Synthesis of Higher Carbohydrates and Iminosugars on Dioxanone Scaffold

A Thesis Submitted to

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In Partial Fulfillment of the Requirements

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In the Department of Chemistry

University of Saskatchewan

Saskatoon, Canada

By

NAGARJUNA PALYAM

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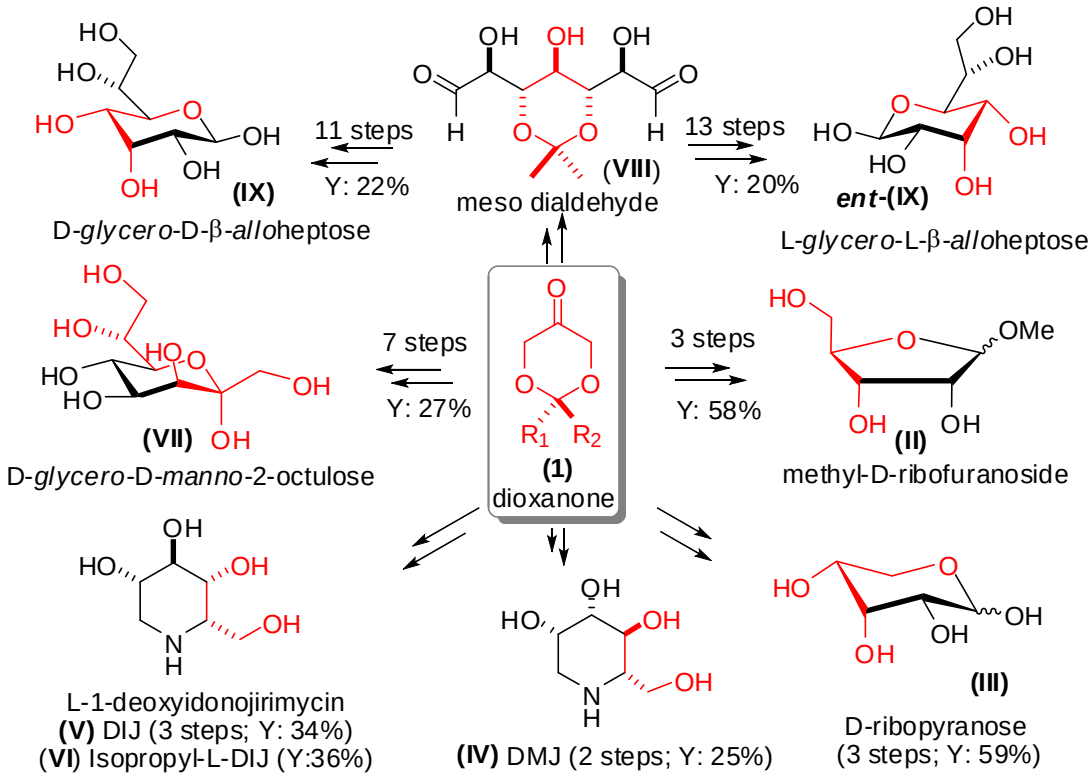
ABSTRACT

Dioxanones (**1**) are ketal- or acetal protected forms of 1,3-dihydroxyacetone (DHA). The thesis presents the stereoselective aldol transformations of dioxanones and applications to the synthesis of natural and higher carbohydrates listed in Scheme 1. (Note: The structural portion of dioxanone scaffold (**1**) incorporated into target compounds are highlighted in red color)



Scheme 1.0: Compounds synthesized from dioxanone scaffold

The field of organocatalysis has recently gained much popularity among the chemical research community. In our group, a set of conditions are developed to perform stereoselective aldol reactions on dioxanone substrate. C_S-symmetrical dioxanones have superior diasteroselectivities than C_{2V}-symmetrical dioxanones (de up to 88% from 34%)

and presence of mild Lewis acid (LiCl) or Brønsted acid additives (PyPTS) enhance the enantioselectivity into synthetically useful ranges (from 60 up to 96 % ee).

The first aldol addition of dioxanone (**1**) to desired aldehydes (possessing masked carbonyl functionality), followed by reduction of the corresponding aldol adduct and upon unmasking the aldehyde functionality (*i.e* dithiane or dimethoxy acetal hydrolysis) resulted in furanose (**II**) and pyranose (**III**) forms of D-ribose.

A new protocol was developed for the synthesis of biologically important deoxyiminosugars such as L-1-deoxymannojirimycin (DMJ, **IV**), L-1-deoxyidonojirimycin (DIJ, **V**) and N-isopropyl DIJ (**IV**) from readily available dioxanone (**1**) precursor. The key steps include diastereoselective proline-catalyzed *syn*-aldol transformation and a reductive amination / cyclization.

D-*glycero*-D-*manno*-2-octulose (**VII**), a higher-carbon sugar isolated from opium poppies has been synthesized in enantiomerically pure form. The short synthetic sequence involved two proline-catalyzed aldol addition reactions of dioxanone (**1**) to appropriate aldehydes. Here, we developed a complete dioxanone methodology towards the higher monosaccharide in a stereocontrolled fashion.

The enantioselective stereodivergent first total synthesis of DD- and LL-*glycero*-β-*allo*-heptopyranose (**IX**, *ent*-**IX**) was accomplished from readily available non-chiral starting materials. The short synthetic sequence involves enamine and enolate mediated aldol reactions at α and α' positions of dioxanone (**1**) hence demonstrated the complementary nature of organocatalysis and organometallic methods.

ACKNOWLEDGMENTS

I would like to take this opportunity to express my gratitude to those people who has made my stay in Saskatoon an educative, enjoyable and memorable.

First and the foremost, I thank my supervisor, more appropriately my Guru and well wisher, Professor Marek Majewski for providing me an opportunity to work under his supervision. I am grateful for his financial support, motivation and guidance in shaping my career towards becoming a good researcher. I truly appreciate the "freedom of thought" that he gave me in exploring the chemistry and has been instrumental in refining interpersonal skills. I am sure that the whole learning process will have a great impact on my future. It was my previlage to have been associated with an outstanding and transparent person. I feel it as a great honor to be his student.

I also thank to my Advisory Committee Members: Dr. Soledade Pedras, Dr. David Palmer, and Dr. Grzegorz Sawicki for valuable suggestions, comments and critics to fine tune my thought process. Also, I am greatful to Dr. Dale Ward, a fine teacher and high caliber professional. Dr. Ward, I will always remember your profound statement that "*In real life-situations there is no guessing, it is either you know or you do not know*" *i.e.* In simple marks terminology, +1 for correct and -2 for a guess!!!!!

I would like to thank the former and present members of Majewski's group. Special regards to my *Polish siostra* Izabella Niewczas for her support and friendship from the very beginning my graduate life. I thank Grzegorz Orlowski, for those thoughtful gossip, animated movies and few good Polish words!!!. Big thanks for Khalil for all his help.

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I would like to thank past and present people from Dr. Ward's group for all their help. Especially, I would like to thank Sandip and Martin for encouragement and intellectual help.

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The financial support of Department of Chemistry, University of Saskatchewan and NSERC Canada is gratefully acknowledged.

I would like to dedicate this work to my parents

Jayalakshmi & Raghunatha Reddy

And my beloved wife and best friend

Aparna

For their eternal support, love and sacrifice

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LIST OF ABBREVIATIONS

α	observed optical rotation in degrees
[α]	specific rotation (deg·mL)/(g·dm)
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
aq	aqueous
Bn	benzyl
Bu	butyl
Bz	benzoyl
br	broad (spectral)
^{13}C NMR	carbon-13 nuclear magnetic resonance
cf.	refer to/compare/confer
Chx	cyclohexyl,
CI	chemical ionization
COSY	correlation spectroscopy
δ	chemical shift in parts per million downfield from tetramethylsilane
DCC	1,3-dicyclohexylcarbodiimide
DHAP	1,3-dihydroxyacetone phosphate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMSO	dimethyl sulphoxide
DCM	dichloromethane
de	diastereomeric excess
dr	diastereomers ratio
ee	nantiomeric excess, for a mixture of two enantiomers *R* and *S*, ee is calculated from equation : ee = ([*R*]-[*S*])/([*R*]+[*S*]) x 100%

EI	electron impact ionization
er	enantiomeric ratio
eq	equivalent(s)
Et_2O	diethyl ether
Et_3N/TEA	triethylamine
EtOAc	ethyl acetate
FCC	flash column chromatography
FT	Fourier transformation
H-bonding	hydrogen bonding
hfc_3	(heptafluoropropylhydroxy-methylene) camphorate
HMBC	heteronuclear multiple bond correlation (2 and 3 bond *J*-CH correlation with inverse detection)
HMQC HMQC	heteronuclear multiple quantum coherence (1 bond *J*-CH correlation with inverse detection)
^{1}H NMR	proton nuclear magnetic resonance
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
i-Pr	isopropyl
IR	infrared
KDN	2-keto-3-deoxy-D-glycero-D-galacto-nonulosonic acid
KDO	3-deoxy-D-manno-oct-2-ulosonic acid
LDA	lithium diisopropylamide
LiCl	lithium chloride
LPS	lipopolysaccharides
J	coupling constant (in NMR spectrometry)
LRMS	low resolution mass spectroscopy
M^+	parent molecular ion
max	maximum
Me	methyl
MeCN	acetonitrile

MeOH	methanol
mp	melting point
MS	mass spectrometry
MW	mol wt molecular weight
m/*z*	mass-to-charge ratio
MS 4 Å	molecular sieves 4Å
NBS	N-bromosuccinimide
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonyloxy (CF_3SO_2O)
Ph	phenyl
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
*i*Pr	isopropyl
p-TsOH	*p*-toluenesulfonic acid (4-methylbenzenesulfonic acid)
Py	pyridine
Ra/Ni	Raney-nickel
Rf	retention factor (in chromatography)
r.t	room temperature, usually 22-25 °C
s	singlet (spectral)
sat.	saturated aqueous solution
t	triplet (spectral)
TBAF	tetra-*n*butylammonium fluoride
TBDMS or TBS	*tert*--butyldimethylsilyl
TBDMSCl or TBSCl	*tert*-butyldimethylsilyl chloride
TFA	trifluoroacetic acid
TFAE	2,2,2-trifluoro-1-(9-anthryl)ethanol
t-Bu	*tert*-butyl (1,1-dimethylethyl)
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate

TLC	thin-layer chromatography
TMS	trimethylsilyl; tetramethylsilane
TMSCl	trimethylsilyl chloride (chlorotrimethylsilane)
TMSOTf	trimethylsilyl trifluoromethanesulfonate
w/w	weight per unit weight (weight-to-weight ratio)

Definitions and Conventions: (IUPAC recommendations 1999 & 1996)

a) **Scaffold**: Core portion of a target molecule on which it is functionalized.

b) **Building Block**: Only part of the structure will be incorporated into the final product

Reference: IUPAC, *Pure Appl. Chem.*, **1999**, *71*, 12, 2349-2365.

Example: Dioxanone (**1**) is a scaffold, whereas dimethoxy acetaldehyde (**2a**), 1,3-dithiane carboxaldehyde (**2b**) and D-glyceraldehyde (**2c**) are building blocks

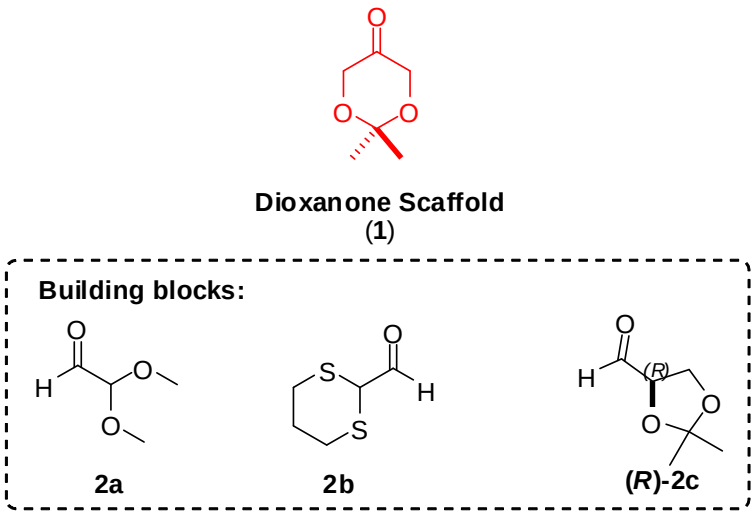


Figure 1.1: Dioxanone scaffold and building blocks: selected examples

- **Nomenclature of carbohydrates**: *Pure & Appl. Chem.*, **1996**, *68*, (10), 1919-2008.
  Web link: http://www.chem.qmul.ac.uk/iupac/2carb/34.html

a) The generic term "carbohydrate" includes monosaccharides, oligosaccharides and polysaccharides as well as substances derived from monosaccharides by reduction of the carbonyl group (alditols), by oxidation of one or more terminal groups to carboxylic acids or by replacement of one or more hydroxyl group (s) by hydrogen atom, an amino group, a thiol group or similar heteroatomic groups.

b) Sugars: The term “sugar” is frequently applied to monosaccharides and lower oligosaccharides.

c) Monosaccharides: The generic term “monosaccharide” denotes a single unit, without glycosidic connection to other such unit. Parent monosaccharides are polyhydroxy aldehydes or polyhydroxy ketones with three or more carbon atoms.

d) Aldoses and ketoses: Monosaccharides with an aldehydic carbonyl group are called as aldoses; those with a ketonic carbonyl group as ketoses.

e) Deoxy sugars: Monosaccharides in which an alcoholic hydroxyl group has been replaced by a hydrogen atom are called deoxy sugars.

f) Amino sugars: Monosaccharides in which an alcoholic hydroxyl group has been replaced by an amino group are called amino sugars.

g) Imino sugar: The term 'imino sugar' may be used as a class name for cyclic sugar derivatives in which the ring oxygen atom has been replaced by nitrogen.

h) Aza sugar: Use of the term 'aza sugar' should be restricted to structures where carbon, not oxygen, is replaced by a nitrogen atom.

i) Higher monosaccharides: Higher monosaccharides also commonly known as higher-carbon sugars are carbohydrates having the backbone longer than the usual six carbon atoms.

j) Nomenclature of higher monosaccharides: The monosaccharides with more than four stereogenic centres is named by adding two or more configurational prefixes to the stem name using the following criteria:

i. The carbon chain is written vertically, with the lowest numbered carbon atom at the top. (In Fischer projection of the acyclic form)

ii. Prefixes are assigned in order to the stereogenic centres in groups of four, beginning with the group proximal to C-1.

iii. The configurational prefixes are printed in lower-case italic. E.g. *glycero*- or *manno*- etc.

iv. The prefix relating to the group of carbon atom (s) farthest from C-1 (which may contain less than four atoms) is cited first.

v. Each configuration group has its own configurational symbol (D or L) according to the configuration at the highest-numbered stereogenic centre of the group.

vi. Racemates or *meso* forms may be indicated by the prefix DL-

vii. New stereogenic centre will be generated during the hemiacetal ring closure process. The two stereoisomers are reffered to as anomers, designated as α- or β- according to the configurational relationship between the anomeric stereogenic centre and the highest numbered stereogenic centre of the ring (next to ring heteroatom)

Examples:

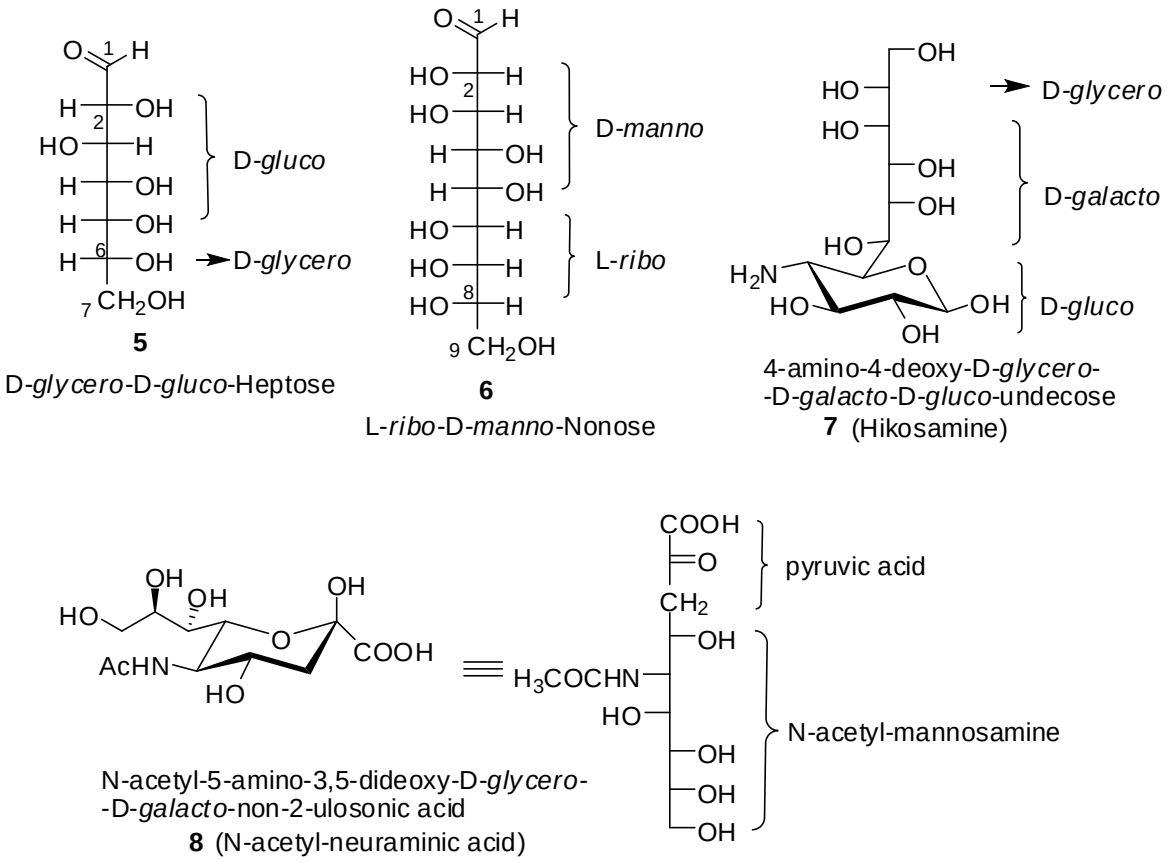
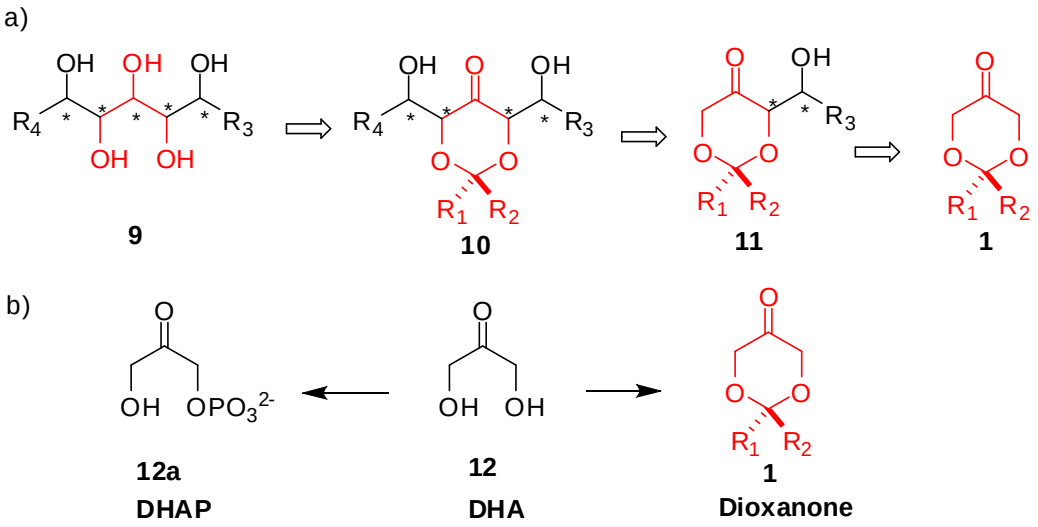


Figure 1.2: Nomenclature of higher monosaccharides: selected examples

1 INTRODUCTION

1.1 Background and Significance

The aldol reaction resembles nature's chemistry. As Sir John Cornforth states, *"Nature, it seems, is an organic chemist having some predilection for the aldol and related condensations"*.[1] Nature employs enzymes in construction of new carbon-carbon bonds and, for example, in synthesis of D-glucose, plants use dihydroxyacetone phosphate (**12a**, DHAP) as the donor component and D-glyceraldehyde-3-phosphate (**15a**) as an acceptor component and the reaction is typically catalyzed by aldolase enzymes.[2] Scheme 1.1a illustrates a "generic" retrosynthetic plan to complex higher carbohydrates starting from nonchiral dioxanone scaffolds (**1**) which has been a subject of our group's research for some time and is continued in this thesis.[10-15]



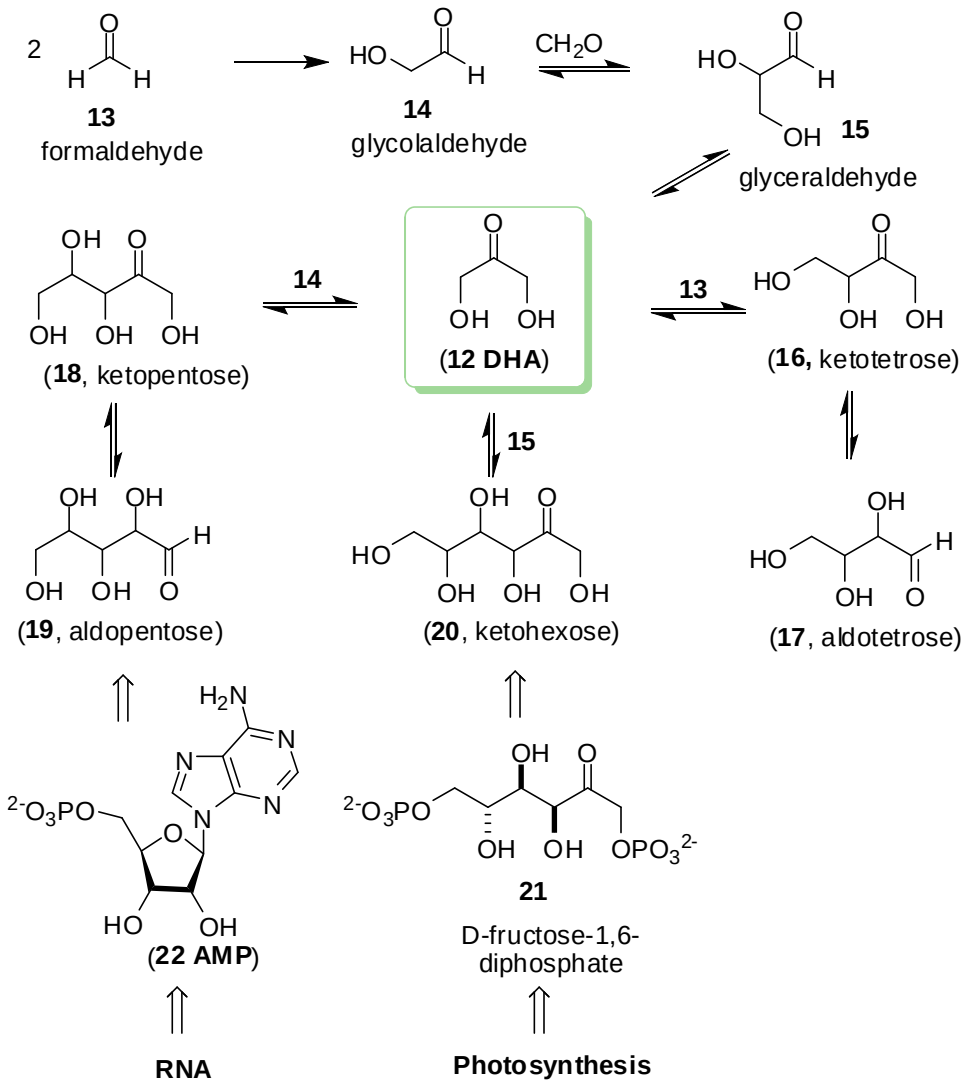
Scheme 1.1: a) Reterosynthetic plan to access polyoxygenated natural products and higher-monoscaaharides from dihydroxyacetone analogues. (b) Dihydroxyacetone and examples of its three-carbon synthetic equivalents.

Although enzyme-catalyzed aldol reactions of dihydroxyacetone phosphate (**12a**, DHAP) are especially useful for stereoselective approach to keto sugars, nevertheless working with enzymes and DHAP (**12a**) is not straightforward and relatively expensive.[2b,2c] Dioxanone scaffolds (**1**) are protected forms of dihydroxyacetone (**12**, DHA), a simple triose carbohydrate and an important three-carbon scaffold in synthesis of higher monosaccharides and various other polyoxygenated natural products (Scheme 1.1b).

The work involved in this thesis primarily deals with aldol reactions of dioxanones (**1**). The aldol reaction has been one of the fundamental tools employed in stereoselective formation of C-C bonds in synthesis of numerous natural products as well as in synthetic versions of biologically active natural compounds.[3] The aldol reaction finds its applications in synthesis of carbohydrates and other poly-oxygenated natural products, and also many other compounds of value in the field of pharmaceuticals and agrochemicals as well as playing an important role in medicinal chemistry.

1.2 The Formose Reaction

The total synthesis of carbohydrates and their analogs have engaged chemists ever since the discovery of the "formose reaction" by Aleksander Butlerow in 1861.[4] The formose reaction generates a mixture of racemic aldoses and ketoses from a $Ca(OH)_2$ catalyzed oligomerization of formaldehyde (**13**, Scheme 1.2).[5] The reaction begins with Benzoin-type condensation of two formaldehyde molecules (**13**) to form glycolaldehyde (**14**) which readily undergoes $Ca(OH)_2$ mediated aldol reaction with another equivalent of formaldehyde (**13**) to produce glyceraldehyde (**15**). Then an aldo-keto isomerization of glyceral (**15**) via Lobry de Bruyn-van Eckenstein rearrangement[6]



Scheme 1.2: Formose reaction cascade for C_3 to C_6 monosaccharides[5]

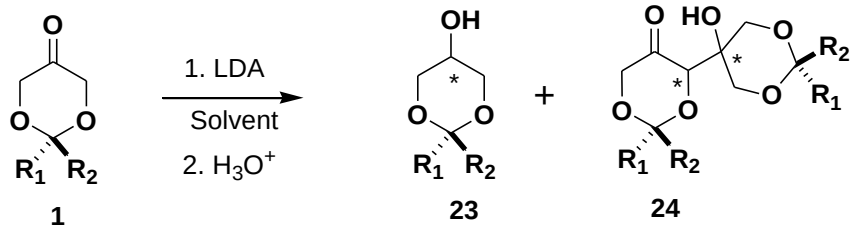
results in the formation of dihydroxyacetone (**12**), a simplest form of triose monosaccharide and crucial intermediate in formose reaction pathway. The enolizable DHA (**12**) can undergo series of aldol transformations with formaldehyde (**13**), glycolaldehyde (**14**) and glyceraldehyde (**15**) to produce a complex mixture of keto and aldo- tetroses, pentoses and hexoses respectively. DHA (**12**) and its analogs are known to be key precursors in numerous biochemical processes including the synthesis of carbohydrates and photosynthesis.[2] It is believed that the "classical formose reaction"

might have played a significant role in the prebiotic synthesis of carbohydrates such as ribose, an important component of RNA.[7]

The synthesis of useful organic molecules from readily available monosaccharides such as, D-glucose, D-mannose, D-glucosamine, D- and L-arabinose are cheaper than from the laboratory total synthetic methods. However, to obtain the unnatural monosaccharides, "rare" enantiomers of useful organic compounds and their functional group manipulation would be much easier and more advantageous from total synthetic methods starting from the readily available precursors. A large number of natural products possess a "scaffold" structure that can be systematically explored in their total synthesis. Dioxanones (**1**) are one such "scaffold" whose utility in asymmetric synthesis of bioactive natural products was illustrated in several publications, reviews and thesis.[8-12] Most often, they are used as synthetic equivalents of 1,3-dihydroxyacetone phosphate (**12a**, DHAP). The objective of this review is to highlight their chemistry and synthetic utility in total synthesis of carbohydrates and polyoxygenated natural products.

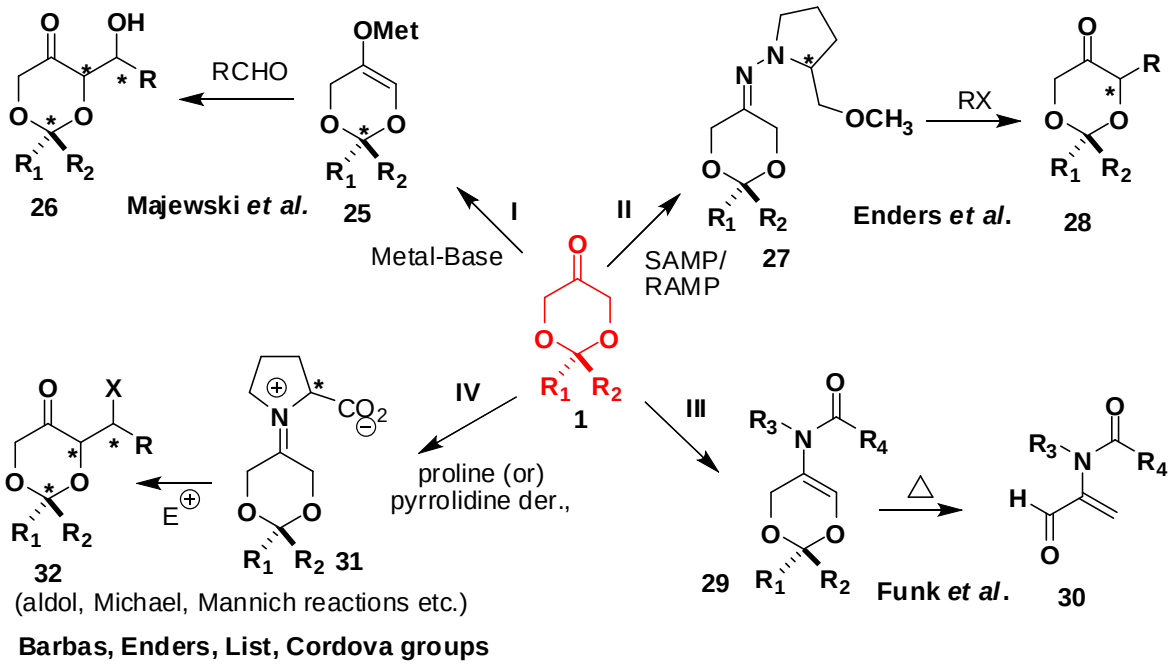
1.3 Dioxanone Chemistry

2,2-Dialkyl substituted 1,3-dioxan-5-ones are commonly known as dioxanones (**1**).[10] They are α-alkoxy heterocyclic ketones and ketal- or acetal protected forms of 1,3-dihydroxyacetone (**12**, DHA).



Scheme 1.3.

The presence of the two alkoxy groups at the α- and α'-position in respect to the carbonyl makes the ketone electron-deficient and thus a much stronger electrophile, thereby exhibiting unusual aldehyde-like properties such as greater susceptibility to reduction via hydride transfer as well as to self-condensation upon treatment with lithium amide bases (Scheme 1.3).[13] The protected dendroketose **(24)** is often a minor product in reactions involving dioxanones including organocatalysis.[14]



Scheme 1.4.

Over the past two decades, Majewski's group has been actively involved in exploring the chemistry on dioxanone substrates (**1**). Mark Gleave worked on developing the reaction conditions for synthesis of dioxanones (**1**).[10] Later, Pawel Nowak employed employed dioxanones (**1**) as three carbon (C_3) scaffolds in synthesis of protected forms of monosaccharides[11,15,16] and in total synthesis of (+)-frontalin (**81**).[11,17] Recently, Izabella Niewczas expanded dioxanone chemistry to include lithium and boron enolate-mediated

double aldol reactions.[12,18] Other research groups focused their efforts to capitalize on the synthetic utility of the dioxanone scaffold (**1**).[19-29] Based on the literature data, the chemistry involving dioxanone scaffolds can be broadly divided into four different methodologies as illustrated in Scheme 1.4.

I. Majewski's enantioselective deprotonation

II. Enders' hydrazone methodology

III. Funk's amidoacrolein methodology

IV. Asymmetric organocatalysis

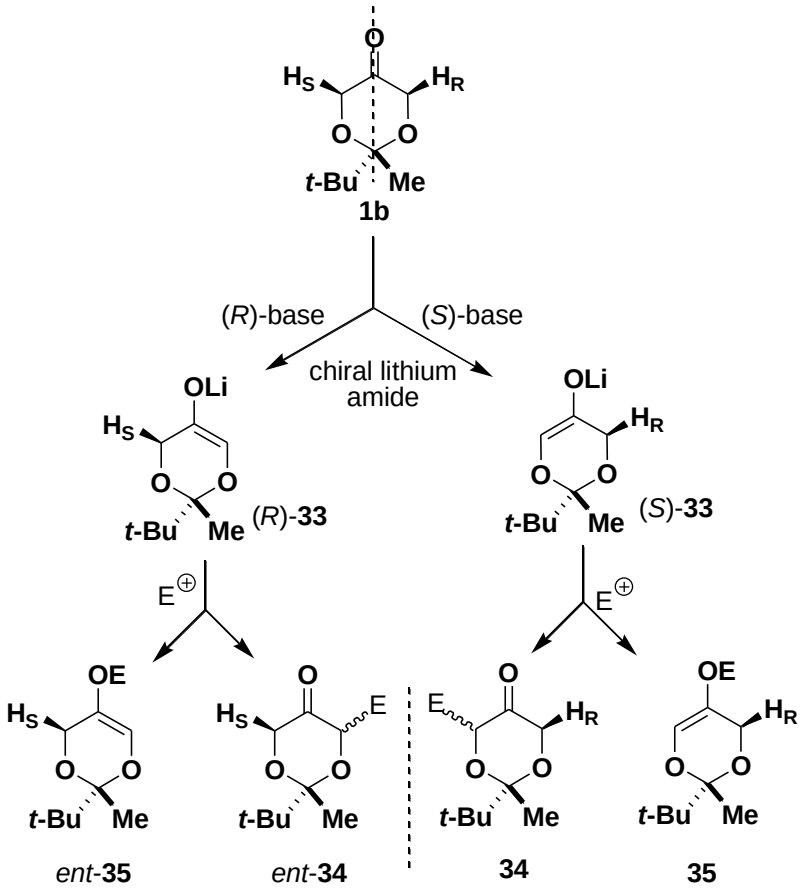
1.4 Dioxanone Methodologies

1.4.1 Majewski's enantioselective deprotonation

As Louis Pasteur stated "*Most natural organic products, the essential products of life are asymmetric and possess such asymmetry that they are not superimposable on their images*".[30] In this context, "asymmetric synthesis" is used as a tool in obtaining the enantiomerically enriched compounds which is especially important in medicinal chemistry and synthesis of pharmaceuticals.[31,32]

In many carbon-carbon bond forming reactions, e.g aldol, Mannich, Michael, Robinson annulation, ketone alkylation or acylation reactions, the first step is the deprotonation of a ketone to produce the corresponding enolate which is then trapped with an appropriate electrophile as required in total syntheses of the target.[33] Enantioselective deprotonation of numerous ketones using chiral lithium amide bases represents an attractive and powerful

method in asymmetric synthesis.[34] Enantioselective deprotonation of dioxanones with chiral lithium amides was first investigated by Majewski's group in early 1990's. Initially, dioxanone substrates proved to be challenging cyclic ketone precursors for enolization but after extensive experimental work by Gleave,[10] Nowak[11] and later by Niewczas[12] conditions were developed that allowed the use of dioxanones in building carbohydrates and polyoxygenated natural products.



Scheme 1.5. [11]

The method is briefly summarized in Scheme 1.5.[11] 2-*tert*-Butyl-2-methyl-1,3-dioxan-5-one (**1b**) is an achiral substrate having an internal plane of symmetry. This C_S-symmetric dioxanone worked very well in enantioselective deprotonation If the dioxanone exists as a

chair conformer, then the pair of axial protons at the C-4 and C-6 of the dioxanone ring are enantiotopic. The presence of the sterically bulky *tert*-butyl group at C-2 "locks" the ring conformation. Depending on the choice of the chiral lithium amide it was feasible to accomplish enantioselective deprotonation of one of the alpha protons H_S or H_R of the ketone **1b** to produce predominantly one of the corresponding enantiomers of the Li-enolate **33** with good selectivity.

The stereochemical information embedded in the chiral base was transferred to the enolates. The reactive chiral enolate **33** can react either at the oxygen center to produce the corresponding alkene **35** or at the enolate carbon center to form the α-substituted dioxanone **34**.

The synthesis of several chiral lithium amides bases was reviewed by Nowak and Niewczas in their respective theses.[12] The scope of this methodology was extended to a number of different cyclic ketones (**36**-**38**) having C_S-symmetry as shown in Figure 1.3.

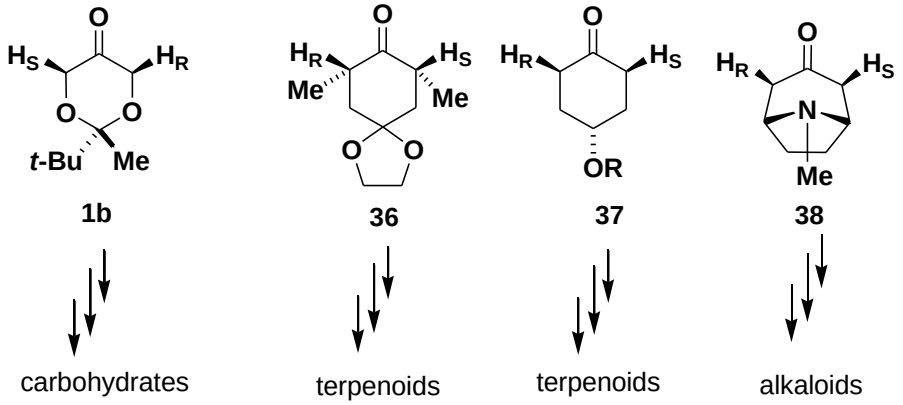
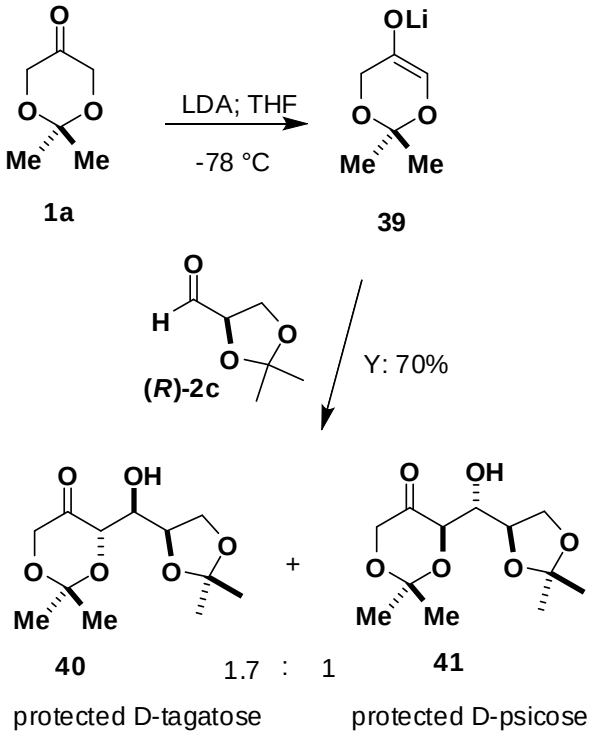


Figure 1.3: Symmetrical cyclic ketones for enantioselective deprotonation studies[34]

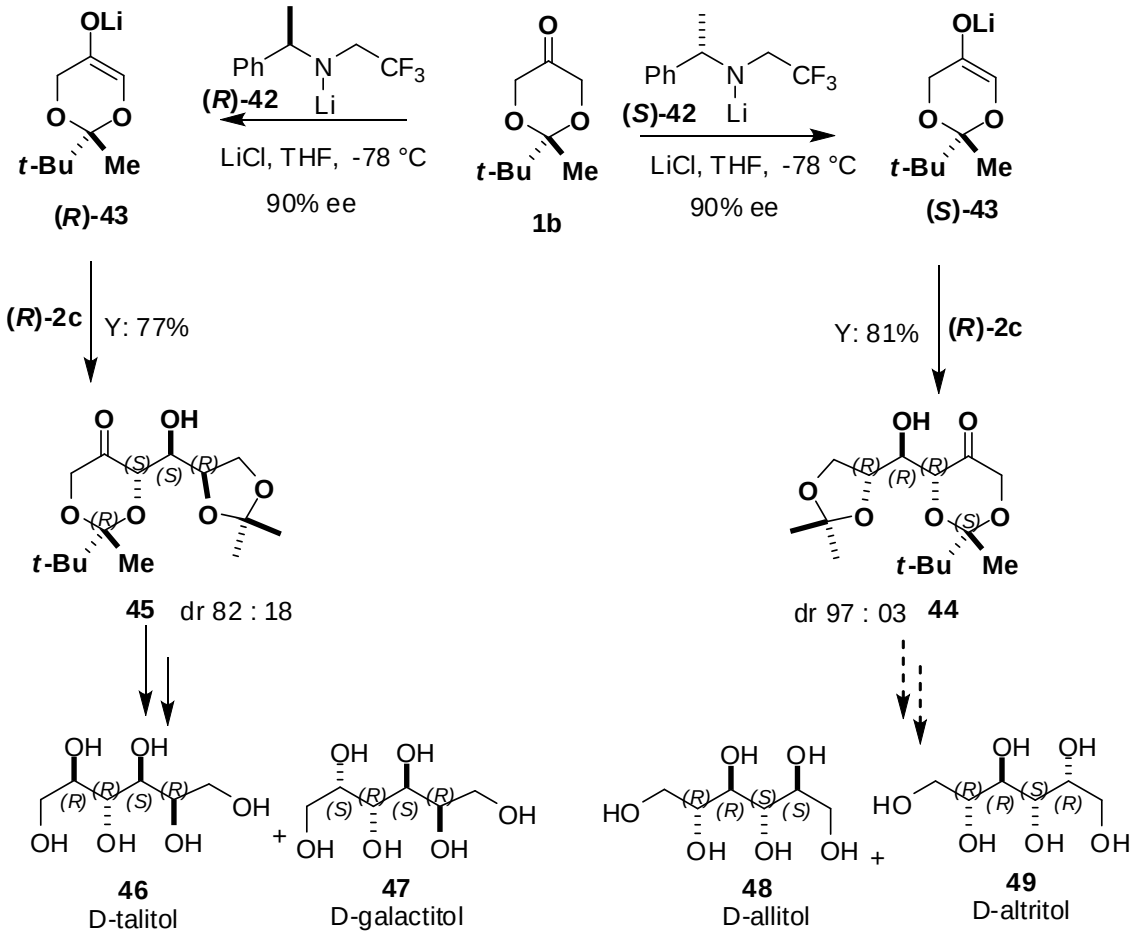
Gleave[10] and Nowak[11] demonstrated that aldol transformations involving the C_S symmetrical 2-*tert*-butyl-2-methyl dioxanone **1b** (Scheme 1.7) proceeded with higher

stereoselectivities in comparison to similar transformations carried out the C_{2v} symmetrical 2,2-dimethyl-1,3-dioxa-5-one (**1a**, Scheme 1.6). The lithium enolate of dioxanone (**1a**) reacted with (*R*)-glyceraldehyde (**2c**) to produce two isomeric protected ketohexoses (**40** and **41**) but the selectivity was rather low.



Scheme 1.6.

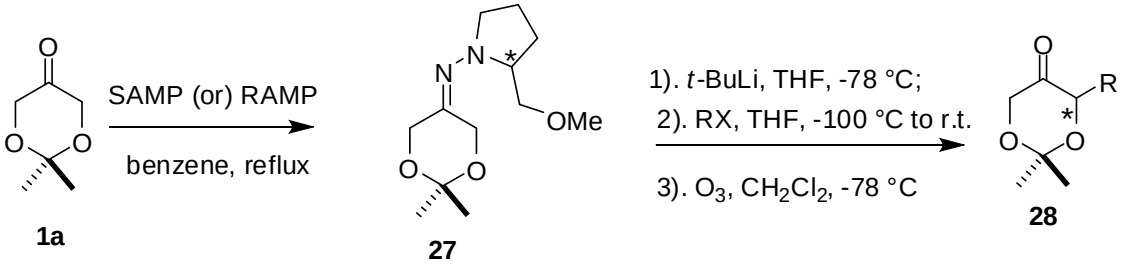
In contrast, enantioselective deprotonation of the C_S-symmetrical dioxanone (**1b**) gave one of the two chiral lithium enolates **43** in high ee. The reaction with the chiral aldehyde (***R***)-**2C** gave derivatives of D-psicose (**44**) or D-tagatose (**45**) in fairly high diastereoselectivity. The ketone reduction followed by acid-catalyzed ketal hydrolysis of aldol adducts (**44** and **45**) provided the known corresponding reduced ketohexoses (**46**-**49**) thus establishing the relative and absolute configuration of the products by the chemical correlation method.[11,16] This particular study eventually became a standard for comparison of stereochemical outcome of aldol reaction of dioxanones.


OLi
t-Bu
Me
(R)-43
Ph
N
CF3
(R)-42
Li
LiCl, THF, -78 °C
90% ee
1b
(S)-42
(S)-43
(R)-2c
Y: 77%
Y: 81%
45
dr 82 : 18
dr 97 : 03
44
46
D-talitol
47
D-galactitol
48
D-allitol
49
D-altritol

Scheme 1.7.

1.4.2 Enders' hydrazone methodology

As discussed in the previous section, dioxanones (**1**) under standard alkylation reaction conditions (e.g., lithium diisopropylamide, LDA, -78 °C or lithium hexamethyldisilazide, LHMDS) tend to undergo reduction of the carbonyl group, self-condensation and decomposition.[35]



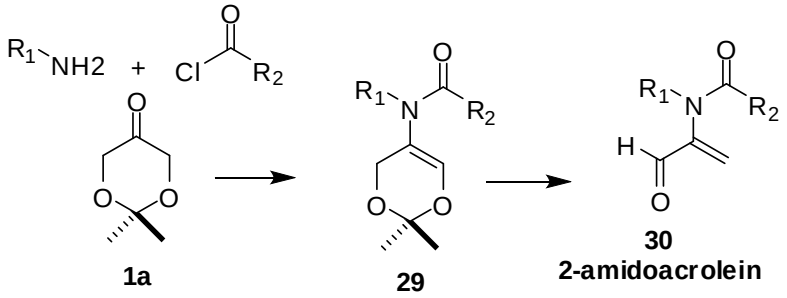
Scheme 1.8.

To date dioxanones (**1**) have been challenging alkylation substrates and the only available method for alkylation of dioxanones relies on using Enders' SAMP/RAMP-hydrazone (**27**) methodology (Scheme 1.8). In 1989 Enders and co-workers developed a method for stereoselective α-alkylation of dioxanones (**28**) that relies on "chirality transfer" of (+)-*S*-1-amino-2-methoxymethylpyrrolidine (SAMP) or its enantiomer (RAMP) to the α reactive site of the dioxanone ring. This methodology was applied in asymmetric synthesis of different classes of natural products.[36]

1.4.3 Funk's amidoacrolein methodology

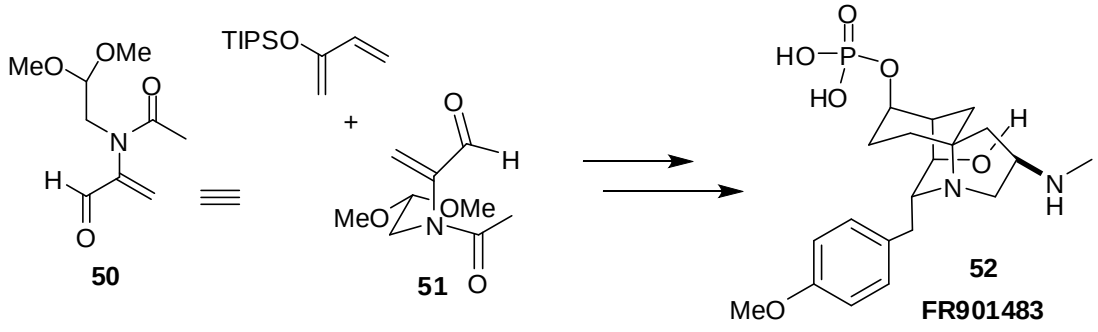
Funk and coworkers have reported total syntheses of several polycyclic alkaloids using a trifunctional 2-amidoacrolein component derived from 2,2-dimethyl-1,3-dioxan-5-one (**1a**).[37] The general procedure involves the formation of an amidodioxin motif (**29**)

starting from dioxanone (**1a**) which under simple heating produces the corresponding amidoacrolein (**30**, Scheme 1.9).



Scheme 1.9.

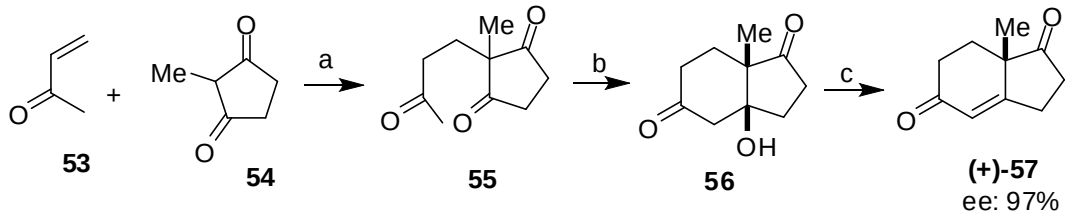
In a quick sequence of Diels-Alder and aldol reactions the three-carbon assembly can be incorporated into the desired natural product ring system. In the past decade Funk's research group employed the dioxanone-amidoacrolein methodology to realize the total synthesis of numerous natural products.[38-40] As an example, In the year 2001, Funk and Maeng applied amidoacrolein methodology in total synthesis of FR901483 (**52**, Scheme 1.10).[41]



Scheme 1.10.

1.4.4 Asymmetric organocatalysis

The field of organocatalysis has received much attention in the field of asymmetric synthesis of chiral organic molecules. Organocatalysis is the process of acceleration of chemical reactions using substoichiometric amounts of a metal-free organic compound.[42] In early 1970's, Hajos and Parrish (at Hoffmann-La Roche Inc, USA)[43,44] and Eder, Sauer and Wiechert (at Schering, Germany)[45] independently reported the first enantioselective synthesis of bicyclic diketone **57**, that was later named the Hajos-Parrish Ketone (HPK). The two-step procedure consisting of an acid-catalyzed Michael addition of methyl vinyl ketone (**53**) with methyl cyclopentanedione **54** gave the intermediate triketone **55,** that, under organocatalytic conditions afforded the enantiomerically enriched hydrindane dione **57** (Scheme 1.11).



Reagents and conditions: (a) aq.AcOH, 70 ºC, Yield 100%;(b) (S)-proline (3 mol%), DMF, 16 ºC, 3 days; (c) p-TsOH (cat.,), PhMe, reflux, yield 71% (two steps).

Scheme 1.11.

Although the first asymmetric organocatalytic recations were reported several decades ago, only in the past decade the field of enantioselective organocatalysis has become an area of active interest.[46] The tremendous work and results obtained in this area are documented in a number of articles, reviews[47-52] and books.[53] My project primarily deals with the proline catalyzed aldol reactions on dioxanone scaffolds. The following section focuses on the concepts relevant to the ongoing project.

1.4.4.1 Proline-catalyzed enantioselective aldol reaction

As described above, proline was first investigated as a small molecule catalyst in what became later known as the Hajos-Parrish reaction[43,44] in 1974. Described by Jacobsen[54] as the "simplest enzyme", L-proline can catalyze a wide array of chemical reactions with moderate to high diastereo- and enantioselectivities. What are the main features that make proline such a good catalyst? In a review[49] on organocatalysis, Dalko points out that: "*Proline is the only natural amino acid with secondary amine functionality and thus has a higher pKa value and enhanced nucleophilicity relative to other amino acids. Proline can therefore react as a nucleophile with carbonyl groups or Michael acceptors to form iminium ions or enamines. As the carboxylic acid functionality of the amino acid acts as a Brønsted acid in these reactions, proline can be regarded as a bifunctional catalyst*."

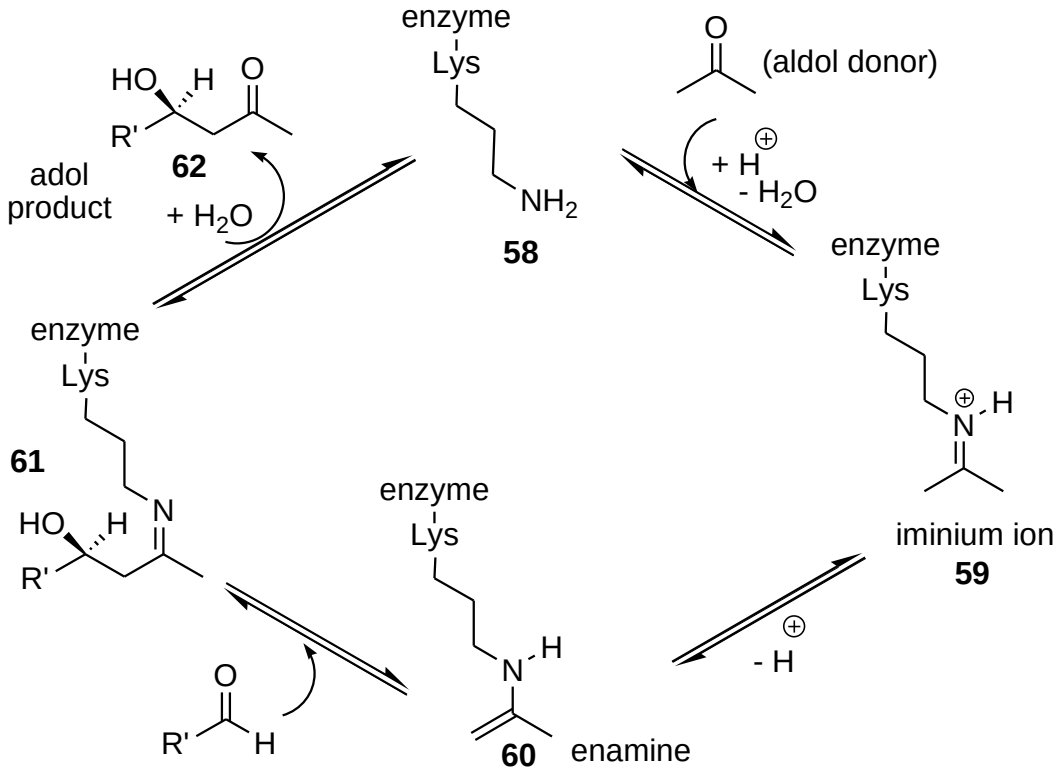


Figure 1.4: Catalytic mechanism of class I aldolases

In the past decade, the field of organocatalysis has gained much popularity among the chemical research community. The proline-catalyzed aldol reaction involving formation of the donor enamine as shown in Figure 1.5, shows a striking similarity to the complex machinery of natural enzymatic catalysis that is shown in an abbreviated form in Figure 1.4.[53a]

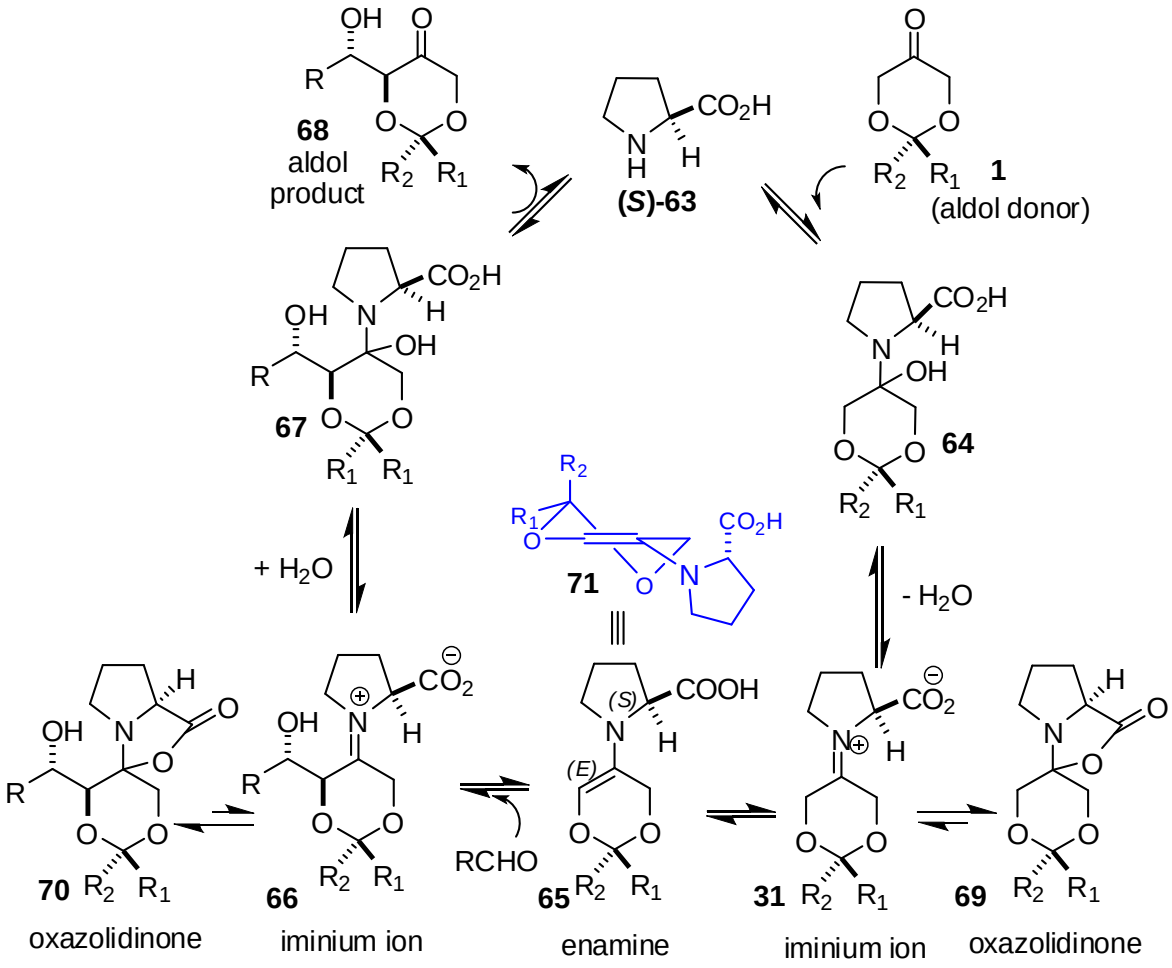


Figure 1.5: Catalytic cycle for L-proline catalyzed asymmetric aldol reaction of dioxanone

The catalytic cycle for the (*S*)-proline-catalyzed asymmetric aldol reaction of dioxanone (**1**) as illustrated in Figure 1.3 is an extrapolation of the concepts available in the literature.[55-57] Dioxanone **(1)** reacts with the secondary amine group of (*S*)-proline (**63**) to

form the corresponding hemiaminal (**64**), which further results in the formation of the iminium intermediate (**31**), which can either form an enamine (**65**) or an oxazolidinone (**69**). Formation of the oxazolidinone (**69**) leads to a decrease in the turnover of the catalyst.[58,55] Similarly, when an aldehyde reacts with the chiral enamine (**65**) this results in the formation of the new carbon-carbon bond and gives the iminium intermediate (**66**), which can also form the corresponding oxazolidinone (**70**). Hydrolysis of the iminium intermediate (**66**) yields an enantiomerically enriched aldol product (**68**) and releases (*S*)-proline (**63**) back into the catalytic cycle.

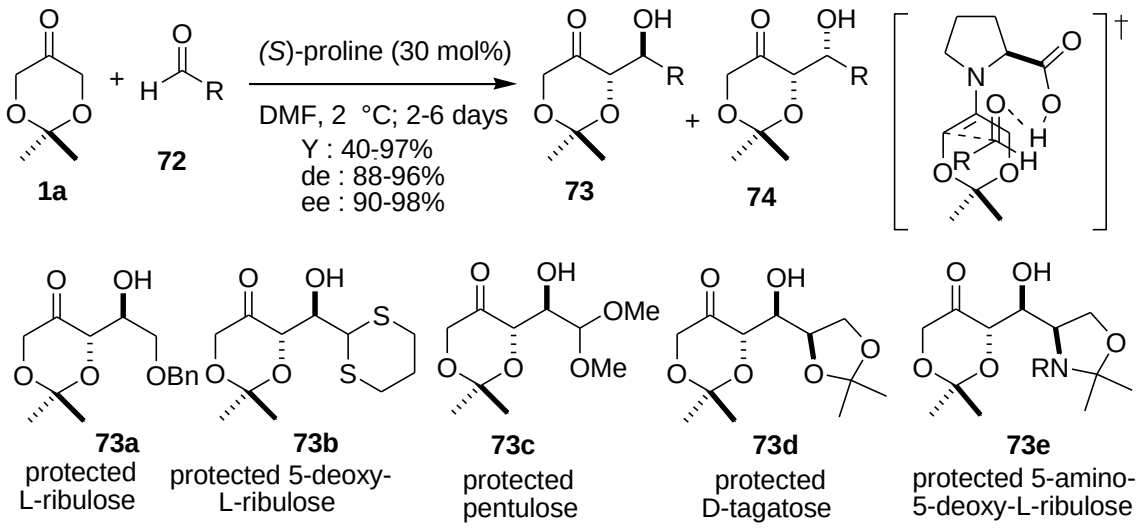
1.4.4.2 Dioxanones as a scaffolds in synthesis of carbohydrates

Majewski's group[11,16] was one of the first to realize the potential of dioxanones in synthesis of pentoses and hexoses using $C_3 + C_n$ strategy where three-carbons are coming from the dioxanone scaffold and C_n-carbons from suitable electrophiles. As discussed in Section 1.4.1, lithium-enolates of dioxanone substrates (**1**) were functionalized via enantioselective aldol reactions to synthesize naturally occurring D-psicose (**44**) and D-tagatose (**45**) which established both the absolute and relative stereochemical outcome of deprotonation and aldol addition. Organocatalysis offered a simpler way of synthesis of monosccharides.

MacMillan *et al.* in a series of articles demonstrated the power of organocatalytic aldol reactions in synthesis of lower monosaccharides (hexoses) in high setereoselectivities on

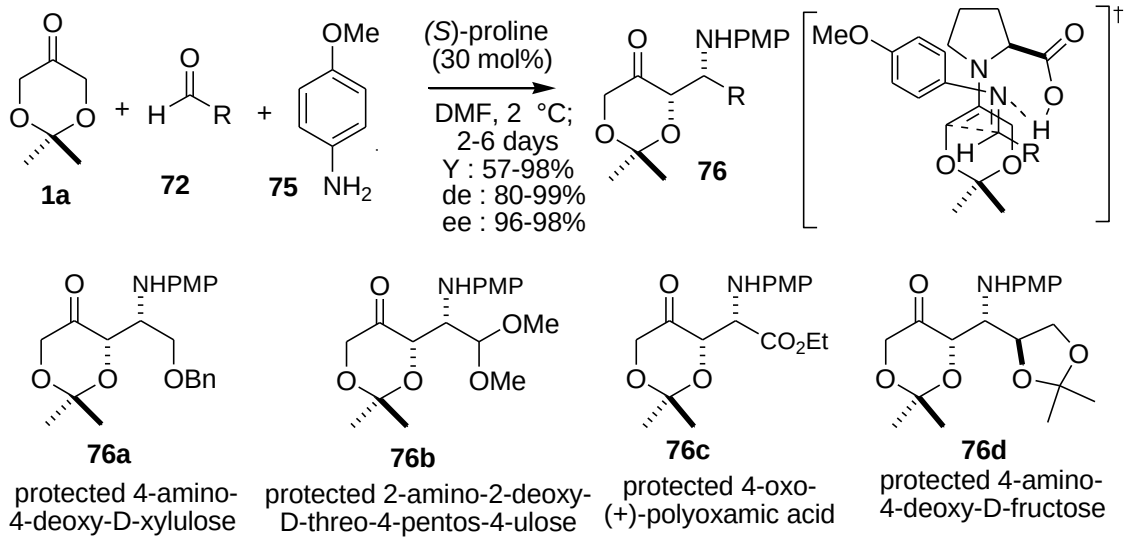
par with natural processes, as well as to alkyl, thio and amino derivatives of those monosaccharides.[27] The scope of proline-catalyzed asymmetric transformations on dioxanones was explored by various research groups,[8] in particular, the research groups of Enders,[20,23,25,27] Barbas[21] and Cordova[22,28] explored the scope of organocatalytic aldol reactions of dioxanones (**1**) in syntheses of carbohydrates. This topic was covered by Niewczas[12] in her thesis and also been reviewed by Mahrwald[8] and Enders.[9] Hence without going into details of the chemistry, the following section is intended to condense the literature information on dioxanone-based methodology towards the synthesis of carbohydrates.

During the past decade, Enders, Barbas, and Cordova research groups independently functionalized dioxanone (**1a**) via organocatalytic aldol reactions to givesynthetically useful protected forms of various pentoses and hexoses shown in Scheme 1.12.



Scheme 1.12.

After extensive screening of reaction conditions, proline proved to be a superior catalyst and structural features of the electrophiles were shown to play an important role in overall yields and selectivity of this transformation. Enders *et al* confirmed the stereochemistry of the major aldol adduct to be the protected D-tagatose **73d.** This was based on the correlation with literature data provided by Nowak.[11,16] It seems that all subsequent publications relied their stereochemical assignments on Enders' work and thus, indirectly, on Nowaks work.

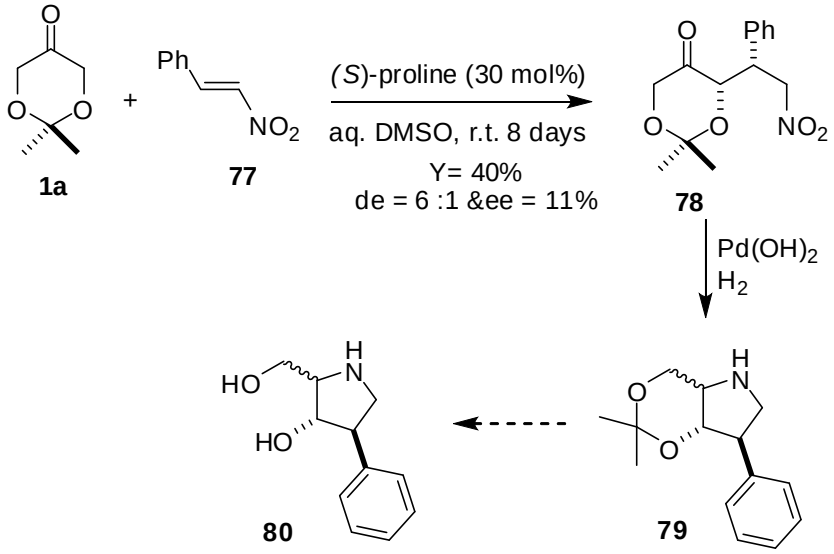


Scheme 1.13.

List and coworkers first developed and explored the proline-catalyzed three-component diastereo- and enantioselective Mannich reaction on dioxanone **1a**. The reaction, as illustrated in Scheme 1.13, involves an interaction between the *si*-face of the dioxanone enamine and the *si*-face of the aldehyde-derived imine to produce preferentially the *syn*-configured Mannich products **76**.[55] The reversal of selectivity from the *anti* in the aldol reaction to the *syn* in the Mannich case can be explained based on the change in facial

selectivity between aldehyde (*re*-face) in aldol and imine (*si*-face) of Mannich with the same *si*-face of dioxanone enamine (**1**)

Cordova's group reported the first proline-catalyzed Michael addition to phenylnitrostyrene (**77**) involving a dioxanone substrate (**1a**) to produce the Michael adduct **78** in low selectivity (Scheme 1.14).[56] The compound **79** was readily hydrogenated to the corresponding dihydroxy pyrrolidine derivative **80,** thereby developing a new route to access iminosugars.



Scheme 1.14.

Using the above methodologies, the synthetic utility of dioxanone scaffolds (**1**) was demonstrated in several target-oriented syntheses of natural products. Most of the compounds listed in Figure 1.6 were reviewed by Enders[9] in 2005 and by Niewczas[12] in her thesis in 2008. The following section of the thesis will focus on reviewing the recent literature related to applications of dioxanone-based methodology in natural product syntheses with prime attention on the reports published after 2006.

1.5 Dioxanone Scaffolds in Total Synthesis of Natural Products: Review of Recent Literature

The literature untill 2006 includes numerous references where dioxanones (**1**) were used as dihydroxyacetone equivalents (DHA) in asymmetric total synthesis of complex natural products most of which were polyoxygenated compounds.[9-29]

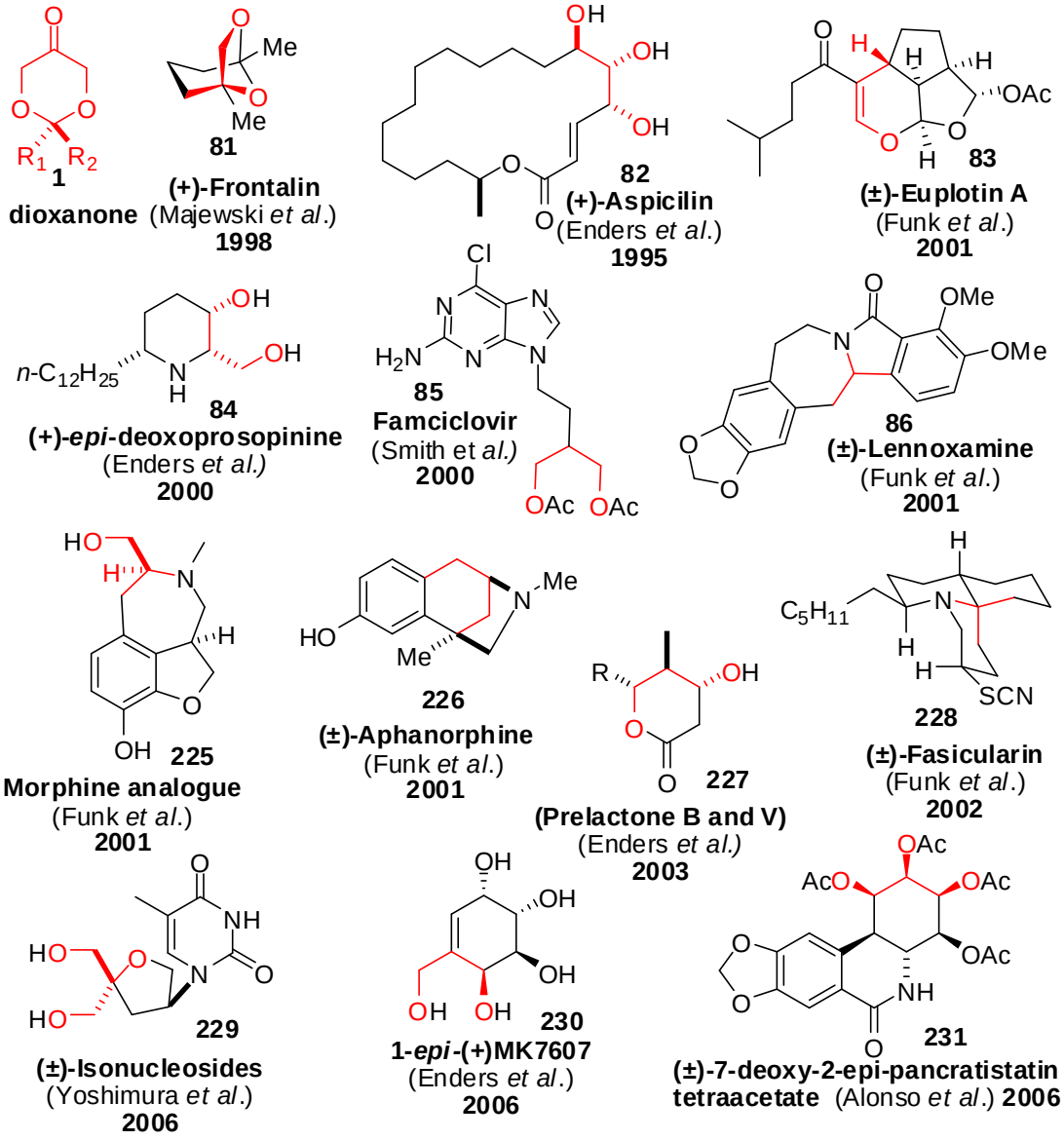
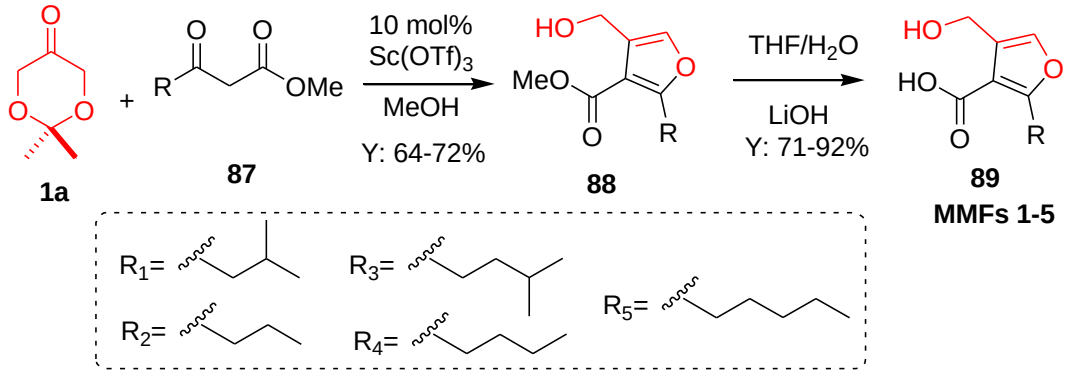


Figure 1.6: Natural products synthesized from dioxanone building blocks until 2006 **(**Note: The structural portion that came from the dioxanone (**1**) is highlighted in red color).

In the following section of the thesis, I will review the reports on syntheses involving the dioxanone methodology which are not covered in the previous reviews.[9,12]

1.5.1 Synthesis of methylenomycin furans (MMFs)

Methylenomycin furans (MMFs) are derivatives of 2-alkyl-4-hydroxymethylfuran-3-carboxylic acid (**89**) that were a recently discovered class of bacterial signaling compounds produced by *Streptomyces coelicolor* bacteria.[59] About two-thirds of the clinically used antibiotics are produced by these soil-dwelling bacteria.[60]

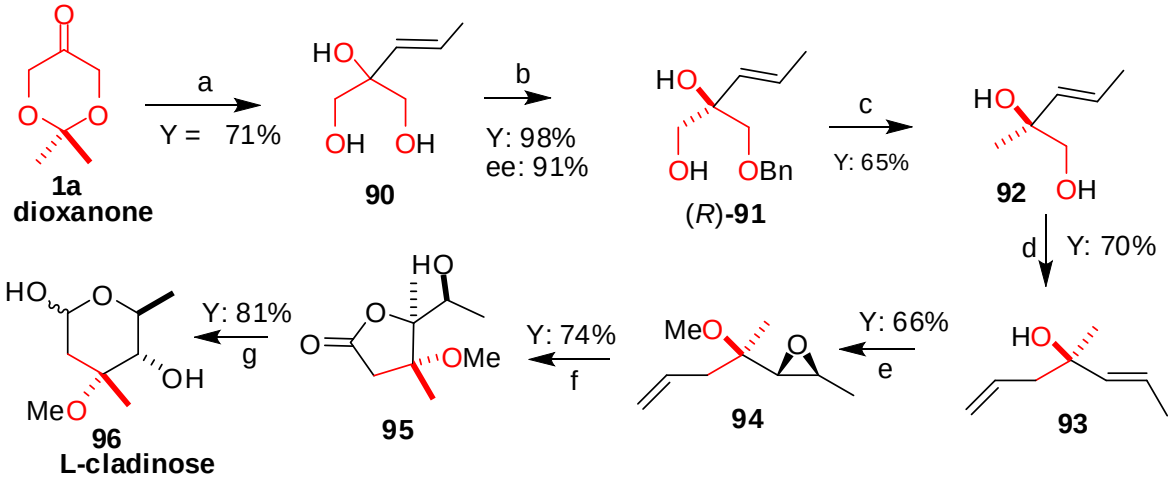


Scheme 1.15: Synthesis of Methylenomycin Furans (MMFs)

Recently, Sello *et al*. reported a two-step synthesis of MMFs starting from dioxanone **1a** (Scheme 1.15).[61] The optimal reaction conditions involved a scandium triflate-catalyzed domino reaction of β-ketoesters **87** and dioxanone **1a** involving three steps: aldol addition, *in situ* trans-ketalization followed by the final dehydrative aromatization and produced the desired target MMFs 1-5 (**89**) in 45 to 66% overall yields

1.5.2 Enantioselective synthesis of L-Cladinose

L-Cladinose (**96**) is a natural sugar found in erythromycins A, B, F and G, as well as in the azithromycins.[62] Kang's protocol[63] began with addition of propenyllithium to the ketone moiety of the dioxanone (**1a**) followed by an acid-catalyzed acetal hydrolysis to afford the glycerol substrate **90**. The desymmetrization of **90** was achieved by benzoylation that was catalyzed by a chiral imine $CuCl_2$ catalyst to furnish the enantiomerically enriched monobenzoate (*R*)-**91** in 98% yield (Scheme 1.16.).



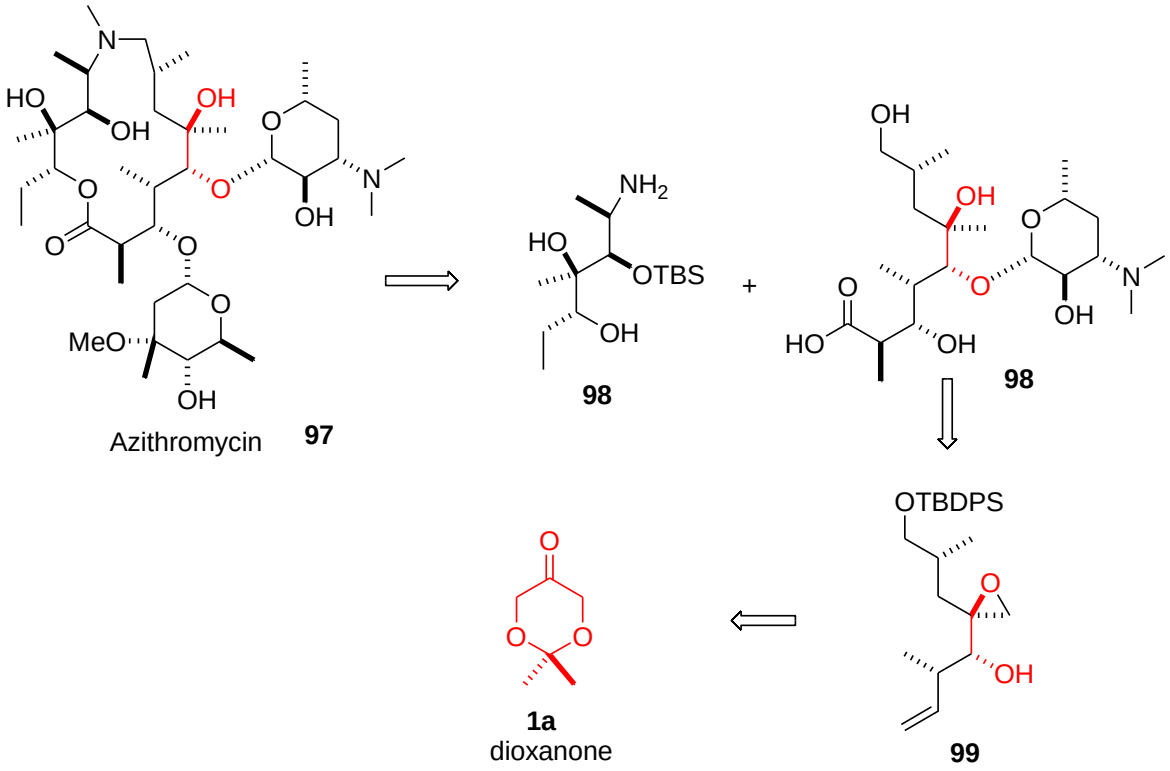
Reagents and conditions: (a) 1. *trans*-MeCH=CHBr, *t*-BuLi, THF, -78 °C; 2. aq. HCl, MeOH, r.t.; (b) (*R*,*S*)-Imine-$CuCl_2$ (20 mol%), BzCl, NEt_3, THF, r.t.; (c) 1. MsCl, NEt_3, CH_2Cl_2, -78 °C, then DBU, r.t.; 2. Red-Al, THF, 0 °C; (d) 1. MsCl, NEt_3, CH_2Cl_2, -78 °C, then DBU, r.t.; 2. CH_2=CHMgBr, CuI, THF, -40 to -20 °C (e) 1. $VO(acac)_2$, *t*-BuO_2H, CH_2Cl_2, 0 °C to r.t.; 2. NaH, MeI, THF, 0 °C to r.t.; (f) 1. $RuCl_3(H_2O)_n$, $NaIO_4$, CH_2Cl_2, MeCN, 15 °C; 2. $BF_3.OEt_2$, CH_2Cl_2, 0 °C to r.t.; (g) DIBAL-H, THF, -78 °C.

Scheme1.16: Enantioselective desymmetrization of dioxanone scaffold to L-cladinose

Subsequently, the benzoate was mesylated, followed by a DBU-mediated cyclization to produce the epoxide intermediate which, upon treatment with Red-Al, underwent debenzoylation to give the corresponding allylic alcohol **92**. A one-pot sequence of mesylation-cyclization of **92** to epoxide followed by treatment with a vinyl Grignard reagent afforded the tertiary alcohol diene **93**. The diene was then subjected to chemo- and

stereoselective Sharpless epoxidation followed by methylation of tertiary hydroxyl group to produce the epoxymethyl ether **94**. The ruthenium-catalyzed oxidative cleavage of the double bond followed by Lewis acid mediated cyclization resulted in butyrolactone **95**. The final DIBAL reduction of lactone proceded with a spontaneous rearrangement from furanose to pyranose and afford the target L-cladinose (**96**). Thus, Kang and co-workers successfully functionalized the dioxanone scaffold (**1a**) into L-cladinose (**96**) in twelve steps with 12.5% overall yield.[63]

1.5.3 Total synthesis of Azithromycin



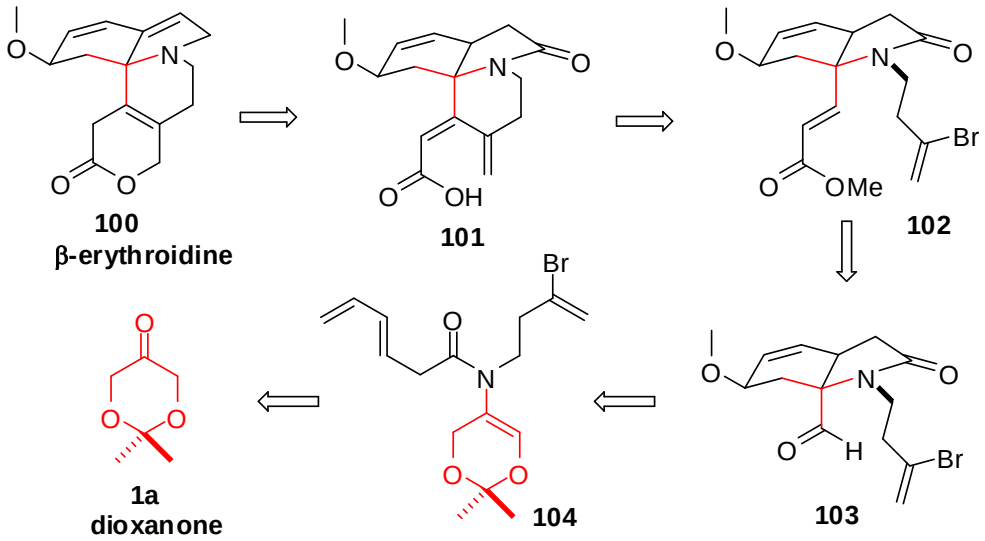
Scheme 1.17: Total synthesis of Azithromycin

Azithromycin (**97**) is a commercially available antibiotic with wide beneficial properties over popular erythromycins.[64] Azithromycin possesses a 15-membered

macrolide structure with complex stereochemical architecture.[65] Last year, Kang *et al*. demonstarted a highly stereoselective total synthesis of azithromycin in 18 linear steps with 5.2% overall yield starting from dioxanone **1a** (Scheme 1.17).[66]

1.5.4 Synthesis of (±)-β-Erythroidine

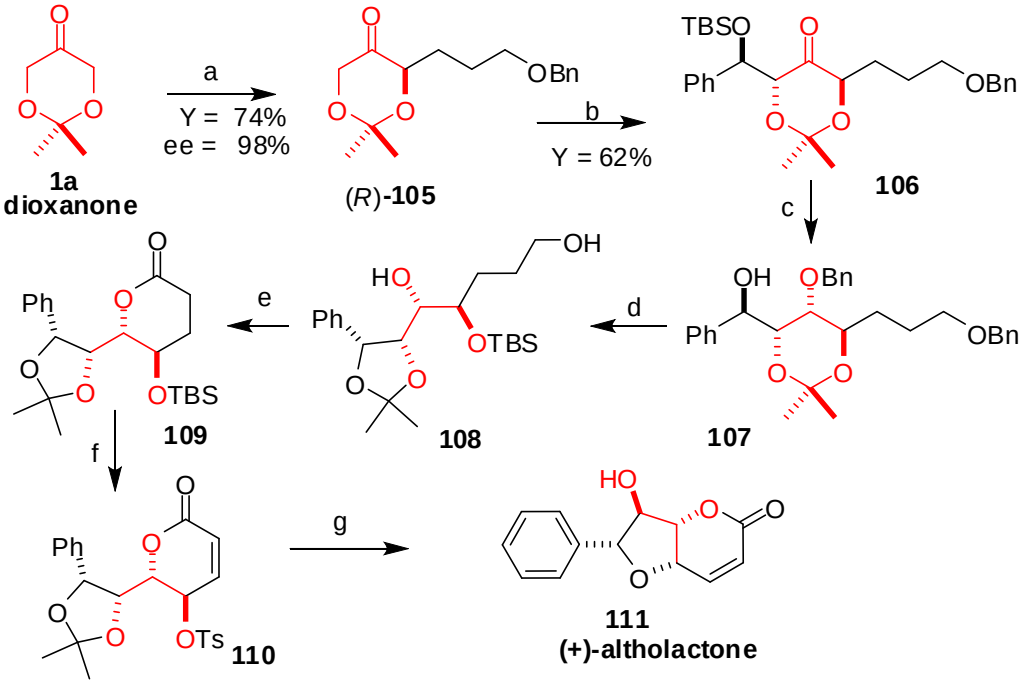
β-Erythroidine alkaloids such as compound **100** exhibit interesting pharmacological properties such as sedative, hypotensive, neuromuscular blocking and CNS activity.[67] Recently, Funk and He demonstrated the usefulness of dioxanone methodology to access the tetracyclic (±)-β-erythroidine (**100**) in 13 steps with 13% overall yield (Scheme 1.18).[68] The key steps in their accomplishment include intramolecular amidoacrolein Diels-Alder cycloaddition followed by a subsequent Heck reaction and an electrocyclic ring closure to realize the polycyclic ring system of the target natural product.



Scheme 1.18: Retrosynthetic plan to (±)-β-erythroidine

1.5.5 Asymmetric synthesis of (+)-Altholactone

(+)-Altholactone (**111**) has a tetrahydrofurano-2-pyrone structural motif and is a member of styryllactone family of natural products occuring in Polyalthia species.[69] (+)-Altholactone is (**111**) known to display cytotoxic and antitumor activities. In 2008, Enders and Barbion succeeded in the first asymmetric synthesis of (+)-altholactone using dioxanone-hydrazone methodology.[70]



Reagents and conditions: (a) 1. RAMP, benzene, reflux; 2. t-BuLi, THF, -78 °C; 3. $Br(CH_2)_3OBn$, -100 °C to r.t.; 4.oxalic acid, Et_2O, r.t.; (b) 1. Cy_2BCl, NEt_3, Et_2O, -78 °C , PhCHO then H_2O_2, MeOH, pH 7 buffer, r.t.; 2. TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t.; (c) 1. L-selectride, THF, -78 °C; 2. BnBr, KH, THF, r.t; 3. TBAF, THF, r.t.; (d) 1. *p*-TsOH (cat.), acetone, r.t.; 2. 2,2-DMP, PPTS (cat.), 3. TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t.; 4. H_2, 10% Pd/C. EtOAc, r.t.; (e) 1. IBX, DMSO, r.t.; 2. TPAP (5 mol%)/NMO, CH_2Cl_2, r.t.; (f) 1. LDA, PhSeCl, THF, -78 °C; 30% H_2O_2, CH_2Cl_2, 0 °C; 2. TBAF, THF, r.t.; 3. DMAP, TsCl, CH_2Cl_2, r.t.; (g) Amberlyst 15, MeOH

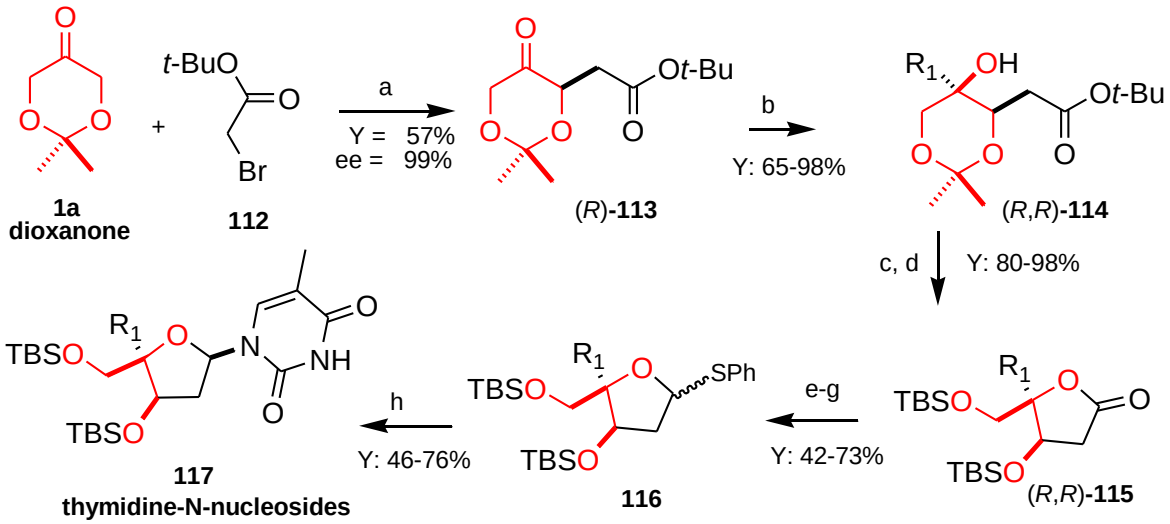
Scheme 1.19: Synthesis of (+)-altholactone

Readily available 2,2-dimethyl-1,3-dioxan-5-one (**1a**) was first transformed into the respective RAMP-hydrazone *via* the standard protocol developed in Ender's research

laboratory (Scheme 1.19). Then, at low temperature, the aza-enolate of the hydrazone was trapped with 3-benzyloxy-1-bromo-propane followed by hydrolysis of the hydrazone moiety to produce the α-alkylated dioxanone (*R*)-**105** in good yield and selectivity. The second nucleophilic site of the dioxanone ring was subjected to boron-mediated aldol reaction with benzaldehyde to produce the *anti-trans* aldol adduct, and simple silyl protection of thehydroxyl functional group resulted in compound **106**. Further, the carbonyl reduction followed by functional group manipulation resulted in dibenzylated alcohol **107**. The sequence involving a trans-acetonide formation, silylation followed by double debenzylation gave the corresponding diol **108**. The γ-lactone **109** was then obtained from the diol **108** using an IBX mediated oxidation and *in situ* cyclization followed by a TPAP/NMO oxidation sequence. Next, the α,β-double bond was introduced into the lactone ring through α-selenylation/elimination and a subsequent TBS deprotection and tosylation gave compound **110**. The last step was carried out under acidic conditions using the Amberlyst resin which induced the acetal deprotection resulting in spontaneous ring-closure with complete inversion of configuration to produce the desired (+)-altholactone (**111**) in eighteen steps starting from dioxanone scaffold(**1a**) with 13.7% overall yield.[70]

1.5.6 Synthesis of an N-nucleoside derivative

Nucleoside-type natural products and their analogues are known to be useful compounds in medicinal chemistry and for a broad range of disease targets.[71] A variety of biologically useful nucleoside analogues have been synthesized to date.[72] Enders and co-workers reported the first asymmetric route to access 4'-quaternary 2'-deoxy-3'/4'-*epi*-nucleosides using dioxanone-hydrazone methodology.[73] The synthesis started with α-alkylation of 2,2-dimethyldioxan-5-one (**1a**) to produce the corresponding *tert*-butyl keto ester (*R*)-**113**. The subsequent diastereoselective Grignard addition to the ketone resulted in a moderate yield of the *syn*-diastereomer of the ester-alcohol **114**.



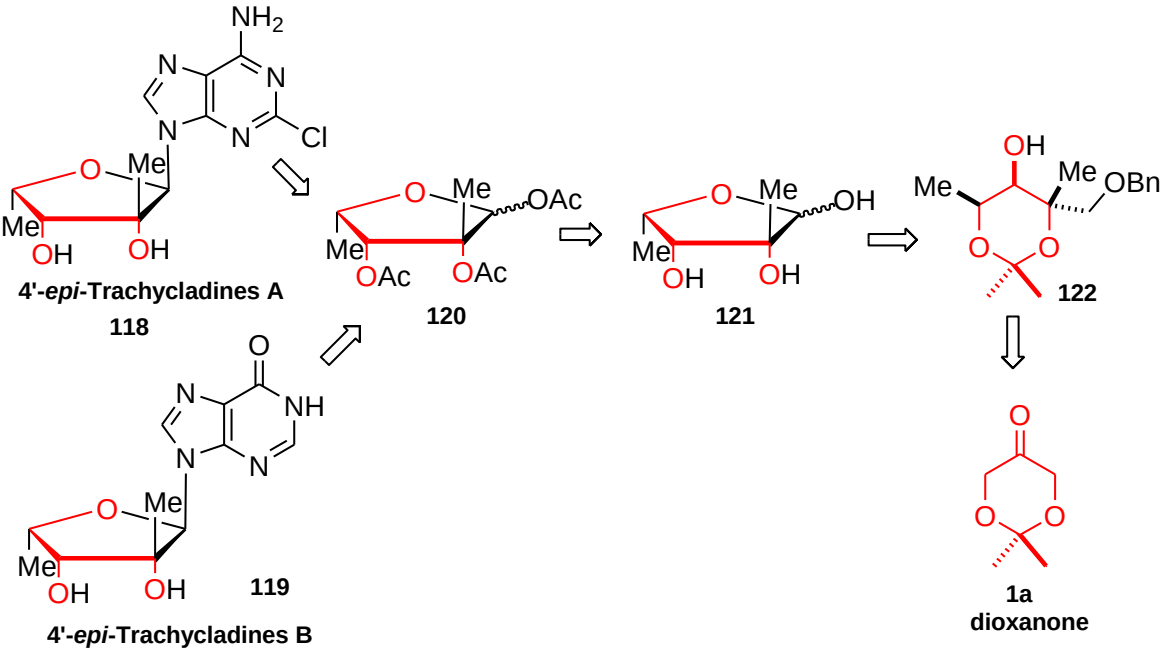
Reagents and conditions: (a) 1. RAMP, benzene, reflux; 2. t-BuLi, THF, -78 °C; 3. O_3, CH_2Cl_2, -78 °C; (b) 1. R_1MgBr, THF, -100 °C; (c) 3N HCl, MeOH, r.t.; (d) TBSOTf, Py, THF, 0 °C; (e) DIBAL-H, CH_2Cl_2, -78 °C; (f) Ac_2O, py, r.y.; (g) TMSSPh, $BF_3.OEt_2$, n-hexane, -95 °C to r.t; (h) bis-TMS-thymine, NBS, 4-°A MS, CH_2Cl_2, -78 to -26 °C.

Scheme 1.20: Synthesis of 4'-quaternary 2'-deoxy-3'-*epi*-β-N-nucleosides

Acid-catalyzed deketalization of **114** resulted in the triol intermediate which readily underwent trans-esterification to a five-membered lactone that was isolated as the disilylated lactone **115**. Now, depending on the reaction conditions, the lactone **115** could be converted into either C- or N-nucleosides. The bioactive thymidine-N-nucleoside **117** was synthesized via a sequence of DIBAL-mediated lactone reduction, and acetylation followed by NBS mediated silyl-Hilbert-Johnson reaction (Scheme 1.20).[73]

1.5.7 Synthesis of 4'-*epi*-Trachycladines A and B

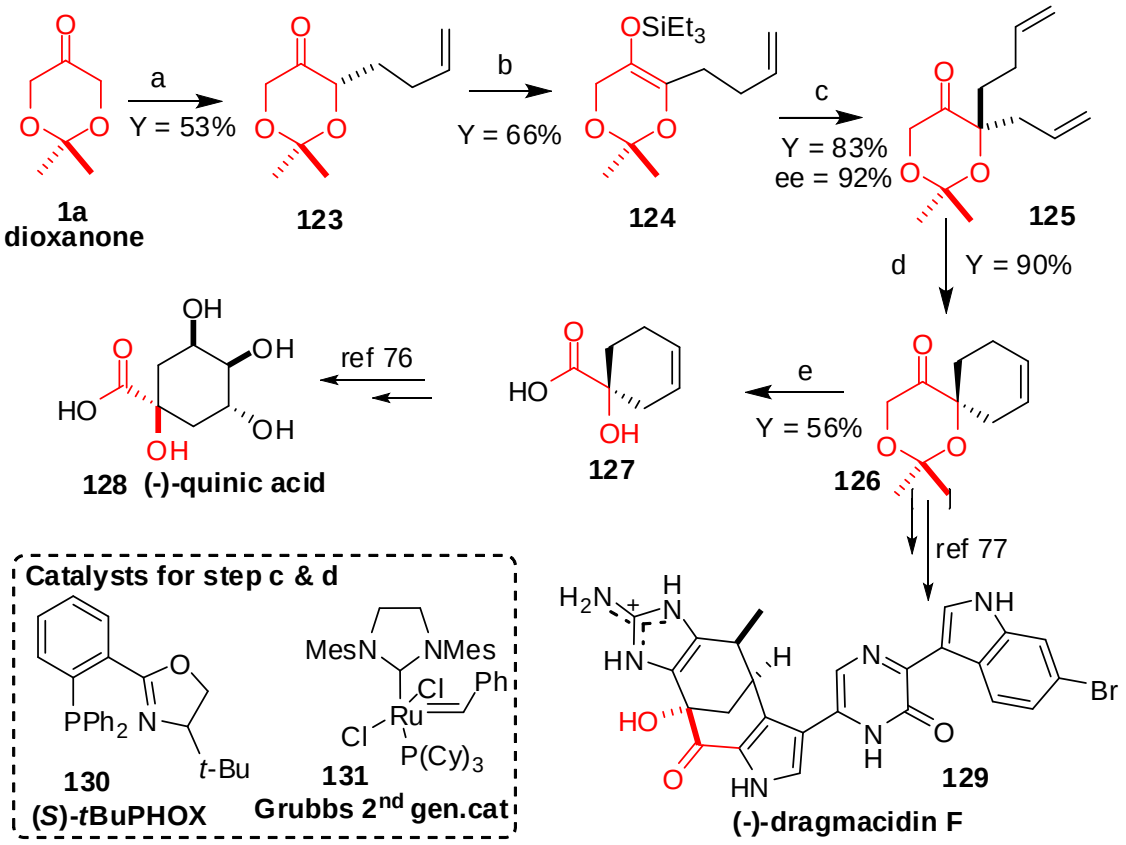
In similar fashion as described above, Enders realized the synthesis of two nucleosides 4'-*epi*-trachycladines A and B (**118** and **119**), using dioxanone methodology as illustrated in the reterosynthetic scheme below (Scheme 1.21). The formal synthesis was accomplished in 14 linear steps starting from the dioxanone scaffold with 20% overall yield. [74]



Scheme 1.21: Retrosynthetic route to 4'-*epi*-trachycladines A and B

1.5.8 Towards the Synthesis of (–)-Quinic acid and (–)-Dragmacidin F

Stoltz envisaged that the structure of the dioxanone scaffold (**1a**) can be embedded into carbocyclic (–)-quinic acid (**128**) and further into more complex molecules as (–)-dragmacidin F (**129**, Scheme 1.22).[75] As a part of the "proof of concept" Stoltz's group performed alkylation on dioxanone (**1a**) *via* Enders' SAMP-hydrazone methodology to obtain 1-butenyl dioxanone (**123**).



Reagents and conditions: (a) 1. SAMP, benzene, reflux; 2. t-BuLi, THF, -78 °C; 3. O_3, CH_2Cl_2, -78 °C; 4. 1-butenylbromide, THF, -100 °C; (b) TESCl, NEt_3, NaI, MeCN; (c) (*S*)-t-BuPHOX (5.5 mol%), $Pd(dmdba)_2$ (5 mol%), TBAT, Diallyl carbonate, PhMe, r.t.; (d) RCM by Grubbs second Gen. catalyst (2 mol%), CH_2Cl_2, 35 °C, 40h; (e) 1. $TsOH.H_2O$, MeOH; 2. H_5IO_6, THF/H_2O.

Scheme 1.22: Synthetic route towards the (–)-quinic acid and (–)-dragmacidin F

The corresponding silyl enol ether **124** was subjected to palladium-catalyzed enantioselective allylation conditions to deliver the demanding tetrasubstituted ketone diene **125** in high yields and selectivity. The α,ω-diene **125** was neatly transformed into spiroalkene **126** *via* ring-closing metathesis using Grubbs second generation catalyst **131**. Finally, cyclohexene compound **126** under acetonide hydrolysis followed by periodic oxidation produced the hydroxyacid **127** a crucial component in the formal syntheses of (–)-quinic acid (**128**)[76] and (–)-dragmacidin F (**129**).[77]

1.5.9 Synthesis of (+)-Polyoxamic acid

The Polyoxins **133** are a group of unusual peptidyl nucleosidic antibiotics isolated from the culture broths of *Streptomyces cacoi var. asoensis.*[78] (+)-Polyoxamic acid (**132**, Figure 1.7) is one of the chief structural components of the polyoxin compounds with carbamoylated polyoxamic acid linked to the sugar moiety by an amide bond.

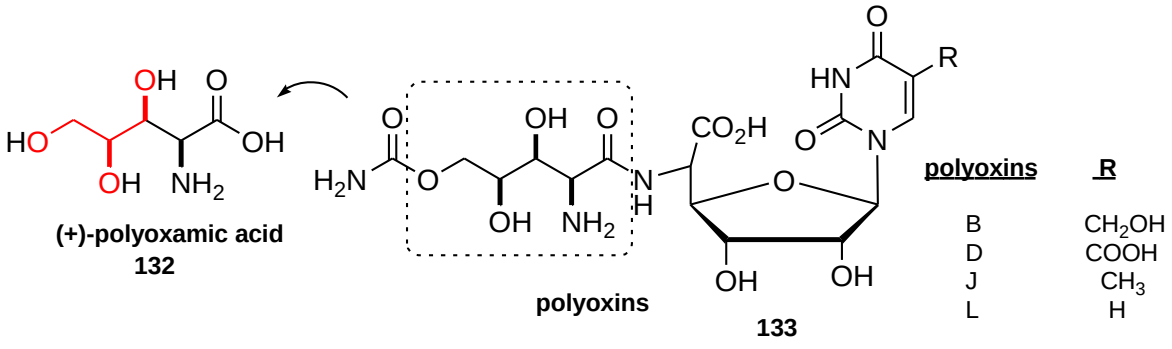
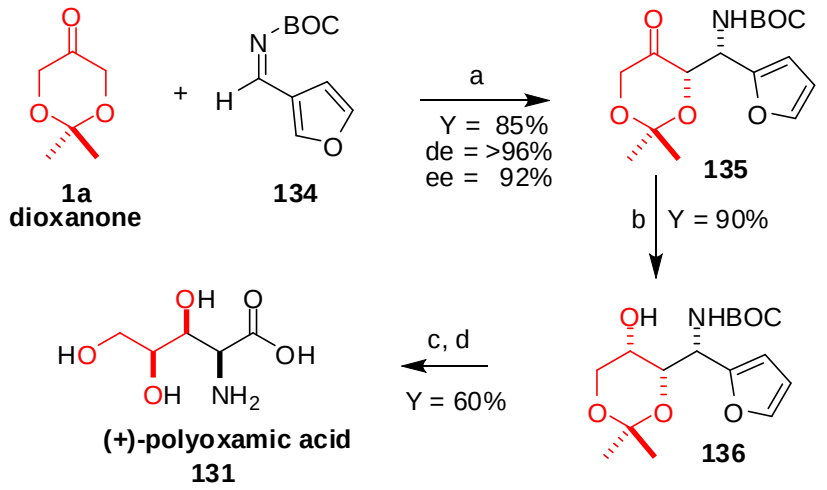


Figure 1.7: Structures of polyoxins and (+)-polyoxamic acid

Polyoxins are known to exhibit antifungal activity against *Candida albicans*, a fungal pathogen that affects humans.[79] The application in the field of medicinal chemistry have

led to the development of new synthetic methodologies towards polyoxamic acid and derivatives.[80]

Enders and Vrettou accomplished an elegant synthesis of (+)-polyoxamic acid (**131**) using an organocatalytic stereoselective Mannich methodology on the dioxanone scaffold (**1a**, Scheme 1.23).[81] The desired *syn* configurational Mannich base (**135**) was obtained from the (*S*)-proline catalyzed reaction of dioxanone with N-BOC furfural imine (**134**) in excellent selectivity and yields. L-Selectride-mediated diastereoselective reduction of the ketone in the Mannich base **135** resulted in the desired *syn* isomer of the corresponding aminoalcohol **136**. Subsequent oxidation of the furyl functionality was achieved by standard ozonolysis followed by aqueous TFA-mediated BOC and acetal groups removal to afford (+)-polyoxamic acid (**131**) in four steps in 46% overall yield.

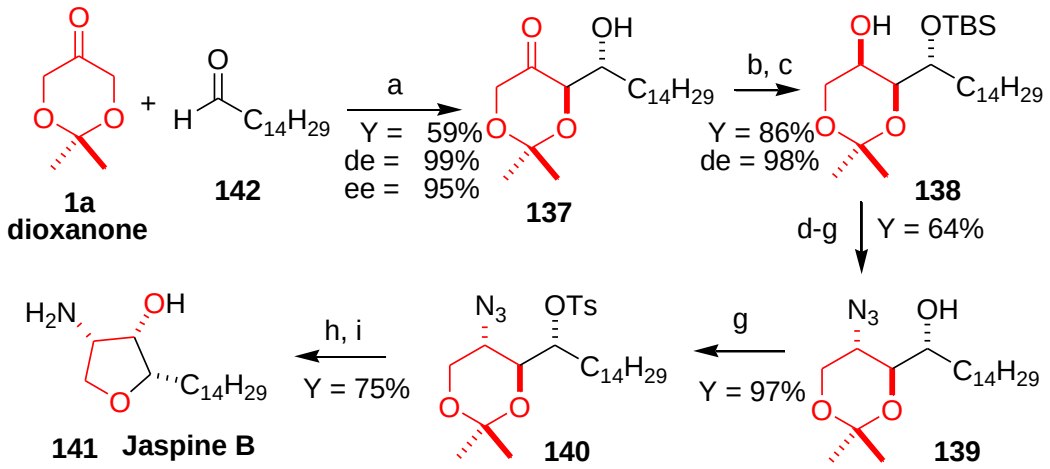


Reagents and conditions: (a) 10mol% (*S*)-proline, CF_3CH_2OH, 2 °C, 7days.
(b) L-selectride, THF, -78 °C, 5 h. (c) O_3, MeOH, -78 °C, 12h. (d) TFA-H_2O, r.t, 12h.

Scheme 1.23: Enders' synthesis of (+)-polyoxamic acid

1.5.10 Synthesis of Jaspine B (Pachatrissamine)

Jaspine B, also known as pachatrissamine (**141**) is a naturally occurring cyclic anhydrophytosphingosine derivative isolated from the Okinawan marine sponge *Pachastrissa sp*. as well as from *Jaspis sp*.[82,83] Jaspine B (**141**) exhibits significant cytotoxic activity against numerous tumor cell lines.[82]



Reagents and conditions: (a) (*R*)-proline 30mol%, $CHCl_3$, r.t., 4 days. (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, -20 °C, 2h. (c) L-selectride, THF, -78 °C, 2 h. (d) MsCl, DMAP, CH_2Cl_2, 0 °C to -10 °C, 15h. (e) NaN_3, 18-crown-6, DMF, 100 °C, 48 h. (f) TBAF, THF, 0 °C to r.t., 24 h. (g) TsCl, DMAP, CH_2Cl_2, 0 °C, 4h. (h) Amberlyst 15, THF, MeOH, 24 h. (i) H_2, Pd/C, MeOH, CH_2Cl_2, r.t., 8h.

Scheme 1.24: Ender's synthesis of (+)-Jaspine B

Enders' envisaged a proline-catalyzed aldol approach to access jaspine B (**141**) starting from the dioxanone scaffold (**1a**).[84] As shown in Scheme 1.24, the anti-aldol adduct **137** was obtained from (*R*)-proline-catalyzed aldol reaction of 2,2-dimethyldioxan-5-one (**1a**) with 1-pentadecanal (**142**). Next, standard silyl protection of the hydroxyl group followed by diastereoselective reduction of ketone with L-selectride gave the *Syn-anti*-configurated

alcohol (**138**) in good yields and selectivities. The free hydroxyl group of alcohol **138** was subjected to mesylation followed by treatment with sodium azide producing the azide, which, upon desilylation with TBAF afforded the *syn*-1,3-azidoalcohol compound **139**. Next, formation of the tosyl intermediate followed by Amberlyst 15 catalyzed deketalization triggered the intramolecular nucleophilic displacement reaction producing the azido tetrahydrofuran intermediate **140**. As the final step, reduction of the azide produced the target jaspine B (**141**) in 24% overall yield, after nine steps starting from the commercially available dioxanone scaffold (**1a**). [84]

1.6 Iminosugars

1.6.1 A short overview

Iminosugars are low molecular-weight polyhydroxylated alkaloidal monosaccharides with nitrogen atom in the place of the ring oxygen of the corresponding carbohydrates.[85] Nojirimycin (**144**, NJ) is a glucose analogue and naturally occurring iminosugar which was first described as an antibiotic compound produced from the bacterial cultures of *Steptomyces rosechromogenes* R-468 and *Streptomyces nojiriensis* SF-426 by Inouye and coworkers in 1966.[86] Since then hundreds of polyhydroxylated alkaloidal iminosugars have been isolated from plants and microorganisms. The natural and unnatural iminosugars are known to mimic the natural sugar moieties in biochemical processes and thereby are believed to modulate and block enzyme-mediated catalytic glycosylation processes.[87] For this reason, iminosugars are considered to have a high potential therapeutic value as antidiabetic drug candidates, antiviral and anti-infective agents or in lysosomal storage disease treatment.[88]

Based on the core structural skeleton, polyhydroxylated alkaloidal iminosugars are broadly classified into five classes: polyhydroxylated pyrrolidines, piperidines, indolizidines, pyrrolizidines and nortropanes.[89] Some of the examples of these structural classes of iminosugars are listed in Figure 1.8.

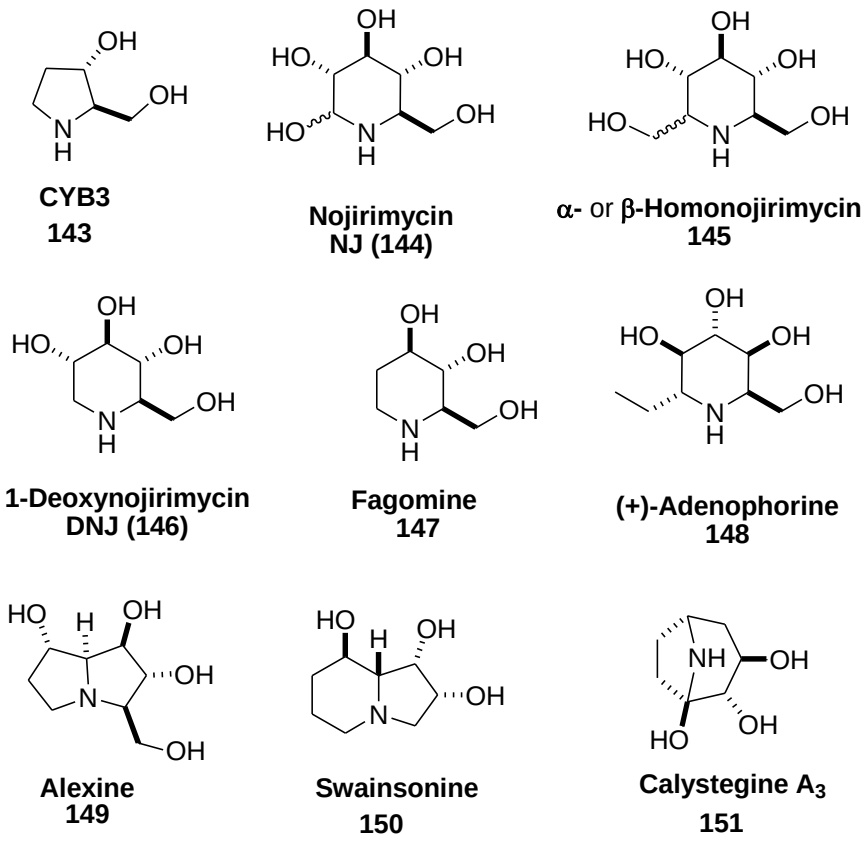


Figure 1.8: Selected examples for imino sugars

Nojirimycin (**144**), which is one of the best known representatives of iminosugars, was shown to be an inhibitor of both α- and β-glycosidases of various origins.[87] Another iminosugar, 1,4-imino-1,2,4-trideoxy-D-arabinitol (**143**, CYB 3), an analogue of 2-deoxyribose, can be found in the leaves and seeds of *Castanospermum austral*,[90] alexine (**149**) was isolated from *Alexa leiopetala*,[91a] swainsonine (**150**) an indolizidine iminosugar

was isolated from *Swainsona canescens*,[91b] calystegine A_3 (**151**) is present in the roots of *Lycium chinense*.[91c] 1-Deoxynojirimycin (**146**, DNJ) is one of the important members of the nojirimycin family and the simplest natural carbohydrate mimic. DNJ (**146**) is also known as 1,5-dideoxy-1,5-imino-D-glucitol or Moranoline.[92]

In recent years, these iminosugars have attracted synthetic community's attention as this class of compounds comprises some potent glycosidase inhibitors as well as candidates with promising drug profiles and wide-ranging biological activities.[93] DNJ (**146**), a glucosidase inhibitor, and *N*-butyl-deoxynojirimycin (**153**, Zavesca®) is an N-alkylated imino sugar which is a prescription drug for a mild to moderate type 1 Gaucher disease; as well it has shown to inhibit human immunodeficiency virus (HIV).[94] Compounds listed in Figure 1.9 represent a few of the many α- and β-glycosidase inhibitors, commercial drugs and candidates in clinical trials for treatment of diabetes, cancer, AIDS, viral infections and metabolic disorders. [95]

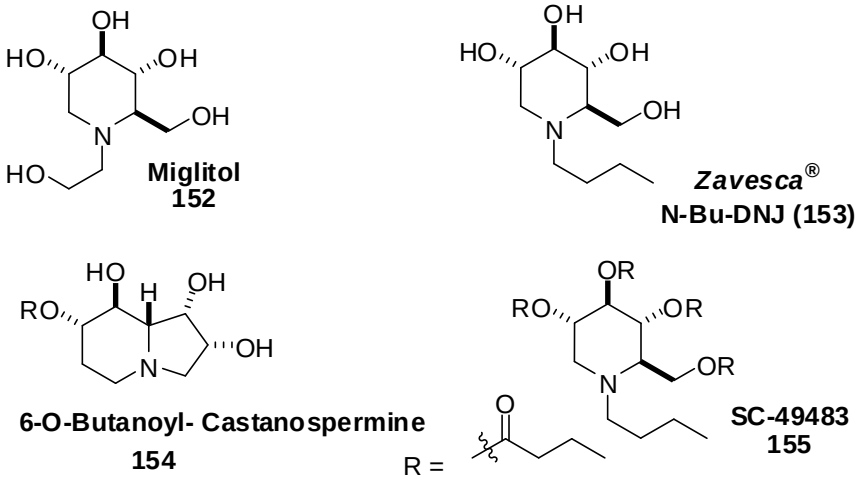


Figure 1.9: Commercial drugs and glycosidase inhibitors of iminosugar derivatives

1.6.2 Synthetic routes to iminosugars

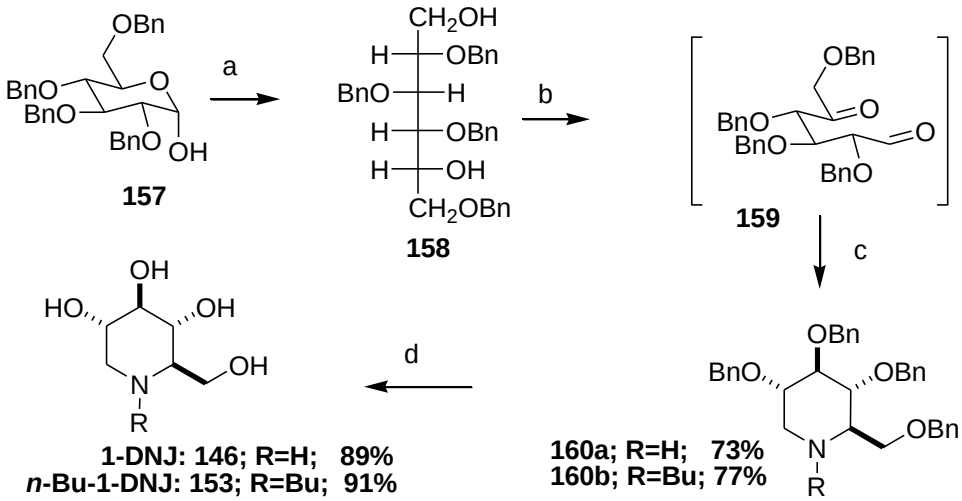
Due to these promising medicinal profiles, a large number of strategies have been developed for iminosugar synthesis. The general synthetic approaches to iminosugars and their derivatives can be broadly classified as follows:

a) Strategies involving readily available furanose and pyranose carbohydrate precursors[91-96]

b) Enzymatic approach mimicking the natural processes[97]

c) Strategies based on use of C_2-symmetrical diols and readily available diethyl L-tartrates to obtain the desired alkaloidal skeleton of the target iminosugars.[98]

1.6.2.1 Carbohydrate- based approach to iminosugars



Reagents and conditions: (a) $LiAlH_4$, THF, 100%; (b) DMSO, $(CF_3CO)_2O$, DCM, TEA (c) $RNH_3^+HCO_2^-$, $NaBH_4CN$, MeOH, Mol., sieve 3 ^oA; (d) Li, NH_3

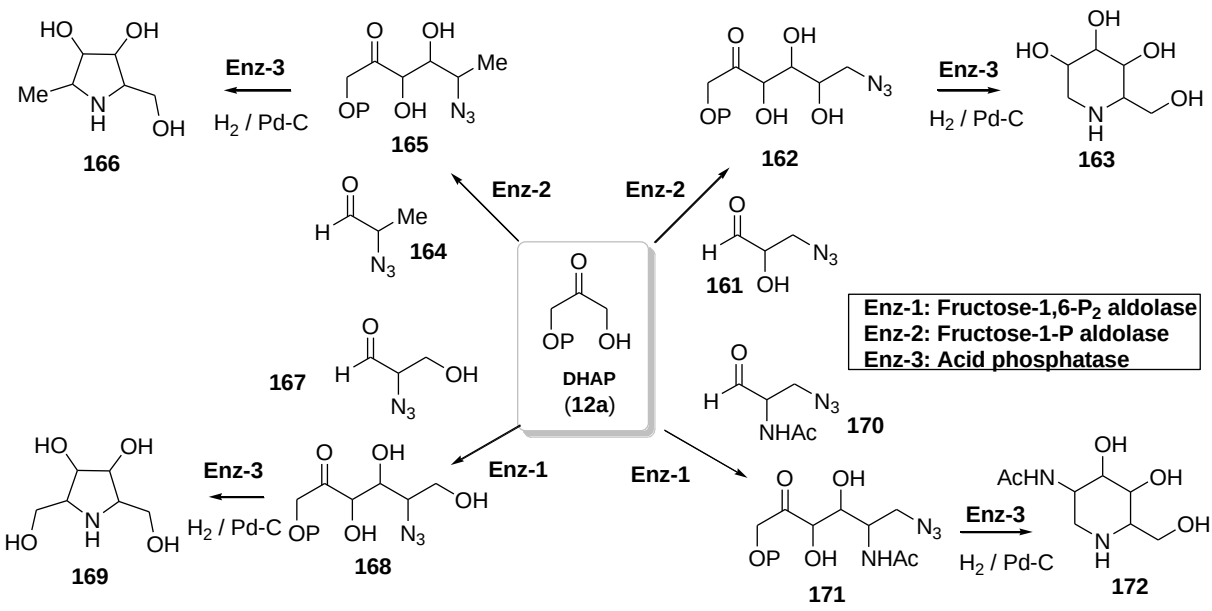
Scheme 1.25: Lopes approach to 1-DNJ and *n*-Bu-1-DNJ

As an example of the type-1 strategy, Lopes realized the synthesis of 1-deoxynojirimycin (**146**) and N-butyl-1-deoxynojirimycin (**153**) starting from inexpensive

2,3,4,6-tetra-O-benzyl-α-glucopyranose (**157**) via 1,5-dicarbonyl intermediate (**159**) being eventually transformed into 1-DNJ (**146**) and N-Bu-1-DNJ (**153**) in 65% and 70% overall yields respectively (Scheme 1.25).[96]

1.6.2.2 Enzymatic approach to iminosugars

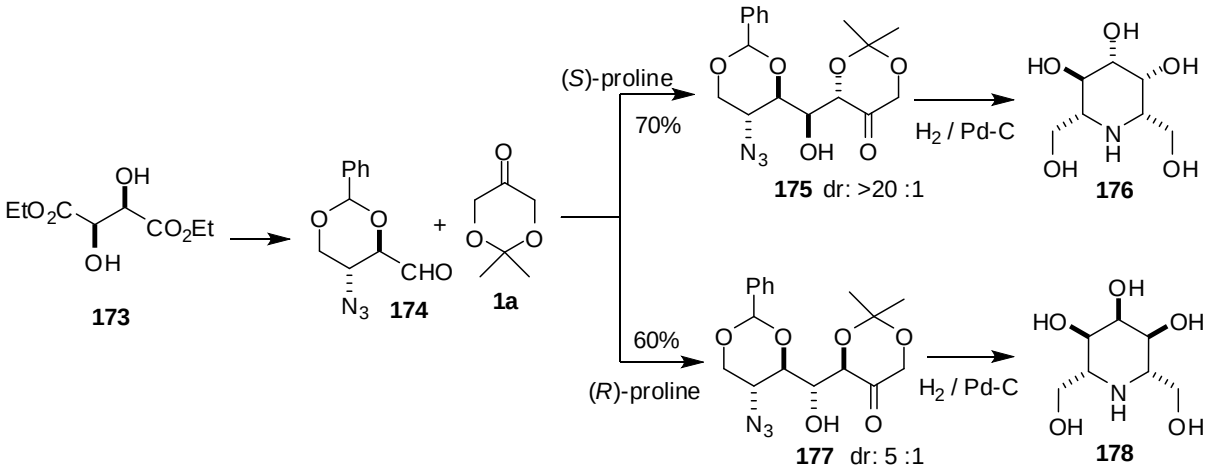
Chi-Huey Wong and coworkers[97] reported a general enzymatic approach to various iminosugars as shown in Scheme 1.26 starting from DHAP **12a** (example for type-2 stratergy). The scheme includes the combination of stereoselective enzymatic aldol reaction and reductive amination sequence to five- and six-membered iminocyclitols.



Scheme 1.26: Enzyme-catalyzed approach to iminosugars

1.6.2.3 Organocatalysis and tartrate approach

In 2006, Fernández-Mayoralas reported a double asymmetric induction on proline-catalyzed aldol reactions of dioxanone (**1a**) with α-azidoaldehyde **174** derived from diethyl tartrate (**173**) in the synthesis of homonojirimycin stereoisomers (Scheme 1.27).[99] Reaction of dioxanone **1a** with **174** under (*S*)-proline-catalyzed aldol addition reaction resulted in 1 : 20 diastereomeric mixture of aldol adduct **175** with 70 % yield. On the other hand, the similar reaction with (*R*)-proline produced **177** in 60% yields and mediocre dr of 1:5. This particular example uncovered a new asymmetric route to biologically active homomannojirimycin iminosugars.



Scheme 1.27: Double asymmetric induction and synthesis of homomannojirimycins

1.7 Higher Monosaccharides: A Short Review

1.7.1 Background and significance

Higher monosaccharides are commonly known as higher-carbon sugars. They are carbohydrate monosaccharides containing a backbone longer than the usual five or six carbon atoms.[100] Some of the examples of these class are heptoses, octoses, nonoses, decoses and beyond. Higher-carbon sugars have been found in Nature. Recently, they have been receiving greater attention due to their potential applications as antibiotics, structural components with wide-ranging biological functions. There are several review articles written on this topic.[101,102]

1.7.1.1 Heptoses and Octoses

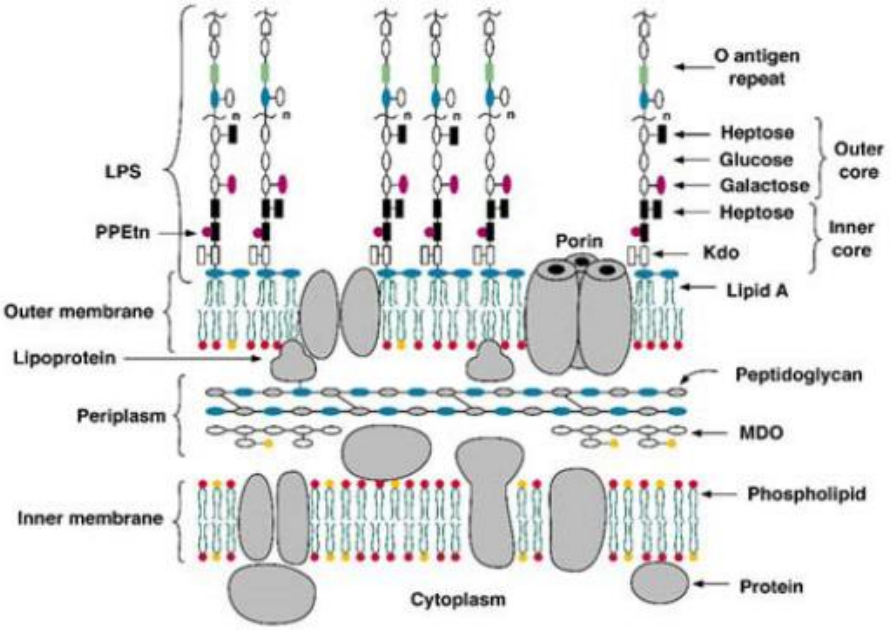


Figure 1.10: Schematic representation *E. coli* bacteria LPS with Kdo and heptoses[105] (Reproduced with permission of the publisher)

Aldo- and ketoheptoses are important classes of higher monosaccharides.[103,104] Naturally occurring aldoheptoses, deoxy-aldoheptoses (Figure 1.10) along with 3-*deoxy*-D-*manno*-*oct*-2-*ulosonic acid* (**185**, Kdo) are chief components of the antigenic endotoxins of

E. coli gram-negative bacteria lipopolysaccharides (LPS).[105] Aldoheptoses contain six consecutive stereogenic centers on the seven-carbon skeleton. From the 64 possible stereoisomers of aldoheptoses, only six have been found in LPS. L-*glycero*-D-*manno*-heptose (**179**) was one of the first aldoheptoses isolated from *Shigella flexneri* polysaccharide by Slein and Schnell,[106] but only meager amounts of these heptoses are available from natural sources. Low natural abundance and the immunological importance of the aldoheptose region of the LPS structure provoked considerable interest towards the development of new synthetic routes to obtain heptoses and their derivatives.[107,108]

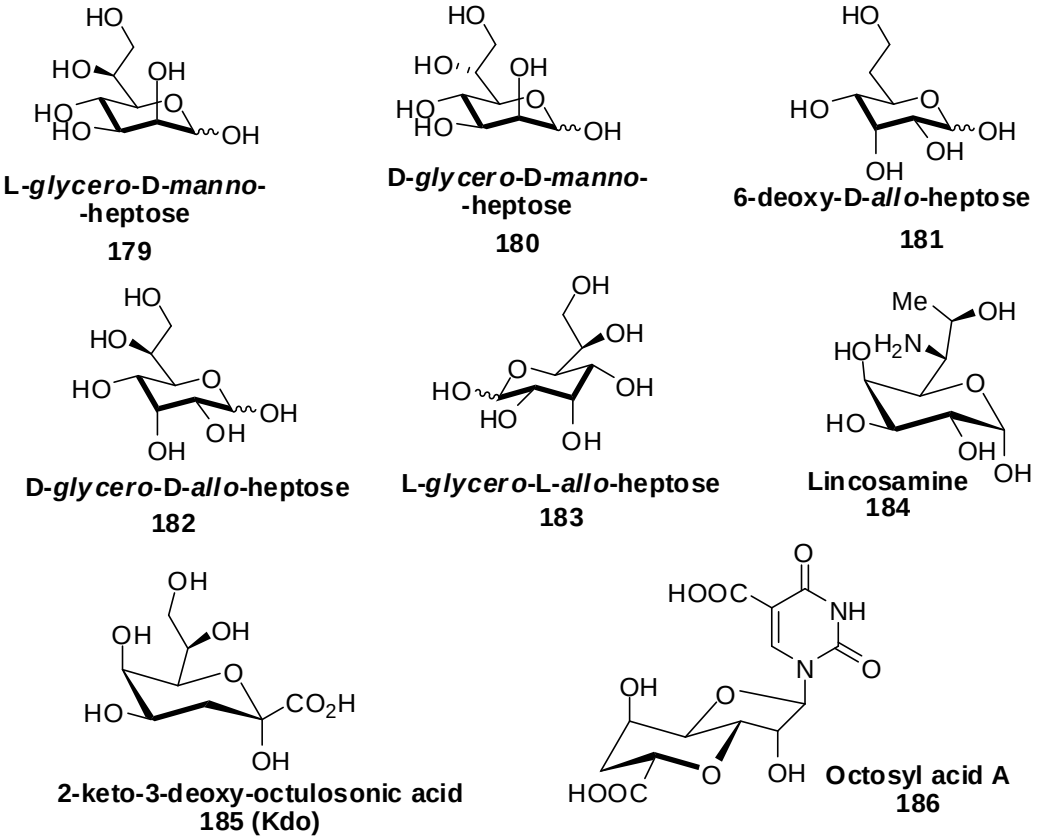


Figure 1.11: Heptoses and octoses compounds

Lincosamine (**184**), a eight carbon aminomonosaccharide and an important moiety of commercially available antibiotic lincomycin.[109] 3-Deoxy-D-manno-2-octulosonic acid

(Kdo, **185**) is one more octose component found on the cell wall lipopolysaccharides of Gram-negative bacteria,[105, 110] and octitol has been found in human eye lenses.[111] The naturally occurring nucleoside octosyl acid A (**186**) is an unusual eight-carbon bicyclic sugar. Its adenine analogue, which can be obtained by transglycosylation, was shown inhibit cyclic-AMP phosphodiesterase.[112]

1.7.1.2 Nine-carbon sugars and derivatives

The nine-carbon sialic acid, 3-deoxy-D-gycero-D-galacto-non-2-ulopyranosonic acid (Kdn, **187,** Figure 1.12) was isolated from polysialoglycoprotein of rainbow trout eggs and N-acetylneuraminic acid (**188**, NANA) plays an important role in the biological cell-to-cell recognition phenomena.[113] Calditol (**189**) is nonose structural component of complex lips of thermoacidophilic bacteria and amipurimycin (**190**) is a branched nine-carbon moiety of glycosyl amino acid core of a complex nucleoside.[114]

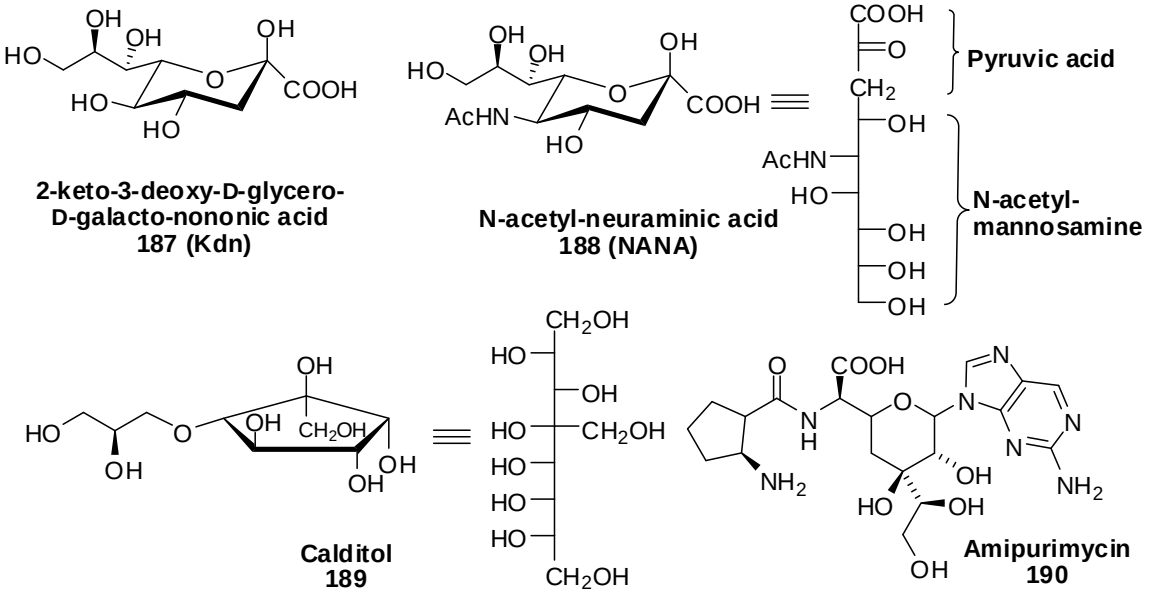


Figure 1.12: Examples for nine-carbon monosaccharides

1.7.1.3 Monosaccharides with ten or more carbon atoms in the skeleton

Monosaccharide derivatives having ten and higher carbon atoms in the carbon skeleton are rare in nature (Figure 1.13). Hikosamine (**192**) is a C_{11} complex higher-sugar component of the nucleoside antibiotic hikizimycin (**191**) which was found to be active against *Helminthosporium* and other plant-pathogenic fungal species.[115] An example of a eleven-carbon aminosugar is tunicamine (**193**), a chief component of antibiotic tunicamycin (**193**).[116]

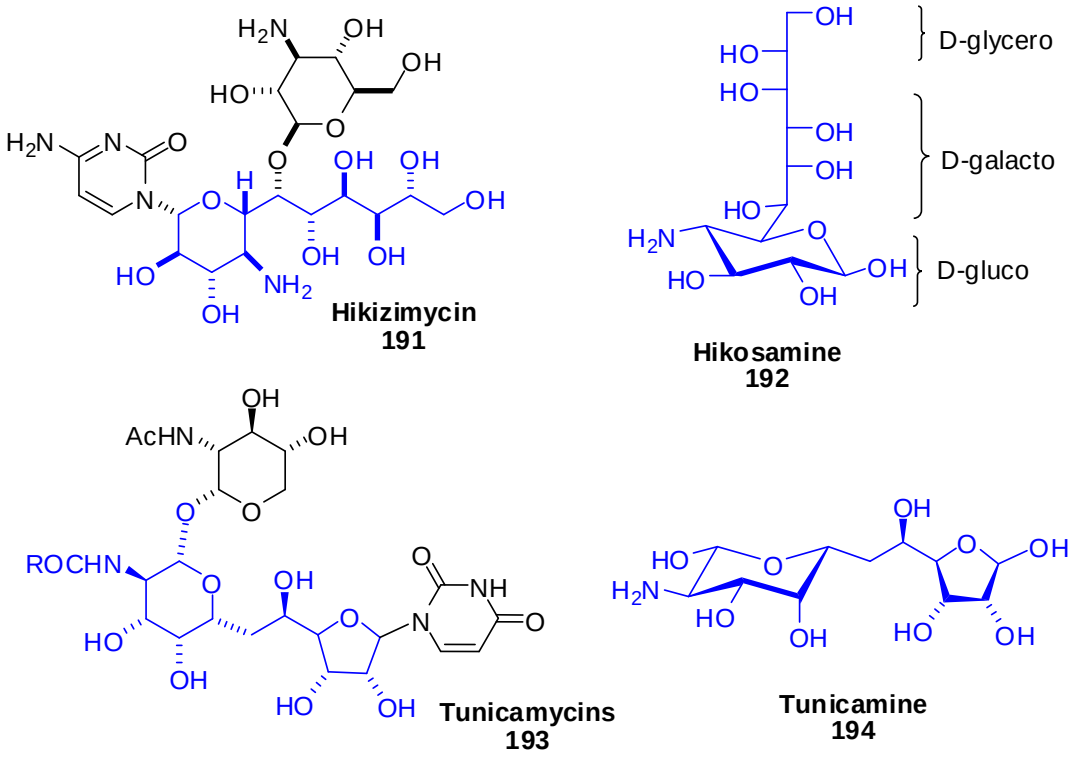


Figure 1.13: Examples for ten or more carbon monosaccharides

1.7.2 Synthetic methodologies for higher monosaccharides

A number of articles, reviews[101] and comprehensive chapters in books[102,103] addressed the biological significance and synthetic efforts towards higher monosaccharides and this section of the thesis aims to summarize briefly the synthetic methodologies prevalent in the literature.[100-119] The general synthetic procedures for obtaining higher-carbon sugars can be broadly classified into following strategies:

a) Classical approaches

b) Danishefsky's hetero-Diels-Alder approach

c) Dondoni's thiazole route

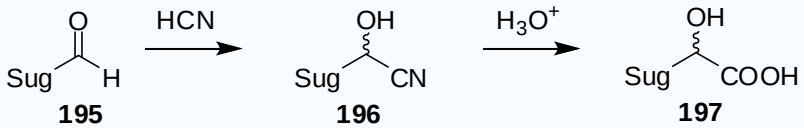
d) Jefford-Hanessian butenolide route

e) Vogel's homologation of 7-oxanorbornenyl

f) Jarosz's "Tail-to-Tail" Method

1.7.2.1 Classical approaches

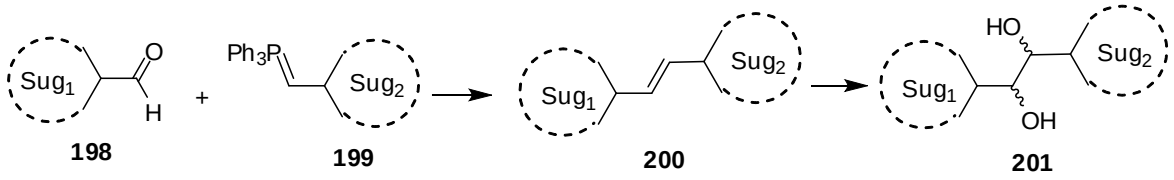
The first of the classical approaches to higher monosaccharides is the well known Kiliani-Fischer homologation of lower monosaccharides. Scheme 1.28 illustrates the general protocol for Kiliani-Fischer homologation.[120] The reaction proceeds via formation of a cyanohydrin intermediate **196**; subsequent hydrolysis produces two epimers of the corresponding aldonic acid **197** resulting in one-carbon chain elongation with intact stereochemistry of the starting monosaccharide (**195**).



195 **196** **197**

Scheme 1.28.

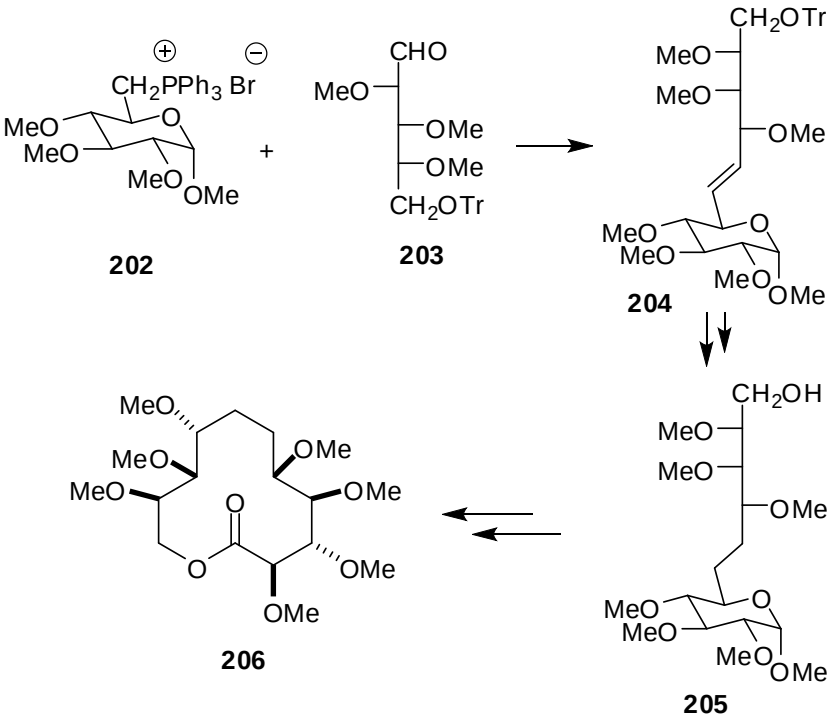
Another powerful elongation method to higher monsaccharides is by Wittig-Horner olefination reaction followed by stereoselective hydroxylation of the generated alkene bond.[101c] The general protocol for this method is shown in Scheme 1.29. The carbonyl functionality of the lower sugar is treated with the phosphorane derivative of another sugar to generate the corresponding olefin, subsequent stereoselective manipulation of the double bond results in the desired higher sugar.



Scheme 1.29.

Kibayashi *et al* explored Wittig-Horner olefination methodology in the synthesis of the powerful glycosidase inhibitor (+)-α-homonojirimycin (**176**).[121] Brimacombe and coworkers have used this approach to make some octoses, decoses and decitols.[101c] Secrist and Barnes demonstrated the usefulness of this method in the synthesis of the eleven-carbon hikosamine (**192**) core portion of the nucleoside antibiotic hikizimycin (**191**).[122]

In 2000, Miljkovic and Habash-Marino[123] expanded the Wittig-Horner olefination approach to the synthesis of a higher-carbon fragment **205** by coupling an aldose derivative **203** with a glycopyranosyl phosphorane (**202**) to yield the alkene intermediate **204**. In a sequence of steps with a crucial "double activated lactonization" of the open-chain intermediate of **205**, they produced the macrocyclic polyhydroxylated lactone **206** (Scheme 1.30).



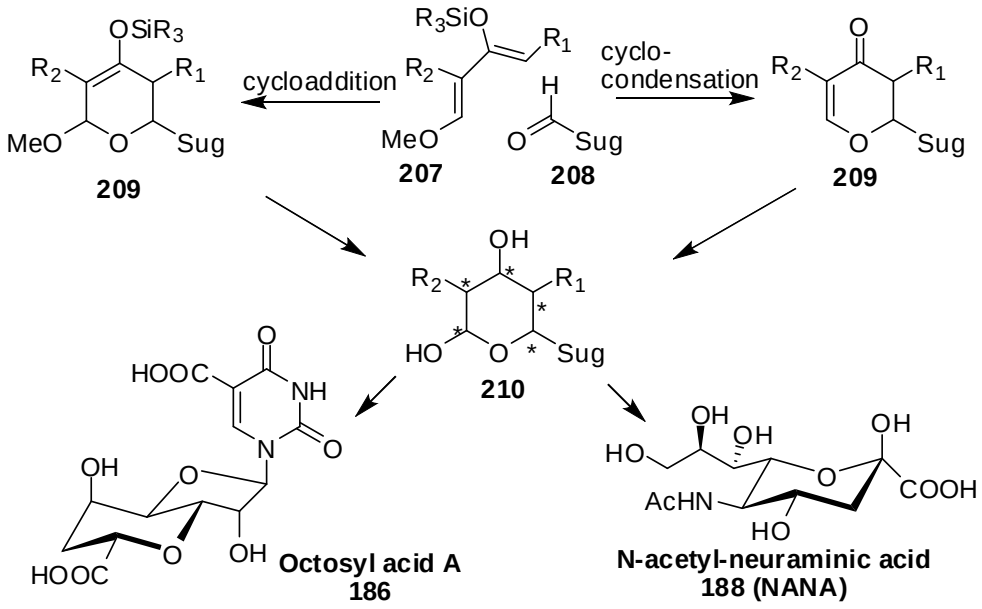
Scheme 1.30.

Other well-precedented methodologies to access higher monosaccharides are by aldol or nitroaldol condensation of chiral aldehydes with chiral ketone enolates[124] as well as nucleophilic additions using vinyl or allyltin reagents as "carbanion equivalents".[125] These methodologies are deliberately not covered in this section as they have been reviewed before.[101]

1.7.2.2 Danishefsky's hetero-Diels-Alder approach

Danishefsky's group has developed the Lewis acid catalyzed hetero-Diels-Alder cycloaddition of highly activated and functionalized siloxydienes (**207**) with sugar aldehydes (**208**) to produce the pyranoid intermediate **210**.[126] Highly oxygenated pyran rings proved to be instrumental in synthesis of numerous higher monosaccharides. As

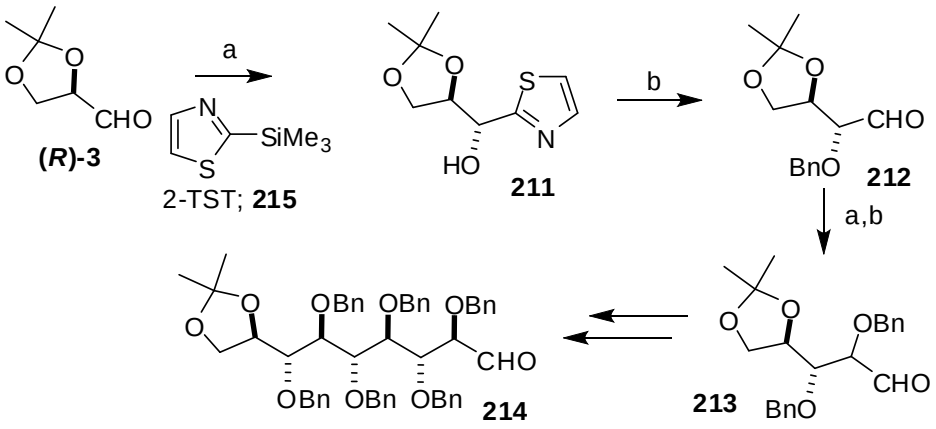
illustrated in Scheme 1.28, Danishefsky's method has been systematically exploited in realizing the total synthesis of octosylacid A (**186**), N-acetylneuraminic acid (**188**).



Scheme 1.31.

1.7.2.3 Dondoni's thiazole route

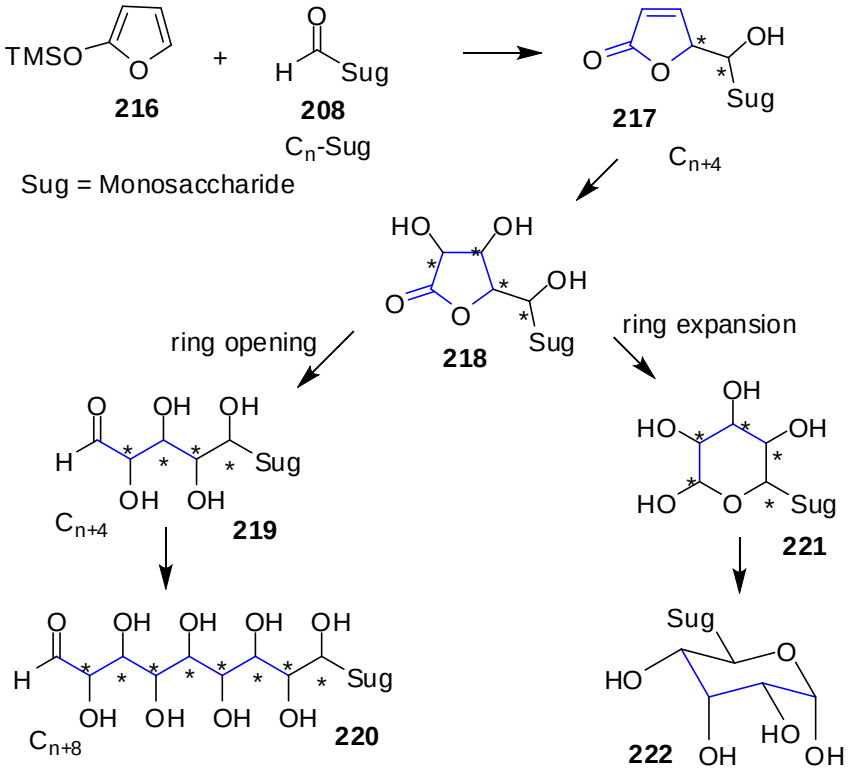
Dondoni and his colleagues developed a methodology which parallels Kiliani-Fischer[120] homologation technology. The thiazole route to higher monosaccharides starts with the formation of D-erythro-thiazole derivative **211** by 2-(trimethylsilyl)thiazole (**215**) addition to D-glyceraldehyde acetonide **(*R*)-3**. A one-pot sequence comprising the standard benzyl protection of **211** and methylation of the resulting thiazole intermediate was followed by an *in situ* reduction to thazoline, which, upon hydrolysis produced the desired aldehyde **212**. Further with repetition of this protocol produces heptoses, octoses, nanoses and higher monosacharides (Scheme 1.32). Dondoni's thiazole route has been used to synthesize various higher carbon sugars. [127]



Reagents & conditions: (a) 2-TST **215**, r.t.; (b) NaH, BnBr, then MeI,MeCN, reflux, then $NaBH_4$, MeOH, then $HgCl_2$, MeCN-H_2O.

Scheme: 1.32.

1.7.2.4 Jefford-Hanessian butenolide route

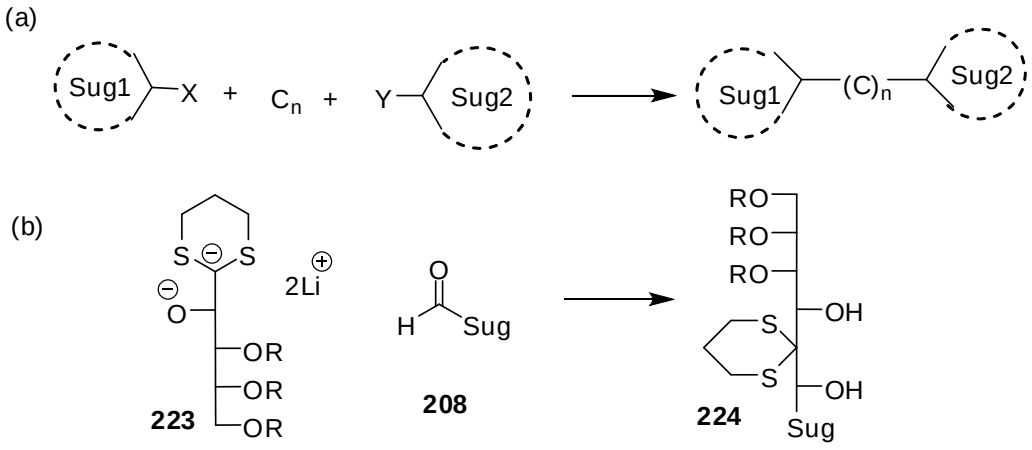


Scheme 1.33.

Butenolides are naturally occuring chiral γ-substituted α,β-unsaturated γ-butyrolactone subunits (**218**). Hanessian[128] and Jefford[129] independently explored γ-butyrolactone templates to higher carbohydrates via aldol-type condensation of 2-(trimethylsiloxy)-furan (**216**) with sugar aldehyde **208** to produce the butenolide intermediate **217,** which subsequently underwent hydroxylation to produce the butyrolactone template **218**. Depending on the type of reaction conditions, compound **218** could be rapidly converted into a higher monosaccharide architecture with a four carbon elongation to the starting sugar **208**. This approach was used in the synthesis of the D-allo-configuration of an 1-deoxynojirimycin homologue and several natural as well as unnatural higher monosaccharides.

1.7.2.5 Jarosz's "Tail-to-Tail" Method

Jarosz is one of the pioneers in synthesis of higher monosaccharides.[101b,101d] The Scheme 1.34 illustrates Jarosz's methodology of "tail-to-tail" coupling of simple monosaccharides to build on the monosaccharide architecture in rapid fashion.



Scheme 1.34.

Here, selectively protected forms of lower monosaccharides with activated "ends" i.e X and Y groups are connected via a C_n bridge sugar unit. For example, when activated carbanion **223** coupling with electrophile **208** results in corresponding skeleton of elongated higher carbon sugar **224**. Jarosz and coworkers have extensively used this approach to construct medium size higher carbon sugars, *i.e*, C_{12} to C_{15} as well as for C_{19} and C_{21} dialdose components. For complete review of "tail-to-tail" methodology, *cf.* references 101c and 101d.

1.8 Scope of Methodology Development

An increasing number of rare unusual higher monosaccharides have been discovered in nature which show promising biological properties and are also used as leads in drug discovery.[117] Their low natural abundance combined with potential biological activity has created a need for efficient synthetic methodologies to access these compounds. The multifunctional groups, presence of numerous stereogenic centers in addition to troublesome isolation of higher monosaccharides makes them interesting and challenging synthetic targets for organic chemists.

The majority of synthetic methodologies for higher monosaccharides, as discussed in section 1.7.2 of the thesis, relies on coupling or sequential homologation of abundant lower monosaccharides such as pentoses and hexoses.[120-130] Although these methods are straightforward they suffer from significant limitations such as side reactions and difficulty in isolation and purification of desired products from polar reaction mixtures.[118] Stereocontrolled aldol reactions play a pivotal role in synthesis of these complex chiral

molecules. Thorough searches of the literature revealed that very few higher monosaccharides were described, especially above nonoses.

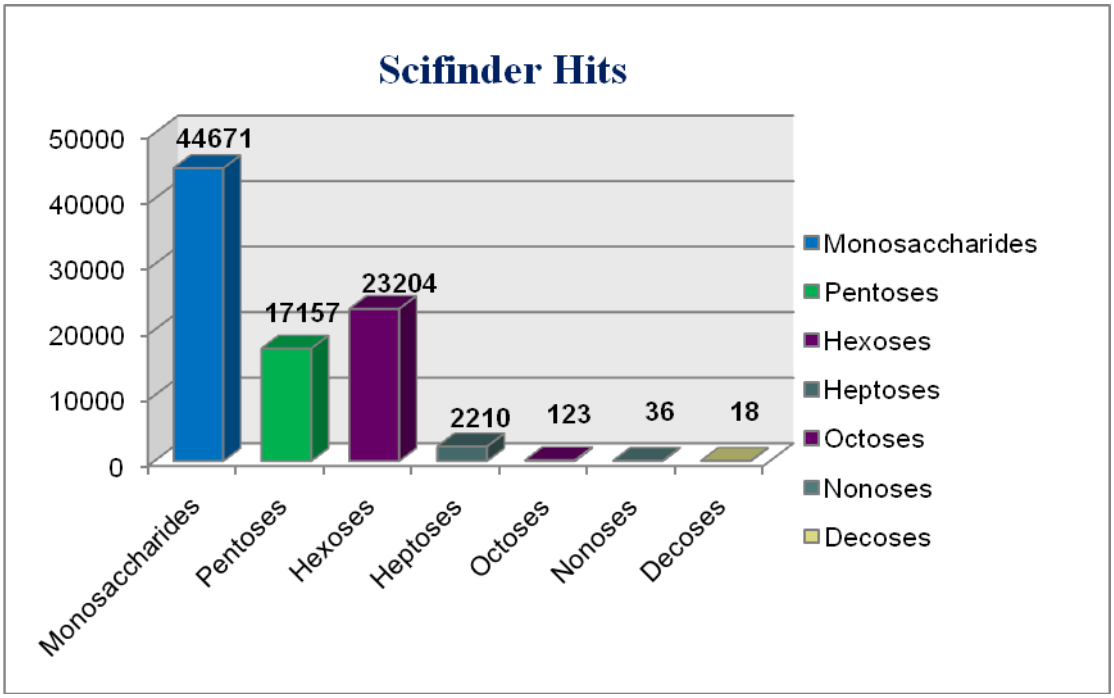


Figure 1.14 Number of SciFinder hits for different monosaccharides.

The SciFinder search illustrates (Figure 1.14) that 92% of the "monosaccharide-related" references concern pentoses and hexoses. The above picture showcases the need for developing simple but powerful synthetic methodologies to access these rare carbohydrates.

Note: The SciFinder search results presented in Figure 1.14 are obtained with the research topics 'monosaccharides and different classes of monosaccharides' as the root word search option. The above representation is an approximation of the number of references obtained through the SciFinder search carried out on 22nd February 2010. The primary objective was to illustrate the research scope for development of new synthetic methodologies towards the higher monosaccharide class of compounds.

1.9 Concluding Remarks

In the introduction chapter of the thesis, I have reviewed the concepts and chemistry related to the dioxanone scaffolds. Based on the literature information, the chemistry involving dioxanone scaffolds was broadly classified into four different methodologies as enantioselective deprotonation, hydrazone methodology, amidoacrolein methodology and asymmetric organocatalysis. The facts, limitations and synthetic applications of these approaches were summarized.

Following that, I have updated the literature with the latest review on dioxanone scaffolds in total synthesis of polyoxygenated natural products.

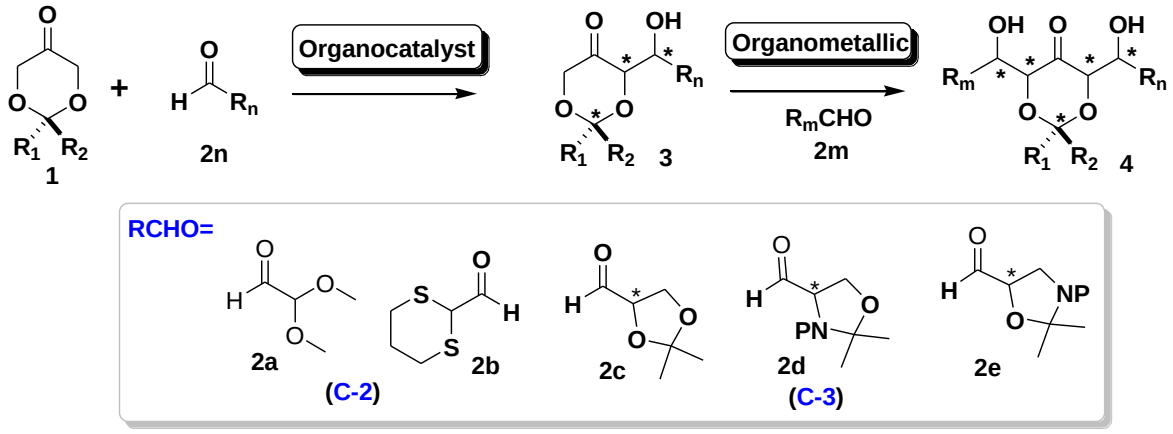
Recently, development of dioxanone based methodologies for the total synthesis of polyoxygenated natural products has been a growing area of research. Many different strategies have been developed; however, new methodologies applying more efficient and cost effective strategies are required. In particular, general methods that provides controlled access to any given stereoisomer.

This thesis work mainly deals with the development of generic synthetic route to iminosugars and higher monosaccharides. In view of the objective, I have presented the background and the significance of these compounds.

The question here was how can we envision dioxanone methodology towards the synthesis of higher monosaccharides and iminosugars? The next two chapters of the thesis are aimed at presenting results and efforts towards the development of versatile dioxanone based $C_m + C_3 + C_n$ methodology to obtain polyoxygenated natural compounds of value.

2 RESULTS AND DISCUSSION

As described in Chapter 1, dioxanones (**1**) were employed as scaffolds in synthesis of biologicaly important natural compounds. Our group has been one of the first to demonstrate the usefulness of dioxanones by developing a synthesis of (+)-frontalin (**81**) and lower monosaccharides.[11,15-17] Recently, Niewczas developed a strategy to bis-functionalized dioxanones generating four stereogenic centers in a sequence of two carbon-carbon bond forming aldol reactions (Scheme 2.1.).[12,18] The objectives of the current project included exploration of the complementary nature of organocatalytic, enamine-mediated and "organometallic", lithium-enolate mediated aldol reactions on dioxanone scaffolds, which is an ongoing research theme within the Majewski group.



Scheme 2.1.

Scheme 2.1 illustrates a generic strategy towards polyoxygenated natural products based on combining three fragments: a dioxanone (three carbon fragment, C3), and two different aldehydes (e.g. a two-carbon and a three-carbon fragment). Overall, this $C_m + C_3 + C_n$ dioxanone-based methodology was envisaged as a rapid entry into densely functionalized

chiral architectures (*cf.*, **4** in Scheme 2.1) often found in polyoxygenated natural compounds such as carbohydrates. This approach parallels Nature's aldol approach to carbohydrates. The relative ease of preparation of dioxanones and various aldehyde electrophiles from the commercially available material provide an additional advantage.

2.1 Research Objectives

The primary goal of the project was to apply dioxanone methodology to the synthesis of higher carbon sugars, iminosugars and polyoxygenated natural products. This project mainly deals with enantioselective aldol reactions of 2, 2-disubstituted-1,3-dioxan-5-ones , commonly known as dioxanones (**1**). Based on the available chemical information and limitations of dioxanone chemistry as discussed in Chapter 1, the following questions were asked at the initial stage of the project:

- Do steric and / or electronic effects of the acetonide component of dioxanones have a role in directing the diastero- and enantioselectivities of proline-catalyzed aldol reactions?
- Does the presence of mild-acid additives improve the stereoselectivity of proline-catalyzed aldol reaction of C_s-symmetrical dioxanones (different substitution at 2^{nd} position of dioxanone ring) as they do in C_2-symmetrical dioxanones?
- Can dioxanones be used as potential starting materials in the synthesis of higher carbon sugars and other poly-oxygenated natural products?
- Limitations in available electrophiles to derivatize dioxanones. Could the scope be broadened by developing methods for alkylation, formylation or acylation of dioxanones?

To answer those questions, the following research objectives were set:

- First, synthesize several C_s-symmetrical dioxanones with the desire to investigate stereoselectivity aspects of proline-catalyzed aldol reactions.
- Study the influence of additives on the proline-catalyzed aldol reaction.
- Investigate the stereocontrolled second aldol reactions on dioxanone scaffolds.
- Apply dioxanone-methodology in synthesis of higher carbon sugars, iminosugars and polyoxygenated natural products of value.

The project was initiated with methodological studies, primarily focusing on the proline-catalyzed aldol reaction. The broader outline of the project is shown in Figure 2.1.

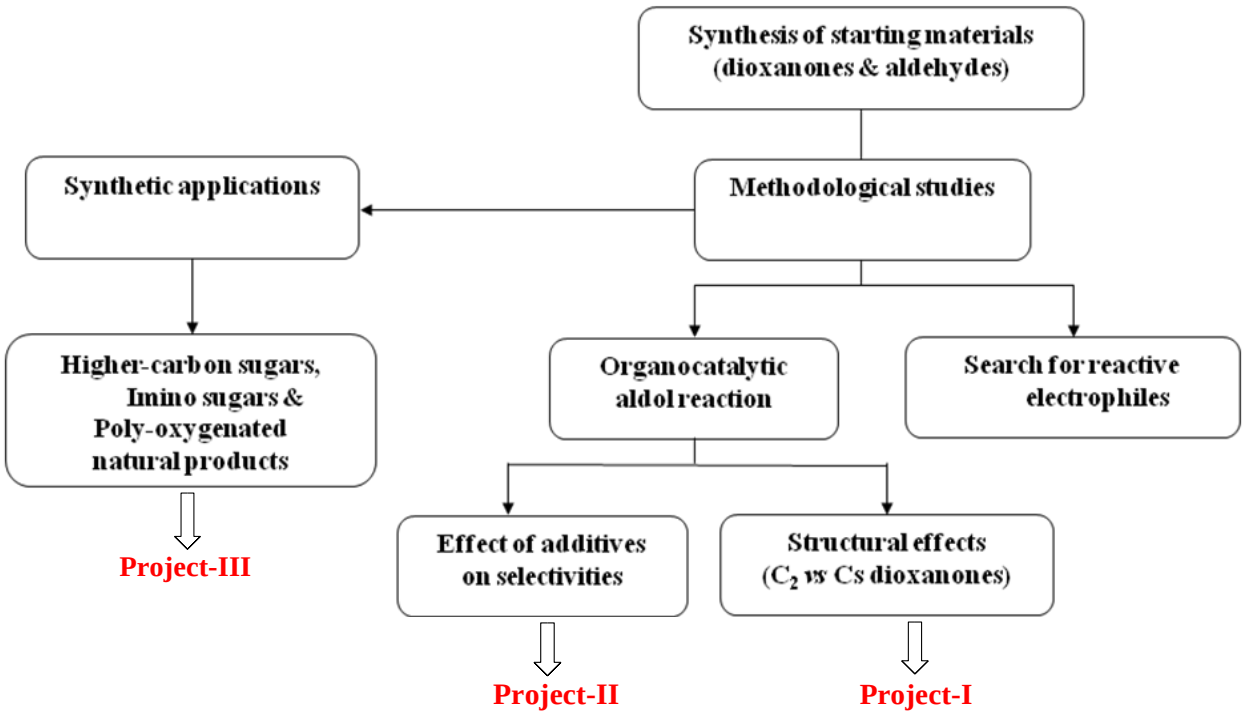


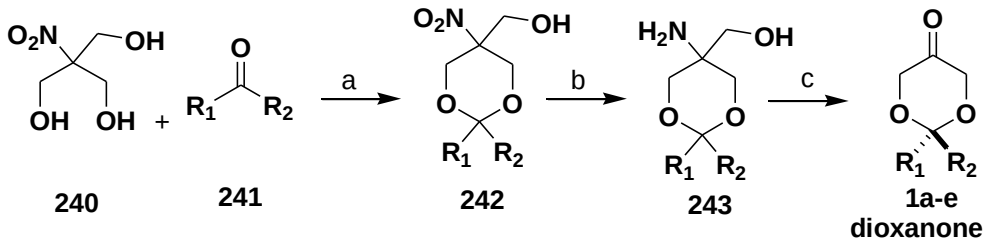
Figure 2.1 Project outline

2.2 Synthesis of 2,2-disubstituted-1,3-dioxan-5-ones

Any synthetic project starts with the synthesis of starting materials, scaffolds, and needed precursors. A practical scaffold is one that can be synthesized from cost-effective, readily-available starting materials and it should be easily scalable to large quantities. This project too began with synthesis of 2,2-disubstituted-1,3-dioxan-5-ones (**1**) based on the simple three-step procedure developed in our laboratory.[13] The symmetrically substituted dioxanones belong to C_{2v} point group of symmetry. The dioxanones which are differentially substituted at the 2nd position are achiral molecules that belong to C_S symmetry point group. Based on the mechanistic understanding the symmetry of dioxanone **1** might play a significant role in dictating the stereochemical outcome of asymmetric transformations on dioxanone substrate **1**.

To investigate the geometry, steric and / or electronic effects of the dioxanone ring on the diastero- and enantioselectivities of the corresponding proline-catalyzed direct aldol reactions, suitable starting materials are essential. The syntheses of dioxanones (**1a-e**) are carried out in accordance with the optimized synthetic procedures developed in our group by Mark Gleave[10] and Pawel Nowak.[11]

Scheme 2.1 illustrates the general synthetic protocol used with various dioxanone substrates. Standard ketalization of tris(hydroxymethyl)nitromethane (**240**) with a desired ketone **241** resulted in formation of the corresponding nitro compound **242** which, upon reduction under catalytic hydrogenation conditions (85 ºC, 1400 psi), produced the corresponding amine **243**. At this point, it was noticed that the same reaction could be carried out at ambient temperature and at reduced hydrogen pressure, *i.e.* from 1400 psi to 50 psi, without compromising the yields.



Reagents and conditions: (a) p-TsOH, benzene, reflux, 8-15 hr; (b) Raney-Nickel, H_2, MeOH, 4-12 hr; (c) $NaIO_4$, MeOH:H_2O (1:4), 0 ^oC ; 2 hr.

Scheme 2.2.

The final step in the sequence was sodium periodate oxidative cleavage of amine **243** that afforded the desired dioxanones (**1a-e**) in moderate yields. The ketone **241** with electron withdrawing groups (entry **1f**; CF_3) did not undergo initial ketal formation. A possible explanation for this observation could be that the reaction equilibrium lies towards the starting material due to strong electronic inductive effect of the CF_3 group. The three step procedure proved simple, economical and easy to scale up. The summary of yields of dioxanones (**1a-e**) is presented in Table 1.

Table 1: Summary of three step approach to dioxanones

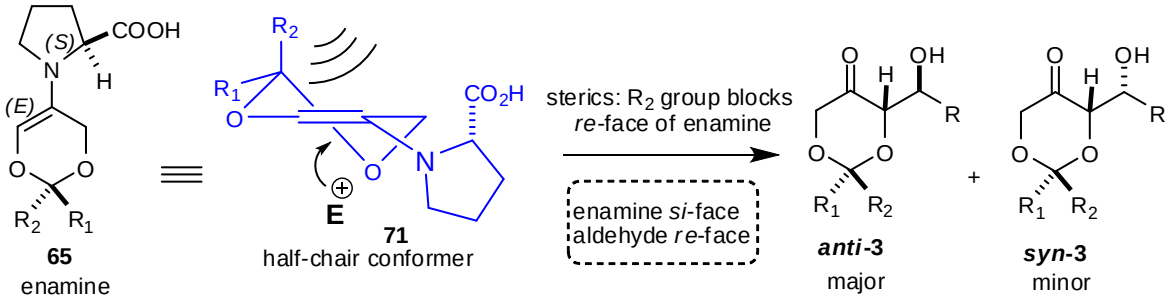
Dioxanone	**R_1**	**R_2**	**Dioxanone overall yield (%)**
1a	Me	Me	66
1b	*t*-Bu	Me	76
1c	Ph	Me	70
1d	Cyclohexanone		80
1e	*p*-CF_3Ph	Me	48
1f	Ph	CF_3	no reaction

2.3 Organocatalytic Aldol Reactions of C_2 - and C_S Symmetrical Dioxanones

The scope of proline-mediated asymmetric transformations on dioxanones was explored by various research groups.[8,9] In our group, Izabella Niewczas has screened a number of amino acids and esters as the catalysts for aldol reactions, but overall yields and selectivities were inferior compared to proline.[12] Initially, her attempts to perform proline-catalyzed aldol reactions on a simple dioxanone substrate **1a** met with difficulties such as formation of dimeric dendroketose (**24**) as shown in Scheme 1.3. Reactions carried out in dry solvents (DMSO or DMF) resulted in lower yields and inconsistent reproducibility.[132] During the same time, Enders group published reaction conditions for the proline-catalyzed aldol recation on dioxanone **1a** with benzaldehyde (**2f**, Scheme 2.4).[20] The reaction resulted in mediocre yields of aldol adduct 3 with low diastereo- and enantioselectivities (*cf*. entry 1, table 2). This particular example showcased the need for developing the methodologicaly to maneuver the reaction conditions to perform stereoselective aldol reactions on the dioxanone scaffold. It was decided to probe the influence of the geometry of dioxanone on the selectivity, as well as the influence of steric and electronic effects of the acetonide moiety on the diastero- and enantioselectivity of proline-catalyzed direct aldol reactions.

2.3.1 Hypothesis: Rationale to enhance selectivity from C_S-dioxanones

In 2000 our group reported that the diastereoselectivity of aldol addition of dioxanone lithium enolates to aldehydes was influenced by the size of the substituents R_1 and R_2 at the C-2 position of the dioxanone ring.[16] Here it was designed to explore the steric aspects of dioxanone run under organocatalytic conditions. An understanding of the mechanistic aspects of the proline-catalyzed aldol reaction involving dioxanones could be fundamental in development of the efficient aldol transformation. As discussed in Chapter 1 (*cf.* Figure 1.5 and also Scheme 2.3 below), the proline moiety in the enamine intermediate **65** acts as the chiral auxiliary in dictating the stereochemistry of the corresponding aldol adduct (**3**). In general, the *si*-face of the enamine (**65**) reacts with the *re*-face of the aldehyde to produce the *anti*-aldol adduct as the major product.

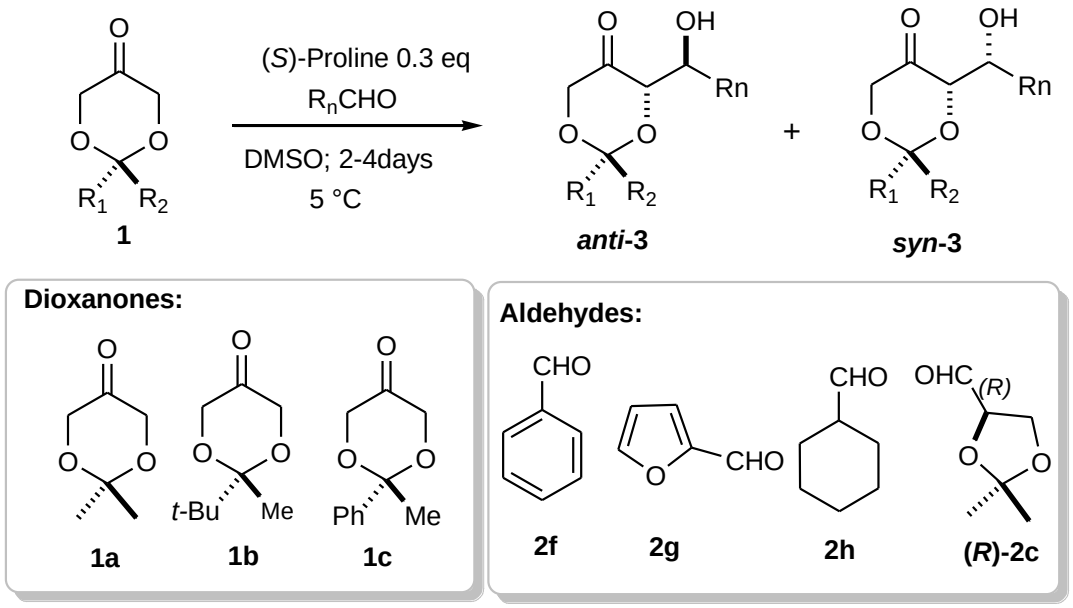


Scheme 2.3.

An interesting aspect of dioxanone chemistry is that the enamine **65** presumably exists in the half-chair conformation (**71**, Scheme 2.3). The presence of a bulky group (*e.g.* R_1 = *tert*-butyl) at C-2 position "locks" the conformer, placing the bulky group in the equatorial position. It was speculated that, depending on the nature of R_2 group in structure **71**, there might be a high probability of blocking the *re*-face of the enamine. This would increase the

prospect for electrophilic addition from the bottom *si*-face of the enamine resulting in higher diastereoselectivity.

2.3.2 Dioxanone structure and stereoselectivity of aldol reactions



Scheme 2.4.

Table 2: Structural effects of dioxanone on proline-catalyzed aldol reactions

Entry	Dioxanone (1eq)	Aldehyde (1.05 eq)	Isolated yield (%)	dr [a] (anti:syn)	er (anti)
1	**1a**	**2f**	54	67 : 33	84 : 16 [b]
2	**1b**	**2f**	65	94 : 06	80 : 20 [b]
3	**1c**	**2f**	72	98 : 02	82 : 18 [b]
4	**1a**	**2g**	21	60 : 40	-
5	**1b**	**2g**	30	95 : 05	84 : 16 [c]
6	**1a**	**2h**	27	62 : 38	70 : 30
7	**1b**	**2h**	61	85 : 15	77 : 23
8	**1a**	**2c**	54	90 : 10	-
9	**1b**	**2c**	46	84 : 16	-

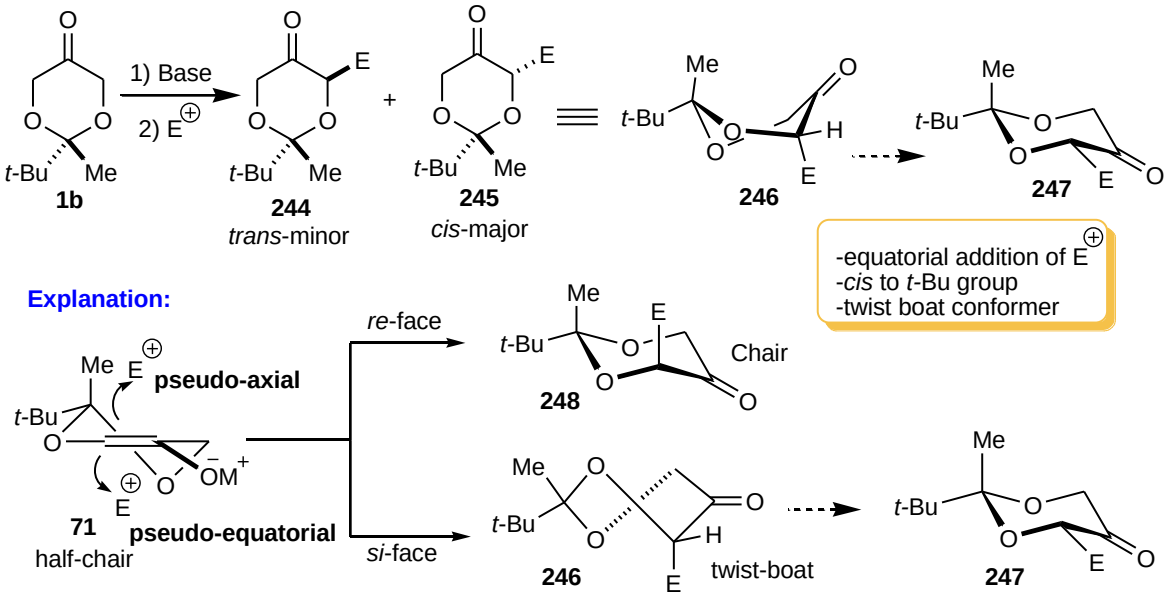
[a]- Determined by ^{1}H NMR of the crude product; [b]- enantiomeric excess for the anti product using Eu(hfc)$_3$ as the shift reagent; [c]- Determined by chiral-phase HPLC analysis on Chiralpak-IB column.

After initial screening for best solvent and other reaction conditions for proline-catalyzed aldol reaction, running the reaction at 5 ^{o}C using DMSO as the solvent proved to be the superior choice. The summary of results obtained from the study of dioxanone symmetry on diastereoselectivity of the (*S*)-proline-catalyzed aldol reactions is shown in Scheme 2.4 and Table 2.

In search for the best starting material four dioxanone substartes (**1a-d**, Scheme 2.4) were investigated. 2-*tert*-Butyl-2-methyl-1,3-dioxan-5-one (**1b**) has a plane of symmetry and belongs to the Cs symmetry point group. The (*S*)-proline catalyzed aldol reaction of achiral dioxanone **1b** with benzaldehyde (**2f**) resulted in the corresponding β-hydroxy ketone in 63% yield. During this transformation three new stereogenic centers were formed and eight stereoisomers were possible. Interestingly, this reaction proved to be highly diastereoselective in comparison with the similar reaction with a higher symmetry (C_{2v}) dimethyl dioxanone **1a** (*cf.* Table 2 entry 2 *vs* entry 1; de increased to 88% from 34%). Based on this initial result further screening was carried out on various dioxanone substrates (**1a-d**) and aldehydes (Table 2). The results from this study supported the initial hypothesis that the presence of a bulky group at C2 of the dioxanone indeed "locks" the conformation of the reactive enamine intermediate and the methyl group blocks the top face of the enamine thereby enhancing the stereoselectivities into synthetically useful range. Dioxanones **1c** did not offer significant advantages over compounds **1a** and **1b**, moreover the spectral data of the aldol adducts of the former compounds were much simpler to analyze.

2.3.3 Dioxanones: Unusual chemistry

Dixanones are deceptively simple heterocyclic ketones. As discussed in Section 1.3, the unusual electrophilicity of dioxanones and their reactivity resembles the aldehydes rather than ketones. Another anomaly related to dioxanone chemistry is the equatorial addition of electrophiles to the reactive dioxanone enamine or enolate intermediate. This observation is contrary to the well known Evans' model for stereochemical considerations of similar transformations on enolates of cyclic ketones such as cyclohexanone.[133] Attempts to rationalize this unusual phenomenon are shown in Scheme 2.5:



Scheme 2.5.

The *tert*-butyl group present in dioxanone **1b** was employed as a reference group for the explanation of the unusual electrophilic addition. In the above reaction, if the electrophilic addition onto the enolate or enamine of dioxanone **1b** occurs in *cis*-relation to the *tert*-butyl group that result in compound **245** as the major product. This approach leads to the

higher energy twist-boat conformation **246**, which then equilibrates to the chair conformar **247**. In contrast, Evans' analysis of similar reactions involving carbocyclic enolates requires that the electrophiles approaches from an "axial trajectory" which was explained by stereoelectronic effects thereby positioning the incoming electrophile and the *tert*-butyl group *trans* to each other as shown in structure **244**. This approach leads directly into the chair conformer of the product.

A plausible explanation for the "dioxanone anomaly" can be proposed based on analyzing the half-chair conformation of the reactive enolate or enamine intermediate **71**. The bulky *tert*-butyl at C-2 position locks the conformer placing methyl group in pseudoaxial position. If the electrophile approaches from the *re*-face of enamine (as commonly seen in simple cyclic enolates) then the half-chair enamine tends to evolve to a stable chair-like conformer **248**. If electrophilic addition occurs from the bottom *si*-face of the enamine, which eventually releases the half-chair conformer into a higher energy twist-boat conformation **246**.

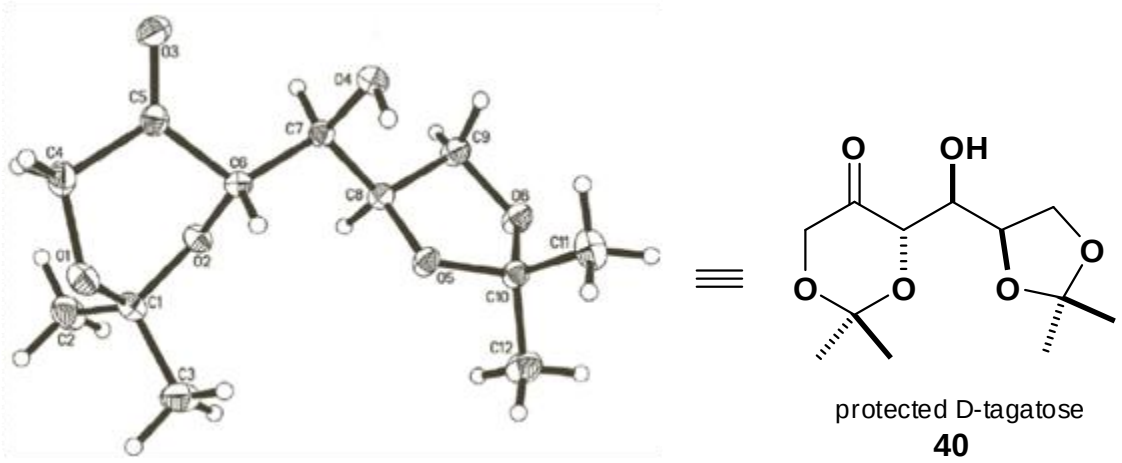


Figure 2.2 Crystal structure for protected D-tagatose[14] (Reproduced with permission of the publisher)

Examination of the literature for evidence of the existence of dioxanone derivatives in the twist-boat conformation revealed that Barbas and coworkers[14] published a crystal structure data for D-tagatose derivative **40** obtained from the proline-catalyzed aldol reaction of dioxanone and protected D-glyceraldehyde (**2c**). The crystal structure in Figure 2.2 clearly shows that the dioxanone moiety in this aldol adducts predominantly exists in the twist-boat conformation.

2.4 Effect of Additives on Organocatalytic Aldol Reactions of Dioxanones

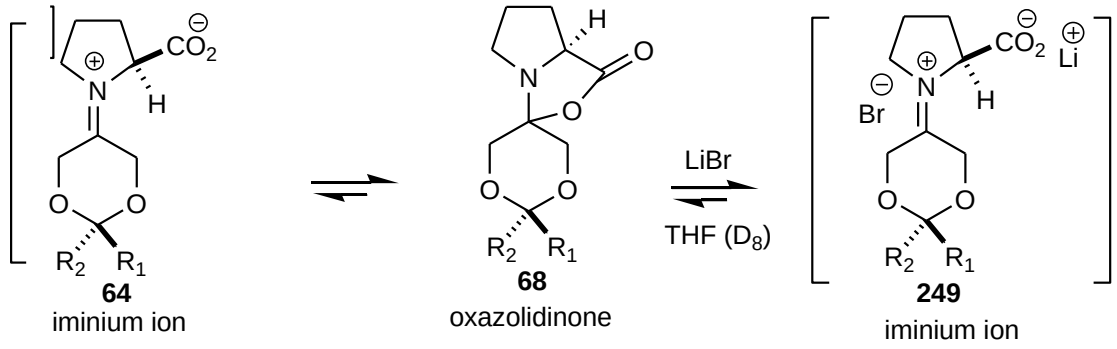
During the optimization of reaction conditions, Niewczas observed that the presence of mild additives such as lithium chloride (LiCl, a weak Lewis acid) and pyridinium-p-toluenesulfonate (PPTS, Brønsted acid) enhance the enantioselectivity of proline-catalyzed aldol reactions of C_2-symmetrical dioxanones **1a**.[12] Based on this information, I started to investigate the question whether mild acid additives have a similar effect on aldol transformations involving C_S-symmetrical dioxanone **1b**. In this context, a study was initiated to evaluate the effect of additives such as lithium halides, and also CsCl, $CeCl_3$, $ZnCl_3$, and $AlCl_3$ on proline-catalyzed aldol reactions.

2.4.1 Hypothesis

In 2004, List *et al.* reported the detection of oxazolidinone derivatives in the NMR based mechanistic studies on the proline-catalyzed aldol reaction of simpler ketones and aldehydes.[55] In that study it was inferred that iminium ions, as well as enamine and oxazolidinone species are involved in the catalytic cycle in which all steps are reversible. The stabilities of oxazolidinones are superior in comparison to their iminium or enamine

carboxylic acid isomers; this factor shifts the equilibrium towards the oxazolidinones. List reported that the formation of oxazolidinones in the proline-catalyzed aldol reaction is a "parasitic process" and reasoned it to be the cause for long reaction times and low yields often observed in this type of reactions. Later Seebach, a pioneer in oxazolidinone chemistry[134] expressed an alternative view on oxazolidinone species.[58] In a review article, he evaluated the relative stability of oxazolidinones towards non-aqueous acids and bases. It was observed that the stable oxazolidinone ring can be opened by stirring these compounds with mild Lewis acid such as LiBr-saturated solution of deuterated THF.

Upon extrapolation of these concepts to proline-catalyzed aldol reactions of dioxanones and based on initial observations made in our laboratory by Niewczas, the following rationale was proposed (Scheme 2.6):

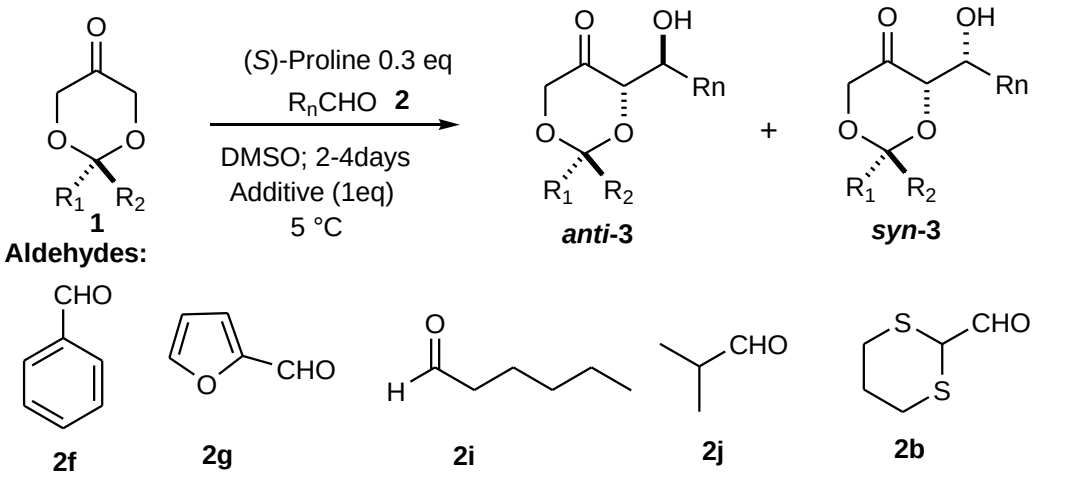


Scheme 2.6.

The iminium intermediate **64** in the dioxanone-proline catalytic cycle can equilibrate to the corresponding enamine or to the more stable oxazolidinone **68**. The reactions carried out in the presence of lithium halide salts are expected to have the equilibrium shifted towards double salt iminium intermediate **249** which can readily tautomerize to the corresponding chiral enamine, a reactive species in the catalytic cycle.

Pihko and his colleagues observed that water as an additive proved to be beneficial to stereoselectivities in numerous reactions,[135] indicating that the deliberate addition of water has positive effect on the stereoselectivity of the proline-catalyzed aldol reactions.

2.4.2 Effect of additives on the selectivity of proline-catalyzed aldol reactions



Scheme 2.7.

The following section elaborates on the effect of additives on proline-catalyzed aldol reactions of dioxanone substrates. After securing the initial results from the previous project, I screened various aldehydes in proline catalyzed aldol reaction of 2,2-disubstituted-1,3-dioxan-5-ones in the presence of different additives as shown in Scheme 2.7. The summary of the results obtained in this study is shown in Table 3.

Table 3: Effect of additives on proline-catalyzed aldol reactions of dioxanones

Entry	Dioxanone		Aldehyde (1eq)	Additive (1eq)	Isolated yield (%)	dr [a] (anti : syn)	er (anti)
	R_1	R_2					
1	Me	Me	**2f**	-	54	67 : 33	84 : 16 [b]
2	*t*-Bu	Me	**2f**	-	63	94 : 06	80 : 20 [b]
3	*t*-Bu	Me	**2f**	LiCl	72	98 : 02	84 : 16 [b]
4	*t*-Bu	t-Bu	**2f**	PPTS (0.3eq)	71	95 : 05	92 : 08 [b]
5	Me	Me	**2g**	-	21	60 : 40	-
6	Me	Me	**2g**	LiCl	33	75 : 25	-
7	*t*-Bu	Me	**2g**	-	30	95 : 05	84 : 16 [c]
8	*t*-Bu	Me	**2g**	LiCl	37	97 : 03	88 : 12 [c]
9*	*t*-Bu	Me	**2g**	-	32	92 : 08	44 : 56 [c]
10	Me	Me	**2i**	-	18	67 : 33	-
11	Me	Me	**2i**	LiCl	28	88 : 12	-
12	*t*-Bu	Me	**2i**	-	30	90 : 10	-
13	*t*-Bu	Me	**2i**	LiCl	44	94 : 06	-
14	*t*-Bu	Me	**2j**	-	65	98 : 02	88 : 12 [d]
15	*t*-Bu	Me	**2j**	LiCl	71	98 : 02	98 : 02 [d]
16	*t*-Bu	Me	**2j**	PPTS	61	98 : 02	96 : 04 [d]
17	*t*-Bu	Me	**2j**	$ZnCl_2$	46	98 : 02	86 : 14 [d]
18*	*t*-Bu	Me	**2j**	-	54	98 : 02	52 : 48 [d]
19	CHX		**2b**	-	72	98 : 02	82 : 18 [b]
20	CHX		**2b**	PPTS	85	98 : 02	91 : 09 [b]
21	CHX		**2b**	PPTS (0.3 eq)	88	98 : 02	92 : 08 [b]
22	CHX		**2b**	LiCl	86	98 : 02	96 : 04 [b]

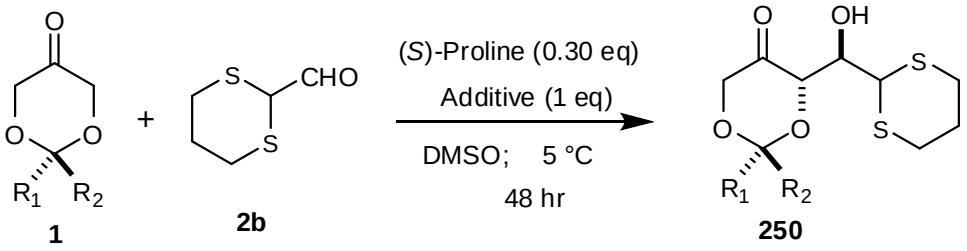
[a] Determined by ^{1}H NMR of the crude product; **[b]** enantiomeric excess for the anti product using $Eu(hfc)_3$ as the shift reagent: **[c]** Reaction time 72 hr & er determined by chiral-phase HPLC analysis on Chiralpak-IB column. **[d]** measured by HPLC using Chiralpak-AD column on the 3,5-dinitrobenzoate derivative. ***** aldol reaction using DL-Proline to get a racemic sample for comparison. CHX= cyclohexanone derivative

Reactions with out additives (Table 3, entry 2) proceeded with the diastereoselectivity (*anti* : *syn*) of 94 : 06 and the enantiomer ratio of 80 : 20 (absolute stereochemistry of the major product was as drawn in Scheme 2.7 for stereochemical assignments *cf.* page 120). Note that a similar transformation carried out by Niewczas, using the symmetrical 2,2-dimethyl-1,3-dioxan-5-one (**1a**, entry 1) resulted in the aldol adduct having low d.r. (67 : 33) and similar ee. Thus, switching from dioxanone **1a** to **1b** substantially improved diastereoselectivity (de change of 34% to 88%). In most of the proline-catalyzed aldol reactions of dioxanones, addition of equimolar amounts of Brønsted acid *p*-toluenesulphonate (PPTS) or lithium chloride proceeded with higher enantioselectivities and better yields in comparison with the reactions carried without those additives (*cf*. entries 2 *vs* 4; 14 *vs* 15; and 19 with 22).

Although an array of additives was screened, I have limited to the experiments that showed some distinctive effect on the selectivity. In general, the selectivities of reactions involving aliphatic aldehydes proved to be higher than reactions involving the aromatic aldehydes, which is a general trend in organocatalysis. The enantiomeric excess values for aliphatic aldol products without any chromophores (entries 14 to 18), were measured by chiral-phase HPLC analysis of the corresponding 3,5-dinitrobenzoate derivatives.

Based on the preliminary work carried out by Niewczas and through the focused methodological studies discussed in the previous sections, we were in possession of a set of reaction conditions for the proline-catalyzed 'first aldol' (*cf.* Scheme 2.1) reactions on dioxanones that looked promising for use in synthesis of polyoxygenated natural products.

2.4.3 Enantiomeric excess measurement by HPLC and NMR methods



Scheme 2.8.

Table 4: Validation of enantiomeric excess by HPLC and NMR techniques

S.No	R_1	R_2	Additive	Yield % (column purified)	dr (^{1}H NMR of crude) anti : syn	er anti product (using $Eu(hfc)_3$ as a shift reagent)	HPLC measurements	
							RT (minutes)	er [a]
1	Me	Me	-	96	98 : 02	77 : 23 ± 2	47.2 : 51.6	81 : 19
2	Me	Me	LiCl	92	98 : 02	97 : 03	47.8 : 52.4	98 : 02
3	*t*-Bu	Me	-	74	98 : 02	24 : 76	31.7 : 35.7	22 : 78
4	*t*-Bu	Me	PPTs	81	98 : 02	11 : 89	31.5 : 35.6	15 : 85
5	*t*-Bu	Me	LiCl	84	98 : 02	09 : 91 ± 1	31.7 : 35.9	11 : 89
6	*t*-Bu	Me	LiF	68	98 : 02	17 : 83	32.0 : 36.2	18 : 82
7	*t*-Bu	Me	LiBr	71	98 : 02	23 : 77	32.1 : 36.4	20 : 80
8	*t*-Bu	Me	LiI	64	98 : 02	17 : 83	31.9 : 36.0	19 : 81
9	*t*-Bu	Me	CsCl	78	98 : 02	19 :81	31.9 : 35.9	20 : 80
10	*t*-Bu	Me	$CeCl_3$	76	98 : 02	11 : 89	31.8 : 35.9	15 : 85
11	*t*-Bu	Me	$ZnCl_2$	53	98 : 02	23 : 77	31.3 : 35.6	21 : 79
12*	*t*-Bu	Me	-	73	98 : 02	52 : 48	30.8 : 34.9	51 : 49

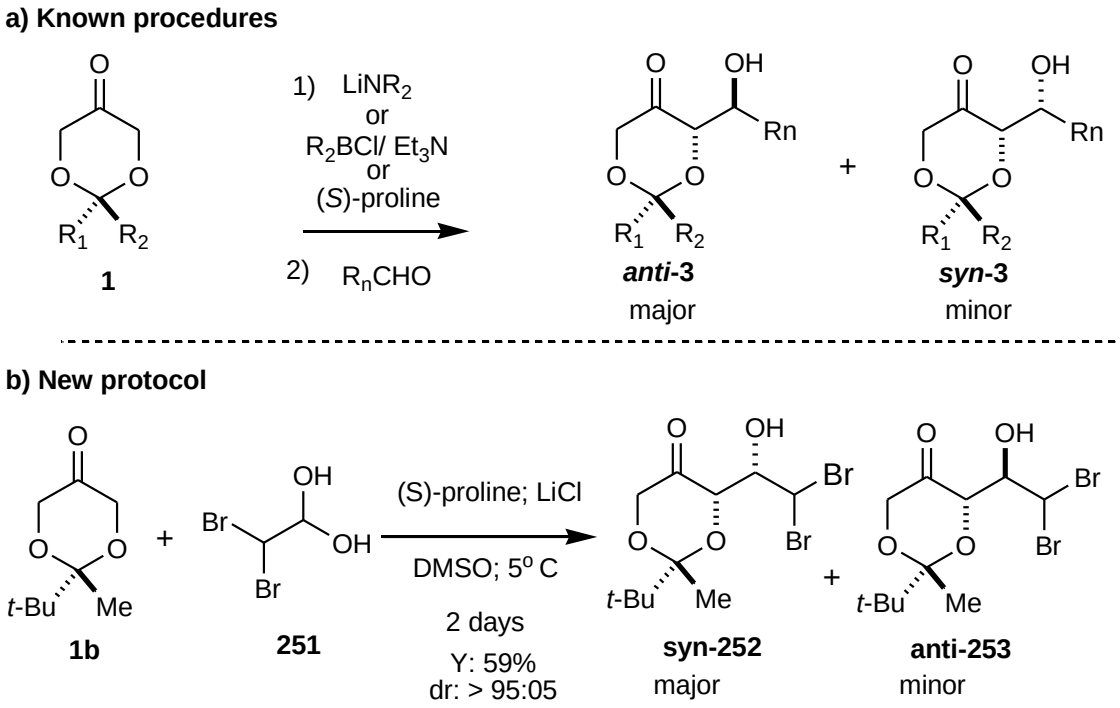
[a]- determined by chiral-phase HPLC analysis on Chiralpak-AD column. *entry 12: Aldol reaction using DL-proline to get the racemic sample.

To have an insight into the accuracy of enantiomeric excess measurements by NMR using shift reagent the following brief study was carried out: The aldol adduct **250** from dioxanone **1** and 1,3-dithiane-2-carboxaldehyde **2b** was chosen as the model system (Scheme 2.8). The two enantiomers had good separation on the Chiralpak-AD column and also a well resolved ^{1}H NMR spectrum of the enantiomeric aldol adducts **250** using $Eu(hfc)_3$ as a shift reagent in C_6D_6 as solvent. The measurements of ee by both methods are summarized in Table 4. Based on the data obtained from this exercise it can be inferred that, although the NMR method is time consuming, with proper choice of shift reagent and

solvent it is possible to get an accurate enantiomeric excess measurements as it is possible by chiral HPLC based analytical methods (Table 4).

2.5 Organocatalytic *syn*-aldol reactions of dioxanones

Another objective of the initial methodological studies was to investigate reaction conditions to obtain *syn*-aldol products preferentially on dioxanone substrates. This was an ambitious project, as the literature records no methodologies to obtain *syn*-selective aldols on dioxanones, despite significant progress made this area of chemistry (Scheme 2.9a). It should be noted, however, that Mannich and Michael addition on dioxanone yielded *syn*-configuration in its products.[25,28,29]



Scheme 2.9.

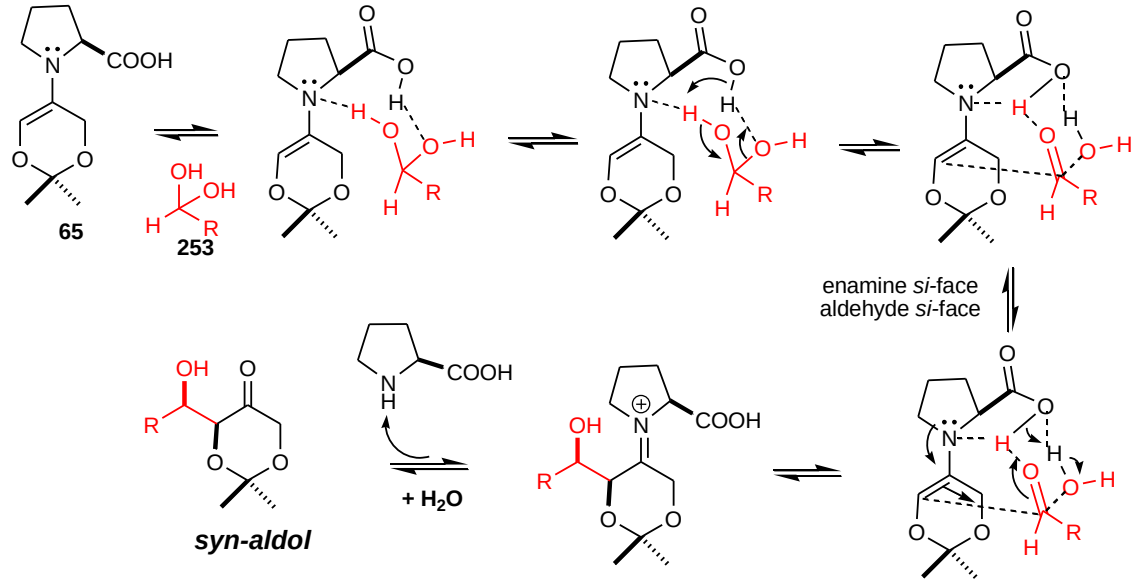
Be it a coincidence or intuition, as a part of ongoing efforts to come up with a set of conditions to perform *syn*-selective aldol reactions on dioxanone, I observed a "*syn*-like"

product in one of the proline-catalyzed aldol reaction of dioxanone with the hydrated form of aldehyde.[136] The configuration across the newly formed carbon-carbon bond of the aldol adduct was assigned based on the observed small J-coupling constant between the two adjacent CH(O) protons. This led to a hypothesis that the 'hydrated form of an aldehyde' might result in a *syn*-aldol adduct. In order to confirm this observation, dioxanone (**1b**) was subjected to proline-catalyzed aldol reaction with readily available chloral hydrate and bromoacetaldehyde hydrate (**251**, Scheme 2.9b). Both the reactions with hydrates resulted in respective *syn*-aldol adducts and especially the reaction with bromoacetaldehyde hydrate was perfectly clean and neat. The complete analysis of the major aldol product by ^{1}H NMR and proton coupling constants (δ 5.9 ppm; J = 2.9 Hz for α-H) disclosed that the relative configuration of the newly formed bond was indeed *syn* and the major compound was found to be **252**. Literature search revealed the existence of a precedent in a similar reaction involving cyclopentanone and chloral hydrate.

2.5.1.1 *Syn*-aldol with hydrates: stereochemical rationale

The reversal of selectivity in proline-catalyzed aldol reactions of dioxanones with hydrated forms of aldehyde can be rationalized using Saito and Yamamoto's hypothesis of hydrogen-bond networking in the transition structures.[137,138] Scheme 2.10 illustrates the possible hydrogen-bond networking between the hydrated form of aldehyde **253** and the proline moiety of the reactive dioxanone enamine **65**. Upon sequential dehydration compound **253** releases the corresponding aldehyde with its *si*-face opened towards the *si*-face of enamine. This type of facial selectivity might be the prime cause for the observed

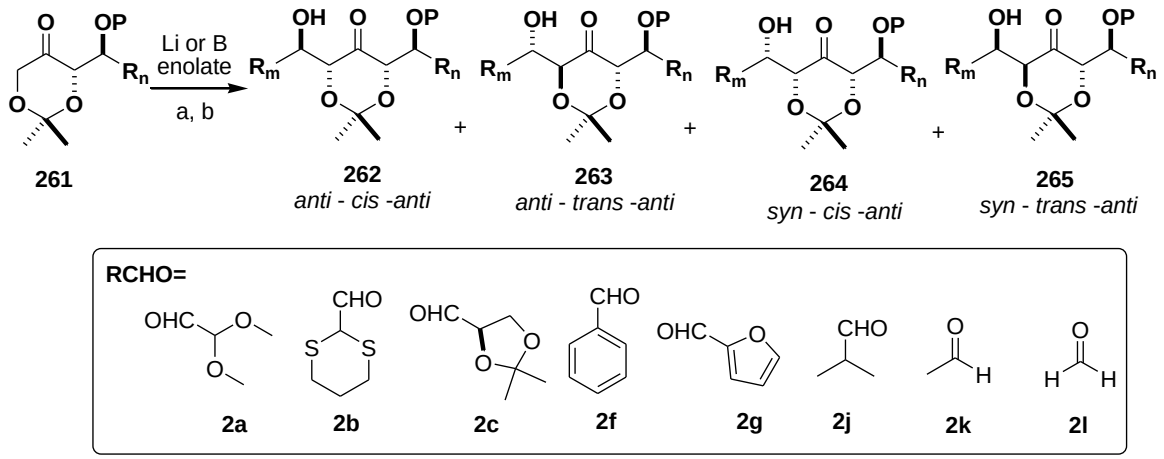
syn-aldol products from the proline-catalyzed aldol reactions of dioxanone with aldehyde hydrates.



Scheme 2.10.

2.6 Second Aldol Reactions on Dioxanones

In the proposed approach to higher sugars and other polyoxygenated natural products double-aldol reactions at the α and α' carbons of the dioxanone scaffold play a pivotal role in constructing the densely oxygenated carbon chain architecture. Since performing the second part of the bis-aldol sequence using organocatalysis proved difficult,[139] the second aldol was attempted with metal-mediated enolate chemistry. In our group, Izabella Niewczas hypothesized that starting materials having Lewis basic sites, such as oxygen atoms, should require excess amounts of LDA for enolization.[12,139] She was able to develop reasonably efficient method for the second aldol reaction by using excess LDA.[139]

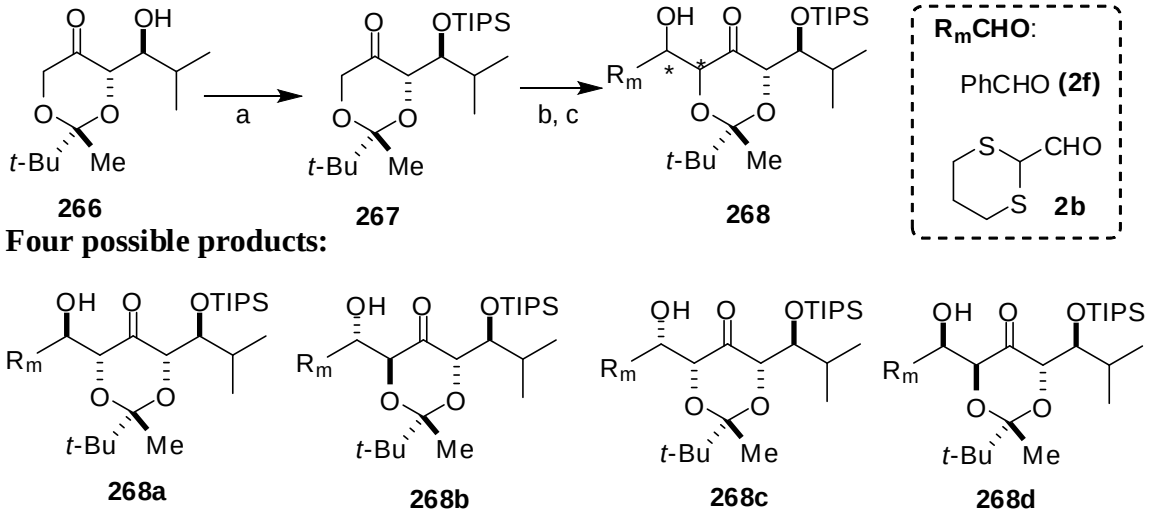


Reagents and condiations: Li enolate method a) LDA (3.3 eq), THF, -78 ^{o}C, 2 hr b) RCHO **2** (3.0 eq), -78 ^{o}C, 0.5 hr. B enolate method: a) Cy_2BCl (3.0 eq, Et_3N (6.0 eq), CH_2Cl_2, 0 ^{o}C b) RCHO **2** (6.0 eq), 0 ^{o}C, 0.5 hr; pH 7 buffer

Scheme 2.11.

Scheme 2.11 summarizes the "second aldol methodology" starting from the protected aldol adduct **261** and using lithium or boron enolates with a variety of aldehydes, based on previous work from our group (Niewczas and Nowak). In the process, the reaction produces two new stereogenic centers from which four possible stereoisomers **262-265** can result. In summary, the experiments involving boron enolates, predominantly gave the *anti-trans-anti* isomer **263**,[11,16] whereas when excess amounts of the LDA base (3.3 eq) and of aldehydes (3 eq.) were used the *anti-cis-anti* isomer **262** and the *anti-trans-anti* **263** isomer were obtained with variable selectivity (from ca 2:1 up tp 10:1 depending on the aldehyde).

2.6.1 Bis-aldol studies on C_S-dioxanones



Reagents and conditions: (a) TIPS-OTf, 2,6-lutidine, CH_2Cl_2, 12 hr, rt, 87% ; (b) LDA (3.3 eq), THF, -78 ^oC, 2 hr; (c) RCHO **2** (3.0 eq), -78 ^oC, 0.5 hr.

Scheme 2.12.

As an extension of the bis-aldol approach, I decided to inspect whether the presence of the bulky *tert*-butyl substituent at the C-2 position of the dioxanone ring influences diastereoselectivity of the second aldol in a similar way to that observed and discussed during studies of the first aldol reaction. The study started from the standard silyl protection of the hydroxyl group in the aldol adduct **266** to give the silylated compound **267**, which was subjected to lithium base-mediated second-aldol reaction with benzaldehyde (**2f**) or 1,3-dithiane-2-carbaldehyde (**2b**) using excess base and excess aldehyde to provide the crude aldol adduct **268**. The TLC analysis showed three spots in each case and diastereoselectivity of the reaction was measured on the crude product. The major product in each case was separated by using flash chromatography, and was characterized and determined to be the *anti-cis-anti* aldol adduct **268a**. The stereochemical

assignment of the configuration was based on the extracted coupling constants from the respective proton NMR spectra. The results are shown in Scheme 2.12 and Table 5.

Table 5: Double aldol reactions on dioxanone substrate

Entry	**RCHO**	**Yield (%)**	**Product ratio [a]** **268a : 268b**
1*	**2b**	74	87 : 13
2	**2b**	71	79 : 21
3*	**2f**	99	84 : 16
4	**2f**	57	75 : 25

[*] similar reaction on 2,2-dimethyl dioxanone aldol adduct (Ref 12)
[a] determined by ^{1}H NMR of the crude product

Depending on the C-2 substituent in the starting dioxanone, the diastereoslectivity of the second aldol reaction varied (*cf*. Table 5, entries 1 *vs.* 2; and 3 *vs* 4). As previously discussed in Section 2.32, the substitution at C-2 position of dioxanone has significant effect on diastereoselectivity of proline-catalyzed aldol reactions of dioxanones. In contrast, the presence of a bulky substituent at C2 decreases diastereoselectivity of the second, lithium enolate-mediated aldol reaction. This observation seems to suggest a dissimilar nature of the transition states involved in the first and second aldol reactions.

2.7 Building Carbohydrates on Dioxanone Scaffold

Encouraged by the promising results from the initial methodological studies described above, my next objective was to use the dioxanone methodology to develop a stereo-controlled approach to interesting natural products: iminosugars and higher monosaccharides. Examination of the literature revealed only a few synthetic strategies to access the rare higher monosaccharides. The enormous research scope and the need for development of new synthetic methodologies to access these biologically important compounds have been discussed in section 1.8 of the thesis. The aim of this project was to develop the stereoselective and practical dioxanone-based protocol towards the synthesis of rare and biologically important monosaccharides. Here, I thought of applying organocatalysis and organometallic mediated $C_m + C_3 + C_n$ strategy on dioxanone scaffolds to obtain the complex chiral architecture often found in those target molecules.

In early 2000, Majewski and Nowak published a milestone article on the dioxanone route to monosaccharide derivatives.[16] Later in that decade, various researchers have followed up with numerous reports and reviews describing the usefulness of dioxanones as scaffolds for synthesis of lower monosaccharides.[8-28] The following sections of this thesis are intended to portray the successful synthetic applications accomplished *via* the dioxanone methodology.

2.7.1 Dioxanone route of 1-deoxyiminosugars

The first synthetic target was to use the dioxanone scaffold towards synthesis of naturally occurring 1-deoxyiminosugar molecules. Iminosugars are natural piperidine amino sugars (*i.e*. 5-amino-5-deoxyaldohexoses) and their corresponding 1-deoxy derivatives, are a class of monosaccharide with the nitrogen atom in place of the ring oxygen of the corresponding carbohydrate. As discussed earlier (section 1.6), the chemistry of iminosugars have attracted the synthetic community's attention as this class of compounds comprises some potent glycosidase inhibitors as well shown promising drug profiles and wide-ranging biological activities.[93] 1-Deoxynojirimycin (DNJ, **146**) is a glucosidase inhibitor and *N*-butyl-deoxynojirimycin (Zavesca® **153**), is a prescription drug for treatment of mild type 1 Gaucher disease as well as a promising HIV inhibitor.[94] Due to their promising medicinal profiles, a large number of strategies have been developed for their syntheses.[96-99] Most recently, Mayoralas *et al* have reported an organocatalytic dioxanone route to homonojirimycin compounds. [99]

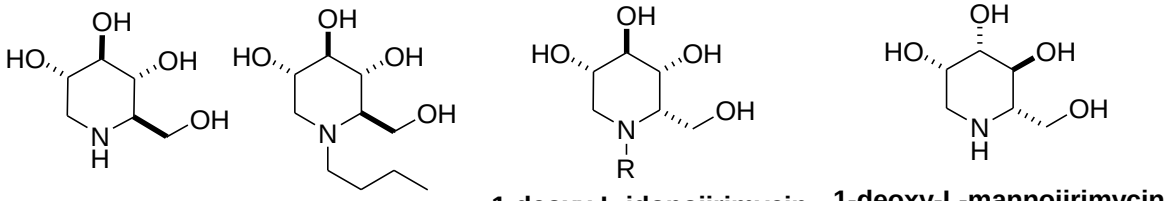
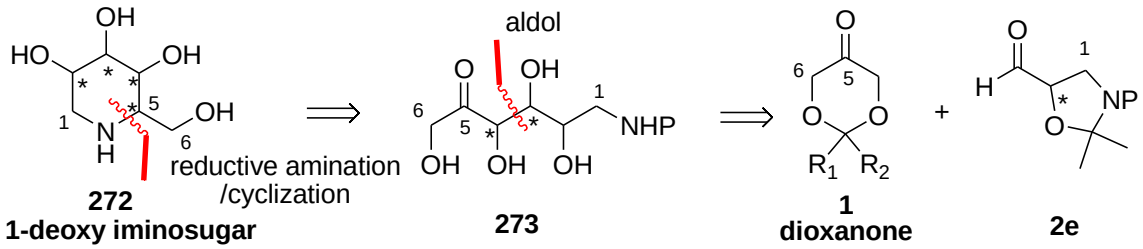


Figure 2.3: Selected examples for piperidine aminosugars

Inspired by Nature's approach to 1-deoxyiminosugars, I proposed a simple synthetic protocol to access L-1-deoxyidonojirimycin (L-DIJ, **269**) N-isopropyl-DIJ **270** and L-1-deoxymannojirimycin (L-DMJ, **271**) *via* proline-catalyzed aldol reactions of isoserinal (**2e**) with dioxanone **1** (Scheme 2.13).[136]

2.7.1.1 Retrosynthetic analysis for iminosugars



272
1-deoxy iminosugar
273
1
dioxanone
2e

Scheme 2.13.

The 1-deoxyiminosugar has four consecutive stereogenic centres from which sixteen stereoisomers are possible of which eight are dextro- and another eight are levorotatory isomers. To till date, only four stereoisomers have been isolated from plants and microorganisms. Many synthetic methodologies were reported to access stereoisomers of 1-deoxyiminosugars and more importantly many of them showed promising biological properties.[140,141]

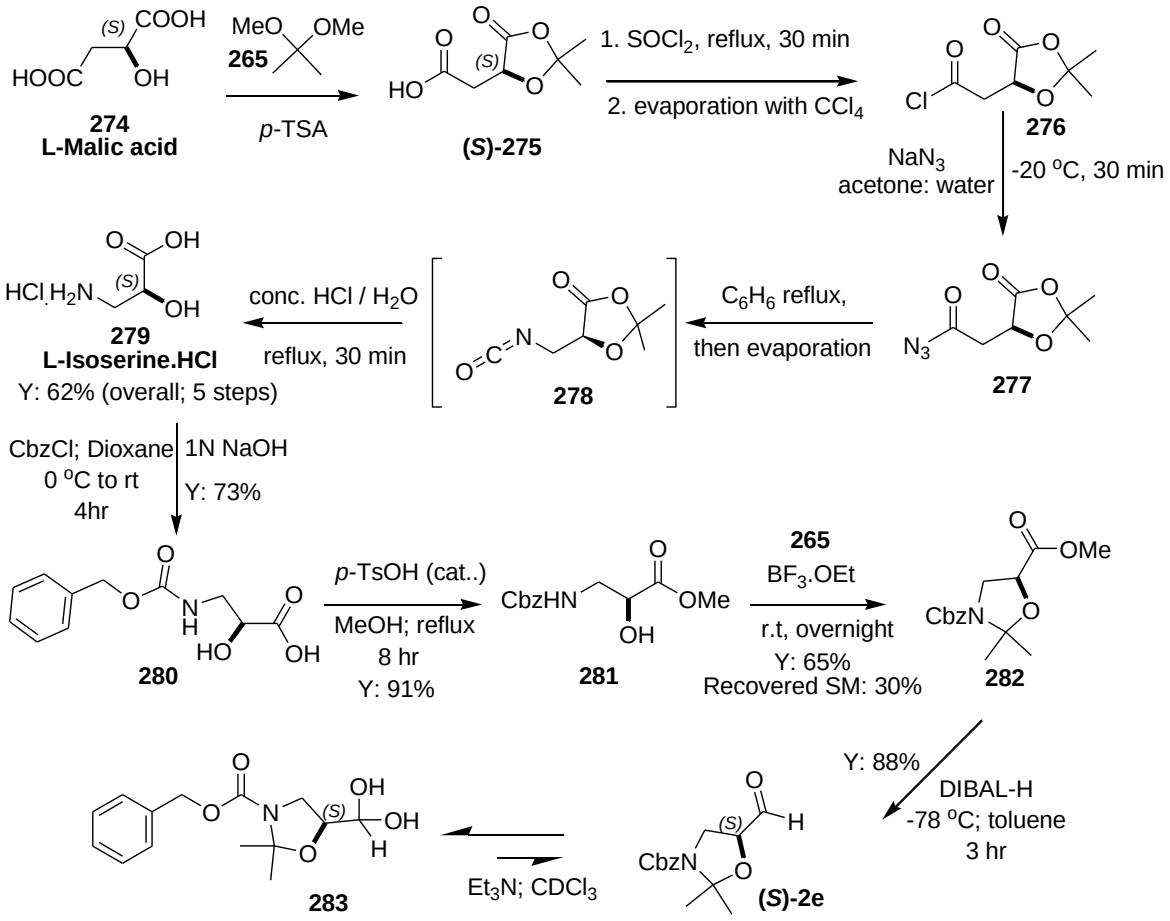
A generic retrosynthetic analysis[142] (Scheme 2.13) shows that the monocyclic 1-deoxyiminosugar **272** skeleton could be fragmented into simple and readily available starting materials such as dioxanone (**1**) and protected isoserinal (**2e**) using simple aldol reactions and intramolecular reductive amination retrons. Thinking in the forward direction, the four stereogenic centres of an iminosugar can be incorporated as follows: the

stereochemistry on carbon-2 can be translated from isoserinal (**2e**); the first-aldol reaction of dioxanone **1** with aldehyde **2e** would result in aldol adduct **273** fixing two stereogenic centers at carbon-3 and carbon-4. It was envisaged that the stereochemistry of compound **273** can be controlled by employing (*S*)- or (*R*)-proline catalyst thereby switching two stereogenic centres respectively. Finally, the positioning of hydroxyl groups on the piperidine frame dictates the stereochemistry on carbon-5 via palladium-catalyzed reductive amination. Upon optimization and refinement of reaction conditions in the above sequence, the method has the potential to obtain all sixteen stereoisomers of 1-deoxyiminosugars.

As previously described, the literature records a number of aldol reactions involving dioxanones and a variety of aldehydes either under organocatalytic conditions or mediated by lithium or boron enolates. In all cases the relative stereochemistry of the major aldol product was *anti*, and the diastereoselectivity (*anti/syn*) was good or excellent. The simplicity associated with high selectivity of proline-catalyzed first-aldol reactions on dioxanones makes this method the most preferred. I hoped that it would be possible to broaden the scope of this strategy by manipulating the reaction conditions to perform selectively either the *anti* or the *syn* aldol transformation.

During the screening for various conditions to perform proline-catalyzed *syn*-aldol reactions on dioxanone, surprisingly, I observed organocatalytic reaction of dioxanone **1b** with an aldehyde hydrate resulted in the formation of only one product that appeared to be of *syn* relative configuration (*cf.*, section 2.5). Chloral hydrate gave a similar result.[136,137] This was a welcome development, because it allowed us to plan the synthesis of some less common deoxynojirimycin isomers.

2.7.1.2 Synthesis of (*S*)-isoserinal hydrate



Scheme 2.14.

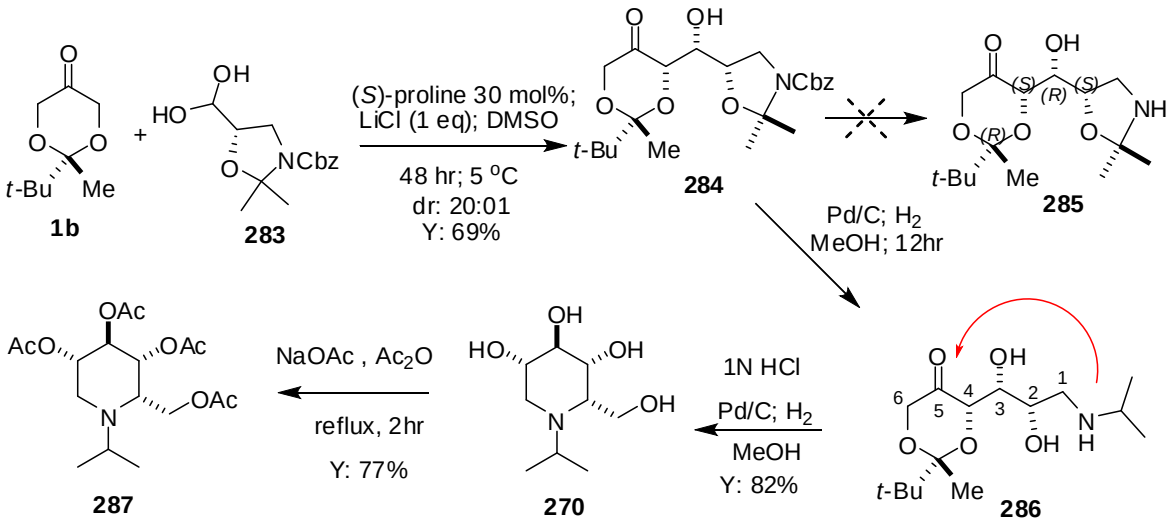
The necessary chiral building block for construction of nojirimycins, the protected (*S*)-isoserinal hydrate (**283**) was synthesized from the commercially available (*S*)-malic acid (**274**) following published procedures with substantial modifications (Scheme 2.14). (*S*)-Malic acid (**274**) was converted into (*S*)-2-(2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (**275**) by acid-catalyzed ketalization with 2,2-dimethoxypropane (**265**). Thus, the hydroxy and carboxyl groups were protected in one step. The β-carboxy group was then transformed into acyl chloride **276** which upon treatment with sodium azide in

aqueous acetone at -20 °C resulted in acyl azide intermediate **277**. The Curtius rearrangement of the acyl azide (**277**) afforded the corresponding isocyanate intermediate **278** which upon boiling with aqueous hydrochloric acid yielded amino acid **279**. Overall, (*S*)-isoserine hydrochloride (**279**) was synthesized in a three-step sequence in "one-pot" with 62% overall yield.[143] Amino acid **279** was transformed into the Cbz-protected (*S*)-isoserinal **280** using the modified Schmidt protocol,[144, 145] which upon stirring with *p*-toluenesulfonic acid in methanol gave the the corresponding methyl ester **281**. (*S*)-Isoserine aldehyde (**2e**) was obtained from the methyl ester **281** via formation of the oxazolidine (**28**2) followed by DIBAL-H reduction of the methyl ester.

Protected (*S*)-isoserinal (**2e**) readily forms the corresponding hydrate **283**. The IR spectrum of this compound showed the absence of the carbonyl and the presence of a broad peak corresponding to the hydroxyl functional groups (3540-3090 cm^{-1}) that confirmed the existence of the (*S*)-isoserinal hydrate. Also, the proton NMR analysis showed a small signal for the aldehyde functional group (CHO) at the chemical shift of 9.7 (integration for 0.23 proton), addition of triethylamine to the sample enhanced the aldehyde peak (integration of 0.62 protons) which implied that the equilibrium has shifted to the aldehyde form **2e**. With the hydrate **283** in hand the stage was set for the organocatalytic aldol reaction.

2.7.1.3 Synthesis of N-isopropyl-L-1-deoxyidonojirimycin

(*S*)-Proline-catalyzed aldol reaction of 2-*tert*-butyl-2-methyl dioxanone (**1b**) with (*S*)-isoserinal hydrate (**283**) gave the aldol adduct **284** in 69% yield and high diastereoselectivity (surprisingly, the *syn*-aldol adduct was the major product). It should be noted that the total number of stereoisomers possible in this reaction are eight. The C-2 substitution at the acetal stereogenic centre and also the *cis* arrangement of the largest groups on the dioxanone ring with respect to electrophile has been discussed earlier in section 2.4. The *syn* relative stereochemistry assignments of the aldol adduct was based on NMR studies carried out on this compound. The extracted coupling constants from proton decoupling experiments were i.e., peak at 4.47 ppm (d, α-CH, J = 3.0 Hz) for compound **284** (for the full spectra and also 2D-NMR data see the experimental section). Based on the extensive NMR studies on compound **284** the absolute stereochemistry of the aldol-adduct is believed to be as drawn (Scheme 2.15).



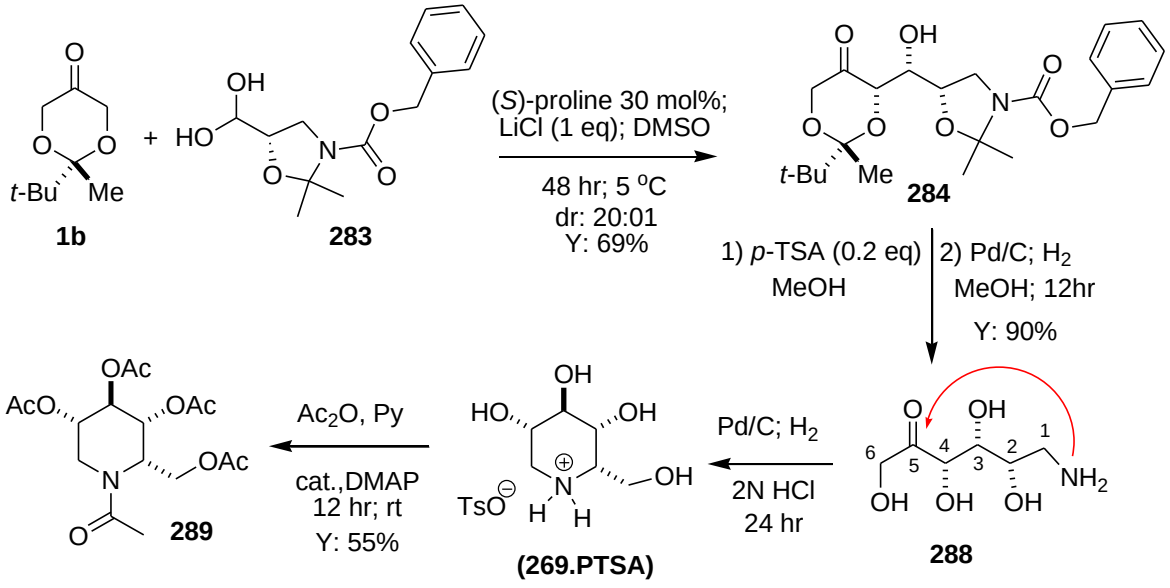
Scheme 2.15.

At this stage, to be sure of the stereochemical assignment of compound **284**, I decided to perform the classical chemical correlation method by transforming the aldol adduct **284** into natural 1-deoxyiminosugar.

Our initial efforts of direct transformation of the aldol adduct **284** to the corresponding iminocyclitol **269** via hydrogenolysis of the Cbz group proceeded with spontaneous deprotection of benzyloxycarbonyl group along with reductive ring opening of oxazolidine to the *N*-isopropyl derivative **286**. This was an unexpected result, but it should be noted that similar observation was made in one instance by Falb during synthesis of chiral pyrrolidines for glycosidase inhibition studies.[146] Compound **286** upon treatment with 1N HCl underwent deketalization followed by reductive amination/cyclization that resulted in N-isopropyl- L-idonojirimycin (**270**) in 82 % yield. The compound was fully characterized as the tetraacetate derivative **287**. The synthesis and characterization of the unnatural derivative N-isopropyl-DIJ was carried out for first time, and thus there was no literature data to correlate and confirm the stereochemical assignment made for the *syn*-aldol adduct **284**. The interesting aspect to note is, as most of the N-alkyl derivatives of 1-deoxynojirimycin are known to be biologically active compounds for numerous disease targets, the new protocol gives an access to N-isopropyl derivatives of 1-deoxyiminosugars.

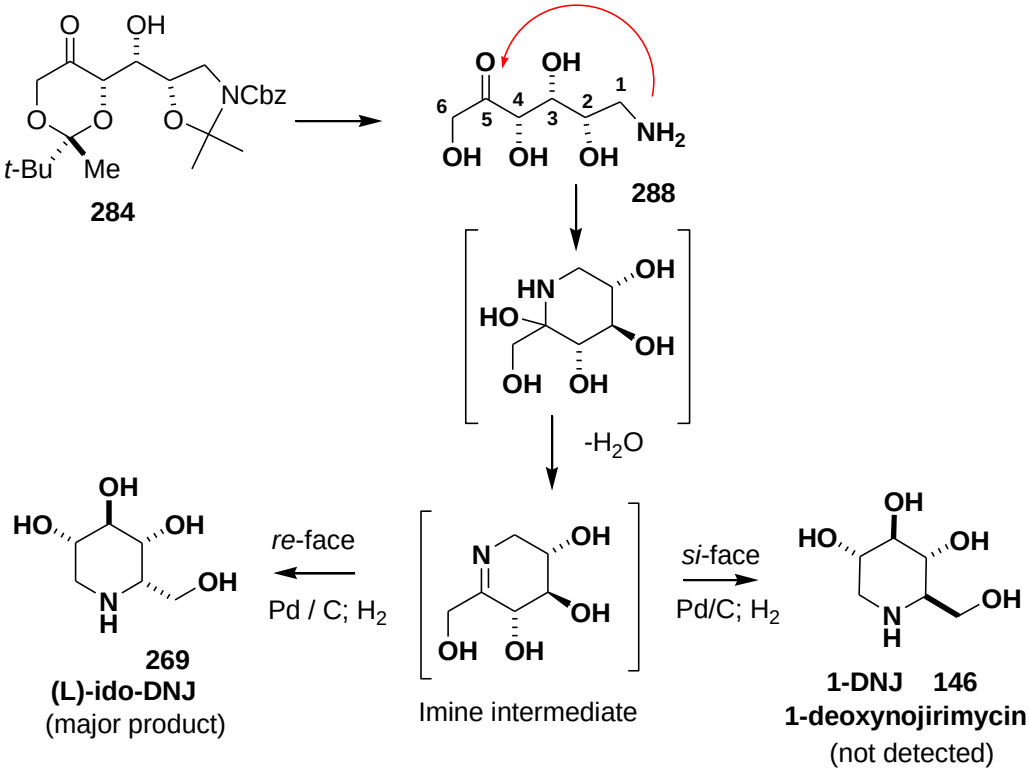
2.7.1.4 Synthesis of L-1-deoxyidonojirimycin

To obtain the free 1-deoxyiminosugar (no alkyl group on nitrogen) I decided to shuffle the deprotection sequence (Scheme 2.16). One-pot hydrolysis of the acetal moiety and the oxazolidine ring of the aldol adduct **284** was carried out with catalytic amount of *p*-toluenesulfonic acid in methanol and was followed by Cbz deprotection via palladium catalyzed hydrogenation, followed in turn by an in situ cyclization and reductive amination of intermediate **288** to give the tosylate salt of 1-deoxy-L-idonojirimycin (**269**). This C5-epimer of 1-deoxynojirimycin was obtained in 66% overall yield and high diastereoselectivity. The reaction mixture was converted into the acetate derivative for complete characterization. The analytical data of tetraacetate derivative **288** were an exact match with the literature data[147] which confirmed the stereochemical assignments for compounds shown in Scheme 2.16



Scheme 2.16.

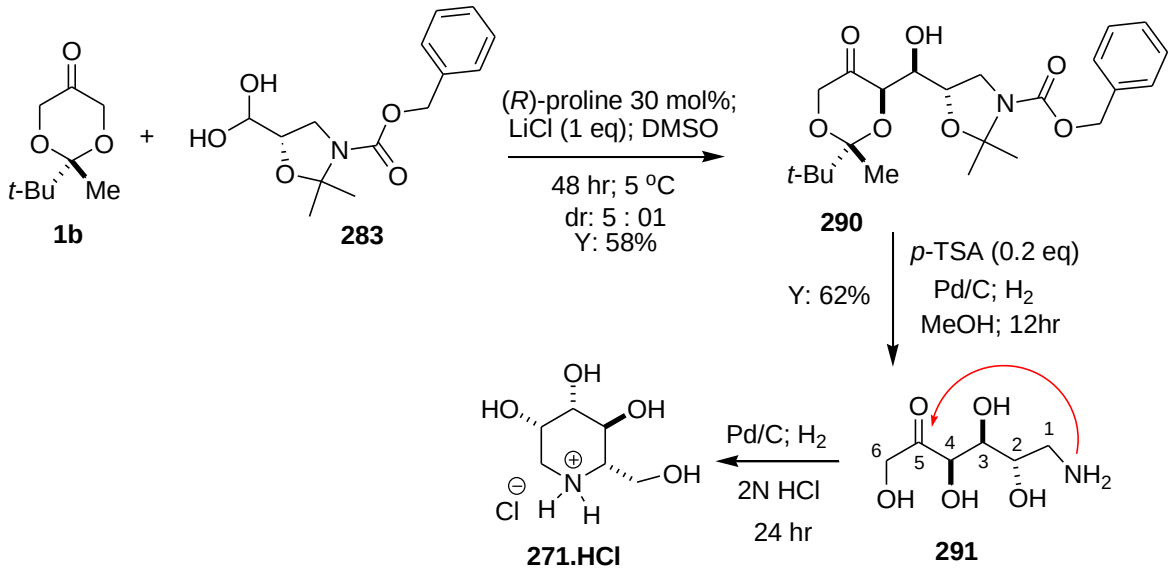
Scheme 2.17 illustrates the stereochemical rationale for the intramolecular reductive amination of ketoamine **288** to give L-1-deoxyidonojirimycin. The ketoamine readily forms the cyclic hemiaminal, which, upon dehydration produces the imine intermediate. Finally, the positioning of hydroxyl groups on iminium piperidine frame dictates the stereochemistry on carbon-5 via palladium-catalyzed reductive amination.[148] Reduction of the imine could occur from the *si*-face of the double bond would result in 1-DNJ **146**, but the double bond was reduced from the *re*-face to afford L-DIJ **269**.



Scheme 2.17.

2.7.1.5 Synthesis of L-deoxymannojirimycin

D-1-Deoxymannojirimycin (the C2-epimer of DNJ), isolated from *Lonchocarpus sericeus* is an inhibitor of α–D-mannosidase, α -D-glucosidase and α -L-fucosidase.[149] To eliminate any uncertainties in stereochemical assignments of the compounds produced in the above protocol, similar transformations were carried out on compounds **1b** and **283** via D-proline-catalyzed aldol reactions to yield the complementary *syn*-aldol adduct **290**. The *syn* relative stereochemistry assignments of the aldol adduct **290** was based on NMR studies. The extracted J-coupling values from proton decoupling experiment for a peak at δ 4.20 ppm (d, α-CH, J = 2.3 Hz) supported the *syn* connectivity.



Scheme 2.18.

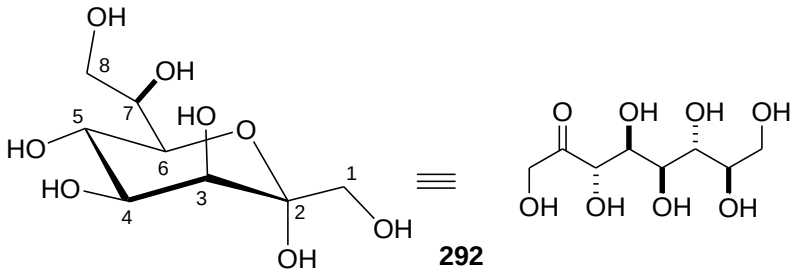
Repeating the deprotection/hydrogenation protocol on compound **290** gave the tosyl salt of L-deoxymannojirimycin. The crude tosyl salt was passed through the cation exchange resin Amberlite IR 120 to obtain the hydrochloride salt of L-1-deoxymannojirimycin

(**271**). The optical rotation, melting point values and NMR data for compound **271** were in good agreement with the previously reported data.[150]

In summary, L-deoxyidonojirimycin (**269**), N-isopropyl-L-deoxynojirimycin (**270**), and L-deoxymannojirimycin (**271**) were synthesized from readily available dioxanone (**1b**) and (*S*)-isoserinal hydrate (**283**) in short sequences of reactions. The key step involved the proline-catalyzed *syn* selective direct aldol reaction. Also, I was able to establish the absolute stereochemistry to the aldol adducts **284** and **290** by correlation with known natural products L-DIJ and L-DMJ.[136]

2.7.2 Stereoselective synthesis of (+) D-glycero-D-manno-2-octulose

My next synthetic target was D-*glycero*-D-*manno*-2-octulose (**292**), a higher-carbon sugar found in opium poppy seeds (*Papaver somniferum L.*)[151] Several synthetic approaches were developed over the years to access such higher ketoses. The majority of the methodologies employed pentoses or hexoses as starting materials and homologation or coupling as the strategy.[152] Dondoni has extensively studied one-carbon sequential chain-elongation of lower monosaccharides[153] and Jarosz[154] tail-to-tail coupling methods are common routes towards the higher ketoses.

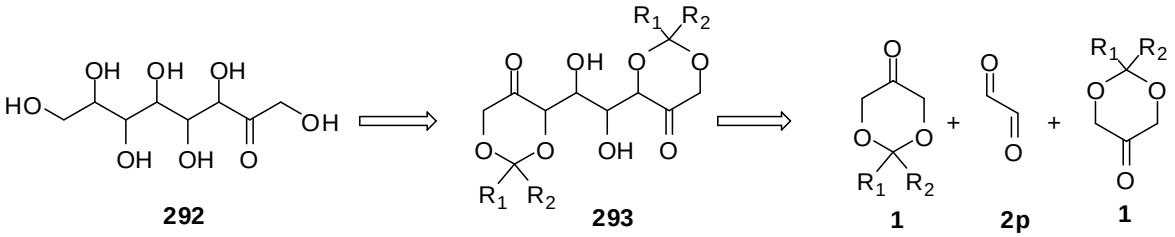


(+)-D-*glycero*-D-*manno*-2-octulose

Figure 2.4: Synthetic target (+)-D-*glycero*-D-*manno*-2-octulose

Dioxanones have proven to be good substrates for reactions involving organocatalysis and several studies on the proline-catalyzed stereoselective transformations of dioxanones were reported, including syntheses of ketohexoses and some higher sugars.[8-16] Below, I describe observations pertaining to stereocontrolled synthesis of higher sugars from dioxanones via proline-catalyzed aldol reaction as the key step.[155]

2.7.2.1 Total dioxanone approach to ketooctulose



Scheme 2.19: Retrosynthetic plan to ketooctulose starting from dioxanones

The retrosynthetic scheme 2.19 illustrates the synthetic strategy towards the target higher monosaccharide **292**. It was visualized that the synthesis of a ketooctulose can be viable from two dioxanone units coupled together with one equivalent of glyoxal (**2p**). Hypothetically, the above sequence could be done either in "one pot" or stepwise, by manipulation with numerous protecting groups.[12] Upon optimization of reaction conditions, this strategy could lead to the stereoselective synthesis of any desired isomer; in order to achieve that, the control of absolute and relative stereochemistry would be necessary. The previous work on dioxanones involving enantioselective deprotonation, as discussed in introduction to this thesis, combined with the observations made during the initial methodological studies on organocatalysis made me optimistic as to the potential for enantioselectivity control. The extensive literature related to diastereoselectivity control in

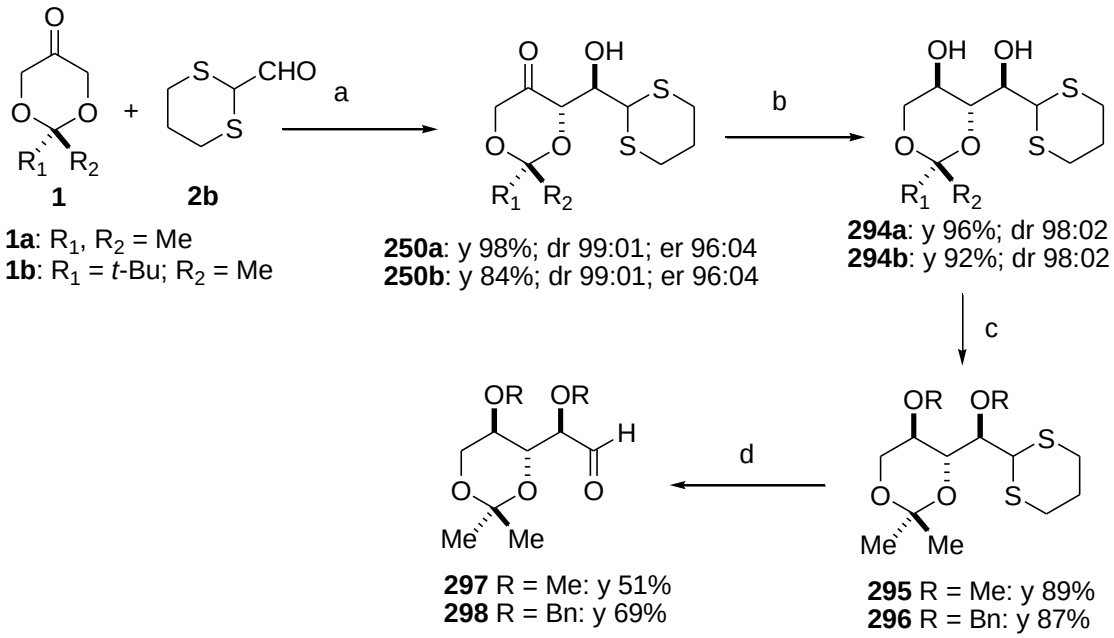
aldol chemistry, indicated that it should be possible to control relative stereochemistry of aldol adducts from dioxanones. The underlying principle was to develop a dioxanone-based versatile synthetic strategy which ultimately would allow synthesis of several ketooctulose stereoisomers (ideally all 32 of them). In the preliminary study, I have focused on synthesis of D-glycero-D-manno-2-octulose which is one of the natural products found in opium poppy.[151]

Initial experimental efforts to perform a "one pot" approach were unpromising. Then I directed my attention to the stepwise approach i.e. C_3+ (C_2 + C_3). The synthetic plan was to treat dioxanone **1** with glyoxal (**2p**) to obtain five-carbon fragment, which upon coupling with another equivalent of dioxanone would give the eight-carbon skeleton of the target ketooctulose **292**.

2.7.2.2 Synthesis of the protected D-ribose building block

1,3-Dithiane-2-carboxaldehyde (**2b**) was used as a synthetic equivalent of glyoxal in the first, organocatalytic step. It should be noted that this aldehyde works well in organocatalytic reactions, as reported by other groups.[27b,156] Aldol adducts **250** were obtained stereoselectively and in good yields. In the next step various reducing agents were screened; the best result was obtained by using $NaBH(OAc)_3$ at -20 °C to produce the *syn*-1,3-diol product **294** in high yield and with excellent diastereoselectivity (98:02). This interesting (note *syn* selectivity and not *anti* that might have been expected) result was in agreement with reports by both Barbas,[14] and Enders.[20] The hydroxyl groups in the reduced product were protected as methyl or benzyl ethers using standard conditions

giving the protected form of D-ribose where the thioacetal group masked the aldehyde functionality.



Reagents and conditions: (a) (S)-Proline (30 mol%), LiCl, DMSO, 5 ^{o}C, 48hr; (b) $NaBH(OAc)_3$, AcOH:DCM (1:5), -20 ^{o}C, 24hr; (c) NaH, BnBr or MeI, TBAI, THF,0 ^{o}C to rt, 6hr; (d) NBS, $AgNO_3$, CH_3CN:H_2O (4:1), 0 ^{o}C, 15min.

Scheme 2.20.

In order to unmask this group compound **296** was first subjected to oxidative hydrolysis conditions using several different protocols ($HgCl_2$/HgO, I_2/$NaHCO_3$, Dess-Martin periodinane) but the reaction gave a mixture of products in each case. Fortunately, Corey's protocol[157] (NBS/$AgNO_3$ in aqueous acetonitrile) gave cleanly aldehyde **298**, a protected form of D-ribose. The oxidative hydrolysis was complete within 5 minutes at 0 °C with moderate yields of 60-70%. This reaction spontaneously generates hydrobromic acid which could potentially destroy the dioxanone ring. The aldehyde **297** turned out to be a volatile compound which appeared to co-distill with the solvents during the workup

procedure. The dibenzylated aldehyde **298** worked well in the aldol reaction as well as it proved to be more convenient to handle.

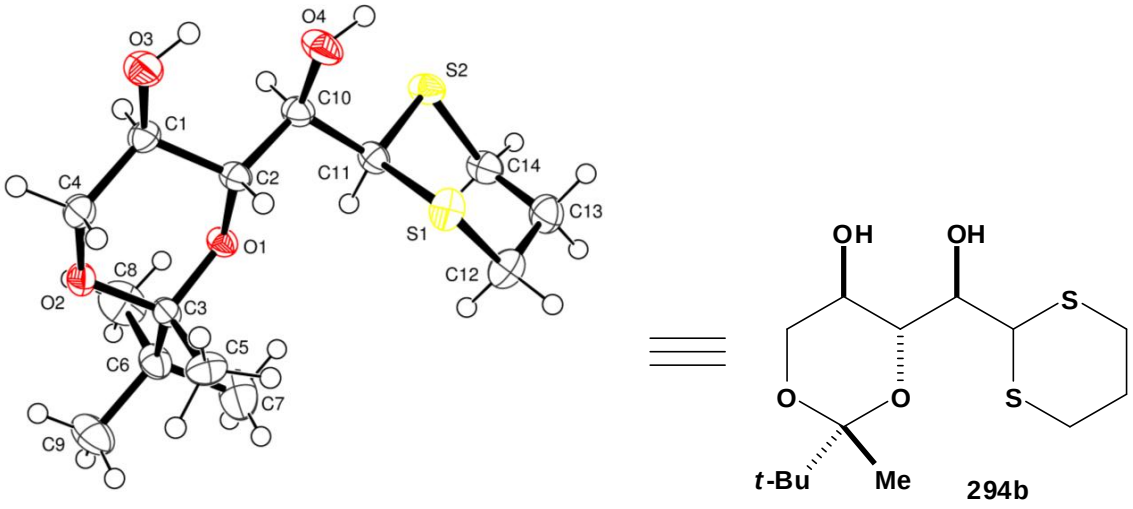
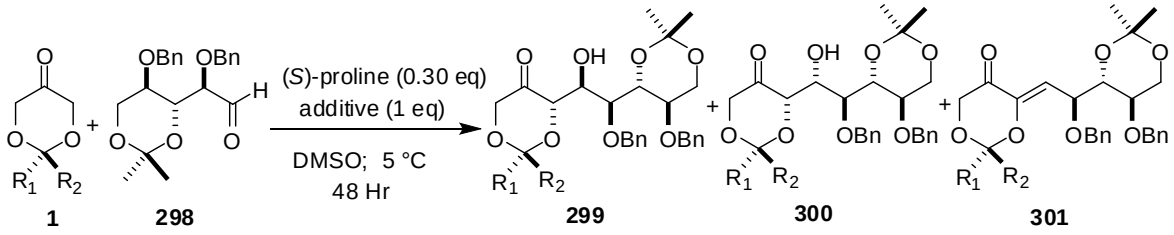


Figure 2.5: ORTEP diagram for compound **294b**

To eliminate any uncertainties in stereochemical assignments we needed a crystalline derivative. Thus, we prepared compound **294b** from *tert*-butylmethyl dioxanone (**1b**) by an analogous approach (Scheme 2.20). Only one diastereoisomer of the aldol was detected by NMR spectroscopy in this case. Fortunately, the corresponding reduction product **294b** was crystalline and provided us with a crystal structure confirming the *cis-anti* stereochemistry of the aldol and the *syn*-arrangement of the two hydroxyl groups in the reduced aldol (Figure 2.5). It should be noted that Evans hypothesized that the bulky reducing agents reduce cyclic β-hydroxy ketones to *anti*-diols as a major product.[162] The formation of *syn*-diols was an interesting observation as it contradicts the broadly successful Evans protocol. Similar observations were made by Enders and co-workers during the reduction process of dioxanone aldol adducts.[20]

2.7.2.3 Synthesis of (+)-D-*glycero*-D-*manno*-2-octulose

With the aldehyde reagent **298** in hand the stage was set for the key aldol reaction. We have used organocatalytic conditions and two different dioxanones as the nucleophiles. The results are summarized in Table 6.



Scheme 2.21.

Table 6: Proline-catalyzed aldol reactions of 2,2-disubstituted-1,3-dioxan-5-ones.

Entry	Dioxanone		Additive [a]	Conversion [a] (%)	Yield (%)[b] 299	dr [a] 299 : 300
	R_1	R_2				
1	Me	Me	-	92	42	67 : 33
2	Me	Me	LiCl	88	51	88 : 12
3	*t*-Bu	Me	-	>98	56	90 : 10
4	*t*-Bu	Me	LiCl	94	69	94 : 06

[a] Determined by ^{1}H NMR of the crude product. [b] After column chromatography

As expected, the reaction gave two different diastereoisomeric aldols (**299** & **300**) and, less expectedly, the corresponding dehydration product (**301**). The aldol product **299** (Scheme 2.21) with an eight-carbon skeleton and the desired stereochemistry seen in the target compound was obtained from (*S*)-proline-catalyzed aldol reaction of 2,2-dialkyl-1,3-dioxan-5-one (**1**) with the protected form of D-ribose **298.** This was a good example which showcases the importance of steric effects on the diastereoselectivity of enamine-mediated

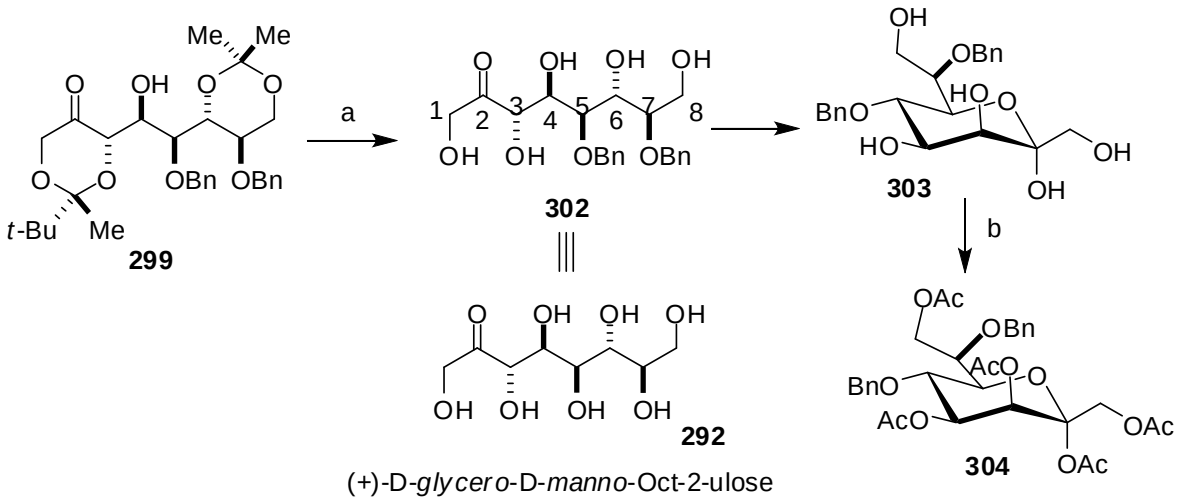
organocatalytic aldol reactions (*cf*. entry 1 vs. 3). The reaction involving 2-*tert*-butyl-2-methyl-1,3-dioxan-5-one (**1b**, achiral) with aldehyde **298** resulted an aldol product **299** in 69% yield with excellent diastereoselectivity (94:06). The similar transformation, using the C_2-symmetrical dioxanone was non-diastereoselective (67:33). Thus, switching from the C_2- to the C_S-symmetrical dioxanone has substantially improved diastereoselectivity (de up to 92% from 34%). As observed before, mild Lewis acid additives such as LiCl showed enhanced effect on the diastereoslectivity (*cf*. entries 1 and 2, and 3 with 4) as summarized in Table 6.

At this stage, the stereochemical assignments for aldol adducts **299** were based on the extensive NMR analysis and also by analogy to previously synthesized compounds. The absolute stereochemistry of compounds **299** and **300** was believed to be as drawn based on the following reasons:

i. Aldol addition of dioxanones to aldehydes under organocatalytic conditions is well known to give *anti* aldols with high selectivity[8,9,14,132]
ii. Aldol addition of dioxanone enolates proceeds via equatorial attack,[16] and
iii. Addition of dioxanone nucleophiles to chiral aldehydes having a stereocentre at the a carbon does not follow the Felkin-Anh model[158] and results in the OH group at the new carbinol stereocentre being *syn* to the α-alkoxy group derived from the aldehyde.[16]

The final deprotection of the aldol product **299** was carried out under acidic conditions (2N HCl solution in THF) to provide the eight carbon monosaccharide **302**, which readily undergoes intramolecular cyclization to form pyranose derivative **303** with the fixed stereochemistry of the target compound. The compound **303** was subjected to standard

acetylation and was isolated and characterized as the acetate derivative i.e. the protected form of (+)-D-*glycero*-D-*manno*-α-oct-2-ulose **304** (25% overall yield in seven steps) as illustrated in Scheme 2.22.



Reagents and conditions: (a) 2N HCl, THF, rt, 2hr; (b) NaOAc , Ac_2O, reflux, 2hr, Yield: 65%.

Scheme 2.22.

In summary, a naturally occuring higher sugar (+)-D-*glycero*-D-*manno*-α-oct-2-ulose **292** was synthesized in seven steps starting from commercially available dioxanone **1**, with the key steps comprising two stereoselective aldol reactions catalyzed by proline and diastereoselective reduction of dioxanone aldol, illustrating the potential of this synthetic strategy. The striking feature of this approach was that six of the eight carbons of the target ketooctulose came from the dioxanone scaffold.

2.7.3 Stereodivergent synthesis of DD- and LL- *glycero*-β-*allo*-Heptopyranoses

2.7.3.1 Background and significance

Aldoheptoses are an important class of higher monosaccharides (*cf.*, section 1.7.1.1). Naturally occurring aldoheptoses and deoxy-aldoheptoses (Figure 2.6) along with 3-*deoxy*-D-*manno*-*oct*-2-*ulosonic acid* (**185**, Kdo) are chief components of the antigenic endotoxins of gram-negative bacterial lipopolysaccharides (LPS).[104,105] Aldoheptoses contain six consecutive stereogenic centers on the seven-carbon skeleton. From the 64 possible stereoisomers of aldoheptoses, six have been found in LPS. L-*Glycero*-D-*manno*-heptose (**179**) was one of the first aldoheptose isolated from *Shigella flexneri* polysaccharide by Slein and Schnell,[106] but only meager amounts of these heptoses are available from natural sources.

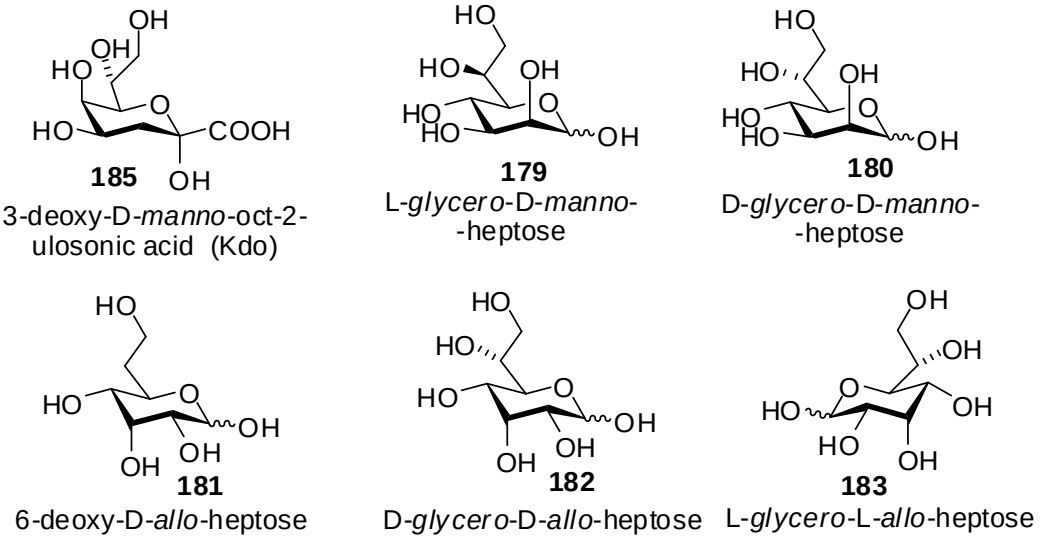


Figure 2.6 Structural components of gram-negative bacterial LPS and human liver tissue

(Synthesis of **182** and **183** is described in the following section)

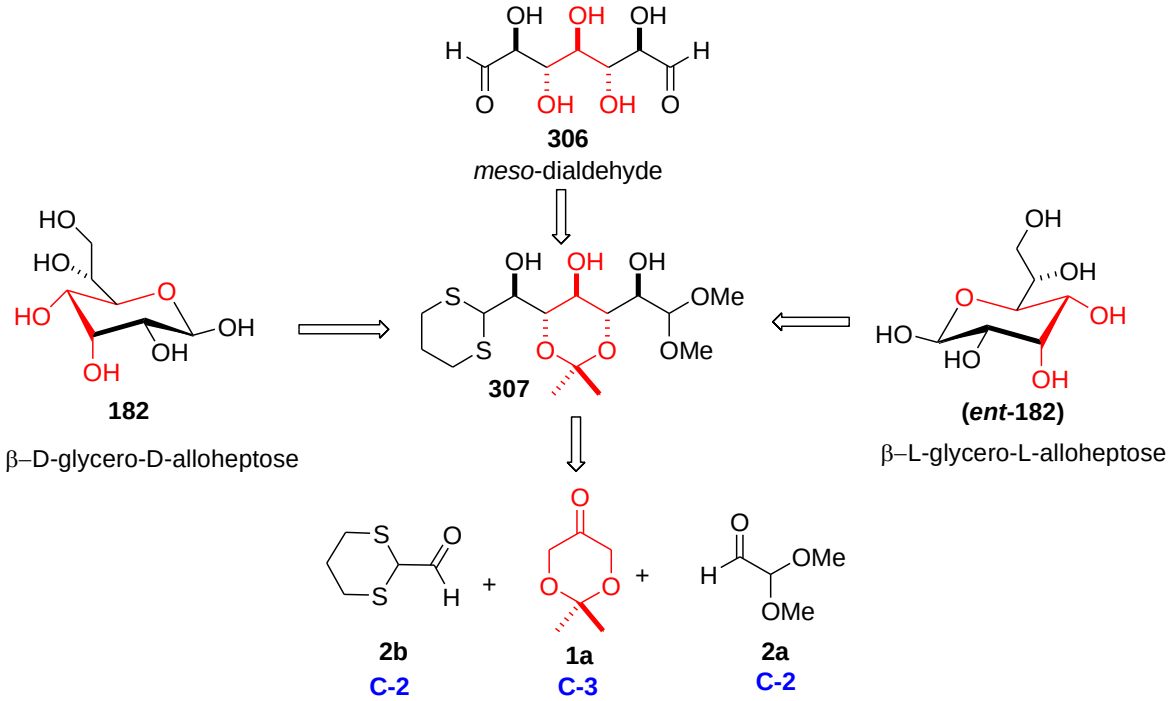
Low natural abundance and immunological importance of the aldoheptoses in LPS structure provoked considerable interest towards the development of new synthetic routes to obtain heptoses and their derivatives.[107,108] In majority of the published cases, synthesis of higher manosaccharides relied on the classical methods of Kiliani-Fischer homologation of abundant lower monosaccharides like pentoses and hexoses. Although these methods are straightforward they suffer from significant limitations such as side reactions and difficulty in isolation and purification of desired products from polar reaction mixtures.[118]

One of the ongoing projects in our laboratory is to explore the synthetic utility of dioxanones (**1**) in construction of rare, higher carbon-sugars and polyhydroxylated natural products. Dioxanone (**1**) has proven to be a valuable substrate for reactions involving organometallic and organocatalytic transformations in organic synthesis.[12,18,132,136,155] The following section presents the recent finding pertaining to a stereodivergent synthesis of DD- and LL-*glycero*-*allo*-heptoses (**182** and **183**) higher sugars starting from readily available non-chiral aldehydes and dioxanone moiety.[159]

The presence of D-*glycero*-D-*allo*-heptose (**182**) in the protein fractions of human liver tissue was first reported by Missale *et al*.[160] In the year 1955 Pratt and Richtmyer described the first synthesis of D-*glycero*-D-*allo*-heptose (**182**) *via* homologation of D-allose.[161]

2.7.3.2 Synthetic plan

During recent studies aimed at developing new approaches to synthesis of higher carbohydrates, I became attracted to the possibility of construction of both enantiomers of an odd-carbon higher sugar from one symmetrical dioxanone precursor **1a** and differentially protected glyoxals **2a** and **2b**.

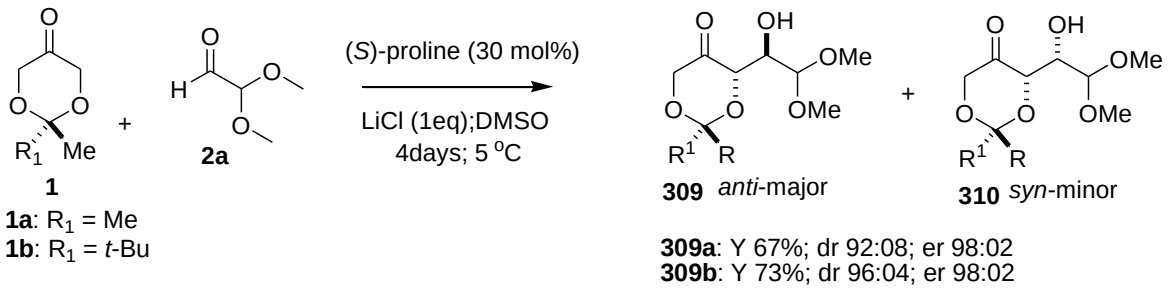


Scheme 2.23.

The sequence of unmasking the two terminal aldehydes in the key intermediate **307** dictates which isomer of the carbohydrate will be produced. The control of stereochemistry rests in the choice of the method for discrimination between the two enantiotopic nucleophilic sites in the ketone (C4 or C6), the relative stereochemistry of both aldol reactions (*syn* or *anti*) and the disposition of both newly attached side chains on the ring (*cis* or *trans*). A combination of these elements such that **306** has C_S symmetry would lead

to compounds **182** and ***ent*-182** being enantiomers *i.e*., to a stereodivergent synthesis. I have focused my attention on compound **307** which is a synthetic equivalent to the meso dialdehyde **306** and should be accessible by reduction of the corresponding double aldol derivative. Thus an aldoheptoses (**182** or ***ent*-182**) could, in principle, be constructed from three building blocks: a dioxanone (**1a**) and two different synthetic equivalents of glyoxal (**2a** and **2b**, Scheme 2.23).

2.7.3.3 Proline-catalyzed aldol reactions of dioxanones and dimethoxyacetaldehyde

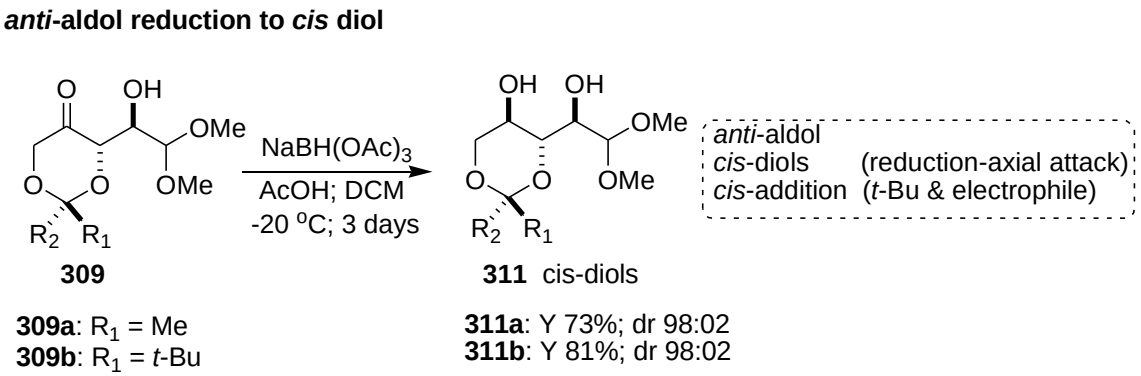


Scheme 2.24.

The first step of the synthetic sequence was the known (*S*)-proline-catalyzed aldol reaction of dioxanones **1a** and **1b** with 60% aqueous solution of dimethoxyacetaldehyde (**2a**) to afford the crude mixture of aldol aducts (Scheme 2.24).[14,20 20] The ^{1}H NMR interpretation of the major component of the reaction mixture revealed an unusually small coupling constants across the newly formed bond *i.e* δ 4.07 ppm (dd, J_1 = 3.1 Hz, J_2 = 6.8 Hz, 1H). This observation was in agreement with the previously published data by the groups of Barbas[14] and Enders[20] for the *anti*-aldol adduct **309a**.

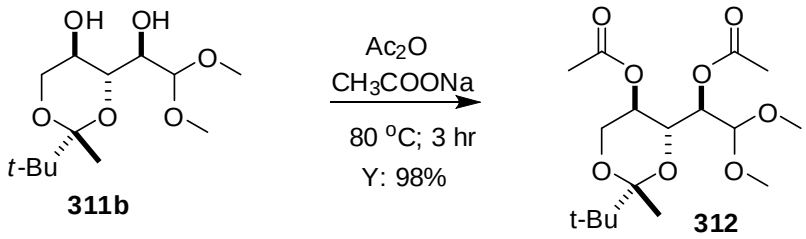
2.7.3.4 Stereochemical assignment of aldol adducts

In order to eliminate the ambiguity of the above observation, I subjected two aldol adducts **309a** and **309b** to stereoselective reduction with $NaBH(OAc)_3$ which led to the corresponding diols **311a** and **311b** respectively (Scheme 2.25). Again, the spectral data for **311a** were in good agreement with the reported data;[14,20] however the ^{1}H NMR coupling constants seemed to suggest the *syn*" aldol rather than the more usual *anti* aldol adduct. The relative stereochemistry between the two hydroxyls seemed to be *anti*. Similar observations were made by Enders and co-workers during the reduction process of some dioxanone aldol adducts.[20] Later, Barbas correlated the reduced aldol adduct with naturally occurring D-ribose upon acid-catalyzed deacetylation.[14]



Scheme 2.25.

To have an additional evidence for the stereochemical assignments, compound **311b** was acetylated under standard conditions to give the diacetate derivative **312** (Scheme 2.26). The ^{1}H NMR of the compound **312** was a well resolved spectrum which also showed a small coupling constant across the newly formed bond *i.e* δ 4.09 ppm (dd, J_1 = 3.2 Hz, J_2 = 6.7 Hz, 1H).



Scheme 2.26.

Fortunately, compound **311b** was crystalline and provided us with a crystal structure confirming the absolute stereochemistry of **311b** as protected form of D-ribose (**313**) i.e. having the *cis* relationship between the *tert*-butyl group and the newly formed C-C bond and being the *anti* aldol derivative with *syn* arrangement of the two hydroxyl groups in compound **311b** (Figure 2.7). [162]

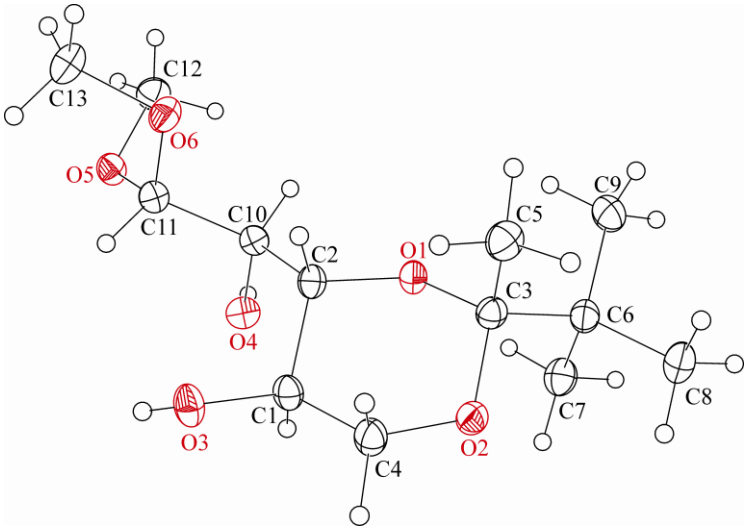
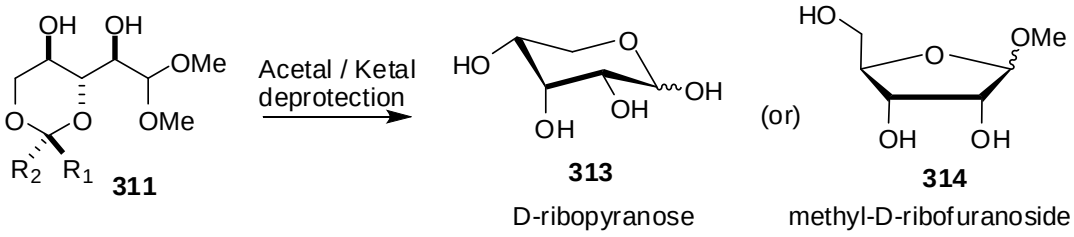


Figure 2.7: ORTEP diagram for compound **311b**

2.7.3.5 Acetal deprotection

To gain further understanding of the underlying process, I subjected the diols **311a** and **311b** to acid-catalyzed acetal hydrolysis which resulted in D-ribopyanose (**313**) as the major product (Scheme 2.27). Not only the spectral data of the product were an exact match with an authentic sample of D-ribose but also these results were consistent with observations made by Barbas[14] (Entry 4, Table 7). Interestingly, a similar reaction under milder conditions (Entry 2, Table 6) resulted in partial hydrolysis of dimethoxyacetal functionality to afford methyl-D-ribofuranoside (**314**).

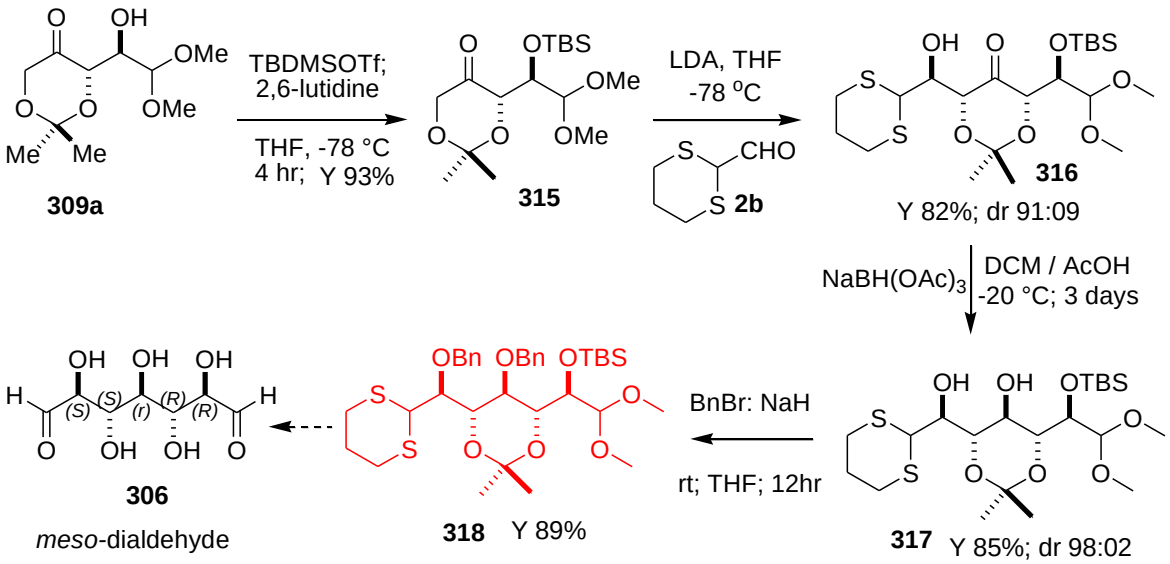


Scheme 2.27.

Table 7. Deacetylation conditions on compound **311** and synthesis of ribose conformers

entry	**reagent**	**reaction conditions**	**ratio of 313 : 314**	**major product anomer ratio** $\beta_p : \alpha_p : \beta_f : \alpha_f$
1	CF_3COOH	0 °C; $CHCl_3$: H_2O (3:1)	**100** : 0	**75 : 17** : 6 : 2
2	CH_3COOH	0 to 40 °C; H_2O	0 : **100**	4 : 2 : **76 : 19**
3	CF_3COOH	90 °C; H_2O	**100** : 0	**74 : 18** : 6 : 2
4	DOWEX 50W2	rt; H_2O	**100** : 0	**74 : 18** : 6 : 2

2.7.3.6 Synthesis of the masked dialdehyde intermediate



Scheme 2.28.

Scheme 2.28 illustrates the synthesis of the chiral compound **318**. It should be noted that **318** is a synthetic equivalent to the orthogonally protected meso dialdehyde **306**. The C_S-symmetry of the deprotected meso dialdehyde of **306** should, in principle, allow a stereodivergent synthesis of either enantiomers of the target aldoheptose (depending on which formyl group is ultimately reduced).

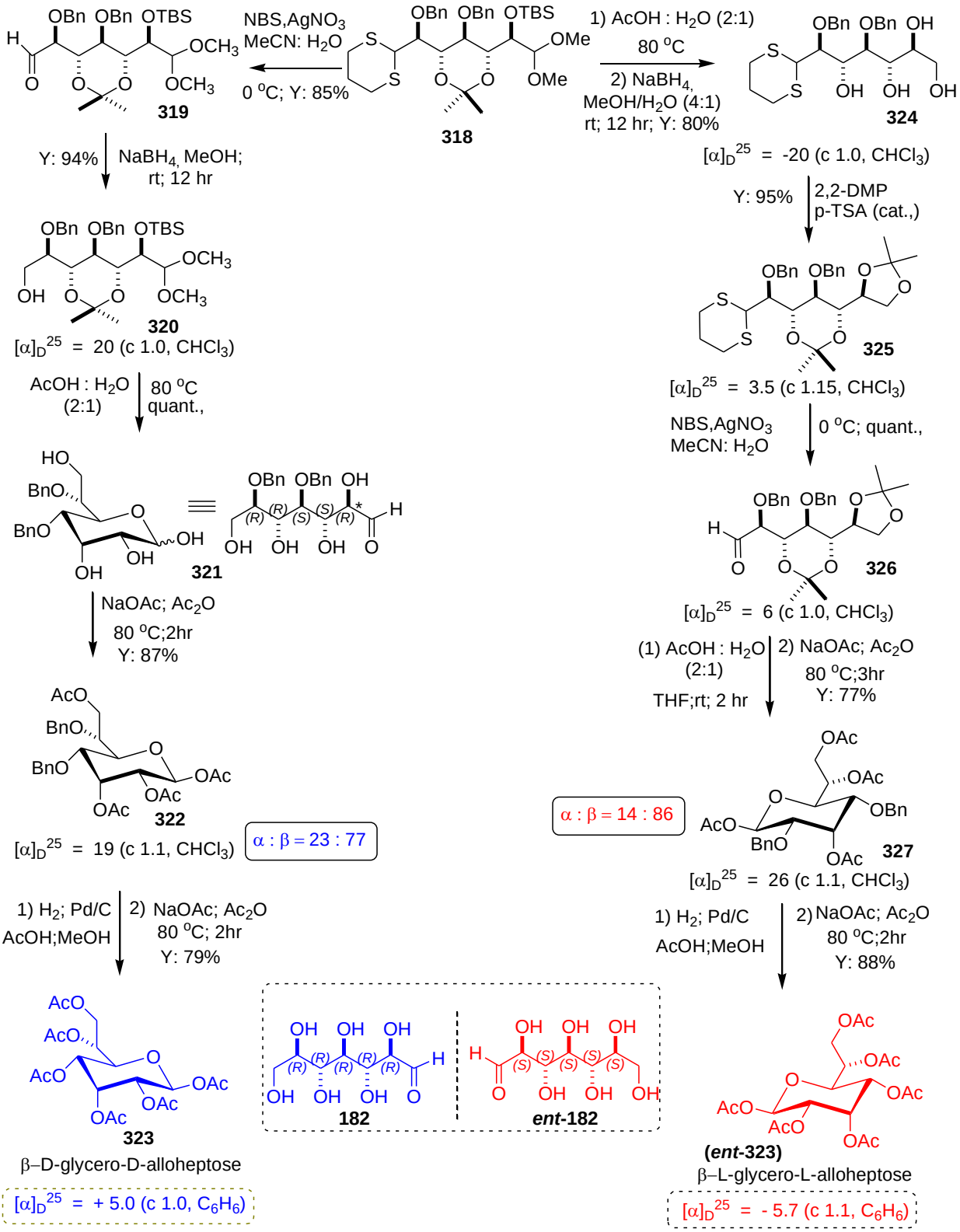
The reaction sequence started with the standard *tert*-butyldimethylsilyl (TBS) protection of the hydroxyl group of the aldol adduct **309a** to obtain the silylated aldol **315**. The silyl compound **315** was then employed in a lithium base-mediated second aldol reaction with 1,3-dithiane-2-carbaldehyde (**2b**) as the electrophile (reaction conditions developed in our laboratory),[139] to provide *anti-cis-anti* aldol adduct **316** in 82% yield with excellent selectivity. Then stereoselective reduction of the aldol adduct **316** with $NaBH(OAc)_3$ led to

the corresponding *cis*-1,3-diol product **317** in high diastereoselctivity and 85 % yield. The hydroxyl groups of compound **317** were protected as benzyl ethers using the standard conditions which resulted in orthogonally protected dialdehyde intermediate **318**.

2.7.3.7 Stereodivergent synthesis: DD- and LL-*glycero*-*allo*-heptoses

The unmasking of the carboxaldehyde functionality embedded in compound **318** played the central role in carrying out the stereodivergent synthesis of both enantiomers of *glycero*-*allo*heptose (Scheme 2.29). Corey's protocol[157] using NBS/$AgNO_3$ in aqueous acetonitrile resulted in dithiane hydrolysis of compound **318** to aldehyde **319** which was consequently reduced to form the alcohol **320** in 80% yield over 2 steps. The compound **320** was subjected to one-pot acid-catalyzed acetal/ketal/TBS deprotection followed by acetylation to afford **322** with anomeric ratio 23 : 77 (α : β) and 87 % overall yield. Then the compound **322** was debenzylated under acid-catalyzed hydrogenolysis and acetylated to form hexaacetate- β-D-*glycero*-D-*allo*-heptopyranose (**323**) in 22 % overall yield in eleven-steps starting from dioxanone **1a**.

A similar approach was applied in synthesis of L-enantiomer *ent*-**323**. Intermediate **318** was subjected to the sequence of dimethoxyacetal hydrolysis followed by reduction of the aldehyde group with $NaBH_4$ to form the tetraol **324**. Unfortunately, subsequent dithiane hydrolysis of the free tetraol **324** did not yield the desired aldehyde. In order to perform radical mediated dithiane hydrolysis, four hydroxyl groups of tetraol **324** needed to be protected using 2,2-dimethoxypropane and catalytic amount of *p*-TsOH.


NBS,AgNO3
MeCN: H2O
0 °C; Y: 85%
318
1) AcOH : H2O (2:1)
80 °C
2) NaBH4,
MeOH/H2O (4:1)
rt; 12 hr; Y: 80%
324
[α]D25 = -20 (c 1.0, CHCl3)
319
Y: 94%
NaBH4, MeOH;
rt; 12 hr
320
[α]D25 = 20 (c 1.0, CHCl3)
AcOH : H2O
(2:1)
80 °C
quant.,
321
NaOAc; Ac2O
80 °C;2hr
Y: 87%
322
[α]D25 = 19 (c 1.1, CHCl3)
α : β = 23 : 77
1) H2; Pd/C
AcOH;MeOH
2) NaOAc; Ac2O
80 °C; 2hr
Y: 79%
323
β–D-glycero-D-alloheptose
[α]D25 = + 5.0 (c 1.0, C6H6)
182
ent-182
Y: 95%
2,2-DMP
p-TSA (cat.,)
325
[α]D25 = 3.5 (c 1.15, CHCl3)
NBS,AgNO3
MeCN: H2O
0 °C; quant.,
326
[α]D25 = 6 (c 1.0, CHCl3)
(1) AcOH : H2O
(2:1)
THF;rt; 2 hr
2) NaOAc; Ac2O
80 °C;3hr
Y: 77%
α : β = 14 : 86
327
[α]D25 = 26 (c 1.1, CHCl3)
1) H2; Pd/C
AcOH;MeOH
2) NaOAc; Ac2O
80 °C;2hr
Y: 88%
(ent-323)
β–L-glycero-L-alloheptose
[α]D25 = - 5.7 (c 1.1, C6H6)

Scheme 2.29.

Then dithiane hydrolysis of **325** resulted in aldehyde **326**, which was subjected to acid-catalyzed ketal deprotection followed by acetylation to afford compound **327** with an anomeric ratio of 14 : 86 (α : β) and 77% overall yield. Debenzylation of **327** under acid-catalyzed hydrogenation followed by acetylation resulted in pure hexaacetate- β-L-*glycero*-L-*allo*-heptopyranose (***ent*-323**) in 20% overall yield in 13 steps starting from dioxanone (**1**).

The optical rotation values for **323** and ***ent*-323** (note opposite signs) were in good agreement with the previously reported data for D-*glycero*-D-*allo*-heptose.[161] The exactly identical ^{1}H and ^{13}C NMR spectra for compounds **323** and ***ent*-323** confirmed the stereodivergent synthesis of both the enantiomers of β-*glycero*-*allo*-heptopyranose.

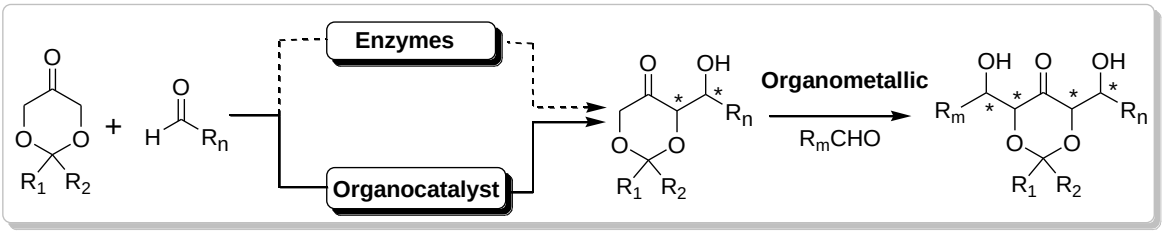
In summary, the two enantiomers DD- and LL-*glycero*-β-*allo*-heptopyranose (**323** and ***ent*-323)** were synthesized starting from commercially available dioxanone **1a** in eleven- and thirteen-steps respectively, with 22 and 20% respective overall yields. This strategy is the first example of a stereodivergent approach to access "rare" aldoheptoses.

3 SUMMARY

The primary objective of the thesis to expand dioxanone based methodology in synthesis of iminosugars and higher monosaccharides was successfully realized. The main synthetic tools are stereoselective aldol reactions of 2-substituted-1,3-dioxan-5-ones.

Broadly the work presented in the thesis is classified into three projects:

- **Project I:** Organocatalytic aldol reactions of C_{2v}- and C_S symmetrical dioxanones
- **Project II:** Effect of additives on the proline-catalytic aldol reactions of dioxanones
- **Project III:** Building carbohydrates on the dioxanone scaffold



Scheme 3.1: Project overview: Generic strategy of $C_m + C_3 + C_n$ methodology

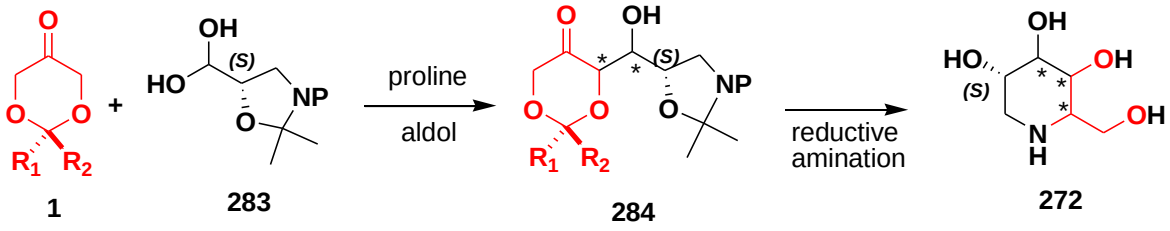
The synthesis of polyoxygenated compounds and higher monosaccharides is viable upon applying organocatalysis and/or enolate chemistry on dioxanones with appropriate aldehyde acceptors (Scheme 3.1).

1) **Methodology**: The initial methodological studies were carried out to obtain a set of reaction conditions to perform stereoselective "first" aldol reactions on a dioxanone substrate.

- Proline-catalyzed aldol reactions of C_S-symmetrical dioxanones produced higher diasteroselective in comparison with C_2-symmetrical dioxanones (de up to 88% from 34%), which demonstrates the role of steric effects of dioxanones on the selectivity of the aldol reactions.

- Presence of additives such as LiCl (a weak Lewis acid) and pyridinium-p-toluenesulfonate (PPTS, Brønsted acid) has enhanced the enatioselectivity of proline catalyzed aldol reactions. Reactions run without additives might not be synthetically useful; these additives move the selectivity into synthetically attractive range (from 60 up to 96 % ee). (*cf.*, *Synlett* **2006**, (15), 2387-2390)[132]

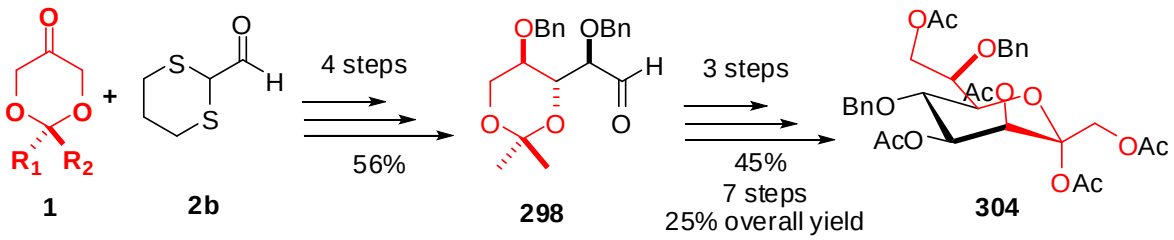
2) Synthesis of 1-deoxyiminosugars: Piperidine amino sugars (iminosugars) such as 5-amino-5-deoxyaldohexoses and their 1-deoxy derivatives are a class of monosaccharides with the nitrogen atom in place of the ring oxygen of the corresponding monosaccharide.



Scheme 3.2: Quick two-step synthesis to 1-deoxyiminosugars

A simple two-step dioxanone route was developed to access L-1-deoxymannojirimycin, L-1-deoxyidonojirimycin, and the *N*-isopropyl deoxyidonojirimycin from readily available starting materials such as dioxanone and (*S*)-isoserinal hydrate (**283**). The key steps include diastereoselective proline-catalyzed *syn*-aldol transformation and a reductive amination/cyclization. (*cf.*, *J. Org. Chem.* **2009**, *74*, (11), 4390-4392)[136]

3) **Synthesis of (+)-D-*glycero*-D-*manno*-2-octulose**: The title compound, a higher-carbon sugar isolated from opium poppies, has been synthesized in enantiomerically pure form. The short synthetic sequence involved two proline-catalyzed aldol addition reactions of 2,2-dialkyl-1,3-dioxan-5-ones to appropriate aldehydes: the first addition to 1,3-dithiane-2-carboxaldehyde (**2b**), followed by reduction to the corresponding diol, protection of the hydroxy groups and dithiane hydrolysis afforded a protected D-ribose (**298**) that was used in the second aldol reaction.

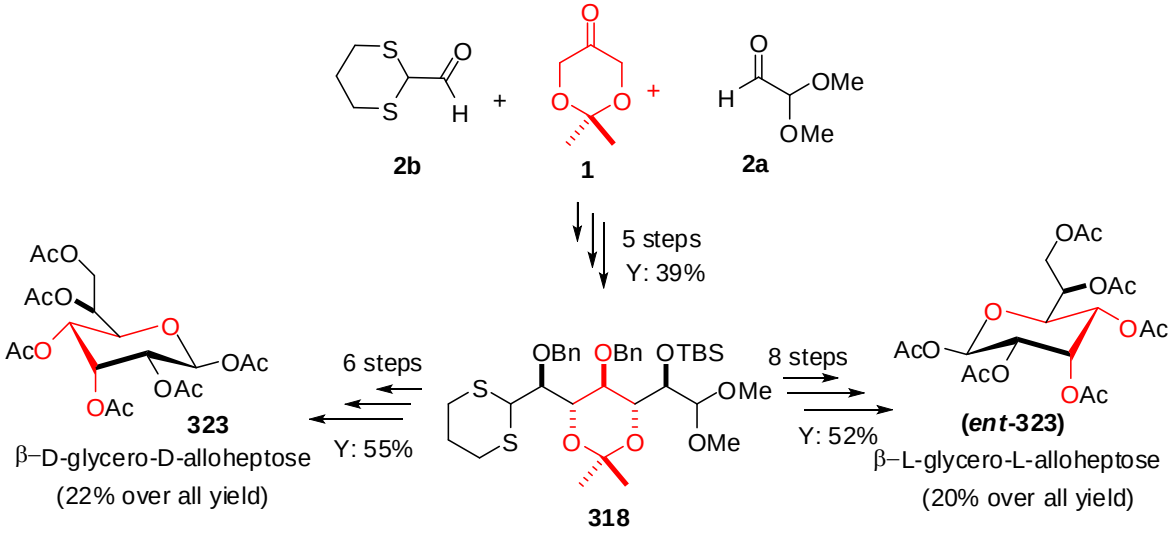


Scheme 3.3: Synthetic D-*glycero*-D-*manno*-2-ocutlose

(+)-D-*Glycero*-D-*manno*-2-octulose **304** was synthesized in seven steps starting from readilly available dioxanone **1** (25% overall yield). There by developed a unique and complete dioxanone methodology to access "rare" higher carbohydrate fragments in a stereocontrolled fashion. (*cf.*, *Tetrahedron Lett.* **2007**, *48*, 9195-98)[155]

4) **Stereodivergent synthesis of DD- and LL- *glycero*-β-*allo*-heptopyranoses**: The second nucleophilic site of dioxanone ring was explored to realize the first stereodivergent synthesis of two enantiomers of *glycero*-*allo*-heptose from readily available non chiral starting materials (Scheme 3.4). The short synthetic sequence involves enamine and enolate mediated aldol reactions at α and α' positions of dioxanone thereby demonstrating the complementary nature of organocatalysis and organometallic methods. The new method for the enantioselective stereodivergent first

total synthesis of DD- and LL-*glycero*-β-*allo*-heptopyranose from simple dioxanone moiety was accomplished.



Scheme 3.4: Stereodivergent synthesis of DD and LL-*glycero*-β-*allo*heptoses

4 EXPERIMENTAL SECTION

4.1 General Methods

All solvents were distilled prior to use by standard procedures.[163,164] Anhydrous solvents were distilled under nitrogen atmosphere as follows: tetrahydrofuran (THF), diethyl ether (Et_2O) and benzene (PhH) from benzophenone sodium ketyl; dichloromethane (CH_2Cl_2) and toluene ($PhCH_3$) from calcium hydride (CaH_2), diisopropylamine (DIA), triethylamine (TEA), diisopropylethylamine (DIPEA) and pyridine were distilled from calcium hydride (CaH_2) under nitrogen and stored over 4 Å molecular sieves. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were dried with (CaH_2) according to the known procedures.[165]

All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask (or vials) capped with a rubber septum, and attached via a needle to a nitrogen manifold. Low temperature baths were ice/water (0 °C), ice/NaCl/MeOH (-20 °C), and CO_2(s)/acetone (-78 °C).[166] Reaction temperatures refer to the bath temperature. All liquid aldehydes and acetic anhydride (Ac_2O) were distilled and stored under nitrogen, dimethoxyacetaldehyde was used as an aqueous solution (60%). *n*-BuLi was periodically titrated using 2,5-dimethoxybenzyl alcohol as the indicator.[167] LiCl was dried at 130-150 °C under vacuum overnight, and it was kept under nitrogen. All other commercially available reagents were used as received without further purification, unless stated otherwise. Concentrated phosphate buffer, used to quench reactions, was prepared by dissolving Na_2HPO_4 (47.0 g) and NaH_2PO_4 (32.0 g) in H_2O (500 mL).

Thin-Layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F_{254}. The compounds were visualized under ultraviolet lamp (254 nm) and by treatment with a solution of $KMnO_4$ followed by charring on a hot plate. Flash column chromatography (FCC) was performed using the standard procedure of Still *et al.*,[168] employing silica gel (230-400 mesh).[169]

4.2 Spectral Data

Nuclear magnetic resonance (NMR) spectra were recorded on Brucker at 500 MHz for ^{1}H, 125 MHz for ^{13}C in deuterated solvents mentioned. All the NMR data were recorded at room temperature unless otherwise mentioned. Chemical shift (δ) values are reported in parts per million (ppm). Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard: $CDCl_3$ (δ 7.24, δ 77.23); C_6D_6 (δ 7.16, δ 128.39); D_2O (δ 4.80).[170] Coupling constant (*J* values) are reported in Hertz (Hz), and spin multiplicities are referred by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad peak). Couplings constants (*J*) were reported to the nearest 0.5 Hz. The ^{1}H NMR assignments were made based on chemical shifts and multiplicities. Where necessary, 2D gradient COSY, and homonuclear decoupling experiments were used to assign coupling constants for overlapping signals in ^{1}H NMR . The ^{13}C NMR assignments were made on the basis of chemical shifts and were confirmed, where necessary, by two dimensional $^{1}H/^{13}C$ correlation experiments (HSQC and/or HMBC).[171]

Optical rotations ($[\alpha]_D$) measurements were determined on a DigiPol 781-T6U automatic polarimeter and reported as the average of five measurements at ambient temperature using a 1 mL, 10 cm cell; the concentrations (*c*) are reported in g/100 mL.

HRMS and LRMS were obtained on an API QSTAR® Pulsar Hybrid LC/MS/MS system and/or 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 Bio-Rad Fourier transform interferometer and only diagnostic peaks are reported.

Melting points and boiling points are uncorrected. Melting points were measured on a Gallencamp melting point apparatus.

The relative configuration of aldol products (*syn* or anti) were assigned based on ^{1}H NMR coupling constant (*syn* J = 2 – 6 Hz, *anti* J = 7 – 10 Hz) of the vicinal C(O)-C<u>H</u>-C<u>H</u>-OH [172]

Chiral HPLC analysis was performed with Gilson 715 Series HPLC utilizing chiralpak AD or chiralpack IB columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with detection at 254 nm or 230 nm.

4.3 General Procedures and Methods

4.3.1 General experimental procedure for the organocatalytic aldol reaction

Procedure P1: (*S*)-Proline-catalyzed aldol reaction without additives[12,14,20]

To a glass vial containing DMSO (1.0 mL) were added dioxanone (**1**, 0.50 mmol), the aldehyde (0.50 mmol), and (*S*)-proline (0.15 mmol), followed by LiCl (0.50 mmol) and the mixture was flushed with nitrogen and stirred at room temperature for 15 min to dissolve all the reactants. The mixture was then refrigerated at 5 ^{o}C until the reaction was complete as shown by TLC (usually 48 hr). Saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring, then the mixture was extracted with ethyl acetate (2x10 mL), and the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4, and concentrated to afford the crude product (the dr was measured by ^{1}H NMR on the crude product) which was then purified using flash column chromatography (FCC) to afford the aldol product.

Procedure P2: (*S*)-Proline-catalyzed aldol reaction with additive[12,132]

A dioxanone (0.50 mmol) and an aldehyde (0.50 mmol) were added to a flame-dried vial charged with (*S*)-proline (0.15 mmol) and respective additive (0.15–0.50 mmol). Dry DMSO (0.30 mL) was added; the vial was flushed with nitrogen and stored in a refrigerator at 4 °C for 1–7 d. The reaction was then quenched with sat. NH_4Cl solution (5.0 mL) and the mixture were extracted with EtOAc. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, concentrated and purified by FCC to afford the aldol product.

4.3.2 General experimental procedure for TBS or TIPS protection reaction

Procedure P3: TIPS/TBS protection in the presence of 2,6-lutidine[173,20]

To a cold solution of a dioxanone aldol (1.0 eq) in dry THF (5.0 mL/1.0 mmol) were added dropwise 2,6-lutidine (2.0 eq) at 0 °C or -78 °C followed by TIPSOTf / TBSOTf (1.2 - 1.5 eq). The reaction was warmed up to room temperature and stirred until no starting material was detected by TLC (usually 1 to 3 hr depending on the substrate. Occasionally, the reaction required overnight stirring). The saturated solution of sodium bicarbonate was then added, the mixture was extracted with dichloromethane (50 mL x 3) and the combined organic layers were washed with saturated solution of sodium chloride, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography to afford the TIPS- or TBS-protected products.

4.3.3 General procedure for aldol reaction of protected β-hydroxydioxanone

(This procedure was adapted from Niewczas' thesis)[12,18]

Procedure P4: A solution of *n*-BuLi in hexaness (2.5 M; 3.8 to 5.5 eq), was added dropwise to the stirred solution of DIA (3.5 to 5.0 eq) in dry THF (5 vol) at 0 °C under nitrogen. After 30 min a solution of a dioxanone mono-aldol (1.0 eq) in THF (5 vol) was added slowly and the mixture was stirred at -78 °C for 0.5-2 h. The aldehyde (3.0 to 5.5 eq) was then added and, after 20 min, the reaction was quenched with concentrated phosphate buffer (pH 7) and extracted with ether (x 3). The combined organic layers were washed with saturated solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated to give the crude product. The crude product was fractionated by FCC to provide the double aldol products.

4.3.4 General experimental procedure for reduction of aldol adducts into corresponding alcohols with $NaBH(OAc)_3$

Procedure P5: Based on modified procedure from ref. 14 and 174

To a solution of β-hydroxyketone (1.0 eq) in dry CH_2Cl_2 (0.40 mL/mmol) AcOH (0.17 eq) and $NaBH(OAc)_3$ (1.2 eq) were added at -20 °C. The reaction was keept at that temperature for 1-5 d (TLC controled).The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (50 mL x 3).The combined organic layers were washed with aqueus saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated to give a crude diols mixture which was purified by flash column chromatography on silica gel to give pure products.

4.3.5 Corey's protocol for dithiane hydrolysis to aldehyde

Procedure P6: To a solution of dithiane compound (1.0 eq.) in 10 mL of acetonitrile: water (4 : 1), at 0^o C added N-bromosuccinimide (4.0 eq.) followed by silver nitrate (4.5 eq.) and stirred at stirred at same temperature for 5 minutes. Reaction was follwed by TLC (generally, product and starting material had similar R_f). The reaction was quenched with 10% sodium sulfite solution and filtered over celite bed ,washed with CH_2Cl_2 (15 ml) and the resulting mixture was extracted with CH_2Cl_2 (2x15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution follwed by brine, dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave the crude aldehyde that was purified by flash chromatography on silica gel to give the desired aldehyde.

4.3.6 General hydrogenolysis procedure

Procedure P7: To the aldol adduct (0.5 mmol) in MeOH (3.0 mL) added 10% Pd/C (30 mg). The resulting suspension was stirred under H_2 (~5 psi) at ambient temperature and the reaction was monitored by TLC (12 to 24 hr). The reaction mixture was then acidified with HCl solution (0.5 mL, 2N), and was stirred under H_2 for 6 hr at room temperature. The catalyst was filtered off through Celite and evaporation of the solvent afforded the crude product.

Procedure P8: (hydrogenolysis under acidic conditions): The aldol adduct (0.50 mmol) in MeOH (3.0 mL), was charged with p-toluenesulfonic acid (0.10 mmol) and the resulting solution was stirred at room temperature for 15 min. The catalyst (10% Pd/C; 30 mg) was then added and the resulting suspension was stirred under H_2 (~5.0 psi) at ambient temperature for 24 hr. The mixture was then acidified with HCl solution (0.50 mL, 2.0 N), and was stirred under H_2 for 6.0 hr at room temperature. The catalyst was filtered off through Celite and evaporation of the solvent afforded the crude product.

4.3.7 General procedure for acetylation

Reduced aldol products were subjected to deprotection using acidic conditions to afford the corresponding monosaccharides which were generally characterized as acetate derivatives.

Procedure P9: To the crude polyol compound were added sodium acetate (12 eq.) and acetic anhydride (5.0 vol.). The resulting mixture was heated to 90 ^{o}C for 2.0 hr and the reaction was quenched with ice and saturated $NaHCO_3$ solution. Then the mixture was extracted with ethyl acetate (3 x 20 mL), and then combined organic layers were washed

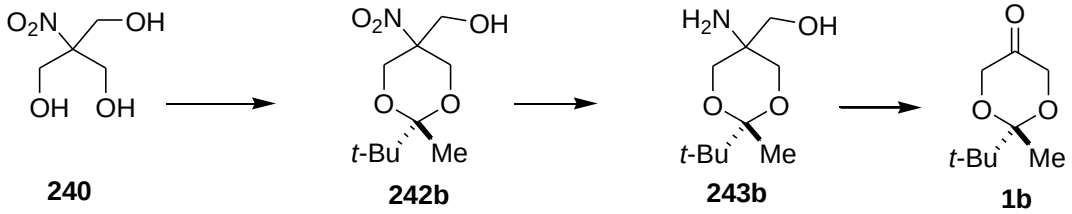
with brine. The organic phase was dried over anhydrous Na_2SO_4, concentrated to get a crude product which was purified by silica-gel flash column chromatography to yield the fully acetylated product.

4.4 Experimental Procedures and Data

Dioxanone **1a** and **1d** were synthesized according to the established procedure within the group and their spectra data were consistent with that reported.[10-13,175] Dimethoxyacetaldehyde (**2a**) was obtained from Aldrich as an aqueous solution (60 wt %), 1,3-dithiane-2-carbaldehyde (**2b**) was prepared according to the Meyers procedure,[176] and D-glyceraldehyde acetonide (**2c**) was prepared using standard procedure from D-mannitol.[177] All other reagents were commercially available and unless otherwise noted, were used as received.

4.4.1 Synthesis of dioxanone starting materials

2-*tert*-Butyl-2-methyl-1,3-dioxan-5-one (1b)[11]



The compound **1b** was prepared according to the modified literature procedure[11]

Tris(hydroxymethyl)nitromethane (**240**, 10.0 g, 66.2 mmol, 1 eq.) and *p*-TsOH.H_2O (127 mg, 0.66 mmol, 0.01 eq.) were dissolved in dry benzene (200 mL). Pinacolone (**241b**, 9.90 mL, 7.95 g, 79.4 mmol, 1.20 eq.) was added and the mixture was refluxed with removal of

water using a Soxhlet apparatus with 4 Å molecular sieves. After the reaction was completed (TLC and ^{1}H NMR monitoring) the reaction mixture was cooled to room temperature and diluted with EtOAc (150 mL). The organic layer was washed with saturated solution of $NaHCO_3$ (150 mL), followed by saturated brine solution (150 mL) and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to yield the crude product **242b** as a mixture of *cis*/*trans* isomers in 1: 1.1 ratio as a pale yellow solid in 89 % yield (13.7 g, 58.9 mmol). No effort was made to separate *cis*/*trans* isomers.

A solution of the crude mixture of both isomers of (2-*tert*-butyl-2-methyl-5-nitro-1,3-dioxan-5-yl) methanol (**242b**) (13.6 g, 58.4 mmol) was dissolved in methanol (100 mL). Raney nickel (ca 0.200 g) was added and the solution was stirred for 5 min, filtered, and a fresh portion of Raney nickel was added (ca 2.00 g). Reaction mixture was hydrogenated overnight (50 psi, room temperature). TLC showed the completion of the reaction. The reaction mixture was filtered through the Celite bed to remove the catalyst. Then the filter bed was washed with methanol (50.0 mL) and the solvent was removed under reduced pressure to provide the crude product **243b** as a mixture of isomers in a ratio of 1 : 1 as a white solid (11.4 g, 56.0 mmol) in 96.0 % yield. No efforts were made to assign *cis*/*trans* configuration.

To an ice cold (0-5 °C) solution of sodium periodate (17.4 g, 81.3 mmol, 1.50 eq) in H_2O (40 mL) added, over 10 min. at 0 °C to the α-amino alcohol **243b** (11.0 g, 54.2 mmol, 1.00 eq) dissolved in H_2O-MeOH (1 : 3; 100 mL). The mixture was stirred at this temperature for 4 h. Next, the white suspension was filtered off and the solution was thoroughly

extracted with CH_2Cl_2 (4 x 75 mL). The combined organic layers were washed with a saturated sodium bicarbonate solution (50 mL), dried with anhydrous Na_2SO_4 and evaporated on a rotovap (temp < 30 °C). The crude product was purified by passing through silica column (hexanes : ethyl acetate 98 : 2) to give pure 2-*tert*-butyl-2-methyl-1,3-dioxan-5-one (**1b**) (8.25 g, 47.9 mmol, 88 %) as a colorless viscous product which crystallized upon storing in refrigerator. Dioxanone **1b** has a characteristic peppermint odor and readily sublimes under reduced pressure.

Melting point: 47-48 °C; (Lit[11]: 47-49 °C)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, J = 18.2 Hz, 2H), 4.23 (d, J = 18.2 Hz, 2H), 1.36 (s, 3H), 1.02 (s, 9H)

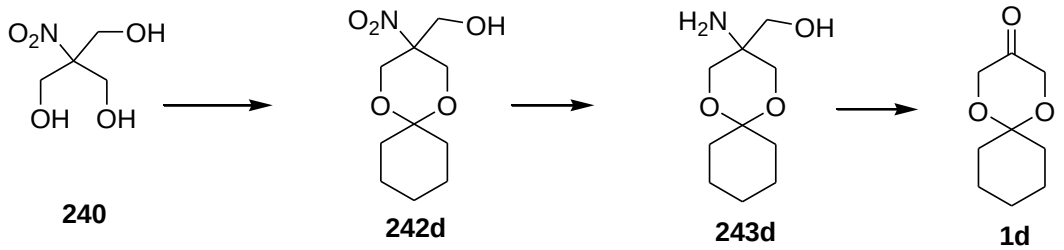
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 103.5, 68.7, 40.4, 25.3, 15.8.

HRMS (CI, NH_3) exact mass calcd for $(C_9H_{16}O_3 + H)^+$ 173.1178, found m/z 173.1178

LRMS (CI, NH_3): m/z (relative intensity %): 173 (M+1, 100), 115 (25).

IR (KBr): 2893 (w), 1735 (s), 1142 (s) cm^{-1}.

1,5-Dioxaspiro[5.5]undecan-3-one (1d)



A similar three step procedure as described for compound **1b** produced dioxanone **1d** (5.04 g, 29.6 mmol, 80 %) as a colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (s, 4H), 1.72 (m, 4H). 1.58 (m, 4H), 1.43 (m, 2H)

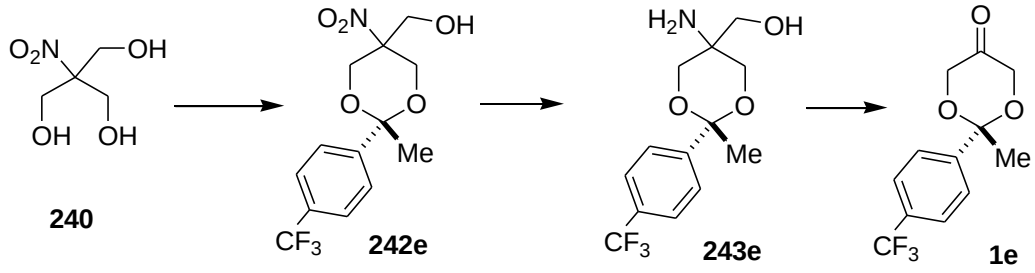
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 102.4, 69.2, 38.4, 26.6, 23.1.

HRMS (CI, NH_3) exact mass calcd for $(C_9H_{14}O_3 + H)^+$ 171.1021, found m/z 171.1015

LRMS (CI, NH_3): m/z (relative intensity %): 171 (M+1, 100), 143 (44), 108 (19).

IR (KBr): 2916-2806 (w), 1739 (s), 1108 (s) cm^{-1}.

2-Methyl-2-(4-(trifluoromethyl)phenyl)-1,3-dioxan-5-one (1d)



The similar three step procedure as described for compound **1b** produced dioxanone **1e** (1.06 g, 4.07 mmol, 48 %) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 4H), 4.26 (d, J = 16.7 Hz, 2H), 4.07 (d, J = 16.7 Hz, 2H), 1.64 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 149.2, 130.1, 127.8, 124.9, 123.3, 104.2, 68.2, 21.1.

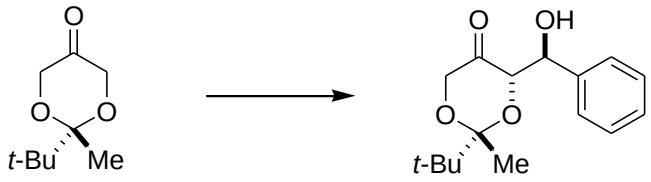
HRMS (CI, NH_3) exact mass calcd for $(C_{12}H_{11}F_3O_3 + H)^+$ 261.0739, found m/z 261.0735

LRMS (CI, NH_3): m/z (relative intensity %): 261 (M+1, 100), 212 (54), 157 (43), 108 (22).

IR (KBr): 3039 (w), 2955 (w), 1745 (s), 1605, 1308 (w), 1111(s) cm^{-1}.

4.4.2 Methodological studies on proline-catalyzed aldol reactions of dioxanones (*c.f.* page 66)

(2*R*,4*S*)-2-*tert*-butyl-4-((*S*)-hydroxy(phenyl)methyl)-2-methyl-1,3-dioxan-5-one (3bf)



1b **3bf**

Procedure P1 (0.50 mmol scale) afforded the viscous crude product. Diastereoselectivity of the reaction was determined on the crude product mixture by integration of ^{1}H NMR peaks at 5.23 ppm (J = 2.8 Hz) and 5.02 ppm (J = 6.5 Hz) and was found to be 6 : 94 (*syn* : *anti*). The crude product was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti* aldol adduct **3bf** (87 mg, 0.315 mmol) in 63 % yield as a yellowish oil. Enantioselectivity was measured by ^{1}H NMR in deuterated benzene with Eu(tfc)$_3$ as a shift reagent and was found to be 60 %.

$[\alpha]^{25}_{D}$ = -29 (c 1.1, $CHCl_3$) (ee: 60 %)

Procedure P2 (0.50 mmol scale) with LiCl as the additive afforded the crude product. ^{1}H NMR spectrum of the crude product mixture showed only the *anti*-diastereoisomer at 5.02 ppm (J = 6.5 Hz). The crude product was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti* aldol adduct **3bf** (101 mg, 0.315 mmol) in 72 % yield as a yellowish oil. Enantioselectivity was measured by ^{1}H NMR in deuterated benzene with Eu(tfc)$_3$ as a shift reagent and was found to be 68 %.

$[\alpha]^{25}_{D}$ = -34 (c 1.0, $CHCl_3$) (ee: 68 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.01 (dd, J_1 = 2.5 Hz, J_2 = 6.3 Hz, 1H), 4.36 (d, J = 6.3 Hz, 1H), 4.23 (d, J = 18.3 Hz, 1H), 4.16 (d, J = 18.3 Hz, 1H), 3.47 (d, J = 2.5 Hz, 1H, OH), 1.25 (s, 3H), 0.94 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.4, 138.8, 128.0, 127.9, 127.0, 104.1, 78.7, 73.7, 69.7, 40.3, 25.1, 16.1

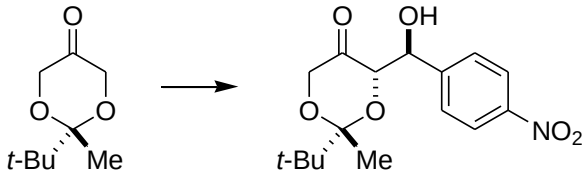
Compound **3bf** was also characterized in benzene: **^{1}H NMR** (500 MHz, C_6D_6) δ: 7.43 (d, J = 7.7 Hz, 2H), 7.15 (d, J = 7.7 Hz, 2H), 7.10 (t, J = 7.7 Hz, 1H), 4.89 (dd, J_1 = 6.3 Hz, J_2 = 2.5 Hz, 1H), 4.10 (d, J = 6.3 Hz, 1H), 3.93 (d, J = 17.9 Hz, 1H), 3.75 (d, J = 17.9 Hz, 1H), 3.3 (d, J = 2.5 Hz, 1H, OH), 0.87 (s, 3H), 0.86 (s, 9H)

HRMS *m/z* calcd for $C_{16}H_{22}O_4$ 278.1518 (M), found 278.1518 (EI)

LRMS (CI, NH_3), *m/z* (relative intensity): 296 ($[M+18]^+$, 52), 279 ($[M+1]^+$, 100), 196 (17), 178 (23), 155 (34), 118 (32).

IR (KBr): 3378 (br), 3069, 3029, 2964, 2912, 1732, 1604, 1453, 1261, 1090, 799, 699 cm^{-1}

(2R,4S)-2-*tert*-Butyl-4-((S)-hydroxy(4-nitrophenyl)methyl)-2-methyl-1,3-dioxan-5-one (330)



1b **330**

Procedure P2 (0.50 mmol scale) with LiCl as the additive afforded a gummy crude product. ^{1}H NMR spectrum of the crude product mixture just showed only the *anti*-diastereoisomer at 5.09 ppm (J = 6.7 Hz). The crude product was purified by FCC (hexanes : ethyl acetate 8 : 2) to provide the *anti* aldol adduct **330** (98.5 mg, 0.305 mmol) in 61 % yield as a yellow solid.

$[\alpha]^{25}_{D}$ = -25 (c 1.0, $CHCl_3$)
Melting Point: 126-128 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.18 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 5.09 (dd, J_1 = 1.5 Hz, J_2 = 6.7 Hz, 1H), 4.31 (dd, J_1 = 1.5 Hz, J_2 = 18.2 Hz, 1H), 4.28 (d, J = 6.7 Hz, 1H), 4.22 (d, J = 18.2 Hz, 1H), 3.73 (br, 1H, OH), 1.24 (s, 3H), 0.93 (s, 9H).

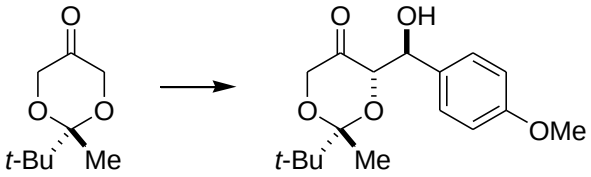
^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.3, 147.9, 146.3, 128.1, 123.3, 104.5, 78.4, 73.0, 69.8, 40.4, 25.3, 16.1.

HRMS *m/z* calcd for $C_{16}H_{21}NO_6$ 323.1369 (M), found 323.1368 (EI)

LRMS (CI, NH_3), *m/z* (relative intensity): 324 ($[M+1]^+$, 100), 286 (16), 222 (46), 156 (76), 108 (28).

IR (KBr): 3449 (br), 3032, 1742, 1544, 1393, 1098 cm^{-1}

(2*R*,4*S*)-2-*tert*-Butyl-4-((*S*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-1,3-dioxan-5-one (331)



Procedure P2 (0.50 mmol scale) with LiCl as the additive resulted in a gummy crude product. ^{1}H NMR spectrum of the crude product mixture showed only the *anti*-diastereoisomer at 4.95 ppm (J = 6.3 Hz). The crude product was purified by FCC (hexanes : ethyl acetate 8 : 2) to provide the *anti* aldol adduct **331** (82 mg, 0.266 mmol) in 53 % yield as a pale yellow solid.

$[\alpha]^{25}_{D}$ = -32 (c 1.1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.95 (d, J = 6.3 Hz, 1H), 4.33 (dd, J_1 = 1.2 Hz, J_2 = 6.3 Hz, 1H), 4.20 (dd, J_1 = 1.2 Hz, J_2 = 18.2 Hz, 1H), 4.13 (d, J = 18.2 Hz, 1H), 3.78 (s, 3H), 3.40 (br, 1H, OH), 1.26 (s, 3H), 0.94 (s, 9H).

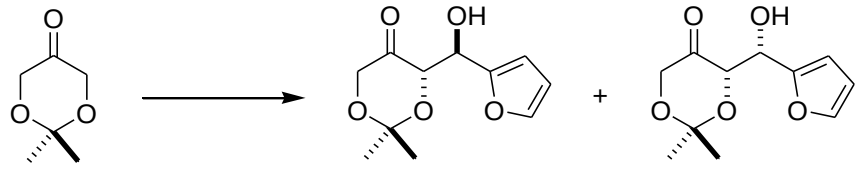
^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.8, 159.6, 131.3, 128.4, 113.6, 104.3, 78.9, 73.5, 69.9, 55.5, 40.5, 25.4, 16.4.

HRMS *m/z* calcd for $C_{17}H_{24}O_5$ 308.1624 (M), found 308.1621 (EI)

LRMS (CI, NH_3), *m/z* (relative intensity): 326 ($[M+18]^+$, 33), 309 ($[M+1]^+$, 44), 254 (32), 196 (100), 154 (16), 118 (26)

IR (KBr): 3491(br), 3048, 1736, 1168, 1086 cm^{-1}

4-(*S*)-4-[(*R*)-Furan-2-yl(hydroxy)methyl]-2,2-dimethyl-1,3-dioxan-5-one (3ag)[12]



1a ***anti*-3ag** ***syn*-3ag**

Procedure P1 with three days of reaction time resulted in a dark gummy crude product. Diastereoselectivity of the reaction was determined by integration of ^{1}H NMR ($CDCl_3$) peaks at 5.21 ppm (J = 2.9 Hz) and 4.97 ppm (J = 7.0 Hz) and was found to be 40 : 60 (*syn* : *anti*). The crude product was purified by FCC (hexanes : ethyl acetate 8 : 2) to provide the mixture of *syn* and *anti* isomers in 21 % yield as a brown liquid.

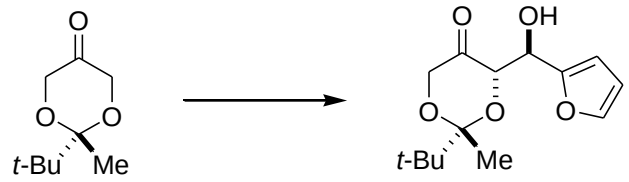
Procedure P2 with three days of reaction time and LiCl as an additive resulted in a mixture of *syn* and *anti* isomers. Diastereoselectivity of the reaction was determined by integration of ^{1}H NMR ($CDCl_3$) peaks at 5.21 ppm (J = 2.9 Hz) and 4.97 ppm (J = 7.0 Hz) and was found to be 25 : 75 (*syn* : *anti*). The crude product was purified by FCC (hexanes : ethyl acetate 8 : 2) to provide the mixture of *syn* and *anti* isomer in 33 % yield as a brown liquid.

The efforts to separate the *syn* and *anti* isomers were unsuccessful hence the optical rotation and enantiomeric excess were not determined. The NMR spectral data were obtained on the mixture of two isomers.

^{1}H NMR (500 MHz, C_6D_6) *δ:* 7.07 (s, 1H), 6.25 (m, 1H), 6.05 (m, 1H), 5.01 (d, J=6.7 Hz, 1H), 4.45 (dd, J_1=1.2 Hz, J_2=6.7 Hz, 1H), 3.79 (dd, J_1=1.2 Hz, J_2=17.3 Hz, 1H), 3.60 (d, J=17.3 Hz, 1H) 3.19 (br s, 1H), 1.16 (s, 3H), 1.03 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 206.4, 153.9, 142.5, 110.8, 108.7, 101.4, 75.7, 67.6, 66.9, 23.9, 23.5

(2*R*,4*S*)-2-(*tert*-Butyl)-4-[(*R*)-furan-2-yl(hydroxy)methyl]-2-methyl-1,3-dioxan-5-one (3bg)



1b **3bg**

Procedure P1 with three days of reaction time resulted in a dark gummy crude product. Diastereoselectivity of the reaction was determined by integration of ^{1}H NMR ($CDCl_3$) peaks at 4.57 ppm (J = 2.6 Hz) and 4.61 ppm (J_1 = 1.0 Hz, J_2 = 5.5 Hz) and was found to be 5 : 95 (*syn* : *anti*). The crude product was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti* isomer **3bg** in 30 % yield as a brown viscous liquid.

Procedure P2 with three days of reaction time and LiCl as the additive afforded the crude product as a brown oil. Diastereoselectivity of the reaction was determined by integration of ^{1}H NMR ($CDCl_3$) peaks at 4.57 ppm (J = 2.6 Hz) and 4.61 ppm (J_1 = 1.0 Hz, J_2 = 5.5 Hz) and was found to be 3 : 97 (*syn* : *anti*). The crude product was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti* isomer in 37 % yield as a brown liquid.

$[\alpha]^{25}_D$ = -51 (c 1.0, $CHCl_3$) (ee: 76%)

Chiral-phase HPLC (Daicel Chiralpac IB column, hexanes/isopropanol 96 : 4, flow rate 1ml/min, λ = 254nm)

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.35 (m, 1H), 6.32 (m, 2H), 5.09 (dd, J_1 = 5.4 Hz, J_2 = 6.8 Hz, 1H), 4.61 (dd, J_1 = 1.3 Hz, J_2 = 5.4 Hz, 1H), 4.28 (dd, J_1 = 1.3 Hz, J_2 = 18.3 Hz, 1H), 4.19 (d, J = 18.3 Hz, 1H), 3.07 (d, J = 6.8 Hz, 1H, OH), 1.38 (s, 3H), 0.94 (s, 9H) ppm

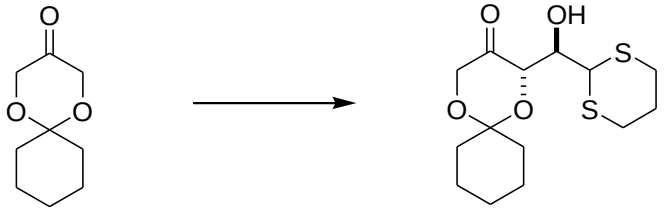
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 207.9, 152.3, 142.3, 110.4, 108.1, 104.1, 77.9, 69.6, 68.4, 40.3, 25.3, 16.0 ppm

HRMS (CI, NH3) *m/z* calcd for ($C_{14}H_{20}O_5$ + NH_4) requires 286.1700, found 286.1701

LRMS (CI, NH3), *m/z* (relative intensity): 286 ($[M+18]^+$, 11), 269 ($[M+1]^+$, 25), 251 (27), 193 (30), 173 (100), 151 (12), 115 (41).

IR (KBr): 3460 (br), 2962, 2915, 2877, 1741, 1597, 1483, 1394, 1278, 1165, 1012 cm^{-1}

(*S*)-2-((*R*)-(1,3-Dithian-2-yl)(hydroxy)methyl)-1,5-dioxaspiro[5.5]undecan-3-one (3db)



1d **3db**

Procedure P1 afforded a viscous crude product. ^{1}H NMR spectrum of the crude product mixture showed only the *anti*-diastereoisomer at 3.96 (d, *J* = 4.8 Hz, 1H). The crude product was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti*-aldol adduct **3db** in 72 % yield as a pale-yellow solid. Enantioselectivity was measured by ^{1}H NMR in deuterated benzene with $Eu(tfc)_3$ as a shift reagent and was found to be 67 %.

$[\alpha]^{25}_D$ = -89 (c 1.1, $CHCl_3$) (ee: 67 %)

Procedure P2 with LiCl as an additive afforded the crude product that was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti*-aldol adduct **3db** in 86% yield as a pale-yellow solid. Enantioselectivity was measured by ^{1}H NMR in deuterated benzene with $Eu(tfc)_3$ as the shift reagent and was found to be 92 %.

Melting point: 69- 70 °C

$[\alpha]^{25}_{D}$ = -125 (c 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, C_6D_6) δ: 4.66 (br, 2H), 4.15 (d, J = 16.4 Hz, 1H), 3.96 (d, J = 4.8 Hz, 1H), 3.71 (d, J = 16.4 Hz, 1H), 3.18 (br, 1H), 2.87 (ddd, J_1 = 2.5 Hz, J_2 = 12 Hz, J_3 = 13.9 Hz 1H), 2.69 (ddd, J_1 = 2.5 Hz, J_2 = 12 Hz, J_3 = 13.9 Hz 1H), 2.04 (m, 1H), 1.92 (m, 1H), 1.63 (m, 4H). 1.42 (m, 4H), 1.17 (m, 2H) ppm

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.56 (d, J = 5.1 Hz, 1H), 4.49 (dd, J_1 = 5.1 Hz, J_2 = 6.6 Hz, 1H), 4.41 (d, J = 17 Hz, 1H), 3.96 (d, J = 17 Hz, 1H), 3.91 (d, J = 6.6 Hz, 1H), 3.15 (br, OH, 1H), 3.01 (ddd, J_1 = 2.9 Hz, J_2 = 10.5 Hz, J_3 = 13.5 Hz 1H), 2.87 (ddd, J_1 = 2.9 Hz, J_2 = 10.5 Hz, J_3 = 13.5 Hz 1H), 2.55 (m, 2H), 2.03 (m, 2H), 1.78 (m, 3H), 1.57 (m, 5H), 1.36 (m, 2H) ppm

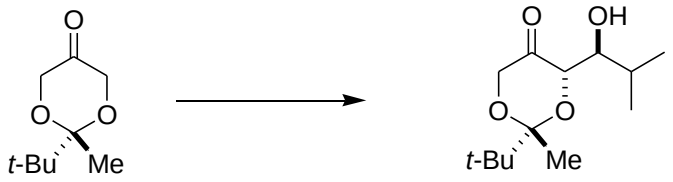
^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.9, 101.1, 74.8, 73.3, 66.6, 43.9, 33.6, 32.3, 26.8, 26.0, 25.4, 25.3, 23.1, 23.0 ppm

HRMS (CI, NH3), *m/z* calcd for ($C_{15}H_{22}O_4$+ NH_4) requires 336.1303 found 336.1301

LRMS (CI, NH3), *m/z* (relative intensity): 336 ($[M+18]^+$ 21), 319 ($[M+1]^+$, 100), 259 (13), 215 (10), 173 (13), 118 (42).

IR (KBr): 3492 (br), 2938, 2864, 1737, 1432, 1366, 1278, 1160, 1122, 910, 730 cm^{-1}

(2*R*,4*S*)-2-*tert*-Butyl-4-((*S*)-1-hydroxy-2-methylpropyl)-2-methyl-1,3-dioxan-5-one (3bj)



1b **3bj**

Procedure P1 afforded a viscous crude product. ^{1}H NMR spectrum of the crude product mixture showed only the *anti*-diastereoisomer at 4.20 (dd, J_1 = 1.3 Hz, J_2 = 6.3 Hz, 1H). The crude product was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti*-aldol adduct **3bj** in 65 % yield as a colorless gummy product. Enantioselectivity was measured by HPLC on 3,5-dinitrobenzoyl derivative of **3bj** and was found to be 67 %. Chiral-phase HPLC (Daicel Chiralpac AD column, hexanes/isopropanol 95 : 5, flow rate 0.5 ml/min, λ = 230 nm) tr = 30.6 (*syn*) tr = 34.7 (*anti*).

$[\alpha]^{25}_{D}$ = -89 (c 1.1, $CHCl_3$) (ee: 67 %)

Procedure P2 with LiCl as an additive afforded a crude product that was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti*-aldol adduct **3db** in 86% yield as a colorless gummy solid. Enantioselectivity was measured by HPLC on 3,5-dinitrobenzoyl derivative of **3bj** and was found to be 92 %. Chiral-phase HPLC (Daicel Chiralpac AD column, hexanes/isopropanol 95 : 5, flow rate 0.5 ml/min, λ = 230 nm) tr = 30.6 (*syn*) tr = 34.7 (*anti*).

$[\alpha]^{25}_{D}$ = -112 (c 1.1, $CHCl_3$) (ee: 92 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.33 (dd, J_1 = 1.3 Hz, J_2 = 18.3 Hz, 1H), 4.20 (dd, J_1 = 1.3 Hz, J_2 = 6.3 Hz, 1H), 4.19 (d, J = 18.3 Hz, 1H), 3.70 (dd, J_1 = 5.6 Hz, J_2 = 6.3 Hz, 1H),

2.97 (br, 1H, OH), 1.98 (m, 1H), 1.39 (s, 3H), 1.02 (s, 9H), 0.98 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H)

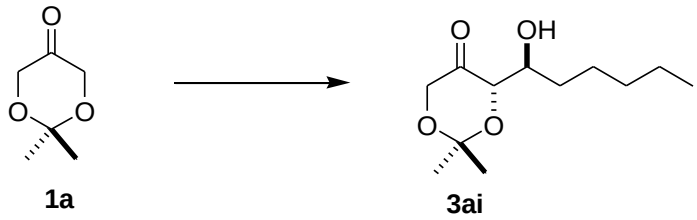
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 211.0, 103.9, 76.8, 76.3, 69.9, 40.6, 29.1, 25.4, 19.3, 16.5, 16.2.

HRMS *m/z* calcd for $C_{13}H_{24}O_4$ 244.1675 (M), found 244.1675 (EI)

LRMS (CI, NH3), *m/z* (relative intensity): 262 ($[M+18]^+$, 36), 245 ($[M+1]^+$, 76), 186 (100), 148 (32), 124 (21), 108 (16)

IR (KBr)**:** 3397 (br), 2966, 2886, 1732, 1464, 1379, 1163, 1018, 954, 899 cm^{-1}

(*S*)-4-((*S*)-1-Hydroxyhexyl)-2,2-dimethyl-1,3-dioxan-5-one (3ai)



1a **3ai**

Procedure P1 afforded a gummy crude product that was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti* aldol adduct **3ai** in 18 % yield along with 20 % yield of the respective dehydrated product.

Procedure P2 with LiCl as the additive afforded the crude product that was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti* aldol adduct **3ai** in 28 % yield along with 18 % yield of the dehydrated product.

$\mathbf{[\alpha]^{25}_D}$ = -41 (1.2, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.23 (dd, J_1 = 1.3 Hz, J_2 = 17.5 Hz, 1H), 4.06 (dd, J_1 = 1.3 Hz, J_2 = 6.9 Hz, 1H), 3.99 (d, J = 17.5 Hz, 1H), 3.85 (dd, J_1 = 3.0 Hz, J_2 = 6.9 Hz, 1H), 2.79 (d, J = 3.0 Hz, 1H, OH), 1.47-1.53 (m, 4H), 1.45 (s, 3H), 1.42 (s, 3H), 1.2-1.35 (m, 6H), 0.87 (t, J = 4.2 Hz, 3H)

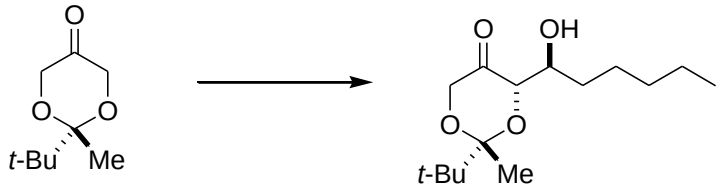
^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.3, 101.2, 76.2, 70.9, 66.9, 32.4, 31.9, 24.9, 23.8, 24.1, 22.8, 16.3, 14.2.

HRMS (CI, NH_3), *m/z* calcd for ($C_{12}H_{22}O_4$+NH_4) requires 248.1862 (M+14), found 248.1862

LRMS (CI, NH_3), *m/z* (relative intensity): 248 ($[M+14]^+$, 100), 231 (23), 212 (33), 173 (54), 109 (13).

IR (KBr): 3447 (br), 2955, 2929, 2860, 1739, 1459, 1376, 1224, 1093, 863 cm^{-1}

(2*R*,4*S*)-2-*tert*-Butyl-4-((*S*)-1-hydroxyhexyl)-2-methyl-1,3-dioxan-5-one (3bi)



1b **3bi**

Procedure P1 afforded a gummy crude product that was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti* aldol adduct **3bi** in 30 % yield along with 12 % yield of the respective dehydrated product.

Procedure P2 with LiCl as the additive afforded the crude product that was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti* aldol adduct **3ai** in 44 % yield along with 5 % yield of the dehydrated product.

$[\alpha]^{25}_{D}$ = -16 (1.0, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.30 (dd, J_1 = 1.3 Hz, J_2 = 18.0 Hz, 1H), 4.18 (d, J = 18.0 Hz, 1H), 4.15 (d, J = 6.1 Hz, 1H), 3.90 (m, 1H), 2.79 (d, J = 4.2 Hz, 1H, OH), 1.4-1.6 (m, 4H), 1.38 (s, 3H), 1.2-1.35 (m, 6H), 1.01 (s, 9H), 0.87 (t, J = 4.2 Hz, 3H)

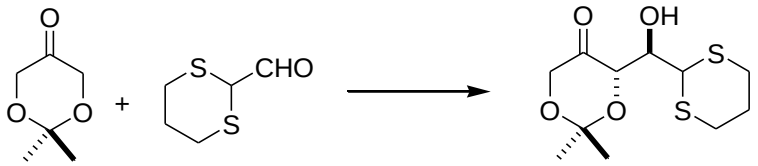
^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.9, 103.8, 78.7, 72.3, 69.9, 40.4, 32.2, 31.9, 25.4, 25.1, 22.8, 16.3, 14.2.

HRMS (CI, NH_3), *m/z* calcd for ($C_{15}H_{28}O_4$+NH_4) requires 290.2331 (M+14), found 290.2327

LRMS (CI, NH3), *m/z* (relative intensity): 290 ($[M+14]^+$ 36), 273 ($[M+1]^+$, 100), 259 (13), 215 (10), 173 (13).

IR (KBr): 3427 (br), 2959, 2929, 2872, 1734, 1467, 1377, 1260, 1164, 1091, 1023, 903, 800 cm^{-1}

4-(*S*)-4-[(*R*)-(1,3-Dithian-2-yl)(hydroxy)methyl]-2,2-dimethyl-1,3-dioxan-5-one (250a)[12,132]



1a **2b** **250a**

To a solution of 2,2-dimethyl-1,3-dioxan-5-one **1a** (1.45g, 0.011 mol) in dry DMSO (10 mL), were added 1,3-dithiane-2-carboxaldehyde **2b** (1.5g, 0.01 mol), L-proline (0.35 g, 0.003 mmol) followed by LiCl (0.44g, 0.01mol) and the resulting mixture was flushed with nitrogen and stirred at room temperature for 15 min to dissolve all the reactants. The mixture was then refrigerated at 5 ^{o}C until the reaction was complete as shown by TLC (48 hr). Saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring, then the mixture was extracted with ethyl acetate (3 x 50 mL), and then combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4, and concentrated to yeld the crude product. Only one isomer was detected by ^{1}H NMR. The crude product was purified by FCC (hexanes : ethyl acetate 9 : 1) to provide the *anti* isomer **250a** in 96 % yield as a white solid. Enantioselectivity was measured by ^{1}H NMR in C_6D_6 with $Eu(tfc)_3$ as the shift reagent and also by HPLC (Daicel Chiralpac AD column, hexanes/isopropanol 95 : 5, flow rate 0.5 ml/min, λ = 230 nm) tr = 47.8 (*anti*), tr = 52.4 (*syn*).

Melting point: 73-75 °C, (**Lit**.[20,12] 74-76 °C)

$[\alpha]^{25}_{D}$ = -110 (c 1.05, $CHCl_3$); (ee = 92 %)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.63 (dd, J_1 = 1.3 Hz, J_2 = 4.2 Hz, 1H), 4.56 (dd, J_1 = 4.0 Hz, J_2 = 7.5 Hz, 1H), 4.46 (dd, J_1 = 1.3 Hz, J_2 = 16.6 Hz, 1H), δ3.99 (d, J = 16.6 Hz, 1H),

3.90 (d, *J* = 7.3 Hz, 1H), 3.14 (d, *J* = 1.9 Hz, OH), 3.05 (m,1H), 2.85 (m,1H), 2.57 (m,1H), 2.51 (m,1H), 2.06 (m, 2H), 1.51 (s, 3H), 1.47 (s, 3H)

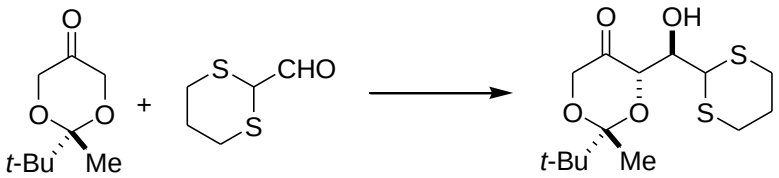
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 207.8, 101.1, 75.4, 72.5, 66.8, 43.5, 26.4, 25.4, 25.2, 24.4, 23.4

HRMS *m/z* calcd for $C_{11}H_{18}O_4S_2$ requires 278.0647 (M), found 278.0639 (EI)

LRMS (CI, NH_3), *m/z* (relative intensity): 279 ($[M+1]^+$, 100), 221 (85), 149 (12), 119 (87)

IR (KBr): 3489, 2986, 2907, 2894, 2833, 1737, 1423, 1375, 1290, 1222, 1164, 1109, 1041, 1003 cm^{-1}

(2*R*,4*S*)-4-((*R*)-(1,3-Dithian-2-yl)(hydroxy)methyl)-2-tert-butyl-2-methyl-1,3-dioxan-5-one (250b):



1b **2b** **250b**

By following a similar procedure as discribed above, the *anti*-isomer **250b** was obtained in 84% yield as a white solid. Enantioselectivity was measured by ^{1}H NMR in C_6D_6 with $Eu(tfc)_3$ as the shift reagent and also by HPLC (Daicel Chiralpac AD column, hexanes/isopropanol 95 : 5, flow rate 0.5 ml/min, λ = 230 nm) tr = 31.7 (*syn*), tr = 35.9 (*anti*).

Melting point: 67-68 °C,

$[\alpha]^{25}_D$ = -34 (c 1.0, $CHCl_3$)**;** (ee = 78 %)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.71(dd, J_1 = 2.2 Hz, J_2 = 9.1 Hz, 1H), 4.67 (d, J_1 = 2.2 Hz, 1H), 4.53 (d, J = 18 Hz, 1H), 4.22 (d, J = 18 Hz, 1H), 3.85 (d, J = 9.1 Hz, 1H), 3.04 (m, 2H), 2.96 (s, OH), 2.71 (t, J = 2.4 Hz, 1H), 2.56 (m, 1H), 2.41 (m, 1H), 2.05 (m, 2H), 1.4 (s, 3H), 1.04 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.4, 103.6, 77.5, 72.3, 69.2, 43.2, 40.4, 25.4, 25.35, 24.9, 24.5, 15.4.

Compound **250b** was also characterized in benzene: **^{1}H NMR** (C_6D_6, 500 MHz): δ 4.79 (ddd, J_1 = 1.9 Hz, J_2 = 2.2 Hz, J_3 = 8.8 1H), 4.72 (d, J_1 = 2.2 Hz, 1H), 4.40 (dd, J_1 = 1.6 Hz, J_2 = 17.8 Hz, 1H), 3.97 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 3.94 (d, J = 17.8 Hz, 1H), 2.88 (d, J = 17.8 Hz, 1H, OH), 2.54 (ddd, J_1 = 2.5 Hz, J_2 = 12.6 Hz, J_3 = 14.5, 1H), 2.39 (ddd, J_1 = 2.5 Hz, J_2 = 12.6 Hz, J_3 = 14.5, 1H), 1.86 (m, 1H), 1.77 (m, 1H), 1.58 (m, 1H), 1.32 (m, 1H), 1.06 (s, 3H), 1.01 (s, 9H).

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{14}H_{24}O_4S_2$) requires 320.1116, found m/z 320.1114.

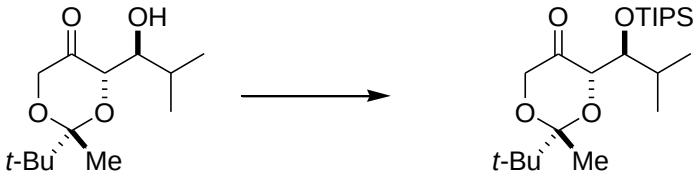
LRMS (EI, 70 eV): m/z (%) = 320 (4) $[M]^+$, 203 (16), 147 (57), 115 (100), 101 (57), 83(33), 57 (71).

IR (KBr): 3472 (br), 2958 (s), 1708 (s), 1486 (w) 1454 (m), 1152 (s) cm^{-1}.

Anal.Calcd for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55. Found: C, 52.76; H, 7.35.

4.4.3 Second aldol reactions on dioxanone aldol derivatives

(2*R*,4*S*)-2-*tert*-Butyl-2-methyl-4-((*S*)-2-methyl-1-(triisopropylsilyloxy)propyl)-1,3-dioxan-5-one (267)



266 **267**

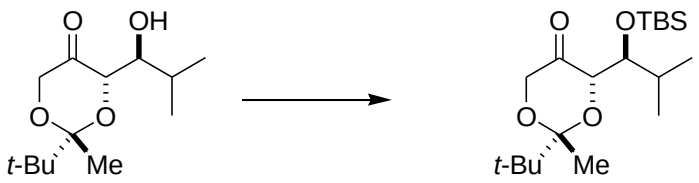
Reaction was done based on procedure P3

To an ice cold solution of **266** (0.30 g, 1.2 mmol, 1.0 eq) in dry THF (5.0 mL) were added dropwise 2,6-lutidine (0.29 mL, 2.5 mmol, 2.0 eq) followed by TIPSOTf (0.50 mL, 1.8 mmol, 1.5 eq). The reaction was stirred at room temperature until no starting material was detected by TLC (6 h). Then saturated solution of $NaHCO_3$ was added, extracted with ether (3 x 20 mL) and the combined organic layers were washed with saturated solution of NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by FCC, product eluted in pure hexanes to afford silylated product **267** (0.43 g, 1.1 mmol, 87 %) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.44 (br (s), 1H), 4.31 (dd, J_1 = 1.6 Hz, J_2 = 18.2 Hz, 1H), 4.18 (d, J = 18.2 Hz, 1H), 4.17 (dd, J_1 = 1.6 Hz, J_2 = 6.6 Hz, 1H), 1.96 (m, 1H), 1.37 (s, 3H), 1.07 (s, 21H), 1.03 (s, 9H), 0.99 (d, J = 6.9 Hz, 3H), 0. 79 (d, J = 6.9 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.1, 103.5, 82.0, 78.6, 69.3, 40.4, 31.9, 26.6, 25.3, 19.9, 19.7, 18.4, 15.0, 13.2.

(2*R*,4*S*)-2-*tert*-Butyl-4-((*S*)-1-(tert-butyldimethylsilyloxy)-2-methylpropyl)-2-methyl-1,3-dioxan-5-one (267a)



266 **267a**

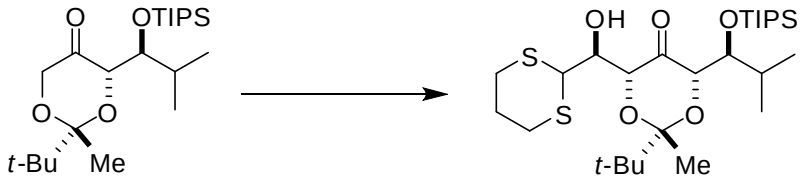
Reaction was done based on modified procedure P3

To an ice cold solution of **266** (0.67 g, 2.1 mmol, 1.0 eq) in dry THF (8.0 mL) were added dropwise 2,6-lutidine (0.71 mL, 6.1 mmol, 2.0 eq) followed by TBSOTf (0.76 mL, 3.3 mmol, 1.2 eq). The reaction was stirred at room temperature until no starting material was detected by TLC (3 h). Then saturated solution of $NaHCO_3$ was added, extracted with ether (3 x 20 mL) and the combined organic layers were washed with saturated solution of NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by FCC, product elutes in pure hexanes to afford silylated product **267a** (0.86 g, 2.4 mmol, 88 %) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.33 (dd, J_1 = 1.3 Hz, J_2 = 18.0 Hz, 1H), 4.32 (br, 1H), 4.15 (d, J = 18.0 Hz, 1H), 3.93 (dd, J_1 = 2.2 Hz, J_2 = 7.3 Hz, 1H), 1.95 (m, 1H), 1.35 (s, 3H), 1.05 (s, 9H), 0.92 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0. 78 (d, J = 6.9 Hz, 3H), 0.06 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.6, 103.8, 81.1, 77.7, 69.7, 40.6, 31.1, 25.9, 25.4, 19.8, 19.5, 18.3, 15.6, -4.3, -4.4.

(2*R*,4*R*,6*R*)-4-((*S*)-(1,3-Dithian-2-yl)(hydroxy)methyl)-2-*tert*-butyl-2-methyl-6-((*S*)-2-methyl-1-(triisopropylsilyl)propyl)-1,3-dioxan-5-one (268ab)



267 **268ab**

Reaction was done based on modified procedure P4

To a stirred solution of diisopropylamine (0.10 mL, 0.79 mmol, 4.8 eq) in dry THF (2.0 mL) at 0 ^{o}C in an ice bath, added *n*-BuLi (0.26 mL, 0.73 mmol, 2.2 M, 4.4 eq) and the mixture was stirred at 0 ^{o}C for 30 minutes. The resulting mixture was cooled to -78 ^{o}C in a dry ice-acetone bath, then the solution of **267** (66 mg, 0.17 mmol, 1.0 eq) in dry THF (2.0 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 2 h and then was added aldehyde **2b** (0.11 g, 0.74 mmol, 4.5 eq). After 20 min. the reaction was quenched with pH 7 buffer solution (2 mL) and slowly brought to room temperature. The mixture was extracted with diethyl ether (3 x 15 mL), the ether layer was washed with saturated NH_4Cl followed by brine and dried over anhydrous Na_2SO_4, and concentrated. The ^{1}H NMR of the crude product showed excess of aldehyde peaks, though spectrum showed the desired product peaks but the spectra was too complicated to determine diasteromeric ratio. The crude product was purified by flash chromatography on silica gel using increasing amounts of EtOAc in hexanes (2%>5%>10%) that yielded 66 mg of compound **268ab** in 71% yield.

$\mathbf{[\alpha]^{22}_D}$ = +24 (c 1.1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 4.52 (d, *J* = 7.4 Hz, 1H), 4.48 (br, 1H), , 4.37 (dd, J_1 = 7.2 Hz, J_1 = 7.4 Hz 1H), 4.25 (d, *J* = 7.2 Hz, 1H), 4.02 (d, *J* = 2.9 Hz, 1H), 3.79 (s, 1H, OH), 3.17 (m, 2H), 2.70 (m, 1H), 2.60 (m, 1H), 2.05 (m, 2H), 1.98 (m, 1H), 1.50 (s, 3H), 1.08 (s, 21H), 1.03 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.76 (d, *J* = 6.9 Hz ,3H)

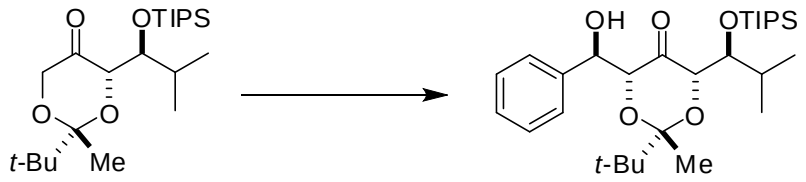
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 209.6, 103.1, 82.2, 78.1, 77.9, 75.7, 44.7, 39.9, 31.4, 28.4, 28.0, 25.8, 25.1, 20.5, 19.7, 18.4, 18.3, 13.3, 13.2.

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{27}H_{52}O_5S_2Si$) requires 548.3025, found m/z 548.3018.

LRMS (CI, NH_3), *m/z* (relative intensity): 566 ($[M+18]^+$, 5), 549 ($[M+1]^+$, 100) 476 (12), 412 (30), 298 (12), 156 (60), 91 (19).

IR (KBr): 3496 (br), 2961, 2868, 1710, 1465, 1386, 1171, 1107, 1014, 920, 883, 813, 677 cm^{-1}.

(2*R*,4*R*,6*R*)-2-*tert*-Butyl-4-((*R*)-hydroxy(phenyl)methyl)-2-methyl-6-((*S*)-2-methyl-1-(triisopropylsilyl)propyl)-1,3-dioxan-5-one (268af)



267 **268af**

Reaction was done based on modified procedure P4

Using procedure P4 on compound 267 (0.15 mmol) with benzaldehyde (**2f**) as the electrophile produced compound **268af** (43 mg) in 57% yield.

$[\alpha]^{22}_{D}$ = +111 (c 1.1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.38-7.25 (m, 5H), 4.89 (d, *J* = 7.9 Hz, 1H), 4.46 (br, 1H), 4.23 (m, 2H), 3.97 (br (s), 1H, OH), 1.89 (m, 1H), 1.33 (s, 3H), 1.06 (s, 21H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.72 (d, *J* = 6.9 Hz, 3H)

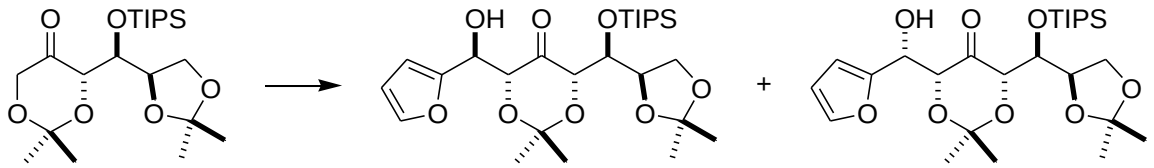
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 209.8, 139.7, 128.5, 128.4, 128.2, 128.1, 127.8, 103.1, 82.4, 78.7, 78.5, 74.9, 40.2, 31.8, 25.1, 20.5, 20.1, 18.7, 18.5, 13.6, 13.4, 13.3.

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{29}H_{50}O_5Si$) requires 506.3428, found m/z 506.3422.

LRMS (CI, NH_3), *m/z* (relative intensity): 507 ($[M+1]^+$, 32) 443 (63), 399 (72), 298 (15), 159 (100), 108 (21)

IR (Kubelka-Munk): 3422 (br), 3098, 2962, 2868, 1722, 1603, 1465, 1385, 1132, 1090, 884, 700 cm^{-1}.

(4*R*,6*R*)-4-((*S*)-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)(triisopropylsilyl)methyl)-6-((*S*)-furan-2-yl(hydroxy)methyl)-2,2-dimethyl-1,3-dioxan-5-one (333)



332 **333** **334**

To a stirred solution of diisopropylamine (0.10 mL, 0.73 mmol, 4.8 eq) in dry THF (3 ml) at 0 ^{o}C in an ice bath was added *n*-BuLi (0.35mL, 0.68 mmol, 1.95 M, 4.5 eq). The resulting solution was stirred at 0 ^{o}C for 30 minutes. The reaction mixtures was cooled to -78 ^{o}C in a dry ice-acetone bath, after 10 minutes the solution of the protected aldol adduct **332** (63 mg, 0.15 mmol, 1eq) in dry THF (1 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 2 h and then 2-furaldehyde **2g** (65 mg, 0.68 mmol, 4.5 eq) was added. After 20 min, the reaction was quenched with a pH 7 buffer solution (2.0 mL) and slowly brought to room temperature. The mixture was extracted with diethyl ether (3 x 15 mL), ether layer was washed with saturated NH_4Cl followed by brine and dried over $NaSO_4$. Concentration yielded the crude product (156 mg). The ^{1}H NMR of the crude product showed excess of aldehyde and although the spectrum showed the typical product peaks it was too complicated to detemine the diasteromeric ratio.The crude product was purified by flash chromatography on silica gel using increasing amounts of EtOAc in hexanes (5%>10%>15%>25%) that yielded two isomers of the desired product.

Compound 333:

^{1}H NMR (500 MHz, ,$CDCl_3$): δ 7.39 (s, 1H), 6.35 (s, 1H), 4.94 (dd, J_1 = 4.8 Hz, J_2 = 7.4 Hz, 1H), 4.65 (d, J = 7.4 Hz, 1H), 4.52 (dd, J_1 = 1.5 Hz, J_2 = 7.1 Hz, 1H), 4.37 (dd, J_1 = 7.1 Hz, J_2 = 7.4 Hz, 1H), 4.29 (br (s), 1H), 3.96 (t, J = 7.9 Hz, 1H), 3.91 (t, J = 7.9 Hz, 1H), 3.33 (d, J = 4.8 Hz, 1H, OH), 1.46 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.13 (m, 3H), 1.1 (br, 18H).

^{13}C NMR (125 MHz $CDCl_3$): 209.1, 152.3, 142.9, 110.2, 109.3, 108.4, 101.9, 78.1, 73.7, 73.1, 66.5, 66.2, 26.6, 25.2, 23.9, 23.4, 18.1, 18.0, 12.4.

HRMS (CI, NH_3), *m/z* calcd for ($C_{26}H_{44}O_8Si$ + NH_4) is 530.3149, found ($M+NH_4$) 530.3156

LRMS (CI, NH_3), *m/z* (relative intensity): 530 ($[M+18]^+$, 50), 495 (15), 472 (7), 414 (22), 359 (17), 257 (6), 185 (13), 151 (100), 58 (14).

IR (KBr): 2963, 2869, 1745, 1596, 1485, 1464, 1392, 1376, 1364, 1344, 1243, 1149, 1013, 920, 884, 823, 809 cm^{-1}

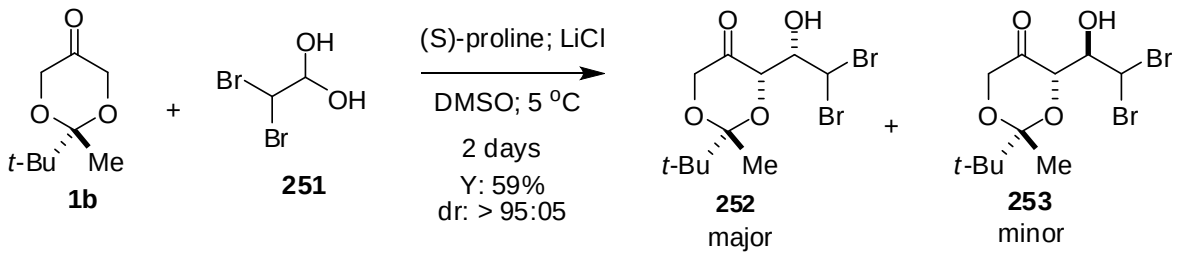
Compound 334:

^{1}HNMR (500 MHz, ,$CDCl_3$): δ 7.38 (s, 1H), 6.36 (s, 1H), 5.19 (dd, J_1 = 3.4 Hz, J_2 = 7.6 Hz, 1H), 4.64 (d, J = 3.4 Hz, 1H), 4.48 (dd, J_1 = 1.7 Hz, J_2 = 7.4 Hz, 1H), 4.37 (dd, J_1 = 7.4 Hz, J_2 = 7.6 Hz, 1H), 4.28 (s, 1H), 3.94 (t, J = 7.6 Hz, 1H), 3.79 (t, J = 7.9 Hz, 1H), 2.67 (d, J = 7.6 Hz, 1H, OH), 1.50 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H), 1.15 (m, 3H), 1.07 (dd, 18H).

^{13}C NMR (125 MHz $CDCl_3$): 205.7, 153.0, 142.1, 110.1, 109.1, 107.6, 101.9, 78.3, 74.9, 73.1, 66.2, 65.4, 26.6, 25.3, 24.3, 23.6, 18.1, 18.0, 12.4.

4.4.4 Dioxanone route of 1-deoxyiminosugars

(2*R*, 4*S*)-*syn*-2-*tert*-Butyl-(2',2'-dibromo-1'-hydroxyethyl)-2-methyl-1,3-dioxan-5-one (252)



Reaction was done based on modified procedure P2

The reaction was carried out using the procedure P2. Dioxanone **1b** (0.09 g; 0.53 mmol) and 2,2-dibromoacetal hydrate **251** (0.11 g; 0.50 mmol) afforded, in the presence of LiCl (21 mg; 0.50 mmol) and H_2O (0.10 mL), the *syn*-aldol adduct **252** in high diastereoselectivity (dr > 95:5). The crude product was fractionated by FCC (10-15% EtOAc in hexanes) to yield the title compound as a pale yellow gummy product (0.10 g, 59%) and a small amount of another stereoisomer **253** (12 mg).

Compound 252 data: $[\alpha]_D^{24}$ = +59 (c 1.1, C_6H_6)

^{1}H NMR (C_6D_6, 500 MHz): δ 5.54 (d, 1H, *J* = 7.4 Hz), 4.77 (d, 1H, *J* = 1.5 Hz), 4.47 (d, 1H, *J* = 7.25 Hz), 3.76 (dd, 1H, J_1 = 1.1, J_2 = 17.6 Hz), 3.64 (d, 1H, *J* = 17.6 Hz), 2.57 (br, 1H), 0.94 (s, 9H), 0.92 (s, 3H);

^{13}C NMR (C_6D_6, 125 MHz): δ 205.5, 106.1, 77.6, 75.2, 67.2, 47.95, 41.3, 25.8 , 17.4

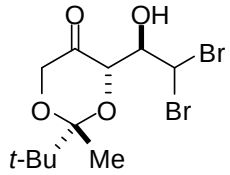
HRMS (CI, NH_3) exact mass calcd for $(C_{11}H_{18}Br_2O_4 + H)^+$ 372.9650, found m/z 372.9665 $[M]^+$, 374.9643 [M+2], 376.9622 [M+4].

LRMS (CI, NH_3): m/z (relative intensity %): 394 ($M+4+NH_3$, 10), 392 ($M+2+NH_3$, 18), 390 ($M+NH_3$, 10), 377 (58), 375 (100), 373 (59), 317 (19), 173 (26), 118 (20).

IR (KBr): 3638-3192 (br), 1747 (s) cm^{-1}.

Spectral data for the minor anti-compound 253

(2R,4S)-*anti*-2-*tert*-Butyl-4-((R)- 2',2'-dibromo-1'-hydroxyethyl)-2-methyl-1,3-dioxan-5-one (253)



253
minor

Compound 253 data:

$[\alpha]_D^{24}$ = -34.4 (c 1.05, C_6H_6)

^{1}H NMR (C_6D_6, 500 MHz): δ 5.87 (d, 1H, *J* = 3.6 Hz), 4.15 (d, 1H, *J* = 6.5 Hz), 3.91 (m, 1H), 3.90 (dd, 1H, J_1 = 1.3, J_2 = 18.1 Hz), 3.70 (d, 1H, *J* = 18.1 Hz), 3.23 (br, 1H), 0.95 (s, 3H), 0.86 (s, 9H).

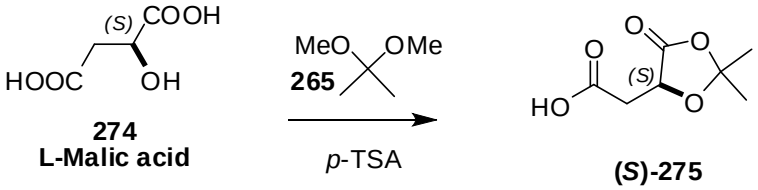
^{13}C NMR (C_6D_6, 125 MHz): δ 207.4, 104.5, 76.7, 76.4, 69.6, 46.95, 40.4, 25.6, 15.8.

HRMS (CI, NH_3) exact mass calcd for $(C_{11}H_{18}Br_2O_4 + H)^+$ 372.9650, found m/z 372.9651 $[M]^+$, 374.9632 [M+2], 376.9616 [M+4].

LRMS (CI, NH_3): m/z (%): 394 ($M+4+NH_3$, 8), 392 ($M+2+NH_3$, 15), 390 ($M+NH_3$, 8), 377 (61), 375 (100), 373 (62), 317 (16), 173 (31), 118 (50).

IR (KBr): 3627-3137 (br), 1739 (s) cm^{-1}.

(*S*)-2-(2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (275)[136,143,178]



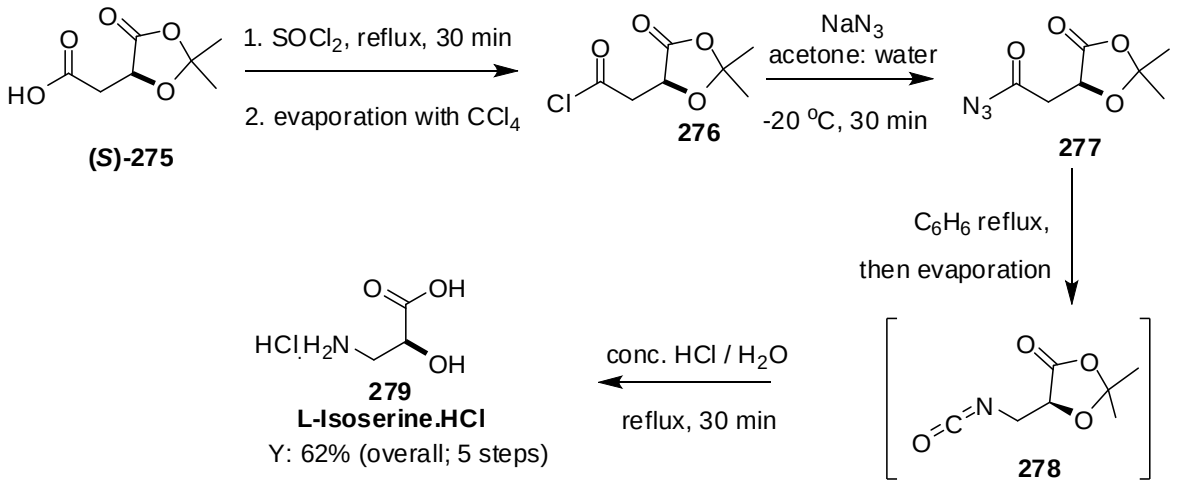
L-(-)-Malic acid (**274**, 10.0 g, 75.0 mmol), 2,2-dimethoxypropane (**265**, 75 mL) and *p*-toluenesulfonic acid monohydrate (0.14 g, 0.8 mmol) were placed in a 250 mL RBF fitted with a N_2 inlet at room temperature. The resulting mixture was stirred at room temperature for 5 hr and then H_2O (50 mL) and $NaHCO_3$ (62 mg, 0.8 mmol) were added. The reaction mixture was extracted with DCM (3 x 100 mL), and the combined organic layers were dried over anhydrous Na_2SO_4; filtration and evaporation yielded the crude product which was dissolved in Et_2O (20 mL) and diluted with hexanes (300 mL). The solvents were concentrated on a rotary evaporator to approx. half volume. The mixture was allowed to stand at 0 ^oC for 30 min and the solid that precipitated was filtered and washed with hexanes to afford compound **(*S*)-275** (11.3 g, 87%) as a white fluffy solid, which has spectroscopic data consistent with the reported data.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.72 (dd, 1H, J_1 = 3.8, J_2 = 6.7 Hz), 3.01 (dd, 1H, J_1 = 3.8, J_2 = 17.3 Hz), 2.86 (dd, 1H, J_1 = 6.7, J_2 = 17.3 Hz), 1.63 (s, 3H), 1.58 (s, 3H).

Literature data[178]: (Denmark, S. E.; Yang, S.–M. *J. Am. Chem. Soc*., **2004**, *126*, 12432.)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.71 (dd, 1H, J_1 = 4.0, J_2 = 7.0 Hz), 3.00 (dd, 1H, J_1 = 4.0, J_2 = 17.5 Hz), 2.86 (dd, 1H, J_1 = 7.0, J_2 = 17.5 Hz), 1.62 (s, 3H), 1.57 (s, 3H).

(*S*)-Isoserine hydrochloride (279) [136,143,144,145]



Compound **(*S*)-275** (10.0 g, 57.0 mmol) was refluxed with thionyl chloride (75 mL) for 30 min. Excess of $SOCl_2$ was evaporated under reduced pressure and traces were removed by co-distillation with CCl_4 (100 mL). The resulting residue was dissolved in acetone (40 mL), cooled to -20 °C and added to a saturated solution of sodium azide (5.6 g, 86 mmol) in water (15 mL). The resulting mixture was stirred at -20 °C for 30 min and acetone was evaporated at 0 °C using high vacuum. The acyl azide **277** was then extracted with benzene (2 x 100 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvent was concentrated to less than half volume (~40 mL) and the reaction mixture was set to reflux (slowly) until release of N_2 has ceased (1 hr), after which time benzene was completely evaporated. The crude isocyanate **278** was treated with 6N HCl (60 mL) and heated to reflux for 4 hr. The reaction mixture was concentrated to yield the crude product. The crude product was dissolved in water (10 mL) and purified on a cation exchange column (Amberlite IR-120, H^+ form). The column was first eluted with water and then with 5% aqueous ammonia. The alkaline phase was concentrated under reduced pressure and co-distilled thrice with toluene to yield a pale yellow solid (hydroscopic). The

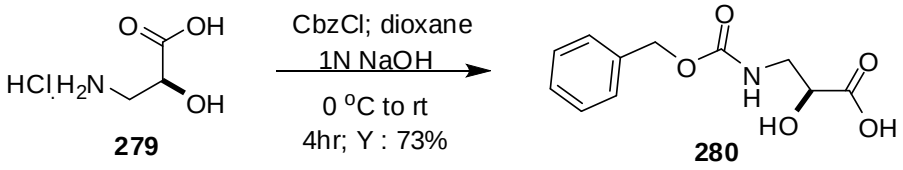
resulting residue was stirred with etheric HCl for 10 minutes, then the solvent was evaporated and the product was dried under high vacuum to afford pure (*S*)-isoserine hydrochloride (**279**, 6.3 g, 78%).

$[\alpha]_D^{24}$ = -30 (c 1.2, H_2O); [Lit. $[\alpha]_D^{24}$ = -32.3 (c 1.3, H_2O)][136,143,144,145]

^{1}H NMR (D_2O, 500 MHz): δ 4.2 (dd, 1H, J_1 = 3.4, J_2 = 7.7 Hz), 3.30 (dd,1H, J_1 = 3.6, J_2 = 13 Hz), 3.09 (dd, 1H, J_1 = 8.4, J_2 = 13 Hz).

^{13}C NMR (D_2O, 125 MHz): δ 177.5 , 68.8, 42.9.

(*S*)-3-(Benzyloxycarbonylamino)-2-hydroxypropanoic acid (280)[136,144,145]



To a stirred solution of (*S*)-isoserine hydrochloride (**279**, 4.1 g, 39 mmol) in 1N aq NaOH (120 mL) at 0 °C was added a solution of benzylchloroformate (6.90 mL, 48.8 mmol) in dioxane (5.0 mL) over a period of 30 minutes. The resulting mixture was stirred at room temperature for 2 hr, then dioxane was evaporated at reduced pressure. The resulting aqueous layer was first washed with Et_2O (50 mL) and next acidified with 1N aq. $KHSO_4$ (50 mL) at 0 °C. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine solution and then dried over $NaSO_4$ and concentrated to give the crude product. The solid product was washed with Et_2O (50 mL) to remove non-polar impurities and then dried over high vacuum to yield compound **280** as a pale-yellow solid. Yield: 5.8 g (61 %) pure and 3.2 g of impure product.

Melting Point: 129-130 ^{o}C (Lit mp: 129 ^{o}C)[144]

$[\alpha]_D^{24}$ = +2.1 (c 1.02, MeOH)

^{1}H NMR (DMSO, 500 MHz): δ 12.1 (br, 1H), 7.38-7.28 (br, 5H), 7.26 (t, 1H, J = 5.8 Hz). 5.04 (br, 1H), 5.01 (s, 2H), 4.02 (dd, 1H, J_1 = 4.9, J_2 = 7.2 Hz), 3.30 (ddd, 1H, J_1 = 5.4, J_2 = 10.4, J_3 = 13.6 Hz), 3.14 (ddd, 1H, J_1 = 6.6, J_2 =10.4, J_3 =13.6 Hz).

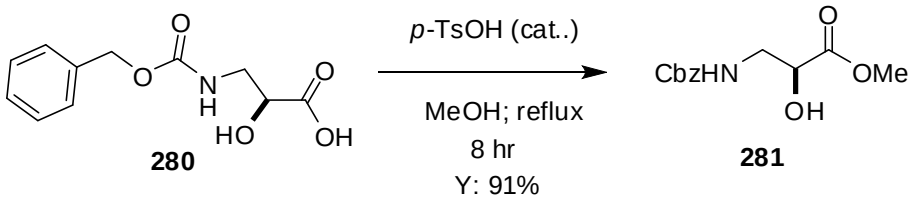
^{13}C NMR (DMSO, 125 MHz): δ 173.9, 156.2, 137.1, 128.3, 127.7, 127.6, 69.3, 65.3, 44.3.

HRMS (EI+, 70 eV) exact mass calcd for ($C_{11}H_{13}NO_5$) 239.0794, found m/z 239.0794.

LRMS (EI+, 70 eV): m/z (%): 239 (100) 221 (22), 194 (12), 148 (9), 108 (17), 91 (22).

IR (KBr): 3430 (m), 3343 (m), 3300-2500 (br), 1738 (s), 1689 (s), cm^{-1}.

(*S*)-Methyl 3-(benzyloxycarbonylamino)-2-hydroxypropanoate (21a) [136,144]



280 **281**

To a solution of α-hydroxyacid **280** (5.1g, 21.3 mmol) in MeOH (60 mL) was added p-toluenesulfonic acid (81 mg, 0.43 mmol) and the mixture was refluxed for 8 hr. After TLC showed no starting material the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAC (100 mL), washed with saturated $NaHCO_3$, water and brine, and dried over anhydrous Na_2SO_4. Purification by FCC on silica gel (6 : 4, hexanes : ethyl acetate) gave α-hydroxy ester **281** (4.9 g, 91%)

Melting Point: 44-45 ^oC

$[\alpha]_D^{24}$ = +19 (c 1.1, MeOH)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.28 (br, 5H), 5.13 (br, 1H), 5.08 (br, 2H), 4.26 (br, 1H), 3.77 (s, 3H), 3.55 (m, 2H), 3.17 (d, 1H, J = 4.7 Hz).

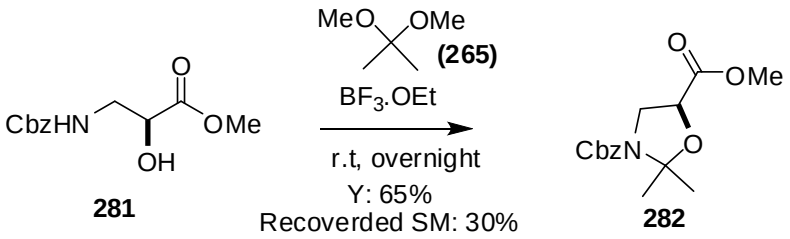
^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 156.8, 136.3, 128.3, 128.0, 127.9, 70.0, 66.7, 52.4, 44.2.

HRMS (EI+, 70 eV) m/z calcd for ($C_{12}H_{15}NO_5$) 253.0950, found m/z 253.0945.

LRMS (EI+, 70 eV): m/z (relative intensity %): 253 (3), 164 (7), 120 (12), 108 (12), 91 (100).

IR ν_{max}: 3550-3120 (br), 3032, 1719 (s) cm^{-1}.

(*S*)-3-Benzyl 5-methyl 2,2-dimethyloxazolidine-3,5-dicarboxylate (282) [136,144]



To a solution of ester **281** (4.40 g, 17.4 mmol) in acetone (70.0 mL) was added 2,2-dimethoxypropane (**265**, 4.30 mL, 34.8 mmol) and four drops of $BF_3.Et_2O$. The mixture was stirred at room temperature for overnight. The solvent was evaporated at reduced pressure and the residue was partitioned between Et_2O (100 mL) and saturated $NaHCO_3$ solution. The organic layers were separated, dried over anhydrous Na_2SO_4 and concentrated at reduced pressure to afford crude product which was purified by FCC (1 : 1, hexanes-ethyl acetate) to afford the desired oxazolidine methylester **282** (3.3 g, 65%) and unreacted **281** (1.3 g, 30%).

$\mathbf{[\alpha]_D^{24}}$ = +15 (c 1.1, MeOH)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.28 (br, 5H), 5.11 (br, 2H), 4.62 (t, 1H, *J* = 7.25 Hz), 3.92 (br, 1H), 3.77 (s, 3H), 3.71 (br, 1H), 1.65 (s, 3H), 1.54 (s, 3H).

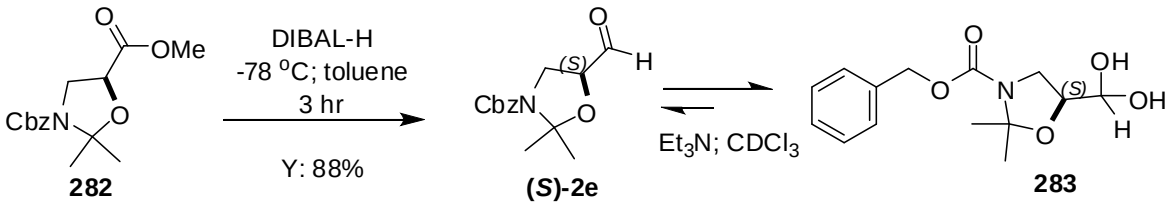
^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.5, 152.1, 136.4, 128.7, 128.3, 128.2, 99.3, 95.8, 72.7, 66.9, 52.6, 47.7, 25.8, 24.9

HRMS (CI) m/z calcd for $(C_{15}H_{20}NO_5 + H)^+$ 294.1341, found m/z 294.1338.

LRMS (CI): m/z (%): 294 (100) $[M+1]^+$, 278 (22), 250 (12), 234 (9), 108 (17), 91 (22).

IR (KBr): 3112 (w), 3032 (w), 2983 (m), 2951 (w), 2892 (w), 1740 (s), 1703 (s) (carbamate C=O), 1498 (w), 1483 (w), 1408(s), 1354 (m), 1256(m), 1213(m), 1072 (s), 911 (m), 867 (w) cm^{-1}.

(*S*)-Benzyl 5-(dihydroxymethyl)-2,2-dimethyloxazolidine-3-carboxylate (283) [136,144]



To a solution of protected isoserine ester **282** (3.20 g, 10.9 mmol) in dry toluene (50.0 mL) cooled under nitrogen to -78 ^{o}C, was added 1N solution of DIBAL in toluene (17 mL, 16.38 mmol) over a period of one hour keeping the reaction temperature below -65 ^{o}C. The resulting mixture was stirred for a furthur two hours at -78 ^{o}C, then quenched with dry methanol (7 mL). The mixture was warmed up to -20 ^{o}C and then poured into a stirred solution of Rochelles's salt (1.2 M potassium sodium tartrate, 60 mL), stirred for an hour, and then extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, evaporated and subjected to flash chromatography on silica gel with 1:1 hexanes: ethylacetate that afforded thehydrated aldehyde **283** (2.5 g, 88%).

Protected (*S*)-isoserinal (**2e**) readily formed the corresponding hydrate **283**. The IR spectrum of this compound showed the absence of the carbonyl signal and the presence of a broad peak corresponding to the hydroxyl functional groups (3540-3090 cm^{-1}) that confirmed the existence of the (*S*)-isoserinal hydrate. Also, the proton NMR analysis showed a small signal for the aldehyde functional group (CHO) at the chemical shift of 9.7 (integration for 0.23 proton), addition of triethylamine to the sample enhanced the aldehyde peak (integration of 0.62 protons) which implied that the equilibrium has shifted to the aldehyde form **2e**.

$[\alpha]_D^{24}$ = -25 (c 1.15, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 2 eq. NEt_3; 500 MHz): δ 9.74 (s, 0.7H, CHO), 7.36-7.28 (br, 5H), 5.10 (s, 2H), 4.41 (dd, 1H , J_1 = 1.2, J_2 = 8.1 Hz), 3.80 (t, 1H, J = 18.1 Hz), 3.71 (dd, 1H, J_1 = 6.4, J_2 = 8.1 Hz), 1.59 (s, 3H), 1.54 (s, 3H).

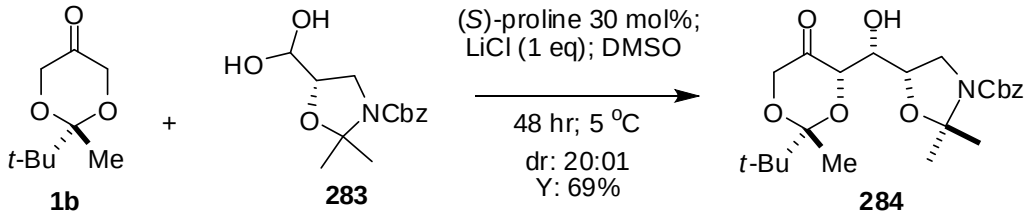
^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.1 (weak), 171.3, 152.3, 136.2, 128.6, 128.3, 98.2, 90.9, 78.2, 66.7, 60.5, 46.9, 25.2, 21.0 ppm.

HRMS (EI+, 70 eV) m/z calcd for ($C_{14}H_{19}NO_5$) 281.1263, found m/z 281.1237.

LRMS (EI+, 70 eV): m/z (relative intensity %): 282 (5), 281 (31), 264 (100), 248 (37), 108 (38), 91 (74).

IR (KBr): (Isoserinal hydrate **283**): 3413 (br), 3032 (w), 2982 (m), 1703 (s), 1072 (s) cm^{-1}

Compound 284



1b **283** **284**

Reaction was done based on modified procedure P2

The reaction was carried out using the procedure P2. Dioxanone **1b** (216 mg, 1.25 mmol), aldehyde hydrate **283** (300 mg, 1.15 mmol), (*S*)-proline (40.0 mg, 0.34 mmol) and LiCl (48.0 mg, 1.15 mmol) were dissolved in DMSO (5.0 mL) and the resulting mixture was flushed with nitrogen and stirred at room temperature for 15 min. The mixture was refrigerated at 5 ^{o}C until the reaction was complete as shown by TLC (48 hr). Saturated NH_4Cl solution and EtOAc were added with vigorous stirring, then the mixture was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford the crude product (dr 96 : 04 was determined at this stage by ^{1}H NMR). The resulting crude product was fractionated by FCC (15-20% EtOAc in hexanes) to yield the title compound **284** as a thick oil (0.34 g, 69 %).

$\mathbf{[\alpha]_D^{24}}$ = -51 (c 1.05, C_6H_6) and $\mathbf{[\alpha]_D^{24}}$ = -61 (c 1.08, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ7.36-7.28 (br, 5H), 5.10 (br, 2H), 4.47 (d, 1H, J = 3.0 Hz), 4.35 (d, 1H, J = 18.1 Hz), 4.30 (ddd, 1H, J_1 = 7.0, J_2 = 7.6, J_3 = 8.1 Hz), 4.19 (d, 1H, J = 18.1 Hz), 4.10 (ddd, 1H, J_1 = 3.0, J_2 = 6.1, J_3 = 7.0 Hz), 3.79 (dd, 1H, J_1 = 8.1, J_2 = 10.6 Hz), 3.48 (dd, 1H, J_1 = 7.6, J_2 = 10.6 Hz), 2.40 (d, 1H, J = 6.1 Hz), 1.54 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H), 1.01 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 206.3, 152.4, 136.6, 128.5, 128.0, 127.8, 103.5, 94.5, 78.34, 73.9, 73.1, 72.6, 69.5, 66.6, 48.5, 40.2, 25.9, 25.4, 25.2, 24.3, 15.9.

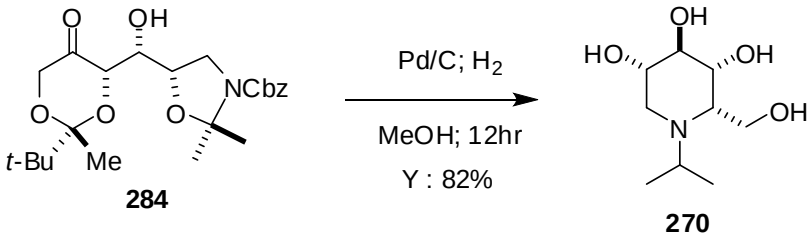
Compound **284** was also characterized in C_6D_6**: ^{1}H NMR** (C_6D_6, 500 MHz): δ7.30-7.02 (br, 5H), 5.10 (br, 2H), 4.30 (br, 2H), 4.17 (dd, 1H, J_1 = 1.3, J_2 = 17.7 Hz), 3.98 (ddd, 1H J_1 = 2.6, J_2 = 6.4, J_3 = 7.8 Hz), 3.90 (dd, 1H, J_1 = 1.1, J_2 = 17.7 Hz), 3.70 (t, 1H, J = 7.8 Hz), 3.38 (t, 1H, J = 8.7 Hz), 1.68 (s, 3H), 1.56 (s, 3H), 1.04 (s, 3H), 0.98 (s, 12H).

^{13}C NMR (C_6D_6, 125 MHz): δ 205.7, 152.9, 137.7, 129.1, 128.7, 128.6, 128.2, 103.7, 95.2, 79.4, 75.0, 73. 8, 70.1, 67.1, 49.5, 40.6, 26.5, 25.8, 25.6, 24. 8, 15.9.

HRMS exact mass calcd for $(C_{23}H_{33}NO_7 + H)^+$ requires 436.2335, found m/z . 436.2335. **LRMS** (EI+, 70 eV): m/z (%): 436 (100) $[M+1]^+$, 420 (38), 360 (57), 336 (25), 108 (48), 91 (37).

IR (KBr): 3622-3202 (br), 2981 (m), 1732(m), 1706 (s), 1163 (s), 1064 (s) cm^{-1}.

N-Isopropyl-L-idonojirimycin (270)



Reaction was done based on modified procedure P7

To a solution of the aldol adduct **284** (90 mg, 0.21mmol) in MeOH (3.0 mL) was added 10% Pd/C (30 mg). The suspension was stirred under H_2 (~5.0 psi) at ambient temperature for 24 hours. The solution was acidified (2N HCl; 0.5 mL) and stirred under H_2 for 6 hr at room temperature. The reaction mixture was then filtered through Celite and the solvent was removed under reduced pressure to yield the crude N-isopropyl iminosugar. The residue was purified by column chromatography on silica gel (hexanes/ethyl acetate 1 : 5) to afford compound **270** as a pale yellow gummy product (34 mg; 82%).

$\mathbf{[\alpha]_D^{24}}$ = -28 (c 1.2, H_2O);

^{1}H NMR (D_2O, 500 MHz): δ 4.33 (br, 1H), 4.30 (br, 1H), 4.09 (dd, 1H, J_1 = 5.2, J_2 = 12.8 Hz), 4.05-3.95 (m, 2H), 3.86 (t, 1H, J = 2.8 Hz), 3.61-3.54 (m, 2H), 3.25 (br, 1H), 1.42 (d, J = 6.5 Hz, 3H), 1.31 (d, J = 6.5 Hz, 3H).

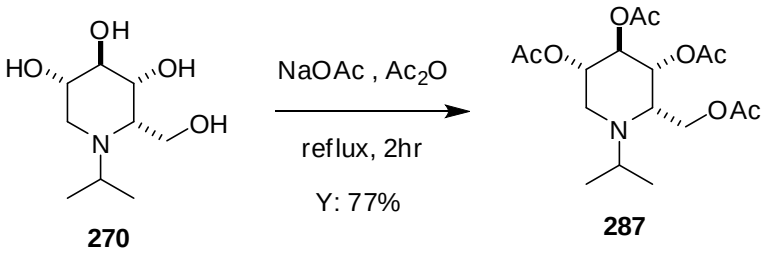
^{13}C NMR (D_2O, 125 MHz): δ 70.04, 66.96, 66.63, 63.82, 58.89, 54.14, 48.69, 17.83, 13.31.

HRMS exact mass calcd for $(C_9H_{19}NO_4 + H)^+$ requires 205.1314, found 205.1311m/z

LRMS (EI+, 70 eV): m/z (%): 205 (100), 188 (46), 156 (22), 120 (37).

IR (KBr): 3560-3100 (br), 2996 (m), 1232 (s) cm^{-1}

N-Isopropyl-L-idonojirimycin tetraacetate (287)



270 **287**

Reaction was done based on modified procedure P9

To the crude compound **270** (20 mg; 0.10 mmol), was added sodium acetate (82 mg, 1.0 mmol) and acetic anhydride (3mL). The resulting mixture was heated to 90 ^{o}C for 2 hr and the reaction was quenched with ice and saturated $NaHCO_3$ solution. Then the mixture was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4, concentrated to get the crude product which was purified by silica-gel flash column chromatography where product eluted at 30-35% EtOAc in hexanes to yield the acetylated title compound **287** (21 mg, 58%) as a thick oil.

$[\alpha]_D^{24}$ = -41 (c 0.85, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.43 (dd, 1H, J_1 = 1.8, J_2 = 6.0 Hz), 5.02 (dd, 1H, J_1 = 1.8, J_2 = 6.0 Hz), 4.85 (ddd, 1H, J_1 = 2.6, J_2 = 5.0, J_3 = 7.6 Hz), 4.39 (dd, 1H, J_1 = 8.2, J_2 = 12.05 Hz), 4.22 (dd, 1H, J_1 = 2.5, J_2 = 12.05 Hz), 3.37 (ddd, 1H, J_1 = 2.5, J_2 = 6.0, J_3 = 8.2 Hz), 3.01 (m, 1H, J = 6.6 Hz), 2.84 (dd, 1H, J_1 = 5.0, J_2 = 12.7 Hz), 2.75 (dd, 1H, J_1 = 7.6, J_2 = 12.7 Hz), 2.11 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.03 (t, 6H, J = 6.6 Hz).

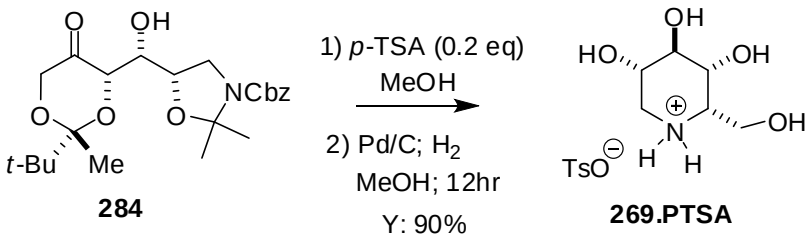
^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.1, 170.09, 170.08, 169.67, 69.5, 68.5, 67.7, 60.8, 57.0, 52.8, 40.2, 21.4, 21.2, 21.17, 21.07, 21.02.

HRMS (EI+, 70 eV) exact mass calcd for $(C_{17}H_{27}NO_8 + H)^+$ requires 373.1737, found m/z 373.1738.

LRMS (EI+, 70 eV): m/z (%): 373 (23), 358 (19), 300 (100), 240 (22), 180 (15), 138 (37).

IR (KBr): 2969 (m), 2934 (w), 2867 (w), 1744 (s), 1435 (w), 1369 (m), 1232 (s), 1033 (m), 1061 (s), 891 (w) cm^{-1}.

1-Deoxy-L-idonorijimycin tosylate (269)



284 **269.PTSA**

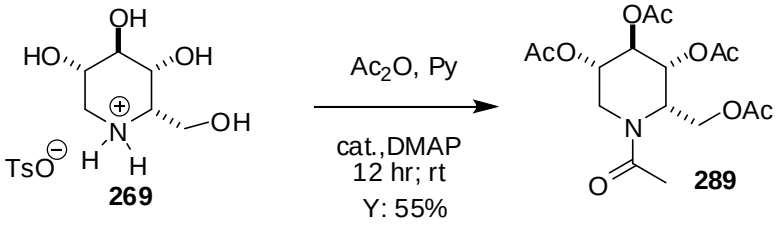
Reaction was done based on modified procedure P8

To a solution of aldol adduct **284** (85 mg, 0.20 mmol) in MeOH (3 mL) was added *p*-TsOH (7.0 mg, 0.04 mmol). The resulting mixture was stirred at ambient temperature for 15 min and then 10% Pd/C (30 mg) was added and the mixture was stirred under H_2 (~5 psi) at ambient temperature for 24 hr. Acid was then added (2N HCl; 0.5 mL) and the mixture was stirred under H_2 for 12 hr at room temperature. The reaction mixture was filtered through Celite and the residue was washed with EtOH/H_2O (10 : 1); evaporation of the solvent afforded a mixture of partially tosylate salt of L-DIJ (**269**) along with free amine of L-DIJ as a light brown solid (57 mg). The crude product was subjected to acetylation without furthur purification.

^{1}H NMR (D_2O, 500 MHz): δ 7.66 (d, 2H, *J* = 7.7 Hz), 7.35 (d, 2H, *J* = 7.7 Hz), 4.22 (br, 1H), 4.14 (br, 1H), 3.86 (m, 2H), 3.50 (d, 1H, *J* = 13.8 Hz), 3.39 (t, 1H, *J* = 6.4 Hz), 3.24 (d, 1H, *J* = 13.8 Hz), 2.94 (br, 1H), 2.37 (s, 3H).

^{13}C NMR (D_2O, 125 MHz): δ 142.7, 139.7, 129.7, 125.6, 67.9, 67.4, 66.9, 60.6, 59.5, 48.6, 20.7.

1-Deoxy-L-idonorijimycin pentaacetate (289)



To a solution of compound **269** (60 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) were added pyridine (0.50 mL), acetic anhydride (0.50 mL), and DMAP (cat. amount). The resulting mixture was stirred at room temperature for 12 hr. Then reaction was quenched with a saturated solution of $NaHCO_3$ (2.0 mL) and extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were dried (Na_2SO_4) concentrated under reduced pressure and dried under high vacuum to yield the crude DIJ-pentaacetate. The residue was purified by FCC over silica gel (the product eluted at 70-75% ethyl acetate in hexanes), evaporation and drying afforded the pentaacetate **289** (36 mg, 55%) as a yellow oil.

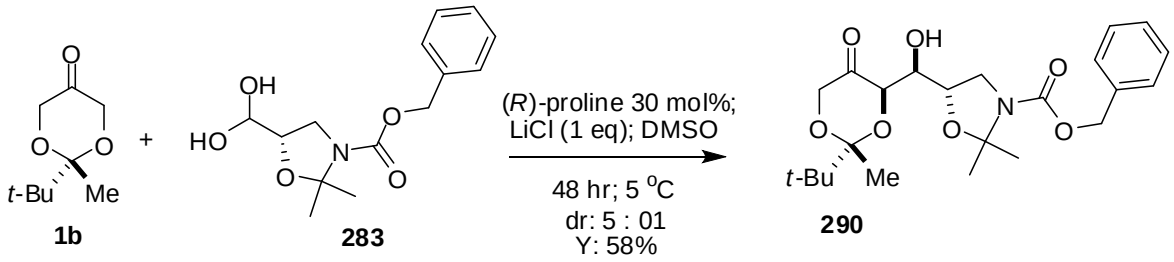
$\mathbf{[\alpha]_D^{24}}$ = -9 (c 1.1, CH_2Cl_2)

^{1}H NMR (95^o C, C_5D_5N, 500 MHz): δ 5.98 (t, 1H, *J* = 2.5 Hz), 5.31 (t, 1H, *J* = 4.2 Hz), 5.13 (ddd, 1H, J_1 = 3.05, J_2 = 5.2, J_3 = 8.2 Hz), 5.00 (t, 1H, *J* = 10.5 Hz), 4.60 (d, 1H, *J* = 11.2 Hz), 3.63 (br, 1H), 3.48 (br, 1H), 2.23 (s, 3H), 2.19 (s, 3H), 2.05 (s, 6H), 2.01 (s, 3H).

HRMS (CI, NH_3) exact mass calcd for $(C_{16}H_{23}NO_9 + H)^+$ requires 374.1451, found m/z 374.1461.

LRMS (CI, NH_3): m/z (%): 391 ($M+NH_3$, 40), 374 (100), 346 (68), 314 (22), 272 (11), 180 (17).

Compound (290)



Reaction was done based on modified procedure P2

(*R*)-Proline catalyzed aldol reaction of dioxanone **1b** (145 mg; 0.840 mmol) and (*S*)-isoserinal hydrate **283** (200 mg, 0.760 mmol) in the presence of LiCl (32 mg, 0.76 mmol) gave a gummy crude product. The product was fractionated by FCC (20-25% EtOAc in hexanes) to yield the title compound **290** as a thick oil (191 mg, 58%).

$[\alpha]_D^{22}$ = +32 (c 1.02, C_6H_6)

^{1}H NMR (C_6D_6, 500 MHz): δ7.31-7.02 (br, 5H), 5.11 (d, 2H, J = 12.5 Hz), 4.20 (br, 2H), 4.05 (dd, 1H, J_1 = 1.1, J_2 = 18 Hz), 3.83 (dd, 1H, J_1 = 1.1, J_2 = 18 Hz), 3.73 (br, 1H), 3.48 (m, 2H), 3.14 (br, 1H), 1.77 (s, 3H), 1.55 (s, 3H), 1.04 (s, 3H), 0.97 (s, 9H).

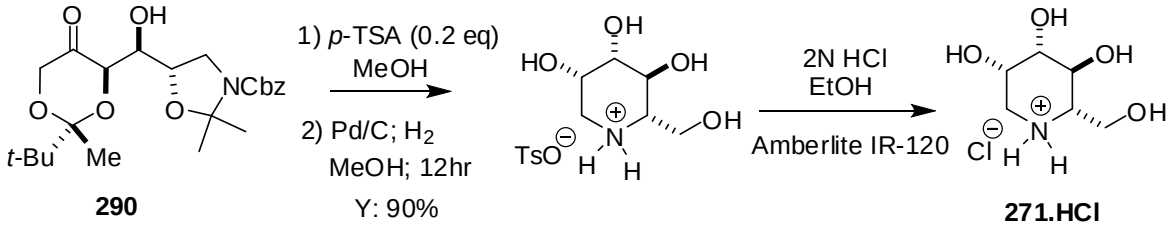
^{13}C NMR (C_6D_6, 125 MHz): δ 209.0, 152.8, 137.9, 129.0, 128.7, 128.6, 128.2, 104.4, 94.8, 76.3, 73.9, 73.7, 71.1, 69.9, 67.1, 48.8, 40.6, 25.6, 25.4, 25.0, 24.3, 16.2.

HRMS exact mass calcd for $(C_{23}H_{33}NO_7 + H)^+$ requires 436.2335, found m/z . 436.2331.

LRMS (EI+, 70 eV): m/z (%): 436 (100), 420 (48), 360 (35), 336 (25), 108 (41), 91 (55).

IR ν_{max}: 3640-3244 (br), 1738 (m), 1710 (s), 1091 (s) cm^{-1}.

1-Deoxy-L-mannorijimycin tosylate salt



290 **271.HCl**

Reaction was done based on modified procedure P8

To a solution of aldol adduct **290** (0.11 g, 0.25 mmol) in MeOH (3.0 mL) was added *p*-TsOH (9.0 mg, 0.25 mmol). The resulting mixture was stirred at ambient temperature for 15 min and then Pd/C was added (10 %, 30 mg) and the mixture was stirred under H_2 (~5 psi) at ambient temperature for 24 hr. Acid (2N HCl, 0.5 mL) was then added and the mixture was stirred under H_2 for 12 hr at room temperature. The reaction mixture was filtered through Celite and the residue was washed with EtOH/H_2O (10 : 1); evaporation of the solvent afforded the tosyl salt of L-DMJ as a light brown gummy compound (55 mg, 62%).

^{13}C NMR (D_2O, 125 MHz): δ 141.7, 136.9, 129.3, 125.2, 72.7, 66.6, 64.4, 59.9, 58.9, 45.9, and 20.3.

1-Deoxy-L-mannorijimycin hydrochloride (271)

To a solution of the tosylate salt (40 mg; 0.12 mmol) in EtOH (5 mL) was added conc. HCl (0.5 mL) and the solution was stirred at room teperature for 2 hr. The solvent was evaporated under reduced pressure to yield a gummy solid. The crude product was purified on a cation exchange column (Amberlite IR-120, H^+ form). The column was first eluted with MeOH and then with 5% aqueous ammonia. The alkaline phase was evaporated under reduced pressure and co-distilled thrice with toluene to yield a gummy product. The resulting residue was stirred with etheric HCl for 10 minutes, then solvent was evaporated and the sample was dried under high vacuum to yield the 1-DMJ hydrochloride (**271**) as a pale yellow solid (15 mg, 66%).

Melting point: 183-186 ^oC; (Lit: [150b] 185-187 ^oC)

$[\alpha]_D^{24}$ = +11.3 (c 0.33; H_2O); (Lit:[150b] $[\alpha]_D^{24}$ = +10.2, c 0.37, H_2O)

^{1}H NMR (D_2O, 500 MHz): δ 4.18 (dd, 1H, J_1 = 2.9, J_2 = 2.2 Hz), 4.08 (ddd, 1H, J_1 = 1.7, J_2 = 4.9, J_3 = 12.2 Hz), 3.90 (dd, 1H, J_1 = 5.2, J_2 = 13.2 Hz), 3.82 (dd, 1H, J_1 = 8.5, J_2 = 13.2 Hz), 3.65 (dd, 1H, J_1 = 2.9, J_2 = 9.5 Hz), 3.52 (dd, 1H, J_1 = 4.9, J_2 = 12.4 Hz), 3.43 (ddd, 1H, J_1 = 2.2, J_2 = 5.2, J_3 = 8.8 Hz), 2.89 (t, 1H, J = 12.4 Hz).

^{13}C NMR (D_2O, 125 MHz): δ 73.17, 67.13, 64.8, 60.3, 59.3, 46.3.

HRMS (ESI) exact mass calcd for $(C_6H_{13}NO_4 + H)^+$ requires 164.0922, found m/z . 164.0920.

Literature data for L-DMJ are provided below for comparison:

Meyers, A. I.; Anders, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron*, **1999**, *55*, 8931-8952

L-deoxymannojirimycin.HCl : $[\alpha]_D^{20}$ = +9.6 (c 1.2, H_2O), mp: 182-184 ^oC

^{1}H NMR (D_2O): δ 4.28 (br(s), 1H), 4.02 (dd, 1H, *J* = 12.5, 3.0 Hz), 3.92 (t, 1H, *J* = 8.8 Hz), 3.89 (d, 1H, *J* = 12.5 Hz), 3.74 (dd, 1H, *J* = 9.5, 2.5 Hz), 3.47 (dd, 1H, *J* = 13.6, 2.2 Hz), 3.30 (d, 1H, *J* = 12.5, 3.0 Hz), 3.21 (m, 1H).

^{13}C NMR (D_2O): δ 73.2, 66.7, 66.5, 61.2, 58.9, 48.3.

Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron*, **1989**, *45*, 1, 319-326

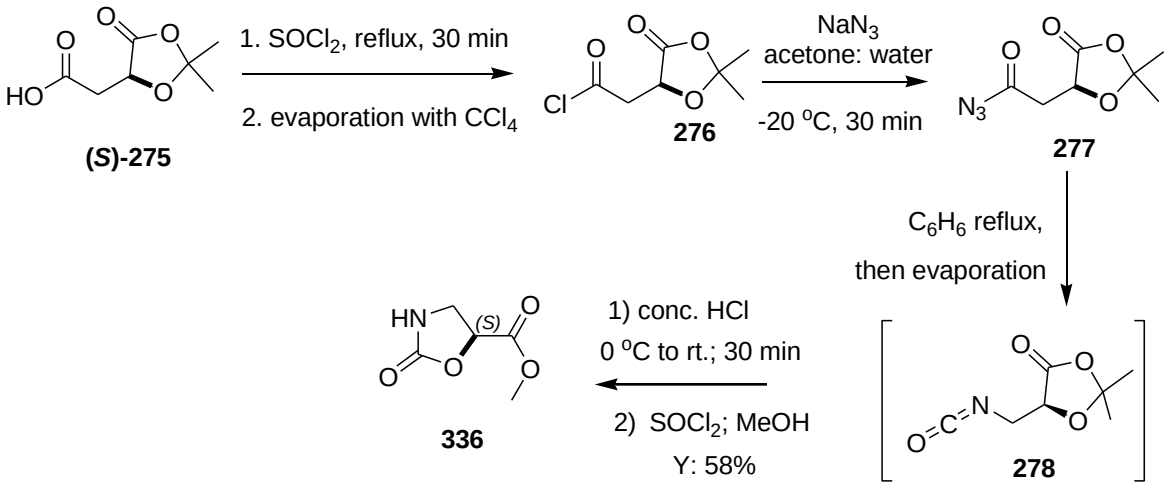
L-deoxymannojirimycin.HCl : $[\alpha]_D^{20}$ +10.2 (c 0.37;H_2O), mp: 185-187 ^oC

^{1}H NMR (D_2O): δ 4.10 (ddd, 1H), 3.72 (dd, 1H), 3.69 (dd, 1H), 3.54 (dd, 1H), 3.27 (dd, 1H), 3.10 (dd, 1H), 3.01 (ddd, 1H).

^{13}C NMR (D_2O): δ 73.1, 66.6, 66.5, 61.1, 58.8, 48.3.

Miscellaneous

(*S*)-Methyl 2-oxooxazolidine-5-carboxylate (336):



Compound **(*S*)-275** (2.5 g, 14.4 mmol) was sequentially transformed into isocyanate intermediate **278** under same conditions as described before. To the resulting isocyanate **278**, concentrated HCl (10 mL) was added at 0 ^{o}C and stirred at room temperature for half-hour. The reaction mixture was evaporated under high vacuum. The resulting residue was dissolved in methanol (25 mL), added $SOCl_2$ (5 mL) at 0 ^{o}C and stirred at room temperature for 6 hours. The solvent was evaporated and the product was purified by FCC afford pure (*S*)-methyl 2-oxooxazolidine-5-carboxylate (**336**, 1.2 g, 58%).

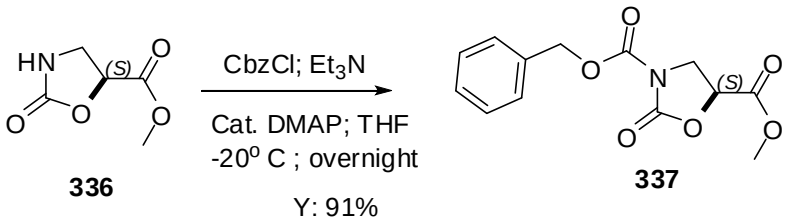
[α] $^{25}_{D}$ = +18 (c 1.05, EtOAc)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.78 (br, 1H (NH)), 5.02 (dd, 1H, J_1 = 5.4 Hz, J_2 = 9.5 Hz), 3.88 (dd, 1H, J_1 = 0.8 Hz, J_2 = 9.5 Hz), 3.83 (s, 3H), 3.69 (ddd, 1H, J_1 = 0.8 Hz, J_2 = 5.4 Hz, J_3 = 9.5 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.6 , 159.1, 72.8, 53.2, 43.8.

IR (KBr): 3288 (br), 2964, 2913, 1756 (s), 1437, 1244, 1094, 1027, 925, 662 cm^{-1}.

(*S*)-3-Benzyl 5-methyl 2-oxooxazolidine-3,5-dicarboxylate (337):



336 **337**

To a stirred solution of oxazolidinone methyl ester **336 (**1.10 g, 7.58 mmol) in 1N aq NaOH (20.0 mL) at 0 ^{o}C was added a solution of benzylchloroformate (1.3 mL, 9.1 mmol) in dioxane (5.0 mL) over a period of 30 minutes. The resulting mixture was stirred at room temperature for 2 hr, then dioxane was evaporated at reduced pressure. The resulting aqueous solution was first washed with Et_2O (30 mL) and was next acidified with 1N aq. $KHSO_4$ (20 mL) at 0 ^{o}C. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine solution and then dried over $NaSO_4$, concentrated to get a crude product. This solid was washed with Et_2O (50 mL) to remove the non-polar impurities and then dried over high vacuum to yield compound **337** (1.9 g, 91%).

Melting Point: 49-50 ^{o}C

[α] $^{25}_{D}$= +24 (c 1.0, $CHCl_3$)

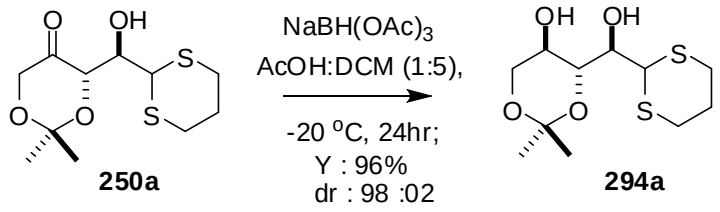
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.41 (m, 5H), 5.29 (s, 2H), 4.92 (dd, 1H, J_1 = 5.1 Hz, J_2 = 9.5 Hz), 4.20 (dd, 1H, J_1 = 9.5, J_2 = 10.7 Hz), 4.08 (ddd, 1H, J_1 = 5.1, J_2 =10.7 Hz), 3.83 (s, 3H).

^{13}C NMR (D_2O, 125 MHz): δ 168.4, 153.1, 150.4, 134.8, 128.8, 128.5, 69.4, 69.0, 53.3, 46.1.

IR (KBr): 3031, 2960, 1822, 1733, 1388, 1286, 1214, 1061, 769, 744, 699 cm^{-1}.

4.4.5 Synthesis of (+) D-*glycero*-D-*manno*-2-octulose

(4*R*,5*R*)-4-[(*R*)-(1,3-Dithian-2-yl)(hydroxy)methyl]-2,2-dimethyl-1,3-dioxan-5-ol (294a)[12,20]



Reaction was done based on modified procedure P5

To a solution of β-hydroxyketone **250a** (1.5g, 5.4 mmol) in dry CH_2Cl_2 (20 mL) were added AcOH (3.8 mL) and $NaBH(OAc)_3$ (1.7 g, 8.1 mmol) at -20 °C. The mixture was stirred at -20 °C for 36 hr (reaction was followed by TLC). The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated to get the crude diol mixture in a ratio of 2 : 98 *trans* : *cis* (by ^{1}H NMR), which was purified by FCC on silica gel (hexanes : ethyl acetate 30%) to give the pure product which was dried under high vacuum to yield **294a** (1.45 g, 96.0%).

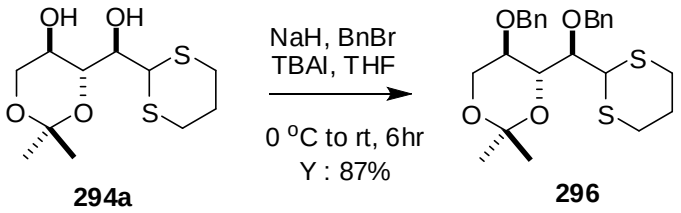
$[\alpha]^{23}_D$ = -15.1 (c 1.2, $CHCl_3$), **Melting point:** 60-61 °C

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 4.42 (d, *J* = 3.1 Hz, 1H,), 3.95 (m, 1H), 3.90 (m, 2H), 3.82 (m, 1H), 3.64 (dd, J_1 = 8.8 Hz, J_2 = 11.4 Hz, 1H), 3.36 (d, *J* = 1.9 Hz, 1H), 3.05 (d, *J* = 3.8 Hz, 1H), 2.93 (m, 1H), 2.83 (m,1H), 2.10 (m, 1H), 1.91 (m, 1H), 1.48 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 99.2, 78.5, 71.8, 67.2, 64.2, 49.1, 29.8, 29.0, 28.5, 26.0, 19.7

IR (KBr): 3412 (b), 2910 (s), 2820 (m), 1478 (w), 1456 (m), 1103 (s) cm^{-1}.

(4*R*,5*R*)-5-(Benzyloxy)-4-((*R*)-benzyloxy(1,3-dithian-2-yl)methyl)-2,2-dimethyl-1,3-dioxane) (296)



294a **296**

To a stirred solution of NaH (80% w/w) (0.24 g, 7.86 mmol) in dry THF (2 mL) at 0° C under inert atmosphere, was added compound **294a** (1.0 g, 3.57 mmol) in dry THF (10 mL). The resulting mixture was stirred at 0 °C for 15 minutes and benzylbromide (0.95 mL, 7.86 mmol) and TBAI (1.3 g, 3.57 mmol) were added. The resulting mixture was stirred at ambient temperature for 6 hr. After TLC showed no starting material the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield the crude product which was purified by flash chromatography on silica gel using hexanes : EtOAc (5%>10%) to give the desired product **296** (1.42 g, 87.0 %).

$[\alpha]^{23}_D$ = -4.2 (c 1.23, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.28 (m, 10H), 4.83 (m, 2H), 4.55 (dd, 2H, J_1 = 11.4 Hz, J_2 = 18.6 Hz), 4.46 (d, 1H, J = 9.2 Hz), 4.30 (dd, 1H, J_1 = 1.9 Hz, J_2 = 8.6 Hz), 3.90 (m, 2H), 3.72 (m, 2H), 2.80 (m, 2H), 2.70 (m, 2H), 2.03 (m, 1H), 1.88 (m, 1H), 1.48 (s, 3H), 1.41 (s, 3H).

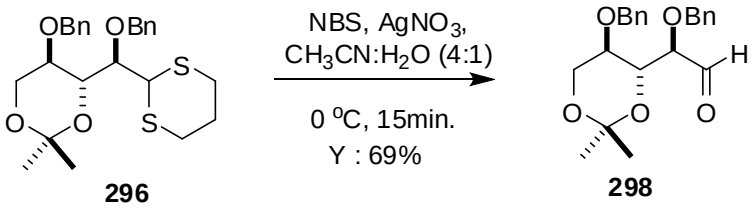
^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.8, 137.7, 137.6, 128.5, 127.98, 127.97, 127.96, 99.2, 83.5, 74.9, 73.2, 72.1, 69.2, 62.6, 28.6, 19.0.

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{25}H_{32}O_4S_2$) requires 460.1742, found m/z 460.1741.

LRMS (EI+, 70 eV): m/z (%) = 460 (0.5) $[M]^+$, 445 (1), 352 (4), 294 (10), 203 (12), 160 (21), 91 (100).

IR (KBr): 3083 (w), 3071 (w), 3019 (w), 2989 (s), 2892 (s), 1496 (w) 1453 (m), 1376 (m), 1090 (s), 735 (m), 698 (s) cm^{-1}.

(*R*)-2-(Benzyloxy)-2-((4*R*,5*R*)-5-(benzyloxy)-2,2-dimethyl-1,3-dioxan-4-yl)acetaldehyde (298)



Reaction was done based on the modified Corey procedure P6[157]

To a solution of dithiane compound **296** (0.560 g, 1.23 mmol) in 10 mL of acetonitrile : water (4 : 1) at 0 °C added N-bromosuccinimide (0.870 g, 4.87 mmol) followed by silver nitrate (0.930 g, 5.48 mmol) and the mixture was stirred at same temperature for 5 minutes. TLC showed no starting material (both product and starting material have similar R_f). The reaction was quenched with 10% sodium sulfite solution and filtered through the celite bed, washed with CH_2Cl_2 (15.0 mL), the resulting mixture was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution followed by brine, dried over anhydrous Na_2SO_4. Concentration under reduced pressure

gave a crude aldehyde (0.41 g, 91 %). Purification by flash chromatography on silica gel and using hexanes : EtOAc (5%>10%) gave the desired product **298** (0.31 g, 68%)

$[\alpha]^{25}_{D}$ = -25.7 (c 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.57 (d, 1H, *J* = 0.92 Hz), 7.4-7.23 (m, 10H), 4.80 (m, 2H), 4.51 (dd, 2H, J_1 = 11.5 Hz, J_2 = 18.1 Hz), 4.15 (dd, 1H, *J* = 9.2 Hz,), 3.97 (d, 1H), 3.86 (m, 2H), 3.65 (dd, 1H, J_1 10.3 Hz, J_2 1 Hz), 1.48 (s, 3H), 1.41(s,3H).

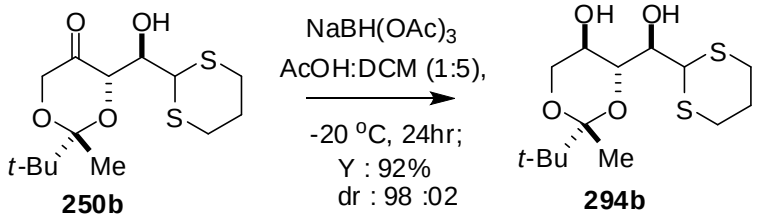
^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.8, 137.7, 137.6, 128.5, 127.98, 127.97, 127.96, 99.2, 83.5, 74.9, 73.2, 72.1, 69.2, 62.6, 28.6, 19.0.

HRMS (CI, NH_3) exact mass calcd for $[M]^+$ ($C_{22}H_{26}O_5$ + NH_4^+) requires 388.2124, found m/z 388.2124.

LRMS (CI, NH_3): m/z (%) = 388 (100) [M + NH_4^+], 371 (26) [M + 1], 330 (27), 280 (10), 198 (11), 149 (13), 108 (55), 91 (37).

IR (KBr): 3077 (w), 3066 (w), 3024 (w), 2992 (s), 2868 (s), 1734 (s), 1496 (w) 1454 (m), 1378 (m), 1096 (s), 866 (m), 739 (m), 699 (s) cm^{-1}.

(2*R*,4*R*,5*R*)-4-((*R*)-(1,3-Dithian-2-yl)(hydroxy)methyl)-2-tert-butyl-2-methyl-1,3-dioxan-5-ol (294b)



*Reaction was done based on modified procedure P5 on compound 250b (5.1 mmol) to afford compound **294b** in 92 % yield.*

Melting Point: 127-129 ^{o}C

$[\alpha]^{25}_{D}$ = -24.3 (c 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ4.38 (d, 1H, *J* = 2.8 Hz), 3.96 (q, 1H, *J* = 2.8 Hz), 3.89 (dd, 1H, J_1 = 5.3 Hz, J_2 = 10.8 Hz), 3.83 (t, 1H, *J* = 8.7 Hz), 3.69 (m, 1H), 3.61 (t, 1H, *J* = 10.6 Hz), 3.25 (d, OH), 2.95 (m, 2H), 2.76 (m, 2H), 2.08 (m, 1H), 1.92 (m, 1H), 1.37 (s, 3H), 0.92 (s, 9H).

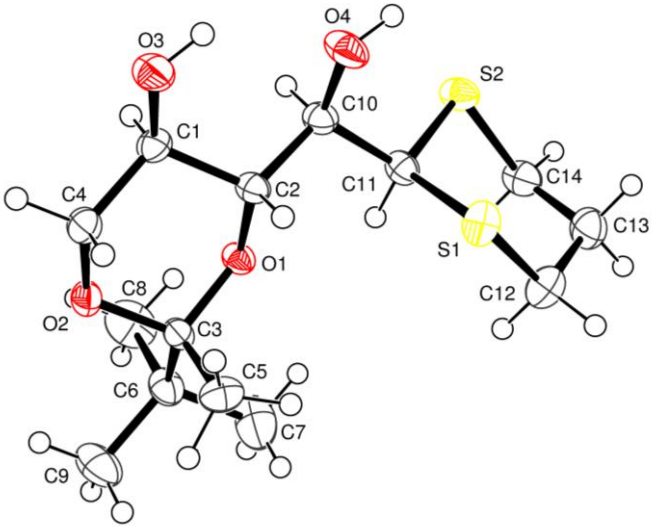
^{13}C NMR ($CDCl_3$, 125 MHz): δ 102.8, 79.1, 71.6, 67.1, 63.8, 49.6, 39.4, 30.1, 29.3, 26.0, 24.9, 12.5.

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{14}H_{24}O_4S_2$) requires 322.1273, found m/z 320.1275.

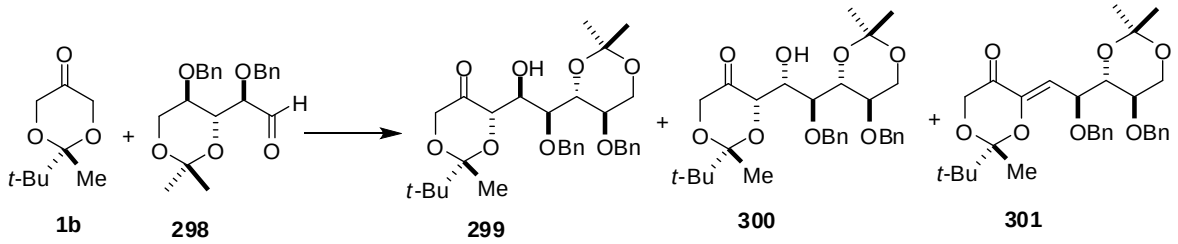
LRMS (EI, 70 eV): m/z (%) = 322 (11) $[M]^+$, 307 (11), 265 (19), 187 (19), 161 (100), 143(22), 101 (33).

IR (KBr): 3377 (br), 2952 (s), 2902 (s), 1486 (w) 1454 (m), 1158 (s), 1098 (s) cm^{-1}.

X-ray structure of compound 294b: (crystal was prepared by slow evaporation of a solution of **294b** in CH_2Cl_2 and hexanes (30 : 70. The ORTEP diagram is shown below.



(2*R*,4*S*)-4-((1*S*,2*S*)-2-(Benzyloxy)-2-((4*R*,5*R*)-5-(benzyloxy)-2,2-dimethyl-1,3-dioxan-4-yl)-1-hydroxyethyl)-2-tert-butyl-2-methyl-1,3-dioxan-5-one (299)



Reaction was done based on modified procedure P2

$[\alpha]^{25}_{D}$ = -54.6 (c 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.34-7.22 (m, 10H), 4.80 (d, 1H, *J* = 11.6 Hz), 4.59 (d, 1H, *J* = 11.6 Hz), 4.47 (s, 2H), 4.41 (d, 1H, *J* = 5.6 Hz), 4.32 (d, 1H, *J* = 17.6 Hz), 4.16 (d, 1H, *J* = 17.7 Hz), 4.10 (m, 2H), 3.95 (m, 1H), 3.88 (dd, 1H, J_1 = 4.6 Hz, J_1 = 11.6 Hz), 3.78 (m, 1H), 3.67 (dd, 1H, J_1 = 7.3 Hz, J_1 = 11.5 Hz), 3.46 (s, OH), 1.41 (s, 3H), 1.36 (s, 3H), 1.24 (s, 3H), 0.96 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.3, 138.8, 137.8, 128.7- 127.8 (8 CH), 103.99, 99.6, 78.7, 76.4, 74.2, 73.9, 72.2, 71.9, 71.8, 70.1, 62.5, 40.3, 27.9, 25.4, 20.2, 16.6.

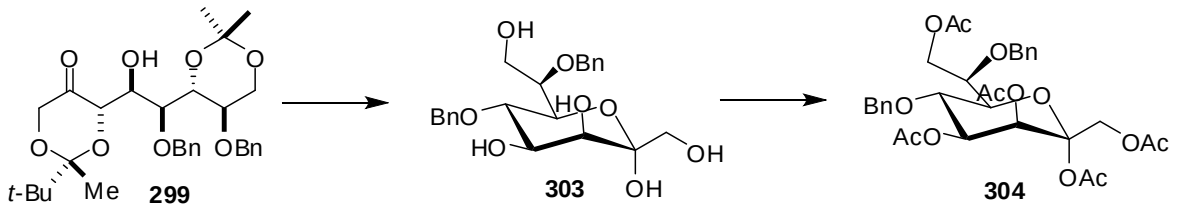
HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{31}H_{42}O_8$) requires 542.2880, found m/z 542.2878.

LRMS (EI+, 70 eV): m/z (%) = 542 (10.6) $[M]^+$, 527 (39), 485 (92), 427 (46), 393 (32), 371 (100), 355 (30), 321 (44), 304 (71).

IR (KBr): 3465 (Br), 3064 (w), 3030 (w), 2982 (s), 2962(s), 2871(s), 1737 (s), 1484 (w) 1453 (m), 1376 (m), 1214(s), 1158 (s), 1087 (s), 889 (m), 726 (m), 690 (s) cm^{-1}.

Anal. Calcd for $C_{31}H_{42}O_8$: C, 68.61; H, 7.8. Found: C, 68.69; H, 7.84.

(3*S*,4*R*,5*S*,6*R*,7*R*)-5,7-bis(Benzyloxy)-1,3,4,6,8-pentahydroxyoctan-2-one (303):



A 25 mL RBF was charged with compound **299 (**32 mg, 0.06 mmol) and THF (2.0 mL) and 2N HCl (2.0 mL) was added. The resulting mixture was stirred at ambient temperature for one hour, after which time TLC showed no staring material. The reaction mixture was concentrated and dried over high vacuum to afford gummy crude product **303** which was subjected to acetylation without further purification.

(3*S*,4*S*,5*S*)-6-((*R*)-2-Acetoxy-1-(benzyloxy)ethyl)-2-(acetoxymethyl)-5-benzyloxy) tetrahydro-2H-pyran-2,3,4-triyl triacetate (304):

Reaction was done based on modified procedure P9

To the crude compound **303** was added sodium acetate (58 mg, 0.70 mmol) and acetic anhydride (3 mL).The resulting mixture was heated to 90 ^{o}C for 2 hr and the reaction was quenched with ice and with saturated $NaHCO_3$ solution. The mixture was then extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4, concentrated to yield the crude product which was purified by silica-gel flash column chromatography where product eluted at 30% EtOAc : hexanes to yield compound **304** (24 mg, 65%).

$[\alpha]^{23}_{D}$ = +44.6 (c 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.19 (m, 10H), 5.43 (d, 1H, J = 3.2 Hz), 5.35 (dd, 1H, J_1 = 3.2 Hz, J_1 = 9.9 Hz), 4.77 (dd, 2H, J_1 = 12.1 Hz, J_2 = 12.0 Hz), 4.65 (dd, 3H, J_1 = 10.1 Hz, J_2 = 11.0 Hz), 4.42 (d, 1H, J = 12.1 Hz), 4.26 (dd, 1H, J_1 = 8.2 Hz, J_2 = 8.1 Hz), 4.18 (dd, 1H, J_1 = 4.1 Hz, J_2 = 4.0 Hz), 4.1 (t, 1H, J = 9.9 Hz), 3.95 (dd, 1H, J_1 = 0.92 Hz, J_2 = 4.0 Hz), 3.82 (dd, 1H, J_1 = 0.92 Hz, J_2 = 9.9 Hz), 2.12 (s, 3H), 2.10 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.92 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 170.2, 170.0, 169.6, 168.0, 138.5, 137.7, 128.7-127.9 (8 CH), 103.99, 77.96, 75.2, 74.8, 73.4, 72.5, 72.3, 67.5, 64.8, 60.6, 22.0, 21.1, 20.95, 20.87, 20.79.

HRMS (CI, NH_3) exact mass calcd for $[M]^+$ ($C_{32}H_{38}O_{13}$ + NH_4^+) requires 648.2656, found m/z 648.2641.

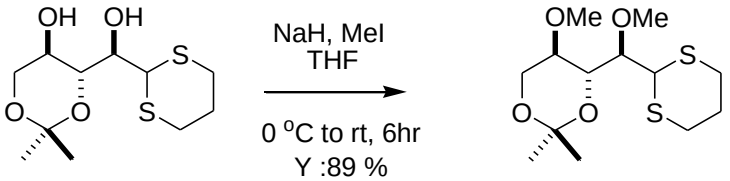
LRMS (CI, NH_3): m/z (%) = 648 (100) [M + NH_4^+], 588 (12), 571 (71), 359 (9), 240 (6), 108 (32), 91 (22), 77 (24).

IR (KBr): 3024 (w), 2928 (m), 2868 (m), 1751 (s), 1493 (w), 1451 (m), 1369 (m), 1217 (s), 1061 (s), 918 (m), 699 (w) cm^{-1}.

Anal. Calcd for $C_{32}H_{38}O_{13}$: C, 60.95; H, 6.07. Found: C, 61.01; H, 6.07.

Miscellaneous

(4*R*,5*R*)-4-((*R*)-(1,3-Dithian-2-yl)(methoxy)methyl)-5-methoxy-2,2-dimethyl-1,3-dioxane (295)



294a **295**

To a stirred suspension of NaH (80 % w/w) (0.320 g, 10.7 mmol) in dry THF (1.0 mL) at 0 ^{o}C under inert atmosphere was added compound **294a** (1.20 g, 4.29 mmol) in dry THF (10.0 mL). The resulting mixture was stirred at 0 ^{o}C for 15 minutes and added MeI (0.67 mL, 10.7 mmol) was added and the resulting mixture was stirred at 0 ^{o}C for an hour. TLC showed no starting material, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated to get the crude product which was purified by flash chromatography on silica gel using hexanes : EtOAc (5%>10%>15%) to give the desired product **295** (1.2 g, 89%) as a thick oil.

$[\alpha]^{23}_{D}$ = -12 (c 1.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.34 (d, 1H, *J* = 7.8 Hz), 4.11 (dd, 1H, J_1 = 3.0 Hz, J_2 = 8.4 Hz), 3.95 (dd, 1H, J_1 = 4.6 Hz, J_2 = 11.4 Hz), 3.68 (dd, 1H, J_1 = 6.9 Hz, J_2 = 11.4 Hz), 3.61(dd, 1H, J_1 = 4.5 Hz, J_2 = 8.4 Hz), 3.60 (s, 3H), 3.45 (dd, 1H, J_1 = 3.0 Hz, J_2 = 7.8 Hz), 3.37 (s, 3H), 2.8-2.9 (m, 4H), 2.01 (m, 1H), 1.93 (m, 1H), 1.44 (s, 3H), 1.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 99.3, 84.5, 74.0, 72.3, 61.6, 61.1, 56.8, 48.5, 29.7, 29.2, 27.5, 25.9, 20.4.

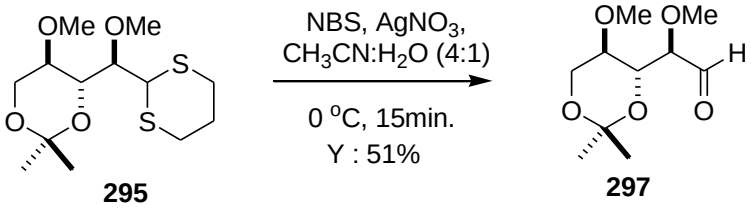
HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{13}H_{24}O_4S_2$) requires 308.1116, found m/z 308.1124.

LRMS (EI, 70 eV): m/z (%) = 308 (6) $[M]^+$, 293 (5), 233 (6), 218 (25), 175 (13), 160 (100), 121 (34), 101 (66), 59 (71).

IR (KBr): 2988 (s), 2928 (s), 2898 (s), 2826 (s), 1438 (m), 1367 (m), 1104 (s) cm^{-1}.

Anal. Calcd for $C_{13}H_{24}O_4S_2$: C, 50.62; H, 7.84. Found: C, 50.65; H, 7.83.

(*R*)-2-Methoxy-2-((*4R*,5*R*)-5-methoxy-2,2-dimethyl-1,3-dioxan-4-yl)acetaldehyde (297)



Reaction was done based on the modified Corey procedure P6[157]

To a solution of dithiane compound **295** (0.41 g, 1.3 mmol) in 20 mL of acetonitrile : water (4 : 1) at 0 °C was added N-bromosuccinimide (1.43 g, 8.01 mmol) followed by silver nitrate (1.48 g, 8.70 mmol) and the mixture was stirred at same temperature for 20 minutes. TLC showed no starting material (both product and SM have similar R_f). The reaction was quenched with 10 % sodium sulfite solution and filtered through the Celite bed, washed with CH_2Cl_2 (15 mL) and the resulting mixture was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution follwed by brine and dried over anhydrous Na_2SO_4,. Up on concentration under reduced

pressure gave the crude aldehyde **297** (0.15 g, 51%). The aldehyde **297** turned out to be a volatile compound which appears to co-distill with the solvents during the workup procedure.

[α] $^{25}_{D}$ = -17 (c 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.58 (d, 1H, *J* = 0.92 Hz), 4.0 (ddd, 2H, J_1 = 4.3 Hz, J_2 = 11.6 Hz, J_3 = 16.2 Hz), 3.73 (br, 1H), 3.62 (dd, 1H, J_1= 9.2 Hz, J_2 = 11.2 Hz), 3.57 (s, 3H), 3.51 (dd, 1H, J_1 = 4.3 Hz, J_2 = 9.2 Hz), 3.32 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H).

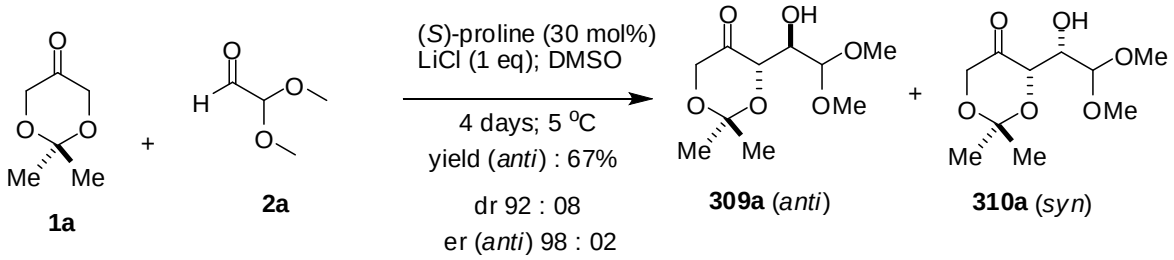
^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.3, 99.9, 85.8, 74.5, 70.7, 62.0, 59.5, 57.3, 28.3, 19.2.

HRMS (CI, NH_3)exact mass calcd for $[M]^+$ ($C_{10}H_{18}O_5$ + NH_4^+) requires 236.1496, found m/z 236.1490.

IR (KBr): 2912, 2892, 1722, 1293, 1116, 1054, 865, 740, 699 cm^{-1}.

4.4.6 Stereodivergent synthesis of DD- and LL- *glycero*-β-*allo*-heptopyranoses

(*S*)-4-[(*R*)-1-Hydroxy-2,2-dimethoxyethyl]-2,2-dimethyl-1,3-dioxan-5-one (309a):



Reaction was done based on modified procedure P2

To the solution of 2,2-dimethyl-1,3-dioxan-5-one **1a** (2.00 g; 14.4 mmol) in dry DMSO (5.0 mL), added 60% aqueous solution of 2,2-dimethoxyacetaldehyde **2a** (2.90 g; 16.9 mmol), (*S*)-proline (530 mg, 4.60 mmol) followed by LiCl (647 mg; 15.4 mmol). The resulting mixture was flushed with nitrogen and stirred at room temperature for 15 min to dissolve all the reactants. The mixture was then refrigerated at 5 ^{o}C until the reaction was complete as shown by TLC (72 hr). Saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring, then the mixture was extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford the crude product. The ratio of diastereoisomers was measured by ^{1}H NMR on the crude product and was found to be 92 : 08 *anti* to *syn*. The crude product was purified by FCC (hexanes : ethyl acetate 7 : 3) to provide the *anti*-aldol adduct **309a** (2.4 g; 67 % yield) as a pale yellow oil. Enantioselectivity was measured by ^{1}H NMR in C_6D_6 with $Eu(tfc)_3$ as a shift reagent.

$[\alpha]^{25}_{D}$ = -134 (c 1.15, $CHCl_3$) (96 % ee), (Lit. **$[\alpha]^{25}_{D}$** = -122 (c 1.05, $CHCl_3$) (90 % ee)[20,14]

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 4.65 (d, *J* = 6.8 Hz, 1H), 4.44 (dd, J_1 = 1.3 Hz, J_2 = 3.1 Hz, 1H), 4.25 (dd, J_1 = 1.5 Hz, J_2 = 16.7 Hz, 1H), 4.07 (dd, J_1 = 3.1 Hz, J_2 = 6.8 Hz, 1H), 3.99 (d, *J* = 16.7 Hz, 1H), 3.43 (s, 3H), 3.38 (s, 3H), 2.42 (br s, 1H), 1.47 (s, 6H).

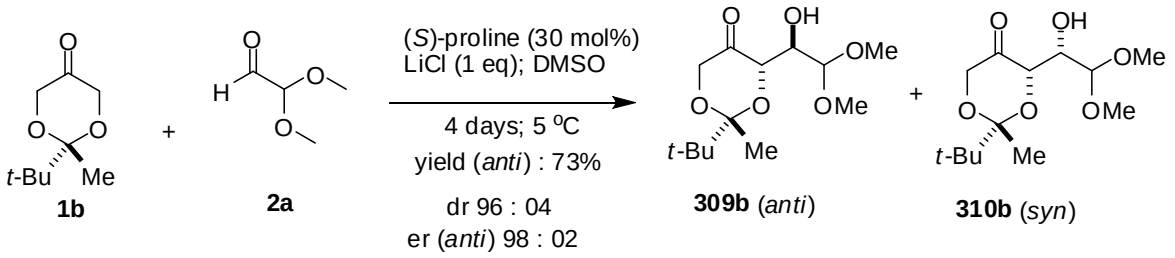
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 206.5, 103.4, 100.5, 76.3, 71.2, 67.1, 55.4, 54.3, 25.0, 23.0.

HRMS (CI, NH_3) exact mass calcd., for $[M + NH_4]^+$ $(C_{10}H_{18}O_6 + NH_4)^+$ requires 252.1447, found 252.1451 m/z.

LRMS (CI, NH_3): m/z (%): 252 ($[M+18]^+$, 20), 238 (22), 220 (56), 206(44), 188 (70), 152 (100), 148 (28).

IR (KBr): 3377 (br), 2941, 1747, 1446, 1377, 1193, 1074 cm^{-1}

(2*R*,4*S*)-2-*tert*-Butyl-4-((*R*)-1-hydroxy-2,2-dimethoxyethyl)-2-methyl-1,3-dioxan-5-one (310b):



1b + **2a** → **309b** (*anti*) + **310b** (*syn*)

The reaction was carried out following a similar procedure to that described above for **309a**. Dioxanone **1b** (1.0 g; 5.8 mmol) reacted with 60% aqueous solution of 2,2-dimethoxyacetaldehyde **2a** (1.1 g; 6.4 mmol) and LiCl (0.24 g; 5.8 mmol) in the presence of (*S*)-proline (0.2 g, 1.7 mmol) in DMSO (3 mL). The ratio of diastereoisomers was measured by ^{1}H NMR of crude product and was found to be 96 : 04 *anti* to *syn*. The crude product was purified by FCC (hexanes : ethyl acetate 8 : 2) to provide the pure compound **309b** (1.2 g; 73 % yield) as a pale yellow oil. Enantioselectivity was measured by ^{1}H NMR in C_6D_6 with $Eu(tfc)_3$ as a shift reagent.

$[\alpha]^{25}_D$ = -45 (c 1.1, chloroform) (96 % ee)

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 4.66 (d, J = 7.4 Hz, 1H), 4.49 (dd, J_1 = 1.4 Hz, J_2 = 2.4 Hz, 1H), 4.31 (dd, J_1 = 1.4 Hz, J_2 = 18.1 Hz, 1H), 4.18 (dd, J_1 = 1.1 Hz, J_2 = 18.1 Hz, 1H), 4.12 (ddd, J_1 = 2.4 Hz, J_2 = 5.1 Hz, J_3 = 7.4 Hz, 1H), 3.39 (s, 3H), 3.37 (s, 3H), 2.26 (d, J = 5.1 Hz, 1H (OH)), 1.38 (s, 3H), 1.03 (s, 9H).

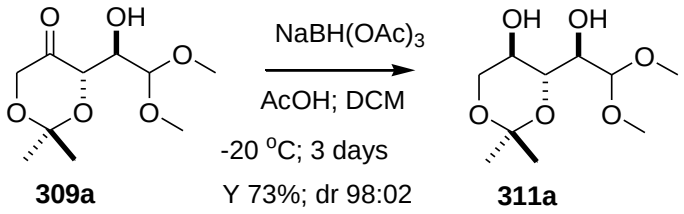
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 205.8, 103.4, 103.1, 78.3, 72.3, 69.4, 55.3, 53.3, 40.2, 25.4, 15.6.

HRMS (CI, NH_3) exact mass calcd., for $[M + NH_4]^+$ $(C_{13}H_{24}O_6 + NH_4)^+$ requires 294.1917, found 294.1920 m/z.

LRMS (CI, NH_3): m/z (%): 294 ($[M+18]^+$, 5), 277 (8), 262 (17), 245 (29), 230(15), 173 (100), 115(24), 75 (34).

IR (KBr): 3467 (br), 2960, 2834, 1730, 1462, 1393, 1166, 1086, 981, 890 cm^{-1}

(4*R*,5*R*)-4-((*R*)-1-Hydroxy-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-ol (311a)[14,20]



309a **311a**

Reaction was done based on modified procedure P5

To a solution of *β*-hydroxyketone **309a** (0.25 g, 1.1 mmol, 1.0 eq) in dry CH_2Cl_2 (3.0 mL) AcOH (0.70 mL) and $NaBH(OAc)_3$ (0.34 g, 1.6 mmol, 1.5 eq) were added at -20 °C. The mixture was stirred at -20 °C for 12 h and then was kept at that temperature for 2 days. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 30 mL).The combined organic layers were washed with aqueous saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated to give a crude diol mixture in a ratio of 2 : 98, which was purified by FCC on silica gel (hexanes : ethyl acetate 60 %) to give the pure product **311a** (0.18 g, 73%).

$[\alpha]^{25}_D$ = -18 (c 1.12, $CHCl_3$), (**Lit. $[\alpha]^{25}_D$** = -7.3 (c 0.52, MeOH)[14]

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 4.44 (d, *J* = 3.0 Hz, 1H), 3.90 (dd, J_1 = 5.5 Hz, J_2 = 11.3 Hz, 1H), 3.80 (m, 2H), 3.72 (dd, J_1 = 6.6 Hz, J_2 = 8.9 Hz, 1H), 3.62 (dd, J_1 = 9.1 Hz, J_2 = 11.3 Hz, 1H), 3.50 (s, 3H), 3.47 (s, 3H), 3.45 (d, *J* = 4.6 Hz, 1H, OH), 3.46 (d, *J* = 4.5 Hz, 1H, OH), 2.58 (d, *J* = 4.3 Hz, 1H, OH), 1.45 (s, 3H), 1.36 (s, 3H) ppm.

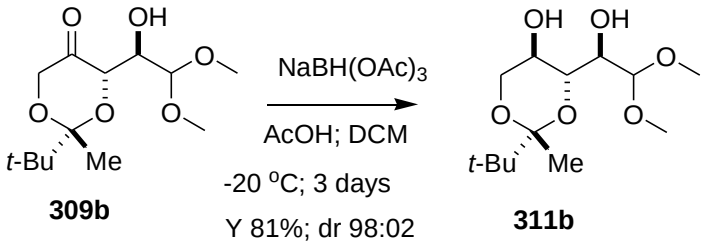
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 103.6, 98.7, 74.8, 72.5, 65.3, 64.0, 56.4, 55.9, 28.4, 19.6 ppm.

HRMS (CI, NH_3) exact mass calcd., for $[M + NH_4]^+$ $(C_{10}H_{20}O_6 + NH_4)^+$ requires 254.1604, found 254.1599 m/z.

LRMS (CI, NH_3): m/z (%): 254 ($[M+18]^+$, 86), 222 (39), 205 (100), 190 (67), 173 (19), 75 (80).

IR (KBr): 3442 (br), 2991, 2939, 2834, 1451, 1374, 1199, 1123, 1068, 975, 864 cm^{-1}

(2*R*,4*R*,5*R*)-2-*tert*-Butyl-4-((*R*)-1-hydroxy-2,2-dimethoxyethyl)-2-methyl-1,3-dioxan-5-ol (311b):



Reaction was done based on modified procedure P5

To a solution of *β*-hydroxyketone **309b** (0.25 g, 0.91 mmol, 1.0 eq) in dry CH_2Cl_2 (3.0 mL). AcOH (0.70 mL) and $NaBH(OAc)_3$ (0.29 g, 1.4 mmol, 1.5 eq) were added at -20 °C. The mixture was stirred at -20 °C for 12 h and then was kept at that temperature for 2 days. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated to give the crude diol as a mixture of two isomers in a ratio of 2 : 98 (by ^1H NMR), which was purified by FCC on silica gel (hexanes : ethyl acetate 1 :1) to give the pure product **311b** (0.21 g, 81%).

Melting point: 82-84 °C

$[\alpha]^{25}_{D}$ = -27 (c 1.1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 4.41 (d, *J* = 2.7 Hz, 1H), 3.89 (ddd, J_1 = 1.5 Hz, J_2 = 4.8 Hz, J_3 = 10.9 Hz, 1H), 3.78 (m, 1H), 3.68 (m, 2H), 3.60 (br, 2H), 3.50 (s, 3H), 3.46 (s, 3H), 2.61 (d, *J* = 4.6 Hz, 1H, OH), 1.36 (s, 3H), 0.92 (s, 9H) ppm.

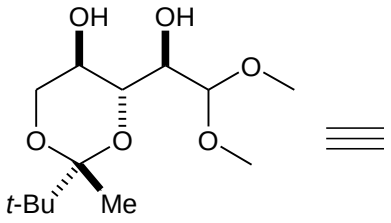
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 103.5, 102.4, 75.9, 71.9, 65.8, 63.6, 57.0, 55.8, 39.4, 24.9, 12.7 ppm.

HRMS (CI, NH_3) exact mass calcd., for $[M + NH_4]^+$ $(C_{13}H_{26}O_6 + NH_4)^+$ requires 296.2073, found 296.2073 m/z.

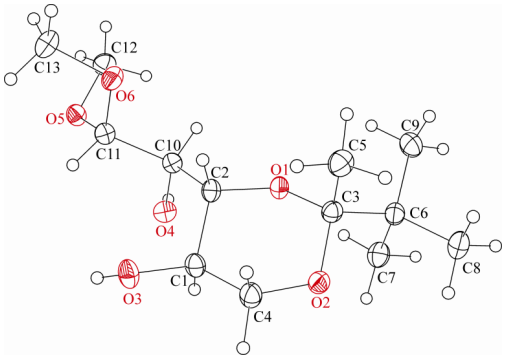
LRMS (CI, NH_3): m/z (%): 296 ($[M+18]^+$, 8), 283 (100), 279 (15), 264 (51), 253 (6).

IR (KBr): 3430(br), 2956, 2876, 2835, 1450, 1374, 1168, 1066, 975, 894 cm^{-1}

X-ray structure of compound 311b

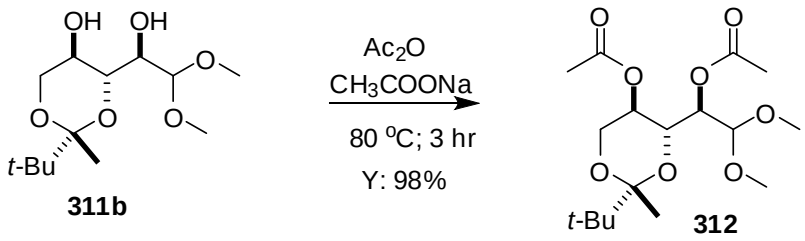


311b



The crystal was prepared by slow evaporation of a solution of **311b** in CH_2Cl_2 and hexanes (30:70). The ORTEP diagram is shown above

(2*R*,4*R*,5*R*)-4-((*R*)-1-Acetoxy-2,2-dimethoxyethyl)-2-*tert*-butyl-2-methyl-1,3-dioxan-5-yl acetate (312):



A 10 mL RBF was charged with diol **311b** (50 mg, 0.18 mmol), sodium acetate (0.18 g, 2.2 mmol) and acetic anhydride (3.0 mL) and the resulting mixture was heated to 90 °C for 2 hr. The reaction was quenched with ice followed by saturated $NaHCO_3$ solution. The mixture was then extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford the crude product which was purified by silica-gel flash column chromatography (20% EtOAc: hexanes) to yield the pure diacetylated product **312** (64 mg, 98%).

$[\alpha]^{25}_{D}$ = -13 (c 1.1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 5.17 (dd, J_1 = 3.2 Hz, J_2 = 6.7 Hz,1H), 4.94 (ddd, J_1 = 4.8 Hz, J_2 = 8.1 Hz, J_3 = 8.6 Hz, 1H), 4.47 (d, J = 6.7 Hz, 1H), 4.09 (dd, J_1 = 3.2 Hz, J_2 = 8.6 Hz, 1H), 3.98 (dd, J_1 = 4.8 Hz, J_2 = 11.2 Hz, 1H), 3.58 (dd, J_1 = 8.1 Hz, J_2 = 11.2 Hz, 1H), 3.37 (s, 3H), 3.33 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 1.36 (s, 3H), 0.92 (s, 9H) ppm.

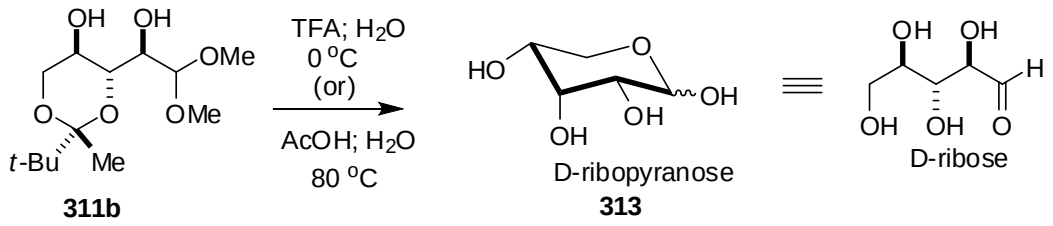
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 169.9, 169.8, 103.1, 101.7, 71.2, 70.7, 66.4, 61.8, 55.3, 53.4, 39.9, 24.9, 21.2, 21.1, 13.6 ppm.

HRMS (CI, NH_3) exact mass calcd., for $[M]^+$ $(C_{17}H_{30}O_8 + NH_4)^+$ requires 362.1941/ $[M+NH_4]^+$ requires 380.2284 , found 380.2280 m/z.

LRMS (CI, NH_3): m/z (%): 380 ($[M+18]^+$, 13), 363 ($[M+1]^+$, 24), 331 (76), 305 (13), 263 (100), 75 (35).

IR (KBr): 2987, 2931, 2856, 1751, 1743 1469, 1374, 1224, 1116, 1000, 864, 836, 778 cm^{-1}

β-D-Ribopyranose (313):



To an ice cooled solution of diol **311b** (50 mg, 0.18 mmol) in $CHCl_3$: H_2O (3 : 1; 2 mL) was added trifluroaceticacid (0.20 mL). The resulting mixture was stirred at 0 °C for 3 hr after which time the TLC showed no staring material. The reaction mixture was concentrated and dried over high vacuum to give D-ribopyranose (**313**; 28 mg, 100%).

Alternative procedure:

A 25 mL RBF was charged with diol **311b** (50 mg, 0.18 mmol) and 40 % aqueous AcOH (2.0 mL) and the resulting mixture was stirred at 90 °C for 3 hr. The reaction mixture was concentrated and dried over high vacuum to give D-ribopyranose (**313**; 24 mg, 89%).

$[\alpha]^{25}_{D}$ = -17.9 (c 1.2, H_2O), (Lit. $[\alpha]^{20}_{D}$ = -19.7 (c 4.0, H_2O)[179]

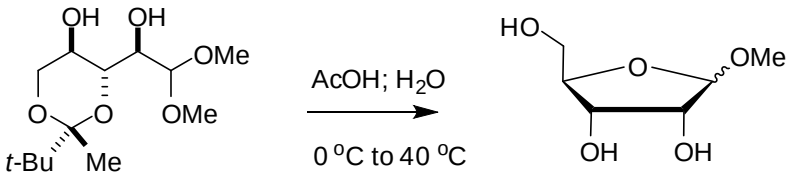
^{1}H NMR (500 MHz, D_2O) *δ:* 4.90(d, *J* = 6.6 Hz, 1H), 4.08 (br, 1H), 3.84 (m, 2H), 3.66 (dd, J_1 = 8.7 Hz, J_2 = 11.1 Hz, 1H), 3.50 (dd, J_1 = 2.7 Hz, J_2 = 6.6 Hz, 1H) ppm.

^{13}C NMR (125 MHz, D_2O) *δ:* 95.3, 72.5, 70.4, 68.7, 64.5 ppm.

HRMS (EI, 70 Ev) exact mass calcd., for $[M]^+$ $(C_5H_{10}O_5)^+$ requires 150.0528, found 150.0522 m/z.

Reference 179: ^{13}C NMR (125 MHz, D_2O) *δ:* 95.3, 72.5, 70.4, 68.7, 64.5
(Reference 179: *Aldrich Chemistry: Handbook of Fine Chemicals* **2009**)
and http://www.omicronbio.com/Pdf/D-ribosenmr.pdf

Methyl-D-ribofuranoside (314):



311 methyl-D-ribofuranoside **314**

A 25 mL RBF was charged with diol **311b** (30 mg, 0.11 mmol) and 40 % aqueous AcOH at 0 °C and the resulting mixture was slowly warmed up to 40 °C over the period of 3 hr. The reaction mixture was concentrated and dried over high vacuum to yield methyl-D-ribofuranoside (**314**; 17 mg, 99%).

$[\alpha]^{25}_{D}$ = -31 (c 0.9, H_2O), (Lit. $[\alpha]^{25}_{D}$ = -38 (c 0.15, H_2O)[180]

^{1}H NMR (500 MHz, D_2O) *δ:* 4.92 (br, 1H), 4.18 (dd, J_1 = 4.7 Hz, J_2 = 6.6 Hz, 1H), 4.05 (m, 2H), 3.82 (dd, J_1 = 3.4 Hz, J_2 = 12.4 Hz, 1H), 3.62 (dd, J_1 = 6.6 Hz, J_2 = 12.4 Hz, 1H), 3.42 (s, 3H) ppm.

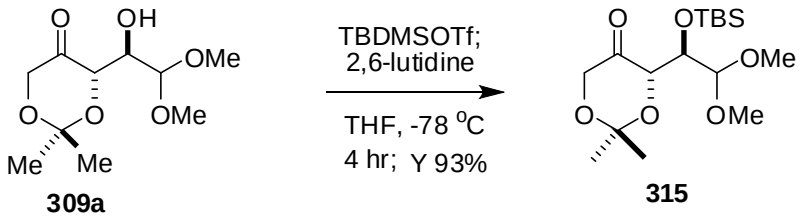
^{13}C NMR (125 MHz, D_2O) *δ:* 107.5, 82.4, 73.7, 70.3, 62.3, 54.7 ppm.

HRMS (EI, 70 Ev) exact mass calcd., for $[M]^+$ $(C_6H_{12}O_5)^+$ requires 164.0685, found 164.0684 m/z.

(*Reference 180*: Li, N.-S.; Lu, J.; Piccirilli, J. A. *Org. Lett*. 2007, 9, 3009-3012)

^{13}C NMR (125 MHz, D_2O) *δ:* 107.5, 82.3, 73.7, 70.3, 62.3, 54.7 ppm.

(*S*)-4-[(R)-1-(*tert*-Butyldimethylsilyloxy)-2,2-dimethoxyethyl]-2,2-dimethyl-1,3-dioxan-5-one (315)[12,14,20,173]



309a **315**

(Using Mander's protocol):[173] To a cold solution of the aldol adduct **309a** (2.2 g, 9.4 mmol) in dry THF (20 mL) was added dropwise 2,6-lutidine (2.20 mL, 18.8 mmol) followed by TBSOTf (3.43 mL, 11.3 mmol). The reaction was stirred at -78 °C until no starting material was detected by TLC (4 h). The saturated solution of $NaHCO_3$ was added, then the mixture was extracted with dichloromethane (3 x 30 mL) and the combined organic layers were washed with saturated solution of brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by FCC (SiO_2, hexanes : ethyl acetate 95 : 5) to afford the TBS-protected product **315** (3.05 g, 93%) as a clear liquid.

$\mathbf{[\alpha]^{25}_D}$ = -95 (c 1.1, $CHCl_3$)

[Lit. $\mathbf{[\alpha]^{25}_D}$ = -101.3 (c 1.0, $CHCl_3$)[20] and $\mathbf{[\alpha]^{25}_D}$ = -88.9 (c 0.69, MeOH)[14]]

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 4.57 (d, *J* = 7.4 Hz, 1H), 4.32 (t, *J* = 1.6 Hz, 1H), 4.20 (dd, J_1 = 1.6 Hz, J_2 = 15.8 Hz, 1H), 4.03 (dd, J_1 = 1.6 Hz, J_2 = 7.4 Hz, 1H), 3.87 (d, *J* = 15.8 Hz, 1H), 3.43 (s, 3H), 3.38 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

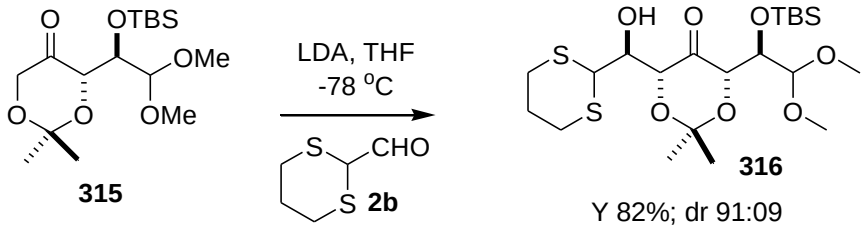
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 206.2, 105.6, 100.3, 77.9, 73.7, 67.3, 56.2, 55.8, 26.0, 25.1, 23.2, 18.1, -4.4, -4.7.

HRMS (CI, NH_3) exact mass calcd., for $[M + NH_4]^+$ $(C_{16}H_{32}O_6Si + NH_4)^+$ requires 366.2312, found 366.2316 m/z.

LRMS (CI, NH_3): m/z (%):366 ($[M+18]^+$, 60), 348 (5), 334 (100), 317 (52), 302 (33), 266 (37), 75 (83).

IR (KBr): 2987, 2931, 2856, 1751, 1469, 1374, 1224, 1116, 1000, 864, 836, 778 cm^{-1}

(4*R*,6*S*)-4-((*S*)-(1,3-Dithian-2-yl)(hydroxy)methyl)-6-((*R*)-1-(*tert*-butyldimethyl silyloxy)-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-one (316):



A solution of *n*-BuLi (4.8 mL, 10 mmol, 2.1 M solution in hexaness, 3.3 eq) was added dropwise to a stirred solution of DIA (1.6 mL, 11 mmol, 3.6 eq) in THF (10 mL) at 0 °C under nitrogen. After 30 min, a solution of compound **315** (1.1 g, 3.1 mmol, 1.0 eq) was added slowly and the mixture was stirred for 2 h at -78 °C. Then dithiane carboxaldehyde **2b** (1.8 g, 12 mmol, 4.0 eq) in dry THF (5.0 mL) was added and the mixture was stirred at -78 °C for 30 min. The reaction was quenched with concentrated phosphate buffer (pH 7.0; 15 mL) and extracted with ether (3x100 mL). The combined organic layers were rinsed with saturated solution of $NaHCO_3$ followed by NaCl and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the diastereoselectivity of the reaction was determined by ^{1}H NMR on the crude product by integration of the peaks at 3.43 ppm and 3.35 ppm and was found to be 9 : 91 *anti-anti-trans* to *anti-anti-cis* aldols. The crude reaction mixture was fractionated by FCC (5-10% ethyl acetate in hexanes) to give the title aldol **316** as a colorless oil (1.33 mg, 87 %).

$\mathbf{[\alpha]^{24}_D}$ = -3 (c 0.33, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 4.50 (d, *J*=7.4 Hz, 1H), 4.37-4.33 (m, 2H), 4.31-4.27 (m, 1H), 4.11-4.04 (m, 2H), 3.73 (br s, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 3.20-3.10 (m, 2H), 2.75-

2.67 (m, 1H), 2.64-2.56 (m, 1H), 2.04-1.95 (m, 2H), 1.50 (s, 3H), 1.47 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H) ppm.

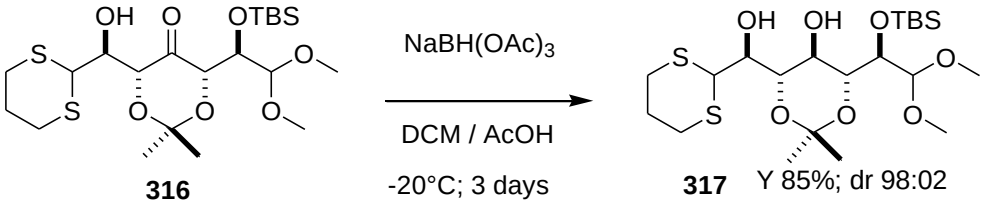
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 208.8, 105.5, 98.9, 79.8, 77.9, 76.0, 74.4, 56.0, 55.9, 44.6, 28.9, 28.8, 28.4, 26.0, 25.9, 20.6, 18.3, -4.4, -4.5 ppm.

HRMS *m/z* calcd for $C_{21}H_{40}O_7S_2Si$ 497.2065 (M+H), found 497.2078 (CI).

LRMS (CI, NH3), *m/z* (relative intensity): 497 ($[M]^+$+1, 56), 465 (44), 407 (8), 366 (17), 334 (98), 317 (100), 276 (44), 185 (20), 159 (32), 119 (72), 75 (84).

IR (KBr): 3487, 1709 cm^{-1}

(4*S*,5*R*,6*R*)-4-((*S*)-(1,3-Dithian-2-yl)(hydroxy)methyl)-6-((*R*)-1-(tert-butyldimethyl silyloxy)-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-ol (317):



Reaction was done based on modified procedure P5

To the solution of *β*-hydroxyketone **316** (1.3 g, 2.6 mmol, 1.0 eq) in dry CH_2Cl_2 (20 mL) AcOH (3.2 mL) and $NaBH(OAc)_3$ (1.1 g, 5.2 mmol, 2.0 eq) were added at -20 °C. Reaction was stirred at -20 °C for 12 h and then was kept at that temperature for 3 days (TLC monitored). The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 100 mL).The combined organic layers were washed with aqueous saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated to give the crude product. Diastereoselectivity of the reaction was measured by integrating peaks at 3.45 ppm and 3.56 ppm and was found to be 2 : 98 *syn* to *anti*. The crude mixture was purified by flash column chromatography on silica gel (hexanes : ethyl acetate 8 : 2) to give the pure diol **317** as a clear oil (1.1 g, 85%).

$\mathbf{[\alpha]^{25}_D}$ = +23 (c 1.0, C_6H_6) and $\mathbf{[\alpha]^{25}_D}$ = +7.0 (c 1.1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 4.93 (br s, 1H (OH)), 4.25 (d, *J* = 3.8 Hz, 1H), 4.24 (d, *J* = 2.6 Hz, 1H), 4.20 (br s, 1H), 4.06 (dd, J_1 = 2.6 Hz, J_2 = 7.8 Hz, 1H), 3.90 (dd, J_1 = 7.8 Hz, J_2 = 9.2 Hz, 1H), 3.88 (dd, J_1 = 1.0 Hz, J_2 = 9.1 Hz, 1H), 3.84 (dd, J_1 = 1.0 Hz, J_2 = 3.8 Hz, 1H), 3.80 (dd, J_1 = 9.1 Hz, J_2 = 9.2 Hz, 1H), 3.56 (s, 3H), 3.42 (s, 3H), 3.12-3.02 (m, 2H),

2.84-2.79 (m, 1H), 2.72-2.67 (m, 1H), 2.07-1.96 (m, 2H), 1.45 (s, 3H), 1.32 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H) 0.07 (s, 3H) ppm.

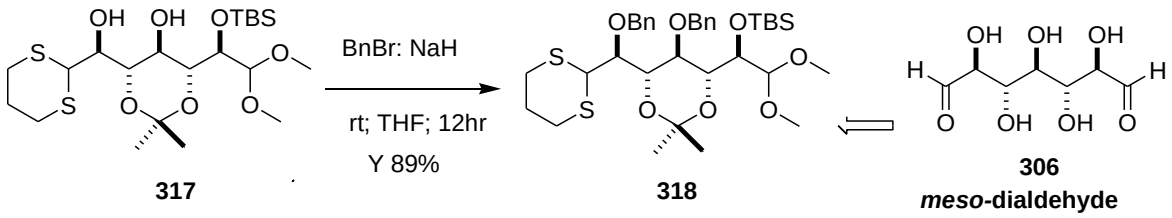
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 106.8, 98.7, 80.8, 76.2, 72.3, 70.5, 65.0, 58.6, 56.5, 47.5, 29.5, 29.1, 28.8, 26.2, 26.0, 19.5, 18.4, -4.2, -4.8 ppm.

HRMS (CI, Na) exact mass calcd., for $(C_{21}H_{42}O_7S_2Si + Na)^+$ $[M + Na]^+$ requires 521.2039, found 521.2038 m/z.

LRMS (CI, Na), *m/z* (relative intensity): 521 ($[M + 23]^+$, 30), 499 ([M + 1], 21), 484 (19), 467 (35), 435 (40), 409 (51), 119 (11), 75 (17).

IR (KBr): 3457 (br), 2991, 2928, 2854, 1463, 1380, 1255, 1166, 1151, 1070, 1001, 836, 779, 731cm^{-1}

((*S*)-1-((4*R*,5*R*,6*S*)-5-(Benzyloxy)-6-((*R*)-benzyloxy(1,3-dithian-2-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2,2-dimethoxyethoxy)(tert-butyl)dimethylsilane (318):



317 **318** **306**
***meso*-dialdehyde**

To a stirred suspension of NaH (80 % w/w) (91 mg, 23 mmol) in dry THF (5.0 mL) at 0 °C under inert atmosphere was added diol **317** (0.60 g, 1.2 mmol) in dry THF (10 mL). The resulting mixture was stirred at 0 °C for 15 minutes and benzyl bromide (0.32 mL, 2.6 mmol) and catalytic amount of TBAI (20 mg) were added. The resulting mixture was stirred at ambient temperature for 12 hr. After TLC showed no starting material the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to get the crude product which was purified by flash chromatography on silica gel using hexanes: EtOAc (5%>10%) to give the desired dibenzylated product **318** (0.73 g, 89%).

$[\alpha]^{25}_{D}$ = +14 (c 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.44-7.22(m, 10H), 4.87 (dd, J_1 = 5.5 Hz, J_2 = 11.6 Hz, 2H), 4.77 (t, J = 12 Hz, 2H), 4.45 (d, J = 10.1 Hz, 1H), 4.28 (d, J= 9.4 Hz, 1H), 4.25 (d, J = 8.2 Hz, 1H), 4.05 (t, J = 9.9 Hz, 1H), 4.00 (t, J = 9.7 Hz, 1H), 3.69 (d, J = 8.2 Hz, 1H), 3.62 (d, J = 9.7 Hz, 1H), 3.28 (s, 3H), 3.27 (s, 3H), 2.71 (m; 1H), 2.61 (m, 2H), 2.36 (m,

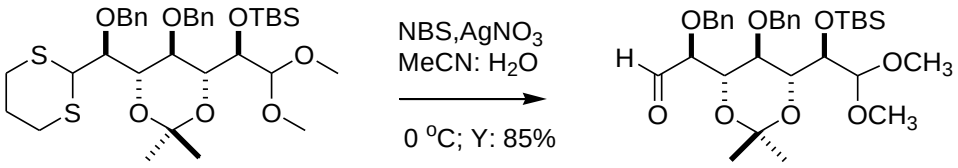
1H), 1.94 (m, 1H), 1.76 (m, 1H), 1.46 (s, 3H), 1.40 (s, 3H), 0.88 (s, 9H), 0.1 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 138.9, 138.3, 128.3, 128.2, 128.1, 127.5, 127.3, 127.0, 105.6, 99.3, 81.7, 75.5, 74.7, 74.0, 73.7, 72.5, 71.1, 55.9, 54.8, 49.9, 40.6, 30.0, 29.4, 26.0, 19.2, 18.5, -4.2, -4.6.

HRMS (CI, Na) exact mass calcd., for $(C_{35}H_{54}O_7S_2Si + Na)^+$ $[M + Na]^+$ requires 701.2978, found 701.2989 m/z.

IR (KBr): 3060, 2993, 2928, 2854, 1457, 1380, 1095, 1076, 1000, 836, 778, 697 cm^{-1}

(*S*)-2-(Benzyloxy)-2-((4*S*,5*R*,6*R*)-5-(benzyloxy)-6-((*R*)-1-(tert-butyldimethylsilyloxy)-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetaldehyde (319):



318 **319**

Reaction was done based on the modified Corey procedure P6[157]

To a stirred solution of freshly recrystalized N-bromosuccinimide (0.10 g, 0.56 mmol, 4.0 eq) and silver nitrate (0.11 g, 0.63 mmol, 4.5 eq) in acetonitrile : water (1 : 1; 2 mL) was added solution of compound **318** (95 mg, 0.14 mmol, 1.0 eq) in acetonitrile (3 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 5 minutes (TLC showed no starting material). The reaction was quenched with sodium sulfite solution (saturated, 3 mL) and the mixture was stirred for additional 10 min. Then it was filtered through the Celite bed, rinsed with CH_2Cl_2 and the resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution followed by brine solution and dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure to give the desired aldehyde **319** (70 mg, 85%).

$[\alpha]^{25}_{D}$ = +8 (c 1.0, $CHCl_3$).

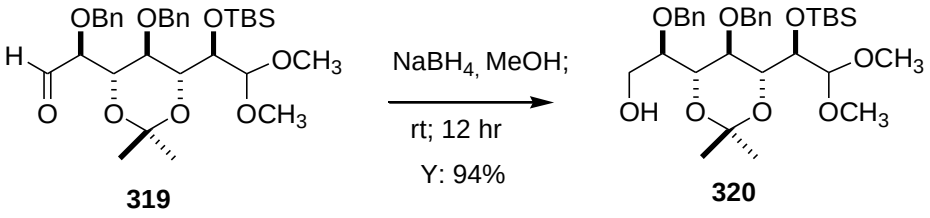
^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.59 (s (br),1H, CHO), 7.38-7.16 (m, 10H), 4.78 (m, 4H), 4.21(dd, J_1 = 6.2 Hz, J_2 = 3.5 Hz, 1H), 4.18 (d, J = 8.2 Hz, 1H), 3.97(m, 3H), 3.69(d, J = 8.2 Hz, 1H), 3.27 (s, 3H), 3.22 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 0.94 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.4, 138.2, 137.6, 128.6, 128.5, 128.1, 128.0, 127.6, 127.1, 105.6, 99.2, 83.5, 75.9, 75.6, 73.3, 72.9, 70.0, 55.9, 55.3, 29.3, 26.2, 19.2, 18.5, -4.2, -4.6 ppm.

HRMS (CI, NH_3) exact mass calcd., for $(C_{32}H_{48}O_8Si + NH_4)^+$ requires 606.3462, found 606.3465 m/z.

IR (KBr): 3117, 2991, 2929, 2855, 1736, 1497, 1380, 1257, 1122, 1092, 837, 778 cm^{-1}

(*R*)-2-(Benzyloxy)-2-((4*R*,5*R*,6*R*)-5-(benzyloxy)-6-((R)-1-(tert-butyldimethylsilyloxy)-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (320):



319 **320**

To the solution of aldehyde **319** (68 mg, 0.12 mmol, 1.0 eq) in MeOH (2.0 mL) was added $NaBH_4$ (13 mg, 0.35 mmol, 3.0 eq) at 0 ° C. The mixture was allowed to warm up to ambient temperature and it was stirred at that temperature for 4 hr (TLC controlled). The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with aqueous saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was purified by passing through a short silica gel plug (hexanes : ethyl acetate 30%) to give the pure alcohol **320** as a clear oil (64 mg, 94%)

$\mathbf{[\alpha]^{24}_D}$ = +20 (1.0, $CHCl_3$)

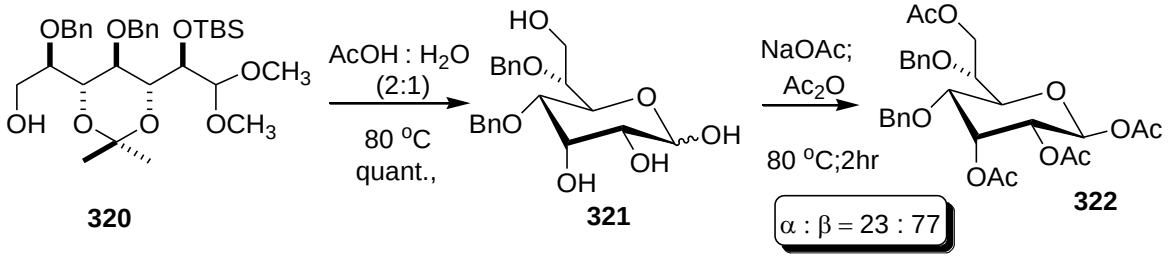
^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 7.34-7.20(m, 10H), 4.74 (dd, J_1 = 12.2 Hz, J_2 = 11.3 Hz, 2H), 4.60 (dd, J_1 = 12.2 Hz, J_2 = 11.3 Hz, 2H), 4.24 (d, J = 8.2 Hz, 1H), 4.03 (d, J = 10.1 Hz, 1H), 3.95 (d, J = 9.5 Hz, 1H), 3.83 (ddd, J_1 = 3.2 Hz, J_2 = 6.4 Hz, J_3 = 11.9 Hz, 1H), 3.75 (t, J = 10.1 Hz, 1H), 3.70 (m, 3H), 3.30 (s, 3H), 3.25 (s, 3H), 2.26 (br, 1H, OH), 1.45 (s, 3H), 1.39 (s, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 138.4, 138.0, 128.6, 128.5, 128.1, 127.9, 127.8, 127.5, 105.6, 98.9, 78.9, 75.5, 74.7, 74.1, 73.5, 72.1, 71.0, 61.9, 56.0, 55.0, 29.4, 26.2, 19.0, 18.5, -4.2, -4.6 ppm.

HRMS (CI, Na) exact mass calcd., for $(C_{32}H_{50}O_8Si + Na)^+$ requires 613.3167, found 613.3153 m/z.

IR (KBr): 3465 (br), 3197, 2991, 2928, 2855, 1470, 1380, 1255, 1124, 1093, 1001, 836, cm^{-1}

4,6-bis(Benzyloxy)- 1,2,3,7-tetra-O-acetyl-β-D-*glycero*-D-*allo*-heptopyranose (322):



320 **321** **322**

A 10 mL RBF was charged with alcohol **320** (0.032 g, 0.054 mmol) and 40 % aqueous AcOH (2.0 mL) and the resulting mixture was stirred at 90 °C for 3 hr. The reaction mixture was concentrated and dried over high vacuum to yield the gummy crude product **321** which was subjected to acetylation without further purification. To the crude **321**, sodium acetate (55 mg, 0.65 mmol) and acetic anhydride (2 mL) were added and the resulting mixture was heated to 90 °C for 2 hr. The reaction was quenched with ice followed by saturated $NaHCO_3$ solution. Then the mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4, concentrated to get the crude product as a mixture of protected of α and β anomers (23 : 77). Further purification by silica-gel simple column chromatography (25% EtOAc : hexanes) yielded the pure products **β-322** (20 mg, 67%) and **α-322** product (6 mg) with 87% overall yield over two steps.

β-322: $[\alpha]^{24}_{D}$ = +18 (c 1.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.21 (m, 10H), 5.95 (d, *J* = 8.6 Hz, 1H), 5.83 (t, *J* = 2.9 Hz, 1H), 4.80 (dd, J_1 = 2.9 Hz, J_2 = 8.6 Hz, 1H), 4.69 (d, J_1 = 12.0 Hz, 1H), 4.61(d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 10.9 Hz, 1H), 4.38 (d, *J* = 10.9 Hz, 1H), 4.21 (dd, J_1 = 7.8 Hz, J_2 = 11.8 Hz, 1H), 4.11 (dd, J_1 = 3.8 Hz, J_2 = 11.8 Hz, 1H), 4.06 (d, *J* = 9.9 Hz, 1H), 3.91

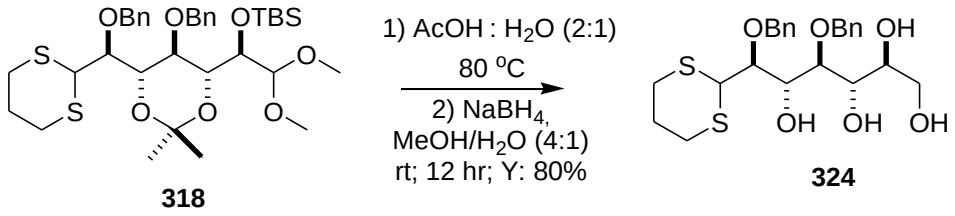
(dd, J_1 = 3.8 Hz, J_2 = 7.8 Hz, 1H), 3.79 (dd, J_1 = 2.9 Hz, J_2 = 9.9 Hz, 1H), 2.12 (s, 3H), 2.09 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 170.4, 169.7, 169.4, 138.5, 136.9, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 90.2, 77.6, 74.9, 73.3, 72.5, 71.7, 69.0, 67.1, 64.5, 21.2, 21.1, 21.0, 20.8 ppm.

HRMS (CI, NH_3) exact mass calcd., for $(C_{29}H_{34}O_{11} + Na)^+$ requires 581.1999, found 581.2004 m/z.

IR (KBr): 3029, 2932, 1746, 1453, 1370, 1216, 1068, 740, 699 cm^{-1}

(2*S*,3*S*,4*S*,5*S*,6*S*)-4,6-bis(Benzyloxy)-6-(1,3-dithian-2-yl)hexane-1,2,3,5-tetraol (324):



318 **324**

A 10 mL RBF was charged with compound **318** (0.30 g, 0.44 mmol) and 40 % aqueous AcOH (3.0 mL) and the resulting mixture was stirred at 90 °C for 2 hr. The reaction mixture was concentrated and dried over high vacuum to afford the gummy crude hemiacetal product (0.22 g) which was subjected to reduction. To the ice cooled solution of crude hemiacetal (0.22 g) in methanol (3 mL) and water (0.5 mL) was added $NaBH_4$ (42 mg, 1.1 mmol). The mixture was allowed to warm upto room temperature and it was stirred at that temperature for 12 hr (TLC monitered). The reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with aqueous saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated to give the crude product that was purified by passing through a short silica gel plug (DCM : MeOH 4%) to give pure tetraol **324** as a white solid (0.17 g, 80%)

Melting point: 46-47 °C

$[\alpha]^{24}_D$ = -20 (1.0, $CHCl_3$);

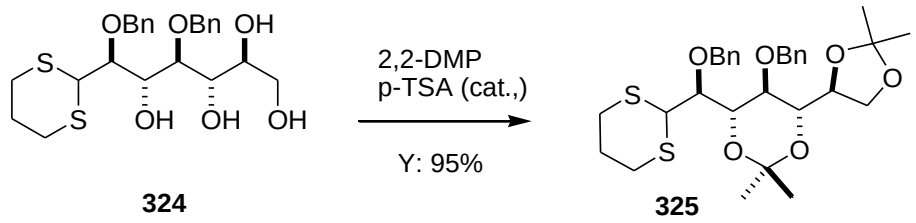
^{1}H NMR (500 MHz, C_6D_6): δ 7.48-7.06 (m, 10H), 5.15 (d, *J* = 10.7 Hz, 1H), 4.82 (d, *J* = 2.7 Hz, 1H), 4.65 (d, *J* = 10.7 Hz, 1H), 4.47 (dd, J_1 = 2.9 Hz, J_2 = 7.6 Hz, 2H), 4.26 (d, *J* = 11.1 Hz, 1H) , 4.13 (dd, J_1 = 2.7 Hz, J_2 = 7.6 Hz, 1H), 3.98 (m, 2H), 3.82 (m; 1H), 3.62 (m, 2H), 3.04 (br, 1H, OH), 2.55 (d, *J* = 4.7 Hz, 1H, OH), 2.40 (m; 4H), 1.61 (br, 1H, OH), 1.42 (m, 1H), 1.33 (m, 1H) ppm.

^{13}C NMR (125 MHz, C_6D_6) *δ:* 139.2, 138.5, 129.3, 129.1, 128.9, 128.7, 128.4, 128.2, 83.8, 80.9, 75.2, 73.1, 72.7, 72.6, 71.8, 64.2, 51.9, 32.1, 30.7, 27.1 ppm.

HRMS (CI, Na) exact mass calcd., for $(C_{24}H_{32}O_6S_2 + Na)^+$ requires 503.1538, found 503.1546 m/z.

IR (KBr): 3406 (br), 3099, 3029, 2927, 2895, 1496, 1453, 1210, 1065, 1028, 908, 738, 699 cm^{-1}

(4*S*,5*S*,6*S*)-5-(Benzyloxy)-4-((*S*)-benzyloxy(1,3-dithian-2-yl)methyl)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-1,3-dioxane (325):



324 **325**

Tetraol **324** (120 mg, 0.25 mmol, 1.0 eq) was transferred to the flame dried round bottom flask. *p*-TsOH.H_2O (0.005 mg, 0.0025 mmol, 0.01 eq) was added under nitrogen followed by freshly distilled 2,2-dimethoxypropane (3.0 mL). The mixture was stirred at room temperature for 6 hr after which time TLC showed no starting material. The reaction was quenched by addition of saturated solution of $NaHCO_3$ and the product was extracted with Et_2O (3 x 30 mL), washed with saturated solution of NaCl and dried with Na_2SO_4. Removal of the solvent under reduced pressure provided the crude product which was purified by FCC (hexanes : EtOAc 95 : 5) to give pure protected **325** as a colorless oil (0.12 g, 95%).

$[\alpha]^{24}_D$ = +3 (1.15, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.27 (m, 10H), 4.83 (s, 2H), 4.67 (d, *J* = 10.4 Hz, 1H), 4.61 (d, *J* = 10.4 Hz, 1H), 4.47 (d, *J* = 9.5 Hz, 1H), 4.28 (dd, J_1 = 1.5 Hz, J_2 = 8.7 Hz, 1H), 4.21 (dd, J_1 = 6.6 Hz, J_2 = 6.8 Hz, 1H), 3.89 (m, 3H), 3.64 (m, 2H), 2.73 (m; 2H), 2.60 (m, 2H), 1.97 (m, 1H), 1.83 (m, 1H), 1.46 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H) ppm.

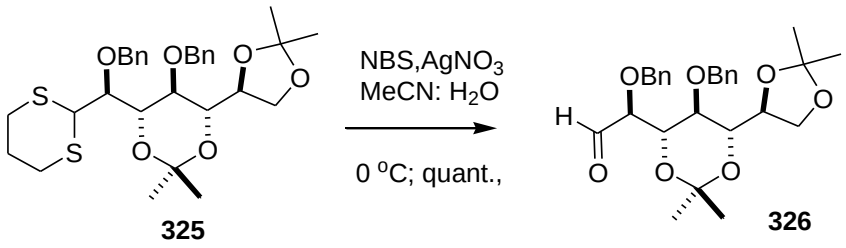
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 138.4, 138.3, 128.5, 128.4, 128.3, 127.9, 127.8, 109.7, 99.0, 82.4, 77.0, 75.2, 74.1, 73.6, 73.4, 73.3, 66.6, 49.9, 30.0, 29.7, 29.5, 26.6, 26.2, 25.8, 20.1 ppm.

HRMS (CI, Na) exact mass calcd., for $(C_{30}H_{40}O_6S_2+NH_4)^+$ requires 578.2610, found 578.2611 m/z.

LRMS (CI, NH_3), *m/z* (relative intensity): 578 ($[M + 18]^+$, 7), 561 (11), 503 (100), 233 (29), 197 (5), 108 (22), 91 (50).

IR (KBr): 3083, 2987, 2934, 2895, 1454, 1379, 1257, 1205, 1094, 851, 734, 699 cm^{-1}

(*S*)-2-(Benzyloxy)-2-((4*S*,5*S*,6*S*)-5-(benzyloxy)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-1,3-dioxan-4-yl)acetaldehyde (326):



Reaction was done based on the modified Corey procedure P6[157]

To a stirred solution of freshly recrystalized N-bromosuccinimide (95 mg, 0.54 mmol, 4.0 eq) and silver nitrate (0.10 g, 0.60 mmol, 4.5 eq) in acetonitrile : water (1 : 1; 2 mL) was added a solution of compound **325** (75 mg, 0.13 mmol, 1.0 eq) in acetonitrile (2.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 5 minutes (TLC showed no starting material). The reaction was quenched with a sodium sulfite solution (saturated, 3.0 mL) and the mixture was stirred for 10 min. Then the mixture was filtered through a Celite bed which was rinsed with CH_2Cl_2 and the resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, NaCl solution and dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure to give the desired aldehyde **326** (62 mg, 99%).

$\mathbf{[\alpha]^{24}_D}$ = +6 (c 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.57 (s (br),1H, CHO), 7.40-7.25 (m, 10H), 4.80 (s, 2H), 4.70 (d, *J* = 10.3 Hz, 1H), 4.51 (d, *J* = 10.3 Hz, 1H), 4.21 (m, 2H), 3.97 (m, 2H), 3.89 (t, *J*

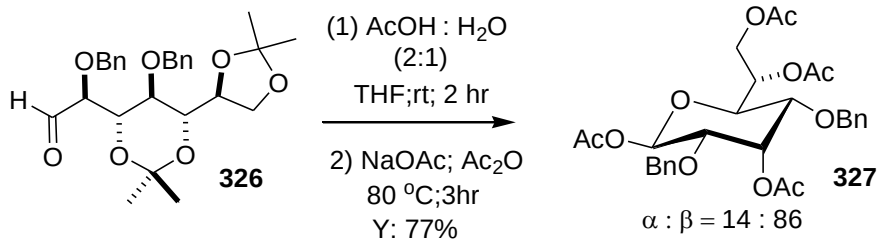
= 7.3 Hz, 1H), 3.84 (dd, J_1 = 5.8 Hz, J_2 = 9.6 Hz, 1H), 3.53 (t, J = 9.6 Hz, 1H), 1.48 (s, 3H), 1.40 (s, 6H), 1.36 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.7, 137.7, 137.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 109.9, 99.1, 83.4, 77.1, 74.9, 73.7, 73.4, 72.9, 66.7, 29.3, 26.6, 25.8, 19.4 ppm. **HRMS** (CI, NH_3) exact mass calcd., for $(C_{27}H_{34}O_7 + NH_4)^+$ requires 488.2648, found 488.2649 m/z.

LRMS (CI, NH_3), *m/z* (relative intensity): 488 ($[M + 18]^+$, 23), 455 (7), 430 (19), 413 (29), 273 (6), 233 (17), 181 (11), 108 (44), 91 (100).

IR (KBr): 3079, 2989, 2933, 2878, 1734, 1453, 1258, 1204, 1097, 850, 738, 699 cm^{-1}

2,4-bis(Benzyloxy)-1,3,6,7-tetra-O-acetyl-β-L-*glycero*-L-*allo*-heptopyranose (327):



To a solution of aldehyde **326** (60 mg, 0.13 mmol) in THF (2.0 mL) was added 40 % aqueous AcOH (2.0 mL) and the resulting mixture was stirred at ambient temperature for 2 hr. The reaction mixture was concentrated and dried over high vacuum to yield a gummy crude hemiacetal product (51 mg) which was directly subjected to acetylation. Sodium acetate (0.13 g, 1.6 mmol) and acetic anhydride (2.0 ml) were added and the resulting mixture was heated to 90 °C for 2 hr. The reaction was quenched with ice followed by saturated $NaHCO_3$ solution. The mixture was then extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to get a crude mixture of α and β anomers (14 : 86). Further purification by silica gel simple column chromatography (25% EtOAc : hexanes) yielded the pure product **β-327** (55 mg, 77%).

β-327: $[\alpha]^{24}_{D}$ = +26 (c 1.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.28 (m, 10H), 5.93 (t, *J* = 2.8 Hz, 1H), 5.84 (d, *J* = 8.4 Hz, 1H), 5.38 (ddd, J_1 = 2.8 Hz, J_2 = 3.2 Hz, J_3 = 6.9 Hz 1H), 4.66 (dd, J_1 = 12.1 Hz, J_2 = 11.1 Hz, 2H), 4.51(d, *J* = 12.1 Hz, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 4.10 (m, 2H), 4.02 (dd, J_1 = 2.8 Hz, J_2 = 9.8 Hz, 1H), 3.46 (dd, J_1 = 2.8 Hz, J_2 = 9.8 Hz, 1H), 3.36 (dd, J_1 = 2.9 Hz, J_2 = 8.2 Hz, 1H), 2.15 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H) ppm.

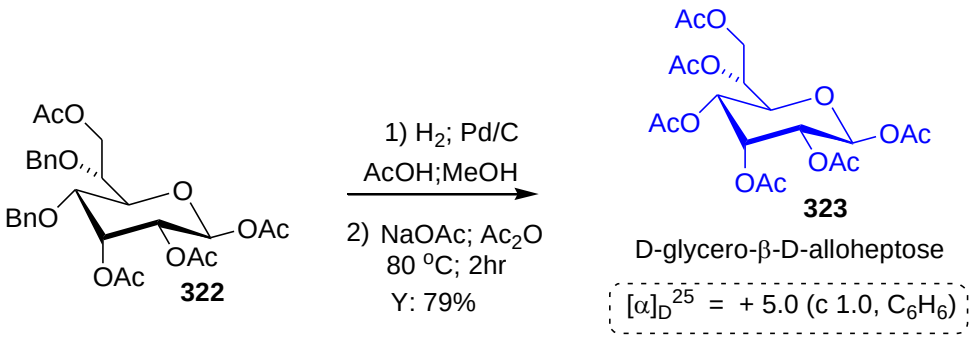
^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 170.6, 170.3, 169.3, 137.5, 136.8, 128.8, 128.7, 128.6, 128.4, 128.2, 127.9, 91.9, 74.7, 73.5, 73.3, 72.0, 71.4, 70.7, 65.9, 62.6, 21.2 (3xMe), 21.0 ppm.

HRMS (CI, NH_3) exact mass calcd., for $(C_{29}H_{34}O_{11} + NH_4)^+$ requires 576.2445, found 576.2460 m/z.

LRMS (CI, NH_3), *m/z* (relative intensity): 576 ($[M + 18]^+$, 100), 499 (46), 279 (12), 224 (10), 181 (8), 139 (11), 108 (37), 91 (93), 60 (16).

IR (KBr): 3025, 2932, 1743, 1454, 1370, 1221, 1074, 1053, 741, 700 cm^{-1}

1,2,3,4,6,7-Hexa-O-acetyl-β-D-*glycero*-D-*allo*-heptopyranose (323):



Solution of dibenzyl compound **β-322** (0.02 g, 0.04 mmol) in MeOH (2.0 mL) was treated with catalytic amount of acetic acid (0.25 mL) and 10% Pd/C catalyst (5.0 mg). The resulting suspension was stirred under H_2 (~5 psi) at ambient temperature for 12 hr. TLC and ^{1}H NMR showed no starting material. The reaction mixture and the catalyst was filtered through Celite bed and evaporation of the solvent afforded the debenzylated crude product which was subjected to complete acetylation. Sodium acetate (45 mg, 0.54 mmol) and acetic anhydride (2.0 mL) were added and the resulting mixture was heated to 90 °C for 2 hr. The reaction was quenched with ice followed by saturated $NaHCO_3$ solution. The mixture was then extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford the crude product, which, upon purification by silica-gel simple column chromatography (65% EtOAc: hexanes) yielded the pure product **β-323** (13 mg, 79%).

β-323: $[\alpha]^{24}_D$ = 5.1 (c 1.0, C_6H_6)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.93 (d, J = 8.6 Hz, 1H), 5.65 (t, J = 3.0 Hz, 1H), 5.19 (ddd, J_1 = 2.8 Hz, J_2 = 4.6 Hz, J_3 = 7.2 Hz 1H), 5.00 (dd, J_1 = 2.9 Hz, J_2 = 10.4 Hz, 1H),

4.92 (dd, J_1 = 3.0 Hz, J_2 = 8.6 Hz, 1H), 4.25 (dd, J_1 = 4.4 Hz, J_2 = 11.8 Hz, 1H), 4.17 (dd, J_1 = 2.9 Hz, J_2 = 10.4 Hz, 1H), 4.11 (dd, J_1 = 7.2 Hz, J_2 = 11.8 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.01 (s, 6H), 1.98 (s, 3H) ppm.

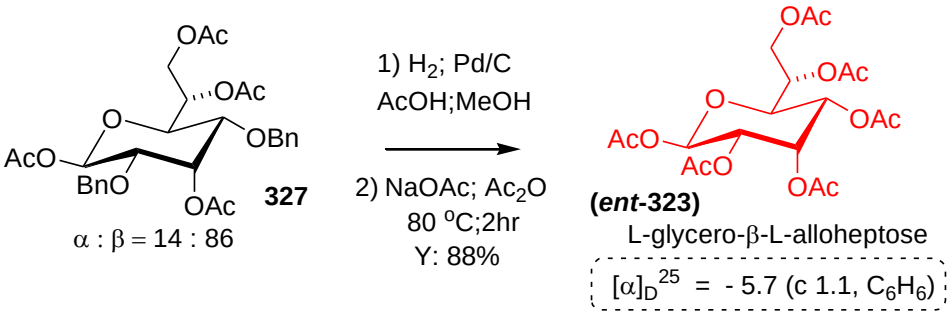
^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.6, 170.1, 169.96, 169.3, 169.3, 169.2, 90.3, 72.5, 69.9, 68.4, 68.1, 66.9, 61.8, 21.17, 21.14, 20.95, 20.93, 20.78, 20.75 ppm.

HRMS (CI, NH_3) exact mass calcd., for $(C_{19}H_{26}O_{13}+ NH_4)^+$ requires 480.1717, found 480.1715 m/z.

LRMS (CI, NH_3), *m/z* (relative intensity): 480 ($[M + 18]^+$, 100), 403 (52), 215 (2), 152 (8), 139 (9), 110 (8), 77 (7), 60 (41).

IR (KBr): 3476 (w), 2965, 1749, 1433, 1370, 1216, 1048, 948, 914, 601 cm^{-1}

1,2,3,4,6,7-Hexa-O-acetyl-β-L-*glycero*-L-*allo*-heptopyranose (*ent*-323):



To the solution of compound **β-327** (0.030 g, 0.054 mmol) in MeOH (2.0 mL) were added catalytic amounts of acetic acid (0.25 mL) and 10% Pd/C catalyst (5.0 mg). The resulting suspension was stirred under H_2 (~5 psi) at ambient temperature for 12 hr. TLC and ^{1}H NMR showed no starting material. The reaction mixture was filtered through Celite bed and evaporation of the solvent afforded the debenzylated crude product which was subjected to complete acetylation. Sodium acetate (67 mg, 0.81 mmol) and acetic anhydride (2.0 mL) and the resulting mixture was heated to 90 °C for 2 hr. The reaction was quenched with ice followed by saturated $NaHCO_3$ solution. The mixture was then extracted with ethyl acetate (3 x 20 mL), the combined organic layers were washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to aford the crude product, which, upon purification by silica-gel simple column chromatography (60-65% EtOAc: hexanes) yielded the pure product ***ent*-β-323** (13 mg, 79%).

β-*ent*-323: $[\alpha]^{24}_D$ = -5.7 (c 1.1, C_6H_6)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.93 (d, J = 8.6 Hz, 1H), 5.65 (t, J = 3.0 Hz, 1H), 5.19 (ddd, J_1 = 2.8 Hz, J_2 = 4.6 Hz, J_3 = 7.2 Hz 1H), 5.00 (dd, J_1 = 2.9 Hz, J_2 = 10.4 Hz, 1H), 4.92 (dd, J_1 = 3.0 Hz, J_2 = 8.6 Hz, 1H), 4.25 (dd, J_1 = 4.4 Hz, J_2 = 11.8 Hz, 1H), 4.17 (dd, J_1

= 2.9 Hz, J_2 = 10.4 Hz, 1H), 4.11 (dd, J_1 = 7.2 Hz, J_2 = 11.8 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.01 (s, 6H), 1.98 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 170.7, 170.1, 169.96, 169.3, 169.3, 169.2, 90.3, 72.5, 69.9, 68.4, 68.1, 66.9, 61.8, 21.19, 21.15, 20.95, 20.93, 20.79, 20.76 ppm.

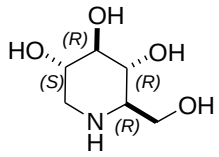
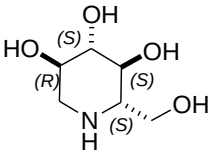
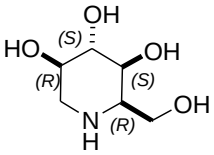
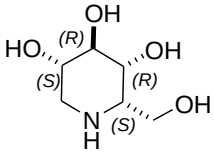
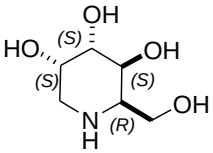
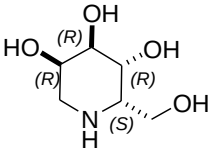
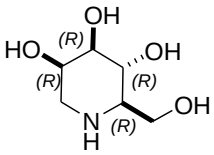
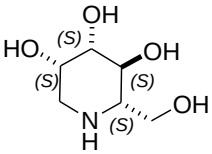
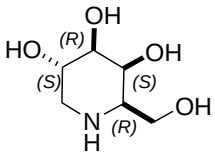
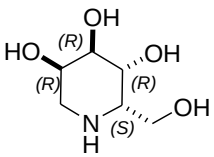
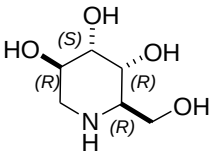
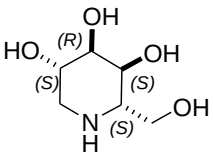
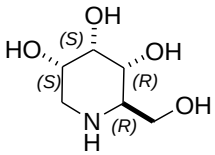
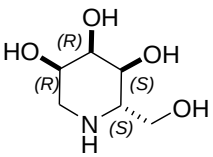
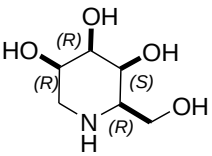
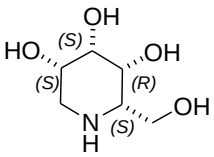
HRMS (CI, NH_3) exact mass calcd., for $(C_{19}H_{26}O_{13}+ NH_4)^+$ requires 480.1717, found 480.1710 m/z.

LRMS (CI, NH_3), *m/z* (relative intensity): 480 ($[M + 18]^+$, 100), 403 (56), 215 (2), 139 (7), 110 (7), 60 (17).

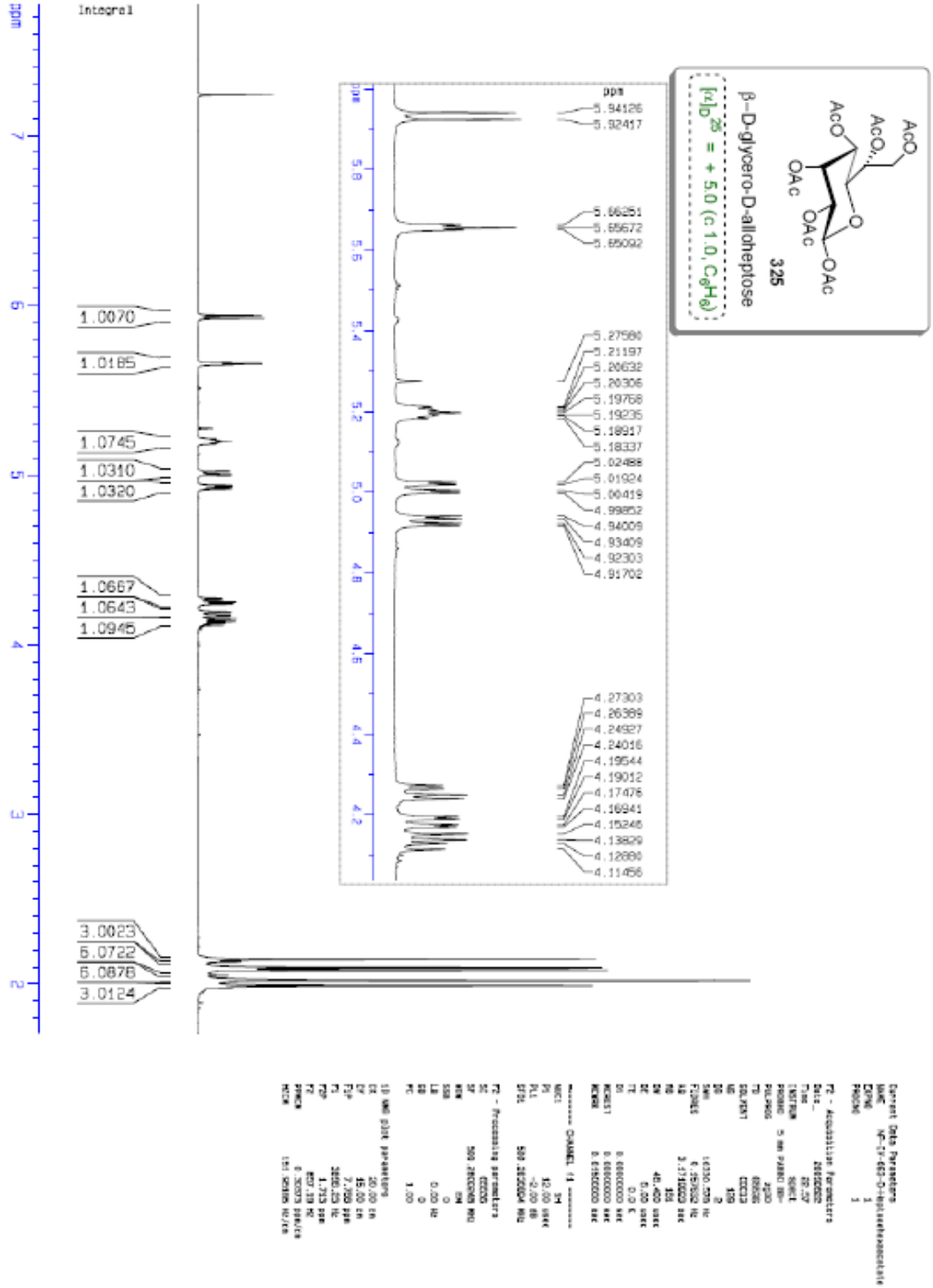
IR (KBr): 3476 (w), 2965, 1747, 1433, 1369, 1215, 1049, 948, 914, 734, 601 cm^{-1}

5 APPENDIX

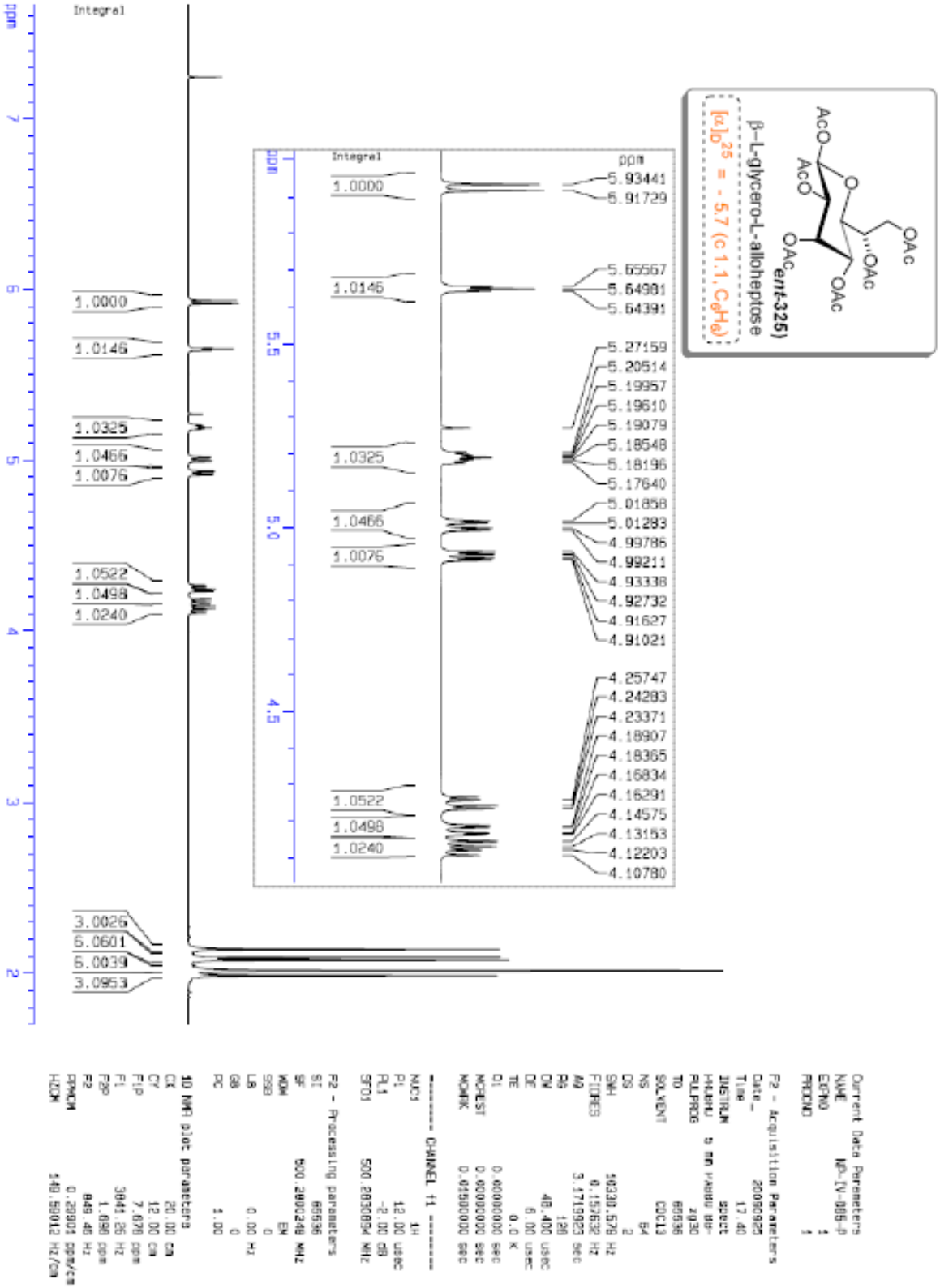
5.1 Appendix A: List of Stereoisomers of 1-Deoxynojirimycin

 **1-Deoxynojirimycin (1-DNJ)**	 **(L)-DNJ**	 **1-Deoxyidonojirimycin (*ido*-DNJ)**	 **(L)-*ido*-DNJ)**
 **1-Deoxygulonojirimycin (*gulo*-DNJ)**	 **(L)-*gulo*-DNJ**	 **1-Deoxymannonojirimycin (1-DMJ)**	 **(L)-DMJ**
 galacto-**DNJ**	 **(L)-**galacto-**DNJ**	 altro-**DNJ**	 **(L)**-altro-**DNJ**
 *allo*-**DNJ**	 **(L)-*allo*-DNJ**	 talo-**DNJ**	 **(L)**-talo-**DNJ**

5.2 Appendix B: ^{1}H NMR Spectra for Compound 323



5.3 Appendix C: ^{1}H NMR Spectra for *ent*-323



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