THIOPYRAN ROUTE TO POLYPROPIONATES: PROLINE CATALYZED ALDOL REACTIONS OF TETRAHYDRO-4*H*-THIOPYRAN-4-ONE

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By

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ABSTRACT

The thiopyran route to polypropionates is an attractive strategy that involves a stepwise iterative aldol homologation of tetrahydro-4*H*-thiopyran-4-one (**I**) with thiopyran aldehyde (**II**) followed by desulfurization to rapidly assemble stereochemically complex polypropionate synthons such as (**III**) and (**IV**) in only a few steps (Figure A).

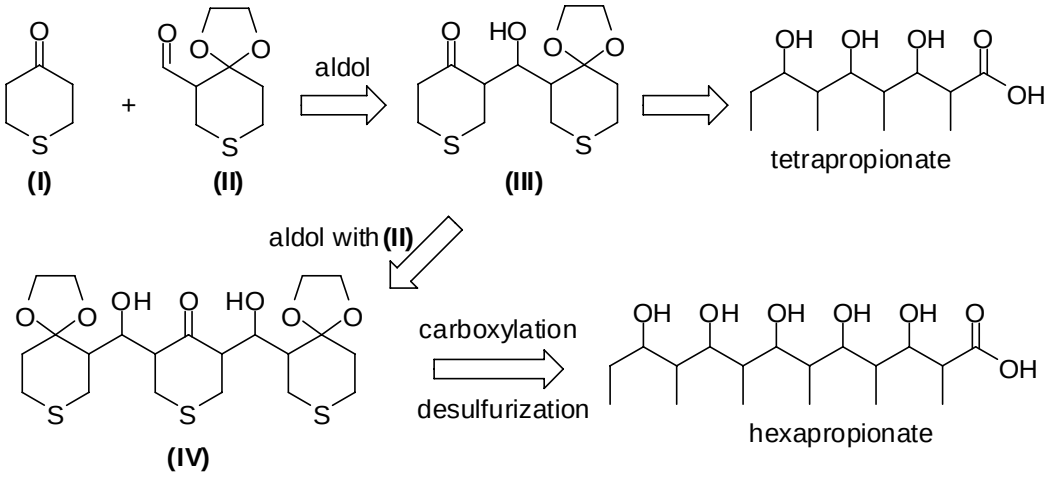


Figure A

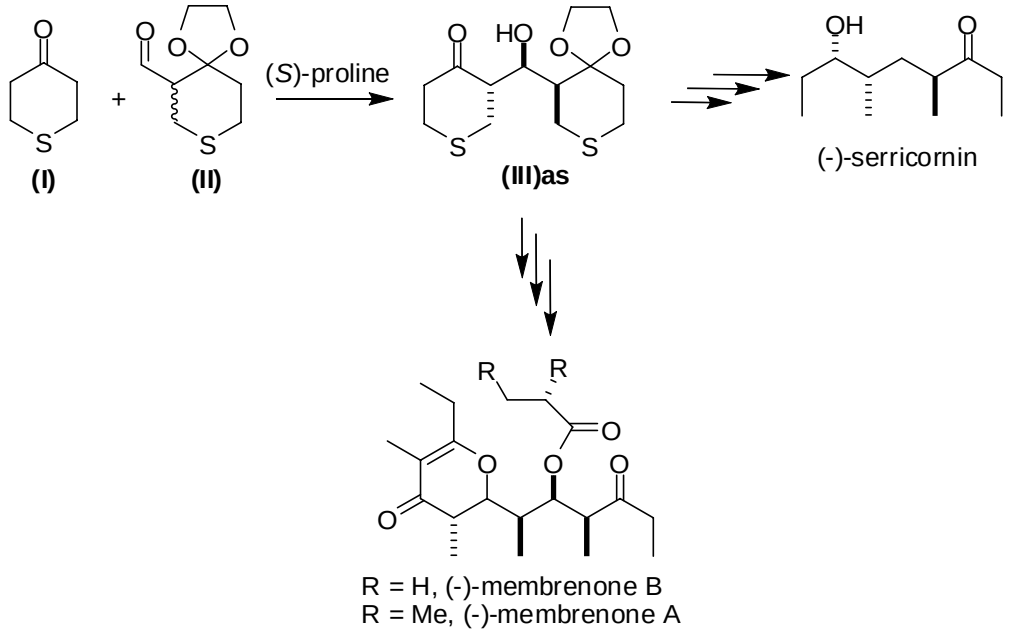
In chapter 1, the thesis is summarized in the context of relevant background research including; a) the basic principle of the thiopyran route; b) dynamic kinetic resolution of α-substituted aldehydes; c) previous syntheses of serricornin; iv) previous syntheses of membrenones.

In chapter 2, proline-catalyzed enantioselective direct intermolecular aldol reactions of tetrahydro-4*H*-thiopyran-4-one (**I**) with various achiral aldehydes were studied. The results provided insights on the behaviour and stereoselectivity profile of thiopyranone (a crucial starting block in the thiopyran design) in the proline-catalyzed aldol reaction.

In chapter 3, inspired by the results of the aldol reaction of ketone (**I**) with achiral aldehydes, we next investigated the proline-catalyzed asymmetric aldol reactions of (**I**) with racemic thiopyran aldehyde (**II**) as a strategy to rapidly prepare enantiomerically pure tetrapropionate synthons without any requirement of enantioenriched aldehyde (**II**). The reaction occurred with high enantiotopic group selectivity and dynamic kinetic resolution (Scheme A).

In chapter 4, a detailed study to ascertain the scope and limitations of the design strategy described in chapter 3 was extended towards other catalysts, aldehydes and ketones.

Finally, applications of the above mentioned strategy towards the synthesis of (–)-serricornin and (–)-membrenones A and B are elaborated in chapters 5 and 6 respectively (Scheme A).



Scheme A

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First and foremost, my military salute [SIR-THANK-YOU-SIR] and sincere gratitude to my supervisor Prof. Dale E. Ward for his mentorship, support and guidance throughout my graduate program. Prof. Dale Ward, many thanks to you for the exciting chemistry and education, I learned under your charismatic supervision. Vishal is definitely a very proud Ward Group Soldier (WGS)!!!!!!

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I would like to thank my families (Jheengut and Chooramun) for their loving support and enthusiasm over the years. - I MISS YOU MOM-

-DEDICATION-

To Jheengut and Chooramun's family

-dadaji & dadiji - nanaji & naniji-

-dad and mom-

-Anju, Maya, Amit, Artee and Yogesh-

and

in memory of our beloved sister
Pratima Jheengut
(28.01.81-28.01.84)

-JAI SHREE RAM-

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LIST OF ABBREVIATIONS

α	observed optical rotation in degrees
$[\alpha]$	specific rotation (expressed without units; the actual units, (deg·mL)/(g·dm), are understood)
Å	angstrom(s)
Ac	acetyl
AIBN	2,2′-azobisisobutyronitrile
anhyd	anhydrous
AO	atomic orbital
ap	apparent (spectral)
aq	aqueous
Ar	aryl
atm	atmosphere(s)
BOM	benzyloxymethyl
Bn	benzyl
br	broad (spectral)
Bu, *n*-Bu	normal (primary) butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
°C	degrees Celsius
calcd	calculated
CAN	ceric ammonium nitrate
CD	circular dichroism

CI	chemical ionization; configuration interaction
cm	centimeter(s)
cm^{-1}	wavenumber(s)
compd	compound
concd	concentrated
concn	concentration
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
δ	chemical shift in parts per million downfield from tetramethylsilane
d	day(s); doublet (spectral); deci
d	density
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
dil	dilute
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*,-diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide

dr	diastereomeric ratio
DRIFT	diffuse reflectance infrared Fourier transform spectroscopy
ee	enantiomeric excess
EI	electron impact
eq	equation
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
FCC	flash column chromatography
FT	Fourier transform
g	gram(s); prefix to NMR abbreviation denoting gradient-selected (e.g., gCOSY, gHSQC)
h	hour(s)
hfc	3-(heptafluoropropylhydroxy-methylene)camphorate
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
IR	infrared
J	coupling constant (in NMR spectrometry)
k	kilo

K	kelvin(s) (absolute temperature)
KHMDS	potassium hexamethyldisilazane, lithium bis(trimethylsilyl) amide
L	liter(s)
LDA	lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazane, lithium bis(trimethylsilyl) amide
lit.	literature (abbreviation used with period)
LRMS	low-resolution mass spectrometry
μ	micro
m	multiplet (spectral); meter(s); milli
M	molar (moles per liter); mega
M^+	parent molecular ion
max	maximum
Me	methyl
MHz	megahertz
min	minute(s); minimum
mM	millimolar (millimoles per liter)
mol	mole(s); molecular (as in mol wt)
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
MW, mol wt	molecular weight
m/*z*	mass-to-charge ratio

N	normal (equivalents per liter)
NIS	*N*-iodosuccinamide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
obs	observed
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB	*para*-methoxy benzyl
PMP	*para*-methoxy phenyl
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
PTLC	preparative thin layer chromatography
Py	pyridine
q	quartet (spectral)
Ra	Raney
rel	relative
Rf	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral); second(s)

SAMP	(*S*)-1-amino-2-methoxymethylpyrolidine
t	triplet (spectral)
TBAF	tetra-*n*butylammonium fluoride
TBDMS, TBS	*tert*-butyldimethylsilyl
TBDPS, TPS	*tert*-butyldiphenylsilyl
temp	temperature
TES	triethylsilyl; triethylsilane
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAE	2,2,2-trifluoro-1-(9-anthryl)ethanol
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl; tetramethylsilane
TOF	time-of-flight
TPAP	Tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
vol	volume
v/v	volume per unit volume (volume-to-volume ratio)
wt	weight
w/w	weight per unit weight (weight-to-weight ratio)

1. Introduction

1.1 Thiopyran route to polypropionates

Polyketides are a therapeutically appealing class of natural products. They are secondary metabolites from bacteria, fungi, plants, and animals and are generally produced from the (stereo)controlled oligomerization of acetyl and propionyl subunits.[1-3] Polypropionates are an important subclass of polyketides and are characterized by the presence of a structural motif containing a linear carbon-carbon chain with alternating methyl and hydroxyl (oxo) substituents.[4-9] In Nature, their biosynthesis involves condensation of suitably activated propionate precursors catalyzed by a family of enzymes or enzyme complexes known as the polyketide synthetase system[10-14] (Figure 1.0). Polypropionate natural products are often associated with numerous biomedical promises[1,2] such as antibiotics, antiparasitic and anti-cancer and intensive research concerning isolation, synthesis and pre-clinical evaluations of new polypropionate macrolides from Nature's reservoir is of concomitant focus in many pharmaceutical laboratories worldwide.

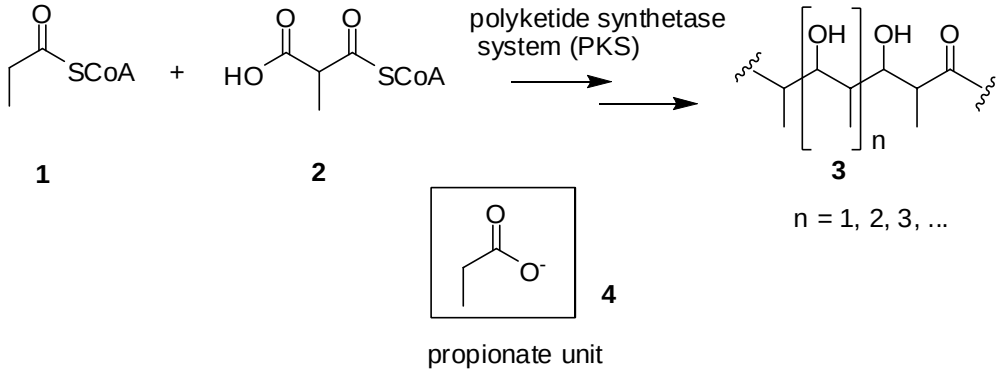


Figure 1.0: Biosynthesis of polypropionates

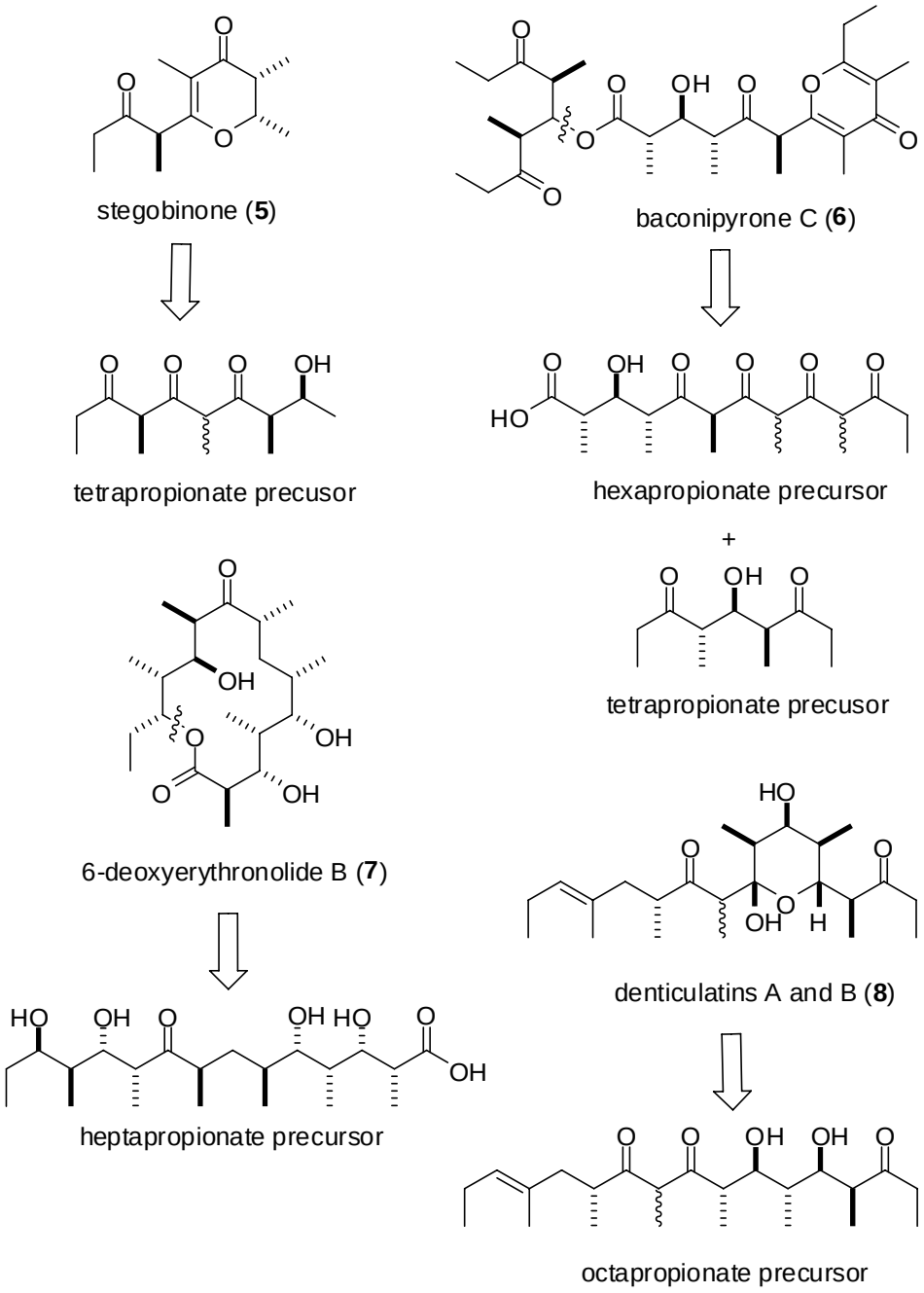


Figure 1.1: Examples of polypropionate natural products

For instance, erythromycin,[1,10] a well-established macrolide antibiotic has been widely used in the treatment of infections caused by gram-positive microorganisms and is used as an alternative for patients allergic to penicillin. The complex molecular architectures

of polypropionates present a challenging benchmark to chemists and have prompted the discovery and development of several stereoselective carbon-carbon bond forming reactions.[15-25] The aldol reaction is widely regarded as one of the most powerful reactions in modern synthetic chemistry for C-C bond formation.[26-35] This reaction has been intensively investigated over the past three decades and has found numerous applications in polyketide natural product synthesis.[5,7,9,17] Some selected examples where stereoselective aldol reactions have contributed to the synthesis of polypropionate targets are stegobinone (**5**),[36,37] erythronolide B (**7**),[38-45] baconipyrone C (**6**)[46-48] and the denticulatins (**8**)[49-57] (Figure 1.1). To date, a number of iterative methods have been developed that, in principle, can provide access to all possible stereoisomers of polypropionates from common building blocks with good stereocontrol generating (up to) two stereocenters for each cycle.[15-25,39,40,58-67] However, most syntheses of polypropionate natural products follow a convergent pathway involving stereoselective synthesis and then coupling of chiral fragments to construct the polypropionate skeleton.[68-73] The union of chiral fragments is complicated by double stereodifferentiation[74,75] and retrosynthetic planning requires judicious selection of a strategic bond for disconnection. Consequently, such convergent pathways tend to be specific to a very small number of stereoisomers; that is, different stereoisomers generally require different synthetic routes and/or precursors.

A potentially more general approach to polypropionate synthesis involves aldol couplings of tetrahydro-4*H*-thiopyran-4-one (**12**) derivatives followed by desulfurization.[76] Developing this strategy has been a recent objective in the Ward laboratory. This so-called thiopyran route to polypropionates involves stepwise iterative

aldol homologations of tetrahydro-4*H*-thiopyran-4-one (**12**) with thiopyran aldehyde **13** as conduit to rapidly assemble stereochemically complex polypropionate synthons **11** (six stereogenic centers) in only a few steps (Figure 1.2).[77-87]

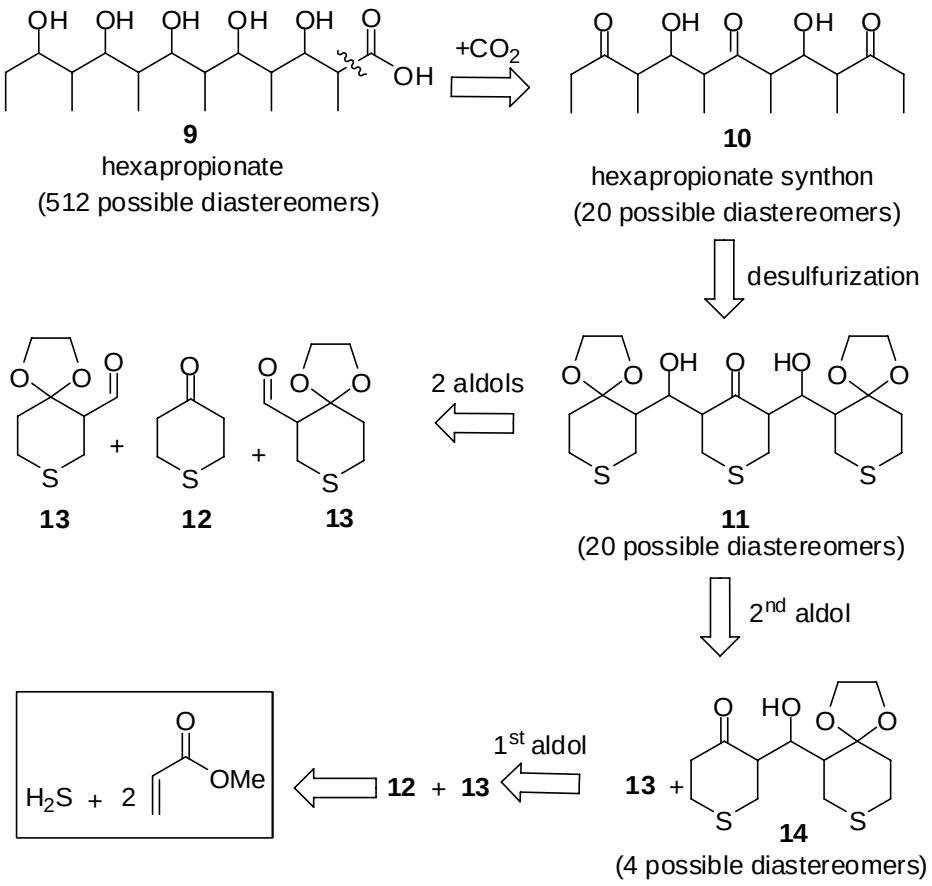
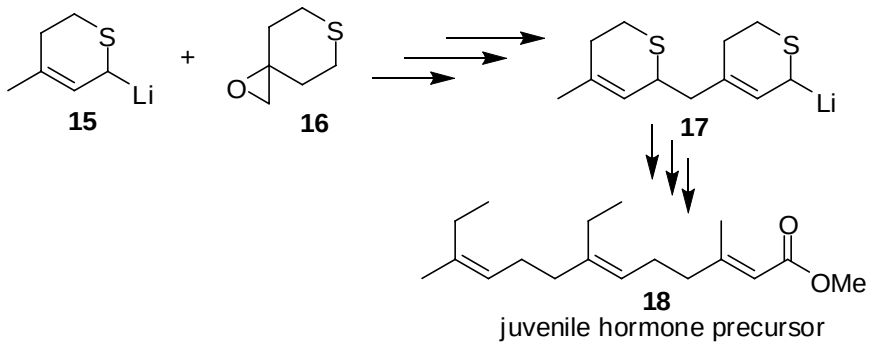


Figure 1.2: The thiopyran route to polypropionates

The use of cyclic sulfides in the synthesis of natural products is a well established synthetic strategy. They offer several advantages such as rapid access to starting materials, versatile chemistry and ease of removal of the sulfur atom from the final product.[88,89] For example, cyclic sulfides have been successfully used to address the

stereochemical issues of the olefin geometry in the synthesis of juvenile hormone precursor (**18**)[89] as shown in Scheme 1.0.



Scheme 1.0: Juvenile hormone precursor approach

In a classical example, Woodward *et al.*[90] exploited two *cis*-fused dithiadecalin scaffolds **21** to construct the C-3-C-8 and C-9-C-13 portions of the erythronolide A seco acid (**20**) where the rigidity of the dithiadecalin cyclic template permitted stereocontrolled introduction of the substituents (Figure 1.3).

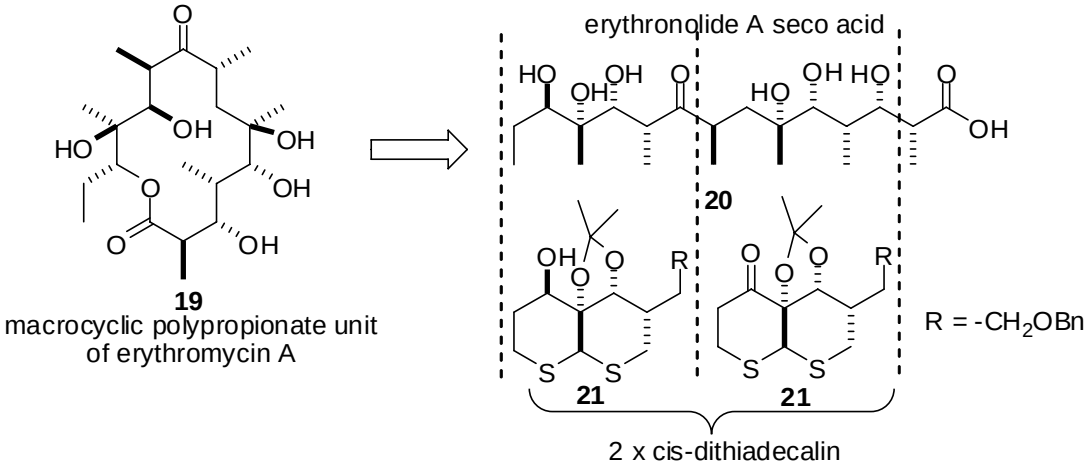
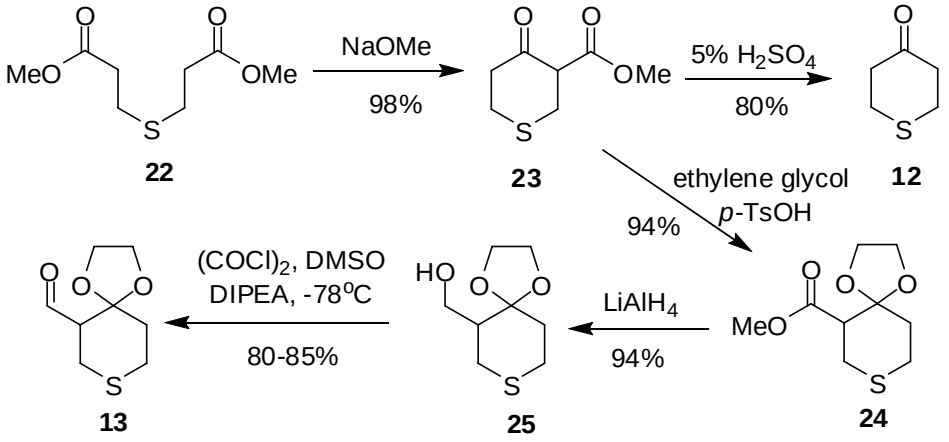


Figure 1.3: Erythronolide A seco acid synthetic approach

Ward's strategy begins with an initial retrosynthetic disconnection of the carboxyl moiety of hexapropionate **9** that leads to triketone **10** after appropriate oxidation state adjustments (Figure 1.2). Interestingly, this step dramatically reduces the number of possible diastereomers (512 to 20) and subsequently facilitates their access. In essence, stereoselective reductions and decarboxylation of **10** will be required to synthesize any desired stereoisomer of **9**. Cyclic template **11** which is the surrogate for triketone **10** can be constructed by simultaneous or stepwise two directional aldol reactions of ketone **12** and aldehyde **13** as shown in Figure 1.2. An additional advantage of the thiopyran route is that all stereoisomers are prepared from the same starting materials **12** and **13** and both are robustly prepared from hydrogen sulfide and methyl acrylate. The ability to control the stereoselectivity of the aldol couplings and easy access of starting materials are crucial to the success of this approach.

Thiopyranone **12** and thiopyran aldehyde **13** are both prepared in multi-gram scale from diester **22** which is commercially available or readily prepared from H_2S and methyl acrylate.[91] The sequence involves a Dieckmann cyclization of diester **22** to β-keto ester **23** in 98% yield using NaOMe followed by decarboxylation under acid reflux to give white crystalline ketone **12** in 80% yield. Alternatively, ketal protection of β-keto ester **23** to **24** followed by reduction and oxidation provides access to aldehyde **13** in excellent overall yield (Scheme 1.1).[80]

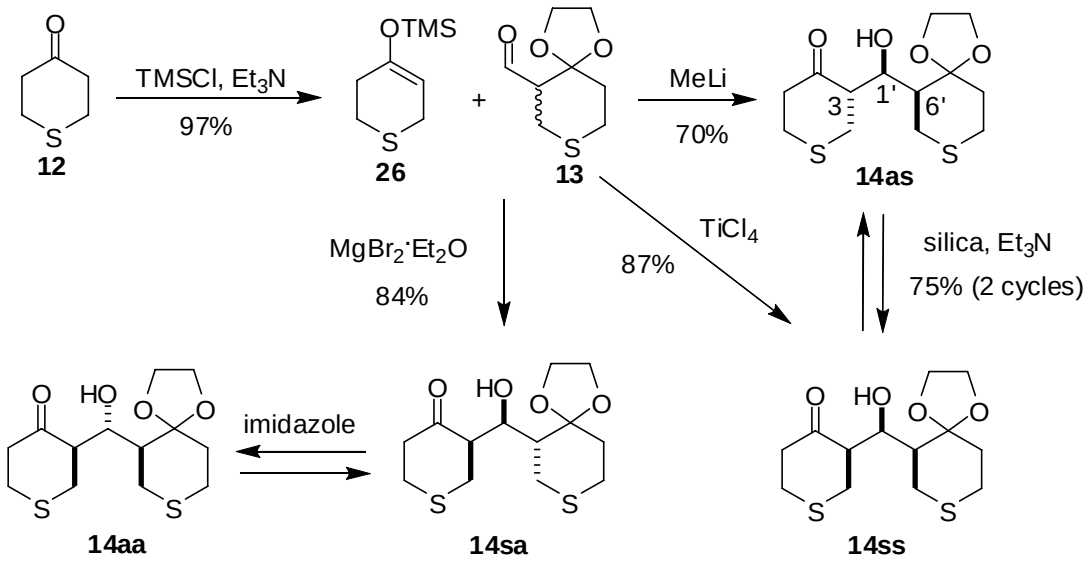


Scheme 1.1: Preparation of starting materials **12** and **13**

The aldol coupling of **12** with **13** can produce four possible diastereomers. The diastereoselectivity of this first aldol is easily modulated by varying the reaction conditions.[80] The amine free lithium enolate of **12**, generated from enol silyl ether **26** by addition of MeLi, reacts with **13** to afford the 1',3-*anti*-1, 6"-*syn* Felkin adduct **14as**[*] as the major aldol in 70% yield (**14as**:**14ss** = 9:1). Isomerization[79,81,85] of **14as** in the presence of silica/Et_3N provides access to the 1',3-*syn*-1, 6"-*syn* Felkin adduct **14ss** in 75% yield (**14ss**:**14as**, K_{eq} = 2:1) after 2 cycles. Alternatively, **14ss** can be selectively generated via aldol reaction of **26** and **13** mediated by $TiCl_4$ in 87% yield as the major product (**14ss**:**14as** = 15:1). Under chelation control, aldol coupling of **26** and **13** promoted by $MgBr_2 \cdot Et_2O$ gives a 3:1 diastereomeric mixture of anti-Felkin adducts **14sa** and **14aa** in 84% combined yield. Furthermore, isomerization of **14sa** in the presence of imidazole provides access to **14aa** diastereomer in synthetically useful amounts (**14sa**:**14aa**, K_{eq}= 1.8:1). Appropriate functionalizations (i.e. carboxylation) of the four

[*] The **as**, **ss, sa** and, **aa** labels refer to the syn (**s**) or anti (**a)** relative configurations at C-3,1' and C-1',6', respectively, in the diastereomers of **14** (e.g. **14as**, Scheme 1.2) or derivatives (i.e. **135**, see Scheme 1.23)

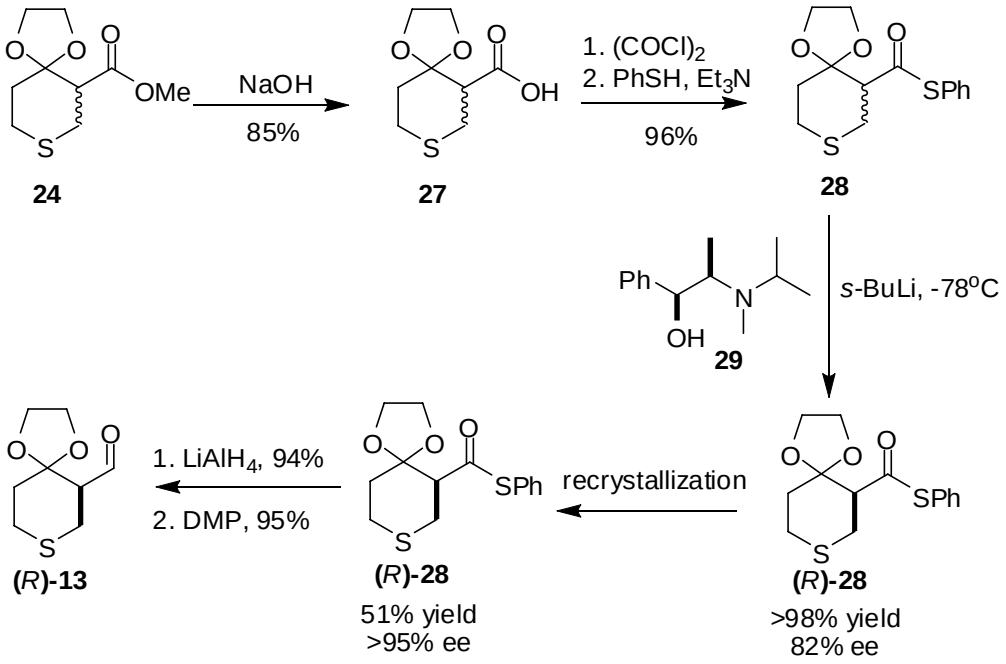
diastereomers of **14** can produce stereochemically diverse tetrapropionate skeletons after desulfurization (Scheme 1.2).



Scheme 1.2: Preparation of the four diastereomeric aldol adducts of **12** and **13**

In Nature, chiral polypropionate natural products are found in enantiopure form. Accordingly, aldol couplings of **12** and enantiopure aldehyde **13** to provide access to chiral nonracemic tetrapropionate synthons **14** were envisaged. Enantioselective protonation[92,93] of the *s*-Buli derived lithium enolate of thioester **28** with *N*-isopropylephedrine **29** gives optically enriched (*R*)-**28** in 51% yield (>95% ee) after recrystallization. Sequential reduction and oxidization of **28** provides enantiomerically enriched (*R*)-**13** (95% ee) (Scheme 1.3).[83] Under conditions identical to those used to generate racemic diastereomers of **14** (Scheme 1.2), enantioenriched diastereomers of **14** can be prepared as required using (*R*)-**13** or its enantiomer.

Although the synthesis of enantiomerically pure **13** (a crucial starting block in the Ward's design) is robust, it nevertheless requires five chemical operations. From a scale-up perspective, developing a shorter and/or a more efficient alternative to prepare enantiopure **13** is highly desired.



Scheme 1.3: Preparation of enantioenriched aldehyde **13**

Unfortunately, attempts to reduce the number of steps required to synthesize enantiomerically enriched **13** via enantioselective protonation were not rewarding. From a synthetic perspective, the goal of the research is to access enantiomerically pure first aldol adducts (**14**) and using enantiopure **13** is only one of the possible options. Consequently, one objective of my thesis research was to design a strategy to generate nonracemic first aldol adducts (**14)** by developing an enantioselective aldol reaction of **12** with (±)-**13** (Figure 1.4). Because aldehyde (±)-**13** is chiral, its use will present a more

challenging and complicated scenario when undergoing an enantioselective process (under a chiral influence) as the possibility of either kinetic resolution or dynamic kinetic resolution (DKR) will arise and therefore careful analysis of literature precedence to tackle the above mentioned objective was required.

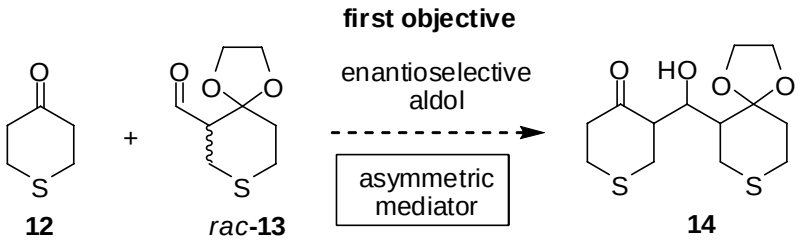
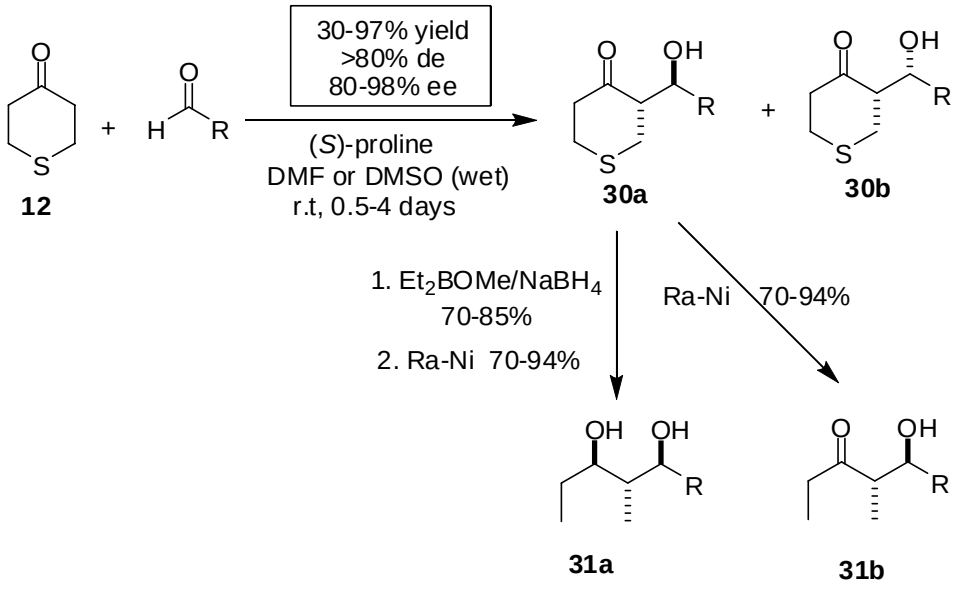


Figure 1.4: Developing an enantioselective aldol reaction of **12** with (±)-**13**

1.2 Organocatalyzed enantioselective direct aldol reactions of ketone 12 with achiral aldehydes

In 2000, the use of the amino acid proline to catalyze highly enantioselective direct intermolecular aldol reactions was disclosed by List, Lerner and Barbas[94] almost 30 years after its intramolecular variant known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction[95,96] was discovered. Subsequently, this disclosure fueled investigations by several other groups towards designing more efficient organocatalysts for the aldol reaction and also elegantly extended this approach to other key carbon-carbon bond forming reactions.[97] Although the stereoselectivities achieved in various organocatalyzed aldol reactions are remarkable, a major limitation of this process is the rather narrow substrate scope. The vast majority of examples to date involve simple achiral reactants. Inspired by these literature findings, we initially investigated the proline-catalyzed enantioselective direct intermolecular aldol reactions of **12** with various achiral aldehydes. Under optimized conditions, *anti* adducts (**30a**) were obtained with high diastereo- and enantioselectivities in moderate to excellent yields (Scheme 1.4). Desulfurization of the aldol adducts provided products (**31**) equivalent to those (directly or indirectly) from an enantioselective aldol reaction of 3-pentanone. This is significant because 3-pentanone is unreactive in proline-catalyzed aldol reactions. An important finding of this study was the beneficial effect of controlled amounts of water to the reactions. The details of this study are presented in ***Chapter 2***.



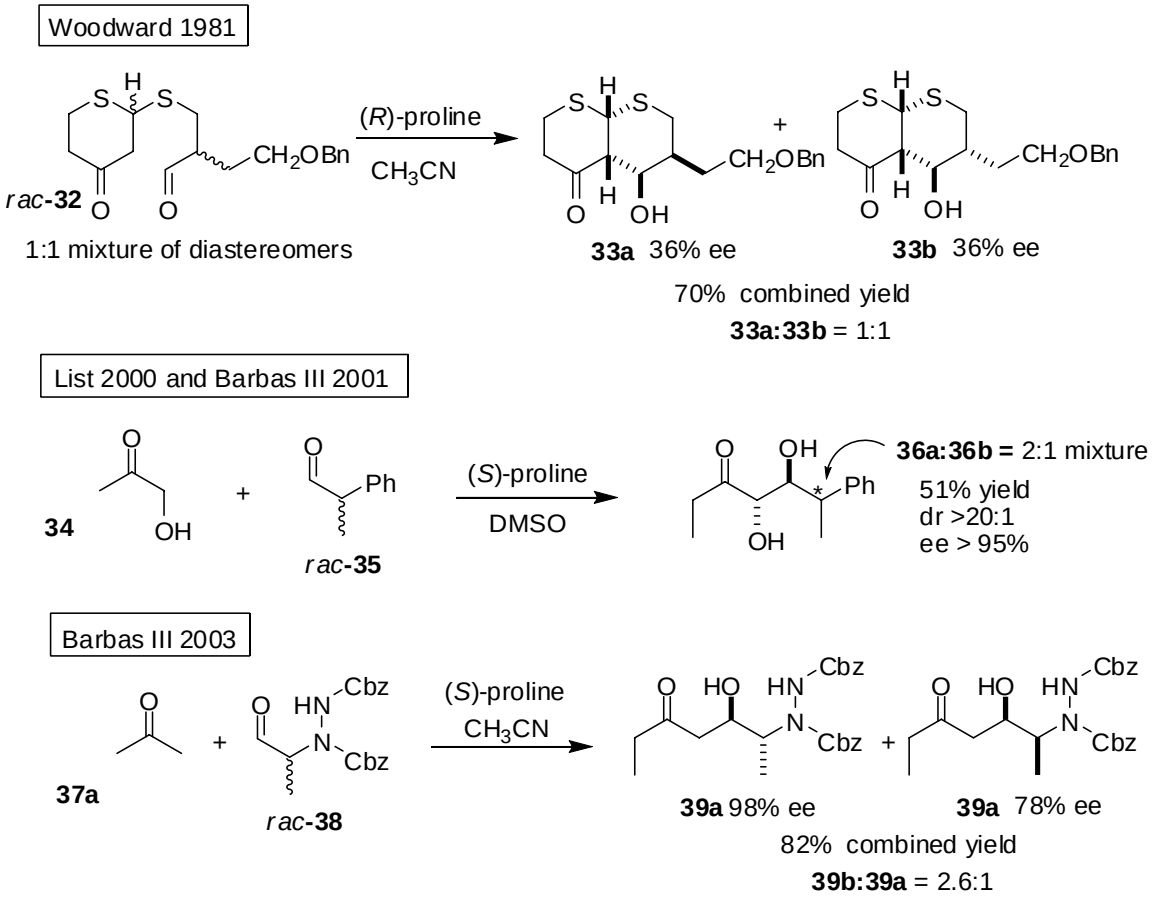
Scheme 1.4: Summary of chapter 2

1.3 Literature review on dynamic kinetic resolution of α-epimerizable aldehydes

The next step was to determine if the conditions developed to effect enantioselective direct aldol reaction of **12** with simple achiral aldehydes could be applied to racemic **13**. It was hoped that the high diastereofacial selectivity previously observed in additions to the aldehyde carbonyl in **13** combined with the high enantioselectivity of the proline-catalyzed reaction would facilitate a kinetic resolution. Although the use of chiral nonracemic aldehydes had been described,[98-111] only scattered examples using racemic aldehydes in dynamic kinetic resolution[112] had been published at the time this work was undertaken.

Kinetic resolution (KR) has found widespread industrial applications but suffers in that only 50% maximum yield can be obtained. Moreover, separation of the desired product from the unreacted enantiomer usually requires chromatography and the enantiopurity of product can be lowered by the extent of conversion. Ideally, these drawbacks can be overcome if the resolution step is combined with an *in situ* racemization/equilibration step where chirally labile substrate enantiomers are in equilibrium thereby inducing dynamic kinetic resolution (DKR). In this case, a maximum theoretical yield of 100% of a single stereoisomer can be achieved and realizing this feature was an important goal of this research. The *in situ* epimerization step can normally be effected either chemically, biocatalytically or even spontaneously. There have been several reviews[113-119] during the past decades highlighting the importance of DKR in asymmetric synthesis.

Interestingly, there has been a limited appreciation of α-epimerizable aldehydes as substrates for dynamic kinetic resolution despite their general tendency towards facile racemization.

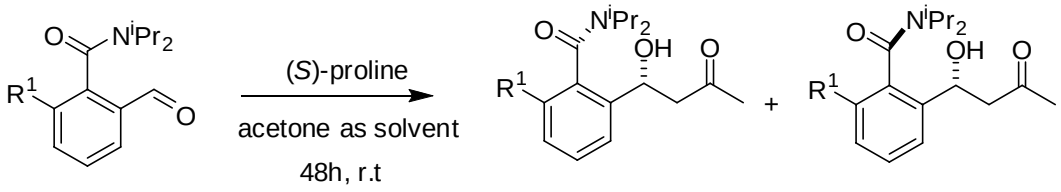


Scheme 1.5: Proline-catalyzed aldol reactions involving DKR

A key step in the Woodward's[90] erythromycin synthesis involved the proline-catalyzed intramolecular aldol cyclization of racemic α-ketoaldehyde **32** (1:1 mixture) with DKR involving (in part) isomerization by enolization to give **33** as a 1:1 mixture in 36% ee. This rather mediocre enantioselectivity of **33** was overcome by a simple recrystallization of an advanced intermediate of **33** to afford enantiomerically pure

compound that was used to fabricate the C-3 to C-15 backbone of erythromycin, thus making the proline-catalyzed aldol reaction very efficient (Scheme 1.5). Other scattered examples involving proline-catalyzed intermolecular aldol reactions with racemic aldehydes occuring with modest levels of enantiotopic group selectivity have been observed by List[120] and Barbas III[121,122] as shown in Scheme 1.5.

Reports of enantioselective synthesis of nonbiaryl atropisomers have been scarce.[123] Atropisomeric aryl carboxamides are chiral due to the orthogonal orientation of aryl and amide groups and readily undergo racemization through rotation about the aryl-carbonyl bond. Walsh et al.[124] recently disclosed the proline catalyzed aldol reaction of atropoisomeric amides **40** with acetone that occurred via dynamic kinetic resolution. As indicated earlier, proline was shown to catalyze efficiently asymmetric aldol reactions[94, 125] and also has a lower affinity for amide carbonyl groups compared to Lewis acids. Proline-catalyzed aldol reactions of acetone with 2-formylaryl carboxamide (**40**) afforded good yields of **41** (80-90%) with reasonable stereoselectivities (dr 2-8:1, 80-100% ee). The presence of substituents at the 6-position (i.e. R^1 group in **40**) were shown to have a pronounced effect in the diastereoselectivity of the reaction (Scheme 1.6 and Table 1.0)



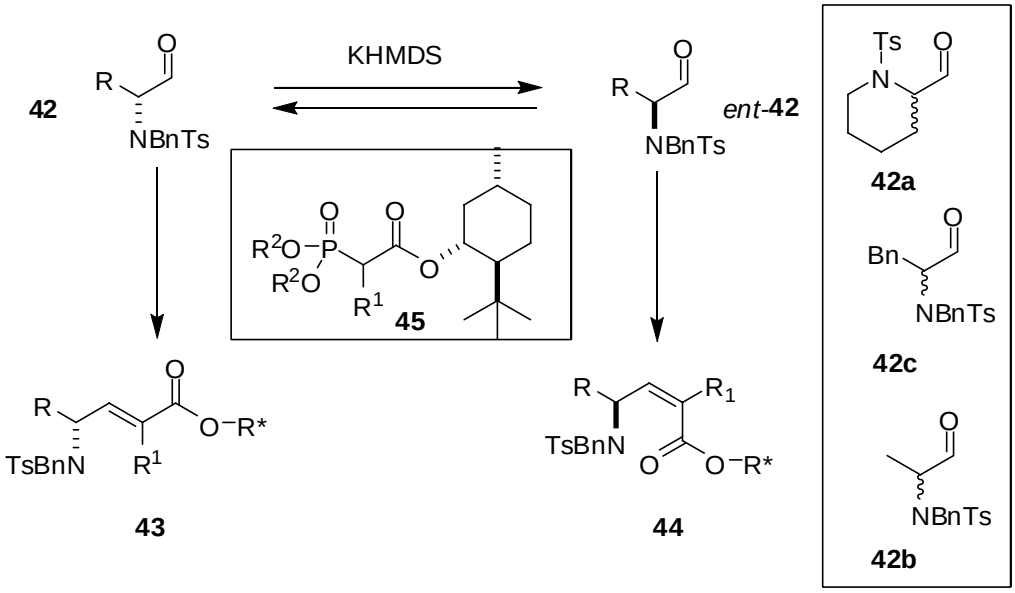
40 **41a** **41b**

Scheme 1.6: Proline-catalyzed aldol reactions of acetone with atropisomeric aryl carboxamides **40**

Table 1.0: Aldol reactions of acetone with racemic atropisomeric aryl carboxamides (**40**) using proline involving DKR

entry	R^1	Yield	dr (**41a:41b**)	ee (**41a**) %
1	NMe_2	92	3.6:1	94
2	CF_3	86	7:1	82
3	TMS	79	8:1	88
4	OMe	80	2.2:1	95
5	Ph	100	3:1	90

Rein and Reiser[126,127] reported the dynamic kinetic resolution α-amino aldehydes in the Horner-Wadworth-Emmons olefination with chiral phosphonate ester **45**. The biological importance of α-amino aldehydes in the synthesis of natural products and their ease for facile racemization make them ideal candidates to be exploited in dynamic kinetic resolution (Scheme 1.7).



Scheme 1.7: Olefination of α-amino aldehydes with chiral phosphonate ester **45**

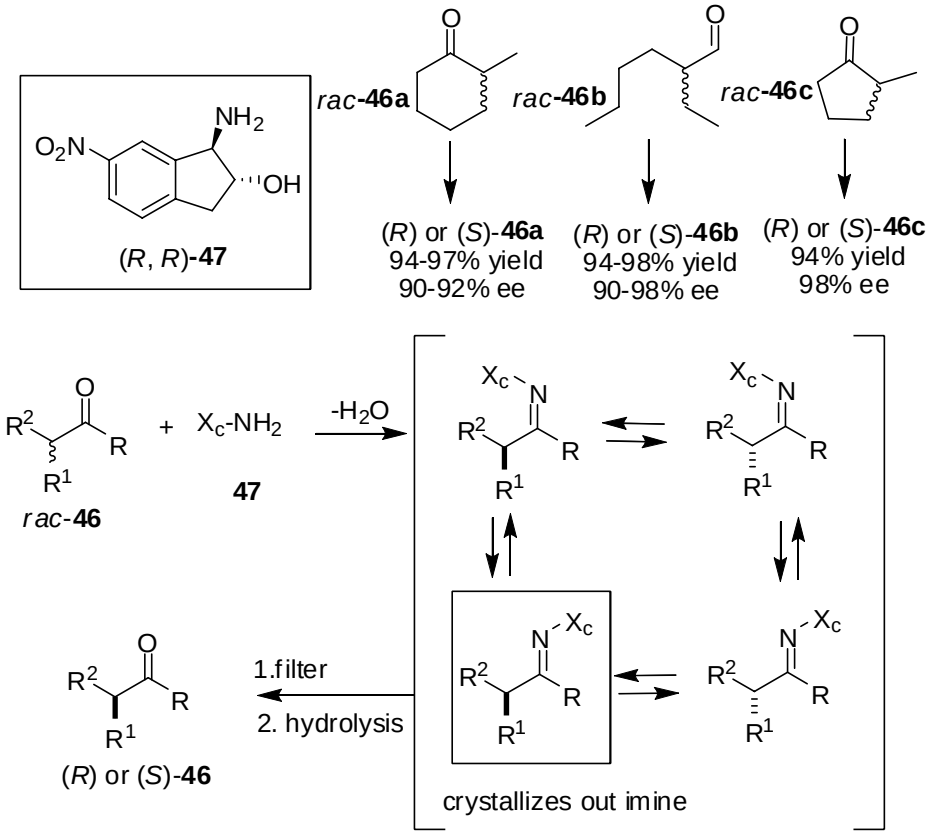
The authors demonstrated that reaction of aldehydes **42** with chiral phosphonate **45** required addition of a slight excess of base (KHMDS) to facilitate racemization of **42** in order to allow dynamic kinetic resolution to operate and which also improved the diastereoselectivity of the reaction. The reactions performed well with addition of only 1.3-1.4 equivalents of the aldehyde substrate and this route was amenable to prepare both *di* and *tri*-substituted alkenes. Furthermore, the *E*/*Z* selectivity of the olefination was easily modulated by the nature of the phosphonate ester (Table 1.1).

Table 1.1: Olefination of racemic aldehydes **42** with chiral phosphonate ester **45**

entry	aldehyde	R^1	R^2	KHMDS (eq)	Yield (%) (major isomer)	dr
1	**42a**	H	$-C_2H_5$	1.0	96(*E*)	81:19
2	**42a**	H	$-C(CH_3)_2$	1.0	94(*E*)	77:23
3	**42a**	H	$-CH_2CF_3$	1.0	62(*Z*)	80:20
4	**42a**	H	$-CH_2CF_3$	1.2	64(*Z*)	94:6
5	**42a**	$-CH_3$	$-CH_2CF_3$	1.0	69(*Z*)	95:5
6	**42b**	H	$-CH_2CF_3$	1.0	86(*Z*)	52:48
7	**42b**	H	$-CH_2CF_3$	1.2	81(*Z*)	52:48
8	**42c**	H	$-CH_2CF_3$	1.0	69 (*Z*)	90:10
9	**42c**	H	$-CH_2CF_3$	1.2	77(*Z*)	95:5

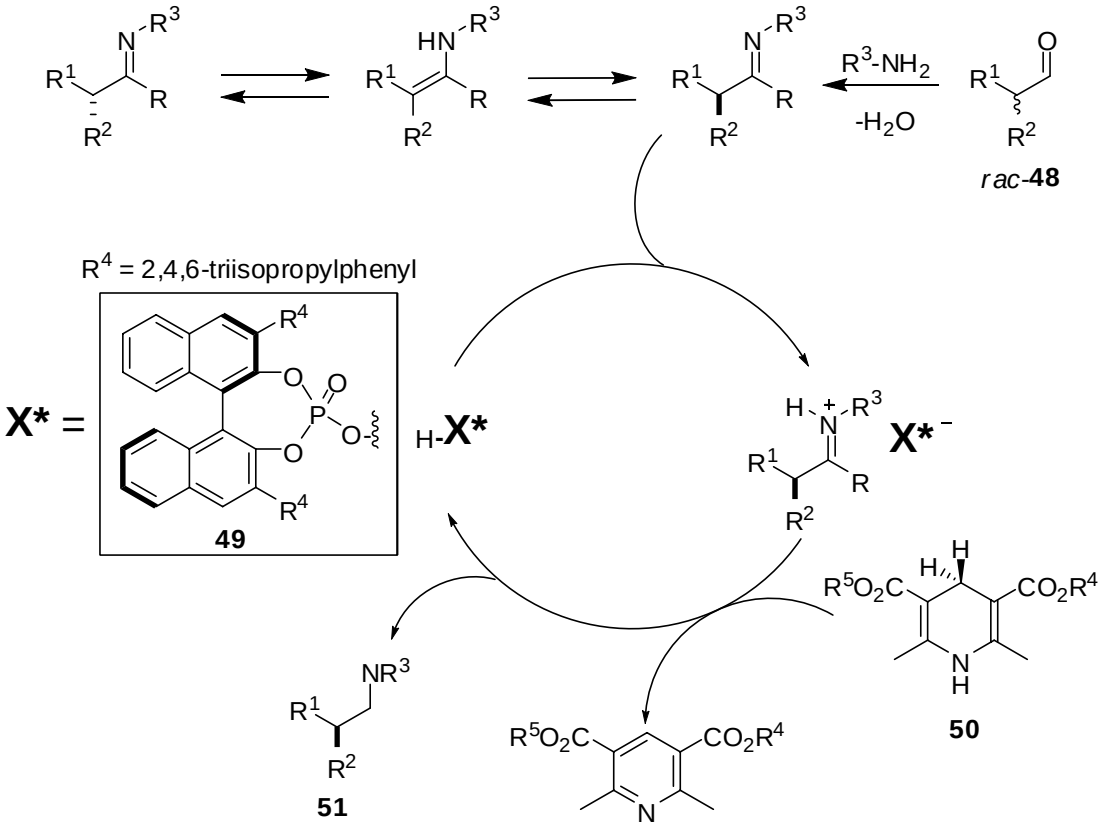
In a collaborative work, Kosmrlj and coworkers[128] recently demonstrated a remarkably simple and efficient process of deracemizing α-substituted ketones and aldehydes via crystallization-induced dynamic resolution (CIDR) of imines. The process involves formation of a crystalline imine derived from reactions of epimerizable ketones/aldehydes with a chiral nonracemic amine. Selective crystallization of one diastereomer of the imine (CIDR) and subsequent hydrolysis of the crystalline diastereomer provided enantioenriched ketone or aldehyde (Scheme 1.8). The

diastereoselectivity of the imines (*E*/*Z* mixture) based on the epimerizable stereogenic center observed for the aldimines (>95% *E* selectivity) were higher than the ketimines (1:1). The reaction performed better in protic solvents (methanol and ethanol) than aprotic solvents. Equilibration of the imines from **46a** in methanol afforded enantioenriched ketone (*R*) or (*S*)-**46a** in 94-97% yield (90-92% ee) after biphasic hydrolysis using hexane/acetic acid-sodium acetate buffer. Deracemization of aldehyde **46b** via CIDR of its aldimines gave enantiomerically enriched aldehyde *ent*-**46b** in 98% ee and 94% yield after hydrolysis with $CuCl_2$.



Scheme 1.8: CIDR of racemic substrates

The enantioselective reduction or hydrogenation of α-branched chiral aldehydes or their derived imines present a major challenge to synthetic chemists because, in contrast to ketones, a new stereogenic center is not generated. Recently, List et al.[129] reported the catalytic asymmetric reductive amination of α-epimerizable aldehydes via dynamic kinetic resolution. The use of Hantzsch ester[130] **50** acting as the hydride source with the chiral Bronsted acid catalyst 3,3'-bis (2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate **49** (TRIP)[131,132] has been previously applied in the organocatalytic enantioselective reduction of ketimines[133,134] and subsequently was extended to aldimines (Scheme 1.9).



Scheme 1.9: Reductive amination of α-substituted aldehydes via DKR

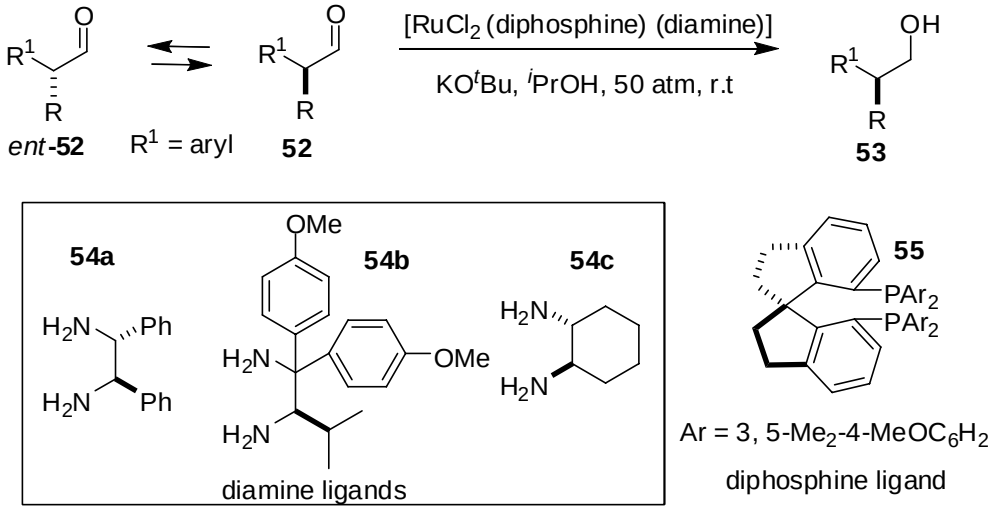
The α-substituted aldehydes undergo facile racemization via an imine/enamine tautomerization in the presence of an amine and the acid catalyst and reduction of one of the imine enantiomers is faster than the other under the chiral influence of **49** (10 mol%), resulting in enantioenriched amines. In general, this approach was amenable to a wide range of α-substituted aldehydes producing high yields of amines with excellent enantioselectivities. Electron rich and deficient aromatic aldehydes performed extremely well and gave high yields (80-96%) and high ees (>90%) but the results from aliphatic aldehydes were more modest (Table 1.2).

Table 1.2: Scope of the catalytic asymmetric reductive amination of **48** with **50**

entry	R^1	R^2	R^3	Yield (**51**)	ee (%) (**51**)
1	Ph	Me	PMP	87	96
2	Ph	Me	Ph	78	94
3	Ph	Me	4-$CF_3C_6H_4$	54	90
4	4-$CH_3C_6H_4$	Me	PMP	86	94
5	2-FC_6H_4	Me	PMP	84	94
6	2-BrC_6H_4	Me	PMP	92	94
7	CF_3	Me	PMP	40	80
8	*n*-Pr	Me	PMP	39	40

The preparation of optically active primary alcohols by Ru-catalyzed asymmetric hydrogenation of racemic α-substituted aldehydes via dynamic kinetic resolution was recently reported by Zhou and coworkers.[135] The asymmetric hydrogenation of a variety of racemic α-arylaldehydes with a catalyst derived from RuCl, **54** and **55** (0.2-0.02 mol%) were successfully achieved (100% conversion obtained in all cases studied) with little influence of the electronic properties exerted by the substituents of aromatic ring observed. The presence of bulky alkyl groups at the α-position of the aldehydes was

found to be crucial to obtain high enantioselectivity in the hydrogenation process (Table 1.3).



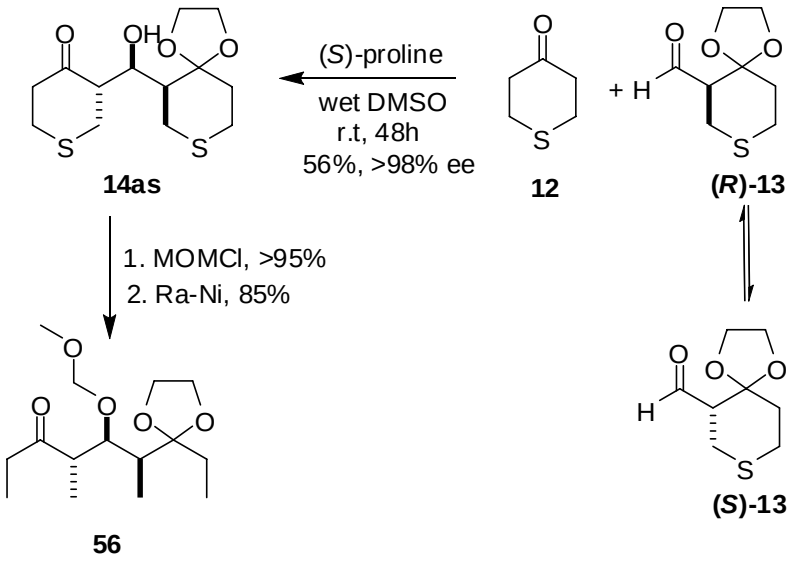
Scheme 1.10: Asymmetric hydrogenation of α-substituted aldehydes via DKR

Table 1.3: Asymmetric hydrogenation of arylaldehydes **52** with [$RuCl_2$(**55**)(**54c**)]

entry	R^1	R	ee (%) (**53**)
1	Ph	Me	78
2	Ph	Et	86
3	Ph	*i*-Pr	96
4	Ph	*c*-Pent	92
5	Ph	*c*-Hex	92
6	2-MeC_6H_4	*i*-Pr	95
7	4-$MeOC_6H_4$	*i*-Pr	84
8	4-ClC_6H_4	*i*-Pr	90

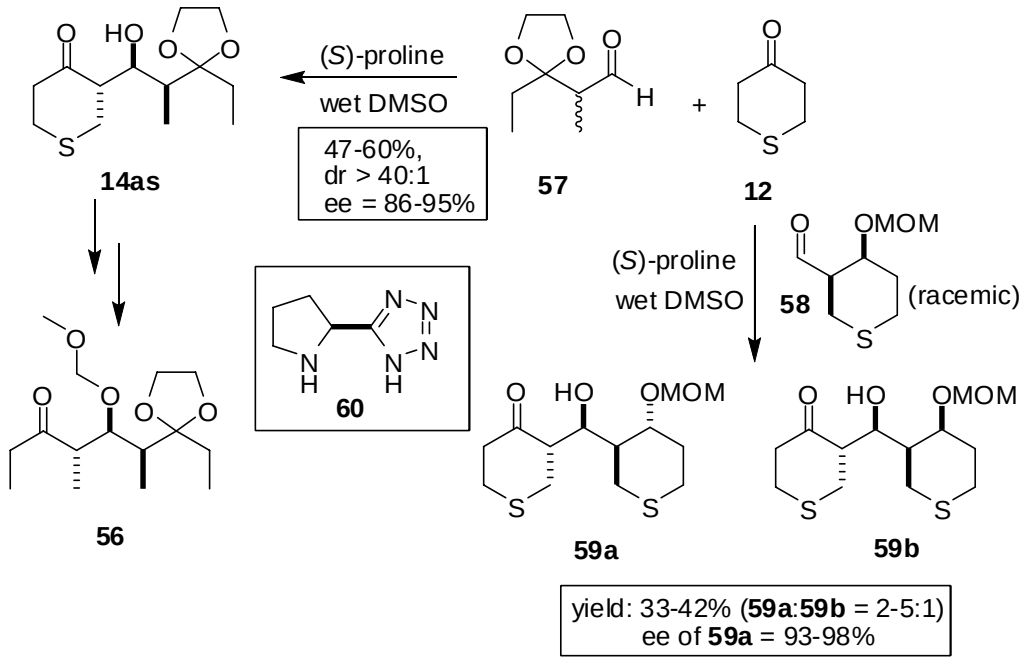
1.4 Organocatalyzed enantioselective aldol reaction of 12 with chiral aldehydes via DKR

Gratifyingly, the proline-catalyzed aldol reaction of **12** with (±)-**13** was also highly diastereo- and enantioselective and proceeded via DKR providing access to enantioenriched **14as** (>98% ee) without the requirement of enantiomerically pure **13** (Scheme 1.11). As in the previous study, the presence of water is highly beneficial. The reaction works even better using the proline-derived catalyst 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole (**60**) (Scheme 1.12). Moreover, because **14as** is readily isomerized to **14ss**, this diastereomer is also available via the process. A detailed description of this research is presented in ***Chapter 3*** (Scheme 1.11).



Scheme 1.11: Summary of chapter 3

The scope and limitations of this enantioselective direct aldol reaction with other cyclic and acyclic chiral aldehydes were investigated (Scheme 1.12). These results are described in ***Chapter 4*** (Scheme 1.12).



Scheme 1.12: Summary of chapter 4

With a robust protocol available to generate enantiopure tetrapropionate synthons **14as** and **14ss**, my second objective was to demonstrate their synthetic utility in natural product synthesis. Serricornin (**61**) was the initial synthetic target (Figure 1.5).

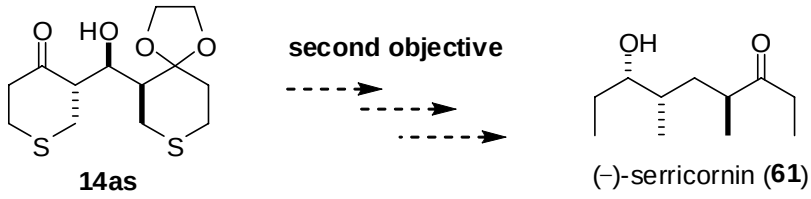


Figure 1.5: Synthesis of serricornin (**61**)

1.5 Literature review on serricornin chemistry

1.5.1 Isolation and structure determination

Serricornin (**61**) is the sex pheromone of the female cigarette beetle (*Lasioderma serricorne* F.), a serious pest of cured tobacco leaves and various dried foodstuffs. Pheromones are naturally occurring substances secreted by living organisms to convey specific signals to other individuals of the same species and are referred to as semiochemicals.[136,137] Pheromones are generally species specific and are attracting commercial interest nowadays because they offer an environmentally friendly alternative to pesticides which are toxic. They are often isolated as volatile oils in minute quantities and determination of their absolute stereochemistries by conventional spectral analysis can be tedious. Consequently, enantioselective syntheses are often required for structure confirmation.

During the course of chemical studies, Chuman and coworkers[138] isolated the sex pheromone (–)-serricornin (**61**) produced by the female cigarette beetle.[139] The two dimensional structure of (–)-serricornin (**61**) was successfully assigned by the original authors to be 7-hydroxy-4,6-dimethylnonanone based on NMR spectral evidence.[138] The relative and absolute configurations were later established from a series of synthetic studies that produced all eight of the possible stereoisomers of **61** and serricornin was consequently determined to be the (4*S*,6*S*,7*S*)-isomer by comparison to the original data.[140-142] Pheromone **61** exists as an equilibrium mixture of the ketol and cyclic hemiacetal forms;[143] it is often characterized as the corresponding acetate **63** (Figure 1.6).

Stereochemistry has a profound effect in pheromone recognition and biological activities. Usually, only one enantiomer of the pheromone is bioactive and the other

enantiomer is not or inhibits the action of the pheromone. Sex pheromone **61** elicits mating behaviors and is commercially available as cigarette beetle traps. The attractant activity of **61** is at least 10^3 greater than any of the other stereoisomers, and the (4*S*,6*S*,7*R*)-diastereomer inhibits the activity of **61** while the (4*R*,6*R*,7*R*)-enantiomer is not bioactive.[144,145]

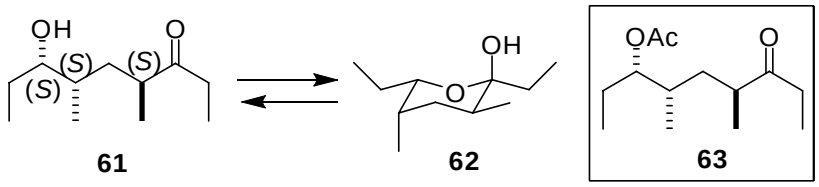
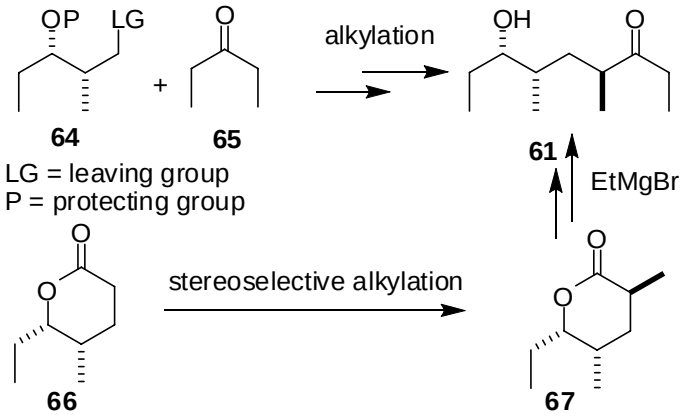


Figure 1.6: Acyclic and cyclic forms of (−)-serricornin

The potential commercial value of **61** has attracted lots of synthetic considerations from the scientific community and to date numerous syntheses of **61** have been reported in the literature. The most common strategies employed involve either Grignard addition of EtMgBr to the lactone **67** or alkylation of 3-pentanone (**65)** with a suitable derivatives of **64** (Scheme 1.13). Selected approaches are documented in the following sections.



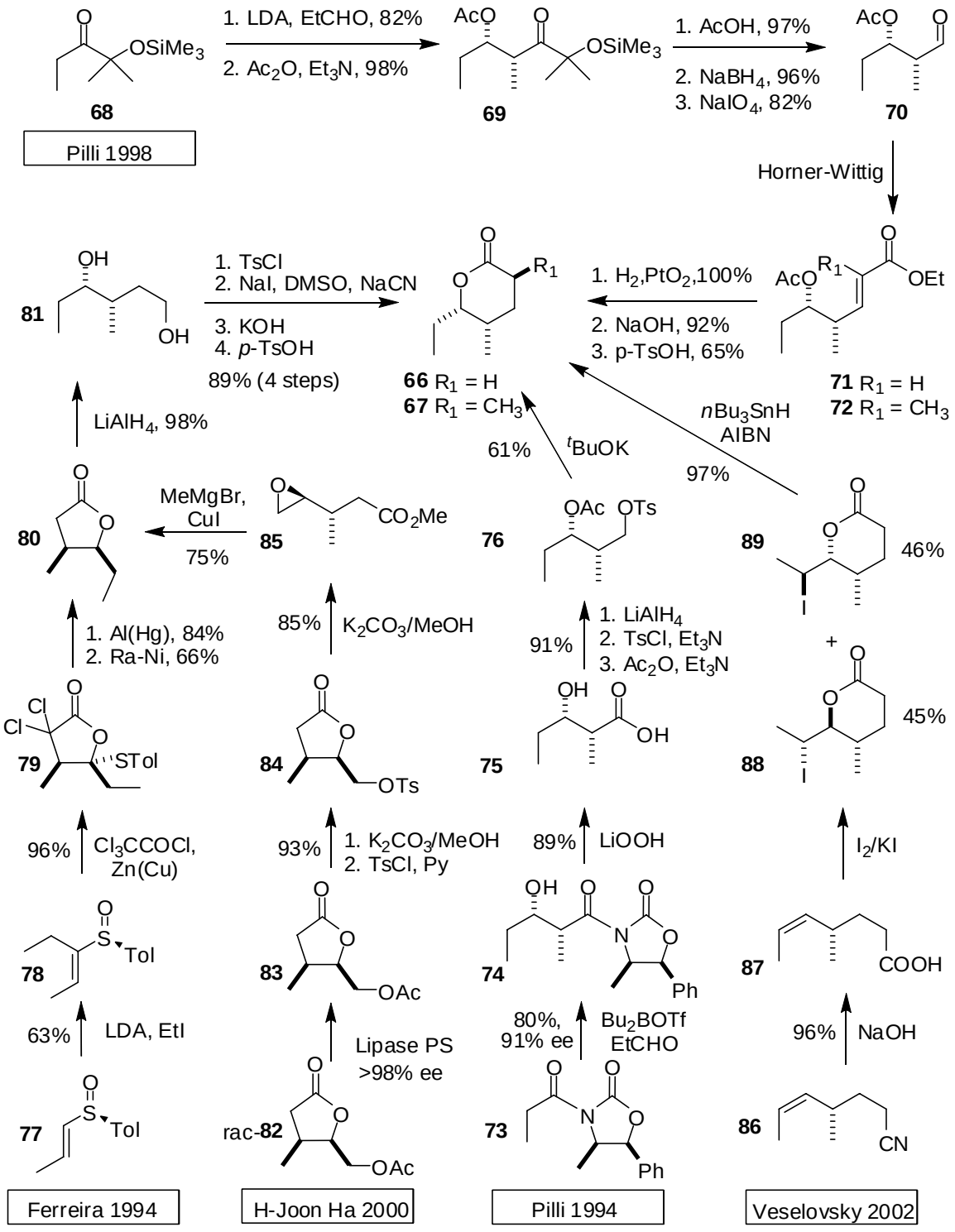
Scheme 1.13: Common strategies employed towards **61**

1.5.2 Synthesis of serricornin (61) via Grignard addition to lactone 67

The majority of the syntheses of **61** involved stereoselective alkylation of lactone **66** followed by EtMgBr addition. Lactone **66** was synthesized using various methodologies from either racemic or nonracemic starting materials as shown in Scheme 1.14. This section summarizes selected syntheses of **66** or **67** that were subsequently converted to **61** or reported as formal synthesis of **61**.

Pilli et al.[146] reported the synthesis of (±)-**61** based on stereoselective addition of the preformed lithium enolate of ketone **68** to propanal followed by acetylation of the resulting β-hydroxy ketone to obtain **69** in high yield and excellent diastereoselectivity (>98% ds). After desilylation of **69** under acidic conditions, the carbonyl group was reduced to the corresponding diol that was uneventfully cleaved to β-acetoxy aldehyde **70** on treatment with $NaIO_4$. Horner-Wittig homologation of aldehyde **70** to **71** or **72** was unselective (*E*:*Z* = 1:1). Nevertheless, **71** and **72** were converted to lactones **66** and **67** respectively after a sequence of hydrogenation of the olefin moiety, hydrolysis of the esters and lactonization promoted by *p*-TsOH. Lactone **67** was eventually converted to (±)-**61** by EtMgBr addition (9 steps in 21% overall yield) (Scheme 1.14).

Pilli[147] also reported the formal synthesis of (–)-**61** utilizing Evan's chiral auxillary. Aldol reaction of the boron enolate of *N*-propionyl oxazolidinone **73** with propanal afforded adduct **74** as the only diastereomer in 80% yield. The remaining steps involved basic hydrolysis of the chiral auxillary, protecting group manipulations, and intramolecular cyclization via nucleophillic attack of the preformed enolate of the acetyl group to secure lactone **66** in 22% overall yield over 6 steps from **73**.



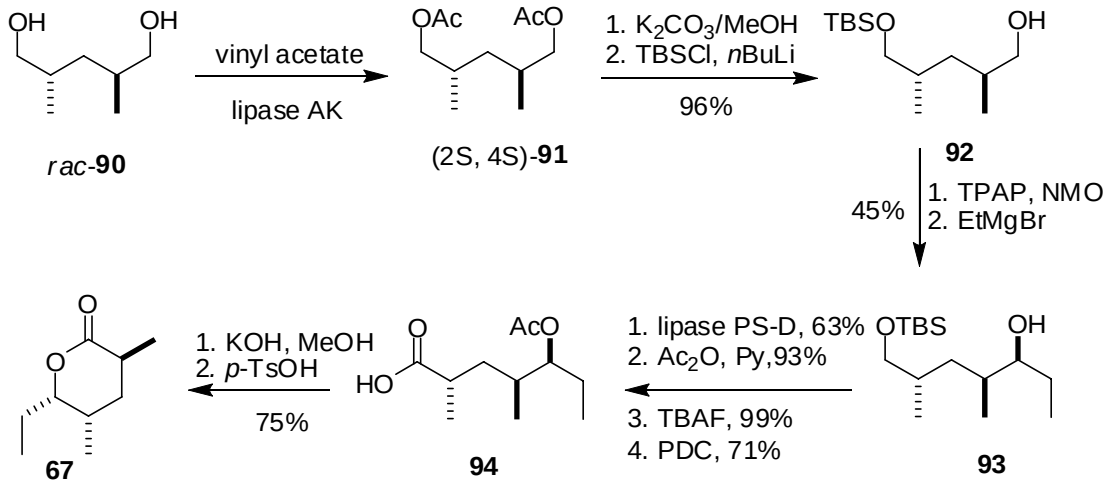
Scheme 1.14: Synthesis of lactones **66** and/or **67**

Ferreira's synthesis[148] started with the alkylation of the LDA-derived sulfoxide anion of optically pure **77** with ethyl iodide to give *E*-disubstituted vinyl sulfoxide **78** in moderate yield. Treatment of **78** with a large excess of dichloroketene afforded a single diastereomer of adduct **79**. Reductive removal of chlorine atoms in **79** was achieved using aluminum amalgam and subsequent Raney nickel desulfurization gave **80** with retention of configuration. Lactone **80** was reduced to diol **81** and the primary alcohol was selectively tosylated and then displaced with sodium cyanide. Hydrolysis of the resulting cyanide and subsequent lactonization gave desired lactone **66** (Scheme 1.14).

The formal synthesis of **61** by H-Joon Ha[149] is based on a lipase mediated hydrolysis of racemic lactone **82** to provide enantiomerically pure acetate **83**. Deacetylation of **83** was followed by tosylation to furnish **84** which upon treatment with K_2CO_3 in methanol gave epoxide **85** in 85% yield. Regioselective methylation of **85** was performed with MeMgBr in the presence of catalytic amount of CuI that afforded lactone **80** in 75% yield (Scheme 1.14).

Veselovsky's synthesis[150] of serricornin (**61)** involved hydrolysis of enantiomerically pure nitrile **86** to the corresponding heptenoic acid **87**. Unfortunately, iodolactonization of carboxylic acid **87** with either I_2/KI or NIS was not selective providing chromatographically separable lactones **88** and **89** in nearly the same amounts. Finally, removal of iodide in **89** by treatment with nBu$_3$SnH furnished **66** in 97% yield (Scheme 1.14).

Asymmetric acetylation of racemic C_2 symmetric diol **90** was resolved to diacetate **91** with vinyl acetate in the presence of lipase AK to give **91** with high ee. Compound **91** was treated with K_2CO_3 in methanol followed by monosilylation of the resulting diol to afford **92** in 96% yield over 2 steps. TPAP oxidation of the primary alcohol in **92** furnished the corresponding aldehyde which was subjected without purification to EtMgBr addition resulting in a 2:1 mixture of (2*S*,4*S*,5*S*)-**93** and its (2*S*,4*S*,5*R*)-isomer. Interestingly, the desired (2*S*,4*S*,5*S*) diastereomer **93** was separated from the 2:1 mixture by treatment with vinyl acetate and lipase PS-D and was subjected sequentially to acetylation, silyl deprotection and PDC oxidation to give the acetoxy acid **94**. Acetate hydrolysis and acid promoted lactonization afforded **67**, a known precursor of serricornin (**61**) (Scheme 1.15).



Scheme 1.15: Mori's synthesis of lactone **67**

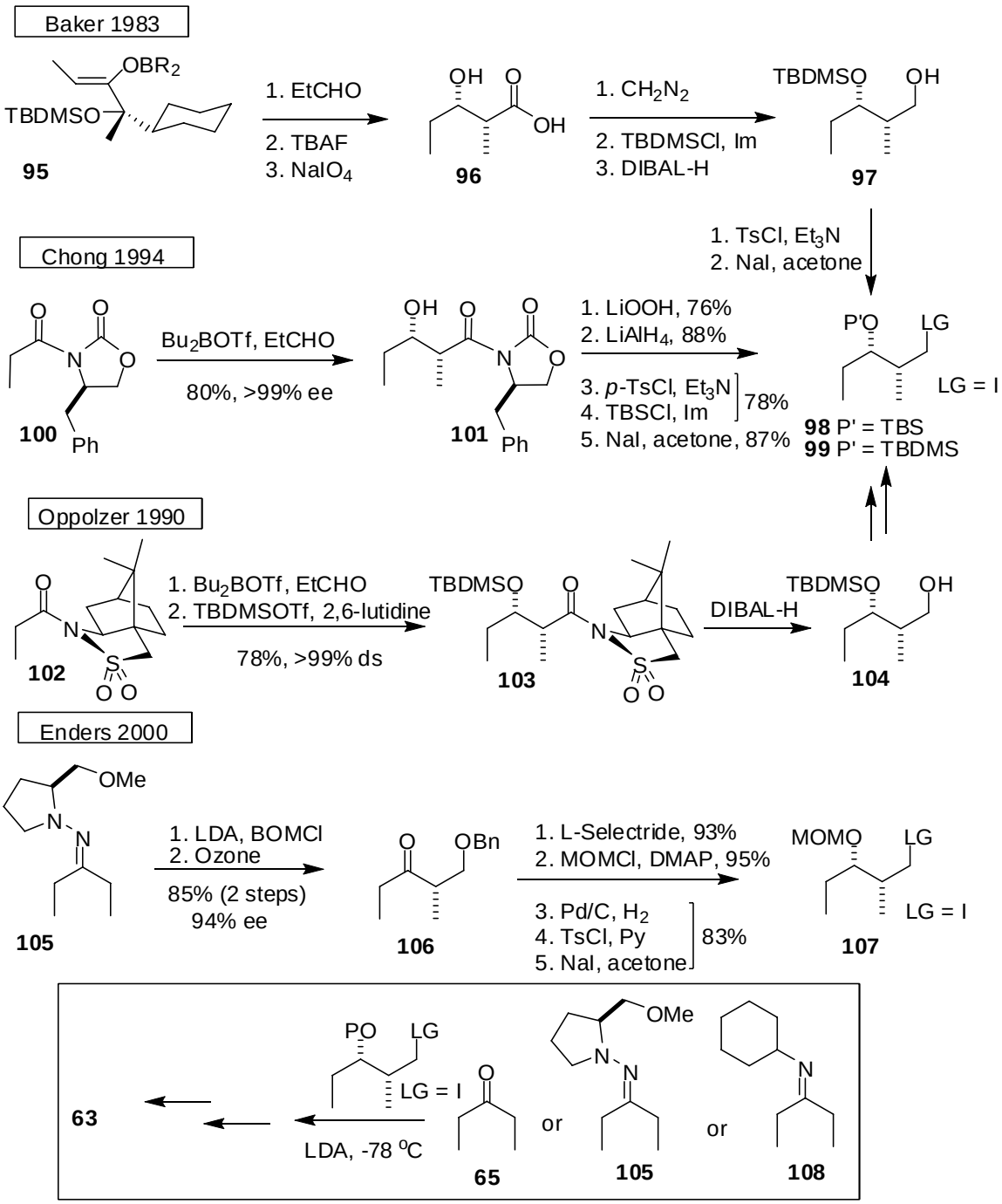
1.5.3 Synthesis of serricornin (61) via alkylation of 3-pentanone with suitable electrophiles (64)

An important number of syntheses of serricornin (**61**) were achieved by alkylation of 3-pentanone with suitable electrophiles. Precursors such as **98** and **99** were synthesized by exploitation of different methodologies by various research groups where the total or formal synthesis of **61** was reported as shown in Scheme 1.16.

Baker's[151] approach began with a diastereoselective aldol reaction of chiral boron enolate **95** with propanal to afford *syn* β-hydroxy-carboxylic acid **96** as the only diastereomer in 70% yield after TBAF removal of the silyl group and oxidative cleavage of the chiral auxillary. Esterification of **96** was followed by TBDMS protection of the alcohol and DIBAL-H reduction to provide alcohol **97** that was tosylated and converted to iodide **99** in 50% overall yield starting from **95**. Finally, (–)-serricornin acetate (**63)** was obtained in 30% via alkylation of the Li-enolate of 3-pentanone (**65**) with **99** (not stereoselective) followed by desilylation and acetylation (Scheme 1.16).

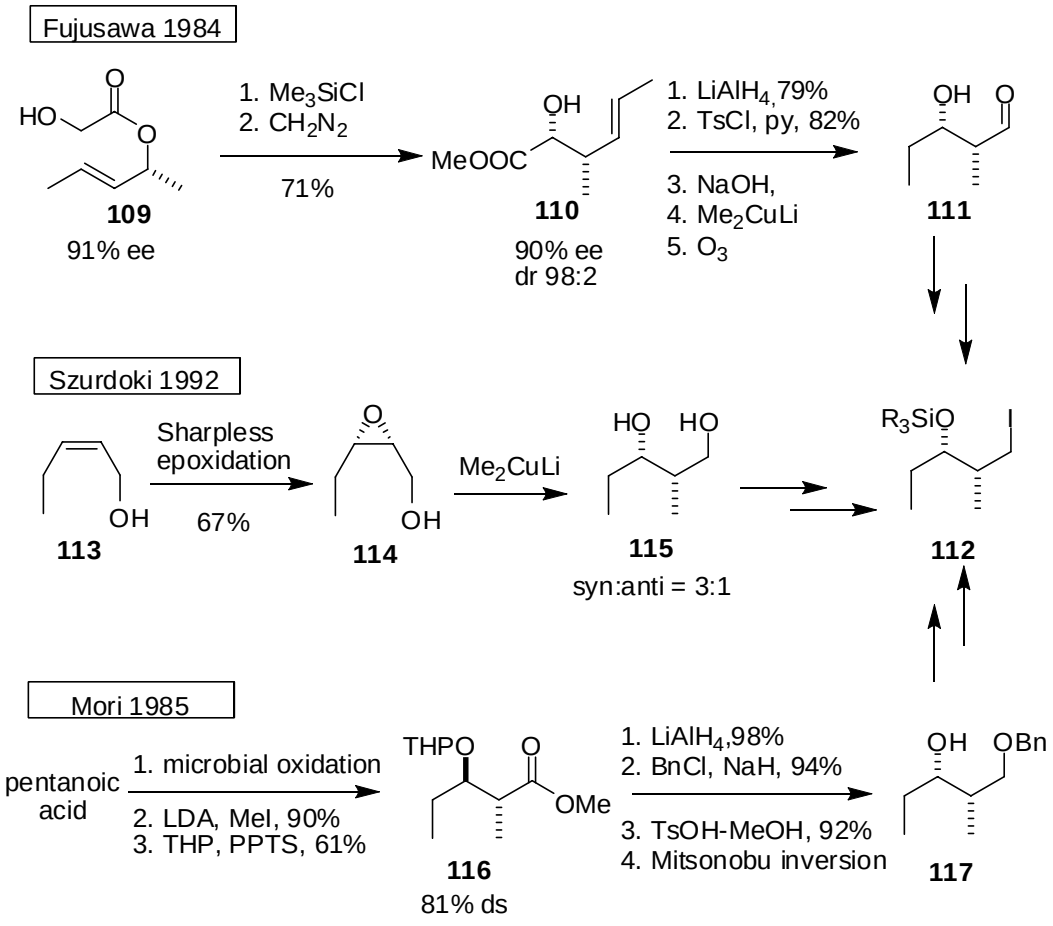
Chong's[152] synthesis employed aldol coupling of the boron enolate of oxazolidinone **100** with propanal to provide crystalline aldol adduct **101** in 80% yield and excellent diastereoselectivity. Sequential hydrolysis, reduction and functional group manipulations gave iodide **98** which was used to alkylate either **65** or its derived hydrazone **108** (not stereoselective) to furnish **63** in 33% yield over 8 steps from oxazolidinone **100** after TBS deprotection and acetylation. Similarly, Oppolzer's[153] strategy was based on aldol reaction of chiral *N*-acylsultam **102** with propanal to give the *syn* adduct **103** (sole diastereomer) in crystalline form after TBDMS protection. DIBAL-

H reduction of **103** afforded the known alcohol **104** that was previously utilized[154] to synthesize **61** (Scheme 1.16).



Scheme 1.16: Alkylating precursors for the synthesis of **61**

Enders[155] utilized the chiral SAMP-hydrazone **105** which was prepared from **65** in quantitative yield. Reaction of hydrazone **105** with LDA/BOMCl and ozonolysis of the resulting substituted hydrazone provided anticipated ketone **106**. Selective reduction of **106** using L-Selectride was followed by a sequence of MOM protection, debenzylation, tosylation, and iodination to give iodide **107** in excellent yield. Finally, **61** was secured by a stereoselective alkylation of hydrazone **105** with **108** using LDA followed by ozonolytic cleavage and MOM protecting group.

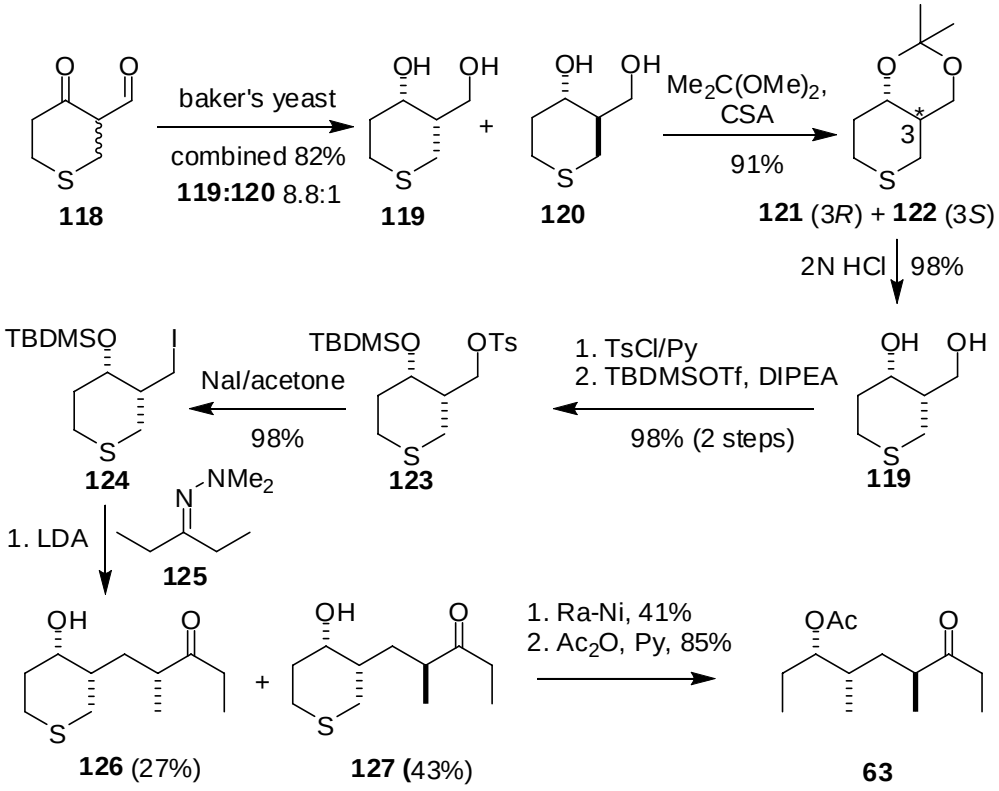


Scheme 1.17: Precursors for the synthesis of **61**

Other approaches towards synthesizing convenient derivatives of **64** for use in alkylation of **65** or its hydrazone derivatives to access serricornin (**61**) include as pivotal steps: a) Claisen rearrangement of (1*R*)-methyl-(2*E*)-butenyl hydroxyacetate (Fujisawa 1984)[156] b) microbial oxidation of pentanoic acid followed by methylation (Mori 1985)[157] and, c) Sharpless epoxidation of (*Z*)-2-pentenol (**113**) followed by dimethyl cuprate regioselective epoxide ring opening (Szurdoki 1992)[158] are outlined in Scheme 1.17.

1.5.4 Other syntheses of serricornin (**61**)

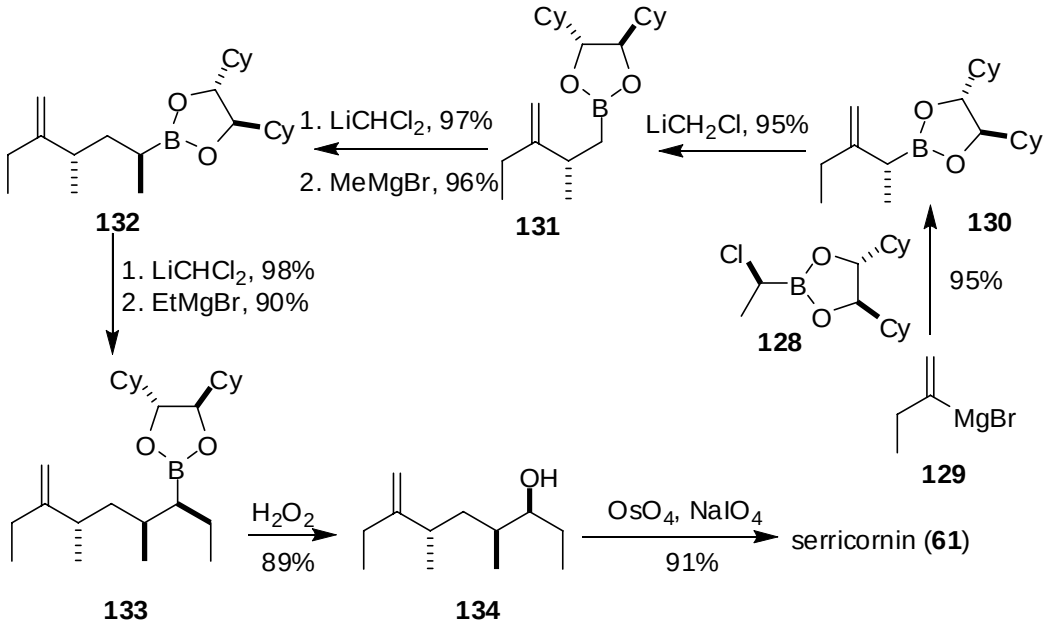
Baker's yeast reduction[159-164] of β-keto esters and aldehydes is an attractive, environmentally benign and inexpensive method for the efficient preparation of enantiomerically pure alcohols. Shimizu et al.[165] successfully demonstrated high stereoselectivities in baker's yeast reductions of a series of β-keto-aldehydes by using sulfur compounds as additives. Enantioselective reduction of β-keto-aldehyde **118** gave diols **119** and **120** (that were separable as their acetonides) with good diastereoselectivity and excellent ee (>99%). Selective tosylation of the primary alcohol **121** and subsequent TBDMS protection of the secondary alcohol provided **123** that was in turn converted to iodide **124** in 98% yield over 2 steps.



Scheme 1.18: Shimizu's synthesis of **61**

Diastereomers **126** and **127** (chromatographically separable) were obtained via alkylation of hydrazone **125** with **124** followed by TBDMS deprotection of the corresponding adduct. Finally, desulfurization and acetylation of the desired compound **127** furnished **63** (Scheme 1.18).

Matteson's[166] synthetic approach to serricornin (**61**) involved reaction of boron reagent **128** with 1-ethylethenylmagnesium bromide **129** to provide **130** in 95% yield which was subsequently converted to boronate **131** by reaction with $LiCH_2Cl$.

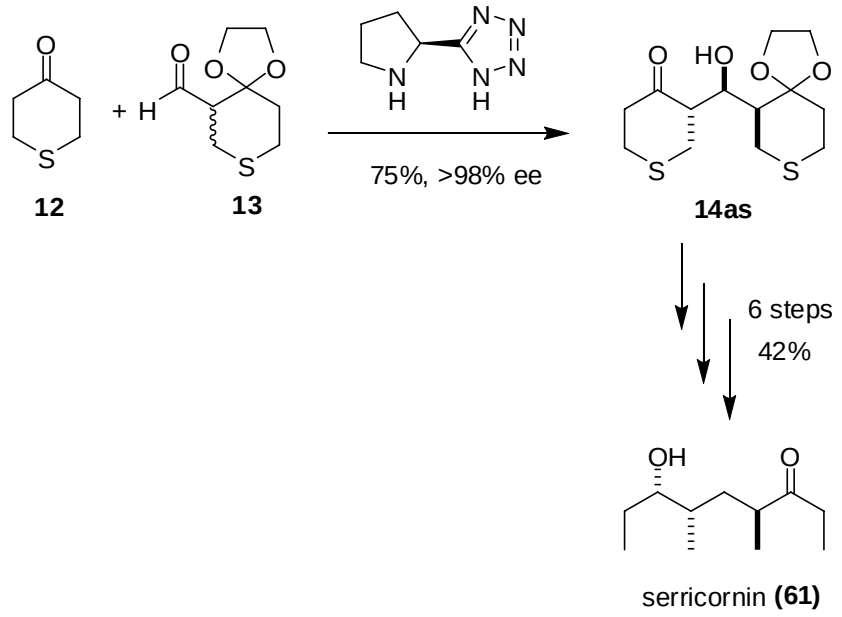


Scheme 1.19: Matteson's synthesis of **61**

Homologation of **131** and **132** were both achieved in a similar fashion by sequential treatment of the corresponding boronate with $LiCHCl_2$ followed by introduction of an alkyl group using the Grignard protocol. This sequential chain extension elegantly installed the desired three dimensional skeleton of **61** in excellent yields. Oxidative

removal of the boron in **133** by treatment with H_2O_2 was followed by conventional cleavage of the olefin in product **134** using OsO_4 and $NaIO_4$ to secure serricornin (**61**) in 33-39% overall yield over 9 steps starting from Grignard reagent **128** (Scheme 1.19).

An efficient synthesis of **61** from **14as** via the thiopyran route to polypropionates is documented in ***Chapter 5*** (Scheme 1.20). In principle, this route can be adapted to provide all possible isomers of **61**.



Scheme 1.20: Summary of chapter 5

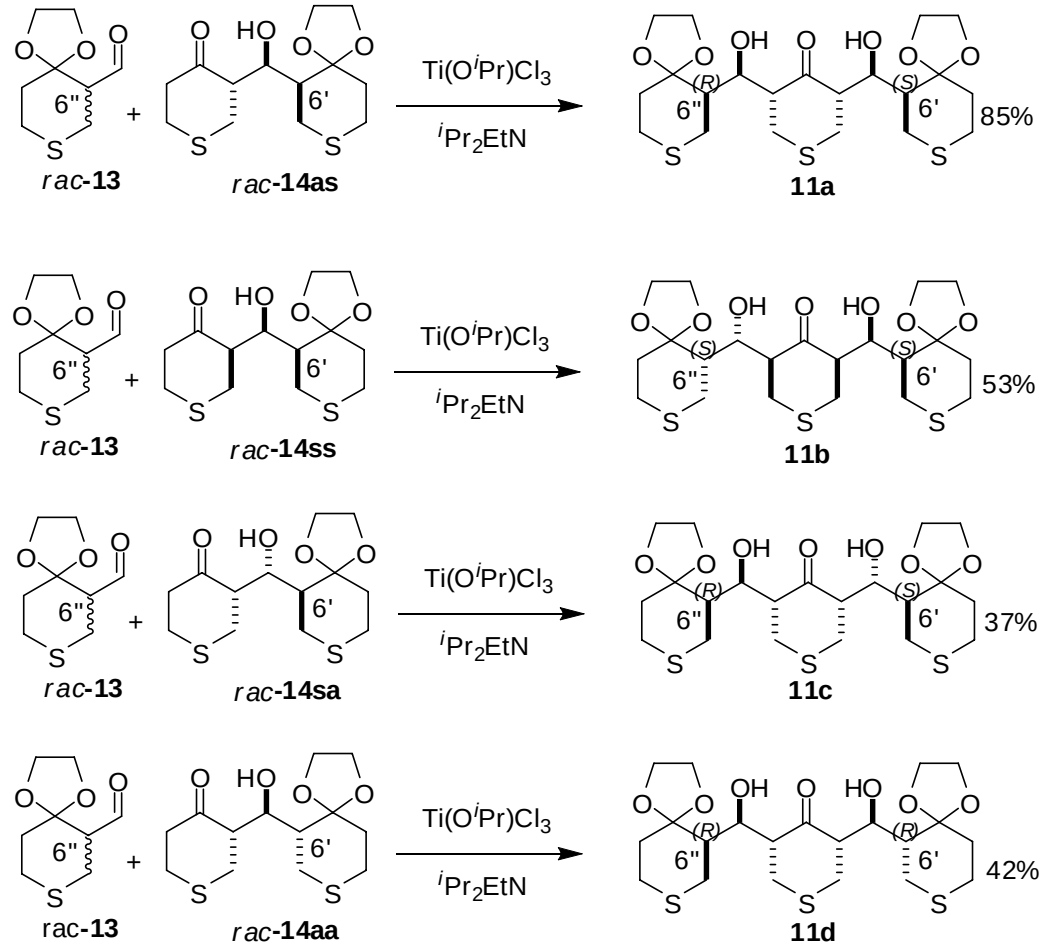
Having successfully demonstrated the synthetic utility of **14as** as a tetrapropionate synthon towards the synthesis of serricornin (**61**) (Scheme 1.20), the next objective was to apply synthetically useful hexapropionate synthons **11** (Figure 1.2) obtainable via aldol reactions of first aldol adducts **14** with aldehyde **13** towards hexapropionate based natural products.

1.6 The thiopyran route to polypropionates: hexapropionate synthons[78,87]

The aldol reaction of **14** and **13** can generate up to 20 diastereomers of **11**, four of which are *meso* and 16 are chiral. Aldol coupling of any diastereomer of (±)-**14** (or derivatives) with (±)-1**3** can generate up to eight possible diastereomeric adducts of **11**, four each from *like* and *unlike*[†] combinations of the reactant enantiomers. Union of racemic fragments is complicated by double stereodifferentiation (DS)[74,167] but careful analysis of the distribution of the products interestingly reveals the complete stereoselectivity profile of such reactions. That is, the diastereoselectivities (i.e. double stereodifferentiation, DS) and relative rates (i.e. mutual kinetic enantioselection, MKE)[168,169] of the *like* and *unlike* combinations of the reactants (i.e. matched or mismatched) are simultaneously determined and can reveal strategies for the exploitation of DS and MKE from a synthetic perspective.

Aldol reaction of (±)-**14as** with (±)-**13** via the Ti(IV) enolate prepared by reaction with $Ti(O^{i}Pr)Cl_3$[170-172] ($TiCl_4$ gave mediocre yields and stereoselectivities) and $^{i}Pr_2EtN$ as base gave *meso* bisaldol adduct **11a** in 85% yield as the only isolable diastereomer. Bisaldol **11a** is an *unlike* adduct that results from a combination of reactants where the absolute configurations at C-6' of **14as** and C-6" of **13** are opposite. The *unlike* reaction can produce up to four diastereomers; however, because only **11a** is isolated, this reaction must be highly diastereoselective. Products from the *like* reaction were not detected implying that the *unlike* reaction must be much more facile (i.e. high MKE) (Scheme 1.21).

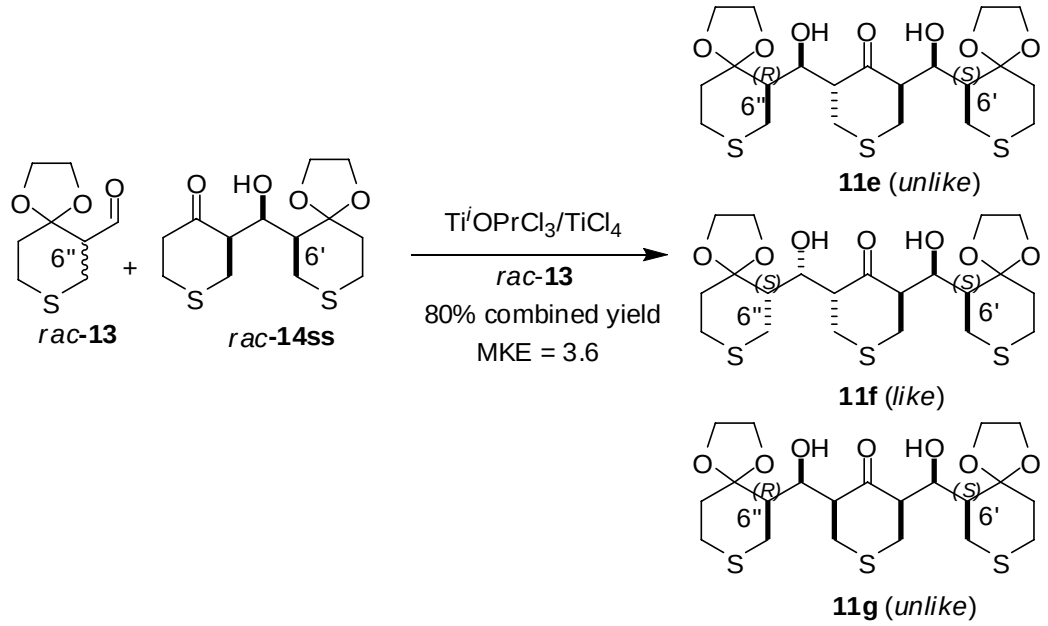
[†] The *like* combination refers to the same absolute configurations at C-6' of **14** and 6" of **13**, while *unlike* refers to the opposite absolute configurations at C-6' of **14** and 6" of **13** (Scheme 1.21).



Scheme 1.21: Aldol reactions of (±)-**14** with (±)-**13**

Under similar conditions, reactions of (±)-**13** with (±)-**14ss**, (±)-**14sa** or (±)-**14aa** via their Ti(IV) enolates also gave primarily single aldol adducts **11b**, **11c** and **11d** respectively (Scheme 1.21). As with the reaction with **14as**, these reactions proceed with high MKE and are highly diastereoselective. In contrast to other diastereomers of **14**, aldol reaction of (±)-**13** with the Ti(IV) enolate of (±)-**14ss**, prepared by reaction with excess $TiCl_4$ (3 equiv) and Ti(O^{i}Pr)Cl$_3$ (1 equiv) followed by ^{i}Pr$_2$EtN, gave a 10:3:1 mixture of three compounds (±)-**11e**, (±)-**11f** and **11g**, respectively (80% combined yield) as shown in

Scheme 1.22. Surprisingly, the product distribution is completely different when aldol reaction of (±)-**14ss** with (±)-**13** was performed with $TiCl_3O^iPr$ alone. Adducts **11e** and **11g** are derived from an *unlike* combination of reactants whereas **11f** results from a *like* combination. Both *like* and *unlike* reactions show good diastereoselectivity (*unlike*, two of four possible adducts in a 10:1 ratio; *like* only one of the four possible adducts detected) and proceed with modest MKE (11:3 in favor of the *unlike* reaction).



Scheme 1.22: Aldol reaction of (±)-**14ss** with (±)-**13** using $TiCl_4$ and $Ti(O^iPr)Cl_3$

Interestingly, when (±)-**14as** was protected as the MOM ether **135as** and then coupled with (±)-**13** via the Ti(IV) enolate, bisaldol adducts (±)-**136a** (*like* adduct; the absolute configurations at C-6' of **135as** and C-6" of **13** are the same) and (±)-**136b** (*unlike* adduct; the absolute configurations at C-6' of **135as** and C-6" of **13** are opposite) were produced in a nearly 1:1 ratio. Analysis of the product distribution indicated that the

reaction of (±)-**135as** and (±)-**13** proceeds with a low level of MKE (*like* and *unlike* combinations react with near equal facility). Interestingly, both the *like* and *unlike* reactions are highly diastereoselective and each gives only one of the four possible adducts. Thus, double stereodifferentiation has been avoided. Under similar conditions, reactions of (±)-**13** with (±)-**135ss**, (±)-**135sa** or (±)-**135aa** via their Ti(IV) enolates also gave predominantly two aldol adducts in nearly equal amounts as shown in Scheme 1.23. As with the reaction with **135as**, these reactions proceed with low level of MKE and are highly diastereoselective.

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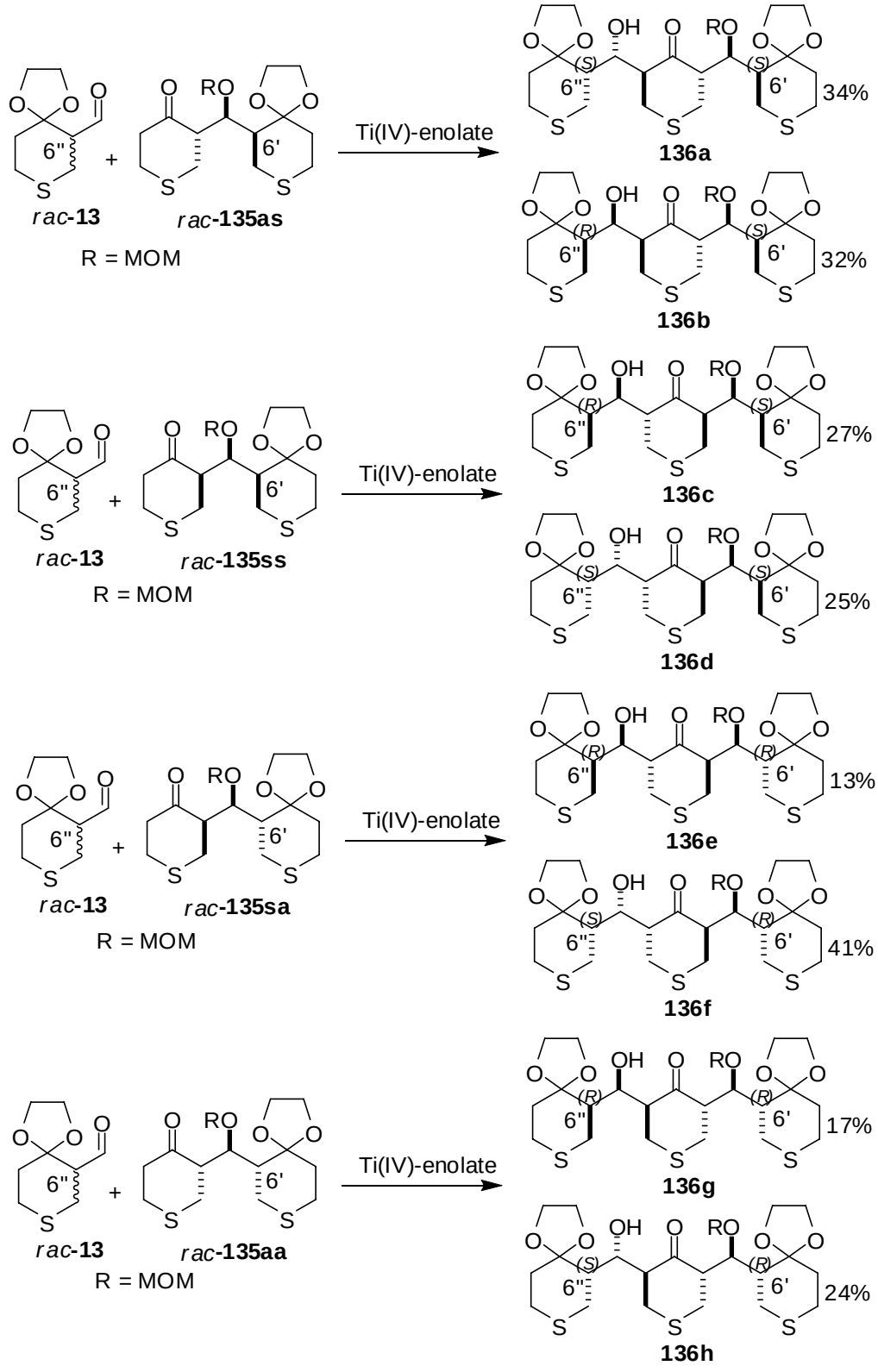
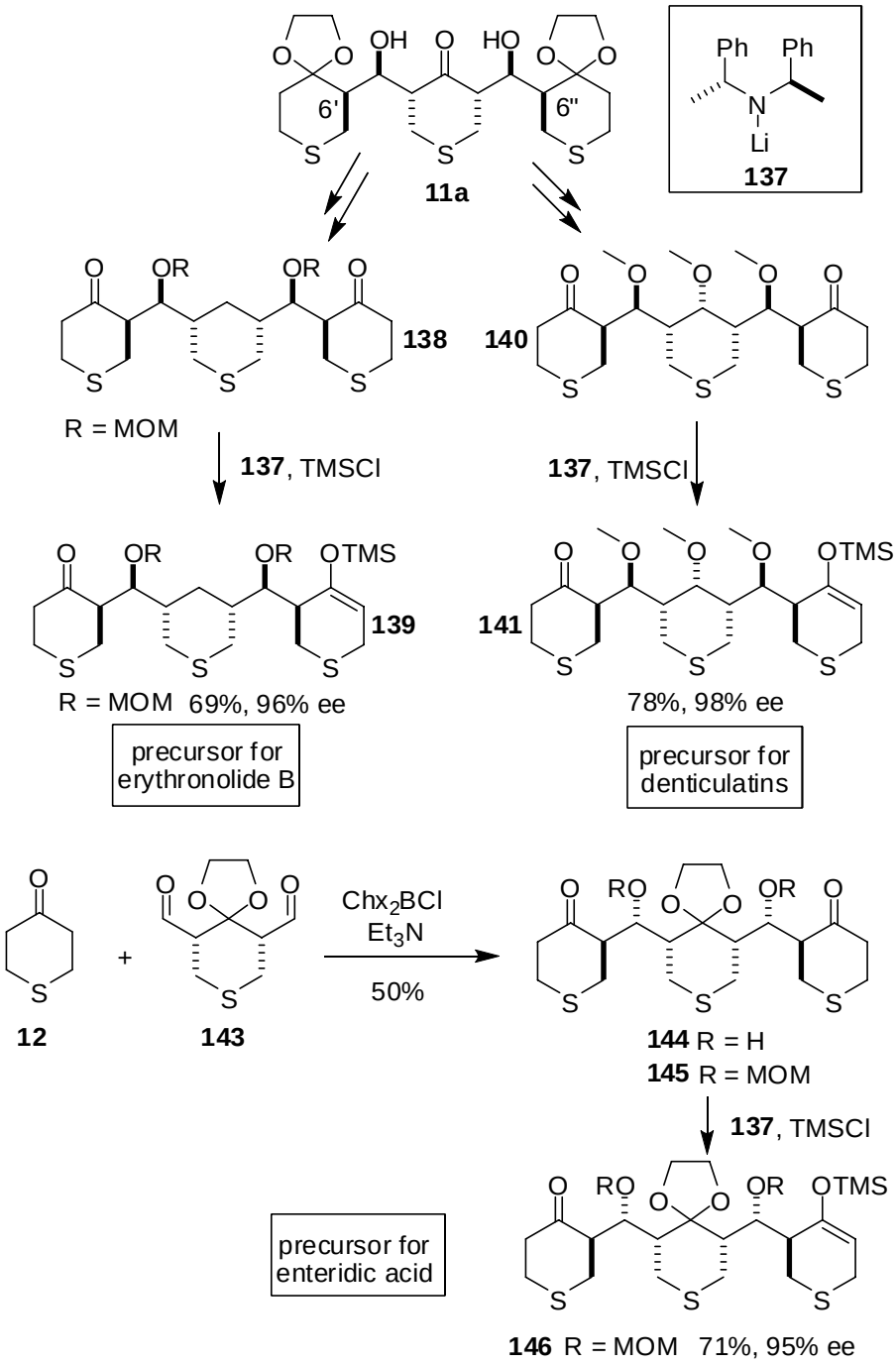


Scheme 1.23: Aldol reactions of (±)-**135** with (±)-**13**

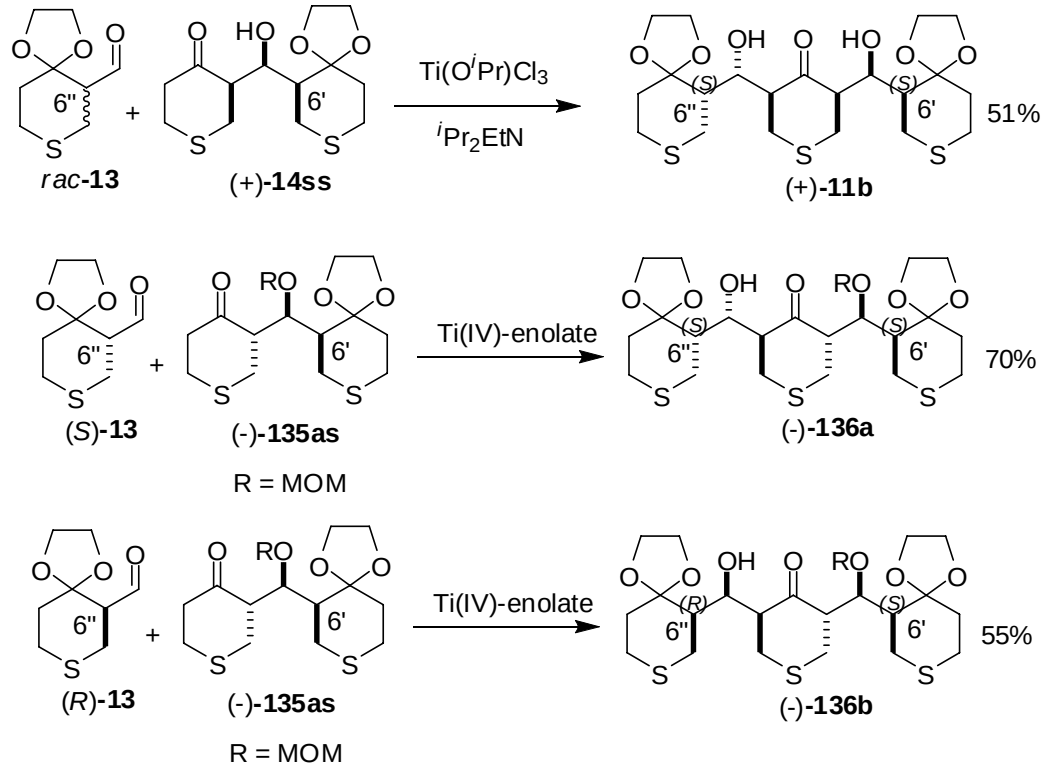
In a synthetic direction, enantiopure bisaldol adducts **11** can be produced via aldol reactions of enantioenriched **14** with enantioenriched **13**, however the *meso* diastereomers require enantioselective desymmetrization[173] to produce enantiomerically enriched hexapropionate fragments **9** (Figure 1.2). Desymmetrization of *meso* diketone **138** to generate nonracemic hexapropionate synthons by sequential enantiotopic group selective enolization has been successfully demonstrated in the Ward group[86] (Scheme 1.24). As indicated earlier, *meso* compound **11a** was prepared in 85% yield from stereoselective aldol coupling of two chiral racemic reactants **14as** and **13** mediated by $Ti^{i}OPrCl_3$[87] while *meso* **144**[86] was obtained via a two-directional boron-mediated aldol reaction of *cis* dialdehyde **143** and **12**. *Meso* adducts **11a** and **143** were easily converted to 1,9-diketones **138**, **140** and **145** as depicted in Scheme 1.24. Enantioselective enolizations of the meso diketones **138**, **140** and **145** by deprotonation using the chiral lithium amide base **137** to give the respective mono-TMS enol ethers **139**, **141** and **146** were successfully achieved with high enantiopurities and excellent overall yields. The synthetic usefulness of this approach was illustrated by desulfurization of nonracemic hexapropionate synthon **141** that occurred without loss of stereochemical integrity. Applications of **139**, **141** and **146** to the synthesis of polypropionates such as denticulatins,[49-57] erythronolide B[10, 39, 40, 42, 43, 174, 175] and enteridic acid[176] respectively are currently underway in the Ward group (Scheme 1.24).



Scheme 1.24: Desymmetrization of *meso* hexapropionate synthons

C_s symmetrical bisaldols such as **11a** can be readily desymmetrized to obtain enantioenriched hexapropionate synthons while other diastereomers of **11** can be generated via aldol reaction of enantioenriched **14** and **13**. A detailed study on the aldol reactions of (±)-**14** with (±)-**13** was elaborated earlier and one can easily conclude that access to other enantiomerically pure bisaldol adducts **11** in a synthetic direction simply requires appropriate coupling of nonracemic reactants **14** and **13**. For instance, using the previously developed proline-catalyzed aldol reaction of **12** and **13** gives ready access to enantiopure **14as** (Scheme 1.11). Isomerization of enantiopure **14as** gives enantiopure **14ss** as shown in scheme 1.2. As described ealier, the aldol reaction of (±)-**14ss** with (±)-**17** was performed with $TiCl_3O^iPr$ alone gave predominatly **11b** in 53% yield (Scheme 1.21). The reaction is highly diastereoselective and proceeds with high MKE in favor of the *like* reaction. This result suggests that useful levels of kinetic resolution will be observed in a similar reaction of an enantioenriched reactant with a racemic reactant to provide access to enantioenriched bisaldol adduct **11b** (Scheme 1.25).

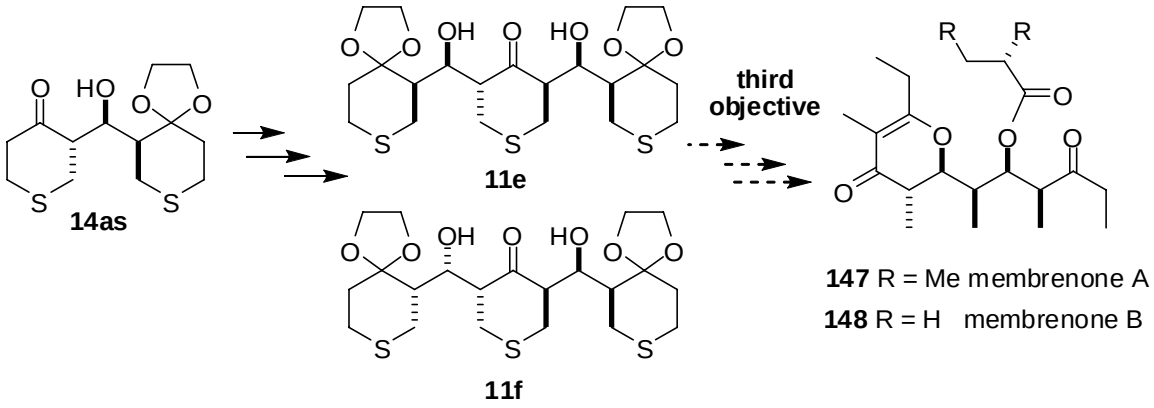
Alternatively, aldol reaction of MOM ether (±)-**135as** with (±)-**13** via the Ti(IV) enolate gives bisaldol adducts (±)-**136a** (*like* adduct) and (±)-**136b** (*unlike* adduct) in a nearly 1:1 ratio. The reaction proceeds with low level of MKE and both the *like* and *unlike* reactions are highly diastereoselective. This result suggests that kinetic resolution will not be observed in a similar reaction of an enantioenriched reactant with a racemic reactant. From a synthetic perspective, access of enantiomerically pure bisaldol adducts **136a** or **136b** simply requires appropriate aldol coupling of nonracemic reactants **14** and **13** (Scheme 1.25).



Scheme 1.25: Accessing enantioenriched **11** vial aldol reactions

In summary, robust procedures are available within the thiopyran protocol to construct eleven stereochemically complex (6 stereocenters) hexapropionate synthons **11** via 2 or 3 steps from **13** and **14**. Enantioselective desymmetrization of *meso* diastereomers of **11** via deprotonation of a derived 1,9-diketones has been demonstrated. Enantioenriched chiral diastereomers of **11** can be prepared from aldol couplings of nonracemic diastereomers of **14** and **13**. My third objective was to demonstrate the synthetic utility of **11** by application to natural products synthesis. I had previously developed an enantioselective aldol reaction of **12** with (±)-**13** to afford **14as** in good yield and with excellent enantiopurity. Isomerization of **14as** provides an efficient route to **14ss**. As described

above, enantioenriched **11b**, **11e**, **11f**, **136a**, **136b**, **136c**, and **136d** can be prepared from enantioenriched **14as** or **14ss**. With this in mind, membrenone B was selected as the synthetic target. The enantioselective total synthesis of membrenone B (**148**) and a formal synthesis of membrenone A (**147**) are described in ***Chapter 6*** (Scheme 1.26).

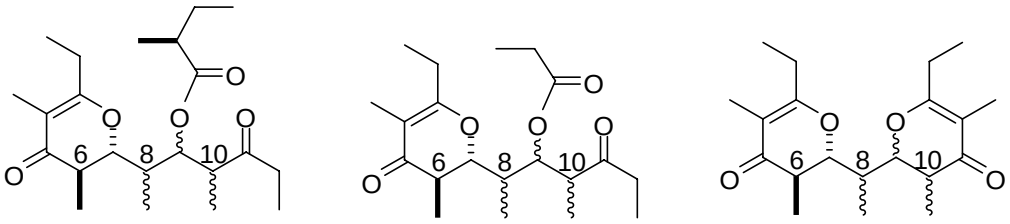


Scheme 1.26: Summary of chapter 6

1.7 The membrenones

1.7.1 Isolation and structure determination

Opisthobranchs, commonly known as sea slugs are soft-bodied and cryptic colored marine molluscs usually deprived of a protective shell.[177-181] Without a protective shell, their defense mechanism against potential predators relies on a number of different strategies such as camouflage, warning coloration, behavioural modifications (e.g. being active at night when predators are asleep), and secretion of chemicals rendering them posionous and/or unpalatable.[182] They are a relatively small group of marine organisms with approximately 6,000 living species studied and only few hundreds of them have been chemically analyzed for their natural products secretion that are mainly derived from three basic secondary metabolic pathways namely acetate, propionate and mevalonate.[178,180] Opisthobranch metabolites have attracted considerable interest by scientists over the years with potential biomedical properties such as antibacterial, antifungal, cytotoxic, antitumor, antineoplastic, etc. In 1993, Ciavatta and coworkers[183] isolated three new structurally similar polypropionates, membrenones A-C (**149A-C**) (Figure 1.7) from the skin of a Mediterranean pleurobranchoidean mollusc species, the notaspidean *Pleurobranchus membrenaceus*.



149A Membrenone A **149B** Membrenone B **149C** Membrenone C

Figure 1.7: Structures of membrenones A-C

The low abundance of **149A-C** isolated as well as the rarity of the Mediterranean pleurobranchoidean mollusc species in the Gulf of Naples where they were initially discovered consequently impeded the disclosure of their biological properties. After extensive NMR spectral analysis, the membrenones were successfully shown to consist of a polypropionate skeleton of 6 propionate units with an unusual γ–dihydropyrone system. The relative configurations at C-6 and C-7 of **149A-C** were assigned to be *trans* based on the large coupling constant observed between H-6 and H-7 (13.8 Hz). The relative configurations at C-8, C-9 and C-10 in **149A** and **149B** were not determined. Diagnostic small coupling between H-9 and H-10 ($J_{9\text{-}10}$ = 2.6 Hz) indicated a *cis* relationship between the substituents at C-9 and C-10 in **149C**. The absolute configuration of the acyl residue in **149A** was determined to be (*R*) by literature comparison of the derived Mosher's ester of 2(*R*)-methylbutanol obtained via $LiAlH_4$ reduction of natural membrenone A. The two dimensional structures of **149A-C** were therefore successfully elucidated while the relative configurations at C-8, C-9 and C-10 and the absolute configurations remained uncertain. In the absence of natural samples, synthesis of all possible diastereomers of **149A-C** and direct comparison to the original data[183] was the only alternative approach available to confirm the three dimensional structures of the natural membrenones.

1.7.2 Perkins's synthesis[184-186] and structural assignment of 149C

Considering the *anti* relative configuration at C-6 and C-7 and *syn* configuration at C-9 and C-10 with an unknown configuration at C-8 suggested four possible diastereomers of **149C** as shown in Figure 1.8. Ideally each diastereomer can be synthesized and the structure of **149C** can be subsequently established by comparison with the original data.

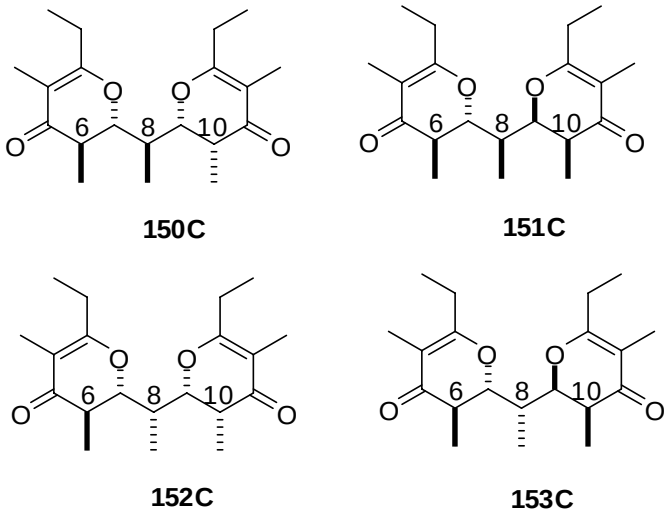
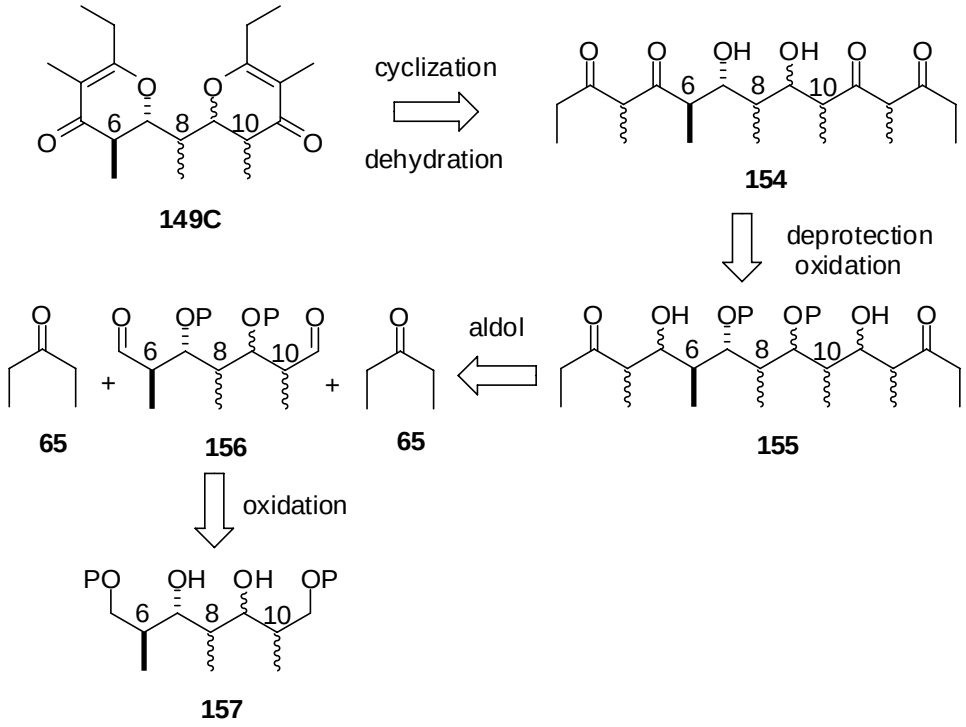


Figure 1.8: Four possible diastereomeric structures of **149C**

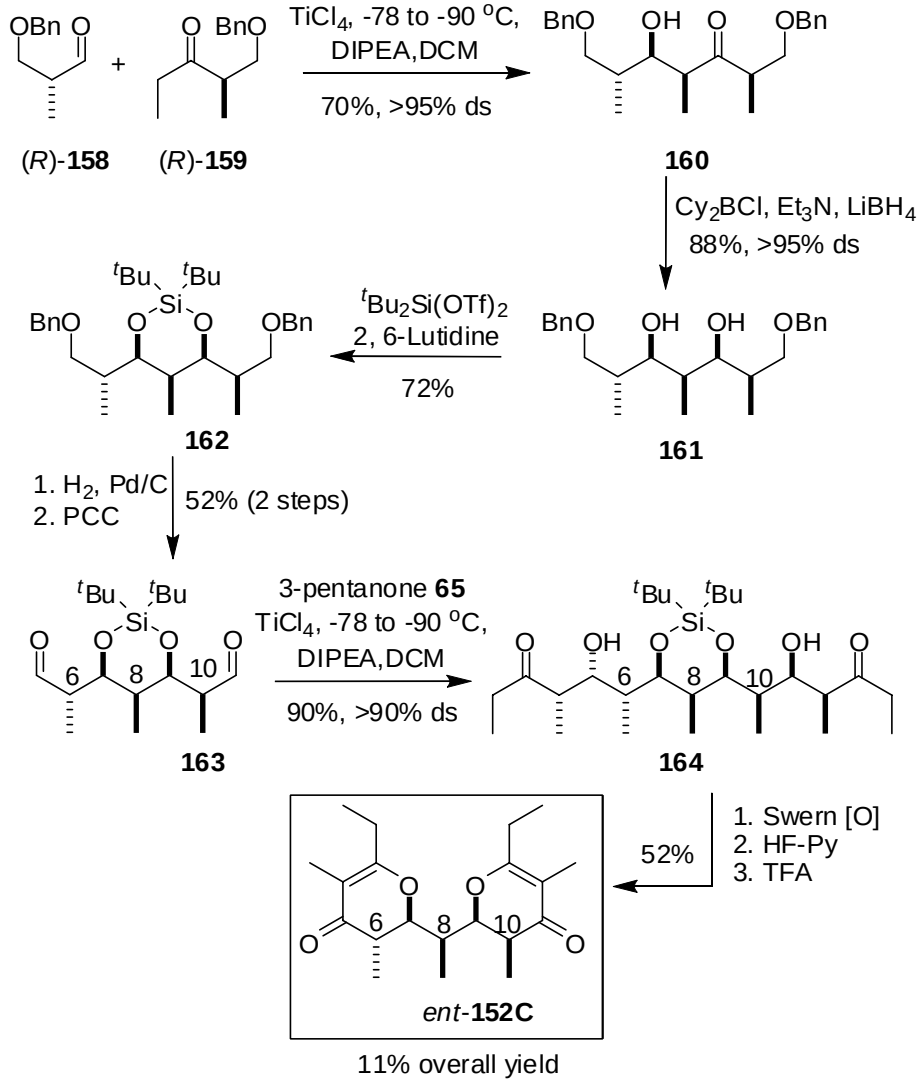
Retrosynthetically, unraveling **149C** led to tetraketone **154**, which was in turn anticipated from deprotection and oxidation state adjustment of the hydroxyl groups from diketone **155**. Perkins adopted a double aldol type disconnection to assemble the C-4-C-5 and C-11-C-12 bonds of diketone **155** from dialdehyde **156** and 3-pentanone (**65)**. The five stereogenic centers in **156** linking C-6 to C-10 were mapped onto Paterson's protocol[17,187-190] for synthesis of structurally diverse stereopentad units **157** (Scheme 1.27).



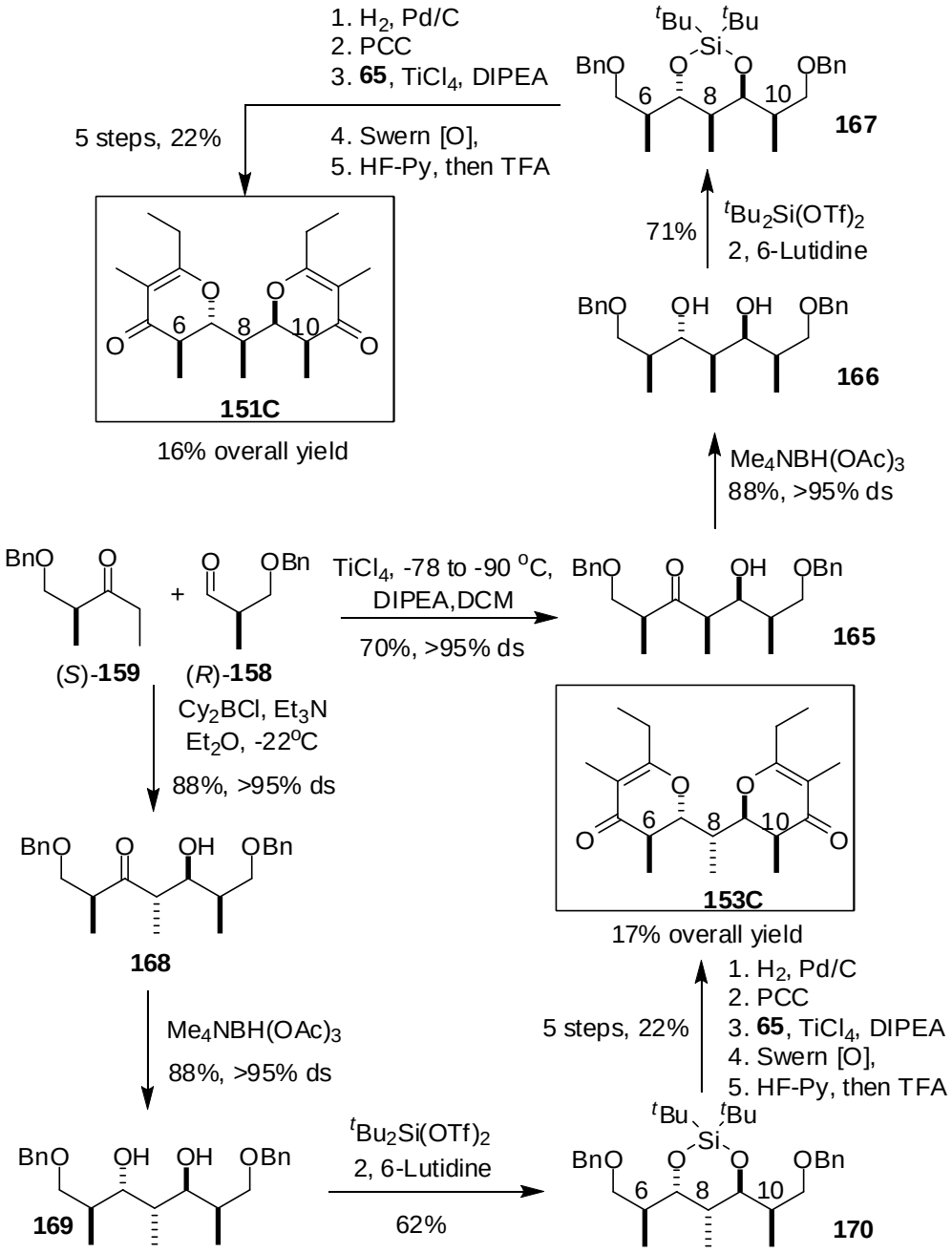
Scheme 1.27: Retrosynthetic analysis of **149C**

The synthesis of *ent*-**152C** commenced with a Ti(IV) mediated stereoselective aldol coupling of chiral nonracemic ketone **159** and enantiopure aldehyde **158** that afforded the *syn*-*syn* aldol adduct **160** in 70% yield and with excellent diastereoselectivity (>95%). Borinate complexation of β-hydroxyl ketone **160** followed by *in situ* reduction using $LiBH_4$ furnished 1,3 *syn* diol **161** in 88% yield (>95% ds) that was subsequently protected as the di-*tert*-butylsilylene acetal (**162**). This sequence of reactions elegantly established the five contiguous stereogenic centers of interest in *ent*-**152C** in 44% overall yield starting from (*R*)-**159** and (*R*)-**158** over 3 steps. Removal of the benzyl group was followed by oxidation to give dialdehyde **163**. Chain elongation was achieved via a two directional double aldol reaction of 3-pentanone (**65)** with dialdehyde **163** promoted by $TiCl_4$ led to diketone **164** in 90% yield (>95% ds). The remaining steps of the synthesis

involved a double Swern oxidation of **164** (100% yield) followed by deprotection of the silyl group using HF in pyridine to give a mixture of diols and hemiacetals that upon treatment with trifluoroacetic acid underwent rapid cyclization and dehydration to give *ent*-**152C** in 52% over 3 steps (Scheme 1.28).



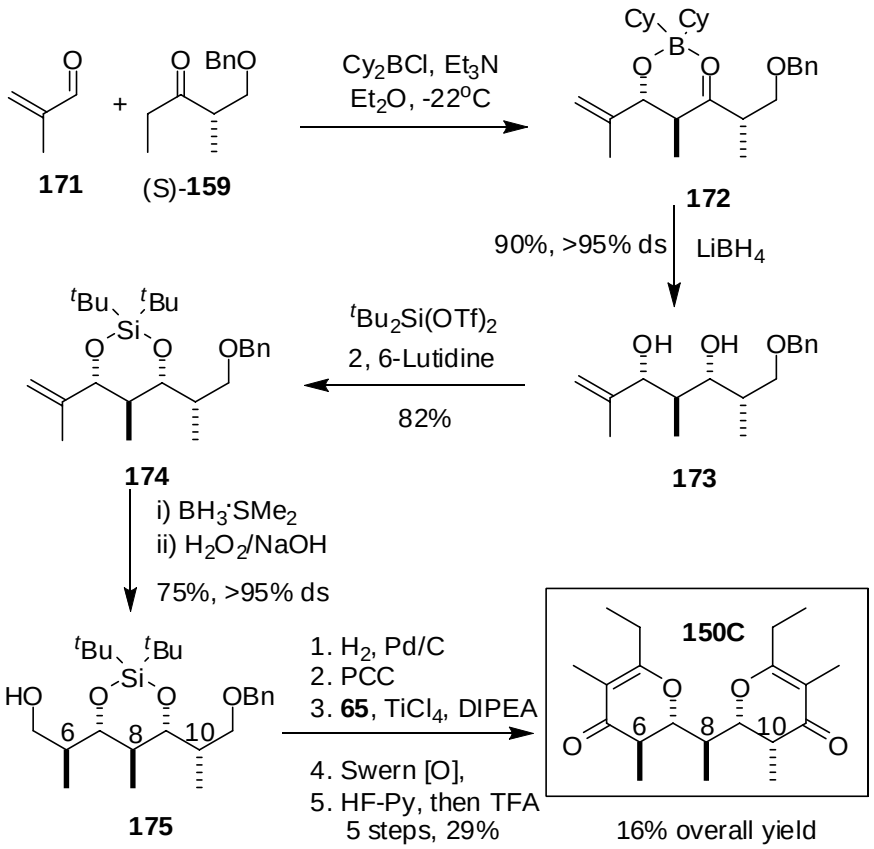
Scheme 1.28: Synthesis of *ent*-**152C**



Scheme 1.29: Synthesis of **151C** and **153C**

Similar approaches were adopted to synthesize diastereomers **151C** and **153C**. The *syn* and *anti* diastereoselection of aldol reactions involving chiral nonracemic ketone **159** and aldehyde **158** were controlled by generating the Ti (IV) and boron enolates respectively to produce the desired stereopentad units **165** and **168**. Entities **165** and **168**

were stereoselectively reduced by $Me_4NBH(OAc)_3$ to give *anti* diols **166** and **169**, respectively, that were both advanced to isomers **151C** and **153C** over 6 steps as outlined in Scheme 1.29. Diastereomer **150C** was synthesized via a boron mediated aldol coupling of methacrolein **171** and chiral ketone (*S*)-**159** to predominantly give the expected *anti* aldol adduct **172** that was reduced *in situ* to 1,3 syn diol **173** using $LiBH_4$. Compound **173** was then protected as the di-*tert*-butylsilylene followed by selective hydroboration of the olefin group using $BH_3{\cdot}SMe_2$ afforded **175** after oxidative work up that was subsequently converted to **150C** over 5 steps in 29% overall yield as shown in Scheme 1.30.



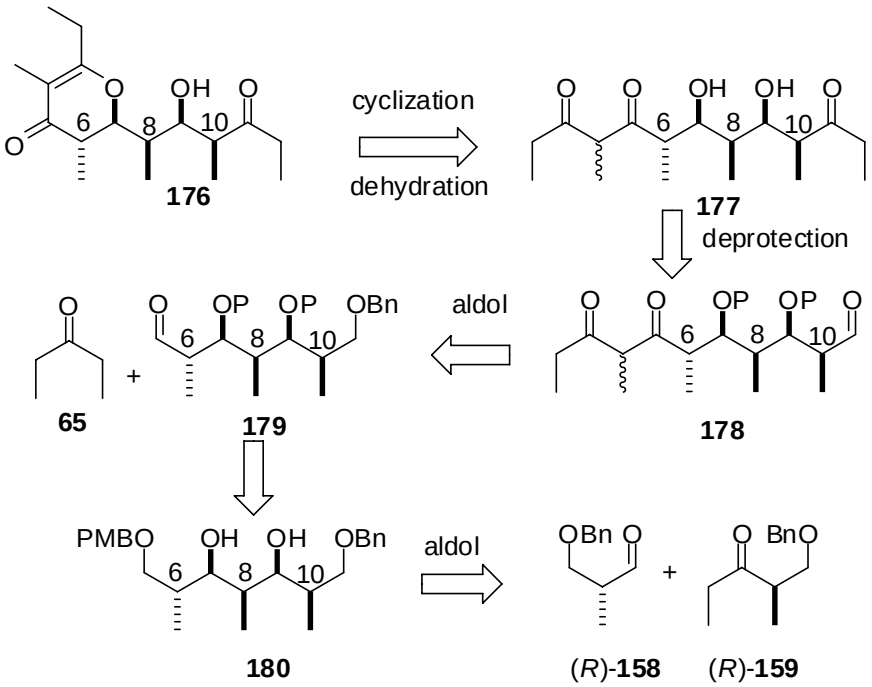
Scheme 1.30: Synthesis of **150C**

With all 4 diastereomers in hand, the ^{1}H and ^{13}C NMR of *ent*-**152C** clearly matched the original data for membrenone C thereby establishing the relative configuration of the natural membrenone C. Diastereomers **150C**, **151C** and **153C** showed significant differences in both the ^{1}H and ^{13}C NMR chemical shifts and coupling constants compared to those reported for natural membrenone C. The signs of the optical rotation reported for the natural sample ($[\alpha]_D$ = -58, *c* 0.1, $CHCl_3$) and that for synthetic *ent*-**152C** ($[\alpha]_D$ = -28, *c* 0.46, $CHCl_3$) were the same although the value for the synthetic sample was somewhat lower in magnitude. However at this point, the same sign of rotation seemed to unambiguously establish the absolute stereochemistry of natural (–)-membrenone C to be *ent*-**152C.**[‡] In summary, Perkins elegantly achieved the total synthesis of *ent*-**152C** in 8 steps in 10.7% overall yield starting from acyclic nonracemic precursors (*R*)-**158** and (*R*)-**159**. The key steps of the synthesis involved a stereoselective aldol coupling followed by reduction to install the C-7 to C-9 stereogenic centers in the stereopentad diol **161**, a two directional chain extension via double aldol coupling mediated by $TiCl_4$, and a critical sequential cyclization and dehydration promoted by trifluoroacetic acid to form the two γ–dihydropyrone rings to give (–)-membrenone C (*ent*-**152C**).

[‡]The optical rotation was later suggested to have been misreported as described by Perkins. See section **1.7.4**

1.7.3 Synthesis of (–)-membenone A and B[191]

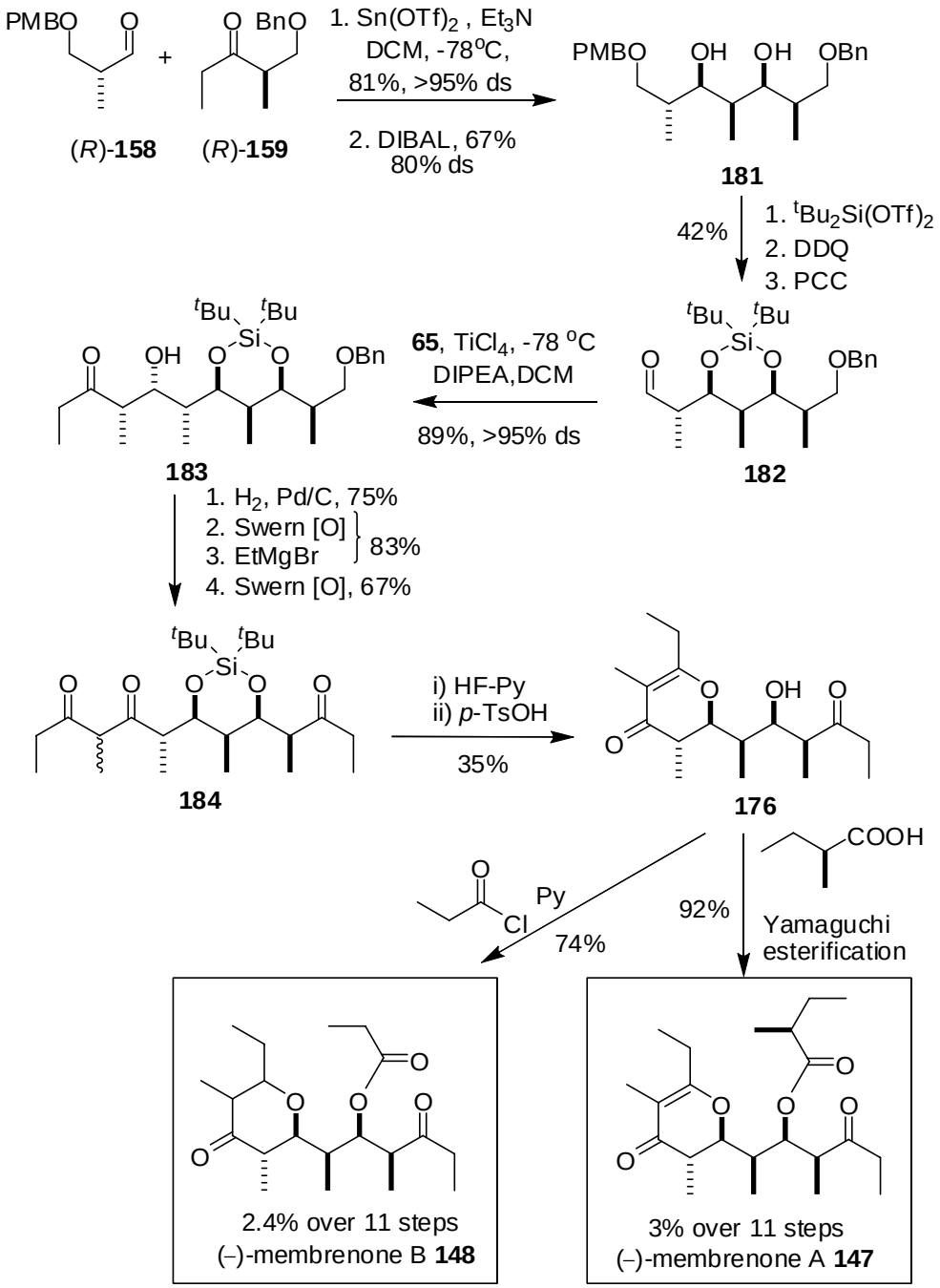
Membrenones A-C are secondary metabolites that were isolated from the same species of marine mollusc. Therefore, assuming a common biosynthesis of the membrenones, membrenones A (**147)** and B (**148)** were proposed to have the same absolute configuration as assigned in (–)-membrenone C (*ent*-**152C**). From a retrosynthetic perspective, deprotection of the acyl substituents in both **147** and **148** lead to β-hydroxyl ketone **176** as the common intermediate. Dihydropyrone **176** was anticipated from deprotection and cyclization of triketone **177** which in turn upon disconnection between C-11-C-12 was envisaged via Grignard addition to aldehyde **178**. Aldol disconnection between C-4-C-5 in **178** lead to aldehyde **179** which was visualized from the protected stereopentad diol **180** that in turn can be constructed from (*R*)-**158** and (*R*)-**159** (Scheme 1.31).



Scheme 1.31: Retrosynthetic analysis of **147** and **148**

The synthesis of **147** and **148** commenced with the $Sn(OTf)_2$ mediated aldol reaction of (*R*)-**159** and chiral aldehyde (*R*)-**158** that gave *syn*-*syn* aldol adduct **181** in 81% yield and with high diastereoselectivity (>95%). DIBAL-H reduction of **181** was followed by DDQ deprotection of the PMB group and oxidation of the corresponding alcohol to furnish aldehyde **182** in 42% yield over 3 steps. The chain extension process was successfully achieved via a second aldol coupling of aldehyde **182** with 3-pentanone (**65**) via the Ti(IV) enolate that afforded adduct **183** in 89% yield and >95% ds. The new stereogenic centers at C-4 and C-5 were produced stereoselectively in the preceding step but were unimportant as they were not present in the final product. Compound **183** was subjected sequentially to debenzylation, oxidation, chemoselective addition of EtMgBr to the resulting β-diketo-aldehyde (1:1 epimeric mixture at C-4), and oxidation to give triketone **184**. Nucleophillic addition was observed only to the aldehyde and not to the β-diketone moiety even when excess Grignard reagent was introduced to the reaction mixture, presumably due to the formation of the β-diketone enolate by α-H proton abstraction by the Grignard reagent. Deprotection of the silyl group in the presence of HF·py gave a mixture of compounds that when subjected to *p*-TsOH afforded a 1:1 mixture of **176** and the corresponding enone resulting from elimination of the C-9 hydroxyl group. The formation of γ-dihydropyrone was less efficient than witnessed earlier in the case of *ent*-**152C** (Scheme 1.28) but nevertheless the anticipated β-hydroxyketone **176** was obtained in 35% yield. Appropriate acylation of **176** gave **147** ($[\alpha]_D$ = -24, *c* 0.51, $CHCl_3$) and **148** ($[\alpha]_D$ = -44, *c* 0.68, $CHCl_3$) in 3% and 2% overall

yields, respectively (Scheme 1.32). The spectral data of synthetic **147** and **148** were in accord with the original published data.[§]



Scheme 1.32: Synthesis of **147** and **148**

[§] See section **1.7.4** for absolute configuration assignments of **147** and **148**

1.7.4 Controversy and structural re-assignment of the membrenones

The optical rotation and the CD curve obtained for synthetic (–)-membrenone A (**147)** (Scheme 1.32) is of opposite sign but the same magnitude as reported for the natural sample.[183] This suggests that **147** is the enantiomer of the natural product which is consequently (+)-membrenone A (i.e. *ent*-**147**). Interestingly, the sign of rotation for (–)-membrenone B (**148)** is the same as in the original publication but with an opposite CD curve. The CD curves for **147** and **148**, which have the same configurations from C-6 to C-10, are identical indicating that the sign of optical rotation of (–)-membrenone B in the original report was misreported and must consequently be (+)-membrenone B (i.e. *ent*-**147**, Scheme 1.32).

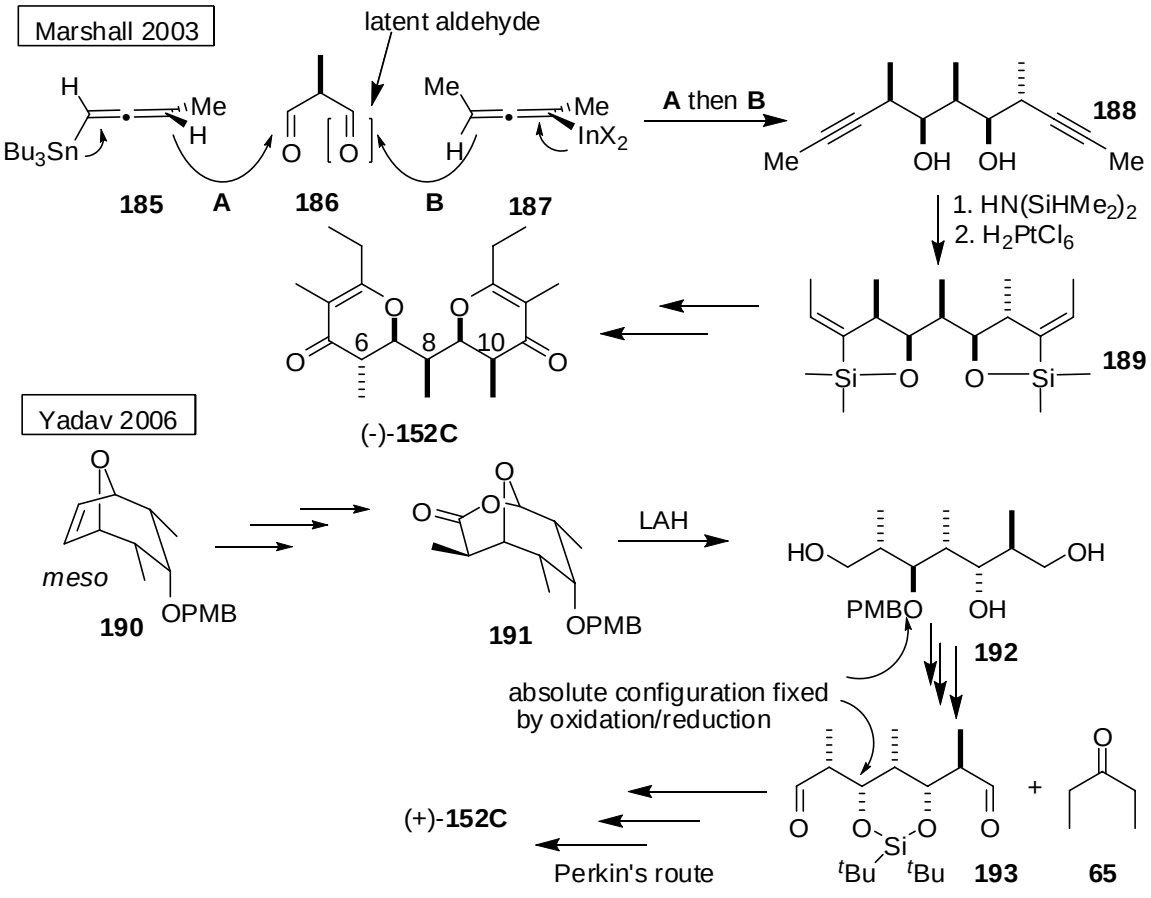
Table 1.4: $[\alpha]_D$ and CD curve analysis for synthetic and natural membrenones A-C.

	Synthetic sample		Natural sample	
147	$[\alpha]_D$ = -24, *c* 0.51, $CHCl_3$	CD curve: $[\theta]_{300}$ +5661(max) $[\theta]_{260}$ -10654 (max)	$[\alpha]_D$ = +25, *c* 0.05, $CHCl_3$	CD curve: $[\theta]_{300}$ -2278 (max) $[\theta]_{270}$ +6126 (max)
148	$[\alpha]_D$ = -44, *c* 0.68, $CHCl_3$	CD curve: $[\theta]_{300}$ +6613 (max) $[\theta]_{267}$ -15438 (max)	$[\alpha]_D$ = -25, *c* 0.2, $CHCl_3$	CD curve: $[\theta]_{302}$ -2354 (max) $[\theta]_{269}$ +6230 (max)
ent-**152C**	$[\alpha]_D$ = -28, *c* 0.46, $CHCl_3$	CD curve: $[\theta]_{300}$ +5550 (max) $[\theta]_{263}$ -16232 (max)	$[\alpha]_D$ = -58, *c* 0.1, $CHCl_3$	CD curve: $[\theta]_{308}$ -166 (max) $[\theta]_{270}$ +2023 (max)

Similarly, assuming that the absolute configuration of membrenones A-C are identical, these results suggest that the sign of rotation of (–)-membrenone C (*ent*-**152C**) is also incorrect as reported and should be (+)-membrenone C (i.e. **152C**) (Table 1.5). Therefore, relative and absolute configurations of the natural membrenones have been

established by Perkins to be *ent*-**147**, *ent*-**148** and **152C**. However, in the absence of natural samples, the absolute stereochemical assignments and signs of rotation remain unsubstantiated.

Recently, Marshall et al.[192] reported the synthesis of (+) and (–)-membrenone C (**152C**) and the key steps in their synthesis involved addition of chiral allenyl reagents to effect chain extension of the polypropionate chain followed by intramolecular hydrosilation and oxidation to install the five contiguous stereocenters of **152C** (C-6 to C-10) in few steps. Yadav and coworkers[193] also reported the synthesis of **152C** via desymmetrization of a bicyclic precursor to introduce the five contiguous centers of **152C** as the highlight of their approach (Scheme 1.33).



Scheme 1.33: Marshall's and Yadav's synthesis of (+) and (–)-**152C**

1.8 Summary of objectives

The preparation of enantiopure hexapropionate synthons **11** (Figure 1.2) requires coupling of nonracemic chiral fragments of **14** and **13**. In turn, the preparation of enantiopure monoaldols **14** were previously possible only via aldol reactions of **12** and enantioenriched aldehyde **13**. Although the synthesis of enantiomerically pure **13** is robust, it requires 5 synthetic operations. My research objectives were to develop an enantioselective aldol reaction of **12** and racemic **13** using organocatalysis as the tool to obtain enantiopure adducts **14** for application towards the synthesis of polypropionate natural products serricornin (**61**) and membrenones A (**147**) and B (**148**).

1.9 References

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2. Proline-Catalyzed Asymmetric Aldol Reactions of Tetrahydro-4*H*-thiopyran-4-one with Aldehydes

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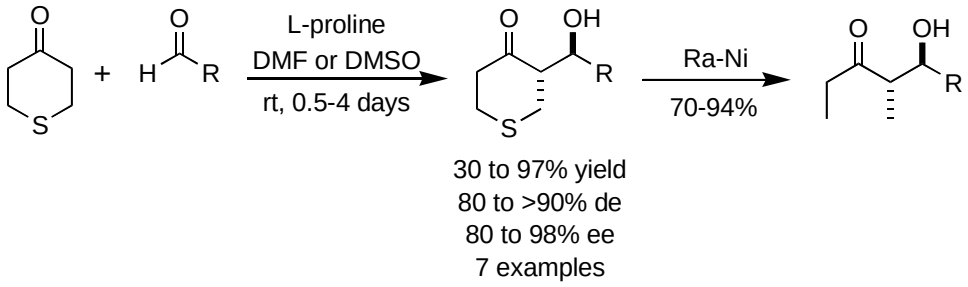
Graphical Abstract



2.1 Preface

Asymmetric organocatalysis is attracting utmost interest nowadays. The use of proline and/or its derivatives to promote direct asymmetric aldol reactions are well documented in recent literature. Organocatalysts are very attractive from an industrial perspective because of their operational simplicity, cheap and environmentally friendly approach. Although impressive, a general limitation is the scope of the substrate, especially unsuccessful applications of 3-pentanone which is an important building block in polypropionate synthesis. The proline-catalyzed aldol reaction of terahydro-4*H*-thiopyran-4-one with different achiral aldehydes followed by desulfurization (as alternative to 3-pentanone) is described in this manuscript.

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Proline-Catalyzed Asymmetric Aldol Reactions of Tetrahydro-4*H*-thiopyran-4-one with Aldehydes

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Abstract—Proline-catalyzed enantioselective direct intermolecular aldol reactions of tetrahydro-4*H*-thiopyran-4-one with various aldehydes give *anti* adducts with high diastereo- and enantioselectivities in moderate to excellent yields. With the aromatic aldehydes best results were obtained in wet DMF whereas dry DMSO generally was superior with the aliphatic aldehydes. Desulfurization of the adducts with Raney Ni provides products equivalent to aldols from 3-pentanone with potential applications in polypropionate synthesis.

The 'directed' aldol reaction[1] of preformed enol(ate) derivatives with aldehydes is among the most powerful methods for stereocontrolled carbon-carbon bond formation[2] as evidenced by numerous applications[3] in natural product syntheses. The development of methods to achieve stereoselective 'direct' aldol reactions of unmodified ketones and(or) aldehydes is an important objective in the evolution of modern aldol chemistry.[4] A

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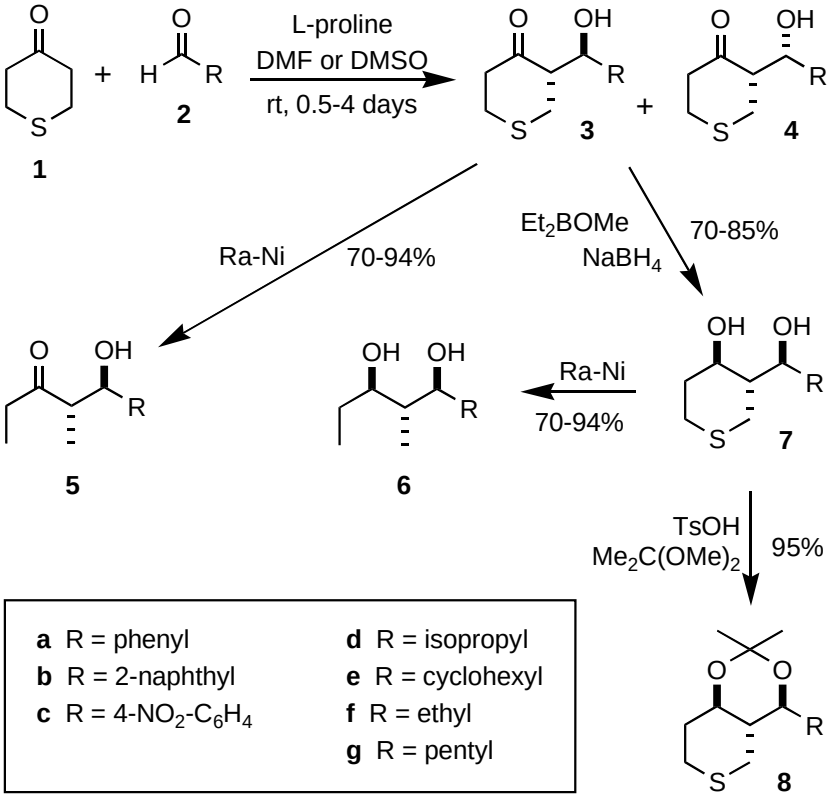
number of strategies have been investigated and methods based on enzyme-, antibody-, organometallic-, and organo-catalysis have been reported recently.[4] In this regard, the use of proline and its derivatives to catalyze enantioselective direct intermolecular aldol reactions has attracted considerable attention since the initial report[5] by List, Lerner, and Barbas.[6,7] Although the results achieved to date are impressive, one of the major limitations of the proline-catalyzed direct aldol reaction is the rather narrow substrate scope.[6] For example, good to excellent stereoselectivity has been realized in certain cross-aldol reactions and generally in reactions of acetone and hydroxyacetone with various aryl and alkyl aldehydes.[6,7] However, reactions of cyclic ketones often proceed with modest diastereoselectivity and other simple ketones such as acetophenone and pentanone are unreactive.[6] In this paper we report that aldol reactions of tetrahydro-4*H*-thiopyranone (**1**) with various aldehydes are effectively catalyzed by proline in wet DMF or DMSO to give the *anti* adducts in good yield with good to excellent enantioselectivity. Desulfurization of these adducts gives products with applications in polypropionate synthesis and equivalent to those that would be derived from the unreactive 3-pentanone.

We have been investigating sequential two-directional aldol reactions of **1**[8] in the context of a thiopyran-based synthetic route to polypropionates.[9] In the course of these studies we noted higher reactivity[9d] and diastereoselectivity[9a,c,f] in aldol reactions of **1** compared to those of cyclohexanone. Thus, despite the relatively mediocre results reported for cyclohexanone in proline-catalyzed enantioselective direct aldol reactions,[6] we were prompted to study the reaction of **1** with benzaldehyde (**2a**) in the presence of proline (Scheme 1, Table 2.1).[10]

Adapting the conditions reported for the reaction of **2a** with cyclohexanone,[11] reaction of **2a** (0.15 M in DMSO) with **1** (3 equiv) in the presence of proline (0.5 equiv) at room temperature for an arbitrary reaction time of 3 days furnished a 2:1 mixture of aldols **3a** (anti) and **4a** (syn), [9a,d] respectively, in low yield (entry 1). Several solvents were screened but only DMF was promising (entry 4).[12] Optimization of these conditions clearly showed increased yields at higher concentrations and superior stereoselectivity in DMF. Conversions were not improved with additional proline (cf. entries 5 and 6)[13] or with prolonged reaction times (cf. entries 8 and 9). Both the ratio of **3a**:**4a** and the ee of **3a** decreased with increased reaction times presumably due



Scheme 2.1

Table 2.1. Proline-catalyzed aldol reactions of **1** with **2a**.[a]

entry	[**2a**] (M)	solvent	H_2O (equiv)	time (d)	%yield [b]	dr [c]	%ee [d]
1	0.15	DMSO	0	3	15	2	
2	1	DMSO	0	3	34	3	78
3	2	DMSO	0	3	33	3.5	83
4	0.15	DMF	0	3	10	10	
5	1	DMF	0	3	44	10	> 98
6	1 [e]	DMF	0	3	43	10	97
7	2	DMF	0	3	46	14	87
8	1	DMF	0	4	55	10	93
9	1	DMF	0	8	52	5	87
10	1	DMF	1	2	51	14	95
11	1	DMF	2	2	53	11	92
12	1	DMF	4	2	52	8	93
13	1	DMF	8	2	60	3	98
14	1	DMF	1	4	70	7	92
15	**2**	**DMF**	**1**	**4**	**92**	**14**	**96**

[a] Reactions at room temperature with **2a** (ca. 0.6 mmol), **1** (3 equiv), L-proline (0.5 equiv).

[b] Isolated yield of **3a** after chromatography; see the Supplementary Material for spectroscopic data.

[c] Ratio of **3a**:**4a** by ^{1}H NMR of the crude reaction mixture

[d] Ee of **3a** determined by ^{1}H NMR in the presence of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) as a chiral solvating agent. The absolute configuration of the major enantiomer is as shown.

[e] With 1 equiv of L-proline

to the reversibility of the reaction (retroaldol) and/or isomerization of **3a** and **4a** via enolization. Although in many examples of proline-catalyzed direct aldol reactions the adducts were shown or assumed to be stable to the conditions,[6] both retroaldol[14] and isomerization[15] by enolization have been observed. We have previously shown the aldols derived from **1** are particularly susceptible to syn-anti isomerization via enolization.[9d] The reaction was substantially improved in the presence of water (entries 10-15) giving much higher yields while maintaining excellent stereoselectivity. Lower stereoselectivity was observed with greater water content (entries 10-13) and with longer reaction times (cf. entries 10 and 14); however, excellent results were obtained under optimized conditions (entry 15). Several authors have reported on the effects of water in proline-catalyzed direct aldol reactions. Although reactions typically proceed with low enantioselectivity in aqueous media,[16] small amounts of water are often tolerated[11b, 17] and are sometimes beneficial.[18] In the present case, the origins of the positive effects from added water are uncertain but presumably relate to improved catalyst turnover and suppression of parasitic equilibria.[19]

To ascertain the scope of the process we investigated reactions of **1** with aldehydes **2b-2g** (Table 2.2). Using the conditions optimized for **2a**, reaction of **2b** gave **3b** in good yield and with excellent stereoselectivity. Similar reaction with the more reactive **2c** gave **3c** with poor diastereoselectivity; however, selectivity commensurate with that observed for **3b** was obtained simply by reducing the reaction time to 12 h. In contrast to the aromatic aldehydes **2a-2c**, reactions of the aliphatic aldehydes **2d-2g** did not benefit from the presence of water and most gave superior results in DMSO compared to DMF. Nonetheless, with minor adjustments in conditions, the anti aldols **3d-**

3g were generally obtained with high stereoselectivity. In keeping with previous reports,[20] reactions with the α-unsubstituted aldehydes **2f** and **2g** gave lower stereoselectivities and yields than reactions with the α-branched aldehydes **2d** and **2e**. The stereoselectivities (particularly the diastereoselectivities) and yields obtained in proline-catalyzed aldol reactions of **1** are generally higher than those reported for similar reactions of cyclohexanone.[11, 16a-c, 20, 21]

The *anti* relative configurations for aldols **3a-3g** was suggested by the characteristic[22] large $^3J_{HH}$ observed for O=CC*H*C*H*OH (7-10 Hz) previously shown to be diagnostic for anti aldols of **1**. [9c,d] This assignment was confirmed for **3a**, **3d**, and **3e** by diastereoselective reductions to the corresponding diols **7a**, **7d**, and **7e**, respectively (Scheme 2.1); ^{1}H and ^{13}C NMR analysis (as detailed earlier) [9a,b] of the derived acetonides **8a**, **8d**, and **8e** fully corroborated the illustrated relative configurations. The absolute configuration for **3b** was established by X-ray crystallographic analysis[†] and is consistent with that expected from previous studies[6] and from the proposed mechanistic model for proline-catalyzed aldol reactions.[23] The absolute configurations for **3a** and **3c-3-g** are assigned by analogy.

Desulfurizations of the enantioenriched aldols **3a**, **3b**, **3d**, and **3e** were achieved using Raney Ni (W-2) in EtOH/THF in the presence of acetate buffer (pH=5.2) and sodium hypophosphite (10 equiv)[24] to give **5a**,[25] **5b**,[26] **5d**,[27] and **5e**,[28]respectively, in good yields (Scheme 2.1, Table 2.3). Despite the mildness of the conditions, the products **5**

[†] Crystallographic data (excluding structure factors) for (+)-**3b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 247160. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk] (See appendix A).

were contaminated with up to 10% of the syn diastereomer presumably originating from syn-anti isomerization of **3** via enolization.[9d]

Table 2.2. Proline-catalyzed aldol reactions of **1** with **2b-2g**.[a]

entry	RCHO	solvent [b]	time (d)	product	%yield [c]	dr [d]	%ee [e]
1	**2b**	DMF/H_2O	4	**3b**	80	> 20	> 98 [f]
2	**2c**	DMF/H_2O	4	**3c**+**4c**	72	2	96(82) [f]
3		DMF/H_2O	0.5	**3c**	97	> 20	95 [f]
4	**2d**	DMF/H_2O	4	**3d**	39		
5		DMF [g]	3		62	9	
6		DMSO/H_2O	4		53	11	
7		DMSO [g]	3		96	> 20	> 98 [h]
8	**2e**	DMSO/H_2O	4	**3e**+**4e**	93	10	76 [i]
9		DMSO	4		68	> 20	92 [i]
10	**2f**	DMF/H_2O	4	**3f**	20	5	
11		DMF [g]	3		47	16	80 [i]
12		DMSO [g]	3		< 5		
13	**2g**	DMSO/H_2O	4	**3g**	38	> 20	90 [j]
14		DMSO	4		28	14	93 [j]

[a] Reactions at room temperature: [194] = **2a** (ca. 0.6 mmol), **1** (3 equiv), L-proline (0.5 equiv).
[b] Containing 1 equiv of H_2O where indicated
[c] Isolated yield of indicated product after chromatography; see the Supplementary Material for spectroscopic data.
[d] Ratio of **3**:**4** by ^{1}H NMR of the crude reaction mixture
[e] ee of **3** (ee of **4** in parenthesis)
[f] Determined by ^{1}H NMR in the presence of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE).
[g] [194] = 1 M
[h] Determined by ^{1}H NMR of the bis Mosher's ester of the derived diol **7e**.
[i] Determined by ^{1}H NMR of the derived Mosher's ester.
[j] Determined by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$.

Table 2.3. Desulfurizations of **3** and **7**.[a]

entry	substrate	temp (°C)	time (h)	product	%yield [b]
1	**3a**	25	1	**5a** [c]	94
2	**3b**	25	9	**5b** [c]	76
3	**3d**	25	9	**5d** [c]	70
4	**3e**	75	1.5	**5e** [c]	94
5	**7a**	25	1.5	**6a**	93
6	**7d**	75	3	**6d**	70
7	**7e**	75	1.5	**6e**	80

[a] Ra-Ni (W-2) in EtOH/THF with acetate buffer (pH=5.2) and NaH_2PO_2 (10 equiv)

[b] Isolated yield of indicated product after chromatography; see the Supplementary Material for spectroscopic data.

[c] A 10-15:1 mixture of **5** and the corresponding syn diastereomer

Isomerization could be completely avoided by desulfurization of the diols **7a**, **7d**, and **7e** to give **6a**,[29] **6d**,[30] and **6e**, respectively (Table 2.3).

In summary, enantioselective direct aldol reactions of tetrahydro-4*H*-thiopyran-4-one with aldehydes is effectively catalyzed by proline. Desulfurization of the aldol adducts or the derived diols gives products equivalent to those that would be obtained from 3-pentanone, a ketone that is unreactive in these reactions. The aldols and their derivatives are useful in polypropionate synthesis and the details of our applications in this context will be communicated in due course.[31]

Acknowledgements

We thank J. Wilson Quail of the Saskatchewan Structural Sciences Center for determination of the X-ray structure of **3b**. Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

2.3 Supplementary Information (Experimental section)

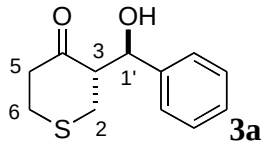
General procedure for aldol reaction: A suspension of **1** (ca. 210 mg, 1.8 mmol) and L-proline (35 mg, 0.30 mmol) in dry DMF or DMSO (0.3 or 0.6 mL) and H_2O (0.011 mL) was stirred at ambient temperature for 2 h and then the aldehyde **2** (0.60 mmol) was added. After stirring for the indicated time, the reaction was quenched by addition of aqueous NH_4Cl (2 mL) and the mixture was extracted with EtOAc (x 3). The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by flash column chromatography (FCC) (EtOAc in hexane) to afford the aldol adducts **3**.

General procedure for aldol reduction: Et_2BOMe (1.0 M in THF; 1.4 equiv) was added to a stirred solution of aldol (0.18-0.20 mmol) in THF (5 mL) and MeOH (1 mL) at –78 °C under argon. The mixture was temporarily removed from the cooling bath to allow the Et_2BOMe to dissolve and then was re-cooled to –78 °C. After 30 min, $NaBH_4$ (2.5 equiv) was added. After for 4-6 h (depending on the substrate; TLC monitoring), the reaction mixture was diluted with dichloromethane (10 mL) and quenched by slow addition of aqueous NaOH (0.1 M; 2 equiv). The organic layer was washed with water (15 mL), dried over Na_2SO_4, concentrated, and fractionated by FCC (50% EtOAc in hexanes) to give the desired diols **7** in 70-85% yield.

General procedure for acetonide formation: A solution of the diol (ca. 5 mg), p-toluenesulfonic acid monohydrate (ca. 1 mg), and 2,2-dimethoxypropane (0.1 mL, excess) in dichloromethane (ca. 0.01 M in diol) was stirred at ambient temperature. After 1-3 h (reaction complete by TLC), the mixture was diluted with dichloromethane, washed

with $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (gradient elution, 0-20% EtOAc in hexanes) to give the corresponding acetonides **8** in >90% yield.

General procedure for desulfurization: Freshly prepared Raney Ni (W-2) (1-2 mL settled volume; added as a suspension in ethanol, 2 mL) and sodium hypophosphite monohydrate (1 M in water; 1 mL) were sequentially added to a well stirred solution of aldol **3** or diol **7** (ca. 0.1 mmol) in ethanol (1mL), THF (1mL), and acetate buffer (pH 5.2; 0.5 mL). For some examples, the resultant mixture was heated under reflux. The reaction was monitored by TLC and, if necessary, another batch of Ra-Ni was added after 1 h. When the reaction was complete (1-9 h), the supernatant was filtered through a pad of Celite® and the residue was suspended in ethanol (5 mL). After stirring for several minutes, the supernatant was filtered (this process was repeated 1-3 times). The combined filtrates were concentrated and the residue taken up in dichloromethane. This solution was washed with water, dried over Na_2SO_4, concentrated, and fractionated by FCC (10-50% EtOAc in hexanes) to give the aldols **5** or diols **6**.



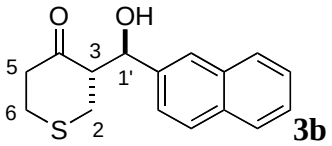
3a

mp 112-114 °C; $[\alpha]_D$ +17, c 1.0, $CHCl_3$ (97% ee);

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40-7.31 (5H, m, Ph), 4.97 (1H, dd, *J* = 3, 9 Hz, HC-1'), 3.40 (1H, d, *J* = 3 Hz, HO), 3.05-2.93 (3H, m, HC-3, H_2C-6), 2.86 (1H, ddd, *J* = 4, 5, 13.5 Hz, HC-5), 2.78 (1H, ddd, *J* = 5,10.5, 13.5 Hz, HC-5), 2.60 (1H, dd, *J* = 10, 14 Hz, HC-2), 2.50 (1H, ddd, *J* = 2, 5, 14 Hz, HC-2);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.1 (s, C-4), 140.3 (s, Ph), 128.9 (d x 2, Ph), 128.6 (d, Ph), 127.1 (d x 2, Ph), 74.1 (d, C-1'), 59.9 (d, C-3), 44.7 (t, C-5), 33.1 (t, C-2), 31.1 (t, C-6);

LRMS (EI), *m/z* (relative intensity): 222 ($[M]^+$, 38), 204 (91), 194 (14), 175 (100), 147 (43), 133 (81). **HRMS** *m/z* calcd for C12H14O2S 222.0715, found 222.0713.



3b

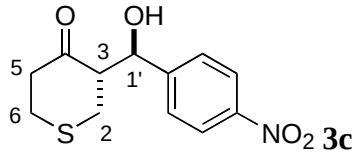
mp 165-166 °C; $[\alpha]_D$ +23, c 1.0, $CHCl_3$ (>98% ee);

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (1H, d, *J* = 8.5 Hz, ArH), 7.87-7.84 (2H, m, ArH), 7.79 (1H, br s, ArH), 7.53-7.49 (3H, m, ArH), 5.16 (1H, dd, *J* = 3, 9 Hz, HC-1'), 3.48 (1H, d, *J* = 3 Hz, HO), 3.12 (1H, ddd, *J* = 5, 9, 10 Hz, HC-3), 3.01 (1H, ddd, *J* = 4, 10.5, 13.5 Hz, HC-6), 2.95 (1H, dddd, *J* = 2, 5, 5, 13.5 Hz, HC-6), 2.89 (1H, ddd, *J* = 4, 5, 13.5

Hz, HC-5), 2.81 (1H, ddd, *J* = 5, 10.5, 13.5 Hz, HC-5), 2.62 (1H, dd, *J* = 10, 14 Hz, HC-2), 2.52 (1H, ddd, *J* = 2, 5, 14 Hz, HC-2);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.1 (s, C-4), 137.7 (s, Ar), 133.5 (s, Ar), 133.3 (s, Ar), 128.9 (d, Ar), 128.2 (d, Ar), 127.9 (d, Ar), 126.6 (d x 2, Ar), 126.4 (d, Ar), 124.4 (d, Ar), 74.3 (d, C-1'), 59.8 (d, C-3), 44.8 (t, C-5), 33.2 (t, C-2), 31.1 (t, C-6);

LRMS (EI), *m/z* (relative intensity): 272 ($[M]^+$, 24), 225 (5), 158 (26), 157 (75), 155 (66), 129 (72), 128 (46), 127 (76), 116 (100). **HRMS** *m/z* calcd for C16H16O2S 272.0871, found 272.0868.



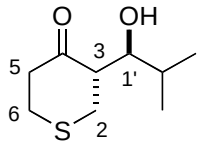
3c

mp 120-122 °C; $[\alpha]_D$ +13, c 1.0, $CHCl_3$ (95% ee);

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23 (2H, d, *J* = 9 Hz, ArH), 7.54 (2H, d, *J* = 9 Hz, ArH), 5.05 (1H, dd, *J* = 4, 8 Hz, HC-1'), 3.66 (1H, d, *J* = 4 Hz, HO), 3.04-2.92 (3H, m, HC-3, H_2C-6), 2.85 (1H, ddd, *J* = 4, 5.5, 13.5 Hz, HC-5), 2.78 (1H, ddd, *J* = 5.5, 11, 13.5 Hz, HC-5), 2.67 (1H, dd, *J* = 11, 14 Hz, HC-2), 2.52 (1H, ddd, *J* = 2, 5, 14 Hz, HC-2);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.4 (s, C-4), 148.0 (s, Ar), 147.8 (s, Ar), 128.0 (d x 2, Ar), 124.0 (d x 2, Ar), 73.4 (d, C-1'), 59.7 (d, C-3), 45.0 (t, C-5), 33.0 (t, C-2), 31.0 (t, C-6);

LRMS (EI), *m/z* (relative intensity): 267 ($[M]^+$, 14), 249 (5), 220 (13), 151 (25), 116 (100), 77 (18). **HRMS** *m/z* calcd for C10H13NO4S 267.0565, found 267.0562.



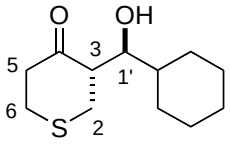
3d

$[\alpha]_D$ –23, c 1.0, $CHCl_3$ (>98% ee);

^{1}H NMR (500 MHz, C6D6) δ: 3.58 (1H, br dd, *J* = 4.5, 7 Hz, HC-1'), 3.17 (1H, br s, HO), 2.70 (1H, ddd, *J* = 4.5, 7, 11 Hz, HC-3), 2.55 (1H, ddd, *J* = 2, 4.5, 13.5 Hz, HC-5), 2.51-2.40 (3H, m, H_2C-2, HC-6), 2.36 (1H, dddd, *J* = 2.5, 5, 5, 13 Hz, HC-6), 2.28 (1H, ddd, *J* = 4.5, 10.5, 13.5 Hz, HC-5), 1.70-1.61 (1H, dqq, *J* = 4.5, 7, 7 Hz, HC-2'), 1.03 (3H, d, *J* = 7 Hz, CH_3), 0.97 (3H, d, *J* = 7 Hz, CH_3);

^{13}C NMR (125 MHz, C_6D_6) δ: 211.7 (s, C-4), 76.2 (d, C-1'), 56.4 (d, C-3), 45.1 (t, C-5), 33.5 (t, C-2), 30.6 (t, C-6), 30.3 (d, C-2'), 20.6 (q, CH_3), 16.2 (q, CH_3);

LRMS (EI), *m/z* (relative intensity): 57 ($[M]^+$, 55), 73 (14), 83 (33), 89 (100), 116 (87), 145 (38), 170 (20), 188 (17). **HRMS** *m/z* calcd for C9H16O2S 188.0871, found 188.0871.



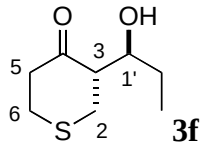
3e

mp 55-57 °C (92% ee);

^{1}H NMR (500 MHz, C_6D_6) δ: 3.52 (1H, dd, *J* = 6, 10 Hz, HC-1'), 3.04 (1H, d, *J* = 6 Hz, HO), 2.74 (1H, ddd, *J* = 6, 9, 10 Hz, HC-3), 2.56-2.53 (2H, m, H_2C-2), 2.43 (1H, ddd, *J* = 5, 11, 13 Hz, HC-6), 2.38 (1H, ddd, *J* = 5, 9.5, 13 Hz, HC-5), 2.30 (1H, dddd, *J* = 2, 5, 9.5, 13 Hz, HC-6), 2.22 (1H, ddd, *J* = 5, 11, 13 Hz, HC-5), 1.86-1.75 (3H, m, ChX), 1.72-1.67 (1H, m, ChX), 1.58-1.49 (1H, m, ChX), 1.48-1.38 (2H, m, Chx), 1.36-1.12 (4H, m, Chx);

^{13}C NMR (125 MHz, C_6D_6) δ: 211.8 (s, C-4), 76.3 (d, C-1'), 55.6 (d, C-3), 45.4 (t, C-5), 40.7 (d, Chx), 33.8 (t, C-2), 30.9 (t x 2, C-6, Chx), 27.2 (t, Chx), 27.2 (t, Chx), 27.1 (t, Chx), 26.9 (t, Chx) ;

LRMS (EI), *m/z* (relative intensity): 55 ($[M]^+$, 21), 57 (35), 67 (12), 83 (32), 88 (16), 89 (53), 95 (22), 116 (100). **HRMS** *m/z* calcd for C12H20O2S 228.1184, found 228.1173.



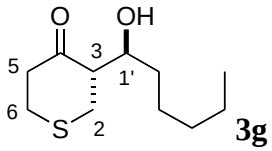
3f

A 16:1 mixture of anti:syn diastereomers (80% ee for the anti isomer).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.77 (1H, ddd, *J* = 4, 6.5, 8,5 Hz, HC-1'), 3.08-2.93 (3H, m), 2.87 (1H, dd, *J* = 10.5, 13.5 Hz, HC-2), 2.80-2.71 (3H, m), 1.68-1.59 (1H, ddq, *J* = 4,14.5, 7.5 Hz, HC-2'), 1.59-1.47 (1H, ddq, *J* = 7.5, 14.5, 8.5 Hz, HC-2'), 1.01 (3H, t, *J* = 7.5 Hz, H_3C-3');

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.5 (s, C-4), 73.1 (d, C-1'), 57.9 (d, C-3), 45.3 (t, C-5), 33.6 (t, C-2), 31.1 (t, C-6), 27.1 (t, C-2'), 9.9 (q, C-3');

LRMS (EI), *m/z* (relative intensity): 53 ($[M]^+$, 13), 55 (58), 57 (100), 59 (30), 67 (15), 73 (11), 127 (11), 156 (27). **HRMS** *m/z* calcd for C8H14O2S 174.0715, found 174.0722.

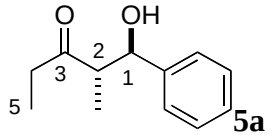


3g

A 10:1 mixture of anti:syn diastereomers (90% ee for anti).

^{1}H NMR (500 MHz, C_6D_6) δ: 3.67 (1H, m, HC-1'), 2.83 (1H, d, *J* = 5.5 Hz, HO), 2.60-2.18 (7H, m, H_2C-2, HC-3, H_2C-5, H_2C-6), 1.59-1.49 (1H, m, HC-2'), 1.51-1.26 (7H, m, HC-2', H_2C-3'-5'), 1.01 (3H, t, *J* = 7 Hz, H_3C-6');

^{13}C NMR (125 MHz, C_6D_6) δ: 211.2 (s, C-4), 72.1 (d, C-1'), 58.8 (d, C-3), 45.2 (t, C-5), 34.8 (t, C-2'), 33.4 (t, C-2), 32.5 (t, C-4'), 30.8 (t, C-6), 25.9 (t, C-3'), 23.4 (t, C-5'), 14.6 (q, C-6').



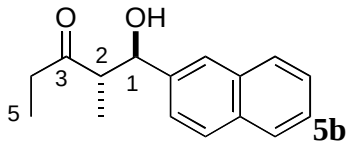
5a

A 11:1 mixture of anti:syn diastereomers;

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39-7.27 (5H, m, Ph), 4.77 (1H, d, *J* = 8 Hz, HC-5), 2.95 (1H, dq, *J* = 8, 7 Hz, HC-4), 2.56 (1H, dq, *J* = 18, 7 Hz, HC-2), 2.45 (1H, dq, *J* = 18, 7 Hz, HC-2), 1.04 (3H, t, *J* = 7 Hz, H_3C-1), 0.95 (3H, d, *J* = 7 Hz, H_3CC-4);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.2 (s), 142.4 (s), 128.7 (d x2), 128.1 (d), 126.7 (d x2), 76.9 (d), 52.8 (d), 36.7 (t), 14.7 (q), 7.6 (q);

LRMS (CI, NH_3), *m/z* (relative intensity): 210 ($[M+18]^+$, 47), 192 (100), 175 (16), 106 (13), 74 (14). **HRMS** *m/z* calcd for C12H16O2 210.1494 ($M+NH_4$), found 210.1487 (CI).



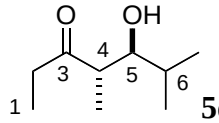
5b

A 15:1 mixture of anti:syn diastereomers;

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.87-7.82 (3H, m, Ar), 7.77-7.76 (1H, m, Ar), 7.52-7.46 (3H, m, Ar), 4.94 (1H, d, *J* = 8.5 Hz, HC-1), 3.06 (1H, dq, *J* = 8.5, 7.5 Hz, HC-2), 3.02 (1H, br s, HO), 2.59 (1H, dq, *J* = 7, 18 Hz, HC-4), 2.47 (1H, dq, *J* = 7, 18 Hz, HC-4), 1.05 (3H, t, *J* = 7 Hz, HC-5), 0.98 (3H, d, *J* = 7 Hz, H_3CC-2);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.2 (s), 139.8 (s), 133.4 (s), 133.3 (s), 128.6 (d), 128.2 (d), 127.9 (d), 126.5 (d), 126.2 (d), 125.9 (d), 124.4 (d), 77.1 (d), 52.7 (d), 36.7 (t), 14.7 (q), 7.6 (q);

LRMS (EI), *m/z* (relative intensity): 242 ($[M]^+$, 31), 157 (100), 156 (64), 155 (48), 128 (37), 127 (60), 86 (65), 57 (46). **HRMS** *m/z* calcd for C16 H18 O2 242.1307, found 242.1304.



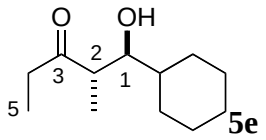
5d

A 12:1 mixture of anti:syn diastereomers;

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.46 (1H, dd, *J* = 5, 6.5 Hz, HC-5), 2.78 (1H, dq, *J* = 6.5, 7 Hz, HC-4), 2.59 (1H, dq, *J* = 18, 7 Hz, HC-2), 2.50 (1H, dq, *J* = 18, 7 Hz, HC-2), 1.74 (1H, dqq, *J* = 5, 7, 7 Hz, HC-6), 1.12 (3H, d, *J* = 7 Hz, H_3C), 1.06 (3H, t, *J* = 7 Hz, H_3C-1), 0.96 (3H, d, *J* = 7 Hz, H_3C), 0.92 (3H, d, *J* = 7 Hz, H_3C);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 217.3 (s), 78.7 (d), 48.3 (d), 36.3 (d), 30.8 (t), 20.2 (q), 16.2 (q), 14.8 (q), 7.7 (q);

LRMS (CI, NH_3), *m/z* (relative intensity): 176 ($[M+18]^+$, 35), 159 ($[M+1]^+$, 100), 141 (12). **HRMS** *m/z* calcd for C9H18O2 159.1385 (M+H), found 159.1380 (CI).

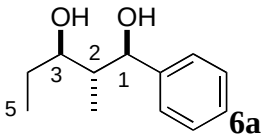


5e

A 10:1 mixture of anti:syn diastereomers;

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.42 (1H, dd, *J* = 5, 6.5 Hz, HC-1), 2.81 (1H, dq, *J* = 6.5, 7 Hz, HC-2), 2.59 (1H, dq, *J* = 18, 7 Hz, HC-5), 2.47 (1H, dq, *J* = 18, 7 Hz, HC-5), 1.82-1.74 (3H, m, Chx), 1.69-1.63 (1H, m, Chx), 1.59-1.53 (1H, m, Chx), 1.42-1.32 (1H, m, Chx), 1.30-1.14 (5H, m, Chx), 1.12 (3H, d, *J* = 7 Hz, H_3CC-3), 1.05 (3H, t, *J* = 7 Hz, H_3C-6);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 217.5 (s), 78.4 (d), 47.6 (d), 41.1 (d), 36.3 (t), 30.5 (t), 27.0 (t), 26.6 (t x 2), 26.3 (t), 14.9 (q), 7.7 (q).



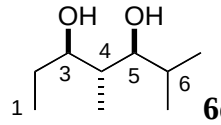
6a

$[\alpha]_D$ +37, c 1.1 (CHCl3);

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39-7.28 (5H, m, Ph), 4.56 (1H, d, *J* = 9 Hz, HC-1), 3.71 (1H, ddd, *J* = 3, 8, 8 Hz, HC-3), 2.26 (2H, br s, HO), 1.93 (1H, ddq, *J* = 8, 9, 7 Hz, HC-2), 1.76-1.64 (1H, ddq, *J* = 3, 14, 7.5 Hz, HC-4), 1.53-1.43 (1H, ddq, *J* = 8, 14, 7.5 Hz, HC-4), 1.01 (3H, t, *J* = 7.5 Hz, H_3C-5), 0.57 (3H, d, *J* = 7 Hz, H_3CC-2);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.6 (s), 128.7 (d x2), 128.1 (d), 127.4 (d x2), 81.1 (d), 78.1 (d), 44.6 (d), 27.8 (t), 13.7 (q), 9.2 (q);

LRMS, *m/z* (relative intensity): 212 ([M+18]$^+$, 17), 194 (40), 177 (11), 136 (100), 119 (26).

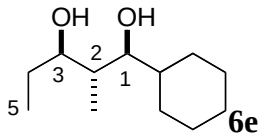


6d

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.60 (1H, ddd, *J* = 3, 8, 8 Hz, HC-5), 3.43 (1H, dd, *J* = 2.5, 9 Hz, HC-3), 2.72 (2H, br s, HO), 1.90 (1H, dqq, *J* = 2.5, 7, 7 Hz, HC-2), 1.68 (1H, ddq, *J* = 3, 14, 7.5 Hz, HC-6), 1.64 (1H, ddq, *J* = 8, 9, 7 Hz, HC-4), 1.44 (1H, ddq, *J* = 8, 14, 7.5 Hz, HC-6), 1.00 (3H, d, *J* = 7 Hz, H_3C), 0.98 (3H, t, *J* = 7.5 Hz, H_3C), 0.87 (3H, d, *J* = 7 Hz, H_3C), 0.79 (3H, d, *J* = 7 Hz, H_3C);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 81.5 (d), 78.1 (d), 41.0 (d), 30.1 (d), 27.7 (t), 20.4 (q), 14.1 (q), 13.3 (q), 9.4 (q) ;

LRMS (CI, NH_3), *m/z* (relative intensity): 178 ([M+18]$^+$, 25), 161 ([M+1]$^+$, 100), 143 (23), 125 (15). **HRMS** *m/z* calcd for C9H20O2 161.1542 (M+H), found 161.1539 (CI).



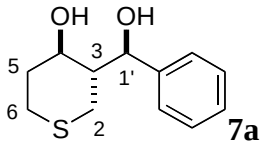
6e

$[\alpha]_D$ -7, c 0.9 ($CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.59 (1H, ddd, *J* = 3, 8, 8 Hz, HC-3), 3.40 (1H, dd, *J* = 2.5, 9 Hz, HC-1), 2.83 (2H, br s, HO), 1.84-1.75 (2H, m), 1.74-1.60 (4H, m), 1.57-1.48 (2H, m), 1.48-1.38 (1H, m), 1.38-1.21 (2H, m), 1.21-1.09 (3H, m), 0.98 (3H, t, *J* = 7 Hz, H_3C-5), 0.78 (3H, d, *J* = 7 Hz, H_3CC-2);

^{3}C NMR (125 MHz, $CDCl_3$) δ: 81.4 (d), 78.1 (d), 40.7 (d), 40.2 (d), 30.8 (t), 27.7 (t), 27.0 (t), 26.8 (t), 26.5 (t), 24.8 (t), 13.5 (t), 9.4 (t);

LRMS (CI, NH_3), *m/z* (relative intensity): 218 ($[M+18]^+$, 26), 201 ($[M+1]^+$, 100), 183 (85), 165 (17), 158 (17), 58 (11). **HRMS** *m/z* calcd for C12H24O2 201.1855 (M+H), found 201.1848 (CI).



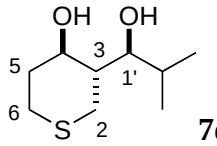
7a

$[\alpha]_D$ -15, c 0.8 (MeOH);

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41-7.31 (5H, m, Ph), 4.70 (1H, d, *J* = 8.5 Hz, HC-1'), 3.70 (1H, ddd, *J* = 4, 9, 10 Hz, HC-4), 2.85-2.21 (2H, br, HO), 2.70-2.57 (2H, m, H_2C-6), 2.32 (1H, dddd, *J* = 3, 3.5, 4, 14 Hz, HC-5), 2.15 (1H, dd, *J* = 12, 14 Hz, HC-2), 2.10-2.02 (2H, m, HC-3, HC-2), 1.82 (1H, m, HC-5);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.9 (s, Ph), 129.0 (d x 2, Ph), 128.6 (d, Ph), 127.3 (d x2, Ph), 80.3 (d, C-1'), 75.2 (d, C-4), 50.9 (d, C-3), 37.0 (t, C-5), 29.4 (t, C-2), 27.6 (t, C-6);

LRMS (EI), *m/z* (relative intensity): 77 ($[M]^+$, 22), 79 (26), 85 (14), 87 (27), 100 (100), 105 (22), 117 (54), 133 (4.5). **HRMS** *m/z* calcd for C12H16O2S 224.0871, found 224.0867.



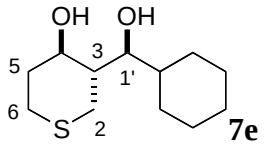
7d

$[\alpha]_D$ -20, c 0.8 ($CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3/D_2O$) δ: 3.64 (1H, ddd, *J* = 4, 9, 10.5 Hz, HC-4), 3.53 (1H, dd, *J* = 3, 8.5 Hz, HC-1'), 2.67 (1H, ddd, *J* = 3, 13.5, 13.5 Hz, HC-6), 2.63 (1H, dddd, *J* = 2, 4, 4, 13.5 Hz, HC-6), 2.57 (1H, ddd, *J* = 2, 4, 13.5 Hz, HC-2), 2.32 (1H, dd, *J* = 11.5, 13.5 Hz, HC-2), 2.28 (1H, dddd, *J* = 3, 4, 4, 13 Hz, HC-5), 1.90 (1H, dqq, *J* = 3, 7, 7 Hz, HC-2'), 1.84-1.74 (2H, m, HC-3, HC-5), 1.02 (3H, d, *J* = 7 Hz, H_3C), 0.92 (3H, d, *J* = 7 Hz, H_3C);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 81.2 (d, C-1'), 74.9 (d, C-4), 47.5 (d, C-3), 36.9 (t, C-5), 30.0 (d, C-2'), 29.5 (t, C-2), 27.5 (t, C-6), 20.0 (q, C-3'), 14.3 (q, C-3');

LRMS (EI), *m/z* (relative intensity): 57 ($[M]^+$, 33), 67 (39), 71 (51), 82 (55), 85 (33), 87 (24), 100 (100), 101 (43). **HRMS** *m/z* calcd for C9H18O2S 190.1028, found 190.1026.



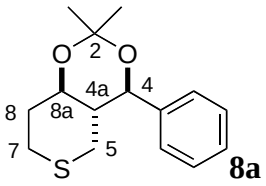
7e

$[\alpha]_D$ -16, c 1.3 ($CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.60 (1H, ddd, *J* = 4, 9, 10.5 Hz, HC-4), 3.49 (1H, dd, *J* = 2.5, 8.5 Hz, HC-1'), 3.17 (2H, br, HO), 2.70 (1H, ddd, *J* = 3, 14, 14 Hz, HC-6), 2.63 (1H, dddd, *J* = 2, 4, 4, 14 Hz, HC-6), 2.55 (1H, ddd, *J* = 2, 3.5, 14 Hz, HC-2), 2.32 (1H, dd, *J* = 11, 14 Hz, HC-2), 2.29 (1H, dddd, *J* = 3, 4, 4, 13 Hz, HC-5), 1.89-1.74 (4H, m, HC-3, HC-5, Chx x2), 1.74-1.66 (2H, m, Chx), 1.59-1.48 (2H, m, Chx), 1.38-1.13 (5H, m, Chx);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 81.1 (d, C-1'), 74.9 (d, C-4), 46.9 (d, C-3), 40.5 (d, Chx), 36.9 (t, C-5), 30.4 (t, Chx), 29.6 (t, C-2), 27.5 (t, C-6), 26.8 (t, Chx), 26.6 (t, Chx), 26.3 (t, Chx), 25.0 (t, Chx) ;

LRMS (EI), *m/z* (relative intensity): 55 ($[M]^+$, 29), 57 (24), 67 (21), 83 (41), 85 (22), 95 (25), 100 (100), 111 (21). **HRMS** *m/z* calcd for C12H22O2S 230.1341, found 230.1336.

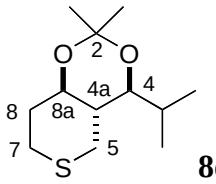


8a

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38-7.28 (5H, m, Ar), 4.46 (1H, d, *J* = 10 Hz, HC-4), 3.71 (1H, ddd, *J* = 3.5, 10, 10 Hz, HC-8a), 2.84 (1H, ddd, *J* = 2.5, 13, 13.5 Hz, HC-7), 2.63 (1H, dddd, *J* = 2.5, 3.5, 3.5, 13.5 Hz, HC-7), 2.37 (1H, dd, *J* = 11.5, 13.5 Hz, HC-5), 2.16 (1H, dddd, *J* = 2.5, 3, 3.5, 13.5 Hz, HC-5), 2.05 (1H, ddd, *J* = 2.5, 3.5, 13.5 Hz, HC-8), 1.90 (1H, dddd, *J* = 3, 10, 10, 11.5 Hz, HC-4a), 1.82 (1H, dddd, *J* = 3.5,10, 13, 13.5 Hz, HC-8), 1.60 (3H, s, H_3C), 1.50 (3H, s, H_3C);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.3 (s, Ph), 128.8 (d x2, Ph), 128.6 (d, Ph), 127.7 (d x2, Ph), 99.4 (s, C-2), 76.6 (d, C-4), 73.3 (d, C-8a), 48.8 (d, C-4a), 34.2 (t, C-8), 30.4 (q, CH_3), 28.2 (t, C-5), 27.9 (t, C-7), 20.0 (q, CH_3);

LRMS (EI), *m/z* (relative intensity): 72 ($[M]^+$, 4), 85 (19), 91 (10), 100 (100), 102 (4), 115 (12), 117 (27), 149 (17). **HRMS** *m/z* calcd for C15H20O2S 264.1184, found 264.1196.

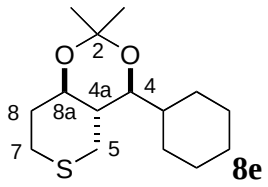


8d

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.50 (1H, ddd, *J* = 4, 10, 10 Hz, HC-8a), 3.39 (1H, dd, *J* = 2, 10 Hz, HC-4), 2.80 (1H, br dd, *J* = 13, 13.5 Hz, HC-7), 2.63 (1H, dddd, *J* = 2, 4, 4, 13.5 Hz, HC-7), 2.45 (1H, ddd, *J* = 2, 3, 13.5 Hz, HC-5), 2.32 (1H, dd, *J* = 11.5, 13.5 Hz, HC-5), 2.10 (1H, dddd, *J* = 2, 4, 4, 13 Hz, HC-8), 1.85-1.71 (3H, m, HC-1', HC-4a, HC-8), 1.42 (3H, s, H_3CC-2), 1.37 (3H, s, H_3CC-2), 0.95 (3H, d, *J* = 7 Hz, H_3CC-1'), 0.89 (3H, d, *J* = 7 Hz, H_3CC-1');

^{13}C NMR (125 MHz, $CDCl_3$) δ: 98.5 (s, C-2), 75.9 (d, C-4), 73.0 (d, C-8a), 44.4 (d, C-4a), 34.2 (t, C-8), 30.2 (q, CH_3C-2), 27.9 (t, C-5), 27.8 (t, C-7), 27.7 (d, C-1'), 20.0 (q, CH_3C-1'), 19.8 (q, CH_3C-2), 14.6 (q, CH_3C-1') ;

LRMS (EI), *m/z* (relative intensity): 55 ($[M]^+$, 31), 57 (13), 59 (11), 73 (18), 99 (43), 100 (100), 101 (53), 116 (15). **HRMS** *m/z* calcd for C12H22O2S 230.3141, found 230.1341.



8e

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.50 (1H, ddd, *J* = 3.5, 10, 10.5 Hz, HC-8a), 3.35 (1H, dd, *J* = 2, 10.5 Hz, HC-4), 2.80 (1H, ddd, *J* = 2.5, 13, 13.5 Hz, HC-7), 2.62 (1H, dddd, *J* = 2, 4, 4, 13.5 Hz, HC-7), 2.46 (1H, ddd, *J* = 2, 3, 13.5 Hz, HC-5), 2.31 (1H, dd, *J* = 11.5, 13.5 Hz, HC-5), 2.08 (1H, dddd, *J* = 2.5, 3.5, 4, 13 Hz, HC-8), 1.81 (1H, dddd, *J* = 3, 10.5, 11.5 Hz, HC-4a), 1.79-1.71 (3H, m, HC-8, Chx x2), 1.68-1.59 (2H, m, Chx), 1.49-1.37 (2H, m, Chx), 1.42 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.33-1.10 (5H, m, Chx);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 98.5 (s, C-2), 76.1 (d, C-4), 73.1 (d, C-8a), 43.5 (d, C-4a), 38.1 (d, Chx), 34.2 (t, C-8), 30.3 (q, CH_3), 30.2 (t, Chx), 27.8 (t, C-5), 27.7 (t, C-7), 27.0 (t, Chx), 26.7 (t, Chx), 26.6 (t, Chx), 25.0 (t, Chx), 19.8 (q, CH_3) ;

LRMS (EI), *m/z* (relative intensity): 55 ($[M]^+$, 25), 67 (33), 81 (21), 85 (22), 95 (16), 100 (100), 109 (19), 195 (58). **HRMS** *m/z* calcd for C15H26O2S 270.1654, found 270.1651.

2.4 References

1. Mukaiyama, T. *Org. React.* **1982,** *28*, 203-331.

2. Reviews: (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998,** *9*, 357-389. (b) Mahrwald, R. *Chem. Rev.* **1999,** *99*, 1095-1120. (c) Arya, P.; Qin, H. *Tetrahedron* **2000,** *56*, 917-947. (d) Carreira, E. M. In *Modern Carbonyl Chemistry*; Otera, J., Ed. Wiley-VCH: Weinhein, Germany, 2000, pp 227-248. (e) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Eur. J.* **2002,** *8*, 36-44.

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7. See the Supplementary Material for a complete list of references on direct intermolecular aldol reactions catalyzed by proline and derivatives.

8. Tetrahydro-4*H*-thiopyran-4-one (**1**) is commercially available but is rather expensive (> $25/g). For a simple and inexpensive (< $25/mol) preparation of **1**, see ref. 9c.

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3. Enantioselective Direct Intermolecular Aldol Reactions with Enantiotopic Group Selectivity and Dynamic Kinetic Resolution

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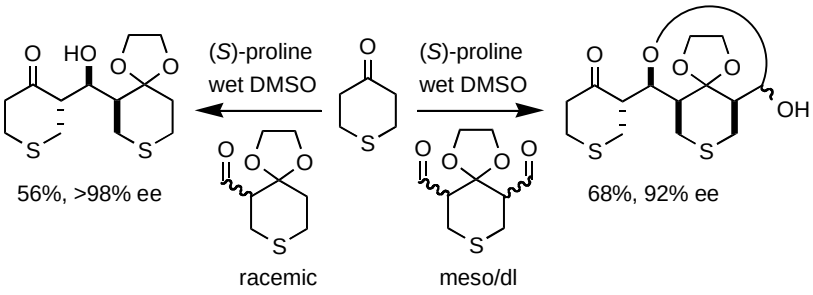
Graphical Abstract



3.1 Preface

Proline-catalyzed aldol reaction of tetrahydro-4*H*-thiopyran-4-one with different achiral aldehydes gave *anti* adducts with high diastereo- and enantioselectivities in moderate to excellent yields and was described in chapter 2. Inspired by these results, we were anxious to investigate the proline-catalyzed asymmetric aldol reactions of tetrahydro-4*H*-thiopyranone with racemic 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde and with meso/dl 1,4-dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxaldehyde as a strategy to rapidly assemble tetrapropionate synthons with potential applications to polypropionate natural products synthesis.

The following manuscript is a verbatim copy of the original paper published in **Organic Letters** (**2005**, Vol. 7, No. 6, 1181–1184) and is formatted as per thesis regulations of the University of Saskatchewan. Permission to reproduce the published material was obtained from the American Chemical Society (ACS) and Olukayode T. Akinnusi (co-author) whose contributions to the manuscript are described in Scheme 3.3; this experimental work is not included in Section 3.3 (Supplementary Information). The remainder of the work was carried out by me and the manuscript was prepared in collaboration with my supervisor.

3.2 Manuscript: Organic Letters (2005) Vol. 7, No. 6, 1181–1184

Enantioselective Direct Intermolecular Aldol Reactions with Enantiotopic Group Selectivity and Dynamic Kinetic Resolution

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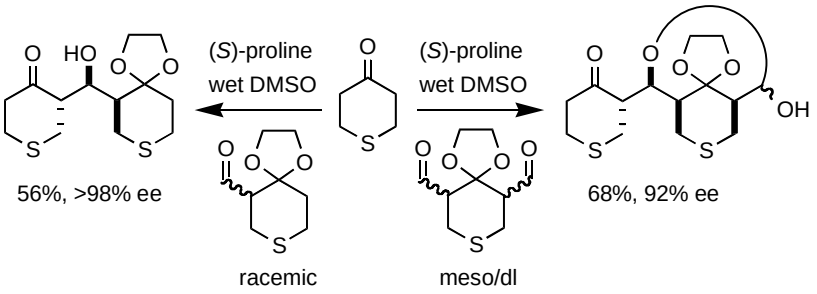
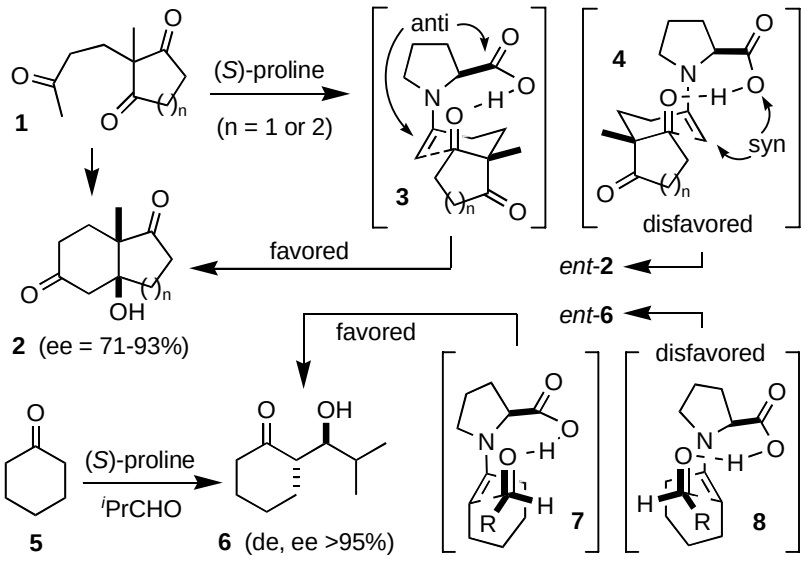


Abstract: Proline-catalyzed aldol reactions of tetrahydro-4*H*-thiopyranone with racemic 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde and with meso/dl 1,4-dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxaldehyde proceed with dynamic kinetic resolution and give single adducts in good yields with excellent ee's. The high enantiotopic group selectivity results from the high intrinsic diastereoface selectivity of the aldehydes. These reactions significantly extend the scope of the enantioselective direct aldol reaction and constitute simple and efficient syntheses of useful tetrapropionate synthons.

In a landmark paper in 2000, List, Lerner, and Barbas described the first examples of proline-catalyzed enantioselective direct intermolecular aldol reactions.[1] This report prompted an extensive investigation by several groups of the use of proline and its derivatives to catalyze aldol (and other) reactions.[2] Although very high stereoselectivity has been observed in several examples, a major limitation of this process has been the rather narrow substrate scope. The vast majority of examples to date have involved simple achiral reactants. In this contribution, we report that proline-catalyzed aldol reactions of **10** with the racemic aldehydes (±)-**9** or (±)-**19** and/or *meso*-**19** proceed with a combination of enantiotopic group selectivity[3] and dynamic kinetic resolution[4] to give adducts in good yields with excellent stereoselectivities. Conceptually, these reactions significantly extend the scope of the direct aldol reaction and constitute exceedingly simple and efficient syntheses of useful tetrapropionate synthons.



Scheme 3.1

Proline-catalyzed enantioselective aldol reactions were first reported in the 1970's in the context of the Hajos-Parrish-Eder-Sauer-Wiechert reaction (i.e. **1**→**2**; Scheme 3.1).[5] Recent mechanistic studies have concluded that the reaction proceeds by intramolecular carboxylic acid catalyzed addition of a proline enamine to the carbonyl group.[6].The transition state structures **3** and **4** for additions to the two cyclic carbonyl groups differ by an anti vs. syn orientation of the enamine and the enantiotopic group selectivity derives from the greater stability of the anti orientation *combined* with the inherent preference for addition trans to the quaternary methyl group.[7] The reaction has been applied to acyclic C_S symmetric diketones[8] and dialdehydes[9] but the stereoselectivity is lower in these cases presumably because of poor enantiotopic group selectivity in the enamine-forming step[10] and/or similar reactivity among the diastereomeric enamines.[7]

The transition state structures proposed for the proline-catalyzed intermolecular aldol reaction (e.g. **5**→**6**) are similar to those for the intramolecular reaction, in this case favoring addition from the *re* face of the α-carbon in an anti-oriented enamine to the *re* face of the aldehyde (cf. **7**).[11] It is convenient to consider that face selectivity for addition to the enamine is controlled by the absolute configuration of the proline catalyst and the face selectivity for addition to the aldehyde is dictated by the 'closed' transition state. In a similar reaction with a chiral aldehyde, the intrinsic diastereoface selectivity can either reinforce or counteract the face selectivity preferred by this 'closed' transition state (i.e. the influence of a chiral R fragment in TS **7**) resulting in double stereodifferentiation and/or kinetic resolution. Only modest levels of enantiotopic group selectivity have been observed among the scattered examples of proline-catalyzed aldol reactions with chiral

aldehyde 'acceptors' reported to date.[12,13] We speculated that these reactions might show significant enantiotopic group selectivity and double stereodifferentiation if the aldehyde possessed sufficient diastereoface selectivity.[14]

We have been developing stereoselective sequential two-directional aldol reactions of **9** and **10** as the foundation of a thiopyran-based synthetic route to polypropionates.[15] Aldehyde **9** emerged as a good candidate for enantiotopic group selective direct aldol because additions to its carbonyl group show exclusive Felkin diastereoface selectivity.[15c] A preliminary study established that proline-catalyzed aldol reactions of **10** with simple achiral aldehydes are highly diastereo- and enantioselective.[16] In the event, proline-catalyzed aldol reaction of **10** with (±)-**9** under the previously established conditions[16] gave the expected[17] adduct **11**[18] as a single diastereomer (Scheme 3.2) albeit in poor yield (33%) and with disappointing enantioselectivity (ca. 50% ee) (Table 3.1, entry 1).

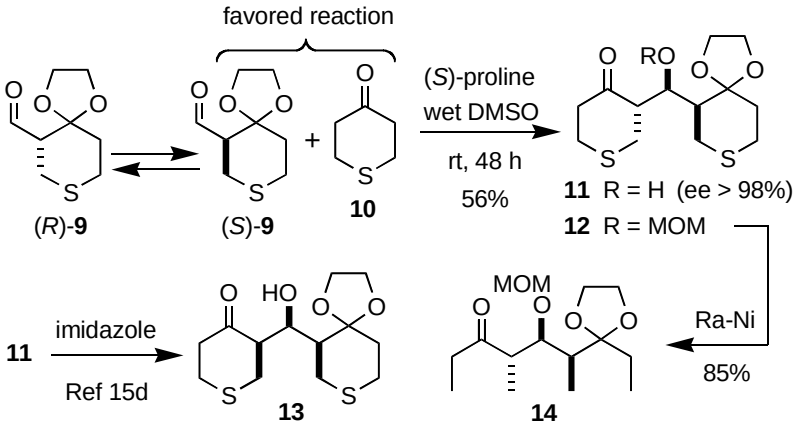
The aldol reaction of **9** and **10** was dramatically improved in the presence of added water,[10b,16] and optimization of the conditions with respect to solvent, concentration, stoichiometry, and protocol allowed efficient preparation of **11** (56%, >98% ee) on gram scale (Table 3.1). We conclude the reaction is under kinetic control and proceeds with dynamic kinetic resolution rather than simple kinetic resolution because: i) (-)-**11** (>98% ee) is re-isolated in >85% yield and >90% ee after exposure to (*S*)- or (*R*)-proline (48 h, wet DMSO); ii) racemic **9** is recovered from the reaction; iii) (*S*)-**9**[18] readily racemizes under the reaction conditions. Previously reported examples of dynamic kinetic resolution[12gh] and of isomerization of aldehydes[12c,f,g] during proline-catalyzed intermolecular aldol reactions have resulted in products with modest stereoselectivity.[19]

Thus it is noteworthy that the reaction of (±)-**9** and **10** proceeds with high enantiotopic group selectivity and high aldol stereoselectivity to give the adduct **11** as a single diastereomer with excellent ee.

Table 3.1. Proline-catalyzed aldol reactions of **9** with **10**.[a]

entry	[**9**]	**10** (# equiv)	solvent (# equiv H_2O)	time (days)	%yield[b]	$[\alpha]_D$[c]
1.	1	3	DMSO	2	33	-22
2.	1	3	DMF	2	18	-19
3.	1	3	DMF (2)	2	17	-29
4.	1	3	DMSO (2)	2	39	-31
5.	0.5	3	DMSO (2)	2	19	[d]
6.	2	3	DMSO (2)	2	47	-20
7.	1	3	DMSO (4)	2	32	-39
8.	1	3	DMSO (8)	2	36	-43
9.	1	3	DMSO (16)	2	19	-44
10.	1	6	DMSO (8)	2	52	-46
11.	1	12	DMSO (8)	2	52	-41
12.	1	6	DMSO (8)	4	48	-46
13.	1	6	DMSO (8)	8	47	-39
14.[e]	1	6	DMSO (8)	2	38	-47
15.[f]	1	6	DMSO (8)	2	37	-47
16.[g]	**1**	**6**	**DMSO (8)**	**2**	**56**	**-47[h]**

[a] Reactions at room temperature with 50 mg of **9** and 0.5 equiv of (*S*)-proline. [b] Isolated yield of **11**. [c] At ambient temperature (ca. 23°C); *c*=1.0, $CHCl_3$; $[\alpha]_D$(max) for **11** = -47. [d] Not determined. [e] 0.25 equiv of (*S*)-proline. [f] 1.0 equiv of (*S*)-proline. [g] 1.0 g of **9**. [h] This sample was shown to be >98% ee by ^{1}H NMR of the derived **12** in the presence of (+)–$Eu(hfc)_3$.

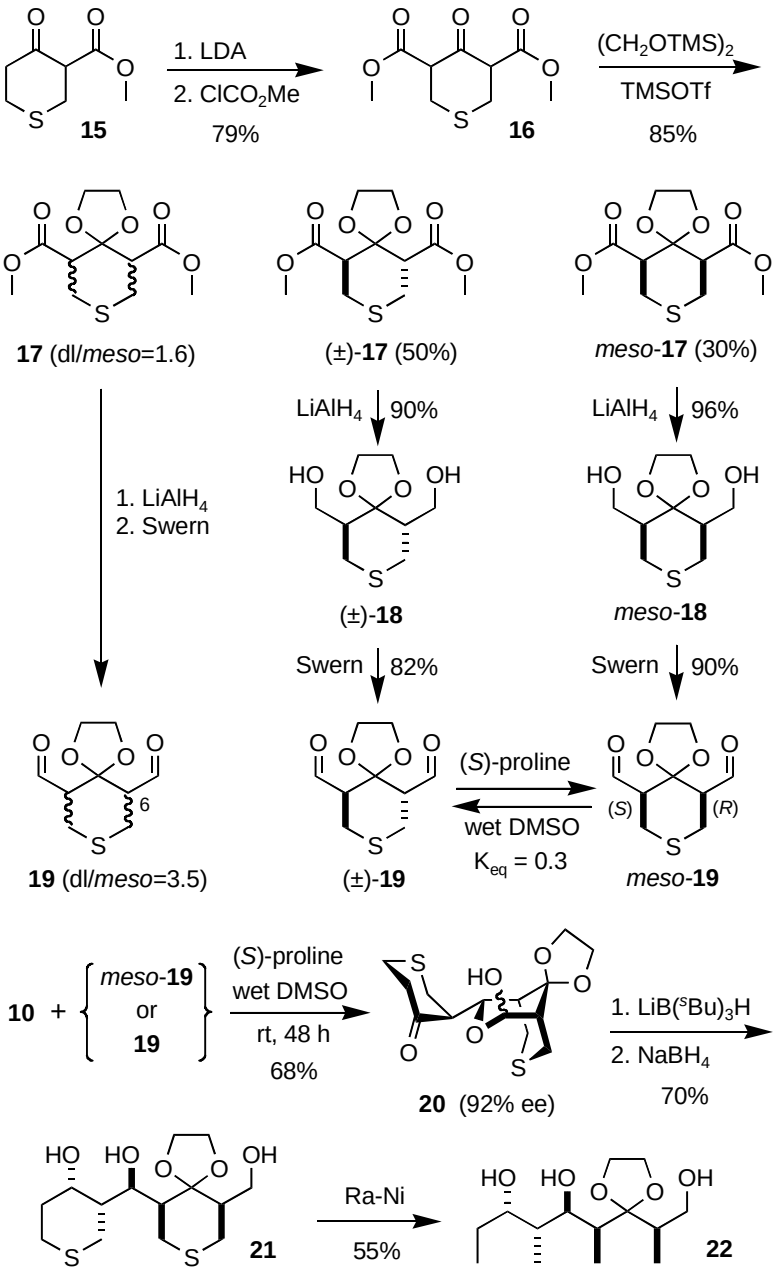


Scheme 3.2

Aldol **11** is a versatile tetrapropionate synthon that can be utilized as a precursor for both *anti-syn* and s*yn-anti* stereotriads because of its differentiated 1,5-dione functionality.[15] We have previously shown[15d] that **11** is readily isomerized to **13** allowing ready access to *syn-syn* stereotriads. Surprisingly,[16] Raney nickel desulfurization of **11** was somewhat capricious; however reaction of the MOM ether derivative **12** gave **14** in good yield.

Encouraged by these results, we attempted to extend the process to desymmetrization of a meso dialdehyde.[20] Carboxylation of **15**[15c] and protection of the resulting ketodiester **16** gave **17** as a readily separable 1.6:1 mixture of (±)-**17** and *meso*-**17**, respectively (Scheme 3.3). $LiAlH_4$ reduction of *meso*-**17** followed by careful Swern oxidation of the product diol *meso*-**18** gave *meso*-**19** in good yield. Reaction of **10** with *meso*-**19** under the optimized conditions gave **20** (a 3:1 mixture of anomers in C_6D_6) as the only aldol adduct in 68% yield and 92% ee. The adduct **20** exists exclusively in the hemiacetal form suggesting that the stereocenter originating from C-6 in **19** could be set under thermodynamic control. Gratifyingly, reaction of **10** with the readily available

3.5:1 mixture of (±)-**19** and *meso*-**19**, respectively, produced **20** in the same yield and ee as when using *meso*-**13** alone.[21] Rapid proline-catalyzed isomerization of *meso*-**19** to give a 3.5:1 equilibrium mixture of (±)-**19** and *meso*-**19**, respectively, was established by ^{1}H NMR.



Scheme 3.3

The selective formation of **20** from *meso*-**19** is readily explained by preferential aldol reaction of **10** with the (α*S*)-aldehyde group of *meso*-**19** (in analogy to the reaction with (±)-**9**).[17] However, **20** might also arise by preferential aldol reaction of **10** with (*S*,*S*)-**19** followed by rapid isomerization and hemiacetal formation. We are unable to distinguish these possibilities; however, in either scenario, the reaction of **10** with **19** occurs with an unusual combination of enantiotopic group selectivity together with dynamic kinetic and thermodynamic resolution. To the best of our knowledge, examples of such reactions have not been previously described. This remarkable process simultaneously generates four stereogenic centers with excellent diastereo- and enantioselectivity. The adduct **20** has versatile functionality and should be a useful tetrapropionate synthon.[22] To illustrate, the ketone and acetal groups in **20** were sequentially reduced to give **21** which gave **22** on desulfurization (Scheme 3.3).

In summary, proline-catalyzed direct aldol reactions of **10** with the chiral aldehydes **9** and **19** are highly diastereo- and enantioselective. The aldol adducts **11** and **20** are useful tetrapropionate synthons.[15] The remarkable stereoselectivity in these reactions is attributable to combination of the high propensity for addition to the aldehyde *re* face imposed by the (*S*)-proline catalyst together with the high Felkin diastereoface selectivity intrinsic to these aldehydes that results in a strong kinetic preference for the 'matched' reaction (i.e. high enantiotopic group selectivity).[14] Because the proline-catalyzed isomerization of the aldehydes is much faster than the aldol, the reactions proceed with dynamic kinetic resolution.[19] This design strategy should be applicable to other substrates in enantioselective direct aldol reactions and significantly expands the scope of this important process.

Acknowledgment We thank J. Wilson Quail of the Saskatchewan Structural Sciences Center for determination of the X-ray structures of (±)-**20** and (+)-**21**. Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

Supporting Information Available Experimental procedures and spectroscopic data for all new compounds synthesized (PDF) and X-ray crystallographic data for **20** and **21** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

3.3 Supplementary Information (Experimental section)

General Methods: All solvents were distilled prior to use. Anhydrous solvents were distilled under argon atmosphere as follows: Tetrahydrofuran (THF) from benzophenone potassium ketyl; ether from benzophenone sodium ketyl; CH_2Cl_2 and toluene from CaH_2; MeOH from $Mg(OMe)_2$. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were ice/water (0 °C) and CO_2(s)/acetone (-78 °C). Reaction temperatures refer to that of the bath.

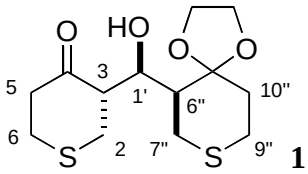
Preparative TLC (PTLC) was carried out on glass plates (20x20 cm) precoated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aqueous sulfuric acid (5% v/v), followed by charring on a hot plate. Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by NMR.

Flash column chromatography (FCC) was performed according to Still et al.[23] with Merck Silica Gel 60 (40-63 μm). Medium pressure chromatography (MPC) was performed essentially as reported by Taber.[24] Dry flash column chromatography was performed according to Harwood.[25] All mixed solvent eluents are reported as v/v solutions.

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. EI ionization was accomplished at 70 eV and CI at 50 eV with ammonia as the reagent gas; only partial data are reported. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 300, 400, or 500 MHz for ^1H and 75, 100, or 125 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); CD_3OD (3.31 δ_H, 49.15 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. Couplings constants (*J*) are reported to the nearest 0.5 Hz. The ^1H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or NOE experiments. The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity[26] (as determined by *J*-modulation[27] or HSQC[28]) and were confirmed, where necessary, by two dimensional $^1H/^{13}C$ correlation experiments (HSQC and/or HMBC[29]).

Materials: The preparations of the following compounds were described previously: (±)-**9** and **15**;[30] (*R*)-(+)-**9**;[31] **10**.[32] $^iPr_2NH$ was distilled from CaH_2. All other reagents were commercially available and unless otherwise noted, were used as received.

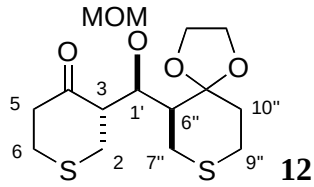
(3*S*)-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl(hydroxy)methyl]tetrahydro-4*H*-thiopyran-4-one (11).



11

A suspension of thiopyranone (**10**) (4.0 g, 34 mmol) and (*S*)-proline (300 mg, 2.60 mmol) in dry DMSO (6 mL) and H_2O (0.8 mL) was stirred at room temperature for 2 h and then the aldehyde **9** (1.0 g, 5.3 mmol) was added. After stirring for 2 days, the reaction was quenched by addition of aqueous NH_4Cl (10 mL) and the mixture was extracted with ethyl acetate (×3). The combined organic layers were dried over Na_2SO_4 and concentrated. The excess **10** was removed at high vacuum (and collected in a cold trap) and the remaining residue was fractionated by FCC (30% ethyl acetate in hexane) to give the known aldol **11** (900 mg, 56%; $[\alpha]_D$ –47, *c*=1.0, $CHCl_3$; >98% ee). The absolute configuration was assigned as (1'*R*,3*S*,6''*S*) by comparison of the sign of the $[\alpha]_D$ with the literature value (Ward, D. E.; Akinnusi, O. T.; Alarcon, I. Q.; Jheengut, V.; Shen, J.; Quail, J. W. *Tetrahedron: Asymmetry* **2004,** *15*, 2425-2430). The ee for **11** was determined by ^{1}H NMR of the derived MOM ether **12** in the presence of (+)-Eu(hfc)$_3$; the ee was conservatively estimated to be >98% because the H_3CO peak for the minor enantiomer was smaller (not detected) than the ^{13}C satellite from the H_3CO peak for the major enantiomer (180:1). Separation of enantiomeric peaks under the conditions was confirmed by spiking with a racemic sample.

(3*S*)-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4*H*-thiopyran-4-one (12).



12

Bu_4NI (400 mg; 1.08 mmol), *i*-Pr_2EtN (0.90 mL, 0.67 g, 4.6 mmol), and MOMCl (0.25 mL, 0.27 g, 3.4 mmol) were sequentially added to a solution of the aldol **11** (314 mg, 1.03 mmol) in dry CH_2Cl_2 (2 mL) at room temperature under argon. After standing for 24 h (reaction complete by TLC), the mixture was diluted with 1M HCl and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was triturated with 50% ethyl acetate in hexane (x3) and the supernatant was filtered through a short pad of SiO_2. The combined filtrates were concentrated to give the titled compound as a solid (330 mg, 92%; ee >98%) that was homogeneous by TLC and ^{1}H NMR: mp 119-120 °C; $[\alpha]_D$ +8.4 (*c* 1.0 $CHCl_3$);

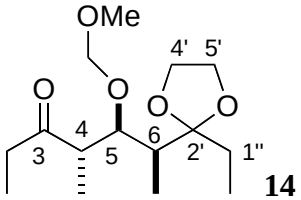
IR λ_{max}: 2912, 1709, 1153, 1132, 1095, 1066, 1031, 889 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.82 (1H, d, *J* = 7 Hz, H_2CO), 4.51 (1H, d, *J* = 7 Hz, H_2CO), 4.46 (1H, dd, *J* = 4.5, 6 Hz, HC-1'), 4.10-3.93 (4H, m, H_2CO x2), 3.32 (1H, s, H_3CO), 3.05 (1H, dd, *J* = 7, 13.5 Hz, HC-2), 2.98 (1H, dd, *J* = 4, 13.5 Hz, HC-2), 2.94-2.88 (5H, m, HC-3, HC-5, H_2C-6, HC-7"), 2.80-2.71 (2H, m, HC-7", HC-9"), 2.70-2.57 (2H, m, HC-5, HC-9"), 2.19 (1H, ddd, *J* = 4, 4.5, 10 Hz, HC-6"), 2.13 (1H, ddd, *J* = 3, 5.5, 14 Hz, HC-10"), 1.70 (1H, ddd, *J* = 3.5, 11, 14 Hz, HC-10");

^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.7 (s, C-4), 108.9 (s, C-5'), 97.7 (t, OCH_2O), 74.9 (d, C-1'), 65.0 (t, CH_2O), 64.7 (t, CH_2O), 58.3 (d, C-3), 56.8 (q, CH_3O), 50.1 (d, C-6''), 43.6 (t, C-5), 36.1 (t, C-10''), 32.8 (t, C-2), 30.5 (t, C-6), 28.9 (t, C-7''), 27.0 (t, C-9'');

LRMS (EI), *m/z* (relative intensity): 348 ($[M]^+$, 4), 286 (9), 224 (10), 197 (11), 159 (13), 133 (22), 132 (61), 99 (100). **HRMS** *m/z* calcd for $C_{15}H_{24}O_5S_2$ 348.1056, found 348.1056.

(4*S*,5*R*,6*S*)-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-(methoxymethoxy)-4-methylheptan-3-one (14).



14

A suspension of freshly prepared Raney-Ni (W-2) (1.5 mL settled volume) in ethanol (2 mL) was added at once to a well stirred solution of **12** (50 mg, 0.14 mmol) in methanol (10 mL) and the mixture was heated under reflux. After 25 min (reaction complete by TLC analysis), the supernatant was filtered through a pad of Celite® and the residue was suspended in ethanol (20 mL) and heated under reflux. The supernatant was filtered and this process was repeated if necessary. The combined filtrates were concentrated and fractionated by FCC (25% ethyl acetate in hexanes) to give the titled compound as a pale yellow oil (35 mg, 85%):

$[\alpha]_D$ = +64 (*c* 0.77, $CHCl_3$);

IR $_{max}$: 2976, 2938, 2884, 1711, 1464, 1200, 1033, 925 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ: 4.69 (1H, d, *J* = 6.5 Hz, HCO_2), 4.55 (1H, d, *J* = 6.5 Hz, HCO_2), 4.16 (1H, dd, *J* = 1, 6.5 Hz, HC-5), 3.57-3.42 (4H, m, H_2CO x2), 3.18 (3H, s, H_3CO), 2.82 (1H, dq, *J* = 6.5, 7 Hz, HC-4), 2.48 (1H, dq, *J* = 7, 18 Hz, HC-2), 2.14 (1H, dq, *J* = 7, 18 Hz, HC-2), 2.02 (1H, dq, *J* = 1, 7 Hz, HC-6), 1.77-1.62 (2H, m, H_2C-1"), 1.14 (3H, d, *J* = 7 Hz, H_3C-7), 1.05 (3H, t, *J* = 7 Hz, H_3C-1), 1.04 (3H, d, *J* = 7 Hz, H_3CC-4), 0.91 (3H, t, *J* = 7 Hz, H_3C-2");

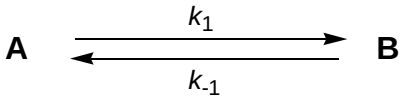
^{13}C NMR (125 MHz, C_6D_6) δ: 211.7 (s, C-3), 113.9 (s, C-2'), 97.43 (t, OCH_2O), 77.1 (d, C-5), 65.5 (t, CH_2O), 65.3 (t, CH_2O), 56.3 (q, CH_3O), 51.2 (d, C-4), 41.0 (d, C-6), 36.7 (t, C-2), 27.2 (t, C-1"), 12.4 (q, C-1), 10.7 (q, C-7), 8.2 (q, CH_3), 8.0 (q, CH_3);

LRMS (CI, NH3), *m/z* (relative intensity): 306 ($[M+18]^+$, 2), 258 (20), 257 (95), 227 (15), 149 (13), 127 (99), 101 (100), . **HRMS** *m/z* calcd for $C_{13}H_{23}O_5$ (M-C_2H_5) 259.1545, found 259.1543 (EI).

Determination of Isomerization Rate Constants

The kinetic model for reversible proline-catalyzed isomerization of aldehyde **A** to aldehyde **B** via enolization assumes that both the forward and reverse reactions are 1st order with respect to the particular 'reactant' at a fixed concentration of proline. The 'composite' rate constants k_1 and k_{-1} can be easily obtained by simply monitoring the rate of appearance or disappearance of the aldol stereoisomers **A** and/or **B**.

For a kinetically first order reversible reaction:



It is easily shown that for a system not at equilibrium (i.e., [**A**] ≠ [**A**]$_e$):[33]

$$(k_1 + k_{-1})t = -\ln\left(\frac{[\mathbf{A}]_t - [\mathbf{A}]_e}{[\mathbf{A}]_0 - [\mathbf{A}]_e}\right) = -\ln\left(\frac{R_t - R_e}{R_t + 1}\right) \quad \text{[equation 1]}$$

where [**A**]$_0$ is the initial concentration of **A**, [**A**]$_e$ is the concentration of **A** at equilibrium, [**A**]$_t$ is the concentration of **A** at time *t*, R_t is the ratio of [**A**]/[**B**] at time *t* and R_e is the equilibrium ratio of [**A**]/[**B**]. In this form, the equation resembles that for an irreversible first order reaction of **A** with a rate constant k_{obs} (= k_1 + k_{-1}) but with the analytical concentration of **A** (i.e. [**A**]$_t$) replaced by the 'active' concentration of **A** (i.e. [**A**]$_t$-[**A**]$_e$) which is that fraction of **A** undergoing transformation). Thus, k_{obs} (= k_1 + k_{-1}) is the first order rate constant for equilibration of a non-equilibrium system.

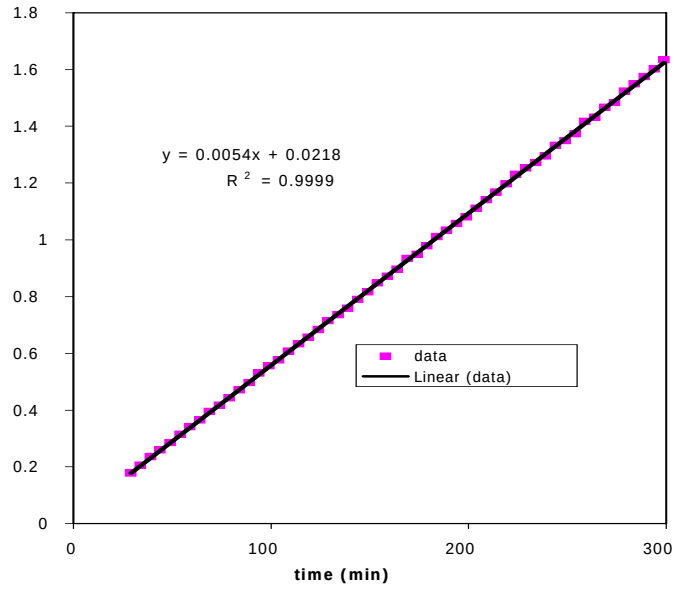
Proline-catalyzed racemization of (+)-**9**

The rate of racemization of **9** under the aldol reaction conditions was investigated by measuring the time dependent change in the optical rotation of a solution of (+)-**9** in wet DMSO in the presence of proline. Thus, a solution of (*S*)-proline (8 mg, 0.07 mmol) and water (0.040 mL, 2.2 mmol) in dry DMSO (2.0 mL) was prepared. The aldehyde (+)-

9[9](12 mg, 0.064 mmol; ca. 88% ee) was dissolved in the above DMSO solution and diluted to 1 mL using a volumetric flask. This solution was transferred into a 1 mL, 10.0 cm polarimetry cell and the optical rotation (α_D) of the solution was measured every 5 min for 15 h (Figure S1a). Because the excess concentration of (+)-**9** is proportional to the optical rotation (α), the first order rate constant for racemization (k_{obs}=5.4 x10^{-3} min^{-1}) under these conditions is obtained from plot of $-\ln[(\alpha_t-\alpha_e)\div(\alpha_0-\alpha_e)]$ vs. t (Figure 3.1a). The half-life ($t_{1/2} = (\ln 2)/k_{obs}$) for the racemization is calculated to be 128 min or 2.1 h. An identical experiment was conducted using (±)-**9** in place of (+)-**9**; the optical rotation (α) changed from –5° to –16° over 15 h. In both cases, the aldehyde **9** was recovered in >85% yield and was shown to be racemic (ee < 5%) by NMR.[9] The optical rotation (α) of the DMSO solution containing (*S*)-proline (4 mg/mL) and water (20 mg/mL) was –13°.

We expect that the rate of isomerization of **9** is considerably faster during aldol reaction than in the above experiment because of the much higher proline concentration (ca. x10).

(a)



(b)

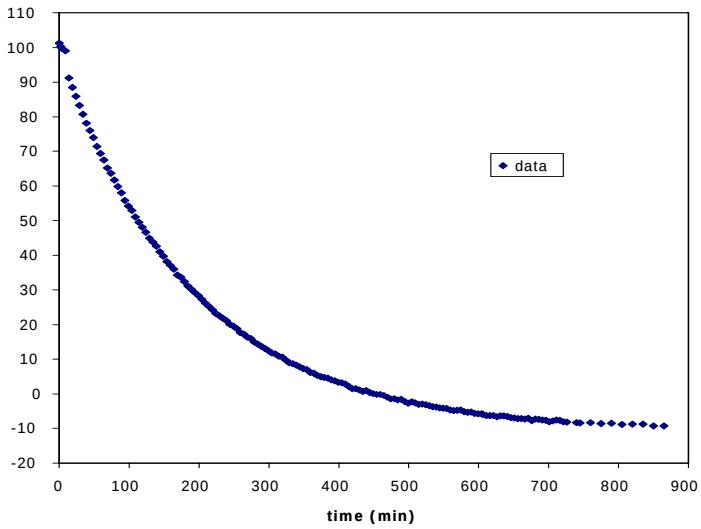


Figure 3.1. Racemization of (+)-**9** (12 mg/mL) in DMSO solution containing water (20 mg/mL) and (*S*)-proline (4 mg/mL): (a) plot of $-\ln[(\alpha_t-\alpha_e)\div(\alpha_0-\alpha_e)]$ versus time (data from the initial 2 half-lives; i.e., t=30-300 min): (b) plot of optical rotation (α_D) versus time at ambient temperature.

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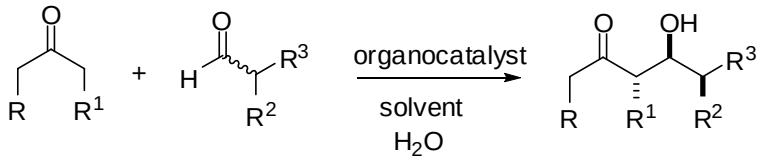
3. Enantioselective Direct Intermolecular Aldol Reactions with Enantiotopic Group Selectivity and Dynamic Kinetic Resolution: Scope and Limitations

Dale E. Ward, Vishal Jheengut, and Garrison E. Beye

Graphical Abstract



4.1 Preface

Proline-catalyzed aldol reaction of tetrahydro-4*H*-thiopyranone with racemic 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde proceeds with dynamic kinetic resolution to give a single adduct in good yield with excellent ee. The high enantiotopic group selectivity of this reaction resulted from the high intrinsic diastereoface selectivity of the aldehyde. In principle, chiral α-substituted aldehydes possessing high intrinsic diastereoface selectivities should also be potential candidates in the proline-catalyzed aldol reactions. A detailed study on the scope and limitations of the research discussed in chapter 3 using different catalysts, aldehydes, and ketones (cyclic and acyclic) is described in this manuscript.

The following manuscript will be submitted to the **Journal of Organic Chemistry** and is formatted in this chapter as per thesis regulations of the University of Saskatchewan. Garrison E. Beye is a co-author in this manuscript and permission to include his unpublished work in my thesis in order to complete this joint project was granted by him. His contributions include aldol reactions of ketones (**1**, **10**, **11**, and **12**) with racemic aldehyde **2** using catalyst **7** and characterization of compounds **10a**, **11a**, and **12** (Section 4.3). The remainder of the work was carried out by me and the manuscript was prepared in collaboration with Garrison Beye and my supervisor.

4.2 Manuscript: To be submitted to the Journal of Organic Chemistry

Enantioselective Direct Intermolecular Aldol Reactions with Enantiotopic Group Selectivity and Dynamic Kinetic Resolution: Scope and Limitations

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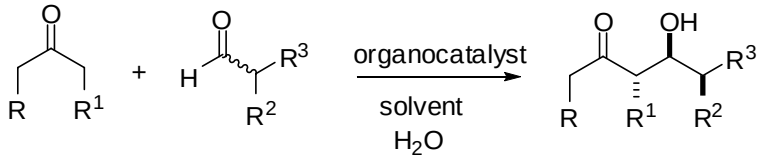
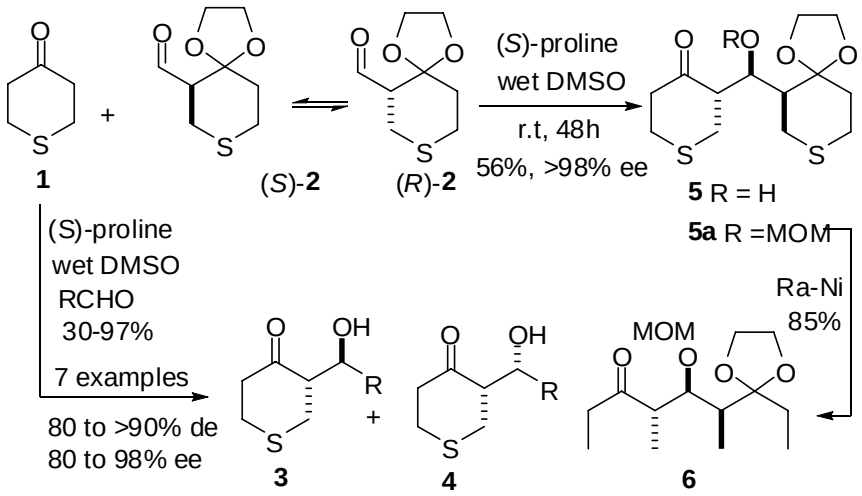


Abstract: Intermolecular direct aldol reactions of tetrahydro-4*H*-thiopyranone with different racemic aldehyde acceptors have been explored using different organocatalysts. Moderate to good yields with excellent diastereo- and enantioselectivities were observed in these reactions. Aldol reactions of other ketone donors such as acetone and 2-butanone with chiral aldehydes are also described. The aldol reactions proceeded with dynamic kinetic resolution and high enantiotopic group selectivity resulting from the high intrinsic diastereoface selectivity of the chiral aldehydes. These reactions significantly extend the scope of the enantioselective direct aldol reaction and constitute simple and efficient syntheses of functionalized oligopropionate synthons with potential application to the synthesis of polypropionate natural products.

The aldol reaction is undoubtly the most instrumental and versatile tool for the construction of carbon-carbon bonds in modern organic synthesis.[1] It involves the nucleophilic addition of ketone enol or enolate derivatives to an aldehyde (up to two new stereogenic centers can be produced) to form a β-hydroxy ketone that is a common structural motif found in many natural products.[2] In 2000, the use of proline to catalyze highly enantioselective direct intermolecular aldol reactions was disclosed by List, Lerner and Barbas[3] almost 30 years after its intramolecular variant known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction[4] was discovered. Subsequently, this report inspired investigations by several other groups towards designing more efficient organocatalysts for the aldol reaction and extending this concept to other key carbon-carbon bond forming reactions.[5] Although the stereoselectivities achieved in various organocatalyzed aldol reactions are remarkable, a major limitation of this process is the rather narrow substrate scope. The vast majorities of examples to date involve simple achiral reactants and functionalized chiral nonracemic aldehydes[6] while only scattered examples using racemic aldehydes in dynamic kinetic resolution[7] have been published. In this regard, we describe organocatalyzed intermolecular direct aldol reactions of different ketones with racemic aldehydes that proceed with diastereo- and enantiotopic group selectivities and dynamic kinetic resolution.

We have been investigating simultaneous and stepwise iterative aldol homologations of tetrahydro-4*H*-thiopyran-4-one **1** with thiopyran aldehyde **2** followed by desulfurization as a conduit to rapidly assemble stereochemically complex polypropionate synthons (six to seven stereogenic centers) in only 2-3 steps in the context of a thiopyran route to polypropionates.[8] We reported preliminary studies of the proline

catalyzed enantioselective direct intermolecular aldol reactions of tetrahydro-4*H*-thiopyran-4-one **1** with various achiral aldehydes[9] that furnished aldol adducts **3** and **4** with high diastereo- and enantioselectivities in moderate to excellent yields (Scheme 4.1). Desulfurization of these aldol adducts or their derived diols afforded products equivalent to those from aldol reactions of 3-pentanone. Consequently, we also demonstrated that the proline-catalyzed aldol reaction of **1** and racemic aldehyde **2** proceeded with high diastereo- and enantioselectivities but in modest yield[10] (Scheme 4.1). The remarkable stereoselectivity of this reaction was attributable to the combination of the high propensity for the addition to the *re* face of (*S*)-**2** imposed by the (*S*)-proline catalyst together with the high Felkin diastereoface selectivity intrinsic of **2** that resulted in a strong kinetic preference for the "matched" reaction (i.e. high enantiotopic group selectivity). Because the proline-catalyzed isomerization of **2** is much faster than the aldol condensation, the reaction proceeds with dynamic kinetic resolution. Herein, we report an extension of this important process using proline and its derivatives towards cyclic/acyclic ketones and racemic aldehydes. Conceptually, these reactions significantly extend the scope of the direct aldol reaction and constitute simple and efficient syntheses of functionalized acetate-propionate synthons with potential synthetic utility in polypropionate synthesis.



Scheme 4.1. Previous work

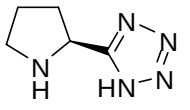
Results and disscussion

Screening of different catalysts: The use of cyclic sulfides to facilitate various chemical transformations is a well established synthetic strategy.[8,11]The synthetic utility of thiopyranone **1** towards polypropionate synthesis has prompted several other groups to investigate its compatibility towards organocatalyzed reactions[12] where the beneficial effect of water as additive in the aldol reactions of **1** with various achiral aldehydes was independently disclosed by Pihko[12b-c] and ourselves.[9] In the event, we also demonstrated the dramatic improvement in the yield and enantioselectivity of the proline-catalyzed aldol reaction of **1** and (±)-**2** in the presence of added water and optimization of the reaction conditions with respect to solvent, concentration, stoichiometry and protocol allowed the efficient preparation of **5** (56%, >98% yield) in gram scale.[10] Desulfurization of the MOM ether derivative **5a** gave the synthetically useful tetrapropionate synthon **6**. We aimed to further improve the aldol reaction of **1** and (±)-**2** by screening other proline

derived organocatalysts having greater solubility than proline in various organic solvents that might increase the reaction efficiency. From the recent literature,[13] catalysts **7** and **8** (Table 4.1) were demonstrated to perform better than proline in certain aldol reactions due to their increased solubility in organic solvents. Using catalysts **7** and **8** under the established conditions[10] for proline-catalyzed aldol reaction of **1** and (±)-**2** (Table 4.1, entry 1) followed by a brief optimization of ketone loading showed that **7** (Table 4.1, entry 4) was a superior catalyst furnishing **5** as a single diastereomer in 77% yield and >98% ee after 3 days. Control experiments carried out by subjecting adduct **5** to catalyst **7** in wet DMSO showed that **5** underwent retro-aldol thereby explaining the drop in yield observed after prolonged reaction times as shown in entries 3-5 (Table 4.1). No significant increase in turn over was recorded when the amount of water was changed (Table 4.1, entries 6 and 7). When the reaction was run at a lower concentration (0.5M) using 12 equivalence of ketone, aldol adduct **5** was obtained in 86% yield with excellent ee (Table 4.1, entry 10). Catalysts **8** and **9**[14] gave poor conversions and were accordingly not further studied. Based on these results, attributing the success of **7** to its increased solubility in DMSO compared to proline might be premature in our case since a study conducted using dissolved proline in DMSO [~0.3M] instead of solid proline added directly to the reaction showed that a lower yield (22%) and ee (~78%) were obtained under the previously optimized conditions[10] (i.e. same reaction conditions as in entry 1, Table 4.1). Interestingly, when the aldol reaction of **1** and (±)-**2** was run under almost neat conditions with DMSO as additive using **7** as catalyst, adduct **5** was obtained in 75% yield over 8 days[15] using only 2 equivalent of **1** (Table 4.1, entry 15). Conclusively, the

use of catalyst **7** significantly improved the efficiency of the aldol reaction of **1** and (±)-**2** over our initial report using (*S*)-proline.

Table 4.1. Aldol reaction[a] of **1** with (±)-**2** under various conditions



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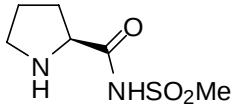

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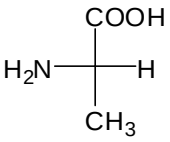


9 L-alanine

Entry	Catalyst	Catalyst (equiv)	H_2O (equiv)	[**2**]M	Ketone **1** (equiv)	Time (days)	Isolated yield of **5** (%)	ee (%)[b]
1	(*S*)-	0.5	8	1	6	2	56	>98
2	proline	0.5	8	1	12	4	48	82
3		0.5	8	1	6	2	56	
4		0.5	8	1	6	3	77	>98
5		0.5	8	1	6	4	57	
6		0.5	4	1	6	3	60	
7	**7**	0.5	12	1	6	3	44	
8		0.5	8	1	12	3	76	>98
9		0.5	8	1	12	4	69	
10		0.5	8	0.5	12	4	86	>98
11		0.2	8	1	6	4	76	>98
12		0.2	8	2	6	3	49	
13	**8**	0.5	8	1	6	3	32	
14	**9**	0.5	8	1	6	2	<5	
15[c]	**7**	0.2	2	neat	2	8	75	>98

[a]All reactions carried out in DMSO at r.t unless specified. [b]ee determined by comparing optical rotation from lit. *c* = 1.0, $CHCl_3$; $[\alpha]_D$ (max) for **3** = –47.[c]Conditions: **1**, 2 equiv; **2**, 1 equiv; DMSO, 1.5 equiv; **7**, 0.2 equiv; water, 2 equiv; r.t; 8d.

Application to different ketones: We were interested to study the aldol reaction of cyclohexanone (**10**) with (±)-**2** as another cyclic ketone to ascertain the scope of our design strategy. Adapting the previously published parameters for aldol reaction of **1** with (±)-**2** using (*S*)-proline,[10] reaction of cyclohexanone with (±)-**2** gave **10a** as a single

diastereomer in low yield (22%). A significant increase in yield of **10a** (66%) with excellent diastereo- and enantioselectivities was noted as a consequence of doubling the amount of ketone (Table 4.2, entry 3). Additionally, catalyst **7** was again proven to be more efficient than proline (Table 4.2, entries 4 and 5) using cyclohexanone **10** as the donor but a higher ketone loading was necessary.

Acetate-propionate synthons such as **11a**, **12a** and **12b** are common structural motifs in many polyketides.[16] By judicious C-C bond disconnection, they can be visualized from aldol reactions from either acetone (**11**) or 2-butanone (**12**) with **2**. Inspired by their synthetic usefulness, we next investigated aldol reaction of (±)-**2** with **11** and **12**. The proline catalyzed aldol reaction of **11** with (±)-**2** was found to be very sensitive to the amount of water added. The reaction behaved best in dry DMSO furnishing diastereomer **11a** in 75% yield (dr = 12:1, 92% ee) and was accompanied by ~6% of elimination product **11c** (entry 8, Table 4.2). Interestingly, no elimination was detected when 1 equiv of water was added to the reaction but the yield was seriously compromised (entry 11, Table 4.2). The aldol reaction of **11** and (±)-**2** occurred with a substantial amount of elimination when catalyzed by **7** (entries 12 and 13, Table 4.2). Subjecting adducts **11a** and **11b** (10:1 mixture) to the reaction conditions using both (*S*)-proline and **7** separately showed that elimination was only observed with **7** (60-70%). 2-Butanone, another interesting ketone with its regioselective issue was also attempted but unfortunately no reasonable success was met even after extensive investigation of different reaction parameters and was not further pursued. In short, an inseparable mixture of two regioisomers **12a** and **12b** (1.6-2:1) in 20-36% combined yield with high diastereo- and enantioselectivities of the major product **12a** were obtained (95% ee, Table

4.2, entry 20). Elimination products (~5%) were also noted in some cases studied. Other ketone donors such as α-hydroxylacetone, 3-pentanone and dihydrothiophen-3(*2H*)-one attempted were not promising. The relative and absolute stereochemistry of **10a**, **11a** and, **12a** were assigned by analogy.[17]

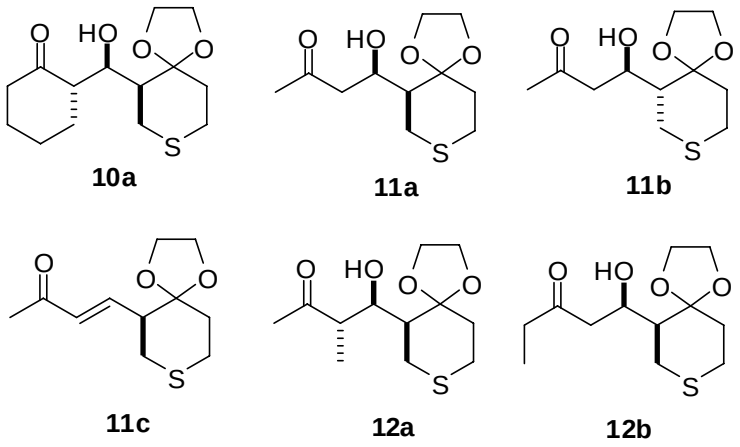


Figure 4.1. Adducts from aldol reactions of (±)-**2** with **10**, **11** and **12**

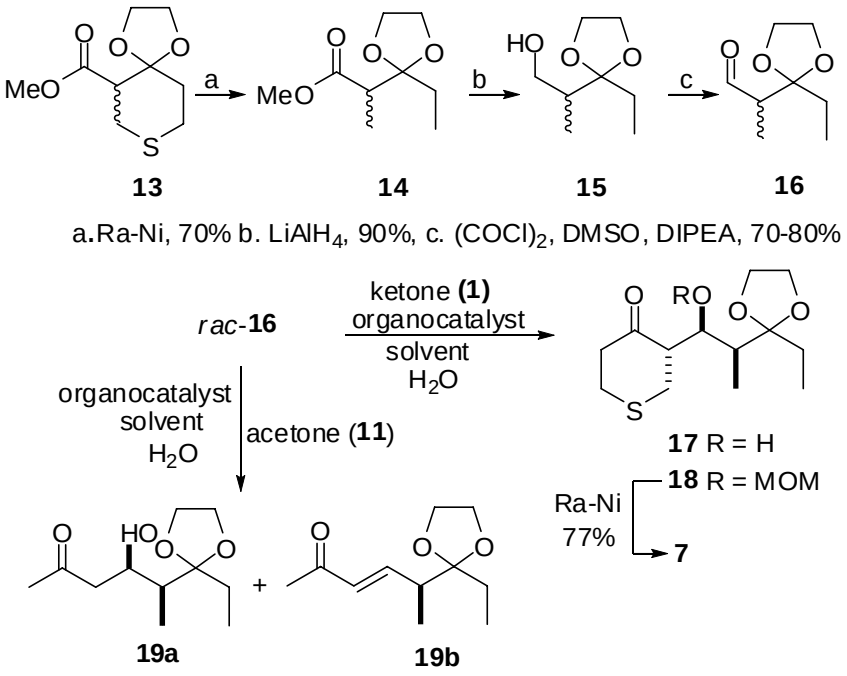
Table 4.2. Aldol reactions[a] of (±)-**2** with cyclohexanone (**10**), acetone (**11**) and 2-butanone (**12**)

Entry	Catalyst	Ketone (equiv)	[**2**]M	H_2O (equiv)	Time (days)	Yield (%)	Adduct(s)	Ratio	ee (%)
		10						**10a (dr)**	**10a**[b]
1	(*S*)-proline	6	1	4	2	25	**10a**	>50:1	[c]
2		6	1	8	2	26		>50:1	[c]
3		12	1	8	2	66		>50:1	93
4	**7**	6	0.5	8	3	80		>50:1	[c]
5		12	0.5	8	4	85		>50:1	>95
		11						**11a:11b**	**11a**[d]
6	(*S*)-proline	20	0.5	0	3	72(13)	**11a(11c)**	10:1	90
7		20	0.5	0.5	3	57(10)		13:1	83
8		40	0.5	0	3	75(6)		12:1	92
9		40	0.5	0.5	3	60(4)		15:1	93
10		20	1	0	3	70(15)		10:1	82
11		20	1	1	3	48(0)		15:1	[c]
12	**7**	20	1	0	2	57(21)		11:1	95
13		20	1	4	2	46(46)		10:1	[c]
		12						**12a:12b**	**12a**[d]
14	(*S*)-proline	20	1	0	3	20	**12a+12b**	1:1	[c]
15		20	1	0.5	3	20		2:1	[c]
16		20	1	4	3	20		2:1	[c]
17		20	1	8	3	21		1.5:1	[c]
18		40	1	0	3	15		2:1	[c]
19	**7**	20	1	0	7	24		1:1.7	[c]
20		20	1	0.5	7	36		1.6:1	95

[a]All reactions carried out in DMSO and 0.5 eq of catalyst. [b]ee determined by resolving the MOM derivative of aldol **10a** by ^{1}H NMR using chiral shift reagent (R)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE). [c]Not determined. [d]ee determined by resolving the aldols by ^{1}H NMR using (TFAE).

Application to different aldehydes: We demonstrated that if a chiral aldehyde possesses high diastereoface selectivity, it will be a good candidate in enantiotopic group selective aldol reactions. The intrinsic high diastereoface selectivity of cyclic aldehyde (±)-**2** was attributed to the presence of the ketal group;[8d] this finding directed our interest to investigate acyclic aldehyde (±)-**16**. Aldehyde (±)-**16** was easily prepared by

desulfurization from known keto-ester **13**[18] followed by $LiAlH_4$ reduction and Swern oxidation. We initially investigated aldol reaction of **1** with (±)-**16** using different catalysts under our previously established conditions.[10] To our delight, adduct **17** was obtained as a single diastereomer in 60% yield with excellent ee (entry 5, Table 4.3) when using **7** as catalyst. MOM protection of **17** followed by desulfurization gave the known tetrapropionate synthon **6**,[10] which unambiguously confirmed the relative and absolute stereochemistry of adduct **17**. Acetone successfully underwent aldol reaction with (±)-**16** using proline in the absence of water to afford **19a** with its minor diastereomer in 70% yield and 91% ee (entry 7, Table 4.3) and was accompanied with a significant amount of elimination product **19b**. The presence of water again proved to suppress elimination but the yield significantly diminished (entry 8, Table 4.3). Re-subjecting the 17:1 mixture of adduct **19a** and its minor diastereomer to the same reaction conditions using either (*S*)-proline or **7** resulted in elimination (10-30%) but negligible retroaldol (~2%) with both catalysts. When 20 equivalents of D_2O or CH_3OD was added to a mixture of either (*S*)-proline or **7** and (±)-**16** in DMSO at ambient temperature for 2 days, recovered **16** showed 90% deuterium incorporation (by ^1H NMR) indicating that aldol reactions of **1** or **11** with (±)-**16** using either proline and **7** proceed with dynamic kinetic resolution (i.e. isomerization of **16** is faster than aldol). Adducts **17** and **19a** are synthetically useful synthons in polypropionate synthesis.



Scheme 4.2. Preparation of (±)-**16** and aldol reactions with **1** and **11**

Table 4.3. Aldol reactions[a] of (±)-**16** with **1** and **11**

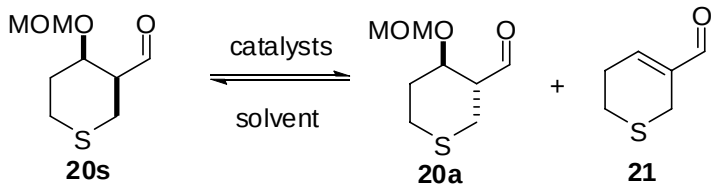
Entry	Catalyst	Catalyst (equiv)	Ketone (equiv)	[**16**]M	H_2O (equiv)	Yield (%)	Adduct(s)	dr	ee (%)
			1						**17**[b]
1	(*S*)-	0.5	6	1	8	42		>50:1	86
2	proline	0.5	6	0.5	8	47		>50:1	>95
3		0.5	6	0.5	8	42		>50:1	[c]
4	**7**	0.2	6	0.5	8	60	**17**	>50:1	[c]
5		0.5	12	0.5	8	60		>50:1	>95
6	**8**	0.5	6	0.5	8	14		>50:1	[d]
			11						**19**[d]
7	(*S*)-	0.5	20	0.5	0	70(10)	**19a**(**19b**)	17:1	91
8	proline	0.5	20	0.5	8	35(0)		17:1	[c]
9	**7**	0.5	20	0.5	8	38(35)		9:1	[c]

[a]Reaction carried out in DMSO as solvent. [b]ee determined by converting **17** to **6** that was resolved by ^{1}H NMR using chiral shift reagent (+)-Eu(hfc)$_3$ and lit. comparison of optical rotation of **6** (ref. 10). [c]Not determined. [d]ee determined by deriving **18** to its 3,5-dinitrobenzoate that was resolved by ^{1}H NMR using chiral shift reagent (+)-Eu(hfc)$_3$.

We next turned our focus to *syn* aldehyde (±)-**20s**[8d] which can possibly epimerize to its *anti* diastereomer (±)-**20a** in presence of bases or acids. The stability of **20s** was questionable initially as some elimination was detected even when kept at -20°C. A brief survey was carried out by exposing **20s** to different catalysts in various organic solvents (Table 4.4) and showed that **20s** readily epimerizes to **20a** and that the latter was more prone to elimination. Elimination of the MOM group in aldehydes **20s** and **20a** will be therefore a major concern during their aldol reactions using proline or **7** as catalysts. Nevertheless, this situation offers the opportunity to study simultaneously diastereotopic and enantiotopic group selectivity in (*S*)-proline catalyzed aldol reaction of **1** and (±)-**20s**. It is appropriate to consider that **20s** and **20a** have the 'matched' diastereoface selectivities for addition to the *re* face by the enamine whose facial selectivity is controlled by the absolute configuration of (*S*)-proline (Scheme 4.3). Aldol reaction of (±)-**20s** with **1** in the presence of (*S*)-proline under the previously established conditions[10] gave adducts **22** and **23** in 20% combined yield over 2 days. Doubling both the amount of ketone and reaction time afforded a 1:2 mixture of **22** and **23** respectively, in 31-37% combined yield with excellent enantiopurity for **23** (entries 3 and 5, Table 4.5). The ratio of products suggests that aldol reaction of **1** with the *anti* diastereomer (±)-**20a** is faster than (±)-**20s** affording two major Felkin aldols **22** and **23**. The two anti-Felkin adducts were also detected as minor products (~5-10%)[19] in all cases studied. These results support our earlier views that the importance of the ketal group in dictating a high diastereoface selectivity in aldehydes **2** and **16**. The aldol reaction of **1** and (±)-**20s** performed slightly better when catalyst **7** was used instead (entry 7, Table 4.5). When the aldol reactions of **1** were done with a mixture of aldehydes, a better selectivity of **22**:**23**

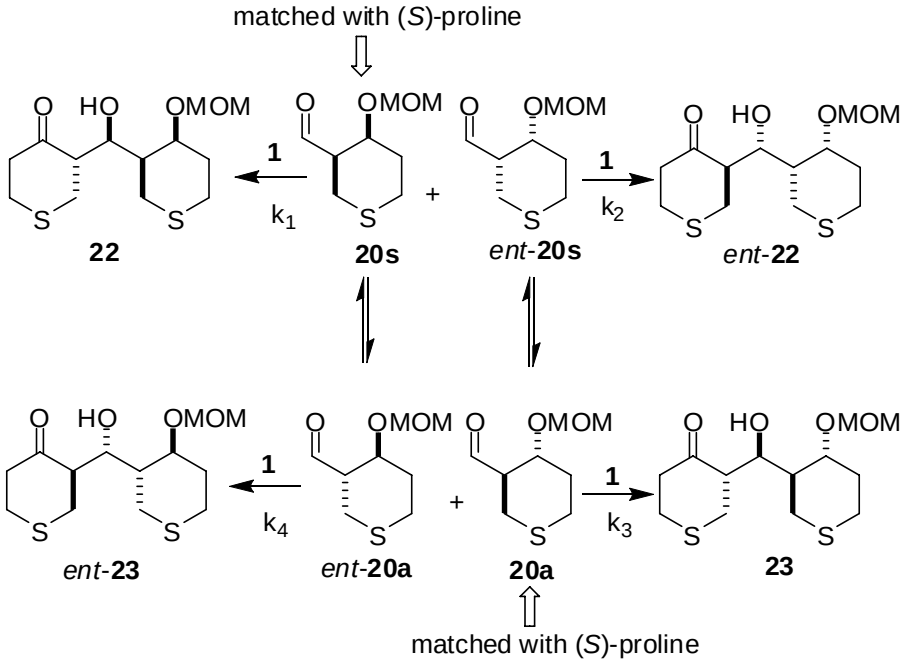
(1:5) was obtained but no improvement in yield was noted. These findings point out that the diastereotopic group selectivity of the aldol reaction can be modulated if **20a** is used as the starting aldehyde instead (entries 8 and 9, Table 4.5). To the best of our knowledge, this is the first example of organocatalyzed aldol reaction that occurs with a combination of diastereotopic and enantiotopic group selectivities. The absolute configurations of **22** and **23**[17] were assigned by analogy to previous examples.

Table 4.4. Epimerization and elimination of **20s** and **20a**



20s **20a** **21**

Entry	Catalyst	Catalyst (equiv)	Solvent	[**20s**]M	Time (h)	**20s**:**20a**:**21**
1	(*S*)-proline	0.5	DMSO	0.1	0	1:0:0
2		0.5	DMSO	0.1	1	10:1:1
3		0.5	DMSO	0.1	24	1.2:1.2:1
4		0.5	DMSO	0.1	48	1:1:1.2
5		0.5	DMSO	0.1	168	>95% of **21**
6		1	DMSO	1	14	2:4:1
7		1	DMF	1	14	2:4:1
7	imidazole	1	CH_2Cl_2	1	14	7:11:1
8		1	CH_2Cl_2	1	48	5:8:1
9	**7**	1	DMSO	1	14	1.3:1.5:1



Scheme 4.3. Aldol reaction of **1** with (±)-**20s** using (*S*)-proline

Table 4.5. Aldol reaction[a] of **1** with (±)-**20s**

Entry	Catalyst	Aldehyde	Concentration of aldehyde	Time (days)	Yield (%) **(22** + **23)**	dr **23**:**22**	ee (%) **23**[b]
1	(*S*)-proline	**20s**	0.5	1	14	2:1	[c]
2			0.5	2	25	2.5:1	[c]
3			0.5	4	37	2.3:1	93
4			1	2	25	2:1	[c]
5			1	4	31	2:1	95
6	*ent*-**7**		0.5	4	33	2:1	[c]
7			1	4	42	2:1	>95
8	(*S*)-proline	**20s**:**20a**:**21** (3:1:0.7)	0.5	4	28	5:1	[c]
9	**7**		1	4	42	5:1	>95

[a]All reactions carried out in DMSO, 12 eq of **1**, 0.5 eq of proline and 8 eq of water. [b]ee was determined by resolving the bis-3,5-dinitrobenzoate derivative of the1,3 *syn* diol that was obtained from $NaBH_4$ reduction of **23** by ^1H NMR using chiral shift reagent (+)-$Eu(hfc)_3$. [c]Not determined.

Conclusion: In summary, we successfully extended the proline-catalyzed direct aldol reaction that proceeded with a combination of dynamic kinetic resolution and enantiotopic group selectivity to other cyclic and acyclic acceptors/donors using different organocatalysts. High ketone loading, narrow substrate scope and long reaction times are among the major limitations to achieve high conversions in these aldol reactions. We also demonstrated that aldol reaction of **1** with (±)-**20s** proceeded with a combination of diastereotopic and enantiotopic group selectivities. This design strategy can be applied to other substrates in enantioselective direct aldol reactions and significantly extends the scope of this important process.

4.3 Supporting Information (Experimental section)

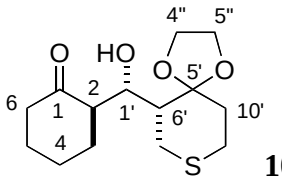
General Methods. All solvents were distilled prior to use. Anhydrous solvents were distilled under argon atmosphere as follows: Tetrahydrofuran (THF) from benzophenone potassium ketyl; ether from benzophenone sodium ketyl; CH_2Cl_2 and toluene from CaH_2; MeOH from $Mg(OMe)_2$. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were ice/water (0 °C) or $CO_{2(s)}$/acetone (-78 °C); reaction temperatures refer to that of the bath. Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator with the final traces of solvent removed at high vacuum (ca. 0.4 Torr). Preparative TLC (PTLC) was carried out on glass plates (20×20 cm) pre-coated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aqueous sulfuric acid (5% v/v), followed by charring on a hot plate. Flash column chromatography (FCC) was performed according to Still et al.[20] with silica gel 60 (40-63 μm). All mixed solvent eluents are reported as v/v solutions. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by ^1H NMR.

Spectral Data. High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a double focusing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI at 50 eV with

ammonia as the reagent gas; only partial data are reported. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 500 MHz for ^1H and 125 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. Couplings constants (*J*) are reported to the nearest 0.5 Hz. The ^1H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or $^1H/^{13}C$ correlation experiments (HSQC and/or HMBC[21] and/or NOE experiments. The ^{13}C NMR assignments were made based on chemical shift and multiplicity[22] (as determined by *J*-modulation[23] or HSQC[24] and were confirmed, where necessary, by two dimensional $^1H/^{13}C$ correlation experiments (HSQC and/or HMBC).

Materials: The preparations of the following compounds were described previously: enantioenriched **5-7**,[25] (±)-**13**,[26] (±)-**20s**,[26] and (±)-**20a**[26] and Raney-Nickel (W-2)[27]. All other reagents were commercially available and unless otherwise noted, were used as received.

(S)-2-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(hydroxy)methyl]cyclohexanone (10a).

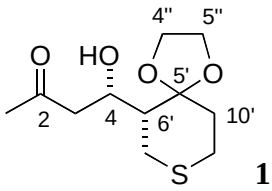


10a

A solution of cyclohexanone (0.33 mL, 310 mg, 3.2 mmol), 5-[(2*R*)-pyrrolidine-2-yl]-1H-tetrazole (19 mg, 0.17 mmol), and water (38 uL, 38 mg, 2.1 mmol) in DMSO (0.27 mL) was stirred at room temperature for 2 h and then aldehyde (50 mg, 0.27 mmol) was added. After 4 days, the reaction was quenched by addition of aqueous NH_4Cl and the mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (15-50% ethyl acetate in hexane) to give the aldol product **10a** (60 mg, 77%; >95% ee by resolving the MOM derivative of aldol **10a** by ^{1}H NMR using TFAE, **see Appendix B**); $[\alpha]_D$ +30 (*c* 1, $CHCl_3$).

IR λ_{max}: 3519, 1694 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 4.29 (1H, dd, *J* = 4, 4, 7 Hz, HC-1'), 4.05-3.90 (4H, m, H_2CO x 2, HC-4" & 5"), 3.18 (1H, d, *J* = 4 Hz, HO), 3.02 (1H, dd, *J* = 10, 14 Hz, HC-7'), 2.78 (1H, ddd, *J* = 3, 11, 13.5 Hz), 2.72 (1H, ddd, *J* = 2, 3, 14 Hz, HC-7'), 2.66 (1H, ddd, *J* = 5, 6.5, 11 Hz, HC-2), 2.60 (1H, dddd, *J* = 2, 3.5, 5.5, 13.5 Hz), 2.44-2.32 (2H, m), 2.09 (1H, ddd, *J* = 3, 4, 10 Hz, HC-6'), 2.07-1.96 (3H, m), 1.91-1.85 (1H, m), 1.75-1.60 (4H, m); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 214.7 (s), 109.7 (s), 68.9 (d), 64.7 (t), 64.2 (t), 54 (d), 47 (d), 42.8 (t), 36.4 (t), 31.6 (t), 28.5 (t), 27.2 (t), 26.9 (t), 24.8 (t); **LRMS** (EI), *m/z* (relative intensity): 286 ([M]$^+$, 3), 269 (2), 159 (8), 132 (13), 55 (100); **HRMS** *m/z* calcd. for C14H22O4S: 286.1239; found: 286.1236 (EI).

(4*S*)-4-[(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl]4-hydroxy-2-butanone (11a).

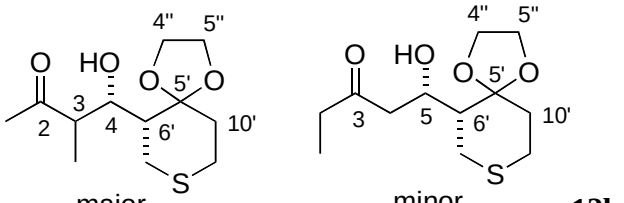


11a

A solution of acetone (1.6 mL, 1.3 g, 22 mmol), 5-[(2*R*)-pyrrolidine-2-yl]-1H-tetrazole (30 mg, 0.22 mmol), and water (76 μL, 76 mg, 4.2 mmol) in DMSO (1.1 mL) was stirred at room temperature for 2 h and then aldehyde (200 mg, 1.1 mmol) was added. After stirring for 4 days, the reaction was taken up in ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, concentrated, and fractionated by FCC (50% ethyl acetate in hexane) to give an inseparable 10:1 mixture of aldol diastereomers (126 mg, 48%; major diastereomer (**11a**) was 95% ee by resolving **11a** by ^{1}H NMR using TFAE (**see Appendix C**); $[\alpha]_D$ -14 (*c* 1, $CHCl_3$). Spectroscopic data for the major diastereomer (**11a**)

IR λ_{max}: 3502, 1700 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 4.67-4.63 (1H, m, HC-4), 4.10-3.94 (4H, m, H_2CO x 2, HC-4" & 5"), 3.14 (1H, d, *J* = 2 Hz, HO), 3.01 (1H, dd, *J* = 10.5, 14 Hz), 2.82-2.69 (3H, m), 2.58 (1H, dddd, *J* = 2, 3.5, 5.5, 13.5 Hz), 2.54 (1H, dd, *J* = 3.5, 16.5 Hz), 2.2 (3H, s, H_3C-1), 2.1 (1H, ddd, *J* = 3, 3, 10.5 Hz), 1.94 (1H, ddd, *J* = 3,.3.5, 10.5 Hz), 1.73 (1H, ddd, *J* = 3.5, 11.5, 14 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 208.3 (s), 109.9 (s), 65.5 (d), 64.7 (t), 64.4 (t), 49.2 (d), 48.7 (t), 36 (t), 30.9 (q), 26.7 (t x 2); **LRMS** (EI), *m/z* (relative intensity): 246 ([M]$^+$, 11), 184 (6), 159 (17), 132 (40), 113 (9), 99 (100); **HRMS** *m/z* calcd. for C11H18O4S: 246.0926; found: 246.0929 (EI).

4-(1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl)-4-hydroxy-3-methyl-2-butanone and 5-(1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl)-5-hydroxy-3-pentanone.



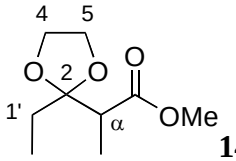
12a **12b**

A solution of butanone (1.9 mL, 1.5 g, 21 mmol), 5-[(2*R*)-pyrrolidine-2-yl]-1H-tetrazole (30 mg, 0.22 mmol), and water (76 uL, 76 mg, 4.2 mmol) in DMSO (1.1 mL) was stirred at room temperature for 3 h and then aldehyde (200 mg, 1.1 mmol) was added. After 7 days, the reaction was taken up in ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give an inseparable 1.5:1 mixture of aldol regioisomers (100 mg, 36%) and ee of major isomer **12a** was >95% determined by resolving **12a** by ^{1}H NMR using TFAE (see **Appendix D**).

IR λ_{max}: 3493, 2923, 1708 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 4.63 (0.4H, ddd, *J* = 3, 6, 9 Hz), 4.25 (0.6H, ddd, *J* = 2.5, 5, 9 Hz), 4.08-3.90 (4H, m), 3.13 (0.6H, d, *J* = 2.5 Hz), 3.1 (0.4H, d, *J* = 2 Hz), 3.05-2.96 (1H, m), 2.81-2.67 (2.6H, m), 2.64 (0.6H, ddd, *J* = 2.5, 3, 14 Hz), 2.58-2.43 (2.2H, m), 2.19 (1.8H, s), 2.09 (0.6H, ddd, *J* = 3, 5, 11.5 Hz), 2.07 (0.4H, ddd, *J* = 3, 5.5, 12 Hz), 2.01 (0.6H, ddd, *J* = 3, 3, 11 Hz), 1.91 (0.4H, ddd, *J* = 3.5, 3.5, 10 Hz), 1.75-1.66 (1H, m), 1.04 (1.2H, t, *J* = 7 Hz), 1.01 (1.8H, d, *J* = 7 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 213 (s, major), 211 (s, minor), 110.3 (s, major), 110 (s, minor), 71.8 (d, major), 65.7 (d, minor), 64.83 (t, major), 64.76 (t, minor), 64.51 (t,

minor), 64.45 (t, major), 49.3 (d, minor), 49.0 (d, major), 47.4 (t, minor), 46.5 (d, major), 37.0 (t, minor), 36.3 (t, major), 36.2 (t, minor), 30.2 (q, major), 26.80 (t, major), 26.77 (t, minor), 26.7 (t, major), 26.2 (t, minor), 13.8 (q, major), 7.8 (q, minor); **LRMS** (EI), *m/z* (relative intensity): 260 ($[M]^+$, 13), 199 (5), 159 (10), 132 (9), 99 (100); **HRMS** *m/z* calcd. for C12H20O4S: 260.1082; found: 260.1083.

Methyl 2-Ethyl-α-methyl-1,3-dioxolane-2-acetate (14).



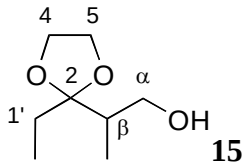
14

A suspension of freshly prepared Raney-Ni (W-2) (8 mL settled volume) in ethanol was added in one portion to a well stirred solution of ketal ester (1.4 g, 6.42 mmol) in methanol (20 mL).The reaction mixture was heated under reflux and progress was monitored by TLC. Additional Raney-Ni (2 mL settled volume) was added each hour until the reaction was complete (2-3 h). The supernatant was filtered through a pad of Celite® and the residue was suspended in methanol (50 mL) and heated under reflux for several minutes. The supernatant was filtered and the residue treated as above (this process repeated 3 times). The combined filtrates were concentrated and fractionated by FCC (20% ethyl acetate in hexane) to give the titled compound as a clear oil (862 mg, 72%).

IR λ_{max}: 1737 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 4.04-3.94 (4H, m, H_2CO x 2, HC-4 & 5), 3.69 (3H, s, H_3CO), 2.86 (1H, q, *J* = 7 Hz, HC-α), 1.81 (1H, dq, *J* = 7.5, 14.5 Hz, HC-1'), 1.75 (1H, dq, *J* = 7.5, 14.5 Hz, HC-1'), 1.20 (3H, d, *J* = 7 Hz, H_3CC-α), 0.90 (3H, t, *J* = 7.5 Hz, H_3C-2'); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 174.1 (s, C=O), 111.8 (s, C-2),

65.9 (t, CH_2O), 65.8 (t, CH_2O), 51.9 (q, CH_3O), 46.9 (d, C-α), 28.1 (t, C-1'), 12.7 (q, CH_3C-α), 7.4 (q, C-2'); **HRMS** *m/z* calcd. for C9H16O4: 211.1049 (M+Na); found: 211.0938 (ESI).

2-Ethyl-α-methyl-1,3-dioxolane-2-ethanol (15). **Known compound: Daniewski, Andrzej Robert; Piotrowska, Emilia; Wojciechowska, Wanda. Liebigs Annalen der Chemie (1989), (11), 1061-4**.

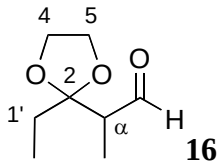


15

A solution of the ester (862 mg, 4.58 mmol) in ether (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (180 mg, 4.74 mmol) in ether (15 mL) at 0 °C under argon. The mixture was allowed to warm to room temperature and after 1 h, was quenched by addition of aqueous NaOH (2 N, 2 mL). The mixture was filtered through a short column of Celite® and Na_2SO_4 washing with THF. The combined filtrate and washings were concentrated to give the titled compound as a clear oil (660 g, 90%).

IR λ_{max}: 3427 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 4.03-3.98 (4H, m, H_2CO x 2, HC-4 & 5), 3.67 (1H, dd, *J* = 8, 11 Hz, HC-α), 3.56 (1H, dd, *J* = 4, 11 Hz, HC-α), 2.84 (1H, br s, HO), 2.08 (1H, m, HC-β), 1.68 (2H, ap q, *J* = 7.5 Hz, H_2C-1'), 0.95 (3H, d, *J* = 7 Hz, H_3CC-β), 0.90 (3H, t, *J* = 7.5 Hz, H_3C-2'); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 114.7 (s, C-2), 65.3 (t, CH_2O), 65.2 (t, CH_2O), 65.1 (t, C-α), 40.6 (d, C-β), 29.7 (t, C-1'), 12.5 (q, CH_3C-β), 7.6 (q, C-2'); **HRMS** *m/z* calcd. for C8H16O3: 183.1099 (M+Na); found: 183.0998 (ESI).

2-Ethyl-α-methyl-1,3-dioxolane-2-acetaldehyde (16).

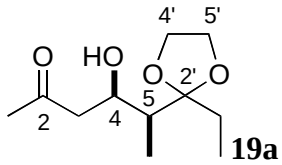


16

DMSO (0.32 mL, 4.46 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.20 mL, 2.30 mmol) in CH_2Cl_2 (10 mL) at -78 °C under argon. After 30 min, a solution of alcohol (340 mg, 2.13 mmol) in CH_2Cl_2 (2 mL) was added. After 30 min, *i*-Pr_2EtN (1.1 mL, 6.4 mmol) was added, and the reaction mixture was allowed to warm at ambient temperature over 1 h. Hexane (25 mL) and toluene (25 mL) were added and reaction mixture was concentrated to a volume of ca. 25 mL. Additional hexane (25 mL) was added and the precipitated amine salt was removed by filtration through Celite® and dried over Na_2SO_4. The filtrate was concentrated and fractionated by FCC (10% ethyl acetate in hexane) to give a clear yellow oil (290 mg, 85%).

IR λ_{max}: 1719 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 9.80 (1H, d, *J* = 2 Hz, CHO), 4.08-4.00 (4H, m, H_2CO x 2, HC-4 & 5), 2.74 (1H, dq, *J* = 2, 7 Hz, HC-α), 1.74 (1H, dq, *J* = 7.5, 14.5 Hz, HC-1'), 1.62 (1H, dq, *J* = 7.5, 14.5 Hz, HC-1'), 1.13 (3H, d, *J* = 7 Hz, H_3CC-α), 0.93 (3H, t, *J* = 7.5 Hz, H_3C-2'); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 203.8 (s, C=O), 112.1 (s, C-2), 65.7 (t, CH_2O), 65.6 (t, CH_2O), 53.0 (d, C-α), 28.9 (t, C-1'), 9.2 (q, CH_3C-α), 7.6 (q, C-2'); **HRMS** *m/z* calcd. for C8H14O3: 181.0943 (M+Na); found: 181.0840 (ESI).

(4*R*,5*S*)-5-(2-Ethyl-1,3-dioxolan-2-yl)-4-hydroxyhexan-2-one (19a).



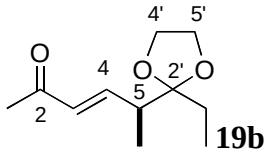
19a

A solution of acetone (0.5 mL, 0.4 g, 7 mmol) and (*S*)-proline (20 mg, 0.17 mmol) in DMSO (0.8 mL) was stirred at room temperature for 2 h and then aldehyde **16** (50 mg, 0.32 mmol) was added. After stirring for 2 days, the reaction was quenched by addition of aqueous NH_4Cl (1 mL) and the mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give an inseparable 17:1 mixture of two aldol diastereomers (49 mg, 72%; $[\alpha]_D$ +24 (*c* 1.3, C_6H_6) and elimination product **19b** (separable) was also observed as a byproduct; ee of **19a** was 91% ee determined by converting **19a** to its 3,5-dinitrobenzoate derivative that was resolved by ^{1}H NMR using chiral shift reagent (+)-Eu(hfc)$_3$ (**see Appendix E**).

Spectroscopic data for the major diastereomer (**19a**): **IR** λ_{max}: 3514, 1714 cm^{-1}; **^{1}H NMR** (500 MHz, C_6D_6) δ: 4.57 (1H, ddd, *J* = 1, 4, 8 Hz, HC-4), 3.43-3.38 (4H, m, H_2CO x 2, HC-4' & 5'), 3.15 (1H, br s, HO), 2.52 (1H, dd, *J* = 8, 16 Hz, HC-3), 2.05 (1H, dd, *J* = 4, 16 Hz, HC-3), 1.79 (1H, m, HC-5), 1.77 (3H, s, HC-1), 1.62 (2H, m, HC-1''), 1.00 (3H, d, *J* = 7.5 Hz, H_3C-6), 0.88 (3H, t, *J* = 7.5 Hz, H_3C-2''); **^{13}C NMR** (125 MHz, C_6D_6) δ: 207.1 (s, C-2), 114.8 (s, C-2'), 67.6 (d, C-4), 65.6 (t, CH_2O), 65.1 (t, CH_2O), 49.2 (t, C-

3), 42.9 (d, C-5), 30.8 (q, C-1), 28.3 (t, C-1"), 8.38 (q, C-6), 8.32 (q, C-2"); **HRMS** *m/z* calcd. for C11H20O4: 239.1362 (M+Na); found: 239.1262 (ESI).

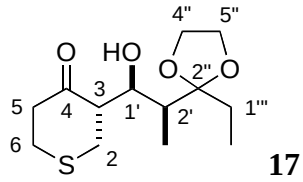
(5*S*,*E*)-5-(2-Ethyl-1,3-dioxolan-2-yl)hex-3-en-2-one (19b).



19b

IR λ_{max}: 1678 cm^{-1}; **^{1}H NMR** (500 MHz, C_6D_6) δ: 6.81 (1H, dd, *J* = 8, 16 Hz, HC-4), 6.04 (1H, d, *J* = 16 Hz, HC-3), 3.49-3.41 (4H, m, H_2CO x 2, HC-4' & 5'), 2.44 (1H, m, HC-5), 1.88 (3H, s, HC-1), 1.50 (2H, m, HC-1"), 0.96 (3H, d, *J* = 7 Hz, HC-6), 0.85 (3H, t, *J* = 7 Hz, H_3C-2"); **^{13}C NMR** (125 MHz, C_6D_6) δ: 196.9 (s, C-2), 148.3 (d, C-4), 132.3 (d, C-3), 113.3 (s, C-2'), 65.87 (t, CH_2O), 65.81 (t, CH_2O), 44.3 (d, C-5), 29.0 (t, C-1"), 27.0 (q, C-1), 14.4 (q, C-6), 7.9 (q, C-2"); **HRMS** *m/z* calcd. for C11H18O3: 221.1256 (M+Na); found: 221.1155 (ESI).

(*S*)-3-[(1*S*,2*S*)-2-(2-Ethyl-1,3-dioxolan-2-yl]-1-hydroxypropyl)dihydro-2H-thiopyran-4(3H)-one (17).



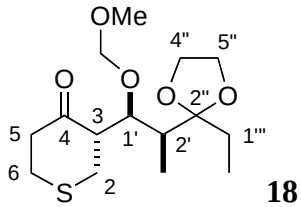
17

A suspension of thiopyranone (400g, 3.4 mmol) and 5-[(2S)-pyrrolidine-2-yl]-1H-tetrazole (25 mg, 0.18 mmol) in dry DMSO (0.5 mL) was stirred at room temperature for 2 h and then the aldehyde (50 mg, 0.32 mmol) was added. After 2 days, the reaction was quenched by addition of aqueous NH_4Cl (1 mL) and the mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. The excess ketone was removed at high vacuum (and collected in a cold trap) and the remaining residue was fractionated by FCC (30% ethyl acetate in hexane) to give the titled compound as a single diastereomer (55 mg, 63%; >95% ee by lit.[25] comparison of the $[\alpha]_D$ of **6** derived from **17** or by resolving **6** by ^{1}H NMR using chiral shift reagent (+)-Eu(hfc)$_3$ (**see Appendix F**).

$[\alpha]_D$ of **17** = -62 (*c* 1.0, C_6H_6); **IR** λ_{max}: 3529, 1719 cm^{-1}; **^{1}H NMR** (500 MHz, C_6D_6) δ: 4.48 (1H, dd, *J* = 2.5, 8 Hz, HC-1'), 3.43-3.36 (4H, m, H_2CO x 2, HC-4" & 5"), 3.05 (1H, br s, HO), 2.83 (1H, ddd, *J* = 4, 8, 8 Hz, HC-3), 2.58-2.28 (6H, m, H_2C-2, H_2C-5, H_2C-6), 1.84 (1H, dq, *J* = 2.5 , 7 Hz, HC-2'), 1.72-1.61 (2H, m, HC-1'''), 1.00 (3H, d, *J* = 7 Hz, H_3C-3'), 0.89 (3H, t, *J* = 7 Hz, H_3C-2'''); **^{13}C NMR** (125 MHz, C_6D_6) δ: 209.2 (s, C-

4), 114.5 (s, C-2''), 70.8 (d, C-1'), 65.6 (t, CH_2O), 65.3 (t, CH_2O), 56.5 (d, C-3), 44.3 (t, C-5), 40.9 (d, C-2'), 34.0 (t, C-2), 31.6 (t, C-6), 28.1 (t, C-2'''), 8.9 (q, C-3'), 8.2 (q, C-2'''); **HRMS** *m/z* calcd. for C13H22O4S: 297.1239 (M+Na); found: 297.1142 (ESI).

(*S*)-3-[(1*S*,2*S*)-2-(2-Ethyl-1,3-dioxolan-2-yl]-1-(methoxymethoxy)propyl)dihydro-2H-thiopyran-4(3H)-one (18).



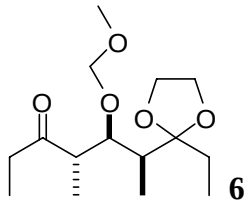
18

Bu_4NI (195 mg; 0.53 mmol), *i*-Pr_2EtN (0.78 mL, 4.5 mmol), and MOMCl (0.24 mL, 3.4 mmol) were sequentially added to a solution of the aldol **17** (120 mg, 0.44 mmol) in dry CH_2Cl_2 (1 mL) at room temperature under argon. After standing for 24 h (reaction complete by TLC), the mixture was diluted with 1 M aq HCl and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was triturated with 50% ethyl acetate in hexane and the supernatant was filtered through a short pad of SiO_2. The combined filtrates were concentrated to give the titled compound as a yellow oil (118 mg, 85%, $[\alpha]_D$ -15 (c 0.67, C_6H_6).

IR λ_{max}: 1714 cm^{-1}; **^{1}H NMR** (500 MHz, C_6D_6) δ: 4.85 (1H, d, *J* = 7 Hz, OCHO), 4.60 (1H, dd, *J* = 2.5, 8 Hz, HC-1'), 4.42 (1H, d, *J* = 7 Hz, OCHO), 3.73-3.50 (4H, m, H_2CO x 2, HC-4'' & 5''), 3.13 (3H, s, H_3CO), 2.90 (1H, ddd, *J* = 4, 7, 8 Hz, HC-3), 2.83 (1H, m, HC-5), 2.70 (1H, dd, *J* = 4, 14 Hz, HC-2), 2.60 (1H, ddd, *J* = 1, 7, 14 Hz, HC-2), 2.47-2.33 (3H, m, HC-5, H_2C-6), 1.98 (1H, dq, *J* = 2.5, 7.5 Hz, HC-2'), 1.75-1.64 (2H, m, HC-

1'''), 1.02 (3H, d, *J* = 7.5 Hz, H_3C-3'), 0.91 (3H, t, *J* = 7.5 Hz, H_3C-2'''); **^{13}C NMR** (125 MHz, C_6D_6) δ: 207.5 (s, C-2), 113.8 (s, C-2''), 98.2 (t, OCH_2O), 77.2 (d, C-1'), 65.7 (t, CH_2O), 65.4 (t, CH_2O), 58.3 (d, C-3), 56.3 (q, H_3CO), 43.5 (t, C-5), 42.2 (d, C-2'), 33.3 (t, C-2), 31.0 (t, C-6), 27.9 (t, C-1'''), 10.6 (q, C-3'), 8.14 (q, C-2'''); **HRMS** *m/z* calcd. for C15H26O5S: 341.1501 (M+Na); found: 341.1387 (ESI).

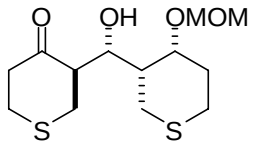
(4*S*,5*R*,6*S*)-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-(methoxymethoxy)-4-methylheptan-3-one (6)



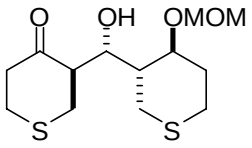
6

A suspension of freshly prepared Raney-Ni (W-2) (2 mL settled volume) in ethanol was added in one portion to a well stirred solution of **18** (28 mg, 0.08 mmol) in methanol (5 mL).The reaction mixture was heated under reflux and progress was monitored by TLC. Additional Raney-Ni (1 mL settled volume) was added each hour until the reaction was complete (2-3 h). The supernatant was filtered through a pad of Celite® and the residue was suspended in methanol (5 mL) and heated under reflux for several minutes. The supernatant was filtered and the residue treated as above (this process repeated 3 times). The combined filtrates were concentrated and fractionated by FCC (30% ethyl acetate in hexane) to give the titled compound as a clear oil (20 mg, 77%, $[\alpha]_D$ +63 (c 0.77, $CHCl_3$). $[\alpha]_D$ and NMR data for **6** was identical to that previously reported.[25]

(*S*)-3-((*S*)-hydroxy((3*S*,4*R*)-4-(methoxymethoxy)tetrahydro-2H-thiopyran-3-yl)methyl)dihydro-2H-thiopyran-4(3H)-one



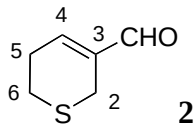
22



23

A suspension of thiopyranone (1.0 g, 8.6 mmol) and 5-[(2*R*)-pyrrolidine-2-yl]-1H-tetrazole (50 mg, 0.36 mmol) and water (110 μL, 6.1 mmol) in dry DMSO (0.9 mL) was stirred at room temperature for 2 h and then aldehyde (130 mg, 0.68 mmol) was added. After stirring for 4 days, the reaction was quenched by addition of aqueous NH_4Cl (1 mL) and the mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (10-25% ethyl acetate in hexane) to give a separable 2:1 mixture aldol adducts **22** and **23**, respectively (88mg, 42%). Pure samples of **23** ($[\alpha]_D$ +19, *c* 1.3 C_6H_6; >95% ee by resolving the bis-3,5-dinitrobenzoate derivative of the derived 1,3 *syn* diol obtained from $NaBH_4$ reduction of **23** by ^1H NMR using chiral shift reagent (+)-Eu(hfc)$_3$ (**see Appendix G**) and **22** ($[\alpha]_D$ –7.6, *c* 0.95, benzene; ee not determined) were obtained by fractionation of the mixture by PTLC. NMR data for **22** and **23** were essentially identical to that previously reported.[26]

5,6-Dihydro-2H-thiopyran-3-carboxaldehyde (21).[elimination product of **20a** and **20s**]



21

IR λ_{max}: 2809, 2712, 1679, 1636 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 9.35 (1H, s), 6.90 (1H, br s), 3.31 (2H, br s), 2.78 (2H, ap t, *J* = 5.5 Hz), 2.67 (2H, br s); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 193.0, 151, 139, 27.7, 24.9, 22.5; **LRMS** (EI), *m/z* (relative intensity): 128 (100), 112 (15), 99 (34), 67 (26), 65 (38), 54 (10), 53 (32); **HRMS** *m/z* calcd. for C6H8OS: 128.0296; found: 128.0295 (EI).

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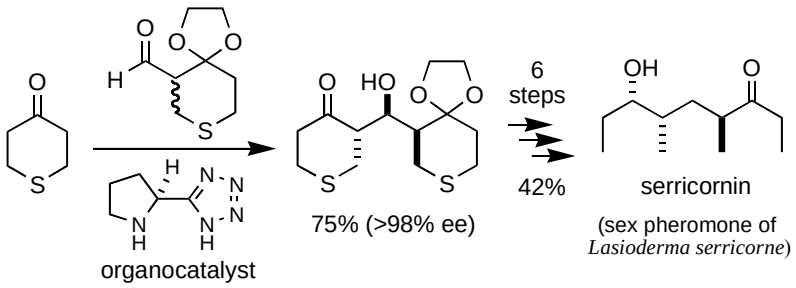
[††] References from the manuscript and supporting information are both combined together.

5. The Thiopyran Route to Polypropionates:

An Efficient Synthesis of Serricornin

Dale. E. Ward, Vishal Jheengut and Garrison E. Beye

Graphical Abstract



5.1 Preface

Proline-catalyzed aldol reaction of tetrahydro-4*H*-thiopyranone with racemic 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde proceeds with dynamic kinetic resolution to give a single adduct in good yield with excellent ee. The reaction constitutes a simple and efficient synthesis of useful tetrapropionate synthon. Application of this tetrapropionate synthon towards an efficient synthesis of (–)-serricornin is described in this manuscript.

The following manuscript is a verbatim copy of the original paper published in **Journal of Organic Chemistry** (**2006**, Vol. 71, 8989–8992) and is formatted as per thesis regulations of the University of Saskatchewan. Permission to reproduce the published material was obtained from the American Chemical Society (ACS) and Garrison E. Beye (co-author) whose contributions includes the 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole catalyzed aldol reaction of tetrahydrothiopyran-4-one with 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde and conversion of **9** to **15** (Section 5.2). The remainder of the work was carried out by me and the manuscript was prepared in collaboration with my supervisor.

5.2 Manuscript: Journal of Organic Chemistry 2006, 71, 8989–8992

The Thiopyran Route to Polypropionates:

An Efficient Synthesis of Serricornin

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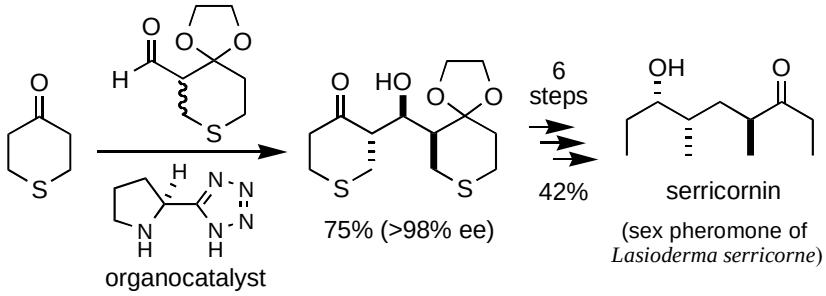
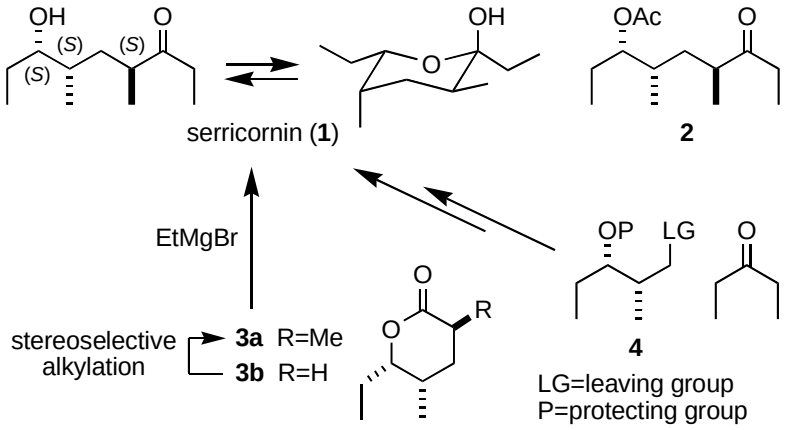


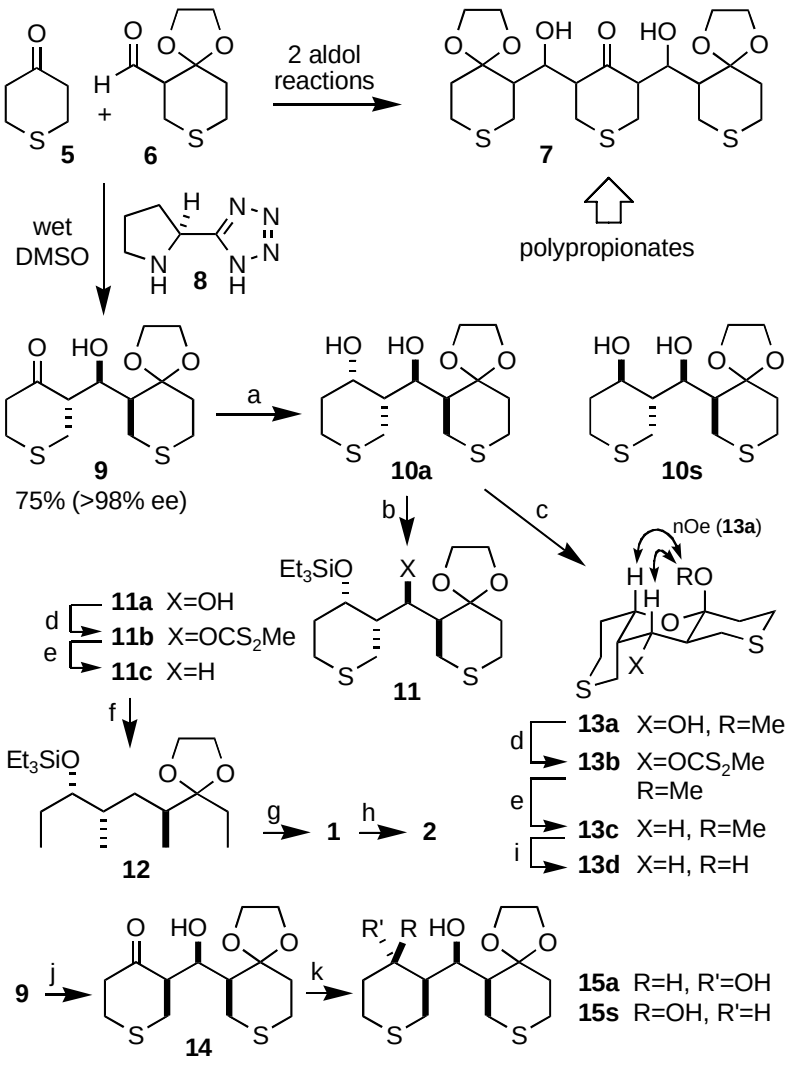
Abstract: The synthesis of serricornin [(4*S*,6*S*,7*S*)-7-hydroxy-4,6-dimethylnonan-3-one], a sex pheromone produced by the female cigarette beetle (*Lasioderma serricorne* F.), in 7 steps from readily available racemic 1,4-dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde (**6**) is described. The key steps include enantioselective aldol reaction of **6** with tetrahydrothiopyran-4-one catalyzed by 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole to fabricate the tetrapropionate skeleton, stereoselective $Li^{s}Bu_3BH$ reduction of the resulting aldol adduct, Barton-McCombie deoxygenation, and Raney nickel desulfurization.

Serricornin (**1**) is the sex pheromone of the female cigarette beetle (*Lasioderma serricorne* F.), a serious pest of cured tobacco leaves and various dried foodstuffs.[1] Because serricornin (**1**) exists as an equilibrium mixture of the ketol and cyclic hemiacetal forms,[2] it is often characterized as the corresponding acetate **2** (Scheme 5.1). The relative and absolute configuration of **1** was determined from a series of synthetic studies that produced all of the possible stereoisomers of **2**.[3] The attractant activity of **1** is at least 10^3 greater than any of the other stereoisomers and the (4*S*,6*S*,7*R*)-diastereomer inhibits the activity of **1**.[4] The potential commercial value of **1** has prompted numerous synthetic studies.[5] The large majority of reported stereoselective syntheses of **1** proceed either by addition of EtMgBr to the lactone **3a**[6,7] or by alkylation of 3-pentanone with a suitable derivative of **4**.[8,9]



Scheme 5.1

We have been developing stereoselective stepwise two-directional aldol reactions of **5** and **6** as the foundation of a thiopyran-based synthetic route to polypropionates (Scheme 5.2).[10] In this regard, we recently reported that (*S*)-proline catalyzes an



[a] Reagents and conditions: (a) Li^{s}Bu$_3$BH, THF, -78 °C (83%); (b) Et$_3$SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (97%); (c) HCl, MeOH (95%); (d) NaH, CS_2, MeI (93%); (e) Bu_3SnH, AIBN, PhMe, 110 °C (91-97%); (f) Raney-Ni, EtOH, reflux (82%); (g) HOAc, CH_2Cl_2; (h) AcCl, DMAP, CH_2Cl_2 (72% from **11**) ; (i) HOAc, H_2O, THF, 50 °C (94%); (j) Et_3N, SiO_2, EtOAc (78%, 2 cycles); (k) DIBALH (**14s**, 92%)[10c] or $Na(OAc)_3BH$ (**14a**, 92%).

Scheme 5.2

enantioselective direct aldol reaction of **5** with (±)-**6** that proceeds with dynamic kinetic resolution[11] to give adduct **9** (>98% ee).[12] In this paper, we describe an improved synthesis of **9** and its efficient conversion into serricornin (**1)** and **2**.

Our reported procedure for the (*S*)-proline–catalyzed (0.5 equiv) aldol reaction of **5** (6 equiv) with **6** (1 M in DMSO with 8 equiv of H_2O) gives **9** as a single isomer in 55-60% yield on 1 g scale (Scheme 5.2).[12] On larger scale the reaction work up is complicated by the need to remove large amounts of **5** by sublimation or chromatography. All attempts to reduce the amount of **5** used in the reaction gave **9** in lower yield and/or enantioselectivity. Interestingly, reactions in the absence of solvent were much less enantioselective than those in DMSO. These reactions were exceedingly slow at room temperature; however, sonication of a mixture of **6**, **5** (1.5 equiv), (*S*)-proline (0.5 equiv), and water (1 equiv) for 60 h at 38 °C gave **9** as the sole aldol diastereomer in 80% yield but in <20% optical purity.[13] We also investigated the more soluble catalyst **8** developed independently by the Ley, Yamamoto, and Arviddson groups.[14] Under optimized conditions (**5**, 2 equiv; DMSO, 1.5 equiv; **8**, 0.2 equiv; room temperature, 8 d) **9** (>98% ee) was obtained in 75% yield from **6** (1 g scale). Reactions run at lower concentrations (e.g., 1 M in DMSO) gave yields of up to 85% but required a large excess of **5** (6-12 equiv).

Aldol adduct **9** contains the complete carbon skeleton of **1** and the synthesis requires only functional group manipulations: deoxygenation of the alcohol, stereoselective reduction of the ketone, desulfurization, and hydrolysis of the ethylene acetal (Scheme 5.2). Stereoselective reduction of **9** with DIBALH is known to give the undesired *syn*-1,3-diol **10s** and attempted reduction with $Na(OAc)_3BH$[15] (usually 1,3-*anti*

selective in these systems)[10c] gave poor selectivity (1:1.5 **10a**:**10s**). The desired *anti*-1,3-diol **10a** was obtained in good yield by reaction of **9** with Li^{s}Bu$_3$BH (Scheme 5.2).[16] The secondary hydroxy groups in **10a** were readily differentiated by treatment with HCl in methanol to give the cyclic acetal **13a**. Deoxygenation of **13a** was achieved by treatment of its xanthate derivative **13b** with Bu_3SnH to give **13c** (80% yield over 2 steps).[17] Unfortunately, attempted Raney nickel desulfurization of **13c (**or **13d**) was capricious and we were unable to isolate the desired product in any significant amount.[18]

Alternatively, reaction of diol **10a** with Et_3SiOTf gave the mono silyl ether **11a** in excellent yield (Scheme 2). Barton-McCombie deoxygenation[17] of **11a** gave **11c** that was smoothly desulfurized by treatment with Raney nickel (W-2) in refluxing ethanol to give the desired serricornin derivative **12** (73% over 3 steps). Exposure of **12** to mild acid gave serricornin (**1**) that was isolated and characterized as the acetate derivative **2** (71% over 2 steps). The spectral properties and specific rotation of **2** were fully consistent with those reported previously.[1,6]

In summary, serricornin (**1**) was prepared in 7 steps from the readily available aldehyde (±)-**6**[10c] (31% overall yield). The key step involves the catalytic enantioselective direct aldol reaction of **6** with **5** that occurs with dynamic kinetic resolution to give adduct **9** in excellent yield and enantiopurity. It is noteworthy that diols **10s**, **15a**, and **15s** are also readily prepared from **9**;[10c,19] thus, the same strategy might be extended to afford each of the possible stereoisomers of **1**.

Experimental Section[‡‡,20]

‡‡ The experimental section of this manuscript is combined with the Supporting Information (Section **5.3**)

Acknowledgement. Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectroscopic data for **13a-13d**, **14**, and **15a**; ^{1}H and ^{13}C NMR spectra for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

5.3 Supplementary Information (Experimental section)

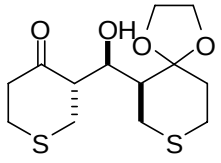
General Methods. All solvents were distilled prior to use. Anhydrous solvents were distilled under argon atmosphere as follows: Tetrahydrofuran (THF) from benzophenone potassium ketyl; ether from benzophenone sodium ketyl; CH_2Cl_2 and toluene from CaH_2; MeOH from $Mg(OMe)_2$. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were ice/water (0 °C) or $CO_{2(s)}$/acetone (-78 °C); reaction temperatures refer to that of the bath. Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator with the final traces of solvent removed at high vacuum (ca. 0.4 Torr). Preparative TLC (PTLC) was carried out on glass plates (20×20 cm) pre-coated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aqueous sulfuric acid (5% v/v), followed by charring on a hot plate. Flash column chromatography (FCC) was performed according to Still et al.[22] with silica gel 60 (40-63 μm). All mixed solvent eluents are reported as v/v solutions. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by ^1H NMR.

Spectral Data. High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a double focusing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI at 50 eV with

ammonia as the reagent gas; only partial data are reported. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 500 MHz for ^1H and 125 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. Couplings constants (*J*) are reported to the nearest 0.5 Hz. The ^1H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or $^1H/^{13}C$ correlation experiments (HSQC and/or HMBC[23] and/or NOE experiments. The ^{13}C NMR assignments were made based on chemical shift and multiplicity[24] (as determined by *J*-modulation[25] or HSQC[26] and were confirmed, where necessary, by two dimensional $^1H/^{13}C$ correlation experiments (HSQC and/or HMBC).

Materials: The preparations of the following compounds were described previously: **5**, (±)-**6**, **10s**, and **15s;**[27] **8**;[28] W-2 Raney nickel;[29] A 1 M solution of $NaBH(OAc)_3$ in acetic acid was prepared by adding glacial acetic acid (2 mL) dropwise with stirring to a round-bottom flask charged with $NaBH_4$ (75 mg) at 0 °C under argon (**CAUTION**: H_2 evolution). The resulting clear, colorless solution was stirred for 10 minutes at 0 °C and at room temperature for 2 h. All other reagents were commercially available and unless otherwise noted, were used as received.

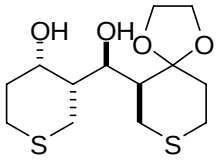
(3*S*)-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(hydroxy)methyl]tetrahydro-4*H*-thiopyran-4-one (9).



9

A solution of ketone **5** (1.25 g, 10.8 mmol), aldehyde **6** (1.01 g, 5.37 mmol), catalyst **8** (145 mg, 1.04 mmol), water (0.10 mL, 0.10 g, 5.6 mmol), and DMSO (0.6 mL) was stirred at room temperature. After 8 days, the brownish semi-solid reaction mixture was taken up in ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, concentrated, and fractionated by FCC (5-10% ethyl acetate in CH_2Cl_2) to give **9** as a white solid (1.22 g, 75%): $[\alpha]_D$ –48, *c* = 1.0, $CHCl_3$ (lit.[12] for **9** of >98% ee: $[\alpha]_D$ – 47, *c* 1.0, $CHCl_3$). Spectroscopic data for **9** were identical to that previously reported.[12] The catalyst could be recovered in >80% yield by concentrating the water layers and precipitating the residue from hot MeOH on addition of benzene.

(α*R*,6*S*)-α-[(3*R*,4*S*)-Tetrahydro-4-hydroxy-2*H*-thiopyran-3-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol (10a).



10a

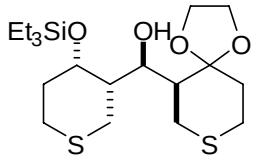
$Li^{s}Bu_3BH$ (1.0 M solution in THF; 10 mL, 10 mmol) was added dropwise via syringe to a stirred solution of ketone **9** (1.03 g, 3.40 mmol) in THF (50 mL) at -78 °C under argon. After 3 h, phosphate buffer (pH=7.5; 10 mL) and 30% aqueous H_2O_2 (5 mL) were sequentially added. The mixture was allowed to stir for 10 min at 0 °C and then was diluted with cold saturated aqueous Na_2SO_3 (20 mL) and extracted with CH_2Cl_2 (x4). The combined organic layers were dried over Na_2SO_4, concentrated and fractionated by FCC (30% ethyl acetate in hexane) to give the titled diol as a colorless oil (852 mg, 83%): $[\alpha]_D$ +41 (*c* 3.0, MeOH); **IR** λ_{max}: 3466 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.35 (1H, ddd, *J* = 1.5, 2, 8.5 Hz), 4.17 (1H, ddd, *J* = 2.5, 3, 4, 7 Hz), 4.13-3.95 (4H, m), 3.31 (1H, d, *J* = 1.5 Hz), 3.12 (1H, d, *J* = 4 Hz), 3.02 (1H, dd, *J* = 11, 14 Hz), 2.97 (1H, ddd, *J* = 3, 11, 14 Hz), 2.85 (1H, dd, *J* = 10, 14 Hz), 2.81 (1H, ddd, *J* = 2.5, 12.5, 14 Hz), 2.71 (1H, ddd, *J* = 3, 3.5, 14 Hz), 2.56 (1H, dddd, *J* = 2, 4.5, 4.5, 14 Hz), 2.39 (1H, dddd, *J* = 1.5, 3, 4, 14 Hz), 2.29 (1H, dd, *J* = 3, 14 Hz), 2.20-2.13 (2H, m), 2.03 (1H, ddd, *J* = 2, 3.5, 11 Hz), 1.97 (1H, dddd, *J* = 2.5, 3, 8.5, 10 Hz), 1.91 (1H, dddd, *J* = 3, 3, 11, 14 Hz), 1.74 (1H, ddd, *J* = 4.5, 12.5, 13.5 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 110.4 (s), 70.2 (d), 67.0 (d), 64.9 (t), 64.3 (t), 47.0 (d), 43.5 (d), 36.1 (t), 34.1 (t), 26.8 (t), 26.7 (t), 26.2 (t), 23.9 (t);

HRMS (EI) *m/z* calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0963.

(α*R*,6*S*)-α-[(3*S*,4*S*)-4-Triethylsilyloxytetrahydro-2*H*-thiopyran-3-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol (11a).



11a

Et_3SiOTf (0.477 mL, 2.11 mmol) was added to a solution of diol **10a** (615 mg, 2.01 mmol) and 2,6-lutidine (2.40 mL, 2.21 g, 20.6 mmol) in CH_2Cl_2 (100 mL) at 0 °C under argon. After 10 min (reaction complete by TLC), the mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexanes) to give the titled product as a colorless liquid (820 mg, 97%): $[\alpha]_D$ +34 (*c* 1.1, benzene);

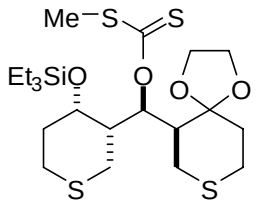
IR λ_{max}: 3526 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ: 4.58 (1H, m), 4.15 (1H, dd, *J* = 2.5, 10 Hz), 3.51 (1H, ddd, *J* = 7, 7.5, 7.5 Hz), 3.40 (1H, ddd, *J* = 5, 7.5, 7.5 Hz), 3.25 (1H, ddd, *J* = 5, 7.5, 7.5 Hz), 3.16 (1H, ddd, *J* = 3, 13, 13 Hz), 3.15-3.09 (2H, m), 3.08 (1H, dd, *J* = 12, 14 Hz), 2.92 (1H, dd, *J* = 12, 13 Hz), 2.60 (1H, ddd, *J* = 2, 13, 14 Hz), 2.55 (1H, ddd, *J* = 2, 3, 14 Hz), 2.15 (1H, dddd, *J* = 2, 3.5, 4, 14 Hz), 2.06-1.96 (3H, m), 1.91 (1H, dddd, *J* = 3, 3, 5, 14 Hz), 1.86 (1H, ddd, *J* = 2, 3, 10, 13.5 Hz), 1.74-1.67 (2H, m), 1.54 (1H, ddd, *J* = 3.5, 13, 13.5 Hz), 1.03 (9H, t, *J* = 8 Hz), 0.65 (6H, q, *J* = 8 Hz);

^{13}C NMR (125 MHz, C_6D_6) δ: 111.1 (s), 68.6 (d), 65.4 (d), 64.6 (t), 64.1 (t), 46.3 (d), 46.2 (d), 37.0 (t), 36.3 (t), 27.0 (t), 26.1 (t), 24.0 (t), 22.3 (t), 7.6 (q x3), 5.8 (t x3);

HRMS *m/z* calcd for $C_{19}H_{36}O_4S_2Si$ 420.1824, found 420.1835.

***O*-(*R*)-[(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]decan-6-yl][(3*S*,4*S*)-4-(triethylsilyloxy)tetrahydro-2*H*-thiopyran-3-yl]methyl *S*-Methyl Carbonodithioate (11b)**.



11b

NaH (50% dispersion in oil; 650 mg, 13.5 mmol) was added to a stirred solution of alcohol **11a** (750 mg, 1.79 mmol) and imidazole (~10 mg) in THF (10 mL) at 0 °C. The mixture was allowed to warm to ambient temperature and, after 30 min, was cooled to 0 °C and CS_2 (1.1 mL, 18 mmol) was added via syringe. The mixture was allowed to warm to ambient temperature and, after 1 h, was cooled at 0 °C and MeI (1.2 mL, 18 mmol) was added via syringe. After 30 min, the reaction was allowed to warm to ambient temperature. After 15 h (reaction complete by TLC), the reaction mixture was cooled to 0 °C and quenched by careful addition of water [**caution**: H_2 evolution]. The mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, concentrated, and fractionated by FCC (5-10% ethyl acetate in hexanes) to give the titled xanthate as a yellow oil (850 mg, 93%): $[\alpha]_D$ +90 (*c* 1.6, benzene);

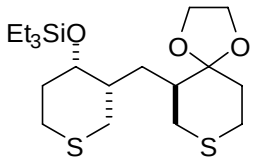
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.18 (1H, dd, *J* = 2, 6 Hz), 4.23 (1H, m), 4.12-4.05 (1H, m), 4.01-3.94 (2H, m), 3.87-3.81 (1H, m), 3.14 (1H, dd, *J* = 12.5, 12.5 Hz), 3.07 (1H, ddd, *J* = 3, 13, 13 Hz), 2.99 (1H, dd, *J* = 12, 14 Hz), 2.86 (1H, ddd, *J* = 3, 13, 13.5 Hz), 2.70 (1H, ddd, *J* = 3, 3, 14 Hz), 2.63 (1H, ddd, *J* = 2, 3, 12 Hz), 2.55 (3H, s), 2.46 (1H, dddd, *J* = 3, 3.5, 4, 13.5 Hz), 2.31 (1H, br d, *J* = 12.5 Hz), 2.24-2.19 (2H, m), 2.14-2.08

(2H, m), 1.83 (1H, dddd, *J* = 1.5, 3.5, 13, 14 Hz), 1.68 (1H, ddd, *J* = 4, 13, 13.5 Hz), 1.00 (9H, t, *J* = 7.5 Hz), 0.72-0.63 (6H, m);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 215 (s), 108.8 (s), 81.9 (d), 67.1 (d), 64.7 (t), 64.5 (t), 48.2 (d), 47.5 (d), 36.6 (t), 36.2 (t), 28.4 (t), 27.0 (t), 24.0 (t), 22.1 (t), 19.2 (q), 7.4 (q x3), 5.6 (t x3);

HRMS (EI) *m/z* calcd for $C_{21}H_{38}O_4S_4Si$ 510.1422, found 510.1420.

{(3*S*,4*S*)-3-[(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]decan-6-ylmethyl]tetrahydro-2*H*-thiopyran-4-yloxy}triethylsilane (11c).



11c

Tributylstannane (0.52 mL, 2.0 mmol) was added to a stirred solution of xanthate **11b** (850 mg, 1.67 mmol) in dry toluene (5 mL) under argon. The mixture was heated under reflux and then AIBN (ca. 15 mg) was added. After 30 min, the reaction was allowed to cool to ambient temperature and then was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and the resulting colorless oil was passed through a short pad of silica gel (eluting first with hexane and then with 5% ethyl acetate in hexane) to afford the titled compound (653 mg, 97%): $[\alpha]_D$ -14 (*c* 1.9, benzene);

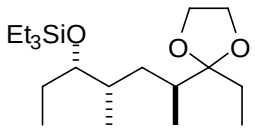
^{1}H NMR (500 MHz, C_6D_6) δ: 3.63 (1H, ddd, *J* = 2.5, 2.5, 5.5 Hz), 3.50-3.36 (4H, m), 2.94 (1H, ddd, *J* = 3, 11, 13 Hz), 2.89-2.82 (2H, m), 2.60-2.54 (3H, m), 2.25 (1H, ddd, *J* = 1.5, 3, 13.5 Hz), 2.13 (1H, dddd, *J* = 1.5, 3.5, 5.5, 13 Hz), 1.92 (1H, ddd, *J* = 3, 10.5,

13.5 Hz), 1.88-1.77 (3H, m), 1.71-1.53 (4H, m), 0.98 (9H, t, *J* = 8 Hz), 0.55 (6H, q, *J* = 8 Hz);

^{13}C NMR (125 MHz, C_6D_6) δ: 109.5 (s), 71.5 (d), 64.7 (t), 64.6 (t), 42.5 (d), 40.9 (d), 35.6 (t), 35.3 (t), 31.6 (t), 30.4 (t), 28.1 (t), 27.0 (t), 23.5 (t), 7.3 (q x3), 4.9 (t x3);

HRMS (EI) *m/z* calcd for $C_{19}H_{36}O_3S_2Si$ 404.1875, found 404.1869.

Triethyl[(3*S*,4*S*,6*S*)-6-(2-ethyl-1,3-dioxolan-2-yl)-4-methylheptan-3-yloxy]silane (12).



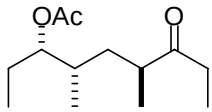
12

A suspension of freshly prepared Raney-Ni (W-2)[21] (4 mL settled volume) in ethanol (2 mL) was added in one portion to a well stirred solution of **11c** (282 mg, 0.698 mmol) in methanol (10 mL). The reaction mixture was heated under reflux and progress was monitored by TLC. Additional Raney-Ni (2 mL settled volume) was added each hour until the reaction was complete (2-3 h). The supernatant was filtered through a pad of Celite® and the residue was suspended in methanol (50 mL) and heated under reflux for several minutes. The supernatant was filtered and the residue treated as above (this process repeated 3 times). The combined filtrates were concentrated and fractionated by FCC (10% ethyl acetate in hexane) to give the titled compound as a clear oil (198 mg, 82%): $[\alpha]_D$ –27 (*c* 1.6, benzene);

^{1}H NMR (500 MHz, C_6D_6) δ: 3.61-3.56 (4H, m), 3.48 (1H, dd, *J* = 5.5, 10 Hz), 1.93 (1H, m), 1.77-1.67 (3H, m), 1.62 (1H, ddd, *J* = 2, 12, 12 Hz), 1.57-1.39 (3H, m), 1.07 (3H, d, *J* = 6.5 Hz), 1.05 (9H, t, *J* = 7.5 Hz), 0.99 (3H, t, *J* = 7.5 Hz), 0.92 (3H, t, *J* = 7.5 Hz), 0.92 (3H, d, *J* = 6.5 Hz), 0.67 (6H, q, *J* = 7.5 Hz);

^{13}C NMR (125 MHz, C_6D_6) δ: 114.7 (s), 79.3 (d), 65.7 (t), 65.6 (t), 37.5 (d), 35.8 (d), 34.9 (t), 27.3 (t), 27.2 (t), 14.5 (q), 14.2 (q), 10.9 (q), 8.2 (q), 7.7 (q x3), 6.1 (t x3); **HRMS** *m/z* calcd for $C_{19}H_{40}O_3Si$ 344.2747, found 344.2740.

(3*S*,4*S*,6*S*)-4,6-Dimethyl-7-oxononan-3-yl acetate (2).



2

Acetic acid (21 μL, 0.37 mmol) was added to a stirred solution of **12** (65 mg, 0.19 mmol) in CH_2Cl_2 (3 mL). After 10 min, DMAP (69 mg, 0.57 mmol) and acetyl chloride (0.1 mL, excess) were added, After 15 min, the mixture was diluted with CH_2Cl_2 (10 mL), washed with aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (pentane and then 5% Et_2O in pentane) to give serricornin acetate (**2**) as a colorless oil (31 mg, 72% yield): $[\alpha]_D$ -20 (*c* 0.3, hexane) (lit.[1,6] –16.1 to –18.7);

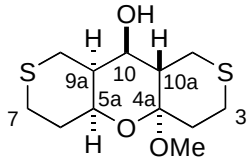
IR λ_{max}: 2964, 2940, 2886, 1732, 1708, 1462, 1367, 1235, 1104, 1014 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.76 (1H, ddd, *J* = 4.5, 4.5, 8.5 Hz), 2.63 (1H, m), 2.56-2.39 (2H, m), 2.06 (3H, s), 1.68 (1H, m), 1.60-1.46 (3H, m), 1.29 (1H, m), 1.05 (3H, t, *J* = 7.5 Hz), 1.04 (3H, d, *J* = 7 Hz), 0.87 (3H, d, *J* = 7 Hz), 0.86 (3H, t, *J* = 7.5 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.3, 171.2, 78.3, 43.7, 36.0, 34.5, 33.8, 24.3, 21.3, 16.8, 14.6, 10.4, 8.0;

LRMS (CI, NH_3), *m/z* (relative intensity): 246 ($[M+18]^+$, 27), 229 ($[M+1]^+$, 7), 189 (41), 169 (100); **HRMS** *m/z* calcd for $C_{13}H_{24}O_3$ 228.1725 (246.2069 for $M+NH_4$), found 246.2063 (CI, NH_3).

(4a*R*,5a*S*,9a*S*,10*R*,10a*S*)-Octahydro-4a-methoxy-1*H*,3*H*,5a*H*-dithiopyrano[4,3-b:3',4'-e]pyran-10-ol (13a).



13a

Concentrated aqueous HCl (12 M, 3.5 mL) was added to a stirred solution of diol **10a** (378 mg, 1.24 mmol) in methanol (17.5 mL) at room temperature. After 1.5 h, the mixture was diluted with CH_2Cl_2 (100 mL), cooled to 0 °C, and quenched by addition of saturated aqueous $NaHCO_3$ (**Caution**: effervescence). The mixture was diluted with water and the phases separated. The aqueous layer was extracted with dichloromethane (x2) and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give the titled product as a white solid (324 mg, 95% yield): $[\alpha]_D$ -87, (*c* 1.5, benzene);

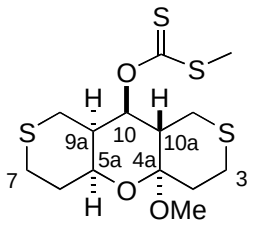
IR λ_{max}: 3449, 2922, 2874, 1420, 1337, 1139, 1056, 882 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ: 3.55 (1H, ddd, *J* = 2.5, 3, 3 Hz, HC-5a), 3.42 (1H, dd, *J* = 5, 11 Hz, HC-10), 2.91 (1H, ddd, *J* = 2.5, 13, 13.5 Hz, HC-7), 2.84 (1H, dd, *J* = 10.5, 13 Hz, HC-1), 2.81 (1H, dd, *J* = 9, 13 Hz, HC-9), 2.69 (3H, s, H_3CO), 2.68 (1H, ddd, *J* = 2, 3, 13 Hz, HC-1), 2.65 (1H, ddd, *J* = 2.5, 13, 13.5 Hz, HC-3), 2.40 (1H, ddd, *J* = 2.5, 3, 13.5 Hz, HC-9), 2.06 (1H, dddd, *J* = 2, 3, 3.5, 13.5 Hz, HC-3), 2.00 (1H, dddd, *J* = 2, 3.5, 3.5, 13.5 Hz, HC-7), 1.96 (1H, ddd, *J* = 2.5, 3, 14 Hz, HC-4), 1.87 (1H, ddd, *J* = 3, 10.5, 11 Hz, HC-10a), 1.86-1.79 (2H, m, HC-6 , HC-9a), 1.60 (1H, dddd, *J* = 3, 3.5, 13.5, 13.5 Hz, HC-6), 1.53 (1H, ddd, *J* = 3.5, 13.5, 14 Hz, HC-4), 0.71 (1H, br s, HOC-10);

^{13}C NMR (125 MHz, C_6D_6) δ: 98.3 (s, C-4a), 69.7 (d, C-10), 64.9 (d, C-5a), 47.8 (d, C-10a), 45.9 (d, CH3O), 43.8 (d, C-9a), 33.4 (t, C-4), 32.6 (t, C-6), 27.1 (t, C-1), 24.9 (t, C-3), 23.1 (t, C-7), 21.9 (t, C-9);

LRMS (EI), *m/z* (relative intensity): 276 ([M]$^+$, 100), 244 (11), 227 (91), 226 (93), 159 (32), 129 (26), 101 (33), 99 (45); **HRMS** *m/z* calcd for $C_{12}H_{20}O_3S_2$ 276.0854, found 276.0856.

***O*-(4a*R*,5a*S*,9a*R*,10*R*,10a*S*)-Octahydro-4a-methoxy-1*H*,3*H*,5a*H*-dithiopyrano[4,3-b:3',4'-e]pyran-10-yl *S*-methyl carbonodithioate (13b)**.



13b

NaH (70% dispersion in oil; 373 mg, 10.9 mmol) to a stirred solution of alcohol **13a** (310 mg, 1.12 mmol) and imidazole (~10 mg) in THF (10 mL) at 0 °C under argon. The mixture was allowed to warm to ambient temperature and, after 30 min, was cooled at 0 °C and CS_2 (0.74 mL, 12.3 mmol) was added via a syringe. The mixture was allowed to warm to ambient temperature and, after 1 h, was cooled at 0 °C and MeI (0.75 mL, 12.0 mmol) was added via syringe. After 30 min, the reaction was allowed to warm to ambient temperature. After 4 h (reaction complete by TLC), the reaction mixture was cooled to 0 °C and quenched by careful addition of water [**caution**: H_2 evolution]. The mixture was diluted with dichloromethane, washed with water, dried over Na_2SO_4, concentrated, and

fractionated by FCC (5-10% ethyl acetate in hexanes) to give the corresponding xanthate as a pale yellow solid (383 mg, 93% yield): $[\alpha]_D$ -87, (*c* 1.0, benzene);

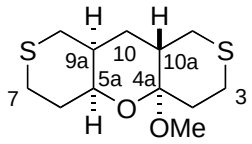
IR λ_{max}: 2928, 2826, 1420, 1331, 1205, 1044, 942, 882 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ: 6.03 (1H, dd, *J* = 5.5, 11.5 Hz, HC-10), 3.63 (1H, ddd, *J* = 3, 3, 3 Hz, HC-5a), 2.95 (1H, dd, *J* = 12, 13 Hz, HC-9), 2.93 (1H, dd, *J* = 12, 13 Hz, HC-1), 2.83 (1H, ddd, *J* = 3, 13.5, 13.5 Hz, HC-7), 2.70 (1H, dddd, *J* = 2.5, 3, 5.5, 12 Hz, HC-9a), 2.61 (3H, s, H_3CO), 2.56 (1H, ddd, *J* = 2, 13.5, 13.5 Hz, HC-3), 2.47 (1H, ddd, *J* = 2, 3, 13 Hz, HC-1), 2.34 (1H, ddd, *J* = 3, 11.5, 12 Hz, HC-10a), 2.32 (1H, dd, *J* = 2.5, 13 Hz, HC-9), 2.05 (3H, s, H_3CS), 1.97 (1H, dddd, *J* = 2, 3.5, 3.5, 13.5 Hz, HC-3), 1.93-1.88 (2H, m, HC-4, HC-7), 1.72 (1H, dddd, *J* = 3, 3, 4, 14 Hz, HC-6), 1.54-1.45 (2H, m, HC-4, HC-6);

^{13}C NMR (125 MHz, C_6D_6) δ: 216.4 (s, C=S), 99.7 (s, 4a), 82.9 (d, C-10), 64.9 (d, C-5a), 46.53 (d, C-10a), 46.50 (q, CH_3O), 40.9 (d, C-9a), 33.9 (t, C-4), 32.7 (t, C-6), 27.4 (t, C-1), 25.3 (t, C-3), 23.2 (t, C-9), 23.0 (t, C-7), 19.2 (q, CH_3S);

LRMS (EI), *m/z* (relative intensity): 366 ($[M]^+$, 15), 333 (87), 259 (86), 227 (26), 169 (100), 139 (80), 105 (22), 79 (14); **HRMS** *m/z* calcd for $C_{14}H_{22}O_3S_4$ 366.0452, found 366.0452.

(4a*R*,5a*S*,9a*S*,10a*S*)-Octahydro-4a-methoxy-1*H*,3*H*,5a*H*-dithiopyrano[4,3-b:3',4'-e]pyran (13c).



13c

Tributylstannane (0.28 mL, 1.0 mmol) was added to a stirred solution of xanthate **13b** (300 mg, 0.82 mmol) in dry toluene (5 mL) under argon. The mixture was heated under reflux and then AIBN (ca. 10 mg) was added. After 30 min, the reaction was allowed to cool to ambient temperature and then was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and the resulting colorless oil was passed through a short pad of silica gel (eluting first with hexane and then with 5% ethyl acetate in hexane) to afford the titled product (195 mg, 91%): $[\alpha]_D$ -40, (*c* 0.7, benzene);

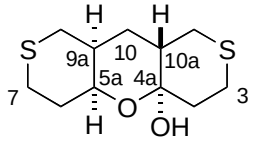
IR λ_{max}: 2922, 2826, 1420, 1325, 1211, 1104, 1044, 942, 882 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ: 3.63 (1H, ddd, *J* = 3, 3, 3 Hz, HC-5a), 3.00 (1H, dd, *J* = 12.5, 13 Hz), 2.89 (1H, ddd, *J* = 3, 13, 13 Hz), 2.79 (1H, dd, *J* = 11.5, 12 Hz), 2.74 (3H, s, H_3CO), 2.68 (1H, ddd, *J* = 3, 13.5, 13.5 Hz), 2.05 (1H, dddd, *J* = 2, 4, 4, 13 Hz), 1.97 (1H, dddd, *J* = 2, 4, 4, 13 Hz), 1.95 (1H, ddd, *J* = 3, 3, 14 Hz), 1.89-1.73 (4H, m), 1.66-1.51 (4H, m), 0.71 (1H, ddd, *J* = 2, 4, 13 Hz);

^{13}C NMR (125 MHz, C_6D_6) δ: 98.6 (s, C-4a), 66.1 (d, C-5a), 46.4 (q, CH_3O), 41.4 (d), 37.0 (d), 34.2 (t), 33.6 (t), 32.6 (t), 31.2 (t), 27.4 (t), 25.7 (t), 23.0 (t);

LRMS (EI), *m/z* (relative intensity): 260 ([M]$^+$, 91), 229 (47), 228 (85), 195 (25), 141 (25), 139 (21), 113 (100), 99 (28), 79 (27); **HRMS** *m/z* calcd for $C_{12}H_{20}O_2S_2$ 260.0905, found 260.0898.

(4a*R*,5a*S*,9a*S*,10a*S*)-Octahydro-1*H*,3*H*,5a*H*-dithiopyrano[4,3-b:3',4'-e]pyran-4a-ol (13d).



13d

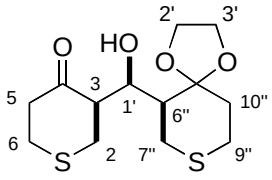
A solution of acetal **13c** (38 mg, 0.15 mmol) in THF (1.25 mL), water (1.25 mL) and acetic acid (4 mL) was stirred at 50 °C. After 1.5 h (reaction complete by TLC), the mixture was cooled to ambient temperature and then diluted with CH_2Cl_2 (20 mL), washed with $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give the titled hemiacetal as a white solid (34 mg, 94% yield): $[\alpha]_D$ -12, (*c* 0.89, benzene);

IR λ_{max}: 3364, 2946, 2910, 1420, 1247, 1133, 1050, 924 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ: 4.01 (1H, ddd, *J* = 3, 3, 3 Hz, HC-5a), 2.99 (1H, dd, *J* = 13, 13 Hz), 2.89 (1H, ddd, *J* = 2.5, 13, 13 Hz), 2.81 (1H, ddd, *J* = 3, 13, 13 Hz), 2.65 (1H, dd, *J* = 11.5, 13 Hz), 2.09 (1H, dddd, *J* = 1.5, 4, 4, 13 Hz), 2.01 (1H, dddd, *J* = 2, 4, 4, 13 Hz), 1.87 (1H, dddd, *J* = 3, 3, 3, 14 Hz), 1.84-1.61 (6H, m), 1.50 (1H, ddd, *J* = 5, 13, 13 Hz), 1.40 (1H, ddd, *J* = 3, 3, 13.5 Hz), 0.73 (1H, ddd, *J* = 2, 4, 13 Hz), 0.73 (1H, s, OH); **^{13}C NMR** (125 MHz, C_6D_6) δ: 96.1 (s), 65.9 (d), 40.9 (t), 40.5 (d), 37.2 (d), 33.9 (t), 32.6 (t), 31.4 (t), 27.3 (t), 26.2 (t), 23.0 (t);

LRMS (EI), *m/z* (relative intensity): 246 ($[M]^+$, 100), 228 (39), 195 (10), 167 (12), 141 (29), 113 (33), 112 (26), 99 (35); **HRMS** *m/z* calcd for $C_{11}H_{18}O_2S_2$ 246.0748, found 246.0751.

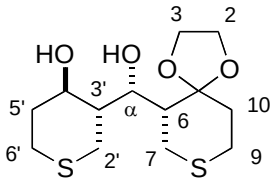
(3*R*)-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(hydroxy)methyl]tetrahydro-4*H*-thiopyran-4-one (14).



14

The isomerization of (±)-**9** to (±)-**14** in the presence of imidazole was reported previously.[30] On preparative scale, the following procedure was more convenient. A slurry of silica gel 60 (230-400 mesh, 3.20 g) and Et_3N (1.9 mL, 1.4 g, 14 mmol) were added to a solution of aldol **9** (1.07 g, 3.5 mmol) in ethyl acetate (14 mL) at room temperature. The resulting slurry was stirred for 8 h to obtain a 2.5:1 equilibrium mixture (by ^1H NMR) of **14** and **9**, respectively. The mixture was filtered the combined filtrate and ethyl acetate washings were concentrated and fractionated by FCC (5-10% ethyl acetate/CH_2Cl_2) to give **14** as a colorless oil (620 mg, 58%) and a 4:1 mixture of **9** and **14**, respectively (440 mg, 41%). The mixture (440 mg) was resubjected to the same conditions (1.5 g silica gel, 0.80 mL Et_3N, 6 mL ethyl acetate) to give additional **13** (218 mg, 50%) and a 4:1 mixture of **9** and **14** (203 mg, 46%). Thus, the combined yield of **14** after 2 cycles of isomerization was 78%: $[\alpha]_D$ +64, *c* 1.0, $CHCl_3$ (lit.[31] for *ent*-**13** of 90% ee: $[\alpha]_D$ –48, *c* 1.3, $CHCl_3$). Spectroscopic data for (+)-**14** closely matched that previously reported for (±)-**14**.

(α*S*,6*R*)-α-[(3*R*,4*R*)-Tetrahydro-4-hydroxy-2*H*-thiopyran-3-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol (*ent*-15a).



ent-**15a**

$NaBH(OAc)_3$ (1 M in glacial acetic acid, 0.74 mL, 0.74 mmol; freshly prepared) was added dropwise via syringe over four min to a stirred solution of *ent*-**14**[32] (55 mg, 0.18 mmol) in acetonitrile (2.9 mL, distilled from CaH_2) at –40 °C under argon. The resulting clear solution was stirred for 2 h at -40 °C and then warmed to –20 °C. After 3 h, saturated aqueous sodium potassium tartrate (5 mL) was added and the resulting cloudy solution was stirred at room temperature for 10 min. The mixture was added to saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (60-80% ethyl acetate in hexanes) to give the titled diol as a white solid (51 mg, 92%): $[\alpha]_D$ –29 (*c* 1.0, $CHCl_3$);

IR λ_{max}: 3420 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.51 (1H, dd, *J* = 2.5, 5.5 Hz, HC-α), 4.12-3.93 (4H, m, H_2CO x2), 3.67 (1H, ddd, *J* = 3.5, 9, 9 Hz, HC-4'), 3.01 (1H, dd, *J* = 12, 12 Hz, HC-7), 2.93-1.47 (7H, m, H_2C-2', H_2C-6', HC-7, H_2C-9), 2.27-2.10 (3H, m, HC-5', HC-6, HC-10), 1.96 (1H, dddd, *J* = 3, 5.5, 8.5, 9.5 Hz, HC-3'), 1.81-1.72 (2H, m, HC-5', HC-10); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 110.1 (s, C-5), 70.6 (d, C-4'), 69.3 (d, C-α), 64.9 (t, CH_2O), 64.6 (t, CH_2O), 48.5 (d, C-3'), 47.0 (d, C-6), 36.2 (t, C-5'), 35.9 (t, C-10), 27.7 (t, C-2'), 27.6 (t, C-7), 26.8 (t, C-6'), 26.6 (t, C-9);

LRMS (EI), *m/z* (relative intensity): 306 ($[M]^+$, 33), 244 (11), 189 (11), 159 (24), 132 (79), 99 (100); **HRMS** *m/z* calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0964.

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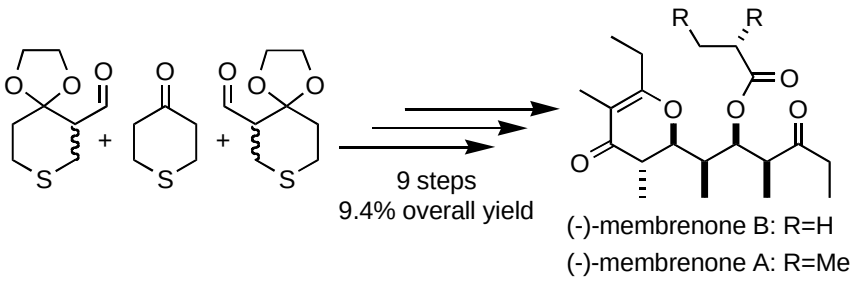
32. Prepared as above from *ent*-**9** (>98% ee) that, in turn, was obtained from the aldol reaction of **5** and **6** catalyzed by *ent*-**8**.[§§]

[§§] References from the manuscript and supporting information are both combined together.

6. The Thiopyran Route to Polypropionates: Enantioselective Synthesis of Membrenone B from Racemic Fragments

Vishal Jheengut and Dale E. Ward

Graphical Abstract



6.1 Preface

Proline-catalyzed aldol reaction of tetrahydro-4*H*-thiopyranone with racemic 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde proceeds with dynamic kinetic resolution to provide easy access to useful enantiomerically pure tetrapropionate synthon. Application of this tetrapropionate synthon towards the synthesis of membrenone B and a formal synthesis of membrenone A is described in this chapter.

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3.2 Manuscript: submitted to the Journal of Organic Chemistry 2007

The Thiopyran Route to Polypropionates: Enantioselective Synthesis of Membrenone B from Racemic Fragments

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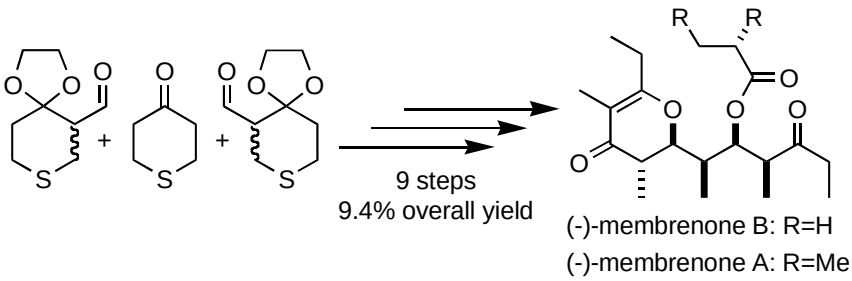
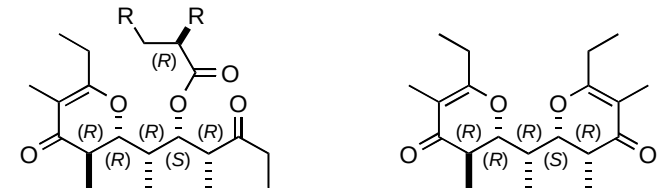


Abstract: (6*S*,7*S*,8*S*,9*R*,10*S*)-(-)-Membrenone B was synthesized in nine steps (9.4% overall yield) beginning with two-directional aldol coupling of tetrahydro-4*H*-thiopyran-4-one with racemic 1,4-dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde. The first aldol reaction occurs with dynamic kinetic resolution to give a single adduct (>98% ee). The second aldol reaction is highly diastereoselective (3 of 8 possible adducts) and both major products are converted to membrenone B. The route also constitutes a formal synthesis of membrenone A.

An important aspect of marine chemical ecology[1] concerns predator-prey interactions. Opisthobranchs (commonly known as sea slugs) are soft-bodied marine molluscs and are often devoid of a protective shell. Their defense mechanism relies on the secretion of chemicals rendering them poisonous or at least extremely distasteful to potential predators.[2] In 1993, Ciavatta *et al*.[3] reported partial structures for membrenones A-C (**1**-**3**; Figure 6.1) isolated from the skin of the notaspidean *Pleurobranchus membranaceus*, a Mediterranean mollusc species. The scarcity of available material limited preliminary bisoassays with membrenone A (**1**), which was shown to be a feeding deterrent to *Carassius auratus*.

In pioneering work conducted by Sampson and Perkins, the relative configurations of **1**-**3** were firmly established by stereoselective synthesis.[4] Considering all available data, a persuasive argument was presented[4c] that the natural products **1**-**3** are the (+)-enantiomers with the absolute configurations indicated in Figure 6.1.[5] This assignment requires the conclusion that the originally reported[3] specific rotations for membrenones B (**2**) and C (**3**) are incorrect (wrong sign) and unfortunately cannot be substantiated because samples of natural material are no longer available. In this paper we report a very concise synthesis of (-)-membrenone B (*ent*-**2**) from racemic fragments.[6]



(+)-membrenone A: R=Me (**1**)
(+)-membrenone B: R=H (**2**)

(+)-membrenone A (**3**)

Figure 6.1. Structures and proposed absolute configurations for membrenones A-C.

The thiopyran route to polypropionates is an attractive strategy for the rapid assembly of stereochemically diverse hexapropionate synthons from simple precursors (Figure 6.2).[7,8,9] For example, we recently demonstrated that 11 of the 20 possible diastereomers of **7** could be selectively prepared in 2 or 3 steps from **4** and **5**.[8b] We chose the hexapropionate (–)–membrenone B (*ent*-**2**) as a synthetic target to test and illustrate this approach.

Both *ent*-**1** and *ent*-**2** are available by appropriate acylation of (-)-**8** (Scheme 6.1).[4c] From a retrosynthetic perspective, hydrolytic ring opening of the α-dihydropyrone in **8** leads to **9** as a potential precursor. The dihydroxytrione **9** should be available by simple functional group manipulation of any of the four possible diastereomers of **11**[10] that in turn, result from sequential two-directional aldol reactions of **5** with **4**. The synthesis of **11** by coupling the chiral fragments **6** and **4** requires management of the issues of double stereodifferentiation and mutual kinetic enantioselection (MKE).[11] Previous work suggested that aldol reaction of (*S*)-**4**[7b] with any of the 4 diastereomers of the MOM-derivatives **10** via their Ti(IV) enolates would produce **11** with the desired absolute configuration (i.e. path *a*).[8b] Although routes to each of the diastereomers of **10** are available,[7] use of (1'*S*,6'*R*)-**10** would be particularly attractive because this isomer is easily prepared via the D-proline catalyzed aldol reaction of **5** with (±)-**4** which proceeds with dynamic kinetic resolution (DKR).[7c] A more appealing and efficient approach would involve reaction of the Ti(IV) enolate of (+)-**6ss** with (±)-**4**, a process expected[8b] to occur with kinetic resolution (i.e. path *b*). Because (+)-**6ss** is also available via an organocatalyzed reaction of **5** with (±)-**4**,[9b] this route would allow the complete assembly of **11** from achiral and racemic fragments.

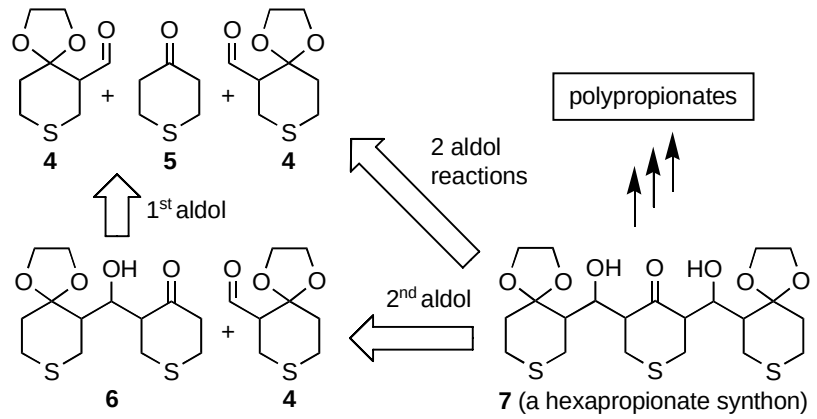
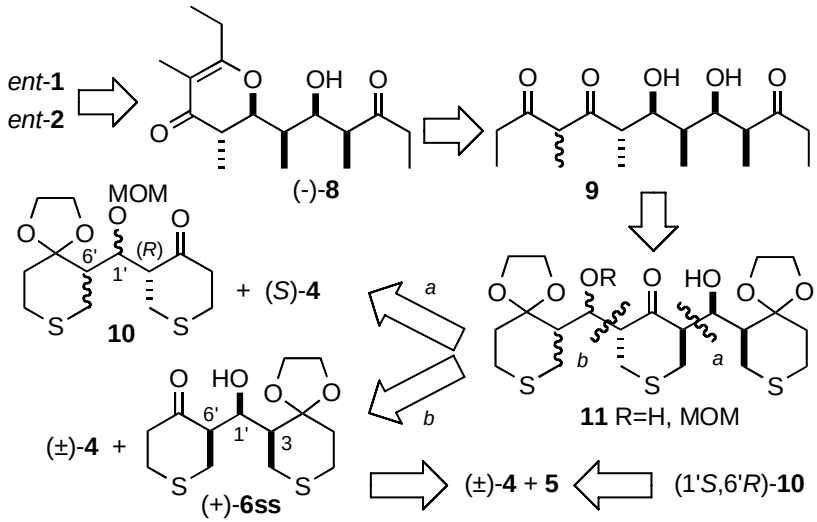


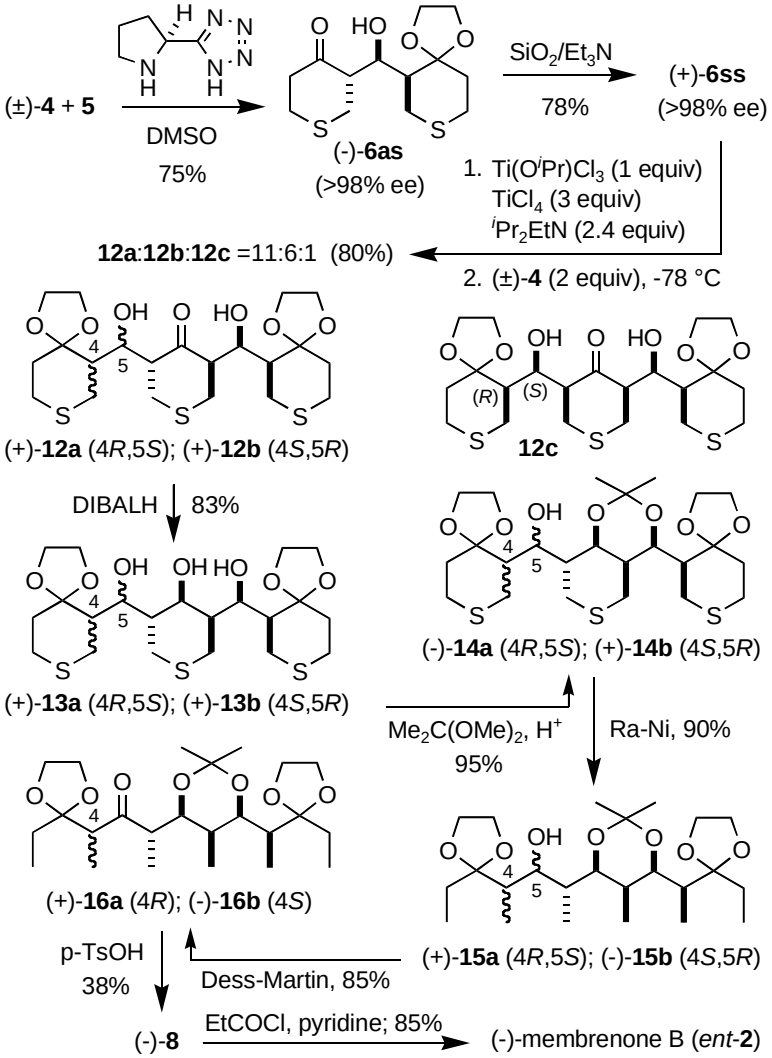
Figure 6.2. The thiopyran route to polypropionates



Scheme 6.1. Retrosynthetic analysis for *ent*-**1** and *ent*-**2**

Enantiomerically enriched (+)-**6ss** (>98% ee) was readily obtained on gram scale in two steps from (±)-**4** and **5** in 59% yield (Scheme 6.2).[9b, 12] Under carefully optimized conditions, aldol reaction of (±)-**4** with (±)-**6ss** via the Ti(IV) enolate gave a 10:3:1 mixture of (±)-**12a**, (±)-**12b**, and **12c**, respectively, in 80% yield.[8b] This result indicates the Ti(IV) enolate of (+)-**6ss** reacts 3-4 times faster with (*R*)-**4** than with (*S*)-**4** and implies

that kinetic resolution will be modest. In the event, reaction of (+)-**6ss** with (±)-**4** (2 equiv) under the same conditions gave a 11:6:1 mixture of (+)-**12a**, (+)-**12b**, and **12c**, respectively, in 80% yield. The slight erosion in the stereoselectivity of the reaction using (+)-**6ss** compared to that with (±)-**6ss** suggests that racemization of **4** is slower than the aldol coupling under these conditions[12] (i.e. no DKR).[11] Although the stereoselectivity of this reaction is modest (3 of 8 possible adducts produced), the two major adducts (94% of the products) have relative and absolute configurations appropriate for the synthesis of membrenones.[13]



Scheme 6.2. Synthesis of (-)-membrenone B (*ent*-**2**)

The diastereomers (+)-**12a** and (+)-**12b** were difficult to separate and highly enriched samples were available only by repeated fractionation on silica gel.[14] Because the individual diastereomers were separately transformed into (-)-**8** with similar efficiencies, the mixture was used without separation (Scheme 6.2). Thus, the 11:6:1 mixture of aldol adducts (+)-**12a**, (+)-**12b**, and **12c**, respectively, was subjected to DIBALH reduction to give a 2.1:1 mixture of (+)-**13a** and (+)-**13b**, respectively, in good yield.[14] Each diol **13** gave the corresponding acetonide **14** with high diastereotopic group selectivity.[14,15] The resulting crude 2.8:1 mixture of (-)-**14a** and (+)-**14b** was desulfurized with Raney nickel to give a 2.8:1 mixture of (+)-**15a** and (-)-**15b** that in turn was oxidized to give a 2.8:1 mixture of (+)-**16a** and (-)-**16b**, respectively, in 72% yield over the three steps. Brief exposure of the mixture of **16** to *p*-TsOH in CH_2Cl_2 gave the known (-)-**8** ($[\alpha]_D$ -130, *c* 0.55, $CHCl_3$; lit.[4c] -114, *c* 0.48, $CHCl_3$) in moderate yield. Various alternative methods (e.g. amberlyst®, $FeCl_3$, $FeCl_3/SiO_2$, H_2SO_4/SiO_2) lead to extensive decomposition.[16] Acylation of (-)-**8** with propanoyl chloride gave (-)-membrenone B (*ent*-**2**) with spectroscopic and chiroptical[17] properties essentially identical to those previously reported.[4c]

In summary, the total synthesis of (6*S*,7*S*,8*S*,9*R*,10*S*)-(–)-membrenone B has been achieved in 9 steps (9.4% overall yield) via two-directional aldol coupling of achiral ketone **5** with racemic aldehyde **4**. Remarkably, although the route involves coupling of chiral fragments, either (+)-**2**, (-)-*ent*-**2**, or (±)-**2** is selectively available from *identical* components simply by altering the catalyst used in the first aldol reaction. It is also noteworthy that the *entire* 17-carbon skeleton of **8** is derived from methyl acrylate as both **4** and **5** are directly and efficiently prepared from this simple precursor (e.g. 6.5% overall

yield of (-)-**8** from methyl acrylate in 13 steps).[17] Because the conversion of (–)-**8** into *ent*-**1** by esterification with (*S*)-2-methylbutanoic acid is also known,[4c] our route constitutes a formal synthesis (-)-membrenone A. Further applications of the thiopyran route to polypropionates are in progress and will be reported in due course.

Experimental section.[***],[18]

Acknowledgment We thank Garrison E. Beye for preliminary experiments on the aldol reaction of (+)-**6ss** with (±)-**4** and for characterization of (+)-**12a** and (+)-**12b**. Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

Supporting Information Available Experimental procedures, spectroscopic data, and NMR spectra for synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

[***] The experimental section of the manuscript is combined with the Supporting Information (Section **6.3**)

6.3 Supplementary Information (Experimental section)

General Methods. Anhydrous solvents were distilled under argon atmosphere as follows: Tetrahydrofuran (THF) from benzophenone sodium ketyl; ether from benzophenone sodium ketyl; CH_2Cl_2 from CaH_2; MeOH from $Mg(OMe)_2$. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were: ice/water (0 °C) and $CO_{2(s)}$/acetone (-78 °C). Unless otherwise noted, reaction temperatures refer to that of the bath.

Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Preparative TLC (PTLC) was carried out on glass plates (20x20 cm) pre-coated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aqueous sulfuric acid (5% v/v), followed by charring on a hot plate. Flash column chromatography (FCC) was performed according to Still et al.[19] with Merck Silica Gel 60 (40-63 μm). All mixed solvent eluents are reported as v/v solutions. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR.

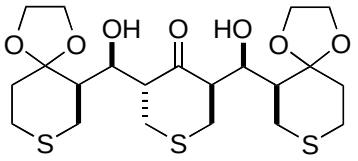
Spectral Data. High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a VG 70E double focusing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI at 50 eV with

ammonia as the reagent gas; only partial data are reported. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 500 MHz for ^1H and 125 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 coupling constants (*J*) corresponds to the order of the multiplicity assignment. Coupling constants (*J*) are reported to the nearest 0.5 Hz (digital resolution ca. 0.2 Hz). The ^1H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or $^1H/^{13}C$ correlation experiments (HSQC and/or HMBC[20)] and/or NOE experiments. The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity[21] (as determined by *J*-modulation[22] or HSQC[23]) and were confirmed, where necessary, by two dimensional $^1H/^{13}C$ correlation experiments (HSQC and/or HMBC). Specific rotations ($[\alpha]_D$) are the average of 5 determinations at ambient temperature using a 1 mL, 10 dm cell; the units are 10^{-1} deg cm^2 g^{-1}, the concentrations (*c*) are reported in g/100 mL, and the values are rounded to reflect the accuracy of the measured concentrations (the major source of error). Circular dichroism (CD) curves were obtained from 240-400 nm at ambient temperature using a 1 mm cell. Molar ellipticities ($[\theta]$) are reported at the wavelengths (in nm) of maximum $|\Delta A|$) and are the average of 5 determinations; the units are 10 deg cm^2 mol^{-1}, the concentrations are reported in mmol/L

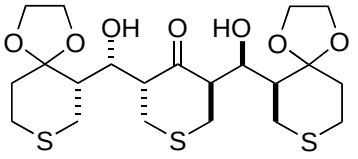
(mM), and the values are rounded to reflect the accuracy of the measured concentrations (the major source of error).

Materials: The preparations of (±)-**4**,[24] **5**,[25] and (+)-**6ss**[26] were previously described. $TiCl_4$ was distilled under argon from CaH_2 and $Ti(O^iPr)_4$ was distilled under argon. $Ti(O^iPr)Cl_3$ (ca. 0.55 M in CH_2Cl_2),[27] W-2 Raney nickel,[28] and the Dess-Martin periodinane (DMP)[29] were prepared by established procedures. All other reagents were commercially available and unless otherwise noted, were used as received. Spectroscopic data for the racemic versions of **12a/b**,[30] **13a/b**,[30a] and **14a/b**[30a] were previously reported; in each case, the NMR data obtained for the highly enantiomerically enriched compounds reported herein were essentially identical to those for the racemic compounds.

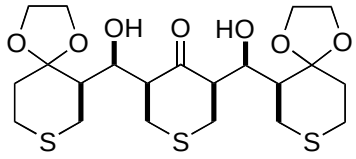
Aldol reaction of (+)-6ss with (±)-4.



(+)-12a



(+)-12b

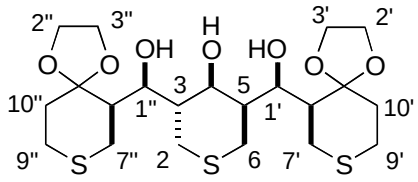


12c

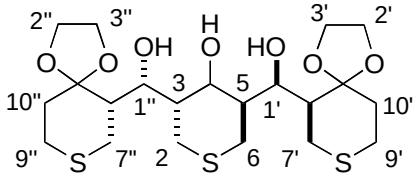
The procedure was according to that reported for reaction of (±)-**6ss** with (±)-**4**. $Ti(O^iPr)Cl_3$ (0.55 M in CH_2Cl_2; 1.7 mL, 0.93 mmol) was added dropwise via syringe to a stirred solution of (+)-**6ss** (284 mg, 0.93 mmol) in CH_2Cl_2 (25 mL) at –78 °C under argon. After 2 min, $TiCl_4$ (0.30 mL, 2.8 mmol) was added dropwise over 1 min and the reaction mixture turned into a yellow slurry. After 2 min, $^iPr_2EtN$ (0.39 mL, 2.2 mmol) was added dropwise via (the yellow slurry solid dissolved and reaction mixture became black). After 1.5 h, (±)-**4** (351 mg, 1.9 mmol) was added neat via syringe. After 6 h, the reaction was quenched by addition of saturated aqueous NH_4Cl, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated FCC to give a 11:6:1 mixture (by ^1H NMR) of **12a**:**12b**:**12c**, respectively, as a white solid (368 mg, 80% combined yield). This mixture was used in the next step without further purification. Highly enriched samples of (+)-**12a** (contaminated with **12b**, ca. 90% purity; $[\alpha]_D$ +73, *c* 0.9, $CHCl_3$) and (+)-**12b** ($[\alpha]_D$ +71, *c* 0.7, $CHCl_3$) could be obtained by repeated fractionation of the mixture by PTLC (40%

ethyl acetate in hexane, multiple elutions). Spectrocopic data for the purified samples were essentially identical to that reported for the racemic compounds. Fractionation of the products from a similar reaction (200 mg of (+)-**6ss**) provided (*S*)-(-)-**4** (ca. 50% yield; $[\alpha]_D$ –27, *c* 1.0, C_6H_6; ca. 20% optical purity) and (+)-**6ss** (ca. 10%).

(3*S*,4*S*,5*S*)-3-[(*S*)-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*R*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4-hydroxy-2H-thiopyran ((+)-13a) and (3*S*,5*S*)-3,5-Bis[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4-hydroxy-2*H*-thiopyran ((+)-13b).



(+)-13a



(+)-13b

DIBAL-H (1.0 M in toluene; 3.6 mL, 3.6 mmol) was added dropwise via syringe to a stirred solution of a 11:6:1 mixture (by ^{1}H NMR) of **12a**:**12b**:**12c**, respectively, (270 mg, 0.55 mmol) in THF (10 mL) at –78 °C under Ar. After 3 h, excess DIBAL was quenched by dropwise addition of MeOH (1 mL) and the resulting mixture was allowed to room temperature over 15-30 min. A saturated aqueous solution of sodium potassium tartrate (10 mL) was slowly added (**Caution**: exothermic) to the well-stirred mixture. After 1 day, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (50-75% ethyl

acetate in hexanes) gave a 2.1:1 **13a** and **13b**, respectively, as a white solid (226 mg, 83%). This mixture was used in the next step without further purification. Pure samples of (+)-**13a** and (+)-**13b** were obtained by careful fractionation of the mixture or from similar reactions with single diastereromers of **12**. Spectrocopic data for the purified samples were essentially identical to that reported for the racemic compounds.[30a]

Data for (+)-**13a**:

$[\alpha]_D$ +24, *c* 1.0, $CHCl_3$;

IR ν_{max} 3487 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (1H, d, *J* = 10.5 Hz, H-4), 4.17-3.93 (9H, m, H-1' or H-1", H_2CO ×4'), 3.88 (1H, br d, H-1' or H-1"), 3.22 (1H, dd, *J* = 3.5, 13.5 Hz), 3.10 (1H, dd, *J* = 12, 14 Hz), 3.00 (1H, dd, *J* = 12, 13 Hz), 2.92 (1H, dd, *J* = 10, 14 Hz), 2.84 (1H, ddd, *J* = 2.5, 13, 13 Hz), 2.83-2.74 (2H, m), 2.68 (1H, ddd, *J* = 2, 2, 14 Hz), 2.62 (1H, m), 2.59 (1H, ddd, *J* = 3, 3, 14 Hz), 2.54-2.49 (2H, m), 2.20-2.11 (3H, m), 2.02-1.90 (3H, m), 1.80 (1H, ddd, *J* = 3.5, 11, 14 Hz); 1.75 (1H, ddd, *J* = 4, 13.5, 13.5 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 110.5 (s), 110.1 (s), 71.3 (d), 68.0 (d), 65.2 (d), 65.1 (t), 64.9 (t), 64.6 (t), 64.5 (t), 46.9 (d), 46.1 (d), 42.9 (d), 41.4 (d), 36.7 (t), 35.8 (t), 26.85 (t), 26.82 (t) 26.7 (t), 26.0 (t), 23.6 (t), 22.9 (t).

Data for (+)-**13b**:

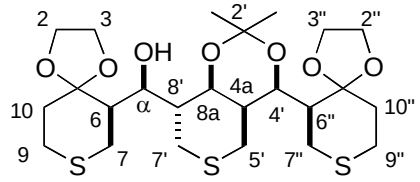
$[\alpha]_D$ +46, *c* 2.1, CH_2Cl_2;

IR ν_{max} 3503 cm^{-1};

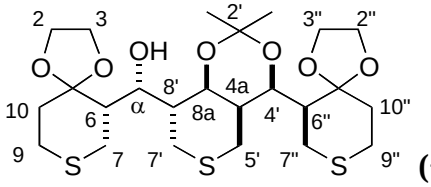
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (1H, d, *J* = 10 Hz, HC-1"), 4.26 (1H, br s, HC-1'), 4.21 (1H, dd, *J* = 1.5, 8 Hz, HC-4), 4.17-3.94 (10H, m), 3.15 (1H, dd, *J* = 3.5, 14 Hz), 3.07-2.96 (4H, m), 2.87-2.76 (3H, m), 2.65-2.50 (4H, m), 2.27 (1H, ddd, *J* = 2, 3.5, 11 Hz), 2.22-2.08 (4H, m), 2.05-1.97 (2H, m), 1.80-1.72 (2H, m);

^{13}C NMR (125 MHz, $CDCl_3$) δ 110.6 (s), 110.5 (s), 71.0 (d), 67.9 (d ×2), 65.1 (t), 64.9 (t), 64.43 (t), 64.40 (t), 46.9 (d), 46.1 (d), 42.8 (d), 41.2 (d), 36.5 (t), 36.3 (t), 26.8 (t), 26.7 (t), 26.5 (t), 25.8 (t), 24.4 (t), 24.3 (t).

(α*S*,6*R*)-α-[(4*S*,4a*S*,8*R*,8a*R*)-4-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yltetrahydro-2,2-dimethyl-4*H*,5*H*-thiopyrano[4,3-d]-1,3-dioxin-8-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol ((-)-14a) and (α*R*,6*S*)-α-[(4*S*,4a*S*,8*R*,8a*R*)-4-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yltetrahydro-2,2-dimethyl-4*H*,5*H*-thiopyrano[4,3-d]-1,3-dioxin-8-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol ((–)-14b).



(-)-14a



(+)-14b

(2,2-Dimethoxypropane (1 mL, excess) and p-toluenesulfonic acid monohydrate (ca. 5 mg) were added to a stirred solution of a 2.1:1 of mixture triols **13a** and **13b**, respectively, (105 mg, 0.21 mmol), in dichloromethane (3 mL) at room temperature.

After 5 min reaction was complete by TLC analysis and was diluted with dichloromethane, washed sequentially with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give a crude 2.8:1 mixture (by ^{1}H NMR) of acetonides **14a** and **14b**, respectively, as a white solid (110 mg; >95% pure by ^{1}HNMR). This mixture was used in the next step without further purification. Pure samples of (-)-**14a** and (+)-**14b** were obtained from similar reactions with single diastereromers of **13**. Spectrocopic data for the purified samples were essentially identical to that reported for the racemic compounds.[30a]

Data for (-)-**14a**:

$[\alpha]_D$ -12, *c* 0.65, CH_2Cl_2;

IR ν_{max} 3525 cm^{-1};

^{1}H NMR (500, $CDCl_3$) δ 4.79 (1H, ddd, *J* = 1.5, 1.5, 10 Hz, HC-α), 4.37 (1H, dd, *J* = 2, 3 Hz H-8a), 4.27 (1H, dd, *J* = 1.5, 9 Hz, HC-4'), 4.18-4.10 (2H, m), 4.06-3.88 (6H, m), 3.24-3.15 (3H, m), 3.04 (1H, dd, *J* = 11.5, 14 Hz), 2.96 (1H, dd, *J* = 3, 14 Hz), 2.84 (1H, ddd, *J* = 2.5, 13, 13 Hz) 2.75 (1H, dd, *J* = 7, 14 Hz), 2.73 (1H, ddd, *J* = 3, 8, 11 Hz), 2.63 (1H, m), 2.60 (1H, ddd, *J* = 3, 3, 14 Hz), 2.56 (1H, dddd, *J* = 2, 4, 4, 13.5 Hz), 2.40 (1H, dd, *J* = 3.5, 13 Hz), 2.21 (1H, ddd, *J* = 3, 4.5, 14 Hz), 2.15 (1H, dddd, *J* = 2, 3.5, 4, 11 Hz), 2.09-1.97 (4H, m), 1.92 (1H, dddd, *J* = 3, 3, 3, 10 Hz), 1.78 (1H, ddd, *J* = 3.5, 12, 14 Hz), 1.74 (1H, ddd, *J* = 3.5, 8, 14 Hz), 1.46 (3H, s), 1.40 (3H, s);

^{13}C NMR (125, $CDCl_3$) δ 110.6 (s), 109.1 (s), 99.7 (s), 71.2 (d), 68.2 (d), 66.9 (d), 65.2 (t), 65.1 (t), 64.3 (t), 64.1 (t), 45.9 (d), 45.0 (d), 41.2 (d), 36.4 (t), 36.0 (d), 35.4 (t), 30.1 (q), 29.3 (t), 26.8 (t ×2), 25.6 (t), 24.6 (t), 22.4 (t), 20.1 (q).

Data for (+)-**14b**:

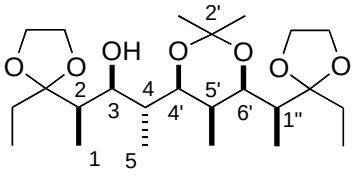
$[\alpha]_D$ +19, *c* 0.56, CH_2Cl_2;

IR ν_{max} 3514 cm^{-1};

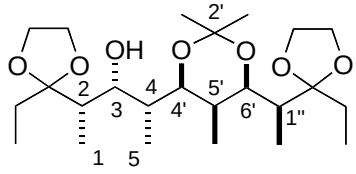
^{1}H NMR (500, C_6D_6) δ 5.01 (1H, d, *J* = 10 Hz, HC-α), 4.23 (1H, d, *J* = 9.5 Hz, HC-4'), 4.06 (1H, br s, HC-8a), 3.67-3.58 (1H, m), 3.40-3.50 (6H, m), 3.33-3.24 (1H, m), 3.25-3.16 (3H, m), 3.11-3.00 (3H, m), 2.88 (1H, dd, *J* = 8, 14 Hz, HC-5), 2.68 (1H, ddd, *J* = 2, 3 , 14 Hz), 2.61 (1H, ddd, *J* = 2.5, 13 , 13 Hz), 2.58 (1H, m), 2.55-2.50 (2H, m), 2.26-2.09 (5H, m), 1.77-1.71 (1H, m), 1.66 (1H, ddd, *J* = 3, 4 , 13 Hz), 1.60-1.47 (2H, m), 1.42 (3H, s), 1.30 (3H, s);

^{13}C NMR (125, C_6D_6) δ 111.0 (s), 109.6 (s), 100.1 (s), 72.7 (d), 69.8 (d), 66.3 (d), 65.2 (t), 65.1 (t), 64.4 (t), 64.0 (t), 48.3 (d), 45.2 (d), 42.5 (d), 37.4 (t), 37.3 (d), 36.1 (t), 30.4 (q), 30.0 (t), 27.1 (t ×2), 26.9 (t), 24.6 (t), 22.3 (t), 19.7 (q).

(2*R*,3*S*,4*R*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4-{(4*R*,5*S*,6*R*)-6-[(*S*)-1-(2-ethyl-1,3-dioxolan-2-yl)ethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}pentan-3-ol ((+)-15a) and (2*S*,3*R*,4*R*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4-{(4*R*,5*S*,6*R*)-6-[(S)-1-(2-ethyl-1,3-dioxolan-2-yl)ethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}pentan-3-ol ((-)-15b).



(+)-15a



(-)-15b

A suspension of freshly prepared W-2 Raney nickel (3 mL settled volume) in ethanol (1 mL) was added at once to a well stirred solution of crude 2.8:1 mixture of (-)-**14a** and (+)-**14a** (110 mg, 0.21 mmol) in methanol (5 mL). The reaction mixture was heated under reflux and progress was monitored by TLC and, if necessary, additional Raney nickel was added until reaction was complete (typically 3-4 h). The supernatant was filtered through a pad of Celite® and the residue was extracted by suspension in MeOH and heating under reflux for several minutes. This process was repeated with methanol and once with a 1:1 mixture acetone and dichloromethane. The combined filtrates were concentrated to give a crude 2.8:1 mixture (by ^{1}H NMR) of **15a** and **15b**, respectively, as a clear oil (88mg, >90% pure by ^{1}H NMR). This mixture was used in the next step without further purification. Pure samples of (-)-**15a** and (+)-**15b** were obtained after fractionation of the crude products from similar reactions with single diastereromers of **14**.

Data for (+)-**15a**:

$[\alpha]_D$ +6, *c* 1.2, C_6H_6;

IR ν_{max} 3479 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ 4.17 (1H, dd, *J* = 1.5, 8 Hz, HC-3), 4.16 (1H, s, HO), 3.93 (1H, dd, *J* = 2, 6.5 Hz, HC-6'), 3.80 (1H, dd, *J* = 2, 9.5 Hz, HC-4'), 3.65-3.57 (4H, m, H_2CO ×2), 3.53-3.43 (4H, m, H_2CO ×2), 2.36 (1H, dq, *J* = 7.5, 14 Hz, EtCC-2), 2.04 (1H, dq, *J* = 7.5, 14 Hz, EtCC-2), 1.98-1.91 (3H, m, HC-1", HC-2, HC-4), 1.84-1.72 (2H, m, HC-5', EtCC-1"), 1.58 (1H, dq, *J* = 7.5, 14 Hz, EtCC-1"), 1.36 (3H, s, H_3CC-2'), 1.30 (3H, s, H_3CC-2'), 1.26 (3H, d, *J* = 7 Hz, H_3CC-2), 1.21 (3H, d, *J* = 7 Hz, H_3CC-1"), 1.08 (3H, t, *J* = 7 Hz, H_3C-5'), 1.04 (3H, d, *J* = 7.5 Hz, EtCC-2), 0.97 (3H, t, *J* = 7.5 Hz, EtCC-1"), 0.66 (3H, d, *J* = 7 Hz, H_3CC-4);

^{13}C NMR (125 MHz, C_6D_6) δ 115.2 (s, CO_2C-2), 113.9 (s, CO_2C-1"), 99.7 (s, C-2'), 80.2 (d, C-4'), 74.9 (d, C-3), 74.5 (d, C-6'), 65.7 (t, CH_2O), 65.6 (t, CH_2O), 65.5 (t, CH_2O), 65.2 (t, CH_2O), 42.7 (d, C-1" or C-2), 42.4 (d, C-1" or C-2), 38.6 (d, C-4), 35.2 (d, C-5'), 30.4 (q, CH_3C-2'), 28.0 (t, EtCC-2), 26.6 (t, EtCC-1"), 19.8 (q, CH_3C-2'), 12.6 (q, CH_3C-1"), 12.1 (q, C-5), 8.9 (q, C-1), 8.0 (q, EtCC-2), 7.5 (q, EtCC-1'), 6.5 (q, CH_3C-5'); **LRMS** (CI, NH_3) *m/z* (relative intensity): 445 ($[M+1]^+$, 4), 325 (6), 257 (5), 131 (10), 120 (9), 101 (100), 84 (11); **HRMS** (CI, NH_3) *m/z* calcd. for $C_{24}H_{44}O_7$: 445.3165 (M+H); found: 445.3158.

Data for (-)-**15b**:

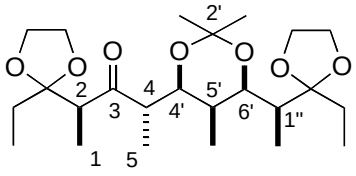
$[\alpha]_D$ -10, *c* 0.69, C_6H_6; **IR** ν_{max} 3524 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ 4.16 (1H, br dd, *J* = 1.5, 6 Hz, HC-3), 3.99 (1H, dd, *J* = 2, 6.5 Hz, HC-6'), 3.80 (1H, dd, *J* = 1.5, 9.5 Hz, HC-4'), 3.53-3.43 (8H, m, H_2CO ×4), 2.93 (1H, s, HO), 2.36 (1H, dq, *J* = 1.5, 7 Hz, HC-2), 2.13 (1H, ddq, *J* = 6, 9.5, 7 Hz, HC-4), 1.99 (1H, dq, *J* = 6.5, 7 Hz, HC-1''), 1.86-1.78 (2H, m, HC-5', EtCC-1''), 1.77-1.70 (2H, ap q, *J* = 7.5 Hz, EtCC-2), 1.62 (1H, dq, *J* = 7.5, 14 Hz, EtCC-1''), 1.45 (3H, s, H_3CC-2'), 1.39 (3H, s, H_3CC-2'), 1.26 (3H, d, *J* = 7 Hz, H_3CC-1''), 1.21 (3H, d, *J* = 7 Hz, H_3CC-2), 1.11 (3H, d, *J* = 7 Hz, H_3CC-5'), 1.07 (3H, d, *J* = 7 Hz, H_3CC-4), 0.98 (3H, t, *J* = 7.5 Hz, EtCC-1''), 0.95 (3H, t, *J* = 7.5 Hz, EtCC-2);

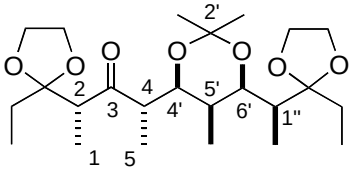
^{13}C NMR (125 MHz, C_6D_6) δ 115.5 (s, CO_2C-2), 114.0 (s, CO_2C-1''), 99.2 (s, C-2'), 77.3 (d, C-4'), 74.6 (d, C-6'), 72.9 (d, C-3), 65.64 (t, CH_2O), 65.60 (t, CH_2O), 65.2 (t, CH_2O), 65.0 (t, CH_2O), 42.8 (d, C-1''), 42.1 (d, C-2), 39.5 (d, C-4), 35.2 (d, C-5'), 30.6 (q, CH_3C-2'), 28.3 (t, EtCC-2), 26.6 (t, EtCC-1''), 20.1 (q, CH_3C-2'), 12.7 (q, CH_3C-1''), 11.5 (q, C-5), 9.5 (q, C-1), 8.7 (q, EtCC-2), 7.5 (q, EtCC-1''), 6.5 (q, CH_3C-5');

LRMS (CI, NH_3) *m/z* (relative intensity): 445 ($[M+1]^+$, 13), 325 (28), 257 (14), 245 (11), 227 (12), 131 (30), 101 (100); **HRMS** (CI, NH_3) *m/z* calcd. for $C_{24}H_{44}O_7$: 445.3165 (M+H); found: 445. 3150.

(2*R*,4*S*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4-{(4*S*,5*S*,6*R*)-6-[(*S*)-1-(2-ethyl-1,3-dioxolan-2-yl)ethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}pentan-3-one ((+)-16a) and (2*S*,4*S*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4-{(4*S*,5*S*,6*R*)-6-[(*S*)-1-(2-ethyl-1,3-dioxolan-2-yl)ethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}pentan-3-one ((-)-16b).



(+)-16a



(-)-16b

DMP (170 mg, 0.40 mmol) was added to a stirred solution of the crude 2.8:1 mixture of **15a** and **15b** (88 mg) in CH_2Cl_2 (3 mL). After 10 min, the mixture was diluted with ethyl acetate and washed sequentially with a 1:1 mixture of 10% aqueous $Na_2S_2O_3$ and sat. aqueous $NaHCO_3$, water and brine (20 mL). The aqueous washings were extracted with ethyl acetate and the combine organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give a 2.8:1 mixture (by ^{1}H NMR) of **16a** and **16b**, respectively, as a white solid (68 mg, 72% from **13** over three steps). Pure samples of (+)-**16a** and (–)–**16b** were obtained from similar reactions with single diastereromers of **15**.

Data for (+)-**16a**:

$[\alpha]_D$ +140, *c* 1.6, C_6H_6;

IR ν_{max}1712 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ 4.03 (1H, dd, *J* = 2, 10 Hz, HC-4'), 3.95 (1H, dd, *J* = 2, 6.5 Hz, HC-6'), 3.64 (1H, m, H_2CO ×0.5), 3.53-3.42 (7H, m, H_2CO ×3.5), 3.34 (1H, q, *J* = 7 Hz, HC-2), 3.20 (1H, dq, *J* = 7, 10.5 Hz, HC-4), 1.98 (1H, dq, *J* = 7, 6.5 Hz, HC-1''), 1.86-1.73 (4H, m, HC-5', H_2C ×1.5), 1.55 (1H, dq, *J* = 14, 7 Hz, H_2C ×0.5), 1.40 (3H, s, H_3CC-2'), 1.34 (3H, d, *J* = 7 Hz, H_3C-1), 1.26 (3H, s, H_3CC-2'), 1.23 (3H, d, *J* = 7 Hz, H_3CC-1''), 1.13 (3H, d, *J* = 7 Hz, H_3CC-5'), 1.05 (3H, d, *J* = 7 Hz, H_3C-5), 0.96 (3H, t, *J* = 7.5 Hz, H_3C), 0.90 (3H, t, *J* = 7.5 Hz, H_3C);

^{13}C NMR (125 MHz, C_6D_6) δ 216.1 (s, C-3), 113.9 (s), 113.2 (s), 99.3 (s, C-2'), 79.6 (d, C-4'), 74.3 (d, C-6'), 65.8 (t, CH_2O), 65.7 (t, CH_2O), 65.5 (t, CH_2O), 65.2 (t, CH_2O), 55.6 (d, C-2), 49.7 (d, C-4), 42.7 (d, C-1''), 34.3 (d, C-5'), 30.5 (q, CH_3C-2'), 27.9 (t), 26.7 (t), 19.7 (q, CH_3C-2'), 12.7 (q, C-1 or CH_3C-1''), 12.6 (q, C-1 or CH_3C-1''), 11.8 (q, C-5), 7.6 (q), 7.5 (q), 6.3 (q, CH_3C-5');

LRMS (CI, NH_3) *m/z* (relative intensity): 443 ($[M+1]^+$, 1), 427 (2), 101 (100); **HRMS** (CI, NH_3) *m/z* calcd. for $C_{24}H_{42}O_7$: 443.3009 (M+H); found: 443.3009.

Data for (-)-**16b**:

$[\alpha]_D$ -34, *c* 0.24, C_6H_6; **IR** ν_{max} 1719 cm^{-1};

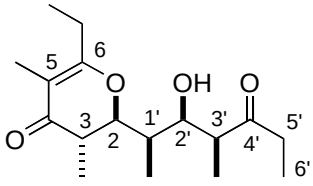
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (1H, dd, *J* = 2, 10 Hz, HC-4'), 4.02-3.89 (8H, m, H_2CO ×4), 3.87 (1H, dd, *J* = 2, 7 Hz, HC-6'), 3.08 (1H, q, *J* = 7 Hz, HC-2), 2.97 (1H, dq, *J* = 9, 7 Hz, HC-4), 1.89 (1H, dq, *J* = 5.5, 7 Hz, HC-1''), 1.80-1.66 (3H, m, H_2CCC-2, EtCC-1''), 1.62-1.50 (2H, m, HC-5', EtCC-1''), 1.36 (3H, s, H_3CC-2'), 1.27 (3H, s, H_3CC-2'), 1.15 (3H, d, *J* = 7 Hz, H_3C-1), 0.97 (3H, d, *J* = 7 Hz, H_3CC-1''), 0.92 (3H, m, *J* = 7

Hz, H_3C-5), 0.90 (3H, d, *J* = 7 Hz, H_3CC-5'), 0.89 (3H, t, *J* = 7 Hz, EtCC-2), 0.88 (3H, t, *J* = 7.5 Hz, EtCC-1");

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.7 (s, C-3), 113.8 (s, CO_2C-1"), 112.4 (s, CO_2C-2), 100.0 (s, C-2'), 75.6 (d, C-4'), 73.6 (d, C-6'), 65.8 (t, CH_2O), 65.6 (t, CH_2O), 65.4 (t, CH_2O), 65.0 (t, CH_2O), 52.5 (d, C-2), 47.5 (d, C-4), 41.9 (d, C-1"), 33.6 (d, C-5'), 30.0 (q, CH_3C-2'), 29.2 (t, EtCC-2), 26.0 (t, EtCC-1"), 19.5 (q, CH_3C-2'), 12.5 (q, C-5), 12.1 (q, C-1 or CH_3C-1"), 12.0 (q, C-1 or CH_3C-1"), 7.8 (q, EtCC-2), 7.1 (q, EtCC-1"), 5.8 (q, CH_3C-5');

LRMS (CI, NH_3) *m/z* (relative intensity): 443 ($[M+1]^+$, 2), 101 (100); **HRMS** (CI, NH_3) .*m/z* calcd. for $C_{24}H_{42}O_7$: 443.3009 (M+H); found: 443.3008.

(2*S*,3*S*)-6-Ethyl-2,3-dihydro-2-[(1*R*,2*R*,3*S*)-2-hydroxy-1,3-dimethyl-4-oxohexyl]-3,5-dimethyl-4*H*-pyran-4-one ((-)-8)



(-)-8

p-Toluenesulfonic acid monohydrate (10 mg, 0.05 mmol) was added to a stirred of a 2.8:1 mixture of **16a** and **16b** (11.8 mg, 0.027 mmol) and in CH_2Cl_2 (1 mL) at room temperature. After 10 min, the mixture was diluted with CH_2Cl_2, washed sequentially with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (30% ethyl acetate in hexanes) to give (-)-**8** as a colorless oil (3 mg, 38%) ($[\alpha]_D$ -130, *c* 0.55, $CHCl_3$; lit.[31] -114, *c* 0.48, $CHCl_3$). Spectroscopic data for (-)-**8** were identical to that reported by Sampson and Perkins.

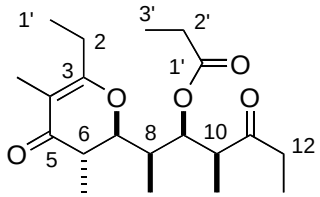
IR ν_{max} 3407, 1717, 1653, 1604 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (1H, ddd, *J* = 2, 4.5, 6 Hz, HC-2'), 3.95 (1H, dd, *J* = 2, 13.5 Hz, HC-2), 3.07 (1H, d, *J* = 2 Hz, HO), 2.78 (1H, dq, *J* = 4, 7 Hz, HC-3'), 2.64-2.26 (5H, m, HC-3, H_2C-5', H_2CC-6), 1.85-1.78 (1H, m, HC-1'), 1.73 (3H, s, H_3CC-5), 1.16 (3H, d, *J* = 7 Hz, H_3CC-3'), 1.12 (3H, t, *J* = 7 Hz, EtC-6), 1.11 (3H, d, *J* = 7 Hz, H_3CC-1'), 1.08 (3H, t, *J* = 7 Hz, H_3C-6'), 1.06 (3H, d, *J* = 7 Hz, H_3CC-3);

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.0 (s, C-4'), 195.0 (s, C-4), 172.0 (s, C-6), 108.9 (s, C-5), 84.3 (d, C-2), 73.2 (d, C-2'), 47.2 (d, C-3'), 40.5 (d, C-3), 36.6 (d, C-1'), 35.3 (t, C-5'), 25.7 (t, CH_2C-6), 11.2 (q), 10.9 (q), 9.6 (q), 9.5 (q), 8.4 (q), 7.9 (q);

LRMS (EI) *m/z* (relative intensity): 296 ($[M]^+$, 4), 155 (58), 153 (47), 142 (31), 137 (23), 113 (100), 109 (22), 86 (26), 69 (20), 57 (52); **HRMS** (EI) *m/z* calcd. for $C_{17}H_{28}O_4$: 296.1988; found: 296.1981.

(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone B ((-)-*ent*-2).



(-)-*ent*-2

The procedure was according to Sampson and Perkins.[31] Pyridine (7 μL, 0.09 mmol and propionyl chloride (8 μL, 0.09 mmol) were sequentially added to a stirred solution of (-)-**8** (5.1 mg, 0.02 mmol) in dry CH_2Cl_2 (1 mL) at room temperature under argon. After 1.5 h, the reaction was diluted with CH_2Cl_2 and washed with sequentially with aqueous citric

acid (2 M) and aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by PTLC (30% ethyl acetate in hexanes) to give the (-)-*ent*-**2** as a white solid (5.4 mg, 89%) Spectroscopic and chiroptical data for (-)-*ent*-**8** were identical to that previously reported:[31,32]

$[\alpha]_D$ -50, *c* 0.46, $CHCl_3$ (lit.[31] -44, *c* 0.68, $CHCl_3$);

CD curve (1.1 mM in $CHCl_3$) $[\theta]_{301}$ +7300, $[\theta]_{269}$ –17,000, $[\theta]_{269}/[\theta]_{301}$=2.3 (lit.:[31] 1 mM in $CHCl_3$: $[\theta]_{300}$ +6613, $[\theta]_{267}$ –15,438, $[\theta]_{267}/[\theta]_{300}$=2.3);

IR ν_{max} 1738, 1722, 1662, 1619 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (1H, dd, *J* = 3, 8.5 Hz), 3.98 (1H, dd, *J* = 2, 13.5 Hz), 2.87 (1H, dq, *J* = 3.5, 7 Hz), 2.74 (1H, dq, *J* = 17.5, 7 Hz), 2.49 (1H, dq, *J* = 13.5, 7 Hz), 2.41-2.30 (5H, m), 2.03 (1H, m), 1.74 (3H, s), 1.19 (3H, t, *J* = 7.5 Hz), 1.14 (3H, t, *J* = 7.5 Hz), 1.07 (3H, d, *J* = 7 Hz), 1.05 (3H, d, *J* = 7.5 Hz), 1.03 (3H, t, *J* = 7 Hz), 0.99 (3H, d, *J* = 7 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 194.7, 174.0, 172.5, 108.9, 82.5, 74.0, 46.9, 40.4, 36.1, 34.8, 27.8, 25.8, 11.3, 9.8, 9.6, 9.5, 9.4, 9.3, 8.0;

LRMS (EI) *m/z* (relative intensity): 352 ($[M]^+$, 12), 278 (11), 193 (12), 153 (52), 137 (100), 113 (42), 109 (50), 57 (62); **HRMS** (EI), *m/z* calcd. for $C_{20}H_{32}O_5$: 352.2250; found: 352.2254.

6.4 References

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5. This assignment relies primarily on the circular dichroism (CD) data obtained from the synthetic (-)-enantiomers of **1**-**3** (i.e., *ent*-**1**-**3**) compared with those reported (ref. 3) for the natural products and is consistent with the (*R*)-configuration for the 2-methylbutanoyl appendage in **1** as determined (ref. 3) by Mosher's ester analysis of a product from $LiAlH_4$ reduction.

6. For a previous synthesis of *ent*-**1** and *ent*-**2**, see ref. 4c. For syntheses of **3** and(or) *ent*-**3**, see ref 4b and: (a) Marshall, J. A.; Ellis, K. C. *Org. Lett.* **2003**, *5*, 1729-1732. (b) Yadav, J. S.; Srinivas, R.; Sathaiah, K. *Tetrahedron Lett.* **2006**, *47*, 1603-1606.

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9. (a) Ward, D. E.; Gillis, H. M.; Akinnusi, O. T.; Rasheed, M. A.; Saravanan, K.; Sasmal, P. K. *Org. Lett.* **2006**, *8*, 2631-2634. (b) Ward, D. E.; Jheengut, V.; Beye, G. E. *J. Org. Chem.* **2006**, *71*, 8989-8992.

10 The configurations at the undefined stereocenters in **11** are not relevant because those centers become trigonal in **8**.

11. For a more complete discussion and references on this phenomenon, see ref. 8b.

12. The **ss** and **as** labels refer to the syn (**s**) or anti (**a)** relative configurations at C-3,1' and C-1',6', respectively, in the diastereomers of **6** (and **10**).

13. Consistent with that hypothesis, (*S*)-(-)-**4** (50% yield; ca. 20% optical purity) was recovered from the reaction.

14. The racemic compounds have been described previously (ref 8a). For determination of the relative configurations for **12**, **13**, and **14**, see ref 8b.

15. The alternative diastereomers would have a trans-fused tetrahydrothiopyrano[4,3-d]1,3-dioxin ring system with a large group in an axial orientation.

16. The presence of elimination and retro-aldol products from **8** were detected (by ^{1}H NMR) in the crude reaction mixtures consistent with the previous synthesis (ref 4c).

17. Ward, D. E. ; Rasheed, M. A.; Gillis, H. M.; Beye, G. E.; Jheengut, V.; Achonduh, G. T. *Synthesis* **2007**, 1584-1586.

18. See Supporting Information

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21 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)

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32. Ciavatta, M. L.; Trivellone, E.; Villani, G.; Cimino, G. *Tetrahedron Lett.* **1993**, *34*, 6791-6794.[†††]

[†††] References from the manuscript and supporting information are both combined together.

7. Conclusions

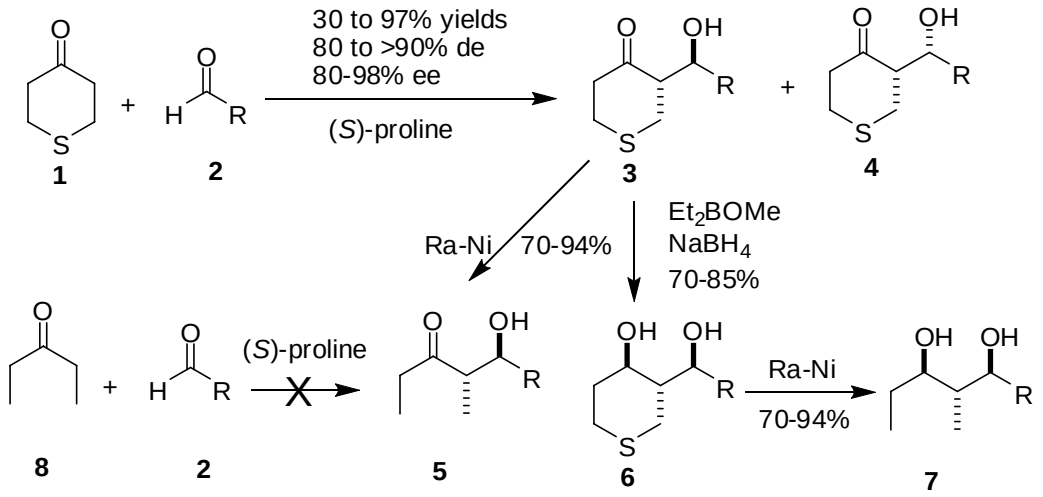
7.1 General summary and conclusions

The synthesis of polypropionates continues to be a major challenge to synthetic chemists due to their stereochemical complexity. Among the various strategies devised, the aldol reaction has found numerous applications in polypropionate natural products synthesis. While acyclic precursors have been widely utilized, cyclic sulfides (in particular thiopyran templates) have found limited applications in polypropionates synthesis despite several inherent advantages over their acyclic counterparts.

The Ward laboratory described a general approach for polypropionate synthesis via aldol couplings of tetrahydro-4*H*-thiopyran-4-one (**1**) derivatives followed by desulfurization. This so-called thiopyran route to polypropionates involves stepwise iterative aldol homologations of **1** with thiopyran aldehyde **9** as conduit to rapidly assemble stereochemically complex polypropionate synthons in only a few steps. As elaborated in chapter one, thiopyran templates offer several advantages such as rapid access to starting materials (starting materials **1** and **9** are both prepared in multi-gram scale from hydrogen sulfide and methyl acrylate), stereochemical control of chemical operations (aldol stereoselectivity), and ready desymmetrization. My contributions to the thiopyran route to polypropionates are summarized below.

Initially, I established conditions for proline-catalyzed enantioselective direct intermolecular aldol reactions of ketone **1** with various achiral aldehydes to give *anti* adducts with high diastereo- and enantioselectivities in moderate to excellent yields. The proline-catalyzed aldol reactions of **1** with aldehydes substantially improved in yields and stereoselectivities upon addition of water. The beneficial effect of water was also

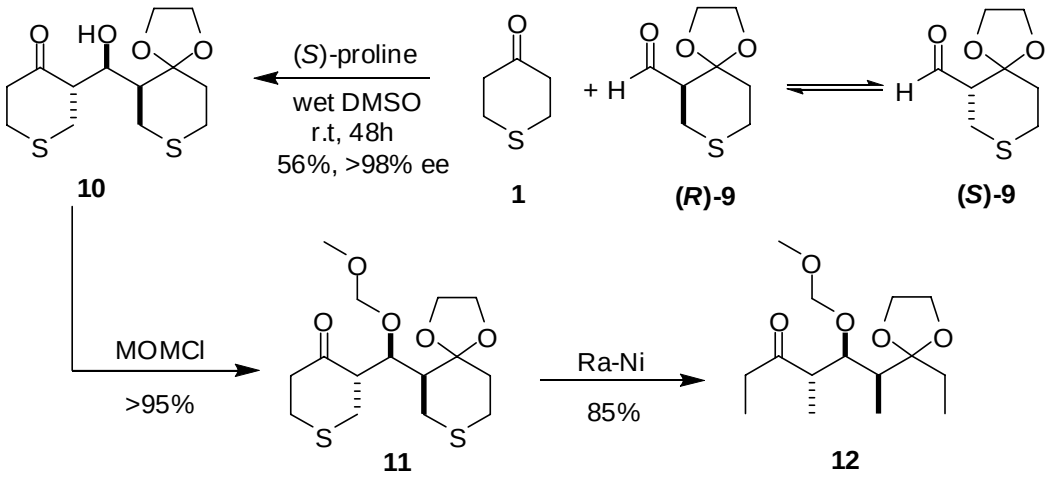
independently disclosed by Pihko and coworkers.[1] In our case, best results were obtained in DMF and water with aromatic aldehydes whereas dry DMSO was generally superior with the aliphatic aldehydes. Desulfurization of the aldol adducts or the derived diols gave products equivalent to those that would be obtained from 3-pentanone, a ketone that is unreactive under the proline-catalyzed aldol reaction conditions (Scheme 7.1, cf. Chapter 2).



Scheme 7.1: Proline-catalyzed asymmetric aldol reactions of **1** with achiral aldehydes

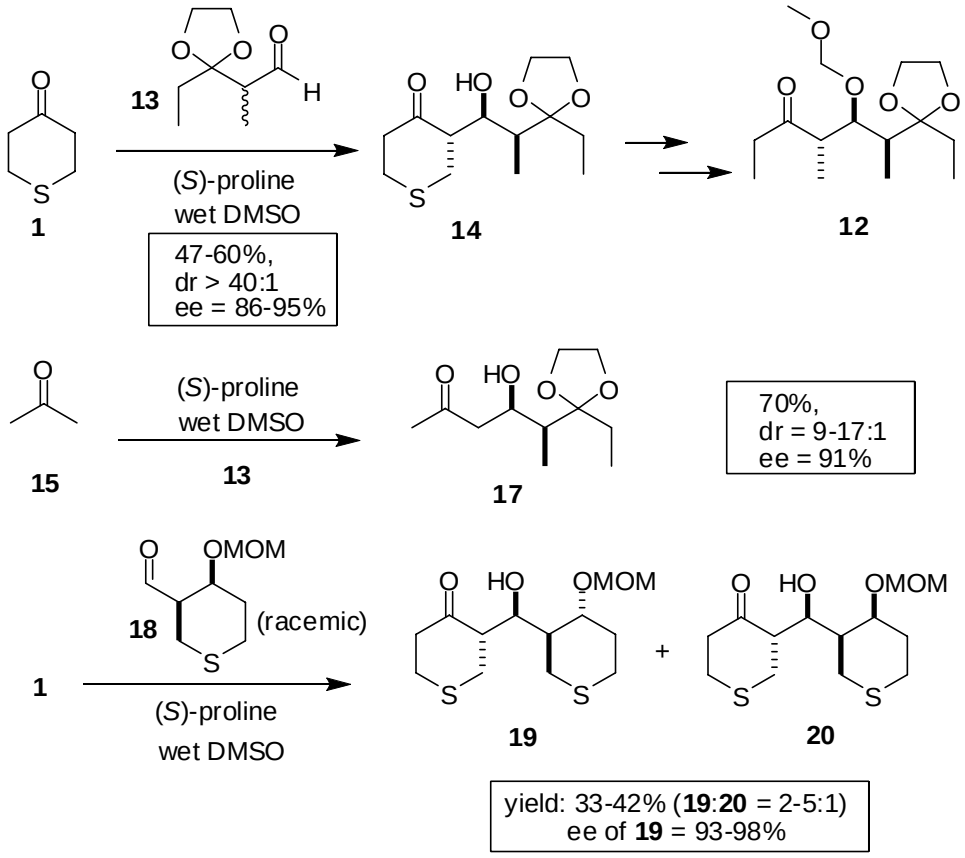
Under similar conditions, we were also able to effect the proline-catalyzed aldol reaction of **1** with racemic aldehyde (±)-**9** affording tetrapropionate synthon **10** in high diastereo- and enantioselectivity. The role of water was again found to be crucial to obtain high yield and stereoselectivity in the reaction. The remarkable stereoselectivity of this reaction was attributable to the combination of the high propensity for the addition to the aldehyde *re* face imposed by the (*S*)-proline catalyst together with the high Felkin diastereoface selectivity intrinsic to aldehyde **9** that resulted in a strong kinetic preference

for the "matched" reaction (i.e., high enantiotopic group selectivity). Because the proline-catalyzed isomerization of the aldehyde **9** is much faster than the aldol, the reaction proceeds with dynamic kinetic resolution (Scheme 7.2, cf. Chapter 3).



Scheme 7.2: Enantioselective aldol reaction of **1** with (±)-**9**

A detailed study about the scope and limitations of this reaction using different catalysts, aldehydes, and ketones (cyclic and acyclic) was successfully conducted. Aldol reactions of ketone donors such as cyclohexanone, acetone, and 2-butanone with chiral aldehydes occurred in moderate to good yields and with excellent diastereo- and enantioselectivities (Scheme 7.3, cf. Chapter 4). In principle, chiral α-substituted aldehydes possessing high intrinsic diastereoface selectivities will be potential candidates in the proline-catalyzed aldol reactions that should occur with high enantiotopic group selectivity. Upon careful assessment, the presence of the ketal group was found to be crucial again in dictating a high Felkin selectivity in aldehydes **9** and **13** as opposed to **18**.



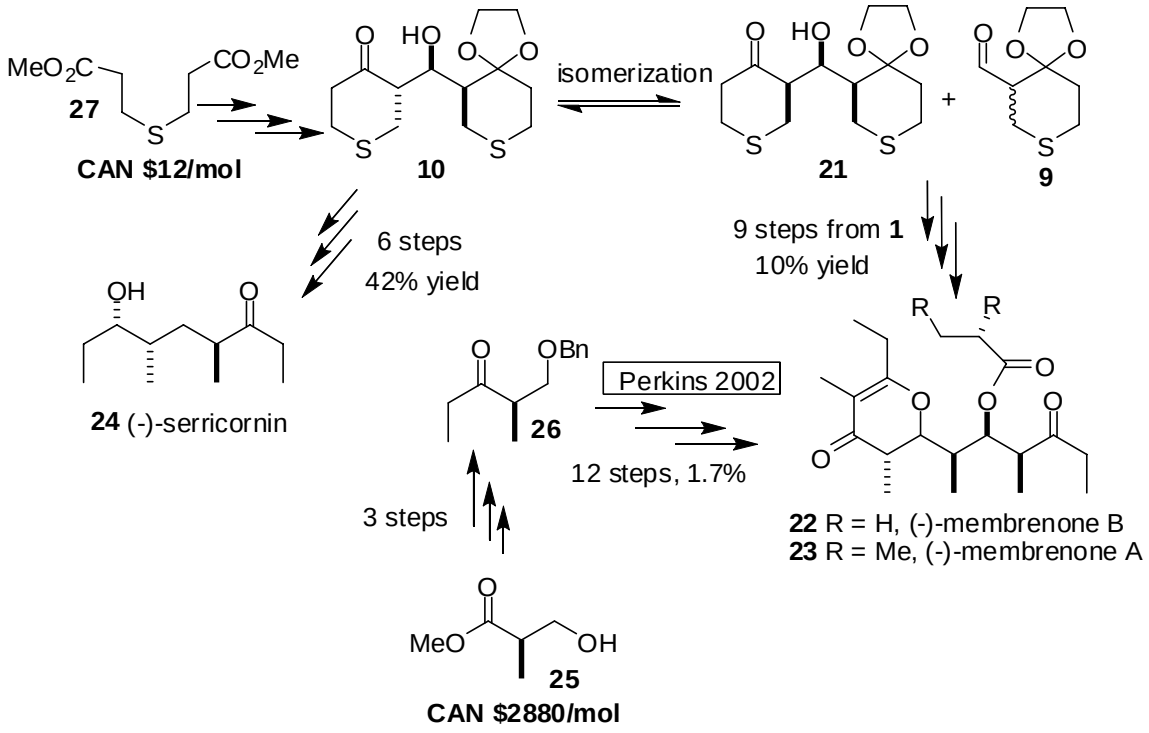
Scheme 7.3: Scope for the aldol reactions of **1** with racemic aldehydes

The objective to synthesize of tetrapropionate synthons **10** and **14** via an enantioselective aldol reaction using racemic aldehyde **9** instead of using enantiopure **9** was therefore accomplished. These reactions significantly extend the scope of the enantioselective direct intermolecular aldol reaction and constitute simple and efficient syntheses of functionalized oligopropionate synthons that should be useful for polypropionate synthesis.

A specific application of tetrapropionate synthon **10** was demonstrated in an efficient synthesis of serricornin [(4*S*,6*S*,7*S*)-7-hydroxy-4,6-dimethylnonan-3-one] (**24**), a sex pheromone produced by the female cigarette beetle (*Lasioderma serricorne* F.) in 7

steps from **9**. The key steps include the enantioselective aldol reaction of **1** with **9** catalyzed by 5-[(2*S*)-pyrrolidine-2-yl]-1*H*-tetrazole to fabricate the tetrapropionate skeleton, stereoselective $Li^{s}Bu_3BH$ reduction of the resulting aldol adduct, Barton-McCombie deoxygenation, and Raney nickel desulfurization (Scheme 7.4, cf. Chapter 5). Our synthesis is very competitive compared to other efficient syntheses of serricornin reported in the literature. The salient features of our approach are easy accessibility and inexpensive starting materials and the same strategy could be extended to afford each of the possible stereoisomers of **24**.

Finally, (–)-membrenone B was synthesized in nine steps (10% overall yield) beginning with a two-directional aldol coupling of **1** with (±)-**9**. The first aldol reaction occurs with dynamic kinetic resolution to give **10** as a single adduct (>98% ee) which was therefore isomerized to **21**. The aldol reaction of **21** with (±)-**9** is highly diastereoselective (3 of 8 possible adducts) and both major products were converted to membrenone B (**22**). It is also noteworthy that the *entire* 17-carbon skeleton of **22** is derived from methyl acrylate as both **1** and **9** are directly and efficiently prepared from this simple precursor (e.g. 6.5% overall yield of (-)-**22** from methyl acrylate in 13 steps). The route also constitutes a formal synthesis (-)-membrenone A (**23**) (Scheme 7.4, Chapter 6). Perkin reported the synthesis of **22** in 1.7% over 12 steps from **26**, which is generally prepared from commercially available **25**[2] (CAN $2880/mol, Aldrich) in three additional steps. Therefore, our route is more efficient (10% over 9 steps) starting from **1** and **9** both prepared from commercially available diester **27** (Scheme 7.4; CAN $12/mol, Aldrich).



Scheme 7.4: Synthesis of serricornin (**24**) and membrenones A (**23**) and B (**22**)

As a general conclusion, my objectives of designing a methodology to make nonracemic tetrapropionate synthons **10** and **21** via an organocatalytic approach using racemic **9** and their application to the synthesis of polypropionate natural products (–)-serricornin (**24**) and (–)-membrenones B (**22**) and formal synthesis of (–)-membrenone A (**23**) were successfully achieved.

7.2 References

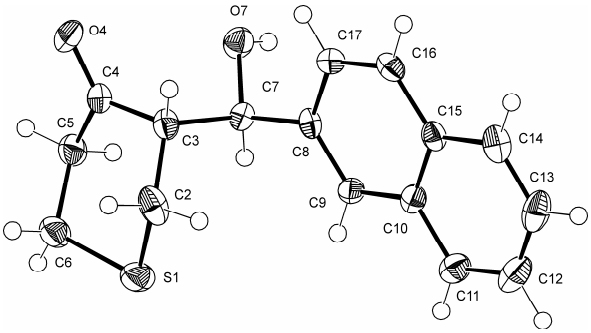
1. Nyberg, A. I.; Usano, A.; Pihko, P. M. Proline-catalyzed ketone-aldehyde aldol reactions are accelerated by water. *Synlett* **2004**, 1891-1896.

2. Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. Studies in macrolide synthesis: A stereocontrolled synthesis of oleandolide employing reagent- and substrate-controlled Aldol reactions of (*S*)-1-(Benzyloxy)-2-methylpentan-3-one. *J. Am. Chem. Soc.* **1994**, 116, 11287-11314.

APPENDICES

Appendix A

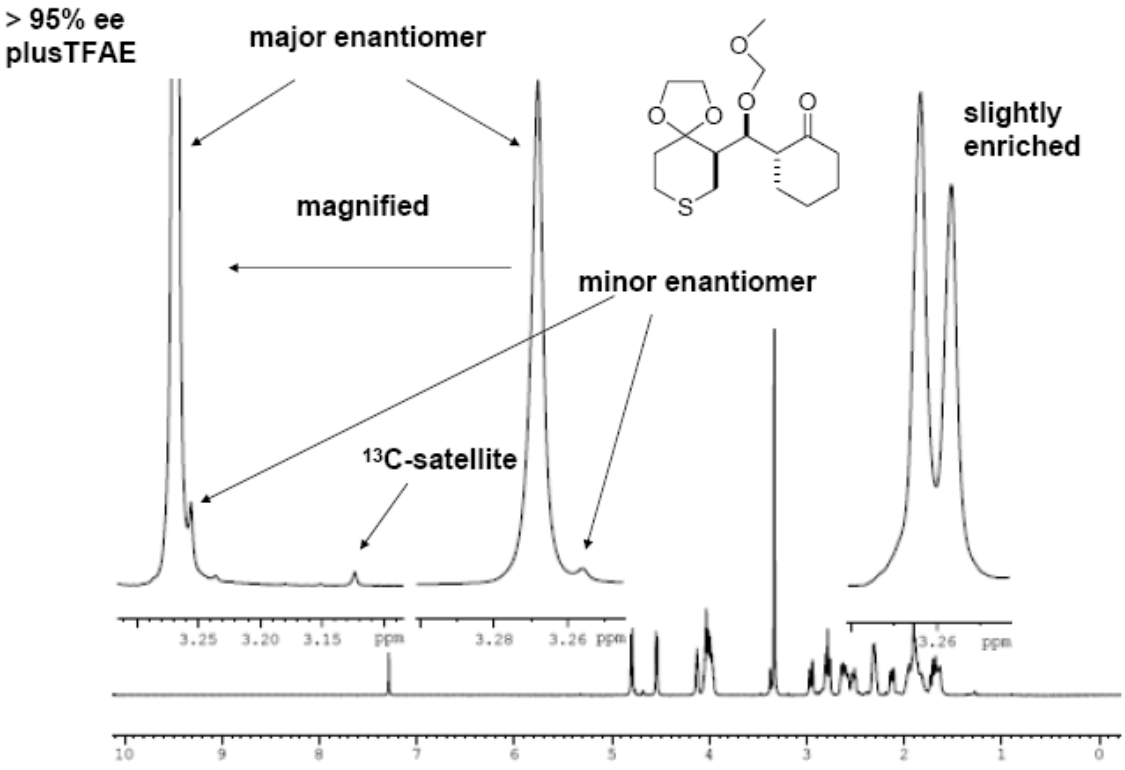
X-ray crystallographic data



ORTEP diagram of compound (+)-**3b** (Chapter 2)

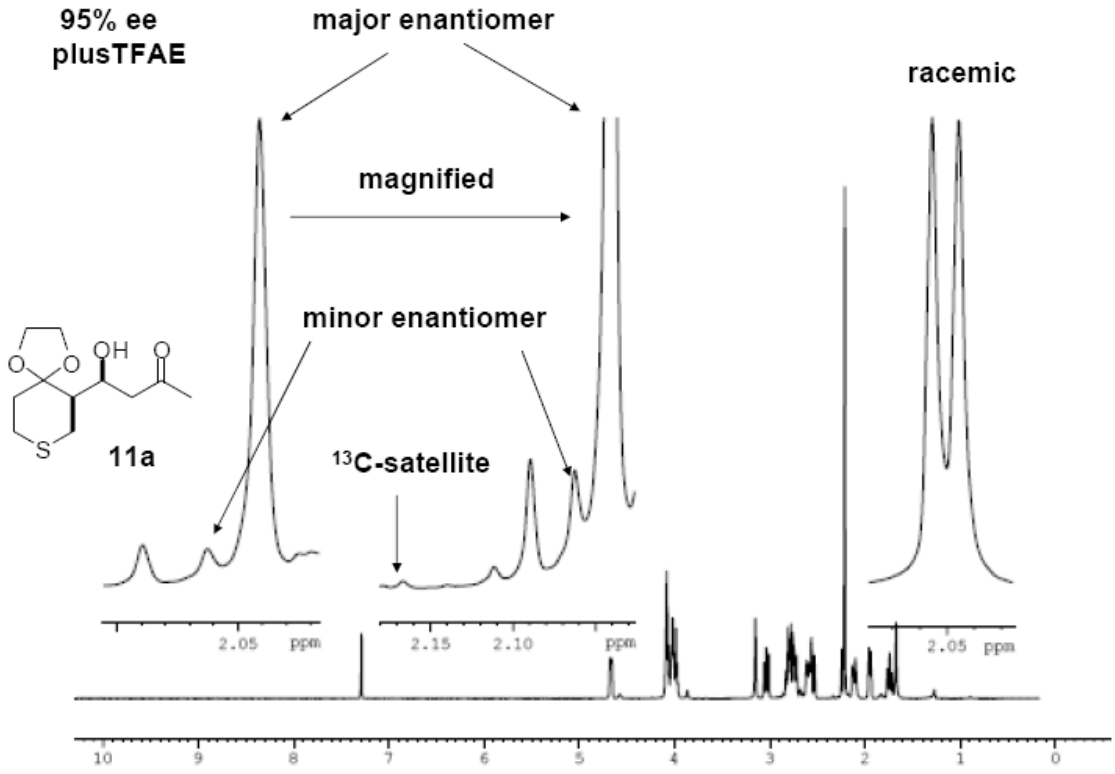
Appendix B

ee determination of aldol **10a**



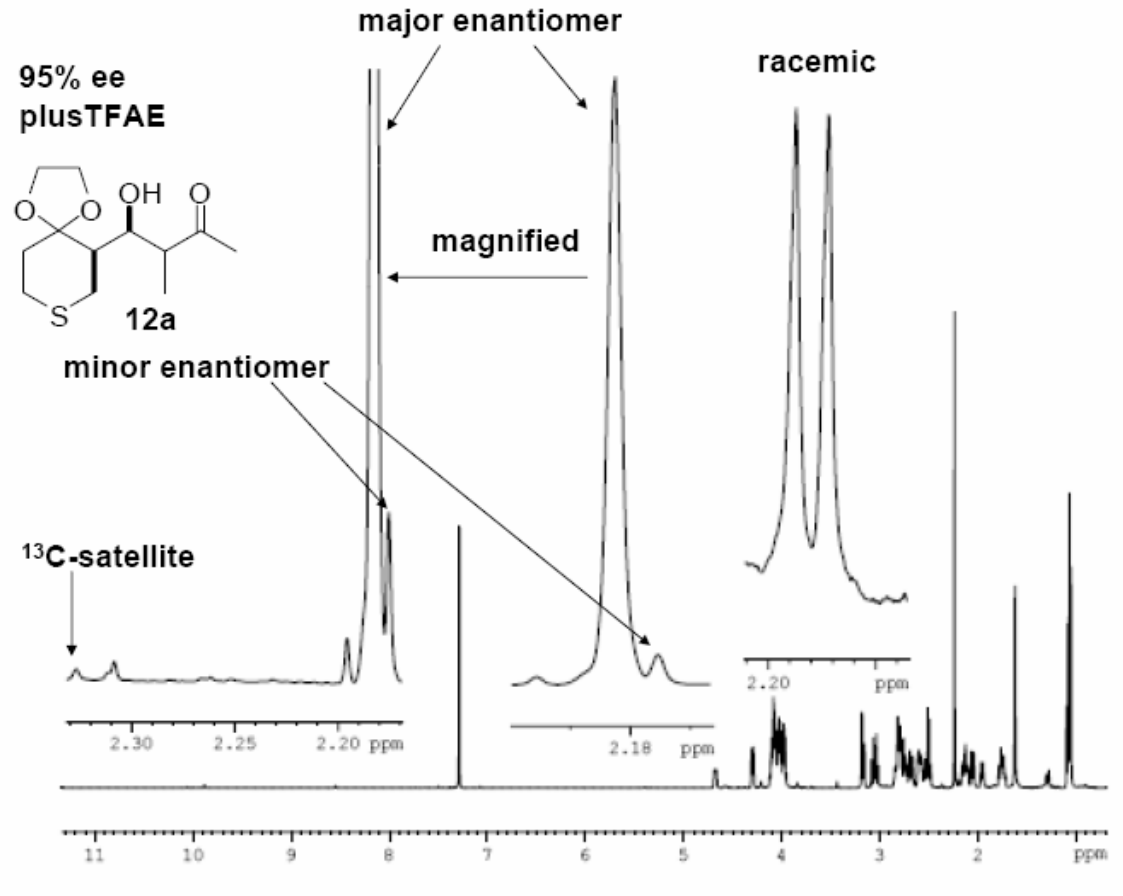
Appendix C

ee determination of aldol **11a**



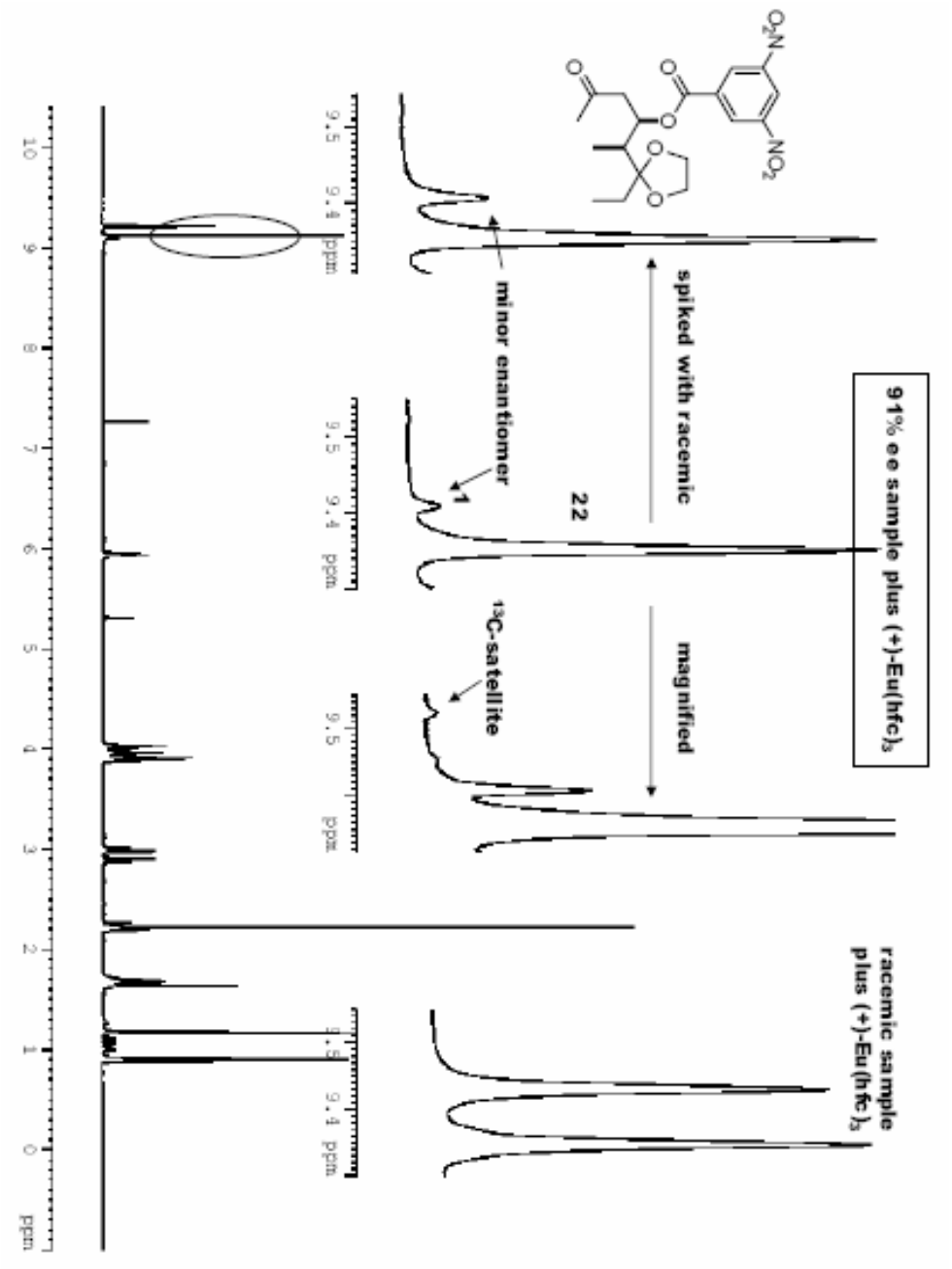
Appendix D

ee determination of aldol **12a**



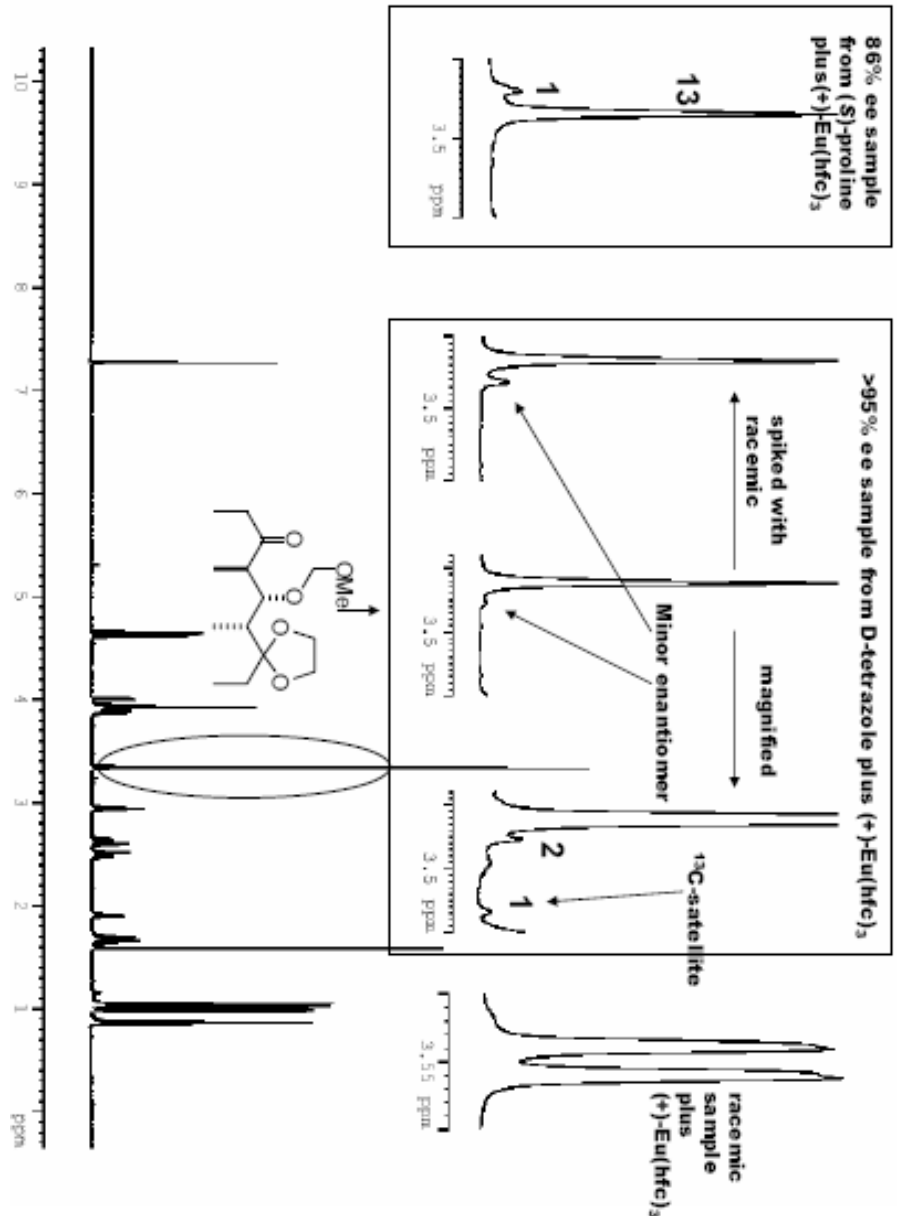
Appendix E

ee determination of aldol **19a**



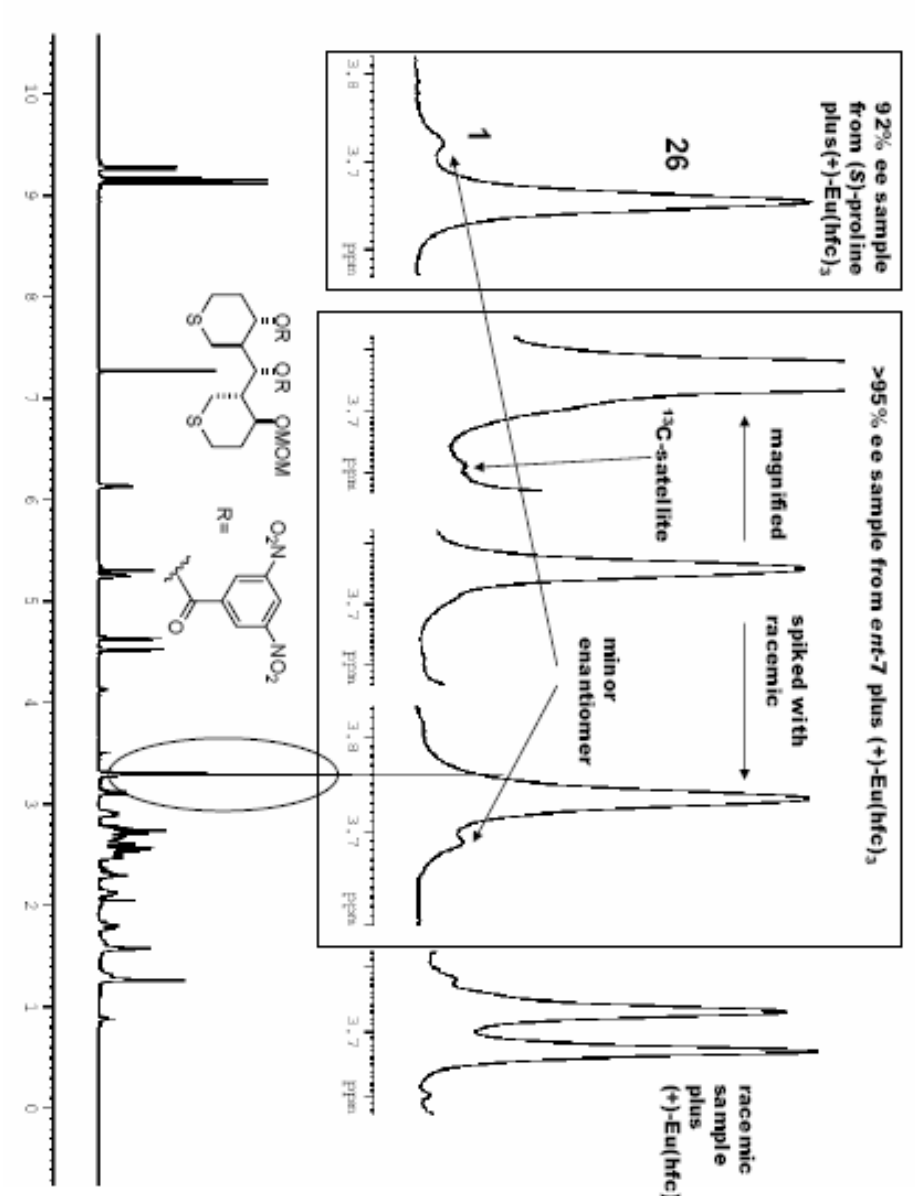
Appendix F

ee determination of aldol **17**



Appendix G

ee determination of aldol **23**



PUBLICATIONS

1. The Thiopyran Route to Polypropionates. Asymmetric Synthesis of the Building Blocks by Enantioselective Protonation. D. E. Ward, O. T. Akinnusi, I. Q. Alarcon, **V. Jheengut**, J. Shen, and J. W. Quail. *Tetrahedron: Asymmetry* **2004**, *15*, 2425-2430

2. Proline-Catalyzed Asymmetric Aldol Reactions of Tetrahydro-*4H*-thiopyran-4-one with Aldehydes. D. E. Ward and **V. Jheengut**. *Tetrahedron Letters* **2004**, *45*, 8347-8350

3. Enantioselective Direct Intermolecular Aldol Reactions with Enantiotopic Group Selectivity and Dynamic Kinetic Resolution. D. E. Ward, **V. Jheengut**, and O. T. Akinnusi. *Organic Letters* **2005**, *7*, 1181-1184

4. The Thiopyran Route to Polypropionates: An Efficient Synthesis of Serricornin D. E. Ward, **V. Jheengut**, and G. E. Beye. *Journal of Organic Chemistry* **2006**, *71*, 8989-8992

5. Simple and Efficient Preparation of Reagents for Thiopyran Introduction: Methyl Tetrahydro-4-oxo-2*H*-thiopyran-3-carboxylate, Tetrahydro-4*H*-thiopyran-4-one and 3,6-Dihydro-4-trimethylsilyloxy-2*H*-thiopyran. D. E. Ward, M. A. Rasheed, H. M. Gillis, G. E. Beye, **V. Jheengut**, G. T. Achonduh. *Synthesis* **2007**, 1584-1586.

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7. Thiopyran Route to Polypropionates: Enantioselective synthesis of Membrenone B from Racemic Fragments. **V. Jheengut** and D. E. Ward *(submitted to the Journal of Organic Chemistry)*

8. Enantioselective Direct Intermolecular Aldol Reactions with Enantiotopic Group Selectivity and Dynamic Kinetic Resolution; Scope and limitations. D. E. Ward, **V. Jheengut**, and G. E. Beye *(manuscript to be submitted to the Journal of Organic Chemistry).*