

**THIOPYRAN ROUTE TO POLYPROPIONATES :  
INCREASING STEREOCHEMICAL  
DIVERSITY OF ALDOL ADDUCTS**

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for the Degree of Doctor of Philosophy  
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University of Saskatchewan

by

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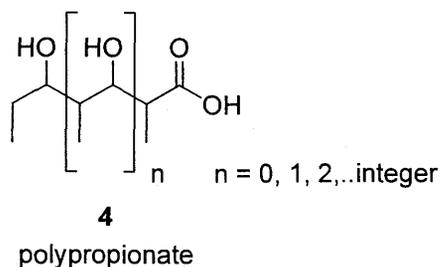
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## Abstract

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.



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.

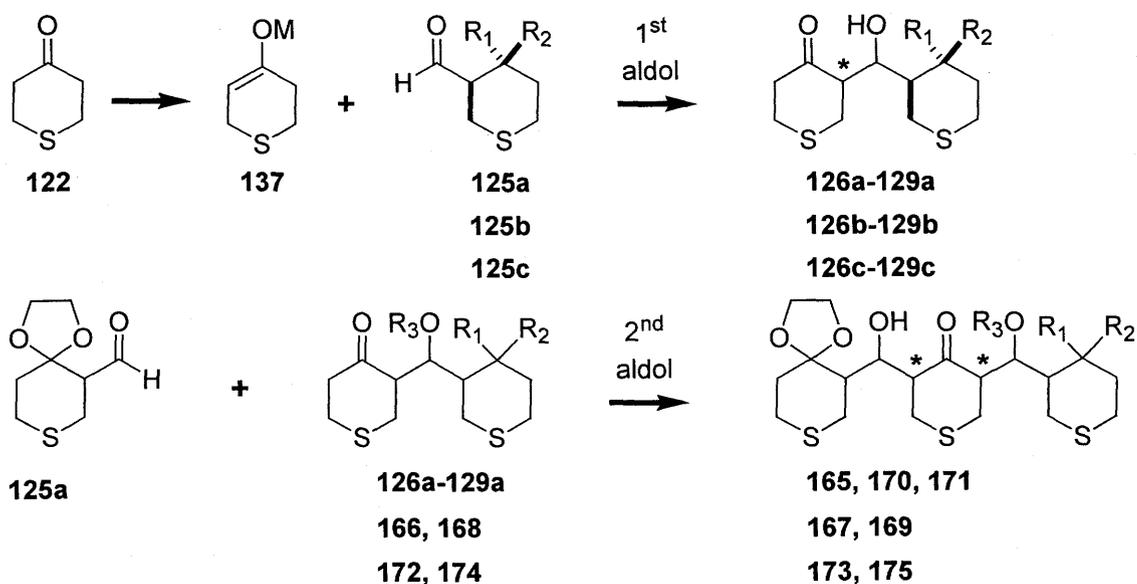
In Section 2.2, the influence of reaction conditions and the relative configuration of the  $\beta$ -alkoxy group of aldehydes *cis*-**125b** and *trans*-**125c** on the diastereoselectivity of the 1<sup>st</sup> aldol coupling are discussed. The results were rationalized according to Evan's merged 1,2- and 1,3-stereoiduction model (nonchelation), with the exception of the  $\text{MgBr}_2 \cdot \text{OEt}_2$  promoted reactions of **137b** ( $\text{M} = \text{TMS}$ ) 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 (*vide infra*).

In Section 2.3, the diastereoselectivities of the aldol reactions of ( $\pm$ )-**125a** with ( $\pm$ )-**126a** and ( $\pm$ )-**127a** (previous work) and reactions of ( $\pm$ )-**125a** with ( $\pm$ )-**128a** and ( $\pm$ )-**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 ( $\pm$ )-**125a** with related  $\beta$ -alkoxy ketones ( $\pm$ )-**166** and ( $\pm$ )-**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.



125a-129a, 165, 170, 171  $R_1 = R_2 = O(CH_2)_2O$ ,  $R_3 = H$

125b-129b  $R_1 = H$ ,  $R_2 = OMOM$

125c-129c  $R_1 = OMOM$ ,  $R_2 = H$

166, 167, 168, 169  $R_1 = H$ ,  $R_2 = OMe$ ,  $R_3 = OMe$

172, 173, 174, 175  $R_1 = R_2 = O(CH_2)_2O$ ,  $R_3 = OMOM$

Designated (\*) stereocentre epimerizes in presence of imidazole.

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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
<sup>13</sup> C NMR	carbon-13 nuclear magnetic resonance
Chx	cyclohexyl
CI	chemical ionization
COSY	correlation spectroscopy
DIBAL	diisobutylaluminium hydride
dil.	dilute
<i>i</i> -Pr <sub>2</sub> EtN	diisopropylethylamine
DMAP	4-( <i>N,N</i> -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 <i>R</i> and <i>S</i> , $ee = \frac{ [R] - [S] }{[R] + [S]} \times 100\%$
EI	electron impact ionization
equiv	equivalent(s)
e.r.	enantiomeric ratio; ratio of ( <i>R</i> ) to ( <i>S</i> )

Et	ethyl
Et <sub>2</sub> O	diethyl ether
Et <sub>3</sub> N	triethylamine
EtOAc	ethyl acetate
FAB	fast-atom bombardment
FCC	flash column chromatography
FTIR	Fourier transform infra red
<sup>1</sup> H NMR	proton nuclear magnetic resonance
h	hour(s)
HMBC	heteronuclear multiple bond correlation (2 and 3 bond $J_{CH}$ correlation with inverse detection)
HMQC	heteronuclear multiple quantum coherence (1 bond $J_{CH}$ correlation with inverse detection)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
<i>i</i> -Bu	isobutyl (2-methylpropyl)
<i>i</i> -Pr	isopropyl
IR	infrared
LA	Lewis Acid
LDA	lithium diisopropylamide
LRMS	low resolution mass spectroscopy
Me	methyl
MeCN	acetonitrile
MeLi	methyllithium
MeOH	methanol
MHz	megahertz; 10 <sup>6</sup> Hertz

min	minute(s)
MOM	methoxymethyl
MPC	medium pressure chromatography
MS	mass spectrometry
MS4A	molecular sieves 4Å
<i>n</i> -BuLi	<i>n</i> -butyllithium
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
OTBDMS	<i>tert</i> -butyldimethylsilyloxy
Ph	phenyl
PMB	<i>p</i> -methoxybenzyl
<sup><i>i</i></sup> Pr	isopropyl
PTLC	preparative thin layer chromatography
<i>p</i> -TsOH	<i>p</i> -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	<i>t</i> -butyldimethylsilyl
TBDMSCl or TBSCl	<i>t</i> -butyldimethylsilyl chloride
TBS or TBDMS	<i>t</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl (1,1-dimethylethyl)
<i>t</i> -BuLi	<i>tert</i> -butyllithium
TEA	triethylamine
THF	tetrahydrofuran (oxolane)

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

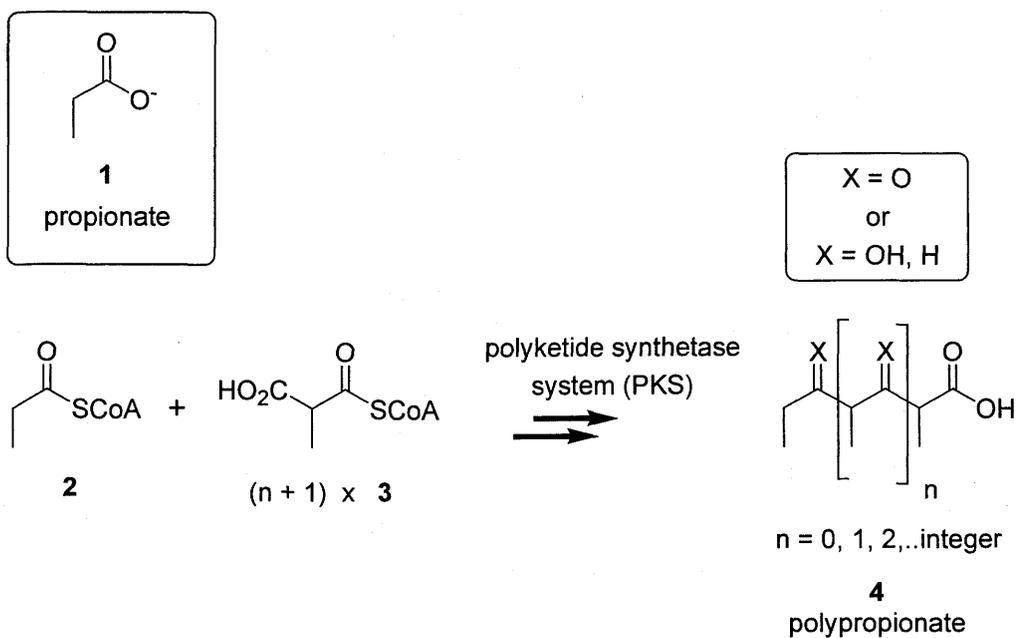
Linear carbon-carbon chains with alternating oxygen (hydroxyl or oxo) and methyl substituents are a common structural motif in various natural products. These structures **4** have been defined as **polypropionates** and their biosynthesis involves the reaction between coenzyme A activated **propionate monomers 2** and **3\*** catalyzed by the polyketide synthase system (PKS) (Figure 1).<sup>1-4</sup> 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.<sup>1-3,5-8</sup> Many of these natural products that show biological activity have been successfully applied in medicine and agriculture.<sup>8</sup> 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.<sup>8</sup> The mode of action of erythromycin A involves the inhibition of the peptidyl transferase center of the bacterial ribosome, thereby inhibiting protein synthesis.<sup>8</sup> 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<sup>†</sup> polypropionates.

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

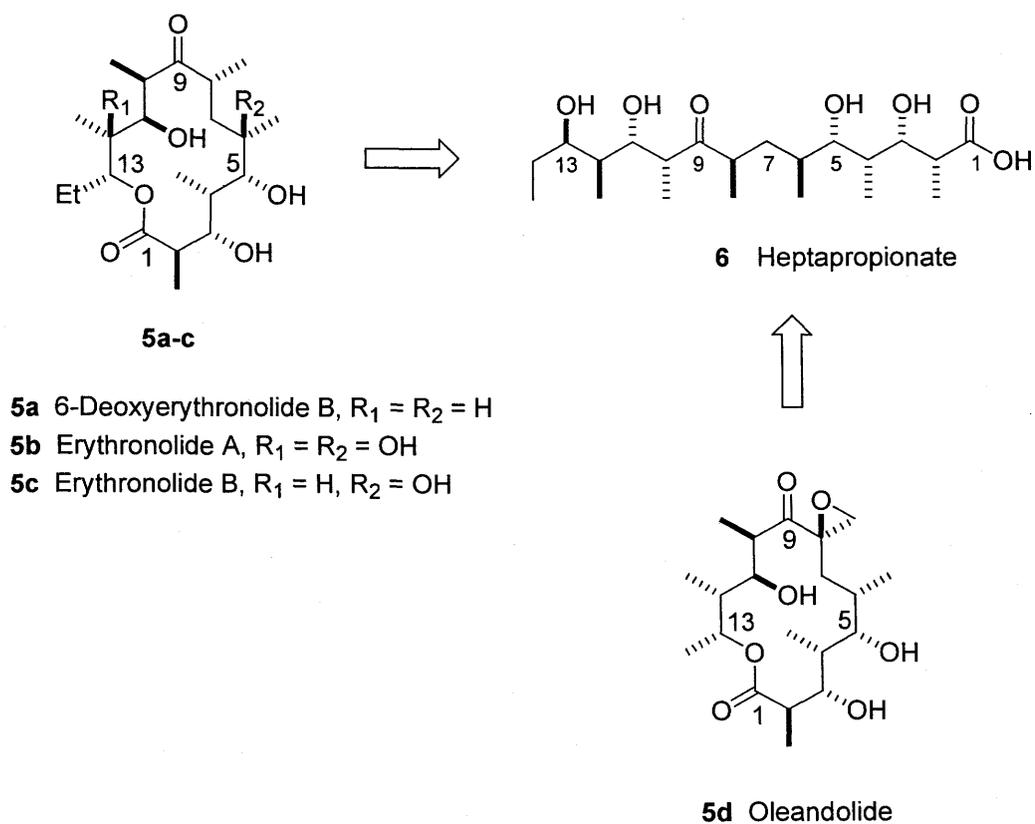
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\* Monomer **3** is synthetically equivalent to a polypropionate monomer since  $\alpha$ -CO<sub>2</sub>H substituent is removed upon chain elongation in the PKS catalyzed biosynthesis.

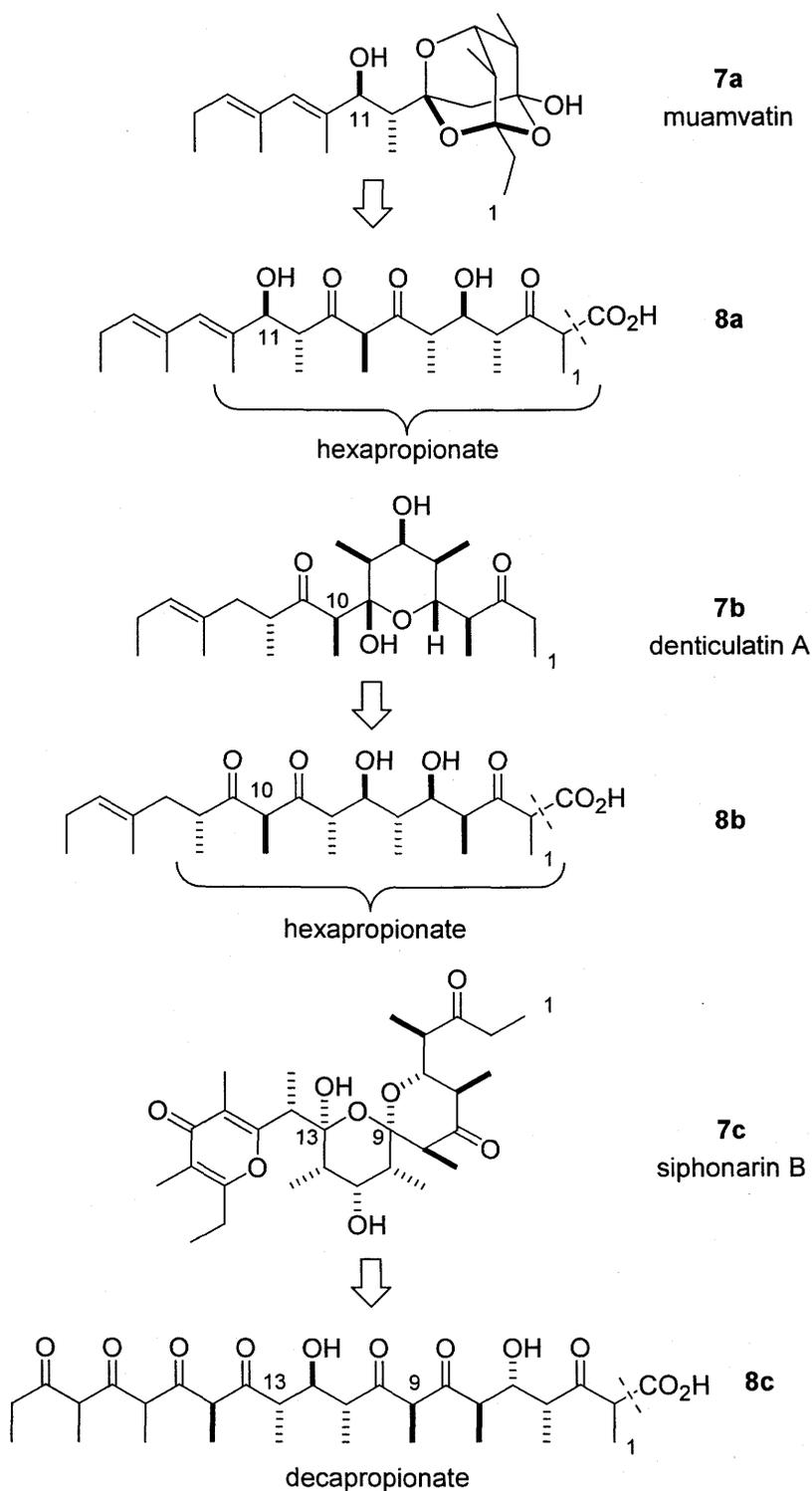
† Each carbon center on the polypropionate backbone that contains an hydroxyl or methyl substituent is a potential stereogenic center.



**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**.

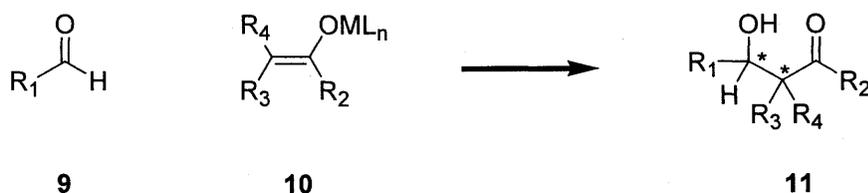
reactions<sup>6,25-44</sup>. The aldol reaction is highly suitable for the synthesis of polypropionates because it gives carbon chains with oxygen functionalities in the 1,3-positions. Highly

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)<sup>16,45,46</sup> (structurally related to the erythromycins **5a-c**, Figure 2), the hexapropionates **7a** (muamvatin)<sup>47,48</sup> and **7b** (denticulatin A)<sup>49-51</sup> and the decapropionate **7c** (siphonarín B)<sup>52</sup> (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  $\beta$ -hydroxy carbonyl product.<sup>53</sup> 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  $\alpha$ -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.<sup>53</sup> 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).<sup>54</sup>

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.<sup>55</sup> The principles governing the stereoselectivity of this versatile coupling reaction are presented in the following sections.



$\text{R}_1, \text{R}_3, \text{R}_4 = \text{H, alkyl, aryl}$

$\text{R}_2 = \text{H, alkyl, alkoxy, NR}_2, \text{SR}$

M = metal counterion such as Li, B, Mg, Sn, Ti

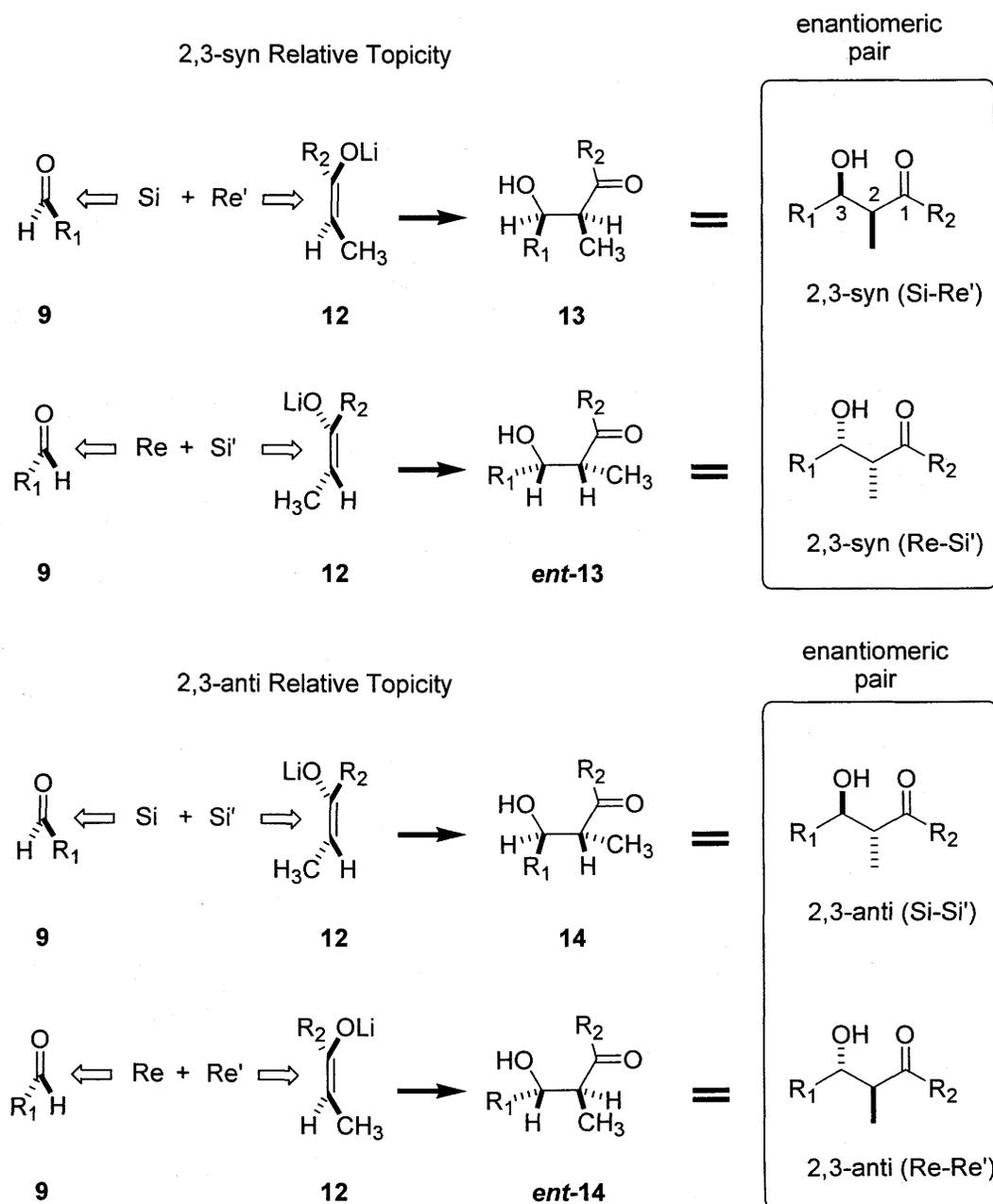
L = appropriate ligand such as halide alkyl, aryl, alkoxy, ester

**Figure 4.** Generalized aldol reaction

### 1.2.1. Relative Topicity with Achiral Substrates

The aldol reaction between achiral reaction partners leads to the formation of up to two stereogenic centers and up to four possible stereoisomeric products.<sup>54</sup> 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.<sup>54</sup> 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.

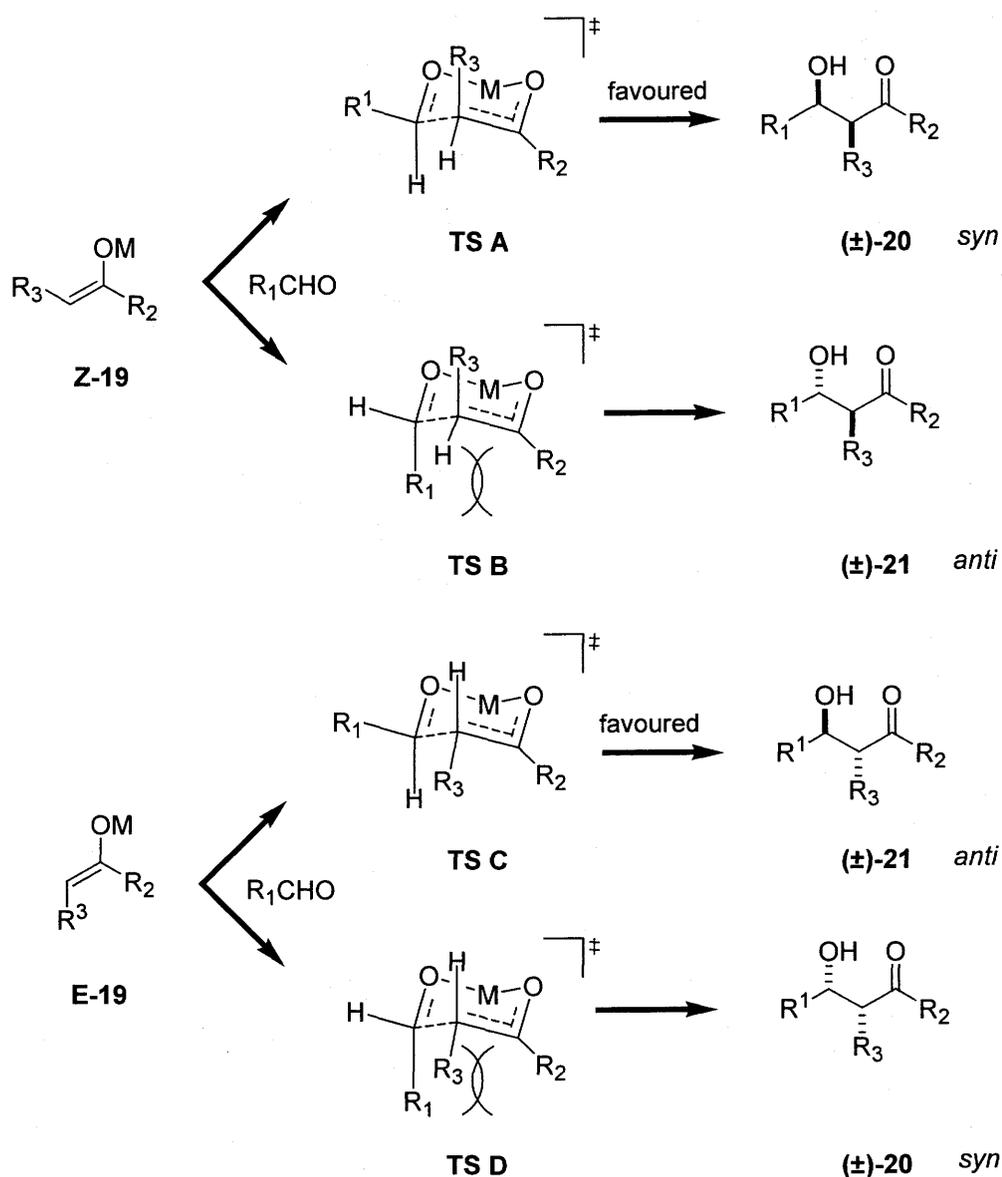
In an achiral environment, enantiomers will be produced in equal amounts; however, the syn and anti diastereomers will generally be produced in different amounts. The relative topicity of an aldol reaction describes the relative orientation of the reacting faces of the aldehyde and enol(ate). Under kinetic 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. *lk* [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:

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

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).<sup>56</sup> Furthermore it was found that with increasing steric bulk of the R<sub>2</sub> moiety (H < C<sub>2</sub>H<sub>5</sub> < *i*-C<sub>3</sub>H<sub>7</sub> < *t*-C<sub>4</sub>H<sub>9</sub>) the *syn* diastereoselectivity of the Z-enolate increased.<sup>57</sup> A similar but less pronounced trend was found for the E-enolate, which increasingly favoured *anti* diastereoselectivity as steric bulk of R<sub>2</sub> moiety increased.<sup>57</sup> These observations were rationalized with the model originally proposed by Zimmerman and Traxler (Figure 6).<sup>58</sup>

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<sub>1</sub> and R<sub>2</sub> occupy the axial orientations leading to a sterically unfavourable 1,3 diaxial interaction. Therefore as the steric demands of R<sub>2</sub> increase, transition state **B** from the Z-enolate will be relatively less favoured due to the increasingly unfavourable R<sub>1</sub>↔R<sub>2</sub> 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<sub>1</sub>↔R<sub>2</sub> steric interactions in TS C.

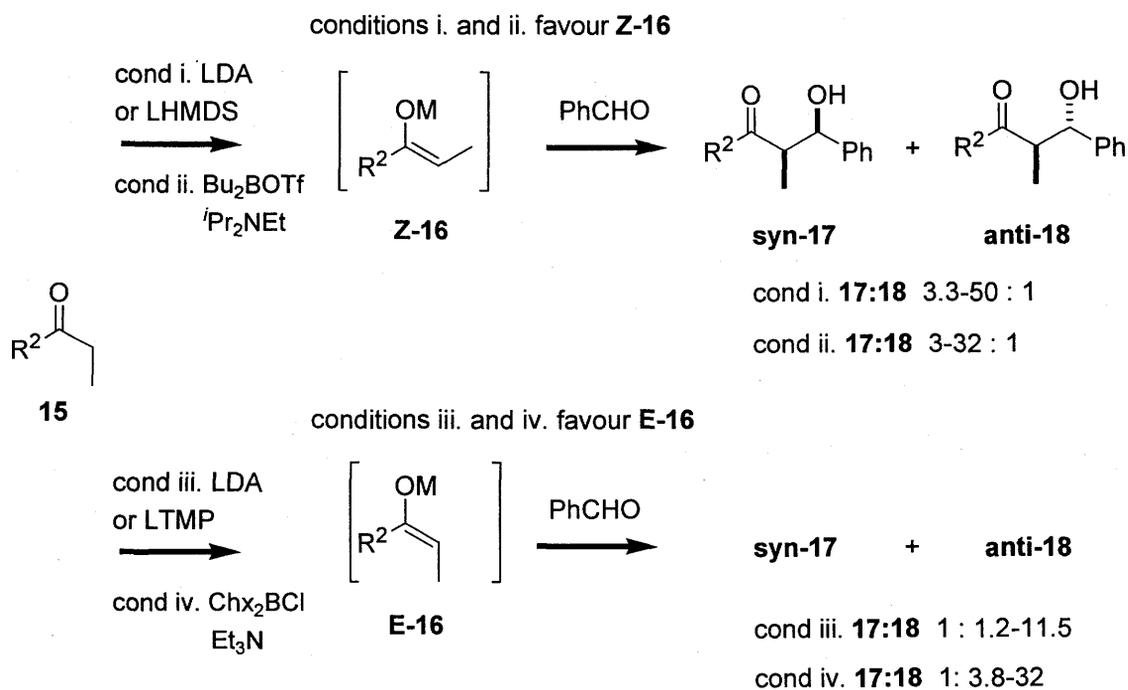


**Figure 6.** The Zimmerman-Traxler model

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).<sup>57</sup> 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. Et<sub>3</sub>N) provide the E-enolate (Scheme 1).<sup>59</sup> 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*-Pr<sub>2</sub>EtN) is used.<sup>60</sup> A theoretical model has been proposed to explain these trends.<sup>61,62</sup>

Mukaiyama found that certain Lewis acids were able to promote the reaction of enolsilanes with aldehydes to give aldol products.<sup>63</sup> 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.<sup>64</sup> From the examples of Lewis acid promoted aldol reactions given in Table 1, it is apparent that the preferred relative topicity of the Mukaiyama reaction is unaffected by the *E/Z* geometry of the enolsilanes. Clearly a Zimmerman-Traxler model cannot explain the observed stereoselectivities.

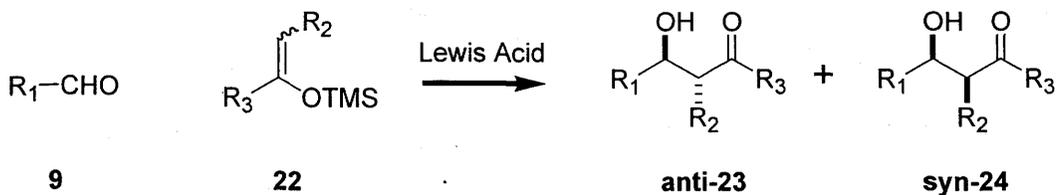


**Scheme 1.** Effect of *Z/E*-enolate geometry on aldol relative topicity<sup>56,57</sup>

Open transition state models place the trigonal carbons of the enolsilane and aldehyde components in a staggered orientation (Figure 7).<sup>65</sup> There are six possible

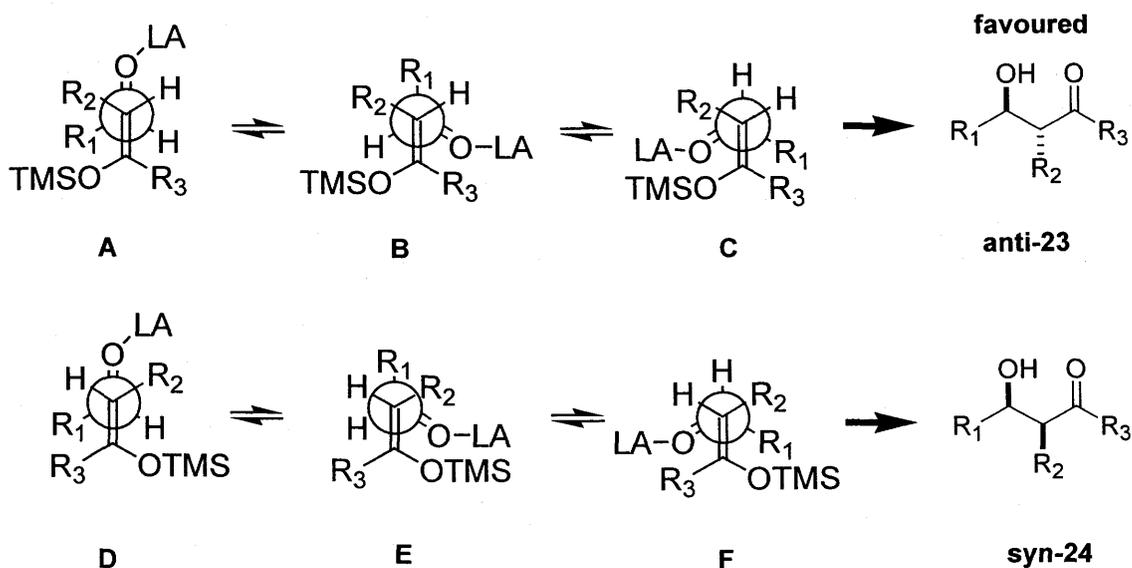
staggered orientations. Product formation is thought to be favoured from those orientations that minimize dipolar repulsion between the oxygens of the aldehyde and enolsilane and avoid unfavourable steric interactions between the substituents.

**Table 1.** Lewis acid promoted aldol reactions<sup>66</sup>



entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Enolsilane Z : E	Lewis acid	23 : 24 (anti:syn)	yield %
1	<sup>i</sup> Pr	Me	OEt	15 : 85	TiCl <sub>4</sub>	93 : 7	75
2	<sup>i</sup> Pr	Me	<sup>t</sup> Bu	100 : 0	BF <sub>3</sub> •OEt <sub>2</sub>	95 : 5	84
3	Ph	Me	OEt	25 : 75	TiCl <sub>4</sub> •PPh <sub>3</sub>	91 : 9	27
4	Ph	Me	<sup>t</sup> Bu	100 : 0	BF <sub>3</sub> •OEt <sub>2</sub>	95 : 5	95
5	Ph	<sup>t</sup> Bu	OEt	76 : 24	TiCl <sub>4</sub>	8 : 92	<sup>a</sup>
6	Ph	<sup>t</sup> Bu	OEt	5 : 95	TiCl <sub>4</sub>	8 : 92	<sup>a</sup>

<sup>a</sup> Not reported.



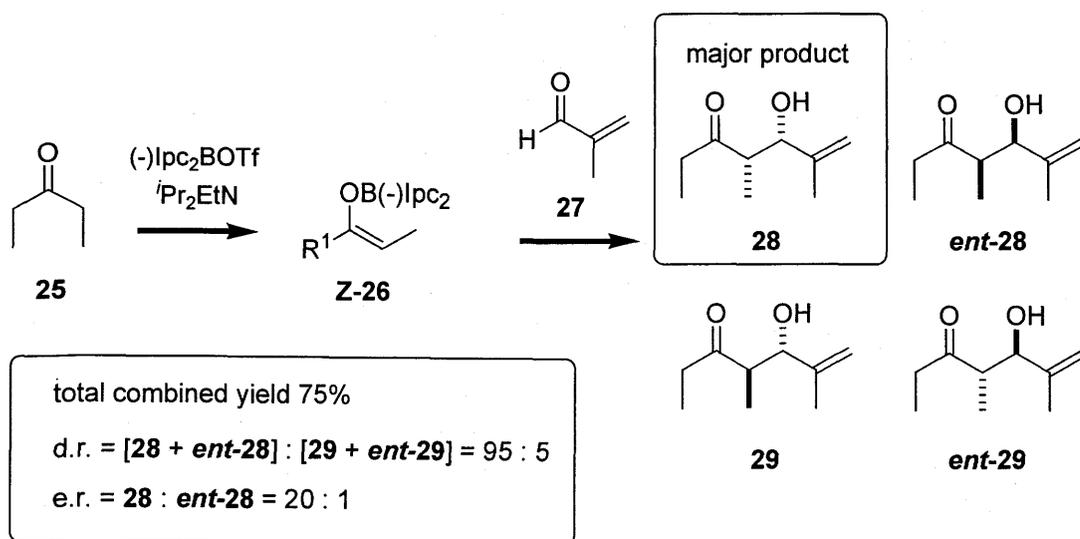
**Figure 7.** Open transition state model for Mukaiyama aldol reaction.

Notice that for entries 2 and 4 (Table 1) the Z-enolsilane 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 enolsilane components. Following the same reasoning as above, the preferred relative topicities of the aldol reactions in Table 1 can be rationalized.

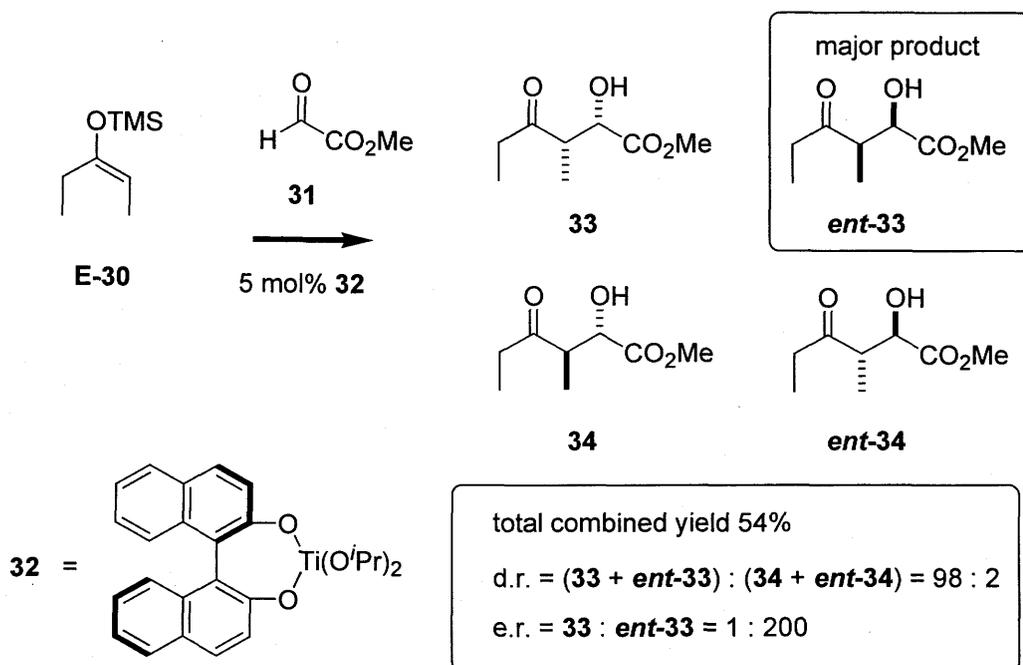
### 1.2.2. Enantioselectivity with Achiral Substrates

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 topology. A means to effect an enantioselective synthesis would require a reaction with a highly preferred relative topology under conditions where addition to one of the enantiotopic 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.<sup>67-70</sup> 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<sup>67</sup>. As expected, the reaction of the boron enolate with Z geometry (**Z-26**) occurred with high preference in the relative topology to give mostly syn adducts<sup>71</sup> (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<sup>67</sup>



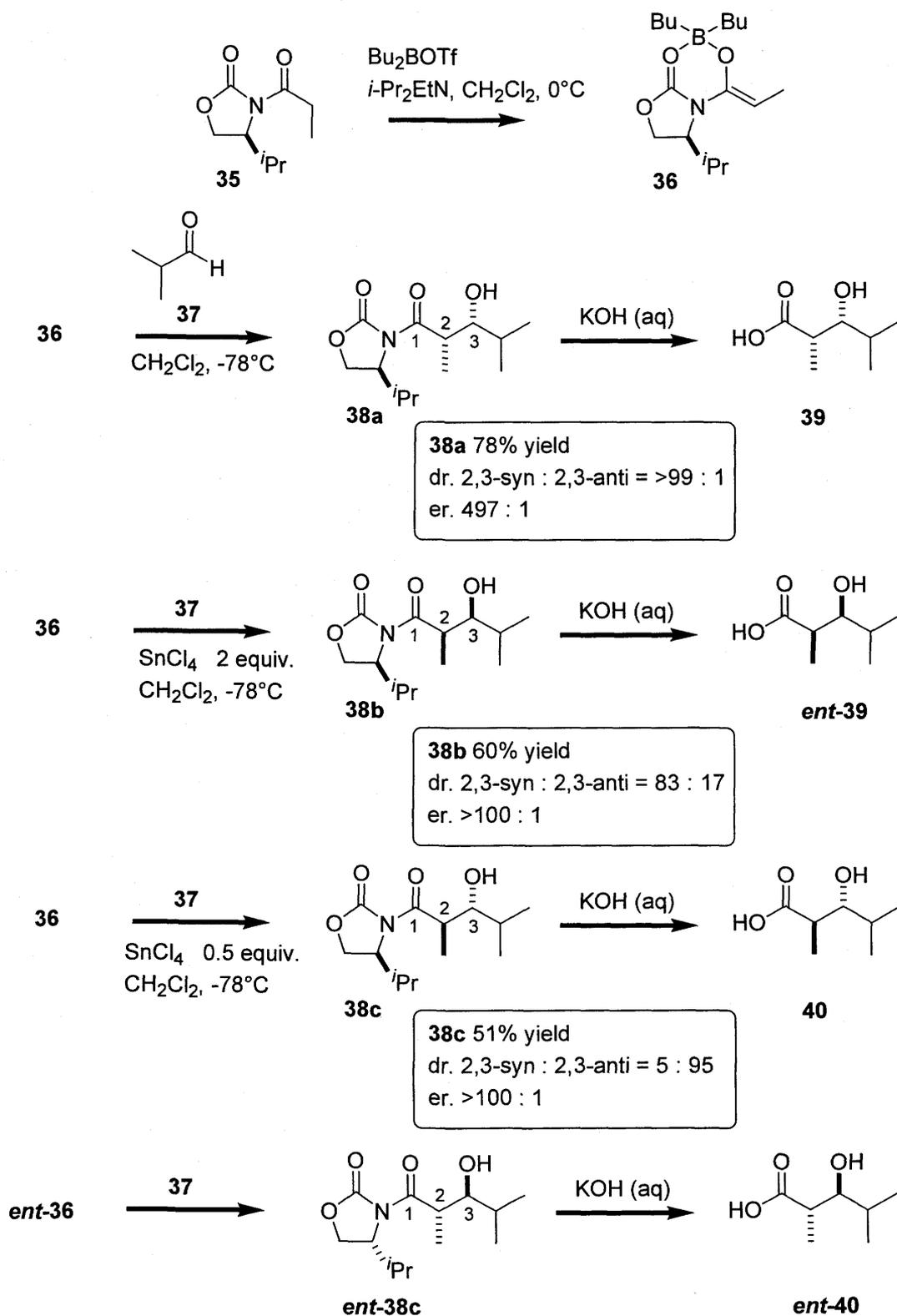
**Scheme 3.** The application of chiral Lewis acids for enantioselective aldol reaction.

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).<sup>72</sup> 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 topicity of Mukaiyama aldol reactions.

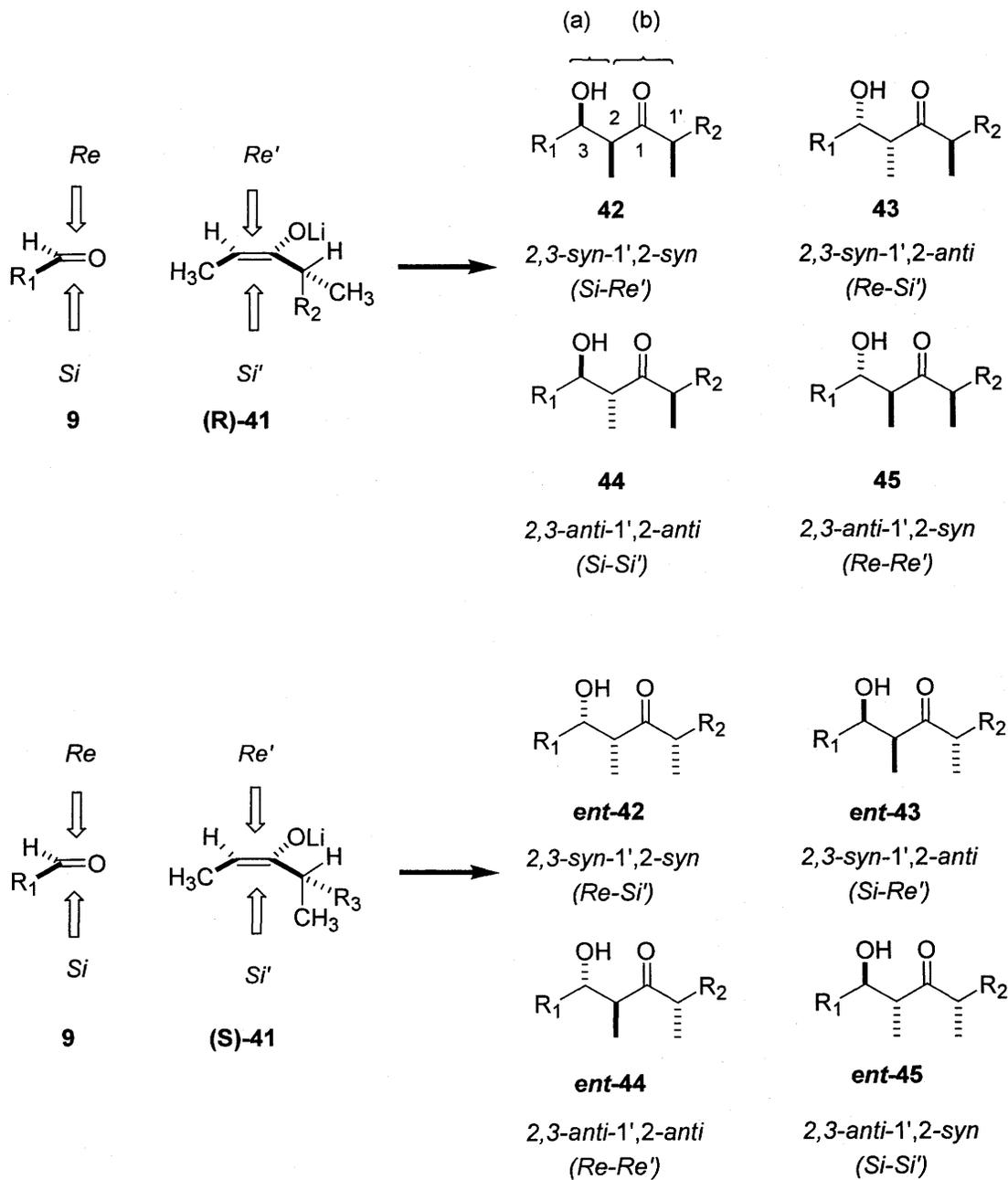
### 1.2.3. Diastereoface Selectivity: Reaction of a Chiral Enol(ate) with an Achiral Aldehyde

The two  $\pi$ -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 auxillary approach is a very powerful method for the stereoselective construction of polypropionate fragments (Scheme 4). An example originally developed by Evans,<sup>73,74</sup> 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 topicity to give syn adduct **38a**. Evans demonstrated that base hydrolysis (KOH) of **38a** gives **39** with negligible isomerization.<sup>73</sup> Heathcock et al. demonstrated that the presence of Lewis acids (SnCl<sub>4</sub>, TiCl<sub>4</sub> and Et<sub>2</sub>AlCl) can extend the scope of of the Evans imides for stereoselective synthesis.<sup>74,75</sup> For example, the reaction of **36** with **37** in presence of 2 equivalents of SnCl<sub>4</sub> stereoselectively gave **38b**, and in the presence of 0.5 equivalents of SnCl<sub>4</sub> 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 auxillary.

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 topology of aldol : 2,3-syn or 2,3-anti

(b) enolate diastereoface selectivity : 1',2-syn or 1',2-anti

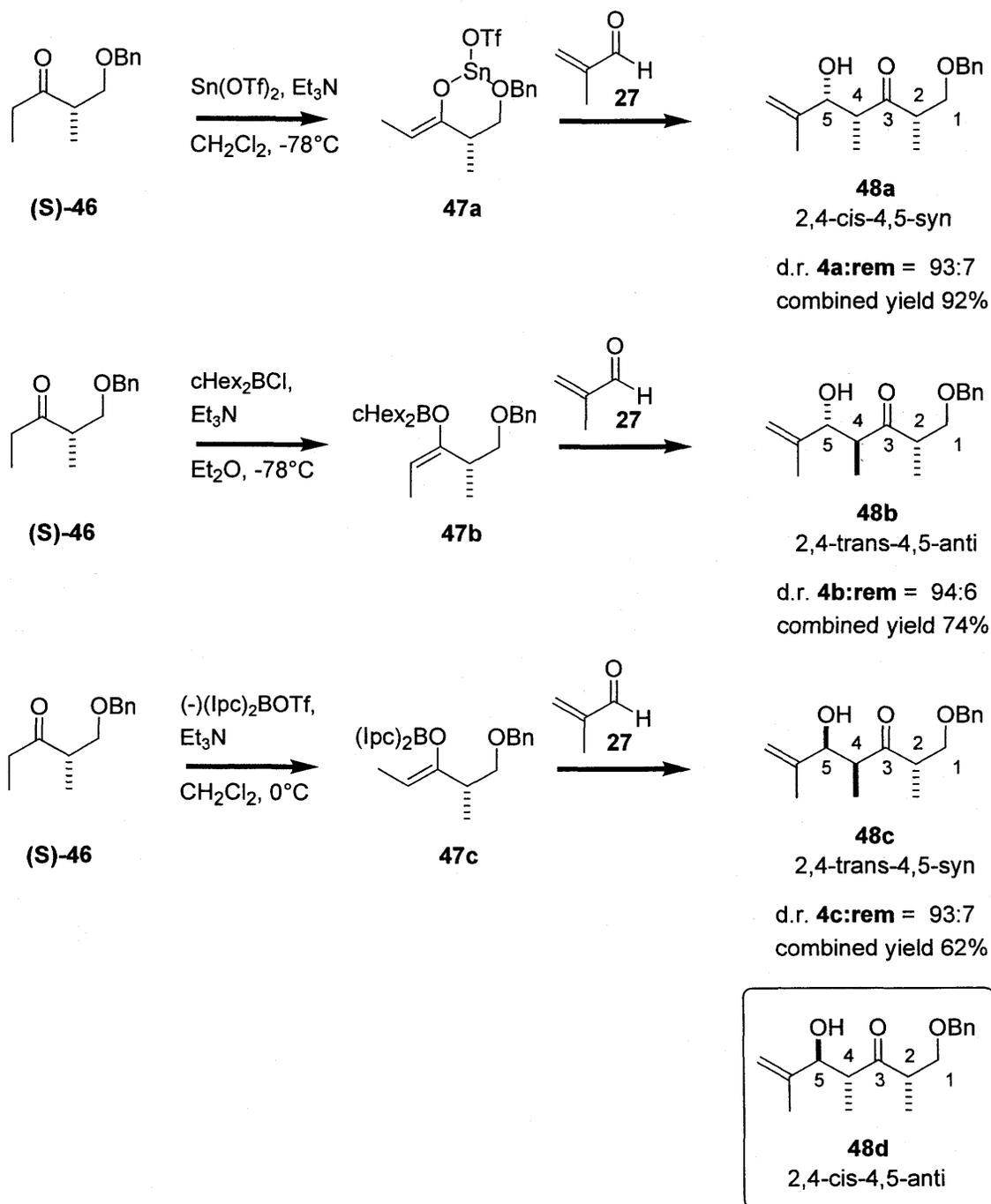
**Figure 8.** Aldol reaction between chiral enolate **41** with achiral aldehyde **9**.

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).<sup>54</sup> 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 ( $\pm$ )-**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 ( $\pm$ )-**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  $([\mathbf{42}] + [\mathbf{45}]) \div ([\mathbf{43}] + [\mathbf{44}])$ .

The application of chiral ethyl ketones **46** to polypropionate synthesis by Paterson et al.<sup>76-79</sup> 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  $\text{Sn}(\text{OTf})_2$  and  $\text{Et}_3\text{N}$  was optimal for the formation of *Z*-enolate **47a** from **(S)-46**<sup>77</sup> (Scheme 5). The aldol reaction of **47a** with **27**

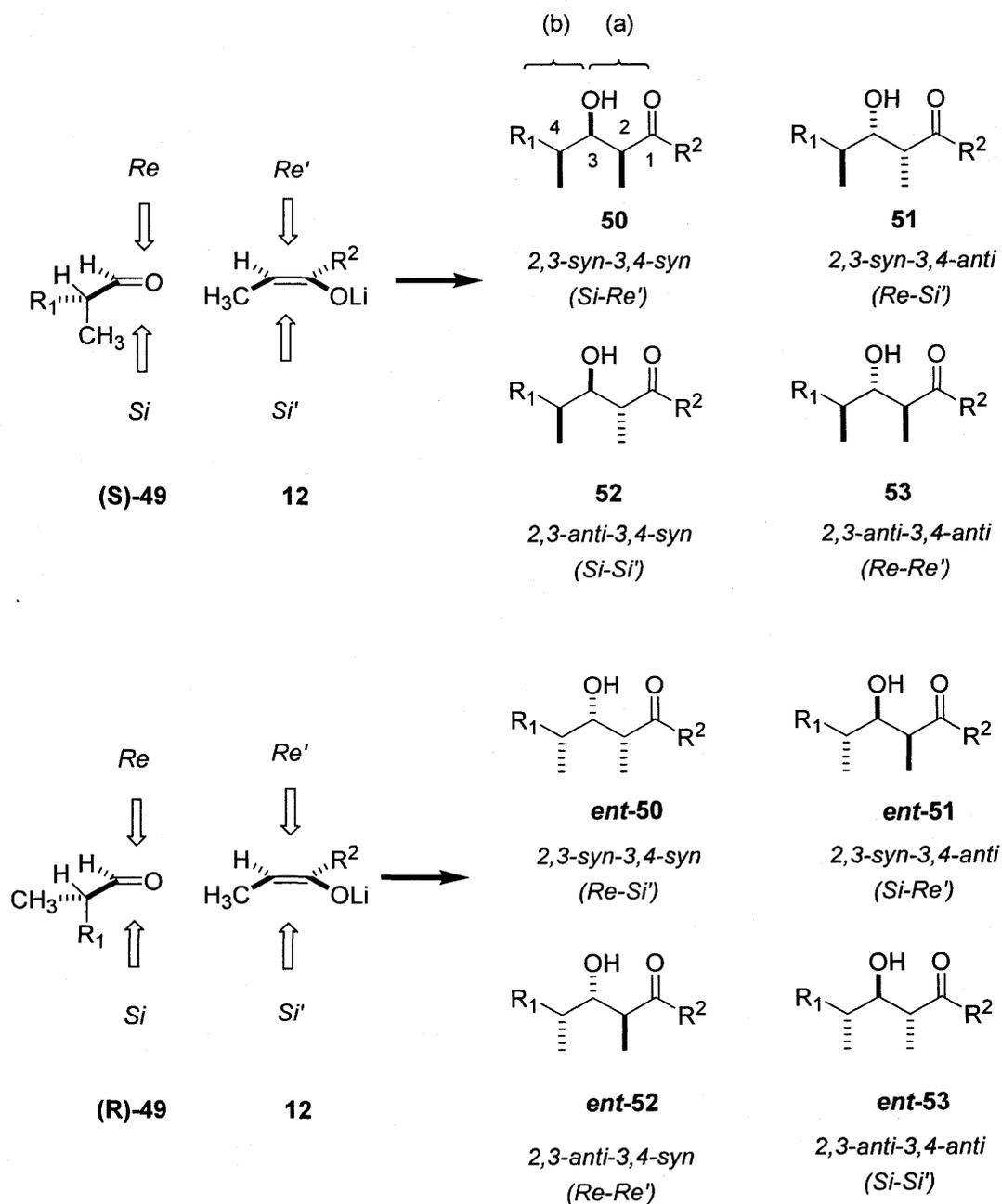
was selective for the formation of **48a** which results from preferential 4,5-syn aldol relative topicity and 2,4-syn enolate diastereoface addition (Scheme 5).<sup>77,80</sup> Reaction of the E-boron enolate **47b** with **27** gave **48b** with excellent stereoselectivity.<sup>79</sup> The observed 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.<sup>78</sup> 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 diastereoface selectivity (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 Enol(ate)

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).<sup>54</sup> 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 diastereomers (*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 ( $\pm$ )-**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 ( $\pm$ )-**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  $([\mathbf{50}] + [\mathbf{52}]) \div ([\mathbf{51}] + [\mathbf{53}])$ .

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.

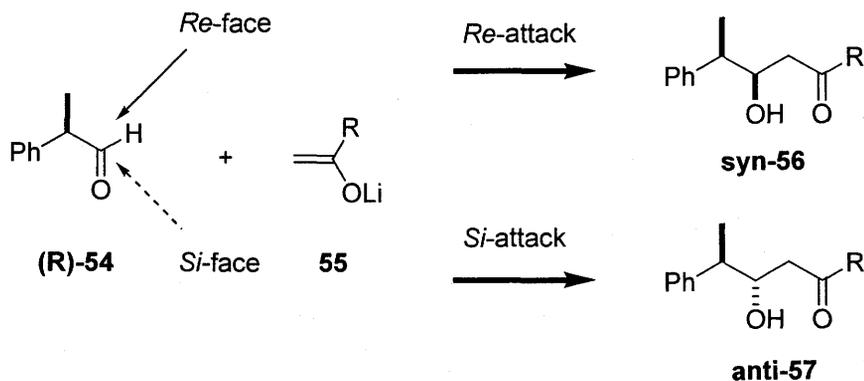
#### 1.2.4.1. 1,2-Stereoinduction models

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).<sup>81</sup>

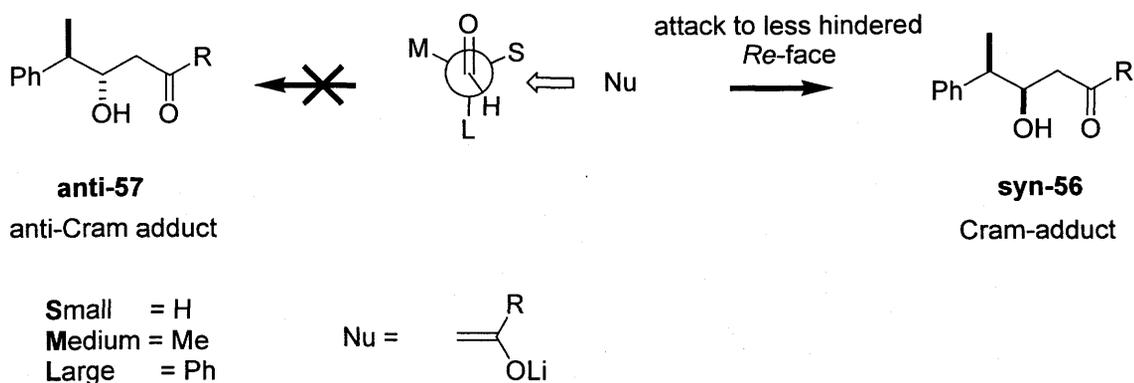
The empirical model originally proposed by Cram for Grignard additions to aldehydes successfully predicted the aldehyde diastereofacial preference of addition of lithium-enolates to  $\alpha$ -methyl substituted aldehydes.<sup>82</sup> Cram's model for aldehydes where the stereogenic center is at the  $\alpha$ -position considers the conformation that orients the largest group **L** of the three  $\alpha$ -substituents *anti* 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**<sup>81</sup>



entry	R	56 : 57	yield (%)
1	Me	3 : 1	89
2	<sup>t</sup> Bu	4 : 1	80
3	MeO	3 : 1	91
4	<sup>t</sup> BuO	4 : 1	70
5	Me <sub>2</sub> N	3 : 1	67

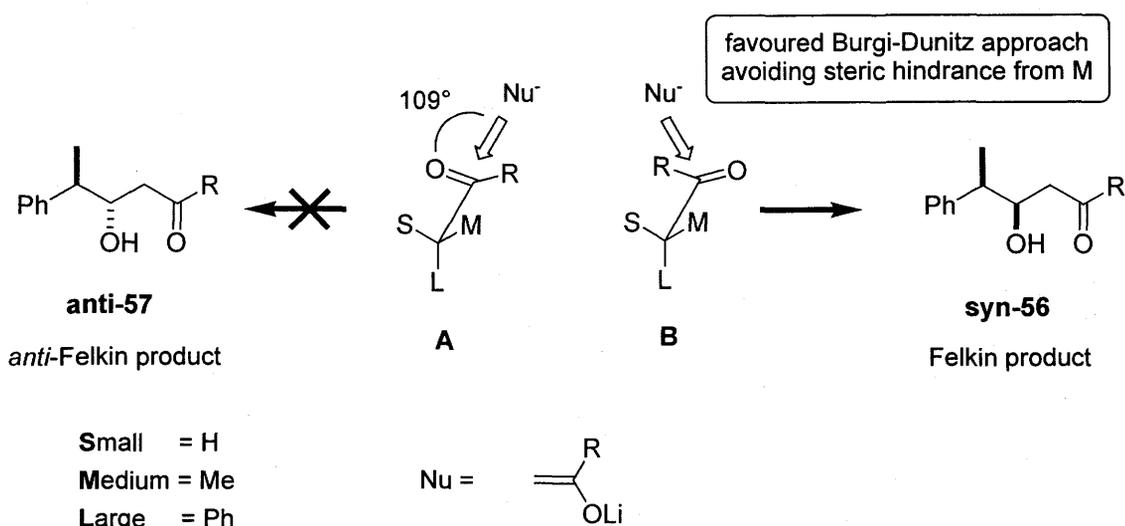


**Figure 10.** The Cram model predicts *Re*-face attack

A more recent explanation to account for the observed *Re*-diastereofacial selectivity presented in Table 2, was proposed by Felkin, Anh and Eisenstein.<sup>66,83-85</sup> 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 a 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  $109^\circ$  angle to the plane of the aldehyde face, the so-called Burgi-Dunitz trajectory.<sup>86-90</sup> 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  $109^\circ$  then TS **B** has less steric hindrance to the nucleophile than TS **A**.



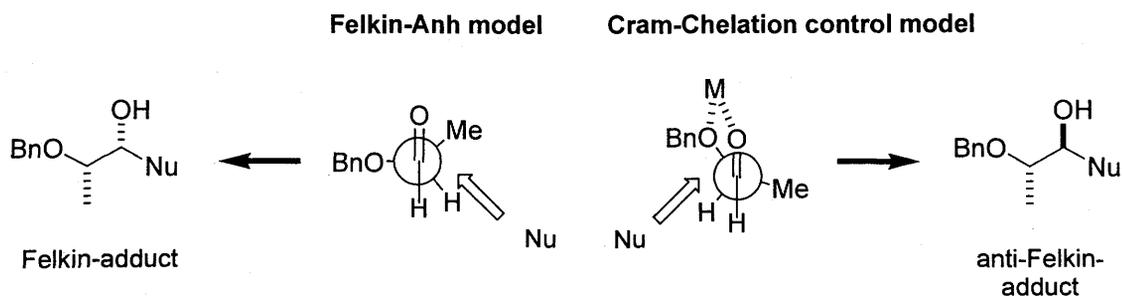
**Figure 11.** Predicting aldehyde diastereoface selectivity with the Felkin-Anh model

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.<sup>91</sup> In this model, it is assumed that the Lewis acidic Mg (II) coordinates to both oxygens, and addition occurs preferentially from the least hindered face of the chelated intermediate (Figure 12).

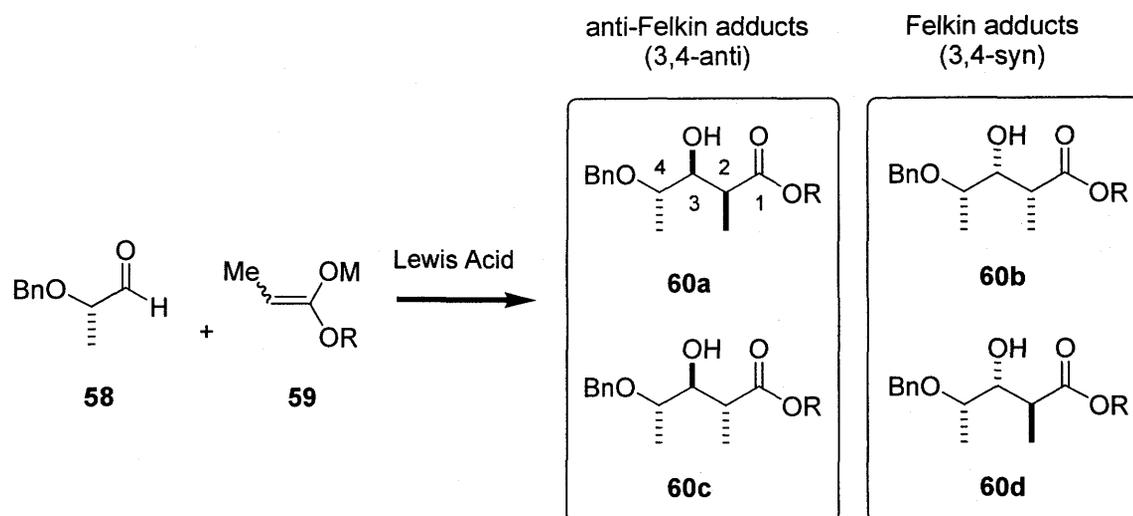
Table 3 presents the results of addition of enolates **59** to the  $\alpha$ -alkoxy aldehyde **58** under several conditions.<sup>92</sup> The aldehyde diastereoface selectivities in entries 1, 2 and 3 are in accordance to the predictions of the Felkin-Anh model. However, the diastereoface selectivities 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).<sup>91</sup> 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  $\alpha$ -alkoxy aldehyde to form a reactive chelated intermediate.<sup>93</sup> 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).<sup>91,93</sup>



**Figure 12.** Felkin-Anh and the Cram-chelation control model to rationalise the 1,2-stereoselection of an  $\alpha$ -alkoxy aldehyde.

**Table 3.** Diastereoface selectivity for addition of **59** to **58**<sup>92</sup>



entry	R	M	Z-59 : E-59	Lewis acid	3,4-syn : 3,4-anti <sup>a</sup>	2,3-syn : 2,3-anti <sup>b</sup>
1	Me	Li	5 : 95	-	20 : 80	69 : 31
2	Me	Li	95 : 5	-	26 : 74	84 : 16
3	<sup>t</sup> Bu	Li	>99 : 1	-	21 : 79	66 : 34
4	Me	TMS	17 : 83	TiCl <sub>4</sub>	>99 : 1	23 : 77
5	Me	TMS	17 : 83	SnCl <sub>4</sub>	>99 : 1	20 : 80
6	<sup>t</sup> Bu	TMS	>99 : 1	TiCl <sub>4</sub>	89 : 11	65 : 35
7	<sup>t</sup> Bu	TMS	>99 : 1	SnCl <sub>4</sub>	88 : 11	66 : 34

<sup>a</sup> The aldehyde diastereoface selectivity i.e. Felkin : anti-Felkin. <sup>b</sup> The relative topicity.

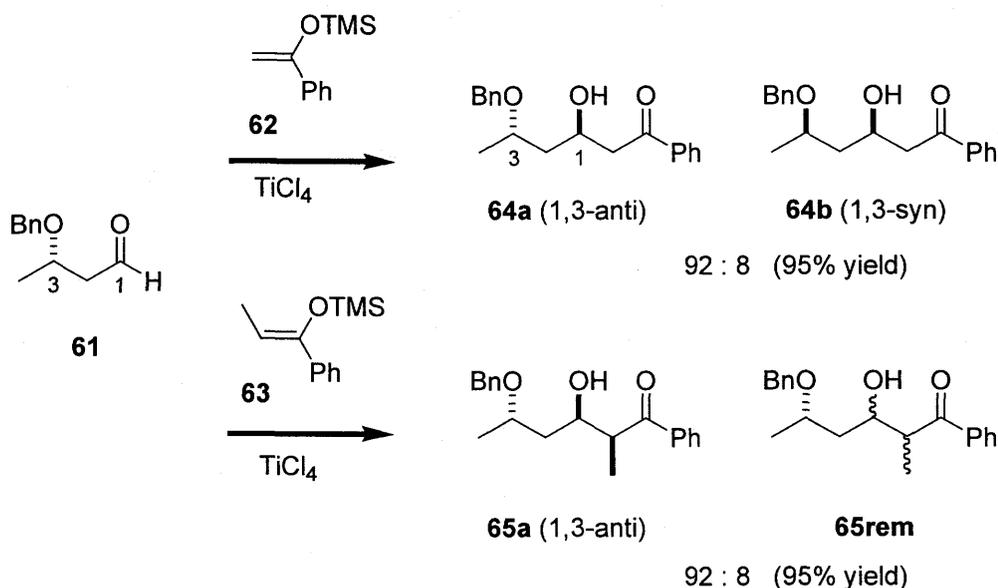
#### 1.2.4.2. 1,3-Stereoinduction models

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

\*  $\beta$ -Position is also known as position 3 where the aldehyde carbon is designated position 1, hence the term 1,3-stereoinduction.

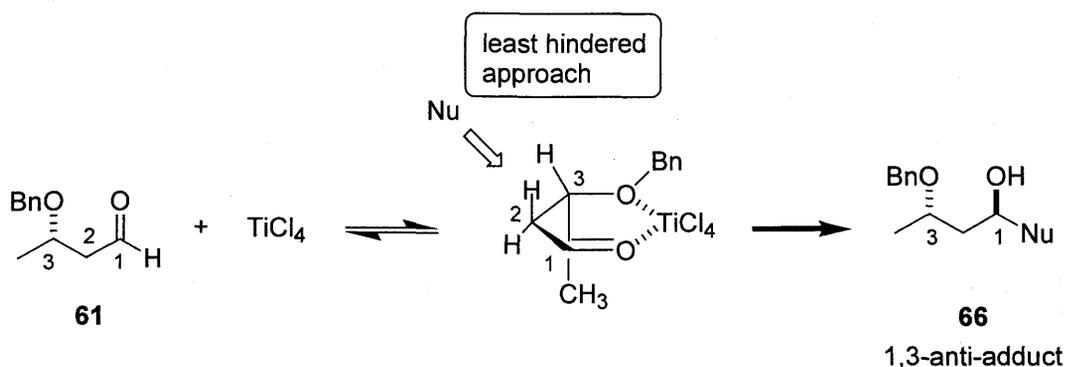
<sup>†</sup> Also known as non-chelation control models.

to study 1,3-stereoselection in the Lewis acid promoted Mukaiyama aldol reactions with enolsilanes (Scheme 6).<sup>94,95</sup>



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

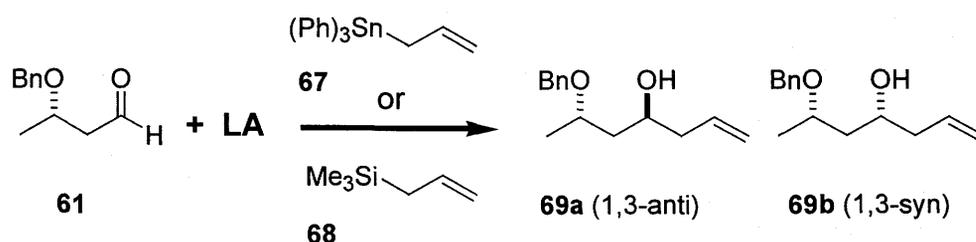
Reactions of **61** with **62** and **63** occur with high aldehyde diastereoface selectivity to give 1,3-anti adducts. To account for the observed diastereofacial preference it was proposed that the addition of the nucleophilic enolsilane occurred from the least hindered face of a Ti-aldehyde chelate (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  $^1\text{H}$  NMR spectra of solutions of  $\text{TiCl}_4$  and **61**. It was concluded that a conformationally rigid 1:1  $\text{TiCl}_4$ :aldehyde complex was formed. The conformation of the chelate aldehyde was derived from an analysis of vicinal coupling constants observed in the  $^1\text{H}$  NMR spectrum. To account for the relatively small vicinal coupling constants between  $\text{H}_2\text{C-2}$  and  $\text{HC-3}$  (4.7 and 4.7 Hz), it was proposed that the 1:1 complex was a chelate with a conformation where proton  $\text{HC-3}$  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.



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

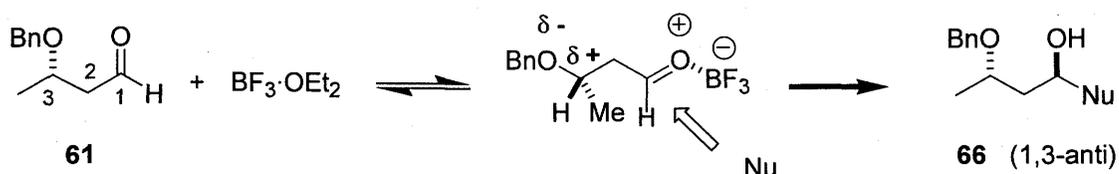
Studies of the effect of various Lewis acids on the diastereoface selective additions of allyl stannane and allyl trimethylsilane to the aldehyde **61** were performed (Table 4).<sup>96,97</sup> The 1,3-anti adduct was formed preferentially in all cases. The diastereoselective formation of **69a** in the presence of Lewis acids TiCl<sub>4</sub>, MgBr<sub>2</sub> and SnCl<sub>4</sub> known to have two vacant coordination sites can be explained using the previously discussed bidentate chelate model (Figure 13). However, because BF<sub>3</sub>•OEt<sub>2</sub> has only one vacant coordination site, BF<sub>3</sub>•OEt<sub>2</sub> cannot coordinate to both heteroatoms simultaneously to give a bidentate chelate, an alternative model is required to rationalize the observed stereoselectivity.

**Table 4.** Lewis acid promoted allyl-stannane **67** and allyl-silane **68** addition to  $\beta$ -substituted aldehyde **61**.<sup>96,97</sup>



69a (1,3-anti) : 69b (1,3-syn)					
entry	Allyl reagent	TiCl <sub>4</sub>	MgBr <sub>2</sub>	SnCl <sub>4</sub>	BF <sub>3</sub> •OEt <sub>2</sub>
1	<b>67</b>	32 : 1	8.1 : 1	3.4 : 1	3.9 : 1
2	<b>68</b>	95 : 5	-	95 : 5	85 : 15

To account for the observed aldehyde diastereoface selectivity Reetz proposed that the coordination of the oxygen of the aldehyde to  $\text{BF}_3 \cdot \text{OEt}_2$  resulted in a complex which assumed an extended linear conformation so as to minimize electrostatic repulsions (Figure 14).<sup>97</sup> 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.

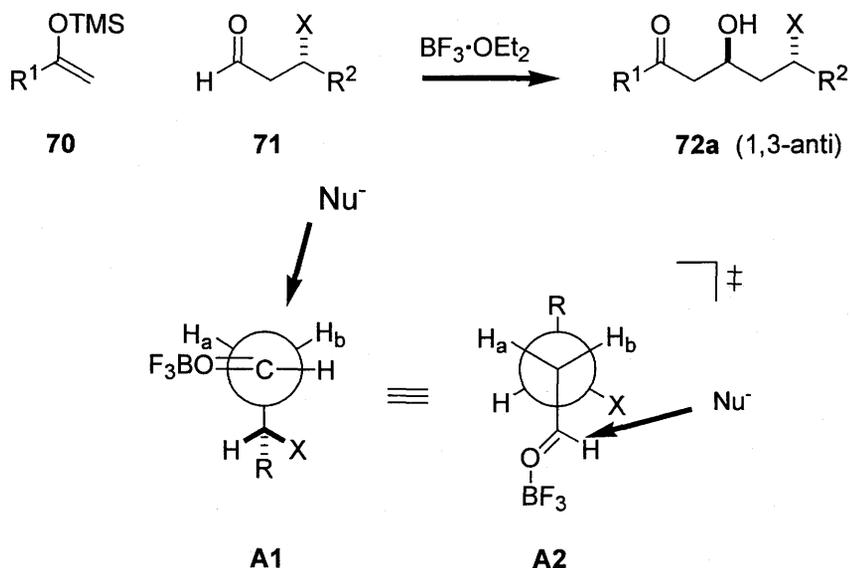


**Figure 14.** Reetz's polar 1,3 stereoinduction model.<sup>97</sup>

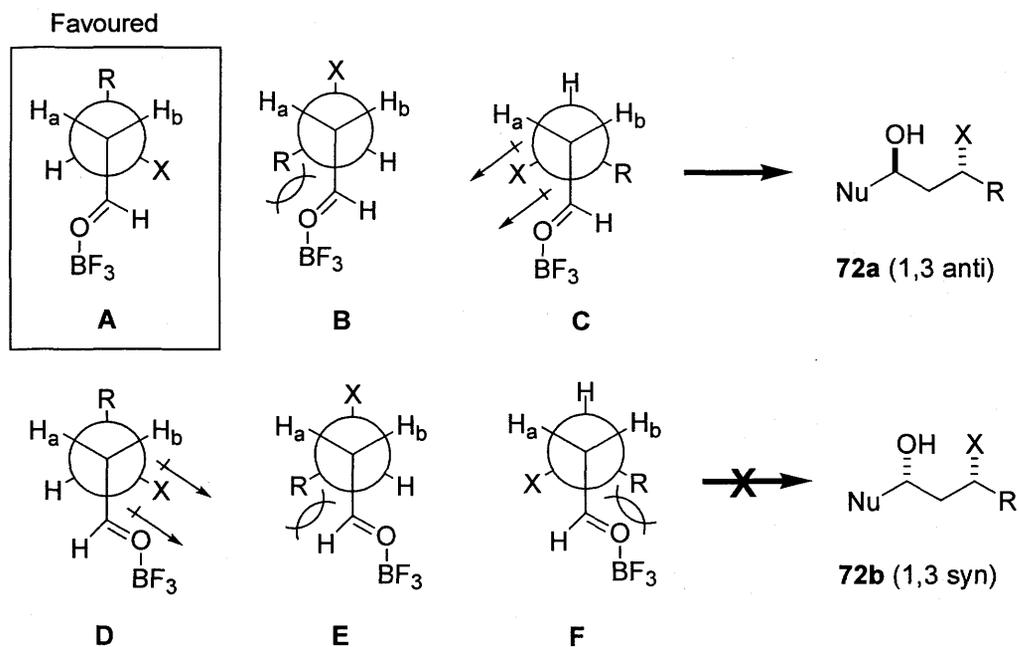
Though Reetz's proposed polar 1,3-stereoinduction model successfully accounts for the aldehyde diastereofacial preference, it did not take into account the electrostatic interactions within the aldehyde substrate that affect the torsion angles along the carbon backbone of the aldehyde. Evans proposed a revised polar 1,3 stereoinduction model based on electrostatic interactions within the aldehyde which also included the effect of  $\alpha$ -substituents according to the Felkin-Anh model for 1,2-stereoinduction.<sup>98</sup> 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  $\alpha$ -substituents such that the largest group at the  $\alpha$ -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  $\beta$  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  $\beta$ -substituent

is orientated *anti* to the C $\alpha$ -C=O bond to minimize steric interactions (Figure 16).



**Figure 15.** Evans revised polar 1,3-stereoreduction model.



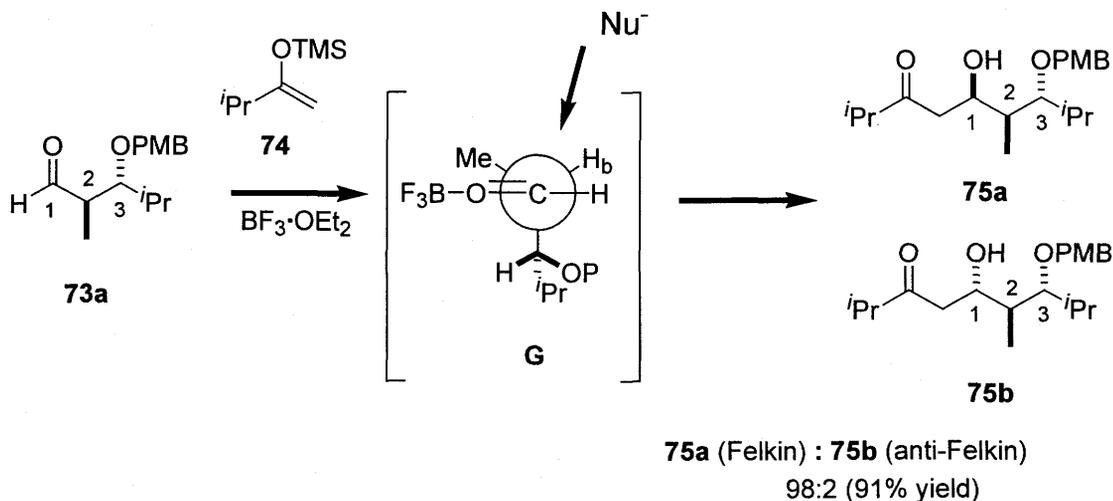
**Figure 16.** Steric and electronic interactions present in the conformers of the BF<sub>3</sub> coordinated aldehyde.

Conformers **B** and **F** are destabilized by the sterically unfavourable *gauche* interaction present between the  $\beta$ -substituent and C=O group. Conformers **C** and **E** are also

expected to become unfavourable as the size of the  $\beta$ -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 *anti* aldol adduct.

#### 1.2.4.3. Merged 1,2- and 1,3-stereoselection model

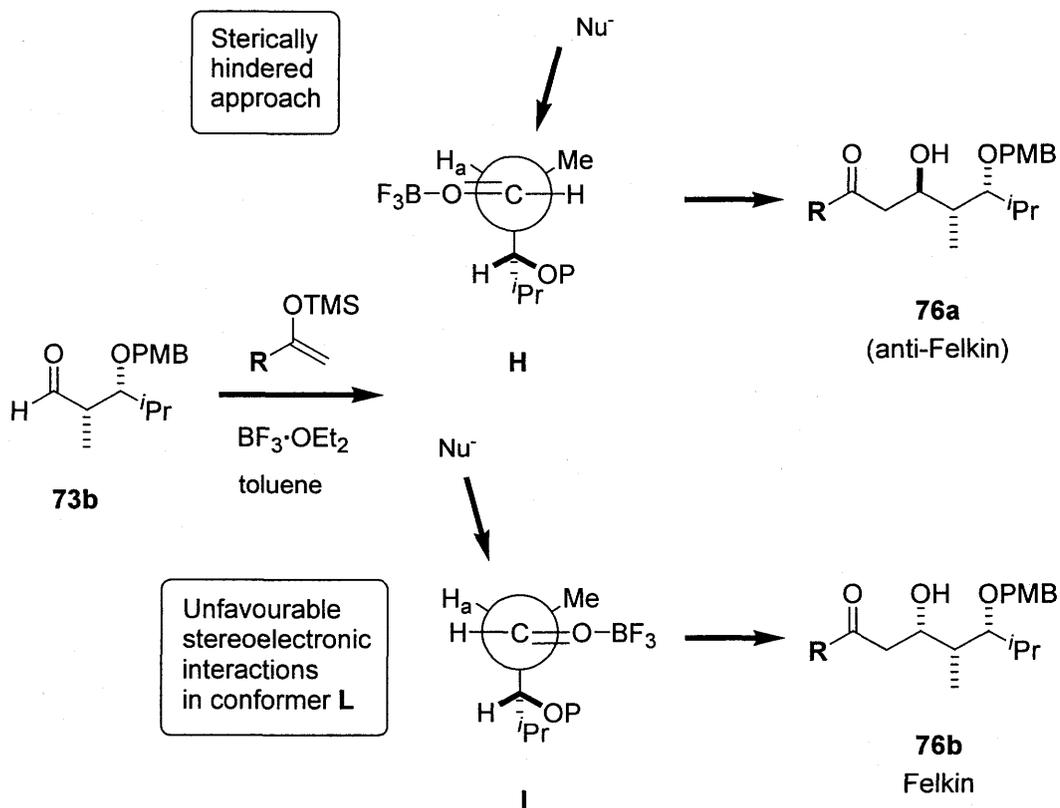
To account for the presence of  $\alpha$ -substituents on the degree of 1,3-stereoselection, Evans has elegantly proposed a merged 1,2- and 1,3-stereoselection model to rationalize the observed selectivities in substrates which have substituents at both the  $\alpha$ - and  $\beta$ -positions to the 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-stereoselection) and Evans's revised polar 1,3-stereoselection model (see section 1.2.4.1 and 1.2.4.2).



**Figure 17.** Evans' merged 1,2- and 1,3-stereoselection model for substrates with a 2,3-*anti* relationship.

In essence, this merged model simply replaced either of the  $H_a$  or  $H_b$  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  $\alpha$ -methyl and  $\beta$ -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-syn relationship.

Alternatively, if  $\text{H}_b$  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  $\alpha$ - and  $\beta$ -stereogenic centers are not known.

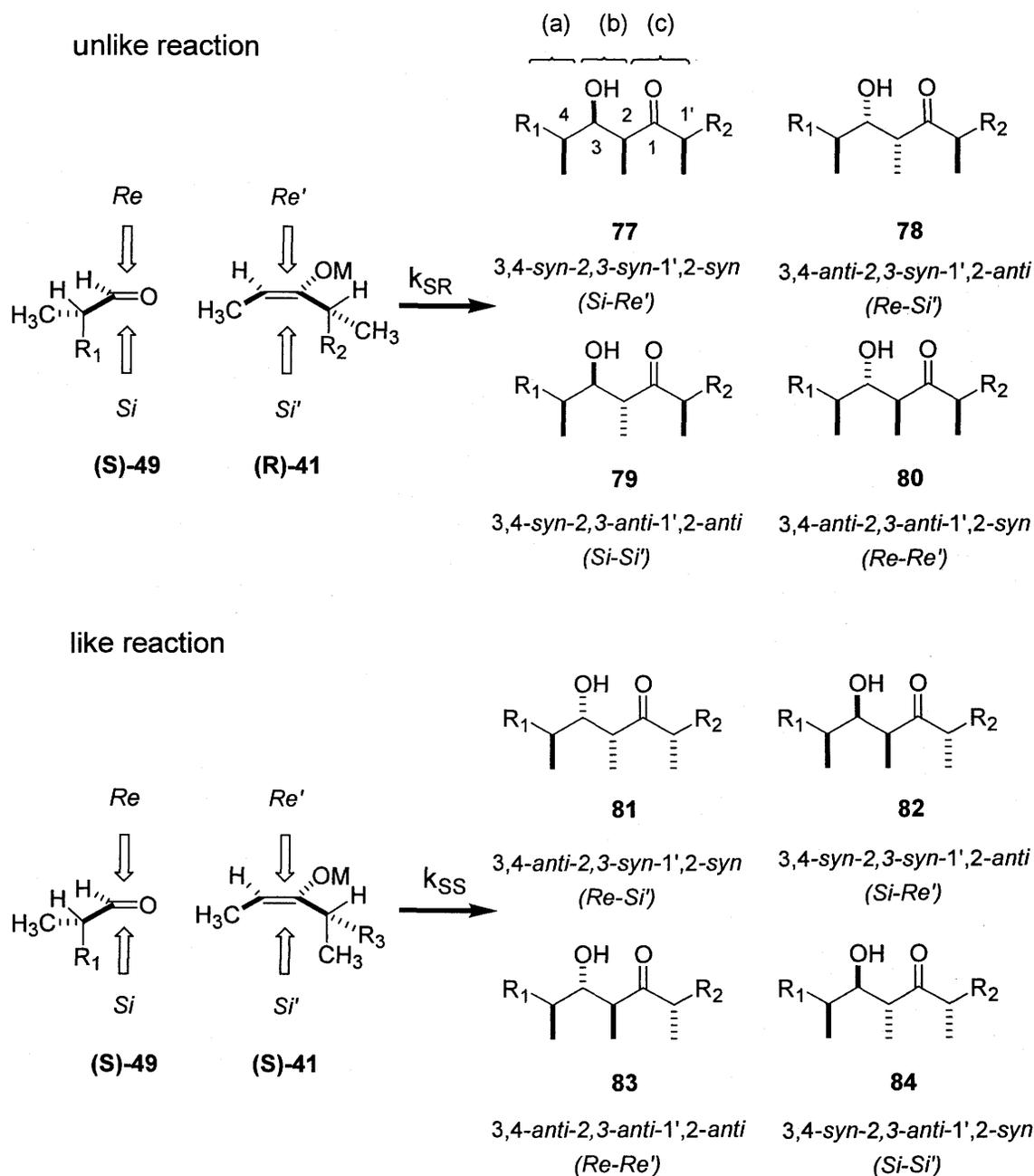
### **1.2.5. Double Stereodifferentiation, Kinetic Resolution, and Mutual Kinetic Enantioselection: Reaction of a Chiral Aldehyde with a Chiral Enol(ate).**

#### *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.



- (a) aldehyde diastereoface selectivity : 3,4-*syn* or 3,4-*anti*  
 (b) aldol relative topicity : 2,3-*syn* or 2,3-*anti*  
 (c) enolate diastereoface selectivity : 1',2-*syn* or 1',2-*anti*

**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.<sup>99</sup>

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'<sup>100</sup> and 'double asymmetric synthesis'.<sup>101</sup> 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.<sup>102</sup> 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.<sup>a</sup>

Entry	Aldol adduct	Aldehyde d.s.	Enolate d.s.	Relative topicity
1	77	3,4-syn	1',2-syn	2,3-syn
2	78	3,4-anti	1',2-anti	2,3-syn
3	79	3,4-syn	1',2-anti	2,3-anti
4	80	3,4-anti	1',2-syn	2,3-anti
5	81	3,4-anti	1',2-syn	2,3-syn
6	82	3,4-syn	1',2-anti	2,3-syn
7	83	3,4-anti	1',2-anti	2,3-anti
8	84	3,4-syn	1',2-syn	2,3-anti

<sup>a</sup> 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

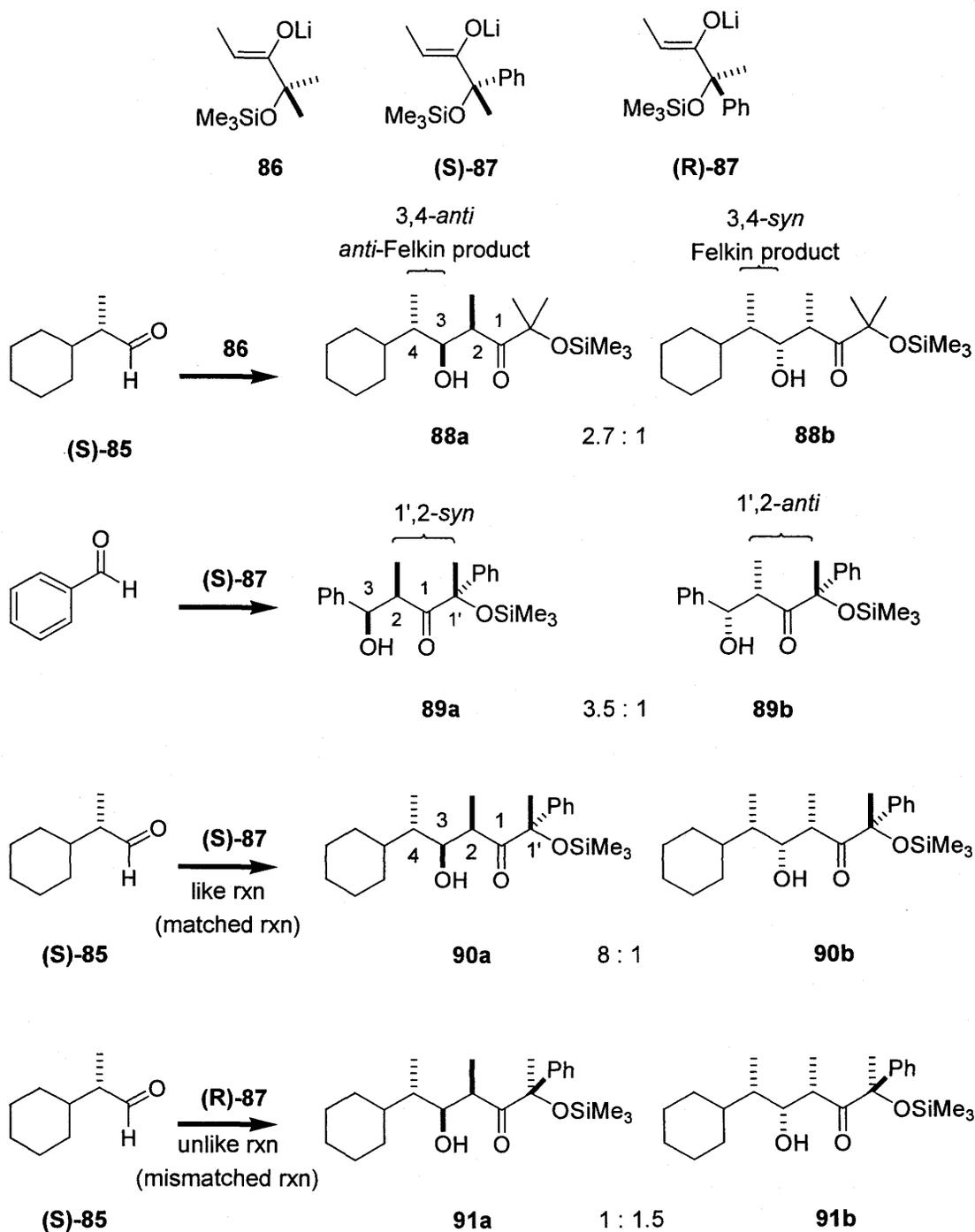
The unlike reaction of (**S**)-**49** with (**R**)-**41** can give adduct **77** (Table 5, entry 1) which results from the favoured selectivities of all three stereochemical control elements; the other three possible adducts (**78**, **79** and **80**) each results from a combination where only one of 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.<sup>101</sup> For example, consider the aldol reaction of **85** and **87** (Figure 20).<sup>101</sup> 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.<sup>103</sup> 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)

#### Rule of Multiplicativity

Diastereoselectivity of matched rxn:

$$90a : 90b = 8 : 1$$

Diastereoselectivity of mismatched rxn:

$$91a : 91b = 1 : 1.5$$

Predicted Diastereoselectivity  
of matched rxn:

Aldehyde d.s. x Enolate d.s

$$3.5 \times 2.7 = 9.5$$

Predicted Diastereoselectivity  
of mismatched rxn:

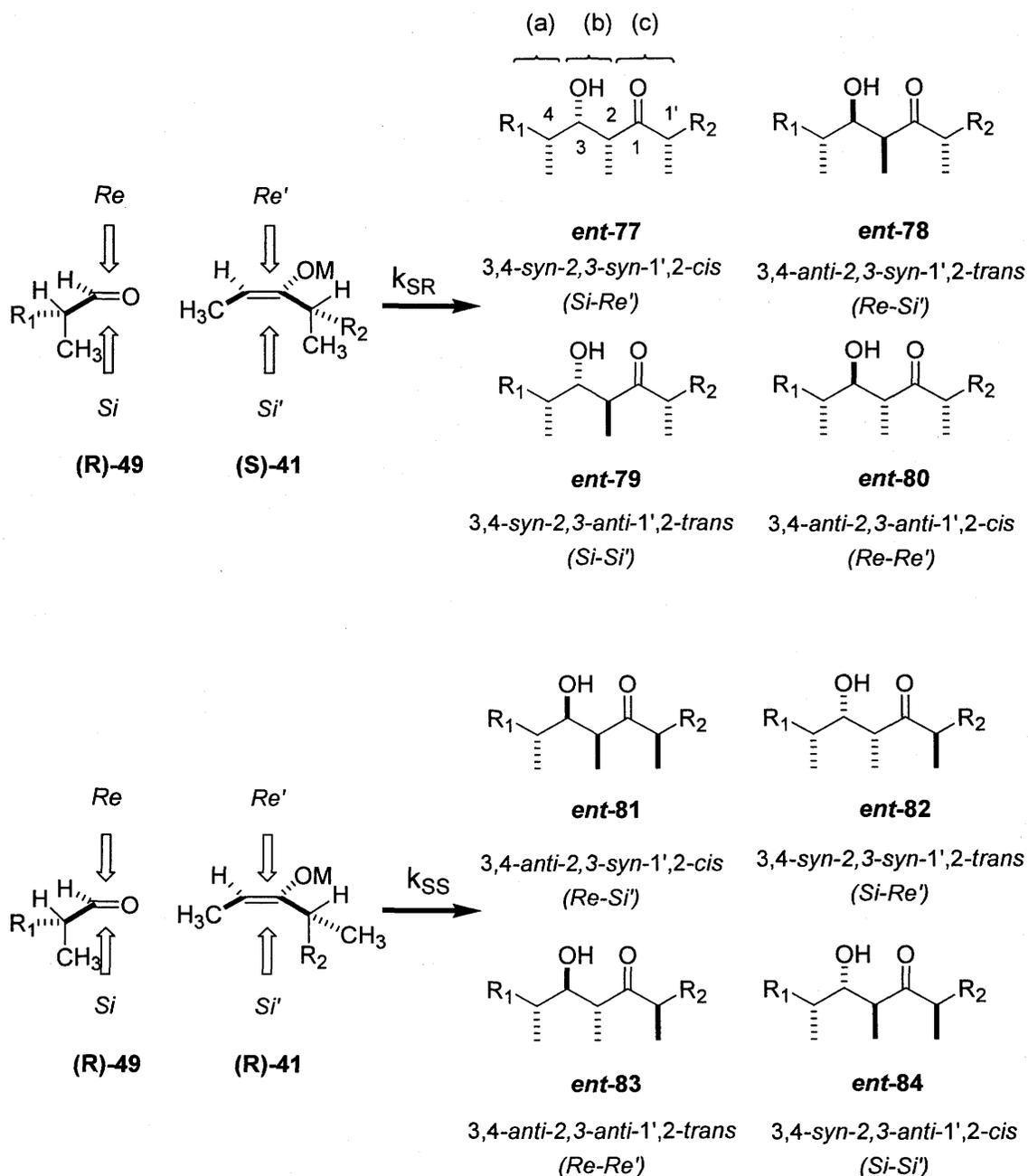
Aldehyde d.s. / Enolate d.s

$$3.5 / 2.7 = 1.3$$

**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'.<sup>104-106</sup>



**Figure 22.** Aldol reaction of **(R)-49** with **(S)-41** and with **(R)-41**.

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 enantioselection (MKE),

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

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.<sup>107</sup> 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.<sup>104,108</sup>

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).<sup>109</sup> 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.<sup>110</sup>

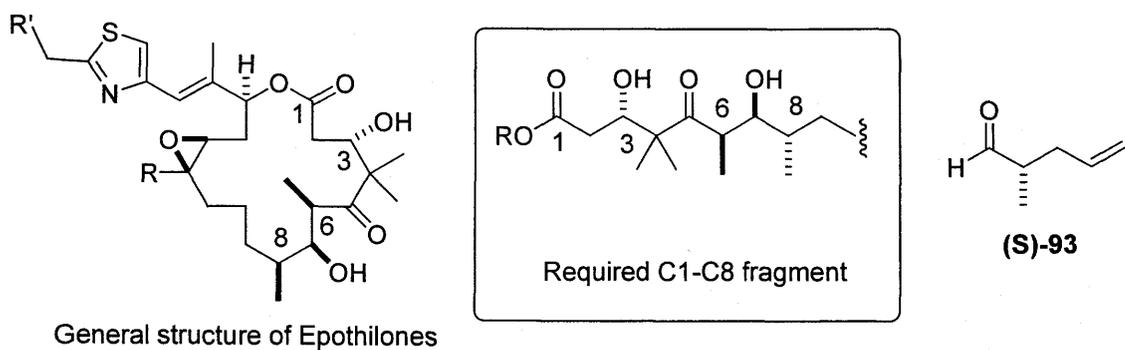
<u>method 1</u>	$\frac{k_{SR}}{k_{SS}} = \frac{k_{RS}}{k_{RR}} = \frac{[\text{sum of unlike products}]}{[\text{sum of like products}]} = \text{MKE}$
racemic + racemic	
<u>method 2</u>	$\frac{k_{SR}}{k_{SS}} = \frac{[\text{sum of unlike products}]}{[\text{sum of like products}]} = \text{MKE}$
enantiopure + excess racemic	
<u>method 3</u>	$\frac{[\text{sum of unlike products}]}{[\text{sum of like products}]} \neq \text{MKE}$
non-racemic + non-racemic	

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

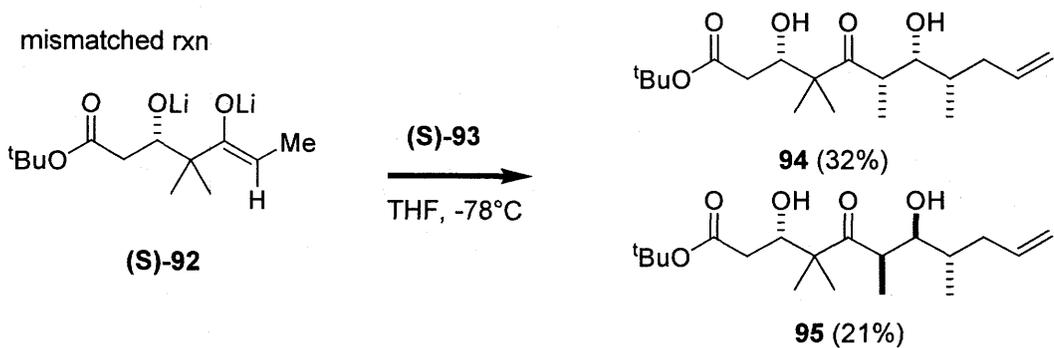
All like and unlike reactions between chiral reactants can display the phenomenon of double stereodifferentiation. Reactions of an enantiopure reactant with a racemic reactant should display some degree of kinetic resolution, and reactions between two racemic reactants should exhibit some level of mutual 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

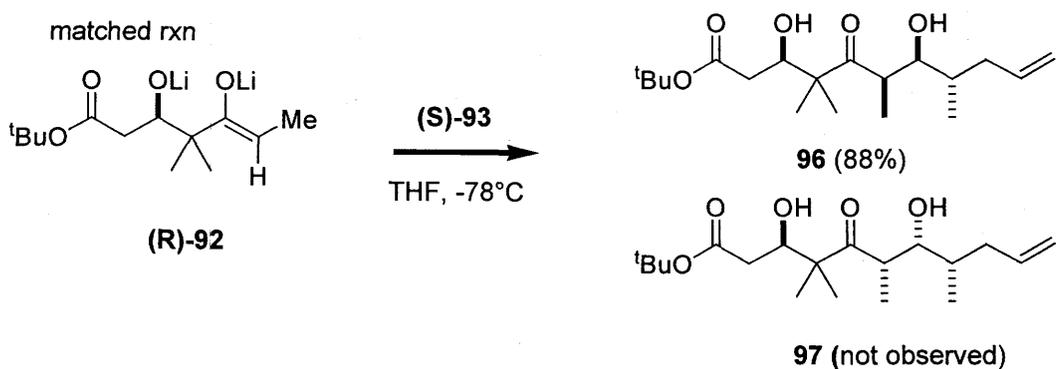
Danishefsky et al. investigated the aldol reaction between (S)-**92** and (S)-**93** in connection with the synthesis of epothilones (Scheme 7).<sup>111,112</sup> The reaction gave the desired adduct **95** but with poor yield and diastereoselectivity. It was suspected that this was the mismatched reaction 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 Mitsunobu type reactions were unsuccessful.<sup>111</sup>



mismatched rxn



matched rxn



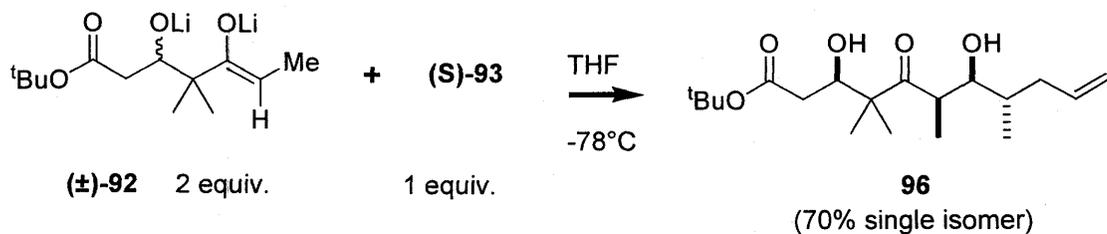
excess racemic reactant

+

enantiopure reactant

→

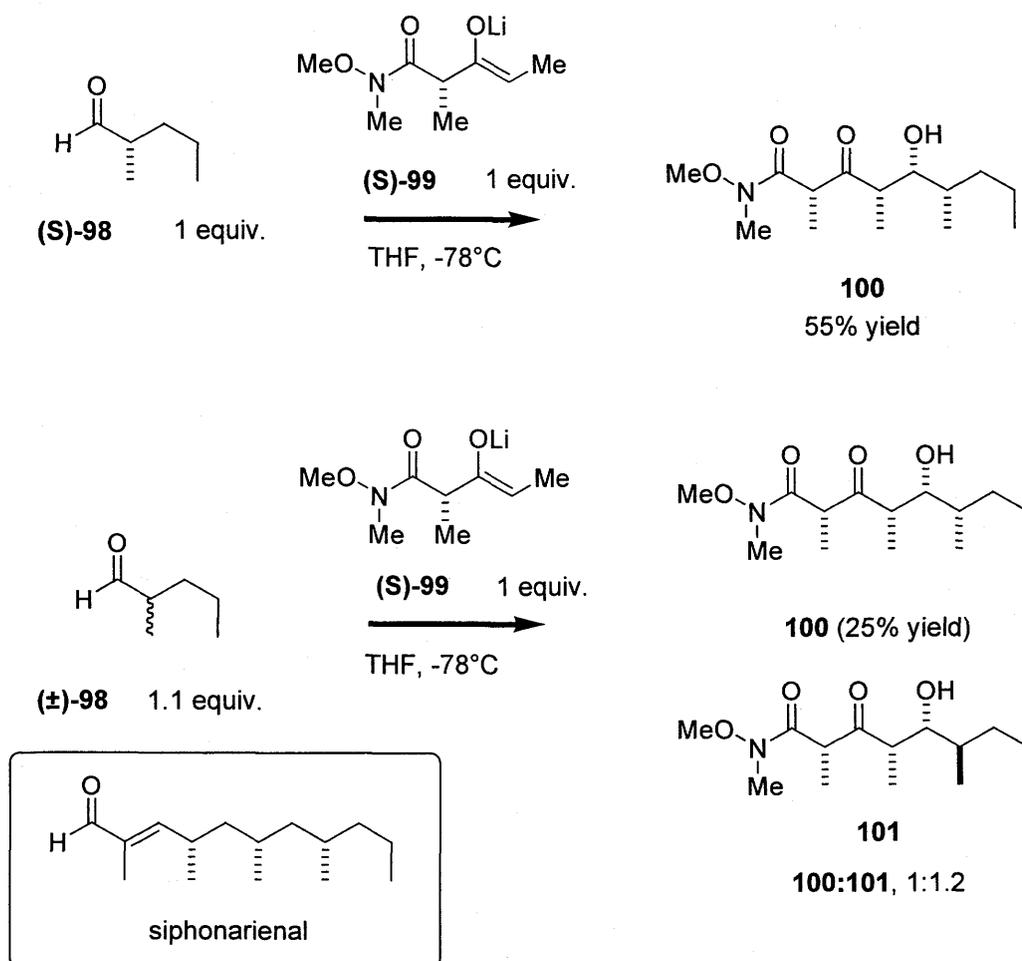
enantiopure product



**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.<sup>29</sup> It was noted that the enantiopure adduct **100** can be applied to the synthesis of the siphonariene class of marine polypropionates.<sup>113,114</sup> 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.



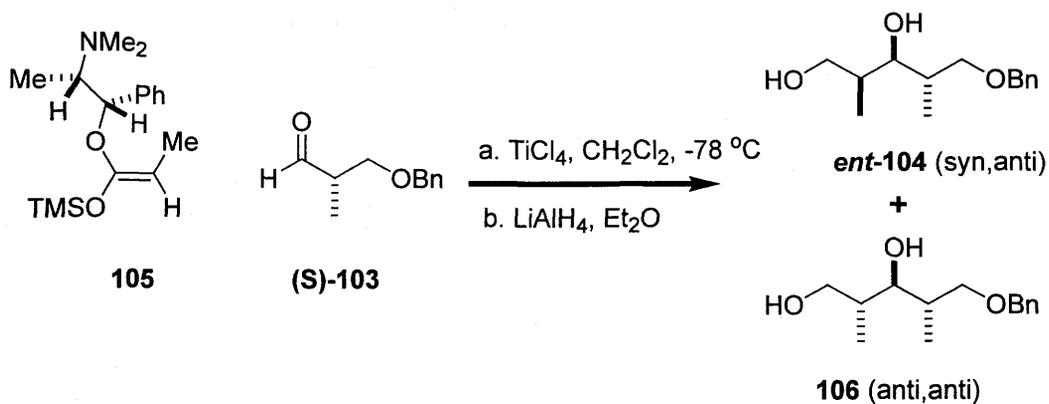
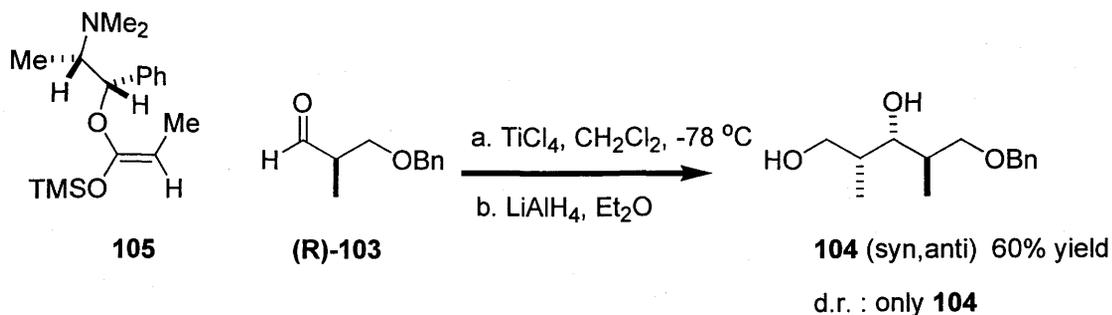
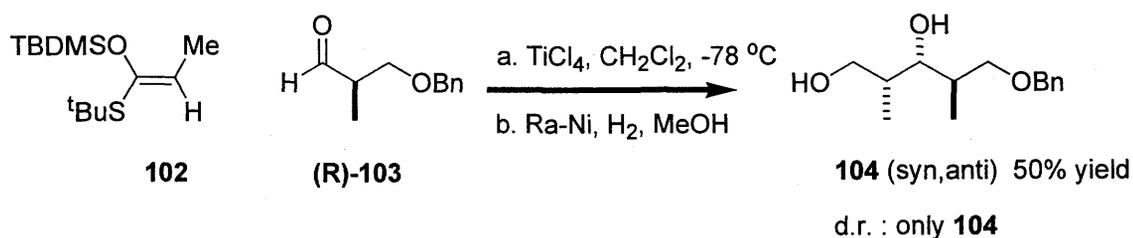
**Scheme 8.** Kinetic resolution experiment for reaction of  $(\pm)\text{-98}$  with  $(S)\text{-99}$ .

In the attempt to obtain the anti,anti stereotriad (such as is found in adduct **106**, Scheme 9) in one step, Gennari et al.<sup>115</sup> investigated the  $\text{TiCl}_4$  promoted aldol reactions of propionate derived silyl ketene acetals to 3-(benzyloxy)-2-methylpropanal (**103**). The reaction of the achiral enolsilane **102** to enantiopure aldehyde  $(R)\text{-103}$  gave a single adduct which upon reduction gave **104**. The diastereoface selectivity for addition of **102** to aldehyde  $(R)\text{-103}$  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 enolsilane **105** with **103** in the hope that double stereodifferentiation may induce an anti-selective aldol relative topicity (Scheme 9).

The aldol reactions of  $(R)\text{-103}$  and  $(S)\text{-103}$  with enantiopure silyl ketene acetal **105** derived from (1*R*,2*S*)-*N*-methylephedrine propionate were conducted (Scheme 9).

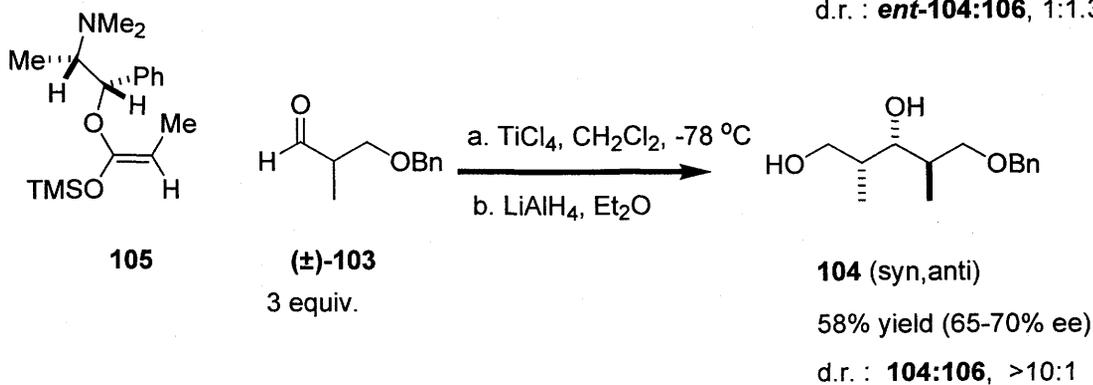
The reaction of **(R)-103** with **105** occurred with high diastereoselectivity (i.e. matched reaction) to afford the syn,anti adduct **104**. The reaction of **(S)-103** with **105** occurred with poor diastereoselectivity (i.e. mismatched reaction) to give a 1:1.3 mixture of *ent*-**104** and **106**, 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.<sup>115</sup> 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**.



combined yield 22%  
d.r. : **ent-104:106**, 1:1.3

kinetic resolution

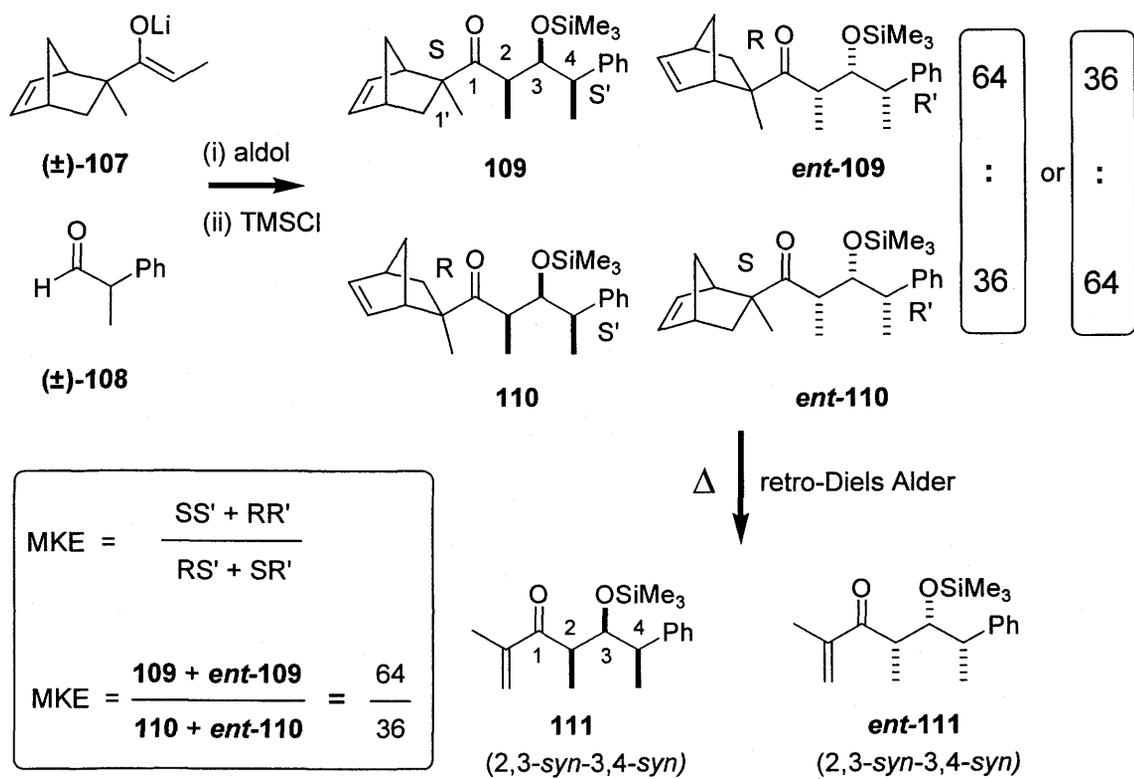


**Scheme 9.** A study of the matched and mismatched aldol reactions of **103** with **105**.

#### 1.5.2.4. Examples of mutual kinetic enantioselection

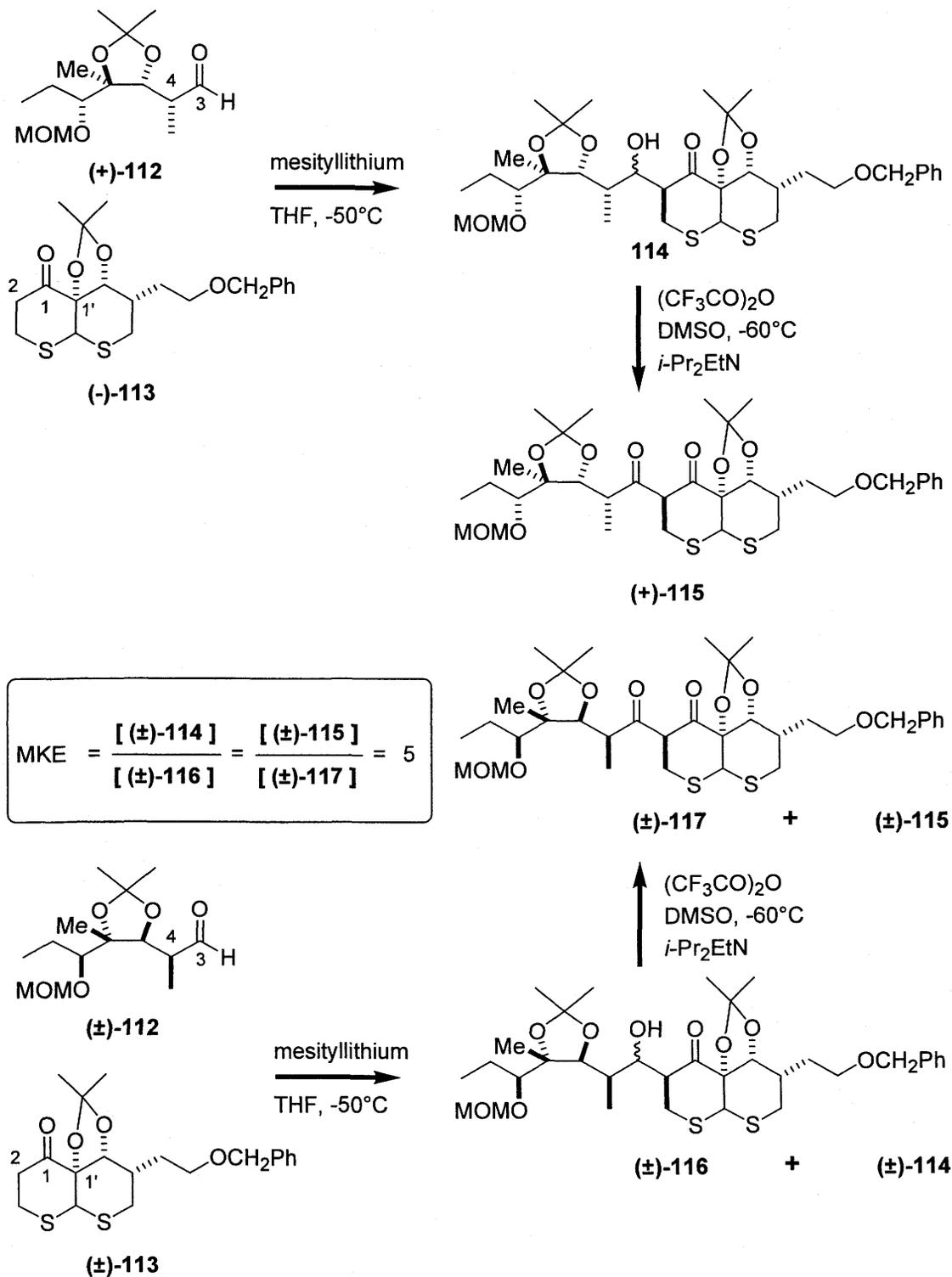
To the best of my knowledge, reported examples of MKE in aldol reactions of racemic aldehyde with racemic enolates are extremely rare. Only two examples will be discussed. In both these reports the phenomenon of MKE was not specifically discussed.

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).<sup>116,117</sup> 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 topicity of the aldol reactions of *Z*-lithium enolate **107** with achiral aldehydes have been shown to be highly *syn*-selective<sup>117</sup> 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.<sup>116</sup> 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 *ca.* 2 (Scheme 10).



**Scheme 10.** MKE of the aldol reaction of (±)-107 with (±)-108.

A key step in the total synthesis of erythromycin by Woodward et al.<sup>118-120</sup> was the aldol coupling of enantiopure fragments of (+)-112 with the 'amine free' Li-enolate of (-)-113 (Scheme 11).<sup>118</sup> 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

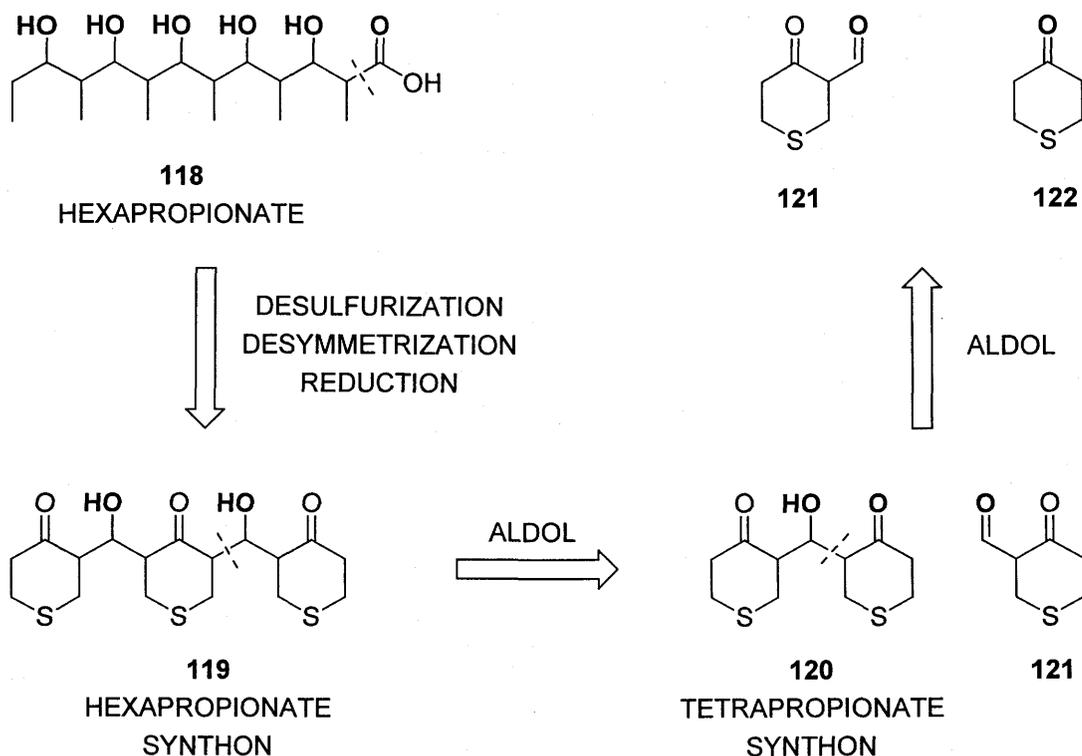
### 2.1. THE THIOPYRANONE ROUTE TO POLYPROPIONATES

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.<sup>121-124</sup> There are numerous examples where thiopyran derived templates have been successfully employed in the synthesis of a variety of targets.<sup>125-128</sup> Recently, Ward et al.<sup>30,36</sup> 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\* 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).

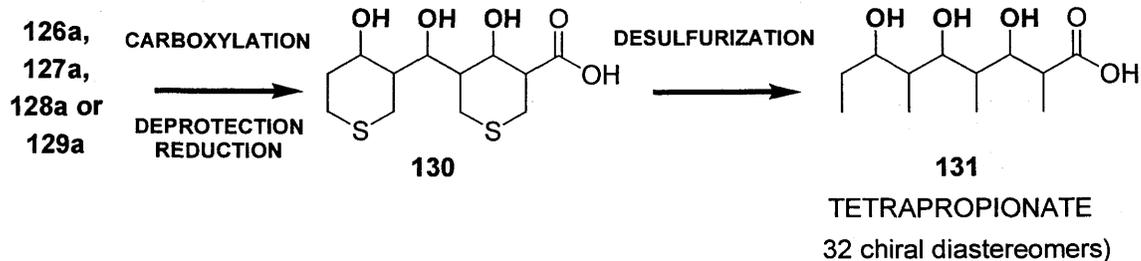
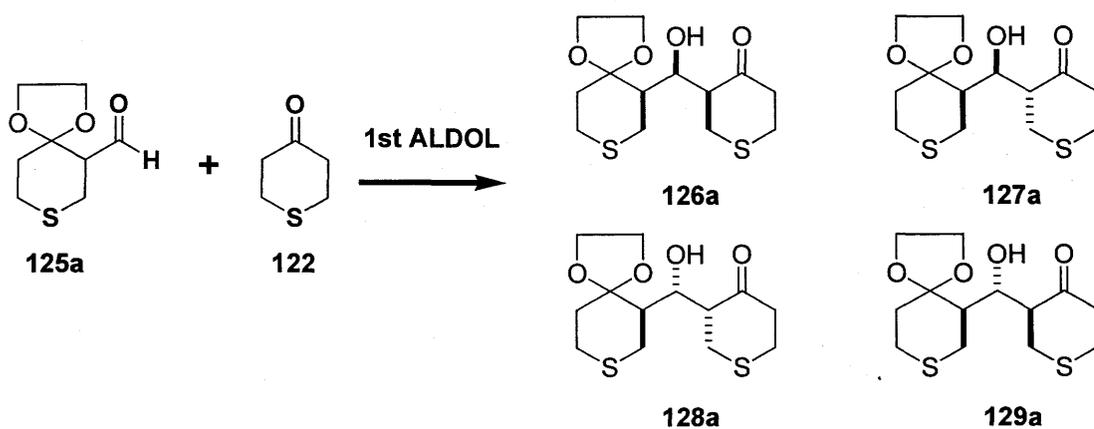
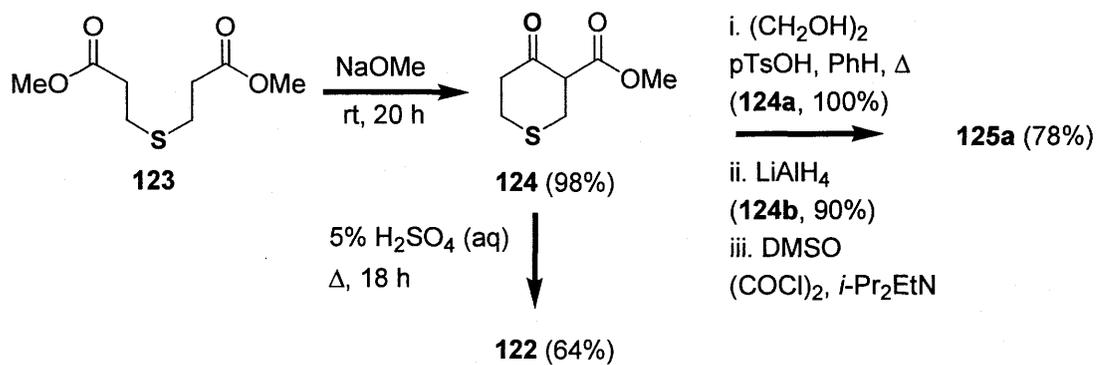
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\* The term scaffold is used in the context of a temporary structure to aid in the construction of the target which is then later removed. In this case, the linked thiopyranone monomers are the scaffold which is 'removed' upon desulfurization to afford the target molecule.

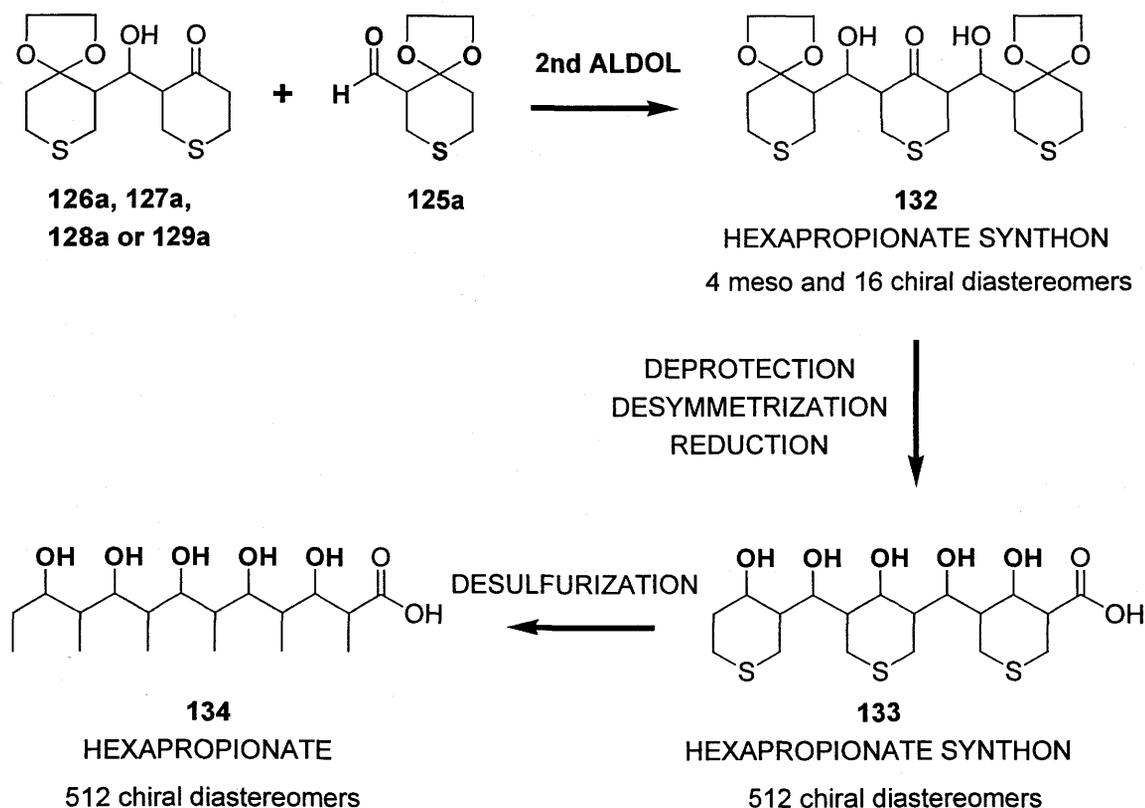


**Figure 24.** A retrosynthetic analysis of an hexapropionate.

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.

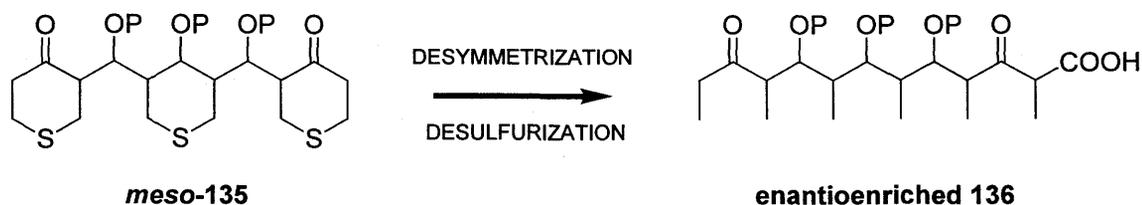


**Figure 26.** The thiopyran route to hexapropionates : The second aldol reaction.

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.



**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.

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\* Work done by I. Alarcon and K. Akinnussi 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  $\beta$ -substituent on reaction diastereoselectivity under various reaction conditions.

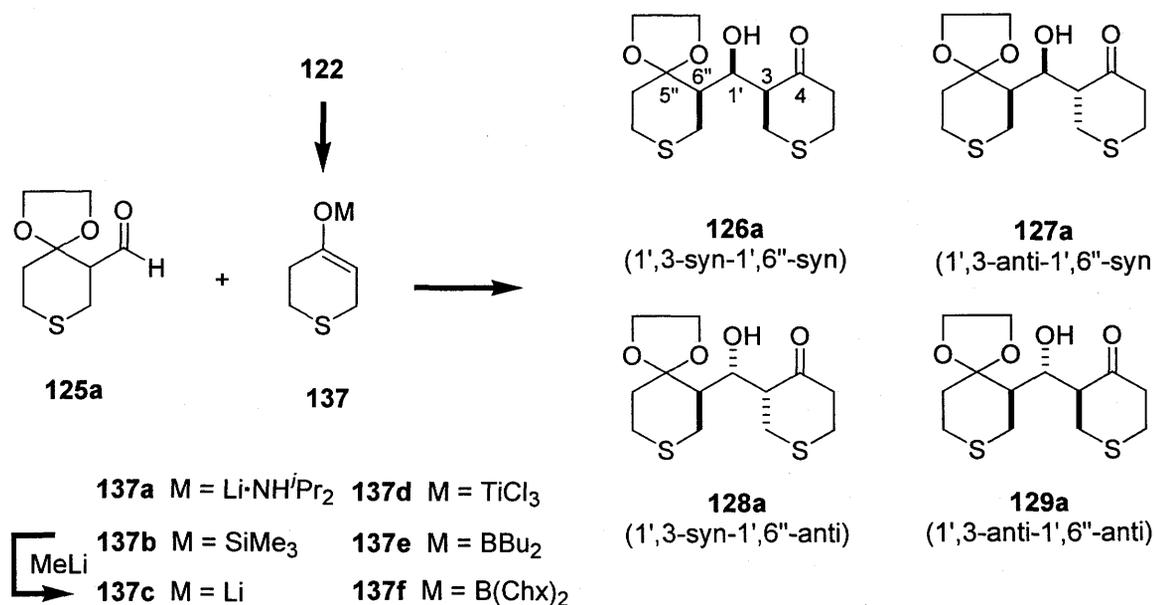
### 2.2.1. The Diastereoselectivity of Aldol Reactions of Ketone **122** with Aldehyde **125a**

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).<sup>40</sup> In an effort to reproduce Hayashi's results the required substrates **122** and **125a** were synthesized<sup>30,36,129</sup> from readily available dimethyl 3,3-thiodipropionate **123** and the aldol couplings were carried out under the reported reaction conditions.<sup>40</sup> Despite extensive experimentation, all attempts by the Ward group<sup>36,130</sup> 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.<sup>131</sup> 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 dithiadecalone proceeded in higher yield using an 'amine free' Li-enolate generated from mesityllithium compared to the use of an LDA generated enolate.<sup>118</sup> 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*-Pr<sub>2</sub>NH product formed from the reaction of LDA with ketones is associated with the enolate (e.g. **137a**) and can affect the ensuing chemistry.<sup>132</sup> Nonetheless, there are few reports of the influence of this phenomenon on aldol diastereoselectivity.

The aldol reaction of **125a** with the putative Mg-enolate<sup>133,134</sup> formed by the reaction of **137c** with MgBr<sub>2</sub>·OEt<sub>2</sub> gave **127a** with poor diastereoselectivity (Table 6, entry 3). Similar reaction of **125a** with the Ti(IV) enolate generated from reaction of **122** with TiCl<sub>4</sub> and *i*-Pr<sub>2</sub>EtN gave **126a** in poor yield and modest diastereoselectivity (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**.

\* 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**.

Entry <sup>a</sup>	Enolate (#equiv)	# Equiv aldehyde <b>125a</b>	Lewis acid (#equiv)	Yield <sup>b</sup> (%)	Ratio of aldols <sup>c</sup>	
					<b>126a</b>	<b>127a</b>
1	<b>137a</b> (1)	1.2		15-40	1	2.5
2	<b>137c</b> (1.5)	1		70	1	9
3	<b>137c</b> (2)	1	MgBr <sub>2</sub> •OEt <sub>2</sub> (2)	77 <sup>d,c</sup>	1	2.5
4	<b>137d</b> (1)	1.2		46 <sup>f</sup>	3.6	1
5	<b>137e</b> (1)	4		82 <sup>g</sup>	1	10
6	<b>137f</b> (1)	4		84 <sup>g</sup>	1	15

<sup>a</sup> The results of entries 1 and 2 were obtained C. C. Man and Dr. C. Guo. Entry 3 obtained during this study and Entries 4-6 was obtained by Dr. P. K. Sasmal.

<sup>b</sup> Percentages represent the total isolated yield of all aldol products. Yield is calculated with respect to the limiting reagent. <sup>c</sup> No aldols **128a** and **129a** were isolated for all entries 1-6. <sup>d</sup> **137c** was stirred with MgBr<sub>2</sub>•OEt<sub>2</sub> for 5 minutes at -78°C followed by the reaction with **125a** for an additional 5 minutes at -78°C <sup>e</sup> The yield reported as percentage conversion of aldehyde **125a** to aldol product. <sup>f</sup> Reaction at -78°C for 5 h.

<sup>g</sup> Reaction at -78°C for 3 h.

The diastereoselectivity of Lewis-acid promoted reactions of enolsilane **137b** with aldehyde **125a** were also investigated (i.e. Mukaiyama reactions).<sup>135,136</sup> The reactions promoted by BF<sub>3</sub>•OEt<sub>2</sub> and SnCl<sub>4</sub> gave mixtures of aldols **126a** and **127a** in good yield but with modest diastereoselectivities (Table 7, entries 1 and 2). By contrast, the TiCl<sub>4</sub> 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**

Entry <sup>a</sup>	Enolate (#equiv)	# Equiv aldehyde 125a	Lewis acid (#equiv)	Yield <sup>b</sup> (%)	Ratio of aldols	
					126a	127a
1	<b>137b</b> (2)	1	BF <sub>3</sub> •OEt <sub>2</sub> (3)	74 <sup>c,d</sup>	1	
2	<b>137b</b> (2)	1	SnCl <sub>4</sub> (3)	72 <sup>e</sup>	1	3
3	<b>137b</b> (1.5)	1	TiCl <sub>4</sub> (1)	87 <sup>e</sup>	16	1

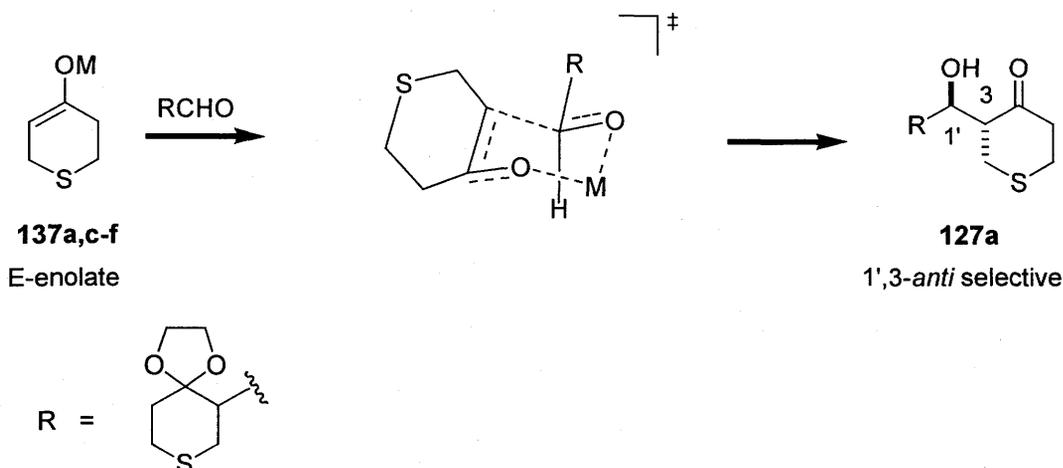
<sup>a</sup> Entries 1 and 2 was obtained in this study and entry 3 was obtained by C. C. Man and C. Guo<sup>36</sup> and confirmed by P. K. Sasmal.<sup>129</sup> <sup>b</sup> Percentages represent the total isolated yield of all aldol products. Yield is calculated with respect to the limiting reagent. <sup>c</sup> Reaction at -78°C for 1 hr. <sup>d</sup> The yield reported as percentage conversion of aldehyde **125a** to aldol product. <sup>e</sup> 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 *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<sup>137,138</sup> and may be responsible for the

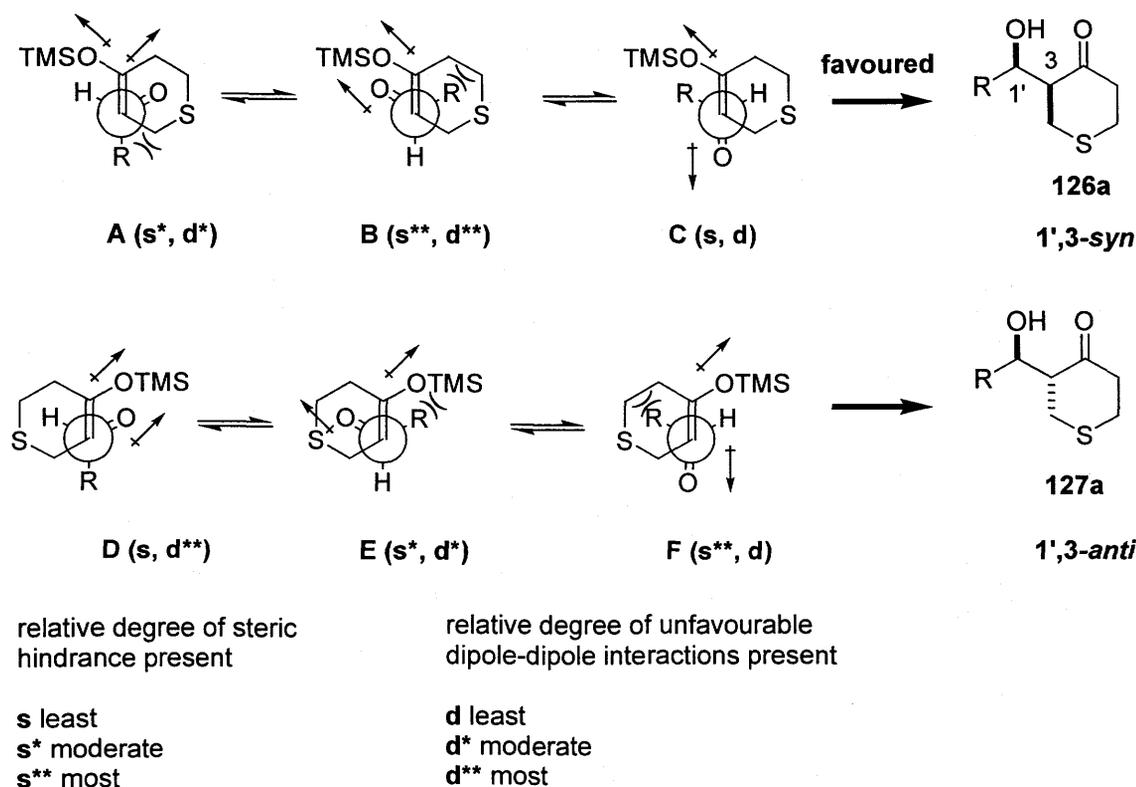
\* Note that the enolates **137a,c-f** are cyclic E-enolates.

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).



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

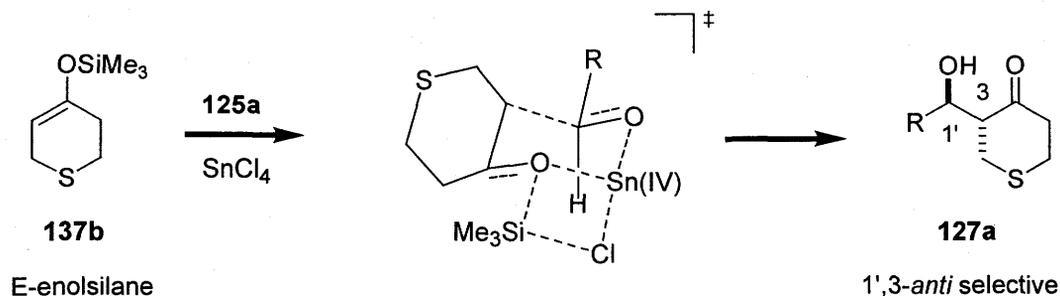
The Lewis acid promoted Mukaiyama reactions are believed to occur through ‘open’ transition states and the energetically favoured relative orientations of the reaction partners in the transition state dictate the relative topology of the aldol reaction (cf. Section 1.2.1 for discussion of topology of 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  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{TiCl}_4$  are *syn*-selective (**126a** is major) and reaction with  $\text{SnCl}_4$  is *anti*-selective (**127a** is major). The *syn*-selective aldol topology obtained from the  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{TiCl}_4$  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<sup>81,139-142</sup> 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.



**Figure 29.** A qualitative 'open' transition state model for  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{TiCl}_4$  promoted reactions.

The Mukaiyama reaction promoted by  $\text{SnCl}_4$  gave 1',3-*anti* relative topology predominantly (Table 7, entry 2). The 1',3-*syn* selectivity of aldol reactions of (E)-enolsilanes promoted by  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{TiCl}_4$  and the 1',3-*anti* selectivity of reactions promoted by  $\text{SnCl}_4$  was also observed by Denmark.<sup>140</sup> Unlike the reactions promoted by  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{TiCl}_4$ , it is proposed that the reactions between **125a** and **137b** promoted by  $\text{SnCl}_4$  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  $\text{SnCl}_4$  promoted reactions to occur through a 'closed' transition state were given by Denmark.<sup>140</sup> These reasons include the attenuated Lewis acidity of  $\text{SnCl}_4$  which would lower the contribution of product from an 'open' transition state, the ability of  $\text{SnCl}_4$  to coordinate to both enol and aldehyde oxygens, and the ability of the chloride counterion in  $\text{SnCl}_4$  to remove the silicon moiety of the enolsilane. The ability of a Lewis acid to coordinate to an enol oxygen has been proposed before.<sup>143-145</sup> Furthermore,  $\text{SnCl}_4$  has been shown to coordinate to both alkoxy and aldehyde oxygens in  $\beta$ -alkoxy aldehyde

substrates\*.<sup>96</sup> 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.<sup>140</sup>

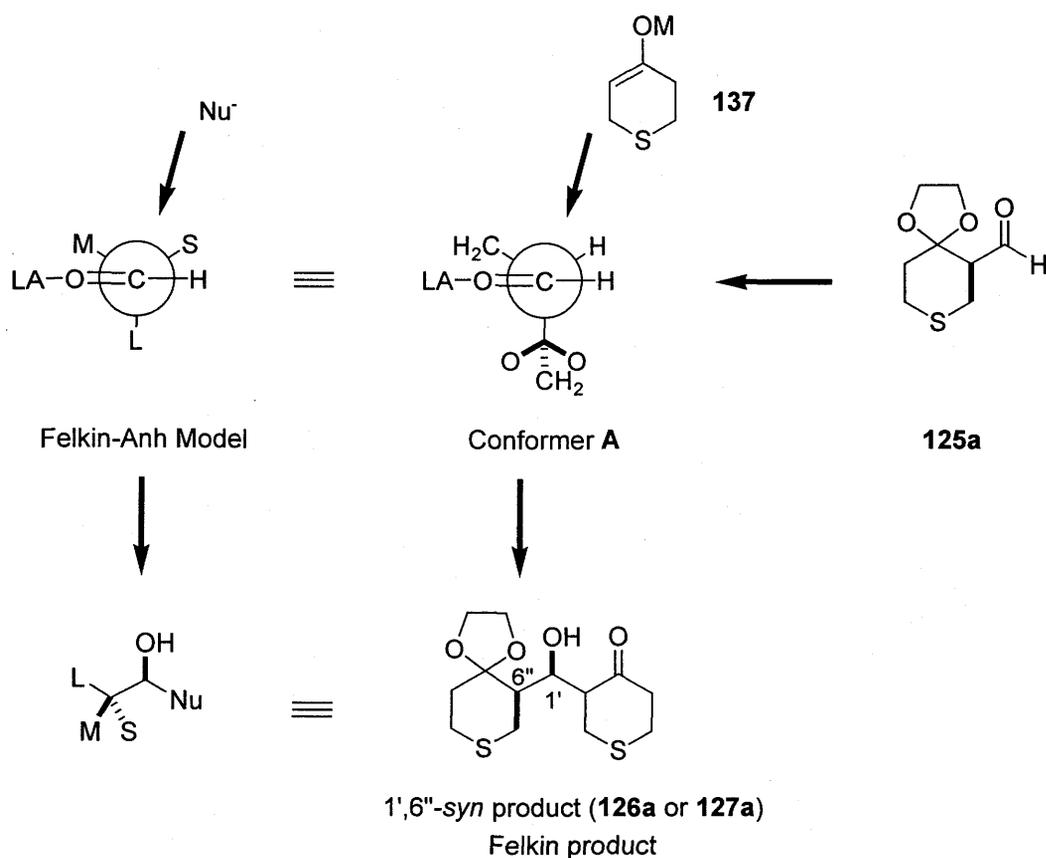


**Figure 30.** Proposed ‘closed’ transition state for aldol reaction of **137b** with **125a** promoted by  $\text{SnCl}_4$ .

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.

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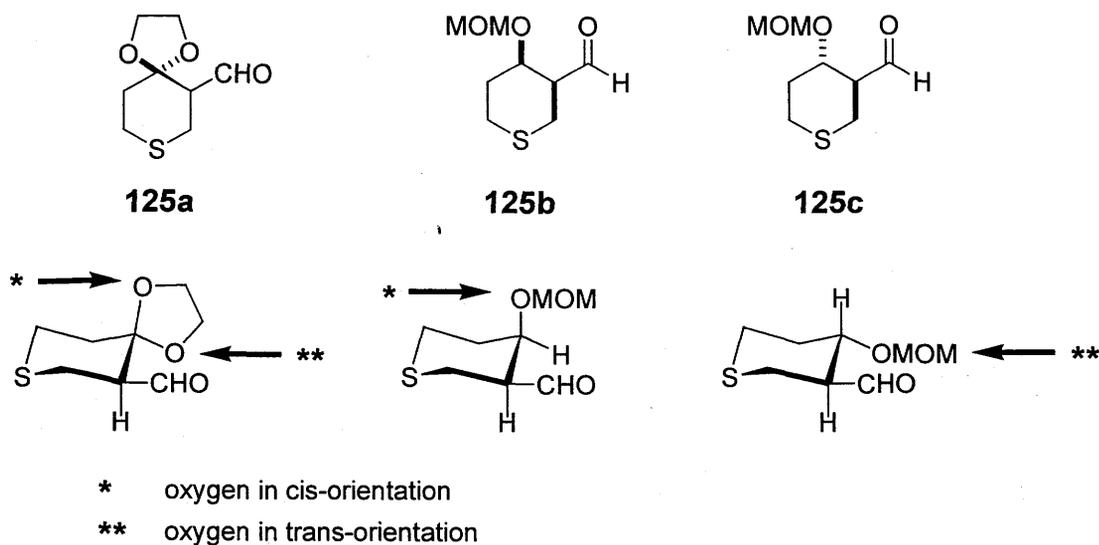
\* Notice that the arrangement of both oxygens of the enolsilane and aldehyde about Sn(IV) in the transition state proposed in Figure 30 can be likened to the arrangement of both oxygens in a  $\beta$ -alkoxy aldehyde chelated to Sn(IV).



**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  $\text{TiCl}_4$  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- $\beta$ -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  $\beta$ -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**.



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

### 2.2.2. Influence of the $\beta$ -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 NaBH<sub>4</sub> has been previously reported.<sup>146</sup> In my hands this reaction gave modest yields of a 1.5-2:1 mixture of **138** and **139**, respectively. Starting  $\beta$ -ketoester **124** was not recovered and it was deduced that **124** was possibly unstable to the basic reaction conditions, prompting the use of NaCNBH<sub>3</sub> as an alternative reducing reagent. Reduction of ketones with NaCNBH<sub>3</sub> is optimal between pH 3-4 and because one equivalent of acid (H<sup>+</sup>) is consumed during the reduction, an additional proton source must be provided to maintain this pH.<sup>147</sup> A modified method by Borch et al.<sup>147</sup> 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*-Pr<sub>2</sub>EtN in the presence of tetrabutylammonium iodide (Bu<sub>4</sub>NI).<sup>148</sup> The LiAlH<sub>4</sub> reductions of the individual esters **140** and **141** occurred without incident to give the alcohols **142** and **143** in good yields.

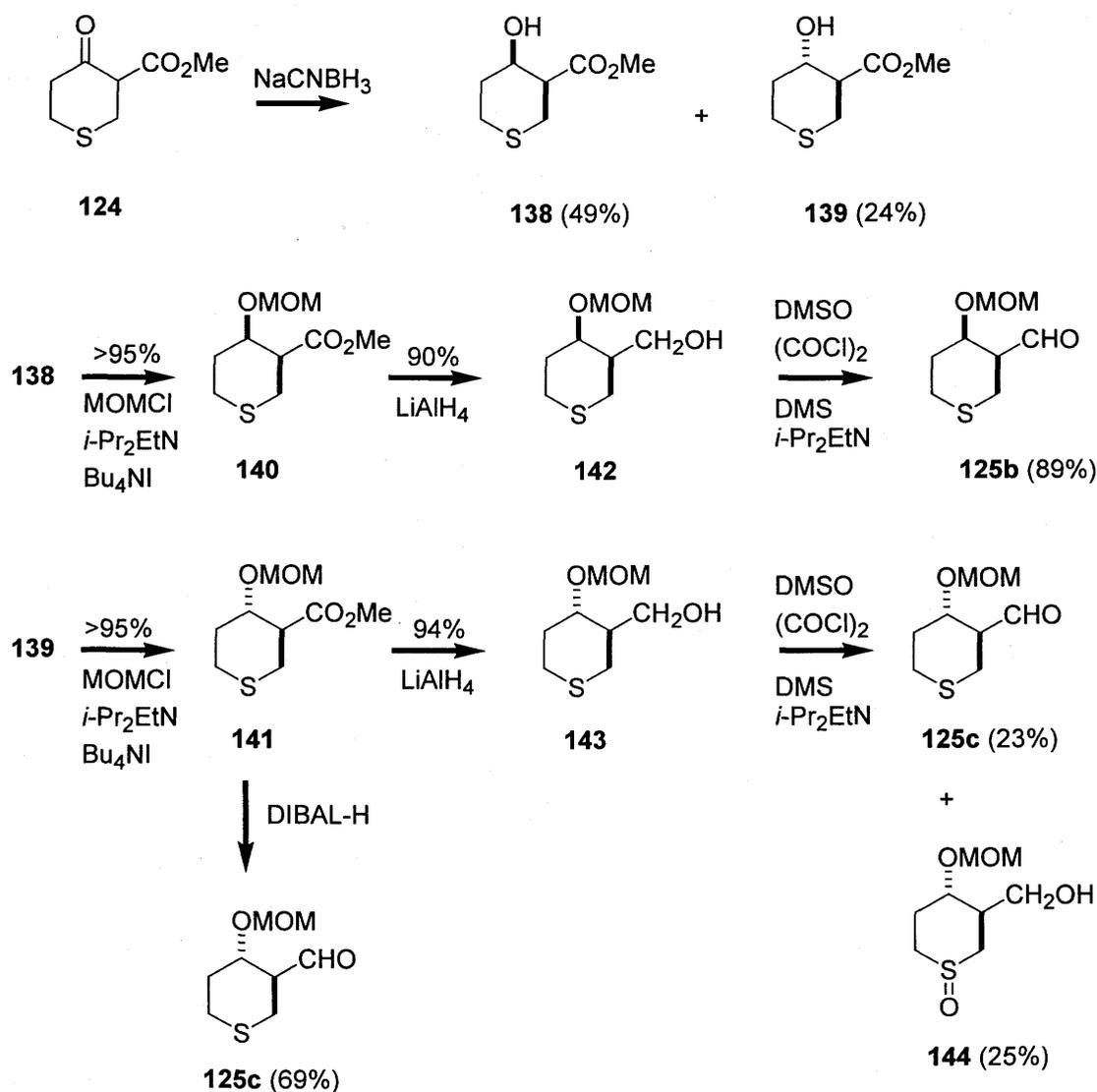
Swern oxidation of alcohol **142** under standard reaction conditions<sup>149</sup> resulted in a poor yield of aldehyde **125b** (40-60% isolated yield). However, the oxidation of **142** with a modified Swern procedure, with two equivalents of dimethyl sulfide as an additive, gave **125b** in excellent yield (89%).

Swern oxidation<sup>149</sup> of alcohol **143** gave poor yields of **125c** (20-50%) together with a significant amount of a side product. Analysis of the <sup>1</sup>H 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

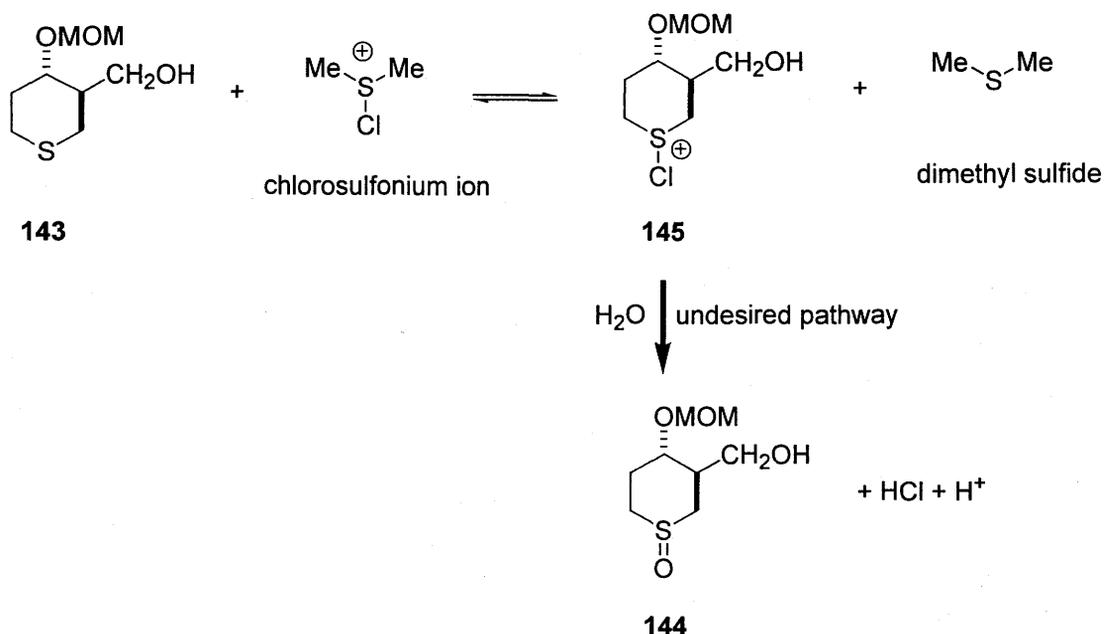
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\* Citric acid is a tricarboxylic acid with three exchangeable hydrogens with pK<sub>a1</sub> = 3.14, pK<sub>a2</sub> = 4.77 and pK<sub>a3</sub> = 6.39. It is the pK<sub>a1</sub> = 3.14 which is responsible for buffering the pH between 3-4 since as the 1 equivalent of NaCNBH<sub>3</sub> reacts to consume one equivalent of H<sup>+</sup> 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.<sup>150</sup>



**Scheme 13.** Synthesis of MOM-protected aldehydes **125b** and **125c**.



**Figure 33.** Undesired pathway during Swern oxidation

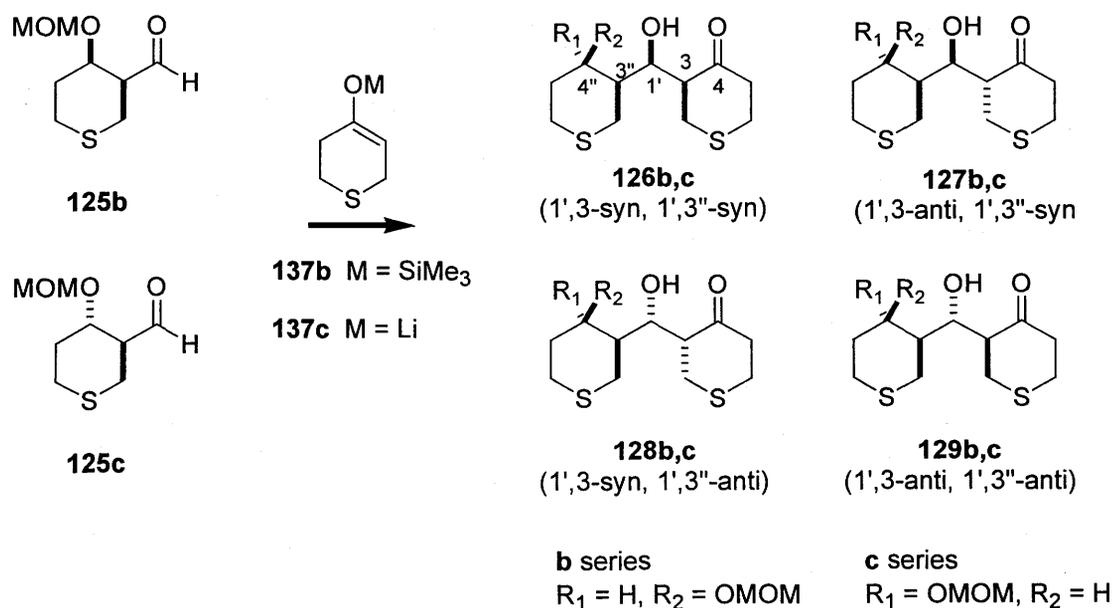
#### 2.2.2.2. *Diastereoselectivity of aldol reactions of 122 with aldehydes 125b and 125c*

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  $\beta$ -alkoxy group in **125** could modulate diastereoface selectivity for addition to the aldehydes.

Aldol adducts were obtained in poor yield from the  $\text{TiCl}_4$  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  $\text{TiCl}_4$ . 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  $\text{TiCl}_4$  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  $\alpha$ -heteroatom substituted aldehydes are known and reports by Mukaiyama, Heathcock and Scolastico have claimed that  $\text{MgBr}_2 \cdot \text{OEt}_2$  effected chelation controlled addition of enolsilane to  $\alpha$ -alkoxy aldehydes.<sup>141,151-155</sup> This literature precedence combined with our experience (work done by M. J. Hrapchak and myself) that  $\text{MgBr}_2 \cdot \text{OEt}_2$  was uniquely able to effect a highly selective chelation controlled addition of TMSCN to  $\alpha$ -alkoxy aldehydes for the diastereoselective formation of cyanohydrins<sup>156</sup> led to the exploration of  $\text{MgBr}_2 \cdot \text{OEt}_2$  to promote the reactions of  $\beta$ -alkoxy aldehydes **125b** and **125c** with **137b**.\*



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

The aldol reactions promoted by  $\text{MgBr}_2 \cdot \text{OEt}_2$  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  $\text{MgBr}_2 \cdot \text{OEt}_2$  to promote aldol reactions between enolsilanes and  $\beta$ -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**)

Entry	Enolate (#equiv)	Aldehyde (#equiv)	Promoter (#equiv)	Aldol series	Yield <sup>a</sup> %	Ratio of aldols			
						126	127	128	129
1	<b>137c</b> (2)	<b>125b</b> (1)	<sup>b</sup>	b	61	1	4	1.5	
2	<b>137c</b> (2)	<b>125c</b> (1)	<sup>b</sup>	c	64	1			
3	<b>137b</b> (2)	<b>125b</b> (1)	TiCl <sub>4</sub> (1) <sup>c</sup>	b	27	1		1.3	
4	<b>137b</b> (2)	<b>125c</b> (1)	TiCl <sub>4</sub> (1) <sup>c</sup>	c	81	20	1		2
5	<b>137b</b> (2)	<b>125b</b> (1)	MgBr <sub>2</sub> •OEt <sub>2</sub> (3)	b	84	3.5		1	
6	<b>137b</b> (2)	<b>125c</b> (1)	MgBr <sub>2</sub> •OEt <sub>2</sub> (3)	c	74	4	7		1

<sup>a</sup> The combined isolated yield of all aldol products. <sup>b</sup> Reaction at  $-78^{\circ}\text{C}$  for 5 minutes. <sup>c</sup> Reaction at  $-78^{\circ}\text{C}$  for 1hr.

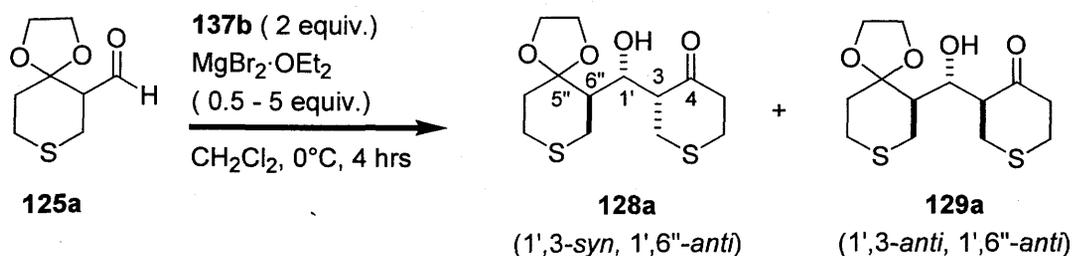
The aldol reaction promoted by MgBr<sub>2</sub>•OEt<sub>2</sub> between **125c** and **137b** proceeded with lower aldehyde diastereoface selectivity giving the 1'-3''-*anti* products **128c** and **129c** and the 1'-3''-*syn* product **126c** (Table 8, entry 6).

The ability of MgBr<sub>2</sub>•OEt<sub>2</sub> promoted aldol reactions of  $\beta$ -alkoxy aldehydes **125b** and **125c** to selectively give anti-Felkin adducts prompted an investigation of MgBr<sub>2</sub>•OEt<sub>2</sub> promoted reactions between **125a** with enolsilane **137b** (see Table 9).

The MgBr<sub>2</sub>•OEt<sub>2</sub> 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 MgBr<sub>2</sub>•OEt<sub>2</sub> (Table 9, entries 1-7) as was previously observed in our study<sup>156</sup> of addition of

'cyanide' (i.e.  $\text{Et}_4\text{NCN}$ ,  $\text{Et}_4\text{NAg}(\text{CN})_2$  and  $\text{TMSCN}$ ) to  $\alpha$ -alkoxy aldehydes. The diastereoselective formation of aldol **128a** was optimum with 3 equivalents of  $\text{MgBr}_2 \cdot \text{OEt}_2$  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  $\text{MgBr}_2 \cdot \text{OEt}_2$  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  $\text{MgBr}_2 \cdot \text{OEt}_2$  on the diastereoselectivity of the aldol reaction of **125a** with **137b**<sup>a</sup>



Entry	[ <b>125a</b> ] M	# equiv $\text{MgBr}_2 \cdot \text{OEt}_2$	% conversion <sup>b</sup>	<b>128a</b> : <b>129a</b>
1	0.04	0.5 <sup>c</sup>	50	1.6 : 1
2	0.04	1.0	23	1.7 : 1
3	0.04	1.5	70	2.6 : 1
4	0.04	2.0	90	3.5 : 1
5	0.04	2.5	95	4.1 : 1
6	0.04	3.0	96	5.1 : 1
7	0.04	5.0	91	5.4 : 1
8	0.08 <sup>d</sup>	3.0	97	3.5 : 1
9	0.2 <sup>d</sup>	3.0	98 (89) <sup>e</sup>	3.0 : 1

<sup>a</sup> Unless otherwise indicated, all reported reaction times are 4 h at 0°C. <sup>b</sup> The percentage of **125a** converted to aldol products **128a** and **129a** as determined by <sup>1</sup>H NMR. <sup>c</sup> Reaction time extended to 6 days at ambient temperature since no product was detected after 4 h.

<sup>d</sup> Reaction time of 1 hour. <sup>e</sup> The 89% reported in parenthesis is the combined isolated yield of **128a** and **129a**.

(>1%) 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.

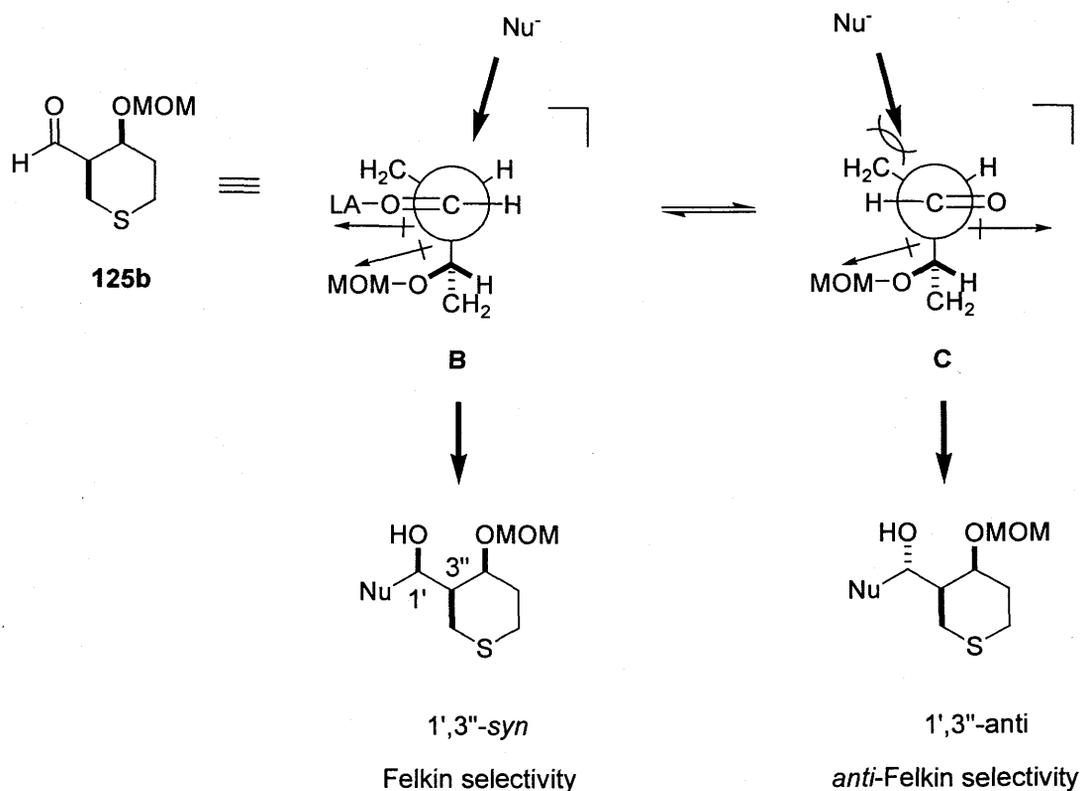
The Zimmerman-Traxler model as depicted earlier in Figure 28 can be applied to rationalize the selective formation of 1',3-anti products from reactions of Li-enolate **137c** with aldehydes **125b** and **125c** (Table 8, entries 1 and 2).

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  $\text{MgBr}_2 \cdot \text{OEt}_2$  (Table 8, entries 5 and 6) and for the reaction of **125c** with **137b** promoted by  $\text{TiCl}_4$  (Table 8, entry 4). It is not clear why the relative topicity of the aldol reaction of **125b** with **137b** promoted by  $\text{TiCl}_4$  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  $\text{TiCl}_4$  (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.<sup>98</sup> that combines the effects of a substituent at the  $\alpha$ -position (1,2- stereinduction) and at the  $\beta$ -position (1,3-stereinduction) 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-stereoreinduction 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

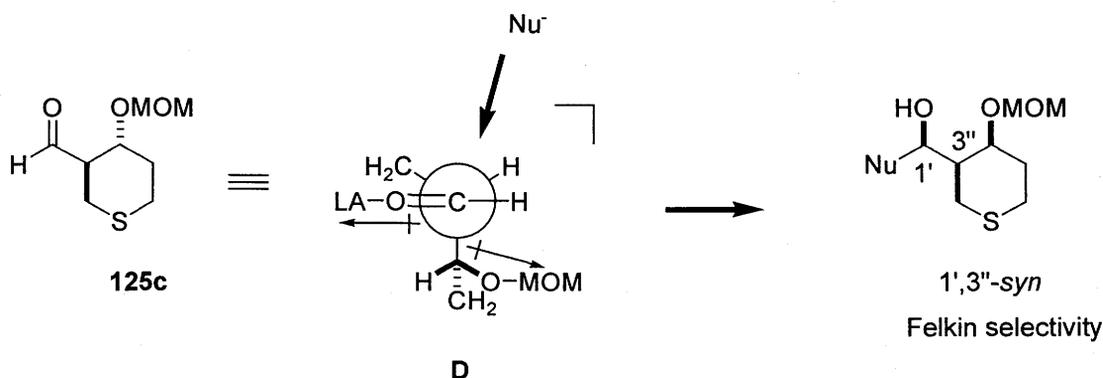


**Figure 34.** Merged 1,2- and 1,3-stereoreinduction model used to rationalize the low aldehyde diastereoface selectivity of addition to **125b**.

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 TiCl<sub>4</sub> (1',3''-syn: -anti, 1 : 1.3, see Table 8, entry 3).

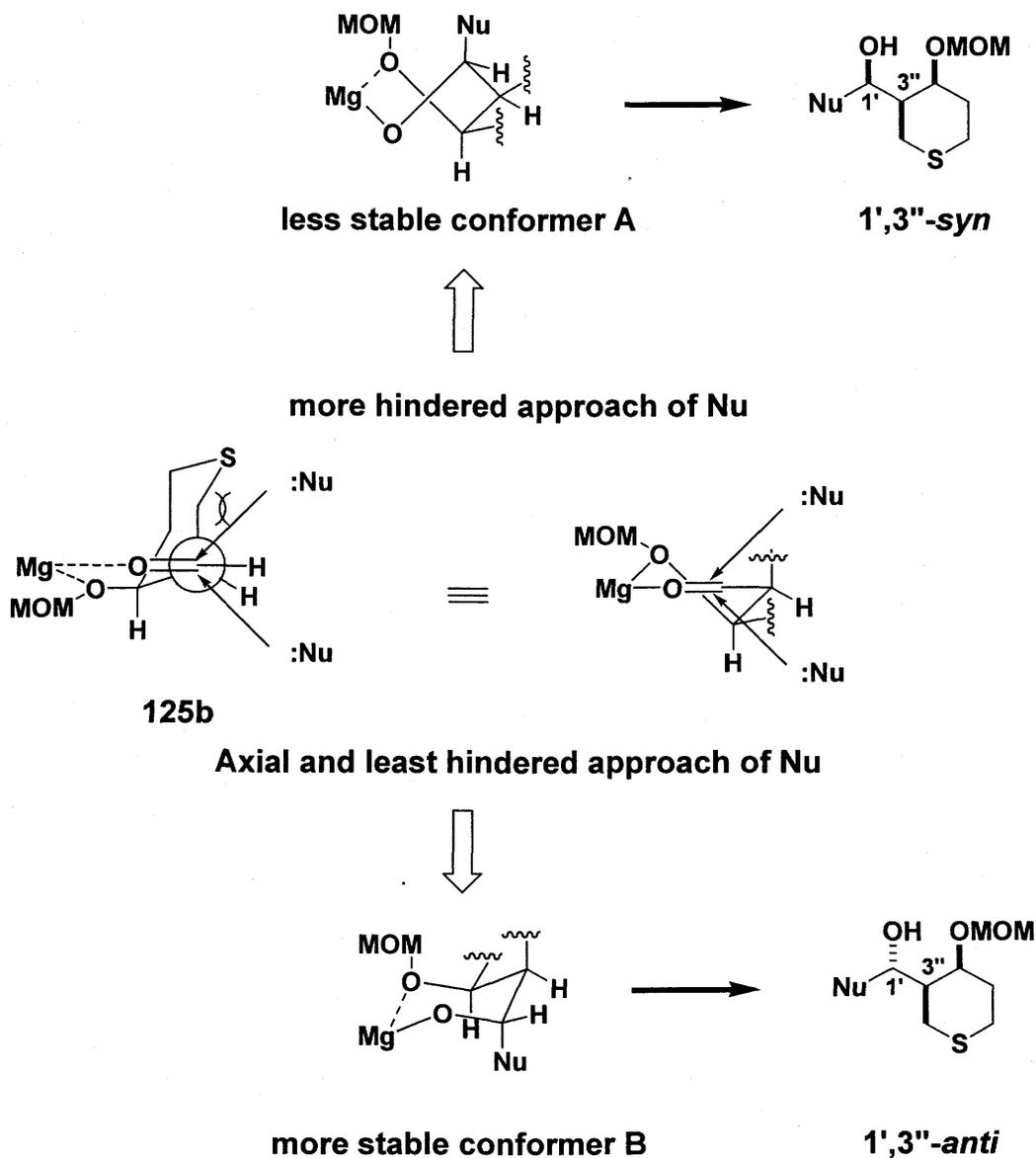
The Evans' model applied to aldehyde **125c** is shown in Figure 35. In conformer **D** the orientation of the α-'methylene' does not sterically impede the approach of the Nu and the orientation of the β-methoxymethoxy substituent does not present an unfavourable dipole-dipole interaction with the carbonyl 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 TiCl<sub>4</sub> (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 MgBr<sub>2</sub>·OEt<sub>2</sub> 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 TiCl<sub>4</sub> promoted reactions with **137b** (Table 8, entries 1-4). This dramatic reversal of the aldehyde diastereoface selectivity from Felkin selective in the presence of TiCl<sub>4</sub> to anti-Felkin selective in the presence of MgBr<sub>2</sub>·OEt<sub>2</sub> strongly supports the hypothesis that MgBr<sub>2</sub>·OEt<sub>2</sub> (and not TiCl<sub>4</sub>) 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

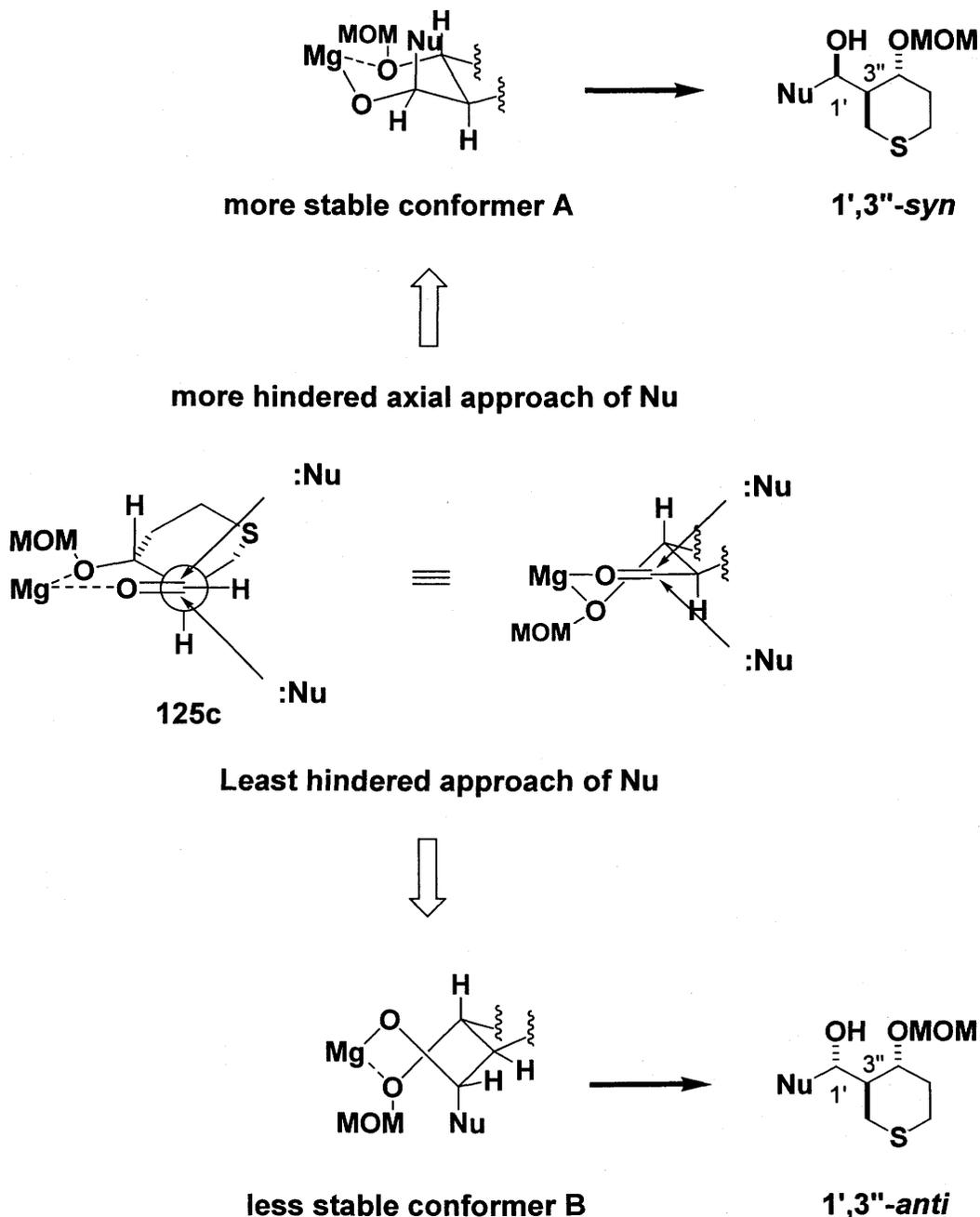
observed for the  $\text{MgBr}_2 \cdot \text{OEt}_2$  promoted addition of **137b** to **125a** (Table 9). Chelation models (Figures 36-38) are proposed to rationalize the anti-Felkin selectivities for the  $\text{MgBr}_2 \cdot \text{OEt}_2$  promoted addition of **137b** to aldehydes **125b**, **125c** and **125a** and are now discussed.



**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  $\text{MgBr}_2 \cdot \text{OEt}_2$  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

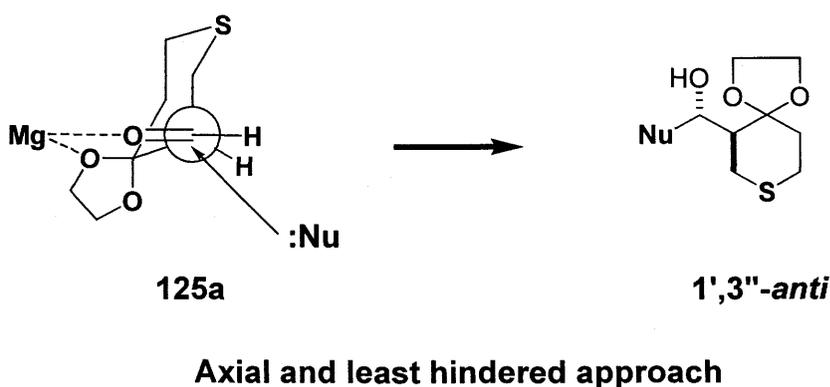


**Figure 37.** Proposed 'chelation controlled addition' model to rationalize moderate *anti*-Felkin (1',3''-*anti* selective) aldehyde diastereoface addition to 125c.

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.

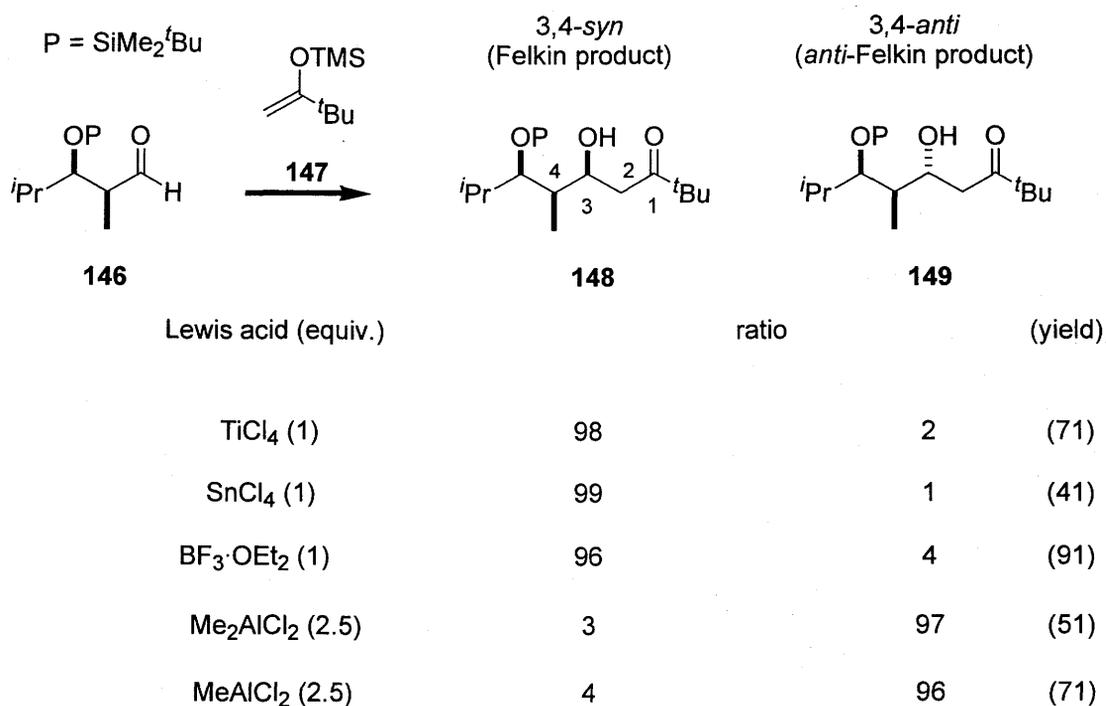
The much more moderate *anti*-Felkin selectivity for addition to aldehyde **125c** is rationalized by the six-membered chelated intermediate model in Figure 37. The least sterically hindered approach of a nucleophile to **125c** leads to the 1',3''-*anti* products. However, this approach leads to the 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  $\text{MgBr}_2 \cdot \text{OEt}_2$  (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  $\text{MgBr}_2 \cdot \text{OEt}_2$  but not with  $\text{TiCl}_4$  and  $\text{SnCl}_4$ . It has been established by NMR that the Lewis acids  $\text{MgBr}_2 \cdot \text{OEt}_2$ ,  $\text{TiCl}_4$  and  $\text{SnCl}_4$  can form chelates with  $\beta$ -alkoxy aldehydes;<sup>157,158</sup> however in a recent study Evans et al.<sup>159</sup> 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  $\text{TiCl}_4$  and  $\text{SnCl}_4$  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  $\text{BF}_3 \cdot \text{OEt}_2$  where chelation is prevented since  $\text{BF}_3 \cdot \text{OEt}_2$  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  $\text{Me}_2\text{AlCl}$  or  $\text{MeAlCl}_2$  (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.<sup>159</sup>

In the present study, chelation control is unlikely in both the  $\text{TiCl}_4$  and  $\text{SnCl}_4$  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  $\text{BF}_3 \cdot \text{OEt}_2$  where chelation is prevented due to  $\text{BF}_3 \cdot \text{OEt}_2$  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  $\text{MgBr}_2 \cdot \text{OEt}_2$  (Table 8, entries 5 and 6 and Table 9) strongly supports a chelated intermediate in these reactions. The superior ability of  $\text{MgBr}_2 \cdot \text{OEt}_2$  compared to  $\text{SnCl}_4$  and  $\text{TiCl}_4$  to be chelated by  $\beta$ -alkoxy aldehydes has also been previously noted by Keck et al.<sup>157,158</sup>

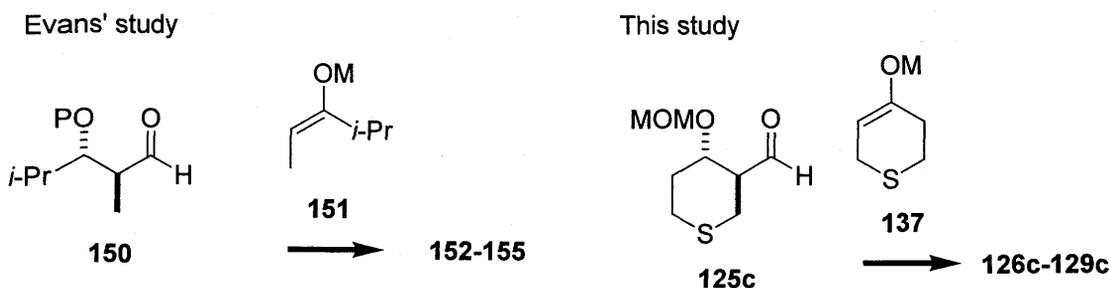
#### 2.2.2.4. Comparison of the diastereoselectivities of the $1^{\text{st}}$ aldol reaction with related acyclic examples

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.<sup>38,160</sup> 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 topology to give the adducts **127c** (exclusive) and **153** (86% ds),\* respectively. The related Mukaiyama reactions of **137b** with **125c** promoted by  $\text{TiCl}_4$  and **151** (M=TMS) with **150** promoted by  $\text{BF}_3 \cdot \text{OEt}_2$  are also highly selective for Felkin addition, but with syn relative topology 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.

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\* 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**.



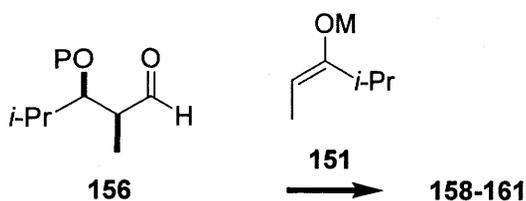
For M = Li, P = PMB  
 For M = TMS, P = SiMe<sub>2</sub><sup>t</sup>Bu

	Product ratios taken from Evans' study		Product ratios taken from this study		
	M = Li	M = TMS (BF <sub>3</sub> )	M = Li	M = TMS (TiCl <sub>4</sub> )	
 <b>152</b>	0-14 <sup>a</sup>	95	--	87	 <b>126c</b>
 <b>153</b>	86	5	100	--	 <b>127c</b>
 <b>154</b>	0-14 <sup>a</sup>	--	--	4	 <b>128c</b>
 <b>155</b>	--	--	--	9	 <b>129c</b>

<sup>a</sup> 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**<sup>38,160</sup> as substrates are compared.

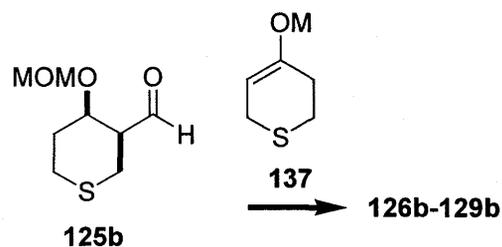
Evans' study



For M = Li, P = PMB

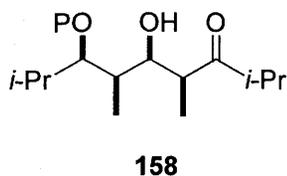
For M = TMS, P = SiMe<sub>2</sub><sup>t</sup>Bu

This study



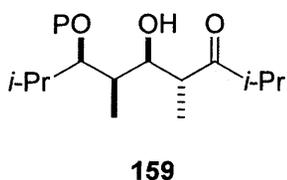
Product ratios taken from Evans' study

M = Li    M = TMS  
(BF<sub>3</sub>)



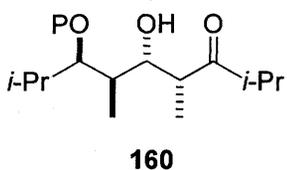
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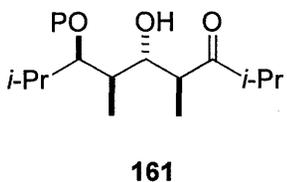
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30



30

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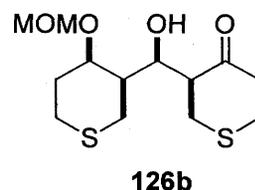


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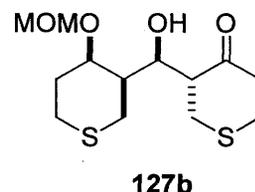
Product ratios taken from this study

M = Li    M = TMS  
(TiCl<sub>4</sub>)



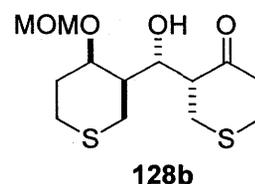
15

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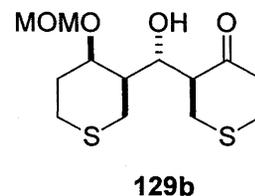
62

43



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23

57

**Figure 41.** The diastereoselectivities when using *cis* aldehyde **125b** and *syn* aldehyde **156**<sup>38,160</sup> 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  $\text{TiCl}_4$  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  $\text{MgBr}_2 \cdot \text{OEt}_2$ . The fourth adduct **129a** can be obtained by isomerization of easily accessible **128a** (cf. Section 2.4.2).<sup>131</sup>

This study clearly demonstrated that the Felkin diastereoface selectivities for additions of **137b** to aldehydes **125a**, **125b** and **125c** mediated by  $\text{TiCl}_4$  or  $\text{SnCl}_4$  can be rationalized using non-chelation control models such as Felkin-Anh and merged 1,2- and 1,3-stereoiduction models. Support for non-chelation control was that Felkin selectivity was also observed for the reaction of **137b** to **125a** mediated by the monodenate  $\text{BF}_3 \cdot \text{OEt}_2$  which precludes chelation; furthermore, the reactions of **137b** with aldehydes **125a**, **125b** and **125c** mediated by  $\text{MgBr}_2 \cdot \text{OEt}_2$  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  $\alpha$ -alkoxy and  $\beta$ -alkoxy aldehydes mediated by  $\text{TiCl}_4$  and  $\text{SnCl}_4$  to chelation control.<sup>92,141,161,162</sup> 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.<sup>98</sup> 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  $\text{TiCl}_4$  which have two vacant coordination sites.<sup>98</sup>

The merged 1,2- and 1,3-stereoiduction model was successfully applied by Evans et al<sup>38,98,160</sup> to rationalize the diastereoface selectivity of addition to the  $\alpha$ -alkyl- $\beta$ -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  $\beta$ -alkoxy groups in **125b** and **125c** are fixed because of conformational rigidity.

This study demonstrated that the orientation of the  $\beta$ -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** +  $\text{TiCl}_4$ ), **125a** exhibits very high Felkin selectivity (similar to **125c** but much higher than **125b**) and under chelating conditions (reactions using **19b** +  $\text{MgBr}_2 \cdot \text{OEt}_2$ ), **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 **132** Figure 26) can be obtained in only two steps from simple precursors. The potential of these products as hexapropionate 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

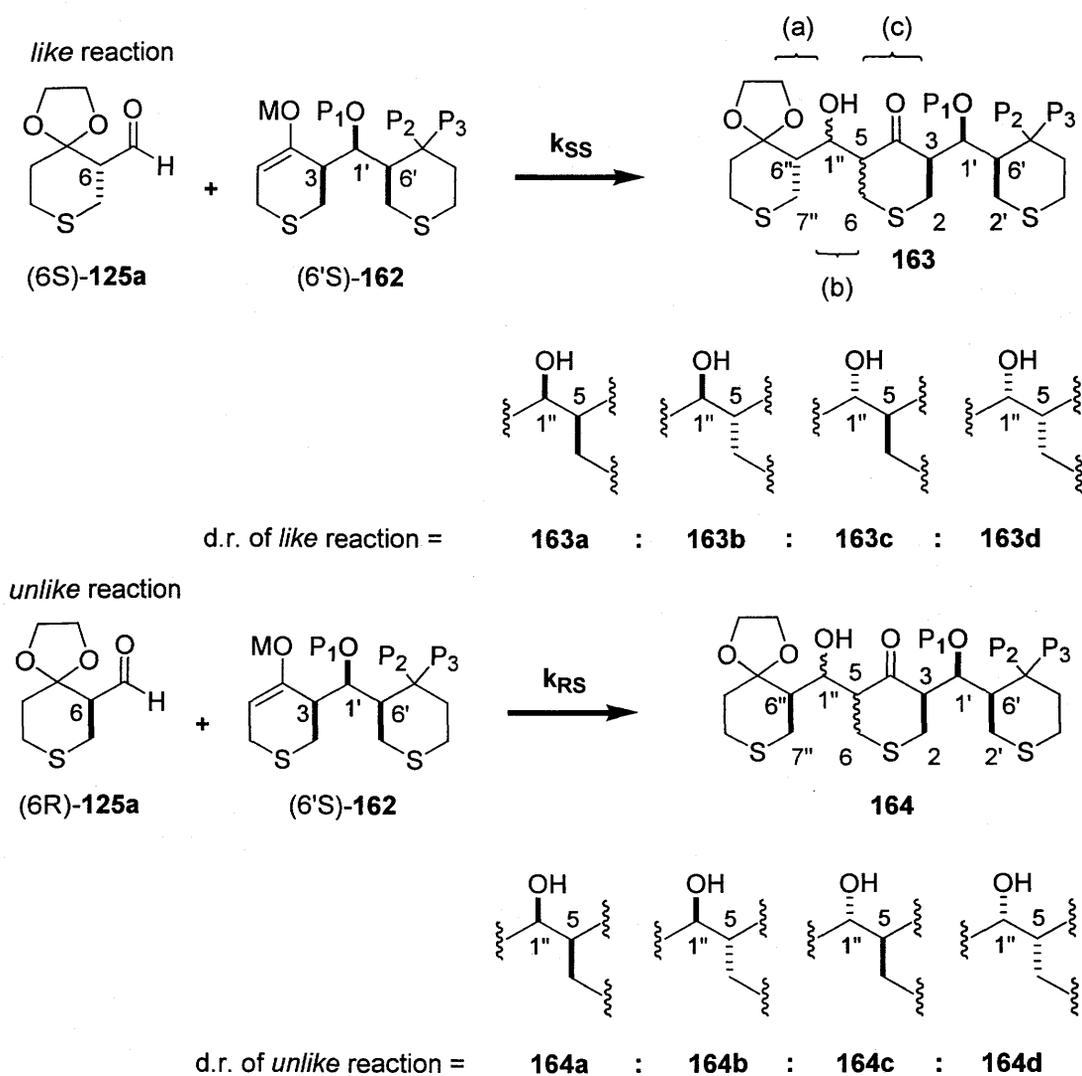
enantiomers of **125a** and **162** need to be considered: the reaction of **(6S)-125a** with **(6''S)-162**<sup>\*</sup> and the reaction of **(6R)-125a** with **(6''S)-162**<sup>†</sup> (see Figure 42). The transition states for the reaction of **(6''S)-162** with **(6S)-125a** and the transition states 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.

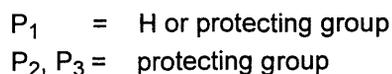
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<sup>\*</sup> The reaction of **(6R)-125a** with **(6''R)-162** is enantiomeric by comparison and will have the same diastereoselectivity as reaction **(6S)-125a** with **(6''S)-162**.

<sup>†</sup> 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**.



$$\text{MKE} = \frac{k_{SS}}{k_{RS}} = \frac{\sum \mathbf{163a-d}}{\sum \mathbf{164a-d}}$$



- (a) aldehyde diastereoface selectivity : 1'',6''-syn (Felkin) or 1'',6''-anti (*anti*-Felkin)  
 (b) relative topicity of aldol : 1'',5-anti or 1'',5-syn  
 (c) enolate diastereoface selectivity : 3,5-cis or 3,5-trans

**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 ( $\pm$ )-125a and ( $\pm$ )-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.

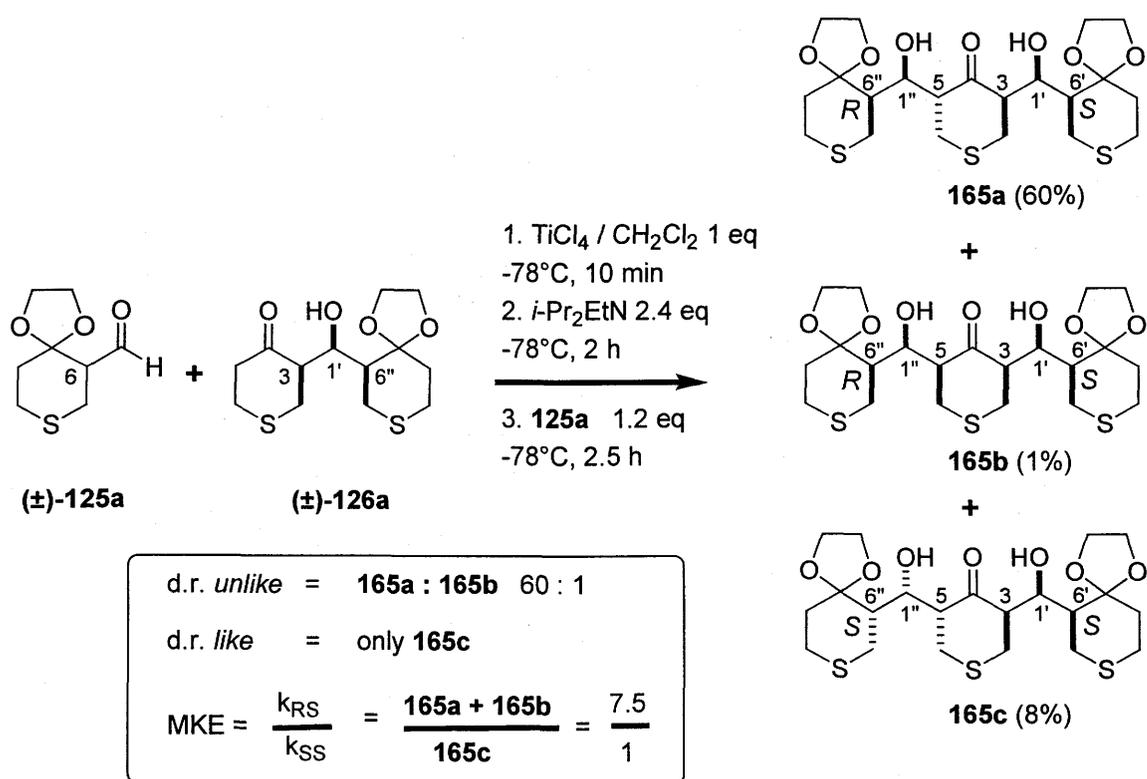
The mutual kinetic enantioselection (MKE) for this reaction, which is the relative preference of one enantiomer of 125a to react with one enantiomer of 162, is defined as the ratio of composite rate constants  $k_{SS}/k_{RS}$  of the competing like and unlike reactions (where  $k_{SS} = k_{163a} + k_{163b} + k_{163c} + k_{163d}$  and  $k_{RS} = k_{164a} + k_{164b} + k_{164c} + k_{164d}$ ). Horeau<sup>109</sup> 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  $\beta$ -hydroxy ketones;<sup>41,163-165</sup> to the best of my knowledge no reports other than Ward et al.<sup>30</sup> were found on reactions of racemic aldehydes with racemic  $\beta$ -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

2.5.2). 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 ( $\pm$ )-**125a** with ( $\pm$ )-**126a** and ( $\pm$ )-**127a**.

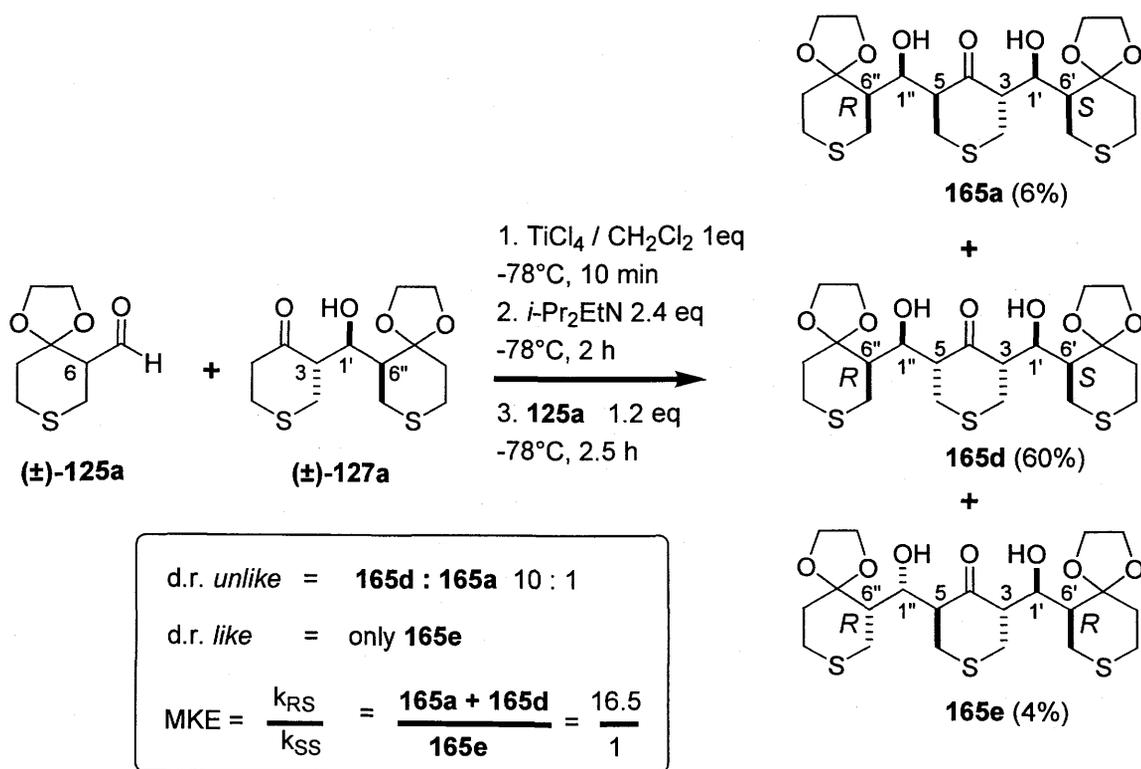
Reactions of **125a** with the Ti (IV) enolates of **126a** and **127a** gave bisaldol products with higher diastereoselectivity and much improved yields compared to reactions with the Li-enolate Li-alkoxide (prepared from **126a** or **127a** with <sup>t</sup>BuLi) (see Schemes 15 and 16).<sup>30</sup> The titanium enolates were synthesised by mixing of **126a** or **127a** with TiCl<sub>4</sub> (1.1 equiv) to generate the titanate (yellow in colouration) followed by the addition of diisopropylethylamine (*i*-Pr<sub>2</sub>EtN, 2.4 equiv) which gave a characteristic red solution typical of titanium enolates.<sup>163</sup> 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 ( $\pm$ )-**125a** and ( $\pm$ )-**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 ( $\pm$ )-**125a** and ( $\pm$ )-**126a** highly diastereoselective for ( $\pm$ )-**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**).<sup>166</sup> 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).



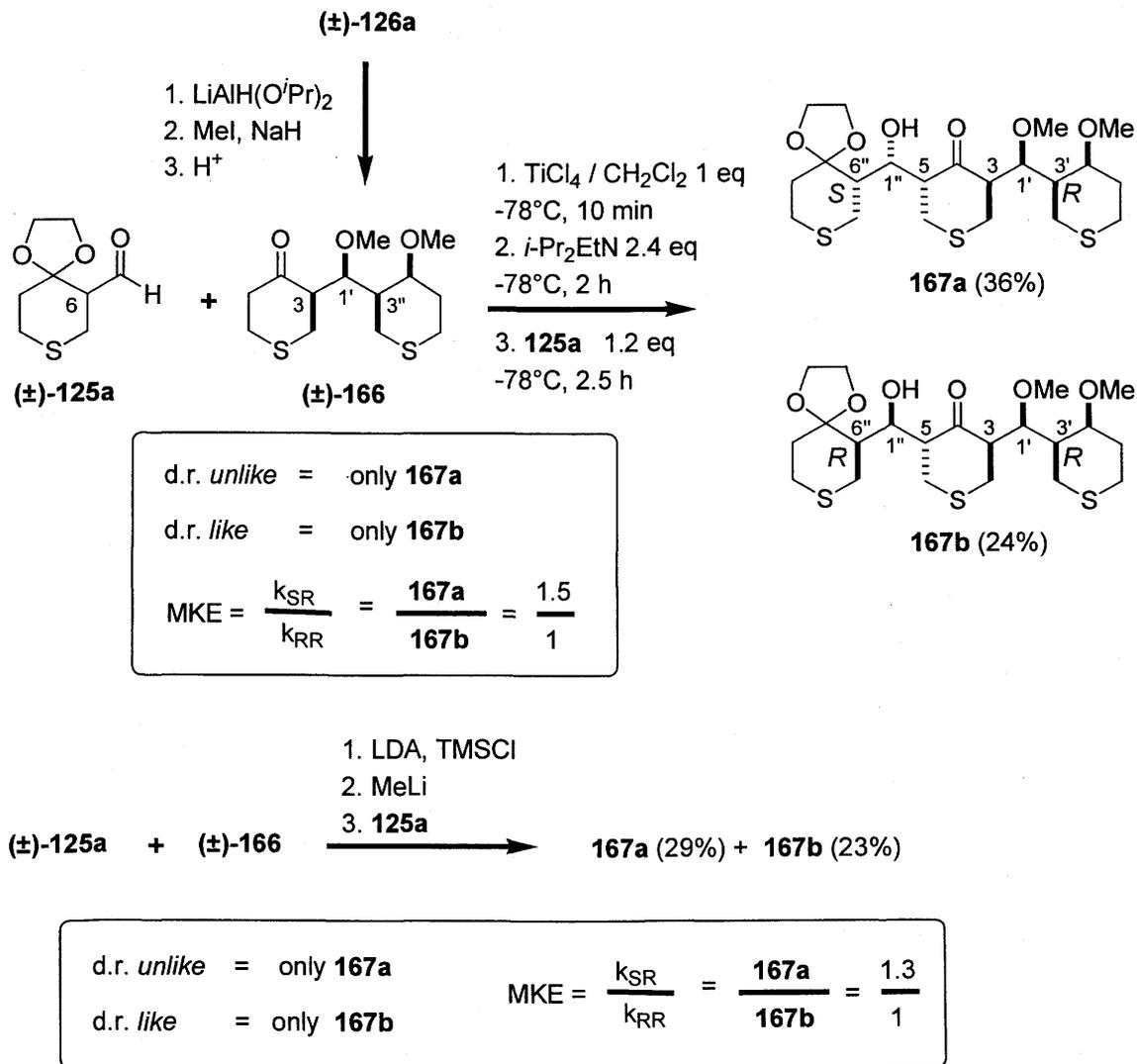
**Scheme 16.** Aldol reaction of enolates derived from (±)-127a with (±)-125a.

### 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  $\text{TiCl}_4$  (1.1 equiv) followed by the addition of  $i\text{-Pr}_2\text{EtN}$  (1.2 equiv) at  $-78^\circ\text{C}$  which generated the characteristic red solution typical of titanium enolates.<sup>163</sup> 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  $\text{TMSCl}$  gave the corresponding trimethylsilyl enol ether which was treated with  $\text{MeLi}$  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).

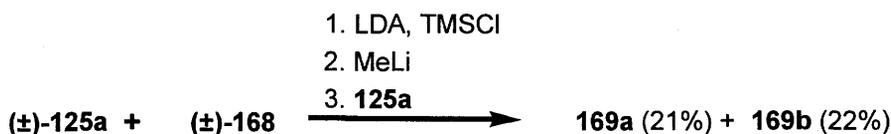
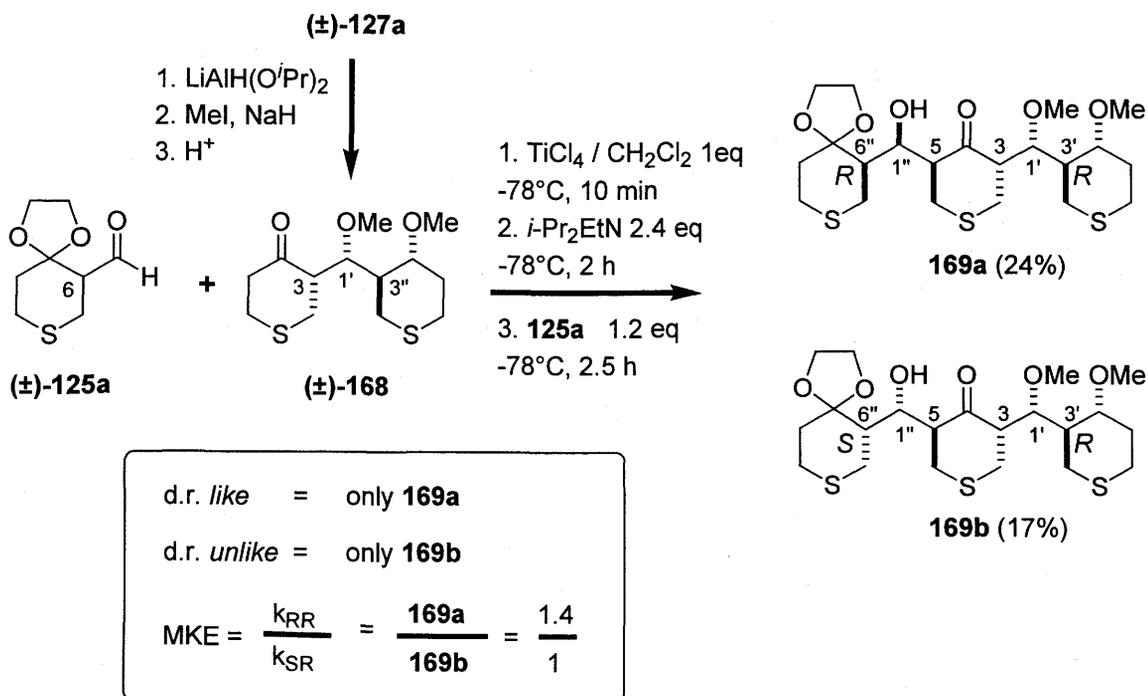


**Scheme 17.** Aldol reaction of enolates derived from **(±)-166** with **(±)-125a**.

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).



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

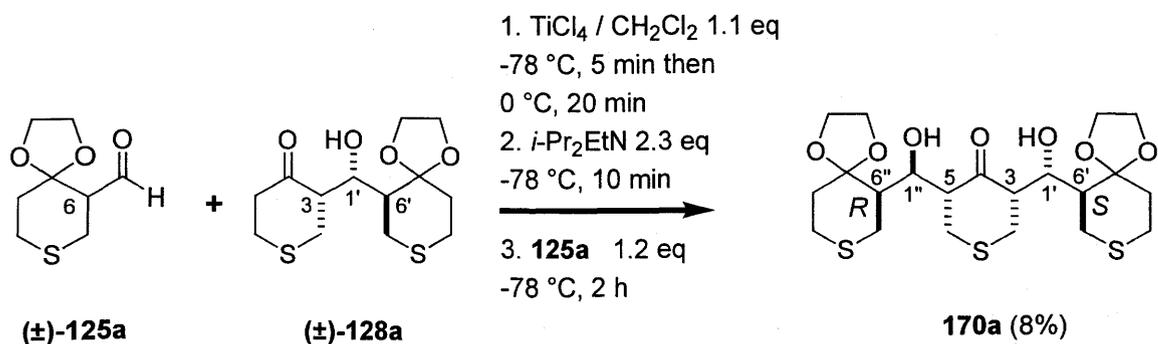
To summarize the results of the previous work, aldol reactions of **125a** with  $\beta$ -hydroxy ketones **126a** and **127a** were highly diastereoselective for the formation of one

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’  $\beta$ -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  $\beta$ -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’  $\beta$ -hydroxyl versus a ‘protected’  $\beta$ -hydroxyl of a ketone to influence the diastereoselectivity of the aldol reaction. To this end, the aldol reactions of two new  $\beta$ -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 ( $\pm$ )-**125a** with ( $\pm$ )-**128a** and ( $\pm$ )-**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  $\text{TiCl}_4$  (1 equiv) at 0 °C for 20 minutes, which resulted in a fine yellow suspension presumably the titanate intermediate. Addition of *i*-Pr<sub>2</sub>EtN (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.

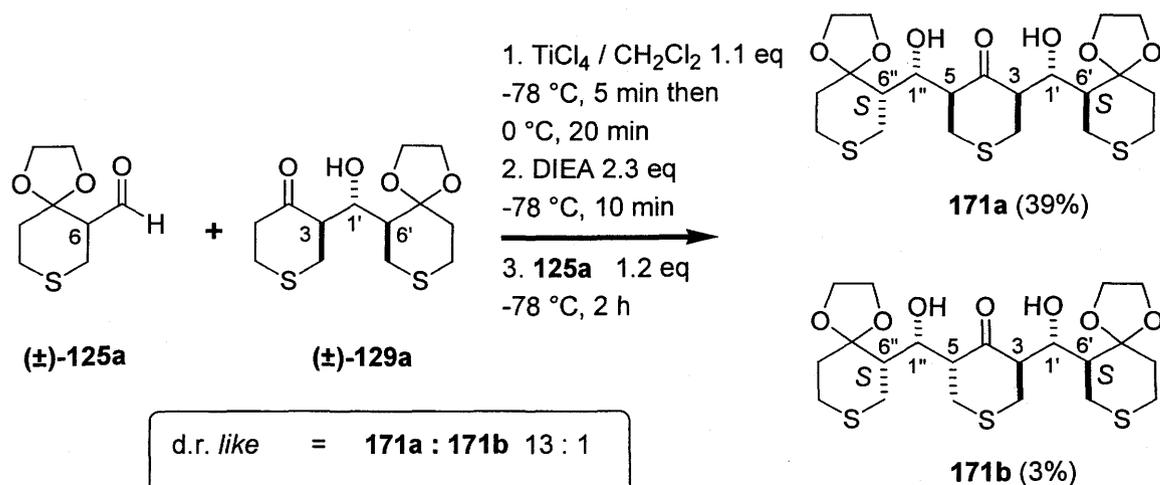


d.r. *unlike* = only **170a**

d.r. *like* = not detected

$$\text{MKE} = \frac{k_{\text{RS}}}{k_{\text{SS}}} = \text{only } k_{\text{RS}}$$

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



d.r. *like* = **171a** : **171b** 13 : 1

d.r. *unlike* = not detected

$$\text{MKE} = \frac{k_{\text{SS}}}{k_{\text{RS}}} = \text{only } k_{\text{SS}}$$

**Scheme 20.** Aldol reaction of enolate derived from **(±)-129a** with **(±)-125a**.

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

<sup>\*</sup> 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*-Pr<sub>2</sub>EtN in the presence of Bu<sub>4</sub>Ni. 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%).<sup>†</sup> 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%).<sup>‡</sup> It is of interest that that the MKE for the aldol

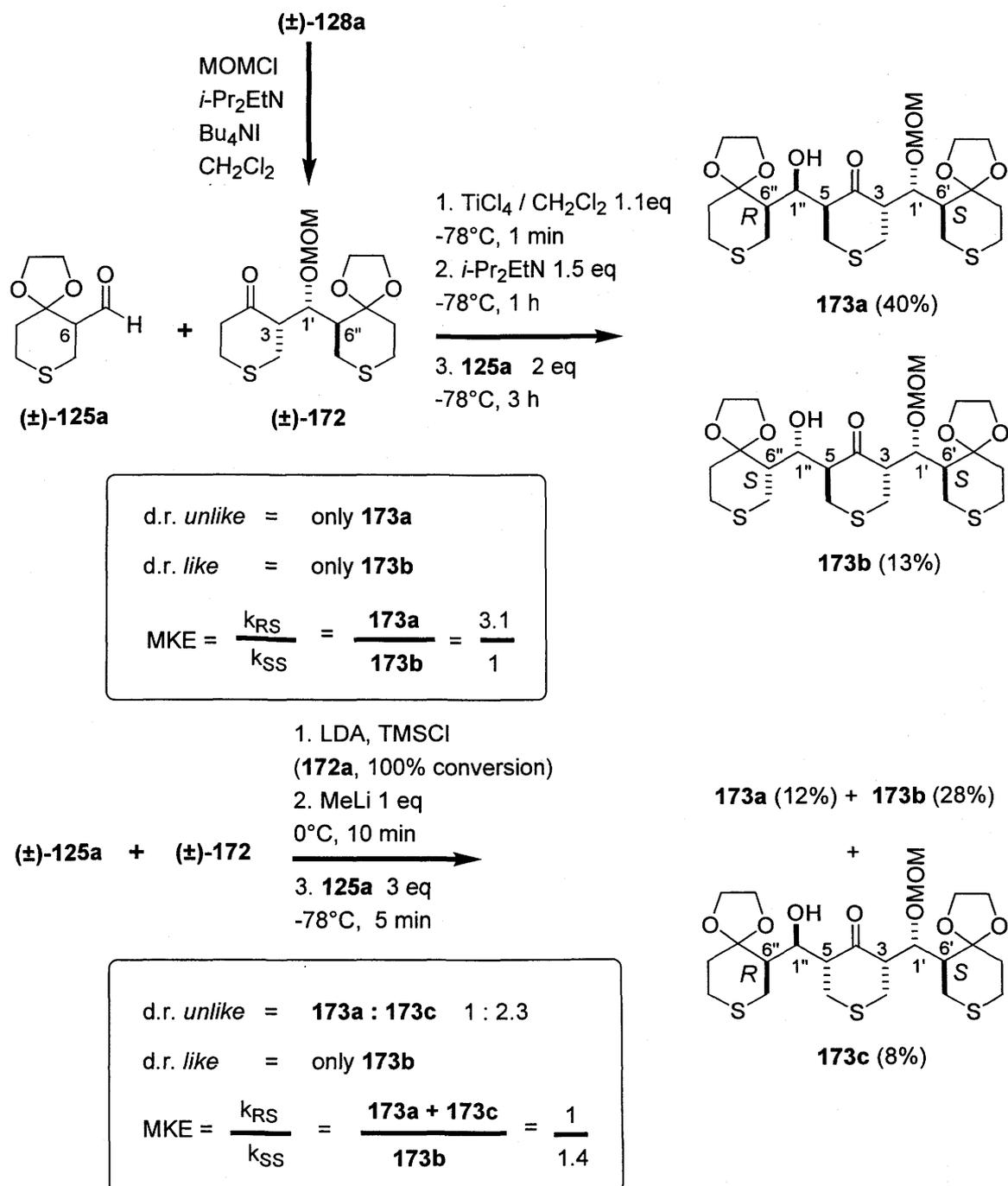
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\* For aldol reactions of **125a** with **128a** and **129a**, the like and unlike are assigned with respect to the relative absolute configurations at C-6 of **125a** and C-6'' of **128a** and **129a**.

<sup>†</sup> Recovered **172** was obtained in 45% isolated yield. Two equivalents of **125a** were used; 48% was recovered by chromatography.

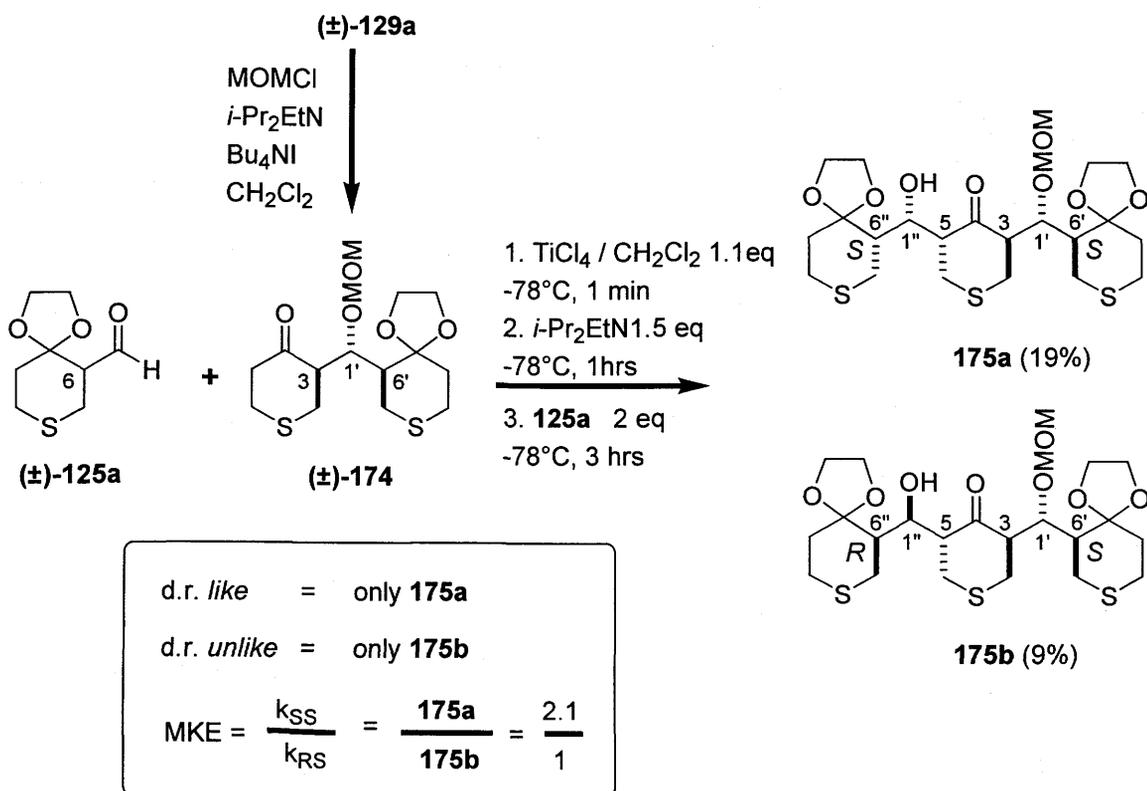
<sup>‡</sup> The 'amine free' Li-enolate was generated by addition of MeLi to the TMS enol ethers of **172**.

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).



**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**.

### 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.

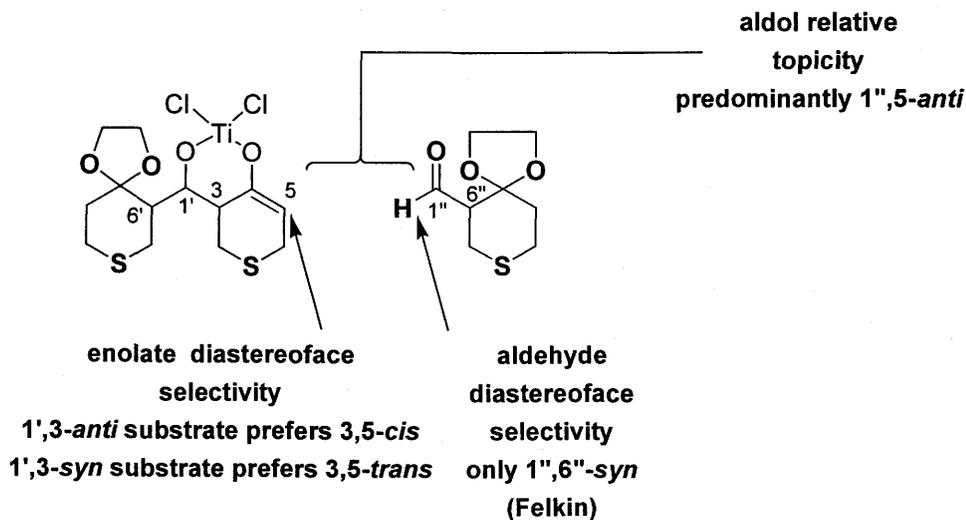
Felkin selective (all products are 1'',6''-syn). For all reactions the relative topicity was highly 1'',5-anti selective. It was found that the enolate diastereoface selectivity (3,5-cis/trans) appeared to be dependant on the 1',3-syn/anti relative configuration of the  $\beta$ -hydroxyketone substrate. 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**

Entry	ketone	product ratios	diastereoface selectivity		relative topicity
			aldehyde 1'',6''syn:anti	enolate 3,5-cis:trans	1'',5-syn:anti
1	<b>126a</b>	<b>165a:165b:165c:</b> 60:1:8	all syn	1:68	1:6.7
2	<b>127a</b>	<b>165a:165d:165e</b> 1.5:15:1	all syn	6:1	1:11
3	<b>128a</b>	<b>170a</b>	syn	cis	anti
4	<b>129a</b>	<b>171a:171b</b> 13:1	all syn	13:1	1:13

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.



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

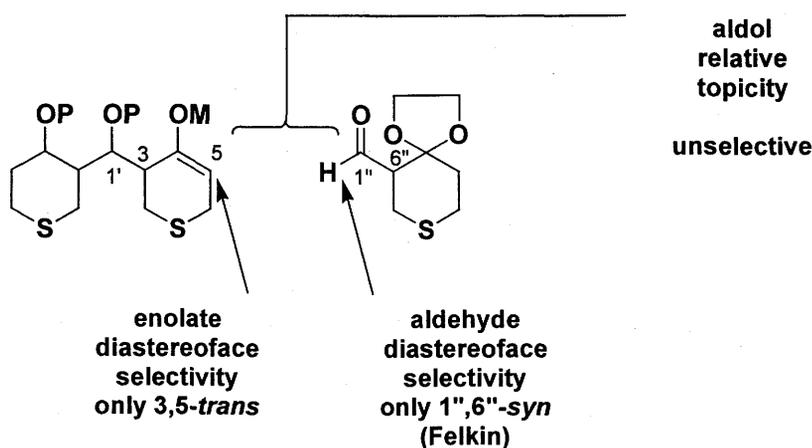
The aldol reactions of the four  $\beta$ -hydroxy ketones **126a-129a** were highly diastereoselective. From an analysis of the stereoselectivities of these reactions it is concluded that they all exhibit high diastereoface selectivities for both the aldehyde and the enolate and high preference in the relative topicity (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  $\beta$ -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  $\beta$ -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**

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



**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 2<sup>nd</sup> Aldol Reaction with Related Acyclic Examples.

Two related studies<sup>38,164</sup> which also used 'free' and/or 'protected'  $\beta$ -hydroxy ketones as substrate in aldol reactions are discussed with special attention to the effect of the  $\beta$ -hydroxyl (free versus protected) on aldol diastereoselectivity.

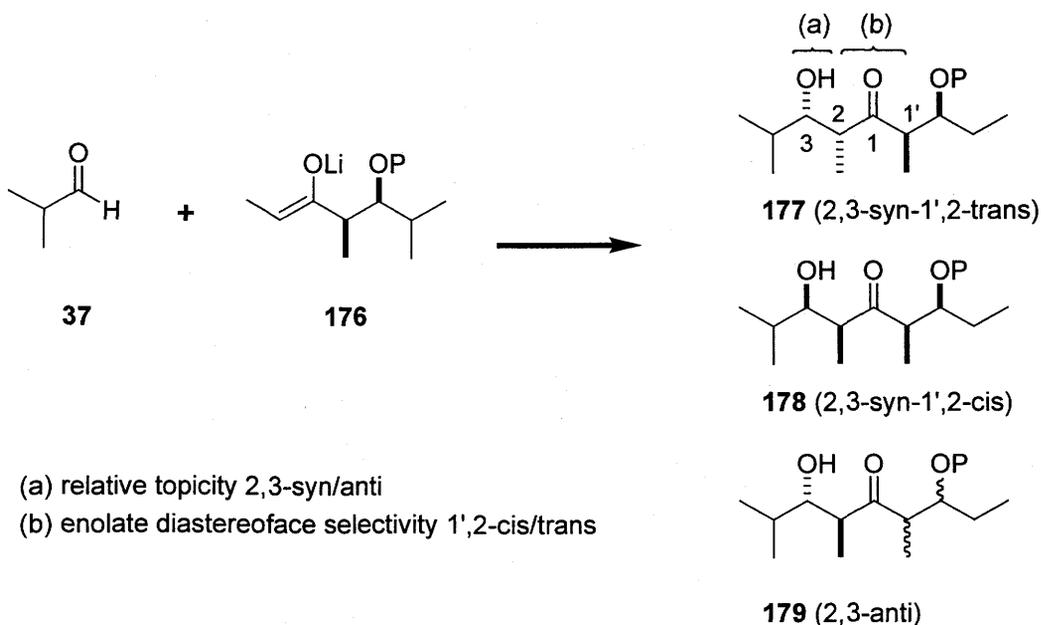
The study by McCarthy et al.<sup>164</sup> compared the effect of the protecting group of the  $\beta$ -hydroxyl on the diastereoselectivity of the aldol reaction of the chiral (*Z*) Li-enolate **176** with achiral 2-propanal (**37**). It was found that protection of the  $\beta$ -hydroxyl group effected 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'  $\beta$ -hydroxy ketones (entries 2-7) was relatively more selective than the reaction of the 'free'  $\beta$ -hydroxy ketone (entry 1). This trend is in contrast to the results of this study where the relative topicity of the aldol reactions of  $\beta$ -hydroxy ketones **126a-129a** was more selective than those of the reactions of the related  $\beta$ -alkoxy ketones **166**, **168**, **172** and **174**.

The study by Evans et al.<sup>38</sup> 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

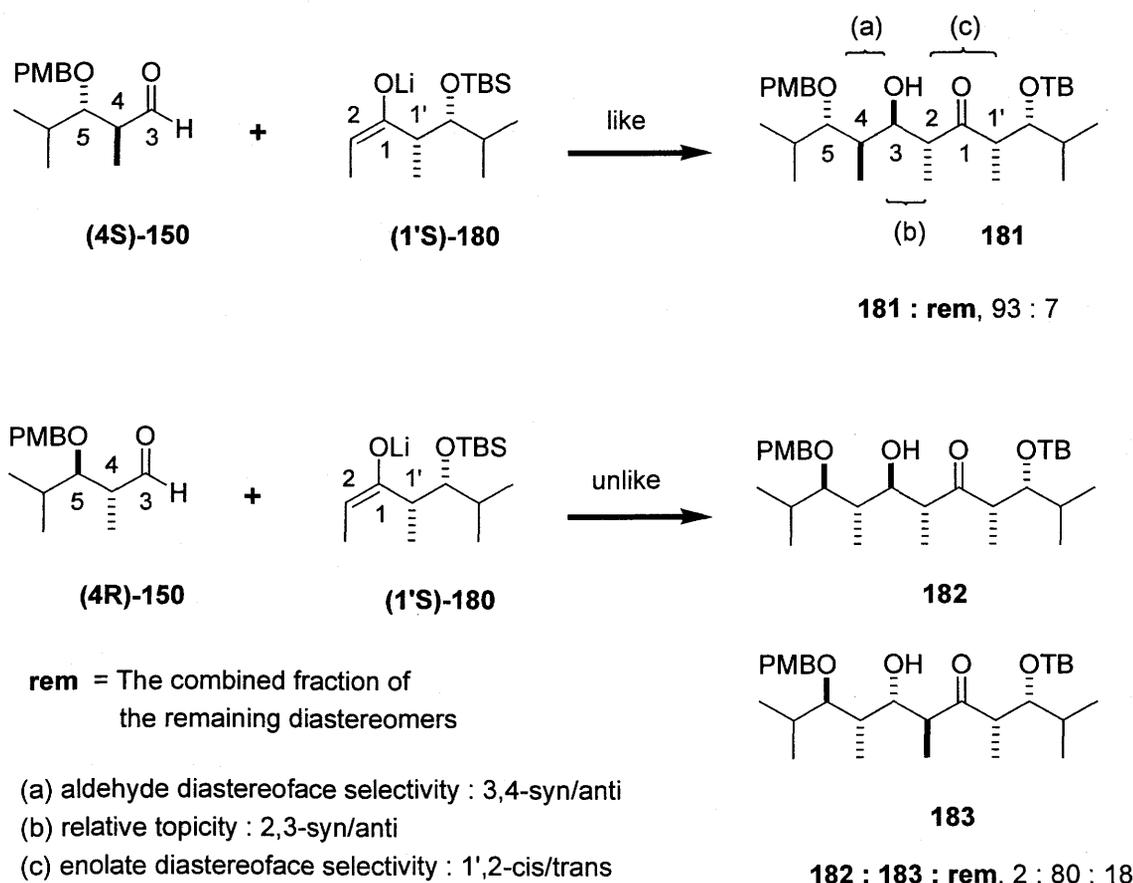
**Table 12.** The selectivities of the aldol reaction of Li-enolate 176 with 37.<sup>164</sup>



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

\* 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  $\beta$ -alkoxy ketones **166**, **168**, **172** and **174**.



**Figure 45.** The selectivities of the like and unlike reaction of Li-enolate **180** with **150**.<sup>38</sup>

The comparison of the selectivities of this study and those of related acyclic examples leads to the conclusion that the  $\beta$ -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<sup>38,164</sup> are not influenced by the  $\beta$ -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  $\beta$ -hydroxy group (free vs. protected) on aldol diastereoselectivity. Reactions of **125a** with the 'free'  $\beta$ -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'  $\beta$ -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'  $\beta$ -hydroxy ketones. However, similar reactions of the 'protected'  $\beta$ -hydroxy ketones proceeded with a much lower relative topicity. Comparison of the above results with those reported<sup>38,164</sup> for aldol reactions of related acyclic substrates showed that aldol diastereoselectivities of thiopyranone derived substrates are substantially different.

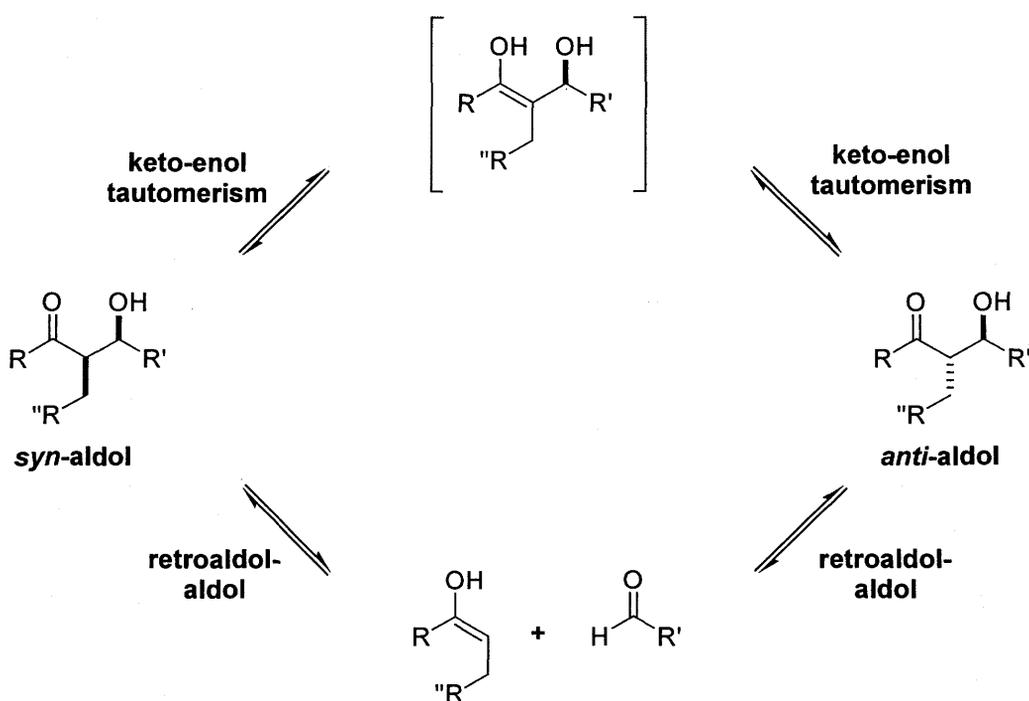
With respect to the thiopyran route to polypropionates, the present study has increased the number of substrates available for use in the 2<sup>nd</sup> aldol reaction. New bisaldols have been synthesized and are potential hexapropionate synthons to be used in the synthesis of polypropionate containing 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<sup>74,76</sup> despite intensive investigations during the past two decades.<sup>54,71</sup> Isomerization of aldol products presents an alternative strategy

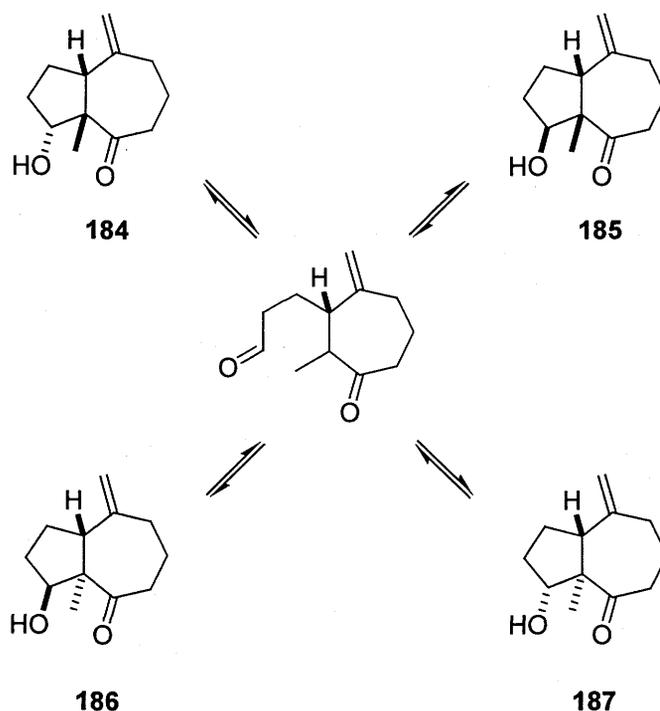
to access various aldol stereoisomers. Retroaldol-aldol and keto-enol tautomerism are the two pathways through which isomerization of aldol adducts can occur (Figure 46). The aldol reaction is readily reversible; fragmentation of the adduct via a C-C bond breaking step (retroaldol) gives the precursor 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<sup>167-173</sup> and acyclic<sup>133,174,175</sup> 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<sup>172</sup> (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

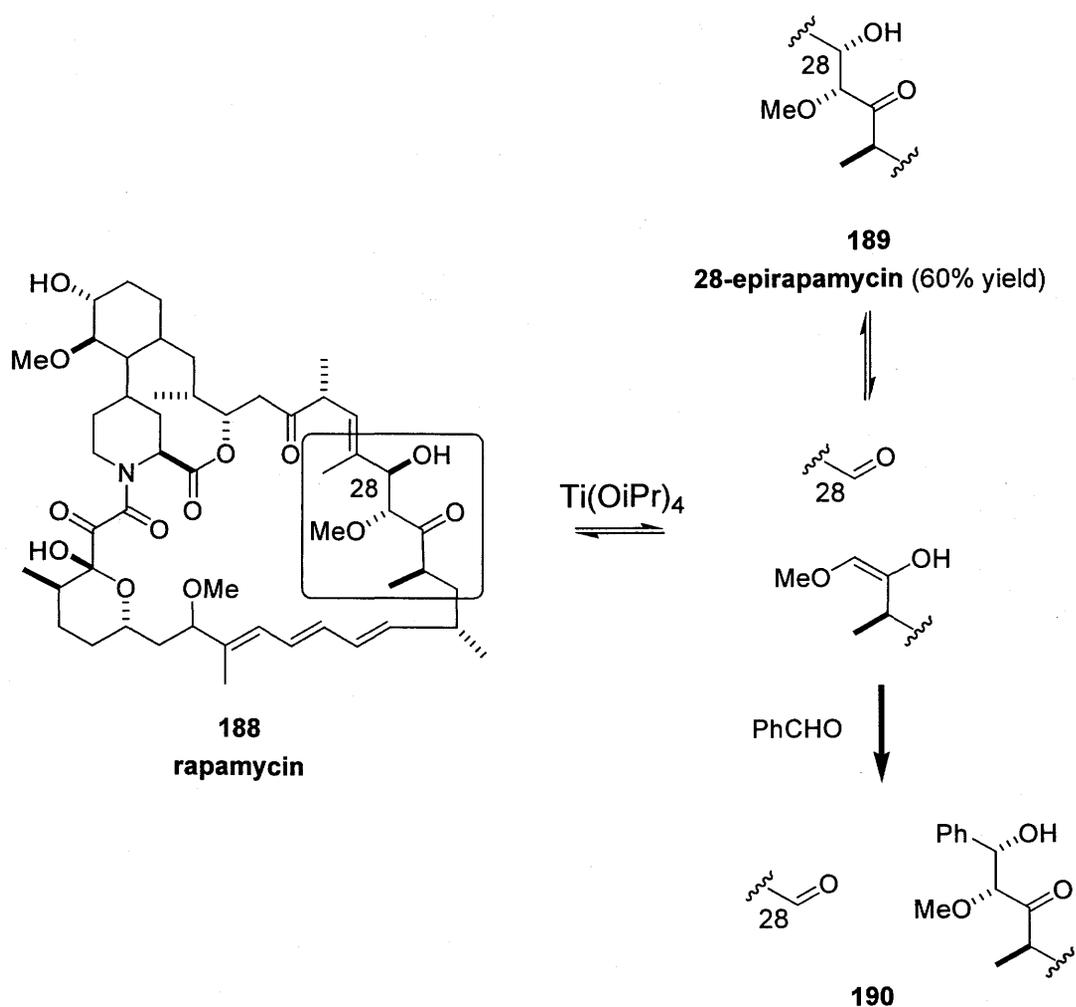
47). The same result was obtained when aldol **185** was treated with the same plethora of bases. It was determined that the equilibrium ratio of **184:185:186:187** was 7:43:35:14 under these basic conditions.



**Figure 47.** The retroaldol-aldol isomerization of perhydroazulenic hydroxyketones **184-187** under basic conditions.

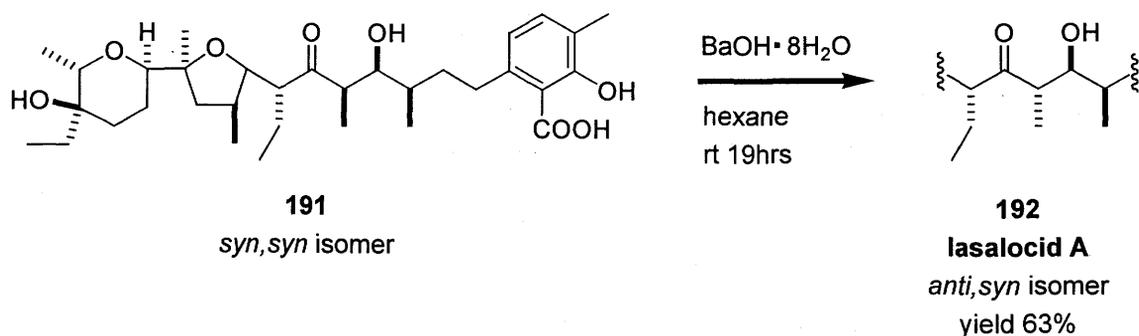
Another example of retroaldol-aldol mechanism for aldol isomerization involves the reaction of rapamycin with titanium (IV) isopropoxide reported by Holt *et al.*<sup>174</sup> This study showed that rapamycin (**188**) underwent isomerization in the presence of titanium (IV) isopropoxide to give **189** 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 *et al* also reported titanium (IV) isopropoxide mediated retroaldol-aldol isomerization of simple acyclic aldols.<sup>174</sup>

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.<sup>165,176</sup>



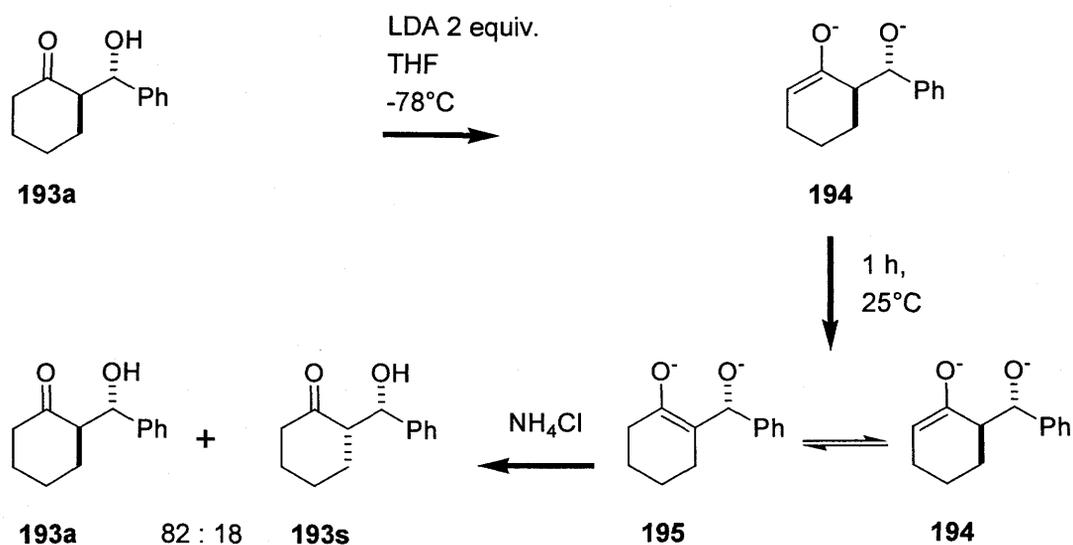
**Figure 48.** Isomerization of rapamycin to 28-epirapamycin via a retroaldol-aldol mechanism mediated by titanium isopropoxide.

Still *et al.*<sup>176</sup> studied the ion-driven isomerization of lasalocid A stereoisomers (Figure 49). It was established that the *syn,syn* isomer of lasalocid A (**191**) (which has low affinity for complexation to  $\text{Ba}^{2+}$ ) underwent isomerization to lasalocid A (**192**) (which has higher affinity for  $\text{Ba}^{2+}$ ). In the presence of  $\text{Ba}(\text{OH})_2$ , lasalocid A (**192**) was the only isomer detected and the absence of *anti,anti* or *syn,anti* isomers in the reaction is consistent with an enolization mechanism.<sup>176</sup> However, the experiments reported are insufficient to rule out a retro-aldol mechanism.



**Figure 49.**  $\text{Ba}^{2+}$ -mediated keto-enol tautomerism of *syn,syn* stereoisomer exclusively gave naturally occurring Lasalocid A.

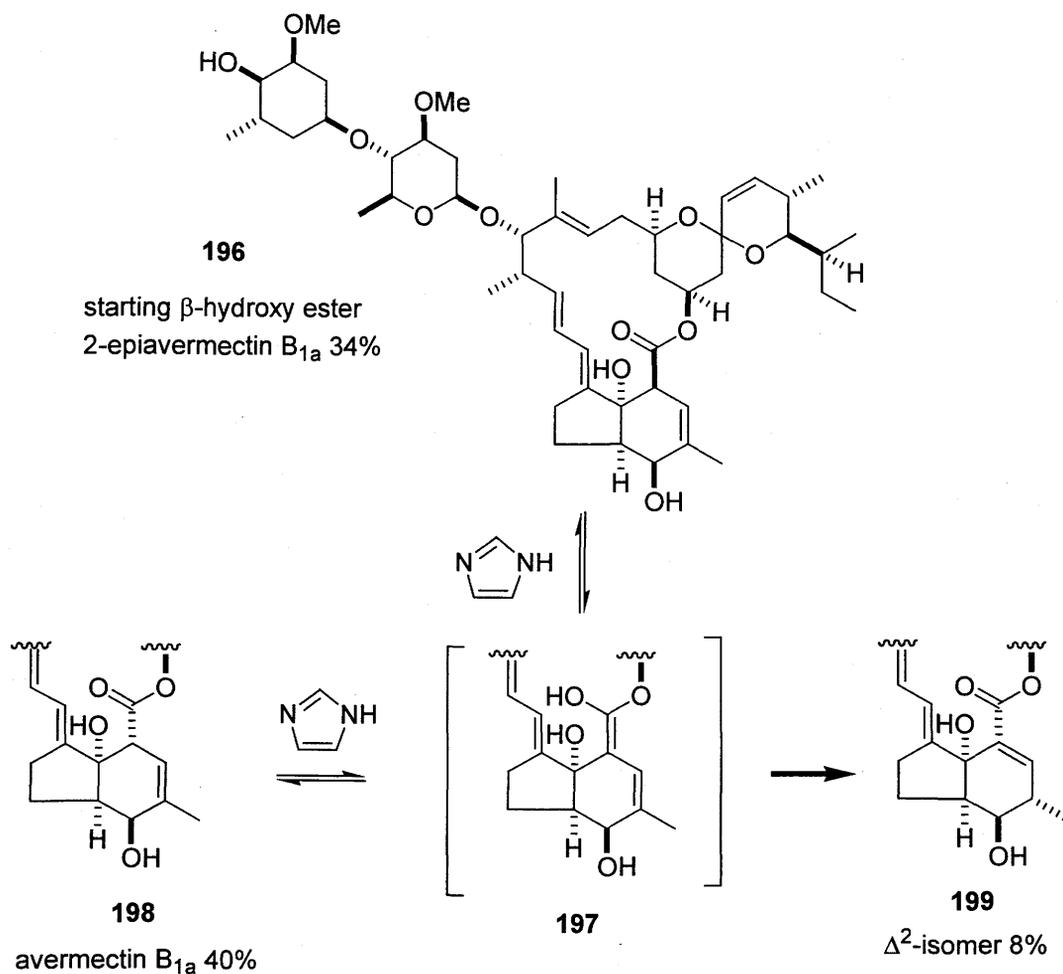
An example of isomerization of an aldol via an enolate intermediate was reported by Albizati et al.<sup>165</sup> In this study the dianion **194** was generated from the anti aldol **193a** by reaction with 2 equivalents of LDA at  $-78^\circ\text{C}$  (Scheme 23). The enolate **194** was stirred at room temperature for 1 hour resulting in a mixture of enolates **194** and **195** that upon quenching with  $\text{NH}_4\text{Cl}$  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  $\beta$ -hydroxy carboxylic acid derivatives by an enolization mechanism via enol<sup>177,178</sup> and enolate<sup>118</sup> intermediates have been reported. An example of isomerization of a  $\beta$ -hydroxyester (cf.  $\beta$ -hydroxyketone) via enolization was reported by Hanessian et al.<sup>178</sup> in their synthesis of avermectin B<sub>1a</sub> (**198**) (Figure 50). A key step in their strategy required the isomerization of 2-epiavermectin B<sub>1a</sub> (**196**) to obtain the natural occurring avermectin B<sub>1a</sub> (**198**) (Figure 50). Isomerizations of avermectins had previously been studied by Pivnichny *et al.*<sup>179</sup> who showed that treatment of **198** with methanolic potassium hydroxide resulted in a mixture of **198**, **196** and the conjugated  $\Delta^2$ -isomer **199**. In a later study by Fraser-Reid *et al.*<sup>180</sup>, **198** was treated with methanolic aqueous sodium hydroxide to give the conjugated  $\Delta^2$ -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<sub>1a</sub> (**198**) in 40% isolated yield together with only 8% of  $\Delta^2$ -isomer (**199**) and 34% of starting 2-epiavermectin (**196**) which could be recycled (Figure 50).<sup>178</sup>

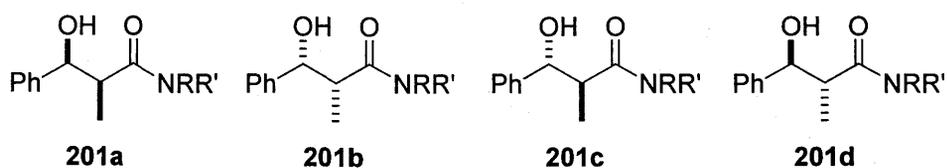
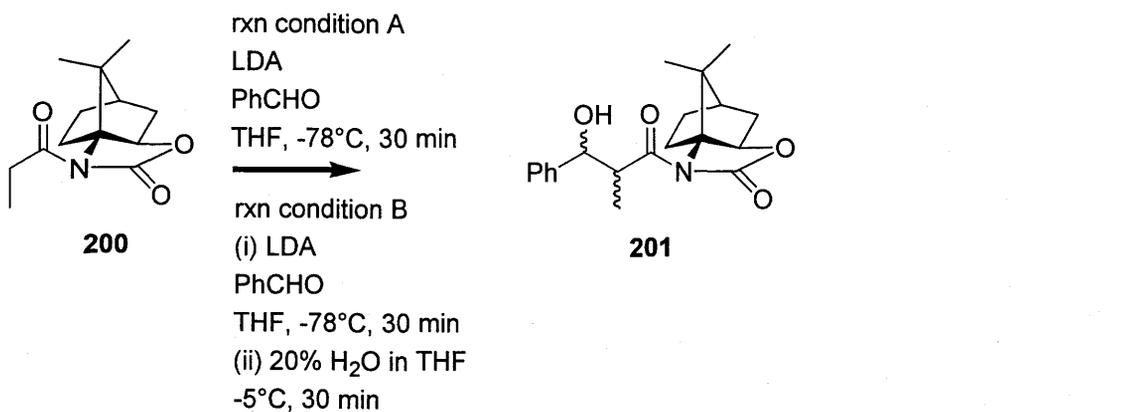
Isomerization of aldol products **201a-d** was reported by Yan et al. (Scheme 24).<sup>177</sup> Although not discussed by the authors, the reported data is clearly consistent with an enolization mechanism. Benzaldehyde was added to a solution of the lithium enolate of **200** at  $-78$  °C and after 30 minutes the reaction was quenched at 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.



**Figure 50.** Imidazole mediated keto-enol tautomerism of 2-epiavermectin B<sub>1a</sub>.

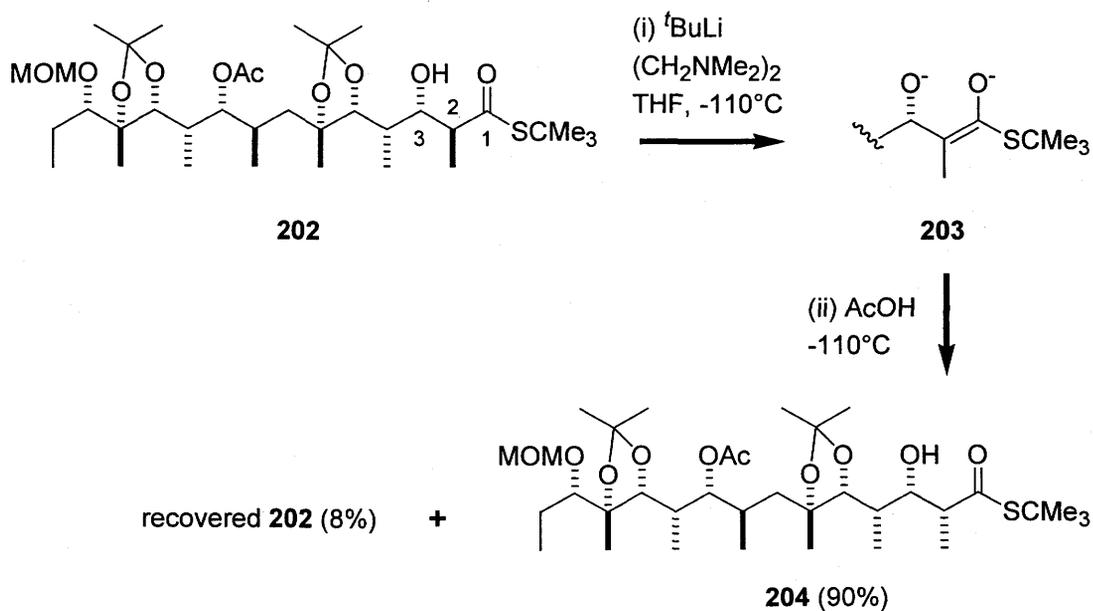
An example of isomerization of a  $\beta$ -hydroxy thioester via an enolate intermediate was reported by Woodward *et al.*<sup>118</sup> Their approach to the total synthesis of erythromycin required the intermediate **204** (Scheme 25). The  $\beta$ -hydroxy thioester **202** was the precursor to **204** and differed in the configuration at C-2. The enolate **203** was generated by treatment of **202** with <sup>t</sup>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.



rxn condition A	1	:	4	:	5	:	0.05
rxn condition B	1	:	9	:	< 0.05	:	< 0.05

**Scheme 24.** Syn/anti isomerization of  $\beta$ -hydroxy carbonyl compounds of **201**.



**Scheme 25.** Isomerization of  $\beta$ -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 TBDMSCl in the presence of imidazole in CH<sub>2</sub>Cl<sub>2</sub>; 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**.

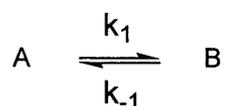
A solution of **128a** (0.03 M) and imidazole (0.4 M) in CDCl<sub>3</sub> was prepared and monitored by <sup>1</sup>H NMR at room temperature. Aldol **129a** slowly formed and after approximately 3 days the ratio of **128a**:**129a** was 1.8:1 and remained constant for several weeks. The aldols **128a** and **129a** were stable throughout the experiment with negligible elimination or retroaldol; less than 5% of aldehyde **125a** was detected by <sup>1</sup>H 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  $k_{\text{enol } 128a}$  and from ketone **129a** with rate constant  $k_{\text{enol } 129a}$ . The enol **207** in turn is converted to ketones **128a** and **129a** with rate constants  $k_{\text{keto } 128a}$  and  $k_{\text{keto } 129a}$ , respectively (Figure 51). This pair of reversible reactions with the corresponding four rate constants



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 :



It can be easily shown that for a system not at equilibrium ( $A \neq A_e$ ) :<sup>181</sup>

$$(k_1 + k_{-1}) t = \ln \frac{A_0 - A_e}{A_t - A_e}$$

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  $-\ln (A_t - A_e)$  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 <sup>1</sup>H NMR spectroscopy as a function of time. A plot of  $-\ln [(R_t - R_e)/(R_t + 1)]$  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  $k_{\text{obs}}$  ( $t_{1/2} = \ln 2/k_{\text{obs}}$ ).

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  $\text{CDCl}_3$  and benzene were *ca.* twice that in  $\text{CD}_2\text{Cl}_2$  or  $\text{CH}_3\text{OH}$  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**<sup>a</sup>

Entry	Starting aldol	Solvent	$K_{\text{eq}}$ ( <b>128a</b> : <b>129a</b> )	$k_{\text{obs}}$ <sup>b</sup> ( $10^{-2} \text{ h}^{-1}$ )	$t_{1/2}$ <sup>c</sup> (h)
1	<b>128a</b>	$\text{CDCl}_3$	1.8:1	5.9 <sup>d</sup>	12
2		$\text{CD}_2\text{Cl}_2$	1.9:1	2.9	24
3		$\text{C}_6\text{D}_6$	1.5:1	5.3	13
4		acetone- $d_6$	1.6:1	0.55	130
5		DMF- $d_7$	2.1:1	0.43	160
6		$\text{CH}_3\text{OH}$	2.0:1	<sup>e</sup>	~1 day
7	<b>129a</b> <sup>f</sup>	$\text{CDCl}_3$	1.8:1	<sup>e</sup>	<sup>e</sup>

<sup>a</sup> Room temperature; [imidazole] = 0.3M; [aldol] = 0.03M. <sup>b</sup> 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 ( $\geq 8$  data points over the initial 2 half-lives;  $R^2 > 0.99$ ). <sup>c</sup> Half-life =  $t_{1/2} = \ln 2/k_{\text{obs}}$ . <sup>d</sup> Data obtained by extrapolation from the plot of  $\ln(k_{\text{obs}})$  vs.  $\ln[\text{imidazole}]$ ; see Table XX. <sup>e</sup> Not determined. <sup>f</sup> Isomerization starting from aldol **129a** confirmed that the equilibrium ratio of [**128a**]:[**129a**] was 1.8:1 in  $\text{CDCl}_3$ .

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.  $\text{C}_6\text{D}_6$ ) compared to polar solvents (e.g.  $\text{CH}_3\text{OH}$ ) 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  $\text{CDCl}_3$  was investigated (Table 15). Isomerization in the presence of DMAP was more facile than with imidazole. The reactions were markedly slower with  $\text{Et}_3\text{N}$  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  $\text{CDCl}_3$  likely contributed to

the failure to observe isomerization with this base. Attempted isomerization under Holt's conditions<sup>174</sup> (i.e. in the presence of Ti(O<sup>*i*</sup>Pr)<sub>4</sub>) only gave the elimination product.

**Table 14.** Solvent effect on imidazole catalysed isomerization of aldols **126a** and **127a**<sup>a,b</sup>

Entry	Starting aldol	Solvent	K <sub>eq</sub> (126a:127a)
1	<b>126a</b>	CDCl <sub>3</sub>	1.5:1
2	<b>127a</b>	CDCl <sub>3</sub>	1.5:1
3	<b>126a</b>	CD <sub>2</sub> Cl <sub>2</sub>	1.6:1
4	<b>127a</b>	CD <sub>2</sub> Cl <sub>2</sub>	1.6:1
5	<b>127a</b>	acetone-d <sub>6</sub>	2.0:1
6	<b>127a</b>	C <sub>6</sub> D <sub>6</sub>	1.4:1
7	<b>127a</b>	CH <sub>3</sub> OH	1.7:1

<sup>a</sup> The data was obtained by Dr. Pradip K. Sasmal. <sup>b</sup> 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 **128a**.<sup>a</sup>

Entry <sup>a</sup>	Base	[base] (M)	[128a] (M)	t <sub>1/2</sub> (h)	k <sub>obs</sub> <sup>b</sup> (E-2 h <sup>-1</sup> )
1	imidazole	0.40	0.030	8.6	8.1
2	DMAP	0.40	0.030	3.6	19
3	Et <sub>3</sub> N	0.40	0.016	110	0.63
4	methylimidazole	0.40	0.040	289	0.24
5	pyridine	0.22	0.016	<sup>c</sup>	
6	1,2,4-triazole	0.05	0.04	<sup>d</sup>	
7	Ti(O <sup><i>i</i></sup> Pr) <sub>4</sub>	0.036	0.018	<sup>e</sup>	

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

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.<sup>182</sup>

**Table 16.** The effect of stoichiometry and concentration on imidazole catalyzed isomerization of **128a** in  $\text{CDCl}_3$ .<sup>a</sup>

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

<sup>a</sup> Room temperature; The  $K_{\text{eq}}$  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  $1.28 \pm 0.13$  (95% confidence interval).

† Linear regression of the four data points used yielded a slope of  $0.96 \pm 0.23$  (95% confidence interval).

**Table 17.** The effect of stoichiometry and concentration on DMAP catalyzed isomerization of **128a** in CDCl<sub>3</sub>.<sup>a</sup>

Entry <sup>a</sup>	[DMAP] (M)	[128a] (M)	k <sub>obs</sub> (10 <sup>-2</sup> h <sup>-1</sup> )	t <sub>1/2</sub> (h)
1	0.10	0.015	3.7	19
2	0.10	0.030	4.4	16
3	0.20	0.030	8.7	8.0
4	0.40	0.030	19	3.6
5	0.40	0.060	18	3.9
6	0.40	0.120	19	3.6
7	0.80	0.030	32	2.2

<sup>a</sup> Room temperature; The K<sub>eq</sub> of [128a]/[129a] was 1.8:1 for all entries.

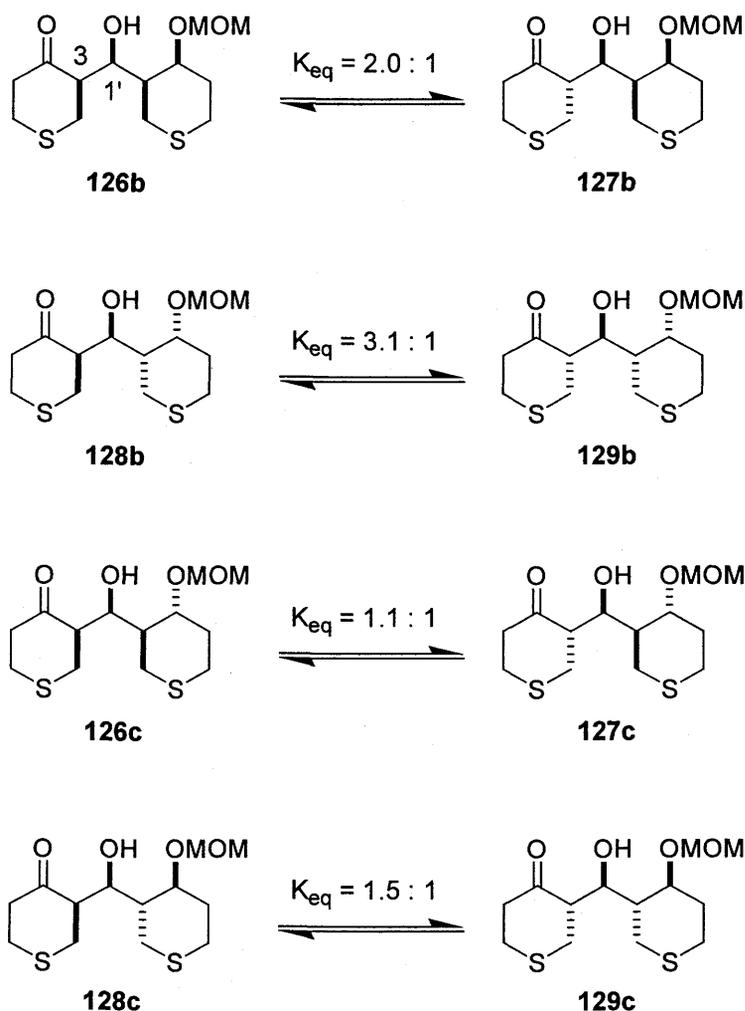
To demonstrate the generality of the imidazole catalysed isomerization of aldols via enolization, the related aldols **126b-129b** and **126c-129c**\* (Figure 52) were examined. The starting aldols used and the ratio of aldol adducts at equilibrium are reported in Table 18. In each case only the starting 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**.

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



**Figure 52.** Imidazole catalysed isomerization of various aldols in  $\text{CDCl}_3$ .

The imidazole catalyzed isomerization of the acyclic aldol **208s**<sup>141</sup> was also attempted (Figure 53). Isomerization of a 9:1 mixture of **208s** and **208a**, respectively in  $\text{CDCl}_3$  in the presence of imidazole (0.4 M) at room temperature was very slow. The rate of isomerization increased significantly in  $\text{C}_6\text{D}_6$  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

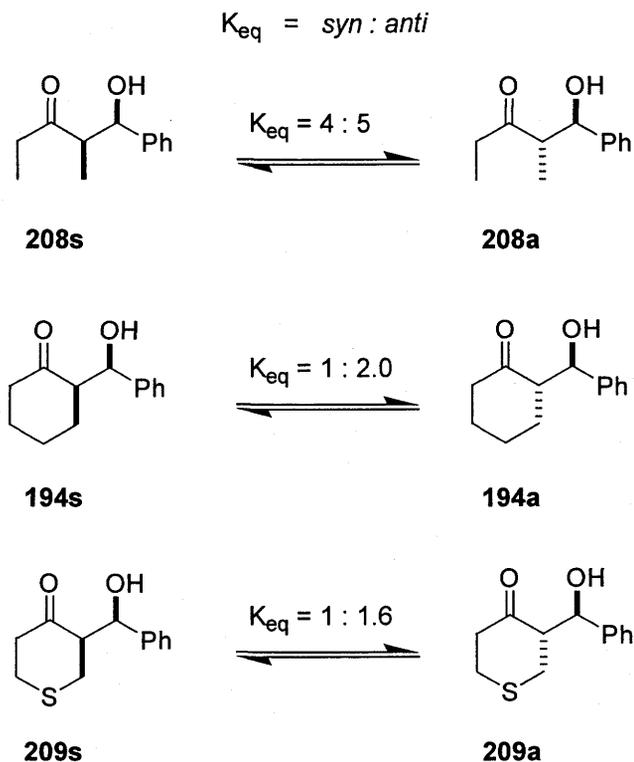
ratio (**208s**:**208a**, 4:5) was obtained by Holt et al. in the presence of  $\text{Ti}(\text{O}^i\text{Pr})_4$ .<sup>174</sup> Despite the harsher conditions of elevated temperature, higher imidazole concentration (1.0 M) and long reaction time, the amount of elimination products was negligible and 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  $\text{CDCl}_3$ .<sup>a</sup>

entry	starting aldol	[imidazole] (M)	aldols at equilibrium (syn:anti)
1	<b>126b</b>	0.40	<b>126b:127b</b> (2.0:1) <sup>b</sup>
2	<b>127b</b>	0.40	<b>126b:127b</b> (2.0:1) <sup>b</sup>
3	<b>128b</b>	0.30	<b>128b:129b</b> (3.1:1)
4	<b>129b</b>	0.30	<b>128b:129b</b> (3.1:1)
5	<b>126c</b>	0.30	<b>126c:127c</b> (1.1:1)
6	<b>127c</b>	0.30	<b>126c:127c</b> (1.1:1)
7	<b>128c</b>	0.30	<b>128c:129c</b> (1.5:1)

<sup>a</sup> Isomerizations at room temperature; [aldol] =  $0.3 \pm 0.1$  M; Equilibrium reached in 5-7 days unless otherwise indicated. <sup>b</sup> 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  $\text{CDCl}_3$  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.

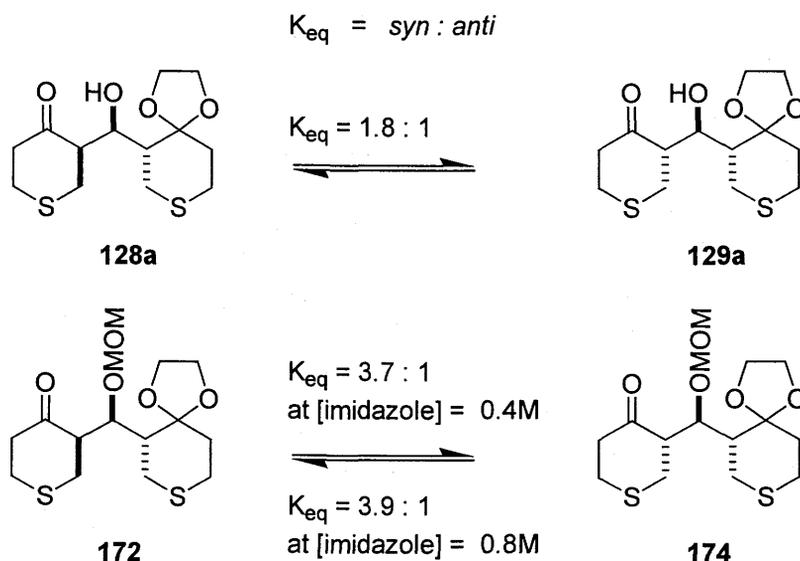


**Figure 53.** Imidazole catalysed isomerization of various aldols in  $\text{CDCl}_3$ .

**Table 19.** Effect of structure on imidazole catalysed isomerization.<sup>a</sup>

Entry	Starting aldol	$K_{eq}$ (anti:syn)	$t_{1/2}$ (h)	$k_{obs}$ ( $10^{-2} \text{ h}^{-1}$ )
1	<b>208s</b> <sup>b</sup>	1.1:1	41	1.7
2	<b>194a</b> <sup>c</sup>	2.0:1	43	1.6
3	<b>209a</b> <sup>c</sup>	1.6:1	15	4.8

<sup>a</sup> All reactions were carried out in  $\text{CDCl}_3$  at ambient temperature unless stated otherwise. <sup>b</sup> A 9:1 mixture of **208s**:**208a** was used. Reaction at  $60^\circ\text{C}$  in  $\text{C}_6\text{D}_6$  for 13 days with imidazole concentration of 1.0 M. Approximately 6% of benzaldehyde was present after 13 days. <sup>c</sup> Imidazole concentration  $0.7 \pm 0.1 \text{ M}$ .



**Figure 54.** Imidazole catalysed isomerization of aldols **128a**, **172** and **174** in  $\text{CDCl}_3$

**Table 20.** Imidazole catalyzed isomerization of  $\beta$ -hydroxy (**128a**) vs.  $\beta$ -alkoxy (**172**, **174**) substrates.<sup>a</sup>

Entry	Starting aldol	[imidazole] (M)	$K_{eq}$ (syn:anti)	$k_{obs}^b$ ( $\text{E}^{-2} \text{h}^{-1}$ )	$t_{1/2}$ (h)
1	<b>128a</b>	0.4	1.8:1	8.1	8.6
2	<b>172</b>	0.4	3.7:1	0.18	380
3	<b>174</b>	0.4	3.7:1	0.21	330
4	<b>128a</b>	0.8	1.8:1	21	3.2
5	<b>172</b>	0.8	3.9:1	0.58	120
6	<b>174</b>	0.8	3.9:1	0.69	100

<sup>a</sup> For all entries, [aldol] = 0.03 M; Room temperature; isomerizations in  $\text{CDCl}_3$ . <sup>b</sup> 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 ( $\geq 8$  data points over the initial 2 half-lives;  $R^2 > 0.99$ ).

The isomerization of **174** was also performed in  $\text{CDCl}_3$  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*

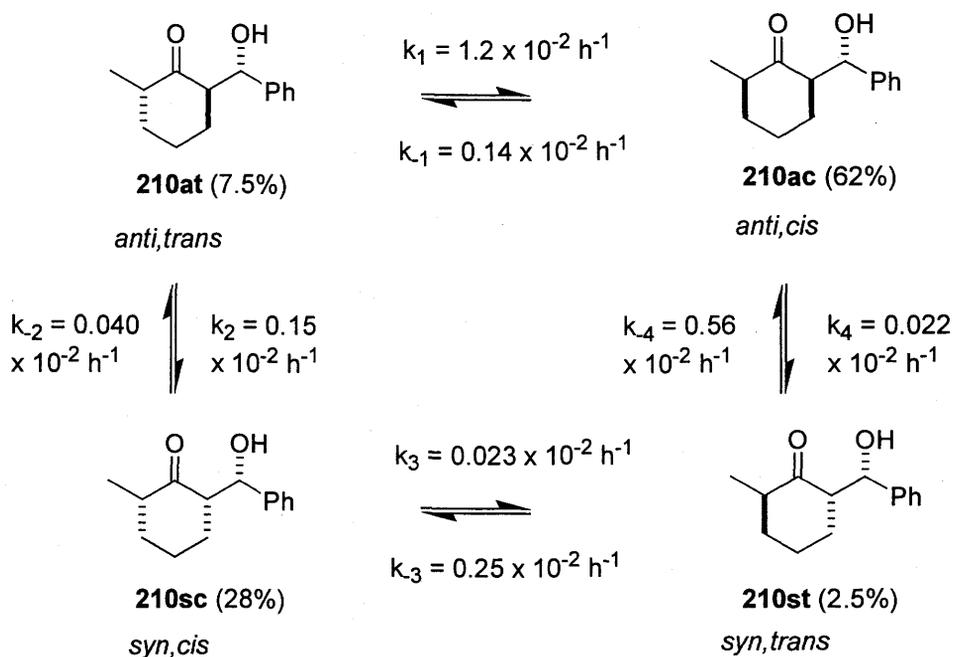
The known<sup>183-189</sup> aldols **210ac,at,sc,st** were individually isomerized in  $\text{CDCl}_3$  in the presence of imidazole (0.4 M) and gave the same equilibrium ratio in each case (Figure 55). The diastereomers with a 1,3-*cis* relative configuration (**210ac**, **210sc**) are predominant at 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

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

† Imidazole concentration of 0.4 M prepared by dissolving  $16 \pm 0.5 \text{ mg}$  imidazole in  $0.60 \pm 0.01 \text{ mL}$   $\text{CDCl}_3$ ; imidazole concentration of 0.8 M prepared by dissolving  $32 \pm 0.5 \text{ mg}$  imidazole in  $0.60 \pm 0.01 \text{ mL}$   $\text{CDCl}_3$ .



Percentages refer to the mole fraction at equilibrium.

**Figure 55.** Isomerization of each of the four aldols **210** with [imidazole] = 0.4 M in  $\text{CDCl}_3$ .

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.<sup>190-192</sup> 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

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

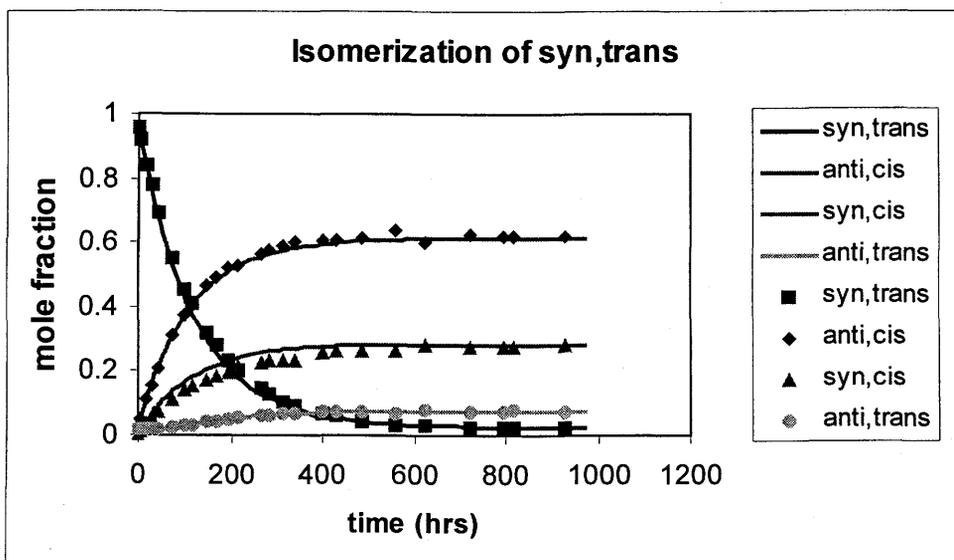
With the aid of this software package, the experimentally obtained concentration versus time profiles were modeled according to the kinetic scheme depicted in Figure 55 to obtain the “best” rate constants. The concentration versus time profiles simulated using these rate constants are depicted in Figures 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  $\text{CDCl}_3$  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**.

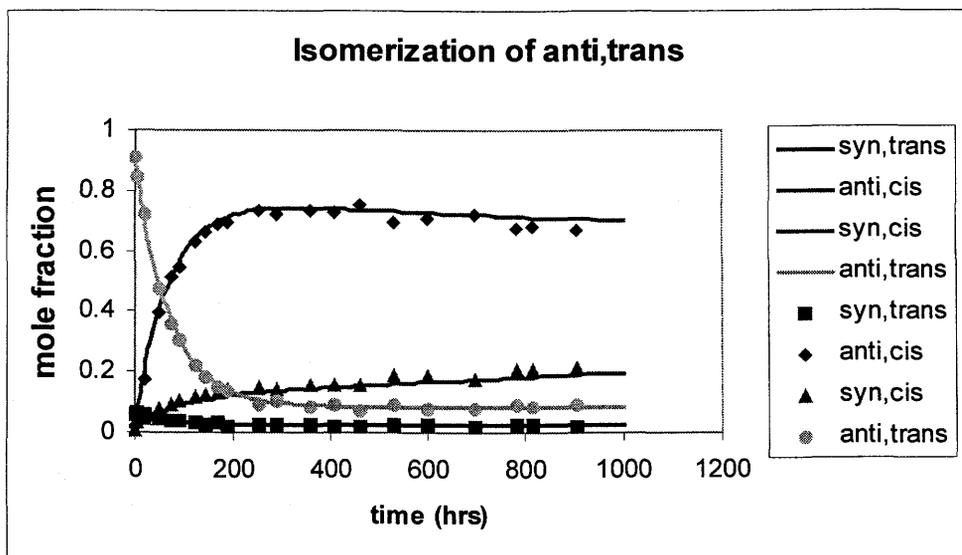
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\* Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, 800 East Kirkwood Ave, Bloomington, IN 47405-7102 (<http://qcpe.chem.indiana.edu> ; email: [qcpe@indiana.edu](mailto:qcpe@indiana.edu))



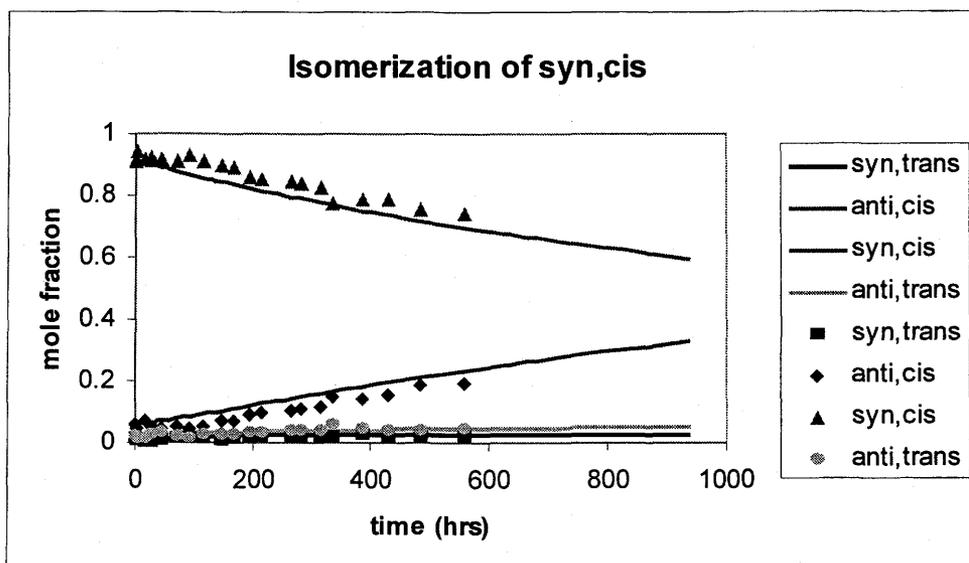
**Figure 56.** Isomerization of a mixture **210st:210ac:210sc:210at** (95:2:1:2)

with a total aldol concentration of 0.014 M in the presence of imidazole (0.4 M) in  $\text{CDCl}_3$ .



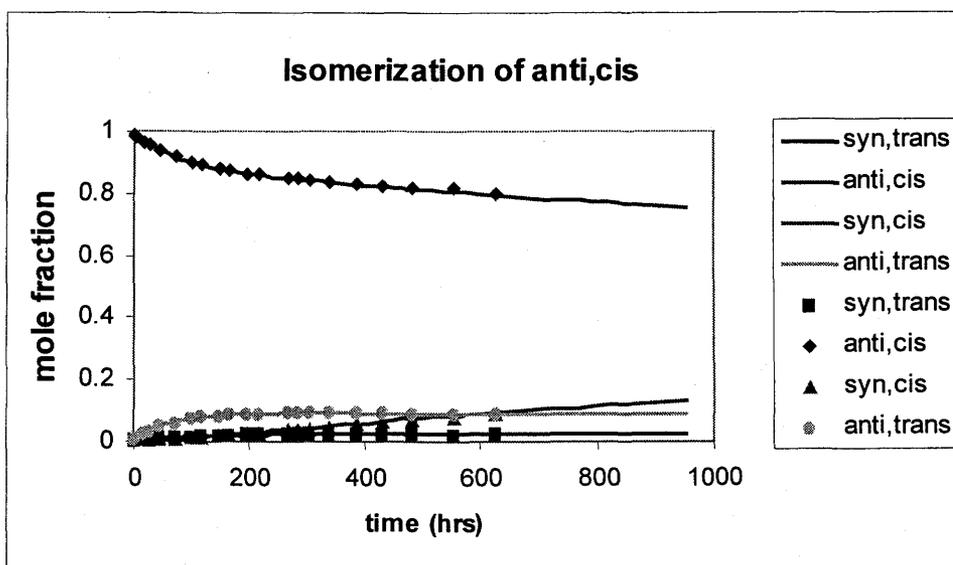
**Figure 57.** Isomerization of a mixture **210st:210ac:210sc:210at** (6:2:1:91)

with a total aldol concentration of 0.014 M in the presence of imidazole (0.4 M) in  $\text{CDCl}_3$ .



**Figure 58.** Isomerization of a mixture **210st:210ac:210sc:210at** (1:6:91:2)

with a total aldol concentration of 0.014 M in the presence of imidazole (0.4 M) in  $\text{CDCl}_3$ .



**Figure 59.** Isomerization of a mixture **210ac:210at** (99:1)

with a total aldol concentration of 0.014 M in the presence of imidazole (0.4 M) in  $\text{CDCl}_3$ .



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.

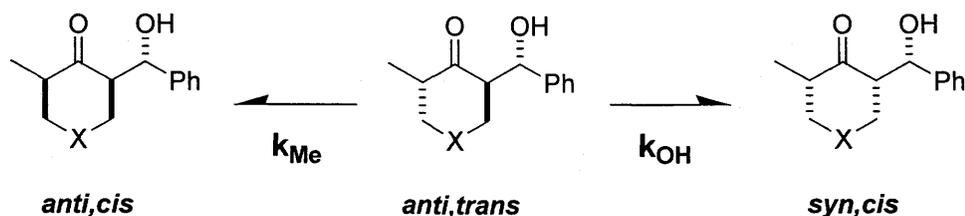
Upon examining the regioselectivity of isomerization it is apparent that the anti aldols **210at** and **210ac** isomerize faster towards the methyl group (entries 1 and 2, Table 21) and the syn aldols **210st** and **210sa** isomerize faster towards the hydroxyalkyl group (entries 3 and 4, Table 21). 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.



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

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

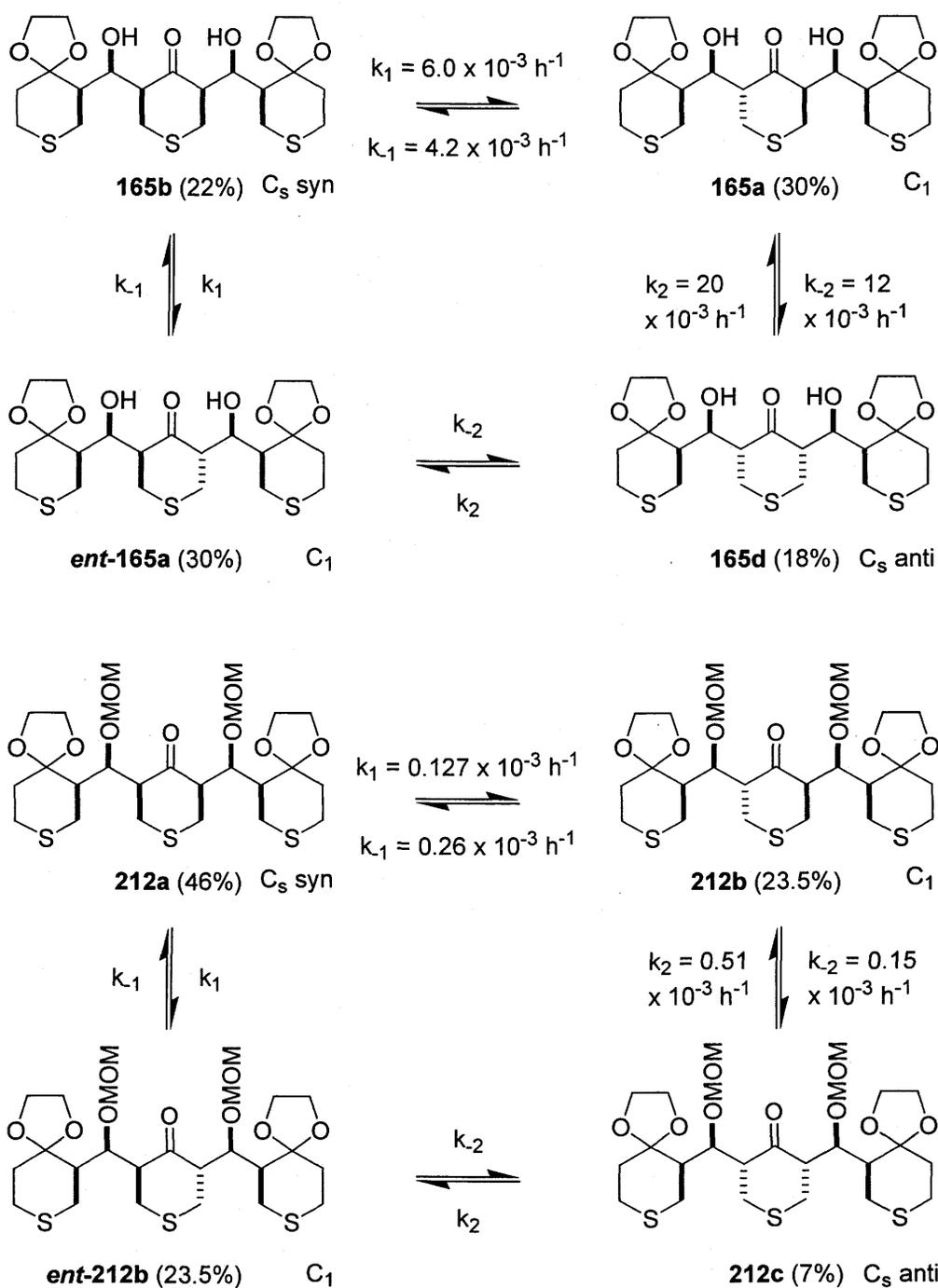
The bisaldols **165a,b,d**, **212a-c** and **213a-d** were used as model substrates to investigate the influence of hydroxy vs. alkoxy groups on isomerization. Each of the purified aldols **165a**, **165b** and **165d** were individually isomerized in CDCl<sub>3</sub> with imidazole (0.4 M); in each 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 CDCl<sub>3</sub> 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 ( $k_2 : k_1$ ) can be used as a measure of the regioselectivity for isomerization of the bisaldols **165a** and **212b**. The aldol **165a** isomerizes faster ( $\times 3$ ) 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**.



Percentages refer to the mole fraction at equilibrium.

Rate constants for isomerization at 0.4 M imidazole (see Table 22)

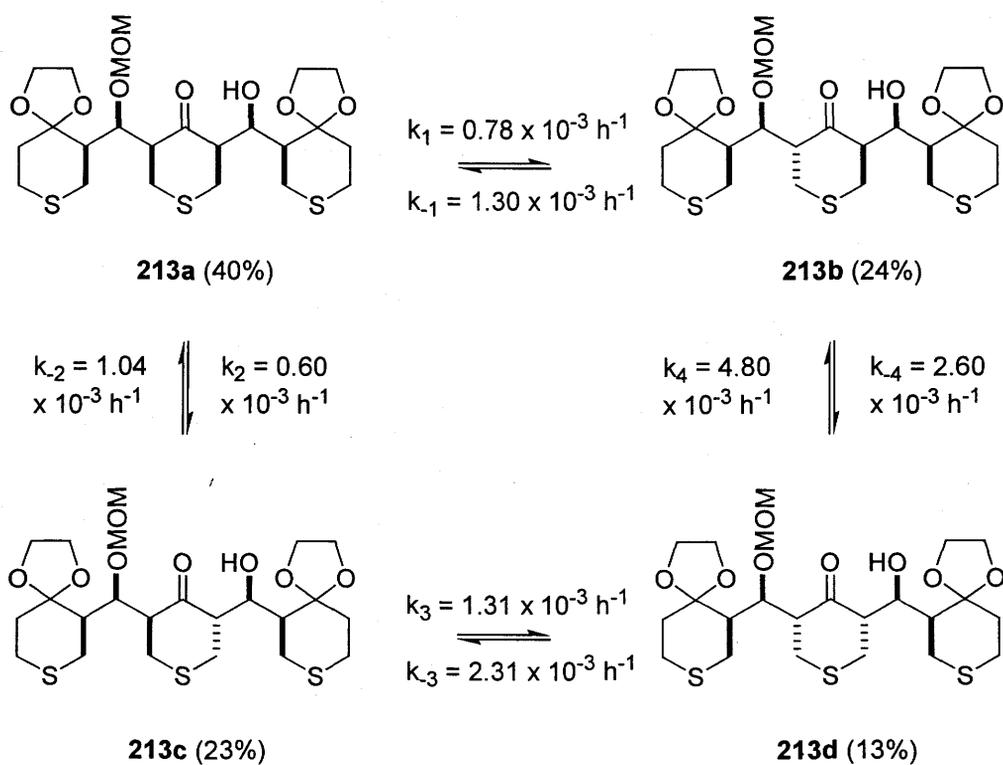
**Figure 61.** Isomerization of aldols **165a**, **165b** and **165d** and the corresponding bis-MOM protected aldols **212a**, **212b** and **212c**.

The aldol **212b** isomerizes faster ( $\times 1.7$ ) 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**.

Entry	aldol series	[imidazole] (M)	rate constants ( $10^{-3} \text{ h}^{-1}$ )				$k_2 : k_1$
			$k_1$	$k_1$	$k_2$	$k_2$	
1	<b>165</b>	0.40	6.0	4.2	20	12	2.9 : 1
2	<b>165</b>	0.80	14	10.3	45	27	2.6 : 1
3	<b>212</b>	0.40	0.127	0.260	0.51	0.150	1 : 1.7

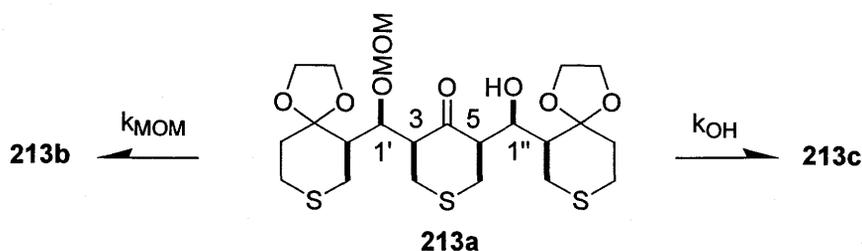
Each of the purified aldols **213a-d** were individually isomerized in  $\text{CDCl}_3$  with imidazole (0.4 M); in each case a 40 : 24 : 23 : 13 equilibrium mixture of **213a**, **213b**, **213c** and **213d**, respectively, was obtained (see Figure 62 and Appendix, Figures A16-A19). The composite rate 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  $k_{\text{MOM}}$  and  $k_{\text{OH}}$  and the regioselectivity of isomerization can be measured as the ratio of rates  $k_{\text{MOM}} : k_{\text{OH}}$  (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**.



Percentages refer to the mole fraction at equilibrium.

**Figure 62.** Isomerization of aldols **213a-d** in with imidazole (0.4M).

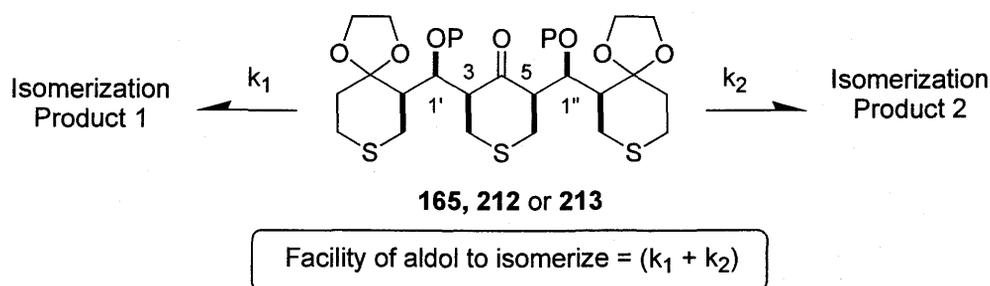
**Table 23.** The effect of a hydroxyalkyl vs. alkoxyalkyl substituent on regioselectivity of isomerization.



entry	aldol	1'',5-syn/anti	$k_{\text{MOM}}$ $10^{-3} \text{ h}^{-1}$	$k_{\text{OH}}$ $10^{-3} \text{ h}^{-1}$	$k_{\text{MOM}} : k_{\text{OH}}$
1	<b>213a</b>	syn	0.60	0.78	1 : 1.3
2	<b>213b</b>	syn	1.04	1.31	1 : 1.3
3	<b>213c</b>	anti	2.60	1.30	2.0 : 1
4	<b>213d</b>	anti	4.80	2.31	2.1 : 1

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** ( $k_1 < k_2$ , Figure 62).

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



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

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 ( $\times 2.3$ ) 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 $\alpha,\alpha'$ -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.

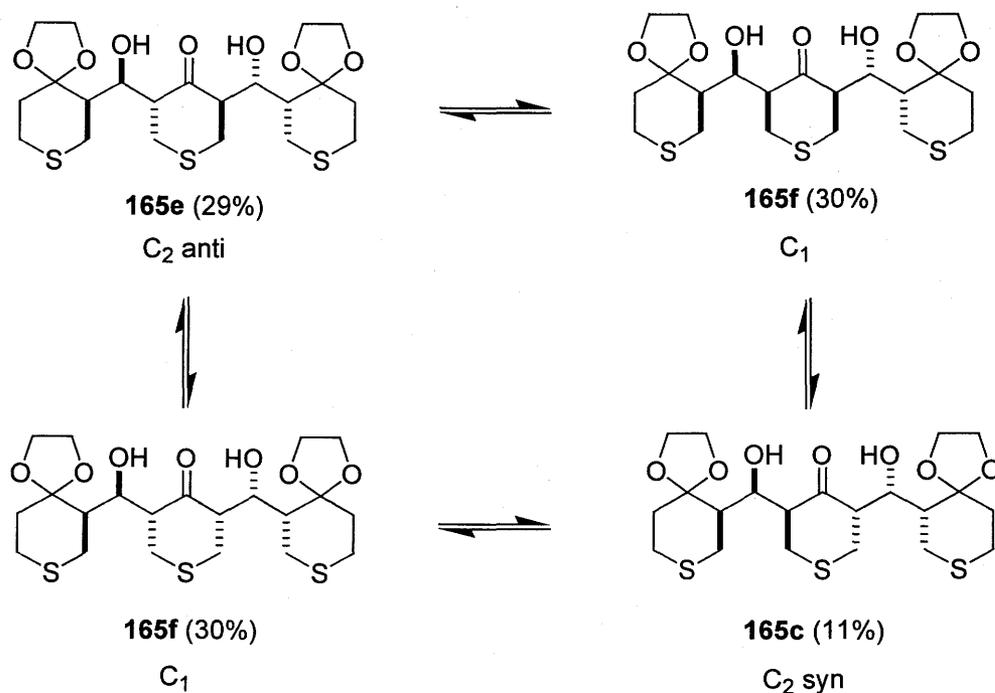
The isomerization of **165e** in  $\text{CH}_2\text{Cl}_2$  with imidazole (1.0 M) for 20 h at room temperature gave a 29 : 60 : 11 mixture of **165e**, **165f** and **165c**, respectively (Figure 63). The individual aldols were isolated by chromatography to give 30%, 44% and 15% isolated yields of **165e**, **165f** and **165c**, respectively. The bisaldol **165e** was obtained from aldol reaction of **125a** with **127a** in 4% isolated yield (Scheme 16).<sup>\*</sup> The isomerization of **165e** gave **165f** (44% isolated yield); at present this is the only route to give **165f**.<sup>30</sup> 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  $\text{CH}_2\text{Cl}_2$  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

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\* 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**.

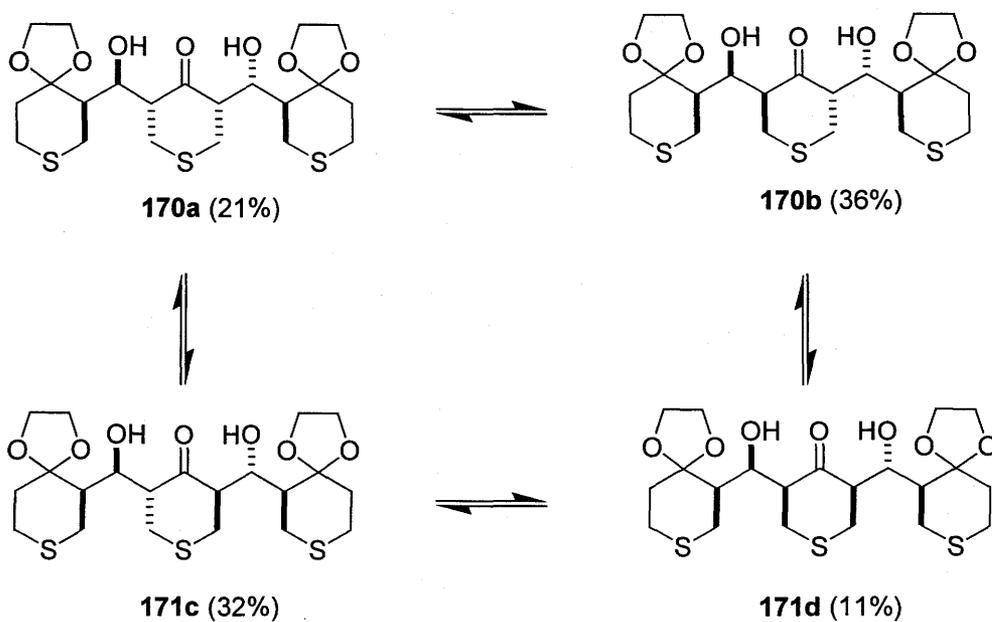
between **125a** and **128a** in 8% isolated yield (Scheme 18). Aldol **170a** was also available from the hydrolysis of the MOM group of **173c** (Figure 96). The products of isomerization **170b** and **171c** are also available from the hydrolysis of the MOM group of **173a** and **175b**, respectively (Figures 97 and 98). However, at present isomerization is the only route to **171d**.



Percentages refer to the mole fraction after 20h.

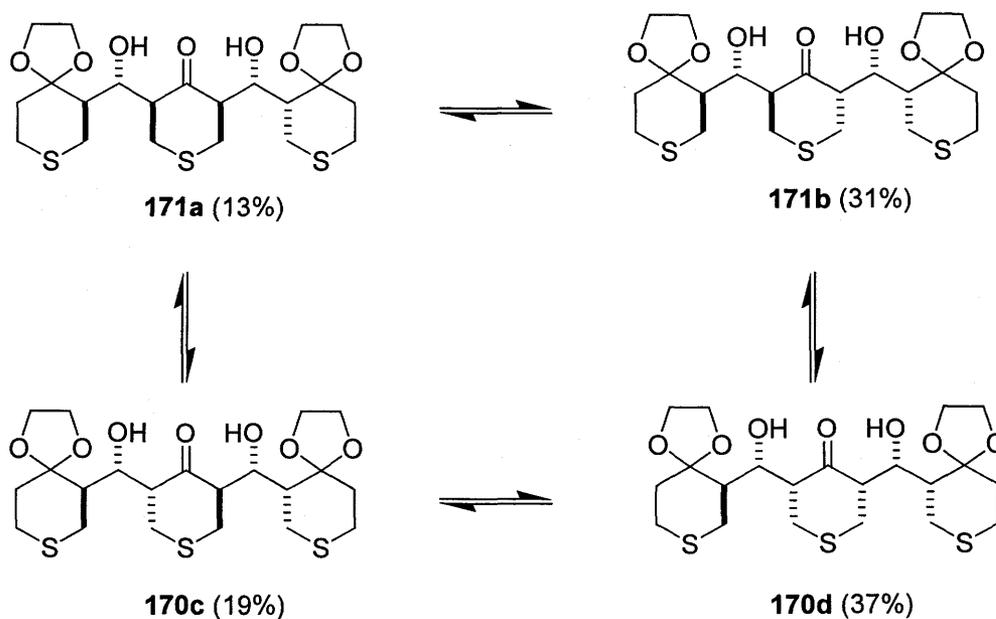
**Figure 63.** Isomerization of **165e** in  $\text{CH}_2\text{Cl}_2$  with imidazole (1.0 M) for 20 h.

The bisaldol **171a** was isomerized in  $\text{CH}_2\text{Cl}_2$  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  $\text{CH}_2\text{Cl}_2$  with imidazole (0.40 M) for 6 days.



Percentages refer to the mole fraction at equilibrium.

**Figure 65.** Isomerization of **171a** in  $\text{CH}_2\text{Cl}_2$  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**.

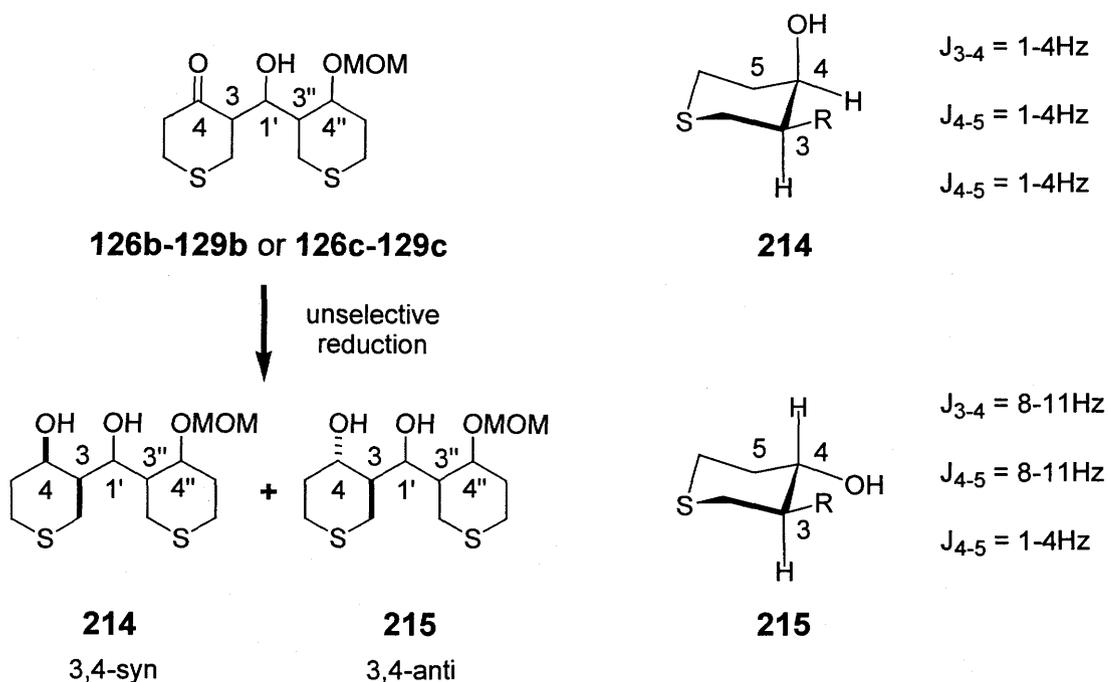
The aldols **126b-129b** and **126c-129c** (Figure 66) each have 4 contiguous stereogenic centers and the relative stereochemical configurations to be assigned are the syn/anti relative relationships at the positions C-1'/C-3, C-1'/C-3'' and C-3''/C-4''. (Note : The determination of any three of the 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

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\* 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''.

coupling constants observed for HC-4'' in the corresponding  $^1\text{H}$  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.

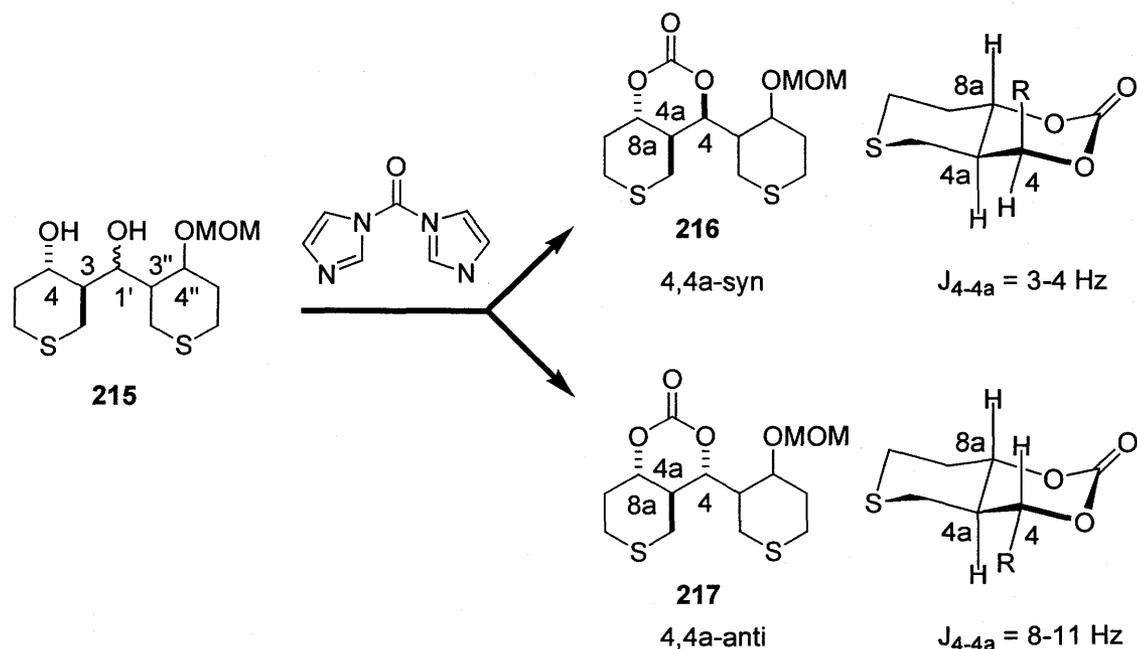
The first step involved an unselective reduction of the aldol adduct to give a mixture of the 3,4-syn (**214**) and 3,4-anti diols (**215**) (Figure 66). The advantage of an unselective reduction is both diols can be isolated and their NMR spectroscopic properties can be compared to ensure correct assignment of the 3,4-relative configuration (i.e. syn or anti). Assuming a chair conformation for the 3-substituted tetrahydro-2*H*-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).



**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

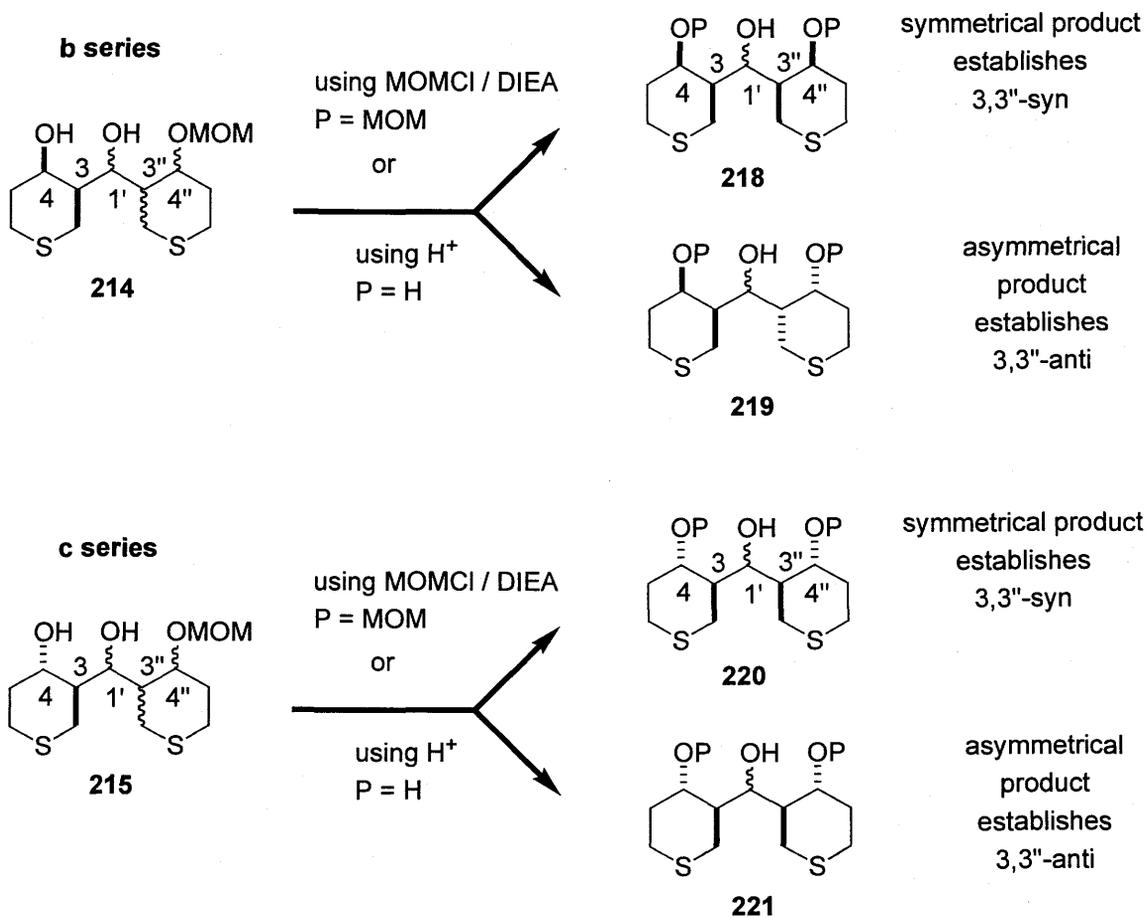
*trans*-fused cyclic carbonate. A favourable property of a *trans*-fused carbonate is the conformational rigidity, which allows for a straightforward interpretation of the vicinal coupling constant between HC-4 and HC-4a. The *trans*-fused cyclic carbonate ensures that the proton HC-4a always has an 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.



**Figure 67.** Establishing the 1',3-*syn/anti* relative configuration.

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'' relative configuration. Isolation of a symmetric product **218**\* would establish the relative configuration as 3,3''-syn, and an asymmetric product would establish the relative configuration as 3,3''-anti (Figure 68). The assignment of this configuration in the triol (or bis-MOM) derivative establishes the 3,3''-syn/anti relative configuration in the precursor aldol.



**Figure 68.** Establishing the 3,3''-syn/anti relative configuration.

\* Symmetric triols gave 6 carbon signals and symmetric bis-MOM derivatives gave 8 carbon signals by <sup>13</sup>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.

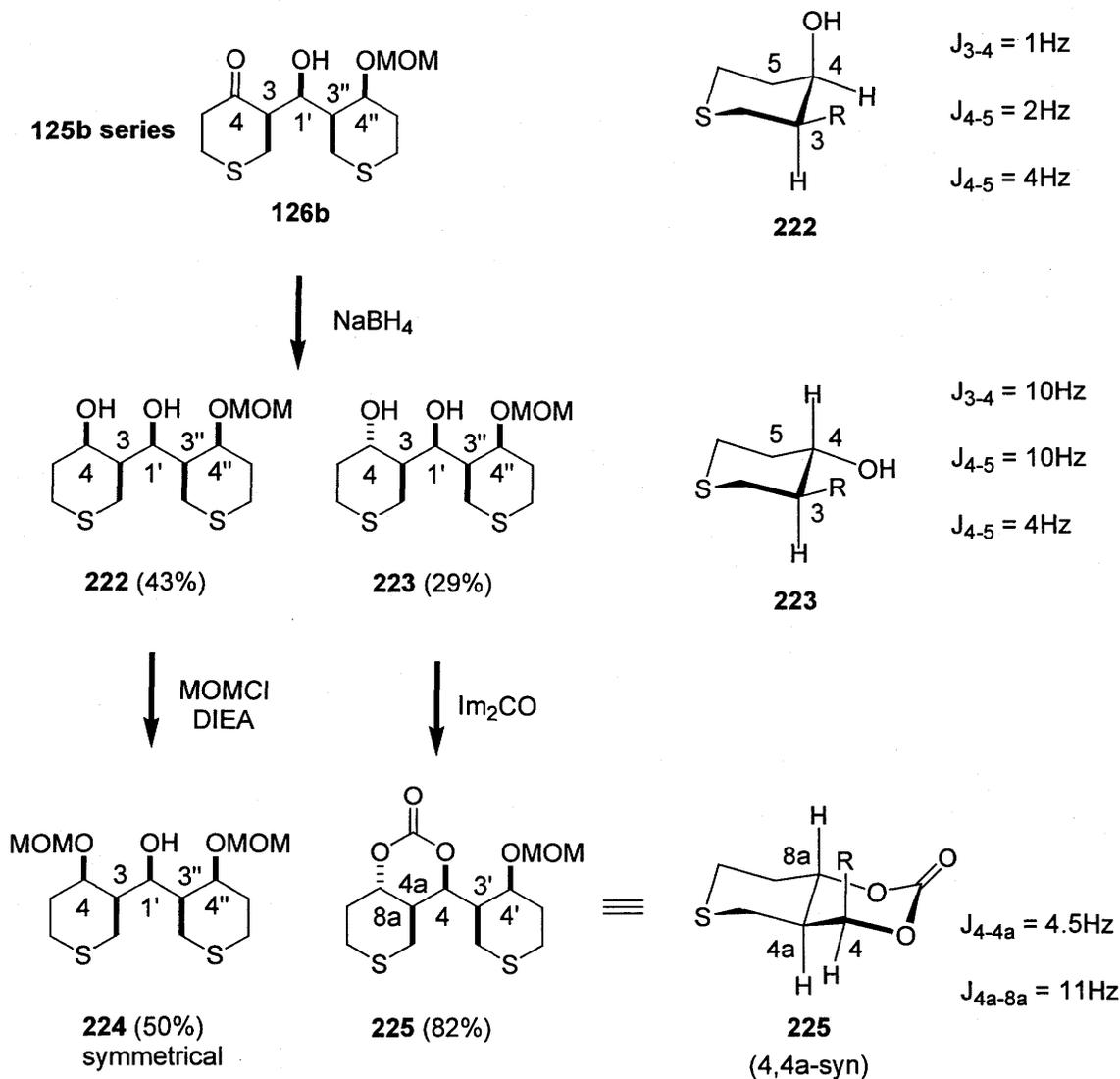
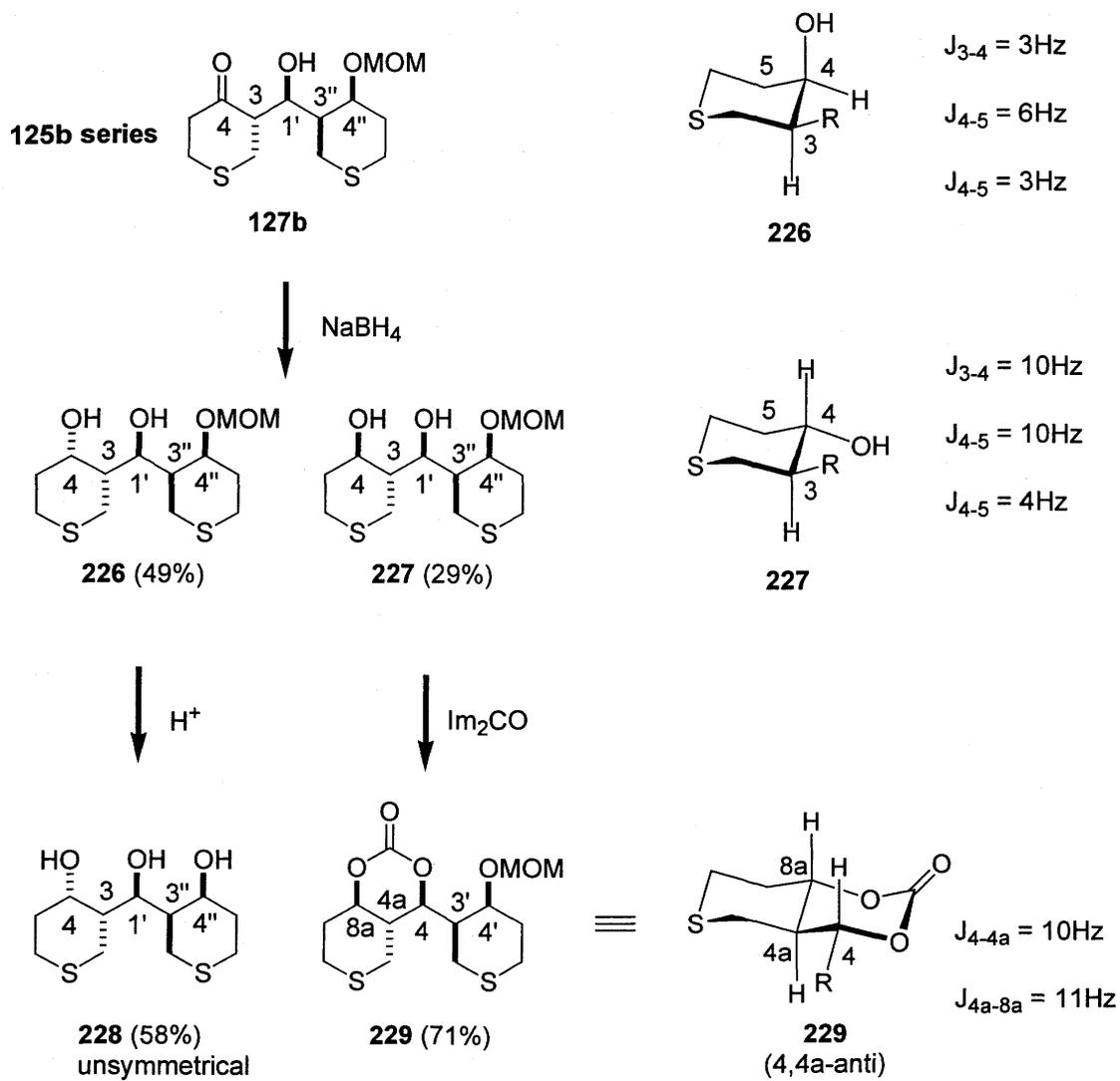
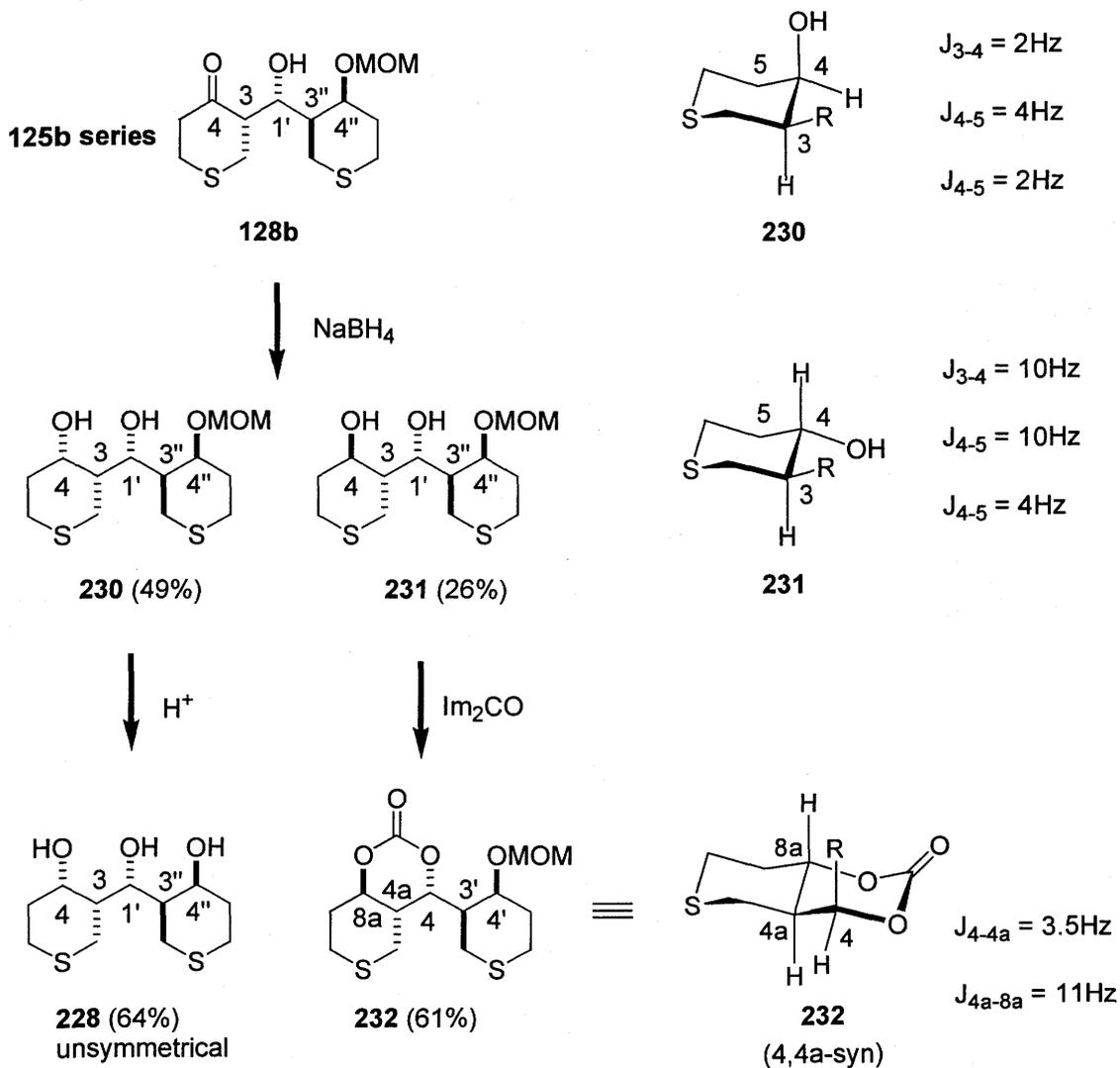


Figure 69. Structure determination of 126b.



**Figure 70.** Structure determination of **127b**.



**Figure 71.** Structure determination of **128b**.

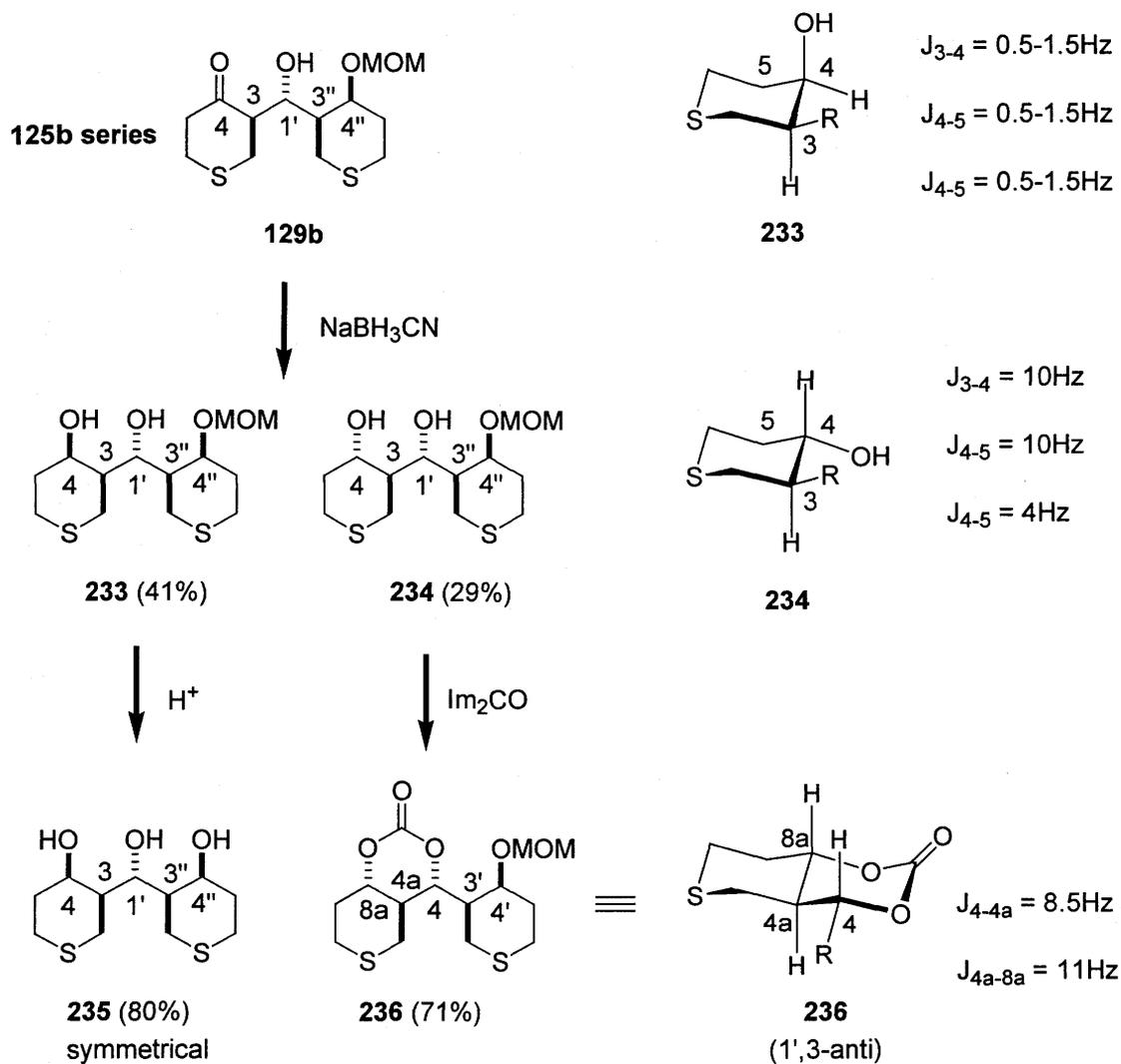
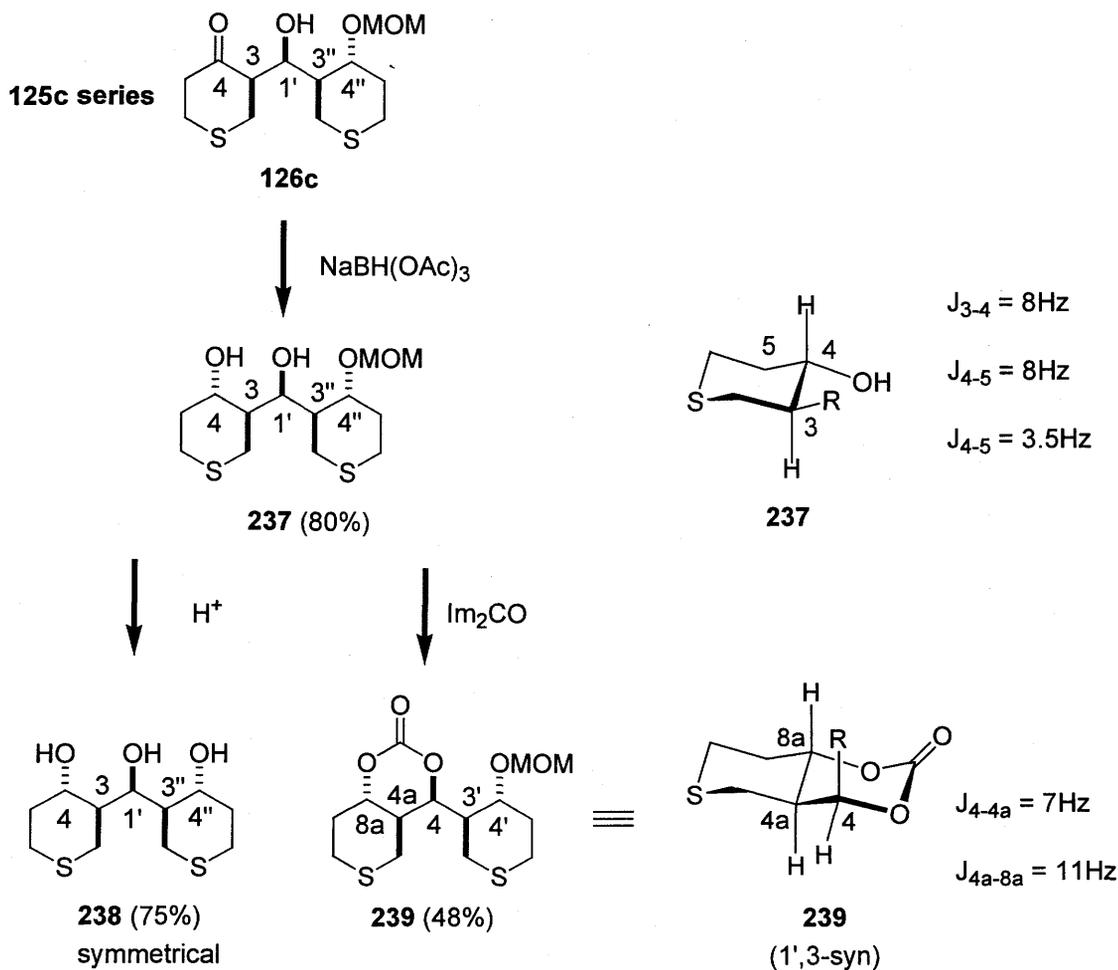
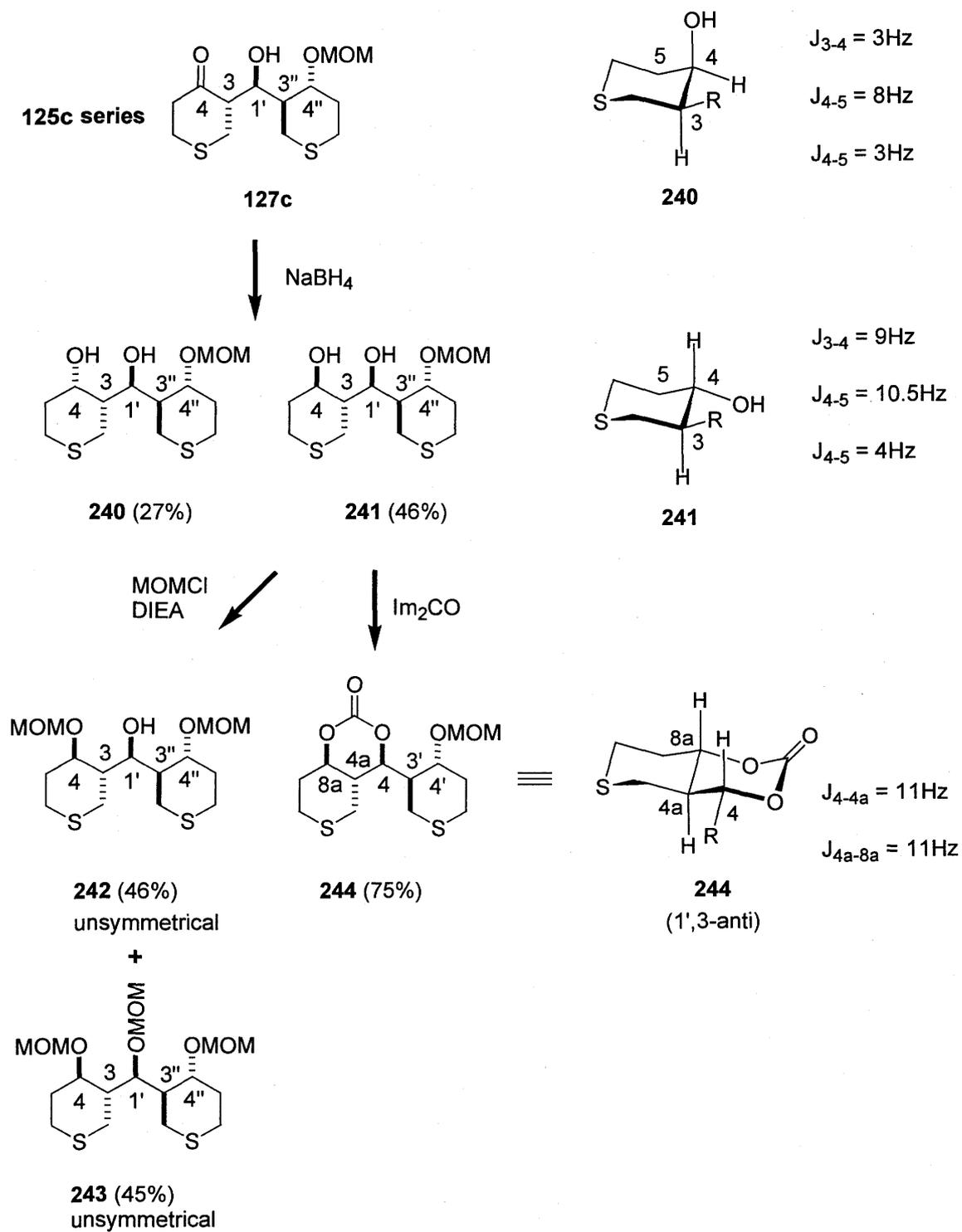


Figure 72. Structure determination of 129b.

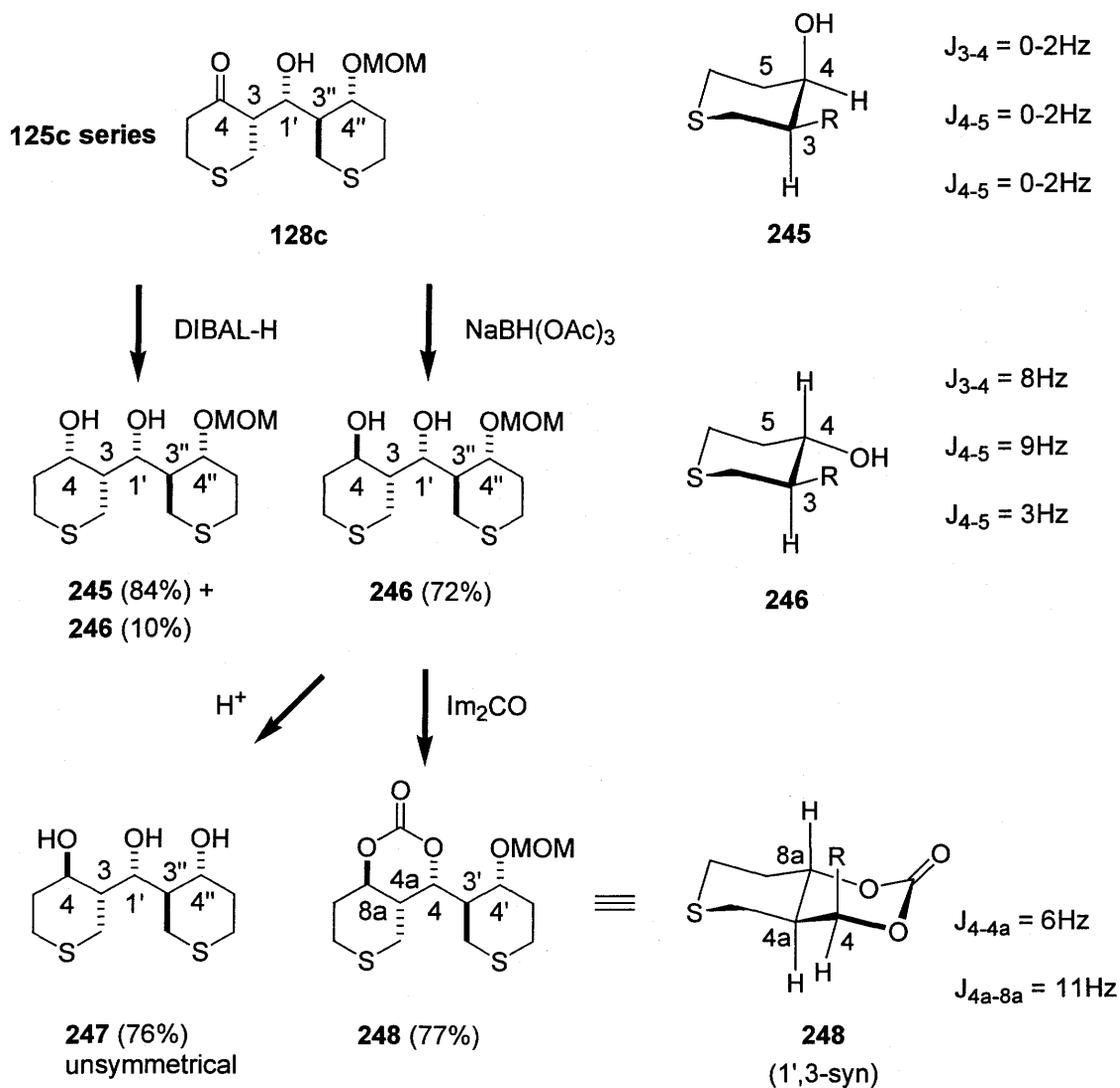


**Figure 73.** Structure determination of **126c**.

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  $\text{NaBH(OAc)}_3$  was used in the reduction of **126c** to give the desired **237** (80% isolated yield) (Figure 73).<sup>193,194</sup>

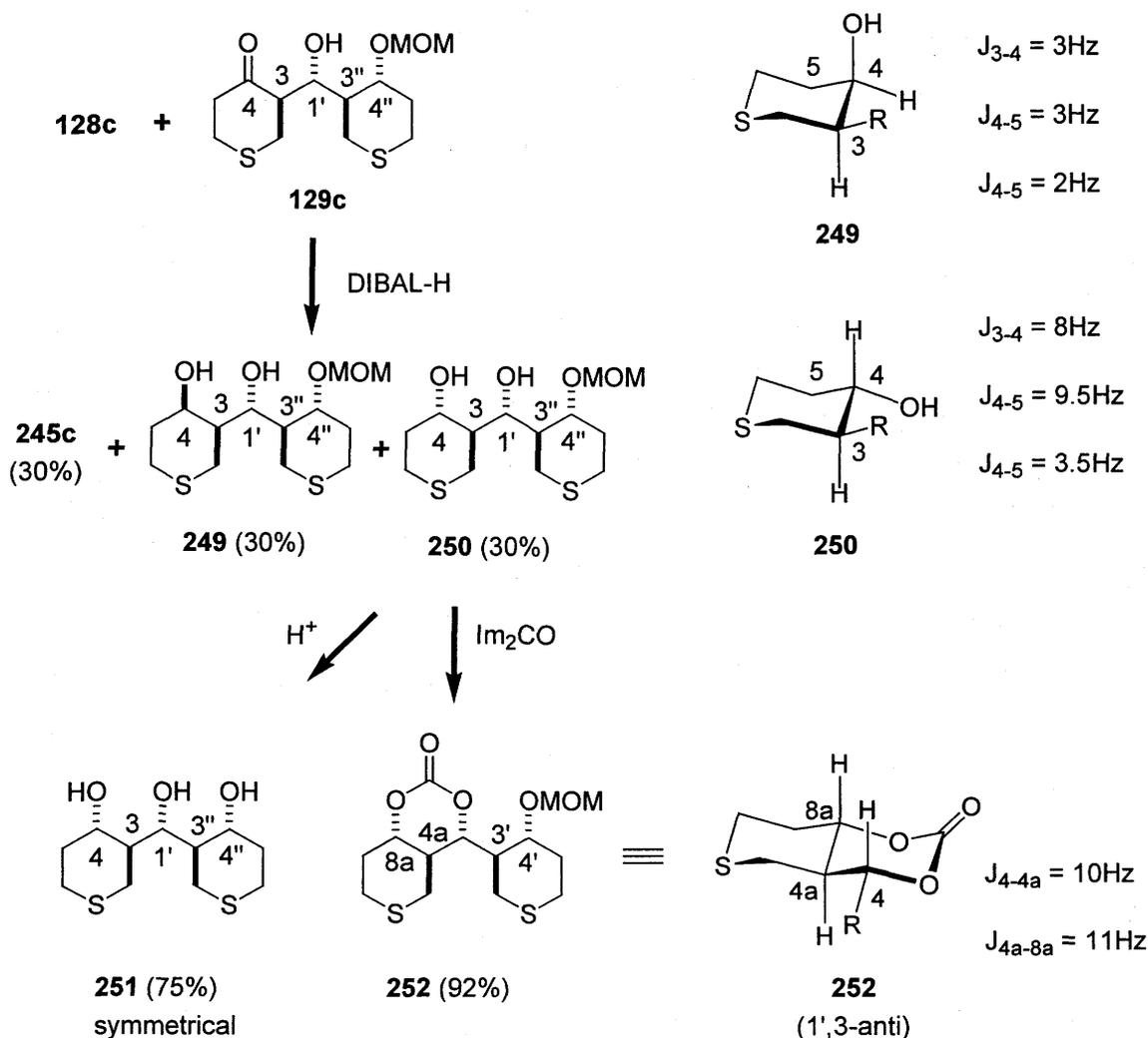


**Figure 74.** Structure determination of **127c**.



**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<sup>195</sup> and NaBH(OAc)<sub>3</sub>.<sup>193,194</sup>, respectively (Figure 75).



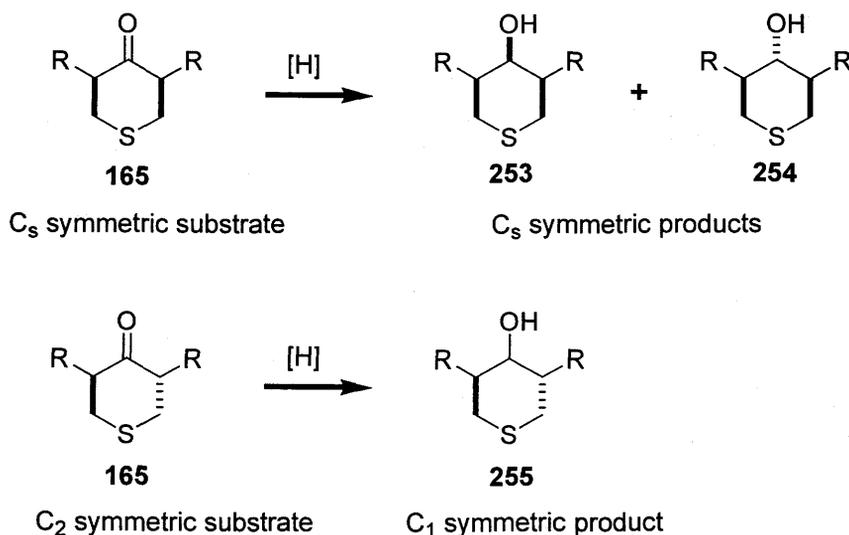
**Figure 76.** Structure determination of **129c**.

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**.

## 2.5.2. Determination of the Relative Configurations of Bisaldols 165, 170, 171, 173 and 175

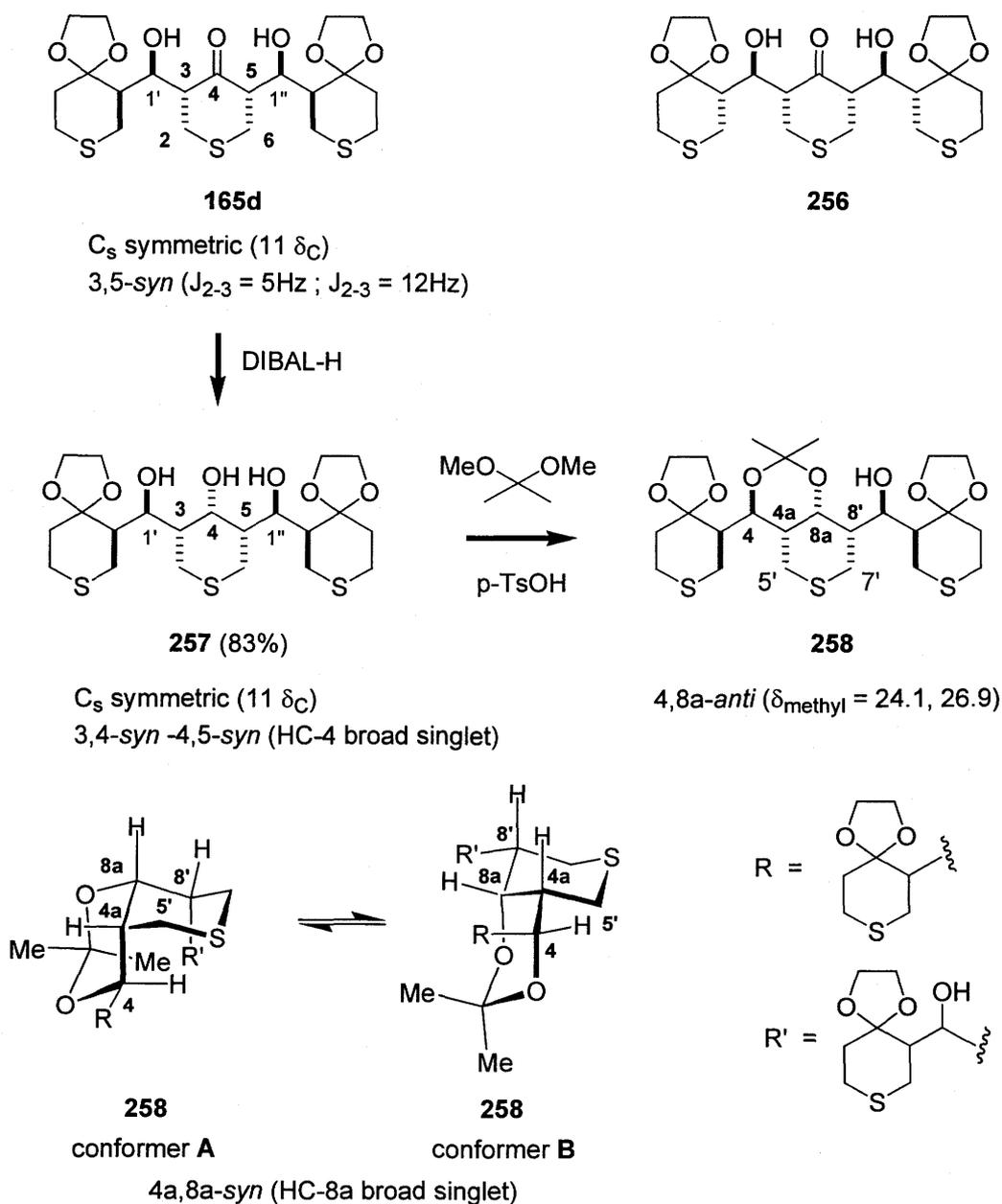
### 2.5.2.1. Bisaldol 165d

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  $^{13}\text{C}$  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).<sup>30</sup>



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

\* Unsymmetric bisaldols have 21 resonances and symmetric bisaldols have 11 resonances in the  $^{13}\text{C}$  NMR spectrum.



**Figure 78.** Structure determination of bisaldol **165d**.

In the  $^1\text{H}$  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  $^1\text{H}$  NMR spectrum of **258**, HC-8a was a broad singlet suggesting the presence of a *cis*-fused tetrahydrothiopyrano[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  $^{13}\text{C}$  NMR of **258**. The work of Rychnovsky *et al.*<sup>196</sup> clearly

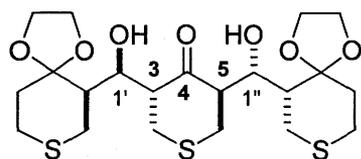
established that the relative configuration of 1,3-diols can be reliably assigned on the basis of the  $^{13}\text{C}$  chemical shifts of the methyl groups in the derived acetonide. In general, acetonide derivatives of *syn* 1,3-diols have acetal methyl shifts near 19 and 30 ppm, acetonides from *anti* 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

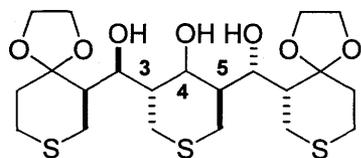
The bisaldol **165e** was obtained as a minor product from the aldol reaction of **127a** and **125a** (Scheme 16). The product was symmetric as evidenced by the presence of only 11 signals in its  $^{13}\text{C}$  NMR spectrum; however, the triol **260** obtained by reaction of **165e** with DIBAL-H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



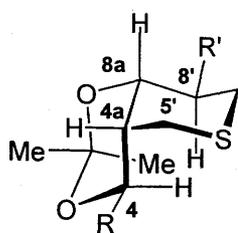
**165e**

$C_2$  symmetric ( $11 \delta_C$ )



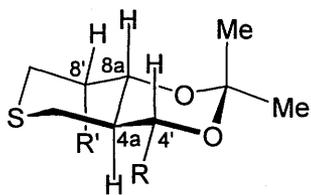
**260**

asymmetric ( $21 \delta_C$ )



**261**

$4a,8a$ -syn ( $J_{4a-8a} = 6\text{Hz}$ )

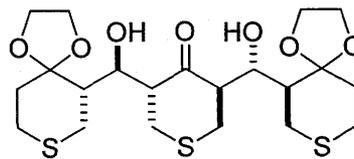


**262**

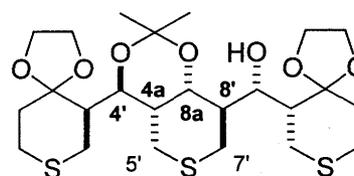
$4',4a$ -anti ( $J_{4'-4a} = 10.5\text{Hz}$ )

$4a,8a$ -anti ( $J_{4a-8a} = 11\text{Hz}$ )

$8'-8a$ -syn ( $J_{8'-8a} = 4.5\text{Hz}$ )



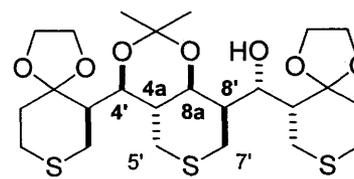
**259**



**261 (70%)**

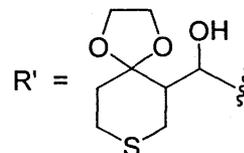
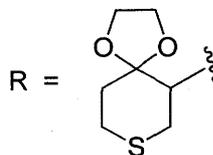
$4',8a$ -anti ( $\delta_{\text{methyl}} = 23.8, 26.2$ )

+



**262 (30%)**

$4',8a$ -syn ( $\delta_{\text{methyl}} = 18.8, 30.2$ )



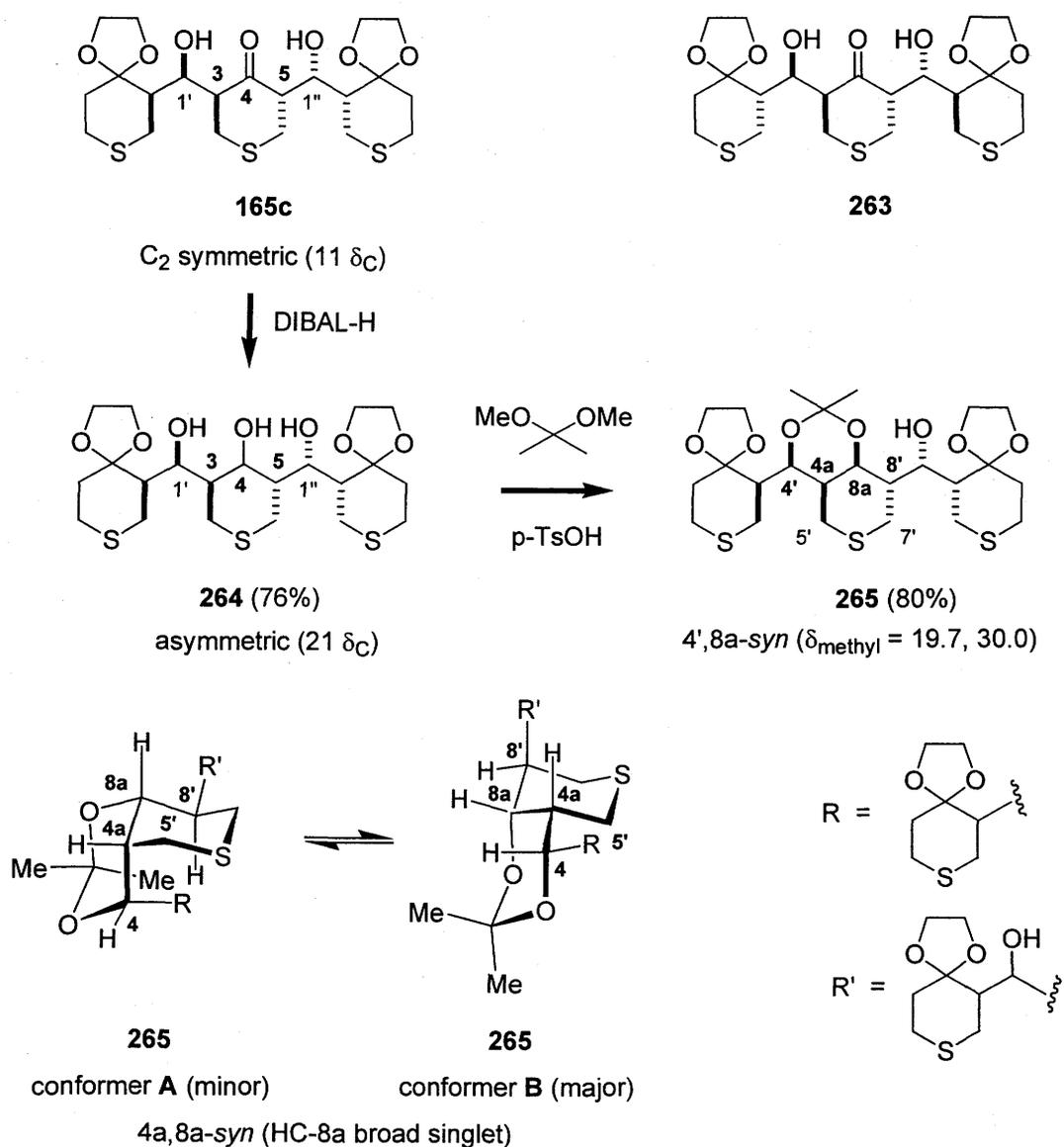
**Figure 79.** Structure determination of bisaldol **165e**.

(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 C<sub>2</sub> 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 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 <sup>13</sup>C NMR spectrum; however, the triol **264** obtained by reaction of **165c** with DIBAL-H was asymmetric (21 signals in the <sup>13</sup>C NMR spectrum) establishing the C<sub>2</sub> 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 <sup>1</sup>H 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 <sup>13</sup>C 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 C<sub>2</sub> 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**.



**Figure 80.** Structure determination of bisaldol **165c**.

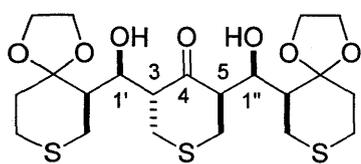
#### 2.5.2.4. Bisaldol **165a**

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 <sup>13</sup>C NMR spectrum confirmed that **165a** was asymmetric. Analysis of the vicinal coupling constants between HC-3 and H<sub>2</sub>C-2 (4 and 5.5 Hz) and those between HC-5 and H<sub>2</sub>C-6 (4 and 9.5 Hz) in the <sup>1</sup>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  $^1\text{H}$  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  $^1\text{H}$  NMR spectrum of **269**, HC-8a is a broad singlet and the small coupling constants between HC-8 and  $\text{H}_2\text{C}-7$  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**.

$^1\text{H}$  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  $^1\text{H}$  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.

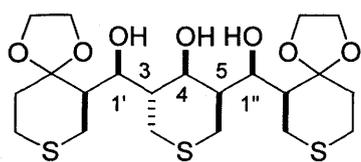


**165a**

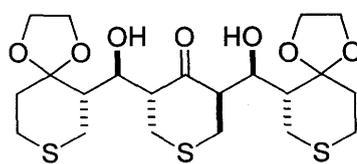
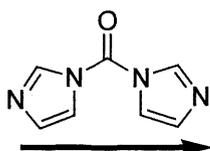
asymmetric (21  $\delta_C$ )

3,5-*anti* ( $J_{2-3} = 4\text{Hz}$  ;  $J_{2-3} = 5.5\text{Hz}$ )

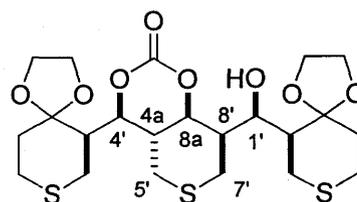
$J_{5-6} = 4\text{Hz}$  ;  $J_{5-6} = 9.5\text{Hz}$ )



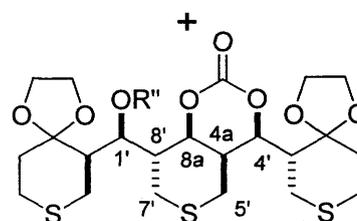
**267 (78%)**



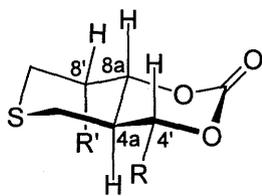
**266**



**268 (15%)**



**269 (65%) + 270 (20%)**

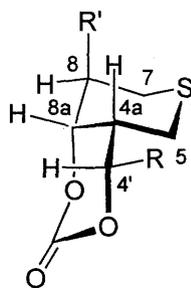


**268**

4',4a-*anti* ( $J_{4'-4a} = 9\text{Hz}$ )

4a-8a-*anti* ( $J_{4a-8a} = 10\text{Hz}$ )

8'-8a-*syn* ( $J_{8'-8a} = 4\text{Hz}$ )



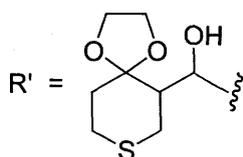
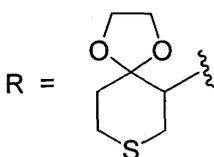
**270**

4a,8a-*syn* (HC-8a  
broad singlet)  
depicted conformer  
is major.

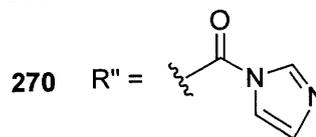
$J_{4a-5} = 12\text{Hz}$

$J_{7-8} = 2.5\text{ Hz}$

$J_{7-8} = 0-2\text{ Hz}$ )



**269** R'' = H



**Figure 81.** Structure determination of bisaldol **165a**.

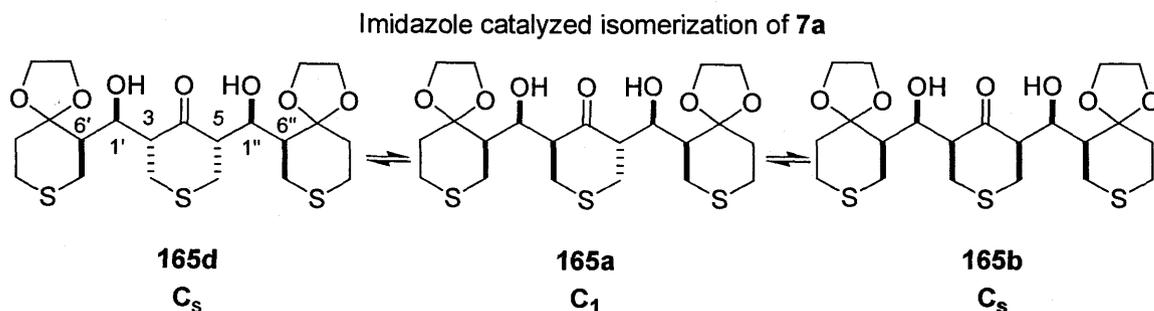
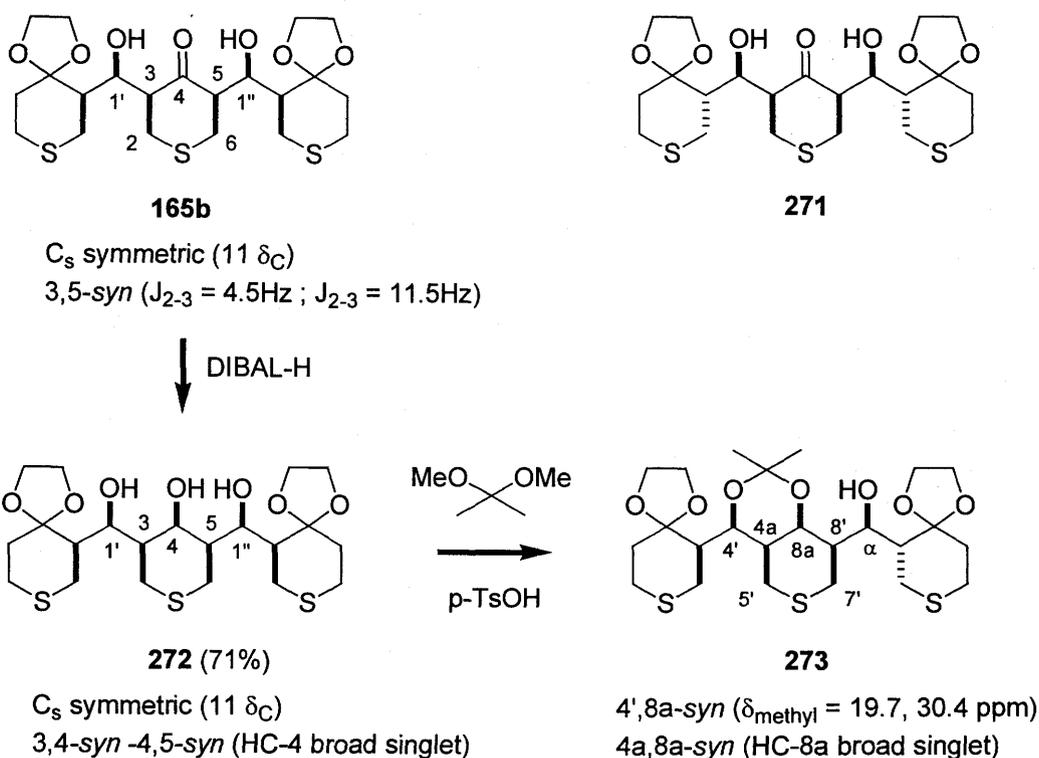
#### 2.5.2.5. Bisaldol 165b

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  $^{13}\text{C}$  NMR spectrum. Reduction of **165b** with DIBAL-H gave a single symmetric triol **272** in 71% isolated yield indicating that bisaldol **165b** was  $\text{C}_s$  symmetric.

In the  $^1\text{H}$  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  $^1\text{H}$  NMR spectrum of **273**, HC-8a was a broad singlet suggesting the presence of a cis-fused tetrahydrothiopyrano[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  $^{13}\text{C}$  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  $\text{C}_s$  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).

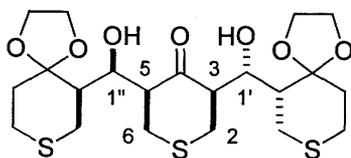


**Figure 82.** Structure determination of bisaldol **165b**.

#### 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  $^{13}\text{C}$  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<sub>2</sub>C-2 (3.5, 11.5 Hz) and between HC-5 and H<sub>2</sub>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.



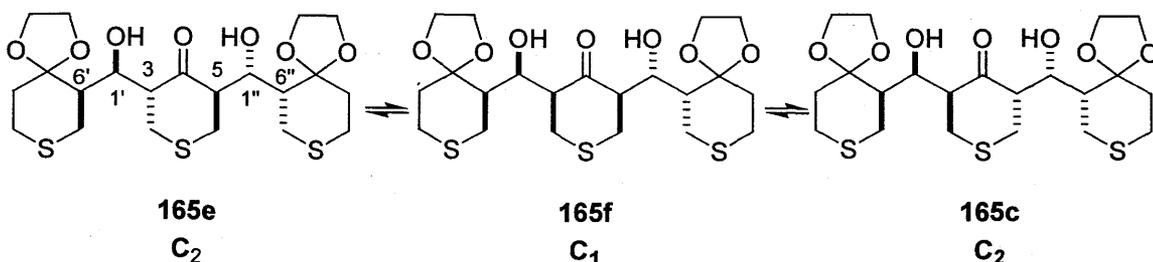
**165f**

asymmetric (21  $\delta_C$ )

3,5-*syn* ( $J_{2-3} = 3.5\text{Hz}$  ;  $J_{2-3} = 11.5\text{Hz}$ )

$J_{5-6} = 3.5\text{Hz}$  ;  $J_{5-6} = 12\text{Hz}$ )

Imidazole catalyzed isomerization of **165e**



**165e**  
**C<sub>2</sub>**

**165f**  
**C<sub>1</sub>**

**165c**  
**C<sub>2</sub>**

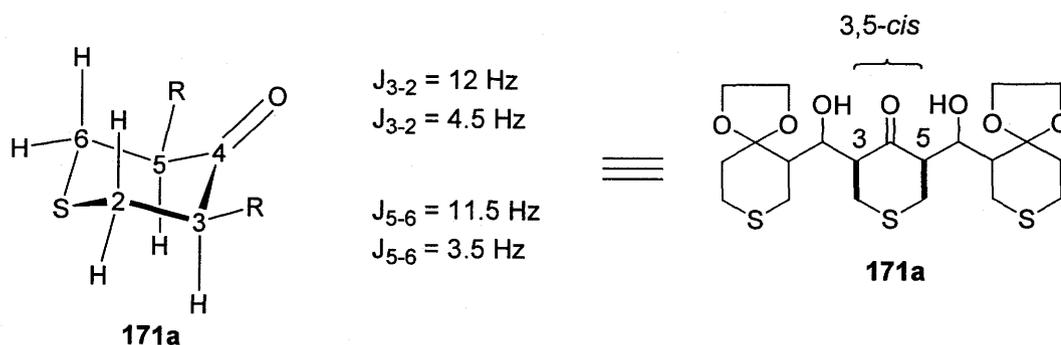
**Figure 83.** Structure determination of bisaldol **165f**.

#### 2.5.2.7. *Bisaldol 171a*

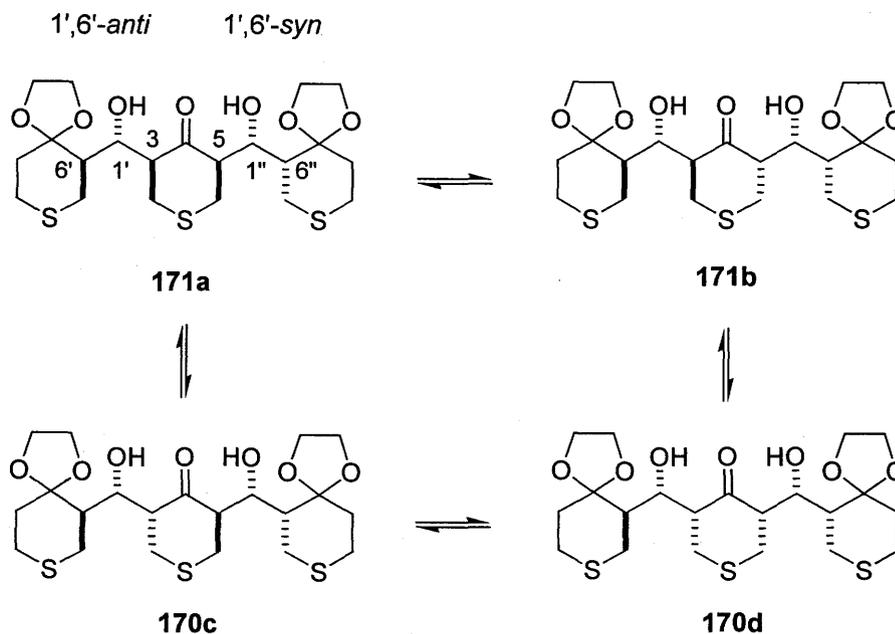
Bisaldol **171a** is the major product from the aldol reaction of **129a** with **125a** (Scheme 20). The presence of 21 signals in the  $^{13}\text{C}$  NMR spectrum established that **171a** was asymmetric. The relative configuration at C-3 and C-5 was established by analysis of the  $^1\text{H}$  NMR spectrum of **171a**. The vicinal coupling constants between HC-3 and H<sub>2</sub>C-2 (4.5 and 12 Hz) and between HC-5 and H<sub>2</sub>C-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  $^{13}\text{C}$  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**.<sup>\*</sup> 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).



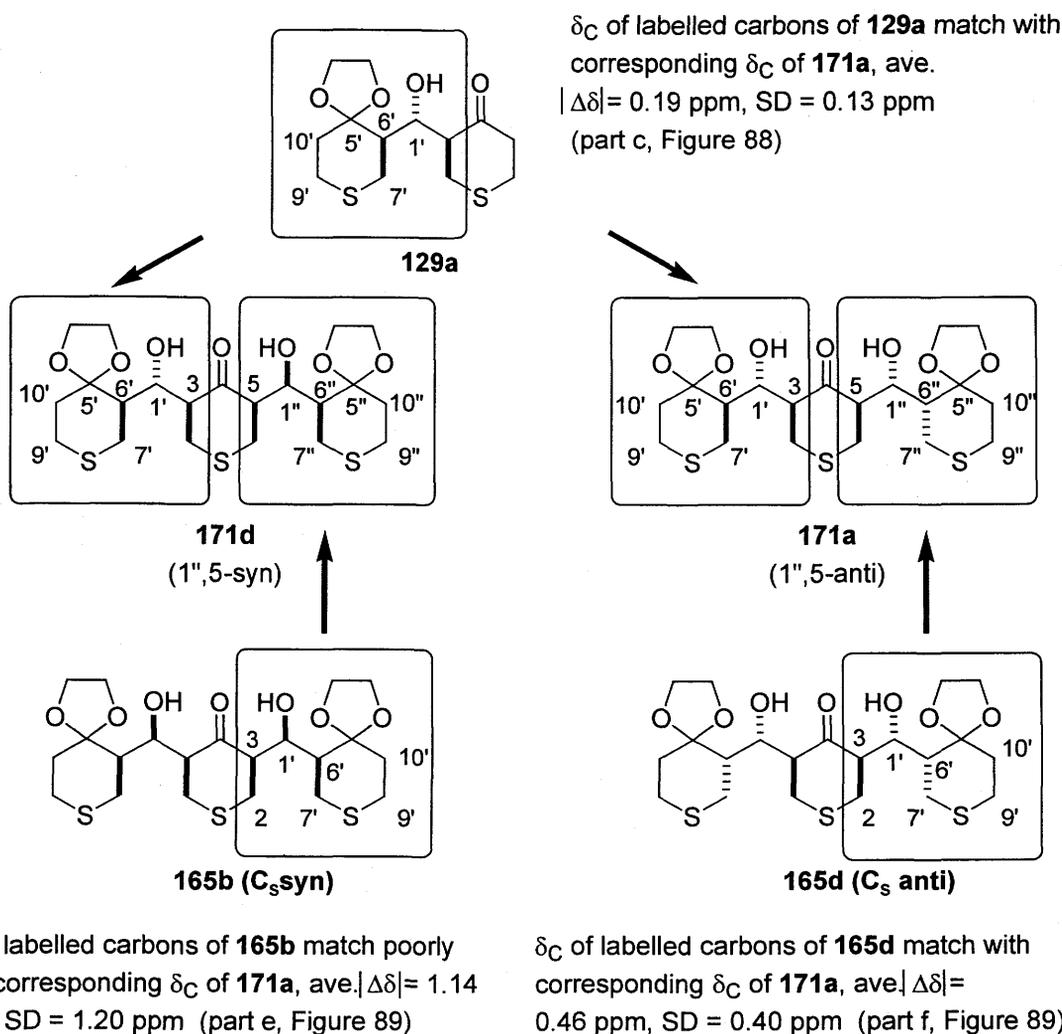
**Figure 84.** Determination of the 3,5-cis relative configuration of **171a**.



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

<sup>\*</sup> 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.

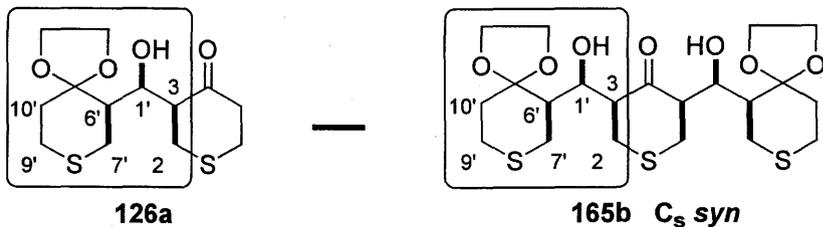
The two possible structures **171a** and **171d** differ only in the relative configuration at positions C-1''/C-5 (Figure 86). The approach used to assign the C'1/C-5 relative configuration is based on the analysis and comparison of  $^{13}\text{C}$  NMR data of monoaldols **126a-129a** and bisaldols **165b**, **165d** and **171a** (Figure 86). The assignment of the signals in the  $^{13}\text{C}$  NMR spectrum of **171a** was made with the aid of two dimensional homonuclear (COSY) and heteronuclear (HMQC and HMBC) correlation experiments. The  $^{13}\text{C}$  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  $^{13}\text{C}$  NMR spectrum of monoaldols **126a-129a** and bisaldols **165b** ( $C_s$  syn) and **165d** ( $C_s$  anti) were unambiguously assigned using the above techniques. Comparison of the  $^{13}\text{C}$  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).



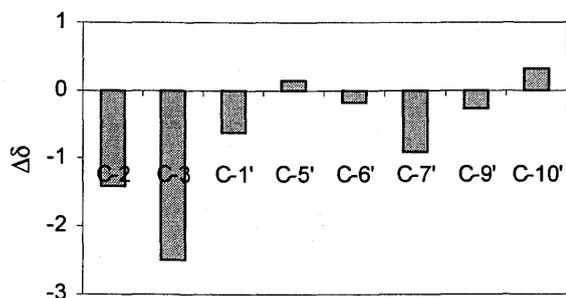
Notice that both **171a** and **171d** have 1',3-anti, 1',6'-anti, 3,5-cis, 1'',6''-syn relative configurations

**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**.

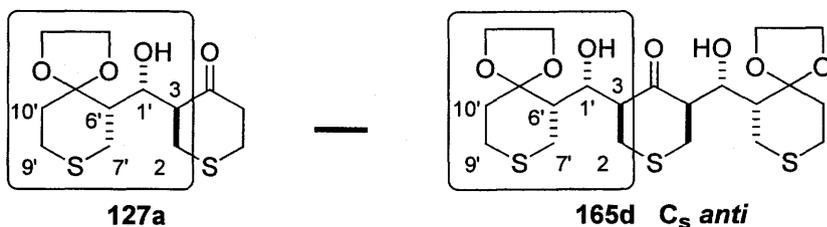
part a



$$\Delta\delta = \delta_C(126a) - \delta_C(165b)$$



part b



$$\Delta\delta = \delta_C(127a) - \delta_C(165d)$$

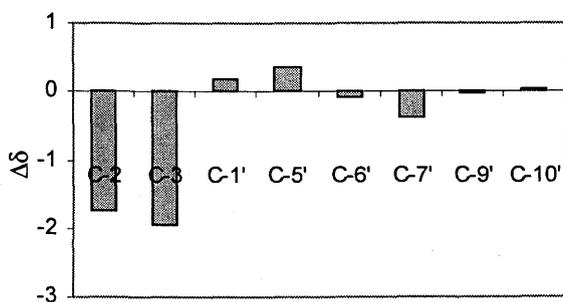
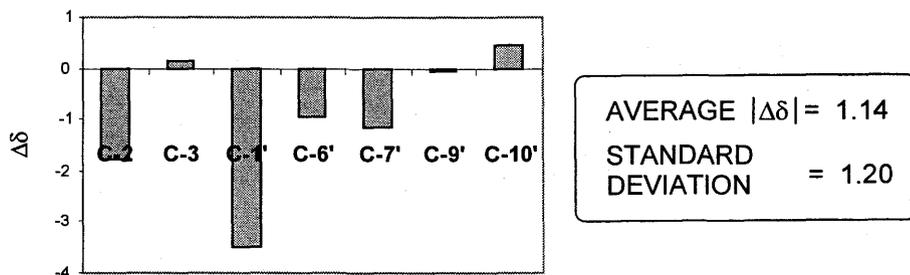
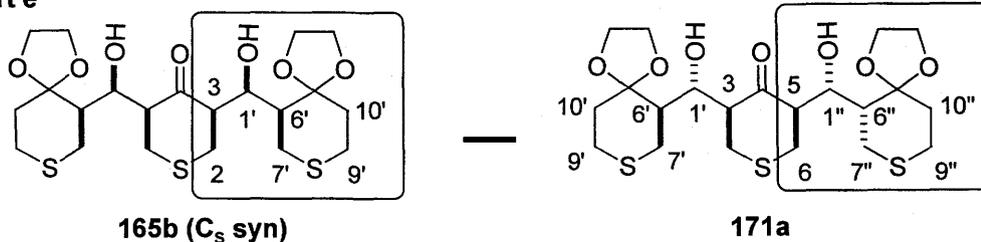


Figure 87. Comparison of the  $^{13}C$  NMR shifts of **126a** with **165b**, and **127a** with **165d**.



part e



part f

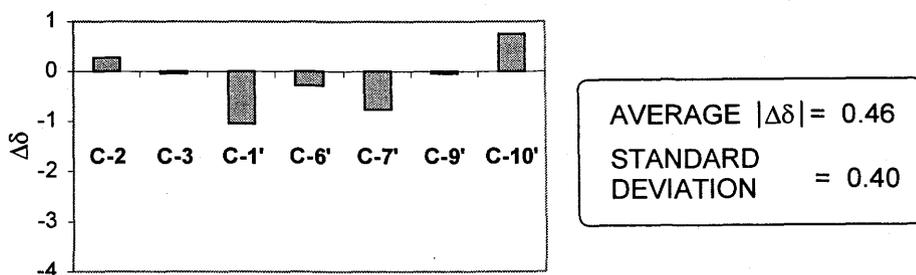
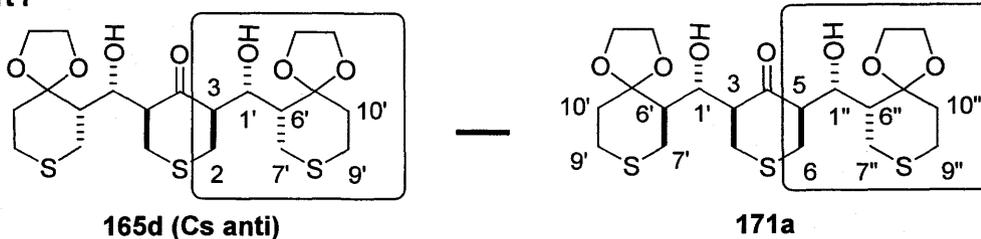


Figure 89. Comparison of the  $^{13}\text{C}$  NMR shifts of **165b** and **165d** with those of **171a**.

### 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  $^{13}\text{C}$  NMR spectrum indicates that **171b** is asymmetric. The vicinal coupling constants between  $\text{H}_2\text{C}-2$  and  $\text{HC}-3$  (4.5 and 10 Hz) and between  $\text{H}_2\text{C}-6$  and  $\text{HC}-5$  (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.

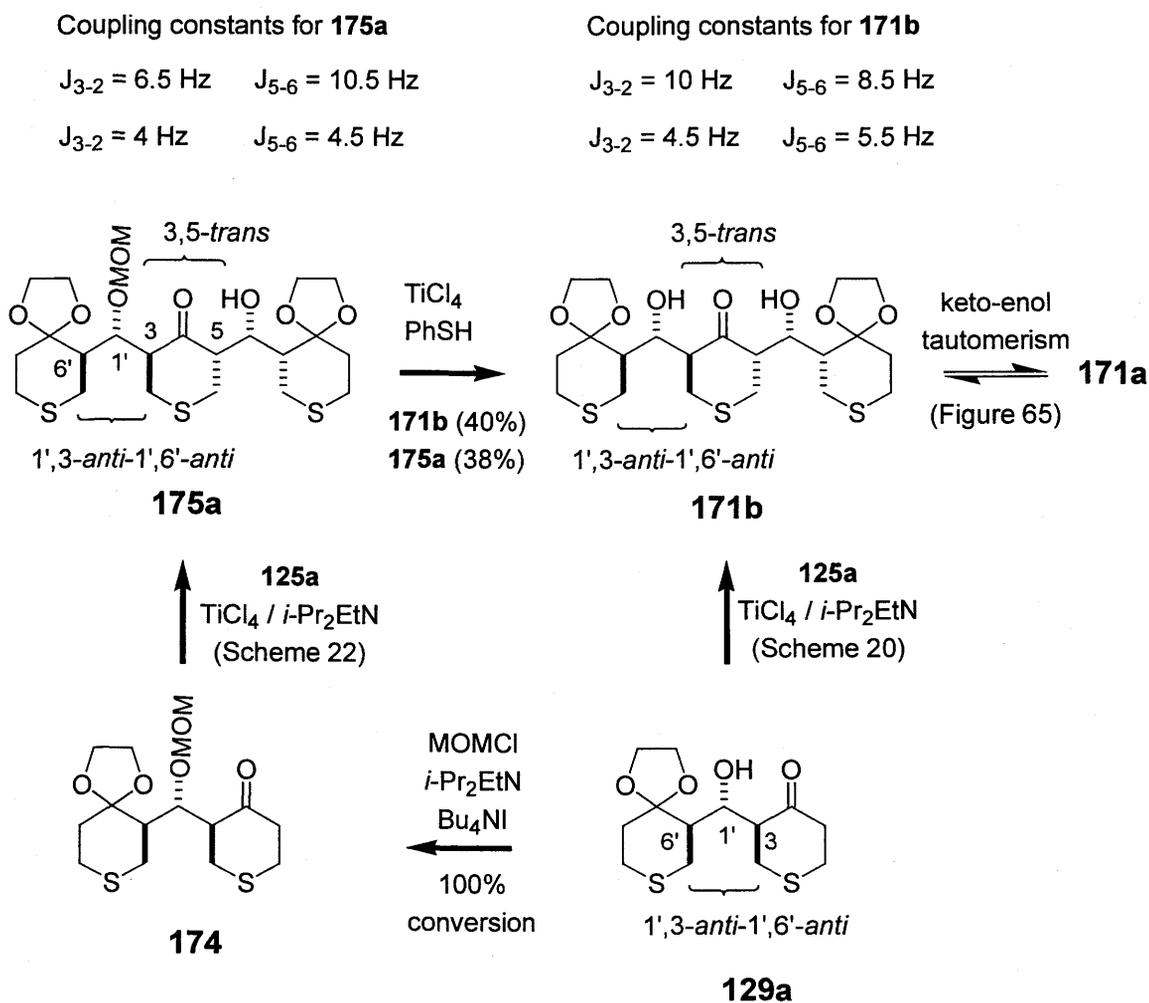
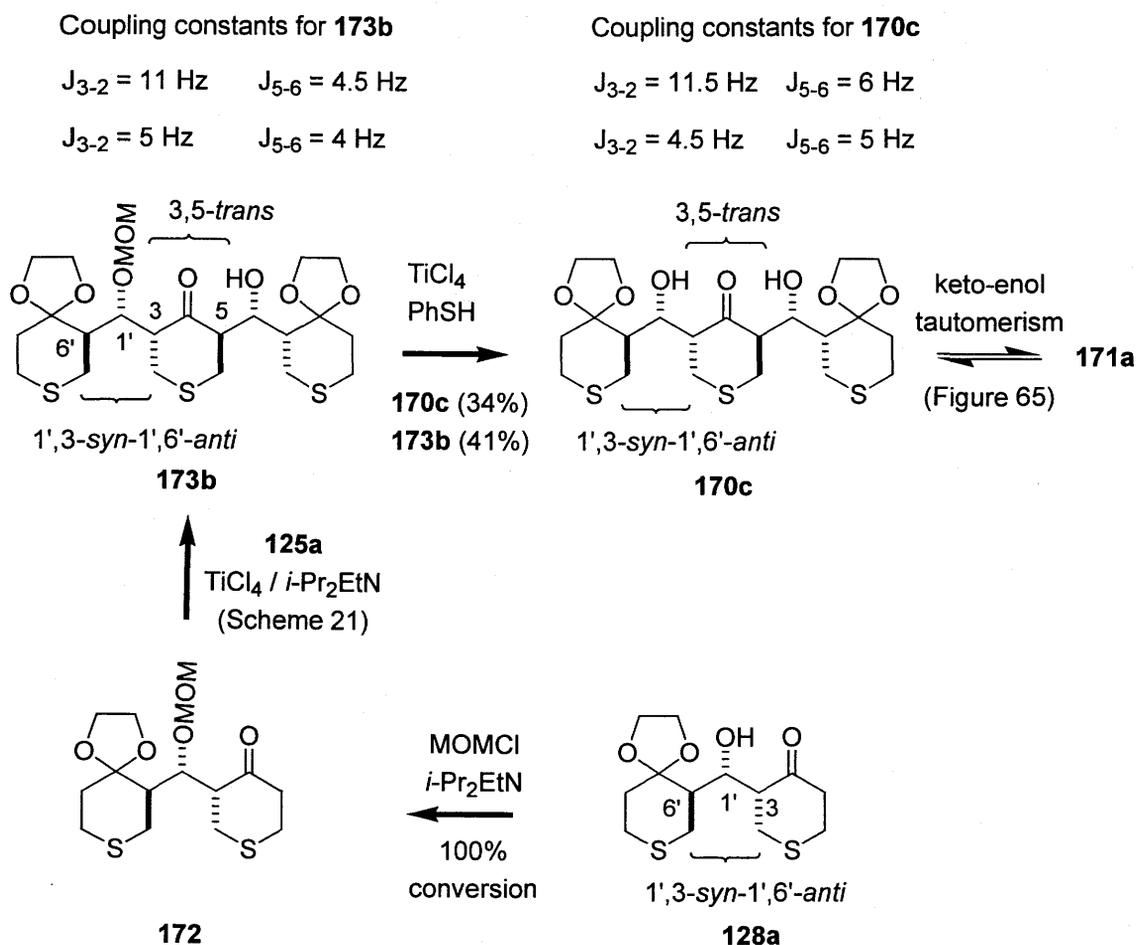


Figure 90. Structure determination of **171b** and **175a**.

Compound **175a** was a major product from the aldol reaction of **174** with **125a** (Scheme 22). The vicinal coupling constants between H<sub>2</sub>C-2 and HC-3 (4 and 6.5 Hz) and between H<sub>2</sub>C-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 TiCl<sub>4</sub> / 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 <sup>13</sup>C NMR spectrum. The vicinal coupling constants between H<sub>2</sub>C-2 and HC-3 (5 and 6 Hz) and between H<sub>2</sub>C-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.



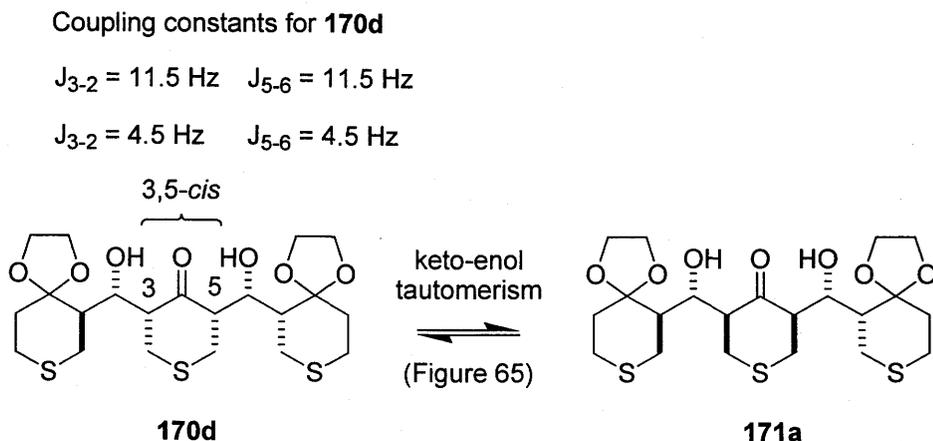
**Figure 91.** Structure determination of bisaldol **170c** and **173b**.

Compound **173b** is obtained from aldol reaction of **172** with **125a**. The vicinal coupling constants between H<sub>2</sub>C-2 and HC-3 (5 and 11 Hz) and between H<sub>2</sub>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<sub>4</sub> / 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 <sup>13</sup>C NMR spectrum. The vicinal couplings constants between H<sub>2</sub>C-2 and HC-3 (4.5 and 11.5 Hz) and between H<sub>2</sub>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**.



**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<sub>2</sub>C-2 (5 and 11.5 Hz) and between HC-5 and H<sub>2</sub>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.

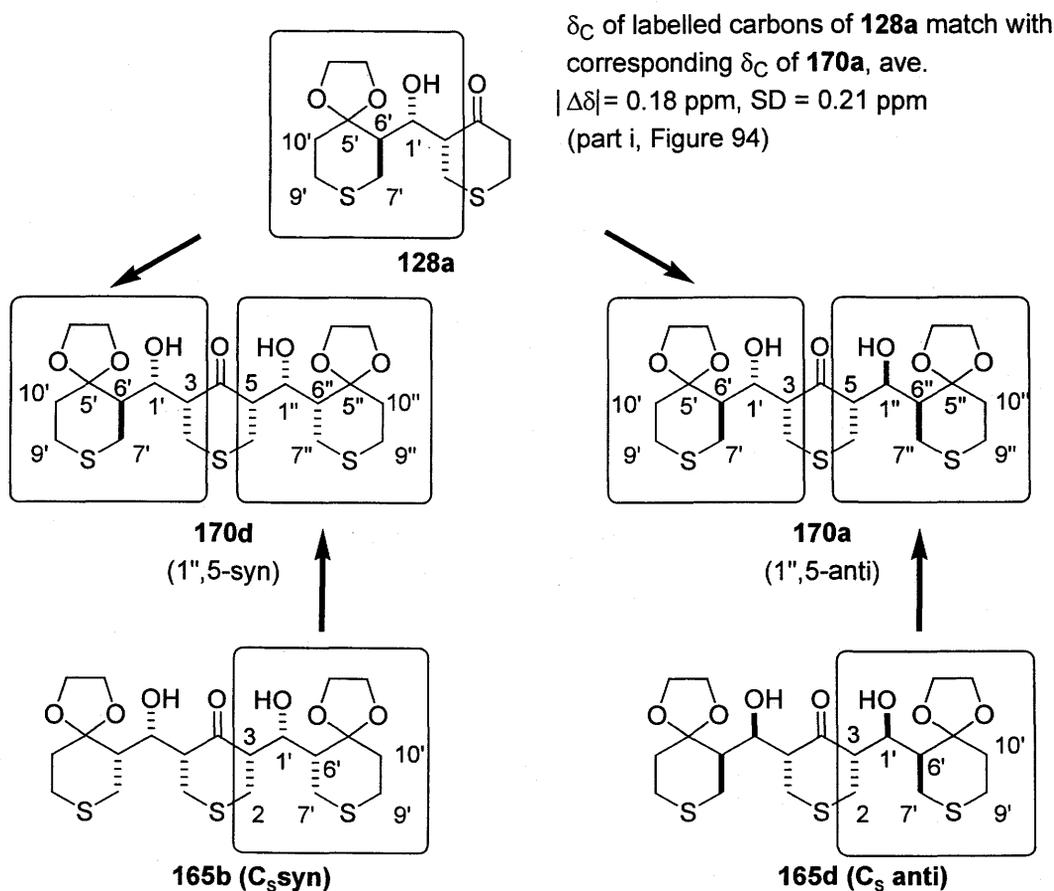
Bisaldol **170a** was subjected to imidazole-catalyzed isomerization (see Figure 64) to give a 2.1:3.6:3.2:1 equilibrium mixture of **170a**, **170b**, **171c** and **171d**, respectively. The bisaldols **170b**, **171c** and **171d** were isolated and each was determined to be asymmetric by  $^{13}\text{C}$  NMR. Obtaining a set of four asymmetric products from keto-enol tautomerism of **170a** is possible only if the C-1'/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**.<sup>\*</sup> 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 <sup>13</sup>C 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 <sup>13</sup>C 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 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).

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<sup>\*</sup> 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.

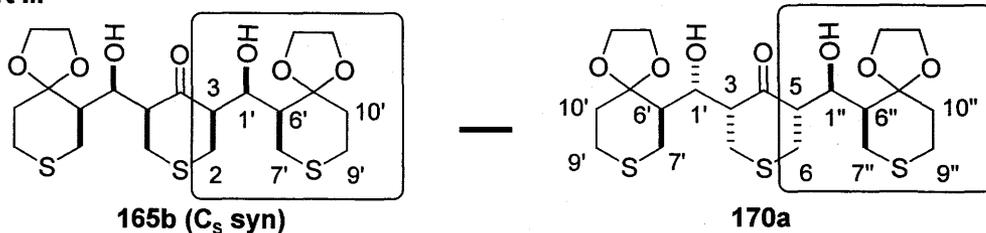


Notice that both **170d** and **170a** have 1',3-syn, 1',6'-anti, 3,5-cis, 1'',6''-syn relative configurations

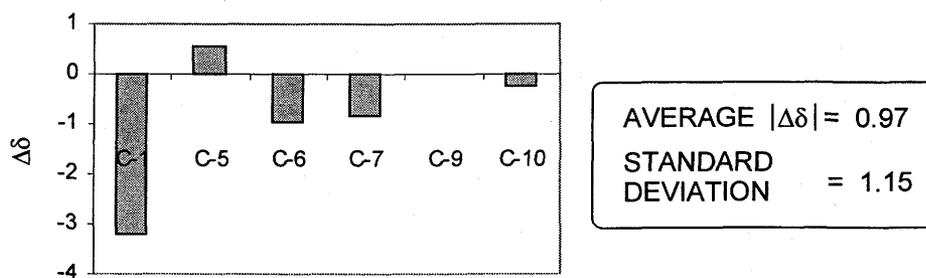
**Figure 93.** Distinguishing between structures **170a** and **170d** by comparison of  $^{13}\text{C}$  NMR data of aldols **128a**, **165b** and **165d** with  $^{13}\text{C}$  NMR data of aldol **170a**.



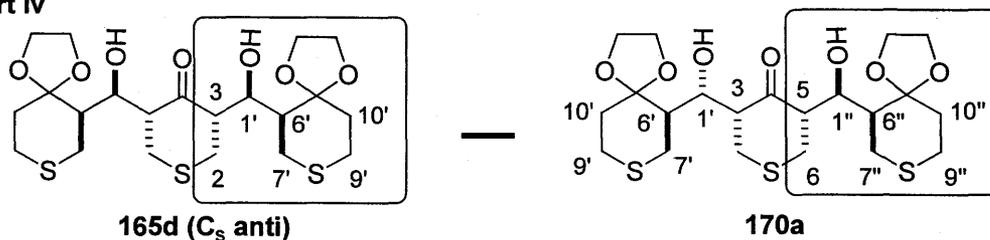
part iii



$$\Delta\delta = \delta_C(165b) - \delta_C(170a)$$



part iv



$$\Delta\delta = \delta_C(165d) - \delta_C(170a)$$

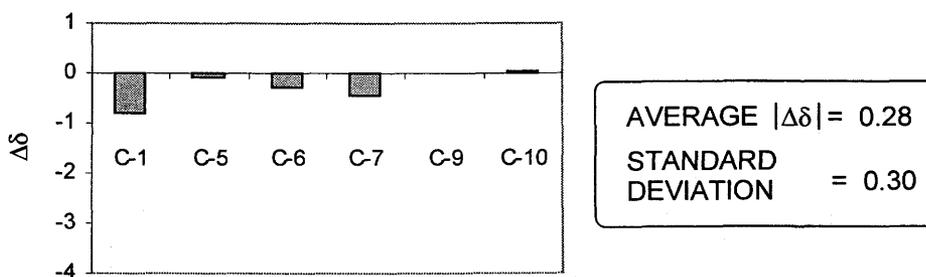
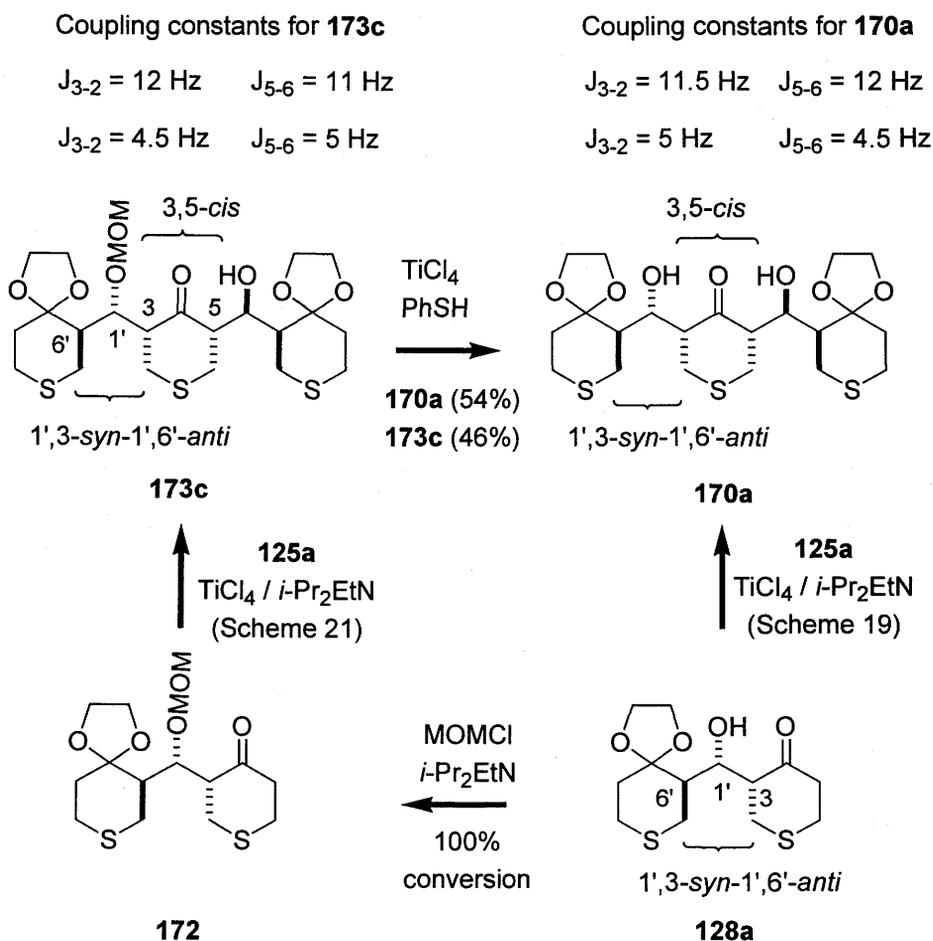


Figure 95. Comparison of the  $^{13}C$  NMR shifts of 165b and 165d with those of 170a.



**Figure 96.** Structure determination of **170a** and **173c**.

Compound **173c** was a minor product from the aldol reaction of **172** with **125a** (Scheme 21). The vicinal coupling constants between H<sub>2</sub>C-2 and HC-3 (4.5 and 12 Hz) and between H<sub>2</sub>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<sub>4</sub> / 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 <sup>13</sup>C NMR spectrum. The vicinal coupling constants between H<sub>2</sub>C-2 and HC-3 (5 and 7 Hz) and between H<sub>2</sub>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**

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

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

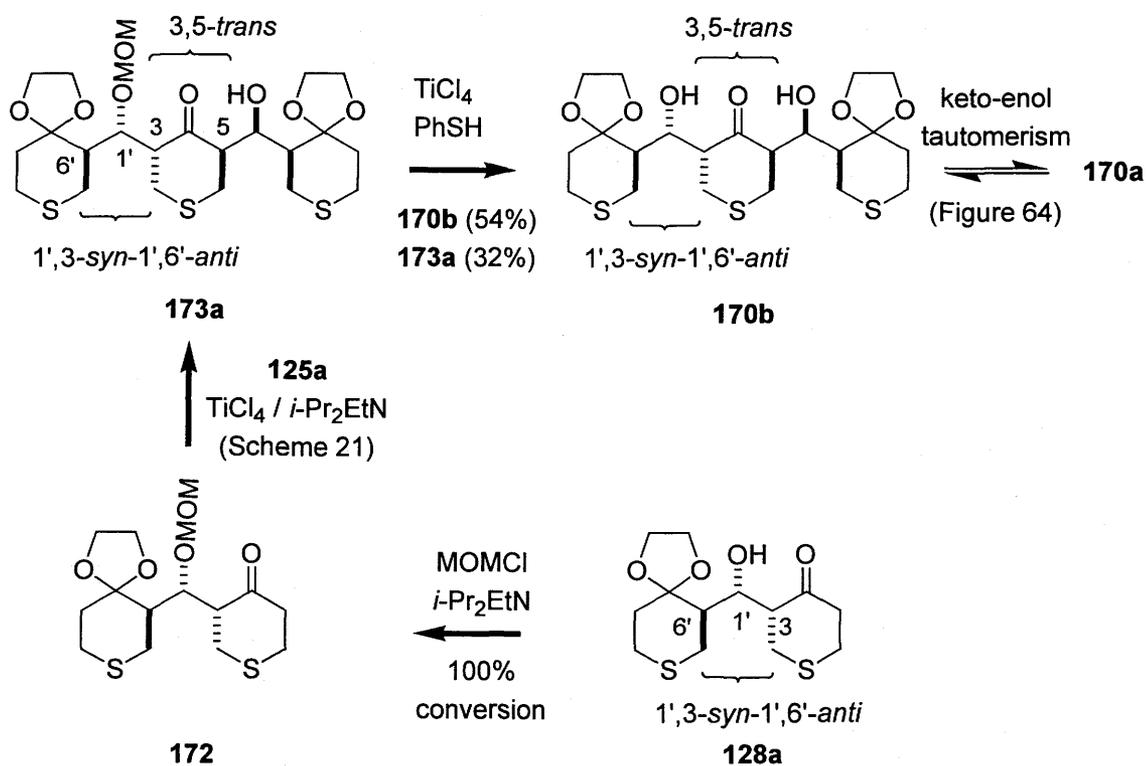


Figure 97. Structure determination of **170b** and **173a**.

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 a 1',3-syn-1',6'anti relative configuration of **128a** (Figure 97). As expected, the vicinal coupling constants between H<sub>2</sub>C-2 and HC-3 (5 and 11 Hz) and between H<sub>2</sub>C-6 and HC-5 (4 and 4.5 Hz) obtained from the <sup>1</sup>H 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 <sup>13</sup>C NMR spectrum. The vicinal coupling constants between H<sub>2</sub>C-2 and HC-3 (4.5 and 11 Hz) and between H<sub>2</sub>C-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 H<sub>2</sub>C-2 and HC-3 (4.5 and 7 Hz) and between H<sub>2</sub>C-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 TiCl<sub>4</sub> / PhSH gave **171c**.

Coupling constants for **175b**

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

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

Coupling constants for **171c**

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

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

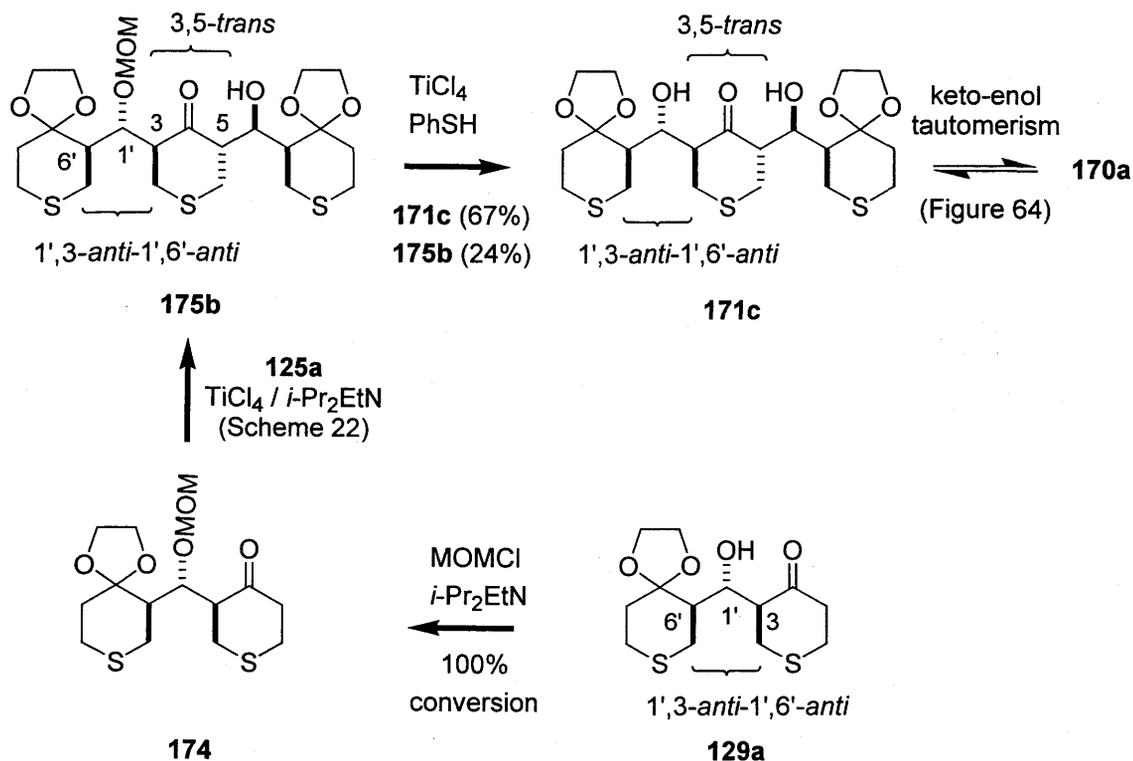


Figure 98. Structure determination of **171c** and **175b**.

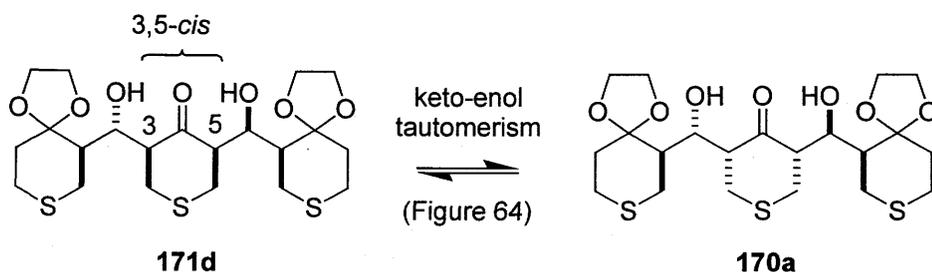
#### 2.5.2.14. Bisaldol **171d**

Bisaldol **171d** is obtained from keto-enol tautomerism of **170a** and is asymmetric based on the observation of 21 signals in its  $^{13}\text{C}$  NMR spectrum (see Figure 64). The vicinal couplings constants between  $\text{H}_2\text{C}-2$  and  $\text{HC}-3$  (5 and 11.5 Hz) and between  $\text{H}_2\text{C}-6$  and  $\text{HC}-5$  (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**

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

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



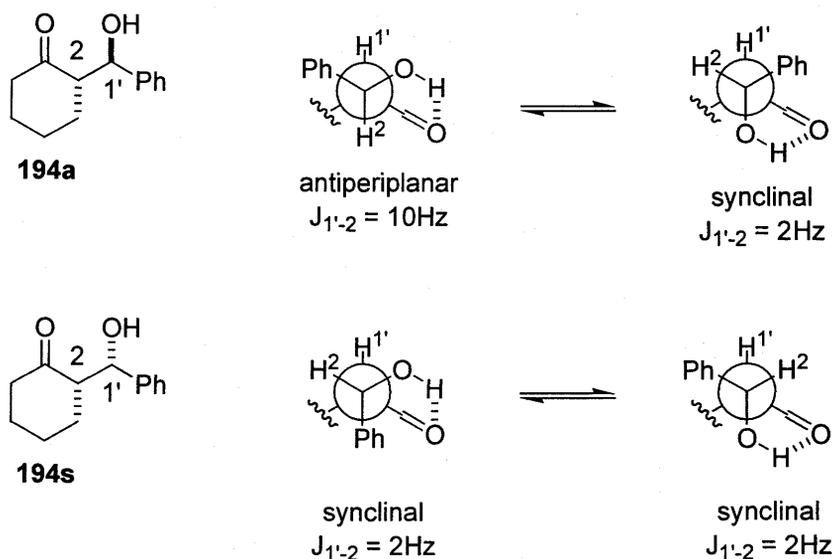
**Figure 99.** Structure determination of **171d**.

### 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  $J_{1',2}$ ,<sup>197</sup> and this method was later extended by House et al.<sup>198</sup> 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  $J_{1',2} = 10$  Hz and the other conformation will place these protons in a synclinal orientation with a predicted  $J_{1',2} = 2$  Hz. Depending on the relative proportions of these conformers it was postulated by House that anti aldols will have observed vicinal coupling constants  $J_{1',2}$  ranging between 6-9 Hz.<sup>198</sup> 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  $J_{1',2}$  for syn aldols will range between 2-4 Hz and be much smaller than the expected couplings for anti aldols.<sup>198</sup>

The vicinal coupling constants  $J_{1',2}$  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.<sup>135</sup> 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.<sup>199</sup> 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.<sup>40</sup>

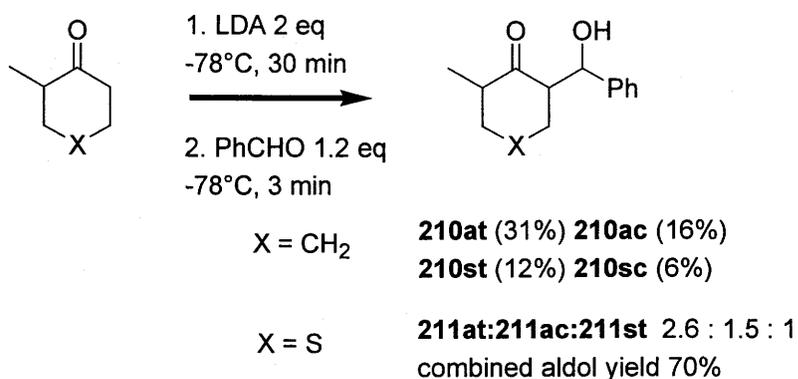


**Figure 100.** Intramolecular hydrogen bonded conformations for 1',2-anti **194a** and 1',2-syn **194s**.<sup>199</sup>

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  $\text{CH}_2\text{Cl}_2$  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  $\pm 0.2$  ppm) to that reported in the literature<sup>183-189</sup>. The vicinal coupling constants  $J_{1'-2}$  (see Table 25) derived from the obtained spectral data also matched closely (within  $\pm 1$  Hz) with the reported values.<sup>135,185,187,189</sup> Furthermore, the  $^{13}\text{C}$  NMR data for the four

aldols **210** closely matched (within  $+0.4 \pm 0.3$  ppm)\* the data reported by Duhamel et al.<sup>189</sup> 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**.

Entry	$J_{1,2}$	Literature <sup>183-189</sup>	Corrected
1	9.5	anti,trans	anti,trans
2	8.5	anti,cis	anti,cis
3	3.0	syn,cis	syn,trans
4	2.5	syn,trans	syn,cis

To the best of my knowledge, Mukaiyama et al. was the first to assign the relative configurations of the aldols **210**.<sup>135</sup> 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 <sup>13</sup>C

\* The constant +0.4 ppm difference in carbon shift is most likely due to a 0.4 ppm difference in the calibration of the CDCl<sub>3</sub> triplet in the accumulated spectra and the reported spectra of Duhamel et al.

NMR data was used for this assignment since no  $^{13}\text{C}$  data was reported by Mukaiyama.<sup>135</sup> 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.<sup>183-189</sup> The report by Duhamel et al. is the only one where both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data for aldols **210** was given; no attempt was made to use the  $^{13}\text{C}$  NMR data to substantiate the previous 2,6-*cis/trans* assignments.<sup>189</sup>

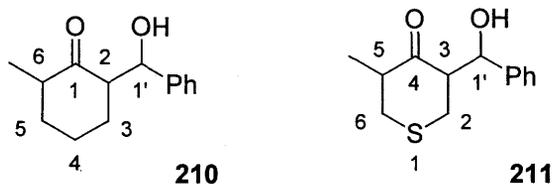
Mukaiyama's assignment of the 1',2-*syn/anti* relative configurations in **210**, based on the Stiles-House rule, is further supported by the  $^{13}\text{C}$  NMR chemical shifts for C-1' (entry 8, Table 26). The anti aldols **12at** and **12ac** have C-1' shifts of 75.01 and 74.93 ppm, respectively, 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  $^1\text{H}$ - $^1\text{H}$  coupling constants of aldols **210** has not been reported in the literature. From the  $^1\text{H}$  NMR of aldol **210ac**, the vicinal coupling constants between protons HC-2 and H<sub>2</sub>C-3 (5.5 and 13 Hz) and between HC-6 and H<sub>2</sub>C-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  $^1\text{H}$  NMR of aldol **210sc** the vicinal coupling constants between protons HC-2 and H<sub>2</sub>C-3 (6.5 and 12.5 Hz) and between HC-6 and H<sub>2</sub>C-5 (5.5 and 12.5 Hz) also suggest a 2,6-*cis* relative configuration (Table 26).

From the  $^1\text{H}$  NMR of aldol **210at** the vicinal coupling constants between protons HC-2 and H<sub>2</sub>C-3 (5.5 and 9.5 Hz) and between HC-6 and H<sub>2</sub>C-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  $^1\text{H}$  NMR of aldol **210st** the coupling constants between protons HC-2 and H<sub>2</sub>C-3 (5.5 and 10 Hz) and between HC-6 and H<sub>2</sub>C-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  $^1\text{H}$ - $^1\text{H}$  coupling constant analysis.

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

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



Entry	Physical property		210anti,trans	210anti,cis	210syn,trans	210syn,cis
1		$J_{1'-2}$	9.5	8.5	3	2.5
2	$^1\text{H}-^1\text{H}$	$J_{2-3}$	9.5	13	10	12.5
3	coupling constant	$J_{2-3}$	5.5	5.5	5.5	6.5
4	(Hz)	$J_{5-6}$	5.5	13	5.5	12.5
5		$J_{5-6}$	5	6	5	5.5
6	$^1\text{H}$ shift	HC-1'	4.86	4.80	5.32	5.38
7	(ppm)	H <sub>3</sub> C	1.21	1.07	1.18	1.06
8	$^{13}\text{C}$ shift	C-1'	75.01	74.93	71.62	70.97
9	(ppm)	CH <sub>3</sub>	16.47	14.43	16.71	14.50
			211anti,trans	211anti,cis	211syn,trans	211syn,cis
10		$J_{1'-3}$	9.5	8.5	4	3
11	$^1\text{H}-^1\text{H}$	$J_{2-3}$	6.5	12.5	9.5	12
12	coupling constant	$J_{2-3}$	4	4.5	4	3.5
13	(Hz)	$J_{5-6}$	9	13	7	12
14		$J_{5-6}$	4.5	4.5	4.5	5
15	$^1\text{H}$ shift	HC-1'	5.30	4.86	5.43	5.38
16	(ppm)	H <sub>3</sub> C	1.27	1.15	1.26	1.14
17	$^{13}\text{C}$ shift	C-1'	74.29	74.08	71.86	71.16
18	(ppm)	CH <sub>3</sub>	15.55	14.70	15.97	14.72

Assuming that the cyclohexanone rings of aldols **210ac** and **210sc** are in a chair conformation, their  $^1\text{H}-^1\text{H}$  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  $^1\text{H}$  (Table 26, entry 7) and  $^{13}\text{C}$  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  $^1\text{H}$  and  $^{13}\text{C}$  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  $^{13}\text{C}$  NMR shifts observed for C-1'. The vicinal coupling constants between H<sub>2</sub>C-2 and HC-3 and between HC-5 and H<sub>2</sub>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  $^1\text{H}$  and  $^{13}\text{C}$  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).

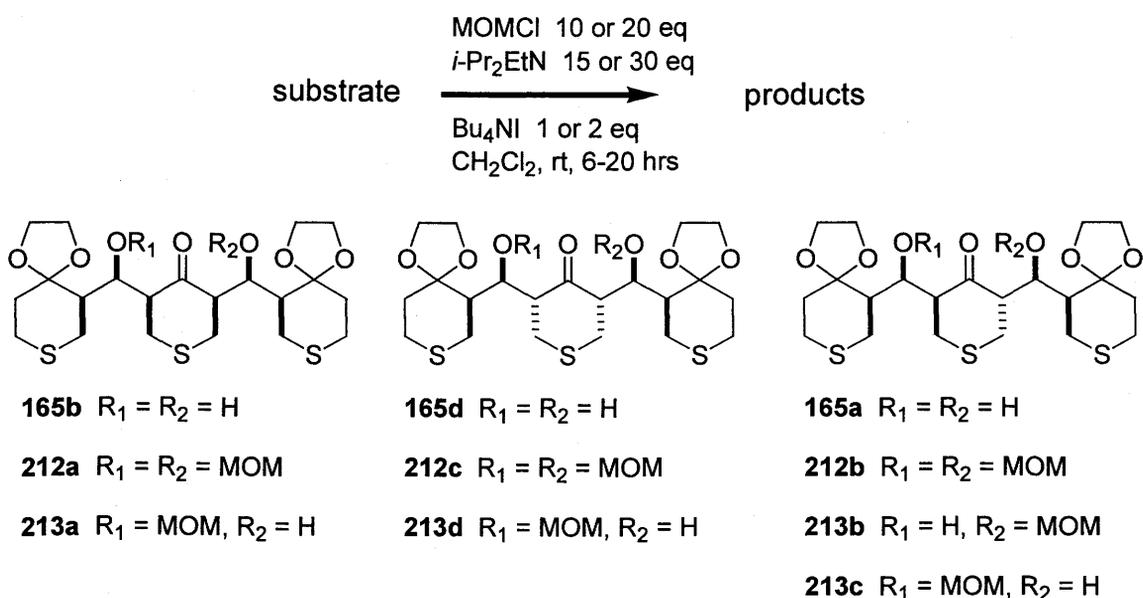
#### 2.5.4. Determination of the Relative Configurations of MOM-Protected Derivatives of Aldols **165a**, **165b** and **165d**

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  $^{13}\text{C}$  NMR shifts of the

CHOH carbon of aldols **213b** and **213c** were compared to similar CHOH carbons in **165a**, **165c** and **165e** (Figure 101).<sup>\*</sup> 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).

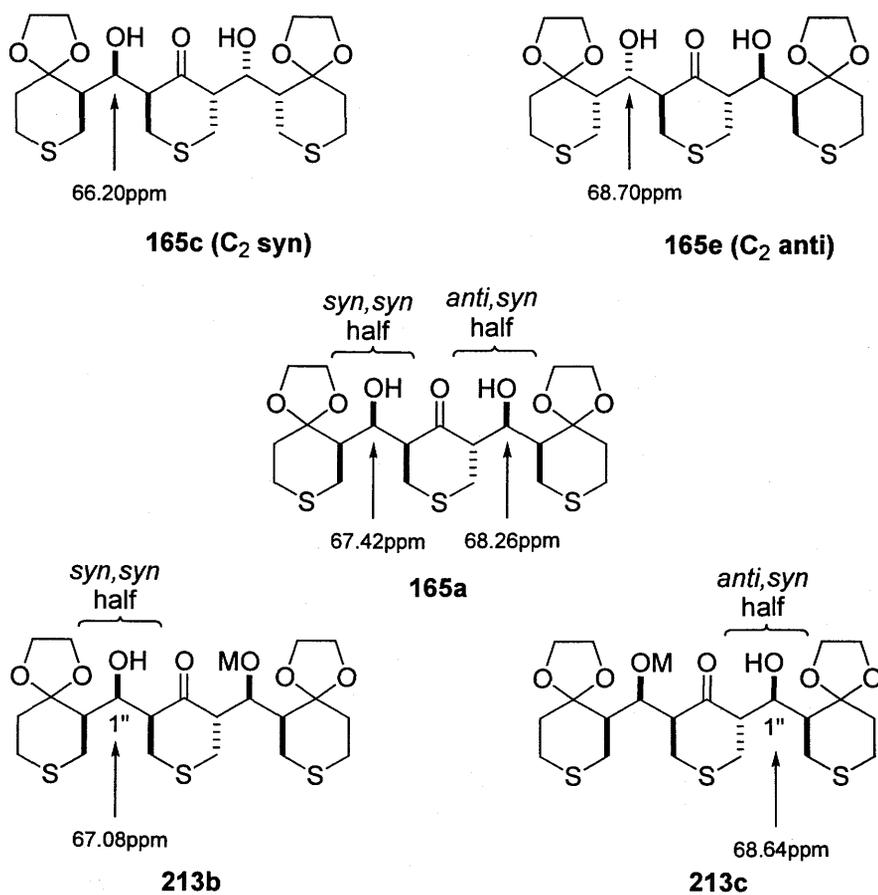
**Table 27.** The synthesis of mono- and bis-MOM derivatives of aldols **165a**, **165b** and **165d**.



entry	substrate	products	recovered substrate
1	<b>165b</b>	<b>212a</b> <sup>a</sup> <b>213a</b> <sup>a</sup>	<b>165b</b> (20%)
2	<b>165d</b>	<b>212c</b> (83%)	
3	<b>165d</b>	<b>213d</b> (47%)	<b>165d</b> (45%)
4	<b>165a</b>	<b>212b</b> (44%) <b>213b</b> (14%) <b>213c</b> (35%)	

<sup>a</sup> Combined isolated yield of **212a** and **213a** is 80%.

<sup>\*</sup> 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<sub>2</sub>Cl<sub>2</sub> and toluene from CaH<sub>2</sub>; MeOH from Mg(OMe)<sub>2</sub>; Et<sub>3</sub>N and TiCl<sub>4</sub> were distilled from CaH<sub>2</sub>. 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<sub>2</sub>(s)/acetone (-78 °C). Reaction temperatures refer to that of the bath.

Preparative thin layer chromatography (PTLC) was carried out on glass plates (20×20 cm) precoated (0.25 mm) with silica gel 60 F<sub>254</sub>. 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.<sup>200</sup> with Merck Silica Gel 60 (40-63 μm). Medium pressure chromatography (MPC) was performed as reported by Taber.<sup>201</sup> Dry flash column chromatography was performed according to Harwood.<sup>202</sup> 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  $\text{CDCl}_3$  solution at 300, 400, or 500 MHz for  $^1\text{H}$  NMR and 75, 100, or 125 MHz for  $^{13}\text{C}$  NMR signals due to the solvent ( $^{13}\text{C}$  NMR) or residual protonated solvent ( $^1\text{H}$  NMR) served as the internal standard:  $\text{CDCl}_3$  (7.27  $\delta_{\text{H}}$ , 77.23  $\delta_{\text{C}}$ );  $\text{CD}_3\text{OD}$  (3.31  $\delta_{\text{H}}$ , 49.15  $\delta_{\text{C}}$ );  $\text{C}_6\text{D}_6$  (7.16  $\delta_{\text{H}}$ , 128.39  $\delta_{\text{C}}$ ). The  $^1\text{H}$  NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of coupling constants ( $J$ ) corresponds to the order of the multiplicity assignment. Couplings constants ( $J$ ) are reported to the nearest 0.5 Hz. The  $^1\text{H}$  NMR assignments were made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by 1D homonuclear decoupling, 2D  $^1\text{H}/^1\text{H}$  homonuclear shift correlation (COSY)<sup>203</sup> and/or 1D NOE experiments. The  $^{13}\text{C}$  NMR assignments were made on the basis of chemical shift and multiplicity\* as determined by  $J$ -modulation<sup>204</sup> and were confirmed, where necessary, by 2D  $^1\text{H}/^{13}\text{C}$  one bond correlation (HSQC)<sup>205</sup> and 2D  $^1\text{H}/^{13}\text{C}$  multiple bond correlation (HMBC)<sup>206</sup> 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  $\text{LiAlH}_4$  (1.1 equiv) in ether (2-3.5 mL/ mmol of  $\text{LiAlH}_4$ ) at 0 °C under argon. After 1 h, the reaction was quenched<sup>207</sup> by sequential dropwise addition of water (1 mL/ g of  $\text{LiAlH}_4$ ), 15% (w/v) sodium hydroxide (1 mL/ g of  $\text{LiAlH}_4$ ), and water (3 mL/ g of  $\text{LiAlH}_4$ ). The resultant gray suspension was stirred until granular white flakes formed (ca. 1-1.5 h). The suspension

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\* Multiplicity of  $^{13}\text{C}$  NMR signals refers to the number of attached H's (*ie.* s = C, d = CH, t =  $\text{CH}_2$ , q =  $\text{CH}_3$ )

was filtered through Celite® washing with 1:1 ether/hexane. The combined filtrate and washings were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the desired alcohol.

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

Methylolithium (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-4*H*-thiopyran-4-one in ether (2 mL/ mmol of enol ether) at 0 °C under argon.<sup>208</sup> 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:** H<sub>2</sub> evolution). The mixture was diluted with saturated aqueous sodium potassium tartrate and extracted with ethyl acetate (×3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the crude diol(s).

### **3.3.4. General Procedure D for NaBH<sub>4</sub> Reduction of Aldols**

NaBH<sub>4</sub> (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:** H<sub>2</sub> 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 (×3). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the crude mixture of *cis* and *trans* diols.

### 3.3.5. General Procedure E for NaCNBH<sub>3</sub> Reduction of Aldols

NaCNBH<sub>3</sub> (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 CH<sub>2</sub>Cl<sub>2</sub> (×3) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the crude mixture of cis and trans diols.

### 3.3.6. General Procedure F for NaBH(OAc)<sub>3</sub> Reduction of Aldols

A 0.33 M solution of NaBH(OAc)<sub>3</sub> in acetic acid was prepared by portion-wise addition of NaBH<sub>4</sub> (25 mg, 0.66 mmol) to cold glacial acetic acid (2 mL) (caution: H<sub>2</sub> evolution) followed by stirring for 5 min. NaBH(OAc)<sub>3</sub> (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 CH<sub>3</sub>CN (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 NaHCO<sub>3</sub> and then was diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (×3). The combined organic layer were dried over Na<sub>2</sub>SO<sub>4</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (×3). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> 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 Na<sub>2</sub>SO<sub>4</sub>, 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 CH<sub>2</sub>Cl<sub>2</sub> (×3). The combined organic layers were dried Na<sub>2</sub>SO<sub>4</sub> 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*-Pr<sub>2</sub>EtN (2 equiv based on MOMCl) in CH<sub>2</sub>Cl<sub>2</sub> (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 CH<sub>2</sub>Cl<sub>2</sub> (×3) and the combined organic layers were, dried over Na<sub>2</sub>SO<sub>4</sub>, 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 NaHCO<sub>3</sub> (caution:CO<sub>2</sub> evolution). The mixture was diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (×3) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the crude triol.

### 3.3.11. General Procedure K for Hydrolysis of MOM Ethers

TiCl<sub>4</sub> (5 equiv) was added dropwise over 10 seconds to a stirred solution of substrate in CH<sub>2</sub>Cl<sub>2</sub> (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  $\text{Na}_2\text{CO}_3^*$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ ). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  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

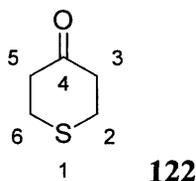
$\text{Bu}_4\text{NI}$  (0.03 equiv), *i*- $\text{Pr}_2\text{EtN}$  (5 equiv) and  $\text{MOMCl}$  (3 equiv) were sequentially added to a solution of monoaldol substrate in  $\text{CH}_2\text{Cl}_2$  (3 mL/ mmol). The reaction was monitored by TLC (50% ethyl acetate in hexane). Within the first day the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

### 3.3.13. General Procedure M for Preparation of MOM Ethers

$\text{Bu}_4\text{NI}$  (1 equiv), *i*- $\text{Pr}_2\text{EtN}$  (15 equiv) and  $\text{MOMCl}$  (10 equiv) were sequentially added to a solution of bisaldol in  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (3 $\times$ 20 mL). The organic extracts were combined, dried over  $\text{Na}_2\text{SO}_4$  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)

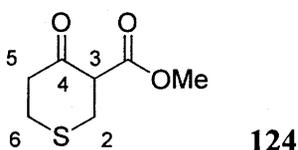


A solution of **124** (22.5 g, 0.13mol) in 5%  $\text{H}_2\text{SO}_4$  (60 mL) was heated under reflux. The reaction was monitored by TLC (50% EtOAc in hexane). Starting material

\* Saturated  $\text{Na}_2\text{CO}_3$  was used to extract PhSH into the aqueous phase.

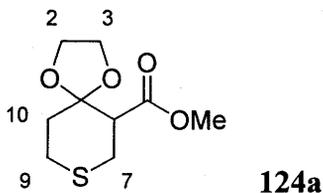
was consumed after 18 h. The reaction was diluted with cold dist water (0 °C, 40 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×). The combined organic extracts were washed with saturated K<sub>2</sub>CO<sub>3</sub> (×1), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give a light 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.<sup>209</sup>

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



Anhydrous methanol (freshly distilled from Mg(OMe)<sub>2</sub>; 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:** H<sub>2</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (×2). The separated aqueous layer of the quenched mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (×4). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> 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.<sup>210</sup>

### Methyl 1,4-Dioxa-8-thiaspiro[4.5]decane-6-carboxylate (**124a**).<sup>211</sup>



A solution of  $\beta$ -ketoester **124** (30 g, 0.17 mol), ethylene glycol (43 g, 0.69 mol) and *p*-TsOH·H<sub>2</sub>O (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 NaHCO<sub>3</sub> (×2), water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, 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**  $\nu_{\max}$  1733 cm<sup>-1</sup>;

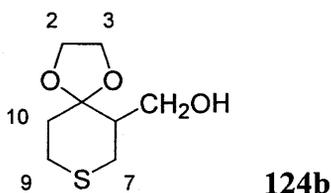
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.00-3.86 (4H, m), 3.71 (3H, s), 3.11 (1H, ap dd, *J* = 8.5, 13.5 Hz), 2.96-2.78 (3H, m), 2.67 (1H, dddd, *J* = 1.5, 3.5, 7, 13.5 Hz), 2.25 (1H, ddd, *J* = 3.5, 7, 13.5 Hz), 1.82 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  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 C<sub>9</sub>H<sub>14</sub>O<sub>4</sub>S 218.0613, found 218.0604 (EI).

**Anal. Calcd** for C<sub>9</sub>H<sub>14</sub>O<sub>4</sub>S: C, 49.53; H, 6.46. Found: C, 49.58; H, 6.39.

### 1,4-Dioxa-8-thiaspiro[4.5]decane-6-methanol (**124b**).<sup>212</sup>



Following General procedure A, a solution of **124a** (22.5 g, 103 mmol) in ether was reduced with LiAlH<sub>4</sub> 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.

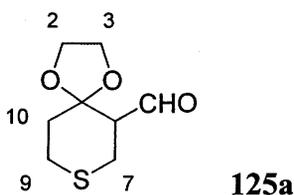
**IR**  $\nu_{\max}$  3442  $\text{cm}^{-1}$ ;

**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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);

**$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_8\text{H}_{14}\text{O}_3\text{S}$  190.0664, found 190.0672 (EI).

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



Swern oxidation: A solution of DMSO (3.6 mL, 4.0 g, 51 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) was added dropwise over 5 minutes via syringe to a stirred solution of oxalyl chloride (2.2 mL, 26 mmol) in  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (2 mL) was added dropwise via syringe over 3 minutes to the reaction mixture. After a further 30 min,  $i\text{-Pr}_2\text{EtN}$  (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  $\text{CH}_2\text{Cl}_2$  ( $\times 3$ ). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , 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%)

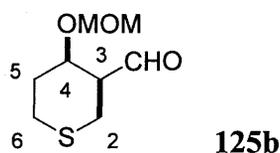
**IR**  $\nu_{\max}$  2840, 2737, 1721  $\text{cm}^{-1}$ ;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 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);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 201.3 (d), 107.8 (s), 64.9 (t), 64.7 (t), 56.6 (d), 36.2 (t), 26.7 (t), 26.4 (t);

**HRMS** *m/z* calcd for C<sub>8</sub>H<sub>12</sub>O<sub>3</sub>S 188.0507, found 188.0512 (EI). Anal. Calcd for C<sub>8</sub>H<sub>12</sub>O<sub>3</sub>S: C, 51.04; H, 6.43. Found: C, 51.20; H, 6.58.

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



**Modified Swern oxidation:** A solution of DMSO (520 μL, 570 mg, 7.30 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was added dropwise over 3 minutes via syringe to a stirred solution of oxalyl chloride (318 μL, 3.65 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub> (1 mL) was added dropwise via syringe over 3 minutes to the reaction mixture. After an additional 3 min, *i*-Pr<sub>2</sub>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<sub>2</sub>Cl<sub>2</sub> (3×). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and fractionated by FCC (30% ethyl acetate in hexane) to give the titled aldehyde as a clear oil (617 mg, 89%).

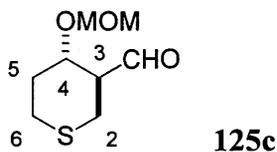
**IR**  $\nu_{\max}$  2823, 2722, 1726 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 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);

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  202.1, 95.3, 70.6, 53.9, 46.9, 31.3, 23.2, 22.9;

HRMS  $m/z$  calcd for  $\text{C}_8\text{H}_{14}\text{O}_3\text{S}$  190.0664, found 190.0666 (EI).

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



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**:<sup>150</sup> 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  $-78\text{ }^\circ\text{C}$  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  $\text{CH}_2\text{Cl}_2$  ( $\times 3$ ). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , 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%):

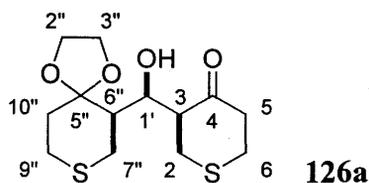
IR  $\nu_{\text{max}}$  2824, 2725, 1721  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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);

$^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_8\text{H}_{14}\text{O}_3\text{S}$  190.0664, found 190.0664 (EI).

**(1'S\*, 3S\*, 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** ( $\text{TiCl}_4$ ). Freshly distilled  $\text{TiCl}_4$  (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  $\text{CH}_2\text{Cl}_2$  (35 mL) at  $-78^\circ\text{C}$  under argon. The resulting fine yellow suspension was stirred for 10 min and then a solution of **137b** (736 mg, 3.91 mmol) in  $\text{CH}_2\text{Cl}_2$  (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  $-78^\circ\text{C}$ , the reaction was allowed to warm to rt over 30 min and then was quenched by sequential addition of a solution of  $\text{Et}_3\text{N}$  (80 mg, 0.79 mmol) and MeOH (100 mg, 3.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) and then sat.  $\text{NH}_4\text{Cl}$  (5 mL). The mixture was diluted with water, extracted with  $\text{CH}_2\text{Cl}_2$  ( $\times 3$ ) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , 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** ( $\text{BF}_3\cdot\text{OEt}_2$ ). Using the same procedure as above but replacing  $\text{TiCl}_4$  with  $\text{BF}_3\cdot\text{OEt}_2$ , **125a** (73 mg, 0.039 mmol) gave a 2:1 mixture of **126a** and **127a** (70%), respectively.

From aldol reaction of **137d** with **125a**.  $\text{TiCl}_4$  (0.030 mL, 52 mg, 0.28 mmol) was added to a stirred solution of **3** (29 mg, 0.25 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 mL) at  $-78^\circ\text{C}$  under argon. After 5 min, *i*- $\text{Pr}_2\text{EtN}$  (0.052 mL, 39 mg, 0.30 mmol) was added and after 2 h at  $-78^\circ\text{C}$ , a solution of **125a** (56 mg, 0.30 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) was added. After 5 h, the reaction was quenched addition of aqueous  $\text{NH}_4\text{Cl}$ . The mixture was diluted with water and extracted with  $\text{CH}_2\text{Cl}_2$  ( $\times 3$ ), and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , 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  $\text{C}_5$  and  $\text{C}_1$  bisaldols (26 mg, 20%).<sup>30</sup>

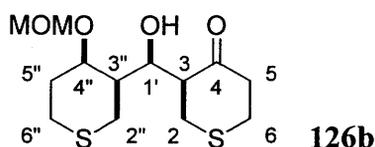
IR  $\nu_{\max}$ , 3507, 1703  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.79 (1H, dd,  $J = 3, 8.5$  Hz, HC-1' [ $^3J_{\text{HC-1'}/\text{HC-3}} = 8.5$  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);

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{13}\text{H}_{20}\text{O}_4\text{S}_2$  304.0803, found 304.0799. Anal. Calcd for  $\text{C}_{13}\text{H}_{20}\text{O}_4\text{S}_2$ : C, 51.29; H, 6.62. Found: C, 51.43; H, 6.44.

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



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 ( $^1\text{H}$  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%).

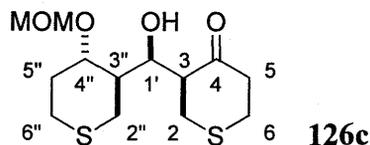
IR  $\nu_{\max}$  3496, 1701  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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' [ $^3J_{\text{HC-1'}/\text{HC-3}} = 5.5$  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);

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $C_{13}H_{22}O_4S_2$  306.0960, found 306.0956 (EI).

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



Aldol reaction of **137b** and **125c** ( $TiCl_4$ ). Following the procedure described for the synthesis of **126a** using  $TiCl_4$  (0.018 mL, 31 mg, 0.16 mmol), the aldehyde **125c** (30 mg, 0.16 mmol), and **137b** (60 mg, 0.32 mmol) in  $CH_2Cl_2$  (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).

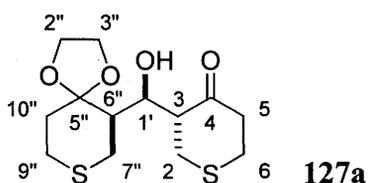
IR  $\nu_{max}$  3472, 1702  $cm^{-1}$ ;

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  4.84 (1H, ddd,  $J = 4, 5, 8.5$  Hz, HC-1' [ $^3J_{HC-1'/HC-3} = 8.5$  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);

$^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  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  $C_{13}H_{22}O_4S_2$  306.0960, found 306.0962 (EI).

**(1'S\*, 3R\*, 6'R\*)-3-[(1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl)hydroxymethyl]tetrahydro-4H-thiopyran-4-one (127a).**



From aldol reaction of **137b** and **125a** ( $\text{SnCl}_4$ ). A solution of  $\text{SnCl}_4$  (270  $\mu\text{L}$ , 0.266 mmol, 1.0 M) in  $\text{CH}_2\text{Cl}_2$  was added dropwise to a stirred solution of aldehyde **125a** (25 mg, 0.133 mmol) in  $\text{CH}_2\text{Cl}_2$ . 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  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  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  $\text{CH}_2\text{Cl}_2$  ( $\times 3$ ). The organic extracts were combined, dried over  $\text{Na}_2\text{SO}_4$ , 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 a solution of glacial acetic acid (1.5 mL) in THF (5 mL). The reaction mixture was removed from the cooling bath and  $\text{CH}_2\text{Cl}_2$  (100 mL) and water (50 mL) were added. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $\times 2$ ) and the combined organic layers were washed sequentially with aqueous  $\text{NaHCO}_3$  and water, dried over  $\text{Na}_2\text{SO}_4$ , 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 CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was added to a stirred solution of Bu<sub>2</sub>BOTf (1 M in CH<sub>2</sub>Cl<sub>2</sub>; 0.26 mL) and *i*-Pr<sub>2</sub>EtN (0.090 mL, 67 mg, 0.52 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at -78 °C under argon. After 3 h, a solution of **125a** (130 mg, 0.69 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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% H<sub>2</sub>O<sub>2</sub> (0.2 mL). The mixture was stirred at 0 °C for 15 min and then aqueous Na<sub>2</sub>SO<sub>3</sub> was added to reduce the H<sub>2</sub>O<sub>2</sub>. The mixture was diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (×3), and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, 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*-C<sub>6</sub>H<sub>11</sub>)<sub>2</sub>BCl in place of Bu<sub>2</sub>BOTf gave a 15:1 mixture of **127a** and **126a** (44 mg, 84%), respectively.

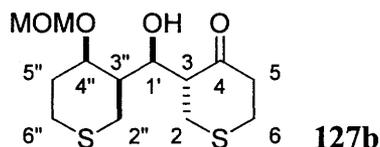
**IR**  $\nu_{\max}$  3488, 3409, 1711 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.50 (1H, dd,  $J = 4.5, 6.5$  Hz, HC-1' [ $^3J_{\text{HC-1'/HC-3}} = 6.5$  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);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  211.5 (s), 109.3 (s), 69.3 (d), 64.4 (t), 64.3 (t), 55.5 (d), 47.0 (d), 44.4 (t), 35.5 (t), 34.3 (t), 31.4 (t), 27.4 (t), 26.5 (t);

**HRMS**  $m/z$  calcd for C<sub>13</sub>H<sub>20</sub>O<sub>4</sub>S<sub>2</sub> 304.0803, found 304.0801. Anal. Calcd for C<sub>13</sub>H<sub>20</sub>O<sub>4</sub>S<sub>2</sub>: C, 51.29; H, 6.62. Found: C, 51.59; H, 6.55.

**(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** (TiCl<sub>4</sub>). The cis aldehyde **125b** was unstable in the presence of TiCl<sub>4</sub> (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).

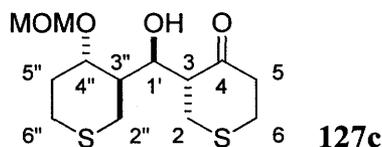
**IR**  $\nu_{\max}$  3508, 1700 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  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' [ $^3J_{\text{HC-1'}/\text{HC-3}} = 6$  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);

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>)  $\delta$  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 C<sub>13</sub>H<sub>22</sub>O<sub>4</sub>S<sub>2</sub> 306.0960, found 306.0961 (EI).

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



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). The presence of other aldol diastereomers was not detected by  $^1\text{H}$  NMR of the crude product.

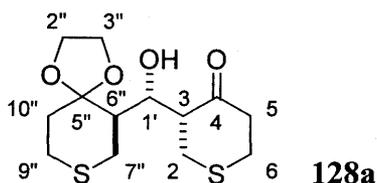
**IR**  $\nu_{\text{max}}$  3516, 1701  $\text{cm}^{-1}$ ;

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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' [ $^3J_{\text{HC-1'}/\text{HC-3}} = 9.5$  Hz]), 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, dddd,  $J = 3, 4, 4, 12.5$  Hz), 1.77 (1H, dddd,  $J = 3, 3, 9.5, 10$  Hz), 1.74 (1H, dddd,  $J = 3, 10.5, 12, 12.5$  Hz);

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{13}\text{H}_{22}\text{O}_4\text{S}_2$  306.0960, found 306.0954 (EI).

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



From aldol reaction of **137b** and **125a** ( $\text{MgBr}_2$ ).  $\text{MgBr}_2 \cdot \text{OEt}_2$  (4.45 g, 17.4 mmol) was added to a stirred solution of aldehyde **125a** (1.08 g, 5.74 mmol) in  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (1 mL) was added dropwise via syringe over 3 min. After stirring 1 h at  $0^\circ\text{C}$ , 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  $\text{CH}_2\text{Cl}_2$  ( $\times 3$ ). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  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%).

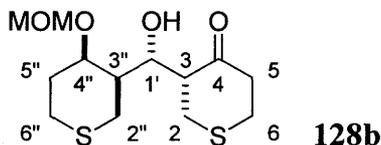
IR  $\nu_{\max}$  3497, 1706  $\text{cm}^{-1}$ ;

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.57 (1H, ddd,  $J = 2.5, 3.5, 7.5$  Hz, HC-1' [ $^3J_{\text{HC-1'}/\text{HC-3}} = 3.5$  Hz]), 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), 2.22-2.13 (1H, m), 2.07 (1H, ddd,  $J = 3.5, 7.5, 8$  Hz), 1.82-1.71 (1H, m);

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{13}\text{H}_{20}\text{O}_4\text{S}_2$  304.0803, found 304.0807. Anal. Calcd for  $\text{C}_{13}\text{H}_{20}\text{O}_4\text{S}_2$ : 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-2*H*-thiopyran-3-yl)methyl]tetrahydrothiopyran-4-one (**128b**).



Aldol reaction of **137b** and **125b** ( $\text{MgBr}_2$ ). 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  $\text{CH}_2\text{Cl}_2$ , multiple development).

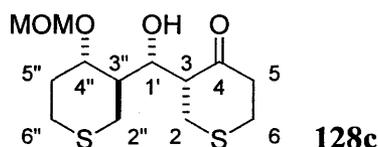
IR  $\nu_{\max}$  3464, 1697  $\text{cm}^{-1}$ ;

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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' [ $^3J_{\text{HC-1'}/\text{HC-3}} = 3.5$  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);

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{13}\text{H}_{22}\text{O}_4\text{S}_2$  306.0960, found 306.0962 (EI).

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



From aldol reaction of **137b** and **125c** ( $\text{MgBr}_2$ ). 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  $\text{CH}_2\text{Cl}_2$ ). A pure sample of **129c** could not be obtained. Extensive fractionation of the above mixture by PTLC (2% methanol in  $\text{CH}_2\text{Cl}_2$ ) gave a 1.5:1 mixture of aldols **129c** and **128c**.

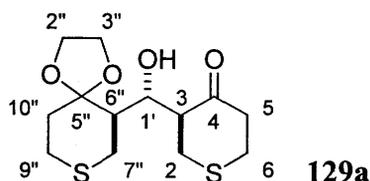
IR  $\nu_{\max}$  3483, 1701  $\text{cm}^{-1}$ ;

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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' [ $^3J_{\text{HC-1'}/\text{HC-3}} = 3$  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 (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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;

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

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



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

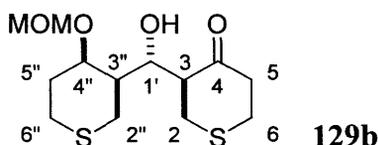
IR  $\nu_{\text{max}}$  3496, 1702  $\text{cm}^{-1}$ ;

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

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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);

HRMS  $m/z$  calcd for  $\text{C}_{13}\text{H}_{20}\text{O}_4\text{S}_2$  304.0803, found 304.0801.

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



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

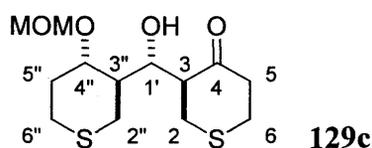
IR  $\nu_{\text{max}}$  3501, 1701  $\text{cm}^{-1}$ ;

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 4.72-4.69 (2H, m), 4.24 (1H, br s), 3.77 (1H, ddd, *J* = 3.5, 8.0, 10 Hz, HC-1' [<sup>3</sup>*J*<sub>HC-1'/HC-3</sub> = 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);

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 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<sub>13</sub>H<sub>22</sub>O<sub>4</sub>S<sub>2</sub> 306.0960, found 306.0956 (EI).

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

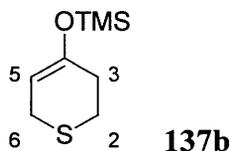


From aldol reaction of **137b** and **125c** (MgBr<sub>2</sub>). See experimental procedure for compound **128c**. From the 1.5:1 mixture\* of **129c** and **128c**; spectral data for **129c** was deduced from that of the mixture by comparison with data for pure **128c**.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 4.70 (2H, ap s), 4.07 (1H, ddd, *J* = 5, 5, 6.5 Hz, HC-1' [<sup>3</sup>*J*<sub>HC-1'/HC-3</sub> = 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);

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 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-2*H*-thiopyan (137b).**<sup>208,213</sup>



\* See experimental of **128c** for origin of this mixture.

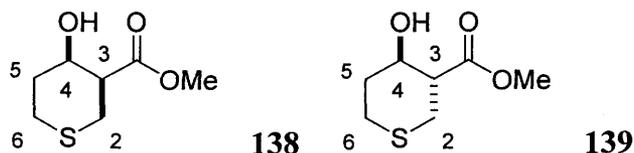
A solution of **122** (5.34 g, 46.0 mmol), Et<sub>3</sub>N (64 mL, 46 g, 0.46 mol) and TMSCl (29 mL, 25 g, 0.23 mol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was stirred at rt under argon in a capped vessel for 10 days. The reaction mixture was concentrated, diluted with ether, and filtered through Celite®. 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 <sup>1</sup>H 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 Et<sub>3</sub>N. This solution could be stored for months at -15 °C with negligible decomposition. The product was recovered as required by concentration of aliquots.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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)

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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 C<sub>8</sub>H<sub>16</sub>OSSi 188.0708, found 188.0705 (EI).

**Methyl (3*S*\*, 4*R*\*)-tetrahydro-4-hydroxy-2*H*-thiopyran-3-carboxylate (**138**) and Methyl (3*R*\*, 4*R*\*)-tetrahydro-4-hydroxy-2*H*-thiopyran-3-carboxylate (**139**).**<sup>146,214</sup>



NaCNBH<sub>3</sub> (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 NaCNBH<sub>3</sub> 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 H<sub>2</sub>O and with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the crude hydroxyesters (a 2:1 mixture of **138** and **139** by <sup>1</sup>H 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 ( $\times 3$ ). The aqueous phases were extracted with ethyl acetate and the combined organic layers dried over  $\text{Na}_2\text{SO}_4$ , 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**  $\nu_{\text{max}}$  3503, 1719  $\text{cm}^{-1}$ ;

**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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);

**$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_7\text{H}_{12}\text{O}_3\text{S}$  176.0507, found 176.0508 (EI);

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

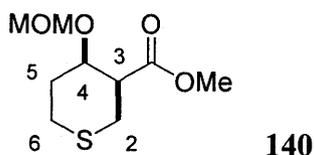
**IR**  $\nu_{\text{max}}$  3452, 1728  $\text{cm}^{-1}$ ;

**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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);

**$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_7\text{H}_{12}\text{O}_3\text{S}$  176.0507, found 176.0508 (EI).

**Methyl (3*S*\*, 4*R*\*)-tetrahydro-4-(methoxymethoxy)-2*H*-thiopyran-3-carboxylate (140).**



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*-Pr<sub>2</sub>EtN (7.4 mL, 5.5 g, 43 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0° 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<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with 1 M HCl (2 × 150 mL) and H<sub>2</sub>O (150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the titled MOM ether (4.75 g, quantitative) which was homogeneous by <sup>1</sup>H NMR and TLC and was used in the next step without further purification:

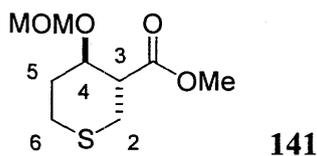
**IR**  $\nu_{\max}$  1738 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.65 (1H, d, *J* = 7 Hz), 4.60 (1H, d, *J* = 7 Hz), 4.37-4.33 (1H, m), 3.71 (3H, s), 3.33 (3H, s), 3.17 (1H, dd, *J* = 12, 13.5 Hz), 3.03-2.92 (1H, m), 2.77 (1H, ddd, *J* = 3, 3.5, 12 Hz), 2.61 (1H, ddd, *J* = 2, 3, 13.5 Hz), 2.38-2.25 (2H, m), 1.87-1.75 (1H, m);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  172.7, 95.9, 72.2, 55.8, 51.9, 48.1, 31.9, 23.7, 22.2;

**HRMS** *m/z* calcd for C<sub>9</sub>H<sub>16</sub>O<sub>4</sub>S 220.0769, found 220.0768 (EI).

**Methyl (3*R*\*, 4*R*\*)-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 <sup>1</sup>H NMR and TLC and was used in the next step without further purification.

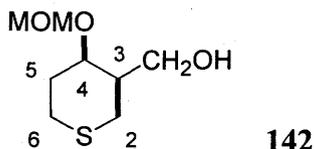
IR  $\nu_{\max}$  1736  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.69 (1H, d,  $J = 7$  Hz), 4.63 (1H, d,  $J = 7$  Hz), 3.80 (1H, ddd,  $J = 4, 9, 10$  Hz), 3.73 (3H, s), 3.34 (3H, s), 2.88-2.58 (5H, m), 2.42-2.32 (1H, m), 1.76 (1H, dddd,  $J = 4, 10, 10, 14$  Hz);

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  173.4, 95.7, 75.7, 55.7, 52.0, 50.2, 32.8, 29.7, 26.9;

HRMS  $m/z$  calcd for  $\text{C}_9\text{H}_{16}\text{O}_4\text{S}$  220.0769, found 220.0771 (EI).

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



Following General procedure A, a solution of cis ester **138** (2.423 g, 11.0 mmol) in THF\* was reduced with  $\text{LiAlH}_4$  in ether (50 mL) to give the alcohol **142** as a clear oil (1.899 g, 90%) which was homogeneous by  $^1\text{H}$  NMR and TLC and was used in the next step without further purification.

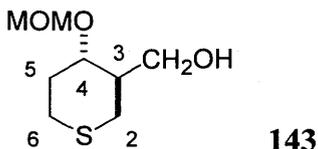
IR  $\nu_{\max}$  3426  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.67 (1H, d,  $J = 6.5$  Hz), 4.60 (1H, d,  $J = 6.5$  Hz), 3.95 (1H, br t,  $J = 2.5, 2.5$  Hz), 3.63 (1H, dd,  $J = 7.5, 11$  Hz), 3.61 (1H, dd,  $J = 7.5, 11$  Hz), 3.38 (3H, s), 2.96-2.71 (2H, m), 2.40-2.25 (3H, m), 2.18 (1H, dddd,  $J = 2, 4, 4, 13$  Hz), 2.03 (1H, m), 1.77 (1H, dddd,  $J = 2.5, 4, 11.5, 14$  Hz);

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  95.8, 73.2, 64.2, 56.1, 43.8, 31.3, 25.9, 23.6;

HRMS  $m/z$  calcd for  $\text{C}_8\text{H}_{16}\text{O}_3\text{S}$  192.0820, found 192.0820 (EI).

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



\* 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 LiAlH<sub>4</sub> in ether (20 mL) to give the alcohol **143** as a clear oil (832 mg, 94%) which was homogeneous by <sup>1</sup>H NMR and TLC and was used in the next step without further purification.

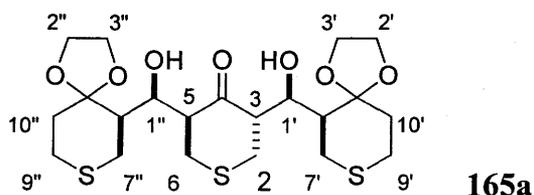
**IR**  $\nu_{\max}$  3451 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  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);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  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 C<sub>8</sub>H<sub>16</sub>O<sub>3</sub>S 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**.<sup>30</sup>

From Isomerization of **165d** (C<sub>s</sub> anti): See experimental procedure of compound **165b**.

**IR** (DRIFT)  $\nu_{\max}$  3512, 2919, 1706, 1426, 1259, 1110, 1050, 1040 cm<sup>-1</sup>.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  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, H<sub>2</sub>CO ×4), 3.29 (1H, d,  $J = 2$  Hz, HOC-1''), 3.25-3.18 (2H, m, HC-5, HC-6;  $J_{\text{HC-5-HC-6}} = 4$  Hz,  $J_{\text{HC-5-HC-6}} = 9.5$  Hz,  $J_{\text{HC-1''-HC-5}} = 9$  Hz),

3.02-2.87 (4H, m, HC-2, HC-6, HC-7', HC-7''), 2.87 (1H, d,  $J = 2$  Hz, HOC-1'), 2.86 (1H, ddd, 4, 5.5, 9.5 Hz;  $J_{\text{HC-2-HC-3}} = 4$  Hz,  $J_{\text{HC-2-HC-3}} = 5.5$  Hz,  $J_{\text{HC-1''-HC-5}} = 9.5$  Hz)

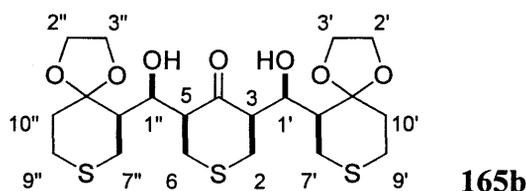
2.86-2.70 (4H, m, HC-2, HC-7'', HC-9', HC-9''), 2.65 (1H, ddd,  $J = 2.5, 3, 14$  Hz, HC-7'), 2.57-2.50 (2H, m, HC-9', HC-9''), 2.20-2.12 (3H, m, HC-6'', HC-10', HC-10''), 1.98 (1H, ddd,  $J = 1.5, 3, 11.5$  Hz, HC-6'), 1.78-1.70 (2H, m, HC-10', HC-10'').

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_2\text{O}$ ), 64.79 (t,  $\text{CH}_2\text{O}$ ), 64.53 (t,  $\text{CH}_2\text{O}$ ), 64.30 (t,  $\text{CH}_2\text{O}$ ), 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 ( $[\text{M}+1]^+$ , 17), 492 ( $[\text{M}]^+$ , 7), 475 (6), 413 (12), 338 (41), 282 (16), 189 (40), 99 (100).

HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{32}\text{O}_7\text{S}_3$  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**.<sup>30</sup>

From isomerization of **165d** ( $\text{C}_s$  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  $\text{CH}_2\text{Cl}_2$  ( $\times 3$ ). The organic extracts were combined, dried over  $\text{Na}_2\text{SO}_4$  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 CH<sub>2</sub>Cl<sub>2</sub>) gave **165b** (30 mg, 65%), titled compound **165b** (12 mg, 26%) and **165d** (4 mg, 8%).

From isomerization of **165d** (C<sub>s</sub> anti) in CH<sub>2</sub>Cl<sub>2</sub> : Aldol **165d** (73 mg, 0.159 mmol) was added to a solution of imidazole (408 mg, 6.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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 CH<sub>2</sub>Cl<sub>2</sub>) gave **165a** (38 mg, 52%), titled compound **165b** (14 mg, 19%) and **165d** (7 mg, 10%).

IR (DRIFT)  $\nu_{\max}$  3511, 2916, 1702, 1427, 1153, 1102, 1038, 734 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.57 (2H, ddd,  $J = 2.5, 4.5, 6.5$  Hz, HC-1', HC-1''), 4.09-3.96 (8H, m, H<sub>2</sub>CO  $\times 4$ ), 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 [ $J_{\text{HC-2-HC-3}} = 4.5, 11.5$  Hz]), 3.06 (2H, d,  $J = 2.5$  Hz, HO  $\times 2$ ), 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'').

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  213.92 (s, C-4), 109.89 (s  $\times 2$ , C-5', C-5''), 66.87 (d  $\times 2$ , C-1', C-1''), 64.61 (t  $\times 2$ , CH<sub>2</sub>O), 64.54 (t  $\times 2$ , CH<sub>2</sub>O), 57.82 (d  $\times 2$ , C-3, C-5), 46.60 (d  $\times 2$ , C-6', C-6''), 35.46 (t  $\times 2$ , C-10', C-10''), 34.26 (t  $\times 2$ , C-2, C-6), 27.54 (t  $\times 2$ , C-7', C-7''), 26.79 (t  $\times 2$ , C-9', C-9'').

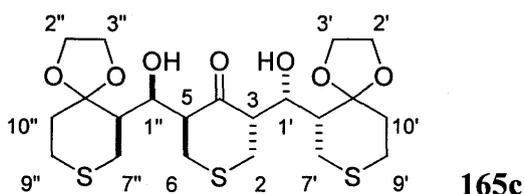
LRMS (EI),  $m/z$  (relative intensity): 492 ([M]<sup>+</sup>, 1), 188 (14), 159 (11), 132 (73), 100 (10), 99 (100), 86 (24), 55 (8).

HRMS  $m/z$  calcd for C<sub>21</sub>H<sub>32</sub>O<sub>7</sub>S<sub>3</sub> 492.1310, found 492.1311 (EI).

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\* **165d** (11 mg, 0.022 mmol) was added to a solution of imidazole (34 mg, 0.5 mmol) in CD<sub>3</sub>COCD<sub>3</sub> (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.

**(3S,5S)-rel-3,5-bis[(S)-(6R)-1,4-Dioxa-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**.<sup>30</sup>

From isomerization of **165e** ( $C_2$  anti) : See experimental procedure of compound **165f**.

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

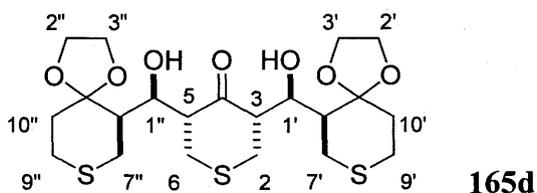
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.79 (2H, d,  $J = 9.5$  Hz, HC-1', HC-1''), 3.92-4.14 (8H, m,  $\text{H}_2\text{CO} \times 4$ ), 3.22-3.14 (2H, m, HC-3, HC-5), 3.05 (2H, br s, HO  $\times 2$ ), 3.01-2.88 (6H, m), 2.77 (2H, ddd,  $J = 2.5, 13, 13$  Hz), 2.69 (2H, ddd,  $J =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

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}+1]^+$ , 24), 492 ( $[\text{M}]^+$ , 9), 475 (7), 338 (52), 225 (26), 189 (49), 132 (12), 99 (100).

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

**(3S,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-4H-thiopyran-4-one (165d)**



First prepared by C. C. Man from aldol reaction of **125a** with **127a**.<sup>30</sup> NMR assignment and analysis this work.

IR (DRIFT)  $\nu_{\max}$ , 3518, 2918, 2888, 1698, 1426, 1261, 1101  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{H}_2\text{CO} \times 4$ ), 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''), 2.73-2.67 (4H, m,  $\text{H}_2\text{C-9'}$ ,  $\text{H}_2\text{C-9''}$ ), 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'').

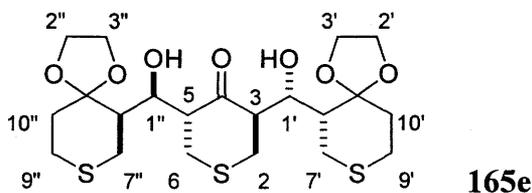
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  216.65 (s, C-4), 109.25 (s  $\times 2$ , C-5'), 69.29 (d  $\times 2$ , C-1'), 64.89 (t  $\times 2$ ,  $\text{CH}_2\text{O}$ ), 64.56 (t  $\times 2$ ,  $\text{CH}_2\text{O}$ ), 57.65 (d  $\times 2$ , C-3), 47.27 (d  $\times 2$ , C-6'), 36.33 (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 ( $[\text{M}+1]^+$ , 69), 475 (31), 305 (25), 199 (37), 189 (38), 99 (100), 67 (37).

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

Anal. Calcd for  $\text{C}_{21}\text{H}_{32}\text{O}_7\text{S}_3$ : C, 51.20; H, 6.55. Found: C, 51.29; H, 6.70.

**(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**.<sup>30</sup> Included here for completeness only.

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

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.65 (2H, br d,  $J = 8$  Hz, H-1', HC-1''), 4.15-3.90 (8H, m,  $\text{H}_2\text{CO} \times 4$ ), 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-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'').

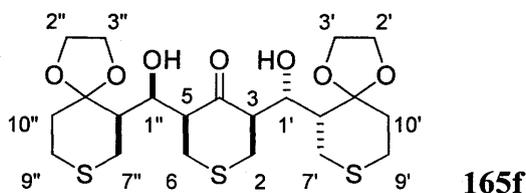
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  212.9 (s), 110.0 (s $\times$ 2), 68.7 (d  $\times$ 2), 65.0 (t  $\times$ 2), 64.6 (t  $\times$ 2), 55.0 (d  $\times$ 2), 47.2 (d  $\times$ 2), 36.4 (t  $\times$ 2), 33.9 (t  $\times$ 2), 26.8 (t  $\times$ 2), 26.7 (t  $\times$ 2).

LRMS (FAB),  $m/z$  (relative intensity): 493 ( $[\text{M}+1]^+$ , 17), 492

( $[\text{M}]^+$ , 6), 475 (4), 338 (27), 189 (25), 132 (10), 99 (100), 67 (23).

HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{32}\text{O}_7\text{S}_3$  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  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  ( $\times$ 4). The organic extracts were combined, dried over  $\text{Na}_2\text{SO}_4$  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  $\text{CH}_2\text{Cl}_2$ ; multiple elutions) gave **165c** (2 mg, 15%), the titled compound **165f** (6 mg, 44%) and **165e** (4 mg, 30%).\*

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

$^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  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,  $\text{H}_2\text{CO} \times 4$ ), 3.24-3.02 (9H, m,  $\text{H}_2\text{CO}$ , HC-2, HC-3, HC-5, HC-6, HC-7',  $\text{H}_2\text{C}-7''$ ), 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.

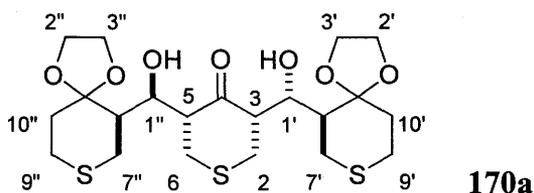
13.5 Hz, HC-7), 2.58 (1H, m,  $J = 4, 8, 13$  Hz, HC-9''), 2.52 (1H, ddd,  $J = 3.5, 3.5, 13$  Hz, HC-2 or HC-6), 2.49 (1H, ddd,  $J = 3, 10.5, 13.5$  Hz, HC-9'), 2.25-2.24 (2H, m, HC-9', HC-9''), 2.21 (1H, ddd,  $J = 3.5, 4, 9.5$  Hz, HC-6'), 2.16 (1H, ddd,  $J = 3.5, 7, 7.5$  Hz, HC-6''), 1.63 (1H, ddd,  $J = 3, 6, 13.5$  Hz, HC-10'), 1.48 (1H, ddd,  $J = 3.5, 10.5, 13.5$  Hz, HC-10'), 1.45-1.36 (2H, m, H<sub>2</sub>C-10''), 4.53 (1H, br d,  $J = 8.5$  Hz, HC-1'), 4.17-3.89 (9H, m, HC-1'', H<sub>2</sub>CO  $\times 4$ ), 3.33 (1H, ddd,  $J = 3.5, 4, 13.5$  Hz, HC-2), 3.27 (1H, ddd,  $J = 3.5, 3.5, 12$  Hz, HC-5), 3.21 (1H, dd,  $J = 12, 13$  Hz, HC-6), 3.10 (1H, d,  $J = 1$  Hz, HOC-1'), 3.09-2.50 (9H, m, HC-3, H<sub>2</sub>C-7', H<sub>2</sub>C-7'', H<sub>2</sub>C-9', H<sub>2</sub>C-9''), 2.97 (1H, d,  $J = 9.5$  Hz, HOC-1''), 2.91 (1H, ddd,  $J = 3, 3.5, 13$  Hz, HC-6), 2.85 (1H, dd,  $J = 11.5, 13.5$  Hz, HC-2), 2.22 (1H, ddd,  $J = 3, 7.5, 7.5$  Hz, HC-6''), 2.16-2.07 (2H, m, HC-6', HC-10' or HC-10''), 1.88 (1H, ddd,  $J = 3, 8.5, 13.5$  Hz, HC-10' or HC-10''), 1.78-1.71 (2H, m, HC-10', HC-10'').

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  215.52 (s, C-4), 110.25 (s, C-5'' or C-5'), 109.02 (s, C-5' or C-5''), 70.92 (d, C-1'), 66.86 (d, C-1''), 64.90 (t, CH<sub>2</sub>O), 64.84 (t, CH<sub>2</sub>O), 64.31 (t, CH<sub>2</sub>O), 63.96 (t, CH<sub>2</sub>O), 57.48 (d, C-5 or C-3), 57.00 (d, C-5 or C-3), 47.51 (d, C-6' or C-6''), 46.63 (d, C-6' or C-6''), 37.08 (t), 35.81 (t), 35.54 (t), 34.62 (t), 29.28 (t), 26.81 (t), 26.67 (t), 26.56 (t).

LRMS (EI),  $m/z$  (relative intensity): 492 ([M]<sup>+</sup>, 1), 304 (8), 188 (15), 159 (12), 132 (73), 99 (100), 86 (24), 55 (21).

HRMS  $m/z$  calcd for C<sub>21</sub>H<sub>32</sub>O<sub>7</sub>S<sub>3</sub> 492.1310, found 492.1310.

**(3S,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 (170a)**



From aldol reaction of **125a** and **128a** : TiCl<sub>4</sub> (24  $\mu$ L, 0.22 mmol) was added dropwise to a stirred solution of **128a** (60 mg, 0.20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) at -78 °C under argon. Upon addition of TiCl<sub>4</sub> a yellow globular slurry developed which turned

into a fine yellow suspension after 5 minutes of stirring at  $-78\text{ }^{\circ}\text{C}$ . The dry ice-acetone bath was replaced with an ice-water bath and the suspension was then stirred for 20 minutes at  $0\text{ }^{\circ}\text{C}$ . The yellow suspension was recooled to  $-78\text{ }^{\circ}\text{C}$  using a dry ice-acetone bath. After 10 minutes, *i*-Pr<sub>2</sub>EtN (78  $\mu\text{L}$ , 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  $0\text{ }^{\circ}\text{C}$  resulting in a deeper red solution. The mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and a solution of aldehyde **125a** (111 mg, 59 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was added dropwise over 10 seconds. The reaction mixture was stirred for 20 minutes at  $0\text{ }^{\circ}\text{C}$  (during this period the deep red solution turned light red) and then a mixture of MeOH:H<sub>2</sub>O (2:1, 2 mL) was added with vigorous stirring. After 10 seconds, NH<sub>4</sub>Cl (5 mL, 1 M) was added and over 2 minutes the mixture turned from light red to colourless. The mixture was diluted with distilled H<sub>2</sub>O and extracted with ethyl acetate ( $\times 3$ ). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> 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)  $\nu_{\text{max}}$  3508, 2914, 1697, 1426, 1106, 1044, 891, 731  $\text{cm}^{-1}$ .

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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, H<sub>2</sub>CO  $\times 4$ ), 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'),

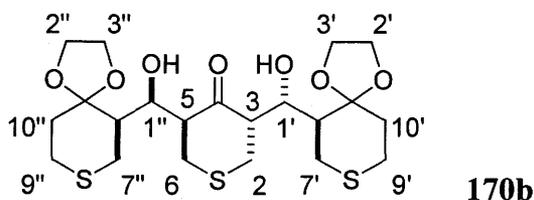
HC-9", HC-9"), 2.20 (1H, ddd,  $J = 5.5, 5.5, 14$  Hz, HC-10'), 2.20-2.14 (2H, m, HC-6', HC-6"), 1.96 (1H, ddd,  $J = 5, 5, 13.5$  Hz, HC-10"), 1.79 (1H, ddd,  $J = 6.5, 6.5, 14$  Hz, HC-10'), 1.72 (1H, ddd,  $J = 6.5, 6.5, 13.5$  Hz, HC-10"),  $\delta$  in  $C_6D_6$  (, ), 4.47 (1H, ddd,  $J = 2.5, 6, 6.5$  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<sub>2</sub>C-2', H<sub>2</sub>C-2", H<sub>2</sub>C-3', H<sub>2</sub>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<sub>2</sub>C-9', H<sub>2</sub>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').

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>O), 64.74 (t, CH<sub>2</sub>O), 64.45 (t, CH<sub>2</sub>O), 64.04 (t, CH<sub>2</sub>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'),  $\delta$  in  $C_6D_6$ , 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<sub>2</sub>O), 64.59 (t, CH<sub>2</sub>O), 64.43 (t, CH<sub>2</sub>O), 63.96 (t, CH<sub>2</sub>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"), 27.14 (t, C-9' or C-9"), 26.99 (t, C-9" or C-9).

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

HRMS  $m/z$  calcd for C<sub>21</sub>H<sub>32</sub>O<sub>7</sub>S<sub>3</sub> 492.1310, found 492.1321 (EI).

**(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 (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  $\text{CH}_2\text{Cl}_2$  (2.0ml). The reaction was stirred for 6 days at rt. The reaction was diluted with citric acid (30 mL, 0.1M) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $\times 3$ ). The organic extracts were combined, dried over  $\text{Na}_2\text{SO}_4$  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  $\text{CH}_2\text{Cl}_2$ ; 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, aldol **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  $\text{cm}^{-1}$ .

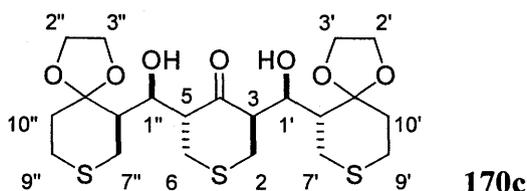
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.68 (1H, ddd,  $J = 1.5, 2.5, 9$  Hz, HC-1''), 4.36 (1H, ddd,  $J = 3.5, 4, 8$  Hz, HC-1'), 4.13-3.93 (9H, m, HOC-1'',  $\text{H}_2\text{CO} \times 4$ ), 3.39 (1H, dd,  $J = 10, 13.5$  Hz, HC-2), 3.33 (1H, dd,  $J = 5.5, 12.5$  Hz, HC-6), 3.23 (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'').

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_2\text{O}$ ), 64.89 (t,  $\text{CH}_2\text{O}$ ), 64.42 (t,  $\text{CH}_2\text{O}$ ), 64.26 (t,  $\text{CH}_2\text{O}$ ), 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''), 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 ( $[\text{M}]^+$ , 0.2), 188 (12), 159 (8), 132 (41), 115 (8), 99 (100), 86 (24), 55 (10).

HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{32}\text{O}_7\text{S}_3$  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  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  ( $\times 3$ ). The organic extracts were combined, dried over  $\text{Na}_2\text{SO}_4$  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)  $\nu_{\text{max}}$  3501, 2915, 1705, 1427, 1260, 1106, 1036, 733  $\text{cm}^{-1}$ .

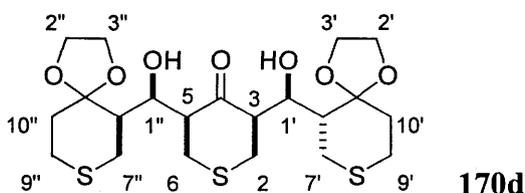
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.69 (1H, ddd,  $J = 2.5, 3.5, 8$  Hz, HC-1''), 4.56 (1H, br dd,  $J = 4.5, 7.5$  Hz, HC-1'), 4.13-3.94 (8H, m,  $\text{H}_2\text{CO}$ ), 3.88 (1H, br s, HOC-1'), 3.25 (1H, dd,  $J = 11.5, 13.5$  Hz, HC-2), 3.11 (1H, d,  $J = 3.5$  Hz, HOC-1''), 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,  $\text{H}_2\text{C-7'}$ , HC-7'',  $\text{H}_2\text{C-9'}$ , 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'').

$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_2\text{O}$ ), 64.86 (t,  $\text{CH}_2\text{O}$ ), 64.60 (t,  $\text{CH}_2\text{O}$ ), 64.20 (t,  $\text{CH}_2\text{O}$ ), 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-7'').

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

HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{32}\text{O}_7\text{S}_3$  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)  $\nu_{\text{max}}$  3508, 2916, 1704, 1427, 1263, 1108, 1039, 736  $\text{cm}^{-1}$ .

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{H}_2\text{CO} \times 4$ ), 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,  $J = 3.5,$

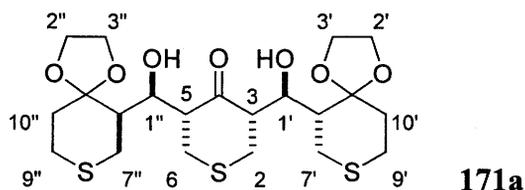
4.5, 13 Hz, HC-2), 3.04 (1H, ddd,  $J = 4.5, 7, 11.5$  Hz, HC-3), 3.04 (1H, ddd,  $J = 4.5, 6, 11.5$  Hz, HC-5), 2.95 (1H, dd,  $J = 11, 13.5$  Hz, HC-7''), 2.92 (1H, dd,  $J = 10, 13.5$  Hz, HC-7), 2.92 (1H, dd,  $J = 11.5, 13$  Hz, HC-6), 2.90 (1H, dd,  $J = 11.5, 13$  Hz, HC-2), 2.80-2.65 (4H, m, 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').

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_2\text{O}$ ), 64.42 (t,  $\text{CH}_2\text{O}$ ), 64.21 (t,  $\text{CH}_2\text{O}$ ), 63.51 (t,  $\text{CH}_2\text{O}$ ), 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 ( $[\text{M}]^+$ , 1), 188 (17), 133 (17), 100 (13), 99 (100), 86 (35), 55 (28).

HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{32}\text{O}_7\text{S}_3$  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** :  $\text{TiCl}_4$  (27  $\mu\text{L}$ , 0.25 mmol) was added dropwise to a stirred solution of **129a** aldol (69.4 mg, 0.228 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at  $-78$   $^\circ\text{C}$  under argon. Upon addition of  $\text{TiCl}_4$  a yellow globular slurry developed which turned into a fine yellow suspension after 5 minutes of stirring at  $-78$   $^\circ\text{C}$ . The dry ice-acetone bath was replaced with an ice-water bath and the suspension was then stirred for 20 minutes at  $0$   $^\circ\text{C}$ . The yellow suspension was recooled to  $-78$   $^\circ\text{C}$  using a dry ice-acetone bath. After 10 minutes,  $i\text{-Pr}_2\text{EtN}$  (91  $\mu\text{L}$ , 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<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>O (2:1, 2 mL) was added with vigorous stirring. After 10 seconds, NH<sub>4</sub>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<sub>2</sub>O and extracted with ethyl acetate (×3). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> 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<sup>-1</sup>.

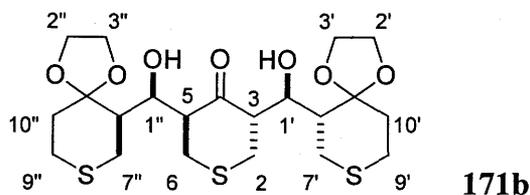
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.16 (1H, ddd,  $J = 4.5, 7, 8$  Hz, HC-1"), 4.10 (1H, ddd,  $J = 3.5, 4.5, 7.5$  Hz, HC-1'), 4.10-3.89 (8H, m, H<sub>2</sub>CO ×4), 3.82 (1H, d,  $J = 4.5$  Hz, HOC-1'), 3.28 (1H, dd,  $J = 11.5, 13$  Hz, HC-2), 3.23 (1H, ddd,  $J = 4.5, 4.5, 12$  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<sub>2</sub>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<sub>2</sub>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").

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>O), 64.67 (t, CH<sub>2</sub>O), 64.28 (t, CH<sub>2</sub>O), 64.06 (t, CH<sub>2</sub>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]<sup>+</sup>, 23), 161 (27), 99 (100), 83 (26), 71 (27), 69 (25), 57 (38), 55 (63).

**HRMS**  $m/z$  calcd for C<sub>21</sub>H<sub>33</sub>O<sub>7</sub>S<sub>3</sub> 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)  $\nu_{\max}$  3496, 2916, 1704, 1427, 1260, 1102, 1051, 948  $\text{cm}^{-1}$ .

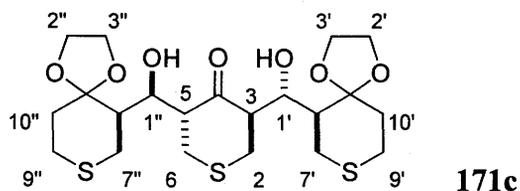
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.68 (1H, ddd,  $J = 1.5, 2.5, 9$  Hz, HC-1''), 4.36 (1H, ddd,  $J = 3.5, 4, 8$  Hz, HC-1'), 4.13-3.93 (9H, m, HOC-1'',  $\text{H}_2\text{CO} \times 4$ ), 3.39 (1H, dd,  $J = 10, 13.5$  Hz, HC-2), 3.33 (1H, dd,  $J = 5.5, 12.5$  Hz, HC-6), 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'').

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_2\text{O}$ ), 64.89 (t,  $\text{CH}_2\text{O}$ ), 64.42 (t,  $\text{CH}_2\text{O}$ ), 64.26 (t,  $\text{CH}_2\text{O}$ ), 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''), 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 ( $[\text{M}]^+$ , 0.2), 188 (12), 159 (8), 132 (41), 115 (8), 99 (100), 86 (24), 55 (10).

HRMS  $m/z$  calcd for  $C_{21}H_{32}O_7S_3$  492.1310, found 492.1316 (EI).

**(3R,5R)-rel-3-[(S)-(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 (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)  $\nu_{\max}$  3504, 2916, 1710, 1427, 1261, 1108, 1052, 734  $\text{cm}^{-1}$ .

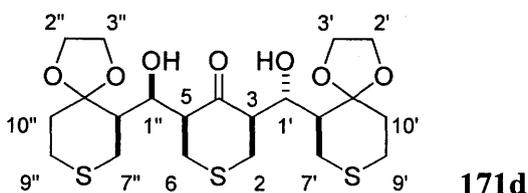
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.82 (1H, ddd,  $J = 0.5, 1, 9$  Hz, HC-1''), 4.23 (1H, ddd,  $J = 3.5, 4, 8.5$  Hz, HC-1'), 4.15-3.93 (8H, m,  $\text{H}_2\text{CO}$ ), 3.90 (1H, d,  $J = 3.5$  Hz, HOC-1'), 3.39 (1H, dd,  $J = 11, 13.5$  Hz, HC-2), 3.17 (1H, ddd,  $J = 4, 4.5, 11$  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'').

$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_2\text{O}$ ), 64.87 (t,  $\text{CH}_2\text{O}$ ), 64.54 (t,  $\text{CH}_2\text{O}$ ), 64.28 (t,  $\text{CH}_2\text{O}$ ), 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'').

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  $C_{21}H_{32}O_7S_3$  492.1310, found 492.1307.

**(3R,5S)-rel-3-[(S)-(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 (171d)**



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

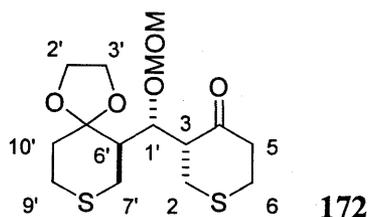
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.59 (1H, ddd,  $J = 2, 5, 5$  Hz, HC-1''), 4.15 (1H, ddd,  $J = 3.5, 3.5, 7.5$  Hz, HC-1'), 4.10-3.95 (8H, m,  $\text{H}_2\text{CO} \times 4$ ), 3.98 (1H, d,  $J = 3.5$  Hz, HOC-1'), 3.29 (1H, dd,  $J = 11.5, 13$  Hz, HC-2), 3.19 (1H, d,  $J = 2$  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'',  $\text{H}_2\text{C}-9'$ ,  $\text{H}_2\text{C}-9''$ ), 2.54 (1H, dd,  $J = 7, 13.5$  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'').

$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_2\text{O}$ ), 64.64 (t,  $\text{CH}_2\text{O}$ ), 64.57 (t,  $\text{CH}_2\text{O}$ ), 64.33 (t,  $\text{CH}_2\text{O}$ ), 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  $C_{21}H_{32}O_7S_3$  492.1310, found 492.1321 (EI).

**(3R)-rel-3-[(R)-(6R)-1,4-Dioxa-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 (1.432g) 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** (1.190g, 99%).

**IR** (DRIFT)  $\nu_{\max}$  2957, 1707, 1164, 1149, 1097, 1055, 1034, 894  $\text{cm}^{-1}$ .

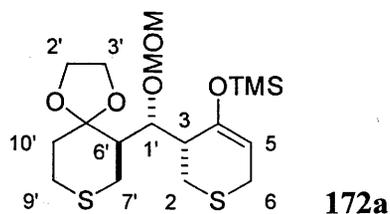
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.88 (1H, dd,  $J = 3, 3$  Hz, HC-1'), 4.69 (1H, d,  $J = 6.5$  Hz, HCO<sub>2</sub>), 4.63 (1H, d,  $J = 6.5$  Hz, HCO<sub>2</sub>), 3.97 (1H, m, H<sub>2</sub>CO), 3.90-3.82 (2H, m, H<sub>2</sub>CO), 3.77 (1H, m, H<sub>2</sub>CO), 3.36 (3H, s, H<sub>3</sub>CO), 3.30 (1H, ddd,  $J = 3, 5.5, 10.5$  Hz, HC-3), 3.02-2.87 (5H, m, H<sub>2</sub>C-2, H<sub>2</sub>C-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').

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  208.88 (s, C-4), 108.92 (s, C-5'), 97.52 (t, OCH<sub>2</sub>O), 71.77 (d, C-1'), 64.46 (t, CH<sub>2</sub>O), 64.23 (t, CH<sub>2</sub>O), 56.22 (q, CH<sub>3</sub>O), 55.78 (d, C-3), 50.88 (t, C-6'), 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 ( $[\text{M}]^+$ , 2), 286 (18), 224 (10), 159 (13), 133 (24), 132 (65), 99 (100), 55 (14).

**HRMS**  $m/z$  calcd for  $\text{C}_{15}\text{H}_{24}\text{O}_5\text{S}_2$  348.1065, found 348.1062.

**(3R)-rel-3-[(S)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]3,6-dihydro--2H-thiopyran-4-yloxy]-trimethylsilane**



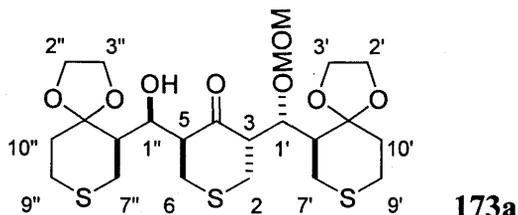
BuLi (2.7 mL, 4.0 mmol) in hexane was added dropwise over 4 minutes to a solution of *i*-Pr<sub>2</sub>NH (0.60 mL, 4.3 mmol) in THF (8 mL) at 0 °C. The solution was then stirred for a further 5 minutes at 0 °C and then cooled to -78 °C. A solution\* of ketone **172** (347 mg, 0.995 mmol) and TMSCl (1.26 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. Et<sub>3</sub>N (2.80 mL, 20 mmol) was added and the cooling bath was removed. After stirring for 1 minute, saturated NaHCO<sub>3</sub> (10 mL) was added and after 2 minutes, the mixture was diluted with distilled H<sub>2</sub>O (40 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×50 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give **172a** as an orange oil that solidified under vacuum (0.5 torr) (431 mg, 100%; 98% pure by <sup>1</sup>H NMR).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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, H<sub>2</sub>CO ×2), 3.28 (3H, s, H<sub>3</sub>CO), 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, (H<sub>3</sub>C)<sub>3</sub>Si).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 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 ×3).

\* Gentle heating to facilitate its dissolution. This solution was allowed to cool to rt before addition of TMSCl.

**(3S,5S)-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 (173a)**



From aldol reaction of **125a** and **172** (Ti enolate):  $\text{TiCl}_4$  (15  $\mu\text{L}$ , 0.137 mmol) was added dropwise over 5 seconds to a solution of ketone **172** (43.1 mg, 0.124 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at  $-78^\circ\text{C}$  (a chunky-globular yellow precipitate formed). The reaction was stirred for 1 minute and gave a fine yellow suspension. *i*- $\text{Pr}_2\text{EtN}$  (32  $\mu\text{L}$ , 0.19 mmol) was added dropwise over 5 seconds and the reaction was stirred for 1 h at  $-78^\circ\text{C}$ . Upon addition of *i*- $\text{Pr}_2\text{EtN}$  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  $\text{CH}_2\text{Cl}_2$  (0.5 mL) was added dropwise over 1 minute and the reaction was stirred for 3 h at  $-78^\circ\text{C}$  (the solution remained red during the 3 h).  $\text{MeOH}:\text{H}_2\text{O}$  (2:1, 2 mL) was added with vigorous stirring and the cooling bath was removed. After 10 seconds,  $\text{NH}_4\text{Cl}$  (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  $\text{H}_2\text{O}$  (40 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ 30 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  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  $\text{MeLi}$  in hexane (1.5M, 0.6 mL, 0.90 mmol) was added dropwise over 30 seconds to a stirred solution of enolsilane **172a** (370 mg, 0.88 mmol) and a spatula point of 1,10-phenanthroline in THF (3 mL) at  $0^\circ\text{C}$ . The resultant deep red solution was stirred for 5 minutes at  $0^\circ\text{C}$  and was then cooled to  $-78^\circ\text{C}$ . 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  $-78\text{ }^{\circ}\text{C}$ . 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  $\text{CH}_2\text{Cl}_2$  (4×40 mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  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)  $\nu_{\text{max}}$  3504, 2913, 1696, 1427, 1261, 1152, 1032, 894  $\text{cm}^{-1}$ .

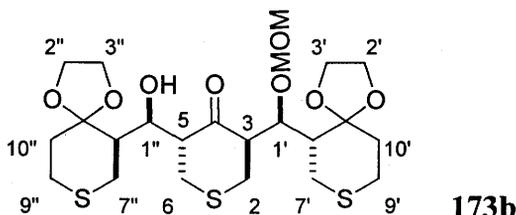
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.89 (1H, ddd,  $J = 1.5, 2, 9$  Hz, HC-1"), 4.71 (1H, d,  $J = 6.5$  Hz, HCO2), 4.69 (1H, dd,  $J = 3, 3$  Hz, HC-1'), 4.64 (1H, d,  $J = 6.5$  Hz, HCO2), 4.14-3.95 (6H, m, HCO ×6), 3.92 (1H, ddd,  $J = 7, 7, 7.5$  Hz, HCO), 3.87 (1H, ddd,  $J = 7, 7.5, 7.5$  Hz, HCO), 3.36 (3H, s,  $\text{H}_3\text{CO}$ ), 3.25 (1H, d,  $J = 1.5$  Hz, HOC-1"), 3.15-2.92 (6H, m,  $\text{H}_2\text{C}$ -2,  $\text{H}_2\text{C}$ -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").

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  210.56 (s, C-4), 110.27 (s, C-5"), 108.90 (s, C-5'), 97.96 (t,  $\text{OCH}_2\text{O}$ ), 73.81 (d, C-1'), 66.47 (d, C-1"), 64.95 (t,  $\text{CH}_2\text{O}$ ), 64.68 (t,  $\text{CH}_2\text{O}$ ), 64.43 (t,  $\text{CH}_2\text{O}$ ), 64.11 (t,  $\text{CH}_2\text{O}$ ), 56.35 (q,  $\text{CH}_3\text{O}$ ), 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** (EI),  $m/z$  (relative intensity): 536 ( $[\text{M}]^+$ , 1), 474 (7), 412 (5), 286 (8), 100 (11), 99 (100), 86 (15), 55 (19).

**HRMS**  $m/z$  calcd for  $\text{C}_{23}\text{H}_{36}\text{O}_8\text{S}_3$  536.1572, found 536.1579 (EI).

**(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  $\text{cm}^{-1}$ .

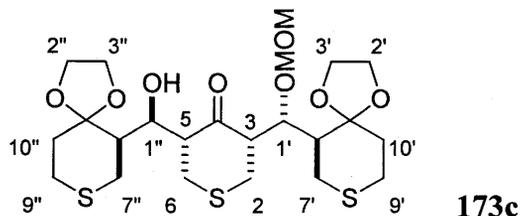
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.90 (1H, ddd,  $J = 3, 4, 9$  Hz, HC-1''), 4.79 (1H, d,  $J = 6.5$  Hz, HCO2), 4.71 (1H, dd,  $J = 2, 3$  Hz, HC-1'), 4.67 (1H, d,  $J = 6.5$  Hz, HCO2), 4.17-3.92 (6H, m, HCO  $\times 6$ ), 3.85-3.77 (2H, m, HCO  $\times 2$ ), 3.55 (1H, ddd,  $J = 2, 5, 11$  Hz, HC-3), 3.38 (3H, s,  $\text{H}_3\text{CO}$ ), 3.06 (1H, dd,  $J = 11, 14$  Hz, HC-2), 3.05 (1H, dd,  $J = 4.5, 14$  Hz, HC-6), 3.01-2.93 (3H, m, HC-2, HC-7', HC-7''), 2.99 (1H, d,  $J = 3$  Hz, HOC-1''), 2.89 (1H, ddd,  $J = 2.5, 11, 13$  Hz, HC-9''), 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), 2.65 (1H, br d,  $J = 12$  Hz, HC-7''), 2.58 (1H, br d,  $J = 13.5$  Hz, HC-9''), 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'), 2.05 (1H, ddd,  $J = 3.5, 4, 11$  Hz, HC-6''), 1.77 (1H, ddd,  $J = 3.5, 11, 14$  Hz, HC-10''), 1.74 (1H, ddd,  $J = 3.5, 11, 12$  Hz, HC-10').

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  210.08 (s, C-4), 110.18 (s, C-5''), 108.86 (s, C-5'), 98.07 (t,  $\text{OCH}_2\text{O}$ ), 73.26 (d, C-1'), 68.84 (d, C-1''), 65.07 (t,  $\text{CH}_2\text{O}$ ), 64.94 (t,  $\text{CH}_2\text{O}$ ), 64.57 (t,  $\text{CH}_2\text{O}$ ), 64.32 (t,  $\text{CH}_2\text{O}$ ), 56.31 (q,  $\text{CH}_3\text{O}$ ), 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 ( $[\text{M}]^+$ , 1), 286 (11), 159 (9), 133 (24), 132 (62), 99 (100), 86 (15), 55 (12).

HRMS  $m/z$  calcd for  $C_{23}H_{36}O_8S_3$  536.1572, found 536.1581 (EI).

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



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

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

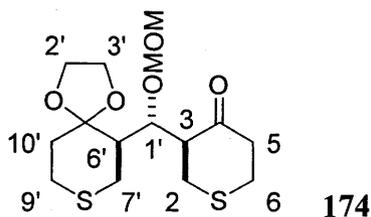
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.75 (1H, d,  $J = 6.5$  Hz, HCO2), 4.68 (1H, dd,  $J = 3, 3$  Hz, HC-1'), 4.66 (1H, d,  $J = 6.5$  Hz, HCO2), 4.24 (1H, ddd,  $J = 4.5, 5.5, 6.5$  Hz, HC-1''), 4.07-3.89 (6H, m, HCO  $\times 6$ ), 3.86-3.73 (2H, m, HCO  $\times 2$ ), 3.56 (1H, ddd,  $J = 3, 4.5, 12$  Hz, HC-3), 3.39 (3H, s,  $\text{H}_3\text{CO}$ ), 3.12 (1H, d,  $J = 5.5$  Hz, HOC-1''), 3.11 (1H, ddd,  $J = 5, 6.5, 11.5$  Hz, HC-5), 3.05-2.73 (8H, m,  $\text{H}_2\text{C}-2, \text{H}_2\text{C}-6, \text{HC}-7', \text{HC}-7'', \text{HC}-9', \text{HC}-9''$ ), 2.55 (1H, m, HC-9''), 2.50 (1H, m, HC-9'), 2.39 (1H, ddd,  $J = 3, 3.5, 12$  Hz, HC-6'), 2.09 (1H, ddd,  $J = 3, 5, 13.5$  Hz, HC-10''), 2.08-2.01 (2H, m, HC-6'', HC-10'), 1.72 (1H, ddd,  $J = 3.5, 13, 13$  Hz, HC-10'), 1.68 (1H, ddd,  $J = 3.5, 12, 13.5$  Hz, HC-10'').

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  213.06 (s, C-4), 109.71 (s, C-5''), 108.91 (s, C-5'), 97.40 (t,  $\text{OCH}_2\text{O}$ ), 71.85 (d, C-1'), 69.01 (d, C-1''), 64.64 (t,  $\text{CH}_2\text{O}$ ), 64.64 (t,  $\text{CH}_2\text{O}$ ), 64.62 (t,  $\text{CH}_2\text{O}$ ), 64.23 (t,  $\text{CH}_2\text{O}$ ), 57.92 (d, C-5), 57.41 (d, C-3), 56.32 (q,  $\text{CH}_3\text{O}$ ), 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 ( $[\text{M}+1]^+$ , 23), 507 (15), 506 (23), 505 (87), 475 (26), 315 (11), 132 (11), 99 (100).

HRMS  $m/z$  calcd for  $C_{23}H_{37}O_8S_3$  537.1651 (M+H), found 537.1654 (FAB).

**(3S)-rel-3-[(R)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (174)**



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

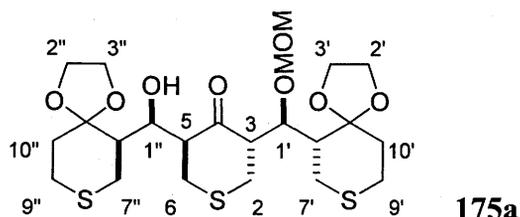
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.78 (1H, d,  $J = 7$  Hz, HCO2), 4.58 (1H, d,  $J = 7$  Hz, HCO2), 4.57 (1H, dd,  $J = 2, 8$  Hz, HC-1'), 4.12-4.02 (3H, m,  $\text{H}_2\text{CO}$ ), 3.91 (1H, m,  $\text{H}_2\text{CO}$ ), 3.13 (1H, ddd,  $J = 1.5, 5.5, 13.5$  Hz, HC-2), 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), 2.93-2.91 (2H, br s,  $\text{H}_2\text{C}-6$ ), 2.89-2.76 (3H, m,  $\text{H}_2\text{C}-7'$ , HC-9'), 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').

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  209.38 (s, C-4), 108.43 (s, C-5'), 96.67 (t,  $\text{OCH}_2\text{O}$ ), 76.42 (d, C-1'), 64.63 (t,  $\text{CH}_2\text{O}$ ), 64.35 (t,  $\text{CH}_2\text{O}$ ), 56.47 (q,  $\text{CH}_3\text{O}$ ), 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** (EI),  $m/z$  (relative intensity): 348 ( $[\text{M}]^+$ , 3), 286 (18), 159 (14), 133 (25), 132 (66), 99 (100), 86 (12), 55 (19).

**HRMS**  $m/z$  calcd for  $\text{C}_{15}\text{H}_{24}\text{O}_5\text{S}_2$  348.1065, found 348.1067.

**(3*S*,5*S*)-rel-3-[(*R*)-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*S*)-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-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  $\text{cm}^{-1}$ .

**$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{H}_2\text{CO} \times 4$ ), 3.38 (3H, s,  $\text{H}_3\text{CO}$ ), 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,  $\text{H}_2\text{C}-7'$ ,  $\text{H}_2\text{C}-7''$ , 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  $\text{C}_6\text{D}_6$  (, ), 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,  $J = 7, 7, 7$  Hz, HCO), 3.54 (1H, ddd,  $J = 5.5, 7, 7$  Hz, HCO), 3.48-2.95 (8H, m, HCO  $\times 6$ ,  $\text{H}_2\text{C}-6$ ), 3.32 (1H, ddd,  $J = 4.5, 7.5, 10.5$  Hz, HC-5), 3.24 (3H, s,  $\text{H}_3\text{CO}$ ), 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,  $J =$

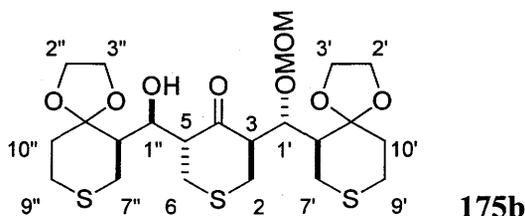
13.5 Hz, HC-9''), 2.18 (1H, br d,  $J = 13.5$  Hz, HC-9'), 1.74-1.67 (2H, m, HC-10', HC-10''), 1.62 (1H, ddd,  $J = 3.5, 12.5, 13$  Hz, HC-10'), 1.53 (1H, ddd,  $J = 3.5, 11, 14.5$  Hz, HC-10'').

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  211.21 (s, C-4), 110.34 (s, C-5''), 108.65 (s, C-5'), 97.18 (t,  $\text{OCH}_2\text{O}$ ), 76.92 (d, C-1'), 67.04 (d, C-1''), 64.86 (t,  $\text{CH}_2\text{O}$ ), 64.69 (t,  $\text{CH}_2\text{O}$ ), 64.34 (t,  $\text{CH}_2\text{O}$ ), 64.31 (t,  $\text{CH}_2\text{O}$ ), 56.06 (q,  $\text{CH}_3\text{O}$ ), 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 (EI),  $m/z$  (relative intensity): 536 ( $[\text{M}]^+$ , 1), 286 (11), 159 (14), 133 (21), 132 (57), 99 (100), 86 (18), 55 (16).

HRMS  $m/z$  calcd for  $\text{C}_{23}\text{H}_{36}\text{O}_8\text{S}_3$  536.1572, found 536.1566 (EI).

**(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**.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.73 (1H, d,  $J = 6.5$  Hz,  $\text{HCO}_2$ ), 4.70 (1H, d,  $J = 6.5$  Hz,  $\text{HCO}_2$ ), 4.50-4.45 (2H, m, HC-1', HC-1''), 4.13-3.90 (8H, m,  $\text{H}_2\text{CO} \times 4$ ), 3.39 (3H, s,  $\text{H}_3\text{CO}$ ), 3.26-3.19 (2H, m, HC-2, HC-3), 3.17 (1H, d,  $J = 4.5$  Hz,  $\text{HOC-1''}$ ), 3.05 (1H, ddd,  $J = 4.5, 7, 9$  Hz, HC-5), 3.03 (1H, dd,  $J = 11.5, 14$  Hz, HC-7''), 2.96-2.73 (7H, m, HC-2,  $\text{H}_2\text{C-6, HC-7', HC-7', HC-9', HC-9''}$ ), 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''),  $\delta$  in  $\text{C}_6\text{D}_6$  (, ), 4.72 (1H, d,  $J = 6.5$  Hz,  $\text{HCO}_2$ ), 4.70 (1H, d,  $J = 6.5$  Hz,  $\text{HCO}_2$ ), 4.56 (1H, ddd,  $J = 3, 5.5, 7$

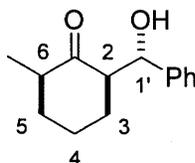
Hz, HC-1''), 4.52 (1H, dd,  $J = 2.5, 7$  Hz, HC-1'), 3.60-3.20 (8H, m, H<sub>2</sub>CO × 2), 3.33 (1H, ddd,  $J = 4.5, 7, 7$  Hz, HC-3), 3.25-3.17 (1H, m, HC-7''), 3.24 (1H, d,  $J = 5.5$  Hz, HOC-1''), 3.23 (3H, s, H<sub>3</sub>CO), 3.11 (1H, ddd,  $J = 5, 7, 9$  Hz, HC-5), 3.10-3.01 (2H, m, HC-2, 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<sub>2</sub>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'').

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  211.74 (s, C-4), 109.92 (s, C-5''), 108.67 (s, C-5'), 97.96 (t, OCH<sub>2</sub>O), 77.99 (d, C-1'), 68.83 (d, C-1''), 65.08 (t, CH<sub>2</sub>O), 64.71 (t, CH<sub>2</sub>O), 64.53 (t, CH<sub>2</sub>O), 64.29 (t, CH<sub>2</sub>O), 56.48 (q, CH<sub>3</sub>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''),  $\delta$  in C<sub>6</sub>D<sub>6</sub>, 211.15 (s, C-4), 110.35 (s, C-5''), 109.19 (s, C-5'), 98.55 (t, OCH<sub>2</sub>O), 78.98 (d, C-1'), 69.87 (d, C-1''), 65.04 (t, CH<sub>2</sub>O), 64.66 (t, CH<sub>2</sub>O), 64.51 (t, CH<sub>2</sub>O), 64.17 (t, CH<sub>2</sub>O), 56.25 (q, CH<sub>3</sub>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]<sup>+</sup>, 1), 286 (9), 159 (11), 133 (15), 132 (50), 99 (100), 86 (18), 55 (21).

HRMS  $m/z$  calcd for C<sub>23</sub>H<sub>36</sub>O<sub>8</sub>S<sub>3</sub> 536.1572, found 536.1576 (EI).

**(2R,6R)-rel-2-[(S)-Hydroxyphenylmethyl]-6-methylcyclohexanone (210ac)**



**210ac**

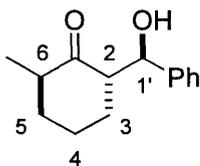
BuLi (4.0 mL, 10 mmol, 2.5 M) in hexane was added dropwise over 5 minutes to a solution of *i*-Pr<sub>2</sub>NH (1.5 mL, 11 mmol) in THF (10 mL) at 0 °C. The solution was stirred for a further 5 minutes at 0 °C and then cooled to -78 °C. A solution of 2-

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  $\text{NH}_4\text{Cl}$  (20 mL, 0.1 M) with vigorous stirring. The mixture was diluted with distilled  $\text{H}_2\text{O}$  (60 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3×40 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  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  $^1\text{H}$  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  $^1\text{H}$  NMR), the titled compound **210ac** (173 mg, 16%; 98% diastereomeric purity by  $^1\text{H}$  NMR), **210at** (336 mg, 31%; 95% diastereomeric purity by  $^1\text{H}$  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  $\text{CH}_2\text{Cl}_2$ ) to give samples with >99% diastereomeric purity by  $^1\text{H}$  NMR.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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, ddddd,  $J = 3, 3, 3, 6, 13$  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,  $\text{H}_3\text{C}$ ).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_3$ ).

**(2S,6R)-rel-2-[(R)-Hydroxyphenylmethyl]-6-methylcyclohexanone (210at)**



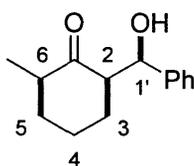
**210at**

For synthesis and isolation see experimental procedure for compound **210ac**.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.39-7.28 (5H, m, ArH), 4.86 (1H, dd, *J* = 3, 9.5 Hz, HC-1'), 3.42 (1H, d, *J* = 3 Hz, HO), 2.76 (1H, ddd, *J* = 5.5, 9.5, 9.5 Hz, HC-2), 2.70 (1H, ddq, *J* = 5, 5.5, 7 Hz, HC-6), 1.96 (1H, m, HC-5), 1.74-1.63 (3H, m, HC-4, HC-4, HC-5), 1.55 (1H, m, HC-3), 1.37 (1H, m, HC-3), 1.21 (3H, d, *J* = 7 Hz, H<sub>3</sub>C).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 218.16 (s, C-1), 141.51 (s, Ar), 128.73 (d ×2, Ar), 128.32 (d, Ar), 127.19 (d ×2, Ar), 75.01 (d, C-1'), 54.88 (d, C-2), 44.48 (d, C-6), 34.23 (t, C-5), 30.09 (t, C-3), 20.26 (t, C-4), 16.47 (q, CH<sub>3</sub>).

**(2R,6R)-rel-2-[(R)-Hydroxyphenylmethyl]-6-methylcyclohexanone (210sc)**



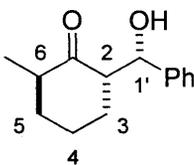
**210sc**

For synthesis and isolation see experimental procedure for compound **210ac**.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.37-7.23 (5H, m, ArH), 5.38 (1H, dd, *J* = 2.5, 3 Hz, HC-1'), 3.15 (1H, d, *J* = 3 Hz, HO), 2.61 (1H, dddd, *J* = 1.5, 2.5, 6.5, 12.5 Hz, HC-2), 2.50 (1H, dddq, *J* = 1.5, 5.5, 12.5, 6.5 Hz, HC-6), 2.12 (1H, ddddd, *J* = 2.5, 2.5, 3.5, 5.5, 13 Hz, HC-5), 1.86-1.75 (2H, m, HC-3, HC-4), 1.74 (1H, dddd, *J* = 3.5, 12.5, 12.5, 13 Hz, HC-3), 1.60 (1H, ddddd, *J* = 3.5, 4.5, 12.5, 12.5, 13 Hz, HC-4), 1.40 (1H, dddd, *J* = 3.5, 12.5, 12.5, 13 Hz, HC-5), 1.06 (3H, d, *J* = 6.5 Hz, H<sub>3</sub>C).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 216.76 (s, C-1), 141.81 (s, Ar), 128.36 (d ×2, Ar), 127.15 (d, Ar), 125.96 (d ×2, Ar), 70.97 (d, C-1'), 57.43 (d, C-2), 46.34 (d, C-6), 37.65 (t, C-5), 27.05 (t, C-3), 25.13 (t, C-4), 14.50 (q, CH<sub>3</sub>).

**(2S,6R)-rel-2-[(S)-Hydroxyphenylmethyl]-6-methylcyclohexanone (210st)**



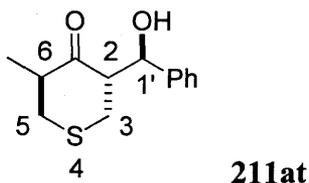
**210st**

For synthesis and isolation see experimental procedure for compound **210ac**.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 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<sub>3</sub>C).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 217.96 (s, C-1), 141.85 (d, Ar), 128.45 (d ×2, Ar), 127.41 (d, Ar), 126.07 (d ×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<sub>3</sub>).

**(3*S*,6*S*)-rel-Tetrahydro-3-[(*R*)-hydroxyphenylmethyl]-5-methyl-4*H*-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 μL, 2.26 mmol) upon workup gave a light yellow oily 1 : 2.6 : 1.5 mixture of **211st**, **211at**, **211ac**, respectively as determined by <sup>1</sup>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<sub>2</sub>Cl<sub>2</sub>/hexane (1:2, 1.5 mL). Upon cooling to 0 °C crystals of the titled compound **211at** (43 mg) were obtained.

IR (DRIFT) ν<sub>max</sub> 3445, 2912, 1706, 1454, 1039, 1024, 768, 701 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 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,

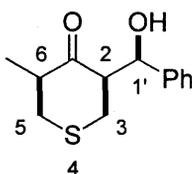
$J = 4, 14$  Hz, HC-2), 2.70 (1H, dd,  $J = 9, 13$  Hz, HC-6), 2.46 (1H, ddd,  $J = 2, 6.5, 14$  Hz, HC-2), 1.27 (3H, d,  $J = 6.5$  Hz,  $H_3C$ ).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_3$ ).

LRMS (EI),  $m/z$  (relative intensity): 236 ( $[\text{M}]^+$ , 1), 130 (100), 129 (26), 107 (36), 97 (39), 87 (33), 79 (27), 77 (30).

HRMS  $m/z$  calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$  236.0871, found 236.0869 (EI).

**(3R,6S)-rel-Tetrahydro-3-[(R)-hydroxyphenylmethyl]-5-methyl-4H-thiopyran-4-one (211sc)**



**211sc**

A 4.4:1:7.2 mixture of **211st**, **211at** and **211ac** (37.6 mg)<sup>\*</sup>, respectively was added to a solution of imidazole (109 mg, 1.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (3 $\times$ 20 mL). The organic extracts were combined, dried over  $\text{Na}_2\text{SO}_4$  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  $^1\text{H}$  NMR. Fractionation by PTLC (2% MeOH in  $\text{CH}_2\text{Cl}_2$ ) gave **211sc** (10.1 mg, 27%), **211at** (10.8 mg, 29%), **211st** (7.1 mg, 19%) and **211ac** (9.5 mg, 25%).<sup>†</sup>

IR (DRIFT)  $\nu_{\text{max}}$  3532, 2971, 2929, 1706, 1451, 1070, 1016, 703  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39-7.25 (5H, m, ArH), 5.38 (1H, br dd,  $J = 1.5, 3$  Hz, HC-1'), 3.12 (1H, d,  $J = 1.5$  Hz, HO), 3.07 (1H, dd,  $J = 12, 12.5$  Hz, HC-2), 3.01 (1H, ddd,  $J = 3, 3.5, 12$  Hz, HC-3), 2.92 (1H, ddq,  $J = 5, 12, 6.5$  Hz, HC-5), 2.88 (1H, ddd,  $J$

<sup>\*</sup> See experimental procedure for compound **211at** for the origin of this mixture.

<sup>†</sup> Aldols are reported in order from higher to lower  $R_f$ .

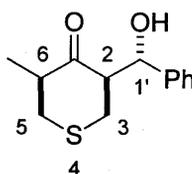
= 3, 5, 13 Hz, HC-6), 2.73 (1H, dd,  $J = 12, 13$  Hz, HC-6), 2.68 (1H, ddd,  $J = 3, 3.5, 12.5$  Hz, HC-2), 1.14 (3H, d,  $J = 6.5$  Hz,  $H_3C$ ).

$^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  214.12 (s, C-4), 140.98 (s, Ar), 128.61 (d  $\times 2$ , Ar), 127.56 (d, Ar), 125.94 (d  $\times 2$ , 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  $C_{13}H_{16}O_2S$  236.0871, found 236.0875 (EI).

**(3R,6S)-rel-Tetrahydro-3-[(S)-hydroxyphenylmethyl]-5-methyl-4H-thiopyran-4-one (211ac)**



**211ac**

For synthesis and isolation see experimental procedure for compound **211sc**.

IR (DRIFT)  $\nu_{max}$  3524, 2974, 2904, 1695, 1453, 1290, 1050, 701  $cm^{-1}$ .

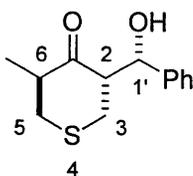
$^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.40-7.30 (5H, m, ArH), 4.86 (1H, dd,  $J = 3.5, 8.5$  Hz, HC-1'), 3.54 (1H, d,  $J = 3.5$  Hz, HO), 3.09 (1H, ddd,  $J = 4.5, 8.5, 12.5$  Hz, HC-3), 2.91 (1H, ddq,  $J = 4.5, 13, 6.5$  Hz, HC-5), 2.90 (1H, ddd,  $J = 3, 4.5, 14.5$  Hz, HC-6), 2.73 (1H, dd,  $J = 13, 14.5$  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,  $H_3C$ ).

$^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  214.19 (s, C-4), 140.46 (s, Ar), 128.87 (d  $\times 2$ , Ar), 128.48 (d, Ar), 127.20 (d  $\times 2$ , 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  $C_{13}H_{16}O_2S$  236.0871, found 236.0874 (EI).

**(3S,6S)-rel-Tetrahydro-3-[(S)-hydroxyphenylmethyl]-5-methyl-4H-thiopyran-4-one (211st)**



**211st**

For synthesis and isolation see experimental procedure for compound **211st**.

IR (DRIFT)  $\nu_{\max}$  3389, 2920, 1701, 1452, 1036, 1025, 766, 701  $\text{cm}^{-1}$ .

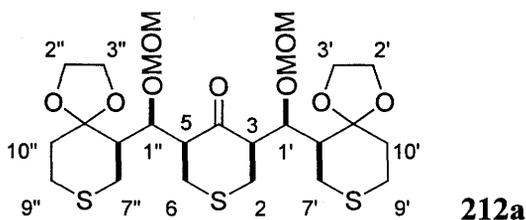
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41-7.27 (5H, m, ArH), 5.43 (1H, dd,  $J = 4, 4$  Hz, HC-1'), 3.13 (1H, ddd,  $J = 1, 9.5, 13$  Hz, HC-2), 3.07 (1H, ddd,  $J = 1, 4.5, 13.5$  Hz, HC-6), 3.07 (1H, ddd,  $J = 4, 4, 9.5$  Hz, HC-3), 2.89 (1H, ddq,  $J = 4.5, 7, 7$  Hz, HC-5), 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,  $\text{H}_3\text{C}$ ).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_3$ ).

LRMS (EI),  $m/z$  (relative intensity): 236 ( $[\text{M}]^+$ , 3), 130 (100), 107 (40), 97 (33), 88 (38), 79 (60), 77 (57), 55 (33).

HRMS  $m/z$  calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$  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)**



**212a**

Following General procedure M for MOM protection, after 4 days the substrate **165b** aldol (15 mg, 0.031 mmol) gave a 4:1 mixture of **212a** and **213a**, respectively. The

mixture was fractionated by PTLC (2% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) 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)  $\nu_{\text{max}}$  2915, 1708, 1427, 1261, 1155, 1103, 1032, 892 cm<sup>-1</sup>.

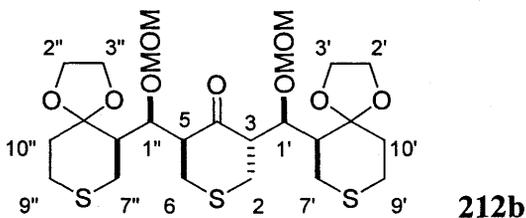
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.66 (2H, d,  $J = 6$  Hz, HCO<sub>2</sub>  $\times 2$ ), 4.63 (2H, d,  $J = 6$  Hz, HCO<sub>2</sub>  $\times 2$ ), 4.55 (2H, dd,  $J = 3, 6.5$  Hz, HC-1', HC-1''), 4.07-3.84 (8H, m, H<sub>2</sub>CO  $\times 4$ ), 3.35 (6H, s, H<sub>3</sub>CO  $\times 2$ ), 3.08 (2H, ddd,  $J = 3, 5.5, 9$  Hz, HC-3, HC-5), 3.01-2.94 (4H, m, H<sub>2</sub>C-2, H<sub>2</sub>C-6), 2.91-2.82 (4H, m, H<sub>2</sub>C-7', H<sub>2</sub>C-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'').

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  208.33 (s, C-4), 109.18 (s  $\times 2$ , C-5', C-5''), 98.60 (t  $\times 2$ , OCH<sub>2</sub>O), 72.26 (d  $\times 2$ , C-1', C-1''), 64.80 (t  $\times 2$ , CH<sub>2</sub>O), 64.55 (t  $\times 2$ , CH<sub>2</sub>O), 59.79 (d  $\times 2$ , C-3, C-5), 56.78 (q  $\times 2$ , CH<sub>3</sub>O), 49.44 (d  $\times 2$ , C-6', C-6''), 35.96 (t  $\times 2$ , C-10', C-10''), 31.17 (t  $\times 2$ , C-2, C-6), 29.10 (t  $\times 2$ , C-7', C-7''), 26.82 (t  $\times 2$ , C-9', C-9'').

LRMS (EI),  $m/z$  (relative intensity): 580 ([M]<sup>+</sup>, 1), 518 (9), 133 (30), 132 (69), 100 (9), 99 (100), 86 (13), 55 (12).

HRMS  $m/z$  calcd for C<sub>25</sub>H<sub>40</sub>O<sub>9</sub>S<sub>3</sub> 580.1834, found 580.1831 (EI).

**(3S,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 (212b)**



Following General procedure M for MOM protection but using 20 equiv of MOMCl and 30 equiv *i*-Pr<sub>2</sub>EtN, 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)  $\nu_{\max}$  2914, 1708, 1428, 1261, 1153, 1097, 1032, 890  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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, , HC-2', HC-2", HC-3', HC-3"), 3.37 (3H, s,  $\text{H}_3\text{COCOC-1}''$ ), 3.36 (3H, s,  $\text{H}_3\text{COCOC-1}'$ ), 3.00 (1H, ddd,  $J = 4.5, 5.5, 6$  Hz, HC-5), 3.13-2.95 (5H, ,  $\text{H}_2\text{C-2, HC-3, HC-6, HC-7}$ ), 2.91-2.69 (6H, , HC-6, HC-7',  $\text{H}_2\text{C-7}''$ , HC-9', HC-9"), 2.56-2.48 (2H, , HC-9', HC-9"), 2.28 (1H, ddd,  $J = 3.5, 4, 11$  Hz, HC-6'), 2.15-2.09 (1H, , 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').

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  208.72 (s, C-4), 109.07 (s, C-5'), 108.80 (s, C-5"), 98.41 (t,  $\text{CH}_2\text{OC-1}''$ ), 97.28 (t,  $\text{CH}_2\text{OC-1}'$ ), 74.55 (d, C-1'), 72.30 (d, C-1"), 64.82 (t,  $\text{CH}_2\text{O}$ ), 64.62 (t,  $\text{CH}_2\text{O}$ ), 64.59 (t,  $\text{CH}_2\text{O}$ ), 64.58 (t,  $\text{CH}_2\text{O}$ ), 57.49 (d, C-3), 57.03 (d, C-5), 56.82 (q,  $\text{CH}_3\text{OCOC-1}''$ ), 56.44 (q,  $\text{CH}_3\text{OCOC-1}'$ ), 49.75 (d, C-6'), 49.04 (d, C-6"), 36.11 (t, C-10"), 35.98 (t, C-10'), 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').

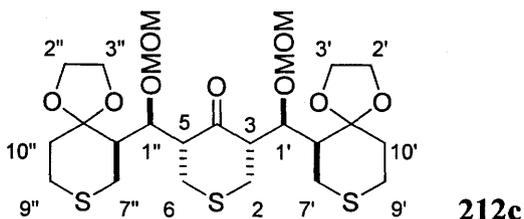
**LRMS** (EI),  $m/z$  (relative intensity): 580 ( $[\text{M}]^+$ , 1), 456 (10), 133 (25), 132 (65), 100 (8), 99 (100), 86 (14), 55 (8).

**HRMS**  $m/z$  calcd for  $\text{C}_{25}\text{H}_{40}\text{O}_9\text{S}_3$  580.1834, found 580.1828 (EI).

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\* Aldols are reported in order from high to lower  $R_f$ .

**(3*S*,5*R*)-rel-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4*H*-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)  $\nu_{\max}$  2913, 1716, 1427, 1152, 1098, 1033, 890, 734  $\text{cm}^{-1}$ .

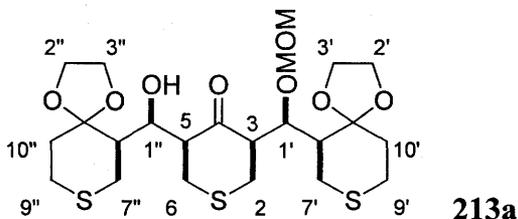
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.70 (2H, d,  $J = 6.5$  Hz,  $\text{HCO}_2 \times 2$ ), 4.60 (2H, d,  $J = 6.5$  Hz,  $\text{HCO}_2 \times 2$ ), 4.12 (2H, dd,  $J = 4.5, 5$  Hz, HC-1', HC-1''), 4.05-3.91 (8H, m,  $\text{H}_2\text{CO} \times 4$ ), 3.37 (6H, s,  $\text{H}_3\text{CO} \times 2$ ), 3.12 (2H, ddd,  $J = 4, 4.5, 12.5$  Hz, HC-3, HC-5), 3.04 (2H, dd,  $J = 12.5, 13$  Hz, HC-2, HC-6), 3.00 (2H, br d,  $J = 14$  Hz, HC-7', HC-7''), 2.90 (2H, br d,  $J = 13$  Hz, HC-2, HC-6), 2.81 (2H, dd,  $J = 9.5, 14$  Hz, HC-7', HC-7''), 2.74 (2H, ddd,  $J = 3, 10.5, 13.5$  Hz, HC-9', HC-9''), 2.59 (2H, br d,  $J = 13.5$  Hz, HC-9', HC-9''), 2.30 (2H, ddd,  $J = 3.5, 5, 9.5$  Hz, HC-6', HC-6''), 2.07 (2H, ddd,  $J = 3, 6, 13.5$  Hz, HC-10', HC-10''), 1.64 (2H, ddd,  $J = 3.5, 10.5, 13.5$  Hz, HC-10', HC-10'').

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  207.24 (s, C-4), 109.06 (s  $\times 2$ , C-5', C-5''), 98.28 (t  $\times 2$ ,  $\text{OCH}_2\text{O}$ ), 75.13 (d  $\times 2$ , C-1', C-1''), 64.93 (t  $\times 2$ ,  $\text{CH}_2\text{O}$ ), 64.51 (t  $\times 2$ ,  $\text{CH}_2\text{O}$ ), 59.72 (d  $\times 2$ , C-3, C-5), 56.70 (q  $\times 2$ ,  $\text{CH}_3\text{O}$ ), 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 ( $[\text{M}]^+$ , 1), 518 (4), 456 (10), 133 (20), 132 (60), 100 (9), 99 (100), 86 (22).

**HRMS**  $m/z$  calcd for  $\text{C}_{25}\text{H}_{40}\text{O}_9\text{S}_3$  580.1834, found 580.1839 (EI).

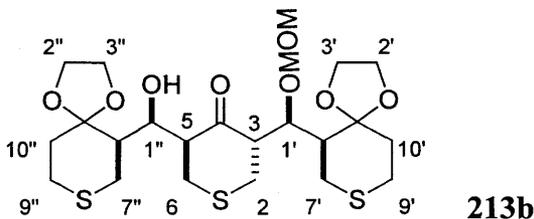
**(3R,5S)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (213a)**



Following General procedure M for MOM protection but using 20 equiv of MOMCl and 30 equiv *i*-Pr<sub>2</sub>EtN, 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 CH<sub>2</sub>Cl<sub>2</sub>; multiple elutions) to give titled compound **213a** (3 mg, 18%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.69 (1H, d, *J* = 6 Hz, HCO<sub>2</sub>), 4.66 (1H, d, *J* = 6 Hz, HCO<sub>2</sub>), 4.64 (1H, m, HC-1''), 4.10-3.86 (8H, m, H<sub>2</sub>CO ×4), 3.36 (3H, s, H<sub>3</sub>CO), 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-yl(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (213b)**



For synthesis and isolation see experimental procedure for compound **212b**.

IR (DRIFT)  $\nu_{\max}$  cm<sup>-1</sup>.

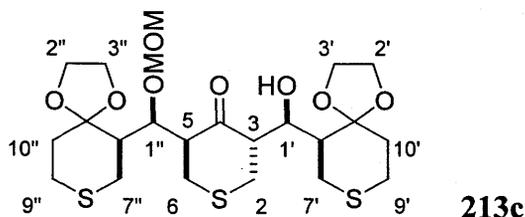
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.72 (1H, ddd,  $J = 2.5, 3, 8$  Hz, HC-1''), 4.70 (1H, d,  $J = 5.5$  Hz, HCO<sub>2</sub>), 4.58 (1H, d,  $J = 5.5$  Hz, HCO<sub>2</sub>), 4.39 (1H, dd,  $J = 4, 6$  Hz, HC-1'), 4.12-3.94 (8H, m, H<sub>2</sub>CO  $\times 4$ ), 3.35 (3H, s, H<sub>3</sub>CO), 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, dd,  $J = 10, 14$  Hz, HC-7''), 2.92 (1H, ddd,  $J = 5, 5.5, 6.0$  Hz, HC-3), 2.92 (1H, dd,  $J = 8.5, 13$  Hz, HC-6), 2.92-2.87 (1H, m, HC-2), 2.84 (1H, ddd,  $J = 2, 3, 14$  Hz, HC-7''), 2.82-2.73 (4H, m, H<sub>2</sub>C-7', HC-9', HC-9''), 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').

$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  210.73 (s, C-4), 110.17 (s, C-5''), 108.72 (s, C-5'), 97.45 (t, OCH<sub>2</sub>O), 73.96 (d, C-1'), 67.08 (d, C-1''), 64.88 (t, CH<sub>2</sub>O), 64.80 (t, CH<sub>2</sub>O), 64.69 (t, CH<sub>2</sub>O), 64.42 (t, CH<sub>2</sub>O), 58.47 (d, C-3), 56.21 (q, CH<sub>3</sub>O), 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 ( $[\text{M}]^+$ , 1), 188 (8), 133 (15), 132 (50), 100 (10), 99 (100), 86 (18), 55 (11).

**HRMS**  $m/z$  calcd for  $\text{C}_{23}\text{H}_{36}\text{O}_8\text{S}_3$  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)  $\nu_{\text{max}}$  3518, 2913, 1711, 1427, 1153, 1133, 1108, 1034  $\text{cm}^{-1}$ .

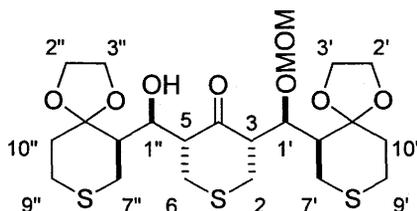
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.69 (1H, ddd,  $J = 2.5, 3, 3.5$  Hz, HC-1'), 4.68 (1H, d,  $J = 6$  Hz, HCO<sub>2</sub>), 4.65 (1H, d,  $J = 6$  Hz, HCO<sub>2</sub>), 4.47 (1H, dd,  $J = 4.5, 5$  Hz, HC-1''), 4.14-3.91 (8H, m, H<sub>2</sub>CO  $\times$ 4), 3.37 (3H, s, H<sub>3</sub>CO), 3.21 (1H, ddd,  $J = 4.5, 5, 9.5$  Hz, HC-5), 3.07 (1H, dd,  $J = 9.5, 13.5$  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<sub>2</sub>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'').

$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  210.97 (s, C-4), 110.07 (s, C-5'), 108.97 (s, C-5''), 98.62 (t, OCH<sub>2</sub>O), 72.79 (d, C-1''), 68.51 (d, C-1'), 65.10 (t, CH<sub>2</sub>O), 64.64 (t, CH<sub>2</sub>O), 64.60 (t, CH<sub>2</sub>O), 64.60 (t, CH<sub>2</sub>O), 57.34 (d, C-5), 56.79 (q, CH<sub>3</sub>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 ( $[\text{M}]^+$ , 1), 188 (8), 133 (11), 132 (44), 100 (10), 99 (100), 86 (20), 54 (13).

HRMS  $m/z$  calcd for  $\text{C}_{23}\text{H}_{36}\text{O}_8\text{S}_3$  536.1572, found 536.1578 (EI).

**(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-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (213d)**



IR (DRIFT)  $\nu_{\text{max}}$  3520, 2917, 1701, 1427, 1100, 1034, 891, 735  $\text{cm}^{-1}$ .

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.72 (1H, d,  $J = 6.5$  Hz, HCO<sub>2</sub>), 4.59 (1H, d,  $J = 6.5$  Hz, HCO<sub>2</sub>), 4.18 (1H, ddd,  $J = 4.5, 6.5, 8$  Hz, HC-1''), 4.07-3.90 (8H, m, H<sub>2</sub>CO  $\times$ 4), 4.00 (1H, dd,  $J = 5, 5$  Hz, HC-1'), 3.38 (3H, s, H<sub>3</sub>CO), 3.23 (1H, ddd,  $J = 4.5, 4.5, 12$  Hz,

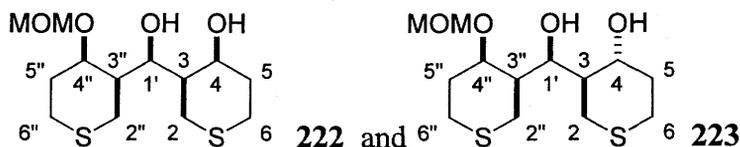
HC-5), 3.22 (1H, ddd,  $J = 4.5, 5, 12$  Hz, HC-3), 3.17-2.91 (6H, m, H<sub>2</sub>C-2, HC-6, HC-7', H<sub>2</sub>C-7''), 2.87 (1H, ddd,  $J = 3.5, 3.5, 13$  Hz, HC-6), 2.79 (1H, dd,  $J = 10, 14$  Hz, HC-7'), 2.78-2.65 (3H, m, HC-9', H<sub>2</sub>C-9''), 2.59 (1H, br d,  $J = 13.5$  Hz, HC-9'), 2.30 (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').

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  213.35 (s, C-4), 109.12 (s, C-5''), 108.96 (s, C-5'), 98.16 (t, OCH<sub>2</sub>O), 74.88 (d, C-1'), 70.34 (d, C-1''), 65.00 (t, CH<sub>2</sub>O), 64.93 (t, CH<sub>2</sub>O), 64.59 (t, CH<sub>2</sub>O), 64.39 (t, CH<sub>2</sub>O), 60.22 (d, C-3), 57.52 (d, C-5), 56.77 (q, CH<sub>3</sub>O), 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]<sup>+</sup>, 1), 158 (6), 133 (12), 132 (41), 100 (11), 99 (100), 86 (12), 55 (8).

HRMS  $m/z$  calcd for C<sub>23</sub>H<sub>36</sub>O<sub>8</sub>S<sub>3</sub> 536.1572, found 536.1571 (EI).

(1'*S*\*, 3*R*\*, 3''*R*\*, 4*S*\*, 4''*R*\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2*H*-thiopyran-3-yl]methyl)tetrahydro-2*H*-thiopyran-4-ol (**222**) and (1'*S*\*, 3*R*\*, 3''*R*\*, 4*R*\*, 4''*R*\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2*H*-thiopyran-3-yl]methyl)tetrahydro-2*H*-thiopyran-4-ol (**223**).



Following General procedure D, the NaBH<sub>4</sub> 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  $\nu_{\max}$  3397, 2926, 1427, 1210, 1150, 1093, 1028, 922 cm<sup>-1</sup>;

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.73 (1H, d,  $J = 7$  Hz, H<sub>2</sub>CO), 4.62 (1H, d,  $J = 7$  Hz, H<sub>2</sub>CO), 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<sub>3</sub>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'');

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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]<sup>+</sup>, 68), 290 (34), 159 (33), 129 (56), 101 (53), 100 (100), 99 (99), 67 (29).

HRMS  $m/z$  calcd for C<sub>13</sub>H<sub>24</sub>O<sub>4</sub>S<sub>2</sub> 308.1116, found 308.1112 (EI).

Data for **223**:

IR  $\nu_{\max}$  3433, 2927, 1429, 1277, 1149, 1095, 1028, 918 cm<sup>-1</sup>;

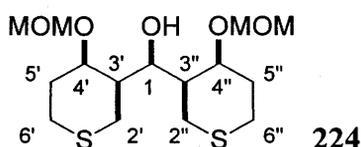
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.70 (1H, d,  $J = 7$  Hz, H<sub>2</sub>CO), 4.66 (1H, d,  $J = 7$  Hz, H<sub>2</sub>CO), 4.16 (1H, dd,  $J = 3.5, 7$  Hz, HC-1'), 3.92 (1H, br ddd,  $J = 2.5, 3, 3.5$  Hz, HC-4''), 3.63 (1H, ddd,  $J = 4, 10, 10$  Hz, HC-4), 3.41 (3H, s, H<sub>3</sub>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'');

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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]<sup>+</sup>, 50), 290 (25), 159 (42), 129 (65), 117 (52), 101 (50), 100 (100), 99 (93).

HRMS  $m/z$  calcd for C<sub>13</sub>H<sub>24</sub>O<sub>4</sub>S<sub>2</sub> 308.1116, found 308.1115 (EI).

(1*s*, 3'*R*\*, 3''*S*\*, 4'*R*\*, 4''*S*\*)-Bis[tetrahydro-4-(methoxymethoxy)-2*H*-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):

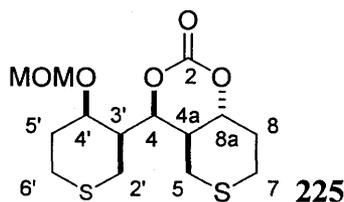
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 4.75 (2H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.62 (2H, d, *J* = 7 Hz, H<sub>2</sub>CO), 3.97-3.95 (2H, br s, HC-4', HC-4''), 3.75 (1H, t, *J* = 5.5 Hz, HC-1'), 3.57 (1H, br s, HOC-1'), 3.41 (6H, s, H<sub>3</sub>CO ×2), 3.02 (2H, dd, *J* = 12, 13 Hz, HC-2', 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'');

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 95.02 (t ×2), 76.41 (d), 74.48 (d ×2), 56.41 (q ×2), 43.58 (d ×2), 31.60 (t ×2), 23.54 (t ×2), 22.39 (t ×2);

**LRMS** (EI), *m/z* (relative intensity): 352 ([M]<sup>+</sup>, 33), 334 (27), 159 (56), 129 (47), 101 (44), 100 (71), 99 (100), 67 (23).

**HRMS** *m/z* calcd for C<sub>15</sub>H<sub>28</sub>O<sub>5</sub>S<sub>2</sub> 352.1378, found 352.1374 (EI).

**(3'*S*\*, 4*R*\*, 4*aR*\*, 4'*R*\* 8*aR*\*)-4*a*,7,8,8*a*-Tetrahydro-4-[tetrahydro-4-(methoxymethoxy)-2*H*-thiopyran-3-yl]-4*H*,5*H*-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<sup>-1</sup>;

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 4.72 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.61 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.53 (1H, dd, *J* = 4.5, 6.5 Hz, HC-4 [<sup>3</sup>*J*<sub>HC-4/HC-4a</sub> = 4.5 Hz]), 4.31 (1H, ddd, *J* = 4.5, 11, 11 Hz, HC-8*a*), 3.68 (1H, br s, HC-4'), 3.44 (3H, s, H<sub>3</sub>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,

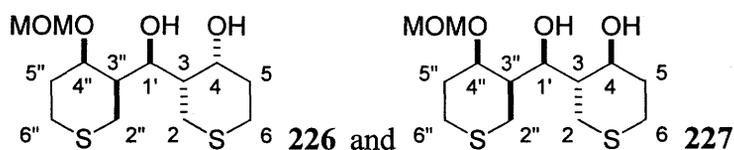
12.5, 14 Hz, HC-5, HC-7), 2.75-2.65 (2H, m, HC-5, HC-7), 2.59-2.49 (3H, m, HC-4a, HC-8), 2.33-2.22 (4H, m, HC-3', HC-5', HC-2', HC-6'), 1.92 (1H, dddd,  $J = 4, 11, 12.5, 12.5$  Hz, HC-8), 1.82-1.74 (1H, m, HC-5');

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  147.78 (s), 95.62 (t), 80.23 (d), 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 ( $[\text{M}]^+$ , 100), 289 (16), 227 (47), 139 (42), 137 (41), 129 (31), 101 (36), 99 (84).

HRMS  $m/z$  calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_5\text{S}_2$  334.0909, found 334.0911 (EI).

(1' $S^*$ , 3 $S^*$ , 3'' $R^*$ , 4 $R^*$ , 4'' $R^*$ )-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2 $H$ -thiopyran-3-yl]methyl)tetrahydrothiopyran-4-ol (**226**) and (1' $S^*$ , 3 $S^*$ , 3'' $R^*$ , 4 $S^*$ , 4'' $R^*$ )-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2 $H$ -thiopyran-3-yl]methyl)tetrahydro-2 $H$ -thiopyran-4-ol (**227**).



Following General procedure D, the  $\text{NaBH}_4$  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  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.77 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.66 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.17 (1H, dddd,  $J = 3, 3, 4.5, 6$  Hz, HC-4), 4.02 (1H, ddd,  $J = 1.5, 2, 3$  Hz, HC-4''), 3.97 (1H, ddd,  $J = 2.5, 3, 7$  Hz, HC-1'), 3.55 (1H, d,  $J = 2.5$  Hz, HOC-1'), 3.43 (3H, s,  $\text{H}_3\text{CO}$ ), 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''),

1.94 (1H, dddd,  $J = 3, 3.5, 10.5, 14$  Hz, HC-5), 1.80 (1H, dddd,  $J = 2, 3.5, 12.5, 14$  Hz, HC-5");

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 71), 290 (20), 159 (31), 129 (54), 117 (33), 101 (48), 100 (100), 99 (96).

HRMS  $m/z$  calcd for  $\text{C}_{13}\text{H}_{24}\text{O}_4\text{S}_2$  308.1116, found 308.1119 (EI).

Data for **227**:

IR  $\nu_{\text{max}}$  3431, 2928, 1428, 1153, 1095, 1072, 1024, 919  $\text{cm}^{-1}$ ;

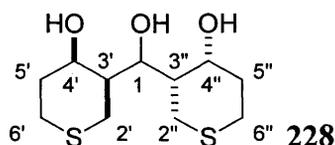
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.99 (1H, s, HO), 4.79 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.68 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.30 (1H, s, HO), 4.09 (1H, br s, HC-4"), 3.80 (1H, d,  $J = 9.5$  Hz, HC-1'), 3.62 (1H, ddd,  $J = 4, 10, 10$  Hz, HC-4), 3.44 (3H, s,  $\text{H}_3\text{CO}$ ), 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,  $\text{H}_2\text{C}-6$ ), 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);

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 72), 159 (46), 129 (69), 117 (52), 101 (48), 100 (100), 99 (100), 67 (33).

HRMS  $m/z$  calcd for  $\text{C}_{13}\text{H}_{24}\text{O}_4\text{S}_2$  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  $\text{cm}^{-1}$ ;

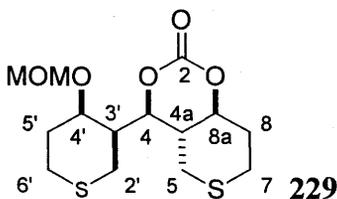
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.25-4.21 (1H, br s, HC-4'/HC-4''), 4.16 (1H, dd,  $J = 2$ , 8.5 Hz, HC-1), 4.08 (1H, ddd,  $J = 3$ , 3, 7.5 Hz, HC-4''/HC-4'), 3.88 (1H, s, HOC-1), 3.18 (1H, dd,  $J = 12$ , 13.5 Hz, HC-2''/HC-2''), 3.11 (1H, ddd,  $J = 2.5$ , 13, 13 Hz, HC-6''/HC-6''), 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'');

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 72), 228 (10), 157 (20), 129 (48), 117 (54), 101 (43), 100 (100), 99 (51).

HRMS  $m/z$  calcd for  $\text{C}_{11}\text{H}_{20}\text{O}_3\text{S}_2$  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  $\nu_{\max}$  2924, 1749, 1217, 1156, 1118, 1095, 1033, 916  $\text{cm}^{-1}$ ;

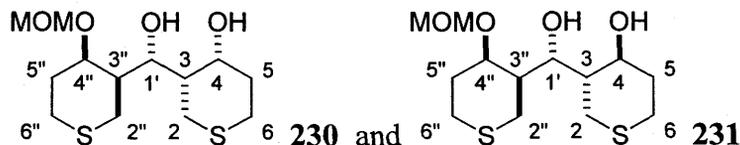
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.72 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.66 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.20 (1H, dd,  $J = 4, 10$  Hz, HC-4 [ $^3J_{\text{HC-4}/\text{HC-4a}} = 10$  Hz]), 4.01 (1H, ddd,  $J = 4, 11, 11$  Hz, HC-8a), 3.94-3.92 (1H, br s, HC-4'), 3.43 (3H, s,  $\text{H}_3\text{CO}$ ), 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, ddd,  $J = 2.5, 3, 13.5$  Hz, HC-5), 2.79 (1H, ddd,  $J = 2, 12.5, 14$  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');

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 100), 271 (33), 227 (53), 139 (46), 137 (61), 99 (83), 85 (32), 67 (46).

HRMS  $m/z$  calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_5\text{S}_2$  334.0909, found 334.0903 (EI).

(1'*R*\*, 3*S*\*, 3''*R*\*, 4*R*\*, 4''*R*\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2*H*-thiopyran-3-yl]methyl)tetrahydro-2*H*-thiopyran-4-ol (**230**) and (1'*R*\*, 3*S*\*, 3''*R*\*, 4*S*\*, 4''*R*\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2*H*-thiopyran-3-yl]methyl)tetrahydro-2*H*-thiopyran-4-ol (**231**).



Following General procedure D, the  $\text{NaBH}_4$  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**:

**IR**  $\nu_{\max}$  3401, 2928, 1426, 1201, 1149, 1095, 1037, 923  $\text{cm}^{-1}$ ;

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.66 (1H, d,  $J = 6$  Hz,  $\text{H}_2\text{CO}$ ), 4.64 (1H, d,  $J = 6$  Hz,  $\text{H}_2\text{CO}$ ), 4.17 (1H, br ddd,  $J = 2, 2, 4$  Hz, HC-4), 4.04 (1H, ddd,  $J = 2.5, 2.5, 5.5$  Hz, HC-4"), 3.86 (1H, dd,  $J = 1.5, 10$  Hz, HC-1'), 3.42 (3H, s,  $\text{H}_3\text{CO}$ ), 3.24-3.15 (2H, m), 2.91 (1H, ddd,  $J = 2, 12, 13.5$  Hz), 2.70 (1H, dd,  $J = 10.5, 13.5$  Hz, HC-2"), 2.37 (1H, dddd,  $J = 1, 3.5, 5, 13.5$  Hz), 2.28 (1H, dd,  $J = 2.5, 13$  Hz), 2.26-2.15 (4H, m), 1.96 (1H, dddd,  $J = 2.5, 3, 10, 10.5$  Hz, HC-3"), 1.93-1.78 (3H, m);

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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;

**LRMS** (EI),  $m/z$  (relative intensity): 308, ( $[\text{M}]^+$ , 83), 290 (24), 159 (52), 129 (48), 117 (39), 101 (51), 100 (100), 99 (81).

**HRMS**  $m/z$  calcd for  $\text{C}_{13}\text{H}_{24}\text{O}_4\text{S}_2$  308.1116, found 308.1114 (EI).

Data for **231**:

**IR**  $\nu_{\max}$  3430, 2927, 1427, 1281, 1147, 1103, 1041, 917  $\text{cm}^{-1}$ ;

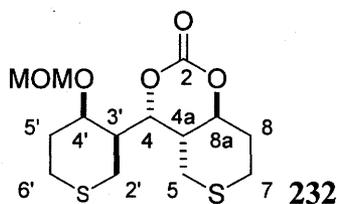
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.68 (1H, d,  $J = 6.5$  Hz,  $\text{H}_2\text{CO}$ ), 4.64 (1H, d,  $J = 6.5$  Hz,  $\text{H}_2\text{CO}$ ), 4.22 (1H, dd,  $J = 2, 10$  Hz, HC-1'), 4.11 (1H, ddd,  $J = 2, 2.5, 2.5$  Hz, HC-4"), 3.73 (1H, ddd,  $J = 4, 10, 10$  Hz, HC-4), 3.42 (3H, s,  $\text{H}_3\text{CO}$ ), 2.80-2.66 (3H, m), 2.95 (1H, br dd,  $J = 12.5, 12.5$  Hz, HC-6"), 2.61 (1H, dddd,  $J = 3, 3, 3, 13.5$  Hz), 2.54 (1H, ddd,  $J = 2.5, 2.5, 14$  Hz), 2.38-2.32 (2H, m), 2.30-2.22 (3H, m), 1.92 (1H, dddd,  $J = 3, 3, 10.5, 10.5$  Hz, HC-3"), 1.82 (1H, dddd,  $J = 2, 3.5, 10.5, 10.5$  Hz, HC-5"), 1.80-1.67 (3H, m);

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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;

**LRMS** (EI),  $m/z$  (relative intensity): 308 (79), 290 (21), 159 (57), 129 (65), 117 (48), 101 (48), 100 (100), 99 (82).

**HRMS**  $m/z$  calcd for  $\text{C}_{13}\text{H}_{24}\text{O}_4\text{S}_2$  308.1116, found 308.1113 (EI).

**(3'S\*, 4S\*, 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 (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**  $\nu_{\max}$  1745, 1427, 1368, 1234, 1177, 1113, 1027, 918  $\text{cm}^{-1}$ ;

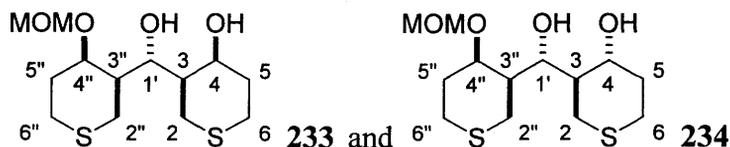
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$  @ 40 °C)  $\delta$  4.78 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.71 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.48 (1H, dd,  $J = 3.5, 9$  Hz, HC-4 [ $^3J_{\text{HC-4}/\text{HC-4a}} = 3.5$  Hz]), 4.33 (1H, ddd,  $J = 4, 11, 11$  Hz, HC-8a), 3.92 (1H, br s, HC-4'), 3.41 (3H, s,  $\text{H}_3\text{CO}$ ), 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,  $\text{H}_2\text{C-5}$ ), 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');

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 82), 227 (39), 139 (57), 138 (38), 137 (53), 101 (47), 99 (100), 67 (78).

**HRMS**  $m/z$  calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_5\text{S}_2$  334.0909, found 334.0910 (EI).

(1'*R*\*, 3*R*\*, 3''*R*\*, 4*S*\*, 4''*R*\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2*H*-thiopyran-3-yl]methyl)tetrahydro-2*H*-thiopyran-4-ol (**233**) and (1'*R*\*, 3*R*\*, 3''*R*\*, 4*R*\*, 4''*R*\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2*H*-thiopyran-3-yl]methyl)tetrahydro-2*H*-thiopyran-4-ol (**234**).



Following General procedure E, the NaCNBH<sub>3</sub> 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**  $\nu_{\max}$  3346, 2921, 1423, 1209, 1143, 1107, 1043, 926 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.51 (1H, d,  $J = 6.5$  Hz, H<sub>2</sub>CO), 4.64 (1H, d,  $J = 6.5$  Hz, H<sub>2</sub>CO), 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, H<sub>3</sub>CO), 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'');

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  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]<sup>+</sup>, 69), 290 (43), 159 (46), 129 (56), 117 (37), 101 (54), 100 (100), 99 (82).

**HRMS**  $m/z$  calcd for C<sub>13</sub>H<sub>24</sub>O<sub>4</sub>S<sub>2</sub> 308.1116, found 308.1115 (EI).

Data for **234**:

**IR**  $\nu_{\max}$  3429, 2925, 1428, 1177, 1149, 1091, 1037, 918 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.82 (1H, s, HOC-4), 4.77 (1H, d,  $J = 7$  Hz, H<sub>2</sub>CO), 4.69 (1H, d,  $J = 7$  Hz, H<sub>2</sub>CO), 4.33 (1H, d,  $J = 8$  Hz, HOC-1'), 4.30 (1H, ddd,  $J = 2, 2, 4$

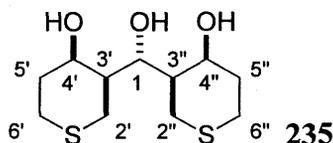
Hz, HC-4''), 3.66 (1H, ddd,  $J = 4, 10, 10$  Hz, HC-4), 3.60 (1H, ddd,  $J = 5, 8, 8$  Hz, HC-1'), 3.46 (3H, s, H<sub>3</sub>CO), 3.20 (1H, dd,  $J = 11.5, 13.5$  Hz, HC-2''), 2.95 (1H, ddd,  $J = 2.5, 13, 15$  Hz, HC-6''), 2.69 (1H, ddd,  $J = 2.5, 12.5, 13.5$  Hz, HC-6), 2.62 (1H, ddd,  $J = 4, 4, 13.5$  Hz, HC-6), 2.42-2.26 (6H, m), 2.14 (1H, dddd,  $J = 2, 2, 4.5, 12$  Hz, HC-5''), 1.89 (1H, m), 1.80-1.70 (2H, m);

**<sup>13</sup>C NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  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]<sup>+</sup>, 46), 290 (41), 159 (74), 129 (89), 117 (54), 101 (59), 99 (100), 85 (46).

**HRMS**  $m/z$  calcd for C<sub>13</sub>H<sub>24</sub>O<sub>4</sub>S<sub>2</sub> 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**  $\nu_{\max}$  3367, 2917, 1423, 1274, 1202, 1135, 1061, 925 cm<sup>-1</sup>;

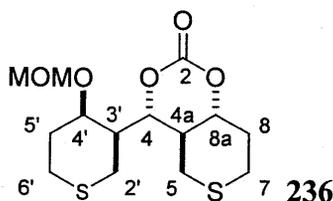
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.30 (2H, ddd,  $J = 2.5, 3, 6$  Hz, HC-4', HC-4''), 4.11 (1H, br t,  $J = 6$  Hz, HC-1), 4.11 (1H, br s, HOC-1), 3.13 (2H, br s, HOC-4', HOC-4''), 3.07 (2H, dd,  $J = 10, 13.5$  Hz, HC-2', HC-2''), 3.02 (2H, ddd,  $J = 3, 11, 13.5$  Hz, HC-6', 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'');

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  76.61 ( $\times 2$ ), 67.82, 42.29 ( $\times 2$ ), 34.44 ( $\times 2$ ), 27.03 ( $\times 2$ ), 23.70 ( $\times 2$ );

**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  $C_{11}H_{20}O_3S_2$  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**  $\nu_{\max}$  1753, 1428, 1220, 1197, 1158, 1095, 1029, 918  $\text{cm}^{-1}$ ;

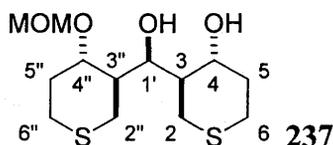
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.72 (1H, d,  $J = 6.5$  Hz,  $\text{H}_2\text{CO}$ ), 4.70 (1H, d,  $J = 6.5$  Hz,  $\text{H}_2\text{CO}$ ), 4.25 (1H, br s, HC-4'), 4.13 (1H, dd,  $J = 8, 8.5$  Hz, HC-4 [ $^3J_{\text{HC-4}/\text{HC-4a}} = 8.5$  Hz]), 3.99 (1H, ddd,  $J = 4, 11, 11$  Hz, HC-8a), 3.41 (3H, s,  $\text{H}_3\text{CO}$ ), 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, dddd,  $J = 2.5, 3, 4, 14$  Hz, HC-7), 2.63 (1H, ddd,  $J = 2, 3.5, 14$  Hz, HC-5), 2.55 (1H, dd,  $J = 11, 14$  Hz, HC-5), 2.48 (1H, dddd,  $J = 3, 3.5, 4, 13$  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');

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $C_{14}H_{22}O_5S_2$  334.0909, found 334.0911 (EI).

(1'*S*\*, 3*R*\*, 3''*R*\*, 4*R*\*, 4''*S*\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2*H*-thiopyran-3-yl]methyl)tetrahydro-2*H*-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  $\nu_{max}$  3432, 2927, 1429, 1279, 1147, 1095, 1027, 916  $cm^{-1}$ ;

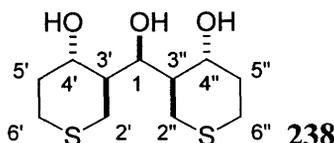
$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  4.72 (1H, d,  $J = 6.5$  Hz,  $H_2CO$ ), 4.72-4.68 (1H, m, HC-1'), 4.64 (1H, d,  $J = 6.5$  Hz,  $H_2CO$ ), 3.78 (1H, br ddd,  $J = 3.5, 8, 8$  Hz, HC-4), 3.56 (1H, ddd,  $J = 3.5, 8, 8$  Hz, HC-4''), 3.45 (3H, s,  $H_3CO$ ), 2.92-2.75 (5H, m), 2.69 (1H, dd,  $J = 13.5, 14$  Hz), 2.67 (1H, dd,  $J = 13.5, 14$  Hz), 2.59-2.49 (2H, m), 2.22-2.13 (2H, m), 1.93-1.85 (5H, m);

$^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  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  $C_{13}H_{24}O_4S_2$  308.1116, found 308.1115 (EI).

(1*r*, 3'*S*\*, 3''*R*\*, 4'*S*\*, 4''*R*\*)-Bis[tetrahydro-4-hydroxy-2*H*-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  $CH_2Cl_2$ .

IR  $\nu_{max}$  3377, 2925, 1429, 1280, 1029, 956  $cm^{-1}$ ;

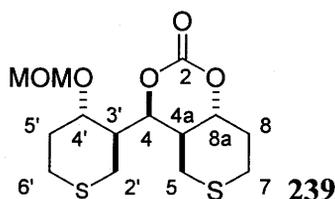
**<sup>1</sup>H NMR** (500 MHz, CD<sub>3</sub>OD) δ 4.77 (1H, t, *J* = 6 Hz, HC-1), 3.66 (2H, ddd, *J* = 3.5, 7.5, 8 Hz, HC-4', HC-4''), 2.85 (2H, br d, *J* = 13.5 Hz, HC-2', HC-2''), 2.76 (2H, dddd, *J* = 1, 3.5, 6.5, 12.5 Hz, HC-6', HC-6''), 2.60 (2H, dd, *J* = 8.5, 13.5 Hz, HC-2', HC-2''), 2.48 (2H, ddd, *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'');

**<sup>13</sup>C NMR** (75 MHz, CD<sub>3</sub>OD) δ 69.2 (× 2), 67.5, 47.4 (× 2), 35.8 (× 2), 27.1 (× 2), 26.5 (× 2);

**LRMS** (EI), *m/z* (relative intensity): 264 ([M]<sup>+</sup>, 76), 129 (87), 117 (100), 100 (94), 99 (46), 87 (52), 83 (41), 57 (63).

**HRMS** *m/z* calcd for C<sub>11</sub>H<sub>20</sub>O<sub>3</sub>S<sub>2</sub> 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):

**IR**  $\nu_{\max}$  2922, 1749, 1386, 1244, 1182, 1089, 1026, 916 cm<sup>-1</sup>;

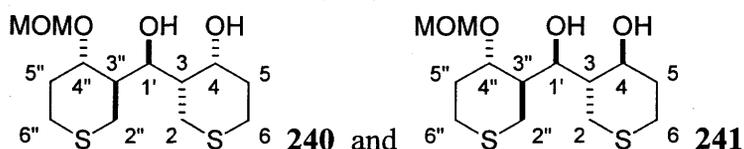
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 5.08 (1H, dd, *J* = 2, 7 Hz, HC-4 [<sup>3</sup>*J*<sub>HC-4/HC-4a</sub> = 7 Hz]), 4.73 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.68 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.26 (1H, ddd, *J* = 4.5, 11, 11 Hz, HC-8a), 3.56 (1H, ddd, *J* = 4, 10, 10.5 Hz, HC-4'), 3.39 (3H, s, H<sub>3</sub>CO), 2.86-2.48 (11H, m, H<sub>2</sub>C-2', HC-4a, H<sub>2</sub>C-5, HC-5', H<sub>2</sub>C-6', H<sub>2</sub>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');

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 69), 272 (38), 201 (37), 139 (59), 101 (40), 99 (100), 85 (49), 67 (60).

HRMS  $m/z$  calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_5\text{S}_2$  334.0909, found 334.0906 (EI).

**1'S\*, 3S\*, 3'R\*, 4R\*, 4''S\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl]methyl)tetrahydro-2H-thiopyran-4-ol (240) (1'S\*, 3S\*, 3'R\*, 4S\*, 4''S\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl]methyl)tetrahydro-2H-thiopyran-4-ol (241).**



Following General procedure D, the  $\text{NaBH}_4$  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  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.69 (1H, d,  $J = 6.5$  Hz,  $\text{H}_2\text{CO}$ ), 4.64 (1H, d,  $J = 6.5$  Hz,  $\text{H}_2\text{CO}$ ), 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,  $\text{H}_3\text{CO}$ ), 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,  $\text{H}_2\text{C}-2''$ ,  $\text{H}_2\text{C}-6''$ ), 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'');

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $C_{13}H_{24}O_4S_2$  308.1116, found 308.1120 (EI).

Data for **241**:

**IR**  $\nu_{\max}$  3379, 2928, 1428, 1147, 1103, 1047, 1028, 914  $\text{cm}^{-1}$ ;

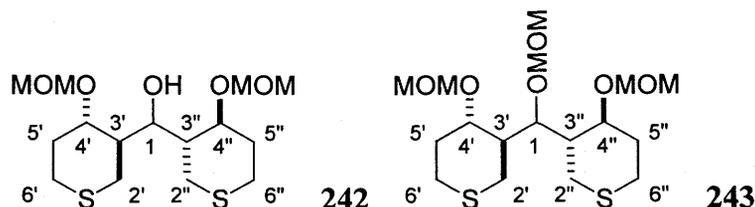
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.96 (1H, br s, HOC-4), 4.66 (1H, d,  $J = 6.5$  Hz,  $\text{H}_2\text{CO}$ ), 4.64 (1H, d,  $J = 6.5$  Hz,  $\text{H}_2\text{CO}$ ), 4.30 (1H, d,  $J = 3.5$  Hz, HOC-1'), 4.15 (1H, ddd,  $J = 2.5, 3.5, 10$  Hz, HC-1'), 3.61 (1H, ddd,  $J = 4, 9, 10.5$  Hz, HC-4), 3.43 (1H, ddd,  $J = 4, 10, 11$  Hz, HC-4''), 3.42 (3H, s,  $\text{H}_3\text{CO}$ ), 2.73-2.54 (6H, m), 2.48 (1H, ddd,  $J = 2.5, 3.5, 14$  Hz), 2.33 (1H, dddd,  $J = 3.5, 4, 4.5, 13$  Hz, HC-5''), 2.31-2.25 (2H, m), 1.88-1.71 (4H, m, HC-3, HC-3'', HC-5, HC-5'');

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $C_{13}H_{24}O_4S_2$  308.1116, found 308.1112 (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**  $\nu_{\max}$  3488, 2930, 1429, 1277, 1147, 1097, 1029, 916  $\text{cm}^{-1}$ ;

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 4.78 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.73 (1H, d, *J* = 6.5 Hz, H<sub>2</sub>CO), 4.70 (1H, d, *J* = 6.5 Hz, H<sub>2</sub>CO), 4.67 (1H, d, *J* = 7 Hz, H<sub>2</sub>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<sub>3</sub>CO), 3.41 (3H, s, H<sub>3</sub>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');

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 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]<sup>+</sup>, 70), 275 (36), 159 (82), 129 (79), 101 (57), 100 (100), 99 (86), 67 (31).

**HRMS** *m/z* calcd for C<sub>15</sub>H<sub>28</sub>O<sub>5</sub>S<sub>2</sub> 352.1378, found 352.1373 (EI).

#### Data for **243**

**IR**  $\nu_{\max}$  2933, 2821, 1431, 1211, 1146, 1095, 1029, 916 cm<sup>-1</sup>;

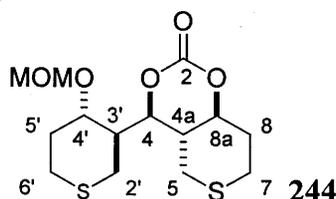
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 4.74 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.72 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.70 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.69 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.67 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 4.66 (1H, d, *J* = 7 Hz, H<sub>2</sub>CO), 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<sub>3</sub>CO), 3.39 (3H, s, H<sub>3</sub>CO), 3.37 (3H, s, H<sub>3</sub>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<sub>2</sub>C-6''/H<sub>2</sub>C-6', H<sub>2</sub>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');

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 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]<sup>+</sup>, 10), 289 (21), 272 (21), 257 (26), 173 (100), 159 (41), 129 (32), 99 (42).

**HRMS** *m/z* calcd for C<sub>17</sub>H<sub>32</sub>O<sub>6</sub>S<sub>2</sub> 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-thiopyrano[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**  $\nu_{\text{max}}$  2920, 1746, 1236, 1164, 1094, 1029 cm<sup>-1</sup>;

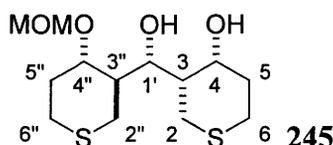
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 4.74 (1H, dd, *J* = 1, 11 Hz, HC-4 [<sup>3</sup>*J*<sub>HC-4/HC-4a</sub> = 11 Hz]), 4.73 (1H, d, *J* = 6.5 Hz, H<sub>2</sub>CO), 4.70 (1H, d, *J* = 6.5 Hz, H<sub>2</sub>CO), 4.10 (1H, ddd, *J* = 4, 11, 11 Hz, HC-8a), 3.66 (1H, ddd, *J* = 4, 10.5, 10.5 Hz, HC-4'), 3.38 (3H, s, H<sub>3</sub>CO), 2.81-2.40 (4H, m), 2.65 (1H, ddd, *J* = 2, 3.5, 14 Hz), 2.63-2.40 (5H, m), 2.12 (1H, dddd, *J* = 3.5, 11, 11, 11 Hz, HC-4a), 1.97-1.87 (2H, m, HC-8, HC-3'), 1.68 (1H, m, HC-5');

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 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]<sup>+</sup>, 64), 289 (34), 227 (39), 139 (56), 137 (41), 99 (100), 85 (47), 67 (64).

**HRMS** *m/z* calcd for C<sub>14</sub>H<sub>22</sub>O<sub>5</sub>S<sub>2</sub> 334.0909, found 334.0907 (EI).

**(1'R\*, 3S\*, 3''R\*, 4R\*, 4''S\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl]methyl)tetrahydro-2H-thiopyran-4-ol (245).**



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**  $\nu_{\max}$  3419, 2925, 1427, 1276, 1149, 1097, 1033, 1070  $\text{cm}^{-1}$ ;

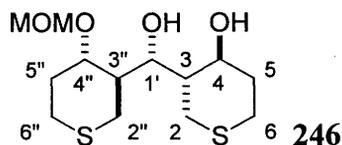
**<sup>1</sup>H NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.82 (1H, d,  $J = 7.5$  Hz,  $\text{H}_2\text{CO}$ ), 4.66 (1H, d,  $J = 7.5$  Hz,  $\text{H}_2\text{CO}$ ), 4.57 (1H, br s, HO), 4.19 (1H, br s, HC-4), 3.99 (1H, br s, HO), 3.92 (1H, dd,  $J = 1.5, 8.5$  Hz, HC-1'), 3.66 (1H, ddd,  $J = 3.5, 10, 10$  Hz, HC-4''), 3.43 (3H, s,  $\text{H}_3\text{CO}$ ), 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, dddd,  $J = 3, 3, 6, 13$  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, dddd,  $J = 3, 9, 10, 10$  Hz), 1.93-1.82 (2H, m), 1.79 (1H, dddd,  $J = 3.5, 10.5, 10.5, 13.5$  Hz);

**<sup>13</sup>C NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 93), 159 (37), 129 (60), 117 (47), 101 (58), 100 (100), 99 (83), 67 (35).

**HRMS**  $m/z$  calcd for  $\text{C}_{13}\text{H}_{24}\text{O}_4\text{S}_2$  308.1116, found 308.1113 (EI).

**(1'R\*, 3S\*, 3''R\*, 4S\*, 4''S\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl]methyl)tetrahydro-2H-thiopyran-4-ol (246).**



Following General procedure F, the  $\text{NaBH}(\text{OAc})_3$  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  $\nu_{\max}$  3426, 2928, 1430, 1278, 1147, 1097, 1035, 917  $\text{cm}^{-1}$ ;

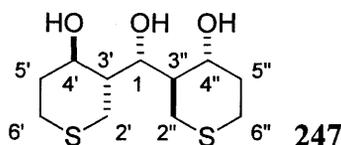
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.80 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.69 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.31 (1H, dd,  $J = 2.5, 9$  Hz, HC-1'), 3.84 (1H, br s, HOC-1'), 3.73 (1H, ddd,  $J = 3, 8, 9$  Hz, HC-4), 3.71 (1H, ddd,  $J = 4, 9.5, 10$  Hz, HC-4''), 3.42 (3H, s,  $\text{H}_3\text{CO}$ ), 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,  $J = 3, 8, 9, 9$  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'');

$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 78), 159 (45), 129 (94), 117 (60), 101 (52), 100 (100), 99 (71), 67 (36).

HRMS  $m/z$  calcd for  $\text{C}_{13}\text{H}_{24}\text{O}_4\text{S}_2$  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  $\text{CH}_2\text{Cl}_2$ :

IR  $\nu_{\max}$  3374, 3284, 2932, 2907, 2505, 1427, 1052, 1025  $\text{cm}^{-1}$ ;

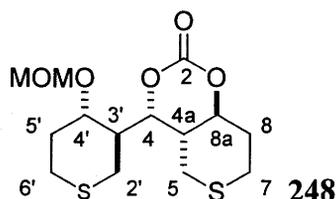
$^1\text{H NMR}$  (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  4.33 (1H, dd,  $J = 2, 9$  Hz, HC-1'), 3.71 (1H, ddd,  $J = 3.5, 9, 9$  Hz, HC-4), 3.54 (1H, ddd,  $J = 4, 10.5, 10.5$  Hz, HC-4''), 2.71-2.52 (6H, m, HC-2, HC-6,  $\text{H}_2\text{C}-2''$ ,  $\text{H}_2\text{C}-6''$ ), 2.50 (1H, ddd,  $J = 2.5, 3, 14$  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'');

$^{13}\text{C}$  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 ( $[\text{M}]^+$ , 93), 129 (90), 117 (99), 100 (100), 99 (49), 87 (51), 83 (39), 67 (36).

HRMS  $m/z$  calcd for  $\text{C}_{11}\text{H}_{20}\text{O}_3\text{S}_2$  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-thiopyrano[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  $\text{cm}^{-1}$ ;

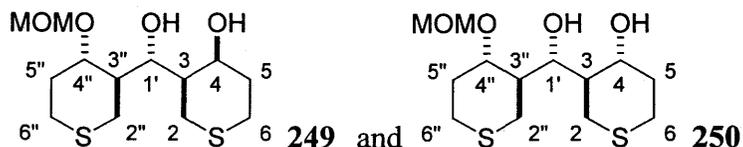
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.74 (1H, dd,  $J = 6, 6$  Hz, HC-4 [ $^3J_{\text{HC-4}/\text{HC-4a}} = 6$  Hz]), 4.71 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.67 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.39 (1H, ddd,  $J = 4.5, 11, 11$  Hz, HC-8a), 3.70 (1H, ddd,  $J = 3, 7.5, 7.5$  Hz, HC-4'), 3.37 (3H, s,  $\text{H}_3\text{CO}$ ), 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);

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 100), 139 (58), 137 (42), 101 (39), 100 (44), 99 (90), 85 (48), 67 (52).

HRMS  $m/z$  calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_5\text{S}_2$  334.0909, found 334.0908 (EI).

(1'S\*, 3S\*, 3''S\*, 4R\*, 4''R\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl]methyl)tetrahydro-2H-thiopyran-4-ol (**249**) (1'S\*, 3S\*, 3''S\*, 4S\*, 4''R\*)-3-(Hydroxy[4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl]methyl)tetrahydro-2H-thiopyran-4-ol (**250**).



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  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.81 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 4.67 (1H, d,  $J = 7$  Hz,  $\text{H}_2\text{CO}$ ), 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,  $\text{H}_3\text{CO}$ ), 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);

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 53), 159 (30), 129 (57), 117 (42), 101 (51), 100 (100), 99 (66), 67 (36).

HRMS  $m/z$  calcd for  $\text{C}_{13}\text{H}_{24}\text{O}_4\text{S}_2$  308.1116, found 308.1112 (EI).

Data for **250**:

IR  $\nu_{\max}$  3394, 2926, 1429, 1147, 1100, 1067, 1034, 915  $\text{cm}^{-1}$ ;

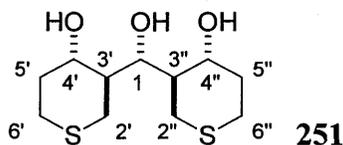
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 4.72 (1H, d, *J* = 6.5 Hz, H<sub>2</sub>CO), 4.69 (1H, d, *J* = 6.5 Hz, H<sub>2</sub>CO), 3.76 (1H, ddd, *J* = 3.5, 8, 9.5 Hz, HC-4), 3.75 (1H, dd, *J* = 3.5, 7 Hz, HC-1'), 3.62 (1H, ddd, *J* = 4, 9, 10.5 Hz, HC-4''), 3.41 (3H, s, H<sub>3</sub>CO), 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'', H<sub>2</sub>C-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, dddd, *J* = 3.5, 3.5, 8, 8 Hz, HC-3), 2.02 (1H, dddd, *J* = 3.5, 7.5, 9, 11 Hz, HC-3''), 1.85 (1H, dddd, *J* = 3, 9.5, 10, 13.5 Hz, HC-5), 1.77 (1H, dddd, *J* = 4, 10, 10.5, 13 Hz, HC-5'');

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 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]<sup>+</sup>, 56), 159 (35), 129 (87), 117 (55), 101 (52), 100 (100), 99 (70), 67 (42).

**HRMS** *m/z* calcd for C<sub>13</sub>H<sub>24</sub>O<sub>4</sub>S<sub>2</sub> 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).**



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**  $\nu_{\max}$  3345, 2925, 2848, 1429, 1336, 1283, 1068, 1034 cm<sup>-1</sup>;

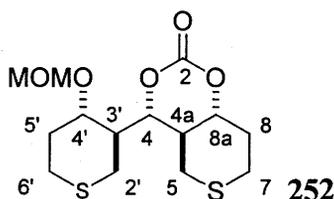
**<sup>1</sup>H NMR** (500 MHz, CD<sub>3</sub>OD) δ 3.86 (1H, t, *J* = 5.5 Hz, HC-1), 3.66 (2H, ddd, *J* = 3.5, 10, 10 Hz, HC-4', HC-4''), 2.71 (2H, dd, *J* = 3, 13.5 Hz, HC-2', HC-2''), 2.64-2.58 (4H, m, H<sub>2</sub>C-6', H<sub>2</sub>C-6''), 2.54 (2H, dd, *J* = 10.5, 13.5 Hz, HC-2', HC-2''), 2.22 (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'');

$^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  79.30 (d), 72.33 (d  $\times 2$ ), 49.52 (d  $\times 2$ ), 37.75 (t  $\times 2$ ), 31.08 (t  $\times 2$ ), 27.86 (t  $\times 2$ );

LRMS (EI),  $m/z$  (relative intensity): 264 ( $[\text{M}]^+$ , 53), 129 (86), 101 (34), 100 (100), 99 (49), 87 (47), 85 (36), 67 (38).

HRMS  $m/z$  calcd for  $\text{C}_{11}\text{H}_{20}\text{O}_3\text{S}_2$  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  $\text{cm}^{-1}$ ;

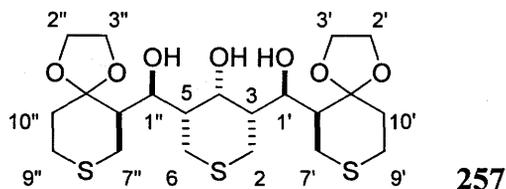
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.68 (2H, ap s,  $\text{H}_2\text{CO}$ ), 4.12 (1H, dd,  $J = 1.5, 10$  Hz, HC-4 [ $^3J_{\text{HC-4}/\text{HC-4a}} = 10$  Hz]), 3.97 (1H, ddd,  $J = 4.5, 11, 11$  Hz, HC-8a), 3.75 (1H, ddd,  $J = 4, 10, 10.5$  Hz, HC-4'), 3.37 (3H, s,  $\text{H}_3\text{CO}$ ), 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,  $\text{H}_2\text{C-6}'$ ), 2.55 (1H, dddd,  $J = 3.5, 3.5, 4, 13.5$  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');

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 100), 272 (85), 271 (86), 201 (44), 139 (57), 137 (38), 99 (75), 67 (42).

HRMS  $m/z$  calcd for  $C_{14}H_{22}O_5S_2$  334.0909, found 334.0909 (EI).

(3R,4s,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-4-hydroxy-2H-thiopyran (257)



Prepared by C. C. Man from reduction of **165d** (Cs anti) with DIBAL-H.<sup>30</sup>  
Included here for completeness only.

IR (DRIFT)  $\nu_{\max}$  3460, 2952, 2916, 1426, 1160, 1107, 1045  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $C_6D_6$ )  $\delta$  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  $\times 3$ ,  $H_2CO \times 4$ ,  $H_2C-3$ ,  $H_2C-5$ ), 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'').

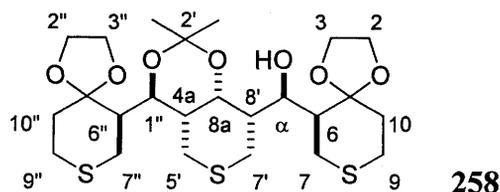
$^{13}\text{C}$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  110.0 (s  $\times 2$ ), 70.5 (d  $\times 2$ ), 64.6 (t  $\times 2$ ), 64.4 (d), 64.2 (t  $\times 2$ ), 47.1 (d  $\times 2$ ), 46.1 (d  $\times 2$ ), 35.8 (t  $\times 2$ ), 26.6 (t  $\times 2$ ), 26.6 (t  $\times 2$ ), 24.7 (t  $\times 2$ ).

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  $C_{21}H_{34}O_7S_3$  494.1467, found 494.1467 (EI).

Anal. Calcd for  $C_{21}H_{34}O_7S_3$ : C, 50.99; H, 6.93. Found: C, 51.12; H, 7.01.

**( $\alpha$ R,6S)-rel- $\alpha$ -[(4S,4aS,8S,8aR)-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 (258)**



Prepared by Dr. C. Guo from reaction of **XX** with dimethoxypropane in the presence of p-TsOH.<sup>30</sup> Included here for completeness only.

**IR** (DRIFT)  $\nu_{\max}$  3515, 2915, 1425, 1258, 1222, 1167, 1107, 1066, 1046, 1028  $\text{cm}^{-1}$ .

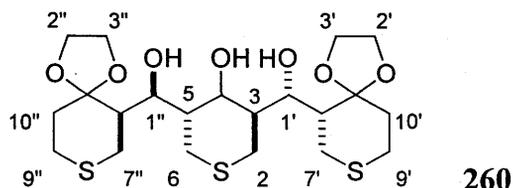
**$^1\text{H}$  NMR** (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  4.68 (1H, br s, HC-8a), 4.35 (1H, ddd,  $J = 2.5, 3, 8.5$  Hz, HC- $\alpha$ ), 3.93 (1H, dd,  $J = 5.5, 5.5$  Hz, HC-4'), 3.29 (1H, d,  $J = 3$  Hz, HO), 3.41-2.80 (14H, m), 2.74 (1H, br d,  $J = 14$  Hz), 2.68-2.51 (3H, m), 2.45 (1H, 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).

**$^{13}\text{C}$  NMR** (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  110.9 (s), 109.3 (s), 101.6 (s), 72.1 (d), 69.6 (d), 64.9 (t  $\times 2$ ), 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 ( $[\text{M}]^+$ , 6), 458 (4), 189 (8), 159 (14), 132 (53), 99 (100), 86 (12), 67 (17).

**HRMS**  $m/z$  calcd for  $\text{C}_{24}\text{H}_{38}\text{O}_7\text{S}_3$  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** ( $\text{C}_2$  anti) with DIBAL-H.<sup>30</sup> NMR assignment and analysis this work.

IR (DRIFT)  $\nu_{\max}$  3435, 2919, 1427, 1259, 1158, 1133, 1107, 1044  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{H}_2\text{CO} \times 4$ ), 3.39 (3H, br s, HO  $\times 3$ ), 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).

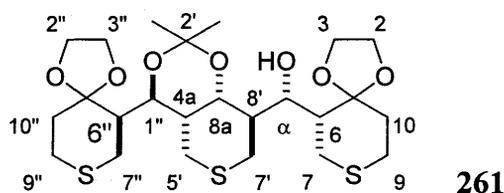
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  110.2 (s), 110.1 (s), 70.7 (d), 68.6 (d), 68.5 (d), 64.8 (t), 64.7 (t), 64.2 (t  $\times 2$ ), 47.4 (d), 46.8 (d), 42.2 (d), 40.5 (d), 36.5 (t), 36.1 (t), 26.7 (t), 26.6 (t  $\times 2$ ), 25.3 (t), 25.7 (t), 25.6 (t).

LRMS (EI),  $m/z$  (relative intensity): 494 ( $[\text{M}]^+$ , 7), 273 (20), 189 (12), 161 (14), 159 (16), 132 (62), 117 (17), 99 (100).

HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{32}\text{O}_7\text{S}_3$  494.1467, found 494.1467 (EI).

Anal. Calcd for  $\text{C}_{21}\text{H}_{32}\text{O}_7\text{S}_3$ : C, 50.99; H, 51.02. Found: C, 6.93; H, 6.89.

( $\alpha\text{S},6\text{R}$ )-rel- $\alpha$ -[(4S,4aS,8R,8aR)-4-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yltetrahydro-2,2-dimethyl-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-8-yl]-1,4-dioxo-8-thiaspiro[4.5]decane-6-methanol (**261**)



Prepared by Dr. C. Guo from reaction of **260** with dimethoxypropane in the presence of  $p\text{-TsOH}$ .<sup>30</sup> NMR assignment and analysis this work.

IR (DRIFT)  $\nu_{\max}$  3509, 2915, 1427, 1378, 1260, 1223, 1161, 1110, 1046  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.55 (1H, d,  $J = 9.5$  Hz, HC- $\alpha$ ), 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,  $J = 3.5, 4,$

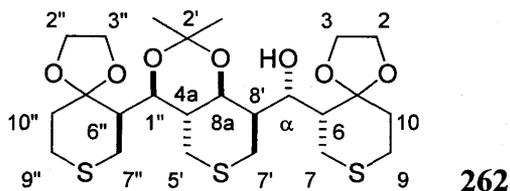
6, 12 Hz, HC-4a), 2.06-1.97 (2H, m), 1.97-1.89 (2H, m, HC-6'', HC-8''), 1.78-1.68 (2H, m, HC-10, HC-10''), 1.32 (3H, s, H<sub>3</sub>C), 1.31 (3H, s, H<sub>3</sub>C).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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]<sup>+</sup>, 10), 458 (6), 281 (6), 189 (9), 159 (14), 132 (50), 117 (6), 99 (100).

HRMS *m/z* calcd for C<sub>24</sub>H<sub>38</sub>O<sub>7</sub>S<sub>3</sub> 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-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 (262)**



Prepared by Dr. C. Guo from reaction of **260** with dimethoxypropane in the presence of p-TsOH.<sup>30</sup> NMR assignment and analysis this work.

IR (DRIFT)  $\nu_{\max}$  3513, 2915, 1425, 1378, 1308, 1167, 1107, 1065, 1046 cm<sup>-1</sup>.

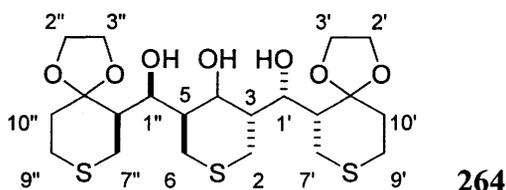
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.84 (1H, br dd, *J* = 2.5, 9.5 Hz, HC-α), 4.26 (1H, d, *J* = 2.5 Hz, HO), 4.22-4.17 (1H, m), 4.13-4.09 (1H, m), 4.03-3.85 (6H, m), 3.93 (1H, dd, *J* = 1.5, 10.5 Hz, HC-4'), 3.89 (1H, dd, *J* = 4.5, 11 Hz, HC-8a), 3.14 (1H, dd, *J* = 12, 14 Hz), 3.00 (1H, 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, dddd, *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, H<sub>3</sub>C), 1.33 (3H, s, H<sub>3</sub>C).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  110.5 (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).

LRMS (EI),  $m/z$  (relative intensity): 534 ( $[\text{M}]^+$ , 7), 458 (4), 189 (7), 159 (14), 132 (57), 99 (100), 86 (12), 67 (11).

HRMS  $m/z$  calcd for  $\text{C}_{24}\text{H}_{38}\text{O}_7\text{S}_3$  534.1780, found 534.1779 (EI).

**(3S,5S)-rel-3,5-bis[(S)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-tetrahydro-4-hydroxy-2H-thiopyran (264)**



Prepared by Dr. C. Guo from reduction of **165c** ( $\text{C}_2$  syn) with DIBAL-H.<sup>30</sup>

Included here for completeness only.

IR (DRIFT)  $\nu_{\text{max}}$  3501, 2917, 1427, 1260, 1131, 1116, 1048, 1035  $\text{cm}^{-1}$ .

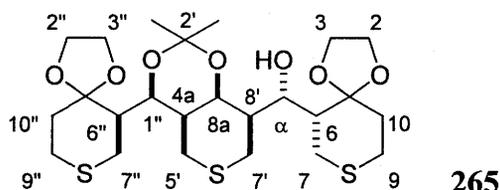
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.79 (1H, d,  $J = 10.5$  Hz, H-4), 4.15-3.94 (9H, m, H-1' or H-1'',  $\text{H}_2\text{CO} \times 4$ ), 3.87 (1H, br d, H-1' or H-1''), 3.22 (1H, dd,  $J = 3.5, 13.5$  Hz), 3.09 (1H, dd,  $J = 12, 14$  Hz), 3.04-2.88 (2H, m), 2.84-2.69 (4H, m), 2.65-2.59 (2H, m), 2.54-2.48 (2H, m), 2.16-2.10 (3H, m), 2.02-1.92 (3H, m), 1.83-1.70 (2H, m).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  110.3 (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  $\times 2$ ), 26.5 (t), 25.8 (t), 23.4 (t), 22.7 (t).

LRMS (EI),  $m/z$  (relative intensity): 494 ( $[\text{M}]^+$ , 8), 273 (12), 188 (16), 159 (15), 131 (71), 117 (15), 99 (100).

HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{34}\text{O}_7\text{S}_3$  494.1467, found 494.1467 (EI).

**( $\alpha$ S,6R)-rel- $\alpha$ -[(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 (265)**



Prepared by Dr. C. Guo from reaction of **264** with dimethoxypropane in the presence of p-TsOH.<sup>30</sup> Included here for completeness only.

**IR** (DRIFT)  $\nu_{\max}$  3529, 2921, 1426, 1260, 1198, 1170, 1151, 1112, 1046  $\text{cm}^{-1}$ .

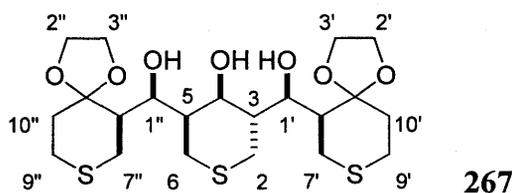
**$^1\text{H}$  NMR** (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.01 (1H, d,  $J = 10$  Hz, HC- $\alpha$ ), 4.23 (1H, d,  $J = 9.5$  Hz, HC-4'), 4.06 (1H, br s, HC-8a), 3.67-3.58 (1H, m), 3.40-3.50 (6H, m), 3.33-3.24 (1H, m), 3.25-3.16 (3H, m), 3.11-2.99 (3H, m), 2.88 (1H, br dd,  $J = 8, 13.5$  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).

**$^{13}\text{C}$  NMR** (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  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  $\times 2$ ), 26.9 (t), 24.6 (t), 22.3 (t), 19.7 (q).

**LRMS** (EI),  $m/z$  (relative intensity): 534 ( $[\text{M}]^+$ , 26), 458 (10), 189 (14), 159 (14), 132 (60), 99 (100), 86 (11), 67 (14).

**HRMS**  $m/z$  calcd for  $\text{C}_{24}\text{H}_{38}\text{O}_7\text{S}_3$  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.<sup>30</sup> Included here for completeness only.

IR (DRIFT)  $\nu_{\max}$  3500, 2917, 1427, 1261, 1158, 1133, 1110, 1042  $\text{cm}^{-1}$ .

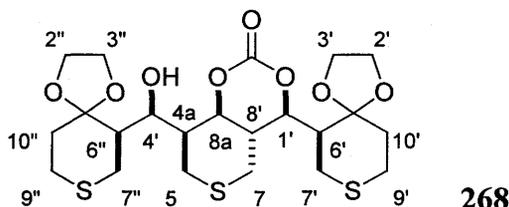
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.72 (1H, d,  $J = 10$  Hz, HC-1'), 4.23 (1H, br s, HC-1''), 4.18 (1H, dd,  $J = 1.5, 8$  Hz, HC-4), 4.14-3.94 (10H, m), 3.13 (1H, dd,  $J = 3, 14$  Hz), 3.06-2.93 (3H, m), 2.86-2.75 (3H, m), 2.61-2.49 (4H, m), 2.25 (1H, ddd,  $J = 2, 3, 10$  Hz), 2.20-2.12 (4H, m), 1.94-2.06 (2H, m), 1.78-1.68 (2H, m).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>21</sub>H<sub>34</sub>O<sub>7</sub>S<sub>3</sub> 494.1467, found 494.1462 (EI).

**(4R,4aR,8S,8aR)-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)**



Prepared by Dr. C. Guo from the reaction of **267** with 1,1'-carbonyldiimidazole.<sup>30</sup> NMR assignment and analysis this work.

IR (DRIFT)  $\nu_{\max}$  3504, 2917, 1754, 1427, 1337, 1255, 1157, 1113, 1044  $\text{cm}^{-1}$ .

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>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-

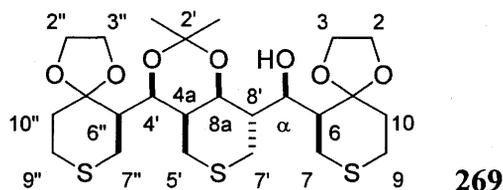
2.42 (6H, m), 2.27 (1H, ddd,  $J = 2.5, 3, 11$  Hz, HC-6'), 2.14 (1H, br dd,  $J = 2, 11$  Hz, HC-6''), 2.13-2.08 (2H, m, HC-10', HC-10''), 1.78-1.69 (2H, m, HC-10', HC-10'').

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\times 2$ ), 26.2 (t).

LRMS (EI),  $m/z$  (relative intensity): 520 ( $[\text{M}]^+$ , 6), 475 (13), 458 (2), 159 (19), 132 (52), 99 (100), 86 (12), 54 (14).

HRMS  $m/z$  calcd for  $\text{C}_{22}\text{H}_{32}\text{O}_8\text{S}_3$  520.1259, found 520.1257 (EI).

**( $\alpha\text{R}, 6\text{S}$ )-rel- $\alpha$ -[(4S,4aR,8S,8aS)-4-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yltetrahydro-2,2-dimethyl-4H,5H-thiopyrano[4,3-d]-1,3-dioxin-8-yl]-1,4-dioxo-8-thiaspiro[4.5]decane-6-methanol (**269**)**



Prepared by Dr. C. Guo from the reaction of **267** with dimethoxypropane in the presence of p-TsOH.<sup>30</sup> Included here for completeness only.

IR (DRIFT)  $\nu_{\text{max}}$  3515, 2921, 1427, 1260, 1199, 1171, 1106, 1048  $\text{cm}^{-1}$ .

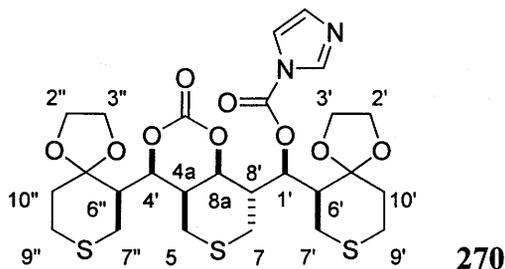
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.78 (1H, d,  $J = 10$  Hz, HC- $\alpha$ ), 4.36 (1H, br s, H-8a), 4.25 (1H, d,  $J = 8.5$  Hz, HC-4'), 4.14-4.09 (2H, m), 4.04-3.89 (7H, m), 3.21-3.12 (2H, m), 3.06-2.91 (2H, m), 2.82 (1H, dd,  $J = 12, 13.5$  Hz), 2.77-2.52 (5H, m), 2.38 (1H, 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).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\times 2$ ), 25.6 (t), 24.6 (t), 22.4 (t), 20.1 (q).

LRMS (EI),  $m/z$  (relative intensity): 534 ( $[\text{M}]^+$ , 28), 458 (11), 326 (7), 199 (10), 189 (15), 159 (15), 132 (65), 99 (100).

HRMS  $m/z$  calcd for  $C_{24}H_{38}O_7S_3$  534.1780, found 534.1782 (EI).

(4S,4aR,8S,8aS)-rel-4-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl-8-[(R)-(6S)-1,4-dioxo-8-thiaspiro[4.5]dec-6-yl(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.<sup>30</sup>

NMR assignment and analysis this work.

IR (DRIFT)  $\nu_{\max}$  2917, 1755, 1752, 1392, 1283, 1241, 1211, 1099  $\text{cm}^{-1}$ .

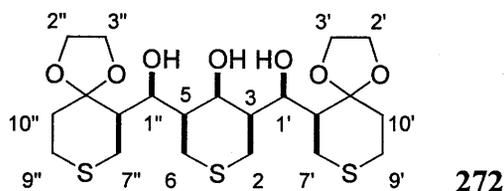
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.41 (1H, br s, ArH), 7.51 (1H, s, ArH), 7.22 (1H, s, ArH), 6.26 (1H, d,  $J = 10.5$  Hz, HC-1'), 4.62 (1H, br d,  $J = 9.5$  Hz, HC-4), 4.59 (1H, br s, HC-8a), 4.10-3.85 (6H, m), 3.80-3.73 (1H, m), 3.70-3.63 (1H, m), 3.19 (1H, dd,  $J = 2.5, 15$  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), 2.31 (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'').

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $[\text{M}]^+$ , 15), 481 (5), 159 (8), 132 (46), 99 (100), 86 (11), 69 (11), 67 (10).

HRMS  $m/z$  calcd for  $C_{26}H_{34}N_2O_9S_3$  614.1426, found 614.1428 (EI).

**(3*S*,4*s*,5*R*)-rel-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4-hydroxy-2*H*-thiopyran (272)**



Prepared by Dr. C. Guo from the reaction of **165b** with DIBAL-H.<sup>30</sup> Included here for completeness only.

**IR** (DRIFT)  $\nu_{\max}$  3510, 1427, 1338, 1261, 1159, 1133, 1111, 1043  $\text{cm}^{-1}$ .

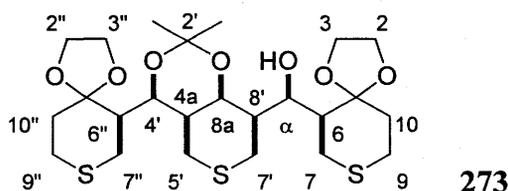
**<sup>1</sup>H NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.24 (2H, dd,  $J = 3, 5.5$  Hz, HC-1', HC-1''), 4.07 (1H, br s, HC-4), 4.05-3.95 (8H, m,  $\text{H}_2\text{CO} \times 4$ ), 3.03 (2H, dd,  $J = 13, 13.5$  Hz, HC-2, HC-6), 2.96 (2H, dd,  $J = 9.5, 14$  Hz, HC-7', HC-7''), 2.82-2.58 (6H, m), 2.47 (2H, dd,  $J = 2.5, 13.5$  Hz, HC-2, HC-6), 2.09-2.19 (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'').

**<sup>13</sup>C NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  109.0 (s  $\times 2$ ), 72.3 (d  $\times 2$ ), 72.0 (d), 64.8 (t  $\times 2$ ), 64.6 (t  $\times 2$ ), 48.0 (d  $\times 2$ ), 46.4 (d  $\times 2$ ), 35.5 (t  $\times 2$ ), 27.5 (t  $\times 2$ ), 26.8 (t  $\times 2$ ), 22.6 (t  $\times 2$ ).

**LRMS** (EI),  $m/z$  (relative intensity): 494 ( $[\text{M}]^+$ , 7), 476 (4), 273 (11), 189 (14), 159 (14), 132 (60), 117 (15), 99 (100).

**HRMS**  $m/z$  calcd for  $\text{C}_{21}\text{H}_{34}\text{O}_7\text{S}_3$  494.1467, found 494.1470 (EI).

**( $\alpha$ *R*,6*S*)-rel- $\alpha$ -[(4*S*,4*aR*,8*R*,8*aS*)-4-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yltetrahydro-2,2-dimethyl-4*H*,5*H*-thiopyrano[4,3-*d*]-1,3-dioxin-8-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol (273)**



Prepared by Dr. C. Guo from the reaction of **272** with dimethoxypropane in the presence of p-TsOH.<sup>30</sup> Included here for completeness only.

**IR** (DRIFT)  $\nu_{\max}$  3516, 2919, 1426, 1261, 1200, 1158, 1104, 1039  $\text{cm}^{-1}$ .

**<sup>1</sup>H NMR** (300 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  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).

**<sup>13</sup>C NMR** (75 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  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).

**LRMS** (EI),  $m/z$  (relative intensity): 534 ( $[\text{M}]^+$ , 11), 458 (5), 414 (7), 199 (7), 189 (7), 159 (14), 132 (65), 99 (100).

**HRMS**  $m/z$  calcd for C<sub>24</sub>H<sub>38</sub>O<sub>7</sub>S<sub>3</sub> 534.1780, found 534.1775 (EI).

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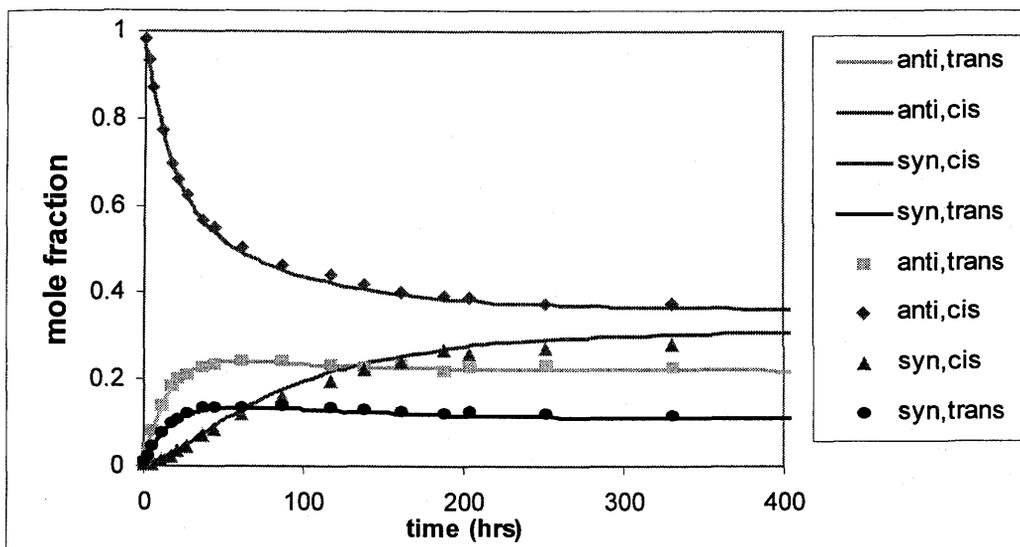
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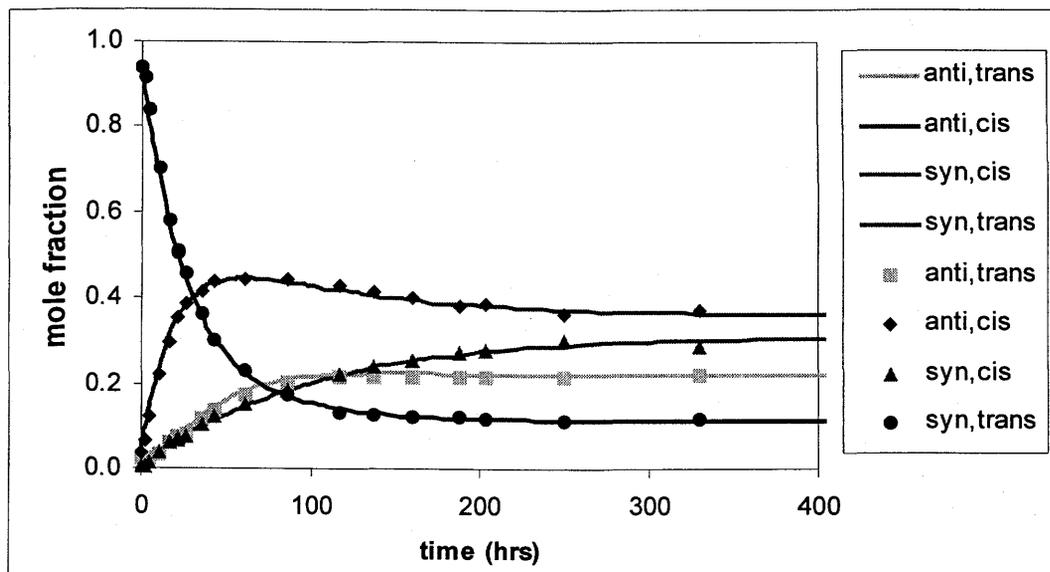
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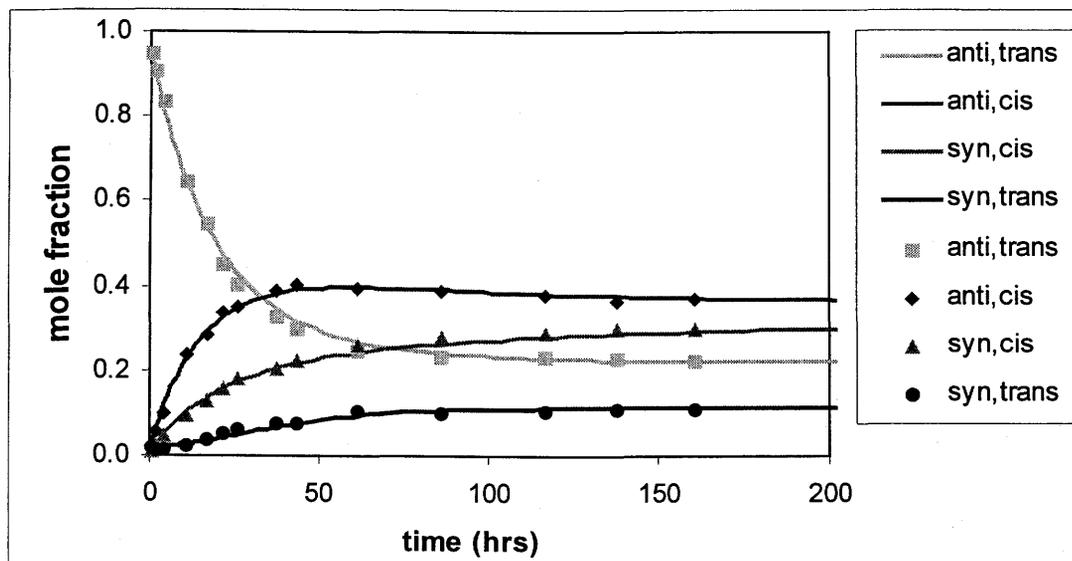
## 5. APPENDIX



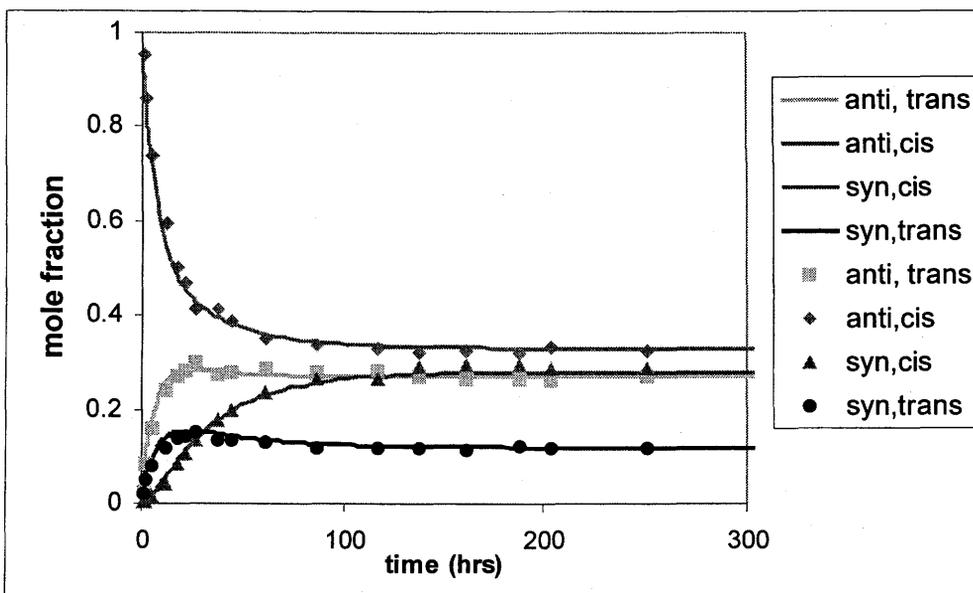
**Figure A1.** Isomerization of a mixture of 211st:211ac:211at (1:98:1) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.4 M) in CDCl<sub>3</sub>.



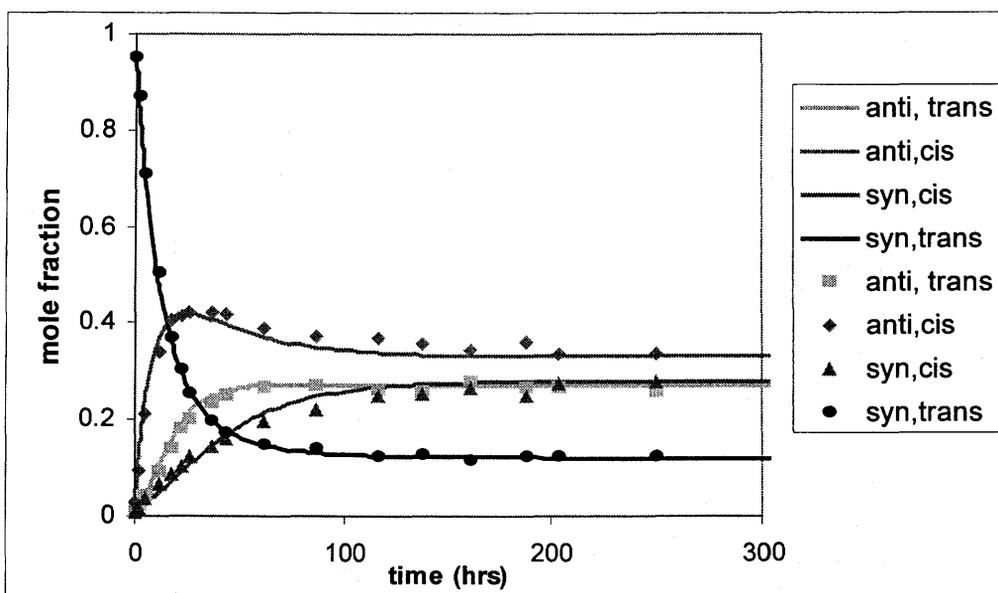
**Figure A2.** Isomerization of a mixture of **211st:211ac:211at** (94:4:2) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.4 M) in  $\text{CDCl}_3$ .



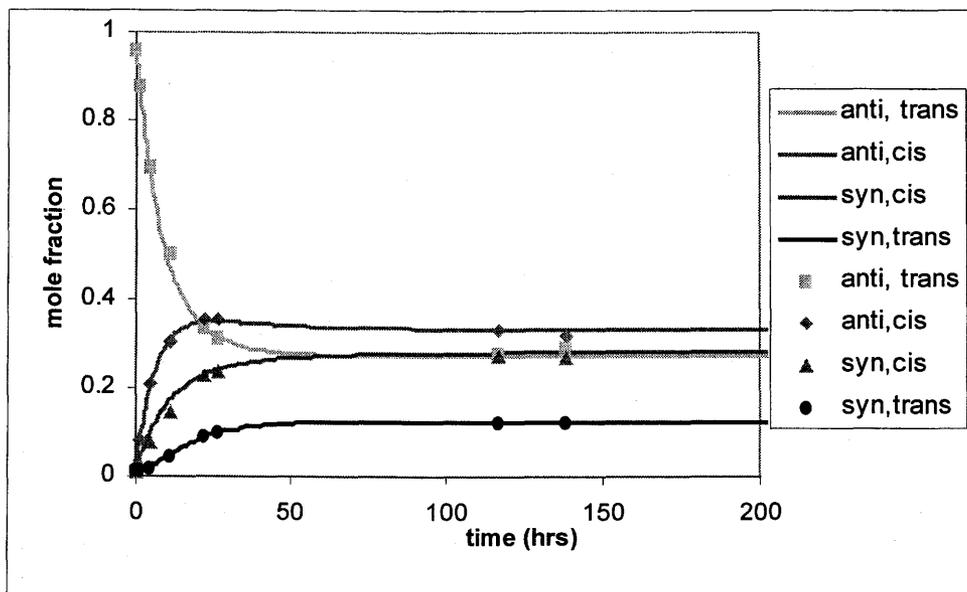
**Figure A3.** Isomerization of a mixture of **211st:211ac:211sc:211at** (2:2:1:95) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.4 M) in  $\text{CDCl}_3$ .



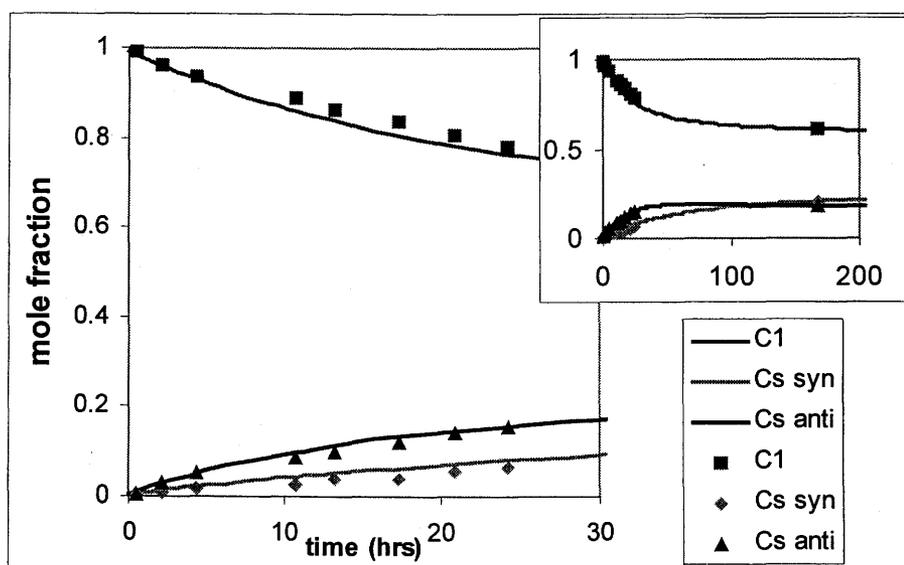
**Figure A4.** Isomerization of a mixture of **211st:211ac:211at** (1:98:1) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.8 M) in  $\text{CDCl}_3$ .



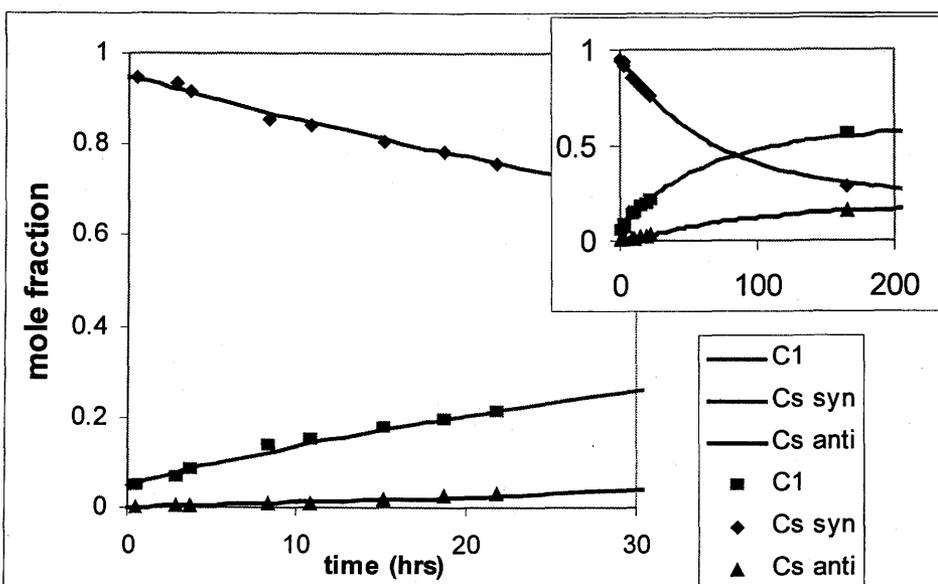
**Figure A5.** Isomerization of a mixture of **211st:211ac:211at** (94:4:2) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.8 M) in  $\text{CDCl}_3$ .



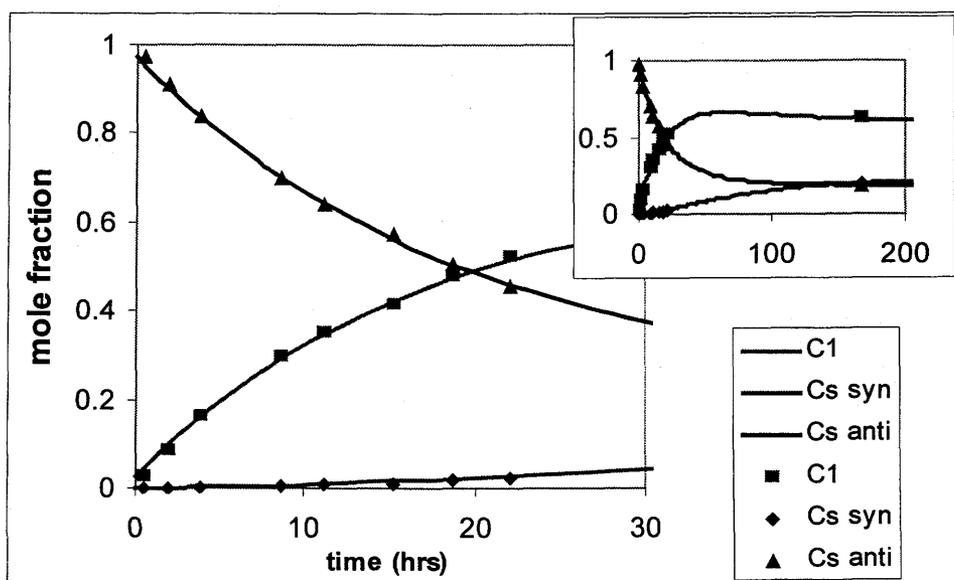
**Figure A6.** Isomerization of a mixture of **211st:211ac:211sc:211at** (2:2:1:95) with a total aldol concentration of 0.03 M (4 mg in 0.6 ml) in the presence of imidazole (0.8 M) in  $\text{CDCl}_3$ .



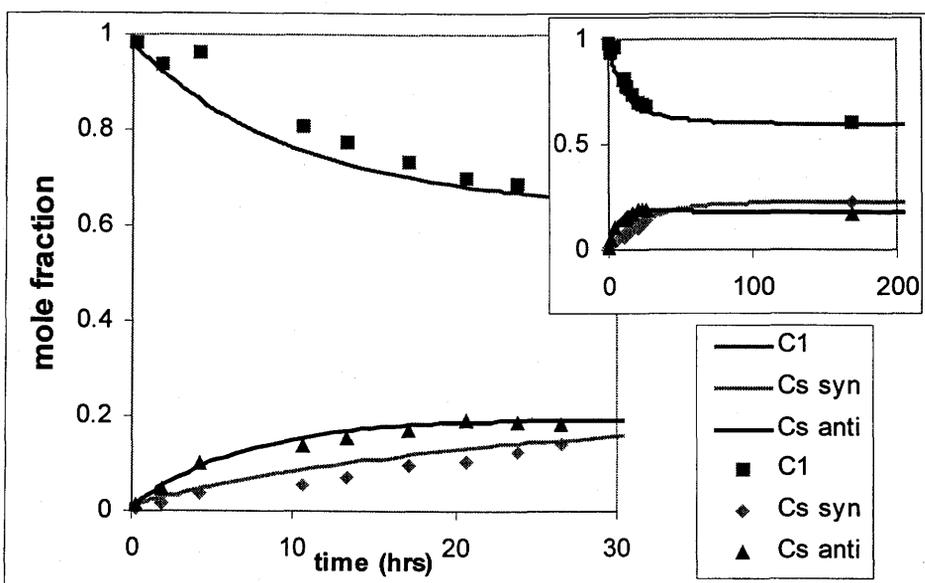
**Figure A7.** Isomerization of a mixture of **165a** ( $C_1$ ):**165d** ( $C_s$  anti) of 99:1 with a total aldol concentration of 0.03 M (8 mg in 0.6 ml) in the presence of imidazole (0.40 M) in  $\text{CDCl}_3$ .



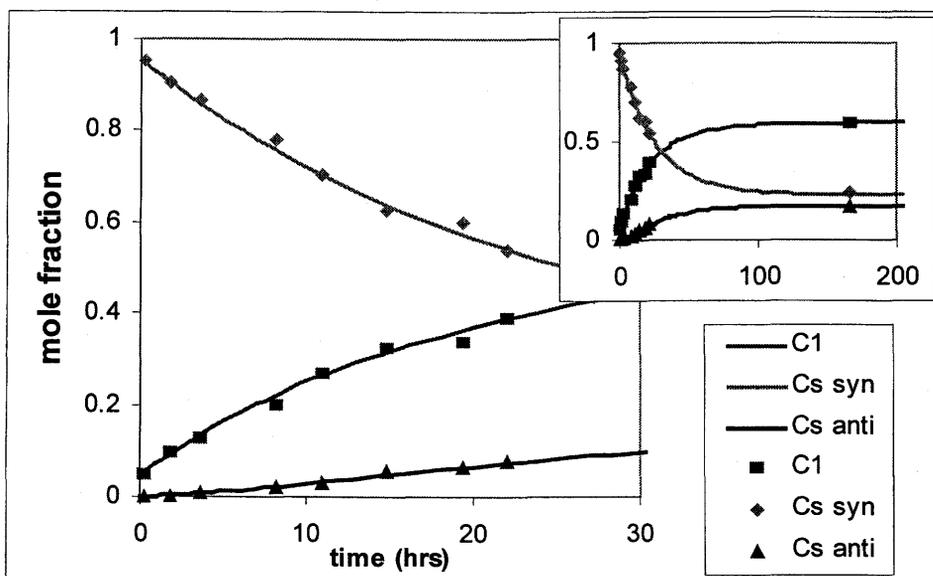
**Figure A8.** Isomerization of a mixture of 165b ( $C_s$  syn):165a ( $C_1$ ) of 95:5 with a total aldol concentration of 0.03 M (8 mg in 0.6 ml) in the presence of imidazole (0.40 M) in  $CDCl_3$ .



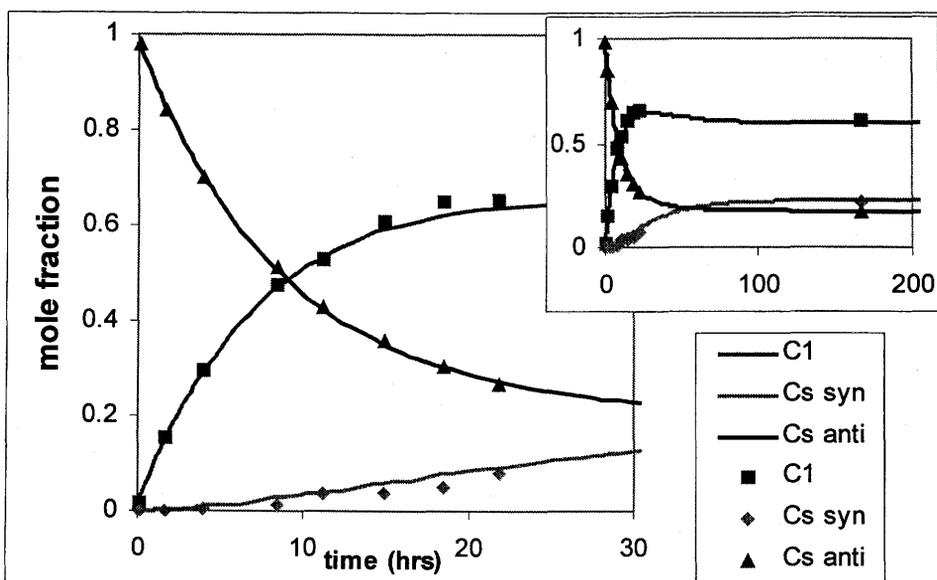
**Figure A9.** Isomerization of a mixture of 165a ( $C_1$ ):165d ( $C_s$  anti) of 3:97 with a total aldol concentration of 0.03 M (8 mg in 0.6 ml) in the presence of imidazole (0.40 M) in  $CDCl_3$ .



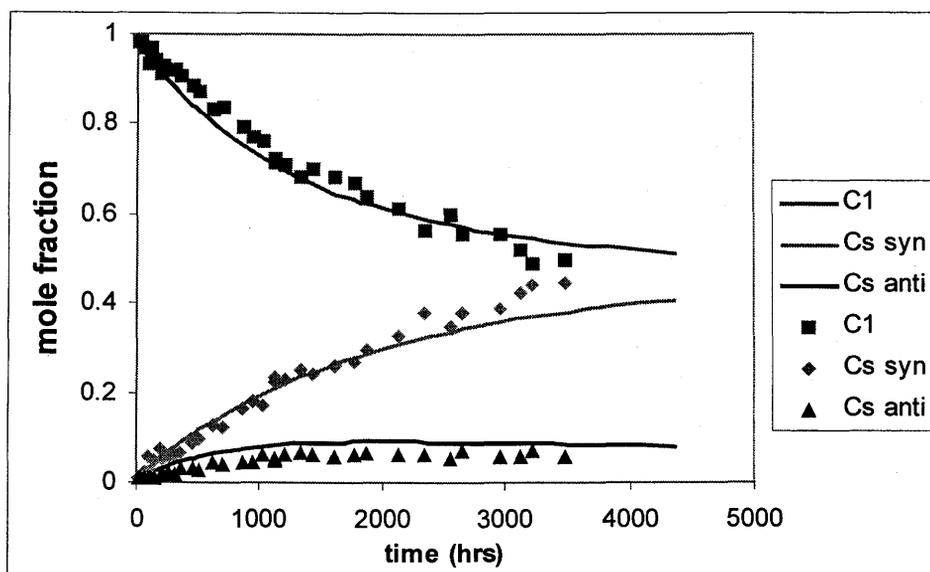
**Figure A10.** Isomerization of a mixture of **165a** ( $C_1$ ):**165d** ( $C_s$  *anti*) of 99:1 with a total aldol concentration of 0.03 M (8 mg in 0.6 ml) in the presence of imidazole (0.80 M) in  $CDCl_3$ .



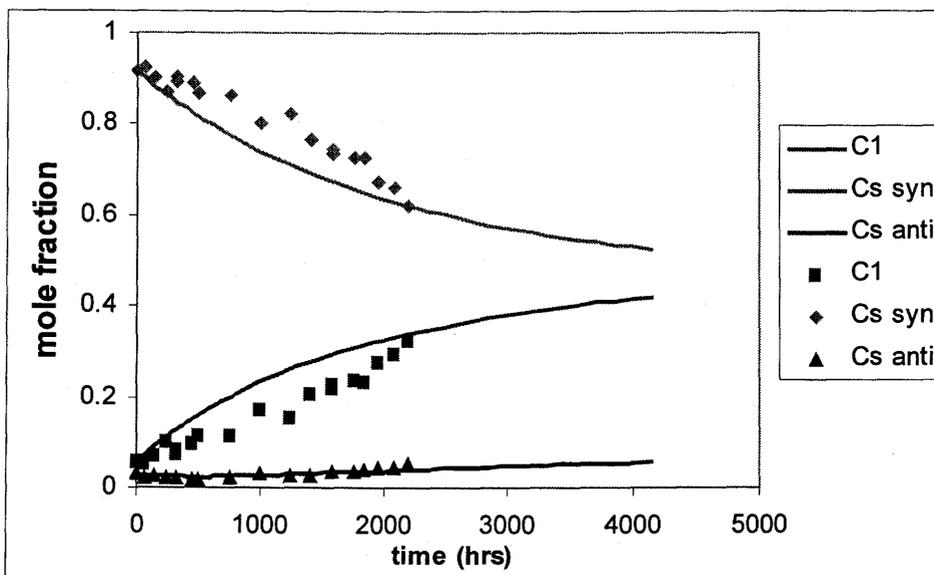
**Figure A11.** Isomerization of a mixture of **165b** ( $C_s$  *syn*):**165a** ( $C_1$ ) of 95:5 with a total aldol concentration of 0.03 M (8 mg in 0.6 ml) in the presence of imidazole (0.80 M) in  $CDCl_3$ .



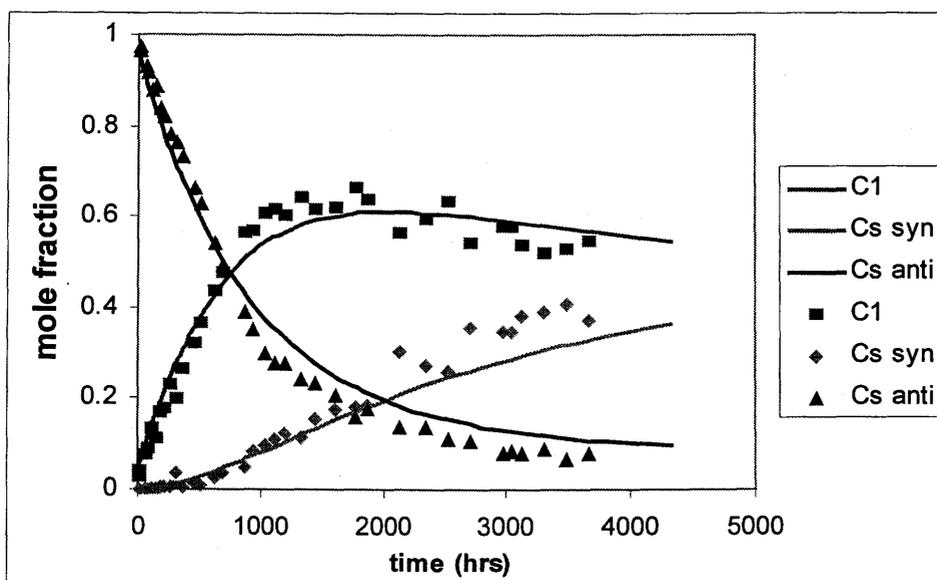
**Figure A12.** Isomerization of a mixture of **165a** ( $C_1$ ):**165d** ( $C_s anti$ ): of 3:97 with a total aldol concentration of 0.03 M (8mg in 0.6ml) in the presence of imidazole (0.80M) in  $CDCl_3$ .



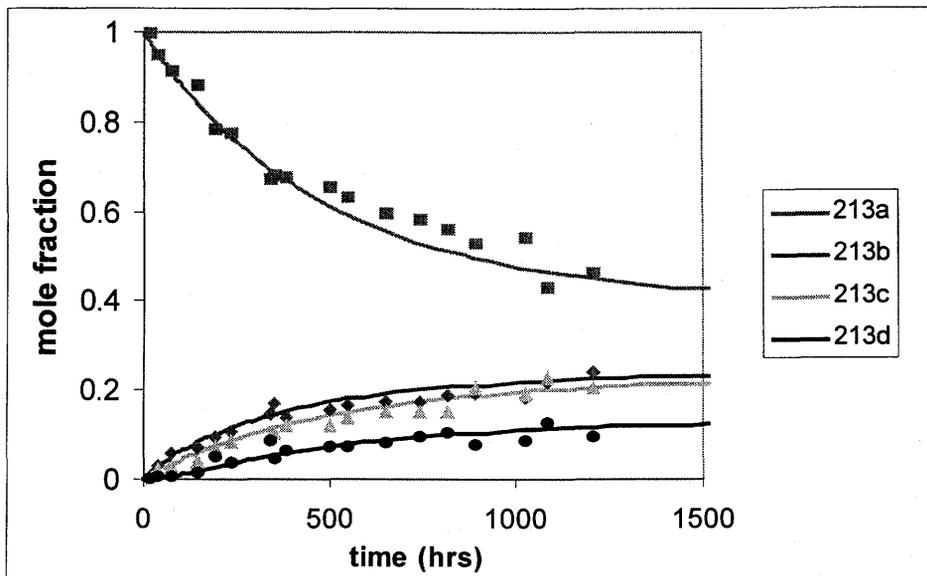
**Figure A13.** Isomerization of a mixture of **212a** ( $C_s syn$ ):**212b** ( $C_1$ ):**212c** ( $C_s anti$ ): of 1:98:1 with a total aldol concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in  $CDCl_3$ .



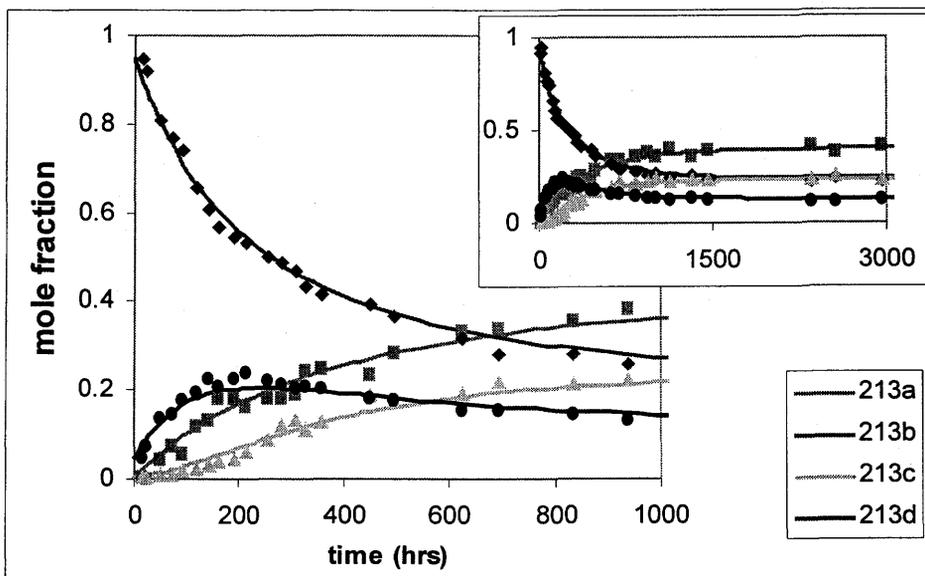
**Figure A14.** Isomerization of a mixture of **212a** (*C<sub>s</sub> syn*):**212b** (*C<sub>1</sub>*):**212c** (*C<sub>s</sub> anti*): of 92:5:3 with a total aldol concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl<sub>3</sub>.



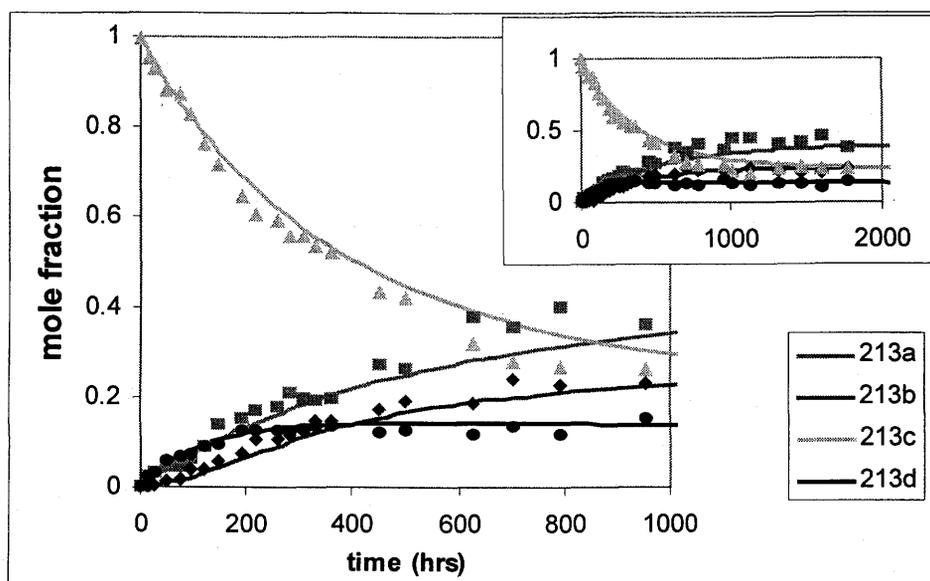
**Figure A15.** Isomerization of a mixture of **212b** (*C<sub>1</sub>*):**212c** (*C<sub>s</sub> anti*) of 4:96 with a total aldol concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in CDCl<sub>3</sub>.



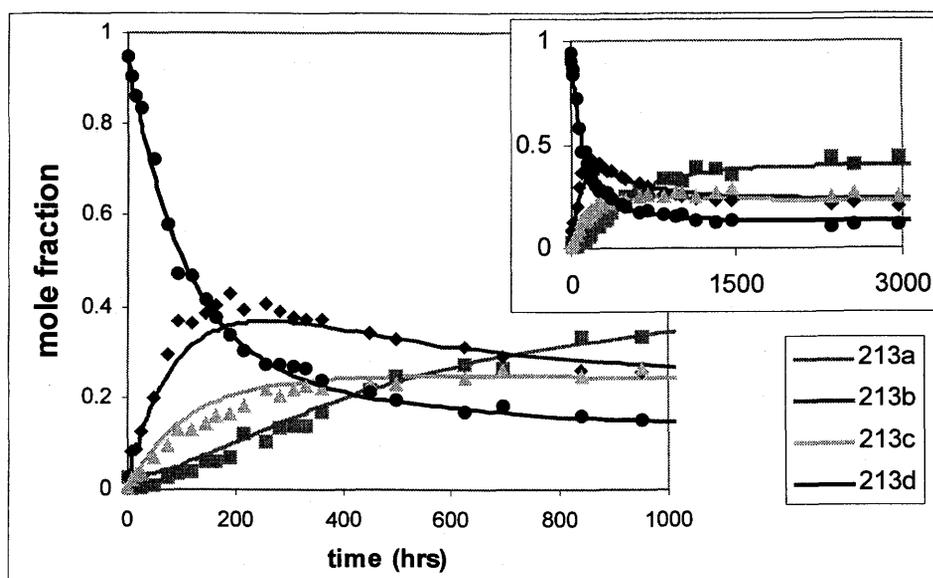
**Figure A16.** Isomerization of a pure **213a** (>99:1) with a concentration of 0.01 M (4 mg in 0.6 ml) in the presence of imidazole (0.40 M) in  $\text{CDCl}_3$ .



**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  $\text{CDCl}_3$ .



**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  $\text{CDCl}_3$ .



**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  $\text{CDCl}_3$ .