B (**8**) (Figure 1.2).⁷ Subsequently, the total syntheses of siphonarin B (**2**) by Paterson et al.⁸ and Beye and Ward,⁹ confirmed the absolute configuration of **1** and **2**.

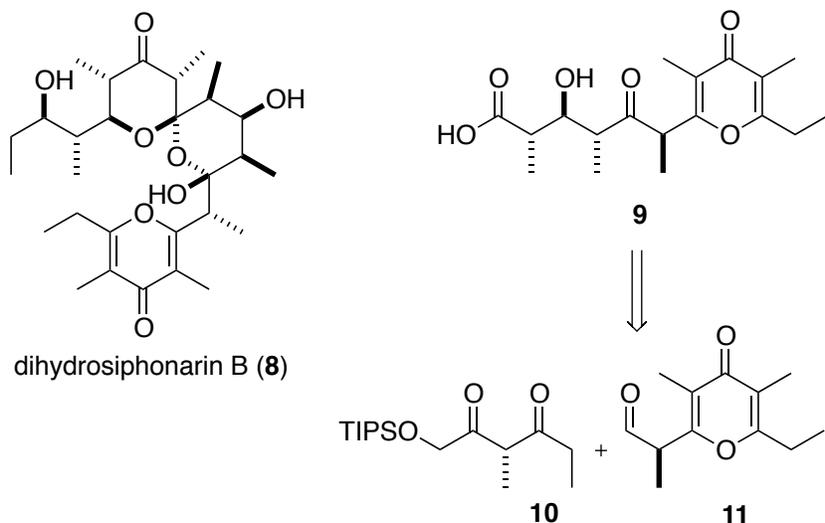
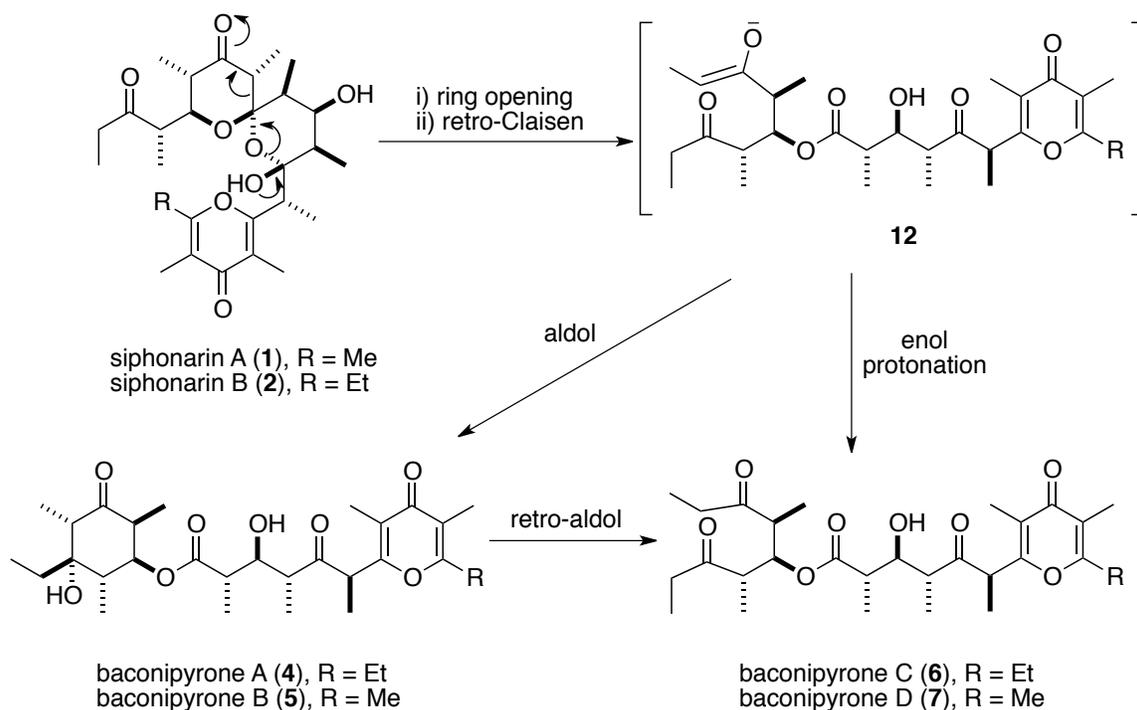


Figure 1.2 Assignment of the absolute configurations of **1** and **2** by synthesis of **9**.

The isolation of the baconipyrones **4-7** from specimens of *Siphonaria baconi** collected at the intertidal zone near Melbourne, Australia (Figure 1.1) was reported in 1989 by Faulkner et al.¹⁰ The amounts isolated for each compound were: **4**, 0.05 mg/animal; **5**, 0.046 mg/animal; **6**, 0.016 mg/animal; **7**, 0.046 mg/animal; and **1**, 0.008 mg/animal. The structure and relative configuration of baconipyrene B (**5**) was determined by X-ray analysis and showed that the configurations at C-4, C-6, C-10, C-11, C-12, and C-14 were identical to those of siphonarins A (**1**) (Figure 1.1). In contrast to **1**, **2**, and **3**, the baconipyrones do not contain a contiguous carbon skeleton of polypropionate units. Due to the stereochemical similarities between the siphonarins and baconipyrones, Faulkner et al.¹⁰ suggested that baconipyrones A (**4**) and B (**5**) are generated from siphonarins A (**1**) and B (**2**), respectively, via a retro-Claisen reaction (Scheme 1.1).

Scheme 1.1 Rationale for the transformation of siphonarins to baconipyrones.



* *Siphonaria baconi* is considered synonymous with *Siphonaria zelandica*

Thus, Faulkner et al.¹⁰ hypothesized that ring opening of siphonarins **1** or **2** followed by a retro-Claisen reaction would produce enolate **12** (Scheme 1.1). Subsequent protonation of **12** would produce baconipyrones C (**6**) or D (**7**), while a stereoselective intramolecular aldol reaction on **12** would afford baconipyrones A (**4**) or B (**5**). Additionally, **4** or **5** might produce **6** or **7**, respectively, via a retro-aldol reaction. Based on the proposed mechanistic rationale, the authors suggested that the relative configuration at the stereogenic centres in baconipyrones C (**6**) and D (**7**) are identical to those in baconipyrones A (**4**) and B (**5**).

After a careful extraction from *S. baconi*, Garson et al. did not observe the presence of any baconipyrones (**4-7**). This observation suggested that the baconipyrones could be artifacts formed during metabolites extraction and isolation.¹¹

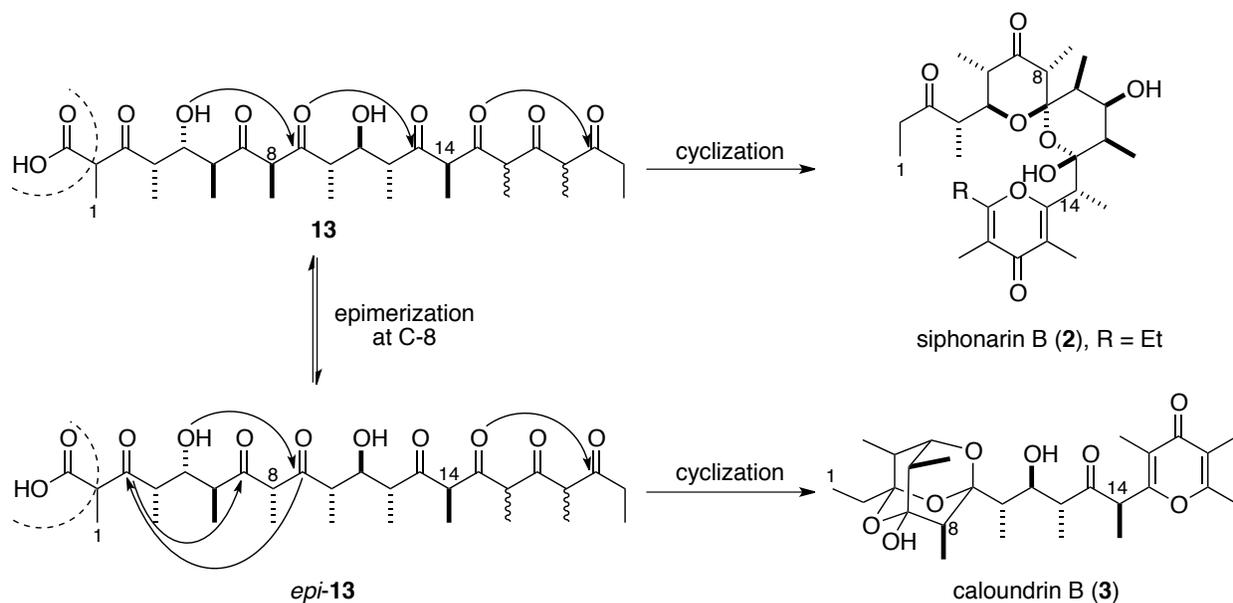
In 2000, Paterson et al. achieved the total synthesis of baconipyrene C (**6**) demonstrating that its absolute configuration corresponded with the independently reported siphonarins **1** and **2**.¹² The synthesis of **6** also corroborate previous studies where the absolute configuration of siphonarins **1** and **2** and baconipyrones **4-7** was confirmed through the synthesis of the γ -pyrone acid **9** (Figure 1.2).⁷ Baconipyrene C (**6**) has also been synthesized by Gillingham and Hoveyda¹³ and Yadav and coworkers;¹⁴ more recently, Beye and Ward synthesized **4** and **6** from its putative acyclic precursor.⁹

In 1994, Garson and coworkers reported the isolation of caloundrin B (**3**) (1.6 mg) together with siphonarins A (**1**) and B (**2**) from 160 specimens of *S. zelandica* collected from rock platforms at Caloundra, Australia.¹⁵ The structure of caloundrin B (**3**) was deduced by spectroscopic methods providing strong evidence for the presence of a γ -pyrone and the trioxadamantane motif with the indicated relative configuration. The C-12 to C-21 fragment seemed to match with the same fragment present in baconipyrene C (**6**) (Figure 1.1). However,

the relative configuration along the chain (C-10 to C-14) and the overall absolute configuration of caloundrin B (**3**) were assigned based on the presumed relationship with the co-metabolite siphonarins B (**2**). These isomers were hypothesized to originate from a common intermediate (Scheme 1.2).

Apparently, the trioxadamantane moiety in caloundrin B (**3**) was not stable and the isolated sample decomposed during the studies. Attempts to re-isolate **3** or isomerize siphonarins B (**2**) under acidic conditions to produce **3** were unsuccessful.¹⁵ To date, there have been no further reports of isolation of caloundrin B (**3**) nor has its total synthesis been disclosed. Therefore, the proposed relative and absolute configuration of **3** as well as the presumed link between **3**, siphonarins B (**2**) and baconipyrones A (**4**) and C (**6**) through a common acyclic precursor remain as hypotheses.

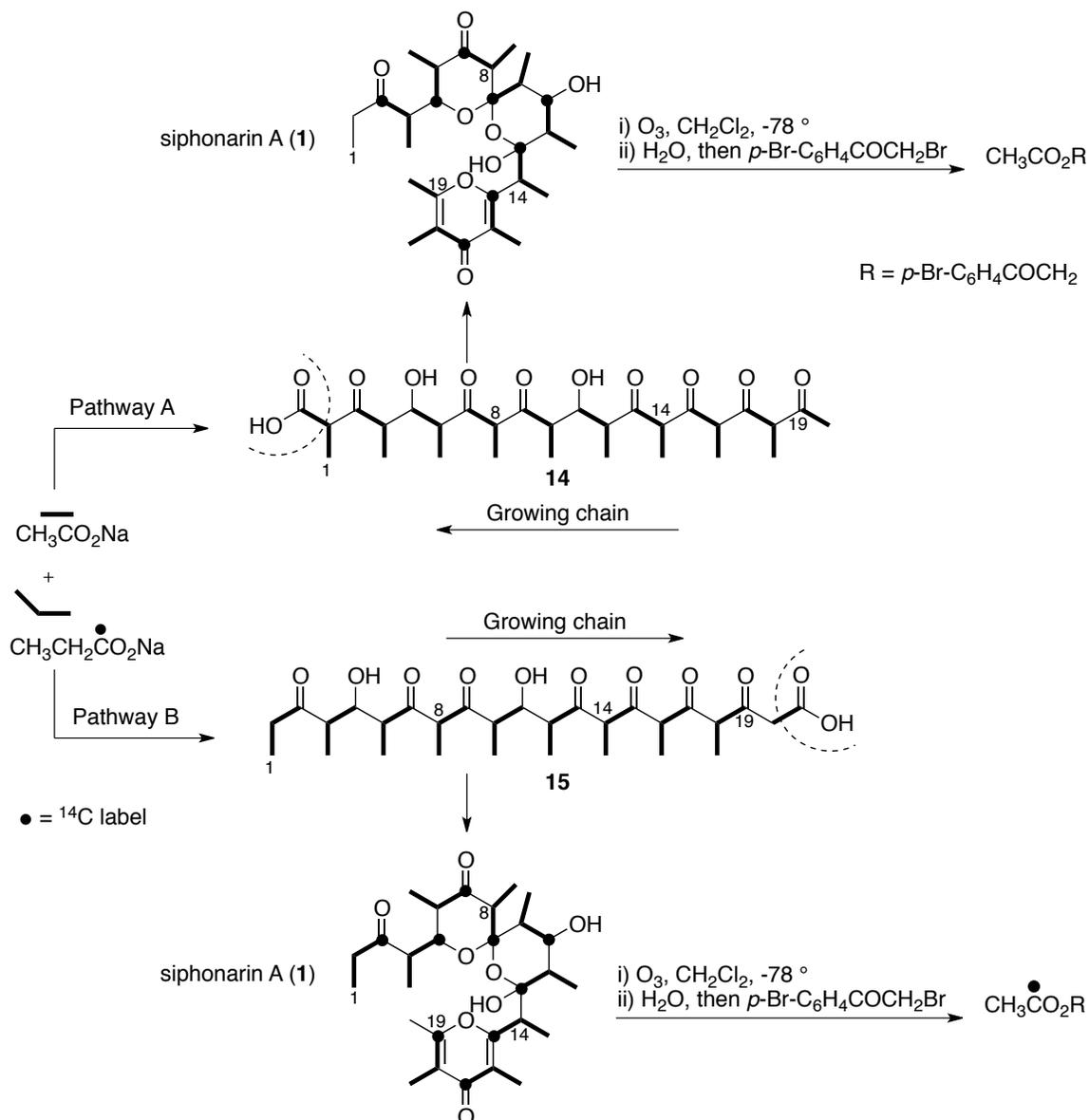
Scheme 1.2 Proposed cyclization pathways for the two epimers at C-8 of **13**.



1.1.2 Biosynthesis

In 1990, Manker, Garson, and Faulkner studied the biosynthesis of the siphonariids denticulatin A (**21**) and denticulatin B (10 *epi*-**21**) isolated from *Siphonaria denticulata* (Figure 1.3).¹⁶ The studies revealed that these metabolites arose from condensation of propionate-derived units similar to the biosynthesis of macrolide¹⁷ and polyether antibiotics.¹⁸ Some years later, Garson et al. studied the biosynthesis of siphonarins A (**1**) and B (**2**).⁶ Similar to the previous observations on denticulatin A (**21**), incorporation of ¹⁴C in **1** and **2** was observed after injection of [1-¹⁴C] propionate to the foot tissue of *Siphonaria zelandica*. Therefore, they suggested that **1** is formed from one acetate and nine propionate units, whereas **2** would come from ten propionate units. In order to determine the direction of the chain assembly in **1**, they studied the biosynthetic origin of C-19. After degradation of ¹⁴C-labeled **1** via ozonolysis and derivatization with *p*-Br(C₆H₄)COCH₂Br, they obtained unlabeled *p*-bromophenacyl acetate coming from C-19. This result is consistent with a chain assembly from C-19 to C-1, as described in pathway A (Scheme 1.3).⁶

Scheme 1.3 Biosynthetic studies on siphonarins A (1).



In addition to the biosynthetic studies, Garson et al. compared the relative configurations of the uncyclized tautomers of siphonarins **1** and **2**, muamvatin (**19**), and denticulatin A (**21**).¹⁹ This comparison revealed a common tetrapropionate unit among these polypropionates. Interestingly, this tetrapropionate unit also matched with the PAPA model proposed by Cane-

Clemer-Westley[†] for the biosynthesis of polyether antibiotics (Figure 1.3).¹⁸ Therefore, it was suggested that siphonariid polypropionates might share a common genetic origin with polyether antibiotics. There were also similarities between the siphonarins and the Celmer macrolide model.^{17, 20}

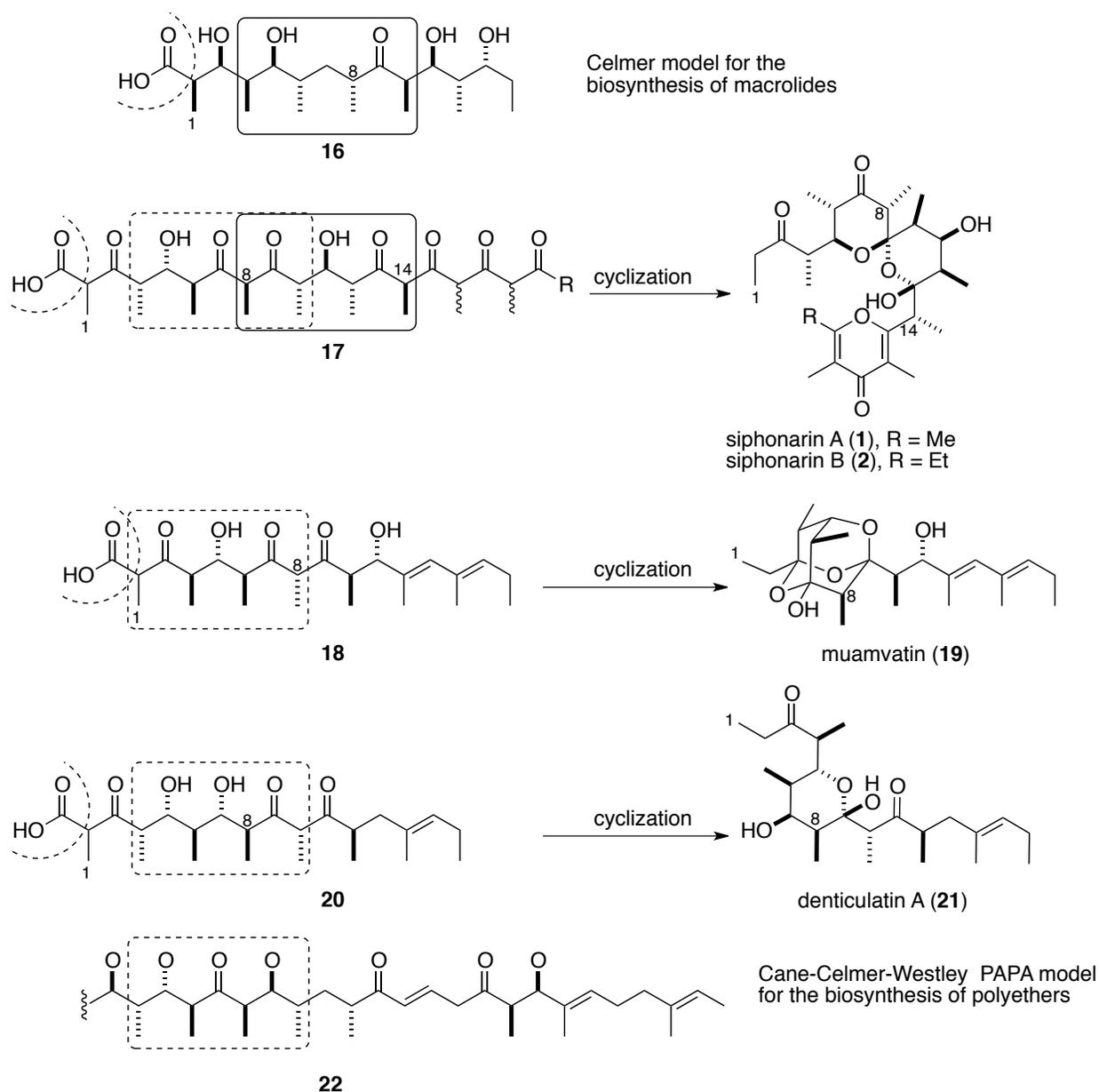


Figure 1.3 Stereochemical comparison of siphonariid polypropionates

[†] PAPA model (Propionate-Acetate-Propionate-Acetate units) is one of the empirical models used as a guide to assign the structure and stereochemistry of polyethers.

1.1.3 Hypothesis on the origin of siphonariid polypropionates

Based on the structural, stereochemical, and biosynthetic studies developed on the siphonariid polypropionates **1** and **2**, it was hypothesized that siphonarins B (**2**), caloundrin B (**3**), and baconipyrones A (**4**) and C (**6**) originated via non-enzymatic processes from a common 'acyclic' biosynthetic precursor (**23**).^{11, 15, 20} Considering that C-8 in **23** is stereochemically labile via keto-enol tautomerism, one epimer would produce siphonarins B (**2**) and the other would generate caloundrin B (**3**). In addition, the baconipyrones **4** and **6** could be artifacts of isolation coming from rearrangements on **2**.¹¹

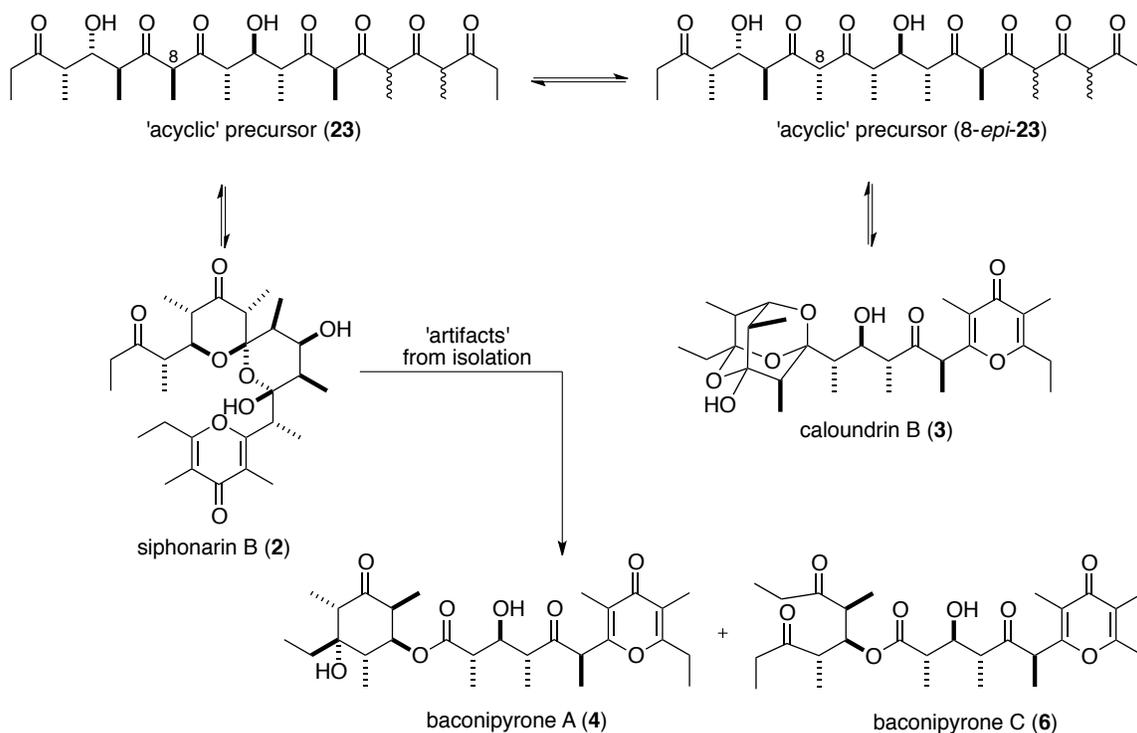


Figure 1.4 Hypothesis about the biosynthetic origin of siphonariid polypropionates

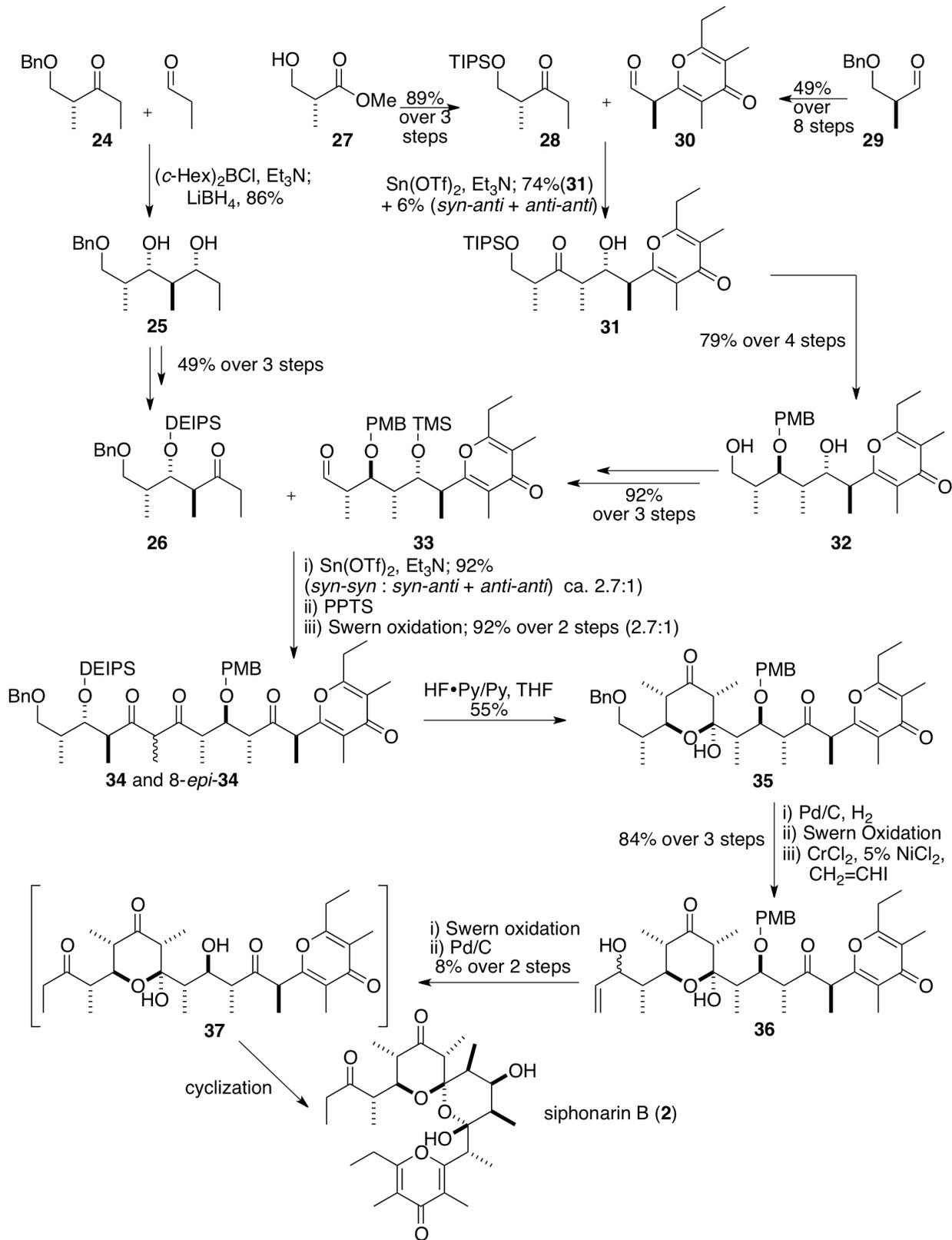
1.2 Total syntheses of siphonarins B

1.2.1 Paterson's synthesis

The approach for the synthesis of siphonarins B by Paterson et al. involved coupling of the two main fragments **26** and **33** via an aldol reaction producing a protected acyclic precursor **34**, which required the introduction of an ethyl group and functional group manipulations to generate siphonarins B (Scheme 1.4).⁸ The preparation of the keto fragment **26** started with the synthesis of ketone **24** ($\geq 97\%$ ee) from the (*R*)-Roche ester in 59% yield over 3 steps.²¹ A boron mediated aldol reaction of **24** with propionaldehyde followed by an in situ *syn* reduction provided diol **25** in 86% yield and $> 95:5$ dr.²² Diol **25** was bis-DEIPS protected, hydrolyzed at the least hindered position, and then oxidized to produce the DEIPS protected ketone **26** in 49% yield over 3 steps. The pyrone containing aldehyde fragment **33** was prepared from the (*S*)-Roche aldehyde 49% yield over 8 steps.^{7, 12} A Sn(II) mediated aldol reaction of **33** with the TIPS protected ketone **28** gave **31** in 59% yield. Functional group manipulations on **31** (i.e., Evans-Tishchenko reduction,²³ PMB protection, TIPS and acetyl removal) produced diol **32**.^{7, 12} Aldehyde **33** was obtained after bis-TMS protection of diol **32**, followed by selective deprotection of the primary alcohol, and oxidation.

Aldol coupling of **33** with **26** via its Sn(II) enolate produced a mixture of three aldol diastereomers in 92% yield. Removal of the TMS protecting group and Swern oxidation produced **34** and 8-*epi*-**34**, which after DEIPS deprotection, furnished hemiacetal **35**. Interestingly, when hemiacetal **35** was exposed to mildly acidic (i.e., SiO₂) or basic conditions, it underwent a retro-Claisen reaction producing a fragment similar to baconipyrones C (**6**). This observation strongly supported the hypothesis that the baconipyrones are rearranged products from siphonarins¹⁰ or artifacts from isolation as Ireland and Garson had proposed.^{11, 20}

Scheme 1.4 Paterson's synthesis of siphonarins B (2).



Careful removal of the Bn group on **35**, followed by oxidation and introduction of a vinyl group employing the Kishi-Nozaki conditions (CrCl_2 , 5% NiCl_2 , DMF)^{24, 25} provided compound **36**, which was then oxidized and hydrogenated to afford siphonarins B (**2**) in low yield. Interestingly, caloundrin B (**3**) was not observed as a product in the final cyclization process. Siphonarins B (**2**) was synthesized in 25 linear steps from the Roche aldehyde **29** in 0.8% overall yield.

1.2.2 Ward's synthesis

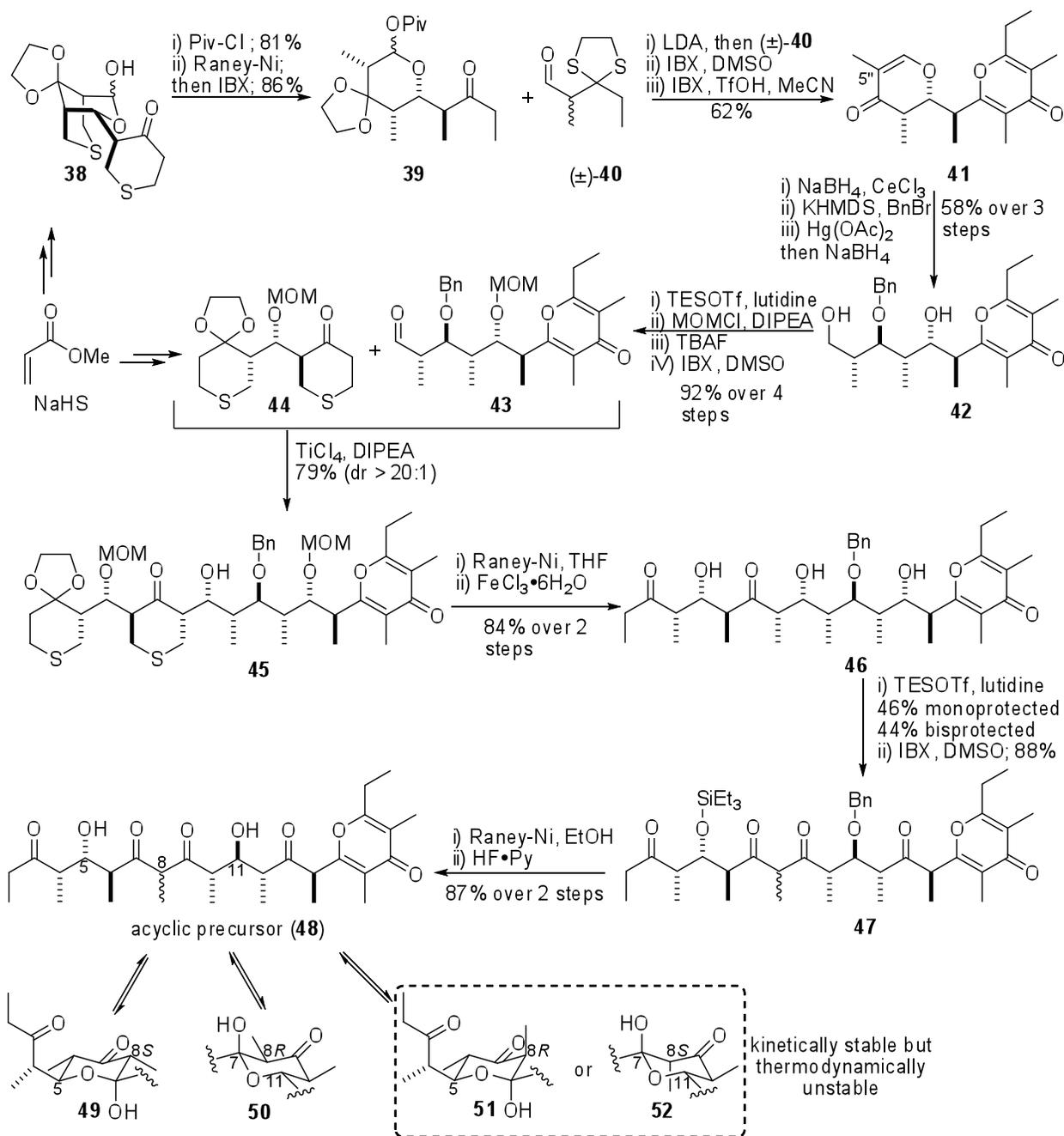
1.2.2.1 Synthesis of siphonarins B from the putative acyclic linear precursor

Ward et al. developed a strategy for the preparation of **48**, the putative acyclic precursor of the siphonariid polypropionates **1-5**.⁹ In contrast with Paterson's synthesis,⁸ this approach involved the construction of the complete carbon skeleton prior to cyclization. Because the formation of γ -pyrones from cyclization of β -triketides requires special conditions,²⁶⁻²⁸ it was considered unlikely that pyrone formation could occur during the isolation process. Therefore, the γ -pyrone motif was installed in the acyclic precursor. The synthesis of **48** allowed studying its cyclization under different conditions thereby directly testing the previous hypotheses about the origin of **2**, **3**, **4**, and **6**.

The synthesis of **48** commenced with the readily available starting materials **38** and **44** prepared via the thiopyran route to polypropionates extensively studied in the Ward group (Scheme 1.5).²⁹ The γ -pyrone was constructed by a sequence where **38** was protected and desulfurized followed by aldol reaction of the resulting ketone **39** with aldehyde **40**. The aldol adduct was oxidized to produce the desired γ -pyrone **41**; however, the reaction conditions also induced hydrolysis of the acetal and elimination of the pivaloate. To reinstall the required stereogenic centre at C-5'' in **41**, diastereoselective Luche reduction and *O*-benzyl protection of

the formed alcohol was followed by oxymercuration^{30, 31} producing diol **42**. Taking advantage of the resistance of the secondary alcohol in **42** to react with triethylsilyl triflate (TESOTf), the primary alcohol was selectively TES-protected, followed by MOM protection of the secondary alcohol. Subsequent removal of the silyl group and oxidation of the resulting alcohol produced the aldehyde **43** which then was coupled with the enantioenriched ketone **44** (>98% ee) via its Ti(IV) enolate to give adduct **45** in 79% yield and >20:1 dr. Simple functional group manipulations on **45** produced the desired acyclic precursor **48**, which existed as a complex mixture of keto-enol and ring-chain tautomers with the three hemiacetal forms **49**, **50**, and **51** or **52** predominating. The synthesis of **48** was achieved in 18 linear steps with an overall yield of 3.1%.

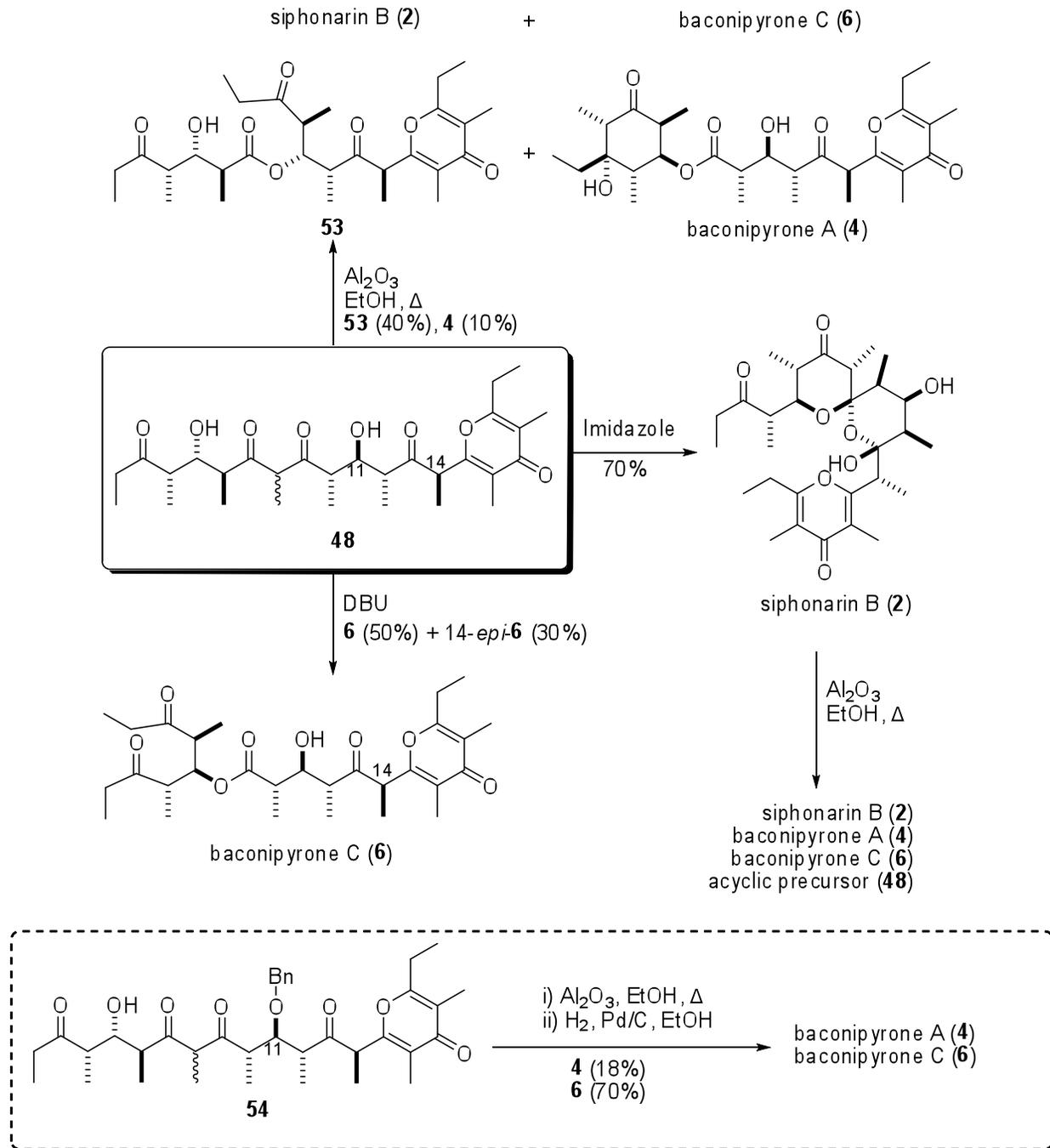
Scheme 1.5 Ward's synthesis of acyclic precursor **48**.



With the acyclic precursor **48** in hand, its isomerisation was studied under different conditions (Scheme 1.6). This was the first time that the thermodynamic equilibrium of siphonariid polypropionates could be studied starting from **48**. As noted above, **48** was a complex mixture of tautomers with three hemiacetal forms **49**, **50**, and **51** or **52** predominating. This mixture was essentially unchanged after 28 days in CDCl₃. However, treatment of **48** with imidazole in CDCl₃ for 24 h produced **2** in 70% isolated yield. Reaction of **48** with DBU in C₆D₆ solution for 1 h produced a mixture of baconipyronone C (**6**) (50%) and its C-14 epimer (30%). Treatment of **48** with neutral alumina in refluxing ethanol produced a 10:3:7:3 mixture of **53** (40% isolated), **4** (10% isolated), **6**, and **2**, respectively. The major product **53**, a structural isomer of baconipyronone C (**6**) arising from retro-Claisen fragmentation of hemiacetal **50** or **52**, had not been previously reported. Finally, treatment of **2** with neutral alumina in refluxing ethanol produced a 2.3:3:1:1 mixture of **2**, **6**, **4**, and **48**, respectively, but not **53**. It is noteworthy that both **4** and **6** were stable to these reaction conditions. Surprisingly, caloundrin B (**3**) was never detected in the isomerization experiments and its presence remained as a missing piece of the puzzle about the origin of all of those polypropionates.⁹

Preparation of compound **54**, where the OH group at C-11 was protected thereby limiting the options for cyclization, allowed the assessment of another isomerisation experiment. After exposure of compound **54** to neutral alumina in refluxing ethanol and then debenzoylation, baconipyrones **4** and **6** were produced in 18% and 70% yields, respectively.

Scheme 1.6 Isomerization of acyclic precursor **48**.



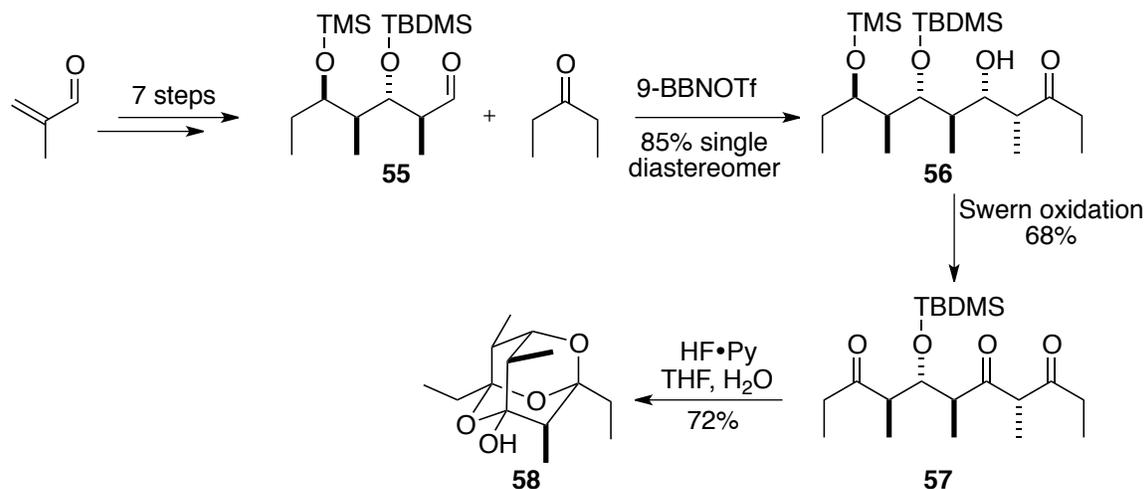
1.2.2.2 Revised hypothesis on the origin of siphonariid polypropionates

Very important conclusions emerged from the Ward and Beye syntheses of siphonarin B (**2**), baconipyronone A (**4**) and C (**6**) from the presumed acyclic precursor **48**.⁹ With the information provided by Ward⁹ and Garson¹¹ it was conclusive that the baconipyrones were likely artifacts from isolation coming from the hemiacetal forms of **48** or by ring-opening of siphonarin B (**2**). These observations supported the previously proposed hypothesis but also established new questions about the origin of those compounds. In this context, it was proposed that if baconipyrones **4** and **6** came from the acyclic precursor **48**; then, the hemiacetal forms **49** and **50**,[‡] compound **53** and 14-*epi*-**6** should be observed during the isolation process. Because none of these compounds had been isolated from *Siphonaria zelandica*, it was most likely that the baconipyrones **4** and **6** originate from **2**. Additionally, **2** could be the biosynthetic product. However, this hypothesis would not explain the origin of **3**.

Therefore, it was hypothesized that **3** could be less stable than **2** or that access to **3** involved a high energy barrier. Indeed, **3** could be the biosynthetic product from which the formation of **2**, **4**, and **6** could be explained. However, this revised hypothesis could only be tested if the synthesis of **3** could be achieved (Figure 1.5).

[‡] The hemiacetal forms **49** and **50** coming from the acyclic precursor **48** were stable to storage in CDCl₃ for 28 d and exposure to SiO₂.

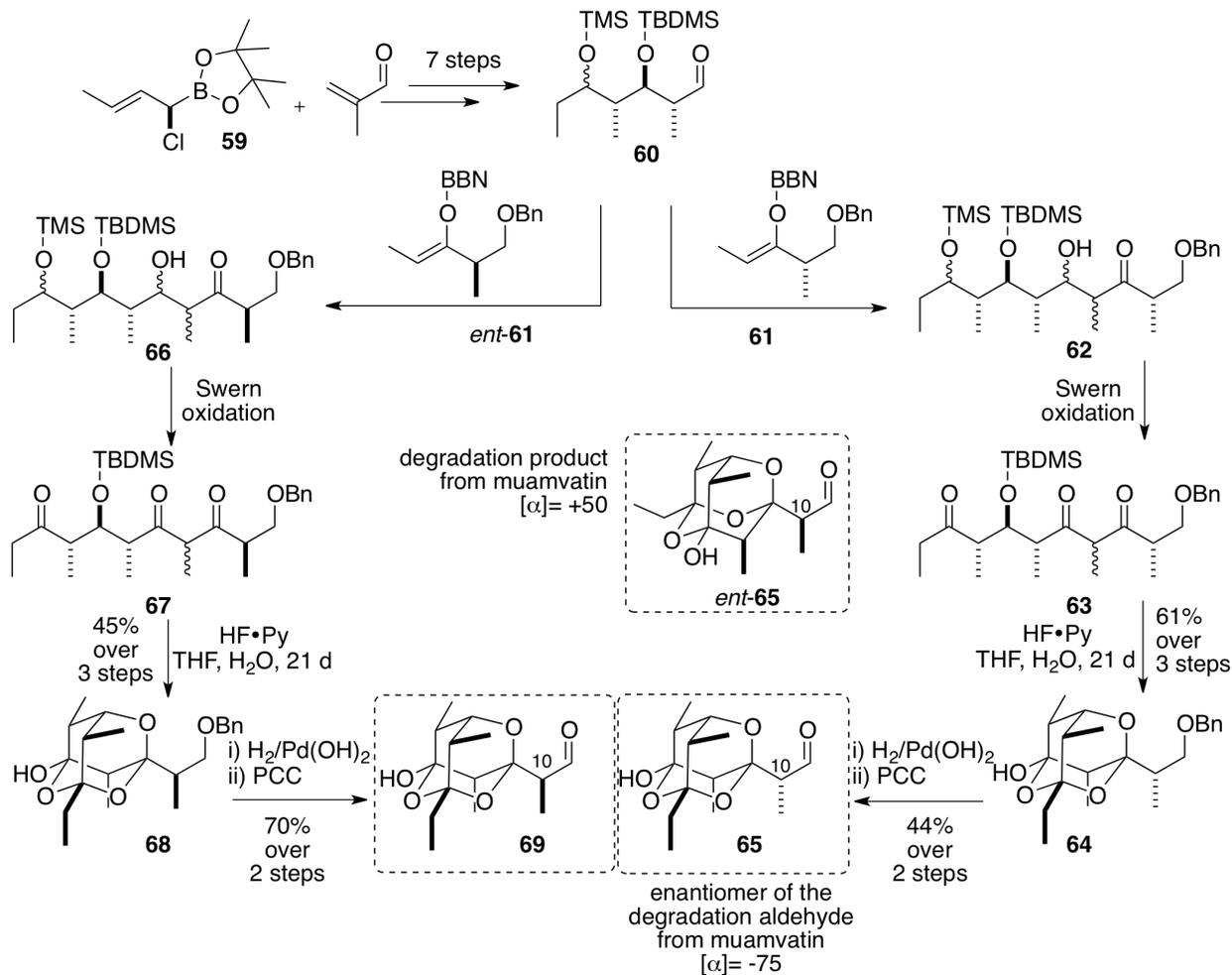
Scheme 1.7 Model studies to form the trioxaadamantane moiety of muamvatin (**19**).



In order to establish the absolute and relative configuration of muamvatin (**19**) at C-10, Hoffmann studied the synthesis of aldehydes **65** and **69** (Scheme 1.8).^{34, 35} One of the aldehydes was previously obtained from degradation of muamvatin (**19**) by Ireland.³²

Hoffmann's approach started from methacrolein and **59** to produce aldehyde **60** in 7 steps. Thereafter, aldol reactions of **60** with the (*Z*)-enol borinates of **61** or *ent*-**61** produced the aldol adducts **62** and **66**, respectively. After Swern oxidation and prolonged exposure to HF•pyridine and H₂O in THF, **62** and **66** were converted to **64** (60%) and **68** (45%), respectively. The aldehydes **65** and **69** were obtained from **64** and **68**, respectively, by *O*-debenzylation and subsequent oxidation. Aldehyde **65**, which possesses the (*S*)-configuration at C-10, has the same relative configuration as the trioxaadamantane fragment present in muamvatin (**19**).

Scheme 1.8 Formation of the trioxadamantane moiety of muamvatin (**19**).

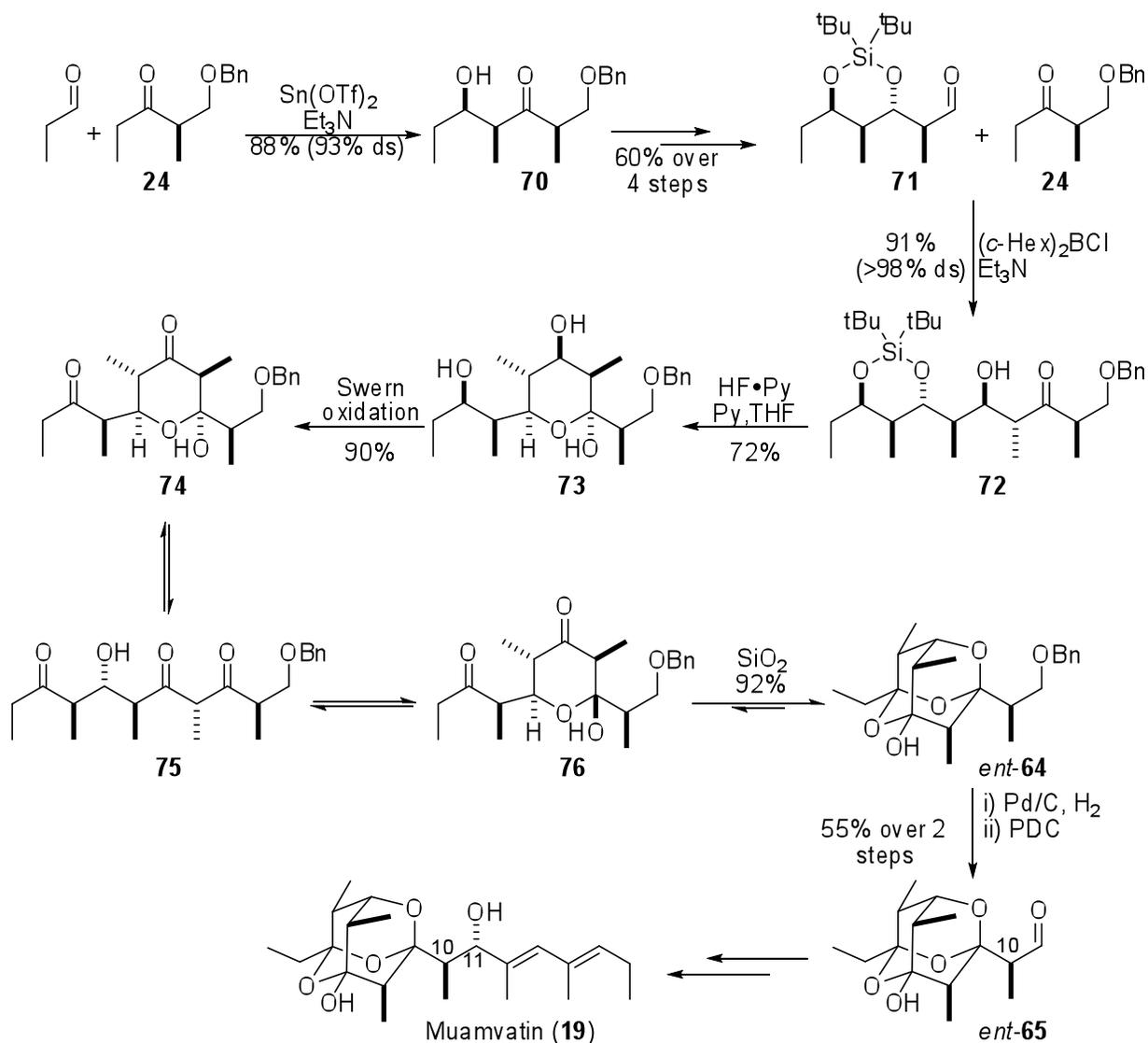


1.3.2 Paterson's synthesis of muamvatin

In 1993, Paterson achieved the first total synthesis of muamvatin (**19**), confirming the relative and absolute configuration of the compound.³⁶ The synthesis of the trioxadamantane moiety *ent*-**64** involved a Sn(II) mediated aldol reaction between ketone **24** and propionaldehyde, followed by a selective *anti* reduction of the aldol adduct **70**, silyl protection, debenzoylation, and oxidation to produce aldehyde **71**. Aldol reaction of **71** with the boron enolate of **24** produced **72**, which after silyl deprotection cyclised to the hemiacetal **73** as a single isomer in 72% yield. Further oxidation of **73** produced the hemiacetal **74**, a tautomer of the trioxadamantane ring system. However, exposure of **74** to acidic conditions, only produced dehydration. In contrast,

exposure of **74** to silica gel for 18 h produced the desired trioxadamantane ring system *ent*-**64** in 92% yield.

Scheme 1.9 Paterson's synthesis of muamvatin (**19**).



Hydrogenolysis of the benzyl ether in *ent*-**64** followed by oxidation of the resulting alcohol generated aldehyde *ent*-**65** which was in agreement with the trioxadamantane aldehyde isolated from degradation of muamvatin **19**.³² Therefore, the relative configuration at C-10 was established. Further manipulations to introduce the diene fragment and establish the configuration at C-11, produced muamvatin (**19**) in 14 steps. Paterson proposed that due to the

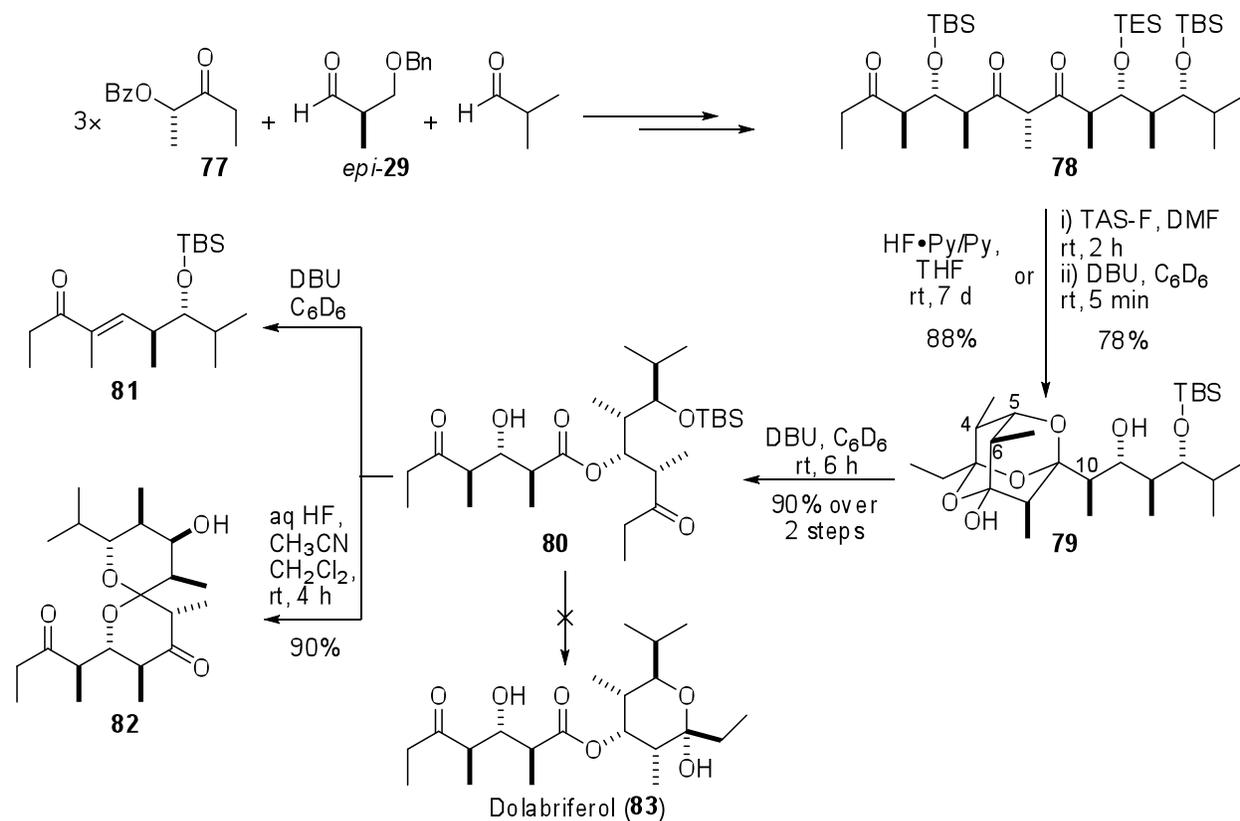
straightforward formation of the trioxadamantane *ent*-**64** under SiO₂ conditions, muamvatin (**19**) could be an artifact of isolation.

1.3.3 Perkins' approach to Dolabriferol

It is interesting that in one of the approaches towards the synthesis of dolabriferol (**83**), Perkins observed the formation of the trioxadamantane ring system **79** (Scheme 1.10).³⁷ When compound **78** (Scheme 1.10) was subjected to tris(dimethylamino)sulphonium difluorotrimethylsilicate (TAS-F) to remove the silyl groups,³⁸ followed by addition of DBU, surprisingly compound **79** was produced in 78%. Similarly, treatment of **78** with HF•pyridine and pyridine in THF efficiently provided the trioxadamantane **79** in 88% yield. These last conditions used to form **79** were very similar to those used by Hoffmann in his model studies for the preparation of trioxadamantanes **64** and **68** (Scheme 1.8). To date, this is the only example of the formation of a trioxadamantane bearing a side chain larger than three carbons from a 3-hydroxy-1,5,7-trione or hemiacetal precursor.

Exposure of **79** to DBU for a longer reaction time produced **80** from a ring opening and retro-Claisen reaction sequence. Finally, the ester was transformed to the enone **81** on prolonged exposure to DBU. On the other hand, spiroketal **82** was obtained when **80** was treated with aqueous HF, a process that presumably involved a Claisen reaction. This is the only example where a retro-Claisen fragmentation (e.g., **79** to **80**) has been shown to be reversible.

Scheme 1.10 Formation of a trioxaadamantane moiety during Perkin's approach towards the synthesis of dolabriferol (**83**).

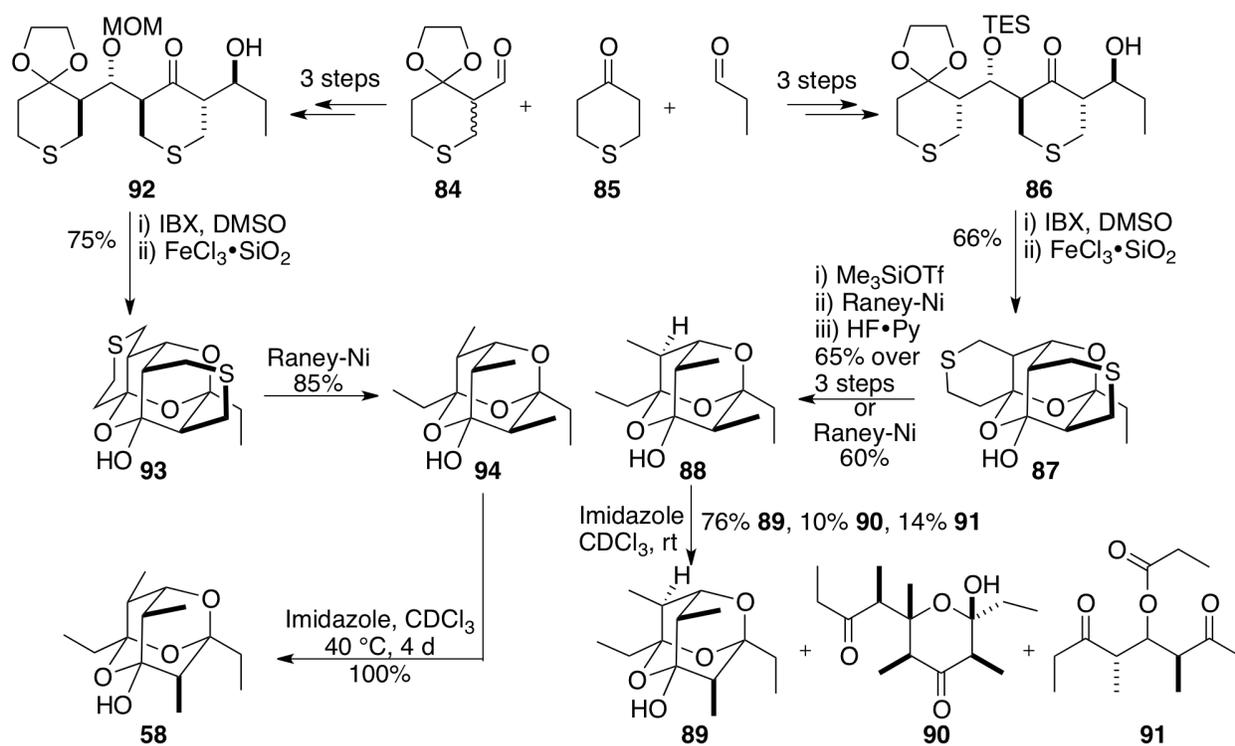


1.3.4 Ward's synthesis of the trioxaadamantane ring systems of muamvatin and caloundrin B

In 2009, Ward et al. performed model studies to form the trioxaadamantane ring systems present in muamvatin (**19**) and caloundrin B (**3**).³⁹ Their strategy, utilized thiopyran fragments to form sulphur-bridged trioxaadamantanes **87** and **93**, that subsequently could be desulfurized and finally isomerized to the more stable trioxaadamantane species **89** and **58**, respectively.³⁹ Interestingly, the isomerizations of trioxaadamantanes, **88** and **94**, were very different. Whereas isomerization of **94** in the presence of imidazole cleanly formed the more stable trioxaadamantane **58** in excellent yield, isomerization of **88** produced the trioxaadamantane **89**

along with the hemiacetal form **90** and the ester **91**; the latter produced from a retro-Claisen reaction of the hemiacetal forms (i.e. **90**). This methodology, allowed the selective preparation of compounds **89**, **90**, and **91**, truncated forms of caloundrin B (**3**), siphonarins B (**2**), and baconipyrones C (**6**), by using the appropriate isomerization conditions. This was the first example where the formation of the trioxaadamantane moiety from caloundrin B (**2**) was demonstrated.

Scheme 1.11 Synthesis of model trioxaadamantanes (**58** and **89**) from muamvatin (**19**) and caloundrin B (**2**).



1.4 Conclusions

To date, the achievements in the synthesis of **2**, **4**, and **6** and their putative acyclic precursor **48** have confirmed their relative and absolute configurations and afforded the study of their inter-relationships. Yet the synthesis of **3** remains a challenge to be solved. Achievement of the synthesis of **3** would allow confirmation of the proposed structure and would allow testing of the revised hypothesis about the origin of the siphonariid polypropionates.

Since caloundrin B (**3**) was not observed during the biomimetic synthesis of **2**, **4**, and **6** from the corresponding acyclic precursor (**48**), the synthesis of **3** should be approached using a different strategy. As an alternative, a convergent synthesis of **3** is proposed, where the γ -pyrone fragment would be coupled with a preformed trioxadamantane fragment. Several different procedures to form the trioxadamantane fragment of muamvatin (**19**) have been reported by Hoffman,³³⁻³⁵ Paterson,³⁶ Perkins,³⁷ and Ward.³⁹ However, the only report for the formation of the trioxadamantane ring system of caloundrin B was disclosed by Ward et al. in 2009.³⁹ With this precedent in hand, research was directed towards the synthesis of caloundrin B.

2 RESULTS AND DISCUSSION

2.1 Research objectives

One of the key objectives in this research project was to explore the relationship between the siphonariid polypropionates caloundrin B (**3**) and its structural isomers siphonarins B (**2**), baconipyrones A (**4**) and C (**6**), all isolated from extracts of *Siphonaria zelandica*. To enable this study, it was essential to have access to caloundrin B (**3**). However, there are no reports on the synthesis of caloundrin B (**3**) and the single report on the isolation of **3** (1.6 mg from 160 animals) revealed that it was unstable. Therefore, a carefully designed synthetic route would be required to obtain **3** by total synthesis (Figure 2.1).

Caloundrin B (**3**) was not observed in various attempts at isomerizations of the putative common acyclic precursor (**48**)⁹ or siphonarins B (**2**).^{9, 15} Therefore, a convergent synthesis of **3** was proposed involving aldol coupling of the trioxadamantane-containing ketone **95** with the γ -pyrone-containing aldehyde (\pm)-**30**. The proposed use of the racemic fragment (\pm)-**30** for this strategy would require studies of methodology on the design of aldol reactions that proceed with kinetic resolution (*vide infra*). On the other hand, the stereoselective synthesis of the trioxadamantane fragment using the thiopyran route to polypropionates^{29, 40} was envisaged. However, the development of a methodology to form a trioxadamantane possessing an appropriate functional ‘handle’ would be required.

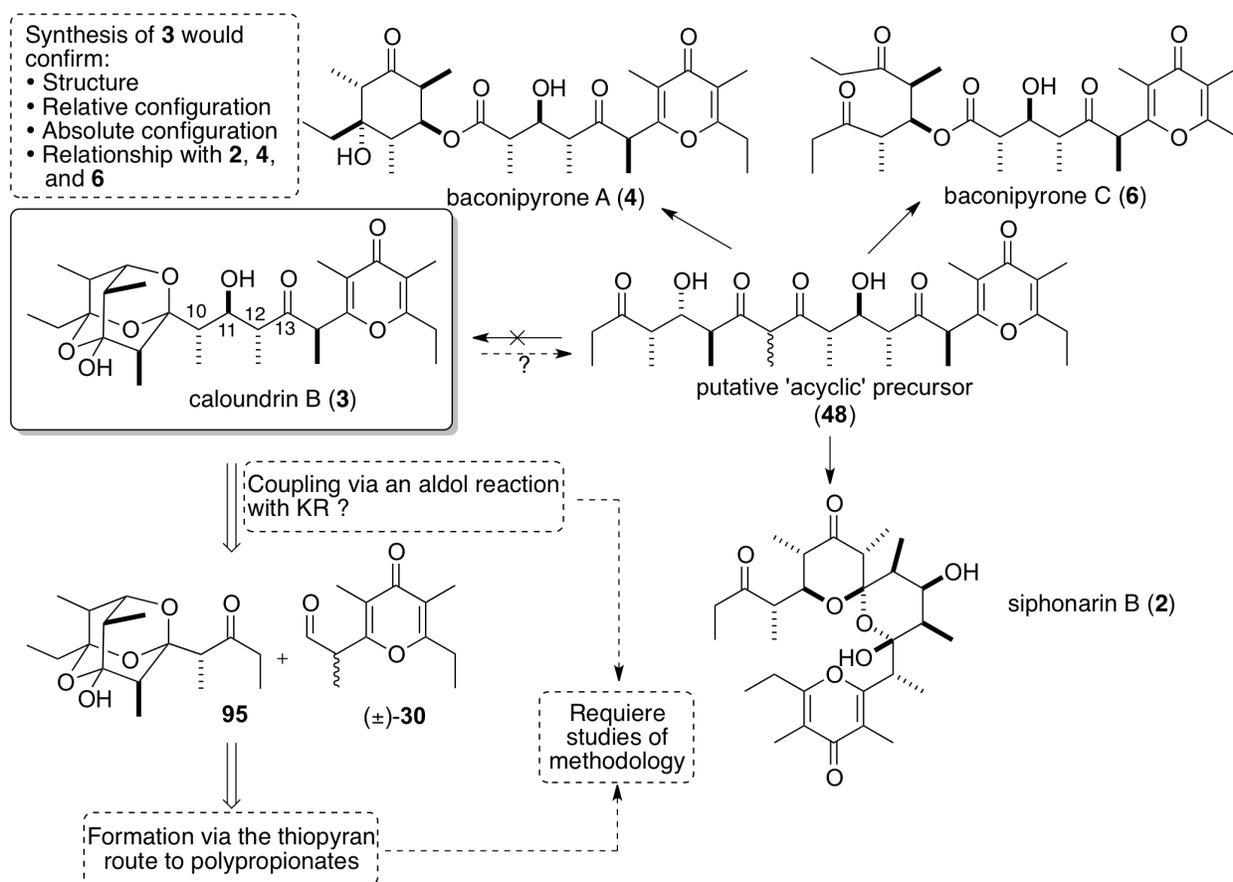


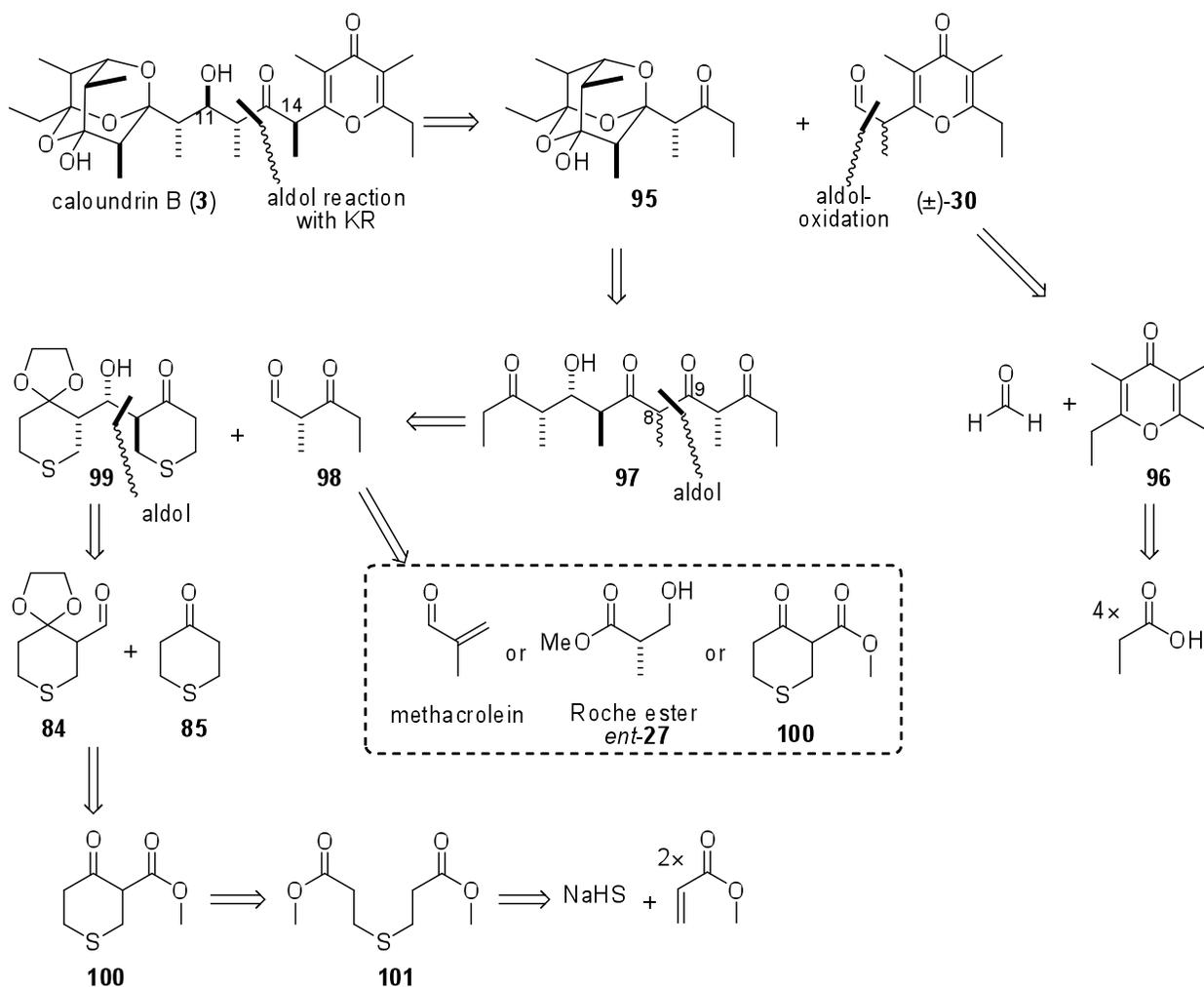
Figure 2.1 Major objectives of the research

2.2 Retrosynthetic analysis of caloundrin B

The failure to produce caloundrin B (**3**) by attempted isomerization of either **2** or **48** seemed to predicate a synthetic plan based on elaboration of a preformed trioxaadamantane fragment.⁹ The presence of the β -hydroxyketone in **3** suggested a convergent approach based on aldol coupling of two fragments of similar size. The perhaps more obvious disconnection of the C-11, C-12 bond was rejected because of anticipated difficulties in forming an enolate in the presence of a pyrone and in achieving the required 10,11-*anti*-11,12-*anti*-12,14-*anti* stereoselectivity. Instead, disconnection of the C-12, C-13 bond was envisaged to produce the two key fragments, **95** and (\pm) -**30** (Scheme 2.1). Both enantiomers of the aldehyde **30** are known^{7, 12, 41} and the unknown (\pm) -**30** should be available from the γ -pyrone **96**,⁴² easily prepared

by oligomerization of propionic acid as described by Mullock and Suschitzky.⁴³ The more challenging fragment **95** could be prepared by strategically cleaving the bond between C-8 and C-9 in its open tautomeric form **97**, which would generate the synthon **98** and fragment **99**. The later fragment (**99**) is easily accessible in enantioenriched form employing the methodology developed in the Ward group for the synthesis of tetrapropionate units.^{29, 40, 44} Finally, the enantiopure fragment **98** could be generated by several different methods; for example, from a thiopyran fragment (i.e. **100**), by hydroboration of an olefin and then insertion of an ethyl group, or employing the Roche ester (*ent*-**27**) followed by functionalization and chain extension.

Scheme 2.1 Synthetic strategies for the synthesis of caloundrin B (**3**).

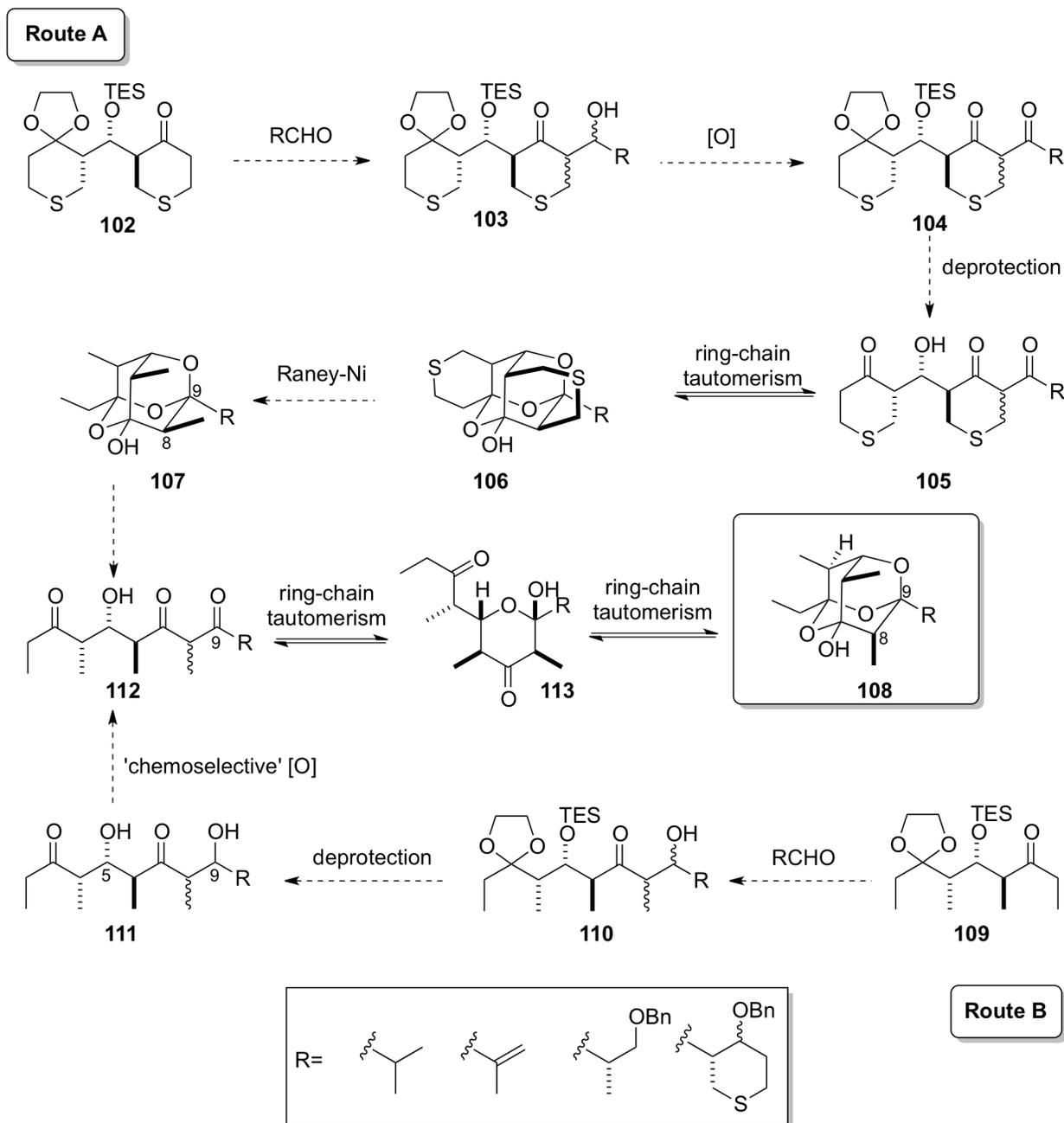


2.3 Formation of the trioxadamantane ring system of caloundrin B

To date, the only study on the formation of the trioxadamantane ring system present in caloundrin B (**3**) was reported by Ward et al.³⁹ In that work, the pentacyclic sulphur-bridged trioxadamantane **106** (R = Et) was produced directly during FeCl₃ mediated deprotection of the TES ether and ethylene acetal present in **104** (R = Et). The latter was easily prepared by an aldol/oxidation sequence on readily available tetrapropionate precursor **102**. Desulfurization of **106** (R = Et) produced the isolable **107** (R = Et) as a thermodynamically unstable protected form of a 3-hydroxy-1,5,7-trione. Ring-chain tautomerism of **107** (R = Et) was studied under various reaction conditions and under thermodynamic control, the isomeric trioxadamantane **108** (R = Et) was virtually the exclusive product. The transformation of **107** to **108** required isomerization at C-8 and this was shown to occur via keto-enol tautomerism of the open form **112** (R = Et). It should be noted that because **108** (R = Et) was produced under thermodynamic control, it could be anticipated that the synthesis of any of the tautomers [e.g., **107** (R = Et), **112** (R = Et), **113** (R = Et)] would also lead to **108** (R = Et) under thermodynamic control.

In the present research, two different approaches were proposed to study the formation of trioxadamantane fragments with different substituents at C-9 that might be suitable for elaboration into the desired **95**. The first route (route A in Scheme 2.2) was analogous to the approach previously developed by Ward et al. to form **108** (R = Et) as a model trioxadamantane ring system for caloundrin B.³⁹ Alternatively, in route B it was proposed to start with the desulfurized aldol adduct **109**. Aldol reaction of **109** with a suitable aldehyde would give **110**. In contrast to **103**, an oxidation/deprotection sequence on **110** would be unproductive as 3-hydroxy-1,5,7-triones are known to be unstable to the acidic conditions necessary to remove an ethylene acetal.^{8, 33, 36} Acid mediated deprotection of **110** should be feasible but would require a chemoselective oxidation of the resulting diol **111** to obtain a tautomer of the desired **108**.

Scheme 2.2 Strategies proposed to form trioxaadamantane systems **108**.

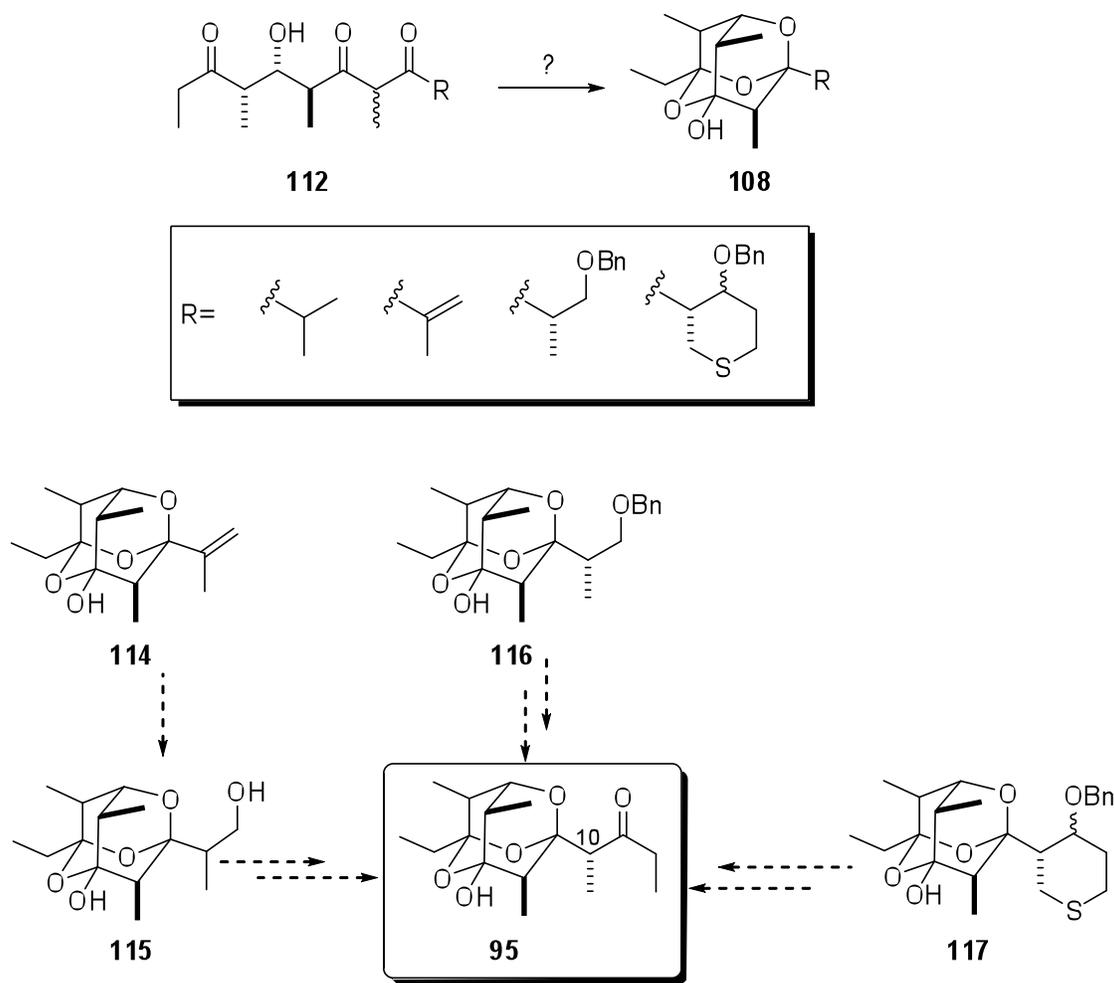


The goal of this study was to identify suitable precursors for the formation of a trioxaadamantane bearing a substituent at C-9 that would allow further manipulation to ketone **95**. The 'R groups' illustrated in Scheme 2.2 were selected for several reasons. The trioxaadamantane needs to be formed under thermodynamic control and it was anticipated that

the steric and electronic properties of the C-9 substituent would influence the equilibrium. Examination of the isopropyl substituent (from ⁱPrCHO) would confirm whether use of a substituent more hindered than ethyl would still favour trioxadamantane formation. Successful formation of trioxadamantane **114** with a 2-propenyl substituent (from acrolein) would allow functionalization, for example via hydroboration to give **115** (Scheme 2.3). Alternatively, producing a trioxadamantane system such as **117** would require minimal functional group manipulations to produce the desired ketone **95**. Finally, the use of Roche ester-derived aldehyde **29** could provide the minimally functionalized trioxadamantane system **116**. The protected hydroxypropyl substituent in aldehyde **29** is similar in size to the isopropyl group and the configuration at C-10 in the resulting trioxadamantane **116** would be fixed. Subsequently, that substituent could be elongated by addition of an ethyl group to produce the desired **95**.

With the above objectives in mind, studies on the formation of the proposed trioxadamantane ring systems were pursued and are described in this section.

Scheme 2.3 Proposed approaches for the generation of trioxaadamantane systems that would allow further manipulation.



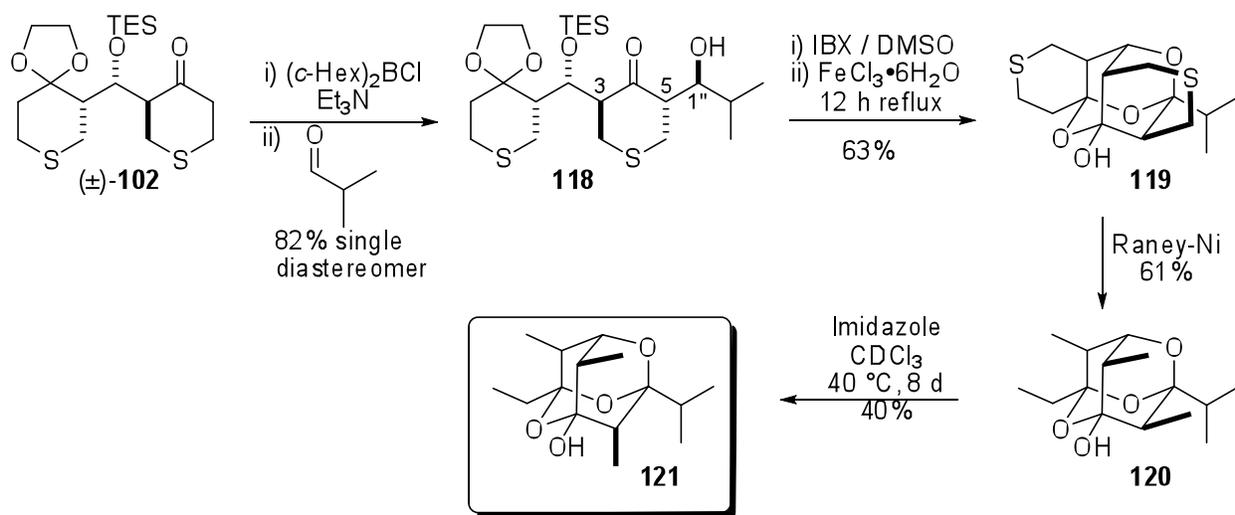
2.3.1 Sulfur-bridged trioxaadamantanes from 5-alkanoyl-3-[hydroxy(4-oxotetrahydro-2*H*-thiopyran-3-yl)methyl]dihydro-2*H*-thiopyran-4(3*H*)-one precursors

2.3.1.1 The isopropyl analogue (from the 5-(2-methylpropanoyl) precursor)

Previously in the Ward group, it was demonstrated that the formation of a trioxaadamantane system bearing an ethyl substituent was possible using route A in Scheme 2.2. Thus, the first question in this project was if the size and complexity of the substituent were increased, would the trioxaadamantane still be thermodynamically favoured? In order to gain some insight on the impact of the size of the C-9 substituent, formation of the isopropyl analogue

following route A (Scheme 2.2) was attempted. The aldol reaction of the boron enolate of racemic **102**[§] with isobutyraldehyde produced **118** as a single diastereomer in 82% yield (Scheme 2.4). Based on previous studies in the Ward group,^{45, 46} aldol reactions of the TES protected boron enolate of (\pm)-**102** are known to produce aldol adducts with a 3,5-*trans*-5,1''-*anti* relative configuration. The aldol product **118** was subjected to oxidation with IBX in DMSO for 10 h; subsequently, the crude product from oxidation was treated with FeCl₃•6H₂O in refluxing acetone for 12 h affording 63% of the desired trioxadithiopentacycle **119**. Raney-Ni desulfurization of **119** afforded trioxaadamantane **120** in 61% yield. Exposure of **120** to imidazole at 40 °C for 8 days gave the thermodynamically more stable isomer **121** in 40% isolated yield.

Scheme 2.4 Formation of trioxaadamantane system bearing an isopropyl substituent following route A.

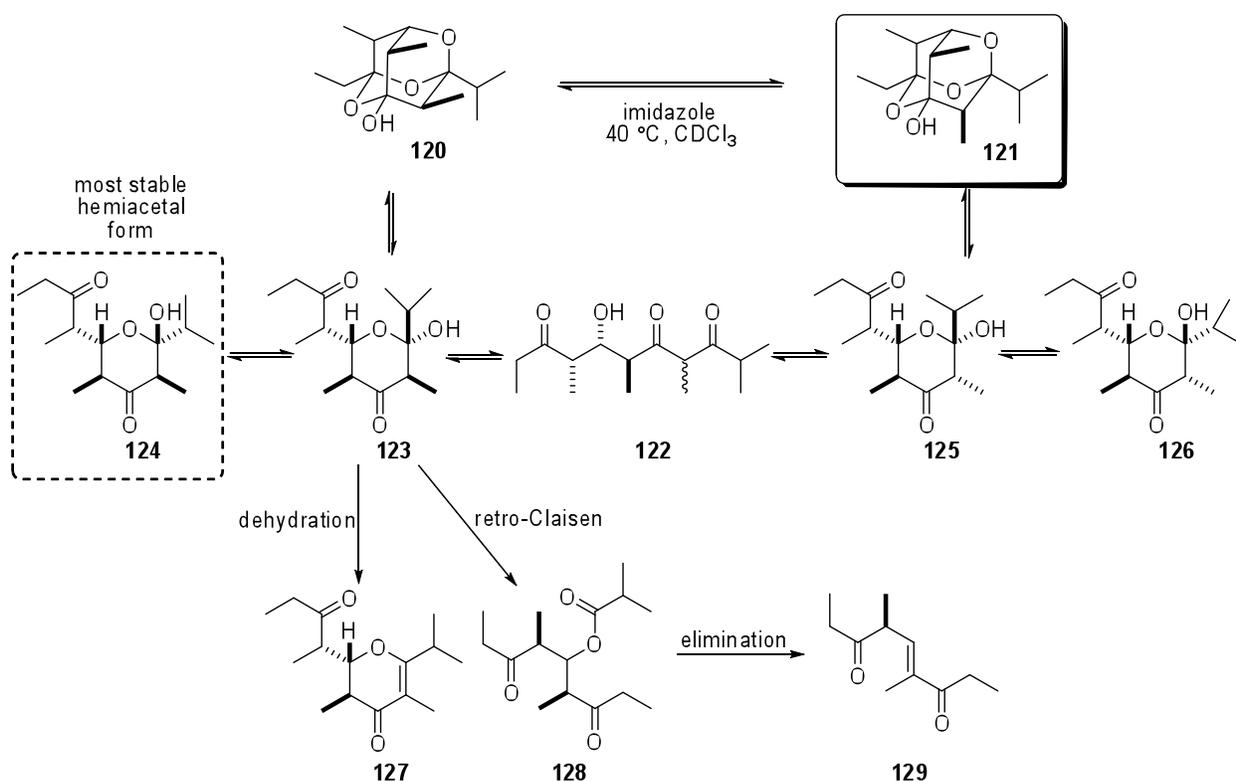


The mechanism for the isomerization of **120** to **121** involved a ring opening of the trioxaadamantane **120** to initially produce hemiacetal **123** that would be in equilibrium with the open form **122** and the other three hemiacetal forms **124**, **125**, and **126** (Scheme 2.5). The more

[§] Preparation of the TES deprotected (\pm)-**102** was optimized to produce 10 g of product in 81% yield.³⁹

stable trioxadamantane **121** would result from cyclization of **125**. In addition to this isomerization process, other side reactions could occur, which in principle are responsible of the reduced yield of **121**. For instance, a retro-Claisen reaction can occur from any of the formed hemiacetal forms **123-126**. Sequentially, the retro-Claisen product **128** can undergo elimination to produce the enone **129**. Additionally, the hemiacetal forms are susceptible to dehydration furnishing dihydropyrone **127**.

Scheme 2.5 Isomerization of trioxadamantane **120** to **121** under basic conditions.



In order to gain more insight about the equilibration process, a sample of trioxadamantane **120**, was exposure to imidazole in CDCl_3 at $40\text{ }^\circ\text{C}$ and its isomerization was followed by $^1\text{H-NMR}$ (Table 2.1). After 8 days, the reaction was worked up and fractionated. During this process, the formation of trioxadamantane **121** and hemiacetal **124** were observed along with **127**, **128**, and **129**. Plotting the relative amounts of **120**, **121**, and **124** as a function of

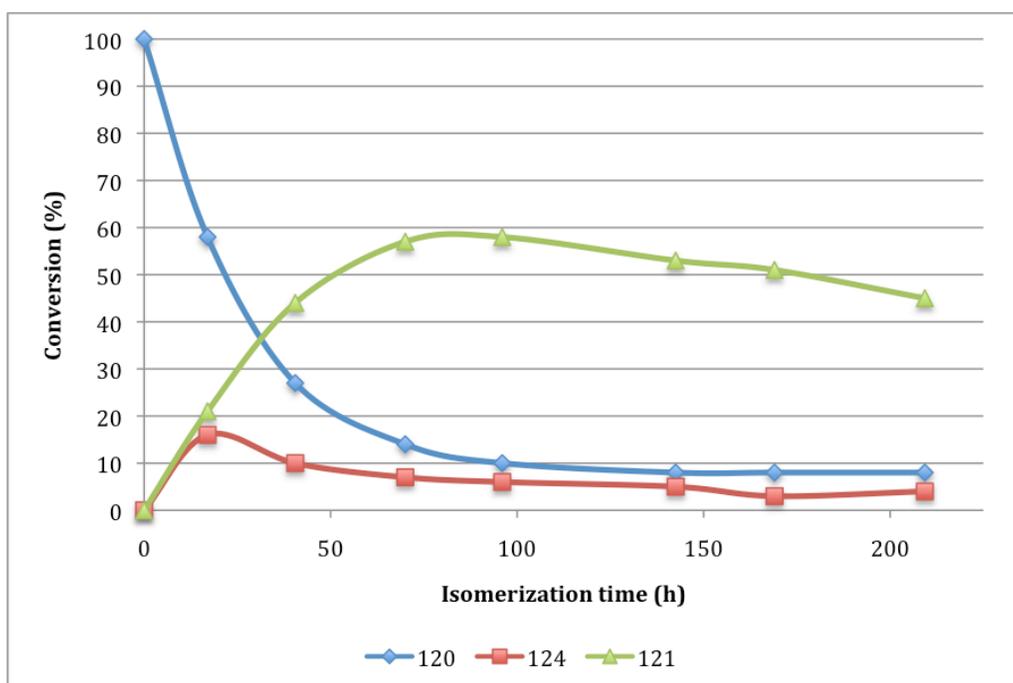
time (Chart 2.1) revealed that the isomerization reached equilibrium after 96 h with a 6:1 ratio of trioxadamantanes **121:120**. At longer reaction times the amount of **121** was reduced because there were increasing amounts of other products formed by irreversible reactions (i.e. retro-Claisen, dehydration, elimination).

Table 2.1 Isomerization of trioxadamantane **120** in CDCl₃.

Time (h)	components present (% by ¹ H NMR)					
	120	128	129	124	127	121
0	100	0	0	0	0	0
17	58	4	0	16	0	21
41	27	12	0	10	7	44
70	14	15	3	7	5	57
96	10	17	4	6	5	58
142	8	19	7	5	7	53
169	8	21	10	3	7	51
209	8	21	12	4	9	45
<i>a</i>	9	20	12	6	8	46
<i>b</i>	6.5	17	5	8	7	40

^a Crude product obtained after 210 h. ^b Isolated products from crude.

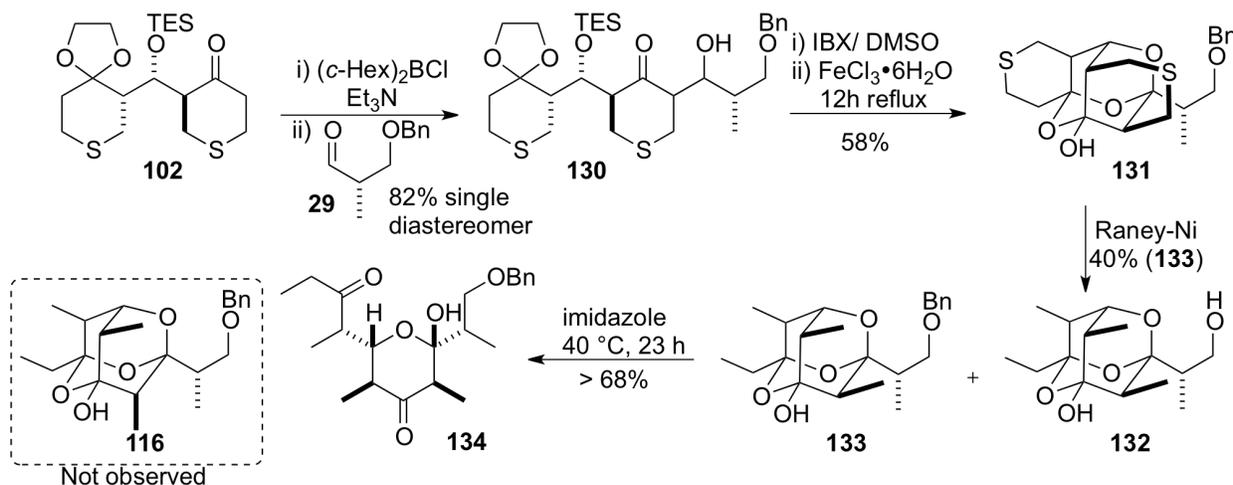
Chart 2.1 Isomerization of trioxadamantane **120** in CDCl₃.



2.3.1.2 The 3-benzyloxy-2-methylpropyl analogue (from the Roche ester)

With the successful synthesis of **121**, the next step was to investigate the formation of a trioxadamantane bearing a (1-benzyloxy)-isopropyl substituent at C-9 using the sequence of reactions described in route A (Scheme 2.2). The boron mediated aldol reaction of enantiopure **102** with the Roche ester-derived aldehyde **29** produced a single diastereomer in 82% yield. Oxidation of the alcohol with IBX in DMSO for 5.5 h followed by deprotection of the TES and acetal groups by treatment with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ for 12 h produced the desired trioxadithiopentacycle **131** in 58% yield over 2 steps. Raney-Ni desulfurization of **131** provided a mixture of trioxadamantane **133** and its debenzylated form **132** in low yield. Surprisingly, isomerization of **133** in the presence of imidazole at 40 °C gave only hemiacetal **134** by ^1H -NMR without evidence for the presence of the expected **116**.

Scheme 2.6 Approach to trioxadamantane **116** from **102** and Roche ester-derived aldehyde **29**.



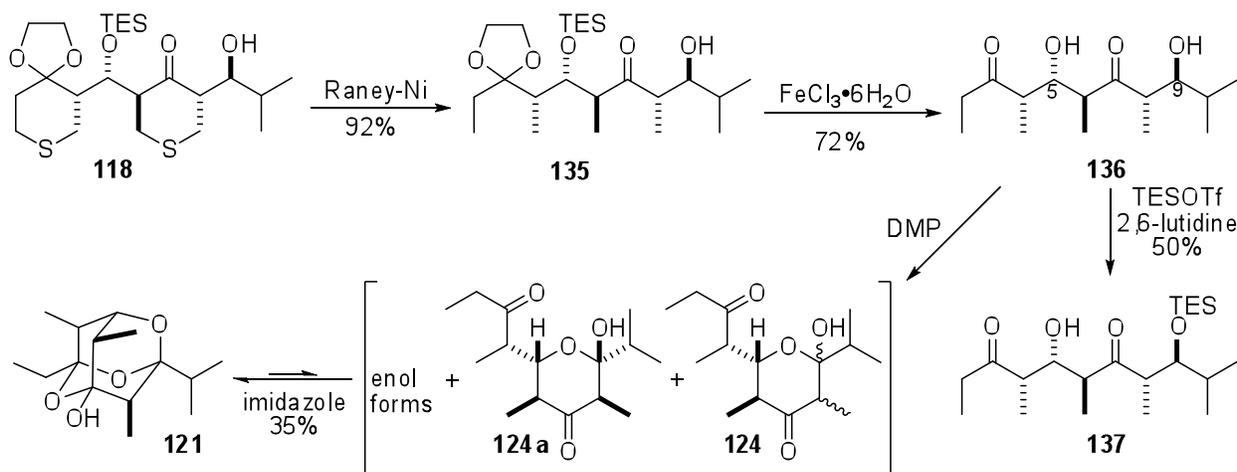
Because of the problems encountered in the formation of the trioxadithiopentacycle **131** and its subsequent desulfurization with Raney-Ni, the possibility for preparation of a trioxadamantane such as **116** employing route B (Scheme 2.2) was considered.

2.3.2 Trioxadamantanes from 2-substituted 7-hydroxy-4,6,8-trimethylundecane-3,5,9-trione precursors

2.3.2.1 7-hydroxy-2,4,6,8-tetramethylundecane-3,5,9-trione precursor

To study route B in Scheme 2.2, the precursor **135** was prepared by desulfurization of aldol **118** in 92% yield. Subsequently, the protecting groups (i.e., TES and ethylene acetal) were hydrolyzed by treatment with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in acetone at room temperature for 1 h to afford **136** in 72% yield. Reaction of **136** with TESOTf was attempted to determine which of the two alcohols was more reactive. At moderate conversion the C-9 protected **137** was produced selectively in 50% yield along with unreacted starting material suggesting that selective oxidation of the C-9 alcohol in diol **136** could be achieved.

Scheme 2.7 Formation of trioxadamantane system **121** following route B.



As anticipated, diol **136** was oxidized with DMP observing predominantly a selective oxidation at C-9 to produce the 5-hydroxy-3,7,9-trione as a mixture of three hemiacetal forms (i.e., **124** and **124a**) along with minor amounts of other tautomers (i.e. enol and keto forms).

Submission of this mixture of tautomers to imidazole at 40 °C in CDCl₃, afforded the expected trioxadamantane **121**. Monitoring the isomerization by ¹H-NMR indicated that the maximum amount of **121** (ca. 70%) was present after ca. 2 days; Table 2.2). After a reaction time of 125 h, **121** was isolated in 35% yield.

Table 2.2 Isomerization to trioxadamantane **121** in CDCl₃.

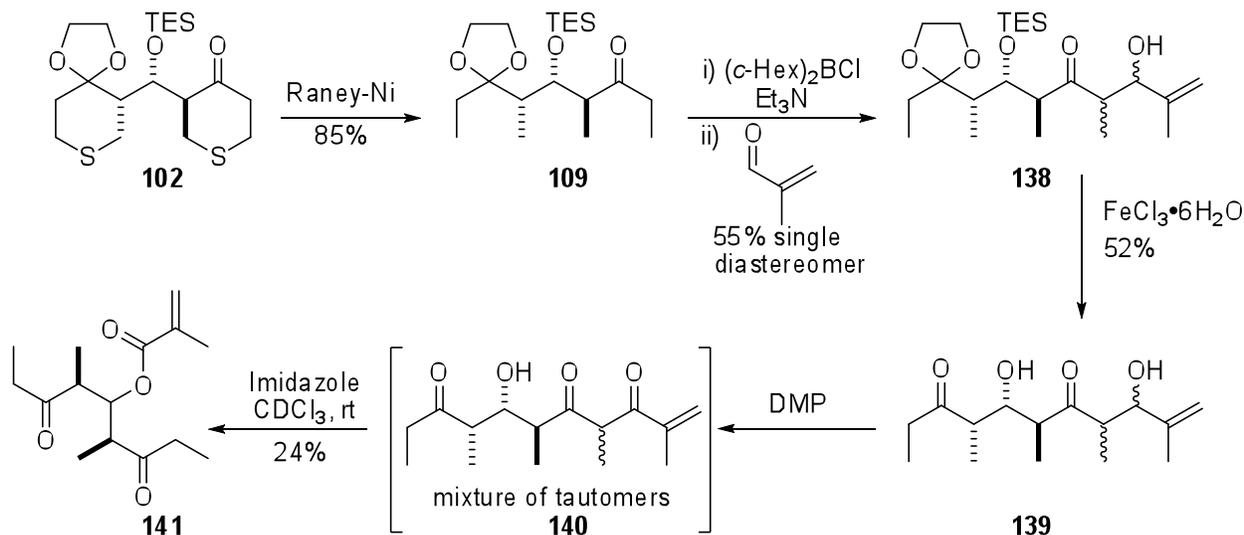
Time (h)	components present (% by ¹ H-NMR)					
	122	128	129	124	127	121
21	0	16	0	9	7	68
53	0	18	0	4	7	71
71	0	18	3	4	8	67
116	0	20	5	4	8	63
a	7	16	4	5	7	61 (35) ^b

^a Crude product after 125 h. ^b Isolated product from crude.

2.3.2.2 2-Methylidene precursor

Raney-Ni desulfurization of the tetrapropionate unit (–)-**102** afforded the enantioenriched ketone (+)-**109** in 85% yield (Scheme 2.8). A boron mediated aldol reaction of (+)-**109** with methacrolein produced **138** as a single diastereomer in 55% yield. Deprotection of the TES and ethylene acetal groups was achieved with FeCl₃·6H₂O to give diol **139** in 52% yield. Although attempted selective oxidation of **139** with MnO₂ did not produce the desired product, treatment with DMP was successful. The resulting product **140**, a mixture of tautomers, was directly submitted to imidazole in CDCl₃ at room temperature for 19 h to give the retro-Claisen product **141** in 24% yield as the only isolable material without evidence of the presence of the desired trioxadamantane **114**. In view that those results were not promising for the formation of the 2-propenyl substituted trioxadamantane system, it was decided to investigate other suitable substituents at C-9.

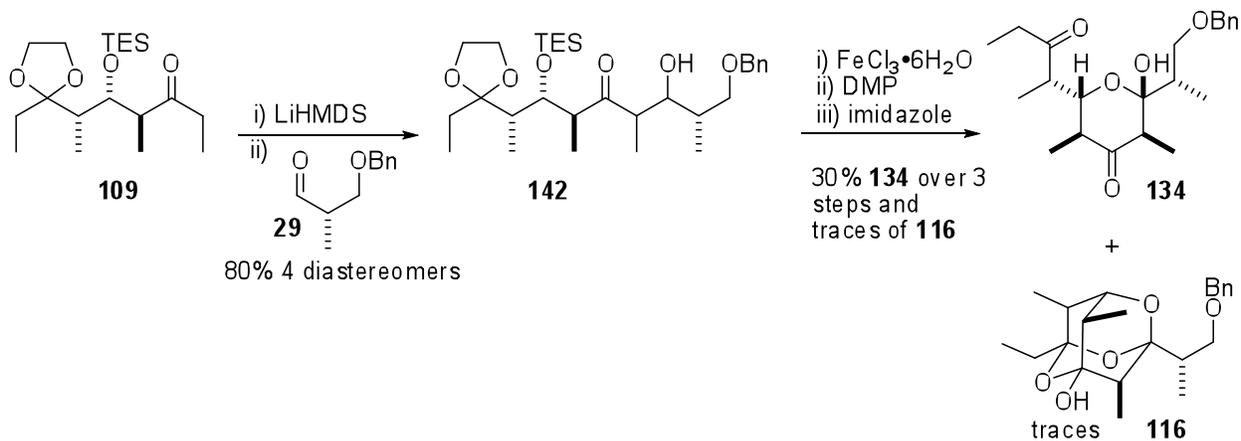
Scheme 2.8 Approach to a trioxaadamantane system bearing a 2-propenyl substituent.



2.3.2.3 2-Benzyloxymethyl precursors (from the Roche ester)

Following route B in Scheme 2.2, aldol reaction of the Roche ester-derived aldehyde **29** with the enantioenriched ketone (+)-**109** via its Ti 'ate' or Li enolate produced keto alcohol **142** as a mixture of 3 or 4 diastereomers. In a three step procedure, hydrolysis of the TES and ethylene acetal protecting groups in **142** followed by chemoselective DMP oxidation of the resulting diol and then exposure to imidazole produced mainly hemiacetal **134** along with traces of the desired trioxaadamantane **116** (Scheme 2.9).

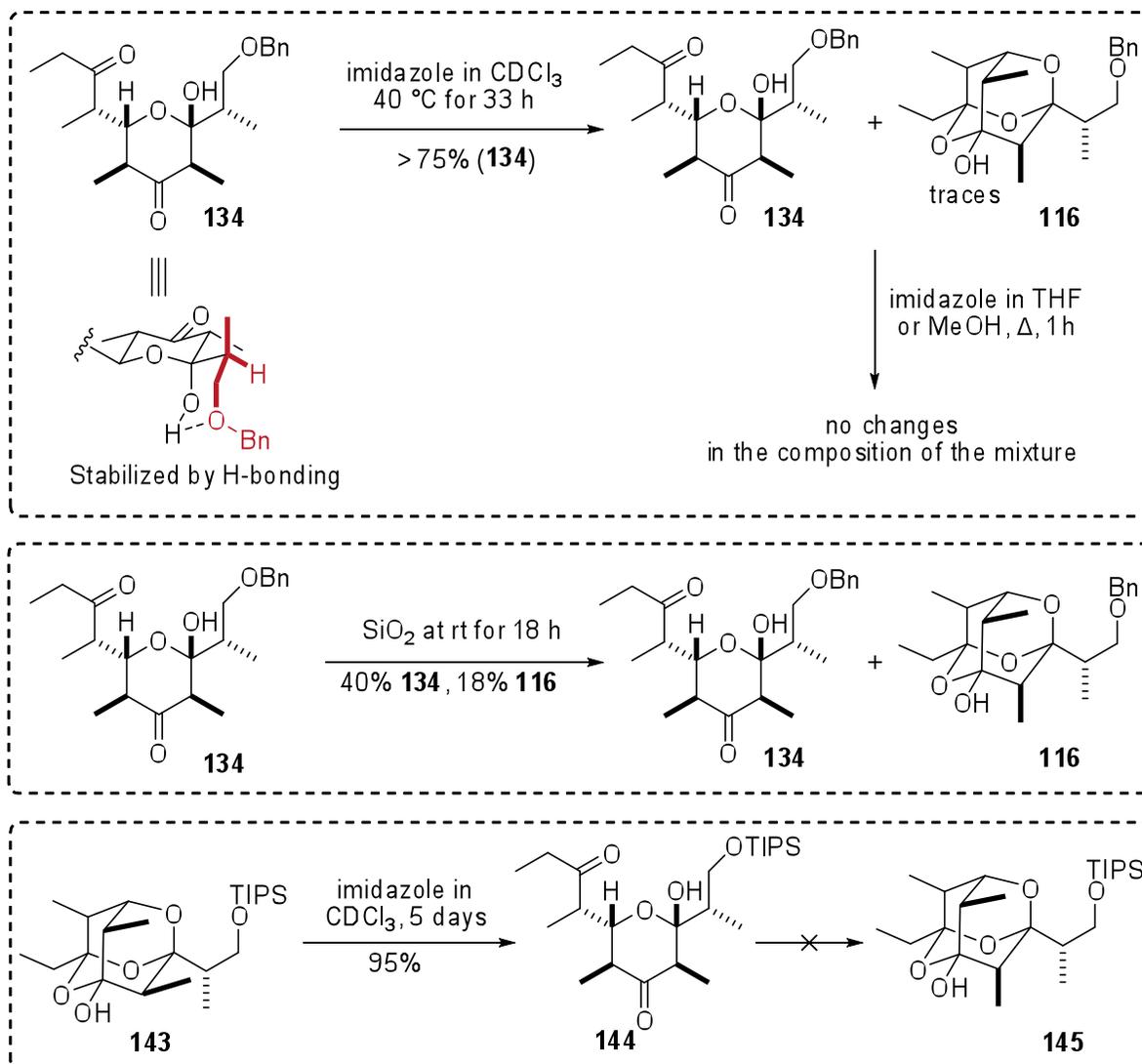
Scheme 2.9 Approach to trioxaadamantane **116** from Roche ester-derived aldehyde **29**.



Several experiments were performed with hemiacetal **134** with the objective of inducing its isomerization to the trioxadamantane **116** (Scheme 2.10). Exposure of hemiacetal **134** to imidazole at 40 °C for 33 h, provided recovered hemiacetal **134** in ca. 75% with traces of the desired trioxadamantane **116** together with other species (e.g., retro-Claisen and elimination products). It was hypothesized that hemiacetal form **134** could be stabilized by H-bonding, thereby disfavoring the trioxadamantane form **116**. Therefore, it was proposed that the use of a polar solvent for the isomerization step (i.e. THF or MeOH), might disrupt the putative intramolecular H-bond in hemiacetal **134**, and facilitate the formation of the desired trioxadamantane **116**. When the hemiacetal **134** was submitted to imidazole in refluxing THF or MeOH for 1 h, the starting hemiacetal form **134** remained as the major compound in the mixture. Motivated by Paterson's report on the synthesis of muamvatin,³⁶ where their respective hemiacetal (**76** in Scheme 1.9) produced the desired trioxadamantane ring system on exposure to silica, a sample of hemiacetal **134** was adsorbed on a SiO₂ PTLC plate and extracted after 18 h. The resulting mixture consisted of hemiacetal **134** (ca, 40%), desired trioxadamantane system **116** (ca. 15%) and other species (e.g. retro-Claisen and/or elimination products; ca. 45%) by ¹H NMR. However, these results were not very promising because the hemiacetal **134** was always the predominant component after attempted isomerization and, at best, only a small amount of the desired trioxadamantane **116** was formed along with significant amounts of side products. Concluding that this method would not provide synthetically useful amounts of trioxadamantane **116**, a final approach involved the use of a TIPS protecting group to disfavor the putative stabilizing intramolecular H-bond in **134**. The TIPS protected trioxadamantane **143** was prepared by desulfurization of **131** (in Scheme 2.6) followed by treatment with TIPS-OTf. Trioxadamantane **143** was stable to imidazole in CDCl₃ at room temperature for 10 h; however,

after 5 days at 40 °C **143** was completely consumed and hemiacetal **144** was the only isolated product.

Scheme 2.10 Attempts for folding hemiacetal **134** or **144** to the trioxaadamantane system **116** or **145**.



The unfavourable results in these experiments deserved a careful conformational analysis in order to find an explanation for the observed outcomes. At this time, it was hypothesized that the configuration at C-10 could be playing an important role in the formation of the trioxaadamantane system. Simple molecular mechanics calculations, employing the software

Spartan,** on the trioxadamantanes **148** and 10-*epi*-**148** suggested that the latter was ca. 0.5 Kcal/mol more stable (Figure 2.2). Similar calculations on the most stable hemiacetal tautomers **146** and 10-*epi*-**146** suggested that **146** was considerably more stable (4.4 Kcal/mol) primarily due to a favourable H-bond between the hemiacetal OH and methyl oxygen. The above calculations suggested that the unfavourable equilibrium observed in the attempted formation of **148** might be reversed in the 10-*epi* diastereomer. To test that hypothesis, the preparation of 10-*epi*-**116** following route B in Scheme 2.2 was attempted.

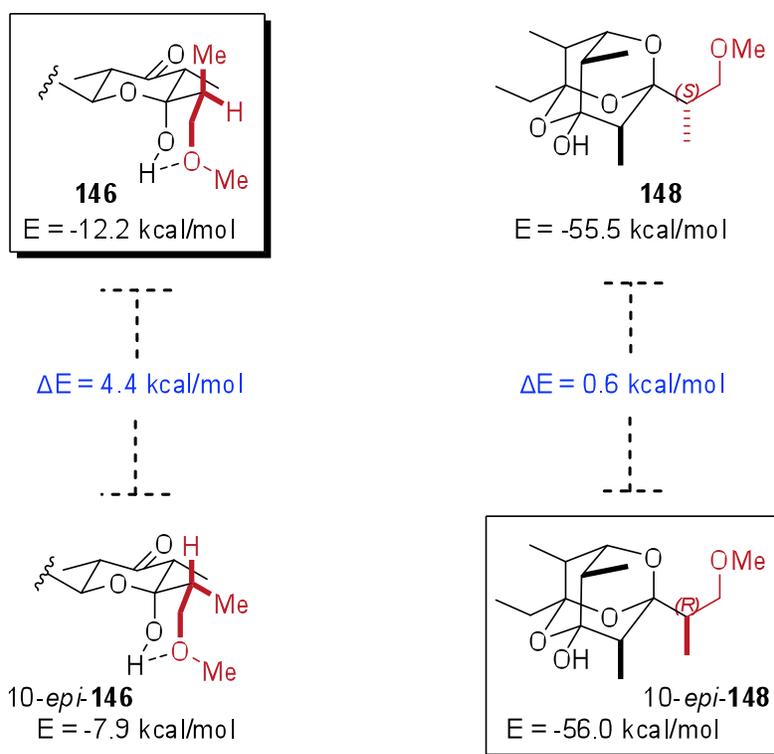


Figure 2.2 Ground state energies for the equilibrium conformer of **146**, 10-*epi*-**146**, **148**, and 10-*epi*-**148**.

** All calculations were performed using the software Spartan '08 V 1.1.2 for Mac from Wavefunction, Inc. The calculations were performed by finding the equilibrium conformer using Molecular Mechanics / MMFF (Merck Molecular Force Field) model and the ground state energies were taken.

The preparation of 10-*epi*-**116** would require ketone **109** and *ent*-**29**; however, *ent*-10-*epi*-**116** could be prepared from *ent*-**109** and **29**. Experimentally, the second option was used because aldehyde **29** was on hand and both enantiomers of **109** were available.^{††}

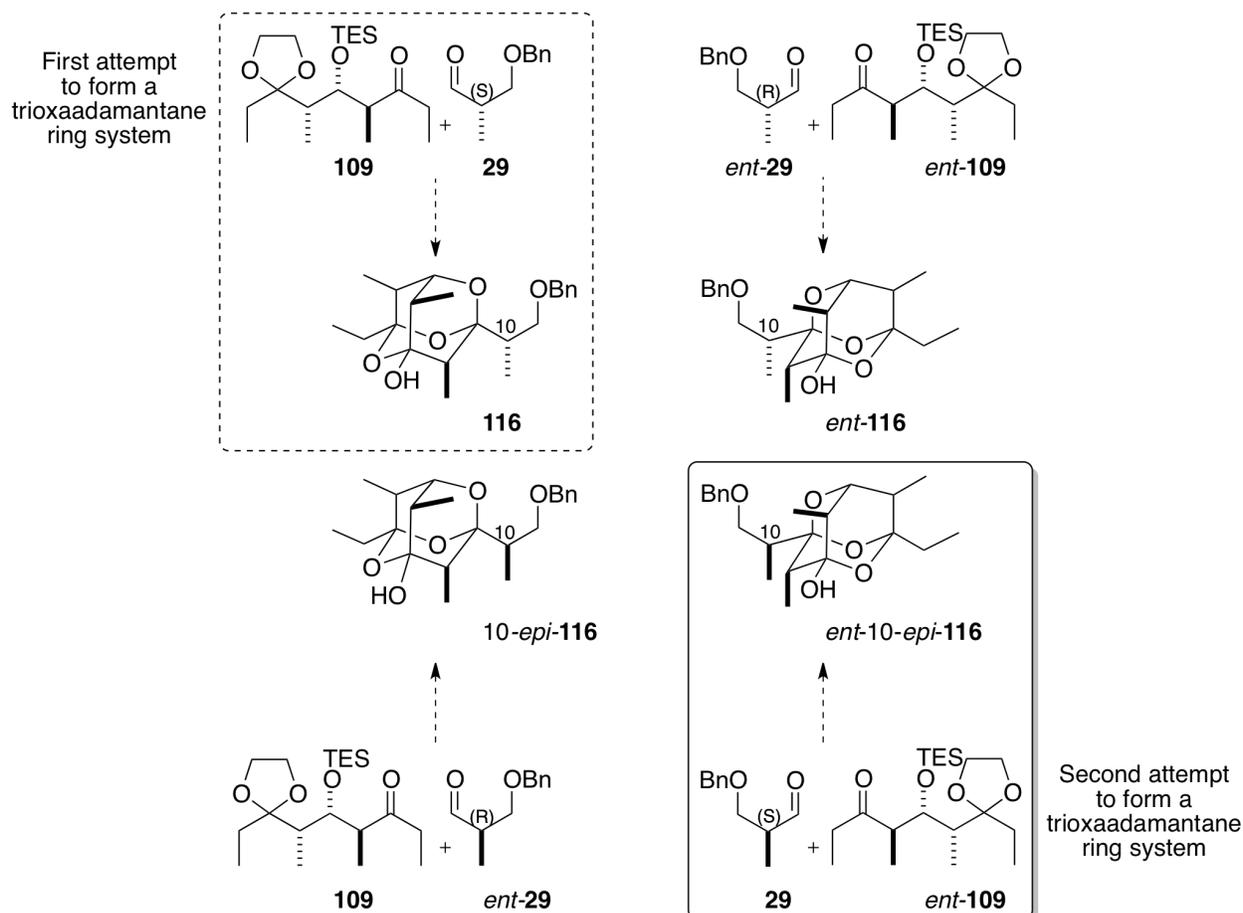
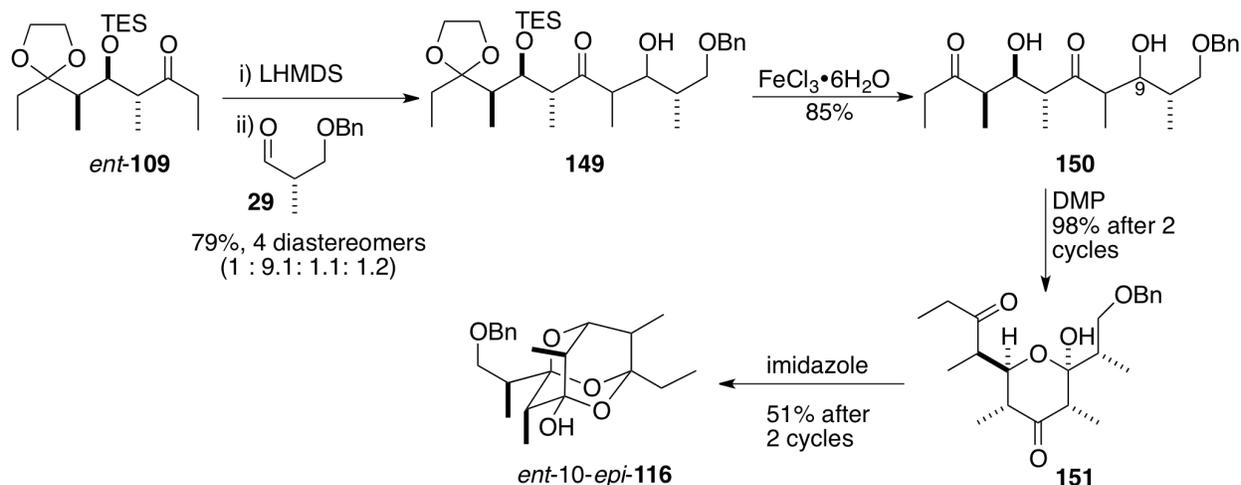


Figure 2.3 Starting materials to prepare trioxadamantanes **116**, *ent*-**116**, 10-*epi*-**116**, and *ent*-10-*epi*-**116**.

Following the same route as illustrated in Scheme 2.9, aldol reaction of **29** with the Ti ‘ate’ or Li enolates of *ent*-**109** gave a mixture of aldol adducts **149** (79-81%). Gratifyingly, after TES and acetal deprotection, DMP oxidation and isomerization with imidazole, **149** was converted to the desired trioxadamantane *ent*-10-*epi*-**116** in 42% overall yield.

^{††} The preparation of the Roche ester-derived aldehyde **29** required 3 steps starting from the commercially available Roche ester.⁴⁶

Scheme 2.11 Synthesis of the trioxaadamantane *ent*-10-*epi*-**116**.



In view of these experimental results and the molecular mechanics calculations, it seemed clear that H-bonding was playing an important role for the stabilization of certain hemiacetal forms, thus favouring the equilibrium towards the hemiacetal **134** in the first attempt (Scheme 2.9) and towards the trioxaadamantane *ent*-10-*epi*-**116** in the second attempt (Scheme 2.11). Comparing hemiacetals **134** and 10-*epi*-**134** (Figure 2.4) where both have all the large groups in equatorial orientations in a chair conformation, H-bonding between the anomeric OH and OBn group in **134** can occur without any *syn* pentane interactions in the molecule. In contrast, the same H-bonding in 10-*epi*-**134** results in a *syn* pentane interaction between the methyl groups as illustrated in Figure 2.4.

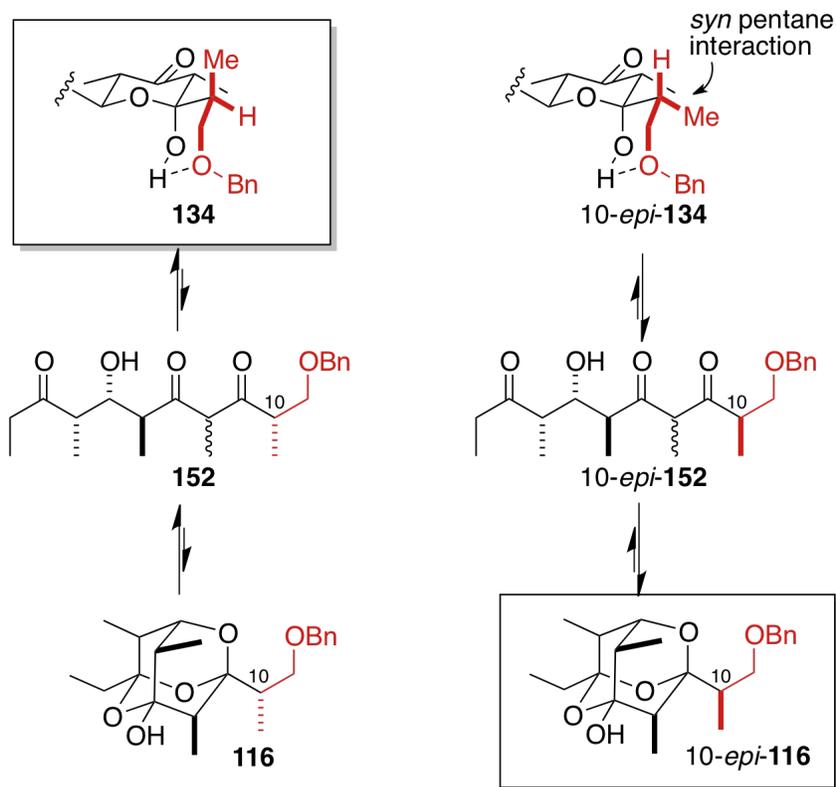


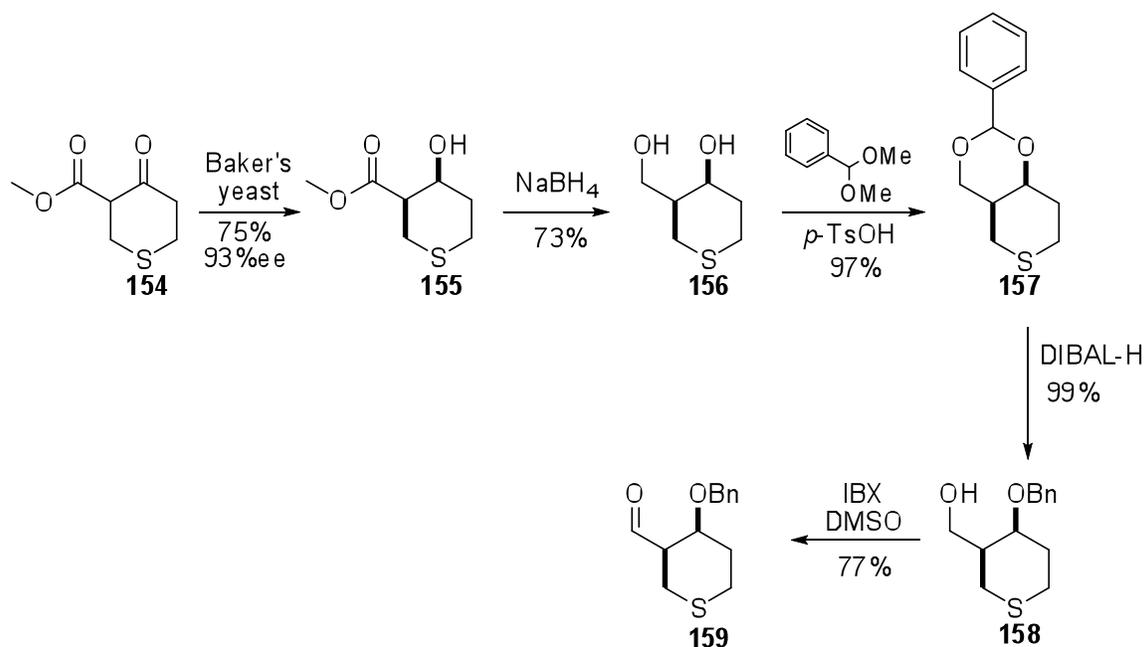
Figure 2.4 Formation of **134** and 10-*epi*-**116** after isomerization with imidazole.

2.3.2.4 2-(4-benzyloxytetrahydro-2*H*-thiopyran-3-yl) precursor

In view of the successful preparation of trioxadamantane *ent*-10-*epi*-**116**, the formation of a trioxadamantane with a 2-(4-benzyloxytetrahydro-2*H*-thiopyran-3-yl) substituent could be another possibility towards the synthesis of caloundrin B (**3**) because this would have all the necessary carbons in place to generate 10-*epi*-**95** (Scheme 2.3). The main question was if the trioxadamantane could be formed with this relatively more hindered substituent. The preparation of the required aldehyde **159** began with a baker's yeast reduction of **154** to yield the enantioenriched *syn*- β -hydroxy ester **155** in 75% and 93% ee (Scheme 2.12).⁴⁷ Subsequently, reduction of the ester **155** with NaBH₄ produced diol **156** that was protected as its benzylidene acetal **157**. Regioselective reduction of the acetal in **157** with DIBAL-H afforded the primary alcohol **158** that was treated with IBX to produce the desired enantioenriched aldehyde **159**.

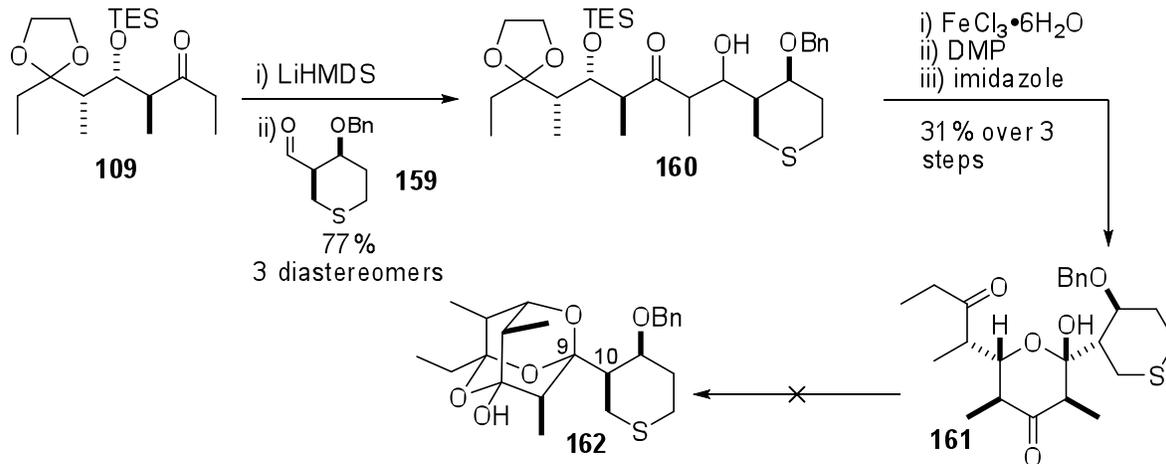
Because **159** was prone to isomerization and decomposition (elimination) it was used immediately in the aldol reaction with **109**.

Scheme 2.12 Preparation of enantioenriched aldehyde **159**.



Reaction of **159** with **109** via its (*Z*)-lithium enolate gave **160** as a mixture of at least three aldol adducts in 77% yield. This mixture of aldol adducts **160** was submitted to the standard three step procedure of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ mediated deprotection of the TES and ethylene acetal groups, chemoselective oxidation of the resulting diol with DMP, and finally submission to imidazole; however, the hemiacetal product **161** was the only product isolated (31% yield over 3 steps) without detection of the desired trioxadamantane **162**.

Scheme 2.13 Approach to trioxadamantane 162.



At this point, it seemed that the nature of C-9 had a profound effect on the facility to fold a trioxadamantane ring system under thermodynamic control. It was concluded that the best option was to continue towards the synthesis of caloundrin B (**3**) via the trioxadamantane system *ent*-10-*epi*-116, because from all previous attempts, this was the only system that would afford the preparation of synthetically useful amounts of the trioxadamantane.

2.3.3 Installing the correct configuration at C-10 for caloundrin B

Despite several attempts to prepare a trioxadamantane fragment suitable for application towards the synthesis of caloundrin B, only *ent*-10-*epi*-116 could be obtained in a reasonable yield. Therefore, it was decided to use *ent*-10-*epi*-116 towards the synthesis of *ent*-caloundrin B (*ent*-**3**). However, to pursue this objective, the configuration at C-10 in *ent*-10-*epi*-116 had to be corrected (Figure 2.5).

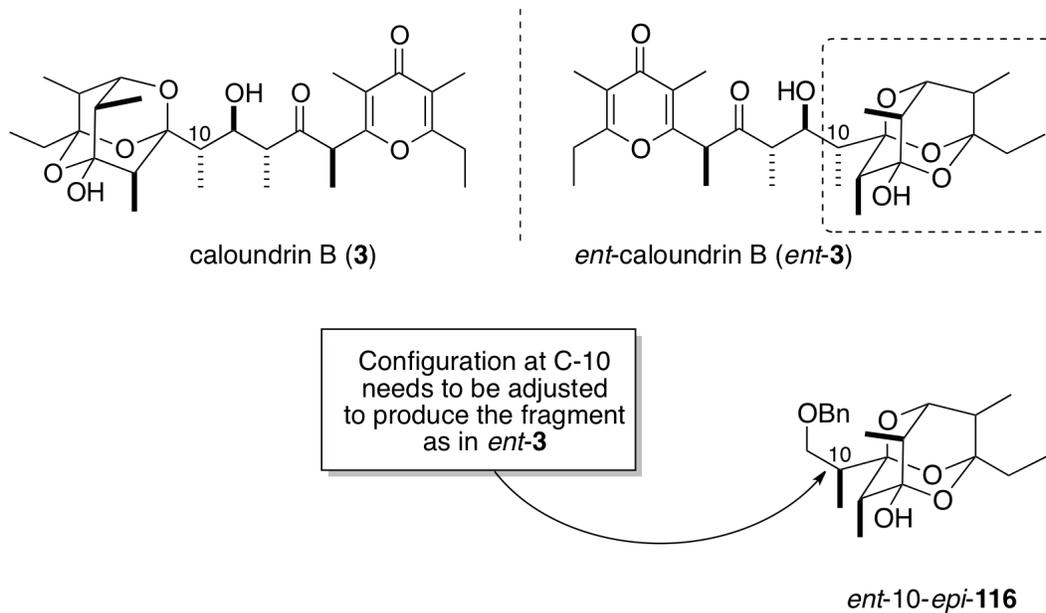
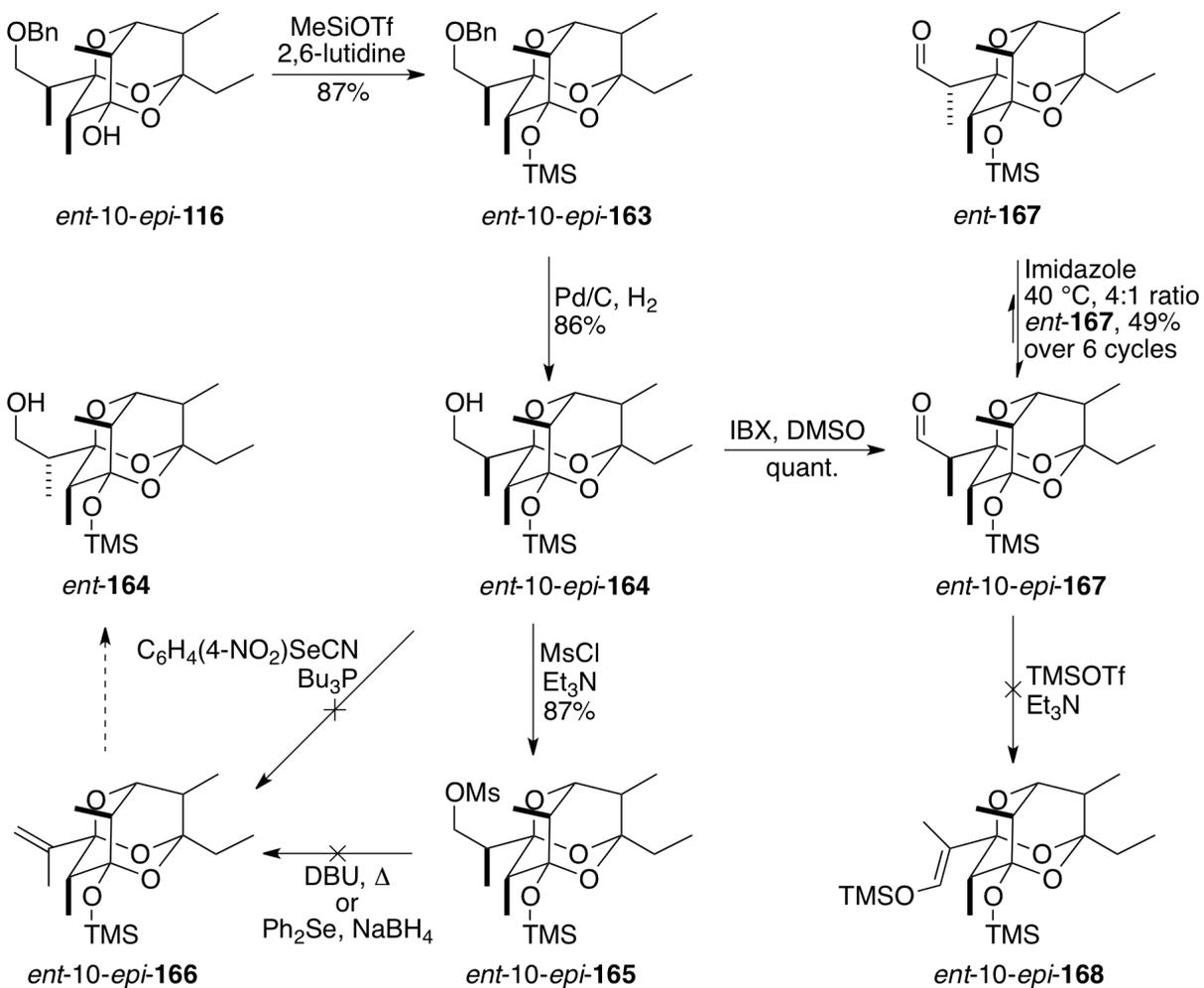


Figure 2.5 Structures of caloundrin B (**3**) and *ent*-**3**.

In order to prevent unfolding of the acid- and base-sensitive trioxaadamantane ring system in *ent*-10-*epi*-**116**, the alcohol was protected as its TMS ether by treatment with TMSOTf to furnish *ent*-10-*epi*-**163** in 87% yield. Then debenylation using Pd/C, H₂⁴⁸ of *ent*-10-*epi*-**163** produced alcohol *ent*-10-*epi*-**164** in 86% yield. At this point, efforts were directed towards elimination of the alcohol group in *ent*-10-*epi*-**164** with the expectation that the desired relative configuration could be installed by hydroboration of the resulting alkene; however, all attempts under different conditions (i.e. selenation,^{49, 50} mesylation) failed (Scheme 2.14).

Scheme 2.14 Attempts to invert the configuration at C-10 of *ent*-10-*epi*-**164** or *ent*-10-*epi*-**167**.



Oxidation of *ent*-10-*epi*-**164** with IBX in DMSO⁵¹ successfully afforded aldehyde *ent*-10-*epi*-**167** in quantitative yield. It was attempted to form the enol ether *ent*-10-*epi*-**167** with hopes of producing the desired aldehyde *ent*-**167** by hydrolysis under kinetic control. Again, all attempts exploring this approach failed.

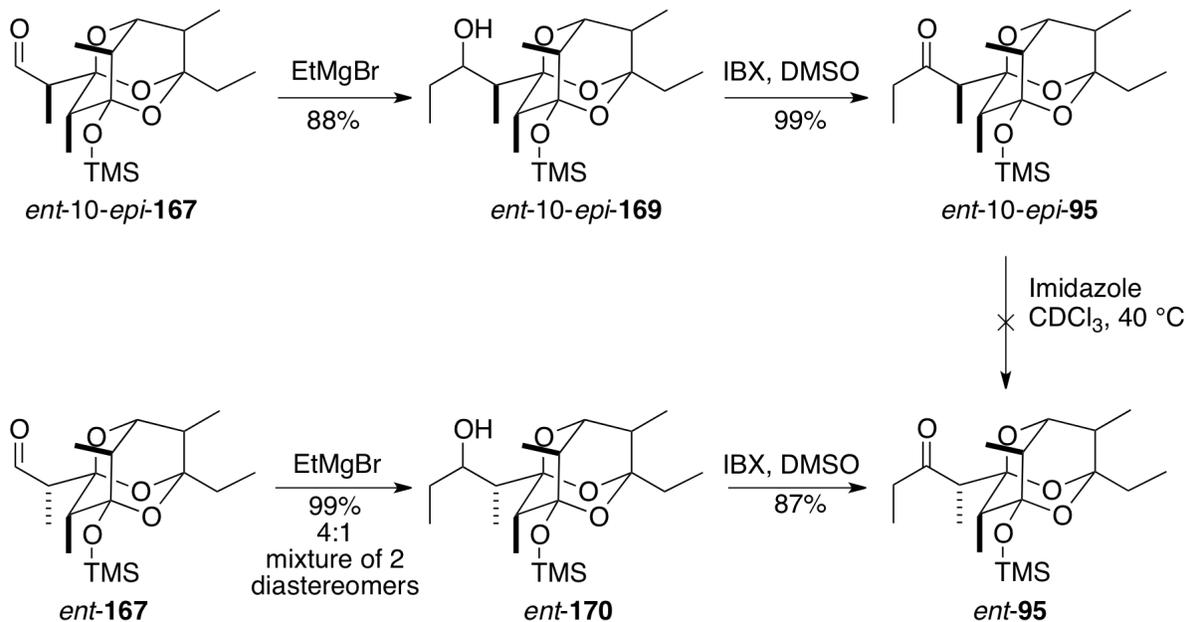
Finally, the isomerization of *ent*-10-*epi*-**167** under basic conditions was investigated. When a solution of *ent*-10-*epi*-**167** in CDCl₃ was exposed to imidazole at 40 °C for 1 day,⁵² a separable 4:1 equilibrium mixture of *ent*-10-*epi*-**167** and *ent*-**167** was produced. Similarly,

exposure of a solution of *ent*-10-*epi*-**167** in DMSO to L-proline⁵³ at room temperature for 10 days produced the same ratio of the two aldehydes. Despite the unfavourable equilibrium, submission of *ent*-10-*epi*-**167** to six isomerization cycles allowed aldehyde *ent*-**167** to be obtained in 49% yield along with recovered *ent*-10-*epi*-**167** in 28% yield.

An alternative method for epimerizing C-10 was attempted with ketone *ent*-10-*epi*-**95**. This ketone was prepared from aldehyde *ent*-10-*epi*-**167** by reaction with EtMgBr to afford essentially a single diastereomer of *ent*-10-*epi*-**169** in 88% yield that was oxidized with IBX in DMSO⁵¹ to produce ketone *ent*-10-*epi*-**95** in 99% yield. Unfortunately, *ent*-10-*epi*-**95** proved to be quite stable and no isomerization was observed in the presence of imidazole in CDCl₃. Nevertheless, the preparation of *ent*-10-*epi*-**95** was useful in the study of aldol reactions with kinetic resolution (see Section 2.4.4).

Reaction of aldehyde *ent*-**167** with EtMgBr produced *ent*-**170** as a 4:1 mixture of the two possible diastereomers in 99% yield. Without separation, *ent*-**170** was oxidized with IBX in DMSO⁵¹ to produce the desired ketone *ent*-**95** in 87% yield (Scheme 2.15). The preparation of *ent*-**95** opened the possibility to continue with the study of the next key step towards the synthesis of *ent*-**3**.

Scheme 2.15 Preparation of ketones *ent*-10-*epi*-95 and *ent*-95.



2.4 Application of aldol coupling with kinetic resolution to the synthesis of caloundrin B

2.4.1 The thiopyran route to polypropionates: design of aldol reactions that proceed with kinetic resolution.

The development of new strategies and their application in the synthesis of polypropionates is one of the main topics of research in the Ward group. A very solid methodology based on the aldol reaction of thiopyran units has been developed and applied to the synthesis of diverse marine polypropionates.²⁹ My contribution to this area involved the study of aldol reactions that proceed with kinetic resolution.⁴⁶

In all aldol reactions between two chiral fragments, three stereocontrol elements contribute to the stereochemical outcome of the resulting aldol products. These are: *i*) aldehyde diastereoface selectivity, *ii*) enolate diastereoface selectivity, and *iii*) relative topicity of the aldol reaction. Therefore, if the three stereocontrol elements are highly selective,^{‡‡} it would be possible

^{‡‡} In Heathcock's studies for acyclic stereoselection in aldol reactions he postulated that: "In reactions involving two chiral racemic compounds, the magnitude of mutual kinetic resolution depends upon the diastereoselectivity shown by the two reactants in their reactions with achiral reaction partners". Thus, application of the multiplicativity rule

to predict which would be the stereochemical outcome of the major product by application of the multiplicativity rule.⁵⁴⁻⁵⁶

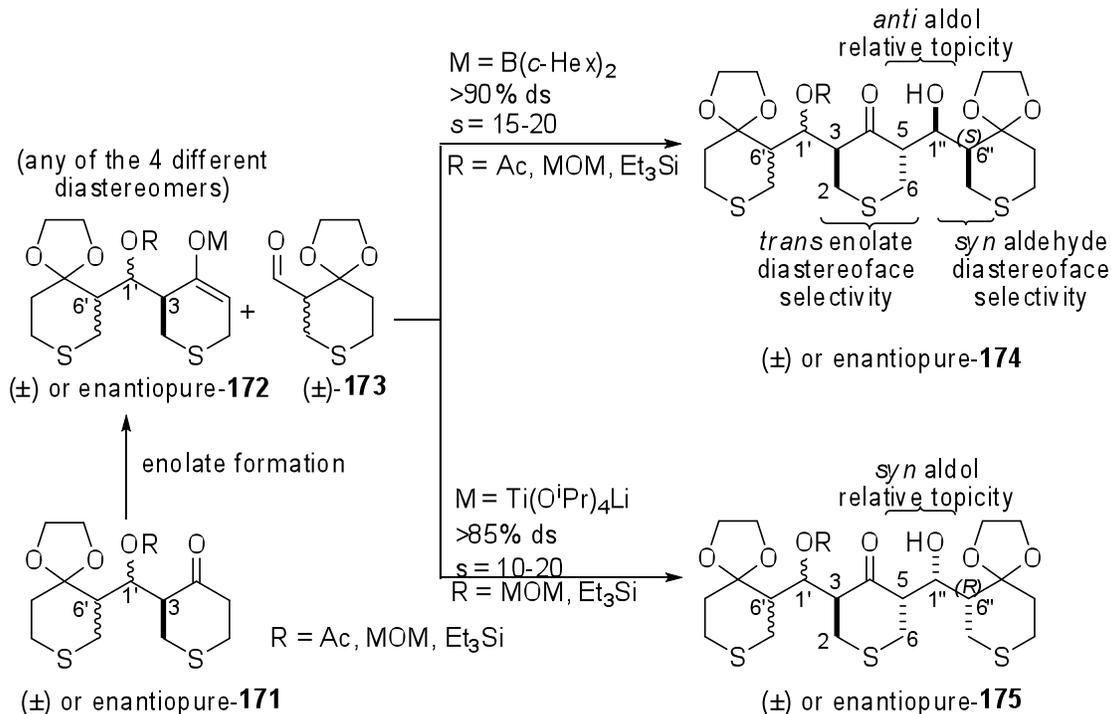
From previous studies in the Ward group, it was established that the enolate diastereoface selectivity of tetrapropionate aldol adducts **171** (Scheme 2.16) could be manipulated by the absence (i.e. 3,5-*syn* selectivity) or presence (i.e. 3,5-*trans* selectivity) of a protecting group on the C-1' OH group.⁴⁵ In addition, the diastereoface selectivity of the aldehyde **173** was shown to be highly Felkin selective; i.e., leading to products with a 1'',6''-*syn* relative configuration.⁴⁵ In this research, the development of conditions to switch the relative topicity (5,1''-*anti* or 5,1''-*syn*) of the aldol reactions between (\pm)-**171** and (\pm)-**173** were studied. Thereafter, the optimized conditions for the aldol reactions were performed with enantiopure ketone **171** in order to achieve kinetic resolution.^{§§}

High 5,1''-*anti* selectivity (i.e. **174**, $s = 15-20$) was achieved in reactions between (\pm)-**173** and the enol dicyclohexylborinates of the four diastereomeric aldol adducts (\pm)-**171**, whereas high 5,1''-*syn* selectivity (i.e. **175**, $s = 10-20$) was achieved in the same reactions by using the Ti(IV) 'ate' enolates of (\pm)-**171** formed by reaction of the LDA-generated Li enolates with Ti(O^{*i*}Pr)₄ (Scheme 2.16). The same aldol reactions using enantiopure ketones **171** with (\pm)-**173** proceeded with kinetic resolution allowing access to enantiopure aldol adducts **174** and **175**, which are useful for further application in synthesis. In addition, this strategy for achieving kinetic resolution was thought to be applicable to aldol reactions with suitable substrates and to other related processes.

to calculate the kinetic resolution selectivities ($s = k_{\text{fast}}/k_{\text{slow}}$) in aldol couplings of chiral reactants gives: $s = (E \cdot R \cdot A + E + R + A) / (E \cdot R + E \cdot A + R \cdot A + 1)$, where E = enolate diastereoface selectivity; A = aldehyde diastereoface selectivity; R = relative topicity of the coupling.

^{§§} This work was developed in collaboration with Mohammad M. Zahedi.

Scheme 2.16 Rational design of aldol reactions with kinetic resolution.



2.4.2 Non-linear effects in the enantiotopic group selectivity of aldol reactions of chiral reactants

To identify conditions for kinetic resolution, reactions of racemic reactants **171** and **173** were screened under numerous conditions. When both reactants are racemic these reactions occur with mutual kinetic enantioselection (MKE) and appropriate analysis of the distribution of diastereomers formed allows determination of the ratio of rate constants in the related KR when one of the reactants is enantiopure and the other is racemic (i.e. $s = k_{\text{fast}}/k_{\text{slow}}$).⁵⁷

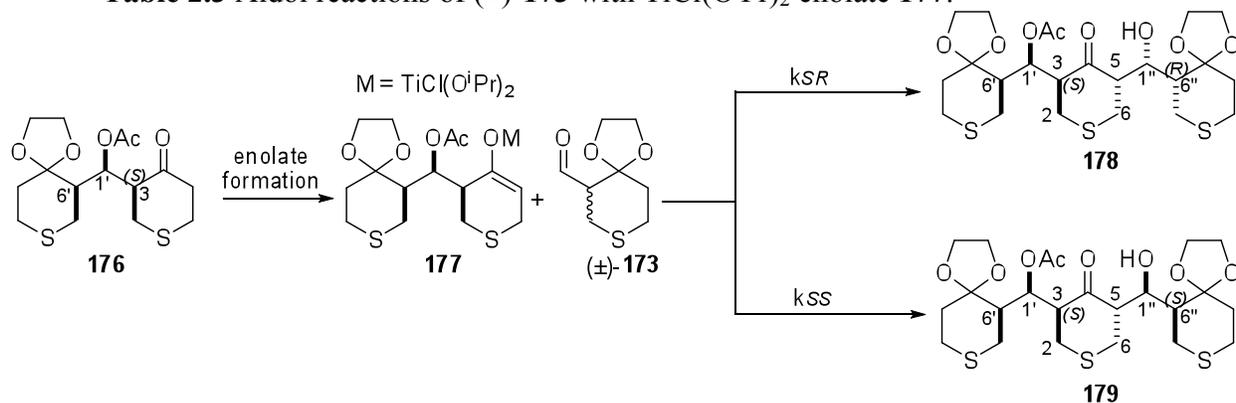
After optimization of the reaction between (\pm)-**176** and (\pm)-**173** with $\text{TiCl}_2(\text{O}^i\text{Pr})_2$ to produce 5,1''-*syn* selectivity,⁵⁸ the same conditions were applied using enantioenriched enolate **177** (i.e. $>94\%$ ee) and racemic (\pm)-**173** in order to perform KR and produce enantioenriched aldol adduct **178**. Surprisingly, the selectivity of this reaction did not follow the expected behaviour (i.e. $SR/SS = k_{SR}/k_{SS}$).

Performing a series of aldol reactions of racemic (\pm)-**173** with ketone **176** of varying enantiomeric purities (Table 2.3, entries 1-7) demonstrated that the diastereoselectivity of the reaction decreased as the ee of **176** increased. In addition, similar results were observed when ketone aldol adduct (3,1'-*syn*, 6',1'-*anti* **171**, R = Ac) was used.^{***} Non-linear relationships between the enantiopurity of a reagent and the enantioselectivity of its reactions have been observed previously and are usually attributed to reaction mechanisms involved dimeric or oligomeric species.⁵⁹⁻⁶² However, there appears to be no previous reports of a non-linear relationship between the enantiopurity of a reactant and its enantiomer selectivity in a kinetic resolution.

It is known that Ti(IV) species can exist as dimers in solution.⁶³ Therefore, if dimeric Ti species are formed during the reaction and both reactants are racemic, then the presence of homochiral or heterochiral Ti(IV) 'dimers' can be present in solution. In contrast, if both reactants are enantiopure, only homochiral 'dimers' are possible. As a consequence, it was hypothesized that different reactivities and concentrations of diastereomeric Ti(IV) 'dimers' were the cause of the observed change in the selectivities of the reactions with racemic vs. enantiopure **177**. That is, the formation of the putative homochiral Ti(IV) 'dimers' would become increasingly favored as the enolate used was increasingly enantioenriched. If the reaction of the putative homochiral Ti 'dimer' was less selective than that of the heterochiral 'dimer' and if the formation of the heterochiral 'dimer' was thermodynamically favored, then the results observed in Table 2.3, entries 1-7, could be rationalized.

^{***} Reactions performed by Mohammad M. Zahedi.

Table 2.3 Aldol reactions of (\pm)-**173** with TiCl(O^{*i*}Pr)₂ enolate **177**.



Entry	Enolate ^a	(\pm)- 173 (equiv)	ee of 176 (%)	Conversion ^d (%)	178/179 ^d
1	(\pm)- 177	2	0	81	15 : 1
2	(-)- 177	2	20	73	13 : 1
3	(-)- 177	2	39	70	10 : 1
4	(-)- 177	2	60	77	6 : 1
5	(-)- 177	2	78	72	4.5 : 1
6	(-)- 177	2	98	81	4 : 1
7	(-)- 177	3	98	81	4 : 1
8	(\pm)- 177 ^b	2	0	84	16 : 1
9	(\pm)- 177 ^c	2	0	55	19 : 1
10	(-)- 177 ^b	2	98	82	4 : 1
11	(-)- 177 ^c	2	98	56	9 : 1
12	(\pm)- 177	0.5	0	quant	17 : 1
13	(\pm)- 177 ^b	(+) 0.5	0	quant	4 : 1

^a Reactions at -78 °C in CH₂Cl₂, TiCl₂(O^{*i*}Pr)₂ (4.0 equiv), ^tPr₂NEt (4.0 equiv), enolization time 4 h, reaction time 3 h, reaction concentration 0.06 M. ^b Reaction concentration 0.1 M. ^c Reaction concentration 0.02 M. ^d Conversions and **178/179** ratios were determined by ¹H-NMR from the crude sample.

Interestingly, when the reaction was performed at lower concentrations, the selectivity slightly improved (Table 2.3, entries 1 and 9). Because lower concentrations should reduce proportion of Ti(IV) 'dimers', this observation implied that the reaction of monomeric species was more selective than that of 'dimers.' Consistent with that observation, when the reactions of enantioenriched enolate were conducted at lower concentration, the selectivity increased markedly (Table 2.3, entries 6 and 11).

Surprisingly, performing the aldol reaction between racemic enolate **177** and a deficiency of enantioenriched aldehyde **173** also showed poor selectivity (Table 2.3, entries 12 and 13). The

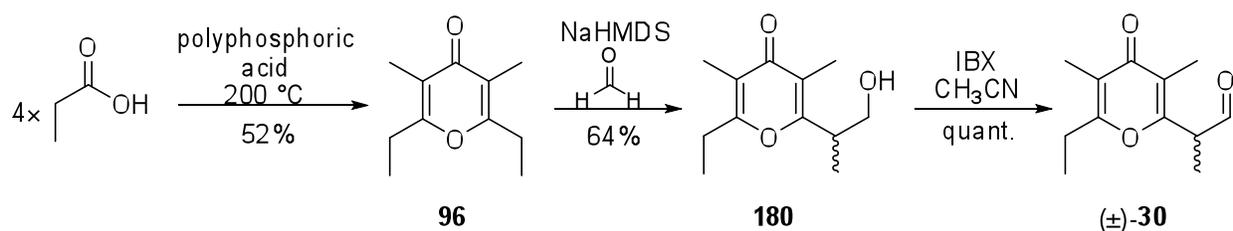
observed result indicates that the enantiopurity of the aldehyde was also contributing to the non-linear behavior. Thus, it seems that a more complex system perhaps involving coordination of aldehyde **173** to a dimeric species of the Ti(IV) enolate of **177** was involved.

In conclusion, the nonlinear effect in the selectivity was characterized using two different substrates. Apparently, both ketone **176** and aldehyde **173** contributed to the selectivity in the reaction, and as a consequence, the relative facility of the *like* vs. *unlike* combination of reactant enantiomers (i.e., k_{SR}/k_{SS}) is dependent on the ee of both reactants, this observation appears to be unprecedented.

2.4.3 Study of the selectivity in the aldol reactions between 3-pentanone and racemic 2-(6-ethyl-3,5-dimethyl-4-oxo-4H-pyran-2-yl)propanal

The racemic aldehyde bearing the γ -pyrone fragment (**30**) was successfully elaborated from propionic acid using the conditions of Mullock and Suschitzky to generate the γ -pyrone **96**.⁴³ Subsequently, an aldol-type reaction of paraformaldehyde with the anion generated by treatment of **96** with NaHMDS afforded alcohol **180**,⁴² that was oxidized with IBX to produce the desired racemic aldehyde **30** in quantitative yield.^{†††}

Scheme 2.17 Preparation of aldehyde (\pm)-**30**.

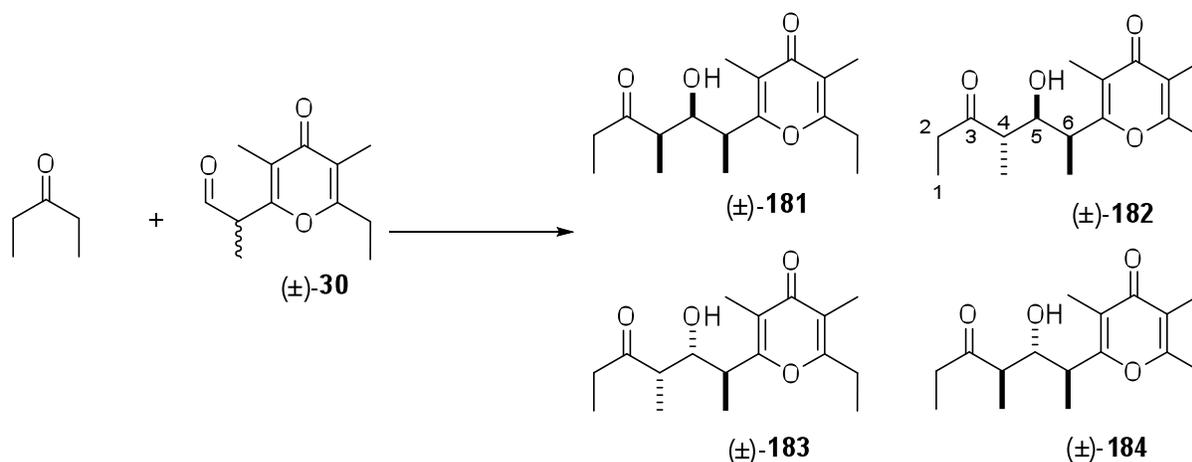


To establish the diastereoface selectivity of aldehyde **30**, various aldol reactions were performed with 3-pentanone (Table 2.4). Reaction of the LiHMDS-generated Li enolate of 3-pentanone⁶⁴ with (\pm)-**30**, produced a mixture of **181** (39%), **182** (9%), and **183** (10%); i.e., 83%

^{†††} The procedure for preparation of aldehyde (\pm)-**30** was studied and developed by Leon Lai, unpublished results.

of products resulted from Felkin addition to **30**. Similar reaction of the Sn(II) enolate of 3-pentanone (prepared by reaction with Sn(OTf)₂/Et₃N,⁶⁵ known to produce *Z* enolates) with (±)-**30** gave the Felkin adduct **181** as the sole product. Reaction of the (*E*)-boron enolate of 3-pentanone (*c*-Hex)₂BCl/Et₃N⁶⁶ gave a 20:1 mixture of the Felkin adducts **182** and **181**, respectively. In contrast, reaction of the (*E*)-lithium enolate of 3-pentanone (LiN^tBu(SiMe₃)⁶⁷ gave a 1.8:1 mixture of the same adducts. Despite the poorly selective relative topicity observed in the reaction, addition to the aldehyde (±)-**30** was highly Felkin selective. Finally, exchange of the LiN^tBu(SiMe₃)-produced Li enolate of 3-pentanone with (*c*-Hex)₂BCl, in order to produce a boron enolate,⁶⁸⁻⁷⁰ followed by reaction with (±)-**30** produced a 5.9:1 mixture of **182** and **181**, respectively. In contrast to the aldol reaction of the unadulterated Li enolate, addition of (*c*-Hex)₂BCl resulted in marked improvement in stereoselectivity favoring the 4,5-*anti* product **182**, but was less selective than the reaction of the traditionally prepared boron enolate. Again, high Felkin selectivity was observed for addition to (±)-**30**.

Table 2.4 Aldol reactions between pentanone and racemic 2-(6-ethyl-3,5-dimethyl-4-oxo-4*H*-pyran-2-yl) propanal.



Entry	Enolate	Aldol products ^f
1 ^a	LiHMDS	181 (39%), 182 (9%), 183 (10%)
2 ^b	Sn(OTf) ₂	181 (67%)
3 ^c	(<i>c</i> -Hex) ₂ BCl	182:181 (20:1), 95% conversion
4 ^d	LiN ^t Bu(SiMe ₃)	182:181 (1.8:1), 90% conversion
5 ^e	i) LiN ^t Bu(SiMe ₃), ii) (<i>c</i> -Hex) ₂ BCl	182:181 (5.9:1), 91% conversion

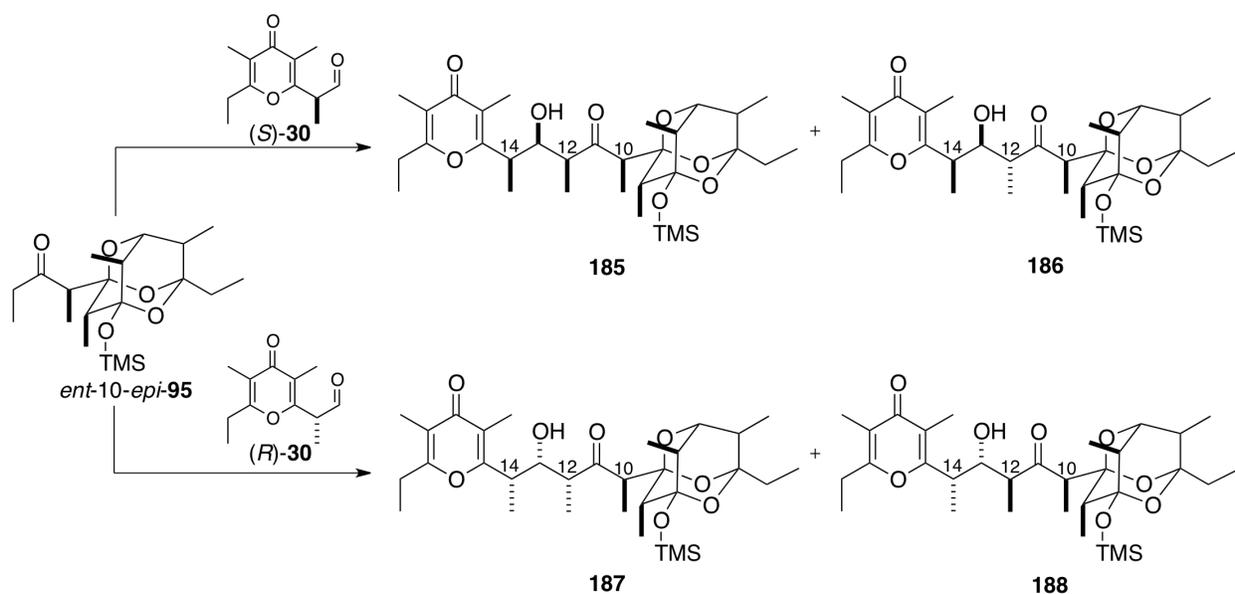
^a 3-pentanone (0.480 mmol, 2 equiv), (±)-**30** (0.240 mmol, 1 equiv), LiHMDS (0.504 mmol, 2.1 equiv), at -78 °C in THF for 30 min. Isolated yield after FCC. ^b 3-pentanone (0.692 mmol, 3 equiv), (±)-**30** (0.230 mmol, 1 equiv), Sn(OTf)₂ (0.899 mmol, 3.9 equiv), Et₃N (1.037 mmol, 4.5 equiv) at -78 °C in CH₂Cl₂. Enolate formation 30 min and aldol reaction for 2 h. Isolated yield after FCC. ^c 3-pentanone (0.120 mmol, 1 equiv), (±)-**30** (0.120 mmol, 1 equiv), (*c*-Hex)₂BCl (0.132 mmol, 1.1 equiv), Et₃N (0.144 mmol, 1.2 equiv), enolate formation at 0 °C for 1 h and aldol reaction at -50 °C for 3 h in ethyl ether. Conversion calculated from ¹H-NMR of the crude. ^d 3-pentanone (0.120 mmol, 1 equiv), (±)-**30** (0.120 mmol, 1 equiv), LiN^tBu(SiMe₃) (0.132 mmol, 1.1 equiv) at -78 °C in THF. Enolate formation 30 min and aldol reaction 5 min. Conversion calculated from ¹H-NMR of the crude. ^e Same amounts as in entry 4. Li enolate formation 15 min and then (*c*-Hex)₂BCl (0.120 mmol, 1 equiv) for 15 min. ^f The set of aldol adducts **181**, **182**, **183**, and **184** were previously synthesized and characterized by Leon Lai.

From the above studies, it was observed that the aldol reactions of 3-pentanone with aldehyde (±)-**30** were highly Felkin selective under a variety of experimental conditions. Therefore, the study of enolate diastereoface selectivity for *ent*-**95** and *ent*-10-*epi*-**95** under different experimental conditions in order to produce the precursor to *ent*-caloundrin B (*ent*-**3**) were investigated.

2.4.4 Study of the stereoselectivity of aldol reactions between the enantiopure trioxaadamantane ketone fragment and the racemic pyrone aldehyde fragment

Having in mind that aldehyde (\pm)-**30** is highly Felkin selective, aldol reactions of (\pm)-**30** with ketones *ent*-**95** and *ent*-10-*epi*-**95** can produce up to four adducts with Felkin selectivity (Scheme 2.18).

Scheme 2.18 Possible products from the aldol reaction of *ent*-10-*epi*-**95** and (\pm)-**30**, assuming that Felkin aldehyde diastereoface selectivity is favored.



As was observed in the aldol reaction of (\pm)-**30** with 3-pentanone, the aldol reaction of the LiHMDS-generated Li enolate of *ent*-10-*epi*-**95** with (\pm)-**30** exhibited poor stereoselectivity producing a mixture of four diastereomers in a 1.3:1.3:0.8:1 ratio as determined by $^1\text{H-NMR}$ of the crude reaction mixture. In contrast, addition of (\pm)-**30** to the putative (*Z*)-boron enolate prepared from reaction of *ent*-10-*epi*-**95** with 9-BBN-OTf and Et_3N ^{66, 71} gave a 7:1 mixture of two aldol adducts. The major adduct, **185**, was isolated in 74% yield. Reduction of **185** with $\text{NaBH}(\text{OAc})_3$ ⁷² afforded 78% yield of crystalline diol **189**. X-ray analysis of diol **189** established the indicated relative configuration of the molecule.

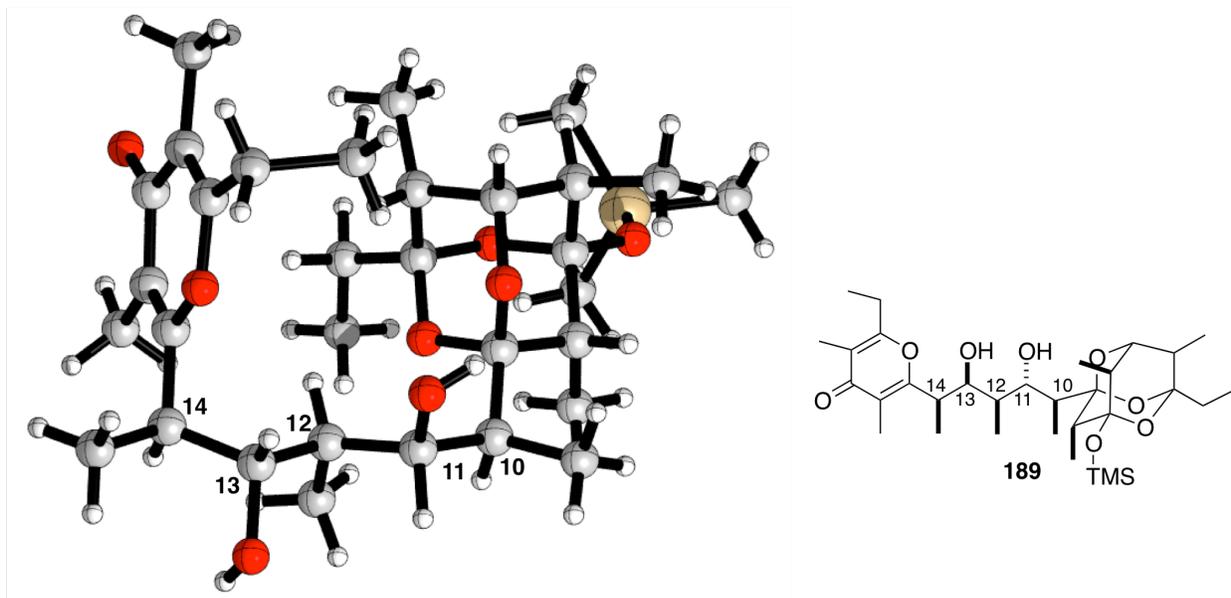


Figure 2.6 ORTEP representation for **189**.

The structure of **189** shows that the initial aldol reaction of *ent*-10-*epi*-**95** with (\pm)-**30** proceeded predominantly with 12,13-*syn* relative topology, Felkin aldehyde diastereoface selectivity (13,14-*syn*), and 10,12-*syn* enolate diastereoface selectivity. The relative topology of the reaction agreed with the reports in the literature for the diastereoselectivity observed from (*Z*)-enolates in acyclic systems.⁶⁶ However, the Felkin aldehyde diastereoface selectivity observed was opposite to the generally expected results in aldol reactions of chiral *Z*-enolates and chiral 2-Me aldehydes (i.e. 10,12-*anti*-12,13-*syn*-13,14-*anti*).⁷³ A possible explanation could be that the pyrone group in aldehyde (\pm)-**30** resembles that of a phenyl group, where the addition to the aldehyde occurs predominantly at the Felkin face.

In addition, the ¹³C chemical shifts from C-12 to C-16 of aldol adduct **185** were very close to those of the model aldol adduct **181** (Table 2.5 and Chart 2.2).

Scheme 2.19 Derivatization of **185** to determine the relative configuration.

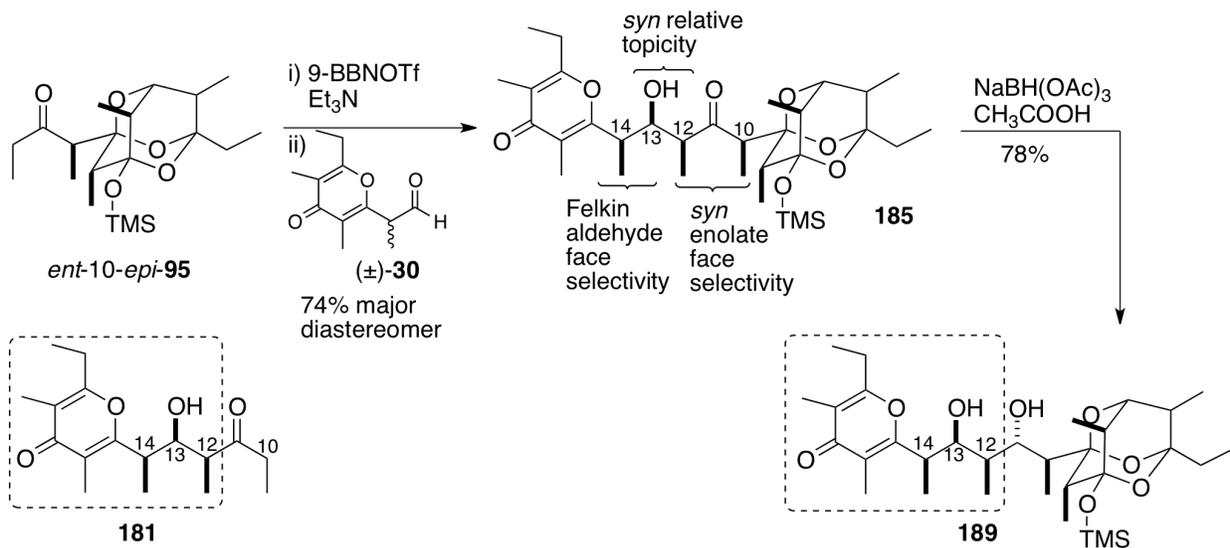
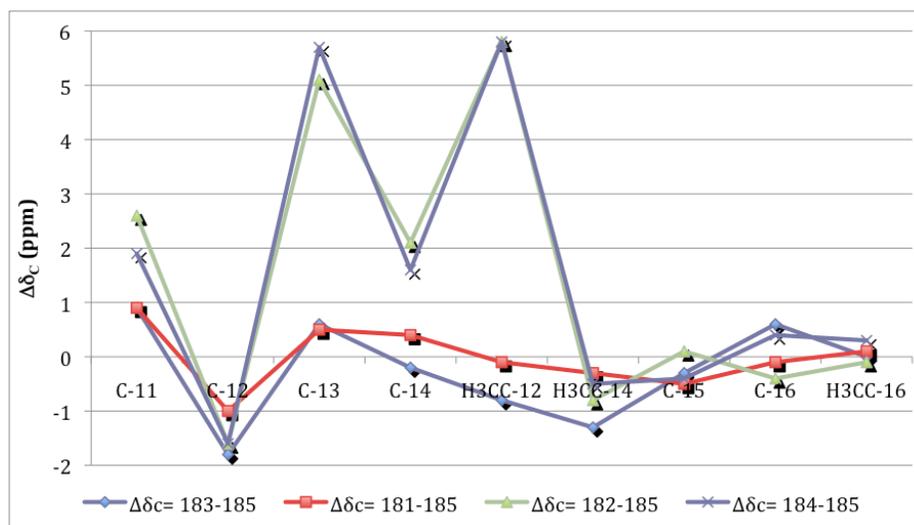


Table 2.5 Comparison of ¹³C-NMR chemical shifts of aldol adducts **181**, **182**, **183**, **184**, and **185**.

Assignment	183	181	182	184	185
	δ _C (ppm)	δ _C (ppm)	δ _C (ppm)	δ _C (ppm)	δ _C (ppm)
	12,13- <i>syn</i> 13,14- <i>anti</i>	12,13- <i>syn</i> 13,14- <i>syn</i>	12,13- <i>anti</i> 13,14- <i>syn</i>	12,13- <i>anti</i> 13,14- <i>anti</i>	
C-11	216.3	216.3	218	217.3	215.4
C-12	46.8	47.6	47.0	47.0	48.6
C-13	72.5	72.4	77.0	77.6	71.9
C-14	38.2	38.8	40.5	40.0	38.4
H ₃ CC-12	9.3	10.0	15.9	15.9	10.1
H ₃ CC-14	14.7	15.7	15.2	15.5	16
C-15	164.1	163.9	164.5	164	164.4
C-16	119.7	119.0	118.7	119.5	119.1
H ₃ CC-16	9.8	9.9	9.7	10.1	9.8

Chart 2.2 Comparison of ^{13}C -NMR chemical shifts of **185** with those of the model aldol adducts (**181**, **182**, **183**, and **184**).



In addition, when the ^1H -NMR chemical shifts of **185** and those of the model adducts **181**, **182**, **183**, and **184** were compared, the characteristic signal for HC-13 indicated that the product had a 12,13-*syn* selectivity and that for H₃CC-14 indicated that the product had a 13,14-*syn* selectivity (Table 2.6). This is, the relative topicity of the aldol reaction was 12,13-*syn* and the diastereoface selectivity for addition to the aldehyde was Felkin (13,14-*syn*) (Table 2.6).

Table 2.6 Comparison of ^1H -NMR chemical shifts of aldol adducts **181**, **182**, **183**, **184** and **185**.

Assignment	183	181	182	184	185
	δ_{H} (ppm)				
	12,13- <i>syn</i>	12,13- <i>syn</i>	12,13- <i>anti</i>	12,13- <i>anti</i>	
	13,14- <i>anti</i>	13,14- <i>syn</i>	13,14- <i>syn</i>	13,14- <i>anti</i>	
HC-12	2.71	2.37-2.28	2.54-2.42	2.78	2.92
HC-13	4.20	4.18	3.68	3.74	4.32
HC-14	3.08	3.00	3.04	3.12	3.07
H ₃ C-12	1.22	1.08	1.22	1.29	1.14
H₃C-14	1.13	1.33	1.32	1.23	1.34
H ₃ C-16	1.95	1.96	1.84	1.97	1.98
H ₃ C-18	1.92	1.92	1.91	1.94	1.92

Aldol reaction of (\pm)-**30** with the putative (*E*)-boron enolate prepared from *ent*-10-*epi*-**95** and (*c*-Hex)₂BCl/Et₃N⁶⁶ produced a 4:1 a mixture of adducts in 83% yield. Following the trends from previous results with the (*Z*)-enolate and knowing that the aldehyde (\pm)-**30** has a strong bias for aldol addition with Felkin selectivity, it was presumed that both products resulted from Felkin addition (13,14-*syn*). Because the products were derived from a (*E*)-boron enolate, presumably both products had a 12,13-*anti* relative configuration. Therefore, it was hypothesized that the enolate diastereoface selectivity led to a major product with 10,12-*syn* relative configuration and a minor compound with 10,12-*anti* relative configuration. Although the relative configurations for the aldol adducts were not confirmed, comparison of their ¹H-NMR signals for HC-13 and H₃CC-14 (Table 2.7) and ¹³C-NMR chemical shifts with those for the model adducts **181**, **182**, **183**, and **184** suggested that the major product was **188** and the minor product was **186** (Chart 2.3 and 2.4).

Table 2.7 Comparison of ¹H-NMR chemical shifts of aldol aducts **181**, **182**, **183**, **184**, **186** and **188**.

Assignment	183	181	182	184	186	188
	δ_H (ppm)	δ_H (ppm)	δ_H (ppm)	δ_H (ppm)	δ_H (ppm)	δ_H (ppm)
	12,13- <i>syn</i> 13,14- <i>anti</i>	12,13- <i>syn</i> 13,14- <i>syn</i>	12,13- <i>anti</i> 13,14- <i>syn</i>	12,13- <i>anti</i> 13,14- <i>anti</i>		
HC-12	2.71	2.37-2.28	2.54-2.42	2.78	3.04	3.12
HC-13	4.20	4.18	3.68	3.74	3.82	3.83
HC-14	3.08	3.00	3.04	3.12	3.38	2.91
H ₃ C-C12	1.22	1.08	1.22	1.29	1.28	1.13
H₃C-C14	1.13	1.33	1.32	1.23	1.31	1.30
H ₃ C-16	1.95	1.96	1.84	1.97	1.88	2.02 or 1.87
H ₃ C-18	1.92	1.92	1.91	1.94	1.93	2.02 or 1.87

Chart 2.3 Comparison of ^{13}C -NMR chemical shifts of **188** (major compound) with those of the model aldol adducts (**181**, **182**, **183**, and **184**).

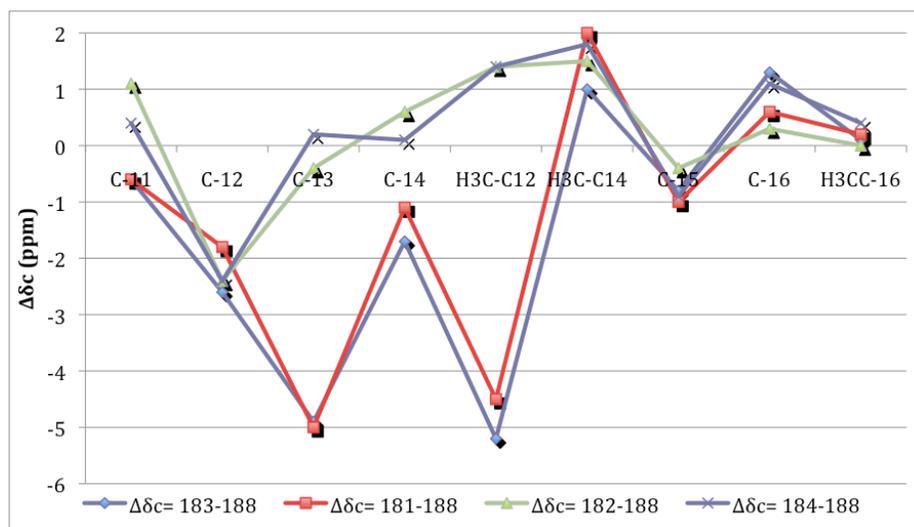
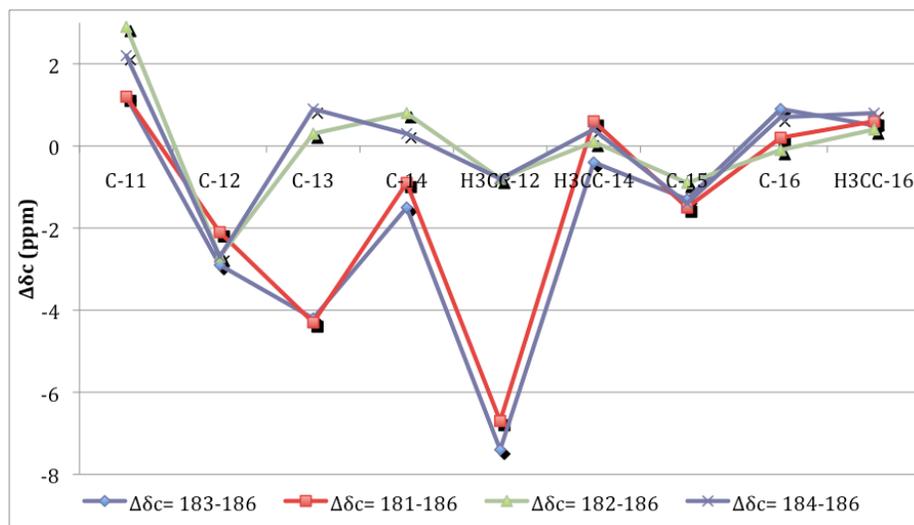


Chart 2.4 Comparison of ^{13}C -NMR chemical shifts of **186** (minor compound) with those of the model aldol adducts (**181**, **182**, **183**, and **184**).

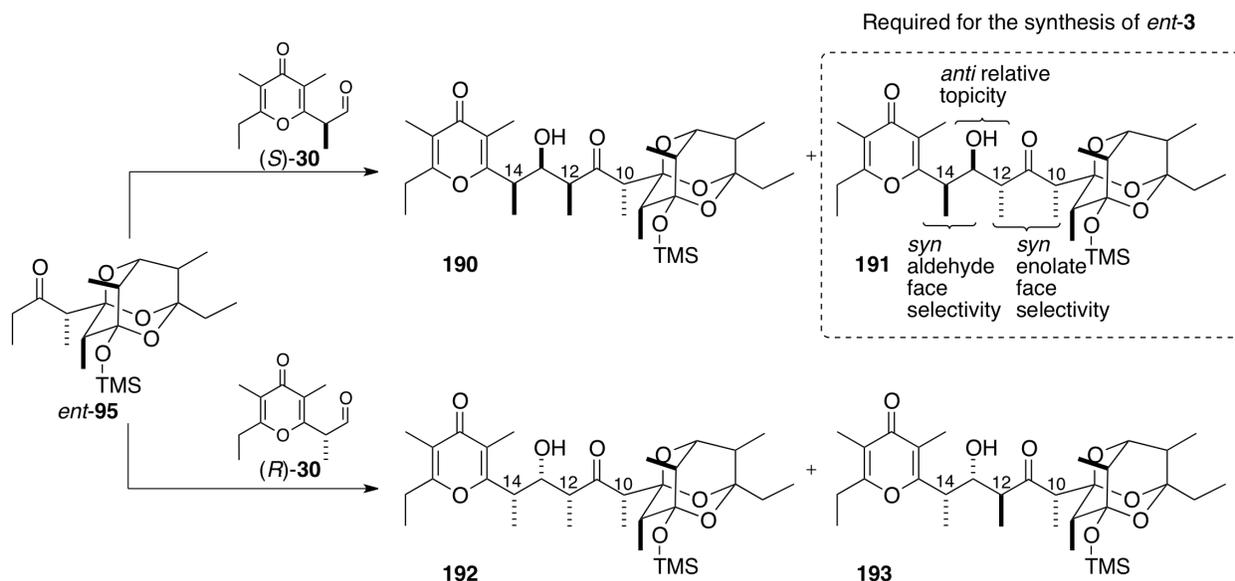


In summary, it was confirmed that the aldehyde (\pm)-**30** had a strong preference towards Felkin selectivity in aldol reactions under the experimental conditions examined. In addition, the enolate diastereoface selectivity for both (*E*) and (*Z*) boron enolates of *ent*-10-*epi*-**95** led

preferentially to 10,12-*syn* aldol adducts and reactions with (\pm)-**30** proceeded with kinetic resolution with moderate selectivity.

In order to synthesize *ent*-**3**, it was necessary to prepare aldol adduct **191**. Compound **191** would arise from an aldol reaction between *ent*-**95** and (*S*)-**30**. From the studies above, it was anticipated that aldol reactions of an (*E*)-boron enolate of *ent*-**95** would produce adducts with 10,12-*syn*-12,13-*anti* relative configuration and that reaction with the Felkin-selective (\pm)-**30** would proceed via kinetic resolution with preferential reaction of (*S*)-**30** to give **191**. However, attempted reaction of *ent*-**95** with (*c*-Hex)₂BCl/Et₃N followed by addition of (\pm)-**30** gave a mixture of mainly *anti* aldol adducts, apparently corresponding to **191** and **193** (Scheme 2.20), in very low yield. The low conversion was attributed to ineffective formation of the boron enolate; thus, alternative conditions to produce the (*E*)-enolate of *ent*-**95** were investigated.

Scheme 2.20 Aldol reaction of enantiopure *ent*-**95** and (\pm)-**30** assuming that Felkin aldehyde diastereoface selectivity is favored.



There are few reports on the stereoselective formation of (*E*) Li-enolates.^{67, 74, 75} As previously attempted with 3-pentanone, the reaction of *ent*-**95** with LiN^tBuSiMe₃, known to

produce (*E*)-Li enolates from ethyl ketones,⁶⁷ followed by addition of (\pm)-**30** produced a mixture of 4 different aldol adducts. After fractionation, the two major aldol products were obtained that were tentatively assigned as 12,13-*syn* aldol adducts **190** and **192** by comparison of their ¹H and ¹³C chemical shifts with those of the model compounds **181**, **182**, **183**, and **184** (Table 2.8, Chart 2.5 and 2.6).

Table 2.8 Comparison of ¹H-NMR chemical shifts of aldol adducts **181**, **182**, **183**, **184**, **190** and **192**.

Assignment	183	181	182	184	190	192
	δ_{H} (ppm)	δ_{H} (ppm)	δ_{H} (ppm)	δ_{H} (ppm)	δ_{H}	δ_{H}
	12,13- <i>syn</i> 13,14- <i>anti</i>	12,13- <i>syn</i> 13,14- <i>syn</i>	12,13- <i>anti</i> 13,14- <i>syn</i>	12,13- <i>anti</i> 13,14- <i>anti</i>		
HC-12	2.71	2.37-2.28	2.54-2.42	2.78	2.78	2.73
HC-13	4.20	4.18	3.68	3.74	4.08	4.05
HC-14	3.08	3.00	3.04	3.12	3.04	3.03
H ₃ CC-12	1.22	1.08	1.22	1.29	1.09	1.07
H₃CC-14	1.13	1.33	1.32	1.23	1.35	1.34
H ₃ C-16	1.95	1.96	1.84	1.97	1.99	1.98
H ₃ C-18	1.92	1.92	1.91	1.94	1.95	1.95

Chart 2.5 Comparison of ¹³C-NMR chemical shifts of **190** (minor compound) with those of the model aldol adducts (**181**, **182**, **183**, and **184**).

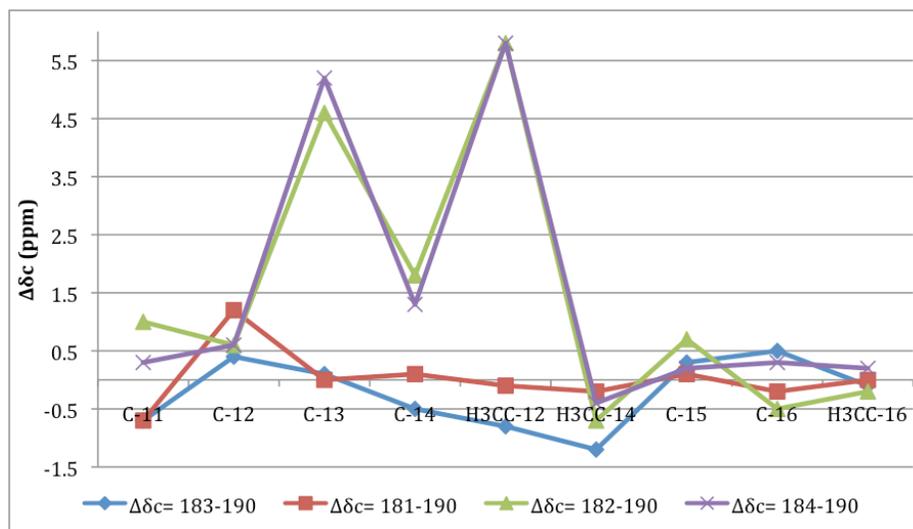
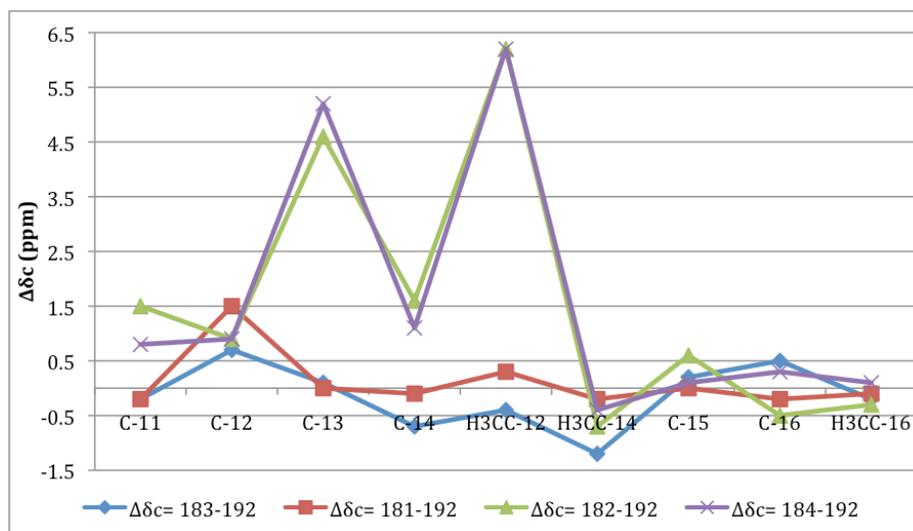


Chart 2.6 Comparison of ^{13}C -NMR chemical shifts of **192** (major compound) with those of the model aldol adducts (**181**, **182**, **183**, and **184**).



Because formation of the (*E*)-boron enolate of *ent*-**95** was not efficient using (*c*-Hex) $_2$ BCl/Et $_3$ N, it was decided to attempt 'transmetallation' of (*E*) Li enolate with (*c*-Hex) $_2$ BCl. The conditions used were inspired by the early reports by Hoffmann et al. on the formation of boron enolates by transmetallation of the corresponding Li enolates.^{68, 69}

Reaction of *ent*-**95** with LiN^{*t*}Bu(SiMe $_3$) followed by addition of (*c*-Hex) $_2$ BCl and, after 75 min, addition of (\pm)-**30** produced one major aldol adduct isolated in 60% yield along with 18% of a 2:1 mixture of other aldol adducts (Scheme 2.21). The stereoselectivity of this reaction was very different from that observed in the reaction of the LiN^{*t*}Bu(SiMe $_3$)-generated enolate without addition of (*c*-Hex) $_2$ BCl. The major product was tentatively assigned as **191** with 12,13-*anti*-13,14-*syn* relative configuration by comparison of its ^1H and ^{13}C chemical shifts with those of the model compounds **181**, **182**, **183**, and **184** (Table 2.9 and Chart 2.7). A 10,12-*syn* relative configuration for **191** was presumed based in literature reports on the diastereoface selectivity of (*E*)-enolates of chiral ethyl ketones in aldol reactions.⁷⁶⁻⁷⁹ Based on its assigned structure, aldol **191** was subjected to the transformations described in Section 2.5 towards the synthesis of *ent*-**3**.

Scheme 2.21 Aldol reactions of *ent*-**95** and (\pm)-**30** under different conditions.

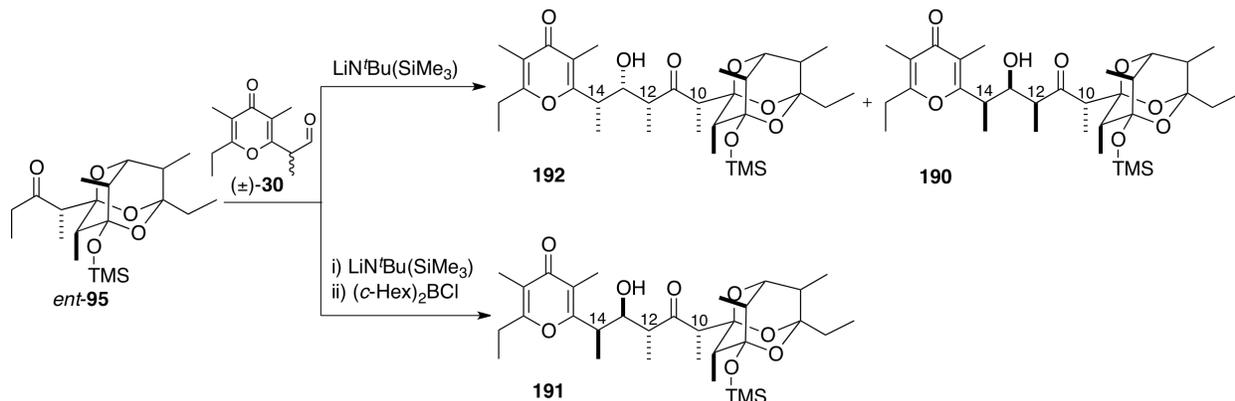
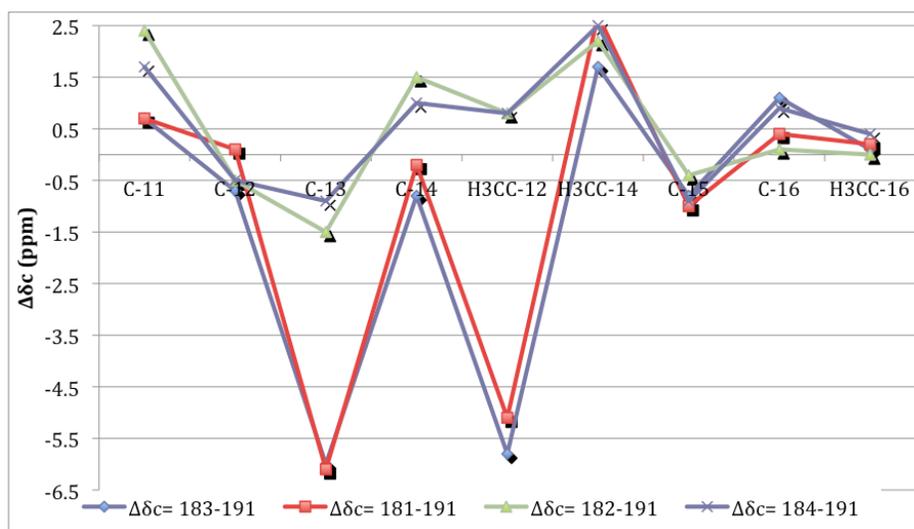


Table 2.9 Comparison of $^1\text{H-NMR}$ chemical shifts of aldol adducts **181**, **182**, **183**, **184**, and **191**.

Assignment	183	181	182	184	191
	δ_{H} (ppm)	δ_{H} (ppm)	δ_{H} (ppm)	δ_{H} (ppm)	δ_{H}
	12,13- <i>syn</i> 13,14- <i>anti</i>	12,13- <i>syn</i> 13,14- <i>syn</i>	12,13- <i>anti</i> 13,14- <i>syn</i>	12,13- <i>anti</i> 13,14- <i>anti</i>	
HC-12	2.71	2.37-2.28	2.54-2.42	2.78	2.93
HC-13	4.20	4.18	3.68	3.74	3.89
HC-14	3.08	3.00	3.04	3.12	3.11
H ₃ C-C12	1.22	1.08	1.22	1.29	1.12
H₃C-C14	1.13	1.33	1.32	1.23	1.29
H ₃ C-16	1.95	1.96	1.84	1.97	1.92 or 1.93
H ₃ C-18	1.92	1.92	1.91	1.94	1.92 or 1.93

Chart 2.7 Comparison of ^{13}C -NMR chemical shifts of **191** (major compound) with those of the model aldol adducts (**181**, **182**, **183**, and **184**).



In summary, aldol reactions of *ent*-10-*epi*-**95** and *ent*-**95** with (\pm)-**30** produced various aldol adducts under different conditions and proceeded with kinetic resolution with moderate to good enantioselectivity. It was possible to establish that additions to (\pm)-**30** were highly Felkin selective under all conditions used. The relative topicity of the aldol reaction could be modulated by varying the enolate geometry to produce either 12,13-*syn* or 12,13-*anti* products and the enolate diastereoface selectivity preferentially gave 10,12-*syn* products in most cases.

2.5 Synthesis of *ent*-caloundrin B (*ent*-**3**)

With aldol adduct **191** in hand, the completion of the synthesis of *ent*-**3** was envisaged. A 1,3-*syn* selective reduction of **191** was achieved by treatment with Et_2BOMe and NaBH_4 to afford the desired *syn*-diol **194** in 84% yield (Scheme 2.22).⁸⁰ When compound **194** was submitted to TESOTf in the presence of 2,6-lutidine, it was observed that reaction of the OH group at C-11 was faster than that at C-13. Therefore, selective protection would be possible. However, because recycling would be complicated, the reaction was stopped at the first

appearance of the bis-silyl ether (<50% conversion) to give the desired **195** (31%) along with recovered **194** (61%). IBX oxidation of **195** produced ketone **196** in excellent yield. Finally, exposure of **196** to HF·pyridine cleanly produced *ent*-**3** ($[\alpha]_D +50$; c 0.2, CHCl_3), that gave spectroscopic data (MS, IR, ^1H and ^{13}C NMR) that matched perfectly with those reported¹⁵ for isolated **3** ($[\alpha]_D -19$; c 0.2, CHCl_3) (Tables 2.10 and 2.11).

Scheme 2.22 Completion of the synthesis of *ent*-**3**.

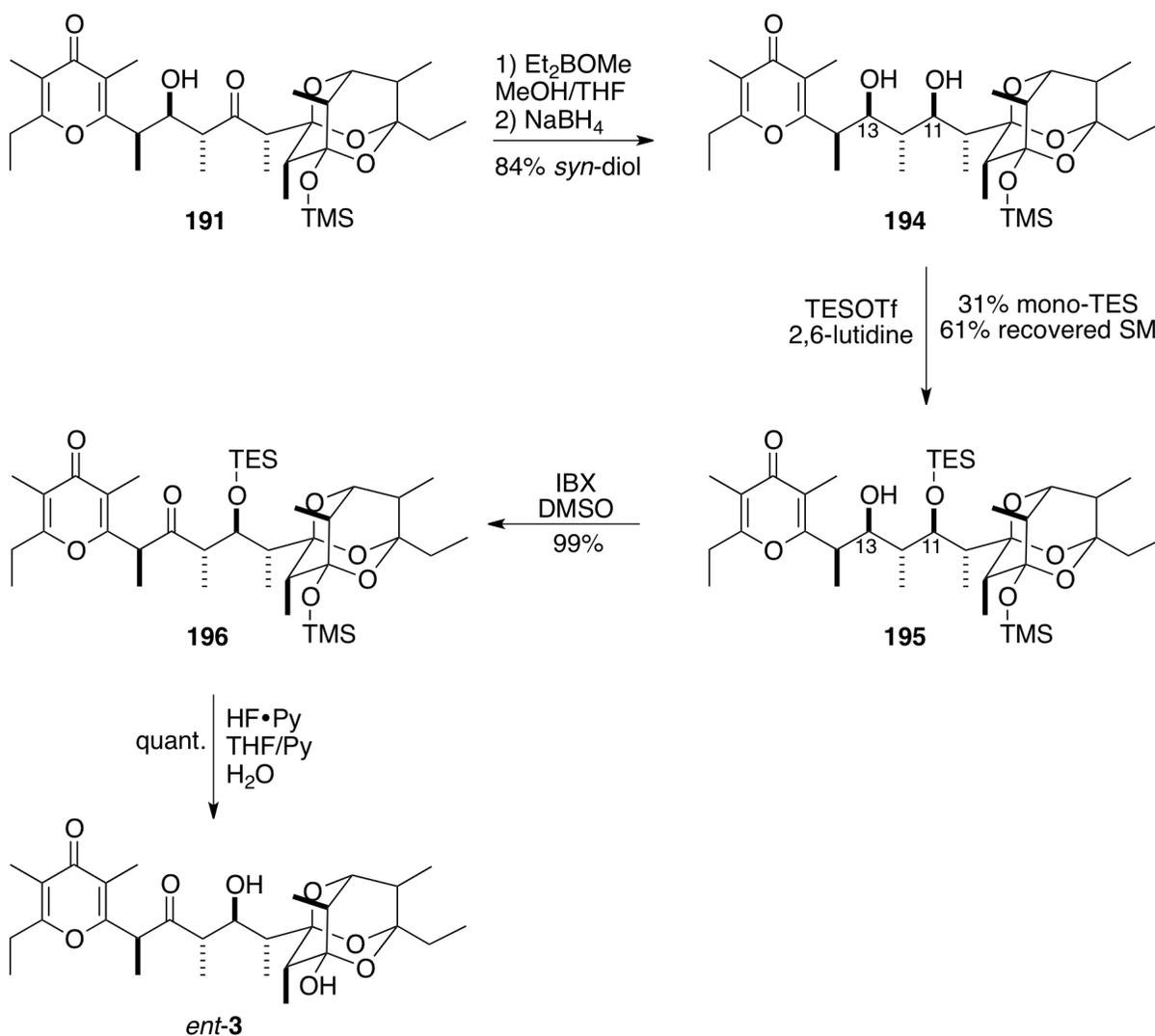
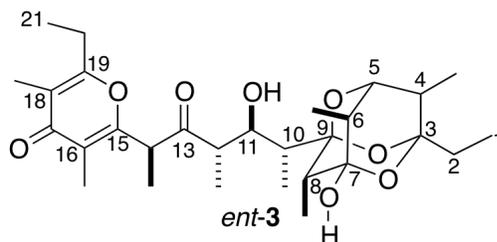


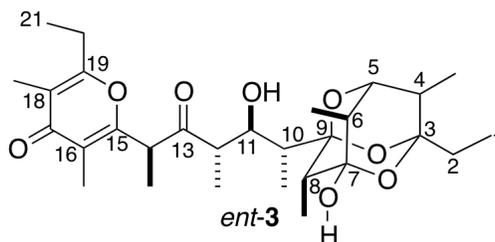
Table 2.10 Comparison of $^1\text{H-NMR}$ spectra (CDCl_3) of natural **3** and synthetic *ent-3*.



Natural ^a caloundrin B (3)			Assignment	Synthetic ^b (<i>ent-3</i>)		
δ_{H} (ppm) (400 MHz)	multiplicity	J (Hz)		δ_{H} (ppm) (500 MHz)	multiplicity	J (Hz)
4.13	q	7	HC-14	4.14	q	7
3.95	d	7.9	HOC-11	3.95	d	7.5
3.81	br d	3.5	HC-5	3.83	br d	3.5
3.67	ddd	7.9, 5, 4.7	HC-11	3.68	ddd	7.5, 5, 5
3.01	dq	7, 5	HC-12	3.03	dq	7, 5
2.6	br s		HOC-7	2.62	br s	
2.55	q	7.6	H ₂ C-20	2.62-2.52	m	
2.22	q	6.7	HC-8	2.24	q	6.5
2.09	dq	7, 3.5	HC-4	2.10	dq	7, 3.5
2.04	dq	7.6, 4.7	HC-10	2.09-2.03	2H, m	
1.96	dq	7, <1	HC-6	overlap		
2.06	s		H ₃ CC-16	2.07	s	
1.94	s		H ₃ CC-18	1.95	s	
1.59	q	7.5	H ₂ C-2	1.65-1.54	m	
1.36	d	6.7	H ₃ CC-14	1.38	d	7
1.15	t	7.6	H ₃ CC-21	1.16	t	7.5
1.08	d	7	H ₃ CC-6	1.09	d	7
1.01	d	7	H ₃ CC-12	1.03	d	7
0.98	d	6.7	H ₃ CC-8	0.99	d	6.5
0.95	d	7	H ₃ CC-10	0.97	d	7
0.91	t	7.5	H ₃ C-1	0.93	t	7.5
0.91	d	7	H ₃ CC-4	0.93	d	7

^a Data and assignments from Garson et al.¹⁵ ^b In this work it was used $\delta_{\text{H}} \text{CHCl}_3 = 7.26$.

Table 2.11 Comparison of ^{13}C -NMR spectra of natural **3** and synthetic *ent*-**3**.



Natural ^a caloundrin B (3) δ_{C} (ppm)	Assignment ^a	Synthetic ^{b,c} (<i>ent</i> - 3) δ_{C} (ppm)
213.1	C-13	213.4
179.6	C-17	179.8
164.8	C-19	165.0
160.1	C-15	160.3
120.2	C-16	120.4
118.5	C-18	118.7
102.9	C-9	103.1
102.8	C-3	103.0
97.2	C-7	97.4
78.4	C-5	78.6
77.4	C-11	77.7
50.4	C-14	50.7
46.2	C-12	46.5
41.7	C-10	42.0
36.7	C-8	36.9
36.6	C-4	36.8
35.6	C-6	35.8
29.7	C-2	29.7
24.7	C-20	24.9
16.1	H ₃ CC-12	16.3
13.4	H ₃ CC-14	13.6
13.4	H ₃ CC-6	13.6
12.3	H ₃ CC-4	12.6
11.3	H ₃ C-21	11.5
11.2	H ₃ CC-10	11.4
10.1	H ₃ CC-16	10.4
9.5	H ₃ CC-18	9.8
7.5	H ₃ CC-8	7.7
6.3	H ₃ C-1	6.5

^a Data and assignments from Garson et al. (inverse detection at 500 MHz).¹⁵

^b ^{13}C -NMR at 125 MHz. ^c Chemical shifts of *ent*-**3** are consistently 0.2-0.3 ppm higher than natural **3** presumably due to a different standard. In this work it was used $\delta_{\text{C}} \text{CDCl}_3 = 77.23$.

In conclusion, the first synthesis of *ent-3* was achieved in 16 linear steps starting from *ent-102*. The key steps in the synthesis involved the formation of the thermodynamically stable trioxaadamantane system *ent-10-epi-116* and its transformation to *ent-167* by isomerization of *ent-10-epi-167*. Finally, the rationally designed aldol reaction between the putative (*E*)-enolate of *ent-95*, formed by transmetallation of the Li enolate with (*c*-Hex)₂BCl, with (\pm)-**30** proceeded with kinetic resolution and constituted the first synthetic application of this unusual transformation.

2.6 Isomerization of *ent-caloundrin* to *ent-siphonar*in B

To investigate the thermodynamic stability and possible isomerization of caloundrin B, *ent-3* was treated with imidazole in CDCl₃ at room temperature and the reaction was monitored by ¹H-NMR (Figure 2.7). The rapid (reversible?) formation of an unidentified species along with the slow accumulation of *ent-2* was observed. After 24 hours, the ¹H-NMR of the crude (after work up) showed that *ent-siphonar*in B (*ent-2*) was the predominant component (ca. 50%). Fractionation of the mixture by PTLC afforded *ent-siphonar*in B (*ent-2*) (50%), a mixture of hemiacetal forms (22%), along with traces of *ent-3* and the unidentified new species observed above. Spectroscopic data (¹H and ¹³C-NMR) for *ent-2* ($[\alpha]_D -50$; *c* 0.1, CHCl₃) were fully consistent with those reported⁵ for siphonar in B ($[\alpha]_D +13.2$; *c* 0.01361, CHCl₃) (see Tables 2.12 and 2.13).

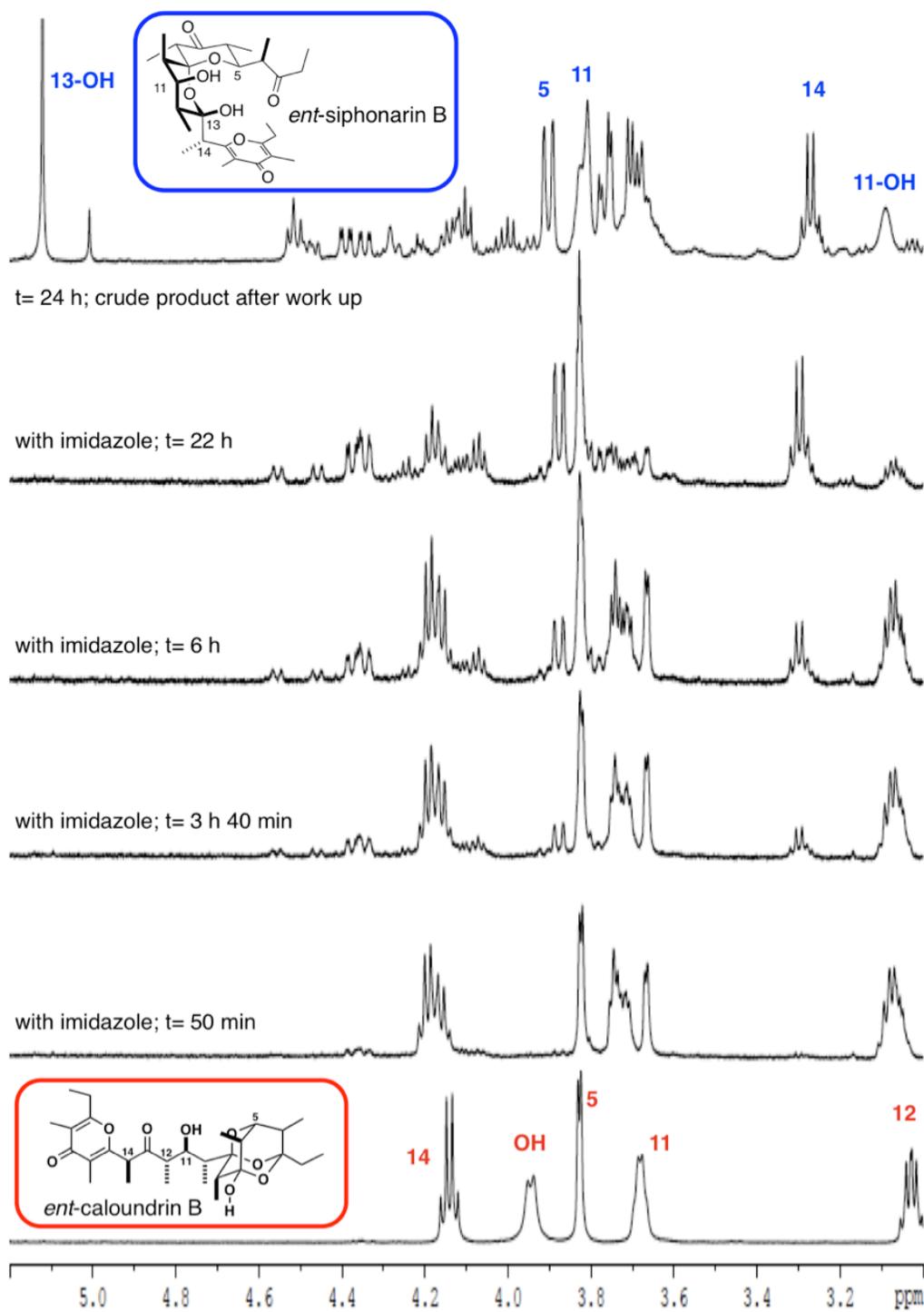
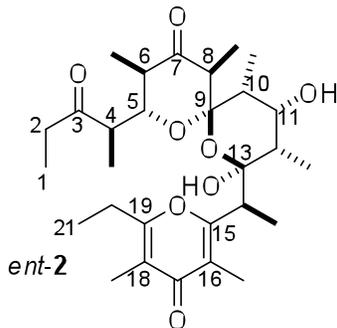


Figure 2.7 $^1\text{H-NMR}$ of the isomerization of *ent-3* in a solution of imidazole in CDCl_3 at room temperature for 1 day.

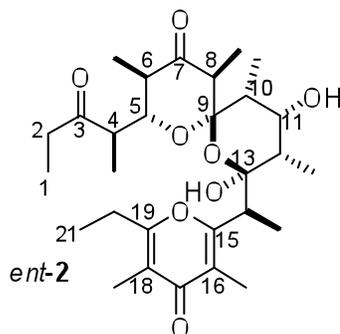
Table 2.12 Comparison of $^1\text{H-NMR}$ spectra of natural **2** and synthetic *ent-2*.



Natural ^a siphonararin B (2)			Assignment	Synthetic ^b (<i>ent-2</i>)		
δ_{H} (ppm)	multiplicity	J (Hz)		δ_{H} (ppm) (600 MHz)	multiplicity	J (Hz)
5.14	s	-	HO	5.12	s	
3.88	br d	10.5	HC-5	3.91	dd	10.5, 1.5
3.81	br s	-	HC-11	3.81	br s	-
3.28	q	7	HC-14	3.27	q	7
3.11	br s	-	HO	3.09	br s	-
2.79	q	7	H ₂ C-20	2.77	ap q	7.5
2.66	q	6.5	HC-8	2.66	dq	7, 1.5
2.61	br q	7	HC-4	2.61	br q	6.5
2.48	dq	18.5, 7	HC-2	2.48	dq	18.5, 7
2.28	dq	10.5, 6.5	HC-6	2.32-2.18	2H, m	-
2.25	dq	18.5, 7	HC-2	-	-	-
2.04	dq	7, 2.5	HC-12	2.05	dq	7, 2.5
2.00	s	-	H ₃ CC-18	1.97	s	-
1.98	s	-	H ₃ CC-16	1.96	s	-
1.83	dq	7, 2	HC-10	1.86	dq	7, 2
1.25	d	7	H ₃ CC-12	1.25	d	7
1.21	d	7	H ₃ CC-10	1.21	d	7
1.20	t	7	H ₃ CC-20	1.21	t	7.5
1.18	d	7	H ₃ CC-14	1.18	d	7
1.07	d	7	H ₃ CC-4	1.07	d	7
1.07	d	6.5	H ₃ CC-8	1.07	d	6.5
0.94	t	7	H ₃ C-1	0.94	t	7
0.76	d	6.5	H ₃ CC-6	0.77	d	6.5

^a Data and assignments from Faulkner et al.^{5, 15} ^b In this work it was used $\delta_{\text{H}} \text{CHCl}_3 = 7.26$.

Table 2.13 Comparison of ^{13}C -NMR spectra of natural **2** and synthetic *ent*-**2** (inverse detection at 600 MHz).



Natural ^a siphonarins B (2) δ_{C} (ppm)	Assignment ^b	Synthetic ^c (<i>ent</i> - 2) δ_{C} (ppm)
213.3	C-3	213.4
206.4	C-7	206.5
179.8	C-17	179.9
165.5	C-19	165.6
161.6	C-15	161.6
121.6	C-16	121.7
117.2	C-18	117.2
105.1	C-9	105.2
103.1	C-13	103.2
74.6	C-5	74.6
74.6	C-11	74.6
50.0	C-8	50.0
46.0	C-4	46.1
45.3	C-6	45.4
42.4	C-14	42.5
38.7	C-12	38.8
38.4	C-10	38.5
35.6	C-2	35.7
24.7	C-20	24.7
13.0	H ₃ CC-10	-
12.6	H ₃ CC-12	12.7
11.9	H ₃ CC-14	12
11.4	H ₃ CC-20	11.5
10.9	H ₃ CC-16	11.1
9.4	H ₃ CC-18	9.4
9.3	H ₃ CC-6	-
8.6	H ₃ CC-8	8.7
8.2	H ₃ CC-4	-
7.4	H ₃ C-1	7.6

^a Data from Faulkner et al.⁴ ^b Assignments from Garson et al.¹⁵ ^c There were four unresolved 'missing' signals at 8.2, 9.3, 13.0, and 74.6.

Following the isomerization of *ent-3* under the conditions used above for 5 days 10 h and then fractionation of the crude by PTLC produced *ent-2* (33%), *ent*-baconipyronone C (*ent-6*) (19%), *ent*-14-*epi*-baconipyronone C (*ent*-14-*epi*-6) (16%), and hemiacetal forms from *ent-48* (ca. 20%).

To follow the isomerization process more closely, to a solution of *ent-3* in CH₃CN was added imidazole and the reaction followed by HPLC (Figure 2.8). Using pure samples, retention times for *ent*-caloundrin B (*ent-3*), siphonarin B (**2**), and the mixture of hemiacetal forms from *ent-48* were established. After 2 hours, ca. 1:1 mixture of *ent-3* and an unknown compound was observed and this ratio remained essentially constant over several days. After 1 day, ca. 20% of the mixture was *ent*-siphonarin B (*ent-2*) growing to ca. 70% after 6 days. The mixture was essentially unchanged after 8 days, and consisted of *ent*-siphonarin B (*ent-2*), mixture of hemiacetal forms from *ent-48*, and other unidentified components with no more than traces of *ent-3* remaining.

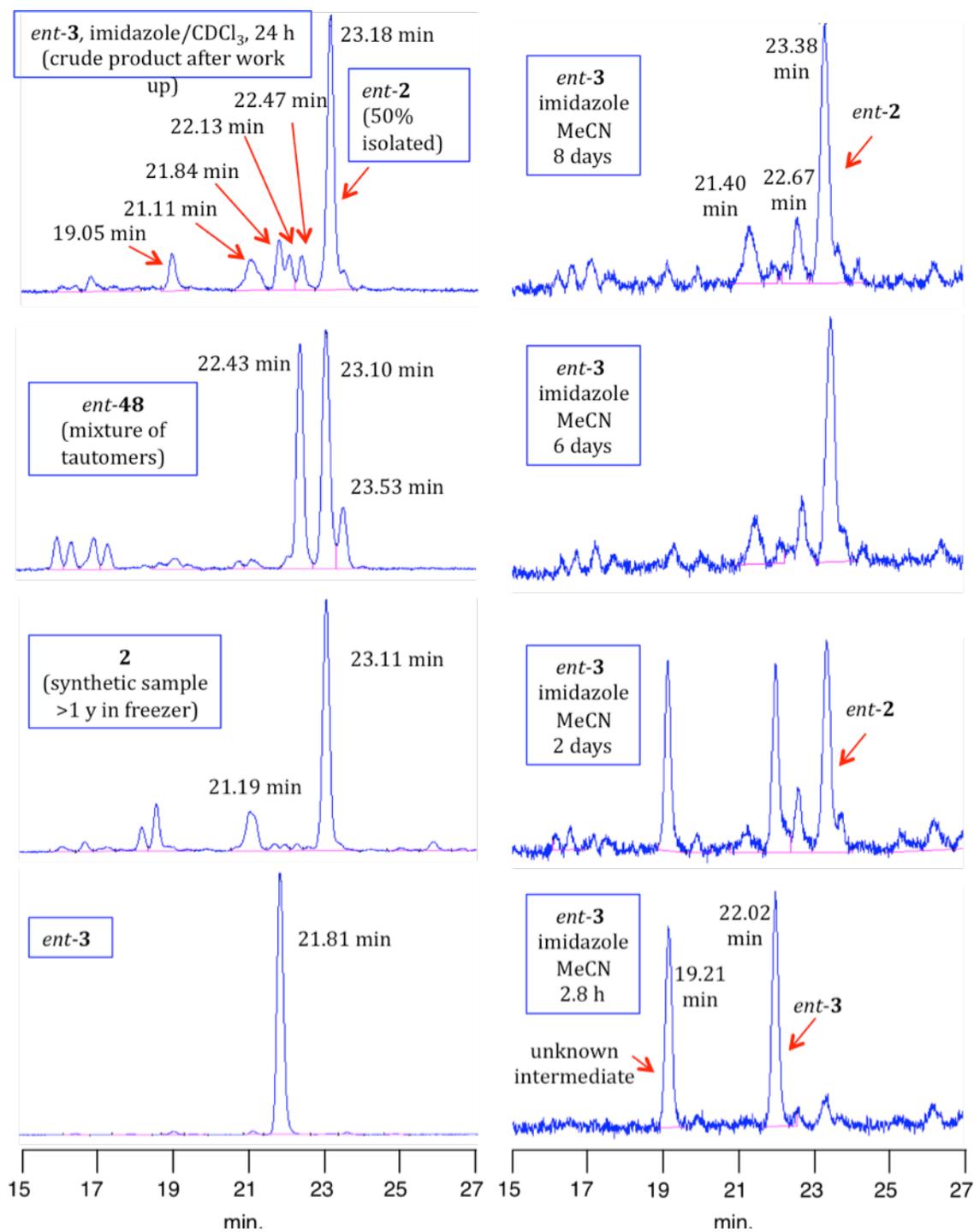
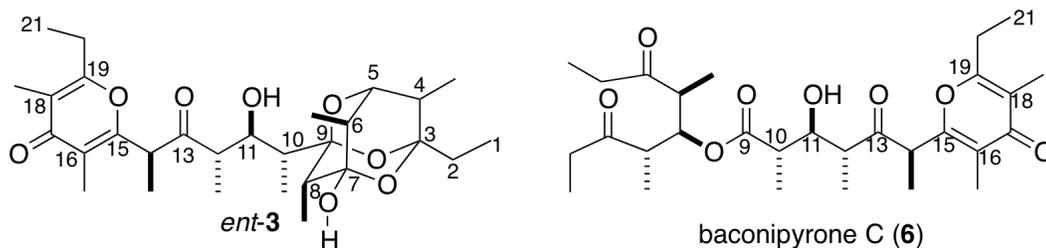


Figure 2.8 HPLC studies for the isomerization of *ent-3* in a solution of imidazole in CH_3CN at room temperature for 8 days.

Monitoring the isomerization of *ent-3* in the presence of imidazole both by ¹H-NMR and HPLC indicated that the process involved a rapid equilibrium between *ent-3* and an unknown intermediate. To determine the identity of this intermediate, the reaction of *ent-3* with imidazole in CDCl₃ was stopped after 1 h affording a 1.3:1 ratio of *ent-3* and the unknown intermediate (by ¹H-NMR). Analysis of the ¹³C-NMR spectrum of the mixture clearly indicated that the unknown contained a trioxadamantane fragment in its structure (signals at δ_C 102.7, 102.8, and 97.6). Comparison of the ¹³C-NMR chemical shifts of *ent-3* and the unknown revealed the same trends as a similar comparison of baconipyrene C (**6**) and 14-*epi*-baconipyrene C (14-*epi-6*) (Table 2.14).⁹ Thus, it was concluded that the unknown intermediate was most likely *ent-14-epi-3*.

Table 2.14 Comparison of ^{13}C -NMR spectra of *ent*-**3**, *ent*-14-*epi*-**3**, **6** and 14-*epi*-**6**.

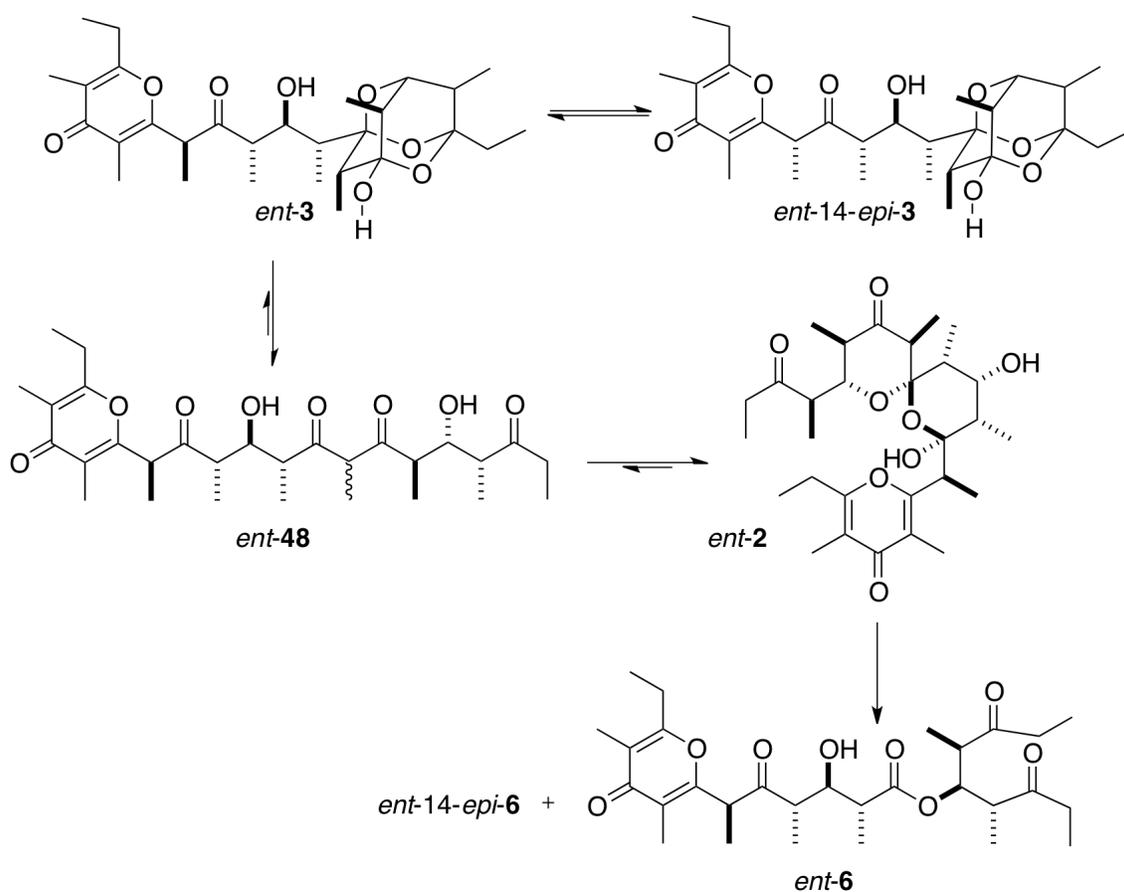


<i>ent</i> - 3 δ_{C} (ppm)	<i>ent</i> -14- <i>epi</i> - 3 δ_{C} (ppm)	Assignment ^a	6 ^b δ_{C} (ppm)	14- <i>epi</i> - 6 ^b δ_{C} (ppm)
6.5	6.5	C-1		
29.7	29.6	C-2		<i>c</i>
103	102.7	C-3		
36.8	36.9	C-4		
78.6	78.2	C-5		
35.8	35.7	C-6		
97.4	97.6	C-7		
36.9	36.9	C-8		
103.1	102.8	C-9		
42.0	42.4	C-10	41.3	42.4
77.7^d	76.2^d	C-11	77.8	76.6
46.5^d	45.1^d	C-12	48.8	47.8
213.4	213.5	C-13	210.7	210.6
50.7^d	47.5^d	C-14	51.2	48.7
160.3^d	159.7^d	C-15	160.8	160.0
120.4	120.4	C-16	120.6	120.4
179.8	179.8	C-17	179.9	179.9
118.7	118.6	C-18	118.5	118.3
165.0	165.1	C-19	164.8	165.0
24.9	24.9	C-20	24.9	25.0
11.5	11.6	C-21	11.5	11.5
12.6	12.5	H ₃ CC-4		
13.6	13.4	H ₃ CC-6		<i>c</i>
7.7	7.6	H ₃ CC-8		
11.4	10.3	H ₃ CC-10	15.3	15.1
16.3	16.9	H ₃ CC-12	14.4	14.9
13.6	13.3	H ₃ CC-14	13.4	13.5
10.4	10.3	H ₃ CC-16	10.1	10.0
9.8	9.7	H ₃ CC-18	9.7	9.7

^b Data and assignments for **6** according to Faulkner.¹⁰ ^b Taken from reference ⁹ ^c Fragments from C1- to C-9 are structurally different between *ent*-**3** and **6**, therefore those chemical shifts are not comparable. ^d $\Delta \delta_{\text{C}} > 0.6$ ppm.

Thus, the initial transformation after exposure of *ent-3* to imidazole was the epimerization at C-14, and then *ent-3* isomerized to *ent*-siphonarins B (*ent-2*). Therefore, during the isomerization process the ratio between *ent-3* and *ent-14-epi-3* remained constant, as observed by HPLC. However, once the equilibrium was reached, mainly *ent-2* was formed in the mixture. In addition, longer reaction time in imidazole also produced *ent*-baconipyrones C (*ent-6*) and *ent-14-epi-6* confirming that baconipyrones **4** and **6** correspond to artifacts from isolation.

Scheme 2.23 Study of the isomerization of *ent-3* into *ent-2*.



The close correspondence of the spectroscopic data of synthetic *ent-3* with those of isolated **3**, clearly demonstrated their enantiomeric relationship. The relative configuration assigned to *ent-3* is based on the relative configuration of the aldol adduct **191**. Although the assignment of the 12,13-*anti*-13,14-*syn* relative configuration in **191** was based on spectroscopic

evidence, the assignment of 10,12-*syn* was tentative and based on literature precedents (see section 2.4.4). The relatively 'clean' isomerization of *ent-3* to *ent-2* of known structure clearly confirms for the both the relative and absolute configuration proposed for caloundrin B (**3**) because both compounds share the same configuration at C-4, C-5, C-6, C-10, C-11, C-12, and C-14, differing only at C-8. Besides, it was proved that *ent-3* is thermodynamically less stable than *ent-2* and therefore, it cannot be an artifact from isolation. In addition, the hypothesis that proposed **3** as the biosynthetic product from which **2**, **4**, and **6** are formed is more viable.

2.7 Conclusions

In summary, the first synthesis of *ent-3* was achieved in 16 linear steps from *ent-102*. In the presence of imidazole, *ent-3* was cleanly isomerized to *ent*-siphonarins B *ent-2* with no more than traces of *ent-3* remaining. The isolation of *ent-3* from this experiment clearly establishes that caloundrin B (**3**) and siphonarins B (**2**) share the same absolute configurations at all stereocentres (except C-8) and confirms the proposed relative and absolute configuration for **3**. These results also firmly establish that caloundrin B (**3**) is thermodynamically much less stable than siphonarins B (**2**) confirming previous calculations and explaining the failure⁹ to obtain **3** by attempted isomerization of **48**. Consequently, caloundrin B (**3**) cannot be an isolation artifact of siphonarins B (**2**) but presumably is formed in an enzyme-mediated or other templated process. Thus, caloundrin B (**2**) must now be considered as a plausible biosynthetic product from which the formation of siphonarins B (**2**), baconipyrones A (**4**), and baconipyrones C (**6**) can be readily explained (see section 1.2.2.2).

The synthesis of *ent-3* required the development of various methodologies that were crucial for understanding the requirements for formation of the desired trioxadamantane ring system and for assembling the complete carbon skeleton of *ent-3* with the correct relative

configuration. It was discovered that the C-10 configuration had a profound influence on the thermodynamic stability of the trioxadamantane ring system. Because of avoidance of *syn*-pentane interaction between the methyl groups at C-8 and C10, the C-10 configuration dictates the orientation between the side chain and the trioxadamantane. This orientation facilitates a stabilizing H-bond in the trioxadamantane or a hemiacetal tautomer that strongly influences the position of the equilibrium. Unfortunately, the 'wrong' C-10 configuration was required to allow formation of the trioxadamantane under thermodynamic control. As a consequence, a correction of the C-10 configuration after formation of a stable trioxadamantane was required. The rather lengthy isomerization sequence used was effective but a second generation synthesis will be much more efficient if a better solution to this problem can be designed.

Applying the multiplicativity rule to rationally design aldol reactions that proceed with kinetic resolution was shown to be possible in a proof-of-concept study.⁴⁶ During the development of this methodology, an unprecedented non-linear effect was discovered and characterized in which the enantioselectivity was shown to be dependent on the enantiopurity of both reactants. Building on the principles established, aldol reactions of achiral ketones with aldehyde (\pm)-**30** were shown to be highly Felkin diastereoface selective suggesting that (\pm)-**30** would react with kinetic resolution with suitable enantiopure ketones. The synthesis of the epimeric ketones *ent*-**95** and *ent*-10-*epi*-**95** allowed preliminary studies that informed the prediction that the (*E*)-boron enolate of *ent*-**95** would react with (\pm)-**30** to produce an aldol adduct with the correct selectivity to permit synthesis of *ent*-**3**. During the studies, it was discovered that the desired (*E*)-enol borinate of *ent*-**95** could be prepared by transmetallation of the LiN^tBu(SiMe₃)-generated (*E*)-Li enolate and its reaction with (\pm)-**30** gave the desired adduct

191 (dr 3.3), as predicted. This method of forming boron enolates will be likely be useful in other difficult cases.

3 EXPERIMENTAL PROCEDURES

3.1 General methods

Anhydrous solvents were distilled under argon atmosphere as follows: Tetrahydrofuran (THF) from benzophenone sodium ketyl; CH_2Cl_2 from CaH_2 ; MeOH from $\text{Mg}(\text{OMe})_2$; DMSO from CaH_2 at reduced pressure (stored over 4Å molecular sieves). All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were: ice/water (0 °C), $\text{CO}_{2(s)}/\text{CH}_3\text{CN}$ (-50 °C), and $\text{CO}_{2(s)}/\text{acetone}$ (-78 °C). Unless otherwise noted, reaction temperatures refer to that of the bath. Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Preparative TLC (PTLC) was carried out on glass plates (20×20 cm) pre-coated (0.25 mm) with silica gel 60 F₂₅₄. 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 (5% v/v) followed by charring on a hot plate. Flash column chromatography (FCC) was performed according to Still et al.¹ with silica gel 60 (40-63 μm). All mixed solvent eluents are reported as v/v solutions. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by ¹H NMR. HPLC experiments were performed using a reverse-phase Zorbax SB-C18[®] column (3.6 μm particle size silica, 3.0-100 mm) and a linear gradient of acetonitrile in water (25% to 75%) was employed as the mobile phase (0 to 35 min).

3.2 Spectral data

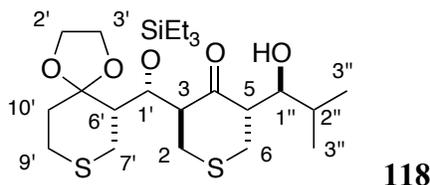
High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a double focusing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI ionization at 50 eV with ammonia as the reagent gas; only partial data are reported. Alternatively, HRMS were obtained on an LC-MS/MS time-of-flight high resolution spectrometer with electrospray ionization (ESI) from acetonitrile solution. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in CDCl_3 solution at 500 MHz for ^1H and 125 MHz for ^{13}C . Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^1H NMR) served as the internal standard: CDCl_3 (7.26 δ_{H} , 77.23 δ_{C}). The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of couplings constants (J) corresponds to the order of the multiplicity assignment. Coupling constants (J) are reported to the nearest 0.5 Hz (i.e., ± 0.25 Hz as consistent with the digital resolution ca. 0.2 Hz/pt). The ^1H NMR assignments were made based on chemical shift and multiplicity and were confirmed by homonuclear decoupling and/or two-dimensional correlation experiments (gCOSY, gHSQC, gHMBC). The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity (as determined by ^{13}C -DEPT or gHSQC) and were confirmed by two-dimensional $^1\text{H}/^{13}\text{C}$ correlation experiments (gHSQC and/or gHMBC). Specific rotations ($[\alpha]_{\text{D}}$) are the average of 5 determinations at ambient temperature using a 1 mL, 10 dm cell; the units are 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$, the concentrations (c) are reported in g/100 mL, and the values are rounded to reflect the accuracy of the measured concentrations (the major source of error).

3.3 Materials

The following compounds and reagents were prepared as described previously: **96**,⁴³ (*S*)-**30**,^{81, 82} (-)-**109** (>98% ee) and (+)-*ent*-**109** (>98% ee),^{40, 46} W-2 Raney nickel,^{83, 84} IBX,⁸⁵ DMP (from IBX).⁸⁶ *i*Pr₂NH was freshly distilled under argon atmosphere from CaH₂. 2,6-Lutidine was distilled from CaH₂ and stored over 4Å molecular sieves. All other reagents were commercially available and unless otherwise noted, were used as received.

3.4 Experimental procedures and characterization data

(3*S*,5*S*)-rel-3-[(*R*)-(6*S*)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*S*)-1-hydroxy-2-methylpropyl]tetrahydro-4*H*-thiopyran-4-one (118**)**



A solution of (±)-**102** (500 mg, 1.19 mmol) in CH₂Cl₂ (8 mL) was added via syringe to a stirred solution of (*c*-C₆H₁₁)₂BCl (1 M in hexanes; 2.4 mL, 2.4 mmol) and Et₃N (0.350 mL, 2.51 mmol) in CH₂Cl₂ (14 mL) at 0 °C under Ar. After 30 min, the reaction mixture was cooled to –78 °C and a solution of isobutyraldehyde (0.218 mL, 2.39 mmol) in CH₂Cl₂ (3.5 mL) was added via syringe over ca. 8 min. After 16 h, the reaction was quenched by sequential addition of phosphate buffer (pH=7; 10 mL), methanol (3 mL) and 30% aq H₂O₂ (6 mL) with vigorous stirring. The mixture was warmed to 0 °C and, after 10 min, was diluted with ice-water and saturated aqueous Na₂SO₃ and extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated to give the crude product whose ¹H NMR spectrum suggest the

presence of a single adduct. Fractionation of the crude by FCC (10-20% ethyl acetate in hexanes) afforded recovered **102** (59 mg, 12%) and the title compound as a colorless oil (485 mg, 82%).

IR ν_{max} 3544 cm^{-1} .

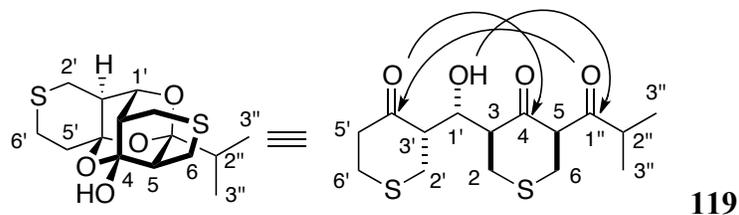
^1H NMR (500 MHz, CDCl_3) δ 4.71 (1H, br s, HC-1'), 3.98-3.82 (4H, m, HC-2', HC-3'), 3.65 (1H, ddd, $J = 4, 4, 7.5$ Hz, HC-1"), 3.20 (1H, dd, $J = 11, 13$ Hz, HC-2), 3.06 (1H, d, $J = 4$ Hz, HO), 2.96 (1H, dd, $J = 5.5, 12.5$ Hz, HC-6), 2.90-2.73 (5H, m, HC-3, HC-5, HC-2, H_2C -7'), 2.67-2.57 (3H, m, HC-6, H_2C -9'), 2.13-2.06 (1H, m, HC-6'), 2.06-1.99 (1H, m, HC-10'), 1.83-1.72 (1H, m, HC-2"), 1.63-1.54 (1H, m, HC-10'), 0.99 (3H, d, $J = 7$ Hz, HC-3"), 0.95 (9H, t, $J = 8$ Hz, $\text{H}_3\text{CCSi} \times 3$), 0.90 (3H, d, $J = 7$ Hz, HC-3"), 0.64 (6H, ap q, $J = 8$ Hz, $\text{H}_2\text{CSi} \times 3$).

^{13}C NMR (125 MHz, CDCl_3) δ 211.9 (s, C-4), 109.0 (s, C-5'), 77.7 (d, C-1"), 69.3 (d, C-1'), 64.5 (t, C-2' or C-3'), 63.8 (t, C-2' or C-3'), 60.6 (d, C-3), 51.3 (d, C-5), 47.8 (d, C-6'), 34.5 (t, C-10'), 29.8 (d, C-2"), 29.4 (t, C-7'), 27.1 (t, C-6), 26.8 (t, C-9'), 26.1 (t, C-2), 20.3 (q, C-3"), 15.4 (q, C-3"), 7.1 (q $\times 3$, CH_3CSi), 5.3 (t $\times 3$, CH_2Si).

LRMS (CI, NH_3), m/z (relative intensity): 491 ($[\text{M}+1]^+$, 1), 419 (24), 389 (23), 303 (37), 287 (70), 229 (100), 132 (36), 99 (53).

HRMS m/z calcd for $\text{C}_{23}\text{H}_{42}\text{O}_5\text{S}_2\text{Si}+\text{H}$: 491.2321; found: 491.2302 (CI, NH_3).

(4*S*,4*aS*,5*aR*,9*aS*,10*R*,10*aS*,12*S*)-*rel*-Octahydro-5*a*,4,10-(epoxymethenoxy)-4*a*-hydroxy-12-(1-methylethyl)-1*H*,4*aH*,5*aH*-bisthiopyrano[4,3-*b*:3',4'-*e*]pyran (119**)**



IBX (1.04 g, 3.71 mmol) was added to a stirred solution of aldol adduct **118** (485 mg, 0.989 mmol) in dry DMSO (70 mL) at room temperature under Ar. After 10 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NaHCO₃, H₂O and brine. The organic layer was dried over Na₂SO₄ and concentrated to give the crude product that was taken up in acetone (225 ml). FeCl₃·6H₂O (374 mg, 1.39 mmol) was added to the stirred solution and the resulting dark brown mixture was heated under reflux. After 12.5 h (the solution was yellow), the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NaHCO₃, H₂O and brine. The organic layer was dried over Na₂SO₄, concentrated and fractionated by FCC (30% ethyl acetate in hexanes) to give the title compound as a yellow solid (219 mg, 63% over 2 steps).

IR ν_{\max} 3397 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.28 (1H, d, J = 3 Hz, HC-1'), 3.55 (1H, dd, J = 3.5, 14 Hz, HC-2), 3.40 (1H, dd, J = 3, 14 Hz, HC-6), 2.97 (1H, ddd, J = 3, 13.5, 13.5 Hz, HC-6'), 2.81 (1H, dd, J = 12.5, 13 Hz, HC-2'), 2.79 (1H, br s, HO), 2.56 (2H, br d, J = 14 Hz, HC-2, HC-6), 2.44 (1H, , J = 2.5, 3, 4, 13.5 Hz, HC-6'), 2.40 (1H, ddd, J = 3, 3, 12.5 Hz, HC-3'), 2.23 (1H, ddd, J = 3, 3, 13 Hz, HC-2'), 2.12 (1H, br s, HC-3), 2.09 (1H, br s, HC-5), 2.04-1.98 (2H, m, HC-2'', HC-5''), 1.87

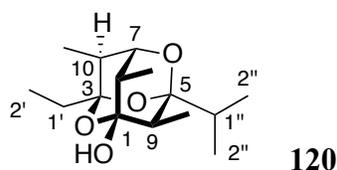
(1H, ddd, $J = 4, 13.5, 13.5$ Hz, HC-5'), 1.04 (3H, d, $J = 7$ Hz, HC-3''), 0.90 (3H, d, $J = 7$ Hz, HC-3').

^{13}C NMR (125 MHz, CDCl_3) δ 102.9 (s, C-1''), 99.0 (s, C-4'), 95.1 (s, C-4), 76.8 (d, C-1'), 45.1 (d, C-3'), 41.5 (d, C-5), 37.6 (t, C-5'), 35.6 (d, C-3), 32.8 (d, C-2''), 28.9 (t, C-2), 27.5 (t, C-2'), 25.2 (t, C-6'), 24.4 (t, C-6), 15.9 (q, C-3''), 15.1 (q, C-3'').

LRMS (EI), m/z (relative intensity): 330 ($[\text{M}]^+$, 100), 242 (34), 209 (29), 154 (31), 153 (35), 126 (52), 99 (37), 71 (61), 67 (70).

HRMS m/z calcd for $\text{C}_{15}\text{H}_{22}\text{O}_4\text{S}_2$: 330.0960; found: 330.0968 (EI).

(1*R*,3*R*,5*R*,7*R*,8*S*,9*S*,10*S*)-*rel*-3-Ethyl-8,9,10-trimethyl-5-(1-methyl)ethyl-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]decan-1-ol (**120**)



Raney nickel (W2; 2 mL settled volume) was transferred to a solution of **119** (50 mg, 0.15 mmol) in absolute ethanol (1 mL) and the resulting suspension was heated under reflux with vigorous stirring in a (previously heated) oil bath at 80 °C. The reaction was monitored by TLC and after 30 min, additional Raney nickel (0.5 mL) was added. After 40 min, the suspension was allowed to settle and the supernatant was decanted. The solid was resuspended in ethanol and heated under reflux for 10 min. This washing procedure was repeated with ethanol, with methanol and acetone. The combined supernatants were filtered through Celite®, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to obtain the title compound as a white solid (25 mg, 61%).

IR ν_{\max} 3398 cm^{-1} .

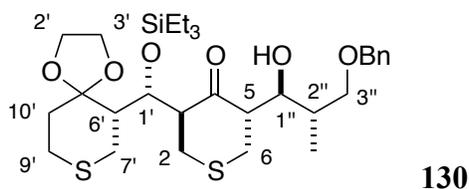
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 3.85 (1H, d, $J = 3$ Hz, HC-7), 2.57 (1H, s, HO), 2.13 (1H, dq, $J = 3, 7$ Hz, HC-10), 2.07 (1H, br q, $J = 7.5$ Hz, HC-8), 1.98 (1H, dq, $J = 1.5, 6.5$ Hz, HC-9), 1.86 (1H, qq, $J = 6.5, 7$ Hz, HC-2''), 1.63-1.49 (2H, m, $\text{H}_2\text{C}-1'$), 1.18 (3H, d, $J = 7.5$ Hz, $\text{H}_3\text{CC}-8$), 1.06 (3H, d, $J = 6.5$ Hz, $\text{H}_3\text{CC}-9$), 0.99 (3H, d, $J = 6.5$ Hz, $\text{H}_3\text{C}-2''$), 0.92-0.86 (9H, m, $\text{H}_3\text{C}-2''$, $\text{H}_3\text{C}-2'$, $\text{H}_3\text{CC}-10$).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 102.9 (s, C-3), 102.7 (s, C-5), 98.9 (s, C-1), 79.1 (d, C-7), 43.8 (d, C-9), 37.3 (d, C-10), 35.4 (d, C-8), 32.7 (d, C-1''), 29.7 (t, C-1'), 16.0 (q, C-2''), 15.2 (q, C-2''), 14.6 (q, $\text{CH}_3\text{C}-8$), 12.9 (q, $\text{CH}_3\text{C}-10$), 10.4 (q, $\text{CH}_3\text{C}-9$), 6.4 (q, C-2').

LRMS (CI, NH_3), m/z (relative intensity): 271 ($[\text{M}+1]^+$, 31), 253 (100), 249 (20), 183 (35), 165 (21), 153 (17), 127 (20), 125 (22), 96 (22), 71 (29).

HRMS m/z calcd for $\text{C}_{15}\text{H}_{26}\text{O}_4+\text{H}$: 271.1909; found: 271.1902 (CI, NH_3).

(3*S*,5*S*)-3-[(*R*)-(6*S*)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*S*)-(2*S*)-1-hydroxy-2-methyl-3-(phenylmethoxy)propyl]tetrahydro-4*H*-thiopyran-4-one (130)



A solution of (-)-**102** (300 mg, 0.716 mmol) in CH_2Cl_2 (4 mL) was added via syringe in 2 min to a stirred solution of (*c*- C_6H_{11}) $_2\text{BCl}$ (1 M in hexanes; 1.4 mL, 1.4 mmol) and Et_3N (0.210 mL, 1.50 mmol) in CH_2Cl_2 (6 mL) at 0 °C under Ar. After 30 min, the reaction mixture was cooled to -78 °C and a solution of Roche aldehyde (*S*)-**29** (241 mg, 1.35 mmol) in CH_2Cl_2 (4

mL) was added slowly via syringe (ca. 10 min). After 18 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 7 mL) and MeOH (2 mL). The mixture was then transferred to an ice bath and 30% aq H₂O₂ (4.5 mL) was added with vigorous stirring. After 10 min, the mixture was diluted with ice-water and saturated aq Na₂SO₃ and extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (2% ethyl acetate in dichloromethane) to obtain recovered **102** (51 mg, 17%) and the title compound as a colorless oil (350 mg, 82%).

$[\alpha]_D -58$ (*c* 2.2, CHCl₃)

IR ν_{\max} 3517 cm⁻¹.

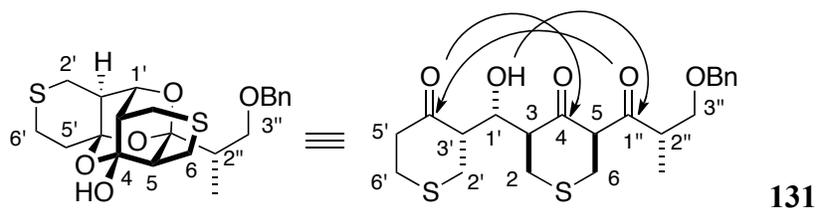
¹H NMR (500 MHz, CDCl₃) δ 7.37-7.25 (5H, m, Ph), 4.70 (1H, br s, HC-1'), 4.52 (1H, d, *J* = 12 Hz, HCPh) 4.49 (1H, d, *J* = 12 Hz, HCPh), 3.90-3.70 (5H, m, HC-1'', H₂C-2', H₂C-3'), 3.65 (1H, dd, *J* = 7, 9 Hz, HC-3''), 3.44 (1H, dd, *H* = 5, 9 Hz, HC-3'') 3.43 (1H, d, *J* = 4.5 Hz, HO), 3.17-3.11 (2H, m, HC-2, HC-6), 3.05 (1H, ddd, *J* = 6, 6, 9 Hz, HC-5), 2.91-2.85 (1H, m, HC-3), 2.85-2.77 (3H, m, HC-2, H₂C-7'), 2.71 (1H, dd, *J* = 9.5, 12 Hz, HC-6), 2.64-2.61 (2H, m, H₂C-9'), 2.11-2.02 (3H, m, HC-2'', HC-6', HC-10'), 1.58 (1H, ap ddd, *J* = 6, 6, 14 Hz, HC-10'), 1.03 (3H, d, *J* = 7 Hz, H₃CC-2''), 0.96 (9H, t, *J* = 8 Hz, H₃CCSi \times 3), 0.64 (6H, ap q, *J* = 8 Hz, H₂CSi \times 3).

¹³C NMR (125 MHz, CDCl₃) δ 211.5 (s, C-4), 138.6 (s, Ph), 128.5 (d \times 2, Ph), 127.7 (d, Ph), 127.6 (d \times 2, Ph), 109.1 (s, C-5'), 75.2 (d, C-1''), 73.5 (t, CH₂Ph), 72.4 (t, C-3''), 69.2 (d, C-1'), 64.5 (t, C-2'), 63.9 (t, C-3'), 60.4 (d, C-3), 51.9 (d, C-5), 47.8 (d, C-6'), 35.6 (d, C-2''), 34.6 (t, C-10'), 29.5 (t, C-7'), 27.7 (t, C-6), 26.9 (t, C-9'), 26.3 (t, C-2), 15.8 (q, CH₃C-2''), 7.2 (q \times 3, CH₃CSi), 5.3 (t, CH₂Si).

LRMS (EI), m/z (relative intensity): 596 ($[M]^+$, 2), 567 (10), 551 (20), 550 (35), 549 (100), 521 (10), 506 (8).

HRMS m/z calcd for $C_{30}H_{48}O_6SiS_2+Na$: 619.2553; found: 619.2540 (ESI).

(4*S*,4*aS*,5*aR*,9*aS*,10*R*,10*aS*,12*S*)-Octahydro-5*a*,4,10-(epoxymethenoxy)-4*a*-hydroxy-12-[(*S*)-1-methyl-2-(phenylmethoxy)ethyl]-1*H*,4*aH*,5*aH*-bisthiopyrano[4,3-*b*:3',4'-*e*]pyran (131**)**



IBX (155 mg, 0.555 mmol) was added to a stirred solution of aldol adduct **130** (88 mg, 0.15 mmol) in dry DMSO (10 mL) at room temperature under Ar. After 5.5 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq $NaHCO_3$, H_2O and brine, dried over Na_2SO_4 , and concentrated to give the crude dione (mainly enol form by 1H NMR). $FeCl_3 \cdot 6H_2O$ (56 mg, 0.21 mmol) was added to a stirred solution of the above crude in acetone (33.6 mL) and the resulting purple solution was heated under reflux. After 12 h (reaction mixture had turned yellow), the mixture was diluted with ethyl acetate and washed sequentially with saturated aq $NaHCO_3$, H_2O and brine, dried over Na_2SO_4 , concentrated, and fractionated by FCC (25% ethyl acetate in hexanes). The fraction containing the desired product was refractionated by PTLC (30% ethyl acetate in hexanes x 3) to give the title compound (38 mg, 58%).

$[\alpha]_D +15$ (c 0.7, $CHCl_3$)

IR ν_{max} 3384 cm^{-1} .

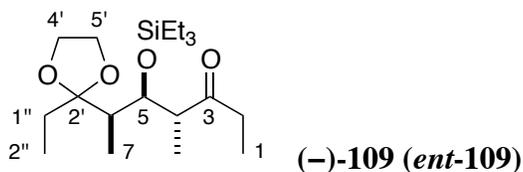
¹H NMR (500 MHz, CDCl₃) δ 7.34 (4H, d, *J* = 4.5 Hz, Ph), 7.31-7.24 (1H, m, Ph), 4.55 (1H, d, *J* = 12 Hz, HCPh), 4.46 (1H, d, *J* = 12 Hz, HCPh), 4.30 (1H, br d, *J* = 3 Hz, HC-1') 4.03 (1H, dd, *J* = 3, 9 Hz, HC-2''), 3.54 (1H, dd, *J* = 3.5, 14 Hz, HC-2), 3.42-3.35 (2H, m, HC-2'', HC-6), 2.95 (1H, dt, *J* = 2.5, 13, 14 Hz, HC-6'), 2.80 (1H, dd, *J* = 12.5, 13 Hz, HC-2'), 2.57-2.53 (2H, m, HC-2, HC-6), 2.43 (1H, dddd, *J* = 3, 3, 4, 14 Hz, HC-6'), 2.35 (1H, ddd, *J* = 3.5, 4, 12.5 Hz, HC-3'), 2.27-2.17 (2H, m, HC-2', HC-2''), 2.14-2.09 (2H, m, HC-3, HC-5), 2.00 (1H, ddd, *J* = 2.5, 3, 14 Hz, HC-5'), 1.81 (1H, dt, *J* = 4, 13, 14 Hz, HC-5'), 1.64 (1H, br s, HO), 1.06 (3H, d, *J* = 7 Hz, HC-3'').

¹³C NMR (500 MHz, CHCl₃) δ 138.9 (s, Ph), 128.5 (d ×2, Ph), 127.8 (d ×2, Ph), 127.6 (d, Ph), 102.9 (s, C-1''), 99.0 (s, C-4'), 95.0 (s, C-4), 76.9 (d, C-1'), 73.4 (t, CH₂Ph), 70.8 (t, C-3''), 45.2 (d, C-3'), 41.4 (d, C-5), 38.8 (d, C-2''), 37.5 (t, C-5'), 35.6 (d, C-3), 28.9 (t, C-2), 27.5 (t, C-2'), 25.2 (t, C-6'), 24.4 (t, C-6), 11.6 (q, CH₃C-1'').

LRMS (EI), *m/z* (relative intensity): 436 ([M]⁺, 29), 259 (23), 241 (20), 153 (15), 91 (100), 67 (25), 55 (16).

HRMS *m/z* calcd for C₂₂H₂₈O₅S₂: 436.1378; found: 436.1390 (EI).

(4*R*,5*S*,6*R*)-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-triethylsilyloxy-4-methylheptan-3-one (ent-109).



Raney nickel (W2; 20 mL settled volume) was transferred to a solution of (+)-**102** (4.20 g, 10.0 mmol) in absolute ethanol (30 mL) and the resulting suspension was heated under reflux with vigorous stirring in an oil bath previously heated to 80 °C. The reaction was monitored by TLC

and additional Raney nickel (5 mL settled volume) was added at ca. 40 min intervals. After a 5.5 h (30 mL of additional Raney nickel added), the reaction mixture was allowed to settle and the supernatant was decanted. The solid was suspended in ethanol (50 mL) and heated under reflux for 10 min with vigorous stirring and then the mixture was allowed to settle and the supernatant was decanted. The washing procedure was repeated 4 times and then 5 times using methanol. The combined supernatants were filtered through Celite®, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to obtain the titled compound as a colorless oil (2.9 g, 80%).

$[\alpha]_D -68$ (*c* 1.0, CHCl₃)

IR ν_{\max} : 1714 cm⁻¹

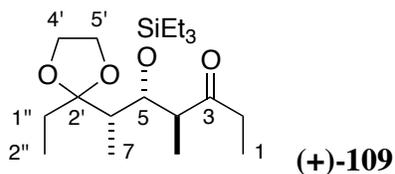
¹H NMR (500 MHz, CDCl₃) δ : 4.26 (1H, dd, *J* = 1.5, 5 Hz, HC-5), 3.90-3.70 (4H, m, H₂C-4', H₂C-5'), 2.79 (1H, dq, *J* = 5.5, 7 Hz, HC-4), 2.59 (1H, dq, *J* = 18, 7 Hz, HC-2), 2.44 (1H, dq, *J* = 18, 7 Hz, HC-2), 1.78 (1H, dq, *J* = 1.5, 7 Hz, HC-6), 1.68 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1"), 1.60 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1"), 1.03 (3H, t, *J* = 7 Hz, H₃C-1), 1.00 (3H, d, *J* = 7 Hz, H₃CC-4), 0.97 (9H, t, *J* = 8 Hz, H₃CCSi ×3), 0.90 (3H, d, *J* = 7 Hz, H₃C-7), 0.82 (3H, t, *J* = 7.5 Hz, H₃C-2"), 0.61 (6H, ap q, *J* = 8 Hz, H₂CSi ×3)

¹³C NMR (125 MHz, CDCl₃) δ : 213.0 (s, C-3), 113.8 (s, C-2'), 70.9 (d, C-5), 65.2 (t, C-4' or C-5'), 64.9 (t, C-4' or C-5'), 54.0 (d, C-4), 40.8 (d, C-6), 36.3 (t, C-2), 26.2 (t, C-1"), 10.9 (q, CH₃C-4), 10.5 (q, C-7), 7.7 (q, C-1), 7.2 (t ×3, CH₂Si), 7.1 (q, C-2"), 5.4 (q ×3, CH₃CSi)

LRMS (CI, NH₃), *m/z* (relative intensity): 359 ([M]⁺, 10), 227 (36), 101 (100)

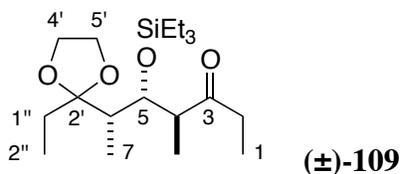
HRMS *m/z* calcd for C₁₉H₃₈O₄Si+H: 359.2618; found: 359.2623 (CI, NH₃).

(4*S*,5*R*,6*S*)-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-triethylsilyloxy-4-methylheptan-3-one (109).



Raney nickel (W2; 20 mL settled volume) was transferred to a solution of (-)-**102** (0.510 g, 1.22 mmol) in absolute ethanol (43 mL) and the resulting suspension was heated under reflux with vigorous stirring in an oil bath previously heated to 80 °C. The reaction was monitored by TLC and after a 25 min, the reaction mixture was allowed to settle and the supernatant was decanted. The solid was suspended in ethanol (50 mL) and heated under reflux for 10 min with vigorous stirring and then the mixture was allowed to settle and the supernatant was decanted. The washing procedure was repeated 2 times and then 3 times using methanol and 3 times using acetone. The combined supernatants were filtered through Celite®, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to obtain the titled compound as a colorless oil (373 mg, 85%). $[\alpha]_D +70$ (*c* 1.0, CHCl₃); NMR data for (+)-**109** were consistent with those reported for (-)-**109**.

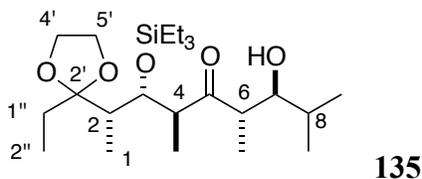
(4*S*,5*R*,6*S*)-rel-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-triethylsilyloxy-4-methylheptan-3-one (109).



Raney nickel (W2; 14 mL settled volume) was transferred to a solution of (±)-**102** (522 mg, 1.246 mmol) in absolute ethanol (44 mL) and the resulting suspension was heated under reflux with vigorous stirring in an oil bath previously heated to 80 °C. The reaction was monitored by TLC and after 20 min, additional Raney nickel (6 mL settled volume) was added. After 30 min,

the reaction mixture was allowed to settle and the supernatant was decanted. The solid was suspended in ethanol and heated under reflux for 10 min with vigorous stirring and then the mixture was allowed to settle and the supernatant was decanted. The washing procedure was repeated 2 times and then 3 times using methanol and 3 times using acetone. The combined supernatants were filtered through Celite®, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to obtain the titled compound as a colorless oil (360 mg, 80%). NMR data for (±)-**109** were consistent with those reported for (-)-**109**.

(2*S*,3*R*,4*S*,6*S*,7*S*)-rel-2-(2-Ethyl-1,3-dioxolan-2-yl)-3-triethylsilyloxy-7-hydroxy-4,6,8-trimethylnonan-5-one (135)



Raney nickel (W2; 10 mL settled volume) was transferred to a solution of aldol adduct **118** (293 mg, 0.597 mmol) in absolute ethanol (10 mL) and the resulting suspension was heated under reflux with vigorous stirring in an oil bath at 80 °C (previously heated). After 40 min, the mixture was allowed to settle and the supernatant decanted. The solid was suspended in ethanol heated under reflux for 10 min, and decanted. The washing procedure was repeated with methanol and acetone. The combined supernatants were filtered through Celite® and concentrated to give the title compound (237 mg, 92%) that was homogeneous by ¹H NMR.

IR ν_{\max} 3508 cm^{-1} .

¹H NMR (500 MHz, CDCl₃) δ 4.27 (1H, dd, $J = 1.5, 5$ Hz, HC-3), 3.90-3.80 (4H, m, H₂C-4', H₂C-5'), 3.44 (1H, ddd, $J = 4, 6, 7$ Hz, HC-7), 3.03 (1H, dq, $J = 5, 7$ Hz, HC-4), 2.89 (1H, dq, $J =$

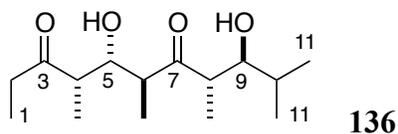
7, 7 Hz, HC-6), 2.27 (1H, d, $J = 6$ Hz, HO), 1.90 (1H, dq, $J = 1, 7$ Hz, HC-2), 1.80-1.57 (3H, m, H₂C-1'', HC-8), 1.07 (3H, d, $J = 7$ Hz, H₃CC-6), 1.04 (3H, d, $J = 7$ Hz, H₃CC-4), 1-0.95 (12H, m, H₃C-9, H₃CCSi $\times 3$), 0.94 (3H, d, $J = 7$ Hz, H₃C-1), 0.91 (3H, d, $J = 6.5$ Hz, H₃C-9), 0.84 (3H, t, $J = 7.5$ Hz, H₃C-2''), 0.64 (6H, ap q, $J = 8$ Hz, H₂CSi $\times 3$).

¹³C NMR (125 MHz, CDCl₃) δ 217.4 (s, C-5), 114.0 (s, C-2'), 79.1 (d, C-7), 69.9 (d, C-3), 65.3 (t, C-4'), 64.9 (t, C-5'), 55.3 (d, C-4), 48.7 (d, C-6), 40.9 (d, C-2), 30.3 (d, C-8), 26.5 (t, C-1''), 20.2 (q, C-9), 15.4 (q, C-9), 13.5 (q, CH₃C-6), 11.4 (q, CH₃C-4), 10.7 (q, C-1), 7.3 (q, C-2''), 7.3 (q $\times 3$, CH₃CSi), 5.5 (t $\times 3$, CH₂Si).

LRMS (CI, NH₃), m/z (relative intensity): 431 ([M+1]⁺, 10), 430 (6), 429 (20), 401 (52), 386 (100).

HRMS m/z calcd for C₂₃H₄₆O₅Si+Na: 453.3006; found: 453.3024 (ESI).

(4S,5S,6S,8S,9S)-rel-5,9-Dihydroxy-4,6,8,10-tetramethylundecane-3,7-dione (136)



FeCl₃·6H₂O (103 mg, 0.382 mmol) was added to a stirred solution of aldol **135** (235 mg, 0.546 mmol) in acetone (124 mL) at room temperature. After 1 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NaHCO₃, water and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to provide the title compound (109 mg, 72%).

IR ν_{\max} 3473 cm⁻¹.

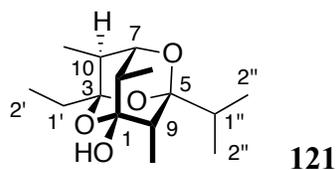
¹H NMR (500 MHz, CDCl₃) δ 4.14 (1H, d, *J* = 8.5 Hz, HC-5), 3.55 (1H, d, *J* = 4.5 Hz, HC-9), 3.48 (1H, br s, HO), 2.89-2.75 (3H, m, HO, HC-6, HC-8), 2.70-2.61 (1H, m, HC-4), 2.61-2.44 (2H, m, HC-2), 1.84-1.72 (1H, m, HC-10), 1.15 (3H, d, *J* = 7 Hz, H₃CC-4), 1.06 (3H, d, *J* = 7 Hz, H₃CC-8), 1.03 (3H, t, *J* = 7.5 Hz, H₃C-1), 1.01 (3H, d, *J* = 7 Hz, H₃CC-6), 0.98 (3H, d, *J* = 7 Hz, H₃C-11), 0.88 (3H, d, *J* = 7 Hz, H₃C-11).

¹³C NMR (125 MHz, CDCl₃) δ 218.8 (s, C-7), 216.0 (s, C-3), 77.7 (d, C-9), 73.0 (d, C-5), 50.2 (d, C-8), 47.6 (d, C-6), 46.7 (d, C-4), 34.9 (t, C-2), 29.8 (d, C-10), 20.3 (q, C-11), 15.2 (q, C-11), 13.8 (q, CH₃C-4 or CH₃C-8), 13.7 (q, CH₃C-4 or CH₃C-8), 9.7 (q, CH₃C-6), 7.8 (q, C-1).

LRMS (CI, NH₃), *m/z* (relative intensity): 273 ([M+1]⁺, 52), 255 (100), 237 (74), 183 (70), 165 (52), 86 (43), 57 (96).

HRMS *m/z* calcd for C₁₅H₂₈O₄+H: 273.2066; found: 273.2069 (EI).

((1*R*,3*R*,5*R*,7*R*,8*S*,9*R*,10*S*)-rel-3-Ethyl-8,9,10-trimethyl-5-(1-methyl)ethyl-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]decan-1-ol (121)



DMP (65 mg, 0.154 mmol) was added to a solution of diol **136** (30 mg, 0.11 mmol) in CH₂Cl₂ (8 mL) at room temperature. After 1 h, the mixture was diluted with ethyl acetate and washed sequentially with a 1:1 (v/v) mixture of saturated aq NaHCO₃ and saturated aq Na₂SO₃, distilled water and brine, dried over Na₂SO₄, and concentrated to produce the crude hydroxytrione as a mixture of hemiacetal, enol and triketone tautomers (28 mg). A solution of imidazole (24 mg, 0.36 mmol) and crude hydroxytriketone (23 mg, 0.084 mmol) in CDCl₃ (0.6

mL; previously neutralized by passing through basic alumina) was heated to 40 °C (oil bath temperature). After 5 days (reaction monitored by ¹H NMR) the mixture was diluted with ethyl acetate and washed sequentially with 1% aq citric acid (3), NaHCO₃ and brine, dried over Na₂SO₄, and concentrated, and fractionated by preparative TLC (20% ethyl acetate in toluene) to give the title compound (8.5 mg, 34% over 2 steps) in addition to other fractions that contained mixtures of retro-Claisen **128**, dehydrated **127**, and hemiacetal **124**.

IR ν_{\max} 3423 cm⁻¹.

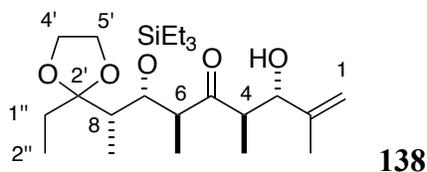
¹H NMR (500 MHz, CDCl₃) δ 3.79 (1H, d, J = 3 Hz, HC-7), 2.63 (1H, s, HO), 2.12-2.05 (2H, m, HC-9, HC-10), 2.02 (1H, br q, J = 7 Hz, HC-8), 1.85 (1H, qq, J = 7, 7 Hz, HC-1''), 1.67-1.53 (2H, m, H₂C-1'), 1.11 (3H, d, J = 7 Hz, H₃CC-8), 1.00-0.87 (15H, m, H₃CC-10, H₃CC-8, H₃C-2', H₃C-2'' \times 2).

¹³C NMR (125 MHz, CDCl₃) δ 103.0 (s, C-3), 102.9 (s, C-5), 97.9 (s, C-1), 78.0 (d, C-7), 36.7 (d, C-10), 35.9 (d, C-8), 34.9 (d, C-9), 32.6 (d, C-1''), 29.7 (t, C-1'), 15.2 (q, C-2''), 15.1 (q, C-2'), 13.3 (q, CH₃C-8), 12.6 (q, CH₃C-10), 6.8 (q, CH₃C-9), 6.6 (q, C-2').

LRMS (CI, NH₃), m/z (relative intensity): 271 ([M+1]⁺, 100), 253 (99), 165 (66), 127 (46), 71 (58).

HRMS m/z calcd for C₁₅H₂₆O₄+H: 271.1909; found: 271.1905 (CI, NH₃).

(3*S*,4*R*,6*S*,7*R*,8*S*)-rel-8-(2-Ethyl-1,3-dioxolan-2-yl)-3-hydroxy-2,4,6-trimethyl-7-(triethylsilyloxy)non-1-en-5-one (138)



(*c*-C₆H₁₁)₂BCl (1 M in hexane; 0.56 mL, 0.56 mmol) was added via syringe to a stirred solution of Et₃N (0.078 mL, 59 mg, 0.58 mmol) CH₂Cl₂ (3 mL) at -78 °C under Ar. After 2 min, a solution of ketone **109** (100 mg, 0.279 mmol) in CH₂Cl₂ (2 mL) was added via syringe. After 2 h, a solution of methacrolein (0.048 mL, 39 mg, 0.56 mmol) CH₂Cl₂ (0.5 mL) was added dropwise via syringe. After 19.5 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 5 mL), MeOH (1 mL) and 30% aq H₂O₂ (1.5 mL) with vigorous stirring. The mixture was warmed to 0 °C and after 10 min, was diluted with ice-water and saturated aqueous Na₂SO₃ and extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated to give the crude product whose ¹H NMR spectrum suggest the presence of a single adduct. Fractionation of the crude by FCC (10-20% ethyl acetate in hexanes) afforded recovered **109** (49 mg, 49%) and the title compound (51 mg, 40%).

IR ν_{max} 3470 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.94 (1H, br s, HC-1), 4.92 (1H, br s, HC-1), 4.30-4.22 (2H, m, HC-3, HC-7), 3.96-3.82 (4H, m, H₂C-4', H₂C-5'), 3.38 (1H, br s, HO), 3.08 (1H, dq, *J* = 4, 7 Hz, HC-6), 2.87 (1H, dq, *J* = 9, 7 Hz, HC-4), 2.04 (1H, br q, *J* = 7 Hz, HC-8), 1.74 (3H, s, H₃CC-2), 1.71-1.53 (2H, m, H₂C-1''), 1.07 (3H, d, *J* = 7 Hz, H₃CC-6), 0.99 (9H, t, *J* = 8 Hz, H₃CCSi ×3),

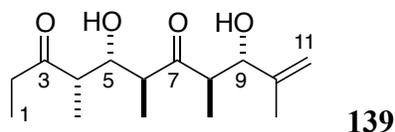
0.94 (3H, d, $J = 7$ Hz, HC-9), 0.92 (3H, d, $J = 7$ Hz, H₃CC-4), 0.83 (3H, t, $J = 7.5$ Hz, HC-2"), 0.65 (6H, ap q, $J = 8$ Hz, H₂CSi ×3).

¹³C NMR (125 MHz, CDCl₃) δ 215.9 (s, C-5), 144.2 (s, C-2), 114.6 (t, C-1), 114.3 (s, C-2'), 77.7 (d, C-3), 69.2 (d, C-7), 65.0 (t, C-4'), 64.8 (t, C-5'), 53.9 (d, C-6), 50.7 (d, C-4), 39.9 (d, C-8), 26.2 (t, C-1"), 16.6 (q, CH₃C-2), 14.7 (q, CH₃C-4), 11.11 (q, CH₃C-6), 11.06 (q, C-9), 7.4 (q, C-2"), 7.2 (q ×3, CH₃CSi), 5.5 (t ×3, CH₂Si).

LRMS (CI, NH₃), m/z (relative intensity): 429 ([M+1]⁺, 13), 367 (82), 302 (63), 297 (52), 285 (100), 273 (35), 199 (58).

HRMS m/z calcd for C₂₃H₄₄O₅Si+H: 429.3036; found: 429.3029 (CI, NH₃).

(4*S*,5*S*,6*S*,8*R*,9*S*)-5,9-Dihydroxy-4,6,8,10-tetramethylundec-10-ene-3,7-dione (139)



FeCl₃·6H₂O (43 mg, 0.158 mmol) was added to a stirred solution of aldol **138** (48 mg, 0.11 mmol) acetone (26 mL) and the mixture was heated under reflux. After 10 min, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NaHCO₃, water and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (50% ethyl acetate in hexane; developed twice) to provide the titled compound (21 mg, 52%).

IR ν_{\max} 3468 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.94 (1H, br s, HC-11), 4.91 (1H, br s, HC-11), 4.19 (1H, d, $J = 9.5$ Hz, HC-9), 4.16 (1H, dd, $J = 3, 8.5$ Hz, HC-5), 3.68 (1H, br s, HOC-5), 3.15 (1H, br s, HOC-

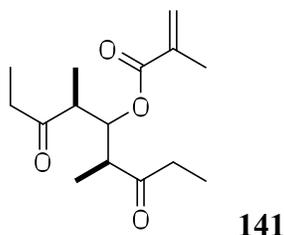
9), 3.04-2.92 (2H, m, HC-6, HC-8), 2.67 (1H, dq, $J = 3, 7$ Hz, HC-4), 2.62-2.45 (2H, m, H₂C-2), 1.73 (3H, s, H₃CC-10), 1.17 (3H, d, $J = 7$ Hz, H₃CC-4), 1.04 (3H, t, $J = 7.5$ Hz, HC-1), 1.02 (3H, d, $J = 7$ Hz, H₃CC-6), 0.90 (3H, d, $J = 7$ Hz, H₃CC-8).

¹³C NMR (125 MHz, CDCl₃) δ 219.4 (s, C-7), 215.9 (s, C-3), 144.4 (s, C-10), 114.8 (t, C-11), 80.0 (d, C-9), 74.4 (d, C-5), 50.4 (d, C-8), 49.4 (d, C-6), 47.0 (d, C-4), 34.9 (t, C-2), 16.5 (q, CH₃C-10), 14.2 (q, CH₃C-8), 13.7 (q, CH₃C-6), 9.8 (q, CH₃C-4), 7.9 (q, C-1).

LRMS (CI, NH₃), m/z (relative intensity): 271 ([M+1]⁺, 51), 253 (100), 201 (70), 200 (51), 183 (50), 171 (22), 167 (27), 153 (18).

HRMS m/z calcd for C₁₅H₂₆O₄+H: 271.1909; found: 271.1904 (CI, NH₃).

(4*S*,6*S*)-rel-4,6-Dimethyl-3,7-dioxononan-5-yl 2-Methylpropenoate (141)



DMP (20 mg, 0.047 mmol) was added to a stirred solution of diol **139** (9 mg, 0.03 mmol) in CH₂Cl₂ (2.3 mL). After 3 h, the reaction was washed sequentially with a 1:1 (v/v) mixture of saturated aq solution of NaHCO₃ and saturated aq Na₂SO₃ and brine, dried over Na₂SO₄, and concentrated to give the crude product (11 mg) that was mixture of at least 4 major components by ¹H NMR. Imidazole (42 mg, 0.62 mmol) was added to a solution of the above crude (11 mg) in CDCl₃ (0.6 mL; previously passed through basic alumina) at room temperature. After 19.5 h, the mixture was diluted in ethyl acetate, washed sequentially with 1% aq citric acid, saturated aq

NaHCO₃ and brine, dried over Na₂SO₄, and fractionated by PTLC (20% ethyl acetate in hexanes; developed twice) to give the title compound (2.4 mg, 24%).

IR ν_{\max} 1720 cm⁻¹.

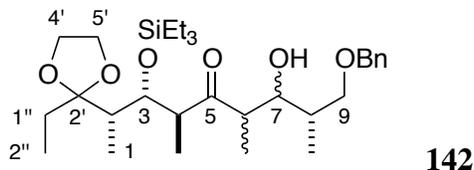
¹H NMR (500 MHz, CDCl₃) δ 6.04 (1H, br s, HC-3), 5.55 (1H, br s, HC-3), 5.53 (1H, dd, $J = 6, 7$ Hz, HC-5'), 2.97-2.83 (2H, m, HC-4', HC-6'), 2.71 (1H, dq, $J = 18, 7$ Hz, HC-2 or HC-8), 2.54-2.39 (3H, m, HC-2, H₂C-8), 1.90 (3H, s, H₃CC-2), 1.13 (3H, d, $J = 7$ Hz, HC₃C-4' or H₃CC-6'), 1.07 (3H, d, $J = 7$ Hz, HC₃C-4' or H₃CC-6'), 1.04 (3H, t, $J = 7$ Hz, HC₃C-1' or H₃CC-9'), 1.01 (3H, t, $J = 7$ Hz, HC₃C-1' or H₃CC-9').

¹³C NMR (125 MHz, CDCl₃) δ 212.2 (s, C-3' or C-7'), 211.9 (s, C-3' or C-7'), 166.4 (s, C-1), 136.0 (s, C-2), 126.1 (t, C-3), 75.0 (d, C-5'), 48.2 (d, C-4' or C-6'), 46.8 (d, C-4' or C-6'), 35.4 (t, C-2' or C-8'), 35.1 (t, C-2' or C-8'), 18.5 (q, CH₃C-2), 13.2 (q, CH₃C-4' or CH₃C-6'), 11.6 (q, CH₃C-4' or CH₃C-6'), 7.9 (q, CH₃C-1' or CH₃C-9'), 7.8 (q, CH₃C-1' or CH₃C-9').

LRMS (CI, NH₃), m/z (relative intensity): 269 ([M+1]⁺, 13), 183 (61), 165 (100), 139 (18), 126 (14), 125 (18), 69 (44), 57 (64).

HRMS m/z calcd for C₁₅H₂₄O₄+H: 269.1753; found: 269.1749 (CI, NH₃).

(2*S*,3*R*,4*S*,8*S*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-3-triethylsilyloxy-7-hydroxy-4,6,8-trimethyl-9-(phenylmethoxy)nonan-5-one (142).



LHMDS (1 M in THF; 0.21 mL, 0.21 mmol) was added to a solution of (+)-**109** (50 mg, 0.14 mmol) in THF (0.7 mL) at $-50\text{ }^{\circ}\text{C}$. After 1 h, the reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of freshly prepared (*S*)-**29** (28 mg, 0.16 mmol) in THF (0.7 mL) was added slowly via syringe. After 1 h, the reaction was quenched by addition of aq. phosphate buffer (pH= 7) and the mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 , concentrated, and fractionated by FCC (2-100% ethyl acetate in CH_2Cl_2) to give recovered (+)-**109** (8 mg, 16%) and the title compound as a ca. 43:25:18:15 mixture of diastereomers (60 mg, 80%).

IR ν_{max} : 3513, 1697 cm^{-1}

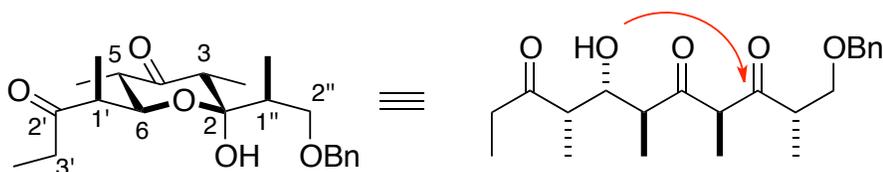
^1H NMR (500 MHz, CDCl_3) δ : 7.38-7.24 (5H, m, Ph), 4.60-4.43 (2H, m, H_2CPh), 4.29 (0.25H, dd, $J = 1, 5\text{ Hz}$, HC-3), 4.25 (0.60H, ap dd, $J = 1, 5\text{ Hz}$, HC-3), 4.23 (0.18H, dd, $J = 1.5, 5\text{ Hz}$, HC-3), 4.01 (0.15H, br d, $J = 9.5\text{ Hz}$, HC-7), 3.93 (0.18H, br d, $J = 10\text{ Hz}$, HC-7), 3.91-3.72 (4.5H, m, $\text{H}_2\text{C-4'}$, $\text{H}_2\text{C-5'}$, HC-7), 3.69-3.39 (2.2H, m, HC-7, $\text{H}_2\text{C-9}$), 3.21 (0.25H, d, $J = 7\text{ Hz}$, HO), 3.12-2.89 (1.7H, m, HC-4, HC-6), 2.85 (0.15H, br q, $J = 7.5\text{ Hz}$, HC-6), 2.83 (0.43H, d, $J = 2\text{ Hz}$, HO), 2.79 (0.18H, dq, $J = 1.5, 7.5\text{ Hz}$, HC-6), 2.02 (0.15H, dq, $J = 1, 7\text{ Hz}$, HC-2), 1.99-1.75 (1.8H, m, HC-2, HC-8), 1.75-1.53 (2H, m, $\text{H}_2\text{C-1''}$), 1.15 (1.8H, br d, $J = 7.5\text{ Hz}$, $\text{H}_3\text{CC-6}$), 1.10-0.90 (19.2H, m), 0.87-0.80 (3H, m, $\text{H}_3\text{C-2''}$), 0.68-0.58 (6H, m, $\text{H}_2\text{CSi} \times 3$)

^{13}C NMR (125 MHz, CDCl_3) δ (major diastereomer*): 218.1, 216.8, 216.5, 216.2*, 138.9, 138.8, 138.3*, 138.2, 128.62, 128.60*, 128.53, 128.46, 127.9, 127.8*, 127.78, 127.74, 127.69*, 127.63, 114.2, 113.99, 113.91*, 78.7, 74.7*, 74.6*, 74.3, 73.69, 73.55, 73.48, 73.44, 72.6, 72.4, 71.9, 70.4, 70.2*, 69.51, 69.45, 65.2*, 65.1, 64.95*, 64.93, 64.8, 55.7, 53.7*, 53.6, 52.5, 50.6, 49.7, 49.1*, 47.2, 40.8*, 40.7, 40.5, 40.0, 36.3*, 36.2, 35.6, 34.9, 26.5*, 26.3, 15.7, 14.0, 13.8, 13.3, 12.9*, 11.8*, 11.4, 10.99, 10.95, 10.93, 10.92, 10.8*, 10.7*, 9.4, 8.9, 7.4, 7.31, 7.26*, 7.21, 7.18, 5.55, 5.48*, 5.43

LRMS (CI, NH_3), m/z (relative intensity): 537 ($[\text{M}+1]^+$, 1), 359 (36), 227 (37), 196 (23), 179 (10), 101 (100), 91 (23)

HRMS m/z calcd for $\text{C}_{30}\text{H}_{52}\text{O}_6\text{Si}+\text{H}$: 537.3611; found: 537.3592 (CI, NH_3)

(2R,3S,5S,6S)-Tetrahydro-2-hydroxy-3,5-dimethyl-6-((S)-1-methyl-2-oxobutyl)-2-((S)-1-methyl-2-(phenylmethoxy)ethyl)-tetrahydro-4H-pyran-4-one (134).



134

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (10.5 mg, 0.039 mmol) was added to a stirred solution of aldol adducts **142** (20 mg, 0.037 mmol) in acetone (1.3 mL) at room temperature. After 1 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NaHCO_3 , H_2O and brine, dried over Na_2SO_4 , and concentrated. The residue was taken up in CH_2Cl_2 (2.6 mL) and DMP (16 mg, 0.038 mmol) was added to the stirred solution. After 3 h, the reaction was washed sequentially with a 1:1 (v/v) mixture of saturated aq NaHCO_3 and saturated aq Na_2SO_3 , H_2O and brine, dried over Na_2SO_4 , and concentrated. The residue was dissolved in a solution of imidazole (22 mg, 0.32

mmol) in CDCl_3 (0.6 mL; previously passed over basic alumina) and heated at 40 °C in an NMR tube. After 19 h, the mixture was diluted in ethyl acetate, washed sequentially with citric acid 1%, saturated aq NaHCO_3 and brine, dried over Na_2SO_4 , concentrated, and fractionated by PTLC (20% ethyl acetate in hexanes; multiple elutions) to afford of the titled compound (4.5 mg, 32% over 3 steps). $[\alpha]_D^{25} +30$ (*c* 0.4, CHCl_3)

IR ν_{max} : 3408, 1719 cm^{-1}

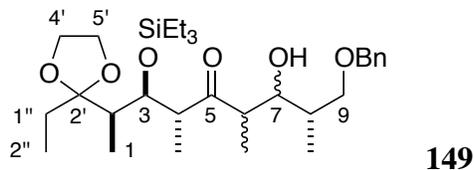
^1H NMR (500 MHz, CDCl_3) δ : 5.58 (1H, d, $J = 2.5$ Hz, HO), 4.51 (1H, d, $J = 11.5$ Hz, HCPH), 4.45 (1H, dd, $J = 2.5, 10.5$ Hz, HC-6), 4.34 (1H, d, $J = 11.5$ Hz, HCPH), 3.70 (1H, dd, $J = 9, 11$ Hz, HC-2''), 3.42 (1H, dd, $J = 4, 9$ Hz, HC-2''), 2.73 (1H, dq, $J = 2.5, 7$ Hz, HC-1'), 2.61 (1H, br q, $J = 6.5$ Hz, HC-3), 2.57-2.42 (3H, m, H_2C -3', HC-5), 2.22 (1H, ddq, $J = 4, 9, 7$ Hz, HC-1''), 1.18 (3H, d, $J = 7$ Hz, H_3CC -1'), 1.04 (3H, t, $J = 7.5$ Hz, H_3C -4'), 104 (3H, d, $J = 6.5$ Hz, H_3CC -3), 103 (3H, d, $J = 7$ Hz, H_3CC -5), 0.88 (3H, d, $J = 7$ Hz, H_3CC -1'')

^{13}C NMR (125 MHz, CDCl_3) δ : 211.2 (s, C-2'), 209.0 (s, C-4), 137.1 (s, Ph), 128.8 (d $\times 2$, Ph), 128.2 (d, Ph), 127.8 (d $\times 2$, Ph), 104.0 (s, C-2), 74.4 (d, C-6), 73.8 (t, CH_2Ph), 73.4 (t, C-2''), 51.1 (d, C-3), 48.0 (d, C-1'), 46.6 (d, C-5), 38.4 (d, C-1''), 33.3 (t, C-3'), 12.3 (q, CH_3C -1''), 9.4 (q, CH_3C -5), 8.29 (q, C-4' or CH_3C -3), 8.29 (q, C-4' or CH_3C -3), 7.8 (q, CH_3C -1')

LRMS (CI, NH_3), m/z (relative intensity): 394 ($[\text{M}+18]^+$, 26), 377 ($[\text{M}+1]^+$, 17), 360 (27), 359 (93), 212 (21), 195 (26), 193 (39), 183 (82), 108 (20), 91 (100)

HRMS m/z calcd for $\text{C}_{22}\text{H}_{32}\text{O}_5+\text{NH}_4$: 394.2593; found: 394.2603 (CI, NH_3).

(2*R*,3*S*,4*R*,8*S*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-3-triethylsilyloxy-7-hydroxy-4,6,8-trimethyl-9-(phenylmethoxy)nonan-5-one (149).



A solution of freshly prepared LDA (0.17 M in THF; 9.5 mL, 1.6 mmol) at 0 °C was added via cannula to a stirred solution of (-)-**109** (*ent*-**109**) (527 mg, 1.47 mmol) in dry THF (26 mL) at –78 °C under argon. After 15 min, Ti(O^{*i*}Pr)₄ (0.99 mL, 0.92 g, 3.2 mmol) was added. The reaction mixture was stirred for 10 min at –78 °C, 30 min at –50 °C, and finally 5 min at –78 °C. A solution of freshly prepared (*S*)-**29** (283 mg, 1.59 mmol) in THF (10 mL) was added over 10 min via syringe. After 19 h, the reaction was quenched by addition of H₂O (14 mL), and the mixture was extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (5% ethyl acetate in CH₂Cl₂) to give recovered *ent*-**109** (85 mg, 16%) and a 82:14:4 mixture of aldol adducts (646 mg, 81%).

[α]_D –59 (*c* 1.0, CHCl₃)

IR ν_{max}: 3508, 1699 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ (major diastereomer only): 7.39-7.21 (5H, m, Ph), 4.52-4.48 (2H, m, CH₂Ph), 4.17 (1H, dd, *J* = 1.5, 4 Hz, HC-3), 3.93 (1H, ddd, *J* = 2, 3, 7 Hz, HC-7), 3.89-3.71 (4H, m, H₂C-4', H₂C-5'), 3.43-3.37 (2H, dd, *J* = 5, 2.5 Hz, H₂C-9), 3.36 (1H, d, *J* = 2 Hz, HO), 3.04 (1H, dq, *J* = 4, 7 Hz, HC-4), 2.88 (1H, dq, *J* = 3, 7 Hz, HC-6), 1.98 (1H, dq, *J* = 1.5, 7 Hz, HC-2), 1.94-1.85 (1H, m, HC-8), 1.66 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1''), 1.56 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1''), 1.17 (3H, d, *J* = 7 Hz, H₃CC-6), 1.09 (3H, d, *J* = 7 Hz, H₃CC-8), 1.04 (3H, d, *J* =

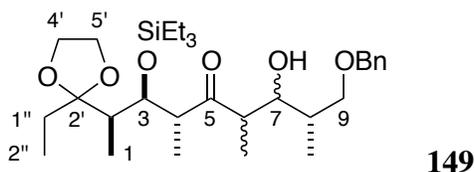
7 Hz, H₃CC-4), 0.96 (9H, t, *J* = 8 Hz, H₃CCSi ×3), 0.93 (3H, d, *J* = 7 Hz, H₃C-1), 0.82 (3H, t, *J* = 7.5 Hz, H₃C-2''), 0.61 (6H, ap q, *J* = 8 Hz, H₂CSi ×3)

¹³C NMR (125 MHz, CDCl₃) δ (major diastereomer only): 217.5 (s, C-5), 138.5 (s, Ph), 128.5 (d ×2, Ph), 127.8 (d, Ph), 127.6 (d ×2, Ph), 114.0 (s, C-2'), 73.9 (t, C-9), 73.5 (t, CH₂Ph), 73.1 (d, C-7), 70.1 (d, C-3), 65.2 (t, C-4' or C-5'), 64.9 (t, C-5' or C-4'), 52.6 (d, C-4), 48.9 (d, C-6), 40.4 (d, C-2), 36.3 (d, C-8), 26.2 (t, C-1''), 14.0 (q, CH₃C-8), 11.2 (q, C-1 or CH₃C-4), 11.1 (q, C-1 or CH₃C-4), 10.6 (q, CH₃C-6), 7.3 (q, C-2''), 7.2 (q ×3, CH₃CSi), 5.5 (t ×3, CH₂Si)

LRMS (EI), *m/z* (relative intensity): 507 ([M-29]⁺, 20), 378 (16), 377 (48), 364 (11), 349 (12), 330 (27), 329 (100)

HRMS *m/z* calcd for C₃₀H₅₂O₆Si+H: 537.3611; found: 537.3591 (CI, NH₃).

(2*R*,3*S*,4*R*,8*S*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-3-triethylsilyloxy-7-hydroxy-4,6,8-trimethyl-9-(phenylmethoxy)nonan-5-one (149).



LHMDS (1 M in THF; 2.2 mL, 2.2 mmol) was added to a solution of (-)-**109** (1.31 g, 3.65 mmol) in THF (31 mL) at -50 °C. After 1 h, the reaction mixture was cooled to -78 °C and a solution of freshly prepared (*S*)-**29** (677 mg, 3.80 mmol) in THF (2 mL) was added slowly via syringe over 5 min. After 1 h, the reaction was quenched by addition of aq phosphate buffer (pH= 7) and the mixture was extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (2% ethyl acetate in CH₂Cl₂) to give

recovered **29** (110 mg, 16%), *ent*-**109** (262 mg, 20%), and a 73:10:9:8 mixture of aldol adducts (1.51 mg, 77%). $[\alpha]_D -51$ (*c* 0.95, CHCl₃)

IR ν_{\max} : 3491, 1706 cm⁻¹

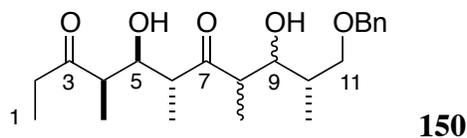
¹H NMR (500 MHz, CDCl₃) δ (major diastereomer only): 7.39-7.23 (5H, m, Ph), 4.57-4.47 (2H, m, H₂CPh), 4.25 (1H, dd, *J* = 1.5, 5 Hz, HC-3), 3.92 (1H, ddd, *J* = 2, 2, 9 Hz, HC-7), 3.90-3.73 (4H, m, H₂C-4', H₂C-5'), 3.62 (1H, dd, *J* = 5, 9 Hz, HC-9) 3.58 (1H, dd, *J* = 7, 9 Hz, HC-9), 3.51 (1H, d, *J* = 2 Hz, HO), 3.11 (1H, d7, *J* = 5, 7 Hz, HC-4), 2.85 (1H, dq, *J* = 2, 7 Hz, HC-6), 2.00-1.90 (1H, m, HC-8), 1.87 (1H, dq, *J* = 1.5, 7 Hz, HC-2), 1.68 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1''), 1.59 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1''), 1.06 (3H, d, *J* = 7 Hz, H₃CC-6), 1.05 (3H, d, *J* = 7 Hz, H₃CC-4), 0.97 (9H, t, *J* = 8 Hz, H₃CCSi \times 3), 0.93 (3H, d, *J* = 7 Hz, H₃C-1), 0.92 (3H, d, *J* = 7 Hz, H₃CC-8), 0.83 (3H, t, *J* = 7.5 Hz, H₃C-2''), 0.63 (6H, q, *J* = 8 Hz, H₂CSi \times 3)

¹³C NMR (125 MHz, CDCl₃) δ : 214.5 (s, C-5), 138.0 (s, Ph), 128.6 (d \times 2, Ph), 127.9 (d, Ph), 127.8 (d \times 2, Ph), 114.0 (s, C-2'), 75.6 (d, C-7), 75.2 (t, C-9), 73.7 (d, C-3), 65.2 (t, C-4' or C-5'), 64.9 (t, C-5' or C-4'), 51.9 (d, C-4), 48.5 (d, C-6), 40.7 (d, C-2), 36.4 (d, C-8), 26.3 (t, C-1''), 13.9 (q, CH₃C-8), 11.1 (q, CH₃C-4), 10.8 (q, C-1), 7.7 (q, CH₃C-6), 7.2 (q \times 3, CH₃CSi), 7.2 (q, C-2''), 5.5 (t \times 3, CH₂Si)

LRMS (CI, NH₃), *m/z* (relative intensity): 537 ([M+1]⁺, 21), 476 (36), 475 (100), 424 (21), 405 (42), 387 (32), 379 (17), 377 (11)

HRMS *m/z* calcd for C₃₀H₅₂O₆Si+H: 537.3611; found: 537.3601 (CI, NH₃).

(4*R*,5*R*,6*R*,10*S*)-5,9-Dihydroxy-4,6,8,10-tetramethyl-11-(phenylmethoxy)undecan-3,7-dione
(150).



FeCl₃·6H₂O (43 mg, 0.16 mmol) was added to a stirred solution of aldol adducts **149** (coming from the reaction with Ti ‘ate’ enolate) (123 mg, 0.230 mmol) in acetone (52 mL) at room temperature. After 1.5 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NaHCO₃, H₂O and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to afford the titled compound (80 mg, 92%). Usually, the crude from this reaction mixture was used in the following reaction without further purification. [α]_D – 20 (*c* 0.05, CHCl₃)

IR ν_{max}: 3489, 1709 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ (major diastereomer only): 7.39-7.24 (5H, m, Ph), 4.50 (1H, d, *J* = 12, CHPh), 4.48 (1H, d, *J* = 12 Hz, CHPh), 4.09 (1H, ddd, *J* = 2.5, 3, 9 Hz, HC-5), 4.05 (1H, ddd, *J* = 3, 4.5, 7 Hz, HC-9), 3.48 (1H, dd, *J* = 4.5, 9.5 Hz, HC-11), 3.43 (1H, dd, *J* = 4.5, 9.5 Hz, HC-11), 3.38 (1H, d, *J* = 3 Hz, HOC-5), 3.08 (1H, d, *J* = 3 Hz, HOC-9), 2.89 (1H, dq, *J* = 9, 7 Hz, HC-6), 2.85 (1H, d, *J* = 4.5, 7 Hz, HC-8), 2.65 (1H, dq, *J* = 2.5, 7 Hz, HC-4), 2.56 (1H, dq, *J* = 18, 7.5 Hz, HC-2), 2.50 (1H, dq, *J* = 18, 7.5 Hz, HC-2), 1.96-1.84 (1H, m, HC-10), 1.13 (3H, d, *J* = 7 Hz, H₃CC-4), 1.11 (3H, d, *J* = 7 Hz, H₃CC-8), 1.09 (3H, d, *J* = 7 Hz, H₃CC-10), 1.05 (3H, t, *J* = 7.5 Hz, H₃C-1), 0.94 (3H, d, *J* = 7 Hz, H₃C-6)

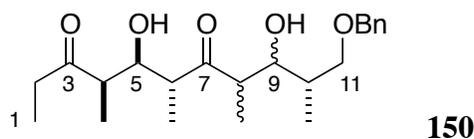
¹³C NMR (125 MHz, CDCl₃) δ (major diastereomer only): 217.9 (s, C-7), 216.5 (s, C-3), 138.6 (s, Ph), 128.6 (d ×2, Ph), 127.8 (d, Ph), 127.7 (d ×2, Ph), 74.3 (t, C-11), 73.6 (d, C-5), 73.5 (t,

CH₂Ph), 73.0 (d, C-9), 50.5 (d, C-8), 46.2 (d ×2, C-4, C-6), 36.1 (d, C-10), 35.0 (t, C-2), 14.0 (q, CH₃C-6), 13.6 (q, CH₃C-10), 10.0 (q, CH₃C-8), 9.3 (q, CH₃C-4), 7.8 (q, C-1)

LRMS (EI), *m/z* (relative intensity): 378 ([M]⁺, 4), 361 (81), 360 (100), 345 (45), 343 (47), 342 (38)

HRMS *m/z* calcd for C₂₂H₃₄O₅+H: 379.2485; found: 379.2490 (CI, NH₃).

(4*R*,5*R*,6*R*,10*S*)-5,9-Dihydroxy-4,6,8,10-tetramethyl-11-(phenylmethoxy)undecan-3,7-dione
(150).



FeCl₃·6H₂O (532 mg, 1.97 mmol) was added to a stirred solution of aldol adducts **149** (coming from the reaction with Li enolate)(1.51 g, 2.81 mmol) in acetone (63 mL) at room temperature. After 1.5 h, the mixture was diluted with ethyl acetate and washed sequentially with a saturated aq NaHCO₃, H₂O and brine, dried over Na₂SO₄, concentrated to afford the crude titled compound (1.26 g) that was used directly in the next step. The crude from a smaller scale reaction as above was fractionated by FCC (30% ethyl acetate in hexane) to give the titled compound (90%). [α]_D +14 (*c* 1.1, CHCl₃)

IR ν_{max}: 3479, 1706 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ: 7.40-7.21 (5H, m, Ph), 4.53 (1H, d, *J* = 12 Hz, HCPh) 4.50 (2H, d, *J* = 12 Hz, HCPh), 4.11 (1H, ddd, *J* = 3, 3.5, 8.5 Hz, HC-5), 3.90 (1H, br d, *J* = 9 Hz, HC-9), 3.82 (1H, br s, HOC-9), 3.61-3.54 (2H, m, H₂C-11), 3.40 (1H, d, *J* = 3.5 Hz, HOC-5), 2.99 (1H, dq, *J* = 8.5, 7 Hz, HC-6), 2.73 (1H, dq, *J* = 2.5, 7 Hz, HC-8), 2.64 (1H, dq, *J* = 3, 7 Hz, HC-4),

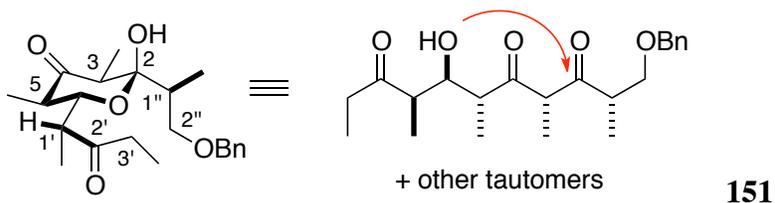
2.61-2.44 (2H, m, H₂C-2), 1.99-1.85 (1H, m, HC-10), 1.14 (3H, d, *J* = 7 Hz, H₃CC-4), 1.14 (3H, d, *J* = 7 Hz, H₃CC-8), 1.04 (3H, t, *J* = 7.5 Hz, H₃C-1), 1.01 (3H, d, *J* = 7 Hz, H₃CC-6), 0.89 (3H, d, *J* = 7 Hz, H₃CC-10)

¹³C NMR (125 MHz, CDCl₃) δ: 218.6 (s, C-7), 215.9 (s, C-3), 138.1 (s, Ph), 128.6 (d ×2, Ph), 127.9 (d, Ph), 127.9 (d ×2, Ph), 75.3 (d, C-9), 74.9 (t, C-11), 73.9 (d, C-5), 73.6 (t, CH₂Ph), 50.1 (d, C-8), 47.0 (d, C-4), 45.7 (d, C-6), 36.2 (d, C-10), 34.9 (t, C-2), 14.3 (q, CH₃C-6), 13.9 (q, CH₃C-10), 9.7 (q, CH₃C-4), 8.1 (q, CH₃C-8), 7.9 (q, C-1)

LRMS (CI, NH₃), *m/z* (relative intensity): 379 ([M+1]⁺, 43), 265 (51), 218 (27), 201 (39), 196 (50), 183 (38), 179 (28), 108 (27), 91 (100)

HRMS *m/z* calcd for C₂₂H₃₄O₅+H: 379.2485; found: 379.2487 (CI, NH₃).

(2*S*,3*R*,5*R*,6*R*)-Tetrahydro-2-hydroxy-3,5-dimethyl-6-((*R*)-1-methyl-2-oxobutyl)-2-((*S*)-1-methyl-2-(phenylmethoxy)ethyl)-4*H*-pyran-4-one (151).



DMP (1.25 g, 2.95 mmol) was added to a stirred solution of the above crude diols (1.26 g; from 1.51 g of aldol adducts) in CH₂Cl₂ (200 mL) at room temperature. After 3 h, the reaction was washed sequentially with a 1:1 (v/v) mixture of saturated aq NaHCO₃ and 10% aq Na₂SO₃, H₂O and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (20-50% ethyl acetate in hexane) to give recovered **150** (200 mg, 19% from **149**) and the titled compound as the predominant component in a mixture of ring-chain tautomers (842 mg, 80% from **149**).

Resubjecting recovered **150** to the above reaction conditions gave additional **151** (148 mg, 14% from **149**).

IR ν_{max} : 3429, 1717 cm^{-1}

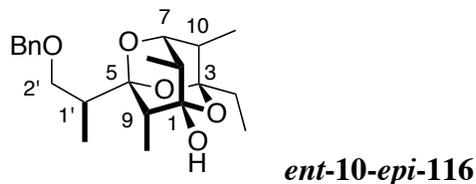
^1H NMR (500 MHz, CDCl_3) δ (major diastereomer only): 7.40-7.20 (5H, m, Ph), 4.15 (1H, d, $J = 12$ Hz, HCPh), 4.41 (1H, d, $J = 12$ Hz, HCPh), 4.32 (1H, dd, $J = 3, 10.5$ Hz, HC-6), 3.59 (1H, dd, $J = 6.5, 9.5$ Hz, HC-2''), 3.49 (1H, dd, $J = 5, 9.5$ Hz, HC-2''), 3.33 (1H, s, HO), 2.77 (1H, br q, $J = 6.5$ Hz, HC-3), 2.64 (1H, dq, $J = 3, 7$ Hz, HC-1'), 2.58-2.35 (3H, m, H_2C -3', HC-5), 2.18 (1H, ddq, $J = 5, 6.5, 7$ Hz, HC-1''), 1.14 (3H, d, $J = 7$ Hz, H_3CC -1'), 1.09 (3H, d, $J = 6.5$ Hz, H_3CC -3), 1.02 (3H, t, $J = 7.5$ Hz, H_3C -4'), 0.99 (3H, d, $J = 6.5$ Hz, H_3CC -5), 0.98 (3H, d, $J = 7$ Hz, H_3CC -1'')

^{13}C NMR (125 MHz, CDCl_3) δ (major diastereomer only): 211.5 (s, C-2'), 209.0 (s, C-4), 138.0 (s, Ph), 128.6 (d $\times 2$, Ph), 127.9 (d, Ph), 127.7 (d $\times 2$, Ph), 102.2 (s, C-2), 74.5 (d, C-6), 73.4 (t, CH_2Ph), 72.8 (t, C-2''), 51.4 (d, C-3), 47.8 (d, C-1'), 46.5 (d, C-5), 41.4 (d, C-1''), 33.4 (t, C-3'), 12.0 (q, CH_3C -1''), 9.4 (q, CH_3C -3 or CH_3C -5), 9.3 (q, CH_3C -3 or CH_3C -5), 8.07 (q, C-4' or CH_3C -1''), 8.06 (q, C-4' or CH_3C -1'')

LRMS (CI, NH_3), m/z (relative intensity): 394 ($[\text{M}+18]^+$, 76), 377 ($[\text{M}+1]^+$, 21), 359 (31), 212 (45), 200 (49), 183 (100), 108 (28), 91 (46)

HRMS m/z calcd for $\text{C}_{22}\text{H}_{32}\text{O}_5+\text{NH}_4$: 394.2593; found: 394.2596 (CI, NH_3).

(1*S*,3*S*,5*S*,7*S*,8*R*,9*S*,10*R*)-3-Ethyl-8,9,10-trimethyl-5-[(*S*)-1-methyl-2-(phenylmethoxy)ethyl]-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]decan-1-ol (*ent*-10-*epi*-116).



A solution of imidazole (539 mg, 7.92 mmol) and hemiacetals **151** (432 mg, 1.15 mmol) in CHCl₃ (14.4 mL; previously neutralized by passing through basic alumina) was stirred at 40 °C. After 50 h, the mixture was diluted in ethyl acetate, washed sequentially with 1% aq citric acid (×3), saturated aq NaHCO₃ and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to crude *ent*-10-*epi*-**116** (234 mg) and recovered hemiacetals **151** (113 mg, 26%). The hemiacetal fraction was resubjected to the isomerization conditions and the crude *ent*-10-*epi*-**116** was fractionated by FCC (5% ethyl acetate in toluene) to yield the titled compound (225 mg, 51%). [α]_D -41 (*c* 1.1, CHCl₃)

IR ν_{\max} : 3424 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ : 7.37-7.23 (5H, m, Ph), 4.56 (1H, d, *J* = 12 Hz, HCPh), 4.46 (1H, d, *J* = 12 Hz, HCPh), 3.90 (1H, dd, *J* = 2.5, 9 Hz, HC-2'), 3.73 (1H, d, *J* = 3.5 Hz, HC-7), 3.35 (1H, dd, *J* = 9, 9.5 Hz, HC-2'), 2.63 (1H, s, HO), 2.10-1.97 (4H, m, HC-1', HC-8, HC-9, HC-10), 1.63 (1H, dq, *J* = 14.5, 7.5 Hz, HCC-3), 1.55 (1H, dq, *J* = 14.5, 7.5 Hz, HCC-3), 1.11 (3H, d, *J* = 7 Hz, H₃CC-8), 1.04 (3H, d, *J* = 7 Hz, H₃CC-1'), 0.97 (3H, d, *J* = 6.5 Hz, H₃CC-9), 0.92 (3H, t, *J* = 7.5 Hz, H₃CCC-3), 0.89 (3H, d, *J* = 7 Hz, H₃CC-10)

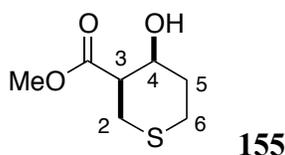
¹³C NMR (125 MHz, CDCl₃) δ : 139.1 (s, Ph), 128.5 (d ×2, Ph), 127.8 (d, Ph), 127.5 (d ×2, Ph), 103.0 (s, C-3), 102.9 (s, C-5), 97.6 (s, C-1), 78.1 (d, C-7), 73.3 (t, CH₂Ph), 71.3 (d, C-2'), 38.8 (d,

C-1'), 36.9 (d, C-10), 35.8 (d, C-8), 34.9 (d, C-9), 29.6 (t, CH₂C-3), 13.3 (q, CH₃C-8), 12.5 (q, CH₃C-10), 11.1 (q, CH₃C-1'), 6.8 (q, CH₃C-9), 6.5 (q, CH₃CC-3)

LRMS (CI, NH₃), *m/z* (relative intensity): 394 ([M+18]⁺, 70), 377 ([M+1]⁺, 33), 376 (15), 359 (100), 227 (33), 212 (33), 183 (69), 165 (34), 101 (56), 91 (57)

HRMS *m/z* calcd for C₂₂H₃₂O₅+NH₄: 394.2594; found: 394.2593 (CI, NH₃).

Methyl (3*R*,4*S*)-Tetrahydro-4-hydroxy-2*H*-thiopyran-3-carboxylate (**155**)



Procedure adapted from Hayakawa R.; Shimizu M. *Synlett* 1999, 1328-1330. A suspension of Bakers' yeast (Fleischmann's; 5.59 g) in distilled water (55.5 mL) was stirred (orbital shaker at 150 rpm) at room temperature. After 30 min, DMSO (0.40 mL) was added and stirring continued for 30 min. A solution of 2-ketoester **154** (326 mg, 1.87 mmol) in absolute ethanol (5.5 mL) was added. After stirring for 1 day, Celite® (40 mL) and ethyl acetate (40 mL) were added and stirring continued for 30 min. The resulting mixture was filtered through a bed of Celite® in a sintered glass funnel rinsing with ethyl acetate and the combined filtrate and washings were extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (50% ethyl acetate in hexanes) to yield the title compound (250 mg, 75%; 93% ee by HPLC analysis of the benzoyl derivative). A similar experiment conducted with 7.3 g of **154** and 130 g of Baker's yeast (distributed in 15 × 250 mL Erlenmeyer flasks) gave the title compound (4.24 g, 57%; 93% ee).

[α]_D +35 (*c* 1.3, benzene)

IR ν_{\max} 3504 cm^{-1} .

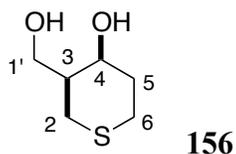
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 4.18 (1H, ddd, $J = 2.5, 2.5, 5$ Hz, HC-4), 3.72 (3H, s, H_3CO), 3.16 (1H, dd, $J = 10.5, 13.5$ Hz, HC-2), 2.98 (1H, ddd, $J = 2.5, 11, 13.5$ Hz, HC-6), 2.85 (1H, dt, $J = 2.5, 2.5, 10.5$ Hz, HC-3), 2.57 (1H, br d, $J = 13.5$ Hz, HC-2), 2.32 (1H, ddd, $J = 3.5, 4, 13.5$ Hz, HC-6), 2.19 (1H, m, $J = 2.5, 4, 5, 14$ Hz, HC-5), 1.89 (1H, ddt, $J = 2.5, 3, 11, 14$ Hz, HC-5).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 174.3 (s, C=O), 65.9 (d, C-4), 52.2 (q, CH_3O), 47.6 (d, C-3), 33.5 (t, C-5), 25.1 (t, C-2), 22.9 (t, C-6).

LRMS (EI), m/z (relative intensity): 176 ($[\text{M}]^+$, 84), 158 (38), 126 (18), 99 (100), 98 (60), 87 (66), 55 (27).

HRMS m/z calcd for $\text{C}_7\text{H}_{12}\text{O}_3\text{S}$: 176.0507; found: 176.0510 (EI).

(3*S*,4*S*)-3-(Hydroxymethyl)-tetrahydro-2*H*-thiopyran-4-ol (156)



NaBH_4 (1.77 g, 45.4 mmol) was added slowly in small portions to a stirred solution of **155** (2.05 g, 11.3 mmol) in methanol (28.3 mL) at room temperature. After 35 min, the mixture was neutralized to pH 7 by addition of 10% aq HCl. The mixture was diluted with MeOH and filtered through a plug of silica gel rinsing with 20% (v/v) methanol in CH_2Cl_2 . The combined filtrate and washings were concentrated. The residue was taken up in 1 M aq NaOH and after stirred for 1 h, the aqueous layer was extracted with CH_2Cl_2 , dried over Na_2SO_4 , concentrated, and fractionated by FCC (50% ethyl acetate in hexanes to 100% ethyl acetate) to yield the title

compound (1.23 g, 73%). [known compound: Hayakawa, R.; Shimizu, M. Synlett 1999, 1298-1300.]

$[\alpha]_D^{+17}$ (c 0.7, CHCl_3)

IR ν_{max} 3372 cm^{-1} .

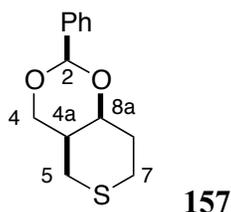
^1H NMR (500 MHz, CDCl_3) δ 4.16 (1H, ddd, $J = 2.5, 3, 5.5$ Hz, HC-4), 3.84 (1H, dd, $J = 5.5, 11$ Hz, HC-1'), 3.82 (1H, dd, $J = 4.5, 11$ Hz, HC-1'), 3.03 (1H, dd, $J = 10.5, 13.5$ Hz, HC-2), 2.99 (1H, ddd, $J = 2.5, 11, 14$ Hz, HC-6), 2.85 (1H, br s, HOC-4), 2.59 (1H, br s, HOC-7), 2.37-2.30 (2H, m, HC-2, HC-6), 2.08 (1H, dddd, $J = 3, 5.5, 5.5, 14$ Hz, HC-5), 2.00 (1H, dddd, $J = 2.5, 3, 4.5, 5.5, 10.5$ Hz, HC-3), 1.91 (1H, dddd, $J = 3, 3.5, 11, 14$ Hz, HC-5).

^{13}C NMR (125 MHz, CDCl_3) δ 69.2 (d, C-4), 66.3 (t, C-1'), 43.2 (d, C-3), 34.4 (t, C-5), 25.6 (t, C-2), 23.1 (t, C-6).

LRMS (EI), m/z (relative intensity): 148 ($[\text{M}]^+$, 81), 130 (24), 112 (25), 99 (100), 87 (40), 79 (31), 74 (39), 57 (43).

HRMS m/z calcd for $\text{C}_6\text{H}_{12}\text{O}_2\text{S}$: 148.0558; found: 148.0552 (EI).

(2*R*,4*aS*,8*aS*)-Hexahydro-2-phenylthiopyrano[4,3-*d*][1,3]dioxine (157)



Benzaldehyde dimethyl acetal (2.65 mL, 18.135 mmol) and *p*-TsOH (58 mg, 0.30 mmol) were added to a stirred solution of diol **156** (896 mg, 6.04 mmol) in CH_2Cl_2 (60.5 mL) at room

temperature under Ar at rt. After 20 min, the mixture was washed with saturated aq NaHCO₃, dried over Na₂SO₄, and concentrated to provide the title compound that was homogeneous by TLC and ¹H NMR (1.38 g, 97%).

[α]_D +6 (c 0.9, CHCl₃)

IR ν_{max} 2914 cm⁻¹.

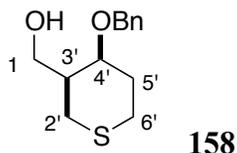
¹H NMR (500 MHz, CDCl₃) δ 7.51 (2H, app d, *J* = 7.5 Hz, Ph), 7.42-7.32 (3H, m, Ph), 5.54 (1H, s, HC-2), 4.21 (1H, br s, HC-8a), 4.06 (1H, dd, *J* = 2.5, 11.5 Hz, HC-4), 3.99 (1H, d, *J* = 11.5 Hz, HC-4), 3.57 (1H, dd, *J* = 12.5, 13 Hz, HC-5), 3.07-3.00 (1H, m, *J* = 13.5 Hz, HC-7), 2.36 (1H, br d, *J* = 13 Hz, HC-5), 2.33-2.24 (2H, m, HC-7, HC-8), 2.02-1.92 (1H, m, HC-8), 1.80 (1H, br d, *J* = 12.5 Hz, HC-4a).

¹³C NMR (125 MHz, CDCl₃) δ 138.7 (s, Ph), 129.2 (d, Ph), 128.5 (d ×2, Ph), 126.4 (d ×2, Ph), 102.4 (d, C-2), 74.1 (d, C-8a), 72.8 (t, C-4), 36.4 (d, C-4a), 33.6 (t, C-8), 26.3 (t, C-5), 22.5 (t, C-7).

LRMS (EI), *m/z* (relative intensity): 236 ([M]⁺, 100), 205 (24), 130 (94), 105 (68), 99 (61), 74 (81).

HRMS *m/z* calcd for C₁₃H₁₆O₂S: 236.0871; found: 236.0869 (EI).

((3*S*,4*S*)-4-Benzoyloxy-tetrahydro-2*H*-thiopyran-3-yl)methanol (158**)**



Procedure adapted from Takano et al, Chem Lett. 1983, 12, 1593-1596. DIBALH (1 M in toluene; 10.6 mL, 10.6 mmol) was added slowly via syringe (ca. 3 min) to a stirred solution of benzylidene acetal **157** (1.0 g, 4.2 mmol) in CH₂Cl₂ (42 mL) at 0 °C under Ar. After 5 min, the cooling bath was removed and the mixture was allowed to reach ambient temperature. After 13.5 h, the mixture was cooled to 0 °C and a saturated solution of Rochelle's salt (30 mL) was added. The mixture was allowed to warm to ambient temperature and after 2 h, was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated to yield the title compound that was homogeneous by TLC and ¹H NMR (1.0 g, 99%).

[α]_D +62 (*c* 1.2, CHCl₃)

IR ν_{max} 3405 cm⁻¹.

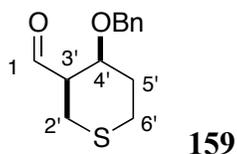
¹H NMR (500 MHz, CDCl₃) δ 7.39-7.27 (5H, m, Ph), 4.64 (1H, d, *J* = 11.5 Hz, HCPh), 4.41 (1H, d, *J* = 11.5 Hz, HCPh), 3.81 (1H, ddd, *J* = 2.5, 2.5, 5 Hz, HC-4'), 3.73 (1H, dd, *J* = 6.5, 11 Hz, HC-1), 3.67 (1H, dd, *J* = 5, 11 Hz, HC-1), 3.02-2.90 (2H, m, HC-2', HC-6'), 2.41-2.29 (3H, m, HC-2', HC-5', HC-6'), 2.20 (1H, br s, HO), 2.05 (1H, dddd, *J* = 5, 6.5 Hz, HC-3'), 1.84-1.75 (1H, m, HC-5').

¹³C NMR (125 MHz, CDCl₃) δ 138.4 (s, Ph), 128.7 (d ×2, Ph), 128.0 (d, Ph), 127.9 (d ×2, Ph), 75.2 (d, C-4'), 70.6 (t, CH₂Ph), 65.3 (t, C-1), 43.8 (d, C-3'), 29.8 (t, C-5'), 26.1 (t, C-2'), 23.4 (t, C-6').

LRMS (EI), *m/z* (relative intensity): 238 ($[M]^+$, 10), 132 (38), 129 (27), 99 (30), 91 (100), 65 (15).

HRMS *m/z* calcd for $C_{13}H_{18}O_2S$: 238.1028; found: 238.1023 (EI).

(3*R*,4*S*)-Tetrahydro-4-benzyloxy-2*H*-thiopyran-3-carbaldehyde (159**)**



IBX (32 mg, 0.11 mmol) was added to a stirred solution of alcohol **158** (12.5 mg, 0.052 mmol) in dry DMSO (0.4 mL) at room temperature under Ar. After 2 h, the mixture was diluted in ethyl acetate, washed sequentially with saturated aq $NaHCO_3$, H_2O and brine, dried over Na_2SO_4 , concentrated, and fractionated by FCC (20% ethyl acetate in hexanes) to provide the title compound as a colorless oil that was homogeneous by TLC and 1H NMR (9.5 mg, 77%).

$[\alpha]_D -14$ (*c* 1.0, C_6H_6)

IR ν_{max} 1727 cm^{-1} .

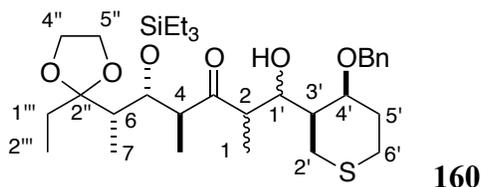
1H NMR (500 MHz, $CDCl_3$) δ 9.55 (1H, s, HC-1), 7.39-7.23 (5H, m, Ph), 4.62 (1H, d, $J = 12$ Hz, HCPh), 4.42 (1H, d, $J = 12$ Hz, HCPh), 4.23 (1H, ddd, $J = 2.5, 2.5, 4.5$ Hz, HC-4'), 3.13 (1H, dd, $J = 12, 14.5$ Hz, HC-2'), 2.98 (1H, ddd, $J = 2.5, 12, 13.5$ Hz, HC-6'), 2.68-2.59 (2H, m, HC-2', HC-3'), 2.43 (1H, dddd, $J = 2.5, 4, 4.5, 14.5$ Hz, HC-5'), 2.35 (1H, dddd, $J = 1.5, 3.5, 4, 13.5$ Hz, HC-6'), 1.84 (1H, dddd, $J = 2.5, 3.5, 12, 14.5$ Hz, HC-5').

^{13}C NMR (125 MHz, CDCl_3) δ 202.4 (s, C-1), 138.0 (s, Ph), 128.7 (d \times 2, Ph), 128.1 (d, Ph), 127.8 (d \times 2, Ph), 71.7 (d, C-4'), 70.6 (t, CH_2Ph), 54.0 (d, C-3'), 29.8 (t, C-5'), 23.0 (t, C-2'), 23.0 (t, C-6').

LRMS (EI), m/z (relative intensity): 236 ($[\text{M}]^+$, 11), 157 (17), 99 (31), 91 (100), 65 (17).

HRMS m/z calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$: 236.0871; found: 236.0865 (EI).

(1*R*,2*S*,4*S*,5*R*,6*S*)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-[(3*S*,4*S*)-tetrahydro-4-(benzyloxy)-2*H*-thiopyran-3-yl]-1-hydroxy-2,4-dimethyl-5-(triethylsilyloxy)heptan-3-one (160)



LHMDS (1 M in THF; 0.21 mL, 0.21 mmol) was added to a solution of (+)-**109** (50 mg, 0.139 mmol) in THF (0.7 mL) at $-50\text{ }^\circ\text{C}$. After 1 h, the reaction mixture was cooled to $-78\text{ }^\circ\text{C}$ and a solution of freshly prepared aldehyde **159** (40 mg, 0.169 mmol) was added dropwise in THF (0.7 mL). After 1 h, the reaction was quenched by addition of phosphate buffer pH= 7 (1 mL), extracted with ethyl acetate, dried over Na_2SO_4 , concentrated and fractionated by FCC (2% ethyl acetate in CH_2Cl_2) to provide a mixture of at least 3 diastereomers by TLC (62 mg, 77%). The mixture was used in the next reaction.

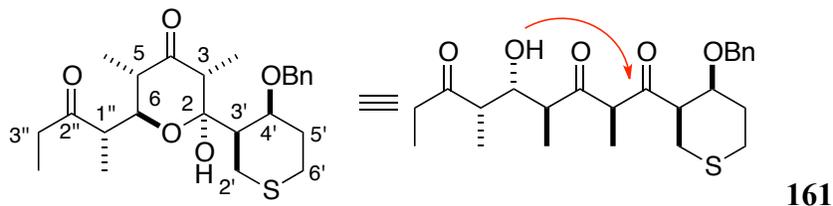
IR ν_{max} 3489 cm^{-1} .

^1H NMR (500 MHz, CDCl_3) - complex

^{13}C NMR (125 MHz, CDCl_3) - complex

HRMS m/z calcd for $C_{32}H_{54}O_6Si_5+Na$: 617.3302; found: 617.3294 (ESI).

(2*S*,3*S*,5*S*,6*S*)-2-((3*R*,4*S*)-4-(Benzyloxy)tetrahydro-2*H*-thiopyran-3-yl)-2-hydroxy-3,5-dimethyl-6-((*S*)-1-methyl-2-oxobutyl)tetrahydro-4*H*-pyran-4-one (161)



$FeCl_3 \cdot 6H_2O$ (6.5 mg, 0.024 mmol) was added to a stirred solution of aldol adducts **160** (20 mg, 0.034 mmol) in acetone (0.8 mL) at room temperature. After 1 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq $NaHCO_3$, H_2O and brine, dried over Na_2SO_4 , and concentrated. The residue (14 mg) was taken up in CH_2Cl_2 (2.4 mL) and DMP (15 mg, 0.035 mmol) was added to the stirred solution. After 3 h, the mixture was washed sequentially with a 1:1 mixture (v/v) of saturated aq $NaHCO_3$ and saturated aq Na_2SO_3 , H_2O and brine, dried over Na_2SO_4 , and concentrated. The residue (16 mg) was taken up in $CDCl_3$ (0.6 mL; previously passed through basic alumina), imidazole (22 mg, 0.32 mmol) was added, and the mixture was heated to 40 °C (oil bath temperature). After 19.5 h (reaction monitored by 1H NMR), the mixture was diluted with ethyl acetate, washed sequentially with 1% aq citric acid, $NaHCO_3$, and brine, dried over Na_2SO_4 , concentrated, and fractionated by PTLC (20% ethyl acetate in hexanes; multiple development) to give the title compound (5.1 mg, 31%).

$[\alpha]_D +90$ (c 0.35, $CHCl_3$)

IR ν_{max} 3384 cm^{-1} .

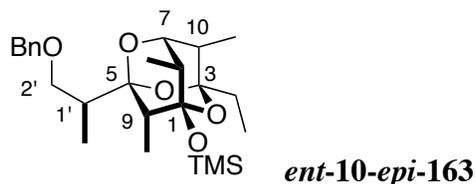
¹H NMR (500 MHz, CDCl₃) δ 7.39-7.22 (5H, m, Ph), 5.51 (1H, s, HO), 4.57 (1H, d, *J* = 11 Hz, HCPh), 4.38 (1H, dd, *J* = 2.5, 10.5 Hz, HC-6), 4.35 (1H, br s, HC-4'), 4.25 (1H, d, *J* = 11 Hz, HCPh), 3.09 (1H, dd, *J* = 13.5, 13.5 Hz, HC-2'), 2.96 (1H, dt, *J* = 2, 13, 13.5 Hz, HC-6'), 2.76 (1H, dq, *J* = 2.5, 7 Hz, HC-1''), 2.65 (1H, dq, *J* = 10.5, 6.5 Hz, HC-5), 2.58 (1H, q, *J* = 7 Hz, HC-3), 2.54-2.47 (3H, m, H₂C-3'', HC-5'), 2.26 (1H, br d, *J* = 13.5 Hz, HC-6'), 2.17-2.09 (2H, m, HC-2', HC-3'), 1.72 (1H, dddd, *J* = 1.5, 3.5, 13, 13.5 Hz, HC-5'), 1.24 (3H, d, *J* = 7 Hz, H₃CC-1''), 1.12 (3H, d, *J* = 7 Hz, H₃CC-3), 1.04 (3H, t, *J* = 7.5 Hz, H₃CC-4''), 1.02 (3H, d, *J* = 6.5 Hz, H₃CC-5).

¹³C NMR (125 MHz, CDCl₃) δ 211.3 (s, C-3''), 210.7 (s, C-4), 137.4 (s, Ph), 128.9 (d ×2, Ph), 128.3 (d, Ph), 127.4 (d ×2, Ph), 102.3 (s, C-2), 74.2 (d, C-6), 73.8 (d, C-4'), 70.1 (t, CH₂Ph), 51.5 (d, C-3), 47.6 (d, C-1''), 45.3 (d, C-3'), 41.8 (d, C-5), 34.0 (t, C-3''), 29.9 (t, C-5'), 22.3 (t, C-2'), 21.9 (t, C-6'), 14.0 (q, CH₃C-3), 9.3 (q, CH₃C-5), 8.3 (q, C-4''), 8.1 (q, CH₃C-1'').

LRMS (EI), *m/z* (relative intensity): 434 ([M]⁺, 1), 245 (18), 100 (19), 91 (100), 69 (11), 57 (25).

HRMS *m/z* calcd for C₂₄H₃₄O₅S: 434.2127; found: 434.2117 (EI).

(1R,3R,5S,7R,8R,9R,10R)-3-Ethyl-8,9,10-trimethyl-5-[(S)-1-methyl-2-(phenylmethoxy)ethyl]-1-trimethylsilyloxy-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]decane (*ent*-10-*epi*-163).



2,6-Lutidine (0.34 mL, 0.31 mg, 2.9 mmol) and TMSOTf (0.21 mL, 0.26 g, 1.2 mmol) were sequentially added to a stirred solution of trioxadamantane *ent*-10-*epi*-**116** (220 mg, 0.584

mmol) in CH_2Cl_2 (7.3 mL) at 0 °C under argon. After 10 min, additional TMSOTf (0.21 mL, 0.26 g, 1.2 mmol) was added. After a further 10 min, the reaction was quenched by addition of 1% aq citric acid (1 mL) and the mixture was diluted with ethyl acetate, washed sequentially with 1% citric acid, saturated aq NaHCO_3 and brine, dried over Na_2SO_4 , concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to provide the titled compound (229 mg, 87%). $[\alpha]_{\text{D}} -27$ (c 1.0, CHCl_3)

IR ν_{max} : 2973, 2941, 2883, 1454, 1249, 1045, 906, 877, 842 cm^{-1}

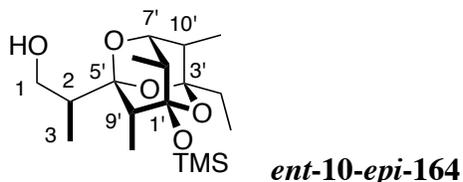
^1H NMR (500 MHz, CDCl_3) δ : 4.56 (1H, d, $J = 12$ Hz, CHPh), 4.45 (1H, d, $J = 12$ Hz, CHPh), 3.90 (1H, dd, $J = 2.5, 9$ Hz, HC-2'), 3.70 (1H, d, $J = 3.5$ Hz, HC-5), 3.33 (1H, dd, $J = 9, 9.5$ Hz, HC-2'), 2.07-1.92 (4H, m, HC-1', HC-8, HC-9, HC-10), 1.62 (1H, dq, $J = 14.5, 7.5$ Hz, HCC-3), 1.52 (1H, dq, $J = 14.5, 7.5$ Hz, HCC-3), 1.06 (3H, d, $J = 7$ Hz, H_3CC -8), 1.02 (3H, d, $J = 7$ Hz, H_3CC -5), 0.93 (3H, t, $J = 7.5$ Hz, H_3CC -1'), 0.90 (3H, d, $J = 7$ Hz, H_3CC -9), 0.88 (3H, d, $J = 7$ Hz, H_3CC -10), 0.16 (9H, s, $\text{H}_3\text{CSi} \times 3$)

^{13}C NMR (125 MHz, CDCl_3) δ : 139.2 (s, Ph), 128.5 (d $\times 2$, Ph), 127.8 (d $\times 2$, Ph), 127.5 (d, Ph), 103.5 (s, C-5), 102.8 (s, C-3), 99.8 (s, C-1), 78.3 (d, C-7), 73.3 (t, CH_2Ph), 71.4 (t, C-2'), 39.1 (d, C-1'), 37.4 (d, C-10), 36.9 (d, C-8), 35.5 (d, C-9), 29.6 (t, CH_2C -3), 13.3 (q, CH_3C -8), 12.6 (q, CH_3C -10), 11.1 (q, CH_3C -1'), 7.7 (q, CH_3C -9), 6.5 (q, CH_3CC -3), 2.2 (q $\times 3$, CH_3Si)

LRMS (EI), m/z (relative intensity): 448 ($[\text{M}]^+$, 15), 379 (100), 364 (5), 363 (14), 324 (17), 323 (61)

HRMS m/z calcd for $\text{C}_{25}\text{H}_{40}\text{O}_5\text{Si}$: 448.2645; found: 448.2644 (EI).

(*S*)-2-[(1*R*,3*R*,5*S*,7*R*,8*R*,9*R*,10*R*)-3-Ethyl-8,9,10-trimethyl-1-trimethylsilyloxy-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]dec-5-yl]propanol (*ent*-10-*epi*-164).



10% Pd/C (163 mg, 0.153 mmol) was added to a solution of trioxaadamantane *ent*-10-*epi*-163 (228 mg, 0.510 mmol) in ethanol (64 mL) at room temperature. After purging the flask with H₂, the mixture was stirred under an atmosphere of H₂ (balloon). After 15 min, the mixture was filtered through wet Celite® and the combined filtrate and EtOH washings were concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to yield the titled compound (158 mg, 86%). [α]_D -9 (*c* 1.2, CHCl₃)

IR ν_{\max} : 3469, 2972, 2942, 2884, 1465, 1249, 1193, 903, 877, 843 cm⁻¹

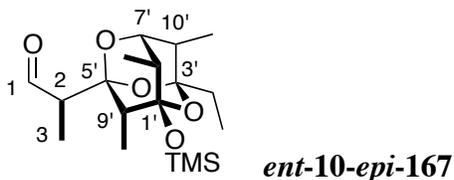
¹H NMR (500 MHz, CDCl₃) δ : 3.82 (1H, dd, *J* = 3.5, 1 Hz, HC-7'), 3.75 (2H, ap dd, *J* = 5, 6 Hz, H₂C-1), 3.07 (1H, t, *J* = 6 Hz, HO), 2.11 (1H, dq, *J* = 3.5, 7 Hz, HC-10'), 2.03-1.96 (2H, m, HC-8', HC-9'), 1.92 (1H, ddq, *J* = 5, 5, 7 Hz, HC-2), 1.66 (1H, dq, *J* = 14, 7.5 Hz, HCC-3'), 1.54 (1H, dq, *J* = 14, 7.5 Hz, HCC-3'), 1.07 (3H, d, *J* = 7 Hz, H₃CC-8'), 0.94 (3H, t, *J* = 7.5 Hz, H₃CCC-3'), 0.92 (3H, d, *J* = 7 Hz, H₃C-3 or H₃CC-10), 0.91 (3H, d, *J* = 7 Hz, H₃C-3 or H₃CC-10), 0.91 (3H, d, *J* = 6.5 Hz, H₃CC-9'), 0.17 (9H, s, H₃CSi \times 3)

¹³C NMR (125 MHz, CDCl₃) δ : 105.5 (s, C-5'), 103.1 (s, C-3'), 99.6 (s, C-1'), 78.4 (d, C-7'), 64.3 (t, C-1), 39.2 (d, C-2), 37.7 (d, C-2), 36.8 (d, C-8'), 35.5 (d, C-9'), 29.6 (t, CH₂C-3'), 13.3 (q, CH₃C-8'), 12.6 (q, CH₃C-10'), 10.1 (q, C-3), 7.6 (q, CH₃C-9'), 6.5 (q, CH₃CC-3'), 2.2 (q \times 3, CH₃Si)

LRMS (EI), m/z (relative intensity): 358 ($[M]^+$, 6), 239 (19), 215 (94), 197 (30), 187 (25), 143 (34), 125 (28), 73 (45), 69 (23), 57 (100)

HRMS m/z calcd for $C_{18}H_{34}O_5Si$: 358.2176; found: 358.2180 (EI).

(S)-2-[(1R,3R,5S,7R,8R,9R,10R)-3-Ethyl-8,9,10-trimethyl-1-trimethylsilyloxy-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]dec-5-yl]propanal (*ent*-10-*epi*-167).



IBX (256 mg, 0.912 mmol) was added to a stirred solution of adamantane *ent*-10-*epi*-**164** (294 mg, 0.820 mmol) in dry DMSO (13 mL) at room temperature under argon. After 12 h, the reaction mixture was diluted with ethyl acetate, washed sequentially with saturated aq $NaHCO_3$, water and brine, dried over Na_2SO_4 , and concentrated to yield the titled compound (292 mg, 99%). $[\alpha]_D -70$ (c 0.8, $CHCl_3$)

IR ν_{max} : 1733 cm^{-1}

1H NMR (500 MHz, $CDCl_3$) δ : 9.97 (1H, s, HC-1), 3.79 (1H, d, $J = 3.5$ Hz, HC-5'), 2.53 (1H, q, $J = 7$ Hz, HC-2), 2.08 (1H, dddd, $J = 3.5, 7$ Hz, HC-10'), 2.00 (1H, br q, $J = 7$ Hz, HC-8'), 1.96 (1H, q, $J = 6.5$ Hz, HC-9'), 1.68 (1H, dq, $J = 14, 7.5$ Hz, HCC-3'), 1.57 (1H, dq, $J = 14, 7.5$ Hz, HCC-3'), 1.07 (3H, d, $J = 7$ Hz, H_3CC -8'), 1.04 (3H, d, $J = 7$ Hz, H_3C -3), 0.96 (3H, t, $J = 7.5$ Hz, H_3CCC -3'), 0.95 (3H, d, $J = 6.5$ Hz, H_3CC -9'), 0.92 (3H, d, $J = 7$ Hz, H_3CC -10'), 0.18 (9H, s, $H_3CSi \times 3$)

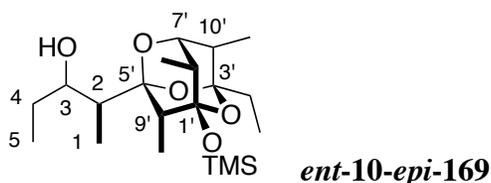
^{13}C NMR (125 MHz, $CDCl_3$) δ : 204.3 (s, C-1), 103.8 (s, C-5'), 103.4 (s, C-3'), 99.7 (s, C-1'), 78.6 (d, C-7'), 50.6 (d, C-2), 37.6 (d, C-10'), 36.9 (d, C-8'), 35.5 (d, C-9'), 29.6 (t, CH_2C -3'), 13.2

(q, CH₃C-8'), 12.6 (q, CH₃C-10'), 7.9 (q, CH₃C-9'), 6.8 (q, C-3), 6.4 (q, CH₃CC-3'), 2.2 (q ×3, CH₃Si)

LRMS (EI), *m/z* (relative intensity): 356 ([M]⁺, 3), 231 (40), 187 (20), 173 (13), 149 (13), 141 (16), 75 (14), 73 (31), 69 (17), 57 (100)

HRMS *m/z* calcd for C₁₈H₃₂O₅Si: 356.2019; found: 356.2020 (EI).

(2*S*,3*R)-2-[(1*R*,3*R*,5*S*,7*R*,8*R*,9*R*,10*R*)-3-Ethyl-8,9,10-trimethyl-1-trimethylsilyloxy-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]dec-5-yl]pentan-3-ol (*ent*-10-*epi*-169).**



EtMgBr (3 M in diethyl ether; 0.071 mL, 0.21 mmol) was added to a stirred solution of aldehyde *ent*-10-*epi*-**167** (63 mg, 0.18 mmol) in THF (3.3 mL) at -78 °C under argon. After 10 min, the reaction was quenched by addition of phosphates buffer (pH=7; 1 mL), diluted with ethyl acetate and washed with phosphate buffer (pH=7). The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over Na₂SO₄, and concentrated to yield the titled compound as a single diastereomer (62 mg, 88%). [α]_D -13 (*c* 0.8, CHCl₃)

IR ν_{\max} : 3554 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ : 4.19 (1H, ap dd, *J* = 6, 8 Hz, HC-3), 3.82 (1H, d, *J* = 3.5 Hz, HC-7'), 3.43 (1H, s, HO), 2.14 (1H, dq, *J* = 3.5, 7 Hz, HC-10'), 2.03 (1H, q, *J* = 6.5 Hz, HC-9'), 1.99 (1H, br q, *J* = 7 Hz, HC-8'), 1.69-1.52 (4H, m, HC-2, H₂CC-3', H₂C-4), 1.30 (1H, ddq, *J* = 8, 14.5, 7.5 Hz, HC-4), 1.07 (3H, d, *J* = 7 Hz, H₃CC-8'), 0.94 (12H, t, *J* = 7.5 Hz, H₃CCC-3'), 0.93

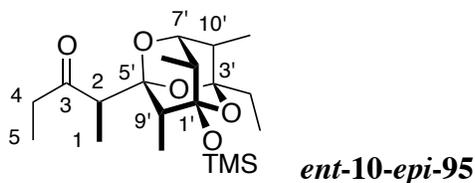
(3H, t, $J = 7.5$ Hz, H₃C-5), 0.90 (3H, d, $J = 7$ Hz, H₃CC-10'), 0.89 (3H, d, $J = 7$ Hz, H₃C-1), 0.87 (3H, d, $J = 6.5$ Hz, H₃CC-8), 0.17 (9H, s, H₃CSi ×3)

¹³C NMR (125 MHz, CDCl₃) δ: 105.5 (s, C-5'), 102.9 (s, C-3'), 99.5 (s, C-1'), 78.6 (d, C-7'), 70.9 (d, C-3), 40.9 (d, C-2), 37.4 (d, C-10'), 36.9 (d, C-8'), 35.5 (d, C-9'), 29.6 (t, CH₂C-3'), 27.6 (t, C-4), 13.2 (q, CH₃C-8'), 12.6 (q, CH₃C-10'), 11.0 (q, C-5), 7.7 (q, CH₃C-9'), 6.5 (q, CH₃CC-3'), 5.3 (q, C-1), 2.2 (q ×3, CH₃Si)

LRMS (EI), m/z (relative intensity): 386 ([M]⁺, 0.4), 243 (99), 197 (46), 187 (42), 153 (40), 129 (36), 97 (71), 73 (77), 57 (100)

HRMS m/z calcd for C₂₀H₃₈O₅Si: 386.2489; found: 386.2490 (EI).

(S)-2-[(1R,3R,5S,7R,8R,9R,10R)-3-Ethyl-8,9,10-trimethyl-1-trimethylsilyloxy-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]dec-5-yl]pentan-3-one (*ent*-10-*epi*-95).



IBX (90 mg, 0.32 mmol) was added to a solution of adamantane *ent*-10-*epi*-169 (62 mg, 0.16 mmol) in dry DMSO (2.6 mL) at room temperature under argon. After 12.5 h, the reaction mixture was diluted with ethyl acetate, washed sequentially with saturated aq NaHCO₃, distilled water and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to yield the titled compound (61 mg, 99%). [α]_D -67 (c 1.1, CHCl₃)

IR ν_{\max} : 1718 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ: 3.80 (1H, d, $J = 3.5$ Hz, HC-7'), 2.87 (1H, q, $J = 7$ Hz, HC-2), 2.76 (1H, dq, $J = 18, 7.5$ Hz, HC-4), 2.46 (1H, dq, $J = 18, 7.5$ Hz, HC-4), 2.02-1.92 (3H, m, HC-

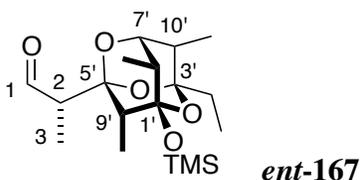
8', HC-9', HC-10'), 1.65 (1H, dq, $J = 14, 7.5$ Hz, HCC-3'), 1.52 (1H, dq, $J = 14, 7.5$ Hz, HCC-3'), 1.05 (3H, d, $J = 7$ Hz, H₃CC-8'), 1.03 (3H, d, $J = 7$ Hz, H₃C-1), 1.01 (3H, t, $J = 7.5$ Hz, H₃C-5), 0.95 (3H, d, $J = 6.5$ Hz, H₃CC-9'), 0.94 (3H, t, $J = 7.5$ Hz, H₃CCC-3'), 0.87 (3H, d, $J = 7$ Hz, H₃CC-10'), 0.16 (9H, s, H₃CSi ×3)

¹³C NMR (125 MHz, CDCl₃) δ: 211.8 (s, C-3), 103.2 (s, C-3'), 103.1 (s, C-5'), 99.8 (s, C-1'), 78.2 (d, C-7'), 50.6 (d, C-2), 37.4 (t, C-4), 37.2 (d, C-10'), 36.8 (d, C-8'), 35.6 (d, C-9'), 29.6 (t, CH₂C-3'), 13.2 (q, CH₃C-8'), 12.5 (q, CH₃C-10'), 9.7 (q, C-1), 8.1 (q, C-5 or CH₃C-9'), 8.0 (q, C-5 or CH₃C-9'), 6.5 (q, CH₃CC-3'), 2.2 (q ×3, CH₃Si)

LRMS (EI), m/z (relative intensity): 384 ([M]⁺, 5), 259 (60), 203 (18), 187 (21), 169 (67), 101 (19), 75 (17), 73 (37), 57 (100)

HRMS m/z calcd for C₂₀H₃₆O₅Si: 384.2332; found: 384.2334 (EI).

(R)-2-[(1R,3R,5S,7R,8R,9R,10R)-3-Ethyl-8,9,10-trimethyl-5-[(S)-1-methyl-2-(phenylmethoxy)ethyl]-1-trimethylsilyloxy-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]dec-5-yl]propanal
(ent-167).



Imidazole (552 mg, 8.11 mmol) was added to a stirred solution of aldehyde *ent-10-epi-167* (419 mg, 1.18 mmol) in CHCl₃ (14.8 mL) that was previously neutralized by passing through basic alumina. After stirring at 40 °C for 1 day, the mixture was diluted with ethyl acetate, washed sequentially with 1% aq citric acid (x3), saturated aq NaHCO₃ and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (5% diethyl ether in hexanes) to yield the titled

compound (62 mg, 14%; dr 16-18) and recovered *ent*-10-*epi*-**167** (338 mg, 80%; dr 16-18). The latter fraction was re-subjected to the isomerization conditions and after a total of six isomerization cycles, recovered *ent*-10-*epi*-**167** (119 mg, 28%; dr 16-18) and the titled compound were obtained (208 mg, 49%; dr 16-18). A similar experiment conducted in CDCl₃ for several days resulted in a 4:1 ratio of *ent*-10-*epi*-**167** and *ent*-**167**, respectively. [α]_D +5 (c 0.5, CHCl₃)

IR ν_{\max} : 1727 cm⁻¹

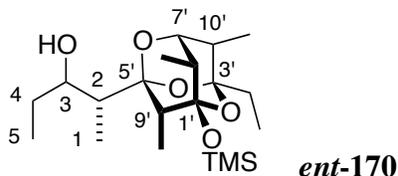
¹H NMR (500 MHz, CDCl₃) δ : 9.74 (1H, d, J = 2.5 Hz, HC-1), 3.80 (1H, d, J = 3 Hz, HC-7'), 2.62 (1H, dq, J = 2.5, 7 Hz, HC-2), 2.13 (1H, dq, J = 3.5, 7 Hz, HC-10'), 2.03-1.99 (2H, m, HC-8', HC-9'), 1.66 (1H, dq, J = 14, 7.5 Hz, HCC-3'), 1.56 (1H, dq, J = 14, 7.5 Hz, HCC-3'), 1.15 (3H, d, J = 7 Hz, H₃C-3), 1.05 (3H, d, J = 7 Hz, H₃CC-8'), 0.96 (3H, t, J = 7.5 Hz, H₃CCC-3'), 0.92 (3H, d, J = 7 Hz, H₃CC-10'), 0.91 (3H, d, J = 6.5 Hz, H₃CC-9'), 0.16 (9H, s, H₃CSi \times 3)

¹³C NMR (125 MHz, CDCl₃) δ : 203.0 (s, C-1), 103.2 (s, C-3'), 101.9 (s, C-5'), 99.6 (s, C-1'), 78.6 (d, C-7'), 52.6 (d, C-2), 37.6 (d, C-10'), 37.0 (d, C-9'), 36.7 (d, C-8'), 29.7 (t, CH₂C-3'), 13.3 (q, CH₃C-8'), 12.7 (q, CH₃C-10'), 7.9 (q, CH₃C-9'), 7.5 (q, C-3), 6.4 (q, CH₃CC-3'), 2.2 (q \times 3, CH₃Si)

LRMS (EI), m/z (relative intensity): 356 ([M]⁺, 7), 231 (49), 187 (29), 141 (21), 101 (25), 73 (31), 71 (21), 69 (27), 57 (100)

HRMS m/z calcd for C₁₈H₃₂O₅Si: 356.2019; found: 356.2019 (EI).

(2*R*,3*R**)-2-[(1*R*,3*R*,5*S*,7*R*,8*R*,9*R*,10*R*)-3-Ethyl-8,9,10-trimethyl-1-trimethylsilyloxy-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]dec-5-yl]pentan-3-ol (*ent*-170).



EtMgBr (3 M in diethyl ether; 0.075 mL, 0.23 mmol) was added to a stirred solution of aldehyde *ent*-167 (62 mg, 0.17 mmol) in THF (3.4 mL) at -78 °C under argon. The reaction was monitored by TLC and additional EtMgBr solution (ca. 0.01 mL) was added every 10 min. After 50 min, the reaction was quenched by addition of phosphates buffer (pH=7; 1 mL), diluted with ethyl acetate and washed with phosphate buffer (pH=7). The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over Na₂SO₄, and concentrated to yield the titled compound as a 4:1 mixture of diastereomers (66 mg, 99%). $[\alpha]_D^{+5}$ (*c* 0.45, CHCl₃)

IR ν_{\max} : 3540 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ (major diastereomer only): 3.82 (1H, d, $J = 3.5$ Hz, HC-7'), 3.79 (1H, ap t, $J = 7$ Hz, HC-2), 3.31 (1H, s, HO), 2.18 (1H, q, $J = 6.5$ Hz, HC-9'), 2.08 (1H, dq, $J = 3.5, 7$ Hz, HC-10'), 1.98 (1H, br q, $J = 7$ Hz, HC-8'), 1.82 (1H, q, $J = 7$ Hz, HC-2), 1.71-1.49 (3H, m, H₂CC-3', HC-4), 1.35 (1H, ddq, $J = 7, 14, 7$ Hz, HC-4), 1.08 (3H, d, $J = 7$ Hz, H₃CC-8'), 0.96 (3H, d, $J = 7$ Hz, H₃C-1), 0.94 (3H, t, $J = 7.5$ Hz, H₃CCC-3'), 0.90 (3H, d, $J = 7$ Hz, H₃CC-10'), 0.89 (3H, t, $J = 6$ Hz, H₃C-5), 0.87 (3H, d, $J = 6.5$ Hz, H₃CC-9'), 0.16 (9H, s, H₃CSi $\times 3$)

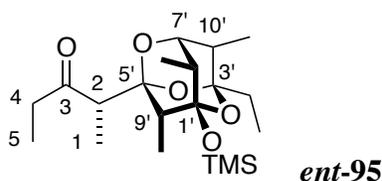
¹³C NMR (125 MHz, CDCl₃) δ (major diastereomer only): 104.7 (s, C-5'), 102.6 (s, C-3'), 99.7 (s, C-1'), 78.7 (d, C-7'), 70.8 (d, C-3), 40.0 (d, C-2), 37.0 (d, C-10'), 36.9 (d, C-8'), 35.8 (d, C-9'),

29.6 (t, CH₂C-3'), 27.4 (t, C-4), 13.5 (q, CH₃C-8'), 12.6 (q, CH₃C-10'), 10.7 (q, C-5), 7.9 (q, CH₃C-9'), 6.5 (q, CH₃CC-3'), 4.5 (q, C-1), 2.2 (q ×3, CH₃Si)

LRMS (CI, NH₃), *m/z* (relative intensity): 387 ([M+1]⁺, 7), 329 (25), 298 (19), 297 (100), 243 (25), 97 (7), 90 (14)

HRMS *m/z* calcd for C₂₀H₃₈O₅Si+H: 387.2567; found: 387.2556 (CI).

(R)-2-[(1R,3R,5S,7R,8R,9R,10R)-3-Ethyl-8,9,10-trimethyl-1-trimethylsilyloxy-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]dec-5-yl]pentan-3-one (*ent*-95).



IBX (217 mg, 0.775 mmol) was added to a stirred solution of *ent*-170 (148 mg, 0.382 mmol) in dry DMSO (6.4 mL) at room temperature under argon. After 14 h, the reaction mixture was diluted with ethyl acetate, washed sequentially with saturated aq NaHCO₃, distilled water and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to yield the titled compound (130 mg, 87%) [α]_D -20 (*c* 0.4, CHCl₃)

IR ν_{\max} : 2980, 2940, 1705, 1249, 900, 878, 843 cm⁻¹

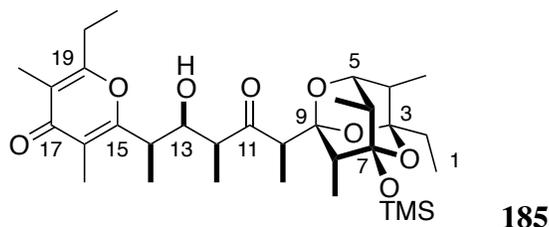
¹H NMR (500 MHz, CDCl₃) δ : 3.81 (1H, d, *J* = 3.5 Hz, HC-7'), 2.81 (1H, q, *J* = 7 Hz, HC-2), 2.62 (1H, dq, *J* = 18, 7.5 Hz, HC-4), 2.48 (1H, dq, *J* = 18, 7.5 Hz, HC-4), 2.08 (1H, dq, *J* = 3.5, 7 Hz, HC-10'), 1.97 (1H, br q, *J* = 7 Hz, HC-8'), 1.87 (1H, q, *J* = 6.5 Hz, HC-9'), 1.62 (1H, dq, *J* = 14, 7.5 Hz, HCC-3'), 1.53 (1H, dq, *J* = 14, 7.5 Hz, HCC-3'), 1.21 (3H, d, *J* = 7 Hz, H₃C-1), 1.04 (3H, d, *J* = 7 Hz, H₃CC-8'), 1.00 (3H, t, *J* = 7.5 Hz, H₃C-5), 0.94 (3H, t, *J* = 7.5 Hz, H₃CCC-3'), 0.93 (3H, d, *J* = 6.5 Hz, H₃CC-9'), 0.90 (3H, d, *J* = 7 Hz, H₃CC-10'), 0.15 (9H, s, H₃CSi ×3)

^{13}C NMR (125 MHz, CDCl_3) δ : 212.2 (s, C-3), 103.1 (s, C-3'), 101.5 (s, C-5'), 99.8 (s, C-1'), 78.5 (d, C-6'), 53.2 (d, C-2), 37.3 (d, C-9'), 37.2 (d, C-10'), 36.8 (d, C-8'), 33.9 (t, C-4), 29.7 (t, $\text{CH}_2\text{C}-3'$), 13.4 (q, $\text{CH}_3\text{C}-8'$), 12.6 (q, $\text{CH}_3\text{C}-10'$), 10.4 (q, C-1), 8.1 (q, C-5 or $\text{CH}_3\text{C}-9'$), 8.0 (q, C-5 or $\text{CH}_3\text{C}-9'$), 6.5 (q, $\text{CH}_3\text{CC}-3'$), 2.2 (q $\times 3$, CH_3Si)

LRMS (EI), m/z (relative intensity): 384 ($[\text{M}]^+$, 9), 259 (45), 239 (16), 197 (17), 187 (23), 169 (61), 73 (33), 57 (100)

HRMS m/z calcd for $\text{C}_{20}\text{H}_{36}\text{O}_5\text{Si}$: 384.2332; found: 384.2328 (EI).

***ent*-(10*R*,12*R*,13*S*)-11-Didehydro-13-dihydro-7-*O*-(trimethylsilyl)caloundrin B (185).**



9-BBNOTf (0.5 M in hexane; 0.31 mL, 0.16 mmol) was added to a stirred solution of Et_3N (0.024 mL, 17 mg, 0.17 mmol) in ethyl ether (1 mL) at -78 °C under argon. After 10 min, a solution of ketone *ent*-10-*epi*-**95** (30 mg, 0.078 mmol) in ether (0.3 mL plus 2 \times 0.1 mL rinses) was added via syringe. After 2 h, a solution of freshly prepared aldehyde (\pm)-**30** (49 mg, 0.23 mmol) via syringe in ether (0.3 mL) was added. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH=7; 3 mL), methanol (0.5 mL) and 30% aq H_2O_2 (0.5 mL) with vigorous stirring. The mixture was warmed to 0 °C and, after 10 min, was extracted with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , concentrated, and fractionated by FCC (20-50% ethyl acetate in hexane) to provide the titled compound (34.5 mg, 74%). $[\alpha]_{\text{D}} -39$ (c 1.9, CHCl_3)

IR ν_{\max} : 3438, 1715, 1656, 1615 cm^{-1}

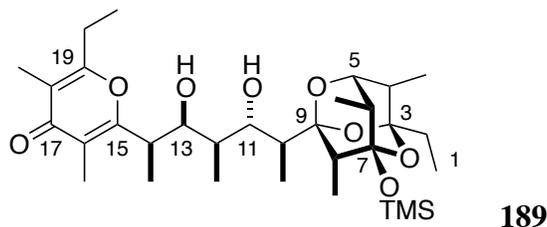
^1H NMR (500 MHz, CDCl_3) δ : 4.32 (1H, d, $J = 10$ Hz, HC-13), 3.62 (1H, d, $J = 3$ Hz, HC-5), 3.07 (1H, dq, $J = 10, 7$ Hz, HC-14), 3.05-2.96 (2H, m, HO, HC-10), 2.92 (1H, br q, $J = 7$ Hz, HC-12), 2.61 (1H, dq, $J = 15, 7.5$ Hz, HC-20), 2.48 (1H, dq, $J = 15, 7.5$ Hz, HC-20), 1.98 (3H, s, H_3CC -16), 1.95-1.87 (2H, m, HC-6, HC-8), 1.92 (3H, s, H_3CC -18), 1.61-1.42 (2H, m, H_2C -2, HC-4), 1.34 (3H, d, $J = 7$ Hz, H_3CC -14), 1.18 (3H, t, $J = 7.5$ Hz, H_3C -21), 1.14 (3H, d, $J = 7.5$ Hz, H_3CC -12), 1.03 (3H, d, $J = 7$ Hz, H_3CC -10), 1.00 (3H, d, $J = 7$ Hz, H_3CC -6), 0.92 (3H, d, $J = 6.5$ Hz, H_3CC -8), 0.82 (3H, t, $J = 7.5$ Hz, H_3C -1), 0.76 (3H, d, $J = 7$ Hz, H_3CC -4), 0.14 (9H, s, $\text{H}_3\text{CSi} \times 3$)

^{13}C NMR (125 MHz, CDCl_3) δ : 215.4 (s, C-11), 179.7 (s, C-17), 164.4 (s, C-15 or C-19), 164.3 (s, C-15 or C-19), 119.1 (s, C-16), 118.1 (s, C-18), 103.4 (s, C-9), 103.0 (s, C-3), 99.6 (s, C-7), 78.4 (d, C-5), 71.9 (d, C-13), 48.6 (d, C-12), 48.5 (d, C-10), 38.4 (d, C-14), 38.4 (d, C-4), 36.6 (d, C-6), 35.6 (d, C-8), 29.5 (t, C-2), 24.9 (t, C-20), 16.0 (q, CH_3C -14), 13.1 (q, CH_3C -6), 12.7 (q, CH_3C -4), 11.5 (q, C-21), 10.1 (q, CH_3C -12), 10.0 (q, CH_3C -10), 9.9 (q, CH_3C -16), 9.8 (q, CH_3C -18), 7.9 (q, CH_3C -8), 6.0 (q, C-1), 2.1 (q $\times 3$, CH_3Si)

LRMS (EI), m/z (relative intensity): 592 ($[\text{M}]^+$, 4), 467 (22), 259 (29), 180 (40), 179 (41), 73 (37), 57 (100)

HRMS m/z calcd for $\text{C}_{32}\text{H}_{52}\text{O}_8\text{Si}$: 592.3432; found: 592.3422 (EI).

***ent*-(10*R*,11*S*,12*R*,13*R*)-13-Dihydro-7-*O*-(trimethylsilyl)caloundrin B (189).**



NaBH(OAc)₃ (32 mg, 0.15 mmol) and acetic acid (77 mg, 73 uL, 1.3 mmol) were added sequentially to a stirred solution of aldol adduct **185** (18 mg, 0.030 mmol) in THF (0.7 mL) under argon at room temperature. After 3 h, distilled water (1.3 mL) was added. The mixture was diluted with ethyl acetate, washed sequentially with saturated aq NaHCO₃ and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (50% ethyl acetate in hexane) to yield the desired product (14 mg, 78%). [α]_D -5 (*c* 1.4, CHCl₃)

IR ν_{max} : 3440, 1655, 1604 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ : 4.92 (1H, br s, HOC-11), 4.35 (1H, br s, HOC-13), 4.16 (1H, d, *J* = 10 Hz, HC-13), 3.98 (1H, dd, *J* = 1.5, 9 Hz, HC-11), 3.81 (1H, d, *J* = 3 Hz, HC-5), 3.09 (1H, dq, *J* = 10, 6.5 Hz, HC-14), 2.64 (1H, dq, *J* = 15, 7.5 Hz, HC-20), 2.49 (1H, dq, *J* = 15, 7.5 Hz, HC-20), 2.10-1.97 (4H, m, HC-4, HC-6, HC-8, HC-10), 2.00 (3H, s, H₃CC-16), 1.92 (3H, s, H₃CC-18), 1.71-1.62 (1H, dq, *J* = 14.5, 7.5 Hz, HC-2), 1.54-1.46 (2H, m, HC-2, HC-12), 1.35 (3H, d, *J* = 6.5 Hz, H₃CC-14), 1.21 (3H, t, *J* = 7.5 Hz, H₃C-21), 1.07 (3H, d, *J* = 7 Hz, H₃CC-12), 1.03 (3H, d, *J* = 7 Hz, H₃CC-6), 0.93 (9H, d, *J* = 6.5 Hz, H₃CC-8), 0.92 (3H, t, *J* = 7.5 Hz, H₃C-1), 0.90 (3H, d, *J* = 7 Hz, H₃CC-4), 0.57 (3H, d, *J* = 7 Hz, H₃CC-10), 0.16 (9H, s, H₃CSi \times 3)

¹³C NMR (125 MHz, CDCl₃) δ : 180.0 (s, C-10), 164.8 (s, C-15), 164.2 (s, C-19), 119.2 (s, C-16), 118.3 (s, C-18), 106.1 (s, C-9), 103.6 (s, C-3), 99.7 (s, C-7), 78.4 (d, C-5), 78.0 (d, C-11), 72.5 (d, C-13), 40.0 (d, C-10), 39.6 (d, C-14), 37.8 (d, C-4), 36.6 (d, C-6), 35.7 (d, C-8 or C-12),

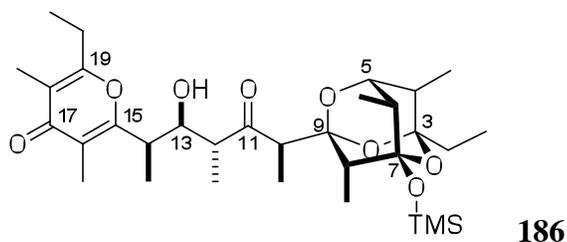
35.6 (d, C-8 or C-12), 29.6 (t, C-2), 25.0 (t, C-20), 15.7 (q, CH₃C-14), 13.2 (q, CH₃C-6), 12.6 (q, CH₃C-4), 11.8 (q, CH₃C-12), 11.4 (q, CH₃C-21), 10.1 (q, CH₃C-16), 9.9 (q, CH₃C-10), 9.7 (q, CH₃C-18), 7.5 (q, CH₃C-8), 6.3 (q, C-1), 2.1 (q ×3, CH₃Si)

LRMS (EI), *m/z* (relative intensity): 594 ([M]⁺, 5), 525 (10), 469 (24), 267 (14), 209 (12), 181 (17), 180 (100), 153 (12), 73 (26), 57 (46)

HRMS *m/z* calcd for C₃₂H₅₄O₈Si: 594.3588; found: 594.3592 (EI).

***ent*-(10*R*,12*S*,13*S*)-11-Didehydro-13-dihydro-7-*O*-(trimethylsilyl)caloundrin B (186)**

10-*epi-anti*-aldol-A



[α]_D -90 (*c* 0.23, CHCl₃)

IR ν_{max}: 3364, 1703, 1654, 1612, 1597 (sh) cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ: 3.82 (1H, ddd, *J* = 4, 8, 9 Hz, HC-13), 3.61 (1H, dd, *J* = 3.5, 1 Hz, HC-5), 3.38 (1H, dq, *J* = 8, 7 Hz, HC-14), 3.04 (1H, dq, *J* = 4, 7.5 Hz, HC-12), 2.98 (1H, q, *J* = 7 Hz, HC-10), 2.89 (1H, d, *J* = 9 Hz, HO), 2.63-2.53 (2H, m, H₂C-20), 1.97-1.86 (2H, m, HC-6, HC-8), 1.93 (3H, s, H₃CC-18), 1.88 (3H, s, H₃CC-16), 1.66-1.47 (2H, m, HC-2, HC-4), 1.40-1.29 (1H, m, HC-2), 1.31 (3H, d, *J* = 7 Hz, H₃CC-14), 1.28 (3H, d, *J* = 7.5 Hz, H₃CC-12), 1.20 (3H, t, *J* = 7.5 Hz, H₃C-21), 1.02 (3H, d, *J* = 7 Hz, H₃CC-10), 1.01 (3H, d, *J* = 7 Hz, H₃CC-6), 0.93 (3H, d, *J* = 6.5 Hz, H₃CC-8), 0.86 (3H, t, *J* = 7.5 Hz, H₃C-1), 0.74 (3H, d, *J* = 7 Hz, H₃CC-4), 0.14 (9H, s, H₃CSi ×3)

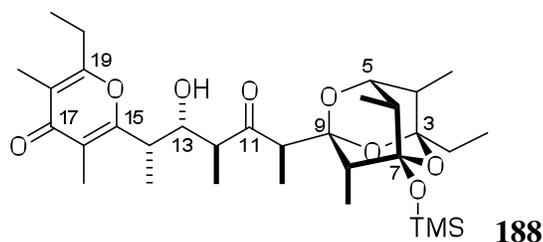
^{13}C NMR (125 MHz, CDCl_3) δ : 215.1 (s, C-11), 179.7 (s, C-17), 165.4 (s, C-15), 164.3 (s, C-19), 118.8 (s, C-16), 118.1 (s, C-18), 103.7 (s, C-9), 103.2 (s, C-3), 99.7 (s, C-7), 78.1 (d, C-5), 76.7 (d, C-13), 49.7 (d, C-12), 48.5 (d, C-10), 39.7 (d, C-14), 37.5 (d, C-4), 36.5 (d, C-6), 35.8 (d, C-8), 29.5 (t, C-2), 24.0 (t, C-20), 16.7 (q, $\text{CH}_3\text{C-12}$), 15.1 (q, $\text{CH}_3\text{C-14}$), 13.1 (q, $\text{CH}_3\text{C-6}$), 12.5 (q, $\text{CH}_3\text{C-4}$), 11.4 (q, C-21), 9.8 (q, $\text{CH}_3\text{C-18}$), 9.3 (q $\times 2$, $\text{CH}_3\text{C-10}$, $\text{CH}_3\text{C-16}$), 8.1 (q, $\text{CH}_3\text{C-8}$), 6.3 (q, C-1), 2.1 (q $\times 3$, CH_3Si)

LRMS (EI), m/z (relative intensity): 592 ($[\text{M}]^+$, 9), 468 (18), 467 (54), 349 (32), 181 (17), 180 (100), 179 (19), 73 (33), 57 (49)

HRMS m/z calcd for $\text{C}_{32}\text{H}_{52}\text{O}_8\text{Si}$: 592.3431; found: 592.3448 (EI).

***ent*-(10*R*,12*R*,13*R*)-11-Didehydro-13-dihydro-7-*O*-(trimethylsilyl)caloundrin B (188)**

10-*epi*-anti-aldol-B



Et_3N (0.008 mL, 6 mg, 0.06 mmol) and $\text{BCl}(c\text{-C}_6\text{H}_{12})_2$ (1 M in hexane; 0.052 mL, 0.052 mmol) were added sequentially to a stirred solution of *ent*-10-*epi*-**95** (9 mg, 0.023 mmol) in ether (0.2 mL) at 0 °C under argon. After 1 h, the reaction mixture was cooled at -78 °C and a solution of freshly prepared aldehyde (\pm)-**30** (16 mg, 0.078 mg) in ether (0.25 mL) was added. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH=7, 0.5 mL), MeOH (0.5 mL), and 30% aq H_2O_2 (0.5 mL) with vigorous stirring. After 10 min at 0 °C, the mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 ,

concentrated, and fractionated by PTLC (50% ethyl acetate in hexane) to provide **186** (anti-aldol, 3 mg, 16%) and **188** (anti-aldol, 9.3 mg, 67%). $[\alpha]_D -60$ (*c* 0.9, CHCl₃)

IR ν_{\max} : 3379, 1716, 1651, 1595 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ : 3.83 (1H, q, *J* = 6.5, Hz, HC-13), 3.80 (1H, br d, *J* = 3 Hz, HC-5), 3.12 (1H, dq, *J* = 6.5, 7 Hz, HC-12), 2.98 (1H, q, *J* = 7 Hz, HC-10), 2.91 (1H, dq, *J* = 6.5, 7 Hz, HC-14), 2.65 (1H, d, *J* = 6.5 Hz, HO), 2.60 (2H, ap q, *J* = 7.5 Hz, H₂C-20), 2.02-1.87 (3H, m, HC-4, HC-6, HC-8), 1.93 (3H, s, H₃CC-16 or H₃CC-18), 1.92 (3H, s, H₃CC-16 or H₃CC-18), 1.65 (1H, dq, *J* = 15, 7.5 Hz, HC-2), 1.44 (1H, dq, *J* = 15, 7.5 Hz, HC-2), 1.30 (3H, d, *J* = 7 Hz, H₃CC-14), 1.20 (3H, t, *J* = 7.5 Hz, H₃C-21), 1.13 (3H, d, *J* = 7 Hz, H₃CC-12), 1.03 (3H, d, *J* = 7 Hz, H₃CC-6), 1.00 (3H, d, *J* = 7 Hz, H₃CC-10), 0.90 (3H, t, *J* = 7.5 Hz, H₃C-1), 0.89 (3H, d, *J* = 7 Hz, H₃CC-8), 0.86 (3H, d, *J* = 7 Hz, H₃CC-4), 0.16 (9H, s, H₃CSi \times 3)

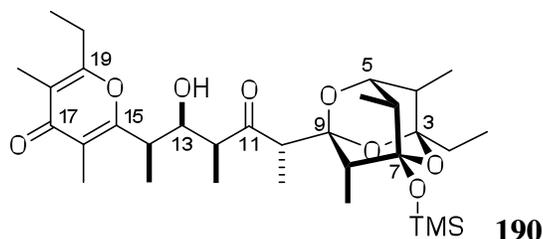
¹³C NMR (125 MHz, CDCl₃) δ : 216.9 (s, C-11), 179.7 (s, C-12), 164.9 (s, C-15), 164.3 (s, C-19), 118.6 (s, C-18), 118.4 (s, C-16), 104.0 (s, C-9), 103.1 (s, C-3), 99.7 (s, C-7), 78.4 (d, C-5), 77.4 (d, C-13), 52.5 (d, C-10), 49.4 (d, C-12), 39.9 (d, C-14), 37.9 (d, C-4), 36.6 (d, C-6), 35.6 (d, C-8), 29.7 (t, C-2), 24.9 (t, C-20), 14.5 (q, CH₃C-12), 13.7 (q, CH₃C-14), 13.2 (q, CH₃C-6), 12.6 (q, CH₃C-4), 11.5 (q, C-21), 9.72 (q, CH₃C-16 or CH₃C-18), 9.66 (q, CH₃C-16 or CH₃C-18), 9.5 (q, CH₃C-10), 7.9 (q, CH₃C-8), 6.1 (q, C-1), 2.2 (q \times 3, H₃CSi)

LRMS (EI), *m/z* (relative intensity): 592 ([M]⁺, 5), 467 (45), 349 (28), 180 (100), 179 (54), 169 (15), 153 (33), 73 (36), 57 (86)

HRMS *m/z* calcd for C₃₂H₅₂O₈Si: 592.3431; found: 592.3418 (EI).

ent-(13S)-11-Didehydro-13-dihydro-7-O-(trimethylsilyl)caloundrin B (190)

syn-aldol-A.



$[\alpha]_D -15$ (c 0.2, CHCl_3)

IR ν_{max} : 3421, 1700, 1653, 1616 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ : 4.08 (1H, d, $J = 10$ Hz, HC-13), 3.74 (1H, d, $J = 3.5$ Hz, HC-5), 1.19 (1H, br s, HO), 3.04 (1H, dq, $J = 10, 7$ Hz, HC-14), 2.89 (1H, q, $J = 7$ Hz, HC-10), 2.78 (1H, br q, $J = 7$ Hz, HC-12), 2.67 (1H, dq, $J = 15, 7.5$ Hz, HC-20), 2.51 (1H, dq, $J = 15, 7.5$ Hz, HC-20), 2.08-1.90 (2H, m, HC-4, HC-6), 1.99 (3H, s, H_3CC -16), 1.95 (3H, s, H_3CC -18), 1.76 (1H, s, $J = 6.5$ Hz, HC-8), 1.68-1.42 (2H, m, HC-2), 1.35 (3H, d, $J = 7$ Hz, H_3CC -14), 1.20 (3H, t, $J = 7.5$ Hz, H_3C -21), 1.14 (3H, d, $J = 7$ Hz, H_3CC -10), 1.09 (3H, d, $J = 7$ Hz, H_3CC -12), 0.99 (3H, d, $J = 7$ Hz, H_3CC -6), 0.87 (3H, t, $J = 7.5$ Hz, H_3C -1), 0.87 (3H, d, $J = 7$ Hz, H_3CC -4), 0.81 (3H, d, $J = 6.5$ Hz, H_3CC -8), 0.14 (9H, s, $\text{H}_3\text{CSi} \times 3$)

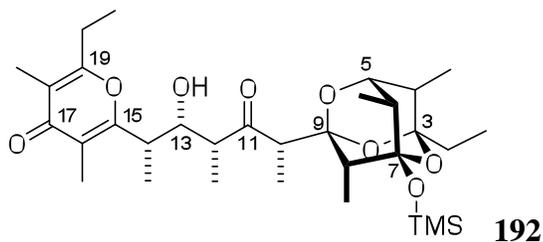
^{13}C NMR (125 MHz, CDCl_3) δ : 217.0 (s, C-11), 179.9 (s, C-17), 164.6 (s, C-19), 163.8 (s, C-15), 119.2 (s, C-16), 118.2 (s, C-18), 103.2 (s, C-3), 101.4 (s, C-9), 99.6 (s, C-7), 78.4 (d, C-5), 72.4 (d, C-13), 52.0 (d, C-10), 46.4 (d, C-12), 38.7 (d, C-14), 37.4 (d, C-8), 37.0 (d, C-4), 36.6 (d, C-6), 29.6 (t, C-2), 25.0 (t, C-20), 15.9 (q, CH_3C -14), 13.2 (q, CH_3C -6), 12.5 (q, CH_3C -4), 11.4 (q, C-21), 10.8 (q, CH_3C -10), 10.1 (q, CH_3C -12), 9.9 (q, CH_3C -16), 9.8 (q, CH_3C -18), 8.3 (q, CH_3C -8), 6.4 (q, C-1), 2.2 (q $\times 3$, CH_3Si)

LRMS (EI), m/z (relative intensity): 592 ($[M]^+$, 10), 467 (57), 349 (63), 209 (19), 180 (70), 179 (39), 169 (22), 73 (42), 57 (100)

HRMS m/z calcd for $C_{32}H_{52}O_8Si$: 592.3431; found: 592.3446 (EI).

***ent*-(13*S*)-11-Didehydro-13-dihydro-7-*O*-(trimethylsilyl)caloundrin B (**192**)**

***syn*-aldol-B**



n-BuLi (2.4 M in hexanes; 0.012 mL, 0.027 mmol) was added to a stirred solution of *tert*-butyl(trimethylsilyl)amine (0.006 mL, 4 mg, 0.03 mmol) in THF (0.1 mL) at 0 °C under argon. After 3 min, the reaction mixture was warmed to room temperature and, after 15 min, was cooled 0 °C. A solution of ketone *ent*-**95** (7 mg, 0.02 mmol) in THF (0.1 mL plus 3 × 0.1 mL rinses) was added. After 10 min, the mixture cooled to -78 °C, and a solution of freshly prepared aldehyde (\pm)-**30** (11.5 mg, 0.055 mmol) in THF (0.3 mL) was added. After 20 min, the reaction was quenched by addition of phosphate buffer (pH=7; 1 mL). The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 , concentrated, and fractionated by FCC (20%-100% ethyl acetate in hexanes) to provide recovered starting ketone *ent*-**95** (2 mg, 28%), and a mixture of aldol adducts that were further fractionated by PTLC (30% ethyl acetate in hexane, multiple elution) to provide a 1.5:1 mixture of two anti aldols (2.5 mg, ca. 23%), *syn*-aldol-A **190** (2 mg, 18%), and *syn*-aldol-B **192** (3 mg, 28%). $[\alpha]_D^{+15}$ (c 0.3, $CHCl_3$)

IR ν_{max} : 3396, 1716, 1653, 1595 cm^{-1}

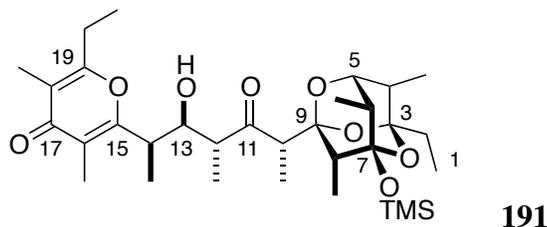
¹H NMR (500 MHz, CDCl₃) δ: 4.05 (1H, d, *J* = 10 Hz, HC-13), 3.77 (1H, d, *J* = 3.5 Hz, HC-5), 3.16 (1H, s, HO), 3.03 (1H, dq, *J* = 10, 7 Hz, HC-14), 2.89 (1H, q, *J* = 7 Hz, HC-10), 2.73 (1H, q, *J* = 7 Hz, HC-12), 2.63 (1H, dq, *J* = 15, 7.5 Hz, HC-20), 2.54 (1H, dq, *J* = 15, 7.5 Hz, HC-20), 2.13 (1H, q, *J* = 6.5 Hz, HC-8), 2.01-1.91 (2H, m, HC-4, HC-6), 1.98 (3H, s, H₃CC-16), 1.95 (3H, s, H₃CC-18), 1.64-1.50 (1H, m, HC-2), 1.50-1.39 (1H, m, HC-2), 1.34 (3H, d, *J* = 7 Hz, H₃CC-14), 1.20 (3H, t, *J* = 7.5 Hz, H₃C-21), 1.15 (3H, d, *J* = 7 Hz, H₃CC-10), 1.10 (3H, d, *J* = 7 Hz, H₃CC-6), 1.07 (3H, d, *J* = 7 Hz, H₃CC-12), 0.88 (3H, d, *J* = 7 Hz, H₃CC-4), 0.84 (3H, t, *J* = 7.5 Hz, H₃C-1), 0.81 (3H, d, *J* = 6.5 Hz, H₃CC-8), 0.14 (9H, s, H₃CSi ×3)

¹³C NMR (125 MHz, CDCl₃) δ: 216.5 (s, C-11), 179.9 (s, C-17), 164.5 (s, C-19), 163.9 (s, C-15), 119.2 (s, C-16), 118.3 (s, C-18), 103.1 (s, C-3), 102.0 (s, C-9), 99.7 (s, C-7), 78.6 (d, C-5), 72.4 (d, C-13), 51.3 (d, C-10), 46.1 (d, C-12), 38.9 (d, C-14), 37.4 (d, C-4), 36.7 (d, C-6), 36.0 (d, C-8), 29.6 (t, C-2), 25.0 (t, C-20), 15.9 (q, CH₃C-14), 13.3 (q, CH₃C-6), 12.6 (q, CH₃C-4), 11.6 (q, C-21), 10.7 (q, CH₃C-10), 10.0 (q, CH₃C-16), 9.9 (q, CH₃C-18), 9.7 (q, CH₃C-12), 8.1 (q, CH₃C-8), 6.3 (q, C-1), 2.1 (q ×3, CH₃Si)

LRMS (EI), *m/z* (relative intensity): 592 ([M]⁺, 11), 468 (24), 467 (73), 349 (76), 209 (25), 180 (97), 179 (44), 73 (64), 57 (100)

HRMS *m/z* calcd for C₃₂H₅₂O₈Si: 592.3431; found: 592.3451 (EI).

***ent*-(13*S*)-11-Didehydro-13-dihydro-7-*O*-(trimethylsilyl)caloundrin B (191).**



n-BuLi (2.4 M in hexanes; 0.070 mL, 0.17 mmol) was added to a stirred solution of *tert*-butyl(trimethylsilyl)amine (0.035 mL, 26 mg, 0.18 mmol) in THF (0.7 mL) at 0 °C under argon. After 1 min, the reaction mixture was warmed to room temperature and, after 15 min, was cooled 0 °C. A solution of ketone *ent*-**95** (48 mg, 0.12 mmol) in THF (0.6 mL plus 3× 0.2 mL rinses) was added, After 10 min, the mixture cooled to -78 °C, and (*c*-C₆H₁₂)₂BCl (1 M in hexane; 0.169 mL, 0.17 mmol) was added. After 15 min, a solution of freshly prepared aldehyde (±)-**30** (95 mg, 0.45 mmol) in THF (0.6 mL) was added. After 7 h, the reaction was quenched by sequential addition of phosphate buffer (pH=7; 1 mL), methanol (1 mL) and 30% aq H₂O₂ (1 mL) with vigorous stirring. The mixture was warmed to 0 °C and, after 10 min, was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (20-50% ethyl acetate in hexane) to provide the titled compound (38 mg, 51%) and a mixture of diastereomers including **191** (24 mg, 31%). Fractionation of the latter mixture by PTLC (30% ethyl acetate in hexane, multiple elution) provided a 2:1 mixture of aldol diastereomers (13 mg, 18%) and additional titled compound (7 mg, 9%; total yield of **191** = 60%). [α]_D +15 (*c* 0.9, CHCl₃)

IR ν_{\max} : 3378, 1703, 1652, 1596 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ : 3.89 (1H, ddd, *J* = 6, 6.5, 7 Hz, HC-13), 3.77 (1H, br d, *J* = 3.5 Hz, HC-5), 3.11 (1H, dq, *J* = 6, 7 Hz, HC-14), 2.93 (1H, dq, *J* = 7, 7 Hz, HC-12), 2.88 (1H, q, *J*

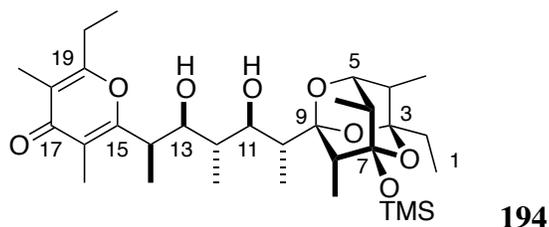
= 7 Hz, HC-10), 2.70 (1H, d, $J = 6.5$ Hz, HO), 2.59 (2H, ap q, $J = 7.5$ Hz, H₂C-20), 2.09-2.00 (2H, m, HC-4, HC-8), 1.97-1.91 (1H, m, HC-6), 1.93 (3H, s, H₃CC-16 or H₃CC-18), 1.92 (3H, s, H₃CC-16, H₃CC-18), 1.59 (1H, dq, $J = 14.5, 7.5$ Hz, HC-2), 1.51 (1H, dq, $J = 14.5, 7.5$ Hz, HC-2), 1.29 (3H, d, $J = 7$ Hz, H₃CC-14), 1.20 (3H, t, $J = 7.5$ Hz, H₃C-21), 1.19 (3H, d, $J = 7$ Hz, H₃CC-10), 1.12 (3H, d, $J = 7$ Hz, H₃CC-12), 1.03 (3H, d, $J = 7$ Hz, H₃CC-6), 0.92 (3H, t, $J = 7.5$ Hz, H₃C-1), 0.92 (3H, d, $J = 6.5$ Hz, H₃CC-8), 0.88 (3H, d, $J = 7$ Hz, H₃CC-4), 0.14 (9H, s, H₃CSi ×3)

¹³C NMR (125 MHz, CDCl₃) δ: 215.6 (s, C-11), 179.8 (s, C-17), 164.9 (s, C-15), 164.4 (s, C-19), 118.6 (s, C-16), 118.3 (s, C-18), 103.1 (s, C-3), 102.2 (s, C-9), 99.8 (s, C-7), 78.5 (d, C-13), 76.6 (d, C-5), 52.1 (d, C-10), 47.5 (d, C-12), 39.0 (d, C-14), 37.2 (d, C-4), 36.9 (d, C-8), 36.8 (d, C-6), 29.6 (t, C-2), 24.9 (t, C-20), 15.1 (q, CH₃C-12), 13.3 (q, CH₃C-6), 13.0 (q, CH₃C-14), 12.6 (q, CH₃C-4), 11.5 (q, C-21), 10.5 (q, CH₃C-10), 9.7 (q, CH₃C-16), 9.7 (q, CH₃C-18), 8.4 (q, CH₃C-8), 6.5 (q, C-1), 2.2 (q ×3, CH₃Si)

LRMS (EI), m/z (relative intensity): 592 ([M]⁺, 8), 523 (11), 467 (53), 349 (55), 180 (100), 179 (43), 169 (22), 73 (54), 57 (56)

HRMS m/z calcd for C₃₂H₅₂O₈Si: 592.3431; found: 592.3441 (EI).

***ent*-(13*R*)-13-Dihydro-7-*O*-trimethylsilyl-caloundrin B (194).**



Et₂BOMe (1M in toluene; 0.27 mL, 0.27 mmol) was added to a stirred solution of aldol adduct **191** (16 mg, 0.027 mmol) in THF (0.23 mL) and MeOH (0.077 mL) at 0 °C under argon. After

30 min, the solution was cooled to $-78\text{ }^{\circ}\text{C}$ and NaBH_4 (44 mg, 1.1 mmol) was added. After 40 min at $-78\text{ }^{\circ}\text{C}$ and 2.5 h at $0\text{ }^{\circ}\text{C}$, phosphate buffer (pH=7; 0.5 mL) and MeOH (0.5 mL) were added to the reaction mixture followed by dropwise addition of 30% aq H_2O_2 (0.5 mL) (caution: exothermic). After 5 min, the mixture was allowed to warm to ambient temperature. After 2 h, the mixture was extracted CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 , concentrated, and fractionated by PTLC (30% ethyl acetate in hexanes) to yield diol **194** (9 mg, 58%) and its borate diester (4.6 mg, 27%). The boronate ester, obtained as above from several experiments, was combined (20 mg) and taken up in THF (2 mL) and *N*-methyldiethanolamine (0.35 mL, 0.38 g, 0.87 mmol) was added. After 10 min, the mixture was cooled at $0\text{ }^{\circ}\text{C}$ and phosphate buffer (pH=7; 2 mL) and 30% aq H_2O_2 (2 mL) were added sequentially. After 5 min, the mixture was warmed at room temperature and, after 2 h, was extracted with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , concentrated, and fractionated by PTLC (50% ethyl acetate in hexane) to yield diol **194** (17 mg, 91%). Thus, the overall yield of **194** was 84%.
[α]_D -3 (*c* 0.3, CHCl_3)

IR ν_{max} : 3413, 1652, 1592 cm^{-1}

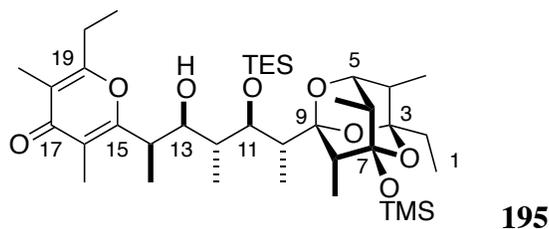
^1H NMR (500 MHz, CDCl_3) δ : 4.42 (1H, br s, HOC-11), 3.98 (1H, br s, HOC-13), 3.80 (1H, d, $J = 3.5$ Hz, HC-5), 3.78 (1H, dd, $J = 6, 6$ Hz, HC-13), 3.61 (1H, dd, $J = 5, 8$ Hz, HC-11), 3.30 (1H, dddd, $J = 7$ Hz, HC-14), 2.61 (2H, ap q, $J = 8$ Hz, H_2C -20), 2.20-2.05 (3H, m, HC-4, HC-8, HC-10), 1.99 (1H, br q, $J = 7$ Hz, HC-6), 1.97 (3H, s, H_3CC -16), 1.94 (3H, s, H_3CC -18), 1.85 (1H, ddq, $J = 6, 8, 7$ Hz, HC-12), 1.63 (1H, dq, $J = 14.5, 7.5$ Hz, HC-2), 1.53 (1H, dq, $J = 14.5, 7.5$ Hz, HC-2), 1.27 (3H, d, $J = 7$ Hz, H_3CC -14), 1.21 (3H, t, $J = 7.5$ Hz, H_3C -21), 1.04 (3H, d, $J = 7$ Hz, H_3CC -10), 1.03 (3H, d, $J = 7$ Hz, H_3CC -6), 0.97-0.91 (6H, d, $J = 7$ Hz, H_3CC -8, H_3CC -12), 0.93 (3H, t, $J = 7.5$ Hz, H_3C -1), 0.90 (3H, d, $J = 7$ Hz, H_3CC -4), 0.16 (9H, s, $\text{H}_3\text{CSi} \times 3$)

^{13}C NMR (125 MHz, CDCl_3) δ : 180.1 (s, C-17), 165.9 (s, C-15), 164.5 (s, C-19), 118.3 (s, C-16), 118.1 (s, C-18), 104.9 (s, C-9), 102.9 (s, C-3), 99.6 (s, C-7), 81.0 (d, C-11), 79.0 (d, C-5), 78.4 (d, C-13), 41.8 (d, C-10), 40.2 (d, C-14), 39.6 (d, C-12), 37.7 (d, C-8), 37.4 (d, C-4), 36.7 (d, C-6), 29.7 (t, C-2), 25.0 (t, C-20), 16.8 (q, $\text{CH}_3\text{C-12}$), 13.8 (q, $\text{CH}_3\text{C-10}$), 13.5 (q, $\text{CH}_3\text{C-6}$), 12.8 (q, $\text{CH}_3\text{C-14}$), 12.6 (q, $\text{CH}_3\text{C-4}$), 11.6 (q, C-21), 9.8 (q, $\text{CH}_3\text{C-16}$), 9.7 (q, $\text{CH}_3\text{C-18}$), 8.8 (q, $\text{CH}_3\text{C-8}$), 6.5 (q, C-1), 2.2 (q $\times 3$, $\text{CH}_3\text{-Si}$)

LRMS (EI), m/z (relative intensity): 594 ($[\text{M}]^+$, 3), 469 (12), 351 (15), 267 (19), 181 (17), 180 (100), 153 (10), 73 (21), 57 (37)

HRMS m/z calcd for $\text{C}_{32}\text{H}_{54}\text{O}_8\text{Si}$: 594.3588; found: 594.3597 (EI).

***ent*-(13*S*)-13-Dihydro-11-*O*-triethylsilyl-7-*O*-trimethylsilyl-caloundrin B (195).**



2,6-Lutidine (46 μL , 42 mg, 0.392 mmol) and TESOTf (0.01 mL, 10 mg, 0.044 mmol) were sequentially added to a solution of diol **194** (23 mg, 0.039 mmol) in CH_2Cl_2 (3.9 mL) at $-50\text{ }^\circ\text{C}$ under argon. After 6 min, the reaction mixture was diluted with ethyl acetate and washed sequentially with 1% aq citric acid, saturated aq NaHCO_3 , and brine. The organic layer was dried over Na_2SO_4 , concentrated, and fractionated by PTLC (30% ethyl acetate in hexanes) to yield recovered diol **194** (14 mg, 61%) and the titled compound as a colorless oil (9 mg, 31%; 79% BORSM). $[\alpha]_{\text{D}}^{+10}$ (c 0.35, CHCl_3)

IR ν_{max} : 3437, 1653, 1611, 1596 cm^{-1}

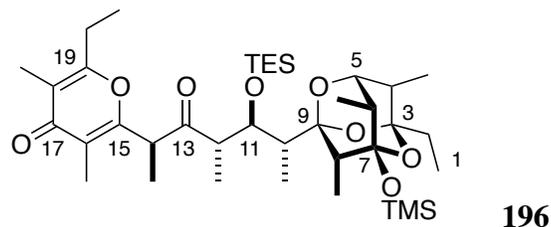
¹H NMR (500 MHz, CDCl₃) δ: 4.00 (1H, dd, *J* = 3, 3 Hz, HC-11), 3.80 (1H, br s, HO), 3.78-3.71 (2H, m, HC-5, HC-13), 3.11 (1H, dq, *J* = 4, 7 Hz, HC-14), 2.62 (2H, ap q, *J* = 7.5 Hz, H₂C-20), 2.37-2.25 (1H, m, HC-12), 2.05 (1H, dq, *J* = 4, 7 Hz, HC-4), 2.02-1.90 (2H, m, HC-6, HC-10), 1.97 (3H, s, H₃CC-16), 1.95 (3H, s, H₃CC-18), 1.85 (1H, q, *J* = 6.5 Hz, HC-8), 1.70-1.46 (2H, m, H₂C-2), 1.24 (3H, d, *J* = 7 Hz, H₃CC-14), 1.21 (3H, t, *J* = 7.5 Hz, H₃C-21), 1.09 (3H, d, *J* = 7 Hz, H₃CC-10), 1.03 (3H, d, *J* = 7 Hz, H₃CC-6), 0.98 (3H, d, H₃CC-8), 0.97 (3H, d, *J* = 7 Hz, H₃CC-12), 0.94 (9H, t, *J* = 8 Hz, H₃CCSi ×3), 0.93 (3H, t, H₃C-1), 0.89 (3H, d, H₃CC-4), 0.61 (6H, ap q, H₂CSi ×3), 0.17 (9H, s, H₃CSi ×3)

¹³C NMR (125 MHz, CDCl₃) δ: 180.3 (s, C-17), 166.5 (s, C-15), 164.6 (s, C-19), 117.9 (s, C-16), 117.7 (s, C-18), 102.7 (s, C-3), 102.6 (s, C-9), 99.7 (s, C-7), 78.4 (d, C-5), 77.7 (d, C-11), 75.6 (d, C-13), 46.6 (d, C-10), 39.0 (d, C-14), 37.5 (d, C-8), 37.3 (d, C-12), 37.0 (d, C-4), 36.8 (d, C-6), 29.7 (t, C-2), 25.1 (t, C-20), 19.2 (q, CH₃C-12), 13.4 (q, CH₃C-6), 12.6 (q, CH₃C-4), 11.5 (q, C-21), 10.6 (q, CH₃C-14), 9.8 (q, CH₃C-16), 9.7 (q, CH₃C-18), 8.6 (q, CH₃C-8), 7.8 (q, CH₃C-10), 7.0 (q ×3, CH₃CSi), 6.5 (q, C-1), 5.2 (t ×3, CH₂Si), 2.2 (q ×3, CH₃Si)

LRMS (EI), *m/z* (relative intensity): 708 ([M]⁺, 3), 381 (12), 255 (17), 209 (37), 181 (15), 180 (100), 115 (15), 73 (20), 57 (22)

HRMS *m/z* calcd for C₃₈H₆₈O₈Si₂: 708.4453; found: 708.4452 (EI).

***ent*-11-*O*-Triethylsilyl-7-*O*-trimethylsilyl-caloundrin B (196).**



IBX (41 mg, 0.1467 mmol) was added to a stirred solution of alcohol **195** (13 mg, 0.0183 mmol) in DMSO (2.4 mL) at room temperature under Ar. After 13 h, the reaction was diluted with ethyl acetate and washed sequentially with saturated aq NaHCO₃, distilled water and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (30% ethyl acetate in hexane) to provide the titled compound (13 mg, 99%). [α]_D +80 (*c* 0.3, CHCl₃)

IR ν_{max} : 1727, 1657, 1621 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ : 4.10 (1H, dd, *J* = 2.5, 7 Hz, HC-11), 4.08 (1H, q, *J* = 7 Hz, HC-14), 3.74 (1H, d, *J* = 3.5 Hz, HC-5), 2.93 (1H, dq, *J* = 7, 7 Hz, HC-12), 2.49-2.57 (2H, m, H₂C-20), 2.08 (3H, s, H₃CC-16), 2.02-1.91 (3H, m, HC-4, HC-6, HC-10), 1.95 (3H, s, H₃CC-18), 1.86 (1H, q, *J* = 6.5 Hz, HC-8), 1.64-1.43 (2H, m, H₂C-2), 1.30 (3H, d, *J* = 7 Hz, H₃CC-14), 1.14 (3H, t, *J* = 7.5 Hz, HC-21), 1.01 (24H, d, *J* = 7 Hz, H₃CC-6), 0.99 (3H, d, *J* = 6.5 Hz, H₃CC-10), 0.97 (3H, d, *J* = 6.5 Hz, H₃CC-8), 0.96 (3H, d, *J* = 6.5 Hz, H₃CC-12), 0.94 (9H, t, *J* = 8 Hz, H₃CCSi \times 3), 0.91 (3H, t, *J* = 7.5 Hz, H₃CC-1), 0.87 (3H, d, *J* = 7 Hz, H₃CC-4), 0.577, 3.5 (6H, ap q, *J* = 8 Hz, H₂CSi \times 3), 0.16 (9H, s, H₃CSi \times 3)

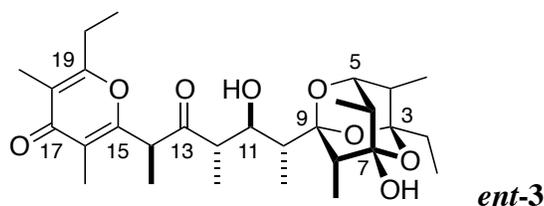
¹³C NMR (125 MHz, CDCl₃) δ : 209.2 (s, C-13), 180.1 (s, C-17), 165.0 (s, C-19), 161.6 (s, C-15), 120.3 (s, C-16), 118.4 (s, C-18), 102.7 (s, C-3), 102.0 (s, C-9), 99.8 (s, C-7), 78.6 (d, C-5), 75.0 (d, C-11), 50.9 (d, C-14), 47.5 (d, C-10), 46.2 (d, C-12), 38.0 (d, C-8), 37.1 (d, C-4), 36.7 (d, C-6), 29.7 (t, C-2), 24.9 (t, C-20), 15.1 (q, CH₃C-12), 13.5 (q, CH₃C-6), 13.2 (q, CH₃C-14),

12.7 (q, CH₃C-4), 11.5 (q, C-21), 10.3 (q, CH₃C-16), 9.7 (q, CH₃C-18), 8.6 (q, CH₃C-10), 7.5 (q, CH₃C-8), 7.1 (q ×3, CH₃Si), 6.4 (q, C-1), 5.4 (t ×3, CH₂Si), 2.2 (q ×3, CH₃Si)

LRMS (EI), *m/z* (relative intensity): 706 ([M]⁺, 8), 678 (18), 677 (37), 581 (56), 527 (30), 379 (43), 349 (100), 255 (49), 180 (46)

HRMS *m/z* calcd for C₃₈H₆₆O₈Si: 706.4296; found: 706.4270 (EI).

***ent*-Caloundrin B (*ent*-3).**



Pyridine (0.16 mL, 16 mg, 2.0 mmol), distilled water (0.007 mL, 7 mg, 0.4 mmol), and HF·pyridine (0.108 mL) were sequentially added to a stirred solution of ketone **196** in THF (2 mL) at room temperature. After 2 h, the mixture was diluted with ethyl acetate and washed sequentially with 1% aq citric acid (×3), saturated aq NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, concentrated, and fractionated by PTLC (50% ethyl acetate in hexanes) to give *ent*-caloundrin B (*ent*-3) (7 mg, quantitative). [α]_D +50 (*c* 0.2, CHCl₃)

IR ν_{\max} : 3385, 1653, 1598 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ : 4.14 (1H, q, *J* = 7 Hz, HC-14), 3.95 (1H, d, *J* = 7.5 Hz, HOC-11), 3.83 (1H, br d, *J* = 3.5 Hz, HC-5), 3.68 (1H, ddd, *J* = 5, 5, 7.5 Hz, HC-11), 3.03 (1H, dq, *J* = 5, 7 Hz, HC-12), 2.62 (1H, br s, HOC-7), 2.62-2.52 (2H, m, H₂C-20), 2.24 (1H, q, *J* = 6.5 Hz, HC-8), 2.10 (1H, dq, *J* = 3.5, 7 Hz, HC-4), 2.09-2.03 (2H, m, HC-6, HC-10), 2.07 (3H, s, H₃CC-16), 1.95 (3H, s, H₃CC-18), 1.65-1.54 (2H, m, H₂C-2), 1.38 (3H, d, *J* = 7 Hz, H₃CC-14), 1.16

(3H, t, $J = 7.5$ Hz, H₃C-21), 1.09 (3H, d, $J = 7$ Hz, H₃CC-6), 1.03 (3H, d, $J = 7$ Hz, H₃CC-12), 0.99 (3H, d, $J = 6.5$ Hz, H₃CC-8), 0.97 (3H, d, $J = 7$ Hz, H₃CC-10), 0.93 (3H, t, $J = 7.5$ Hz, H₃C-1), 0.93 (3H, d, $J = 7$ Hz, H₃CC-4)

¹³C NMR (125 MHz, CDCl₃) δ : 213.4 (s, C-13), 179.8 (s, C-17), 165.0 (s, C-19), 160.3 (s, C-15), 120.4 (s, C-16), 118.7 (s, C-18), 103.1 (s, C-9), 103.0 (s, C-3), 97.4 (s, C-7), 78.6 (d, C-5), 77.7 (d, C-11), 50.7 (d, C-14), 46.5 (d, C-12), 42.0 (d, C-10), 36.9 (d, C-8), 36.8 (d, C-4), 35.8 (d, C-6), 29.7 (t, C-2), 24.9 (t, C-20), 16.3 (q, CH₃C-12), 13.6 (q $\times 2$, CH₃C-6 an CH₃C-14), 12.6 (q, CH₃C-4), 11.5 (q, C-21), 11.4 (q, CH₃C-10), 10.4 (q, CH₃C-16), 9.8 (q, CH₃C-18), 7.7 (q, CH₃C-8), 6.5 (q, C-1)

LRMS (EI), m/z (relative intensity): 520 ([M]⁺, 1), 236 (9), 207 (3), 181 (13), 180 (100), 179 (16), 153 (12), 125 (8), 69 (7), 57 (42)

HRMS m/z calcd for C₂₉H₄₄O₈: 520.3036; found: 520.3027 (EI).

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