THE TOTAL SYNTHESIS OF DOLABRIFEROL: A RETRO-CLAISEN APPROACH FROM ITS PUTATIVE PRECURSOR

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by

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ABSTRACT

Dolabriferol is a polypropionate natural product first isolated by Gavagnin and coworkers from the skin of the anaspidean mollusk, *Dolabrifera dolabrifera*. An unusual structural feature of dolabriferol is its noncontiguous carbon backbone that is proposed to arise via a retro-Claisen rearrangement of the cyclic hemiacetal precursor 164, perhaps as an artifact of isolation. Computational evaluations of the various cyclization/rearrangement manifolds available to the acyclic precursor 4 have suggested that the pathway to dolabriferol from linear precursor 4 is plausible.

The research presented herein describes the total synthesis of putative precursor 4, evaluation of its properties, and a study of its retro-Claisen rearrangement. This study
ultimately gave dolabriferol which suggests this compound may be formed during isolation; thus, the linear precursor 4 (along with its tautomeric forms) is a plausible natural product. This is the first total synthesis of dolabriferol via its putative precursor 4. Previous synthetic attempts/syntheses either involve esterification or induce retro-Claisen mid-stage to give dolabriferol. The approach to the synthesis of 4 involves aldol coupling of the readily available tetrapropionate fragment (±)-141 with enantioenriched aldehyde 124 furnishing 142, a reaction that proceeded with kinetic resolution. The enantioenrichment of 124 is derived from a proline-catalyzed intermolecular aldol reaction of 75 with isobutyraldehyde furnishing 97 (dr >20:1, er 24:1). Subsequent functional group manipulations of 142 provided the desired 4 as a mixture of hemiacetals.
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LIST OF ABBREVIATIONS

α  observed optical rotation in degrees

[α]D  specific rotation at the sodium D line (expressed without units; implied actual units are: (deg·mL)/(g·dm))

Ac  acetyl

AcOH  acetic acid

anti  antiperiplanar

ap  apparent (NMR signal)

atm  atmosphere(s) (as a measure of pressure)

aq  aqueous

9-BBN  9-borabicyclo[3.3.1]nonyl

Bn  benzyl

BOM  benzyloxymethyl

bp  boiling point

br  broad (description of a spectral signal)

n-BuLi  n-butyllithium

t-Bu  tert-butyl

t-BuLi  tert-butyllithium

t-BuOH  tert-butyl alcohol

°C  degrees Celsius (temperature)

cat.  catalytic (abbreviation used with period)

Cl  chemical ionization (in mass spectrometry)

13C NMR  carbon 13 nuclear magnetic resonance

COSY  correlation spectroscopy

m-CPBA  meta-chloroperoxybenzoic acid

Cy  cyclohexyl
\( \delta \)  NMR chemical shift in parts per million downfield from TMS

d  day(s); doublet (spectral signal)

DBU  1,8-diazabicyclo[5.4.0]undec-7-ene

DCM  dichloromethane

DDQ  2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DEPT  distortionless enhancement by polarization transfer (an NMR technique)

DIBAL-H  diisobutyaluminum hydride

dil  dilute

DIPA  \( N,N \)-diisopropylamine

DIPEA  \( N,N \)-diisopropylethylamine

DMAP  4-\( N,N \)-dimethylaminopyridine

DMF  \( N,N \)-dimethylformamide

DMP  Dess-Martin periodinane

DMSO  dimethyl sulfoxide

dr  diastereomer ratio

DRIFT  diffuse reflectance Fourier transform infrared

\( E \) and \( Z \)  configurational descriptors for alkenes. \( E \) denotes that the substituents of highest CIP (Cahn-Ingold-Prelog) priority at each end of the double bond are on opposite sides. If the pertinent substituents are on the same side, the descriptor is \( Z \).

\( ee \)  enantiomeric excess

EI  electron impact ionization

\( \text{ent} \)  enantiomer of

\( \text{epi} \)  epimer of

equiv  equivalents

\( \text{er} \)  enantiomeric ratio

Et  ethyl
FCC  flash column chromatography
h  hour(s)
HMBC  heteronuclear multiple bond correlation
HMDS  hexamethyldisilazane, bis(trimethylsilyl)amide
$^1$H NMR  proton nuclear magnetic resonance
HPLC  high-performance liquid chromatography
HRMS  high resolution mass spectrometry
HSQC  heteronuclear single quantum correlation
Hz  Hertz
IBX  2-iodoxybenzoic acid
IR  infrared
$J$  coupling constant (in NMR spectrometry)
J  Joule(s)
K  Kelvin (absolute temperature)
KHMDS  potassium bis(trimethylsilyl)amide
KJ  kiloJoule(s)
KR  kinetic resolution
LDA  lithium diisopropylamide
LiHMDS  lithium bis(trimethylsilyl)amide
m  multiplet (spectral); meter(s); milli
M  molar (moles per liter)
$M^+$  parent molecular ion
Me  methyl
MHz  megahertz
min  minute(s)
MKE  mutual kinetic enantioselection
mol  mole(s)
MOM  methoxymethyl
mp  melting point
MS  mass spectrometry
MW, mol wt  molecular weight
nm  nanometer(s)
NMR  nuclear magnetic resonance
NOE  nuclear Overhauser enhancement
OTf  trifluoromethanesulfonyloxy
PG  protecting group
Ph  phenyl
PMA  phosphomolybdic acid
PMB  p-methoxybenzyl
PPTS  pyridinium p-toluenesulfonate
iPr  isopropyl
PTLC  preparative thin layer chromatography
PTSA  p-toluenesulfonic acid
q  quartet
rac  racemic
Ref, ref  reference
rt  room temperature
s  singlet (spectral)
sat  saturated
syn  synperiplanar
t  triplet (spectral)
TASF  tris(dimethylamino)sulfonium difluorotrimethylsilicate
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tbody>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBSCI</td>
<td>tert-butyldimethylsilyl chloride</td>
</tr>
<tr>
<td>TBSOTf</td>
<td>tert-butyldimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPPTS</td>
<td>tris(3-sulfophenyl)phosphine trisodium salt</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>p-toluenesulfonic acid</td>
</tr>
</tbody>
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INTRODUCTION

1.1. Introduction to Structures, Biosynthesis, and Studies of Dolabriferol

1.1.1. Opisthobranchs and the Curious Chemist

Opisthobranchs are gastropod mollusks found exclusively in marine habitats around the globe. A common attribute among these mollusks is the lack of a complete shell, with only a few species having shells big enough for the animal to completely withdraw itself. For most cases, the shell is either reduced in size, internalized, or lost completely. Very often, non-shelled gastropods are characterized as being slimy and unattractive with the connotation usually referring to their terrestrial counterparts. The Opisthobranchs are much different showing a vast color array between species but their grand color schemes and beauty are only witnessed by deep sea divers.¹

Only a few thousand species comprise the Opisthobranchs with most animals never exceeding ten centimeters in length. Externally, the Opisthobranchs show little evolutionary difference between other mollusks. Their chemical biology, however, is very unique within the animal kingdom often relating to foraging or defensive strategies. These include usage of intact chloroplasts from algal cells for feeding strategies, storage of intact cnidocysts (organelles capable of penetrating target organisms and injecting toxins) from cnidarians, the ability to synthesize toxic compounds, or to uptake secondary metabolites to chemically arm themselves against potential predators. From a biochemical standpoint, isolation and synthesis of these metabolites and toxic compounds are important for understanding their role in the chemical ecology.¹
Despite their size and primitive stature in the animal kingdom, these mollusks are capable of producing an array of metabolites with diverse structural and dense stereochemical manifolds. Among the metabolites isolated, a large number are polypropionate based with some showing pharmaceutical activity; for example, some compounds are able to cure infections in patients who are sensitive to penicillin. The ongoing interest in natural products on their origin, their pharmaceutical activity, and sheer curiosity in their possible synthesis has pushed the field into developing methodology to allow access to these complex and interesting molecules. Although there has been extensive development in polypropionate synthesis, many natural products still pose a challenge to mimic in a laboratory setting.

1.1.2. From Simple Chains to Architecturally Complex Molecules

Before discussing polypropionate based natural products and their importance, the biosynthesis of such compounds is noteworthy. Polypropionates are formed by an extension of the polyketide process shown in Scheme 1.1. In organisms, the polyketide process begins with formation of an acyl anion equivalent of malonyl CoA through anionic decarboxylation. Addition of this intermediate to acetyl CoA forms acetoacetyl CoA and, if the process is allowed to continue, formation of longer chains is possible. From here, a wide variety of natural product classes can emerge, from aromatic compounds and lactones to unsaturated fatty acids and polyacetates.²
Scheme 1 illustrates select transformations that enzymes are capable of performing as part of the polyketide pathway. The steps shown are not necessarily the order of functional group manipulations and may in fact exist in any possible order. Therefore, the complete carbon skeleton does not have to be synthesized directly, in fact, methylations, reductions, eliminations, hydrogenations, cyclizations, and many other changes can occur before the complete carbon skeleton is assembled. Looking specifically at methylations, reductions, and carbon extensions as the sole reactions allowed provides access to linear compounds with dense stereochemical arrays. Every methylation or reduction that occurs, results in two more stereoisomers being possible. By methylating once at every position adjacent to a carbonyl or hydroxy functionality, moves the class of natural products from polyketides into the realm of polypropionates. Methylation of polyketides is not the predominant biosynthetic pathway to polypropionates; in fact, a similar route starting with methyl malonyl CoA exists and gives rise to the many known polypropionate natural products. The pathway begins by forming the acyl anion equivalent of methylmalonyl CoA by anionic decarboxylation and addition to propionyl CoA forming intermediate 2. Subsequent carbon extension with methylmalonyl CoA and
reductions with ketoreductases provide natural products with alternating methyl and hydroxy/ketone substitution down the carbon backbone.

**Scheme 1.2: Possible Biosynthesis of Polypropionates**

Not only are enzymes extremely efficient at synthesizing the long carbon chains, they are able to selectively produce a single stereoisomer with amazing turnover making them true masters of organic synthesis. The linear polyketides that are formed are not always the final product. In many cases, the linear form can undergo various reactions to form compounds that are no longer linear (Figure 1.1).
In the above example (Figure 1.1), a single linear precursor 3 can undergo various reaction pathways to form three unique natural products; all found in extracts of the sea mollusk *Siphonaria zelandica*. It was unclear if the three natural products were formed enzymatically or if precursor 3 was the biosynthetic product and baconipyrone A, baconipyrone C, and siphonarin B were artifacts of isolation. Despite their efficiency in assembling these unique molecules, the amount of material that can be harvested for testing and analysis is very limited, requiring synthetic material to test the origin of these natural products. In 2010, the linear precursor 3 was prepared by total synthesis and under mild conditions, was converted to each of the isolated natural products. These natural products were prepared from 3 without the use of enzymes to induce rearrangements, which suggests that these compounds may in fact be artifacts of isolation.³
1.2. Dolabriferol

1.2.1. Isolation, Structure Determination, and Biosynthesis

Dolabriferol was first isolated by Gavagnin and co-workers from the skin of the anaspidean mollusk, *Dolabrifera dolabrifera*. The specimens were collected off the coast of Cuba by SCUBA divers and the animals were frozen and immediately transferred. The frozen animals were soaked in acetone and the extract purified to afford pure dolabriferol (7.5 mg). The relative configuration of 1 was determined by X-ray crystallography but the absolute configuration was unknown until the first total synthesis of 1 by Vogel et al.

![Scheme 1.3: Formation of Dolabriferol via Retro-Claisen Rearrangement](image)

In 1996, Gavagnin commented on the unique structure of dolabriferol by saying "it is very surprising the finding of an ester obtained by coupling a polypropionate acid with a polypropionate alcohol." However, he proposed a tentative rationalization that 1 could be derived from the linear polypropionate precursor 4 by ring closing of the C-11 hydroxy onto the C-7 carbonyl. The cyclic hemiacetal 5 could then undergo retro-Claisen rearrangement forming the ester linkage and furnishing dolabriferol 1 (Scheme 1.3). Although the pathway shows precursor 4 going directly to dolabriferol, in reality, an enormous number of competing reactions are possible. If the linear precursor is allowed to cyclize, undergo retro-Claisen rearrangement, eliminate, and so on; one could envision a myriad of products.
1.2.2. Computational Studies by Goodman

In an attempt to understand the various possible pathways, Goodman et al. developed a reaction prediction program named ROBIA (Reaction Outcomes By Informatics Analysis) capable of predicting the outcome of organic reactions given the starting materials and conditions. ROBIA was used to study the various cyclization manifolds that linear precursor 4 may undergo. The proposed reaction pathway starting from 4 is hemi-acetal formation, retro-Claisen, followed by hemi-acetal formation to furnish 1, therefore the transformations for each possible manifold would follow the same sequence. To begin, the linear precursor 4 was allowed to form any possible hemi-acetal disregarding any compounds containing four-membered ring systems due to angle strain. ROBIA then transformed the two-dimensional structures into three-dimensional ones for calculations. The structures were minimized to give the most stable conformation resulting in 49 unique structures. Once the hemi-acetal was formed, the program allowed each unique structure to undergo a retro-Claisen rearrangement which resulted in a second set of intermediate structures (repeating conformational analysis and minimization of energy). These intermediates underwent a second hemi-acetal formation to produce the final set of structures. The previous sequence of filtering, generating all stereoisomers, transforming the structures into 3D, conformational analysis, and energy minimization were performed on all intermediates.
Scheme 1.4: Structures Predicted by ROBIA

Through the three reaction parameters, ROBIA generated 234 unique structures. Of all the structures determined, ROBIA concluded that the most stable stereoisomers are dolabriferol, its C-9 epimer (which would equilibrate to give dolabriferol), and three hemiortho esters shown in Scheme 1.4. Calculations put the esters higher in energy than the hemiortho esters, which are inconsistent both with experimental observations and higher levels of theory; hence, the hemiortho esters were discarded. These computational evaluations of the various cyclizations available to the acyclic precursor 4 suggest that the pathway to dolabriferol is thermodynamically favorable. Although these calculations support Gavagnin’s hypothesis for the formation of dolabriferol, proof requires direct evidence. Synthesis of the linear precursor 4 would provide an opportunity to experimentally test Gavagnin’s hypothesis.
1.3. Synthetic Studies on Dolabriferol

Synthetic studies on dolabriferol have been reported by five groups with two successful total syntheses by Vogel and by Goodman. Three different synthetic approaches have been described in the literature to construct dolabriferol.

Scheme 1.5: Retrosynthetic Approaches to Dolabriferol

The typical retrosynthetic design paradigm is to cleave the ester linkage forming the corresponding acid and alcohol moieties. The Dias and Chenevert approach allowed access to acid 6 and alcohol 7; however, neither group was able to esterify the two fragments.\textsuperscript{7,8,9} Lister and Perkins employed a retro-Claisen approach to obtain a protected derivative of dolabriferol but the deprotection was unsuccessful.\textsuperscript{10} Vogel reversed the sequence of reaction events by esterifying acid 8 and alcohol 9 first and delaying the formation of the lactol until the final step.\textsuperscript{5} It is worth noting that the absolute configuration of dolabriferol was unknown until Vogel reported his synthesis in 2010. Looking back at the first attempts at the synthesis of dolabriferol, Dias and Lister/Perkins were using the incorrect enantiomers. If either of these routes had been successful, the product synthesized would have been ent-dolabriferol. Finally,
inspired by his calculations, Goodman completed the synthesis of dolabriferol via a retro-
Claisen approach.\textsuperscript{11}

1.3.1. Dias Route to Dolabriferol

Dias et al. tackled dolabriferol by conceptually cleaving the ester linkage to give acid 21 and alcohol 16 with each of the two complex fragments being attainable from a common Weinreb amide precursor 12. The synthesis of 12 begins with a diastereoselective aldol addition of the boron enolate of acyloxazolidinone 10 with propionaldehyde furnishing 11 selectively. The corresponding Weinreb amide was formed and the hydroxyl group protected as its TBS ether to provide 12. Treatment of 12 with ethylmagnesium bromide formed ketone 13 which underwent aldol reaction with isobutyraldehyde followed by a syn-selective reduction to form the desired diol 14. Silyl deprotection of 14 followed by regioselective oxidation gave lactol fragment 16 in 8 steps (17% yield overall) starting from 10. Synthesis of acid fragment 21 started with reduction of Weinreb amide 12 to the corresponding aldehyde followed by Wittig homologation to give the desired α,β-unsaturated ester 17. Reduction of 17 with diisobutylaluminum hydride gave the corresponding allylic alcohol which was treated with \textit{m}-CPBA to form epoxide 18 as a single product. Epoxide opening of 18 was induced by reaction with Me\textsubscript{2}CuCNLi\textsubscript{2} to give diol 19 that possessed the desired \textit{syn-anti-anti} relative configuration for the four contiguous stereocenters. The final steps involved protection of the central hydroxyl as its PMB ether, deprotection of the silyl ether, and oxidation state adjustment to afford the desired acid fragment 21 in 13 steps (32% overall) starting from acyloxazolidinone 10. Attempts to couple the two fragments to form the natural product were not reported.\textsuperscript{7}
Although this route was close to completing the synthesis, the project had no new methodology, was a lengthy synthesis (24 steps total), and used an expensive starting material to form precursor 12. The project objectives were to provide a route to determine the absolute configuration of dolabriferol and to provide material for biological studies.

1.3.2. Chenevert Route to Dolabriferol

Chenevert et al. were also able to synthesize alcohol 16 and acid 32 from a common precursor obtained via an enzymatic desymmetrization of 23 obtained by hydroboration of diene 22. Using vinyl acetate in the presence of Candida rugosa lipase resulted in enantioselective acylation of 23 to give 24 in high yield. Addition of intact molecular sieves to the medium was required to achieve high enantioselectivity by trapping acetaldehyde.
molecular sieves or using powdered molecular sieves caused enzyme deactivation. Once acylated, oxidation of the terminal alcohol in 24 gave aldehyde 25 which was treated with ethylmagnesium bromide to give 26 as a mixture of diastereomers. Oxidation of the mixture gave the desired acid fragment 32 in 6 steps (50% overall) starting from diene 22.

Scheme 1.7: Chenevert Route to Dolabriferol

With acid fragment 32 synthesized, formation of lactol 16 was pursued and envisioned to come from intermediate 24. Desilylation of 24, protection of the resulting 1,3 diol as its p-methoxybenzylidene acetal, and base induced ester hydrolysis gave 27.Formation of aldehyde 28 was achieved using Dess-Martin periodinane oxidation of 27 which was subsequently alkylated with isopropylmagnesium bromide yielding 29. The Grignard reaction unfortunately gave the undesired configuration at the C-3 stereocenter. The stereocenter was adjusted by a
simple redox sequence to give the desired 3-(S) configuration (10:1 dr). Silylation of 3-(S)-29 with TBSOTf followed by DIBAL-H reductive acetal opening gave alcohol 30. Oxidation of 30 to the resulting aldehyde followed by Grignard reaction with ethylmagnesium bromide gave a diastereomeric mixture of alcohols, which upon oxidation, gave ketone 31. Finally, deprotection of the PMB ether and silyl ethers gave the desired hemiacetal 16 (16 steps from 22, 14% overall yield). There was no mention of attempted coupling of the two fragments to give dolabriferol.

1.3.3. Lister and Perkins Route to Dolabriferol

Lister and Perkins discussed their attempts at coupling acid fragment 21 and alcohol 16 but concluded that esterification was not possible under a variety of conditions. To overcome direct esterification, Lister and Perkins described a “biomimetic” retro-Claisen approach to form the desired ester linkage. The aldehyde 42 and ketone 38 were synthesized from stereocontrolled boron aldol reactions starting from the lactate derived 34. The (E)-enol dicyclohexylborinate of 34 was reacted with chiral aldehyde 33 to give 39 in excellent yield. The alcohol in 39 was protected as its TBS ether and subjected to SmI$_2$ reductive benzoate removal to give 40. Reduction and protection of 40 using NaBH$_4$ followed by PMB-imidate was required to avoid hemiacetal formation upon benzyl ether removal. Selective debenzylation of 41 with RANEY® nickel followed by oxidation furnished aldehyde 42. Ketone 38 was also prepared starting from intermediate 34. Reaction of the (E)-enol dicyclohexylborinate of ketone 34 with isobutyraldehyde gave ketone 35. After protection of the alcohol in 35 as its TBS ether, reaction with LiBH$_4$ gave a 1,2 diol that was oxidatively cleaved to produce aldehyde 36. Coupling of the (E)-enol dicyclohexylborinate of ketone 34 with aldehyde 36 gave a single detectable adduct 37.
Protection of the newly formed hydroxyl in 37 as its TES ether, followed by SmI$_2$ induced benzoate cleavage gave ketone 38.

Scheme 1.8: Lister/Perkin’s Route to Dolabriferol

The linear carbon chain 43 was prepared using a selective lithium aldol reaction to couple fragments 38 and 42, followed by PMB deprotection and a double oxidation using Swern’s protocol. Treating compound 43 with HF•pyridine/pyridine to remove the silyl ethers gave instead the doubly deprotected trioxaadamantane ring system 44. Exposure of 44 to DBU caused the tricyclic system to collapse and undergo retro-Claisen rearrangement to give 45, a TBS protected derivative of dolabriferol (31% yield, 12 steps).
All attempts to deprotect 45 using various methods resulted in undesired products including elimination of hydroxyl groups and formation of spiroacetals which were non-reversible. Although Perkins and Lister were unable to complete their synthesis, they provided a very elegant approach to the synthesis of dolabriferol and concluded that direct esterification of acid 21 and alcohol 16 was not a trivial transformation.

1.3.4. Vogel’s Route to Dolabriferol

Vogel et al. overcame the problem of late stage coupling of the linear acid with the heterocyclic alcohol by reversing the order of steps. Using their reaction cascade, which combines electron-rich dienes and (E)-enoxysilanes through SO$_2$ umpolung, allowed for rapid access to $\alpha,\beta,\gamma$-anti,anti-stereotriads in a one-pot reaction. Dolabriferol contains two $\alpha,\beta,\gamma$-anti,anti-stereotriads which allowed both fragments to be assembled in similar fashion. It is worth noting that the starting dienes incorporate the inexpensive enantiomerically enriched 1-arylethanol as a chiral auxiliary. The synthesis of the two anti,anti-stereotriads 48 and 54 showcased the methodology developed by Vogel by providing six stereocenters selectively in two steps. Selective reduction of 48, Alloc protection of the resulting alcohol, and removal of the chiral auxiliary furnished the desired alcohol 51.
Ozonolysis of 54 provided acid subunit 55 that was coupled with 51 using Paterson’s protocol yielding compound 56. Global deprotection of 56 induced cyclization to give dolabriferol 1 in 10 steps (7.9% overall) starting from diene 47. Vogel established the absolute configuration of dolabriferol through his synthesis, fifteen years after Gavagnin’s report.

**1.3.5. Goodman’s Route to Dolabriferol**

Inspired by their calculations and the previous work of Lister and Perkins, Goodman et al. proposed the linear precursor should cyclize to give dolabriferol as the thermodynamically more stable compound. To synthesize the carbon skeleton of 67, a Sn(OTf)2 mediated aldol was envisioned to couple fragments 62 and 66. These two fragments were assembled starting from
Evans’ $\beta$-ketoimide 10 and diol 63 synthesized using MacMillan’s organocatalytic cross-aldol methodology.

**Scheme 1.10: Total Synthesis of Dolabiferol by Goodman**

Addition of propionyl chloride to the lithium enolate of oxazolidinone 10 gave the desired $\beta$-ketoimide 58 in high selectivity (24:1). Generation of the titanium enolate of 58 and subsequent addition of propionaldehyde smoothly afforded 59. Hydroxy directed reduction of 59 furnished the 1,3-anti-diol 60 that was subsequently protected as the anti-PMP acetal 61. Cleavage of the auxiliary using LiBH$_4$ gave the corresponding alcohol which upon oxidation gave aldehyde coupling partner 62. Synthesis of ketone 66 started from PMP acetal formation from diol 63, followed by regioselective reductive cleavage of the PMP acetal with DIBAL-H, and subsequent oxidation of the resulting alcohol gave the desired aldehyde 64. Addition of
aldehyde 64 to the (E)-enol dicyclohexylborinate of 65, protection of the newly formed hydroxyl as its TES ether, followed by SmI$_2$ mediated cleavage of the benzoate afforded ketone coupling partner 66.

Coupling of fragments 62 and 66 was achieved via the tin enolate of 66 yielding a mixture of aldol adducts in high yield (83%, 12.6:1 dr). Oxidation of the aldol adducts with Dess-Martin periodinane gave 67 with no evidence of the enol tautomer by $^1$H NMR and no observed epimerization at the C-8 stereogenic center. With 67 in hand, deprotection of the TES ether unveiled a hydroxydiketone precursor for retro-Claisen rearrangement. Adopting the conditions from Lister and Perkins, exposure of the hydroxy-diketone to DBU effected the desired transformation to give 68 as the only product in high yield. With the ester linkage in place, all that remained was hydrolysis of the PMP acetal, chemoselective oxidation of the C-3 hydroxy group, and PMB removal to give dolabriferol.$^{11}$ Goodman’s synthesis provided the desired product in 14 steps from propionaldehyde in 4% overall yield in the longest linear sequence. Although Goodman was able to form dolabriferol via a retro-Claisen approach, the precursor still contains protecting groups and is not in the correct oxidation state. This demonstrated that compounds like 67 undergo rearrangement under mild base but did not shed light on the origin of dolabriferol.

1.4. Conclusion

The above approaches towards the synthesis of dolabriferol show that the synthesis of the target molecule is challenging. Forming the ester linkage between the two final fragments being unsuccessful with the methods tested. Although the route by Vogel is elegant and allowed for the absolute configuration to be determined, the question still remains if the acyclic
precursor is on the biosynthetic pathway and if cyclization is induced non-enzymatically. The route by Lister and Perkins through 44 shows promise as a feasible precursor to dolabriferol. Allowing the compound to cyclize allows for internal protection to the more robust trioxaadamantane. This highly unusual ring system has been identified in only two siphonariid natural products: muamvatin\textsuperscript{12} and caloundrin B\textsuperscript{13}, both of which have been synthesized by the Ward group. The methodology developed in the group should allow for formation of an intermediate similar to 44 and may be exploited to access a route to dolabriferol through its acyclic intermediate 4.
RESULTS AND DISCUSSION

2.1. Research Objectives

Within the Ward group, a recent strategy for polypropionate synthesis involves preparation of the linear precursor of certain polypropionate natural products and studying their cyclization patterns. So far, baconipyrone A, baconipyrone C, siphonarin B, and muamvatin have been synthesized from their putative ‘acyclic’ precursors suggesting that perhaps these acyclic precursors are the biosynthetic products (Scheme 2.1).\textsuperscript{3,14} This implies that many isolated polypropionates may not be the products formed during the biosynthetic pathway but are instead artifacts of isolation; i.e., the cyclizations and/or rearrangements are not induced enzymatically.

\begin{equation}
\text{Putative Precursor} \xrightarrow{a} 70\% \xrightarrow{b} \text{baconipyrone C (70\%)}
\end{equation}

\begin{equation}
\text{Putative Precursor 4} \xrightarrow{\text{unknown relationship}} \text{dolabriferol 1}
\end{equation}

a) imidazole b) aluminum oxide activated basic

\textbf{Scheme 2.1: Synthesis of Polypropionates Through Their Putative Precursors}
Of the possible pathways to form dolabriferol, a retro-Claisen approach was chosen to test if the linear precursor is the biosynthetic product. Therefore, the synthesis of precursor 4 should be the primary focus and, if achieved, may shed light on the origin of dolabriferol. The extensive methodology developed in the Ward group provides a precedent to synthesize contiguous carbon frameworks with control over the stereocenters being formed. Along with the preparation of the linear precursor, a method to perform an aldol reaction proceeding with kinetic resolution where the aldehyde is the enantioenriched fragment (and limiting in the reaction) was contemplated, a reaction not done before within the thiopyran route to polypropionates.

### 2.2. The Thiopyran Route to Polypropionates

The thiopyran route to polypropionates has been a core research theme in the Ward group for over a decade and allows for rapid access of various tetrapropionate (4 diastereomers of 76) and hexapropionate (20 diastereomers of 77) precursors stereoselectively. These complex starting materials are prepared in a few steps from starting ketone 75 and aldehyde 74 which themselves are prepared in a few steps and in high yield.\(^\text{15}\) This route begins with commercially available diester 70 which is prepared from inexpensive methyl acrylate 69 and sodium hydrosulfide.\(^\text{16}\) Dieckmann cyclization of 70 with sodium methoxide gives β-ketoester 71\(^\text{17}\) which is subsequently subjected to acetal protection, lithium aluminum hydride reduction, and oxidation with IBX to yield the desired aldehyde 74.\(^\text{18}\) Preparation of ketone 75 is achieved by decarboxylation of 71 under acidic conditions to give the desired compound as a free flowing white solid.\(^\text{17}\) These steps provide 74 and 75 in pure form without chromatography and can be done on large scale (>40g for 74 and >200g for 75). Aldol coupling of ketone 75 and aldehyde 74
has been extensively studied and all four diastereomers of 76 (referred to as “mono-aldols”) are available in high yield and enantiopure form.\(^{19}\)

With rapid access to the four diastereomers of 76, it seemed feasible that aldol coupling with a second equivalent of aldehyde 74 could furnish 77 providing a general strategy to rapidly assemble stereochemically complex hexapropionate synthons derived from simple starting materials. After extensive study, access to all twenty diastereomers of 77 (referred to as “bis-aldols”) was possible by varying the reaction conditions to favor the desired diastereomer, however, the compounds prepared were racemic.\(^{20,21}\) To obtain a single enantiomer the reaction would require either coupling of two enantioenriched fragments or coupling of one enantioenriched fragment to a racemic fragment through kinetic resolution. In a simple sense, kinetic resolution is the result of a difference in reaction rates of enantiomers in a chiral environment and exploiting this phenomenon could allow for assembly of enantioenriched hexapropionate synthons from racemic aldehyde 74.
Knowing the developed aldol coupling methodology was moderate to highly diastereoselective depending on the reaction conditions, it can be predicted that using enantioenriched diastereomers of 76 should give the same adducts but in enantioenriched form with similar diastereoselectivities to those observed (using racemic diastereomers of 76). All four diastereomers of 76 were prepared in enantioenriched form and tested to validate the prediction. In each case, the desired diastereomer was obtained with similar stereoselectivity while maintaining the enantiomeric excess in the starting material 76 (e.g., aldol coupling of ketone 78 with aldehyde 74 gave enantioenriched bis-aldol 79).

Scheme 2.2: Thiopyran Route to Polypropionates and Kinetic Resolution
concept should apply if aldehyde 74 was prepared in enantioenriched form and coupled to racemic ketone 78 (an unprecedented reaction within the thiopyran route).

The thiopyran route to polypropionates provides a simple and scalable protocol to produce starting material quickly with minimal chromatography. This is crucial for maintaining progress in a target directed synthetic project since a good deal of time can be required if starting material synthesis is difficult. The diastereomers of 76 have been extensively studied in aldol reactions providing the desired precedent for comparison when different chiral aldehydes are employed. Although this route provides a method for constructing polypropionate based frameworks effectively (and has been used in the synthesis of a number of natural products), application to natural products still poses quite a challenge.

2.3. Synthetic Considerations

The synthesis of the acyclic precursor 4 requires control of the relative configuration of the eight stereocenters. The configuration must also be controlled in an absolute sense since an enantioenriched product is desired. Control over the stereochemical outcome and construction of the carbon backbone can be achieved using existing methodologies within the thiopyran route to polypropionates. To obtain a single enantiomer the synthesis will require coupling of two enantioenriched fragments or coupling a racemic fragment with an enantioenriched fragment via kinetic resolution. Exploitation of one of these methods should provide the means to tackle the complexity of dolabriferol.
Taking a closer look at the structures of both dolabriferol and its linear precursor unveils functional groups that may be difficult to handle. Dolabriferol contains a six-membered lactol and a polypropionate fragment both known to undergo elimination under acidic conditions. The ester linkage can be cleaved under basic conditions. Although these reactions are possible, they require quite harsh conditions to occur. The linear precursor 4 is much more sensitive and difficult to handle. The position at C-8 is located between two ketones making the hydrogen located there quite acidic and easy to epimerize. Handling diketones, in general, makes the characterization and purification difficult since they are usually an equilibrating mixture of tautomers. The 5-hydroxy-3,7,9-triketone motif is very prone to decompose under acidic conditions (elimination) and under basic conditions (retro-Claisen). Revealing this complex moiety will need to be done at a late stage and under mild conditions to prevent side reactions from occurring.

2.4. Retrosynthetic Analysis

In order to test the hypothesis of the origin of dolabriferol, access to the linear precursor is crucial. The effort by Lister and Perkins to form dolabriferol via the trioxaadamantane intermediate is particularly intriguing from a synthetic standpoint. Incorporating this tricyclic moiety may provide a very concise solution to the total synthesis of dolabriferol.
dolabriferol that can overcome the problems encountered in previous attempts. The trioxaadamantane ring system would act as an internal protection of the sensitive 5-hydroxy-3,7,9-triketone.

![Chemical structure](image)

**Scheme 2.3: Formation of Trioxaadamantane Ring System**

The trioxaadamantane ring system has only been identified in two natural products to date: muamvatin\textsuperscript{12} and caloundrin B\textsuperscript{13}, both of which have been synthesized in the Ward group providing precedent on their formation. Starting from ketone 86, a simple aldol with propanal, oxidation of the newly formed hydroxyl, and mild deprotection is required to reveal the desired 5-hydroxy-3,7,9-triketone 89.\textsuperscript{23} Under thermodynamic control, compound 89 undergoes ring-chain tautomerism forming the dithiapentacycle 90.\textsuperscript{23} Subjecting 90 to RANEY\textsuperscript{®} nickel removes the sulfur atoms producing compound 91 containing a destabilizing syn-pentane interaction.\textsuperscript{23} Allowing this thermodynamically unstable compound to isomerize in the presence of imidazole provides the desired ring system 92 exclusively.\textsuperscript{23}
Because the trioxyadamantane ring system is also unstable, its formation would have to be induced at a late stage in the synthesis. Knowing that the ring system can be formed using the thiopyran route, the main focus of the synthesis would be on preparing the trioxyadamantane ring system to form the internally protected 93 known to be less susceptible to side reactions compared to 94 (Scheme 2.4). Once prepared, the tricyclic system would be subjected to mild basic conditions (eg. DBU) to induce the expected retro-Claisen rearrangement. The protecting group selection is crucial for the formation of acyclic precursor 4. The hydroxy protecting group at C-5 must be orthogonal to the hydroxy protecting groups at C-11 and C-13, as this allows control in the deprotection strategy if the acyclic precursor 4 fails to cyclize to give dolabriferol. By leaving strategic protecting groups in place, the compound could be orchestrated to cyclize in the desired fashion. Using benzyl ethers as the protecting group at C-11 and C-13 would allow these groups to remain unchanged as a silyl ether at C-5 and acetal are deprotected under mild acidic conditions. This should unveil the desired 5-hydroxy-3,7,9-triketone which would cyclize to 93. The benzyl ethers and the sulfur atoms could be removed using RANEY® nickel to produce the acyclic precursor 4 along with its ring-chain tautomeric forms.
Scheme 2.4: Retrosynthetic Analysis

Disconnection of the C-8 and C-9 bond in 94, leads to ketone 95 and aldehyde 96 as desired precursors (Scheme 2.4). The disconnection here is beneficial for synthetic reasons in the forward coupling sequence. The aldol coupling of ketone 95 and aldehyde 96 represent a matched pair and should give high diastereoselectivity resulting in one diastereomer predominately. Oxidation of the newly formed hydroxyl at C-9 in the aldol adduct would produce diketone 94. The C-8 position can now be easily epimerized creating an equilibrating mixture of diketones and their enol form. Upon deprotection, 94 should cyclize to the trioxaadamantane 93. An ongoing theme within the Ward group is the development of reactions that proceed with kinetic resolution. This approach to coupling chiral fragments...
presents a powerful tool that is usually overlooked. Since both ketone 98 and aldehyde 96 can be prepared in enantioenriched form via the thiopyran route to polypropionates, the selection of which compound will be enantioenriched is based on their relative ease of preparation. Aldehyde 96 was thought to be much easier to prepare in enantiomerically enriched form starting from a proline catalyzed aldol reaction between ketone 75 and isobutyraldehyde. Ketone 98 is readily available in racemic form via a Mukaiyama aldol between 74 and the TMS enol ether 84. If any problem arose from the thiopyran based ketone 98, a simple alternative would be to desulfurize compound 98 to furnish ketone 99 (now capable of Z-enolate formation). If ketone 99 showed promising results, compound 99 could be prepared from 100 and 101 using existing methodology in the Ward group coined as the “Acyclic Route to Polypropionate”.

2.5. Building the Fragment Analogues that Nature Makes Look Easy

2.5.1. Enantiomeric Excess from Nature to Laboratory

The synthesis of enantiopure aldehyde 96 begins with a proline mediated aldol reaction between tetrahydrothiopyran-4-one 75 and isobutyraldehyde, that provides the desired aldol adduct 97 with high diastereo- and enantioselectivity. The synthesis of diol 111 and 112 has previously been accomplished by Pramod Jahdav, a former Ward group member. The discussion hereafter, will be covering optimization of the synthetic sequence up to compounds 111 and 112, isomerization of 111 into 112, and the synthesis of the desired aldehyde fragment 96.

![Scheme 2.5: Early Stage Preparation of Enantioenriched Aldehyde](image-url)

a) TES-Cl, Et$_3$N, DCM  b) $^1$BuLi, then methyl cyanoformate, THF  c) 5% HF, MeCN  d) Et$_2$BOMe, NaBH$_4$, THF:MeOH (4:1)
The use of (S)-proline allows for achiral ketone 75 to be transformed into the corresponding enantiopure enamine 103 which then reacts with isobutyraldehyde through two possible transition states, TS-104 or TS-105. In TS-105, reaction of the si face of the aldehyde orients the large group above the ring system causing steric clash which is an unfavorable interaction resulting in slow formation of 106. In contrast, addition to the aldehyde’s re face via TS-104 minimizes this steric repulsion by placing the smallest group above the ring. The energy required to reach TS-104 is lower than TS-105 and this difference in energy dictates the diasteromeric ratio formed; in this case a greater than 20:1 mixture of the desired compound 97. The transition states with the enamine oriented anti relative to the carboxylic acid and alkene are favored over the syn relative orientation. This orientation preference and intermolecular hydrogen bonding selects one face of the ketone to react predominately. Since the two faces of the ketone are not equivalent, the result is an enantioenriched product.

Aldol adduct 97 was protected as its corresponding silyl ether 107 by reaction with triethylsilyl chloride and triethylamine. With compound 107 in hand, a direct deprotonation was performed with iBuLi to form the lithium enolate which underwent carbonylation with Mander’s reagent (methyl cyanoformate) to give an equilibrating mixture of β-ketoesters 108. The silyl ether in 108 was removed by treatment with hydrofluoric acid to give 109 as a mixture of β-ketoesters along with its enol form. Syn-selective reduction of 109 with diethylmethoxyborane and sodium borohydride produced a 1:1.5 mixture of syn diols 111 and 112, respectively. The desired 2,3-trans diol 112 was separated by column chromatography and carried through subsequent reactions. An interesting observation was noted when potassium hydride was added to 111 during an attempted double benzyl protection. Under these
conditions, \textbf{111} underwent isomerization at C-2 giving the desired compound \textbf{112} as the only product. Exploiting this phenomenon could provide a convergent synthesis to the desired 2,3-\textit{trans} diol \textbf{112} from a mixture of \textbf{111} and \textbf{112}.

\textbf{2.5.2. Isomerization Studies}

The isomerization under excess potassium hydride is not a known method to converge a mixture of 3-hydroxyesters to a single diastereomer. Presumably the mixture \textbf{113} can undergo two pathways for isomerization: enolate formation followed by selective protonation to give \textbf{112}; a retro-aldol to break the thiopyran template forming the acyclic enolate \textbf{117} which then undergoes selective aldol addition. In both routes the mixture is transformed into the presumed more thermodynamically stable, 2,3-\textit{trans} compound \textbf{112} which has all substituents of the chair in equatorial positions.

\textbf{Scheme 2.6: Possible Routes to Isomerization}

The use of potassium hydride as the base was found to be troublesome, with reactions requiring an excess (2-3 equivalents) most likely due to the low solubility of potassium hydride in ethereal solvents. On small scale (<20 mg of starting material), the reaction of \textbf{113} produced
112 rapidly and in high yield (Table 2.1, entry 1). However, trying to scale the reaction to anything larger (>100 mg, Table 2.1, entry 2), resulted in incomplete isomerization or decomposition to an unidentified compound. Puzzled by these results, the base was switched from potassium hydride (insoluble in THF) to the more soluble potassium hexamethyldisilazide (KHMDS). Using KHMDS allowed for control of the amount of base in solution, and could possibly remove the requirement of excess base noted in the preliminary results.

The reaction of 113 with KHDMS at decreased temperature allowed the isomerization to occur effectively (Table 2.1, entry 3-5). A sample of the 2,3-trans compound 112 was stable to the reaction conditions (Table 2.1, entry 6). Despite success on small scale, scaling the reaction to anything larger (>100 mg) again resulted in partial isomerization requiring more base to complete or, in most cases, decomposition to unidentified byproducts. Despite failure on a larger scale, the results showed promise that the difference in energy between 2,3-cis and 2,3-trans can be exploited to isomerize the mixture 113 to the required compound 112 on the pathway to dolabriferol. This problem was extensively studied by Naveen Diddi, a colleague in the Ward group.28
Table 2.1: Optimized Isomerization Results

![Diagram of chemical structures](image)

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<sup>a</sup>By <sup>1</sup>H NMR spectroscopy unless otherwise indicated<sup>b</sup> Isolated yield

Having demonstrated that the desired transformation to streamline the synthesis was possible, the base was switched to potassium tert-butoxide.<sup>28</sup> Using a base that is capable of deprotonating secondary alcohols but not basic enough to form a substantial amount of...
enolate may simplify the problem. Subjecting the 2,3-trans 111 to these new conditions gave the desired 112 in reasonable yield (80%) with a very polar impurity accounting for the rest of the material (Table 2.1, entry 9). With prolonged reaction times, 112 was eventually largely transformed into a polar material which was later identified as the corresponding carboxylic acid 121. Adding copper(I) iodide to the reaction media suppressed hydrolysis and produced 112 in high yield (85%, Table 2.1, entry 11). However, exposing the mixture of isomers 113 to the same conditions resulted in lower yield (61%) and a substantial amount of compound 121 (Table 2.1, entry 12). Switching to the benzyl ester analogue 119, decreased the rate of ester hydrolysis resulting in an excellent yield of the corresponding 120 in a scalable procedure (Scheme 2.8).  

Scheme 2.7: Overview on the Synthesis of Enantioenriched Aldehyde

a) (S)-proline, DMSO b) TES-Cl, Et$_3$N, DCM c) $^t$BuLi, then benzyl cyanoformate, THF d) 5% HF, MeCN e) $^t$BuLi, then methyl cyanoformate, THF f) 5% HF, MeCN g) Et$_2$BOMe, NaBH$_4$, THF:MeOH (4:1) h) KO$^t$Bu, Cul, Et$_2$O i) Et$_2$BOMe, NaBH$_4$, THF:MeOH (4:1) j) KO$^t$Bu, Cul, Et$_2$O k) dimethoxyphenylmethane, TsOH, DCM l) LiAlH$_4$, THF m) oxalyl chloride, DMSO, Et$_3$N, DCM
With the desired esters 112 or 120 in hand, the next step involved protection of the 1,3 diol. As mentioned in the retrosynthetic analysis, the strategy was to protect the diol with a group orthogonal to the protecting group on the ketone fragment (in this case a BOM or silyl ether group). The protecting group would also need to be labile under mild conditions. With these required criteria, benzyl ethers or a benzylidene acetal were chosen as possible protecting groups, both removable by hydrogenolysis. The predominant method for protecting alcohols as benzyl ethers is to subject the starting material to strong base in the presence of benzyl bromide. As described above, 112 is unstable to strongly basic conditions typical for alcohol benzylation. If direct benzylation was to be pursued, the reaction would need to be done under conditions where isomerization would be suppressed; i.e. not strongly basic media. Within the literature, other methods have been developed to synthesize benzyl ethers in neutral and acidic media. Of these methods, none gave the desired dibenzyl ether protected ester of 112/120 but instead resulted in no reaction or decomposition of the starting material. Switching to the formation of the benzylidene acetal resulted in a promising alternative, the 1,3-cis diols 112 or 120 could be protected using dimethoxyphenylmethane and reduced to give alcohol 123 (Scheme 2.7). Finally, oxidation of 123 using Swern’s protocol gave the desired aldehyde fragment 124 in excellent yield. The synthesis of alcohol 123 via 122 has been optimized by Naveen Diddi, a colleague in the Ward group.

2.5.3. Synthesis of Racemic Ketone

As mentioned earlier, the synthesis of tetrapropionate fragments via the thiopyran route has been highly optimized for rapid access on multi-gram scale. The route begins with diketoester 70 which undergoes Dieckmann cyclization to form the cyclic β-keto-ester 71
(Scheme 2.9). From here the syntheses of the aldehyde 74 and silyl enol ether 84 diverge. Subjecting 8-keto-ester 71 to acidic media for decarboxylation followed by treatment with TMS-Cl and triethylamine gave silyl enol ether 84. Treatment of 71 with ethylene glycol in the presence of acid gave the corresponding protected ester 72. Reduction of 72 with LiAlH₄ followed by oxidation with IBX in acetonitrile afforded aldehyde 74.

\[ \text{Scheme 2.8: Preparation of Various Protected } \textit{anti-anti} \text{ Ketones} \]

Silyl enol ether 84 and aldehyde 74 were subjected to Mukaiyama aldol conditions in the presence of MgBr₂•OEt₂ to form a mixture of \textit{syn-anti} 125 and \textit{anti-anti} 98 in a 3:1 ratio respectively.²⁰ Aldol adduct 125 could be isolated by fractional crystallization in methanol leaving the mother liquor containing a 6-10:1 mixture of 98 and 125 respectively. The mixture of aldol adducts was separated by column chromatography giving the desired \textit{anti-anti} aldol 98.
Subjection of 125 to imidazole induced isomerization to provide a 2:1 mixture of 125 and 98 respectively.\textsuperscript{20} The process of fractional crystallization and separation by column chromatography can be repeated in several cycles in order to access the less thermodynamically stable 98. Finally the free alcohol was protected as its corresponding MOM, BOM, TES, and TBS ether to furnish (±)-86\textsuperscript{21}, (±)-126, (±)-127\textsuperscript{21}, and (±)-128 respectively.

2.5.4. Kinetic Resolution and Exploitation of the Principle

With aldehyde 124 and several ketone candidates in hand, the next challenge requires a selective aldol coupling of these two fragments. Directing the stereochemical outcome of the aldol reaction can be difficult and may result in a mixture of products if stereoselectivity is not high. Traditionally, coupling of two enantioenriched fragments is employed to simplify the problem by decreasing the number of possible aldol adducts formed. Although this method is very effective, it requires the synthesis of two enantiopure coupling partners where each can be difficult to prepare, expensive, and require more steps to prepare than their racemic counterparts. To overcome some of these issues, an underutilized synthetic approach involves coupling of an enantioenriched fragment with a racemic fragment via kinetic resolution. Kinetic resolution is defined as a process where enantiomers have unequal reactivities in the presence of a chiral agent (reagent, catalyst, solvent, etc.). The development of coupling reactions that proceed with kinetic resolution is an ongoing theme in the Ward group, where convergent coupling of chiral fragments through aldol reactions has shown great application in natural product syntheses.\textsuperscript{3,23}
Scheme 2.9: Demonstration of Kinetic Resolution with Racemic Aldehyde

In one of numerous examples from the Ward group (Scheme 2.9), kinetic resolution is shown utilizing ketone 129 (similar ketone proposed in the synthesis of dolabriferol). Reactions of racemic ketones (such as 129) with racemic aldehydes (such as 74) can result in eight possible racemic aldol adducts. The stereoselectivities of such reactions can be factorized into three stereocontrol elements: i) diastereoface selectivity of the enolate, ii) diastereoface selectivity of the aldehyde, and iii) the relative topicity of the aldol coupling. As long as all three of these elements are highly biased, predominately one aldol adduct will be formed. Reaction of the boron enolate (Cy$_2$BCl, TEA) of (±)-129 with (±)-74 gave racemic trans-anti-Felkin adduct 130 selectively (dr 18:1, 80% yield). This result suggests that reaction of the (3R)-enantiomer of 129 with the (6R)-enantiomer of 74 is highly diastereoselective and much faster than the alternative reaction with (6S)-74 (Similarly, (3S)-129 must react preferentially with (6S)-74). By substituting the racemic ketone with its enantioenriched counterpart 129 (91% ee), reaction with (±)-74 under identical conditions, should give diastereomer 130 with similar diastereoselectivity but the products will be enantioenriched. As predicted, reaction of (+)-129
(91% ee) with (±)-74 under these conditions resulted in preferential coupling with (6R)-74 to give aldol adduct (-)-130 selectively (dr 14:1, 74% yield, 91% ee).\textsuperscript{21} Applying the same concept to couple fragments 95 and 124 should, in theory, follow the same paradigm where varying the reaction conditions should select the correct enantiomer of racemic ketone 95 to react preferentially with enantioenriched aldehyde 124.

\[ \text{Boron Mediated} \]

**Scheme 2.10:** Proposed Aldol Coupling for Dolabriferol

The illustrated example (Scheme 2.9) and proposal for dolabriferol (Scheme 2.10) demonstrate the application of kinetic resolution but do not explain how kinetic resolution works and what is required for a successful reaction. Kinetic resolution works by irreversibly differentiating a pair of enantiomers due to differences in activation energies. While both enantiomers of a racemate (in this case the ketone/enolate 95) are at the same energy level (Figure 2.2), the presence of an enantioenriched reactant, such as aldehyde 124, generates two diastereomeric aldol transitions states at different energies (TS2\textsubscript{R} vs TS2\textsubscript{S}). The difference in these competing transition state energies (ΔΔG\textsuperscript{‡}) defines the ratio of rate constants for the fast-
reacting and slow-reacting enantiomers, and this ratio \( \frac{k_{\text{fast}}}{k_{\text{slow}}} \), defined as stereoselectivity factor, or \( S \), controls the product distribution.

**Figure 2.2:** Energy Diagram of a Reaction Proceeding with Kinetic Resolution

Due to the fact that two enantiomeric species are reacting simultaneously at different rates, the relative concentrations of \( \text{SM}_{R}/\text{SM}_{S} \) and \( \text{Aldol}_{R}/\text{Aldol}_{S} \) are changing as the reaction proceeds and, as a consequence, the enantiomeric composition of the starting material and the stereoisomeric composition of the product become a function of conversion. Not surprisingly, the larger the difference in reaction rates (larger value of \( S \)), the more selective the reaction is. However, when using a stoichiometric ratio of reactants the selectivity diminishes with reaction conversion, eventually becoming unselective regardless of the selectivity factor \( (S) \) (Figure 2.3). This phenomenon is due to depletion of the fast reacting enantiomer in the early stages of the reaction leaving a higher concentration of the undesired enantiomer to react. Therefore, in order to maintain high selectivities, the racemic reactant is used in excess thereby maintaining
a high concentration of the fast reacting enantiomer. Consequently, the reaction is stopped at low conversion with respect to the racemate but high conversion with respect to the enantioenriched fragment. Although using a very large excess would provide the maximum selectivity, practically, purification of the product from a large excess of racemate can be difficult. In the Ward group, an excess of three equivalents is usually used which sacrifices some selectivity but keeps purification relatively straightforward.

Figure 2.3: Effect of Selectivity Factor on Stereoisomeric Excess

The concept of an aldol reaction proceeding with kinetic resolution is exactly the same regardless of which fragment is racemic and which is enantioenriched. Although Figure 2.3 sheds light on reaction design, the equations used assume pseudo first-order kinetics for the substrate and does not account for nonlinear effects. Within the thiopyran route, the aldehyde
has always been the racemic fragment due to its ease in preparation. For the proposal strategy in the synthesis of the linear precursor 4, the ketone will be the racemic fragment, i.e. needs to be used in excess. This reversal of reactant roles is unprecedented and worth studying for its applicability in natural product synthesis. This may however require a different approach of optimization with the reversal of the reactant used in excess.

2.6. Aldol Studies

2.6.1. Thiopyran Based Ketones as Aldol Coupling Partners

A potential concern with the aldol fragment coupling within the thiopyran route to polypropionates is the amount of reagent needed to generate the enolate. For most of the thiopyran based ketones, an excess of reagent is required to achieve high conversion. The excess reagent remaining after enolization can consume the aldehyde by undergoing undesired reactions. When the aldehyde is used in excess, any such decomposition does not affect the reaction outcome. The synthetic plan for dolabriferol is quite the opposite, excess ketone with excess enolizing reagent may react with the limiting aldehyde and, consequently, reduce the overall yield of the desired aldol adduct. The aldol coupling of ketone 95 with 74 (3 equiv.) using Cy₂BCl and Et₃N to generate the enol borinate has been heavily optimized to give the corresponding bis-aldol 134 in good yield with excellent diastereoselectivity (Table 2.2, entry 1). When the same reaction was conducted with one equivalent of BCy₂Cl, the yield of 134 decreased to 35% (Table 2.2, entry 2) and using stoichiometric amounts of 74 did not produce the adduct 134 (Table 2.2, entry 3). However, as mentioned earlier, the reaction requires two equivalents of BCy₂Cl to proceed in high yield.
Table 2.2: Effect of Aldehyde and Mediator Equivalents on Reaction Yield

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone (1 equiv.)</th>
<th>Equiv. 74</th>
<th>Equiv. BCy₂Cl</th>
<th>Equiv. 'BuNH₂</th>
<th>Product (yield, dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>134 (80%, 13:1)</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>134 (35%, 13:1)</td>
</tr>
<tr>
<td>3</td>
<td>86</td>
<td>0.5</td>
<td>2</td>
<td>0</td>
<td>No Reaction</td>
</tr>
<tr>
<td>4</td>
<td>127</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>135 (87%, 10:1)</td>
</tr>
<tr>
<td>5</td>
<td>127</td>
<td>0.50</td>
<td>2</td>
<td>2</td>
<td>135 (83%, 10:1)</td>
</tr>
</tbody>
</table>

Thus, having the ketone in excess and the aldehyde limiting (conditions required for the proposed dolabriferol synthesis) is not suitable for aldol reaction via the enol borinate. This problem is not resolved by reducing the amount of BCy₂Cl used. A potential solution to this problem is to “quench” any excess BCy₂Cl prior to aldehyde addition to prevent decomposition of the aldehyde. A method would need to be developed where quenching of the excess borane reagent would not also cause quenching of the borane enolate. It is known in the literature that BPh₂Cl reacts with primary or secondary amines to form aminoboranes in moderate to high yield. Of particular interest is the use of primary amines, such as tert-butyl amine. Although the reaction gave the highest yield when the mixture was refluxed, the reaction could be performed at lower temperatures (-50°C). For the proposed application, it is crucial the reagent is able to quench the borane at low temperatures because the enol borinate is not stable at elevated temperatures. As shown, enolization of ketone 127 follows the standard conditions within the Ward group of using excess borane to achieve high conversion for enolate formation.
(Table 2.2, entry 4). The excess borane remaining is reactive towards aldehydes causing an unwanted side reaction which ultimately leads to decomposition but with the excess aldehyde 74 this decomposition does not affect the yield. If, tert-butyl amine were added before aldehyde addition, the reactive chloroborane should react to form an aminoborane which may be inert towards aldehydes.

Once the excess borane is quenched, the aldehyde can be added and the reaction should proceed without any decomposition. However, the effect of tert-butyl amine on enol borinates, if any, is unknown and would need to be tested. Adding two equivalents of tert-butyl amine to the enol borinate of 127 followed by addition of aldehyde resulted in high conversion and high diastereoselectivity to the desired aldol adduct 135 (83%, 10:1 dr, Table 2.2, entry 5). Lowering the amount of tert-butyl amine resulted in decreased conversion presumably due to incomplete quench of the borane reagent. Adding more than two equivalents had no noticeable difference in conversion. With a modified aldol procedure developed, the reaction could then be applied to an appropriate ketone for the synthesis of linear precursor 4.

![Scheme 2.11: Selection of an Appropriate Ketone](image-url)
Of the four synthesized ketones shown in scheme 2.11, ketones 86, 126, and 128 were not suitable for the synthesis of precursor 4. Ketone 86 requires harsh conditions for MOM ether deprotection which is not suitable for a substrate that is both acid and base sensitive. Ketone 126 suffers for a similar reason, as shown; attempts to desulfurize the compound resulted in BOM removal as well. Despite this protecting group being removed late stage, deprotection at the same stage as desulfurization would result in a 5-hydroxy-7,9-diketone with removal of the acetal at C-3 being required. The desired 5-hydroxy-3,7,9-triketone is acid sensitive and potentially unstable under ketal removal conditions (requires acid to undergo); therefore, ketone 126 was deemed as an inappropriate candidate. Ketone 128 failed to enolize efficiently under various conditions (temperature, concentration, reaction time, etc.) so this ketone was also abandoned. Ketone 127 on the other hand gave a very promising result, under the modified conditions the reaction gave aldol adduct 135 in high yield and high diastereoselectivity (83%, 10:1 dr, Table 2.2, entry 5). By simply switching the aldehyde partner from 74 to 124 should result in similar conversion and diastereoselectivity to give the carbon skeleton of linear precursor 4. As predicted, reaction of 124 with the boron enolate of 127 gave 136 in similar yield while maintaining high selectivity (80%, dr >15:1).
Desulfurization of 136 proceeded smoothly giving the desired carbon skeleton 137 with the final steps to reach 4 involving deprotection and redox chemistry. Unfortunately, all attempts to remove the acetal in the presence of the silyl ether failed due to the silyl ether being more labile than the acetal. At this point, there were three possible solutions. Firstly, through a series of protection/deprotection sequences of 138, the desired 139 could be synthesized. For instance, protection of the free hydroxyl in 138, removal of the acetal and silyl ether, reparation of the silyl ether at C-5, followed by deprotection of C-9 would give the desired 139. This, although possible, would be lengthy and not streamline the synthesis towards linear precursor 4. Secondly, by simply switching to a more stable protecting group should solve this problem; however as mentioned earlier, various protected ketones of 98 failed to give high conversion during enolate formation or were unsuitable for late stage deprotection. Thirdly, if the sulfur atoms were removed prior to aldol addition, the resulting
acyclic ketone analogue 140 may allow for different protecting groups to be viable in the coupling reaction (Scheme 2.13).

Switching to an acyclic ketone raises new synthetic considerations. Previously an (E)-boron enolate was used to couple 95 and 124 via kinetic resolution with a preferential reaction of (3R)-95. Using the same conditions with ketone 140 would be predicted to result in preferential reaction of (3R)-141 leading to the undesired aldol adduct. Alternatively, using a (Z)-boron or (Z)-titanium enolate should lead to preferential reaction of (3R)-140 and 124 giving the desired 6,8-syn-8,9-syn-9,10-Felkin adduct 141 (Scheme 2.13). The pathways leading to 132 and 141 converge when either compound is subjected to desulfurization and oxidation to give diketone 142. The convergence is due to the C-8 (R in 132, S in 141) center becoming epimerizable in 142 and likely existing in both keto forms. Finally, a deprotection sequence of diketone 142 should provide a route to linear precursor 4.
Focusing on aldol studies of ketone 140, a substantial portion of the methodology has recently been developed in the Ward group, where the four diastereomers of the tetrapropionate ketone 140 were investigated in aldol coupling reactions. In this work, the four diastereomers were transformed into the corresponding (Z)-lithium, (Z)-titanium, (Z)-boron, (E)-lithium, and (E)-boron enolates and reacted with isobutyraldehyde. After workup, the distributions of aldol adducts were analyzed, the aldol adducts isolated, and their structures determined. This study on the aldol reactions with isobutyraldehyde is the most comprehensive to date (four diastereomers, two protecting groups for each, five enolate types for each, forty

\textbf{Scheme 2.13}: Redesign of Aldol Coupling Partners on the Path to Dolabriferol
examples total) and clearly demonstrates that the aldol diastereoselectivities are influenced by
the relative configuration, protecting group, and enolate type.\textsuperscript{27}

\textbf{Table 2.3: Effect of Mediator and Protecting Group on Stereoselectivity}

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG\textsuperscript{1}</th>
<th>Enolate Formation</th>
<th>Aldol Adducts (Ratio);\textsuperscript{a} Conversion\textsuperscript{a,b}</th>
<th>Yield\textsuperscript{c} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MOM</td>
<td>9-BBNOTf/Et\textsubscript{3}N</td>
<td>\textbf{144ss, 144sa} (8.5:1); 95%</td>
<td>77 (9)</td>
</tr>
<tr>
<td>2</td>
<td>MOM</td>
<td>LiHMDS then, TiCl(O\textsubscript{i}-Pr\textsubscript{3})</td>
<td>\textbf{144ss, 144as} (13:1); 90%</td>
<td>76 (5)</td>
</tr>
<tr>
<td>3</td>
<td>TES</td>
<td>9-BBNOTf/Et\textsubscript{3}N</td>
<td>\textbf{144ss, 144as} (2:1); 70%</td>
<td>38 (17)</td>
</tr>
<tr>
<td>4</td>
<td>TES</td>
<td>LiHMDS then, TiCl(O\textsubscript{i}-Pr\textsubscript{3})</td>
<td>\textbf{144ss, 144as, 144sa} (4:1:0.7); 90%</td>
<td>62 (14)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Determined by \textsuperscript{1}H NMR of the crude reaction mixture. \textsuperscript{b}Estimated from the ratio of adducts to starting ketone present in the crude reaction mixture by \textsuperscript{1}H NMR. \textsuperscript{c}Isolated yield of the major adduct (isolated yield of minor adduct in parentheses).

Of particular interest were reactions of the (Z)-boron and (Z)-titanium enolates of ketone \textbf{140} with isobutyraldehyde (Table 2.3). The major compound in all examples was the 4,6-syn-6,7-syn diastereomer \textbf{143ss} with the stereoselectivity ranging from moderate (2:1) to high (13:1). Among the various enolates, the titanium enolate prepared from the MOM protected \textbf{140} by reaction of the lithium (Z)-enolate with TiCl(O\textsubscript{i}-Pr\textsubscript{3}) gave the highest stereoselectivity (Table 2.3, entry 2). With this knowledge, the synthetic plan was to use this methodology to couple acyclic ketone \textbf{140} with aldehyde \textbf{124} under titanium enolate
conditions. As discussed earlier, the use of MOM and TES as protecting groups would be problematic in the planned deprotection sequence. To overcome this hurdle, it was envisioned that replacing MOM with BOM should maintain the high aldol stereoselectivity, allow for reductive removal under mild conditions late stage, and would not fall victim to the same fate as ketone 126 (acetal removal before desulfurization). Likewise, replacing the TES group with TBS should increase the stability of the silyl ether towards acid catalyzed acetal removal conditions. To this end, these two ketones were selected as suitable candidates for the synthesis of linear precursor 4.

2.6.2. Acyclic Ketones as Aldol Coupling Partners

The synthesis of hydroxy ketone 99 could be achieved simply by desulfurization of the thiopyran analogue 98. Although this method works and in moderate yield, the synthesis is not economical and requires an additional step, which would only be beneficial if a significant improvement in overall yield was achieved. A more direct route to 99 begins with ethyl propionate undergoing a Claisen condensation furnishing β-keto-ester 144 (Scheme 2.14).27 Treatment of 144 with ethylene glycol in the presence of catalytic p-toluenesulfonic acid gave the corresponding ketal protected ester. Reduction with LiAlH₄ followed by oxidation under Swern conditions or with IBX produced aldehyde 145.27
With aldehyde 145 in hand, the next step required the preparation of silyl enol ether 149 and subjection to Mukaiyama aldol conditions. Reaction of 145 with 149 mediated by MgBr₂•Et₂O gave a 1:1 mixture of the desired anti-anti 99 and syn-anti 148 in good yield. The desired 99 was obtained by chromatography and protected as its BOM ether 151 (26% over 6 steps) or its TBS ether 150 (28% over 6 steps) both starting from ethyl propionate. Alternatively, Mukaiyama aldol reaction of 149 with aldehyde 74 under Mukaiyama conditions gave a 4:1 mixture 147aa and 147sa, respectively. The higher diastereomeric ratio of the desired aldol adduct (4:1 vs 1:1) translated to higher overall yields (BOM ketone 151 (38% over 7 steps) and TBS ketone 150 (40% over 7 steps)) compared to the previous route despite requiring an extra step to desulfurize. Both routes were scalable, which is an important aspect to consider when conducting a multi-step synthesis. Regardless of routes, ketones 150 and 151 were prepared...
and subjected to aldol reaction with 124 via their titanium enolates (Scheme 2.15). As predicted from the model study, 124 reacted preferentially with the 4R enantiomer of 150 and 151 selectively giving the 2,4-syn-1,2-syn-1,8'-syn diastereomers 152 and 153, respectively.

**Scheme 2.15: Aldol Coupling of Acrylic Ketones and Proof of Correct Pairing**

Reaction of (±)-150 with 124 resulted in an inseparable 4:1 mixture of diastereomers in high yield (84%). The reaction of (±)-151 with 124 was more selective and the diastereomers were separable (79% of desired, 7:1 dr). To confirm which enantiomer of (±)-151 had reacted with enantioenriched 124 and the structure of 153, the unreacted ketone was recovered ((+)-151, [α]D=5.2)). If the reaction consumed the desired 4R-enantiomer during coupling, the recovered 151 should be enriched in the 4S-enantiomer. Desulfurization by a known method of (-)-98 (90% ee) gave (-)-(4R)-99 (90% ee, [α]D= -6.3). Similarly, deprotection of ketone (+)-151
with RANEY® Nickel gave (+)-99 ([α]_D = +1.3) that must be enriched in the 4S enantiomer. Two important conclusions follow from this result. Firstly, the expected 4R enantiomer of 151 must have reacted preferentially during the aldol coupling. Secondly, the magnitude of the recovered 151, suggests a ca. 20% enantiomeric excess, assuming the rotation is linearly correlated with enantiomeric excess. Inserting this value into the equations used in Figure 2.3, gives a stereoselectivity factor of 7.5:1 for the kinetic resolution which closely fits the 7:1 ratio of diastereomers.

2.6.3. Deprotection Sequence of TBS Aldol Adduct to Precursor 4

The 4:1 mixture of aldol adducts obtained from the reaction of 124 with (+)-150 was subjected to iron (III) chloride catalyzed acetal removal to give a separable mixture of diastereomers from which dione 154 was isolated in 69% yield (Scheme 2.16). Desulfurization of 154 with RANEY® Nickel, followed by oxidation with IBX gave 155, a protected version of the target 4. The sequence of deprotection of the TBS ether and benzyldiene group could be done in either order. Treating compound 155 with TAS-F removed the TBS ether to give 156 which existed primarily in two keto forms. Alternatively, hydrogenolysis of 155 with palladium black under hydrogen atmosphere removed the benzyldiene to furnish hemiacetal 157 predominately (14:1). To remove the silyl group in 157 required some investigation for deprotection methods. The compound is acid sensitive, so conventional acidic deprotection methods were out of the question. Using a mild deprotection method, such as HF•pyr/pyr or Et₃N•3HF resulted in no reaction and spiroketal 158 formation respectively.

Compound 158 is interesting, not towards the synthesis of dolabriferol but for structural analysis. With this rigid bicyclic system, the two fragments coupled in the aldol reaction of 150
and 124 can now be correlated to one another through space using NOE techniques. This is not the first synthesis of 158; Lister and Perkins synthesized a very small amount of 158 as a byproduct during their synthetic attempts towards dolabriferol. Lister and Perkins suggest the structure to exist in a chair-chair monoanomeric conformer that places the C-10 methyl group in a sterically unfavorable position. Instead, a chair-boat conformer is proposed that allows for all substitution to be equatorial and pseudoequatorial in the chair and boat conformers respectively (confirmed by $J$ coupling) and makes the spiroketal doubly anomeric. The relative configuration of the C-8 center cannot be assigned by $J$ coupling because this position is isolated. Using NOE allowed for the assignment of the methyl group at C-8 to be pseudo-equatorial which Lister and Perkins assigned as axial. Finally, a NOE correlation of the hydrogens at C-5 and C-8 strongly supports the chair-boat conformer and is impossible for a chair-chair conformer. With the structure of 158 firmly established, the assigned structures for 155 and 157 are confirmed.
a) FeCl₃, acetone  b) RANEY® Nickel, EtOH, reflux  c) IBX, DMSO  d) TAS-F, DMF  e) Pd, H₂, iPrOH  f) Pd, H₂, iPrOH  g) TAS-F, DMF  h) HF•pyr/pyr, H₂O, THF  i) Et₃N•3HF, Et₃N, THF

**Scheme 2.16:** Final Deprotection Sequence of TBS Route to Linear Precursor 4

Returning to the deprotection of 157, reaction with TAS-F allowed for mild removal of the TBS ether giving linear precursor 4 (10.1% overall, 16 steps from 70) that existed predominately as a mixture of two hemiacetal forms (1:0.7) in C₆D₆ solution (Scheme 2.16). The linear precursor 4 can also be obtained by hydrogenolysis of 156 (11.4% overall, 16 steps from...
With this route complete, the focus would now be on synthesis of linear precursor 4 from the BOM protected aldol and attempts to synthesize dolabriferol via a retro-Claisen approach.

2.6.4. Deprotection Sequence of BOM Aldol Adduct to Precursor 4

Synthesis of the linear precursor 4 from the BOM aldol adduct 153 began with acetal removal with catalytic iron (III) chloride to furnish 159 in high yield (Scheme 2.17). Oxidation of the hydroxy group in 159 with IBX gave trione 160 as a mixture of keto and enol tautomers. Reaction of 160 with RANEY® nickel resulted in simultaneous desulfurization and BOM deprotection to give 156 that existed as a mixture similar in ratio to that observed for 156 obtained from the the TBS route. Finally, under the known hydrogenolysis conditions, compound 156 gave the desired linear precursor 4 in 86% yield (14.3% overall, 15 steps from 70).
With the two routes complete, focus changed to the properties of the putative precursor 4 in an effort to better understand the origin of dolabriferol.

2.7. Dolabriferol – Artifact of Isolation or Enzymatically Controlled?

2.7.1. Properties of the Linear Precursor

As discussed earlier, the linear precursor 4 may exist in a myriad of different ring-chain tautomeric forms and as a study of compound 4, the forms it exists in are of particular interest. Deprotection of TBS triketone 157 gave a mixture of hemiacetals 167/168 (Figure 2.4) in almost equal population (1.4:1). Deprotection of the hydroxy triketone 156 gave the same two hemiacetals but in a slightly different ratio (1:1). To better understand the equilibrium of tautomers, the mixture was subjected to mild basic conditions (imidazole in CDCl₃) to
determine if the ratio of hemiacetals would change over time and, if other hemiacetals would begin to appear in detectable amounts. After 24 hours, the sample still contained the same two hemiacetals 167/168 but the ratio had changed (dr 4:1). From the computational analysis by Goodman (Figure 2.4), compounds 161-168 are the lowest energy hemiacetals calculated by ROBIA. Hemiacetals 167 (-93.6 KJ/mol) and 168 (-95.7 KJ/mol) are at least 10 KJ/mol lower in energy than the next lowest hemiacetal form 162 (-83.9 KJ/mol), this difference in energy would approximately equate to a 120:50:1 mixture of 168, 167, and 162 respectively. Thermodynamically, it appears that the C-13-OH to C-9 hemiacetal is the most stable form of the linear precursor both by calculation and experimentally.
In order to form dolabriferol, a retro-Claisen rearrangement must occur from one or more of the C-11-OH to C-7 hemiacetals 164-166 and these tautomers are not detected in the mixture. Hence, this process may be slow or disfavored relative to unwanted side reactions.
2.7.2. Retro-Claisen Attempts on the Linear Precursor

With the linear precursor 4 (as a mixture of hemiacetals 167 and 168) in hand, attempts at inducing a retro-Claisen rearrangement were initiated. Reaction of 4 with DBU in C₆D₆ was monitored by ¹H NMR. Surprisingly, the reaction was sluggish compared to related examples by Lister/Perkins,¹⁰ Goodman,¹¹ and Ward.¹⁴ After five days, the reaction was quenched to determine the product distribution. Five distinct products were isolated and characterized: dolabriferol 1 (15%), epi-dolabriferol 170 (25%), known lactone 173 (20%)³³, cyclic ketone 174 (10%), and a different mixture of hemiacetals 169 (30%). This result was very intriguing; it appeared that the desired retro-Claisen of the C-11-OH to C-7 hemiacetal 164 (not detectable in starting material) was occurring faster than retro-Claisen of 167/168 (the only forms visible within detection). This desired pathway gives rise to almost half of the recovered material as dolabriferol and its epimer 170 so this result was very promising.
Scheme 2.18: Subjecting Precursor 4 to DBU and Product Distribution
Products 173 and 174 arise from an unwanted retro-Claisen pathway. The likely pathway begins with hemiacetal 161 (C-5-OH to C-9 hemiacetal of 4) undergoing a retro-Claisen rearrangement to give TS-171. This “enolate” then undergoes an intramolecular aldol reaction to give compound 171. Intramolecular transesterification of 171 (C-13 OH to C-9) would yield the two compounds 172 and 173. The appearance of 170 in the reaction mixture suggests that the conditions are too basic resulting in epimerization. Consequently, the new hemiacetals 169 recovered from the reaction may arise from epimerization of 4. Resubjecting 170 to identical conditions gave no detectable amount of dolabriferol suggesting epimerization occurs prior to retro-Claisen rearrangement.

Table 2.4: Selected $^1$H NMR Data for Dolabriferol 1 and 170

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta_H$</th>
<th>Multiplicity $\left(J$'s in Hz$\right)$</th>
<th>Assignment</th>
<th>$\delta_H$</th>
<th>Multiplicity $\left(J$'s in Hz$\right)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-epi-dolabriferol (170)</td>
<td>2.74</td>
<td>dq (7.0, 9.0)</td>
<td>HC-4</td>
<td>2.78</td>
<td>dq (7.0, 7.0)</td>
</tr>
<tr>
<td></td>
<td>4.24</td>
<td>ddd (3.0, 4.0, 9.0)</td>
<td>HC-6</td>
<td>3.75</td>
<td>ddd (5.0, 8.0, 8.0)</td>
</tr>
<tr>
<td></td>
<td>2.63</td>
<td>dq (3.0, 7.0)</td>
<td>HC-7</td>
<td>2.73</td>
<td>dq (5.0, 7.0)</td>
</tr>
<tr>
<td></td>
<td>1.87</td>
<td>dq (3.0, 7.0)</td>
<td>HC-13</td>
<td>1.91</td>
<td>dq (3.0, 7.0)</td>
</tr>
<tr>
<td></td>
<td>5.25</td>
<td>dd (3.0, 3.0)</td>
<td>HC-15</td>
<td>5.25</td>
<td>dd (2.5, 2.5)</td>
</tr>
<tr>
<td></td>
<td>1.76</td>
<td>ddq (3.0, 7.0, 10.5)</td>
<td>HC-16</td>
<td>1.78</td>
<td>ddq (2.5, 7.0, 10.0)</td>
</tr>
<tr>
<td></td>
<td>3.63</td>
<td>dd (2.0, 10.5)</td>
<td>HC-18</td>
<td>3.61</td>
<td>dd (2.0, 10.5)</td>
</tr>
<tr>
<td>dolabriferol (1)</td>
<td>4.03</td>
<td>d (4.5)</td>
<td>OH-6</td>
<td>3.63</td>
<td>d (8.0)</td>
</tr>
</tbody>
</table>
Table 2.5: Selected $^{13}$C NMR Data for Dolabriferol 1 and 170

<table>
<thead>
<tr>
<th>4-epi-dolabriferol (170)</th>
<th>dolabriferol (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta_C$</td>
<td>Assignment</td>
</tr>
<tr>
<td>47.9</td>
<td>C-4</td>
</tr>
<tr>
<td>13.9</td>
<td>C-5</td>
</tr>
<tr>
<td>72.5</td>
<td>C-6</td>
</tr>
<tr>
<td>42.3</td>
<td>C-7</td>
</tr>
<tr>
<td>10.3</td>
<td>C-8</td>
</tr>
<tr>
<td>174.9</td>
<td>C-9</td>
</tr>
<tr>
<td>32.9</td>
<td>C-10</td>
</tr>
<tr>
<td>98.9</td>
<td>C-12</td>
</tr>
<tr>
<td>39.5</td>
<td>C-13</td>
</tr>
<tr>
<td>76.4</td>
<td>C-15</td>
</tr>
<tr>
<td>36.3</td>
<td>C-16</td>
</tr>
<tr>
<td>72.6</td>
<td>C-18</td>
</tr>
</tbody>
</table>

The NMR data for *epi*-dolabriferol 170 was compared with dolabriferol 1 to possibly determine at which position isomerization had occurred. As shown in Tables 2.4 and 2.5, the signals for the hemiacetal ring system (C-8 through C-14) in 170 and 1 are almost identical. However, signals for the carboxylic acid fragment (C-1 through C-7) of 170 and 1 are very different. Due to these differences, it is likely the center that was epimerized is located on the acid fragment (C-1 through C-7). Of the positions on this fragment, C-4 and C-6 are the most acidic (i.e. prone to epimerization via keto-enol tautomerization) so compound 170 is likely 4-epi or 6-epi dolabriferol. Conformational analysis (Spartan '14) suggests that the 4-epi 170 better matches the data.

To reduce the basicity of the retro-Claisen conditions, neutral alumina was selected. Subjecting hemiacetals 167/168 to neutral alumina was very solvent dependent. In refluxing ethanol, no reaction was observed even after several hours. However, in benzene at room
temperature, the starting material was completely consumed in 72 hours to give a mixture of products from which only 175 could be isolated (Table 2.6). Product 175 arises from the correct retro-Claisen rearrangement followed by elimination. Controlling the reaction may provide a route to the desired dolabriferol 1. Finally, subjecting a benzene solution of hemiacetals 167/168 to a column of neutral alumina and eluting after 15 minutes gave dolabriferol 1 as the only product (75% yield, Table 2.6). A plausible explanation for the difference in reactivity may be due to solvent polarity. In ethanol, the compound may be dissolved in the organic phase and have very little contact time on the alumina. Changing the solvent to benzene (less polar) and applying the sample to neutral alumina allowed for increased contact and therefore a faster reaction. The NMR data for synthetic dolabriferol 1 fully matches those reported by Gavagnin4 (Tables 2.6 and 2.7) and clearly demonstrates that hemiacetals 167/168 can undergo a retro-Claisen rearrangement to produce dolabriferol under mild conditions. This suggests that dolabriferol may indeed be an artifact of isolation and that 4 (along with its tautomers) is a plausible natural product.
Table 2.6: Comparison of $^1$H NMR Data for “Natural” and Synthetic Dolabriferol

<table>
<thead>
<tr>
<th>“natural” dolabriferol</th>
<th>Assignment</th>
<th>“natural” dolabriferol</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta_H$ (ppm)</td>
<td>Multiplicity (J’s in Hz)</td>
<td>$\delta_H$ (ppm)</td>
<td>Multiplicity (J’s in Hz)</td>
</tr>
<tr>
<td>1.04</td>
<td>t (7.2)</td>
<td>1.05</td>
<td>t (7.0)</td>
</tr>
<tr>
<td>2.46</td>
<td>dq (7.2, 14.5)$^a$</td>
<td>2.46</td>
<td>dq (7.0, 18.0)</td>
</tr>
<tr>
<td>2.57</td>
<td>dq (7.2, 14.5)$^a$</td>
<td>2.57</td>
<td>dq (7.0, 18.0)</td>
</tr>
<tr>
<td>2.78</td>
<td>dq (7.1, 7.1)</td>
<td>2.78</td>
<td>dq (7.0, 7.0)</td>
</tr>
<tr>
<td>1.14</td>
<td>d (7.1)</td>
<td>1.15</td>
<td>d (7.0)</td>
</tr>
<tr>
<td>3.75</td>
<td>m</td>
<td>3.75</td>
<td>ddd (5.0, 8.0, 8.0)</td>
</tr>
<tr>
<td>2.73</td>
<td>dq (4.3, 7.1)</td>
<td>2.73</td>
<td>dq (5.0, 7.0)</td>
</tr>
<tr>
<td>1.32</td>
<td>d (7.1)</td>
<td>1.33</td>
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<tr>
<td>1.60</td>
<td>m</td>
<td>1.61</td>
<td>m</td>
</tr>
<tr>
<td>0.91</td>
<td>t (7.4)</td>
<td>0.91</td>
<td>t (7.5)</td>
</tr>
<tr>
<td>1.90</td>
<td>dq (2.5, 7.2)</td>
<td>1.91</td>
<td>dq (3.0, 7.0)</td>
</tr>
<tr>
<td>0.99$^b$</td>
<td>d (7.2)</td>
<td>1.00</td>
<td>d (7.0)</td>
</tr>
<tr>
<td>5.24</td>
<td>dd (2.5, 2.7)</td>
<td>5.25</td>
<td>dd (2.5, 2.5)</td>
</tr>
<tr>
<td>1.78</td>
<td>ddq (2.7, 7.0, 10.5)</td>
<td>1.78</td>
<td>ddq (2.5, 7.0, 10.0)</td>
</tr>
<tr>
<td>0.78</td>
<td>d (7.0)</td>
<td>0.78</td>
<td>d (7.0)</td>
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<tr>
<td>3.60</td>
<td>dd (2.0, 10.5)</td>
<td>3.61</td>
<td>dd (2.0, 10.5)</td>
</tr>
<tr>
<td>1.83</td>
<td>ddq (2.0, 6.8, 6.8)</td>
<td>1.82</td>
<td>ddq (2.0, 7.0, 7.0)</td>
</tr>
<tr>
<td>1.00$^b$</td>
<td>d (6.8)</td>
<td>0.99</td>
<td>d (7.0)</td>
</tr>
<tr>
<td>0.83</td>
<td>d (6.8)</td>
<td>0.83</td>
<td>d (7.0)</td>
</tr>
<tr>
<td>3.65</td>
<td>OH-6</td>
<td>3.63</td>
<td>d (8.0)</td>
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<tr>
<td>3.45</td>
<td>OH-12</td>
<td>3.42</td>
<td>bs</td>
</tr>
</tbody>
</table>

$^a$The large coupling constant is misassigned and needs to be corrected.

$^b$Incorrect assignment.
Table 2.7: Comparison of $^{13}$C NMR Data for “Natural” and Synthetic Dolabriferol

<table>
<thead>
<tr>
<th></th>
<th>“natural” dolabriferol$^a$</th>
<th>synthetic dolabriferol$^b$</th>
<th>“natural” dolabriferol$^a$</th>
<th>synthetic dolabriferol$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta_C$</td>
<td>Assignment</td>
<td>$\delta_C$</td>
<td>Assignment</td>
<td>$\delta_C$</td>
</tr>
<tr>
<td>7.4</td>
<td>C-1</td>
<td>7.5</td>
<td>98.5</td>
<td>C-12</td>
</tr>
<tr>
<td>36.0</td>
<td>C-2</td>
<td>36.2</td>
<td>39.4</td>
<td>C-13</td>
</tr>
<tr>
<td>215.1</td>
<td>C-3</td>
<td>215.4</td>
<td>20.2</td>
<td>C-14$^c$</td>
</tr>
<tr>
<td>49.4</td>
<td>C-4</td>
<td>49.6</td>
<td>76.9</td>
<td>C-15</td>
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<td>14.4</td>
<td>C-5</td>
<td>14.6</td>
<td>36.5</td>
<td>C-16</td>
</tr>
<tr>
<td>75.7</td>
<td>C-7</td>
<td>75.9</td>
<td>12.9</td>
<td>C-17</td>
</tr>
<tr>
<td>43.7</td>
<td>C-7</td>
<td>43.9</td>
<td>72.3</td>
<td>C-18</td>
</tr>
<tr>
<td>15.6</td>
<td>C-8</td>
<td>15.8</td>
<td>28.0</td>
<td>C-19</td>
</tr>
<tr>
<td>173.7</td>
<td>C-9</td>
<td>173.9</td>
<td>12.9</td>
<td>C-20$^c$</td>
</tr>
<tr>
<td>32.5</td>
<td>C-10</td>
<td>32.7</td>
<td>14.0</td>
<td>C-21</td>
</tr>
<tr>
<td>7.2</td>
<td>C-11</td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Ref 4; used $\delta_C$ CDCl$_3$=77.00
$^b$Chemical shifts for synthetic material are consistently 0.1-0.3 ppm higher than those reported from the natural product due to a different reference standard; used $\delta_C$ CDCl$_3$=77.23
$^c$Incorrect assignment
2.8. Conclusion

In summary, dolabriferol was synthesized via a retro-Claisen rearrangement of its linear precursor 4 (existing mainly as hemiacetals 167/168). This work provides the first experimental evidence for the retro-Claisen origin of dolabriferol from a contiguous polypropionate (i.e., 1) and suggests that dolabriferol is a plausible artifact of isolation.

Scheme 2.19: Overview of the Total Synthesis of Dolabriferol

The synthesis of 4 proceeded in a longest linear sequence of 16 steps in 14.3% (via ketone 151) or 17 steps in 11.4% (via ketone 150) starting from 70 (23 and 24 total steps respectively). The aldol reactions of ketones 150 or 151 with aldehyde 124 proceeded with kinetic resolution furnishing the carbon skeleton of 4 with the correct absolute configuration, as
predicted. Cheap and achiral precursors were used to prepare the key reactants 150, 151, and 124. A proline mediated aldol set two of the four stereocenters in aldehyde 124 (C-12 and 13; dr >20:1, er 24:1). The remaining stereocenters result from a stereoselective carbonyl reduction (C-11; >20:1) and an unprecedented isomerization of a dihydroxy ester (C-10; >20:1). Synthesis of racemic ketones 150 and 151 via a Muikayama aldol of 74 and 149 gave the final three stereocenters (C-4, 5, 6; dr 4:1) in linear precursor 4.

Under mild basic conditions (neutral alumina), the mixture of hemiacetals 167/168 rapidly equilibrated to hemiacetals 164-166 that underwent retro-Claisen rearrangement to give dolabriferol. Thus, dolabriferol is a likely artifact of isolation. Using DBU in CDCl₃ to effect a retro-Claisen rearrangement (reported by previous groups including the Ward group) was sluggish and resulted in a mixture of compounds. The mixture contained dolabriferol (15%), 4-epi dolabriferol 170 (25%), known lactone 173 (20%), cyclic ketone 174 (10%), and a different mixture of hemiacetals 169 (30%), likely from isomerization of C-4. Resubjecting the epimer 170 to the same conditions resulted in no observable formation of dolabriferol suggesting isomerization occurs prior to the rearrangement.
2.9. Suggestions for Future Work

On the basis that dolabriferol is likely an artifact of isolation, similar non-contiguous polypropionate ester natural products may also be derived from a linear precursor undergoing rearrangement. These compounds are therefore potential targets to test this hypothesis. In 2012, Jiménez-Romero et al isolated two new polypropionates along with dolabrferol from *Dolabrifera dolabrifera* off the coast of Puerto Rico. Of particular interest is dolabriferol B which is not only a non-contiguous polypropionate; it also has an identical stereochemical array as dolabriferol.

![Scheme 2.20: Proposed Retrosynthetic Approach to Dolabriferol B](image)

Adapting a similar retrosynthetic design as the one used for dolabriferol (where synthesis of the linear precursor 4 was the goal) gives the linear precursor 176. Starting with 176, the retrosynthetic design is almost identical where the only difference being 177 being a des-methyl analogue of 124. This would be accomplished by coupling propanal instead of...
isobutyraldehyde with 75 in the proline catalyzed aldol. From there, the synthesis would follow identical steps. Alternatively, diketone 178 can be used as the ketone coupling partner to aldehyde 177. Current research in the Ward group has shown promising results of a 1,5-diketone undergoing bisenolate formation. The control over which ketone reacts has been shown in several examples to give the corresponding mono-aldol.28 With further development of this methodology and the synthesis of aldehyde fragments 177, application of this new methodology should allow access to precursor 176 and, ultimately, to dolabriferol B.
3. EXPERIMENTAL

3.1. General Methods

Anhydrous solvents were distilled under argon atmosphere as follows. Tetrahydrofuran (THF) from benzophenone sodium ketyl; CH$_2$Cl$_2$ from CaH$_2$; MeOH from Mg(OMe)$_2$. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum and attached via a needle and connecting tubing to a mercury bubbler under argon atmosphere. Low temperature baths were: ice/water (0 °C), CO$_2$(s)/acetonitrile (-45 °C), and CO$_2$(s)/acetone (-78 °C). Unless otherwise noted, reaction temperatures refer to that of the bath.

Palladium hydrogenations were conducted at room temperature in a vial which was placed in a Parr hydrogenation apparatus. The atmosphere was purged with argon and then filled with hydrogen (H$_2$, 50-60 psi). After the reactions were completed, the catalyst was removed by filtration through Celite, followed by thorough washing of the filter cake with MeOH. RANEY® nickel desulfurizations were conducted in refluxing ethanol in a round bottom flaked equipped with a reflux condenser and a balloon filled with hydrogen (H$_2$) attached via a needle.

Preparative TLC was carried out on glass plates (20x20 cm) pre-coated (0.25 mm) with silica gel 60 F$_{254}$. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aq. sulfuric acid (5% v/v), or with basic KMnO$_4$ [KMnO$_4$ (1.5 g), K$_2$CO$_3$ (10 g), 10% aq. NaOH (1.25 mL), in H$_2$O (200 mL)],
followed by charring on a hot plate. TLC was carried out on glass plates (1x3 cm) pre-coated (0.25 mm) with silica gel 60 F$_{254}$ and was visualized in the same manner as described for PTLC.

Flash column chromatography (FCC) was performed according to Still et al.\textsuperscript{36} with Merck silica gel 60 (40-63 mm). All mixed solvents eluents are reported as v/v solutions. Unless otherwise noted, all reported compounds were homogenous by thin layer chromatography (TLC) and by $^1$H NMR spectroscopy.

Concentration refers to removal of volatiles with a rotary evaporator under vacuum supplied by a water aspirator. Evacuation at ca. 0.5 torr with a vacuum pump generally followed rotary evaporation.

3.2. Spectral Data

High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a VG 70E double focussing high resolution spectrometer; only partial data are reported. Electron impact (EI) ionization was accomplished at 70 eV, chemical ionization (CI) at 50 eV with ammonia as the reagent gas. Alternatively, HRMS was obtained on a LC-MS/MS time-of-flight high resolution spectrometer with electrospray ionization (ESI) from acetonitrile solution.

Infrared spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic peaks and/or intense peaks are reported. Unless otherwise noted, all experiments used DRIFT.
Unless otherwise noted, NMR spectra were measured in CDCl$_3$ solution at 500 MHz for $^1$H and 125 MHz for $^{13}$C. Signals due to the solvent ($^{13}$C NMR) or residual protonated solvent ($^1$H NMR) served as the internal standard: CDCl$_3$ (7.26 $\delta_H$, 77.23 $\delta_C$); C$_6$D$_6$ (7.16 $\delta_H$, 128.39 $\delta_C$). The $^1$H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of couplings constants ($J$) corresponds to the order of the multiplicity assignment. Coupling constants are reported to the nearest 0.5 Hz (digital resolution ca, 0.1 Hz/pt) or the nearest 0.1 Hz (digital resolution ca. 0.03 Hz/pt.). The $^1$H NMR assignments were made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or two-dimensional correlation experiments ($g$COSY, $g$HSQC, $g$HMBC). The $^{13}$C NMR assignments were made on the basis of chemical shift and multiplicity (as determined by $^{13}$C-DEPT or $g$HSQC) and were confirmed, where necessary, by two-dimensional $^1$H/$^{13}$C correlation experiments ($g$HSQC and/or $g$HMBC). The multiplicity of $^{13}$C NMR signals refers to the number of attached hydrogens (i.e., s = C, d = CH, t = CH$_2$, q = CH$_3$).

Specific rotations ($[\alpha]_D$) are the average of five determinations at ambient temperature using 1 mL, 10 dm cell; the units are 10$^{-1}$ deg cm$^2$ g$^{-1}$ and the concentrations ($c$) are reported in g/100 mL. The values reported are rounded to reflect the accuracy of the measured concentrations (the major source of error). HPLC analyses were carried out using am Agilent Technologies 1200 series liquid chromatograph.
3.3. Materials

The following compounds and reagents were prepared as described previously: 71, 72, 73, 74, 75, 76, 84, 86, 98, 99, 125, 127, 144, 145, 148, 149, IBX, W-2 RANEY® Nickel, methyl cyanoformate, and benzyl cyanoformate. Et3N and DIPEA were distilled from KOH under argon and were stored over KOH. n-Butyl lithium and t-butyl lithium were titrated using diphenylacetic acid as the titrant and indicator. TiCl4 and HMDS were distilled under argon atmosphere from CaH2. All other reagents were commercially available and, unless otherwise noted, were used as received.
3.4. Experimental Procedures and Spectral Data for Compounds

Dolabriferol (1).

Linear precursor 4 (2 mg, 5.2 micromol) was dissolved in benzene (0.2 mL) and transferred to a pipette containing neutral alumina (3 cm height, Brockmann I) and the solvent pushed down until the solvent line was below the alumina line. After 15 minutes, the column was eluted with EtOAc (3x) and the solvent evaporated under reduced pressure to give the title compound (1.5 mg, 75%, >95% purity by $^1$H NMR analysis).

Colorless oil, TLC $R_f = 0.3$ (40% ethyl acetate in hexane);

$^1$H NMR (CDCl$_3$) $\delta$: 5.25 (1H, dd, $J = 2.5$, 2.5 Hz, HC-15), 3.75 (1H, ddd, $J = 5$, 8, 8 Hz, HC-6), 3.63 (1H, d, $J = 8$ Hz, HOC-6), 3.61 (1H, dd, $J = 2$, 10.5 Hz, HC-18), 3.42 (1H, bs, HOC-12), 2.78 (1H, dq, $J = 7$, 7 Hz, HC-4), 2.73 (1H, dq, $J = 5$, 7 Hz, HC-7), 2.57 (1H, dq, $J = 18$, 7 Hz, HC-2), 2.46 (1H, dq, $J = 18$, 7 Hz, HC-2), 1.91 (1H, dq, $J = 3$, 7 Hz, HC-13), 1.82 (1H, dqq, $J = 2$, 7, 7 Hz, HC-19), 1.78 (1H, ddd, $J = 2.5$, 10, 7 Hz, HC-16), 1.68-1.50 (2H, m, H$_2$C-10), 1.33 (3H, d, $J = 7$ Hz, HC-8), 1.15 (3H, d, $J = 7$ Hz, H$_3$C-5), 1.05 (3H, t, $J = 7$ Hz, H$_3$C-1), 1.00 (3H, d, $J = 7$ Hz, H$_3$C-14), 0.99 (3H, d, $J = 7$ Hz, H$_3$C-20), 0.91 (3H, t, $J = 7.5$ Hz, H$_3$C-11), 0.83 (3H, d, $J = 7$ Hz, H$_3$C-21), 0.78 (3H, d, $J = 7$ Hz, H$_3$C-17);
$^{13}$C NMR (CDCl$_3$) δ: 215.4 (s, C-3), 173.9 (s, C-9), 98.7 (s, C-12), 77.1 (d, C-15), 75.9 (d, C-6), 72.5 (d, C-18), 49.6 (d, C-4), 43.9 (d, C-7), 39.6 (d, C-13), 36.7 (d, C-16), 36.2 (t, C-2), 32.7 (t, C-10), 28.2 (d, C-19), 20.5 (q, C-20), 15.8 (q, C-8), 14.6 (q, C-5), 14.2 (q, C-21), 13.1 (q, C-14), 13.0 (q, C-17), 7.5 (q, C-1), 7.4 (q, C-11);
(4S,5R,6R,10S,11S,12S,13S)-5,11,13-Trihydroxy-4,6,8,10,12,14-hexamethylpentadecane-3,7,9-trione (4).

From TBS-diol. Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F; 24 mg, 0.087 mmol) was added to a stirring solution of 157 (10 mg, 0.020 mol) in DMF (0.3 mL) at room temperature under argon. After 3 h, the mixture was diluted with ethyl acetate and washed sequentially by saturated aq NaHCO₃, water, and brine, dried over Na₂SO₄, concentrated and fractionated by FCC (30%-50% ethyl acetate in hexane) to give the title compound (6 mg, 78%) that was predominantly a 3:2 mixture of two hemiacetal forms (HOC-13 → O=C-9; presumably epimeric at C-8) in C₆D₆ solution.

From Benzylidene. Freshly prepared palladium black (98 mg, 0.92 mmol) was added to a stirred solution of 156 (20 mg, 0.042 mmol) in i-PrOH (5 mL) at ambient temperature under Ar. The reaction vessel was evacuated and placed under a H₂ atmosphere (60 psi). After stirring for 16 h, the supernatant was removed and the Pd was washed with MeOH (×2). The organic layers were filtered through Celite® and the combined filtrate was concentrated and fractionated by FCC (30-50% ethyl acetate in hexane) to give the title compound (14 mg, 86%) that was predominantly a 1:1 mixture of two hemiacetal forms (HOC-13 → O=C-9; presumably epimeric at C-8) in C₆D₆ solution.
colorless oil, TLC R_f = 0.3 (50% ethyl acetate in hexane);

[α]_D –30 (c 0.5, C_6H_6);

IR ν max: 3414, 1699 cm⁻¹;

^1H NMR (C_6D_6) δ (* denotes signals for the minor hemiacetal): 5.50 (0.6H, s, HOC-9), 5.00 (0.4H, s, HOC-9*), 3.84-3.68 (2H, m, HC-5, HC-5*, HOC-11, HOC-11*), 3.65 (0.4H, dd, J = 2, 11 Hz, HC-13*), 3.58 (0.6H, dd, J = 2, 11 Hz, HC-13), 3.36 (0.6H, dq, J = 7, 7 Hz, HC-6), 3.13 (0.4H, ddd, J = 2.5, 2.5, 7 Hz, HC-11*), 3.11-2.99 (2.4H, m, HC-6, HC-8, HC-8*, HC-11, HC-11*), 2.53 (0.4H, dq, J = 4.5, 7 Hz, HC-4*), 2.51 (0.6H, dq, J = 4.5, 7 Hz, HC-4), 2.23 (0.4H, dq, J = 18.5, 7 Hz, HC-2*), 2.21 (0.4H, d, J = 7.5 Hz, HOC-11*), 2.17-2.03 (2.2H, m, HC-2*, H_2C-2, HOC-11 ), 1.74-1.62 (1H, m, HC-14, HC-14*), 1.51 (0.4H, dq, J = 2.5, 7 Hz, HC-10*), 1.35 (0.6H, dq, J = 2.5, 7 Hz, HC-10), 1.31 (0.4H, ddq, J = 2.5, 11, 7 Hz, HC-12*), 1.24 (1.2H, d, J = 7 Hz, H_3CC-8*), 1.21 (0.6H, ddq, J = 2.5, 11, 7 Hz, HC-12), 1.15 (1.2H, d, J = 7 Hz, H_3CC-10*), 1.14 (1.8H, d, J = 7 Hz, H_3CC-8*), 1.103 (1.8H, d, J = 7 Hz, H_3CC-6 or H_5CC-15), 1.102 (1.8H, d, J = 7 Hz, H_3CC-6 or H_5CC-15), 1.06 (1.2H, d, J = 7 Hz, H_3CC-15*), 1.02 (1.2H, d, J = 7 Hz, H_3CC-4*), 1.00 (1.2H, d, J = 7 Hz, H_3CC-6*), 0.97 (1.2H, t, J = 7 Hz, H_3C-1*), 0.96 (1.8H, d, J = 7 Hz, H_3CC-4), 0.95 (1.8H, d, J = 7 Hz, H_3CC-10), 0.93 (1.8H, t, J = 7 Hz, H_3C-1), 0.87 (1.8H, d, J = 7 Hz, H_3C-15), 0.85 (1.2H, d, J = 7 Hz, H_3C-15*), 0.71 (1.2H, d, J = 7 Hz, H_3CC-12*), 0.65 (1.8H, d, J = 7 Hz, H_3CC-12);

^13C NMR (C_6D_6) δ (* denotes signals for the minor hemiacetal): 218.5* (s, C-7), 217.4 (s, C-7), 215.4 (s, C-3), 215.0* (s, C-3), 102.4 (s, C-9), 101.8* (s, C-9), 78.8 (d, C-5), 78.0* (d, C-5), 77.2* (d, C-11), 76.7 (d, C-11), 72.7* (d, C-13), 72.6 (d, C-13), 54.5* (d, C-8), 54.2 (d, C-8), 49.6 (d, C-6), 49.2* (d, C-6), 48.33* (d, C-4), 48.31 (d, C-4), 41.5* (d, C-10), 39.1 (d, C-10), 38.2* (d, C-12), 37.9
(d, C-12), 36.5 (t, C-2), 35.9* (t, C-2), 28.9 (d, C-14), 28.7* (d, C-14), 21.1 (q, C-15), 20.9* (q, C-15), 15.32* (q, H3CC-6), 15.25 (q, H3CC-6), 15.13 (q, H3CC-4), 15.08* (q, H3CC-4), 14.9* (q, H3CC-15), 14.84 (q, H3CC-15), 14.76* (q, H3CC-10), 13.92 (q, H3CC-12), 13.85* (q, H3CC-12), 13.6 (q, H3C-C10), 12.5 (q, H3CC-8), 11.8* (q, H3CC-8), 7.94* (q, C-1), 7.92 (q, C-1);

**HRMS m/z calcd. for C21H38O6+Na 409.2561, found 409.2564 (ESI).**
(S)-3-[(S)-1-Hydroxy-2-methylpropyl]dihydro-2H-thiopyran-4(3H)-one (97)

L-Proline (5.1 g, 44 mmol) was added in one portion to a stirred solution of 75 (10.0 g, 86.2 mmol) and isobutyraldehyde (23.6 mL, 18.6 g, 258 mmol) in DMSO (30 mL). After 4 days, the mixture was diluted with ethyl acetate and washed sequentially with saturated NH₄Cl, water and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to furnish the title compound (12.5 g, 77%; ee 24:1 by HPLC). H NMR data were consistent with those previously reported.²⁶

colorless oil; TLC Rf = 0.30 (20% ethyl acetate in hexane);

[α]D −22 (c 2.2, CHCl₃) (lit.²⁶ [α]D −23; c 1.0, CHCl₃; 98% ee)
(4R,5S,6S)-rel-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-hydroxy-4-methylheptan-3-one (99).

A suspension of Raney nickel (W2; 10 mL settled volume) in EtOH (20 mL) was added to 147aa (2.83 g, 10.3 mmol) and the mixture was heated under reflux with vigorous stirring. After 5 h (reaction was complete by TLC analysis), the mixture was decanted and the solid was suspended in EtOH (3 mL) and heated under reflux with vigorous stirring for several min. This washing procedure was repeated with acetone (×2) and methanol. The combined organic layers were filtered through Celite®, concentrated, and fractionated by FCC (25% Et₂O in hexane) to give the title compound as a colorless oil (2.21 g, 88%); NMR data were consistent with those reported previously.⁲⁷
(S)-3-(S)-2-Methyl-1-((triethylsilyl)oxy)propyl)dihydro-2H-thiopyran-4(3H)-one (107).

![Chemical Structure](attachment:image.png)

Et$_3$N (10.5 mL, 7.62 g, 75.5 mmol) and Et$_3$SiCl (9.6 mL, 8.6 g, 57 mmol) were sequentially added to a stirred solution of 97 (7.16 g, 38.1 mmol) in CH$_2$Cl$_2$ (50 mL) room temperature under Ar. After 16 h, the reaction was diluted with CH$_2$Cl$_2$, washed with saturated aq NH$_4$Cl and brine, dried over Na$_2$SO$_4$, and concentrated to give the crude product as a dark brown oil. The crude product was fractionated by FCC (0-10% ethyl acetate in hexane) to furnish the title compound as a pale yellow oil (10.82 g, 94%).

colorless liquid, TLC $R_f = 0.30$ (5% ethyl acetate in hexane); [α]$_D^{–} = 99$ (c 5.2, CHCl$_3$);

IR (DRIFT) $\nu_{\text{max}}$ 1712 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.20 (1H, dd, $J$ = 4, 6 Hz, HC-1'), 2.98-2.88 (3H, m, HC-2, H$_2$C-6), 2.83-2.73 (3H, m, HC-2, HC-3, HC-5), 2.66 (1H, ap ddd, $J$ = 5.5, 8.5, 14 Hz, HC-5), 1.71 (1H, dqq, $J$ = 4, 6.5, 6.5 Hz, HC-2'), 0.93 (9H, t, $J$ = 8 Hz, H$_3$CCSi×3), 0.89 (3H, d, $J$ = 6.5 Hz, H$_3$C-3'), 0.87 (3H, d, $J$ = 6.5 Hz, H$_3$C-3'), 0.59 (6H, ap q, $J$ = 8 Hz, H$_2$CSi×3).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.1 (s, C-4), 74.9 (d, C-1'), 58.7 (d, C-3), 44.0 (t, C-5), 31.6 (t, C-2), 30.9 (d, C-2'), 30.5 (t, C-6), 20.6 (q, C-3'), 17.0 (q, C-3'), 7.2 (q ×3, CH$_3$CSi), 5.5 (t ×3, CH$_2$Si).

HRMS $m/z$ calcd. for C$_{15}$H$_{30}$O$_2$SiS 302.1736, found 302.1730 (EI).
Methyl (5S)-5-((S)-2-Methyl-1-(hydroxy)propyl)-4-oxotetrahydro-2H-thiopyran-3-carboxylate (109).

\[
\text{MeO} \quad \text{OH} \quad \text{Me} \quad \text{S} \quad \text{O} \quad \text{O} \quad \text{CO} \\
2 \quad 3 \quad 6 \quad 1' \quad 2'' \quad 3' \text{ enol} \quad \text{2× keto} \quad \text{3× keto}
\]

109

t-BuLi (1.5 M in hexanes; 31 mL, 47 mmol) was added dropwise to a stirred solution of 107 (10.31 g, 34.1 mmol) and 1,10-phenanthroline (100 mg, 0.55 mmol) in THF (200 mL) at –78 °C under Ar until a deep purple colored persisted. After 10 min, CH$_3$O$_2$CCN (5.7 mL, 6.1 g, 72 mmol) was added. After 10 min, the mixture became bright yellow and the reaction was quenched by addition of saturated aq NH$_4$Cl. The mixture was extracted with ethyl acetate and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated to give a yellow oil that was taken up in CH$_3$CN (120 mL) and aq HF (5 wt. %; 30 mL) was added to the stirred solution. After 2 h, the mixture was diluted with ethyl acetate, washed with NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give the title compound as a 2:3:3 mixture of enol and two keto tautomers, respectively (7.53 g, 91%).

pale yellow oil, TLC $R_f$ = 0.3 (20% ethyl acetate in hexane);

IR $\nu_{\text{max}}$: 3544, 1744, 1697, 1645, 1608 cm$^{-1}$;

$^1$H NMR (CDCl$_3$) $\delta$ (*denotes signals from enol form): 12.99* (0.19H, s, HO enol), 3.85-3.71 (0.66H, m, HC-1', 2× keto), 3.80 (s), 3.78 (s) and 3.77 (s) (3H, H$_3$CO enol & 2× keto), 3.67-3.63 (0.22H, m, HC-1' enol), 3.51-3.40 (1H, m, enol & 2× keto), 3.37-3.23 (1H, m, enol & 2× keto),
3.18-2.82 (3.77H, m), 2.80-2.62 (0.88H, m), 2.57 (0.36H, d, J = 8 Hz, HO keto), 1.99 (0.23H, dq, J = 5, 7, 7 Hz, HC-2' enol), 1.82 (0.39H, dq, J = 5, 7, 7 Hz, HC-2' keto), 1.05-0.92 (6.2H, m, H3C-3' (×2) enol & 2× keto);

$^{13}$C NMR (CDCl$_3$) δ (*denotes signals from enol form): 208.2 (s), 207.7 (s), 173.5* (s), 172.4* (s), 169.1 (s), 169.0 (s), 98.7* (s), 80.1* (d), 78.0 (d), 76.2 (d), 60.8 (d), 58.6 (d), 56.9 (d), 54.3 (d), 52.9 (q), 52.6 (q), 52.2* (q), 42.2* (d), 34.5 (t), 34.4 (t), 33.5 (t), 33.2 (t), 31.4* (d), 31.3 (d), 30.3 (d), 29.3* (t), 23.6* (t), 20.3 (q), 19.9* (q), 19.8 (q), 17.6 (q), 17.1* (q), 16.5 (q);

HRMS m/z calcd. for C$_{11}$H$_{18}$O$_4$S 246.0926, found 246.0926 (EI).
Methyl (3R,4S,5S)-4-Hydroxy-5-((S)-1-hydroxy-2-methylpropyl)tetrahydro-2H-thiopyran-3-carboxylate (111).

See the preparation of 112

white amorphous solid; TLC $R_f = 0.30$ (45% ethyl acetate in hexane)

$[\alpha]_D = -48$ (c 1.3, CHCl$_3$);

IR $\nu_{\text{max}}$: 3448, 1712 cm$^{-1}$;

$^1$H NMR (CDCl$_3$) $\delta$: 4.19 (1H, br s, HC-4), 3.76 (3H, s, H$_3$CO), 3.69 (1H, dd, $J = 3.5$, 8 Hz, HC-1'), 3.66 (1H, br s, HO), 3.19-3.13 (2H, m, HC-2, HC-3), 2.96 (1H, dd, $J = 3.5$, 14 Hz, HC-6), 2.79 (1H, br s, HO), 2.63 (1H, dd, HC-2), 2.29 (1H, dd, $J = 7$, 14 Hz, HC-6), 2.12 (1H, dddd, $J = 3.5$, 7, 7, 8 Hz, HC-5), 1.86 (1H, dqq, $J = 3.5$, 7, 7 Hz, HC-2'), 1.00 (3H, d, $J = 7$ Hz, H$_3$C-3'), 0.89 (3H, d, $J = 7$ Hz, H$_3$C-3');

$^{13}$C NMR (CDCl$_3$) $\delta$: 174.4 (s, CO), 77.8 (d, C-1'), 69.9 (d, C-4), 52.4 (q, CH$_3$O), 45.3 (d, C-3), 42.8 (d, C-5), 30.2 (d, C-2'), 27.5 (t, C-6), 26.7 (t, C-2), 20.2 (q, C-3'), 15.1 (q, C-3');

HRMS $m/z$ calcd. for C$_{11}$H$_{20}$O$_4$S: 248.1082; found: 248.1090 (EI).
Methyl (3S,4S,5S)-4-Hydroxy-5-((S)-1-hydroxy-2-methylpropyl)tetrahydro-2H-thiopyran-3-carboxylate (112).

From 109: Et₂BOMe (1.4 mL, 1.1 g, 11 mmol) was added to a stirred solution of 109 (1.86 g, 7.69 mmol) in THF (100 mL) at room temperature under argon. After 30 min, the mixture was cooled to –78 °C and MeOH (25 mL) was added. After 15 minutes, solid NaBH₄ (803 mg, 21.2 mmol) was added. After 1 h, the reaction vessel was removed from the bath and the mixture allowed to warm with stirring. After 30 min, the mixture was cooled to 0 °C and the reaction was quenched by sequential addition of phosphate buffer (pH = 6.8; 1 M, 50 mL) and 30% aq H₂O₂ (6.8 mL, 60 mmol). After 15 min, the mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed sequentially with saturated Na₂SO₃, water and brine, dried over Na₂SO₄, and concentrated to give the crude product whose ¹H NMR spectrum indicated the presence of a 1.3:1 mixture of diastereomeric diols. Fractionation of the crude product by FCC (40% ethyl acetate in hexane) gave the trans_syn_diol (710 mg, 38%) the title compound (830 mg, 45%).

From isomerization of 111 (this procedure was developed by Naveen Diddi). Freshly sublimed KO'Bu (657 mg, 5.83 mmol) was added to a stirred solution 111 (710 mg, 2.91 mmol) and CuI (55 mg, 0.29 mmol) in dry Et₂O (60 mL) at 0 °C under argon. After 5 min, the reaction was quenched by addition of saturated aq NH₄Cl. The mixture was diluted with Et₂O and the...
combined organic layers were washed sequentially with saturated aq NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, concentrated, and the residue fractionated by FCC (40% ethyl acetate in hexane) to afford the title compound (517 mg, 73%).

white amorphous solid; TLC $R_f = 0.30$ (40% ethyl acetate in hexane)

$[\alpha]_0 +30$ (c 1.0, CHCl$_3$);

$\textbf{IR } \nu_{\text{max}}$: 3360, 3193, 1728 cm$^{-1}$;

$^1$H NMR (C$_6$D$_6$) $\delta$: 3.67 (1H, dd, $J = 9.5, 9.5$ Hz, HC-4), 3.28 (3H, s, H$_3$CO), 3.06 (1H, dd, $J = 3, 7.5$ Hz, HC-1'), 2.78 (1H, ddd, $J = 4, 10, 11.5$ Hz, HC-3), 2.51 (1H, dd, $J = 11.5, 13.5$ Hz, HC-2), 2.45 (1H, ddd, $J = 2.5, 4, 13.5$ Hz, HC-2), 2.10 (1H, ddd, HC-6), 1.87-1.77 (2H, m, HC-5, HC-6), 1.41 (1H, dqq, $J = 3, 7, 7$ Hz, HC-2'), 0.86 (3H, d, $J = 7$ Hz, H$_3$C-3'), 0.75 (3H, d, $J = 7$ Hz, H$_3$C-3');

$^{13}$C NMR (C$_6$D$_6$) $\delta$: 174.1 (s, CO), 80.7 (d, C-1'), 76.3 (d, C-4), 53.2 (d, C-3), 51.9 (d, CH$_3$O), 47.5 (d, C-5), 30.5 (d, C-2'), 30.2 (t, C-2), 29.9 (t, C-6), 20.4 (q, C-3'), 14.7 (q, C-3');

$\textbf{HRMS} \ m/z$ calcd. for C$_{11}$H$_{20}$O$_4$S: 248.1082; found: 248.1079 (EI).
Methyl (2S,4S,4aS,8S,8aS)-4-Isopropyl-2-phenylhexahydrothiopyrano[4,3-d][1,3]dioxine-8-carboxylate (112a).

PhCH(OCH₃)₂ (2.1 mL, 2.1 g, 14 mmol) and p-TsOH·H₂O (118 mg, 0.62 mmol) were sequentially added to a stirred solution of 112a (651 mg, 2.67 mmol) in CH₂Cl₂ (30 mL) at ambient temperature. After 16 h, the reaction was diluted with CH₂Cl₂, washed sequentially with saturated aq NaHCO₃ and brine, dried over Na₂SO₄, and concentrated to afford a pale yellow oil containing the title compound and PhCH(OCH₃)₂. The oil was dissolved in refluxing hexane (~50 mL) and, after cooling to ambient temperature, the solution was left in a freezer (-20°C) overnight to induce crystallization. The white solid was collected by filtration and the combined filtrate and washings were concentrated to give an oil that was subjected to a second round of crystallization. The combined solids were dried under high vacuum to afford the title compound (815 mg, 89%).

White crystalline solid, mp 171-173°C, TLC Rₜ = 0.3 (20% ethyl acetate in hexane);

[α]₀ +30 (c 0.6, CHCl₃);

IR νₘₐₓ: 1732 cm⁻¹;
$^1$H NMR (C$_6$D$_6$) δ: 7.58 (2H, ap d, J = 7.5 Hz, Ph), 7.17-7.13 (2H, m, Ph), 7.09 (1H, ap t, J = 7.5 Hz, Ph), 5.43 (1H, s, HC-2), 3.63 (1H, dd, J = 10, 10 Hz, HC-8a), 3.28 (3H, s, H$_3$CO), 3.02 (1H, ddd, J = 3.5, 10, 12 Hz, HC-8), 2.94 (1H, dd, J = 2, 9.5 Hz, HC-4), 2.82 (1H, dd, J = 12, 13.5 Hz, HC-7), 2.37 (1H, ddd, J = 1.5, 3.5, 13.5 Hz, HC-7), 2.05-1.95 (2H, m, HC-4a, HC-5), 1.82 (1H, dd, J = 12.5, 13.5 Hz, HC-5), 1.44 (1H, ddq, J = 2, 7, 7 Hz, HC-1'), 0.97 (3H, d, J = 7 Hz, H$_3$C-2'), 0.81 (3H, d, J = 7 Hz, H$_3$C-2');

$^{13}$C NMR (C$_6$D$_6$) δ: 172.8 (s, C=O), 139.3 (s, Ph), 128.8 (d, Ph), 128.4 (d ×2, Ph), 126.5 (d ×2, Ph), 101.1 (d, C-2), 83.5 (d, C-4), 81.2 (d, C-8a), 51.4 (q, CH$_3$O), 50.3 (d, C-8), 43.2 (d, C-4a), 30.2 (t, C-7), 28.2 (d, C-1'), 27.2 (t, C-5), 20.0 (q, C-2'), 14.8 (q, C-2');

HRMS m/z calcd. for C$_{18}$H$_{24}$O$_4$S 336.1395, found 336.1400 (EI).
((25,4S,4aS,8R,8aR)-4-Isopropyl-2-phenylhexahydrothiopyrano[4,3-d][1,3]dioxin-8-yl)methanol (123).

LiAlH₄ (92 mg, 2.4 mmol) was added in one portion to a stirred solution of 112a (815 mg, 2.43 mmol) in THF (20 mL) at 0 °C under argon. After 15 min, the ice bath was removed and stirring continued until the reaction was complete by TLC analysis (ca. two hours). The reaction was quenched by sequential addition of water (0.1 mL), 15% aq NaOH (0.1 mL), and water (0.3 mL) with vigorous stirring. After the hydrogen evolution had subsided, the mixture was concentrated and the resulting residue was suspended in Et₂O (50 mL) with vigorous stirring. The initially grey suspension became a fine white powder (ca. 1 h). The mixture was filtered through a column of Celite® and the combined filtrate and ethyl acetate washings were concentrated to give a white solid. The solid was fractionated by FCC (20% ethyl acetate in hexane) to give the title compound as a white solid (728 mg, 97%).

White crystalline solid, mp 183-184°C, TLC Rₜ = 0.3 (40% ethyl acetate in hexane);

[α]₀ –8.7 (c 1.2, CHCl₃);

IR νₘₐₓ: 3344 cm⁻¹;
$^1$H NMR (CDCl$_3$) $\delta$: 7.45-7.28 (5H, m, Ph), 5.61 (1H, s, HC-2), 3.83 (1H, dd, $J = 6$, 11 Hz, H$_2$CO), 3.64 (1H, dd, $J = 4.5$, 11 Hz, H$_2$CO), 3.50 (1H, dd, $J = 10$, 10 Hz, HC-8a), 3.42 (1H, dd, $J = 2$, 10 Hz, HC-4), 2.65-2.55 (2H, m, H$_2$C-7), 2.50 (1H, br d, $J = 13.5$ Hz, HC-5), 2.34 (1H, dd, $J = 12$, 13.5 Hz, HC-5), 2.25-2.15 (2H, m, HC-8, HO), 2.11 (1H, dddd, $J = 3.5$, 10, 10, 12 Hz, HC-4a), 1.93 (1H, dqq, $J = 2$, 7, 7 Hz, HC-1'), 1.08 (3H, d, $J = 7$ Hz, H$_3$C-2'), 0.98 (3H, d, $J = 7$ Hz, H$_3$C-2');

$^{13}$C NMR (CDCl$_3$) $\delta$: 138.6 (s, Ph), 129.0 (d, Ph), 128.4 (d $\times 2$, Ph), 126.1 (d $\times 2$, Ph), 100.9 (d, C-2), 84.2 (d, C-8a), 84.0 (d, C-4), 65.9 (t, CH$_2$O), 45.6 (d, C-8), 43.4 (d, C-4a), 29.7 (t, C-7), 28.5 (d, C-1'), 27.7 (t, C-5), 20.2 (q, C-2'), 15.1 (q, C-2');

HRMS m/z calcd. for C$_{17}$H$_{24}$O$_3$S 308.1446, found 308.1442 (EI).
Oxalyl chloride (0.32 mL, 0.48 g, 3.7 mmol) was added over 5 min to a stirred solution of DMSO (0.27 mL, 0.30 g, 3.8 mmol) in CH$_2$Cl$_2$ (60 mL) at -78 °C under argon. After 20 min, a solution of 123 (728 mg, 2.36 mmol) in CH$_2$Cl$_2$ (20 mL) at -78 °C under argon was added to the reaction mixture via a cannula. After 40 min, Et$_3$N (1.2 mL, 0.87 g, 8.6 mmol) was added and the cooling bath was removed. After 30 min, the mixture was diluted with CH$_2$Cl$_2$ and washed sequentially with saturated aq NH$_4$Cl, saturated aq NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the title compound (673 mg, 92%).

white amorphous solid, TLC $R_f = 0.3$ (20% ethyl acetate in hexane);

$[\alpha]_D^{+} 72 \,(c 1.2, \text{CHCl}_3);$

IR $\nu_{\text{max}}: 1727 \text{ cm}^{-1}$ ;

$^1$H NMR (CDCl$_3$) $\delta$: 9.92 (1H, d, $J = 1.5$ Hz, HC=O), 7.45-7.32 (5H, m, Ph), 5.61 (1H, s, HC-2), 3.79 (1H, dd, $J = 10$, 10 Hz, HC-8a), 3.47 (1H, dd, $J = 2$, 10 Hz, HC-4), 2.98 (1H, dddd, $J = 1.5$, 4, 10, 11...
Hz, HC-8), 2.84-2.71 (2H, m, H₂C-7), 2.51 (1H, br d, J = 13 Hz, HC-5), 2.36 (1H, br dd, J = 10, 13 Hz, HC-5), 2.15 (1H, ddd, J = 3, 10, 10, 12 Hz, HC-4a), 1.94 (1H, dqq, J = 2, 7, 7 Hz, HC-1'), 1.08 (3H, d, J = 7 Hz, H₃C-2'), 1.01 (3H, d, J = 7 Hz, H₃C-2');

¹³C NMR (CDCl₃) δ: 202.7 (d, C=O), 138.3 (s, Ph), 129.0 (d, Ph), 128.4 (d ×2, Ph), 126.1 (d ×2, Ph), 100.8 (d, C-2), 83.9 (d, C-4), 81.2 (d, C-8a), 54.6 (d, C-8), 43.5 (d, C-4a), 28.5 (d, C-1'), 27.4 (t, C-5), 27.1 (t, C-7), 20.1 (q, C-2'), 15.1 (q, C-2');

HRMS m/z calcd. for C₁₇H₂₂O₃S 306.1290, found 306.1284 (El).
(3R)-rel-3-[(S)-(6S)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(benzyloxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (126).

Diisopropylethylamine (3.8 mL, 18 mmol) and benzyl chloromethyl ether (2.5 mL, 18 mmol) were added to a stirred solution of 98 (1.11 g, 3.65 mmol) and in DMF (10 mL) at room temperature under Ar. After 16 h, a second portion of diisopropylethylamine (1.3 mL, 6.2 mmol) and benzyl chloromethyl ether (1.0 mL, 7.3 mmol) were added. After 5 h (reaction complete by TLC analysis), the reaction was quenched by addition of MeOH (20 mL). After 1 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NH₄Cl, water and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to furnish the title compound (1.34 g, 87%).

colorless oil, TLC Rₜ = 0.3 (20% ethyl acetate in hexane);

IR νMax: 1708 cm⁻¹;

¹H NMR (CDCl₃) δ: 7.40-7.22 (5H, m, Ph), 4.88 (1H, d, J = 7 Hz, HCO₂), 4.77 (1H, d, J = 7 Hz, HCO₂), 4.62 (1H, dd, J = 1.5, 8 Hz, HC-1'), 4.58 (1H, d, J = 12 Hz, HCPH), 4.52 (1H, d, J = 12 Hz, HCPH), 4.12-3.87 (4H, m, H₂C-2', H₂C-3'), 3.12 (1H, ddd, J = 1.5, 5.5, 13.5 Hz, HC-2), 3.07 (1H, ddd, J = 3.5, 5.5, 8 Hz, HC-3), 2.99 (1H, dd, J = 3.5, 13.5 Hz, HC-2), 2.95-2.73 (6H, m, HC-5, H₂C-6
H$_2$C-7', HC-9'), 2.63-2.48 (2H, m, HC-5, HC-9'), 2.42 (1H, ddd, J = 2, 3.5, 10.5 Hz, HC-6'), 2.12 (1H, ddd, J = 3, 5, 13.5 Hz, HC-10'), 1.73 (1H, ddd, J = 3.5, 12, 13.5 Hz, HC-10');

$^{13}$C NMR (CDCl$_3$) $\delta$: 209.4 (s, C-4), 137.9 (s, Ph), 128.6 (d $\times$2, Ph), 128.0 (d $\times$2, Ph), 127.9 (d, Ph), 108.5 (s, C-5'), 94.8 (t, OCH$_2$O), 76.8 (d, C-1'), 70.5 (t, CH$_2$Ph), 64.6 (t, C-2'), 64.3 (t, C-3'), 54.8 (d, C-3), 50.5 (d, C-6'), 43.2 (t, C-5), 36.6 (t, C-10'), 33.7 (t, C-2), 31.0 (t, C-6), 29.1 (t, C-7'), 26.9 (t, C-9');

HRMS m/z calcd. for C$_{21}$H$_{32}$O$_5$Na$^+$ 447.1270, found 447.1281 (ESI).
(3R,5R)-3-((S)-(S)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)((triethylsilyloxy)methyl)-5-((R)-hydroxy((2S,4S,4aS,8R,8aR)-4-isopropyl-2-phenylhexahydrothiopyran-4(3H)-one (136).

(c-Hex)$_2$BCl (1.07 M in hexane; 4.5 mL, 4.8 mmol) and by Et$_3$N (0.71 mL, 0.52 g, 5.1 mmol) were sequentially added to a stirred solution of 127 (1.02 g, 2.44 mmol) in CH$_2$Cl$_2$ (3 mL) at −45 °C under argon. After 2 h, t-BuNH$_2$ (0.51 mL, 0.35 g, 4.9 mmol) was added. After 1 h, the mixture was cooled to −78 °C, and a solution of 124 (247 mg, 0.81 mmol) in CH$_2$Cl$_2$ (2 mL) added. After 8 h, the reaction was quenched by the addition of phosphate buffer (pH = 7; 1 M, 5 mL), methanol (5 mL), and 30% aq H$_2$O$_2$ (2.5 mL) with vigorous stirring. The reaction vessel was transferred to an ice bath and, after vigorous stirring for 20 min, the mixture was diluted with water and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated to give a yellow oil whose $^1$H NMR spectrum suggested the presence of a 15:1 mixture of aldol adducts. The crude material was fractionated by FCC (20% ethyl acetate in hexane) to give recovered 127 (612 mg, 60%) and the title compound (468 mg, 80%)

table yellow oil, TLC $R_f$ = 0.3 (30% ethyl acetate in hexane);

$[\alpha]_D$ −19 (c 1.1, CHCl$_3$);
IR $\nu_{max}$: 3555, 1699 cm$^{-1}$;

$^1$H NMR (CDCl$_3$) $\delta$: 7.52-7.28 (5H, m, Ph), 5.63 (1H, s, HC-2"), 4.85 (1H, br d, $J = 6$ Hz, HC-1'), 4.48 (1H, br d, $J = 9.5$ Hz, HC-1''), 4.08-3.83 (4H, m, H$_2$C-2', H$_2$C-3'), 3.80 (1H, dd, $J = 10$, 10 Hz, HC-8a''), 3.43 (1H, dd, $J = 2$, 9.5 Hz, HC-4''), 3.16 (1H, d, $J = 3$ Hz, HO), 3.17-3.12 (1H, ddd, HC-2), 3.07 (1H, ddd, $J = 4.5$, 5, 6 Hz, HC-3), 2.97-2.72 (7H, m, HC-2, HC-5, HC-6, H$_2$C-7' HC-9', HC-7''), 2.62-2.41 (4H, m, HC-6, HC-9', HC-5'', HC-7''), 2.41-2.32 (2H, m, HC-6', HC-5''), 2.14 (1H, br d, $J = 14$ Hz, HC-10'), 2.09-1.92 (3H, m, HC-4a'', HC-8'', HCC-4''), 1.66 (1H, ddd, $J = 3.5$, 12.5, 14 Hz, HC-10'), 1.09 (3H, 7, $J = 7$ Hz, H$_3$CCC-4''), 0.98 (3H, d, $J = 7$ Hz, H$_3$CCC-4''), 0.97 (9H, t, $J = 8$ Hz, H$_3$CCSi $\times 3$), 0.73-0.62 (6H, m, H$_2$CSi $\times 3$);

$^{13}$C NMR (CDCl$_3$) $\delta$: 213.3 (s, C-4), 139.1 (s, Ph), 128.7 (d, Ph), 128.3 (d $\times 2$, Ph), 126.1 (d $\times 2$, Ph), 108.6 (d, C-5'), 100.6 (d, C-2''), 83.8 (d, C-4''), 79.3 (d, C-8a''), 70.7 (d, C-1'), 67.4 (d, C-1''), 64.4 (t, C-2'), 64.0 (t, C-3'), 55.1 (d, C-3), 54.5 (d, C-6'), 53.0 (d, C-5), 44.1 (d $\times 2$, C-4a'', C-8''), 36.9 (t, C-10'), 33.2 (t, C-2), 31.1 (t, C-6), 28.5 (d, CHC-4''), 27.5 (t, C-5''), 27.2 (t, C-7'), 26.9 (t, C-9'), 25.7 (t, C-7''), 20.3 (q, CH$_3$CC-4''), 15.1 (q, CH$_3$CC-4''), 7.2 (q, CH$_3$CSi), 5.4 (t, CH$_3$Si);

HRMS m/z calcd. for C$_{36}$H$_{56}$O$_7$S$_3$Si+Na$^+$ 747.2850, found 747.2853 (ESI).
(15,2R)-rel-1-Hydroxy-2-methyl-1-((S)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)pentan-3-one (147aa).

MgBr$_2$·OEt$_2$ (8.35 g, 32.4 mmol) was added to a stirred solution of 74 (2.98 g, 15.9 mmol) and 149 (Z:E ca. 5:1; 4.44 g, 28.1 mmol) in CH$_2$Cl$_2$ (125 mL) at 0 °C under argon. After 1 h (reaction complete by TLC analysis), the reaction was quenched by addition of ice-cold phosphate buffer (pH 6.8, 100 mL) with vigorous stirring. After 15 min, the organic layer was removed, and the aq layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated to give the crude product as a pale yellow oil whose $^1$H NMR spectrum indicated the presence of a 4:1 mixture of the title compound and its C2 epimer 147sa, respectively. Fractionation of the crude product by FCC (60% Et$_2$O in hexane) gave the titled compound (2.83 g, 65%).

pale yellow viscous oil, TLC $R_f = 0.45$ (50% ethyl acetate in hexane);

IR $v_{max}$: 3495, 1698 cm$^{-1}$;

$^1$H NMR (CDCl$_3$) $\delta$: 4.16-4.10 (2H, m, HO, HC-1), 4.03-3.95 (4H, m, H$_2$C-2', H$_2$C-3'), 2.87 (1H, dd, $J = 3$, 14 Hz, HC-7'), 2.80 (1H, dq, $J = 4.5$, 7 Hz, HC-2), 2.74 (1H, dd, $J = 7.5$, 14 Hz, HC-7'), 2.71 (1H, ddd, $J = 3.5$, 8.5, 13.5 Hz, HC-9'), 2.65 (1H, ddd, $J = 3.5$, 7.5, 13.5 Hz, HC-9'), 2.61-2.48 (2H, m,
H₂C-4), 2.13 (1H, J = 3, 8.5, 13.5 Hz, HC-10'), 2.01 (1H, ddd, J = 3, 7, 7.5 Hz, HC-6'), 1.75 (1H, ddd, J = 3.5, 7.5, 13.5 Hz, HC-10'), 1.21 (3H, d, J = 7 Hz, H₃CC-2), 0.99 (3H, t, J = 7 Hz, C-1);

¹³C NMR (CDCl₃) δ: 215.2 (s, C-3), 110.6 (s, C-5'), 74.6 (d, C-1), 64.7 (t, C-2'), 64.0 (t, C-3'), 49.4 (d, C-2), 46.5 (d, C-6'), 35.3 (t, C-4), 34.7 (t, C-10'), 30.0 (t, C-7'), 26.8 (t, C-9'), 14.2 (q, CH₃C-2), 7.7 (q, C-5);

HRMS m/z calcd. for C₁₃H₂₂O₄S 274.1239, found 274.1237 (El).
(4R,5S,6S)-rel-5-(t-Butyldimethylsilyl)oxy-6-(2-ethyl-1,3-dioxolan-2-yl)-4-methylheptan-3-one (150).

\[
\begin{align*}
&\text{O} \\
&\text{O} \\
&\text{1} \\
&\text{2} \\
&\text{3} \\
&\text{4} \\
&\text{5} \\
&\text{TBS} \\
&\text{6} \\
&\text{7} \\
&\text{1'} \\
&\text{2'} \\
&\text{3'} \\
&\text{4'} \\
&\text{5'} \\
\end{align*}
\]

150

t-Butyldimethylchlorosilane (4.7 g, 31 mmol) was added to a stirred solution of 99 (5.08 g, 20.8 mmol) and Et₃N (5.8 mL, 4.2 g, 42 mmol) in DMF (50 mL) at room temperature. After 18 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NH₄Cl, water and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the title compound as a yellow oil (7.16 g, 96%).

pale yellow oil, TLC Rf = 0.3 (10% ethyl acetate in hexane);

IR νmax: 1718 cm⁻¹;

\(^1\text{H NMR}\) (CDCl₃) δ: 4.03 (1H, dd, J = 2.5, 6.5 Hz, HC-5), 3.98-3.85 (4H, m, H₂C-4' H₂C-5'), 2.93 (1H, dq, J = 6.5, 7 Hz, HC-4), 2.61-2.42 (2H, m, H₂C-2), 2.08 (1H, dq, J = 2.5, 7 Hz, HC-6), 1.68 (2H, ap q, J = 7.5 Hz, H₂C-1''), 1.05 (3H, d, J = 7 Hz, H₃CC-4), 1.01 (3H, d, J = 7 Hz, H₃C-7), 1.00 (3H, t, J = 7 Hz, H₃C-1), 0.87 (3H, t, J = 7.5 Hz, H₃C-2''), 0.83 (9H, s, (H₃C)₃C), 0.06 (3H, s, H₃CSi), 0.01 (3H, s, H₃CSi);
$^{13}$C NMR (CDCl$_3$) δ: 214.8 (s, C-3), 113.2 (s, C-2'), 75.6 (d, C-5), 65.7 (t, C-4'), 65.1 (t, C-5'), 49.0 (d, C-4), 45.4 (d, C-6), 36.8 (d, C2), 29.1 (q, C-1''), 26.2 (q ×3, (CH$_3$)$_3$C), 18.4 (s, CSi), 15.6 (q, CH$_3$C-4), 10.2 (q, C-7), 8.1 (q, C-2''), 7.7 (q, C-1), –4.2 (q, CH$_3$Si), –4.6 (q, CH$_3$Si);

HRMS m/z calcd. for C$_{19}$H$_{38}$O$_4$Si+H 359.2618, found 359.2616 (Cl, NH$_3$).
(4R,5S,6S)-rel-5-(Benzyloxy)methoxy-6-(2-ethyl-1,3-dioxolan-2-yl)-4-methylheptan-3-one (151).

PhCH₂OCH₂Cl (purity ca. 75%; 2.5 mL, 2.8 g, 13 mmol) was added to a stirring solution of 99 (2.21 g, 9.06 mmol) and i-Pr₂EtN (4.0 mL, 3.0 g, 23 mmol) in DMF (50 mL) at room temperature. After 18 h, a second addition of i-Pr₂EtN (4.0 mL, 3.0 g, 23 mmol) and PhCH₂OCH₂Cl (purity ca. 75%; 2.5 mL, 2.8 g, 13 mmol). After 6 h (reaction complete by TLC analysis), the reaction was quenched by addition of methanol (20 mL). After 1 h, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NH₄Cl, water and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the title compound (3.01 g, 91%).

Yellow oil, TLC Rᶠ = 0.3 (15% ethyl acetate in hexane);

IR νmax: 1714 cm⁻¹;

¹H NMR (CDCl₃) δ: 7.40-7.22 (5H, m, Ph), 4.68 (1H, d, J = 6.5 Hz, HCO₂), 4.66 (1H, d, J = 6.5 Hz, HCO₂), 4.58 (1H, d, J = 12 Hz, HCPH), 4.52 (1H, d, J = 12 Hz, HCPH), 4.01-3.92 (4H, m, H₂C-4', H₂C-5'), 3.84 (1H, dd, J = 3, 8 Hz, HC-5), 3.17 (1H, dq, J = 7, 8 Hz, HC-4), 2.52 (2H, m, J = 7.5, 18 Hz,
H₂C-2), 2.19 (1H, dq, J = 3, 7 Hz, HC-6), 1.84-1.68 (2H, m, H₂C-1''), 1.07 (3H, d, J = 7 Hz, H₃C-4), 1.06 (3H, d, J = 7 Hz, H₃C-7), 1.02 (3H, t, J = 7 Hz, H₃C-1), 0.89 (3H, t, J = 7.5 Hz, H₃C-2'');

¹³C NMR (CDCl₃) δ: 215.0 (s, C-3), 138.2 (s, Ph), 128.6 (d ×2, Ph), 128.0 (d ×2, Ph), 127.8 (d, Ph), 113.6 (s, C-2''), 96.1 (t, OCH₂O), 83.2 (d, C-5), 70.4 (t, CH₂Ph), 65.5 (t, C-4''), 65.3 (t, C-5''), 48.7 (d, C-4), 41.8 (d, C-6), 37.1 (t, C-2), 28.9 (t, C-1''), 14.8 (q, CH₃C-4), 12.4 (q, C-7), 7.8 (q ×2, C-1, C-2'');

HRMS m/z calcd. for C₂₁H₃₂O₅⁺Na⁺ 387.2143, found 387.2133 (ESI).
A solution of LiHMDS was prepared by addition of \textit{n}-BuLi (2.3 M in hexane; 1.3 mL, 3.0 mmol) was added to a stirred solution of \((\text{Me}_3\text{Si})_2\text{NH}\) (0.65 mL, 0.50 g, 3.1 mmol) in THF (10 mL) at 0°C under argon. After 15 minutes, the reaction mixture was cooled to \(-78\,\text{°C}\) and a solution of 150 (1.06 g, 2.96 mmol) in THF (5 mL) was added dropwise via syringe over 5 min. After 15 min, the mixture was warmed to \(-50\,\text{°C}\) and stirring continued for 90 min. The mixture was cooled to \(-78\,\text{°C}\) and a solution of TiCl(\text{Oi-Pr})_3 (0.73 M in \text{CH}_2\text{Cl}_2; 8.9 mL, 6.5 mmol) was added dropwise via syringe over 5 min. After 15 min, mixture was warmed to \(-50\,\text{°C}\) and stirring continued for 90 min. The reaction mixture was cooled \(-78\,\text{°C}\) and a solution of 124 (305 mg, 0.997 mmol) in THF (2 mL) was added dropwise via a syringe. After 5 h, the reaction was quenched by addition of saturated aq NH_4Cl. The mixture was extracted with \text{Et}_2\text{O} and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^1\text{H} NMR spectrum indicated the presence of a 4:1 mixture of aldol adducts. The crude product was fractionated by FCC (20% ethyl acetate in hexane) to the title compound as an
inseparable 4:1 mixture of diastereomers (553 mg, 84%) as a colorless oil. colorless oil, TLC R<sub>f</sub> = 0.3 (20% ethyl acetate in hexane);

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (* denotes signals from the minor diastereomer): 7.55-7.28 (5H, m, Ph), 5.63* (0.2H, s, HC-2'), 5.52 (0.8H, s, HC-2'), 4.45* (0.2H, dd, J = 1, 9.5 Hz, HC-1), 4.24 (0.8H, br dd, J = 2, 6 Hz, HC-1), 4.19* (0.2H, dd, J = 2, 9 Hz, HC-5), 4.07 (0.8H, dd, J = 2.5, 7 Hz, HC-5), 4.05-3.80 (4H, m, H<sub>2</sub>C-4'', H<sub>2</sub>C-5''), 3.72* (0.2H, dd, J = 10, 10 Hz, HC-8a'), 3.48 (0.8H, dd, J = 2, 10 Hz, HC-8a'), 3.45* (0.2H, dd, J = 2, 10 Hz, HC-8a'), 3.38 (0.8H, bs, HO), 3.18* (0.2H, dq, J = 7, 7 Hz), 3.11 (0.8H, dq, J = 2.5, 7 Hz, HC-2), 3.08-2.98 (1.6H, m, HC-4, HC-7'), 2.87* (0.2H, dd, J = 12.5, 13.5 Hz), 2.74* (0.2H, dq, J = 9.5, 7 Hz), 2.65 (0.8H, dd, J = 11, 14 Hz, HC-7'), 2.51 (0.8H, m, HC-5'), 2.47* (0.2H, m, HC-5'), 2.35* (0.2H, dd, J = 12, 13 Hz, HC-5'), 2.29 (0.8H, dd, J = 12, 13 Hz, HC-5'), 2.15-2.02 (3H, m, HC-6, HC-4a', HC-8'), 2.00-1.90 (1H, m, HCC-4'), 1.75-1.65 (2H, m, H<sub>2</sub>CC-2''), 1.19 (2.4H, d, J = 7 Hz, H<sub>3</sub>CC-2), 1.11* (0.6H, d, J = 7 Hz), 1.10* (0.6H, d, J = 7 Hz), 1.06* (0.6H, d, J = 7 Hz), 1.05 (2.4H, d, J = 7 Hz, H<sub>3</sub>CCC-4'), 1.01 (2.4H, d, J = 7 Hz, H<sub>3</sub>CC-4), 0.98 (0.6H, d, J = 7 Hz), 0.96 (2.4H, d, J = 7 Hz, H<sub>3</sub>CCC-4'), 0.93-0.83 (6H, m, H<sub>3</sub>C-7, H<sub>3</sub>CCC-2''), 0.82 (9H, s, (H<sub>3</sub>C)<sub>3</sub>C), 0.11 (0.6H, s, CH<sub>3</sub>Si), 0.05 (2.4H, s, CH<sub>3</sub>Si), −0.02 (0.6H, s, CH<sub>3</sub>Si), −0.05 (2.4H, s, CH<sub>3</sub>Si);

<sup>13</sup>C NMR (CDCl<sub>3</sub>) δ (minor isomer): 217.6 (s, C-3), 139.1 (s, Ph), 128.6 (d, Ph), 128.2 (d ×2, Ph), 126.0 (d ×2, Ph), 113.2 (d, C-2''), 100.3 (d, C-2'), 83.9 (d, C-4'), 79.8 (d, C-8a'), 74.5 (d, C-5), 69.3 (d, C-1), 65.7 (t, C-4''), 64.9 (t, C-5''), 48.9, 48.2, 45.5, 44.6, 44.0, 29.4, 28.47, 27.5, 26.3, 25.8, 20.3, 18.5, 15.2, 15.1, 12.9, 10.2, 8.2, −3.8, −4.6; δ (major isomer): 219.9 (s, C-3), 139.0 (s, Ph), 128.8 (d, Ph), 128.3 (d ×2, Ph), 126.3 (d ×2, Ph), 112.9 (s, C-2''), 101.0 (d, C-2'), 84.0 (d, C-4'),
82.2 (d, C-8a'), 75.5 (d, C-5), 70.4 (d, C-1), 65.8 (t, C-4'"'), 64.8 (t, C-5'"'), 51.2 (d, C-2), 46.7 (d, C-4), 46.1 (d ×2, C-6, C-8'), 43.8, 29.3 (t, CH₂C-2'"), 29.1 (t, C-7'), 28.45 (d, CHC-4'), 27.5 (t, C-5'), 26.3 (q ×3, (CH₃)₃C), 20.2 (q, CH₃CC-4'), 18.4 (s, CSi), 15.7 (q, H₃CC-4), 15.0 (q, CH₃CC-4'), 10.4 (q, H₃CC-2), 9.4 (q, C-7), 8.3 (q, CH₃CC-2'"'), −4.2 (q, CH₂Si), −4.5 (q, CH₃Si);

**HRMS** m/z calcd. for C₃₆H₆₀O₂SiS⁺Na⁺ 687.3721, found 687.3743 (ESI).
(1S,2S,4R,5S,6S)-5-((Benzyloxy)methoxy)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-hydroxy-1-
((2S,4S,4aR,8R,8aR)-4-isopropyl-2-phenylhexahydrothiopyran[4,3-d][1,3]dioxin-8-yl)-2,4-
dimethylheptan-3-one (153).

A solution of LiHMDS was prepared by addition of n-BuLi (2.3 M in hexane; 1.2 mL, 2.8
mmol) was added dropwise via a syringe to a stirred solution of (Me$_3$Si)$_2$NH (0.64 mL, 0.50 g, 3.1
mmol) in THF (10 mL) at 0 °C under argon. After 15 min, the solution was cooled to −78 °C and a
solution of 151 (963 mg, 2.65 mmol) in THF (5 mL) was added dropwise via a syringe over 5
minutes. After 15 min, the solution was warmed to −50 °C and stirred at this temperature for
90 min. The reaction mixture was cooled to −78 °C and TiCl(Oi-Pr)$_3$ (0.73 M in THF; 7.3 mL, 5.3
mmol) was added dropwise via a syringe over 5 min. After 15 min, the mixture was warmed to
−50°C and stirred at this temperature for 90 min. The reaction mixture was cooled to −78 °C
and a solution of 124 (250 mg, 0.817 mmol) in THF (2 mL) was added via a syringe. After 5 h, the
reaction was quenched by addition of saturated aq NH$_4$Cl. The mixture was diluted with water
and extracted with Et$_2$O. The combined organic layers were dried over Na$_2$SO$_4$, and
concentrated to give the crude product whose $^1$H NMR spectrum indicated the presence of a
7:1 mixture of aldol adducts along with 124 (ca. 95% conversion) and 151. The crude product
was fractionated by FCC (20% ethyl acetate in hexane) to give recovered 151 [678 mg, 70%; [α]_D +5.2 (c 2.3, CHCl_3)] and the title compound (431 mg, 79%).

Colorless oil, TLC R_f = 0.3 (30% Et_2O in toluene);

[α]_D +0.60 (c 1.2, CHCl_3);

IR ν_{max}: 3499, 1707 cm^{-1};

^{1}H NMR (CDCl_3) δ: 7.51-7.20 (10H, m, Ph ×2), 5.55 (1H, s, HC-2'), 4.60 (2H, ap s, OCH_2O), 4.49 (1H, d, J = 12 Hz, H_2CPh), 4.43 (1H, d, J = 12 Hz, H_2CPh), 4.40 (1H, ddd, J = 3.5, 4, 4 Hz, HC-1), 3.96-3.83 (4H, m, H_2C-4'', H_2C-5''), 3.82 (1H, dd, J = 2, 9 Hz, HC-5), 3.51 (1H, dd, J = 9.5, 10 Hz, HC-8a'), 3.36 (1H, dd, J = 2, 10 Hz, HC-4'), 3.34 (1H, dq, J = 9, 7 Hz, HC-4), 3.04 (1H, dq, J = 3.5, 7 Hz, HC-2), 2.93 (1H, d, J = 4 Hz, HO), 2.88 (1H, ddd, J = 2.5, 3, 14 Hz, HC-7'), 2.67 (1H, dd, J = 11.5, 14 Hz, HC-7'), 2.47 (1H, ddd, J = 2.5, 3, 13.5 Hz, HC-5'), 2.29 (1H, dd, J = 12, 13.5 Hz, HC-5'), 2.18 (1H, dq, J = 2, 7 Hz, HC-6), 2.14 (1H, dddd, J = 3, 4, 10, 11.5 Hz, HC-8'), 2.06 (1H, dddd, J = 3.5, 9.5, 10, 12 Hz, HC-4a'), 1.93 (1H, ddq, J = 2, 7, 7 Hz, HCC-4'), 1.76-164 (2H, m, H_2CC-2''), 1.15 (3H, d, J = 7 Hz, H_3CC-2), 1.05 (3H, d, J = 7 Hz, H_3CCC-4'), 1.02 (3H, d, J = 7 Hz, H_3C-7), 0.98 (3H, d, J = 7 Hz, H_3CC-4), 0.95 (3H, d, J = 7 Hz, H_3CCC-4'), 0.86 (3H, t, J = 7.5 Hz, H_3CCC-2'');

^{13}C NMR (CDCl_3) δ: 218.3 (s, C-3), 139.0 (s, Ph), 138.0 (s, Ph), 128.8 (d, Ph), 128.6 (d ×2, Ph), 128.3 (d ×2, Ph), 128.0 (d ×2, Ph), 127.8 (d, Ph), 126.3 (d ×2, Ph), 113.4 (s, C-2''), 101.0 (d, C-2'), 96.1 (t, OCH_2O), 84.0 (d, C-4'), 83.2 (d, C-5), 82.7 (d, C-8a'), 70.7 (t, CH_2Ph), 69.5 (d, C-1), 65.6 (t, C-4''), 65.1 (t, C-5''), 51.8 (d, C-2), 46.9 (d, C-4), 46.1 (d, C-8'), 43.9 (d, C-4a'), 41.6 (d, C-6), 29.0
(t, CH₂C-2''), 28.44 (d, CHC-4'), 28.39 (t, C-7'), 27.5 (t, C-5'), 20.2 (q, CH₃CC-4'), 15.3 (q, CH₃C-4), 15.0 (q, CH₃CC-4'), 12.0 (q, C-7), 10.2 (q, CH₃CC-2), 7.9 (q, CH₃CC-2'');

HRMS m/z calcd. for C₃₈H₅₄O₈S 670.3539, found 670.3586 (FD).
(1S,2S,4S,5R,6S)-5-((1-Butyldimethylsilyl)oxy)-1-hydroxy-1-((2S,4S,4aS,8R,8aR)-4-isopropyl-2-phenylhexahydrothiopyran-4,3-d[1,3]dioxin-8-yl)-2,4,6-trimethylnonane-3,7-dione (154).

\[
\begin{align*}
\text{154}
\end{align*}
\]

\(p\)-TsOH·H\(_2\)O (32 mg, 0.16 mmol) was added to a stirred solution of 152 (4:1 mixture of diastereomers; 553 mg, 0.833 mmol) in acetone (20 mL) at ambient temperature. After 16 h, the reaction was quenched by the addition of saturated aq NaHCO\(_3\) and the mixture was extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried over Na\(_2\)SO\(_4\), concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give 154a (94 mg, 18%) and the title compound (357 mg, 69%).

colorless oil, TLC \(R_f = 0.3\) (20% ethyl acetate in hexane);

\([\alpha]_D +2.0\) (c 1.2, CHCl\(_3\));

\(\text{IR } \nu_{\text{max}}: 3510, 1709 \text{ cm}^{-1}\);

\(\text{\(^1\)H NMR}\) (CDCl\(_3\)) \(\delta\): 7.50-7.30 (5H, m, Ph), 5.52 (1H, s, HC-2'), 4.43 (1H, dd, \(J = 5.5, 7 \text{ Hz, HC-5}\), 4.18 (1H, ddd, \(J = 3, 3, 6 \text{ Hz, HC-1}\)), 3.48 (1H, dd, \(J = 9.5, 9.5 \text{ Hz, HC-8a'}\)), 3.38 (1H, dd, \(J = 2, 10 \text{ Hz, HC-4'}\)), 3.16 (1H, dq, \(J = 3, 7 \text{ Hz, HC-2}\)), 2.94 (1H, d, \(J = 3.4 \text{ Hz, HO}\)), 2.93 (1H, ddd, \(J = 2.5, 3, 14 \text{ Hz, HC-7'}\)), 2.82 (1H, dq, \(J = 7, 7 \text{ Hz, HC-4}\)), 2.68-2.62 (2H, m, HC-6, HC-7'), 2.55-2.38 (3H, m, H\(_2\)C-8, HC-5'), 2.30 (1H, dd, \(J = 12, 13 \text{ Hz, HC-5'}\)), 2.22-2.05 (2H, m, HC-4a', HC-8'), 1.94 (1H, dqq,
J = 2, 7, 7 Hz, HC-1'''), 1.17 (3H, d, J = 7 Hz, H₃CC-2), 1.08 (3H, d, J = 7 Hz, H₃CC-1'''), 1.02 (3H, t, J = 7.5 Hz, H₃C-9), 0.97 (3H, d, J = 7 Hz, H₃CC-1'''), 0.89 (3H, d, J = 7 Hz, H₃CC-6), 0.82 (3H, d, J = 7 Hz, H₃CC-4), 0.80 (9H, s, (H₃C)₃CSi), 0.04 (3H, s, H₃CSi), –0.03 (3H, s, H₃CSi);

¹³C NMR (CDCl₃) δ: 217.9 (s, C-3), 212.1 (s, C-7), 138.9 (s, Ph), 128.9 (s, Ph), 128.3 (d ×2, Ph), 126.3 (d ×2, Ph), 101.2 (d, C-2'), 84.0 (d, C-4'), 82.2 (d, C-8a'), 74.4 (d, C-5), 70.1 (d, C-1), 51.5 (d, C-6), 50.1 (d, C-2), 49.1 (d, C-4), 46.2 (d, C-8'), 43.8 (d, C-4a'), 35.7 (t, C-8), 28.7 (t, C-7'), 28.5 (d, C-1''), 27.5 (t, C-5'), 26.0 (q ×3, (CH₃)₃C), 20.2 (q, CH₃C-1''), 18.2 (s, CSi), 15.0 (q, CH₃C-1''), 12.2 (q, CH₃C-4), 11.1 (q, CH₃C-2), 10.6 (q, CH₃C-6), 7.8 (q, C-9), –4.4 (q, CH₃Si), –4.7 (q, CH₃Si);

HRMS m/z calcd. for C₃₄H₅₆O₆Si+Na⁺ 643.3459, found 643.3465 (ESI).
(15,25,4S,5S,6R)-5-((Butyldimethylsilyl)oxy)-1-hydroxy-1-((25,4S,4aS,8R,8aR)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-d][1,3]dioxin-8-yl)-2,4,6-trimethylnonane-3,7-dione (154a).

See the preparation of 154.

colorless oil, TLC R\text{f} = 0.3 (15% ethyl acetate in hexane);

[\alpha]_D^0 +15 (c 1.2, CHCl\text{3});

IR \nu_{max}: 3510, 1710 cm\textsuperscript{-1};

\textsuperscript{1}H NMR (CDCl\text{3}) \delta: 7.50-7.30 (5H, m, Ph), 5.52 (1H, s, HC-2'), 4.54 (1H, dd, J = 5.5, 7 Hz, HC-5), 4.37 (1H, ddd, J = 2, 5, 9.5 Hz, HC-1), 3.65 (1H, dd, J = 9.5, 10 Hz, HC-8a'), 3.43 (1H, dd, J = 2, 10 Hz, HC-4'), 2.94 (1H, dq, J = 7, 7 Hz, HC-4), 2.84 (1H, dq, J = 7, 10 Hz, HC-2), 2.82 (1H, dd, J = 12, 14 Hz, HC-7'), 2.74 (1H, dq, J = 5.5, 7 Hz, HC-6), 2.61-2.43 (4H, m, H\textsubscript{2}C-8, HC-5', HC-7'), 2.41 (1H, d, J = 5 Hz, HO), 2.37 (1H, dd, J = 12, 13.5 Hz, HC-5'), 2.13-2.04 (2H, m, HC-4a', HC-8'), 1.96 (1H, dqq, J = 2, 7, 7 Hz, HC-1''), 1.10 (3H, d, J = 7 Hz, H\textsubscript{3}CC-1''), 1.04 (3H, d, J = 7 Hz, H\textsubscript{3}CC-2), 1.02 (3H, t, J = 7.5 Hz, H\textsubscript{3}C-9), 0.99 (3H, d, J = 7 Hz, H\textsubscript{3}CC-6), 0.97 (3H, d, J = 7 Hz, H\textsubscript{3}CC-1''), 0.90 (3H, d, J = 7 Hz, H\textsubscript{3}CC-4), 0.84 (9H, s, (H\textsubscript{3}C)\textsubscript{3}C), 0.08 (3H, s, H\textsubscript{3}CSi), 0.03 (3H, s, H\textsubscript{3}CSi);
$^{13}$C NMR (CDCl$_3$) $\delta$: 216.0 (s, C-3), 212.6 (s, C-7), 138.9 (s, Ph), 128.7 (s, Ph), 128.3 (d $\times$2, Ph), 126.1 (d $\times$2, Ph), 100.5 (d, C-2'), 84.0 (d, C-4'), 79.9 (d, C-8a'), 73.5 (d, C-5), 70.2 (d, C-1), 51.5 (d, C-6), 51.1 (d, C-4), 47.8 (d, C-2), 44.8 (d, C-8'), 43.9 (d, C-4a'), 35.8 (t, C-8), 28.5 (d, C-1''), 27.5 (t, C-5'), 26.0 (q $\times$3, (CH$_3$)$_3$C), 25.8 (t, C-7'), 20.3 (q, CH$_3$C-1''), 18.2 (s, CSi), 15.1 (q, CH$_3$C-1''), 13.2 (q, CH$_3$C-2), 11.7 (q, CH$_3$C-6), 10.8 (q, CH$_3$C-4), 7.8 (q, C-9), $-4.2$ (q, CH$_3$Si), $-4.8$ (q, CH$_2$Si);

HRMS $m/z$ calcd. for $C_{34}H_{56}O_6$Si$^+$Na$^+$ 643.3459, found 643.3469 (ESI).
(4S,5R,6R,8S,9R,10R)-5-((Butyldimethylsilyl)oxy)-9-hydroxy-10-((2S,4R,5S,6S)-6-isopropyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)-4,6,8-trimethylundecane-3,7-dione (155a).

A suspension of Raney nickel (W2; 4 mL settled volume) in EtOH (10 mL) was added to a solution of 154 (357 mg, 0.538 mmol) in EtOH (5 mL) and the resulting mixture was heated under reflux with vigorous stirring. After 4 h (reaction was complete by TLC analysis), the mixture was decanted, and the solid was suspended in ethyl acetate (10 mL) and heated under reflux with vigorous stirring for several min. This washing procedure was repeated with acetone (×2) and MeOH. The combined organic layers were filtered through Celite, concentrated, and fractionated by FCC (25% ethyl acetate in hexane) to give the title compound (291 mg, 85%).

Colorless oil, TLC R$_f$ = 0.3 (15% ethyl acetate in hexane);

[α]$_D$ −16 (c 0.80, CHCl$_3$);

IR $\nu_{\text{max}}$: 3523, 1708 cm$^{-1}$;

$^1$H NMR (CDCl$_3$) $\delta$: 7.50-7.30 (5H, m, Ph), 5.45 (1H, s, HC-2'), 4.40 (1H, dd, $J = 2.5$, 8.5 Hz, HC-5), 4.24 (1H, br d, $J = 10$ Hz, HC-9), 3.48 (1H, dd, $J = 1.5$, 9.5 Hz, HC-4'), 3.30 (1H, dd, $J = 2$, 10 Hz, HC-6'), 3.28 (1H, br s, HO), 2.94 (1H, dq, $J = 9.5$, 7 Hz, HC-8), 2.88 (1H, dq, $J = 2.5$, 7 Hz, HC-6), 2.82 (1H, dq, $J = 8.5$, 7 Hz, HC-4), 2.52 (1H, dq, $J = 18.5$, 7 Hz, HC-2), 2.46 (1H, dq, $J = 18.5$, 7 Hz,
HC-2), 2.12-1.98 (2H, m, HC-5', HC-1''), 1.92 (1H, br q, J = 7 Hz, HC-10), 1.27 (3H, d, J = 7 Hz, H_3CC-8), 1.16 (3H, d, J = 7 Hz, H_3CC-10), 1.14 (3H, d, J = 7 Hz, H_3CC-6), 1.08 (3H, d, J = 7 Hz, H_3CC-1''), 1.02 (3H, t, J = 7 Hz, H_3C-1), 0.88 (3H, d, J = 7 Hz, H_3CC-1''), 0.85 (9H, s, (H_3C)_3C), 0.83 (3H, d, J = 7 Hz, H_3CC-4), 0.79 (3H, d, J = 6.5 Hz, H_3CC-5'), 0.10 (3H, s, H_3Si), –0.02 (3H, s, H_3Si)

^13C NMR (CDCl₃) δ: 214.5 (s, C-7), 213.6 (s, C-3), 139.0 (s, Ph), 128.8 (s, Ph), 128.4 (d ×2, Ph), 126.0 (d ×2, Ph), 101.2 (d, C-2'), 88.7 (d, C-4'), 86.3 (d, C-6'), 73.7 (d, C-5), 70.7 (d, C-9), 51.6 (d, C-6), 49.7 (d, C-4), 48.6 (d, C-8), 37.3 (t, C-2), 34.5 (d, C-10), 33.1 (d, C-5'), 28.7 (d, C-1''), 26.0 (q ×3, (CH₃)₃C), 20.6 (q, CH₃C-1''), 18.2 (s, CSi), 15.9 (q, CH₃C-8), 15.5 (q, CH₃C-1''), 13.5 (q, CH₃C-4), 11.8 (q, CH₃C-10), 11.3 (q, CH₃C-5'), 9.9 (q, CH₃C-6), 7.5 (q, C-1), –4.5 (q, CH₃Si), –4.7 (q, CH₃Si);

HRMS m/z calcd. for C_{34}H_{58}O_{6}Si+Na⁺ 613.3894, found 613.3877 (ESI).
(2S,4R,6R,7S)-7-((tert-Butyldimethylsilyl)oxy)-2-((2S,4S,5S,6S)-6-isopropyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)-4,6,8-trimethylundecane-3,5,9-trione (155).

IBX (62 mg, 0.22 mmol) was added to a stirred solution of 155a (100 mg, 0.169 mmol) in DMSO (2 mL) at ambient temperature under argon. After 20 h, the mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed sequentially with saturated NaHCO$_3$, water and then brine, dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to afford the title compound (98 mg, 98%).

colorless oil, TLC $R_f = 0.3$ (10% ethyl acetate in hexane);

$[\alpha]_D -28$ (c 0.80, CHCl$_3$);

**IR** $\nu_{\text{max}}$: 1716, 1691 cm$^{-1}$;

$^1$H NMR (C$_6$D$_6$) $\delta$: 7.58 (2H, ap d, $J = 7.5$ Hz, Ph), 7.23 (2H, ap dd, $J = 7.5, 7.5$ Hz, Ph), 7.15 (1H, t, $J = 7.5$ Hz, Ph), 5.29 (1H, s, HC-2'), 4.58 (1H, dd, $J = 5.5, 6.5$ Hz, HC-7), 4.22 (1H, q, $J = 7$ Hz, HC-4), 3.12 (1H, dq, $J = 6.5, 7$ Hz, HC-6), 3.04 (1H, br d, $J = 10$ Hz, HC-6'), 2.87 (1H, dq, $J = 3, 7$ Hz, HC-2), 2.61 (1H, dq, $J = 5.5, 7$ Hz, HC-8), 2.23 (1H, dq, $J = 18, 7$ Hz, HC-10), 2.08 (1H, dq, $J = 18, 7$ Hz, HC-10), 1.81-1.72 (2H, m, HC-1'', HC-5'), 1.39 (3H, d, $J = 7$ Hz, HC-3), 1.31 (3H, d, $J = 7$ Hz, H$_3$C-1), 1.05 (3H, d, $J = 7$ Hz, H$_3$CC-1''), 0.98 (3H, d, $J = 7$ Hz, H$_3$CC-
8), 0.96 (3H, t, J = 7 Hz, H₃C-11), 0.92 (3H, d, J = 7 Hz, H₃CC-1''), 0.90 (9H, s, (H₃C)₃C), 0.88 (3H, d, J = 7 Hz, H₃CC-6), 0.62 (3H, d, J = 6.5 Hz, H₃CC-5'), 0.12 (3H, s, H₃Si), 0.09 (3H, s, H₃CSi);

¹³C NMR (C₆D₆) δ: 210.6 (s, C-9), 208.7 (s, C-3), 208.4 (s, C-5), 139.6 (s, Ph), 128.8 (d, Ph), 128.4 (d ×2, Ph), 126.4 (d ×2, Ph), 101.2 (d, C-2'), 85.8 (d, C-6'), 84.5 (d, C-4'), 74.7 (d, C-7), 57.9 (d, C-4), 51.3 (d, C-8), 49.9 (d, C-2), 48.5 (d, C-6), 35.6 (t, C-10), 34.2 (d, C-5'), 28.6 (d, C-1''), 26.2 (q ×3, (CH₃)₃C), 20.5 (q, CH₃C-1''), 18.3 (s, C₆Si), 14.8 (q, CH₃C-1''), 14.5 (q, CH₃C-4), 13.9 (q, C-1), 12.5 (q, CH₃C-6), 11.7 (q, CH₃C-5'), 11.6 (q, CH₃C-8), 7.8 (q, C-11), −4.3 (q, CH₃Si), −4.8 (q, CH₃Si);

HRMS m/z calcd. for C₃₄H₅₆O₆Si⁺Na⁺ 611.3738, found 611.3720 (ESI).
(2S,4S,6R,7R,8S)-7-Hydroxy-2-((2S,4S,5S,6S)-6-isopropyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)-4,6,8-trimethylundecane-3,5,9-trione (156).

From BOM. A suspension of Raney Nickel (W2; 0.5 mL settled volume) in EtOH (5 mL) was transferred to a solution of 160 (60 mg, 0.096 mmol) in EtOH (2 mL) and the resulting suspension was heated under reflux with vigorous stirring. After 3 h, the mixture was allowed to settle and then was decanted. The solid was suspended in ethyl acetate and the mixture was heated under reflux with vigorous stirring for 10 min, and then decanted. This washing procedure was repeated with acetone (×2) and methanol. The combined organic layers were filtered through Celite®, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give the titled compound as a colorless oil (37 mg, 81%).

From TBS. Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F; 51 mg, 0.19 mmol) was added to a stirred solution of 155 (44 mg, 0.075 mmol) in DMF (1 mL) at ambient temperature under argon. After 2 h, the mixture was diluted with ethyl acetate and washed sequentially by saturated aq NaHCO₃, water, and brine, dried over Na₂SO₄, concentrated and fractionated by FCC (30% ethyl acetate in hexane) to give the title compound as an ca. 1:1:0.04 mixture of two keto and enol tautomeric forms, respectively (32 mg, 90%).

colorless oil, TLC Rₓ = 0.3 (25% ethyl acetate in hexane);
[\alpha]_D +34 (c 1.2, CHCl_3);

\textbf{IR} v_{\text{max}}: 3457, 1715 cm^{-1};

\textbf{^1H NMR} (CDCl_3) \delta: 7.48-7.28 (5H, m, Ph), 5.44 (1H, ap s, HC-2'), 4.13 (0.5H, q, J = 7 Hz, HC-4), 4.11 (0.5H, q, J = 7 Hz, HC-4), 3.63 (0.5H, dd, J = 4.5, 10 Hz, HC-4'), 3.60 (0.5H, dd, J = 4.5, 10 Hz, HC-4'), 3.58 (0.5H, d, J = 10 Hz, HO), 3.56 (0.5H, ddd, J = 5.5, 7, 9.5 Hz, HC-7), 3.38 (0.5H, d, J = 9.5 Hz, HO), 3.37 (0.5H, ddd, J = 5, 7, 10 Hz, HC-7), 3.313 (0.5H, dd, J = 2, 10 Hz, HC-6'), 3.308 (0.5H, dd, J = 2, 10 Hz, HC-6'), 3.05 (0.5H, dq, J = 4.5, 7 Hz, HC-2), 2.83 (0.5H, dq, J = 7, 7 Hz, HC-8), 2.62 (0.5H, dq, J = 5, 7 Hz, HC-6), 2.61 (0.5H, dq, J = 5.5, 7 Hz, HC-6), 2.58-2.33 (2H, m, H_2C-10), 2.07-1.97 (1H, m, HC-1''), 1.90-1.76 (1H, m, HC-5'), 1.31 (1.5H, d, J = 7 Hz, H_3C-1), 1.28 (1.5H, d, J = 7 Hz, H_3C-1), 1.25 (1.5H, d, J = 7 Hz, H_3C-4), 1.21 (1.5H, d, J = 7 Hz, H_3C-4), 1.10-0.98 (6H, m, H_3CC-6, H_3CC-8, H_3CC-1'', H_3CC-1''), 1.03 (1.5H, t, J = 7 Hz, H_3C-11), 1.01 (1.5H, t, J = 7 Hz, H_3C-11), 0.94 (3H, ap d, J = 7 Hz, H_3C-C1''), 0.93 (1.5H, d, J = 7 Hz, H_3C-C8), 0.89 (1.5H, d, J = 6.5 Hz, H_3C-C5'), 0.84 (1.5H, d, J = 6.5 Hz, H_3C-C5'), 0.83 (1.5H, d, J = 7 Hz, H_3C-C6), 17.09 (0.08H, s, HO-enol), 1.93 (0.24H, s, H_3CC-4 enol);

\textbf{^{13}C NMR} (CDCl_3) \delta: 216.4 and 216.0 (s, C-9), 213.1 and 212.2 (s, C-5), 210.4 and 208.6 (s, C-3), 139.0 and 138.9 (s, Ph), 129.0 and 128.7 (d, Ph), 128.4 and 128.2 (d x2, Ph), 126.3 and 126.1 (Ph, Ph), 101.2 and 100.6 (d, C-2'), 86.0 and 85.9 (d, C-6'), 85.4 and 85.1 (d, C-4'), 77.6 and 77.4 (d, C-5'), 60.8 and 58.1 (d, C-4), 50.1 and 50.0 (d, C-2), 48.5 and 48.0 (d, C-8), 47.7 and 46.4 (d, C-6), 36.8 and 36.3 (t, C-10), 35.4 and 35.3 (d, C-5'), 28.52 and 28.47 (d, C-1''), 20.51 and 20.47
(q, CH₃-C₁′′′), 15.1, 15.01, 14.98, 14.96, 14.94 and 14.91 (q, CH₃-C₄, CH₃-C-6, and CH₃-C-1′′′), 14.8 and 14.7 (q, C-1), 13.3 and 12.9 (q, CH₃-C₄), 12.3 and 12.2 (q, CH₃-C₅′), 7.62 and 7.58 (q, C-11);

**HRMS m/z calcd. for C_{28}H_{42}O_{6}+Na^+ 497.2874, found 497.2897 (ESI).**
(4S,5R,6R,8S,10S,11S,12S,13S)-5-((tert-Butyldimethylsilyl)oxy)-11,13-dihydroxy-4,6,8,10,12,14-hexamethylpentadecane-3,7,9-trione (157).

Preparation of Palladium Black – Palladium acetate (200 mg, 0.891 mmol) in i-PrOH (5 mL) was placed under hydrogen atmosphere (60 psi) and stirred until the brown solution became clear with a black precipitate (~15 minutes). The supernatant was removed by pipette and saturated aq NaHCO₃ was added. After stirring for 15 min, the suspension was allowed to settle and the supernatant removed. The solid was washed (as above) with water (×3) and acetone (×2). Residual solvent was removed at high vacuum to yield neutral palladium black (93 mg, 98%).

Freshly prepared palladium black (25 mg, 0.23 mmol) was added to a stirred solution of 155 (28 mg, 0.048 mmol) in i-PrOH (10 mL) at ambient temperature under Ar. The reaction vessel was evacuated and placed under a H₂ atmosphere (60 psi). After stirring for 16 h, the supernatant was removed and the Pd was washed with MeOH (×2). The organic layers were filtered through Celite® and the combined filtrate was concentrated and fractionated by FCC (20% ethyl acetate in hexane) to give the title compound (21 mg, 88%) that was predominantly a single hemiacetal form (HOC-13 \(\rightarrow\) O=C-9) in C₆D₆ solution.
colorless oil, TLC $R_f = 0.3$ (20% ethyl acetate in hexane);

$[\alpha]_D^{\text{o}} -16$ (c 1.2, C$_6$H$_6$);

IR $\nu_{\text{max}}$: 3418, 1699 cm$^{-1}$;

$^1$H NMR (C$_6$D$_6$) $\delta$: 4.97 (1H, s, HOC$_{-9}$), 4.51 (1H, dd, $J = 5$, 7 Hz, HC-5), 3.65 (1H, dd, $J = 2.5$, 11 Hz, HC-13), 3.31 (1H, dq, $J = 7$, 7 Hz, HC-6), 3.08 (1H, ddd, $J = 2.5$, 2.5, 6.5 Hz, HC-11), 3.06 (1H, q, $J = 7$ Hz, HC-8), 2.68 (1H, dq, $J = 5$, 7 Hz, HC-4), 2.35 (1H, dq, $J = 7$, 18 Hz, HC-2), 2.17 (1H, dq, $J = 7$, 18 Hz, HC-2), 1.99 (1H, d, $J = 6.5$ Hz, HOC-11), 1.67 (1H, dqq, $J = 2.5$, 7, 7 Hz, HC-14), 1.53 (1H, dq, $J = 2.5$, 7 Hz, HC-10), 1.49 (3H, d, $J = 7$ Hz, H$_3$CC-8), 1.24 (1H, dqq, $J = 2.5$, 10.5, 7 Hz, HC-12), 1.19 (3H, d, $J = 7$ Hz, H$_3$CC-10), 1.11 (3H, d, $J = 7$ Hz, H$_3$C-15), 1.11 (3H, d, $J = 7$ Hz, H$_3$CC-4), 1.10 (3H, d, $J = 7$ Hz, H$_3$C-6), 1.02 (3H, t, $J = 7$ Hz, H$_3$C-1), 0.93 (9H, s, (H$_3$)$_3$C), 0.85 (3H, d, $J = 7$ Hz, H$_3$C-15), 0.64 (3H, d, $J = 7$ Hz, H$_3$CC-12), 0.16 (3H, s, H$_3$CSi), 0.11 (3H, s, H$_3$CSi);

$^{13}$C NMR (C$_6$D$_6$) $\delta$: 215.8 (s, C-7), 211.0 (s, C-3), 101.2 (s, C-9), 77.1 (d, C-11), 76.5 (d, C-5), 72.5 (d, C-13), 54.9 (d, C-8), 51.9 (d, C-4), 47.7 (d, C-6), 41.4 (d, C-10), 38.1 (d, C-12), 36.0 (t, C-2), 28.8 (d, C-14), 26.6 (q x3, (CH$_3$)$_3$C), 21.1 (q, C-15), 18.7 (s, CSi), 15.2 (q, C-15), 14.5 (q, CH$_3$C-10), 14.3 (q, CH$_3$C-6), 13.7 (q, CH$_3$C-12), 12.3 (q, CH$_3$C-4), 10.7 (q, CH$_3$C-8), 8.2 (q, C-1), $-3.8$ (q, CH$_3$Si), $-4.5$ (q, CH$_3$Si);

HRMS m/z calcd. for C$_{27}$H$_{52}$O$_6$SiNa$^+$ 523.3425, found 523.3429 (ESI).

Et$_3$N (1.2 mL, 0.87 g, 8.6 mmol) and Et$_3$N•3HF (1.2 mL, 1.2 g, 7.4 mmol) were sequentially added to a stirred solution of 157 (15 mg, 0.030 mmol) in THF (1 mL) at ambient temperature under argon. After 3 days, the disappearance of starting material was evident by TLC analysis. The reaction mixture was diluted with ethyl acetate and washed sequentially with saturated NaHCO$_3$, water and brine, dried over Na$_2$SO$_4$, concentrated, and fractionated by PTLC (30% ethyl acetate in hexane) to afford the title compound (9 mg, 82%) whose $^1$H and $^{13}$C NMR data closely matched those previously reported.$^{10}$

colorless oil, TLC $R_f$ = 0.3 (30% ethyl acetate:in hexane);

$[\alpha]_D$ –60 (c 0.8, C$_6$H$_6$);

IR $\nu_{\text{max}}$: 3501, 1724, 1713 cm$^{-1}$;

$^1$H NMR (CDCl$_3$) $\delta$: 3.73 (1H, dd, $J = 2$, 11 Hz, HC-8), 3.61 (1H, dd, $J = 2.5$, 11.5 Hz, HC-2), 3.38 (1H, ddd, $J = 2.5$, 3, 10.5 Hz, HC-10), 3.07 (1H, d, $J = 10.5$ Hz, HO), 2.65 (1H, dq, $J = 7$, 11.5 Hz, HC-3), 2.34 (1H, q, $J = 6.5$ Hz, HC-5), 2.26 (1H, dq, $J = 2.5$, 7 Hz, HC-2'), 2.07 (1H, dq, $J = 7$, 18.5...
Hz, HC-4'), 1.98 (1H, dq, J = 7, 18.5 Hz, HC-4'), 1.71 (1H, dqq, J = 2.7, 7 Hz, HC-1''), 1.40 (1H, dq, J = 3, 7 Hz, HC11), 1.27 (1H, ddq, J = 2.5, 7, 11 Hz, HC-9), 1.06 (3H, d, J = 6.5 Hz, H₃CC-5), 0.98 (3H, d, J = 7 Hz, H₃C-1'), 0.970 (3H, d, J = 7 Hz, H₃CC-11), 0.966 (3H, d, J = 7 Hz, H₃CC-1''), 0.96 (3H, d, J = 7 Hz, H₃CC-9), 0.95 (3H, t, J = 7 Hz, H₃C-5'), 0.94 (3H, d, J = 7 Hz, H₃CC-3), 0.75 (3H, d, J = 7 Hz, H₃CC-1'');

¹³C NMR (C₆D₆) δ: 210.0 (s, C-3'), 207.9 (s, C-4), 104.9 (s, C-6), 79.6 (d, C-2), 74.9 (d, C-10), 73.2 (d, C-8), 47.8 (d, C-2'), 46.3 (d, C-5), 45.3 (d, C-3), 39.6 (d, C-11), 38.3 (d, C-9), 36.5 (t, C-4'), 28.8 (d, C-1''), 21.0 (q, CH₃C-1''), 14.48 (q, C-1' or CH₃C-1''), 14.44 (q, C-1' or CH₃C-1''), 14.3 (q, CH₃-C3), 13.0 (q, CH₃-C11), 12.2 (q, CH₃-C9), 8.7 (q, CH₃C-5), 8.0 (q, C-5');

HRMS m/z calcd. for C₂₁H₃₆O₅Na⁺ 647.2455, found 391.2454 (ESI).
(1S,2S,4R,5R,6S)-5-((Benzyloxy)methoxy)-1-hydroxy-1-((2S,4S,4aS,8R,8aR)-4-isopropyl-2-phenylhexahydrothiopyran[4,3-d][1,3]dioxin-8-yl)-2,4,6-trimethylnonane-3,7-dione (159).

Anhydrous FeCl$_3$ (12 mg, 76 µmol) was added to a stirred solution of 153 (253 mg, 0.378 mmol) in acetone (25 mL) at ambient temperature under argon. After 1 h, the mixture was diluted with ethyl acetate and washed sequentially with water and brine, dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (25% ethyl acetate in hexane) to give the title compound (217 mg, 92%).

colorless oil, TLC R$_f$ = 0.3 (30% Et$_2$O in toluene);

[α]$_D$ +16 (c 1.0, CHCl$_3$);

IR v$_{max}$: 3498, 1708 cm$^{-1}$;

$^1$H NMR (CDCl$_3$) δ: 7.50-7.25 (10H, m, Ph ×2), 5.55 (1H, s, HC-2'), 4.63 (2H, s, H$_2$CO$_2$), 4.49 (1H, d, J = 11.5 Hz, H$_2$CPh), 4.44 (1H, d, J = 11.5 Hz, H$_2$CPh), 4.31 (1H, ddd, J = 4, 4, 4 Hz, HC-1), 4.16 (1H, dd, J = 4.5, 8.5 Hz, HC-5), 3.52 (1H, dd, J = 9.5, 10 Hz, HC-8a'), 3.38 (1H, dd, J = 2, 10 Hz, HC-4'), 3.03 (1H, dq, J = 4, 7 Hz, HC-2), 3.01 (1H, dq, J = 8.5, 7 Hz, HC-4), 2.90 (1H, dq, J = 4.5, 7 Hz, HC-6), 2.82 (1H, ddd, J = 2.5, 3, 14 Hz, HC-7'), 2.69 (1H, dd, J = 11.5, 14 Hz, HC-7'), 2.63 (1H, d, J = 4
Hz, HO), 2.55-2.39 (3H, m, H₂C-8, HC-5'), 2.31 (1H, dd, J = 12, 13 Hz, HC-5'), 2.13 (1H, dddd, J = 3.5, 4, 10, 11.5 Hz, HC-8'), 2.05 (1H, dddd, J = 3.5, 9.5, 10, 12 Hz, HC-4a'), 1.94 (1H, dqq, J = 2, 7, 7 Hz, HC-1''), 1.15 (3H, d, J = 7 Hz, H₃C-2), 1.05 (3H, d, J = 7 Hz, H₂C-6), 1.01 (3H, t, J = 7.5 Hz, H₃C-9), 0.95 (3H, d, J = 7 Hz, H₂C-1''), 0.82 (3H, d, J = 7 Hz, H₃C-4);

¹³C NMR (CDCl₃) δ: 217.1 (s, C-3), 212.2 (s, C-7), 139.0 (s, Ph), 137.7 (s, Ph), 128.9 (d, Ph), 128.7 (d ×2, Ph), 128.3 (d ×2, Ph), 128.01 (d, Ph), 127.96 (d ×2, Ph), 126.3 (d ×2, Ph), 101.2 (d, C-2'), 95.9 (t, OCH₂O), 84.0 (d, C-4'), 82.4 (d, C-8a'), 81.7 (d, C-5), 70.6 (t, CH₂Ph), 69.5 (d, C-1), 50.9 (d, C-2), 49.1 (d, C-6), 47.4 (d, C-4), 46.2 (d, C-8'), 44.0 (d, C-4a'), 35.3 (t, C-8), 28.4 (d, C-1''), 28.2 (t, C-7'), 27.6 (t, C-5'), 20.2 (q, CH₃C-1''), 15.0 (q, CH₃C-1''), 13.4 (q, CH₃C-4), 11.1 (q, CH₃C-6), 10.9 (q, CH₃C-2), 8.0 (q, C-9);

HRMS m/z calcd. for C₃₆H₅₀O₇S 626.3277, found 626.3261 (FD).
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IBX (140 mg, 0.500 mmol) was added to a stirred solution of 159 (205 mg, 0.327 mmol) in DMSO (5 mL) at ambient temperature under argon. After 20 h, the mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed sequentially with saturated NaHCO₃, water and then brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to afford the title compound (187 mg, 92%) as an ca. 5:9:1 mixture of enol and two keto forms, respectively.

colorless oil, TLC Rf = 0.3 (20% ethyl acetate:in hexane);

[α]₀ +19 (c 1.0, CHCl₃);

IR νmax: 1713 cm⁻¹;

¹H NMR (CDCl₃) δ: 17.15 (0.5H, s, HO enol), 7.42-7.21 (15H, m, Ph ×2), 5.51 (0.5H, s, HC-2' enol), 5.49 (1H, s, HC-2' keto), 4.66 (1H, d, J = 7 Hz, OCH₂O keto), 4.64 (1H, d, J = 7 Hz, OCH₂O keto), 4.59 (0.5H, d, J = 7 Hz, OCH₂O enol), 4.53 (0.5H, d, J = 7 Hz, OCH₂O enol), 4.51 (1H, d, J = 12 Hz, H₂CPh keto), 4.46 (1H, d, J = 12 Hz, H₂CPh keto), 4.37 (0.5H, d, J = 12 Hz, H₂CPh enol), 4.31
(0.5H, d, J = 12 Hz, H₂CPh enol), 4.17 (1.5H, ap dd, J = 5, 7 Hz, HC-5 keto & enol), 3.98 (1H, q, J = 7 Hz, CH₃C-2 keto), 3.89 (0.5H, dd, J = 10, 10 Hz, HC-8a' enol), 3.72 (1H, dd, J = 10, 10 Hz, HC-8a' keto), 3.45 (0.5H, dd, J = 2, 10 Hz, HC-4' enol), 3.41 (1H, dd, J = 2, 10 Hz, HC-4' keto), 3.34 (0.5H, ddd, J = 3, 10, 11.5 Hz, HC-8' enol), 3.21 (1H, dq, J = 7, 7 Hz, HC-7' keto), 3.05 (0.5H, ddd, J = 11.5, 13.5 Hz, HC-7' keto), 3.01-2.87 (3.5H, m, HC-4 keto, HC-6 keto & enol, HC-7' keto), 2.72 (1H, dddd, J = 3, 10, 10, 11.5 Hz, HC-4a' enol), 2.05 (1H, dddd, J = 3.5, 10, 10, 11.5 Hz, HC-4a' keto), 1.96 (1.5H, s, H₃CC-2 enol), 2.00-1.88 (1.5H, m, HC-1'' keto & enol), 1.25 (3H, d, J = 7 Hz, H₃CC-2 keto), 1.11-1.06 (9H, m, H₃CC-6 keto & enol, H₃CC-1'' keto & enol), 1.04 (1.5H, d, J = 7 Hz, H₃CC-4 enol), 1.04 (1.5H, t, J = 7 Hz, H₃C-9 enol), 1.02 (3H, t, J = 7 Hz, H₃C-9 keto), 1.00-0.96 (7.5, m, H₃C-4 keto, H₃CC-1'' keto & enol);

¹³C NMR (CDCl₃) δ (major keto form): 212.6 (s, C-7), 210.5 (s, C-3), 209.2 (s, C-1), 138.4 (s, Ph), 137.6 (s, Ph), 128.8 (s, Ph), 128.65 (d ×2, Ph), 128.27 (d ×2, Ph), 128.02 (d ×2, Ph), 127.98 (s, Ph), 125.88 (d ×2, Ph), 100.6 (d, C-2'), 95.67 (t, OCH₂O), 83.76 (d, C-4), 82.9 (d, C-8a'), 81.3 (d, C-5), 70.5 (t, CH₂Ph), 62.0 (d, C-2), 55.3 (d, C-8'), 48.9 (d, C-6), 47.9 (d, C-4), 43.3 (d, C-4a'), 35.6 (d, C-8), 29.9 (t, C-7'), 28.37 (d, C-1''), 27.53 (t, C-5'), 20.09 (q, CH₃C-1''), 15.04 (q, CH₃C-1''), 13.23 (q, CH₃C-4), 11.8 (q, CH₃C-2), 11.5 (q, CH₃C-6), 7.92 (q, C-9); (enol form): 212.8 (s, C-7), 195.4 (s, C-3), 193.0 (s, C1), 138.7 (s, Ph), 137.9 (s, Ph), 128.61 (s, Ph), 128.57 (d ×2, Ph), 128.08 (d ×2, Ph), 127.85 (d ×2, Ph), 127.83 (s, Ph), 125.94 (d ×2, Ph), 106.4 (s, C-2), 100.4 (d, C-2'), 95.69 (t, OCH₂O), 83.71 (d, C-4), 81.6 (d, C-5), 81.4 (d, C-8a'), 70.3 (t, CH₂Ph), 48.99 (d, C-6), 48.2 (d, C-8'),
43.5 (d, C-4a’), 41.4 (d, C-4), 35.4 (d, C-8), 30.4 (t, C-7’), 28.41 (d, C-1’’), 27.62 (t, C-5’), 20.1 (q, CH₃-C1’’), 15.02 (q, CH₃-C1’’), 13.29 (q, CH₃-C4), 12.4 (q, CH₃-C2), 12.0 (q, CH₃-C-6), 8.0 (q, C-9);

HRMS m/z calcd. for C_{36}H_{48}O_{7}S+Na⁺ 647.3013, found 647.3021 (ESI).
4-epi-Dolabriferol (170).

A solution of DBU (5 mg; 0.03 mmol) in C₆D₆ (0.1 mL) was added to a solution of 4 (12 mg, 0.031 mmol) in C₆D₆ (0.6 mL) in a 5 mm NMR tube band the reaction was monitored by ¹H NMR. After 5 days, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq citric acid, saturated aq NaHCO₃ and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (50% ethyl acetate in hexane) to give a 6:3:1 mixture of 4-epi-dolabriferol 170, dolabriferol 1, and an unknown dolabriferol epimer, respectively (4.5 mg, 38%), an inseparable 2:1 mixture of 173 and 174 (4 mg, 30%), and a mixture of hemiacetals (4 mg, 30%). The fraction containing 170 dolabriferol 1, and an unknown epimer was further fractionated by PTLC (30% ethyl acetate in hexane) to give a 3:1 mixture of dolabriferol 1 and an unknown dolabriferol epimer, respectively (1.5 mg, 13%), and the title compound (3 mg, 25%).

colorless oil, TLC R_f = 0.3 (40% Et₂O in hexane);

[α]₀²⁰ = −8 (c 0.3, C₆H₆);

IR ν max: 3445, 1732, 1712 cm⁻¹;
\textbf{\textsuperscript{1}H NMR} (CDCl$_3$) $\delta$: 5.25 (1H, dd, $J = 3$, 3 Hz, HC-15), 4.24 (1H, ddd, $J = 3$, 4.5, 9 Hz, HC-6), 4.03 (1H, d, $J = 4.5$ Hz, HOC-6), 3.63 (1H, dd, $J = 2$, 10.5 Hz, HC-18), 2.74 (1H, dq, $J = 7$, 9 Hz, HC-4), 2.63 (1H, dq, $J = 3$, 7.5 Hz, HC-7), 2.61 (1H, br s, HOC-12), 2.56 (2H, ap q, $J = 7$ Hz, H$_2$C-2), 1.87 (1H, dq, $J = 3$, 7 Hz, HC-13), 1.83 (1H, dqq, $J = 2$, 7, 7 Hz, HC-19), 1.76 (1H, ddq, $J = 3$, 7, 10.5 Hz, HC-16), 1.68-1.57 (2H, m, H$_2$C-10), 1.27 (3H, d, $J = 7.5$ Hz, H$_3$C-8), 1.06 (3H, t, $J = 7$ Hz, H$_3$C-1), 1.005 (3H, d, $J = 7$ Hz, H$_3$C-5 or H$_3$C-20), 0.998 (3H, d, $J = 7$ Hz, H$_3$C-5 or H$_3$C-20), 0.92 (3H, d, $J = 7$ Hz, H$_3$C-14), 0.90 (3H, t, $J = 7.5$ Hz, H$_3$C-11), 0.83 (3H, d, $J = 7$ Hz, H$_3$C-21), 0.79 (3H, d, $J = 7$ Hz, H$_3$C-17);

\textbf{\textsuperscript{13}C NMR} (CDCl$_3$) $\delta$: 215.5 (s, C-3), 174.9 (s, C-9), 98.9 (s, C-12), 76.4 (d, C-15), 72.6 (d, C-6 or C-18), 72.5 (d, C-6 or C-18), 47.9 (d, C-4), 42.3 (d, C-7), 39.6 (d, C-13), 37.1 (t, C-2), 36.3 (d, C-16), 32.9 (t, C-10), 28.1 (d, C-19), 20.5 (q, C-20), 14.1 (q, C-21), 13.9 (q, C-5), 13.1 (q, C-17), 12.7 (q, C-14), 10.3 (q, C-8), 7.7 (q, C-1), 7.4 (q, C-11);

\textbf{HRMS} $m/z$ calcd. for C$_{21}$H$_{38}$O$_6$+Na 409.2561, found 409.2579 (ESI).
(3S,4S,5R,6S)-4-Hydroxy-6-isopropyl-3,5-dimethyltetrahydro-2H-pyran-2-one (173) and (2R,3S,4S,5R,6S)-3-Ethyl-3,5-dihydroxy-2,4,6-trimethylcyclohexanone (174).

![Molecular structures of 173 and 174]

A 2:1 mixture of 173 and 174, respectively was obtained in preparation of 170. Lactone 173 is a known compound and the ¹H and ¹³C NMR data for the major component of the mixture closely matched those reported for 173. The minor component is tentatively assigned as 174 based on its ¹H and ¹³C NMR data.

Lactone 173

¹H NMR (CDCl₃) δ: 4.32 (1H, dd, J = 2, 11 Hz, HC-6), 3.87 (1H, br s, HC-4), 2.54 (1H, dq, J = 3, 7 Hz, HC-3), 1.98 (1H, ddq, J = 2, 11, 7 Hz, HC-5), 1.90 (1H, dqq, J = 2, 7, 7 Hz, HC-1'), 1.84 (1H, br s, HO), 1.36 (3H, d, J = 7 Hz, H₃CC-3), 1.14 (3H, d, J = 7 Hz, H₃CC-1'), 1.09 (3H, d, J = 7 Hz, H₃CC-5), 0.92 (3H, d, J = 7 Hz, H₃CC-1');

¹³C NMR (CDCl₃) δ: 174.0 (s, C-1), 85.1 (d, C-6), 73.6 (d, C-4), 42.6 (d, C-3), 36.2 (d, C-5), 29.2 (q, C-1'), 20.3 (q, H₃CC-1'), 14.5 (q, H₃CC-5), 14.3 (q, H₃CC-1'), 13.0 (q, H₃CC-3)

Cyclohexanone 174
$^1$H NMR (CDCl$_3$) $\delta$: 4.11 (1H, br s, HC-5), 2.73 (1H, ddq, $J = 1, 3.5, 6.5$ Hz, HC-6), 2.67 (1H, dq, $J = 1, 6.5$ Hz, HC-2), 2.42 (1H, bs, HO), 2.21 (1H, dq, $J = 3, 7$ Hz, HC-4), 1.69 (1H, dq, $J = 14.5, 7.5$ Hz, HC-1'), 1.51 (1H, dq, $J = 14.5, 7.5$ Hz, HC-1'), 1.25 (3H, d, $J = 7$ Hz, H$_3$CC-4), 1.18 (3H, d, $J = 6.5$ Hz, H$_3$CC-6), 1.08 (3H, d, $J = 6.5$ Hz, H$_3$CC-2), 0.90 (3H, t, $J = 7.5$ Hz, H$_3$C-2');

$^{13}$C NMR (CDCl$_3$) $\delta$: 211.5 (s, C-1), 83.6 (d, C-3), 81.5 (d, C-5), 51.2 (d, C-6), 50.7 (d, C-2), 39.2 (d, C-4), 29.8 (t, C-1'), 12.0 (q, H$_3$CC-4), 11.0 (q, H$_3$CC-6), 8.9 (q, H$_3$CC-2'), 7.1 (q, H$_3$CC-2)
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27. Pramod Jadhav, unpublished results.


32. Sushital Jana, unpublished results.


