ALDOL COUPLINGS OF CHIRAL FRAGMENTS WITH KINETIC RESOLUTION: SCOPE AND LIMITATIONS

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by

Alieh Kazemeini

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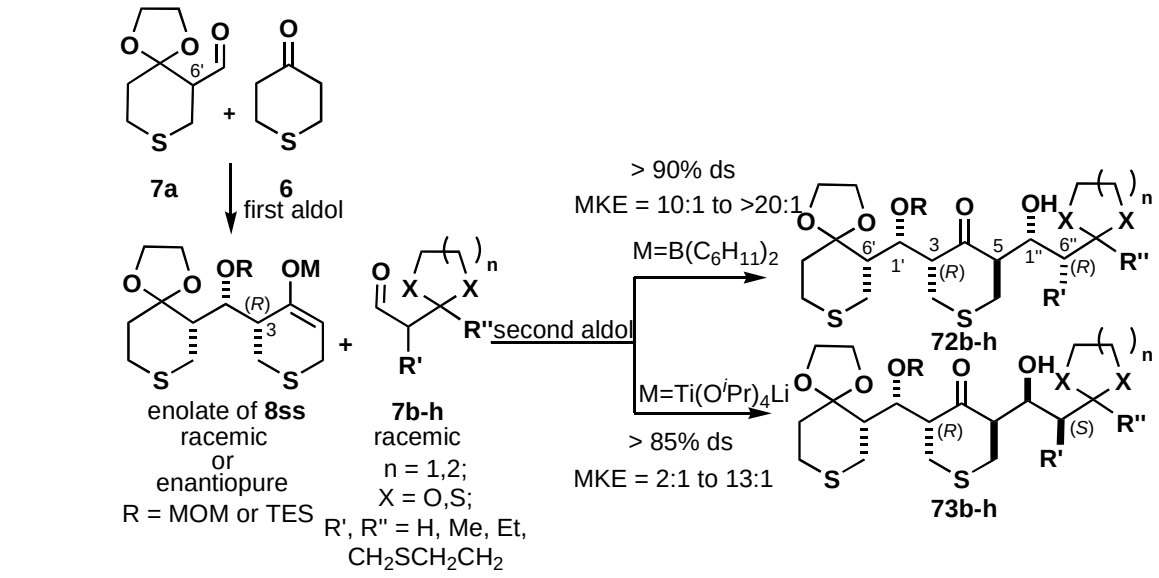
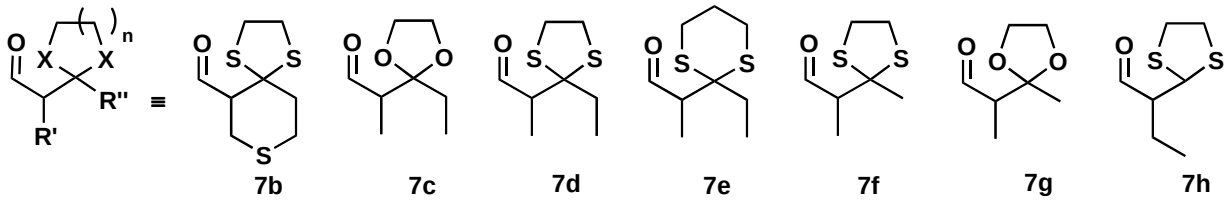
Abstract

"The Thiopyran Route to Polypropionates" is a synthetic strategy that involves the stepwise aldol reactions of **6** and **7a** to rapidly access stereochemically complex tetrapropionate **8** and hexapropionate synthons **72** or **73**. Coupling racemic **7a** with any of the four enantioenriched diastereomers **8** with kinetic resolution (KR) is possible with rational design of the reaction using the 'multiplicativity' rule. Thus, any of two of the eight possible aldol adducts, **72** or **73**, are selectively available from the same reactants.





The research in this thesis describes the effort to explore the scope and limitations of the above paradigm to design aldol reactions with KR. The synthesis of a variety of 'designed' aldehydes (**7b-h**), with an ethylene ketal, dithiolane, or dithiane

group at the β-position, and stereoselectivities of their reactions with boron and titanium "ate" enolates of **8ss** (R = MOM or TES) are described. Each of the aldehydes **7b-h** has one or two structural feature(s) different from aldehyde **7a**.

The reactions of boron enolates of (±)-**8ss** (R = MOM or TES) with aldehydes (±)-**7b-g** are highly *anti*-selective and proceeded with high mutual kinetic enantioselection (MKE) and produce one of the eight possible adducts, (±)-**72b-g**, with high selectivity. For reactions of racemic reactants, the MKE is the ratio of rate constants for reaction of a *like* versus *unlike* combination of reactant enantiomers. The MKE is simply determined by the ratio of product diastereomers. The reactions of titanium "ate" enolates of (±)-**8ss** (R = MOM or TES) with aldehydes (±)-**7b-g** are mostly *syn*-selective and proceed with moderate to good MKE producing (±)-**73b-g** but with lower selectivity compared to the boron enolates.

In principle, the MKE determined for a reaction of racemic reactants will be equal to the selectivity constant (*s*) in a kinetic resolution (KR) when one of the reactants is enantiopure. Comparison of the results of current study with those reported for the boron and titanium "ate" mediated aldol reactions of aldehyde **7a** shows that the aldol reactions of suitable enolates of enantioenriched **8** with aldehydes (+)-**7b-g** will occur with synthetically useful KR selectivity. As expected, reactions of (-)-**8ss** (R=MOM) with (±)-**7f** via the boron and titanium "ate" enolates produce enantiopure adducts with the stereoselectivity commensurate with the MKE observed using racemic reactants.

Some of the new aldol adducts accessed via coupling of enolate of **8** with new aldehydes **7b-g** have decreased symmetry because of the presence of different ketal protecting groups. This structural feature makes them potentially useful for future synthetic application.

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List of Abbreviations

α	observed optical rotation in degrees
$[\alpha]_D$	specific rotation at the sodium D line (expressed without units; implied actual units are: (deg·mL)/(g·dm))
Ac	acetyl
AcOH	acetic acid
ap	apparent (NMR signal)
aq	aqueous
Bn	benzyl
br	broad (description of a spectral signal)
n-BuLi	*n*-butyllithium
°C	degrees Celsius (temperature)
CI	chemical ionization (in mass spectrometry)
^{13}C NMR	carbon 13 nuclear magnetic resonance
$(COCl)_2$	oxalyl chloride
δ	NMR chemical shift in parts per million downfield from TMS
d	day(s); doublet (spectral signal)
dil	dilute
DIPA	*N*,*N*-diisopropylamine
DIPEA	*N*,*N*-diisopropylamine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomer ratio
DRIFT	diffuse reflectance Fourier transform infrared
DS	double stereodifferentiation
E and *Z*	configurational descriptors for alkenes. *E* denotes that the substituents of highest CIP (Cahn-Ingold-Prelog) priority at each end

	of the double bond are on opposite sides. If the pertinent substituents are on the same side, the descriptor is *Z*.
Et_3N	triethylamine
EtOAc	ethyl acetate
FCC	flash column chromatography
h	hour(s)
HF	hydrofluoric acid
^1H NMR	proton nuclear magnetic resonance
HRMS	high resolution mass spectrometry
IBX	2-Iodoxybenzoic acid
KR	kinetic resolution
like	stereodescriptor denoting those stereoisomers of a set whereby two designated stereogenic centers are *R* and *S* or vice/versa
MBDA	4,4'-Methylenebis(N,N-dimethylaniline)
MHz	megahertz
min	minute(s)
MKE	mutual kinetic enantioselection
NaOMe	sodium methoxide
PhSH	thiophenol
PTLC	preparative thin layer chromatography
R and *S*	absolute stereochemical configuration descriptors in the CIP (Cahn-Ingold-Prelog) system
rt	room temperature
sat	saturated
syn	synperiplanar
TES	triethylsilyl
TESCl	triethylsilyl chloride
THF	tetrahydrofuran
p-TsOH	*p*-toluenesulfonic acid

1. INTRODUCTION

1.1. Polypropionates

Over the past 50 years, polyketide natural products have attracted many researchers. These natural products have been the subject of many reviews in chemistry and biochemistry and have provided the opportunity to conduct interdisciplinary research.[1, 2] Polypropionates are a class of polyketides that include a structural motif consisting of alternating stereogenic centers bearing methyl and hydroxyl functionalities (Figure 1).[3] Polypropionate synthesis in vivo proceeds through the reaction of coenzyme A activated monomers catalyzed by the polyketide synthase system (PKS).[4]

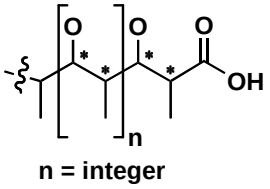


Figure 1. General structural motif of polypropionates (*= stereogenic center).

Numerous polypropionate metabolites have been isolated from marine organisms, with mollusks being the most common source.[5] Many polypropionate natural products have valuable therapeutic properties such as anticancer, antifungal and antibiotic.[6] Some interesting examples of polypropionate natural products are shown below (Figure 2). Due to their biological activity, the synthesis of polypropionates has attracted great interest leading to development of many successful synthetic methods. Despite these successes, general methods are lacking and access to a single diastereoisomer of a polypropionate becomes increasingly challenging as the number of

carbons in the chain increases. Consequently, there is continuing need for new synthetic approachs.[7]

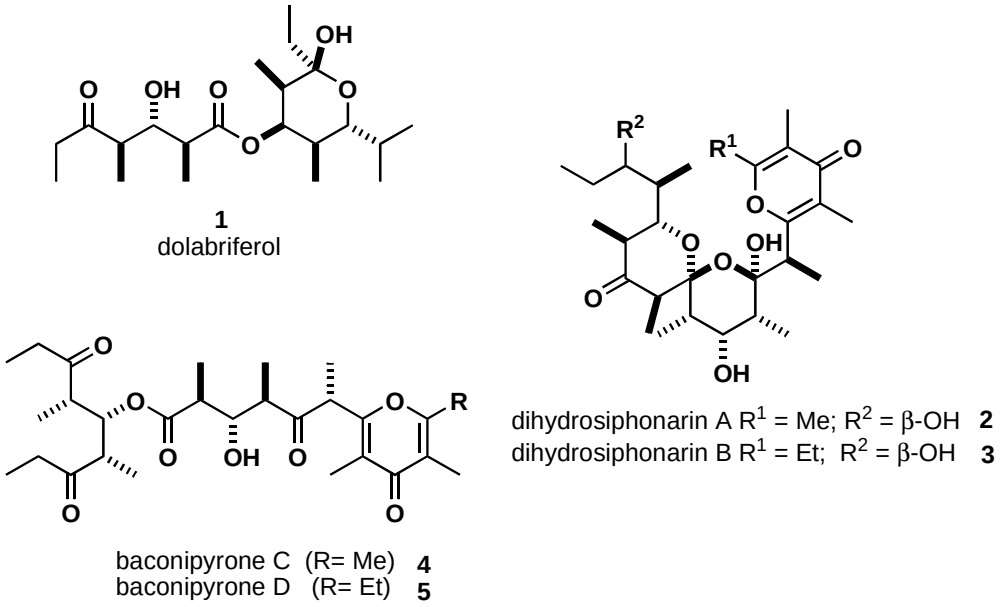


Figure 2. Examples of polypropionate natural products.

In the past, numerous methodologies were developed for polypropionate synthesis including Claisen rearrangements,[8] iodocarbonylations,[9] allenylmetal additions,[10] crotyl metal additions,[11] Diels-Alder cycloadditions,[12] and metal mediated aldol reactions with those using titanium,[13] tin[13] or boron[13, 14] enolates being the most commonly employed. For example, the total synthesis of polypropionates anhyroserricornin,[15] amphotericin B,[16] and baconipyrone C[17] using aldol reactions have been reported.[18]

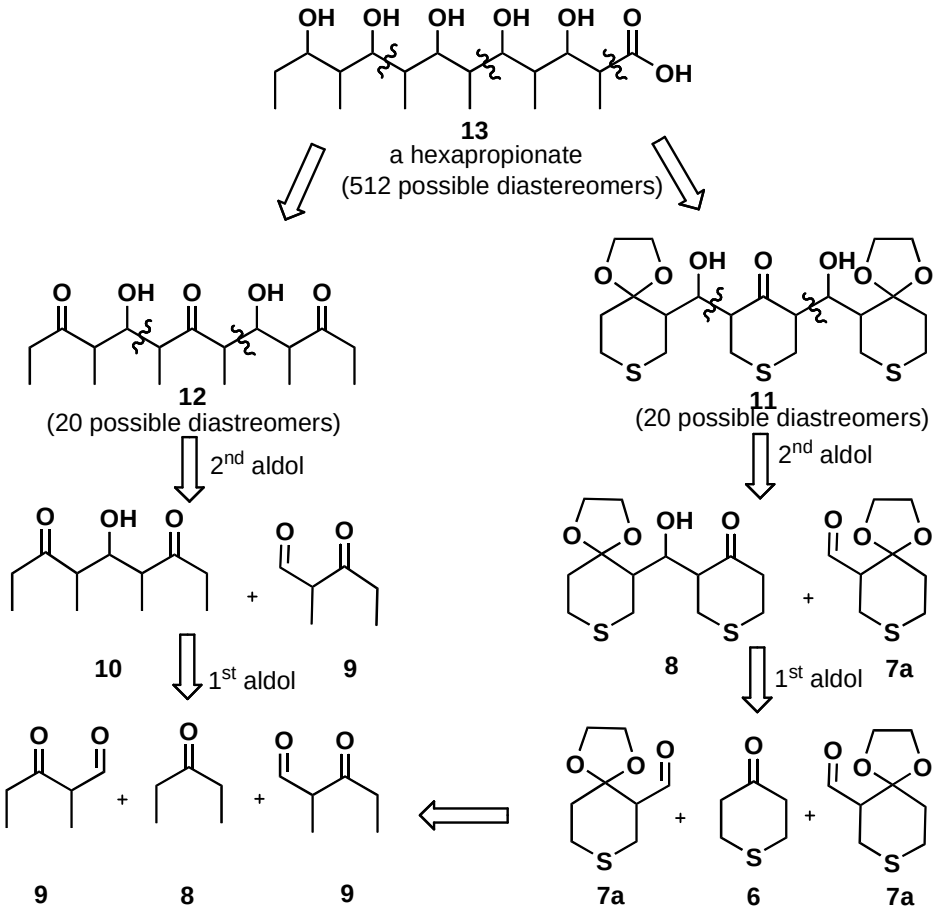
1.2. The thiopyran route to polypropionate

1.2.1. Overview

The thiopyran route to polypropionates is a well developed strategy for polypropionate synthesis developed by the Ward group.[19] This strategy permits the rapid

assembly of stereochemically complex polypropionate motifs from common precursors. One aspect of this approach concerns the synthesis of hexapropionate synthons **13**. Retrosynthetic disconnection of the carboxyl group from a prototypical hexapropionate **13** and oxidation state adjustment leads to trione **12** (Scheme 1). Trione **12** can be accessed by aldol couplings of **8** and **9**. Three routes are possible depending on the sequence of the aldol couplings. The Ward group has been developing this strategy employing thiopyran precursors **6** and **7a** as reagents synthetically equivalent to **8** and **9**. The stereocontrol of the aldol couplings of **6** and **7a** is quite versatile and 11 of 20 possible diastereomers of **11** have been selectively obtained by our group in 2-4 steps.[19]

Scheme 1. Ward's strategy for polypropionates synthesis.

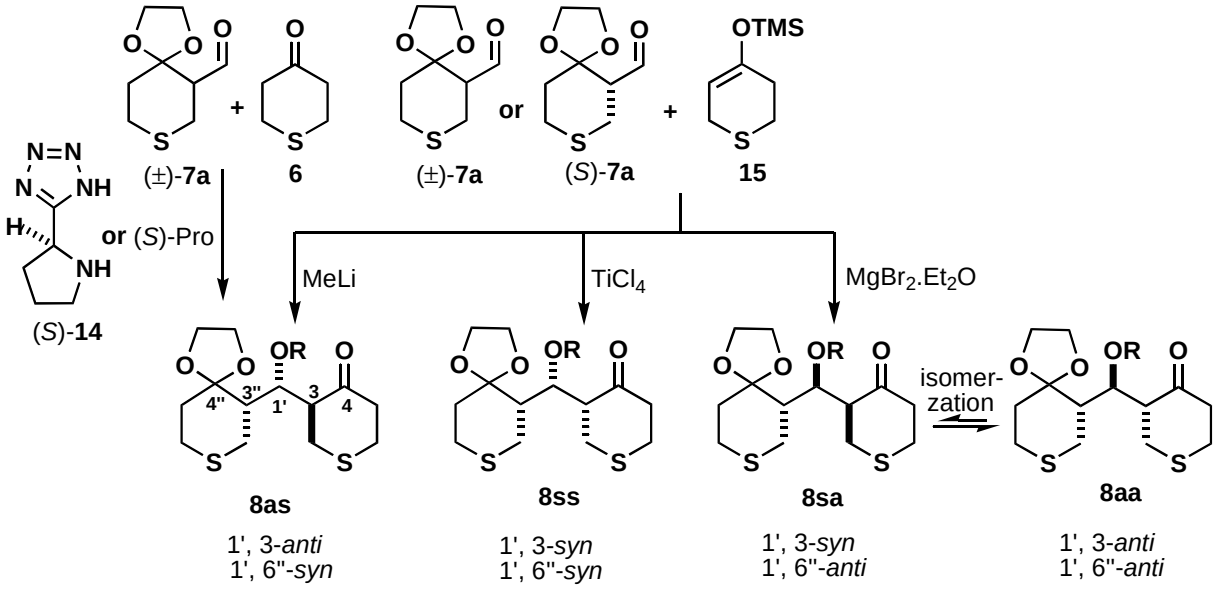


1.2.2. First aldol reaction: the tetrapropionate synthon

Each of the four possible diastereomers of the tetrapropionate synthon **8** are available via diastereoselective and enantioselective aldol reactions of the common starting materials **6** and **7a** (Scheme 2).[20] The aldol reactions of enolates of tetrahydro-4H-thiopyran-4-one **15** with chiral aldehydes (±)-**7a** or (*S*)-**7a** are highly diastereoselective and give different aldol adducts depending on the reaction conditions. For example, reaction of **15** and (±)-**7a** gives the racemic diastereomers **8as**, **8ss** and **8sa** stereoselectively when MeLi, $TiCl_4$ and $MgBr_2$, respectively, are employed as mediators

(Scheme 2). The fourth diastereomer, **8aa**, can be obtained from **8sa** by imidazole-catalyzed isomerisation.[21] The aldol reaction of tetrahydro-4H-thiopyran-4-one **6** with racemic aldehyde (±)-**7a** in the presence of 5-[(2*S*)-pyrrolidine-2-yl]-1H-tetrazole (*S*)-**14** [22] proceeds with dynamic kinetic resolution to give enantiomerically pure **8as** in excellent yield without chromotography.[7] Isomerization of **8as** provides a viable route to enantiopure **8ss**. Highly enantioenriched **8sa** is obtained by $MgBr_2$ mediated reaction of **15** with (*S*)-**7a**.[23,24] Enantioenriched **8aa** is obtained by isomerization of enantioenriched **8sa**.[23]

Scheme 2. Synthesis of the four racemic and enantiopure diastereomers of aldol adduct **8**.

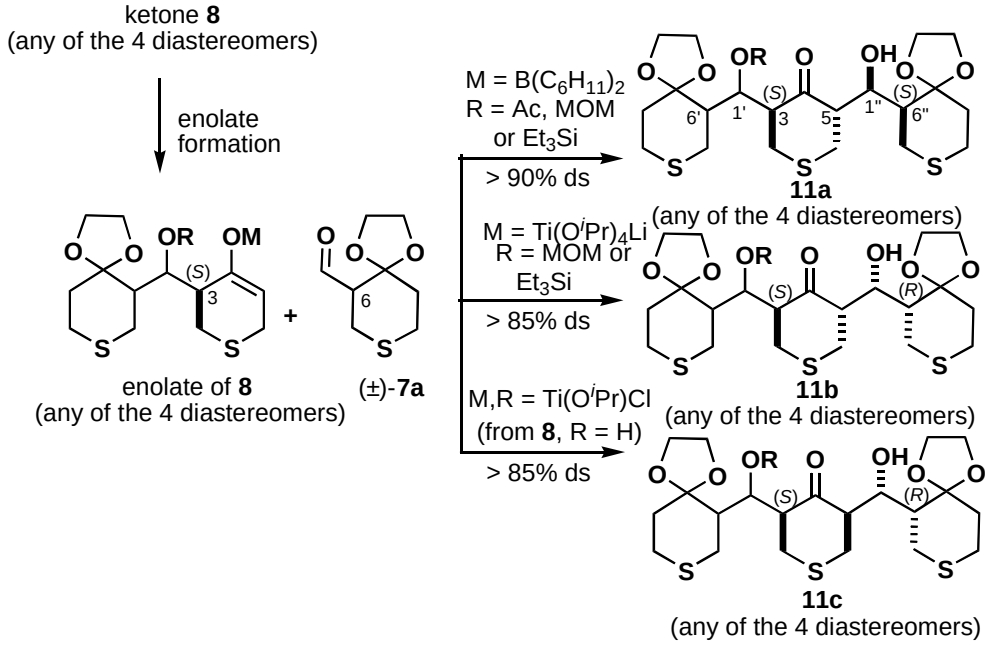


1.2.3. Second aldol reaction : the hexapropionate synthon

The hexapropionate synthons **11** are prepared by the highly stereoselective aldol couplings of **7a** with **8** (Scheme 1). Depending on the enolate mediator (titanium or boron) and the status of OH group (i.e., protected or not), each of the diastereomers of

enantioenriched **8** can be coupled with (±)-**7a** to give any of 3 diastereomers of **11a** or **11b** or **11c** selectively (Scheme 3). Thus, by subjecting each of the four diastereomers of **8** to the three different reaction conditions, 11 of 20 possible diastereomers of **11** can be selectively obtained from **6** and **7a** in 2-4 steps.[23,25]

Scheme 3. Summary of synthesis of the 3 diastereomers of bisaldol adduct **11** via KR.



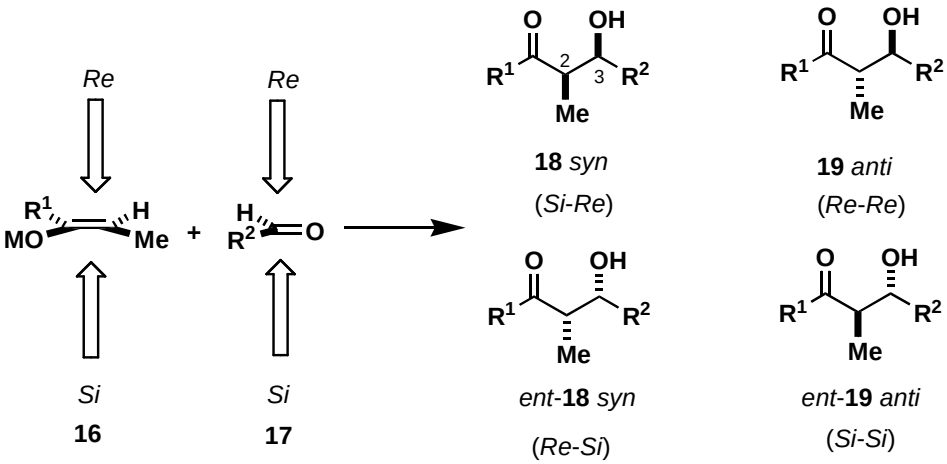
Each of the reactions in Scheme 3 can give up to eight aldol adducts. These highly selective reactions are the outcome of an effective kinetic resolution where the "fast" reaction is highly diastereoselective. In the following Sections, a more detailed discussion on this significant achievement is provided.

1.3. Stereoselectivity in the second aldol reaction: stereocontrol elements of the aldol reaction

1.3.1. Relative topicity of the aldol coupling: aldol reaction of an achiral enolate with an achiral aldehyde

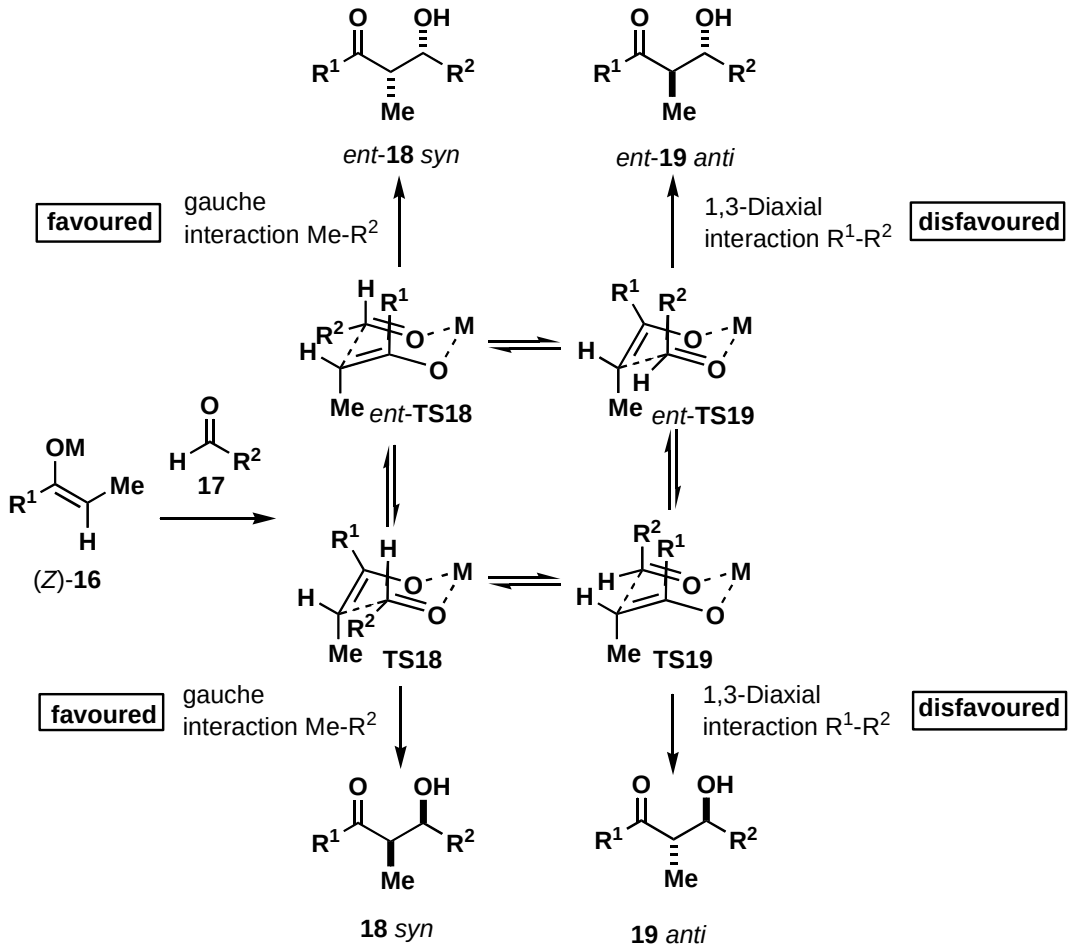
The stereocontrol element influencing the stereochemical outcome of the aldol reaction of achiral reactants is the relative topicity of the coupling, also referred to as simple diastereoselctivity. The relative configuration of the two newly formed stereogenic centres is designated *syn* or *anti* as illustrated in Scheme 4. The stereochemical outcome of the reaction depends on which of the two π-faces of the enolate reacts with which of the two π-faces of the aldehyde. In the transition state, the orientation of these faces dictates the relative and absolute configuration of the newly formed stereogenic centres. Applying the CIP rules,[26] the two π-faces for each reactant can be designated as *Re* or *Si* face. There are four possible combinations of reacting faces leading to two possible diastereisomers (Scheme 4).[27, 28]

Scheme 4. Four possible stereoisomers from the reaction of enolate **16** and aldehyde **17**.



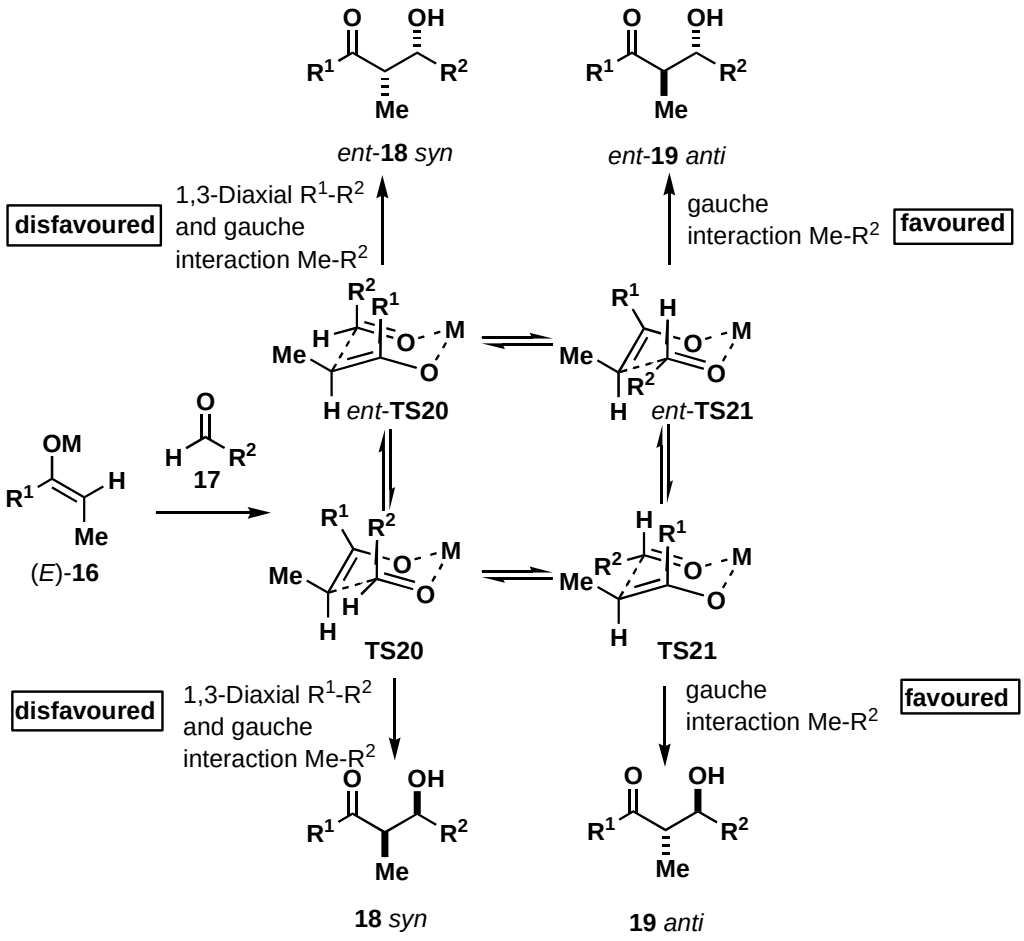
The relative topicity of aldol reaction is often directly dependent on the *E*/*Z* geometry of the enolate. In general, *Z*-enolates give *syn* aldols and *E*-enolates give *anti* aldols. The Zimmerman-Traxler model[29] can be used to explain the observed relative topicity of aldol coupling. In this model the transition state is a six membered ring which forms by coordination of the enolate metal with the aldehyde. In the case of enolate **16** and aldehyde **17**, this coordination leads to formation of four chair-like transition states with different orientations of the substituents. Repulsive interactions between substituents on the aldehyde and enolate raise the relative energy of the transition state, decreasing the probability of the corresponding adduct being formed. In the case of a *Z*-enolate, destabilizing 1,3 diaxial repulsion between the substituents occurs in the **TS19** that leads to *anti* aldol adducts, thus the formation of *syn* aldol adduct is favoured via **TS18** (Scheme 5). [30, 31] R1 and R2 are achiral, therefore the products **18** and *ent*-**18** are equally favoured.

Scheme 5. Zimmerman-Traxler transition states of enolate (*Z*)-**16**.



In the case of a *E*-enolate, the formation of anti aldol can be explained by formation of a more stable chair-like transition state (Scheme 6). In this case, destabilizing 1,3 diaxial repulsion between the substituents occurs in the **TS20** that leads to the *syn* aldol adduct, thus the formation of the *anti* aldol adduct is favoured via **TS21** (Scheme 6). R1 and R2 are achiral, therefore the products **18** and *ent*-**18** are equally favoured.

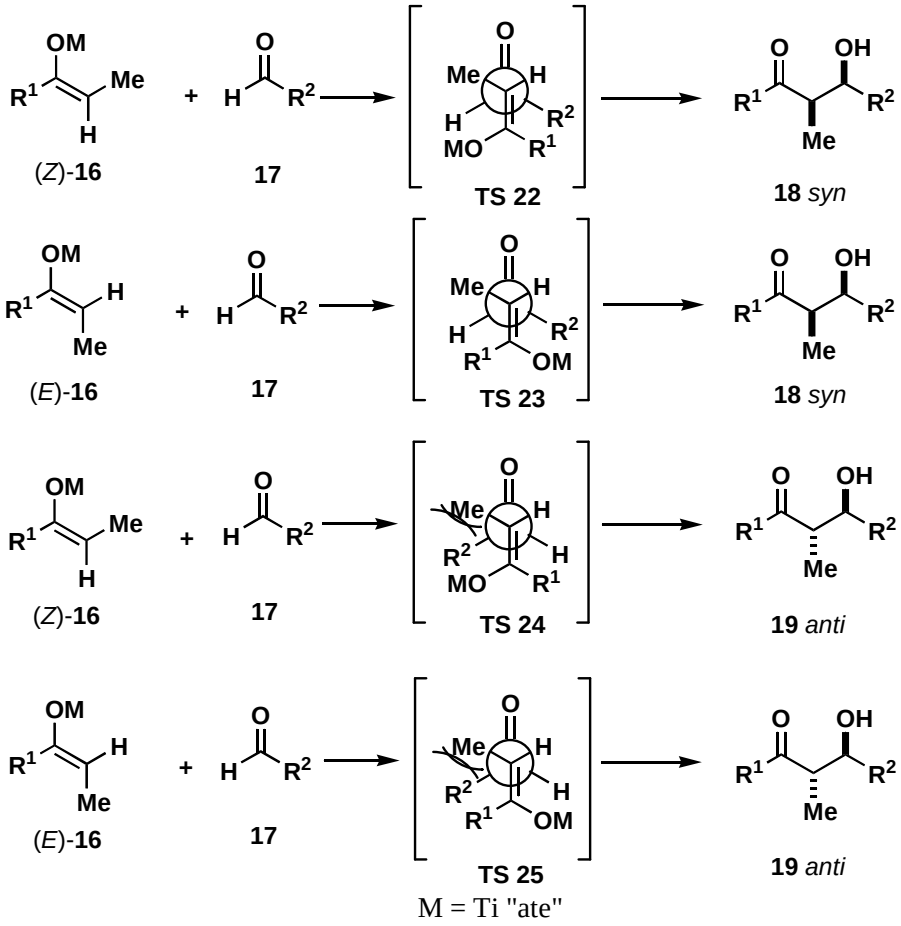
Scheme 6. Zimmerman-Traxler transition states of enolate (*E*)-**16**.



The above model provides a simple explanation for the observed relative topicity of boron mediated (*i.e.*, M = B in **16**) aldol coupling of cyclic ketone **8** with aldehyde **7a** (Scheme 3). In some reactions, the Zimmerman-Traxler model fails to predict the observed relative topicity of the aldol reaction. For example the titanium "ate" mediated aldol coupling of ketone **8** with aldehyde **7a** favoured *syn* relative topicity (Scheme 3).[23] The relative topicity of aldol coupling is dependent on the nature of the metal, the size of the substituents on the reactants and the reaction conditions.[32] Due to the lower Lewis acidity and higher nucleophilicity of the titanium "ate" enolate, an open transition state

might be postulated to rationalize the observed *syn* selectivity for this enolate.[33] Regardless of the *E/Z* enolate geometry, the *syn* product would be favoured in this type of aldol reaction as the competing *anti* transition states **TS24** and **TS25** possess unfavourable gauche interactions between the Me and R^2 groups (Scheme 7).[32]

Scheme 7. *E/Z* enolate open transition states models for titanium "ate" aldol reaction.

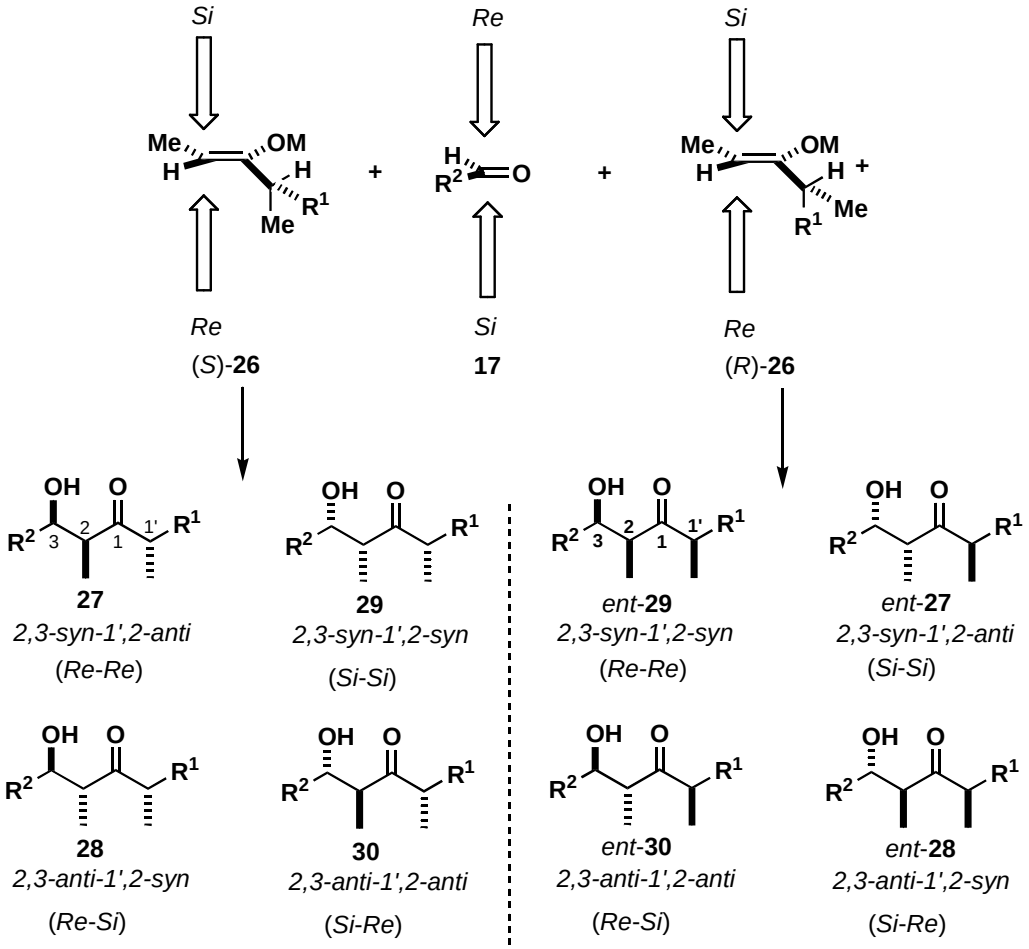


1.3.2. Diastereofacial selectivity of the enolate: aldol reaction of a chiral enolate with an achiral aldehyde

There are two stereocontrol elements affecting the diastereoselectivity of aldol reaction of chiral enolate with achiral aldehyde. The first one is the relative topicity of the

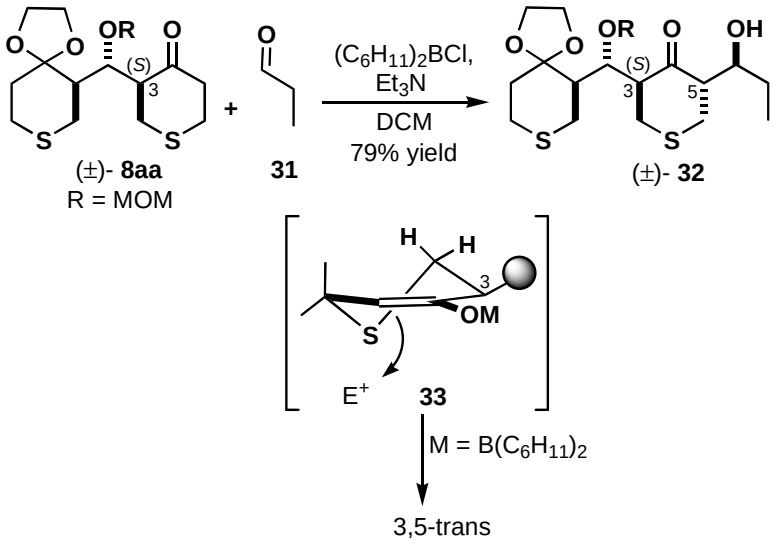
coupling which was discussed in Section 1.3.1 and the second one is the enolate diastereofacial selectivity. In the aldol reaction of racemic chiral enolate **26** and aldehyde **17** (Scheme 8), eight possible adducts can form. Considering the favoured product(s), diastereofacial selectivity of the enolate can be indentified from the absolute configuration of C2 of the favoured product. Usually, this reaction will not afford these diastereomeric products in equal amounts and some of the possible products might not form due to the high energy of their corresponding transition states relative to the other product's transition states.

Scheme 8. Aldol reaction of chiral racemic enolate **26** and aldehyde **17**.



In boron mediated aldol reaction of racemic chiral enolate (±)-**8aa (**R = MOM) with propanal, the *Si* face of the enolate **8aa** is favoured (Scheme 9). Adduct (±)-**32** was obtained in 79% yield from a 9:1 mixture of product diastereomers.[34] The diastereofacial selectivity of the enolate **8aa** can be designated from the absolute configuration of C3. In this reaction, addition occurs from the stereoelectronically preferred and sterically more accessible side opposite the large substituent at C3 in half-chair **33**. Thus, the diastereofacial selectivity of the enolate **8aa** is 3,5-trans.

Scheme 9. Aldol reaction of chiral racemic enolate of **8aa** (R = MOM) with propanal **31**.

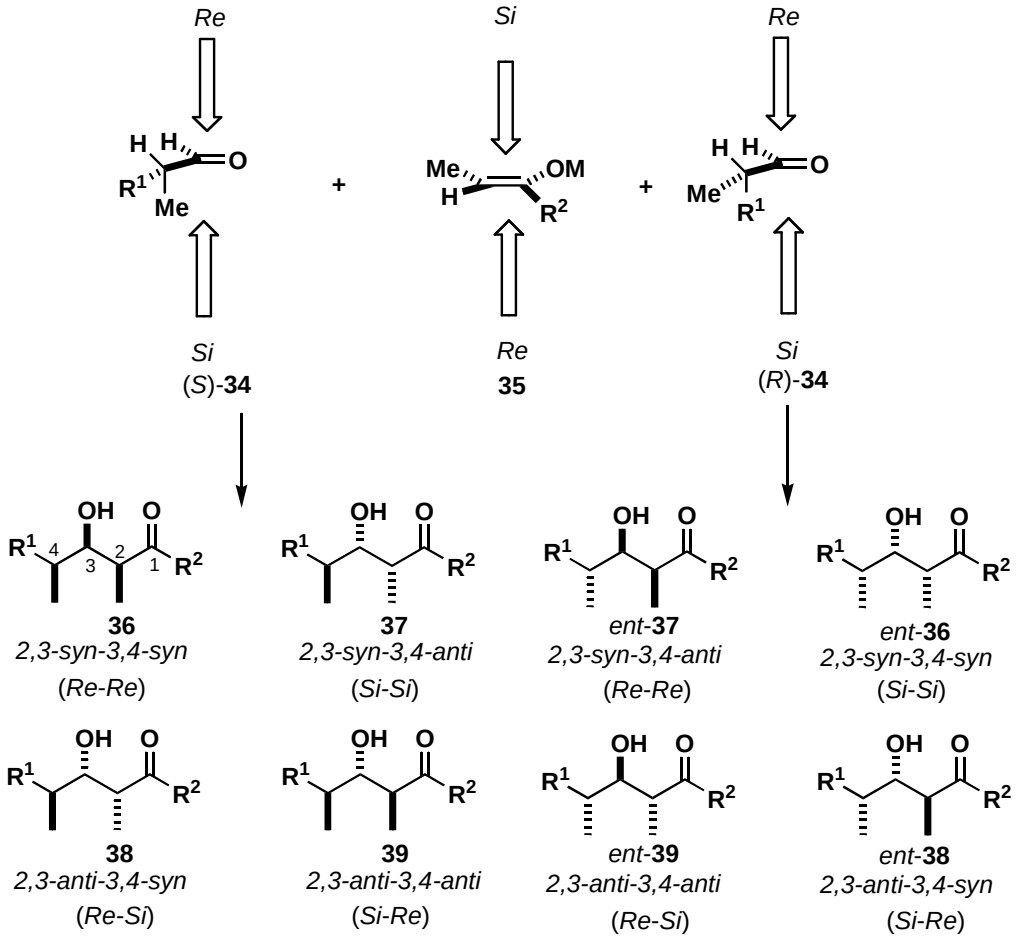


1.3.3. Diastereofacial selectivity of the aldehyde: aldol reaction of an achiral enolate with a chiral aldehyde

The stereochemical outcome of the aldol reaction of achiral enolate with chiral aldehyde can be predicted considering the two stereocontrol elements governing the stereoselectivity of this reaction (Scheme 10). One stereocontrol element is the relative topicity of the aldol coupling which can be identified by C2,3 *syn/anti* relative

configuration. Factors that affect the relative topicity of aldol coupling were previously discussed (Section 1.3.1). The second stereocontrol element is the diastereofacial selectivity of the aldehyde determined by C3,4 *syn/anti* relative configuration. There are eight possible products that can be formed in the aldol reaction of a racemic chiral aldehyde **34** with an achiral enolate **35**. In a kinetically controlled reaction, the ratio of the diastereomers produced in this reaction reflects the relative stability of their transition states (Scheme 10). In the absence of any external chiral influences, such as a chiral catalyst, the diastereomeric products will be racemic.

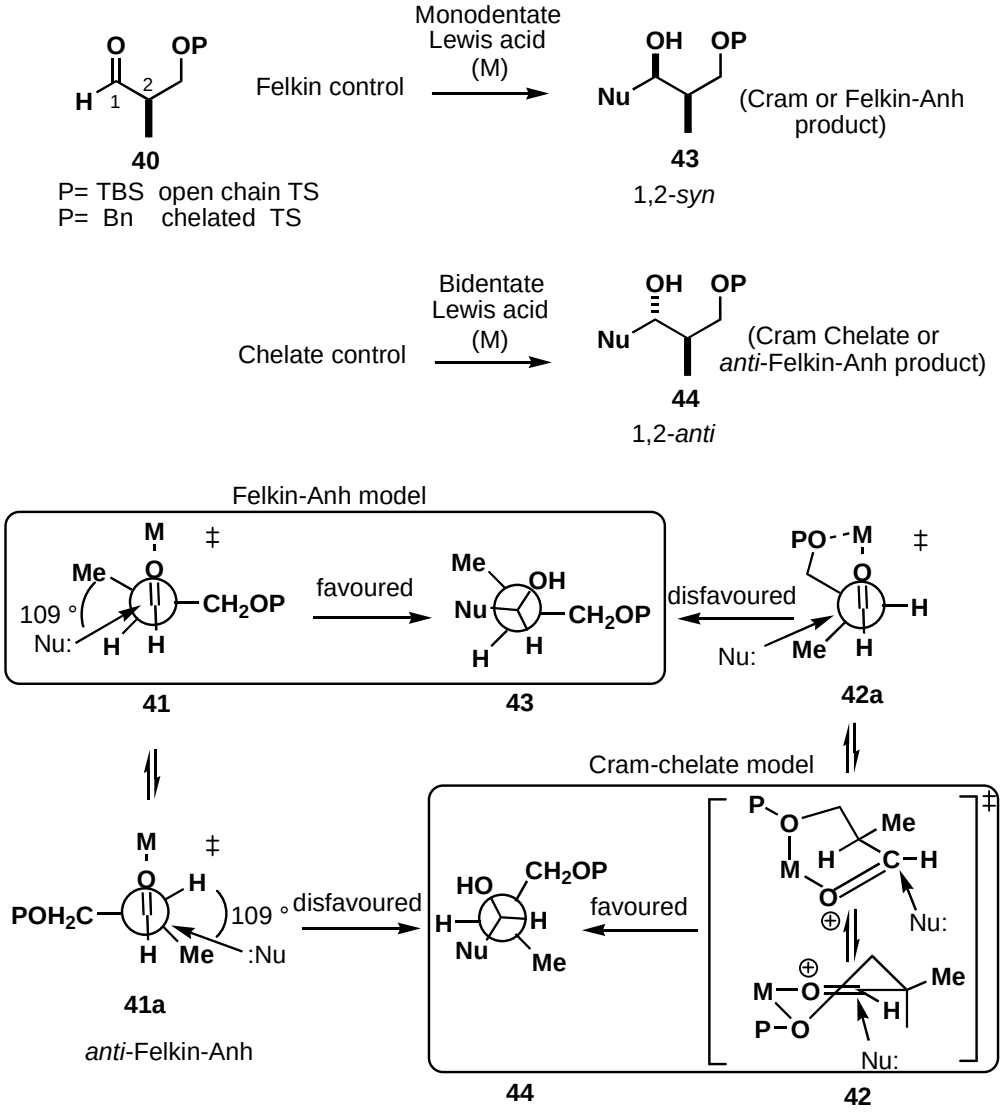
Scheme 10. The aldol reaction of chiral aldehyde **34** with enolate **35**.



The π-facial selective addition of nucleophiles to carbonyl compounds has been extensively investigated. Two modes of carbonyl activation of an aldehyde bearing a stereogenic centre at the α-position by a Lewis acid can be considered: "chelated" and "open-chain" (Felkin) transition states (Scheme 11). To anticipate which modes of activation are involved in a Lewis acid-substrate reaction, a number of factors should be considered, including the nature of the coordinating Lewis acid (*e.g.* $TiCl_4$ vs $BF_3.OEt_2$) and the nature of the oxygen protecting group (*e.g.* Bn vs t-$BuMe_2Si$), and the reaction solvent (*e.g.* THF vs CH_2Cl_2). The stereochemical outcome in each type of activation can be predicted by two different models: the Cram-chelate model and the Felkin-Anh model.[35]

In 1952, Cram and Abd-Elhafez demonstrated a model which predicts the stereochemical outcome of the nucleophilic addition on a chiral aldehyde with a bidentate Lewis acid. Metal ion chelation to the carbonyl and β-oxygen substituents forms a six-membered ring transition state **42** which has differentiated diastereofaces (Scheme 11). The nucleophile preferentially attacks the less hindered side of the transition state **42** which affords the *anti*-Felkin product with 1,2-*anti* hydroxy-methyl relationship in the adduct **44** (Scheme 11). [36, 37]

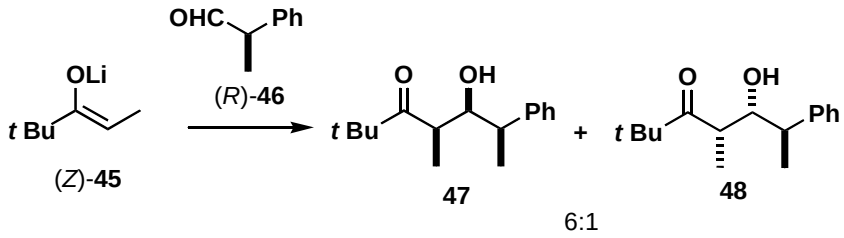
Scheme 11. Cram-chelate model and Felkin-Anh model.



Felkin[38] and Anh[39] proposed a model based on torsional strain **41** (Scheme 11) which proposes that attack of the nucleophile is *anti* to the largest substituent at an angle of 109˚ (Burgi-Dunitz trajectory)[40] from the least hindered face of aldehyde carbonyl. The stereochemical outcome of the reaction based on this model is the Felkin product **43** with 1,2-*syn* hydroxy-methyl relationship (Scheme 11).

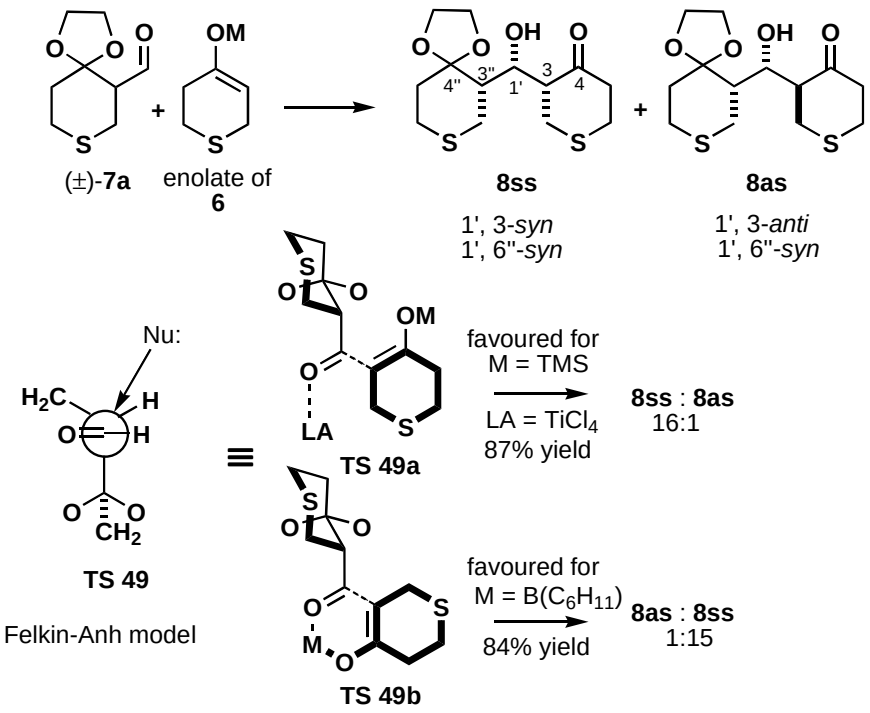
To illustrate how analysis of operational stereocontrol elements can relate to the stereochemical outcome of a reaction, consider the reaction of aldehyde (*R*)-**46** with enolate (Z)-**45** which gives aldol adducts **47** and **48** in a 6:1 ratio (Scheme 12).[30] Aldol reaction of Li-enolate (*Z*)-**45** are known to give *syn* relative topicity as predicted by the Zimmerman-Traxler model. Addition to the aldehyde (*R*)-**46** should preferentially occur from the *Re* face as predicted by the Felkin-Anh model. Therefore, addition of enolate (*Z*)-**45** to the Felkin-Anh preferred *Re* face of the aldehyde (*R*)-**46** via a closed Zimmerman-Traxler transition state model affords **47** as the major product of this reaction. Product **48** is obtained from the Zimmerman-Traxler transition state model (*syn* relative topicity) and arises from *anti*-Felkin addition. In this case, *syn* relative topicity is a stronger stereocontrol element than Felkin diastereoface selectivity of the aldehyde (*R*)-**46**, as both product **47** and **48** form with *syn* relative topicity.

Scheme 12. Analysis of stereocontrol elements in the aldol reaction of (*R*)-**46** with (*Z*)-**45**.



Reaction of enolate of **6** with the racemic chiral aldehyde **7a** via **TS49** would preferentially give 1',6''-*syn* selectivity (Scheme 13).[20] Depending on the enolate mediator 1',3-*syn* or 1',3-*anti* can be obtained via **TS49a** or **TS49b**. Although **TS49** has an unfavorable interaction between the carbonyl and cis *β*-oxygen of the ketal group, all other possible conformations with staggered relationships between the forming bond and the α-substituents have additional unfavorable steric or dipole interactions.[20]

Scheme 13. Aldol reaction of achiral enolate of **6** with racemic chiral aldehyde (±)-**7a**.



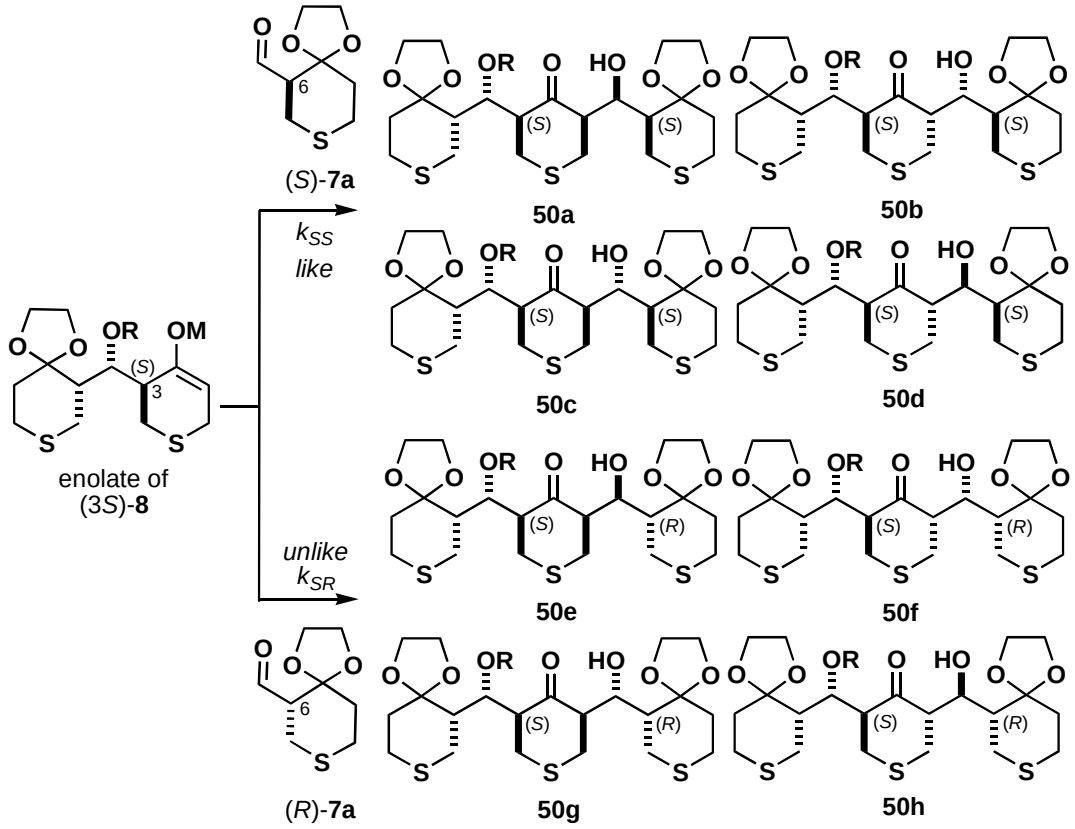
1.4. Stereoselectivity in the aldol reaction with kinetic resolution

1.4.1. Double stereodifferentiation and mutual kinetic enantioselection in the aldol reaction: aldol reaction of a chiral enolate with a chiral aldehyde

Diastereoselectivity of aldol reaction of a chiral racemic enolate with a chiral racemic aldehyde adds the elements of MKE and DS. To illustrate the distereoselectivity of such an aldol reaction, consider the aldol reaction of racemic chiral aldehyde (±)-**7a** and racemic chiral enolate of (±)-**8** (Schemes 14 and 15). In the aldol reaction of two racemic reactants, there are four possible parallel reactions occurring simultaneously. Reaction of each enantiomer of enolate of **8** with racemic aldehyde (±)-**7a** can give up to eight adducts: four each from *like* and *unlike* combination of reacting enantiomers. Seebach and Prelog[41] proposed the terms *like* and *unlike* to differentiate the possible

reactions of chiral reactants. *Like* (the same configuration) and *unlike* (the opposite configuration) are defined with respect to the configuration of C3 of **8** and C6 of **7a**.[25] Four adducts (**50a-d**) from the *like* reaction of enolate of (3*S*)-**8** with (*S*)-**7a** (Scheme 14) are the enantiomers of the four adducts (*ent*-**50a-d**) from the enantiotopos *like* reaction of (3*R*)-**8** with (*R*)-**7a** (Scheme 15). The enantiotopos reactions have a non-superimposable mirror image relationship.[19]

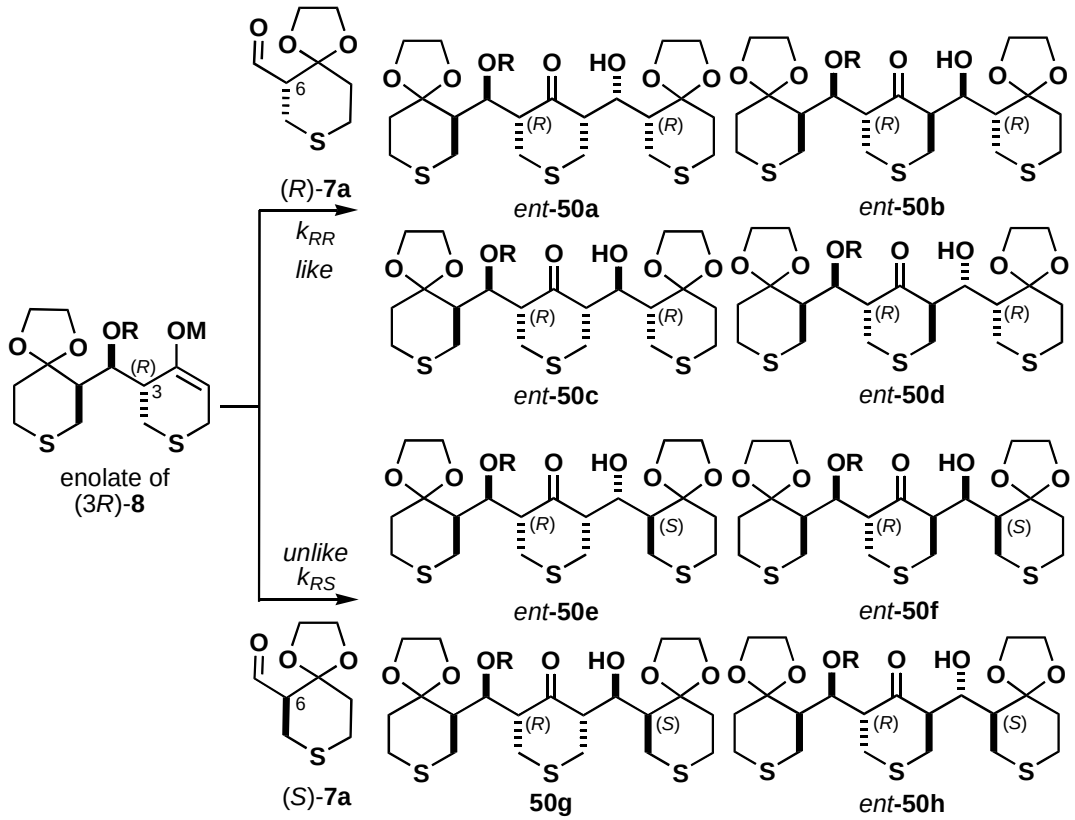
Scheme 14. Aldol reaction of enolate of (3*S*)-**8** with racemic aldehyde (±)-**7a**.



Similarly, the four adducts from the *unlike* reaction of enolate of (3*R*)-**8** with (*R*)-**7a** are the enantiomers of the four adducts from the enantiotopos *unlike* reaction of enolate of (3*S*)-**8** with (*S*)-**7a**. Due to the symmetry relationship, the *like* reaction of

enolate of (3*S*)-**8** with (*S*)-**7a** and the *like* reaction of enolate of (3*R*)-**8** with (*R*)-**7a** have identical rate constants ($k_{SS} = k_{RR}$) and diastereoselectivities. Similarly, the *unlike* reactions have identical rate constants ($k_{SR} = k_{RS}$) and diastereoselectivities.

Scheme 15. Aldol reaction of enolate of (3*R*)-**8** with racemic aldehyde (±)-**7a**.



Since there is no symmetry relationship between *like* and *unlike* reactions, these reactions are expected to have different rate constants and diastereoselectivities ($k_{RR} \neq k_{RS}$, $k_{SS} \neq k_{SR}$) (Schemes 14 and 15).

The difference between individual diastereoselectivities of the *like* and *unlike* reactions is referred to as double stereodifferentiation, DS.[42] For each reaction in Schemes

14 and 15, the diastereoselectivity can be expressed by the ratio of the major product to the other products formed:

DS : dr of the *like* reaction compared to dr of the *unlike* reaction

or

major product : others from the *like* reaction

compared to

major product : others from the *unlike* reaction

The kinetic preference for reaction of an *unlike* or *like* combination of enantiomers of racemic reactants is referred to as mutual kinetic enantioselection, MKE. If one of the reactants is enantiopure, this kinetic preference is referred to as kinetic resolution, KR. The adducts from an aldol reaction with KR will be enantiopure (or meso). When the aldol reaction of two racemic chiral reactants proceeds with significant mutual kinetic enantioselection (MKE) remarkably high diastereoselectivity can result. As a consequence of this phenomena, one of the eight possible racemic aldol adducts can form with high selectivity. Similar high diastereoselectivity is obtained in the aldol reaction which proceeds with kinetic resolution (KR).[43]

One method for determining the MKE is by measuring the ratio of diastereomeric products from the *like* and *unlike* reaction which is equal to the ratio of the rate constants according to Horeau's rule (Figure 3).[44] This ratio is independent from the initial amount of racemic reactants and the degree of conversion. Similarly, in the reaction of an enantiopure species with a racemic reactant, the ratio of the rate constants can be determined by the ratio of diastereomeric products from the *like* and *unlike* reaction. However, in this case the ratios are only equal at low conversion or if racemic reactant is in large excess as the individual amount of each enantiomer must remain effectively

constant, otherwise the kinetic of the reaction is more complex in this case. In KR, the selectivity factor (*s*) is expressed by the ratio of k_{RS} / k_{RR}.

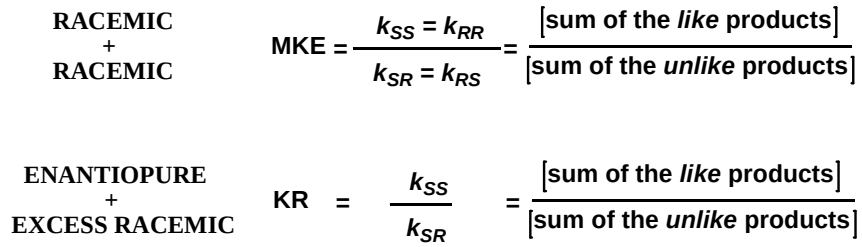


Figure 3. Measurement of MKE and KR based on product distribution.

As noted, diastereoselectivities of the *like* and *unlike* reactions are different. The reaction (*like* or *unlike*) that achieves higher diastereoselectivity is called the 'matched' reaction, whereas the reaction with lower or diminished diastereoselectivity is referred to as the 'mismatched' reaction. This terminology is used to explain the interaction involved in the aldol reaction of two chiral reactants considering their individual diastereofacial selectivity.

Both mutual kinetic enantioselection (MKE) and kinetic resolution (KR) are the consequence of significant differences between rate constants for the *like* and *unlike* reactions.[23] The faster reaction is the combination of 'matched' pair of enantiomers, whereas the slower reaction is the combination of the 'mismatched' pair of enantiomers.

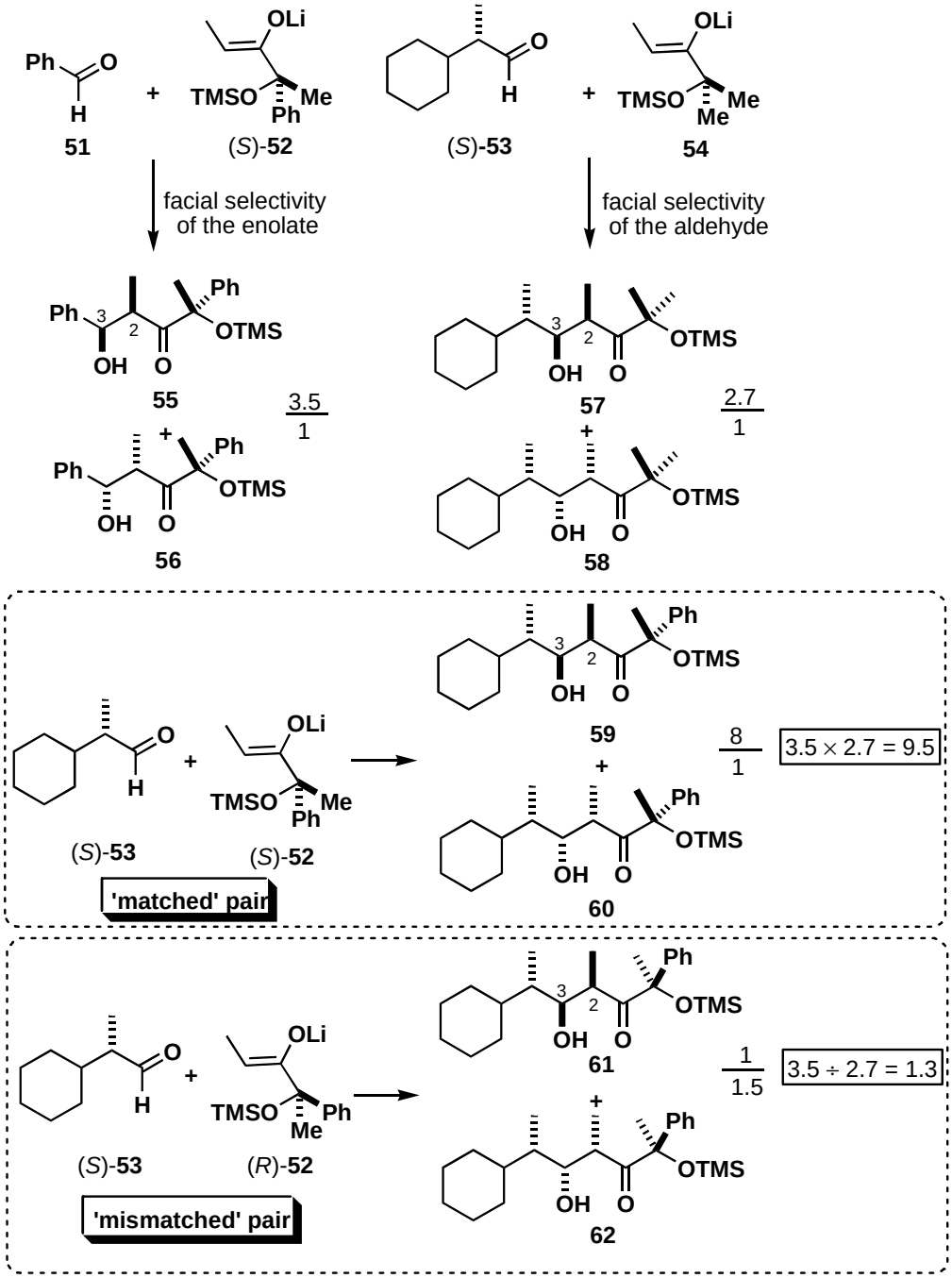
1.4.2. Multiplicativity rule in the aldol reaction

The diastereoselectivity for aldol coupling of chiral reactants can be qualitiatively predicted by application of the multiplicativity rule. Masamune et al. rationalized the outcome of the reaction of chiral aldehyde (*S*)-**53** with racemic enolate (±)-**52** by applying the multiplicativity rule (Scheme 16).[42] The aldol reaction of

enantiopure (*S*)-**52** with an achiral aldehyde such as benzaldehyde **51** gives products **55** and **56** in a ratio of 3.5:1. This ratio represents the diastereofacial selectivity of the enolate **52**. The absolute configuration of C2 indicates that the diastereofacial selectivity of the reacting enolate (*S*)-**52** favours the reaction of the *Re* face. Similarly, the diastereofacial selectivity of aldehyde (*S*)-**53** is identified by its aldol reaction with achiral enolate **54**. This reaction affords products **57** and **58** in a ratio of 2.7: 1. In this case, the relative configuration of C3 and C4 results from the diastereofacial selectivity of the reacting aldehyde (*S*)-**53** (Scheme 16). The absolute configuration of C3 in major products from the two reactions shows that (*S*)-**53** and (*S*)-**52** are a 'matched' pair. As expected, the reaction of this pair leads to the diastereoselectivity enhancement (**59** and **60** in a ratio of 8:1) as a result of favourable interaction between reacting faces of the two reactants (Scheme 16).

In contrast, the diastereofacial selectivities of (*S*)-**53** and (*R*)-**52** counteract each other, thereby producing a low diastereomeric ratio (**61** and **62** in a ratio of 1:1.5) (Scheme 16). Masamune hypothesized that the degree of asymmetric induction can be approximately calculated as $\boldsymbol{E} \times \boldsymbol{A}$ in the case of a 'matched' pair and $\boldsymbol{E} \div \boldsymbol{A}$ in the case of a 'mismatched' pair where $\boldsymbol{E}$ and $\boldsymbol{A}$ are the diastereofacial selectivity of the two reaction components.

Scheme 16. Multiplicativity rule in aldol reaction of (*S*)-**53** with racemic (±)-**52**.



Due to the complexity of the reaction, the multiplicativity of the diastereofacial selectivities is valid only under ideal conditions. In reality, all secondary effects on the

selectivity of the reaction are ignored. As a consequence of secondary effects number obtained does not necessarily give number observed (*e.g.* 9.5 versus 8 in Scheme 16). Furthermore, multiplicativity rule does not predict the facial selectivity value as a fixed number, the value varies depending on the achiral model substrate.[42]

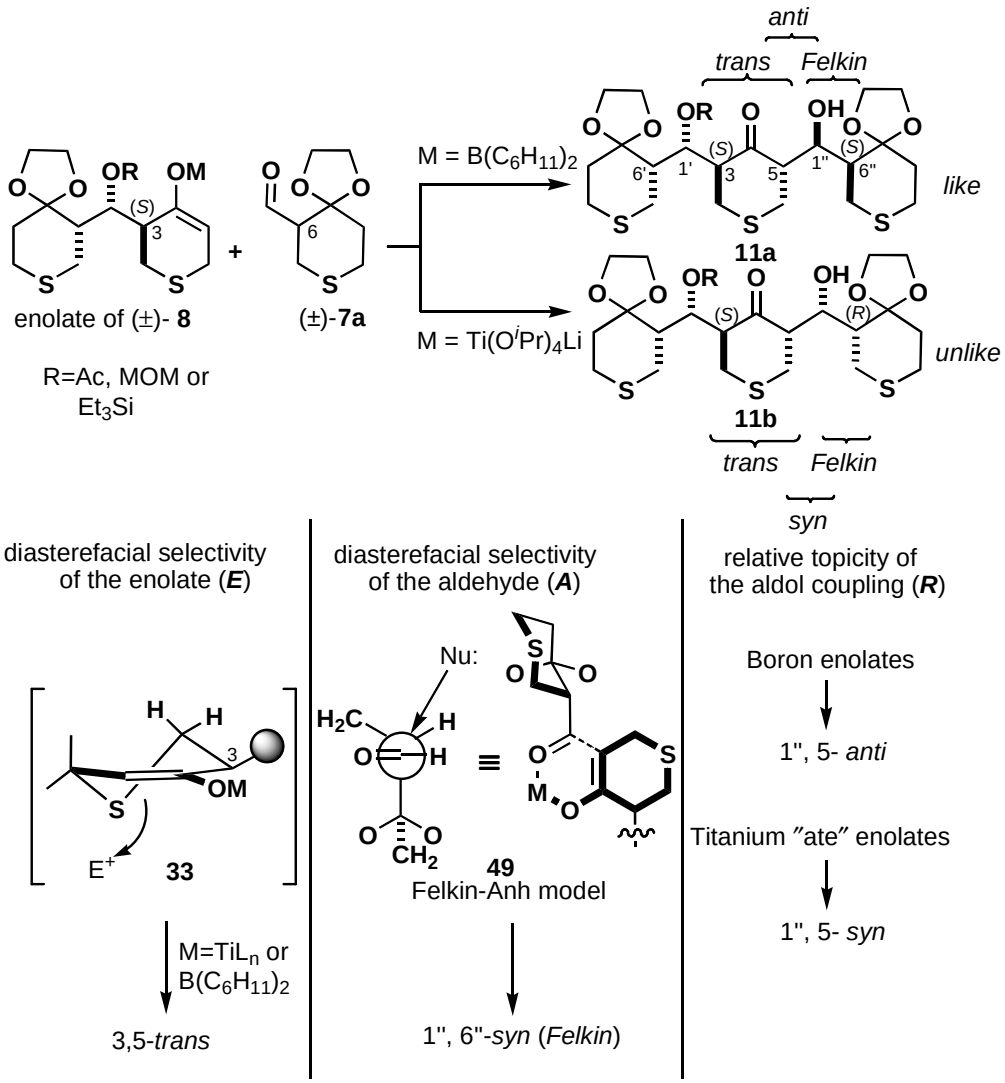
As Ward pointed out,[19,23] the diastereoselectivity of the aldol reaction of enolate of **8** and aldehyde **7a**, can be predicted and rationalized by extending the multiplicativity rule to incorporate relative topicity as the third stereocontrol element (Scheme 17). In that approach, the stereoselectivity of aldol coupling of chiral reactants is factorized into three stereocontrol elements: the diastereofacial selectivity for the ketone enolate (***E***; *cis* or *trans* with respect to the substituent at C3 of **8**); the diastereofacial selectivity for the aldehyde (***A***; *Felkin* or *nonFelkin* with respect to the stereocenter at C6 of **7a**) and the relative topicity of the aldol coupling (***R***; *anti* or *syn* with respect to the newly formed stereocenters in the products).

According to the multiplicativity rule, the relative facilities for formation of each adduct can be predicted with respect to the biases of the individual stereocontrol elements in the reaction. Upon inspection of an adduct's structure, the relative facility for its formation is predicted by the product of those stereocontrol elements that have been satisfied. The diastereoselectivity of the reaction can be predicted and rationalized according to the ratio of major adduct to the other adducts.

Each reaction in Scheme 17 can form up to eight possible adducts. The relative facility for each of the eight possible adducts from the boron mediated aldol reaction of (±)-**8** (R = MOM) with the aldehyde (±)-**7a** (Scheme 17) can be predicted, provided the three stereocontrol elements are biased as: ***E*** (*trans* selective), ***R*** (*anti* selective) and ***A***

(*Felkin* selective), the relative facility of the aldol adduct **11a** is ***E*·*R*·*A***, for adduct **11b** is ***E*·*A*** and so on. The same concept can be applied to predict the relative facility for each of the eight possible adducts from the titanium "ate" mediated aldol reaction of (±)-**8** (R = MOM) with the aldehyde (±)-**7a** (Scheme 17).

Scheme 17. Three stereocontrol elements in the reaction of enolate of **8** with aldehyde **7a**.



In this case three stereocontrol element are biased as follow: ***E*** (*trans* selective), ***R*** (*syn* selective) and ***A*** (*Felkin* selective), thus the relative facility of the aldol adduct **11b** is ***E·R·A***, for adduct **11a** is ***E·A*** and so on.

As Masamune suggested,[42] a simpler model reaction can be performed to estimate the individual diastereofacial selectivity of the reacting components. For example the reaction of the lithium enolate of **8** with benzaldehyde can be done to identify the ratio of 3,5-*cis* versus 3,5-*trans* adduct. From this result an estimation of the diastereofacial selectivity (***E***) of the enolate **8** may be obtained.[19]

Diastereoselectivity of the 'matched' reaction (*like* reaction in boron mediated aldol reaction of (±)-**8** with (±)-**7a**) and 'mismatched' reaction (*unlike* in boron mediated aldol reaction of (±)-**8** with (±)-**7a**) can be predicted as the following equations (Scheme 17):

Predicted 'matched' reaction dr =

major product from the *like* reaction/other products from the *like* reaction =

$$(\boldsymbol{E}\cdot\boldsymbol{R}\cdot\boldsymbol{A}) / (\boldsymbol{E} + \boldsymbol{R} + \boldsymbol{A}).$$

***

Predicted 'mismatched' reaction dr =

major product from the *unlike* reaction /other products from the *unlike* reaction =

$$(\boldsymbol{R}\cdot\boldsymbol{A}) / (\boldsymbol{E}\cdot\boldsymbol{A} + \boldsymbol{E}\cdot\boldsymbol{R} + \boldsymbol{1}).$$

(assumption $\boldsymbol{R}, \boldsymbol{A} > \boldsymbol{E}$)

According to the multiplicativity rule, the diastereoselectivity of the aldol reaction of chiral reactants can be predicted and rationalized, provided the biases of stereocontrol elements are known.

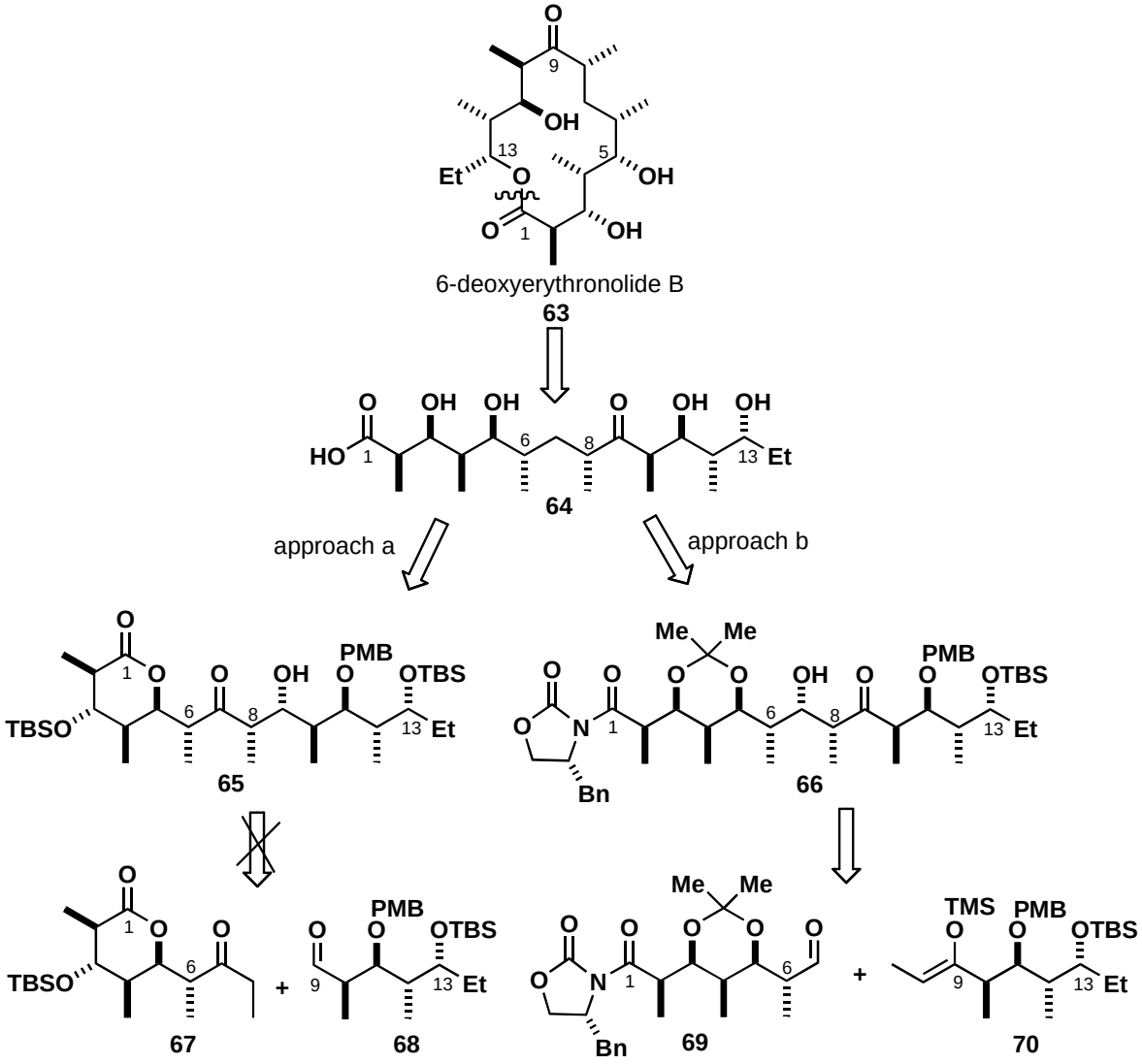
According to the concept outlined in Figure 3, MKE can be predicted by the ratio of k_{fast} / k_{slow}. The MKE of the boron mediated aldol reaction in Scheme 17 can be calculated as follows:

Predicted relative facility of the 'matched' vs 'mismatched' reaction :

$$\text{MKE} = k_{fast} / k_{slow} = (\boldsymbol{E{\cdot}R{\cdot}A} + \boldsymbol{E} + \boldsymbol{R} + \boldsymbol{A}) / (\boldsymbol{R{\cdot}A} + \boldsymbol{E{\cdot}A} + \boldsymbol{E{\cdot}R} + \boldsymbol{1}).$$

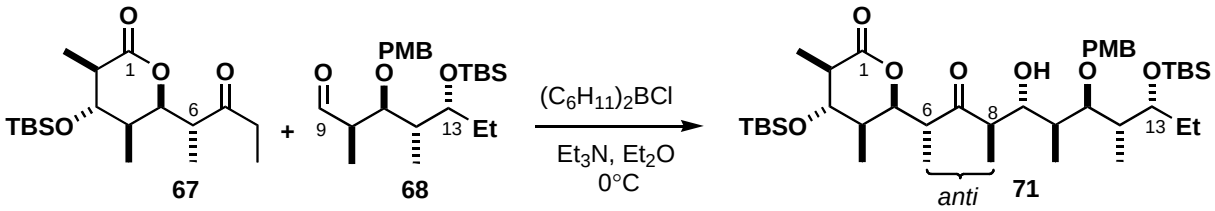
In natural products total synthesis, the double stereodifferentiation in the aldol reaction can be advantageously employed to achieve high stereoselectivity provided the desired adduct is formed from a 'matched' reaction. However, when the desired isomer is not the product of a 'matched' reaction, the approach to the natural product must be redesigned. For example, Evan's synthesis of 6-deoxyerythronolide B **63**,[45] initially incorporated the boron promoted aldol coupling of **67** and **68** which was expected to give the desired *syn* relationship between methyl groups at C6 and C8 in intermediate **65** (Scheme 18).

Scheme 18. Evans retrosynthesis of 6-deoxyerythronolide B **63**.



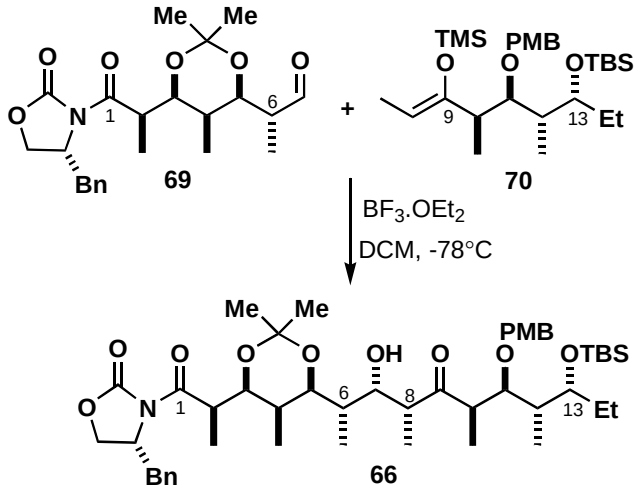
However, when the boron mediated aldol reaction of **67** and **68** was attempted, the undesired aldol adduct **71** was formed through double stereodifferention (Scheme 19). The undesired intermediate **71** with *anti* relationship between methyl groups at C6 and C8 was formed in 80% isolated yield as a single isomer from the 'matched' reaction of **67** and **68**.

Scheme 19. Aldol reaction of **67** and **68**.



Therefore approach 'a' in the preparation of precursor **64** (Scheme 18) was abandoned. The retrosynthetic plan was redesigned and approach 'b' was pursued. In this approach, the intermediate **66** as single isomer was obtained from the 'matched' Mukaiyama aldol reaction of TMS enolate **70** and aldehyde **69** in 83% yield (Scheme 20).

Scheme 20. Aldol reaction of **69** with **70**.



1.4.3. Rational design of aldol reactions with kinetic resolution

One of the most highly desired goals in modern synthetic organic chemistry is the ability to perform a chemical transformation in a way to obtain only one diastereomer or enantiomer as favoured product. There are a couple of advantages in development of stereoselective synthetic methods. First, the difficult process of isomeric separation is

eliminated. Second, the valuable starting material is not transformed into undesirable stereoisomers. Furthermore, by controlling the stereochemical outcome in a chemical transformation, any stereoisomeric analogue of a biologically active compound can be accessed.[46] Thus, it is quite advantageous to be able to control the stereochemical outcome of the aldol coupling as one of the most important C-C bond formation strategies in asymmetric synthesis. Regarding this fact, the ability to design aldol reactions proceeding with KR can be useful in the asymmetric syntheses of stereochemically complex targets.

As discussed in Section 1.4.2, the stereoselectivity of aldol reaction of chiral reactants is factorized into three stereocontrol elements: diastereofacial selectivity for the ketone enolate (***E***), the diastereofacial selectivity for the aldehyde (***A***) and the relative topicity of the aldol coupling (***R***). According to the multiplicativity rule, the diastereoselectivity of the aldol reaction is qualitatively predicted and rationalized from the relative facilities of the aldol adducts forming in the reaction.[19, 23] In a double stereodifferentiating aldol reaction proceeding with KR or MKE, the selectivity of the reaction ($s = k_{fast} / k_{slow}$) can be calculated quantitatively by assigning hypothetical values to the stereocontrol elements as follows (Table 1):

Table 1. Hypothetical values for selectivity of aldol reaction with MKE or KR.[23]

Entry	***E***	***R***	***A***	*s*
1	100	1	100	**1**
2	100	3	100	**2.8**
3	100	10	100	**8.4**
4	10	10	10	**3.4**
5	30	30	30	**10**

$$s = k_{fast} / k_{slow} = (\boldsymbol{E{\cdot}R{\cdot}A} + \boldsymbol{E} + \boldsymbol{R} + \boldsymbol{A}) / (\boldsymbol{R{\cdot}A} + \boldsymbol{E{\cdot}A} + \boldsymbol{E{\cdot}R} + \boldsymbol{1})$$

This analysis demonstrates that the KR selectivity is limited by the least selective of the three stereocontrol elements (entries 1-3). Synthetically useful selectivity ($s > 10$) is obtained when each of these elements is highly biased (entry 5).[23]

In order to design an aldol reaction with KR, a large body of previous research needs to be considered which indicates that all the three stereocontrol elements in the aldol reaction of chiral reactants can be modulated rationally by the choice of protective groups, enolate type and ligands and additives in order to obtain the desired selectivity.[47] Applying this approach, the Ward group designed new aldol reactions proceeding with KR with remarkably high stereoselectivity through screening various diastereomers of ketone enolate **8**, different protecting groups on the enolate **8** and different enolate mediators.[23,25]

Scheme 21. Boron mediated aldol reactions of **8** with aldehyde **7a** proceeding with KR.

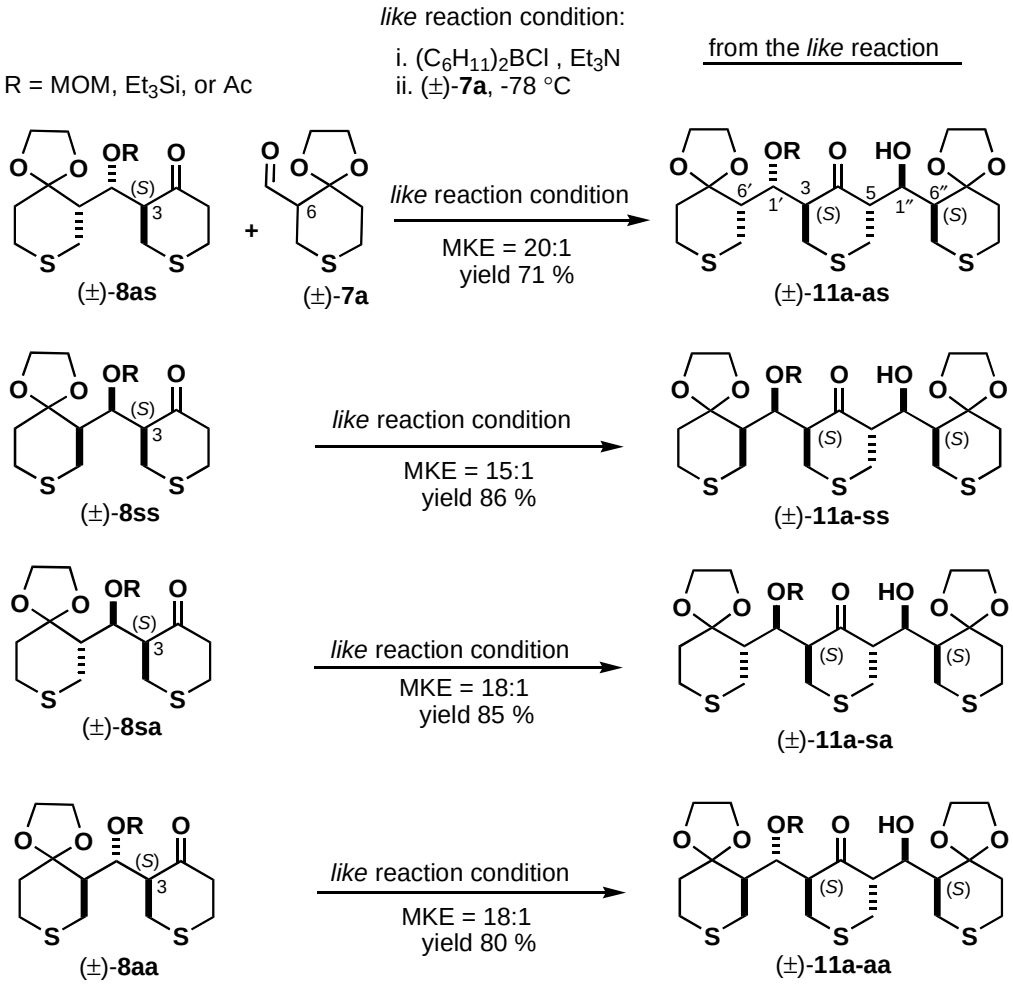


Table 2. KR results for boron mediated aldol reactions.

ketone	KR	yield%
(-)-8as	15:1	80%
(-)-8ss	9:1	77%
(+)-8sa	14:1	80%
(+)-8aa	14:1	74%

The best results of this extensive study are summarized in Scheme 21 and 22. Each of the diastereomers of **8** (racemic or enantiopure) reacts with the racemic aldehyde (±)-**7a** under optimized conditions (Scheme 21 and 22). Two adducts form from each reaction. The boron mediated reaction of each diastereomer of (±)-**8** with aldehyde (±)-**7a** gave two adducts in favour of *like* adduct (Scheme 21). The Titanium "ate" mediated reaction of each diastereomer of (±)-**8** with aldehyde (±)-**7a** gave two adducts in favour of *unlike* adduct (Scheme 22).

Unlike and *like* reactions occurred with similar facility and both reactions proceeded with the same diastereofacial selectivity of the aldehyde (Felkin: 1", 6"-*syn*) and the same diastereofacial selectivity of the enolate (3,5-*trans*). The boron and titanium "ate" mediated aldol reactions differed in the aldol relative topicity; 5, 1"-*anti* in the boron mediated reaction versus 5, 1"-*syn* in the titanium "ate" mediated reaction.

Scheme 22. Titanium "ate" mediated aldol reactions of **8** with aldehyde **7a** proceeding with KR.

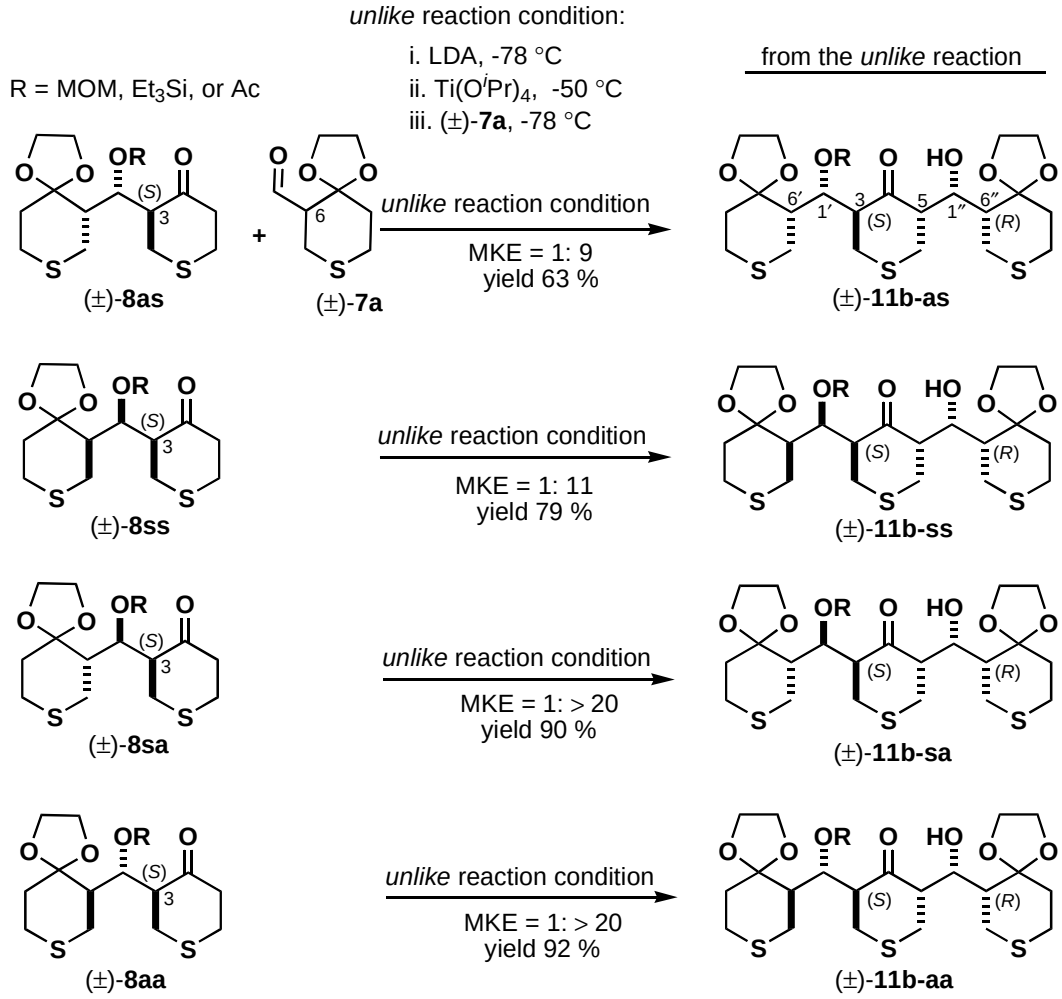


Table 3. KR results for titanium "ate" mediated aldol reactions.

ketone	KR	yield%
(-)-8as	1:8	66%
(-)-8ss	1:9	67%
(-)-8sa	1:>20	81%
(-)-8aa	1:16	72%

Together with the high diastereofacial selectivity of the aldehyde **7a** and enolate **8**, the use of enolate mediators, LDA / $Ti(O^{i}Pr)_4$ or $(C_6H_{11})_2BCl$ / Et_3N which strongly favoured *syn* or *anti* relative topicity, resulted in strongly biased stereocontrol elements. Thus, this design paradigm efficiently leads to the aldol reactions with remarkable selectivity through KR (and MKE).[23, 25] These highly enantioselective aldol reactions with KR were employed in the total synthesis of polypropionate natural products such as membrenone B,[19] siphonarin B,[17] baconipyrone A and C,[17] and *ent*-caloundrin B[48] by the Ward group. In this research, the scope and limitations of this design were explored and the obtained results are discussed in the following chapter.

2. RESULTS AND DISCUSSION

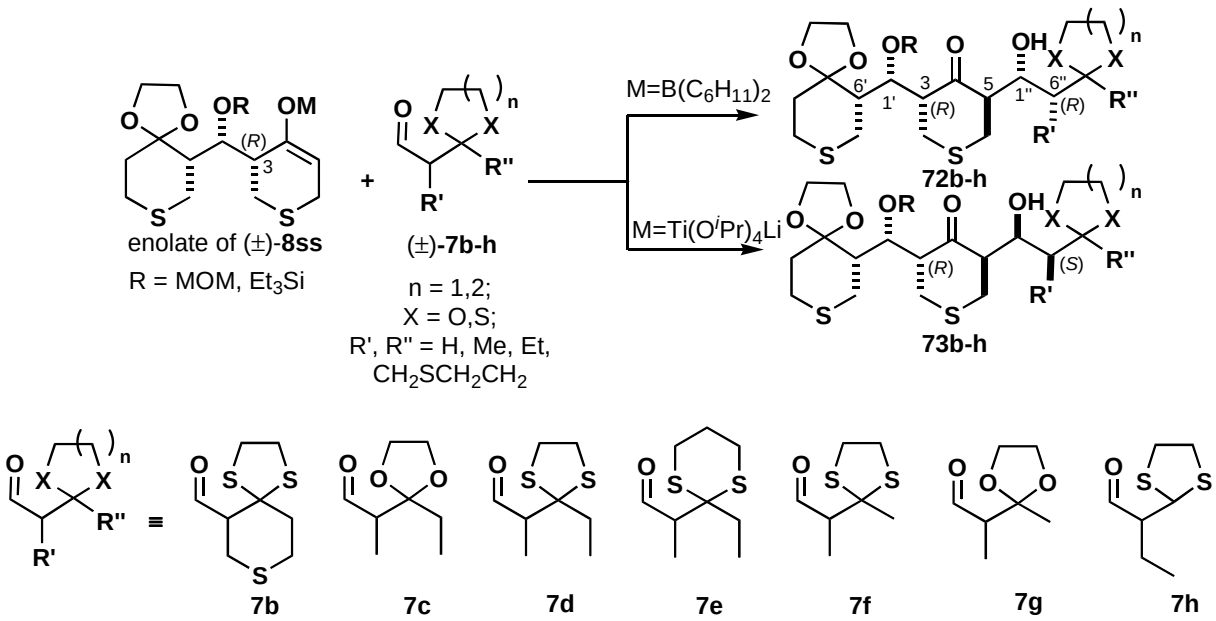
2.1. Research objectives

Given the remarkable results discussed in Section 1.4.3, the goal of this research was to explore the scope and limitations of the design paradigm for aldol reactions with KR. Thus various α-substituted racemic aldehydes with an ethylene ketal, dithiolane, or dithiane group at the β position were reacted with boron and titanium "ate" enolates of **8** under the previously optimized conditions. Those conditions resulted from extensive studies on the reaction of aldehyde **7a** with various enolates of **8** (Schemes 21 and 22). Each of the aldehydes **7b-h** had one or two structural feature(s) different from aldehyde **7a** (Scheme 23).

As explained in the introduction, aldehyde **7a** is known to react with high Felkin diastereoface selectivity. The influence of a heteroatom substituent at the aldehyde β-position on diastereoface selectivity was investigated and both chelation control and 'open' transition state models have been proposed to explain the observed stereoselectivity for additions of nucleophiles (Section 1.3.3). In addition, it has been reported recently that aldehydes bearing a β-dithiolane groups also have high Felkin diastereofacial selectivity (***A***).[49] According to the multiplicativity rule, if the three stereocontrol elements governing the stereoselectivity of the aldol reaction are highly biased, these reactions should proceed with KR. Previous work has shown that enolates of **8ss** have high diastereoface selectivity resulting in aldol adducts with 3,5-*trans* relative configuration. Similarly, boron and titanium "ate" enolates of **8ss** were highly selective giving aldol adducts with 5,1"-*anti* and 5,1"-*syn* relative configuration, respectively. Thus, to explore

the scope and limitations of this approach, the stereoselectivities of aldol reactions of aldehydes (±)-**7b-h** with ketones (±)-**8ss** (R = MOM or Et_3Si) via the boron and titanium "ate" enolates were investigated (Scheme 23).

Scheme 23. Research objectives.



Initially this investigation was performed using racemic reactants. The advantage of using racemic reactants is that both the diastereoselectivities of the individual *like* and *unlike* reactions and the MKE can be obtained from the analysis of the product distribution of a single reaction; the disadvantage is that the increased number of possible products complicates the analysis. Furthermore, an assessment of the three stereochemical control elements is also obtained from the product distribution and can aid in understanding of the factors governing the diastereoselectivity of the reaction. Based on the precedent established by the previous results[23, 25] the expectation was that these reactions would show high levels of MKE under optimized conditions. The MKE was measured for each reaction by determining the ratio of products from the *like* and *unlike*

reactions. According to Horeau's rule[44] the MKE is equal to the ratio of rate constants for the *like* and *unlike* reactions and the selectivity constant (*s*) in the related kinetic resolution where one reactant is enantiopure and the other one is racemic. To demonstrate that conjecture the boron and titanium "ate" mediated aldol reactions of enantiopure **8ss** (R = MOM) with aldehyde (±)-**7f** were shown to proceed with KR under condition where high MKE was observed using (±)-**8ss** (R = MOM).

The following questions were addressed in this research:

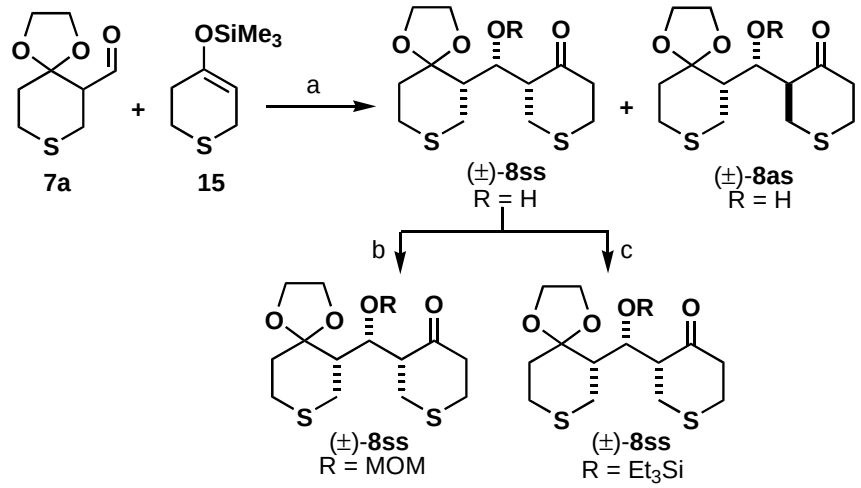
1. Is it possible to extend the highly selective aldol reactions of **8ss** with aldehyde **7a** to aldehydes **7b-h** based on their expected high Felkin diastereoface selectivity?

2. How does the nature of the structural differences between aldehydes **7a** and **7b-h** affect the stereoselectivity of their aldol reactions?

2.2. Synthesis of starting materials

To pursue the objectives of this research, it was first necessary to synthesize the starting materials. Using procedures established in the Ward group, racemic and enantiopure ketone **8ss** (R = MOM or Et_3Si) were synthesized.[23, 25] Racemic ketone **8ss** (R = H) was prepared by $TiCl_4$ mediated aldol reaction of silyl enol ether **15** with aldehyde **7a** (Scheme 24).[20] Enantiopure ketone **8ss** was obtained from (*S*)-**14** catalyzed aldol reaction of ketone **6** with aldehyde **7a** followed by isomerization of (+)-**8as** (R = H) to obtain (-)-**8ss** (R = H) (> 98% ee) in 60 % yield over two steps (Scheme 25).[22]

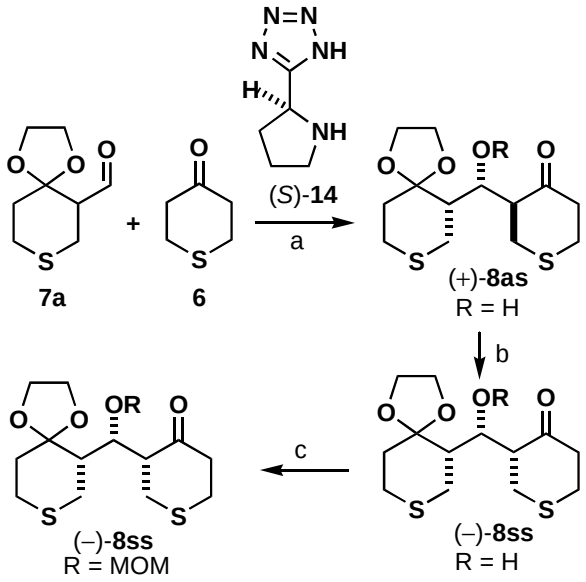
Scheme 24. Synthesis of racemic ketone **8ss** (R = MOM or Et_3Si).



a) $TiCl_4$, DCM,-78°C, 86%, 8a:8b 10:1, b) MOMCl, bis-DMA, DCM, rt, 98%,
c) Et_3SiOTf, DMF, rt, 88%

The MOM protection of racemic and enantiopure **8ss** (R = H) were done according to the newly developed procedure in the Ward group. This method includes addition of MBDA (4,4'-Methylenebis(N,N-dimethylaniline)) and MOMCl to the ketone **8ss** (R = H) at room temperature (Schemes 24 and 25).

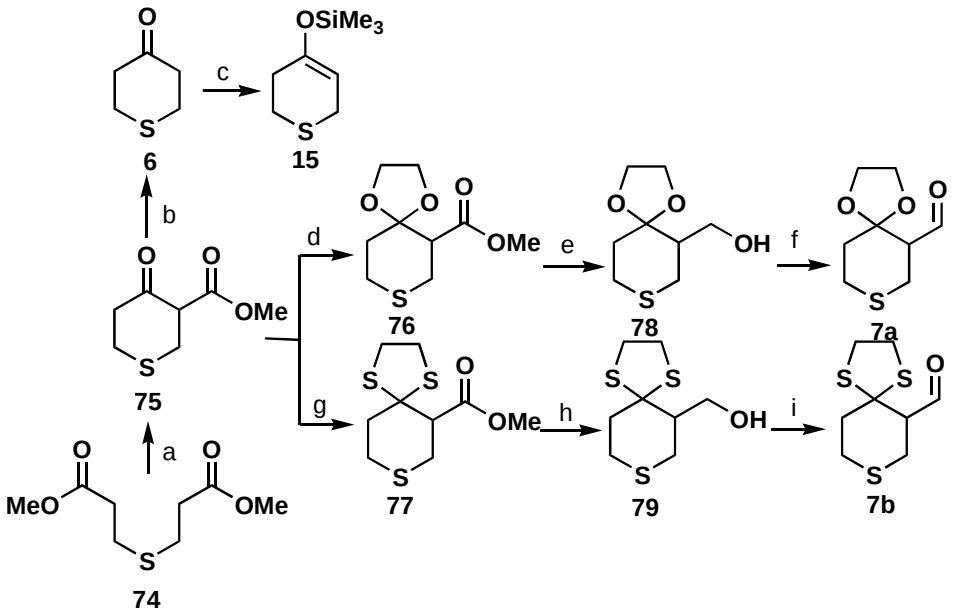
Scheme 25. Synthesis of enantiopure ketone **8ss** (R = MOM or Et_3Si).



a) wet DMSO, (*S*)-**14**, 75% , > 98% ee, b) Et_3N, SiO_2, EtOAC, 78% over 2 cycles, c) MOMCl, MBDA, DCM, rt, 96%

Aldehyde **7a** was prepared using the known route starting from commercially available diester **74**.[7] Aldehydes **7a** and **7b** were obtained from the common intermediate **75** by protection with the desired ketal group following by LAH reduction of the resulting esters **76** and **77** and IBX oxidation of the corresponding alcohols **78** and **79** (Scheme 26).

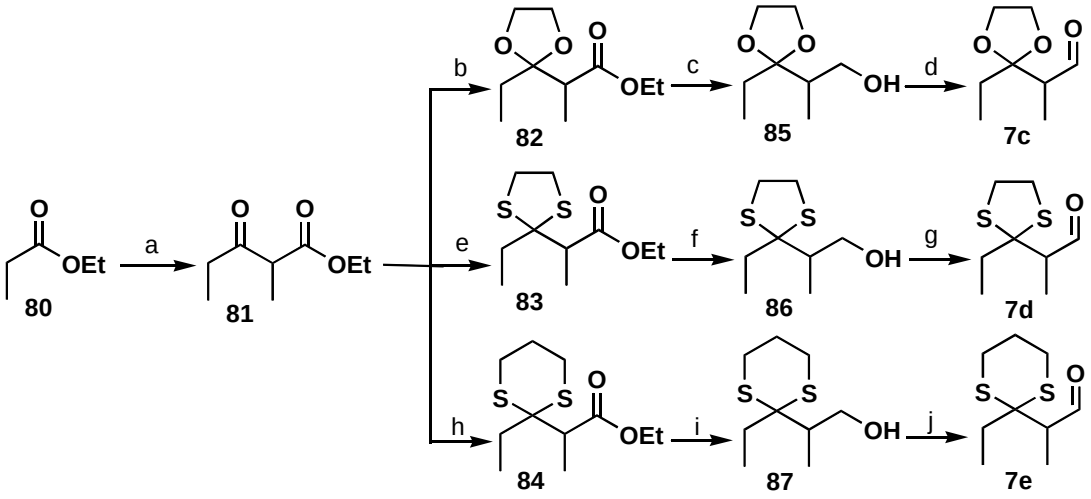
Scheme 26. Preparation of aldehydes **7a** and **7b.**



a) NaOMe, 90% b) 10% H_2SO_4, 80% c) TMSCl, Et_3N, rt, > 95% d) $(HOCH_2)_2$, *p*-TsOH.H_2O, C_6H_6, reflux, 90% e) LiAlH4,THF,86% f) IBX, CH_3CN, reflux, 92% g) $(HSCH_2)_2$, *p*-TsOH.H_2O, C_6H_6, reflux, 90% h) LiAlH4,THF, 93% i) IBX, DMSO, rt, 99%.

Compound **81**, obtained from Claisen condensation of **80**,[17]was a common intermediate for syntheses of aldehydes **7c**,[50] **7d**[17] and **7e**. Protection of **81** with desired ketal protecting group, followed by LAH reduction of the resulting esters **82**, **83**, and **84** and IBX oxidation of the corresponding alcohols **85**, **86**, and **87** gave aldehydes **7c**, **7d**, and **7e**, respectively (Scheme 27).

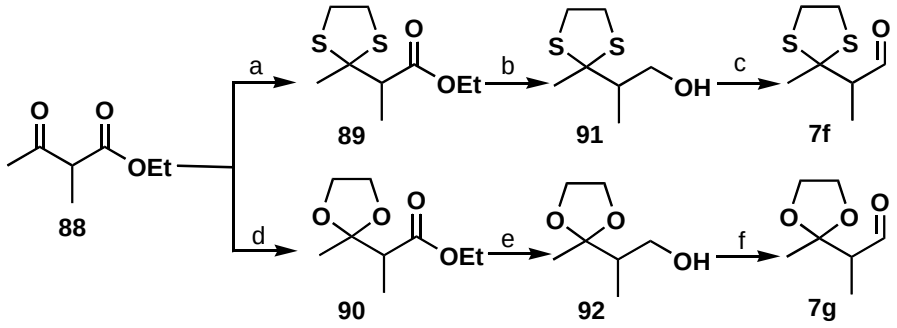
Scheme 27. Preparation of aldehydes **7c**, **7d** and **7e**.



a) KH, THF, 95% b) $(HOCH_2)_2$, *p*-TsOH.H_2O, C_6H_6, reflux, 79% c) LiAlH4,THF, 96% d) IBX, DMSO, rt, 98% e) $(HSCH_2)_2$, BF_3.OEt_2, DCM, 97% f) LiAlH4,THF, 88% g) IBX, DMSO, rt, 96% h) $(HSCH_2)_2CH_2$, BF_3.OEt_2, DCM, 86% i) LiAlH4,THF, 89% j) IBX,DMSO, rt, 83%

Aldehydes **7f** and **7g** were obtained by protection of commercially available **88** with desired ketal protecting group, followed by LAH reduction of the resulting esters **89** and **90** and IBX oxidation of the corresponding alcohols **91** and **92** (Scheme 28).

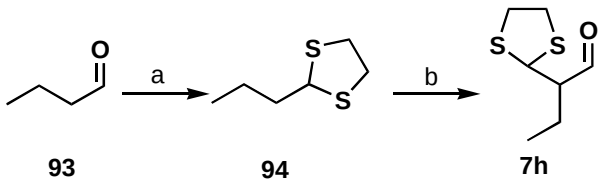
Scheme 28. Preparation of aldehydes **7f** and **7g**.



a) $(HSCH_2)_2$, $BF_3.OEt_2$, DCM, 97% b) LiAlH4,THF, 96% c) IBX, DMSO, rt, 90% d) $(HOCH_2)_2$, *p*-TsOH.H_2O, C_6H_6, reflux, 98% e) LiAlH4, THF, 97% f) IBX, DMSO, rt, 92%.

Aldehyde **7h** was prepared in two steps by dithiolane protection of butanal **93** followed by Vilsmeier reaction of the resulting **94** according to the known procedure (Scheme 29).[51]

Scheme 29. Preparation of aldehyde **7h**.



a) $(HSCH_2)_2$, $BF_3.OEt_2$, DCM, 99% b) DMF-$(COCl)_2$, 82%

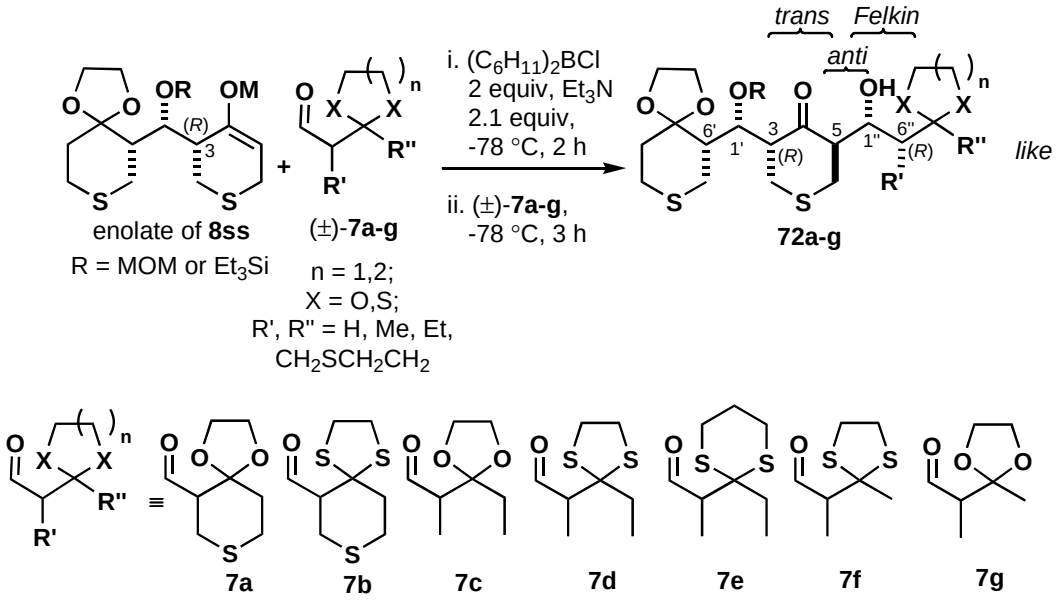
2.3. The diastereoselectivity of the aldol reaction of 8ss with aldehydes 7a-h

2.3.1. *Anti*-selective relative topicity with boron enolates

The boron mediated aldol reaction of (±)-**8ss** (R = MOM, Et_3Si or Ac) with the aldehyde (±)-**7a** occurs with high mutual kinetic enantioselection (MKE) in favour of the

like reaction.[23] The *like* adduct **72a** (Figure 4) was isolated from the reaction of MOM protected derivative in excellent yield (86 %) and high diastereoselectivity (*like*: *unlike* in a ratio of 15:1) (Scheme 30). Aldol reactions of cyclic ketones such as **8ss** via their boron enolates are known to proceed with high *anti* relative topicity (***R***).[23,25] The boron enolate of **8ss** is highly *3,5-trans* selective (***E***) and the aldehyde **7a** reacts with high Felkin diastereofacial selectivity (***A***). Thus, the three stereocontrol elements governing the diastereoselectivity of this reaction are highly biased leading to high MKE. The aldehydes **7b-g** were expected to have high Felkin diastereofacial selectivity (***A***) [49] thus the boron mediated aldol reactions of (±)-**8ss** (R = MOM or Et_3Si) with the aldehydes (±)-**7b-g** were expected to occur with high MKE in favour of the *like* reaction according to the design paradigm (Scheme 30).

Scheme 30. Aldol reactions of (±)-**7a-g** with the boron enolates of (±)-**8ss** (R = MOM or Et_3Si).



As expected, reactions of (±)-**7b-g** with the boron enolate of (±)-**8ss** (R = MOM or Et_3Si) gave adducts (±)-**72b-g** respectively in excellent yields and with high diastereoselectivities. The yields of the reactions varied from 76 to 89% and the MKE's for the reactions (ratio of *like* adduct (±)-**72b-g** and *unlike* adduct (±)-**73b-g**) varied from 10:1 to >20:1. These reactions proceed with remarkably high MKE in favour of the *like* reaction under optimized condition.[23] *Unlike* adducts (±)-**73b-g** were observed as the minor products from these reactions in most cases (Table 4 and Figure 4). The boron mediated aldol reactions are presumed to proceed via a "closed" transition state, thus the ratio of (±)-**72b-g** and (±)-**73b-g** adducts (*like* and *unlike* adducts*)* is dependent on the relative rate constants for reactions of the *like* combination of enantiomers of **7b-g** and **8ss** via a chairlike transition state (*anti* relative topicity) to give (±)-**72b-g** versus reactions of the *unlike* combination of enantiomers via a twist boat-like transition state (*syn* relative topicity) to give (±)-**73b-g**.[23]

Table 4. Reactions of aldehydes (±)-**7a-g** with boron enolates of (±)-**8ss** or (-)-**8ss**.

entry	ketone	R	aldehyde (equiv)	aldol adducts[a] (ratio)[b]; conversion[c] (%)	total isolated yield %
1	(±)-**8ss**	MOM	**7a** (2)	(±)-**72a** : (±)-**73a** (15:1); 92%	-----
2	(±)-**8ss**	Et_3Si	**7a** (2)	(±)-**72a** : (±)-**73a** (25:1); 95%	-----
3	(±)-**8ss**	MOM	**7b** (2)	(±)-**72b** : (±)-**73b** (10:1); 91%	89
4	(±)-**8ss**	Et_3Si	**7b** (2)	(±)-**72b** : (±)-**73b** (11:1); 92%	77
5	(±)-**8ss**	MOM	**7c** (2)	(±)-**72c** : (±)-**71c** (>20:1); 92%	89
6	(±)-**8ss**	Et_3Si	**7c** (2)	(±)-**72c** : (±)-**73c** (>20:1); 93%	76
7	(±)-**8ss**	MOM	**7d** (2)	(±)-**72d** : (±)-**73d** (17:1); 88%	84
8[e]	(±)-**8ss**	Et_3Si	**7d** (2)	(±)-**72d** : (±)-**73d** (>20:1); 89%	79
9	(±)-**8ss**	MOM	**7e** (2)	(±)-**72e**: (±)-**73e** (>20:1); 96%	89
10	(±)-**8ss**	Et_3Si	**7e** (2)	---------	-------
11	(±)-**8ss**	MOM	**7f** (2)	(±)-**72f** : (±)-**73f** (>20:1); 90%	66
12	(±)-**8ss**	Et_3Si	**7f** (2)	(±)-**72f** : (±)-**73f** (>20:1); 97%	75
13	(±)-**8ss**	MOM	**7g** (2)	(±)-**72g** : (±)-**73g** (>20:1); 94%	78
14	(±)-**8ss**	Et_3Si	**7g** (2)	------	-------
15	(-)-**8ss**	MOM	**7f** (3)	(+)-**72f** : (+)-**73f** (>20:1); 99%	81

a)Refer to Figure 4 for **72a-g** and **73a-g** structures. b) Determined by ^{1}H NMR of the crude reaction mixture. c) Estimated from the ratio of adducts and starting ketone present in the crude reaction mixture. d) **71c** was assigned as sulfoxide formed during the work up. e) Reaction time, 16 h.

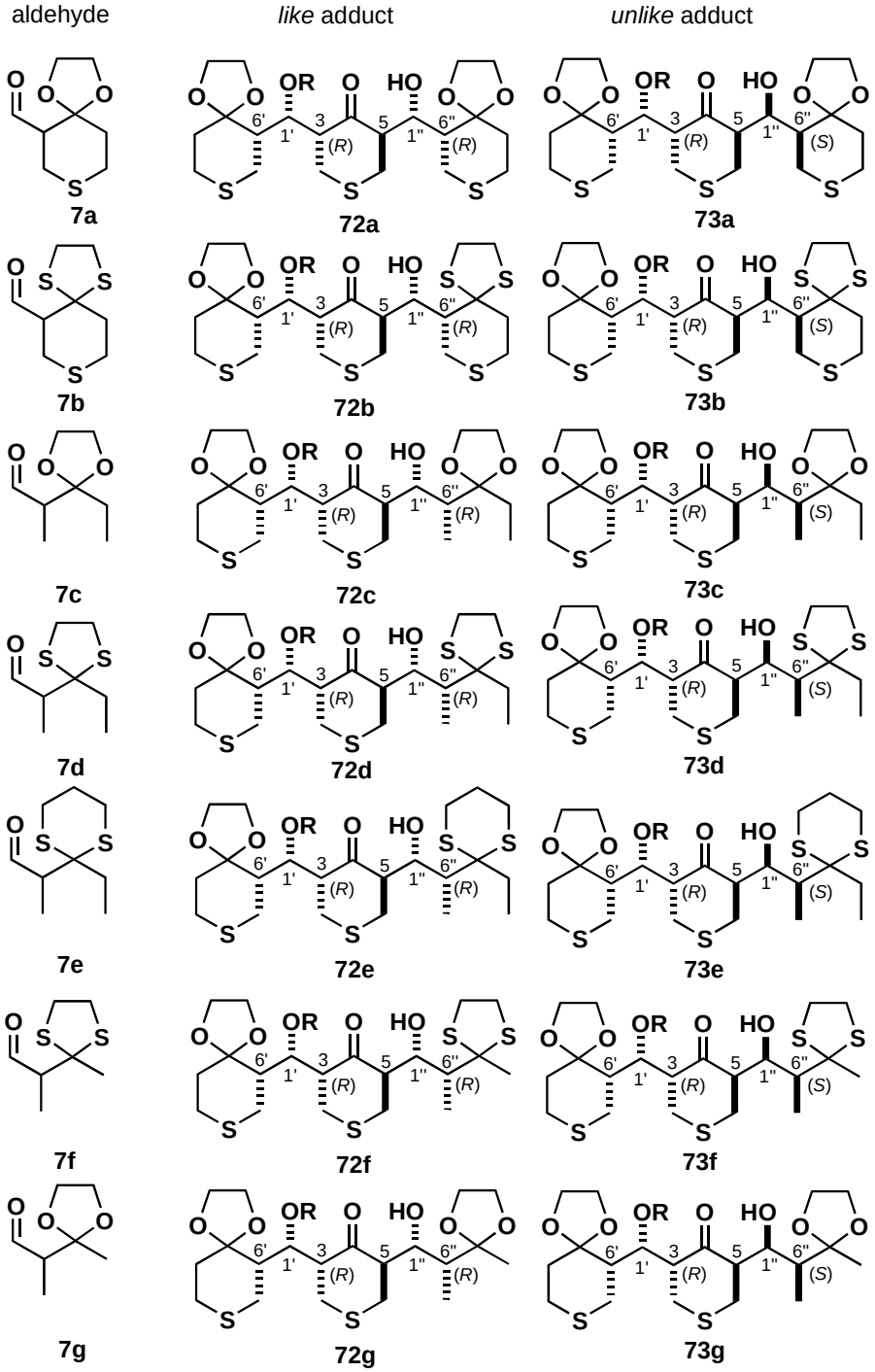


Figure 4. *like* and *unlike* adducts for aldehydes **7a-g**.

Reaction of (±)-**7b** with the boron enolate of (±)-**8ss** (R = MOM) gave aldol adduct (±)-**72b** with excellent yield (80%) and high diastereoselectivity (Table 4 entry 3). This reaction can give up to eight diastereomers assuming there is no isomerization of starting ketone **6ss** or aldol adducts during the reaction and workup. Considering the obtained results, this reaction occurred with high MKE in favour of the *like* reaction (*like*: *unlike* in a ratio of 10:1). Adduct (±)-**73b** was isolated as the minor product of this reaction. The MKE of this reaction was confirmed after assigning the relative configurations of the products (Section 2.4.1). Reaction of the Et_3Si-protected derivative of (±)-**8ss** with (±)-**7b** gave similar diastereoselectivity ((±)-**72b**:(±)-**73b**, 11:1) (Table 4 entry 4). However, the yield of this reaction was lower due to retro-aldol upon extending the reaction time after addition of aldehyde (±)-**7b**.

Among the aldehydes **7b-g**, reactions of 'acyclic' aldehydes **7c** or **7f** or **7g** gave very high diastereoselectivities compared to cyclic aldehyde **7b** (Table 4 entries 6 and 11-13). The adducts from these reactions (±)-**72c**, (±)-**72f** and (±)-**72g** result from a *like* reaction of these aldehydes with **8ss** and were the only products detected.

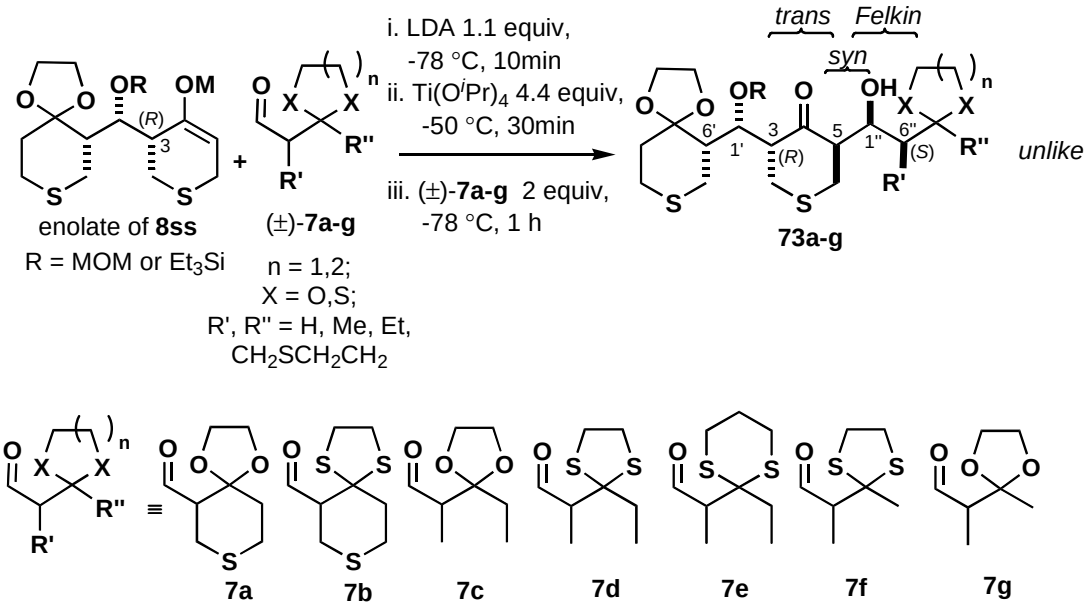
In the reaction of aldehyde (±)-**7d** with the boron enolate of (±)-**8ss** (R = Et_3Si), the major adduct (±)-**72d** was obtained in high yield 76% and with higher selectivity by extending the reaction time to 16 h (3 h, (±)-**72d**:(±)-**73d** = 11:1; 16 h, (±)-**72d**:(±)-**73d** = >20:1) (Table 4 entry 8). The adduct (±)-**72f** (R = Et_3Si) (Figure 4) was obtained as single product from reaction of (±)-**7f** with (±)-**8ss** (R = Et_3Si) (Table 4 entry 12). The yield of this reaction was diminished by retro-aldol upon extending the reaction time, whereas the yield of (±)-**72f** (R = MOM) was not affected by extending the reaction time.

Aldehyde **7g** was prepared to investigate the influence of a β-dioxolane group versus a β-dithiolane group (cf. **7f)** on the aldol reaction diastereoselectivity (Scheme 31). Reactions of aldehyde (±)-**7g** with the boron enolate of (±)-**8ss** (R = MOM) gave results to the analogous to the analogous reactions with aldehyde (±)-**7f** (Table 4 entries 11 and 13). Boron mediated aldol reactions of **8ss** (R = MOM) with the aldehydes **7f** and **7g** were highly diastereoselective affording *like* adducts (±)-**72f** and (±)-**72g**, respectively, as the only adducts detected.

2.3.2. *Syn*-selective relative topicity with titanium "ate" enolates

The titanium "ate" mediated aldol reaction of (±)-**8ss** (R = MOM) with the aldehyde (±)-**7a** proceeded with high MKE in favour of the *unlike* reaction. Similar reaction with (±)-**8ss** (R = Et_3Si) showed low MKE.[23] Under the optimized conditions this reaction strongly favours *syn* relative topicity. The optimized conditions for aldol reaction via titanium "ate" enolate involve addition of freshly prepared LDA (1.1 equiv) to the ketone (±)-**8ss** (R = MOM) at -78 ˚C followed by addition of $Ti(O^iPr)_4$ (2.2 equiv or more) at -78 ˚C, warming to -50 ˚C bath for 30 min (required for transmetalation), and addition of the aldehyde at -78 ˚C. The *unlike* adduct (±)-**73a** (Figure 4) was isolated from the reaction of the MOM protected **8ss** derivative in excellent yield (79 %) and high diastereoselectivity ((±)-**73a**: (±)-**72a** in a ratio of 11:1) (Scheme 31).[23]

Scheme 31. Aldol reactions of (±)-**7a-g** with the titanium "ate" enolates of (±)-**8ss** (R = MOM or Et_3Si).



The scope of the aldol reactions of (±)-**8ss** (R = MOM or Et_3Si) via its titanium "ate" enolate was investigated by applying the optimized conditions to the reactions with the aldehydes (±)-**7b-g** (Scheme 31 and Table 5). The MKE for these reactions were determined after establishing the relative configurations of the adducts (Section 2.4.4). Reaction of (±)-**7b** with the titanium "ate" enolate of (±)-**8ss** (R = MOM) afforded bisaldol adduct (±)-**73b** (Figure 4) as the major product in 73 % yield (Table 5 entry 3). Under optimized conditions, the reaction proceeded with remarkable MKE in favour of *unlike* adduct (±)-**73b** ((±)-**73b**: (±)-**72b** in a ratio of 13:1). The MKE was improved using 4.4 equivalent of Ti(O^{i}Pr)$_4$ (cf. 2.2 equiv; (±)-**73b**:(±)-**72b** = 9:1). This result is consistent with the Thornton[52] finding of improved selectivity of titanium "ate" mediated aldol reactions using an excess of Ti(O^{i}Pr)$_4$.

Table 5. Reactions of (±)-**7a-g** with titanium "ate" enolates of (±)-**8ss** or (-)-**8ss**.

entry	ketone	R	aldehyde (equiv)	aldol adducts[a] (ratio)[b]; conversion[c] (%)	total isolated yield %
1	(±)-**8ss**	MOM	**7a** (2)	(±)-**72a** : (±)-**73a** (1:10); 91%	------
2	(±)-**8ss**	Et_3Si	**7a** (2)	(±)-**72a** : (±)-**73a** (1:2); 88%	------
3[d]	(±)-**8ss**	MOM	**7b** (2)	(±)-**72b** : (±)-**73b** (1:13); 96%	79
4	(±)-**8ss**	Et_3Si	**7b** (2)	(±)-**72b** : (±)-**73b** (1:2); 89%	66
5	(±)-**8ss**	MOM	**7c** (2)	(±)-**72c** : (±)-**73c** (1:4); 90%	88
6	(±)-**8ss**	Et_3Si	**7c** (2)	(±)-**72c** : (±)-**73c** (3:1); 98%	84
7	(±)-**8ss**	MOM	**7d** (2)	(±)-**72d** : (±)-**73d** (1:8); 94%	77
8	(±)-**8ss**	Et_3Si	**7d** (2)	(±)-**72d** : (±)-**73d** (1.6:1); 73%	53
9	(±)-**8ss**	MOM	**7e** (2)	(±)-**72e** : (±)-**73e** (2:1); 94%	82
10	(±)-**8ss**	Et_3Si	**7e** (2)	------	-------
11[d]	(±)-**8ss**	MOM	**7f** (2)	(±)-**72f** : (±)-**73f** (1:6); 92%	77
12	(±)-**8ss**	Et_3Si	**7f** (2)	(±)-**72f** : (±)-**73f** (3:1); 87%	75
13[d]	(±)-**8ss**	MOM	**7g** (2)	(±)-**72g** : (±)-**73g** (1:3); 93%	71
14	(±)-**8ss**	Et_3Si	**7g** (2)	-----	-----
15[d]	(-)-**8ss**	MOM	**7f** (3)	(+)-**72f** : (+)-**73f** (1:4); 88%	77

a) Refer to Figure 4 for **72a-g** and **73a-g** structures. b) Determined by ^{1}H NMR of the crude reaction mixture. c) Estimated from the ratio of adducts and starting ketone present in the crude reaction mixture. d) 4.4 equiv of $Ti(O^iPr)_4$ was used.

Contrary to the reactions of aldehydes **7c-g**, extending the reaction time up to 17 hours after addition of aldehyde (±)-**7b** to the titanium "ate" enolate (±)-**8ss** (R = MOM) improved the selectivity of the reaction, however allowing more time for transmetalation (0.5-2 h) prior to the addition of (±)-**7b** had no effect on the ratio of the *unlike*:*like* adducts.

Similar reaction with Et_3Si derivative of **8ss** had considerably lower MKE ((±)-**73b**: (±)-**72b** in a ratio of 2:1) (Table 5 entry 4). Extending the reaction time did not affect the diastereoselectivity of this reaction. Similar selectivity was observed in the titanium "ate" mediated aldol reaction of aldehyde (±)-**7b** with (±)-**8ss** (R = Et_3Si) ((±)-**73b**: (±)-**72b** in a ratio of 2:1) (Table 5 entry 2).[23]

The diastereoselectivity decreased markedly by changing from cyclic to acyclic aldehydes. There is significant difference between diastereoselectivities of reactions of (±)-**8ss** (R = MOM) with the cyclic aldehydes such as (±)-**7a** or (±)-**7b** and acyclic aldehydes (±)-**7c-g** (Table 5: entries 1 and 3 versus entries 5, 7, 9, 11 and 13). Among the acyclic aldehydes **7c-g**, the MKE for the reaction varied from 8:1 to 1:2. Unexpectedly, the reactions of acyclic aldehydes (±)-**7c-d** or (±)-**7f** with (±)-**8ss** (R = Et_3Si) occurred with low to moderate MKE in favour of *like* reaction (Table 5: entries 6, 8 and 12). These results indicate that among acyclic aldehydes changing the protective group on the enolate (±)-**8ss** from MOM to Et_3Si causes the reaction to proceed with very low MKE moderately favouring the *like* reaction with *anti* relative topicity. Similar selectivity was observed in the reaction of aldehyde (±)-**7e** with (±)-**8ss** (R = MOM) (Table 5 entry 9). Contrary to the observed results for the reaction with aldehyde **7b**, the diastereoselectivity of this reaction was not improved by increasing the amount of $Ti(O^iPr)_4$ reagent used.

Extending the reaction time for reaction of aldehyde (±)-**7d** with (±)-**8ss** (R = MOM) did not improve the diastereoselectivity. Also, allowing more time for transmetalation (0.5-2 h) prior to the addition of aldehyde (±)-**7d** had no effect on the products ratio. Contrary to the report by Thornton[52] and observed in the reaction of aldehyde (±)-**7b**, increasing the amount of $Ti(O^iPr)_4$ reagent (4.4 or 8.8 equiv) had no effect on the diastereoselectivity of titanium "ate" mediated reactions of aldehyde (±)-**7d** with (±)-**8ss** (R = MOM or Et_3Si). Using excess $TiCl(O^iPr)_3$ reagent instead of $Ti(O^iPr)_4$ reagent for preparation of the enolate did not improve the diastereoselectivity of this reaction. The $TiCl(O^iPr)_3$ used in this study was prepared by two different methods; one method included the neat reaction of 3 mole $Ti(O^iPr)_4$ with 1 mole $TiCl_4$ at 0 ˚C followed by distillation of the $TiCl(O^iPr)_3$; [53] the other procedure [54] involved in situ preparation of $TiCl(O^iPr)_3$ by addition of the same two reagents in the same ratio in DCM as a solvent at 0 ˚C. $TiCl(O^iPr)_3$ prepared by both methods were used for the reaction of aldehyde (±)-**7d** with (±)-**8ss** (R = MOM) in separate experiments. None of these experiments led to an improvement of the diastereoselectivity of the reaction.

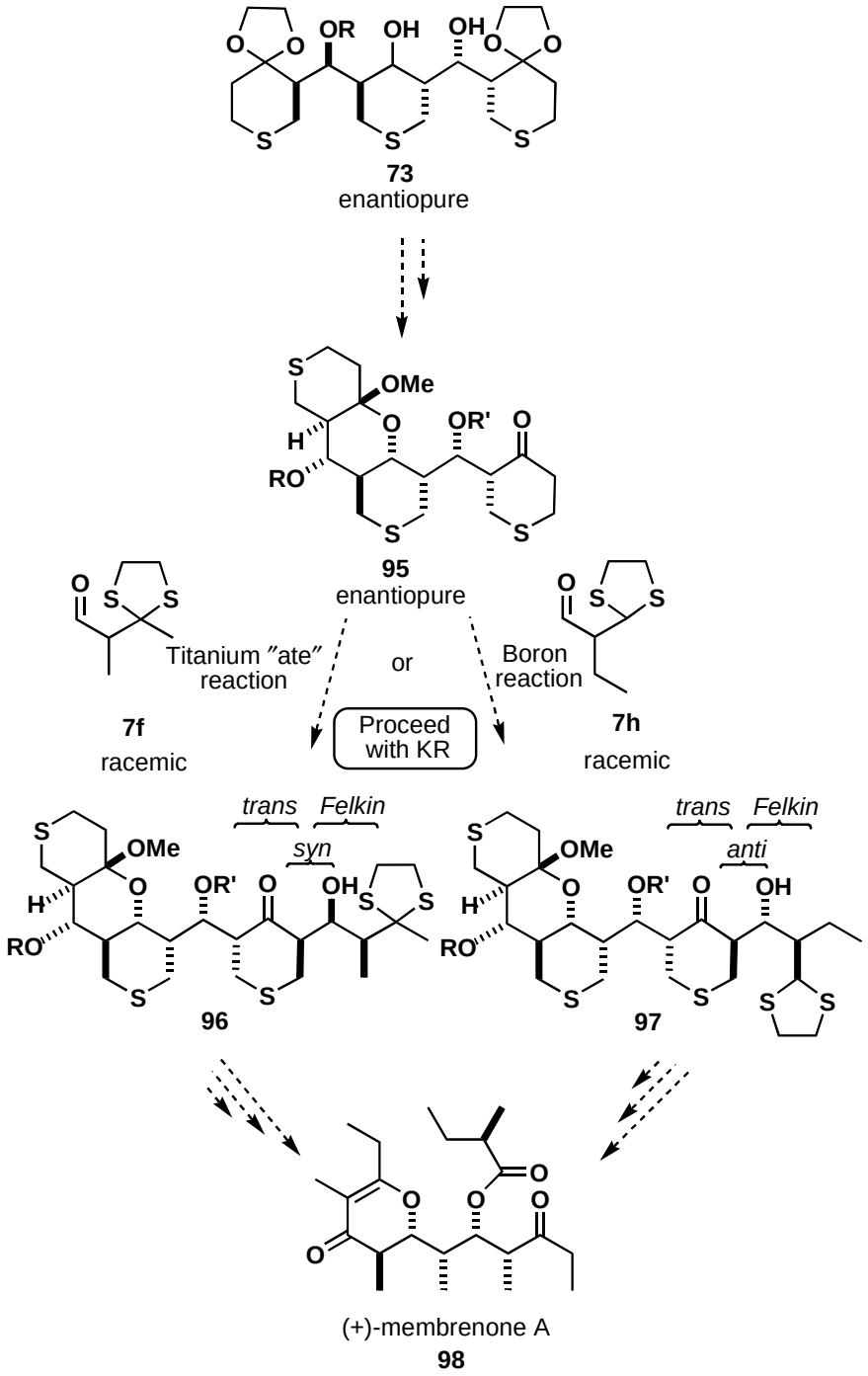
In another attempt to improve the diastereoselectivity of the reaction of (±)-**8ss** (R = MOM) with aldehyde (±)-**7d**, $Ti(O^iPr)_4$ was added to the "amine free" Li-enolate of (±)-**8ss** (R = MOM) prior to the addition of aldehyde (±)-**7d**. Reaction of (±)-**8ss** (R = MOM) with LDA followed by addition of TMSCl gave the corresponding trimethylsilyl enol ether which was treated with *t*-BuLi to give the "amine free" Li-enolate of (±)-**8ss** (R = MOM). Subsequent reaction with (±)-**7d** gave two bisaldol adducts (±)-**73d** and (±)-**72d** with a ratio of 3:1 in favour of the *unlike* adduct (±)-**73d**. Thus replacing LDA enolate by "amine free" Li-enolate did not affect the diastereoselectivity of the reaction.

2.3.3. MKE and KR from the aldol reactions of (±)-8ss (R = MOM or Et3Si) with aldehyde (±)-7f and (±)-7h

The aldehydes **7f** and **7h** were designed for application in a projected synthesis of (+)-membrenone A **98** (Scheme 32). The aldol adduct **96** with desired stereochemistry should be obtained from reaction of aldehyde (±)-**7f** with the titanium "ate" enolate of enantipure **95**. Alternatively, reaction of aldehyde (±)-**7h** with the boron enolate of enantipure **95** should provide the synthetically analogous adduct **97** (Scheme 32). Desulphurization of **96** or **97** would give the same product. Unfortunately, the reactions of (±)-**8ss** (R = MOM or Et_3Si) with (±)-**7h** via the boron enolate showed low MKE.

To assess the possibility of achieving KR with aldehyde **7f**, reactions with both boron and titanium "ate" enolates of (-)-**8ss** (R = MOM) were investigated.

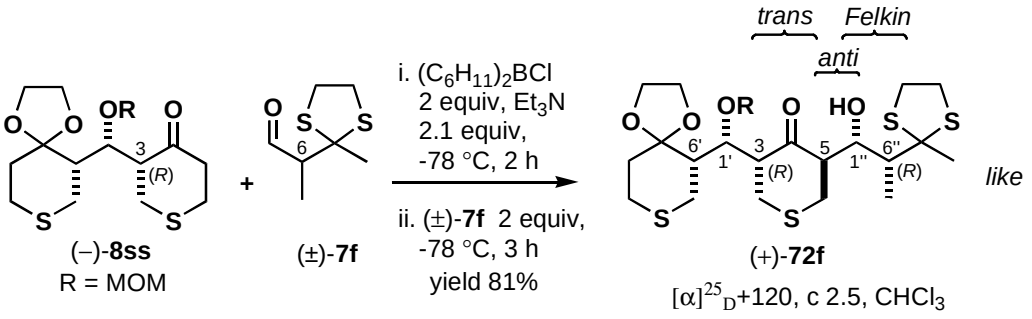
Scheme 32. Synthetic plan for (+)-membrenone A **98.**



Reactions of aldehyde (±)-**7f** with the boron enolates of (±)-**8ss** (R = MOM or Et_3Si) were highly selective giving one adduct (±)-**72f** (R = MOM or Et_3Si) (Table 4:

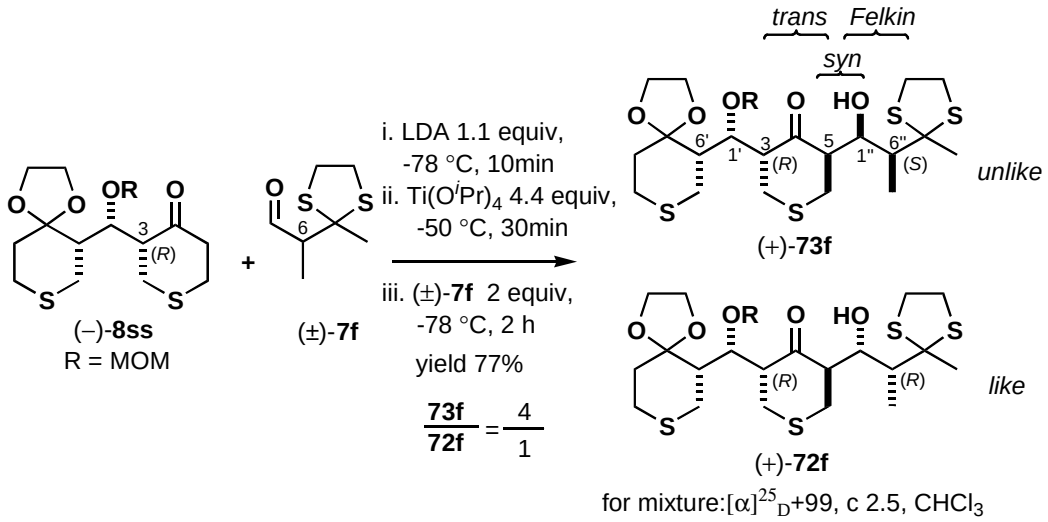
entries 11 and 12). Both reactions occurred with very high MKE (>20:1). As noted in Section 2.1, the MKE observed for reaction of racemic reactants should be equal to the selectivity constant (*s*) in the analogous KR where one reactant is enantiopure and the other is racemic.[23] To validate this opportunity to achieve KR, the reaction of aldehyde (±)-**7f** with the boron enolate of highly enantioenriched (-)-**8ss** (R = MOM) was conducted under the reaction conditions used for the reaction of racemic reactants. As expected, enantiopure (+)-**72f** (from the *like* reaction) was obtained as the sole product in excellent yield 81% (Scheme 33) (Table 4 entry 15).

Scheme 33. Reaction of (±)-**7f** with the boron enolate of (-)-**8ss** (R = MOM).



Reaction of aldehyde (±)-**7f** with the titanium "ate" enolate of (±)-**8ss** (R = MOM) gave two aldol adducts (±)-**73f** and (±)-**72f** with a ratio of 6:1 in favour of the *unlike* adduct (±)-**73f** (Table 5 entry 11). To achieve that selectivity required the use of 4.4 equivalent of $Ti(O^iPr)_4$ (cf. 2.2 equiv; (±)-**73f**: (±)-**72f**, 4:1). The use of 8.8 equivalent of $Ti(O^iPr)_4$ did not improve the selectivity further. Reaction of aldehyde (±)-**7f** with the titanium "ate" enolate of highly enantioenriched (-)-**8ss** (R = MOM) under these conditions gave an inseparable 4:1 mixture of (+)-**73f** and (+)-**72f**, respectively (Scheme 34).

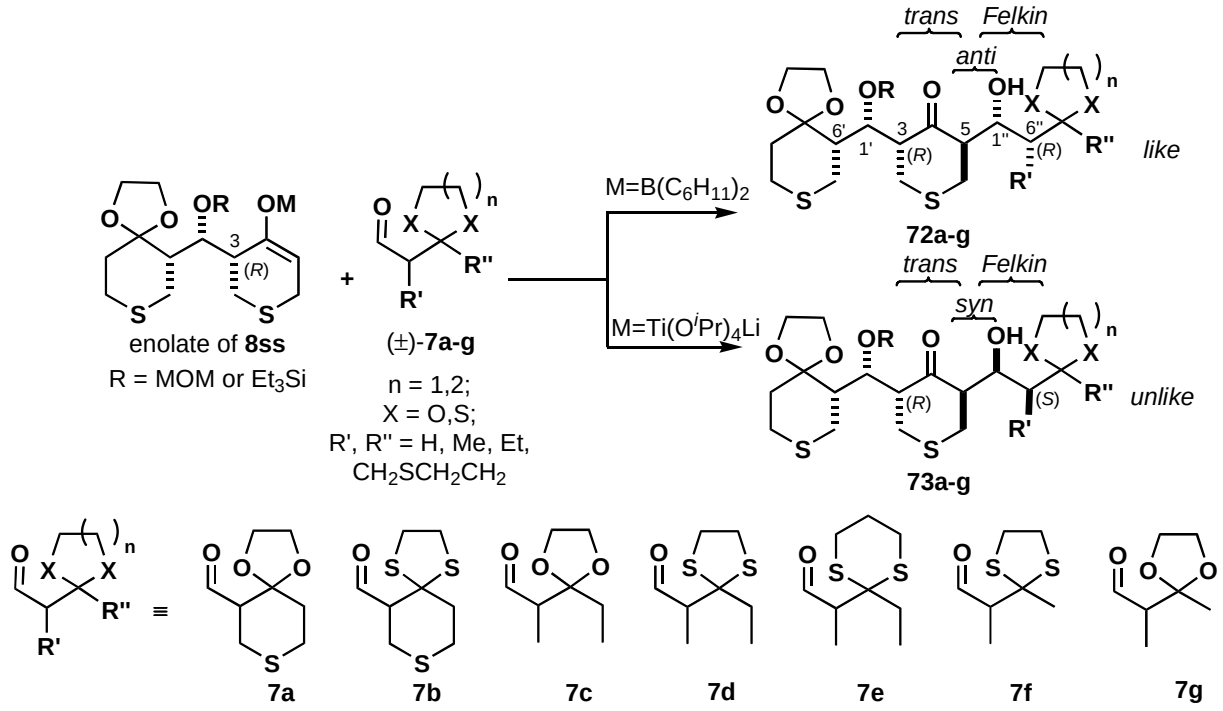
Scheme 34. Reaction of (±)-**7f** with the titanium "ate" enolate of (-)-**8ss** (R = MOM).



2.3.4. Summary of results for boron and titanium "ate" mediated reactions (±)-8ss (R = MOM or Et_3Si) with aldehydes (±)-7a-g

Reactions of aldehydes (±)-**7a-g** with the boron enolates of (±)-**8ss** (R = MOM or Et_3Si) were highly selective and proceeded with high MKE in favour of the *like* adducts **72a-g** (Scheme 35 and Table 4). The ratio of products is dependent on the relative rate constants for the *like* and the *unlike* reactions. The *like* reactions of aldehydes **7a-g** with the boron enolate of **8ss** proceed via chair-like transition state **99** affording products **72a-g** with *anti* relative topicity (Scheme 36). The *unlike* reactions of aldehydes **7a-g** with the boron enolate of **8ss** presumably proceed via twist boat-like transition state **100** giving products **73a-g** with *syn* relative topicity.

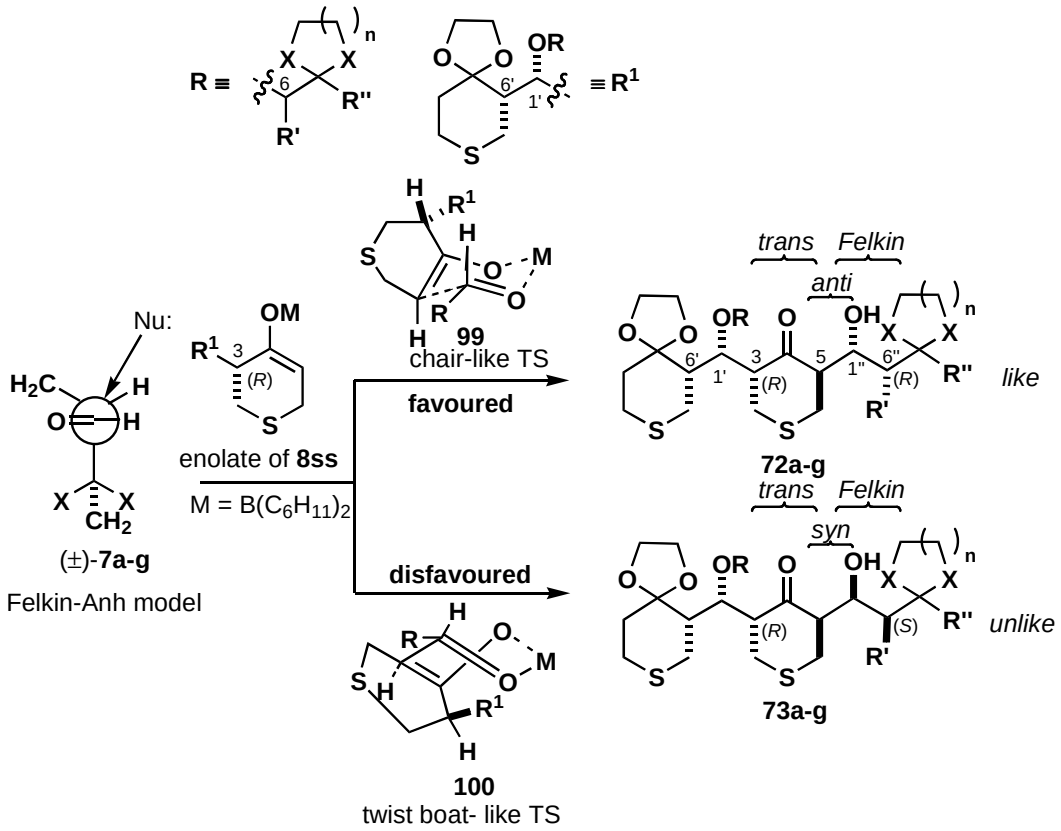
Scheme 35. Summary of boron and titanium "ate" mediated aldol reactions of (±)-**8ss** (R = MOM or Et_3Si) with the aldehydes (±)-**7a-g**.



The chair-like transition state **99** is favoured over the twist boat-like transition state **100**, thus *like* adduct is major product from the aldol reaction via boron enolate (Scheme 36). Under the optimized conditions for boron mediated aldol reaction, *anti* relative topicity is strongly favoured, thus all three stereocontrol elements of the reaction are strongly biased leading to high MKE. The selectivity of this reaction was independent of the structure of the aldehyde (acyclic or cylic) and nature of the *β*-protecting group on the aldehyde (dithiolane, dioxolane or dithiane). Also nature of the protecting group on the enolate **8ss** (MOM or Et_3Si) had little effect on the diastereoselectivity of this reaction. This is consistent with the finding that the *β*-protecting group has minimal effect

on the diastereoselectivity of aldol reactions of boron enolates of β-alkoxy acyclic chiral ketones.[23]

Scheme 36. Transition states for boron mediated reaction of **8ss** with aldehydes **7a-g**.



Reactions of aldehydes (±)-**7a-g** with the titanium "ate" enolate of (±)-**8ss** (R = MOM) gave moderate to good MKE (Scheme 35 and Table 5). Comparison of the results of boron and titanium "ate" mediated aldol reactions (Tables 4 and 5) indicates that the boron mediated aldol reactions generally proceed with much higher MKE than titanium "ate" mediated aldol reactions in both MOM and Et_3Si protected (±)-**8ss**.

As Ward has pointed out,[23] the structure and aggregation state of titanium "ate" enolates are uncertain and it is not clear whether the competing transition states for the

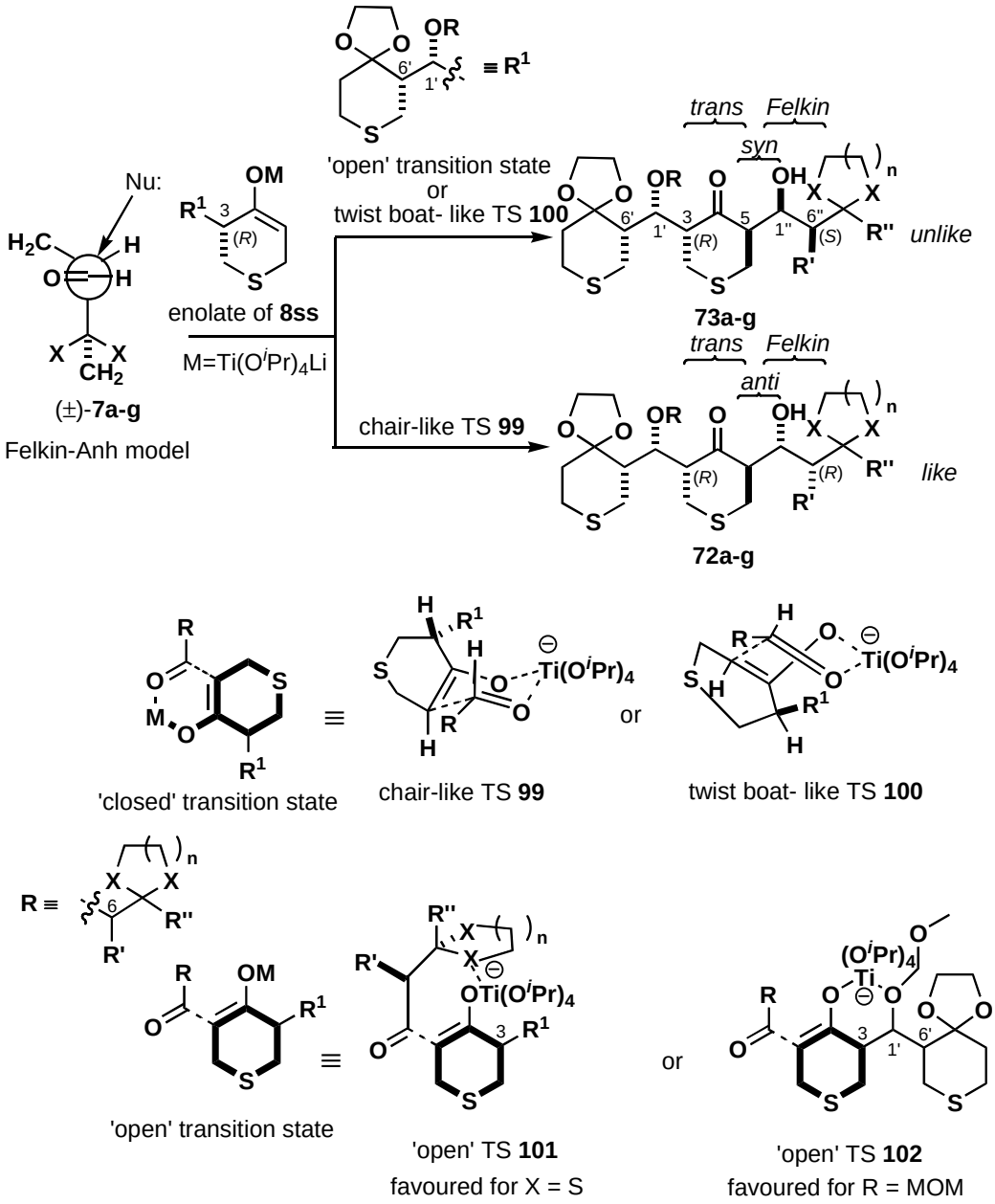
like and *unlike* reactions are the same type (e.g., "closed" chair versus twist-boat) or different types (e.g., "closed" versus "open"). Results of titanium "ate" mediated aldol reactions of cyclic or acyclic aldehydes with MOM protected **8ss** show that presence of *β*-dithiolane protecting group versus *β*-dioxolane protecting group on the aldehyde leads to higher selectivity (Table 5: entry 3 versus entry 1 and entry 7 versus entry 5). This can be presumably caused by coordination of titanium centre with the *β*-dithiolane protecting group as a result of the strong affinity of Ti(IV) for sulphur. Such an interaction would give octahedral geometry at titanium and facilitate aldol reaction via a transition state (cf. **101**) analogous to an 'open' transition state affording an *unlike* adduct (Scheme 37).

The selectivity of the titanium "ate" mediated reaction of acyclic aldehydes (±)-**7c-d** or (±)-**7f** with (±)-**8ss** drops significantly upon changing the protecting group of the enolates from MOM to Et_3Si to the degree that in some cases *like* (*anti*) adduct is favoured over the *unlike* (*syn*) adduct (Table 5: entries 6, 8 and 12).

A similar trend was observed in case of cyclic aldehydes (±)-**7a** and (±)-**7b** (Table 5: entries 2 and 4). The nature of MOM and Et_3Si protecting group is different. As Ward pointed out,[23] intramolecular coordination of Ti with O-MOM would give octahedral geometry of the titanium "ate" enolate and perhaps facilitate aldol reaction via an 'open' transition state **102** (Scheme 37). For the TES protected titanium "ate" enolate, the lower Lewis basicity of an O-TES versus O-MOM oxygen should diminish the tendency for intramolecular coordination with Ti(IV) thereby leaving an open site for coordination of the aldehyde carbonyl resulting in a 'closed' transition state **100**. The *like* adduct from the titanium "ate" enolate of Et_3Si protected **8ss** is presumably obtained via 'closed' chair-like transition state **99**. Whether the *unlike* reaction occurs via an 'open' transition state or 'closed' twist boat-like transition state **100** or combination of both

transition states, changing the protecting group on the enolate from MOM to Et_3Si can affect the relative energies of the competing transition states and and facilitate formation of *like* adduct via a 'closed' chair like transition state **99** (Scheme 37).

Scheme 37. Transition states for titanium "ate" mediated reaction of **8ss** with aldehydes **7a-g**.

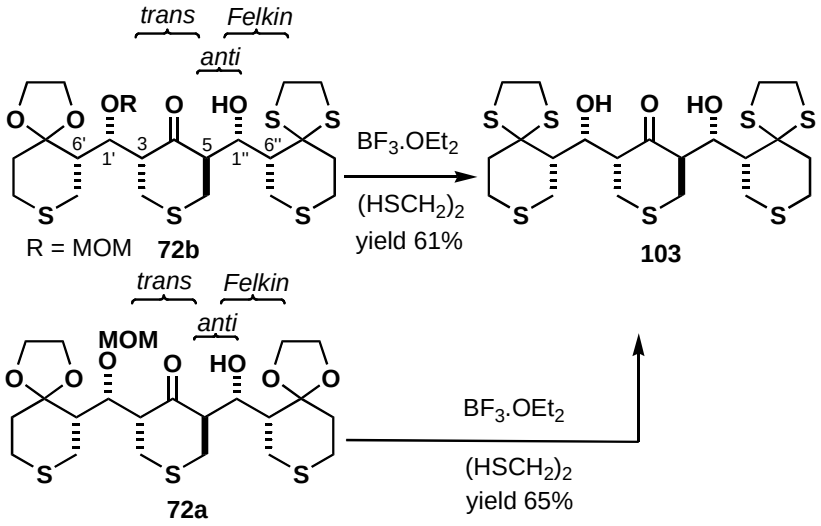


2.4. Structure determination of aldol adducts 72 and 73

2.4.1. Determination of the relative configurations of aldol adducts 72b and 73b

The adduct **72b** was obtained as the major product from the boron mediated aldol reaction of **8ss** (R = MOM) with the aldehyde **7b**. The relative configuration of the adduct **72b** was confirmed by reaction of this adduct with $BF_3{\cdot}OEt_3/(HSCH_2)_2$ affording **103** in 61% yield. The aldol adduct **72a** with known relative configuration[25] was obtained from boron mediated aldol reaction of **8ss** (R = MOM) with the aldehyde **7a**. Reaction of aldol adduct **72a** with $BF_3.OEt_3/(HSCH_2)_2$ gave **103** (65% yield) establishing the relative configuration of **72b** by correlation to **72a** (Scheme 38).

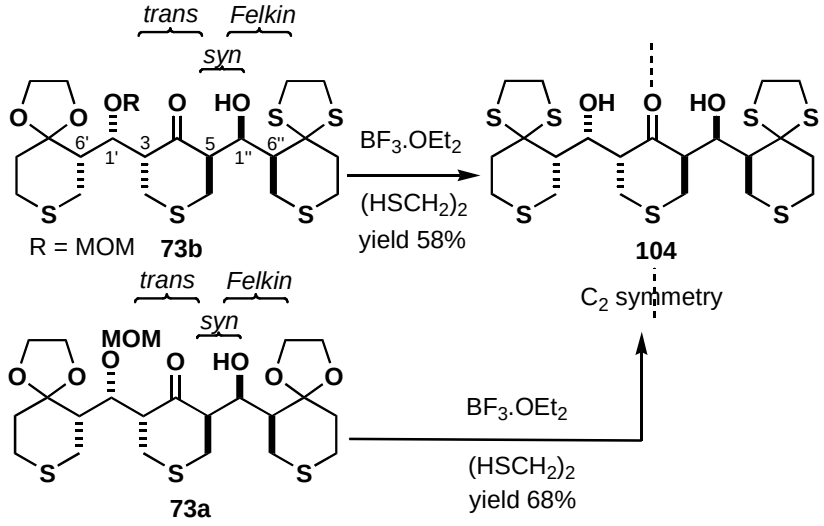
Scheme 38. Determination of the relative configuration of aldol adduct **72b** (R = MOM).



Adduct **73b** was obtained as the major product from titanium "ate" mediated aldol reaction of **8ss** (R = MOM) with the aldehyde **7b**. Reaction of **73b** with $BF_3{\cdot}OEt_3/(HSCH_2)_2$ gave **104** in 58% yield. Reaction of **73a** (known relative

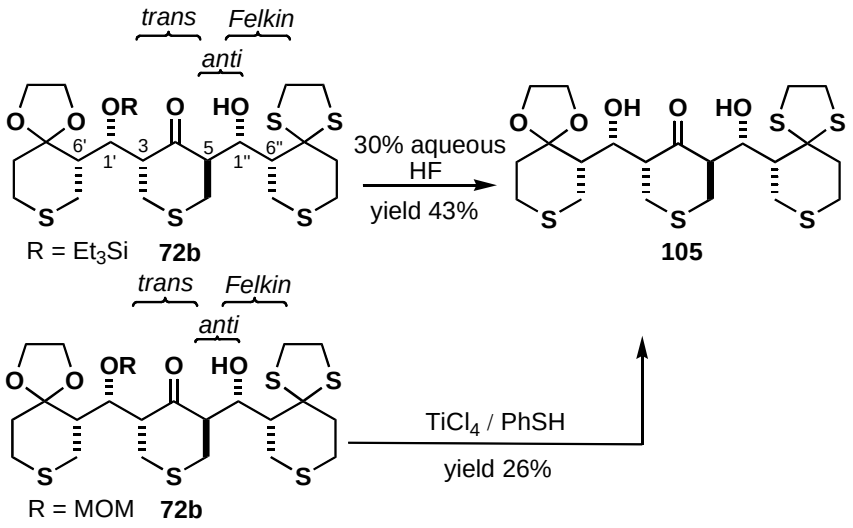
configuration) [25] with $BF_3{\cdot}OEt_3/(HSCH_2)_2$ gave **104** in 68% yield establishing the relative configuration of **73b** by correlation to **73a** (Scheme 39).

Scheme 39. Determination of the relative configuration of aldol adduct **73b** (R = MOM).



Adduct **72b** (R = Et_3Si) was obtained as the major product from reaction of boron enolate of **8ss** (R = Et_3Si) with the aldehyde **7b**. Removal of the silyl protecting group in **72b** (R = Et_3Si) by treatment with aqueous 30% HF solution gave **105** in 43% yield. Removal of the MOM ether in **72b** (R = MOM) by treatment with $TiCl_4$/PhSH gave **105** in 26% yield.

Scheme 40. Determination of the relative configuration of aldol adduct **72b** (R = TES).

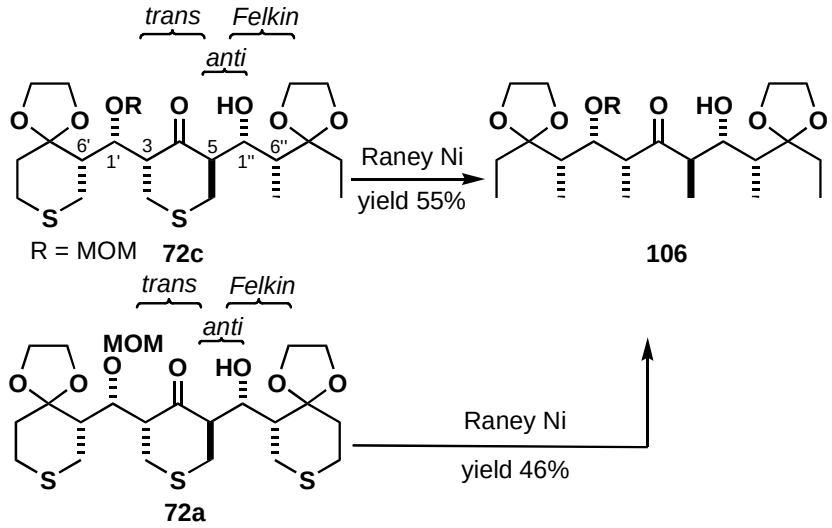


Considering the relative configuration of **72b** (R = MOM) previously established (Scheme 38), this result confirms the relative configuration of adduct **72b** (R = Et_3Si) (Scheme 40).

2.4.2. Determination of the relative configurations of aldol adducts 72c and 73c

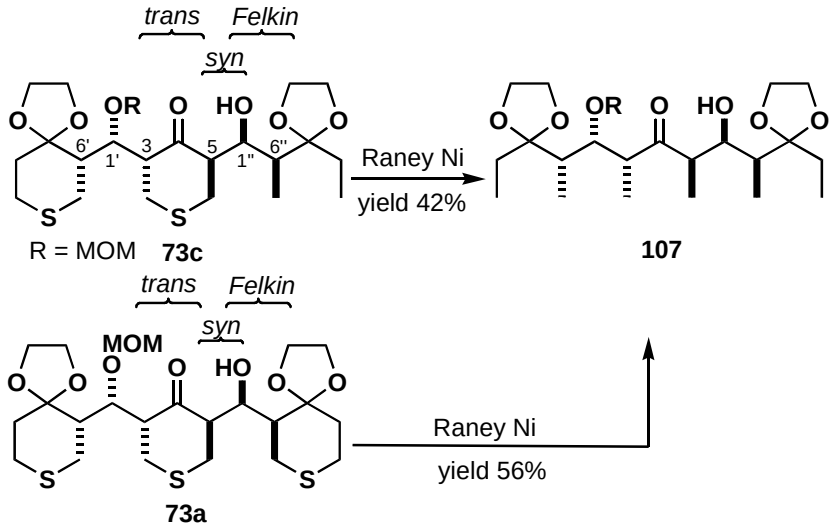
Adduct **72c** was obtained as the major product from boron mediated aldol reaction of **8ss** (R = MOM) with the aldehyde **7c**. Desulphurization of **72c** by treatment with Raney Ni gave **106** in 55 % yield. Raney Ni desulphurization of **72a** (known relative configuration)[25] also gave **106** thereby confirming the relative configuration of **72c** by correlation to **72a** (Scheme 41).

Scheme 41. Determination of the relative configuration of aldol adduct **72c**.



Adduct **73c** is the major product from titanium "ate" mediated aldol reaction of **8ss** (R = MOM) with the aldehyde **7c**. Raney Ni desulphurization of **73c** gave **107** in 42% yield. The same product was obtained by desulphurization of **73a** with known relative configuration thereby confirming the relative configuration of **73c** by correlation to **107** (Scheme 42).

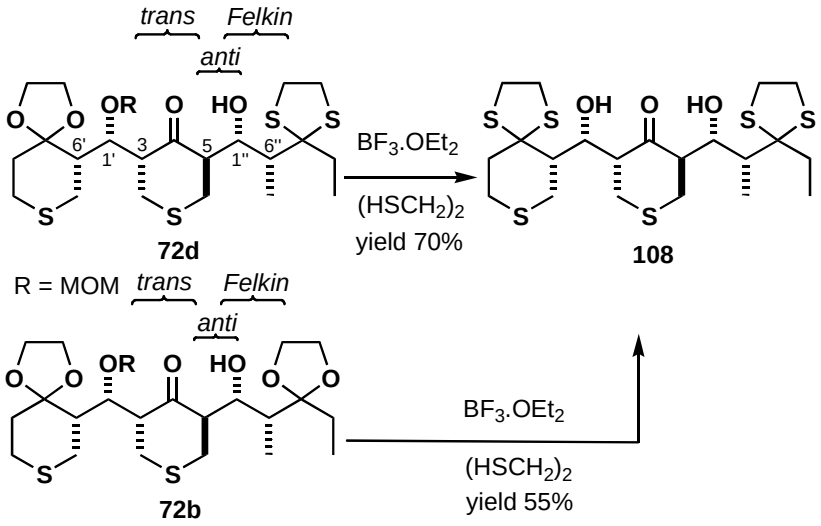
Scheme 42. Determination of the relative configuration of aldol adduct **73c**.



2.4.3. Determination of the relative configurations of aldol adducts 72d and 73d

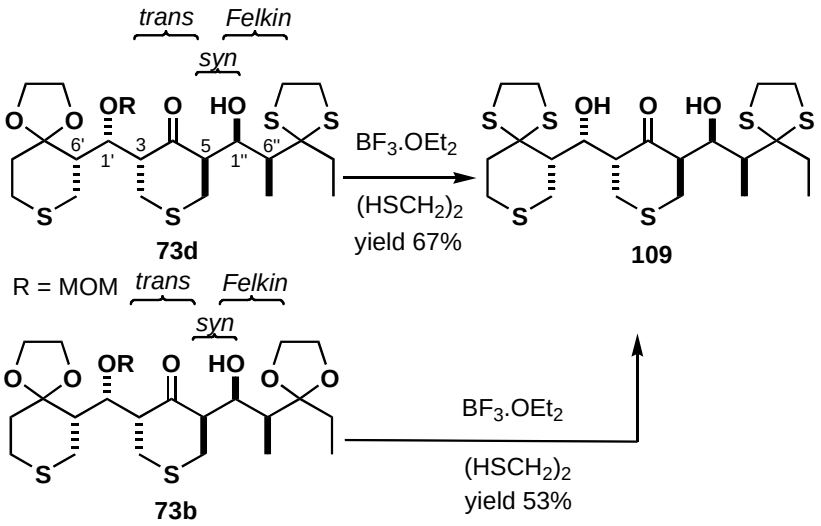
Adduct **72d** was obtained as the major product from boron mediated aldol reaction of **8ss** (R = MOM) with the aldehyde **7d**. Reaction of **72d** with $BF_3{\cdot}OEt_3/(HSCH_2)_2$ gave **108** in 70% yield. The same product was obtained from reaction of **72b** (of known relative configuration; Scheme 41) with $BF_3{\cdot}OEt_3/(HSCH_2)_2$ in 55% yield thereby confirming the relative configuration of adduct **72d** by correlation to **72b** (Scheme 43).

Scheme 43. Determination of the relative configuration of aldol adduct **72d**.



Adduct **73d** was the major product from titanium "ate" mediated aldol reaction of **8ss** (R = MOM) with the aldehyde **7d**. Reaction of **73d** with $BF_3{\cdot}OEt_3/(HSCH_2)_2$ gave **109** in 67% yield (Scheme 44).

Scheme 44. Determination of the relative configuration of aldol adduct **73d**.

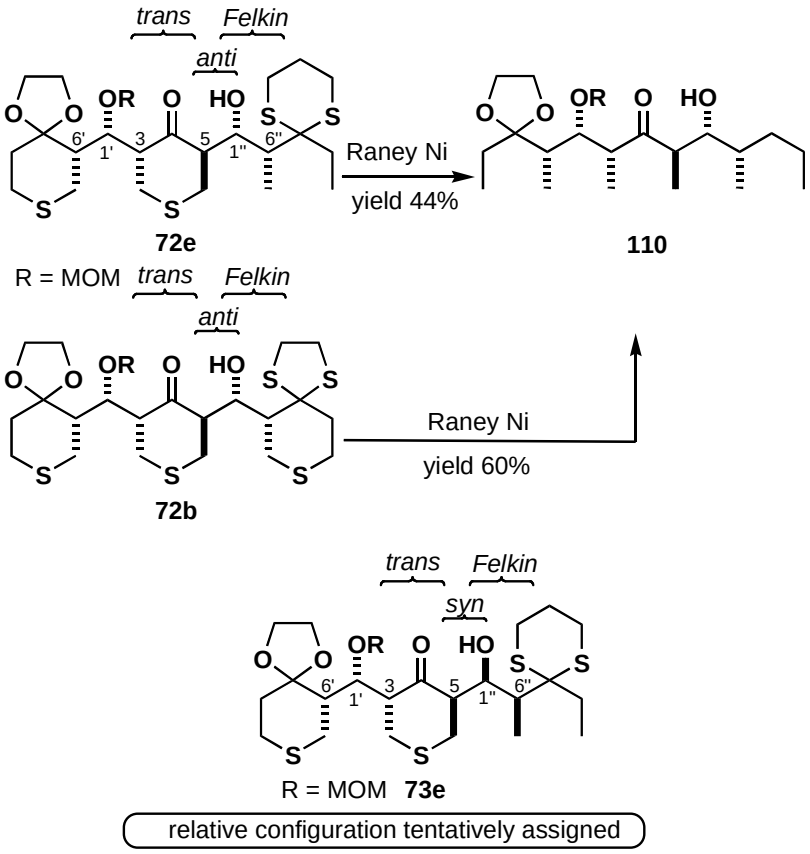


The same product was obtained in 53% yield by treatment of **73b** (of known relative configuration; Scheme 42) with $BF_3{\cdot}OEt_3/(HSCH_2)_2$ thereby confirming the relative configuration of **73d** by correlation to **73b** (Scheme 44).

2.4.4. Determination of the relative configurations of aldol adducts 72e and 73e

Adduct **72e** was obtained as the major product from both the boron and titanium "ate" mediated aldol reactions of **8ss** (R = MOM) with the aldehyde **7e**. Both reactions also gave **73e** as the minor product.

Scheme 45. Determination of the relative configuration of aldol adduct **72e** and **73e**.

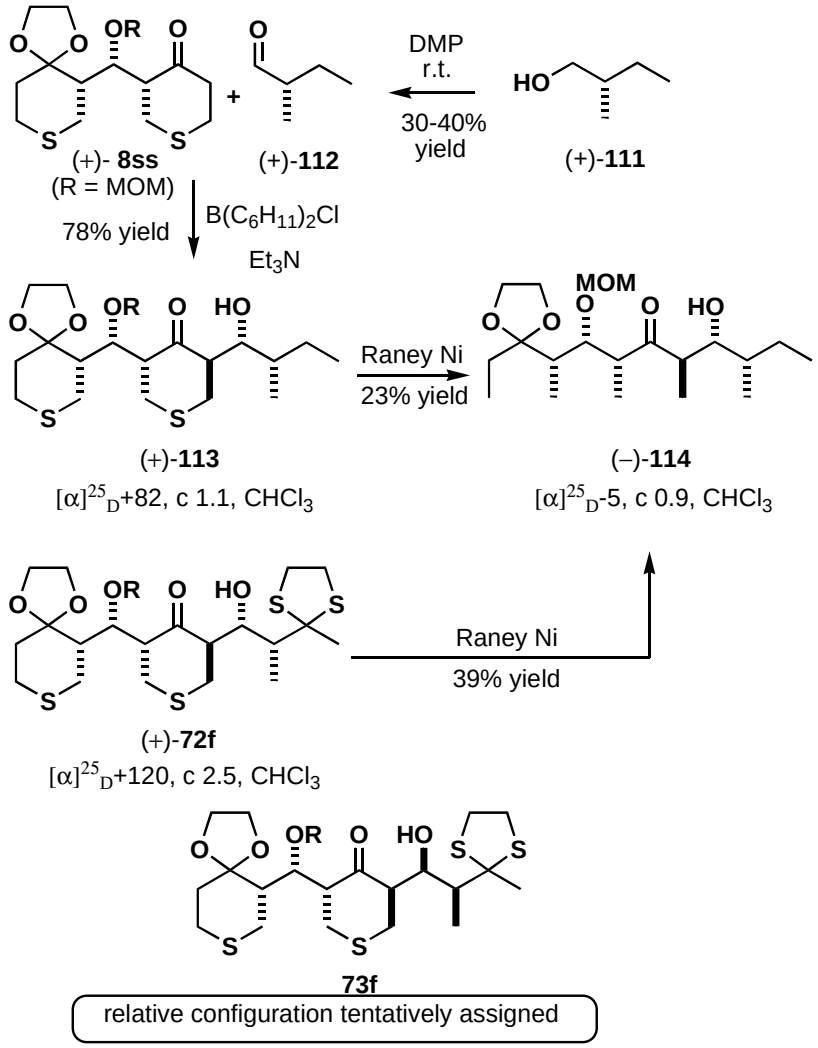


In order to assign the relative configuration of **72e**, this adduct was desulphurized by treatment with Raney Ni to give **110** in 44% yield. The same product was obtained from desulphurization of **72b** (Scheme 45). Because the relative configuration of **72b** is known (Section 2.4.1), the relative configuration **72e** is established by correlation to **72b**. The relative configuration of **73e** is tentatively assigned as shown in Scheme 45 in analogy with previous results.

2.4.5. Determination of the relative configurations of aldol adducts 72f and 73f

Adduct **72f** was obtained as the major product from boron mediated aldol reaction of **8ss** (R = MOM) with the aldehyde **7e**. In order to assign the relative configuration of **72f**, enantiopure **114** was synthesized (Scheme 46). The enantiopure aldehyde (+)-**112** was prepared by DMP oxidation of commercially available enantiopure alcohol **111** according to the known procedure (Scheme 46).[55] Reaction of (+)-**112** with the boron enolate of enantioenriched (-)-**8ss** (R = MOM) gave enantiopure **113** which was desulphurized by Raney Ni affording **114**. The relative configurations of **113** and **114** are assigned based on the known configuration of stereogenic centre present in aldehyde **112** and the numerous examples of aldol reactions of the boron enolate of **8ss** to give 3,5-*trans*-5,1''-*anti* adducts. Desulphurization of (+)-**72f** also produced **114**. This result confirms the relative configuration of **72f** by correlation to **114** (Scheme 46). The relative configuration of **73f** was assigned based on analogy.

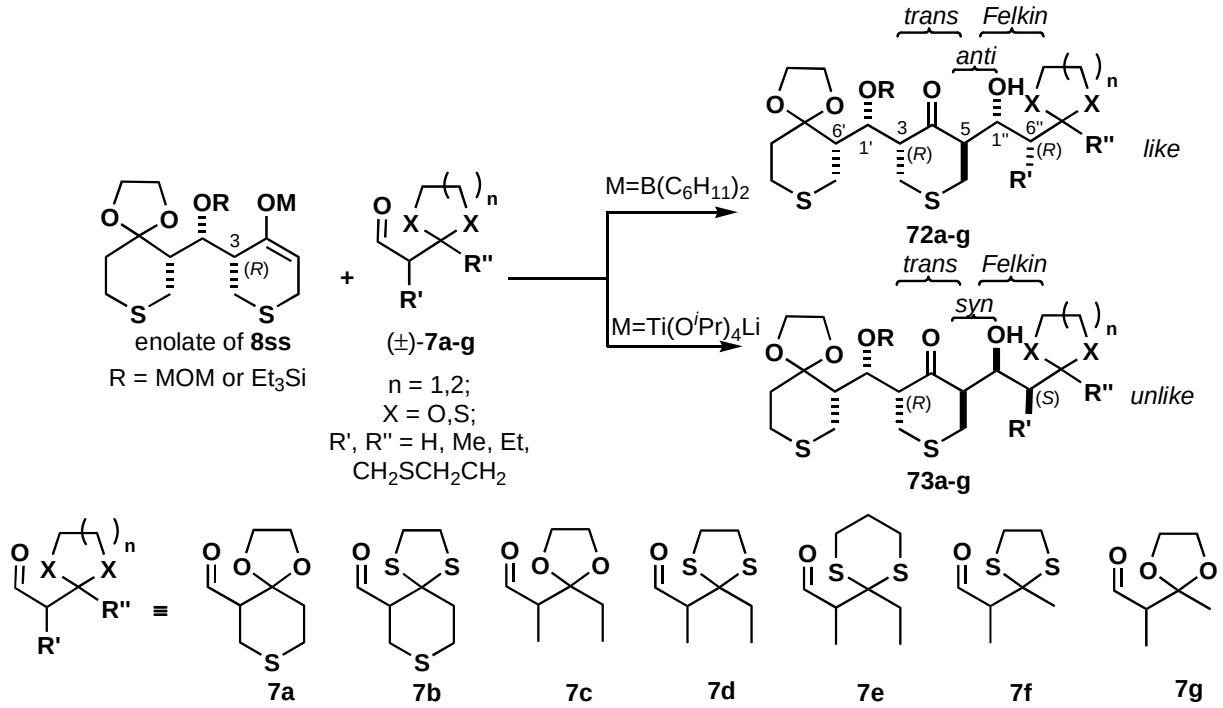
Scheme 46. Determination of the relative configuration of aldol adduct **72f** and **73f**.



3. CONCLUSIONS

The goal of this study was to expand the scope of aldol reactions with KR by designing new aldol reactions between the known ketone **8ss** (R = MOM or TES) and newly designed aldehydes **7b-h**. The diastereoselectivities of the aldol reactions can be predicted and rationalized by applying the multiplicativity rule to the three stereocontrol elements governing aldol couplings of chiral reactants. Considering the results of this study, designing new aldol reactions proceeding with KR is achieved by applying multiplicativity rule.

Scheme 47. Summary of boron and titanium "ate" mediated aldol reactions of (±)-**8ss** (R = MOM or Et_3Si) with the aldehydes (±)-**7a-g**.



Each of the stereocontrol elements (relative topicity of aldol coupling, aldehyde and enolate diastereoface selectivity) were strongly biased in the boron mediated aldol reaction of ketone **8ss** and the aldehydes (±)-**7a-g**, thus the boron mediated aldol reactions

of these chiral reactants occurred with high MKE and high diastereoselectivity. However, titanium "ate" mediated aldol reactions of these reactants proceeded with moderate to good MKE. Further optimization of the titanium "ate" mediated aldol reactions condition might improve the selectivity of these reactions.

Comparison of the results of current study with those reported for the boron and titanium "ate" mediated aldol reactions of aldehyde **7a** shows that the aldol reactions of suitable enolates of **8** with aldehydes **7b-g** should proceed with synthetically useful selectivity in KR. Some of the new aldol adducts synthesized in this project contain two different ketal protecting groups which decreases their symmetry. The two protected ketones can be potentially differentiated by selectively removing one or the other of the protecting groups using different conditions. This unique structural feature makes these adducts useful for future synthetic applications.

4. EXPERIMENTAL

4.1. General Methods

All solvents were distilled prior to use. Et_3N and DIPEA were distilled from CaH_2 and stored over KOH. Anhydrous solvents were distilled under argon atmosphere as follows: Tetrahydrofuran (THF) from benzophenone potassium ketyl; CH_2Cl_2 from CaH_2; acetonitrile (CH_3CN) from CaH_2 and stored over 4 Å molecular sieves; DMF over P_2O_5 and stored over 4 Å molecular sieves. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum, and attached via a needle and connecting tubing to a mercury bubbler under argon atmosphere. Low temperature baths were ice/water (0 °C), CO_2(s)/CH_3CN (-50 °C) and CO_2(s)/acetone (-78 °C).

Preparative TLC was carried out on glass plates (20 x 20 cm) pre-coated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm). Flash column chromatography (FCC) was performed with Merck Silica Gel 60 (40-63 mm). All mixed solvents eluents are reported as v/v solutions.

4.2. Spectral Data

High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a VG 70E double focussing high resolution spectrometer; only partial data are reported. Electron impact (EI) ionization was accomplished at 70 eV, chemical ionization (CI) at 50 eV with ammonia as the reagent gas, and fast-atom bombardment (FAB) in positive ion mode from a glycerol and methanol matrix. Infrared spectra were

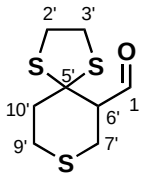
recorded on a Biorad FTS-40 Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic peaks are reported. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 300 MHz for ^1H and 75 MHz for ^{13}C. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^1H NMR) served as the internal standard: $CDCl_3$ (7.26 δ_H, 77.23 δ_C); C_6D_6 (7.16 δ_H, 128.39 δ_C). The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. ^1H NMR spectra were normally obtained with a digital resolution of 0.153 Hz/pt (sweep width = 10000 Hz, FID = 64 K data points) and coupling constants are reported to the nearest 0.5 Hz. The ^1H NMR assignments were made on the basis of chemical shift, multiplicity, and consistency within a series of similar structures. The multiplicity of ^{13}C NMR signals refers to the number of attached H's (i.e., s = C, d = CH, t = CH_2, q = CH_3) and was determined by DEPT-135. Optical rotations ($[\alpha]_D$) were determined at ambient temperature on a Perkin-Elmer 141 using a 1 mL, 10 dm cell; the units are 10^{-1} deg cm^2 g^{-1} and the concentrations (*c*) are reported in g/100 mL.

4.3. Materials

NMR solvent $CDCl_3$ was passed through basic Al_2O_3 before use. *n*-BuLi was titrated using diphenyl acetic acid as the titrant and indicator. All other reagents were comercially available and, unless otherwise noted, were used as received.

4.4. Experimental procedures and spectral data

1,4,8-Trithiaspiro[4.5]decane-6-carbaldehyde (7b)



7b

IBX (4.7 g, 17 mmol) was added to a stirred solution of alcohol precursor **79** (1.90 g, 8.56 mmol) in anhydrous DMSO (15 mL) at room temperature. After 1.5 h (reaction was complete by TLC analysis), the mixture was diluted with ethyl acetate (200 mL) and washed sequentially with sat. $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4, concentrated, and fractionated by FCC (50% ethyl acetate in hexane) to give the titled compound as a pale yellow oil (1.81 g, 96%).

IR (DRIFT) ν_{max} 1715 cm^{-1}.

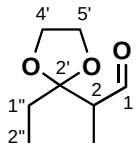
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.90 (1H, d, *J* = 0.7 Hz), 3.37-3.27 (4H, m), 2.97 (1H, ddd, *J* = 1.5, 3, 14 Hz), 2.91 (1H, dd, *J* = 3, 9 Hz), 2.86 (1H, ddd, *J* = 3, 10, 14 Hz), 2.74 (1H, dd, *J* = 9, 14 Hz), 2.65 (1H, m, *J* = 1.5, 3, 6, 14 Hz), 2.43 (1H, ddd, *J* = 3, 6, 14 Hz), 2.30 (1H, ddd, *J* = 3, 10, 14 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.5, 67.6, 58.4, 44.7, 39.7, 39.1, 29.4, 27.9.

LRMS (EI), *m/z* (relative intensity): 220 ($[M]^+$, 65), 192 (33), 164 (32), 136 (64), 99 (100), 97 (26), 71 (77).

HRMS *m/z* calcd. for $C_8H_{12}OS_3$: 220.0050; found: 220.0047 (EI).

2-(2-Ethyl-1,3-dioxolan-2-yl)propanal (7c)



7c

IBX (1.4 g, 5 mmol) was added to a stirred solution of alcohol **85** (396 mg, 2.47 mmol) in anhydrous DMSO (5 mL) at room temperature. After 1.5 h (reaction was complete by TLC analysis), the mixture was diluted with diethyl ether (100 mL), and washed sequentially with sat. $NaHCO_3$, water and brine. The organic layer was filtered through a short pad of silica gel and Na_2SO_4, and the combined filtrate and washings were concentrated to give the titled compound as a colorless oil (390 mg, 98%).

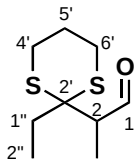
IR (DRIFT) ν_{max} 1725 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.75 (1H, d, *J* = 0.5 Hz), 4.01-3.93 (4H, m), 2.7-2.66 (1H, dq, *J* = 1.5, 7 Hz), 1.69 (1H, dq, *J* = 14.5, 7.5 Hz), 1.56 (1H, dq, *J* = 14.5, 7.5 Hz), 1.07 (3H, d, *J* = 7 Hz), 0.87 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.7 (d), 112.0 (s), 65.6 (t), 65.5 (t), 52.9 (d), 28.9 (t), 9.1 (q), 7.6 (q).

HRMS *m/z* calcd. for $C_8H_{14}O_3$+Na: 181.0835; found: 181.0837 (ESI).

2-(2-Ethyl-1,3-dithian-2-yl)propanal (7e)



7e

IBX (3.1 g, 11 mmol) was added to a stirred solution of alcohol **87** (1.52 g, 7.4 mmol) in anhydrous DMSO (37 mL) at room temperature. After 2 h (reaction was

complete by TLC analysis), the mixture was diluted with ethyl acetate (200 mL) and washed sequentially with sat. $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the titled compound (1.24 g, 83%).

IR (DRIFT) ν_{max} 1716, 2830, 2733 cm^{-1}.

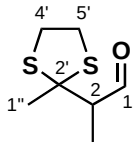
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.96 (1H, d, *J* = 2.5 Hz), 2.86-2.79 (5H, m), 2.12 (1H, dq, *J* = 7.5, 15 Hz), 2.01-1.89 (2H, m), 1.18 (3H, d, *J* = 7 Hz), 1.03 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.5 (s), 54.5 (s), 50.8 (d), 29.4 (t), 26.1 (t), 25.5 (t), 24.9 (t), 9.7 (q), 9.4 (q).

LRMS (EI), *m/z* (relative intensity): 204 ($[M]^+$, 23), 175 (9), 147 (100), 107 (16), 102 (20), 87 (7), 73 (28).

HRMS *m/z* calcd. for $C_9H_{16}OS_2$: 204.0643; found: 204.0650 (EI).

2-(2-Methyl-1,3-dithiolan-2-yl)propanal (7f)



7f

IBX (1.8 g,6.5 mmol) was added to a stirred solution of alcohol **91** (583 mg, 3.27 mmol) in anhydrous DMSO (8 mL) at room temperature. After 1.5 h (reaction was complete by TLC analysis), the mixture was diluted with ethyl acetate and washed sequentially with sat. $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give the titled compound (520 mg, 90%).

IR (DRIFT) ν_{max} 2832, 2726, 1721 cm^{-1}.

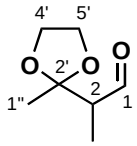
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.79 (1H, d, *J* = 2 Hz), 3.40-3.26 (4H, m), 2.76 (1H, dq, *J* = 2, 7 Hz), 1.75 (3H, s), 1.25 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.3 (s), 66.6 (s), 56.8 (d), 40.2 (t), 39.9 (t), 31.6 (q), 13.2 (t).

LRMS (EI), *m/z* (relative intensity): 176 ($[M]^+$, 49), 133 (13), 121 (42), 119 (100), 88 (53), 61 (45), 59 (64).

HRMS *m/z* calcd. for $C_7H_{12}OS_2$: 176.0330; found: 176.0335 (EI).

2-(2-Methyl-1,3-dioxolan-2-yl)propanal (7g)



7g

IBX (6.6 g, 23.6 mmol) was added to a stirred solution of alcohol **92** (1.72 g, 11.8 mmol) in anhydrous DMSO (24 mL) at room temperature. After 1.5 h (reaction was complete by TLC analysis), the mixture was diluted with ether (200 mL) and washed sequentially with sat. $NaHCO_3$, water and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (40% ethyl acetate in hexane) to give the titled compound (1.56 g, 92%).

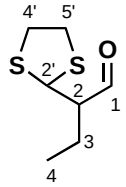
IR (DRIFT) ν_{max} 1726 cm^{-1}.

^{1}H NMR (MHz,) δ: 9.75 (1H, d, *J* = 2 Hz), 4.0-3.94 (4H, m), 2.63 (1H, dq, *J* = 2, 7 Hz), 1.29 (3H, s), 1.10 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.4 (d), 109.9 (s), 65.0 (t), 64.8 (t), 54.5 (d), 22.4 (q), 9.3 (q).

HRMS *m/z* calcd. for $C_7H_{12}O_3$+Na: 167.0678; found: 167.0681 (ESI).

2-(1,3-Dithiolan-2-yl)butanal (7h)



7h

Prepared by adaptation of the published procedure.[51] Oxalyl chloride (0.95 mL, 1.4 g, 11 mmol) was added via syringe to a stirred solution of DMF (0.90 mL, 0.84 g, 11.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C under Ar in a two neck flask equipped with condenser. Upon addition of oxalyl chloride the mixture turned yellow. After stirring for 30 min, a solution of 2-propyldithiolane **94** (680 mg, 4.59 mmol) in CH_2Cl_2 (5 mL) was added dropwise via syringe over 5 min. Anhydrous p-TSOH (79 mg, 0.46 mmol) was added and the mixture was heated under reflux. After 24 h (reaction complete by TLC analysis), the reaction was quenched by addition of ice water and the mixture was transferred to a separatory funnel with the aid of CH_2Cl_2. The organic phase was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the titled compound (664 mg, 82%). 1H NMR data for **7h** were consistent with those previously reported.

IR (DRIFT) ν_{max} 2835, 2728, 1720 cm^{-1}.

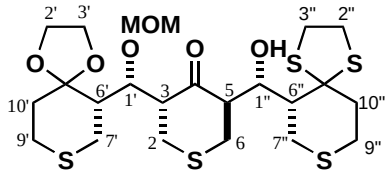
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.69 (1H, d, *J* = 2.5 Hz), 4.7 (1H, d, *J* = 7.5 Hz), 3.24-3.17 (4H, m), 2.56-2.50 (1H, m), 1.83-1.69 (2H, m), 0.92 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.8 (s), 59.6 (s), 52.0 (d), 38.7 (t), 38.4 (t), 22.7 (t), 11.4 (q).

LRMS (EI), *m/z* (relative intensity): 176 ($[M]^+$, 40), 143 (60), 115 (42), 105 (100).

HRMS *m/z* calcd. for $C_7H_{12}OS_2$: 176.0329; found: 176.0330 (EI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*S*)-(6*S*)-1,4,8-trithiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (72b (R = MOM))



72b (R = MOM)

A solution of (±)-**8ss** (R = MOM) (141 mg, 0.40 mmol) in CH_2Cl_2 (2 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.81 mL, 0.81 mmol) and Et_3N (0.12 mL, 86 mg, 0.85 mmol) in CH_2Cl_2 (1 mL; 5 mL/mmol of **8ss**) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7b** (179 mg, 0.81 mmol) in CH_2Cl_2 (1.4 mL; 0.6 M) was added slowly via syringe (ca. 5 min). After 12 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1.0 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that 1H NMR indicated the presence of a 10:1 mixture of *anti*-aldol and *syn*-aldol, respectively. Fractionation of the crude FCC (20-40% ethyl acetate in hexane) afforded recovered aldehyde (±)-**7b** (79 mg, 44%), a 2:1 mixture (by ^{1}H NMR) of (±)-**8ss** (R = MOM) and *syn*-aldol (±)-**73b** (R = MOM) (35 mg), respectively, and the titled compound (156 mg, 69%).

IR (DRIFT) ν_{max} 3463, 1712 cm^{-1}.

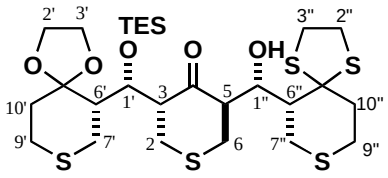
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.86 (1H, br dd, *J* = 5, 7 Hz), 4.70 (1H, d, *J* = 6 Hz), 4.66 (1H, d, *J* = 6 Hz), 4.46 (1H, dd, *J* = 4.5, 5.5 Hz), 4.1-3.91 (4H, m), 3.42-3.22 (4H, m), 3.37 (3H, s), 3.19-3.15 (1H, m), 3.03-2.89 (7H, m), 2.89-2.69 (6H, m), 2.50-2.46 (3H, m), 2.28 (1H, ddd, *J* = 3, 12, 13.5 Hz), 2.13-2.06 (3H, m), 1.70 (1H, ddd, *J* = 3.5, 13, 13 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.9 (s), 108.9 (s), 98.5 (t), 73.6 (s), 72.3 (d), 71.6 (d), 64.7 (t), 64.6 (t), 57.6 (d), 56.8 (q), 56.1 (d), 51.6 (d), 49.2 (d), 47.2 (t), 39.7 (t), 39.3 (t), 36.4 (t), 33.4 (t), 31.9 (t), 28.9 (t), 28.2 (t), 28.1 (t), 26.7 (t).

LRMS (ESI), *m/z* (relative intensity): 591 ($[M+23]^+$, 100), 371 (50).

HRMS *m/z* calcd. for $C_{23}H_{36}O_6S_5$+Na: 591.1007; found: 591.0997 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*S*)-(6*S*)-1,4,8-trithiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (72b (R = TES))



72b (R = TES)

A solution of (±)-**8ss** (R = TES) (29 mg, 0.069 mmol) in CH_2Cl_2 (0.4 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.14 mL, 0.14 mmol) and Et_3N (20 µL, 14 mg, 0.14 mmol) in CH_2Cl_2 (0.4 mL; 5 mL/mmol of **8ss**) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7b** (31 mg, 0.14 mmol) in CH_2Cl_2 (0.2 mL; 0.6 M) was added slowly via syringe (ca. 5 min). After 15 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL). The mixture was stirred at 0 °C for 20 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of an 11:1 mixture of **72b** (R = TES) and **73b** (R = TES), respectively. Fractionation of the crude by PTLC (10% ethyl acetate in hexane, multiple elution) afforded recovered aldehyde (±)-**7b** (12 mg, 39%), *syn*-aldol **73b** (R = TES) (3mg, 7%) and the titled compound (31mg, 70%).

IR (DRIFT) ν_{max} 3467, 1710 cm^{-1}.

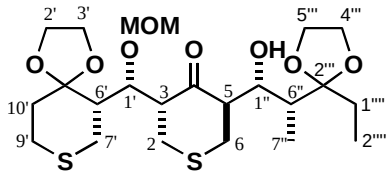
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.06 (1H, br dd, *J* = 3, 8 Hz), 4.65 (1H, dd, *J* = 2, 7.5 Hz), 4.02-3.82 (4H, m), 3.44-3.24 (4H, m), 3.21-3.18 (1H, m), 3.06-2.93 (4H, m), 2.87-2.68 (8H, m), 2.56 (1H, br d, *J* = 14 Hz), 2.51-2.46 (2H, m), 2.29 (1H, ddd, *J* = 3, 12, 13.5 Hz), 2.11-1.99 (3H, m), 1.68 (1H, ddd, *J* = 4, 12, 13.5 Hz), 0.93 (9H, t, *J* = 8 Hz), 0.67-0.60 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.1 (s), 109.5 (s), 73.4 (s), 71.2 (d), 66.4 (d), 64.84 (t), 64.82 (t), 58.4 (d), 55.6 (d), 51.9 (d), 49.8 (d), 47.3 (t), 39.8 (t), 39.5 (t), 37.1 (t), 32.7 (t), 29.8 (t), 29.2 (t), 28.7 (t), 28.3 (t), 26.7 (t), 7.4 (q ×3), 5.4 (t ×3).

LRMS (ESI), *m/z* (relative intensity): 661 ($[M+23]^+$, 70), 468 (100), 296 (30), 206 (20).

HRMS *m/z* calcd. for $C_{27}H_{46}O_5SiS_5$+Na: 661.1610; found: 661.1623 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*R*,2*R*)-2-(2-ethyl-1,3-dioxolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (72c (R = MOM))



72c (R = MOM)

A solution of (±)-**8ss** (R = MOM) (135 mg, 0.387 mmol) in CH_2Cl_2 (2 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.77 mL, 0.77 mmol) and Et_3N (0.11 mL, 82 mg, 0.81 mmol) in CH_2Cl_2 (2 mL) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7c** (122 mg, 0.77 mmol) in CH_2Cl_2 (0.5 mL; 0.6 M) was added slowly via syringe (ca. 5 min). After 3 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 7 mL), MeOH (7 mL), and 30% aq H_2O_2 (4 mL). The mixture was stirred at 0 °C for 10 min and then was

diluted with ice-water and saturated aq Na_2SO_3 (ca. 15 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a single aldol adduct (>20:1). Fractionation of the crude FCC (15-90% ethyl acetate in hexane followed by 20% methanol in dichloromethane) afforded recovered aldehyde (±)-**7c** (7 mg, 6%), (±)-**8ss** (R = MOM) (2 mg, 1%), and the titled compound (162 mg. 83%).

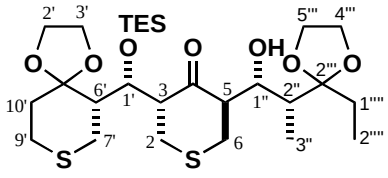
IR (DRIFT) ν_{max} 3521, 1712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.69 (1H, br d, *J* = 9.5 Hz), 4.67 (1H, d, *J* = 6 Hz), 4.65 (1H, d, *J* = 6 Hz), 4.38 (1H, dd, *J* = 5, 5 Hz), 4.01-3.90 (8H, m), 3.35 (3H, s), 3.31 (1H, ddd, *J* = 4.5, 5, 10 Hz), 3.03-2.94 (1H, m), 2.91 (1H, d, *J* = 2 Hz), 2.83-2.75 (1H, m), 2.58 (1H, ddd, *J* = 2, 5, 14 Hz), 2.48-2.45 (1H, m), 2.11 (1H, ddd, *J* = 4.5, 5, 10 Hz), 2.04 (1H, ddd, *J* = 3, 4.5, 13.5 Hz), 1.91 (1H, br q, *J* = 7, 14 Hz), 1.80-1.69 (2H, m), 1.66 (1H, ddd, *J* = 3.5, 12.5. 13.5 Hz), 0.93 (3H, , *J* = 7 Hz), 0.89 (3H, , *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.7 (s), 114.5 (s), 109.0 (s), 98.7 (t), 72.9 (d), 69.3 (d), 65.8 (t), 65.1 (t), 64.7 (t), 64.5 (t), 56.8 (d), 56.6 (q), 54.9 (d), 49.0 (d), 39.3 (d), 36.4 (t), 32.5 (t), 31.5 (t), 28.4 (t), 28.3 (t), 26.7 (t), 8.2 (q), 7.0 (q).

HRMS *m/z* calcd. for $C_{23}H_{38}O_8S_2$+Na: 529.1900; found: 529.1898 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(1*R*,2*R*)-2-(2-ethyl-1,3-dioxolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (72c (R = TES))



72c (R = TES)

A solution of (±)-**8ss** (R = TES) (37 mg, 0.088 mmol) in CH_2Cl_2 (0.4 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in

CH_2Cl_2; 0.18 mL, 0.18 mmol) and Et_3N (25 µL, 18 mg, 0.18 mmol) in CH_2Cl_2 (0.4 mL; 5 mL/mmol of **8ss**) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7c** (28 mg, 0.18 mmol) in CH_2Cl_2 (0.3 mL; 0.6 M) was added slowly via syringe (ca. 5 min). After 3 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a single bisaldol adduct (dr >20). Fractionation of the crude by FCC (25% ethyl acetate in hexane) afforded recovered aldehyde (±)-**7c** (7 mg, 25%) and the titled compound (39 mg, 76%).

IR (DRIFT) ν_{max} 3518, 1711 cm^{-1}.

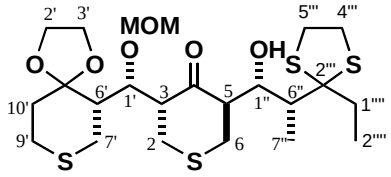
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.80 (1H, br d, *J* = 10 Hz), 4.62 (1H, dd, *J* = 1.5, 8 Hz), 4.03-3.85 (8H, m), 3.37 (1H, ddd, *J* = 1.5, 5, 11.5 Hz), 3.04 (1H, dd, *J* = 11.5, 13.5 Hz), 2.98 (1H, dd, *J* = 3.5, 14 Hz), 2.89 (1H, br s), 2.87 (1H, ddd, *J* = 3, 4.5, 13.5 Hz), 2.81 (1H, ddd, *J* = 3, 13, 13.5 Hz), 2.77-2.63 (3H, m), 2.61 (1H, ddd, *J* = 3, 3, 14 Hz), 2.48 (1H, br d, *J* = 13.5 Hz), 2.10 (1H, ddd, *J* = 4, 8, 11 Hz), 2.04-1.95 (2H, m), 0.96-0.90 (15H, m), 0.69-0.60 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.5 (s), 114.7 (s), 109.5 (s), 69.5 (d), 66.6 (d), 65.9 (t), 65.2 (t), 65.0 (t), 64.8 (t), 57.2 (d), 54.9 (d), 49.7 (d), 39.1 (d), 37.2 (t), 32.2 (t), 29.8 (t), 29.2 (t), 28.5 (t), 26.6 (t), 8.3 (q), 7.3 (q ×3), 6.7 (q), 5.3 (q ×3).

LRMS (ESI), *m/z* (relative intensity): 599 ([M+23]$^+$, 100), 279 (80).

HRMS *m/z* calcd. for $C_{27}H_{48}O_7SiS_2$+Na: 599.2502; found: 599.2485 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*S*,2*R*)-2-(2-ethyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (72d (R = MOM))



72d (R = MOM)

A solution of (±)-**8ss** (R = MOM) (84 mg, 0.24 mmol) in CH_2Cl_2 (1.2 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.48 mL, 0.48 mmol) and Et_3N (70 µL, 51 mg, 0.50 mmol) in CH_2Cl_2 (1.2 mL; 5 mL/mmol of **8ss**) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7d** (91 mg, 0.48 mmol) in CH_2Cl_2 (0.8 mL; 0.6 M) was added slowly via syringe (ca. 5 min). After 3 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 6 mL), MeOH (6 mL), and 30% aq H_2O_2 (3 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 15 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR indicated the presence of a 17:1 mixture of **72d** (R = MOM) and **73d** (R = MOM), respectively. Fractionation of the crude FCC (30-40% ethyl acetate in hexane) afforded recovered aldehyde (±)-**7d** (21 mg, 23%), (±)-**8ss** (R = MOM) (10 mg, 11%), *syn*-aldol (±)-**73d** (R = MOM) (6 mg, 5%) and the titled compound (102 mg 79%).

IR (DRIFT) ν_{max} 3508, 1707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.80 (1H, dd, *J* = 3, 9 Hz), 4.67 (1H, d, *J* = 6 Hz), 4.65 (1H, d, *J* = 6 Hz), 4.42 (1H, dd, *J* = 5, 5 Hz), 4.04-3.90 (4H,), 3.35 (3H, s), 3.32-3.20 (5H, m), 3.06-2.92 (4H, m), 2.85-2.73 (4H, m), 2.67 (1H, dd, *J* = 5.5, 13.5 Hz), 2.48 (1H, br d,

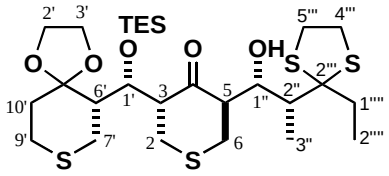
J = 13.5 Hz), 2.12-1.95 (5H, m), 1.69-1.63 (1H, ddd, *J* = 3.5, 12.5, 13.5 Hz), 1.09 (3H, d, *J* = 7 Hz), 1.06 (3H, t, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.1 (s), 109.0 (t), 98.7 (t), 77.8 (s), 72.8 (d), 71.0 (d), 64.6 (t), 64.5 (t), 57.3 (d), 56.7 (q), 55.8 (d), 49.0 (d), 44.4 (d), 40.4 (t), 39.8 (t), 36.2 (t), 35.9 (t), 32.5 (t), 31.3 (t), 28.3 (t), 26.7 (t), 11.3 (q), 10.8 (q).

LRMS (ESI), *m/z* (relative intensity): 561 ($[M+23]^+$, 100), 529 (10), 507 (40), 475 (5).

HRMS *m/z* calcd. for $C_{23}H_{38}O_6S_4$+Na: 561.1443; found: 561.1460 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(1*S*,2*R*)-2-(2-ethyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (72d (R = TES))



72d (R = TES)

A solution of (±)-**8ss** (R = TES) (33 mg, 0.079 mmol) in CH_2Cl_2 (0.4 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.16 mL, 0.16 mmol) and Et_3N (24 µL, 17 mg, 0.17 mmol) in CH_2Cl_2 (0.4 mL; 5 mL/mmol of **8ss**) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7d** (30 mg, 0.16 mmol) in CH_2Cl_2 (0.3 mL; 0.6 M) was added slowly via syringe (ca. 5 min). After 16 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a >20:1 mixture of **72d** (R = TES) and **73d** (R = TES), respectively. Fractionation of the crude by

PTLC (10% ethyl acetate in hexane, 2 elutions) afforded recovered aldehyde (±)-**7d** (10 mg, 33%), (±)-**8ss** (R = TES) (2 mg, 6%), and the titled compound (36 mg, 75%).

IR (DRIFT) ν_{max} 3500, 1708 cm^{-1}.

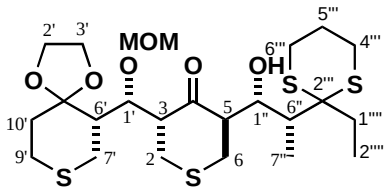
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.97 (1H, dd, *J* = 3, 9 Hz), 4.64 (1H, dd, *J* = 1.5, 7.5 Hz), 3.99-3.82 (4H, m), 3.38-3.25 (5H, m), 3.03 (1H, dd, *J* = 11.5, 13.5 Hz), 2.98 (1H, dd, *J* = 3, 13.5 Hz), 2.93 (2H, m, *J* = 3 Hz), 2.87 (4H, m, *J* = 2.5, 4.5, 13.5 Hz), 2.81 (1H, ddd, *J* = 2.5, 12.5, 13.5 Hz), 2.78-2.62 (4H, m), 2.48 (1H, br d, *J* = 13.5 Hz), 2.09 (1H, ddd, *J* = 4, 7.5, 11 Hz), 2.08-1.95 (3H, m), 1.67 (1H, ddd), 1.09 (3H, d, *J* = 7 Hz), 1.08 (3H, t, *J* = 7 Hz), 0.94 (9H, t, *J* = 8 Hz), 0.71-0.59 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.7 (s), 109.5 (s), 77.7 (s), 71.1 (d), 66.6 (d), 64.9 (t), 64.7 (t), 58.1 (d), 55.9 (d), 49.6 (d), 44.5 (d), 40.5 (t), 39.9 (t), 37.0 (t), 36.5 (t), 32.2 (t), 29.6 (t), 29.2 (t), 26.7 (t), 11.4 (q), 10.9 (q), 7.3 (q ×3), 5.3 (t ×3).

LRMS (ESI), *m/z* (relative intensity): 631 ($[M+23]^+$, 30), 468 (15), 296 (15), 229 (100), 206 (20).

HRMS *m/z* calcd. for $C_{27}H_{48}O_5SiS_4$+Na: 631.2046; found: 631.2023 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*S*,2*R*)-2-(2-ethyl-1,3-dithian-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (72e (R = MOM))



72e (R = MOM)

A solution of (±)-**8ss** (R = MOM) (24 mg, 0.069 mmol) in CH_2Cl_2 (0.3 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.14 mL, 0.14 mmol) and Et_3N (20 µL, 14 mg, 0.14 mmol) in CH_2Cl_2 (0.3 mL; 5 mL/mmol of **8ss**) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7e** (29

mg, 0.14 mmol) in CH_2Cl_2 (0.2 mL; 0.6 M) was added slowly via syringe (ca. 5 min). After 3 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR indicated the presence of a single adduct (dr >20). Fractionation of the crude by FCC (30% ethyl acetate in hexane) afforded recovered (±)-**7e** (8 mg, 27%), (±)-**8ss** (R = MOM) (2 mg, 8%), and the titled compound (34 mg, 89%).

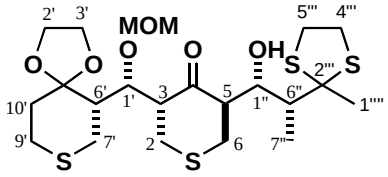
IR (DRIFT) ν_{max} 3500, 1706 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.04 (1H, dd, *J* = 4.5, 9 Hz), 4.69 (1H, d, *J* = 6 Hz), 4.67 (1H, d, *J* = 6 Hz), 4.46 (4H, dd, *J* = 5, 5 Hz), 4.06-3.93 (4H, m), 3.36 (3H, s), 3.25 (1H, ddd, *J* = 4.5, 5, 9.5 Hz), 3.11-2.64 (12H, m), 2.70 (1H, d, *J* = 4.5 Hz), 2.50 (1H, br d, *J* = 13 Hz), 2.29 (1H, dq, *J* = 7.5, 15 Hz), 2.11-1.97 (4H, m), 1.93-1.85 (2H, m), 1.68 (1H, ddd, *J* = 3.5, 12, 13.5 Hz), 1.09 (3H, d, *J* = 7 Hz), 0.99 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.2 (s), 108.9 (s), 98.6 (t), 72.7 (d), 70.2 (d), 64.6 (t), 64.6 (t), 59.4 (s), 57.4 (d), 56.8 (q), 55.9 (d), 49.1 (d), 41.3 (d), 36.2 (t), 32.9 (t), 31.5 (t), 29.2 (t), 28.4 (t), 26.7 (t), 26.1 (t), 25.9 (t), 25.2 (t), 9.6 (q), 7.6 (q).

HRMS *m/z* calcd. for $C_{24}H_{40}O_6S_4$+Na: 575.1599 ; found: 575.1600 (ESI).

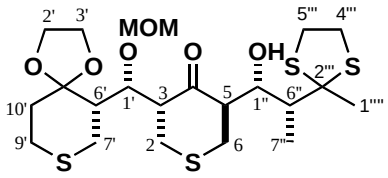
(3*R*,5*R*)-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*S*,2*R*)-2-(2-methyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (72f (R = MOM))



72f (R = MOM)

A solution of (+)-**8ss** (R = MOM) (31 mg, 0.089 mmol) in CH_2Cl_2 (0.4 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.18 mL, 0.18 mmol) and Et_3N (26 µL, 19 mg, 0.19 mmol) in CH_2Cl_2 (0.4 mL; 5 mL/mmol of **8ss**) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7f** (48 mg, 0.27 mmol) in CH_2Cl_2 (0.4 mL; 0.6 M) was added slowly via syringe (ca. 5 min). After 3 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^1H NMR spectrum indicated the presence of a single bisaldol adduct. Fractionation of the crude by FCC (10-50 % ethyl acetate in hexane) afforded recovered aldehyde (±)-**7f** (21 mg, 43%) and the titled compound (38 mg, 81%) ($[\alpha]_D$ +120; *c* 2.5, $CHCl_3$).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6yl(methoxymethoxy)methyl] -5-[(1*S*,2*R*)-2-(2-methyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (72f (R = MOM))



72f (R = MOM)

A solution of (±)-**8ss** (R = MOM) (45 mg, 0.13 mmol) in CH_2Cl_2 (0.7 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.26 mL, 0.26 mmol) and Et_3N (38 µL, 27 mg, 0.27 mmol) in CH_2Cl_2 (0.7 mL; 5 mL/mmol of **8ss**) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7f** (46 mg, 0.26 mmol) in CH_2Cl_2 (0.4 mL; 0.6 M) was added slowly via syringe (ca. 5 min). After 3 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a single bisaldol adduct. Fractionation of the crude by FCC (30-50 % ethyl acetate in hexane) afforded recovered aldehyde (±)-**7f** (18 mg, 39%) and the titled compound (45 mg, 66%).

IR (DRIFT) ν_{max} 3512, 1704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.70-4.63 (3H, m), 4.49 (1H, dd, *J* = 5, 5.5 Hz), 4.08-3.91 (4H, m), 3.38-3.24 (4H, m), 3.36 (3H, s), 3.17 (1H, ddd, *J* = 4, 5.5, 9 Hz), 3.10 (1H, dd, *J* = 9, 13.5 Hz), 3.02-2.94 (1H, m), 2.92 (1H, d, *J* = 4 Hz), 2.90-2.65 (5H, m, *J* = 7 Hz),

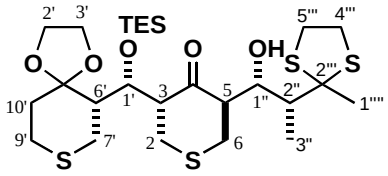
2.50 (1H, br d, *J* = 13.5 Hz), 2.10-2.07 (2H, m), 2.00 (1H, br q, *J* = 7 Hz), 1.83 (3H, s), 1.67 (1H, ddd, *J* = 3.5, 12, 13.5 Hz), 1.15 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.1 (s), 108.9 (s), 98.6 (t), 72.9 (d), 72.3 (s), 71.8 (d), 64.7 (t), 64.6 (t), 57.8 (d), 56.8 (q), 55.4 (d), 49.0 (d), 46.9 (d), 40.1 (t), 39.7 (t), 36.2 (t), 32.2 (t), 31.8 (q), 31.2 (t), 28.3 (t), 26.7 (t), 11.5 (q).

LRMS (ESI), *m/z* (relative intensity): 547 (100), 493 (10), 371 (20), 275 (5), 130 (40).

HRMS *m/z* calcd. for $C_{22}H_{36}O_6S_4$+Na: 547.1286; found: 547.1298 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(1*S*,2*R*)-2-(2-methyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (72f (R = TES))



72f (R = TES)

A solution of (±)-**8ss** (R = TES) (25 mg, 0.060 mmol) in CH_2Cl_2 (0.3 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.12 mL, 0.12 mmol) and Et_3N (18 µL, 13 mg, 0.13 mmol) in CH_2Cl_2 (0.3 mL; 5 mL/mmol of **8ss**) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7f** (21 mg, 0.12 mmol) in CH_2Cl_2 (0.2 mL; 0.6 M) was added slowly via syringe (ca. 5 min). After 3 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a single bisaldol (dr >20), unreacted **8ss** (R = TES) and aldehyde **7f**. Fractionation of the crude by PTLC (10%

ethyl acetate in hexane, multiple elution) afforded recovered aldehyde (±)-**7f** (9 mg, 43%), (±)-**8ss** (R = TES) (2 mg, 8%), and the titled compound (27 mg, 75%).

IR (DRIFT) ν_{max} 3500, 1706 cm^{-1}.

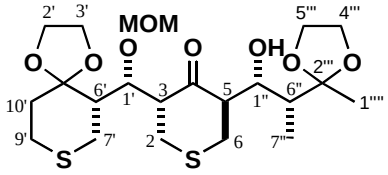
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.85 (1H, dd, *J* = 4, 9 Hz), 4.65 (1H, br d, *J* = 7 Hz), 4.01-3.85 (4H, m), 3.39-3.27 (4H, m), 3.23 (1H, br dd, *J* = 3.5, 9 Hz), 3.06-2.95 (2H, m), 2.87 (1H, dd, *J* = 3.5, 13.5 Hz), 2.80 (1H, ddd, *J* = 2, 12.5, 13.5 Hz), 2.76 (1H, d, *J* = 4 Hz), 2.75-2.65 (4H, m), 2.48 (1H, br d, *J* = 13.5 Hz), 2.09-1.96 (3H, m), 1.83 (3H, s), 1.66 (1H, ddd, *J* = 3.5, 12.5, 13.5 Hz), 1.13 (3H, d, *J* = 7 Hz), 0.93 (9H, t, *J* = 8 Hz), 0.66-0.60 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.6 (s), 109.5 (s), 72.1 (d), 71.8 (s), 66.6 (d), 64.8 (t), 64.7 (t), 58.3 (d), 55.7 (d), 49.7 (d), 47.0 (d), 40.1 (t), 39.9 (t), 36.9 (t), 32.4 (q), 31.8 (t), 29.3 (t), 29.1 (t), 26.7 (t), 11.4 (q), 7.3 (q ×3), 5.4 (t ×3).

LRMS (ESI), *m/z* (relative intensity): 617 ($[M+23]^+$, 100), 463 (5), 297 (5).

HRMS *m/z* calcd. for $C_{26}H_{46}O_5SiS_4$+Na: 617.1889; found: 617.1900 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*R*,2*R*)-2-(2-methyl-1,3-dioxolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (72g (R = MOM))



72g (R = MOM)

A solution of (±)-**8ss** (R = MOM) (23 mg, 0.066 mmol) in CH_2Cl_2 (0.3 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.13 mL, 0.13 mmol) and Et_3N (20 µL, 14 mg, 0.14 mmol) in CH_2Cl_2 (0.3 mL) at -78 °C under Ar. After 2 h, a solution of aldehyde (±)-**7g** (19 mg, 0.13 mmol) in CH_2Cl_2 (0.15 mL) was added slowly via syringe (ca. 5 min). After 3 h, the reaction was

quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to the crude product whose ^{1}H NMR spectrum indicated the presence of a single aldol adduct. Fractionation of the crude by FCC (30% ethyl acetate in hexane) afforded recovered aldehyde (±)-**7g** (3 mg, 16%), (±)-**8ss** (R = MOM) (2 mg, 9%), and the titled compound (25 mg, 78%).

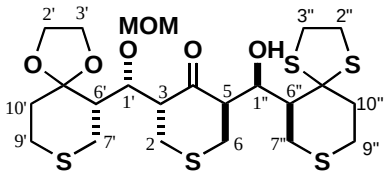
IR (DRIFT) ν_{max} 3524, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.70-4.64 (3H, m), 4.43 (1H, dd, *J* = 5, 5 Hz), 4.05-3.90 (8H, m), 3.36 (3H, s), 3.27 (1H, ddd, *J* = 4, 5, 9.5 Hz), 3.06 (1H, dd, *J* = 10, 13.5 Hz), 2.99-2.94 (2H, m), 2.87-2.75 (5H, m), 2.61 (1H, ddd, *J* = 1.5, 6, 13.5 Hz), 2.49 (1H, br d, *J* = 13.5 Hz), 2.10 (1H, ddd, *J* = 4, 5, 10.5 Hz), 2.06 (1H, ddd, *J* = 3, 4.5, 13.5 Hz), 1.82 (1H, br q, *J* = 7 Hz), 1.67 (1H, ddd, *J* = 3.5, 12.5, 13.5 Hz), 1.37 (3H, s), 0.98 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.1 (s), 112.5 (s), 109.0 (s), 98.7 (t), 73 (d), 69.4 (d), 65.1 (t), 64.7 (t), 64.64 (t), 64.57 (t), 57 (d), 56.8 (q), 54.8 (d), 49.1 (d), 42.4 (d), 36.4 (t), 32.3 (t), 31.3 (t), 28.4 (t), 26.7 (t), 22.4 (q), 7.5 (q).

HRMS *m/z* calcd. for $C_{22}H_{36}O_8S_2$+Na: 515.1743; found: 515.1761 (ESI).

(3*S*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxmethyl]-5-[(*S*)-(6*S*)-1,4,8-trithiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (73b R = MOM))



73b (R = MOM)

A solution of freshly prepared LDA (0.5 M in THF; 0.34 mL, 0.17 mmol) at 0 °C was added via syringe to a stirred solution of (±)-**8ss** (R = MOM) (51 mg, 0.15 mmol) in THF (1.5 mL, 0.1 M) at -78 °C under Ar. After 15 min, $Ti(O^iPr)_4$ (0.20 mL, 190 mg, 0.66 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -50 °C (CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7b** (66 mg, 0.30 mmol) in THF (0.4 mL, 0.8 M) was added via syringe. After 1 h, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The organic layers were filtered through a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and the combined filtrates and washings were concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 13:1 mixture of **73b** (R = MOM) and **72b** (R = MOM), respectively [note: 1H NMR of the crude from a similar experiment using 2.2 equiv of $Ti(O^iPr)_4$ showed a 9:1 mixture of **73b** (R = MOM) and **72b** (R = MOM), respectively. Fractionation of the crude by FCC (20-40% ethyl acetate in hexane) afforded recovered aldehyde (±)-**7b** (22 mg, 33%), (±)-**8ss** (R = MOM) (2 mg, 4%), *anti* aldol (±)-**72b** (R = MOM) (5 mg, 6%) and the titled compound (62 mg, 73%).

IR (DRIFT) ν_{max} 3453, 1699 cm^{-1}.

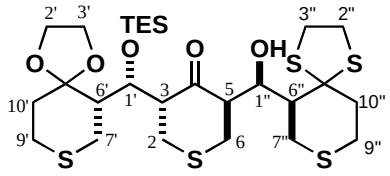
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.11 (1H, br dd, *J* = 2, 9 Hz), 4.69 (1H, d, *J* = 6 Hz), 4.63 (1H, d, *J* = 6 Hz), 4.59 (1H, dd, *J* = 3, 6.5 Hz), 4.10-43.92 (4H, m), 3.50 (1H, d, *J* = 2 Hz), 3.39-3.28 (4H, m), 3.37 (3H, s), 3.18 (1H, br dd, *J* = 3.5, 13.5 Hz), 3.10-2.92 (6H, m), 2.88 (1H, dd, *J* = 11.5, 13.5 Hz), 2.82 (1H, ddd, *J* = 3, 13, 13 Hz), 2.78-2.68 (3H, m), 2.58-2.35 (4H, m), 2.08 (1H, ddd, *J* = 4.9, 8.8 Hz), 2.01 (1H, dd), 1.92 (1H, ddd, *J* = 3, 3.5, 11.5 Hz), 1.77 (1H, ddd, *J* = 4, 13, 13 Hz) .

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.5 (s), 108.9 (s), 98.5 (t), 73.8 (s), 71.7 (d), 69.5 (d), 64.8 (t), 64.5 (t), 58.3 (d), 56.8 (q), 55.7 (d), 50.1 (d), 49.9 (d), 47.3 (t), 39.5 (t), 39.4 (t), 36.2 (t), 33.8 (t), 32.8 (t), 28.15 (t), 28.07 (t), 28.05 (t), 26.8 (t).

LRMS (ESI), *m/z* (relative intensity): 591 ($[M+23]^+$, 100), 537 (33), 371 (15), 317 (7).

HRMS *m/z* calcd. for $C_{23}H_{36}O_6S_5$+Na: 591.1007; found: 591.1015 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*R*)-(6*R*)-1,4,8-trithiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (73b (R = TES))



73b (R = TES)

A solution of freshly prepared LDA (0.5 M in THF; 0.2 mL, 0.1 mmol,) at 0 °C was added via syringe to a stirred solution of (±)-**8ss** (R = TES) (37 mg, 0.088 mmol) in THF (0.9 mL, 0.1 M) at -78 °C under Ar. After 15 min, $Ti(O^iPr)_4$ (57 µL, 54 mg, 0.19 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -50°C (CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7b** (40 mg, 0.18 mmol) in THF (0.2 mL, 0.8 M) was added via syringe. After 16 h, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The organic layers were filtered through a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and the combined filtrates and washings were concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 2:1 mixture of **73b** (R = TES) and **72b** (R = TES), respectively. Fractionation of the crude by PTLC (10% ethyl acetate in hexane, multiple elution) afforded recovered aldehyde (±)-**7b** (10 mg, 25%),

(±)-**8ss** (R = TES) (6 mg, 23%), *anti* aldol **72b** (R = TES) (11 mg, 20%), and the titled compound (26 mg, 46%)

IR (DRIFT) ν_{max} 3448, 1698 cm^{-1}.

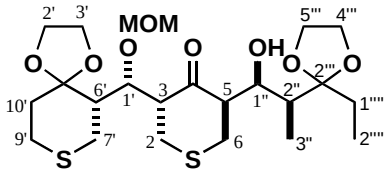
^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.26 (1H, br d, *J* = 10 Hz), 4.74 (1H, br s), 4.07-3.89 (4H, m), 3.50 (1H, br s), 3.42-3.23 (4H, m), 3.12 (1H, br d, *J* = 13.5 Hz), 3.05-2.73 (10H, m), 2.67 (1H, br d, *J* = 13.5 Hz), 2.55 (1H, br d, *J* = 14 Hz), 2.49-2.43 (2H, m), 2.31 (1H, ddd, *J* = 2.5, 12, 13.5 Hz), 2.05-2.00 (2H, m), 1.94 (1H, dd, *J* = 6.5, 7 Hz), 1.69 (, ddd, *J* = 3.5, 13, 13.5 Hz), 0.94 (9H, t, *J* = 8 Hz), 0.68-0.57 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.9 (s), 109.6 (s), 73.6 (s), 69.4 (d), 65.4 (d), 65.1 (t), 64.4 (t), 59.9 (d), 55.9 (d), 51.0 (d), 49.4 (d), 47.0 (t), 39.7 (t), 39.5 (t), 36.3 (t), 33.0 (t), 30.7 (t), 28.8 (t), 28.2 (t), 28.0 (t), 26.6 (t), 7.3 (q ×3), 5.3 (t ×3).

LRMS (ESI), *m/z* (relative intensity): 661 ($[M+23]^+$, 70), 468 (100), 296 (40), 206 (30).

HRMS *m/z* calcd. for $C_{27}H_{46}O_5SiS_5$+Na: 661.1610; found: 661.1604 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*S*,2*S*)-2-(2-ethyl-1,3-dioxolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (73c (R = MOM))



73c (R = MOM)

A solution of freshly prepared LDA (0.5 M in THF; 0.60 mL, 0.30 mmol) at 0 °C was added via syringe to a stirred solution of (±)-**8ss** (R = MOM) (95 mg, 0.27 mmol) in THF (2.7 mL; 0.1 M) at -78 °C under Ar. After 15 min, $Ti(O^iPr)_4$ (0.18 mL, 168 mg, 0.59 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -

50 °C (CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7c** (85 mg, 0.54 mmol) in THF (0.7 mL, 0.8 M) was added via syringe. After 30 min, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The combined organic layers were filtered through a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and the combined filtrate and ethyl acetate washings were concentrated to give the crude product whose ^{1}H NMR indicated the presence of a 4:1 mixture of *syn*-aldol, *anti*-aldol, respectively. Fractionation of the crude by FCC (30-50% ethyl acetate in hexane) afforded recovered aldehyde (±)-**7c** (20 mg, 24%), (±)-**8ss** (R = MOM) (9 mg, 9%), anti-aldol (±)-**72c** (R = MOM) (26 mg, 19%), and the titled compound (95 mg. 69%).

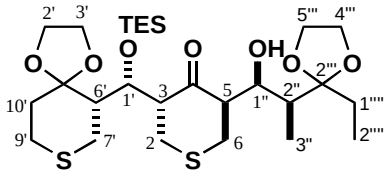
IR (DRIFT) ν_{max} 3515, 1700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.66 (1H, d, *J* = 6 Hz), 4.63 (1H, d, *J* = 6 Hz), 4.55 (1H, br d, *J* = 9.5 Hz), 4.53 (1H, dd, *J* = 4.5, 5.5 Hz), 4.04-3.90 (8H, m), 3.35 (3H, s), 3.16-3.06 (2H, m), 3.12 (1H, br d), 3.03-2.88 (4H, m), 2.84 (1H, dd, *J* = 11, 14 Hz), 2.82-2.70 (2H, v), 2.49 (1H, br d, *J* = 13.5 Hz), 2.05 (1H, ddd, *J* = 3, 4.5, 13.5 Hz), 1.91 (1H, ddd, *J* = 3.5, 4, 11 Hz), 1.82 (1H, dq, *J* = 1, 7 Hz), 1.73-1.65 (2H, m), 1.60 (1H, ddd, *J* = 3.5,12, 13.5 Hz), 0.96 (3H, d, *J* = 7 Hz), 0.89 (3H, T, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.6 (s), 114.9 (s), 108.8 (s), 98.6 (t), 72.3 (d), 67.8 (d), 65.6 (t), 65.2 (t), 64.61 (t), 64.55 (t), 56.8 (q), 56.7 (d), 55.1 (d), 49.2 (d), 39.8 (d), 36.1 (t), 32.8 (t), 31.8 (t), 28.2 (t), 28.1 (t), 26.7 (t), 8.2 (q), 7.6 (q).

HRMS *m/z* calcd. for $C_{23}H_{38}O_8S_2$+Na: 529.1900; found: 529.1912 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(1*S*,2*S*)-2-(2-ethyl-1,3-dioxolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (73c (R = TES))



73c (R = TES)

A solution of freshly prepared LDA (0.5 M in THF; 0.12 mL, 0.06 mmol) at 0 °C was added via syringe to a stirred solution of (±)-**8ss** (R = TES) (22 mg, 0.053 mmol) in THF (0.5 mL, 0.1 M) at -78 °C under Ar. After 15 min, $Ti(O^iPr)_4$ (36 µL, 34 mg, 0.12 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -50°C (CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7c** (17 mg, 0.11 mmol) in THF (0.14 mL, 0.8 M) was added via syringe. After 15 h, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The organic layers were filtered through a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and the combined filtrates and ethyl acetate washings were concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 3:1 mixture of *anti*-aldol **72c** (R = TES) and the titled compound, respectively. Fractionation of the crude by PTLC (25% ethyl acetate in hexane) afforded recovered aldehyde (±)-**7c** (2 mg, 12%), (±)-**8ss** (R = TES) (3 mg, 14%), *anti*-aldol (±)-**72c** (R = TES) (21 mg, 68%), and the titled compound (5 mg, 16%).

IR (DRIFT) ν_{max} 3515, 1700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.71-4.66 (2H, m), 4.08-3.79 (8H, m), 3.18 (1H, br s), 3.13 (1H, ddd, *J* = 2, 4.5, 3.5 Hz), 3.08-2.98 (2H, m), 2.88-2.74 (4H, m), 2.73-2.68 (2H, m), 2.52-2.47 (1H, ddd, *J* = 3.5, 4, 13.5 Hz), 2.03-1.97 (2H, m), 1.79-1.66 (3H, m), 1.61

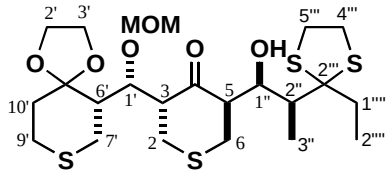
(1H, ddd, *J* = 3.5, 12, 13.5 Hz), 0.98 (3H, d, *J* = 7 Hz), 0.94 (9H, t, *J* = 8 Hz), 0.88 (3H, t, *J* = 7.5 Hz), 0.69-0.57 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.0 (s), 114.9 (s), 109.4 (s), 67.5 (d), 66.1 (d), 65.9 (t), 65.3 (t), 64.6 (t), 64.5 (t), 59.2 (d), 55.4 (d), 49.7 (d), 40.1 (d), 36.4 (t), 32.0 (t), 29.8 (t), 29.0 (t), 28.5 (t), 26.7 (t), 8.3 (q), 7.45 (q), 7.34 (q ×3), 5.4 (q ×3).

(ESI), *m/z* (relative intensity):.

HRMS *m/z* calcd. for $C_{27}H_{48}O_7SiS_2$+Na: 599.2502; found: 599.2525 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*R*,2*S*)-2-(2-ethyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (73d (R = MOM))



73d (R = MOM)

A solution of freshly prepared LDA (0.5 M in THF; 0.74 mL, 0.37 mmol) at 0 °C was added via syringe to a stirred solution of (±)-**8ss** (R = MOM) (117 mg, 0.34 mmol) in THF (3.4 mL, 0.1 M) at -78 °C under Ar. After 15 min, Ti(O^iPr)$_4$ (0.22 mL, 0.21 g, 0.74 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -50 °C (CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7d** (128 mg, 0.67 mmol) in THF (0.8 mL, 0.8 M) was added via syringe. After 30 min, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The organic layers were filtered through a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and the combined filtrates and washings were concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of an 8:1 mixture of **73d** (R = MOM) and **72d** (R = MOM), respectively. Fractionation of

the crude by FCC (25-35% ethyl acetate in hexane) afforded recovered aldehyde (±)-**7d** (50 mg, 59%), (±)-**8ss** (R = MOM) (25 mg, 21%), a 4:1 mixture of anti-aldol (±)-**72d** (R = MOM) and (±)-**73d** (R = MOM) (15 mg, 8%) and the titled compound (124 mg, 69%).

IR (DRIFT) ν_{max} 3455, 1700 cm^{-1}.

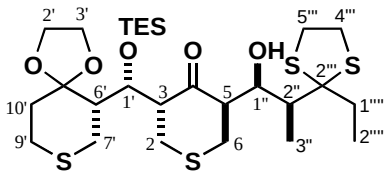
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.05 (1H, br d, *J* = 9.5 Hz), 4.66 (1H, d, *J* = 6 Hz), 4.62 (1H, d, *J* = 6 Hz), 4.50 (1H, dd, *J* = 4, 4.5 Hz), 4.07-3.92 (4H, m), 3.46 (1H, br s), 3.34 (3H, s), 3.33-3.25 (4H, m), 3.12-3.08 (2H, m), 3.07-2.95 (3H, m), 2.89-2.72 (4H, m), 2.49 (1H, br d, *J* = 13.5 Hz), 2.09-1.89 (4H, m), 1.83 (1H, br q, *J* = 7 Hz), 1.60 (1H, ddd, *J* = 3.5, 12.5, 13.5 Hz), 1.05 (3H, d, *J* = 7 Hz), 1.03 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.4 (s), 108.8 (t), 98.4 (t), 78.0 (s), 72.1 (d), 69.1 (d), 64.7 (t), 64.5 (t), 57.6 (d), 56.7 (q), 56.3 (d), 49.6 (d), 42.8 (d), 40.3 (t), 39.8 (t), 37.0 (t), 36.1 (t), 33.0 (t), 32.1 (t), 28.2 (t), 26.7 (t), 11.5 (q), 10.8 (q).

LRMS (ESI), *m/z* (relative intensity): 561 ($[M+23]^+$, 40), 529 (10), 371 (100), 317 (5), 226 (6) .

HRMS *m/z* calcd. for $C_{23}H_{38}O_6S_4$+Na: 561.1443; found: 561.1455 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(1*R*,2*S*)-2-(2-ethyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (73d (R = TES))



73d (R = TES)

A solution of freshly prepared LDA (0.5 M in THF; 0.14 mL, 0.068 mmol) at 0 °C was added via syringe to a stirred solution of (±)-**8ss** (R = TES) (26 mg, 0.062 mmol) in THF (0.6 mL, 0.1 M) at -78 °C under Ar. After 15 min, $Ti(O^iPr)_4$ (42 µL, 40 mg, 0.14 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -50 °C

(CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7d** (23 mg, 0.12 mmol) in THF (0.15 mL, 0.8 M) was added via syringe. After 16 h, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The organic layers were filtered through a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and the combined filtrate and washings were concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 1.3:1 mixture of **72d** (R = TES) and **73d** (R = TES), respectively. Fractionation of the crude by PTLC (10% ethyl acetate in hexane, multiple elutions) afforded recovered aldehyde (±)-**7d** (5 mg, 22%), (±)-**8ss** (R = TES) (6 mg, 23%), *anti* aldol (±)-**72d** (R = TES) (11 mg, 29%), and the titled compound (9 mg, 24%).

IR (DRIFT) ν_{max} 3474, 1710 cm^{-1}.

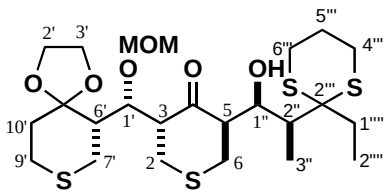
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.11 (1H, dd, *J* = 2, 10 Hz), 4.71 (1H, dd, *J* = 2.5, 6 Hz), 4.05-3.81 (4H, m), 3.44 (1H, d, *J* = 2 Hz), 3.36-3.23 (4H, m), 3.16 (1H, ddd, *J* = 2, 4.5, 13.5 Hz), 3.07-2.96 (2H, m), 2.94-2.85 (2H, m), 2.81-2.65 (4H, m), 2.549 (1H, br d, *J* = 13.5 Hz), 2.05-1.94 (4H, m), 1.81 (1H, br q, *J* = 7 Hz), 1.61 (1H, ddd, *J* = 3.5, 12, 13.5 Hz), 1.08 (3H, d, *J* = 7 Hz), 1.04 (3H, t, *J* = 7 Hz), 0.93 (9H, t, *J* = 8 Hz), 0.66-0.58 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.1 (s), 109.4 (s), 77.9 (s), 69.0 (d), 66.0 (d), 64.9 (t), 64.5 (t), 59.1 (d), 56.2 (d), 50.1 (d), 42.8 (d), 40.5 (t), 40.0 (t), 37.0 (t), 36.5 (t), 32.2 (t), 30.0 (t), 29.0 (t), 26.7 (t), 11.6 (q), 10.9 (q), 7.4 (q ×3), 5.4 (t ×3).

LRMS (ESI), *m/z* (relative intensity): 631 ($[M+23]^+$, 50), 468 (5), 441 (100).

HRMS *m/z* calcd. for $C_{27}H_{48}O_5SiS_4$+Na: 631.2046; found: 631.2066 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*R*,2*S*)-2-(2-ethyl-1,3-dithian-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (73e (R = MOM))



73e (R = MOM)

A solution of freshly prepared LDA (0.5 M in THF; 0.20 mL, 0.10 mmol) at 0 °C was added via syringe to a stirred solution of (±)-**8ss** (R = MOM) (31 mg, 0.089 mmol) in THF (0.9 mL, 0.1 M) at -78 °C under Ar. After 15 min, $Ti(O^iPr)_4$ (60 µL, 57 mg, 0.20 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -50 °C (CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7e** (37 mg, 0.18 mmol) in THF (0.23 mL, 0.8 M) was added via syringe. After 30 min, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The combined organic layers were filtered through a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and the combined filtrates and ethyl acetate washings were concentrated to give the crude product whose ^1H NMR spectrum indicated the presence of a 2:1 mixture of *anti*-aldol **72e** (R = MOM) and *syn*-aldol **73e** (R = MOM), respectively. Fractionation of the crude by FCC (30% ethyl acetate in hexane) afforded recovered aldehyde (±)-**7e** (8 mg, 22%), (±)-**8ss** (R = MOM) (2 mg, 6%), *anti*-aldol (±)-**72e** (R = MOM) (26 mg, 53%) and the titled compound (14 mg, 29%). A similar reaction conducted for 12 h gave a 1:1 mixture of **72e** (R = MOM) and **73e** (R = MOM) (80%).

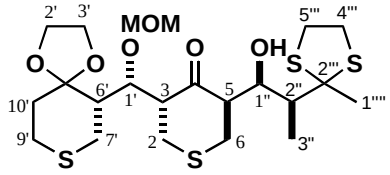
IR (DRIFT) ν_{max} 3500, 1700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.08 (1H, dd, *J* = 3.5, 9 Hz), 4.68 (1H, d, *J* = 6 Hz), 4.63 (1H, d, *J* = 6 Hz), 4.57 (1H, dd, *J* = 3.5, 6 Hz), 4.06-3.92 (4H, m), 3.35 (3H, s), 3.15-3.11 (2H, m), 3.03-2.62 (10H, m), 2.70 (1H, d, *J* = 3.5 Hz), 2.49 (1H, br d, *J* = 13.5 Hz), 2.29 (1H, dq, *J* = 7.5, 15 Hz), 2.08-1.85 (5H,), 1.79 (1H, br q, *J* = 7 Hz), 1.62-1.55 (1H, ddd, *J* = 3.5, 12, 13.5 Hz), 1.05 (3H, d, *J* = 7 Hz), 0.96 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.5 (s), 108.7 (s), 98.5 (t), 72.3 (d), 68.4 (d), 64.7 (t), 64.5 (t), 59.6 (s), 57.9 (d), 56.7 (q), 55.9 (d), 49.3 (d), 41.5 (d), 36.1 (t), 32.8 (t), 31.8 (t), 29.6 (t), 28.1 (t), 26.7 (t), 26.0 (t), 25.9 (t), 25.3 (t), 9.7 (q), 7.4 (q).

HRMS *m/z* calcd. for $C_{24}H_{40}O_6S_4$+Na: 575.1599; found: 575.1614 (ESI).

(3*R*,5*R*)-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*R*,2*S*)-2-(2-methyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (73f (R = MOM))

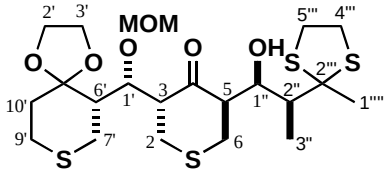


73f (R = MOM)

A solution of freshly prepared LDA (0.5 M in THF; 0.20 mL, 0.10 mmol) at 0 °C was added via syringe to a stirred solution of (+)-**8ss** (R = MOM) (32 mg, 0.092 mmol) in THF (0.9 mL, 0.1 M) at -78 °C under Ar. After 15 min, $Ti(O^iPr)_4$ (0.12 mL, 0.11 g, 0.39 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -50 °C (CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7f** (49 mg, 0.28 mmol) in THF (0.3 mL, 0.8 M) was added via syringe. After 4 h, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The organic layers were passed over a short column layered with

Na_2SO_4, SiO_2, and Na_2SO_4 and concentrated to give the crude product whose ^1H NMR spectrum indicated the presence of a 5:1 mixture of **73f** (R = MOM) and **72f** (R = MOM), respectively. Fractionation of the crude by PTLC (5% ethyl ether in CH_2Cl_2) afforded recovered aldehyde (±)-**7f** (16 mg, 33%), (+)-**8ss** (R = MOM) (4 mg, 13%), and an inseparable 5:1 mixture of (+)-**73f** (R = MOM) and (+)-**72f** (R = MOM), respectively (37 mg, 77%) ($[\alpha]_D$ +99; *c* 2.5, $CHCl_3$).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy) methyl]-5-[(1*R*,2*S*)-2-(2-methyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (73f (R = MOM))



73f (R = MOM)

A solution of freshly prepared LDA (0.5 M in THF; 0.20 mL, 0.10 mmol) at 0 °C was added via syringe to a stirred solution of (±)-**8ss** (R = MOM) (31 mg, 0.089 mmol) in THF (0.9 mL, 0.1 M) at -78 °C under Ar. After 15 min, $Ti(O^iPr)_4$ (0.12 mL, 0.11 g, 0.39 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -50 °C (CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7f** (32 mg, 0.18 mmol) in THF (0.22 mL, 0.8 M) was added via syringe. After 2 h, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The organic layers were passed over a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and concentrated to give the crude product whose ^1H NMR spectrum indicated the presence of a 7:1 mixture of **73f** (R = MOM) and **72f** (R = MOM), respectively. Fractionation of the crude by PTLC (5% ethyl ether in CH_2Cl_2) afforded

recovered aldehyde (±)-**7f** (16 mg, 50%), (±)-**8ss** (R = MOM) (4 mg, 13%), and an inseparable 7:1 mixture of (±)-**73f** (R = MOM) and (±)-**72f** (R = MOM) respectively compound (36 mg, 77%).

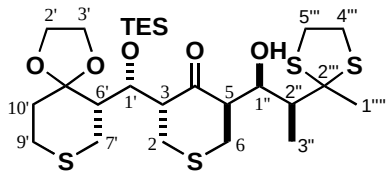
IR (DRIFT) ν_{max} 3458, 1700 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ: 5.25 (1H, dd, *J* = 2, 9 Hz), 4.72-4.69 (2H, m), 4.63 (1H, d, *J* = 6 Hz), 3.52-3.424 (4H, m), 3.23-3.12 (2H, m), 3.16 (3H, s), 3.12-2.83 (6H, m), 2.82-2.64 (6H, m), 2.26-2.21 (1H, m), 2.17 (1H, ddd, *J* = 4, 4, 10.5 Hz), 2.02 (1H, br q, *J* = 7 Hz), 1.84 (3H, s), 1.69 (1H, ddd, *J* = 3, 4.5, 13.5 Hz), 1.55 (1H, ddd, *J* = 3.5, 12, 15.5 Hz), 1.25 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, C_6D_6) δ: 209.6 (s), 109.2 (s), 98.5 (t), 72.6 (s), 72.5 (d), 69.7 (t), 64.5 (t), 64.3 (t), 58.1 (d), 57.0 (d), 56.2 (q), 50.1 (d), 46.5 (d), 40.1 (t), 39.7 (t), 36.5 (t), 33.1 (q), 32.6 (t), 31.7 (t), 28.8 (t), 26.9 (t), 11.5 (q) .

HRMS *m/z* calcd. for $C_{22}H_{36}O_6S_4$+Na: 547.1286; found: 547.1272 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(1*R*,2*S*)-2-(2-methyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (73f (R = TES))



73f (R = TES)

A solution of freshly prepared LDA (0.5 M in THF; 0.22 mL, 0.11 mmol) at 0 °C was added via syringe to a stirred solution of (±)-**8ss** (R = TES) (43 mg, 0.10 mmol) in THF (1 mL, 0.1 M) at -78 °C under Ar. After 15 min, Ti($O^{i}Pr$)$_4$ (66 µL, 63 mg, 0.22 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -50°C (CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7f** (35 mg,

0.2 mmol) in THF (0.25 mL, 0.8 M) was added via syringe. After 3 h, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate (80 mL). The organic layers were filtered through a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and the combined filtrates were concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 3:1 mixture of *anti* aldol **72f** (R = TES) and *syn* aldol **73f** (R = TES), respectively. Fractionation of the crude by PTLC (10% ethyl acetate in hexane, multiple elution) afforded recovered aldehyde (±)-**7f** (10 mg, 29%), (±)-**8ss** (R = TES) (6 mg, 14%), *anti* aldol (±)-**72f** (R = TES) (26 mg, 44%), a 3:1 mixture of **72f** (R = TES) and **73f** (R = TES), respectively (8 mg, 14%), and the titled compound (10 mg, 17%).

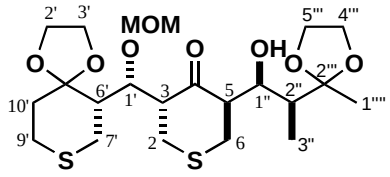
IR (DRIFT) ν_{max} 3453, 1699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.13 (1H, dd, *J* = 3, 9.5 Hz), 4.68 (1H, dd, *J* = 2, 6.5 Hz), 4.05-3.79 (4H, m), 3.39-3.31 (4H, m), 3.18 (1H, ddd, *J* = 3, 3.5, 14 Hz), 3.12 (1H, d, *J* = 3 Hz), 3.04 (1H, dd, *J* = 10.5, 13 Hz), 2.99 (1H, dd, *J* = 3.5, 14 Hz), 2.95-2.84 (2H, m), 2.82-2.68 (2H, m), 2.49 (1H, ddd, *J* = 3.5, 3.5, 13.5 Hz), 2.05-1.99 (2H, m), 1.82 (3H, s), 1.75 (1H, q, *J* = 6.5 Hz), 1.64 (1H, ddd, *J* = 3.5, 12, 13.5 Hz), 1.15 (3H, d, *J* = 7 Hz), 0.93 (9H, t, *J* = 8 Hz), 0.67-0.57 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.1 (s), 109.6 (s), 72.1 (s), 69.3 (d), 65.9 (d), 64.9 (t), 64.5 (t), 59.3 (d), 56.5 (d), 50.3 (d), 45.5 (d), 40.5 (t), 40.0 (t), 36.3 (t), 33.7 (q), 32.3 (t), 30.0 (t), 29.1 (t), 26.7 (t), 11.4 (q), 7.3 (q ×3), 5.4 (t ×3).

HRMS *m/z* calcd. for $C_{26}H_{46}O_5SiS_4$+Na: 617.1889; found: 617.1913 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*S*,2*S*)-2-(2-methyl-1,3-dioxolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (73g (R = MOM))



73g (R = MOM)

A solution of freshly prepared LDA (0.5 M in THF; 0.15 mL, 0.075 mmol) at 0 °C was added via syringe to a stirred solution of (±)-**8ss** (R = MOM) (24 mg, 0.069 mmol) in THF (0.7 mL, 0.1 M) at -78 °C under Ar. After 15 min, $Ti(O^iPr)_4$ (0.091 mL, 85 mg, 0.30 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C, 30 min at -50 °C (CH_3CN/dry ice bath), and finally 5 min at -78 °C. A solution of aldehyde (±)-**7g** (20 mg, 0.14 mmol) in THF (0.2 mL, 0.8 M) was added via syringe. After 1 h, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The organic layers were passed over a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 3:1 mixture of **73g** (R = MOM) and **72g** (R = MOM), respectively. Fractionation of the crude by FCC (30% ethyl acetate in hexane) afforded recovered aldehyde (±)-**7g** (3 mg, 15%), (±)-**8ss** (R = MOM) (1 mg, 4%), *anti* aldol (±)-**72g** (R = MOM) (6 mg, 18%) and the titled compound (18 mg, 53%).

IR (DRIFT) ν_{max} 3513, 1701 cm^{-1}.

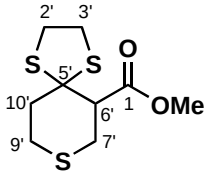
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.70-4.62 (3H, m), 4.47 (1H, dd, *J* = 4, 5 Hz), 4.07-3.92 (8H, m), 3.35 (3H, s), 3.15 (1H, dd, *J* = 4, 13.5 Hz), 3.08-3.01 (3H, m), 2.99-2.89 (3H, m), 2.87-2.72 (3H, m), 2.49 (1H, br d, *J* = 13.5 Hz), 2.07 (1H, ddd, *J* = 3, 4, 14 Hz), 1.95

(1H, ddd, *J* = 3.5, 4, 10.5 Hz), 1.69 (1H, br q, *J* = 7 Hz), 1.63 (1H, ddd, *J* = 3.5, 13, 14 Hz), 1.34 (3H, s), 0.99 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.9 (s), 112.7 (s), 108.9 (s), 98.6 (t), 72.4 (d), 67.8 (d), 65.1 (t), 64.65 (t), 64.60 (t), 64.5 (t), 57.8 (d), 56.7 (q), 55.4 (d), 49.4 (d), 42.7 (d), 36.1 (t), 32.8 (t), 32.1 (t), 28.2 (t), 26.8 (t), 22.3 (q), 7.8 (q).

HRMS *m/z* calcd. for $C_{22}H_{36}O_8S_2$+Na: 515.1743; found: 515.1763 (ESI).

Methyl 1,4,8-Trithiaspiro[4.5]decane-6-carboxylate (77)



77

A solution of beta-ketoester **75** (7.3 g, 42 mmol), 1,2-ethanedithiol (4.2 mL, 4.7g, 50 mmol), and p-TsOH.H_2O (1.6g, 8.4 mmol) in 50mL benzene was heated under reflux with continous removal of water (0.8 mL) with a Dean-Stark trap. After the reaction was complete via TLC (overnight, 20 hours), the reaction mixture was cooled and transferred to a separatory funnel with the aid of ether (150mL). The organic phase was washed sequentially with saturated $NaHCO_3$ (2 x 100 mL), water (1 x 100 mL) and brine (1 x 100 mL) then dried over Na_2SO_4 and concentrated. The crude product was purified by column with 50% ether in hexane gives pure product (9.4 g, 90%).

IR (DRIFT) ν_{max} 1730 cm^{-1}.

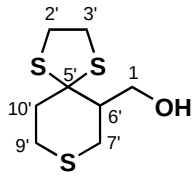
^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.73 (3H, s), 3.30-3.15 (6H, m), 3.02 (1H, ap ddd, *J* = 1.5,4.5,14 Hz), 2.91-2.84 (2H, m), 2.65-2.59 (1H, m), 2.21-2.16 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.7 (s), 68.2 (s), 54.3 (d), 52.1 (q), 40.4 (t), 39.4 (t), 38.6 (t), 31.7 (t), 28.4 (t).

LRMS (EI), *m/z* (relative intensity): 250 ($[M]^+$, 69), 189 (19), 157 (38), 136 (100), 118 (25), 85 (22), 71 (48), 59 (84).

HRMS *m/z* calcd. for $C_9H_{14}O_2S_3$: 250.0156; found: 250.0149 (EI).

1,4,8-Trithiaspiro[4.5]decan-6-ylmethanol (79)



79

A solution of ester **77** (3.03 g, 12.1 mmol) in THF (4 mL plus 2× 2 mL rinses) was added via syringe to a stirred suspension of $LiAlH_4$ (0.35 g, 9.1 mmol) in THF (10 mL) at 0 °C under Ar. The ice bath was removed and, after 4 h, the reaction was complete by TLC. The mixture was cooled to 0 °C and water (0.4 mL) (CAUTION: H_2 evolution), 15% (w/v) NaOH (0.4 mL), and water (1.2 mL) were added sequentially with vigorous stirring. The ice bath was removed and the grayish suspension turned white over 1 h. The mixture was filtered through a short pad of Na_2SO_4 and Celite®, washing with ethyl acetate. The combined filtrate and washings were concentrated to give the crude compound that was fractionated by FCC (20% ethyl acetate in hexane) to give the titled compound as a pale yellow oil (2.5 g, 93%).

IR (DRIFT) ν_{max} 3396 cm^{-1}.

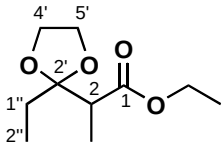
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.08 (1H, dd, *J* = 4.5, 11.5 Hz), 3.86 (1H, dd, *J* = 6, 11.5 Hz), 3.33-3.23 (4H, m), 2.93 (1H, br d, *J* = 14 Hz), 2.84 (1H, ddd, *J* = 2.5, 9.5, 13.5 Hz), 2.70-2.64 (2H, m), 2.38 (1H, ddd, *J* = 3, 6.5, 14 Hz), 2.29-2.22 (2H, m), 2.22 (1H, br s).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 71.4 (s), 64.9 (t), 50.9 (d), 44.9 (br t), 39.39 (t), 39.10 (t), 31.2 (t), 28.0 (t).

LRMS (EI), *m/z* (relative intensity): 222 ($[M]^+$, 100), 194 (10), 164 (60), 136 (96), 99 (32), 71 (30).

HRMS *m/z* calcd. for $C_8H_{14}OS_3$: 222.0207; found: 222.0207 (EI).

Ethyl 2-(2-Ethyl-1,3-dioxolan-2-yl)propanoate (82)



82

A stirred solution of beta-ketoester **81** (12.0 g, 76 mmol), ethylene glycol (5.5 mL, 6.1 g, 99 mmol), and p-TsOH·H_2O (0.70 g, 3.8 mmol) in benzene (38 mL) was heated under reflux with removal of water via a Dean-Stark trap. After 14 h (reaction was completed by TLC analysis; 1.4 mL H_2O collected), the mixture was diluted with ethyl acetate (200 mL) and washed sequentially with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give the titled compound as a colorless oil (12.1 g, 79%).

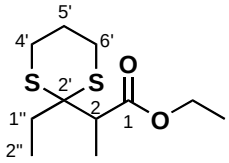
IR (DRIFT) ν_{max} 1736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.19-4.11 (2H, m), 4.03-3.95 (4H, m), 2.83 (1H, q, *J* = 7 Hz), 1.83 (1H, dq, *J* = 14.5, 7.5 Hz), 1.74 (1H, dq, *J* = 14.5, 7.5 Hz), 1.26 (3H, t, *J* = 7 Hz), 1.19 (3H, d, *J* = 7 Hz), 0.90 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (500 MHz, $CDCl_3$) δ: 173.7 (s), 111.9 (s), 65.9 (t), 65.8 (t), 60.6 (t), 47.0 (d), 28.2 (t), 14.4 (q), 12.8 (q), 7.5 (q). .

HRMS *m/z* calcd. for $C_{10}H_{18}O_4$+H: 203.1283; found: 203.1288 (CI, NH_3).

Ethyl 2-(2-Ethyl-1,3-dithian-2-yl)propanoate (84)



84

$F_3B{\cdot}OEt_2$ (6.2 mL, 6.9 g, 49 mmol) was added to a stirred solution of beta-ketoester **81** (7.0 g, 45 mmol) and 1,2-dithioethane (4.8 mL, 5.4 g, 47 mmol) in CH_2Cl_2 (64 mL) at room temperature under Ar. After 30 min (reaction complete by TLC analysis), the mixture was diluted with diethyl ether (300 mL) and sat. $NaHCO_3$ (200 mL) was added with vigorous stirring (Caution: effervesence). After 30 min, the organic layer was washed sequentially with water and brine, dried over Na_2SO_4, concentrated and fractionated by FCC (15% ethyl acetate in hexane) to give the titled compound as a pale yellow oil (9.5 g, 86%).

IR (DRIFT) ν_{max} 1734 cm^{-1}.

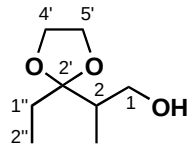
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.22.4.09 (2H, m), 3.40 (1H, q, *J* = 7 Hz), 3.12 (1H, ddd, *J* = 3, 11.5, 14.5 Hz), 2.93 (1H, ddd, *J* = 3, 11.5, 14.5 Hz), 2.71-2.66 (2H, m), 2.19 (1H, dq, *J* = 7.5, 15 Hz), 2.05-1.99 (1H, m), 1.89-1.78 (2H, m), 1.31 (3H, d, *J* = 7 Hz), 1.27 (3H, t, *J* = 7 Hz), 1.10 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.5 (s), 60.6 (t), 55.6 (s), 46.3 (d), 27.9 (t), 26.2 (t), 26.1 (t), 24.8 (t), 14.4 (q), 13.7 (q), 9.4 (q).

LRMS (EI), *m/z* (relative intensity): 248 ($[M]^+$, 20), 219 (13), 147 (100), 128 (20), 100 (7), 68 (10).

HRMS *m/z* calcd. for $C_{11}H_{20}O_2S_2$: 248.0905; found: 248.0904 (EI).

2-(2-Ethyl-1,3-dioxolan-2-yl)propan-1-ol (85)



85

A solution of ester **82** (3.2 g, 15.8 mmol) in THF (6 mL plus 2× 4 mL rinses) was added via syringe to a stirred suspension of $LiAlH_4$ (0.66 g, 17.4 mmol) in THF (10 mL) at 0 °C under Ar. The ice bath was removed and, after 1 h (the reaction was complete by TLC analysis), the mixture was cooled to 0 °C and water (0.7 mL) (CAUTION: H_2 evolution), 15% (w/v) NaOH (0.7 mL), and water (2.1 mL) were added sequentially with vigorous stirring. The ice bath was removed and the grayish suspension turned white over 1 h. The mixture was filtered through a short pad of Na_2SO_4 and Celite®, washing with ethyl acetate. The combined filtrate and washings were concentrated and fractionated by FCC (50% ethyl acetate in hexane) to give the titled compound as a pale yellow oil (2.4 g, 96%).

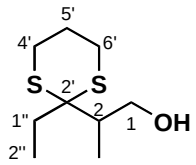
IR (DRIFT) ν_{max} 3440 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.98-3.95 (4H, m), 3.64 (1H, dd, *J* = 8, 11 Hz), 3.52 (1H, dd, *J* = 4, 11 Hz), 2.91 (1H, br s), 2.06 (1H, ddq, *J* = 4, 8, 7 Hz), 1.66 (2H, ap q, *J* = 7.5 Hz), 0.93 (3H, d, *J* = 7 Hz), 0.89 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 114.7 (s), 65.3 (t), 65.2 (t), 65.0 (t), 40.6 (d), 26.7 (t), 12.5 (q), 7.6 (q).

HRMS *m/z* calcd. for $C_8H_{16}O_3$+H: 161.1177; found: 161.1172 (CI, NH_3).

2-(2-Ethyl-1,3-dithian-2-yl)propan-1-ol (87)



87

A solution of ester **84** (5.5 g, 22 mmol) in THF (20 mL + 2× 10 mL rinses) was added via syringe to a stirred suspension of $LiAlH_4$ (1.5 g, 38.5 mmol) in THF (30 mL) at 0 °C under Ar. The ice bath was removed and, after 9 h (reaction complete by TLC analysis), the mixture was cooled to 0 °C and water (1.5 ml) (Caution: hydrogen evolution), 15% (w/v) aq NaOH (1.5 ml), and water (4.5 ml) were added sequentially. The ice bath was removed and the greyish suspension turned white over 1 h. The mixture was filtered through a short pad of Na_2SO_4 and Celite® and the combined filtrate and ethyl acetate washings were concentrated and fractionated by FCC (20 % ethyl acetate in hexane) to give the titled compound (4.0 g, 89%).

IR (DRIFT) ν_{max} 3419 cm^{-1}.

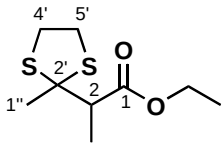
^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.96 (1H, ddd, *J* = 5.5, 6,11.5 Hz), 3.73 (1H, ddd, *J* = 5.5, 6.5,11.5 Hz), 2.89-2.72 (4H, m) , 2.40 (1H, dd, *J* = 6, 6.5 Hz), 2.25-2/17 (1H, m), 2.11 (1H, dq, *J* = 7.5, 15 Hz), 1.97-1.87 (3H, m), 1.11 (3H, d, *J* = 7 Hz), 1.03 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 65.5 (t), 57.8 (s), 41.1 (d), 28.8 (t), 25.9 (t), 25.8 (t), 25.3 (t), 12.8 (q), 9.4 (q).

LRMS (EI), *m/z* (relative intensity): 206 ($[M]^+$, 13), 177 (10), 147 (100), 99 (10), 73 (17).

HRMS *m/z* calcd. for $C_9H_{18}OS_2$: 206.0790; found: 206.0792 (EI).

Ethyl 2-(2-Methyl-1,3-dithiolan-2-yl)propanoate (89)



89

$F_3B{\cdot}OEt_2$ (2.0 mL, 2.3 g, 16 mmol) was added to a stirred solution of Ethyl 2-methylacetoacetate **88** (2.10 g, 14.6 mmol) and 1,2-ethane dithiol (1.3 mL, 1.4 g, 15 mmol) in CH_2Cl_2 (21 mL) at room temperature under Ar. After 2 h (reaction complete by TLC analysis), the mixture was diluted with ether (200 mL) and saturated $NaHCO_3$ (150 mL) was added with vigorous stirring (Caution: effervesence). After 30 min, the organic layer was washed with saturated sequentially with water and brine, dried over Na_2SO_4, concentrated and fractionated by FCC (15% ethyl acetate in hexane) to give the titled compound as a pale yellow oil (3.1 g, 97%).

IR (DRIFT) ν_{max} 1731 cm^{-1}.

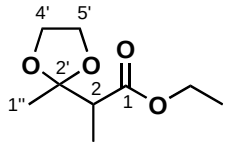
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.15 (2H, ap q, *J* = 7 Hz), 3.34-3.22 (4H, m), 2.97 (1H, q, *J* = 7 Hz), 1.85 (3H, s), 1.38 (3H, d, *J* = 7 Hz), 1.26 (3H, t, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.1 (s), 68.0 (s), 60.7 (t), 52.5 (d), 40.1 (t), 39.9 (t), 29.5 (q), 16.1 (q), 14.4 (q).

LRMS (EI), *m/z* (relative intensity): 220 ($[M]^+$, 59), 205 (9), 175 (10), 121 (82), 120 (31), 85 (17), 71 (25), 59 (100).

HRMS *m/z* calcd. for $C_9H_{16}O_2S_2$: 220.0592; found: 220.0595 (EI).

Ethyl 2-(2-Methyl-1,3-dioxolan-2-yl)propanoate (90)



90

A stirred solution of ethyl 2-methylacetoacetate **88** (1.80 g, 12.5 mmol), ethylene glycol (1.4 mL, 1.6 g, 25 mmol), and p-TsOH·H_2O (0.12 g, 0.63 mmol) in benzene (63 mL) was heated under reflux with continuous removal of water with a Dean-Stark trap. After 12 h (the reaction was complete by TLC analysis; 0.2 mL H_2O collected), the mixture was diluted with ethyl acetate (200 mL), washed sequentially with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give the titled compound (2.30 g, 98%).

IR (DRIFT) ν_{max} 1734 cm^{-1}.

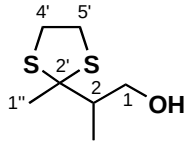
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.15 (2H, q, *J* = 7 Hz), 4.02-3.89 (4H, m), 2.75 (1H, q, *J* = 7 Hz), 1.40 (3H, s), 1.26 (3H , t, *J* = 7 Hz), 1.21 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.4 (s), 109.9 (s), 65.0 (t), 65.0 (t), 60.5 (t), 48.1 (d), 21.5 (q), 14.3 (q), 13.0 (q).

LRMS (EI), *m/z* (relative intensity): 173 ($[M-15]^+$, 6), 87 (100).

HRMS *m/z* calcd. for $C_9H_{16}O_4$+H: 189.1126; found: 189.1125 (CI, NH_3).

2-(2-Methyl-1,3-dithiolan-2-yl)propan-1-ol (91)



91

A solution of ester **89** (2.90 g, 13.2 mmol) in THF (6 mL plus 2 x 2 mL rinses) was added via syringe to a stirred suspension of $LiAlH_4$ (0.55 g, 14 mmol) in THF (10 mL) at 0 °C under Ar. The ice bath was removed and, after 1.5 h,(reaction was complete by TLC analysis), the mixture was cooled to 0 °C and water (0.6 mL) (CAUTION: H_2 evolution), 15% (w/v) NaOH (0.6 mL), and water (1.8 mL) were added sequentially with vigorous stirring. The ice bath was removed and the grayish suspension turned white over 1 h. The mixture was filtered through a short pad of Na_2SO_4 and Celite®, washing with ethyl acetate. The combined filtrate and washings were concentrated to give the crude compound that was fractionated by FCC (20% ethyl acetate in hexane) to give the titled compound as a pale yellow oil (2.25 g, 96%).

IR (DRIFT) ν_{max} 3389 cm^{-1}.

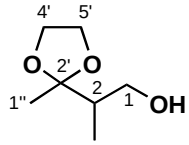
^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.87 (1H, dd, *J* = 5.5, 11 Hz), 3.62 (1H, dd, *J* = 5.5, 11 Hz), 3.35-3.26 (4H, m), 2.33 (1H, br s), 2.14 (1H, ddq, *J* = 5.5, 5.5, 7 Hz), 1.73 (3H, s), 1.15 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 70.4 (s), 66.7 (t), 47.7 (d), 39.8 (t), 39.6 (t), 31.0 (q), 16.0 (q).

LRMS (EI), *m/z* (relative intensity): 178 ($[M]^+$, 5), 133 (3), 119 (100), 59 (26).

HRMS *m/z* calcd. for $C_7H_{14}OS_2$: 178.0486; found: 178.0481 (EI).

2-(2-Methyl-1,3-dioxolan-2-yl)propan-1-ol (92)



92

A solution of ester **90** (2.30 g, 12.2 mmol) in THF (30 mL + 2× 5 mL rinses) was added via syringe to a stirred suspension of $LiAlH_4$ (0.550 g, 14.6 mmol) in THF (20 mL) at 0 °C under Ar. The ice bath was removed and, after 45 min (the reaction complete by TLC analysis), the reaction mixture was cooled to 0 °C and quenched by sequential addition of water (0.55 mL), 15% (w/v) NaOH (0.55 mL), and water (1.6 mL) with vigorous stirring. The ice bath was removed and the grayish suspension turned white over 1 h. The mixture was filtered through a short pad of Na_2SO_4 and Celite® and the combined filtrate and ether washings filtrate were concentrated to give the titled compound (1.72 g, 97%).

IR (DRIFT) ν_{max} 3444 cm^{-1}.

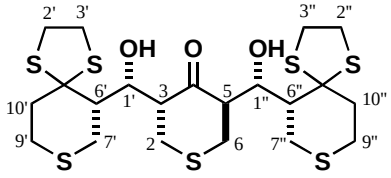
^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.99-3.94 (4H, m), 3.66-3.61 (1H, ddd, *J* = 2, 7.5, 11.5 Hz), 3.54-3.50 (1H, ddd, *J* = 4, 7.5, 11.5 Hz), 3.10-2.70 (1H, br dd, *J* = 2, 7.5 Hz), 2.0-1.96 (1H, ddq, *J* = 4, 7.5, 7 Hz), 1.28 (3H, s), 0.94 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 112.7 (s), 65.0 (t), 64.6 (t), 64.4 (t), 42.8 (d), 20.4 (q), 12.6 (q).

LRMS (ESI), *m/z* (relative intensity): 169 ($[M+23]^+$, 100), 147 (15), 117 (18).

HRMS *m/z* calcd. for $C_7H_{14}O_3$+Na: 169.0835; found: 169.0828 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*R*)-1,4,8-Trithiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*S*)-(6*S*)-1,4,8-trithiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (103)



103

From known **72a** (R = MOM): $F_3B{\cdot}OEt_2$ (8 µL, 9 mg, 0.07 mmol) was added to a stirred solution of bisaldol **72a** (R = MOM) (16 mg, 0.030 mmol) and 1,2-ethanedithiol (10 µL, 11 mg, 0.12 mmol) in CH_2Cl_2 (0.3 mL, 0.1 M) at room temperature under Ar. After 1 h (reaction complete by TLC analysis), the mixture was diluted with CH_2Cl_2 (50 mL) and aq NaOH (10% w/v; 25 mL) was added with vigorous stirring. After 30 min, the organic layer was washed sequentially with water and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (40% ethyl acetate in hexane) to give the titled compound (11 mg, 65%).

From unknown **72b** (R = MOM): Treatment of the unknown **72b** (R = MOM) (19 mg, 0.033 mmol) with $F_3B{\cdot}OEt_2$ (8 µL, 9 mg, 0.07 mmol) and 1,2-ethanedithiol (11 µL, 12 mg, 0.13 mmol) according to the above procedure gave the titled compound (11 mg, 61%).

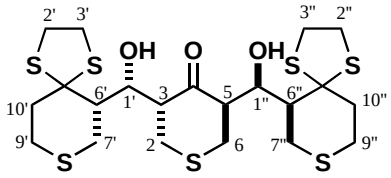
IR (DRIFT) ν_{max} 3454, 1705 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.09 (1H, br dd, *J* = 3, 9 Hz), 4.09 (1H, dbr d, *J* = 2, 9.5 Hz), 3.48 (1H, d, *J* = 3 Hz), 3.47-3.22 (9H, m), 3.18 (1H, ddd, *J* = 4, 9, 9.5 Hz), 3.07-2.87 (6H, m), 3.01 (1H, d), 2.84-2.66 (5H, m), 2.61-2.52 (2H, m), 2.52-2.44 (2H, m), 2.38-2.27 (2H, m), 2.23 (1H, br dd, *J* = 3, 10 Hz), 2.09-2.03 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.4 (s), 73.6 (s), 73.3 (s), 70.8 (d), 69.9 (d), 56.6 (d), 55.8 (d), 51.5 (d), 49.1 (d), 47.4 (t), 46.8 (t), 39.9 (t), 39.6 (t), 39.3 (t), 39.2 (t), 34.6 (t), 34.3 (t), 28.8 (t), 28.3 (t ×2), 28.1 (t).

HRMS *m/z* calcd. for $C_{21}H_{32}O_3S_7$+Na: 579.0288; found: 579.0301 (ESI).

(3*R*,5*R*)-*rel*-3,5-bis[(*R*)-(6*R*)-1,4,8-Trithiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (104)



104

From known **73a** (R = MOM): $F_3B{\cdot}OEt_2$ (26 µL, 30 mg, 0.21 mmol) was added to a solution of bisaldol **73a** (R = MOM) (51 mg, 0.095 mmol) and 1,2-ethanedithiol (32 µL, 36 mg, 0.38 mmol) in CH_2Cl_2 (1 mL, 0.1 M) at room temperature under Ar. After 1 h (reaction complete by TLC analysis), the mixture was diluted with CH_2Cl_2 (50 mL) and aq NaOH (10% w/v; 25 mL) was added with vigorous stirring. After 30 min, the organic layer was washed sequentially with water and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (40% ethyl acetate in hexane) to give the titled compound (36 mg, 68%).

From unknown **73b** (R = MOM): Treatment of the unknown **73b** (R = MOM) (19 mg, 0.033 mmol) with $F_3B{\cdot}OEt_2$ (6 µL, 7 mg, 0.05 mmol) and 1,2-ethanedithiol (7 µL, 8 mg, 0.8 mmol) according to the above procedure gave the titled compound (7 mg, 58%).

IR (DRIFT) ν_{max} 3447, 1696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.12 (2H, br dd, *J* = 2, 9 Hz), 3.43 (2H, d, *J* = 2 Hz), 3.42-3.24 (5H, m), 3.21-3.15 (1H, m), 3.07-2.94 (7H, m), 2.80-2.70 (4H, m), 2.59-2.53 (2H, m), 2.46-2.40 (4H, m), 1.94 (2H, ap dd, *J* = 4.5, 9.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.2 (s), 73.7 (s ×2), 69.0 (d ×2), 56.6 (d ×2), 50.9 (d ×2), 47.4 (t ×2), 39.6 (t ×2), 39.5 (t ×2), 34.4 (t ×2), 28.4 (t ×2), 28.3 (t ×2).

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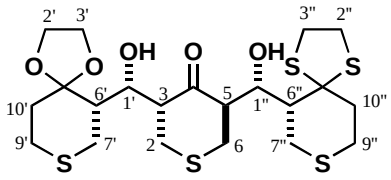
HRMS *m/z* calcd. for $C_{21}H_{32}O_3S_7$+Na: 579.0288; found: 579.0304 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*S*)-(6*S*)-1,4,8-trithiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (105)



105

From new **72b** (R = TES): A solution of 30% aq HF (0.9 mL) was added to a stirred solution of **72b** (R = TES) (9 mg, 0.014 mmol) in CH_3CN (2 mL) at 0 °C. After 5 min (reaction complete by TLC analysis), the mixture was diluted with ethyl acetate and washed sequentially with saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (30% ethyl acetate in hexane, multiple elution) to give the titled compound (3 mg, 43%).

From known **72b** (R = MOM): $TiCl_4$ (29 µL, 49 mg, 0.26 mmol) was added dropwise via syringe to a stirred solution of **72b** (R = MOM) (29 mg, 0.051 mmol) in CH_2Cl_2 (2.6 mL, 0.02 M) at –78 °C under argon. After 5 min, a fine yellow slurry developed and thiophenol (52 µL, 56 mg, 0.51 mmol) was added dropwise to the mixture resulting in a red-orange fine slurry. After 2 h, MeOH (2 mL) was added (the mixture

became colorless) and the cooling bath was removed. Phosphate buffer (pH=7; 8 mL) was added and, after 3 min, the mixture was diluted with aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, concentrated, and fractionated by FCC (40 % ethyl acetate in hexane) to give recovered **72b** (R = MOM) (17mg, 59%) and the titled compound (7mg, 26%).

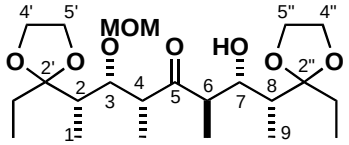
IR (DRIFT) ν_{max} 3500, 1706 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.17 (1H, dd, *J* = 2.5, 9 Hz), 4.59-4.54 (1H, br d, *J* = 8.5 Hz), 4.11-3.94 (4H, m), 3.46-3.20 (6H, m), 3.3.26 (1H, br s), 3.08-2.91 (4H, m), 2.87-2.69 (7H, m), 2.60-2.46 (3H, m), 2.30 (1H, ddd, *J* = 3,11.5, 14 Hz), 2.21 (1H, ddd, *J* = 2, 3, 10 Hz), 2.15 (1H, ddd, *J* = 2.5, 4.5, 13.5 Hz), 2.04 (1H, ap dd, *J* = 5, 8.5 Hz), 1.75 (1H, ddd, *J* = 3.5, 11, 13.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.3 (s), 110.3 (s), 73.2 (s), 70.8 (d), 67.5 (d), 64.8 (t), 64.3 (t), 56.5 (d), 54.6 (d), 51.7 (d), 47.3 (t), 45.7 (d), 40 (t), 39.6 (t), 36.0 (t), 34.4 (t), 34.2 (t), 28.7 (t), 28.3 (t), 26.7 (t), 26.3 (t).

HRMS *m/z* calcd. for $C_{21}H_{32}O_5S_5$+Na: 547.0745; found: 547.0729 (ESI).

(2*S*,3*R*,4*R*,6*R*,7*S*,8*R*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-methoxymethoxy-4,6-dimethylnonan-5-one (106)



106

From known **72a** (R = MOM): A suspension of Raney Ni (W-2) (0.5 mL settled volume) in ethanol was added in one portion to a stirred solution of **72a** (R = MOM) (16 mg, 0.030 mmol) in ethanol (3 mL, 0.01 M) and the reaction mixture was heated under reflux. After 30 min, the mixture was decanted and the solid suspended in ethanol and

heated under reflux with rapid stirring for several min. The above washing procedure was repeated with ethyl acetate and acetone. The supernatants were filtered through a pad of Celite® and the combined filtrates were concentrated and fractionated by PTLC (30% ethyl acetate in hexane) to give the titled compound (6 mg; ca. 90% pure).

From unknown **72c** (R = MOM): Treatment of bisaldol **72c** (R = MOM) (50 mg, 0.099 mmol) with Raney Ni as described above gave the titled compound (24 mg, 55%).

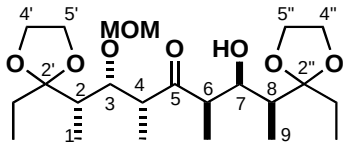
IR (DRIFT) ν_{max} 3519, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.70 (1H, d, *J* = 6.5 Hz), 4.59 (1H, d, *J* = 6.5 Hz), 4.03 (1H, dd, *J* = 3.5, 4 Hz), 4.01-3.93 (9H, m), 3.35 (3H, s), 3.12-3.06 (2H, m), 2.97 (1H, dq, *J* = 7, 9.5 Hz), 2.05-1.98 (2H, m), 1.72 (2H, ap q, *J* = 7.5 Hz), 1.69 (2H, ap q, *J* = 7.5 Hz), 1.10 (3H, d, *J* = 7 Hz), 0.97 (3H, d, *J* = 7 Hz), 0.95 (3H, d, *J* = 7 Hz), 0.94 (3H, d, *J* = 7 Hz), 0.88 (6H, ap t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 217.3 (s), 114.9 (s), 113.8 (s), 97.0 (t), 76.4 (d), 74.3 (d), 65.7 (t), 65.28 (t), 65.26 (t), 64.9 (t), 56.4 (q), 53.2 (d), 48.2 (d), 42.2 (d), 38.4 (q), 28.3 (t), 26.9 (t), 13.2 (q), 11.3 (q), 10.7 (q), 8.4 (q), 7.7 (q), 6.6 (q).

HRMS *m/z* calcd. for $C_{23}H_{42}O_8$+Na: 469.2771; found: 469.2769 (ESI).

(2S,3*R*,4*R*,6*R*,7*R*,8*S*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-methoxymethoxy-4,6-dimethylnonan-5-one (107)



107

From known **73a** (R = MOM): A suspension of Raney Ni (W-2) (0.5 mL settled volume) in ethanol was added in one portion to a stirred solution of bisketal **73a** (R =

MOM) (52 mg, 0.097 mmol) in ethanol (10 mL, 0.01 M) and the reaction mixture was heated under reflux. After 1 h, the mixture was decanted and the solid suspended in ethanol and heated under reflux with rapid stirring for several min. The above washing procedure was repeated with ethyl acetate and acetone. The supernatants were filtered through a pad of Celite® and the combined filtrates were concentrated and fractionated by PTLC (30% ethyl acetate in hexane) to give the titled compound (24 mg; ca. 85% purity).

From unknown **73c** (R = MOM): Treatment of bisaldol **73c** (R = MOM) (30 mg, 0.059 mmol) with Raney Ni as described above gave the titled compound (11 mg, 42%).

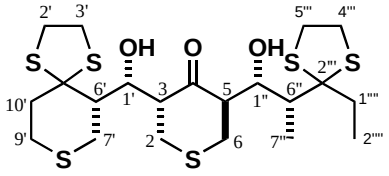
IR (DRIFT) ν_{max} 3526, 1704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.69 (1H, d, *J* = 6.5 Hz), 4.59 (1H, d, *J* = 6.5 Hz), 4.06-4.03 (2H, m), 4.01-3.93 (8H, m), 3.35 (3H, s), 3.05 (1H, br s), 3.01-2.93 (2H, m), 1.91 (1H, dq, *J* = 3, 7 Hz), 1.80 (1H, dq, *J* = 1.5, 7 Hz), 1.75-1.64 (4H, m), 1.21 (3H, d, *J* = 7 Hz), 1.10 (3H, d, *J* = 7 Hz), 0.96 (3H, d, *J* = 7 Hz), 0.94 (3H, d, *J* = 7 Hz), 0.86 (3H, t, *J* = 7.5 Hz), 0.85 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.1 (s), 114.7 (s), 113.6 (s), 97.6 (t), 76.4 (d), 72.0 (d), 65.7 (t), 65.3 (t), 65.2 (t), 65.0 (t), 56.5 (q), 51.9 (d), 49.4 (d), 42.5 (d), 39.8 (d), 28.1 (t), 27.1 (t), 14.1 (q), 12.3 (q), 10.4 (q), 8.1 (q), 7.7 (q), 7.6 (q).

HRMS *m/z* calcd. for $C_{23}H_{42}O_8$+Na: 469.2771; found: 469.2792 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*R*)-1,4,8-Trithiaspiro[4.5]dec-6-yl(hydroxy)methyl]-5-[(1*S*,2*R*)-2-(2-ethyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (108)



108

From unknown **72d** (R = MOM): $F_3B{\cdot}OEt_2$ (9 µL, 10 mg, 0.07 mmol) was added to a solution of bisaldol **72d** (R = MOM) (16 mg, 0.030 mmol) and 1,2-ethanedithiol (10 µL, 11 mg, 0.12 mmol) in CH_2Cl_2 (0.3 mL, 0.1 M) at room temperature under Ar. After 1 h (reaction complete by TLC analysis), the mixture was diluted with CH_2Cl_2 (50 mL) and aq NaOH (10% w/v; 25 mL) was added with vigorous stirring. After 30 min, the organic layer was washed sequentially with water and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give the titled compound (11 mg, 70%).

From known **72c** (R = MOM): Treatment of the known **72c** (R = MOM) (21 mg, 0.041 mmol) with $F_3B{\cdot}OEt_2$ (11 µL, 13 mg, 0.09 mmol) and 1,2-ethanedithiol (13 µL, 15 mg, 0.16 mmol) according to the above procedure gave the titled compound (12 mg, 55%).

IR (DRIFT) ν_{max} 3454, 1704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.02 (1H, br dd, *J* = 3, 9 Hz), 4.97 (1H, br dd, *J* = 2.5, 9.5 Hz), 3.52 (1H, d, *J* = 3 Hz), 3.40-3.19 (10H, m), 3.04 (1H, d, *J* = 2.5 Hz), 3.00 (1H, dd, *J* = 4, 13.5 Hz), 2.78-2.89 (2H, m), 2.86 (1H, ddd, *J* = 4.5, 5, 9.5 Hz), 2.80-2.67 (3H, m), 2.56 (1H, br d, *J* = 13.5 Hz), 2.49 (1H, ddd, *J* = 2.5, 5, 14 Hz), 2.33 (2H, ddd, *J* = 3, 11, 14 Hz), 2.22 (1H, dd, *J* = 4, 9.5 Hz), 2.10-1.99 (2H, m), 1.96 (1H, q, *J* = 7 Hz), 1.11 (3H, d, *J* = 7 Hz), 1.07 (3H, t, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.1 (s), 77.7 (s), 73.6 (s), 70.9 (d), 70.0 (d), 56.9 (d), 55.8 (d), 49.0 (d), 46.6 (t), 44.1 (d), 40.5 (t), 40.0 (t), 39.4 (t), 39.2 (t), 36.4 (t), 34.7 (t), 34.1 (t), 28.2 (t), 28.1 (t), 11.7 (q), 10.9 (q).

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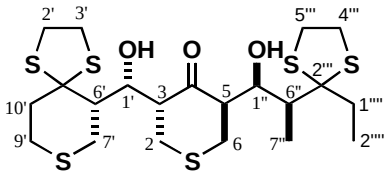
HRMS *m/z* calcd. for $C_{21}H_{34}O_3S_6$+Na: 549.0724; found: 549.0720 (ESI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*R*)-1,4,8-Trithiaspiro[4.5]dec-6-yl(hydroxy)methyl]-5-[(1*R*,2*S*)-2-(2-ethyl-1,3-dithiolan-2-yl)-1-hydroxypropyl]tetrahydro-4*H*-thiopyran-4-one (109)



109

From known **73c** (R = MOM): $F_3B{\cdot}OEt_2$ (8 µL, 9 mg, 0.06 mmol) was added to a solution of bisketal **73c** (R = MOM) (14 mg, 0.028 mmol) and 1,2-ethanedithiol (9 µL, 10 mg, 0.11 mmol) in CH_2Cl_2 (0.3 mL, 0.1 M) at room temperature under Ar. After 0.5 h (reaction complete by TLC analysis), the mixture was diluted with CH_2Cl_2 (50 mL) and aq NaOH (10% w/v; 25 mL) was added with vigorous stirring. After 30 min, the organic layer was washed sequentially with water and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (25% ethyl acetate in hexane) to give the titled compound (8 mg, 53%).

From unknown **73d** (R = MOM): Treatment of the bisaldol **73d** (R = MOM) (12 mg, 0.022 mmol) with $F_3B{\cdot}OEt_2$ (6 µL, 7 mg, 0.05 mmol) and 1,2-ethanedithiol (7 µL, 8 mg, 0.09 mmol) according to the above procedure gave the titled compound (8 mg, 67%).

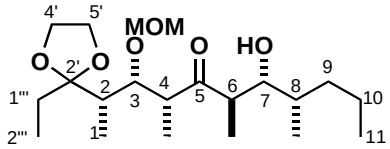
IR (DRIFT) ν_{max} 3450, 1696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.11 (1H, br d, *J* = 9.5 Hz), 5.04 (1H, dd, *J* = 2, 9 Hz), 3.55 (1H, d, *J* = 2 Hz), 3.41-3.26 (9H, m), 3.22 (1H, dd, *J* = 4, 13.5 Hz), 3.13 (2H, ap d, *J* = 5 Hz), 3.10-3.05 (1H, ddd, *J* = 4.5, 8.5, 9 Hz), 3.0-2.92 (3H, m), 2.78-2.70 (2H, m), 2.54 (1H, br d, *J* = 14 Hz), 2.46 (1H, ddd, *J* = 2.5, 4, 14 Hz), 2.27 (1H, ddd, *J* = 3, 12, 14 Hz), 2.08-1.96 (3H, m), 1.78 (1H, q, *J* = 7 Hz), 1.082 (3H, d, *J* = 7 Hz), 1.079 (3H, t, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.8 (s), 78.2 (s), 73.7 (s), 69.4 (d), 69.1 (d), 57.4 (d), 56.4 (d), 50.6 (d), 47.6 (t), 43.6 (d), 40.5 (t), 40.1 (t), 39.4 (t), 39.3 (t), 37.0 (t), 34.4 (t), 34.3 (t), 28.6 (t), 28.1 (t), 11.8 (q), 10.9 (q).

HRMS *m/z* calcd. for $C_{21}H_{34}O_3S_6$+Na: 549.0724; found: 549.0741 (ESI).

(2*S*,3*R*,4*R*,6*R*,7*R*,8*S*)-*rel*-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-methoxymethoxy-4,6,8-trimethylundecan-5-one (110)



110

From unknown **72e** (R = MOM): A suspension of Raney Ni (W-2) (0.5 mL settled volume) in ethanol was added in one portion to a stirred solution of **72e** (R = MOM) (22 mg, 0.040 mmol) in ethanol (4 mL, 0.01 M) and the reaction mixture was heated under reflux. After 2 h, the mixture was decanted and the solid suspended in ethanol and heated under reflux with rapid stirring for several min. The above washing procedure was repeated with ethyl acetate and acetone. The supernatants were filtered through a pad of Celite® and the combined filtrates were concentrated and fractionated by PTLC (25% ethyl acetate in hexane) to give the titled compound (7 mg; ca. 85% pure).

From known **72b** (R = MOM): Treatment of bisaldol **72b** (R = MOM) (51 mg, 0.090 mmol) with Raney Ni as described above gave the titled compound (21 mg, 60%).

IR (DRIFT) ν_{max} 3504, 1707 cm^{-1}.

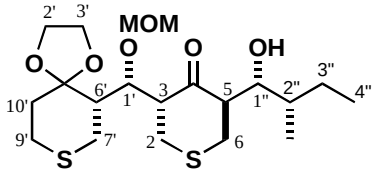
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.70 (1H, d, *J* = 6.5 Hz), 4.59 (1H, d, *J* = 6.5 Hz), 4.06 (1H, ddd, *J* = 3, 5.5 Hz), 3.96 (4H, br s), 3.63 (1H, ddd, *J* = 3, 5.5, 8.5 Hz), 3.36 (3H, s), 3.03 (2H, dq, *J* = 6, 7 Hz), 2.97 (1H, dq, *J* = 8.5, 7 Hz), 2.15 (1H, d, *J* = 5.5 Hz), 1.94 (1H, dq, *J* = 3, 7 Hz), 1.76-1.65 (2H, m), 1.60-1.50 (1H, m), 1.40-1.20 (4H, m), 1.13 (3H,

d, *J* = 7 Hz), 1.04 (3H, d, *J* = 7 Hz), 0.95 (3H, d, *J* = 7 Hz), 0.89 (3H, t, *J* = 7 Hz), 0.87 (3H, d, *J* = 7 Hz), 0.87 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 218.3 (s), 113.6 (s), 97.5 (t), 76.7 (d), 76.6 (d), 65.3 (t), 65.2 (t), 56.5 (q), 52.0 (d), 48.4 (d), 42.3 (d), 36.6 (t), 34.5 (d), 27.1 (t), 20.6 (t), 14.5 (q), 13.8 (q), 12.7 (q), 12.4 (q), 10.4 (q), 7.7 (q).

HRMS *m/z* calcd. for $C_{21}H_{40}O_6$+Na: 411.2722; found: 411.2714 (ESI).

(3*R*,5*R*)-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(1*R*,2*S*)-1-hydroxy-2-methylbutyl]tetrahydro-4*H*-thiopyran-4-one (113)



113

A solution of (+)-**8ss** (R = MOM) (29 mg, 0.083 mmol) in CH_2Cl_2 (0.4 mL; 0.2 M) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in CH_2Cl_2; 0.17 mL, 0.17 mmol) and Et_3N (24 µL, 17 mg, 0.17 mmol) in CH_2Cl_2 (0.4 mL; 5 mL/mmol of **8ss**) at -78 °C under Ar. After 2 h, a solution of aldehyde (+)-**112** (0.15 mL from a 1.1 M solution of aldehyde **112** in CH_2Cl_2; 15 mg, 0.17 mmol) was added slowly via syringe (ca. 5 min). After 23 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice-water and saturated aq Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 14:1 mixture of the titled compound and a side product, respectively, along with unreacted (+)-**8ss** (R = MOM). Fractionation of the crude by FCC (20-30% ethyl acetae in hexane) afforded side product (4 mg, 11%) recovered (+)-

8ss (R = MOM) (2 mg, 7%) and the titled compound (28 mg, 78 %) ($[\alpha]_D$ +82 ; *c* 1.1 , $CHCl_3$).

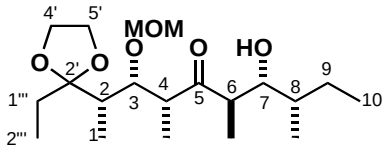
IR (DRIFT) ν_{max} 3526, 1704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.70 (1H, d, *J* = 6 Hz), 4.61 (1H, d, *J* = 6 Hz), 4.56 (1H, dd, *J* = 4.5, 6.5 Hz), 4.10-3.91 (4H, m), 4.03-3.90 (1H, ddd, *J* = 3, 5.5, 8 Hz), 3.36 (3H, s), 3.19 (1H, ddd, *J* = 1, 7.5, 13.5 Hz), 3.06-3.01 (1H, m, *J* = 4.5, 7, 7 Hz), 2.98-2.89 (3H, m), 2.84-2.64 (4H , m), 2.59 (1H, d, *J* = 5.5 Hz), 2.50 (1H, br d, *J* = 13.5 Hz), 2.07 (1H, ddd, *J* = 3, 4.5, 13.5 Hz), 2.03 (1H, ddd, *J* = 4, 4, 10.5 Hz), 1.65 (1H, ddd, *J* = 3.5, 12, 13.5 Hz), 1.57-1.40 (2H, m), 1.38-1.29 (1H, m), 0.92 (3H, t, *J* = 7 Hz), 0.88 (3H, d, *J* = 6.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.3 (s), 108.9 (s), 98.5 (t), 72.95 (t), 72.93 (d), 64.7 (t), 64.5 (t), 58.3 (d), 56.8 (q), 53.8 (d), 49.0 (d), 36.3 (d), 36.1 (t), 31.4 (q), 30.3 (t), 28.2 (t), 27.0 (t), 26.7 (t), 12.4 (q), 12.1 (q).

HRMS *m/z* calcd. for $C_{20}H_{34}O_6S_2$+Na: 457.1689; found: 457.1697 (ESI).

(2*S*,3*R*,4*R*,6*R*,7*R*,8*S*)-*rel*-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-methoxymethoxy-4,6,8-trimethyldecan-5-one (114)



114

From known **113**: A suspension of Raney Ni (W-2) (0.5 mL settled volume) in ethanol was added in one portion to a stirred solution of (+)-**113** (25 mg, 0.058 mmol) in ethanol (6 mL, 0.01 M) and the reaction mixture was heated under reflux. After 2 h, the mixture was decanted and the solid suspended in ethanol and heated under reflux with rapid stirring for several min. The above washing procedure was repeated with ethyl acetate and acetone. The supernatants were filtered through a pad of Celite® and the

combined filtrates were concentrated and fractionated by PTLC (25% ethyl acetate in hexane) to give retro-aldol/elimination **115** (9 mg, 69%) and the titled compound (5 mg; 23%).

From unknown **72f** (R = MOM): Treatment of bisldol (+)-**72f** (R = MOM) (32 mg, 0.061 mmol) with Raney Ni as described above gave the titled compound (9 mg, 39%) ($[\alpha]_D$ -5; *c* 0.9, $CHCl_3$).

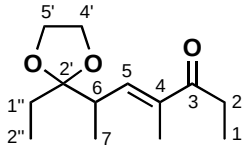
IR (DRIFT) ν_{max} 3503, 1706 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.71 (1H, d, *J* = 6.5 Hz), 4.59 (1H, d, *J* = 6.5 Hz), 4.07 (1H, dd, *J* = 3, 5.5 Hz), 3.96 (4H, ap s), 3.69-3.63 (1H, m), 3.37 (3H, s), 3.02 (1H, dq, *J* = 5.5, 7 Hz), 2.97 (1H, dq, *J* = 8.5, 7 Hz), 2.14 (1H, d, *J* = 5.5 Hz), 1.96 (1H, dq, *J* = 3, 7 Hz), 1.76-1.65 (2H, m), 1.49-1.38 (2H, m), 1.33-1.24 (1H, m), 1.14 (3H, d, *J* = 7 Hz), 1.04 (3H, d, *J* = 7 Hz), 0.96 (3H, d, *J* = 7 Hz), 0.92 (3H, t, *J* = 7.5 Hz), 0.88 (3H, d, *J* = 7 Hz), 0.87 (3H, t, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 218.3 (s), 113.6 (s), 97.6 (t), 76.6 (t), 76.4 (d), 65.3 (t), 65.2 (t), 56.5 (q), 52.0 (d), 48.5 (d), 42.3 (d), 36.7 (q), 27.1 (t ×2), 13.8 (q), 12.5 (q), 12.4 (q), 12.1 (q), 10.4 (q), 7.7 (q).

HRMS *m/z* calcd. for C20H38O6+Na: 397.2560; found: 397.2567 (ESI).

(*E*)-6-(2-Ethyl-1,3-dioxolan-2-yl)-4-methylhept-4-en-3-one (115)



115

see experimental procedure for compound **114**.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.57 (1H, d, *J* = 10 Hz), 4.0-3.85 (4H, m), 2.95 (1H, dq, *J* = 7, 10 Hz), 2.69 (2H, ap , *J* = 7.5 Hz), 1.80 (3H, s), 1.67 (1H, dq, *J* = 14.5, 7.5 Hz), 1.58

(1H, dq, *J* = 14.5, 7.5 Hz), 1.09 (3H, t, *J* = 7.5 Hz), 1.02 (3H, d, *J* = 7 Hz), 0.88 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.0 (s), 143.1 (d), 137.1 (s), 113.3 (s), 66.10 (t), 66.04 (t), 40.8 (d), 30.7 (t), 29.5 (t), 14.5 (q), 11.8 (q), 9.0 (q), 7.9 (q).

HRMS (EI), *m/z* (relative intensity): 226 ($[M]^+$, 30), 197 (10), 101 (100).

HRMS *m/z* calcd. for $C_{13}H_{22}O_3$: 226.1569; found: 226.1571 (EI).

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