SYNTHETIC STUDIES ON SIPHONARIID POLYPROPIONATES:
THE TOTAL SYNTHESIS OF SIPHONARIN B, BACONIPYRONE A,
BACONIPYRONE C, AND THEIR PUTATIVE COMMON PRECURSOR

A Thesis Submitted to the
College of Graduate Studies and Research
In Partial Fulfillment of the Requirements
For the Degree of Doctor of Philosophy
In the Department of Chemistry
University of Saskatchewan

by

Garrison Eduard Beye

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The Head
Department of Chemistry
University of Saskatchewan
110 Science Place
Saskatoon, SK, S7N 5C9
CANADA
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“Always finish what you start.” – A father to his son.
**ABSTRACT**

*Siphonaria zelandica*, a pulmonate mollusk, has been the subject of many natural product isolation studies by several, independent research groups. These studies have yielded several polypropionate structures (e.g. 4, 6, 8, and 10), which, upon careful inspection, were proposed to be related. There has been speculation that none of these isolated structures (4, 6, 8, and 10) are biosynthetic products, but are artifacts of isolation. Instead, it has been proposed that an unstable, acyclic precursor, such as 14/15 is the biosynthetic product produced by this mollusk; the putative acyclic precursor has not been isolated or synthesized. None of the synthetic studies on this series of compounds have attempted to address the potential relationships between these structures or speak to their status as natural products.
This work describes the enantioselective synthesis of the putative acyclic precursor 14/15 and its isomerization to siphonarin B (4). This was the first enantioselective synthesis of siphonarin B (4). Siphonarin B (4) was shown to readily undergo a retro-Claisen rearrangement to afford baconipyrone C (6) and concurrently undergo a retro-Claisen rearrangement/aldol cascade to provide baconipyrone A (6). This was the first total synthesis of baconipyrone A (6) through an unprecedented retro-Claisen rearrangement/aldol cascade and the first total synthesis of baconipyrene C (8) by a “biomimetic” route versus the classical esterification route. The fourth compound in this series of potentially related compounds, caloundrin B (10), was never observed despite a careful search of each reaction crude where it may have been present.

The relationships between these compounds were probed and it was found, that under the conditions examined, the putative acyclic precursor 14/15 is not a biosynthetic product. Instead, siphonarin B (4) or perhaps caloundrin B (10), are the most likely biosynthetic products of the mollusk. Baconipyrone C (8) is not a precursor of baconipyrone A (6). The processes responsible for baconipyrones A (6) and C (8) are irreversible. As had been previously hypothesized, baconipyrone A (6) and C (8) are most likely artifacts of isolation (i.e., not natural products). The missing link in this series of compounds is caloundrin B (10) and its isomerization and rearrangement behavior.
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LIST OF ABBREVIATIONS

\( \alpha \) observed optical rotation

\([\alpha]_D\) specific rotation (expressed without units; the actual units, \((\text{deg} \cdot \text{mL})/(\text{g} \cdot \text{dm})\), are understood)

Ac acetyl

ap apparent (spectral)

aq aqueous

Ar aryl

atm atmosphere(s)

Bn benzyl

BORSM based on recovered starting material

bp boiling point

br broad (spectral)

Bu, \(^n\)Bu normal (primary) butyl

\(^t\)Bu \textit{tert}-butyl

°C degrees Celsius

calcd calculated

Chx cyclohexyl

CI chemical ionization

\( \text{cm}^{-1} \) wavenumber(s)

CN nitrile (as in acetonitrile (CH\(_3\)CN)

concd concentrated

COSY correlation spectroscopy
Cp   cyclopentadienyl
CSA  camphorsulfonic acid
δ    chemical shift in parts per million
d    day(s); doublet (spectral); deci
d    density
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ  2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de  diastereomeric excess
DEPT distortionless enhancement by polarization transfer
DEIPS diethylisopropylsilyl ether
dil  dilute
DIBAL-H diisobutylaluminum hydride
DIPT diisopropyltartrate
DIPEA diisopropylethyl amine
DMAP 4-(N,N-dimethylamino)pyridine
DME  1,2-dimethoxyethane
DMF  dimethylformamide
DMP  Dess-Martin periodinane
DMSO dimethyl sulfoxide
dr   diastereomeric ratio
DRIFT diffuse reflectance infrared Fourier transform spectroscopy
ee   enantiomeric excess
ent  a prefix used to denote enantiomer of
equiv  equivalents
er  enantiomeric ratio
ESI  electrospray ionization
Et  ethyl
FAB  fast atom bombardment
FCC  flash column chromatography
g  gram(s); prefix to NMR abbreviation denoting gradient-selected (e.g., gCOSY, gHSQC)
h  hour(s)
HMBC  heteronuclear multiple bond correlation
HMDS  hexamethyldisilazane
HMPA  hexamethylphosphoric triamide (hexamethylphosphoramide)
HRMS  high-resolution mass spectrometry
HSQC  heteronuclear single quantum correlation
Hz  hertz
IB  2-iodobenzoic acid
IBA  2-iodosobenzoic acid
IBX  2-iodoxybenzoic acid
Im  Imidazole
IPC  isopinocampheyl
IR  infrared
J  coupling constant (in NMR spectrometry)
J  Joule(s)
k  kilo
K  kelvin (absolute temperature)
L  liter(s)
LDA  lithium diisopropylamide
lit.  literature (abbreviation used with period)
LRMS  low-resolution mass spectrometry
µ  micro
m  multiplet (spectral); meter(s); milli
M  molar (moles per liter); mega
M+  parent molecular ion
max  maximum
Me  methyl
Mes  mesityl (2,4,6-trimethylphenyl)
MHz  megahertz
min  minute(s); minimum
mM  millimolar (millimoles per liter)
MMFF  Merck Molecular Force Field
MMPP  monoperoxyphthalic acid magnesium salt
mol  mole(s); molecular (as in mol wt)
MOM  methoxymethyl
mp  melting point
MS  mass spectrometry
MW, mol wt  molecular weight
m/z  mass-to-charge ratio
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>normal (equivalents per liter)</td>
</tr>
<tr>
<td>nm</td>
<td>nanometer(s)</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>obsd</td>
<td>observed</td>
</tr>
<tr>
<td>ORTEP</td>
<td>Oak Ridge Thermal Ellipsoid Plot</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PKS</td>
<td>polyketide synthetase</td>
</tr>
<tr>
<td>PMA</td>
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</tr>
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<td>ppm</td>
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<td>PPTS</td>
<td>pyridinium para-toluenesulfonate</td>
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<td>'Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>pt</td>
<td>point, data point (spectral)</td>
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<tr>
<td>PTLC</td>
<td>preparative thin layer chromatography</td>
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<td>q</td>
<td>quartet (spectral)</td>
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<td>rac</td>
<td>racemic, racemization</td>
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<td>Ref, ref</td>
<td>reference</td>
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<td>rel</td>
<td>relative</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
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<td>Abbreviation</td>
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<td>------------</td>
</tr>
<tr>
<td>s</td>
<td>singlet (spectral); second(s)</td>
</tr>
<tr>
<td>SAM</td>
<td>S-adenosyl methionine</td>
</tr>
<tr>
<td>t</td>
<td>triplet (spectral)</td>
</tr>
<tr>
<td>TASF</td>
<td>tris(dimethylamino)sulfonium difluorotrimethylsilicate</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS, TBS</td>
<td><em>tert</em>-butyldimethylsilyl</td>
</tr>
<tr>
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<td>temperature</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl (triflyl)</td>
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<td>tetrahydrofuran</td>
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<tr>
<td>TIPS</td>
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<td>thin-layer chromatography</td>
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<tr>
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</tr>
<tr>
<td>TOF</td>
<td>time-of-flight (in mass spectrometry)</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl (p-CH$_3$C$_6$H$_4$SO$_2$)</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
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<td>weight per unit weight (weight-to-weight ratio)</td>
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INTRODUCTION

1.1 Introduction to structures, relationships, isolation, and biosynthesis

1.1.1 Siphonariid mollusks and examples of isolated structures

Siphonariid mollusks are non-descript animals found in temperate and tropical ocean intertidal zones – the area of coastline dry at low tide and underwater at high tide – throughout the world. These limpet-like creatures, sometimes referred to as false limpets, are superbly adapted to their environment with both a primitive lung and gills and may represent an evolutionary link between land and sea mollusks. Of all the pulmonates, the siphonariids are considered the most primitive.

Despite their non-descript outward appearance and primitive evolutionary status, these organisms are credited with being the grand architects of an incredibly diverse array of complex polypropionate natural products. The polypropionates produced by siphonariid mollusks have been classified into three groups (Figure 1): simple (cf. denticulatin A (1), and muamvatin (3), α-pyrones (cf. diemenensin (2)), and γ-pyrene containing (cf. siphonarins A (5) and B (4) and baconipyrones A - D (6 - 9)). Interestingly, these animals produce the same polypropionate secondary metabolite profile regardless of geographical location.

---

1 A subclass of gastropod, comprising one half of all mollusk species.
Upon careful inspection and analysis, the rich structural diversity can be attributed to varying intramolecular cyclization events that occur along the heavily oxygenated carbon backbone.\textsuperscript{2, 10} For example, the production of $\gamma$-pyrones from 1,3,5-triones, dihydro-4-pyrones and tetrahydro-2-hydroxypyrones from 5-hydroxy-1,3-diones, and spiroacetals from 9-hydroxy-1,5-diones. It has been suggested that some of the polypropionate secondary metabolites produced by the siphonariids may be related through unstable acyclic precursors that undergo different cyclization events. Such a connection was proposed for several
seemingly different \( \gamma \)-pyrone-containing decapropionate metabolites: siphonarin B (4), baconipyrones A (6) and C (8) and caloundrin B (10)\(^9\) (Figure 1.2).\(^{11}\)

\[\text{contiguous carbon skeletons} \quad \text{non-contiguous carbon skeletons}\]

\[\text{contiguous carbon skeletons} \quad \text{non-contiguous carbon skeletons}\]

\[\text{siphonarin B (4)} \quad \text{baconipyrone C (8)}\]

\[\text{caloundrin B (10)} \quad \text{baconipyrone A (6)}\]

**Figure 1.2** Potentially related siphonariid decapropionates

**1.1.2 Proposed relationships between siphonariid polypropionates**

The baconipyrones A (8) and C (6) are rare examples of polypropionate natural products containing a non-contiguous carbon skeleton.\(^4\), \(^11\), \(^12\) Their formation was originally proposed to occur through a rearrangement of the parent decapropionate, most likely siphonarin B (4), which was contemporaneously co-isolated (Figure 1.3).\(^4\)
**Figure 1.3** Proposed formation of baconipyrones A (8) and C (8)

Caloundrin B (10) and siphonarin B (4) were proposed to be related via alternative cyclization modes, attributable to the orientation of the C-8 methyl (C-6,8 syn vs. C-6,8 anti); C-8 is flanked by two carbonyls and is expected to be readily epimerizable (**Figure 1.4**). ⁹,¹¹
Figure 1.4 Alternative contiguous carbon skeleton cyclization modes

It was proposed that the configuration at C-8 controls the cyclization preference because of destabilizing syn-pentane interactions between the C-8 and C-10 methyl groups in 13 and the C-6 and C-8 methyl in 16 (i.e., the alternative cyclization modes presented in Figure 1.4).\textsuperscript{11}

These destabilizing interactions are highlighted in structures 13a and 16a (Figure 1.5).
These analyses led to a refinement in the hypothesis surrounding the formation and relationships between these compounds (4, 6, 8, and 10) and, as a result of this analysis, significant doubt was placed upon their natural product status. It was proposed that siphonarin B (4) and caloundrin B (10) may be formed non-enzymatically (i.e., formation and abundance governed by each compound’s relative stability) from an unstable acyclic precursor, such as 14 and 15. However, even the unstable acyclic precursors 14 and 15 may not be real natural products because the \( \gamma \)-pyrone moiety was suggested to be a result of isolation.ii, 3, 11

---

ii Spontaneous formation, during isolation, of the \( \gamma \)-pyrone from a 1,3,5-triketone is unlikely (vide infra).
Additional doubt about the natural product status of some of these structures is presented by baconipyrone C (6). This structure has been detected numerous times in independent isolation studies,4,12 as would be expected if it were biosynthetically produced by the mollusk. However, a later, “careful”, reexamination of S. baconii,13 extracts by Garson, based on the notion that these structures may be artifacts of isolation, found no trace of baconipyrone C (8); siphonarin B (4), as expected, was isolated from this study.12 It was proposed that a delicate precursor, susceptible to a retro-Claisen rearrangement (cf. 11, Figure 1.3), might be the real natural product and that baconipyrone A (6) and C (8) might owe their origin to events transpiring outside the organism. Retro-Claisen rearrangements have been shown to occur in similar systems,12,14-17 but a “biomimetic” synthesis of baconipyrone C (8) has not been demonstrated and retro-Claisen rearrangement/aldol cascades leading to baconipyrone A (6), or even a simple model compound, appears to be unprecedented.

Despite the number of observations supporting the aforementioned hypotheses, there remains a significant, unanswered problem regarding the origin of this series of compounds. If their formation was non-enzymatic (i.e., under thermodynamic control), then it should be expected that siphonarin B (4) and caloundrin B (10) would be isolated in a ratio reflecting their relative stabilities. Siphonarin B (4) has been isolated numerous times in independent studies by several different research groups.4,8,9 Caloundrin B (10), however, has been observed and isolated just once.9 Realistically, caloundrin B (10) should have been observed on more than just this one occasion given the number of isolation studies that these mollusks have “participated” in.

iii S. baconi is synonymous with S. zelandica.
The same arguments apply to siphonarin A (5) and baconipyones B (7) and D (9). These compounds are C-20 desmethyl analogues of 4, 6, and 8, respectively. No C-20 desmethyl compound analogous to caloundrin B (10) has been isolated.

1.1.3 Isolation and structure determination

Siphonarin B (4) was the first of these related polypropionates to be isolated and characterized. The sample originated from a collection of S. zelandica obtained from New South Wales, Australia in an approximate yield of 0.05 mg/animal. The structure was determined by NMR comparison to siphonarin A (5) whose structure and relative configuration was unambiguously determined by X-ray diffraction studies.

Baconipyrones A (6) and C (8) were later isolated and characterized from a collection of S. Baconi obtained near Melbourne, Australia in an approximate yield of 0.05 and 0.016 mg/animal, respectively. Co-isolated with baconipyrones A (6) and C (8) were siphonarin A (5) and baconipyrones B (7), and D (9). The structures of baconipyrones A (6) and C (8) were determined on the basis of NMR comparison and biosynthetic considerations to baconipyrone B (7), whose structure and relative configuration was unambiguously determined by X-ray diffraction studies.

Caloundrin B (10) was the last of these four related structures to be isolated. It originated from a sample of S. zelandica obtained from Shelley and Kings Beach, Caloundra, Australia in an approximate yield of 0.01 mg/animal and was the only structure in this series of compounds that was not isolated and characterized by Faulkner and co-workers. Expecting to find only siphonarins A (5) and B (4), Garson and co-workers described the discovery of this new metabolite (co-isolated with 4 and 5) as surprising. The structure was determined by extensive NMR studies and comparison to related structures. During the course of the NMR
studies to determine the structure, caloundrin B (10) decomposed. Attempts, under unspecified conditions, to generate more caloundrin B (10) from siphonarin B (4) were unsuccessful.

1.1.4 Siphonariid polypropionate biosynthesis

There are two conceivable possibilities for the biosynthesis of siphonariid polypropionates: direct condensation of propionate units (pathway A, Figure 1.6) or through a polyacetate chain and methylation by S-adenosyl methionine (pathway B, Figure 1.6). Examples of both possibilities are well documented in the literature for other organisms known to produce polypropionates.

Figure 1.6 Biosynthetic possibilities

Garson and Faulkner, as part of their long standing investigation into the polypropionates produced by siphonariid mollusks, investigated the biosynthesis of

---

iv Isolation included aqueous extraction and extensive chromatography. Decomposition occurred in the NMR tube, following isolation.
denticulatin (1) (Figure 1.7). This investigation was the first reported effort into establishing the biosynthetic origin of the compounds produced by siphonariid mollusks. Through injection of sodium [1-\textsuperscript{14}C]propionate into the foot muscle of \textit{S. denticulata} and by transdermal uptake of sodium [1-\textsuperscript{14}C]propionate from inoculated aquarium water, it was shown conclusively that the biosynthesis of denticulatin (1) is of propionate origin (i.e., pathway A, Figure 1.6).

\textbf{Figure 1.7} Biosynthetic studies on denticulatin (1)

An intriguing problem in the biosynthesis of the siphonariid polypropionates is the direction of chain growth, which cannot be simply determined by inspection due to a decarboxylation event that occurs during biosynthesis. Two modes of chain extension are possible in that chain propagation may proceed from C-1 to C-19 or in the reverse manner. Garson et al. investigated this issue in the siphonarins (4 and 5), concurrent to confirming the propionate origin of these molecules (i.e., verification of the previous conclusion regarding siphonariid polypropionate biosynthesis).
Garson reasoned that the problem could be solved by determining the origin of C-19 in siphonarin A (5) by “feeding” experiments (via injection in the foot muscle of S. zelandica) of sodium [1-14C]propionate (Figure 1.8). Depending on direction of chain growth, C-19 would either show 14C labeling from incorporation of sodium [1-14C]propionate or not; siphonarin A (5) is constructed through condensation of 9 propionate units and 1 acetate unit. In addition to confirming the propionate origin of 4 and 5, it was definitively shown that there was no incorporation of 14C in any of the acetate-related degradation compounds isolated following degradation experiments. Thus, the direction of chain growth was determined to be C-19 to C-1. By analogy, siphonarin B (4) was also reasoned to grow C-19 to C-1. These studies also confirmed the de novo biosynthesis of these compounds as opposed to bioaccumulation from food sources.¹

Garson, Goodman, and Paterson rationalized that the other siphonariid polypropionate metabolites should be assembled in a similar manner on the basis that the

¹ Siphonarin B (4) is constructed from 10 propionate units.
isolated structures are related. A comparison of the acyclic structures of the siphonarin B (4), muamvatin (3), and denticulatin (1) all show a common tetrapropionate motif near the terminus of the chain that shares similarity with Cane, Celmer, and Westley’s model for polyether antibiotic biogenesis (Figure 1.9). This observation suggests a genetic commonality between bacteria and the siphonariids, but, to date, no common proteins have been disclosed. 

\[ \text{siphonarin B (4)} \]

\[ \text{muamvatin (3)} \]

\[ \text{denticulatin A (1)} \]

\[ \text{Cane, Celmer, and Westley acyclic precursor} \]

**Figure 1.9** Biosynthetic model
1.2 Synthetic studies on these related siphonariid polypropionates

1.2.1 Synthetic studies on baconipyrone C (6): establishment of absolute configuration

A key unresolved issue in the study of baconipyrone C (6), and of all these related compounds, was the determination of absolute configuration. Paterson elected to tackle this issue through the synthesis of a known siphonariid polypropionate degradation product, carboxylic acid 40 (the known degradation product is actually ent-40, vide infra) (Scheme 1.1).\(^\text{21}\)
Scheme 1.1
The carbon skeleton of the carboxylic acid fragment was constructed via three aldol reactions. Starting from Roche ester derivative 31, two unselective titanium (IV)-mediated aldol reactions produced the carbon skeleton required to access a key intermediate, γ-pyrene aldehyde 35. Subjection of diol 33 to DMP oxidation followed by Yamamura’s γ-pyrene conditions gave the desired γ-pyrene 34 in moderate yield. Hydrogenolysis, followed by oxidation gave the reportedly sensitive (i.e., prone to racemization) γ-pyrene aldehyde 35.

To complete the carbon skeleton of the target (40), a Sn(II)-mediated aldol reaction between γ-pyrene aldehyde 35 and 36 was conducted. The oxidation states of the aldol adduct were then reversed in addition to setting the last stereogenic center via a Evans-Tishchenko reduction. The orthogonal protecting groups were removed and PMB diol 39 was oxidized over a two (2) step sequence to the corresponding keto-acid. Finally, the PMB group was removed via hydrogenolysis to give carboxylic acid 40.

The carboxylic acid matched the reported spectroscopic data for this fragment and the corresponding fragment of baconipyrone C (8). However, the optical rotation (synthetic: [α]D +115 (c 0.5, CH2Cl2)) was not of the same sign as the isolated material (natural: [α]D -87 (c 0.052, CH2Cl2)). This suggested that the siphonariid polypropionates were enantiomeric to carboxylic acid 40 (i.e, ent-40).

1.2.2 Total syntheses of baconipyrone C (8)

To date, there are two reported syntheses of baconipyrone C (8) and one report on the enantioselective synthesis of the unnatural antipode (ent-8). All three synthetic efforts

---

vi Available in 3 steps, 88% overall yield from methyl (R)-3-hydroxy-2-methylpropionate.
vii Available in 3 steps, 86% overall yield from methyl (S)-3-hydroxy-2-methylpropionate.
were designed around disconnection at the ester linkage, but featured significantly different approaches and methodologies to construct each fragment (41 and 42) (Figure 1.10). No attempt was made in subsequent syntheses to improve on the coupling strategy and final steps pioneered in the first.28

![Figure 1.10 Baconipyrone C (8) synthetic strategy](image)

**1.2.2.1 Paterson’s synthesis**

Paterson approached the total synthesis of baconipyrone (8) based on his earlier work in constructing carboxylic acid 40 (Scheme 1.1).21 Knowing the required absolute configuration, he began with the opposite enantiomeric series\(^\text{viii}\) from what was used previously (Scheme 1.2). The steps pioneered previously were followed without deviation; however, several notable improvements to the efficiency of the process were made. For example, using the alternative Yamamura protocol\(^\text{24}\) (CCl\(_4\)/PPh\(_3\)) to form the Bn-protected pyrone (ent-34, Scheme 1.1) improved the yield from 54% to 88%. Another notable

\(^{\text{viii}}\) See Scheme 1.1. The absolute configurations used in the synthesis of baconipyrone C (8) are, however, opposite to that shown in Scheme 1.1. Paterson started the synthesis of baconipyrone C (8) with ent-31.
improvement was the Sn-mediated aldol reaction\textsuperscript{25} to form \textit{ent-37}: the yield of this transformation was improved from 59\%\textsuperscript{21} to 80\%\textsuperscript{28} with the same selectivity. Overall, PMB-protected keto-acid \textbf{42} was produced in a longest linear sequence of 18\textsuperscript{ix} steps in an astounding overall yield of 25\%.

\begin{center}
\begin{tikzpicture}
  \node[draw,align=center] (a) at (0,0) {ent-31 \quad 15 steps \quad 42};
  \draw[->] (a.east) -- (a.east -| a.east + (1,0));
\end{tikzpicture}
\end{center}

\begin{center}
\textit{Obtained in:}
\textit{3 steps, 88\% yield}
\end{center}

\textbf{Scheme 1.2}

Attention then turned towards the synthesis of the remaining fragment, hydroxydione \textbf{41} (\textbf{Scheme 1.3}). An enantioselective aldol of 3-pentanone (\textbf{43}) with (\textit{E})-2-methyl-2-pentenal (\textbf{44}) using previously established conditions\textsuperscript{31} gave the desired aldol adduct in moderate yield and enantioselectivity (57\%, 85\% ee). Protection as the corresponding \textsuperscript{t}butyldimethylsilyl ether, hydroboration,\textsuperscript{32} oxidation under Swern conditions, and deprotection finished the synthesis of the desired alcohol \textbf{41} over 5 steps in 32\% overall yield.

In the same study,\textsuperscript{28} Paterson also presented an alternative diastereoselective synthesis of \textbf{41}, starting from (\textit{R})-ethyl lactate. The synthesis was slightly longer (9 steps) than the enantioselective synthesis shown in Scheme 1.3, but was very efficient (38\% overall yield) and delivered the desired compound (\textbf{41}) with excellent ee, as would be expected from a synthesis starting from the chiral pool.

\textsuperscript{ix}21 steps inclusive of the 3 steps required to make \textit{ent-36}. 

Completion of the synthesis required what Paterson described as a challenging esterification step due to, what was thought to be, epimerization occurring at C-14 (Scheme 1.4); HC-14 is $\alpha$ to a ketone (C-13) and a vinlylagous ester (the $\gamma$-pyrone moiety), thus HC-14 should be the most acidic proton and the stereocenter most sensitive to epimerization. After much experimentation, a modified Yamaguchi esterification protocol finally gave 73% combined yield of a 10:1 mixture of C-14 diastereomers.\(^x\) The remaining protecting group was oxidatively removed and the minor diastereomer chromatographically separated to provide baconipyrone C (8) in 67% yield.

\(^x\) Epimerization at C-14 was assumed based on sound reasoning, but was not rigorously proven.
From commercially-available starting material, the longest linear sequence was 20\textsuperscript{xi} steps. Despite the length, the described synthesis was extremely efficient giving an overall yield of 11%. This remarkable achievement confirmed the structure proposed for baconipyrone C (8), as well as its absolute configuration.

1.2.2.2 Hoveyda’s synthesis

Hoveyda’s synthesis was the first enantioselective synthesis of the unnatural enantiomer of baconipyrone C (\textit{ent}-8).\textsuperscript{30} The strategy employed was based on the extensive use of chiral metal complexes to enantioselectively access each fragment.

The key catalytic asymmetric allylic alkylation (CAAA) step in the synthesis of the alcohol required diene 53, which was accessed in 22% yield over 7 steps from commercially-available starting material (\textbf{Scheme 1.5}). Subjecting diene 53 to the CAAA protocol developed to support this synthesis, gave the desired doubly alkylated product 55 in 61% yield and >98% ee. Removal of the allyl protecting group,\textsuperscript{33} followed by ozonolysis gave the

\textsuperscript{xi} Inclusive of 41, the synthesis had a total of 28 steps.
desired alcohol fragment (ent-41). In summary, hydroxydione ent-41 was synthesized in 10 steps with an overall yield of 7% (>98% ee).

\[
\text{Scheme 1.5}
\]

The synthesis of carboxylic acid ent-42 was based on the desymmetrization of oxabicycle 58, accessible in 4 steps from commercially available starting materials (Scheme 1.5).
1.6). The first 2 steps in this sequence are known\textsuperscript{xii,34} but later two steps are not reported and, therefore, must be estimated based on analogy.\textsuperscript{xiii,35} Desymmetrization was achieved via a previous established asymmetric ring-opening metathesis/cross metathesis reaction\textsuperscript{36} that was somewhat optimized in this synthesis to access pyran \textit{61} in moderate yield (62%) and enantioselectivity (88% ee, 15:1 er). Pyran \textit{61} was then opened by dissolving metal reduction. The moderate yield of this step was the result of competitive loss of the PMB group to form the corresponding diol. Nevertheless, \textit{62} was a compound that could be elaborated into the desired compound. This would, however, require the stereoselective addition of another methyl group in addition to the \(\gamma\)-pyrone moiety.

Hoveyda first tackled stereoselective addition of the required methyl group to \textit{62}. Consistent with the theme of this synthetic effort, he extended the carbon skeleton through a catalytic Si-tethered ring-closing metathesis reaction\textsuperscript{37,38} and then performed a diastereoselective allylic alkylation with \textit{Me}_2\textit{Zn} and \textit{CuCN}.

---

\textsuperscript{xii} Obtained in 36% overall yield.
\textsuperscript{xiii} Yadav reported the synthesis of the related Bn ether. Yields of the reduction and protection steps are 74 and 94%, respectively.
Scheme 1.6

With all the stereogenic centers now correctly installed, attention turned to towards formation of the γ-pyrone moiety (Scheme 1.7). Protection of 65, followed by ozonolysis and reduction in the same pot gave diol 66. Differentiation of the two primary alcohols was now required to continue the synthesis. Fortunately, experimentation found that the two alcohols reacted at different rates with TBSOTf. By using substoichiometric amounts of reagent, at low temperature, and resubjecting recovered starting material to the reaction
conditions, desired alcohol 67 could be produced in 60% yield.\textsuperscript{xiv} The exposed \(1^\circ\) alcohol was oxidized to give 68 and the stage was now set to install the \(\gamma\)-pyrone and complete the total synthesis.

\begin{equation}
\begin{array}{cccc}
65 & \text{a, b} & \text{72\%} & 66 \\
\text{HO} & \text{HO} & \text{HO} \\
\end{array}
\begin{array}{cccc}
\text{a} & \text{60\% (4 runs)} & 67 \\
\text{TBSO} & \text{TBSO} & \text{TBSO} \\
\end{array}
\begin{array}{cccc}
\text{c} & \text{98\%} & 68 \\
\text{OH} & \text{OH} & \text{OH} \\
\end{array}
\begin{array}{cccc}
\text{70} & \text{d} & \text{64\%} & 69 \\
\text{TIPS} & \text{TIPS} & \text{TIPS} \\
\end{array}
\begin{array}{cccc}
\text{e} & \text{64\%} & 70 \\
\text{TBSO} & \text{TBSO} & \text{TBSO} \\
\end{array}
\begin{array}{cccc}
\text{71} & \text{3 steps (2 known)} & \text{60\%} & \text{ent-42} \\
\text{TBSO} & \text{TBSO} & \text{TBSO} \\
\end{array}
\end{equation}

\begin{itemize}
\item a) TBSOTf, 2,6-lutidine
\item b) ozonolysis
\item c) DMP
\item d) LDA, then 68
\item e) DBU
\end{itemize}

**Scheme 1.7**

\textsuperscript{xiv} Four runs (four individual experiments) of subjecting starting material to the reaction conditions was required to achieve this modest yield of the protected compound (67).
Hoveyda opted to use a novel method of his own design to form the $\gamma$-pyrone rather than use any of the more mild methods more recently introduced (Scheme 1.7). Following an aldol reaction of aldehyde 68 with 69 and oxidation of the aldol with DMP, Hoveyda found that a DBU-promoted dehydrative cyclization gave desired pyrone 71 in good yield. Hydrolysis of both TBS-ethers produced the enantiomer of same intermediate used by Paterson in the first total synthesis of baconipyrone C (8). Repetition of steps pioneered by Paterson (see Scheme 1.4) furnished the unnatural enantiomer of baconipyrone C (ent-8) in yields comparable to those obtained previously.

1.2.2.3 Yadav’s synthesis

Yadav’s synthetic strategy, like Hoveda’s, was based on the desymmetrization of oxabicycle 58 to construct a key section of carboxylic acid fragment 42. This strategy and methodology had been used successfully by Yadav in synthetic studies on several natural products.

Desymmetrization of oxabicycle 58 by enantioselective hydroboration and its elaboration into lactone 72 has not been described in the open literature; however, a closely-related analogue (Bn vs. PMB) has been partially described (Scheme 1.8). It can be assumed that similar steps were employed; yields (and selectivities) are expected to be similar, but this is speculation.

---

xv Few mild methods to form $\gamma$-pyrones from 1,3,5-triketone (or protected derivatives) were available to Hoveyda at the time this work was published. More recently, additional investigations into this problem have been published (vide infra).

xvi Obtained in four steps in 36% yield.
Scheme 1.8

Reduction of lactone 72\textsuperscript{xvii} gave triol 73. In order to isolate C-15-OH (siphonariid numbering), a significant protecting-group game was engaged. Once isolated, the alcohol was oxidized with IBX in DMSO to give aldehyde 76 and the stage was set to install the remaining carbon atoms, form the \(\gamma\)-pyrone, and complete the synthesis of carboxylic acid 42 (Figure 1.10).

Installation of the \(\gamma\)-pyrone proceeded according to methodology developed by Yamamura (Scheme 1.9); the lithium dianion of 4-methyl-3,5-heptanediione (77) was reacted with aldehyde 76, followed by DMP oxidation to give triketone 78.\textsuperscript{23, 24} The resulting triketone was then subjected to PPh\(_3/CCl\(_4\) in THF to form desired \(\gamma\)-pyrone 79. Deprotection

\textsuperscript{xvii} Accessible in 4 steps from commercially-available material. Like Hoveyda (Section 1.2.2.2), no yields, selectivities, or procedures are given; overall yield is assumed (\textit{vide supra}).
of the MOM and benzyl groups gave ent-39, the same compound first made by Paterson\textsuperscript{28} and a key intermediate in the total synthesis of baconipyrone C (8). Oxidation, as reported by Paterson, gave the desired carboxylic acid in 23 steps. The overall yield to obtain carboxylic acid 42 was 3.0\%.\textsuperscript{xviii}

![Chemical structures and reactions](image)

Scheme 1.9

Yadav’s approach to hydroxydione 41 was significantly longer than both prior reports (Scheme 1.10). He opted for an enzymatic resolution as a means to obtain the product in

\textsuperscript{xviii} Assuming that the 8 unreported steps are as efficient as those reported for the Bn derivative.
enantioenriched form. In total, hydroxydione 41 was accessed in 14 steps in 3% overall yield. The ee of 41 was not stated, but can be inferred from the optical rotation Yadav obtained and comparison to prior reports.\textsuperscript{28, 30}

\begin{center}
\includegraphics[width=\textwidth]{scheme1.png}
\end{center}

\textbf{Scheme 1.10}

\textbf{1.2.2.4 Synthetic comparison and summary}

The synthesis of baconipyrone C (8) presented by Paterson is by far the most efficient, has the least number of steps in the longest linear sequence, and the least number of steps overall (Section 1.2.2.1). Paterson’s synthesis is a clear demonstration of just how
powerful the methodology he has developed to efficiently construct polypropionate motifs. The only weakness of Paterson’s synthesis is the use of expensive, enantiopure reagents.

Hoveyda’s synthetic approach was interesting from several different perspectives (Section 1.2.2.2). Each fragment in the synthesis relied upon an enantioselective reaction based on a chiral metal complex. Carboxylic acid fragment 42 relied upon the desymmetrization of a meso compound using an AROM/CM reaction. Hydroxydione 41 used an interesting catalytic asymmetric allylic alkylation (CAAA) protocol that was developed specifically to support the synthesis. However, to be clear, Hoveyda never synthesized baconipyrone C (8) because the correct enantiomer was not accessed. It is unclear why catalysts with the appropriate absolute configuration were not utilized in this synthetic effort.

Yadav’s synthesis was largely based on methodology previously shown to be effective in synthetic studies of several natural products (Section 1.2.2.3). However, in the case of this target, Yadav was forced to make significant use of protecting groups in order to coax his starting material into the final target. These protecting group manipulations detract from the key chemistry employed in this synthesis - desymmetrization of a meso compound by enantioselective hydroboration - and as such do not showcase the power of this methodology well. Further, Yadav turned to an enzymatic resolution as a means to enantioselectively access hydroxydione 41, rather than explore a more modern approach - like the desymmetrization methodology highlighted in this synthesis - to access this fragment.

Despite the innovative and powerful chemistry shown in these three syntheses of baconipyrone C (8), none addressed the hypothesis regarding the formation of this compound. Additionally, neither of the two subsequent syntheses improved on any aspect of
Paterson’s synthesis, except for the issue of accessing baconipyrone C (8) through completely enantioselective routes.

![Chemical structure](image)

<table>
<thead>
<tr>
<th></th>
<th>Paterson 2000(^a)</th>
<th>Hoveyda 2007(^b, c)</th>
<th>Yadav 2009(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longest linear sequence</td>
<td>18</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Total number of steps</td>
<td>21</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Yield</td>
<td>25%</td>
<td>2.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td>([\alpha]_D)^(^e)</td>
<td>-96.5(^{c, 0.4})</td>
<td>+69.1(^{c, 0.19})</td>
<td>-94.2(^{c, 0.75})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Paterson 2000(^a)</th>
<th>Hoveyda 2007(^b, c)</th>
<th>Yadav 2009(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longest linear sequence</td>
<td>5</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Total number of steps</td>
<td>5</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Yield</td>
<td>32%</td>
<td>7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>([\alpha]_D)^(^e)</td>
<td>-16.4(^{c, 1.1})</td>
<td>+12(^{c, 1.0})</td>
<td>-15.6(^{c, 2.0})</td>
</tr>
</tbody>
</table>

\(^a\) Ref 28. \(^b\) Ref 30. \(^c\) Antipodes of 41 and 42 prepared. \(^d\) Ref 29. \(^e\) CHCl\(_3\). \(^f\) Also synthesized diastereoselectively from (R)-ethyl lactate (9 steps; 38% overall yield). \(^g\) Not reported.

**Figure 1.11** Baconipyrone C (8) synthetic comparison

### 1.2.3 Synthetic studies on baconipyrone A (6)

Baconipyrone A (6) has never been synthesized, but the cyclohexanone subunit (87) has been the subject of two synthetic studies.\(^{50, 51}\)
1.2.3.1 Vogel’s synthetic study on the cyclohexanone subunit (87)

Vogel accessed the cyclohexanone subunit (87) of baconipyrone A (6) through a very concise route starting from 88 (Scheme 1.11). An SO₂-induced oxyallylation of 88 followed by retro-ene elimination of SO₂ (the intermediate is shown as 90) gave 91 in a single pot. Transesterification of 91 with Bu₃SnOMe presumably generated the corresponding Sn-enolate which underwent an efficient intramolecular aldol reaction. Hydrogenolysis gave the desired cyclohexane subunit (87) of baconipyrone A (6). The cyclohexane subunit (87) fortuitously crystallized, which provided the means to unambiguously prove the structure of the compound obtained.
Scheme 1.11

There is no comment in Vogel’s report on the synthesis of 87 on whether any effort was made to make carboxylic acid fragment ent-40 and attempt to complete the first total synthesis of baconipyrone A (6).

1.2.3.2 Plumet’s synthetic study towards the cyclohexanone subunit (87)

Plumet was actually the first to report a synthetic effort towards the synthesis of (±)-87. However, as unambiguously shown by Vogel in his subsequent synthesis of the cyclohexane subunit (87), the compound claimed to be (±)-87 by Plumet was, most likely, a diastereomer of 87. Vogel showed that the last step in Plumet’s synthesis had gone awry; subjection of authentic 87 to the reaction conditions described by Plumet resulted in complete transformation to other compounds, including decomposition. The synthetic
sequence reported by Plumet is shown in Scheme 12, noting the failure to produce the desired product.

Scheme 1.12

Lastly, as Vogel pointed out, there was no discussion of structure proof in Plumet’s report nor was any data provided that could facilitate a retrospective analysis of the structure.\(^5\)
1.2.4 Synthetic studies on siphonarin B (4)

Shortly after completing the first total synthesis of baconipyrone C (8), Paterson and coworkers published an elegant synthesis of siphonarin B (4).\textsuperscript{15} This synthetic effort clearly showed the degree of difficulty that the construction of such natural products present.

In an initial attempt towards siphonarin B (4), Paterson utilized key fragment \textit{ent-39}, which had been previously used in the synthesis of baconipyrone C (8) (Scheme 1.13).\textsuperscript{28} Protecting group manipulation exposed the \textit{1°} alcohol towards oxidation by DMP. A Sn-mediated aldol reaction between aldehyde 102 and ketone 103, again derived from the previous baconipyrone C (8) synthesis, afforded aldol 104.\textsuperscript{28, 49} Hydrolysis of the triethylsilyl group, followed by bis-oxidation of the exposed alcohols provided triketone 105.

The plan at this stage was to remove the silylidene protecting group of 105 and allow the C-7-OH to form a hemiacetal with the C-9 carbonyl. Unfortunately, the C-3-OH formed a hemiacetal with the C-7 carbonyl instead. Oxidative removal of the PMB group then formed spiroacetal 106 (C-11-OH onto C-7 hemiacetal), which resisted all attempts to undergo ring-chain tautomerism to a form more amenable to the synthesis at hand; a revision in strategy was thus required. This attempt clearly shows that the protecting group strategy employed must work hand-in-hand with the redox strategy to create and unveil functionality at the correct time.
Scheme 1.13

In the second attempt, Paterson retooled ketone \textbf{110}, derived from ketone \textbf{109}, and modified acceptor aldehyde \textbf{108} (Scheme 1.14). These changes were made to orthogonally protect C-3 and C-5-OH (siphonariid numbering) in order to control the release of each hydroxyl group and thus establish some level of control over hemiacetal formation that thwarted the previous effort.

\textsuperscript{xix} Available in 3 steps, 62\% overall yield from (S)-methyl-3-hydroxy-2-methylpropionate
Upon release of the DEIPS protecting group of 112 with HF•pyridine, the desired ring-chain tautomerism of C-5-OH onto C-9 carbonyl occurred and internally protected C-5-OH from further reaction (cf. 113). Hydrogenolysis of 113 released the benzyl group and the resulting hydroxyl group was oxidized under Swern conditions. The sensitive aldehyde was immediately subjected to the Kishi-Nozaki protocol\textsuperscript{56, 57} with vinyl iodide to give allylic

Scheme 1.14
alcohols 114. A second Swern oxidation gave the corresponding enone, which was subjected to hydrogenation with palladium on carbon in order to reduce the olefin and hydrogenolyze the PMB group. Extended reaction time (16 hours) was required for hydrogenolysis, which resulted in what was described as significant, competing decomposition. However, a small amount of spirocyclization occurred to afford siphonarin B (4) in 8% yield over the final two transformations of the synthesis.

In total, this remarkable diastereoselective synthesis of siphonarin B (4) - reportedly described as a sensitive compound - was achieved in a longest linear sequence of 28 steps and 0.86% overall yield from commercially available starting material.xx,58

1.3 Conclusions

There have been several synthetic efforts over the years that have answered a limited number of questions about this series of related structures. The previous efforts primarily focused on proof of structure and determination of absolute configuration. However, even these aspects have not been fully addressed because two of the four structures (caloundrin B (10) and baconipyone A (6))xxi have never been synthesized: caloundrin B (10) has not been the subject of any synthetic study.

There remain many unanswered questions in this series of potentially related compounds. For example, no study has addressed the formation and potential relationships between these molecules. Specifically, is there an acyclic precursor (cf. 14 or 15) that gives rise to caloundrin B (10) and siphonarin B (4) via alternative folding patterns and is this folding under thermodynamic control? Why is it that siphonarin B (4) has been observed multiple times, but caloundrin B (10) only a single time? Are the baconipyrones A (6) and C

xx The synthesis was described as starting from ent-31, but ent-31 is a synthetic product and is available 3 steps, 88% overall yield from (S)-(++)-3-hydroxy-2-methylpropionate.
xxi Conceivably routes to fragments of this compound exist, but the fragments have never been coupled.
(8) formed from any of the former via retro-Claisen rearrangement (cf. 8) and retro-Claisen rearrangement/aldol cascades (cf. 6)? Further, is baconipyrone C (8) the precursor of baconipyrone A (6)? If this were the case, then how is it possible that the resulting aldol reaction is face and group selective since no other diastereomers have been observed?

As shown in these synthetic studies, accessing siphonariid polypropionates in reasonable yield is extremely challenging due to the sensitivity of these molecules towards even mild conditions,15, 28, 51 storage,30 and in the case of caloundrin B (10), decomposition during NMR studies to determine structure.9 Further, the strategy to reveal and create functionality has to be carefully planned and executed otherwise a synthetic approach can rapidly reach a dead end due to unexpected ring-chain tautomerization events15 or undesirable epimerization events.28

These unresolved questions coupled with the inherent synthetic challenge present the possibility of an intriguing research project.
RESULTS AND DISCUSSION

2.1 Research objectives

The objectives of this research project were to establish relationships between siphonarin B (4), baconipyrone A (6), baconipyrone C (8), and caloundrin B (10), ideally through the putative acyclic precursor (cf. 14 and 15) (Figure 2.1). With the acyclic precursor in hand, conditions could be investigated to attempt to control these alternative cyclization pathways and/or facilitate the proposed chemical transformations that would lead to the observed structures. Additionally, with one, or more, of these isolated structures in hand, conditions could be investigated to test for conversion of one isolated structure to another. If successful, some comment could be made about the natural product status of this series of compounds; a subject which has not been broached by any of the synthetic studies performed on this series of compounds.

Model studies would be used where literature precedent is weak or non-existent. These studies are, however, not research objectives per se, but are tools to determine how to progress towards answering the above research questions.

A secondary research objective was to showcase the power that the Thiopyran Route to Polypropionates (see Section 2.3) provides in rapidly assembling polypropionate structural motifs. The available adducts from this synthetic strategy are useful building blocks for the total synthesis of complex polypropionate natural products.
2.2. Target selection and synthetic considerations

Of the four isolated, related structures (4, 6, 8 and 10), the target that was selected to become the primary focus for synthetic study was caloundrin B (10) (Figure 2.2). This selection was made primarily because of the structures containing contiguous carbon...
skeletons (siphonarin B (4) and caloundrin B (10)), only caloundrin B (10) has never before been synthesized. This molecule also contains several unique structural features and eight stereogenic centers, providing significant synthetic challenge in its construction. Further, caloundrin B (10) is reportedly unstable,\(^9\) presenting an even higher degree of challenge.

\[ \text{OH} \quad 8 \]

\[ \text{OH} \quad 4 \]

\[ \text{O} \quad 14 \]

\[ \text{O} \quad 11 \]

\[ \text{trioxaadamantane ring system} \]

\[ \gamma\text{-pyrone} \]

\[ \text{caloundrin B (10)} \]

8 stereogenic centers

**Figure 2.2** Caloundrin B (10) structural features

Any synthesis of caloundrin B (10) would require control over the relative configuration of the eight stereogenic centers present in the molecule, as well as control over the absolute configuration since these natural products exist as single enantiomers (**Figure 2.2**). The Thiopyran Route to Polypropionates (**Section 2.3**) was envisioned to provide the control required for both of these aspects.

Caloundrin B (10) contains an intriguing and unusual bis-acetal/hemiacetal ring system (hereafter referred to as “trioxaadamantane ring system” or “trioxaadamantane”) (**Figure 2.2**), a rare structural feature present in just one other marine polypropionate natural product, muamvatin (3) (**Figure 1.1**).\(^6\) There are very few synthetic studies on trioxaadamantanes and these are limited to muamvatin (3)\(^{59-62}\) and related systems.\(^{16}\) Thus, the caloundrin B (10) trioxaadamantane ring system would require study through a model
system in order to determine how to form it and gain an understanding of the conditions that it may be stable towards in order to develop a synthetic strategy (Section 2.4).

In addition to studying the trioxaadamantane ring system, the synthesis also requires installation of a γ-pyrone moiety (Figure 2.2). The timing and conditions required for the formation of the γ-pyrone moiety also require study (Section 2.5).

2.3 The Thiopyran Route to Polypropionates

The Thiopyran Route to Polypropionates is a long-standing research theme in Prof. Ward’s research group (Figure 2.3).63-76 The route has been designed and optimized to rapidly and efficiently construct tetrapropionate synthons 118 (4 diastereomers) and hexapropionate synthons 119 (20 diastereomers). These synthons are useful building blocks for the synthesis of polypropionate natural products. Thus far, the Thiopyran Route to Polypropionates has been utilized in the synthesis of serricornin (123)72 and membrenone B (121).77

A key aspect of any synthetic strategy, and indeed the Thiopyran Route to Polypropionates, is the preparation of starting materials through, ideally, simple, efficient, scalable, and cost-effective procedures with minimal chromatography (Figure 2.3). My contribution in this area included: 1) optimizing a multi-gram procedure (ca. 0.5 kilogram) to prepare Dieckmann product 126;74 2) development of a multi-gram procedure (ca. 100 gram) to prepare ketone 117 in free-flowing, white, crystalline form;74 3) and the investigation of an alternative oxidation protocol78 to prepare multi-gram (ca. 40 gram) quantities of aldehyde (±)-116,xxii a previously challenging endeavor under available standard laboratory

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xxii Athanasios Karagiannis, unpublished results. Experimental conception and design under my supervision.
Following optimization, all of the aforementioned reactions no longer required chromatography to produce their respective products in excellent yield and purity.

**Figure 2.3 The Thiopyran Route to Polypropionates**

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iiii The volumes of solvent (CH$_2$Cl$_2$) involved to conduct a Swern reaction at this scale (>2 L) exceed available equipment and cooling (-78 °C) mechanisms.

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The syntheses of polypropionate natural products, generally speaking, require single enantiomers to be accessed. Control over absolute configuration has been established in the Thiopyran Route to Polypropionates in the synthesis of the tetrapropionate synthons 118 and 119 via an enantiotopic group selective reaction (desymmetrization reaction). With respect to the tetrapropionate synthons 118, access to all four enantioenriched diastereomers has been established via diastereoselective aldol reactions though the use of enantioenriched aldehyde 116. Alternatively, a direct aldol reaction between (±)-116 and 117 that occurs with enantiotopic group selectivity and dynamic kinetic resolution accesses 122 in >98% ee has been established (Scheme 2.1).

The latter chemistry presented an opportunity for improvement as the yield of the proline-mediated version of the reaction was a modest 56% (>98% ee) and required a substantial amount (6 equivalents) of ketone 117 (Scheme 2.1). Considering that the direct aldol reaction between 117 and (±)-116, mediated by proline, had been extensively optimized to achieve this remarkable result, one of the few avenues left to explore was the catalyst employed in the reaction (Scheme 2.1). Tetrazole catalyst 127 is known to be more soluble than proline. By employing this catalyst, the yield of the direct aldol reaction between 117 and (±)-116 was improved (86%, >98% ee). It was also found that by increasing the concentration of the reaction substantially (9 M in (±)-116 vs. 1 M), that the amount of ketone 117 could be reduced (from 12 equivalents to 2) while maintaining a similar yield (75%, >98% ee) at gram scale. Conditions to isomerize aldol 122 to 128 were identified and optimized. Thus two of the four tetrapropionate synthons 118 (cf. 122 and 128) could

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xxiv This reaction has been performed at ca. 40 gram scale in >70% isolated yield (>98% ee) with no chromatography; Athanasios Karagiannis, unpublished results.
be obtained in enantiopure form from a racemic reactant \((\pm)-116\) in high yield and enantioselectivity.

Scheme 2.1

An aldol reaction between tetrapropionate synthon \(118\) and aldehyde \(116\) produces the next layer of complexity in the Thiopyran Route to Polypropionates: hexapropionate synthons \(119\) (also referred to as “bisaldols”) (Figure 2.3). Now, however, there are twenty\(^{xxv}\) possible diastereomers (all known).\(^{64, 73, 76, 86}\) My contribution to this area was related to deepening the understanding of the stereochemical control elements operating in the aldol reactions between tetrapropionate synthons \(129\) and \(130\) and aldehyde \(116\) (Figure 2.4).\(^{73}\) The systematic study of these reactions allowed a model to be developed that rationalized the stereochemical outcome of these reactions. From this model, reactions were designed to exploit these stereochemical control elements to access single diastereomers of \(134\) or \(135\)^{xxvi} in high yield and diastereoselectivity through the kinetic resolution of \((\pm)-116\).\(^{76}\)

\(^{xxv}\) Chiral diastereoisomers (even \# of stereogenic centers, \(n\)) = \(2^{n-2}\); meso forms = \(2^{(n-2)/2}\).

\(^{xxvi}\) Eight (8) stereoisomers are possible from an aldol reaction of tetrapropionate synthon \(129\) (or \(130\)) with aldehyde \((\pm)-116\). Protecting groups other than MOM were used in the subsequent study.


4 possible diastereomers

\( \text{MOMCl, DIPEA, } (\text{^t^6} \text{Bu)}_4 \text{NI} > 90\% \)

\[ \text{TiL}_x\text{L}_y, \text{DIPEA} \]

\[ \text{L}_x = \text{Cl}_3 \]
\[ \text{L}_y = \text{Cl or } ' \text{OPr} \]

Figure 2.4 Model for stereoselectivity in aldol reaction of 129 and 130 with (±)-116

2.4 Trioxaadamantane ring system synthesis and isomerization: model study

This model study has been previously published in *Organic Letters*.\(^{75}\) Much of the original text and tables have been included herein, with some modification for clarity and consistency with this thesis. The schemes and figures in the following are somewhat different.
than in the *Organic Letters* publication, which was done to be consistent with the graphical presentation of this thesis.

![Figure 2.5](image-url) Natural products containing a trioxaadamantane ring system

The highly unusual trioxaadamantane ring system has been identified in only two siphonariid natural products: muamvatin (3) and caloundrin B (10) (Figure 2.5). The difference between the trioxaadamantane ring systems in muamvatin (3) and caloundrin B (10) is the configuration of C-4. This difference is used to distinguish between the two ring systems in the following discussion.

The trioxaadamantane ring system is formally derived from ring-chain tautomerism of a 3-hydroxy-1,5,7-trione (Scheme 2.2). Although this ring system is thermodynamically stable, its formation is impeded because it proceeds via the less stable of the intermediate hemiacetal anomers (i.e., 140/141 and 148/149 vs. 138/139 and 146/147), and these hemiacetals readily undergo dehydration (to 152/153) or retro-Claisen (to 154/155) under acidic and basic conditions. Consequently, the precursor hydroxytrione rearrangement (i.e., 136/137 or 144/145) must be unveiled under very mild conditions.
Scheme 2.2

Synthetic studies are limited to the muamvatin (3) ring system (cf. 151), but despite the limited study two different approaches have been described (Scheme 2.3). The first approach, utilized by Hoffmann and Perkins, approached formation of the muamvatin-related trioxaadamantane ring system via the deprotection of a silyl-protected triketone. Treatment of these silyl-protected triketones (157 and 158) under mild conditions provided the desired trioxaadamantane ring system in good yield. Paterson approached the formation of the trioxaadamantane moiety based on trihydroxy ketone 160. Internal protection of one of the alcohols as a hemiacetal served as a means to differentiate one of the three alcohols present in 160. Oxidation of the exposed alcohols of 160 via a double Swern followed by exposure to silica gel provided the desired trioxaadamantane ring system 162 in
excellent yield. All of these studies underscored the mildness of the conditions required to generate the trioxaadamantane moiety.

1) Deprotection of a silyl-protected hydroxytriketone

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{TBS} & \quad \text{TBS}
\end{align*}
\]

157 \quad a \quad 72\%

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{TBS} & \quad \text{SiEt}_3
\end{align*}
\]

158 \quad b, c, 78\%

or

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OTBS} & \quad \text{OTBS}
\end{align*}
\]

159 \quad a, 88\%

2) Oxidation of a trihydroxy ketone followed by cyclization

\[
\begin{align*}
\text{OH} & \quad \text{OBn} \\
\text{HO} & \quad \text{HO} \\
\text{H} & \quad \text{OBn} \\
\text{HO} & \quad \text{HO} \\
\text{OBn} & \quad \text{OBn}
\end{align*}
\]

160 \quad d \quad 90\%

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OBn} & \quad \text{OBn}
\end{align*}
\]

161 \quad e \quad 92\%

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OBn} & \quad \text{OBn}
\end{align*}
\]

162

a) HF\cdot\text{pyridine, pyridine, H}_2\text{O (cat.)}, b) TASF c) DBU d) (COCl)_2, DMSO, Et_3N e) silica gel, ca. 18 h

Scheme 2.3

It was reasoned that by exploiting a thiopyran template like 163/164, formation of sulfur-bridged trioxaadamantane 167 or 168 would not require such mild conditions. Acidic conditions could be used because dehydration of the required intermediate hemiacetal anomer 165/166 is disfavored by Bredt’s rule (Scheme 2.4).\textsuperscript{87, 88}
Scheme 2.4

2.4.1 Muamvatin’s trioxaadamantane ring system and isomerization

To test the hypothesis outlined in Section 2.4, the preparation of known\textsuperscript{61} trioxaadamantane (±)-151 related to muamvatin (3) was attempted (Scheme 2.5). Aldol 169 was first protected as its corresponding MOM ether 170,\textsuperscript{69, 73} which was followed by an aldol reaction of the enol borinate of (±)-170 with propanal gave aldol adduct (±)-171\textsuperscript{xxvii, 73, 76} as a 9:1 mixture of diastereomers. Oxidation of (±)-171 with IBX in DMSO followed by treatment of the crude reaction mixture with FeCl\textsubscript{3}\textbullet 6H\textsubscript{2}O in refluxing acetone/MeOH\textsuperscript{xxviii, 89} served to hydrolyze the acetal protecting groups and catalyze the formation of unusual trioxadithiapentacycle (±)-168 in good yield. Desulfurization of (±)-168 with Raney nickel surprisingly provided trioxaadamantane (±)-143, whose structure was confirmed by X-ray crystallography (Figure 2.6).

\textsuperscript{xxvii} The relative configuration shown was assumed based on precedent established in refs 73 and 76.
\textsuperscript{xxviii} MeOH was added to facilitate removal of the MOM protecting group.
Scheme 2.5

The isolation of (±)-143 was surprising because it is thermodynamically unstable relative to its epimer (±)-151 due to the syn-pentane relationship between the C-8 and C-9 methyl groups. It was expected that under the conditions for desulfurization (refluxing ethanol) that epimerization would have occurred spontaneously. Investigation of suitable isomerization conditions was required to overcome the unexpected kinetic stability of (±)-143.
Considering previous studies on this ring system (Scheme 2.3), there were several conditions that could be attempted: HF•pyridine,\textsuperscript{60-62} silica,\textsuperscript{59} and DBU.\textsuperscript{16} In addition to attempting these conditions, imidazole in chloroform was also attempted based on previous experience with this catalyst in the isomerizations (via keto-enol tautomerization) of sensitive aldol adducts (Table 2.1).\textsuperscript{65,69}

\textsuperscript{xxix} Thermal ellipsoids shown at 30% probability. Hydrogen atoms omitted for clarity. X-ray data is available at the Cambridge Crystallographic Data Center: CCDC 721137 and ref 75.
Table 2.1 Isomerization studies on (±)-143

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp.</th>
<th>Time</th>
<th>Product Distribution (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(±)-143</td>
</tr>
<tr>
<td>1</td>
<td>silica gel&lt;sup&gt;b&lt;/sup&gt;</td>
<td>rt</td>
<td>1 d</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>rt</td>
<td>5 d</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>HF•pyridine/pyridine/H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;c&lt;/sup&gt;</td>
<td>rt</td>
<td>1 d</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>rt</td>
<td>7 d</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>40 °C</td>
<td>1 d</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>40 °C</td>
<td>5 d</td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>DBU/C&lt;sub&gt;6&lt;/sub&gt;D&lt;sub&gt;6&lt;/sub&gt;&lt;sup&gt;e&lt;/sup&gt;</td>
<td>rt</td>
<td>2 d</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>rt</td>
<td>5 d</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>rt</td>
<td>10 d</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>rt</td>
<td></td>
<td>&gt;95</td>
</tr>
<tr>
<td>11</td>
<td>Im/CDCl&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;f&lt;/sup&gt;</td>
<td>40 °C</td>
<td>1 d</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>40 °C</td>
<td>4 d</td>
<td>100</td>
</tr>
</tbody>
</table>

<sup>a</sup> By <sup>1</sup>H NMR spectroscopy.  
<sup>b</sup> Absorption of a CH<sub>2</sub>Cl<sub>2</sub> solution of (±)-143 onto silica gel 60 (a 0.25 mm PTLC plate) followed by elution after the indicated time.  
<sup>c</sup> Pyridine (1.2 mL), HF•pyridine (0.4 mL), and H<sub>2</sub>O (50 μL) were added to a solution of (±)-143 (10-20 mg) in THF (2 mL).  
<sup>d</sup> Tentatively identified.  
<sup>e</sup> DBU (0.02 M; ca. 1 equiv.).  
<sup>f</sup> Imidazole 0.6 M.  
<sup>g</sup> 85% isolated yield on 20 mg scale.

Absorption of (±)-143 onto silica gel produced (±)-151 very slowly (entries 1 and 2).

Reaction of (±)-143 with HF•pyridine at room temperature also slowly produced (±)-151; isomerization was accelerated at elevated temperature (40 °C), but small amounts of dehydrated product (±)-153 were detected at longer reaction times (entry 6). Treatment of (±)-143 with DBU in C<sub>6</sub>D<sub>6</sub> at room temperature gave (±)-151 in addition to (±)-156 (entries 7-9). The formation of (±)-156 presumably results from elimination of propanoic acid from
an initially formed retro-Claisen ester 155.xxx Alternatively, a warm (40 °C) solution of (±)-143 in CDCl₃ containing imidazole (0.6 M) cleanly produced (±)-151 in 85% isolated yield (entry 12).

2.4.1.1 Structure determination of (±)-143, (±)-153, (±)-156, and (±)-168

The structure of (±)-151 is knownxxx,⁶¹ and the structure of (±)-143 was confirmed by X-ray crystallography (Figure 2.6). The structure of (±)-168 was inferred on the basis of the X-ray crystal structure of (±)-143 and by analogy to 167 – the structure of which was confirmed by an X-ray crystal structure (vide infra).

![Chemical structures]

Figure 2.7 Structure determination of (±)-168, (±)-143, and (±)-151

The significant spectroscopic differences (in C₆D₆) between (±)-151 and (±)-143 include: i) the small ⁴J coupling (W-coupling) between HC-8 and HC-9 (as revealed by COSY) in the latter that is absent in the former; ii) the large upfield shift for C-9 in (±)-151 (δC 36.0) compared to (±)-143 (δC 44.7) due to the axial-axial interaction between H₃C-8 and HC-9 in (±)-151 (Figure 2.7).

---

xxx The retro-Claisen ester was never observed in the crude reaction mixture or by following the reaction by ¹H NMR spectroscopy.

xxx The retro-Claisen ester was never observed in the crude reaction mixture or by following the reaction by ¹H NMR spectroscopy.

xxxi Hoffman reported obtaining an X-ray crystal structure of this compound.
2.4.2 Caloundrin B’s trioxaadamantane ring system and isomerization

Armed with the knowledge obtained from the production of known trioxaadamantane (±)-151, the synthesis of its 4S diastereomer 150 – the trioxaadamantane corresponding to caloundrin B (10) – was attempted (Scheme 2.6). Enantiopure 122, readily available from the organocatalyzed direct aldol reaction of 117 and (±)-116 (Section 2.3),70, 72 protected as its triethylsilyl ether 172, was subjected to a boron-mediated aldol reaction with propanal to give aldol adduct 173xxxii, 73, 76 in excellent yield. Oxidation of 173 with IBX followed by treatment with FeCl₃-impregnated silica gel⁹⁰ provided trioxadithiapentacycle 167, which readily crystallized to provide a crystal suitable for X-ray crystallography (Figure 2.8).

![Figure 2.8 ORTEP plot of 167.xxxiii](image)

---

xxxii The relative configuration shown was assumed based on precedent established in refs 73 and 76.

xxxiii Thermal ellipsoids shown at 30% probability. Hydrogen atoms omitted for clarity. X-ray data is available at the Cambridge Crystallographic Data Center: CCDC 721136 and ref 75.
Scheme 2.6

Desulfurization of 167 with Raney nickel gave the anticipated trioxaadamantane ring system, 142 (Scheme 2.6). The yield of this step was variable (ca. 30 – 60%) and could not be optimized, which could reflect a lower stability of 142 relative to (±)-143 (vide infra). Alternatively, reaction of 167 with (CH₃)₃SiOTf (or Et₃SiOTf) gave silyl acetal 174 in excellent yield, which could be readily desulfurized with Raney-nickel to afford 175. Attempts to hydrolyze the silyl-protecting group of 175a with TBAF in THF led to rapid
decomposition and employing aqueous HF in MeCN led to quantitative formation of 152 (from 175b). Brief treatment of 175a with HF•pyridine, however, cleanly gave 142 in good yield (80%). Interestingly, the design of this strategy to access these trioxaadamantane ring systems was validated by reversing the steps (i.e., desulfurization of 173, oxidation by IBX in DMSO, and then FeCl$_3$•6H$_2$O in acetone quantitatively gave 152).

Applying the isomerization conditions developed for (±)-143 to 142, clearly showed a difference in reactivity and several additional products were isolated (Table 2.2). For example, (±)-143 was relatively stable to silica gel, but 142 (entry 1) gave a mixture of trioxaadamantanes 142 and 150, hemiacetal 146, dihydropyrone 152, and retro-Claisen ester 154 products. Whereas (±)-143 was isomerized to (±)-151 by HF•pyridine at 40 °C, only the dihydropyrone 152 was obtained from the trimethylsilyl ether of 142 (cf. 175a) under these conditions (entry 5). At room temperature, hemiacetal 138 accumulated and could be isolated in reasonable yield (entry 3).

Exposure of 138 to HF•pyridine produced a 5:1 mixture of 142 and 150 at low conversion demonstrating the reversible formation of 142 (entries 6 and 7). In contrast to (±)-143, treatment of 142 with DBU in C$_6$D$_6$ rapidly gave a 1:2 mixture of 150 and 154, respectively (entries 8 and 9), presumably via 138 (entry 13). Similar treatment of 150 also produced 154 although much more slowly (entries 10-12). In all cases, treatment with DBU led to 156 via elimination of propanoic acid from 154 (entries 9-15). Attempts to isolate 156 met with failure presumably because of its volatility and thus 156 was tentatively identified by NMR spectroscopy as a mixture of 156 and the propanoic salt of DBU (see Figure 2.12). Imidazole catalyzed the isomerization of 142 at room temperature predominantly gave 150 along with smaller amounts of 138 and 154 (entries 16 and 17).
Table 2.2 Isomerization studies on 142

<table>
<thead>
<tr>
<th>Entry</th>
<th>SM&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Conditions</th>
<th>Temp.</th>
<th>Time</th>
<th>Product Distribution (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
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<td>142</td>
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<tr>
<td>1</td>
<td>142</td>
<td>silica gel&lt;sup&gt;c&lt;/sup&gt;</td>
<td>rt</td>
<td>1 d</td>
<td>13</td>
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<tr>
<td>2</td>
<td>175&lt;sup&gt;d&lt;/sup&gt;</td>
<td>rt</td>
<td>2 h</td>
<td></td>
<td>86</td>
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<tr>
<td>3</td>
<td></td>
<td>rt</td>
<td>2 d</td>
<td></td>
<td>22</td>
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<td>4</td>
<td></td>
<td>HF•pyridine/pyridine/H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;e&lt;/sup&gt;</td>
<td>40 °C</td>
<td>5 d</td>
<td>4</td>
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<td>5</td>
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<td>6</td>
<td>146</td>
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<td>1 d</td>
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<td>7</td>
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<td>rt</td>
<td>3 d</td>
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<td>8</td>
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<td>rt</td>
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<td>26</td>
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<td>9</td>
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<td>150</td>
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<td>1 d</td>
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<td>67</td>
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<td>11</td>
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<td>rt</td>
<td>7 d</td>
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<td>40</td>
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<td>12</td>
<td>138</td>
<td>rt</td>
<td>18 d</td>
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<td>13</td>
<td>154</td>
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<td>8 h</td>
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<td>16</td>
<td>142</td>
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<td>19</td>
<td>146</td>
<td>rt</td>
<td>1 d</td>
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<td>5</td>
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</tbody>
</table>

<sup>a</sup> By <sup>1</sup>H NMR spectroscopy. <sup>b</sup> Starting material. <sup>c</sup> Absorption of a CH<sub>2</sub>Cl<sub>2</sub> solution of 142 onto silica gel 60 (a 0.25 mm PTLC plate) followed by elution after the indicated time. <sup>d</sup> The trimethylsilyl ether 175<sup>a</sup> was used. <sup>e</sup> Pyridine (1.2 mL), HF•pyridine (0.4 mL), and H<sub>2</sub>O (50 µL) were added to a solution of 142 (10-20 mg) in THF (2 mL). <sup>f</sup> 49% isolated yield on 40 mg scale. <sup>g</sup> DBU (0.02 M; ca. 1 equiv.). <sup>h</sup> 47% yield on 45 mg scale. <sup>i</sup> Tentatively identified by NMR spectroscopy, but not isolated (<em>vide infra</em>). <sup>j</sup> Imidazole 0.6 M. <sup>k</sup> 77% isolated yield on 16 mg scale.
Similar results were obtained from 138, confirming the reversible formation of 142 (entry 19). Thus, any of 138, 150, 152, 154, or 156 can be obtained as major products from 142 depending upon the conditions selected.

2.4.2.1 Structure determination of 138, 142, 150, 152, 154, 156, and 167

The structure of 167 was verified by X-ray crystallography (Figure 2.8).

![Diagram of structures](image)

Figure 2.9 Structure determination of 142, 150, and 167

The structures of 142 and 150 were assumed based on analogy to (±)-143 and (±)-151 (Figure 2.9). In analogy to (±)-143 and (±)-151, there is a small \( J_{HH} \) coupling (W-coupling) between HC-8 and HC-9 (as revealed by COSY) in 142 that is absent in 150. Similarly, there is a large upfield shift for C-9 in 150 (\( \delta_C \) 36.6) compared to 142 (\( \delta_C \) 45.4). The significant NMR spectroscopic differences (in CD\(_2\)D\(_6\)) between (±)-151/143 and 150/142 include: i) the chemical shifts for C-8 in 150/142 (\( \delta_C \) 36.5/36.9) are well upfield from those in (±)-151/143
(\(\delta_C 43.3/43.3\)); ii) the \(^3J\) coupling constants between HC-7 and HC-10 are much larger in \(\text{150/142}\) (3.5/2.5 Hz) than in (\(\pm\)-151/143) (<2Hz); iii) the \(^1H\) chemical shifts (in C\(_6\)D\(_6\)) for H\(_2\)CC-10 in \(\text{150/142}\) (\(\delta_H\) 0.65/0.63) are well upfield from those in (\(\pm\)-151/143) (\(\delta_H\) 1.10/1.11). These differences in the NMR spectrum are consistent with the data reported for muamvatin (3)\(^6\) and caloundrin B (10).\(^9\) The absolute configuration of 142 is based on that of 167. The absolute configuration of 150 is based on that of 142.

Figure 2.10 Structure determination of 138

The relative configuration of 138 was determined by \(^1H\) NMR spectroscopy (Figure 2.10). The trans diaxial relationship between the HC-5 and HC-6 was confirmed by the 10.7 Hz coupling constant between them. The axial OH group was suggested by a positive NOE on HC-6 on irradiation of the OH and vice versa. This assignment was also supported by a small \(^4J\) coupling constant (1.6 Hz) between the OH and HC-3 (this W-coupling is consistent with a trans diaxial OH and HC-3). The axial position of HC-3 was suggested by the small \(^4J\) coupling constant (1.1 Hz) between the HC-3 and HC-5; this observation is consistent with that reported in related compounds.\(^17\) The relative configuration at C-1" is assumed based on no change from 150. It is notable that 138 was the only hemiacetal isolated and is calculated to be the most stable of the possible hemiacetals (i.e., 138-141 and 146-149) (see Scheme 2.2) (vide infra). The absolute configuration is assumed based on that of 150.
The trans relative configuration for the substituents at C-2 and C-3 in 152 was assigned based on the large coupling constant observed between the protons at these positions consistent with the large $J$ values reported for several related compounds (Figure 2.11). The C-1’ diastereomer 153 is known and its reported NMR data are significantly different from 152; thus the relative configuration at C-1’ in 152 is assigned as indicated. The absolute configuration for 152 is assumed based on 150.

The assigned relative configuration of 154 is confirmed by its $C_1$ symmetry (14 signals in the $^{13}$C NMR spectrum; the $4R,6S$ diastereomers (e.g., 155) are meso). The absolute configuration is assumed based on 150.

Compound 156 was observed in various isomerization experiments (Table 2.1 and 2.2) in the presence of DBU in C$_6$D$_6$. In a larger scale reaction, DBU (10 µL, 10 mg, 0.07 mmol) was added to a solution of 154 (8 mg, 0.03 mmol) in C$_6$D$_6$ (0.4 mL) at room temperature (Figure 2.12). The reaction was monitored by $^1$H NMR spectroscopy and after 14 days, <5% of 154 remained. Attempted isolation of 156 from the reaction mixture by standard aqueous workup failed. However, the structure for 156 was assigned based on its NMR data that were easily extracted by comparison of the $^{13}$C spectra of the reaction mixture with that obtained from a mixture of DBU and propanoic acid (i.e., the other components in the reaction mixture). The presence of two ketone carbonyls ($\delta_C$ 209.1, 200.9), two isolated
CH$_3$CH$_2$- groups, and a -(CH$_3$)C=CHCH(CH$_3$)- spin system were readily identified and confirmed by COSY, DEPT and HSQC. The (E) configuration is tentatively assigned based on the absence of NOE between the vinyl CH$_3$ and vinyl H and the presence of a weak NOE between the vinyl CH$_3$ and the allylic CH. The specific rotation of 156 (from 154) was not determined.
Figure 2.12 Structure determination of 156

12 μL DBU + 10 μL propionic acid acid in 0.4 mL C₆D₆
2.4.3 Trioxaadamantane ring system comparison and conclusions

Compounds 150 and (±)-151 differ by a single stereocenter (C-4), yet their isomerization behavior is remarkably different. In an attempt to identify the reasons for these differences, Prof. Jonathan M. Goodman was contacted about the possibility of studying these systems computationally. Figure 2.13 illustrates the results of the computational experiments graphically.

The computational studies found that the preferred conformation of 140 was the chair with equatorial methyl groups, and those of 141 and 149 were twist boats stabilized by H-bonding (Figure 2.14). The more facile isomerizations of 142 compared to (±)-143 (cf. Tables 2.1 and 2.2) and to 150 (Table 2.2, entries 9 and 10) are consistent with the differences in energies between these trioxaadamantanes and their hemiacetal precursors (140-142, 16.8 kJ/mol; 141-143, 23.8 kJ/mol; 150-148, 32 kJ/mol). The lack of intermediates observed in the isomerization of (±)-143 to (±)-151 (Table 2.1) can be rationalized by considering the much smaller differences in energies between 139 and 149 (7.3 kJ/mol) vs. 141 (13.3 kJ/mol) (i.e., transformation of 139 to 151 should be faster than that of 143 to 139) and the low equilibrium concentration expected for 139.

Although a similar analysis of 138, 140, and 148 supports a greater persistence and equilibrium concentration of 138 (i.e., facilitating more elimination and retro-Claisen rearrangement) compared to 139, it does not account for the significant accumulation of 138 on treatment of 142 with HF•pyridine.

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xxxiv University Chemical Laboratory, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, U.K.; a computational chemist with significant experience computationally studying polypropionate natural products.

xxxv All computations were made by Prof. Goodman.

xxxvi The computed energies are for ground states.

xxxvii Relative reaction facilities are based on Hammond’s postulate (more stable intermediates are formed faster).
Figure 2.13 B3LYP/6-31G** energies (kJ/mol) relative to 151
Figure 2.14 Illustrations of the preferred conformations of 140, 141, and 149, as determined by computational studies.

In conclusion, the isomerization of 142 under different conditions leads selectively to 138, 150, or 154. These compounds represent structural motifs present in siphonarin B (4), caloundrin B (10), and baconipyrene C (8), respectively. In principle, each compound in this series of natural products could be accessed via a structure analogous to 142.
2.5 γ-Pyrone formation model study

The synthesis of γ-pyrones can be accomplished through a variety of means and methods, but none of these methods are general. A common approach used in the synthesis of marine polypropionate natural products is through the dehydrative cyclization of 1,3,5-triketones (e.g. 179, Scheme 2.7).  

![Scheme 2.7](image)

a) H⁺ or (COCl)₂, DMSO or PPh₃, CCl₄  b) DBU or Δ

Scheme 2.7

Early methods to dehydratively cyclize 1,3,5-triketones typically relied upon strong acid, which are not well suited to the synthesis of complex, potentially acid and base sensitive, polypropionate natural products, such as caloundrin B (10). This issue was recognized by several research groups and several alternative approaches have been disclosed, i.e.: PPh₃/CCl₄, amberlyst-15 with celite-supported P₂O₅, DMSO/(COCl)₂, bulky Brønsted acids, base and thermal cyclization of silyl-protected triketones. The most popular of these methods is Yamamura’s methodology, which has been used in the synthesis of several natural products. However, even this method has not been proven general.
Even rarer are examples of $\gamma$-pyrones accessed directly from protected 1,3,5-triketones.$^{30, 93, 96}$ An example is provided by Hoveyda$^{30}$ (178 $\rightarrow$ 71) in his synthesis of baconipyrone C (8). Hoveyda’s sequence for installation of the $\gamma$-pyrone was later adapted by Jung in his synthesis of auripyrone A.$^{93}$

The $\gamma$-pyrone required for the synthesis at hand was envisioned coming from a 1,3,5-triketone via Yamamura’s or a related methodology (Scheme 2.8).$^{23, 24}$ We opted to form 1,3,5-triketone 182, in protected form (cf. 181), through an aldol reaction with dithioacetal aldehyde 179 followed by oxidation to the protected diketone. Hydrolysis of the dithioacetal protecting group of 181 would provide 1,3,5-triketone 182. Known$^{97}$ $\gamma$-pyrone 177 would then be accessed through established methodology.
Dithioacetal aldehyde 179 was accessed in three steps from readily-available\textsuperscript{98} \(\beta\)-keto-ester 184 (Scheme 2.8). \(\beta\)-Keto-ester 184 was protected as its corresponding dithioacetal 185 by treatment with ethanedithiol and BF\(_3\)\(\bullet\)OEt\(_2\) as catalyst. Reduction of 185 with LiAlH\(_4\) gave 186, which was oxidized in excellent yield by oxidation with IBX in DMSO to afford aldehyde 179. The synthesis of aldehyde 179 from 183 was accomplished on multi-gram scale in high yield without chromatography.
Aldehyde 179 was then subjected to an LDA-mediated aldol reaction with 3-pentanone (43) to form a complicated mixture of aldol adducts (Scheme 2.8). An attempted oxidation with IBX in hot (80 °C) acetonitrile of this mixture of aldol adducts failed to provide the anticipated diketone 181. Instead, known γ-pyrone 177 was directly obtained in ca. 30% yield.

If the yield of this process could be improved, then a rapid synthetic sequence to γ-pyrones could be realized. Further, this initial result indicated that it might be possible to annulate a pyrone onto a ketone through an aldol reaction followed by oxidation: conceivably, only two steps would be required for this process, a possible advantage over other methodologies. Further, variation of the dithioacetal aldehyde or the ketone employed in the reaction could provide the means to easily substitute the γ-pyrone ring at any position: there are no known general methodologies or strategies capable of this.

Investigation of yield improvements through aldol did not reveal any promising possibilities through the usual reaction optimization parameters (time, temperature, solvent, reagent amounts, concentration, etc.) (entry 1, Table 2.3). Considering, however, what must occur during the process, namely, oxidation of the aldol to the corresponding diketone 181, provided an alternative front for investigation.

Oxidation of aldol under alternative oxidation conditions (i.e., IBX in DMSO) provided diketone 181 in excellent yield. Subjecting diketone 181 to IBX in hot (80 °C) acetonitrile gave γ-pyrone 177 in much improved yield (entry 2). The reaction proved responsive to the amount of IBX employed in the reaction (entries 2-4). Alternative

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xxxviii An aldol reaction between 3-pentanone (43) and aldehyde 180 can form up to 8 stereoisomers. In the present reaction, 4 products were obtained, but these could not be separated and were not characterized.

xxxix IBX is soluble in DMSO. IBX-mediated oxidation in DMSO is a fairly recent discovery by Santagostino.
solvents (entries 5 and 6) were unproductive or led to decomposition products that were unidentifiable. Interestingly, heating diketone 181 with IBX in DMSO led to decomposition (entry 6), but under similar conditions, without the application of heat, diketone 181 is stable and can be isolated in excellent yield from the oxidation of 180.\textsuperscript{x1} The addition of H\textsubscript{2}O (entries 7 and 8), to aid hydrolysis of the ethanedithiol protecting group,\textsuperscript{101-104} significantly attenuated the rate of the reaction or was unproductive.

\textbf{Table 2.3 $\gamma$-Pyrone 177 optimization studies}

\begin{table}[h]
\centering
\begin{tabular}{llllllll}
\hline
Entry & SM$^a$ & Solvent & Equiv. IBX & Additive & Temp. & Time & Yield (\%)$^b$
\hline
1 & 180 & MeCN & Various$^c$ & - & 80 °C & various & <30 \\
2 & 181 & MeCN & 1 & - & 80 °C & 24 h & 63 \\
3 & MeCN & 1.5 & - & 80 °C & 24 h & 77 \\
4 & MeCN & 2 & - & 80 °C & 24 h & 77 \\
5 & MeCN & 2 & - & 80 °C & 24 h & NR$^d$ \\
6 & EtOAc & 2 & - & 80 °C & 24 h & decomp.$^e$ \\
7 & DMSO & 2 & H\textsubscript{2}O$^f$ & 80 °C & 24 h & <40 \\
8 & DMSO & 2 & H\textsubscript{2}O$^f$ & 80 °C & 4 h & NR$^d$ \\
9 & 185 & MeCN & 2 & - & 80 °C & 24 h & <15$^g$ \\
10 & 181 & MeCN & 2 & $p$-TsOH & 80 °C & 24 h & 100$^h$ \\
11 & MeCN & 0 & $p$-TsOH & 80 °C & 24 h & NR$^d$ \\
12 & MeCN & 2 & CF\textsubscript{3}SO\textsubscript{3}H & rt & 18 h & 92 \\
\hline
\end{tabular}
\end{table}

$^a$ Starting material. $^b$ Yield of 177, unless stated otherwise. $^c$ Various conditions attempted including: solvent, reaction time, equiv. IBX, concentration. $^d$ No reaction. $^e$ No identifiable products obtained. $^f$ 5\% (v/v). $^g$ Deprotection to 184; as judged by $^1$H NMR spectroscopy of the crude reaction mixture. $^h$ Yield by $^1$H NMR spectroscopy using an internal standard (ClCH=CCl\textsubscript{2}).

\textsuperscript{x1} This reaction takes 24 h to go to completion.
The fate of the ethanedithiol protecting group in this reaction was unknown because no products attributable to ethanedithiol could be detected in the crude reaction mixture or by monitoring the reaction by $^1$H NMR spectroscopy. It is known that the sulphur atoms of an S,S-acetal protecting group can be oxidized by IBX; it is conceivable that a sulfinic or a sulfonic acid could be formed in situ and thus promote the reaction through acid catalysis. Interestingly, exposure of ester 185 to IBX resulted in very slow deprotection to 184 (entry 9) suggesting the involvement of the diketone functionality (perhaps through its enol tautomer) in facilitating the observed reaction. Therefore, the effect of added acid on the reaction was investigated. Dramatic improvement of yield was observed with the addition of $p$-TsOH (entry 10). Attempts to promote the formation of $\gamma$-pyrone 177 with $p$-TsOH, in the absence of IBX, returned starting material (entry 11). The use of triflic acid (entry 12) with IBX, however, allowed the reaction to be performed at room temperature with excellent conversion to desired $\gamma$-pyrone 177.

2.5.1 $\gamma$-Pyrone model study conclusions

A simple, three-step procedure to annulate a $\gamma$-pyrone onto a ketone was optimized to a high-yielding process. The scope and limitations of this method have not yet been fully explored. However, sufficient information was obtained through this model study to attempt installation of the required $\gamma$-pyrone of caloundrin B (10) through novel conditions.

The use of triflic acid as a catalyst in the reaction is concerning due to its high acidity (pKa = 2.6 in MeCN; for comparison CH$_3$COOH in H$_2$O = 4.76 and in MeCN = 23.5). The use of this method could, therefore, present a problem in a more complicated, and

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xli The reaction was conducted in an NMR tube using MeCN-d$_3$, which allowed real-time monitoring.
xlii Trichloroethylene as an internal standard for $^1$H NMR spectroscopic determination of yield was validated through isolation of the product following determination of yield by internal standard.
xliii Athanasios Karagiannis, unpublished results.
potentially sensitive, substrate. However, the original plan to access the $\gamma$-pyrone could still be explored (i.e., hydrolysis of 181 to triketone 182, followed by $\gamma$-pyrone formation through a known method\textsuperscript{24} to give 177) should this novel method fail.

2.6 Retrosynthetic analysis

Based on the model studies performed (Sections 2.4 and 2.5) and the known instability of the trioxaadamantane ring system, it was clear that the sensitive trioxaadamantane would have to be installed late in the synthesis of caloundrin B (10) (Figure 2.15). Thus, working backwards, the synthesis would be geared towards production of trioxadithiapentacycle 187.

![Figure 2.15 Retrosynthetic analysis of caloundrin B (10)](image-url)
Disconnection of the C-3”,7’ bond in 187, leads to 188 - a protected version of 122, which is available from the Thiopyran Route to Polypropionates in enantiopure form (Scheme 2.1) - and aldehyde 189. A significant advantage of this disconnection is that the reaction to couple these two fragments together does not require any stereoselectivity.xliv

The γ-pyrone aldehyde 189 was seen as being accessed via the chemistry developed in the model study described in Section 2.5, leading to dithioacetal aldehyde 179 and ketone 190 available70 in enantioenriched form from the Thiopyran Route to Polypropionates.

The protecting group strategy is critical to the success of this synthesis. Not only must the P1 protecting group (cf. 189) be orthogonal to protecting groups P2 (cf. 188) and P3 (cf. 189), P1 must also survive the conditions required to form the trioxadithiapentacycle (cf. 187) and be removable under mild conditions that will not interfere with the sensitive trioxaadamantane ring system. P2 (cf. 188) must be removable under the aforementioned conditions in order to form the trioxadithiapentacycle.xlv The final protecting group, P3 (cf. 189), must be robust enough to survive through the synthesis of aldehyde 189 and the steps that lead up to the formation of 187. An ideal situation would be P3’s concomitant removal during the reaction to form trioxadithiapentacycle 187 (see Section 2.4).

2.7 Synthesis of key aldehyde

2.7.1 γ-Pyrone formation

As discussed previously (Section 2.6), the synthesis of γ-pyrone containing aldehyde 189 requires the enantioselective synthesis of known70 ketone 190 (Scheme 2.10). Few changes were made to the reactions to obtain ketone 190 with the exception of the preparation of dial 196 (Scheme 2.9). Oxidation of diols 194 and 195 under the previously

xlv The aldol reaction between 188 and 189 would form an alcohol at C-7’ (cf. 187) which, upon oxidation, both the C-7’ and C-3” stereocenters will be destroyed (C-7”) and/or exist as an epimeric/enol mixture (C-3”).

xlv C-1” of 187 initiates trioxaadamantane formation by forming a hemiacetal with the C-7’ carbonyl.
established Swern conditions\textsuperscript{70} presented a significant problem in regards to scale-up due to low solubility of trans-diol 194. Due to these issues, reaction scale is limited using available laboratory equipment. Investigation into an alternative oxidation protocol for 194 to 196 was warranted to support this synthesis.

\[
\begin{align*}
\text{Scheme 2.9} \\
\text{Oxidation of a ca. 1.5:1 mixture of diols 194 and 195 with IBX in hot (80 °C) acetonitrile\textsuperscript{78} produced desired dialdehyde 196 as an inseparable mixture of meso/dl forms and lactone 197 (Scheme 2.9). Lactone 197 could be separated from dialdehyde 196, but its production reduces the yield of dialdehyde 196. Upon considering this dilemma, it was realized that lactone 197 would only be produced from oxidation of cis-diol 195.\textsuperscript{xlvii} In this particular sequence, only diesters 192 and 193 are separable; therefore, 192 and 193 were}
\end{align*}
\]

\textsuperscript{xlvii} The production of lactone 197 requires production of a hemiacetal precursor, which can undergo further oxidation to form the lactone.
separated and carried through separately. Oxidation of 194 and 195 under different conditions maximized the overall yield of dialdehyde 196.

The enantioselective aldol reaction between dialdehyde 196 (mixture of meso and d/l forms) and 117 to enantioselectively produce hemiacetal 190 had undergone rigorous screening of reaction parameters when the reaction was first developed (Scheme 2.10). In analogy to the improvements made to the enantioselective direct aldol between 117 and (±)-116 (Scheme 2.1), tetrazole catalyst 127 was attempted. Unfortunately, none of the attempts or conditions investigated appeared promising; therefore, the reaction was scaled (ca. 8 grams of dialdehyde 196) to a level appropriate to support this synthesis.

Scheme 2.10

At this stage, hemiacetal 190 had to be set up to receive dithioacetal aldehyde 179. Protection of hemiacetal 190 by reaction with pivoyl chloride produced 198 as a 1:1 mixture.
of anomers that could not be separated and was carried forward as a mixture. The sulfur atoms in 198 were no longer required and were removed by reaction with Raney nickel in refluxing THF.\textsuperscript{xlvii} These conditions resulted in the production (ca. 10%) of reduction products (via hydrogenation of the ketone), which were dealt with by treatment of the crude reaction mixture with IBX in DMSO. The resulting anomers of 199 (1:1) could be separated, but were typically carried forward as a mixture in subsequent reactions.

The structure of each anomer of 199 was inferred based upon the assumption that no isomerization occurred during pivoylation or the reaction with Raney nickel (the structure of 190 is secure).\textsuperscript{70} The two different anomers were distinguished on the basis of NOE. The conformation of $\beta$-199 shown in \textbf{Figure 2.16} was established based on the small ($<1$ Hz) $^4J_{HH}$ (W-coupling) between HC-6 and HC-10 (as revealed by COSY): this coupling was absent in $\alpha$-199. The axial position of the pivaloate in $\beta$-199 was established based on a positive NOE on HC-6 and HC-9 on irradiation of the $t$-Bu group of the pivaloate and vice versa. Further, C-6-methyl exhibited a positive NOE upon irradiation of HC-7 and vice versa, which is consistent with the conformation shown in \textbf{Figure 2.16}. The absolute configuration of 199 is based on 190. By default, the configuration of the pivaloate in $\alpha$-199 was established.

\textbf{Figure 2.16} Structure elucidation of $\beta$-199

\textsuperscript{xlvii} Desulfurization in alcoholic solvent led to significant reduction products and side products which were not isolated or characterized.
An unselective LDA-mediated aldol reaction between \textit{199} and dithioacetal aldehyde \textit{179} produced a complicated mixture of aldol adducts \textit{200} that were not separable, but, as previously discussed (\textit{Section 2.6}), selectivity was unimportant relative to a high yielding process (\textit{Scheme 2.11}).

\begin{center}
\begin{tikzpicture}
  \node[draw, shape=rectangle, rounded corners=5, align=center] (a) {
    \begin{minipage}{0.9\textwidth}
    \begin{center}
    \textbf{Table 2.5}
    \end{center}
    \begin{tabular}{ll}
    \textbf{a)} LDA, \textit{179} & \textbf{b)} IBX, DMSO
    \end{tabular}
  \end{minipage}
  \end{tikzpicture}
\end{center}

\textbf{Scheme 2.11}

As a first step toward formation of the $\gamma$-pyrrole (see \textit{Section 2.5}), $\beta$-diketone \textit{201} was subjected to IBX in hot (80 °C) MeCN to test if this adduct would form the desired $\gamma$-pyrrole as a mixture of anomers \textit{203} (\textit{Scheme 2.11}). Instead of generating the expected products \textit{203}, pyrrole-dihydropyrrole \textit{202} was produced in low yield (ca. 30%). In addition to the formation of the expected $\gamma$-pyrrole moiety, the C-4$''$ carbonyl was revealed and the pivaloate was eliminated across C-5$''$,6$''$. A mechanism is proposed in Figure 2.17, based on the known sulfur oxidation of S,S-acetals by IBX.
Figure 2.17 Proposed mechanism for the formation of pyrone-dihydropyrone 202

Generation of pyrone-dihydropyrone 202 provided a mixed blessing in that a step could be saved due to the hydrolysis of the ethylene ketal that occurred during the reaction. Additionally, the C-4” carbonyl was isolated and conditions could be investigated to reduce it with the correct configuration followed by protection. However, the stereocenter at C-5” had
been lost; the C-5",6" double bond would have to be regio- and stereoselectively hydrated to reestablish the aldehyde functionality at C-6" and concomitantly reset the C-5" stereocenter.

The source of the additional transformations (acetal deprotection and pivaloate elimination) was of interest and was thus investigated. Exposure of 199 (1:1 mixture of anomers), as a model substrate, to IBX in hot (80 °C) MeCN for 24 hours returned starting material (entry 1, Table 2.4). Exposure of the recovered starting material to IBAXlviii in hot (80 °C) MeCN for 24 hrs also returned starting material (entry 2). Exposure of 199 to 2-iodobenzoic acid (IB) also returned starting material (entry 3). Thus IBX and its reduction products were not responsible for the additional reaction chemistry observed in the formation of pyrone-dihydropyrone 202 (Scheme 2.11). Exposure once again to IBX in hot (80 °C) MeCN along with the addition of a controlled amount of ethanedithiol (entry 4), produced dihydropyrone 208 as the sole product in the reaction crude (56% yield, unoptimized). Further, dihydropyrone 208 could be produced by brief exposure of 199 (1:1 mixture of anomers) to 1M HCl in THF. This confirmed the prior hypothesis (Section 2.5) that an acid (perhaps a sulfinic or a sulfonic acid) was produced during the course of the reaction to form the γ-pyrone. The acid produced in the reaction catalyzed acetal deprotection and elimination of the pivaloate. Unfortunately, despite several attempts, the acidic compound(s) responsible could not be observedxl ix or isolated from the reaction mixture.

xlviii Obtained from the IBX oxidation of isopropanol (of solvent) in hot (80°C) MeCN for several days.
xlix Monitoring the reaction by 1H NMR spectroscopy over time in MeCN-d3 and analysis of the crude reaction mixture.
Table 2.4 Dehydration and deprotection of 199

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Reagent 1</th>
<th>Reagent 2</th>
<th>Product</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>IBX</td>
<td>-</td>
<td></td>
<td>199</td>
</tr>
<tr>
<td>2</td>
<td>IBA</td>
<td>-</td>
<td></td>
<td>199</td>
</tr>
<tr>
<td>3</td>
<td>199</td>
<td>IB</td>
<td>-</td>
<td>199</td>
</tr>
<tr>
<td>4</td>
<td>IBX</td>
<td>(CH₂SH)₂</td>
<td></td>
<td>208</td>
</tr>
<tr>
<td>5</td>
<td>1M HCl</td>
<td>-</td>
<td></td>
<td>208</td>
</tr>
</tbody>
</table>

At this stage, it was worthwhile to attempt optimization of the initial poor yield of pyrone-dihydropyrone 202 because this adduct afforded several positive attributes, as discussed previously. Despite repeated attempts (entries 1-3, Table 2.5), the yield could not be improved to the levels seen previously with IBX alone in the model substrate (cf. Section 2.5, Table 2.3). Addition of p-TSOH at elevated temperature improved yield somewhat (entry 4), but isomerization\(^1\) was also detected. At lower temperature, isomerization was attenuated and the desired compound was isolated in slightly improved yield (entries 5 and 6). Addition of CF₃SO₂H under previously optimized conditions improved yield significantly (entry 7) in a small-scale reaction. Upon scale up (same stoichiometry, concentration, etc.), the reaction still performed well (entry 8), but not to the same level as the small-scale reaction. The reasons for this disparity are unclear.

\(^{1}\) Isomerization presumably occurred at C-3’ (of 202) to lead to the more stable pseudo-equatorial diastereomer; however, this was not rigorously established since the minor diastereomer could not be separated from the desired product (202).
Table 2.5 Pyrone-dihydropyrone 202 optimization studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Equiv. IBX</th>
<th>Additive</th>
<th>Temp.</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>80 °C</td>
<td>24 h</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>80 °C</td>
<td>48 h</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>80 °C</td>
<td>36 h</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>80 °C</td>
<td>24 h</td>
<td>60b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>p-TsOH</td>
<td>rt</td>
<td>48 h</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>p-TsOH</td>
<td>rt</td>
<td>72 h</td>
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<td></td>
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<tr>
<td>7c</td>
<td>2</td>
<td>CF₃SO₃H</td>
<td>rt</td>
<td>16 h</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>8d</td>
<td>2</td>
<td>CF₃SO₃H</td>
<td>rt</td>
<td>17 h</td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>

*a* IBX added portion-wise. *b* Accompanied with ca. 20% isomerization. *c* 117 mg scale. *d* 2.41 g scale.

This improvement of the yield of pyrone-dihydropyrone 202 could make this approach viable synthetically, provided the C-5”,6” double bond could be hydrated with reasonable selectivity when resetting the C-5” stereocenter.

### 2.7.2 Hydration of pyrone-dihydropyrone 202

Prior to attempting any experiments to hydrate pyrone-dihydropyrone 202, reduction of the C-4” carbonyl was attempted (Scheme 2.12). Inspired by Danishefsky, reduction under Luche conditions provided an extremely selective reaction (>20:1). At this stage, the selectivity shown in alcohol 209 was assumed based upon the well-documented delivery of the hydride to a pseudo-axial position in the product. Protection of C-4”-OH of 209 as its corresponding acetate 211 and benzyl ether 210 provided substrates for attempted hydration of the C-5”,6” double bond.
It is well known that such systems (cf. 209 - 211) are prone to Ferrier rearrangement.\textsuperscript{114} Danishefsky exploited this facility towards Ferrier rearrangement as a multi-step solution to hydrate similar dihydropyrans obtained by his LACDAC (Lewis-acid catalyzed diene-aldehyde cyclocondensation) chemistry.\textsuperscript{106-109, 115-119} This series of transformations, however well precedented, would significantly increase the number of steps in the synthesis at hand. A direct method to hydrate the C-5\textsuperscript{"},6\textsuperscript{"} double bond and concomitantly reset the C-5\textsuperscript{"} stereocenter would be highly advantageous, but such a method appears to be unprecedented in C-5\textsuperscript{"} substituted dihydropyrans.

There are a number of methodologies that have been developed over the years to hydrate C-5\textsuperscript{"} unsubstituted dihydropyrans based on Lewis acids,\textsuperscript{120-122} transition metal complexes,\textsuperscript{123} electrophilic iodine,\textsuperscript{124} acidic resin,\textsuperscript{125} Brønsted acids,\textsuperscript{126-128} triphenylphosphine hydrobromide,\textsuperscript{126, 129, 130} and hydroxymercuration/demercuration.\textsuperscript{131-133} Of these methods,
triphenylphosphine hydrobromide (PPh₃•HBr) had been used beyond model studies¹³⁴, ¹³⁵ and hydroxymercuration/demercuration is a well-established approach to olefin and enol ether hydration.¹³⁶ Both methods looked promising from this perspective and were thus attempted concurrently.

Figure 2.18 Electrophile addition to dihydropyran 211

It was expected that reagent addition would occur from the top face because the bottom face is more sterically hindered (due to the C-3” pseudo-axial methyl), based on conformational analysis of the dihydropyran (Figure 2.18). Regioselectivity would be ‘controlled’ through the oxygen atom of the dihydropyran ring and its ability to stabilize the resulting carbocation.

Treatment of 211 (Scheme 2.13) with PPh₃•HBr and methanol in CH₂Cl₂ gave Ferrier product 212 and a small amount of starting material (ca. 10%) detected in the crude reaction mixture. The configuration of the methoxy group was suggested by a positive NOE on HC-2” upon irradiation of the methoxy group and vice versa.
Scheme 2.13

In parallel, hydroxymercuration/demercuration of benzyl-dihydropyran 210 was attempted (Scheme 2.14). The initial reaction resulted in the production of two fully-reduced compounds in low yield with structures proposed to be 213 and 214.

Scheme 2.14
At this stage, it was unknown which of the two compounds produced, 213 or 214, corresponded to the required configuration at C-6'. Further, none of the structures in this synthetic sequence (198 → 213 and 214) had been rigorously established. Fortunately, an analogue of these two compounds (cf. ent-39, Scheme 1.9) had been used in the three previous syntheses of baconipyrone C (8): the difference between the two unknown compounds and the known baconipyrone C intermediate, PMB-diol ent-39, was the aromatic group of the C-5’ ether (4-methoxyphenyl vs. phenyl).

Comparison of the $^1$H NMR spectra of Bn-diols 213 and 214 with the data reported by Hovedya$^{30}$ for 39 showed a close match (Table 2.6) to Bn-diol 213. The major difference in the spectra for 39 and Bn-diol 213 was the methyl singlet at 3.78 ppm for 39 and the signals in the aromatic region of the spectrum – essentially differences attributable to differences in the aromatic moiety of the respective protecting groups. Bn-diol 214 showed a significant number of differences in its $^1$H NMR spectra compared with that of 39, not inclusive of differences attributable to the protecting group. Thus, tentative assignments were made based on $^1$H NMR spectroscopy. This tentative assignment was confirmed by comparison of the $^{13}$C NMR spectra (Table 2.7).
Table 2.6 $^1$H NMR (CDCl$_3$) comparison of 213, 214 and 39

<table>
<thead>
<tr>
<th>$\delta_H$</th>
<th>multiplicity ($J$'s in Hz)</th>
<th>$\delta_H$</th>
<th>multiplicity ($J$'s in Hz)</th>
<th>$\delta_H$</th>
<th>multiplicity ($J$'s in Hz)</th>
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<tr>
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<td>7.33-7.26</td>
<td>m</td>
<td>7.35-7.26</td>
<td>m</td>
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<td></td>
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</tr>
<tr>
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<td>q (10.6)</td>
<td>4.72-4.66</td>
<td>m</td>
<td>4.67</td>
<td>d (11)</td>
</tr>
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<td>4.21</td>
<td>d (9.7)</td>
<td>4.22</td>
<td>br d (10)</td>
<td>4.63</td>
<td>d (11)</td>
</tr>
<tr>
<td>3.81-3.68</td>
<td>m</td>
<td>3.84-3.77</td>
<td>m</td>
<td>4.22</td>
<td>br d (10)</td>
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<tr>
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<td>3.75-3.68</td>
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<td>3.70-3.61</td>
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<td>3.55</td>
<td>dd (3.7, 8.1)</td>
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<tr>
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<td>m</td>
<td>2.65-2.48</td>
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<tr>
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<td>2.09-1.99</td>
<td>m</td>
<td>2.11-1.98</td>
<td>m</td>
</tr>
<tr>
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<td>s</td>
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<td>d (7)</td>
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<td>1.07</td>
<td>d (7)</td>
<td>1.02</td>
<td>d (7)</td>
</tr>
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</table>

$^a$ Ref 30. $^b$ Ref 28., 300 MHz in ref 29. $^c$ 400 MHz, 7.26 ppm as reference. $^d$ 500 MHz, 7.26 ppm as reference. $^e$ Reported as a triplet (t), but is clearly a doublet (d) in the provided supporting information.
Table 2.7 $^{13}$C NMR (CDCl$_3$) comparison of 213, 214 and 39

<table>
<thead>
<tr>
<th></th>
<th>213</th>
<th>214</th>
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<tr>
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<td>δ$_{C}^{e,f}$</td>
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<td>-</td>
</tr>
<tr>
<td>129.8</td>
<td>128.3</td>
<td>-</td>
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<tr>
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<td>0.1</td>
</tr>
<tr>
<td>9.7</td>
<td>9.7</td>
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</tr>
</tbody>
</table>

$^{a}$ Ref 30. $^{b}$ Ref 28, 75 MHz in ref 29. $^{c}$ 100 MHz, δ$_{C}$ in ppm. $^{d}$ 77.16 ppm selected as reference. $^{e}$ 125 MHz, δ$_{C}$ in ppm. $^{f}$ 77.23 ppm selected as reference. $^{g}$ |Difference between 39 and the applicable adduct|. $^{h}$ $^{13}$C resonances belonging to the protecting group . $^{i}$ not applicable. $^{j}$ Reported as a 118.9 ppm, but the attached peak-picked spectra provided in the supporting information clearly shows this signal is at 118.0 ppm.
As shown in Table 2.7, comparable $^{13}$C signals for 213 are only 0.1-0.3 ppm different from known compound 39. The $^{13}$C signals for C-6' epimer 214 are as high as 2.6 ppm different from known compound 39. Based on this analysis, the tentative assignment based on the $^1$H NMR spectroscopy is far more secure, but not absolute. Additional work to secure the structures of these compounds is required (vide infra).

With the desired transformation of 210 to 213 (and minor compound 214) now known to occur using hydroxymercuration/demercuration, the initial low yield and selectivity observed would have to be investigated to establish this approach as a synthetic possibility.

**Table 2.8** Hydration of 210

<table>
<thead>
<tr>
<th>Entry</th>
<th>SM&lt;sup&gt;a&lt;/sup&gt;</th>
<th>THF: H&lt;sub&gt;2&lt;/sub&gt;O</th>
<th>Equiv. Hg(OAc)&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Additive</th>
<th>Reaction Time</th>
<th>Conversion (%)</th>
<th>Selectivity (213:214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>210</td>
<td>10:1</td>
<td>2</td>
<td>-</td>
<td>40 h</td>
<td>48&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.7:1</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>8:1</td>
<td>1.5</td>
<td>-</td>
<td>48 h&lt;sup&gt;c&lt;/sup&gt;</td>
<td>80</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2:1</td>
<td>2</td>
<td>-</td>
<td>1 h</td>
<td>60</td>
<td>1:1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1:1</td>
<td>2</td>
<td>-</td>
<td>1 h</td>
<td>95</td>
<td>1:1</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1:1</td>
<td>1</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.5 h</td>
<td>&gt;95</td>
<td>3:1</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>1:1</td>
<td>1</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10 min</td>
<td>9</td>
<td>3:1</td>
</tr>
<tr>
<td>7</td>
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<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>30 min</td>
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<td>1:1</td>
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<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1 h</td>
<td>&gt;95&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3:1</td>
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<td>2 h</td>
<td>&gt;95&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.5:1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Starting Material. <sup>b</sup>Isolated yield of 213 (33%), 214 (15%), and 210 (52%). <sup>c</sup>16 h at 2-8 °C then 24 h at rt. <sup>d</sup>Isolated yield of 213 (62%) and 214 (16%).

Initially, the hydroxymercuration/demercuration reaction produced low levels of conversion and marginal selectivity in favour of the desired Bn-diol 213 (Table 2.8). It was found that reactivity could be improved through adjustment of solvent composition (entries
1-4), seemingly at the expense of selectivity. This could be the result of reaction reversibility and other equilibrium processes, which according to Brown, are well known in hydromercuration/demercuration reactions.\textsuperscript{137} These competitive reactions can be suppressed through the addition of base to the reaction, just prior to the radical\textsuperscript{138} demercuration step, but the time between addition of base and NaBH$_4$ must be carefully controlled to obtain reproducible results.\textsuperscript{137} Attempting this modification (entry 5) by addition of aq. Na$_2$CO$_3$ improved conversion substantially with reasonable selectivity in favour of the desired compound. Based on this result, the amount of time required before base was added to the reaction was investigated to determine if conversion and selectivity changed as a function of time. As shown in entries 6-8, the reaction progresses over the course of an hour with no change in selectivity; selectivity may be a result of the radical mechanism\textsuperscript{138} operating in the demercuration step when using NaBH$_4$. Other research groups have found that sodium amalgam (Na/Hg) reduces organomercurials with complete retention of configuration.\textsuperscript{139} This modification was attempted without success.

Attempting the established conditions in subsequent reactions, showed no change in selectivity, but, conversion was not always consistently high.\textsuperscript{i} Solvent composition and reaction time before addition of base were adjusted (entry 9, \textbf{Table 2.8}) to attain reproducibility.

Attempts were made to make the hydroxymercuriation/demercuration reaction and the subsequent reduction of the hemiacetals\textsuperscript{iii} into a one-pot reaction. Unfortunately, some of the constituents of the reaction mixture were not stable to the conditions and decomposition occurred: presumably, extended exposure to base was responsible for the decomposition.

\textsuperscript{i} Conversion in subsequent experiments under these conditions ranged from 90->95%.

\textsuperscript{iii} Reduction of the hemiacetals is slow. After 3 h, only 50-60% reduction had occurred (by $^1$H NMR spectroscopy): complete reduction was consistently observed after 16 h.
products. Therefore, the reaction of 210 to 213 and 214 was conducted as a two-pot process: work-up between demercuration and hemiacetal reduction.

2.7.3 Formal synthesis of baconipyrone C (8)

With a method to deliver Bn-diol 213 in reasonable yield, a simple change of the protecting group from Bn to PMB could deliver PMB-diol ent-39 used in three previous syntheses of baconipyrone C (8) (Scheme 2.15). Obtaining ent-39 through the same reaction sequence that produced Bn-diol 213 (substitution of BnBr for PMBCl) would secure the structure 213 by analogy and all previous compounds leading to 213 from 190. However, to claim a formal synthesis of baconipyrone C (8), a synthetic route to hydroxydione 41 would also be required.

Scheme 2.15

The PMB series of compounds was accessed as anticipated with only minor modification to the established procedures for the Bn series of compounds (210, 213, and 214) (Scheme 2.16). In general, the yields obtained were slightly lower than the Bn series,
but the reaction selectivity in the hydroxymercuration/demercuration step was the same.\textsuperscript{liii} Comparison of the $^1$H and $^{13}$C NMR of the two PMB diols (ent-39 and 216) obtained from the hydroxymercuration/demercuration of 215 showed an excellent match to the previously reported data.\textsuperscript{29,30} Comparison of the optical rotation for ent-39,\textsuperscript{liv} $[\alpha]_D$ -15 (c 0.45, CHCl$_3$) to literature values $[\alpha]_D$ -9.9 (c 0.91, CHCl$_3$) for ent-39\textsuperscript{29} and $[\alpha]_D$ +8.4 (c 0.15, CHCl$_3$) for 39,\textsuperscript{30} confirmed that the required absolute configuration was accessed.

![Scheme 2.16](image)

**Scheme 2.16**

The synthesis of hydroxydione 41 was seen coming directly from the Thiopyran Route to Polypropionates (Section 2.3), specifically through aldol diastereomer 122 that can be obtained in excellent yield (86%) and enantioselectivity (>98% ee) from 116 and 117.

\textsuperscript{liii} Reactions performed with 215 were attempted a limited number of times; i.e., not optimized to the same degree as the reaction with 210.

\textsuperscript{liv} The adduct produced in this synthesis.
(Scheme 2.1). From 122, all that is required to obtain 41 is desulfurization and deprotection of the ethylene acetal (Scheme 2.17).

Towards this end, aldol 122 was subjected to Raney nickel in refluxing THF, which smoothly desulfurized (Scheme 2.17). At the end of the reaction, the reaction mixture was cooled and aq. HCl was added to destroy the Raney nickel. The aqueous acid also served to deprotect the ethylene acetal. Thus 41 was obtained from 122 in a one-pot process in excellent yield (79%). The NMR data matched previously reported data.

![Scheme 2.17](image)

**Scheme 2.17**

Comparison of the three previous routes to the two key intermediates previously used in the synthesis of baconipyrone C (8) to this work are shown in Table 2.9.

As shown in Table 2.9, the synthetic route to both 41 and ent-39 compare favorably to Paterson’s synthesis. While fewer steps are required in this synthesis to construct ent-39, Paterson’s synthesis is over three times as efficient, a truly amazing feat. The same is not true for 41, despite one extra step, the yield of 41 in this synthesis is nearly twice that of Paterson’s and was produced with much higher ee than what Paterson achieved. Both the Hoveyda and Yadav syntheses are longer and less efficient than the current work.

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iv It is known that the use of alcoholic solvent increases the ability of Raney nickel to reduce other functionality by increasing available H₂ through hydrogenolysis of the solvent to its corresponding carbonyl compound.

lv For clarity, Hoveyda never synthesized baconipyrone C (8).
Table 2.9 Key baconipyrone C (8) intermediates synthesis comparison

<table>
<thead>
<tr>
<th></th>
<th>This Work</th>
<th>Paterson 2000(^a)</th>
<th>Hoveyda 2007(^b), (^c)</th>
<th>Yadav 2009(^d)</th>
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<tr>
<td><strong>ent-39</strong></td>
<td></td>
<td></td>
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<tr>
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<td>16</td>
<td>20</td>
<td>21</td>
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<tr>
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<td>22</td>
<td>22</td>
</tr>
<tr>
<td>steps</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yield</td>
<td>7.3%</td>
<td>26%</td>
<td>2.3%</td>
<td>3.8%</td>
</tr>
<tr>
<td>([\alpha]_D)(^e)</td>
<td>-15(\text{ c 0.45})</td>
<td>NR(^f)</td>
<td>+8.4(\text{ c 0.15})</td>
<td>-9.9(\text{ c 0.91})</td>
</tr>
<tr>
<td><strong>41</strong></td>
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</tr>
<tr>
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<tr>
<td>Total number of</td>
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<td>10</td>
<td>14</td>
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<tr>
<td>steps</td>
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<tr>
<td>Yield</td>
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<td>32%</td>
<td>7%</td>
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<td>-16.4(\text{ c 1.1})</td>
<td>+12(\text{ c 1.0})</td>
<td>-15.6(\text{ c 2.0})</td>
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</tbody>
</table>

\(^a\)Ref 28. \(^b\)Ref 30. \(^c\)Antipodes of *ent-*39 and 41 prepared. \(^d\)Ref 29. \(^e\)CHCl\(_3\). \(^f\)Not reported. \(^g\)Also synthesized diastereoselectively from \((R)\)-ethyl lactate (9 steps; 38% overall yield).

2.7.4 Aldehyde 218 synthesis

In Paterson’s 1\(^{st}\) attempted synthesis of siphonarin B (4) (Scheme 1.13), PMB-diol ent-39 could be bis-silylated by treatment with Et\(_3\)SiOTf and 2,6-lutidine and then the 1\(^{\circ}\) triethylsilyl ether was selectively deprotected; both reactions occurred in excellent yield.\(^{15}\)

The same sequence was attempted with Bn-diol 213 (Scheme 2.18). Despite the similarity between *ent-*39 and 213, the C-3’-OH of 213 could not be silylated.\(^{\text{lvii}}\) This observation was capitalized upon through a one-pot reaction scheme by transient protection of the C-7’-OH (of 213): C-7’-OH was silylated with Et\(_3\)SiOTf, followed by methoxymethylation of the C-

\(^{\text{lvii}}\)Repeated attempts employing extended reaction times (>24 h) and excess reagents (>5 equivalents in both Et\(_3\)SiOTf and 2,6-lutidine) were met without success. In all cases, only the C-7’-OH of 213 would silylate.
3’-OH. After TLC indicated complete reaction, MeOH\textsuperscript{lviii} and TBAF were added, cleanly removing the triethylsilyl group and delivering 217 in excellent yield.

\[
\begin{align*}
    \text{213} & \quad \text{a) i. } \text{Et}_3\text{SiOTf, 2,6-lutidine } \\
    & \quad \text{ii. } \text{MOMCl, DIPEA, } \text{^7Bn}_4\text{N} \ 	ext{iii. } \text{MeOH, } \text{^7Bn}_4\text{NF} \\
\end{align*}
\]

\textbf{Scheme 2.18}

Oxidation of the C-7’-OH to the corresponding aldehyde (218) was accomplished with IBX in DMSO in quantitative yield without need for chromatography (Scheme 2.19). IBX in hot (80 °C) MeCN (cf. Scheme 2.9, oxidation of diol 194 to dialdehyde 196) was attempted with a C-3’-acetate derivative (Scheme 2.20). This resulted in elimination and isomerization products.\textsuperscript{lix} Acetate derivative 221 was prepared as an alternative to aldehyde 218 and to investigate conditions to produce aldehyde 221 without competing isomerization and elimination pathways. Aldehyde 221 was not explored further other than to establish appropriate oxidation conditions for 217.

\textsuperscript{lviii} Added as a sacrificial alcohol to prevent possible MOMylation of the C-7’-OH after removal of the silyl protecting group.

\textsuperscript{lix} Elimination was speculated to occur across the C-2,3 bond and isomerization at C-2 through tautomerism, but this could not be proven because all three compounds were inseparable from each other.
a) IBX, DMSO

Scheme 2.19

a) Ac₂O, DMAP b) K₂CO₃, MeOH, H₂O c) IBX, DMSO

Scheme 2.20
2.8 Total synthesis of siphonarin B (4) and baconipyrones A (6) and C (8)

2.8.1 Carbon skeleton completion: total synthesis of the putative common precursor

With $222^{\text{lx}}$ and aldehyde $218$ in hand, an aldol reaction to couple these reactants could be attempted. Aldol reactions between $222$ (and its diastereomers) (see Figure 2.4) and chiral aldehydes have been extensively studied in the Ward group in order to determine and exploit the stereocontrol elements present in these reactions.$^{64, 73, 76}$ Based on these studies, the configurations at C-3 (of $222$) and C-2 and C-3 (of $218$) provide guidance as to the selection of an aldol mediator to efficiently couple these two reactants (Figure 2.19).

![Figure 2.19 Considerations for the required aldol coupling of 222 and 218](image)

The aldol reactions of $222$ (and its diastereomers) are unerringly trans selective (C-3 and C-5 of $222$) with aldehyde $116$. This is a result of pseudo-axial delivery of the electrophile for stereoelectronic reasons: conformational analysis places the existing C-3 ligand (of $222$) in a pseudo-equatorial position thus necessitating a trans relationship of the existing ligand at C-3 and the newly installed ligand. Further, the anti relative configuration of the $\alpha$-methyl and $\beta$-OBn substituents of aldehyde $218$ are expected to reinforce Felkin

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$^{\text{lx}}$ Methoxymethylation of $122$ produced $222$. Compound $188$ ($P_2 = \text{MOM}$, Figure 2.15) is the generic version of $222$. 

96
selective addition to the carbonyl.\textsuperscript{141} These strong diastereoface selectivities require an aldol mediator with either no selectivity preference or one that favours \textit{syn} relative aldol topicity.

The aldol mediators investigated with \textit{222} (and its diastereomers) that show either no selectivity or are \textit{syn} selective are based on titanium(IV). Ward et al. have shown that the transmetalation of Li enolates of \textit{222} (and its diastereomers) with Ti(O\textit{i}Pr)\textsubscript{4} produces Ti(O\textit{i}Pr)\textsubscript{4}Li “ate” enolates that react with \textit{syn} relative aldol topicity selectively with one enantiomer of (±)-\textit{116} (\textbf{Figure 2.4}) to produce single compounds (i.e., \textit{134}).\textit{13i,76} Titanium(IV) enolates of \textit{222} based on TiCl\textsubscript{4} or TiCl\textsubscript{3}O\textit{i}Pr have also been shown to efficiently couple \textit{222} and \textit{116}.\textit{73} These reactions occur without significant preference of relative aldol topicity. In general, the latter reaction format is faster and is a simpler procedure to execute than the former.

Based on the above analysis, TiCl\textsubscript{4} was selected as the mediator for the aldol reaction between \textit{222} and \textit{218} (\textbf{Scheme 2.21}). Gratifyingly, this reaction gave a 79\% yield of essentially one diastereomer (>20:1, as judged by \textit{\textsuperscript{1}H NMR spectroscopy), clearly showing the effectiveness of the selected conditions.

\textsuperscript{13i} Such reactions are kinetic resolutions of (±)-\textit{116}.
The structure of aldol adduct 223 was assumed to have the configuration shown (Scheme 2.21), based on the model in Figure 2.4. The relative configurations of C-3” and C-7’ were not rigorously proven: all stereocenters present in 222 and 218 were assumed to be unchanged from starting material.

The relative configurations of C-3” and C-7’ of 223 are not critical to the success or failure of this synthetic effort because C-7’-OH will be oxidized and the C-3” stereocenter in resulting C-4”,7’ β-diketone will be susceptible to keto-enol tautomerism.

### 2.8.2 Attempted trioxadithiapentacycle formation

With aldol adduct 223 in hand, the oxidation of C-7’-OH to the corresponding C-4”,7’ β-diketone was attempted (Scheme 2.22). The resulting oxidized compounds proved to be a complicated mixture of keto (2 diastereomers) and enol forms and was taken forward as a crude product, as previously described in the model study (Section 2.4)
Scheme 2.22

Despite numerous attempts using various conditions, nothing corresponding to trioxadithiapentacycle 224 could be isolated from the attempted reactions (Scheme 2.22). Indeed, no pure compounds could be identified and, although deprotection of acetal groups was occurring, the precise course of the reaction could not be determined. Unfortunately, the synthetic strategy outlined in Section 2.6 had failed.

2.8.3 Alternative avenues of investigation

Despite the failures encountered in the attempted formation of desired trioxadithiapentacycle 224, aldol adduct 223 still offered some potential towards addressing the objectives of this research project. Additionally, it was hoped that exploration with this adduct may offer some insight into reasons for the failure to form trioxadithiapentacycle 224, which had so readily formed in the earlier model study (Section 2.4).

As a first attempt, aldol adduct 223 was subjected to FeCl₃•6H₂O, which gave a mixture of desired deprotected compound 225 and retro-aldol adduct 226 (Scheme 2.23). Unfortunately, desired deprotected compound 225 was only isolated in ca. 80% purity (too

lxii In this particular case, the resulting hemiacetal, obtained as a result of a retro-aldol reaction, was trapped as a methoxy acetal.
impure to characterize) and was produced in similar yield to retro-aldol adduct 226 (39% isolated yield).

Scheme 2.23

Retro-aldol adduct 226 was obtained as a pure compound (Scheme 2.23). The structure was assumed to have undergone no isomerization events. The configuration of the methoxy group was suggested by a positive NOE on HC-4’’ and HC-2’’ on irradiation of the methoxy group and vice versa. A positive NOE on HC-2’’ on irradiation of HC-4’’ and vice versa was also observed.

Noting the propensity of aldol adduct 223 towards retro-aldol and anticipating the need for a desulfurization reaction soon in the reaction sequence, an adjustment was made in the order of steps. Desulfurization of 223 followed by deprotection of the three acetal groups with FeCl$_3$•6H$_2$O in acetone/MeOH (5% v/v), cleanly furnishing 227 in 87% yield (Scheme 2.24) over two steps without detectable retro-aldol 226 (Scheme 2.23).
In order to effectively utilize 227, the C-5, C-9, and C-13 alcohols require differentiation before oxidation of C-9 and C-13 alcohols could be attempted. Fortunately, C-13-OH was previously shown to be unreactive towards Et₃SiOTf in a related compound (cf. C-3’-OH in diol 213, Scheme 2.19). It was hoped that this lack of reactivity would translate to 227, leaving two alcohols to differentiate, C-5 and C-9. Considering the C-5 and C-9 alcohols have considerable differences in their surrounding environments, it was speculated that these two alcohols should have different reactivities. Depending on their relative reactivities, two potential strategies could be investigated: 1) the C-5-OH (of 227) could be selectively protected; or, 2) the bis-protected compound (cf. 229, Scheme 2.24) could be selectively hydrolyzed (i.e., if C-9-OH of 229 would be more reactive towards silylation, it should also be more reactive towards selective hydrolysis).
Treatment of 227 with Et₃SiOTf produced a 5:1 mixture of 228 and the C-9 triethylsilyl ether, as well as 229 and some recovered starting material (Scheme 2.24). The mono-silylated compounds were not separable from each other; therefore, the reaction was typically run to nearly equal ratios of 228 and 229 to avoid complication of carrying the minor C-9 triethylsilyl ether forward. Bis-silylated derivative 229 could be efficient recycled to starting material 227.

The position of the silyl-protecting group of 228 was determined by NOE (Figure 2.20). A positive NOE was detected on HC-5 upon irradiation of the methylene (-H₂C-) group of the silyl-protecting group and vice versa. No NOE was detected on HC-9 upon irradiation of the methylene (-H₂C-) group\textsuperscript{xiii} of the silyl-protecting group and vice-versa.

\begin{center}
\includegraphics[width=0.5\textwidth]{figure220.png}
\end{center}

\textbf{Figure 2.20} NOE results for 228

Obtaining compound 228 provided an avenue for further investigation because C-5-OH was differentially protected from C-9 and C-13-OH. Where the previous strategy had failed (Section 2.8.2), a new possibility emerged that could address the objectives of this research project (Section 2.1).

\textsuperscript{xiii} The methylene H’s of the silyl group are interchangeable. Figure 2.19 is drawn arbitrarily.
2.8.4 Synthesis and isomerization of the putative common precursor

Oxidation of 228 with IBX in DMSO gave the corresponding tetraone 230 in good yield (Scheme 2.25). Hydrogenolysis of the benzyl group with Raney nickel gave a complicated mixture of compounds that was not characterized, but was immediately subjected to HF•pyridine to hydrolyze the triethylsilyl group. Interestingly, a mixture of hemiacetals (ca. 80% of the reaction mixture; identified by the signals at ca. δ_H 6.19, 6.35, 6.39, and 6.46 ppm and acetal carbons δ_C 104.4, 104.6, and 104.7) was produced with a very small amount of enol, β-diketone tautomers (2 diastereomers; C-8 signals at δ_C 61.9 and 61.1) content and a trace amount of siphonarin B (4) (ca. 2% of the reaction mixture).\textsuperscript{lxiv} This mixture of hemiacetals was speculated to be the elusive putative common precursor 14/15 of the siphonariid polypropionates (4, 6, 8, and 10). If this were the case, this would be the first enantioselective synthesis of putative acyclic precursor 14/15, but to claim this, the mixture of hemiacetals would have to be isomerized to one, or more, of the known compounds (4, 6, 8, and 10) (\textit{vide infra}).

\textsuperscript{lxiv} Diagnostic signal at 5.12 ppm (1H NMR spectrum; CDCl\textsubscript{3}).
Scheme 2.25<sup>lxxv</sup>

Putative common precursor 14/15 exists primarily as a mixture of hemiacetals 231 – 234 (Figure 2.21). This mixture of hemiacetals bears a strong resemblance to the impurities present in the <sup>1</sup>H NMR spectroscopy of natural siphonarin B (4), provided by Garson and reported in Paterson’s total synthesis of siphonarin B (4).<sup>15</sup> It is proposed that of the four observed hemiacetals, two (i.e., 231 and 233) arise from addition of the C-5-OH group onto C-9 carbonyl and two (i.e., 232 and 234) arise from addition of the C-11-OH group on the C-7 carbonyl. The relationships between 231 and 232 and between 233 and 234 are very close; i.e., they have identical configuration around the ring with only subtle differences in the substituents at C-9 and C-5 (in 231/233) versus those at C-7 and C-11 (in 232/234). It is important to note that an additional four hemiacetals are possible (8 total) from the two

---

<sup>lxxv</sup> Atom numbering in the intermediates leading up to the natural products was performed according to IUPAC. Atom numbering of the natural products was performed according to the numbering scheme applied by the scientists responsible for isolation and structure determination.
different cyclization pathways (C-5-OH $\rightarrow$ C-9 carbonyl and C-11-OH $\rightarrow$ C-7 carbonyl) that have the opposite configuration at the acetal carbon (i.e., C-9 in 213/233 and C-7 in 232/234). However, the additional four hemiacetals (two from each cyclization pathway) do not benefit from anomeric stabilization (i.e., the hemiacetal OH group is in an equatorial orientation) and were discounted as possible contributors to the observed equilibrium. This hypothesis is consistent with the experimental and computation results from the model study (Section 2.4).

The hemiacetals 231 - 234 were remarkably stable to silica gel chromatography. Further support of their stability was provided by allowing the mixture to stand at room temperature (in the dark) in CDCl$_3$; the mixture of hemiacetals slowly produced sipholarin B (4) (ca. 9% of the reaction mixture after 28 days) with very little change in the hemiacetal ratio. None of the other known sipholariid polypropionates (6, 8, and 10) were detected.
Figure 2.21 | H NMR spectrum of the putative common precursor

- enol $\delta_H = 17.05$
- siphonarin B $\delta_H = 5.12$
- C-5-OH $\rightarrow$ C-9 carbonyl
- C-11-OH $\rightarrow$ C-7 carbonyl
- readily epimerizable

$\delta_H$ values:
- 6.4
- 6.3
- 6.19
- 6.46
- 6.39
- 6.35
Turning towards the earlier model study (Section 2.4) for guidance on how to proceed in isomerizing 14/15 into one or more of the isolated polypropionate structures (4, 6, 8, and 10), the first condition attempted was imidazole in CDCl₃ (Scheme 2.26).⁷⁵ Based on the previous work, this condition was viewed as having the best chance to form caloundrin B (10) (Section 2.4).

Exposure of 14/15 (primarily as a mixture of hemiacetals 231 – 234) to imidazole in CDCl₃ produced siphonarin B (4) as the only identifiable natural product in 70% isolated yield after 1 day along with some remaining 14/15. This experiment conclusively showed that the putative common precursor 14/15 had been synthesized, as had been previously speculated, and concluded the first enantioselective total synthesis of siphonarin B (4).

Subjecting purified siphonarin B (4) to imidazole in CDCl₃ for 2 days, returned siphonarin B (4) and 14/15. The 14/15 obtained from this experiment existed as a different ratio of hemiacetals than that obtained from triethylsilyl hydrolysis of 230 (see Figure 2.21). This experiment showed that, under these conditions, the formation of siphonarin B (4) is reversible. Caloundrin B (10) was not observed as a product of any of the isomerization experiments with imidazole in CDCl₃.

Scheme 2.26
The NMR data of natural and synthetic siphonarin B (4) are compared in Tables 2.10 and 2.11.

**Table 2.10.** $^1$H NMR (CDCl$_3$) comparison of natural and synthetic siphonarin B (4)

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$^a$ Data and assignments according to ref 8.
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<sup>a</sup>Ref 8.  <sup>b</sup>Assignments from ref 9.  <sup>c</sup>Chemical shifts for synthetic material are consistently 0.2-0.3 ppm higher than those reported for the natural product presumably due to a different reference standard; δ<sub>C</sub> CDCl₃ = 77.23 was used for this study.

The specific rotations of natural ([α]<sub>D</sub> +13 (c 0.14, CHCl₃)) and synthetic<sup>lxvi, 15</sup> ([α]<sub>D</sub> +12 (c 0.1, CHCl₃)) compare favorably.

Of the four hemiacetals 231 – 234 originally present in 14/15, only two hemiacetals were present in any appreciable amount (δ<sub>H</sub> 6.39 and 6.19) following isomerization with

<sup>lxvi</sup>Paterson obtained ([α]<sub>D</sub> +10.5 (c 0.12, CHCl₃)) for his synthetic sample.
imidazole. These hemiacetals are hypothesized to be 231 and 232, considering Figure 2.21. This conclusion is further rationalized based on the results of the trioxaadamantane model study (Section 2.4): 231 is assumed to be the most stable hemiacetal from 14 (8S, C-5-OH → C-9 carbonyl) and 232 is the most stable from 15 (8R, C-11-OH → C-7 carbonyl). No definitive structure proof was attempted.

Continuing with investigation of the conditions identified in the earlier model study (Section 2.4), exposure of 14/15 to DBU in benzene-d₆ rapidly induced a retro-Claisen rearrangement (Scheme 2.27). However, significant C-14 epimerization occurred during the course of the reaction to give a 1.4:1 ratio of baconipyrone C (8): 14-epi-baconipyrone C (235). Baconipyrone C (8) was isolated from this reaction mixture in 50% yield providing the first total synthesis of 8 via the proposed retro-Claisen rearrangement from the contiguous carbon skeleton. 14-epi-baconipyrone C (235) was isolated from the crude reaction mixture in 30% yield for a combined yield of 80%.

The isomerization of baconipyrone C (8) to 14-epi-baconipyrone C (235) was verified by exposing baconipyrone C (8) to DBU in benzene-d₆ (Scheme 2.27). Rapid epimerization occurred to give a 1.3:1 ratio of 8 and 235, respectively, within 45 minutes. Interestingly, the C-14 epimer 235 isolated from these experiments did not match the NMR data, specific rotation, and Rᵢ (same mobile and stationary phases as reported previously) of a compound that was tentatively assigned as 14-epi-baconipyrone C (235) in a previous study.¹lvii, 28, 142

¹lvii Data for the putative 14-epi-baconipyrone C (actually C-10 epimer 236) was provided by Prof. Paterson in a private communication. See also Chen, D. Y-K. Ph.D. Thesis, University of Cambridge, Cambridge, U.K., 2002.
Scheme 2.27

Comparison of the $^{13}$C NMR data (CDCl$_3$) for all three compounds (baconipyrone C (8), the 14-epi-baconipyrone C (235) isolated from this study, and the putative 14-epi-baconipyrone C (236)$^{l_{viii}}$ isolated by Paterson$^{28}$) led to the hypothesis that 10-epi-baconipyrone C (236) had been formed in all three syntheses based on the esterification approach.$^{l_{sx}, 28-30}$

$l_{viii}$ Likely the C-10 epimer (vide infra).

$l_{sx}$ It is possible that C-10 epimerization occurred via enolization of the activated ester and/or ketene formation.
Table 2.12. $^{13}$C NMR (CDCl$_3$) comparison of baconipyrone C (8), 14-epi-baconipyrone C (235), and 10-epi-baconipyrone C (236)

<table>
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<th>8</th>
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<th>10-epi-baconipyrone C (236)</th>
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<td>$\delta_{C}^{b}$</td>
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<td>7.7</td>
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</table>

$^a$ Assignments made via COSY, HSQC and HMBC. Although two different sets of signals can be assigned for two different CH$_3$CH$_2$C(O)CH(Me) - fragments, the fragments cannot be assigned (e.g. C-4 vs. C-6). Assignments only apply to 8 and 235. $^b$ Reference standard: $\delta_{C}$ CDCl$_3$ = 77.23. $^c$ Reference standard: $\delta_{C}$ CDCl$_3$ = 77.0.
The assignment of 235 is supported in two ways. The most acidic proton in baconipyrone C (8) is expected to be HC-14 (vinyllogous β-ketoester): brief treatment of 8 with base (DBU) produced 235 as the only product. The 13C NMR of 8 and 235 are very similar with Δδc only 0.8-1.2 ppm for C-10, C-11, C-12, and the largest difference (2.5 ppm) for C-14. However, 236 is quite different from that of 8 with 7 carbons having Δδc>1.5 and there are significant differences in the chemical shifts for the methyl signals. Unfortunately, the hypothesis that the latter is actually the C-10 epimer 236 cannot be confirmed because assignments for the 13C data are not available.

Considering the conditions explored in the earlier model study (Section 2.4), lengthy exposure of 14/15 to HF•pyridine remained as a possible route to caloundrin B (10). Exposure of 14/15 for 16 hrs HF•pyridine gave a small amount (20% isolated) of siphonarin B (4) and recovered starting hemiacetals (60% isolated). Resubjecting the hemiacetals for a longer period of time under identical conditions was unproductive and led to unidentifiable compounds.

2.4.8.1 Conclusions on the synthesis and isomerization of the putative common precursor 14/15

The enantioselective total synthesis of putative common precursor 14/15 was achieved in 18 steps in 3.1% overall yield (20 total steps). The putative common precursor 14/15 exists mainly as a mixture of four hemiacetals, speculated to be hemiacetals 231 - 234 (Figure 2.21). The hemiacetals 231 - 234 proved to be remarkably stable to silica gel chromatography and did not spontaneously form any of the polypropionate structures isolated from siphonariid extracts (i.e., 4, 6, 8, and 10) upon standing (28 days in CDCl3).
The isomerization conditions identified in the model study (Section 2.4) were attempted with the putative common precursor 14/15.

Imidazole in chloroform readily isomerized 14/15 to provide siphonarin B (4) (Scheme 2.26). This work was the first enantioselective synthesis of siphonarin B (4). Interestingly, these conditions were effective in the model study to provide trioxaadamantane ring system 150 (see Section 2.4), but the presence of caloundrin B (10) was not detected in the reaction mixture.

HF•pyridine, a reagent proven favourable in the model system (Section 2.4) to produce the truncated structure of siphonarin B (4) (cf. 138, Scheme 2.2), was not as productive or clean when applied to 14/15.

Exposure of 14/15 to DBU in benzene-d_6 readily induced retro-Claisen rearrangement. Baconipyrone C (8) was obtained was obtain in 50% yield (final step). This is first total synthesis of baconipyrone C (8) via the proposed “biomimetic” route and the first synthesis to explore a route other than that based on esterification. Unfortunately, these conditions also readily epimerized baconipyrone C (8) to provide 14-epi-baconipyrone C (235). Baconipyrone A (6) was not detected; i.e., no retro-Claisen rearrangement/aldol cascade occurred under these conditions.

Caloundrin B (10) was never observed in any of these isomerization experiments. Other conditions, or an alternative strategy, would have to be investigated to access the elusive caloundrin B (10).

2.8.5 Investigation of alternative conditions

An early experiment to determine the correct order of deprotection of tetraone 230 to access putative common precursor 14/15 (Scheme 2.25), found that triethylsilyl hydrolysis
followed by attempted hydrogenolysis of the Bn group with a very small amount of Raney nickel in refluxing EtOH gave what appeared to be a mixture of Bn-protected retro-Claisen rearrangement products by $^1$H NMR spectroscopy.\textsuperscript{lxv} It was hypothesized that exposure of 14/15 to a solid phase might induce retro-Claisen rearrangement under more controlled conditions.\textsuperscript{lxvi} Silica gel and aluminum oxide are known to induce retro-Claisen rearrangement in related systems during chromatography.\textsuperscript{14, 15}

Subjecting 14/15 to neutral aluminum oxide in refluxing ethanol\textsuperscript{lxvii} gave a 3: 5: 7: 10 mixture of baconipyrone A (6), siphonarin B (4), baconipyrone C (8), and retro-Claisen ester 237 (Scheme 2.28). Ester 237 arises from the alternative hemiacetal formed from C-11-OH addition onto the C-7 carbonyl. Interestingly, ester 237 from the alternative hemiacetal was the dominant compound (40%) in the reaction mixture. Also, for the first time, baconipyrone A (6) was detected.

The observation of 237 confirmed the hypothesis (Section 2.8.4) that the alternative addition of C-11-OH onto C-7 carbonyl to form hemiacetals 232 and 234 (Figure 2.21) was occurring. Under these conditions, isomerization to the alternative hemiacetals arising from C-5-OH onto C-9 carbonyl is slow relative to retro-Claisen rearrangement.

\textsuperscript{lxv} Essentially, hydrogenolysis of the benzyl group had failed; diagnostic ester peaks were observed in the $^1$H NMR (ca. 5.0 – 5.5 ppm) spectrum of the crude reaction mixture. The products of this reaction were not characterized.
\textsuperscript{lxvi} Reactions employing Raney nickel with this substrate were capricious.
\textsuperscript{lxvii} A control experiment of 14/15 in refluxing ethanol returned unaltered starting material.
a) aluminum oxide, EtOH, Δ

Scheme 2.28

The structure of 237 was determined by two dimensional NMR spectroscopy: COSY, HSQC, and HMBC (Figure 2.22). Eight isolated spin systems were determined by COSY. One bond connectivity (H to C) was established by HSQC. Three of the spin systems corresponded to the γ-pyrone methyl (x2) and ethyl group signals. There were two additional isolated ethyl groups, two spin systems each containing a proton correlated to a carbinol signal (δC 76.1 and 73.1 ppm) (as determined by HSQC), and an isolated proton at 4.03 ppm. The isolated proton, HC-1’, was identified by its diagnostic ¹H NMR chemical shift and multiplicity (HC-1’: quartet, 4.03 ppm). H3CC-1’ (as determined by COSY) showed an HMBC correlation to C-3’ and C-2”. The HC-4’ to HC-6’ spin system (as determined by COSY) showed an HMBC correlation from H3CC-4’ to C-3’. The isolated ethyl signals were distinguished on the basis of HMBC correlation from H3CC-9’ to C-7’; an HMBC correlation from H3CC-6’ to C-7’ was also detected. HC-2 was differentiated from HC-4 on the basis of HMBC correlations from their respective methyl groups: H3CC-2 to C-1 (δC 174.3) and H3CC-4 to C-5 (δC 215.4). The remaining ethyl group showed an HMBC correlation from H3C-7 to C-5. It is assumed that no isomerization events occurred.
Figure 2.22 Structure determination of 237

Exposure of siphonarin B (4) to aluminum oxide in refluxing ethanol gave recovered starting material (siphonarin B (4)), baconipyrone C (8), and baconipyrone A (6) in a ratio of 2.3: 3: 1 (Scheme 2.29). Retro-Claisen ester 237 was not detected in the $^1$H NMR spectrum (CDCl$_3$) of the crude reaction mixture. Under these conditions, isomerization to the alternative C-11-OH addition onto C-7 carbonyl is slow relative to the retro-Claisen reaction.

Scheme 2.29

With this latter experiment in mind and armed with the following knowledge:

1) No C-14 epimerization occurred in the reactions of siphonarin B (4) and 14/15 with aluminum oxide.
2) Paterson found no cyclization of the C-9 hemiacetal onto the C-13 carbonyl in any of the PMB derivatives leading up to the culmination of his total synthesis of siphonarin B (4) (cf. Scheme 1.14) (i.e., no C-11 PMB-protected siphonarin B was formed).

3) The alternative C-11-OH addition onto C-7 carbonyl cannot occur with C-11-OH blocked as its corresponding benzyl ether. Therefore, leaving the benzyl group intact prior during the retro-Claisen rearrangement reaction could provide a means to access baconipyrone C (8) without epimerization that had been so extensive when 14/15 was subjected to DBU (Scheme 2.27).

Scheme 2.30
The triethylsilyl ether protecting group was hydrolyzed by brief treatment with HF•pyridine (Scheme 2.30). Gratifyingly, subjecting 238 to basic aluminum oxide in refluxing EtOH gave a 1:4 mixture of products that were speculated to be the Bn-protected derivatives of baconipyrones A (6) and C (8), 242 and 243, respectively (Figure 2.23). Treating this mixture with palladium on carbon (10%) under an atmosphere of H₂ slowly (ca. 16 hours) hydrogenolyzed the benzyl ether protecting groups to give baconipyrones A (6) and C (8) in excellent isolated yield (88% combined yield over two steps). There was no evidence of 14-epi-baconipyrone C (235), 237, or siphonarin B (4) in the ¹H NMR spectrum of the crude reaction mixture.

The selectivity of this transformation can be rationalized by the transition state model proposed by Vogel to explain a related aldol reaction (see 241, Figure 2.23). In the reaction of 238 with aluminum oxide, group selectivity between C-3 and C-7 carbonyls is achieved as a result of the retro-Claisen rearrangement (cf. 239 → 240). Ketonization of enol(ate) 240 provides 242, whereas intramolecular attack of enol(ate) 240 onto C-3 carbonyl, via 241, results in 243. This type of retro-Claisen rearrangement/aldol cascade reaction appears to be unprecedented.

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lxxiii Neutral aluminum oxide proved ineffective in this case.
lxxiv Characteristic signals (dd’s) above 5 ppm (¹H NMR spectrum (CDCl₃)). No attempt was made to separate or characterize the individual compounds, presumed to be benzyl-protected precursors of 6 and 8.
lxxv Paterson also observed slow hydrogenolysis of a similar PMB ether under these conditions.
Figure 2.23 Proposed retro-Claisen rearrangement and retro-Claisen rearrangement/aldol cascade pathways

A comparison of NMR data for natural and synthetic baconipyrones A (6) and C (8) are shown in Tables 2.13, 2.14, 2.15, and 2.16. The specific rotations of natural ([α]_D -82.0 (c 0.47, CHCl_3)) and synthetic ([α]_D -96 (c 0.13, CHCl_3)) baconipyrone A (6) compare
favorably as do those for natural\textsuperscript{hxxvi}, \textsuperscript{4, 28}: $[\alpha]_D$ -82 (c 0.16, MeOH) and synthetic\textsuperscript{hxxvii}, \textsuperscript{28-30}: $[\alpha]_D$ -81 (c 0.1, MeOH) baconipyrone C (8).

\textsuperscript{hxxvi} Initially reported by Faulkner as $[\alpha]_D$ -19 (c 0.90, MeOH), but revised by Paterson in a subsequent report. \textsuperscript{hxxvii} Paterson: $[\alpha]_D$ -73.3 (c 0.77, MeOH); Yadav: $[\alpha]_D$ -70.20 (c 0.4, MeOH); Hoveyda: $[\alpha]_D$ +11.8 (c 0.09, MeOH).
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<th>assignment&lt;sup&gt;a,b&lt;/sup&gt;</th>
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<td>t (7.5)</td>
</tr>
<tr>
<td>1.09</td>
<td>d (7.2)</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;CC-12&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.09</td>
<td>d (7)</td>
</tr>
<tr>
<td>1.02</td>
<td>d (6.9)</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;CC-6</td>
<td>1.02</td>
<td>d (7)</td>
</tr>
<tr>
<td>1.01</td>
<td>t (7.2)</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;CC-8</td>
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<td>t (7.5)</td>
</tr>
<tr>
<td>0.91</td>
<td>t (7.2)</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;CC-2</td>
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<td>t (7)</td>
</tr>
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<td>0.85</td>
<td>d (6.8)</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;CC-4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.86</td>
<td>d (7)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data and assignments according to ref 4.  
<sup>b</sup>Although two different sets of signals can be assigned for two different CH<sub>3</sub>CH<sub>2</sub>C(O)CH(Me)- fragments, the assignment of the individual fragments (e.g., C-4 vs. C-6) should be considered as arbitrary.  
<sup>c</sup>Other workers have reported this signal at 3.38 and 3.39 ppm.<sup>28, 29</sup>  
<sup>d</sup>Other workers have reported this signal at 2.09 ppm.<sup>28, 29</sup>  
<sup>e</sup>Assignments are reversed compared to ref 4. The methyls at C-4 (or C-6)<sup>b</sup> and C-12 were assigned by HMBC through their correlations to C-5 and C-11, respectively.
Table 2.14. Comparison of $^{13}$C NMR spectra of natural and synthetic baconipyrone C (8)

<table>
<thead>
<tr>
<th>natural assignment $^a$</th>
<th>synthetic</th>
<th>natural assignment $^a$</th>
<th>synthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta_C$ $^b$</td>
<td>$\delta_C$ $^c$</td>
<td>$\delta_C$ $^b$</td>
<td>$\delta_C$ $^c$</td>
</tr>
<tr>
<td>211.9 C-7 or C-3</td>
<td>212.1</td>
<td>41.1 C-10</td>
<td>41.3</td>
</tr>
<tr>
<td>210.9 C-3 or C-7</td>
<td>211.1</td>
<td>35.1 $^d$ C-2 or C-8</td>
<td>35.32</td>
</tr>
<tr>
<td>210.4 C-13</td>
<td>210.7</td>
<td>24.7 C-20</td>
<td>24.9</td>
</tr>
<tr>
<td>179.7 C-17</td>
<td>179.9</td>
<td>15.0 CH$_3$C-10</td>
<td>15.3</td>
</tr>
<tr>
<td>174.0 C-9</td>
<td>174.3</td>
<td>14.1 CH$_3$C-12</td>
<td>14.4</td>
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<tr>
<td>164.7 C-19</td>
<td>164.8</td>
<td>13.8 CH$_3$C-4 or CH$_3$C-6</td>
<td>13.7</td>
</tr>
<tr>
<td>160.6 C-15</td>
<td>160.8</td>
<td>13.1 CH$_3$C-14</td>
<td>13.4</td>
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<td>120.6</td>
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<tr>
<td>118.2 C-18</td>
<td>118.5</td>
<td>9.9 CH$_3$C-16</td>
<td>10.1</td>
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<td>77.5 C-11</td>
<td>77.8</td>
<td>9.6 CH$_3$C-6 or CH$_3$C-4</td>
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<tr>
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<td>74.0</td>
<td>9.5 CH$_3$C-18</td>
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<td>50.9 C-14</td>
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<td>7.7 CH$_3$C-8 or CH$_3$C-2</td>
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<td>48.6 C-12</td>
<td>48.8</td>
<td>7.2 CH$_3$C-2 or CH$_3$C-8</td>
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<tr>
<td>47.2 C-4 or C-6</td>
<td>47.5</td>
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</tr>
<tr>
<td>45.7 C-6 or C-4</td>
<td>46.0</td>
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$^a$ Data from ref 4. $^b$ Assignments made via COSY, HSQC and HMBC. Although two different sets of signals can be assigned for two different CH$_3$CH$_2$C(O)CH(Me) - fragments, the fragments cannot be assigned (e.g. C-4 vs. C-6). $^c$ Chemical shifts for synthetic material are consistently 0.2-0.3 ppm higher than those reported for the natural product presumably due to a different reference standard; we used $\delta_C$ CDCl$_3$ = 77.23. $^d$ Two (2) overlapping signals.
Table 2.15. $^1$H NMR (CDCl$_3$) comparison of natural and synthetic baconipyrone A (6)

<table>
<thead>
<tr>
<th>$\delta_H$</th>
<th>multiplicity ($J$'s in Hz)</th>
<th>assignment $^a$</th>
<th>$\delta_H$</th>
<th>multiplicity ($J$'s in Hz)</th>
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</thead>
<tbody>
<tr>
<td>5.05</td>
<td>dd (4.7, 6.3)</td>
<td>HC-5</td>
<td>5.00</td>
<td>dd (4.5, 6.5)</td>
</tr>
<tr>
<td>4.09</td>
<td>q (6.9)</td>
<td>HC-14</td>
<td>4.04</td>
<td>q (7)</td>
</tr>
<tr>
<td>3.68</td>
<td>ddd (3.4, 8.6, 9.6)</td>
<td>HC-11</td>
<td>3.62</td>
<td>ddd (3.5, 8.5, 9.5)</td>
</tr>
<tr>
<td>3.43</td>
<td>d (9.6)</td>
<td>HOC-11</td>
<td>3.35</td>
<td>d (9.5)</td>
</tr>
<tr>
<td>3.00</td>
<td>dq (4.7, 7.2)</td>
<td>HC-6</td>
<td>2.96</td>
<td>(dq (4.5, 7)</td>
</tr>
<tr>
<td>2.84</td>
<td>dq (8.6, 6.9)</td>
<td>HC-12</td>
<td>2.79</td>
<td>(dq (8.5, 7)</td>
</tr>
<tr>
<td>2.65</td>
<td>dq (3.4, 7.2)</td>
<td>HC-10</td>
<td>2.64</td>
<td>dq (3.5, 7)</td>
</tr>
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<td>2.60</td>
<td>q (6.8)</td>
<td>HC-8</td>
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<tr>
<td>2.60</td>
<td>m</td>
<td>H$_2$C-20</td>
<td>2.62-2.51</td>
<td>m</td>
</tr>
<tr>
<td>2.13</td>
<td>dq (6.3, 6.9)</td>
<td>HC-4</td>
<td>2.13</td>
<td>dq (6.5, 7)</td>
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<tr>
<td>2.05</td>
<td>s</td>
<td>H$_3$CC-16</td>
<td>2.05</td>
<td>s</td>
</tr>
<tr>
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<td>s</td>
<td>H$_3$CC-18</td>
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<td>s</td>
</tr>
<tr>
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<td>H$_3$CC-10</td>
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<td>1.16</td>
<td>t (7.5)</td>
<td>H$_3$CC-20</td>
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<td>t (7.5)</td>
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<td>d (6.8)</td>
<td>H$_3$CC-8</td>
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<td>H$_3$C-1</td>
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<td>t (7.5)</td>
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$^a$ Data and assignments according to ref 4.
Table 2.16. $^{13}$C NMR (CDCl$_3$) comparison of natural and synthetic baconipyrone A (6)

<table>
<thead>
<tr>
<th>natural$^a$</th>
<th>assignment$^b$</th>
<th>$\delta_C$</th>
<th>synthetic</th>
<th>$\delta_C$</th>
<th>$\delta_C$$^c$</th>
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<th>assignment$^b$</th>
<th>$\delta_C$</th>
<th>synthetic</th>
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<td>221.4$^d,e$</td>
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<td>210.2</td>
<td>C-13</td>
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<td>11.5</td>
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<tr>
<td>77.1</td>
<td>C-11 or C-5</td>
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<td>11.3</td>
<td>CH$_3$C-20</td>
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<td>CH$_3$C-18</td>
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<td>C-12</td>
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<td>8.8</td>
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<td>9.0</td>
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<td>44.7</td>
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</tbody>
</table>

$^a$ Ref 4. $^b$ Assignments made via HSQC and HMBC. $^c$ Chemical shifts for synthetic material are consistently 0.2-0.3 ppm higher than those reported for the natural product presumably due to a different reference standard; we used $\delta_C$ CDCl$_3$=77.23. $^d$ With the exception of the signals due to the $\gamma$-pyrone moiety, the chemical shifts reported for baconipyrone A (6) are within 0.1 ppm for those for baconipyrone B (7). $^e$ This value is much too high and must be an error (211.2 in baconipyrone B (7)). $^f$ This signal (76.1 in baconipyrone B (7)) would be obscured by solvent; the value from this study was obtained from a DEPT experiment.
Scheme 2.31

Several control experiments were performed to determine the origin of baconipyrone A (6) and its relationship to baconipyrone C (8) (Scheme 2.31). Exposure of baconipyrone C (8) to neutral alumina oxide (conditions that had induced retro-Claisen rearrangement in siphonarin B (4), Scheme 2.29), returned baconipyrone C (8) with no sign of epimerization (cf. 235, Scheme 2.27) and no baconipyrone A (6). Repeating with basic aluminum oxide gave a 3:1 ratio of baconipyrone C (8) to C-14 epimer 235, again with no detectable baconipyrone A (6). These control experiments suggest that the sequence of events leading to baconipyrone A (6) from the acyclic precursor or either of the contiguous carbon skeleton structures (4 and possibly 10) does not proceed through baconipyrone C (8). Subjection of baconipyrone A (6) to neutral alumina oxide in refluxing ethanol returned starting material,

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[^1]: Epimerization under these conditions and not during the transformation of 234 to 6 and 8 suggests that the C-11-OH may be facilitating HC-14 epimerization, perhaps through hydrogen bonding.
indicating that the reaction leading to 6 is not reversible under these conditions. No attempt was made to use basic aluminum oxide due to the high likelihood of inducing HC-14 epimerization, as demonstrated by baconipyrone C (8) producing 235 under these conditions.

2.8.5.1 Conclusion of the investigations into alternative conditions

Exposure of putative common precursor 14/15 to aluminum oxide in refluxing ethanol for 1 hour produced ester 237, a compound never isolated from siphonariid extracts (Scheme 2.28). Ester 237 was not observed when siphonarin B (4) was exposed to the same conditions, but these conditions produced baconipyrones A (6) and C (8) in addition to recovered starting material (siphonarin B (4)) (Scheme 2.29). This implies that 14/15 is not present in any appreciable amount when retro-Claisen rearrangement occurred in the isolation experiments on siphonariid mollusks. Either isomerization to siphonarin B (4) preceded retro-Claisen rearrangement or 14/15 is not a biosynthetic product.

The investigation of alternative conditions led to the total synthesis of baconipyrones A (6) and C (8) in excellent combined yield without competing C-14 epimerization (Scheme 2.30). This was the first total synthesis of baconipyrone A (6). Interestingly, under the conditions examined, the processes leading to baconipyrones A (6) and C (8) are irreversible implying that baconipyrone C (8) is not a precursor to baconipyrone A (6).

2.9 Conclusions

In summary, the siphonariid polypropionate: siphonarin B (4), baconipyrone A (6), and baconipyrone C (8) were synthesized from their putative common precursor 14/15 (existing mainly as hemiacetals 231 - 234). This work constitutes the first enantioselective synthesis of siphonarin B (4), baconipyrone A (6), and the putative common precursor 14/15. The synthesis of baconipyrones A (6) and C (8) were achieved "biomimetically" via the
proposed retro-Claisen rearrangement (8) and an unprecedented retro-Claisen rearrangement/aldol cascade (6). This work is the first total synthesis of baconipyrone C (8) via a route other than the "classical" route based on esterification.

Figure 2.24 Synthetic summary

The synthesis of 14/15 proceeded in a longest linear sequence of 18 steps in 3.1% overall yield (20 total steps) by convergent aldol coupling of simple achiral, meso, or racemic precursors. Enantioselective organocatalyzed direct aldol reactions proceeding with dynamic kinetic resolution generated five of the seven stereocenters in the putative acyclic precursor (C-4, 5, 6, 12, 14; dr >20:1). The remaining two stereocenters result from carbonyl reduction (C-11; dr >20:1) and an unusual enol ether oxymercuration/demercuration (C-10; dr 3.5:1).

Evidence was provided showing that both baconipyrones A (6) and C (8) can be derived from siphonarin B (4) and, as such, the baconipyrones are likely artifacts of isolation.
Under the conditions examined, baconipyrone A (6) could not be generated from baconipyrone C (8) and vice-versa indicating that the processes at work are irreversible and that baconipyrone C (8) is not a precursor of baconipyrone A (6). Despite all the experiments performed and paying keen attention to the products of each reaction, caloundrin B (10) was never detected.

Interestingly, experiments have shown that the common precursor 14/15 (existing as hemiacetals 231 - 234) under the same conditions that produced the baconipyrones A (6) and C (8) from siphonarin B (4) also produced ester 237 from retro-Claisen rearrangement of an alternative hemiacetal (C-11-OH addition onto C-7 carbonyl). This sequence of events occurred with equal facility to the events that produced the known compounds, baconipyrone A (6) and C (8). Ester 237 has never been observed in any isolation experiment. Based on this, it seems unlikely that hemiacetals 231 - 234 are the precursors of baconipyrone A (6) and C (8) unless equilibration to siphonarin B (4) occurred before retro-Claisen rearrangement. Considering that siphonarin B (4) has always been co-isolated with every compound in this series, siphonarin B (4) is more likely a biosynthetic product as opposed to 14/15. This is further supported by the remarkable stability that 14/15 exhibits.

Caloundrin B (10) is the 'missing link' in this work: it was never observed despite careful analysis. This fact challenges the hypothesis that caloundrin B (10) is an artifact of isolation because 10 should be present at a level that represents its relative stability. It is possible that caloundrin B (10) is a biosynthetic product, which isomerizes to more stable ring-chain tautomers (4) and/or rearranges to baconipyrones A (6) and C (8).
2.10 Suggestions for future research

The missing piece of this puzzle is caloundrin B (10). With this compound in hand, it would have been possible to more clearly determine which of these compounds are artifacts of isolation and what might be the real biosynthetic product.

Considering the failure to form the pentacyclic ring system in the elaborated structure (cf. 223 \rightarrow 224, Section 2.82), it would be worthwhile to test whether a more truncated system would form the required ring system, but still have functionality to use a handle to install more of the structure (Figure 2.25).

In a preliminary experiment, pentacyclic compound 245 was formed from 172 and isobutyraldehyde (244) (unoptimized and uncharacterized, but the NMR spectra of this compound were consistent to 167, Section 2.4) through the previously established synthetic sequence described in Section 2.4. Based on this result, it seems likely that the increased steric hindrance (or the presence of a branched chain) present in 223 (or 224), versus 245, may not be the culprit in the observed failure.

It is suggested to continue this line of research and test whether 172 and ent-31 will form the corresponding pentacyclic compound 246 (Figure 2.25). A positive result from this reaction would provide a substrate that could be synthetically viable. A negative result could implicate the benzyl protecting group as the source of the problem. If the benzyl group is the source of the problem, a change of this protecting group might solve the observed failure (i.e., appropriate selection of P in 247).

Either way, there are still several avenues of investigation left to explore that could lead to a first total synthesis of caloundrin B (10), an unusual and intriguing compound.
Figure 2.25 Proposed continuation of this research
EXPERIMENTAL

3.1 General methods

Anhydrous solvents were distilled under argon atmosphere as follows: Tetrahydrofuran (THF) from benzophenone sodium ketyl; diethyl ether from benzophenone sodium ketyl; CH$_2$Cl$_2$ from CaH$_2$; MeOH from Mg(O Me)$_2$. 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 an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were: ice/water (0 °C) and CO$_2$(s)/acetone (-78 °C). Unless otherwise noted, reaction temperatures refer to that of the bath.

Preparative TLC (PTLC) was carried out on glass plates (20×20 cm) pre-coated (0.25 mm) with silica gel 60 F$_{254}$. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aq sulfuric acid (5% v/v), or with basic KMnO$_4$ [KMnO$_4$ (1.5 g), K$_2$CO$_3$ (10 g), 10% aq. NaOH (1.25 mL), in H$_2$O (200 ml)], followed by charring on a hot plate. TLC was carried out on glass plates (1×3 cm) pre-coated (0.25 mm) with silica gel 60 F$_{254}$ and was visualized in the same manner as that described for PTLC.

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.

Flash column chromatography (FCC) was performed according to Still et al.$^{143}$ with Merck Silica Gel 60 (40-63 μm). All mixed solvent eluents are reported as v/v solutions.
Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by $^1$H NMR spectroscopy.

3.2 Spectral data

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

IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT) or by Thin Film; only diagnostic and/or intense peaks are reported. Unless otherwise noted all experiments used DRIFT.

Unless otherwise noted, NMR spectra were measured in CDCl$_3$ solution at 500 MHz for $^1$H and 125 MHz for $^{13}$C. Signals due to the solvent ($^{13}$C NMR spectroscopy) or residual protonated solvent ($^1$H NMR spectroscopy) served as the internal standard: CDCl$_3$ (7.26 $\delta_H$, 77.23 $\delta_C$); C$_6$D$_6$ (7.16 $\delta_H$, 128.39 $\delta_C$). The $^1$H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of couplings constants ($J$) corresponds to the order of the multiplicity assignment. Couplings constants ($J$) are reported to the nearest 0.5 Hz (digital resolution ca. 0.2 Hz/pt) or the nearest 0.1 Hz (digital resolution ca. 0.03 Hz/pt). The $^1$H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or two-dimensional correlation experiments (gCOSY, gHSQC,
The $^{13}$C NMR assignments were made on the basis of chemical shift and multiplicity (as determined by $^{13}$C-DEPT or gHSQC) and were confirmed, where necessary, by two-dimensional $^1$H/$^{13}$C correlation experiments (gHSQC and/or gHMBC). The multiplicity of $^{13}$C NMR signals refers to the number of attached H's (i.e., $s = C$, $d = CH$, $t = CH_2$, $q = CH_3$).

Specific rotations ($[\alpha]_D$) are the average of 5 determinations at ambient temperature using a 1 mL, 10 dm cell; the units are $10^{-1}$ deg cm$^2$ g$^{-1}$, the concentrations ($c$) are reported in g/100 mL, and the values are rounded to reflect the accuracy of the measured concentrations (the major source of error).

### 3.3 Materials

The following compounds and reagents were prepared as described previously:

124, lxxix, 66  
125, lxxx, 66  
127, 85  
169, 66  
170, 69  
184, 98  
190, lxxxi, 70  
191, 70  
192 and 193, lxxxi, 70  
194 and 195, 70  
196, lxxxii, 70, IBX, 145  
W-2 Raney nickel, 146 and FeCl$_3$-impregnated silica gel. 90  
Et$_3$N and $i$Pr$_2$NEt (DIPEA) were distilled from KOH under argon and were stored over KOH.  
TiCl$_4$ and $i$Pr$_2$NH were distilled under argon atmosphere from CaH$_2$. All other reagents were commercially available and unless otherwise noted, were used as received.

### 3.4 Computational procedures

Computation procedures were carried out by Prof. Goodman (see Section 2.4).  
Conformation searches were carried out using the MMFF force field as implemented in Batchmin until all low energy structures had been found at least four times. The lowest energy structures were then reminimized at the B3LYP/6-31G** level using Jaguar.

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lxxix Routinely performed at ca. 100 g scale.  
lxxx Routinely performed at 100-200 g scale.  
lxxxi Reaction scaled to ca. 8 g of 196.  
lxxxi Reaction scaled to ca. 20 g.  
lxxxii Known procedure applied to 195. See below for a revised procedure to oxidize 194 to 196.
In cases where the lowest energy MMFF conformations had similar energies, all the low energy structures were reminimized with B3LYP/6-31G**. Except for 141 and 149, in all cases the lowest energy MMFF structure corresponded to the lowest energy B3LYP/6-31G** structure; for 141 and 149, the preferred conformations were chairs (with the C-8 methyl group equatorial) according to MMFF, but were twist boats according to B3LYP/6-31G**.

3.5 Experimental Procedures and Spectral Data for Compounds

Spectral data and experimental procedures are presented in order by compound number with the exception of the natural products: these are presented last by compound number (i.e., 4, 6, 8).

2-((2S,3S,4S,5R,6R)-3,7-Dihydroxy-5-((4-methoxybenzyl)oxy)-4,6-dimethylheptan-2-yl)-6-ethyl-3,5-dimethyl-4H-pyran-4-one (ent-39)

This procedure was not optimized. A solution of Hg(OAc)_2 (12 mg, 0.038 mmol) in water (1.5 mL) was added to a stirred solution of 215 (15 mg, 0.035 mmol) in THF (1.5 mL) at rt. The resulting yellow suspension was stirred at this temperature for 2 h and then a solution of Na₂CO₃ (20 mg, 0.19 mmol) in water (2 mL) was added in one portion. After 10 min, a solution of NaBH₄ (32 mg, 0.84 mmol) in water (2 mL) was added. After 1 min, the reaction was diluted with a 1:1 mixture of brine and water and extracted with CH₂Cl₂. The combined
organic layers were dried over Na₂SO₄, concentrated, and the residue taken up in ethanol (2 mL), and then NaBH₄ (12 mg, 0.32 mmol) was added to the stirred solution at rt. After ca. 48 h, the mixture was diluted with water and extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (100% ethyl acetate, two elutions) to give 216 (3 mg; ca. 90% pure, ca.17%) and the known 28-30 titled compound (8 mg, 51%)([α]D -15 (c 0.45, CHCl₃)).

**IR** ν max: 3430, 1652, 1609, 1588 cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 7.23 (2H, ap d, J = 8.5 Hz, ArH), 6.84 (2H, ap d, J = 8.5 Hz, ArH), 4.63 (1H, d, J = 10.5 Hz, H₂CAr), 4.59 (1H, d, J = 10.5 Hz, H₂CAr), 4.21 (1H, br d, J = 9.5 Hz, HC-3'), 3.83-3.74 (1H, m, HC-7'), 3.78 (3H, s, H₃CO), 3.71 (1H, dd, J = 5, 10.5 Hz, HC-7'), 3.55 (1H, dd, J = 3.5, 8 Hz, HC-5'), 3.14-3.06 (2H, m, HO, HC-1), 2.61 (1H, dq, J = 15, 7.5 Hz, H₂C-C-6), 2.58 (1H, dq, J = 15, 7.5 Hz, H₂C-C-6), 2.09-1.94 (2H, m, HC-4', HC-6'), 1.99 (3H, s, H₃CC-3), 1.92 (3H, s, H₃CC-5), 1.18 (3H, t, J = 7.5 Hz, H₃CCH₂), 1.15 (3H, d, J = 7 Hz, H₃CC-4'), 1.09 (3H, d, J = 7 Hz, H₃C-1'), 1.04 (3H, d, J = 7 Hz, H₃CC-6').

**¹³C NMR** (125 MHz, CDCl₃) δ: 180.0 (s, C-4), 164.8 (s, C-2), 164.2 (s, C-6), 159.8 (s, Ar), 129.9 (s, Ar), 129.8 (d ×2, Ar), 119.6 (s, C-3), 118.1 (s, C-5), 114.2 (d ×2, Ar), 88.4 (d, C-5'), 76.4 (t, CH₂Ar), 72.1 (d, C-3'), 65.6 (t, C-7'), 55.5 (q, CH₃O), 39.0 (d, C-2'), 38.0 (d, C-6'), 35.5 (d, C-4'), 25.0 (t, CH₂C-6), 15.3 (q, CH₃C-6'), 14.7 (q, C-1'), 11.5 (q, CH₃CH₂), 11.2 (q, CH₃C-4'), 9.9 (q, CH₃C-3 or CH₃C-5), 9.7 (q, CH₃C-3 or CH₃C-5).

**LRMS:** m/z (relative intensity) 446 ([M]+, 1), 310 (7), 209 (13), 180 (36), 121 (100) (EI).

**HRMS:** m/z calcd for C₂₆H₃₈O₆ 446.2668, found 446.2672 (EI).
(4S,6S)-5-Hydroxy-4,6-dimethylnonane-3,7-dione (41)

Raney nickel (W2; 1 mL settled volume) was washed with THF (x3) and transferred to a solution of 122 (50 mg, 0.16 mmol) in THF (8 mL) and the resulting suspension was heated under reflux with vigorous stirring. After 5 h, the reaction mixture was allowed to cool to rt and aqueous HCl (1 M; 4 mL) was added. Concentrated HCl (12 M) was added dropwise (ca. 1 drop/min; CAUTION: H2 evolution) until effervescence ceased (ca. 1 hr; pH<1). After 40 h, the mixture was diluted with ethyl acetate and washed sequentially with sat. NaHCO3 and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na2SO4, concentrated, and fractionated by PTLC (20% acetone in hexanes; 2 elutions) to give the known28-30 titled compound (26 mg, 79%) ([α]D -20 (c 1.1, CHCl3)).

IR νmax: 3498, 1709 cm⁻¹.

¹H NMR (500 MHz, CDCl3): δ 4.02 (1H, ddd, J = 3.5, 4.5, 8 Hz), 3.22 (1H, d, J = 4.5 Hz), 2.73-2.62 (2H, m), 2.61-2.42 (4H, m), 1.15 (3H, d, J = 7 Hz), 1.05 (3H, t, J = 7 Hz), 1.04 (3H, d, J = 7 Hz), 104 (3H, t, J = 7 Hz).

¹³C NMR (125 MHz, CDCl3): δ 216.0 (s), 215.9 (s), 73.2 (d), 47.7 (d), 47.6 (d), 36.6 (t), 35.1 (t), 14.2 (q), 10.3 (q), 7.9 (q), 7.6 (q).

LRMS: m/z (relative intensity) 218 ([M+18]+, 100), 210 (77), 183 (27), 101 (6) (Cl, NH3).
HRMS: \( m/z \) calcd for \( C_{11}H_{20}O_3 \) 200.1412 (218.1756 for \( M+NH_4 \)), found 218.1754 (CI, \( NH_3 \)).

1,4-Dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde (116)<sup>lxxxiv</sup>

![116]

IBX (71.9 g, 0.257 mol, 1.2 equiv), was added to a stirred solution of 124<sup>66</sup> (40.6 g, 0.214 mol) in acetonitrile (800 mL). The heterogeneous mixture was heated to 80 °C (oil bath temperature) and stirred at this temperature for 2 h. The reaction mixture was cooled in an ice bath for 1 h and then passed through a sintered glass funnel. The solid was washed with ethyl acetate (2 x 150 mL) and the combined filtrate and washings were concentrated to give an orange oil that was passed through a column of basic alumina (120 g; column diameter, 5.5 cm) eluting with ethyl acetate in hexane (1:1, 1200 mL). Concentration gave the titled compound as a pale yellow oil (33.3 g, 83%) that was homogeneous by \(^1\)H NMR. The solids (62.5 g; mainly 2-iodosobenzoic acid by \(^1\)H NMR in DMSO-d6) were reoxidized to IBX (58.3 g, 81% yield based on initial amount of IBX used) with oxone® (1 equiv) according to Santagostino’s procedure.<sup>lxxxv, 145</sup>

IR \( \nu_{\text{max}} \): 2840, 2737, 1721\text{-}cm^{-1}.

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<sup>lxxxiv</sup> Athanasios Karagiannis, unpublished results: under my direction.

<sup>lxxxv</sup> There is an error in Santagostino’s procedure to prepare IBX. They state that they used 1.3 equivalents of oxone®; however, by calculation they used 1.45 equivalents. In my experience, using 1.3 equivalents of oxone® did not cleanly produce IBX.
**1H NMR** (300 MHz, CDCl₃): \( \delta \) 9.85 (1H, s), 4.07-3.94 (4H, m), 2.96 (1H, dd, \( J = 9.5, 13.5 \) Hz), 2.86 (1H, br d, \( J = 13.5 \) Hz), 2.81-2.72 (2H, m), 2.64 (1H, m), 2.08 (1H, ddd, \( J = 3, 6, 13.5 \) Hz), 1.89 (1H, ddd, \( J = 3.5, 10, 13.5 \) Hz).

**13C NMR** (75 MHz, CDCl₃): \( \delta \) 201.3 (d), 107.8 (s), 64.9 (t), 64.7 (t), 56.6 (d), 36.2 (t), 26.7 (t), 26.4 (t).

**HRMS**: \( m/z \) calcd for \( \text{C}_8\text{H}_{12}\text{O}_3\text{S} \) 188.0507, found 188.0512 (EI). Anal. Calcd for \( \text{C}_8\text{H}_{12}\text{O}_3\text{S} \): C, 51.04; H, 6.43. Found: C, 51.20; H, 6.58.

**Tetrahydro-4H-thiopyran-4-one (117)**

![Image of tetrahydro-4H-thiopyran-4-one](image)

Keto ester **126** (100 g, 0.57 mol) was added via a dropping funnel over 3–5 min to a well-stirred solution of 10% aq H₂SO₄ (1 L) heated under reflux. After ca. 1 h, the reaction was complete by TLC analysis (30% EtOAc in hexane) and the mixture was cooled to 40 °C with the aid of an ice bath. The aqueous layer was decanted from a yellow oil that separated and settled. The yellow oil was washed with H₂O (500 mL) at 40 °C and the combined aqueous layers were extracted with CH₂Cl₂ (3 × 200 mL) with each extract passed through a column of basic Al₂O₃ (Brockmann I, ca. 150 mesh; 200 g). The column was finally eluted with CH₂Cl₂ (600 mL) and the combined eluates were concentrated and then reconcentrated from
hexane to give the titled compound as a white, freely flowing, crystalline solid (52 g, 78%); mp 59–60 °C.

**IR** $v_{max}$: 1704 cm$^{-1}$.

**$^1$H NMR** (500 MHz, CDCl$_3$): $\delta$ 2.99–2.94 (m, 4H), 2.72–2.68 (m, 4H).

**$^{13}$C NMR** (125 MHz, CDCl$_3$): $\delta$ 210.0, 44.7, 30.6.

**HRMS**: $m/z$ calcd for C$_5$H$_8$OS: 116.0296; found: 116.0293 (EI).

$(3S)$-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(hydroxy)-methyl]tetrahydro-4$H$-thiopyran-4-one (122)

![Structure of 122](image)

A solution of ketone 117 (1.25 g, 10.8 mmol), aldehyde 117 (1.01 g, 5.37 mmol), catalyst 127 (145 mg, 1.04 mmol), water (0.10 mL, 0.10 g, 5.6 mmol), and DMSO (0.6 mL) was stirred at room temperature. After 8 days, the brownish semisolid reaction mixture was taken up in ethyl acetate and washed with water. The organic layer was dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (5-10% ethyl acetate in CH$_2$Cl$_2$) to give 122 as a white solid (1.22 g, 75%): $[\alpha]_D$ -48, $c$ 1.0, CHCl$_3$ (lit. for 122 of >98% ee: $[\alpha]_D$ -47, $c$ 1.0,
CHCl$_3$). The catalyst could be recovered in >80% yield by concentrating the water layers and precipitating the residue from hot MeOH on addition of benzene.$^{lxxxvi}$

IR $\nu_{\text{max}}$: 3488, 3409, 1711 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 4.50 (1H, dd, $J = 4.5, 6.5$ Hz, HC-1), 4.05-3.92 (4H, m), 3.08-2.58 (12H, m), 2.12 (1H, ddd, $J = 4.5, 4.5, 9$ Hz), 2.03 (1H, ddd, $J = 3.5, 6.5, 13.5$ Hz), 1.74 (1H, ddd, $J = 4, 9.5, 13.5$ Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 211.5 (s), 109.3 (s), 69.3 (d), 64.4 (t), 64.3 (t), 55.5 (d), 47.0 (d), 44.4 (t), 35.5 (t), 34.3 (t), 31.4 (t), 27.4 (t), 26.5 (t).

HRMS: $m/z$ calcd for C$_{13}$H$_{20}$O$_4$S$_2$ 304.0803, found 304.0801. Anal. Calcd for C$_{13}$H$_{20}$O$_4$S$_2$: C, 51.29; H, 6.62. Found: C, 51.59; H, 6.55.

Methyl Tetrahydro-4-oxo-2H-thiopyran-3-carboxylate (126)

![Methyl Tetrahydro-4-oxo-2H-thiopyran-3-carboxylate (126)](image)

Anhydrous MeOH (41 mL, 32 g, 1.0 mol) was added via a dropping funnel over 30 min to a stirred suspension of Na metal (21.7 g, 0.95 mol; Na metal was cut into pieces weighing ca. 50–100 mg (3–5 mm per side). The rate of Na consumption depends on the size of pieces; with larger pieces, more time is required to reach 90% conversion.) in THF (300 mL) at 0 °C

$lxxxvi$ Prepared on ca. 40 gram scale by the same procedure in 70% yield (no chromatography). Athanasios Karagiannis, unpublished results: under my direction.
(ice bath) under argon **(Caution! H₂ evolution).** The ice bath was removed and stirring continued at rt for 15–20 h, at which point most of the Na was consumed (ca. 90%; more time may be required if the Na pieces are larger than specified) leaving a grayish-white mixture of NaOMe in THF. The mixture was cooled in an ice bath and the diester 115 (150 g, 0.728 mol) was added via a dropping funnel over 1 h (the dropping funnel was rinsed with 15 mL of THF). The ice bath was removed and the mixture, initially a thick slurry, became a homogeneous amber solution (a few specks of Na metal may be present). After stirring for 3 h at rt, the reaction was complete by TLC analysis (30% EtOAc in hexane). The mixture was transferred to a beaker equipped with a mechanical stirrer and cooled in an ice bath. Aq H₂SO₄ (0.475 mol; prepared by adding 47.5 g of 98% H₂SO₄ to ca. 45 g of ice) was added slowly with stirring maintaining the temperature below 20 °C; the final pH was 6–7. To the resulting creamy yellow mixture, CH₂Cl₂ (400 mL) was added after which the Na₂SO₄ hydrate precipitated as granules that readily settle, leaving a pale yellow solution; occasionally, a small amount of H₂O (2–10 mL) must be added to achieve the desired consistency. Na₂SO₄ (20 g) and solid NaHCO₃ (21 g) were added with stirring and after 30 min, the supernatant was filtered through cotton wool and the residue was washed with CH₂Cl₂ (200 mL). The combined filtrate and washings were concentrated to give the titled compound as a pale yellow oil (stench!); yield: 124.5 g (98%); >95% purity by NMR. The oil solidified (keto form) on standing for several days at 5 °C.

**IR** ν<sub>max</sub>: 3100 (br), 1745, 1720, 1658, 1617 cm<sup>−1</sup>.

**¹H NMR** (500 MHz, CDCl₃): δ (for the enol tautomer) = 12.5 (s, 1H), 3.79 (s, 3 H), 3.36 (s, 2 H), 2.80 (app t, J = 5.5 Hz, 2 H), 2.60 (app t, J = 5.5 Hz, 2 H); δ (for the keto tautomer) =
3.80 (s, 3 H), 3.70 (dd, \( J = 4, 8.5 \) Hz, 1 H), 3.31 (dd, \( J = 8.5, 14 \) Hz, 1 H), 3.06 (dd, \( J = 4, 14 \) Hz, 1 H), 2.99–2.94 (m, 2 H), 2.91–2.85 (m, 1 H), 2.77–2.72 (m, 1 H).

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)): \( \delta \) (for the enol tautomer) = 172.0, 169.3, 97.4, 51.9, 30.9, 24.6, 23.4; \( \delta \) (for the keto tautomer) = 203.7, 172.6, 58.7, 52.7, 43.7, 32.6, 30.5.

HRMS: \( m/z \) calcd for C\(_7\)H\(_{10}\)O\(_3\)S: 174.0351; found: 174.0348 (EI).

\((2R,3S,5S,6S)-2\text{-Ethyl}-2,3,5,6\text{-tetrahydro}-2\text{-hydroxy-3,5-dimethyl-6-[(1S)-1-methyl-2-oxobutyl]-4H-pyran-4-one}\) (138)

Pyridine (1.2 mL, 1.2 g, 15 mmol), HF•pyridine (0.4 mL), and water (0.050 mL, 2.8 mmol) were added to a stirred solution of 175a (50 mg, 0.15 mmol) in THF (2 mL). After 2 days, the mixture was diluted with ethyl acetate, washed with 2% aqueous citric acid (×3), NaHCO\(_3\) and brine, dried over Na\(_2\)SO\(_4\), concentrated, and fractionated by FCC (40% diethyl ether in hexane) to give a 14:1 mixture of 150 and 142, respectively (13 mg, 33%), and the titled compound (19 mg, 49%): \([\alpha]_D^{+24} (c 1.1, \text{C}_6\text{H}_6)\).

IR \( \nu_{\text{max}} \): 3475, 1711 cm\(^{-1}\).

\(^1\text{H NMR}\) (600 MHz, C\(_6\)D\(_6\)): \( \delta \) 4.26 (1H, dd, \( J = 2.6, 10.7 \) Hz, HC-6), 2.32 (variable) (1H, d, \( J = 1.6 \) Hz, HO), 2.19 (1H, dq, \( J = 18, 7.1 \) Hz, HC-3"), 2.16 (1H, dq, \( J = 2.6, 7.0 \) Hz, HC-1"),
2.10 (1H, dqd, \(J = 1.1, 1.6, 6.7\) Hz, HC-3), 2.06 (1H, dq, \(J = 18, 7.1\) Hz, HC-3'), 1.98 (1H, ddq, \(J = 1.1, 10.7, 6.6\) Hz, HC-5), 1.40 (1H, dq, \(J = 13.9, 7.4\) Hz, HC-1'), 1.28 (3H, dq, \(J = 13.9, 7.4\) Hz, HC-1'), 1.07 (3H, d, \(J = 6.7\) Hz, H3CC-3), 1.03 (3H, t, \(J = 7.1\) Hz, H3C-4''), 1.02 (3H, d, \(J = 7.0\) Hz, H3CC-1''), 0.70 (1H, t, \(J = 7.4\) Hz, H3C-2').

\(^{13}\text{C NMR}\) (125 MHz, C\(_6\)D\(_6\)) \(\delta\) 209.5 (s, C-2''), 206.9 (s, C-4), 102.8 (s, C-2), 75.3 (d, C-6), 50.9 (d, HC-3), 48.2 (d, HC-7), 46.6 (d, HC-5), 33.4 (t, C-3''), 33.1 (t, C-1''), 9.7 (q, CH\(_3\)C-5), 9.2 (q, CH\(_3\)C-3), 8.5 (q, C-4'' or CH\(_3\)C-1''), 8.4 (q, C-4'' or CH\(_3\)C-1''), 7.8 (q, C-2').

\(\text{LRMS:}\) \(m/z\) (relative intensity) 274 ([M+18]\(^+\), 49), 257 ([M+1\(^+\), 7), 239 (34), 200 (51), 183 (100), 160 (26), 143 (25), 74 (22) (Cl, NH\(_3\)).

\(\text{HRMS:}\) \(m/z\) calcd for C\(_{14}\)H\(_{24}\)O\(_4\) 256.1675 (274.2018 for M+NH\(_4\)), found 274.2009 (Cl, NH\(_3\)).

\((1R,3R,5R,7R,8S,9S,10S)-3,5\text{-Diethyl-8,9,10-trimethyl-2,4,6-trioxatrcyclo [3.3.1.1}^{3,7}])\) decan-1-ol (142)

From 167: A suspension of Raney nickel (W2; 2 mL settled volume) in EtOH (4 mL) was added to 167 (17 mg, 0.054 mmol) and the mixture was heated under reflux with vigorous stirring. After 45 min, the mixture was decanted and the solid suspended in ethanol and heated under reflux with rapid stirring for several min. This washing procedure was repeated
once with EtOH, once with CH\textsubscript{2}Cl\textsubscript{2}/acetone (1:1), and once with ethyl acetate. The combined organic layers were filter through Celite® and concentrated. The residue was fractionated by PTLC (33% diethyl ether in hexane) to give the titled compound (8 mg, 60%).

From 175a: Pyridine (1.2 mL), HF•pyridine (0.4 mL), and water (2.8 mmol, 50 mL) were sequentially added to a stirred solution of 175a (50 mg, 0.15 mmol) in THF (2 mL) at ambient temperature. After 2 h, the mixture was diluted with ethyl acetate, washed sequentially with 2% aqueous citric acid (×3), NaHCO\textsubscript{3} and brine, dried over Na\textsubscript{2}SO\textsubscript{4}, concentrated, and fractionated by FCC (40% diethyl ether in hexane) to give 138 (3 mg, 8%) and the titled compound (ca. 95% pure by \textsuperscript{1}H NMR; 31 mg, 80%): ([\alpha]_{D} +11 (c 1.0, C\textsubscript{8}H\textsubscript{6}).

IR $\nu_{\text{max}}$: 3407 cm\textsuperscript{-1}.

\textbf{\textsuperscript{1}H NMR} (500 MHz, C\textsubscript{6}D\textsubscript{6}): $\delta$ 3.68 (1H, br d, $J = 2.5$ Hz, HC-7), 2.23 (1H, br s, HO), 2.07 (1H, dq, $J = 3.5$, 7 Hz, HC-10), 1.91 (1H, br q, $J = 7.5$ Hz, HC-8), 1.85-1.77 (2H, m, HC-9, HCC-5), 1.70 (1H, dq, $J = 15$, 7.5 Hz, HCC-3), 1.57 (1H, dq, $J = 7.5$, 15 Hz, HCC-5), 1.54 (1H, dq, $J = 7.5$, 15 Hz, HCC-3), 1.12 (3H, d, $J = 7.5$ Hz, H\textsubscript{3}CC-8), 1.05 (3H, t, $J = 7.5$ Hz, H\textsubscript{3}CC-5), 1.02 (3H, t, $J = 7.5$ Hz, H\textsubscript{3}CC-3), 0.97 (3H, d, $J = 7.5$ Hz, H\textsubscript{3}CC-9), 0.63 (3H, d, $J = 7$ Hz, H\textsubscript{3}CC-10).

\textbf{\textsuperscript{13}C NMR} (125 MHz, C\textsubscript{6}D\textsubscript{6}): $\delta$ 103.2 (s, C-3), 102.3 (s, C-5), 98.9 (s, C-1), 79.3 (d, C-7), 45.4 (d, C-9), 37.9 (d, C-10), 35.9 (d, C-8), 30.4 (t, CH\textsubscript{2}C-5), 30.2 (t, CH\textsubscript{2}C-3), 14.8 (q, CH\textsubscript{3}C-8), 13.0 (q, CH\textsubscript{3}C-10), 11.2 (q, CH\textsubscript{3}C-9), 7.1 (q, CH\textsubscript{3}CC-5), 6.9 (q, CH\textsubscript{3}CC-3).

\textbf{LRMS}: $m/z$ (relative intensity) 256 ([M]$^+$, 4), 182 (11), 153 (13), 125 (18), 113 (38), 96 (14), 86 (15), 69 (12), 57 (100) (EI).
HRMS: \( m/z \) calcd for \( C_{14}H_{24}O_4 \) 256.1675, found 256.1667 (EI).

\((1R,3R,5R,7R,8S,9S,10R)-rel-3,5\)-Diethyl-8,9,10-trimethyl-2,4,6 trioxatricyclo[3.3.1.1^{3,7}]decan-1-ol (143)

![Chemical structure of 143](image)

A suspension of W2 Raney nickel (5 mL settled volume) in ethanol (10 mL) was added to \((\pm)-168\) (98 mg, 0.31 mmol) and the mixture was heated under reflux with vigorous stirring. After 45 min, the mixture was decanted and the solid suspended in ethanol and heated under reflux with rapid stirring for several min. This washing procedure was repeated twice with EtOH and once with ethyl acetate. The combined organic layers were filtered through Celite® and concentrated to give the titled compound (67 mg, 85%) that was homogeneous by \(^1\)H NMR. A crystal suitable for X-ray crystallography was obtained from a petroleum ether solution.

\textbf{IR} \( \nu_{max} \): 3383 cm\(^{-1}\).

\textbf{\(^1\)H NMR} (500 MHz, CDCl\(_3\)): \( \delta \) 3.83 (1H, br s, HC-7), 2.90 (1H, br s, HO), 1.95 (1H, br q, \( J = 7 \) Hz, HC-8), 1.92 (1H, br q, \( J = 7.5 \) Hz, HC-9), 1.74-1.47 (5H, m, HC-10, H\(_2\)C \( \times \) 2), 1.19 (3H, d, \( J = 7.5 \) Hz, H\(_3\)CC-8), 1.11 (3H, d, \( J = 7 \) Hz, H\(_3\)CC-10), 1.06 (3H, d, \( J = 7.5 \) Hz, H\(_3\)CC-9), 0.96 (3H, t, \( J = 7.5 \) Hz, H\(_3\)C), 0.89 (3H, t, \( J = 7.5 \) Hz, H\(_3\)C).
\[ ^{13}C\text{ NMR} \ (125 \text{ MHz, CDCl}_3): \delta 102.8 \ (s, \text{C-3}), \ 102.0 \ (s, \text{C-5}), \ 98.8 \ (s, \text{C-1}), \ 79.6 \ (d, \text{C-7}), \ 44.7 \ (d, \text{C-9}), \ 43.3 \ (d, \text{C-8}), \ 38.1 \ (d, \text{C-10}), \ 29.85 \ (t, \text{CH}_2), \ 29.79 \ (t, \text{CH}_2), \ 14.5 \ (q, \text{CH}_3\text{C-8}), \ 13.9 \ (q, \text{CH}_3\text{C-10}), \ 10.8 \ (q, \text{CH}_3\text{C-9}), \ 6.4 \ (q, \text{CH}_3\text{CH}_2\text{C-5}), \ 6.1 \ (q, \text{CH}_3\text{CH}_2\text{C-3}). \]

\[ \text{LRMS: m/z (relative intensity) 256 ([M]^+, 1), 126 (10), 125 (11), 113 (28), 96 (10), 86 (13), 69 (10), 57 (100) (EI). } \]

\[ \text{HRMS: m/z calcd for C}_{14}\text{H}_{24}\text{O}_4 \ 256.1675, \text{ found 256.1672 (EI). } \]

(1\(R\),3\(R\),5\(R\),7\(R\),8\(S\),9\(R\),10\(S\))-3,5-Diethyl-8,9,10-trimethyl-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]decan-1-ol (150)

Pyridine (1.2 mL), HF•pyridine (0.4 mL), and water (50 mL) were sequentially added to a stirred solution of 175a (20 mg, 0.061 mmol) in THF (2 mL) at ambient temperature. After 2 h, the mixture was diluted with ethyl acetate, washed with 2% aqueous citric acid (×3), NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The residue (crude 142) was taken up in chloroform (2 mL) and imidazole (75 mg, 1.1 mmol) was added. After 5 d, the mixture was diluted with ethyl acetate, washed sequentially with 1% aqueous citric acid (×3), NaHCO₃ and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (40% ethyl acetate in hexane) to give the titled compound (12 mg, 77%): \([\alpha]_D +34 (c \ 1.0, \text{C}_6\text{H}_6)\).
IR $\nu_{\text{max}}$: 3428 cm$^{-1}$.

$^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 3.62 (1H, br d, $J = 2.5$ Hz, HC-7), 2.06-1.98 (2H, m, HO, HC-10), 1.92 (1H, br q, $J = 6.5$ Hz, HC-9), 1.79 (1H, dq, $J = 14$, 7.5 Hz, HCC-5), 1.77 (1H, br q, $J = 6.5$ Hz, HC-8), 1.69 (1H, dq, $J = 14$, 7.5 Hz, HCC-3), 1.59-1.47 (2H, m, HCC-3, HCC-5), 1.06 (3H, d, $J = 7.5$ Hz, H$_3$CC-8), 1.04 (3H, t, $J = 8$ Hz, H$_3$CCC-3), 1.00 (3H, t, $J = 7.5$ Hz, H$_3$CCC-5), 0.96 (3H, d, $J = 6.5$ Hz, H$_3$CC-9), 0.65 (3H, d, $J = 7$ Hz, H$_3$CC-10).

$^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 103.1 (s, C-3), 102.5 (s, C-5), 97.9 (s, C-1), 78.6 (d, C-7), 37.8 (d, C-10), 36.6 (d, C-9), 36.5 (d, C-8), 30.6 (t, CH$_2$C-5), 30.2 (t, CH$_2$C-3), 13.7 (q, CH$_3$C-8), 12.8 (q, CH$_3$C-10), 7.7 (q, CH$_3$C-9), 6.80 (q, CH$_3$CH$_2$), 6.75 (q, CH$_3$CH$_2$).

LRMS: m/z (relative intensity) 256 ([M]$^+$, 4), 182 (17), 126 (22), 125 (25), 113 (65), 96 (30), 86 (25), 69 (20), 57 (100) (EI).

HRMS: m/z calcd for C$_{14}$H$_{24}$O$_4$ 256.1675, found 256.1683 (EI).

(1R,3R,5R,7R,8S,9R,10R)-rel-3,5-Diethyl-8,9,10-trimethyl-2,4,6-trioxatricyclo[3.3.1.1$^{3,7}$]decan-1-ol (151)

A solution of 143 (20 mg, 0.31 mmol) and imidazole (15 mg, 0.22 mmol) in CDCl$_3$ (0.4 mL) was heated to 40 °C (oil bath temperature). After 4 days (isomerization was complete by $^1$H NMR), the mixture was diluted with ethyl acetate, washed with 1% aqueous citric acid ($\times$3),
NaHCO₃, and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (40% ethyl acetate in hexane) to give the known\textsuperscript{xxxvii,61} titled compound (17 mg, 85%).

IR \( \nu_{\text{max}} \): 3417 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 3.78 (1H, br s, HC-7), 2.56 (1H, br s, HO), 1.97 (1H, q, \( J = 6.5 \) Hz, HC-9), 1.91 (1H, br q, \( J = 7 \) Hz, HC-8), 1.73-1.49 (5H, m, HC-10, H\(_2\)C \( \times 2 \)), 1.15 (3H, d, \( J = 7 \) Hz, H\(_3\)C-8), 1.10 (3H, d, \( J = 7 \) Hz, H\(_3\)CC-10), 0.98 (3H, d, \( J = 6.5 \) Hz, H\(_3\)CC-9), 0.96 (3H, t, \( J = 7.5 \) Hz, H\(_3\)C), 0.94 (3H, t, \( J = 7.5 \) Hz, H\(_3\)C).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 102.6 (s, C-3), 102.2 (s, C-5), 97.7 (s, C-1), 78.9 (d, C-7), 43.3 (d, C-8), 37.7 (d, C-10), 36.0 (d, C-9), 30.1 (t, CH\(_2\)), 30.0 (t, CH\(_2\)), 13.8 (q, CH\(_3\)C-10), 13.5 (q, CH\(_3\)C-8), 7.3 (q, CH\(_3\)C-9), 6.3 (q, CH\(_3\)CH\(_2\)C-5), 6.1 (q, CH\(_3\)CH\(_2\)C-3).

LRMS: \( m/z \) (relative intensity) 256 ([M]+, 2), 182 (8), 153 (6), 126 (13), 113 (35), 86 (14), 57 (100) (EI).

HRMS: \( m/z \) calcd for C\(_{14}\)H\(_{24}\)O\(_4\) 256.1675, found 256.1675 (EI).

\textsuperscript{xxxvii} Only a few specific \(^1\)H NMR resonances are reported for \textbf{151} (data obtained at 300 MHz); our data (obtained at 500 MHz) is within 0.02-0.04 ppm. Our \(^{13}\)C NMR chemical shifts are consistently 0.2-0.4 ppm higher than those reported, presumably due to a different assignment of the reference frequency (we used \( \delta_C = 77.23 \) for CDCl\(_3\)).
(2S,3S)-6-Ethyl-2,3-dihydro-3,5-dimethyl-2-[(1S)-1-methyl-2-oxobutyl]-4H-pyran-4-one (152)

Aqueous HF (2 wt.%; 0.4 mL) was added to a stirred solution of 175b (21 mg, 0.057 mmol) in MeCN (2 mL). After 2 h, the mixture was diluted with ethyl acetate, washed with NaHCO₃ and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (10% diethyl ether in CH₂Cl₂) to give the titled compound (12 mg, 99%): [α]D -90 (c 0.6, CHCl₃).

**IR** νmax: 1715, 1663, 1616 cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 4.42 (1H, dd, J = 4, 11.5 Hz, HC-2), 2.77 (1H, dq, J = 4, 7 Hz, HC-1'), 2.53 (2H, ap q, J = 7 Hz, H₂C-3'), 2.39 (1H, dq, J = 11.5, 7 Hz, HC-3), 2.36-2.22 (2H, m, H₂C-1''), 1.71 (3H, s, H₃CC-5), 1.21 (3H, d, J = 7 Hz, H₃CC-1'), 1.11 (3H, d, J = 7 Hz, H₃CC-3), 1.07 (3H, t, J = 7 Hz, H₃C-4'), 1.06 (3H, t, J = 7.5 Hz, H₃C-2'').

**¹³C NMR** (125 MHz, CDCl₃): δ 211.3 (s, C-2'), 194.9 (s, C-4), 172.4 (s, C-6), 108.5 (s, C-5), 82.8 (d, C-2), 47.6 (d, C-1'), 41.1 (d, C-3), 34.4 (t, C-3'), 25.6 (t, C-1''), 11.2 (q, CH₃C-3), 11.0 (q, C-4'), 9.8 (q, CH₃C-1'), 9.4 (q, CH₃C-5), 8.0 (q, C-2'').

**LRMS:** m/z (relative intensity) 238 ([M]+, 8), 181 (7), 153 (27), 125 (11), 113 (73), 83 (7), 57 (100) (EI).

**HRMS:** m/z calcd for C₁₄H₂₂O₃ 238.1569, found 238.1577 (EI).
Pyridine (1.2 mL), HF•pyridine (0.4 mL), and water (0.050 mL) were added to a stirred solution of 175a (55 mg, 0.17 mmol) in THF (2 mL). After 2 h, the mixture was diluted with ethyl acetate, washed sequentially with 2% aqueous citric acid (×3), NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The resulting crude 142 was taken up in benzene (4 mL) and DBU (0.010 mL, 10 mg, 0.066 mmol) was added. After 24 h, the mixture was diluted with ethyl acetate, washed sequentially with 1% aqueous citric acid (×3), NaHCO₃ and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (10% diethyl ether in CH₂Cl₂) to give 150 (13 mg, 32%) and the titled compound (20 mg, 47%): [α]D +67 (c 1.0, CHCl₃).

IR νmax: 1742, 1715, 1180 cm⁻¹.

¹H NMR (500 MHz, C₆D₆): δ 5.64 (1H, dd, J = 5, 8 Hz, HC-5'), 2.65 (1H, dq, J = 8, 7 Hz, HC-4'), 2.57 (1H, dq, J = 7, 18 Hz, HC-2'), 2.44 (1H, dq, J = 5, 7 Hz, HC6'), 2.19-2.04 (2H, m, H₂C-8'), 2.03-1.90 (3H, m, H₂C-2, HC-2'), 1.06 (3H, t, J = 7 Hz, H₃C-1'), 0.95 (3H, t, J = 7 Hz, H₃C-9'), 0.90 (3H, d, J = 7 Hz, H₃CC-6'), 0.89 (3H, t, J = 7.5 Hz, H₃C-3), 0.74 (3H, d, J = 7 Hz, H₃CC-4').
\(^{13}\text{C} \text{NMR}\) (125 MHz, C\(_6\)D\(_6\)): \(\delta\ 210.7\) (s, C-3' or C-7'), 210.4 (s, C-3' or C-7'), 173.0 (s, C-1), 74.6 (d, C-5'), 48.3 (d, C-4'), 46.8 (d, C-6'), 35.6 (t, C-8'), 35.2 (t, C-2'), 27.9 (t, C-2), 13.2 (q, CH\(_3\)C-4'), 11.1 (q, CH\(_3\)C-6'), 9.6 (q, C-3), 8.3 (q, C-1' or C-9'), 8.1 (q, C-1' or C-9').

**LRMS**: \(m/z\) (relative intensity) 274 ([M+18]\(^+\), 92), 257 ([M+1]+, 20), 200 (30), 183 (100), 165 (14), 126 (10), 57 (8) (CI, NH\(_3\)).

**HRMS**: \(m/z\) calcd for C\(_{14}\)H\(_{24}\)O\(_4\) 256.1675 (274.2018 for M+NH\(_4\)), found 274.2012 (CI, NH\(_3\)).

\((4E)-4,6\text{-Dimethylnon-4-en-3,7-dione (156)}\)

This compound was observed in various isomerization experiments of 138, 142, 143, and 150, and 154 in the presence of DBU in C\(_6\)D\(_6\). In a larger scale reaction, DBU (10 \(\mu\)L, 10 mg, 0.07 mmol) was added to a solution of 154 (8 mg, 0.03 mmol) in C\(_6\)D\(_6\) (0.4 mL) at room temperature. The reaction was monitored by NMR and after 14 days, <5% of 154 remained. Attempted isolation of the titled compound from the reaction mixture by standard aqueous workup failed.

\(^1\text{H} \text{NMR}\) (500 MHz, C\(_6\)D\(_6\)): \(\delta\ 6.26\) (1H, qd, \(J = 1, 10\) Hz, HC-5), 3.09 (1H, dq, \(J = 10, 7\) Hz, HC-6), 2.19 (2H, ap q, \(J = 7.5\) Hz, H\(_2\)C-2), 1.99-1.87 (2H, m, H\(_2\)C-8), 1.73 (3H, d, \(J = 1\) Hz, H\(_3\)C-3), 0.99 (3H, t, \(J = 7.5\) Hz, H\(_3\)C-1), 0.96 (3H, d, \(J = 7\) Hz, H\(_3\)CC-5), 0.91 (3H, t, \(J = 7\) Hz, H\(_3\)C-9).
$^{13}$C NMR (125 MHz, C₆D₆): δ 209.1 (s, C-3), 200.9 (s, C-7), 139.6 (d, C-5), 138.5 (s, C-4), 46.9 (s, C-6), 34.9 (t, C-8), 30.7 (t, C-2), 16.6 (q, C-11), 12.2 (q, C-10), 9.0 (q, C-1), 8.2 (q, C-9).

(4S,4aR,5aR,9aS,10R,10aS,12R)-12-Ethyl-octahydro-5a,4,10-(epoxymethenoxy)-1H,4aH,5aH bisthiopyrano [4,3-b:3’,4’-e]pyran-4a-ol (167)

IBX (660 mg, 2.4 mmol) was added to a stirred solution of 173 (290 mg, 0.61 mmol) in DMSO (20 mL) at ambient temperature. After 5 h, the mixture was diluted with ethyl acetate and washed with water (×3) and brine. The organic phase was dried over Na₂SO₄ and concentrated. The residue was taken up in acetone (15 mL) and FeCl₃-impregnated silica gel (60-200 mesh, ca.7% FeCl₃; 760 mg) was added. The resulting yellowish suspension was heated under reflux with stirring for 30 min. The mixture was filtered through a small silica gel pad eluting with 50% ethyl acetate. The combined filtrate and washings were concentrated and fractionated by FCC (15% diethyl ether in CH₂Cl₂) to give the titled compound (128 mg, 66%): [α]D +14 (c 1, CHCl₃). A crystal suitable for X-ray crystallography was obtained from CH₂Cl₂/hexane.
IR ν<sub>max</sub>: 3385 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 4.29 (1H, br d, J = 3.5 Hz, HC-1'), 3.57 (1H, dd, J = 3.5, 14 Hz, HC-2), 3.55 (1H, dd, J = 3, 14 Hz, HC-6), 2.98 (1H, ddd, J = 2.5, 13.5, 13.5 Hz, HC-6'), 2.83 (1H, dd, J = 13, 13 Hz, HC-2'), 2.59-2.53 (2H, m, HC-2, HC-6), 2.47-2.40 (2H, m, HC 3', HC-6'), 2.25 (1H, ddd, J = 2.5, 3, 13 Hz, HC-2''), 1.89 (1H, ddd, J = 4, 13.5, 14 Hz, HC-5'), 1.83 (1H, dq, J = 14.5, 7.5 Hz, HC-2''), 1.65 (1H, dq, J = 14.5, 7.5 Hz, HC-2''), 0.98 (3H, t, J = 7.5 Hz, H<sub>3</sub>C-3 '').

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 102.1 (s, C-4' or C-1''), 99.2 (s, C-4' or C-1''), 95.0 (s, C-4), 76.9 (d, C-1'), 45.1 (d, C-3'), 43.1 (d, C-5), 37.6 (t, C-5''), 35.8 (d, C-3), 29.7 (t, C-2''), 29.0 (t, C-2), 27.5 (t, C-2'), 25.2 (t, C-6'), 24.8 (t, C-6), 6.4 (q, C-3 '').

LRMS: m/z (relative intensity) 316 ([M]<sup>+</sup>, 100), 298 (10), 241 (18), 209 (21), 171 (7), 152 (30), 126 (35), 99 (45), 67 (61) (EI).

HRMS: m/z calcd for C<sub>14</sub>H<sub>20</sub>O<sub>4</sub>S<sub>2</sub> 316.0803, found 316.0792 (EI).
(4S,4aR,5aR,9aR,10R,10aS,12R)-12-Ethylctahydro-5a,4,10-(epoxymethenoxy)-1H,4aH,5aH-bisthiopyrano[4,3-b:3',4'-e]pyran-4a-ol (168)

IBX (1.0 g, 3.6 mmol) was added to a stirred solution of (±)-171 (270 mg, 0.67 mmol) in DMSO (20 mL) at ambient temperature. After 6 h, the mixture was diluted with ethyl acetate and washed with water (∗3) and brine. The organic phase was dried over Na₂SO₄ and concentrated. The residue was taken up in acetone (20 mL) and MeOH (1 mL) and FeCl₃•6H₂O (200 mg, 0.74 mmol) was added. The resulting yellowish solution was heated under reflux for 1 h and then diluted with water and extracted with CH₂Cl₂. The combined organic layers were washed with water, dried over Na₂SO₄, concentrated, and filtered through a small silica gel pad eluting with 50% ethyl acetate in hexane to give the titled compound (157 mg, 75%) as a yellowish solid.

IR ν max: 3390 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 4.25 (1H, br s, HC-1′), 3.55 (1H, dd, J = 2.5, 13 Hz, HC-2), 3.43 (1H, dd, J = 2, 13.5 Hz, HC-6), 3.28 (1H, dd, J = 12.5, 13 Hz, HC-2′), 2.97 (1H, ddd, J = 2, 13, 13.5 Hz, HC-6′), 2.81 (1H, br s, HO), 2.63-2.55 (2H, m, HC-2, HC-6), 2.45-2.33 (2H, m, HC-2′, HC-6′), 2.09 (1H, br s, HC-3), 2.07 (1H, ddd, J = 3, 3, 13.5 Hz, HC-5′), 1.98 (1H, br s, HC-5), 1.90 (1H, dq, J = 14, 7.5 Hz, HC-2″), 1.84 (1H, dd, J = 2.5, 12.5 Hz, HC-
\(3\'), 1.82 (1H, ddd, \(J = 4, 13, 13.5\) Hz, HC-5'), 1.64 (1H, dq, \(J = 14, 7.5\) Hz, HC-2''), 1.05 (3H, t, \(J = 7.5\) Hz, H_2C-3'').

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)): \(\delta 101.8\) (s, C-4' or C-1''), 98.5 (s, C-4', or C-1''), 94.3 (s, C-4), 77.5 (d, C-1'), 44.6 (d, C-3'), 43.3 (d, C-5), 41.6 (d, C-3), 38.4 (t, C-5'), 30.0 (t, C-2''), 29.3 (t, C-2), 28.3 (t, C-2'), 24.9 (t, C-6'), 24.8 (t, C-6), 6.4 (t, C-3').

LRMS: \(m/z\) (relative intensity) 316 ([M]^+ 81), 242 (28), 209 (20), 153 (31), 126 (35), 99 (39), 67 (71), 57 (100) (EI).

HRMS: \(m/z\) calcd for C\(_{14}\)H\(_{20}\)O\(_4\)S\(_2\) 316.0803, found 316.0801 (EI).

\((3S,5S)-\text{rel-3-}[(R)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(S)-1-hydroxypropyl]tetrahydro-4H-thiopyran-4-one\) (171)

![](image)

A solution of \((\pm)\)-170 (400 mg, 1.15 mmol) in CH\(_2\)Cl\(_2\) (3 mL) was added dropwise via syringe to a stirred solution of triethylamine (0.48 mL, 0.35 g, 3.5 mmol) and chlorodicyclohexylborane (1 M in hexanes; 2.3 mL, 2.3 mmol) in CH\(_2\)Cl\(_2\) (15 mL) at 0 °C under argon. After 20 min, the mixture was cooled to –78 °C and a solution of propanal (0.8 mL, 0.6 g, 0.01 mol) in CH\(_2\)Cl\(_2\) (3 mL) was slowly added via syringe. After 1 h, MeOH (4 mL), pH 7 phosphate buffer (pH 7; 6 mL), and 30% aqueous H\(_2\)O\(_2\) (6 mL) were sequentially added. The reaction mixture was transferred to a 0 °C bath and vigorously stirred for 10 min.
Saturated aqueous Na$_2$SO$_3$ was slowly added (**CAUTION**: effervescence) and then the mixture was then extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (40% ethyl acetate in hexane and then 50% ether in CH$_2$Cl$_2$) to give a 9:1 mixture of the titled compound and an unidentified diastereomer (368 mg, 79%).

**IR** $\nu_{\text{max}}$: 3513, 1701 cm$^{-1}$.

**$^1$H NMR** (500 MHz, CDCl$_3$): $\delta$ 4.71-4.68 (2H, m, HC-'OCHO'), 4.65 (1H, d, $J$ = 6.5 Hz, OCHO), 4.12-4.01 (4H, m, H2CO ×2), 3.71-3.65 (1H, m, HC-'OCHO'), 3.38 (3H, s, H3CO), 3.20 (1H, ddd, $J$ = 2.5, 4.5, 14 Hz, HC-2'), 3.06-3.00 (2H, m, HO, HC-3'), 2.97 (1H, ddd, $J$ = 4, 4.5, 8.5 Hz, HC-5'), 2.93-2.72 (6H, m, HC-2, H2C-6, H2C-7', HC-9'), 2.53-2.47 (2H, m, HC 6', HC-9'), 2.13 (1H, ddd, $J$ = 3, 4, 13.5 Hz, HC-10'), 1.74 (1H, ddd, $J$ = 3.5, 13.5, 13.5 Hz, HC-10'), 1.58 (1H, ddq, $J$ = 3.5, 14.5, 7.5 Hz, HC-2''), 1.50 (1H, ddq, $J$ = 7, 14.5, 7.5 Hz, HC-2''), 0.99 (3H, t, $J$ = 7.5 Hz, H3C-3'').

**$^{13}$C NMR** (125 MHz, CDCl$_3$): $\delta$ 213.2 (s, C-4), 108.4 (s, C-5'), 96.9 (t, OCH$_2$O), 76.2 (d, C-1'), 73.4 (d, C-1''), 64.7 (t, CH$_2$O), 64.2 (t, CH$_2$O), 56.7 (q, CH$_3$O), 54.9 (d, C-5), 54.7 (d, C-3), 50.8 (d, C-6'), 36.6 (t, C-10'), 33.4 (t ×2, C-2, C-6), 28.3 (t, C-7'), 27.1 (t, C-2''), 26.9 (t, C-9'), 10.1 (q, C-3'').

**LRMS**: m/z (relative intensity) 406 ([M]$^+$, 0.4), 343 (3), 282 (11), 159 (14), 157 (11), 132 (40), 99 (100), 86 (11) (EI).

**HRMS**: m/z calcd for C$_{18}$H$_{30}$O$_6$S$_2$ 406.1484, found 406.1480 (EI).
(3S)-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]tetrahydro-
4H-thiopyran-4-one (172)

Pyridine (0.17 mL, 0.17 g, 2.1 mmol) and Et₃SiOTf (0.42 mL, 0.70 g, 1.8 mmol) were
sequentially added to a stirred solution of 122 (>98% ee; 500 mg, 1.64 mmol) in CH₂Cl₂ (16
mL) at 0 °C under Ar. After 15 min, the mixture was diluted with ethyl acetate and washed
sequentially with saturated aqueous NaHCO₃ and brine. The organic layer was dried over
Na₂SO₄, concentrated, and fractionated by FCC (20-30% ethyl acetate in hexane) to afford
the titled compound as a colorless oil (662 mg, 96%): [α]D -60 (c 1.2, CHCl₃).

IR νmax: 1700 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 4.88 (1H, br d, J = 5 Hz, HC-1'), 3.95-3.82 (4H, m, H₂CO ×2), 3.11 (1H, dd, J = 11, 13 Hz, HC-2), 2.96-2.86 (3H, m, HC-2, HC-6, HC-7''), 2.84-2.70
(4H, m, HC-3, HC-5, HC-6, HC-7''), 2.69-2.54 (3H, m, HC-5, H₂C-9''), 2.13-2.03 (2H, m,
HC-6'', HC-10''), 1.60 (1H, ap ddd, J = 3.5, 8, 13 Hz, HC-10'), 0.95 (9H, t, J = 8 Hz, H₃C×3),
0.63 (6H, ap q, J = 8 Hz, H₂CSi ×3).

lxxxviii Characterization by Fabiola Becerril-Jimenez.
\textsuperscript{13}C NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 206.5 (s, C-4), 109.3 (s, C-5\'''), 68.5 (d, C-1'), 64.5 (t, CH\textsubscript{2}O), 63.7 (t, CH\textsubscript{2}O), 60.2 (d, C-3), 47.7 (d, C-6'''), 43.0 (t, C-5), 34.5 (t, C-10'), 29.6 (t, C-6), 29.2 (t, C-2), 27.8 (t, C-7''), 26.9 (t, C-9'''), 7.2 (q \times 3, CH\textsubscript{3}), 5.3 (t \times 3, CH\textsubscript{2}Si).

LRMS: \textit{m/z} (relative intensity) 419 ([M+1]+, 46), 389 (31), 303 (27), 287 (59), 229 (100), 225 (19), 132 (28), 99 (64) (Cl, NH\textsubscript{3}).

HRMS: \textit{m/z} calcd for C\textsubscript{19}H\textsubscript{34}O\textsubscript{4}S\textsubscript{2}Si 418.1668 (389.1277 for M-C\textsubscript{2}H\textsubscript{5}), found 389.1276 (EI).

\((3S,5S)-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(S)-1-hydroxypropyl]tetrahydro-4H-thiopyran-4-one (173)\)

A solution of 172 (763 mg, 1.8 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (2 mL) was added dropwise via syringe to a stirred solution of triethylamine (0.76 mL, 0.56 g, 5.5 mmol) and chlorodicyclohexylborane (1 M in hexanes; 3.7 mL, 3.7 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (15 mL) at 0 °C under Ar. After 20 min, the mixture was cooled to −78 °C and a solution of propanal (1.0 mL, 0.80 g, 14 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1 mL) was slowly added via syringe. After 1 h, MeOH (4 mL), pH 7 phosphate buffer (pH 7; 10 ml), and 30% aqueous H\textsubscript{2}O\textsubscript{2} (10 mL) were sequentially added. The reaction mixture was transferred to a 0 °C bath and vigorously stirred for 10 min. Saturated aqueous Na\textsubscript{2}SO\textsubscript{3} was slowly added (CAUTION: effervescence) and then the mixture was then extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4}, concentrated,
and fractionated by FCC (8% Et₂O in CH₂Cl₂) to afford the titled compound (813 mg, 94%): 
\([\alpha]_D -90 \ (c 1.0, \text{CHCl}_3)\).

**IR** \(\nu_{\text{max}}: 3513, 1699 \ \text{cm}^{-1}\).

**\(^1\text{H NMR}\)** (500 MHz, CDCl₃): \(\delta 4.74 \ (1\text{H}, \text{br d, } J = 4.5 \ \text{Hz, HC-1'}), 3.99-3.86 \ (4\text{H, m, H}_2\text{CO} \times 2), 3.83-3.77 \ (1\text{H, m, HC-1''}), 3.21 \ (1\text{H, dd, } J = 11, 13 \ \text{Hz, HC-2}), 3.18 \ (1\text{H, d, } J = 3.5 \ \text{Hz, HO}), 3.00 \ (1\text{H, dd, } J = 5, 12 \ \text{Hz, HC-6}), 2.89-2.76 \ (5\text{H, m, HC-2, HC-3, HC-5, H2C-7'}), 2.73-2.61 \ (2\text{H, m, HC-6. H}_2\text{C-9'}), 2.11 \ (1\text{H, ap ddd, } J = 3.5, 7, 7.5 \ \text{Hz, HC-6'}), 2.08-2.01 \ (1\text{H, m, HC-10'}), 1.65-1.55 \ (2\text{H, m, HC-2'', HC-10'}), 1.50 \ (1\text{H, ddq, } J = 7, 7.5, 15 \ \text{Hz, HC 2''}), 0.99 \ (3\text{H, t, } J = 7.5 \ \text{Hz, H}_3\text{C-3''}), 0.97 \ (9\text{H, t, } J = 8 \ \text{Hz, H}_3\text{CCSi} \times 3), 0.66 \ (6\text{H, ap q, } J = 8 \ \text{Hz, H}_2\text{CSi} \times 3)\).

**\(^{13}\text{C NMR}\)** (125 MHz, CDCl₃): \(\delta 211.5 \ (s, \text{C-4}), 109.1 \ (s, \text{C-5'}), 73.3 \ (d, \text{C-1''}), 69.4 \ (d, \text{C-1'}), 64.6 \ (t, \text{CH}_2\text{O}), 63.9 \ (t, \text{CH}_2\text{O}), 60.7 \ (d, \text{C-3}), 53.0 \ (d, \text{C-5}), 47.9 \ (d, \text{C-6'}), 34.5 \ (t, \text{C-10'}), 29.5 \ (t, \text{C-7'}), 27.4 \ (t, \text{C-6}), 27.1 \ (t, \text{C-2''}), 26.9 \ (t, \text{C-9'}), 26.2 \ (t, \text{C-2}), 9.9 \ (t, \text{C-3''}), 7.2 \ (t \times 3, \text{CH}_2\text{Si}), 5.3 \ (q \times 3, \text{CH}_3\text{CSi})\).

**LRMS:** \(m/z\) (relative intensity) 477 ([M+1]⁺, 24), 419 (99), 389 (36), 345 (62), 287 (100), 229 (86), 132 (38), 99 (46) (Cl, NH₃).

**HRMS:** \(m/z\) calcd for C₂₂H₄₀O₅S₂Si 476.2086 (477.2165 for M+H), found 477.2183 (Cl, NH₃).
(4S,4aS,5aR,9aS,10R,10aS,12R)-12-Ethyloctahydro-5a,4,10-(epoxymethenoxy)-4a-trimethylsilyloxy-1H,4aH,5aH-bisthiopyrano[4,3-b:3',4'-e]pyran (174a)

2,6-Lutidine (0.50 mL, 0.46 g, 4.3 mmol) and Me₃SiOTf (0.20 mL, 0.25 g, 1.1 mmol) were added to a stirred solution of 167 (271 mg, 0.86 mmol) in CH₂Cl₂ (10 mL) at room temperature under Ar. After 1 h, the mixture was diluted with ethyl acetate, washed sequentially with 1% (w/v) aqueous citric acid monohydrate (×3), sat. NaHCO₃ and brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give the titled compound as a clear oil (309 mg, 93%): [α]D +18 (c 1, C₆H₆).

IR \( \nu_{\text{max}} \): 2924, 1248, 1149, 1083, 883, 851 cm⁻¹.

\(^1\)H NMR (500 MHz, C₆D₆): \( \delta \)

- 3.79 (1H, br d, \( J = 3.5 \) Hz, HC-1'), 3.41 (1H, dd, \( J = 3.5, 13.5 \) Hz, HC-2), 3.37 (1H, dd, \( J = 3, 14 \) Hz, HC-6), 2.87 (1H, ddd, \( J = 3, 13.5, 13.5 \) Hz, HC-6'), 2.51 (1H, dd, \( J = 12.5, 13 \) Hz, HC-2'), 2.32 (1H, ddd, \( J = 3.5, 3.5, 12.5 \) Hz, HC-3'), 2.25 (1H, ddd, \( J = 2, 3, 14 \) Hz, HC-6), 2.08 (1H, ddd, \( J = 2, 2, 13.5 \) Hz, HC-2), 2.02 (1H, dddd, \( J = 2.5, 3.5, 13.5, 13.5 \) Hz, HC-6'), 1.94 (1H, ddd, \( J = 3, 3.5, 13.5 \) Hz, HC-5'), 1.92-1.82 (3H, m, HC-2", HC-5, HC-5'), 1.63 (1H, ddd, \( J = 2.5, 3, 13 \) Hz, HC-2'), 1.62-1.59 (1H, m, HC-3), 1.54 (1H, dq, \( J = 15, 7.5 \) Hz, HC-2"), 1.00 (3H, t, \( J = 7.5 \) Hz, H₃C-3''), 0.20 (9H, s, H₃CSi ×3).
\(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)): \(\delta\) 102.7 (s, C-4' or C-1''), 99.6 (s, C-4' or C-1''), 97.5 (s, C-4), 76.9 (d, C-1'), 45.9 (d, C-3'), 44.4 (d, C-5), 38.4 (t, C-5'), 37.3 (d, C-3), 30.3 (t, C-2''), 29.4 (t, C-2), 27.8 (t, C-2'), 25.6 (t, C-6'), 25.3 (t, C-6), 6.9 (t, C-3''), 2.6 (q \(\times\)3, CH\(_3\)Si).

**LRMS:** \(m/z\) (relative intensity): 388 ([M]\(^+\), 71), 314 (10), 286 (15), 225 (23), 198 (42), 155 (31), 73 (100) (EI).

**HRMS:** \(m/z\) calcld for C\(_{17}\)H\(_{28}\)O\(_4\)S\(_2\)Si 388.1198, found 388.1198 (EI).

(4S,4aS,5aR,9aS,10R,10aS,12R)-12-Ethyloctahydro-5a,4,10-(epoxymethenoxy)-4a-triethylsilyloxy-1\(H\),4\(a\)H,5a\(H\)-bisthiopyrano[4,3-b:3',4'-e]pyran (174b)

2,6-Lutidine (0.11 mL, 0.10 g, 0.93 mmol) and (CH\(_3\)CH\(_2\))\(_3\)OTf (0.10 mL, 0.12 g, 0.45 mmol) were sequentially added to a stirred solution of \(167\) (59 mg, 0.19 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at room temperature under Ar. After 2 h, the mixture was diluted with ethyl acetate, washed sequentially with 1% (w/v) aqueous citric acid (\(\times\)3), sat. NaHCO\(_3\) and brine, dried over Na\(_2\)SO\(_4\), concentrated, and fractionated by FCC (15% ethyl acetate in hexane) to give the titled compound as a clear oil (78 mg, 97%): \([\alpha]_D\) +1.0 (c 1.1, CHCl\(_3\)).

**IR** \(\nu_{\max}\): 2952, 2925, 1267, 1150, 1082, 896, 768 cm\(^{-1}\).
\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}): \(\delta\) 4.25 (1H, br d, \(J = 3\) Hz, HC-1'), 3.54 (1H, dd, \(J = 3.5, 13.5\) Hz, HC-2), 3.41 (1H, dd, \(J = 3, 14\) Hz, HC-6), 2.96 (1H, ddd, \(J = 2.5, 13.5, 13.5\) Hz, HC-6'), 2.99 (1H, dd, \(J = 12.5, 13\) Hz, HC-2'), 2.53-2.44 (3H, m, HC-2, HC-6, HC-6'), 2.40 (1H, ddd, \(J = 3.5, 3.5, 12.5\) Hz, HC-3'), 2.24 (1H, ddd, \(J = 3, 3, 13\) Hz, HC-2'), 2.06-2.00 (2H, m, HC-3, HC-5'), 1.94 (1H, br s, HC-5), 1.88 (1H, ddd, \(J = 4, 13.5, 13.5\) Hz, HC-5'), 1.80 (1H, dq, \(J = 15, 7.5\) Hz, HC-2''), 1.61 (1H, dq, \(J = 15, 7.5\) Hz, HC-2''), 0.99 (9H, t, \(J = 8\) Hz, H\textsubscript{3}C \times 3), 0.96 (3H, t, \(J = 7.5\) Hz, H\textsubscript{3}C-3''), 0.71-0.65 (6H, m, H\textsubscript{2}CSi \times 3).

\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl\textsubscript{3}): \(\delta\) 102.2 (s, C-4' or C-1''), 99.1 (s, C-4' or C-1''), 96.3 (s, C-4), 77.0 (d, C-1'), 45.3 (d, C-3'), 43.8 (d, C-5), 37.7 (t, C-5'), 37.0 (d, C-3), 29.8 (t, C-2''), 29.1 (t, C-2), 27.7 (t, C-2'), 25.4 (t, C-6'), 24.9 (t, C-6), 7.3 (q \times 3, CH\textsubscript{3}), 6.8 (t \times 3, CH\textsubscript{2}Si), 6.4 (q, C-3 '').

\textbf{LRMS}: \(m/z\) (relative intensity) 430 ([M]\textsuperscript{+}, 77), 327 (47), 240 (31), 225 (63), 155 (38), 115 (46), 87 (59), 67 (100) (EI).

\textbf{HRMS}: \(m/z\) calcd for C\textsubscript{20}H\textsubscript{34}O\textsubscript{4}S\textsubscript{2}Si 430.1668, found 430.1665 (EI).
(1\textit{R},3\textit{R},5\textit{R},7\textit{R},8\textit{S},9\textit{S},10\textit{S})-3,5-Diethyl-8,9,10-trimethyl-2,4,6-trioxatricyclo [3.3.1.1^{3,7}] \textit{dec}-1-yloxy(trimethyl)silane (175a)

From \textbf{142}: Triethylamine (0.10 mL, 73 mg, 0.73 mmol), 2,6-lutidine (0.50 mL, 0.46 g, 4.3 mmol) and Me\textsubscript{3}SiCl (0.050 mL, 43 mg, 0.40 mmol) were sequentially added to a stirred solution of \textbf{142} (8 mg, 0.03 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1 mL) at ambient temperature. After 3 d, the mixture was concentrated and the resulting residue was suspended in hexane and filtered through Celite®. The combined filtrate and hexane washings were concentrated and fractionated by PTLC (20% ethyl acetate in hexane) to give the titled compound (6 mg, 59%).

From \textbf{174a}: A suspension of Raney nickel (W2; 12 mL settled volume) in ethanol (20 mL) was added to \textbf{174a} (309 mg, 0.8 mmol) and the mixture was heated under reflux with vigorous stirring. After 45 min, the mixture was decanted and the solid suspended in ethanol and heated under reflux with rapid stirring for several min. This washing procedure was repeated twice with EtOH and once with ethyl acetate. The combined organic layers were filter through Celite® and concentrated to give the titled compound (231 mg, 88%) that was homogeneous by \textsuperscript{1}H NMR: $[\alpha]_D$ -9 (c 0.5, C\textsubscript{6}H\textsubscript{6}).
IR ν max: 2792, 2940, 2883, 1465, 1455, 1380, 1352, 1328 cm⁻¹.

¹H NMR (500 MHz, C₆D₆): δ 3.70 (1H, br d, J = 3.5 Hz, HC-7), 2.09-2.03 (2H, m, HC-9, HC-10), 2.00 (1H, br q, J = 7.5 Hz, HC-8), 1.82 (1H, dq, J = 15, 7.5 Hz, HCC-5), 1.60 (1H, dq, J = 15, 7.5 Hz, HCC-3), 1.57 (1H, dq, J = 15, 7.5 Hz, HCC-5), 1.45 (1H, dq, J = 15, 7.5 Hz, HCC-3), 1.18 (3H, d, J = 7.5 Hz, H₃CC-8), 1.08 (3H, d, J = 7.5 Hz, H₃CC-9), 1.07 (3H, t, J = 7.5 Hz, H₃CCC-5), 1.01 (3H, t, J = 7.5 Hz, H₃CCC-3), 0.63 (3H, d, J = 7 Hz, H₃CC-10), 0.30 (9H, s, H₃CSi ×3).

¹³C NMR (125 MHz, C₆D₆): δ 103.3 (s, C-3), 102.6 (s, C-5), 101.0 (s, C-1), 79.2 (d, C-7), 46.3 (d, C-9), 38.2 (d, C-10), 37.3 (d, C-8), 30.5 (t, CH₂C-5), 30.2 (t, CH₂C-3), 14.8 (q, CH₃C-8), 13.1 (q, CH₂C-10), 11.2 (q, CH₃C-9), 7.0 (q, CH₃CC-5), 6.9 (q, CH₃CC-3), 2.7 (q ×3, CH₃Si).

LRMS: m/z (relative intensity) 328 ([M]⁺, 4), 239 (13), 203 (72), 197 (22), 187 (18), 113 (25), 73 (38), 57 (100) (EI).

HRMS: m/z calcd for C₁₇H₃₂O₄Si 328.2070, found 328.2062 (EI).
(1R,3R,5R,7R,8S,9S,10S)-3,5-Diethyl-8,9,10-trimethyl-2,4,6-trioxatricyclo [3.3.1.1^{3,7}]
dec-1-yloxy(triethyl)silane (175b)

A suspension of Raney nickel (W2; 2 mL settled volume) in EtOH (10 mL) was added to
174b (72 mg, 0.17 mmol) and the mixture was heated under reflux with vigorous stirring.
After 30 min, the mixture was decanted and the solid suspended in ethanol and heated under
reflux with rapid stirring for several min. This washing procedure was repeated three times
with EtOH and once with ethyl acetate. The combined organic layers were filter through
Celite®, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the
titled compound (51 mg, 83%).

\[ \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3; \delta 3.81 (1H, br d, } J = 3.5 \text{ Hz, HC-7) 2.11 (1H, dq, } J = 3.5, 7 \text{ Hz, HC-10) 1.99 (1H, br q, } J = 7.5 \text{ Hz, HC-8) 1.87 (1H, br q, } J = 7.5 \text{ Hz, HC-9) 1.67-1.46 (4H, m, H}_2\text{C } \times 2) 1.13 (3H, d, } J = 7.5 \text{ Hz, H}_3\text{CC-8) 1.01 (3H, d, } J = 7.5 \text{ Hz, H}_3\text{CC-9) 0.97 (9H, t, } J = 8 \text{ Hz, H}_3\text{CCSi } \times 3) 0.92 (3H, t, } J = 7.5 \text{ Hz, H}_3\text{CCC-3 or H}_3\text{CCC-5) 0.91 (3H, t, } J = 7.5 \text{ Hz, H}_3\text{CCC-3 or H}_3\text{CCC-5) 0.87 (3H, d, } J = 7 \text{ Hz, H}_3\text{CC-10) 0.64 (6H, ap q, } J = 8 \text{ Hz, H}_2\text{CSi } \times 3). \]

\[ \text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3; \delta 102.8 (s, C-3), 102.2 (s, C-5) 99.8 (s, C-1), 79.3 (d, C-7) 45.6 (d, C-9), 37.8 (d, C-10) 36.8 (d, C-8), 29.9 (t, CH}_2\text{C-5 or CH}_2\text{C-3) 29.7 (t, CH}_2\text{C-3 or} \]

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CH$_2$C-5), 14.5 (q, CH$_3$C-8) 13.1 (q, CH$_3$C-10), 10.7 (q, CH$_3$C-9) 7.2 (q ×3, CH$_3$Si), 6.7 (t ×3, CH$_2$Si) 6.6 (q, CH$_3$CC-5 or CH$_3$CC-3), 6.4 (q, CH$_3$CC-3 or CH$_3$CC-5).

**LRMS:** $m/z$ (relative intensity) 370 ([M]$^+$, 7) 267 (47) 245 (92) 229 (23) 171 (23) 75 (22) 71 (60) 57 (100) (EI).

**HRMS:** $m/z$ calcd for C$_{20}$H$_{38}$O$_4$Si 370.2539, found 370.2538 (EI).

2-(2-Ethyl-1,3-dithiolan-2-yl)propanal (179)

![](image)

IBX (2.5 g, 8.9 mmol) was added to a stirred solution of 186 (1.13 g, 5.88 mmol) in anhydrous DMSO (30 mL) at rt. Reaction progress was monitored by TLC and after 2 h, the mixture was diluted with ethyl acetate (200 mL) and washed sequentially with sat. NaHCO$_3$, water, and brine. The organic layer was dried over Na$_2$SO$_4$ and concentrated to give the titled compound as a clear oil (1.10 g, 98%) that was homogeneous by NMR.

**IR** $\nu$$_{\text{max}}$: 1718 cm$^{-1}$.

**$^1$H NMR** (500 MHz, CDCl$_3$): $\delta$ 9.87 (1H, d, $J = 2$ Hz, HC-1), 3.35-3.23 (4H, m, H$_2$CS ×2), 2.80 (1H, dq, $J = 2.7$ Hz, HC-2), 2.01 (1H, dq, $J = 14.5, 7$ Hz, HC-1"), 1.93 (1H, dq, $J = 14.5, 7$ Hz, HC-1"), 1.25 (3H, d, $J = 7$ Hz, H$_3$C-3), 1.08 (3H, t, $J = 7$ Hz, H$_3$C-2").
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 204.1 (s, C-1), 72.4 (s, C-2'), 54.3 (d, C-2), 40.3 (t, CH$_2$S), 40.2 (t, CH$_2$S), 36.5 (t, C-1''), 13.2 (q, C-3), 10.7 (q, C-2'').

LRMS: $m/z$ (relative intensity): 190 ([M]+, 7), 161 (10), 133 (100), 102 (12), 73 (25), 61 (18) (EI).

HRMS: $m/z$ calcd for C$_8$H$_{14}$OS$_2$ 190.0486, found 190.0484 (EI).

Ethyl 2-(2-Ethyl-1,3-dithiolan-2-yl)propanoate (185)

$\text{BF}_3\cdot\text{OEt}_2$ (7.8 mL, 8.8 g, 6.2 mmol) was added to a stirred solution of 184 (8.91 g, 56.4 mmol) and 1,2-dithioethane (5.0 mL, 5.6 g, 5.9 mmol) in CH$_2$Cl$_2$ (80 mL) at rt under Ar. Reaction progress was monitored by TLC and after 10 min, the mixture was diluted with ether (300 mL) and sat. NaHCO$_3$ (200 mL) (CAUTION! effervescence) and the two-phase mixture was stirred for 30 min at rt. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated to give the titled compound as a pale yellow oil (13.07 g, 99%) that was homogeneous by NMR.

IR $\nu_{\text{max}}$: 1731 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.18 (2H, q, $J = 7$ Hz, H$_2$CO), 3.25-3.20 (4H, m, H$_2$CS $\times 2$), 3.02 (1H, q, $J = 7$ Hz, HC-2), 2.09 (1H, dq, $J = 14.5, 7$ Hz, HC-1''), 1.94 (1H, dq, $J = 14.5, 7$ Hz, HC-2')
Hz, HC-1")], 1.42 (3H, d, J = 7 Hz, H3C-3), 1.27 (3H, t, J = 7 Hz, H3CCH2O), 1.12 (3H, t, J = 7 Hz, H3C-2").

\[^{13}C \text{ NMR} \ (125 \text{ MHz, CDCl}_3): \delta 174.4 \text{ (s, C-1)}, 74.3 \text{ (s, C-2')}, 60.7 \text{ (t, CH}_2\text{O)}, 50.7 \text{ (d, C-2)}, 40.5 \text{ (t, CH}_2\text{S)}, 40.2 \text{ (t, CH}_2\text{S)}, 34.8 \text{ (t, C-1')}, 15.7 \text{ (q, C-3)}, 14.4 \text{ (q, CH}_3\text{CH}_2\text{O)}, 10.7 \text{ (q, C-2')}.\]

**LRMS:** m/z (relative intensity) 234 ([M]\(^+\), 17), 205 (44), 133 (100), 105 (10), 89 (12), 73 (19) (EI).

**HRMS:** m/z calcd for C\(_{10}\)H\(_{18}\)O\(_2\)S\(_2\) 234.0748, found 234.0745 (EI).

### 2-(2-Ethyl-1,3-dithiolan-2-yl)propan-1-ol (186)

A solution of 185 (13.2 g, 56.4 mmol) in THF (20 mL + 2×5 mL rinses) was added dropwise via syringe to a stirred suspension of LiAlH\(_4\) (2.6 g, 68 mmol) in THF (100 mL) at 0 °C under Ar. The mixture was allowed to warm to ambient temperature and the reaction progress was monitored by TLC. After 3 h, the mixture was cooled to 0 °C and then water (2.6 mL) (*CAUTION! H\(_2\) evolution), 15% aqueous NaOH (w/v; 2.6 mL), and water (7.8 mL) were sequentially added with vigorous stirring. The cooling bath was removed and the grayish suspension turned white over 1 h. The mixture was filtered through a short pad of Na\(_2\)SO\(_4\) and Celite® and washed with ethyl acetate. The combined filtrate and washings
were concentrated to give the titled compound as a pale yellow oil (9.97 g, 92%) that was homogeneous by NMR.

**IR** \( \nu_{\text{max}} \): 3377 cm\(^{-1}\).

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)): \( \delta \) 3.95 (1H, dd, \( J = 5.5, 11 \) Hz, HC-1), 3.70 (1H, br dd, \( J = 5, 11 \) Hz, HC-1), 3.28-3.23 (4H, m, H\(_2\)CS \( \times 2 \)), 2.52 (1H, br s, HO), 2.17 (1H, ddq, \( J = 5, 5.5, 7 \) Hz, HC-2), 2.03 (1H, dq, \( J = 14.5, 7 \) Hz, HC-1”), 1.93 (1H, dq, \( J = 14.5, 7 \) Hz, HC-1”), 1.12 (3H, d, \( J = 7 \) Hz, H\(_3\)C-3), 1.07 (3H, t, \( J = 7 \) Hz, H\(_3\)C-2”).

**\(^13\)C NMR** (125 MHz, CDCl\(_3\)): \( \delta \) 76.5 (s, C-2”), 66.7 (t, C-1), 44.5 (d, C-2), 40.1 (t, CH\(_2\)S), 39.8 (t, CH\(_2\)S), 36.4 (t, C-1”), 15.7 (q, C-3), 10.8 (q, C-2”).

**LRMS**: \( m/z \) (relative intensity) 192 ([M]+, 3), 163 (13), 133 (100), 105 (9), 73 (8) (EI).

**HRMS**: \( m/z \) calcd for C\(_8\)H\(_{16}\)O\(_2\) S \( 192.0643 \), found 192.0638 (EI).

(\(6R,10S\))-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxaldehyde (\(meso\)-196); (\(6R,10R\))-rel-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxaldehyde ((\(\pm\))-196)

IBX (23.2 g, 82.9 mmol) was added to a stirred solution of (\(\pm\))-194\(^{70}\) (7.6 g, 35 mmol) in MeCN (250 mL) at 80 °C (oil bath temperature). After 2.5 h, the suspension was cooled and then filtered through a medium-porosity sintered glass funnel. The combined filtrate and
ethyl acetate washings were concentrated and fractionated by FCC (50% ethyl acetate in hexanes) to give the titled compound (7.18 g, 96%) as a variable mixture of meso/dl isomers (dl: meso, 4-25:1) by $^1$H NMR (CD$_6$). The recovered solid (20.1 g, mainly IBA, >90%) could be reoxidized to IBX with Oxone® in >80% yield.78

Data included here for completeness.

**meso-196:**

$^1$H NMR (500 MHz, CD$_6$): $\delta$ 9.46 (2H, s, HC=O $\times$2), 3.11 (4H, br s, H$_2$CO $\times$2), 2.82 (2H, ap dd, $J = 13, 13$ Hz, HC-7, HC-9), 2.42-239 (4H, m, HC-6, HC-7, HC-9, HC-10).

$^{13}$C NMR (125 MHz, CD$_6$): $\delta$ 199.0 ($\times$2, C=O), 110.2 (C-5), 66.5 (CH$_2$O), 66.3 (CH$_2$O), 60.3 ($\times$2, C-6, C-10), 26.6 ($\times$2, C-7, C-9).

**LRMS:** (EI), m/z (relative intensity): 216 ([M]$^+$, 12), 188 (9), 160 (6), 113 (11), 99 (100), 86 (5), 54 (18).

**HRMS:** m/z calcd for C$_9$H$_{12}$O$_4$S 216.0456, found 216.0458. Anal. Calcd for C$_9$H$_{12}$O$_4$S: C, 49.99; H, 5.59. Found: C, 49.79; H, 5.59.

**(±)-196:**

$^1$H NMR (500 MHz, CD$_6$): $\delta$ 9.62 (2H, br s, HC=O $\times$2), 3.12-3.02 (4H, m, H$_2$CO $\times$2), 2.73 (2H, dd, $J = 7.5, 14$ Hz, HC-2, HC-6), 2.56 (2H, ddd, $J = 1.5, 3.5, 14$ Hz, HC-2, HC-6), 2.23 (2H, dd, $J = 3.5, 7.5$ Hz, HC-3, HC-5).

$^{13}$C NMR (125 MHz, CD$_6$): $\delta$ 199.4 ($\times$2, C=O), 108.3, 65.1 ($\times$2, CH$_2$O), 55.1 ($\times$2, C-3. C-5), 27.1 ($\times$2, C-2, C-6).
3-/oxa-7-thiaspiro[bicyclo[3.3.1]nonane-9,2'-[1,3]dioxolan]-2-one (197)

Isolated as a minor component in the IBX oxidation of mixtures of (±)-195 and (±)-194. (±)-197 was not detected when pure (±)-194 was used.

IR $\nu_{\text{max}}$: 1734 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.59 (1H, ddd, $J$ = 2, 6, 11.5 Hz, HC-4), 4.43 (1H, d, $J$ = 11.5 Hz, HC-4), 4.06-3.93 (4H, m, H$_2$CO x2), 3.34 (1H, ddd, $J$ = 2, 2, 13.5 Hz, HC-6), 3.32 (1H, dd, $J$ = 2.5, 13 Hz, HC-8), 2.94 (1H, ddd, $J$ = 2, 2.5, 4 Hz, HC-1), 2.78 (1H, ddd, $J$ = 2.5, 4, 13 Hz, HC-8), 2.54 (1H, ddd, $J$ = 2.5, 4, 13.5 Hz, HC-6), 2.26-2.21 (1H, m, HC-5).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 171.0 (s, C-2), 105.1 (s, C-9), 71.1 (t, C-4), 65.4 (t, CH$_2$O), 64.9 (t, CH$_2$O), 47.8 (d, C-1), 36.4 (d, C-5), 32.3 (t, C-6), 30.5 (t, C-8).

LRMS: $m/z$ (relative intensity) 216 ([M]$^+$, 65), 183 (24), 169 (7), 144 (80), 131 (8), 115 (18), 99 (100) (EI).

HRMS: $m/z$ calcd. for C$_9$H$_{12}$O$_4$S 216.0456, found 216.0460 (EI).
(1S,2R,4RS,5R)-2-((S)-4-Oxotetrahydro-2H-thiopyran-3-yl)-3-oxa-7-thiaspiro[3.3.1]nonane-9,2'-[1,3]dioxolan-4-yl Pivalate (198)

Trimethylacetyl chloride (1.5 mL, 1.5 g, 12 mmol), DMAP (1.3 g, 10 mmol), and Et$_3$N (4 mL, 2.9 g, 29 mmol) were added to a stirred solution of 190 (3.5 g, 10 mmol) in CH$_2$Cl$_2$ (100 mL) at rt. After ca. 16 h, the mixture was diluted with ethyl acetate and washed sequentially with 1N aq. HCl, sat. NaHCO$_3$, and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (40% ethyl acetate in hexanes) to give the titled compound as a ca. 1:1 mixture of anomers (3.56 g, 81%).

IR $\nu_{max}$: 1737, 1715 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.08 (1H, s, HC-4 ($4R$)), 6.05 (1H, br s, HC-4 ($4S$)), 5.19 (1H, br d, $J = 10$ Hz, HC-2 ($4R$)), 4.90 (1H, br d, $J = 10$ Hz, HC-2 ($4S$)), 4.19-3.92 (8H, m, H$_2$CO $\times 4$), 3.48 (1H, dd, $J = 3$, 13 Hz, HC-6 ($4R$)), 3.45 (1H, m, $J = 4$. 14 Hz, HC-8 ($4S$)), 3.41 (1H, dd, $J = 2.5$, 14 Hz, HC-8 ($4R$)), 3.31 (1H, dd, $J = 3$, 13.5 Hz, HC-6 ($4S$)), 3.17-3.11 (2H, m, HC-3' ($4R$ & $4S$)), 3.08-2.80 (10H, m), 2.75-2.49 (8H, m), 2.11 (1H, br s, HC-5 ($4R$)), 2.01 (1H, br s, HC-5 ($4R$)), 1.78 (2H, br s, HC-1 ($4R$ & $4S$)), 1.26 (9H, s, (H$_3$C)$_3$C), 1.20 (9H, s, (H$_3$C)$_3$C).

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\[^{13}\text{C} \text{ NMR} \) (125 MHz, CDCl\(_3\)): \( \delta \) 207.8 (s, C-4'), 207.7 (s, C-4'), 177.0 (s, Piv), 176.7 (s, OC=O), 107.1 (s, C-9), 105.7 (s, C-9), 96.6 (d, C-4 (4R)), 94.1 (d, C-4 (4S)), 72.9 (d, C-2 (4S)), 72.1 (d, C-2 (4R)), 64.9 (t, CH\(_2\)O), 64.7 (t, CH\(_2\)O), 64.6 (t, CH\(_2\)O), 64.2 (t, CH\(_2\)O), 53.9 (d, C-3' (4R)), 53.3 (d, C-3' (4S)), 43.0 (t, C-5'), 42.3 (t, C-5'), 40.7 (d, C-5 (4S)), 39.1 (s x2, C(CH\(_3\))\(_3\)), 39.0 (d, C-5 (4R)), 36.9 (d, C-1), 36.8 (d, C-1), 32.9 (t, C-2' or C-6'), 32.7 (t, C-2' or C-6'), 32.2 (t, C-2' or C-6'), 32.0 (t, C-2' or C-6'), 29.7 (t, C-6 (4R)), 27.2 (q x6, (CH\(_3\))\(_3\)C x2), 25.9 (t, C-8 (4S)), 25.6 (t, C-8 (4R)), 25.0 (t, C-6 (4S)).

\( \text{LRMS}: m/z \) (relative intensity) 416 ([M]^+, 10), 314 (18), 226 (6), 199 (10), 131 (12), 99 (100) (EI).

\( \text{HRMS}: m/z \) calcd for C\(_{19}\)H\(_{28}\)O\(_6\)S\(_2\) 416.1327, found 416.1348 (EI).

\((6R, 7RS, 9R, 10S)\)-6, 10-Dimethyl-9-((S)-3-oxopentan-2-yl)-1, 4, 8-trioxaspiro[4.5]decan-7-yl Pivalate (199)

Raney Nickel (W2; 60 mL settled volume) was washed with THF (x3) and THF (150 mL) and 198 (2.76 g, 6.6 mmol) were added. 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, heated under reflux for 10 min, and decanted. This washing procedure was repeated with ethyl acetate and then acetone. The combined organic layers were filtered through Celite® and concentrated to give the crude desulfurized product.

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that contained a variable amount (up to 10% by $^1$H NMR) of alcohol (from hydrogenation of
the ketone). IBX (1.73 g, 6.2 mmol) was added to a stirred solution of the crude reaction
mixture in DMSO (30 mL) at rt. After 15 h, the mixture was diluted with ethyl acetate and
washed sequentially with sat. NaHCO$_3$, water, and brine. The aqueous layers were back
extracted with ethyl acetate. The organic layers were combined, dried over Na$_2$SO$_4$,
concentrated, and fractionated by FCC (30% diethyl ether in hexanes) to give the titled
compounds as a 1:1 mixture of anomers (2.02 g, 86%). Pure samples of the individual
anomers could be obtained by fractionation of the mixture by PTLC (30% diethyl ether in
hexanes).

(6$R$,7$S$,9$R$,10$S$)-6,10-Dimethyl-9-((S)-3-oxopentan-2-yl)-1,4,8-trioxaspiro[4.5]decan-7-yl
Pivalate (α-199)

\[
\text{IR } \nu_{\text{max}}: 1735, 1718 \text{ cm}^{-1}.
\]

\[\text{IR } \nu_{\text{max}}: 1735, 1718 \text{ cm}^{-1}.\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.70 (1H, d, $J$ = 3 Hz, HC-7), 3.98-3.92 (4H, m, H 2CO ×2),
3.90 (1H, dd, $J$ = 2, 10.5 Hz, HC-9), 2.73 (1H, dq, $J$ = 10.5, 7 Hz, HC-1'), 2.59-2.43 (2H, m,
HC-3'), 1.95 (1H, dq, $J$ = 1.5, 7.5 Hz, HC-6), 1.68 (1H, br q, $J$ = 7.5 Hz, HC-10), 1.17 (9H,
s), 1.06 (3H, d, $J$ = 7.5 Hz, H$_3$CC-6), 1.03 (3H, d, $J$ = 7.5 Hz, H$_3$CC-10), 1.00 (3H, t, $J$ = 7
Hz, HC-4'), 0.93 (3H, d, $J$ = 7 Hz, H$_3$CC-1').
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 213.9 (s, C-3'), 176.5 (s, OC=O), 110.8 (s, C-5), 94.7 (d, C-7), 77.9 (d, C-9), 64.7 (t, CH$_2$O), 64.5 (t, CH$_2$O), 47.4 (d, C-1'), 41.4 (d, C-6), 39.1 (s, C(CH$_3$)$_3$), 38.6 (d, C-10), 35.0 (t, C-4'), 27.2 (q $\times$3, (CH$_3$)$_3$C), 12.6 (q, C-1'), 9.1 (q, CH$_3$C-10), 8.9 (q, CH$_3$C-6), 7.5 (q, C-5').

**LRMS:** $m/z$ (relative intensity) 374 ([M+18]$^+$, 47), 272 (11), 255 (100), 185 (5), 129 (19), 100 (8) (CI, NH$_3$).

**HRMS:** $m/z$ calcd for C$_{19}$H$_{32}$O$_6$ 356.2199 (374.2543 for M+NH$_4$), found 374.2454 (CI, NH$_3$).

(6R,7R,9R,10S)-6,10-Dimethyl-9-((S)-3-oxopentan-2-yl)-1,4,8-trioxaspiro[4.5]decan-7-yl Pivalate (β-199)

\[
\text{\[
\begin{align*}
\beta-199
\end{align*}
\]
}
\]

[$\alpha$]$_D$ +67 (c 0.9, CHCl$_3$).

**IR** $\nu_{\text{max}}$: 1735, 1718 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.74 (1H, br s, HC-7), 4.35 (1H, dd, $J$ = 2, 10.5 Hz, HC-9), 3.99-3.87 (4H, m, H$_2$CO $\times$2), 2.73 (1H, dq, $J$ = 10.5, 7 Hz, HC-2'), 2.56 (1H, dq, $J$ = 18, 7 Hz, HC-4'), 2.46 (1H, dq, $J$ = 18, 7 Hz, HC-4'), 1.91 (1H, br q, $J$ = 7.5 Hz, HC-6), 1.80 (1H, br q, $J$ = 7.5 Hz, HC-10), 1.22 (9H, s, (H$_3$)$_3$C), 1.11 (3H, d, $J$ = 7.5 Hz, H$_3$CC-6), 1.03 (3H, d, $J$ = 7.5 Hz, H$_3$CC-10), 0.99 (3H, t, $J$ = 7 Hz, H$_3$C-5'), 0.92 (3H, d, $J$ = 7 Hz, H$_3$C-1').

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 213.8 (s, C-3'), 177.4 (s, OC=O), 109.3 (s, C-5), 96.8 (d, C-7), 74.4 (d, C-9), 64.7 (t, CH$_2$O), 64.5 (t, CH$_2$O), 46.9 (d, C-2'), 39.9 (d, C-6), 39.1 (s,
C(CH₃)₃), 38.7 (d, C-10), 36.3 (t, C-3'), 27.2 (q ×3, (CH₃)₃C), 14.2 (q, CH₃C-6), 12.5 (q, C-1'), 8.8 (q, CH₃C-10), 7.5 (q, C-5').

**LRMS**: m/z (relative intensity) 374 ([M+18]+, 19), 272 (22), 255 (100), 197 (6), 129 (12). (Cl, NH₃).

**HRMS**: m/z calcd for C₁₉H₃₂O₆ 356.2199 (374.2543 for M+NH₄), found 374.2543 (Cl, NH₃).

2-((S)-1-((2R,3S)-3,5-Dimethyl-4-oxo-3,4-dihydro-2H-pyran-2-yl)ethyl)-6-ethyl-3,5-dimethyl-4H-pyran-4-one (202)

A solution of 199 (ca. 1:1 mixture of anomers; 2.04 g, 5.7 mmol) in THF (20 mL plus 2x10 mL rinses) was added to a stirred solution of LDA [freshly prepared from DIPA (1.0 mL, 0.74 g, 7.3 mmol) and n-BuLi (2.2 M in hexanes, 2.9 mL, 6.3 mmol)] in THF (100 mL) at -78 °C under Ar. After 30 min, neat 179 (3.3 g, 17.4 mmol) was added dropwise over 3 - 5 min. After 30 min, the mixture was diluted with ethyl acetate and washed sequentially with 1M HCl (x2), sat. NaHCO₃, and brine. The organic layer was dried over Na₂SO₄, concentrated, and fractionated by FCC (30-80% diethyl ether in hexanes) to give a complex mixture of aldol diastereomers (200) (2.84 g, 91%) and recovered aldehyde (2.2 g, 67%).
IBX (2.8 g, 10 mmol) was added to a stirred solution of the above aldol mixture (200) (2.67 g, 4.9 mmol) in dry DMSO (100 mL) at rt. After 24 h, the mixture was diluted with ethyl acetate and washed sequentially with sat. NaHCO₃, water, and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (25% ethyl acetate in hexanes) to give a mixture of diketones (201) (keto and enol forms) (2.53 g, 95%).

IBX (2.5 g, 8.9 mmol) and CF₃SO₃H (0.39 mL, 660 mg, 4.4 mmol) were added to a stirred solution of the above 201 (2.41 g, 4.4 mmol) in MeCN (120 mL) at rt. After 17 h, the mixture was diluted with ethyl acetate and washed with sat. NaHCO₃ (x2) and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (40% acetone in hexanes) to give the titled compound (961 mg, 71%; 62% from 199 over 3 steps): [α]D -35 (c 0.7, CH₂Cl₂).

**IR** νₘₐₓ: 1659, 1611 cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 7.09 (1H, s, HC-6’’), 4.45 (1H, br d, J = 10 Hz, HC-2’’), 3.39 (1H, dq, J = 10, 7 Hz, HC-1’’), 2.59 (2H, q, J = 7.5 Hz, H₂CCH₃), 2.52 (1H, dq, J = 1.5, 7 Hz, HC-3’’), 1.99 (3H, s, H₃CC-3 or H₃CC-5), 1.94 (3H, s, H₃CC-5 or H₃CC-3), 1.64 (3H, s, H₃CC-5’’), 1.17 (3H, t, J = 7.5 Hz, H₃CCH₂), 1.16 (3H, d, J = 7 Hz, H₃CC-1’’), 1.13 (3H, d, J = 7 Hz, H₃CC-3’’).

**¹³C NMR** (125 MHz, CDCl₃): δ 197.2 (s, C-4’’), 179.9 (s, C-4), 164.4 (s, C-6), 162.2 (s, C-2), 159.0 (d, C-6’’), 120.0 (s, C-3), 118.3 (s, C-5), 112.7 (s, C-5’’), 82.4 (d, C-2’’), 41.2 (d, C-7’’),
36.2 (d, C-1'), 24.9 (t, CH₂C-6), 13.6 (q, CH₃-C1'), 11.5 (q, CH₃CH₂), 10.7 (q, CH₃C-5’), 9.7 (q ×2, CH₃C-3, CH₃C-5), 9.4 (q, CH₃C-3’).

**LRMS**: m/z (relative intensity) 304 ([M]+, 41), 256 (50), 180 (100), 129 (29), 73 (75) (EI).

**HRMS**: m/z calcd for C₁₈H₂₄O₄ 304.1675, found 304.1682 (EI).

**(2R,3S)-3,5-dimethyl-2-((S)-3-oxopentan-2-yl)-2H-pyran-4(3H)-one (208)**

![208](image)

IBX (24 mg, 0.086 mmol) and ethanedithiol (6 µL, 6 mg, 0.07 mmol) were added to a stirred solution of 199 (ca. 1:1 mixture of anomers; 24 mg, 0.7 mmol) in MeCN (4 mL) at 80 °C (oil bath temperature). After 1 d, the solution was diluted with ethyl acetate and washed with sat. NaHCO₃ (x2) and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (50% ethyl acetate in hexanes) to give the titled compound (8 mg, 56%, unoptimized).

**IR** νₘₚₐₓ: 1718, 1672, 1623 cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 7.12 (1H, s, HC-6), 4.49 (1H, dd, J = 3, 10.5 Hz, HC-2), 3.03 (1H, dq, J = 10.5, 7 Hz, HC-2’), 2.64-2.49 (2H, m, H₂C-4’), 2.40 (1H, dq, J = 3, 7.5 Hz, HC-3), 1.64 (3H, s, H₃CC-5), 1.08 (3H, t, J = 7 Hz, H₃C-5’), 1.07 (3H, d, J = 7.5 Hz, H₃CC-3), 0.99 (3H, d, J = 7 Hz, H₃C-1’).
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 212.4 (s, C-3'), 197.2 (s, C-4), 159.0 (d, C-6), 112.8 (s, C-5), 83.2 (d, C-2), 56.0 (d, C-2'), 41.0 (d, C-3'), 36.8 (t, C-4'), 12.6 (q, C-1'), 10.7 (q, CH\(_3\)C-5), 9.7 (q, CH\(_3\)C-3), 7.6 (q, C-5').

**LRMS:** \(m/z\) (relative intensity) 210 ([M]\(^{+}\), 15), 195 (12), 153 (12), 141 (9), 125 (19), 85 (52), 69 (13), 57 (100) (EI).

**HRMS:** \(m/z\) calcd. for C\(_{12}\)H\(_{18}\)O\(_3\) 210.1256, found 210.1248 (EI).

\[ \text{2-}((S)-1-((2S,3R,4S)-4-Hydroxy-3,5-dimethyl-3,4-dihydro-2H-pyran-2-yl)ethyl)-6-ethyl-3,5-dimethyl-4H-pyran-4-one (209) } \]

CeCl\(_3\)\(\cdot\)7H\(_2\)O (2.3 g, 6.1 mmol) was added to a stirred solution of 202 (460 mg, 1.5 mmol) in EtOH (50 mL) at 0 °C. After 20 min, NaBH\(_4\) (150 mg, 3.9 mmol) was added and the suspension stirred at 0 °C for 3 h. The cooling bath was removed and after 3 h, the mixture was diluted with ethyl acetate and washed sequentially with sat. NaHCO\(_3\) and brine. The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated to give the titled compound (437 mg, 94%): \([\alpha]_D\) -29 (c 0.5, CHCl\(_3\)).

**IR** \(\nu_{\text{max}}\): 3364, 1720, 1655, 1610 cm\(^{-1}\).
\[ ^{1}H\text{ NMR} \text{ (500 MHz, CDCl}_3\text{): } \delta \text{ 5.96 (br s, 1H, HC-6"), 4.50 (br d, 1H, } J = 6 \text{ Hz, HC-4")}, 4.04 \text{ (br d, 1H, } J = 10.5 \text{ Hz, HC-2"), 3.27 (dq, 1H, } J = 10.5, 7 \text{ Hz, HC-1')}, 2.60 \text{ (q, 2H, } J = 7.5 \text{ Hz, } \text{H}_2\text{CC-6), 2.25 (dq, 1H, } J = 6, 7 \text{ Hz, HC-3"), 1.96 (s, 3H, } \text{H}_3\text{CC-3), 1.94 (s, 3H, } \text{H}_3\text{CC-5), 1.57 (s, 3H, } \text{H}_3\text{CC-5"), 1.20 (t, 3H, } J = 7.5 \text{ Hz, } \text{H}_3\text{CCH}_2\text{), 1.15 (d, 3H, } J = 7 \text{ Hz, H}_3\text{CC-1'), 0.98 (d, 3H, } J = 7 \text{ Hz, H}_3\text{CC-3")}.\]

\[ ^{13}C\text{ NMR (125 MHz, CDCl}_3\text{): } \delta \text{ 180.1 (s, C-4), 164.3 (s, C-6), 164.0 (s, C-2), 139.7 (d, C-6"), 119.6 (s, C-3), 118.0 (s, C-5), 109.7 (s, C-5"), 79.4 (d, C-2"), 69.4 (d, C-4"), 36.9 (d, C-1'), 33.2 (d, C-3"), 25.0 (t, CH}_2\text{C-6), 14.1 (q, CH}_3\text{C-1'), 13.6 (q, CH}_3\text{C-5"), 11.6 (q, CH}_3\text{CCH}_2), 9.7 (q \times 2, CH}_3\text{C-3, CH}_3\text{C-5), 5.0 (q, CH}_3\text{C-3")}.\]

**LRMS:** m/z (relative intensity) 306 ([M]⁺, 55), 221 (24), 205 (15), 180 (100), 109 (7) (EI).

**HRMS:** m/z calcd for C₁₈H₂₆O₄ 306.1831, found 306.1828 (EI).

2-(((S)-1-((2S,3S,4S)-4-(Benzyloxy)-3,5-dimethyl-3,4-dihydro-2H-pyran-2-yl)ethyl)-6-ethyl-3,5-dimethyl-4H-pyran-4-one (210)

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

KH-MDS (0.5 M in toluene; 3 mL, 1.5 mmol) was added portion-wise (1 mL every 10 min) to a stirred solution of 209 (170 mg, 0.56 mmol), HMPA (2 mL), BnBr (0.4 mL, 0.57 g, 3.3 mmol), and t-BuOH (130 mg, 1.8 mmol) in THF (20 mL) at 0 °C under Ar. After 10 min, the mixture was diluted with ethyl acetate and washed sequentially with water, sat. NaHCO₃ and
brine, dried over Na₂SO₄, concentrated, and fractionated by FCC (40% ethyl acetate in hexanes) to give the titled compound (183 mg, 83%): [α]_D -10 (c 1.7, C₆H₆).

**IR** ν_max: 1658, 1610 cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 7.42-7.28 (5H, m, ArH), 5.96 (1H, s, HC-6''), 4.70 (1H, d, J = 12 Hz, H₂CO), 4.47 (1H, d, J = 12 Hz, H₂CO), 4.22 (1H, br d, J = 6 Hz, HC-4''), 4.00 (1H, d, J = 10.5 Hz, HC-2''), 3.27 (1H, dq, J = 10.5, 7 Hz, HC-1''), 2.59 (2H, q, J = 7.5 Hz, H₂CC-6), 2.36 (1H, dq, J = 6, 7 Hz, HC-3''), 1.97 (3H, s, H₃CC-3), 1.94 (3H, s, H₃CC-5), 1.58 (3H, s, H₃CC-5''), 1.19 (3H, t, J = 7.5 Hz, H₃CCH₂), 1.16 (3H, d, J = 7 Hz, H₃CC-1''), 0.99 (3H, d, J = 7 Hz, H₃CC-3'').

**¹³C NMR** (125 MHz, CDCl₃): δ 180.1 (s, C-4), 164.2 (s, C-6), 163.9 (s, C-2), 139.8 (d, C-6''), 138.8 (s, Ph), 128.6 (d ×2, Ph), 127.8 (d, Ph), 127.7 (d ×2, Ph), 119.7 (s, C-3), 118.0 (s, C-5), 109.4 (s, C-5''), 79.0 (d, C-2''), 76.2 (d, C-4''), 70.9 (t, CH₂O), 37.0 (d, C-1''), 29.8 (d, C-4''), 25.0 (t, CH₂C-6), 14.2 (q, CH₃C-1' or CH₃C-5''), 14.1 (q, CH₃C-1' or CH₃C-5''), 11.6 (q, CH₃CH₂), 9.7 (q ×2, CH₃C-3, CH₃C-5), 5.2 (q, CH₃C-4'').

**LRMS:** m/z (relative intensity): 396 ([M⁺], 8), 305 (17), 221 (41), 180 (69), 91 (100) (EI).

**HRMS:** m/z calcld for C₂₅H₃₂O₄ 396.2301, found 396.2293 (EI).
(2S,3S,4S)-2-((S)-1-(6-ethyl-3,5-dimethyl-4-oxo-4H-pyran-2-yl)ethyl)-3,5-dimethyl-3,4-dihydro-2H-pyran-4-yl acetate (211)

Ac₂O (ca. 50 µL, 46 mg, 0.45 mmol) and DMAP (10 mg, 0.08 mmol) were added to a stirred solution of 209 (16 mg, 0.05 mmol) in CH₂Cl₂ (1 mL) at room temperature. After 1 h, the mixture was concentrated and fractionated by PTLC (80% ethyl acetate in hexanes) to give the titled compound (19 mg, 100%): [α]D -15 (c 0.6, C₆H₆).

**IR** νmax: 1735, 1659, 1610 cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 6.12 (1H, s, HC-6), 5.62 (1H, br d, J = 6.5 Hz, HC-4), 4.16 (1H, br d, J = 10 Hz, HC-2), 3.12 (1H, dq, J = 10, 7 Hz, HC-1'), 2.67 (2H, q, J = 7.5 Hz, H₂CCH₃), 2.52 (1H, dq, J = 6.5, 7.5 Hz, HC-3), 2.20 (3H, s, H₃CC(O)), 2.03 (3H, s, H₃CC-3''), 2.01 (3H, s, H₃CC-5''), 1.56 (3H, s, H₃CC-5), 1.27 (3H, t, J = 7.5 Hz, H₃CCH₂), 1.21 (3H, d, J = 7 Hz, H₃CC-1'), 1.00 (3H, d, J = 7 Hz, H₃CC-3).

**¹³C NMR** (125 MHz, CDCl₃): δ 180.1 (s, C-4''), 171.2 (s, COO), 164.3 (s, C-6''), 163.6 (s, C-2''), 141.2 (d, C-6), 119.7 (s, C-5''), 118.0 (s, C-3''), 106.7 (s, C-5), 78.8 (d, C-2), 71.7 (d, C-4), 36.8 (d, C-1'), 30.1 (d, C-3), 25.0 (t, CH₂CH₃), 21.2 (q, CH₃C(O)), 14.0 (q, CH₃C-1'), 13.6
(q, CH₃C-5'), 11.5 (q, CH₃CH₂), 9.7 (q, CH₃C-3"or CH₃C-5"), 9.7 (q, CH₃C-3"or CH₃C-5"), 5.7 (q, CH₃C-3).

**LRMS:** $m/z$ (relative intensity) 348 ([M]$^+$, 38), 289 (16), 221 (13), 180 (100), 109 (82) (EI).

**HRMS:** $m/z$ calcd. for C₂₀H₂₈O₅ 348.1937, found 348.1933 (EI).

2-ethyl-6-((S)-1-(2S,3R,6S)-6-methoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)ethyl)-3,5-dimethyl-4H-pyran-4-one (212)

![Chemical Structure](image)

Triphenylphosphine hydrobromide (ca. 1 mg) and MeOH (20 μL) were added to a stirred solution of 211 (6 mg, 0.17 mmol) in CH₂Cl₂ (1 mL). The solution was stirred for 1 day and added to ethyl acetate. The organic layer was washed with sat. NaHCO₃ and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (30% acetone in hexanes; 2 elutions) to give the titled compound (4 mg, 73%).

**IR** $\nu_{max}$: 1657, 1613 cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 5.69 (1H, d, $J = 5.5$ Hz, HC-4"), 4.44 (1H, s, HC-6"), 4.08 (1H, dd, $J = 2$, 10.5 Hz, HC-2"), 3.12 (1H, dq, $J = 10.5$, 7 Hz, HC-1"), 2.97 (3H, s, H₂CO), 2.68-2.55 (2H, m, H₂CH₃), 2.17-2.09 (1H, m, HC-3"), 2.01 (3H, s, H₃C-5), 1.95 (3H, s,
H$_3$C-3), 1.66 (3H, s, H$_3$C-5''), 1.23 (3H, t, $J = 7.5$ Hz, H$_3$CCH$_2$), 1.15 (3H, d, $J = 5$ Hz, H$_3$C-1'), 0.98 (3H, d, $J = 5$ Hz, H$_3$C-3'').

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 180.1, 164.8, 164.3, 131.6, 129.7, 119.8, 118.0, 99.3, 71.1, 55.2, 37.0, 30.3, 25.0, 25.0, 13.8, 12.1, 11.6, 9.9, 9.8.

LRMS: $m/z$ (relative intensity): 320 ([M]$^+$, 31), 289 (28), 180 (100), 141 (9), 113 (62), 83 (35) (EI).

HRMS: $m/z$ calcd. for C$_{19}$H$_{28}$O$_4$ 320.1988, found 320.1979 (EI).

2-((2S,3S,4S,5R,6R)-5-(Benzyloxy)-3,7-dihydroxy-4,6-dimethylheptan-2-yl)-6-ethyl-3,5-dimethyl-4$H$-pyran-4-one (213)

A solution of Hg(OAc)$_2$ (130 mg, 0.41 mmol) in water (14 mL) was added to a stirred solution of 210 (139 mg, 0.35 mmol) in THF (14 mL) at rt. The resulting yellow suspension was stirred at this temperature for 2 h and then a solution of Na$_2$CO$_3$ (120 mg, 1.1 mmol) in water (10 mL) was added in one portion. After 10 min, a solution of NaBH$_4$ (32 mg, 0.84 mmol) in water (2 mL) was added. After 1 min, the mixture was diluted with water and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and the residue taken up in ethanol (10 mL), and then NaBH$_4$ (105 mg, 2.8 mmol) was added.
to the stirred solution at rt. After ca. 16 h, the mixture was diluted with water and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and fractionated by FCC (100% ethyl acetate) to give 214 (24 mg, 16%) and the titled compound (91 mg, 62%): [α]$_D$ -9 (c 0.6, CHCl$_3$).

**IR** ν$_{max}$: 3401, 1652, 1589 cm$^{-1}$.

**$^1$H NMR** (500 MHz, CDCl$_3$): δ 7.33-7.26 (5H, m, Ar H), 4.72-4.66 (2H, m, H$_2$CPh), 4.22 (1H, br d, $J = 10$ Hz, HC-3'), 3.84-3.77 (1H, m, HC-7'), 3.75-3.68 (1H, m, HC-7'), 3.59 (1H, dd, $J = 4$, 7.5 Hz, HC-5'), 3.13 (1H, br s, HOC-3'), 3.11 (1H, dq, $J = 10$, 7 Hz, HC-2'), 2.64-2.51 (2H, m, H$_2$CC-6), 2.22 (1H, br s, HOC-7'), 2.09-2.03 (1H, m, HC-6'), 2.03-1.97 (1H, m, HC-4'), 1.98 (3H, s, H$_3$CC-3), 1.90 (3H, s, H$_3$CC-5), 1.17 (3H, t, $J = 7.5$ Hz, H$_3$CCH$_2$), 1.14 (3H, d, $J = 7$ Hz, H$_3$CC-4'), 1.10 (3H, d, $J = 7$ Hz, H$_3$C-1'), 1.07 (3H, d, $J = 7$ Hz, H$_2$CC-6').

**$^{13}$C NMR** (125 MHz, CDCl$_3$): δ 180.0 (s, C-4), 164.8 (s, C-2), 164.2 (s, C-6), 137.8 (s, Ph), 128.8 (d ×2, Ph), 128.3 (d, Ph), 128.0 (d ×2, Ph), 119.6 (s, C-3), 118.0 (s, C-5), 88.2 (d, C-5'), 76.6 (t, CH$_2$Ph), 72.1 (s, C-3'), 65.3 (d, C-7'), 39.1 (d, C-2'), 38.0 (d, C-6'), 35.6 (d, C-4'), 25.0 (t, CH$_2$C-6), 15.2 (q, CH$_3$C-6'), 14.7 (q, C-1'), 11.4 (q, CH$_3$CH$_2$), 11.0 (q, CH$_3$C-4'), 9.9 (q, CH$_3$C-3 or CH$_3$C-5), 9.7 (q, CH$_3$C-3 or CH$_3$C-5).

**LRMS:** m/z (relative intensity) 416 ([M]$^+$, 0.4), 357 (2), 270 (3), 180 (100), 91 (56) (EI).

**HRMS:** m/z calcd for C$_{25}$H$_{36}$O$_5$ 416.2563, found 416.2559 (EI).
2-((2S,3S,4S,5R,6S)-5-(Benzyloxy)-3,7-dihydroxy-4,6-dimethylheptan-2-yl)-6-ethyl-3,5-dimethyl-4H-pyran-4-one (214)

Isolated as a minor compound in the preceding reaction.

$[\alpha]_D^{-19} (c \ 1.0, \text{CHCl}_3)$.

**IR** $\nu_{\text{max}}$ (Thin Film): 3399, 1653, 1592, 1557 cm$^{-1}$.

**$^1$H NMR** (500 MHz, CDCl$_3$): $\delta$ 7.25-7.26 (5H, m, ArH), 4.67 (1H, d, $J$ = 11 Hz, CHPh), 4.63 (1H, d, $J$ = 11 Hz, CHPh), 4.22 (1H, br d, $J$ = 10 Hz, HC-3'), 3.70-3.61 (3H, m, HC-5', H$_2$C-7'), 3.11 (1H, dq, $J$ = 10, 7 Hz, HC-2'), 2.64-2.49 (2H, m, H$_2$CC-6), 2.10-2.03 (2H, m, HC-6'), 2.03-1.96 (1H, m, HC-4'), 1.98 (3H, s, H$_3$CC-3), 1.91 (3H, s, $J$ = 7.5 Hz, H$_3$CC-5), 1.14 (3H, t, $J$ = 7 Hz, H$_3$CCH$_2$), 1.11 (3H, d, $J$ = 7 Hz, H$_3$C-1'), 1.03 (3H, d, $J$ = 7 Hz, H$_3$CC-6'), 1.02 (3H, d, H$_3$CC-4').

**$^{13}$C NMR** (125 MHz, CDCl$_3$): $\delta$ 180.0 (s, C-4), 164.9 (s, C-2), 164.3 (s, C-6), 138.5 (s, Ph), 128.0 (d ×2, Ph), 127.9 (d, Ph), 127.9 (d ×2, Ph), 119.7 (s, C-3), 118.1 (s, C-5), 83.8 (d, C-5'), 75.6 (t, CH$_2$Ph), 72.4 (d, C-3'), 66.2 (t, C-7'), 39.5 (d, C-2'), 38.5 (d, C-6'), 35.6 (d, C-4'), 25.0 (t, CH$_2$C-6), 14.8 (q, C-1'), 12.0 (q, CH$_3$C-6'), 11.4 (q, CH$_3$CH$_2$), 10.2 (q, CH$_3$C-4'), 9.9 (q, CH$_3$C-3 or CH$_3$C-5), 9.7 (q, CH$_3$C-3 or CH$_3$C-5).

**LRMS**: $m/z$ (relative intensity) 417 ([M+1]$^+$, 100), 236 (7), 209 (10), 181 (31) (Cl, NH$_3$).
HRMS: \( m/z \) calcd for \( C_{25}H_{36}O_5 \) 416.2563 (417.2641 for M+H), found 417.2636 (CI, NH₃).

6-Ethyl-2-((S)-1-((2S,3S,4S)-4-((4-methoxybenzyl)oxy)-3,5-dimethyl-3,4-dihydro-2\(H\)-pyran-2-yl)ethyl)-3,5-dimethyl-4\(H\)-pyran-4-one (215)

![Structural diagram]

KHMDS (0.40 mL, 0.20 mmol; 0.5 M in toluene) was added in 3 portions (0.16, 0.16 and 0.08 mL) over 20 min to a solution of 210 (24 mg, 0.08 mmol), HMPA (0.5 mL), PMBCl (50 \( \mu \)L, 56 mg, 0.36 mmol), and \( t \)-BuOH (20 mg, 0.27 mmol) in THF (5 mL) at rt under Ar. After 10 min, the mixture was diluted with ethyl acetate, washed sequentially with sat. NaHCO₃, water, and brine, dried over Na₂SO₄, concentrated, and fractionated by PTLC (80% ethyl acetate in hexanes) to give the titled compound (24 mg, 74%; unoptimized): \([\alpha]_{D} -14 \) (c 1.5, C₆H₆).

IR \( \nu_{\text{max}} \): 1656, 1610 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 7.31 (2H, ap d, \( J = 8.5 \) Hz, ArH), 6.90 (2H, ap d, \( J = 8.5 \) Hz, ArH), 5.94 (1H, s, HC-6\( '' \)), 4.62 (1H, d, \( J = 11.5 \) Hz, H₂CO), 4.39 (1H, d, \( J = 11.5 \) Hz, H₂CO), 4.19 (1H, d, \( J = 6 \) Hz, HC-4\( '' \)), 3.99 (1H, br d, \( J = 10.5 \) Hz, HC-2\( '' \)), 3.80 (3H, s, H₃CO), 3.26 (1H, dq, \( J = 10.5, 7 \) Hz, HC-1\( '' \)), 2.59 (2H, q, \( J = 7.5 \) Hz, H₂CC-6), 2.34 (1H, ddq, \( J = 1.5, 6, 7 \) Hz, HC-3\( '' \)), 1.96 (3H, s, H₃CC-3), 1.93 (3H, s, H₃CC-5), 1.54 (3H, s,
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 180.1 (s, C-4), 164.2 (s, C-6), 164.0 (s, C-2), 159.4 (s, Ar), 139.7 (d, C-6''), 130.9 (s, Ar), 129.3 (d $\times$2, Ar), 119.6 (s, C-3), 118.0 (s, C-5), 114.0 (d $\times$2, Ar), 109.4 (s, C-5''), 79.1 (d, C-2''), 75.8 (d, C-4''), 70.6 (t, CH$_2$O), 55.5 (q, CH$_3$O), 37.0 (d, C-1'), 29.8 (d, C-3''), 25.0 (t, CH$_2$C-6), 14.2 (q, CH$_3$C-1' or CH$_3$C-5'), 14.1 (q, CH$_3$C-1' or CH$_3$C-5'), 11.6 (q, CH$_3$CH$_2$), 9.7 (q $\times$2, CH$_3$C-3, CH$_3$C-5), 5.2 (q, CH$_3$C-3'').

**LRMS:** $m/z$ (relative intensity) 426 ([M]$^+$, 6), 290 (50), 221 (26), 180 (39), 121 (100) (EI).

**HRMS:** $m/z$ calcd for C$_{26}$H$_{34}$O$_5$ 426.2406, found 426.2391 (EI).

2-((2S,3S,4S,5R,6S)-3,7-Dihydroxy-5-((4-methoxybenzyl)oxy)-4,6-dimethylheptan-2-yl)-6-ethyl-3,5-dimethyl-4H-pyran-4-one (216)

Further fractionation of 80 by PTLC (10% MeOH in CH$_2$Cl$_2$) gave a pure sample (2.5 mg, 16%).

**IR** $\nu_{\text{max}}$: 3397, 1651, 1588 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.24 (2H, ap d, $J = 8.5$ Hz, ArH), 6.84 (2H, ap d, $J = 8.5$ Hz, ArH), 4.60 (1H, d, $J = 11$ Hz, CHAr), 4.55 (1H, d, $J = 11$ Hz, CHAr), 4.21 (1H, br d, $J = 10$...
Hz, HC-3'), 3.78 (3H, s, H3CO), 3.64-3.61 (3H, m, HC-5', H2C-7'), 3.15-3.07 (1H, m, HC-2'), 2.65-2.53 (2H, m, H2CC-6), 2.41 (1H, br s, HOC-3'), 2.10-2.03 (1H, m, HC-6'), 2.01-1.91 (1H, m, HC-4'), 1.99 (3H, s, H3CC-3), 1.93 (3H, s, H3CC-5), 1.17 (3H, t, J = 7.5 Hz, H3CCH2), 1.11 (3H, d, J = 7 Hz, H3C-1'), 1.03 (3H, d, J = 7 Hz, H3CC-6'), 1.01 (3H, d, J = 7 Hz, H3CC-4').

13C NMR (125 MHz, CDCl3): δ 180.0 (s, C-4), 164.8 (s, C-2), 164.2 (s, C-6), 159.6 (s, Ar), 130.5 (s, Ar), 129.6 (d x 2, Ar), 119.7 (s, C-3), 118.1 (s, C-5), 114.1 (d x 2, Ar), 83.8 (d, C-5'), 75.2 (t, CH2Ar), 72.4 (d, C-3'), 66.2 (t, C-7'), 55.5 (q, CH3O), 39.4 (d, C-2'), 38.5 (d, C-6'), 36.4 (d, C-4'), 25.0 (t, CH2C-6), 14.8 (q, C-1'), 12.2 (q, CH3C-6'), 11.5 (q, CH3CH2), 10.4 (q, CH3C-4'), 9.9 (q, CH3C-3 or CH3C-5), 9.8 (q, CH3C-3 or CH3C-5).

LRMS: m/z (relative intensity) 446 ([M]+, 1), 310 (7), 209 (12), 180 (55), 121 (100) (EI).
HRMS: m/z calcd for C26H38O6 446.2668, found 446.2672 (EI).

2-((2S,3S,4R,5R,6R)-5-(Benzyloxy)-7-hydroxy-3-(methoxymethoxy)-4,6-dimethylheptan-2-yl)-6-ethyl-3,5-dimethyl-4H-pyran-4-one (217)

2,6-Lutidine (35 µL, 38 mg, 0.36 mmol) and Et3SiOTf (57 µL, 67 mg, 0.25 mmol) were sequentially added to a stirred solution of 216 (100 mg, 0.24 mmol) in CH2Cl2 (2 mL) at room temperature under Ar. After 1 h, DIPEA (0.42 mL, 0.31 g, 2.4 mmol),
tetrabutylammonium iodide (95 mg, 0.26 mmol) and MOMCl (0.2 mL, 0.2 g, 2.4 mmol) were sequentially added and then the flask was fitted with a stopper. After 4 d, MeOH (2 mL) and tetrabutylammonium fluoride (100 mg, 0.38 mmol) were sequentially added. After 3 h, the mixture was diluted with ethyl acetate and washed sequentially with HCl (1 M), sat. NaHCO₃, and brine. The organic layer was dried over Na₂SO₄, concentrated, and fractionated by FCC (80% ethyl acetate) to give the titled compound (102 mg, 92%): [α]D -77 (c 1.5, CH₂Cl₂).

**IR** νₘₐₓ: 3419, 1654, 1609, 1593 cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 7.36-7.23 (5H, m, ArH), 4.82 (1H, d, J = 11 Hz, HCPH), 4.73 (1H, d, J = 11 Hz, HCPH), 4.29 (1H, d, J = 7 Hz, OCHO), 4.26 (1H, d, J = 7 Hz, OCHO), 4.03 (1H, br d, J = 9.5 Hz, HC-3'), 3.89 (1H, dd, J = 3, 11 Hz, HC-7'), 3.67-3.61 (1H, m, HC-7'), 3.53 (1H, br d, J = 8 Hz, HC-5'), 3.22-3.16 (1H, m, HC-2'), 3.21 (3H, s, H₃CO), 2.89 (1H, br s, HO), 2.55-2.40 (2H, m, H₂CCH₃), 2.07-1.95 (2H, m, HC-4', HC-6'), 1.97 (3H, s, H₃CC-3), 1.91 (3H, s, H₃CC-5), 1.25 (3H, d, J = 7 Hz, H₃CC-6'), 1.12 (3H, d, J = 7 Hz, H₃C-1'), 1.06 (3H, t, J = 7.5 Hz, H₃CCH₂), 0.94 (3H, d, J = 7 Hz, H₃CC-4').

**¹³C NMR** (125 MHz, CDCl₃): δ 180.0 (s, C-4), 164.7 (s, C-2), 164.2 (s, C-6), 138.8 (s, Ph), 128.6 (d ×2, Ph), 127.8 (d, Ph), 127.3 (d ×2, Ph), 119.7 (s, C-3), 118.1 (s, C-5), 98.0 (t, OCH₂O), 86.5 (d, C-5'), 82.0 (d, C-3'), 75.4 (t, CH₂Ph), 64.7 (t, C-7'), 55.7 (q, CH₃O), 39.2 (d, C-2'), 38.8 (d, C-4'), 36.5 (d, C-6'), 24.9 (t, CH₂C-6), 16.8 (q, CH₃C-6'), 15.1 (q, C-1'), 11.5 (q, CH₃CH₂), 10.5 (q, CH₃C-4'), 9.8 (q, CH₃C-3 or CH₃C-5), 9.7 (q, CH₃C-3 or CH₃C-5).

**LRMS:** m/z (relative intensity) 461 ([M+1]+, 100), 224 (43), 180 (37), 91 (15) (Cl, NH₃).
HRMS: \( m/z \) calcd for C\(_{27}\)H\(_{40}\)O\(_6\) 460.2903 (461.2903 for M+H), found 461.2918 (CI, NH\(_3\)).

(2S,3S,4R,5S,6S)-3-(Benzyloxy)-6-(6-ethyl-3,5-dimethyl-4-oxo-4\(H\) pyran-2-yl)-5-(methoxymethoxy)-2,4-dimethylheptanal (218)

IBX (50 mg, 0.14 mmol) was added to a stirred solution of 217 (56 mg, 0.12 mmol) in dry DMSO (2 mL) at room temperature under Ar. After 3 h, the mixture was diluted with ethyl acetate and washed sequentially with sat. NaHCO\(_3\), water and brine, dried over Na\(_2\)SO\(_4\), and concentrated to give the titled compound (56 mg, 100%): [\(\alpha\)]\(_D\) -52 (c 0.8, C\(_6\)H\(_6\)).

\(\text{IR } \nu_{\text{max}}: 1721, 1655, 1609 \text{ cm}^{-1}\).

\(\text{H NMR (500 MHz, C}_6\text{D}_6\): } \delta 9.64 (1H, s, HC-1), 7.32 (2H, ap d, \( J = 7.5 \text{ Hz, ArH}\)), 7.20 (2H, ap t, \( J = 7.5 \text{ Hz, ArH}\)), 7.15-7.10 (1H, ap t, \( J = 7.5 \text{ Hz, ArH}\)), 4.47 (1H, d, \( J = 11 \text{ Hz, HCPH}\)), 4.43 (1H, d, \( J = 11 \text{ Hz, HCPH}\)), 4.19 (1H, br d, \( J = 9.5 \text{ Hz, HC-5}\)), 4.19 (1H, d, \( J = 7 \text{ Hz, OCHO}\)), 4.14 (1H, d, \( J = 7 \text{ Hz, OCHO}\)), 3.84 (1H, dd, \( J = 3.5, 10 \text{ Hz, HC-3}\)), 3.00 (3H, s, H\(_3\)CO), 2.98 (1H, dq, \( J = 10, 7 \text{ Hz, HC-6}\)), 2.50 (1H, ap dq, \( J = 2, 7 \text{ Hz, HC-2}\)), 2.11 (3H, s, H\(_3\)CC-3\(')\), 2.10-2.00 (2H, m, H\(_2\)CCH\(_3\)), 1.95 (3H, s, H\(_3\)CC-5\(')\), 1.94-1.82 (1H, m, HC-4), 1.11 (3H, d, \( J = 7 \text{ Hz, H}_3\text{CC-2}\)), 0.84 (3H, d, \( J = 7 \text{ Hz, H}_3\text{C-7}\)), 0.83 (3H, t, \( J = 7.5 \text{ Hz, H}_3\text{CCH}_2\)), 0.73 (3H, d, \( J = 7 \text{ Hz, H}_3\text{CC-4}\)).
\(^{13}\text{C NMR}\) (125 MHz, C\(_6\)D\(_6\)): \(\delta\) 202.5 (d, C-1), 179.3 (s, C-4'), 164.2 (s, C-2'), 163.5 (s, C-6'), 139.4 (s, Ph), 129.0 (d \(\times\) 2, Ph), 128.7 (d, Ph), 128.1 (d \(\times\) 2, Ph), 120.1 (s, C-3'), 118.4 (s, C-5'), 98.6 (t, OCH\(_2\)O), 82.3 (d, C-5), 81.6 (d, C-3), 72.8 (t, CH\(_2\)Ph), 55.9 (q, CH\(_3\)O), 48.6 (d, C-2), 39.3 (d, C-6), 38.2 (d, C-4), 24.9 (t, CH\(_2\)C-6'), 15.0 (q, C-7), 11.7 (q, CH\(_3\)CH\(_2\)), 10.2 (q, CH\(_3\)), 10.1 (q \(\times\) 2, CH\(_3\) \(\times\) 2), 9.6 (q, CH\(_3\)C-2).

**LRMS**: \(m/z\) (relative intensity) 459 ([M+1]+, 100), 351 (51), 224 (76), 180 (16), 91 (14) (Cl, NH\(_3\)).

**HRMS**: \(m/z\) calcd for C\(_{27}\)H\(_{38}\)O\(_6\) 458.2668 (459.2747 for M+H), found 459.2741 (Cl, NH\(_3\)).

\((2R,3R,4R,5S,6S)-3-(\text{Benzyloxy})-6-(6\text{-ethyl-3,5-dimethyl-4-oxo-4H-pyran-2-yl})-2,4\)-dimethylheptane-1,5-diyldiacetate (219)

Acetic anhydride (0.2 mL, 0.2 g, 2 mmol) and DMAP (70 mg, 0.57 mmol) were added to a stirred solution of 216 (67 mg, 0.16 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at room temperature. After 3 h, the mixture was concentrated and the residue fractionated by FCC (80% ethyl acetate in hexanes) to give the titled compound (78 mg, 97%).

**IR** \(\nu_{\text{max}}\): 1737, 1656, 1610 cm\(^{-1}\).
^1H NMR (500 MHz, CDCl₃): δ 7.38-7.34 (2H, m, Ph), 7.32 (2H, m, Ph), 7.29-7.24 (1H, m, Ph), 5.50 (1H, br d, J = 10 Hz, HC-5), 4.60-4.54 (2H, m, H₂CPh), 4.29 (1H, dd, J = 5, 11 Hz, HC-1), 4.04 (1H, dd, J = 8, 11 Hz, HC-1), 3.23 (1H, dq, J = 10, 7 Hz, HC-6), 3.16 (1H, dd, J = 3.5, 8.5 Hz, HC-3), 2.61-2.47 (2H, m, H₂CCH₃), 2.24 (1H, dddq, J = 3.5, 5, 8, 7 Hz, HC-2), 2.09 (1H, ddq, J = 8.5, 10, 7 Hz, HC-4), 2.05 (3H, s, H₃COOC-5), 1.96 (3H, s, H₃CC-3'), 1.91 (3H, s, H₃CC-5'), 1.76 (3H, s, H₃CCOOCC-1), 1.17 (3H, d, J = 7 Hz, H₃CC-2), 1.15 (3H, t, J = 7.5 Hz, H₂CCH₂), 1.14 (3H, d, J = 7 Hz, H₃CC-6), 1.05 (3H, d, J = 7 Hz, H₃CC-4).

^13C NMR (125 MHz, CDCl₃): δ 179.9 (s, C-4'), 171.3 (s, COOC-5 ), 169.9 (s, COOC-1), 164.9 (s, C-6'), 163.1 (s, C-2'), 138.9 (s, Ph), 128.4 (d x2, Ph), 127.8 (d x2, Ph), 127.7 (d, Ph), 119.5 (d, C-3'), 117.9 (d, C-5'), 83.9 (d, C-3), 75.6 (t, CH₂Ph), 74.3 (d, C-5), 66.0 (t, C-1), 37.7 (d, C-6), 37.1 (d, C-4), 35.3 (d, C-2), 24.9 (t, CH₃CH₂), 21.2 (q, CH₃COOC-5 ), 20.8 (q, CH₃COOC-1), 16.3 (q, CH₃C-6), 14.5 (q, CH₃C-2), 11.2 (q, CH₃CH₂), 10.4 (q, CH₃C-4), 9.8 (q, CH₃C-3' or CH₃C-5'), 9.7 (q, CH₃C-3' or CH₃C-5').

LRMS: m/z (relative intensity) 500 ([M]^+, 4), 394 (19), 335 (34), 251 (13), 180 (86), 91 (100) (EI)

HRMS: m/z calcd. for C₂₉H₄₀O₇ 500.2774, found 500.2774 (EI).
K₂CO₃ (109 mg, 0.79 mmol) was added to a stirred solution of 219 (78 mg, 0.16 mmol) in MeOH (8 mL) and water (0.4 mL). After 3 h at rt, the mixture was diluted with water and extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, and concentrated to give the titled compound (71 mg, 99%): [α]D -84 (c 1.5, C₆H₆).

IR νmax: 3432, 1737, 1653, 1609, 1593 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.38 (2H, ap d, J = 7 Hz, Ph), 7.35-7.27 (3H, m, Ph), 5.53 (1H, br d, J = 10 Hz, HC-3), 4.65 (1H, d, J = 10 Hz, HCPH), 4.58 (1H, d, J = 10 Hz, HCPH), 3.86 (1H, dd, J = 4, 11 Hz, HC-7), 3.64 (1H, dd, J = 4, 11 Hz, HC-7), 3.28-3.20 (2H, m, HC-2, HC-4), 2.71 (1H, br s, HO), 2.62-2.49 (2H, m, H₂CCH₃), 2.12 (1H, dq, J = 8.5, 7 Hz, HC-4), 2.05-2.12 (1H, m, HC-6), 1.96 (3H, s, H₃CC-3’), 1.92 (3H, s, H₃CC-5’), 1.77 (3H, s, H₃CCO), 1.23 (3H, d, J = 7 Hz, H₃CC-6), 1.17 (3H, d, J = 7 Hz, H₃CC-2), 1.17 (3H, t, J = 7.5 Hz, H₃CCH₂), 1.02 (3H, d, J = 7 Hz, H₃CC-4).

¹³C NMR (125 MHz, CDCl₃): δ 179.9 (s, C-4’), 169.9 (s, COOC-3), 164.9 (s, C-6’), 163.0 (s, C-2’), 138.4 (s, Ph), 128.6 (d x2, Ph), 128.1 (d x2, Ph), 128.0 (d, Ph), 119.5 (s, C-3’), 117.9 (s,
C-5'), 86.1 (d, C-5), 76.1 (t, CH₂Ph), 74.2 (d, C-3), 64.6 (t, C-7), 37.7 (d, C-2), 37.5 (d, C-4), 36.8 (d, C-6), 24.9 (t, CH₂CH₃), 20.8 (q, CH₃COOC-3), 16.5 (q, CH₃C-6), 14.5 (q, CH₃C-2), 11.3 (q, CH₃CH₂), 10.6 (q, CH₃C-4), 9.8 (q, CH₃C-3' or CH₃C-5'), 9.7 (q, CH₃C-3' or CH₃C-5').

**LRMS:** m/z (relative intensity) 458 ([M]⁺, 5), 399 (12), 352 (19), 293 (17), 251 (10), 180 (100), 91 (90) (EI).

**HRMS:** m/z calcd. for C₂₇H₃₈O₆ 458.2668, found 458.2669 (EI).

(2S,3S,4R,5S,6S)-5-(Benzyloxy)-2-(6-ethyl-3,5-dimethyl-4-oxo-4H-pyran-2-yl)-4,6-dimethyl-7-oxoheptan-3-yl Acetate (221)

![Structure of 221](image)

IBX (30 mg, 0.11 mmol) was added to a stirred solution of 220 (30 mg, 0.066 mmol) in dry DMSO (2 mL) at rt. The solution was stirred for 5 hours at rt and added to ethyl acetate. The organic layer was washed with sat. NaHCO₃, water, and brine, dried over Na₂SO₄, and concentrated to give the titled compound (26 mg, 87%).

**¹H NMR** (500 MHz, CDCl₃):  δ 9.81 (1H, br s, HC-7), 7.38 (2H, ap d, J = 7.5 Hz, Ph), 7.35-7.27 (3H, m, Ph), 5.62 (1H, br d, J = 10 Hz, HC-3), 4.56-4.49 (2H, m, H₂CPh), 3.57 (1H, dd,
$J = 3, 9 \text{ Hz}, \text{HC-5}$), 3.27 (1H, dq, $J = 10, 7 \text{ Hz}, \text{HC-2}$), 2.84 (1H, ddq, $J = <1, 3, 7 \text{ Hz}, \text{HC-6}$), 2.65-2.49 (2H, m, H$_2$CCH$_3$), 2.08 (1H, dq, $J = 9, 7 \text{ Hz}, \text{HC-4}$), 1.95 (3H, s), 1.93 (3H, s), 1.81 (3H, s), 1.25 (3H, d, $J = 7 \text{ Hz}$), 1.18 (3H, t, $J = 7.5 \text{ Hz}, \text{H}_3\text{CCH}_2$), 1.16 (3H, d, $J = 7 \text{ Hz}$), 0.91 (3H, d, $J = 7 \text{ Hz}$).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 203.9, 180.0, 169.9, 165.0, 163.0, 138.2, 128.5, 128.2, 128.0, 119.5, 117.9, 81.7, 74.0, 73.9, 48.6, 37.5, 37.0, 24.9, 20.8, 14.4, 11.2, 10.1, 9.9, 9.8, 9.7.

LRMS: $m/z$ (relative intensity) 456 ([M]$^+$, 1), 321 (8), 180 (100), 91 (58) (EI).

HRMS: $m/z$ calcd. for C$_{27}$H$_{36}$O$_6$ 456.2512, found 456.2491 (EI).

2-((2S,3S,4R,5R,6R,7R)-5-(Benzyloxy)-7-hydroxy-3-(methoxymethoxy)-7-((3S,5S)-5-((R)-(methoxymethoxy)((S)-1,4-dioxo-8-thiaspiro[4.5]decan-6-yl)methyl)-4-oxotetrahydro-2H-thiopyran-3-yl)-4,6-dimethylheptan-2-yl)-6-ethyl-3,5-dimethyl-4H-pyran-4-one (223)

A solution of TiCl$_4$ (30 $\mu$L, 52 mg, 0.27 mmol) in CH$_2$Cl$_2$ (0.3 mL) was added to a stirred solution of 222 (88 mg, 0.25 mmol) in CH$_2$Cl$_2$ (6 mL) at -78 °C under Ar. The resulting yellow suspension was stirred for 2 min and then DIPEA (130 $\mu$L, 96 mg, 0.74 mmol) was
added. The resulting red solution was stirred for 1.5 hrs and then a solution of 218 (56 mg, 0.12 mmol) in CH₂Cl₂ (0.5 mL plus 2 x 0.5 mL rinses) was added dropwise via syringe. Over the course of 3 h, the red color faded to orange. The mixture was diluted with ethyl acetate and washed sequentially with sat. NH₄Cl (x2), sat. NaHCO₃, water, and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (50-70% ethyl acetate in hexanes) to give recovered ketone (46 mg, 52%) and the titled compound essentially as a single diastereomer (dr>20:1 by ¹H NMR) (78 mg, 79%): [α]D -69 (c 0.7, C₆H₆).

IR νmax: 3456, 1706, 1654, 1609 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.35-7.26 (5H, m, ArH), 4.85 (1H, d, J = 11 Hz, HCPH), 4.81 (1H, d, J = 11 Hz, HCPH), 4.68 (1H, d, J = 5.5 Hz, HCO-1‴′), 4.57 (1H, d, J = 5.5 Hz, HCO-1‴), 4.47 (1H, br d, J = 9.5 Hz, HC-7‴), 4.29-4.23 (2H, m, HC-1‴, HCOC-3‴), 4.15 (1H, d, J = 7 Hz, HCOC-3‴), 4.14-3.92 (5H, m, HC-3‴, H₂CO ×2), 4.12 (1H, s, HO), 3.60 (1H, br d, J = 10 Hz, HC-5‴), 3.35 (3H, s, H₃CO), 3.25 (3H, s, H₃CO), 3.27-3.17 (2H, m, HC-2‴, HC-2″), 3.11-3.00 (2H, m, HC-3‴, HC-6‴), 2.92-2.81 (3H, m, HC-2‴′, HC-5‴′), 2.81-2.71 (3H, m, H₂C-7‴, HC-9‴), 2.56-2.37 (3H, m, H₂CC-6. HC-9‴′), 2.22-2.09 (3H, m, HC-4‴, HC-6‴′, HC-10‴′), 2.02-1.94 (1H, m, HC-6‴′), 1.97 (3H, s, H₃CC-3‴), 1.91 (3H, s, H₃CC-5‴), 1.65 (1H, ddd, J = 3, 12, 13.5 Hz, HC-10‴′), 1.24 (3H, d, J = 7 Hz, H₃CC-6‴′), 1.15 (3H, d, J = 7 Hz, H₃C-1‴), 1.04 (3H, t, J = 7.5 Hz, H₂CCH₂), 1.00 (3H, d, J = 7 Hz, H₃C 4‴).

¹³C NMR (125 MHz, CDCl₃): δ 210.1 (d, C-4‴), 180.0 (s, C-4), 164.7 (s, C-2), 164.1 (s, C-6), 138.4 (s, Ph), 128.7 (d ×2, Ph), 127.9 (d, Ph), 127.2 (d ×2, Ph), 119.8 (s, C-3), 118.2 (s, C-5), 108.7 (s, C-5‴), 97.8 (t, CH₂OC-3‴), 97.4 (t, CH₂OC-1‴″), 88.4 (d, C-5‴′), 82.3 (d, C-3‴),

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75.9 (t, CH$_2$Ph), 74.2 (d, C-1''), 68.5 (d, C-7'), 64.9 (t, CH$_2$O), 64.7 (t, CH$_2$O), 59.1 (d, C-5''), 56.3 (q, CH$_3$O), 55.7 (q, CH$_3$O), 53.7 (d, C-3''), 50.2 (d, C-6''), 39.2 (d, C-2'''), 38.4 (d, C-4''), 36.1 (t, C-10''), 35.6 (d, C-6'), 32.0 (t, C-7''), 31.9 (t, C-2''), 28.4 (t, C-7''''), 26.8 (t, C-9''), 24.9 (t, CH$_2$C-6), 15.3 (q, C-1'), 13.0 (q, CH$_3$C-6'), 11.6 (q, CH$_3$CH$_2$), 10.2 (q, CH$_3$C-4'), 9.8 (q, CH$_3$C-3 or CH$_3$C-5), 9.7 (q, CH$_3$C-3 or CH$_3$C-5).

**LRMS**: m/z (relative intensity) 829 ([M+23]$^+$, 35), 807 ([M+1]$^+$, 100), 459 (4), 351 (6) (ESI).

**HRMS**: m/z calcd for C$_{42}$H$_{62}$O$_{11}$S$_2$ 806.3634 (807.3812 for [M+H]$^+$), found 807.3816 (ESI).

2-((S)-1-((2S,3R,4S,5S,6S)-4-(Benzyloxy)-6-methoxy-3,5-dimethyltetrahydro-2$H$-pyran-2-yl)ethyl)-6-ethyl-3,5-dimethyl-4$H$-pyran-4-one (226)

![Structure](image)

FeCl$_3$$\cdot$6H$_2$O (34 mg, 0.13 mmol) was added to a stirred solution of 223 (34 mg, 0.042 mmol) in acetone (12 mL) and methanol (0.6 mL) and the resulting yellow solution was heated under reflux. After 3.5 h, the mixture was diluted with CH$_2$Cl$_2$ and washed sequentially with water and brine. The aqueous layers were back extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and fractionated by PTLC (90% ethyl acetate in hexanes) to give the putative deprotected compound (12 mg, crude) that was insufficiently pure for characterization (and could not be purified further) and the titled compound (7 mg, 39%): [$\alpha$]$_D$ 34 (c 0.4, C$_6$H$_6$).
IR $\nu_{\text{max}}$: 1656, 1612 cm$^{-1}$.

$^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 7.31 (2H, ap d, $J = 7.5$ Hz, Ph), 7.19 (2H, ap d, $J = 7.5$ Hz, Ph), 7.10 (1H, ap t, $J = 7.5$ Hz, Ph), 4.32-4.16 (3H, m, HC-6', H$_2$CPh), 3.97 (1H, dd, $J = 2.5$, 10.5 Hz, HC-2'), 3.89 (1H, dd, $J = 5.5$, 5.5 Hz, HC-4'), 3.12 (1H, dq, $J = 10.5$, 7 Hz, HC-1'), 2.81 (3H, s, H$_3$CO), 2.24 (3H, s, H$_3$CC-3), 2.26-2.05 (4H, m, HC-5', 3', H$_2$CCH$_3$), 1.99 (3H, s, H$_3$CC-5), 1.06 (3H, d, $J = 7$ Hz, H$_3$CC-5'), 1.06 (3H, d, $J = 7$ Hz, H$_3$CC-3'), 0.92 (3H, t, $J = 7.5$ Hz, H$_3$CCH$_2$), 0.88 (3H, d, $J = 7$ Hz, H$_3$CC-1').

$^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 179.3 (s, C-4), 164.1 (s, C-2), 163.2 (s, C-6), 139.8 (s, Ph), 128.9 (d x2, Ph (DEPT)), 128.0 (d, Ph), 127.9 (d x2, Ph (DEPT)), 120.5 (s, C-3), 118.6 (s, C-5), 104.7 (d, C-6'), 76.0 (d, C-4'), 71.9 (d, C-2'), 70.1 (t, CH$_2$Ph), 54.5 (q, CH$_3$O), 37.3 (d, C-1'), 37.1 (d, C-5'), 34.0 (d, C-3'), 25.0 (t, CH$_2$CH$_3$), 13.7 (q, CH$_3$C-5'), 13.5 (q, CH$_3$C-1'), 11.8 (q, CH$_3$CH$_2$), 10.5 (q, CH$_3$C-3), 10.2 (q, CH$_3$C-5), 8.1 (q, CH$_3$C-3').

LRMS: $m/z$ (relative intensity): 429 ([M+1]$^+$, 100) (ESI).

HRMS: $m/z$ calcd. for C$_{26}$H$_{36}$O$_5$ 428.2563 (429.2635 for [M+H]$^+$), found 429.2635 (ESI).
(4S,5S,8S,9R,10R,11S,12S,13S,14S)-11-(Benzyloxy)-14-(6-ethyl-3,5-dimethyl-4-oxo-4H-pyran-2-yl)-5,9,13-trihydroxy-4,6,8,10,12-pentamethylpentadecane-3,7-dione (227)

From aldol 223. Raney nickel (W2; 0.5 mL settled volume) was washed with THF (x3) and then transferred to a solution of 223 (42 mg, 0.052 mmol) in THF (5 mL) and the resulting suspension was heated under reflux with vigorous stirring. After 3 h, the mixture was allowed to settle and then decanted. The solid was suspended in THF (10 mL), heated under reflux for 10 min, and decanted. This washing procedure was repeated with ethyl acetate and then acetone. The combined organic layers were filtered through Celite® and concentrated to give the crude desulfurized product (40 mg). A solution of FeCl₃•6H₂O (40 mg, 0.15 mmol) in acetone (1 mL) was added to a solution of the residue (40 mg) in acetone (5 mL) and methanol (0.3 mL) and the resulting yellow solution was heated under reflux. After 5 h, the mixture was diluted with ethyl acetate and washed sequentially with sat. NH₄Cl (x2), sat. NaHCO₃, and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by PTLC (80% ethyl acetate in hexanes) to give the titled compound (27 mg, 84%): [α]D -33 (c 1, C₆H₆).

From bisTES 229. HF•pyridine (0.13 mL) was added to a stirred solution of 229 (20 mg, 0.024 mmol) in THF (2 mL), pyridine (0.4 mL), and water (50 μL) at room temperature.
After 24 h, the mixture was diluted with ethyl acetate and washed sequentially with 0.2 M aq. citric acid (x2), sat. NaHCO₃, and brine. The organic layer was concentrated and fractionated by PTLC (80% ethyl acetate in hexanes) to give the titled compound (14 mg, 96%).

**IR** $\nu_{\text{max}}$: 3450, 1708, 1652, 1588 cm$^{-1}$.

**$^1$H NMR** (500 MHz, C$_6$D$_6$): $\delta$ 7.52 (2H, ap d, $J = 7.5$ Hz, ArH), 7.22-7.12 (3H, m, ArH), 5.14 (1H, d, $J = 11$ Hz, HCPH), 4.75 (1H, d, $J = 11$ Hz, HCPH), 4.60 (1H, br d, $J = 9.5$ Hz, HC-9), 4.46 (1H, br d, $J = 9.5$ Hz, HC-13), 4.19 (1H, dd, $J = 4$, 8 Hz, HC-5), 3.92 (1H, br d, $J = 9$ Hz, HC-11), 3.11 (1H, dq, $J = 9.5$, 7 Hz, HC-14), 2.88 (1H, dq, $J = 9.5$, 7 Hz, HC-8), 2.67 (1H, dq, $J = 8$, 7 Hz, HC-6), 2.39 (1H, br dq, $J = 9$, 7 Hz, HC-12), 2.22 (1H, dq, $J = 4$, 7 Hz, HC-4), 2.18-1.87 (8H, m, H$_2$C-2, HC-10, H$_2$CC-6), 2.09 (3H, s, H$_3$CC-3’), 1.60 (3H, s, H$_3$CC-5’), 1.45 (3H, d, $J = 7$ Hz, H$_3$CC-8), 1.23 (3H, d, $J = 7$ Hz, H$_3$CC-10), 1.22 (3H, d, $J = 7$ Hz, H$_3$CC-12), 0.96 (3H, d, $J = 7$ Hz, H$_3$CC-4), 0.91 (3H, d, $J = 7$ Hz, H$_3$CC-14), 0.90 (3H, t, $J = 7.5$ Hz, H$_3$C-1), 0.85 (3H, t, $J = 7.5$ Hz, H$_3$CCH$_2$), 0.80 (3H, d, $J = 7$ Hz, H$_3$CC-6).

**$^{13}$C NMR** (125 MHz, C$_6$D$_6$): $\delta$ 217.5 (s, C-7), 214.1 (s, C-3), 180.3 (s, C-4’), 166.3, 164.4 (s, C-6’), 139.7 (s, Ph), 129.1 (d $\times$2, Ph), 128.6 (d $\times$2), 128.2 (d, Ph), 120.3 (s, C-3’), 117.9 (s, C-5’), 88.2 (d, C-11), 77.0 (t, CH$_2$Ph), 73.3 (d, C-5), 72.1 (d, C-13), 71.4 (d, C-9), 50.6 (d, C-8), 48.5 (d, C-6), 48.0 (d, C-4), 40.8 (d, C-14), 38.1 (d, C-12), 36.8 (d, C-10), 34.7 (t, C-2), 25.2 (t, CH$_2$C-6’), 14.9 (q, H$_3$CC-8), 14.4 (q, H$_3$CC-14), 14.0 (q, H$_3$CC-6), 12.9 (q, H$_3$CC-10), 11.5 (q, H$_3$CCH$_2$), 10.7 (q, H$_3$CC-3’), 10.5 (q, H$_3$CC-4), 9.9 (q, H$_3$CC-5’), 9.3 (q, H$_3$CC-12), 8.1 (q, H$_3$C-1).

**LRMS**: $m/z$ (relative intensity) 637 ([M+23]$^+$, 25), 615 ([M+1]$^+$, 100), 599 (15), 501 (20) (ESI).
**HRMS:** \( m/z \) calcd for \( C_{36}H_{54}O_8 \) 614.3819 (615.3897 for [M+H]+), found 615.3883 (ESI).

\((4S,5S,6S,8S,9R,10R,11S,12S,13S,14S)-11-(Benzyloxy)-14-(6-ethyl-3,5-dimethyl-4-oxo-4H-pyran-2-yl)-9,13-dihydroxy-4,6,8,10,12-pentamethyl-5-((triethylsilyl)oxy)pentadecane-3,7-dione (228)\)

Triethylsilyltriflate (25 μL, 29 mg, 0.11 mmol) was added to a stirred solution of 2,6-lutidine (50 μL, 50 mg, 0.47 mmol) and 227 (33 mg, 0.054 mmol) in dry CH\(_2\)Cl\(_2\) (3 mL) at 0 °C under Ar. After 1 h, the mixture was diluted with ethyl acetate and washed with 0.2 M citric acid (x2), sat. NaHCO\(_3\), and brine. The organic layer was dried over Na\(_2\)SO\(_4\), concentrated, and fractionated by PTLC (80% ethyl acetate in hexanes) to give the 229 (20 mg, 44%) and the titled compound (18 mg, 46% [80% BORSM]): \([\alpha]_D\) 1.0 (c 1.3, C\(_6\)H\(_6\)).

**IR** \( \nu_{\text{max}} \): 3422, 1711,1652, 1590 cm\(^{-1}\).

**\(^1\)H NMR** (500 MHz, C\(_6\)D\(_6\)): \( \delta \) 7.49 (2H, ap d, \( J = 7 \) Hz, ArH), 7.22-7.10 (3H, m, ArH), 5.08 (1H, d, \( J = 11 \) Hz, CHPh), 4.71 (1H, d, \( J = 11 \) Hz, CHPh), 4.64 (1H, dd, \( J = 4, 7 \) Hz, HC-5), 4.54 (1H, br d, \( J = 9 \) Hz, HC-9), 4.42 (1H, br d, \( J = 10 \) Hz, HC-13), 3.89-3.81 (2H, m, HC-11, HOC-11), 3.11-3.08 (1H, m, HC-14), 2.93 (1H, dq, \( J = 9, 7 \) Hz, HC-8), 2.88 (1H, dq,
$J = 7, 7 \text{ Hz, HC-6}$, 2.47 (1H, dq, $J = 4, 7 \text{ Hz, HC-4}$), 2.41-2.29 (2H, m, HC-2, HC-12), 2.16-2.06 (3H, m, HC-2, H$_2$CC-6'), 2.08 (3H, s, H$_3$CC-3'), 2.00 (1H, br q, $J = 7 \text{ Hz, HC-10}$), 1.63 (3H, s, H$_3$CC-5'), 1.46 (3H, d, $J = 7 \text{ Hz, H}_3\text{CC-8}$), 1.20 (3H, d, $J = 7 \text{ Hz, H}_3\text{CC-10}$), 1.15 (3H, d, $J = 7 \text{ Hz, H}_3\text{CC-12}$), 1.08-1.04 (6H, m, H$_3$C-1, H$_3$C-4), 1.05 (9H, t, $J = 8 \text{ Hz, H}_3\text{CCSi} \times 3$), 0.94 (3H, d, $J = 7 \text{ Hz, H}_3\text{CC-6}$), 0.87 (3H, d, $J = 7.5 \text{ Hz, H}_3\text{CC-14}$), 0.84 (3H, t, H$_3$CCH$_2$), 0.76-0.70 (6H, m, H$_2$CSi $\times 3$).

$^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 214.5 (s, C-7), 211.8 (s, C-3), 180.1 (s, C-4'), 166.0 (s, C-2'), 164.2 (s, C-6'), 139.6 (s, Ph), 129.1 (d $\times 2$, Ph), 128.7 (d $\times 2$, Ph), 128.6 (d, Ph), 120.3 (s, C-3), 117.9 (s, C-5), 88.2 (d, C-11), 77.0 (t, CH$_2$Ph), 73.3 (d, C-5), 72.1 (d, C-13), 71.8 (d, C-9), 52.1 (d, C-6), 50.1 (d, C-8), 49.1 (d, C-4), 40.7 (d, C-14), 38.0 (d, C-12), 36.6 (d, C-10), 35.3 (t, C-2), 25.1 (t, CH$_2$C-6'), 14.7 (q, CH$_3$C-8), 14.4 (q, CH$_3$C-14), 13.00 (q, CH$_3$C-6 or CH$_3$C-10), 12.96 (q, CH$_3$C-6 or CH$_3$C-10), 12.4 (q, CH$_3$C-4), 11.5 (q, CH$_3$CH$_2$), 10.7 (q, CH$_3$C-3'), 9.9 (q, CH$_3$C-5'), 9.3 (q, CH$_3$C-12), 8.2 (q, C-1), 7.7 (q $\times 3$, (CH$_3$CH$_2$)$_3$Si), 5.9 (t $\times 3$, (CH$_3$CH$_2$)$_3$Si).

LRMS: m/z (relative intensity) 751 ([M+23]$^+$, 10), 729 ([M+1]$^+$,100) (ESI).

HRMS: m/z calcd for C$_{42}$H$_{68}$O$_8$Si 728.4883 (729.4756 for [M+H]$^+$), found 729.4762 (ESI).
(4S,5S,6S,8S,9R,10S,11S,12S,13S,14S)-11-(Benzyloxy)-14-(6-ethyl-3,5-dimethyl-4-oxo-4H-pyran-2-yl)-13-hydroxy-4,6,8,10,12-pentamethyl-5,9-bis((triethylsilyl)oxy)pentadecane-3,7-dione (229)

\[
\begin{align*}
\text{IR } \nu_{\text{max}}: & \ 3374, 1713, 1655, 1610, 1593 \ \text{cm}^{-1}. \\
^{1}H \text{ NMR} \ (500 \ \text{MHz}, \ C_{6}D_{6}): & \ \delta \ 7.41 \ (2H, \text{ ap d, } J = 7.5 \ \text{Hz, ArH}), \ 7.20-7.10 \ (2H, \text{ m, ArH}), \ 7.05 \ (1H, \text{ ap t, } J = 7 \ \text{Hz, ArH}), \ 4.74-4.66 \ (2H, \text{ m, H}_{2}CPh), \ 4.61 \ (1H, \text{ dd, } J = 5, 6 \ \text{Hz, HC-5}), \ 4.44 \ (1H, \text{ br d, } J = 6.5 \ \text{Hz, HC-9}), \ 4.32 \ (1H, \text{ br d, } J = 10 \ \text{Hz, HC-13}), \ 3.52 \ (1H, \text{ br d, } J = 8.5 \ \text{Hz, HC-11}), \ 3.40 \ (1H, \text{ br s, HO}), \ 3.07 \ (1H, \text{ dq, } J = 6, 7 \ \text{Hz, HC-14}), \ 2.96-2.89 \ (2H, \text{ m, HC-6, HC-8}), \ 2.53 \ (1H, \text{ dq, } J = 5, 7 \ \text{Hz, HC-4}), \ 2.33 \ (1H, \text{ dq, } J = 18, 7.5 \ \text{Hz, HC-2}), \ 2.24 \ (3H, \text{ s, H}_{3}CC-16), \ 2.17 \ (2H, \text{ ap q, } J = 7.5 \ \text{Hz, H}_{2}CC-6'), \ 2.15-2.03 \ (2H, \text{ m, HC-2, HC-10}), \ 2.01-1.94 \ (1H, \text{ m, HC-12}), \ 1.97 \ (3H, \text{ s, H}_{3}CC-5'), \ 1.25 \ (3H, \text{ d, } J = 7 \ \text{Hz, H}_{3}CC-8), \ 1.15 \ (3H, \text{ d, } J = 7 \ \text{Hz, H}_{3}CC-12), \ 1.09-0.95 \ (27H, \text{ m, H}_{3}C-1, H_{3}C-4, H_{3}C-6, H_{3}CCSi \times 6), \ 1.00-0.95 \ (9H, \text{ m, H}_{3}C-10, H_{3}C-14, H_{3}CCH_{2}C-6'), 1.76-0.68 \ (12H, \text{ m, H}_{2}CSi \times 6).
\end{align*}
\]

\[
\begin{align*}
^{13}C \text{ NMR} \ (125 \ \text{MHz}, \ C_{6}D_{6}): & \ \delta \ 213.6 \ (s, \text{ C-7}), \ 212.0 \ (s, \text{ C-3}), \ 179.4 \ (s, \text{ C-4'}), \ 164.4 \ (s, \text{ C-2'}), \ 163.2 \ (s, \text{ C-6'}), \ 138.4 \ (s, \text{ Ph}), \ 129.2 \ (d \times 2, \text{ Ph}), \ 128.7 \ (d, \text{ Ph}), \ 128.1 \ (d \times 2, \text{ Ph}), \ 120.1 \ (s, \text{ C-3'}), \ 118.4 \ (s, \text{ C-5'}), \ 88.4 \ (d, \text{ C-11}), \ 76.8 \ (t, \text{ CH}_{2}\text{Ph}), \ 74.4 \ (d, \text{ C-9}), \ 73.0 \ (d, \text{ C-5}), \ 72.5 \ (d, \text{ C-13}), \ 53.1 \ (d, \text{ C-6}), \ 52.2 \ (d, \text{ C-8}), \ 48.9 \ (d, \text{ C-4}), \ 41.7 \ (d, \text{ C-10}), \ 39.5 \ (d, \text{ C-14}), \ 35.5 \ (d, \text{ C-}
\end{align*}
\]

[α]_D 30 (c 1.3, C₆H₆).
12), 35.4 (t, C-2), 25.0 (t, CH<sub>2</sub>-6'), 14.6 (q, CH<sub>3</sub>-8 or CH<sub>3</sub>-14), 14.5 (q, CH<sub>3</sub>-8 or CH<sub>3</sub>-14), 13.1 (q, CH<sub>3</sub>-4), 12.4 (q ×2, CH<sub>3</sub>-6, CH<sub>3</sub>-10 or CH<sub>3</sub>-12), 11.9 (q, CH<sub>3</sub>-10 or CH<sub>3</sub>-12), 11.6 (q, CH<sub>3</sub>CH<sub>2</sub>), 10.5 (q, CH<sub>3</sub>-C-3'), 10.2 (q, CH<sub>3</sub>-C-5'), 8.2 (q, C-1), 7.8 (q ×3, (CH<sub>3</sub>CH<sub>2</sub>)<sub>3</sub>Si), 7.7 (q ×3, (CH<sub>3</sub>CH<sub>2</sub>)<sub>3</sub>Si), 6.7 (t ×3, (CH<sub>3</sub>CH<sub>2</sub>)<sub>3</sub>Si), 5.9 (t ×3, (CH<sub>3</sub>CH<sub>2</sub>)<sub>3</sub>Si).

**LRMS:** m/z (relative intensity) 865 ([M+23]<sup>+</sup>, 25), 843 ([M+1]<sup>+</sup>, 100) (ESI).

**HRMS:** m/z calcd for C<sub>48</sub>H<sub>82</sub>O<sub>8</sub>Si<sub>2</sub> 842.5548 (843.5626 for [M+H]<sup>+</sup>), found 843.5630 (ESI).

(4S,5S,6S,10S,11S,12R,14R)-11-(Benzyloxy)-14-(6-ethyl-3,5-dimethyl-4-oxo-4H-pyran-2-yl)-4,6,8,10,12-pentamethyl-5-((triethylsilyl)oxy)pentadecane-3,7,9,13-tetraone (230)

IBX (70 mg, 0.25 mmol) was added to a solution of 228 (22 mg, 0.03 mmol) in anhydrous DMSO (4 mL) at rt. After 2 d, the mixture was diluted with ethyl acetate and washed sequentially with sat. NaHCO<sub>3</sub>, water, and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated, and fractionated by PTLC (60% ethyl acetate in hexanes) to give the titled compound (18 mg, 82%) as a 25:65:10 mixture of enol and 2 keto forms (by <sup>1</sup>H NMR), respectively.

Only partial data reported.
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 17.22 (0.25H, s), 7.39-7.12 (5H, m), 4.57-4.28 (3H, m), 4.20-3.84 (2.7H, m), 3.38-2.78 (3H, m), 2.78-2.40 (5H, m), 2.03 (3H, s), 1.96 (3H, s), 1.90 (0.7H, s), 1.32-0.85 (33H, m), 0.65-0.45 (6H, m).

$^{13}$C NMR (125 MHz, CDCl$_3$) partial data: $\delta$ 195.8 & 194.5 (enol form), 84.5 & 84.3 & 83.7 (C-11, 3 major forms), 60.8 & 60.6 (C-8 of $\beta$-diketone form, 2 diastereomers).

LRMS: m/z (relative intensity) 747 ([M+23]$^+$, 100), 725 ([M+1]$^+$, 40), 543 (5), 521 (2), 255 (4) (ESI).

HRMS: m/z calcd for C$_{42}$H$_{64}$O$_8$Si 724.4371 (725.4443 for [M+H]$^+$), found 725.4454 (ESI).

(4S,5S,6S,8RS,10S,11S,12R,14R)-14-(6-Ethyl-3,5-dimethyl-4-oxo-4$H$-pyran-2-yl)-5,11-dihydroxy-4,6,8,10,12-pentamethylpentadecane-3,7,9,13-tetraone (14/15)

Raney nickel (W2; 0.2 mL settled volume) was added to a solution of 230 (8 mg, 0.011 mmol) in EtOH (2 mL) at rt and the resulting suspension was heated under reflux with vigorous stirring. After 50 min, the mixture was allowed to settle and then was decanted. The solid was suspended in ethyl acetate, heated under reflux for 10 min, and decanted. This washing procedure was repeated with ethyl acetate and then acetone. The organic layers were filtered over Celite® and the combined filtrates were concentrated. The residue was taken up
in THF (2 mL) and pyridine (0.4 mL, 0.4 g, 5 mmol), water (50 µL, 50 mg, 3 mmol), and HF•pyridine (0.13 mL) were sequentially added to the stirred solution at rt. After 4 h, the mixture was diluted with ethyl acetate and washed with 0.2 M citric acid (x2), sat. NaHCO₃, and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated and fractionated by PTLC (40% acetone in hexanes) to give the titled compound (5 mg, 87%) that was a complicated 8: 3: 1: 16 mixture of hemiacetals along with small amounts of keto-enol tautomers and a trace of siphonarin B (4) (by NMR).

The ratio of isomers present remained essentially unchanged on standing in CDCl₃ solution at ambient temperature; however, after 28 days the ratio of the major hemiacetals was 3:2:1 and the amount of siphonarin B (4) present had increased to ca. 9%.

Only partial data reported.

¹H NMR (500 MHz, CDCl₃): δ 17.05 (0.02H, s, HO-enol), 6.46 (0.2H, s, HO-hemiacetal), 6.39 (0.1H, s, HO-hemiacetal), 6.19 (0.4H, s, HO-hemiacetal), 5.12 (0.02, s, HO-4), 4.6-3.6 (4H, m), 3.00-2.25 (8H, m), 2.15-1.95 (6H, several s), 1.50-0.58 (24H, m).

¹³C NMR (125 MHz, CDCl₃): δ numerous tautomers.

LRMS: m/z (relative intensity) 543 ([M+23]+, 25), 521 ([M+1]+, 100), 139 (7) (ESI).

HRMS: m/z calcd for C₂₉H₄₄O₈ 520.3036 (521.3108 for [M+H]+), found 521.3096 (ESI).
14-epi-Baconipyrone C (235)

From 14/15: DBU (ca. 1 μL) was added to a solution of 14/15 (5 mg, 0.01 mmol) in C₆D₆ (0.4 mL) at rt. After 1 h, 14/15 was consumed (by ¹H NMR). The mixture was diluted with ethyl acetate and washed sequentially with 0.2 M citric acid, sat. NaHCO₃, and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by PTLC (40% acetone in hexanes) to give the baconipyrone C (8) (2.5 mg, 50%) and 14-epi-baconipyrone C (235) (1.5 mg, 30%).

From baconipyrone C (8): DBU (1 μL) was added to a solution of baconipyrone C (8) (6.2 mg) in C₆D₆ (0.4 mL). After 45 min, the presence of a 1.3:1 mixture of 8 and 235 was detected by ¹H NMR. The mixture was concentrated and fractionated by PTLC (40% acetone in hexanes) to give baconipyrone C (8) (3.4 mg, 55%) and 14-epi-baconipyrone C (235) (2.4 mg, 39%): [α]D -6 (c 0.1, CHCl₃).

IR νmax: 3412, 1716, 1653, 1608 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 5.48 (1H, dd, J = 3.5, 9 Hz, HC-5), 4.20 (1H, q, J = 7 Hz, HC-14), 3.64 (1H, ddd, J = 4.5, 8, 10 Hz, HC-11), 3.14 (1H, d, J = 10 Hz, HO), 2.93-2.86 (2H, m, HC-4 or HC-6, HC-12), 2.83 (1H, dq, J = 3.5, 7 Hz, HC-6 or HC-4), 2.78 (1H, dq, J
= 18, 7.5 Hz, HC-2 or HC-8), 2.65-2.48 (4H, m, HC-2 or HC-8, HC-10, H2CC-19), 2.47-2.36
(2H, m, HC-2, HC-8), 2.03 (3H, s, H3C-16), 1.94 (3H, s, H3C-18), 1.45 (3H, d, J = 7 Hz,
H3C-14), 1.20 (3H, t, J = 7.5 Hz, H3CCH2C-19), 1.11 (3H, d, J = 7 Hz, H3C-C-4), 1.09 (3H, d,
J = 7 Hz, H3C-10), 1.06 (3H, d, J = 7 Hz, H3C-12), 1.03 (3H, t, J = 7.5 Hz, H3C-C-2 or H3C-C-8),
1.02 (3H, d, J = 7 Hz, H3C-C-6), 1.01 (3H, t, J = 7.5 Hz, H3C-C-2 or H3C-C-8).

13C NMR (125 MHz, CDCl3): δ 212.3 (s, C-7 or C-3), 211.6 (s, C-3 or C-7), 210.6 (s, C-13),
179.9 (s, C-17), 173.8 (s, C-9), 165.0 (s, C-19), 160.0 (s, C-15), 120.4 (s, C-16), 118.4 (s, C-
18), 76.6 (d, C-11), 74.1 (d, C-5), 48.7 (d, C-14), 47.8 (d, C-12), 47.6 (d, C-4 or C-6), 46.1
(d, C-6 or C-4), 42.4 (d, C-10), 35.5 (t, C-2 or C-8), 35.4 (t, C-2 or C-8), 25.0 (t, CH2C-19),
15.1 (q, CH3C-10 or CH3C-12), 14.9 (q, CH3C-10 or CH3C-12), 13.7 (q, CH3C-4 or CH3C-
6), 13.5 (q, C-14), 11.5 (q, CH3CH2C-19), 10.03 (q, CH3C-16), 9.99 (q, CH3C-6 or CH3C-4),
9.7 (q, CH3C-18), 7.9 (q, CH3C-8 or CH3C-2), 7.7 (q, CH3C-2 or CH3C-8).

LRMS: m/z (relative intensity) 543 ([M+23]+, 30), 521 ([M+1]+, 100), 503 (3), 485 (3), 242
(3), 132 (2) (ESI).

HRMS: m/z calcd for C29H44O8 520.3036 (521.3108 for [M+H]+), found 521.3098 (ESI).
(2S,3S,4S)-(2R,4R,5R,6S)-2-(6-Ethyl-3,5-dimethyl-4-oxo-4H-pyran-2-yl)-4,6-dimethyl-3,7-dioxononan-5-yl-3-hydroxy-2,4-dimethyl-5-oxoheptanoate (237)

Activated neutral aluminum oxide (50 mg; Brockmann I, standard grade, ca. 150 mesh, 58 Å) was added to a solution of 14/15 (5 mg, 0.01 mmol) in EtOH (2 mL) and the resulting suspension was heated under reflux. After 1 h, the suspension was filtered through Celite® washing with ethyl acetate. The combined filtrate and washings were concentrated. $^1$H NMR of the residue indicated the presence of a 10:7:5:3 mixture of 237, baconipyrone C (8), siphonarin B (4), and baconipyrone A (6), respectively. Fractionation of the residue by PTLC (80% ethyl acetate in hexanes) gave a 1:1 mixture of siphonarin B (4) and baconipyrone C (8), respectively (2 mg), and a 4:1 mixture of 237 and baconipyrone A (6), respectively (2.5 mg). Further fractionation of the latter mixture by PTLC (50% ethyl ether in CH$_2$Cl$_2$) gave baconipyrone A (6) (0.5 mg) and the titled compound (2 mg, 40%): $[\alpha]_D$ -92 (c 0.1, CHCl$_3$).

**IR** $\nu_{\text{max}}$: 3401, 1712, 1653, 1610 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.37 (1H, dd, $J = 5$, 7.5 Hz, HC-5'), 4.03 (1H, q, HC-2'), 4.01 (1H, ddd, $J = 4$, 4.5, 7.5 Hz, HC-3), 3.15 (1H, d, $J = 4.5$ Hz, HO), 3.06 (1H, dq, $J = 7.5$, 7 Hz, HC-4'), 2.89 (1H, dq, $J = 5$, 7 Hz, HC-6'), 2.66 (1H, dq, $J = 4$, 7 Hz, HC-4), 2.62-2.49
(6H, m, H2C-6, H2C-8', H2C-6''), 2.46 (1H, dq, J = 7.5, 7 Hz, HC-2), 2.08 (3H, s, H3CC-3''), 1.95 (3H, s, H3CC-5''), 1.37 (3H, d, J = 7 Hz, H3CC-2'), 1.15 (3H, t, J = 7.5 Hz, H3CCH2C-6''), 1.14 (3H, d, J = 7 Hz, H3CC-4), 1.10 (3H, d, J = 7 Hz, H3CC-6'), 1.07 (3H, d, J = 7 Hz, H3CC-2), 1.06 (3H, t, J = 7.5 Hz, H3C-7), 1.02 (3H, t, J = 7.5 Hz, H3C-9'), 0.89 (3H, d, J = 7 Hz, H3CC-4').

13C NMR (125 MHz, CDCl3) δ: 215.4 (s, C-5), 211.4 (s, C-7'), 207.6 (s, C-3'), 179.8 (s, C-4''), 174.3 (s, C-1), 165.0 (s, C-6''), 159.9 (s, C-2''), 120.5 (s, C-3''), 118.7 (s, C-5''), 76.1 (d, C-5'), 73.1 (d, C-3), 50.2 (d, C-2'), 48.1 (d, C-6'), 47.4 (d, C-4), 45.8 (d, C-4'), 43.4 (d, C-2), 35.0 (d, C-6 or 8'), 35.0 (t, C-6 or 8'), 24.9 (t, CH2C-6''), 14.3 (q, C-1), 13.7 (q, CH3C-4'), 13.5 (q, CH3C-2'), 12.4 (q, CH3C-6'), 11.5 (q, CH3CH2C-6''), 10.3 (q, CH3C-3' or CH3C-4), 10.2 (q, CH3C-3' or CH3C-4), 9.8 (q, CH3C-5''), 7.8 (q ×2, C-7, C-9').

LRMS: m/z (relative intensity) 543 ([M+23]⁺, 100), 521 ([M+1]⁺, 20), 355 (6), 333 (6) (ESI).

HRMS: m/z calcd for C29H44O8 520.3036 (521.3108 for [M+H]⁺), found 531.3127 (ESI).
(4S,5S,6S,10S,11S,12R,14R)-11-(Benzyloxy)-14-(6-ethyl-3,5-dimethyl-4-oxo-4H-pyran-2-yl)-4,6,8,10,12-pentamethyl-5-hydroxy-4,6,8,10,12-pentamethylpentadecane-3,7,9,13-tetraone (238)

IBX (50 mg, 0.18 mmol) was added to a solution of 228 (15 mg, 0.021 mmol) in anhydrous DMSO (2 mL) at rt. After 2 d, the mixture was diluted with ethyl acetate and washed sequentially with sat. NaHCO₃, water, and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue that was taken up in THF (2 mL) and pyridine (0.4 mL, 0.4 g, 5 mmol), water (50 μL, 50 mg, 3 mmol), and HF•pyridine (0.13 mL) were added sequentially to the stirred solution at rt. After 4 h, the mixture was diluted with ethyl acetate and washed sequentially with 0.2 M citric acid (0.2 M; ×2), sat. NaHCO₃, and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by PTLC (60% ethyl acetate in hexanes) to give the titled compound (11 mg, 88%) as a complicated mixture consisting of enol (ca. 5%), hemiacetal (one diastereomer, ca. 40%), and β-diketone (ca. 55% as a 4:3 mixture of diastereomers) forms (by NMR).

Only partial data reported.
\[ ^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3). \ \delta \ 17.14 \ (0.05 \text{H}, \text{s, HO (enol)}), \ 7.42-7.12 \ (5 \text{H, m, ArH}), \ 6.13 \ (0.4 \text{H, br s, hemiacetal OH}), \ 4.60-3.70 \ (4 \text{H, m}), \ 3.20-2.30 \ (8 \text{H, m}), \ 2.17-1.80 \ (6 \text{H, several s, pyrone CH}_3\text{'s}), \ 1.35-0.80 \ (24 \text{H, m}). \]

\[ ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \text{ (partial data): } \delta \ 104.6 \text{ (C-9 hemiacetal)}, \ 85.3 \ & 84.8 \ & 84.3 \text{ (C-11, 3 major forms)}, \ 61.8 \ & 61.4 \text{ (C-8 keto form, 2 diastereomers)}. \]

**LRMS:** \( m/z \) (relative intensity) 633 ([M+23]+, 45), 611 ([M+1]+, 100), 593 (10) (ESI).

**HRMS:** \( m/z \) calcd for C\(_{36}\)H\(_{50}\)O\(_8\) 610.3506 (611.3578 for [M+H]+), found 611.3597 (ESI).

**Siphonarin B (4)**

\[ \text{From 238: Raney nickel (W2; 0.2 mL settled volume in EtOH) was transferred to a solution of 238 (6 mg, 0.01 mmol) in EtOH (3 mL) at rt and the resulting suspension was heated under reflux with vigorous stirring. After 45 min, the mixture was allowed to settle and then was decanted. The solid was suspended in EtOH (10 mL), heated under reflux for 10 min, and decanted. This washing procedure was repeated with ethyl acetate. The organic layers were passed over Celite®, combined, concentrated, and fractionated by PTLC (70% ether in CH}_2\text{Cl}_2\) to give baconipyrone C (8) (1 mg, 20%) and siphonarin B (4) (1.5 mg, 27%). \]
From 14/15: Imidazole (10 mg, 0.15 mmol) was added to a solution of 14/15 (3.5 mg, 6.7 μmol) in CDCl₃ (0.4 mL) at rt. After 24 hr, the mixture was diluted with ethyl acetate and washed with 0.2 M citric acid, sat. NaHCO₃, and brine. The aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, and concentrated to give the crude product that, by ¹H NMR, contained a mixture of 4 (δH 5.12) and hemiacetals (δH 6.46, 6.39, 6.19 in a 0.1:1.5:1 ratio). [Note: similar mixtures were also obtained from similar reactions starting from 14/15 and from 4 after 48 h.] Fractionation of the residue by PTLC (50% ether in CH₂Cl₂) gave the titled compound containing ca. 10% of a δH 5.01 impurity (3 mg, 85%). Further fractionation by PTLC (7% iPrOH in CH₂Cl₂) gave the titled compound (2.5 mg, 70%): [α]D +12 (c 0.1, CHCl₃).

¹H NMR (500 MHz, CDCl₃): δ 5.12 (1H, s), 3.91 (1H, d, J = 10.5 Hz), 3.81 (1H, br s), 3.27 (1H, q, J = 7 Hz), 3.08 (1H, br s), 2.77 (2H, ap q, J = 7 Hz), 2.66 (1H, q, J = 7 Hz), 2.61 (1H, q, J = 6.5 Hz), 2.48 (1H, dq, J = 18.5, 7 Hz), 2.32-2.18 (2H, m), 2.05 (1H, dq, J = 2.5, 7.5 Hz), 1.97 (3H, s), 1.96 (3H, s), 1.86 (1H, dq, J = 2, 7 Hz), 1.25 (3H, d, J = 7 Hz), 1.21 (3H, d, J = 7 Hz), 1.20 (3H, t, J = 7.5 Hz), 1.19 (3H, d, J = 7 Hz), 1.07 (3H, d, J = 6.5 Hz), 1.07 (3H, d, J = 7 Hz), 0.94 (3H, t, J = 7 Hz), 0.77 (3H, d, J = 6.5 Hz).

¹³C NMR (125 MHz, CDCl₃): δ 213.5, 206.7, 180.1, 165.7, 161.8, 121.8, 117.5, 105.4, 103.4, 74.82, 74.80, 50.2, 46.8, 45.5, 42.7, 38.9, 38.6, 35.9, 24.9, 13.2, 12.8, 12.1, 11.6, 11.1, 9.6, 9.5, 8.8, 8.4, 7.6.
Activated basic aluminum oxide (50 mg; Brockmann I, standard grade, 58 Å) was added to a stirred solution of 238 (10 mg, 0.016 mmol) in EtOH (2 mL) and the resulting suspension was heated under reflux. After 7 h, the cooled mixture was filtered through Celite®, washing with ethyl acetate. The combined filtrate and washings were concentrated and the residue taken up in EtOH (2 mL) and 5% Pd-C (10 mg) was added. The resulting black suspension was stirred under a H₂ atmosphere 24 h and then was filtered through Celite®, washing with ethyl acetate. The combined filtrate and washings were concentrated and fractionated by PTLC (80% ethyl acetate in hexanes) to give baconipyrone A (6) (1.5 mg, 18%) and baconipyrone C (8) (6 mg, 70%): [α]D -96 (c 0.13, CHCl₃).

**IR** νₘₓ: 1718, 1652, 1597 cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 5.00 (1H, dd, J = 4.5, 6 Hz, HC-5), 4.04 (1H, q, J = 7 Hz, HC-14), 3.62 (1H, ddd, J = 3.5, 8.5, 9.5 Hz, HC-11), 3.35 (1H, d, J = 9.5 Hz, HOC-11), 2.96 (1H, dq, J = 4.5, 7 Hz, HC-6), 2.79 (1H, dq, J = 8.5, 7 Hz, HC-12), 2.64 (1H, dq, J = 3.5, 7 Hz, HC-10), 2.62-2.51 (2H, m, HC-8. H₂CC-19), 2.13 (1H, dq, J = 6.5, 7 Hz, HC-4), 2.05 (3H, s, H₃CC-16), 1.95 (3H, s, H₃CC-18), 1.66 (1H, dq, J = 14.5, 7 Hz, HC-2), 1.52 (1H, dq, J = 14.5, 7 Hz, HC-2), 1.38 (3H, d, J = 7 Hz, H₂CC-14), 1.29 (3H, d, J = 7 Hz, H₃CC-10),
1.16 (3H, t, $J = 7.5$ Hz, H$_3$CH$_2$C-19), 1.07 (3H, d, $J = 7$ Hz, H$_3$CC-4 or H$_3$CC-8), 1.06 (3H, d, $J = 7$ Hz, H$_3$CC-4 or H$_3$CC-8), 1.00 (3H, d, $J = 7$ Hz, H$_3$CC-6), 0.90 (3H, d, $J = 7$ Hz, H$_3$CC-12), 0.86 (3H, d, $J = 7$ Hz, H$_3$C-1).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 211.5 (s, C-7), 210.5 (s, C-13), 179.8 (s, C-17), 175.0 (s, C-9), 165.0 (s, C-19), 160.5 (s, C-15), 120.5 (s, C-16), 118.7 (s, C-18), 77.5 (d, C-5 or C-11), 77.4 (d, C-5 or C-11), 76.6 (s, C-3), 51.4 (d, C-14), 48.3 (d, C-12), 46.4 (d, C-8), 44.8 (d, C-6), 41.6 (d, C-10), 38.0 (d, C-4), 30.5 (t, C-2), 25.0 (t, CH$_2$C-19), 15.4 (q, CH$_3$C-10), 14.5 (q, CH$_3$C-12), 13.2 (q, CH$_3$C-14), 12.1 (q, CH$_3$C-4 or CH$_3$C-6), 11.8 (q, CH$_3$C-4 or CH$_3$C-6), 11.5 (q, CH$_3$CH$_2$C-19), 10.2 (q, CH$_3$C-18), 9.8 (q, CH$_3$C-18), 9.0 (q, C-1), 7.6 (q, CH$_3$C-8).

LRMS: m/z (relative intensity) 543 ([M+23]$^+$, 90), 521 ([M+1]$^+$, 100) (ESI).

HRMS: m/z calcd for C$_{29}$H$_{44}$O$_8$ 520.3036 (521.3108 for [M+H]$^+$), found 521.3104 (ESI).

Baconipyrone C (8)

From 238: Activated basic aluminum oxide (Brockmann I, standard grade, 58 Å; 50 mg) was added to a stirred solution of 238 (10 mg, 0.016 mmol) in EtOH (2 mL) and the resulting suspension was heated under reflux. After 7 h, the cooled mixture was filtered through Celite®, washing with ethyl acetate. The combined filtrate and washings were concentrated
and the residue taken up in EtOH (2 mL) and 5% Pd-C (10 mg) was added. The resulting black suspension was stirred under a H₂ atmosphere 24 h and then was filtered through Celite®, washing with ethyl acetate. The combined filtrate and washings were concentrated and fractionated by PTLC (80% ethyl acetate in hexanes) to give baconipyrone A (6) (1.5 mg, 18%) and baconipyrone C (8) (6 mg, 70%): [α]_D -81 (c 0.1, MeOH).

From 14/15: DBU (ca. 1 μL) was added to a solution of 14/15 (5 mg, 0.01 mmol) in C₆D₆ (0.4 mL) at rt. After 1 h, the mixture was diluted with ethyl acetate and washed with 0.2 M citric acid, sat. NaHCO₃, and brine. Each aq. layer was sequentially back extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by PTLC (40% acetone in hexanes) to give the titled compound (2.5 mg, 50%) and 14-epi-baconipyrone C (235) (1.5 mg, 30%).

1H NMR (500 MHz, CDCl₃): δ 5.47 (1H, dd, J = 3.5, 9 Hz, HC-5), 4.15 (1H, q, J = 7 Hz, HC-4), 3.55 (1H, ddd, J = 3, 9, 10 Hz, HC-11), 3.38 (1H, d, J = 10 Hz, HO), 2.89-2.19 (3H, m, HC-4, HC-6, HC-12), 2.75 (1H, dq, J = 18, 7 Hz, HC-8 or HC-2), 2.60-2.45 (4H, m, HC-2 or HC-8, HC-10, H₂CC-19), 2.44-2.29 (2H, m, HC-2, HC-8), 2.09 (3H, s, H₃CC-16), 1.93 (3H, s, H₃CC-18), 1.38 (3H, d, J = 7 Hz, H₃CC-14), 1.22 (3H, d, J = 7 Hz, H₂CC-10), 1.16 (3H, t, J = 7.5 Hz, H₃CCH₂C-19), 1.09 (3H, d, J = 7 Hz, H₃CC-4 or H₃CC-6), 1.02 (3H, d, J = 7 Hz, H₃CC-6 or H₃CC-4), 1.01 (3H, t, J = 7.5 Hz, H₂CC-8 or H₂CC-2), 0.91 (3H, t, J = 7 Hz, H₂CC-2 or H₂CC-8), 0.86 (3H, d, J = 7 Hz, H₃CC-12).

13C NMR (125 MHz, CDCl₃): δ 212.1 (s, C-7 or C-3), 211.0 (s, C-3 or C-7), 210.7 (s, C-13), 179.9 (s, C-17), 174.3 (s, C-9), 164.8 (s, C-19), 160.8 (s, C-16), 120.6 (s, C-16), 118.5 (s, C-
18), 77.8 (d, C-11), 74.0 (d, C-5), 51.2 (d, C-14), 48.8 (d, C-12), 47.5 (d, C-4 or C-6), 46.0
(d, C-6 or C-4), 41.3 (d, C-10), 35.32 (t, C-2 or C-8), 35.28 (t, C-2 or C-8), 24.9 (t, CH₂C-
19), 15.3 (q, CH₃C-10), 14.4 (q, CH₃C-12), 13.7 (q, CH₃C-4 or CH₃C-6), 13.4 (q, CH₃C-14),
11.5 (q, CH₃CH₂C-19), 10.4 (q, CH₃C-16), 9.9 (q, CH₃C-6 or CH₃C-4), 9.7 (q, CH₃C-18),
7.9 (q, CH₃C-8 or CH₃C-2), 7.5 (q, CH₃C-2 or CH₃C-8).

**LRMS: m/z** (relative intensity): 520 ([M]⁺, 2), 339 (3), 236 (8), 209 (5), 180 (100), 151 (10),
121 (43), 57 (54) (EI).

**HRMS: m/z** calcd for C₂₉H₄₄O₈ 520.3036, found 520.3028 (EI).
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