THIOPYRAN ROUTE TO POLYPROPIONATES:
INCREASING STEREOCHEMICAL
DIVERSITY OF ALDOL ADDUCTS

A Thesis Submitted to the
College of Graduate Studies and Research
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by

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Abstract

Linear carbon-carbon chains with alternating hydroxyl and methyl substituents are a common motif in various natural products. Many of these so-called polypropionates (i.e. 4) show biological activity and are useful in the fields of medicine and agriculture. The stereoselective synthesis of polypropionates has been extensively investigated and numerous strategies and tactics have been developed.

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{O} & \quad \text{OH} \\
\text{n} & \quad \text{n = 0, 1, 2,...integer}
\end{align*}
\]

\text{polypropionate}

The sequential aldol reactions of thiopyran derivatives 122 and 125 followed by desulfurization of aldol adducts is a strategy to rapidly construct hexapropionate synthons (e.g. 165). The present work concerns the control of the stereoselectivity in the two key aldol coupling steps inherent in this strategy.

In Section 2.2, the influence of reaction conditions and the relative configuration of the \(\beta\)-alkoxy group of aldehydes cis-125b and trans-125c on the diastereoselectivity of the 1\(^{st}\) aldol coupling are discussed. The results were rationalized according to Evan's merged 1,2- and 1,3-stereoinduction model (nonchelation), with the exception of the \(\text{MgBr}_2\cdot\text{OEt}_2\) promoted reactions of 137b (\(M = \text{TMS}\)) with 125a, 125b and 125c, which were accommodated by assuming chelation control. Under appropriate conditions, three (126a-128a) of the four possible diastereomers could be obtained stereoselectively. The fourth diastereomer (129a) was readily available by isomerization (\textit{vide infra}).

In Section 2.3, the diastereoselectivities of the aldol reactions of (±)-125a with (±)-126a and (±)-127a (previous work) and reactions of (±)-125a with (±)-128a and (±)-129a (this work) are presented. These reactions occurred with high mutual kinetic enantioselection (MKE) and were highly diastereoselective for the formation of one out of eight possible diastereomers. The diastereoselectivity of aldol reactions of (±)-125a with related \(\beta\)-alkoxy ketones (±)-166 and (±)-168 (previous work) and reactions with
(±)-172 and (±)-174 (this work) were also investigated. Contrary to the aldol reactions of β-hydroxy ketones (126a-129a), reactions of β-alkoxy ketones (166, 168, 172, 174) proceeded without significant MKE. These reactions were also highly diastereoselective giving two products, one each from the like and unlike reactions.

In Section 2.4, the use of imidazole as an effective catalyst for syn/anti isomerization of aldols via keto-enol tautomerism is described. A large variety of aldol (e.g. 126) and bisaldol (e.g. 165) adducts were shown to undergo efficient isomerization with minimal retroaldol and elimination reactions. The rate constants for this process were determined for several substrates. It was found that thiopyranone derived aldols isomerize much faster than related cyclohexanone aldols and the β-hydroxy ketones (e.g. 128a) isomerize faster than β-alkoxy derivatives (e.g. 172).

In section 2.5, the relative configuration of aldol adducts was rigorously determined using chemical correlations and NMR methods.
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In Memory of my Beloved Father

Helio Reis Sales
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List of Abbreviations

Ac  acetyl (ethanoyl)
AcOH  acetic acid
aq  aqueous
Bn  benzyl
Bu  butyl
$^{13}$C NMR  carbon-13 nuclear magnetic resonance
Chx  cyclohexyl
CI  chemical ionization
COSY  correlation spectroscopy
DIBAL  diisobutylaluminium hydride
dil.  dilute
$i$-Pr$_2$EtN  diisopropylethylamine
DMAP  4-(N,N-dimethylamino)pyridine
DMF  dimethylformamide
DMP  2,2-dimethoxypropane
DMS  dimethylsulphide
DMSO  methyl sulphoxide
d.r.  diastereomeric ratio
DRIFT  diffuse reflectance infrared Fourier transform
ee  enantiomeric excess; for a mixture of two enantiomers $R$ and $S$, $ee = |([R]-[S])/([R]+[S])| \times 100$
EI  electron impact ionization
equiv  equivalent(s)
e.r.  enantiomeric ratio; ratio of $(R)$ to $(S)$
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>FAB</td>
<td>fast-atom bombardment</td>
</tr>
<tr>
<td>FCC</td>
<td>flash column chromatography</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transform infra red</td>
</tr>
<tr>
<td>&lt;sup&gt;1&lt;/sup&gt;H NMR</td>
<td>proton nuclear magnetic resonance</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation (2 and 3 bond $J_{CH}$ correlation with inverse detection)</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple quantum coherence (1 bond $J_{CH}$ correlation with inverse detection)</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>i-Bu</td>
<td>isobutyl (2-methylpropyl)</td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis Acid</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LRMS</td>
<td>low resolution mass spectroscopy</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MeLi</td>
<td>methyllithium</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz; $10^6$ Hertz</td>
</tr>
</tbody>
</table>
min  
minute(s)

MOM  
methoxymethyl

MPC  
medium pressure chromatography

MS  
mass spectrometry

MS4A  
molecular sieves 4Å

n-BuLi  
n-butyllithium

NMR  
nuclear magnetic resonance

nOe  
nuclear Overhauser enhancement

OTBDMS  
 tert-butyldimethylsilyloxy

Ph  
phenyl

PMB  
p-methoxybenzyl

iPr  
isopropyl

PTLC  
preparative thin layer chromatography

p-TsOH  
p-toluenesulfonic acid (4-methylbenzenesulfonic acid)

Pyr  
pyridine

rt  
room temperature; ca. 22-24 °C

sat.  
saturated; as in a saturated aqueous solution

s  
second(s)

TBDMS or TBS  
t-butyldimethylsilyl

TBDMScI or TBSCI  
t-butyldimethylsilyl chloride

TBS or TBDMS  
t-butyldimethylsilyl

t-Bu  
tert-butyl (1,1-dimethylethyl)

t-BuLi  
tert-butyllithium

TEA  
triethylamine

THF  
tetrahydrofuran (oxolane)

xxv
TLC  thin-layer chromatography
TMS  trimethylsilyl or tetramethylsilane
TMSCl trimethylsilyl chloride (chlorotrimethylsilane)
TMSCN trimethylsilyl cyanide (cyanotrimethylsilane)
Tol  toluene
TS   transition state
v/v  volume relative to volume measure
1. INTRODUCTION

1.1. POLYPROPIONATES

Linear carbon-carbon chains with alternating oxygen (hydroxyl or oxo) and methyl substituents are a common structural motif in various natural products. These structures have been defined as polypropionates and their biosynthesis involves the reaction between coenzyme A activated propionate monomers 2 and 3\(^*\) catalyzed by the polyketide synthase system (PKS) (Figure 1).\(^{1-4}\) Natural products that incorporate polypropionates have attracted a lot of attention during the past 50 years with progress in areas such as isolation, characterization, biosynthesis, and improved methods in their total synthesis.\(^{1-3,5-8}\) Many of these natural products that show biological activity have been successfully applied in medicine and agriculture.\(^8\) For example, the heptapropionates 5a (6-deoxyerythronolide B), 5c (erythronolide B) and the related erythromycin A (5b glycosylated at the C-2 and C-5 positions) (Figure 2) have antifungal and antimicrobial activity. Erythromycin A is widely used in the treatment of many infectious diseases by oral administration.\(^8\) The mode of action of erythromycin A involves the inhibition of the peptidyl transferase center of the bacterial ribosome, thereby inhibiting protein synthesis.\(^8\) Antibiotic resistance to these natural products is a growing concern. It would be desirable to synthesise novel libraries of erythromycin analogues to probe the structure activity relationships (SAR) responsible for their biological activity and discover new analogues with increased potency against resistant microbes. Such an approach will require improved synthetic methodologies to allow the facile synthesis of these stereochemically complex\(^\dagger\) polypropionates.

Numerous synthetic methodologies have been used for stereoselective synthesis of polypropionate fragments including Claisen rearrangements,\(^9,10\) iodocarbonylations,\(^11\) allenylmetal additions,\(^12-15\) crotyl metal additions,\(^16-19\) Diels-Alder,\(^6,20-24\) and aldol

\(^*\) Monomer 3 is synthetically equivalent to a polypropionate monomer since \(\alpha\)-CO\(_2\)H substituent is removed upon chain elongation in the PKS catalyzed biosynthesis.

\(^\dagger\) Each carbon center on the polypropionate backbone that contains an hydroxyl or methyl substituent is a potential stereogenic center.
**Figure 1.** Biosynthesis of polypropionates from reaction from 2 and 3.

**Figure 2.** Heptapropionate natural products 5a-d.
Figure 3. Polypropionate natural products 7a-c.

reactions. The aldol reaction is highly suitable for the synthesis of polypropionates because it gives carbon chains with oxygen functionalities in the 1,3-positions. Highly
stereoselective aldol reactions have contributed immensely to the efficiency of the synthesis of polypropionate containing natural products. Examples are the stereoselective synthesis of the heptapropionate 5d (oleandolide)\(^{16,45,46}\) (structurally related to the erythromycins 5a-c, Figure 2), the hexapropionates 7a (muamvatin)\(^{47,48}\) and 7b (denticulatin A)\(^{49-51}\) and the decapropionate 7c (siphonarin B)\(^{52}\) (Figure 3). The origin of stereoselective aldol reactions is the natural result of understanding the underlying stereochemical control elements present in the aldol reaction and these will be discussed in section 1.2.

1.2. ALDOL STEREOSELECTION

The aldol addition reaction is a C-C bond forming reaction that involves the addition of an enol equivalent to an aldehyde (or ketone) resulting in the formation of a β-hydroxy carbonyl product.\(^{53}\) Traditionally, aldol addition reactions were carried out under protic conditions where the enol or enolate was generated reversibly in the presence of the electrophilic carbonyl compound. Under these conditions, the reaction is reversible and product formation is under thermodynamic control. There are many limitations when the aldol reaction is conducted under equilibrating reaction conditions. For example, when the two carbonyl components to be coupled are not identical and both possess a hydrogen at an α-position to the carbonyl it is possible that an enol(ate) could be generated from either carbonyl component and the subsequent addition of these enol(ate)s to either of the carbonyl components results in the formation of complex mixtures. This shortcoming was overcome by generating the enol- or enolate-component quantitatively prior to the addition of the electrophilic carbonyl component.\(^{53}\) This so called ‘directed’ aldol reaction generally gives products under kinetic control. An aldol reaction leads to C-C bond formation with the potential of generating two new stereogenic centers (Figure 4).\(^{54}\)

The discovery and implementation of methodologies that allow the generation of the newly formed stereogenic centers in a highly stereoselective manner has made the aldol reaction a powerful tool for organic synthesis.\(^{55}\) The principles governing the stereoselectivity of this versatile coupling reaction are presented in the following sections.
The aldol reaction between achiral reaction partners leads to the formation of up to two stereogenic centers and up to four possible stereoisomeric products. The absolute and relative configuration of these newly generated centers is dependant on the relative orientation of the $\pi$-faces of the enol(ate) and aldehyde in the transition state for formation of the aldol adduct (Figure 5). The two enantiotopic faces of the aldehyde and of the enolate are distinguished as Re/Si nomenclature according to IUPAC rules (Figure 5). The relative configuration of the products can be defined using syn/anti nomenclature. The syn (same side) and the anti (opposite side) stereochemical descriptors for aldols 13 and 14 refer to the relative disposition of the designated pairs of non-hydrogen substituents with respect to the plane defined by the carbon chain (C-1)-(C-2)-(C-3)-(C-4) in an extended (zigzag) conformation.

There are four ways in which the faces of the aldehyde and enol(ate) can be orientated relative to each other in the the transition state. For example, the Si face of aldehyde 9 can approach the Re face of enol(ate) 12 to give 2,3-syn 13 (Si-Re' adduct) or it can approach the Si face of enol(ate) 12 to give 2,3-anti 14 (Si-Si' adduct). Following the same logic, the Re face of aldehyde 9 can approach the Si face of enolate 12 to give 2,3-syn ent-13 (Re-Si' adduct), and approach of the Re aldehyde face of aldehyde 9 to the Re face of enolate 12 gives the 2,3-anti ent-14 (Re-Re' adduct) (Figure 5). The two stereoisomers that have 2,3-syn relative configuration are enantiomers (i.e. 13 and ent-13) as are the two stereoisomers with 2,3-anti relative configuration (i.e. 14 and ent-14).
Figure 5. Aldol reaction of an achiral aldehyde with an achiral enolate.

In an achiral environment, enantiomers will be produced in equal amounts; however, the syn and anti diastereomers will generally be produced in different amounts. The relative topicity of an aldol reaction describes the relative orientation of the reacting faces of the aldehyde and enol(ate). Under kinetic control, one relative topicity will be preferred reflecting a particular preference for a particular relative orientation of the aldehyde and enol(ate) faces in the transition state (i.e. $l_k$ [Re-Re’ or
Si-Si’] vs. ul [Re-Si’ or Si-Re’]. The relative topicity in the transition state is directly related to the relative configuration of the product and, for convenience, is denoted according to product stereochemistry. For example, the relative topicity of an aldol reaction where the Si face of aldehyde 9 adds to the Re face of enolate 12 to give adduct 13 with 2,3-syn relative configuration will be described as syn (Figure 2). The preferred Relative Topicity can be determined from the product distribution, where:

\[
\text{Relative Topicity} = \frac{\text{syn/anti}}{\text{[13 + ent-13]}/\text{[14 + ent-14]}}
\]

Much effort has been invested to discover the factors influencing the preferred relative topicity of the aldol reaction. It was found early on that the enolate geometry (E or Z) can strongly influence the preferred relative topicity. Generally Z-enolates produce syn aldol adducts selectively, whereas E-enolates give predominantly anti aldol adducts (Scheme 1).\textsuperscript{56} Furthermore it was found that with increasing steric bulk of the \( R_2 \) moiety (H<C\(_2\)H\(_5\)<i-C\(_3\)H\(_7\)<t-C\(_4\)H\(_9\)) the syn diastereoselectivity of the Z-enolate increased.\textsuperscript{57} A similar but less pronounced trend was found for the E-enolate, which increasingly favoured anti diastereoselectivity as steric bulk of \( R_2 \) moiety increased.\textsuperscript{57} These observations were rationalized with the model originally proposed by Zimmerman and Traxler (Figure 6).\textsuperscript{58}

The Zimmerman-Traxler model assumes a closed six-membered chairlike transition state that involves coordination of the oxygen atoms of both the aldehyde and enolate to a metal (e.g. lithium or boron) center as illustrated in Figure 6. As a result of the six-membered closed-transition state the greatest steric interaction will occur when both groups \( R_1 \) and \( R_2 \) occupy the axial orientations leading to a sterically unfavourable 1,3 diaxial interaction. Therefore as the steric demands of \( R_2 \) increase, transition state B from the Z-enolate will be relatively less favoured due to the increasingly unfavourable \( R_1 \leftrightarrow R_2 \) steric interaction. Thus the Z-enolate selectively leads to the syn adduct due to the absence of unfavourable steric interactions in TS A. The relative topicity of the aldol reaction with the E-enolate is anti selective due to the absence of these unfavourable \( R_1 \leftrightarrow R_2 \) steric interactions in TS C.
Figure 6. The Zimmerman-Traxler model

To take advantage of these relationships, the stereoselective preparation of enolates is necessary. Studies of the addition of various lithium enolates of ketones 15 to benzaldehyde revealed that enolates generated with LHMDS usually give more Z-enolate (Z-16) compared to enolates generated from LDA, while enolates generated from LTMP usually give more E-enolate (E-16) (Scheme 1). In general, the formation of boron enolates using reagents with sterically demanding ligands (eg. c-hex) and a poor leaving group on boron (eg. Cl) in the presence of a small amine base (eg. Et₃N) provide the E-enolate (Scheme 1). The Z-enolate is preferentially obtained when
reagents with small ligands (eg. n-Bu), a good leaving group (eg. OTf) and a hindered amine (eg. i-Pr₂EtN) is used. A theoretical model has been proposed to explain these trends.

Mukaiyama found that certain Lewis acids were able to promote the reaction of enolsilanes with aldehydes to give aldol products. Unlike the aldol reactions of boron- and lithium enolates, the Mukaiyama reaction does not involve the formation of metal-enolates. This reaction is facilitated by the increased electrophilicity of the aldehyde component due to coordination of the Lewis acid. From the examples of Lewis acid promoted aldol reactions given in Table 1, it is apparent that the preferred relative topiety of the Mukaiyama reaction is unaffected by the E/Z geometry of the enolsilanes. Clearly a Zimmerman-Traxler model cannot explain the observed stereoselectivities.

Scheme 1. Effect of Z/E-enolate geometry on aldol relative topiety

Open transition state models place the trigonal carbons of the enolsilane and aldehyde components in a staggered orientation (Figure 7). There are six possible
staggered orientations. Product formation is thought to be favoured from those orientations that minimize dipolar repulsion between the oxygens of the aldehyde and enolsilane and avoid unfavourable steric interactions between the substituents.

Table 1. Lewis acid promoted aldol reactions

<table>
<thead>
<tr>
<th>entry</th>
<th>R_1</th>
<th>R_2</th>
<th>R_3</th>
<th>Enolsilane</th>
<th>Lewis acid</th>
<th>23 : 24 (anti: syn)</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>^Pr</td>
<td>Me</td>
<td>OEt</td>
<td>15 : 85 TiCl_4</td>
<td>93 : 7</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>^Pr</td>
<td>Me</td>
<td>tBu</td>
<td>100 : 0 BF_3•OEt_2</td>
<td>95 : 5</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Me</td>
<td>OEt</td>
<td>25 : 75 TiCl_4•PPh_3</td>
<td>91 : 9</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Me</td>
<td>tBu</td>
<td>100 : 0 BF_3•OEt_2</td>
<td>95 : 5</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>tBu</td>
<td>OEt</td>
<td>76 : 24 TiCl_4</td>
<td>8 : 92</td>
<td>a</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>tBu</td>
<td>OEt</td>
<td>5 : 95 TiCl_4</td>
<td>8 : 92</td>
<td>a</td>
<td></td>
</tr>
</tbody>
</table>

* Not reported.

Figure 7. Open transition state model for Mukaiyama aldol reaction.
Notice that for entries 2 and 4 (Table 1) the Z-enol silane selectively leads to the formation of **anti-23** whereas the Zimmerman-Traxler model would have predicted the formation of **syn-24** from a Z-enolate. An Open Transition State model accounts for the observed selectivity. The transition state **A**, which leads to **anti-23**, is favoured because it avoids dipolar repulsion and minimizes steric interactions. Transitions states **B, C, D** and **F** are disfavoured due to the steric interactions between $R_3 \leftrightarrow R_1$ and $R_3 \leftrightarrow LA$, and transition **C** and **E** are also further disfavoured due to dipolar repulsion arising from the orientation of the two oxygens present in the aldehyde and enol silane components. Following the same reasoning as above, the preferred relative topicities of the aldol reactions in Table 1 can be rationalized.

### 1.2.2. Enantioselectivity with Achiral Substrates

There are up to four stereoisomers possible in an aldol reaction between achiral substrates (Figure 5). Racemic syn or anti adducts can be diastereoselectively obtained from aldol reactions that have good control of the relative topicity. A means to effect an enantioselective synthesis would require a reaction with a highly preferred relative topicity under conditions where addition to one of the enantiotropic faces of the aldehyde or of the enolate is preferred. Two approaches have frequently been used. In one, chiral ligands are coordinated to the metal enolate rendering the faces of the enolate diastereotopic and of different reactivity.$^{67-70}$ In the second approach, chiral ligands are coordinated to the Lewis acidic metal used to promote a Mukaiyama aldol reaction; coordination of the aldehyde to this chiral Lewis acid renders the aldehyde faces diastereotopic and of different reactivity.

An example of the first approach is the use of chiral (-)-diisopinocampheyl ligands attached to boron enolate. There are four possible stereoisomers from the aldol reaction of **Z-26** with **27** (Scheme 2). For this aldol reaction Paterson et al. obtained a single stereoisomer **28** with high selectivity.$^67$ As expected, the reaction of the boron enolate with Z geometry (**Z-26**) occurred with high preference in the relative topicity to give mostly syn adducts$^{71}$ (i.e. d.r. = syn : anti = 95 : 5), and isomer **28** was obtained selectively due to the difference in the rates of addition of **27** to the two diastereotopic faces of enolate **Z-26**.
Scheme 2. The application of chiral boron enolates for enantioselective aldol reaction.

Scheme 3. The application of chiral Lewis acids for enantioselective aldol reaction.

An example of the second approach is the Mukaiyama aldol reaction of enolsilane E-30 with 31 catalyzed by the chiral Lewis acid 32 (i.e. (R)-BINOL-Ti(IV) complex) (Scheme 3). Under the same reaction conditions the aldol reaction of Z-30 with 31 gave ent-33 with similar selectivity observed for reaction with E-30; this is
another example where E/Z-enolate geometry has little influence on the relative topicality of Mukaiyama aldol reactions.

1.2.3. Diastereoface Selectivity: Reaction of a Chiral Enol(ate) with an Achiral Aldehyde

The two π-faces of a chiral enolate are diastereotopic. As a consequence, an aldehyde would add to the two diastereotopic faces of the enolate at different rates and with different diastereoselectivity. Chiral enolates are encountered in various contexts and it is useful to differentiate those enolates where chirality is temporarily introduced as part of a synthetic strategy to control diastereoselectivity from enolates where the chirality is an integral part of the target structure. For example, the chirality can be solely due to ligands attached to the coordinating metal of the enolate (see Scheme 2). Alternatively, an otherwise achiral enolate of a carboxylic acid derivative can be made chiral by using an ester of a chiral alcohol, or by using an amide or imide of a chiral amine. This so-called chiral auxilary approach is a very powerful method for the stereoselective construction of polypropionate fragments (Scheme 4). An example originally developed by Evans, is the stereoselective aldol reactions of the boron enolates (e.g. 36) generated from the chiral imide 35. Evans et al. stereoselectively obtained aldol adduct 38a from the aldol reaction of 36 with 37. As expected, the reaction of the boron enolate with Z geometry (36) occurred with high preference in the relative topicality to give syn adduct 38a. Evans demonstrated that base hydrolysis (KOH) of 38a gives 39 with negligible isomerization. Heathcock et al. demonstrated that the presence of Lewis acids (SnCl₄, TiCl₄ and Et₂AlCl) can extend the scope of of the Evans imides for stereoselective synthesis. For example, the reaction of 36 with 37 in presence of 2 equivalents of SnCl₄ stereoselectively gave 38b, and in the presence of 0.5 equivalents of SnCl₄ stereoselectively gave 38c. Conceptually, the remaining stereoisomer ent-38c can be stereoselectively obtained from the reaction of the enantiomer of ent-36 with 37. If desired, the base hydrolysis of these adducts can give the four stereoisomers 39, ent-39, 40 and ent-40.
Scheme 4. Use of Evan’s chiral auxiliary.
The synthesis of polypropionates often involves aldol reaction of chiral ketone fragments with aldehydes. To illustrate the stereochemical outcome of an aldol reaction of chiral enolate with achiral aldehyde the reaction between 41 (where the stereogenic center is part of the enolate carbon skeleton) with 9 is discussed (Figure 8).

(a) relative topicity of aldol: 2,3-syn or 2,3-anti
(b) enolate diastereoface selectivity: 1',2-syn or 1',2-anti

Figure 8. Aldol reaction between chiral enolate 41 with achiral aldehyde 9.
The reaction of an enantiopure enolate such as (R)-41 with an achiral aldehyde 9 can potentially lead to the formation of four diastereoisomers (i.e. 42-45, Figure 8). The four diastereomers are produced from the four possible relative orientations for the faces of the enolate and aldehyde in the bond forming step of the aldol reaction (Figure 8).\textsuperscript{54} For example, addition of the Re-face of enolate (R)-41 to Si-face of aldehyde 9 gives adduct 42 (Figure 8).

The reaction of an enantiopure enolate (S)-41 (the enantiomer of (R)-41) with achiral 9 can also lead to the formation of four diastereomers (ent-42 - ent-45). These four diastereomers are the enantiomers of the four diastereomers produced from (R)-41 and 9 (Figure 8). The reaction of racemic chiral enolate (±)-41 with achiral aldehyde 9 will lead to the formation of eight stereoisomers consisting of 4 enantiomeric pairs (42 - 45 and ent-42 - ent-45) (Figure 8). In the absence of an external chiral influence, all products will be racemic. In general, the ratio of diastereomers produced from the reaction of achiral 9 with (R)-41, (S)-41, or (±)-41 will be identical under identical reaction conditions.

There are two stereocontrol elements that need to be considered when an achiral aldehyde adds to the diastereotopic faces of a chiral enolate. The relative topicity of the aldol determines the 2,3-syn/anti relative configuration, just as the case for the reaction between achiral reaction partners (compare Figure 5 and label (a) in Figure 8). The second stereochemical control element is the diastereoface selectivity for addition to the chiral enolate which determines the 1',2-syn/anti relative configuration in the aldol adducts (see label (b) in Figure 8). For convenience, the reacting enolate diastereoface is defined according to the relative configuration present in the product. For example, the aldol reaction where the aldehyde 9 adds to the Re-face of enolate (R)-41 gives products 42 and 45 with 1',2-syn relative configuration (Figure 8), will be described as a syn addition. The diastereoface selectivity for the reaction is determined from the product distribution. For example, the 1',2-syn / 1',2-anti selectivity for the reaction of (R)-41 with 9 is ([42] + [45]) / ([43] + [44]).

The application of chiral ethyl ketones 46 to polypropionate synthesis by Paterson et al.\textsuperscript{76-79} is presented to illustrate diastereoselective aldol reactions of chiral
Scheme 5. Diastereoselective aldol reactions of chiral enolates 47a-c with 27.

achiral aldehydes (Scheme 5). The use of Sn(OTf)$_2$ and Et$_3$N was optimal for the formation of Z-enolate 47a from (S)-46$^{77}$ (Scheme 5). The aldol reaction of 47a with 27
was selective for the formation of 48a which results from preferential 4,5-syn aldol relative
topicity and 2,4-syn enolate diastereoface addition (Scheme 5). \(^77,80\) Reaction of
the E-boron enolate 47b with 27 gave 48b with excellent stereoselectivity. \(^79\) The
observed selectivity is accounted for by the expected 4,5-anti relative topicity for an E-
boron enolate and 2,4-anti addition of the aldehyde to the chiral enolate. The
diastereoselective synthesis of 48c required a reaction with preferential 4,5-syn aldol
relative topicity and 2,4-anti enolate diastereoface selectivity. Paterson et al.\(^78\) achieved
the diastereoselective synthesis of 48c by using a Z-boron enolate with chiral ligands
attached to boron. The Z-boron enolate gave a preferential 4,5-syn relative topicity and
the chiral ligands on boron overpowered the innate enolate diastereofaceselectivity (cf.
48a from (S)-47a) to give 2,4-anti selectivity predominantly. The direct synthesis of
48d using similar methodology was not achieved.

1.2.4. Diastereoface Selectivity: Reaction of a Chiral Aldehyde with an
Achiral Enolate

The reaction of an enantiopure aldehyde such as (S)-49 with an achiral enolate
12 can potentially lead to the formation of four diastereoisomers (i.e. aldol adducts 50-
53, Figure 9). The four diastereomers are produced from the four possible relative
orientations the faces of the aldehyde and enolate adopt in the bond forming step of the
aldol reaction (Figure 9).\(^54\) For example, addition of the Si-face of aldehyde (S)-49 to
Re-face of enolate 12 gives adduct 50 (Figure 9).

The reaction of an enantiopure aldehyde (R)-49 (the enantiomer of (S)-49) with
achiral 12 can also lead to the formation of four diasteromers (ent-50 - ent-53). These
four diastereomers are the enantiomers of the four diastereomers produced from (S)-49
and 12 (Figure 9). The reaction of racemic chiral aldehyde (±)-49 with achiral enolate
12 will lead to the formation of eight stereoisomers consisting of 4 enantiomeric pairs
(50-53 and ent-50 – ent-53) (Figure 9). In the absence of an external chiral influence,
all products will be racemic. In general, the ratio of diastereomers produced from the
reaction of achiral 12 with (S)-49, (R)-49, or (±)-49 will be identical under identical
reaction conditions.
There are two stereochemical control elements that need to be considered when an achiral enolate adds to the diastereotopic faces of a chiral aldehyde. The relative

(a) relative topicity of aldol: 2,3-syn or 2,3-anti
(b) aldehyde diastereoface selectivity: 3,4-syn or 3,4-anti

Figure 9. Aldol reaction between a chiral aldehyde and an achiral enol(ate).
topicity of the aldol reaction determines the 2,3-syn/anti relative configuration, just as in the case of the reaction between achiral reaction partners (compare Figure 5 and label (a) in Figure 9) and in the case of the reaction between chiral enolate and achiral aldehyde (compare labels (a) in Figures 8 and 9). The second stereochemical control element is the diastereoface selectivity for addition to the chiral aldehyde which determines the 3,4-syn/anti relative configuration in the aldol adducts (see label (b) in Figure 9). For convenience, the reacting aldehyde diastereoface is defined according to the relative configuration present in the product. For example, the aldol reaction where the enolate 12 adds to the $Si$-face of the aldehyde (S)-49 gives products 50 and 52 with 3,4-syn relative configuration (Figure 9), will be described as a syn-selective addition.

The diastereoface selectivity for the reaction is determined from the product distribution. For example, the 3,4-syn / 3,4-anti selectivity for the reaction of (S)-49 with 12 is $([50]) + [52]) ÷ ([51] + [53])$.

Under kinetically controlled conditions, an achiral enolate will preferentially add to the diastereotopic aldehyde face that gives the more stable transition state. Various models that have been postulated to predict and account for the observed aldehyde diastereoface selectivities are discussed below.

1.2.4.1. 1,2-Stereoinduction models

The presence of a stereogenic center at the $\alpha$-position of an aldehyde can strongly influence the diastereoface selectivity for addition of an enolate. For example, a Re-facial preference has been found for the addition of lithium-enolates to (R)-54 (Table 2).81

The empirical model originally proposed by Cram for Grignard additions to aldehydes successfully predicted the aldehyde diastereofacial preference of addition of lithium-enolates to $\alpha$-methyl substituted aldehydes.82 Cram's model for aldehydes where the stereogenic center is at the $\alpha$-position considers the conformation that orients the largest group L of the three $\alpha$-substituents antit to the C-O bond of the aldehyde. Nucleophilic attack is predicted to occur preferentially on the face of the aldehyde coincident with the smallest group S (Figure 10). It must be noted that the Cram model is an empirical model which was derived by correlating the structures of the preferred
products with those of the starting aldehydes. No attempt was made to use transition state theory to predict the diastereofacial preference for addition to the aldehyde.

Table 2. Aldehyde diastereoface selectivities of addition of lithium enolates 55 to 54

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>56 : 57</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>3 : 1</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>tBu</td>
<td>4 : 1</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>MeO</td>
<td>3 : 1</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>tBuO</td>
<td>4 : 1</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Me2N</td>
<td>3 : 1</td>
<td>67</td>
</tr>
</tbody>
</table>

Figure 10. The Cram model predicts Re-face attack

A more recent explanation to account for the observed Re-diastereofacial selectivity presented in Table 2, was proposed by Felkin, Anh and Eisenstein. The so-called Felkin-Anh model uses arguments based on torsional strain to propose a
reacting conformer. Felkin postulated that torsional strain present in partially formed bonds represents a substantial fraction of the strain in fully formed bonds. This hypothesis led to the assumption of a preferred transition state based on an aldehyde conformation in which the bulkiest of the ligands $\alpha$ to the carbonyl (L) is oriented perpendicular to the plane of the carbonyl group and to further minimize torsional strain the next most demanding substituent (M) is oriented gauche to the carbonyl (e.g. TS B depicted in Figure 11). A nucleophile will preferentially approach the carbonyl anti to the bulky moiety L as depicted in TS B (Figure 11). A further evaluation of Felkin’s proposed model using *ab initio* calculations by Anh and Eisenstein found that the conformer B is energetically the most favoured, not only for occasions where all $\alpha$-substituents are alkyl groups, but also where one of the $\alpha$-substituents is an heteroatom. In these cases, the heteroatom takes the place of the large ligand L, thereby minimizing Coulombic repulsion between the electronegative heteroatom and the incoming nucleophile.

Molecular modelling studies determined that the favoured approach of a nucleophile occurred at a 109° angle to the plane of the aldehyde face, the so-called Burgi-Dunitz trajectory. A Burgi-Dunitz trajectory for the incoming nucleophile makes the assumption that the medium sized group should be gauche to the carbonyl oxygen unnecessary. Both TS A and B (Figure 11) have the group L perpendicular to the plane of the carbonyl group and have the nucleophile approaching the carbonyl anti to the L group. If the angle of attack is 109° then TS B has less steric hindrance to the nucleophile than TS A.
Both the Cram and Felkin-Anh models predict the same stereochemical outcome; the difference between these two stereochemical models is that Cram's model identifies the sense of the relationship between starting material and product by an empirical correlation. Whereas, the Felkin-Anh model attempts to give a mechanism-based rationale for this relationship.

The presence of a heteroatom substituent such as oxygen at the $\alpha$-position of an aldehyde can strongly influence the diastereoface selectivity for addition of a nucleophile. In 1959, Cram proposed a chelation model to account for the observed stereoselectivity of addition of the Grignard reagent $\text{CH}_3\text{MgI}$ to $\alpha$-oxygen substituted ketones. In this model, it is assumed that the Lewis acidic $\text{Mg (II)}$ coordinates to both oxygens, and addition occurs preferentially from the least hindered face of the chelated intermediate (Figure 12).

Table 3 presents the results of addition of enolates [59] to the $\alpha$-alkoxy aldehyde [58] under several conditions. The aldehyde diastereoface selectivities in entries 1, 2 and 3 are in accordance to the predictions of the Felkin-Anh model. However, the diastereoface selectivities obtained in entries 4-7 are contrary to the predictions of the Felkin-Anh model. The so-called anti-Felkin products are rationalized by a chelation control model (first proposed by Cram). That is the Lewis acids $\text{TiCl}_4$ and $\text{SnCl}_4$, which have two vacant coordination sites, are assumed to be coordinated by both
oxygen of the α-alkoxy aldehyde to form a reactive chelated intermediate. Under these chelation controlled conditions, addition of a nucleophile to the less sterically hindered diastereotopic face of the aldehyde leads to the anti-Felkin aldol adduct (see Figure 12). \(^{91,93}\)

**Figure 12.** Felkin-Anh and the Cram-chelation control model to rationalise the 1,2-stereoinduction of an α-alkoxy aldehyde.
Table 3. Diastereoface selectivity for addition of 59 to 58\textsuperscript{92}

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>M</th>
<th>Z-59 : E-59</th>
<th>Lewis acid</th>
<th>3,4-syn : 3,4-anti\textsuperscript{a}</th>
<th>2,3-syn : 2,3-anti\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Li</td>
<td>5 : 95</td>
<td>-</td>
<td>20 : 80</td>
<td>69 : 31</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Li</td>
<td>95 : 5</td>
<td>-</td>
<td>26 : 74</td>
<td>84 : 16</td>
</tr>
<tr>
<td>3</td>
<td>tBu</td>
<td>Li</td>
<td>&gt;99 : 1</td>
<td>-</td>
<td>21 : 79</td>
<td>66 : 34</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>TMS</td>
<td>17 : 83</td>
<td>TiCl\textsubscript{4}</td>
<td>&gt;99 : 1</td>
<td>23 : 77</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>TMS</td>
<td>17 : 83</td>
<td>SnCl\textsubscript{4}</td>
<td>&gt;99 : 1</td>
<td>20 : 80</td>
</tr>
<tr>
<td>6</td>
<td>tBu</td>
<td>TMS</td>
<td>&gt;99 : 1</td>
<td>TiCl\textsubscript{4}</td>
<td>89 : 11</td>
<td>65 : 35</td>
</tr>
<tr>
<td>7</td>
<td>tBu</td>
<td>TMS</td>
<td>&gt;99 : 1</td>
<td>SnCl\textsubscript{4}</td>
<td>88 : 11</td>
<td>66 : 34</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The aldehyde diastereoface selectivity i.e. Felkin : anti-Felkin. \textsuperscript{b} The relative topicity.

1.2.4.2. 1,3-Stere induction models

The influence of an heteroatom substituent at the aldehyde \(\beta\)-position\textsuperscript{*} on diastereoface selectivity has been investigated and both chelation control- and 'open' transition state\textsuperscript{†} models have been proposed to explain the observed stereoselectivity for additions of nucleophiles. 3-Benzylxybutanal (61) has been used as a model substrate.

\textsuperscript{*} \(\beta\)-Position is also known as position 3 where the aldehyde carbon is designated position 1, hence the term 1,3-stereinduction.

\textsuperscript{†} Also known as non-chelation control models.
to study 1,3-stereoinduction in the Lewis acid promoted Mukaiyama aldol reactions with enolsilanes (Scheme 6). \[94,95\]

\[
\begin{align*}
\text{OTMS} & \quad \text{Ph} \\
\rightarrow & \\
\text{62} & \\
\text{TiCl}_4 & \\
\end{align*}
\]

![Reaction Scheme](image)

**Scheme 6.** The diastereoselectivity of Lewis acid promoted coupling of 61 with enolsilanes 62 and 63.

Reactions of 61 with 62 and 63 occur with high aldehyde diastereoface selectivity to give 1,3-anti adducts. To account for the observed diastereofacial preference it was proposed that the addition of the nucleophilic enol silane occurred from the least hindered face of a Ti-aldehyde chelate (Figure 13). Evidence for the presence of a chelate was obtained by Keck in a study of the effect of stoichiometry and temperature on the $^1$H NMR spectra of solutions of TiCl$_4$ and 61. It was concluded that a conformationally rigid 1:1 TiCl$_4$:aldehyde complex was formed. The conformation of the chelate aldehyde was derived from an analysis of vicinal coupling constants observed in the $^1$H NMR spectrum. To account for the relatively small vicinal coupling constants between H$_2$C-2 and HC-3 (4.7 and 4.7 Hz), it was proposed that the 1:1 complex was a chelate with a conformation where proton HC-3 was in a pseudo-equatorial orientation and the methyl substituent in a pseudo-axial orientation. The observed diastereofacial selectivity can then be rationalized by addition of the nucleophile to the least sterically hindered face of the aldehyde in the chelate as depicted in Figure 13.
Studies of the effect of various Lewis acids on the diastereoface selective additions of allyl stannane and allyl trimethylsilane to the aldehyde 61 were performed (Table 4). The 1,3-anti adduct was formed preferentially in all cases. The diastereoselective formation of 69a in the presence of Lewis acids TiCl₄, MgBr₂ and SnCl₄ known to have two vacant coordination sites can be explained using the previously discussed bidentate chelate model (Figure 13). However, because BF₃·OEt₂ has only one vacant coordination site, BF₃·OEt₂ cannot coordinate to both heteroatoms simultaneously to give a bidentate chelate, an alternative model is required to rationalize the observed stereoselectivity.

**Figure 13.** Addition to the least hindered face of the chelated β-substituted aldehyde 61.

**Table 4.** Lewis acid promoted allyl-stannane 67 and allyl-silane 68 addition to β-substituted aldehyde 61.

<table>
<thead>
<tr>
<th>entry</th>
<th>Allyl reagent</th>
<th>TiCl₄</th>
<th>MgBr₂</th>
<th>SnCl₄</th>
<th>BF₃·OEt₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>32 : 1</td>
<td>8.1 : 1</td>
<td>3.4 : 1</td>
<td>3.9 : 1</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>95 : 5</td>
<td>-</td>
<td>95 : 5</td>
<td>85 : 15</td>
</tr>
</tbody>
</table>
To account for the observed aldehyde diastereoface selectivity Reetz proposed that the coordination of the oxygen of the aldehyde to BF₃·OEt₂ resulted in a complex which assumed an extended linear conformation so as to minimize electrostatic repulsions (Figure 14). The nucleophile approaches from the least sterically hindered aldehyde face (anti to the methyl group depicted in Figure 14) to afford the 1,3-anti product.

![Figure 14. Reetz’s polar 1,3 stereoinduction model.](image)

Though Reetz’s proposed polar 1,3-stereoinduction model successfully accounts for the aldehyde diastereofacial preference, it did not take into account the electrostatic interactions within the aldehyde substrate that affect the torsion angles along the carbon backbone of the aldehyde. Evans proposed a revised polar 1,3 stereoinduction model based on electrostatic interactions within the aldehyde which also included the effect of α-substituents according to the Felkin-Anh model for 1,2-stereoinduction. In Evans’ model two assumptions common to the Felkin-Anh model were made. The first assumption was that the preferred conformer sets the aldehyde in a staggered relationship between the forming bond and the aldehyde α-substituents such that the largest group at the α-position would be orthogonal to the aldehyde face (see A1 in Figure 15). The second assumption was that the Nu would approach the carbonyl from the Burgi-Dunitz angle. The nucleophile preferentially attacks the least hindered aldehyde face and thus the forming bond would be orientated anti instead of gauche to the β stereogenic center. The approach of the Nu as depicted in diagrams A1 and A2 (Figure 15) correctly predicts that additions will be selective for the 1,3-anti diastereomer.

The factors that favour conformer A as depicted in Figure 15 can be identified from a consideration of the steric and electronic interactions present in the aldehyde conformers A-F (Figure 16). Conformers A and D are favoured since the β-substituent
is orientated \textit{anti} to the Cα-C=O bond to minimize steric interactions (Figure 16).

\begin{center}
\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure15.png}
\caption{Evans revised polar 1,3-stereoinduction model.}
\end{figure}
\end{center}

\begin{center}
\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure16.png}
\caption{Steric and electronic interactions present in the conformers of the BF$_3$ coordinated aldehyde.}
\end{figure}
\end{center}

Conformers B and F are destabilized by the sterically unfavourable \textit{gauche} interaction present between the β-substituent and C=O group. Conformers C and E are also
expected to become unfavourable as the size of the β-substituent increases. In conformers C and D, there is an added presence of a destabilising dipolar interaction between the C-X bond (where X = heteroatom substituent) and the C=O bond. From a process of elimination the conformer A is correctly identified to be the favoured conformer which reacts with the Nu to deliver the 1,3 \textit{anti} aldol adduct.

\textbf{1.2.4.3. Merged 1,2- and 1,3-stereoinduction model}

To account for the presence of α-substituents on the degree of 1,3-stereoinduction, Evans has elegantly proposed a merged 1,2- and 1,3-stereoinduction model to rationalize the observed selectivities in substrates which have substituents at both the α- and β-positions to the aldehyde. The origin of this model was a natural progression from an integration of both the Felkin-Anh model (which accounted for the observed 1,2-stereoinduction) and Evan's revised polar 1,3-stereoinduction model (see section 1.2.4.1 and 1.2.4.2).

![Diagram of Evans' merged 1,2- and 1,3-stereoinduction model for substrates with a 2,3-anti relationship.](image)

\textbf{Figure 17.} Evans' merged 1,2- and 1,3-stereoinduction model for substrates with a 2,3-anti relationship.

In essence, this merged model simply replaced either of the H\textsubscript{a} or H\textsubscript{b} hydrogens depicted in the favoured conformer A (Figure 15) with an alkyl substituent. The approach of the Nu is then predicted to occur from the least hindered face. A 2,3-anti relationship between the α-methyl and β-alkoxy substituents will mutually reinforce the
preferential approach of the Nu from the same aldehyde face as depicted in Figure 17. This mutual reinforcement leads to a prediction of enhanced diastereoface selectivity for nucleophilic addition to aldehydes of this type. This prediction is borne out by the excellent 98:2 selectivity observed for the Felkin adduct of 75a from reaction of 73a with 74 (Figure 17).

Figure 18. Evans' merged 1,2- and 1,3-stereoinduction model for substrates with a 2,3-sy\textsuperscript{y}l relationship.

Alternatively, if H\textsubscript{b} in A (Figure 15) is replaced with an alkyl substituent resulting in a syn relationship between the $\alpha$-alkyl and $\beta$-alkoxy substituents the preferred aldehyde face for addition predicted by the Felkin-Anh model (Figure 11) will be contrary to that predicted by the 1,3-stereoinduction model (Figure 15). Thus a syn relationship between the substituents at the $\alpha$- and $\beta$-positions is said to be nonreinforcing. For example, the 1,3-polar stereoinduction model suggests preferential approach of the Nu as depicted in H in Figure 18; however, the Felkin-Anh model suggests preferential approach of the Nu as depicted in conformer I in Figure 18. From
this analysis, it becomes apparent that the diastereofacial selectivity of addition of a Nu to the aldehyde is likely to be modest and cannot be reliably predicted if the relative contributions towards stereocontrol from both α- and β-stereogenic centers are not known.

1.2.5. Double Stereodifferentiation, Kinetic Resolution, and Mutual Kinetic Enantioselection: Reaction of a Chiral Aldehyde with a Chiral Enol(ate).

1.2.5.1. Double stereodifferentiation and the rule of multiplicativity

In the aldol reaction between a chiral aldehyde and chiral enolate there are three identifiable stereochemical control elements that influence the reaction diastereoselectivity (Figure 19). These are the aldehyde- and enolate-diastereoface selectivities and the relative topicity of the aldol reaction. These selectivities are influenced by the absolute configurations of the stereogenic centers present in both the chiral aldehyde and chiral enolate. In an aldol reaction between an enantiopure aldehyde and an enantiopure enolate, there are up to four possible diastereomeric products resulting from the four possible relative orientations of the aldehyde and enolate faces in the bond forming step. For example, adduct 77 is derived from bond formation step where the Si-face of aldehyde (S)-49 is orientated towards the Re face of the enolate (R)-41 (Figure 19). Conversely, the relative configuration about the positions C-3/C-4, C-2/C-3 and C-1'/C-2 can be used to define the stereoselectivity with respect to the three stereochemical control elements (Figure 19). For example, the formation of aldol adduct 77 is the result of a 3,4-syn aldehyde diastereoface addition, a 1',2-syn enolate diastereoface addition and 2,3-syn relative topicity.

* For convenience the aldehyde and enolate diastereoface selectivity and the relative topicity are defined according to the resultant relative configurations present in the product. For example, addition to the Si face of aldehyde (S)-49 is equivalent to a 3,4-syn aldehyde diastereoface addition; Addition to the Re face of enolate (R)-41 is equivalent to a 1',2-syn enolate diastereoface addition; addition to the Si-face of (S)-49 and to the Re-face of (R)-41 is equivalent to 2,3-syn relative topicity.
Figure 19. Aldol reactions of (S)-49 with (R)-41 and with (S)-41.

The aldol reaction of (S)-49 with (R)-41 can give four diastereomeric adducts 77-80 and the reaction between aldehyde (S)-49 and enolate (S)-41 (the enantiomer of (R)-41) can give four diastereomeric aldol adducts 81-84 (Figure 19). These two
reactions depicted in Figure 19 are stereochemically related and can be defined as the like and unlike reactions, where like refers to the reaction where the absolute configurations of the fiducial stereogenic centers in 49 and 41 are identical (i.e. (S)-49 and (S)-41 as depicted in Figure 19), and the unlike reaction is where the absolute configuration of the fiducial stereogenic centers in 49 and 41 are different (i.e. (S)-49 and (R)-41 as depicted in Figure 19). The terms ‘like’ and ‘unlike’, that describe reactions where both reactants are chiral, was defined by Seebach and Prelog.\(^99\)

The transition states for the unlike reaction of (S)-49 with (R)-41 are diastereotopic with those for the like reaction of (S)-49 with (S)-41 and give diastereomeric products. The rates of product formation for the like and unlike reactions will be different as will the product distributions (i.e. diastereoselectivities). The reaction with the higher diastereoselectivity is labeled the matched reaction, and the other reaction with relatively lower diastereoselectivity is labeled the mismatched reaction.

The phenomenon responsible for the differences in the diastereoselectivity between the like and unlike reactions is often termed ‘double stereodifferentiation’. Double Stereodifferentiation which is present in any reaction between chiral reactants has been described by the terms ‘double asymmetric induction’\(^100\) and ‘double asymmetric synthesis’\(^101\). Generally, the term ‘asymmetry’ has been freely used to describe many stereoselective processes, the description ‘double stereodifferentiation’ is however a more precise description of the phenomenon and is preferred.\(^102\) The origin of the differences in diastereoselectivity of the like and unlike reactions can be understood from a consideration of the selectivities of the three stereochemical control elements. For illustrative purposes the directions of the selectivities of the three stereochemical control elements will be arbitrarily assigned and the consequences of these selectivities on the diastereoselectivities of the like and unlike reactions will be discussed. Table 5 presents the directions for each of the three stereocontrol elements required for the formation of the eight aldol adducts from the reaction of (S)-49 with (R)-41 and (S)-41. It is arbitrarily assumed that for aldol reaction of 49 and 41, the preferential selectivities for the aldehyde diastereoface addition is 3,4-syn selective, the
enolate diastereoface addition is 1',2-syn selective and the relative topicity of the aldol reaction is 2,3-syn selective.

Table 5. Relative configurations present in the unlike (77-80) and like (81-84) adducts.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldol adduct</th>
<th>Aldehyde d.s.</th>
<th>Enolate d.s.</th>
<th>Relative topicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>3,4-syn</td>
<td>1',2-syn</td>
<td>2,3-syn</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>3,4-anti</td>
<td>1',2-anti</td>
<td>2,3-syn</td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>3,4-syn</td>
<td>1',2-anti</td>
<td>2,3-anti</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>3,4-anti</td>
<td>1',2-syn</td>
<td>2,3-anti</td>
</tr>
<tr>
<td>5</td>
<td>81</td>
<td>3,4-anti</td>
<td>1',2-syn</td>
<td>2,3-syn</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>3,4-syn</td>
<td>1',2-anti</td>
<td>2,3-syn</td>
</tr>
<tr>
<td>7</td>
<td>83</td>
<td>3,4-anti</td>
<td>1',2-anti</td>
<td>2,3-anti</td>
</tr>
<tr>
<td>8</td>
<td>84</td>
<td>3,4-syn</td>
<td>1',2-syn</td>
<td>2,3-anti</td>
</tr>
</tbody>
</table>

\(^a\) Text in grey cells are the favoured relative configurations which, for the sake of illustration, were arbitrarily assigned as 3,4-syn, 1'2-syn and 2,3-syn for the aldehyde d.s., enolate d.s. and relative topicity, respectively

The unlike reaction of (S)-49 with (R)-41 can give adduct 77 (Table 5, entry 1) which results from the favoured selectivities of all three stereochemical control elements; the other three possible adducts (78, 79 and 80) each results from a combination where only one of the stereochemical control elements is in the favoured direction (Table 5, entries 2-4). It can be expected that this unlike reaction will be highly diastereoselective for adduct 77.

Of the four possible adducts from the like reaction of (S)-49 with (S)-41, three (81, 82 and 84) result from combination where two stereochemical control elements are in the favoured direction, and one adduct (83) is disfavoured by all three stereocontrol elements. It can be expected that this like reaction will have low diastereoselectivity since three adducts 81, 82 and 84 are expected in comparable amounts. From an examination of the preferences of the stereocontrol elements the double stereodifferentiation of the like and unlike reactions can be rationalized. For this particular example (Figure 19 and Table 5), the unlike reaction should be the matched
reaction (high diastereoselectivity) and the like reaction should be the mismatched reaction (low diastereoselectivity).

Masamune has discussed double stereodifferentiation in terms of the inherent diastereoface selectivities of each substrate in aldol reactions that proceed with highly selective relative topicity. For example, consider the aldol reaction of 85 and 87 (Figure 20). The inherent diastereoface selectivities of the chiral substrates 85 and 87 were determined from the diastereoselectivities of their respective reactions with appropriate achiral reaction partners (Figure 20).

Reaction of (S)-85 with achiral 86 gave a 2.7:1 mixture of 88a and 88b, respectively. Both products result from an aldol reaction with 2,3-syn relative topicity as expected from a lithium Z-enolate according to the Zimmerman-Traxler model. The products differ by which diastereotopic face of (S)-85 that the enolate adds to; 88a results from 3,4-anti addition (anti-Felkin) and 88b results from 3,4-syn addition (Felkin). Thus, aldehyde (S)-85 is seen to exhibit a 2.7:1 preference for addition of enolates (like 86) to the Re face giving 3,4-anti adducts. Similarly, the reaction of (S)-87 with benzaldehyde gave a 3.5:1 mixture of 89a and 89b, respectively. Both products result from an aldol reaction with 2,3-syn relative topicity but differ by which diastereoface of (S)-87 addition of benzaldehyde occurred; 89a results from a 1’,2-syn addition and 89b from 1’,2-anti addition. Thus enolate (S)-87 has a 3.5:1 preference for addition to the Si face to give 1’,2-syn products.
Note: The highly selective relative topicity for all reactions results in only 2,3-syn adducts.

Figure 20. Determining the inherent diastereoface selectivities of chiral aldehyde 85 and chiral enolate 87.
The reaction of (S)-85 and (S)-87 (like reaction) gives a 8:1 mixture of 90a and 90b, respectively (Figure 20). Adduct 90a results from the preferred 3,4-anti aldehyde diastereoface addition and the preferred 1',2-syn enolate diastereoface addition. By contrast, adduct 90b results from the disfavoured 3,4-syn aldehyde diastereoface addition and disfavoured 1',2-anti enolate diastereoface addition. It stands to reason that the diastereoselective formation of adduct 90a is expected on the basis of the innate diastereoface selectivities of (S)-85 and (S)-87. The related reaction of (S)-85 and (R)-87 (unlike reaction) gives a 1:1.5 mixture of 91a and 91b, respectively (figure 20). Adduct 91a results from the preferred 3,4-anti aldehyde diastereoface addition and the disfavoured 1',2-anti enolate diastereoface addition. Adduct 91b results from the disfavoured 3,4-syn aldehyde diastereoface addition and the preferred 1',2-syn enolate diastereoface addition. Thus, the formation of both 91a and 91b results from the innate diastereoface selectivity of one reactant but not the other. Consequently, lower diastereoselectivity is anticipated and found for the unlike reaction (i.e. mismatched) compared to the like reaction (i.e. matched).

It is possible to evaluate the magnitude of the diastereoselectivities for the like and unlike aldol reactions in terms of the individual aldehyde- and enolate-diastereoface selectivities. Masamune proposed that the diastereoselectivity of the matched pair can be predicted from the product of the aldehyde and enolate diastereoface selectivities provided that the relative topicity of the reaction was strongly biased (see Figure 21). Furthermore, the diastereoselectivity of the mismatched pair can be predicted from the ratio of the aldehyde and enolate diastereoface selectivities. This observation was coined by Masamune as the ‘Rule of Multiplicativity’. For reactions which are under kinetic control the Rule of Multiplicativity has been derived using transition state theory. The Rule of Multiplicativity does not apply quantitatively to every aldol reaction of chiral reaction partners. However, the rule is valid in a qualitative sense since the resultant diastereoselectivity of a matched reaction will always be higher than the individual diastereoface selectivities, and the diastereoselectivity for the mismatched pair will always be lower than the individual diastereoface selectivities.
Enolate d.s. of 87 = 2.7  
(Figure 20)

Aldehyde d.s. of 85 = 3.5  
(Figure 20)

Diastereoselectivity of matched rxn:
90a : 90b = 8 : 1

Diastereoselectivity of mismatched rxn:
91a : 91b = 1 : 1.5

\[ \text{Predicted Diastereoselectivity of matched rxn:} \]
\[ \text{Aldehyde d.s.} \times \text{Enolate d.s} = 3.5 \times 2.7 = 9.5 \]

\[ \text{Predicted Diastereoselectivity of mismatched rxn:} \]
\[ \text{Aldehyde d.s.} / \text{Enolate d.s} = 3.5 / 2.7 = 1.3 \]

Figure 21. Application of the Rule of Multiplicativity

1.5.2.2. Kinetic resolution and mutual kinetic enantioselection

Another possible scenario for reactions of chiral substrates is when one reactant is enantiopure and the other is racemic. For example the reaction of enantiopure aldehyde (S)-49 with racemic enolate 41. This reaction would involve the two parallel reactions of (S)-49 with (S)-41 and of (S)-49 with (R)-41 and can give a total of eight diastereomeric products (77-84, Figure 19). Because the like and unlike reactions occur at different rates (i.e. \( k_{SR} \neq k_{SS} \)), it follows that the enantiopure (S)-49 will preferentially react with one of the enantiomers of enolate 41. It is expected that the matched reaction will be the faster process. This kinetic preference for reaction of one enantiomer of the racemate results in ‘kinetic resolution’.104-106
Another scenario to consider is for reactions of chiral substrates where both reactants are racemic. An example would be the aldol reaction of racemic 49 with racemic 41. This reaction can be illustrated by a consideration of the four parallel reactions depicted in Figures 19 and 22. This reaction can give 16 stereoisomers comprised of eight enantiomeric pairs (i.e. eight diastereomers ent-77 to ent-84 which
are the enantiomers of the 8 diastereomeric aldol adducts 77 to 84). The rate constants for these four parallel reactions are labeled in Figures 19 and 22. Due to the enantiomeric relationship between the reactions of (S)-49 with (R)-41 and (R)-49 with (S)-41, their rate constants are equal (i.e. $k_{SR} = k_{RS}$). Similarly, the reactions of (S)-49 with (S)-41 and (R)-49 with (R)-41 have equal rate constants (i.e. $k_{SS} = k_{RR}$). In the reactions of racemic substrates there will be competition between the enantiomers (R)-41 and (S)-41 to react with the enantiomer (S)-49 and there will also be competition between (R)-41 and (S)-41 to react with (R)-49. The relative rates of these competing reactions can be measured and is expressed as the mutual kinetic enantioselectivity (MKE),

$$\text{MKE} = \frac{k_{SR}}{k_{SS}} = \frac{k_{RS}}{k_{RR}}$$

The term ‘Mutual Kinetic Enantioselection’ used in the description of diastereoselective reactions between reaction partners that are both chiral and racemic was originally coined by Heathcock and Oare.\textsuperscript{107} Mutual kinetic ‘resolution’ was the original term used to describe these diastereoselective reactions but since the process involves the kinetic preference of one enantiomer of a racemic substrate to preferentially react with one of the enantiomers of a racemic reagent the term ‘enantioselection’ was preferred.\textsuperscript{104,108}

Horeau determined that the mutual kinetic enantioselection (MKE) can be accurately measured from the ratio of diastereomers from a reaction where both reaction partners are racemic (method 1, Figure 23).\textsuperscript{109} In the reaction between racemic reaction partners the ratio of product diastereomers is constant and independent of the degree of conversion and the initial relative amounts of racemic reaction partners. A second method to obtain the MKE is to react an ‘enantiopure’ reactant with an excess of a racemic reaction partner (method 2, Figure 23). The use of excess racemate is to ensure that the reaction is pseudo-first order in the enantiopure reactant which allows the approximation to be made that the product distribution is a good reflection of the relative rates of reaction ($k_{SR}/k_{SS}$). Another method to potentially measure the mutual kinetic enantioselection would be to react non-racemic with non-racemic and analyse the product distribution. This method is not convenient since the product distribution is not directly proportional to the MKE (method 3, Figure 23). A numerical method has to
be employed where the reaction is modeled as four simultaneous second order reactions and then the resultant product distribution can be used to obtain the respective rate constants of these parallel reactions.  

\[
\text{method 1} \quad \frac{k_{SR}}{k_{SS}} = \frac{k_{RS}}{k_{RR}} = \frac{\text{[sum of unlike products]}}{\text{[sum of like products]}} = \text{MKE}
\]

\[
\text{method 2} \quad \frac{k_{SR}}{k_{SS}} = \frac{\text{[sum of unlike products]}}{\text{[sum of like products]}} = \text{MKE}
\]

\[
\text{method 3} \quad \frac{\text{[sum of unlike products]}}{\text{[sum of like products]}} \neq \text{MKE}
\]

**Figure 23.** Methods to measure the mutual kinetic enantioselection (MKE) based on product distribution.

All like and unlike reactions between chiral reactants can display the phenomenon of double stereodifferentiation. Reactions of an enantiopure reactant with a racemic reactant should display some degree of kinetic resolution, and reactions between two racemic reactants should exhibit some level of mutual kinetic enantioselection (MKE). Examples of kinetic resolution are discussed below and examples of MKE are discussed in Section 1.5.2.4.

### 1.5.2.3. Examples of kinetic resolution

Danishefsky et al. investigated the aldol reaction between (S)-92 and (S)-93 in connection with the synthesis of epothilones (Scheme 7). The reaction gave the desired adduct 95 but with poor yield and diastereoselectivity. It was suspected that this was the mismatched reaction of these chiral reactants. By comparison, reaction of (R)-92 with (S)-93 was highly diastereoselective and gave adduct 96 in 88% yield. For epothilone synthesis, inversion of the stereogenic center at C-3 of adduct 96 was necessary; however, attempts to invert this position using Mitsonobu type reactions were unsuccessful.
Scheme 7. Double stereodifferentiation and kinetic resolution in the reaction of 92 and 93.
The highly diastereoselective reaction of (R)-92 with (S)-93 prompted the question whether this matched pair was also kinetically favoured. Reaction of racemic enolate 92 with enantiopure aldehyde (S)-93 selectively gave adduct 96 in good yield (70%) (Scheme 7) demonstrating that the matched reaction was also the faster reaction.

The aldol reaction of enantiopure aldehyde (S)-98 with enantiopure Li-enolate (S)-99 was reported by Calter et al. to give a single adduct 100 in 55% yield.\textsuperscript{29} It was noted that the enantiopure adduct 100 can be applied to the synthesis of the siphonariene class of marine polypropionates.\textsuperscript{113,114} Presumably, in the hope that the like reaction (i.e. reaction of (S)-98 with (S)-99) would also be the kinetically favoured reaction in a kinetic resolution experiment, the reaction of (S)-99 with 1.1 equivalent of racemic 98 was attempted. Unfortunately, a 1.2:1 mixture of 101 and 100, respectively was obtained from which the desired 100 was isolated in 25% yield. This result suggest the possibility of a kinetic preference for the unlike reaction; however the nature of the reported experiment (i.e. a 1:1 stoichiometry without the conversion dependance of the product ratio) does not allow for an unambiguous conclusion.
Scheme 8. Kinetic resolution experiment for reaction of (±)-98 with (S)-99.

In the attempt to obtain the anti,anti stereotriad (such as is found in adduct 106, Scheme 9) in one step, Gennari et al.\textsuperscript{115} investigated the TiCl\textsubscript{4} promoted aldol reactions of propionate derived silyl ketene acetal to 3-(benzyloxy)-2-methylpropanal (103). The reaction of the achiral enol silane 102 to enantiopure aldehyde (R)-103 gave a single adduct which upon reduction gave 104. The diastereoface selectivity for addition of 102 to aldehyde (R)-103 was anti-Felkin; unfortunately, the aldol relative topicity was syn selective to give the syn,anti adduct 104 (Scheme 9). Due to the already favourable anti-Felkin preference, it was decided to investigate the aldol reaction of the chiral enol silane 105 with 103 in the hope that double stereodifferentiation may induce an anti-selective aldol relative topicity (Scheme 9).

The aldol reactions of (R)-103 and (S)-103 with enantiopure silyl ketene acetal 105 derived from (1R,2S)-N-methylephedrine propionate were conducted (Scheme 9).
The reaction of (R)-103 with 105 occurred with high diastereoselectivity (i.e. matched reaction) to afford the syn,anti adduct 104. The reaction of (S)-103 with 105 occurred with poor diastereoselectivity (i.e. mismatched reaction) to give a 1:1.3 mixture of ent-104 and 106, respectively.

The possibility for kinetic resolution was examined by reaction of excess racemic 103 with 104 which gave an ca. 10:1 mixture of 104 (65-70% ee) and 106, respectively, in moderate yield. This result implies an 8.5:1.5:1 mixture of 104, ent-104 and 106, respectively and therefore a 3.4:1 kinetic preference for reaction of 104 with (R)-103 compared to (S)-103.
Scheme 9. A study of the matched and mismatched aldol reactions of 103 with 105.
1.5.2.4. Examples of mutual kinetic enantioselection

To the best of my knowledge, reported examples of MKE in aldol reactions of racemic aldehyde with racemic enolates are extremely rare. Only two examples will be discussed. In both these reports the phenomenon of MKE was not specifically discussed.

Bloch reported that the reaction of racemic 107 with racemic 108 led to the formation of two observable diastereomers in a ratio of 64:36 (Scheme 10).\textsuperscript{116,117} Subjecting these diastereomers to heat promotes a retro Diels-Alder reaction and gave racemic 111 in 95% yield. The relative configuration of diastereomer 111 was expected because the relative topicality of the aldol reactions of Z-lithium enolate 107 with achiral aldehydes have been shown to be highly syn-selective\textsuperscript{117} and the aldol reactions of Z-lithium enolate 107 with a number of chiral aldehydes have been shown to be highly Felkin selective to afford the 3,4-syn relative configuration.\textsuperscript{116} It can be deduced that the relative configuration for all four stereoisomers 109, ent-109, 110 and ent-110 is 2,3-syn-3,4-syn because retro Diels-Alder of these stereoisomers gives only 111 and ent-111. The absolute configurations at position C-1' of the four stereoisomeric aldol adducts (109, ent-109, 110, ent-110) was not established. With the observation that the aldol reaction of 107 and 108 gives two diastereomers with a ratio of 64:36, it can be concluded that the ratio of the enantiomeric pairs (109 and ent-109) to (110 and ent-110) is equal to 64:36 or 36:64; hence the MKE in the reaction is \textit{ca.} 2 (Scheme 10).
A key step in the total synthesis of erythromycin by Woodward et al.\textsuperscript{118-120} was the aldol coupling of enantiopure fragments of (+)-112 with the ‘amine free’ Li-enolate of (-)-113 (Scheme 11).\textsuperscript{118} This unlike reaction between enantiopure fragments gave a mixture of diastereomers 114 which upon oxidation gave a single product (+)-115. The similar reaction between racemic reactants gave a mixture of diastereomers (±)-114 and (±)-116. Oxidation of this mixture gave a 5:1 mixture of (±)-115 and (±)-117, respectively. Consequently, the MKE of the aldol reaction between (±)-112 and (±)-113 was 5:1 in favour of (+)-112 with (-)-113.
Scheme 11. MKE in the aldol reaction of (±)-112 and (±)-113.
2. RESULTS AND DISCUSSION

2.1. THE THIOPYRANONE ROUTE TO POLYPROPIONATES

Cyclic sulfides have been widely used as templates to facilitate and control various chemical transformations. Their popularity is largely derived from their ease of preparation, versatile chemistry and the ready removal of sulfur from the final product.\textsuperscript{121-124} There are numerous examples where thiopyran derived templates have been successfully employed in the synthesis of a variety of targets.\textsuperscript{125-128} Recently, Ward et al.\textsuperscript{30,36} have proposed the use of aldol reactions of tetrahydro-4H-thiopyran-4-one derived derivatives followed by desulfurization as a strategy for the synthesis of polypropionates. The basis of the present research was to explore the stereoselectivity of the two key aldol coupling steps inherent in this strategy (Figure 24) with the goal of increasing the stereochemical diversity of polypropionate fragments that can be synthesized and to gain a greater understanding of the stereochemical control elements that govern product distribution.

The thiopyranone route to polypropionates can be illustrated by its application to the synthesis of a hexapropionate 118 (Figure 24). The hexapropionate 118 is obtained by a carboxylation and desulfurization of the parent hexapropionate synthon 119. It is evident that synthon 119 can be considered as a scaffold\textsuperscript{*} comprised of three thiopyranone (122) monomers. The disconnection of hexapropionate synthon 119 reveals that it can readily be obtained from two aldol reactions. This disconnection also reveals a tetrapropionate synthon 120 that can be useful for the synthesis of tetrapropionate fragments (Figure 25).

\textsuperscript{*} The term scaffold is used in the context of a temporary structure to aid in the construction of the target which is then later removed. In this case, the linked thiopyranone monomers are the scaffold which is 'removed' upon desulfurization to afford the target molecule.
Figure 24. A retrosynthetic analysis of an hexapropionate.

The hexapropionate synthon 119 is synthesized in two steps from 121 and 122. Aldol reaction of 122 (or 120) with 121 is impractical and the protected reagent 125a was selected as a synthetic equivalent of 121 (Figures 25 and 26). A practical advantage of this approach is that both 122 and 125a are derived from the cyclic \( \beta \)-ketoester 124 which is easily prepared from the commercially available diester 123 (Figure 25). The initial aldol reaction of 122 and 125a can produce up to four diastereomers 126a-129a. The subsequent aldol reactions of 126a-129a with 125a can give up to 20 diastereomers (16 enantiomeric pairs and 4 meso compounds) of hexapropionate synthon 132 (Figure 26). Thus single or consecutive aldol reactions using 122 and 125a as the only building blocks promise to be efficient one step or two step approaches to stereochemically diverse tetrapropionate 126a-129a and hexapropionate 132 synthons, respectively. The success of such an approach will crucially depend on the extent to which the diastereoselectivity of the aldol reactions can be controlled (Figures 25 and 26).
Figure 25. The thiopyran route to tetrapropionates: The first aldol reaction.
Figure 26. The thiopyran route to hexapropionates: The second aldol reaction.

To gain an appreciation of the challenge involved in the stereoselective syntheses of these polypropionate synthons 126a-129a and 132, the stereochemical control elements involved in the first and second aldol reactions should be considered. The four diastereomers from the reaction of 122 and 125a arise from the combination of the diastereoface selectivity for addition to the chiral aldehyde 125a and the relative topicity of the aldol coupling. In Section 2.2 the results towards the diastereoselective synthesis of each of the four diastereomers will be discussed. The diastereoselectivity of the second aldol reaction involves the diastereoface selectivity for addition to the chiral enol(ate) of 126a-129a, the diastereoface selectivity for addition to carbonyl of aldehyde 125a, and the relative topicity of aldol coupling. Because the ketones 126a-129a and the aldehyde 125a are chiral, the diastereoselectivity of their aldol reactions will be modulated by double stereodifferentiation (cf. Section 1.2.5.1). Furthermore, because the ketones 126a-129a and aldehyde 125a used in this study were racemic, the diastereoselectivity of the aldol reaction is additionally influenced by mutual kinetic
enantioselection (MKE) (cf. Section 1.5.2.2). The results of the investigation of the diastereoselectivity of the second aldol reaction are discussed in Section 2.3.

Although polypropionates in nature are found in enantiopure form their enantioselective synthesis is not the subject of this investigation. However, it has been demonstrated that polypropionate synthons can be synthesized in enantioenriched form with the use of enantioenriched substrate 125a. The synthesis of enantioenriched substrate 125a and its application to the synthesis of enantioenriched aldols is a subject of investigation within the Ward group.* Another approach to obtain enantioenriched polypropionate synthons involves the desymmetrization of a meso diastereomer of 135 via an enantiotopic group selective reaction (Figure 27). There are four possible meso diastereomers of 135. The desymmetrization of meso-135 has also been a topic of investigation in the Ward group.† The great advantage of this approach is that easily obtainable racemic substrates could be used in the synthesis of the four possible meso-135 compounds.

\[
\text{meso-135} \quad \rightarrow \quad \text{enantioenriched 136}
\]

Figure 27. Enantioenriched polypropionates by desymmetrization of a meso-135.

Irrespective of which approach is used to obtain enantioenriched polypropionates it is imperative to have prior knowledge of the diastereoselectivities of the first and second aldol coupling reactions. The importance of executing the first and second aldol reactions diastereoselectively cannot be overemphasized. These issues are addressed in the sections to follow.

* Work done by I. Alarcon and K. Akinmussi has led to the synthesis of enantioenriched 125a. The work of I. Alarcon has led to synthesis of enantioenriched aldol 126a.

† Success in the desymmetrization of meso compounds 135 has been demonstrated by Dr. K. Saravanan and H. M. Gillis.
2.2. CONTROLLING THE DIASTEREOSELECTIVITY OF THE FIRST ALDOL REACTION

The results of the efforts towards a diastereoselective synthesis of each of the four diastereomers 126a-129a are discussed. The investigation comprised a study of the effect of the aldehyde β-substituent on reaction diastereoselectivity under various reaction conditions.

2.2.1. The Diastereoselectivity of Aldol Reactions of Ketone 122 with Aldehyde 125a

Section 2.2.1 contains previous contributions made by members of the Ward group, and describes the progress made towards the diastereoselective synthesis of the four possible diastereomers 126a-129a.

The aldol reaction between 125a and the lithium diisopropylamide generated enolate 137a was first reported by Hayashi to give adduct 127a in 85% yield with excellent diastereoselectivity (126a:127a = 1:50). In an effort to reproduce Hayashi’s results the required substrates 122 and 125a were synthesized from readily available dimethyl 3,3-thiodipropionate 123 and the aldol couplings were carried out under the reported reaction conditions. Despite extensive experimentation, all attempts by the Ward group to reproduce the yield and diastereoselectivity reported by Hayashi for the reaction of 125a with 137a were unsuccessful (Table 6, entry 1). It was initially suspected that the adducts ‘profound tendency towards retroaldolization’ reported by Hayashi was responsible for the inability to reproduce the reported results. However, it was demonstrated that both aldol adducts 126a and 127a were recovered unchanged (>85% yield) after treatment with LDA under the reaction conditions reported by Hayashi. Eventually use of an ‘amine free’ Li-enolate was investigated based on a note in Woodward’s erythromycin A synthesis indicating that an important aldol coupling of a dithiadeclalone proceeded in higher yield using an ‘amine free’ Li-enolate generated from mesityllithium compared to the use of an LDA generated enolate. The ‘amine free’ enolate 137c was generated by the addition of MeLi to the enolsilane 137b. Fortunately the aldol coupling between aldehyde 125a and 137c
reproducibly gave a readily separable* 9:1 mixture of adducts 127a and 126a, respectively in 70% total isolated yield (Table 6, entry 2). That the behaviour of LDA generated enolates and ‘amine free’ enolates are different is not unexpected because it is well established that the i-Pr2NH product formed from the reaction of LDA with ketones is associated with the enolate (e.g. 137a) and can affect the ensuing chemistry.132 Nonetheless, there are few reports of the influence of this phenomenon on aldol diastereoselectivity.

The aldol reaction of 125a with the putative Mg-enolate133,134 formed by the reaction of 137c with MgBr2•OEt2 gave 127a with poor diastereoselectivity (Table 6, entry 3). Similar reaction of 125a with the Ti(IV) enolate generated from reaction of 122 with TiCl4 and i-Pr2EtN gave 126a in poor yield and modest diastereselectivity (Table 6, entry 4). The aldol reactions of 125a with the boron-enolates 137e and 137f gave 127a selectively in good yield. (Table 6, entries 4 and 5). However, for large scale preparation of aldol 127a the use of the ‘amine free’ Li-enolate 137c was preferred since the adduct 127a could be directly crystallized from the crude reaction mixture.

![Scheme 12. Aldol reaction between 125a and 137.](image)

*The major aldol 127a was directly crystallized from the crude reaction mixture.
Table 6. The diastereoselectivity of aldol reactions between 125a and various enolates 137a, c-f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enolate (#equiv)</th>
<th># Equiv aldehyde 125a</th>
<th>Lewis acid (#equiv)</th>
<th>Yield (%)</th>
<th>Ratio of aldols 126a</th>
<th>127a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>137a (1)</td>
<td>1.2</td>
<td></td>
<td>15-40</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>137c (1.5)</td>
<td>1</td>
<td>MgBr₂·OEt₂ (2)</td>
<td>77</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>137e (2)</td>
<td>1</td>
<td></td>
<td>46</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>137d (1)</td>
<td>1.2</td>
<td></td>
<td>46 f</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>137e (1)</td>
<td>4</td>
<td></td>
<td>82 g</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>137f (1)</td>
<td>4</td>
<td></td>
<td>84 g</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>

The diastereoselectivity of Lewis-acid promoted reactions of enolsilane 137b with aldehyde 125a were also investigated (i.e. Mukaiyama reactions). The reactions promoted by BF₃·OEt₂ and SnCl₄ gave mixtures of aldols 126a and 127a in good yield but with modest diastereoselectivities (Table 7, entries 1 and 2). By contrast, the TiCl₄ promoted aldol reaction proceeded in high yield and with excellent diastereoselectivity favouring aldol 126a.
Table 7. Diastereoselectivity of Lewis acid promoted aldol reactions of 137b with 125a

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Enolate(#)equiv</th>
<th># Equiv aldehyde 125a</th>
<th>Lewis acid(#)equiv</th>
<th>Yield(^b) (%)</th>
<th>Ratio of aldols</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>137b (2)</td>
<td>1</td>
<td>BF(_3)OEt(_2) (3)</td>
<td>74(^c,d)</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>137b (2)</td>
<td>1</td>
<td>SnCl(_4) (3)</td>
<td>72(^e)</td>
<td>1 3</td>
</tr>
<tr>
<td>3</td>
<td>137b (1.5)</td>
<td>1</td>
<td>TiCl(_4) (1)</td>
<td>87(^c)</td>
<td>16 1</td>
</tr>
</tbody>
</table>

\(^a\) Entries 1 and 2 was obtained in this study and entry 3 was obtained by C. C. Man and C. Guo\(^\text{18}\) and confirmed by P. K. Sasmal.\(^\text{129}\) \(^b\) Percentages represent the total isolated yield of all aldol products. Yield is calculated with respect to the limiting reagent. \(^c\) Reaction at -78°C for 1 hr. \(^d\) The yield reported as percentage conversion of aldehyde 125a to aldol product. \(^e\) Reaction at 0°C for 2 h.

In the aldol reactions of aldehyde 125a and enolates 137a-f there are four diastereomeric adducts possible i.e. 126a-129a. There are two control elements that influence the diastereoselectivity of this reaction which is the aldehyde diastereoface selectivity and the relative topicity of the reaction. Appropriate models explaining the observed relative topicities (1',3-syn or anti in aldols 126a-129a) given in Tables 6 and 7 are discussed, followed by a discussion of an appropriate model to rationalize the observed aldehyde diastereoface selectivities (1',6'-syn or anti in aldols 126a-129a).

The observation that the relative topicities are \textit{anti}-selective for the reactions involving Li-, B- and Mg-enolates (Table 6, entries 1-5) can be rationalized by invoking participation of the necessarily (E)-enolates\(^*\) in ‘closed’ chairlike Zimmerman-Traxler transition states (Figure 28). (cf. Section 1.2.1 for discussion of Zimmerman-Traxler model). The trend that boron enolates are more selective than Li-enolates has been attributed to the shorter B-O bond lengths compared to the Li-O bond lengths present in the ‘closed’ Zimmerman-Traxler transition state\(^\text{137,138}\) and may be responsible for the

\(^\text{*}\) Note that the enolates 137a,c-f are cyclic E-enolates.
observed higher selectivities obtained from boron enolates 137e and 137f (Table 6, entries 5 and 6) compared to Li-enolate 137c (Table 6, entry 2).

\[ \text{OM} \rightarrow \text{RCHO} \]

137a,c-f

E-enolate

\[ \text{R} = \text{RCHO} \]

127a

1',3-anti selective

Figure 28. The Zimmerman-Traxler model predicts anti-selective relative topicity for additions of E-enolates 137a,c-f to 125a.

The Lewis acid promoted Mukaiyama reactions are believed to occur through ‘open’ transition states and the energetically favoured relative orientations of the reaction partners in the transition state dictate the relative topicicity of the aldol reaction (cf. Section 1.2.1 for discussion of topicity of Lewis Acid promoted aldol reactions). Among the possible 4 diastereomeric products 126a-129a, the aldol reactions reported in Table 7 each produced a mixture of only two products of 126a and 127a, and there was a wide variation in the observed 126a:127a ratios. Reactions with BF$_3$OEt$_2$ and TiCl$_4$ are syn-selective (126a is major) and reaction with SnCl$_4$ is anti-selective (127a is major). The syn-selective aldoltopicity obtained from the BF$_3$OEt$_2$ and TiCl$_4$ promoted reactions can be accounted for by a qualitative examination of the steric and electronic interactions of the substituents in the ‘open’ transition states (TS) represented by structures A-F (Figure 29). The most unfavourable steric and dipole-dipole interactions occur in TS B, D and F and these are predicted to be highly disfavoured. TS A and E both have moderately disfavoured steric and dipole-dipole interactions and these TS are expected to be disfavoured relative to TS C. The work of Denmark and Heathcock$^{81,139-142}$ is in support of the above qualitative assessment where the factors which favour staggered arrangements in open transition states such as depicted by C are discussed.
The Mukaiyama reaction promoted by SnCl₄ gave 1',3-anti relative topicity predominantly (Table 7, entry 2). The 1',3-syn selectivity of aldol reactions of (E)-enolsilanes promoted by BF₃•OEt₂ and TiCl₄ and the 1',3-anti selectivity of reactions promoted by SnCl₄ was also observed by Denmark.¹⁴⁰ Unlike the reactions promoted by BF₃•OEt₂ and TiCl₄, it is proposed that the reactions between 125a and 137b promoted by SnCl₄ occurs through a closed transition state where a chloride ligand facilitates the reaction by removal of the silicon moiety (Figure 30). Rationale for the preference of SnCl₄ promoted reactions to occur through a ‘closed’ transition state were given by Denmark.¹⁴⁰ These reasons include the attenuated Lewis acidity of SnCl₄ which would lower the contribution of product from an ‘open’ transition state, the ability of SnCl₄ to coordinate to both enol and aldehyde oxygens, and the ability of the chloride counterion in SnCl₄ to remove the silicon moiety of the enolsilane. The ability of a Lewis acid to coordinate to an enol oxygen has been proposed before.¹⁴³-¹⁴⁵ Furthermore, SnCl₄ has been shown to coordinate to both alkoxy and aldehyde oxygens in β-alkoxy aldehyde
Evidence for the participation of the counterion in the transition state was the observation by Denmark that the selectivity of the aldol reaction is dependant on the nature of the counterion where selectivity decreased in the order of Cl > Br > I > OTf.\(^{140}\)

**Figure 30.** Proposed ‘closed’ transition state for aldol reaction of 137b with 125a promoted by SnCl\(_4\).

For all of the examples described thus far (Tables 6 and 7), the diastereoface selectivity for addition to aldehyde 125a was very high resulting in 1,6”-syn aldol products (i.e. 126a and 127a) exclusively. The various models used to rationalize and predict the diastereofacial selectivity of addition of nucleophiles to chiral aldehydes have been discussed in Section 1.2.4. Amongst these, the Felkin-Anh model is appropriate to rationalize the observed 1’,6”-syn diastereoselectivity (Figure 31). Thus, assuming the acetal carbon to be the large group, application of the Felkin-Anh model to 125a suggests preferential addition to conformer A via the Burgi-Dunitz trajectory to give products with 1’,6”-syn relative configuration (Figure 31). The product predicted by the Felkin-Anh model is denoted as the ‘Felkin’ product.

\(^{*}\) Notice that the arrangement of both oxygens of the enolsilane and aldehyde about Sn(IV) in the transition state proposed in Figure 30 can be likened to the arrangement of both oxygens in a β-alkoxy aldehyde chelated to Sn(IV).
Figure 31. Felkin model applied to rationalize the observed selectivities for addition to aldehyde 125a.

From this earlier work done by the Ward group it was established that two out of the four possible diastereomers could be selectively prepared in good yield. The TiCl₄ promoted aldol reaction afforded adduct 126a (1’3-syn-1’,6”-syn) and the reaction of the ‘amine free’ Li-enolate 137c with 125a selectively afforded adduct 127a (1’3-anti-1’,6”-syn). The aldol adducts 128a and 129a were not detected under the reaction conditions previously attempted. For the aldol reaction of 122 with 125a to be of general utility towards the synthesis of tetrapropionate synthons (Figure 25) it was essential to devise conditions to access the elusive aldol adducts 128a and 129a. Such adducts would result from addition to aldehyde 8a with anti-Felkin diastereoface selectivity leading to products with 1’,6”-anti relative configurations. The synthesis of these elusive aldols 128a and 129a was an important objective of this study of the first aldol reaction.
Although the Felkin-Anh model can account for the diastereoselective formation of 1',6''-syn aldol adducts from reaction of enolates of 122 with 125a under various reaction conditions (see Tables 6 and 7), the influence of the ketal substituent of 125a towards the aldehyde diastereoface selectivity was not clear. To probe the influence of the cis- and trans-ketal oxygens of aldehyde 125a on the aldehyde diastereoface selectivity the cis- and trans-β-alkoxy aldehydes 125b and 125c were proposed as substrates for the aldol reaction (Figure 32). The aldol reactions of these model substrates would provide a greater understanding of the influence of the relative configuration of the β-alkoxy substituent on the aldehyde diastereoface selectivity and may provide insight towards obtaining the elusive 1',6''-anti (anti-Felkin) aldol adducts 128a and 129a.

![Diagram of substrates 125a, 125b, and 125c](image)

* oxygen in cis-orientation
** oxygen in trans-orientation

**Figure 32. Proposed substrates 125b and 125c to investigate the relative configuration of the β-alkoxy substituent on aldol diastereoselectivities.**

### 2.2.2. Influence of the β-Alkoxy-Substituent on the Diastereoselectivity of Aldol Reactions of Aldehyde 125

In the sections to follow, the synthesis and aldol reactions of aldehydes 125b and 125c is presented and models to account for the observed aldol diastereoselectivities are proposed.
2.2.2.1. Preparation of aldehydes 125b and 125c

Reduction of 124 with NaBH₄ has been previously reported. In my hands this reaction gave modest yields of a 1.5-2:1 mixture of 138 and 139, respectively. Starting β-ketoester 124 was not recovered and it was deduced that 124 was possibly unstable to the basic reaction conditions, prompting the use of NaCNBH₃ as an alternative reducing reagent. Reduction of ketones with NaCNBH₃ is optimal between pH 3-4 and because one equivalent of acid (H⁺) is consumed during the reduction, an additional proton source must be provided to maintain this pH. A modified method by Borch et al. involves reaction in the presence of indicators (bromocresol green or methyl orange) with methanolic HCl added dropwise to maintain the appropriate indicator colour. In my modification, the reduction was conveniently conducted in the presence of 1 equivalent of citric acid which maintained the optimal pH between 3-4. With this protocol the reduction of 124 was conveniently carried out on 40 g scale to provide alcohols 138 and 139 in 49% and 24% isolated yield, respectively (Scheme 13). The individually isolated alcohols 138 and 139 were converted to the corresponding MOM-protected derivatives 140 and 141 in high yields, respectively, by reaction with MOMCl and i-Pr₂EtN in the presence of tetrabutylammonium iodide (Bu₄NI). The LiAlH₄ reductions of the individual esters 140 and 141 occurred without incident to give the alcohols 142 and 143 in good yields.

Swern oxidation of alcohol 142 under standard reaction conditions resulted in a poor yield of aldehyde 125b (40-60% isolated yield). However, the oxidation of 142 with a modified Swern procedure, with two equivalents of dimethyl sulfide as an additive, gave 125b in excellent yield (89%).

Swern oxidation of alcohol 143 gave poor yields of 125c (20-50%) together with a significant amount of a side product. Analysis of the ¹H NMR spectrum of the side product suggested structure 144 (Scheme 13). It was proposed that 144 was derived from the reaction of the sulfur atom in 143 with the chlorodimethylsulfonium ion

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*Citric acid is a tricarboxylic acid with three exchangeable hydrogens with pKa₁ = 3.14, pKa₂ = 4.77 and pKa₃ = 6.39. It is the pKa₁ = 3.14 which is responsible for buffering the pH between 3-4 since as the 1 equivalent of NaCNBH₃ reacts to consume one equivalent of H⁺ the conjugate base of citric acid is generated internally and the reaction system is buffered around the pH of 3.14.
generated under Swern conditions (Scheme 33); quenching the reaction with water converts 145 to 144. To minimize the putative transfer of the chloro-ligand from 145 to 144, two equivalents of dimethyl sulfide was added. Unfortunately, the use of this modified Swern procedure did not lead to an improvement in yield of 125c (only 23%) and 144 remained a major side product (25%). An alternative route to aldehyde 125c was the reduction of ester 141 with DIBAL-H (Scheme 13). This reaction occurred without incident to give consistent yields (>60%) of 125c provided that care was taken to ensure destruction of excess DIBAL-H prior to workup.\(^{150}\)

Scheme 13. Synthesis of MOM-protected aldehydes 125b and 125c.
2.2.2.2. Diastereoselectivity of aldol reactions of 122 with aldehydes 125b and 125c

Reactions of the ‘amine free’ lithium enolate 137c with the aldehydes 125b and 125c (Table 8, entries 1 and 2) led to the diastereoselective formation of aldol adducts with 1',3-anti-1',3''-syn relative configurations (i.e. 127b and 127c, Scheme 14). Reaction of 137c with 125c gave the adduct 127c exclusively in good yield (Table 8, entry 2). The reaction of 125b with 137c led to the formation of 127b with modest diastereoselectivity along with two other diastereomers. Significantly, this latter reaction gave isolable amounts of aldol adduct 129b with the elusive 1',3-anti-1',3''-anti relative configuration establishing that the orientation of the β-alkoxy group in 125 could modulate diastereoface selectivity for addition to the aldehydes.

Aldol adducts were obtained in poor yield from the TiCl₄ mediated reaction of 125b with 137b (Table 8, entry 3). The low yield is attributed to the propensity of 125b to undergo elimination in the presence of TiCl₄. Though aldol 129b possessing the 1,3''-anti relative configuration was obtained, the yield and diastereoselectivity for this product were too poor to be of any practical value. By contrast, the TiCl₄ promoted
reaction between 125c and 137b gave 126c in good yield and with good diastereoselectivity (Table 8, entry 4).

Mg (II) promoted aldol reactions of enolsilanes to α-heteroatom substituted aldehydes are known and reports by Mukaiyama, Heathcock and Scolastico have claimed that MgBr₂•OEt₂ effected chelation controlled addition of enolsilane to α-alkoxy aldehydes.¹⁴¹,¹⁵¹-¹⁵⁵ This literature precedence combined with our experience (work done by M. J. Hrapchak and myself) that MgBr₂•OEt₂ was uniquely able to effect a highly selective chelation controlled addition of TMSCN to α-alkoxy aldehydes for the diastereoselective formation of cyanohydrins¹⁵⁶ led to the exploration of MgBr₂•OEt₂ to promote the reactions of β-alkoxy aldehydes 125b and 125c with 137b.*

Scheme 14. Aldol reaction of 125b and 125c with 137.

The aldol reactions promoted by MgBr₂•OEt₂ between 125b and 137b proceeded with high aldehyde diastereoface selectivity since only the 1'-3''-anti products 128b and 129b were obtained (Table 8, entry 5). The total isolated yield of aldol adducts was 84% and the reaction was selective for the formation of aldol 128b. The aldol 128b could be obtained in 57% yield by crystallization from the crude

* To the best of my knowledge the use of MgBr₂•OEt₂ to promote aldol reactions between enolsilanes and β-alkoxy aldehydes have not been reported.
reaction mixture. The resultant supernatant was subjected to chromatography to yield the remaining 27% of combined aldols 128b and 129b.

Table 8. Investigation of the diastereoselectivity of aldol reactions of cis-MOM (125b) and trans-MOM (125c)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enolate (#equiv)</th>
<th>Aldehyde (#equiv)</th>
<th>Promoter (#equiv)</th>
<th>Aldol series</th>
<th>Yield%</th>
<th>Ratio of aldols</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>137c (2)</td>
<td>125b (1)</td>
<td>b</td>
<td>b</td>
<td>61</td>
<td>1 4 1.5</td>
</tr>
<tr>
<td>2</td>
<td>137c (2)</td>
<td>125c (1)</td>
<td>b</td>
<td>c</td>
<td>64</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>137b (2)</td>
<td>125b (1)</td>
<td>TiCl₄ (1)</td>
<td>b</td>
<td>27</td>
<td>1 1.3</td>
</tr>
<tr>
<td>4</td>
<td>137b (2)</td>
<td>125c (1)</td>
<td>TiCl₄ (1)</td>
<td>c</td>
<td>81</td>
<td>20 1 2</td>
</tr>
<tr>
<td>5</td>
<td>137b (2)</td>
<td>125b (1)</td>
<td>MgBr₂·OEt₂ (3)</td>
<td>b</td>
<td>84</td>
<td>3.5 1</td>
</tr>
<tr>
<td>6</td>
<td>137b (2)</td>
<td>125c (1)</td>
<td>MgBr₂·OEt₂ (3)</td>
<td>c</td>
<td>74</td>
<td>4 7 1</td>
</tr>
</tbody>
</table>

*a The combined isolated yield of all aldol products.  
*b Reaction at −78°C for 5 minutes.  
*c Reaction at −78°C for 1hr.

The aldol reaction promoted by MgBr₂·OEt₂ between 125c and 137b proceeded with lower aldehyde diastereoface selectivity giving the 1'"-3"'-anti products 128c and 129c and the 1'"-3"'-syn product 126c (Table 8, entry 6).

The ability of MgBr₂·OEt₂ promoted aldol reactions of β-alkoxy aldehydes 125b and 125c to selectively give anti-Felkin adducts prompted an investigation of MgBr₂·OEt₂ promoted reactions between 125a with enolsilane 137b (see Table 9).

The MgBr₂·OEt₂ promoted reactions between 125a and 137b resulted in the exclusive formation of the anti-Felkin (1"',6"'-anti) adducts 128a and 129a (Table 9). The diastereoselectivity increased with the number of equivalents of MgBr₂·OEt₂ (Table 9, entries 1-7) as was previously observed in our study₁⁵⁶ of addition of
'cyanide' (i.e. Et₄NCN, Et₄NAg(CN)₂ and TMSCN) to α-alkoxy aldehydes. The diastereoselective formation of aldol 128a was optimum with 3 equivalents of MgBr₂·OEt₂ with no significant increase with greater amounts. By increasing the aldehyde concentration the reaction time required for high conversion was greatly reduced (Table 9, entries 8 and 9). With the use of three equivalents of MgBr₂·OEt₂ and an aldehyde 125a concentration of 0.2 M complete conversion to aldol product was achieved in 1 h. These optimized reaction conditions (entry 9) left little unreacted 125a

Table 9. The stoichiometry effect of MgBr₂·OEt₂ on the diastereoselectivity of the aldol reaction of 125a with 137b

<table>
<thead>
<tr>
<th>Entry</th>
<th>[125a] M</th>
<th># equiv MgBr₂·OEt₂</th>
<th>% conversionb 128a : 129a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.04</td>
<td>0.5</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>0.04</td>
<td>1.0</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>0.04</td>
<td>1.5</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>0.04</td>
<td>2.0</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>0.04</td>
<td>2.5</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>0.04</td>
<td>3.0</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>0.04</td>
<td>5.0</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>0.08d</td>
<td>3.0</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>0.2d</td>
<td>3.0</td>
<td>98 (89)e</td>
</tr>
</tbody>
</table>

a Unless otherwise indicated, all reported reaction times are 4 h at 0°C. b The percentage of 125a converted to aldol products 128a and 129a as determined by ¹H NMR. c Reaction time extended to 6 days at ambient temperature since no product was detected after 4 h. d Reaction time of 1 hour. e The 89% reported in parenthesis is the combined isolated yield of 128a and 129a.
and allowed the expedient crystallization of 128a directly from the crude reaction mixture. The remaining material in the supernatant was fractionated by chromatography to afford a further 6% of 128a and 22% of 129a. A convenient procedure for the preparation of aldol 128a had thus been developed.

2.2.2.3. Transition-state models used to rationalize diastereoselectivities of aldol reactions

Reactions of chiral aldehydes 125b and 125c with achiral enolates of 122 (137a-137f) involved two stereocontrol elements: the relative topicity of the aldol reaction (1',3-syn/anti selectivity) and the aldehyde diastereoface selectivity (1',3"-syn/anti selectivity). Both 'closed' and 'open' transition state models are used to rationalize the observed relative topicities of the aldol reactions given in Table 8, and are now discussed. This will be followed by a discussion of the models used to account for the observed aldehyde diastereoface selectivities of the aldol reactions given in Table 8.

The Zimmerman-Traxler model as depicted earlier in Figure 28 can be applied to rationalize the selective formation of 1',3-anti products from reactions of Li-enolate 137c with aldehydes 125b and 125c (Table 8, entries 1 and 2).

The open transition state model as depicted earlier in Figure 29 can be used to rationalize the selective formation of 1',3-syn products from reactions of 137b with 125b or 125c promoted by MgBr2·OEt2 (Table 8, entries 5 and 6) and for the reaction of 125c with 137b promoted by TiCl4 (Table 8, entry 4). It is not clear why the relative topicity of the aldol reaction of 125b with 137b promoted by TiCl4 was selective for the 1',3-anti products 127b and 129b (Table 8, entry 3). However, the observed predominance of 127b and 129b may not represent the true selectivity of this reaction because 126b was not stable to TiCl4 (mainly elimination) and the low yield of aldol products (27% combined isolated yield of aldols 127b and 129b) precluded a confident assessment of the selectivity.

The stereochemical model recently proposed by Evans et al.98 that combines the effects of a substituent at the α-position (1,2-stereoinduction) and at the β-position (1,3-stereoinduction) of the aldehyde is well suited to predict and rationalize the
diastereoface selectivity of addition to the aldehyde in 125b and 125c (cf. Section 1.2.4.3).

The Evans’ merged 1,2- and 1,3-stereoinduction model as applied to aldehyde 125b is shown in Figure 34. In conformer B the \(\alpha\)-‘methylene’ substituent directs the nucleophilic attack to favour 1’,3”-syn products (Felkin selectivity) however this conformer B has an unfavourable dipole-dipole interaction. In conformer C the unfavourable dipole-dipole interaction between the \(\beta\)-methoxymethoxy substituent and

\[
\begin{align*}
\text{125b} & \equiv \\
\text{B} & \equiv \\
\text{C} & \equiv
\end{align*}
\]

Figure 34. Merged 1,2- and 1,3-stereoinduction model used to rationalize the low aldehyde diastereoface selectivity of addition to 125b.

the carbonyl group is removed and 1’,3”-anti products are favoured, but this conformer C presents an unfavourable steric interaction with the approaching nucleophile. For aldehyde 125b these models illustrate that the \(\alpha\)- and \(\beta\)-substituents are in a non-reinforcing relationship and that a low diastereoface selectivity for addition to the aldehyde may result. This model accounts for the low aldehyde diastereoface selectivity
(i.e. poor 1',3''-syn/anti product ratios) observed in the reactions of 125b with Li-enolate 137c (1',3''-syn: -anti, (1+4) : 1.5, see Table 8, entry 1) and with enolsilane 137b in the presence of TiCl₄ (1',3''-syn: -anti, 1 : 1.3, see Table 8, entry 3).

The Evans’ model applied to aldehyde 125c is shown in Figure 35. In conformer D the orientation of the α-‘methylene’ does not sterically impede the approach of the Nu and the orientation of the β-methoxymethoxy substituent does not present an unfavourable dipole-dipole interaction with the carbonyl group. The α- and β-substituents are in a reinforcing relationship and the Evans’ model predicts a high Felkin aldehyde diastereoface selectivity favouring 1',3''-syn products. Reactions of 125c with Li-enolate 137c (only one 1',3''-syn product detected, Table 8, entry 2) and with enolsilanes 137b in the presence of TiCl₄ (1',3''-syn: -anti, 20 : (1+2), see Table 8, entry 4) are highly Felkin (1',3''-syn) selective.

Figure 35. Merged 1,2- and 1,3-stereoinduction model used to rationalize high Felkin aldehyde diastereoface selectivity of addition to 125c.

The aldol reactions of 125b and 125c with 137b promoted by MgBr₂•OEt₂ were highly selective for the formation of anti-Felkin (1',3''-anti) products (Table 8, entries 5 and 6). This is in contrast to the predominant Felkin selectivity (1',3''-syn) obtained with the use of Li-enolate 137c and in TiCl₄ promoted reactions with 137b (Table 8, entries 1-4). This dramatic reversal of the aldehyde diastereoface selectivity from Felkin selective in the presence of TiCl₄ to anti-Felkin selective in the presence of MgBr₂•OEt₂ strongly supports the hypothesis that MgBr₂•OEt₂ (and not TiCl₄) is effecting chelation controlled addition of enolsilane 137b to the aldehydes 125b and 125c. The reversal in aldehyde diastereoface selectivity (i.e. from 1',6''-syn to 1',6''-anti selective) was also
observed for the MgBr₂·OEt₂ promoted addition of 137b to 125a (Table 9). Chelation models (Figures 36-38) are proposed to rationalize the anti-Felkin selectivities for the MgBr₂·OEt₂ promoted addition of 137b to aldehydes 125b, 125c and 125a and are now discussed.

![Chelation Models](image)

Figure 36. Proposed ‘chelation controlled addition’ model to rationalize high anti-Felkin (1′,3″-anti selective) aldehyde diastereoface addition to 125b.

Exclusive anti-Felkin aldehyde diastereoface selectivity was observed for the MgBr₂·OEt₂ promoted addition of 137b to 125b to give products 128b and 129b only (Table 8, entry 5). It is proposed that the six-membered Mg-chelated intermediate
assumes a half-chair conformation (Figure 36). An axial approach of a nucleophile, responsible for the formation 1',3''-anti adducts, leads to the initial formation of a more thermodynamically stable chair conformer B (Figure 36). Not only is a nucleophilic

![Chemical structure](image)

more stable conformer A

more hindered axial approach of Nu

Least hindered approach of Nu

less stable conformer B

Figure 37. Proposed ‘chelation controlled addition’ model to rationalize moderate anti-Felkin (1’,3”-anti selective) aldehyde diastereoface addition to 125c.
approach which leads to the formation of 1',3''-syn adducts the more sterically hindered approach, it is also the approach which leads to the initial formation of the less thermodynamically stable twist boat conformer A (Figure 36). Both the steric argument as well as the resultant formation of the less stable conformer A disfavours the formation of 1',3''-syn adducts, whilst the sterically less hindered axial approach coupled with the resultant formation of a more thermodynamically stable conformer B is responsible for the high anti-Felkin selectivity.

The much more moderate anti-Felkin selectivity for addition to aldehyde 125c is rationalized by the six-membered chelated intermediate model in Figure 37. The least sterically hindered approach of a nucleophile to 125c leads to the 1',3''-anti products. However, this approach leads to the initial formation of the less thermodynamically stable twist boat conformer B, and as a result the 1',3''-anti selectivity will be attenuated. The axial approach which gives 1',3''-syn adducts leads to the formation of the thermodynamically more stable conformer A, but the axial approach is also more sterically hindered; therefore the 1',3''-syn selectivity is attenuated. In contrast to 125b, the faces of the aldehyde 125c are not decisively differentiated leading to lower selectivity.

A similar six-membered chelated model in a half-chair conformation proposed in Figure 36 is used to account for the anti-Felkin selectivity (see Table 9) of additions to 125a in the presence of MgBr₂·OEt₂ (Figure 38).

Figure 38. Proposed ‘chelation controlled addition’ model for nucleophilic attack to 125a.
Several arguments support my hypothesis of chelation controlled additions of 137b to aldehydes 125a, 125b and 125c in the presence of MgBr₂-0Et₂ but not with TiCl₄ and SnCl₄. It has been established by NMR that the Lewis acids MgBr₂-0Et₂, TiCl₄ and SnCl₄ can form chelates with β-alkoxy aldehydes;¹⁵⁷,¹⁵⁸ however in a recent study Evans et al.¹⁵⁹ demonstrated that the use of Lewis acids with two vacant coordination sites do not necessarily result in a reaction via a chelated bidentate intermediate. In that study it was shown that chelation control was unlikely in both the TiCl₄ and SnCl₄ promoted reactions of 146 to 147 (Figure 39) since the high Felkin selectivity (i.e. in favour of 148) for these examples was also obtained in the presence of BF₃-0Et₂ where chelation is prevented since BF₃-0Et₂ only has one vacant coordination site. Furthermore, in that study the dramatic reversal of the aldehyde diastereoface selectivity for addition of 147 to aldehyde 146 in the presence of 2.5 equivalents of Me₂AlCl or MeAlCl₂ (Figure 39) strongly suggested a chelated intermediate in these reactions.

Figure 39. A demonstration of the reversal of aldehyde diastereoface selectivity by Evans et al.¹⁵⁹
In the present study, chelation control is unlikely in both the TiCl₄ and SnCl₄ promoted reactions of 137b to 125a (Table 7, entries 2 and 3) since the exclusive Felkin selectivity (1',6''-syn) observed for these examples was also obtained in the presence of the BF₃·OEt₂ where chelation is prevented due to BF₃·OEt₂ having only one vacant coordination site (Table 7, entry 1). Furthermore, in this study the dramatic reversal of the aldehyde diastereoface selectivity for addition of 137b to aldehydes 125a, 125b and 125c in the presence of MgBr₂·OEt₂ (Table 8, entries 5 and 6 and Table 9) strongly supports a chelated intermediate in these reactions. The superior ability of MgBr₂·OEt₂ compared to SnCl₄ and TiCl₄ to be chelated by β-alkoxy aldehydes has also been previously noted by Keck et al.¹⁵⁷,¹⁵⁸

2.2.2.4. Comparison of the diastereoselectivities of the 1st aldol reaction with related acyclic examples

It is instructive to compare the diastereoselectivities obtained in this study of the aldol reactions of enolsilane 137b with aldehydes 125b and 125c to those that were reported by Evans et al.³⁸,¹⁶⁰ for similar aldol reactions of the structurally related acyclic aldehyde (150, 156) and enolate (151) analogues (Figures 40 and 41). The trans aldehyde 125c and the related anti aldehyde 150 give very similar diastereoselectivities under similar conditions (Figure 40). For example, the reaction of the lithium (E)-enolate 137c with 125c and the reaction of (E)-enolate 151 with 150 are highly selective for Felkin addition and for anti relative topicity to give the adducts 127c (exclusive) and 153 (86% ds),* respectively. The related Mukaiyama reactions of 137b with 125c promoted by TiCl₄ and 151 (M=TMS) with 150 promoted by BF₃·OEt₂ are also highly selective for Felkin addition, but with syn relative topicity to give adducts 126c (87% ds) and 152 (95% ds), respectively. Interestingly, the minor adduct 153 from the Mukaiyama reaction of 151 (M = TMS) is also derived from Felkin addition, whereas the minor adducts 128c and 129c from the reaction of 125c are from anti-Felkin addition.

* Percent diastereoselectivity (ds) is defined here as the mole fraction of the designated diastereomer.
The diastereoselectivities of the reactions of the cis aldehyde 125b and the related syn aldehyde 156 are also similar but much lower than above. For example, the reactions of 137c with 125b and 151 (M=Li) with 156 gave only modest diastereoselectivity (Figure 41). In both cases, the major product arises from Felkin addition and anti relative topicity to give adducts 127b (62% ds) and 159 (51% ds). The anti/syn relative topicity ratios among the Felkin adducts are also similar in the two reactions (i.e. 127b:126b, 4:1; 159:158, 4.5:1); however in this same reaction, the anti-Felkin syn adduct 160 (30% ds) is the second most abundant adduct from aldehyde 156, but the analogous diastereomer 128b is not detected in the reaction of 125b. Due to the low yield (27%) of the Mukaiyama reaction of 137b with 125b no confident determination of diastereoselectivity could be established for this reaction and no meaningful comparison can be made to the selectivity obtained from the reaction of 151 (M=TMS) with 156.
Evans' study

\[
\begin{array}{c}
\text{PO} \\
\text{i-Pr} \\
\text{H}
\end{array} 
\quad \rightarrow \quad 
\begin{array}{c}
\text{OM} \\
\text{i-Pr}
\end{array} 
\]

For \( M = \text{Li}, \ P = \text{PMB} \)

For \( M = \text{TMS}, \ P = \text{SiMe}_2^{+}\text{Bu} \)

This study

\[
\begin{array}{c}
\text{MOMO} \\
\text{OH} \\
\text{0-14}^a \\
\text{pr} \\
\text{pr}
\end{array} 
\quad \rightarrow \quad 
\begin{array}{c}
\text{MOMO} \\
\text{OH} \\
\text{126c} \\
\text{129c}
\end{array} 
\]

Product ratios taken from Evans' study

\[
\begin{array}{c}
\text{M = Li} \\
\text{M = TMS}
\end{array} 
\]

\[
\text{Product ratios taken from this study}
\]

\[
\begin{array}{c}
\text{M = Li} \\
\text{M = TMS}
\end{array} 
\]

\[
\begin{array}{c}
\text{152} \\
0-14^a \\
95
\end{array} 
\]

\[
\begin{array}{c}
\text{153} \\
86 \\
5
\end{array} 
\]

\[
\begin{array}{c}
\text{154} \\
0-14^a \\
-- \\
-- \\
4
\end{array} 
\]

\[
\begin{array}{c}
\text{155} \\
-- \\
-- \\
-- \\
9
\end{array} 
\]

\[^a\text{The combined mole fraction of adduct 152 and 154 is 14%}.\]

**Figure 40.** The diastereoselectivity of aldol reactions of trans aldehyde 125c and anti aldehyde 150\textsuperscript{38,160} as substrates are compared.
Evans' study

For $M = \text{Li}$, $P = \text{PMB}$
For $M = \text{TMS}$, $P = \text{SiMe}_2i\text{Bu}$

Product ratios taken from Evans' study

<table>
<thead>
<tr>
<th>$M = \text{Li}$</th>
<th>$M = \text{TMS}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>158</td>
<td>159</td>
</tr>
<tr>
<td>160</td>
<td>161</td>
</tr>
</tbody>
</table>

Product ratios taken from this study

<table>
<thead>
<tr>
<th>$M = \text{Li}$</th>
<th>$M = \text{TMS}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>125b</td>
<td>126b-129b</td>
</tr>
</tbody>
</table>

Figure 41. The diastereoselectivites when using cis aldehyde 125b and syn aldehyde 156 as substrates are compared.
2.2.3. Conclusion

Progress towards the execution of the first aldol reaction to diastereoselectively synthesise all four possible adducts 126a-129a has been made. Prior work demonstrated that two of the diastereomers 126a and 127a could be diastereoselectively synthesized using various reaction conditions; 126a is selectively obtained from the reaction of enolsilane 137b with 125a in the presence of TiCl₄ and 127a is selectively obtained with the reaction of Li-enolate 137c with 125a. This study demonstrated a diastereoselective synthesis of a third adduct 128a with the reaction of 137b with 125a in the presence of MgBr₂·OEt₂. The fourth adduct 129a can be obtained by isomerization of easily accessible 128a (cf. Section 2.4.2).

This study clearly demonstrated that the Felkin diastereoface selectivities for additions of 137b to aldehydes 125a, 125b and 125c mediated by TiCl₄ or SnCl₄ can be rationalized using non-chelation control models such as Felkin-Anh and merged 1,2- and 1,3-stereoinduction models. Support for non-chelation control was that Felkin selectivity was also observed for the reaction of 137b to 125a mediated by the monodenate BF₃·OEt₂ which precludes chelation; furthermore, the reactions of 137b with aldehydes 125a, 125b and 125c mediated by MgBr₂·OEt₂ showed a dramatic reversal in aldehyde diastereoface selectivity to anti-Felkin and strongly suggested chelation control. The literature is divided on the ability of Lewis acids with two vacant coordination sites to effect chelation control. There are reports which attribute the selectivities of addition reactions to α-alkoxy and β-alkoxy aldehydes mediated by TiCl₄ and SnCl₄ to chelation control. Evans has pointed out that these claims of chelation controlled addition are purely based on product analysis and that there is no direct evidence of a chelated intermediate. Furthermore, Evans has proposed nonchelation models as a viable alternative to rationalize the selectivities of addition reactions to aldehydes mediated by Lewis acids such as TiCl₄ which have two vacant coordination sites.

The merged 1,2- and 1,3-stereoinduction model was successfully applied by Evans et al. to rationalize the diastereoface selectivity of addition to the α-alkyl-β-alkoxy aldehydes 150 and 156. Despite the presence of the sulfur atom and the associated ring that restricts the number of possible transition states, the
diastereoselectivities for aldol reactions of 125b and 125c are strikingly similar to those obtained with the related acyclic analogues 150 and 156 and can also be rationalized using Evans’ model. The validity of Evans’ model is supported because the orientation of the β-alkoxy groups in 125b and 125c are fixed because of conformational rigidity.

This study demonstrated that the orientation of the β-alkoxy substituent on aldehydes 125b and 125c can modulate the aldehyde diastereoface selectivity. Furthermore, when comparing the reactions of 125a to the reactions of 125b and 125c, they suggest that the ketal group is a versatile stereocontrol element for aldehyde diastereoface selectivity. Under nonchelating conditions (reactions using 19c or 19b + TiCl₄), 125a exhibits very high Felkin selectivity (similar to 125c but much higher than 125b) and under chelating conditions (reactions using 19b + MgBr₂·OEt₂), 125a exhibits very high anti-Felkin selectivity (similar to 125b but much higher than 125c).

2.3. THE DIASTEREOSELECTIVITY OF THE SECOND ALDOL REACTION

An attractive aspect of the Thiopyran Route to Polypropionates is that stereochemically rich intermediates (6 stereogenic centers with 36 possible stereoisomers, see Figure 26) can be obtained in only two steps from simple precursors. The potential of these products as hexaproionate synthons for the synthesis of polypropionate containing natural products depends on understanding and controlling the diastereoselectivity of the aldol reaction of 125a with enolates derived from 126a-129a. The determination of the diastereoselectivity of this second aldol reaction requires the isolation and identification of the bisaldol adducts. The structure determination of these adducts is no menial task and has been a continuous exercise within the Ward group and this study (cf. Section 2.5). Besides simply ascertaining the identity of bisaldol products from the second aldol reaction, contributions towards understanding the diastereoselectivity of this aldol reaction must take into consideration the stereochemical issues responsible for the observed selectivities.

In Figure 42 a reaction depicting the coupling between aldehyde 125a and an enolate 162 derived from aldol 126a is used to illustrate the stereochemical issues present in all aldol reactions between chiral enolates derived from 126a-129a with chiral 125a. To address these stereochemical issues only two combinations of
enantiomers of 125a and 162 need to be considered: the reaction of (6S)-125a with (6”S)-162* and the reaction of (6R)-125a with (6”S)-162† (see Figure 42). The transition states for the reaction of (6”S)-162 with (6S)-125a and the transition states for the reaction of (6”S)-162 with (6R)-125a are diastereotopic by comparison and the rates of product formation for each reaction pair will be different; the result is that the diastereoselectivities of these two reactions will be different. This phenomenon of different diastereoselectivities for the reactions of two chiral reactants is termed ‘double stereodifferentiation’.

The two reactions depicted in Figure 42 can be defined as the like and unlike reaction pair, where like refers to that reaction pair with identical absolute configurations at designated positions (e.g. C-6 in 125a and C-6” in 162) and unlike refers to that reaction pair with opposite absolute configurations at those positions. For example, the reaction of (6S)-125a with (6”S)-162 is like as is the reaction of (6R)-125a with (6”R)-162. Reactions of (6S)-125a with (6”R)-162 and of (6R)-125a with (6”S)-162 are unlike. Due to their diastereotopic relationship, the diastereoselectivities of the like and unlike reactions should be different and the reaction with the higher diastereoselectivity is labeled as the ‘matched’ reaction, and the reaction with relatively lower diastereoselectivity is labeled the ‘mismatched’ reaction.

* The reaction of (6R)-125a with (6”R)-162 is enantiomeric by comparison and will have the same diastereoselectivity as reaction (6S)-125a with (6”S)-162.
† The reaction of (6S)-125a with (6”R)-162 is enantiomeric by comparison and will have the same diastereoselectivity as reaction (6R)-125a with (6”S)-162.
Figure 42. The like and unlike reactions of the aldol reaction between chiral 125a and chiral 162.

Racemic reactants were used in this study and thus all four reaction combinations are possible. The like reactions are enantiotopic and produce enantiomeric...
products with equal facility (in an achiral environment). The unlike reactions are similarly related. Each of the like and unlike reactions can produce 4 diastereomeric adducts (i.e. the like reaction between (6S)-125a and (6'S)-162 can give 163a-d and the unlike reaction between (6R)-8a and (6'S)-162 can give 164a-d). Therefore, in a reaction between racemic reactants (±)-125a and (±)-162 there are 8 diastereomeric products possible (see Figure 42). All products will be racemic.

Upon identification of products derived from the like and unlike combinations, the diastereoselectivity of these individual reactions can be determined and expressed, for example, by the d.r. (diastereomeric ratio) of like products and the d.r. of unlike products, respectively (Figure 42). The matched and mismatched reaction pair can be assigned from a comparison of the diastereomeric ratios of the like and unlike reactions.

The mutual kinetic enantioselection (MKE) for this reaction, which is the relative preference of one enantiomer of 125a to react with one enantiomer of 162, is defined as the ratio of composite rate constants $k_{ss}/k_{RS}$ of the competing like and unlike reactions (where $k_{ss} = k_{163a} + k_{163b} + k_{163c} + k_{163d}$ and $k_{RS} = k_{164a} + k_{164b} + k_{164c} + k_{164d}$). Horeau$^{109}$ showed that for the reaction between racemic reactants the MKE can be measured from the ratio of the sum of the products from the like reaction with the sum of products from the unlike reaction (Figure 42). In principle, the advantages of conducting a reaction between racemic 125a and racemic 162 is that both the diastereoselectivity of the individual like and unlike reactions and the MKE can be obtained from an analysis of the product distribution of this reaction; the disadvantage is that more products are possible making analysis difficult. Furthermore, an assessment of the three stereochemical control elements (labelled as (a-c) in Figure 42) is also obtained from the product distribution and can aid in the understanding of the factors governing the diastereoselectivity of the aldol reaction.

There have been very few studies of aldol reactions of β-hydroxy ketones$^{41,163-165}$ to the best of my knowledge no reports other than Ward et al.$^{30}$ were found on reactions of racemic aldehydes with racemic β-hydroxy ketones. The results discussed in Sections 2.3.1 and 2.3.2 are from the work of previous researchers in the Ward group (i.e. Dr. C. Guo, Dr. P. K. Pradip and Mr. C. C. Man) where my contribution related to the structure determination of isolated bisaldol adducts and their derivatives (cf. Section
The previous work investigated the diastereoselectivity of aldol reactions of \(125a\) with enolates derived from \(126a\) and \(127a\) (Section 2.3.1.) and of aldol reactions of \(125a\) with enolates of \(\beta\)-methoxy ketones \(166\) and \(167\) derived from \(126a\) and \(127a\), respectively (Section 2.3.2). The present study investigates the diastereoselectivity of aldol reactions of \(125a\) with enolates derived from the remaining two aldol diastereomers \(128a\) and \(129a\) (Section 2.3.3) and with enolates derived from \(\beta\)-MOM protected derivatives \(172\) and \(173\) derived from \(128a\) and \(129a\), respectively. The results are discussed with special attention to the effect of structure of the ketone substrate on aldol diastereoselectivity. Determination of the structures of the bisaldol adducts is presented and discussed separately in Section 2.5.

### 2.3.1. Aldol Reactions of (±)-125a with (±)-126a and (±)-127a.

Reactions of \(125a\) with the Ti (IV) enolates of \(126a\) and \(127a\) gave bisaldol products with higher diastereoselectivity and much improved yields compared to reactions with the Li-enolate Li-alkoxide (prepared from \(126a\) or \(127a\) with \(t\)BuLi) (see Schemes 15 and 16). The titanium enolates were synthesised by mixing of \(126a\) or \(127a\) with \(\text{TiCl}_4\) (1.1 equiv) to generate the titanate (yellow in colouration) followed by the addition of diisopropylethylamine \((i\text{-Pr}_2\text{EtN}, 2.4 \text{ equiv})\) which gave a characteristic red solution typical of titanium enolates. Reaction of the titanium enolate of \(126a\) with \(125a\) was highly diastereoselective \(165a\), \(165b\) and \(165c\) in 60%, 1% and 8% isolated yields, respectively (Scheme 15). As mentioned earlier, an aldol reaction between (±)-125a and (±)-126a can give up to eight diastereomers assuming there is no isomerization of substrate \(126a\) or bisaldol products during the reaction and workup. Not only was the reaction between (±)-125a and (±)-126a highly diastereoselective for (±)-165a, the reaction also occurred with remarkable mutual kinetic enantioselection (MKE) in favour of the unlike reaction (unlike:like = \([165a + 165b] : 165c\) of 7.5:1.) That is both \(165a\) and \(165b\) result from the combinations of an enantiomer of \(125a\) with an enantiomer of \(126a\) where the absolute configurations at C-6 of \(125a\) and C-6'' of \(126a\) are unlike (i.e. (6R)-125a + (6''S)-126a and (6S)-125a + (6''R)-126a). The diastereoselectivity of the like and unlike reactions can be obtained from examination of
Scheme 15. Aldol reactions of enolates derived from (±)-126a with (±)-125a.

the product distribution. The products 165a and 165b are derived from unlike reaction and this reaction is highly diastereoselective (d.r. for 165a:165b = 60:1). The only product detected from the like reaction is 165c; however the yield of this product is too low to draw any conclusion regarding the diastereoselectivity of this reaction.

The reaction between titanium enolate (±)-127a with (±)-125a led to the diastereoselective formation of 165d in 60% isolated yield with minor bisaldols 165a and 165e in 6% and 4%, respectively (Scheme 16). This reaction proceeded with significant MKE favouring the coupling of unlike reaction partners (unlike:like = [165a + 165d] : 165e = 16.5:1). The diastereoselectivity of the unlike reaction partners was high (d.r. for 165d:165a = 10:1). The diastereoselectivity of the like reaction could not be determined with confidence due to the low yield of 165e (the only like product detected).
2.3.2. Aldol Reactions of (±)-125a with (±)-166 and (±)-168.

In early work, all attempts to prepare ether derivatives of aldols 126a and 127a failed. Consequently, aldols 126a and 127a were both diastereoselectively converted to 166 and 168, respectively, with DIBAL-H reduction, methylation of the resultant diols, and thioketal hydrolysis (Scheme 17 and 18). The titanium enolate of 166 was generated by addition of TiCl₄ (1.1equiv) followed by the addition of i-Pr₂EtN (1.2 equiv) at -78°C which generated the characteristic red solution typical of titanium enolates. Addition of 125a to the titanium enolate of 166 gave aldol adducts 167a (36%) and 167b (24%). Reaction of 166 with LDA followed by addition of TMSCI gave the corresponding trimethylsilyl enol ether which was treated with MeLi to give the “amine free” Li-enolate of 166. Addition of 125a to the so prepared Li-enolate gave 167a (29%) and 167b (23%) (Scheme 17).

From the structures of the products obtained from the reaction of 125a with 166 it was evident that 167a is derived from an unlike reaction and 167b is from a like
reaction. Both the like and unlike reactions are highly diastereoselective since each reaction led to the apparent formation of only one product. The level of MKE observed for those reactions was modest with a slight preference for the unlike combination (unlike:like = 167a:167b = 1.3-1.5:1) (Scheme 17).

\[
\begin{align*}
\text{d.r. unlike} &= \text{only } 167a \\
\text{d.r. like} &= \text{only } 167b \\
\text{MKE} &= \frac{k_{SR}}{k_{RR}} \\
&= \frac{167a}{167b} = \frac{1.5}{1}
\end{align*}
\]

\[
\begin{align*}
\text{d.r. unlike} &= \text{only } 167a \\
\text{d.r. like} &= \text{only } 167b \\
\text{MKE} &= \frac{k_{SR}}{k_{RR}} \\
&= \frac{167a}{167b} = \frac{1.3}{1}
\end{align*}
\]

**Scheme 17.** Aldol reaction of enolates derived from (±)-166 with (±)-125a.

The titanium-enolate of 168 was generated under conditions analogous to those used for ketone 166. Addition of 125a to the titanium enolate of 168 gave aldol adducts

* For aldol reactions of 125a with 166 or 168, the like and unlike reactions are assigned according to the absolute configurations at position C-6 of 125a and position C-3" of 166 and 168.
169a (24%) and 169b (17%) (Scheme 18). Reaction of 125a with the 'amine-free' Li-enolate of 168 gave 169a (21%) and 169b (22%) (Scheme 18). The product structures indicate that both the like reactions (which only gave 169a) and the unlike reactions (which only gave 169b) are highly diastereoselective (Scheme 18). The MKE observed in these reactions was low with a slight kinetic preference for the like reaction (like:unlike = 169a:169b = 1-1.4:1) (Scheme 18).

\[
d.r. \text{ like} = \text{only 169a} \\
d.r. \text{ unlike} = \text{only 169b} \\
\text{MKE} = \frac{k_{RR}}{k_{SR}} = \frac{169a}{169b} = 1.4 \\
\]

\[
1. \text{ LiAlH(OiPr)$_2$} \\
2. \text{ Me, NaH} \\
3. \text{ H}^+ \\
\]

\[
(\pm)-125a + (\pm)-168 \xrightarrow{125a \ 1.2 \text{ eq}} 169a (21\%) + 169b (22\%) \\
\]

\[
d.r. \text{ like} = \text{only 169a} \\
d.r. \text{ unlike} = \text{only 169b} \\
\text{MKE} = \frac{k_{RR}}{k_{SR}} = \frac{169a}{169b} = \frac{1}{1} \\
\]

Scheme 18. Aldol reaction of enolates derived from (±)-168 with (±)-125a.

To summarize the results of the previous work, aldol reactions of 125a with β-hydroxy ketones 126a and 127a were highly diastereoselective for the formation of one
bisaldol adduct (Schemes 15 and 16). The formation of predominantly one diastereomer is the result of high MKE where the favoured reaction (like or unlike) is also highly diastereoselective. In contrast, the aldol reactions of 125a with enolates derived from the ‘protected’ β-hydroxy ketones 166 and 168 all gave two diastereomeric products in modest yield (Schemes 17 and 18). The product structures established that one product came from a like reaction and the other came from an unlike reaction. Thus, the formation of two major products results from low MKE, where both the like and unlike reactions are highly diastereoselective. This previous study concluded that a “free” versus “protected” hydroxyl group in β-hydroxyketone substrates significantly influences the MKE of the aldol reaction.

The aim of the present study was to obtain a more comprehensive assessment of the ability of a ‘free’ β-hydroxyl versus a ‘protected’ β-hydroxyl of a ketone to influence the diastereoselectivity of the aldol reaction. To this end, the aldol reactions of two new β-hydroxy ketones 128a and 129a and their corresponding MOM protected derivatives 172 and 174 were investigated. These results are discussed in the sections to follow.

2.3.3. Aldol Reactions of (±)-125a with (±)-128a and (±)-129a.

Because of prior success in generating reactive titanium enolates from 126a and 127a (Section 2.3.1), the same conditions were initially used to generate a titanium enolate of 128a. However, addition of 125a to the supposed titanium enolate of 128a generated under these conditions did not give aldol adducts. Finally, after exploring a number of variations one aldol adduct 170a (8%) was isolated under optimized reaction conditions (Scheme 19). The optimal procedure involved stirring 128a with TiCl₄ (1 equiv) at 0 °C for 20 minutes, which resulted in a fine yellow suspension presumably the titanate intermediate. Addition of i-Pr₂EtN (2.3 equiv) to this fine yellow suspension at −78 °C gave a clear red solution within 10 minutes and then 125a was added. It was suspected that the rate of enolate decomposition was faster than that of enolate formation and that the amount of enolate formed in 10 minutes was greater than after 2-3 h used for ketones 166 and 168. This low yielding reaction could not be improved despite considerable effort.
1. TiCl$_4$ / CH$_2$Cl$_2$ 1.1 eq  
-78 °C, 5 min then  
0 °C, 20 min  
2. i-Pr$_2$EtN 2.3 eq  
-78 °C, 10 min  
3. 125a 1.2 eq  
-78 °C, 1 h 

$\text{d.r. unlike} = \text{only 170a}$  
$\text{d.r. like} = \text{not detected}$  
$\text{MKE} = \frac{k_{RS}}{k_{SS}} = \text{only } k_{RS}$

Scheme 19. Aldol reaction of enolate derived from (±)-128a with (±)-125a.

$d.r.\ unlike = \text{only 170a} $  
$d.r.\ like = \text{not detected} $  
$\text{MKE} = \frac{k_{RS}}{k_{SS}} = \text{only } k_{RS}$

Using the same conditions, reaction of the titanium-enolate of 129a with 125a gave adducts 171a (39%) and 171b (3%) (Scheme 20). The structure of the products

* Recovered 129a and 125a was 47% and 70%, respectively. Note that two equivalents of 125a was used.
indicates that both adducts 171a and 171b are derived from a like reaction. The diastereoselectivity of the like reaction was 13:1 in favour of the anti adduct 171a. It follows that the MKE for this reaction was very high in favour of the like reaction because no products from an unlike reaction were detected.

2.3.4. Aldol Reactions of (±)-125a with (±)-172 and (±)-174.

The methoxymethoxy (MOM) derivatives of 128a and 129a were prepared to investigate the influence of an alkoxy versus an hydroxy group on aldol diastereoselectivity (Schemes 21 and 22). The approach used in the previous study to obtain β-alkoxy derivatives was indirect and required three steps (Section 2.3.2). Subsequently, it was discovered by Dr. P. K. Sasmal that the hydroxy groups in 126a and 127a could be readily protected as the corresponding MOM ethers by reaction with MOMCl and i-Pr2EtN in the presence of Bu4NI. Similar reaction of 128a and 129a gave the corresponding MOM-protected derivatives 172 and 174. This method provided a direct route to obtain 'protected' β-hydroxyl derivatives without significant retroaldol or elimination side reactions.

The Ti-enolates of 172 and 174 were generated using the same procedure employed for 166 and 168 (see Section 2.3.2). The reaction of the titanium enolate of 172 with 125a gave aldol adducts 173a (40%) and 173b (13%). Adduct 173a was formed from the unlike reaction and adduct 173b was formed from the like reaction. Because both the like and unlike reactions each produced only one product, it follows that both reactions are highly diastereoselective. The MKE of this reaction is modest and favours the unlike reaction (unlike:like = 173a:173b = 3.1:1).

The 'amine-free' Li-enolate of 172 was prepared as previously described for 166 and 168. Reaction of 125a with the 'amine free' Li-enolate of 172 gave aldols 173a (12%), 173b (28%) and 173c (8%). It is of interest that that the MKE for the aldol

* For aldol reactions of 125a with 128a and 129a, the like and unlike are assigned with respect to the relative absolute configurations at C-6 of 125a and C-6" of 128a and 129a.
† Recovered 172 was obtained in 45% isolated yield. Two equivalents of 125a were used; 48% was recovered by chromatography.
‡ The 'amine free' Li-enolate was generated by addition of MeLi to the TMS enol ethers of 172.
reaction of the ‘amine free’ Li-enolate of 172 with 125a slightly favoured the like reaction (like:unlike = [173a + 173c : 173b] = 1:1.4). This is a reversal in the kinetic preference of the reaction of the titanium-enolate of 172 with 125a (Scheme 21).

\[
\begin{align*}
\text{d.r. unlike} &= \text{only 173a} \\
\text{d.r. like} &= \text{only 173b} \\
\text{MKE} &= \frac{k_{RS}}{k_{SS}} = \frac{173a}{173b} = 3.1 \\
1. \text{ TiCl}_4 / \text{CH}_2\text{Cl}_2 \ 1.1 \text{eq} \\
&\text{-78°C, 1 min} \\
2. \text{ i-Pr}_2\text{EtN} \ 1.5 \text{ eq} \\
&\text{-78°C, 1 h} \\
3. 125a \ 2 \text{ eq} \\
&\text{-78°C, 3 h}
\end{align*}
\]

\[
\begin{align*}
\text{d.r. unlike} &= 173a : 173c \ 1 : 2.3 \\
\text{d.r. like} &= \text{only 173b} \\
\text{MKE} &= \frac{k_{RS}}{k_{SS}} = \frac{173a + 173c}{173b} = 1.4
\end{align*}
\]

Scheme 21. Aldol reaction of enolate derived from (±)-172 with (±)-125a.
The reaction of the titanium enolate of 174 with 125a proceeded in low yield to give 175a (19%) and 175b (9%).* From the product structures it is apparent that 175a results from a like reaction and 175b results from an unlike reaction. Because only one like and one unlike product was detected, both reactions appear to be highly diastereoselective. The reaction occurred with moderate MKE (like:unlike = 175a : 175b = 2.1 : 1).

![Scheme 22. Aldol reaction of enolate derived from (±)-174 with (±)-125a.](image)

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. TiCl₄ / CH₂Cl₂ 1.1 eq</td>
<td>-78°C, 1 min</td>
</tr>
<tr>
<td>2. i-Pr₂EtN 1.5 eq</td>
<td>-78°C, 1 hrs</td>
</tr>
<tr>
<td>3. 125a 2 eq</td>
<td>-78°C, 3 hrs</td>
</tr>
</tbody>
</table>

- **d.r. like** = only 175a
- **d.r. unlike** = only 175b

\[
MKE = \frac{k_{SS}}{k_{RS}} = \frac{175a}{175b} = 2.1
\]

2.3.5. The Influence of the Stereochemical Control Elements on Aldol Diastereoselectivity

It is informative to examine the various stereocontrol elements (i.e. the relative topicity, aldehyde and enolate diastereoface selectivities) that contribute to the diastereoselectivity in the aldol reactions discussed in sections 2.3.1-2.3.4 (Table 10). For all reactions it was evident that the aldehyde diastereoface selectivity was highly

* Recovered 174 and 125a in 58% and 51% isolated yield, respectively.
Felkin selective (all products are $1',6''$-syn). For all reactions the relative topicity was highly $1',5$-anti selective. It was found that the enolate diastereoface selectivity (3,5-cis/trans) appeared to be dependant on the $1',3$-syn/anti relative configuration of the $\beta$-hydroxyketone substrate. The $1',3$-anti $\beta$-hydroxyketones 127a and 129a gave predominantly 3,5-cis bisaldol adducts and the $1',3$-syn $\beta$-hydroxyketone 126a gave predominantly 3,5-trans adducts. The $1',3$-syn ketone 128a is an apparent violation of the trend giving a 3,5-cis adduct; however, the very low yield in the reaction precludes firm conclusion. The trends in the stereoselectivities for all these reactions are summarized in Figure 43.

Table 10. Stereoselectivities of reactions of titanium enolates of 126a-129a with 125a

<table>
<thead>
<tr>
<th>Entry</th>
<th>ketone</th>
<th>product ratios</th>
<th>diastereoface selectivity</th>
<th>relative topicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>aldehyde $1',6''$syn:anti</td>
<td>enolate 3,5-cis:trans</td>
</tr>
<tr>
<td>1</td>
<td>126a</td>
<td>165a:165b:165c: 60:1:8</td>
<td>all syn</td>
<td>1:68</td>
</tr>
<tr>
<td>2</td>
<td>127a</td>
<td>165a:165d:165e 1.5:15:1</td>
<td>all syn</td>
<td>6:1</td>
</tr>
<tr>
<td>3</td>
<td>128a</td>
<td>170a</td>
<td>syn</td>
<td>cis</td>
</tr>
<tr>
<td>4</td>
<td>129a</td>
<td>171a:171b</td>
<td>all syn</td>
<td>13:1</td>
</tr>
</tbody>
</table>

In Table 11 the relative configuration that characterizes the diastereoselectivity of the reactions of enolates of $\beta$-alkoxyketones 166, 168, 172 and 174 are given. The enolate diastereoface selectivity strongly favoured 3,5-trans adducts for all reactions irrespective of the $1',3$-syn/anti relative configuration of the $\beta$-alkoxyketone substrate. For all aldol reactions the aldehyde diastereoface selectivity was exclusively Felkin (all products are $1',6''$-syn). The relative topicity of the aldol reactions was unselective and this poor preference allowed the formation of the two major products where one product
has 1",5-syn and the other product has 1",5-anti relative configuration. The trends in the stereoselectivities for all these reactions are summarized in Figure 44.

![Diagram showing aldol reaction with enolate and aldehyde diastereoface selectivity]

Figure 43. Trends in stereoselectivities for reactions of 125a with enolates of 126a-129a.

The aldol reactions of the four β-hydroxy ketones 126a-129a were highly diastereoselective. From an analysis of the stereoselectivities of these reactions it is concluded that they all exhibit high diastereoface selectivities for both the aldehyde and the enolate and high preference in the relative topicality (Table 10 and Figure 43). Between the competing like and unlike reactions, the reaction where all three of these stereocontrol elements are mutually reinforcing will be the kinetically favoured reaction. This reaction is “matched” and will have the high diastereoselectivity. The corresponding mismatched reaction should be slower and have lower diastereoselectivity because at most the bias for only two stereoselectivities can be accommodated. The diastereoselective formation of one major product from the aldol reactions of the β-hydroxy ketones is a consequence of having three strong stereocontrol elements which leads to high diastereoselectivity and high kinetic preference for the matched reaction.

The reactions of the related β-alkoxy ketones 166, 168, 172 and 174 were diastereoselective for the formation of two products. One product was derived from the like reaction and the other was from the unlike reaction. Comparison of the structures of
the two products reveals that the like and unlike reactions occurred with the same aldehyde diastereoface selectivity (i.e. Felkin; 1",6"-syn) and the same enolate diastereoface selectivity (i.e. 3,5-trans) but with opposite relative topicity (i.e. 1",5-syn and 1",5-anti) (Figure 44). The fact that the two adducts are formed in comparable amounts (i.e. with low MKE) suggests that the Ti(IV) enolate imposes only a weak bias for the syn vs. anti aldol coupling. Consequently, the diastereoselectivity is dominated by the face selectivities of the aldehyde and enolate thereby allowing both the like and unlike reactions to proceed with high diastereoselectivity.

Table 11. Stereoselectivities of reactions of enolates of 166, 168, 172 and 174 with 125a

<table>
<thead>
<tr>
<th>Entry</th>
<th>ketone</th>
<th>Li/Ti-enolate</th>
<th>product ratios</th>
<th>diastereoface selectivity</th>
<th>relative topicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>aldehyde 1&quot;,6&quot;-syn:anti</td>
<td>enolate 3,5-cis:trans</td>
<td>1&quot;,5-syn:anti</td>
</tr>
<tr>
<td>1</td>
<td>166</td>
<td>Li</td>
<td>167a:167b 1.3:1</td>
<td>all syn</td>
<td>all trans</td>
</tr>
<tr>
<td>2</td>
<td>166</td>
<td>Ti</td>
<td>167a:167b 1.5:1</td>
<td>all syn</td>
<td>all trans</td>
</tr>
<tr>
<td>3</td>
<td>168</td>
<td>Li</td>
<td>169a:169b ~1:1</td>
<td>all syn</td>
<td>all trans</td>
</tr>
<tr>
<td>4</td>
<td>168</td>
<td>Ti</td>
<td>169a:169b 1.4:1</td>
<td>all syn</td>
<td>all trans</td>
</tr>
<tr>
<td>5</td>
<td>172</td>
<td>Li</td>
<td>173a:173b:173c 1.5:3.5:1</td>
<td>all syn</td>
<td>1:5</td>
</tr>
<tr>
<td>6</td>
<td>172</td>
<td>Ti</td>
<td>173a:173b 3.1:1</td>
<td>all syn</td>
<td>all trans</td>
</tr>
<tr>
<td>7</td>
<td>174</td>
<td>Ti</td>
<td>175a:175b 2.1:1</td>
<td>all syn</td>
<td>all trans</td>
</tr>
</tbody>
</table>
aldol relative topicity
unselective

Figure 44. Trends in stereoselectivities for reactions of enolates 166, 168, 172 and 174 with 125a

2.3.6. Comparison of the Diastereoselectivities of the 2nd Aldol Reaction with Related Acyclic Examples.

Two related studies\textsuperscript{38,164} which also used ‘free’ and/or ‘protected’ β-hydroxy ketones as substrate in aldol reactions are discussed with special attention to the effect of the β-hydroxyl (free versus protected) on aldol diastereoselectivity.

The study by McCarthy et al.\textsuperscript{164} compared the effect of the protecting group of the β-hydroxyl on the diastereoselectivity of the aldol reaction of the chiral (Z) Li-enolate 176 with achiral 2-propanal (37). It was found that protection of the β-hydroxyl group effected a reversal in the enolate diastereoface selectivity (Table 12, compare entry 1 with entries 2-7). Furthermore, it was found that the enolate diastereoface selectivity increased with the use of silyl ether protecting groups (Table 12, entries 5-7).

Interestingly, the relative topicity of the aldol reactions of the ‘protected’ β-hydroxy ketones (entries 2-7) was relatively more selective than the reaction of the ‘free’ β-hydroxy ketone (entry 1). This trend is in contrast to the results of this study where the relative topicity of the aldol reactions of β-hydroxy ketones 126a-129a was more selective than those of the reactions of the related β-alkoxy ketones 166, 168, 172 and 174.

The study by Evans et al.\textsuperscript{38} of the aldol reaction of chiral (E) Li-enolates 180 with chiral aldehydes 150 provides a closer comparison to this study because both
studies used chiral reactants and E-enolates* (Figure 45). The like reaction of enantiopure (4S)-150 with (1'S)-180 was highly diastereoselective for 181. The unlike reaction of enantiopure (4R)-150 with the same enolate (1'S)-180 was less selective and gave 183 as the major product. The formation of one major product in each of the like

Table 12. The selectivities of the aldol reaction of Li-enolate 176 with 37.164

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protecting group (P)</th>
<th>Product ratios 177:178:179</th>
<th>Enolate d.s. 1',2-cis:trans</th>
<th>Relative topicity 2,3-syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1:2.1:0.8</td>
<td>2.1:1</td>
<td>4:1</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>1.1:1:-</td>
<td>1:1.1</td>
<td>all syn</td>
</tr>
<tr>
<td>3</td>
<td>MEM</td>
<td>1.4:1:0.1</td>
<td>1:1.4</td>
<td>24:1</td>
</tr>
<tr>
<td>4</td>
<td>BOM</td>
<td>2.0:1:0.2</td>
<td>1:2</td>
<td>15:1</td>
</tr>
<tr>
<td>5</td>
<td>TBS</td>
<td>4.5:1:0.4</td>
<td>1:4.5</td>
<td>13.8:1</td>
</tr>
<tr>
<td>6</td>
<td>TMS</td>
<td>6:1:0.7</td>
<td>1:6</td>
<td>10:1</td>
</tr>
<tr>
<td>7</td>
<td>TES</td>
<td>6.4:1:0.8</td>
<td>1:6.4</td>
<td>9.3:1</td>
</tr>
</tbody>
</table>

* All enolates generated from cyclic ketones 126a-129a, 166, 168, 172 and 174 used in this study are constrained to give only E-geometries.
and unlike reactions is a consequence of the diastereoselectivity being dominated by a high aldehyde diastereoface selectivity (favouring 3,4-syn) and a high preference in the relative topicity (favouring 2,3-anti) where the low enolate diastereoface selectivity imposes only a weak bias in the cis vs. trans relationship. Interestingly, these selectivities are in contrast to the results of this study, where it was the high selectivity for both the aldehyde- and enolate-diastereoface selectivities coupled with a weak bias in the aldol relative topicity that was responsible for the major product in each of the like and unlike reactions of the β-alkoxy ketones 166, 168, 172 and 174.

Figure 45. The selectivities of the like and unlike reaction of Li-enolate 180 with 150.38

The comparison of the selectivities of this study and those of related acyclic examples leads to the conclusion that the β-hydroxyl group (free vs. protected) has a considerable effect on the diastereoselectivity of the aldol reaction. Furthermore, the selectivities of the stereochemical control elements (aldehyde-, enolate-diastereoface...
selectivity and the relative topicity) of the reactions of cyclic chiral reactants (this study) and the reactions of acyclic chiral reactants\textsuperscript{38,164} are not influenced by the β-hydroxyl group (free vs. protected) in the same manner.

2.3.7 Conclusion

This study has provided additional examples to probe the effect of the β-hydroxy group (free vs. protected) on aldol diastereoselectivity. Reactions of 125a with the ‘free’ β-hydroxy ketones examined previously (126a and 127a) and in this study (128a and 129a) occurred with high MKE and were highly diastereoselective for formation of one out of eight possible diastereomers. Similar reactions with the ‘protected’ β-hydroxy ketones from previous work (166 and 168) and in this study (172 and 174) proceeded without significant MKE. These reactions were also highly diastereoselective giving two products, one each from the like and unlike reactions.

Each of the stereocontrol elements (relative topicity, aldehyde- and enolate-diastereoface selectivity) were strongly biased in the reaction of ‘free’ β-hydroxy ketones. However, similar reactions of the ‘protected’ β-hydroxy ketones proceeded with a much lower relative topicity. Comparison of the above results with those reported\textsuperscript{38,164} for aldol reactions of related acyclic substrates showed that aldol diastereoselectivities of thiopyranone derived substrates are substantially different.

With respect to the thiopyran route to polypropionates, the present study has increased the number of substrates available for use in the 2\textsuperscript{nd} aldol reaction. New bisaldols have been synthesized and are potential hexapropionate synthons to be used in the synthesis of polypropionate containing natural products.

2.4. SYN-ANTI ISOMERIZATION OF ALDOLS BY ENOLIZATION

2.4.1. Introduction

An aldol reaction of a ketone and an aldehyde can produce up to two new stereogenic centers and several stereoisomeric products are possible. The ability to produce each of the possible stereoisomers selectively, especially when coupling chiral substrates, remains a significant challenge\textsuperscript{74,76} despite intensive investigations during the past two decades.\textsuperscript{54,71} Isomerization of aldol products presents an alternative strategy
to access various aldol stereoisomers. Retroaldol-aldol and keto-enol tautomerism are the two pathways through which isomerization of aldol adducts can occur (Figure 46). The aldol reaction is readily reversible; fragmentation of the adduct via a C-C bond breaking step (retroaldol) gives the precursor aldehyde and enol. Reformation of this C-C bond via an aldol reaction can give the original aldol adduct or a different stereoisomer. Alternatively, the aldol adduct can undergo an acid or base catalyzed enolization to give the enol(ate) intermediate which upon ketonization can give the original adduct or a stereoisomer where a stereogenic center adjacent to the ketone has epimerized.

**Figure 46.** Retroaldol-aldol and keto-enol tautomerism pathways for syn-anti isomerization of an aldol adduct.

There are several reports of isomerization of cyclic\textsuperscript{167-173} and acyclic\textsuperscript{133,174,175} aldols via a retroaldol-aldol mechanism. An example of a retroaldol-aldol pathway for isomerization of a cyclic aldol is taken from the work of Vandewalle\textsuperscript{172} (Figure 47). The study involved the isomerization of perhydroazulenic hydroxyketones 184 and 185 under various basic conditions. It was found that treatment of aldol 184 with a variety of bases (eg. NaOH, KOH, NaH, LDA) led to a mixture of all four aldols 184-187 (Figure 104).
The same result was obtained when aldol 185 was treated with the same plethora of bases. It was determined that the equilibrium ratio of 184:185:186:187 was 7:43:35:14 under these basic conditions.

![Figure 47. The retroaldol-aldol isomerization of perhydroazulenic hydroxyketones 184-187 under basic conditions.](image)

Another example of retroaldol-aldol mechanism for aldol isomerization involves the reaction of rapamycin with titanium (IV) isopropoxide reported by Holt et al.\textsuperscript{174} This study showed that rapamycin (188) underwent isomerization in the presence of titanium (IV) isopropoxide to give 189 in 60\% isolated yield. Evidence for a retroaldol-aldol mechanism was obtained by trapping the 'enol' intermediate with benzaldehyde in a cross-over experiment to give 190 (Figure 48). Holt \textit{et al} also reported titanium (IV) isopropoxide mediated retroaldol-aldol isomerization of simple acyclic aldols.\textsuperscript{174}

In contrast to the many reports of isomerization of aldols via retroaldol-aldol, to the best of my knowledge there are only two reported examples of isomerization of aldols via an enolization mechanism.\textsuperscript{165,176}
Figure 48. Isomerization of rapamycin to 28-epirapamycin via a retroaldol-aldol mechanism mediated by titanium isopropoxide.

Still et al.\textsuperscript{176} studied the ion-driven isomerization of lasalocid A stereoisomers (Figure 49). It was established that the \textit{syn,syn} isomer of lasalocid A (191) (which has low affinity for complexation to Ba\textsuperscript{2+}) underwent isomerization to lasalocid A (192) (which has higher affinity for Ba\textsuperscript{2+}). In the presence of Ba(OH)\textsubscript{2}, lasalocid A (192) was the only isomer detected and the absence of \textit{anti,anti} or \textit{syn,anti} isomers in the reaction is consistent with an enolization mechanism.\textsuperscript{176} However, the experiments reported are insufficient to rule out a retro-aldol mechanism.
Figure 49. Ba$^{2+}$-mediated keto-enol tautomerism of syn,syn stereoisomer exclusively gave naturally occurring Lasalocid A.

An example of isomerization of an aldol via an enolate intermediate was reported by Albizati et al.$^{165}$ In this study the dianion 194 was generated from the anti aldol 193a by reaction with 2 equivalents of LDA at -78°C (Scheme 23). The enolate 194 was stirred at room temperature for 1 hour resulting in a mixture of enolates 194 and 195 that upon quenching with NH$_4$Cl gave a mixture of the anti (193a) and syn (193s) aldols. According to the authors, the possibility of obtaining 193s from a retroaldol-aldol process was excluded because of the low propensity of 193a to undergo retroaldol under these conditions.

Scheme 23. Syn/anti isomerization of 193a through the formation and protonation of the enolate.
Scattered examples of isomerization of β-hydroxy carboxylic acid derivatives by an enolization mechanism via enol\textsuperscript{177,178} and enolate\textsuperscript{118} intermediates have been reported. An example of isomerization of a β-hydroxyester (cf. β-hydroxyketone) via enolization was reported by Hanessian et al.\textsuperscript{178} in their synthesis of avermectin B\textsubscript{1a} (198) (Figure 50). A key step in their strategy required the isomerization of 2-epiavermectin B\textsubscript{1a} (196) to obtain the natural occurring avermectin B\textsubscript{1a} (198) (Figure 50) Isomerizations of avermectins had previously been studied by Pivnichny et al.\textsuperscript{179} who showed that treatment of 198 with methanolic potassium hydroxide resulted in a mixture of 198, 196 and the conjugated Δ\textsuperscript{2}-isomer 199. In a later study by Fraser-Reid et al.\textsuperscript{180}, 198 was treated with methanolic aqueous sodium hydroxide to give the conjugated Δ\textsuperscript{2}-isomer 199 (70%) and 196 (25%). From these earlier studies it was clear that alternative conditions had to be found to minimize the formation of 199 during the isomerization of 196. Hanessian et al. found that isomerization of 196 in the presence of a large excess of imidazole in refluxing benzene gave the desired avermectin B\textsubscript{1a} (198) in 40% isolated yield together with only 8% of Δ\textsuperscript{2}-isomer (199) and 34% of starting 2-epiavermectin (196) which could be recycled (Figure 50).\textsuperscript{178}

Isomerization of aldol products 201a-d was reported by Yan et al. (Scheme 24).\textsuperscript{177} Although not discussed by the authors, the reported data is clearly consistent with an enolization mechanism. Benzaldehyde was added to a solution of the lithium enolate of 200 at −78 °C and after 30 minutes the reaction was quenched to give a 1 : 4 : 5 : 0.05 mixture of 201a:201b:201c:201d, respectively (reaction condition A, Scheme 24). In a second experiment the reaction mixture was stirred at −5 °C for 30 minutes after quenching (reaction condition B, Scheme 24) and gave a 1 : 9 : < 0.05 : < 0.05 mixture of 201a:201b:201c:201d, respectively. Comparing the results from these two experiments indicates that 201c is converted to 201b during the 30 min at −5 °C which is consistent with an enolization mechanism. This conclusion is further supported by the lack of change in the relative amounts of products 201a and 201d during the isomerization; a retroaldol-aldol mechanism would be expected to equilibrate among all four isomers.
starting β-hydroxy ester
2-epiavermectin B_{1a} 34%

Figure 50. Imidazole mediated keto-enol tautomerism of 2-epiavermectin B_{1a}.

An example of isomerization of a β-hydroxy thioester via an enolate intermediate was reported by Woodward et al.\textsuperscript{118} Their approach to the total synthesis of erythromycin required the intermediate 204 (Scheme 25). The β-hydroxy thioester 202 was the precursor to 204 and differed in the configuration at C-2. The enolate 203 was generated by treatment of 202 with \textsuperscript{1}BuLi and protonation of 203 selectively gave the desired product 204 (90%) (Scheme 25).

To conclude, there are two general mechanisms by which aldols can undergo isomerization. The products of isomerization can potentially distinguish which mechanism is in operation because keto-enol tautomerism can interconvert only two stereoisomers whereas a retroaldol-aldol mechanism can lead to the formation of all possible stereoisomers.
Scheme 24. Syn/anti isomerization of β-hydroxy carbonyl compounds of 201.

Scheme 25. Isomerization of β-hydroxy thioester 203 by enolate formation.
2.4.2. Imidazole Catalyzed Syn-Anti Isomerization of Aldols by Enolization

The propensity of imidazole to isomerize thiopyranone-derived aldols was first observed by Dr. P. K. Sasmal during a failed attempt to protect the hydroxyl group in 127a by reaction with TBDMSCI in the presence of imidazole in CH₂Cl₂; after 5 days approximately 30% of 126a was detected and isolated from the reaction mixture. It was proposed that imidazole was responsible for the isomerization of 127a and it was decided to explore the generality of this phenomenon using 128a as substrate. Aldol 128a was selected for the study because three of the four possible diastereomers (126a, 127a and 128a) had been prepared stereoselectively on a large scale and a successful isomerization of 128a to 129a would allow for a convenient route for the preparation of the fourth diastereomer 129a from readily accessible 128a.

A solution of 128a (0.03 M) and imidazole (0.4 M) in CDCl₃ was prepared and monitored by ¹H NMR at room temperature. Aldol 129a slowly formed and after approximately 3 days the ratio of 128a:129a was 1.8:1 and remained constant for several weeks. The aldols 128a and 129a were stable throughout the experiment with negligible elimination or retroaldol; less than 5% of aldehyde 125a was detected by ¹H NMR spectroscopy (Figure 51). The equilibrium ratio of 1.8:1 was confirmed by subjecting aldol 129a to the identical reaction conditions. The aldols 126a and 127a, which should arise from retroaldol-aldol mechanism, were not detected during the isomerizations of either 128a or 129a. Aldols 128a and 129a were not detected in the isomerization of 127a. A solution of 122 and 125a in the presence of imidazole does not give any aldol products under the conditions employed for isomerization. It was concluded that the isomerizations of 126a-129a proceeded via keto-enol tautomerism catalyzed by imidazole and not through a retroaldol-aldol mechanism.

Isomerization of an aldol by keto-enol tautomerism can be divided into two distinct steps, enol formation and ketone formation, that are governed by different rate constants. For example, enol 207 is formed from ketone 128a with rate constant kₑ₂₈a and from ketone 129a with rate constant kₙ₂₉a. The enol 207 in turn is converted to ketones 128a and 129a with rate constants kₖ₂₈a and kₖ₂₉a, respectively (Figure 51). This pair of reversible reactions with the corresponding four rate constants
determines the rate at which the equilibrium is reached as well as the equilibrium ratio of $128a:129a$.

Figure 51. Possible pathways for isomerization of aldols $126a-129a$. 

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In these examples, the concentration of 207 is much lower than 128a and 129a and the rate of isomerization can be described as proceeding without an intermediate 207. In this case, the rate constant \( k_1 \) for conversion of 128a to 129a is a composite rate constant equal to the product of rate constants \( k_{\text{enol} \ 128a} \) and \( k_{\text{keto} \ 129a} \) (Figure 51). Similarly, the rate constant \( k_{-1} \) for the reverse reaction is equal to the product of rate constants \( k_{\text{enol} \ 129a} \) and \( k_{\text{keto} \ 128a} \). The rate constants \( k_1 \) and \( k_{-1} \) can be easily obtained by simply monitoring the rate of appearance or disappearance of the aldol substrates 128a and 129a. By contrast, determination of the four individual rate constants requires a more sophisticated approach that must involve direct or indirect detection of the enol intermediate 207.

For a kinetically first order reversible reaction:

\[
\begin{align*}
A & \xrightleftharpoons[k_{-1}]{k_1} B
\end{align*}
\]

It can be easily shown that for a system not at equilibrium \( (A \neq A_e) \): \(^{181}\)

\[
(k_1 + k_{-1}) \ t = \ln \left( \frac{A_0 - A_e}{A_t - A_e} \right)
\]

where \( A_0 \) is the initial concentration of \( A \), \( A_e \) is the concentration of \( A \) at equilibrium, and \( A_t \) is the concentration of \( A \) at time \( t \). In this form, the equation resembles that for an irreversible first order reaction of \( A \) with a rate constant \( k_{\text{obs}} (= k_1 + k_{-1}) \) but with the analytical concentration of \( A \) (i.e. \( A_t \)) replaced by the ‘active’ concentration of \( A \) (i.e. \( A_t - A_e \); which is that fraction of \( A \) undergoing transformation). Thus \( k_{\text{obs}} \) is the first order rate constant for equilibration of a non-equilibrium system. A plot of \( -\ln \left( \frac{A_t - A_e}{A_t} \right) \) versus \( t \) gives a line with slope \( k_{\text{obs}} \) and because \( k_{\text{obs}} = k_1 + k_{-1} \) and \( K_{\text{eq}} = k_1/k_{-1} \) the constants \( k_1 \) and \( k_{-1} \) can be readily derived. Accordingly, the rate of isomerization (i.e. \( k_{\text{obs}} \)) of 128a to 129a was determined by monitoring their ratio by \(^1\)H NMR spectroscopy as a function of time. A plot of \( -\ln \left( \frac{(R_t - R_e)}{(R_t + 1)} \right) \) versus \( t \) where \( R_t \) is the ratio of 128a/129a at time \( t \) and \( R_e \) is the equilibrium ratio of 128a/129a yields a line of slope \( k_{\text{obs}} \). Generally, at least eight data points were obtained during the first two half-lives and these points gave a
line with $R^2 > 0.99$. The ‘half-life’ for equilibration ($t_{1/2}$) was calculated from the so obtained $k_{obs}$ ($t_{1/2} = \ln 2/k_{obs}$).

Initially the effect of solvent on the rate and equilibrium constants for the isomerization of 128a was examined (Table 13). The rates of isomerization in CDCl$_3$ and benzene were ca. twice that in CD$_2$Cl$_2$ or CH$_3$OH and ca. ten times greater than in acetone-d$_6$ or DMF-d$_7$.

**Table 13.** Solvent effect on imidazole catalysed isomerization on aldols 128a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting aldol</th>
<th>Solvent</th>
<th>$K_{eq}$ (128a:129a)</th>
<th>$k_{obs}$ (10$^{-2}$ h$^{-1}$)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>128a</td>
<td>CDCl$_3$</td>
<td>1.8:1</td>
<td>5.9$^d$</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>CD$_2$Cl$_2$</td>
<td>1.9:1</td>
<td>2.9</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>C$_6$D$_6$</td>
<td>1.5:1</td>
<td>5.3</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>acetone-d$_6$</td>
<td>1.6:1</td>
<td>0.55</td>
<td>130</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>DMF-d$_7$</td>
<td>2.1:1</td>
<td>0.43</td>
<td>160</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>CH$_3$OH</td>
<td>2.0:1</td>
<td>c</td>
<td>~1 day</td>
</tr>
<tr>
<td>7</td>
<td>129a$^f$</td>
<td>CDCl$_3$</td>
<td>1.8:1</td>
<td>c</td>
<td>e</td>
</tr>
</tbody>
</table>

$^a$ Room temperature; [imidazole] = 0.3M; [aldol] = 0.03M. $^b$ The slope of the line obtained by plotting $-\ln[(R_t-R_e)/(R_t+1)]$ vs. $t$ where $R_t$ is [128a]/[129a] at time $t$ and $R_e$ is [128a]/[129a] at equilibrium (≥8 data points over the initial 2 half-lives; $R^2 > 0.99$). $^c$ Half-life = $t_{1/2} = \ln 2/k_{obs}$. $^d$ Data obtained by extrapolation from the plot of ln($k_{obs}$) vs. ln[imidazole]; see Table XX. $^e$ Not determined. $^f$ Isomerization starting from aldol 129a confirmed that the equilibrium ratio of [128a]:[129a] was 1.8:1 in CDCl$_3$.

The syn diastereomer 128a was favoured in all solvents (see Table 13). Relatively more of the anti diastereomer 129a was present at equilibrium in less polar solvents (e.g. C$_6$D$_6$) compared to polar solvents (e.g. CH$_3$OH) but this effect was minor. Qualitatively similar results were obtained in the isomerizations of 126a and 127a (Table 14).

The effect of the base on the rate of isomerization of 128a in CDCl$_3$ was investigated (Table 15). Isomerization in the presence of DMAP was more facile than with imidazole. The reactions were markedly slower with Et$_3$N or with N-methylimidazole and isomerization was not observed in the presence of pyridine. The poor solubility of 1,2,4-triazole (ca. 3 mg/mL, 0.04 M) in CDCl$_3$ likely contributed to
the failure to observe isomerization with this base. Attempted isomerization under Holt’s conditions\textsuperscript{174} (i.e. in the presence of Ti(OiPr)\textsubscript{4}) only gave the elimination product.

**Table 14.** Solvent effect on imidazole catalysed isomerization of aldols 126\textsubscript{a} and 127\textsubscript{a}\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting aldol</th>
<th>Solvent</th>
<th>K\textsubscript{eq} (126\textsubscript{a}:127\textsubscript{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>126\textsubscript{a}</td>
<td>CDCl\textsubscript{3}</td>
<td>1.5:1</td>
</tr>
<tr>
<td>2</td>
<td>127\textsubscript{a}</td>
<td>CDCl\textsubscript{3}</td>
<td>1.5:1</td>
</tr>
<tr>
<td>3</td>
<td>126\textsubscript{a}</td>
<td>CD\textsubscript{2}Cl\textsubscript{2}</td>
<td>1.6:1</td>
</tr>
<tr>
<td>4</td>
<td>127\textsubscript{a}</td>
<td>CD\textsubscript{2}Cl\textsubscript{2}</td>
<td>1.6:1</td>
</tr>
<tr>
<td>5</td>
<td>127\textsubscript{a}</td>
<td>acetone-d\textsubscript{6}</td>
<td>2.0:1</td>
</tr>
<tr>
<td>6</td>
<td>127\textsubscript{a}</td>
<td>C\textsubscript{6}D\textsubscript{6}</td>
<td>1.4:1</td>
</tr>
<tr>
<td>7</td>
<td>127\textsubscript{a}</td>
<td>CH\textsubscript{3}OH</td>
<td>1.7:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The data was obtained by Dr. Pradip K. Sasmal. \textsuperscript{b} Room temperature; [imidazole] = 0.3 ± 0.1M; [aldol] = 0.03 ± 0.01 M.

**Table 15.** The effect of base on the rate of isomerization of 128\textsubscript{a}\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry\textsuperscript{a}</th>
<th>Base</th>
<th>[base] (M)</th>
<th>[128\textsubscript{a}] (M)</th>
<th>t\textsubscript{1/2} (h)</th>
<th>k\textsubscript{obs}\textsuperscript{b} (E-2 h\textsuperscript{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>imidazole</td>
<td>0.40</td>
<td>0.030</td>
<td>8.6</td>
<td>8.1</td>
</tr>
<tr>
<td>2</td>
<td>DMAP</td>
<td>0.40</td>
<td>0.030</td>
<td>3.6</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>Et\textsubscript{3}N</td>
<td>0.40</td>
<td>0.016</td>
<td>110</td>
<td>0.63</td>
</tr>
<tr>
<td>4</td>
<td>methylimidazole</td>
<td>0.40</td>
<td>0.040</td>
<td>289</td>
<td>0.24</td>
</tr>
<tr>
<td>5</td>
<td>pyridine</td>
<td>0.22</td>
<td>0.016</td>
<td></td>
<td>c</td>
</tr>
<tr>
<td>6</td>
<td>1,2,4-triazole</td>
<td>0.05</td>
<td>0.04</td>
<td></td>
<td>d</td>
</tr>
<tr>
<td>7</td>
<td>Ti(OiPr)\textsubscript{4}</td>
<td>0.036</td>
<td>0.018</td>
<td></td>
<td>e</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Room temperature; isomerizations in CDCl\textsubscript{3} unless indicated otherwise; The K\textsubscript{eq} of [128\textsubscript{a}]/[129\textsubscript{a}] was 1.8:1 for entries 1-4. \textsuperscript{b} The slope of the line obtained by plotting \(-\ln[(R\textsubscript{t}-R\textsubscript{e})/(R\textsubscript{t} + 1)]\) vs. t where R\textsubscript{t} is [128\textsubscript{a}]/[129\textsubscript{a}] at time t and R\textsubscript{e} is [128\textsubscript{a}]/[129\textsubscript{a}] at equilibrium (≥8 data points over the initial 2 half-lives; \(R^2 > 0.99\)). \textsuperscript{c} No isomerization observed after 200h. \textsuperscript{d} No isomerization observed after 140 h. The reported concentration of triazole is the observed solubility in CDCl\textsubscript{3} (i.e. approx. 3mg/ml) as determined via integration of \textsuperscript{1}H NMR spectrum with aldol 128\textsubscript{a} used as the internal standard. \textsuperscript{e} Reaction in CH\textsubscript{2}Cl\textsubscript{2} at 0°C for 5 h gave elimination product only (77% conversion).  

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The effects of stoichiometry and concentration on the rate of imidazole mediated isomerization of 128a were examined (Table 16). As expected, the rate of isomerization was not dependant on the concentration of 128a (see entries 4, 5, 6), but the rate increased with increasing concentration of imidazole (entries 3, 4 and 7). The reaction order in imidazole was determined to be 1.3 from the slope of the line obtained by plotting $\ln k_{\text{obs}}$ versus $\ln [\text{imidazole}]$ using the data from entries 1, 3, 4 and 7 in Table 16. This non-integer value implies a complex mechanism for enolization.

Table 16. The effect of stoichiometry and concentration on imidazole catalyzed isomerization of 128a in CDCl₃. *

<table>
<thead>
<tr>
<th>Entry</th>
<th>[imidazole] (M)</th>
<th>[128a] (M)</th>
<th>$k_{\text{obs}}$ (E⁻² h⁻¹)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.10</td>
<td>0.015</td>
<td>1.5</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>0.20</td>
<td>0.016</td>
<td>3.6</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>0.20</td>
<td>0.030</td>
<td>3.6</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>0.40</td>
<td>0.030</td>
<td>8.1</td>
<td>8.6</td>
</tr>
<tr>
<td>5</td>
<td>0.40</td>
<td>0.060</td>
<td>7.7</td>
<td>9.0</td>
</tr>
<tr>
<td>6</td>
<td>0.40</td>
<td>0.120</td>
<td>7.8</td>
<td>8.9</td>
</tr>
<tr>
<td>7</td>
<td>0.80</td>
<td>0.030</td>
<td>21</td>
<td>3.2</td>
</tr>
</tbody>
</table>

* Room temperature; The $K_{eq}$ of [128a]/[129a] was 1.8:1 for all entries.

The effect of stoichiometry and concentration on the rate of DMAP mediated isomerization of 128a was also examined (Table 17). The rate was independent of the concentration of 128a (entries 4, 5 and 6) but linearly dependant of the concentration of DMAP (entries 3, 4 and 7). The reaction order in DMAP was determined to be 0.96 from the slope of the line obtained by plotting $\ln k_{\text{obs}}$ versus $\ln [\text{DMAP}]$ using the data in entries 2, 3, 4 and 7 in Table 17. This value is within experimental error of the expected simple first order dependance of base on enolization of 128a.

* Linear regression of the four data points used yielded a slope of 1.28 ± 0.13 (95% confidence interval).

† Linear regression of the four data points used yielded a slope of 0.96 ± 0.23 (95% confidence interval).
Table 17. The effect of stoichiometry and concentration on DMAP catalyzed isomerization of 128a in CDCl₃.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[DMAP] (M)</th>
<th>[128a] (M)</th>
<th>k_{obs} (10^2 h⁻¹)</th>
<th>t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.10</td>
<td>0.015</td>
<td>3.7</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>0.10</td>
<td>0.030</td>
<td>4.4</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>0.20</td>
<td>0.030</td>
<td>8.7</td>
<td>8.0</td>
</tr>
<tr>
<td>4</td>
<td>0.40</td>
<td>0.030</td>
<td>19</td>
<td>3.6</td>
</tr>
<tr>
<td>5</td>
<td>0.40</td>
<td>0.060</td>
<td>18</td>
<td>3.9</td>
</tr>
<tr>
<td>6</td>
<td>0.40</td>
<td>0.120</td>
<td>19</td>
<td>3.6</td>
</tr>
<tr>
<td>7</td>
<td>0.80</td>
<td>0.030</td>
<td>32</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* Room temperature; The $K_{eq}$ of [128a]/[129a] was 1.8:1 for all entries.

To demonstrate the generality of the imidazole catalysed isomerization of aldols via enolization, the related aldols 126b-129b and 126c-129c* (Figure 52) were examined. The starting aldols used and the ratio of aldol adducts at equilibrium are reported in Table 18. In each case only the starting aldol and the corresponding adduct predicted from a keto-enol tautomerism pathway were present at equilibrium. In no case were diastereomers that could only be derived from a retro-aldol pathway detected. Similar to aldol series 126a-129a, the 1',3-syn aldol diastereomer was favoured at equilibrium for all cases and equilibrium was generally reached within one week.

To explore whether the sulphur atom in the cyclic aldols was essential for isomerization the related cyclic aldols 194 and 209 were examined (Figure 53; Table 19). The isomerization of 194a and 209a led to similar equilibrium ratios of 1:2.0 (194s:194a) and 1:1.6 (209s:209a). However, the rates at which equilibrium was reached differed substantially; the half-lives for the isomerizations of 194a and 209a were 43 h and 15 h, respectively. Because the sulphur atom in aldols 209, the corresponding HC-2/HC-4 and HC-4/HC-6 diaxial interactions present in aldols 194 are absent in aldols 209. The absence of these sterically unfavourable 1,3-diaxial interactions in aldols 209 may lead to transitions states (TS) of enolization with

* The aldol adducts 126b-129b and 126c-129c were synthesized as described in Section 2.2.2.2.
relatively lower activation energies than the corresponding TS of aldols 194 and hence faster rates of isomerization for 209 compared to 194.

\[
K_{eq} = 1',3\text{-syn} : 1',3\text{-anti}
\]

![Diagram of isomerization reactions](image)

Figure 52. Imidazole catalysed isomerization of various aldols in CDCl₃.

The imidazole catalyzed isomerization of the acyclic aldol 208s¹⁴¹ was also attempted (Figure 53). Isomerization of a 9:1 mixture of 208s and 208a, respectively in CDCl₃ in the presence of imidazole (0.4 M) at room temperature was very slow. The rate of isomerization increased significantly in C₆D₆ solution in the presence of imidazole (1.0 M) at 60 °C (Table 19, entry 1). Under these conditions a 1:1.1 equilibrium mixture of 208s:208a was obtained after 13 days. A similar equilibrium
ratio (208s:208a, 4:5) was obtained by Holt et al. in the presence of Ti(O\text{I-Pr})_4.\textsuperscript{174}

Despite the harsher conditions of elevated temperature, higher imidazole concentration (1.0 M) and long reaction time, the amount of elimination products was negligible and the minor presence of benzaldehyde (6\%) indicated minimal retroaldol of both 208s and 208a.

Table 18. Examples of imidazole-catalysed keto-enol tautomerism of aldols 126b-129b and 126c-129c in CDCl\textsubscript{3}.

<table>
<thead>
<tr>
<th>entry</th>
<th>starting aldol</th>
<th>[imidazole] (M)</th>
<th>aldols at equilibrium (syn:anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>126b</td>
<td>0.40</td>
<td>126b:127b (2.0:1)\textsuperscript{b}</td>
</tr>
<tr>
<td>2</td>
<td>127b</td>
<td>0.40</td>
<td>126b:127b (2.0:1)\textsuperscript{b}</td>
</tr>
<tr>
<td>3</td>
<td>128b</td>
<td>0.30</td>
<td>128b:129b (3.1:1)</td>
</tr>
<tr>
<td>4</td>
<td>129b</td>
<td>0.30</td>
<td>128b:129b (3.1:1)</td>
</tr>
<tr>
<td>5</td>
<td>126c</td>
<td>0.30</td>
<td>126c:127c (1.1:1)</td>
</tr>
<tr>
<td>6</td>
<td>127c</td>
<td>0.30</td>
<td>126c:127c (1.1:1)</td>
</tr>
<tr>
<td>7</td>
<td>128c</td>
<td>0.30</td>
<td>128c:129c (1.5:1)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isomerizations at room temperature; [aldol] = 0.3 ± 0.1 M; Equilibrium reached in 5-7 days unless otherwise indicated. \textsuperscript{b} Equilibrium reached in 28 days.

The effect of the \(\beta\)-hydroxy group on isomerization of aldols was studied (Table 20). Aldol 128a was chosen as model substrate because the rates of isomerization were already established (Table 16) The isomerization of 172 in CDCl\textsubscript{3} in the presence of 0.4 M imidazole gave a 3.7:1 equilibrium mixture of 172 and 174, respectively. The isomerization of 172 in 0.8 M imidazole gave a similar 3.9:1 equilibrium mixture of 172 and 174, respectively. At both concentrations of imidazole, the syn diastereomer 172 was far more predominant at equilibrium than the syn aldol 128a at equilibrium (Table 20, compare entries 1 and 4 with entries 2 and 5, respectively). The conversion of the ‘hydroxyl’ group in 128a to a MOM ether in 172 greatly reduced the rate of imidazole catalyzed isomerization of 172 (Table 20, compare \(t_{1/2}\) values of entries 1 and 4 with entries 2 and 5, respectively). These results suggests that the presence of a \(\beta\)-hydroxyl group facilitates the imidazole-catalyzed isomerization.
Figure 53. Imidazole catalysed isomerization of various aldols in CDCl₃.

Table 19. Effect of structure on imidazole catalysed isomerization.²

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting aldol</th>
<th>$K_{eq}$ (anti:syn)</th>
<th>$t_{1/2}$ (h)</th>
<th>$k_{obs}$ ($10^{-2}$ h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>208s</td>
<td>1.1:1</td>
<td>41</td>
<td>1.7</td>
</tr>
<tr>
<td>2</td>
<td>194a</td>
<td>2.0:1</td>
<td>43</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>209a</td>
<td>1.6:1</td>
<td>15</td>
<td>4.8</td>
</tr>
</tbody>
</table>

² All reactions were carried out in CDCl₃ at ambient temperature unless stated otherwise. A 9:1 mixture of 208s:208a was used. Reaction at 60°C in C₆D₆ for 13 days with imidazole concentration of 1.0 M. Approximately 6% of benzaldehyde was present after 13 days. Imidazole concentration 0.7 ± 0.1 M.
\[ K_{eq} = \text{syn: anti} \]

\[ K_{eq} = 1.8 : 1 \]

\[ \text{128a} \quad \text{129a} \]

\[ K_{eq} = 3.7 : 1 \]

\[ \text{at [imidazole]} = 0.4 \text{M} \]

\[ \text{K}_{\text{eq}} = 3.9 : 1 \]

\[ \text{at [imidazole]} = 0.8 \text{M} \]

\[ \text{172} \quad \text{174} \]

**Figure 54.** Imidazole catalysed isomerization of aldols 128a, 172 and 174 in CDCl₃.

**Table 20.** Imidazole catalyzed isomerization of β-hydroxy (128a) vs. β-alkoxy (172, 174) substrates.ᵃ

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting aldol</th>
<th>[imidazole] (M)</th>
<th>Keq (syn:anti)</th>
<th>kₜₐₜₜ b (E⁻² h⁻¹)</th>
<th>t₁/₂ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>128a</td>
<td>0.4</td>
<td>1.8:1</td>
<td>8.1</td>
<td>8.6</td>
</tr>
<tr>
<td>2</td>
<td>172</td>
<td>0.4</td>
<td>3.7:1</td>
<td>0.18</td>
<td>380</td>
</tr>
<tr>
<td>3</td>
<td>174</td>
<td>0.4</td>
<td>3.7:1</td>
<td>0.21</td>
<td>330</td>
</tr>
<tr>
<td>4</td>
<td>128a</td>
<td>0.8</td>
<td>1.8:1</td>
<td>21</td>
<td>3.2</td>
</tr>
<tr>
<td>5</td>
<td>172</td>
<td>0.8</td>
<td>3.9:1</td>
<td>0.58</td>
<td>120</td>
</tr>
<tr>
<td>6</td>
<td>174</td>
<td>0.8</td>
<td>3.9:1</td>
<td>0.69</td>
<td>100</td>
</tr>
</tbody>
</table>

ᵃ For all entries, [aldol] = 0.03 M; Room temperature; isomerizations in CDCl₃. ᵇ For example, the slope of the line obtained by plotting \(-\ln[(R_t-R_e)/(R_t+1)]\) vs. t where \(R_t\) is [128a]/[129b] at time t and \(R_e\) is [128a]/[129a] at equilibrium (≥8 data points over the initial 2 half-lives; \(R^2 > 0.99\)).

The isomerization of 174 was also performed in CDCl₃ at imidazole concentrations 0.4 M and 0.8 M (Table 20, entries 3 and 6). The isomerizations of 174 resulted in equilibrium ratios identical to those obtained from the isomerizations of 172, as expected (Table 20); however, the rates of isomerization for 174 differed slightly
from those of 172. This unexpected difference in the measured rates of isomerization is attributed to experimental error in preparation of the imidazole solutions (i.e. estimated error in the imidazole concentrations is \( \pm 0.01 \text{ M} \)).

2.4.3. Imidazole Catalyzed Isomerization of \( \alpha,\alpha' \)-Disubstituted Thiopyranones and Cyclohexanones

The aldols examined in the previous sections presented only one site for isomerization by an enolization mechanism. Appropriately substituted aldols could isomerize at two sites via regioisomeric enols and it was of interest to determine the regioselectivity of such processes.

2.4.3.1. The effect of alkyl vs. hydroxyalkyl substitution on the rate of isomerization

The known\textsuperscript{183-189} aldols 210ac,at,sc,st were individually isomerized in CDCl\textsubscript{3} in the presence of imidazole (0.4 M) and gave the same equilibrium ratio in each case (Figure 55). The diastereomers with a 1,3-cis relative configuration (210ac, 210sc) are predominant at equilibrium (90%). This is expected because the cis-relative configuration allows both substituents to occupy thermodynamically favoured equatorial orientations in a cyclohexanone chair conformation. Among the two 1,3-cis diastereomers the anti aldol 210ac predominated over the syn aldol 210sc at equilibrium (Figure 55). This trend was also observed for the two trans diastereomers where the anti aldol 210at was favoured over the syn aldol 210st (Figure 55).

During the isomerization of each of the four aldols 210, the relative concentration of each of the components as a function of time was obtained by \(^1\text{H} \) NMR and this data is presented in Figures 56-59. In order to obtain rate constants for this four component equilibration the change in concentration of the individual components as a

\* From Table 20, compare rates 0.18 E\textsuperscript{2} h\textsuperscript{-1} and 0.21 E\textsuperscript{2} h\textsuperscript{-1} obtained with 0.4 M imidazole; compare rates 0.58 E\textsuperscript{2} h\textsuperscript{-1} and 0.69 E\textsuperscript{2} h\textsuperscript{-1} obtained with 0.8 M imidazole

\dagger Imidazole concentration of 0.4 M prepared by dissolving 16 ± 0.5 mg imidazole in 0.60 ± 0.01 mL CDCl\textsubscript{3}; imidazole concentration of 0.8 M prepared by dissolving 32 ± 0.5 mg imidazole in 0.60 ± 0.01 mL CDCl\textsubscript{3}.
Figure 55. Isomerization of each of the four aldols 210 with [imidazole] = 0.4 M in CDCl₃.

function of time has to be fitted to a chemical kinetics model. A hurdle in modeling these equilibrations is that the experimental observations are concentration versus time profiles, whereas the rate expressions involve changes in concentration versus time (i.e. d[C]/dt). Therefore, to compare theory with experiment it is necessary to integrate the rate expressions of the kinetic model to obtain concentration versus time profiles. The rate constants are adjusted incrementally to obtain the best fit to the experimental data. A software package which allows for the incremental adjustment of rate constants until the predicted concentration versus time profiles match the experimental profiles has been developed by F. J. Wiegert and R. J. McKinney.* Their program is based on fitting the experimental data with Gear Algorithm Integration of Chemical Kinetic Equations.¹⁹⁰⁻¹⁹² This program with a manual and further relevant references is available

* Central Research and Development Department, E. I. Du Pont de Nemours and Co. Experimental Station 328; Wilmington, Delaware 19898

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for purchase from the Quantum Chemistry Program Exchange (QCPE Product Program number: QCMP022).

With the aid of this software package, the experimentally obtained concentration versus time profiles were modeled according to the kinetic scheme depicted in Figure 55 to obtain the "best" rate constants. The concentration versus time profiles simulated using these rate constants are depicted in Figures 56-59 as solid lines. The close fit of the simulations to the observed data gives credence to the assumption that the rates of isomerization are "first order" with respect to each individual aldol concentration at a fixed concentration of imidazole. The eight composite rate constants derived from these simulations are given in Figure 55. It must be noted that the data from all four experimental concentration versus time profiles were incorporated when calculating the set of composite rate constants. This same set of rate constants were used to simulate all the profiles depicted as solid lines in Figures 56-59.

Using the same approach, three of the four possible diastereomers of 211 were separately isomerized in CDCl₃ solution in the presence of imidazole (0.4 M and 0.8 M) (Figure 60). As expected, equilibrium was achieved more rapidly (2 days) with 0.8 M imidazole than with 0.4 M imidazole (4 days) (see Appendix Figures A1-A6). Interestingly, the equilibrium ratios were slightly different at the different imidazole concentrations. Thus, the concentration of imidazole can influence the equilibrium ratio (similar to a solvent effect), as observed previously with 172 (Table 8, compare entries 2 and 5). As observed for 210, the diastereomers of 211 with 1,3-cis relative configuration were favoured over those with 1,3-trans relative configuration and anti aldols were favoured over syn aldols.

Comparing the equilibrium ratios obtained for aldols 210 and 211 (see Figures 55 and 60) it is apparent that there is a larger difference in thermodynamic stability amongst the four aldols 210 than amongst the four aldols 211. This is explained due to the presence of the sulphur atom in 211, which reduces the relative steric interaction for the axial substituent in the 1,3-trans diastereomers in aldols 211 compared to aldols 210.
Figure 56. Isomerization of a mixture $210_{st}:210_{ac}:210_{sc}:210_{at}$ (95:2:1:2) with a total aldol concentration of 0.014 M in the presence of imidazole (0.4 M) in CDCl$_3$.

Figure 57. Isomerization of a mixture $210_{st}:210_{ac}:210_{sc}:210_{at}$ (6:2:1:91) with a total aldol concentration of 0.014 M in the presence of imidazole (0.4 M) in CDCl$_3$. 
Figure 58. Isomerization of a mixture $\text{210}^\text{st}:\text{210}^\text{ac}:\text{210}^\text{sc}:\text{210}^\text{at}$ (1:6:91:2) with a total aldol concentration of 0.014 M in the presence of imidazole (0.4 M) in CDCl$_3$.

Figure 59. Isomerization of a mixture $\text{210}^\text{ac}:\text{210}^\text{at}$ (99:1) with a total aldol concentration of 0.014 M in the presence of imidazole (0.4 M) in CDCl$_3$. 
Figure 60. Imidazole catalyzed isomerization of aldols 211.

Aldols 210 and 211 can isomerize at two sites via regioisomeric enols and it was of interest to determine the regioselectivity of this isomerization. The composite rate constants depicted in Figures 55 and 60 can be used to access the regioselectivity of the
isomerization. For example, the rate constant $k_1$ is the facility for isomerization of 210at by enolization towards the methyl group to give 210ac and the rate constant $k_2$ is the facility for isomerization by enolization towards the hydroxyalkyl group to give aldol 210sc (see Figure 55). These rates $k_1$ and $k_2$ have been redefined in Table 21 as $k_{Me}$ and $k_{OH}$, respectively, to reflect the direction of enolization. Therefore the ratio of $k_{Me}$:$k_{OH}$ is an indication of the regioselectivity of the isomerization.

Upon examining the regioselectivity of isomerization it is apparent that the anti aldols 210at and 210ac isomerize faster towards the methyl group (entries 1 and 2, Table 21) and the syn aldols 210st and 210sa isomerize faster towards the hydroxyalkyl group (entries 3 and 4, Table 21). However, upon examination of the equilibrium ratio, it is apparent that each adduct favours isomerization towards the more thermodynamically stable of the two possible isomerization products (Figure 55).

The regioselectivity for isomerization of aldols 211 at both concentrations of imidazole (0.4 M and 0.8 M) follow the same trend as observed for aldols 210. The anti aldols 211at and 211ac isomerize faster towards the methyl group (entries 5, 6, 9 and 10, Table 21) and the syn aldols 211st and 211sa isomerize faster towards the hydroxyalkyl group (entries 7, 8, 11 and 12). Similarly, the rates of isomerization for each adduct 211 favours isomerization towards the more thermodynamically stable of the two possible isomerization products (Figure 60).

The sum of the rate constants ($k_{Me}$ + $k_{OH}$) for each aldol adduct is an indication of the facility of that adduct to isomerize. According to this measure ($k_{Me}$ + $k_{OH}$), the facility of each of the aldols 211 to isomerize was greater ($\times$ 3-15) than the corresponding aldols 210 (Table 21, comparison of ($k_{Me}$ + $k_{OH}$) values of entries 1, 2, 3, 4 with entries 5, 6, 7 and 8, respectively).

As expected, the facility of each of the aldols 211 to isomerize increased ($\times$ 2-3) with an increase in the concentration of imidazole from 0.4 M to 0.8 M (Table 21, compare ($k_{Me}$ + $k_{OH}$) values of entries 5, 6, 7, 8 with entries 9, 10, 11 and 12, respectively).
Table 21. The regioselectivity of isomerization.

![Chemical structures and reaction arrows]

<table>
<thead>
<tr>
<th>entry</th>
<th>[imidazole] (M)</th>
<th>Series X=</th>
<th>aldol</th>
<th>$k_{Me}$ $10^{-2}$ h$^{-1}$</th>
<th>$k_{OH}$ $10^{-2}$ h$^{-1}$</th>
<th>$k_{Me} : k_{OH}$</th>
<th>$k_{Me} + k_{OH}$ $10^{-2}$ h$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.40</td>
<td>CH$_2$</td>
<td>210at</td>
<td>1.2</td>
<td>0.15</td>
<td>8 : 1</td>
<td>1.35</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>210ac</td>
<td>0.14</td>
<td>0.022</td>
<td>6.4 : 1</td>
<td>0.36</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>210st</td>
<td>0.25</td>
<td>0.56</td>
<td>1 : 2.2</td>
<td>0.81</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>210sc</td>
<td>0.023</td>
<td>0.040</td>
<td>1 : 1.7</td>
<td>0.063</td>
</tr>
<tr>
<td>5</td>
<td>0.40</td>
<td>S</td>
<td>211at</td>
<td>2.8</td>
<td>1.1</td>
<td>2.5 : 1</td>
<td>3.9</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>211ac</td>
<td>1.7</td>
<td>0.86</td>
<td>2 : 1</td>
<td>2.56</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>211st</td>
<td>0.43</td>
<td>2.8</td>
<td>1 : 6.5</td>
<td>3.23</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>211sc</td>
<td>0.15</td>
<td>0.80</td>
<td>1 : 5.3</td>
<td>0.95</td>
</tr>
<tr>
<td>9</td>
<td>0.80</td>
<td>S</td>
<td>211at</td>
<td>6.0</td>
<td>2.7</td>
<td>2.2 : 1</td>
<td>8.7</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>211ac</td>
<td>4.9</td>
<td>2.4</td>
<td>2 : 1</td>
<td>7.3</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>211st</td>
<td>0.44</td>
<td>6.6</td>
<td>1 : 15</td>
<td>7.04</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td>211sc</td>
<td>0.19</td>
<td>2.6</td>
<td>1 : 14</td>
<td>2.79</td>
</tr>
</tbody>
</table>

2.4.3.2. The effect of the hydroxyalkyl vs. alkoxyalkyl substitution on the rate of isomerization of bisaldols

The bisaldols 165a,b,d, 212a-c and 213a-d were used as model substrates to investigate the influence of hydroxy vs. alkoxy groups on isomerization. Each of the purified aldols 165a, 165b and 165d were individually isomerized in CDCl$_3$ with imidazole (0.4 M); in each case a 22 : 30 : 30 : 18 equilibrium mixture of 165b, 165a, ent-165a* and 165d, respectively, was obtained (see Figure 61 and Appendix, Figures

* This compound is racemic. Presentation in this form as enantiomers facilitates comparison of rates for all series (see Tables 22-24).
A7-A9). Contrary to expectations, aldol 165a was the most stable despite a 3,5-trans relative configuration necessitating the presence of an axial orientated substituent on the 'central' thiopyranone ring in a chair conformation. Perhaps the greater thermodynamic stability of 165a originates from more favourable hydrogen bonding interactions compared to those in aldols 165b and 165d. Interestingly the isomerization of 165d in acetone with imidazole (1.0 M) for 8 days gave a 10 : 61 : 29 equilibrium mixture of 165d, 165a and 165b, respectively. The individual aldols were isolated by chromatography to give 8%, 65% and 26% isolated yields of 165d, 165a and 165b, respectively. In the Ward group, bisaldol 165b was previously obtained in low yield (~1%) from the aldol reaction between 125a and 126a (see Scheme 15). Therefore the isomerization of 165d provides a convenient approach to afford 165b in reasonable quantities.

Each of the purified aldols 212a-c were individually isomerized in CDCl₃ with imidazole (0.4 M); in each case a 46 : 23.5 : 23.5 : 7 equilibrium mixture of 212a, 212b, ent-212b* and 212c, respectively, was obtained (see Figure 61 and Appendix, Figures A13-A15). Aldol 212a, with a 3,5-cis relative configuration where both hydroxyalkyl substituents can have equatorial orientations in a chair conformation, was predominant at equilibrium. Interestingly, aldol 212c which also has a 3,5-cis relative configuration, was the least stable aldol.

The composite rate constants for isomerization of aldols 165a, 165b and 165d and aldols 212a-c in imidazole (0.4 – 0.8 M) were determined using the approach described previously (Section 2.4.3.1 and Appendix, Figures A17-A15). These rate constants are given in Figure 61 and Table 22. The ratio of rate constants (k₂ : k₁) can be used as a measure of the regioselectivity for isomerization of the bisaldols 165a and 212b. The aldol 165a isomerizes faster (×3) towards the side of the thiopyranone ring with a 1',3-syn relative configuration to give aldol 165d (Table 22, entries 1 and 2). Contrary to the trend observed for aldols 210 and 211 (section 2.4.3.1), aldol 165a isomerizes faster towards 165d which is thermodynamically less stable than the alternative isomerization product 165b.
\[ k_1 = 6.0 \times 10^{-3} \text{ h}^{-1} \]
\[ k_1 = 4.2 \times 10^{-3} \text{ h}^{-1} \]
\[ k_2 = 20 \times 10^{-3} \text{ h}^{-1} \]
\[ k_2 = 12 \times 10^{-3} \text{ h}^{-1} \]
\[ k_1 = 0.127 \times 10^{-3} \text{ h}^{-1} \]
\[ k_1 = 0.26 \times 10^{-3} \text{ h}^{-1} \]
\[ k_2 = 0.51 \times 10^{-3} \text{ h}^{-1} \]
\[ k_2 = 0.15 \times 10^{-3} \text{ h}^{-1} \]

Percentages refer to the mole fraction at equilibrium.
Rate constants for isomerization at 0.4 M imidazole (see Table 22)

**Figure 61.** Isomerization of aldols 165a, 165b and 165d and the corresponding bis-MOM protected aldols 212a, 212b and 212c.
The aldol 212b isomerizes faster (×1.7) towards the side of the thiopyranone ring with 1',3-anti relative configuration to give 212a (Table 22 entry 3) which is the thermodynamically more stable of the two possible isomerization products (212a and 212c).

Table 22. The rates of isomerization of aldols 165a, 165b, 165d and 212a-c.

<table>
<thead>
<tr>
<th>Entry</th>
<th>aldol series</th>
<th>[imidazole] (M)</th>
<th>rate constants (10^{-3} h^{-1})</th>
<th>k_2 : k_1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>k_1</td>
<td>k_1</td>
</tr>
<tr>
<td>1</td>
<td>165</td>
<td>0.40</td>
<td>6.0</td>
<td>4.2</td>
</tr>
<tr>
<td>2</td>
<td>165</td>
<td>0.80</td>
<td>14</td>
<td>10.3</td>
</tr>
<tr>
<td>3</td>
<td>212</td>
<td>0.40</td>
<td>0.127</td>
<td>0.260</td>
</tr>
</tbody>
</table>

Each of the purified aldols 213a-d were individually isomerized in CDCl₃ with imidazole (0.4 M); in each case a 40 : 24 : 23 : 13 equilibrium mixture of 213a, 213b, 213c and 213d, respectively, was obtained (see Figure 62 and Appendix, Figures A16-A19). The composite rate constants for isomerization of aldols 213a-d were determined using the previous approach (section 2.4.3.1) and are given in Figure 62. The corresponding rate constants are relabeled as k_{MOM} and k_{OH} and the regioselectivity of isomerization can be measured as the ratio of rates k_{MOM} : k_{OH} (Table 23). Noticeable trends in regioselectivity of isomerization were apparent. The aldols 213a and 213b with 1″,5-syn relative configuration favour isomerization towards the hydroxylalkyl side of the ketone (entries 1 and 2, Table 23), whereas the aldols 213c and 213d with 1′,5-anti relative configuration favour isomerization towards the alkoxyalkyl side (entries 3 and 4, Table 23). These trends in regioselectivity are identical to those found for aldols 210 and 211 where the syn diastereomers favour isomerization towards the hydroxyalkyl group and the anti diastereomers favour isomerization towards the methyl group. These similar trends in regioselectivity of isomerization suggests that the alkoxyalkyl group in aldols 213 has a similar influence on the regioselectivity as the methyl group in aldols 210 and 211.
Figure 62. Isomerization of aldols 213a-d in with imidazole (0.4M).

Table 23. The effect of a hydroxyalkyl vs. alkoxyalkyl substituent on regioselectivity of isomerization.

<table>
<thead>
<tr>
<th>entry</th>
<th>aldol</th>
<th>1&quot;-5-syn/anti</th>
<th>( k_{\text{MOM}} ) (10^{-3}\ h^{-1})</th>
<th>( k_{\text{OH}} ) (10^{-3}\ h^{-1})</th>
<th>( k_{\text{MOM}} : k_{\text{OH}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>213a</td>
<td>syn</td>
<td>0.60</td>
<td>0.78</td>
<td>1 : 1.3</td>
</tr>
<tr>
<td>2</td>
<td>213b</td>
<td>syn</td>
<td>1.04</td>
<td>1.31</td>
<td>1 : 1.3</td>
</tr>
<tr>
<td>3</td>
<td>213c</td>
<td>anti</td>
<td>2.60</td>
<td>1.30</td>
<td>2.0 : 1</td>
</tr>
<tr>
<td>4</td>
<td>213d</td>
<td>anti</td>
<td>4.80</td>
<td>2.31</td>
<td>2.1 : 1</td>
</tr>
</tbody>
</table>

Percentages refer to the mole fraction at equilibrium.
Contrary to the trend observed for aldols 210 and 211, the rate constants for isomerization of aldols 213 did not consistently favour the more thermodynamically stable isomerization product. For example, aldol 213b clearly isomerizes faster towards the thermodynamically less stable product 213d ($k_1 < k_4$, Figure 62).

Table 24. Comparison of the facility of aldols 165, 212 and 213 towards imidazole-catalyzed isomerization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldol</th>
<th>[imidazole] M</th>
<th>$k_1$ ($10^{-3}$ h$^{-1}$)</th>
<th>$k_2$ ($10^{-3}$ h$^{-1}$)</th>
<th>$(k_1 + k_2)$ ($10^{-3}$ h$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>165b</td>
<td>0.40</td>
<td>6.0</td>
<td>6.0</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>165a</td>
<td>0.40</td>
<td>4.2</td>
<td>12</td>
<td>16.2</td>
</tr>
<tr>
<td>3</td>
<td>165d</td>
<td>0.40</td>
<td>20</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>165b</td>
<td>0.80</td>
<td>14</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>165a</td>
<td>0.80</td>
<td>10.3</td>
<td>27</td>
<td>37.3</td>
</tr>
<tr>
<td>6</td>
<td>165d</td>
<td>0.80</td>
<td>45</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>212a</td>
<td>0.40</td>
<td>0.127</td>
<td>0.127</td>
<td>0.254</td>
</tr>
<tr>
<td>8</td>
<td>212b</td>
<td>0.40</td>
<td>0.260</td>
<td>0.150</td>
<td>0.410</td>
</tr>
<tr>
<td>9</td>
<td>212c</td>
<td>0.40</td>
<td>0.51</td>
<td>0.51</td>
<td>1.02</td>
</tr>
<tr>
<td>10</td>
<td>213a</td>
<td>0.40</td>
<td>0.78</td>
<td>0.60</td>
<td>1.38</td>
</tr>
<tr>
<td>11</td>
<td>213b</td>
<td>0.40</td>
<td>1.30</td>
<td>2.60</td>
<td>3.90</td>
</tr>
<tr>
<td>12</td>
<td>213c</td>
<td>0.40</td>
<td>1.04</td>
<td>1.31</td>
<td>2.35</td>
</tr>
<tr>
<td>13</td>
<td>213d</td>
<td>0.40</td>
<td>4.80</td>
<td>2.31</td>
<td>7.11</td>
</tr>
</tbody>
</table>

To examine the effect of alkoxy vs. hydroxy substitution on the facility of each of the aldols to isomerize in the presence of imidazole, the sum of the rates ($k_1 + k_2$) (see Table 24) of each of the aldols 165, 212 and 213 were calculated and are given in
Table 24. As expected, the facility of each of the aldols 165a, 165b and 165d to isomerize increased (× 2.3) with an increase in the imidazole concentration from 0.4 M to 0.8 M. (Table 24, compare entries 1, 2, and 3 with 4, 5, and 6). In the presence of 0.4 M imidazole, the facility of aldols 165a, 165b and 165d to isomerize was ca. 40 times greater than the corresponding bis-MOM protected aldols 212a-c. Clearly, the protection of the hydroxy groups as MOM ethers inhibits the rate of isomerization. This effect was previously observed when comparing the facility of aldols 128a with aldols 172 and 174 to isomerize (see Table 20). As expected, the facility of each of the mono-MOM aldols 213a-d to isomerize was intermediate compared to that of bisaldols 165a, 165b and 165d and bis-MOM aldols 212a-c (Table 24, entries 10-13).

2.4.3.3. Other examples of isomerization of α,α'-disubstituted hydroxyalkyl thiopyranones

To further demonstrate the generality of the imidazole catalyzed isomerization of aldols via enolization the bisaldols 165e, 170a and 171a were examined (see Figures 63-65). In each case only the starting aldol and those diastereomers predicted from a keto-enol tautomerism pathway were present at equilibrium. In no case were diastereomers that could only be derived from a retro-aldol pathway detected.

The isomerization of 165e in CH₂Cl₂ with imidazole (1.0 M) for 20 h at room temperature gave a 29 : 60 : 11 mixture of 165e, 165f and 165c, respectively (Figure 63). The individual aldols were isolated by chromatography to give 30%, 44% and 15% isolated yields of 165e, 165f and 165c, respectively. The bisaldol 165e was obtained from aldol reaction of 125a with 127a in 4% isolated yield (Scheme 16). The isomerization of 165e gave 165f (44% isolated yield); at present this is the only route to give 165f. This is an example where isomerization provides access to bisaldol diastereomers that cannot directly be obtained from aldol reaction.

The aldol 170a was isomerized in CH₂Cl₂ with imidazole (0.40 M) for 6 days at room temperature to give a 21 : 36 : 32 : 11 equilibrium mixture of 170a, 170b, 171c and 171d, respectively (Figure 64). Aldol 170a was obtained from the aldol reaction of 125a with 127a in 4% isolated yield (Scheme 16). Subsequently, the work of I. Alarcon in the Ward group has shown that 165e can be obtained in good yield from the aldol reaction of enantiopure 125a with enantiopure 127a.
between 125a and 128a in 8% isolated yield (Scheme 18). Aldol 170a was also available from the hydrolysis of the MOM group of 173c (Figure 96). The products of isomerization 170b and 171c are also available from the hydrolysis of the MOM group of 173a and 175b, respectively (Figures 97 and 98). However, at present isomerization is the only route to 171d.

The bisaldol 171a was isomerized in CH$_2$Cl$_2$ with imidazole (0.80 M) for 15 days at room temperature to give a 13 : 31 : 19 : 37 equilibrium mixture of 171a, 171b, 170c and 170d, respectively (Figure 65). Aldols 171a and 171b are available from aldol reaction of 125a with 129a in 39% and 3% isolated yields (Scheme 20). The products of isomerization 171b and 170c are also available from the hydrolysis of the MOM group of 175a and 173b, respectively (Figures 90 and 91). However, at present isomerization is the only route to 170d.
Percentages refer to the mole fraction at equilibrium.

**Figure 64.** Isomerization of 170a in CH$_2$Cl$_2$ with imidazole (0.40 M) for 6 days.

Percentages refer to the mole fraction at equilibrium.

**Figure 65.** Isomerization of 171a in CH$_2$Cl$_2$ with imidazole (0.80 M) for 15 days.
2.4.4. Conclusion

It has been demonstrated that imidazole is an effective catalyst for the syn/anti isomerization of a variety of aldols via a keto-enol tautomerization mechanism. These isomerizations are high yielding with little or no detectable side products arising from elimination or retroaldol reactions. The rates of isomerization of \( \alpha \)-substituted (Section 2.4.2) as well as \( \alpha,\alpha' \)-disubstituted thiopyranones (Section 2.4.3) were investigated. It was found that the rate of isomerization of thiopyranone derivatives (209 and 211) was far greater than the corresponding cyclohexanone derivatives (194 and 210), which in turn was much greater than an acyclic aldol (208). A ‘free’ \( \beta \)-hydroxy group was shown to facilitate the imidazole-catalyzed isomerization of aldols; the rate of isomerization of the corresponding MOM ether derivatives was much slower. Successive MOM-derivatization of bisaldols 165 progressively impedes the imidazole-catalyzed isomerization (i.e. the facility of aldols to isomerize is in the order of 165 > 213 > 212). It was demonstrated that imidazole-catalyzed isomerization of aldols is a useful tool to obtain products (e.g. 165f, 170d and 171d) that are otherwise unobtainable through aldol reactions (Section 2.4.3.3).

2.5. Structure Determination of Aldol Adducts

2.5.1. Determination of the Relative Configurations of Aldols 126b-129b and 126c-129c.

The aldols 126b-129b and 126c-129c (Figure 66) each have 4 contiguous stereogenic centers and the relative stereochemical configurations to be assigned are the syn/anti relative relationships at the positions C-1'/C-3, C-1'/C-3" and C-3''/C-4". (Note: The determination of any three of the possible six relative relationships will unambiguously assign the relative configuration of the 4 contiguous stereogenic centers). The syn/anti relative configuration at C-3''/C-4" of each adduct 126b-129b and 126c-129c is assigned according to the corresponding configuration present in the parent aldehyde 125b or 125c and was confirmed by the multiplicity and vicinal

* The six possible relative relationships in aldols 126b-129b and 126c-129c are the syn/anti relationships about the positions C-1'/C-3, C-1'/C-3", C-3''/C-4", C-3/C-3", C-3/C-4" and C-1'/C-4".

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coupling constants observed for HC-4" in the corresponding $^1$H NMR spectrum. The relative relationships at the positions C-1'/C-3 and C-3/C-3" were chosen as the remaining two relationships to be assigned and the following strategy was used to obtain these relationships.

The first step involved an unselective reduction of the aldol adduct to give a mixture of the 3,4-syn (214) and 3,4-anti diols (215) (Figure 66). The advantage of an unselective reduction is both diols can be isolated and their NMR spectroscopic properties can be compared to ensure correct assignment of the 3,4-relative configuration (i.e. syn or anti). Assuming a chair conformation for the 3-substituted tetrahydro-2H-thiopyran-4-ol fragment (where substituent is designated as the ‘R’ moiety in Figure 66), three small vicinal coupling constants to HC-4 are expected for diol 214 (3,4-syn), and one small and two large vicinal coupling constants to HC-4 are expected for diol 215 (3,4-anti).

\[
\begin{align*}
J_{3-4} &= 1-4\text{Hz} \\
J_{4-5} &= 1-4\text{Hz} \\
J_{4-5} &= 1-4\text{Hz}
\end{align*}
\]

Figure 66. Discriminating between the 3,4-syn and 3,4-anti diol derivatives.

To assign the C-1'/C-3 relative configuration of the aldol adduct the diol 215 was converted into the corresponding carbonate by reaction with 1,1'-carbonyldiimidazole. Only the trans diol 215 (and not 214) was derivatized to give a
trans-fused cyclic carbonate. A favourable property of a trans-fused carbonate is the conformational rigidity, which allows for a straightforward interpretation of the vicinal coupling constant between HC-4 and HC-4a. The trans-fused cyclic carbonate ensures that the proton HC-4a always has an axial orientation, therefore an axial-equatorial coupling (3-4 Hz) between HC-4a and HC-4 indicates that the R moiety has an axial orientation and that the relative configuration is 4,4a-syn. An axial-axial coupling between HC-4a and HC-4 (9-11 Hz) indicates that the R moiety has an equatorial orientation and the relative configuration is 4,4a-anti. The assignment of the 4,4a-syn/anti relative configuration in the carbonate derivative establishes the 1’,3-syn/anti relative configuration in the precursor aldol.

The C-3/C-3” relative configuration of an aldol adduct was established from the symmetry of a triol (or bis-MOM) derivative prepared from the diol (214 or 215) with identical relative configurations at C-3/C-4 and C-3”/C-4” (i.e. the relative configurations of the derivative must be either 3,4-syn-3”,4”-syn or 3,4-anti-3”,4”-anti). For example, for aldol adducts in the b series (i.e. adducts derived from 125b) which have 3”,4”-syn relative configuration, the derived diol 214 (and not 215) with 3,4-syn relative configuration is converted to the triol (or bis-MOM) 218 or 219 (see Figure 68).
The symmetry of this triol (or bis-MOM) product will then establish the C-3/C-3\textsuperscript{"a} relative configuration. Isolation of a symmetric product 218\textsuperscript{*} would establish the relative configuration as 3,3\textsuperscript{"a}*-syn, and an asymmetric product would establish the relative configuration as 3,3\textsuperscript{"a}*-anti (Figure 68). The assignment of this configuration in the triol (or bis-MOM) derivative establishes the 3,3\textsuperscript{"a}*-syn/anti relative configuration in the precursor aldol.

**Figure 68.** Establishing the 3,3\textsuperscript{"a}*-syn/anti relative configuration.

\textsuperscript{*} Symmetric triols gave 6 carbon signals and symmetric bis-MOM derivatives gave 8 carbon signals by \textsuperscript{13}C NMR.
The following Figures 69-76 contain pertinent data used to establish the configurations of the individual aldol adducts according to the aforementioned strategy, together with reagents used and isolated yields. The Figures 69-76 are self explanatory and only a few are accompanied by short commentary as deemed necessary.

**Figure 69.** Structure determination of 126b.
Figure 70. Structure determination of 127b.
Figure 71. Structure determination of 128b.
Figure 72. Structure determination of 129b.
Figure 73. Structure determination of 126c.

For aldols in the c series only the 3,4-anti diol derivative was required as substrate for subsequent conversion to triol and cyclic carbonate derivatives. Therefore the 1,3-anti selective reducing reagent NaBH(OAc)$_3$ was used in the reduction of 126c to give the desired 237 (80% isolated yield) (Figure 73).$^{193,194}$
Figure 74. Structure determination of 127c.
Figure 75. Structure determination of 128c.

Aldol 128c was used as substrate to successfully demonstrate both a 1,3-syn selective reduction and a 1,3-anti selective reduction with the reagents DIBAL-H\textsuperscript{195} and NaBH(OAc)\textsubscript{3}\textsuperscript{193,194}, respectively (Figure 75).
Reduction of an enriched sample of 129c (128c:129c, 1:1.5) gave a mixture of three diols which were isolated to give diols 245, 249 and 250 (Figure 76). Diol 245 had been previously isolated from similar reduction of a pure sample of 128c. The two remaining diols 249 and 250 were not detected from the prior reduction of pure aldol 128c which provided evidence that these diols are derived from aldol 129c.

Figure 76. Structure determination of 129c.
2.5.2. Determination of the Relative Configurations of Bisaldols 165, 170, 171, 173 and 175

2.5.2.1. Bisaldol 165d

Bisaldol 165d was the major product obtained from aldol reaction of 127a with aldehyde 125a (Scheme 16) and was found to be symmetric* as shown by the presence of only 11 resonances in the $^{13}$C NMR spectrum. Symmetric bisaldols can have $C_s$ or $C_2$ symmetry. $C_s$ symmetric bisaldols can be distinguished from $C_2$ symmetric bisaldols by reduction to the corresponding triol; $C_s$ symmetric bisaldols will give $C_s$ symmetric triols 253 and 254 whereas $C_2$ symmetric bisaldols will give asymmetric triols 255 (Figure 77). Reduction of 165d with DIBAL-H gave a single symmetric triol 257 in 83% isolated yield indicating that bisaldol 165d was $C_s$ symmetric (Figure 78).30

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{165} & \quad \text{[H]} \quad \text{R} & \quad \text{OH} & \quad \text{R} \\
& & + \quad \text{R} & \quad \text{OH} & \quad \text{R} \\
& & \text{253} & \quad \text{254}
\end{align*}
\]

$C_s$ symmetric substrate $C_s$ symmetric products

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{165} & \quad \text{[H]} \quad \text{R} & \quad \text{OH} & \quad \text{R} \\
& & \text{255}
\end{align*}
\]

$C_2$ symmetric substrate $C_1$ symmetric product

Figure 77. The symmetry relationship between bisaldol substrate and triol product.

*Unsymmetric bisaldols have 21 resonances and symmetric bisaldols have 11 resonances in the $^{13}$C NMR spectrum.
In the $^1$H NMR spectrum of 257, HC-4 is a broad singlet suggesting the 3,4,5 all syn relative configuration for the central thiopyran ring. Reaction of 257 with dimethoxypropane in the presence of p-TsOH gave the acetonide 258. In the $^1$H NMR spectrum of 258, HC-8a was a broad singlet suggesting the presence of a cis-fused tetrahydrothiopyran[4,3-d]1,3-dioxin ring system as expected from the all cis 257.

Definitive evidence for the 1',3-anti relative configuration in triol 257 was obtained from the $^{13}$C NMR of 258. The work of Rychnovsky et al. clearly
established that the relative configuration of 1,3-diols can be reliably assigned on the basis of the \(^{13}\text{C}\) chemical shifts of the methyl groups in the derived acetonide. In general, acetonide derivatives of syn 1,3-diols have acetal methyl shifts near 19 and 30 ppm, acetonides from anti 1,3-diols have both acetal methyl shifts near 25 ppm. The ketal methyl shifts of 258 appear at 24.1 and 26.9 ppm and clearly suggest a 4,8a-anti relative configuration for 258. Thus, triol 257 is established to possess both a 3,4-cis and a 1’,4-anti relative configuration thereby inferring a 1’,3-anti relative configuration for the precursor bisaldol 165d.

There are only two possible bisaldols that satisfy the conditions of C\(_s\) symmetry and 1’,3-anti relative configuration (i.e. 165d and 256, Figure 78). The assigned structure is firmly established because only 165d can result from an aldol reaction of 127a. To obtain 256 from 127a would require isomerization of 127a (or 165d) by a retroaldol pathway. Such a process is ruled out because 127a is isolated intact from the reaction mixture and different diastereomers of 127a (i.e. 126a, 128a and 129a) give different bisaldols under identical reaction conditions.

2.5.2.2. Bisaldol 165e

The bisaldol 165e was obtained as a minor product from the aldol reaction of 127a and 125a (Scheme 16). The product was symmetric as evidenced by the presence of only 11 signals in its \(^{13}\text{C}\) NMR spectrum; however, the triol 260 obtained by reaction of 165e with DIBAL-H was asymmetric (21 signals in the triols \(^{13}\text{C}\) NMR spectrum) establishing the C\(_2\) symmetry of bisaldol 165e (Figure 79).

Reaction of 260 with dimethoxypropane in the presence of p-TsOH gave 261 and 262 in 70% and 30% isolated yields, respectively (Figure 79). NMR analysis of the major acetonide 261 revealed a 6 Hz coupling constant between HC-4a and HC-8a suggesting the presence of a cis-fused tetrahydrothiopyran[4,3-d]1,3-dioxin ring system. The \(^{13}\text{C}\) chemical shifts for the acetal methyl groups in 261 (23.8 and 26.2 ppm) indicated a 4‘,8a-anti relative configuration. Similar NMR analysis of the minor acetonide 262 showed an 11 Hz coupling between HC-4a and HC-8a consistent with a trans-fused ring system. The \(^{13}\text{C}\) chemical shifts for the acetyl methyl groups in 262
Figure 79. Structure determination of bisaldol 165e.
(18.8 and 30.2 ppm) indicates a 4',8a-syn relative configuration. Thus, both 261 and 262 are shown to have a 4',4a-anti relative configuration establishing that 165e has a 1',3-anti relative configuration. Only two bisaldol structures are C₂ symmetric and have a 1',3-anti relative configuration (165e and 259) but only 7b can result from reaction of 127a with 125a. (For a more detailed discussion, see argument for 165a, Section 2.5.2.1).

2.5.2.3. Bisaldol 165c

The bisaldol 165c was obtained as a minor product from the aldol reaction of 126a and 125a (Scheme 15). The product was symmetric as evidenced by the presence of only 11 signals in its ¹³C NMR spectrum; however, the triol 264 obtained by reaction of 165c with DIBAL-H was asymmetric (21 signals in the ¹³C NMR spectrum) establishing the C₂ symmetry of bisaldol 165c (Figure 80).

Reaction of 264 with dimethoxypropane in the presence of p-TsOH gave 265 in 80% isolated yield. In the ¹H NMR of 265, HC-8a was a broad singlet, suggesting the presence of a cis-fused tetrahydrothiopyran[4,3-d]1,3-dioxin ring system (i.e. 4a,8a-syn). The ¹³C chemical shifts for the acetal methyl groups in 265 (19.7 and 30.0 ppm) indicated a 4',8a-syn relative configuration. These relative configurations support a 4',4a-syn relative configuration in 265 which establishes the 1',3-syn relative configuration in the precursor bisaldol 165c. Only two bisaldol structures are C₂ symmetric and have a 1',3-syn relative configuration (165c and 263, see Figure 80) but only 165c can result from reaction of 126a with 125a.
Bisaldol 165a is the major product from aldol coupling of 126a with 125a and is a minor product from aldol reaction of 127a with 125a (Schemes 15 and 16). The presence of 21 signals in the $^{13}$C NMR spectrum confirmed that 165a was asymmetric. Analysis of the vicinal coupling constants between HC-3 and H$_2$C-2 (4 and 5.5 Hz) and those between HC-5 and H$_2$C-6 (4 and 9.5 Hz) in the $^1$H NMR spectrum of 165a indicated that the substituents at positions C-3 and C-5 of the thiopyranone ring were
trans and that the conformer with an axial substituent at C-3 predominated (Figure 81). Reduction of 165a with DIBAL-H gave triol 270 (78%) from which three carbonate derivatives 268, 269 and 270 were isolated after reaction with 1,1’-carbonyldiimidazole (Figure 81). The multiplicity and coupling constants for HC-8a (broad singlet) in the $^1$H NMR spectrum of the major product 270 suggests a cis-fused ring junction. A large coupling constant between HC-4a and HC-5 (12 Hz) suggests that HC-4a has an axial orientation with respect to the thiopyranone ring (Figure 81). In the $^1$H NMR spectrum of 269, HC-8a is a broad singlet and the small coupling constants between HC-8 and H$_2$C-7 suggests that HC-8a and HC-8 both have equatorial orientations with respect to the thiopyranone ring (Figure 81). Overall, this analysis suggests a relative configuration of 4’,4a-syn-4a,8a-syn-8a,8’-anti for carbonate 270.

$^1$H NMR analysis of the minor carbonate 268 showed a large coupling constant between HC-4a and HC-8a (10 Hz) indicating a trans-fused ring junction (Figure 81). The large coupling between HC-4 and HC-4a (9 Hz) suggests that both hydrogens have an axial orientation. An equatorial orientation for HC-8 is suggested by its small coupling with HC-8a (4 Hz). This $^1$H NMR analysis assigns the relative configuration of 268 as 4,4a-anti-4a,8a-anti-8a,8-syn.

From the relative configurations of the carbonate derivatives 268 and 270 it can be concluded that 165a has 1’,3-anti-3,5-anti-1”,5-syn relative configuration. Although there are four possible bisaldol diastereomers that would satisfy these conditions (165a, 170c, 171b, and 266), only 165a can arise from aldol reactions of 125a with 126a and 127a. Moreover, 165a is related to 165d and 165b by imidazole catalyzed isomerization (see Figure 16). Thus the indicated structure is firmly established.
Figure 81. Structure determination of bisaldol 165a.
2.5.2.5. Bisaldol 165b

Bisaldol 165b was a very minor product (1% isolated yield) obtained from the aldol reaction of 126a with 125a (Scheme 15) and was found to be symmetric as shown by the presence of only 11 resonances in the $^{13}$C NMR spectrum. Reduction of 165b with DIBAL-H gave a single symmetric triol 272 in 71% isolated yield indicating that bisaldol 165b was C$_s$ symmetric.

In the $^1$H NMR spectrum of 272, HC-4 is a broad singlet suggesting the 3,4,5 all syn relative configuration for the central thiopyran ring in 272 (Figure 82). Reaction of 272 with dimethoxypropane in the presence of p-TsOH gave the acetonide 273. In the $^1$H NMR spectrum of 273, HC-8a was a broad singlet suggesting the presence of a cis-fused tetrahydrothiopyran[4,3-d]1,3-dioxin ring system as expected from the all cis 272.

Definitive evidence for the 1',3-syn relative configuration in triol 272 was obtained from the $^{13}$C NMR of 273. The acetal methyl shifts of 273 of 19.7 and 30.4 ppm clearly suggest a 4,4a-syn relative configuration for acetonide 273. Thus, triol 272 is established to possess both a 3,4-syn and a 1',4-syn relative configuration thereby inferring a 1',3-syn relative configuration for the precursor bisaldol 165b.

There are only two possible bisaldols that satisfy the conditions of C$_s$ symmetry and 1',3-syn relative configuration (i.e. 165b and 271, Figure 82). The assigned structure is established because only 165b can result from an aldol reaction of 126a. Finally, the obtention of 165b from imidazole catalyzed isomerization of 165d firmly established the indicated structure (see Figure 61).
Figure 82. Structure determination of bisaldol 165b.

2.5.2.6. Bisaldol 165f

Bisaldol 165f was obtained from imidazole-catalyzed isomerization of bisaldol 165e (see Section 2.4.3.3) and was shown to be asymmetric on the basis of 21 signals in the $^{13}$C NMR spectrum (Figure 83). A 3,5-syn relative configuration for 165f was assigned on the basis of the coupling constants between HC-3 and H$_2$C-2 (3.5, 11.5 Hz) and between HC-5 and H$_2$C-6 (3.5, 12 Hz) indicative of cis equatorial substituents on a six-membered ring in a chair conformation (Figure 83). Structure 165f is firmly
established as keto-enol tautomerism of 165e (Figure 83) can produce only one asymmetric diastereomer.

![Structure of 165f](image)

asymmetric (21 δC)
3.5-syn (J₂-₃ = 3.5Hz ; J₂-₃ = 11.5Hz
J₅-₆ = 3.5Hz ; J₅-₆ = 12Hz)

Imidazole catalyzed isomerization of 165e

![Imidazole catalyzed isomerization of 165e](image)

Figure 83. Structure determination of bisaldol 165f.

2.5.2.7. Bisaldol 171a

Bisaldol 171a is the major product from the aldol reaction of 129a with 125a (Scheme 20). The presence of 21 signals in the ¹³C NMR spectrum established that 171a was asymmetric. The relative configuration at C-3 and C-5 was established by analysis of the ¹H NMR spectrum of 171a. The vicinal coupling constants between HC-3 and H₂C-2 (4.5 and 12 Hz) and between HC-5 and H₂C-6 (3.5 and 11 Hz) suggests that both HC-3 and HC-5 have an axial orientation within a six-membered ring in a chair conformation thereby establishing the 3,5-cis relative configuration (Figure 84).

Bisaldol 171a was subjected to imidazole-catalyzed isomerization (see Section 2.4.3.3), which gave a 1:2.9:1:2:2.6 equilibrium mixture of 171a, 171b, 170c and 170d, respectively (Figure 85). The bisaldols 171b, 170c and 170d were isolated and each was determined to be asymmetric by ¹³C NMR analysis. Obtaining a set of four asymmetric diastereomers from keto-enol tautomerism of 171a is possible only if the C-1’/C-6’ and
C-1″/C-6″ relative configurations of 171a are different (i.e. 1′,6″-syn-1″,6″-anti or 1′,6″-anti-1″,6″-syn). Assuming that the aldol reaction of 129a with 125a occurs without isomerization, bisaldol products will retain the 1′,3-anti-1″,6″-anti relative configuration from the substrate 129a. Thus, bisaldol 171a is shown to have 3,5-cis, 1′,3-anti, 1″,6″-anti and 1″,6″-syn relative configurations. There are two possible structures that satisfy these conditions; i.e. 171a and 171d (Figure 86).

Figure 84. Determination of the 3,5-cis relative configuration of 171a.

Figure 85. Imidazole-catalyzed keto-enol tautomerism of bisaldol 171a gave a mixture of four asymmetric bisaldols 170c, 170d, 171a and 171b.

* This assumption is reasonable because unreacted 129a was recovered intact (47% isolated yield) without detection of other diastereomers which could result from isomerization and because similar aldol reactions of 125a with 126a, 127a or 128a give different bisaldol products.
The two possible structures 171a and 171d differ only in the relative configuration at positions C-1'/C-5 (Figure 86). The approach used to assign the C’1/C-5 relative configuration is based on the analysis and comparison of $^{13}$C NMR data of monoaldols 126a-129a and bisaldols 165b, 165d and 171a (Figure 86). The assignment of the signals in the $^{13}$C NMR spectrum of 171a was made with the aid of two dimensional homonuclear (COSY) and heteronuclear (HMQC and HMBC) correlation experiments. The $^{13}$C NMR spectrum of 171a could be unambiguously assigned to two spin systems. That is, the set of shifts for C-2, C-3, C-1', C-5', C-6', C-7', C-9' and C-10' was distinguished from the the set for C-5, C-6, C-1'', C-5'', C-6'', C-7'', C-9'' and C-10''; however, this method does not allow for assignment of a given set of shifts to a given spin system. To resolve this issue, the $^{13}$C NMR spectrum of monoaldols 126a-129a and bisaldols 165b (Cs syn) and 165d (Cs anti) were unambiguously assigned using the above techniques. Comparison of the $^{13}$C NMR chemical shifts for carbons 2, 3, 1', 5', 6', 7', 9' and 10' for 126a and 165b revealed a close correspondence ($\Delta \delta < 0.9$ ppm) for all carbons except C-2 and C-3 (Figure 87, part a). Similar comparison of the chemical shifts for 127a and 165d gave a $\Delta \delta < 0.4$ ppm (Figure 87, part b). Considering the above, the two sets of chemical shifts corresponding to carbons 1', 5', 6' 7', 9' and 10' (prime labeled carbons) and carbons 1'', 5'', 6'', 7'', 9'' and 10'' (double prime labeled carbons) in 171a were individually compared to the set of shifts for carbons 1', 5', 6' 7', 9' and 10' of monoaldol 129a (Figure 88, part c and d). As is clearly illustrated in Figure 88, a close match is obtained for only one of the sets and on this basis the chemical shifts for carbons 2, 3, 1', 5', 6' 7', 9' and 10' were assigned. The remaining set of chemical shifts for 171a must correspond to carbons 5, 6, 1'', 5'', 6'', 7'', 9'' and 10'' of either 171a or 171d. Comparison of these chemical shifts with the same carbons in 165b and 165d shows a much closer correspondence with 165d (average $|\Delta \delta| = 0.4$ ppm) than with 165b (average $|\Delta \delta| = 1.1$ ppm) and on this basis 171a is assigned the indicated structure (Figure 89, part e and f).
\( \delta_c \) of labelled carbons of 129a match with corresponding \( \delta_c \) of 171a, ave. 
\( |\Delta \delta| = 0.19 \text{ ppm, SD} = 0.13 \text{ ppm} \) (part c, Figure 88)

\( \delta_c \) of labelled carbons of 165b match poorly with corresponding \( \delta_c \) of 171a, ave. \( |\Delta \delta| = 1.14 \) ppm, SD = 1.20 ppm (part e, Figure 89)

\( \delta_c \) of labelled carbons of 165d match with corresponding \( \delta_c \) of 171a, ave. \( |\Delta \delta| = 0.46 \) ppm, SD = 0.40 ppm (part f, Figure 89)

Notice that both 171a and 171d have 1',3-anti, 1',6'-anti, 3,5-cis, 1",6"-syn relative configurations

**Figure 86.** Distinguishing between structures 171a and 171d by comparison of \(^{13}\text{C}\) NMR data of aldols 129a, 165b and 165d with \(^{13}\text{C}\) NMR data of 171a.
Figure 87. Comparison of the $^{13}$C NMR shifts of 126a with 165b, and 127a with 165d.
Figure 88. Comparison of the $^{13}$C NMR shifts of 129a with those of 171a.
\[ \Delta \delta = \delta_C(165b) - \delta_C(171a) \]

Figure 89. Comparison of the \(^{13}\)C NMR shifts of 165b and 165d with those of 171a.
2.5.2.8. Bisaldols 171b and 175a

Bisaldol 171b was the minor product from the aldol reaction of ketone 129a with aldehyde 125a (Scheme 20). The observation of 21 carbon resonances in the $^{13}$C NMR spectrum indicates that 171b is asymmetric. The vicinal coupling constants between H$_2$C-2 and HC-3 (4.5 and 10 Hz) and between H$_2$C-6 and HC-5 (5.5 and 8.5 Hz) suggest that 171b has a 3,5-trans relative configuration with the substituent at C-5 being mostly in the axial orientation (Figure 90). Bisaldol 171b is related to 171a by keto-enol tautomerism. Thus, assuming that 171b retains the 1',3-anti-1',6'-anti relative configuration of the precursor 129a (Figure 90) then only the indicated structure satisfies the above data.

**Coupling constants for 175a**

- $J_{3-2} = 6.5$ Hz
- $J_{5-6} = 10.5$ Hz
- $J_{3-2} = 4$ Hz
- $J_{5-6} = 4.5$ Hz

**Coupling constants for 171b**

- $J_{3-2} = 10$ Hz
- $J_{5-6} = 8.5$ Hz
- $J_{3-2} = 4.5$ Hz
- $J_{5-6} = 5.5$ Hz

**Figure 90.** Structure determination of 171b and 175a.
Compound 175a was a major product from the aldol reaction of 174 with 125a (Scheme 22). The vicinal coupling constants between H2C-2 and HC-3 (4 and 6.5 Hz) and between H2C-6 and HC-5 (4.5 and 10 Hz) in 175a suggest a trans 3,5-disubstituted thiopyranone ring in which the substituent at C-3 is mostly in an axial orientation. Removal of the MOM ether in 175a by reaction with TiCl4 / PhSH gave 171b (Figure 90).

2.5.2.9. Bisaldols 170c and 173b

Bisaldol 170c was obtained from imidazole catalyzed keto-enol tautomerism of bisaldol 171a and is asymmetric based on the observation of 21 signals in its 13C NMR spectrum. The vicinal coupling constants between H2C-2 and HC-3 (5 and 6 Hz) and between H2C-6 and HC-5 (4.5 and 11.5 Hz) in bisaldol 170c suggests a trans 3,5-disubstituted thiopyranone ring with the substituent at C-5 mostly in the axial orientation (Figure 91). The only possible bisaldols with a 3,5-trans relative configuration that can arise from keto-enol tautomerism of 171a are 170c and 171b (see Figure 65). Structure 170c is assigned as indicated because structure 171b (see Section 2.5.2.8) has been unambiguously assigned to a different product.
Compound 173b is obtained from aldol reaction of 172 with 125a. The vicinal coupling constants between H$_2$C-2 and HC-3 (5 and 11 Hz) and between H$_2$C-6 and HC-5 (4 and 4.5 Hz) in 173b suggests trans 3,5-disubstituted thiopyranone ring with the substituent at C-5 mostly in the axial orientation (Figure 91). Removal of the MOM ether in 173b by reaction with TiCl$_4$ / PhSH gave 170c.

2.5.2.10. Bisaldol 170d

Bisaldol 170d is obtained from keto-enol tautomerism of 171a (see Figure 65) and is asymmetric based on the observation of 21 signals in its $^{13}$C NMR spectrum. The vicinal couplings constants between H$_2$C-2 and HC-3 (4.5 and 11.5 Hz) and between H$_2$C-6 and HC-5 (4.5 and 11.5 Hz) in 170d suggest a cis 3,5-disubstituted thiopyranone in a chair conformation (Figure 92). Structure 170d is assigned as indicated because
there is only one possible product with a 3,5-cis relative configuration that can arise from keto-enol tautomerism of 171a.

Coupling constants for 170d

\[
\begin{align*}
J_{3-2} &= 11.5 \text{ Hz} & J_{5-6} &= 11.5 \text{ Hz} \\
J_{3-2} &= 4.5 \text{ Hz} & J_{5-6} &= 4.5 \text{ Hz}
\end{align*}
\]

Figure 92. Structure determination of 170d.

2.5.2.11. Bisaldols 170a and 173c

Bisaldol 170a was the only product isolated from the aldol reaction of 128a with 125a (Scheme 19). The presence of 21 signals in the \(^{13}\text{C}\) NMR spectrum established that 170a was asymmetric. The vicinal coupling constants between HC-3 and H\textsubscript{2}C-2 (5 and 11.5 Hz) and between HC-5 and H\textsubscript{2}C-6 (4.5 and 12 Hz) in the \(^1\text{H}\) NMR spectrum of 170a suggests that both HC-3 and HC-5 have an axial orientation within a six-membered ring in a chair conformation, thereby establishing the 3,5-cis relative configuration.

Bisaldol 170a was subjected to imidazole-catalyzed isomerization (see Figure 64) to give a 2.1:3.6:3.2:1 equilibrium mixture of 170a, 170b, 171c and 171d, respectively. The bisaldols 170b, 171c and 171d were isolated and each was determined to be asymmetric by \(^{13}\text{C}\) NMR. Obtaining a set of four asymmetric products from keto-enol tautomerism of 170a is possible only if the C-1'\textsuperscript{v}/C-6' and C-1''/C-6'' relative configurations of 170a are different (i.e. 1',6'-syn-1''',6'''-anti or 1',6'-anti-1''',6'''-syn). Assuming that the aldol reaction of 128a with 125a occurs without isomerization bisaldol products will retain the 1',3-syn-1',6'-anti relative configuration from the
substrate 128a. Thus, bisaldol 170a is shown to have 3,5-cis, 1',3-syn, 1',6'-anti and
1",6"-syn relative configurations. There are two possible structures that satisfy these
conditions, 170a and 170d (Figure 93).

The structure 170a has been assigned as indicated because 170d has already
been unambiguously assigned to a different product (see Section 2.5.2.10). However,
the structure of 170a is also confirmed by analysis of the 13C NMR data using the
approach applied earlier (section 2.5.2.7) to assign the structure of 171a (Figure 93).
The assignment of the signals in the carbon spectrum of 170a was made with the aid of
two dimensional homonuclear (COSY) and heteronuclear (HMQC and HMBC)
correlation experiments. The 13C NMR spectrum of 170a could be unambiguously
assigned to two spin systems. That is, the set of shifts for C-2, C-3, C-1', C-5', C-6', C-
7', C-9' and C-10' was distinguished from the set for C-5, C-6, C-1", C-5", C-6", C-
7", C-9" and C-10"; however, this method does not allow for assignment of a given set
of shifts to a given spin system. To resolve this issue, the two sets of chemical shifts
corresponding to carbons 1', 5', 6', 7', 9' and 10' (prime labeled carbons) and carbons
1", 5", 6", 7", 9" and 10" (double prime labeled carbons) in 170a were individually
compared to the set of shifts for carbons 1', 5', 6', 7', 9' and 10' of monoaldol 128a
(Figure 94, part i and ii). As is clearly illustrated in Figure 94, a close match is obtained
for only one of the sets and on this basis the chemical shifts for carbons 2, 3, 1', 5', 6'
7', 9' and 10' were assigned. The remaining set of chemical shifts for 170a must
correspond to carbons 5, 6, 1", 5", 6", 7", 9" and 10" of either 170a or 170d.
Comparison of these chemical shifts with the same carbons in 165b and 165d shows a
much closer correspondence with 165d (average $|\Delta \delta| = 0.5$ ppm) than with 165b
(average $|\Delta \delta| = 1.0$ ppm) and on this basis 170a is assigned the indicated structure
(Figure 95, part iii and iv).

* This assumption is reasonable because unreacted 128a was recovered intact (57% isolated yield)
without detection of other diastereomers which could result from isomerization and because similar aldol
reactions of 126a, 127a or 129a with 125a give different bisaldol products.
δC of labelled carbons of 128a match with corresponding δC of 170a, ave. \(|\Delta \delta| = 0.18\) ppm, SD = 0.21 ppm (part i, Figure 94)

\[
\begin{align*}
\text{128a} & \\
\text{170d} & (1'',5\text{-syn}) \\
\text{170a} & (1'',5\text{-anti}) \\
\text{165b (C}_2\text{syn}) & \\
\text{165d (C}_2\text{ anti}) & 
\end{align*}
\]

δC of labelled carbons of 165b match poorly with corresponding δC of 170a, ave. \(|\Delta \delta| = 0.97\) ppm, SD = 1.15 ppm (part iii, Figure 95)

δC of labelled carbons of 165d match with corresponding δC of 170a, ave. \(|\Delta \delta| = 0.28\) ppm, SD = 0.30 ppm (part iv, Figure 95)

Notice that both 170d and 170a have 1',3-syn, 1',6'-anti, 3,5-cis, 1'',6''-syn relative configurations

**Figure 93.** Distinguishing between structures 170a and 170d by comparison of \(^{13}\)C NMR data of aldols 128a, 165b and 165d with \(^{13}\)C NMR data of aldol 170a.
Figure 94. Comparison of the $^{13}$C NMR shifts of 128a with those of 170a.
Figure 95. Comparison of the $^{13}$C NMR shifts of 165b and 165d with those of 170a.
Compound 173c was a minor product from the aldol reaction of 172 with 125a (Scheme 21). The vicinal coupling constants between H$_2$C-2 and HC-3 (4.5 and 12 Hz) and between H$_2$C-6 and HC-5 (5 and 11 Hz) in 173c suggest that both HC-3 and HC-5 have an axial orientation within a six-membered ring in a chair conformation thereby establishing the 3,5-cis relative configuration (Figure 96). Removal of the MOM ether in 173c by reaction with TiCl$_4$ / PhSH gave 170a (Figure 96).

2.5.2.12. Bisaldols 170b and 173a

Bisaldol 170b was obtained from imidazole catalyzed keto-enol tautomerism of bisaldol 170a (see Figure 64) and is asymmetric based on the observation of 21 signals in its $^{13}$C NMR spectrum. The vicinal coupling constants between H$_2$C-2 and HC-3 (5 and 7 Hz) and between H$_2$C-6 and HC-5 (4.5 and 11 Hz) in bisaldol 170b suggest a
trans 3,5-disubstituted thiopyranone ring with the substituent at C-3 mostly in the axial orientation. The only possible bisaldols with a 3,5-trans relative configuration that can arise from keto-enol tautomerism of 170a are 170b and 171c (see Figure 64). This is resolved since 170b also comes from 173a (which has a 1',3-syn-1',6'-anti relative configuration) and there is only one possible structure that can be obtained from keto-enol tautomerism of 170a which also has a 1',3-syn-1',6'-anti relative configuration (see Figure 97).

**Coupling constants for 173a**

\[ J_{3-2} = 10.5 \text{ Hz} \quad J_{5-6} = 4.5 \text{ Hz} \]

\[ J_{3-2} = 5.5 \text{ Hz} \quad J_{5-6} = 4.5 \text{ Hz} \]

**Coupling constants for 170b**

\[ J_{3-2} = 7 \text{ Hz} \quad J_{5-6} = 11 \text{ Hz} \]

\[ J_{3-2} = 5 \text{ Hz} \quad J_{5-6} = 4.5 \text{ Hz} \]

![Coupling constants table](Figure 64)

---

**Figure 97. Structure determination of 170b and 173a.**
Compound 173a is obtained from aldol reaction of 172 with 125a. Compound 172 in turn is obtained from 128a and it can be concluded that 173a will have 1',3-syn-1',6'anti relative configuration of 128a (Figure 97). As expected, the vicinal coupling constants between H2C-2 and HC-3 (5 and 11 Hz) and between H2C-6 and HC-5 (4 and 4.5 Hz) obtained from the ¹H NMR spectrum of 173a suggested a trans 3,5-disubstituted thiopyranone ring with the substituent at C-5 mostly in the axial orientation (Figure 97).

2.5.2.13. Bisaldols 171c and 175b

Bisaldol 171c was obtained from imidazole catalyzed keto-enol tautomerism of bisaldol 170a and is asymmetric based on the observation of 21 signals in its ¹³C NMR spectrum. The vicinal coupling constants between H2C-2 and HC-3 (4.5 and 11 Hz) and between H2C-6 and HC-5 (5 and 4.5 Hz) in bisaldol 171c suggest a trans 3,5-disubstituted thiopyranone ring with the substituent at C-5 mostly in the axial orientation (Figure 98). The only possible bisaldols with a 3,5-trans relative configuration that can arise from keto-enol tautomerism of 170a are 170b and 171c (see Figure 64). Structure 171c is assigned as indicated because 170b has been unambiguously assigned to a different product (see Section 2.5.2.12).

Compound 175b is obtained from aldol reaction of 174 with 125a. The vicinal coupling constants between H2C-2 and HC-3 (4.5 and 7 Hz) and between H2C-6 and HC-5 (5 and 9 Hz) in 175b suggests a trans 3,5-disubstituted thiopyranone ring (Figure 98). Removal of the MOM ether in 175b by reaction with TiCl₄ / PhSH gave 171c.
Coupling constants for $^{175b}$

$J_{3-2} = 7 \text{ Hz}$ \quad $J_{5-6} = 9 \text{ Hz}$

$J_{3-2} = 4.5 \text{ Hz}$ \quad $J_{5-6} = 5 \text{ Hz}$

Coupling constants for $^{171c}$

$J_{3-2} = 11 \text{ Hz}$ \quad $J_{5-6} = 5 \text{ Hz}$

$J_{3-2} = 4.5 \text{ Hz}$ \quad $J_{5-6} = 4.5 \text{ Hz}$

Figure 98. Structure determination of $^{171c}$ and $^{175b}$.

2.5.2.14. Bisaldol $^{171d}$

Bisaldol $^{171d}$ is obtained from keto-enol tautomerism of $^{170a}$ and is asymmetric based on the observation of 21 signals in its $^{13}$C NMR spectrum (see Figure 64). The vicinal couplings constants between $H_2C-2$ and $HC-3$ (5 and 11.5 Hz) and between $H_2C-6$ and $HC-5$ (4.5 and 12 Hz) in $^{171d}$ suggest a cis 3,5-disubstituted thiopyranone in a chair conformation (Figure 99). Structure $^{171d}$ is assigned as indicated because there is only one possible product with a 3,5-cis relative configuration that can arise from keto-enol tautomerism of $^{170a}$. 
Coupling constants of 171d

\[ J_{3-2} = 11.5 \text{ Hz} \quad J_{5-6} = 12 \text{ Hz} \]

\[ J_{3-2} = 5 \text{ Hz} \quad J_{5-6} = 4.5 \text{ Hz} \]

\[ 3,5\text{-cis} \]

\[ \text{keto-enol tautomerism} \]

\[ 171d \]

\[ 170a \]

(Figure 64)

**Figure 99.** Structure determination of 171d.

2.5.3. **Determination of the Relative Configuration of Aldols 194, 209, 210 and 211.**

The relative configurations of aldols 194a and 194s have been established by conformational analysis of these aldols in solution with the use of the House-Stiles rule. Based on empirical evidence at the time, Stiles was the first to postulate that the syn-anti relative configuration of an aldol can be assigned based on the magnitude of the vicinal coupling constant \( J_{1'\cdot2} \), and this method was later extended by House et al. This empirical rule assumes the presence of intramolecular hydrogen bonding, which will favour two conformations (Figure 100). The one dominant conformation for an anti-aldol will place the HC-1' and HC-2 protons in an antiperiplanar arrangement with a predicted \( J_{1'\cdot2} = 10 \text{ Hz} \) and the other conformation will place these protons in a synclinal orientation with a predicted \( J_{1'\cdot2} = 2 \text{ Hz} \). Depending on the relative proportions of these conformers it was postulated by House that anti aldols will have observed vicinal coupling constants \( J_{1'\cdot2} \) ranging between 6-9 Hz. However, both conformers predicted for intramolecularly hydrogen bonded syn aldols will have synclinal orientations where the expected vicinal couplings constants for both conformers are 2 Hz. For this reason House stated that the observed coupling constant \( J_{1'\cdot2} \) for syn aldols will range between 2-4 Hz and be much smaller than the expected couplings for anti aldols.

The vicinal coupling constants \( J_{1'\cdot2} \) of 9 and 2 Hz for aldols 194a and 194s, respectively had been used by Mukaiyama to assign the syn/anti relative configuration.
based on the Stiles-House rule. This assignment was later verified by X-ray crystallographic analysis of structures of 194a and 194b reported by Noyori et al. which showed that the Stiles-House rule can be applied to these substrates. The syn/anti configuration of structurally similar aldols 209a and 209s with vicinal coupling constants of 9 and 2 Hz, respectively were assigned by Hayashi using this rule.

All four diastereomers 210at, 210ac, 210st and 210sc were isolated from aldol reaction of benzaldehyde with Li-enolate of 2-methylcyclohexanone (Scheme 26). Three diastereomers 211at, 211ac and 211st were isolated from aldol reaction of benzaldehyde with Li-enolate of 3-methylthiopyranone (Scheme 26). The remaining aldol 211sc was obtained from isomerization of a 1 : 7.2 : 4.4 mixture of 211at, 211ac and 211st, respectively in the presence of imidazole (0.8 M) in CH₂Cl₂ at room temperature. After 4 days a 2.4 : 2.8 : 1 : 2.1 mixture of 211at, 211ac, 211st and 211sc, respectively was obtained. Aldol 211sc was isolated from this mixture by chromatography.

The NMR data accumulated for the four aldols 210 correspond closely (within ±0.2 ppm) to that reported in the literature. The vicinal coupling constants J₁⁻₂ (see Table 25) derived from the obtained spectral data also matched closely (within ±1 Hz) with the reported values. Furthermore, the ¹³C NMR data for the four
aldols 210 closely matched (within +0.4 ± 0.3 ppm)* the data reported by Duhamel et al.¹⁸⁹ However, upon closer examination of the accumulated data it became evident that the literature assignment of the relative configurations of 210sc and 210st were incorrect (Table 25).

Scheme 26. Synthesis of aldols 210 and 211.

Table 25. Comparison of reported and corrected relative configurations of 210.

<table>
<thead>
<tr>
<th>Entry</th>
<th>J₁-₂</th>
<th>Literature¹⁸³-¹⁸⁹</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.5</td>
<td>anti,trans</td>
<td>anti,trans</td>
</tr>
<tr>
<td>2</td>
<td>8.5</td>
<td>anti,cis</td>
<td>anti,cis</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>syn,cis</td>
<td>syn,trans</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>syn,trans</td>
<td>syn,cis</td>
</tr>
</tbody>
</table>

To the best of my knowledge, Mukaiyama et al. was the first to assign the relative configurations of the aldols 210.¹³⁵ The assignment of the 1',2-syn/anti relative configuration was based on the Stiles-House rule, which assigns larger HC-1'/HC-2 vicinal coupling constants to anti- and the smaller coupling constants to syn-relative configurations (Table 25). However, the approach used to assign the 2,6-cis/trans relative configuration of aldols 210 was not reported and it cannot be assumed that ¹³C

* The constant +0.4 ppm difference in carbon shift is most likely due to a 0.4 ppm difference in the calibration of the CDCl₃ triplet in the accumulated spectra and the reported spectra of Duhamel et al.
NMR data was used for this assignment since no $^{13}$C data was reported by Mukaiyama.\cite{135} Subsequent reports of aldols 210 all refer to Mukaiyama’s earlier assignment but with no mention of the method used to assign the 2,6-cis/trans relative configuration.\cite{183-189} The report by Duhamel et al. is the only one where both the $^1$H and $^{13}$C NMR data for aldols 210 was given; no attempt was made to use the $^{13}$C NMR data to substantiate the previous 2,6-cis/trans assignments.\cite{189}

Mukaiyama’s assignment of the 1’2-syn/anti relative configurations in 210, based on the Stiles-House rule, is further supported by the $^{13}$C NMR chemical shifts for C-1’ (entry 8, Table 26). The anti aldols 12at and 12ac have C-1’ shifts of 75.01 and 74.93 ppm, respectively, which are more downfield than the C-1’ shifts for the syn aldols 210st and 210sc of 71.62 and 70.97 ppm, respectively.

A thorough analysis of the $^1$H-$^1$H coupling constants of aldols 210 has not been reported in the literature. From the $^1$H NMR of aldol 210ac, the vicinal coupling constants between protons HC-2 and H2C-3 (5.5 and 13 Hz) and between HC-6 and H2C-5 (6 and 13 Hz) suggested a 2,6-cis relative configuration where both protons HC-2 and HC-6 are in the axial orientation (Table 26). From the $^1$H NMR of aldol 210sc the vicinal coupling constants between protons HC-2 and H2C-3 (6.5 and 12.5 Hz) and between HC-6 and H2C-5 (5.5 and 12.5 Hz) also suggest a 2,6-cis relative configuration (Table 26).

From the $^1$H NMR of aldol 210at the vicinal coupling constants between protons HC-2 and H2C-3 (5.5 and 9.5 Hz) and between HC-6 and H2C-5 (5 and 5.5 Hz) suggest a 2,6-trans relative configuration where the methyl substituent is predominantly in the axial orientation (Table 26). From the $^1$H NMR of aldol 210st the coupling constants between protons HC-2 and H2C-3 (5.5 and 10 Hz) and between HC-6 and H2C-5 (5 and 5.5 Hz) also suggest a 2,6-trans relative configuration where the methyl substituent is predominantly in the axial orientation (Table 26). Therefore the 2,6-cis/trans relative configuration of all four aldols 210 can be assigned from $^1$H-$^1$H coupling constant analysis.

Further support for the assignment of the 2,6-cis/trans relative configuration can be found from a comparison of the $^1$H and $^{13}$C NMR shifts of the methyl substituent.

182
Table 26. NMR data used to assign relative configuration of aldols 210 and 211

![Image of aldols 210 and 211](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Physical property</th>
<th>210anti,trans</th>
<th>210anti,cis</th>
<th>210syn,trans</th>
<th>210syn,cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$^1$H-$^1$H</td>
<td>9.5</td>
<td>8.5</td>
<td>3</td>
<td>2.5</td>
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<tr>
<td>2</td>
<td>coupling constant (Hz)</td>
<td>9.5</td>
<td>13</td>
<td>10</td>
<td>12.5</td>
</tr>
<tr>
<td>3</td>
<td>$^1$H shift (ppm)</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>6.5</td>
</tr>
<tr>
<td>4</td>
<td>$^1$H shift (ppm)</td>
<td>5.5</td>
<td>13</td>
<td>5.5</td>
<td>12.5</td>
</tr>
<tr>
<td>5</td>
<td>$^1$H shift (ppm)</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>5.5</td>
</tr>
<tr>
<td>6</td>
<td>$^1$H shift (ppm)</td>
<td>4.86</td>
<td>4.80</td>
<td>5.32</td>
<td>5.38</td>
</tr>
<tr>
<td>7</td>
<td>$^1$H shift (ppm)</td>
<td>1.21</td>
<td>1.07</td>
<td>1.18</td>
<td>1.06</td>
</tr>
<tr>
<td>8</td>
<td>$^1$H shift (ppm)</td>
<td>75.01</td>
<td>74.93</td>
<td>71.62</td>
<td>70.97</td>
</tr>
<tr>
<td>9</td>
<td>$^1$H shift (ppm)</td>
<td>16.47</td>
<td>14.43</td>
<td>16.71</td>
<td>14.50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Physical property</th>
<th>211anti,trans</th>
<th>211anti,cis</th>
<th>211syn,trans</th>
<th>211syn,cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>$^1$H-$^1$H</td>
<td>9.5</td>
<td>8.5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>coupling constant (Hz)</td>
<td>6.5</td>
<td>12.5</td>
<td>9.5</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>$^1$H shift (ppm)</td>
<td>4</td>
<td>4.5</td>
<td>4</td>
<td>3.5</td>
</tr>
<tr>
<td>13</td>
<td>$^1$H shift (ppm)</td>
<td>9</td>
<td>13</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>$^1$H shift (ppm)</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>$^1$H shift (ppm)</td>
<td>5.30</td>
<td>4.86</td>
<td>5.43</td>
<td>5.38</td>
</tr>
<tr>
<td>16</td>
<td>$^1$H shift (ppm)</td>
<td>1.27</td>
<td>1.15</td>
<td>1.26</td>
<td>1.14</td>
</tr>
<tr>
<td>17</td>
<td>$^1$H shift (ppm)</td>
<td>74.29</td>
<td>74.08</td>
<td>71.86</td>
<td>71.16</td>
</tr>
<tr>
<td>18</td>
<td>$^1$H shift (ppm)</td>
<td>15.55</td>
<td>14.70</td>
<td>15.97</td>
<td>14.72</td>
</tr>
</tbody>
</table>

Assuming that the cyclohexanone rings of aldols 210ac and 210sc are in a chair conformation, their $^1$H-$^1$H vicinal coupling constants indicate that both aldols 210ac and 210sc have their methyl substituents in the equatorial orientation. Therefore it can be predicted that these methyl groups have similar chemical environments. This similarity in chemical environment is evident in the similar $^1$H (Table 26, entry 7) and $^{13}$C NMR
shifts (Table 26, entry 9) of aldols 12ac and 12sc. A similar argument can be made for aldols 210at and 210st where the methyl substituents are predominantly in the axial orientation and are expected to have similar chemical environments. This expectation is confirmed by the similar $^1$H and $^{13}$C NMR shifts for the methyl groups in aldols of aldols 210at and 210st (Table 26, entries 7 and 9).

The assignment of the relative configurations of the aldols 211 was based on an analysis similar to that used to assign the relative configurations of the structurally related aldols 210. The vicinal coupling constants between HC-1' and HC-3 were used to assign the syn/anti relative configurations according to the House-Stiles rule (Table 26, entry 10). These assignments were corroborated by the $^{13}$C NMR shifts observed for C-1'. The vicinal coupling constants between H$_2$C-2 and HC-3 and between HC-5 and H$_2$C-6 for each aldol were used to assign the 3,5-cis/trans relative configurations (Table 26, entries 11-14). The assignment of the 3,5-cis/trans relative configuration was further supported by the trends observed in the $^1$H and $^{13}$C NMR shifts of the methyl substituents. The shifts for the methyl groups in the cis aldols 211ac and 211sc were similar, and the shifts for the methyl groups in the trans aldols 211at and 211st were similar (Table 26, see entries 16 and 18).

2.5.4. Determination of the Relative Configurations of MOM-Protected Derivatives of Aldols 165a, 165b and 165d

The assignment of the relative configurations of the mono-MOM (213a-d) and bis-MOM (212a-c) derivatives of aldols 165a, 165b and 165d mentioned in Table 27 is based on the assumption that the relative configurations of the aldols 165a, 165b and 165d was conserved during the derivatization reaction (Table 27, entries 1-4). Support for this assumption follows from the isolation of recovered 165b from the derivatization reaction in reasonable yield (20%) without detection of the isomerized aldols 165a and 165d (Table 27, entry 1). Similarly, derivatization of aldol 165d gave 45% of recovered 165d without detection of isomerized aldols 165b and 165a.

Although the relative configurations of aldols 213b and 213c is clear due to the relationship of these aldols to the precursor 165a, the position of the MOM substituent in 213b and 213c is ambiguous (i.e. whether the MOM group is on the syn,syn half or on the anti,syn half of the aldol adduct). To resolve this issue, the $^{13}$C NMR shifts of the
CHOH carbon of aldols 213b and 213c were compared to similar CHOH carbons in 165a, 165c and 165e (Figure 101). Thus the CHOH NMR shift for 213b of 67.08 ppm compares favourably with the CHOH NMR shifts of 165c and the syn,syn half of 165a suggesting a syn,syn configuration about the CHOH position in 213b (Figure 101). Similarly, comparing the similar CHOH NMR shifts for 213c, 165c and the anti,syn half of 165a suggest an anti,syn relative configuration about the CHOH position in 213c (Figure 101).

Table 27. The synthesis of mono- and bis-MOM derivatives of aldols 165a, 165b and 165d.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>products</th>
<th>recovered substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>165b</td>
<td>212a(^a) 213a(^a)</td>
<td>165b (20%)</td>
</tr>
<tr>
<td>2</td>
<td>165d</td>
<td>212c (83%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>165d</td>
<td>213d (47%)</td>
<td>165d (45%)</td>
</tr>
<tr>
<td>4</td>
<td>165a</td>
<td>212b (44%) 213b (14%) 213c (35%)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Combined isolated yield of 212a and 213a is 80%.

The carbons belonging to the two halves of the aldols 165a, 213b and 213c were assigned with the aid of COSY, HMQC and HMBC experiments.
Figure 101. Determination of the position of the MOM-substituent in aldols 213b and 213c by comparison of the CHOH NMR shifts in aldols 165a, 165c and 165e with shifts in 213b and 213c.
3. EXPERIMENTAL

3.1. GENERAL METHODS

All solvents were distilled prior to use. Anhydrous solvents were distilled under argon atmosphere as follows: Tetrahydrofuran (THF) from benzophenone potassium ketyl; ether from benzophenone sodium ketyl; CH$_2$Cl$_2$ and toluene from CaH$_2$; MeOH from Mg(OMe)$_2$; Et$_3$N and TiCl$_4$ were distilled from CaH$_2$. All experiments involving air- and/or moisture-sensitive compounds were conducted in oven dried round-bottom flasks capped with rubber septa, 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). Reaction temperatures refer to that of the bath.

Preparative thin layer chromatography (PTLC) was carried out on glass plates (20x20 cm) precoated (0.25 mm) with silica gel 60 F$_{254}$. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by cutting a 1 cm vertical strip from the plate and wetting this strip with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aqueous sulfuric acid (5% v/v), followed by charring on a hot plate.

Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator followed by evacuation at 0.5-1 torr obtained with a vacuum pump. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by NMR.

Flash column chromatography (FCC) was performed according to Still et al. with Merck Silica Gel 60 (40-63 μm). Medium pressure chromatography (MPC) was performed as reported by Taber. Dry flash column chromatography was performed according to Harwood. All mixed solvent eluents are reported as v/v solutions.

3.2. SPECTRAL DATA

High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a VG 70E double focussing high resolution spectrometer; only partial
data are reported. Electron impact (EI) ionization was accomplished at 70 eV and chemical ionization (CI) at 50 eV with ammonia as the reagent gas; only partial data are reported. Infrared (IR) spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in CDCl₃ solution at 300, 400, or 500 MHz for ¹H NMR and 75, 100, or 125 MHz for ¹³C NMR signals due to the solvent (¹³C NMR) or residual protonated solvent (¹H NMR) served as the internal standard: CDCl₃ (7.27 δH, 77.23 δC); CD₃OD (3.31 δH, 49.15 δC); C₆D₆ (7.16 δH, 128.39 δC). The ¹H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of coupling constants (J) corresponds to the order of the multiplicity assignment. Couplings constants (J) are reported to the nearest 0.5 Hz. The ¹H NMR assignments were made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by 1D homonuclear decoupling, 2D ¹H/¹H homonuclear shift correlation (COSY)²⁰³ and/or 1D NOE experiments. The ¹³C NMR assignments were made on the basis of chemical shift and multiplicity* as determined by J-modulation²⁰⁴ and were confirmed, where necessary, by 2D ¹H/¹³C one bond correlation (HSQC)²⁰⁵ and 2D ¹H/¹³C multiple bond correlation (HMBC)²⁰⁶ experiments.

3.3. General Experimental Procedures

3.3.1. General Procedure A for Reduction of Esters

A solution of ester (1 equiv) in anhydrous ether or THF (1 mL/ mmol) was added dropwise via syringe to a stirred suspension of LiAlH₄ (1.1 equiv) in ether (2-3.5 mL/ mmol of LiAlH₄) at 0 °C under argon. After 1 h, the reaction was quenched²⁰⁷ by sequential dropwise addition of water (1 mL/ g of LiAlH₄), 15% (w/v) sodium hydroxide (1 mL/ g of LiAlH₄), and water (3 mL/ g of LiAlH₄). The resultant gray suspension was stirred until granular white flakes formed (ca. 1-1.5 h). The suspension

* Multiplicity of ¹³C NMR signals refers to the number of attached H's (i.e. s = C, d = CH, t = CH₂, q = CH₃)
was filtered through Celite® washing with 1:1 ether/hexane. The combined filtrate and washings were washed with brine, dried over Na₂SO₄, and concentrated to give the desired alcohol.

3.3.2. **General Procedure B for Preparation of 'Amine Free' Lithium Enolate 137c.**

Methyllithium (1-1.5 M in diethyl ether, 1 equiv) was added dropwise via a syringe to a stirred solution of the trimethylsilyl enol ether of the tetrahydro-4H-thiopyran-4-one in ether (2 mL/ mmol of enol ether) at 0 °C under argon. The reaction mixture was warmed to rt (note: the Li enolate precipitates from the solution) and after 1 h, THF (2 mL/ mmol of enol ether) was added via syringe. After stirring for 5 min (note: enolate dissolves), the reaction mixture was cooled to -78 °C.

3.3.3. **General Procedure C for DIBAL-H Reduction of Aldols**

DIBAL-H (1.5 M in toluene; 2 equiv) was added dropwise via a syringe to a stirred solution of the aldol in THF (10 mL/ mmol of aldol) at -78 °C under argon. After 3 h, excess DIBAL was quenched by dropwise addition of MeOH (caution: H₂ evolution). The mixture was diluted with saturated aqueous sodium potassium tartrate and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give the crude diol(s).

3.3.4. **General Procedure D for NaBH₄ Reduction of Aldols**

NaBH₄ (2-3 equiv) was added to a stirred solution of the aldol in EtOH (10 mL/ mmol of aldol) at rt. After 1 h, the reaction was quenched by dropwise addition of 1 M HCl until effervescence ceased (caution: H₂ evolution). The reaction mixture was made basic by addition of 15% NaOH (base added to hydrolyze cyclic borates that were persistent for some examples) and, after 30 min, the mixture was diluted with brine and extracted with ethyl acetate (x3). The combined organic layers were dried over Na₂SO₄ and concentrated to give the crude mixture of cis and trans diols.
3.3.5. General Procedure E for NaCNBH₃ Reduction of Aldols

NaCNBH₃ (2 equiv) was added portion-wise (effervescence was observed) to a stirred suspension of aldol and citric acid (2 equiv) in EtOH (5 mL/0.1 mmol of aldol) at 0 °C. The reaction mixture was allowed to warm to rt and, after 3 h, saturated aqueous sodium potassium tartrate was added. After 40 min, the mixture was diluted with water and extracted with CH₂Cl₂ (×3) and the combined organic layers were dried over Na₂SO₄ and concentrated to give the crude mixture of cis and trans diols.

3.3.6. General Procedure F for NaBH(OAc)₃ Reduction of Aldols

A 0.33 M solution of NaBH(OAc)₃ in acetic acid was prepared by portion-wise addition of NaBH₄ (25 mg, 0.66 mmol) to cold glacial acetic acid (2 mL) (caution: H₂ evolution) followed by stirring for 5 min. NaBH(OAc)₃ (0.33 M in acetic acid; 4 equiv) was added dropwise via syringe over 30 seconds to a stirred solution of the aldol in dry CH₃CN (1 mL/0.1 mmol of aldol) at 0 °C. After 90 min, the reaction mixture was added to a vigorously stirred saturated aqueous sodium potassium tartrate solution. The mixture was neutralized by addition of cold saturated aqueous NaHCO₃ and then was diluted with water and extracted with CH₂Cl₂ (×3). The combined organic layer were dried over Na₂SO₄ and concentrated to give the crude diol(s).

3.3.7. General Procedure G for Preparation of Carbonates

A solution of diol and 1,1'-carbonyldiimidazole (3-6 equiv) in benzene (6 mL/mmol of diol) was heated under reflux under argon. The reaction was monitored by TLC (80% ethyl acetate in hexane) and, when the diol was consumed (ca. 4-20 h), the mixture was diluted with water and extracted with CH₂Cl₂ (×3). The combined organic layers were dried over Na₂SO₄ and concentrated to give the crude carbonate.

3.3.8. General Procedure H for Preparation of Carbonates

For some 1,3-anti diols (from syn aldols) the formation of the cyclic carbonate was slow and competitive with production of the biscarbamate derivative. Thus, when the diol was consumed in reaction with 1,1'-carbonyldiimidazole as above (ca. 2-8 h), the mixture was diluted with ethyl acetate and washed with water (×2). The organic
phase was dried over Na₂SO₄, concentrated, and dried under high vacuum (0.5 Torr) overnight. The residue was taken up in toluene (6 mL/ mmol of diol) and the solution heated under reflux. When carbonate formation was complete (TLC, 80% ethyl acetate in hexane) (20-48 h), the mixture was diluted with water and extracted with CH₂Cl₂ (×3). The combined organic layers were dried Na₂SO₄ and concentrated to give the crude carbonate.

3.3.9. General Procedure I for Preparation of MOM Ethers

MOMCl (10-20 equiv based on diol) was added dropwise to a stirred solution of diol and i-Pr₂EtN (2 equiv based on MOMCl) in CH₂Cl₂ (20 mL/ mmol of diol) at rt. After ca. 2.5 h (diol not detected by TLC: 50% ethyl acetate in hexane), the mixture was diluted by HCl (20 mL, 1M), extracted with CH₂Cl₂ (×3) and the combined organic layers were, dried over Na₂SO₄, concentrated to give the crude MOM ether(s).

3.3.10. General Procedure J for Hydrolysis of MOM Ethers

A 2:1 (v/v) mixture of a solution of MOM ether diol in THF (0.05 M) and aqueous HCl (6 M) was stirred at rt for 10-15 h. The reaction was cooled in an ice bath and quenched by portion-wise addition of solid NaHCO₃ (caution: CO₂ evolution). The mixture was diluted with water and extracted with CH₂Cl₂ (×3) and the combined organic layers were dried over Na₂SO₄ and concentrated to give the crude triol.

3.3.11. General Procedure K for Hydrolysis of MOM Ethers

TiCl₄ (5 equiv) was added dropwise over 10 seconds to a stirred solution of substrate in CH₂Cl₂ (50 mL/ mmol) at -78 °C under argon. After 5 minutes a fine yellow slurry developed. Thiophenol (10 equiv) was added dropwise over 10 seconds and the resultant red-orange fine slurry was stirred for a further 10 minutes at -78 °C. MeOH (0.5 mL) was added and the cooling bath was removed (reaction became colourless upon addition of MeOH). The solution was stirred vigorously for 1 minute followed by the addition of phosphate buffer (3 mL, pH 7). After 3 minutes, the mixture
was diluted with saturated Na$_2$CO$_3$* and extracted with CH$_2$Cl$_2$ (3×). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated to give the crude product that contained varying amounts of starting material.

3.3.12. General Procedure L for Preparation of MOM Ethers

Bu$_4$NI (0.03 equiv), i-Pr$_2$EtN (5 equiv) and MOMCl (3 equiv) were sequentially added to a solution of monoaldol substrate in CH$_2$Cl$_2$ (3 mL/ mmol). The reaction was monitored by TLC (50% ethyl acetate in hexane). Within the first day the reaction colour was deep orange and complete conversion was usually obtained after 3 days. The reaction was diluted with HCl and extracted with CH$_2$Cl$_2$ (×3). The organic extracts were combined, dried over Na$_2$SO$_4$ and concentrated to give crude product as a light yellow oil.

3.3.13. General Procedure M for Preparation of MOM Ethers

Bu$_4$NI (1 equiv), i-Pr$_2$EtN (15 equiv) and MOMCl (10 equiv) were sequentially added to a solution of bisaldol in CH$_2$Cl$_2$ (50 mL/ mmol) under argon. After a suitable time (TLC monitoring) the reaction was diluted with citric acid (15 mL, 0.1M) and extracted with CH$_2$Cl$_2$ (3×20 mL). The organic extracts were combined, dried over Na$_2$SO$_4$ and concentrated to give crude product/s that contained varying amounts of starting material.

3.4. Experimental Procedures and Spectral Data for Compounds

Tetrahydro-thiopyran-4-one (122)

A solution of 124 (22.5 g, 0.13mol) in 5% H$_2$SO$_4$ (60 mL) was heated under reflux. The reaction was monitored by TLC (50% EtOAc in hexane). Starting material

* Saturated Na$_2$CO$_3$ was used to extract PhSH into the aqueous phase.
was consumed after 18 h. The reaction was diluted with cold dist water (0 °C, 40 mL) and extracted with CH₂Cl₂ (3×). The combined organic extracts were washed with saturated K₂CO₃ (×1), dried over Na₂SO₄ and concentrated to give a light yellow oil which solidified upon standing (12.5 g). Hexane (300 mL) was added to the yellow solid (12.5 g) and after heating the mixture to boiling, the cloudy hexane supernatant was decanted from the insoluble yellow oil. This process was repeated (×1). The combined supernatants were cooled to 0 °C to yield white crystals (9.6 g, 64%). Spectral data for the product was in accord with that previously reported.²⁰⁹

Methyl Tetrahydro-4-oxo-2H-thiopyran-3-carboxylate (124)

Anhydrous methanol (freshly distilled from Mg(OMe)₂; 155.0 mL, 122.6g, 3.83 mol) was added dropwise by dropping funnel over 8 h to a stirred suspension of finely cut sodium metal (40.0 g, 1.74 mol) in ether (100 mL) and THF (200 mL) at 0 C under argon (caution: H₂ evolution). The mixture was stirred for 30 h at rt and a fine white suspension was obtained. A solution of dimethyl 3,3′-thiodipropionate 123 (140 g, 0.679 mmol) in THF (50 mL) was then added dropwise over 4 h by dropping funnel to the NaOMe suspension at 0°C. The reaction mixture was stirred at rt for a further 20 h and an orange coloured suspension was obtained. The reaction mixture was transferred to a dropping funnel and added over 20 min to a solution of citric acid (183g, 0.871 mol) in dist. water (800 mL) (pH = 5 after addition of suspension to citric acid solution) at 0 °C. The organic layer was separated and washed with brine (×2) and the brine extracts were combined and extracted with CH₂Cl₂ (×2). The separated aqueous layer of the quenched mixture was extracted with CH₂Cl₂ (×4). The combined organic layers were dried over Na₂SO₄ and concentrated to give a clear oil which later solidified to a white solid (116 g, 98%). Spectral data for the product was in accord with that previously reported.²¹⁰
Methyl 1,4-Dioxa-8-thiaspiro[4.5]decane-6-carboxylate (124a).  

A solution of β-ketoester 124 (30 g, 0.17 mol), ethylene glycol (43 g, 0.69 mol) and p-TsOH·H₂O (1.7 g, 8.9 mmol) in benzene (800 mL) was heated under reflux for 16 h with removal of water via a Dean-Stark trap. The cooled (rt) reaction mixture was concentrated under reduced pressure, diluted with ether, washed sequentially with saturated aqueous NaHCO₃ (x2), water and brine, dried over Na₂SO₄, and concentrated to give the titled compound as a colorless oil (32-37 g, 85-98%) which was homogeneous by TLC and NMR and was used without further purification:

**IR** ν max 1733 cm⁻¹;

**¹H NMR** (300 MHz, CDCl₃) δ 4.00-3.86 (4H, m), 3.71 (3H, s), 3.11 (1H, ap dd, J = 8.5, 13.5 Hz), 2.96-2.78 (3H, m), 2.67 (1H, dddd, J = 1.5, 3.5, 7, 13.5 Hz), 2.25 (1H, ddd, J = 3.5, 7, 13.5 Hz), 1.82 (1H, ddd, J = 3.5, 9.5, 13.5 Hz);

**¹³C NMR** (75 MHz, CDCl₃) δ 171.0 (s), 107.2 (s), 65.1 (t), 64.7 (t), 51.8 (d), 51.2 (q), 36.0 (t), 29.6 (t), 26.7 (t);

**HRMS** m/z calcd for C₉H₁₄O₄S 218.0613, found 218.0604 (EI).


1,4-Dioxa-8-thiaspiro[4.5]decane-6-methanol (124b).  

Following General procedure A, a solution of 124a (22.5 g, 103 mmol) in ether was reduced with LiAlH₄ in ether (200 mL) to give the titled compound as a pale
yellow viscous oil (17.0-18.5 g, 86-94%) which was homogeneous by TLC and NMR and was used without further purification.

IR $\nu_{\text{max}}$ 3442 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.03-3.97 (4H, m), 3.91 (1H, dd, $J = 6.5$, 11 Hz), 3.66 (1H, dd, $J = 4.5$, 11 Hz), 2.80-2.71 (3H, m), 2.65 (1H, ddd, $J = 4$, 7, 13.5 Hz), 2.25 (1H, br s), 2.19-2.13 (1H, m), 2.07 (1H, ddd, $J = 3.5$, 7, 13.5 Hz), 1.77 (1H, ddd, $J = 4$, 9.5, 13.5 Hz);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 109.5 (s), 64.7 (t), 64.4 (t), 62.3 (t), 47.0 (d), 35.1 (t), 29.3 (t), 26.6 (t);

HRMS $m/z$ calcd for C$_{8}$H$_{14}$O$_{3}$S 190.0664, found 190.0672 (EI).

1,4-Dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde (125a).

Swern oxidation: A solution of DMSO (3.6 mL, 4.0 g, 51 mmol) in CH$_2$Cl$_2$ (2.0 mL) was added dropwise over 5 minutes via syringe to a stirred solution of oxalyl chloride (2.2 mL, 26 mmol) in CH$_2$Cl$_2$ (25 mL) at -78 °C under argon. After 30 min at -78 °C, a solution of alcohol 124b (3.27 g, 17.1 mmol) in CH$_2$Cl$_2$ (2 mL) was added dropwise via syringe over 3 minutes to the reaction mixture. After a further 30 min, i-Pr$_2$EtN (15 mL, 86 mmol) was added over 1 minute and the reaction mixture was allowed to warm to 0 °C over 5 min. The reaction mixture was diluted with ice-cold HCl (0 °C, 100 mL, 1 M) and the resultant mixture was quickly extracted with CH$_2$Cl$_2$ (x3). The combined organic layers were dried over Na$_2$SO$_4$, concentrated and fractionated by DFC (5-10% ethyl acetate in hexane; gradient elution) to give the titled aldehyde as a clear oil (2.09-2.60 g, 65-80%)

IR $\nu_{\text{max}}$ 2840, 2737, 1721 cm$^{-1}$;
\textbf{1H NMR} (300 MHz, CDCl$_3$) $\delta$ 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);

\textbf{13C NMR} (75 MHz, CDCl$_3$) $\delta$ 201.3 (d), 107.8 (s), 64.9 (t), 64.7 (t), 56.6 (d), 36.2 (t), 26.7 (t), 26.4 (t);

\textbf{HRMS} $m/z$ calcd for C$_{8}$H$_{12}$O$_{3}$S 188.0507, found 188.0512 (EI). Anal. Calcd for C$_{8}$H$_{12}$O$_{3}$S: C, 51.04; H, 6.43. Found: C, 51.20; H, 6.58.

(3S*, 4R*)-Tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-carboxaldehyde (125b).

![Diagram of 125b]

Modified Swern oxidation: A solution of DMSO (520 µL, 570 mg, 7.30 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added dropwise over 3 minutes via syringe to a stirred solution of oxalyl chloride (318µL, 3.65 mmol) in CH$_2$Cl$_2$ (8 mL) at $-78$ °C under argon. After 30 min at $-78$ °C, a solution of alcohol 142 (701 mg, 3.65 mmol) and dimethyl sulfide (536 µL, 7.29 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise via syringe over 3 minutes to the reaction mixture. After an additional 3 min, i-Pr$_2$EtN (1.91 mL, 10.9 mmol) was added over 10 seconds and the reaction mixture was allowed to warm to rt over 20 minutes with vigorous stirring. The reaction mixture was diluted with 1 M HCl (60 mL) and quickly followed by extraction with CH$_2$Cl$_2$ (3×). The combined organic layers were dried over Na$_2$SO$_4$, concentrated and fractionated by FCC (30% ethyl acetate in hexane) to give the titled aldehyde as a clear oil (617 mg, 89%).

\textbf{IR} $v_{\text{max}}$ 2823, 2722, 1726 cm$^{-1}$;

\textbf{1H NMR} (300 MHz, CDCl$_3$) $\delta$ 9.63 (1H, s), 4.69 (1H, d, $J = 7$ Hz), 4.57 (1H, d, $J = 7$ Hz), 4.40 (1H, ddd, $J = 2.5, 2.5, 5$ Hz), 3.31 (3H, s), 3.04 (1H, ap dd, $J = 12.5, 12.5$ Hz), 2.93 (1H, ap dd, $J = 12, 12.5$ Hz), 2.70-2.60 (2H, m), 2.41-2.26 (2H, m), 1.90-1.78 (1H, m);
From Modified Swern oxidation of 143: Using the above procedure, 143 (761 mg) was converted into the trans aldehyde 125c (170 mg, 23%).

From DIBAH reduction of 141: Cold DIBAL-H (0.5 M in toluene; 26.2 mL, 13 mmol) was added dropwise via syringe pump over 3 h to a stirred solution of the ester 141 (1.581 g, 7.18 mmol) in toluene (10 mL) at −78 °C under argon. This addition was achieved by having the output from the syringe pump run down the side of a cold finger condenser (dry-ice/acetone) mounted above the reaction mixture. After 3 h, the reaction was quenched by the addition of cold MeOH (9 mL) via syringe pump over 2 h as above. The reaction mixture was allowed to warm to rt over several hours and then ice cold 1 M HCl (50 mL) was added. After 10 min of vigorous stirring, the mixture was diluted with brine and extracted with CH₂Cl₂ (×3). The combined organic layers were dried over Na₂SO₄, concentrated and fractionated by MPC (30% ethyl acetate in hexane) to give the alcohol 143 (193 mg, 14%) and the aldehyde 125c (939 mg, 69%):

IR νmax 2824, 2725, 1721 cm⁻¹;

¹H NMR (300 MHz, CDCl₃) δ 9.80 (1H, d, J = 1.5 Hz), 4.73 (1H, d, J = 7 Hz), 4.62 (1H, d, J = 7 Hz), 3.94 (1H, ddd, J = 3.5, 8, 8 Hz), 3.35 (3H, s), 2.97 (1H, br d, J = 12.5 Hz), 2.86-2.66 (3H, m), 2.52 (1H, ddd, J = 3, 9, 13.5 Hz), 2.23 (1H, dddd, J = 3, 3.5, 7.5, 13 Hz), 1.85 (1H, dddd, J = 3, 8, 9, 13.5 Hz);

¹³C NMR (300 MHz, CDCl₃) δ 202.6 (d), 95.4 (t), 73.5 (d), 55.9 (q), 54.1 (d), 31.7 (t), 26.1 (t), 25.7 (t);

HRMS m/z calcd for C₈H₁₄O₃S 190.0664, found 190.0666 (EI).
(1'S*, 3'S*, 6'R*)-3-[(1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl)hydroxymethyl]tetrahydro-4H-thiopyran-4-one (126a).

From aldol reaction of 137b and 125a (TiCl₄). Freshly distilled TiCl₄ (0.30 mL, 0.51 g, 2.7 mmol) was added dropwise over 1 min to a stirred solution of the aldehyde 125a (500 mg, 2.66 mmol) in CH₂Cl₂ (35 mL) at −78 °C under argon. The resulting fine yellow suspension was stirred for 10 min and then a solution of 137b (736 mg, 3.91 mmol) in CH₂Cl₂ (7.5 mL) was added dropwise via syringe over 2 min whereupon the yellow suspension turned to a clear dark orange and then red solution. After 1 h at −78 °C, the reaction was allowed to warm to rt over 30 min and then was quenched by sequential addition of a solution of Et₃N (80 mg, 0.79 mmol) and MeOH (100 mg, 3.1 mmol) in CH₂Cl₂ (1 mL) and then sat. NH₄Cl (5 mL). The mixture was diluted with water, extracted with CH₂Cl₂ (×3) and the combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (gradient elution 20-50% ethyl acetate in hexane) to give the aldol 127a (18 mg, 5%) as a white solid and the aldol 126a (663 mg, 82%) as a white solid.

From aldol reaction of 137b and 125a (BF₃·OEt₂). Using the same procedure as above but replacing TiCl₄ with BF₃·OEt₂, 125a (73 mg, 0.039 mmol) gave a 2:1 mixture of 126a and 127a (70%), respectively.

From aldol reaction of 137d with 125a. TiCl₄ (0.030 mL, 52 mg, 0.28 mmol) was added to a stirred solution of 3 (29 mg, 0.25 mmol) in CH₂Cl₂ (4 mL) at −78 °C under argon. After 5 min, i-Pr₂EtN (0.052 mL, 39 mg, 0.30 mmol) was added and after 2 h at −78 °C, a solution of 125a (56 mg, 0.30 mmol) in CH₂Cl₂ (0.5 mL) was added. After 5 h, the reaction was quenched addition of aqueous NH₄Cl. The mixture was diluted with water and extracted with CH₂Cl₂ (×3), and the combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (20-50% ethyl acetate in hexane; gradient elution) to give 126a (20 mg, 26%) and a 1:1 mixture of C₃ and C₁ bisaldols (26 mg, 20%).
IR $\nu_{\text{max}}$, 3507, 1703 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.79 (1H, dd, $J = 3$, 8.5 Hz, HC-1$'$ [$^3$J$_{HC-1'/HC-3} = 8.5$ Hz]), 4.10-3.96 (4H, m), 3.19-2.88 (7H, m), 2.81-2.67 (4H, m), 2.58-2.54 (1H, m), 2.11 (1H, ddd, $J = 3$, 5.5, 14 Hz), 1.93 (1H, ddd, $J = 3$, 3, 10.5 Hz), 1.73 (1H, ddd, $J = 3.5$, 11.5, 14 Hz);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 210.1 (s), 109.8 (s), 66.1 (d), 64.6 (t), 64.2 (t), 56.0 (d), 46.2 (d), 44.2 (t), 35.6 (t), 32.6 (t), 31.2 (t), 26.4 (t), 26.3 (t);

HRMS m/z calcd for C$_{13}$H$_{20}$O$_4$S$_2$ 304.0803, found 304.0799. Anal. Calcd for C$_{13}$H$_{20}$O$_4$S$_2$: C, 51.29; H, 6.62. Found: C, 51.43; H, 6.44.

$(1'R^*, 3S^*, 3''R^*, 4''R^*)$-3-[Hydroxy(4-(methoxymethoxy)tetrahydro-$2H$-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (126b).

\[
\begin{array}{c}
\text{MOMO} \\
\text{5'} \quad \text{4'} \\
\text{6'} \\
\text{S} \\
\text{2'} \quad \text{3'} \\
\text{1'} \\
\text{O} \quad \text{O}
\end{array}
\]

From aldol reaction of 137c and 125b (Li-enolate). Following the corresponding procedure described for the synthesis of 127a, reaction of 125b (580 mg, 3.05 mmol) with the 'amine-free' Li enolate 137c (following General procedure B, 137b (1.15 g, 6.11 mmol) gave 137c) gave a yellow oil (1.413 g) which contained a 4.1:1.7:1 mixture of aldols 127b, 129b, and 126b, respectively ($^1$H NMR). Fractionation of the crude product by MPC (25% ethyl acetate in hexane) gave 126b (88 mg, 9%), the 127b (220 mg, 24%), and a 1.1:1 mixture of the 129b and 127b aldols (258 mg, 28%).

IR $\nu_{\text{max}}$ 3496, 1701 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.74 (1H, d, $J = 7$ Hz), 4.60 (1H, d, $J = 7$ Hz), 4.23 (1H, br t, $J = 5.5$, 5.5 Hz, HC-1$'$ [$^3$J$_{HC-1'/HC-3} = 5.5$ Hz]), 3.96 (1H, ddd, $J = 2$, 2.5, 5 Hz), 3.36 (3H, s), 3.07-2.85 (8H, m), 2.75-2.71 (2H, m), 2.57 (1H, br dd, $J = 3$, 13 Hz), 2.34-2.28 (2H, m), 1.90 (1H, dddd, $J = 2.5$, 3, 5.5, 11.5 Hz), 1.77 (1H, m);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 211.37, 94.86, 73.92, 71.17, 56.36, 54.77, 45.27, 43.74, 31.57, 31.29, 31.23, 23.86, 22.49;
HRMS m/z calcd for C₁₃H₂₂O₄S₂ 306.0960, found 306.0956 (EI).

(1'R*, 3S*, 3"R*, 4"S*)-3-[Hydroxy(4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (126c).

Aldol reaction of 137b and 125c (TiCl₄). Following the procedure described for the synthesis of 126a using TiCl₄ (0.018 mL, 31 mg, 0.16 mmol), the aldehyde 125c (30 mg, 0.16 mmol), and 137b (60 mg, 0.32 mmol) in CH₂Cl₂ (5 mL) gave, after work up, a light orange oil (78 mg) which contained a 10:1 mixture of aldols 126c and 129c, respectively, and ca. 8% of remaining 125c (¹H NMR). The crude was fractionated by MPC (35% ethyl acetate in hexane) to give a 20:2:1 mixture of aldols 126c, 129c, and 128c, respectively (40 mg, 81%). A pure sample of 126c was obtained by fractionation of a portion of the above mixture by PTLC (50% ethyl acetate in hexane).

IR νmax 3472, 1702 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 4.84 (1H, ddd, J = 4, 5, 8.5 Hz, HC-1' [³JHC-1'/HC-3 = 8.5 Hz]), 4.73 (1H, d, J = 6.5 Hz), 4.63 (1H, d, J = 6.5 Hz), 3.47 (1H, ddd, J = 3.5, 9, 9, Hz), 3.47 (3H, s), 3.17 (1H, d, J = 5 Hz, OH), 3.12 (2H, ap d, J = 5 Hz), 2.99-2.94 (2H, m), 2.86 (1H, ap ddd, J = 5, 5, 8.5 Hz), 2.79 (1H, ddd, J = 2, 3, 13.5 Hz), 2.72-2.65 (3H, m), 2.64 (1H, dd, J = 9.5, 13.5 Hz), 2.57 (1H, ddd, J = 3, 11, 13.5 Hz), 2.20 (1H, dddd, J = 3, 3.5, 6, 13 Hz), 1.79 (1H, dddd, J = 3.5, 9, 11, 13 Hz), 1.72 (1H, dddd, J = 3, 4, 9, 9.5 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 210.29, 96.33, 76.79, 66.30, 56.55, 55.26, 45.61, 44.19, 33.32, 33.11, 31.50, 26.85, 26.24;

HRMS m/z calcd for C₁₃H₂₂O₄S₂ 306.0960, found 306.0962 (EI).
(1'S*, 3'R*, 6''R*)-3-[(1,4-Dioxo-8-thiaspiro[4.5]dec-6-y1)hydroxymethyl]tetrahydro-4H-thiopyran-4-one (127a).

From aldol reaction of 137b and 125a (SnCl₄). A solution of SnCl₄ (270 µL, 0.266 mmol, 1.0 M) in CH₂Cl₂ was added dropwise to a stirred solution of aldehyde 125a (25 mg, 0.133 mmol) in CH₂Cl₂. The resulting fine white suspension was stirred for 10 min at 0 °C and then a solution of 137b (50 mg, 0.266 mmol) in CH₂Cl₂ (0.5 mL) was added dropwise via syringe over 10 seconds whereupon the white suspension turned to a light orange coloured suspension (Note that the colour of a pure solution enolsilane in CH₂Cl₂ is light orange). After stirring for 2 h at 0 °C the reaction was quenched by the addition of phosphate buffer (10 mL, pH 7, 0.1 M) which gave a fine white ppt. The mixture was passed through Celite® followed by washing with phosphate buffer (20 mL), the filtrate was then extracted with CH₂Cl₂ (x3). The organic extracts were combined, dried over Na₂SO₄, concentrated, and fractionated by FCC (50% ethyl acetate in hexane) to give a 3:1 mixture of 127a and 126a (29 mg, 72%), respectively.

From aldol reaction of 137c and 125a (Li-enolate). A solution of 125a (2.32 g, 12.3 mmol) in THF (5 mL) was added rapidly via syringe to a solution of the 'amine free' lithium enolate 137c (following General procedure B, 137b (3.48 g, 18.5 mmol) gave 137c) at -78°C. After stirring for 5 min, the reaction was quenched by rapid addition of glacial acetic acid (1.5 mL) in THF (5 mL). The reaction mixture was removed from the cooling bath and CH₂Cl₂ (100 mL) and water (50 mL) were added. The aqueous layer was extracted with CH₂Cl₂ (x2) and the combined organic layers were washed sequentially with aqueous NaHCO₃ and water, dried over Na₂SO₄, and concentrated to give a pale yellow semi-solid. Trituration of the crude product with ether gave a yellowish powder that was recrystallized from benzene to give the pure 127a (2.06 g, 55%; mp 148-149 °C). The ether from trituration and the mother liquor from recrystallization were combined and concentrated and ketone 122.
(910 mg, 42%) was recovered by sublimation (rt, 0.5 Torr). The residue was fractionated by FCC (10-50% EtOAc in hexane; gradient elution) to give recovered aldehyde 125a (541 mg, 23%), the aldol 126a (270 mg, 7%), and aldol 127a (300 mg, 8%).

From aldol reaction of 137e (137f) with 125a. A solution of 122 (20 mg, 0.17 mmol) in CH₂Cl₂ (0.5 mL) was added to a stirred solution of Bu₂BOTf (1 M in CH₂Cl₂; 0.26 mL) and i-Pr₂EtN (0.090 mL, 67 mg, 0.52 mmol) in CH₂Cl₂ (5 mL) at -78 °C under argon. After 3 h, a solution of 125a (130 mg, 0.69 mmol) in CH₂Cl₂ (0.5 mL) was added to the reaction mixture. After 3 h, the reaction was quenched by the sequential addition of phosphate buffer (pH 7, 0.5 mL), methanol (3.5 mL), and 30% H₂O₂ (0.2 mL). The mixture was stirred at 0 °C for 15 min and then aqueous Na₂SO₃ was added to reduce the H₂O₂. The mixture was diluted with water and extracted with CH₂Cl₂ (×3), and the combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by FCC (20-40% ethyl acetate in hexane; gradient elution) to give recovered 125a (58 mg, 45%), 126a (4 mg, 8%), and 127a (39 mg, 74%). A similar experiment using (c-C₆H₁₁)₂BCl in place of Bu₂BOTf gave a 15:1 mixture of 127a and 126a (44 mg, 84%), respectively.

IR νmax 3488, 3409, 1711 cm⁻¹;

¹H NMR (300 MHz, CDCl₃) δ 4.50 (1H, dd, J = 4.5, 6.5 Hz, HC-1' [$^3J_{HC-1'}/HC-3$ = 6.5 Hz]), 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);

¹³C NMR (75 MHz, CDCl₃) δ 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);

(1'R*, 3R*, 3''R*, 4'R*)-3-[Hydroxy(4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (127b).

From aldol reaction of 137b and 125b (TiCl₄). The cis aldehyde 125b was unstable in the presence of TiCl₄ (elimination). Following the procedure described for the synthesis of 126a, 125b (73 mg, 0.38 mmol) gave the aldol 127b (11 mg, 9%), the aldol 129b (15 mg, 12%), and recovered 125b (16 mg, 22%) after fractionation by MPC (30% ethyl acetate in hexane).

IR \( \nu_{\text{max}} \) 3508, 1700 cm⁻¹;

\(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 4.71 (1H, d, \( J = 7 \) Hz), 4.59 (1H, d, \( J = 7 \) Hz), 3.96 (1H, ddd, \( J = 3, 6, 7.5 \) Hz, HC-1' \( J_{\text{HC-1'/HC-3}} = 6 \) Hz), 3.89 (1H, ddd, \( J = 2.5, 3, 5 \) Hz), 3.41 (3H, s), 3.15-2.94 (7H, m), 2.90 (1H, br dd, \( J = 12, 13 \) Hz), 2.81-2.71 (2H, m), 2.64 (1H, br d, \( J = 13.5 \) Hz), 2.34 (1H, br ddd, \( J = 3.5, 4, 13 \) Hz), 2.26 (1H, dddd, \( J = 2.5, 4, 5, 14.5 \) Hz), 2.14 (1H, dddd, \( J = 3, 3.5, 6, 11 \) Hz), 1.77 (1H, dddd, \( J = 2.5, 3.5, 12, 14.5 \) Hz);

\(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 211.84 (s), 94.89 (t), 74.97 (d), 74.37 (d), 56.39 (q), 54.06 (d), 45.12 (d), 45.05 (t), 35.20 (t), 31.69 (t), 31.15 (t), 24.98 (t), 23.09 (t);

HRMS \( m/z \) calcd for C₁₃H₂₂O₄S₂ 306.0960, found 306.0961 (EI).

Aldol reaction of 137c and 125c (Li-enolate). Following the procedure described for the synthesis of 127a, reaction of the trans aldehyde 125c (525 mg, 2.76 mmol) with the 'amine-free' Li enolate 137c (following General procedure B, 137b (1.08 g, 5.73 mmol) gave 137c) gave aldol 127c (542 mg, 64%) after fractionation by MPC (35% ethyl acetate in hexane).

IR \( \nu_{\text{max}} \) 3508, 1700 cm⁻¹;

\(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 4.71 (1H, d, \( J = 7 \) Hz), 4.59 (1H, d, \( J = 7 \) Hz), 3.96 (1H, ddd, \( J = 3, 6, 7.5 \) Hz, HC-1' \( J_{\text{HC-1'/HC-3}} = 6 \) Hz), 3.89 (1H, ddd, \( J = 2.5, 3, 5 \) Hz), 3.41 (3H, s), 3.15-2.94 (7H, m), 2.90 (1H, br dd, \( J = 12, 13 \) Hz), 2.81-2.71 (2H, m), 2.64 (1H, br d, \( J = 13.5 \) Hz), 2.34 (1H, br ddd, \( J = 3.5, 4, 13 \) Hz), 2.26 (1H, dddd, \( J = 2.5, 4, 5, 14.5 \) Hz), 2.14 (1H, dddd, \( J = 3, 3.5, 6, 11 \) Hz), 1.77 (1H, dddd, \( J = 2.5, 3.5, 12, 14.5 \) Hz);

\(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 211.84 (s), 94.89 (t), 74.97 (d), 74.37 (d), 56.39 (q), 54.06 (d), 45.12 (d), 45.05 (t), 35.20 (t), 31.69 (t), 31.15 (t), 24.98 (t), 23.09 (t);

HRMS \( m/z \) calcd for C₁₃H₂₂O₄S₂ 306.0960, found 306.0961 (EI).
acetate in hexane). The presence of other aldol diastereomers was not detected by $^1$H NMR of the crude product.

**IR** $\nu_{\text{max}}$ 3516, 1701 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.72 (1H, d, $J = 6.5$ Hz), 4.70 (1H, d, $J = 6.5$ Hz), 4.47 (1H, ddd, $J = 2.5, 4, 9.5$ Hz, HC-1'), 3.61 (1H, ddd, $J = 4, 10, 10.5$ Hz), 3.43 (3H, s), 3.22 (1H, d, $J = 4$ Hz, OH), 3.03-2.93 (2H, m), 2.92-2.83 (2H, m), 2.82-2.65 (5H, m), 2.58 (1H, m, $J = 2.5, 3.5, 4, 13.5$ Hz), 2.51 (1H, ddd, $J = 2.5, 3, 13.5$ Hz), 2.42 (1H, ddd, $J = 3, 4, 4, 12.5$ Hz), 1.77 (1H, ddd, $J = 3, 3, 9.5, 10$ Hz), 1.74 (1H, ddd, $J = 3, 10.5, 12, 12.5$ Hz);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 212.35 (s, CO), 96.52 (t), 76.18 (d), 67.72 (d), 56.03 (q), 55.45 (d), 45.73 (d), 44.99 (t), 34.90 (t), 32.42 (t), 31.07 (t), 27.75 (t), 26.31 (t);

**HRMS** $m/z$ calcd for C$_{13}$H$_{22}$O$_4$S$_2$ 306.0960, found 306.0954 (EI).

(1'R*, 3R*, 6''R*)-3-[(1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl)hydroxymethyl]tetrahydro-4H-thiopyran-4-one (128a):

From aldol reaction of 137b and 125a (MgBr$_2$). MgBr$_2$·0Et$_2$ (4.45 g, 17.4 mmol) was added to a stirred solution of aldehyde 125a (1.08 g, 5.74 mmol) in CH$_2$Cl$_2$ (26 mL) at rt under argon. After 2 min, the resulting creamy off-white suspension was placed in an ice bath and, after 15 min, a solution of 137b (2.16 g, 11.5 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise via syringe over 3 min. After stirring 1 h at 0°C, the reaction mixture was poured onto ice-cold phosphate buffer (pH 7; 50 mL) with vigorous stirring. The mixture was diluted with water and extracted with CH$_2$Cl$_2$ ($\times$3). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated to give an orange colored oil which contained a 3:1 mixture of 128a and 129a in addition to ketone 122 and aldehyde 125a (ca. 3%). The relatively volatile 122 (621 mg, 47% based on 137b) was easily recovered from the crude by sublimation at high vacuum (rt).
The remaining residue was crystallized from methanol to give the aldol 128a (mp 152-153 °C; 1.07 g, 61%). The mother liquor (ca. 4:1 mixture of 129a:128a) was concentrated and fractionated by MPC (25-50% ethyl acetate in hexane; gradient elution) to give 128a (101 mg, 6%) and 129a (381 mg, 22%).

**IR** $\nu_{\text{max}}$ 3497, 1706 cm$^{-1}$;

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 4.57 (1H, ddd, $J = 2.5$, 3.5, 7.5 Hz, HC-1'), 4.10-3.89 (4H, m), 3.85 (1H, d, $J = 2.5$ Hz, OH), 3.13 (1H, dd, $J = 11$, 13.5 Hz), 3.0 (1H, ddd, $J = 4$, 10.5, 13.5 Hz), 2.91-2.57 (9H, m), 2.07 (1H, ddd, $J = 3.5$, 7.5, 8 Hz), 1.82-1.71 (1H, m);

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$ 209.1 (s), 110.8 (s), 69.7 (d), 64.8 (t), 64.1 (t), 55.3 (d), 46.2 (d), 44.1 (t), 34.9 (t), 29.7 (t), 29.4 (t), 29.3 (t), 26.7 (t);

**HRMS** $m/z$ calcd for C$_{13}$H$_{20}$O$_4$S$_2$ 304.0803, found 304.0807. Anal. Calcd for C$_{13}$H$_{20}$O$_4$S$_2$: C, 51.29; H, 6.62. Found: C, 51.34; H, 6.66.

(1'S*, 3'R*, 3''R*, 4''R*)-3-[Hydroxy(4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (128b).

\[
\begin{array}{c}
\text{MOMO} \\
5^* \quad 4^* \quad 3^* \quad 3 \quad 4 \quad 5 \quad 6^* \\
\text{S} \quad 2^* \quad 2 \quad 2 \quad 2 \quad 2 \quad 2
\end{array}
\]

Aldol reaction of 137b and 125b (MgBr$_2$). Following the procedure described for the synthesis of 128a, the cis aldehyde 125b (573 mg, 3.01 mmol) gave an orange to yellow colored oil on work up which contained a 4:1 mixture of aldols 128b and 129b in addition to 122 and 125b (ca. 2%). The relatively volatile 122 (321 mg, 46% based on 137b) was easily recovered from the crude at high vacuum (rt). The remaining residue was crystallized from methanol to give 128b (525 mg, 57%) and the mother liquor was fractionated by MPC (30% ethyl acetate in hexane) to give a 2.5:1 mixture of 129b and 128b (257 mg, 27%). A pure sample of 129b was obtained by fractional crystallization of the above mixture from methanol resulting in a mother liquor enriched in 129b (ca. 5:1) which was further fractionated by PTLC (2% MeOH in CH$_2$Cl$_2$, multiple development).
IR $\nu_{\text{max}}$ 3464, 1697 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.71 (1H, d, $J = 6.5$ Hz), 4.67 (1H, d, $J = 6.5$ Hz), 4.23 (1H, m), 4.20 (1H, ddd, $J = 3.5$, 5, 9 Hz, HC-1' $[^3J_{\text{HC-1'/HC-3}} = 3.5$ Hz]), 3.43 (3H, s), 3.21 (1H, d, $J = 5$ Hz, OH), 3.11 (1H, dd, $J = 10.5$, 14 Hz), 3.06-2.82 (5H, m), 2.80-2.66 (3H, m), 2.35-2.25 (2H, m), 2.10 (1H, dd, $J = 2$, 13.5 Hz), 1.83 (1H, dddd, $J = 2$, 3, 9, 11 Hz), 1.73 (1H, m);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 211.0, 96.3, 71.4, 69.2, 56.3, 54.9, 44.7, 43.6, 31.9, 30.4, 29.9, 24.7, 22.4;

HRMS $m/z$ calcd for C$_{13}$H$_{22}$O$_4$S$_2$ 306.0960, found 306.0962 (EI).

$^{1'S^*, 3'R^*, 3''R^*, 4'S^*}$-[Hydroxy(4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (128c).

From aldol reaction of 137b and 125c (MgBr$_2$). Following the procedure described for the synthesis of 128a, the trans aldehyde 125c (206 mg, 1.08 mmol) gave a 7:4:1 mixture of aldols 128c, 126c, and 129c, respectively (245 mg, 74%) after fractionation by MPC (30% ethyl acetate in hexane). A pure sample of 128c was obtained by further fractionation of a portion of the above mixture by PTLC (2% methanol in CH$_2$Cl$_2$). A pure sample of 129c could not be obtained. Extensive fractionation of the above mixture by PTLC (2% methanol in CH$_2$Cl$_2$) gave a 1.5:1 mixture of aldols 129c and 128c.

IR $\nu_{\text{max}}$ 3483, 1701 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.70 (1H, d, $J = 6.5$ Hz), 4.67 (1H, d, $J = 6.5$ Hz), 4.52 (1H, ddd, $J = 3$, 5, 8 Hz, HC-1' $[^3J_{\text{HC-1'/HC-3}} = 3$ Hz]), 3.95 (1H, ddd, $J = 3$, 6, 7 Hz), 3.40 (3H, s), 3.16 (1H, d, $J = 5$ Hz, OH), 3.09-2.87 (7H, m), 2.80-2.75 (2H, m), 2.43 (1H, dddd, $J = 1$, 3.5, 7, 12.5 Hz), 2.32 (1H, ddd, $J = 1$, 6.5, 13.5 Hz), 2.20 (1H, dddd, $J = 3$, 3.5, 10, 13.5 Hz), 1.94-1.85 (2H, m);
\(^{13}\text{C NMR} \text{ (100 MHz, CDCl}_3\) } \delta \text{ 211.45, 95.65, 74.40, 69.99, 55.95, 55.66, 45.10, 42.02, 30.86, 30.46, 29.86, 27.44, 24.85;}

\text{HRMS m/z} \text{ calcd for C}_{13}\text{H}_{22}\text{O}_{4}\text{S}_{2} \text{ 306.0960, found 306.0962 (EI).}

\((1'R^*,3S^*,6''R^*)-3-((1,4\text{-Dioxa}-8\text{-thiaspiro}[4.5]\text{dec-6-yl})\text{hydroxymethyl})\text{tetrahydro-4H-thiopyran-4-one (129a).}\)

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

From aldol reaction of \textbf{137b} and \textbf{125a} (MgBr\(_2\)). See experimental procedure for compound \textbf{128a}.

\text{IR } \nu_{\text{max}} \text{ 3496, 1702 cm}^{-1};

\textbf{1H NMR} \text{ (300 MHz, CDCl}_3\) \delta \text{ 4.24 (1H, ddd, } J = 3.5, 3.5, 7.5 \text{ Hz, HC-1'}[^{3}J_{\text{HC-1'}/\text{HC-3} = 3.5 \text{ Hz})], 4.12-3.95 (4H, m), 3.93 (1H, d, } J = 3.5 \text{ Hz, OH}), 3.25 (1H, dd, } J = 11.5, 14.5 \text{ Hz), 3.02 (1H, ddd, } J = 4, 10, 13.5 \text{ Hz), 2.95-2.56 (9H, m), 2.41 (1H, ddd, } J = 3, 7.5, 7.5 \text{ Hz), 2.15 (1H, ddd, } J = 4, 9, 13.5 \text{ Hz), 1.79 (1H, ddd, } J = 3.5, 7, 13.5 \text{ Hz);}

\text{13C NMR} \text{ (75 MHz, CDCl}_3\) \delta \text{ 210.1 (s), 110.5 (s), 72.9 (d), 64.7 (t), 64.2 (t), 54.7 (d), 46.4 (d), 44.2 (t), 34.5 (t), 33.2 (t), 30.0 (t), 29.4 (t), 26.8 (t);}

\text{HRMS m/z} \text{ calcd for C}_{13}\text{H}_{20}\text{O}_{4}\text{S}_{2} \text{ 304.0803, found 304.0801.}

\((1'S^*,3S^*,3''R^*,4''R^*)-3-[(\text{Hydroxy}(4-(\text{methoxymethoxy})\text{tetrahydro-2H-thiopyran-3-yl})\text{methyl})\text{tetrahydrothiopyran-4-one (129b).}\)

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

From aldol reaction of \textbf{137b} and \textbf{125b} (MgBr\(_2\)). See experimental procedure for compound \textbf{128b}.

\text{IR } \nu_{\text{max}} \text{ 3501, 1701 cm}^{-1};
\(^{1}\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 4.72-4.69 (2H, m), 4.24 (1H, br s), 3.77 (1H, ddd, \(J = 3.5, 8.0, 10\) Hz, HC-1' \([^3J_{\text{HC-1'/HC-3}} = 3.5\) Hz]), 3.42 (3H, s), 3.29 (1H, d, \(J = 10\) Hz), 3.16 (1H, dd, \(J = 9.5, 13\) Hz), 3.04-2.88 (6H, m), 2.83-2.67 (2H, m), 2.39-2.28 (2H, m), 2.22-2.10 (2H, m), 1.82-1.73 (1H, m);

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 211.41, 96.25, 74.14, 71.60, 56.28, 54.29, 45.12, 45.01, 35.10, 31.95, 31.14, 25.73, 22.66;

HRMS m/z calcd for C\(_{13}\)H\(_{22}\)O\(_4\)S\(_2\) 306.0960, found 306.0956 (EI).

\((1'S^*, 3S^*, 3''R^*, 4''S^*)-3-[\text{Hydroxy(4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl)methyl}]\text{tetrahydrothiopyran-4-one (129c).}\)

From aldol reaction of 137b and 125c (MgBr\(_2\)). See experimental procedure for compound 128c. From the 1.5:1 mixture \(^*\) of 129c and 128c; spectral data for 129c was deduced from that of the mixture by comparison with data for pure 128c.

\(^{1}\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 4.70 (2H, ap s), 4.07 (1H, ddd, \(J = 5, 5, 6.5\) Hz, HC-1' \([^3J_{\text{HC-1'/HC-3}} = 5\) Hz]), 3.87 (1H, ddd, \(J = 3, 8, 8\) Hz), 3.40 (3H, s), 3.33 (1H, d, \(J = 6.5\) Hz, OH), 3.15-2.88 (5H, m), 2.85-2.68 (4H, m), 2.55 (1H, dd, \(J = 8, 13.5\) Hz), 2.51 (1H, ddd, \(J = 2.5, 9, 12.5\) Hz), 2.29 (1H, dddd, \(J = 3, 3.5, 8, 13.5\) Hz), 2.06 (1H, dddd, \(J = 3, 5, 8, 8\) Hz), 1.83 (1H, dddd, \(J = 3, 8, 9, 13.5\) Hz);

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 212.62, 95.86, 74.92, 74.41, 56.24, 56.06, 45.08, 43.80, 34.10, 31.78, 31.06, 29.98, 25.86.

3,6-Dihydro-4-trimethylsilyloxy-2H-thiopyan (137b).\(^{208,213}\)

* See experimental of 128c for origin of this mixture.
A solution of 122 (5.34 g, 46.0 mmol), Et3N (64 mL, 46 g, 0.46 mol) and TMSCI (29 mL, 25 g, 0.23 mol) in CH2Cl2 (50 mL) was stirred at rt under argon in a capped vessel for 10 days. The reaction mixture was concentrated, diluted with ether, and filtered through Celite®. The combined filtrate and ether washings were concentrated and the residue placed under high vacuum (0.5 torr) for several hours to give the titled compound as a yellow oil (8.0-8.5 g, 92-98%) which was homogeneous by 1H NMR and was used without further purification. The material slowly decomposed (mainly hydrolysis) upon storage under argon at −15 °C. Thus, if the material was not used directly a convenient method of storage involved making a solution of known concentration in benzene (ca. 1 M) containing 2 equiv of Et3N. This solution could be stored for months at −15 °C with negligible decomposition. The product was recovered as required by concentration of aliquots.

1H NMR (300 MHz, CDCl3) δ 5.06-5.04 (1H, m), 3.15-3.14 (2H, m), 2.76-2.72 (2H, m), 2.27-2.23 (2H, m), 0.17 (9H, s)

13C NMR (75 MHz, CDCl3) δ 151.3 (s), 102.2 (d), 31.2 (t), 25.7 (t), 25.1 (t), 0.3 (q ×3)

HRMS m/z calcd for C8H16O2Si 188.0708, found 188.0705 (EI).

Methyl (3S*, 4R*)-tetrahydro-4-hydroxy-2H-thiopyran-3-carboxylate (138) and Methyl (3R*, 4R*)-tetrahydro-4-hydroxy-2H-thiopyran-3-carboxylate (139).\(^{146,214}\)

NaCNBH3 (14.0 g, 0.223 mol) was added in four equal portions at 5 minute intervals to a stirred solution of β-ketoester 124 (40.0 g, 0.225 mole) and citric acid (48 g, 0.228 mole) in ethanol (200 mL) at 0 °C (Note: addition of NaCNBH3 is exothermic). The ice-bath was removed and the reaction progress was monitored by TLC (50% ethyl acetate in hexane); after ca. 40 minutes, 124 had been consumed. The reaction mixture was concentrated and then taken up in ethyl acetate and washed with H2O and with brine, dried over Na2SO4, and concentrated to give the crude hydroxyesters (a 2:1 mixture of 138 and 139 by 1H NMR) as a light yellow colored oil (32.6 g). [Note: If
reaction was left for longer than 1 h, a gel-like suspension formed and this impeded the removal of ethanol by rotary evaporation. In these cases, the mixture was diluted with ethyl acetate and washed with brine (×3). The aqueous phases were extracted with ethyl acetate and the combined organic layers dried over Na₂SO₄, and concentrated to give the crude hydroxyesters 138 and 139. The crude product was fractionated by DFC (5-50% ethyl acetate in hexane; gradient elution) to give the cis hydroxyester 138 as a colorless oil (19.89 g, 49%):

IR ν max 3503, 1719 cm⁻¹;

¹H NMR (300 MHz, CDCl₃) δ 4.17 (1H, ddd, J = 3, 3, 5.5 Hz), 3.72 (3H, s), 3.16 (1H, dd, J = 10.5, 13 Hz), 3.10-2.90 (1H, m), 2.99 (1H, ddd, J = 3, 11.5, 14 Hz), 2.85 (1H, ddd, J = 3, 3, 10.5 Hz), 2.57 (1H, dd, J = 3, 13.5 Hz), 2.32 (1H, dddd, J = 1.5, 4, 5, 13.5 Hz), 2.16 (1H, dddd, J = 3, 5.5, 5.5, 14 Hz), 1.89 (1H, dddd, J = 3, 3, 11, 14 Hz);

¹³C NMR (75 MHz, CDCl₃) δ 174.5 (s), 66.0 (d), 52.4 (q), 47.6 (d), 33.5 (t), 25.3 (t), 23.1 (t);

HRMS m/z calcd for C₇H₁₂O₃S 176.0507, found 176.0508 (EI);

and the trans hydroxy ester 139 as a colorless solid (9.85 g, 24%):

IR ν max 3452, 1728 cm⁻¹;

¹H NMR (300 MHz, CDCl₃) δ 3.72 (1H, ddd, J = 4, 11, 11 Hz), 3.70 (3H, s), 3.00 (1H, br s), 2.83 (1H, ddd, J = 2, 3, 12 Hz), 2.71-2.61 (3H, m), 2.62 (1H, ddd, J = 3, 11.5, 11.5 Hz), 2.28 (1H, dddd, J = 3.5, 3.5, 3.5, 13.5 Hz), 1.68 (1H, dddd, J = 5, 11, 11, 13 Hz);

¹³C NMR (75 MHz, CDCl₃) δ 174.0 (s), 70.3 (d), 52.3 (q), 52.0 (d), 35.3 (t), 29.8 (t), 27.7 (t);

HRMS m/z calcd for C₇H₁₂O₃S 176.0507, found 176.0508 (EI).
Methyl (3S*, 4R*)-tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-carboxylate (140).

\[
\text{MOMCl (3.2 mL, 3.4 g, 42 mmol) was added dropwise over 2 min to a stirred solution of the 138 (3.76 g, 21.3 mmol) and } i-\text{-Pr}_2\text{EtN (7.4 mL, 5.5 g, 43 mmol) in CH}_2\text{Cl}_2 (20 mL) \text{ at } 0°\text{C. The reaction was allowed to stand at rt with periodic monitoring by TLC (50% ethyl acetate in hexane). After 3 days (reaction complete by TLC) the mixture was diluted with CH}_2\text{Cl}_2 (200 mL), washed with 1 M HCl (2 × 150 mL) and H}_2\text{O (150 mL), dried over Na}_2\text{SO}_4, \text{and concentrated to give the titled MOM ether (4.75 g, quantitative) which was homogeneous by } ^1\text{H NMR and TLC and was used in the next step without further purification:}
\]

\[
\text{IR } \nu_{\text{max}} 1738 \text{ cm}^{-1};
\]

\[
^1\text{H NMR} (300 \text{ MHz, CDCl}_3) \delta 4.65 (1\text{H, d}, J = 7 \text{ Hz}), 4.60 (1\text{H, d}, J = 7 \text{ Hz}), 4.37-4.33 (1\text{H, m}), 3.71 (3\text{H, s}), 3.33 (3\text{H, s}), 3.17 (1\text{H, dd}, J = 12, 13.5 \text{ Hz}), 3.03-2.92 (1\text{H, m}), 2.77 (1\text{H, ddd}, J = 3, 3.5, 12 \text{ Hz}), 2.61 (1\text{H, ddd}, J = 2, 3, 13.5 \text{ Hz}), 2.38-2.25 (2\text{H, m}), 1.87-1.75 (1\text{H, m});
\]

\[
^{13}\text{C NMR} (75 \text{ MHz, CDCl}_3) \delta 172.7, 95.9, 72.2, 55.8, 51.9, 48.1, 31.9, 23.7, 22.2;
\]

\[
\text{HRMS } m/z \text{ calcd for C}_9\text{H}_{16}\text{O}_4\text{S 220.0769, found 220.0768 (EI).}
\]

Methyl (3R*, 4R*)-tetrahydro-4-(methoxymethoxy)thiopyran-3-carboxylate (141).

Following the same procedure as described for the synthesis of 140, 139 (5.32 g, 30.2 mmol) was converted into the titled MOM ether (7.0 g, quantitative) which was homogeneous by $^1$H NMR and TLC and was used in the next step without further purification.
\textbf{IR} \ \nu_{\text{max}} \ 1736 \ \text{cm}^{-1};

\textbf{\textit{\textsuperscript{1}H NMR}} (300 MHz, CDCl\textsubscript{3}) \ \delta \ 4.69 \ (1\text{H}, \text{d}, \ J = 7 \ \text{Hz}), \ 4.63 \ (1\text{H}, \text{d}, \ J = 7 \ \text{Hz}), \ 3.80 \ (1\text{H}, \text{ddd}, \ J = 4, \ 9, \ 10 \ \text{Hz}), \ 3.73 \ (3\text{H}, \text{s}), \ 3.34 \ (3\text{H}, \text{s}), \ 2.88-2.58 \ (5\text{H}, \text{m}), \ 2.42-2.32 \ (1\text{H}, \text{m}), \ 1.76 \ (1\text{H}, \text{dddd}, \ J = 4, \ 10, \ 10, \ 14 \ \text{Hz});

\textbf{\textit{\textsuperscript{13}C NMR}} (75 MHz, CDCl\textsubscript{3}) \ \delta \ 173.4, \ 95.7, \ 75.7, \ 55.7, \ 52.0, \ 50.2, \ 32.8, \ 29.7, \ 26.9;

\textbf{HRMS} m/z \ \text{calcd for} \ C_{9}H_{16}O_{4}S \ 220.0769, \ \text{found} \ 220.0771 \ (\text{EI}).

\((3'R^*, 4'R^*)\)-[Tetrahydro-4-(methoxymethoxy)-2\textit{H}-thiopyran-3-yl]methanol (142).

\[
\begin{array}{c}
\text{MOMO} \\
\text{5} \\
\text{4} \\
\text{CH_2OH} \\
\text{6} \\
\text{S} \\
\text{2}
\end{array}
\]

Following General procedure A, a solution of cis ester 138 (2.423 g, 11.0 mmol) in THF\textsuperscript{*} was reduced with LiAlH\textsubscript{4} in ether (50 mL) to give the alcohol 142 as a clear oil (1.899 g, 90\%) which was homogeneous by \textit{\textsuperscript{1}H NMR} and TLC and was used in the next step without further purification.

\textbf{IR} \ \nu_{\text{max}} \ 3426 \ \text{cm}^{-1};

\textbf{\textit{\textsuperscript{1}H NMR}} (300 MHz, CDCl\textsubscript{3}) \ \delta \ 4.67 \ (1\text{H}, \text{d}, \ J = 6.5 \ \text{Hz}), \ 4.60 \ (1\text{H}, \text{d}, \ J = 6.5 \ \text{Hz}), \ 3.95 \ (1\text{H}, \text{br t}, \ J = 2.5, \ 2.5 \ \text{Hz}), \ 3.63 \ (1\text{H}, \text{dd}, \ J = 7.5, \ 11 \ \text{Hz}), \ 3.61 \ (1\text{H}, \text{dd}, \ J = 7.5, \ 11 \ \text{Hz}), \ 3.38 \ (3\text{H}, \text{s}), \ 2.96-2.71 \ (2\text{H}, \text{m}), \ 2.40-2.25 \ (3\text{H}, \text{m}), \ 2.18 \ (1\text{H}, \text{dddd}, \ J = 2, \ 4, \ 4, \ 13 \ \text{Hz}), \ 2.03 \ (1\text{H}, \text{m}), \ 1.77 \ (1\text{H}, \text{dddd}, \ J = 2.5, \ 4, \ 11.5, \ 14 \ \text{Hz});

\textbf{\textit{\textsuperscript{13}C NMR}} (75 MHz, CDCl\textsubscript{3}) \ \delta \ 95.8, \ 73.2, \ 64.2, \ 56.1, \ 43.8, \ 31.3, \ 25.9, \ 23.6;

\textbf{HRMS} m/z \ \text{calcd for} \ C_{8}H_{16}O_{3}S \ 192.0820, \ \text{found} \ 192.0820 \ (\text{EI}).

\((3'R^*, 4'S^*)\)-[Tetrahydro-4-(methoxymethoxy)-2\textit{H}-thiopyran-3-yl]methanol (143).

\[
\begin{array}{c}
\text{MOMO} \\
\text{5} \\
\text{4} \\
\text{CH_2OH} \\
\text{6} \\
\text{S} \\
\text{2}
\end{array}
\]

\* THF, and not ether, was used due to improved solubility of ester.
Following General procedure A, a solution of 139 (1.016 g, 4.62 mmol) in THF was reduced with LiAlH₄ in ether (20 mL) to give the alcohol 143 as a clear oil (832 mg, 94%) which was homogeneous by ¹H NMR and TLC and was used in the next step without further purification.

IR νₘₐₓ 3451 cm⁻¹;

¹H NMR (300 MHz, CDCl₃) δ 4.73 (1H, d, J = 7 Hz), 4.60 (1H, d, J = 7 Hz), 3.82 (1H, dd, J = 4.5, 11 Hz), 3.66 (1H, dd, J = 4.5, 11 Hz), 3.44 (1H, ddd, J = 3.5, 10, 10 Hz), 3.40 (3H, s), 2.75-2.53 (4H, m), 2.45 (1H, br s), 2.31 (1H, dddd, J = 3.5, 4, 4, 13 Hz), 1.96-1.87 (1H, m), 1.79-1.66 (1H, m);

¹³C NMR (75 MHz, CDCl₃) δ 95.5 (t), 77.8 (d), 64.7 (t), 56.0 (q), 46.3 (d), 33.4 (t), 30.1 (t), 27.4 (t);

HRMS m/z calcd for C₉H₁₆O₃S 192.0820, found 192.0820 (EI).

(3S,5S)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (165a)

First prepared by Dr. C. Guo from aldol reaction of 126a with 125a and from aldol reaction of 127a (anti,syn) with 125a.³⁰

From Isomerization of 165d (C₅ anti): See experimental procedure of compound 165b.

IR (DRIFT) νₘₐₓ 3512, 2919, 1706, 1426, 1259, 1110, 1050, 1040 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.88 (1H, ddd, J = 2, 2, 9.5 Hz, HC-1'), 4.62 (1H, ddd, J = 2, 2, 9 Hz, HC-1''), 4.15-3.93 (8H, m, H₂CO ×4), 3.29 (1H, d, J = 2 Hz, HO-C-1'), 3.25-3.18 (2H, m, HC-5, HC-6; J_HC-5-HC-6 = 4 Hz, J_HC-5-HC-6 = 9.5 Hz, J_HC-1''-HC-5 = 9 Hz),
3.02-2.87 (4H, m, HC-2, HC-6, HC-7', HC-7''), 2.87 (1H, d, J = 2 Hz, HO-C-1'), 2.86
(1H, ddd, 4, 5.5, 9.5 Hz; J_{HC-2,HC-3} = 4 Hz, J_{HC-2,HC-3} = 5.5 Hz, J_{HC-1',HC-5} = 9.5 Hz)
2.86-2.70 (4H, m, HC-2, HC-7'', HC-9', HC-9''), 2.65 (1H, ddd, J = 2.5, 3, 14 Hz, HC-
7'), 2.57-2.50 (2H, m, HC-9', HC-9''), 2.20-2.12 (3H, m, HC-6'', HC-10', HC-10''), 1.98
(1H, ddd, J = 1.5, 3, 11.5 Hz, HC-6'), 1.78-1.70 (2H, m, HC-10', HC-10'').

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 211.72 (s, C-4), 110.24 (s, C-5''), 110.07 (s, C-5'),
68.26 (d, C-1'), 67.42 (d, C-1''), 65.04 (t, CH$_2$O), 64.79 (t, CH$_2$O), 64.53 (t, CH$_2$O),
64.30 (t, CH$_2$O), 55.47 (d, C-3), 54.56 (d, C-5), 47.21 (d, C-6'), 45.64 (t, C-6''), 36.43 (t,
C-10' or C-10''), 36.01 (t, C-10'' or C-10'), 34.29 (t, C-6), 34.11 (t, C-2), 26.72 (t, C-9' or
C-9''), 26.62 (t, C-9'' or C-9'), 26.21 (t, C-7'), 26.16 (t, C-7').

LRMS (FAB), m/z (relative intensity): 493 ([M+1]$^+$, 17), 492 ([M]$^+$, 7), 475 (6), 413
(12), 338 (41), 282 (16), 189 (40), 99 (100).

HRMS m/z calcd for C$_{21}$H$_{32}$O$_7$S$_3$ 492.1310, found 492.1313 (EI).

(3R,5S)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-
(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-
one (165b)

Obtained by Dr. C. Guo from aldol reaction of 125a and 126a.\(^{30}\)

From isomerization of 165d (C$_s$ anti) in acetone: Aldol 165d (46 mg, 0.093
mmol) was added to a solution of imidazole (680 mg, 10.0 mmol) in acetone (10 mL).
The reaction was stirred for 8 days at rt. The reaction was diluted with citric acid (60
mL, 0.1 M) and extracted with CH$_2$Cl$_2$ (x3). The organic extracts were combined, dried
over Na$_2$SO$_4$ and concentrated and gave a 6.2 : 3.0: 1 mixture of 165a, 165b and 165d,
respectively. Fractionation with PTLC (multiple elutions with 2% MeOH in CH₂Cl₂) gave 165b (30 mg, 65%), titled compound 165b (12 mg, 26%) and 165d (4 mg, 8%).

From isomerization of 165d (C₃ anti) in CH₂Cl₂: Aldol 165d (73 mg, 0.159 mmol) was added to a solution of imidazole (408 mg, 6.0 mmol) in CH₂Cl₂ (3.0 mL). The reaction was stirred for 14 days. Workup same as above procedure gave a 6.0:2.1:1 mixture of 165a, 165b and 165d, respectively. Fractionation with PTLC (3.5% MeOH in CH₂Cl₂) gave 165a (38 mg, 52%), titled compound 165b (14 mg, 19%) and 165d (7 mg, 10%).

IR (DRIFT) νmax 3511, 2916, 1702, 1427, 1153, 1102, 1038, 734 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.57 (2H, ddd, J = 2.5, 4.5, 6.5 Hz, HC-1', HC-1''), 4.09-3.96 (8H, m, H₂CO ×4), 3.25 (2H, br d, J = 13.5 Hz, HC-2, HC-6), 3.09 (2H, ddd, J = 4.5, 6.5, 11.5 Hz, HC-3, HC-5 [JHC-2-HC-3 = 4.5, 11.5 Hz]), 3.06 (2H, d, J = 2.5 Hz, HO x2), 2.98 (2H, dd, J = 9.5, 14 Hz, HC-7', HC-7''), 2.91 (2H, dd, J = 11.5, 13.5 Hz, HC-2, HC-6), 2.78-2.71 (4H, m, HC-7', HC-7'', HC-9', HC-9''), 2.64 (2H, m, HC-9', HC-9''), 2.11 (2H, ddd, J = 3.5, 4.5, 9.5 Hz, HC-6', HC-6''), 2.09 (2H, ddd, J = 3, 6.5, 14 Hz, HC-10', HC-10''), 1.77 (2H, ddd, J = 3.5, 10, 14 Hz, HC-10', HC-10'').

¹³C NMR (125 MHz, CDCl₃) δ 213.92 (s, C-4), 109.89 (s ×2, C-5', C-5''), 66.87 (d ×2, C-1', C-1''), 64.61 (t ×2, CH₂O), 64.54 (t ×2, CH₂O), 57.82 (d ×2, C-3, C-5), 46.60 (d ×2, C-6', C-6''), 35.46 (t ×2, C-10', C-10''), 34.26 (t ×2, C-7', C-7''), 27.54 (t ×2, C-7', C-7''), 26.79 (t ×2, C-9', C-9'').

LRMS (EI), m/z (relative intensity): 492 ([M]⁺, 1), 188 (14), 159 (11), 132 (73), 100 (10), 99 (100), 86 (24), 55 (8).

HRMS m/z calcd for C₂₁H₃₂O₇S₃ 492.1310, found 492.1311 (EI).

---

¹65d (11 mg, 0.022 mmol) was added to a solution of imidazole (34 mg, 0.5 mmol) in CD₃COCD₃ (0.5 mL) the ratio of aldol products were monitored until an equilibrium ratio was reached after 13 days which gave 165a : 165b : 165d : of 7.9 : 3.8 : 1.

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(3S,5S)-rel-3,5-bis[(S)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (165c)

First prepared by Dr. P. K. Sasmal from aldol reaction of 125a with 126a.\textsuperscript{30}

From isomerization of 165e (C\textsubscript{2} anti): See experimental procedure of compound 165f.

IR (DRIFT) \(\nu_{\text{max}}\) 3514, 2921, 1701, 1426, 1153, 1131, 1114, 1052 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.79 (2H, d, \(J = 9.5\) Hz, HC-1', HC-1''), 3.92-4.14 (8H, m, H\(_2\)CO \(\times 4\)), 3.22-3.14 (2H, m, HC-3, HC-5), 3.05 (2H, br s, HO \(\times 2\)), 3.01-2.88 (6H, m), 2.77 (2H, ddd, \(J = 2.5, 13, 13\) Hz), 2.69 (2H, ddd, \(J = 2.5, 3, 14\) Hz), 2.49 (2H, br d, \(J = 13.5\) Hz), 2.13 (2H, ddd, \(J = 3, 4, 14\) Hz, H-10', H-10''), 1.75-1.84 (4H, m, H-6', H-6'', H-10', H-10'').

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 211.4 (s), 110.4 (s \(\times 2\)), 66.2 (d \(\times 2\)), 65.0 (t \(\times 2\)), 64.4 (t \(\times 2\)), 55.4 (d \(\times 2\)), 47.1 (d \(\times 2\)), 36.1 (t \(\times 2\)), 34.4 (t \(\times 2\)), 26.7 (t \(\times 2\)), 25.7 (t \(\times 2\)).

LRMS (FAB), \(m/z\) (relative intensity): 493 ([M+1]\(^+\), 24), 492 ([M]\(^+\), 9), 475 (7), 338 (52), 225 (26), 189 (49), 132 (12), 99 (100).

HRMS \(m/z\) calcd for C\(_{21}\)H\(_{32}\)O\(_7\)S\(_3\) 492.1310, found 492.1307 (EI).

(3S,5R)-rel-3-[(R)-(6S)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (165d)

First prepared by C. C. Man from aldol reaction of 125a with 127a.\textsuperscript{30} NMR assignment and analysis this work.
IR (DRIFT) \( \nu_{\text{max}} \) 3518, 2918, 2888, 1698, 1426, 1261, 1101 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.32 (2H, ddd, \( J = 5, 6, 6.5 \) Hz, HC-1\', HC-1\"), \( J_{\text{HC-1':HC-3}} = 6 \) Hz), 4.10-3.88 (8H, m, H\(_2\)CO \( \times 4 \)), 3.25 (2H, ddd, \( J = 5, 6, 12 \) Hz, HC-3, HC-5 \( J_{\text{HC-2:HC-3}} = 5, 12 \) Hz), 3.12 (2H, d, \( J = 6.5 \) Hz, HO \( \times 2 \)), 3.04 (2H, dd, \( J = 12, 13 \) Hz, HC-2, HC-6), 3.02 (2H, dd, \( J = 8.5, 14 \) Hz, HC-7\', HC-7\"), 2.91-2.83 (4H, m, HC-2, HC-6, HC-7\', HC-7\"), 2.73-2.66 (4H, m, H\(_2\)C-9\', H\(_2\)C-9\"), 2.07 (2H, ddd, \( J = 3.5, 5, 8.5 \) Hz, HC-6\', HC-6\"), 1.97 (2H, ddd, \( J = 5, 5.5, 14 \) Hz, HC-10', HC-10\"), 1.73 (2H, ddd, \( J = 5.5, 6.5, 14 \) Hz, HC-10', HC-10\").

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 216.65 (s, C-4), 109.25 (s \( \times 2 \), C-5\'), 69.29 (d \( \times 2 \), C-1\'), 64.89 (t \( \times 2 \), CH\(_2\)O), 64.56 (t \( \times 2 \), CH\(_2\)O), 57.65 (d \( \times 2 \), C-3), 47.27 (d \( \times 2 \), C-6\'), 36.33 (t \( \times 2 \), C-2), 35.76 (t \( \times 2 \), C-10\'), 27.93 (t \( \times 2 \), C-7\'), 26.80 (t \( \times 2 \), C-9\').

LRMS (FAB), \( m/z \) (relative intensity): 493 ([M+1]\(^+\), 69), 475 (31), 305 (25), 199 (37), 189 (38), 99 (100), 67 (37).

HRMS \( m/z \) calcd for C\(_{21}\)H\(_{32}\)O\(_7\)S\(_3\) 493.1388 (M+H), found 493.1394 (FAB).


(3R,5R)-rel-3,5-bis[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (165e)

First prepared by Dr. C. Guo from aldol reaction of 125a with 127a.\(^{30}\) Included here for completeness only.

IR (DRIFT) \( \nu_{\text{max}} \) 3511, 2917, 1697, 1426, 1259, 1102, 1048 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 4.65 (2H, br d, \( J = 8 \) Hz, H-1\', HC-1\"), 4.15-3.90 (8H, m, H\(_2\)CO \( \times 4 \)), 3.13 (2H, br s, HO \( \times 2 \)), 3.11-2.48 (14H, m), 2.13 (2H, ddd, \( J = 3, 5, 13.5 \) Hz, HC-6\', HC-6\"), 1.97 (2H, ddd, \( J = 5, 5.5, 14 \) Hz, HC-10', HC-10\"), 1.73 (2H, ddd, \( J = 5.5, 6.5, 14 \) Hz, HC-10', HC-10\").
Hz, HC-10', HC-10'""). 2.03 (2H, ddd, J = 3, 3, 11 Hz, HC-6', HC-6'"), 1.73 (2H, ddd, J = 3.5, 12, 13.5 Hz, HC-10', HC-10'").

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 212.9 (s), 110.0 (s×2), 68.7 (d ×2), 65.0 (t ×2), 64.6 (t ×2), 55.0 (d ×2), 47.2 (d ×2), 36.4 (t ×2), 33.9 (t ×2), 26.8 (t ×2), 26.7 (t ×2).

LRMS (FAB), m/z (relative intensity): 493 ([M+1]$^+$, 17), 492
([M]$^+$, 6), 475 (4), 338 (27), 189 (25), 132 (10), 99 (100), 67 (23).

HRMS m/z calc'd for C$_{21}$H$_{32}$O$_7$S$_3$ 492.1310, found 492.1307 (FAB).

(3R,5S)-rel-3,5-bis[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (165f)

From isomerization of 165e: Bisaldol 165e (13.5 mg, 0.027 mmol) was added to a solution of imidazole (136 mg, 2.00 mmol) in CH$_2$Cl$_2$ (2.0ml). The reaction was stirred for 20 h at rt. The reaction was diluted with citric acid (20 mL, 0.1M) and extracted with CH$_2$Cl$_2$ (×4). The organic extracts were combined, dried over Na$_2$SO$_4$ and concentrated and gave a 3.0 : 6.2 : 1 mixture (12 mg) of 165e, 165f, and 165c, respectively. Fractionation of the mixture by PTLC (2% MeOH in CH$_2$Cl$_2$; multiple elutions) gave 165e (2 mg, 15%), the titled compound 165f (6 mg, 44%) and 165e (4 mg, 30%).

IR (DRIFT) $\nu$max 3518, 2917, 1694, 1427, 1153, 1131, 1101, 1042 cm$^{-1}$.

$^1$H NMR (500 MHz, C$_6$D$_6$) δ 4.69 (1H, ddd, J = 1.5, 3.5, 6 Hz, HC-1"), 4.17 (1H, ddd, J = 3.5, 7.5, 10 Hz, HC-1"), 3.45-3.24 (6H, m, H$_2$CO ×4), 3.24-3.02 (9H, m, H$_2$CO, HC-2, HC-3, HC-5, HC-6, HC-7', H$_2$C-7"), 3.13 (1H, d, J = 1.5 Hz, HOC-1"), 2.85 (1H, dd, J = 11.5, 13 Hz, HC-2 or HC-6), 2.77 (1H, d, J = 10 Hz, HOC-1"), 2.72 (1H, br d, J =

* Isolated aldols are reported from higher to lower R$_f$ on PTLC plate.
From aldol reaction of 125a and 128a: TiCl₄ (24 μL, 0.22 mmol) was added dropwise to a stirred solution of 128a (60 mg, 0.20 mmol) in CH₂Cl₂ (1.5 mL) at -78 °C under argon. Upon addition of TiCl₄ a yellow globular slurry developed which turned
into a fine yellow suspension after 5 minutes of stirring at -78 °C. The dry ice-acetone bath was replaced with an ice-water bath and the suspension was then stirred for 20 minutes at 0 °C. The yellow suspension was recooled to -78 °C using a dry ice-acetone bath. After 10 minutes, i-Pr2EtN (78 μL, 0.45 mmol) was added dropwise over 10 seconds; upon addition the yellow suspension became a light red solution. After 5 minutes a deep red colour developed; the dry ice-acetone bath was replaced with an ice-water bath and the solution was stirred for 30 minutes at 0 °C resulting in a deeper red solution. The mixture was cooled to -78 °C and a solution of aldehyde 125a (111 mg, 59 mmol) in CH2Cl2 (0.5 mL) was added dropwise over 10 seconds. The reaction mixture was stirred for 20 minutes at 0 °C (during this period the deep red solution turned light red) and then a mixture of MeOH:H2O (2:1, 2 mL) was added with vigorous stirring. After 10 seconds, NH4Cl (5 mL, 1 M) was added and over 2 minutes the mixture turned from light red to colourless. The mixture was diluted with distilled H2O and extracted with ethyl acetate (×3). The combined organic extracts were dried over Na2SO4 and concentrated to give a light yellow oil (180 mg). The oil was fractionated by MPC (40-80% ethyl acetate in hexane; gradient elution) to give recovered aldehyde 125a (97 mg, 87%) and 128a (34 mg, 57%) and titled compound 170a (7.4 mg, 8%).

From hydrolysis of 173c: Following General procedure K for MOM hydrolysis, aldol 173c (30.2 mg, 0.056 mmol) gave a mixture which was fractionated by PTLC (80% ethyl acetate in hexane) to give recovered 173c (14.3 mg, 47%) and titled compound 170a (15.1 mg, 54%).

IR (DRIFT) νmax 3508, 2914, 1697, 1426, 1106, 1044, 891, 731 cm⁻¹.

1H NMR (500 MHz, CDCl3) δ 4.39 (1H, ddd, J = 2.5, 5, 6.5 Hz, HC-1"), 4.21 (1H, ddd, J = 5, 6.5, 6.5 Hz, HC-1"), 4.13-3.90 (8H, m, H2CO ×4), 3.87 (1H, d, J = 2.5 Hz, HOC-1"), 3.23 (1H, ddd, J = 4, 5, 12 Hz, HC-5), 3.14 (1H, dd, J = 12, 12 Hz, HC-6), 3.11-3.06 (3H, m, HOC-1", HC-2, HC-3), 3.04 (1H, d, J = 13.5 Hz, HC-2), 2.99 (1H, dd, J = 8.5, 14 Hz, HC-7"), 2.91 (1H, dd, J = 3, 14 Hz, HC-7"), 2.88 (1H, ddd, J = 2, 4, 12 Hz, HC-6), 2.81 (1H, dd, J = 3, 13.5 Hz, HC-7"), 2.75-2.68 (5H, m, HC-7", HC-9", HC-9", HC-9", HC-9", HC-9", HC-9", HC-9", HC-9", HC-9").
HC-9", HC-9"), 2.20 (1H, ddd, $J = 5.5$, 5.5, 14 Hz, HC-10'), 2.20-2.14 (2H, m, HC-6', HC-6"'), 1.96 (1H, ddd, $J = 5$, 5, 13.5 Hz, HC-10''), 1.79 (1H, ddd, $J = 6.5$, 6.5, 14 Hz, HC-10''), 1.72 (1H, ddd, $J = 6.5$, 6.5, 13.5 Hz, HC-10''), δ in C$_6$D$_6$ (, ), 4.47 (1H, ddd, $J = 2.5$, 6, 6.5 Hz, HC-1''), 4.35 (1H, ddd, $J = 5$, 5.5, 7.5 Hz, HC-1''), 3.85 (1H, d, $J = 2.5$ Hz, HOC-1''), 3.43-3.16 (9H, m, HC-2, H$_2$C-2', H$_2$C-2", H$_2$C-3', H$_2$C-3''), 3.22 (1H, ddd, $J = 4.5$, 5, 12 Hz, HC-5), 3.18 (1H, ddd, $J = 5$, 6.5, 11.5 Hz, HC-3), 3.15 (1H, dd, $J = 9$, 14 Hz, HC-7''), 3.05 (1H, d, $J = 7.5$ Hz, HOC-1''), 2.96 (1H, dd, $J = 12$, 13 Hz, HC-6), 2.95 (1H, dd, $J = 11.5$, 13 Hz, HC-2), 2.92 (1H, br d, $J = 14$ Hz, HC-7''), 2.71 (1H, dd, $J = 3$, 13.5 Hz, HC-7'), 2.64 (1H, dd, $J = 8$, 13.5 Hz, HC-7'), 2.54 (1H, ddd, $J = 3$, 4.5, 13.5 Hz, HC-6), 2.52-2.32 (4H, m, H$_2$C-9', H$_2$C-9''), 2.18 (1H, ddd, $J = 4$, 5.5, 9 Hz, HC-6''), 2.22-2.15 (1H, m, HC-6'), 1.80 (1H, ddd, $J = 5$, 6, 13.5 Hz, HC-10'), 1.59 (1H, ddd, $J = 3.5$, 6.5, 13.5 Hz, HC-10''), 1.51 (1H, ddd, $J = 4$, 9, 13.5 Hz, HC-10''), 1.48 (1H, ddd, $J = 5$, 7.5, 13.5 Hz, HC-10').

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 213.68 (s, C-4), 110.73 (s, C-5'), 109.34 (s, C-5''), 70.08 (d, C-1''), 69.94 (d, C-1'), 64.92 (t, CH$_2$O), 64.74 (t, CH$_2$O), 64.45 (t, CH$_2$O), 64.04 (t, CH$_2$O), 57.69 (d, C-3), 57.62 (d, C-5), 47.57 (d, C-6''), 46.22 (d, C-6'), 35.93 (t, C-6), 35.71 (t, C-10''), 35.13 (t, C-10'), 33.52 (t, C-2), 30.28 (t, C-7''), 28.37 (t, C-7''), 26.81 (t, C-9' or C-9''), 26.74 (t, C-9'' or C-9''), δ in C$_6$D$_6$, 213.82 (s, C-4), 111.03 (s, C-5'), 109.93 (s, C-5''), 70.93 (d, C-1'), 70.32 (d, C-1''), 64.91 (t, CH$_2$O), 64.59 (t, CH$_2$O), 64.43 (t, CH$_2$O), 63.96 (t, CH$_2$O), 59.38 (d, C-3), 58.45 (d, C-5), 48.27 (d, C-6''), 47.44 (d, C-6''), 36.51 (t, C-6), 36.31 (t, C-10''), 35.89 (t, C-10'), 35.16 (t, C-2), 31.04 (t, C-7''), 28.83 (t, C-7''), 26.88 (t, C-9'' or C-9').

LRMS (EI), m/z (relative intensity): 492 ([M]$^+$, 1), 304 (6), 188 (10), 132 (83), 100 (10), 99 (100), 86 (21), 55 (17).

HRMS m/z calcd for C$_{21}$H$_{32}$O$_7$S$_3$ 492.1310, found 492.1321 (EI).
(3S,5S)-rel-3-[R)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[((S)-
(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-
one (170b)

From isomerization of 170a: Aldol 170a (13 mg, 0.0266 mmol) was added to a
solution of imidazole (54 mg, 0.80 mmol) in CH$_2$Cl$_2$ (2.0 ml). The reaction was stirred
for 6 days at rt. The reaction was diluted with citric acid (30 mL, 0.1 M) and extracted
with CH$_2$Cl$_2$ (×3). The organic extracts were combined, dried over Na$_2$SO$_4$ and
concentrated to give a 2.1 : 3.6 : 3.2 : 1 equilibrium mixture of 170a, 170b, 171c and
171d (15 mg). The mixture was fractionated by PTLC (80% ethyl acetate in hexane) to
give 170b (5 mg, 39%), 170a (3.0 mg, 23%) and a mixture of 171c and 171d (5.5 mg).
The mixture was further fractionated by PTLC (2% MeOH in CH$_2$Cl$_2$; multiple
elutions) and gave 171c (3.5 mg, 26%) and 171d (1 mg, 7%).

From hydrolysis of 173a: Following General procedure K for MOM hydrolysis,
alcohol 173a (11.7 mg, 0.022 mmol) gave a mixture which was fractionated by PTLC
(70% ethyl acetate in hexane) to give recovered 173a (3.7 mg, 32%) and titled
compound 170b (5.8 mg, 54%).

IR (DRIFT) $\nu_{\text{max}}$ 3496, 2916, 1704, 1427, 1260, 1102, 1051, 948 cm$^{-1}$.

$^{1}$H NMR (500 MHz, CDCl$_3$) δ 4.68 (1H, ddd, $J = 1.5, 2.5, 9$ Hz, HC-1$''$), 4.36 (1H, ddd,
$J = 3.5, 4, 8$ Hz, HC-1$'$), 4.13-3.93 (9H, m, HOC-1$''$, H$_2$CO ×4), 3.39 (1H, dd, $J = 10,$
13.5 Hz, HC-2), 3.33 (1H, dd, $J = 5.5, 12.5$ Hz, HC-6), 3.23 (1H, ddd, $J = 5.5, 8.5, 9$
Hz, HC-5), 3.14 (1H, d, $J = 1.5$ Hz, HOC-1$''$), 3.00 (1H, dd, $J = 3,$ 14 Hz, HC-7$'$), 2.96
(1H, ddd, $J = 4, 4.5, 10$ Hz, HC-3), 2.95 (1H, dd, $J = 11, 13.5$ Hz, HC-7$''$), 2.88 (1H, dd,
$J = 8.5, 12.5$ Hz, HC-6), 2.85-2.75 (5H, m, HC-2, HC-7$'$, HC-7$''$, HC-9$'$, HC-9$''$), 2.66
(1H, m, HC-9$''$), 2.51 (1H, br d, $J = 12.5$ Hz, HC-9$''$), 2.21-2.10 (3H, m, HC-6$'$, HC-10$'$,
HC-10$''$), 2.01 (1H, ddd, $J = 2.5, 3.5, 11$ Hz, HC-6$''$), 1.81 (1H, ddd, $J = 3, 6.5, 13.5$ Hz,
HC-10$'$), 1.71 (1H, ddd, $J = 3.5, 12, 13.5$ Hz, HC-10$''$).
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 212.86 (s, C-4), 110.55 (s, C-5'), 110.28 (s, C-5''), 72.76 (d, C-1'), 67.35 (d, C-1''), 64.91 (t, CH$_2$O), 64.89 (t, CH$_2$O), 64.42 (t, CH$_2$O), 64.26 (t, CH$_2$O), 55.00 (d, C-3), 52.78 (d, C-5), 46.71 (d, C-6'), 45.90 (d, C-6''), 36.28 (t, C-10'), 31.93 (t, C-2), 30.70 (t, C-6), 30.07 (t, C-7), 27.00 (t, C-9'), 26.70 (t, C-9''), 26.24 (t, C-7'').

LRMS (EI), $m/z$ (relative intensity): 492 ([M]$^+$, 0.2), 188 (12), 159 (8), 132 (41), 115 (8), 99 (100), 86 (24), 55 (10).

HRMS $m/z$ calcd for C$_{21}$H$_{32}$O$_7$S$_3$ 492.1310, found 492.1316 (EI).

(3R,5R)-rel-3-[{(R)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (170c)

From isomerization of 171a: Aldol 171a (72 mg, 0.15 mmol) was added to a solution of imidazole (218 mg, 3.20 mmol) in CH$_2$Cl$_2$ (4.0ml). The reaction was stirred for 15 days at rt. The reaction was diluted with citric acid (25 mL, 0.1M) and extracted with CH$_2$Cl$_2$ ($\times$3). The organic extracts were combined, dried over Na$_2$SO$_4$ and concentrated and gave a 1.5 : 3.0 : 1 : 2.5 equilibrium mixture of 170c, 170d, 171a and 171b (65 mg). The mixture was fractionated by MPC (40-60% ethyl acetate in hexane; gradient elution) to give the titled compound 170c (10 mg, 14%) along with 170d (23 mg, 32%), recovered 171a (4 mg, 5%) and 171b (24 mg, 34%).

From hydrolysis of 173b: Following general procedure K for MOM hydrolysis, aldol 173b (9.5 mg, 0.018 mmol) gave a mixture which was fractionated by PTLC (80% ethyl acetate in hexane) to give recovered 173b (4 mg, 41%) and titled compound 170c (3 mg, 34%).

IR (DRIFT) $\nu_{max}$ 3501, 2915, 1705, 1427, 1260, 1106, 1036, 733 cm$^{-1}$. 

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\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.69 (1H, ddd, \(J = 2.5, 3.5, 8\) Hz, HC-1"), 4.56 (1H, br dd, \(J = 4.5, 7.5\) Hz, HC-1'), 4.13-3.94 (8H, m, H\(_2\)CO), 3.88 (1H, br s, HOC-1'), 3.25 (1H, dd, \(J = 11.5, 13.5\) Hz, HC-2), 3.11 (1H, d, \(J = 3.5\) Hz, HOC-1"), 3.10 (1H, dd, \(J = 5, 13\) Hz, HC-6), 3.03 (1H, ddd, \(J = 5, 6, 8\) Hz, HC-5), 3.02 (1H, dd, \(J = 11.5, 14\) Hz, HC-7"), 3.01 (1H, ddd, \(J = 4.5, 4.5, 11.5\) Hz, HC-3), 2.85-2.64 (8H, m, HC-2, HC-6, H\(_2\)C-7', HC-7", H\(_2\)C-9', HC-9''), 2.56 (1H, br d, \(J = 13\) Hz, HC-9"'), 2.19 (1H, ddd, \(J = 3.5, 7.5, 13\) Hz, HC-10'), 2.16 (1H, ddd, \(J = 3, 4.5, 13.5\) Hz, HC-10"'), 2.04 (1H, ddd, \(J = 2, 7.5, 8.5\) Hz, HC-6'), 2.03 (1H, ddd, \(J = 3.5, 3.5, 11.5\) Hz, HC-6"'), 1.80 (1H, ddd, \(J = 3.5, 8.5, 13\) Hz, HC-10'), 1.75 (1H, ddd, \(J = 3.5, 11.5, 13.5\) Hz, HC-10'').

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 211.81 (s, C-4), 110.68 (s, C-5'), 110.04 (s, C-5"), 70.39 (d, C-1'), 68.73 (d, C-1''), 65.03 (t, CH\(_2\)O), 64.86 (t, CH\(_2\)O), 64.60 (t, CH\(_2\)O), 64.20 (t, CH\(_2\)O), 54.82 (d, C-3), 53.55 (d, C-5), 47.41 (d, C-6' or C-6"'), 47.29 (d, C-6" or C-6''), 36.42 (t, C-10'), 35.35 (t, C-10''), 31.10 (t, C-6), 29.79 (t, C-7), 28.80 (t, C-2), 26.80 (t, C-9' or C-9''), 26.78 (t, C-9' or C-9"'), 26.58 (t, C-9" or C-9'').

LRMS (FAB), \(m/z\) (relative intensity): 493 ([M+1]\(^+\), 39), 225 (20), 199 (18), 189 (33), 161 (17), 133 (18), 132 (24), 99 (100).

HRMS \(m/z\) calcd for C\(_{21}\)H\(_{32}\)O\(_7\)S\(_3\) 493.1388 (M+H), found 493.1392 (FAB).

(3R,5S)-rel-3-[(R)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (170d)

From isomerization of 171a: See experimental procedure for compound 170c.

IR (DRIFT) \(\nu_{\max}\) 3508, 2916, 1704, 1427, 1263, 1108, 1039, 736 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.54 (1H, br dd, \(J = 4, 7\) Hz, HC-1"), 4.13 (1H, ddd, \(J = 5, 5.5, 6\) Hz, HC-1''), 4.10-3.93 (8H, m, H\(_2\)CO \(\times 4\)), 3.58 (1H, d, \(J = 5\) Hz, HOC-1''), 3.24 (1H, ddd, \(J = 3.5, 4.5, 13\) Hz, HC-6), 3.18 (1H, br s, HOC-1''), 3.16 (1H, ddd, \(J = 3.5, 4.5, 8\) Hz, HOC-1''), 3.06 (1H, dd, \(J = 3.5, 8\) Hz, HOC-1"'), 3.02 (1H, br s, HOC-1"'), 2.96 (1H, br s, HOC-1''), 2.85-2.64 (8H, m, HC-2, HC-6, H\(_2\)C-7', HC-7", H\(_2\)C-9', HC-9''), 2.56 (1H, br d, \(J = 13\) Hz, HC-9"'), 2.19 (1H, ddd, \(J = 3.5, 7.5, 13\) Hz, HC-10'), 2.16 (1H, ddd, \(J = 3, 4.5, 13.5\) Hz, HC-10''), 2.04 (1H, ddd, \(J = 2, 7.5, 8.5\) Hz, HC-6'), 2.03 (1H, ddd, \(J = 3.5, 3.5, 11.5\) Hz, HC-6"'), 1.80 (1H, ddd, \(J = 3.5, 8.5, 13\) Hz, HC-10'), 1.75 (1H, ddd, \(J = 3.5, 11.5, 13.5\) Hz, HC-10'').
4.5, 13 Hz, HC-2), 3.04 (1H, ddd, J = 4.5, 7, 11.5 Hz, HC-3), 3.04 (1H, ddd, J = 4.5, 6, 11.5 Hz, HC-5), 2.95 (1H, dd, J = 11, 13.5 Hz, HC-7"), 2.92 (1H, dd, J = 10, 13.5 Hz, HC-7), 2.92 (1H, dd, J = 11.5, 13 Hz, HC-6), 2.90 (1H, dd, J = 11.5, 13 Hz, HC-2), 2.80-2.65 (4H, m, HC-7", HC-7", HC-9", HC-9"), 2.63-2.53 (2H, m, HC-9", HC-9"), 2.36 (1H, ddd, J = 3, 5.5, 10 Hz, HC-6"), 2.20-2.07 (2H, m, HC-10", HC-10"), 2.13 (1H, ddd, J = 3.5, 4, 11 Hz, HC-6"), 1.79-1.70 (2H, m, HC-10", HC-10").

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 212.53 (s, C-4), 111.45 (s, C-5'), 110.08 (s, C-5''), 72.44 (d, C-1'), 67.66 (d, C-1''), 64.69 (t, CH$_2$O), 64.42 (t, CH$_2$O), 64.21 (t, CH$_2$O), 63.51 (t, CH$_2$O), 58.78 (d, C-3), 57.58 (d, C-5), 43.43 (d, C-6''), 45.00 (d, C-6'), 35.83 (t, C-10''), 35.32 (t, C-10'), 34.58 (t, C-2), 34.43 (t, C-6), 30.47 (t, C-7'), 27.01 (t, C-7''), 26.74 (t, C-9' or C-9''), 26.59 (t, C-9" or C-9'').

LRMS (EI), m/z (relative intensity): 492 ([M]$^+$, 1), 188 (17), 133 (17), 100 (13), 99 (100), 86 (35), 55 (28).

HRMS m/z calcld for C$_{21}$H$_{32}$O$_7$S$_3$ 492.1310, found 492.1317.

(3S,5R)-rel-3-[(R)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (171a)

From aldol reaction of 129a with 125a: TiCl$_4$ (27 µL, 0.25 mmol) was added dropwise to a stirred solution of 129a aldol (69.4 mg, 0.228 mmol) in CH$_2$Cl$_2$ (2 mL) at −78 °C under argon. Upon addition of TiCl$_4$ a yellow globular slurry developed which turned into a fine yellow suspension after 5 minutes of stirring at −78 °C. The dry ice-acetone bath was replaced with an ice-water bath and the suspension was then stirred for 20 minutes at 0 °C. The yellow suspension was recooled to −78 °C using a dry ice-acetone bath. After 10 minutes, i-Pr$_2$EtN (91 µL, 0.52 mmol) was added dropwise over 10 seconds; upon addition the yellow suspension became a light red solution. After 10 minutes of stirring a deep red colour developed. A solution of aldehyde (86 mg, 46
mmol) in CH$_2$Cl$_2$ (0.3 mL) was added dropwise over 10 seconds. The reaction was stirred for 2 h at −78 °C (during this period the deep red solution turned light red). The dry ice-acetone bath was removed and MeOH:H$_2$O (2:1, 2 mL) was added with vigorous stirring. After 10 seconds, NH$_4$Cl (5 mL, 1M) was added and over 2 minutes the mixture turned from light red to colourless. The mixture was diluted with distilled H$_2$O and extracted with ethyl acetate (×3). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated to give a light yellow oil (160 mg). The oil was fractionated by MPC (40-60% ethyl acetate in hexane; gradient elution) to give recovered aldehyde 125a (60 mg, 70%), 129a (33 mg, 48%), the titled compound 171a (44 mg, 39%) and 171b (3.2 mg, 3%).

IR (DRIFT) $\nu_{\text{max}}$ 3511, 2916, 1697, 1426, 1261, 1102, 1047, 892 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.16 (1H, ddd, $J$ = 4.5, 7, 8 Hz, HC-1"), 4.10 (1H, ddd, $J$ = 3.5, 4.5, 7.5 Hz, HC-1'), 4.10-3.89 (8H, m, H$_2$CO ×4), 3.82 (1H, d, $J$ = 4.5 Hz, HOC-1"), 3.28 (1H, dd, $J$ = 11.5, 13 Hz, HC-2), 3.23 (1H, ddd, $J$ = 4.5, 4.5, 12 Hz, HC-5), 3.15 (1H, dd, $J$ = 12, 13 Hz, HC-6), 3.06 (1H, d, $J$ = 8 Hz, HOC-1"), 3.04 (1H, ddd, $J$ = 3.5, 3.5, 11.5 Hz, HC-3), 2.98-2.95 (2H, m, H$_2$C-7"), 2.94 (1H, ddd, $J$ = 3.5, 3.5, 13 Hz, HC-2), 2.85 (1H, ddd, $J$ = 3.5, 4.5, 13 Hz, HC-6), 2.81 (1H, dd, $J$ = 2.5, 14 Hz, HC-7), 2.75 (1H, ddd, $J$ = 3.5, 9, 12.5 Hz, HC-9"), 2.71-2.63 (3H, m, HC-9', H$_2$C-9"), 2.54 (1H, dd, $J$ = 7, 14 Hz, HC-7'), 2.44 (1H, ddd, $J$ = 2.5, 7, 7.5 Hz, HC-6'), 2.19-2.12 (2H, m, HC-6", HC-10"), 1.92 (1H, m, HC-10"), 1.80 (1H, ddd, $J$ = 3.5, 7.5, 13.5 Hz, HC-10'), 1.72 (1H, m, HC-10").

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 214.16 (s, C-4), 110.32 (s, C-5"), 109.29 (s, C-5"), 72.51 (d, C-1'), 70.35 (d, C-1"), 64.77 (t, CH$_2$O), 64.67 (t, CH$_2$O), 64.28 (t, CH$_2$O), 64.06 (t, CH$_2$O), 57.68 (d, C-5), 56.34 (d, C-3), 47.57 (d, C-6"), 45.91 (d, C-6'), 36.11 (t, C-2), 36.03 (t, C-6), 35.01 (t, C-10"), 34.49 (t, C-10'), 29.81 (t, C-7"), 28.67 (t, C-7'), 26.83 (t, C-9'/C-9"), 26.71 (t, C-9"/C-9').

LRMS (FAB), $m/z$ (relative intensity): 493 ([M+1]$^+$, 23), 161 (27), 99 (100), 83 (26), 71 (27), 69 (25), 57 (38), 55 (63).

HRMS $m/z$ calcd for C$_{21}$H$_{33}$O$_7$S$_3$ 493.1388 (M+H), found 493.1384 (FAB).
(3S,5S)-rel-3-[(R)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (171b)

From aldol reaction of 129a and 125a: See experimental procedure for compound 171a.

From hydrolysis of 175a: Following General procedure K for MOM hydrolysis aldol 175a (16.5 mg, 0.031 mmol) gave a mixture which was fractionated by PTLC (70% ethyl acetate in hexane) to give recovered 175a (6 mg, 38%) and titled compound 171b (6 mg, 40%).

IR (DRIFT) $\nu_{\text{max}}$ 3496, 2916, 1704, 1427, 1260, 1102, 1051, 948 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.68 (1H, ddd, $J = 1.5, 2.5, 9$ Hz, HC-1$''$), 4.36 (1H, ddd, $J = 3.5, 4, 8$ Hz, HC-1$'$), 4.13-3.93 (9H, m, HOC-1$''$, H$_2$CO x4), 3.39 (1H, dd, $J = 10, 13.5$ Hz, HC-2), 3.33 (1H, dd, $J = 5.5, 12.5$ Hz, HC-6), 3.23 (1H, ddd, $J = 5.5, 8.5, 9$ Hz, HC-5), 3.14 (1H, d, $J = 1.5$ Hz, HOC-1$''$), 3.00 (1H, dd, $J = 3, 14$ Hz, HC-7$''$), 2.96 (1H, ddd, $J = 4, 4.5, 10$ Hz, HC-3), 2.95 (1H, ddd, $J = 11, 13.5$ Hz, HC-7$'$), 2.88 (1H, dd, $J = 8.5, 12.5$ Hz, HC-6), 2.85-2.75 (5H, m, HC-2, HC-7$'$, HC-9$'$, HC-9$''$), 2.66 (1H, m, HC-9$''$), 2.51 (1H, br d, $J = 12.5$ Hz, HC-9$'$), 2.21-2.10 (3H, m, HC-6$'$, HC-10$'$, HC-10$''$), 2.01 (1H, ddd, $J = 2.5, 3.5, 11$ Hz, HC-6$''$), 1.81 (1H, ddd, $J = 3, 6.5, 13.5$ Hz, HC-10$'$), 1.71 (1H, ddd, $J = 3.5, 12, 13.5$ Hz, HC-10$''$).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 212.86 (s, C-4), 110.55 (s, C-5$'$), 110.28 (s, C-5$''$), 72.76 (d, C-1$'$), 67.35 (d, C-1$''$), 64.91 (t, CH$_2$O), 64.89 (t, CH$_2$O), 64.42 (t, CH$_2$O), 64.26 (t, CH$_2$O), 55.00 (d, C-3), 52.78 (d, C-5), 46.71 (t, C-6$''$), 45.90 (d, C-6$'$), 36.28 (t, C-10$''$), 34.43 (t, C-10$'$), 31.93 (t, C-2), 30.70 (t, C-6), 30.07 (t, C-7$'$), 27.00 (t, C-9$'$), 26.70 (t, C-9$''$), 26.24 (t, C-7$''$).

LRMS (EI), $m/z$ (relative intensity): 492 ([M]$^+$, 0.2), 188 (12), 159 (8), 132 (41), 115 (8), 99 (100), 86 (24), 55 (10).
HRMS m/z calcd for C_{21}H_{32}O_{7}S_{3} 492.1310, found 492.1316 (EI).

(3R,5R)-rel-3-[(S)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (171c)

From isomerization of 170a : See experimental procedure for compound 170b.

From hydrolysis of 175b : Following General procedure K for MOM hydrolysis aldol 175b (8 mg, 0.015 mmol) gave a mixture which was fractionated by PTLC (70% ethyl acetate in hexane) to give recovered 175b (2 mg, 24%) and titled compound 171c (5 mg, 67%).

IR (DRIFT) \( \nu_{\text{max}} \) 3504, 2916, 1710, 1261, 1108, 1052, 734 cm\(^{-1} \).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.82 (1H, ddd, \( J = 0.5, 1, 9 \) Hz, HC-1\('\)), 4.23 (1H, ddd, \( J = 3.5, 4, 8.5 \) Hz, HC-1\('\)), 4.15-3.93 (8H, m, H\(_2\)CO), 3.90 (1H, d, \( J = 3.5 \) Hz, HOC-1\('\)), 3.39 (1H, dd, \( J = 11, 13.5 \) Hz, HC-2), 3.17 (1H, ddd, \( J = 4, 4.5, 11 \) Hz, HC-3), 3.10 (1H, dd, \( J = 4.5, 13.5 \) Hz, HC-6), 3.04-2.96 (2H, m, HC-7', HC-7\('\)), 3.03 (1H, d, \( J = 1 \) Hz, HOC-1\('\)), 2.95 (1H, ddd, \( J = 4.5, 5, 9 \) Hz, HC-5), 2.87-2.74 (4H, m, HC-2, HC-7', HC-9', HC-9\('\)), 2.72-2.59 (3H, m, HC-6, HC-7\('\), HC-9'), 2.54 (1H, br d, \( J = 13.5 \) Hz, HC-9\('\)), 2.46 (1H, m, HC-6'), 2.21-2.14 (2H, m, HC-10', HC-10\('\)), 2.00 (1H, ddd, \( J = 0.5, 3.5, 11 \) Hz, HC-6'), 1.82 (1H, ddd, \( J = 3, 6, 13.5 \) Hz, HC-10'), 1.74 (1H, ddd, \( J = 3.5, 12.5, 13.5 \) Hz, HC-10\('\)).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 211.26 (s, C-4), 110.46 (s, C-5\('\)), 110.15 (s, C-5\('\)), 72.86 (d, C-1\('\)), 68.69 (d, C-1\('\)), 65.12 (t, CH\(_2\)O), 64.87 (t, CH\(_2\)O), 64.54 (t, CH\(_2\)O), 64.28 (t, CH\(_2\)O), 54.65 (d, C-5), 52.58 (d, C-3), 47.25 (d, C-6\('\)), 45.50 (d, C-6\('\)), 36.43 (t, C-10\('\)), 33.91 (t, C-10\('\)), 33.80 (t, C-2), 32.23 (t, C-6), 29.44 (t, C-7\('\)), 26.99 (t, C-9\('\)), 26.76 (t, C-9\('\)), 26.22 (t, C-7\('\)).

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LRMS (EI), m/z (relative intensity): 492 ([M]⁺, 1), 188 (15), 159 (16), 133 (11), 132 (68), 99 (100), 86 (23), 55 (14).

HRMS m/z calcd for C₂₁H₃₂O₇S₃ 492.1310, found 492.1307.

(3R,5S)-rel-3-[(S)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (171d)

\[ \text{1H NMR (500 MHz, CDCl}_3 \text{)} \delta 4.59 (1H, ddd, J = 2, 5, 5 Hz, HC-1'''), 4.15 (1H, ddd, J = 3.5, 3.5, 7.5 Hz, HC-1'''), 4.10-3.95 (8H, m, H₂CO x4), 3.98 (1H, d, J = 3.5 Hz, HOC-1'''), 3.29 (1H, dd, J = 11.5, 13 Hz, HC-2'), 3.19 (1H, d, J = 2 Hz, HOC-1''), 3.17 (1H, ddd, J = 3.5, 4.5, 12.5 Hz, HC-6), 3.09 (1H, ddd, J = 4.5, 5, 10.5 Hz, HC-5), 3.05-2.91 (3H, m, HC-6, HC-2, HC-7''), 3.00 (1H, ddd, J = 3.5, 5, 11.5 Hz, HC-3), 2.84 (1H, dd, J = 2.5, 13.5 Hz, HC-7'), 2.84-2.61 (5H, m, HC-7'', H₂C-9', H₂C-9''), 2.54 (1H, ddd, J = 7, 13.5 Hz, HC-7'), 2.46 (1H, ddd, J = 2.5, 7, 7.5 Hz, HC-6'), 2.16 (1H, ddd, J = 3.5, 9, 13.5 Hz, HC-10'), 2.10 (1H, ddd, J = 3.5, 5, 9 Hz, HC-6''), 2.07 (1H, ddd, J = 3, 6.5, 13.5 Hz, HC-10''), 1.82 (1H, ddd, J = 3.5, 7.5, 13.5 Hz, HC-10''), 1.77 (1H, ddd, J = 3.5, 10, 13.5 Hz, HC-10'').

13C NMR (125 MHz, CDCl₃) δ 212.97 (s, C-4), 110.40 (s, C-5'), 109.80 (s, C-5''), 73.16 (s, C-1'), 67.58 (d, C-1''), 64.81 (t, CH₂O), 64.64 (t, CH₂O), 64.57 (t, CH₂O), 64.33 (t, CH₂O), 58.08 (d, C-5), 55.34 (d, C-3), 46.57 (d, C-6''), 46.57 (d, C-6''), 35.51 (t, C-10'), 35.35 (t, C-2), 34.51 (t, C-10'), 32.60 (t, C-6), 30.09 (t, C-7'), 27.66 (t, C-7''), 26.93 (t, C-9'), 26.78 (t, C-9'').

LRMS (EI), m/z (relative intensity): 492 ([M]⁺, 1), 304 (5), 286 (6), 188 (9), 156 (6), 132 (53), 99 (100), 86 (23).

HRMS m/z calcd for C₂₁H₃₂O₇S₃ 492.1310, found 492.1321 (EI).
(3R)-rel-3-[(R)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (172)

Following General procedure L for MOM protection, aldol 128a (1.043 g, 3.426 mmol) upon workup gave a light yellow oil which later solidified (1.432 g) when dried under vacuum (0.5 torr). The solid (1.432 g) was suspended in ethyl acetate (10 mL) and refluxed for 8 minutes and a yellow saturated solution was obtained. Product 172 crystallized from solution upon standing at rt for 4 h, the mixture was then stored overnight (12 h) in a refrigerator (5 °C). The fine needle-like crystals were washed with cold hexane (0 °C) and gave pure crystals of 172 (1.190 g, 99%).

IR (DRIFT) νmax 2957, 1707, 1164, 1149, 1097, 1055, 1034, 894 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.88 (1H, dd, J = 3, 3 Hz, HC-1'), 4.69 (1H, d, J = 6.5 Hz, HCO₂), 4.63 (1H, d, J = 6.5 Hz, HCO₂), 3.97 (1H, m, H₂CO), 3.90-3.82 (2H, m, H₂CO), 3.77 (1H, m, H₂CO), 3.36 (3H, s, H₃CO), 3.30 (1H, ddd, J = 3, 5.5, 10.5 Hz, HC-3), 3.02-2.87 (5H, m, H₂C-2, H₂C-6, HC-7'), 2.86 (1H, ddd, J = 2.5, 13, 13 Hz, HC-9'), 2.83 (1H, ddd, J = 3, 3, 13 Hz, HC-7'), 2.77 (1H, ddd, J = 4, 4, 13.5 Hz, HC-5), 2.68 (1H, ddd, J = 5.5, 11.5, 13.5 Hz, HC-5), 2.51 (1H, ddd, J = 3, 3.5, 4, 13.5 Hz, HC-9'), 2.43 (1H, ddd, J = 3, 3, 12 Hz, HC-6'), 2.07 (1H, ddd, J = 2.5, 4, 13.5 Hz, HC-10'), 1.73 (1H, ddd, J = 3.5, 13, 13.5 Hz, HC-10').

¹³C NMR (125 MHz, CDCl₃) δ 208.88 (s, C-4), 108.92 (s, C-5'), 97.52 (t, OCH₂O), 71.77 (d, C-1'), 64.46 (t, CH₂O), 64.23 (t, CH₂O), 56.22 (q, CH₃O), 55.78 (d, C-3), 50.88 (t, C-5'), 44.46 (t, C-5), 37.09 (t, C-10'), 32.12 (t, C-2), 30.29 (t, C-6), 28.07 (t, C-7'), 27.02 (t, C-9').

LRMS (EI), m/z (relative intensity): 348 ([M⁺], 2), 286 (18), 224 (10), 159 (13), 133 (24), 132 (65), 99 (100), 55 (14).

HRMS m/z calcd for C₁₅H₂₄O₃S₂ 348.1065, found 348.1062.
BuLi (2.7 mL, 4.0 mmol) in hexane was added dropwise over 4 minutes to a solution of i-Pr₂NH (0.60 mL, 4.3 mmol) in THF (8 mL) at 0 °C. The solution was then stirred for a further 5 minutes at 0 °C and then cooled to -78 °C. A solution* of ketone 172 (347 mg, 0.995 mmol) and TMSCI (1.26 mL, 9.95 mmol) in THF (2 mL) was added dropwise over 4 minutes to the above LDA solution. The reaction was stirred for 30 minutes at -78 °C. Et₃N (2.80 mL, 20 mmol) was added and the cooling bath was removed. After stirring for 1 minute, saturated NaHCO₃ (10 mL) was added and after 2 minutes, the mixture was diluted with distilled H₂O (40 mL) and extracted with CH₂Cl₂ (3×50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give 172a as an orange oil that solidified under vacuum (0.5 torr) (431 mg, 100%; 98% pure by ¹H NMR).

¹H NMR (500 MHz, CDCl₃) δ 5.05 (1H, br d, J = 6.5 Hz, HC-5), 4.59 (1H, d, J = 6.5 Hz, HCO2), 4.57 (1H, dd, J = 2.5, 5.0 Hz, HC-1'), 4.49 (1H, d, J = 6.5 Hz, HCO2), 3.94-3.81 (4H, m, H₂CO x2), 3.28 (3H, s, H₃CO), 3.23 (1H, ddd, J = 2.5, 2.5, 16 Hz, HC-6), 2.96 (1H, dd, J = 9.5, 13.5 Hz, HC-7"), 2.87-2.70 (5H, m), 2.59 (1H, m, HC-3), 2.49 (1H, br d, J = 13.5 Hz, HC-9"), 2.45 (1H, ddd, J = 4.5, 5.0, 9.5 Hz, HC-6"), 2.02 (1H, ddd, J = 3, 5, 13.5 Hz, HC-10"), 1.65 (1H, ddd, J = 3.5, 11.5, 13.5 Hz, HC-10"), 0.13 (9H, s, (H₃C)₃Si).

¹³C NMR (125 MHz, CDCl₃) δ 152.71 (s), 109.24 (s), 104.14 (d), 97.93 (t), 74.72 (d), 64.37 (t), 64.14 (t), 56.28 (q), 50.71 (d), 43.75 (d), 36.89 (t), 29.49 (t), 27.28 (t), 27.20 (t), 25.25 (t), 0.52 (q x3).

* Gentle heating to facilitate its dissolution. This solution was allowed to cool to rt before addition of TMSCI.
(3S,5S)-rel-3-[(S)-(6S)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl[methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (173a)

From aldol reaction of 125a and 172 (Ti enolate): TiCl$_4$ (15 μL, 0.137 mmol) was added dropwise over 5 seconds to a solution of ketone 172 (43.1 mg, 0.124 mmol) in CH$_2$Cl$_2$ (2 mL) at -78 °C (a chunky-globular yellow precipitate formed). The reaction was stirred for 1 minute and gave a fine yellow suspension. i-Pr$_2$EtN (32 μL, 0.19 mmol) was added dropwise over 5 seconds and the reaction was stirred for 1 hr at -78 °C. Upon addition of i-Pr$_2$EtN the yellow suspension changed to a red solution and any remaining precipitate slowly dissolved during the 1 hr period. A solution of aldehyde 125a (47 mg, 0.25 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added dropwise over 1 minute and the reaction was stirred for 3 h at -78 °C (the solution remained red during the 3 h). MeOH:H$_2$O (2:1, 2 mL) was added with vigorous stirring and the cooling bath was removed. After 10 seconds, NH$_4$Cl (5 mL, 1 M) was added and the over 1 minute the colour changed from red to light yellow. The mixture was diluted with distilled H$_2$O (40 mL) and extracted with CH$_2$Cl$_2$ (3×30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated to give a light yellow oil (110 mg). The oil was fractionated by MPC (40% ethyl acetate in hexane) to give recovered aldehyde 125a (23 mg, 48%), recovered ketone 172 (20 mg, 46%), titled compound 173a (28 mg, 41%) and 173b (9 mg, 13%).

From aldol reaction of 125a and 172 (Li enolate): A solution of MeLi in hexane (1.5M, 0.6 mL, 0.90 mmol) was added dropwise over 30 seconds to a stirred solution of enol silane 172a (370 mg, 0.88 mmol) and a spatula point of 1,10-phenanthroline in THF (3 mL) at 0 °C. The resultant deep red solution was stirred for 5 minutes at 0 °C and was then cooled to -78 °C. A solution of aldehyde 125a (332 mg, 1.76 mmol) in THF (0.5 mL) was added dropwise over 15 seconds and the resultant yellow solution
was stirred for 2 minutes at −78 °C. A solution of acetic acid (85 mg, 1.4 mmol) in THF (1 mL) was added to the vigorously stirred reaction mixture and the cooling bath was removed. After 30 seconds a solution of MeOH (2 mL) and phosphate buffer (1 mL, pH 7, 0.1 M) was added. After 1 minute, the mixture was diluted with additional phosphate buffer (50 mL) and extracted with CH₂Cl₂ (4×40 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated to give a light orange oil (682 mg). The oil was fractionated by FC (40-70% ethyl acetate in hexane; gradient elution) to give recovered aldehyde 125a (206 mg, 62%), ketone 172 (115 mg, 37%), titled compound 173a (59 mg, 12%), 173b (132 mg, 28%) and 173c (38 mg, 8%).

IR (DRIFT) vmax 3504, 2913, 1696, 1427, 1261, 1152, 1032, 894 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.89 (1H, ddd, J = 1.5, 2, 9 Hz, HC-1"), 4.71 (1H, d, J = 6.5 Hz, HCO2), 4.69 (1H, dd, J = 3, 3 Hz, HC-1"'), 4.64 (1H, d, J = 6.5 Hz, HCO2), 4.14-3.95 (6H, m, HCO ×6), 3.92 (1H, ddd, J = 7, 7, 7.5 Hz, HCO), 3.87 (1H, ddd, J = 7, 7.5, 7.5 Hz, HCO), 3.36 (3H, s, H₃CO), 3.25 (1H, d, J = 1.5 Hz, HOC-1"), 3.15-2.92 (6H, m, H₂C-2, H₂C-6, HC-7', HC-7"'), 3.13 (1H, ddd, J = 3, 5.5, 10.5 Hz, HC-3), 2.95 (1H, ddd, J = 4.5, 4.5, 9 Hz, HC-5), 2.86 (1H, ddd, J = 2.5, 13, 13 Hz, HC-9"), 2.83-2.75 (3H, m, HC-7", HC-7", HC-9"'), 2.55-2.49 (2H, m, HC-9", HC-9"'), 2.46 (1H, ddd, J = 3, 3, 11.5 Hz, HC-6'), 2.12 (1H, ddd, J = 2.5, 5, 13.5 Hz, HC-10"), 2.09 (1H, ddd, J = 2.5, 4, 13.5 Hz, HC-10"'), 1.81 (1H, ddd, J = 2, 3, 11 Hz, HC-6"'), 1.74 (1H, ddd, J = 3.5, 13, 13 Hz, HC-10"'), 1.64 (1H, ddd, J = 3.5, 12, 13.5 Hz, HC-10"').

¹³C NMR (125 MHz, CDCl₃) δ 210.56 (s, C-4), 110.27 (s, C-5"'), 108.90 (s, C-5"'), 97.96 (t, OCH₂O), 73.81 (d, C-1"'), 66.47 (d, C-1"'), 64.95 (t, CH₂O), 64.68 (t, CH₂O), 64.43 (t, CH₂O), 64.11 (t, CH₂O), 56.35 (q, CH₃O), 54.98 (d, C-3), 54.75 (d, C-5), 51.04 (d, C-6'), 46.57 (d, C-6"'), 37.03 (t, C-10"), 36.20 (t, C-10"'), 30.85 (t, C-2), 30.66 (t, C-6), 28.96 (t, C-7'), 27.15 (t, C-9'), 26.62 (t, C-9"'), 26.11 (t, C-7"').

LRMS (El), m/z (relative intensity): 536 ([M]+, 1), 474 (7), 412 (5), 286 (8), 100 (11), 99 (100), 86 (15), 55 (19).

HRMS m/z calcd for C₂₃H₃₆O₈S₃ 536.1572, found 536.1579 (El).
(3R,5R)-rel-3-[(R)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (173b)

From aldol reaction of 125a and 172: See both experimental procedures of compound 173a.

IR (DRIFT) \( \nu_{\text{max}} \) 3506, 2895, 1710, 1428, 1261, 1167, 1040, 896 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \):

- 4.90 (1H, ddd, \( J = 3, 4, 9 \) Hz, HC-1'''), 4.79 (1H, d, \( J = 6.5 \) Hz, HCO2),
- 4.71 (1H, dd, \( J = 2, 3 \) Hz, HC-1'''), 4.67 (1H, d, \( J = 6.5 \) Hz, HCO2),
- 4.17-3.92 (6H, m, HCO \( \times 6 \)), 3.85-3.77 (2H, m, HCO \( \times 2 \)), 3.55 (1H, ddd, \( J = 2, 5, 11 \) Hz, HC-3),
- 3.38 (3H, s, H3CO), 3.06 (1H, d, \( J = 11, 14 \) Hz, HC-2),
- 3.01-2.93 (3H, m, HC-2, HC-7'', HC-7'''),
- 2.90-2.80 (2H, m, HC-5, HC-7'),
- 2.81 (1H, ddd, \( J = 3, 11, 13.5 \) Hz, HC-9''),
- 2.67 (1H, ddd, \( J = 2.5, 4, 14 \) Hz, HC-6),
- 2.52 (1H, br d, \( J = 13 \) Hz, HC-9''),
- 2.45 (1H, ddd, \( J = 2, 3, 11.5 \) Hz, HC-6'),
- 2.20 (1H, ddd, \( J = 3, 4.5, 14 \) Hz, HC-10''),
- 2.06 (1H, ddd, \( J = 2.5, 4, 12 \) Hz, HC-10'),
- 1.77 (1H, ddd, \( J = 3.5, 11, 14 \) Hz, HC-10''),

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \):

- 210.08 (s, C-4), 110.18 (s, C-5''),
- 108.86 (s, C-5'),
- 98.07 (t, OCH2O), 73.26 (d, C-1'),
- 68.84 (d, C-1''),
- 65.07 (t, CH2O),
- 64.94 (t, CH2O),
- 64.57 (t, CH2O),
- 64.32 (t, CH2O),
- 56.31 (q, CH3O),
- 54.52 (d, C-5),
- 54.06 (d, C-3),
- 51.44 (d, C-6'),
- 46.61 (d, C-6''),
- 37.41 (t, C-10'),
- 36.42 (t, C-10''),
- 32.07 (t, C-6),
- 31.62 (t, C-2),
- 28.76 (t, C-7'),
- 27.14 (t, C-9'),
- 26.76 (t, C-9''),
- 26.03 (t, C-7'').

LRMS (EI), \( m/z \) (relative intensity): 536 ([M]+, 1), 286 (11), 159 (9), 133 (24), 132 (62), 99 (100), 86 (15), 55 (12).
HRMS m/z calcd for C_{23}H_{36}O_{8}S_{3} 536.1572, found 536.1581 (EI).

(3S,5R)-rel-3-[(S)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (173c)

From aldol reaction of 125a and 172 (Li enolate) : See experimental procedure of compound 173a.

IR (DRIFT) \( \nu_{\text{max}} \) 3520, 2914, 1697, 1427, 1099, 1034, 892, 731 cm \(^{-1} \).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.75 (1H, d, \( J = 6.5 \) Hz, HCO2), 4.68 (1H, dd, \( J = 3, 3 \) Hz, HC-1’), 4.66 (1H, d, \( J = 6.5 \) Hz, HCO2), 4.24 (1H, dddd, \( J = 4.5, 5.5, 6.5 \) Hz, HC-1’), 4.07-3.89 (6H, m, HCO \times 6), 3.86-3.73 (2H, m, HCO \times 2), 3.56 (1H, dddd, \( J = 3, 4.5, 12 \) Hz, HC-3), 3.39 (3H, s, H3CO), 3.12 (1H, d, \( J = 5.5 \) Hz, HOC-1’), 3.11 (1H, dddd, \( J = 5, 6.5, 11.5 \) Hz, HC-5), 3.05-2.73 (8H, m, H2C-2, H2C-6, HC-7’, HC-7”, HC-9’, HC-9”), 2.55 (1H, m, HC-9”), 2.50 (1H, m, HC-9’), 2.39 (1H, dddd, \( J = 3, 3.5, 12 \) Hz, HC-6’), 2.09 (1H, dddd, \( J = 3, 5, 13.5 \) Hz, HC-10”), 2.08-2.01 (2H, m, HC-6”, HC-10’), 1.72 (1H, dddd, \( J = 3.5, 12, 13.5 \) Hz, HC-10”).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 213.06 (s, C-4), 109.71 (s, C-5”), 108.91 (s, C-5’), 97.40 (t, OCH2O), 71.85 (d, C-1’), 69.01 (d, C-1”), 64.64 (t, CH2O), 64.64 (t, CH2O), 64.62 (t, CH2O), 64.23 (t, CH2O), 57.92 (d, C-5), 57.41 (d, C-3), 56.32 (q, CH3O), 50.94 (d, C-6’), 47.55 (d, C-6”), 37.28 (t, C-10’), 36.55 (t, C-10”), 35.33 (t, C-6), 34.99 (t, C-2), 27.92 (t, C-7”), 27.31 (t, C-7”), 27.04 (t, C-9’), 26.72 (t, C-9”).

LRMS (FAB), m/z (relative intensity): 537 ([M+1]\(^+ \), 23), 507 (15), 506 (23), 505 (87), 475 (26), 315 (11), 132 (11), 99 (100).

HRMS m/z calcd for C_{23}H_{37}O_{8}S_{3} 537.1651 (M+H), found 537.1654 (FAB).
Following General procedure L for MOM protection, aldol 129a (311.5 mg, 1.023 mmol) upon workup gave a light yellow oil (360 mg) which was fractionated by MPC (35% ethyl acetate in hexane) to give the titled compound as a white solid (343 mg, 96%).

IR (DRIFT) $\nu_{\text{max}}$ 2909, 1708, 1428, 1264, 1153, 1032, 916, 730 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.78 (1H, d, $J = 7$ Hz, HCO2), 4.58 (1H, d, $J = 7$ Hz, HCO2), 4.57 (1H, dd, $J = 2$, 8 Hz, HC-1'), 4.12-4.02 (3H, m, H$_2$CO), 3.91 (1H, m, H$_2$CO), 3.13 (1H, ddd, $J = 1.5$, 5.5, 13.5 Hz, HC-2), 3.03 (1H, ddd, $J = 4$, 5.5, 8 Hz, HC-3), 2.98 (1H, dd, $J = 4$, 13.5 Hz, HC-2), 2.95-2.89 (1H, m, HC-5), 2.62 (1H, m, HC-5), 2.53 (1H, br d, $J = 13.5$ Hz, HC-9'), 2.38 (1H, ddd, $J = 2$, 3.5, 11 Hz, HC-6'), 2.14 (1H, ddd, $J = 3$, 5, 13.5 Hz, HC-10'), 1.75 (1H, ddd, $J = 3.5$, 12, 13.5 Hz, HC-10').

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.38 (s, C-4), 108.43 (s, C-5'), 96.67 (t, OCH$_2$O), 76.42 (d, C-1'), 64.63 (t, CH$_2$O), 64.35 (t, CH$_2$O), 56.47 (q, CH$_3$O), 54.80 (d, C-3), 50.67 (d, C-6'), 43.01 (t, C-5), 36.63 (t, C-10'), 33.68 (t, C-2), 31.09 (t, C-6), 28.93 (t, C-7'), 26.86 (t, C-9').

LRMS (El), $m/z$ (relative intensity): 348 ([M]$^+$, 3), 286 (18), 159 (14), 133 (25), 132 (66), 99 (100), 86 (12), 55 (19).

HRMS $m/z$ calcd for C$_{13}$H$_{24}$O$_5$S$_2$ 348.1065, found 348.1067.
(3S, 5S)-rel-3-[(R)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (175a)

From aldol reaction of 125a and 174 (Ti enolate): Following the same experimental procedure as described for compound 173a, the aldol reaction between ketone 174 (58 mg, 0.17 mmol) and aldehyde 125a (94 mg, 0.50 mmol) upon workup gave an oil (175 mg). The oil was fractionated by FCC (40-60% ethyl acetate in hexane; gradient elution) and gave recovered aldehyde 125a (48 mg, 51%), recovered ketone 174 (34 mg, 58%), titled compound 175a (17 mg, 19%) and 175b (8 mg, 9%).

IR (DRIFT) \( \nu_{max} \) 3515, 2914, 1705, 1427, 1261, 1130, 1033, 734 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.72 (1H, ddd, \( J = 2, 2, 11 \) Hz, HC-1"), 4.71 (1H, d, \( J = 6.5 \) Hz, HCO2), 4.66 (1H, d, \( J = 6.5 \) Hz, HCO2), 4.52 (1H, dd, \( J = 1.5, 8 \) Hz, HC-1"), 4.13-3.87 (8H, m, \( H_2CO \times 4 \)), 3.38 (3H, s, \( H_3CO \)), 3.21 (1H, ddd, \( J = 2, 4.5, 13 \) Hz, HC-2), 3.18-3.05 (4H, m, HOC-1", HC-3, HC-5, HC-6), 3.02-2.73 (8H, m, HC-2, HC-6, \( H_2C-7", H_2C-7", HC-9", HC-9" \)), 2.58-2.49 (2H, m, HC-9", HC-9"), 2.46 (1H, ddd, \( J = 1.5, 3, 11.5 \) Hz, HC-6"), 2.15-2.09 (2H, m, HC-10", HC-10"), 2.07 (1H, ddd, \( J = 2, 3, 10.5 \) Hz, HC-6"), 1.76 (1H, ddd, \( J = 3.5, 12.5, 13.5 \) Hz, HC-10"), 1.71 (1H, ddd, \( J = 3.5, 11.5, 14 \) Hz, HC-10"), \( \delta \) in C\(_6\)D\(_6\) ( ), 5.04 (1H, ddd, \( J = 2, 3, 7.5 \) Hz, HC-1"), 4.74 (1H, d, \( J = 6.5 \) Hz, HCO2), 4.65 (1H, d, \( J = 6.5 \) Hz, HCO2), 4.59 (1H, dd, \( J = 1.5, 8.5 \) Hz, HC-1"), 3.68 (1H, ddd, \( J = 7, 7 \) Hz, HCO), 3.54 (1H, dd, \( J = 5.5, 7 \) Hz, HCO), 3.48-2.95 (8H, m, HCO \times 6, H\(_2\)C-6), 3.32 (1H, dd, \( J = 4.5, 7.5, 10.5 \) Hz, HC-5), 3.24 (3H, s, \( H_3CO \)), 3.21 (1H, ddd, \( J = 4, 6.5, 8.5 \) Hz, HC-3), 3.18 (1H, d, \( J = 2 \) Hz, HOC-1"), 3.02 (1H, dd, \( J = 10.5, 13 \) Hz, HC-7"), 2.99 (1H, dd, \( J = 11.5, 13.5 \) Hz, HC-7"), 2.88 (1H, ddd, \( J = 1.5, 6.5, 13.5 \) Hz, HC-2), 2.77 (1H, dd, \( J = 4, 13.5 \) Hz, HC-2), 2.74-2.64 (2H, m, HC-9", HC-7"), 2.57 (1H, ddd, \( J = 2.5, 11, 13.5 \) Hz, HC-9"), 2.56 (1H, ddd, \( J = 1.5, 3.5, 11.5 \) Hz, HC-6"), 2.30 (1H, ddd, \( J = 3, 3.5, 10.5 \) Hz, HC-6"), 2.25 (1H, br d, \( J = \)
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 211.21 (s, C-4), 110.34 (s, C-5$''$), 108.65 (s, C-5$'$), 97.18 (t, OCH$_2$O), 76.92 (d, C-1$'$), 67.04 (d, C-1$''$), 64.86 (t, CH$_2$O), 64.69 (t, CH$_2$O), 64.34 (t, CH$_2$O), 64.31 (t, CH$_2$O), 56.06 (q, CH$_3$O), 55.31 (d, C-3), 54.01 (d, C-5), 49.77 (d, C-6$'$), 46.42 (d, C-6$''$), 37.24 (t, C-10), 35.95 (t, C-10$''$), 33.99 (t, C-6), 33.23 (t, C-2), 29.03 (t, C-7$'$), 26.92 (t, C-9$'$ or C-9$''$), 26.78 (t, C-9$''$ or C-9$'$), 26.38 (t, C-7$''$).

LRMS (El), m/z (relative intensity): 536 ([M$^+$, 1), 286 (11), 159 (14), 133 (21), 132 (57), 99 (100), 86 (18), 55 (16).

HRMS m/z calcd for C$_{23}$H$_{36}$O$_8$S$_3$ 536.1572, found 536.1566 (El).

(3R,5R)-rel-3-[(S)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (175b)

From aldol reaction of 125a and 174: See experimental procedure for compound 175a.

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.73 (1H, d, J = 6.5 Hz, HCO2), 4.70 (1H, d, J = 6.5 Hz, HCO2), 4.50-4.45 (2H, m, HC-1'$'$, HC-1$''$), 4.13-3.90 (8H, m, H$_2$CO ×4), 3.39 (3H, s, H$_3$CO), 3.26-3.19 (2H, m, HC-2, HC-3), 3.17 (1H, d, J = 4.5 Hz, HOC-1$''$), 3.05 (1H, ddd, J = 4.5, 7, 9 Hz, HC-5), 3.03 (1H, ddd, J = 11.5, 14 Hz, HC-7$''$), 2.96-2.73 (7H, m, HC-2, H$_2$C-6,HC-7', HC-7', HC-9', HC-9$''$), 2.67 (1H, ddd, J = 2.5, 2.5, 14 Hz, HC-7$''$), 2.60 (1H, br d, J = 13.5 Hz, HC-9$'$), 2.56-2.49 (2H, m, HC-6', HC-9$''$), 2.17-2.11 (2H, m, HC-10', HC-10$''$), 2.03 (1H, ddd, J = 2.5, 3, 11.5 Hz, HC-6$''$), 1.77 (1H, ddd, J = 2.5, 11, 14 Hz, HC-10'), 1.73 (1H, ddd, J = 3.5, 13, 13.5 Hz, HC-10$''$), δ in C$_6$D$_6$ (, ), 4.72 (1H, d, J = 6.5 Hz, HCO2), 4.70 (1H, d, J = 6.5 Hz, HCO2), 4.56 (1H, ddd, J = 3, 5.5, 7
Hz, HC-1"), 4.52 (1H, dd, J = 2.5, 7 Hz, HC-1"), 3.60-3.20 (8H, m, H$_2$CO ×2), 3.33 (1H, ddd, J = 4.5, 7, 7 Hz, HC-3), 3.25-3.17 (1H, m, HC-7"), 3.24 (1H, d, J = 5.5 Hz, HOC-1"), 3.23 (3H, s, H$_3$CO), 3.11 (1H, ddd, J = 5, 7, 9 Hz, HC-5), 3.10-3.01 (2H, m, HC-2, HC-7"), 2.86 (1H, br d, J = 13 Hz, HC-7"), 2.77 (1H, ddd, J = 2.5, 2.5, 14 Hz, HC-7"), 2.74 (1H, ddd, J = 3.5, 3.5, 10.5 Hz, HC-6"), 2.73-2.56 (6H, m, HC-2, H$_2$C-6, HC-6', HC-9', HC-9"), 2.31 (1H, br d, J = 13.5 Hz, HC-9'), 2.21 (1H, br d, J = 13.5 Hz, HC-9"), 2.12 (1H, ddd, J = 3, 3, 11 Hz, HC-6"), 1.75 (1H, ddd, J = 3, 5.5, 13.5 Hz, HC-10'), 1.73 (1H, ddd, J = 3, 4.5, 13.5 Hz, HC-10"), 1.65-1.57 (2H, m, HC-10', HC-10").

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 211.74 (s, C-4), 109.92 (s, C-5"), 108.67 (s, C-5'), 97.96 (t, OCH$_2$O), 77.99 (d, C-1'), 68.83 (d, C-1"), 65.08 (t, CH$_2$O), 64.71 (t, CH$_2$O), 64.53 (t, CH$_2$O), 64.29 (t, CH$_2$O), 56.48 (q, CH$_3$O), 54.58 (d, C-5), 54.43 (d, C-3), 49.54 (d, C-6'), 47.72 (d, C-6''), 36.99 (t, C-10''), 36.24 (t, C-10''), 33.78 (t, C-2), 33.51 (t, C-6), 28.94 (t, C-7'), 26.94 (t, C-9'), 26.76 (t, C-9''), 26.65 (t, C-7''), δ in C$_6$D$_6$, 211.15 (s, C-4), 110.35 (s, C-5''), 109.19 (s, C-5'), 98.55 (t, OCH$_2$O), 78.98 (d, C-1'), 69.87 (d, C-1''), 65.04 (t, CH$_2$O), 64.66 (t, CH$_2$O), 64.51 (t, CH$_2$O), 64.17 (t, CH$_2$O), 56.25 (q, CH$_3$O), 55.40 (d, C-5), 55.02 (d, C-3), 50.11 (d, C-6'), 48.75 (d, C-6''), 37.53 (t, C-10''), 36.93 (t, C-10'), 33.99 (t, C-2), 33.90 (t, C-6), 29.52 (t, C-7'), 27.50 (t, C-7''), 27.29 (t, C-9'), 27.09 (t, C-9').

LRMS (EI), m/z (relative intensity): 536 ([M]$^+$, 1), 286 (9), 159 (11), 133 (15), 132 (50), 99 (100), 86 (18), 55 (21).

HRMS m/z calcd for C$_{23}$H$_{36}$O$_8$S$_3$ 536.1572, found 536.1576 (EI).

(2R,6R)-rel-2-[(S)-Hydroxyphenylmethyl]-6-methylcyclohexanone (210ac)

BuLi (4.0 mL, 10 mmol, 2.5 M) in hexane was added dropwise over 5 minutes to a solution of i-Pr$_2$NH (1.5 mL, 11 mmol) in THF (10 mL) at 0 °C. The solution was stirred for a further 5 minutes at 0 °C and then cooled to −78 °C. A solution of 2-
methylcyclohexanone (557 mg, 4.97 mmol) in THF (0.5 mL) was added dropwise over 30 seconds to the above LDA solution and stirred for a further 30 minutes. Benzaldehyde (0.60 mL, 6.00 mmol) was then added over 10 seconds. After 3 minutes, the reaction was poured onto ice-cold NH₄Cl (20 mL, 0.1 M) with vigorous stirring. The mixture was diluted with distilled H₂O (60 mL) and extracted with CH₂Cl₂ (3×40 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give a clear oil that was a 9:21:46:24 mixture of 210sc, 210st, 210at and 210ac (1.32 g), respectively as determined by ¹H NMR. The oil was fractionated by MPC (10-30% ethyl acetate in hexane; gradient elution) to give 210sc (65 mg, 6%; 95% diastereomeric purity by ¹H NMR), the titled compound 210ac (173 mg, 16%; 98% diastereomeric purity by ¹H NMR), 210at (336 mg, 31%; 95% diastereomeric purity by ¹H NMR) and a 5:1 mixture of 210st and 210ac, respectively (130 mg, 12%). To obtain highly enriched samples, 10 mg of each of the above enriched samples were further purified by PTLC (2% MeOH in CH₂Cl₂) to give samples with >99% diastereomeric purity by ¹H NMR.

¹H NMR (500 MHz, CDCl₃) δ 7.38-7.26 (5H, m, ArH), 4.80 (1H, dd, J = 3, 8.5 Hz, HC-1'), 3.91 (1H, d, J = 3 Hz, HO), 2.64 (1H, dddd, J = 1, 5.5, 8.5, 13 Hz, HC-2), 2.47 (1H, dddq, J = 1, 6, 13, 6.5 Hz, HC-6), 2.12 (1H, dddd, J = 3, 3, 3, 6, 13 Hz, HC-5), 1.77 (1H, m, HC-4), 1.69-1.56 (2H, m, HC-3, HC-4), 1.39 (1H, dddd, J = 4, 13, 13, 13 Hz, HC-5), 1.33 (1H, dddd, J = 4, 13, 13, 13 Hz, HC-3), 1.07 (3H, d, J = 6.5 Hz, H₃C).

¹³C NMR (125 MHz, CDCl₃) δ 216.97 (s, C-1), 141.35 (s, Ar), 128.57 (d ×2, Ar), 128.05 (d, Ar), 127.22 (d ×2, Ar), 74.93 (d, C-1'), 57.89 (d, C-2), 46.42 (d, C-6), 37.39 (t, C-5), 32.10 (t, C-3), 25.16 (t, C-4), 14.43 (q, CH₃).

(2S,6R)-rel-2-[(R)-Hydroxyphenylmethyl]-6-methylcyclohexanone (210at)

For synthesis and isolation see experimental procedure for compound 210ac.
\[^1\text{H} \text{ NMR} \ (500 \text{ MHz, CDCl}_3) \delta \ 7.39-7.28 \ (5\text{H, m, ArH}), \ 4.86 \ (1\text{H, dd, } J = 3, \ 9.5 \text{ Hz, HC-1'}), \ 3.42 \ (1\text{H, d, } J = 3 \text{ Hz, HO}), \ 2.76 \ (1\text{H, ddd, } J = 5.5, \ 9.5, \ 9.5 \text{ Hz, HC-2}), \ 2.70 \ (1\text{H, ddq, } J = 5, \ 5.5, \ 7 \text{ Hz, HC-6}), \ 1.96 \ (1\text{H, m, HC-5}), \ 1.74-1.63 \ (3\text{H, m, HC-4, HC-4, HC-5}), \ 1.55 \ (1\text{H, m, HC-3}), \ 1.37 \ (1\text{H, m, HC-3}), \ 1.21 \ (3\text{H, d, } J = 7 \text{ Hz, H}_3\text{C}).\]

\[^{13}\text{C} \text{ NMR} \ (125 \text{ MHz, CDCl}_3) \delta \ 218.16 \ (s, \text{ C-1}), \ 141.51 \ (s, \text{ Ar}), \ 128.73 \ (d \times 2, \text{ Ar}), \ 128.32 \ (d, \text{ Ar}), \ 127.19 \ (d \times 2, \text{ Ar}), \ 75.01 \ (d, \text{ C-1'}), \ 54.88 \ (d, \text{ C-2}), \ 44.48 \ (d, \text{ C-6}), \ 34.23 \ (t, \text{ C-5}), \ 30.09 \ (t, \text{ C-3}), \ 20.26 \ (t, \text{ C-4}), \ 16.47 \ (q, \text{ CH}_3).\]

(2R,6R)-rel-2-[(R)-Hydroxyphenylmethyl]-6-methylcyclohexanone (210sc)

\[\text{(2R,6R)-rel-2-[(R)-Hydroxyphenylmethyl]-6-methylcyclohexanone (210sc)}\]

For synthesis and isolation see experimental procedure for compound 210ac.

\[^1\text{H} \text{ NMR} \ (500 \text{ MHz, CDCl}_3) \delta \ 7.37-7.23 \ (5\text{H, m, ArH}), \ 5.38 \ (1\text{H, dd, } J = 2.5, \ 3 \text{ Hz, HC-1'}), \ 3.15 \ (1\text{H, d, } J = 3 \text{ Hz, HO}), \ 2.61 \ (1\text{H, dddd, } J = 1.5, \ 2.5, \ 6.5, \ 12.5 \text{ Hz, HC-2}), \ 2.50 \ (1\text{H, ddq, } J = 1.5, \ 5.5, \ 12.5, \ 6.5 \text{ Hz, HC-6}), \ 2.12 \ (1\text{H, dddd, } J = 2.5, \ 2.5, \ 3.5, \ 5.5, \ 13 \text{ Hz, HC-5}), \ 1.86-1.75 \ (2\text{H, m, HC-3, HC-4}), \ 1.74 \ (1\text{H, dddd, } J = 3.5, \ 12.5, \ 12.5, \ 13 \text{ Hz, HC-3}), \ 1.60 \ (1\text{H, dddd, } J = 3.5, \ 4.5, \ 12.5, \ 12.5, \ 13 \text{ Hz, HC-4}), \ 1.40 \ (1\text{H, dddd, } J = 3.5, \ 12.5, \ 12.5, \ 13 \text{ Hz, HC-5}), \ 1.06 \ (3\text{H, d, } J = 6.5 \text{ Hz, H}_3\text{C}).\]

\[^{13}\text{C} \text{ NMR} \ (125 \text{ MHz, CDCl}_3) \delta \ 216.76 \ (s, \text{ C-1}), \ 141.81 \ (s, \text{ Ar}), \ 128.36 \ (d \times 2, \text{ Ar}), \ 127.15 \ (d, \text{ Ar}), \ 125.96 \ (d \times 2, \text{ Ar}), \ 70.97 \ (d, \text{ C-1'}), \ 57.43 \ (d, \text{ C-2}), \ 46.34 \ (d, \text{ C-6}), \ 37.65 \ (t, \text{ C-5}), \ 27.05 \ (t, \text{ C-3}), \ 25.13 \ (t, \text{ C-4}), \ 14.50 \ (q, \text{ CH}_3).\]

(2S,6R)-rel-2-[(S)-Hydroxyphenylmethyl]-6-methylcyclohexanone (210st)

\[\text{(2S,6R)-rel-2-[(S)-Hydroxyphenylmethyl]-6-methylcyclohexanone (210st)}\]

For synthesis and isolation see experimental procedure for compound 210ac.

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\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.39-7.24 (5H, m, ArH), 5.32 (1H, br d, \(J = 3\) Hz, HC-1'), 2.84 (1H, br s, HO), 2.77 (1H, ddd, \(J = 3,\) 5.5, 10 Hz, HC-2), 2.60 (1H, ddq, \(J = 5,\) 5.5, 7 Hz, HC-6), 1.92 (1H, m, HC-5), 1.83 (1H, m, HC-3), 1.74-1.65 (2H, m, HC-4, HC-4), 1.71 (1H, m, HC-5), 1.69 (1H, m, HC-3), 1.18 (3H, d, \(J = 7\) Hz, H\(_3\)C).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 217.96 (s, C-1), 141.85 (d, Ar), 128.45 (d \(\times 2\), Ar), 127.41 (d, Ar), 126.07 (d \(\times 2\), Ar), 71.62 (d, C-1'), 53.86 (d, C-2), 45.21 (d, C-6), 33.68 (t, C-5), 25.87 (t, C-3), 20.03 (t, C-4), 16.71 (q, CH\(_3\)).

\((3S,6S)\)-rel-Tetrahydro-3-\([(R)\)-hydroxyphenylmethyl\]-5-methyl-4H-thiopyran-4-one (211at)

Following the same procedure as described for the synthesis of 210ac, the aldol reaction of 2-methylthiopyranone (196 mg, 1.51 mmol) and benzaldehyde (230 \(\mu\)L, 2.26 mmol) upon workup gave a light yellow oily 1 : 2.6 : 1.5 mixture of 211st, 211at, 211ac, respectively as determined by \(^{1}\)H NMR. The oil was fractionated by FCC (25% ethyl acetate in hexane) and two fractions were obtained. The first fraction was an oily 4.4 : 1 : 7.2 mixture of 211st, 211at and 211ac, respectively (106 mg, combined aldol yield 30%). The second fraction was an oil which later solidified upon standing consisting of a 1 : 10 : 1 mixture of 211st, 211at and 211ac, respectively (143 mg, combined aldol yield 40%). A portion of the second fraction (57 mg) was dissolved in the minimum amount of hot CH\(_2\)Cl\(_2\)/hexane (1:2, 1.5 mL). Upon cooling to 0 °C crystals of the titled compound 211at (43 mg) were obtained.

IR (DRIFT) \(v_{\text{max}}\) 3445, 2912, 1706, 1454, 1039, 1024, 768, 701 cm\(^{-1}\).

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.43-7.32 (5H, m, ArH), 5.30 (1H, dd, \(J = 3.5, 9.5\) Hz, HC-1'), 3.09 (1H, ddq, \(J = 4.5, 9, 6.5\) Hz, HC-5), 3.01 (1H, ddd, \(J = 4, 6.5, 9.5\) Hz, HC-3), 3.01 (1H, ddd, \(J = 2, 4.5, 13\) Hz, HC-6), 2.73 (1H, d, \(J = 3.5\) Hz, HO), 2.72 (1H, dd,
$J = 4, 14 \text{ Hz, HC-2}$), 2.70 (1H, dd, $J = 9, 13 \text{ Hz, HC-6}$), 2.46 (1H, ddd, $J = 2, 6.5, 14 \text{ Hz, HC-2}$), 1.27 (3H, d, $J = 6.5 \text{ Hz, H}_3\text{C}$).

$\text{^{13}C NMR}$ (125 MHz, CDCl$_3$) $\delta$ 213.02 (s, C-4), 141.16 (s, Ar), 129.02 (d $\times 2$, Ar), 128.75 (d, Ar), 127.04 (d $\times 2$, Ar), 74.29 (d, C-1'), 58.02 (d, C-3), 45.55 (d, C-5), 37.68 (t, C-6), 32.89 (t, C-2), 15.55 (q, CH$_3$).

LRMS (EI), m/z (relative intensity): 236 ([M]$^+1$, 1), 130 (100), 129 (26), 107 (36), 97 (39), 87 (33), 79 (27), 77 (30).

HRMS m/z calcd for C$_{13}$H$_{16}$O$_2$S 236.0871, found 236.0869 (EI).

(3R,6S)-rel-Tetrahydro-3-[(R)-hydroxyphenylmethyl]-5-methyl-4H-thiopyran-4-one (211sc)

\[
\text{211sc}
\]

A 4.4:1:7.2 mixture of 211st, 211at and 211ac (37.6 mg)*, respectively was added to a solution of imidazole (109 mg, 1.6 mmol) in CH$_2$Cl$_2$ (2 mL) and the solution was stirred for 4 days at rt. The solution was diluted with citric acid (20 mL, 0.1 M) and extracted with CH$_2$Cl$_2$ (3x20 mL). The organic extracts were combined, dried over Na$_2$SO$_4$ and concentrated to give a 4:2.8:1:2.1 mixture of 211at, 211ac, 211st and 211sc, respectively (35.3 mg, 94% mass recovery) as determined by $^1$H NMR. Fractionation by PTLC (2% MeOH in CH$_2$Cl$_2$) gave 211sc (10.1 mg, 27%), 211at (10.8 mg, 29%), 211st (7.1 mg, 19%) and 211at (9.5 mg, 25%).

IR (DRIFT) $\nu_{\text{max}}$ 3532, 2971, 2929, 1706, 1451, 1070, 1016, 703 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.39-7.25 (5H, m, ArH), 5.38 (1H, br dd, $J = 1.5, 3 \text{ Hz, HC-1'}$), 3.12 (1H, d, $J = 1.5 \text{ Hz, HO}$), 3.07 (1H, dd, $J = 12, 12.5 \text{ Hz, HC-2}$), 3.01 (1H, ddd, $J = 3, 3.5, 12 \text{ Hz, HC-3}$), 2.92 (1H, ddq, $J = 5, 12, 6.5 \text{ Hz, HC-5}$), 2.88 (1H, ddd, $J$

* See experimental procedure for compound 211at for the origin of this mixture.

† Aldols are reported in order from higher to lower $R_f$.
3, 5, 13 Hz, HC-6), 2.73 (1H, dd, J = 12, 13 Hz, HC-6), 2.68 (1H, ddd, J = 3, 3.5, 12.5 Hz, HC-2), 1.14 (3H, d, J = 6.5 Hz, H3C).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 214.12 (s, C-4), 140.98 (s, Ar), 128.61 (d ×2, Ar), 127.56 (d, Ar), 125.94 (d ×2, Ar), 71.16 (d, C-1'), 60.09 (d, C-3), 49.31 (d, C-5), 39.07 (t, C-6), 30.85 (t, C-2), 14.72 (q, CH$_3$).

LRMS (EI), m/z (relative intensity): 236 ([M]$^+$, 5), 189 (35), 130 (100), 107 (52), 105 (30), 97 (41), 79 (53), 77 (54).

HRMS m/z calcd for C$_{13}$H$_{16}$O$_2$S 236.0871, found 236.0875 (EI).

(3R,6S)-rel-Tetrahydro-3-[(S)-hydroxyphenylmethyl]-5-methyl-4H-thiopyran-4-one (211ac)

![Chemical Structure](image)

For synthesis and isolation see experimental procedure for compound 211se.

IR (DRIFT) $\nu_{max}$ 3524, 2974, 2904, 1695, 1453, 1290, 1050, 701 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.40-7.30 (5H, m, ArH), 4.86 (1H, dd, J = 3.5, 8.5 Hz, HC-1'), 3.54 (1H, d, J = 3.5 Hz, HO), 3.09 (1H, ddd, J = 4.5, 8.5, 12.5 Hz, HC-3), 2.91 (1H, ddq, J = 4.5, 13, 6.5 Hz, HC-5), 2.90 (1H, ddd, J = 3, 4.5, 14.5 Hz, HC-6), 2.73 (1H, dd, J = 13, 14.5 Hz, HC-6), 2.66 (1H, dd, J = 12.5, 13.5 Hz, HC-2), 2.44 (1H, ddd, J = 3, 4.5, 13.5 Hz, HC-2), 1.15 (3H, d, J = 6.5 Hz, H3C).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 214.19 (s, C-4), 140.46 (s, Ar), 128.87 (d ×2, Ar), 128.48 (d, Ar), 127.20 (d ×2, Ar), 74.08 (d, C-1'), 60.62 (d, C-3), 49.37 (d, C-5), 39.04 (t, C-6), 34.29 (t, C-2), 14.70 (q, CH$_3$).

LRMS (EI), m/z (relative intensity): 236 ([M]$^+$, 4), 189 (23), 130 (100), 107 (45), 97 (46), 88 (37), 79 (30), 77 (28).

HRMS m/z calcd for C$_{13}$H$_{16}$O$_2$S 236.0871, found 236.0874 (EI).
(3S,6S)-rel-Tetrahydro-3-[(S)-hydroxyphenylmethyl]-5-methyl-4H-thiopyran-4-one (211st)

For synthesis and isolation see experimental procedure for compound 211st.

IR (DRIFT) $\nu_{\text{max}}$ 3389, 2920, 1701, 1036, 1025, 766, 701 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41-7.27 (5H, m, ArH), 5.43 (1H, dd, $J = 4$, 4 Hz, HC-1'), 3.13 (1H, ddd, $J = 1$, 9.5, 13 Hz, HC-2), 3.07 (1H, ddd, $J = 1$, 4.5, 13.5 Hz, HC-6), 3.07 (1H, ddd, $J = 4$, 4, 9.5 Hz, HC-3), 2.89 (1H, ddq, $J = 4.5$, 7, 7 Hz, HC-5), 2.72 (1H, d, $J = 4$ Hz, HO), 2.71 (1H, ddd, $J = 2$, 4, 13 Hz, HC-2), 2.67 (1H, ddd, $J = 2$, 7, 13.5 Hz, HC-6), 1.26 (3H, d, $J = 7$ Hz, H$_3$C).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 213.70 (s, C-4), 140.98 (s, Ar), 128.78 (d $\times$2, Ar), 127.98 (d, Ar), 126.16 (d $\times$2, Ar), 71.86 (d, C-1'), 56.63 (d, C-3), 46.57 (d, C-5), 36.63 (t, C-6), 29.62 (t, C-2), 15.97 (q, CH$_3$).

LRMS (EI), $m/z$ (relative intensity): 236 ([M]$^+$, 3), 130 (100), 107 (40), 97 (33), 88 (38), 79 (60), 77 (57), 55 (33).

HRMS $m/z$ calcd for C$_{13}$H$_{16}$O$_2$S 236.0871, found 236.0871 (EI).

(3R,5S)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (212a)

Following General procedure M for MOM protection, after 4 days the substrate 165b aldol (15 mg, 0.031mmol) gave a 4:1 mixture of 212a and 213a, respectively. The
mixture was fractionated by PTLC (2% MeOH in CH₂Cl₂) to give titled compound 212a (5.4 mg, 30%) and a 2.5:1 mixture of 212a and 213a (12.4 mg), respectively.

IR (DRIFT) ν_{max} 2915, 1708, 1261, 1155, 1103, 1032, 892 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.66 (2H, d, J = 6 Hz, HCO₂X₂), 4.63 (2H, d, J = 6 Hz, HCO₂X₂), 4.55 (2H, dd, J = 3, 6.5 Hz, HC-1', HC-1''), 4.07-3.84 (8H, m, H₂CO ×4), 3.35 (6H, s, H₃CO ×2), 3.08 (2H, ddd, J = 3, 5.5, 9 Hz, HC-3, HC-5), 3.01-2.94 (4H, m, H₂C-2, H₂C-6), 2.91-2.82 (4H, m, H₂C-7', H₂C-7''), 2.77 (2H, ddd, J = 3, 11, 13.5 Hz, HC-9', HC-9''), 2.58 (2H, ddd, J = 3.5, 5.5, 13.5 Hz, HC-9', HC-9''), 2.11 (2H, ddd, J = 4.5, 6.5, 9 Hz, HC-6', HC-6''), 2.05 (2H, ddd, J = 3, 5.5, 13.5 Hz, HC-10', HC-10''), 1.67 (2H, ddd, J = 3.5, 11, 13.5 Hz, HC-10', HC-10'').

¹³C NMR (125 MHz, CDCl₃) δ 208.33 (s, C-4), 109.18 (s ×2, C-5', C-5''), 98.60 (t ×2, OCH₂O), 72.26 (d ×2, C-1', C-1''), 64.80 (t ×2, CH₂O), 64.55 (t ×2, CH₂O), 59.79 (d ×2, C-3, C-5), 56.78 (q ×2, CH₂O), 49.44 (d ×2, C-6', C-6''), 35.96 (t ×2, C-10', C-10''), 31.17 (t ×2, C-2, C-6), 29.10 (t ×2, C-7', C-7''), 26.82 (t ×2, C-9', C-9'').

LRMS (EI), m/z (relative intensity): 580 ([M]+, 1), 518 (9), 133 (30), 132 (69), 100 (9), 99 (100), 86 (13), 55 (12).

HRMS m/z calcd for C₂₅H₄₀O₉S₃ 580.1834, found 580.1831 (EI).

(3S,5S)-rel-3-[(R)-(68)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (212b)

Following General procedure M for MOM protection but using 20 equiv of MOMCl and 30 equiv i-Pr₂EtN, after 20 h the substrate 165a (32 mg 0.065 mmol) gave a 3:1:2.5 mixture of 212b, 213b and 213c, respectively. The mixture was fractionated.
by PTLC (50% ethyl acetate in hexane; multiple elutions) to give titled compound 212b (16.6 mg, 44%), 213b (5.0 mg, 14%) and 213c (12.2 mg, 35%).

**IR** (DRIFT) \(\nu_{\text{max}}\) 2914, 1708, 1428, 1261, 1153, 1097, 1032, 890 cm\(^{-1}\).

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 4.72 (1H, d, \(J = 5.5\) Hz, HCOC-1'), 4.71 (1H, d, \(J = 6\) Hz, HCOC-1''), 4.63 (1H, d, \(J = 5.5\) Hz, HCOC-1'''), 4.56 (1H, d, \(J = 6\) Hz, HCOC-1'''), 4.53 (1H, d, \(J = 4, 6\) Hz, HC-1'''), 4.16 (1H, dd, \(J = 3.5, 4\) Hz, HC-1'''), 4.08-3.92 (8H, \(\delta\) HC-2', HC-2'', HC-3', HC-3''), 3.73 (3H, s, \(\delta\) H\(_3\)COCOC-1''), 3.67 (3H, s, \(\delta\) H\(_3\)COCOC-1''), 3.00 (1H, ddd, \(J = 4.5, 5.5, 6\) Hz, HC-5), 3.13-2.95 (5H, \(\delta\) H\(_2\)C-2, HC-3, HC-6,HC-7), 2.91-2.69 (6H, \(\delta\) HC-6, HC-7; HC-7'', HC-9', HC-9''), 2.56-2.48 (2H, \(\delta\) HC-9', HC-9''), 2.28 (1H, ddd, \(J = 3.5, 4, 11\) Hz, HC-6'), 2.15-2.09 (1H, \(\delta\) HC-10'), 2.11 (1H, ddd, \(J = 4, 4, 11\) Hz, HC-6''), 1.69 (1H, ddd, \(J = 3.5, 12.5, 13.5\) Hz, HC-10''), 1.65 (1H, ddd, \(J = 3.5, 12, 13\) Hz, HC-10').

**\(^{13}\)C NMR** (125 MHz, CDCl\(_3\)) \(\delta\) 208.72 (s, C-4), 109.07 (s, C-5'), 108.80 (s, C-5''), 98.41 (t, CH\(_2\)OC-1''), 97.28 (t, CH\(_2\)OC-1''), 74.55 (d, C-1'), 72.30 (d, C-1''), 64.82 (t, CH\(_2\)O), 64.62 (t, CH\(_2\)O), 64.59 (t, CH\(_2\)O), 64.58 (t, CH\(_2\)O), 57.49 (d, C-3), 57.03 (d, C-5), 56.82 (q, CH\(_3\)OCOC-1''), 56.44 (q, CH\(_3\)OCOC-1''), 49.75 (d, C-6'), 49.04 (d, C-6''), 36.11 (t, C-1''), 35.98 (t, C-1'''), 31.13 (t, C-6), 29.42 (t, C-2), 28.63 (t, C-7'), 28.29 (t, C-7''), 26.84 (t, C-9' or C-9''), 26.76 (t, C-9' or C-9'').

**LRMS** (EI), m/z (relative intensity): 580 ([M]+, 1), 456 (10), 133 (25), 132 (65), 100 (8), 99 (100), 86 (14), 55 (8).

**HRMS** m/z calcd for C\(_{25}\)H\(_{40}\)O\(_9\)S\(_3\) 580.1834, found 580.1828 (EI).

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* Aldols are reported in order from high to lower \(R_f\).
(3S,5R)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (212c)

Following General procedure M for MOM protection but with 2.5 times higher concentration, after 20 h the substrate 165d (24 mg, 0.049 mmol) gave a white solid that was fractionated by PTLC (60% ethyl acetate in hexane) to give titled compound 212c (24 mg, 83%).

**IR** (DRIFT) $\nu_{\text{max}}$ 2913, 1716, 1427, 1152, 1098, 1033, 890, 734 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.70 (2H, d, $J = 6.5$ Hz, HCO$_2\times2$), 4.60 (2H, d, $J = 6.5$ Hz, HCO$_2\times2$), 4.12 (2H, dd, $J = 4.5$, 5 Hz, H-C-1', H-C-1''), 4.05-3.91 (8H, m, H$_2$CO), 3.37 (6H, s, H$_3$CO), 3.04 (2H, dd, $J = 12.5$, 13 Hz, H-C-2, H-C-6), 3.00 (2H, br d, $J = 14$ Hz, H-C-7', H-C-7''), 2.90 (2H, br d, $J = 13$ Hz, H-C-2, H-C-6), 2.81 (2H, dd, $J = 9.5$, 14 Hz, H-C-7', H-C-7'').

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 207.24 (s, C-4), 109.06 (s $\times 2$, C-5', C-5''), 98.28 (t $\times 2$, OCH$_2$O), 75.13 (d $\times 2$, C-1', C-1''), 64.93 (t $\times 2$, CH$_2$O), 64.51 (t $\times 2$, CH$_2$O), 59.72 (d $\times 2$, C-3, C-5), 56.70 (q $\times 2$, CH$_2$O), 48.39 (d $\times 2$, C-6', C-6''), 35.72 (t $\times 2$, C-10', C-10''), 34.27 (t $\times 2$, C-2, C-6), 29.10 (t $\times 2$, C-7', C-7''), 26.89 (t $\times 2$, C-9', C-9'').

LRMS (EI), $m/z$ (relative intensity): 580 ([M]$^+$, 1), 518 (4), 456 (10), 133 (20), 132 (60), 100 (9), 99 (100), 86 (22).

HRMS $m/z$ calcd for C$_{25}$H$_{40}$O$_9$S$_3$ 580.1834, found 580.1839 (EI).
(3R,5S)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-y1(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (213a)

Following General procedure M for MOM protection but using 20 equiv of MOMCl and 30 equiv i-Pr₂EtN, after 6 h the substrate 165b (13 mg 0.027 mmol) gave a 1:1:2 mixture of products 165b, 212a and 213a, respectively. The mixture was fractionated by PTLC (50% ethyl acetate in hexane; multiple elutions) to give recovered 165b (3 mg, 21%) and a 1:2 mixture of 212a and 213a (12 mg, 80% total yield), respectively. This mixture was further fractionated by PTLC (2% MeOH in CH₂Cl₂; multiple elutions) to give titled compound 213a (3 mg, 18%).

¹H NMR (500 MHz, CDCl₃) δ 4.69 (1H, d, J = 6 Hz, HCO₂), 4.66 (1H, d, J = 6 Hz, HCO₂), 4.64 (1H, m, HC-1°), 4.10-3.86 (8H, m, H₂CO ×4), 3.36 (3H, s, H3CO), 3.24-3.18 (2H, m), 3.05 (1H, d, J = 2 Hz, HOC-1°), 3.05-2.70 (11H, m), 2.69-2.56 (2H, m), 2.14 (1H, ddd, J = 4, 4, 10 Hz, HC-6° or HC-6°), 2.11-2.03 (3H, m, HC-6° or HC-6°, HC-10°, HC-10°), 1.73 (1H, ddd, J = 3.5, 10.5, 14 Hz, HC-10° or HC-10°), 1.68 (1H, ddd, J = 3.5, 9.5, 13 Hz, HC-10° or HC-10°).

(3S,5S)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-y1(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (213b)

For synthesis and isolation see experimental procedure for compound 212b.

IR (DRIFT) v max cm⁻¹.
^1H NMR (500 MHz, CDCl₃) δ 4.72 (1H, ddd, J = 2.5, 3, 8 Hz, HC-1"), 4.70 (1H, d, J = 5.5 Hz, HCO2), 4.58 (1H, d, J = 5.5 Hz, HCO2), 4.39 (1H, ddd, J = 4, 6 Hz, HC-1'), 4.12-3.94 (8H, m, H₂C=O ×4), 3.35 (3H, s, H₃CO), 3.20 (1H, ddd, J = 1, 5, 13 Hz, HC-6), 3.15 (1H, d, J = 2.5 Hz, HOC-1"), 3.13 (1H, ddd, J = 5, 8, 8.5 Hz, HC-5), 3.03 (1H, m, HC-2), 2.97 (1H, ddd, J = 10, 14 Hz, HC-7"), 2.92 (1H, ddd, J = 5, 5.5, 6.0 Hz, HC-3), 2.92 (1H, d, J = 8.5, 13 Hz, HC-6), 2.82-2.73 (4H, m, HC-2, HC-6'), 2.61-2.52 (2H, m, HC-9', HC-9'"), 2.18 (1H, ddd, J = 4, 5.5, 9 Hz, HC-6'), 2.18-2.11 (2H, m, HC-10', HC-10'"), 2.06 (1H, ddd, J = 3, 3, 10 Hz, HC-6"), 1.73 (1H, ddd, J = 3.5, 10.5, 13 Hz, HC-10"), 1.70 (1H, ddd, J = 3.5, 10.5, 13 Hz, HC-10').

^13C NMR (125 MHz, CDCl₃) δ 210.73 (s, C-4), 110.17 (s, C-5"), 108.72 (s, C-5'), 97.45 (t, OCH₂O), 73.96 (d, C-1'), 67.08 (d, C-1'"), 64.88 (t, CH₂O), 64.80 (t, CH₂O), 64.69 (t, CH₂O), 64.42 (t, CH₂O), 58.47 (d, C-3), 56.21 (q, CH₃O), 53.77 (d, C-5), 49.98 (d, C-6'), 46.40 (d, C-6'"), 36.16 (t, C-10'), 35.85 (t, C-10'"), 32.02 (t, C-2), 31.44 (t, C-6), 28.37 (t, C-7'), 26.86 (t, C-9' or C-9'"), 26.79 (t, C-9' or C-9"), 26.66 (t, C-7'').

LRMS (EI), m/z (relative intensity): 536 ([M]+, 1), 188 (8), 133 (15), 132 (50), 100 (10), 99 (100), 86 (18), 55 (11).

HRMS m/z calcld for C₂₃H₃₆O₈S₃ 536.1572, found 536.1561 (EI).

(3S,5S)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (213c).

For synthesis and isolation see experimental procedure for compound 212b.

IR (DRIFT) νmax 3518, 2913, 1711, 1427, 1153, 1133, 1108, 1034 cm⁻¹.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.69 (1H, ddd, $J = 2.5, 3, 3.5$ Hz, HC-1'), 4.68 (1H, d, $J = 6$ Hz, HCO2), 4.65 (1H, d, $J = 6$ Hz, HCO2), 4.47 (1H, ddd, $J = 4.5, 5$ Hz, HC-1''), 4.14-3.91 (8H, m, H$_2$CO x4), 3.37 (3H, s, H$_3$CO), 3.21 (1H, ddd, $J = 4.5, 5, 9.5$ Hz, HC-5), 3.07 (1H, ddd, $J = 9.5, 13.5$ Hz, HC-6), 3.04-2.92 (5H, m, HOC-1', HC-2, HC-3, HC-6, HC-7), 2.88-2.69 (5H, m, HC-2, H$_2$C-7', HC-9', HC-9''), 2.66 (1H, ddd, $J = 2, 3, 13.5$ Hz, HC-7'), 2.53 (1H, m, HC-9'), 2.50 (1H, m, HC-9''), 2.16 (1H, ddd, $J = 3, 4, 13.5$ Hz, HC-10'), 2.10 (1H, ddd, $J = 3.5, 4.5, 11$ Hz, HC-6''), 2.07 (1H, ddd, $J = 3, 4, 13.5$ Hz, HC-10''), 2.01 (1H, ddd, $J = 2.5, 3, 11.5$ Hz, HC-6'), 1.74 (1H, ddd, $J = 3.5, 13, 13$ Hz, HC-10'), 1.69 (1H, ddd, $J = 3.5, 13, 13$ Hz, HC-10'').

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 210.97 (s, C-4), 110.07 (s, C-5'), 108.97 (s, C-5''), 98.62 (t, OCH$_2$O), 72.79 (d, C-1''), 68.51 (d, C-1'), 65.10 (t, CH$_2$O), 64.64 (t, CH$_2$O), 64.60 (t, CH$_2$O), 64.60 (t, CH$_2$O), 57.34 (d, C-5), 56.79 (q, CH$_3$O), 54.69 (d, C-3), 49.14 (d, C-6'), 47.48 (d, C-6'), 36.69 (t, C-10''), 36.33 (t, C-10'), 32.75 (t, C-2), 31.44 (t, C-6), 28.27 (t, C-7'), 26.78 (t, C-9' or C-9''), 26.75 (t, C-9' or C-9''), 26.29 (t, C-7').

LRMS (EI), m/z (relative intensity): 536 ([M]$^+$, 1), 188 (8), 133 (11), 132 (44), 100 (10), 99 (100), 86 (20), 54 (13).

HRMS m/z calcd for C$_{23}$H$_{36}$O$_8$S$_3$ 536.1572, found 536.1578 (EI).

(3S,5R)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-y](methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-y]hydroxymethyl]tetrahydro-4H-thiopyran-4-one (213d)

IR (DRIFT) v$_{max}$ 3520, 2917, 1701, 1427, 1100, 1034, 891, 735 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.72 (1H, d, $J = 6.5$ Hz, HCO2), 4.59 (1H, d, $J = 6.5$ Hz, HCO2), 4.18 (1H, ddd, $J = 4.5, 6.5, 8$ Hz, HC-1''), 4.07-3.90 (8H, m, H$_2$CO x4), 4.00 (1H, ddd, $J = 5, 5$ Hz, HC-1''), 3.38 (3H, s, H$_3$CO), 3.23 (1H, ddd, $J = 4.5, 4.5, 12$ Hz,
HC-5), 3.22 (1H, ddd, J = 4.5, 5, 12 Hz, HC-3), 3.17-2.91 (6H, m, H2C-2, HC-6, HC-7', H2C-7"), 2.87 (1H, ddd, J = 3.5, 3.5, 13 Hz, HC-6), 2.79 (1H, dd, J = 10, 14 Hz, HC-7'), 2.78-2.65 (3H, m, HC-9', H2C-9'"), 2.59 (1H, br d, J = 13.5 Hz, HC-9'"), 2.30 (1H, ddd, J = 3.5, 5, 10 Hz, HC-6'), 2.17 (1H, ddd, J = 3.5, 6.5, 7.5 Hz, HC-6'"), 2.07 (1H, ddd, J = 3, 5.5, 13.5 Hz, HC-10'), 1.93 (1H, ddd, J = 4, 7, 13 Hz, HC-10'"), 1.73 (1H, ddd, J = 4.5, 8, 13 Hz, HC-10'"), 1.65 (1H, ddd, J = 3.5, 11, 13.5 Hz, HC-10').

13C NMR (125 MHz, CDCl3) δ 213.35 (s, C-4), 109.12 (s, C-5'"), 108.96 (s, C-5"), 98.16 (t, OCH2O), 74.88 (d, C-1'), 70.34 (d, C-1'"), 65.00 (t, CH2O), 64.93 (t, CH2O), 64.59 (t, CH2O), 64.39 (t, CH2O), 60.22 (d, C-3), 57.52 (d, C-5), 56.77 (q, CH3O), 48.89 (d, C-6'), 47.76 (d, C-6'"), 36.09 (t, C-6), 35.89 (t, C-10'), 35.72 (t, C-2), 35.59 (t, C-10'"), 29.05 (t, C-7'), 28.69 (t, C-7'"), 26.86 (t, C-9' or C-9'"), 26.84 (t, C-9' or C-9').

LRMS (EI), m/z (relative intensity): 536 ([M]+, 1), 158 (6), 133 (12), 132 (41), 100 (11), 99 (100), 86 (12), 55 (8).

HRMS m/z calcld for C23H36O8S3 536.1572, found 536.1571 (EI).

(1'S*, 3R*, 3'R*, 4S*, 4'R*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl][methyl])tetrahydro-2H-thiopyran-4-ol (222) and (1'S*, 3R*, 3'R*, 4R*, 4'R*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl][methyl])tetrahydro-2H-thiopyran-4-ol (223).

Following General procedure D, the NaBH₄ reduction of aldol 126b (50 mg, 0.16 mmol) gave the trans alcohol 223 (14 mg, 28%) and the cis alcohol 222 (22 mg, 43%) after fractionation of the crude product by DFC (10-60% ethyl acetate in hexane; gradient elution).

Data for 222:

IR v_max 3397, 2926, 1427, 1210, 1150, 1093, 1028, 922 cm⁻¹;

1H NMR (500 MHz, CDCl3) δ 4.73 (1H, d, J = 7 Hz, H2CO), 4.62 (1H, d, J = 7 Hz, H2CO), 4.17 (1H, ddd, J = 1, 2, 4 Hz, HC-4), 3.93 (1H, ddd, J = 1, 2, 4 Hz, HC-4"),
3.83 (1H, dd, J = 4, 6 Hz, HC-1'), 3.40 (3H, s, H$_3$CO), 3.16-2.90 (4H, m, HC-2, HC-2'', HC-6, HC-6''), 2.54 (1H, br d, J = 13 Hz, HC-2/HC-2''), 2.38 (1H, br d, J = 13 Hz, HC-2''/HC-2), 2.36-2.30 (2H, m, HC-5'', HC-6''), 2.28 (1H, dddd, J = 2, 2.5, 3, 13 Hz, HC-6), 2.14 (1H, dddd, J = 2, 3, 3, 14 Hz, HC-5), 2.04-1.99 (2H, m, HC-3, HC-3''), 1.94 (1H, dddd, J = 2.5, 4, 13, 14 Hz, HC-5), 1.79 (1H, m, HC-5'');

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 95.11 (t), 77.67 (d), 74.22 (d), 69.84 (d), 56.37 (q), 44.29 (d), 43.86 (d), 35.78 (t), 31.43 (t), 24.34 (t), 22.69 (t), 22.14 (t), 21.94 (t);

LRMS (EI), m/z (relative intensity): 308 ([M]$^+$, 68), 290 (34), 159 (33), 129 (56), 101 (53), 100 (100), 99 (99), 67 (29).

HRMS m/z calcd for C$_{13}$H$_{24}$O$_4$S$_2$ 308.1116, found 308.1112 (EI).

Data for 223:

IR $\nu_{\text{max}}$ 3433, 2927, 1429, 1277, 1149, 1095, 1028, 918 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.70 (1H, d, J = 7 Hz, H$_2$CO), 4.66 (1H, d, J = 7 Hz, H$_2$CO), 4.16 (1H, dd, J = 3.5, 7 Hz, HC-1'), 3.92 (1H, br ddd, J = 2.5, 3, 3.5 Hz, HC-4''), 3.63 (1H, dddd, J = 4, 10, 10 Hz, HC-4), 3.41 (3H, s, H$_3$CO), 3.01 (1H, br dd, J = 11, 12.5 Hz, HC-2''), 2.95 (1H, br dd, J = 12.5, 12.5 Hz, HC-6''), 2.71-2.55 (5H, m), 2.35-2.27 (3H, m, HC-5, HC-5''), 1.99 (1H, dddd, J = 2.5, 3, 7, 11 Hz, HC-3''), 1.92 (1H, dddd, J = 3, 3.5, 10, 10 Hz, HC-3), 1.81-1.70 (2H, m, HC-5, HC-5'');

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 95.44 (t), 74.25 (d), 72.37 (d), 70.40 (d), 56.24 (q), 47.64 (d), 44.42 (d), 37.40 (t), 31.65 (t), 27.35 (t), 27.05 (t), 24.74 (t), 22.55 (t);

LRMS (EI), m/z (relative intensity): 308 ([M]$^+$, 50), 290 (25), 159 (42), 129 (65), 117 (52), 101 (50), 100 (100), 99 (93).

HRMS m/z calcd for C$_{13}$H$_{24}$O$_4$S$_2$ 308.1116, found 308.1115 (EI).

(1S, 3'R*, 3''S*, 4'R*, 4''S*)-Bis[tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-yl]methanol (224).
Following General procedure I for MOM ether formation, the diol 222 (7 mg, 0.02 mmol) gave the titled 224 (4 mg, 50%) after fractionation by PTLC (50% ethyl acetate in hexane):

$^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.75 (2H, d, $J = 7$ Hz, H$_2$CO), 4.62 (2H, d, $J = 7$ Hz, H$_2$CO), 3.97-3.95 (2H, br s, HC-4', HC-4") 3.75 (1H, t, $J = 5.5$ Hz, HC-1'), 3.57 (1H, br s, HOC-1'), 3.41 (6H, s, H$_3$CO $\times 2$), 3.02 (2H, dd, $J = 12$, 13 Hz, HC-2', HC-2") 2.95 (2H, ddd, $J = 2$, 13, 13 Hz, HC-6', HC-6") 2.51 (2H, br d, $J = 13$ Hz, HC-2', HC-2") 2.36-2.30 (2H, m, HC-5', HC-5") 2.30-2.24 (2H, m, HC-6', HC-6") 2.02-1.97 (2H, m, HC-3', HC-3") 1.76 (2H, dddd, $J = 1.5$, 2, 12.5, 13 Hz, HC-5', HC-5")

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 95.02 (t $\times 2$), 76.41 (d), 74.48 (d $\times 2$), 56.41 (q $\times 2$), 43.58 (d $\times 2$), 31.60 (t $\times 2$), 23.54 (t $\times 2$), 22.39 (t $\times 2$);

LRMS (EI), m/z (relative intensity): 352 ([M]$^+$, 33), 334 (27), 159 (56), 129 (47), 101 (44), 100 (71), 99 (100), 67 (23).

HRMS m/z calcd for C$_{15}$H$_{28}$O$_5$S$_2$ 352.1378, found 352.1374 (EI).

$(3'S^*, 4R^*, 4a R^*, 4'R^* 8a R^*)$-4a,7,8,8a-Tetrahydro-4-[tetrahydro-4- (methoxymethoxy)-2H-thiopyran-3-yl]-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-2-one (225).

Following General procedure H, the trans diol 223 (9 mg, 0.029 mmol) gave the titled carbonate (8 mg, 82%) after fractionation by PTLC (70% ethyl acetate in hexane):

IR $\nu_{\max }$ 2922, 1743, 1234, 1181, 1124, 1112, 1093, 1027 cm$^{-1}$;

$^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.72 (1H, d, $J = 7$ Hz, H$_2$CO), 4.61 (1H, d, $J = 7$ Hz, H$_2$CO), 4.53 (1H, dd, $J = 4.5$, 6.5 Hz, HC-4 [3$J_{HC-4HC-4a} = 4.5$ Hz]), 4.31 (1H, ddd, $J = 4.5$, 11, 11 Hz, HC-8a), 3.68 (1H, br s, HC-4'), 3.44 (3H, s, H$_3$CO), 3.16 (1H, dd, $J = 12.5$, 14 Hz, HC-2'), 3.00 (1H, dd, $J = 11.5$, 12.5 Hz, HC-6'), 2.78 (1H, ddd, $J = 2.5$, 254
12.5, 14 Hz, HC-5, HC-7), 2.75-2.65 (2H, m, HC-5, HC-7), 2.59-2.49 (3H, m, HC-4a, HC-8), 2.33-2.22 (4H, m, HC-3', HC-5', HC-2', HC-6'), 1.92 (1H, dddd, J = 4, 11, 12.5, 12.5 Hz, HC-8), 1.82-1.74 (1H, m, HC-5');

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 147.78 (s), 95.62 (t), 77.43 (d), 73.16 (d), 56.57 (q), 44.13 (d), 42.88 (d), 34.24 (t), 31.29 (t), 28.19 (t), 27.06 (t), 24.45 (t), 21.96 (t);

LRMS (EI), m/z (relative intensity): 334 ([M]$^+$, 100), 289 (16), 227 (47), 139 (42), 137 (41), 129 (31), 101 (36), 99 (84).

HRMS m/z calcd for C$_{14}$H$_{22}$O$_5$S$_2$ 334.0909, found 334.0911 (EI).

$(1'S^*, 3S^*, 3''R^*, 4R^*, 4''R^*)$-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl]methyl)tetrahydrothiopyran-4-ol (226) and $(1'S^*, 3S^*, 3''R^*, 4S^*, 4''R^*)$-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl]methyl)tetrahydro-2H-thiopyran-4-ol (227).

Following General procedure D, the NaBH$_4$ reduction of aldol 127b (252 mg, 0.823 mmol) gave the trans alcohol 227 (73 mg, 29%) and the cis alcohol 226 (124 mg, 49%) after fractionation by MPC (40% ethyl acetate in hexane).

Data for 226:

IR $\nu_{\text{max}}$ 3378, 2922, 1426, 1286, 1151, 1091, 1030, 923 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.77 (1H, d, J = 7 Hz, H$_2$CO), 4.66 (1H, d, J = 7 Hz, H$_2$CO), 4.17 (1H, dddd, J = 3, 3, 4.5, 6 Hz, HC-4), 4.02 (1H, dddd, J = 1.5, 2, 3 Hz, HC-4$''$), 3.97 (1H, dddd, J = 2.5, 3, 7 Hz, HC-1$'$), 3.55 (1H, d, J = 2.5 Hz, HOC-1$'$), 3.43 (3H, s, H$_3$CO), 3.13 (1H, d, J = 4.5 Hz, HOC-4), 3.08 (1H, dd, J = 11.5, 13.5 Hz, HC-2$''$), 3.02-2.90 (3H, m, HC-2, HC-6, HC-6$''$), 2.50 (1H, br d, J = 13.5 Hz, HC-2$''$), 2.45-2.29 (4H, m, HC-2,HC-5$''$, HC-6, HC-6$''$), 2.15 (1H, dddd, J = 3, 6, 6, 14 Hz, HC-5), 2.07 (1H, dddd, J = 3, 3, 7, 10 Hz, HC-3), 1.98 (1H, dddd, J = 1.5, 3, 3, 11.5 Hz, HC-3$''$),
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 94.98, 77.17, 76.17, 67.63, 56.48, 44.13, 42.53, 34.23, 31.40, 27.33, 24.12, 22.98, 22.53;
LRMS (EI), m/z (relative intensity): 308 ([M]$^+$, 71), 290 (20), 159 (31), 129 (54), 117 (33), 101 (48), 100 (100), 99 (96).
HRMS m/z calc'd for C$_{13}$H$_{24}$O$_4$S$_2$ 308.1116, found 308.1119 (EI).

Data for 227:

IR $\nu_{\max}$ 3431, 2928, 1428, 1153, 1095, 1072, 1024, 919 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.99 (1H, s, HO), 4.79 (1H, d, $J=7$ Hz, H$_2$CO), 4.68 (1H, d, $J=7$ Hz, H$_2$CO), 4.30 (1H, s, HO), 4.09 (1H, br s, HC-4"), 3.80 (1H, d, $J=9.5$ Hz, HC-1''), 3.62 (1H, ddd, $J=4$, 10, 10 Hz, HC-4), 3.44 (3H, s, H$_3$CO), 3.15 (1H, dd, $J=12$, 14 Hz, HC-2''), 2.93 (1H, ddd, $J=2.5$, 13, 13 Hz, HC-6''), 2.69-2.60 (2H, m, H$_2$C-6), 2.51 (1H, dd, $J=2$, 14 Hz, HC-2), 2.42 (1H, dd, $J=2$, 14 Hz, HC-2''), 2.39 (1H, dddd, $J=3.5$, 3.5, 3.5, 14 Hz, HC-5''), 2.34-2.26 (3H, m, HC-2, HC-5, HC-6''), 2.01 (1H, br d, $J=12$ Hz, HC-3''), 1.88-1.77 (2H, m, HC-3, HC-5''), 1.74 (1H, dddd, $J=5.5$, 11, 11, 14 Hz, HC-5);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 94.82, 82.02, 77.49, 73.80, 56.61, 46.36, 43.40, 36.12, 31.37, 29.57, 27.47, 22.39, 21.86;
LRMS (EI), m/z (relative intensity): 308 ([M]$^+$, 72), 159 (46), 129 (69), 117 (52), 101 (48), 100 (100), 99 (100), 67 (33).
HRMS m/z calc'd for C$_{13}$H$_{24}$O$_4$S$_2$ 308.1116, found 308.1117 (EI)

(3'S*, 3"S*, 4'R*, 4"R*)-Bis[tetrahydro-4-hydroxy-2H-thiopyran-3-yl]methanol (228).
From 226: Following General procedure J for hydrolysis of MOM ethers, 226 (20 mg, 0.065 mmol) gave the titled triol (10 mg, 58%) after fractionation by MPC (80% ethyl acetate in hexane).

From 230: Following General procedure J for hydrolysis of MOM ethers, 230 (31 mg, 0.10 mmol) gave the titled triol (17 mg, 64%) after fractionation by MPC (80% ethyl acetate in hexane):

IR $\nu_{max}$ 3356, 2913, 1425, 1285, 1179, 1053, 924, 732 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.25-4.21 (1H, br s, HC-4'/HC-4'”), 4.16 (1H, dd, $J$ = 2, 8.5 Hz, HC-1), 4.08 (1H, ddd, $J$ = 3, 3, 7.5 Hz, HC-4''/HC-4”), 3.88 (1H, s, HOC-1), 3.18 (1H, dd, $J$ = 12, 13.5 Hz, HC-2''/HC-2'”), 3.11 (1H, ddd, $J$ = 2.5, 13, 13 Hz, HC-6''/HC-6”), 2.90 (1H, ddd, $J$ = 2.5, 9.5, 12.5 Hz, HC-6''/HC-6’), 2.84 (1H, br s, HOC-4''/HOC-4”), 2.78 (1H, br dd, $J$ = 8.5, 14 Hz, HC-2''/HC-2’), 2.78 (1H, br s, HOC-4''/HOC-4”), 2.50 (1H, ddd, $J$ = 3.5, 7.5, 13 Hz, HC-6''/HC-6’), 2.41 (1H, dd, $J$ = 3, 14 Hz, HC-2''/HC-2’), 2.32 (1H, br d, $J$ = 13 Hz, HC-2’/HC-2”), 2.30-2.25 (1H, m, HC-6’/HC-6’”), 2.20-2.05 (3H, m, HC-5”/HC-5’), 2.03-1.94 (2H, m, HC-5”/HC-5’), 1.94-1.89 (1H, m, HC-5’/HC-5”);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 77.04 (d), 71.34 (d), 68.89 (d), 43.27 (d), 42.19 (d), 35.78 (t), 33.68 (t), 27.76 (t), 24.95 (t), 22.09 (t), 21.31 (t);

LRMS (EI), $m/z$ (relative intensity): 264 ([M]$^+$, 72), 228 (10), 157 (20), 129 (48), 117 (54), 101 (43), 100 (100), 99 (51).

HRMS $m/z$ calcd for C$_{11}$H$_{20}$O$_3$S$_2$ 264.0854, found 264.0856 (EI).

(3'S*, 4R*, 4aS*, 4'R* 8aS*)-4a,7,8,8a-Tetrahydro-4-[tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-yl]-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-2-one (229).
Following General Procedure G, the trans diol 227 (18 mg, 0.058 mmol) gave the titled carbonate (14 mg, 71%) after fractionation by FCC (70% ethyl acetate in hexane):

IR $\nu_{\text{max}}$ 2924, 1749, 1217, 1156, 1118, 1095, 1033, 916 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.72 (1H, d, $J = 7$ Hz, H$_2$CO), 4.66 (1H, d, $J = 7$ Hz, H$_2$CO), 4.20 (1H, dd, $J = 4$, 10 Hz, HC-4 $[^2J_{\text{HC-4/HC-4a}} = 10$ Hz]), 4.01 (1H, dddd, $J = 4$, 11, 11 Hz, HC-8a), 3.94-3.92 (1H, br s, HC-4'), 3.43 (3H, s, H$_3$CO), 3.17 (1H, dd, $J = 11.5$, 13.5 Hz, HC-2'), 3.03 (1H, ap dd, $J = 11$, 12.5 Hz, HC-6'), 2.83 (1H, dddd, $J = 2.5$, 3, 13.5 Hz, HC-5), 2.79 (1H, dddd, $J = 2$, 12.5, 14 Hz, HC-7), 2.72 (1H, dddd, $J = 2.5$, 3, 4, 14 Hz, HC-7), 2.48 (1H, dd, $J = 11$, 13.5 Hz, HC-5), 2.50-2.44 (1H, m, HC-8), 2.40 (1H, br d, $J = 13.5$ Hz, HC-2'), 2.36-2.30 (2H, m, HC-5', HC-6'), 2.22-2.17 (1H, m, HC-3'), 2.20 (1H, dddd, $J = 3$, 10, 11, 11 Hz, HC-4a), 1.91 (1H, dddd, $J = 4$, 11, 12.5, 12.5 Hz, HC-8), 1.86-1.77 (1H, m, HC-5');

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 148.83, 95.71, 84.85, 79.36, 73.60, 56.54, 46.82, 42.24, 33.11, 32.20, 29.55, 27.07, 23.76, 22.89;

LRMS (EI), m/z (relative intensity): 334 ([M]+, 100), 271 (33), 227 (53), 139 (46), 137 (61), 99 (83), 85 (32), 67 (46).

HRMS m/z calcd for C$_{14}$H$_{22}$O$_2$S$_2$ 334.0909, found 334.0903 (EI).


Following General procedure D, the NaBH$_4$ reduction of aldol 128b (34 mg, 0.11 mmol) gave the trans alcohol 231 (9 mg, 26%) and the cis alcohol 230 (17 mg, 49%).

Data for 230:
\[ \text{IR} \ \nu_{\text{max}} \ 3401, 2928, 1426, 1201, 1149, 1095, 1037, 923 \text{ cm}^{-1}; \]

\[ ^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \ \delta \ 4.66 (1\text{H, d, } J = 6 \text{ Hz, H}_2\text{CO}), 4.64 (1\text{H, d, } J = 6 \text{ Hz, H}_2\text{CO}), 4.17 (1\text{H, br ddd, } J = 2, 2, 4 \text{ Hz, HC-4}), 4.04 (1\text{H, ddd, } J = 2.5, 2.5, 5.5 \text{ Hz, HC-4}), 3.86 (1\text{H, dd, } J = 1.5, 10 \text{ Hz, HC-1}), 3.42 (3\text{H, s, H}_3\text{CO}), 3.24-3.15 (2\text{H, m}), 2.91 (1\text{H, dddd, } J = 2, 12, 13.5 \text{ Hz}), 2.70 (1\text{H, dd, } J = 10.5, 13.5 \text{ Hz, HC-2}), 2.28 (1\text{H, dd, } J = 2.5, 13 \text{ Hz}), 2.26-2.15 (4\text{H, m}), 1.96 (1\text{H, dddd, } J = 2.5, 3, 10, 10.5 \text{ Hz, HC-3}), 1.93-1.78 (3\text{H, m}); \]

\[ ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \ \delta \ 96.06, 76.49, 72.52, 71.19, 56.08, 43.10, 42.56, 35.14, 31.17, 25.72, 23.25, 22.09, 20.75; \]

\[ \text{LRMS} \ (\text{EI}), \ m/z \ (\text{relative intensity}): \ 308, ([M]^+ \ 83), 290 (24), 159 (52), 129 (48), 117 (39), 101 (51), 100 (100), 99 (81). \]

\[ \text{HRMS} \ m/z \ \text{calcd for C}_{13}\text{H}_{24}\text{O}_4\text{S}_2 \ 308.1116, \ \text{found 308.1114 (EI)}. \]

\[ \text{Data for 231:} \]

\[ \text{IR} \ \nu_{\text{max}} \ 3430, 2927, 1427, 1281, 1147, 1103, 1041, 917 \text{ cm}^{-1}; \]

\[ ^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \ \delta \ 4.68 (1\text{H, d, } J = 6.5 \text{ Hz, H}_2\text{CO}), 4.64 (1\text{H, d, } J = 6.5 \text{ Hz, H}_2\text{CO}), 4.22 (1\text{H, dd, } J = 2, 10 \text{ Hz, HC-1}), 4.11 (1\text{H, ddd, } J = 2, 2.5, 2.5 \text{ Hz, HC-4}), 3.73 (1\text{H, dddd, } J = 4, 10, 10 \text{ Hz, HC-4}), 3.42 (3\text{H, s, H}_3\text{CO}), 2.80-2.66 (3\text{H, m}), 2.95 (1\text{H, br dd, } J = 12.5, 12.5 \text{ Hz, HC-6}), 2.61 (1\text{H, dddd, } J = 3, 3, 3, 13.5 \text{ Hz}), 2.54 (1\text{H, ddd, } J = 2.5, 2.5, 14 \text{ Hz}), 2.38-2.32 (2\text{H, m}), 2.30-2.22 (3\text{H, m}), 1.92 (1\text{H, dddd, } J = 3, 3, 10.5, 10.5 \text{ Hz, HC-3}), 1.82 (1\text{H, dddd, } J = 2, 3.5, 10.5, 10.5 \text{ Hz, HC-5}), 1.80-1.67 (3\text{H, m}); \]

\[ ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \ \delta \ 96.28, 72.98, 70.13, 67.93, 56.21, 47.69, 43.44, 37.90, 31.57, 27.95, 26.51, 25.37, 23.09; \]

\[ \text{LRMS} \ (\text{EI}), \ m/z \ (\text{relative intensity}): \ 308 (79), 290 (21), 159 (57), 129 (65), 117 (48), 101 (48), 100 (100), 99 (82). \]

\[ \text{HRMS} \ m/z \ \text{calcd for C}_{13}\text{H}_{24}\text{O}_4\text{S}_2 \ 308.1116, \ \text{found 308.1113 (EI)}. \]
(3'S*, 4'S*, 4aS*, 4'R* 8aS*)-4a,7,8,8a-Tetrahydro-4-[tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-yl]-4H,5H-thiopyran[4,3-d]-1,3-dioxin-2-one (232).

Following General procedure G, the trans diol 231 (30 mg, 0.097 mmol) gave the carbonate (20 mg, 61%) after fractionation by FCC (40% ethyl acetate in hexane):

**IR** \( \nu_{\text{max}} \): 1745, 1427, 1368, 1234, 1177, 1113, 1027, 918 cm\(^{-1} \);

**\(^1\)H NMR** (500 MHz, CDCl\(_3\) @ 40 °C) \( \delta \):
- 4.78 (1H, d, \( J = 7 \) Hz, H\(_2\)CO), 4.71 (1H, d, \( J = 7 \) Hz, H\(_2\)CO), 4.48 (1H, dd, \( J = 3.5, 9 \) Hz, HC-4 [\( ^3J_{\text{HC-4/HC-4a}} = 3.5 \) Hz]), 4.33 (1H, ddd, \( J = 4, 11, 11 \) Hz, HC-8a), 3.92 (1H, br s, HC-4'), 3.41 (3H, s, H\(_3\)CO), 3.04-2.98 (1H, m, HC-6'), 2.88 (1H, dd, \( J = 10.5, 13 \) Hz, HC-2'), 2.79 (1H, ddd, \( J = 2.5, 12.5, 14 \) Hz, HC-7), 2.75-2.68 (1H, m, HC-7), 2.66-2.56 (3H, m, HC-4a, H\(_2\)C-5), 2.52 (1H, dddd, \( J = 3, 3.5, 4, 13 \) Hz, HC-8), 2.45-2.33 (3H, m, HC-5', HC-6', HC-2'), 2.23 (1H, dddd, \( J = 2.5, 3, 9, 9.5 \) Hz, HC-3'), 1.93 (1H, dddd, \( J = 4, 11.5, 12.5, 13 \) Hz, HC-8), 1.91-1.84 (1H, m, HC-5');

**\(^{13}\)C NMR** (125 MHz, CDCl\(_3\) \( \delta \): 147.82 (s), 96.80 (t), 80.07 (d), 77.26 (d), 73.36 (d), 56.30 (q), 43.18 (d), 42.94 (d), 34.46 (t), 32.20 (t), 28.77 (t), 27.62 (t), 27.15 (t), 23.93 (t);

**LRMS** (EI), \( m/z \) (relative intensity): 334 ([M]\(^+\), 82), 227 (39), 139 (57), 138 (38), 137 (53), 101 (47), 99 (100), 67 (78).

**HRMS** \( m/z \) calcd for C\(_{14}\)H\(_{22}\)O\(_5\)S\(_2\) 334.0909, found 334.0910 (EI).

Following General procedure E, the NaCNBH₃ reduction of aldol 129b gave the trans alcohol 234 (13 mg, 29%) and the cis alcohol 233 (18 mg, 41%) after fractionation by MPC (40% ethyl acetate in hexane).

Data for 233:

**IR** \( \nu_{\text{max}} \) 3346, 2921, 1423, 1209, 1143, 1107, 1043, 926 cm\(^{-1}\);

**\(^1\)H NMR** (400 MHz, CDCl₃) \( \delta \) 3.51 (1H, d, \( J = 6.5 \) Hz, H₂CO), 4.64 (1H, d, \( J = 6.5 \) Hz, H₂CO), 4.34 (1H, br t, \( J = 1.5 \) Hz, HC-4), 4.25 (1H, d, \( J = 4.5 \) Hz, HOC-1'), 4.14 (1H, ddd, \( J = 2.5, 3, 5.5 \) Hz, HC-4''), 3.87 (1H, s, HOC-4), 3.74 (1H, ddd, \( J = 2.5, 4.5, 8.5 \) Hz, HC-1'), 3.41 (3H, s, H₃CO), 3.41 (1H, dd, \( J = 12, 13 \) Hz, HC-2), 3.17 (1H, ddd, \( J = 2.5, 13, 13 \) Hz, HC-6), 2.93 (1H, ddd, \( J = 2.5, 12, 13 \) Hz, HC-6''), 2.77 (1H, dd, \( J = 10.5, 13.5 \) Hz, HC-2''), 2.37 (1H, ddd, \( J = 3.5, 3.5, 13 \) Hz, HC-6''), 2.30-2.13 (4H, m, HC-2''HC-5, HC-5'', HC-6), 2.12-2.04 (2H, m, HC-2, HC-3''), 1.90 (1H, br d, \( J = 12 \) Hz, HC-3), 1.88-1.74 (2H, m, HC-5, HC-5'');

**\(^1\)C NMR** (100 MHz, CDCl₃) \( \delta \) 96.05 (t), 76.51 (d), 72.92 (d), 65.90 (d), 56.18 (q), 43.43 (d), 42.24 (d), 34.86 (t), 31.33 (t), 26.77 (t), 25.96 (t), 23.22 (t), 22.50 (t);

**LRMS** (EI), \( m/z \) (relative intensity): 308 ([M]+, 69), 290 (43), 159 (46), 129 (56), 117 (37), 101 (54), 100 (100), 99 (82).

**HRMS** \( m/z \) calcd for C₁₃H₂₄O₄S₂ 308.1116, found 308.1115 (EI).

Data for 234:

**IR** \( \nu_{\text{max}} \) 3429, 2925, 1428, 1177, 1149, 1091, 1037, 918 cm\(^{-1}\);

**\(^1\)H NMR** (500 MHz, CDCl₃) \( \delta \) 4.82 (1H, s, HOC-4), 4.77 (1H, d, \( J = 7 \) Hz, H₂CO), 4.69 (1H, d, \( J = 7 \) Hz, H₂CO), 4.33 (1H, d, \( J = 8 \) Hz, HOC-1'), 4.30 (1H, ddd, \( J = 2, 2, 4 \) Hz, HC-4), 4.25 (1H, ddd, \( J = 2.5, 7, 13 \) Hz, HC-6), 3.87 (1H, ddd, \( J = 2.5, 4.5, 13 \) Hz, HC-4), 3.74 (1H, s, HOC-4), 3.41 (3H, s, H₃CO), 3.41 (1H, dd, \( J = 12, 13 \) Hz, HC-2), 3.17 (1H, ddd, \( J = 2.5, 13, 13 \) Hz, HC-6), 2.93 (1H, ddd, \( J = 2.5, 12, 13 \) Hz, HC-6''), 2.77 (1H, dd, \( J = 10.5, 13.5 \) Hz, HC-2''), 2.37 (1H, ddd, \( J = 3.5, 3.5, 13 \) Hz, HC-6''), 2.30-2.13 (4H, m, HC-2''HC-5, HC-5'', HC-6), 2.12-2.04 (2H, m, HC-2, HC-3''), 1.90 (1H, br d, \( J = 12 \) Hz, HC-3), 1.88-1.74 (2H, m, HC-5, HC-5'');

**\(^1\)C NMR** (100 MHz, CDCl₃) \( \delta \) 96.05 (t), 76.51 (d), 72.92 (d), 65.90 (d), 56.18 (q), 43.43 (d), 42.24 (d), 34.86 (t), 31.33 (t), 26.77 (t), 25.96 (t), 23.22 (t), 22.50 (t);
Hz, HC-4”), 3.66 (1H, ddd, J = 4, 10, 10 Hz, HC-4), 3.60 (1H, ddd, J = 5, 8, 8 Hz, HC-1’), 3.46 (3H, s, H3CO), 3.20 (1H, dd, J = 11.5, 13.5 Hz, HC-2”), 2.95 (1H, ddd, J = 2.5, 13, 15 Hz, HC-6”), 2.69 (1H, ddd, J = 2.5, 12.5, 13.5 Hz, HC-6), 2.62 (1H, ddd, J = 4, 13.5 Hz, HC-6), 2.42-2.26 (6H, m), 2.14 (1H, ddd, J = 2, 2, 4.5, 12 Hz, HC-5”), 1.89 (1H, m), 1.80-1.70 (2H, m);

13C NMR (500 MHz, CDCl3) δ 95.23, 80.42, 74.05, 72.45, 56.92, 47.43, 43.75, 36.47, 31.17, 30.05, 27.55, 26.28, 22.56;

LRMS (EI), m/z (relative intensity): 308 ([M]+, 46), 290 (41), 159 (74), 129 (89), 117 (54), 101 (59), 99 (100), 85 (46).

HRMS m/z calcd for C13H24O4S2 308.1116, found 308.1124 (EI).

(1s, 3’S*, 3”R*, 4’R*, 4”S*)-Bis[tetrahydro-4-hydroxy-2H-thiopyran-3-yl]methanol (235).

Following General procedure J for hydrolysis of MOM ethers, diol 233 (13 mg, 0.042 mmol) gave the titled triol (8 mg, 71%) after fractionation by MPC (80% ethyl acetate in hexane):

IR νmax 3367, 2917, 1423, 1274, 1202, 1135, 1061, 925 cm⁻¹;

1H NMR (400 MHz, CDCl3) δ 4.30 (2H, ddd, J = 2.5, 3, 6 Hz, HC-4’, HC-4”), 4.11 (1H, br t, J = 6 Hz, HC-1), 4.11 (1H, br s, HOC-1), 3.13 (2H, br s, HOC-4’, HOC-4”), 3.07 (2H, dd, J = 10, 13.5 Hz, HC-2’, HC-2”), 3.02 (2H, ddd, J = 3, 11, 13.5 Hz, HC-6’, HC-6”), 2.40 (2H, dddd, J = 1, 3.5, 5, 13.5 Hz, HC-6’, HC-6”), 2.31 (2H, ddd, J = 1, 2, 13.5 Hz, HC-2’, HC-2”), 2.16 (2H, dddd, J = 3, 5, 6, 14 Hz, HC-5’, HC-5”), 2.10-2.03 (2H, dddd, J = 2, 3, 6, 10 Hz, HC-3’, HC-3”), 1.93 (2H, dddd, J = 2.5, 3.5, 11, 14 Hz, HC-5’, HC-5”);

13C NMR (100 MHz, CDCl3) δ 76.61 (×2), 67.82, 42.29 (×2), 34.44 (×2), 27.03 (×2), 23.70 (×2);
LRMS (EI), m/z (relative intensity): 264 ([M]+, 66), 129 (47), 117 (51), 101 (44), 100 (100), 99 (49), 87 (54), 57 (47).

HRMS m/z calcd for C_{11}H_{20}O_{3}S_{2} 264.0854, found 264.0859 (EI).

(3'S*, 4S*, 4aR*, 4'R* 8aR*)-4a,7,8,8a-Tetrahydro-4-[tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-yl]-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-2-one (236).

Following General procedure G, the trans diol 234 (14 mg, 0.045 mmol) gave the titled carbonate (12 mg, 79%) after fractionation by FCC (35% ethyl acetate in hexane):

IR ν_{max} 1753, 1428, 1220, 1197, 1158, 1095, 1029, 918 cm⁻¹;

^1H NMR (500 MHz, CDCl₃) δ 4.72 (1H, d, J = 6.5 Hz, H₂CO), 4.70 (1H, d, J = 6.5 Hz, H₂CO), 4.25 (1H, br s, HC-4'), 4.13 (1H, dd, J = 8, 8.5 Hz, HC-4 [^3]J_{HC-4/HC-4a} = 8.5 Hz]), 3.99 (1H, ddd, J = 4, 11, 11 Hz, HC-8a), 3.41 (3H, s, H₃CO), 3.06 (1H, dd, J = 11, 13 Hz, HC-2'), 3.06-3.00 (1H, m, HC-6'), 2.80 (1H, ddd, J = 2.5, 12.5, 14 Hz, HC-7), 2.73 (1H, ddd, J = 2.5, 3, 4, 14 Hz, HC-7), 2.63 (1H, ddd, J = 2, 3.5, 14 Hz, HC-5), 2.55 (1H, d, J = 11, 14 Hz, HC-5), 2.48 (1H, ddd, J = 3, 3.5, 4, 13 Hz, HC-8), 2.41 (1H, dddd, J = 3, 3, 4, 14.5 Hz, HC-5'), 2.31 (1H, ddd, J = 2, 3, 13 Hz, HC-6'), 2.24 (1H, br d, J = 2, 2.5, 13 Hz, HC-2'), 2.18 (1H, dddd, J = 3.5, 8.5, 11, 11 Hz, HC-4a), 2.05 (1H, dddd, J = 2.5, 3, 8, 11 Hz, HC-3'), 1.92 (1H, dddd, J = 4, 11, 12.5, 13 Hz, HC-8), 1.76 (1H, dddd, J = 1.5, 4, 12.5, 14.5 Hz, HC-5');

^13C NMR (125 MHz, CDCl₃) δ 149.44 (s), 96.32 (t), 82.98 (d), 78.57 (d), 70.37 (d), 56.32 (q), 48.25 (d), 42.65 (d), 32.92 (t), 31.98 (t), 30.84 (t), 27.14 (t), 24.25 (t), 22.41 (t);

LRMS (EI), m/z (relative intensity): 334 ([M]+, 86), 271 (70), 227 (22), 201 (26), 139 (41), 137 (45), 99 (100), 67 (78).
HRMS m/z calcd for C_{14}H_{22}O_{3}S_{2} 334.0909, found 334.0911 (EI).

\[(1'S^*, 3'R^*, 3''R^*, 4'R^*, 4''S^*)-3-\text{(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl]methyl)}\text{tetrahydro-2H-thiopyran-4-ol (237).}\]

Following General procedure F, the NaBH(OAc)₃ reduction of aldol 126c (21 mg, 0.069 mmol) gave the trans alcohol 237 (17 mg, 80%) after fractionation by PTLC (60% ethyl acetate in hexane):

IR \( \text{v}_{\text{max}} \) 3432, 2927, 1429, 1279, 1147, 1095, 1027, 916 cm\(^{-1}\);

\(^1H\) NMR (400 MHz, CDCl₃) \( \delta \) 4.72 (1H, d, \( J = 6.5 \text{ Hz, H}_2\text{CO} \)), 4.72-4.68 (1H, m, H-C'1'), 4.64 (1H, d, \( J = 6.5 \text{ Hz, H}_2\text{CO} \)), 3.78 (1H, br ddd, \( J = 3.5, 8, 8 \text{ Hz, HC-4} \)), 3.56 (1H, ddd, \( J = 3.5, 8, 8 \text{ Hz, HC-4''} \)), 3.45 (3H, s, H₃CO), 2.92-2.75 (5H, m), 2.69 (1H, dd, \( J = 13.5, 14 \text{ Hz} \)), 2.67 (1H, dd, \( J = 13.5, 14 \text{ Hz} \)), 2.59-2.49 (2H, m), 2.22-2.13 (2H, m), 1.93-1.85 (5H, m);

\(^{13}C\) NMR (100 MHz, CDCl₃) \( \delta \) 96.20, 75.70, 68.79, 67.00, 56.41, 45.81, 44.76, 34.88, 32.41, 26.48, 26.48, 26.17, 25.50;

LRMS (EI), m/z (relative intensity): 308 ([M]+, 88), 159 (41), 129 (94), 117 (65), 101 (57), 100 (100), 99 (66), 67 (35).

HRMS m/z calcd for C_{13}H_{24}O_{4}S_{2} 308.1116, found 308.1115 (EI).

\[(1r, 3'S^*, 3''R^*, 4'S^*, 4''R^*)-\text{Bis[tetrahydro-4-hydroxy-2H-thiopyran-3-yl]methanol (238).}\]

Following General procedure J for hydrolysis of MOM ethers, diol 237 (20 mg, 0.065 mmol) gave the titled triol (13 mg, 75%) after trituration with CH₂Cl₂.

IR \( \text{v}_{\text{max}} \) 3377, 2925, 1429, 1280, 1029, 956 cm\(^{-1}\);
\( ^1\text{H NMR} \) (500 MHz, CD\(_3\)OD) \( \delta \) 4.77 (1H, t, \( J = 6 \) Hz, HC-1), 3.66 (2H, ddd, \( J = 3.5, 7.5, 8 \) Hz, HC-4', HC-4''), 2.85 (2H, br d, \( J = 13.5 \) Hz, HC-2', HC2''), 2.76 (2H, ddd, \( J = 1, 3.5, 6.5, 12.5 \) Hz, HC-6', HC-6''), 2.60 (2H, dd, \( J = 8.5, 13.5 \) Hz, HC-2', HC-2''), 2.48 (2H, dd, \( J = 2.5, 9.5, 12.5 \) Hz, HC-6', HC-6''), 2.15 (2H, dddd, \( J = 2.5, 3.5, 7.5, 13.5 \) Hz, HC-5', HC-5''), 1.78-1.71 (4H, m, HC-3', HC-3'', HC-5', HC-5'');

\( ^{13}\text{C NMR} \) (75 MHz, CD\(_3\)OD) \( \delta \) 69.2 (x 2), 67.5, 47.4 (x 2), 35.8 (x 2), 27.1 (x 2), 26.5 (x 2);

\( \text{LRMS} \) (EI), \( m/z \) (relative intensity): 264 ([M]+, 76), 129 (87), 117 (100), 100 (94), 99 (46), 87 (52), 83 (41), 57 (63).

\( \text{HRMS} \) \( m/z \) calcd for C\(_{11}\)H\(_{20}\)O\(_5\)S\(_2\) 264.0854, found 264.0858 (EI).

(3'S*, 4R*, 4aR*, 4'S* 8aR*)-4a,7,8,8a-Tetrahydro-4-[tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-yl]-4H,5H-thiopyrano [4,3-d]-1,3-dioxin-2-one (239).

Following General procedure H, the trans diol 237 (23 mg, 0.075 mmol) gave the titled carbonate (12 mg, 48%) after fractionation by PTLC (80% ethyl acetate in hexane):

\( \text{IR} \ \nu_{\text{max}} \) 2922, 1749, 1386, 1244, 1182, 1089, 1026, 916 cm\(^{-1}\);

\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \) 5.08 (1H, dd, \( J = 2, 7 \) Hz, HC-4 [\( ^3 J_{\text{HC-4/HC-4a}} = 7 \) Hz]), 4.73 (1H, d, \( J = 7 \) Hz, H\(_2\)CO), 4.68 (1H, d, \( J = 7 \) Hz, H\(_2\)CO), 4.26 (1H, ddd, \( J = 4.5, 11, 11 \) Hz, HC-8a), 3.56 (1H, ddd, \( J = 4, 10, 10.5 \) Hz, HC-4'), 3.39 (3H, s, H\(_3\)CO), 2.86-2.48 (11H, m, H\(_2\)C-2', HC-4a, H\(_2\)C-5, HC-5', H\(_2\)C-6', H\(_2\)C-7, HC-8), 1.99 (1H, dddd, \( J = 2, 3, 10, 11 \) Hz, HC-3'), 1.87 (1H, dddd, \( J = 4.5, 11, 12.5, 12.5 \) Hz, HC-8), 1.72 (1H, m, \( J = 3.5, 10.5, 13, 13 \) Hz, HC-5');
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 148.28, 96.16, 77.88, 77.85, 76.50, 56.15, 45.75, 41.92, 34.95, 34.27, 28.70, 27.98, 27.60, 26.92;

LRMS (EI), $m/z$ (relative intensity): 304 ([M]$^+$, 69), 272 (38), 201 (37), 139 (59), 101 (40), 99 (100), 85 (49), 67 (60).

HRMS $m/z$ calcd for C$_{14}$H$_{22}$O$_5$S$_2$ 334.0909, found 334.0906 (EI).

Following General procedure D, the NaBH$_4$ reduction of aldol 127c (310 mg, 1.01 mmol) gave the trans alcohol 241 (143 mg, 46%) and the cis alcohol 240 (85 mg, 27%) after fractionation by DFC (10-70% ethyl acetate in hexane).

Data for 240:

IR $\nu_{\text{max}}$ 3429, 2926, 1426, 1146, 1103, 1050, 1026, 924 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.69 (1H, d, $J = 6.5$ Hz, H$_2$CO), 4.64 (1H, d, $J = 6.5$ Hz, H$_2$CO), 4.51 (1H, ddd, $J = 4.5, 5.5, 9$ Hz, HC-1'), 4.13 (1H, dddd, $J = 3, 3, 4.5, 8$ Hz, HC-4), 3.48 (1H, d, $J = 5.5$ Hz, HOC-1'), 3.47 (1H, ddd, $J = 4, 10.5, 10.5$ Hz, HC-4''), 3.44 (3H, s, H$_3$CO), 3.30 (1H, d, $J = 4.5$ Hz, HOC-4), 2.93 (1H, ddd, $J = 3, 9.5, 13$ Hz, HC-6), 2.82 (1H, dd, $J = 9, 13.5$ Hz, HC-2), 2.72-2.59 (4H, m, H$_2$C-2'', H$_2$C-6''), 2.46 (1H, ddd, $J = 3.5, 7, 13.5$ Hz, HC-6), 2.39 (1H, dd, $J = 3, 13.5$ Hz, HC-2), 2.27 (1H, dddd, $J = 3.5, 3.5, 4.5, 13$ Hz, HC-5''), 2.12 (1H, dddd, $J = 3, 7, 8, 13.5$ Hz, HC-5), 2.05 (1H, dddd, $J = 3, 3, 9, 9$ Hz, HC-3), 1.98 (1H, dddd, $J = 3, 3.5, 9.5, 13.5$ Hz, HC-5), 1.89-1.76 (2H, m, HC-3'', HC-5'');

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 96.28 (t), 76.83 (d), 69.32 (d), 68.45 (d), 56.16 (q), 45.87 (d), 41.73 (d), 34.03 (t), 33.78 (t), 27.31 (t), 27.19 (t), 26.22 (t), 24.67 (t);
LRMS (EI), m/z (relative intensity): 308 ([M]+, 75), 159 (24), 129 (53), 117 (52), 101 (54), 100 (100), 99 (71), 67 (36).

HRMS m/z calcd for C_{13}H_{24}O_{4}S_{2} 308.1116, found 308.1120 (EI).

Data for 241:

IR \nu_{\text{max}} 3379, 2928, 1428, 1147, 1103, 1047, 1028, 914 cm^{-1};

^{1} \text{H NMR} \ (500 \ \text{MHz, CDCl}_3) \ \delta \ 4.96 (1\text{H, br s, HOC-4}), 4.66 (1\text{H, d, } J = 6.5 \ \text{Hz, H}_2\text{CO}), 4.64 (1\text{H, d, } J = 6.5 \ \text{Hz, H}_2\text{CO}), 4.30 (1\text{H, d, } J = 3.5 \ \text{Hz, HOC-1'}), 4.15 (1\text{H, ddd, } J = 2.5, 3.5, 10 \ \text{Hz, HC-1'}), 3.61 (1\text{H, ddd, } J = 4, 4, 9, 10.5 \ \text{Hz, HC-4}), 3.43 (1\text{H, ddd, } J = 4, 10, 11 \ \text{Hz, HC-4''}), 3.42 (3\text{H, s, H}_3\text{CO}), 2.73-2.54 (6\text{H, m}), 2.48 (1\text{H, ddd, } J = 2.5, 3.5, 14 \ \text{Hz}), 2.33 (1\text{H, dddd, } J = 3.5, 4, 4.5, 13 \ \text{Hz, HC-5''}), 2.31-2.25 (2\text{H, m}), 1.88-1.71 (4\text{H, m, HC-3, HC-3'', HC-5, HC-5''});

^{13} \text{C NMR} \ (125 \ \text{MHz, CDCl}_3) \ \delta \ 96.30 (t), 77.12 (d), 75.29 (d), 73.96 (d), 55.93 (q), 46.76 (d), 45.49 (d), 36.69 (t), 34.65 (t), 28.74 (t), 27.97 (t), 27.56 (t), 26.27 (t);

LRMS (EI), m/z (relative intensity): 308 ([M]+, 75), 290 (10), 246 (17), 228 (21), 159 (35), 129 (33), 117 (36), 100 (100).

HRMS m/z calcd for C_{13}H_{24}O_{4}S_{2} 308.1116, found 308.1120 (EI).

(3'R^*, 3''R^*, 4'S, 4''S*)-Bis[tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-yl]methanol (242); (3'S*, 3''S*, 4'S*, 4''S*)-Bis[tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-yl](methoxymethoxy)methane (243).

Following General procedure I for MOM ether formation, diol 241 (19 mg, 0.062 mmol) gave, after fractionation by PTLC (60% ethyl acetate in hexane), the bisMOM ether 242 (10 mg, 46%) and the trisMOM ether 243 (11 mg, 45%).

Data for 242

IR \nu_{\text{max}} 3488, 2930, 1429, 1277, 1147, 1097, 1029, 916 cm^{-1};
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.78 (1H, d, $J = 7$ Hz, H$_2$CO), 4.73 (1H, d, $J = 6.5$ Hz, H$_2$CO), 4.70 (1H, d, $J = 6.5$ Hz, H$_2$CO), 4.67 (1H, d, $J = 7$ Hz, H$_2$CO), 4.35 (1H, ddd, $J = 1.5$, 2, 9.5 Hz, HC-1), 3.84 (1H, ddd, $J = 3$, 8, 8 Hz, HC-4'/HC-4"), 3.76 (1H, d, $J = 1.5$ Hz, HO), 3.58 (1H, ddd, $J = 4$, 10.5, 10.5 Hz, HC-4"/HC-4'), 3.43 (3H, s, H$_3$CO), 3.41 (3H, s, H$_3$CO), 2.87 (1H, br d, $J = 13.5$ Hz, HC-2'/HC-2"), 2.83 (1H, m, HC-6'/HC-6"), 2.76 (1H, dd, $J = 11.5$, 13.5 Hz, HC-2"/HC-2'), 2.70 (1H, ddd, $J = 3$, 11, 13 Hz, HC-6"/HC-6'), 2.62 (1H, ddd, $J = 3.5$, 4, 13 Hz, HC-6"/HC-6'), 2.55-2.49 (2H, m, HC-2'/HC-2", HC-6'/HC-6"), 2.39 (1H, dddd, $J = 3$, 3.5, 4, 13 Hz, HC-5'/HC-5'), 2.33-2.25 (2H, m, HC-2'/HC-2", HC-5'/HC-5"), 1.95 (1H, dddd, $J = 3$, 8, 8, 9.5 Hz, HC-3'/HC-3"), 1.89-1.82 (2H, m, HC-3'/HC-3", HC-5'/HC-5"), 1.78 (1H, dddd, $J = 4$, 10, 11, 13 Hz, HC-5'/HC-5");

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 96.63 (t), 95.00 (t), 77.92 (d), 76.83 (d), 69.96 (d), 56.14 (q), 55.98 (q), 46.28 (d), 43.64 (d), 35.02 (t), 31.20 (t), 27.94 (t), 27.58 (t), 26.38 (t), 25.87 (t);

LRMS (EI), m/z (relative intensity): 352 ([M]$^+$, 70), 275 (36), 159 (82), 129 (79), 101 (57), 100 (100), 99 (86), 67 (31).

HRMS m/z calcd for C$_{13}$H$_{28}$O$_5$S$_2$ 352.1378, found 352.1373 (EI).

Data for 243

IR $\nu$$_{max}$ 2933, 2821, 1431, 1211, 1146, 1095, 1029, 916 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.74 (1H, d, $J = 7$ Hz, H$_2$CO), 4.72 (1H, d, $J = 7$ Hz, H$_2$CO), 4.70 (1H, d, $J = 7$ Hz, H$_2$CO), 4.69 (1H, d, $J = 7$ Hz, H$_2$CO), 4.67 (1H, d, $J = 7$ Hz, H$_2$CO), 4.66 (1H, d, $J = 7$ Hz, H$_2$CO), 4.47 (1H, dd, $J = 2.5$, 6.5 Hz, HC-1), 3.71 (1H, ddd, $J = 3.5$, 7.5, 7.5 Hz, HC-4'/HC-4"), 3.49 (1H, ddd, $J = 4$, 10, 10 Hz, HC-4"/HC-4'), 3.41 (3H, s, H$_3$CO), 3.39 (3H, s, H$_3$CO), 3.37 (3H, s, H$_3$CO), 3.02 (1H, br dd, $J = 3$, 13 Hz, HC-2'/HC-2"), 2.83 (1H, br ddd, $J = 3$, 8.5, 13 Hz, HC-6'/HC-6"), 2.70-2.56 (4H, m, H$_2$C-6"/H$_2$C-6'), H$_2$C-2"/HC-2'), 2.50-2.40 (3H, m, HC-5"/HC-5, HC-6'/HC-6", HC-2'/HC-2"), 2.26 (1H, dddd, $J = 3$, 3, 8.5, 13.5 Hz, HC-5'/HC-5"), 2.07 (1H, dddd, $J = 3$, 6.5, 7.5, 7.5 Hz, HC-3'/HC-3"), 1.93-1.85 (2H, m, HC-5'/HC-5", HC-3"/HC-3'), 1.75 (1H, dddd, $J = 4$, 10, 10, 13.5 Hz, HC-5"/HC-5");
\[ ^{13}\text{C NMR} \] (125 MHz, CDCl\(_3\)) \( \delta \) 98.43 (t), 96.65 (t), 96.16 (t), 77.06 (d), 76.98 (br d), 75.02 (br d), 56.19 (q), 56.02 (q), 55.73 (q), 46.07 (d), 44.80 (br d), 34.67 (t), 32.00 (br t), 27.94 (t), 27.91 (br t), 27.43 (t), 25.58 (br t);

LRMS (EI), \( m/z \) (relative intensity): 396 ([M]\(^+\), 10), 289 (21), 272 (21), 257 (26), 173 (100), 159 (41), 129 (32), 99 (42).

HRMS \( m/z \) calcd for C\(_{17}\)H\(_{32}\)O\(_6\)S\(_2\) 396.1640, found 396.1646 (EI).

\[(3'S^*, 4R^*, 4aS^*, 4'S^* 8aS^*)-4a,7,8,8a-Tetrahydro-4-[tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-yl]-4H,5H-thiopyran[4,3-d]-1,3-dioxin-2-one \] (244).

Following General procedure G, the trans diol 241 (11 mg, 0.036 mmol) gave the titled carbonate (9 mg, 75%) after fractionation by DFC (10-60% ethyl acetate in hexane; gradient elution):

IR \( v_{\text{max}} \) 2920, 1746, 1236, 1164, 1094, 1029 cm\(^{-1}\);

\[ ^1\text{H NMR} \] (500 MHz, CDCl\(_3\)) \( \delta \) 4.74 (1H, dd, \( J = 1, 11 \text{ Hz}, \text{HC-4} \left [ J_{\text{HC-4/HC-4a}} = 11 \text{ Hz} \right] \), 4.73 (1H, d, \( J = 6.5 \text{ Hz}, \text{H}_2\text{CO} \)), 4.70 (1H, d, \( J = 6.5 \text{ Hz}, \text{H}_2\text{CO} \)), 4.10 (1H, ddd, \( J = 4, 11, 11 \text{ Hz}, \text{HC-8a} \)), 3.66 (1H, ddd, \( J = 4, 10.5, 10.5 \text{ Hz}, \text{HC-4'} \)), 3.38 (3H, s, H\(_3\text{CO} \)), 2.81-2.40 (4H, m), 2.65 (1H, ddd, \( J = 2, 3.5, 14 \text{ Hz} \)), 2.63-2.40 (5H, m), 2.12 (1H, dddd, \( J = 3.5, 11, 11, 11 \text{ Hz}, \text{HC-4a} \)), 1.97-1.87 (2H, m, HC-8, HC-3'), 1.68 (1H, m, HC-5');

\[ ^{13}\text{C NMR} \] (125 MHz, CDCl\(_3\)) \( \delta \) 148.26, 96.36, 80.31, 79.74, 75.08, 55.99, 45.31, 39.32, 35.17, 33.11, 28.18, 27.68, 27.05, 25.93;

LRMS (EI), \( m/z \) (relative intensity): 334 ([M]\(^+\), 64), 289 (34), 227 (39), 139 (56), 137 (41), 99 (100), 85 (47), 67 (64).

HRMS \( m/z \) calcd for C\(_{14}\)H\(_{22}\)O\(_5\)S\(_2\) 334.0909, found 334.0907 (EI).
Following General procedure C, the DIBAH reduction of aldol 128c (25 mg, 0.81 mmol) gave, after fractionation by PTLC (80% ethyl acetate in hexane), the trans diol 246 (2.5 mg, 10%) and the cis diol 245 (21 mg, 84%):

IR νmax 3419, 2925, 1427, 1276, 1149, 1097, 1033, 1070 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 4.82 (1H, d, J = 7.5 Hz, H₂CO), 4.66 (1H, d, J = 7.5 Hz, H₂CO), 4.57 (1H, br s, HO), 4.19 (1H, br s, HC-4), 3.99 (1H, br s, HO), 3.92 (1H, dd, J = 1.5, 8.5 Hz, HC-1"), 3.66 (1H, ddd, J = 3.5, 10, 10 Hz, HC-4"), 3.43 (3H, s, H₃CO), 3.27 (1H, dd, J = 12.5, 13 Hz), 3.19 (1H, ddd, J = 3, 13, 13 Hz), 2.75-2.67 (2H, m), 2.61 (1H, ddd, J = 3, 11, 14 Hz), 2.40 (1H, ddd, J = 3, 3, 6, 13 Hz), 2.32 (1H, dd, J = 10, 14 Hz), 2.24 (1H, br d, J = 13 Hz), 2.20-2.14 (2H, m), 1.98 (1H, ddd, J = 3, 9, 10, 10 Hz), 1.93-1.82 (2H, m), 1.79 (1H, ddd, J = 3.5, 10.5, 10.5, 13.5 Hz);

¹³C NMR (500 MHz, CDCl₃) δ 94.76, 80.48, 80.03, 70.91, 56.45, 45.81, 43.30, 35.30, 32.61, 28.71, 26.92, 22.20, 20.77;

LRMS (EI), m/z (relative intensity): 308 ([M]+, 93), 159 (37), 129 (60), 117 (47), 101 (58), 100 (100), 99 (83), 67 (35).

HRMS m/z calcd for C₁₃H₂₄O₄S₂ 308.1116, found 308.1113 (EI).

Following General procedure F, the NaBH(OAc)₃ reduction of aldol 128c (30 mg, 0.11 mmol) gave the trans alcohol 246 (24 mg, 72%) after fractionation of the crude product by PTLC (90% ethyl acetate in hexane):
IR $\nu_{\text{max}}$ 3426, 2928, 1430, 1278, 1147, 1097, 1035, 917 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.80 (1H, d, $J = 7$ Hz, H$_2$CO), 4.69 (1H, d, $J = 7$ Hz, H$_2$CO), 4.31 (1H, dd, $J = 2.5, 9$ Hz, HC-1'), 3.84 (1H, br s, HOC-1'), 3.73 (1H, ddd, $J = 3, 8, 9$ Hz, HC-4), 3.71 (1H, ddd, $J = 4, 9.5, 10$ Hz, HC-4''), 3.42 (3H, s, H$_3$CO), 2.80-2.70 (4H, m, HC-2, HC-2'', HC-6, HC-6''), 2.65-2.56 (2H, m, HC-6, HC-2''), 2.50 (1H, ddd, $J = 2.5, 2.5, 14$ Hz, HC-6''), 2.40 (1H, dddd, $J = 3, 3.5, 6.5, 13.5$ Hz, HC-5), 2.37-2.30 (2H, m, HC-2, HC-5''), 1.97 (1H, dddd, $J = 3, 8, 9$ Hz, HC-3), 1.83 (1H, dddd, $J = 3.5, 9, 10.5, 13.5$ Hz, HC-5), 1.77-1.72 (2H, m, HC-3'', HC-5'');

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 95.14, 79.75, 71.16, 69.78, 56.25, 48.10, 44.90, 37.66, 32.27, 28.25, 28.00, 26.51, 26.36;

LRMS (EI), m/z (relative intensity): 308 ([M]$^+$, 78), 159 (45), 129 (94), 117 (60), 101 (52), 100 (100), 99 (71), 67 (36).

HRMS m/z calcd for C$_{13}$H$_{24}$O$_4$S$_2$ 308.1116, found 308.1119 (EI).

(3'S*, 3"S*, 4'S*, 4"S*)-Bis[tetrahydro-4-hydroxy-2H-thiopyran-3-yl]methanol (247).

Following General procedure J for hydrolysis of MOM ethers, 246 (24 mg, 0.078 mmol) gave the titled triol (16 mg, 76%) as a white solid after trituration of the crude product with CH$_2$Cl$_2$:  

IR $\nu_{\text{max}}$ 3374, 3284, 2932, 2907, 2505, 1427, 1052, 1025 cm$^{-1}$;

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 4.33 (1H, dd, $J = 2, 9$ Hz, HC-1'), 3.71 (1H, ddd, $J = 3.5, 9, 9$ Hz, HC-4), 3.54 (1H, ddd, $J = 4, 10.5, 10.5$ Hz, HC-4''), 2.71-2.52 (6H, m, HC-2, HC-6, H$_2$C-2'', H$_2$C-6''), 2.50 (1H, ddd, $J = 2.5, 3, 14$ Hz, HC-6), 2.34-2.27 (2H, m, HC-2, HC-5''), 2.21 (1H, dddd, $J = 3, 3.5, 6, 13.5$ Hz, HC-5), 1.76 (1H, dddd, $J = 3, 9, 9, 9$ Hz, HC-3), 1.75-1.62 (3H, m, HC-3'', HC-5, HC-5'');
$^{13}$C NMR (125 MHz, CDOD) $\delta$ 74.10 (d), 72.97 (d), 70.16 (d), 49.36 (d), 47.24 (d), 38.95 (t), 36.70 (t), 29.04 (t), 28.77 (t), 27.30 (t), 27.28 (t);

LRMS (EI), $m/z$ (relative intensity): 264 ([M]+, 93), 129 (90), 117 (99), 100 (100), 99 (49), 87 (51), 83 (39), 67 (36).

HRMS $m/z$ calcd for C$_{11}$H$_{20}$O$_3$S$_2$ 264.0854, found 264.0862 (EI).

(3'S*, 4S*, 4aS*, 4'S* 8aS*)-4a,7,8,8a-Tetrahydro-4-[tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-yl]-4H,5H-thiopyran[4,3-d]-1,3-dioxin-2-one (248).

Following General procedure H, the trans diol 246 (24 mg, 0.078 mmol) gave the titled carbonate (20 mg, 77%) after fractionation by PTLC (80% ethyl acetate in hexane):

IR $\nu_{\text{max}}$ 2922, 1745, 1428, 1241, 1182, 1099, 1038, 918 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.74 (1H, dd, $J = 6, 6$ Hz, HC-4 [$^3J_{\text{HC}-4/\text{HC}-4a} = 6$ Hz]), 4.71 (1H, d, $J = 7$ Hz, H$_2$CO), 4.67 (1H, d, $J = 7$ Hz, H$_2$CO), 4.39 (1H, ddd, $J = 4.5, 11, 11$ Hz, HC-8a), 3.70 (1H, ddd, $J = 3, 7.5, 7.5$ Hz, HC-4'), 3.37 (3H, s, H$_3$CO), 2.86 (1H, br d, $J = 12.5$ Hz, HC-2'), 2.82-2.77 (1H, m), 2.75 (1H, ddd, $J = 2.5, 12.5, 14$ Hz, HC-7), 2.71 (1H, dddd, $J = 1.5, 4, 4, 14$ Hz, HC-7), 2.67-2.59 (2H, ), 2.55-2.41 (5H, ), 2.19 (1H, dddd, $J = 3.5, 6, 7.5, 7.5$ Hz, HC-3'), 1.92-1.83 (2H, m, HC-5', HC-8);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 148.5, 97.15, 81.01 (br), 76.57, 75.41 (br), 56.02, 42.44, 42.08 (br), 33.93, 32.40 (br), 30.86 (br), 27.92, 26.99, 25.34 (br);

LRMS (EI), $m/z$ (relative intensity): 334 ([M]$^+$, 100), 139 (58), 137 (42), 101 (39), 100 (44), 99 (90), 85 (48), 67 (52).

HRMS $m/z$ calcd for C$_{14}$H$_{22}$O$_3$S$_2$ 334.0909, found 334.0908 (EI).

Following General procedure C, the DIBAH reduction of a 1.5:1 mixture of the aldols 129c and 128c (3 mg, 0.01 mmol), respectively gave 246 (1 mg, 30%), 249 (1 mg, 30%), and 250 (1 mg, 30%).

Data for 249:

IR $\nu_{\max}$ 3389, 2918, 1428, 1149, 1098, 1033, 924 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.81 (1H, d, $J = 7$ Hz, H$_2$CO), 4.67 (1H, d, $J = 7$ Hz, H$_2$CO), 4.67 (1H, d, $J = 1.5$ Hz, HOC-1'), 4.32 (1H, ddd, $J = 2$, 3, 3 Hz, HC-4), 3.96 (1H, s, HOC-4), 3.83 (1H, ddd, $J = 1.5$, 3, 8 Hz, HC-1'), 3.68 (1H, ddd, $J = 3.5$, 9.5, 9.5 Hz, HC-4"), 3.42 (3H, s, H$_3$CO), 3.39 (1H, dd, $J = 11.5$, 13 Hz, HC-2), 3.18 (1H, ddd, $J = 2.5$, 13, 13 Hz, HC-6), 2.76-2.65 (2H, m, HC-2", HC-6"), 2.63 (1H, ddd, $J = 3$, 11, 13.5 Hz, HC-6"), 2.42 (1H, dddd, $J = 3$, 3.5, 5.5, 13.5 Hz, HC-5"), 2.36 (1H, dd, $J = 10$, 13.5 Hz, HC-2"), 2.27 (1H, br d, $J = 13$ Hz, HC-6), 2.19 (1H, dddd, $J = 2.5$, 3, 3, 11 Hz, HC-5), 2.18-2.11 (2H, m, HC-2, HC-3"), 2.02 (1H, dddd, $J = 2$, 3, 3, 11.5 Hz, HC-3), 1.84 (1H, dddd, $J = 3.5$, 9.5, 11, 13.5 Hz, HC-5"), 1.83-1.75 (1H, m, HC-5);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 94.87, 80.35, 79.75, 65.94, 56.43, 45.84, 42.73, 34.67, 32.80, 29.17, 26.95, 26.33, 22.50;

LRMS (EI), m/z (relative intensity): 308 ([M]$^+$, 53), 159 (30), 129 (57), 117 (42), 101 (51), 100 (100), 99 (66), 67 (36).

HRMS m/z calcd for C$_{13}$H$_{24}$O$_4$S$_2$ 308.1116, found 308.1112 (EI).

Data for 250:

IR $\nu_{\max}$ 3394, 2926, 1429, 1147, 1100, 1067, 1034, 915 cm$^{-1}$;

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\( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.72 (1H, d, \( J = 6.5 \) Hz, H2CO), 4.69 (1H, d, \( J = 6.5 \) Hz, H2CO), 3.76 (1H, ddd, \( J = 3.5, 8, 9.5 \) Hz, HC-4), 3.75 (1H, dd, \( J = 3.5, 7 \) Hz, HC-1'), 3.62 (1H, ddd, \( J = 4, 9, 10.5 \) Hz, HC-4"), 3.41 (3H, s, H\(_3\)CO), 2.87 (1H, br d, \( J = 13.5 \) Hz, HC-2), 2.81-2.73 (1H, m, HC-6), 2.72-2.60 (4H, m, HC-2, HC-2", H2C-6"), 2.57 (1H, ddd, \( J = 3, 10, 13 \) Hz, HC-6), 2.40 (1H, dd, \( J = 11, 13.5 \) Hz, HC-2"), 2.36 (1H, dddd, \( J = 3, 3.5, 7, 13.5 \) Hz, HC-5), 2.27 (1H, dddd, \( J = 3, 4, 4, 13 \) Hz, HC-5"), 2.10 (1H, ddd, \( J = 3.5, 3.5, 8, 8 \) Hz, HC-3), 2.02 (1H, ddd, \( J = 3.5, 7.5, 9, 11 \) Hz, HC-3"), 1.85 (1H, ddd, \( J = 3, 9.5, 10, 13.5 \) Hz, HC-5), 1.77 (1H, dddd, \( J = 4, 10, 10.5, 13 \) Hz, HC-5");

\( ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 95.71, 81.12, 76.02, 74.48, 56.05, 48.84, 44.32, 36.95, 32.69, 31.01, 30.20, 27.47, 26.18;

LRMS (EI), \( m/z \) (relative intensity): 308 ([M\(^+\)], 56), 159 (35), 129 (87), 117 (55), 101 (52), 100 (100), 99 (70), 67 (42).

HRMS \( m/z \) calcd for C\(_{13}\)H\(_{24}\)O\(_4\)S\(_2\) 308.1116, found 308.1118 (EI).

(1\(S\), 3'\(S\)*, 3"\(R\)*, 4'\(S\)*, 4"\(R\)*)-Bis[tetrahydro-4-hydroxy-2\(H\)-thiopyran-3-yl]methanol (251).

\[
\begin{align*}
&\text{HO} \\
&\text{S} \\
&\text{2' S} \\
&\text{2'' S} \\
&\text{6' S} \\
&\text{6'' S} \\
\end{align*}
\]

Following General procedure J for hydrolysis of MOM ethers, diol 250 (14 mg, 0.045 mmol) gave the titled triol (9 mg, 75%) after fractionation by MPC (80% ethyl acetate in hexane):

IR \( \nu_{\text{max}} \) 3345, 2925, 2848, 1429, 1336, 1283, 1068, 1034 cm\(^{-1}\);

\( ^1H \) NMR (500 MHz, CD\(_3\)OD) \( \delta \) 3.86 (1H, t, \( J = 5.5 \) Hz, HC-1), 3.66 (2H, ddd, \( J = 3.5, 10, 10 \) Hz, HC-4', HC-4"), 2.71 (2H, dd, \( J = 3, 13.5 \) Hz, HC-2', HC-2"), 2.64-2.58 (4H, m, H\(_2\)C-6', H\(_2\)C-6"), 2.54 (2H, dd, \( J = 10.5, 13.5 \) Hz, HC-2', HC-2"), 2.22 (2H, dddd, \( J = 3.5, 4, 4, 13 \) Hz, HC-5', HC-5"), 2.02 (2H, dddd, \( J = 3, 5.5, 10, 10.5 \) Hz, HC-3', HC-3"), 1.74-1.66 (2H, m, HC-5', HC-5");
$^{13}$C NMR (125 MHz, CD$_3$OD) δ 79.30 (d), 72.33 (d ×2), 49.52 (d ×2), 37.75 (t ×2), 31.08 (t ×2), 27.86 (t ×2);

LRMS (EI), m/z (relative intensity): 264 ([M]$^+$, 53), 129 (86), 101 (34), 100 (100), 99 (49), 87 (47), 85 (36), 67 (38).

HRMS m/z calcd for C$_{11}$H$_{20}$O$_3$S$_2$ 264.0854, found 264.0856 (EI).

(3'S*, 4S*, 4aR*, 4'S* 8aR*)-4a,7,8,8a-Tetrahydro-4-[tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3-yl]-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-2-one (252).

Following General procedure G, the trans diol 250 (4 mg, 0.013 mmol) gave the titled carbonate (4 mg, 92%) after fractionation by PTLC (70% ethyl acetate in hexane):

IR $\nu_{\text{max}}$ 2920, 1751, 1225, 1190, 1116, 1093, 1031, 919 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.68 (2H, ap s, H$_2$CO), 4.12 (1H, dd, $J = 1.5$, 10 Hz, HC-4 [3$J_{\text{HC-4/HC-4a}} = 10$ Hz]), 3.97 (1H, ddd, $J = 4.5$, 11, 11 Hz, HC-8a), 3.75 (1H, ddd, $J = 4$, 10, 10.5 Hz, HC-4'), 3.37 (3H, s, H$_3$CO), 2.90 (1H, dd, $J = 11.5$, 13.5 Hz, HC-2'), 2.83 (1H, ddd, $J = 2.5$, 3, 13 Hz, HC-5), 2.77 (1H, ddd, $J = 3$, 12.5, 14 Hz, HC-7), 2.71 (1H, ddd, $J = 3.5$, 4.5, 14 Hz, HC-7), 2.68-2.61 (3H, HC-4a, H$_2$C-6'), 2.55 (1H, dddd, $J = 3.5$, 3.5, 13.5 Hz, HC-5'), 2.51 (1H, br d, $J = 13.5$ Hz, HC-2'), 2.44 (1H, dddd, $J = 3$, 3.5, 4.5, 13 Hz, HC-8), 2.41 (1H, dd, $J = 11$, 13 Hz, HC-5), 2.12 (1H, dddd, $J = 1.5$, 3, 10, 11.5 Hz, HC-3'), 1.88 (1H, dddd, $J = 4.5$, 11, 12.5, 13 Hz, HC-8), 1.75 (1H, dddd, $J = 5$, 10.5, 10.5, 13.5 Hz, HC-5');

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 148.73, 96.38, 86.60, 80.50, 76.78, 56.21, 45.01, 42.36, 34.67, 33.04, 31.57, 28.87, 27.18, 27.02;

LRMS (EI), m/z (relative intensity): 334 ([M]$^+$, 100), 272 (85), 271 (86), 201 (44), 139 (57), 137 (38), 99 (75), 67 (42).
(3R,4s,5S)-rel-3-[(R)-(6S)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4-hydroxy-2H-thiopyran (257)

Prepared by C. C. Man from reduction of 165d (Cs anti) with DIBAL-H.\textsuperscript{30}

Included here for completeness only.

IR (DRIFT) $\nu$\textsubscript{max} 3460, 2952, 2916, 1426, 1160, 1107, 1045 cm$^{-1}$.

$^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 5.10 (1H, br s, HC-4), 4.32 (1H, br d, $J = 3, 7$ Hz, HC-1', HC-1''), 3.50-3.18 (15H, m, HO x3, H$_2$CO x4, H$_2$C-3, H$_2$C-5), 3.12 (2H, dd, $J = 10, 14$ Hz, HC-7', HC-7''), 2.84 (2H, br d, $J = 14$ Hz, HC-7', HC-7''), 2.58 (2H, ddd, $J = 3, 11, 14$ Hz, HC-9', HC-9''), 2.32 (2H, br d, $J = 14$ Hz, HC-9', HC-9''), 2.20-2.00 (4H, m, HC-3, HC-5, HC-6', HC-6''), 1.71 (2H, ddd, $J = 3, 5.5, 13.5$ Hz, HC-10', HC-10''), 1.58 (2H, ddd, $J = 3.5, 11, 13.5$ Hz, HC-10', HC-10'').

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 110.0 (s x2), 70.5 (d x2), 64.6 (t x2), 64.4 (d), 64.2 (t x2), 47.1 (d x2), 46.1 (d x2), 35.8 (t x2), 26.6 (t x2), 26.6 (t x2), 24.7 (t x2).

LRMS (EI), m/z (relative intensity): 494 ([M$^+$], 14), 414 (10), 273 (11), 255 (12), 189 (14), 161 (17), 132 (70), 117 (19), 99 (100).

HRMS m/z calcd for C$_{21}$H$_{34}$O$_7$S$_3$ 494.1467, found 494.1467 (EI).

(αR,6S)-rel-α-[(4S,4aS,8S,8aR)-4-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yltetrahydro-2,2-dimethyl-4H,5H-thiopyran[4,3-d]-1,3-dioxin-8-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol (258)

Prepared by Dr. C. Guo from reaction of XX with dimethoxypropane in the presence of p-TsOH.30 Included here for completeness only.

IR (DRIFT) νmax 3515, 2915, 1425, 1258, 1222, 1167, 1107, 1066, 1046, 1028 cm⁻¹.

¹H NMR (300 MHz, C₆D₆) δ 4.68 (1H, br s, HC-8a), 4.35 (1H, ddd, J = 2.5, 3, 8.5 Hz, HC-α), 3.93 (1H, dd, J = 5.5, 5.5 Hz, HC-4'), 3.29 (1H, d, J = 3 Hz, HO), 3.41-2.80 (14H, m), 2.74 (1H, br d, J = 14 Hz), 2.68-2.51 (3H, m), 2.45 (1H, dd, J = 4, 13 Hz), 2.25-2.17 (4H, m), 1.93 (1H, ddd, J = 3, 5.5, 8.5 Hz, HC-4a), 1.80-1.50 (4H, m), 1.49 (3H, s), 1.35 (3H, s).

¹³C NMR (75 MHz, C₆D₆) δ 110.9 (s), 109.3 (s), 101.6 (s), 72.1 (d), 69.6 (d), 64.9 (t x2), 64.5 (t), 64.4 (t), 63.9 (d), 50.4 (d), 47.3 (d), 44.9 (d), 44.6 (d), 37.0 (t), 36.7 (t), 29.0 (t), 28.6 (t), 27.4 (t), 27.0 (t), 26.9 (q), 26.8 (t), 25.5 (t), 24.1 (q).

LRMS (EI), m/z (relative intensity): 534 ([M]+, 6), 458 (4), 189 (8), 159 (14), 132 (53), 99 (100), 86 (12), 67 (17).
HRMS m/z calcd for C₂₄H₃₈O₇S₃ 534.1780, found 534.1783 (EI).

(3R,5R)-rel-3,5-bis[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-tetrahydro-4-hydroxy-2H-thiopyran (260)

Prepared by Dr. C. Guo from reduction of 165e (C₂ anti) with DIBAL-H.30 NMR assignment and analysis this work.
IR (DRIFT) νmax 3435, 2919, 1427, 1259, 1158, 1133, 1107, 1044 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.57 (1H, d, J = 9 Hz, HC-4), 4.35 (1H, br d, J = 3 Hz, HC-1' or HC-1'"), 4.32 (1H, d, J = 7.5 Hz, HC-1" or HC-1"'), 4.10-3.94 (8H, m, H₂CO x4), 3.39 (3H, br s, HO x3), 3.07-2.99 (3H, m), 2.89 (1H, dd, J = 10, 13 Hz), 2.86-2.77 (2H, m), 2.74 (1H, ddd, J = 2.5, 3, 14 Hz), 2.61 (1H, ddd, J = 2.5, 3, 14 Hz), 2.55-2.49 (2H, m), 2.24 (1H, dd, J = 3, 13 Hz), 2.18-2.09 (5H, m), 2.04-2.01 (2H, m), 1.76-1.70 (2H, m).

¹³C NMR (75 MHz, CDCl₃) δ 110.2 (s), 110.1 (s), 70.7 (d), 68.6 (d), 68.5 (d), 64.8 (t), 64.7 (t), 64.2 (t x2), 47.4 (d), 46.8 (d), 42.2 (d), 40.5 (d), 36.5 (t), 36.1 (t), 26.7 (t), 26.6 (t x2), 25.3 (t), 25.7 (t), 25.6 (t).

LRMS (EI), m/z (relative intensity): 494 ([M]+, 7), 273 (20), 189 (12), 161 (14), 159 (16), 132 (62), 117 (17), 99 (100).

HRMS m/z calcld for C₂₁H₃₂O₇S₃ 494.1467, found 494.1467 (EI).


(αS,6R)-rel-α-[(4S,4aS,8R,8aR)-4-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yltetrhydro-2,2-dimethyl-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-8-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol (261)

 Prepared by Dr. C. Guo from reaction of 260 with dimethoxypropane in the presence of p-TsOH. NMR assignment and analysis this work.

IR (DRIFT) νmax 3509, 2915, 1427, 1378, 1260, 1223, 1161, 1110, 1046 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ 4.55 (1H, d, J = 9.5 Hz, HC-α), 4.21 (1H, dd, J = 3, 3.5 Hz, HC-4'), 4.12-3.99 (3H, m), 3.97-3.91 (5H, m), 3.74 (1H, dd, J = 3, 6 Hz, HC-8a), 3.14 (1H, s, HO), 3.05-2.75 (6H, m), 2.72 (1H, br d, J = 14 Hz), 2.58-2.47 (3H, m), 2.30 (1H, dd, J = 3.5, 13 Hz), 2.21-2.15 (2H, m, HC-10, HC-10"'), 2.10 (1H, dddd, J = 3.5, 4, 278
6, 12 Hz, HC-4a), 2.06-1.97 (2H, m), 1.97-1.89 (2H, m, HC-6", HC-8"), 1.78-1.68 (2H, m, HC-10, HC-10"), 1.32 (3H, s, H3C), 1.31 (3H, s, H3C).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 110.4 (s), 108.9 (s), 101.0 (s), 70.6 (d), 67.8 (d), 65.0 (t), 64.8 (t ×2), 64.3 (t), 64.2 (d), 51.2 (d), 46.3 (d), 40.4 (d), 39.9 (d), 37.4 (t), 36.4 (t), 27.4 (t), 27.0 (t), 26.8 (t ×2), 26.2 (q), 25.7 (t), 25.4 (t), 23.8 (q).

LRMS (EI), m/z (relative intensity): 534 ([M]$^+$, 10), 458 (6), 281 (6), 189 (9), 159 (14), 132 (50), 117 (6), 99 (100).

HRMS m/z calcd for C$_{24}$H$_{38}$O$_7$S$_3$ 534.1780, found 534.1776 (EI).

(αS,6R)-rel-α-[((4S,4aS,8R,8aS)-4-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylltetrahydro-2,2-dimethyl-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-8-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol (262)

Prepared by Dr. C. Guo from reaction of 260 with dimethoxypropane in the presence of p-TsOH. NMR assignment and analysis this work.

IR (DRIFT) $\nu_{\text{max}}$ 3513, 2915, 1425, 1378, 1308, 1167, 1107, 1065, 1046 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.84 (1H, br dd, J = 2.5, 9.5 Hz, HC-α), 4.26 (1H, d, J = 2.5 Hz, HO), 4.22-4.17 (1H, m), 4.13-4.09 (1H, m), 4.03-3.85 (6H, m), 3.93 (1H, dd, J = 1.5, 10.5 Hz, HC-4"), 3.89 (1H, dd, J = 4.5, 11 Hz, HC-8a), 3.14 (1H, dd, J = 12, 14 Hz), 3.00 (1H, dd, J = 12, 14 Hz), 2.98-2.83 (3H, m), 2.65 (1H, ddd, J = 2.5, 2.5, 14 Hz), 2.55-2.43 (1H, m), 2.33 (1H, dd, J = 11.5, 14 Hz), 2.05-2.07 (1H, ddd, J = 2.5, 10.5, 11, 11 Hz, HC-4a), 1.84 (1H, dd, J = 3, 3.5, 13.5 Hz, HC-10 or HC-10"), 2.08-2.01 (3H, m, HC-6", HC-8", HC-10 or HC-10"), 1.86 (1H, dd, J = 3, 11.5 Hz, HC-6"), 1.76 (1H, ddd, J = 3.5, 13, 13.5 Hz, HC-10 or HC-10"), 1.72 (1H, ddd, J = 4, 13, 13.5 Hz, HC-10 or HC-10"), 1.39 (3H, s, H3C), 1.33 (3H, s, H3C).
\[ ^{13} \text{C NMR} \ (75 \text{ MHz, } \text{CDCl}_3) \delta 110.5 \text{ (s), 110.3 \ (s), 102.8 \ (s), 68.7 \ (d), 68.6 \ (d), 67.4 \ (d),} \\
65.4 \ (t), 65.1 \ (t), 65.0 \ (t), 64.4 \ (t), 50.4 \ (d), 47.6 \ (d), 40.9 \ (d), 38.4 \ (t), 38.2 \ (t), 37.9 \ (d), \\
31.3 \ (t), 30.2 \ (q), 29.3 \ (t), 27.1 \ (t), 27.0 \ (t), 26.8 \ (t), 26.7 \ (t), 18.8 \ (q). \]

\[ \text{LRMS (EI), } m/z \text{ (relative intensity): 534 ([M]^{+}, 7), 458 (4), 189 (7), 159 (14), 132 (57),} \\
99 (100), 86 (12), 67 (11). \]

\[ \text{HRMS } m/z \text{ calcd for C}_{24}\text{H}_{38}\text{O}_{7}\text{S}_{3} 534.1780, \text{ found 534.1779 (EI)}. \]

(3S,5S)-rel-3,5-bis[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-tetrahydro-4-hydroxy-2H-thiopyran (264)

Prepared by Dr. C. Guo from reduction of 165c (C\textsubscript{2} syn) with DIBAL-H.\textsuperscript{30}

Included here for completeness only.

\[ \text{IR (DRIFT) } \nu_{\text{max}} 3501, 2917, 1427, 1260, 1131, 1116, 1048, 1035 \text{ cm}^{-1}. \]

\[ ^{1}\text{H NMR} \ (300 \text{ MHz, } \text{CDCl}_3) \delta 4.79 \ (1\text{H, d, } J = 10.5 \text{ Hz, H}-4), 4.15-3.94 \ (9\text{H, m, H-1'} \text{ or H-1''}, \text{ H}_2\text{CO }\times4), 3.87 \ (1\text{H, br d, H-1' or H-1''}), 3.22 \ (1\text{H, dd, } J = 3.5, 13.5 \text{ Hz}), 3.09 \ (1\text{H, dd, } J = 12, 14 \text{ Hz}), 3.04-2.88 \ (2\text{H, m}), 2.84-2.69 \ (4\text{H, m}), 2.65-2.59 \ (2\text{H, m}), 2.54-2.48 \ (2\text{H, m}), 2.16-2.10 \ (3\text{H, m}), 2.02-1.92 \ (3\text{H, m}), 1.83-1.70 \ (2\text{H, m}). \]

\[ ^{13}\text{C NMR} \ (75 \text{ MHz, } \text{CDCl}_3) \delta 110.3 \text{ (s), 109.9 \ (s), 71.1 \ (d), 67.8 \ (d), 65.0 \ (d), 64.9 \ (t),} \\
64.7 \ (t), 64.4 \ (t), 64.3 \ (t), 46.7 \ (d), 45.9 \ (d), 42.7 \ (d), 41.2 \ (d), 36.5 \ (t), 35.6 \ (t), 26.6 \ (t \times2), 26.5 \ (t), 25.8 \ (t), 23.4 \ (t), 22.7 \ (t). \]

\[ \text{LRMS (EI), } m/z \text{ (relative intensity): 494 ([M]^{+}, 8), 273 (12), 188 (16), 159 (15), 131} \\
(71), 117 (15), 99 (100). \]

\[ \text{HRMS } m/z \text{ calcd for C}_{21}\text{H}_{34}\text{O}_{7}\text{S}_{3} 494.1467, \text{ found 494.1467 (EI)}. \]
(αS,6R)-rel-α-[(4S,4aR,8S,8aS)-4-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-
yl)dihydro-2,2-dimethyl-4H,5H-thiopyran[4,3-d]-1,3-dioxin-8-yl]-1,4-dioxa-8-
thiaspiro[4.5]decane-6-methanol (265)

Prepared by Dr. C. Guo from reaction of 264 with dimethoxypropane in the
presence of p-TsOH. Included here for completeness only.

IR (DRIFT) ν\text{max} 3529, 2921, 1426, 1260, 1198, 1170, 1151, 1112, 1046 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) δ 5.01 (1H, d, \(J = 10\) Hz, HC-α), 4.23 (1H, d, \(J = 9.5\) Hz,
HC-4'), 4.06 (1H, br s, HC-8a), 3.67-3.58 (1H, m), 3.40-3.50 (6H, m), 3.33-3.24 (1H,
m), 3.25-3.16 (3H, m), 3.11-2.99 (3H, m), 2.89 (1H, br dd, \(J = 8, 13.5\) Hz, HC-5'), 2.71-
2.50 (5H, m), 2.26-2.15 (5H, m), 1.81-1.66 (2H, m), 1.64-1.44 (2H, m), 1.42 (3H, s),
1.30 (3H, s).

\(^{13}\)C NMR (75 MHz, C\(_6\)D\(_6\)) δ 111.0 (s), 109.6 (s), 100.0 (s), 72.7 (d), 69.8 (d), 66.3 (d),
65.2 (t), 65.1 (t), 64.4 (t), 64.0 (t), 48.3 (d), 45.2 (d), 42.5 (d), 37.4 (t), 37.2 (d), 36.1 (t),
30.4 (q), 30.0 (t), 27.1 (t ×2), 26.9 (t), 24.6 (t), 22.3 (t), 19.7 (q).

LRMS (EI), \(m/z\) (relative intensity): 534 ([M]+, 26), 458 (10), 189 (14), 159 (14), 132
(60), 99 (100), 86 (11), 67 (14).

HRMS \(m/z\) calcd for C\(_{24}\)H\(_{38}\)O\(_7\)S\(_3\) 534.1780, found 534.1775 (EI).

(3R,4R,5R)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-
[(S)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4-hydroxy-
2H-thiopyran (267)
Prepared by Dr. C. Guo from reaction of 165a with DIBAL-H.\textsuperscript{30} Included here for completeness only.

IR (DRIFT) \(\nu_{\text{max}}\) 3500, 2917, 1427, 1261, 1158, 1133, 1110, 1042 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.72 (1H, d, \(J = 10\) Hz, HC-1\('\)), 4.23 (1H, br s, HC-1\('\)), 4.18 (1H, dd, \(J = 1.5\), 8 Hz, HC-4), 4.14-3.94 (10H, m), 3.13 (1H, dd, \(J = 3\), 14 Hz), 3.06-2.93 (3H, m), 2.86-2.75 (3H, m), 2.61-2.49 (4H, m), 2.25 (1H, ddd, \(J = 2\), 3, 10 Hz), 2.20-2.12 (4H, m), 1.94-2.06 (2H, m), 1.78-1.68 (2H, m).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 110.6 (s), 110.5 (s), 71.0 (d), 67.8 (d \(\times\)2), 65.1 (t), 64.9 (t), 64.4 (t), 64.3 (t), 46.9 (d), 46.1 (d), 42.8 (d), 41.2 (d), 36.5 (t), 36.3 (t), 26.8 (t), 26.7 (t), 26.5 (t), 25.8 (t), 24.4 (t), 24.3 (t).

LRMS (EI), \(m/z\) (relative intensity): 494 ([M]\(^+\), 7), 476 (4), 273 (11), 189 (13), 159 (12), 132 (60), 117 (15), 99 (100).

HRMS \(m/z\) calcd for C\(_{21}\)H\(_{34}\)O\(_7\)S\(_3\) 494.1467, found 494.1462 (EI).

\((4R,4aR,8S_{8a}R)-rel-4-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl-8-[(S)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(hydroxy)methyl]tetrahydro-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-2-one (268)\)

\[\text{268}\]

Prepared by Dr. C. Guo from the reaction of 267 with 1,1'-carbonyldiimidazole.\textsuperscript{30} NMR assignment and analysis this work.

IR (DRIFT) \(\nu_{\text{max}}\) 3504, 2917, 1754, 1427, 1337, 1255, 1157, 1113, 1044 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.89 (1H, br dd, \(J = 2.5\), 8 Hz, HC-1\('\)), 4.49 (1H, br d, \(J = 9\) Hz, HC-4 [\(J_{\text{HC-4-HC-4a}} = 9\) Hz]), 4.24 (1H, dd, \(J = 4\), 10 Hz, HC-8a [\(J_{\text{HC-8a-HC-4a}} = 10\) Hz]), 4.13-3.92 (8H, m, H\(_2\)CO \(\times\)4), 3.40 (1H, br s, HO), 3.18-3.10 (2H, m), 2.98 (1H, dd, \(J = 11,13.5\) Hz, HC-7\('\)), 2.92 (1H, ddd, \(J = 2, 13, 13.5\) Hz), 2.82-2.68 (4H, m), 2.57-
2.42 (6H, m), 2.27 (1H, ddd, J = 2.5, 3, 11 Hz, HC-6'), 2.14 (1H, br dd, J = 2, 11 Hz, HC-6''), 2.13-2.08 (2H, m, HC-10', HC-10''), 1.78-1.69 (2H, m, HC-10', HC-10'').

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 147.7 (s), 110.5 (s), 108.0 (s), 82.4 (d), 78.8 (d), 65.9 (d), 65.2 (t), 65.0 (t), 64.9 (t), 64.6 (t), 48.2 (d), 47.5 (d), 39.4 (d), 37.7 (t), 36.1 (t), 34.9 (d), 30.3 (t), 30.1 (t), 26.8 (t), 26.7 (t ×2), 26.2 (t).

LRMS (EI), m/z (relative intensity): 520 ([M$^+$], 6), 475 (13), 458 (2), 159 (19), 132 (52), 99 (100), 86 (12), 54 (14).

HRMS $m/z$ calcd for C$_{22}$H$_{32}$O$_8$S$_3$ 520.1259, found 520.1257 (EI).

(aR,6S)-rel-α-[(4S,4aR,8S,8aS)-4-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yltetrahydro-2,2-dimethyl-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-8-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol (269)

![Diagram of 269](image)

Prepared by Dr. C. Guo from the reaction of 267 with dimethoxypropane in the presence of p-TsOH.\textsuperscript{30} Included here for completeness only.

IR (DRIFT) $\nu_{\text{max}}$ 3515, 2921, 1427, 1260, 1199, 1171, 1106, 1048 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) δ 4.78 (1H, d, J = 10 Hz, HC-α), 4.36 (1H, br s, H-8a), 4.25 (1H, d, J = 8.5 Hz, HC-4'), 4.14-4.09 (2H, m), 4.04-3.89 (7H, m), 3.21-3.12 (2H, m), 3.06-2.91 (2H, m), 2.82 (1H, dd, J = 12, 13.5 Hz), 2.77-2.52 (5H, m), 2.38 (1H, br d, J = 13.5 Hz), 2.21-2.11 (2H, m), 2.06-1.97 (3H, m), 1.98-1.88 (2H, m), 1.81-1.69 (2H, m), 1.44 (3H, s), 1.39 (3H, s).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 110.6 (s), 109.1 (s), 99.7 (s), 71.2 (d), 68.2 (d), 66.9 (d), 65.2 (t), 65.1 (t), 64.3 (t), 64.1 (t), 45.9 (d), 45.0 (d), 41.2 (d), 36.4 (t), 36.0 (d), 35.4 (t), 30.1 (q), 29.3 (t), 26.8 (t ×2), 25.6 (t), 24.6 (t), 22.4 (t), 20.1 (q).

LRMS (EI), m/z (relative intensity): 534 ([M$^+$], 28), 458 (11), 326 (7), 199 (10), 189 (15), 159 (15), 132 (65), 99 (100).
HRMS m/z calcd for C_{24}H_{38}O_{7}S_{3} 534.1780, found 534.1782 (EI).

(4S,4aR,8S,8aS)-rel-4-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl-8-[(R)-(6S)-1,4-dioxa-8-thiaspiro[4.5]dec-6-y1(1-imidazolecarbonyloxy)methyl]tetrahydro-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-2-one (270)

Prepared by Dr. C. Guo from reaction of 267 with 1,1'-carbonyldiimidazole.

NMR assignment and analysis this work.

IR (DRIFT) \nu_{\text{max}} 2917, 1755, 1752, 1392, 1283, 1241, 1211, 1099 cm^{-1} .

$^1$H NMR (500 MHz, CDCl$_3$) \delta 8.41 (1H, br s, ArH), 7.51 (1H, s, ArH), 7.22 (1H, s, ArH), 6.26 (1H, d, J = 10.5 Hz, HC-1'), 4.62 (1H, br d, J = 9.5 Hz, HC-4), 4.59 (1H, br s, HC-8a), 4.10-3.85 (6H, m), 3.80-3.73 (1H, m), 3.70-3.63 (1H, m), 3.19 (1H, dd, J = 2.5, 15 Hz, HC-7), 3.09 (1H, dd, J = 3, 14 Hz, HC-7''), 3.04 (1H, dd, J = 12.5, 13 Hz, HC-7'), 2.95 (1H, br d, J = 12 Hz, HC-4a), 2.83-2.56 (H, m), 2.51 (1H, br d, J = 10.5 Hz, HC-8), 2.48 (1H, br d, J = 14 Hz), 2.36 (1H, br d, J = 15 Hz, HC-7), 2.51 (1H, dd, J = 2, 12.5 Hz, HC-6'), 2.25 (1H, ddd, J = 3, 9, 9.5 Hz, HC-6''), 2.15 (1H, ddd, J = 2.5, 3, 11 Hz, HC-10' or HC-10''), 2.01-1.92 (1H, m, HC-10' or HC-10''), 1.78-1.65 (2H, m, HC-10', HC-10'').

$^{13}$C NMR (75 MHz, CDCl$_3$) \delta 148.7 (s), 148.1 (s), 125.2 (d), 117.8 (d), 108.5 (s), 108.2 (s), 81.7 (d \times 2), 74.2 (d), 64.9 (t), 64.7 (t), 64.3 (t), 64.0 (t), 46.1 (d), 44.9 (d), 39.5 (d), 35.9 (t), 35.2 (t), 33.4 (d), 28.8 (t), 26.8 (t), 26.5 (t), 26.2 (t), 24.6 (t), 21.6 (t).

LRMS (EI), m/z (relative intensity): 614 ([M]$^+$, 15), 481 (5), 159 (8), 132 (46), 99 (100), 86 (11), 69 (11), 67 (10).

HRMS m/z calcd for C_{26}H_{34}N_{2}O_{8}S_{3} 614.1426, found 614.1428 (EI).
(3S,4S,5R)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4-hydroxy-2H-thiopyran (272)

Prepared by Dr. C. Guo from the reaction of 165b with DIBAL-H. Included here for completeness only.

**IR (DRIFT)** $\nu_{\text{max}}$ 3510, 1427, 1338, 1261, 1159, 1133, 1111, 1043 cm$^{-1}$.

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 4.24 (2H, dd, $J = 3$, 5.5 Hz, HC-1', HC-1''), 4.07 (1H, br s, HC-4), 4.05-3.95 (8H, m, H$_2$CO x4), 3.03 (2H, dd, $J = 13$, 13.5 Hz, HC-2, HC-6), 2.96 (2H, dd, $J = 9.5$, 14 Hz, HC-7', HC-7''), 2.82-2.58 (6H, m), 2.47 (2H, dd, $J = 2.5$, 13.5 Hz, HC-2, HC-6), 2.09-1.92 (4H, m, HC-6', HC-6'', HC-10', HC-10''), 1.88-1.92 (2H, dddd, $J = 2$, 2.5, 5.5, 13 Hz, HC-3, HC-5), 1.79 (2H, ddd, $J = 3.5$, 10, 13.5 Hz, HC-10', HC-10 '').

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$ 109.0 (s x2), 72.3 (d x2), 72.0 (d), 64.8 (t x2), 64.6 (t x2), 48.0 (d x2), 46.4 (d x2), 35.5 (t x2), 27.5 (t x2), 26.8 (t x2), 22.6 (t x2).

**LRMS (EI)**, m/z (relative intensity): 494 ([M]$^+$, 7), 476 (4), 273 (11), 189 (14), 159 (14), 132 (60), 117 (15), 99 (100).

**HRMS** m/z calcd for C$_{21}$H$_{34}$O$_7$S$_3$ 494.1467, found 494.1470 (EI).

(αR,6S)-rel-α-[(4S,4aR,8R,8aS)-4-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yltetrahydro-2,2-dimethyl-4H,5H-thiopyran[4,3-d]-1,3-dioxin-8-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol (273)

**273**

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Prepared by Dr. C. Guo from the reaction of 272 with dimethoxypropane in the presence of p-TsOH.\textsuperscript{30} Included here for completeness only.

\textbf{IR (DRIFT)} $\nu_{\text{max}}$ 3516, 2919, 1426, 1261, 1200, 1158, 1104, 1039 cm$^{-1}$.

\textbf{\textsuperscript{1}H NMR} (300 MHz, C$_6$D$_6$) $\delta$ 4.55 (1H, d, $J = 9.5$ Hz, HC-41), 4.43 (1H, dd, $J = 2.5, 6$ Hz, HC-\(\alpha\)), 4.22 (1H, br s, HC-8a), 3.39 (1H, dd, $J = 13, 13.5$ Hz), 3.33-3.05 (13H, m), 2.96 (1H, br dd, $J = 5.5, 13$ Hz, HC-7"), 2.78-2.52 (4H, m), 2.23-2.31 (4H, m), 2.01 (1H, ddd, $J = 4, 5.5, 9.5$ Hz, HC-6"), 1.71 (1H, ddd, $J = 3, 5, 13.5$ Hz), 1.62-1.54 (1H, m), 1.50-1.36 (2H, m), 1.48 (3H, s), 1.40 (3H, s).

\textbf{\textsuperscript{13}C NMR} (75 MHz, C$_6$D$_6$) $\delta$ 110.6 (s), 109.1 (s), 100.1 (s), 72.1 (d), 70.7 (d), 70.6 (d), 65.1 (t), 64.6 (t), 64.4 (t), 63.9 (t), 46.7 (d), 46.4 (d), 44.5 (d), 41.5 (d), 36.9 (t), 34.5 (t), 30.4 (q), 29.8 (t), 27.3 (t), 27.2 (t), 27.1 (t), 25.2 (t), 23.0 (t), 19.7 (q).

\textbf{LRMS (EI), m/z (relative intensity)}: 534 ([M$^+$, 11], 458 (5), 414 (7), 199 (7), 189 (7), 159 (14), 132 (65), 99 (100).

\textbf{HRMS} m/z calcd for C$_{24}$H$_{38}$O$_7$S$_3$ 534.1780, found 534.1775 (EI).
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Figure A1. Isomerization of a mixture of $\text{211st:211ac:211at}$ (1:98:1) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.4 M) in CDCl$_3$. 

5. APPENDIX
Figure A2. Isomerization of a mixture of 211st:211ac:211at (94:4:2) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.4 M) in CDCl₃.

Figure A3. Isomerization of a mixture of 211st:211ac:211se:211at (2:2:1:95) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.4 M) in CDCl₃.
**Figure A4.** Isomerization of a mixture of 211st:211ac:211at (1:98:1) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.8 M) in CDCl₃.

**Figure A5.** Isomerization of a mixture of 211st:211ac:211at (94:4:2) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.8 M) in CDCl₃.
Figure A6. Isomerization of a mixture of 211st:211ac:211sc:211at (2:2:1:95) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.8 M) in CDCl₃.

Figure A7. Isomerization of a mixture of 165a (C₁):165d (C₅ anti) of 99:1 with a total aldol concentration of 0.03 M (8 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl₃.
Figure A8. Isomerization of a mixture of 165b (C₅ syn):165a (C₁) of 95:5 with a total aldol concentration of 0.03 M (8 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl₃.

Figure A9. Isomerization of a mixture of 165a (C₁):165d (C₅ anti) of 3:97 with a total aldol concentration of 0.03 M (8 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl₃.
Figure A10. Isomerization of a mixture of 165a (C₁):165d (C₅ anti) of 99:1 with a total aldol concentration of 0.03 M (8 mg in 0.6 ml) in the presence of imidazole (0.80 M) in CDCl₃.

Figure A11. Isomerization of a mixture of 165b (C₅ syn):165a (C₁) of 95:5 with a total aldol concentration of 0.03 M (8 mg in 0.6 ml) in the presence of imidazole (0.80 M) in CDCl₃.
Figure A12. Isomerization of a mixture of $165a$ ($C_1$):$165d$ ($C_s$ anti): of 3:97 with a total aldol concentration of 0.03M (8mg in 0.6ml) in the presence of imidazole (0.80M) in CDCl$_3$.

Figure A13. Isomerization of a mixture of $212a$ ($C_s$ syn):$212b$ ($C_1$):$212c$ ($C_s$ anti): of 1:98:1 with a total aldol concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl$_3$. 
Figure A14. Isomerization of a mixture of 212a (C<sub>s</sub> syn):212b (C<sub>1</sub>):212c (C<sub>s</sub> anti): of 92:5:3 with a total aldol concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl<sub>3</sub>.

Figure A15. Isomerization of a mixture of 212b (C<sub>1</sub>):212c (C<sub>s</sub> anti) of 4:96 with a total aldol concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl<sub>3</sub>. 

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Figure A16. Isomerization of a pure 213a (>99:1) with a concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl₃.

Figure A17. Isomerization of a mixture of 213b:213d (95:5) with a total aldol concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl₃.
Figure A18. Isomerization of pure of 213c (>99:1) with a concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl₃.

Figure A19. Isomerization of a mixture of 213a:213b:213d (3:2:95) with a total aldol concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl₃.