

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

A Thesis Submitted to the
College of Graduate Studies and Research
in Partial Fulfillment of the Requirements
for the Degree of Master of Science
in the Department of Chemistry
University of Saskatchewan

by

Athanasios Karagiannis

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CANADA**

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank Professor Dale Ward for all his support throughout this research. Your support, engagement in my work/education, and your constant push into the unknown is what fueled my progress in the lab. I truly appreciate the countless hours we spent discussing problems in research, reactions I conducted, and NMR spectra, as well as the odd discussion of my work bench being too “dirty” (maybe not so much appreciation for that one). Your guidance and advice have been invaluable throughout my journey. Thank you for helping me get to where I am today.

I would also like to acknowledge former Ward group members: Drs. Garrison Beye, Fabiola Becerril-Jiménez, and Mohammed (Pooyan) Zahedi. The three of you taught me the basics of working in a laboratory and what it takes to pursue a graduate degree in chemistry; For that, I am very grateful. I am proud to call them my former colleagues and good friends. My current lab mates: Mr. Naveen Diddi, Mr. Sushital Jana, Mr. Diptarghya Kundu, Mr. Leon Lai, Mr. Muxi Cheng, and Mr. Mojtaba Biniiaz are acknowledged for making the lab a great place to work and conduct research in. Your conversations, advice, jokes, and the random pranks put a smile on my face almost every day I spent in lab. Again, thank you for your support. The Ward group was a second family to me, I wish the group luck and success in all endeavors they pursue.

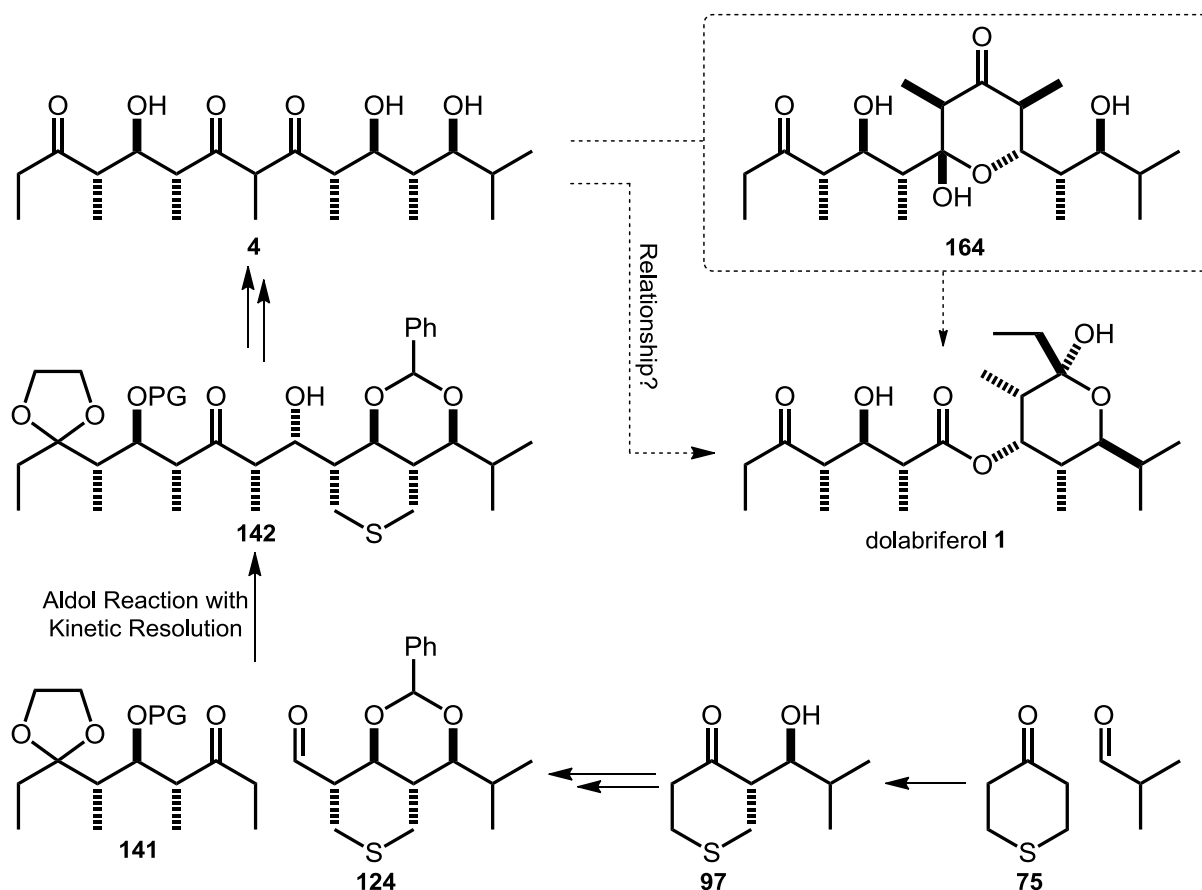
I would like to thank my advisory committee members especially Dr. Michel Gravel. His knowledge and expertise were helpful in my research. He is a part of the reason I chose to pursue a degree in chemistry. In the various courses I took from him, he demonstrated the

importance of chemistry research which ranged in topics from methods of acetal formation to removing the pigment in red wine. These types of discussions made me realize that organic chemistry was where I belonged. Thank you, I would not be here without you. I would also like to thank all Saskatchewan Structural Science Center (SSSC) staff members especially Dr. Keith Brown who spent countless hours optimizing NMR experiments and Mr. Ken Thoms who promptly returned mass data. Even when I had filled his samples bench completely with my own compounds, he would still finish them quickly.

Lastly, but certainly not least, I would like to thank my family and friends for their constant support and encouragement. I am especially grateful to my parents Andy and Francine Karagiannis, who supported me emotionally and financially throughout this journey. My parents taught my sisters and me to finish what we have started. I would not have made it this far without them. My two younger sisters, Anna and Chrissa, the two of you were the comedy duo I needed the odd time research was frustrating. You two could put a smile on my face regardless of the work day I just had, thank you for everything. My good friends Josh Jean, Kerry Gardner, Steven Kessler, and Paula Sather are also acknowledged for their support throughout my master's degree. Thank you for your encouragement, advice, and most of all your humor.

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 (\pm)-**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
$[\alpha]_D$	specific rotation at the sodium D line (expressed without units; implied actual units are: (deg·mL)/(g·dm))
Ac	acetyl
AcOH	acetic acid
<i>anti</i>	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)
<i>n</i> -BuLi	<i>n</i> -butyllithium
<i>t</i> -Bu	<i>tert</i> -butyl
<i>t</i> -BuLi	<i>tert</i> -butyllithium
<i>t</i> -BuOH	<i>tert</i> -butyl alcohol
°C	degrees Celsius (temperature)
cat.	catalytic (abbreviation used with period)
CI	chemical ionization (in mass spectrometry)
¹³ C NMR	carbon 13 nuclear magnetic resonance
COSY	correlation spectroscopy
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Cy	cyclohexyl

δ	NMR chemical shift in parts per million downfield from TMS
d	day(s); doublet (spectral signal)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer (an NMR technique)
DIBAL-H	diisobutylaluminum hydride
dil	dilute
DIPA	<i>N,N</i> -diisopropylamine
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomer ratio
DRIFT	diffuse reflectance Fourier transform infrared
<i>E</i> and <i>Z</i>	configurational descriptors for alkenes. <i>E</i> 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 <i>Z</i> .
<i>ee</i>	enantiomeric excess
EI	electron impact ionization
<i>ent</i>	enantiomer of
<i>epi</i>	epimer of
equiv	equivalents
er	enantiomeric ratio
Et	ethyl

FCC	flash column chromatography
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane, bis(trimethylsilyl)amide
^1H 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
<i>J</i>	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	<i>p</i> -methoxybenzyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
<i>i</i> Pr	isopropyl
PTLC	preparative thin layer chromatography
PTSA	<i>p</i> -toluenesulfonic acid
q	quartet
<i>rac</i>	racemic
Ref, ref	reference
rt	room temperature
s	singlet (spectral)
sat	saturated
<i>syn</i>	synperiplanar
t	triplet (spectral)
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate

TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
TBSCl	<i>tert</i> -butyldimethylsilyl chloride
TBSOTf	<i>tert</i> -butyldimethylsilyl trifluoromethanesulfonate
TES	triethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPPTS	tris(3-sulfophenyl)phosphine trisodium salt
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid

INTRODUCTION

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

1.1.1. Opisthobranchs and the Curious Chemist

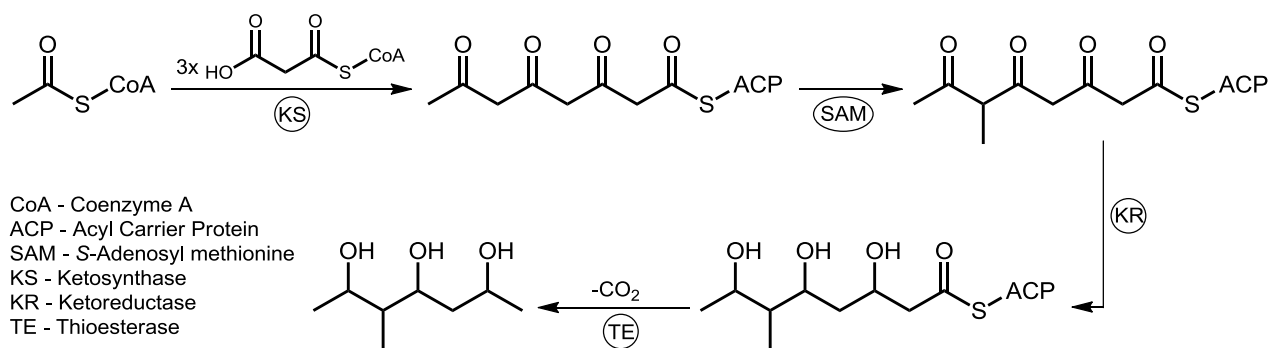
Opisthobranchs are gastropod mollusks found exclusively in marine habitats around the globe. A common attribute among these mollusks is the lack of a complete shell, with only a few species having shells big enough for the animal to completely withdraw itself. For most cases, the shell is either reduced 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 cnidocytes (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

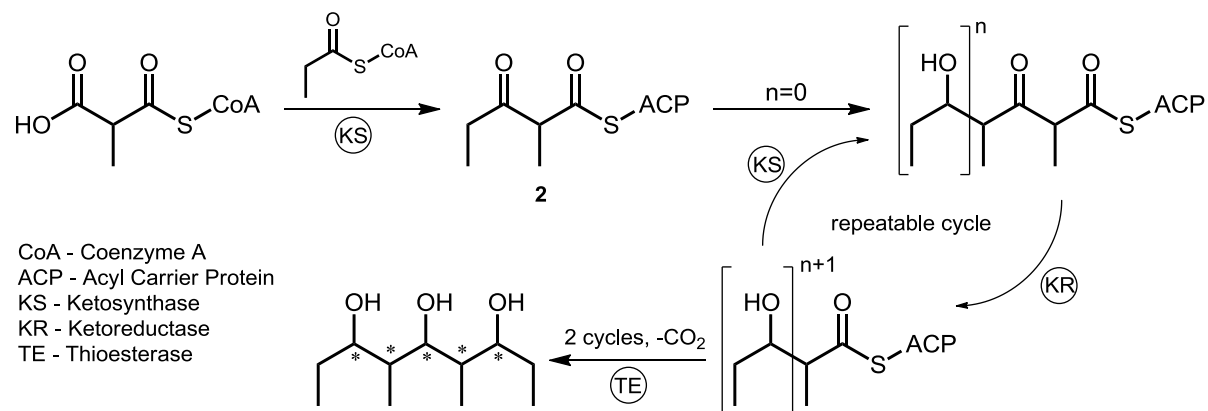
Before discussing polypropionate based natural products and their importance, the biosynthesis of such compounds is noteworthy. Polypropionates are formed by an extension of the polyketide process shown in Scheme 1.1. In organisms, the polyketide process begins with formation of an acyl anion equivalent 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 1.1: Simplified Overview of Polyketide Biosynthesis

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).

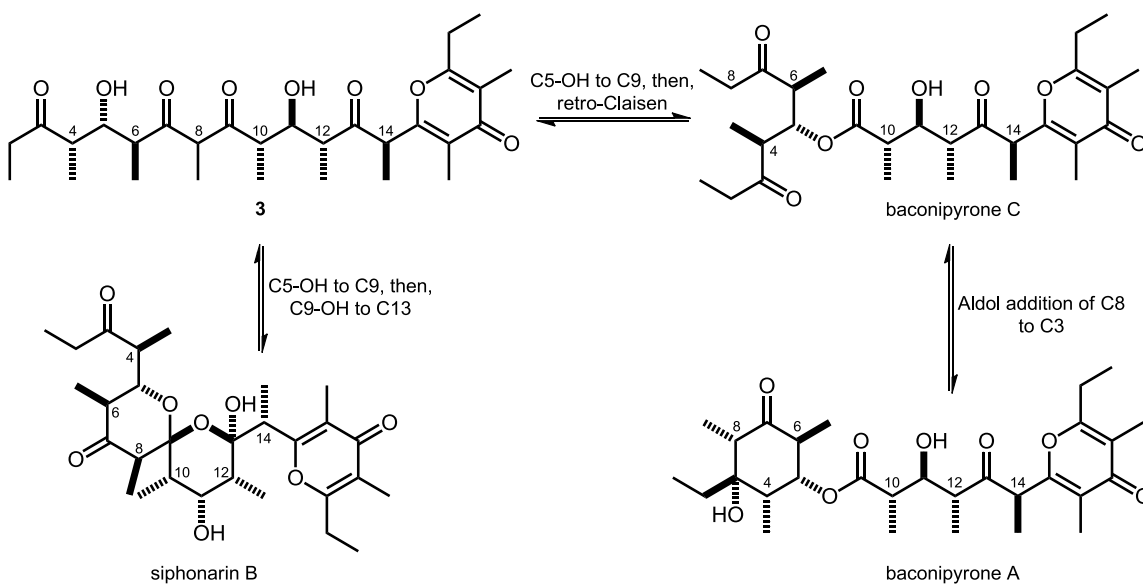


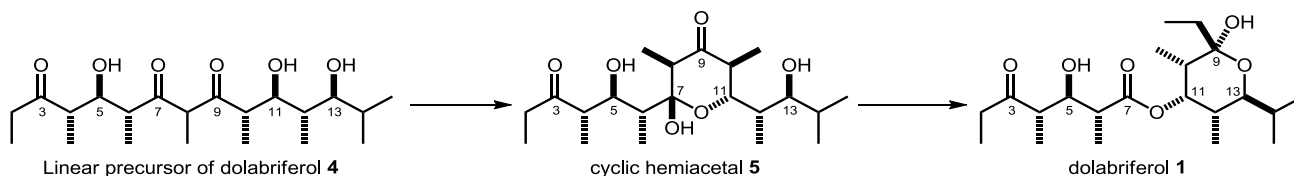
Figure 1.1: Complex Natural Products from a Common Precursor

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 baconipyrones A, baconipyrones C, and siphonarins 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*.⁴ 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.⁵

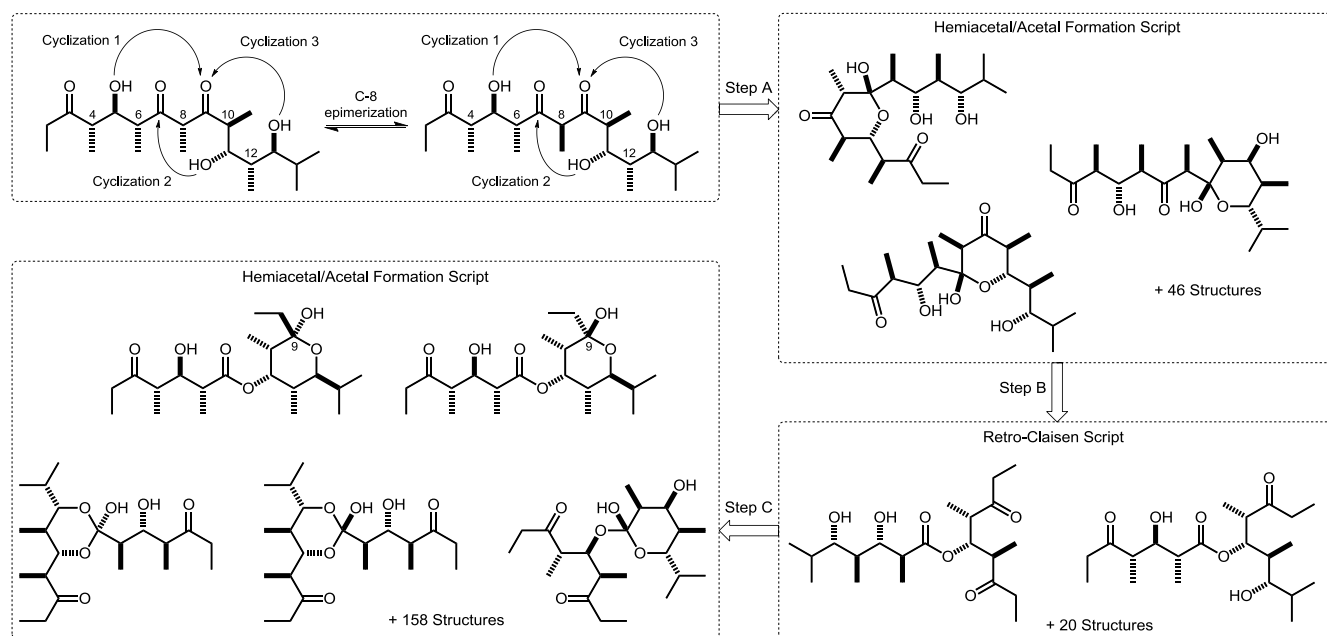


Scheme 1.3: Formation of Dolabriferol via Retro-Claisen Rearrangement

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.⁶ 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.

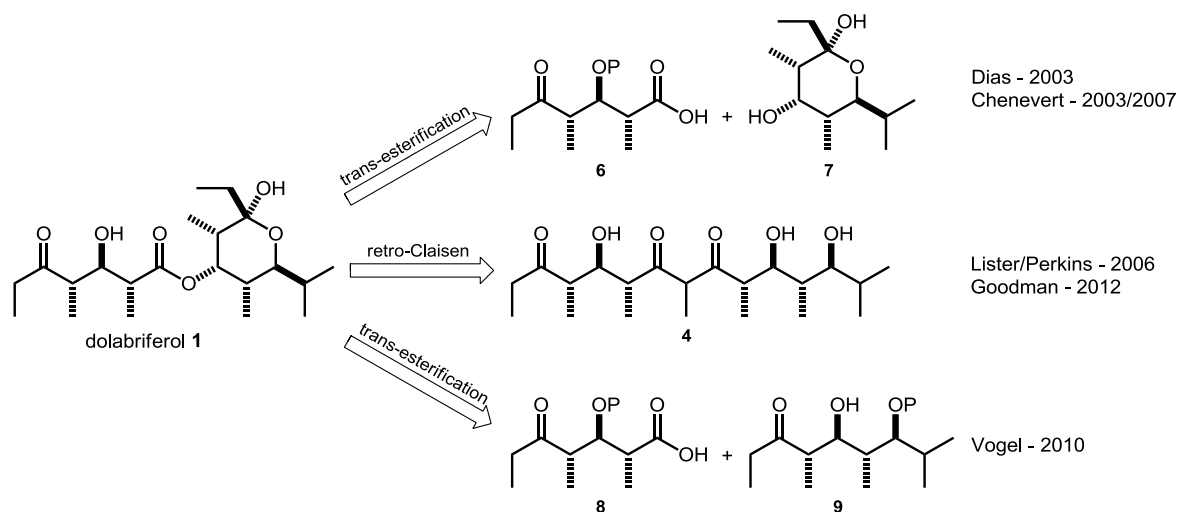


Scheme 1.4: Structures Predicted by ROBIA

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 hemioortho esters shown in Scheme 1.4. Calculations put the esters higher in energy than the hemioortho esters, which are inconsistent both with experimental observations and higher levels of theory; hence, the hemioortho 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.



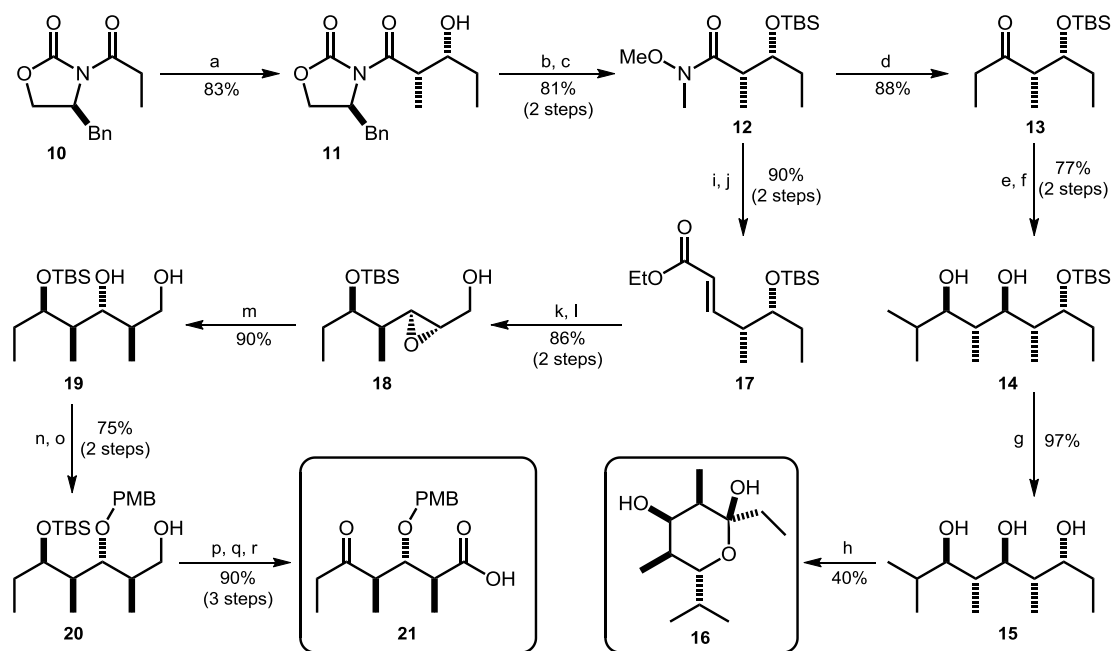
Scheme 1.5: Retrosynthetic Approaches to Dolabriferol

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.^{7,8,9} Lister and Perkins employed a retro-Claisen approach to obtain a protected derivative of dolabriferol but the deprotection was unsuccessful.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.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.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 *m*-CPBA to form epoxide **18** as a single product. Epoxide opening of **18** was induced by reaction with $\text{Me}_2\text{CuCNLi}_2$ to give diol **19** that possessed the desired *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.⁷



a) $n\text{-Bu}_2\text{OTf}$, Et_3N , propionaldehyde, DCM b) Me_3Al , MeONHMe , HCl , THF c) TBSCl , imidazole, DMF d) EtMgBr , THF e) Cy_2BCl , Et_3N , isobutyraldehyde, DCM f) $\text{Zn}(\text{BH}_4)_2$, THF g) DOWEX-50, MeOH h) $(\text{COCl})_2$, DMSO, Et_3N , DCM i) DIBAL-H , DCM j) $\text{Ph}_3\text{PCHCO}_2\text{Et}$, DCM k) DIBAL-H , DCM l) $m\text{-CPBA}$, DCM m) $\text{Me}_2\text{CuCNLi}_2$, THF n) PPTS, anisaldehyde dimethyl acetal, DCM o) DIBAL-H , toluene p) DOWEX-50, MeOH q) $(\text{COCl})_2$, DMSO, Et_3N , DCM r) NaClO_2 , 2-methyl-2-butene, Na_2HPO_4 , $t\text{-BuOH}$

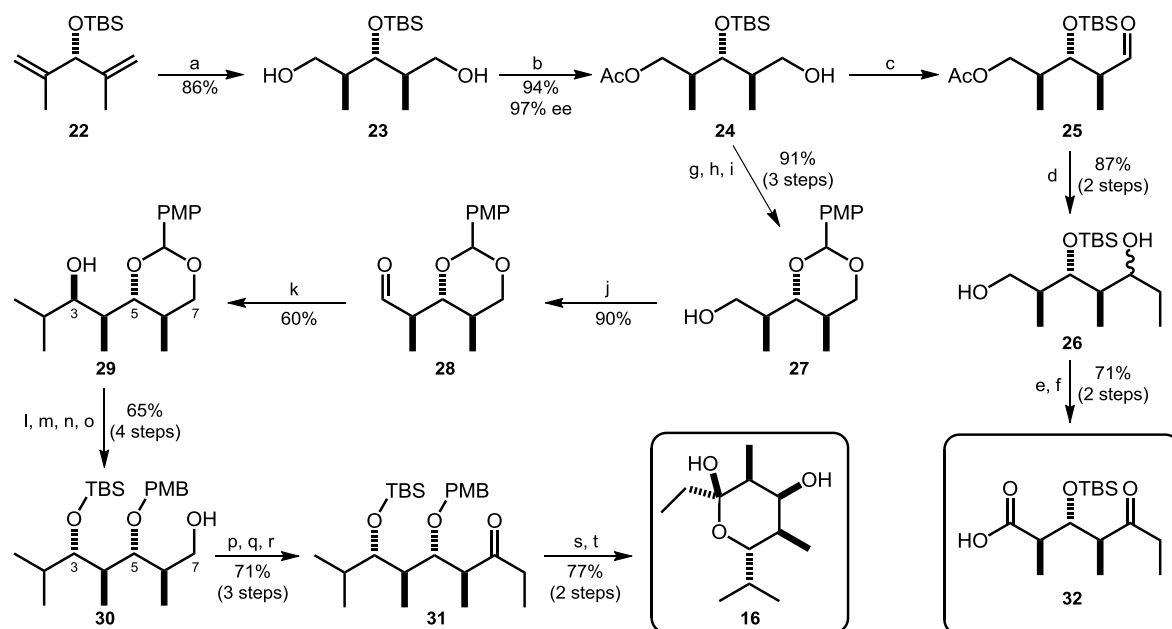
Scheme 1.6: Dias Route to Dolabriferol

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. Omitting

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**.⁸



a) 9-BBN, NaOOH b) *Candida rugosa* lipase, vinyl acetate, hexane c) Dess-Martin periodinane, DCM d) EtMgBr, THF e) (COCl)₂, DMSO, Et₃N, DCM f) RuCl₃, NaIO₄, CCl₄, H₂O, MeCN g) TBAF, AcOH, THF h) TsOH, anisaldehyde dimethyl acetal, DCM i) KOH, MeOH j) Dess-Martin periodinane, DCM k) Mg_(s), isopropyl bromide, THF l) Dess-Martin periodinane, pyridine, DCM m) LiAlH₄, THF n) TBSOTf, 2,6-lutidine, DCM o) DIBAL-H, DCM p) Dess-Martin periodinane, pyridine, DCM q) EtMgBr, THF r) Dess-Martin periodinane, pyridine, DCM s) DDQ, H₂O, DCM t) TBAF, AcOH, THF

Scheme 1.7: Chenevert Route to Dolabiferol

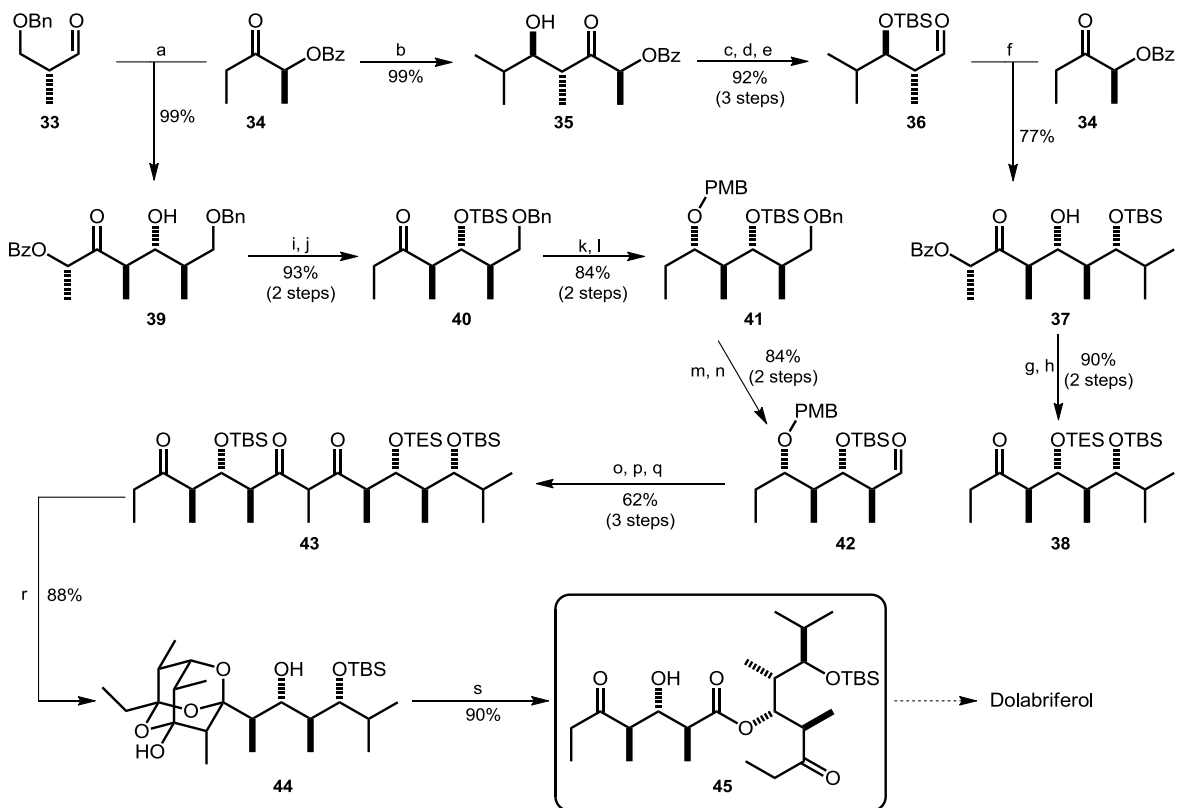
With acid fragment **32** synthesized, formation of lactol **16** was pursued and envisioned to come from intermediate **24**. Desilylation of **24**, protection of the resulting 1,3 diol as its *p*-methoxybenzylidene acetal, and base induced ester hydrolysis gave **27**. Formation of aldehyde **28** 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).⁹ 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 debenzoylation 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 Sml_2 induced benzoate cleavage gave ketone **38**.



a) Cy_2BCl , Me_2Net , Et_2O b) Cy_2BCl , Me_2Net , isobutyraldehyde, Et_2O c) TBSOTf, 2,6-lutidine, DCM d) LiBH_4 , THF e) NaIO_4 , MeOH, H_2O f) Cy_2BCl , Me_2Net , Et_2O g) TESOTf, 2,6-lutidine, DCM h) Sml_2 , THF, MeOH i) TBSOTf, 2,6-lutidine, DCM j) Sml_2 , THF k) NaBH_4 , EtOH l) PMB-imidate, Et_2O m) W2-RANEY[®] nickel, EtOH n) Dess-Martin periodinane, DCM o) LiHMDS, THF p) DDQ, DCM q) $(\text{COCl})_2$, DMSO, Et_3N , DCM r) $\text{HF}\cdot\text{pyridine}/\text{pyridine}$, THF s) DBU, C_6D_6

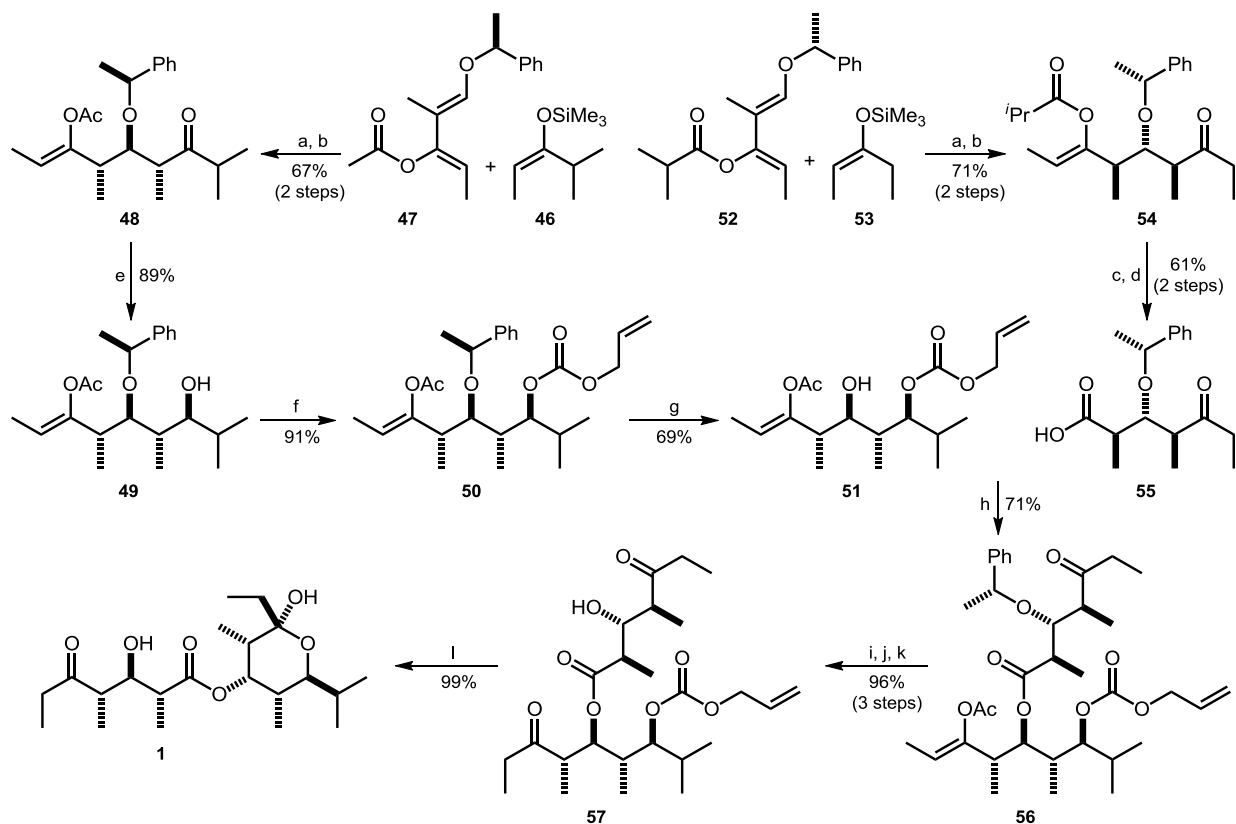
Scheme 1.8: Lister/Perkin's Route to Dolabiferol

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 $\text{HF}\cdot\text{pyridine}/\text{pyridine}$ 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 dolabiferol (31% yield, 12 steps).¹⁰

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 SO₂ umpolung, allowed for rapid access to α,β,γ -*anti,anti*-stereotriads in a one-pot reaction. Dolabriferol contains two α,β,γ -*anti,anti*-stereotriads which allowed both fragments to be assembled in similar fashion.⁵ 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**.



a) SO_2 , Tf_2NH , DCM b) $\text{Pd}(\text{OAc})_2$, PPh_3 , *i*PrOH, MeCN, K_2CO_3 c) O_3 , DCM d) Me_2S , H_2O e) Me_2AlCl , Bu_3SnH , DCM f) allyl chloroformate, pyridine, THF g) TiCl_4 , DCM h) 2,4,6-trichlorobenzoyl chloride, Et_3N , DMAP, toluene i) Bu_3SnOMe j) KF , H_2O k) CF_3COOH , anisole, DCM l) $\text{Pd}(\text{OAc})_2$, Et_2NH , TPPTS, MeCN/ H_2O

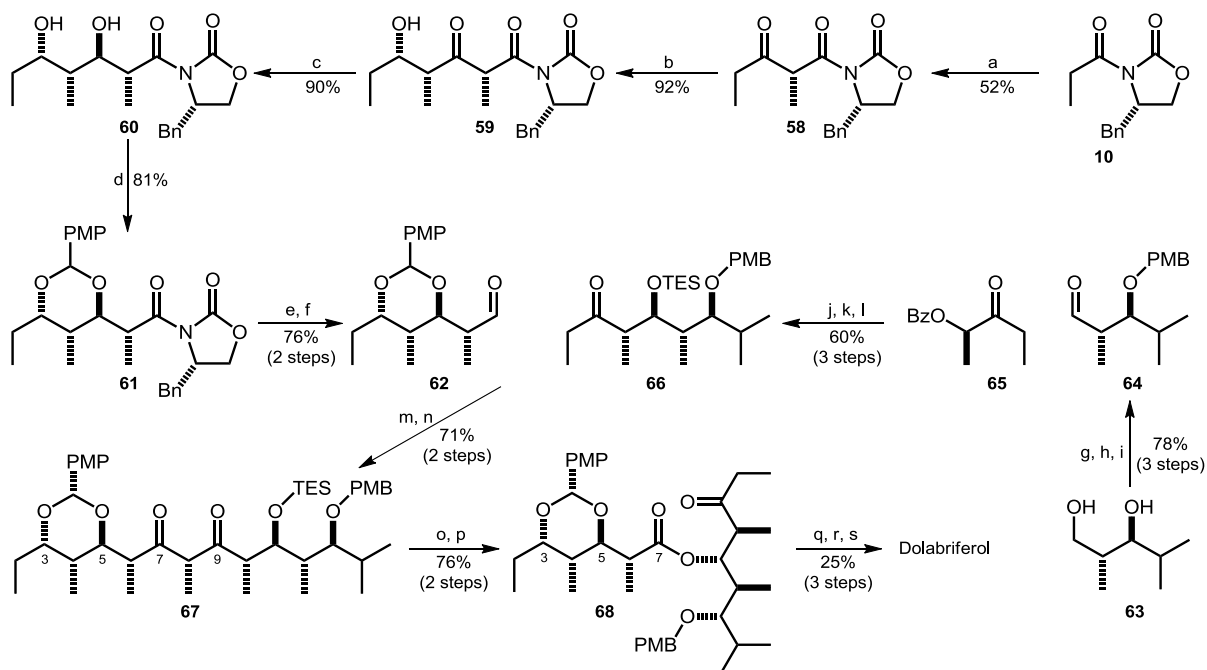
Scheme 1.9: Total Synthesis of Dolabriferol by Vogel

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 $\text{Sn}(\text{OTf})_2$ mediated aldol was envisioned to couple fragments **62** and **66**. These two fragments were assembled starting from

Evans' β -ketoimide **10** and diol **63** synthesized using MacMillan's organocatalytic cross-aldol methodology.



a) EtCOCl, LDA, MgBr₂•Et₂O, THF b) TiCl₄, DIPEA, EtCHO, DCM c) Me₄NBH(OAc)₃, AcOH, MeCN d) anisaldehyde dimethyl acetal, TsOH e) LiBH₄, MeOH, THF f) (COCl)₂, DMSO, Et₃N, DCM g) anisaldehyde dimethyl acetal, TsOH h) DIBAL-H, DCM i) (COCl)₂, DMSO, Et₃N, DCM j) Cy₂BCl, Et₃N, DCM k) TESOTf, 2,6-lutidine, DCM l) SmI₂, THF, MeOH m) Sn(OTf)₂, Et₃N, DCM n) Dess-Martin periodinane, NaHCO₃, DCM o) HF•pyridine/pyridine, THF p) DBU, benzene q) CSA, MeOH r) Dess-Martin periodinane, NaHCO₃, DCM s) DDQ, pH buffer 7, DCM

Scheme 1.10: Total Synthesis of Dolabiferol by Goodman

Addition of propionyl chloride to the lithium enolate of oxazolidinone **10** gave the desired β -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 LiBH₄ 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 ^1H 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

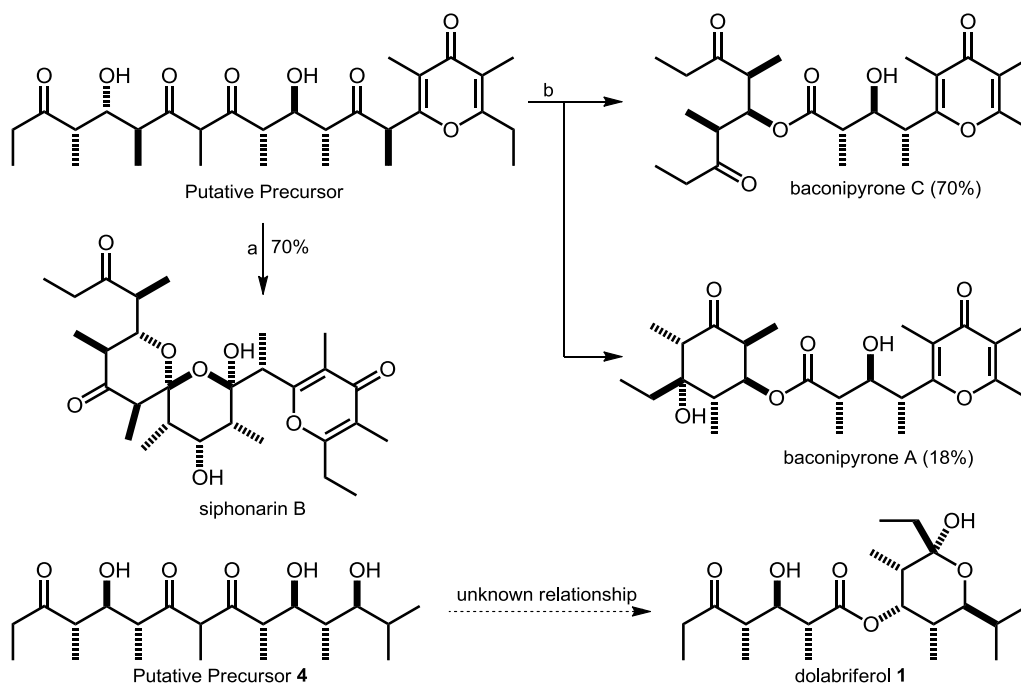
The above approaches towards the synthesis of dolabriferol show that the synthesis of the target molecule is challenging. Forming the ester linkage between the two final fragments being unsuccessful with the methods tested. Although the route by Vogel is elegant and allowed for the absolute configuration 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 trioxadamantane. This highly unusual ring system has been identified in only two siphonariid natural products: muamvatin¹² and caloundrin B¹³, 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, baconipyronone A, baconipyronone C, siphonarins B, and muamvatin have been synthesized from their putative 'acyclic' precursors suggesting that perhaps these acyclic precursors are the biosynthetic products (Scheme 2.1).^{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.



a) imidazole b) aluminum oxide activated basic

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.

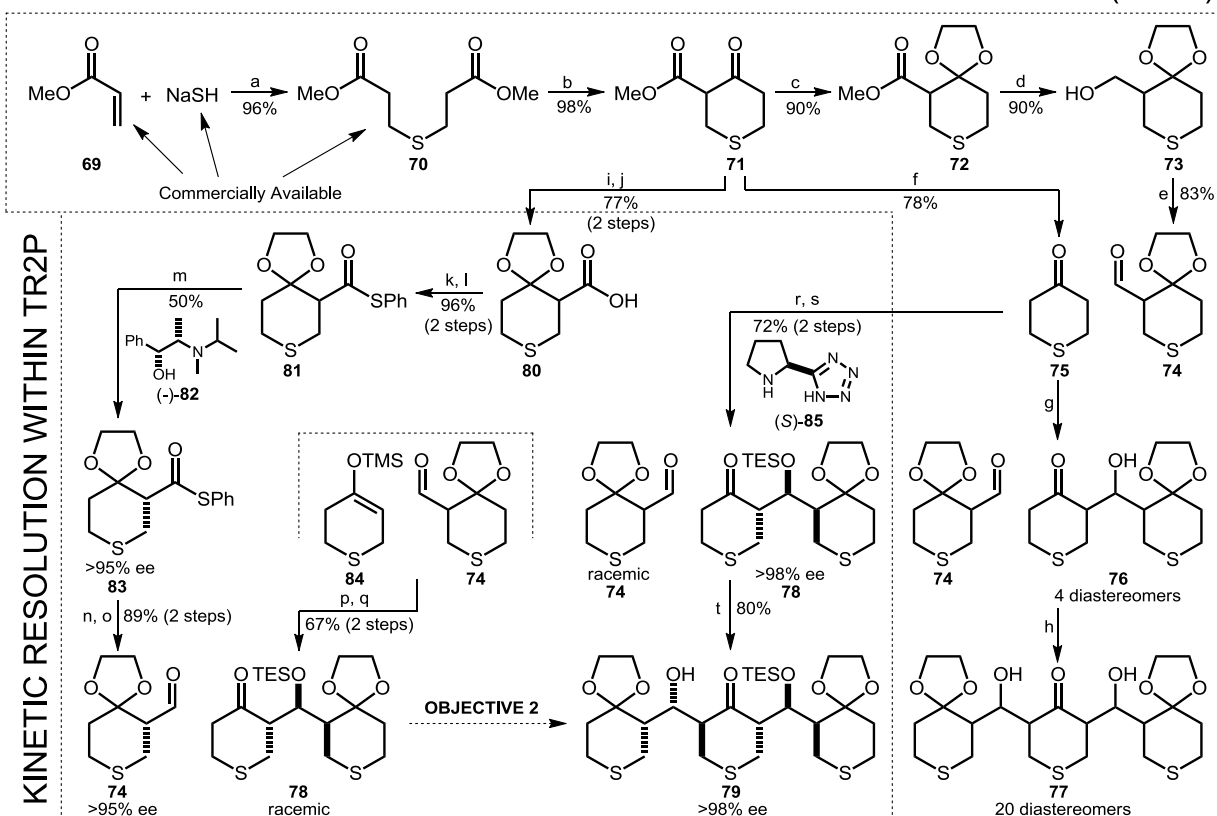
2.2. The Thiopyran Route to Polypropionates

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.¹⁵ This route begins with commercially available diester **70** which is prepared from inexpensive methyl acrylate **69** and sodium hydrosulfide.¹⁶ Dieckmann cyclization of **70** with sodium methoxide gives β -ketoester **71**¹⁷ which is subsequently subjected to acetal protection, lithium aluminum hydride reduction, and oxidation with IBX to yield the desired aldehyde **74**.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.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**.

THIOPYRAN ROUTE TO POLYPROPIONATES (TR2P)



a) NaHCO_3 b) Na, MeOH c) ethylene glycol, TsOH (cat.), benzene, reflux d) LiAlH_4 , THF e) IBX, MeCN f) 10% H_2SO_4 , reflux g) ref 16 h) ref 17 & 18 i) ethylene glycol, TsOH (cat.), benzene, reflux j) NaOH, H_2O , MeOH k) $(\text{COCl})_2$, benzene l) thiophenol, Et_3N , THF m) *s*-BuLi then (-)-**82**, THF n) LiAlH_4 , THF o) Dess-Martin periodinane, H_2O , DCM p) MeLi q) TESOTf, pyridine, DCM r) (*S*)-**85** (20 mol%), wet DMSO s) TESOTf, pyridine, DCM t) BCl_2 , Et_3N , DCM

Scheme 2.2: Thiopyran Route to Polypropionates and Kinetic Resolution

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.^{20,21} 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**).²⁰ The same

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),^{3,14,22} 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.

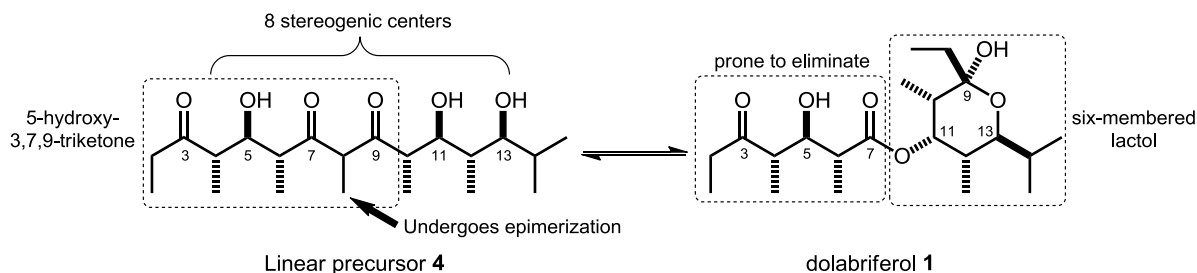


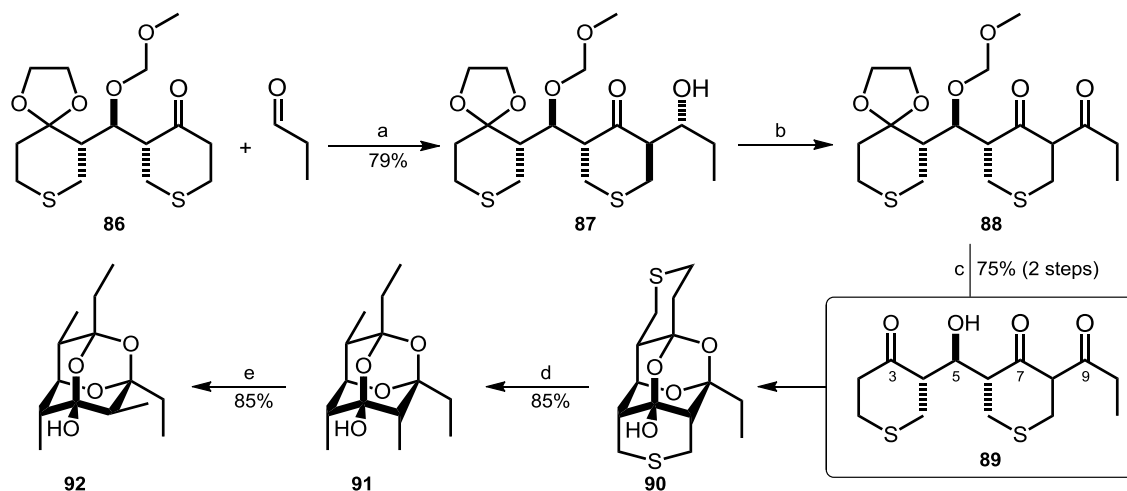
Figure 2.1: Structural Features of Dolabriferol and its Linear Precursor

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 trioxadamantane intermediate is particularly intriguing from a synthetic standpoint. Incorporating this tricyclic moiety may provide a very concise solution to the total synthesis of

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.

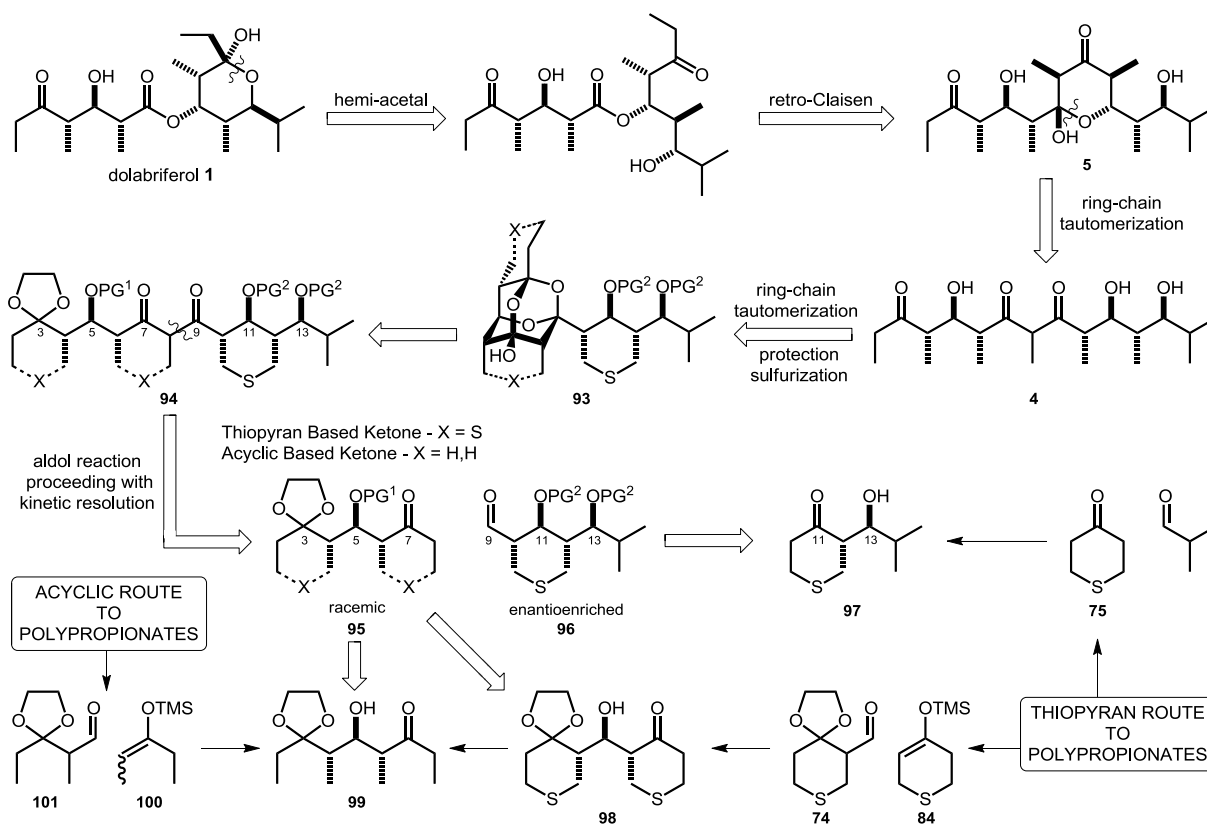


a) Cy_2BCl , Et_3N b) IBX c) $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ d) RANEY® Nickel e) imidazole

Scheme 2.3: Formation of Trioxaadamantane Ring System

The trioxaadamantane ring system has only been identified in two natural products to date: muamvatin¹² and caloundrin B¹³, 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**.²³ Under thermodynamic control, compound **89** undergoes ring-chain tautomerism forming the dithiapentacycle **90**.²³ Subjecting **90** to RANEY® nickel removes the sulfur atoms producing compound **91** containing a destabilizing *syn*-pentane interaction.²³ Allowing this thermodynamically unstable compound to isomerize in the presence of imidazole provides the desired ring system **92** exclusively.²³

Because the trioxadamantane 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 trioxadamantane 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 dolabiferol. 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

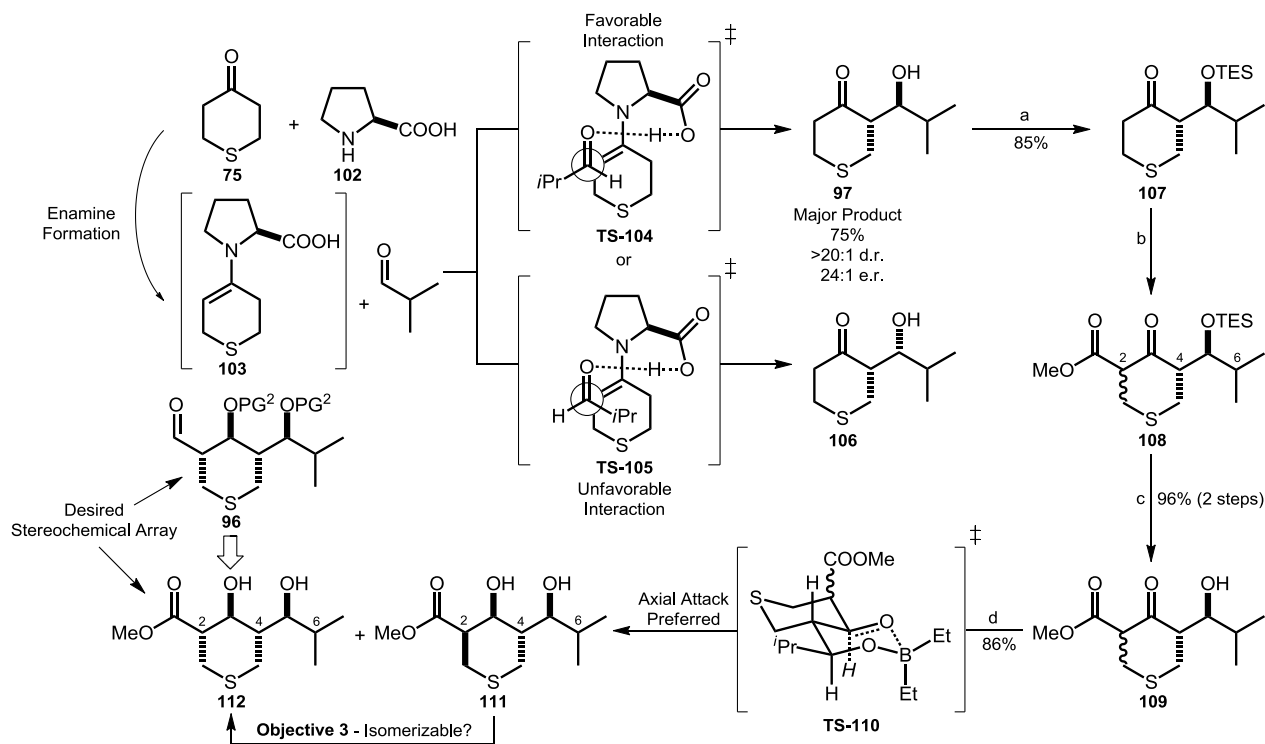
Disconnection of the C-8 and C-9 bond in **94**, leads to ketone **95** and aldehyde **96** as desired precursors (Scheme 2.4). The disconnection here is beneficial for synthetic reasons in the forward coupling sequence. The aldol coupling of ketone **95** and aldehyde **96** represent a matched pair 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 trioxadamantane **93**. An ongoing theme within the Ward group is the development of reactions that proceed with kinetic resolution.^{3,20} This approach to coupling chiral fragments

presents a powerful tool that is usually overlooked. Since both ketone **98**²⁴ 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.²⁵ 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 Polypropionates”.²⁶

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.²⁵ The synthesis of diol **111** and **112** has previously been accomplished by Pramod Jahdav, a former Ward group member.²⁷ 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**.



a) TES-Cl, Et₃N, DCM b) ^tBuLi, then methyl cyanoformate, THF c) 5% HF, MeCN d) Et₂BOMe, NaBH₄, THF:MeOH (4:1)

Scheme 2.5: Early Stage Preparation of Enantioenriched Aldehyde

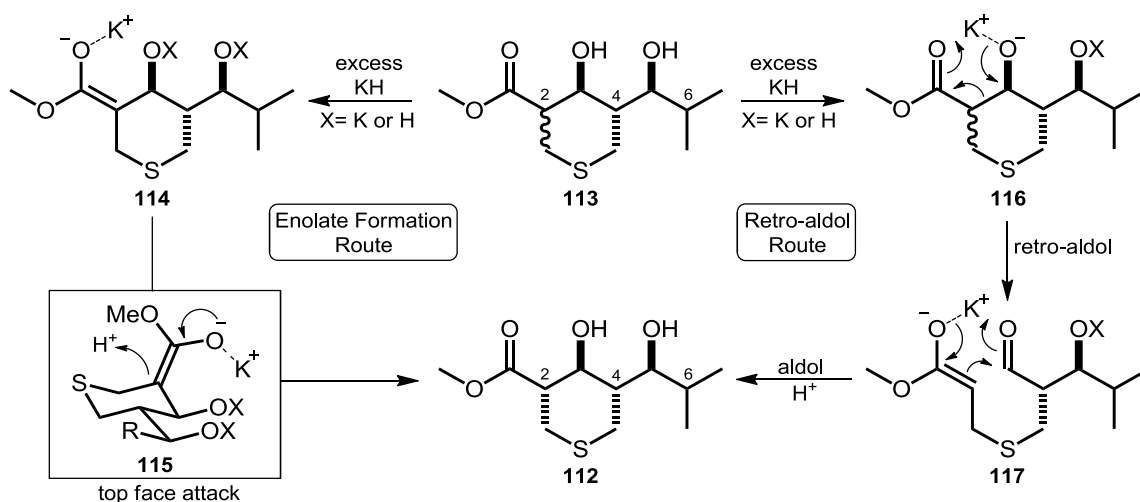
The use of (*S*)-proline allows for achiral ketone **75** to be transformed into the corresponding enantiopure enamine **103** which then reacts with isobutyraldehyde through two possible transition states, **TS-104** or **TS-105**. In **TS-105**, reaction of the *si* face of the aldehyde orients the 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 diastomeric 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 ^tBuLi to form the lithium enolate which underwent carbonylation with Mander's reagent (methyl cyanofornate) to give an equilibrating mixture of β -ketoesters **108**.²⁷ 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.²⁷ *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.²⁷ Under these

conditions, **111** underwent isomerization at C-2 giving the desired compound **112** as the only product. Exploiting this phenomenon could provide a convergent synthesis to the desired 2,3-*trans* diol **112** from a mixture of **111** and **112**.

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 **113** can undergo two pathways for isomerization: enolate formation followed by selective protonation to give **112**; a retro-aldol to break the thiopyran template forming the acyclic enolate **117** which then undergoes selective aldol addition. In both routes the mixture is transformed into the presumed more thermodynamically stable, 2,3-*trans* compound **112** which has all substituents of the chair in equatorial positions.



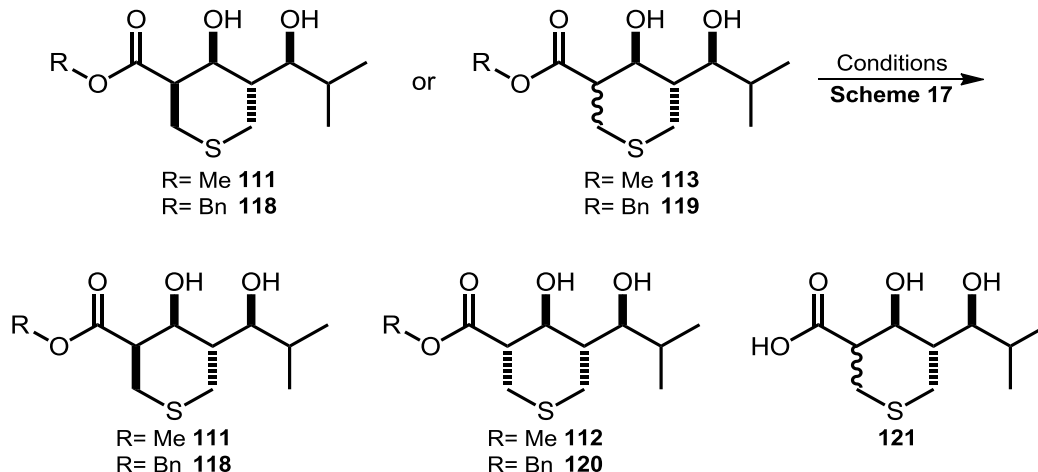
Scheme 2.6: Possible Routes to Isomerization

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 **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 KHMDS 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 dolabiferol. This problem was extensively studied by Naveen Diddi, a colleague in the Ward group.²⁸

Table 2.1: Optimized Isomerization Results

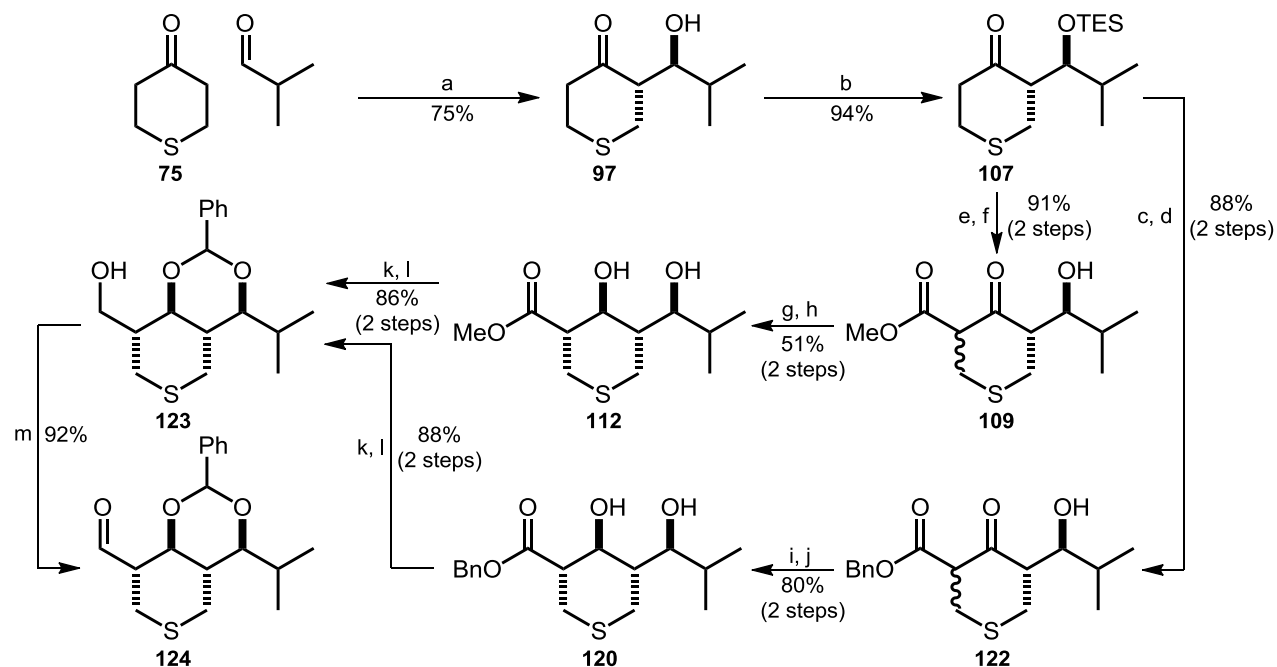


Entry	SM	Conditions (Base)	Product Distribution (%) ^a				
			111	112	118	120	121
KH, 0 °C, 2 h							
1	113	3 equiv.		100%			
2	113	3 equiv.	30%	70%			
KHMDS, -78 °C, 1 h							
3	113	1 equiv.	38%	62%			
4	113	2 equiv.	25%	75%			
5	113	3 equiv.	18%	82%			
6	112	2 equiv.		100%			
7	111	2 equiv.	25%	75%			
NaH, 0 °C, 24 h							
8	111	2 equiv.					100%
KO^tBu, Et₂O							
9	111	2 equiv.		80% ^b			
10	119	2 equiv.					76% ^b
KO^tBu, CuI, Et₂O							
11	111	2 equiv.		85% ^b			
12	113	2 equiv.		61% ^b			
13	119	2 equiv.					93% ^b

^a By ¹H NMR spectroscopy unless otherwise indicated ^b Isolated yield

Having demonstrated that the desired transformation to streamline the synthesis was possible, the base was switched to potassium *tert*-butoxide.²⁸ 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).²⁸ 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).²⁸



a) (*S*)-proline, DMSO b) TES-Cl, Et₃N, DCM c) ^tBuLi, then benzyl cyanofornate, THF d) 5% HF, MeCN e) ^tBuLi, then methyl cyanofornate, THF f) 5% HF, MeCN g) Et₂BOMe, NaBH₄, THF:MeOH (4:1) h) KO^tBu, CuI, Et₂O i) Et₂BOMe, NaBH₄, THF:MeOH (4:1) j) KO^tBu, CuI, Et₂O k) dimethoxyphenylmethane, TsOH, DCM l) LiAlH₄, THF m) oxalyl chloride, DMSO, Et₃N, DCM

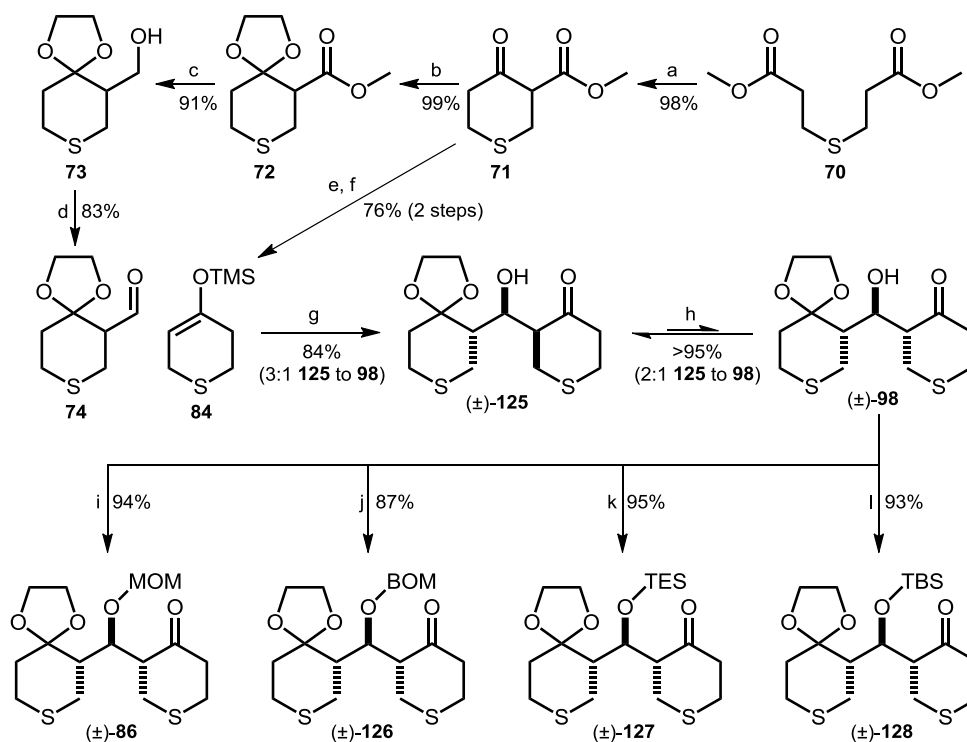
Scheme 2.7: Overview on the Synthesis of Enantioenriched Aldehyde

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 neutral²⁹ and acidic media³⁰. 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.²⁸

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.²⁰ 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 β -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**.



a) Na, MeOH b) ethylene glycol, TsOH, benzene, reflux c) LiAlH₄, THF d) IBX, MeCN e) 10% H₂SO₄, reflux f) TMS-Cl, TEA, CHCl₃ g) MgBr₂•OEt₂, DCM h) imidazole, DCM i) MOM-Cl, DIPEA, DCM j) BOM-Cl, DIPEA, DMF k) TES-OTf, 2,6-lutidine, DCM l) TBS-OTf, 2,6-lutidine, DCM

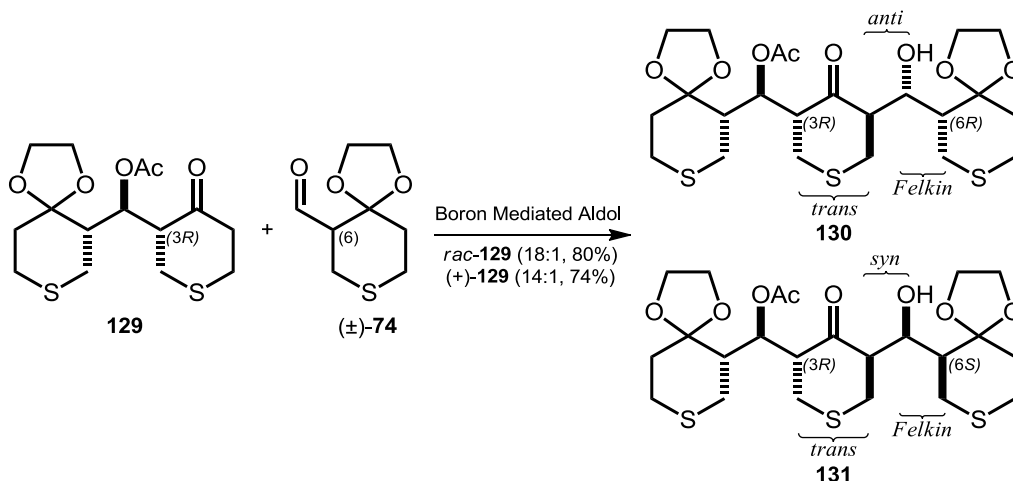
Scheme 2.8: Preparation of Various Protected *anti-anti* Ketones

Silyl enol ether **84** and aldehyde **74** were subjected to Mukaiyama aldol conditions in the presence of MgBr₂•OEt₂ to form a mixture of *syn-anti* **125** and *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 *anti-anti* aldol **98**.

Subjection of **125** to imidazole induced isomerization to provide a 2:1 mixture of **125** and **98** respectively.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 (\pm)-**86**²¹, (\pm)-**126**, (\pm)-**127**²¹, and (\pm)-**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.^{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 dolabiferol).²¹ 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_2BCl , TEA) of (\pm)-**129** with (\pm)-**74** gave racemic *trans-anti-Felkin* adduct **130** selectively (dr 18:1, 80% yield). This result suggests that reaction of the (3*R*)-enantiomer of **129** with the (6*R*)-enantiomer of **74** is highly diastereoselective and much faster than the alternative reaction with (6*S*)-**74** (Similarly, (3*S*)-**129** must react preferentially with (6*S*)-**74**). By substituting the racemic ketone with its enantioenriched counterpart **129** (91% ee), reaction with (\pm)-**74** under identical conditions, should give diastereomer **130** with similar diastereoselectivity but the products will be enantioenriched. As predicted, reaction of (+)-**129**

reacting and slow-reacting enantiomers, and this ratio (k_{fast}/k_{slow} , defined as stereoselectivity factor, or S) controls the product distribution.

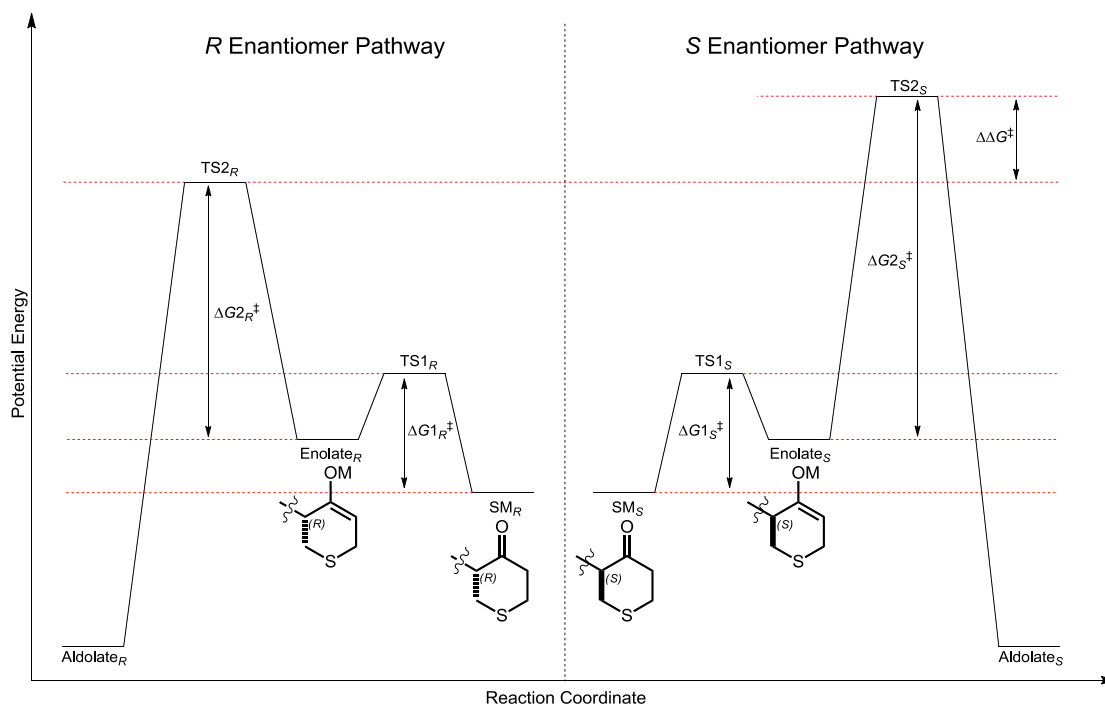


Figure 2.2: Energy Diagram of a Reaction Proceeding with Kinetic Resolution

Due to the fact that two enantiomeric species are reacting simultaneously at different rates, the relative concentrations of SM_R/SM_S and $Aldol_R/Aldol_S$ 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.

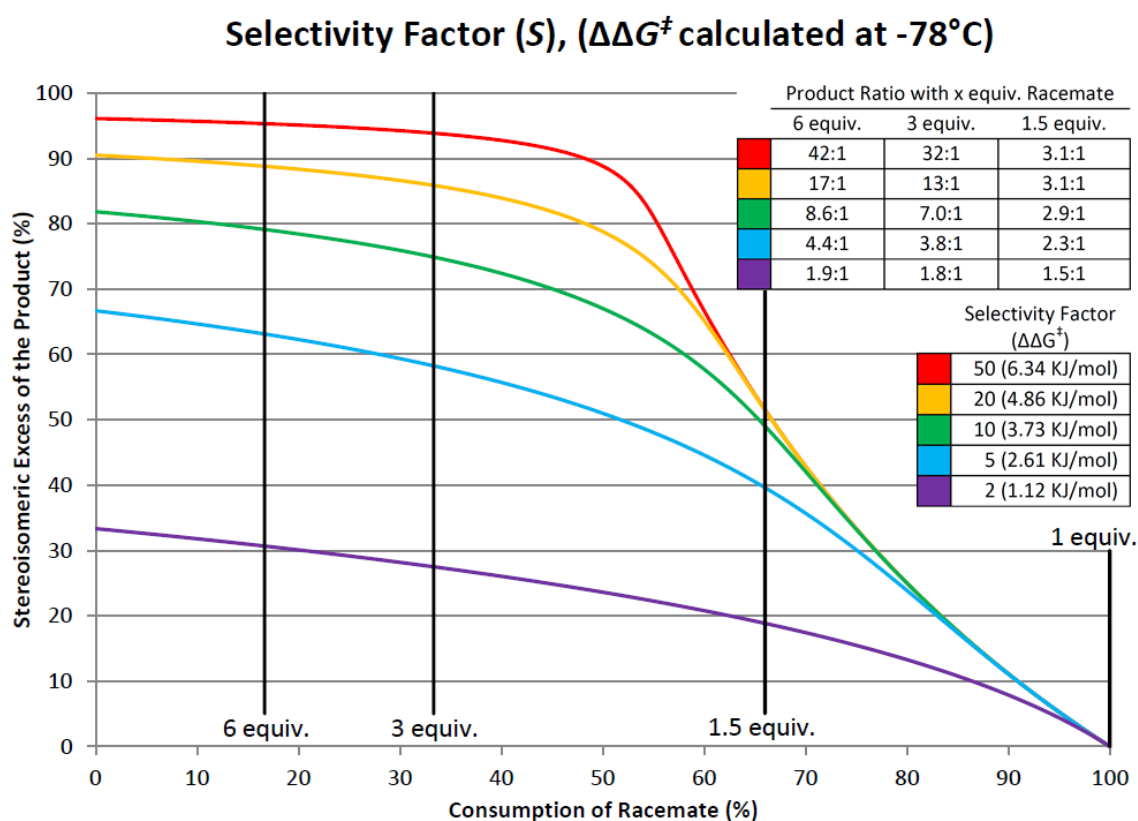


Figure 2.3: Effect of Selectivity Factor on Stereoisomeric Excess

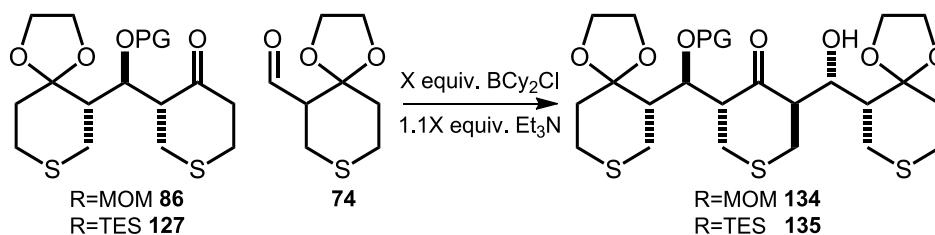
The concept of an aldol reaction proceeding with kinetic resolution is exactly the same regardless of which fragment is racemic and which is enantioenriched. Although Figure 2.3 sheds light on reaction design, the equations used assume pseudo first-order kinetics for the substrate and does not account 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 Cy_2BCl and Et_3N 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).²¹ When the same reaction was conducted with one equivalent of BCy_2Cl , 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 BCy_2Cl to proceed in high yield.

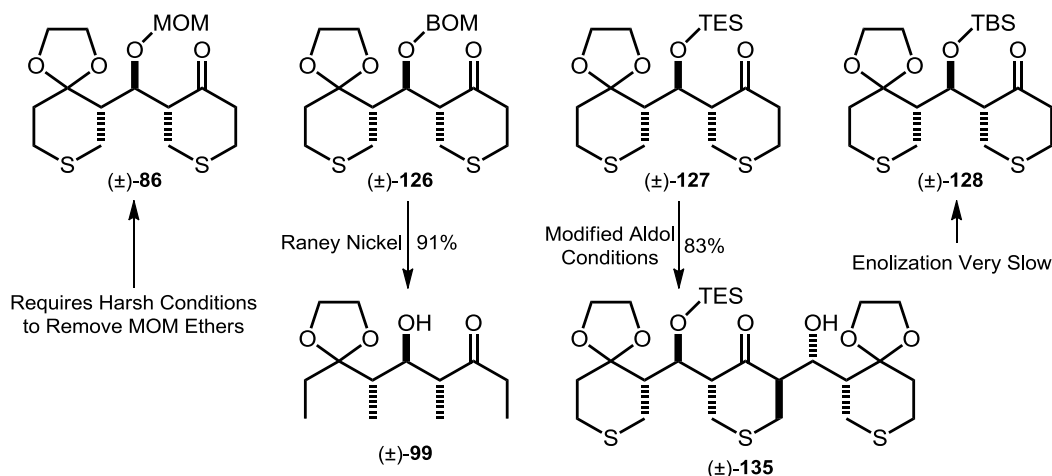
Table 2.2: Effect of Aldehyde and Mediator Equivalents on Reaction Yield

Entry	Ketone (1 equiv.)	Equiv. 74	Equiv. BCy ₂ Cl	Equiv. ^t BuNH ₂	Product (yield, dr)
1	86	3	2	0	134 (80%, 13:1)
2	86	3	1	0	134 (35%, 13:1)
3	86	0.5	2	0	No Reaction
4	127	3	2	0	135 (87%, 10:1)
5	127	0.50	2	2	135 (83%,10:1)

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.³¹ 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

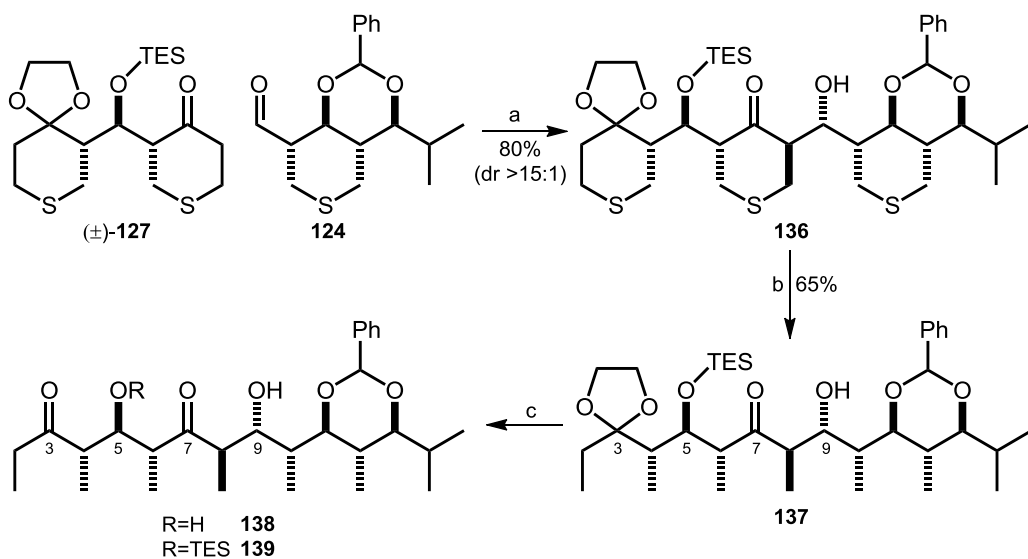
(Table 2.2, entry 4). The excess borane remaining is reactive towards aldehydes causing an unwanted side reaction which ultimately leads to decomposition but with the excess aldehyde **74** this decomposition does not affect the yield. If, *tert*-butyl amine were added before aldehyde addition, the reactive 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

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).



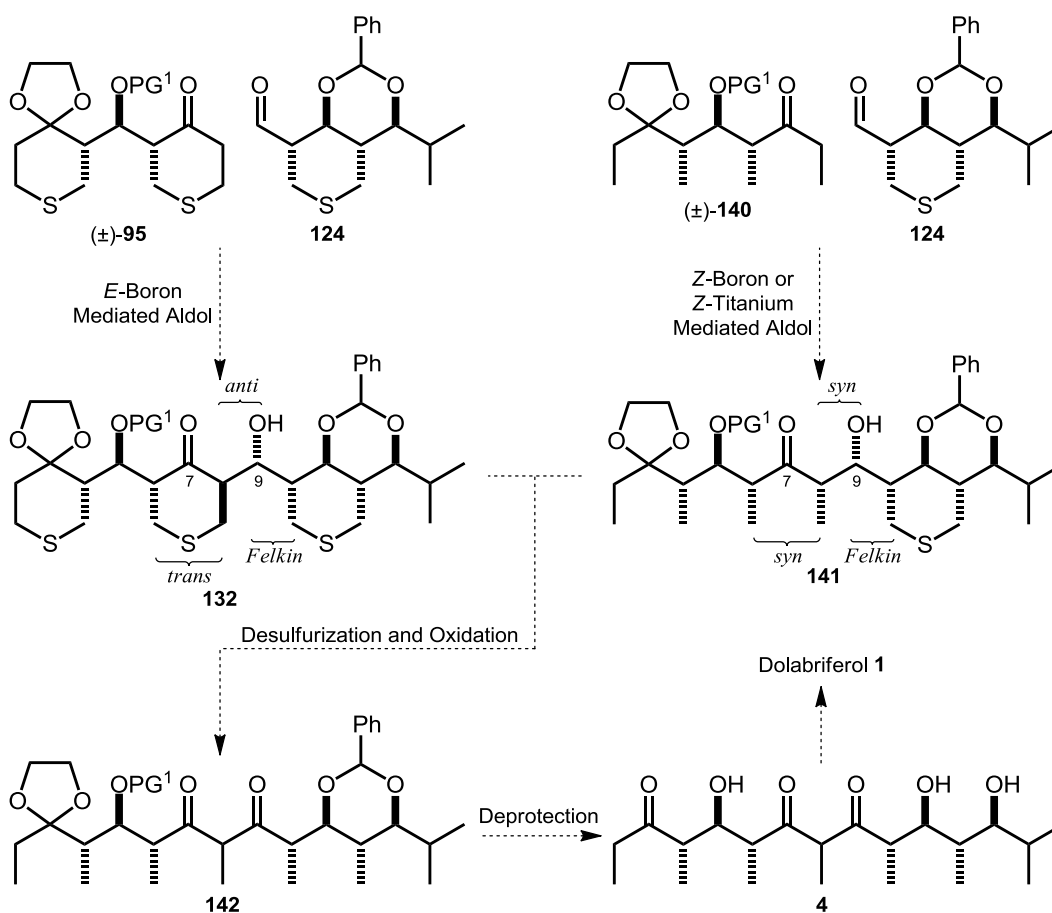
a) BCl_2 , Et_3N , $t\text{BuNH}_2$, DCM b) RANEY® Nickel, EtOH, reflux c) Various Deprotection Conditions

Scheme 2.12: Aldol Coupling and Synthetic Attempts to Linear Precursor

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, reprotection 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**.

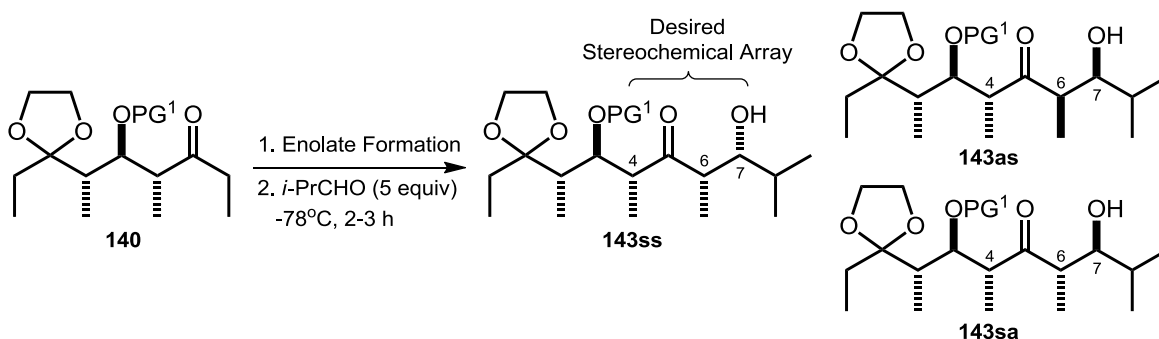


Scheme 2.13: Redesign of Aldol Coupling Partners on the Path to Dolabiferol

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.²⁷ 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

examples total) and clearly demonstrates that the aldol diastereoselectivities are influenced by the relative configuration, protecting group, and enolate type.²⁷

Table 2.3: Effect of Mediator and Protecting Group on Stereoselectivity



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

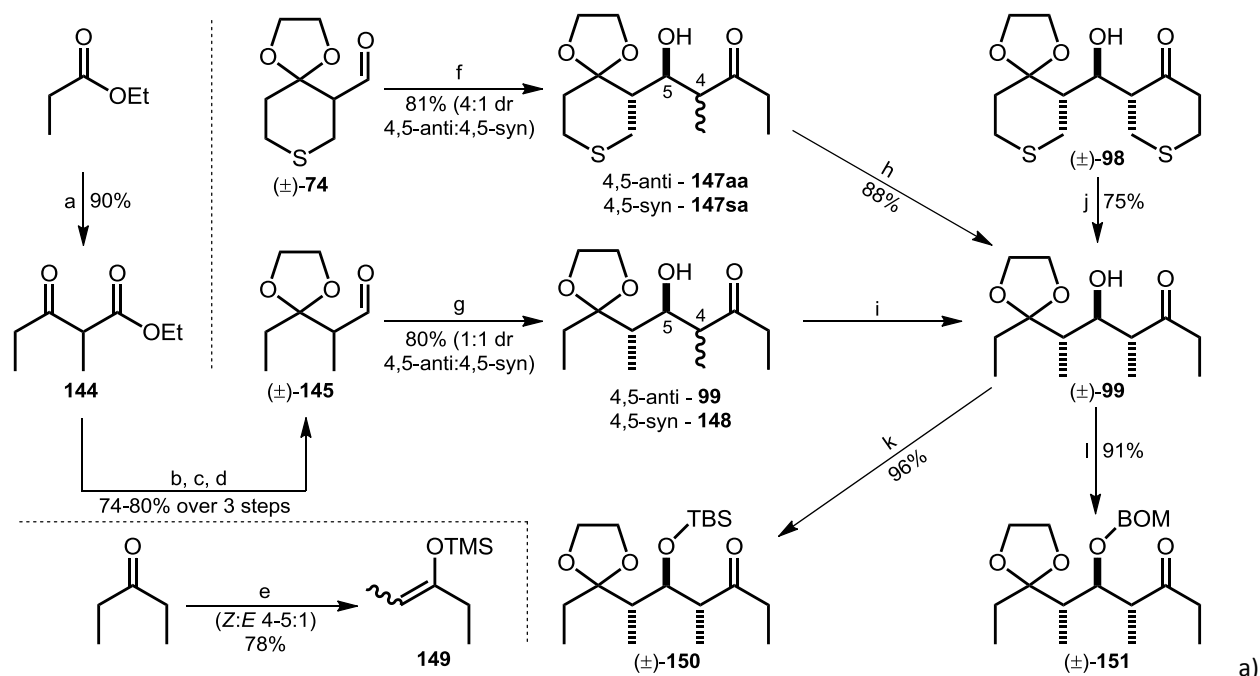
^aDetermined by ¹H NMR of the crude reaction mixture. ^bEstimated from the ratio of adducts to starting ketone present in the crude reaction mixture by ¹H NMR. ^cIsolated yield of the major adduct (isolated yield of minor adduct in parentheses).

Of particular interest were reactions of the (*Z*)-boron and (*Z*)-titanium enolates of ketone **140** with isobutyraldehyde (Table 2.3). The major compound in all examples was the 4,6-*syn*-6,7-*syn* diastereomer **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 **140** by reaction of the lithium (*Z*)-enolate with TiCl(O*i*-Pr)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 **140** with aldehyde **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

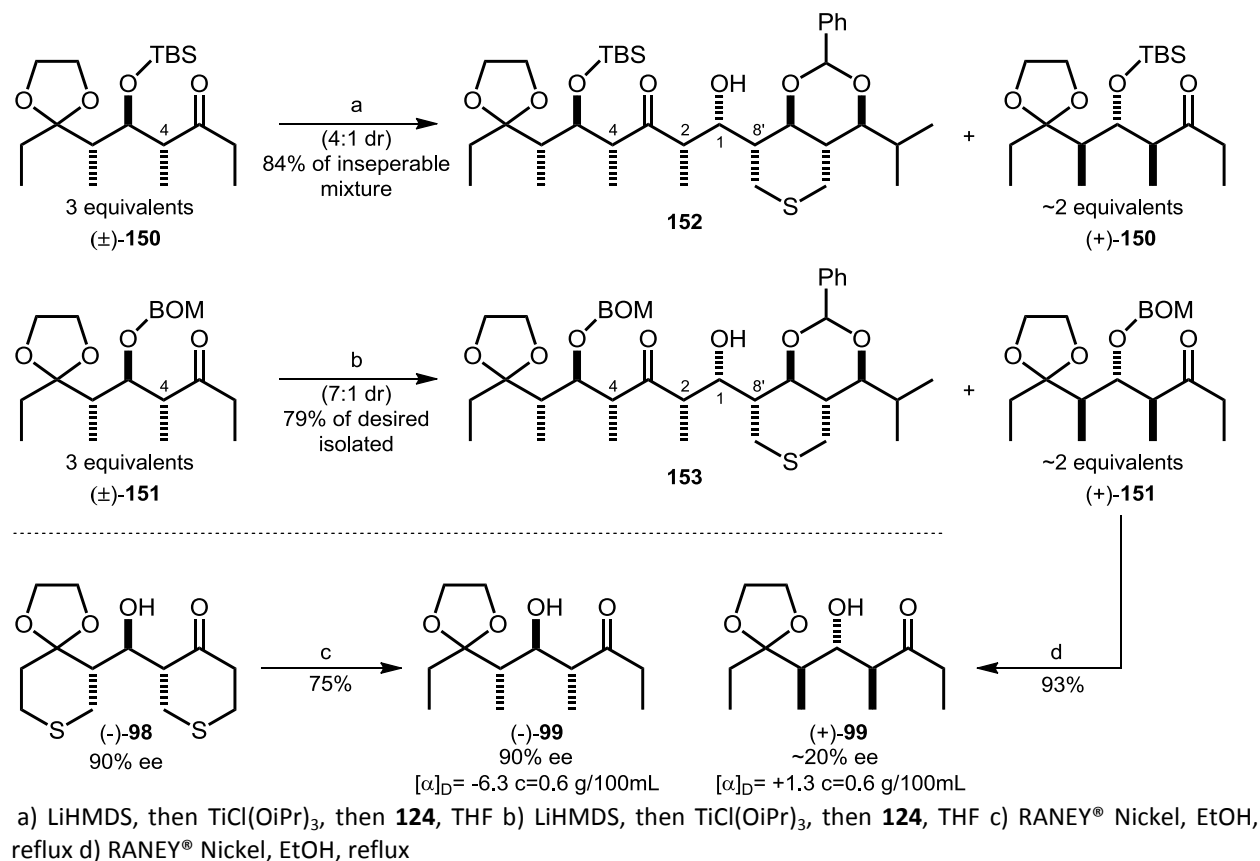


KO^tBu, THF b) ethylene glycol, TsOH, Benzene, reflux c) LiAlH₄, THF d) IBX, MeCN, Δ or oxalyl chloride, DMSO, Et₃N, DCM e) TMS-Cl, NaBr, DMF f) **149**, MgBr₂•Et₂O, DCM g) **149**, MgBr₂•Et₂O, DCM h) RANEY® Nickel, EtOH, reflux i) Separation of Isomers j) RANEY® Nickel, EtOH, reflux k) TBS-Cl, Et₃N, DMF l) BOM-Cl, DIPEA, DMF

Scheme 2.14: Various Synthetic Routes to Access Acyclic Ketone **99**

With aldehyde **145** in hand, the next step required the preparation of silyl enol ether **149**²⁷ and subjection to Mukaiyama aldol conditions. Reaction of **145** with **149** mediated by MgBr₂•OEt₂ gave a 1:1 mixture of the desired *anti-anti* **99** and *syn-anti* **148** in good yield.²⁷ 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.³² 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 4*R* 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 Acyclic 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 4*R*-enantiomer during coupling, the recovered **151** should be enriched in the 4*S*-enantiomer. Desulfurization by a known method²⁷ of (-)-**98** (90% ee) gave (-)-(4*R*)-**99** (90% ee, [α]_D= -6.3). Similarly, deprotection of ketone (+)-**151**

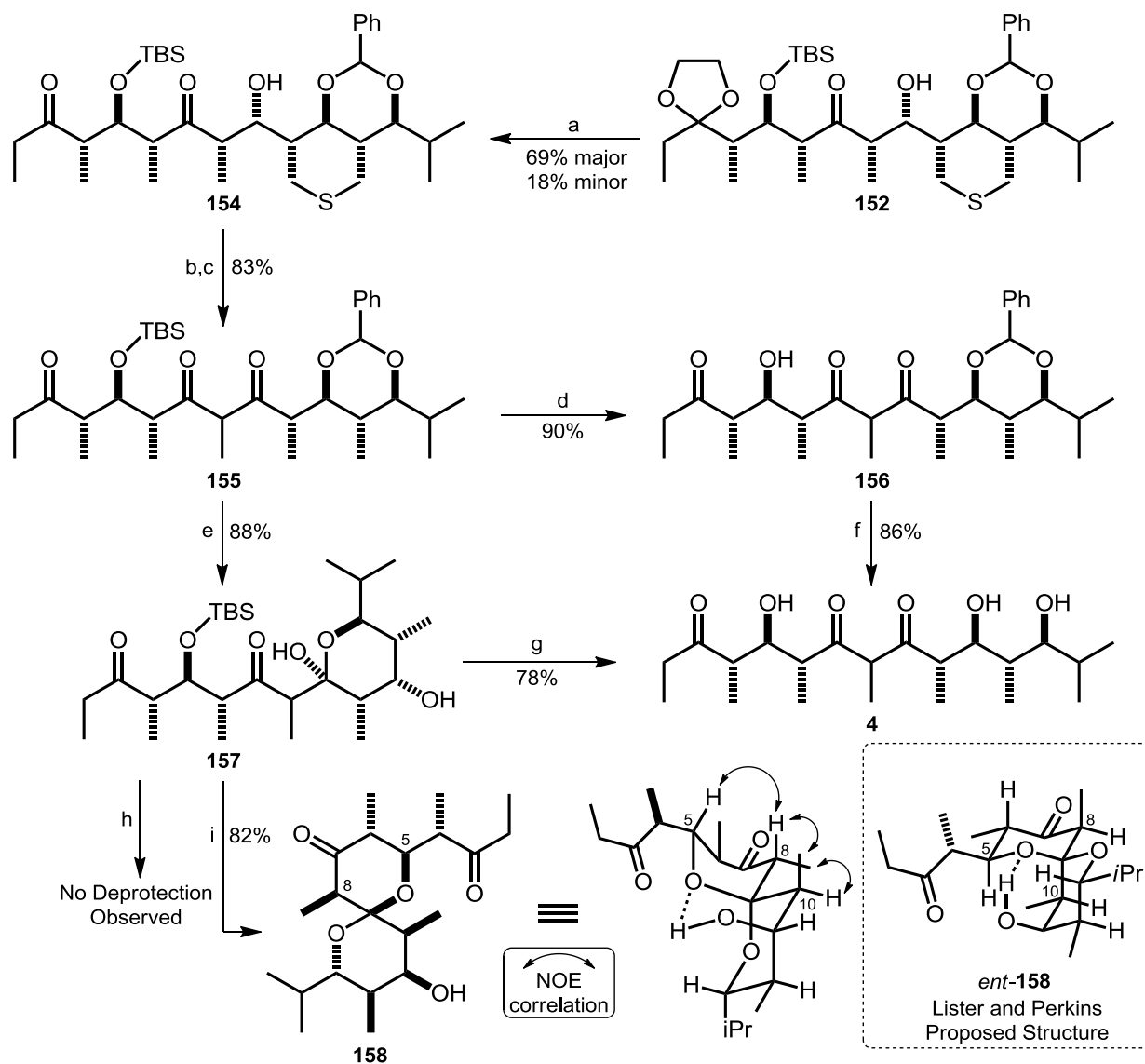
with RANEY® Nickel gave (+)-**99** ($[\alpha]_D = +1.3$) that must be enriched in the 4*S* enantiomer. Two important conclusions follow from this result. Firstly, the expected 4*R* enantiomer of **151** must have reacted preferentially during the aldol coupling. Secondly, the magnitude of the recovered **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 (\pm)-**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 benzylidene 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 benzylidene 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 dolabiferol 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.¹⁰ 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.



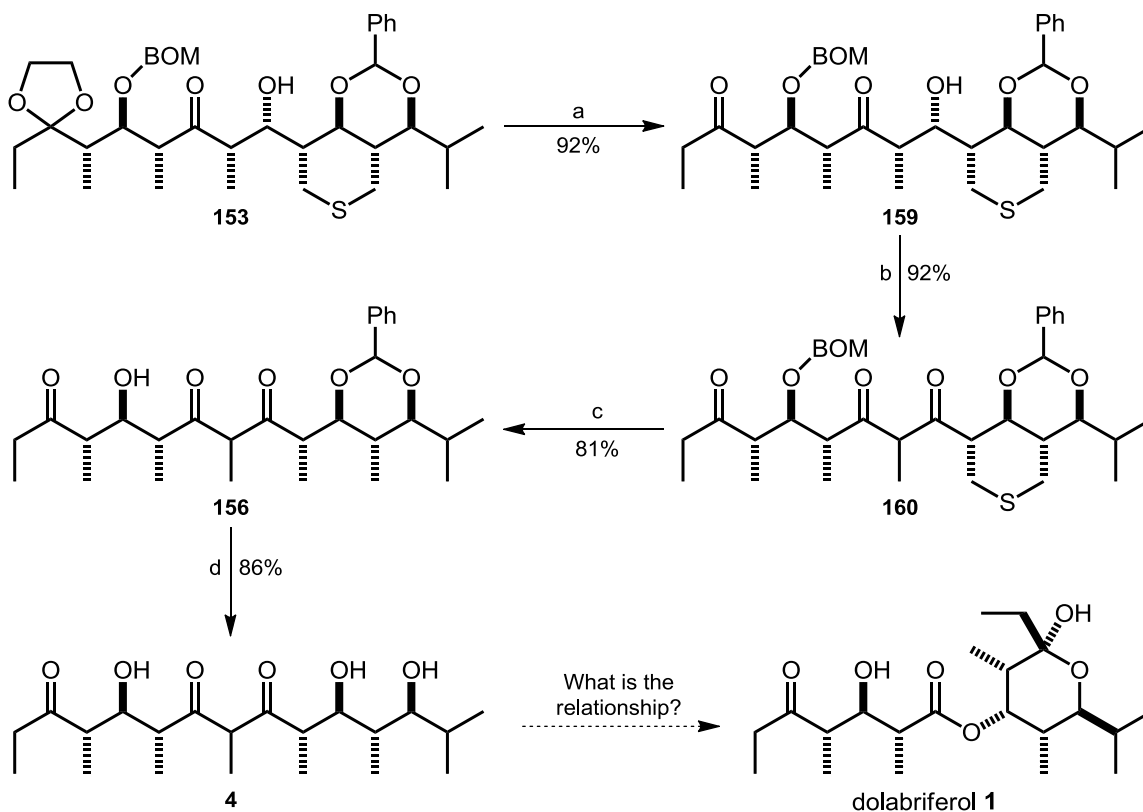
Scheme 2.16: Final Deprotection Sequence of TBS Route to Linear Precursor **4**

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 C_6D_6 solution (Scheme 2.16). The linear precursor **4** can also be obtained by hydrogenolysis of **156** (11.4% overall, 16 steps from

70). 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**).



a) FeCl_3 , acetone b) IBX, DMSO c) RANEY® Nickel, EtOH, reflux d) Pd, H_2 , *i*PrOH

Scheme 2.17: Final Deprotection Sequence of BOM Route to Linear Precursor 4

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 CDCl_3) 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.⁶ 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.

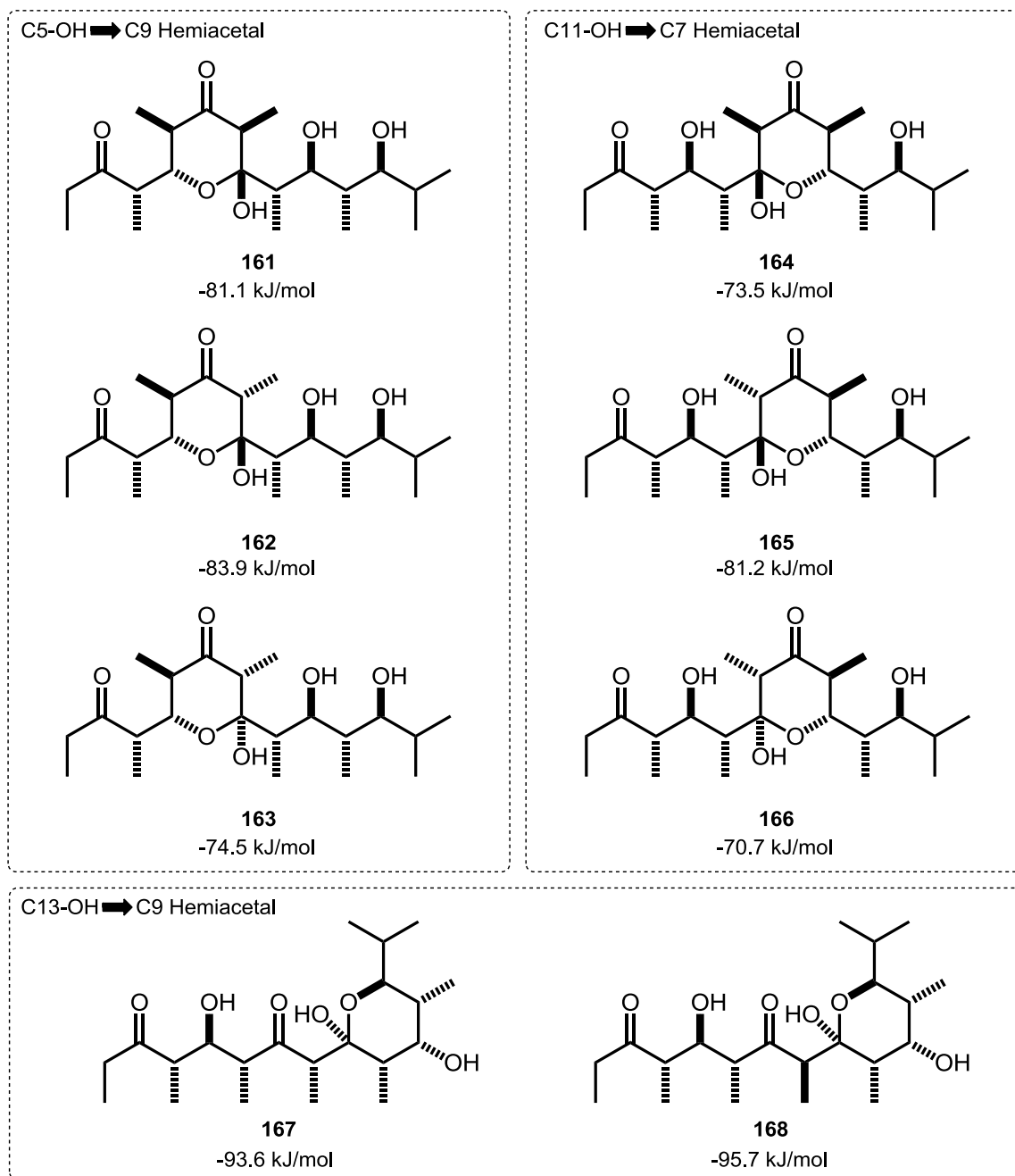
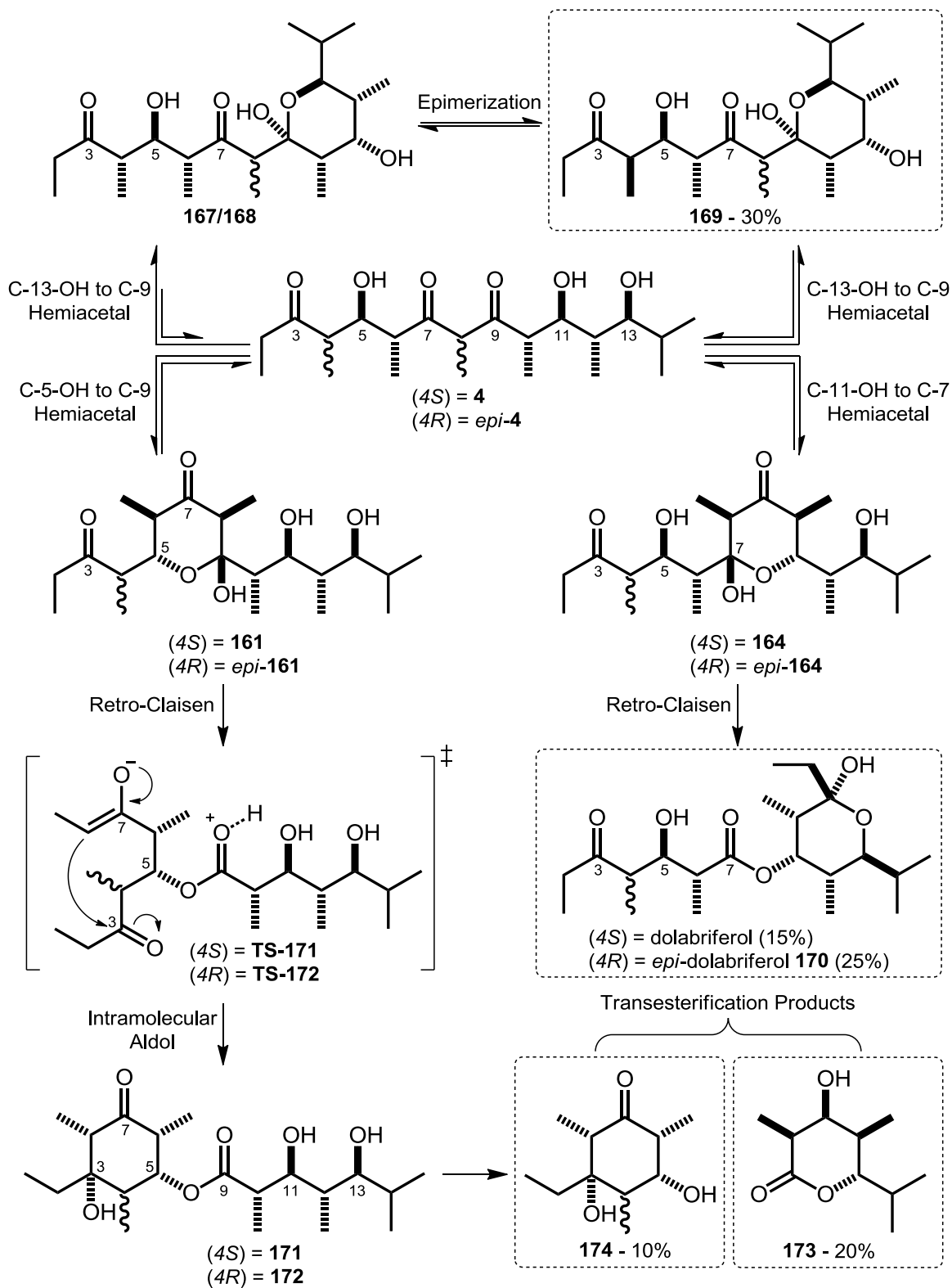


Figure 2.4: Goodman's Calculated Energies for Various Hemiacetals of **4**

In order to form dolabiferol, 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

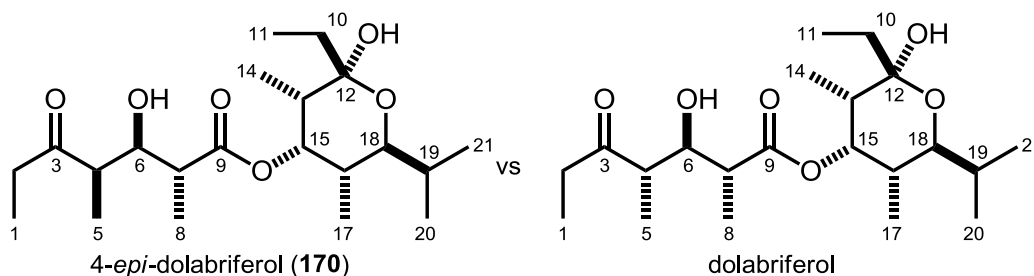
With the linear precursor **4** (as a mixture of hemiacetals **167** and **168**) in hand, attempts at inducing a retro-Claisen rearrangement were initiated. Reaction of **4** with DBU in C₆D₆ was monitored by ¹H NMR. Surprisingly, the reaction was sluggish compared to related examples by Lister/Perkins,¹⁰ 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

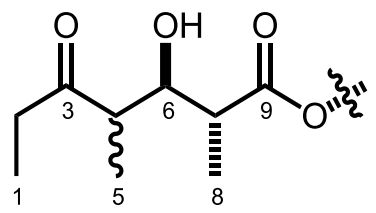
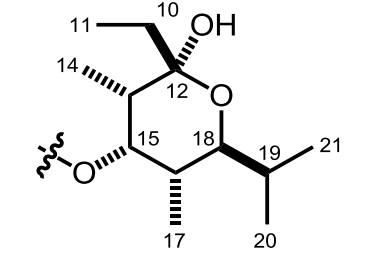
Products **173** and **174** arise from an unwanted retro-Claisen pathway. The likely pathway begins with hemiacetal **161** (C-5-OH to C-9 hemiacetal of **4**) undergoing a retro-Claisen rearrangement to give **TS-171**. This “enolate” then undergoes an intramolecular aldol reaction to give compound **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 ^1H NMR Data for Dolabriferol **1** and **170**



<u>4-epi-dolabriferol (170)</u>			<u>dolabriferol (1)</u>	
δ_{H}	Multiplicity (J 's in Hz)	Assignment	δ_{H}	Multiplicity (J 's in Hz)
2.74	dq (7.0, 9.0)	HC-4	2.78	dq (7.0, 7.0)
4.24	ddd (3.0, 4.0, 9.0)	HC-6	3.75	ddd (5.0, 8.0, 8.0)
2.63	dq (3.0, 7.0)	HC-7	2.73	dq (5.0, 7.0)
1.87	dq (3.0, 7.0)	HC-13	1.91	dq (3.0, 7.0)
5.25	dd (3.0, 3.0)	HC-15	5.25	dd (2.5, 2.5)
1.76	ddq (3.0, 7.0, 10.5)	HC-16	1.78	ddq (2.5, 7.0, 10.0)
3.63	dd (2.0, 10.5)	HC-18	3.61	dd (2.0, 10.5)
4.03	d (4.5)	OH-6	3.63	d (8.0)

Table 2.5: Selected ^{13}C NMR Data for Dolabriferol **1** and **170**

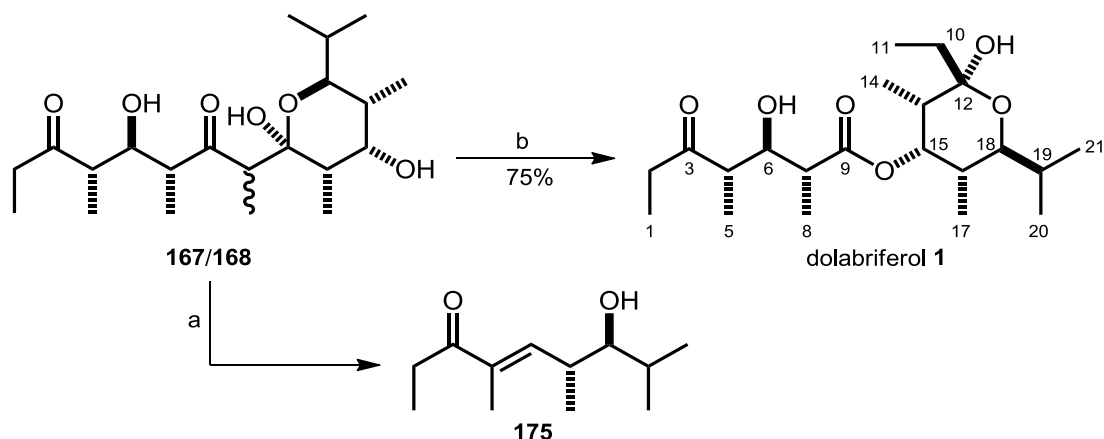
<u>4-<i>epi</i>-dolabriferol (170)</u>		<u>dolabriferol (1)</u>	
δ_{C}	Assignment	δ_{C}	
47.9	C-4	49.6	
13.9	C-5	14.6	
72.5	C-6	75.9	
42.3	C-7	43.9	
10.3	C-8	15.8	
174.9	C-9	173.9	
32.9	C-10	32.7	
98.9	C-12	98.7	
39.5	C-13	39.6	
76.4	C-15	77.1	
36.3	C-16	36.7	
72.6	C-18	72.5	

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.³⁴ 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 ^1H NMR Data for “Natural” and Synthetic Dolabriferol



a) neutral aluminum oxide, benzene, 72 hours b) neutral aluminum oxide, 15 minutes

<u>“natural” dolabriferol</u>			<u>synthetic dolabriferol</u>	
δ_{H}	Multiplicity (J 's in Hz)	Assignment	δ_{H}	Multiplicity (J 's in Hz)
1.04	t (7.2)	HC-1	1.05	t (7.0)
2.46	dq (7.2, 14.5) ^a	HC-2	2.46	dq (7.0, 18.0)
2.57	dq (7.2, 14.5) ^a	HC-2	2.57	dq (7.0, 18.0)
2.78	dq (7.1, 7.1)	HC-4	2.78	dq (7.0, 7.0)
1.14	d (7.1)	HC-5	1.15	d (7.0)
3.75	m	HC-6	3.75	ddd (5.0, 8.0, 8.0)
2.73	dq (4.3, 7.1)	HC-7	2.73	dq (5.0, 7.0)
1.32	d (7.1)	HC-8	1.33	d (7.0)
1.60	m	HC-10	1.61	m
0.91	t (7.4)	HC-11	0.91	t (7.5)
1.90	dq (2.5, 7.2)	HC-13	1.91	dq (3.0, 7.0)
0.99 ^b	d (7.2)	HC-14	1.00	d (7.0)
5.24	dd (2.5, 2.7)	HC-15	5.25	dd (2.5, 2.5)
1.78	ddq (2.7, 7.0, 10.5)	HC-16	1.78	ddq (2.5, 7.0, 10.0)
0.78	d (7.0)	HC-17	0.78	d (7.0)
3.60	dd (2.0, 10.5)	HC-18	3.61	dd (2.0, 10.5)
1.83	dqq (2.0, 6.8, 6.8)	HC-19	1.82	dqq (2.0, 7.0, 7.0)
1.00 ^b	d (6.8)	HC-20	0.99	d (7.0)
0.83	d (6.8)	HC-21	0.83	d (7.0)
3.65		OH-6	3.63	d (8.0)
3.45		OH-12	3.42	bs

^aThe large coupling constant is misassigned and needs to be corrected⁴ ^bIncorrect assignment⁴

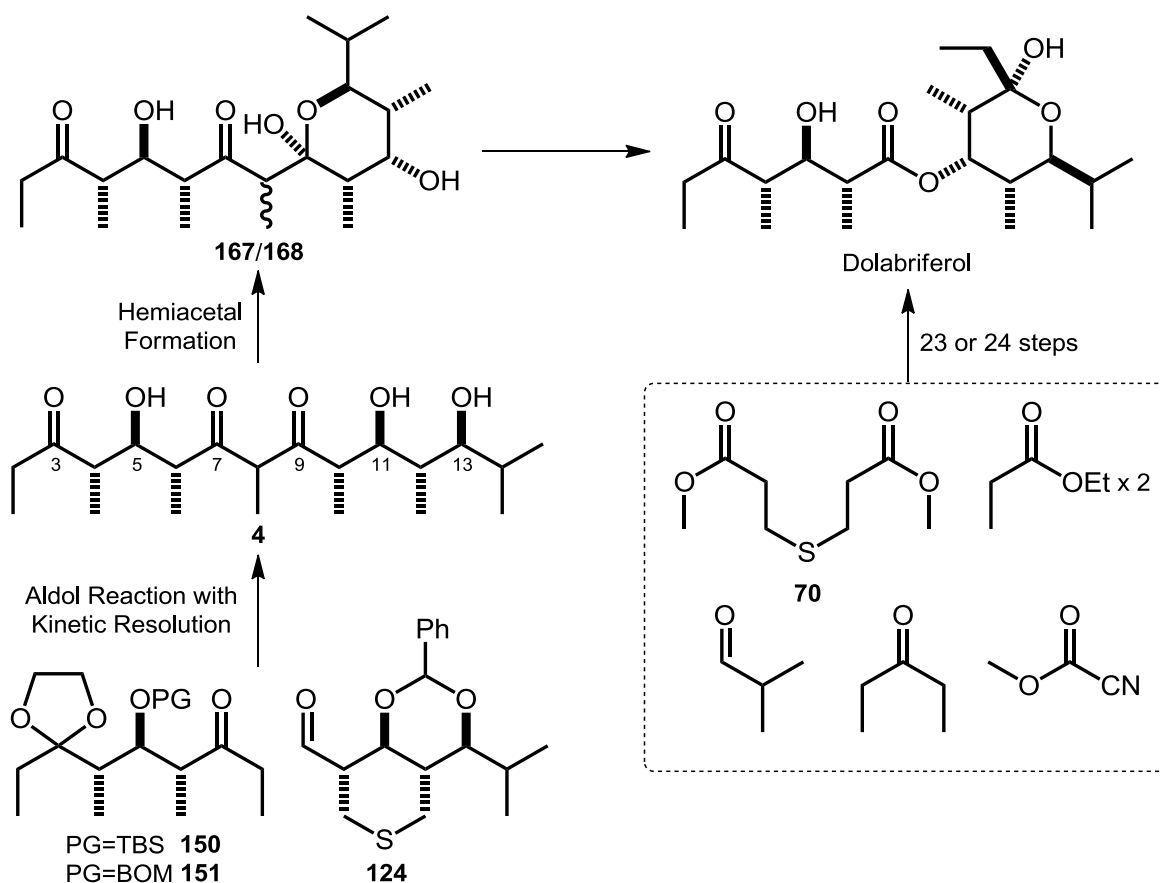
Table 2.7: Comparison of ¹³C NMR Data for “Natural” and Synthetic Dolabriferol

<u>“natural” dolabriferol^a</u>		<u>synthetic dolabriferol^b</u>		<u>“natural” dolabriferol^a</u>		<u>synthetic dolabriferol^b</u>	
δ_c	Assignment	δ_c		δ_c	Assignment	δ_c	
7.4	C-1	7.5		98.5	C-12	98.7	
36.0	C-2	36.2		39.4	C-13	39.6	
215.1	C-3	215.4		20.2	C-14 ^c	13.1	
49.4	C-4	49.6		76.9	C-15	77.1	
14.4	C-5	14.6		36.5	C-16	36.7	
75.7	C-7	75.9		12.9	C-17	13.0	
43.7	C-7	43.9		72.3	C-18	72.5	
15.6	C-8	15.8		28.0	C-19	28.2	
173.7	C-9	173.9		12.9	C-20 ^c	20.5	
32.5	C-10	32.7		14.0	C-21	14.2	
7.2	C-11	7.4					

^aRef 4; used δ_c CDCl₃=77.00 ^bChemical 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 δ_c CDCl₃=77.23 ^cIncorrect assignment⁴

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

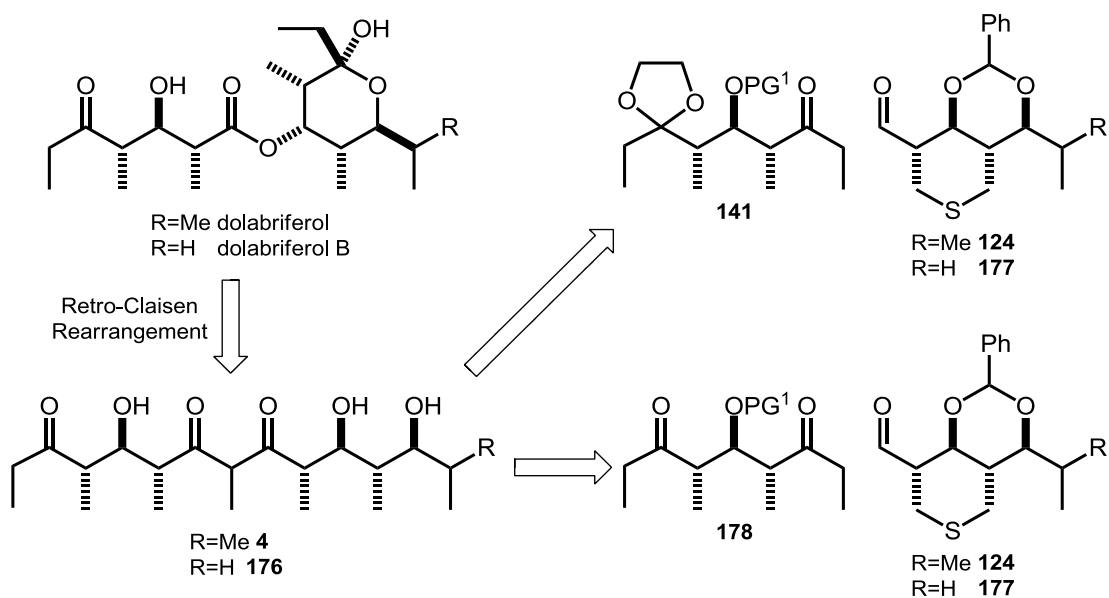
The synthesis of **4** proceeded in a longest linear sequence of 16 steps in 14.3% (via ketone **151**) or 17 steps in 11.4% (via ketone **150**) starting from **70** (23 and 24 total steps respectively). The aldol reactions of ketones **150** or **151** with aldehyde **124** proceeded with kinetic resolution 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 Mukayama 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 dolabriferol from *Dolabrifera dolabrifera* off the coast of Puerto Rico.³⁵ 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

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_2Cl_2 from CaH_2 ; MeOH from $\text{Mg}(\text{OMe})_2$. 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), $\text{CO}_2(\text{s})/\text{acetonitrile}$ (-45 °C), and $\text{CO}_2(\text{s})/\text{acetone}$ (-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 flask 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 F₂₅₄. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aq. sulfuric acid (5% v/v), or with basic KMnO_4 [KMnO_4 (1.5 g), K_2CO_3 (10 g), 10% aq. NaOH (1.25 mL), in H_2O (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 F₂₅₄ and was visualized in the same manner as described for PTLC.

Flash column chromatography (FCC) was performed according to Still et al.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 ¹H 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 CDCl₃ solution at 500 MHz for ¹H and 125 MHz for ¹³C. Signals due to the solvent (¹³C NMR) or residual protonated solvent (¹H NMR) served as the internal standard: CDCl₃ (7.26 δ_H, 77.23 δ_C); C₆D₆ (7.16 δ_H, 128.39 δ_C). The ¹H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. Coupling constants are reported to the nearest 0.5 Hz (digital resolution ca, 0.1 Hz/pt) or the nearest 0.1 Hz (digital resolution ca. 0.03 Hz/pt.). The ¹H 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 (gCOSY, gHSQC, gHMBC).³⁷ The ¹³C NMR assignments were made on the basis of chemical shift and multiplicity (as determined by ¹³C-DEPT or gHSQC) and were confirmed, where necessary, by two-dimensional ¹H/¹³C correlation experiments (gHSQC and/or gHMBC).³⁷ The multiplicity of ¹³C NMR signals refers to the number of attached hydrogens (ie., s = C, d = CH, t = CH₂, q = CH₃).

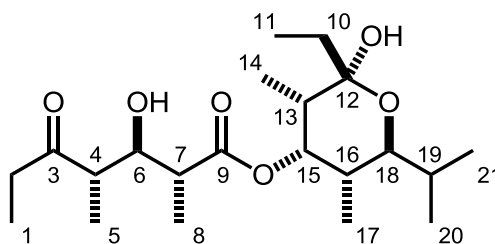
Specific rotations ($[\alpha]_D$) are the average of five determinations at ambient temperature using 1 mL, 10 dm cell; the units are 10⁻¹ deg cm² g⁻¹ and the concentrations (*c*) are reported in g/100 mL. The values reported are rounded to reflect the accuracy of the measured concentrations (the major source of error). HPLC analyses were carried out using an Agilent Technologies 1200 series liquid chromatograph.

3.3. Materials

The following compounds and reagents were prepared as described previously: **71**,¹⁷ **72**,¹⁷ **73**,¹⁷ **74**,²⁷ **75**,¹⁸ **84**,¹⁷ **86**,²⁰ **98**,¹⁹ **99**,²⁶ **125**,¹⁹ **127**,²⁰ **144**,²⁶ **145**,²⁶ **148**,²⁶ **149**,²⁶ IBX,³⁸ W-2 RANEY® Nickel,³⁹ methyl cyanoformate,⁴⁰ and benzyl cyanoformate.⁴¹ 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).



1

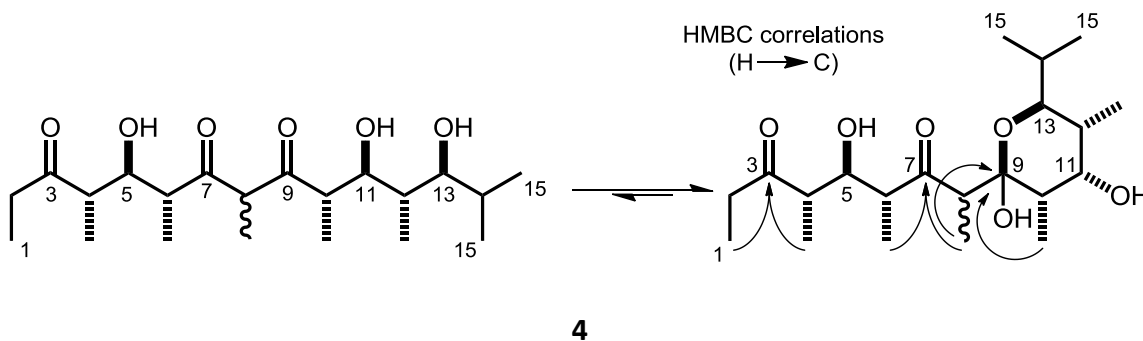
Linear precursor **4** (2 mg, 5.2 micromol) was dissolved in benzene (0.2 mL) and transferred to a pipette containing neutral alumina (3 cm height, Brockmann I) and the solvent pushed down until the solvent line was below the alumina line. After 15 minutes, the column was eluted with EtOAc (3x) and the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

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

^1H NMR (CDCl_3) δ : 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, dq, J = 2, 7, 7 Hz, HC-19), 1.78 (1H, ddq, J = 2.5, 10, 7 Hz, HC-16), 1.68-1.50 (2H, m, H_2C -10), 1.33 (3H, d, J = 7 Hz, HC-8), 1.15 (3H, d, J = 7 Hz, H_3C -5), 1.05 (3H, t, J = 7 Hz, H_3C -1), 1.00 (3H, d, J = 7 Hz, H_3C -14), 0.99 (3H, d, J = 7 Hz, H_3C -20), 0.91 (3H, t, J = 7.5 Hz, H_3C -11), 0.83 (3H, d, J = 7 Hz, H_3C -21), 0.78 (3H, d, J = 7 Hz, H_3C -17);

¹³C NMR (CDCl₃) 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);

(4*S*,5*R*,6*R*,10*S*,11*S*,12*S*,13*S*)-5,11,13-Trihydroxy-4,6,8,10,12,14-hexamethylpentadecane-3,7,9-trione (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);

$[\alpha]_D -30$ (c 0.5, C_6H_6);

IR ν_{max} : 3414, 1699 cm^{-1} ;

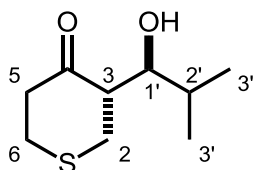
1H NMR (C_6D_6) δ (* denotes signals for the minor hemiacetal): 5.50 (0.6H, s, HOC-9), 5.00 (0.4H, s, HOC-9*), 3.84-3.68 (2H, m, HC-5, HC-5*, HOC-11, HOC-11*), 3.65 (0.4H, dd, $J = 2, 11$ Hz, HC-13*), 3.58 (0.6H, dd, $J = 2, 11$ Hz, HC-13), 3.36 (0.6H, dq, $J = 7, 7$ Hz, HC-6), 3.13 (0.4H, ddd, $J = 2.5, 2.5, 7$ 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);

^{13}C 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)



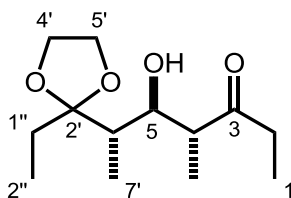
97

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 NH_4Cl , water and brine, dried over Na_2SO_4 , concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to furnish the title compound (12.5 g, 77%; er 24:1 by HPLC). ^1H NMR data were consistent with those previously reported.²⁶

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

$[\alpha]_D -22$ (*c* 2.2, CHCl_3) (lit.²⁶ $[\alpha]_D -23$; *c* 1.0, CHCl_3 ; 98% ee)

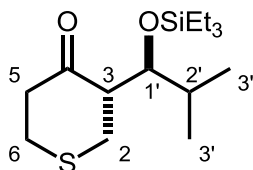
(4*R*,5*S*,6*S*)-rel-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-hydroxy-4-methylheptan-3-one (99).



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 ($\times 2$) 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.²⁷

(S)-3-((S)-2-Methyl-1-((triethylsilyl)oxy)propyl)dihydro-2H-thiopyran-4(3H)-one (107).



107

Et₃N (10.5 mL, 7.62 g, 75.5 mmol) and Et₃SiCl (9.6 mL, 8.6 g, 57 mmol) were sequentially added to a stirred solution of **97** (7.16 g, 38.1 mmol) in CH₂Cl₂ (50 mL) room temperature under Ar. After 16 h, the reaction was diluted with CH₂Cl₂, washed with saturated aq NH₄Cl and brine, dried over Na₂SO₄, 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, CHCl₃);

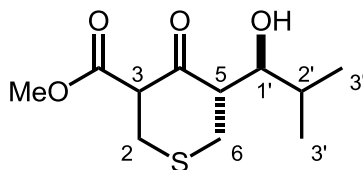
IR (DRIFT) ν_{max} 1712 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.20 (1H, dd, *J* = 4, 6 Hz, HC-1'), 2.98-2.88 (3H, m, HC-2, H₂C-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, dq, *J* = 4, 6.5, 6.5 Hz, HC-2'), 0.93 (9H, t, *J* = 8 Hz, H₃CCSi ×3), 0.89 (3H, d, *J* = 6.5 Hz, H₃C-3'), 0.87 (3H, d, *J* = 6.5 Hz, H₃C-3'), 0.59 (6H, ap q, *J* = 8 Hz, H₂CSi ×3).

¹³C NMR (125 MHz, CDCl₃) δ 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, CH₃CSi), 5.5 (t ×3, CH₂Si).

HRMS *m/z* calcd. for C₁₅H₃₀O₂SiS 302.1736, found 302.1730 (EI).

**Methyl (5S)-5-((S)-2-Methyl-1-(hydroxy)propyl)-4-oxotetrahydro-2H-thiopyran-3-carboxylate
(109).**



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, $\text{CH}_3\text{O}_2\text{CCN}$ (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_4Cl . The mixture was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4 and concentrated to give a yellow oil that was taken up in CH_3CN (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_2SO_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 ν_{max} : 3544, 1744, 1697, 1645, 1608 cm^{-1} ;

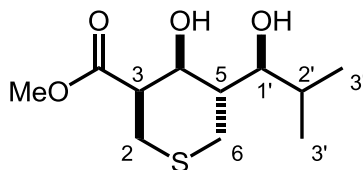
$^1\text{H NMR}$ (CDCl_3) δ (*denotes signals from enol form): 12.99* (0.19H, s, HO enol), 3.85-3.71 (0.66H, m, HC-1', 2 \times keto), 3.80 (s), 3.78 (s) and 3.77 (s) (3H, H_3CO enol & 2 \times keto), 3.67-3.63 (0.22H, m, HC-1' enol), 3.51-3.40 (1H, m, enol & 2 \times keto), 3.37-3.23 (1H, m, enol & 2 \times 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, dqq, $J = 5, 7, 7$ Hz, HC-2' enol), 1.91 (0.38H, dqq, $J = 6, 7, 7$ Hz, HC-2' keto), 1.82 (0.39H, dqq, $J = 5, 7, 7$ Hz, HC-2' keto), 1.05-0.92 (6.2H, m, H₃C-3' (×2) enol & 2× keto);

¹³C NMR (CDCl₃) 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 C₁₁H₁₈O₄S 246.0926, found 246.0926 (EI).

Methyl (3*R*,4*S*,5*S*)-4-Hydroxy-5-((*S*)-1-hydroxy-2-methylpropyl)tetrahydro-2*H*-thiopyran-3-carboxylate (111**).**



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);

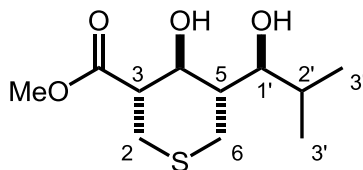
IR ν_{max} : 3448, 1712 cm^{-1} ;

$^1\text{H NMR}$ (CDCl_3) δ : 4.19 (1H, br s, HC-4), 3.76 (3H, s, H_3CO), 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, dq, $J = 3.5, 7, 7$ Hz, HC-2'), 1.00 (3H, d, $J = 7$ Hz, $\text{H}_3\text{C-3}'$), 0.89 (3H, d, $J = 7$ Hz, $\text{H}_3\text{C-3}'$);

$^{13}\text{C NMR}$ (CDCl_3) δ : 174.4 (s, CO), 77.8 (d, C-1'), 69.9 (d, C-4), 52.4 (q, CH_3O), 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 $\text{C}_{11}\text{H}_{20}\text{O}_4\text{S}$: 248.1082; found: 248.1090 (EI).

Methyl (3*S*,4*S*,5*S*)-4-Hydroxy-5-((*S*)-1-hydroxy-2-methylpropyl)tetrahydro-2*H*-thiopyran-3-carboxylate (112**).**



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^tBu (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 NaHCO₃ and brine, dried over Na₂SO₄, 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)

[α]_D +30 (c 1.0, CHCl₃);

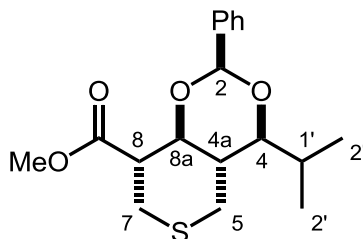
IR ν_{max}: 3360, 3193, 1728 cm⁻¹;

¹H NMR (C₆D₆) δ: 3.67 (1H, dd, *J* = 9.5, 9.5 Hz, HC-4), 3.28 (3H, s, H₃CO), 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, dq, *J* = 3, 7, 7 Hz, HC-2'), 0.86 (3H, d, *J* = 7 Hz, H₃C-3'), 0.75 (3H, d, *J* = 7 Hz, H₃C-3');

¹³C NMR (C₆D₆) δ: 174.1 (s, CO), 80.7 (d, C-1'), 76.3 (d, C-4), 53.2 (d, C-3), 51.9 (d, CH₃O), 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');

HRMS *m/z* calcd. for C₁₁H₂₀O₄S: 248.1082; found: 248.1079 (EI).

Methyl (2*S*,4*S*,4*aS*,8*S*,8*aS*)-4-Isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxine-8-carboxylate (112a).



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 R_f = 0.3 (20% ethyl acetate in hexane);

[α]_D +30 (c 0.6, CHCl₃);

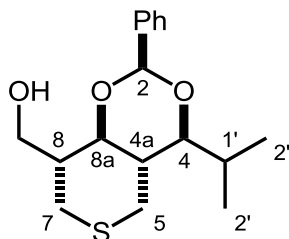
IR ν_{max}: 1732 cm⁻¹;

¹H NMR (C₆D₆) 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, H₃CO), 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, H₃C-2'), 0.81 (3H, d, *J* = 7 Hz, H₃C-2');

¹³C NMR (C₆D₆) 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, CH₃O), 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 C₁₈H₂₄O₄S 336.1395, found 336.1400 (EI).

((2*S*,4*S*,4*aS*,8*R*,8*aR*)-4-Isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)methanol (123**).**



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 R_f = 0.3 (40% ethyl acetate in hexane);

[α]_D -8.7 (c 1.2, CHCl₃);

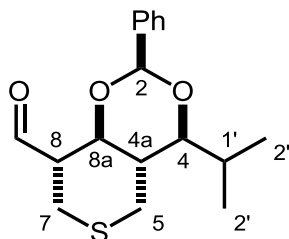
IR ν_{max}: 3344 cm⁻¹;

¹H NMR (CDCl₃) δ: 7.45-7.28 (5H, m, Ph), 5.61 (1H, s, HC-2), 3.83 (1H, dd, *J* = 6, 11 Hz, H₂CO), 3.64 (1H, dd, *J* = 4.5, 11 Hz, H₂CO), 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, H₂C-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, dq, *J* = 2, 7, 7 Hz, HC-1'), 1.08 (3H, d, *J* = 7 Hz, H₃C-2'), 0.98 (3H, d, *J* = 7 Hz, H₃C-2');

¹³C NMR (CDCl₃) δ: 138.6 (s, Ph), 129.0 (d, Ph), 128.4 (d ×2, Ph), 126.1 (d ×2, Ph), 100.9 (d, C-2), 84.2 (d, C-8a), 84.0 (d, C-4), 65.9 (t, CH₂O), 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 C₁₇H₂₄O₃S 308.1446, found 308.1442 (EI).

(2*S*,4*S*,4*aS*,8*S*,8*aS*)-4-Isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxine-8-carbaldehyde (124**).**



124

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 CH₂Cl₂ (60 mL) at -78 °C under argon. After 20 min, a solution of **123** (728 mg, 2.36 mmol) in CH₂Cl₂ (20 mL) at -78 °C under argon was added to the reaction mixture via a cannula. After 40 min, Et₃N (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 CH₂Cl₂ and washed sequentially with saturated aq NH₄Cl, saturated aq NaHCO₃ and brine, dried over Na₂SO₄, 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);

[α]_D +72 (c 1.2, CHCl₃);

IR ν_{max}: 1727 cm⁻¹;

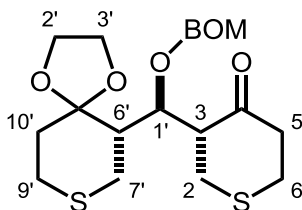
¹H NMR (CDCl₃) δ: 9.92 (1H, d, J = 1.5 Hz, HC=O), 7.45-7.32 (5H, m, Ph), 5.61 (1H, s, HC-2), 3.79 (1H, dd, J = 10, 10 Hz, HC-8a), 3.47 (1H, dd, J = 2, 10 Hz, HC-4), 2.98 (1H, dddd, J = 1.5, 4, 10, 11

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, dddd, *J* = 3, 10, 10, 12 Hz, HC-4a), 1.94 (1H, dq, *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 (EI).

(3*R*)-rel-3-[(*S*)-(6*S*)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(benzyloxymethoxy)methyl]tetrahydro-4*H*-thiopyran-4-one (126).



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 R_f = 0.3 (20% ethyl acetate in hexane);

IR ν_{max}: 1708 cm⁻¹;

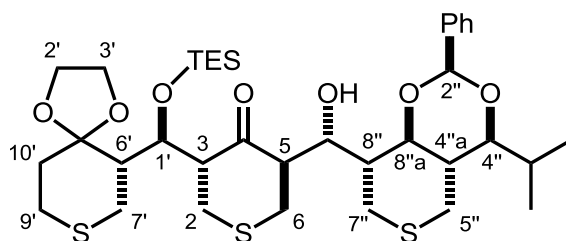
¹H NMR (CDCl₃) δ: 7.40-7.22 (5H, m, Ph), 4.88 (1H, d, *J* = 7 Hz, HCO₂), 4.77 (1H, d, *J* = 7 Hz, HCO₂), 4.62 (1H, dd, *J* = 1.5, 8 Hz, HC-1'), 4.58 (1H, d, *J* = 12 Hz, HCPH), 4.52 (1H, d, *J* = 12 Hz, HCPH), 4.12-3.87 (4H, m, H₂C-2', H₂C-3'), 3.12 (1H, ddd, *J* = 1.5, 5.5, 13.5 Hz, HC-2), 3.07 (1H, 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)

H₂C-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');

¹³C NMR (CDCl₃) δ: 209.4 (s, C-4), 137.9 (s, Ph), 128.6 (d ×2, Ph), 128.0 (d ×2, Ph), 127.9 (d, Ph), 108.5 (s, C-5'), 94.8 (t, OCH₂O), 76.8 (d, C-1'), 70.5 (t, CH₂Ph), 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 C₂₁H₃₂O₅+Na⁺ 447.1270, found 447.1281 (ESI).

(3*R*,5*R*)-3-((*S*)-((*S*)-1,4-dioxo-8-thiaspiro[4.5]decan-6-yl)((triethylsilyl)oxy)methyl)-5-((*R*)-hydroxy((2*S*,4*S*,4*aS*,8*R*,8*aR*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one (136).



136

(*c*-Hex)₂BCl (1.07 M in hexane; 4.5 mL, 4.8 mmol) and by Et₃N (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 CH₂Cl₂ (3 mL) at –45 °C under argon. After 2 h, *t*-BuNH₂ (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 CH₂Cl₂ (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 H₂O₂ (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 CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated to give a yellow oil whose ¹H 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%).

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

[α]_D –19 (*c* 1.1, CHCl₃);

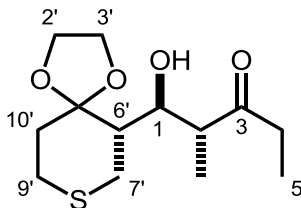
IR ν_{\max} : 3555, 1699 cm^{-1} ;

^1H NMR (CDCl_3) δ : 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, $\text{H}_2\text{C}-2'$, $\text{H}_2\text{C}-3'$), 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, $\text{H}_2\text{C}-7'$, 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, t, $J = 7$ Hz, $\text{H}_3\text{CCC}-4''$), 0.98 (3H, d, $J = 7$ Hz, $\text{H}_3\text{CCC}-4''$), 0.97 (9H, t, $J = 8$ Hz, $\text{H}_3\text{CCSi} \times 3$), 0.73-0.62 (6H, m, $\text{H}_2\text{CSi} \times 3$);

^{13}C NMR (CDCl_3) δ : 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, $\text{CH}_3\text{CC}-4''$), 15.1 (q, $\text{CH}_3\text{CC}-4''$), 7.2 (q, CH_3CSi), 5.4 (t, CH_2Si);

HRMS m/z calcd. for $\text{C}_{36}\text{H}_{56}\text{O}_7\text{S}_3\text{Si}+\text{Na}^+$ 747.2850, found 747.2853 (ESI).

(1*S*,2*R*)-rel-1-Hydroxy-2-methyl-1-((*S*)-1,4-dioxo-8-thiaspiro[4.5]decan-6-yl)pentan-3-one
(147aa).



147aa

MgBr₂·OEt₂ (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 CH₂Cl₂ (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 CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated to give the crude product as a pale yellow oil whose ¹H 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% Et₂O 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 ν_{max}: 3495, 1698 cm⁻¹;

¹H NMR (CDCl₃) δ: 4.16-4.10 (2H, m, HO, HC-1), 4.03-3.95 (4H, m, H₂C-2', H₂C-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,

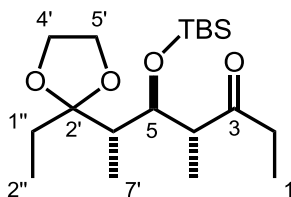
H₂C-4), 2.13 (1H, , $J = 3, 8.5, 13.5$ Hz, HC-10'), 2.01 (1H, ddd, $J = 3, 7, 7.5$ Hz, HC-6'), 1.75 (1H, ddd, $J = 3.5, 7.5, 13.5$ Hz, HC-10'), 1.21 (3H, d, $J = 7$ Hz, H₃CC-2), 0.99 (3H, t, $J = 7$ Hz, C-1);

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 (EI).

(4*R*,5*S*,6*S*)-*rel*-5-(*t*-Butyldimethylsilyloxy)-6-(2-ethyl-1,3-dioxolan-2-yl)-4-methylheptan-3-one

(150).



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 R_f = 0.3 (10% ethyl acetate in hexane);

IR ν_{max}: 1718 cm⁻¹;

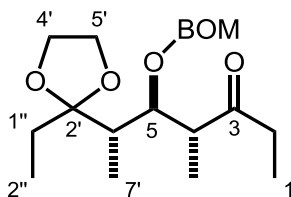
¹H NMR (CDCl₃) δ: 4.03 (1H, dd, *J* = 2.5, 6.5 Hz, HC-5), 3.98-3.85 (4H, m, H₂C-4' H₂C-5'), 2.93 (1H, dq, *J* = 6.5, 7 Hz, HC-4), 2.61-2.42 (2H, m, H₂C-2), 2.08 (1H, dq, *J* = 2.5, 7 Hz, HC-6), 1.68 (2H, ap q, *J* = 7.5 Hz, H₂C-1''), 1.05 (3H, d, *J* = 7 Hz, H₃CC-4), 1.01 (3H, d, *J* = 7 Hz, H₃C-7), 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);

¹³C NMR (CDCl₃) 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, (CH₃)₃C), 18.4 (s, CSi), 15.6 (q, CH₃C-4), 10.2 (q, C-7), 8.1 (q, C-2''), 7.7 (q, C-1), -4.2 (q, CH₃Si), -4.6 (q, CH₃Si);

HRMS *m/z* calcd. for C₁₉H₃₈O₄Si+H 359.2618, found 359.2616 (Cl, NH₃).

(4*R*,5*S*,6*S*)-*rel*-5-(Benzyloxy)methoxy-6-(2-ethyl-1,3-dioxolan-2-yl)-4-methylheptan-3-one

(151).



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 R_f = 0.3 (15% ethyl acetate in hexane);

IR ν_{max}: 1714 cm⁻¹;

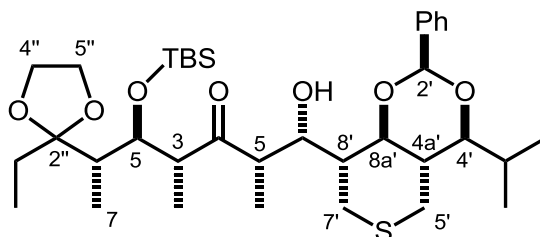
¹H NMR (CDCl₃) δ: 7.40-7.22 (5H, m, Ph), 4.68 (1H, d, *J* = 6.5 Hz, HCO₂), 4.66 (1H, d, *J* = 6.5 Hz, HCO₂), 4.58 (1H, d, *J* = 12 Hz, HCPH), 4.52 (1H, d, *J* = 12 Hz, HCPH), 4.01-3.92 (4H, m, H₂C-4', H₂C-5'), 3.84 (1H, dd, *J* = 3, 8 Hz, HC-5), 3.17 (1H, dq, *J* = 7, 8 Hz, HC-4), 2.52 (2H, m, *J* = 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, H₃CC-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).

(1*S*,2*S*,4*R*,5*S*,6*S*)-5-((^tButyldimethylsilyl)oxy)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-hydroxy-1-((2*S*,4*S*,4*aS*,8*R*,8*aR*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4-dimethylheptan-3-one (152).



152

A solution of LiHMDS was prepared by addition of *n*-BuLi (2.3 M in hexane; 1.3 mL, 3.0 mmol) was added to a stirred solution of (Me₃Si)₂NH (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°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 °C and stirring continued for 90 min. The mixture was cooled to –78 °C and a solution of TiCl(Oi-Pr)₃ (0.73 M in CH₂Cl₂; 8.9 mL, 6.5 mmol) was added dropwise via syringe over 5 min. After 15 min, mixture was warmed to –50 °C and stirring continued for 90 min. The reaction mixture was cooled –78 °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 NH₄Cl. The mixture was extracted with Et₂O and the combined organic layers were dried over Na₂SO₄ and concentrated to give the crude product whose ¹H 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_f = 0.3 (20% ethyl acetate in hexane);

^1H NMR (CDCl_3) 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, $\text{H}_2\text{C-4}''$, $\text{H}_2\text{C-5}''$), 3.72* (0.2H, dd, $J = 10, 10$ Hz, HC-8a'), 3.48 (0.8H, dd, $J = 10, 10$ Hz, HC-8a'), 3.45* (0.2H, dd, $J = 2, 10$ Hz, HC-4'), 3.38 (0.8H, dd, $J = 2, 10$ Hz, HC-4'), 3.34 (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, $\text{H}_2\text{CC-2}''$), 1.19 (2.4H, d, $J = 7$ Hz, $\text{H}_3\text{CC-2}$), 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, $\text{H}_3\text{CCC-4}'$), 1.01 (2.4H, d, $J = 7$ Hz, $\text{H}_3\text{CC-4}$), 0.98 (0.6H, d, $J = 7$ Hz), 0.96 (2.4H, d, $J = 7$ Hz, $\text{H}_3\text{CCC-4}'$), 0.93-0.83 (6H, m, $\text{H}_3\text{C-7}$, $\text{H}_3\text{CCC-2}''$), 0.82 (9H, s, $(\text{H}_3\text{C})_3\text{C}$), 0.11 (0.6H, s, CH_3Si), 0.05 (2.4H, s, CH_3Si), -0.02 (0.6H, s, CH_3Si), -0.05 (2.4H, s, CH_3Si);

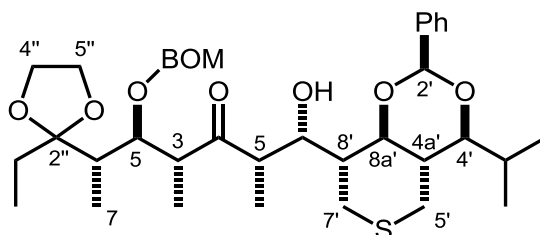
^{13}C NMR (CDCl_3) δ (minor isomer): 217.6 (s, C-3), 139.1 (s, Ph), 128.6 (d, Ph), 128.2 (d $\times 2$, Ph), 126.0 (d $\times 2$, Ph), 113.2 (d, C-2''), 100.3 (d, C-2'), 83.9 (d, C-4'), 79.8 (d, C-8a'), 74.5 (d, C-5), 69.3 (d, C-1), 65.7 (t, C-4''), 64.9 (t, C-5''), 48.9, 48.2, 45.5, 44.6, 44.0, 29.4, 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 $\times 2$, Ph), 126.3 (d $\times 2$, 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, CH₃Si), -4.5 (q, CH₃Si);

HRMS *m/z* calcd. for C₃₆H₆₀O₇SiS+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,4aS,8R,8aR)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-d][1,3]dioxin-8-yl)-2,4-dimethylheptan-3-one (**153**).



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 $(\text{Me}_3\text{Si})_2\text{NH}$ (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 $\text{TiCl}(\text{O}i\text{-Pr})_3$ (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_4Cl . The mixture was diluted with water and extracted with Et_2O . The combined organic layers were dried over Na_2SO_4 , and concentrated to give the crude product whose ^1H NMR spectrum indicated the presence of a 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%; $[\alpha]_D$ +5.2 (c 2.3, CHCl₃)] and the title compound (431 mg, 79%).

colorless oil, TLC R_f = 0.3 (30% Et₂O in toluene);

$[\alpha]_D$ +0.60 (c 1.2, CHCl₃);

IR ν_{\max} : 3499, 1707 cm⁻¹;

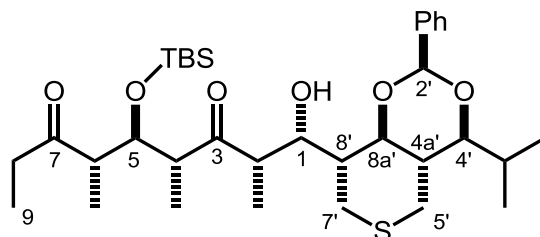
¹H NMR (CDCl₃) δ : 7.51-7.20 (10H, m, Ph \times 2), 5.55 (1H, s, HC-2'), 4.60 (2H, ap s, OCH₂O), 4.49 (1H, d, J = 12 Hz, H₂CPh), 4.43 (1H, d, J = 12 Hz, H₂CPh), 4.40 (1H, ddd, J = 3.5, 4, 4 Hz, HC-1), 3.96-3.83 (4H, m, H₂C-4'', H₂C-5''), 3.82 (1H, dd, J = 2, 9 Hz, HC-5), 3.51 (1H, dd, J = 9.5, 10 Hz, 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'), 1.76-1.64 (2H, m, H₂CC-2''), 1.15 (3H, d, J = 7 Hz, H₃CC-2), 1.05 (3H, d, J = 7 Hz, H₃CCC-4'), 1.02 (3H, d, J = 7 Hz, H₃C-7), 0.98 (3H, d, J = 7 Hz, H₃CC-4), 0.95 (3H, d, J = 7 Hz, H₃CCC-4'), 0.86 (3H, t, J = 7.5 Hz, H₃CCC-2'');

¹³C NMR (CDCl₃) δ : 218.3 (s, C-3), 139.0 (s, Ph), 138.0 (s, Ph), 128.8 (d, Ph), 128.6 (d \times 2, Ph), 128.3 (d \times 2, Ph), 128.0 (d \times 2, Ph), 127.8 (d, Ph), 126.3 (d \times 2, Ph), 113.4 (s, C-2''), 101.0 (d, C-2'), 96.1 (t, OCH₂O), 84.0 (d, C-4'), 83.2 (d, C-5), 82.7 (d, C-8a'), 70.7 (t, CH₂Ph), 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).

(1*S*,2*S*,4*R*,5*R*,6*S*)-5-((*t*-Butyldimethylsilyloxy)-1-hydroxy-1-((2*S*,4*S*,4*aS*,8*R*,8*aR*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6-trimethylnonane-3,7-dione (154).



154

p-TsOH·H₂O (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 NaHCO₃ and the mixture was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, 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);

[α]_D +2.0 (*c* 1.2, CHCl₃);

IR ν_{max}: 3510, 1709 cm⁻¹;

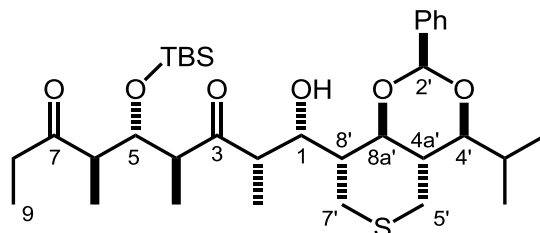
¹H NMR (CDCl₃) δ: 7.50-7.30 (5H, m, Ph), 5.52 (1H, s, HC-2'), 4.43 (1H, dd, *J* = 5.5, 7 Hz, HC-5), 4.18 (1H, ddd, *J* = 3, 3, 6 Hz, HC-1), 3.48 (1H, dd, *J* = 9.5, 9.5 Hz, HC-8a'), 3.38 (1H, dd, *J* = 2, 10 Hz, HC-4'), 3.16 (1H, dq, *J* = 3, 7 Hz, HC-2), 2.94 (1H, d, *J* = 3.4 Hz, HO), 2.93 (1H, ddd, *J* = 2.5, 3, 14 Hz, HC-7'), 2.82 (1H, dq, *J* = 7, 7 Hz, HC-4), 2.68-2.62 (2H, m, HC-6, HC-7'), 2.55-2.38 (3H, m, H₂C-8, HC-5'), 2.30 (1H, dd, *J* = 12, 13 Hz, HC-5'), 2.22-2.05 (2H, m, HC-4a', HC-8'), 1.94 (1H, dq, *J* = 7, 7 Hz, HC-4), 1.82 (1H, d, *J* = 3.4 Hz, HO), 1.72 (1H, d, *J* = 3.4 Hz, HO), 1.68 (1H, d, *J* = 3.4 Hz, HO), 1.64 (1H, d, *J* = 3.4 Hz, HO), 1.60 (1H, d, *J* = 3.4 Hz, HO), 1.56 (1H, d, *J* = 3.4 Hz, HO), 1.52 (1H, d, *J* = 3.4 Hz, HO), 1.48 (1H, d, *J* = 3.4 Hz, HO), 1.44 (1H, d, *J* = 3.4 Hz, HO), 1.40 (1H, d, *J* = 3.4 Hz, HO), 1.36 (1H, d, *J* = 3.4 Hz, HO), 1.32 (1H, d, *J* = 3.4 Hz, HO), 1.28 (1H, d, *J* = 3.4 Hz, HO), 1.24 (1H, d, *J* = 3.4 Hz, HO), 1.20 (1H, d, *J* = 3.4 Hz, HO), 1.16 (1H, d, *J* = 3.4 Hz, HO), 1.12 (1H, d, *J* = 3.4 Hz, HO), 1.08 (1H, d, *J* = 3.4 Hz, HO), 1.04 (1H, d, *J* = 3.4 Hz, HO), 1.00 (1H, d, *J* = 3.4 Hz, HO), 0.96 (1H, d, *J* = 3.4 Hz, HO), 0.92 (1H, d, *J* = 3.4 Hz, HO), 0.88 (1H, d, *J* = 3.4 Hz, HO), 0.84 (1H, d, *J* = 3.4 Hz, HO), 0.80 (1H, d, *J* = 3.4 Hz, HO), 0.76 (1H, d, *J* = 3.4 Hz, HO), 0.72 (1H, d, *J* = 3.4 Hz, HO), 0.68 (1H, d, *J* = 3.4 Hz, HO), 0.64 (1H, d, *J* = 3.4 Hz, HO), 0.60 (1H, d, *J* = 3.4 Hz, HO), 0.56 (1H, d, *J* = 3.4 Hz, HO), 0.52 (1H, d, *J* = 3.4 Hz, HO), 0.48 (1H, d, *J* = 3.4 Hz, HO), 0.44 (1H, d, *J* = 3.4 Hz, HO), 0.40 (1H, d, *J* = 3.4 Hz, HO), 0.36 (1H, d, *J* = 3.4 Hz, HO), 0.32 (1H, d, *J* = 3.4 Hz, HO), 0.28 (1H, d, *J* = 3.4 Hz, HO), 0.24 (1H, d, *J* = 3.4 Hz, HO), 0.20 (1H, d, *J* = 3.4 Hz, HO), 0.16 (1H, d, *J* = 3.4 Hz, HO), 0.12 (1H, d, *J* = 3.4 Hz, HO), 0.08 (1H, d, *J* = 3.4 Hz, HO), 0.04 (1H, d, *J* = 3.4 Hz, HO), 0.00 (1H, d, *J* = 3.4 Hz, HO).

$J = 2, 7, 7$ 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 \times 2, Ph), 126.3 (d \times 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 \times 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 C₃₄H₅₆O₆SSi+Na⁺ 643.3459, found 643.3465 (ESI).

(1*S*,2*S*,4*S*,5*S*,6*R*)-5-((*t*-Butyldimethylsilyl)oxy)-1-hydroxy-1-((2*S*,4*S*,4*aS*,8*R*,8*aR*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6-trimethylnonane-3,7-dione (154a).



154a

See the preparation of **154**.

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

$[\alpha]_D +15$ (c 1.2, CHCl_3);

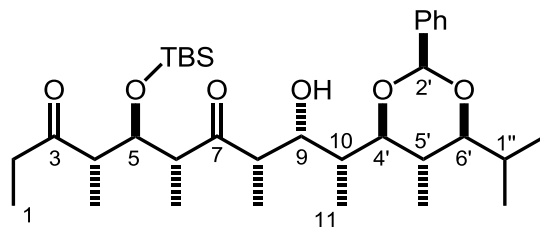
IR ν_{max} : 3510, 1710 cm^{-1} ;

$^1\text{H NMR}$ (CDCl_3) δ : 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, $\text{H}_2\text{C}-8$, 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, dq, $J = 2, 7, 7$ Hz, HC-1''), 1.10 (3H, d, $J = 7$ Hz, $\text{H}_3\text{CC}-1''$), 1.04 (3H, d, $J = 7$ Hz, $\text{H}_3\text{CC}-2$), 1.02 (3H, t, $J = 7.5$ Hz, $\text{H}_3\text{C}-9$), 0.99 (3H, d, $J = 7$ Hz, $\text{H}_3\text{CC}-6$), 0.97 (3H, d, $J = 7$ Hz, $\text{H}_3\text{CC}-1''$), 0.90 (3H, d, $J = 7$ Hz, $\text{H}_3\text{CC}-4$), 0.84 (9H, s, $(\text{H}_3\text{C})_3\text{C}$), 0.08 (3H, s, H_3CSi), 0.03 (3H, s, H_3CSi);

¹³C NMR (CDCl₃) δ: 216.0 (s, C-3), 212.6 (s, C-7), 138.9 (s, Ph), 128.7 (s, Ph), 128.3 (d ×2, Ph), 126.1 (d ×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 ×3, (CH₃)₃C), 25.8 (t, C-7'), 20.3 (q, CH₃C-1''), 18.2 (s, CSi), 15.1 (q, CH₃C-1''), 13.2 (q, CH₃C-2), 11.7 (q, CH₃C-6), 10.8 (q, CH₃C-4), 7.8 (q, C-9), -4.2 (q, CH₃Si), -4.8 (q, CH₃Si);

HRMS *m/z* calcd. for C₃₄H₅₆O₆SSi+Na⁺ 643.3459, found 643.3469 (ESI).

(4*S*,5*R*,6*R*,8*S*,9*R*,10*R*)-5-((^tButyldimethylsilyloxy)-9-hydroxy-10-((2*S*,4*R*,5*S*,6*S*)-6-isopropyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)-4,6,8-trimethylundecane-3,7-dione (155a).



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);

$[\alpha]_D -16$ (c 0.80, CHCl₃);

IR ν_{\max} : 3523, 1708 cm⁻¹;

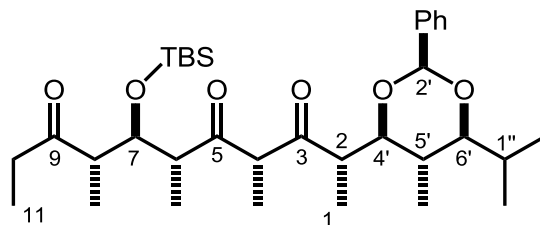
¹H NMR (CDCl₃) δ : 7.50-7.30 (5H, m, Ph), 5.45 (1H, s, HC-2'), 4.40 (1H, dd, J = 2.5, 8.5 Hz, HC-5), 4.24 (1H, br d, J = 10 Hz, HC-9), 3.48 (1H, dd, J = 1.5, 9.5 Hz, HC-4'), 3.30 (1H, dd, J = 2, 10 Hz, HC-6'), 3.28 (1H, br s, HO), 2.94 (1H, dq, J = 9.5, 7 Hz, HC-8), 2.88 (1H, dq, J = 2.5, 7 Hz, HC-6), 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, H₃CC-8), 1.16 (3H, d, $J = 7$ Hz, H₃CC-10), 1.14 (3H, d, $J = 7$ Hz, H₃CC-6), 1.08 (3H, d, $J = 7$ Hz, H₃CC-1''), 1.02 (3H, t, $J = 7$ Hz, H₃C-1), 0.88 (3H, d, $J = 7$ Hz, H₃CC-1''), 0.85 (9H, s, (H₃C)₃C), 0.83 (3H, d, $J = 7$ Hz, H₃CC-4), 0.79 (3H, d, $J = 6.5$ Hz, H₃CC-5'), 0.10 (3H, s, H₃CSi), -0.02 (3H, s, H₃CSi);

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 $\times 2$, Ph), 126.0 (d $\times 2$, 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 $\times 3$, (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 C₃₄H₅₈O₆Si+Na⁺ 613.3894, found 613.3877 (ESI).

(2*S*,4*S*,6*R*,7*R*,8*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-((2*S*,4*S*,5*S*,6*S*)-6-isopropyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)-4,6,8-trimethylundecane-3,5,9-trione (155).



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 NaHCO₃, water and then brine, dried over Na₂SO₄, 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, CHCl₃);

IR ν_{\max} : 1716, 1691 cm⁻¹;

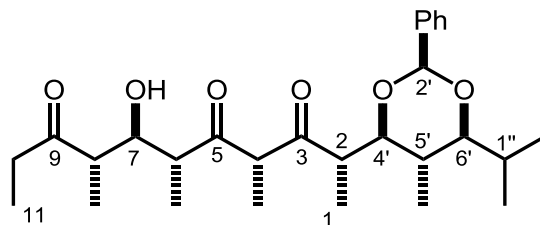
¹H NMR (C₆D₆) δ : 7.58 (2H, ap d, J = 7.5 Hz, Ph), 7.23 (2H, ap dd, J = 7.5, 7.5 Hz, Ph), 7.15 (1H, t, J = 7.5 Hz, Ph), 5.29 (1H, s, HC-2'), 4.58 (1H, dd, J = 5.5, 6.5 Hz, HC-7), 4.22 (1H, q, J = 7 Hz, HC-4), 3.29 (1H, dd, J = 3, 10 Hz, HC-4'), 3.12 (1H, dq, J = 6.5, 7 Hz, HC-6), 3.04 (1H, br d, J = 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, H₃CC-4), 1.31 (3H, d, J = 7 Hz, H₃C-1), 1.05 (3H, d, J = 7 Hz, H₃CC-1''), 0.98 (3H, d, J = 7 Hz, H₃CC-

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, H₃CSi), 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 \times 2, Ph), 126.4 (d \times 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 \times 3, (CH₃)₃C), 20.5 (q, CH₃C-1''), 18.3 (s, CSi), 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).

(2*S*,4*S*,6*R*,7*R*,8*S*)-7-Hydroxy-2-((2*S*,4*S*,5*S*,6*S*)-6-isopropyl-5-methyl-2-phenyl-1,3-dioxan-4-yl)-4,6,8-trimethylundecane-3,5,9-trione (156).



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 R_f = 0.3 (25% ethyl acetate in hexane);

$[\alpha]_D +34$ (c 1.2, CHCl_3);

IR ν_{max} : 3457, 1715 cm^{-1} ;

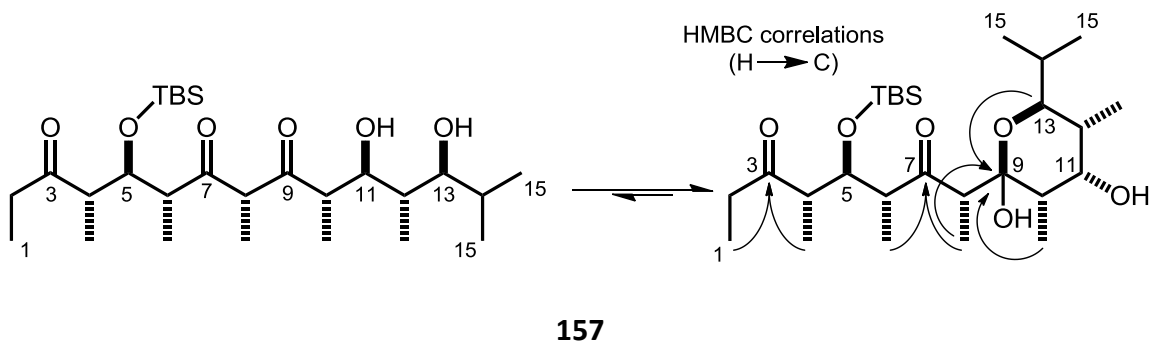
$^1\text{H NMR}$ (CDCl_3) δ : 7.48-7.28 (5H, m, Ph), 5.44 (1H, ap s, HC-2'), 4.13 (0.5H, q, $J = 7$ Hz, HC-4), 4.11 (0.5H, q, $J = 7$ Hz, HC-4), 3.63 (0.5H, dd, $J = 4.5, 10$ Hz, HC-4'), 3.60 (0.5H, dd, $J = 4.5, 10$ Hz, HC-4'), 3.58 (0.5H, d, $J = 10$ Hz, HO), 3.56 (0.5H, ddd, $J = 5.5, 7, 9.5$ Hz, 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), 3.01 (0.5H, dq, $J = 4.5, 7$ Hz, HC-2), 2.83 (0.5H, dq, $J = 7, 7$ Hz, HC-8), 2.81 (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, $\text{H}_2\text{C-10}$), 2.07-1.97 (1H, m, HC-1''), 1.90-1.76 (1H, m, HC-5'), 1.31 (1.5H, d, $J = 7$ Hz, $\text{H}_3\text{C-1}$), 1.28 (1.5H, d, $J = 7$ Hz, $\text{H}_3\text{C-1}$), 1.25 (1.5H, d, $J = 7$ Hz, $\text{H}_3\text{C-C4}$), 1.21 (1.5H, d, $J = 7$ Hz, $\text{H}_3\text{C-C4}$), 1.10-0.98 (6H, m, $\text{H}_3\text{CC-6}$, $\text{H}_3\text{CC-8}$, $\text{H}_3\text{CC-1''}$, $\text{H}_3\text{CC-1''}$), 1.03 (1.5H, t, $J = 7$ Hz, $\text{H}_3\text{C-11}$), 1.01 (1.5H, t, $J = 7$ Hz, $\text{H}_3\text{C-11}$), 0.94 (3H, ap d, $J = 7$ Hz, $\text{H}_3\text{C-C1''}$), 0.93 (1.5H, d, $J = 7$ Hz, $\text{H}_3\text{C-C8}$), 0.89 (1.5H, d, $J = 6.5$ Hz, $\text{H}_3\text{C-C5'}$), 0.84 (1.5H, d, $J = 6.5$ Hz, $\text{H}_3\text{C-C5'}$), 0.83 (1.5H, d, $J = 7$ Hz, $\text{H}_3\text{C-C6}$), 17.09 (0.08H, s, HO-enol), 1.93 (0.24H, s, $\text{H}_3\text{CC-4 enol}$);

$^{13}\text{C NMR}$ (CDCl_3) δ : 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 $\times 2$, 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, CH₃C-6, and CH₃C-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 C₂₈H₄₂O₆+Na⁺ 497.2874, found 497.2897 (ESI).

(4*S*,5*R*,6*R*,8*S*,10*S*,11*S*,12*S*,13*S*)-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 → O=C-9) in C₆D₆ solution.

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

$[\alpha]_D -16$ (c 1.2, C_6H_6);

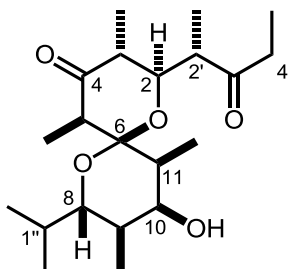
IR ν_{max} : 3418, 1699 cm^{-1} ;

1H NMR (C_6D_6) δ : 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, dq, $J = 2.5, 7, 7$ Hz, HC-14), 1.53 (1H, dq, $J = 2.5, 7$ Hz, HC-10), 1.49 (3H, d, $J = 7$ Hz, H_3CC -8), 1.24 (1H, ddq, $J = 2.5, 10.5, 7$ Hz, HC-12), 1.19 (3H, d, $J = 7$ Hz, H_3CC -10), 1.11 (3H, d, $J = 7$ Hz, H_3C -15), 1.11 (3H, d, $J = 7$ Hz, H_3CC -4), 1.10 (3H, d, $J = 7$ Hz, H_3CC -6), 1.02 (3H, t, $J = 7$ Hz, H_3C -1), 0.93 (9H, s, $(H_3C)_3C$), 0.85 (3H, d, $J = 7$ Hz, H_3C -15), 0.64 (3H, d, $J = 7$ Hz, H_3CC -12), 0.16 (3H, s, H_3CSi), 0.11 (3H, s, H_3CSi);

^{13}C NMR (C_6D_6) δ : 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 $\times 3$, $(CH_3)_3C$), 21.1 (q, C-15), 18.7 (s, CSi), 15.2 (q, C-15), 14.5 (q, CH_3C -10), 14.3 (q, CH_3C -6), 13.7 (q, CH_3C -12), 12.3 (q, CH_3C -4), 10.7 (q, CH_3C -8), 8.2 (q, C-1), -3.8 (q, CH_3Si), -4.5 (q, CH_3Si);

HRMS m/z calcd. for $C_{27}H_{52}O_6Si+Na^+$ 523.3425, found 523.3429 (ESI).

(2*R*,3*R*,5*S*,6*R*,8*S*,9*R*,10*S*,11*S*)-10-Hydroxy-8-isopropyl-3,5,9,11-tetramethyl-2-((*S*)-3-oxopentane-2-yl)-1,7-dioxaspiro[5.5]undecan-4-one (158).



158

Et₃N (1.2 mL, 0.87 g, 8.6 mmol) and Et₃N•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 NaHCO₃, water and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (30% ethyl acetate in hexane) to afford the title compound (9 mg, 82%) whose ¹H and ¹³C NMR data closely matched those previously reported.¹⁰

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

[α]_D -60 (c 0.8, C₆H₆);

IR ν_{max}: 3501, 1724, 1713 cm⁻¹;

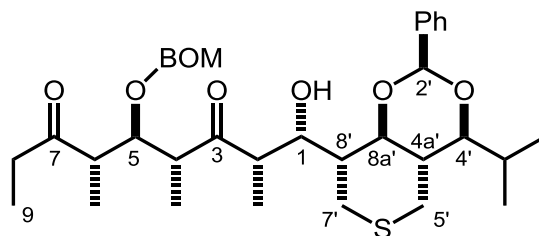
¹H NMR (CDCl₃) δ: 3.73 (1H, dd, *J* = 2, 11 Hz, HC-8), 3.61 (1H, dd, *J* = 2.5, 11.5 Hz, HC-2), 3.38 (1H, ddd, *J* = 2.5, 3, 10.5 Hz, HC-10), 3.07 (1H, d, *J* = 10.5 Hz, HO), 2.65 (1H, dq, *J* = 7, 11.5 Hz, HC-3), 2.34 (1H, q, *J* = 6.5 Hz, HC-5), 2.26 (1H, dq, *J* = 2.5, 7 Hz, HC-2'), 2.07 (1H, dq, *J* = 7, 18.5

Hz, HC-4'), 1.98 (1H, dq, $J = 7, 18.5$ Hz, HC-4'), 1.71 (1H, dq, $J = 2.7, 7$ 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 C₂₁H₃₆O₅+Na⁺ 647.2455, found 391.2454 (ESI).

(1*S*,2*S*,4*R*,5*R*,6*S*)-5-((Benzyloxy)methoxy)-1-hydroxy-1-((2*S*,4*S*,4*aS*,8*R*,8*aR*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6-trimethylnonane-3,7-dione (159).



159

Anhydrous FeCl₃ (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 Na₂SO₄, 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% Et₂O in toluene);

[α]_D +16 (c 1.0, CHCl₃);

IR ν_{max}: 3498, 1708 cm⁻¹;

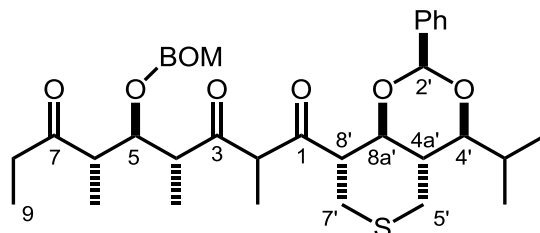
¹H NMR (CDCl₃) δ: 7.50-7.25 (10H, m, Ph ×2), 5.55 (1H, s, HC-2'), 4.63 (2H, s, H₂CO₂), 4.49 (1H, d, J = 11.5 Hz, H₂CPh), 4.44 (1H, d, J = 11.5 Hz, H₂CPh), 4.31 (1H, ddd, J = 4, 4, 4 Hz, HC-1), 4.16 (1H, dd, J = 4.5, 8.5 Hz, HC-5), 3.52 (1H, dd, J = 9.5, 10 Hz, HC-8a'), 3.38 (1H, dd, J = 2, 10 Hz, HC-4'), 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, dq, *J* = 2, 7, 7 Hz, HC-1''), 1.15 (3H, d, *J* = 7 Hz, H₃CC-2), 1.05 (3H, d, *J* = 7 Hz, H₃CC-1''), 1.03 (3H, d, *J* = 7 Hz, H₃CC-6), 1.01 (3H, t, *J* = 7.5 Hz, H₃C-9), 0.95 (3H, d, *J* = 7 Hz, H₃CC-1''), 0.82 (3H, d, *J* = 7 Hz, H₃CC-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).

(4*R*,5*R*,6*S*)-5-((Benzyloxy)methoxy)-1-hydroxy-1-((2*S*,4*S*,4*aS*,8*S*,8*aS*)-4-isopropyl-2-phenylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-8-yl)-2,4,6-trimethylnonane-1,3,7-trione (160).



160

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 $R_f = 0.3$ (20% ethyl acetate:in hexane);

$[\alpha]_D +19$ (c 1.0, CHCl₃);

IR ν_{\max} : 1713 cm⁻¹;

¹H NMR (CDCl₃) δ : 17.15 (0.5H, s, HO enol), 7.42-7.21 (15H, m, Ph $\times 2$), 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

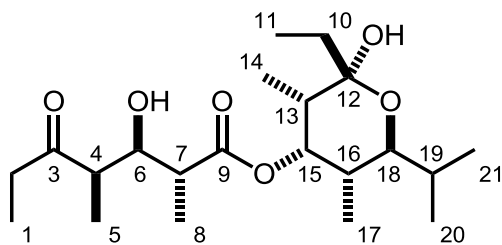
(0.5H, d, $J = 12$ Hz, H₂CPh enol), 4.17 (1.5H, ap dd, $J = 5, 7$ Hz, HC-5 keto & enol), 3.98 (1H, q, $J = 7$ Hz, CH₃C-2 keto), 3.89 (0.5H, dd, $J = 10, 10$ Hz, HC-8a' enol), 3.72 (1H, dd, $J = 10, 10$ Hz, HC-8a' keto), 3.45 (0.5H, dd, $J = 2, 10$ Hz, HC-4' enol), 3.41 (1H, dd, $J = 2, 10$ Hz, HC-4' keto), 3.34 (0.5H, ddd, $J = 3, 10, 11.5$ Hz, HC-8' enol), 3.21 (1H, dq, $J = 7, 7$ Hz, HC-4 enol), 3.08 (1H, ddd, $J = 3, 10, 11.5$ Hz, HC-8' keto), 3.05 (0.5H, dd, $J = 11.5, 13.5$ Hz, HC-7' enol), 3.01-2.87 (3.5H, m, HC-4 keto, HC-6 keto & enol, HC-7' keto), 2.72 (1H, ddd, $J = 2, 3, 13.5$ Hz, HC-7' keto), 2.61-2.30 (7.5H, m, H₂C-8 keto & enol, H₂C-5' keto & enol, HC-7' enol), 2.12 (0.5H, 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 \times 2, Ph), 128.27 (d \times 2, Ph), 128.02 (d \times 2, Ph), 127.98 (s, Ph), 125.88 (d \times 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 \times 2, Ph), 128.08 (d \times 2, Ph), 127.85 (d \times 2, Ph), 127.83 (s, Ph), 125.94 (d \times 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 C₃₆H₄₈O₇S+Na⁺ 647.3013, found 647.3021 (ESI).

4-*epi*-Dolabriferol (170).



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 and 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]_D -8 (c 0.3, C₆H₆);

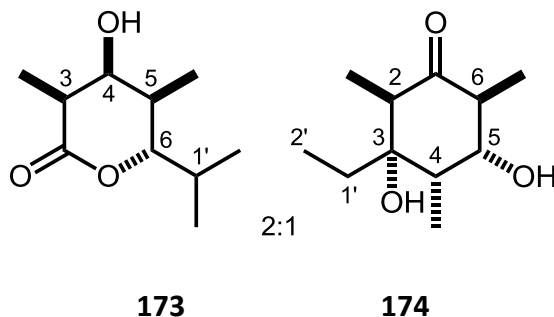
IR ν_{max}: 3445, 1732, 1712 cm⁻¹;

¹H NMR (CDCl₃) δ: 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, H₂C-2), 1.87 (1H, dq, *J* = 3, 7 Hz, HC-13), 1.83 (1H, dq, *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, H₂C-10), 1.27 (3H, d, *J* = 7.5 Hz, H₃C-8), 1.06 (3H, t, *J* = 7 Hz, H₃C-1), 1.005 (3H, d, *J* = 7 Hz, H₃C-5 or H₃C-20), 0.998 (3H, d, *J* = 7 Hz, H₃C-5 or H₃C-20), 0.92 (3H, d, *J* = 7 Hz, H₃C-14), 0.90 (3H, t, *J* = 7.5 Hz, H₃C-11), 0.83 (3H, d, *J* = 7 Hz, H₃C-21), 0.79 (3H, d, *J* = 7 Hz, H₃C-17);

¹³C NMR (CDCl₃) δ: 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);

HRMS *m/z* calcd. for C₂₁H₃₈O₆+Na 409.2561, found 409.2579 (ESI).

(3*S*,4*S*,5*R*,6*S*)-4-Hydroxy-6-isopropyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one (173) and (2*R*,3*S*,4*S*,5*R*,6*S*)-3-Ethyl-3,5-dihydroxy-2,4,6-trimethylcyclohexanone (174).



A 2:1 mixture of **173** and **174**, respectively was obtained in preparation of **170**. Lactone **173** is a known compound³⁴ 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, dq, *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**

¹H NMR (CDCl₃) δ: 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, H₃CC-4), 1.18 (3H, d, *J* = 6.5 Hz, H₃CC-6), 1.08 (3H, d, *J* = 6.5 Hz, H₃CC-2), 0.90 (3H, t, *J* = 7.5 Hz, H₃C-2');

¹³C NMR (CDCl₃) δ: 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, H₃CC-4), 11.0 (q, H₃CC-6), 8.9 (q, H₃CC-2'), 7.1 (q, H₃CC-2)

REFERENCES

1. Waegele, H., Klussmann-Kolb, A. Opisthobranchia (Mollusca, Gastropoda) - more than just slimy slugs. Shell reduction and its implications on defence and foraging. *Frontiers in Zoology* **2005**, 2 (3), 1-18.
2. Davies-Colman, M. T., Garson, M. J. Marine polypropionates. *Natural Product Reports*. **1998**, 15 (5), 477-493.
3. Beye, G. E., Ward, D. E. On the Origin of Siphonariid Polypropionates: Total Synthesis of Baconipyrone A, Baconipyrone C, and Siphonaridin B via their Putative Common Precursor *Journal of the American Chemical Society*. **2010**, 132 (20), 7210-7215.
4. Ciavatta, M. L., Gavagnin, M., Puliti, R., Cimino, G., Martinez, E., Ortea, J., Mattia, C. A. Dolabriferol: A new polypropionate from the skin of the anaspidean Mollusc *Dolabrifera dolabrifera*. *Tetrahedron* **1996**, 52 (39), 12831-12838.
5. Laclef, S., Turks, M., Vogel, P. Total Synthesis and Determination of the Absolute Configuration of (-)-Dolabriferol. *Angewandte Chemie International Edition*. **2010**, 49 (45), 8525-8527.
6. Socorro, I. M., Taylor, K., Goodman, J. M. ROBIA: A reaction prediction program. *Organic Letters*. **2005**, 7 (16), 3541-3544.
7. Dias, L. C., de Sousa, M. A. Synthetic studies directed toward the total synthesis of dolabriferol. *Tetrahedron Letters*. **2003**, 44 (30), 5625-5628.
8. Chenevert, R., Courchesne, G., Caron, D. Chemoenzymatic enantioselective synthesis of the polypropionate acid moiety of dolabriferol. *Tetrahedron: Asymmetry* **2003**, 14 (17), 2567-2571.
9. Pelchat, N., Caron, D., Chenevert, R. Enantioselective synthesis of the alcohol moiety of dolabriferol. *Journal of Organic Chemistry*. **2007**, 72 (22), 8484-8488.
10. Lister, T., Perkins, M. V. A retro-Claisen approach to dolabriferol. *Organic Letters*. **2006**, 8 (9), 1827-1830.
11. Currie, R. H., Goodman, J. M. In Silico Inspired Total Synthesis of (-)-Dolabriferol. *Angewandte Chemie International Edition*. **2012**, 51 (19), 4695-4697.
12. Roll, D. M., Biskupiak, J. E., Mayne, C. L., Ireland, C. M. Muamvatin, A Novel Tricyclic Spiroketal from the Fijian Mollusk *Siphonaria-Normalis*. *Journal of the American Chemical Society*. **1986**, 108 (21), 6680-6682.
13. Blanchfield, J. T.; Brecknell, D. J.; Brereton, I. M.; Garson, M. J.; Jones, D. D. Caloundrin-B and Funiculatin-A - New Polypropionates from Siphonariid Limpets. *Australian Journal of Chemistry*. **1994**, 47 (12), 2255-2269.

14. Ward, D. E., Zahedi, M. M. Total Synthesis of Muamvatin. *Organic Letters* **2012**, 14, 6246-6249.
15. Ward, D. E. The Thiopyran Route to Polypropionates. *Chemical Communications*. **2011**, 47 (41), 11375-11393.
16. Rule, N. G., Detty, M. R., Kaeding, J. E., Sinicropi, J. A. Syntheses of 4H-Thiopyran-4-one 1, 1-Dioxides as Precursors to Sulfone-Containing Analogs of Tetracyanoquinodimethane. *Journal of Organic Chemistry*. **1995**, 60, 1665-1673.
17. Ward, D. E., Rasheed, M., Gillis, M., Beye, G. E., Jheengut, V., Achonduh, G. Simple and Efficient Preparation of Reagents for Thiopyran Introduction: Methyl Tetrahydro-4-oxo-2H-thiopyran-3-carboxylate, Tetrahydro-4H-thiopyran-4-one, and 3,6-Dihydro-4-trimethylsilyloxy-2H-thiopyran. *Synthesis* **2007**, 10, 1584–1586.
18. Ward, D. E., Jheengut, V., Beye, G. E., Gillis, M., Karagiannis, A., Becerril-Jiménez, F. Enantioselective Direct Aldol Reactions of Achiral Ketones with Racemic Enolizable α -Substituted Aldehydes: Scope and Limitations. *Synlett* **2011**, 4, 508–512.
19. Ward, D. E., Sales, M., Man, C., Shen, J., Sasmal, P. K., Guo, C. Influence of the β -Alkoxy Group on the Diastereoselectivity of Aldol Reactions of Tetrahydro-4H-thiopyran-4-one with 4-Alkoxytetrahydro-2H-thiopyran-3-carboxaldehydes. *Journal of Organic Chemistry* **2002**, 67, 1618-1629.
20. Ward, D. E., Becerril-Jiménez, F., Zahedi, M. M. Rational Design of Aldol Reactions that Proceed via Kinetic Resolution with Switchable Enantioselectivity. *Journal of Organic Chemistry* **2009**, 74, 4447-4454.
21. Ward, D. E., Beye, G. E., Sales, M., Alarcon, I., Gillis, M., Jheengut, V. Thiopyran Route to Polypropionates: Exploiting and Overcoming Double Stereodifferentiation and Mutual Kinetic Enantioselection in Aldol Couplings of Chiral Fragments. *Journal of Organic Chemistry* **2007**, 72, 1667-1674.
22. Becerril-Jiménez, F., Ward, D. E. On the Origin of Siphonariid Polypropionates: Total Synthesis of Caloundrin B and Its Isomerization to Siphonarin B. *Organic Letters* **2012**, 14, 1648-1651.
23. Ward, D. E., Goodman, J. M., Beye, G. E. Synthetic Studies on Siphonariid Polypropionates: Synthesis and Isomerization of the Caloundrin B Trioxadamantane Ring System. *Organic Letters* **2009**, 11, 1373-1376.
24. Ward, D. E., Akinnusi, O. T., Alarcon, I. Q., Jheengut, V., Shen, J., Quail, W. The thiopyran route to polypropionates. Asymmetric synthesis of the building blocks by enantioselective protonation. *Tetrahedron: Asymmetry* **2004**, 15, 2425–2430.
25. Ward, D. E., Jheengut, V. Proline-catalyzed asymmetric aldol reactions of tetrahydro-4H-thiopyran-4-one with aldehydes. *Tetrahedron Letters* **2004**, 45 (45), 8347-8350.

26. Ward, D. E., Kundu, D., Biniiaz, M., Jana, S. A Systematic Study of the Effects of Relative Configuration, Protecting Group, and Enolate Type on the Diastereoselectivities of Aldol Reactions of a Chiral Ethyl Ketone with 2-Methylpropanal. *Journal of Organic Chemistry* **2014**, 79, 6868-6894.
27. Pramod Jadhav, unpublished results.
28. Naveen Diddi, unpublished results.
29. Poon, K. W. C., Dudley, G. B. Mix-and-Heat Benzoylation of Alcohols Using a Bench-Stable Pyridinium Salt. *Journal of Organic Chemistry* **2006**, 71, 3923-3927.
30. Eckenberg, P., Groth, U., Huhn, T., Richter, N., Schmeck, C. A Useful Application of Benzyl Trichloroacetimidate for the Benzoylation of Alcohols. *Tetrahedron* **1993**, 8, 1619-1624.
31. Brown, C. R., Cragg, H., Miller, T.J., Smith, D. Contributions to organoboron chemistry: XV. Aminodiphenylboranes. *Journal of Organometallic Chemistry* **1981**, 217, 139-149.
32. Sushital Jana, unpublished results.
33. Vogel, P., Exner, C. J., Laclef, S., Poli, F., Turks, M. Total Asymmetric Syntheses of β -Hydroxy- δ -lactones via Umpolung with Sulfur Dioxide. *Journal of Organic Chemistry* **2011**, 76, 840-845.
34. Sundram, U., Albizati, K. Synthesis and absolute configuration of polypropionate metabolites of siphonaria australis. *Tetrahedron Letters* **1992**, 33, 437-440.
35. Jiménez-Romero, C., González, K., Rodríguez, A. D. Dolabriferols B and C, non-contiguous polypropionate esters from the tropical sea hare Dolabrifera dolabrifera. *Tetrahedron Letters* **2012**, 53, 6641-6645.
36. Still, W. C., Kahn, M., Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *Journal of Organic Chemistry* **1978**, 43, 2923-2925.
37. Reynolds, W.F., Enriquez R. G. Choosing the Best Pulse Sequences, Acquisition Parameters, Postacquisition Processing Strategies, and Probes for Natural Product Structure Elucidation by NMR Spectroscopy. *Journal of Natural Products* **2002**, 65, 221-244.
38. Frigerio, M., Santagostino, M. M, Sputore, S. A User Friendly Entry to 2-Iodoxybenzoic Acid (IBX). *Journal of Organic Chemistry* **1999**, 64, 4537-4538.
39. Mozingo, R. Catalyst, Raney nickel. *Organic Syntheses* **1941**, 21, 15-17.
40. Mander, L., Sethi, S. P. Regioselective synthesis of β -ketoesters from lithium enolates and methyl cyanofornate. *Tetrahedron Letters* **1983**, 24, 5425.

41. Weber W. P., Childs, M. E. Preparation of Cyanofornates. Crown Ether Phase Transfer Catalysis. *Journal of Organic Chemistry* **1976**, 41, 3486-3487.