CHIRAL AUXILIARY DESIGN FOR THE STEREOSELECTIVE ADDITION OF α-ALKOXYMETHYL CARBANIONS TO ALDEHYDES AND KETONES

by

Robert Peter Smyj

A thesis

presented to the University of Waterloo

in fulfilment of the

thesis requirement for the degree of

Doctor of Philosophy

in

Chemistry

Waterloo, Ontario, Canada, 2001

The University of Waterloo requires the signatures of all persons using or photocopying this thesis. Please sign below, and give address and date.

Abstract

A new method has been developed that allows for the stereoselective addition of α-alkoxymethylcarbanions to aldehydes and ketones with the use of a chiral auxiliary on the nucleophile in up to 81% de. Recovery of the chiral auxiliary and the enantiomerically enriched 1,2-diol product was also possible and was demonstrated for the first time. The Sn-Li exchange process was employed to generate the chiral α-alkoxymethylcarbanions. Several chiral auxiliaries with different structural features including carbohydrate derivatives have been synthesized in order to optimize the level of stereoselectivity.

Glucose-derived chiral auxiliaries were able to induce diastereoselectivity in up to 59% de. Additions to electron rich aldehydes provided the highest levels of stereoselectivity, while additions to pentafluorobenzaledehyde resulted in a reversal in the sense of stereoselectivity. The C-glycoside group on the auxiliary was believed to be an important structural feature involved in the stereodifferentiating process. Stereoselectivity was optimized by employing an organotitanium species, however the yield dropped drastically to impractical levels.

A glucosamine-derived chiral auxiliary was unable to induce greater levels of stereoselectivity than glucose-derived chiral auxiliaries. The synthesis of the glucosamine-derived chiral auxiliary was also more difficult due to low yields.

Auxiliaries that were less "sugar like" in structure were also studied such as a 3-methoxy-tetrahydropyran chiral auxiliary. However addition to 3,4-dimethoxybenzaldehyde resulted in only 31% de. Furthermore a relatively long 12 step synthesis was used to prepare the 3-methoxy-tetrahydropyran chiral auxiliary derivative.

It was possible to synthesize 5-membered ring auxiliary derivatives in fewer steps; however unprecedented racemization occurred in the final step. Nevertheless the racemic 5-membered ring auxiliaries were unable to induce diastereoselectivity.

Finally, a tetrahydropyran chiral auxiliary without a 3-methoxy substituent was able to induce stereoselective additions in up to 81% de. A transition state structure different from what other auxiliary derivatives experienced was believed to occur. The importance of employing coordination additives in order to achieve higher levels of stereoselectivity was also realized.

Acknowledgements

I like to first thank Mike Chong for being an excellent supervisor and teacher. I have learnt a great deal from him and I am grateful for his suggestions and enthusiasm. I also like to acknowledge my advisory committee for their suggestions as well.

I would like to thank Peter Frese for conducting the preliminary work on this project. Also I like to acknowledge past and present labmates who where helpful to me and I like to thank Kelvin Yong for advice on chemistry and for entertaining discussions.

I also like to express thanks to Jan Venne for helping me acquire NOE data.

The financial support of the Ontario government for OGSST scholarships and the University of Waterloo for a graduate scholarship is also gratefully appreciated.

To my parents,

for their support and encouragement.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Ac	acetyl
AD	asymmetric dihydroxylation
Ar	aryl
BINOL	binaphthol
Bn	benzyl
bp	boiling point
br	broad
Bu	butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
calcd	calculated
cat.	catalytic
CSA	camphorsulfonic acid
conf.	configuration
d	doublet
de	diastereomeric excess
DIAB	3-*exo*-dimethyl(amino)isoborneol
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess

EI	electron impact
Et	ethyl
eq.	equivalent
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
h	hour(s)
HPLC	high-performance liquid chromatography
HMQC	heteronuclear multiple quantum coherence
HRMS	high-resolution mass spectrum
Hz	hertz
IR	infrared
J	coupling constant
L	liter(s)
LiDBB	lithium 4,4'-di-*tert*-butylbiphenyl
m	multiplet
M	moles per liter
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mmol	millimole(s)
mp	melting point
MS	mass spectrometry

MTPA	α-methoxy-α-(trifluoromethyl)phenylacetyl
m/z	mass to charge ratio
oct	octet
Ph	phenyl
PTSA	*p*-toluenesulfonic acid
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PCC	pyridinium chlorochromate
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
q	quartet
R_f	retention factor
rt	room temperature
s	singlet
sept	septet
t	triplet
TBME	*tert*-butyl methyl ether
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran

Ti-TADDOLate	(*R*,*R*)-diisopropoxy-(α,α,α',α'-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanolato) titanium
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethyl-1,2-ethylenediamine
TMS	tetramethylsilane
TsOH	*p*-toluenesulfonic acid
vs.	versus
v/v	volume/volume

CHAPTER 1

INTRODUCTION

1.1 Asymmetric Synthesis

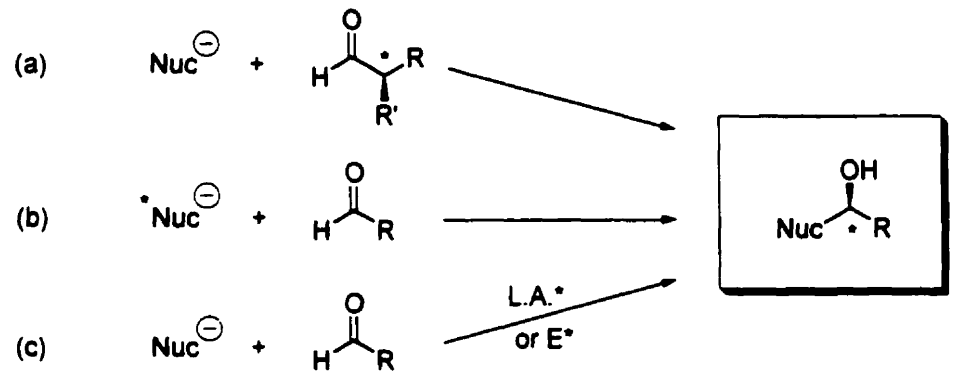
Research in synthetic organic chemistry is aimed towards constructing molecules of biological significance (i.e. natural product/medicinal chemistry), unnatural products of theoretical interest, or finding new methods to build molecules (i.e. methodology). Developing methods for the synthesis of enantiomerically enriched substances continues to be one of the great challenges for synthetic organic chemists. Obtaining enantiomerically enriched molecules is extremely important in the synthesis of pharmaceuticals since many drugs require correct stereochemistry for their desired activity.[1] Usually only one enantiomer of a chiral drug exhibits the desired pharmacological properties, while the opposite enantiomer of the active species may exhibit negative characteristics. The undesired enantiomer may be inactive, antagonistic, side-effect producing, or even be toxic. The methodology that aims to produce enantiomerically enriched compounds by introducing specific stereochemistry selectively in a molecule *via* a chemical reaction is called asymmetric synthesis.[2] Other methods that are available to obtain enantiomerically enriched compounds are resolution[3] or by employing chiral pool starting materials.[4] However these alternate methods may not always be convenient if for instance, chromatography is required on a large scale preparation to separate stereoisomers or if the unwanted isomer cannot be recycled. A chiral pool synthesis can also be limited in its applicability if a natural chiral source cannot be found to be incorporated into the target molecule. Therefore an asymmetric synthesis can sometimes be more feasible than the above methods in order to obtain enantiomerically enriched compounds.

1.2 Asymmetric 1,2-Additions of Organometallics to Aldehydes and Ketones

The addition of a nucleophile to a carbonyl group is a fundamental reaction in organic synthesis. Many asymmetric reactions of this class have been developed and discovering new methods continues to be an active area of research. Examples of transformations include asymmetric reductions of ketones,[5] asymmetric aldol reactions,[6] and the asymmetric additions of other carbon nucleophiles.[7] The advantage of introducing a stereocenter selectively with a carbon nucleophile is that a carbon-carbon bond *and* a new chiral center are formed in one reaction. Therefore the number of steps in a syntheic sequence for a chiral target molecule can possibly be reduced. This section introduces some of the important aspects and strategies involved in the asymmetric 1,2-addition of non-enolate carbon nucleophiles. Only selected illustrative examples will be presented in this section since it is not meant to be a comprehensive review, and the goal is therefore to place the research accomplished in this thesis into a greater context. More focus will be placed on the asymmetric 1,2-additions of α-heteroatom nucleophiles in Section 1.3.

In order to produce a new stereogenic center selectively in a 1,2-addition to a carbonyl group, the nucleophile must attack one prochiral face of the carbonyl compound selectively. There are three types of main strategies employed in order to influence a selective attack on a carbonyl group (Figure 1). One strategy (Figure 1a) involves the asymmetric addition of achiral nucleophiles to chiral aldehydes (Section 1.2.1), a second strategy (Figure 1b) involves the asymmetric addition of chiral nucleophiles to achiral aldehydes (Section 1.2.2), and a third method (Figure 1c) involves the asymmetric addition of achiral nucleophiles to achiral aldehydes mediated by chiral Lewis acids (L.A.*) or enzymes (E*) (Section 1.2.3).

Figure 1. Three strategies (a-c) for the asymmetric 1,2-addition of nucleophiles to an aldehyde.



1.2.1 Asymmetric 1,2- Additions of Achiral Nucleophiles to Chiral Aldehydes

A stereocenter adjacent or in close proximity to a carbonyl group can direct an achiral nucleophile to react stereoselectively onto one prochiral face of the carbonyl. The presence or absence of a heteroatom at the chiral center adjacent to the carbonyl group can have a profound influence on the direction and level of stereoselectivity that can be achieved. The directing chiral center can be a part of an auxiliary that can be removed later from the product (Section 1.2.1.3) or it can be incorporated in the final product (Section 1.2.1.1 and 1.2.1.2). The class of non-auxiliary stereoselective additions has been reviewed,[8] as many examples are present in the literature.

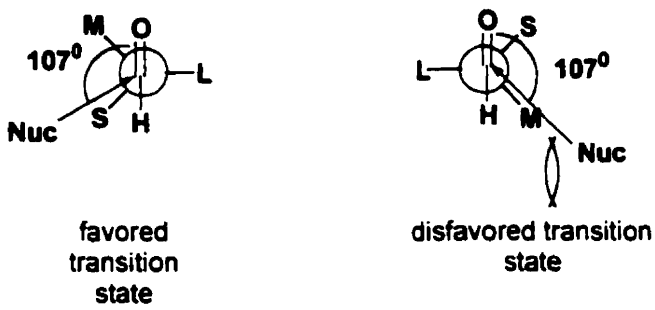
1.2.1.1 Cram/Felkin-Ahn Models

When potential metal chelating atoms adjacent (α) or β to the carbonyl group are absent both the Cram rule,[9] and Felkin-Anh model[10] are used to explain and predict stereochemistry. The Felkin-Ahn model is considered to be the most appropriate based on theoretical work;[10b] however

Cram's rule predicts the same result provided by the Felkin-Ahn model and both Cram's rule and the Felkin-Ahn model remain valid to account for experimental observations.

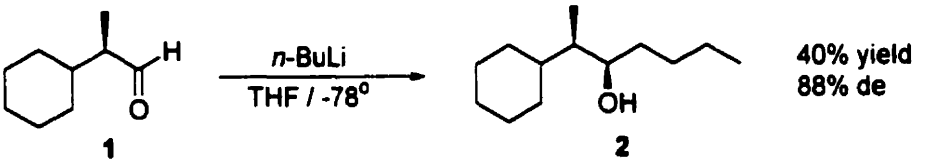
The Felkin-Ahn transition state model involves the positioning of the large α-substituent or a non-chelating electron-withdrawing group (L) perpendicular to the carbonyl group (Figure 2).[8, 10, 11] Nucleophilic attack occurs at a 107° angle[12] to the carbonyl group preferably at the side of the smallest α-substituent (S), and not at the medium group (M) side in order to minimize steric interaction between the nucleophile and the α-substituent.

Figure 2. Felkin-Ahn transition state models.



A literature example of a nucleophilic addition explained by the Felkin-Ahn/Cram model is included in a study directed towards the total synthesis of the natural product rhizoxin.[13] Addition of *n*-BuLi to the chiral aldehyde **1**, results in the formation of the addition product **2** in 88% de, the major diastereomer being the one predicted by the Felkin-Ahn/Cram model (Scheme 1).

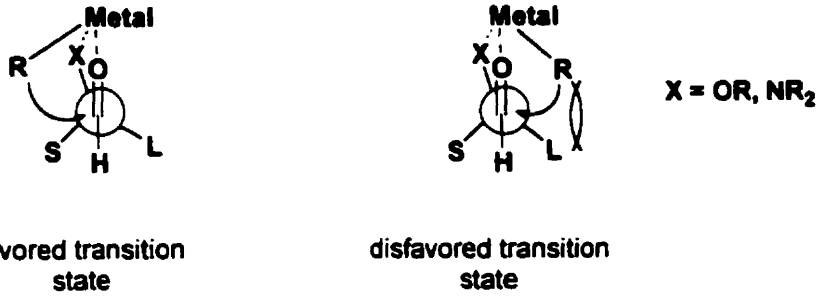
Scheme 1



1.2.1.2 Cram-Chelation

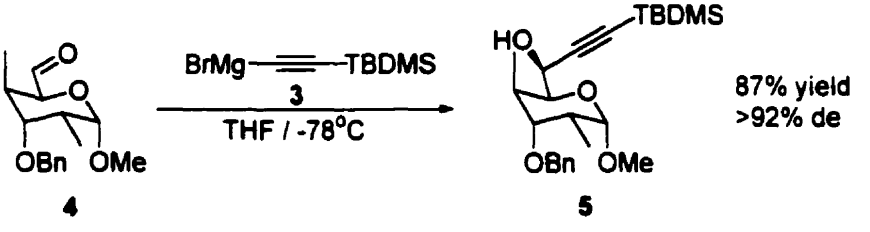
The presence of a potentially metal chelating atom such as oxygen or nitrogen at a chiral center α or β to the carbonyl group can cause a reversal in the direction of selectivity from that observed with the Felkin-Ahn/Cram model. The metal of the nucleophile can chelate between the heteroatom substituent (X) and the carbonyl group to form either 5 or 6-membered rings as intermediates (Figure 3). The chelated intermediate then undergoes nucleophilic addition according to the Cram-chelate rule.[8, 9, 14] The nucleophile prefers to attack at the side of the carbonyl where the smallest substituent (S) is present and not at the side of the large size substituent (L).

Figure 3. Cram-chelate model with an α-chelating atom.



The levels of selectivity obtained by chelation control are generally higher than those obtained by the non-chelation.[15] Selectivity can be higher since chelation reduces conformational flexibility in the transition state and thus provides a rigid template onto which nucleophilic addition can occur. Due to the greater success of chelation control methods, many more recent literature examples are reported such as in studies involving the total synthesis of natural products,[16] and in the synthesis of other biologically active compounds.[17] The greater popularity of the chelation control method is also due to its applicability in establishing a chiral 1,2-heteroatom functionality stereoselectively on adjacent carbon atoms, which is present in many biologically active compounds. For instance, during the total synthesis of the macrolide soraphen $A_{1\alpha}$,[16c] the authors introduce an alkynyl Grignard reagent **3** to the chiral aldehyde **4** to form the synthetic intermediate **5** in greater than 92% de (Scheme 2).

Scheme 2



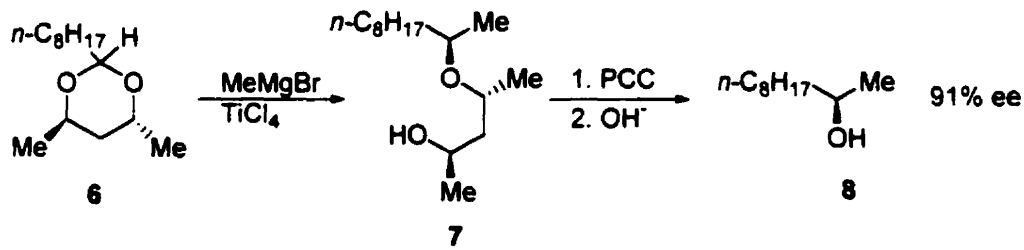
Sometimes organomagnesium nucleophiles react in greater levels of selectivity than organolithium reagents. For example in the above transformation (Scheme 2), the alkynyllithium provided **5** in only 43% de.

1.2.1.3 Chiral Auxiliaries

As has been shown, a source of chirality on the aldehyde can direct the stereoselective addition of the nucleophile onto one prochiral face of the aldehyde. However, the initial chirality present on the aldehyde may not be desired in the final product and the chiral directing group must be removed. In these instances, a chiral auxiliary bonded to the aldehyde is used to direct stereoselective nucleophilic additions and is then removed after the nucleophilic addition step to give a final product incorporating only the stereochemistry formed at the carbonyl carbon.

Usually, the carbonyl compound is linked to the auxiliary *via* an acetal bond. The linkage can be direct if the chiral auxiliary acts like a protecting group forming an acetal bond with the carbonyl, which then undergoes nucleophilic attack as seen in Scheme 3.[18] The acetal **6** is opened stereoselectively upon nucleophilic attack and the (*R*,*R*)-2,4-pentanediol auxiliary is removed from the addition product **7** to afford the enantiomerically enriched alcohol **8** in 91% ee.[18d]

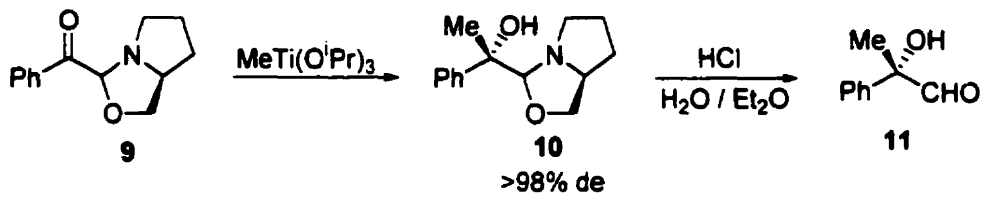
Scheme 3



The linkage can also be less direct with the point of attachment of the auxiliary occurring α to the carbonyl undergoing the nucleophilic attack.[19] For example an α-carbonyl group can be linked to a proline-derived auxiliary *via* an acetal bond as shown in **9** (Scheme 4).[20] The addition

occurs in >98% de and the auxiliary can be removed from **10** under acidic conditions in order to recover the optically active α-hydroxyaldehyde **11**.

Scheme 4



1.2.2 Asymmetric Addition of Chiral Nucleophiles to Achiral Aldehydes

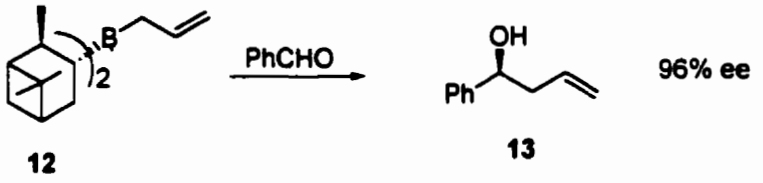
An alternative route to introduce nucleophiles to aldehydes and ketones stereoselectively is to employ chiral nucleophiles. The chirality is this case is transferred from the nucleophile to the electrophile, opposite to what was introduced in Section 1.2.1. There are three different practical methods for introducing chiral nucleophiles to aldehydes and ketones stereoselectively. One method involves the use of a chiral reagent (Section 1.2.2.1), a second method involves the use of a chiral auxiliary (Section 1.2.2.2) and the third method involves the use of a chiral catalyst (Section 1.2.2.3).

1.2.2.1 Chiral Reagents

Chiral reagent nucleophiles are employed in stoichiometric amounts in asymmetric additions. Synthetic manipulations of the product are not required as in the chiral auxiliary approaches since the chiral component of the reagent usually does not associate with the product and sometimes only an aqueous work-up is required. The most popular methodology developed in this area include asymmetric allyl additions, using chiral allyl boranes or boronates.[21] For example, the

diisopinocampheylborane forms the chiral component of the chiral allyl reagent **12** (Scheme 5).[22] Addition of reagent **12** to benzaldehyde occurs to give homoallylic alcohol **13** in 96% ee.

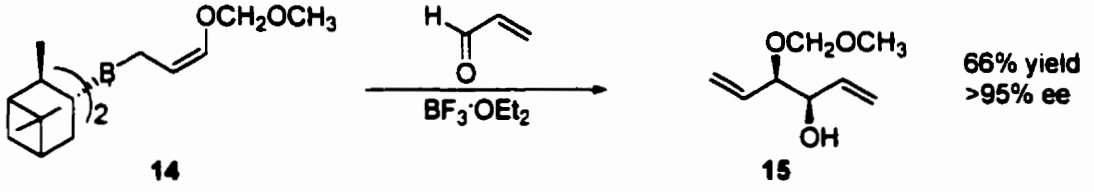
Scheme 5



12 **13**

Diisopinocampheylborane also forms the chiral component of chiral γ-alkoxyallyl reagents.[23] γ-Alkoxyallyldiisopinocampheylborane reagents also allow for the stereoselective introduction of heteroatom functionality to a molecule while forming a carbon-carbon bond. For instance, during a synthetic study directed towards the azinomycins, which are naturally occurring antitumor agents, the authors were able to add the chiral reagent **14** to acrolein to form the 1,2-diol **15** in >95% ee (Scheme 6).[23b]

Scheme 6



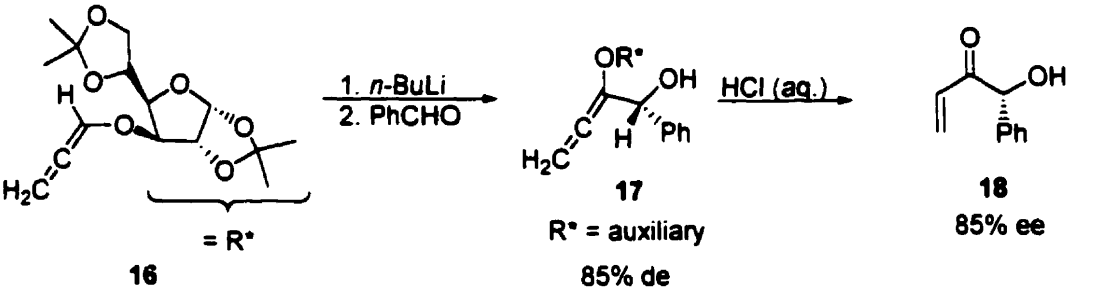
14 **15**

Other chiral reagent examples exist for asymmetric additions of other functionalities such as alkyl,[24] aryl,[24] or alkynyl groups.[25]

1.2.2.2 Chiral Auxiliaries

Attachment of a chiral auxiliary to the nucleophilic component is possible; however there are fewer examples that provide higher levels of selectivity than those achieved with chiral auxiliaries being attached to the electrophile.[26] Synthetic manipulations of the addition product are required in the chiral auxiliary approaches since the chiral component of the reagent does associate with the product usually *via* a heteroatom-carbon bond that must be broken in order to obtain the product free from the auxiliary. Examples of chiral auxiliary approaches include the use of carbohydrate-derived auxiliaries in asymmetric allylations,[27] vinyl additions,[28] γ-hydroxyallylations,[29] and in alkoxyallene anion additions.[30] For example, the asymmetric addition of the allene **16** to benzaldehyde occurs in 85% de (Scheme 7).[30] The sugar auxiliary is cleaved off from **17** under acidic conditions to afford the enantiomerically enriched vinyl ketone **18**, with no loss in stereochemical integrity.

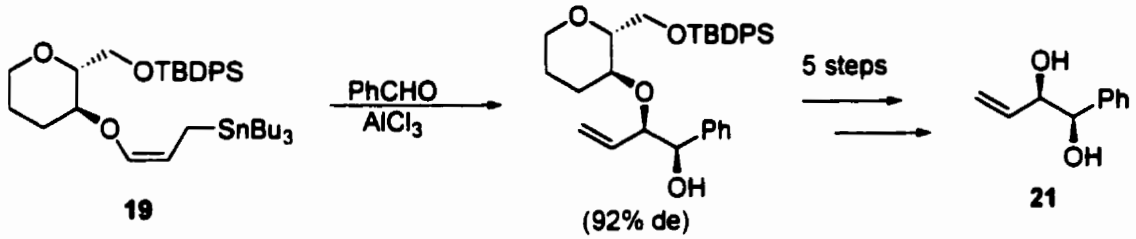
Scheme 7



In another example involving a carbohydrate-derived chiral auxiliary, a chiral γ-hydroxyallylstannane **19** is added stereoselectively to benzaldehyde to afford **20** in 92% de (Scheme 8).[29b] The enantiomerically enriched 1,2-diol **21** is cleaved from the auxiliary in a subsequent 5

steps. The use of carbohydrate-derived auxiliaries in asymmetric synthesis will be further discussed in Section 1.4.

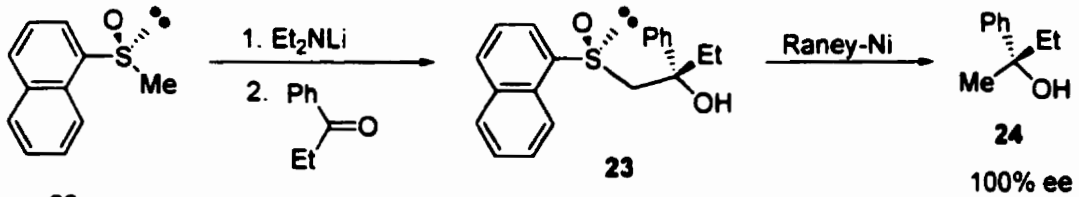
Scheme 8



19 **20** (92% de) **21**

Another class of chiral auxiliary containing nucleophiles include chiral sulfoxides, which allow for the asymmetric addition of methyl and carbonyl groups to aldehydes and ketones.[26, 31] Reactions with chiral sulfoxides are generally poorly stereoselective; however in one example a high amount of stereoselectivity is achieved with the addition of chiral sulfoxide **22** to propiophenone (Scheme 9).[31] The auxiliary from **23** is removed by desulfurization with Raney nickel to obtain the alcohol **24** in a reported 100% ee.

Scheme 9

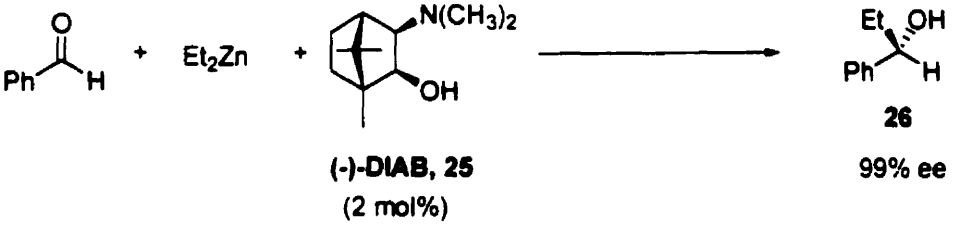


22 **23** 100% de **24** 100% ee

1.2.2.3 Chiral Catalysts

The only chiral nucleophilic organometallic reagent shown to be amenable to catalytic methods involve organozinc reagents.[32] Organolithium and oranganomagnesium reagents are not very suitable to catalytic methods due to their high reactivities. Dialkylzinc compounds are not very reactive with aldehydes on their own; however the complexation of an amino alcohol or diamine to the zinc atom greatly enhances the 1,2 addition of the alkyl group onto aldehydes. Therefore chiral amino alcohols and diamines are used as catalysts in enantioselective 1,2-additions to aldehydes. For example, the addition of diethylzinc catalyzed by (-)-3-*exo*-dimethyl(amino)isoborneol (**25**) or (-)-DIAB to benzaldehyde occurs to form the alcohol **26** in 99% ee (Scheme 10).[33]

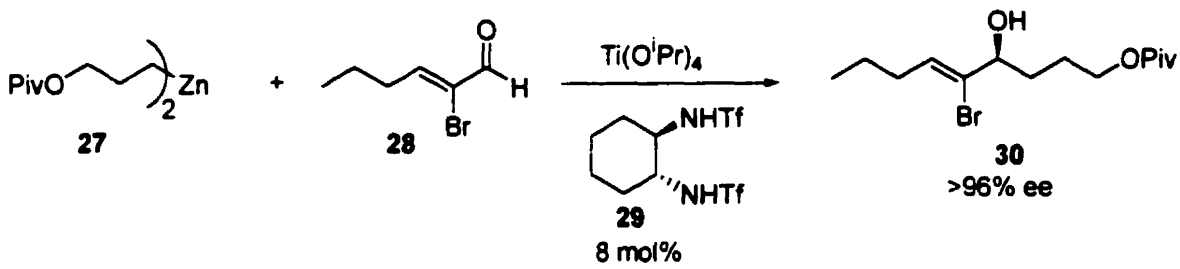
Scheme 10



Limitations to organozinc chemistry involve the type of group that can be transferred, since mostly methods involving the addition of simple hydrocarbon groups without any heteroatom functionality have been developed. However, in more recent research efforts,[34] a few examples exist where heteroatom functionalized zinc reagents are added to aldehydes with high stereoselectivity as seen in Scheme 11.[34c] The oxygen containing organozinc nucleophile **27**, reacts with the aldehyde **28**, in the presence of a catalytic amount of **29** to form the alcohol **30** in >96% ee. Nevertheless examples are limited to cases where at least a 3 carbon spacer unit is located between the metal and

heteroatom of the nucleophile. Examples of nucleophiles with the heteroatom closer to the metal are unknown in catalytic asymmetric additions of oraganozinc reagents to aldehydes. An advantage of the organozinc method is that the chiral catalyst does not need to be of high enantiomeric purity to be effective in providing high ee in 1,2-additions.[32]

Scheme 11



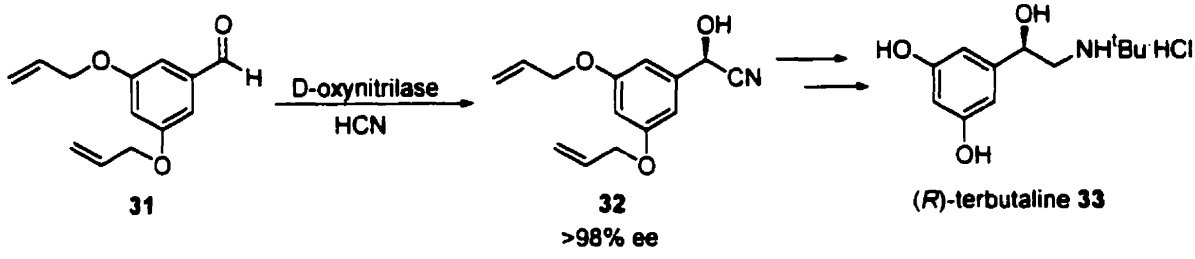
1.2.3 Asymmetric 1,2-Additions of Achiral Nucleophiles to Achiral Aldehydes

An achiral aldehyde can be made "chiral" *in situ* with the complexation of a chiral Lewis acid or by the association with an enzyme, so that a chiral environment can form around the aldehyde.[35] Both Lewis acids and enzymes act as catalysts to make the carbonyl group more electrophilic towards nucleophilic attack. Therefore, the catalytic approaches are limited to nucleophiles that are low enough in reactivity that require Lewis acid or enzymatic activation of the aldehyde for nucleophilic addition to occur.

Metallic and non-metallic chiral Lewis acids and enzymes have been used to catalyze the enantioselective addition of cyanide to aldehydes. For example, the enzyme D-oxynitrilase, which is isolated from almonds, catalyzes the addition of hydrogen cyanide to **31** in >98% ee (Scheme 12).[36] The cyanohydrin **32** was then transformed to the β-adrenoreceptor drug and bronchodilator (*R*)-

turbutaline **33** in subsequent steps. The significance in forming β-adrenoreceptor drugs stereoselectively with functionalized heteroatom containing nucleophiles such as cyanide will be discussed further in Section 1.3.1.

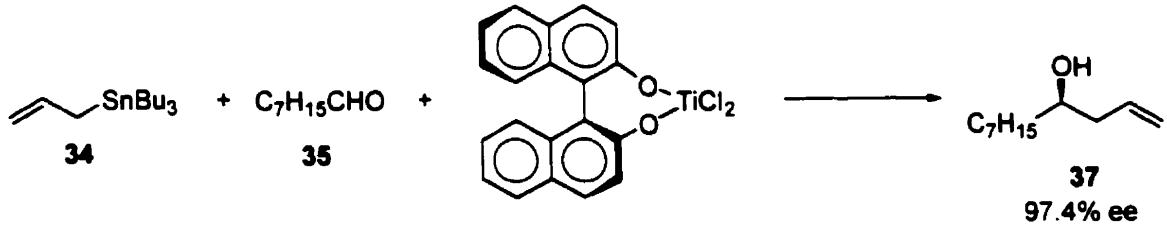
Scheme 12



31 **32** >98% ee (*R*)-terbutaline **33**

Similar strategies have been used for catalyzed additions of allylsilanes and allylstannanes to aldehydes by using metallic chiral Lewis acids. For instance the allylstannane **34** was added to octanal **35** in the presence of the BINOL-$TiCl_2$ catalyst **36**, to afford the alcohol **37** in 97.4% ee (Scheme 13).[37]

Scheme 13

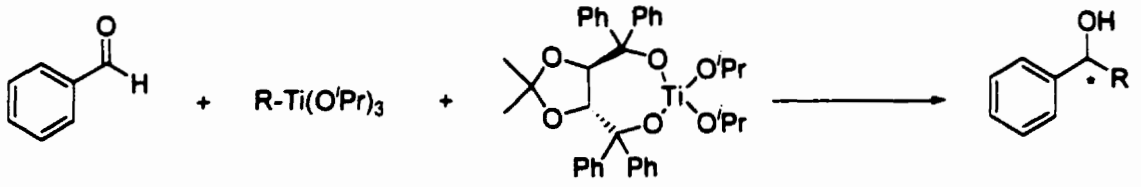


34 **35** **36** 20 mol% **37** 97.4% ee

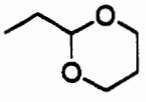
Other examples involving the use of chiral titanium Lewis acid catalysts include the use of (*R*,*R*)-diisopropoxy-(α,α,α',α'-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanolato) titanium

(Ti-TADDOLate **38**) in additions of achiral organotitanium reagents to aldehydes (Table 1).[38] Additions of unfunctionalized alkyl nucleophiles to benzaldehyde (entries 1-3), occur with very high selectivities. Heteroatom functionalized nucleophiles (entries 4 and 5) can also react with high levels of selectivities; however the level of stereoselectivity decreases as the heteroatom is positioned closer to the metal of the nucleophile (entries 6-9). Therefore at least a 3 carbon spacer unit is required between the metal and heteroatom for high levels of enantioselectivity to occur. A similar limitation was noted earlier for catalytic organozinc chemistry with respect to the placement of the heteroatom in the nucleophile (Section 1.2.2.3).

Table 1. Ti-TADDOLate **38** catalyzed additions of R-Ti(O^{i}Pr)$_3$ to benzaldehyde.



38
0.2 eq.

Entry	R	Product ee (%)
1	Et	99
2	*n*-Pr	99
3	*n*-Bu	99
4	$(CH_2)_6OMOM$	96
5	$(CH_2)_6OTBDMS$	92
6		70
7	$CH_2CH_2CO_2Et$	30
8	CH_2SMe	38
9	2-dithianyl	0

1.3 Asymmetric 1,2-Additions of α-Heteroatom Nucleophiles to Aldehydes and Ketones

It is important to develop asymmetric synthetic methodology for the introduction of heteroatom functionality in molecules since most biologically active compounds are rich in atoms such as oxygen and nitrogen. β-Amino alcohols such as β-adrenoreceptor receptor drugs are a class

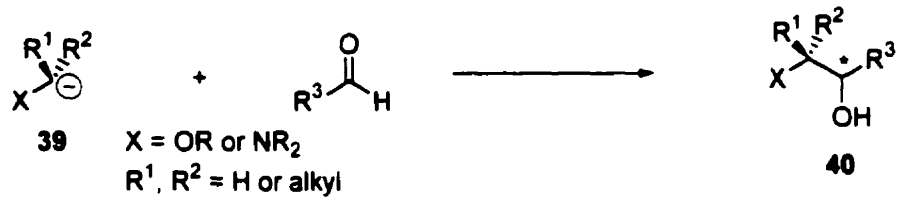
of compounds that fit into the category of heteroatom containing biologically active compounds. The significance of β-adrenoreceptor receptor drugs to this thesis will be discussed in Section 1.3.1.

Methods that can be used for the stereoselective introduction of heteroatoms to molecules can include some of the strategies introduced in Section 1.2 and other methods have been reviewed in the literature.[39] The addition of achiral nucleophiles to chiral α or β heteroatom containing chiral aldehydes as in Cram-chelate additions (Section 1.2.1.2) is a well-known method to establish a 1,2 or 1,3 chiral heteroatom pattern on a carbon chain. However, methods that allow for the stereoselective introduction of heteroatom functionality through the use of heteroatom containing chiral nucleophiles are far fewer. The only exception is the well established asymmetric aldol chemistry which allows for the introduction of a heteroatom containing nucleophile to an aldehyde to create a 1,3 heteroatom functionality on a carbon skeleton.[6] Only a few other examples exist such as in the addition of chiral γ-alkoxyallyl (Sections 1.2.2.1 and 1.2.2.2), functionalized organozinc (Section 1.2.2.3), alkoxy allene (Section 1.2.2.2), cyanide (Section 1.2.3) and functionalized organotitanium (Section 1.2.3) nucleophiles.

Another way to introduce chiral 1,2 heteroatom functionality on adjacent carbon atoms is to employ α-heteroatom nucleophiles such as **39** in stereoselective additions to aldehydes (Scheme 14). The asymmetric 1,2-addition of α-heteroatom carbanions such as **39** to aldehydes has been relatively unexplored and undeveloped. This section will present the 3 strategies used to introduce carbanion **39** to aldehydes and ketones stereoselectively. One strategy involves the addition of achiral reagents **39** (R^1, R^2=H, X=achiral) to chiral aldehydes (R^3=chiral) (Section 1.3.3). The second strategy involves the addition of chiral nucleophiles to achiral aldehydes with the chiral center on the carbanion **39** (R^1=alkyl, R^2=H or alkyl). The third strategy is the area explored in this thesis and involves employing a chiral nucleophile with a chiral group or auxiliary on X, with the charged

carbon atom being achiral (R^1, R^2=H) (Section 1.3.4). These methods allow for the formation of enantiomerically enriched 1,2-diols (**40** : X = OR), and β-amino alcohols (**40** : X = NR_2). The stability and generation of carbanions **39** by Sn-Li exchange will be discussed in Section 1.3.2.

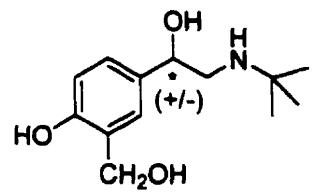
Scheme 14



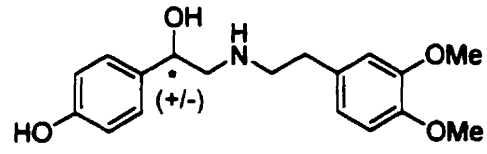
1.3.1 β-Adrenoreceptor Drugs

β-Adrenoreceptor drugs, also known as β-blocker drugs, possess β-amino alcohol functionality and have pharmacological activities against β-adrenergic receptors and are beneficial in the treatment of heart disease, asthma, and hypertension (Figure 4).[40] Examples of β-adrenoreceptor drugs include albuterol **41**, denopamine **42**, propranolol **43**, and levalbuterol **44**. The common structural feature of β-adrenergic receptor drugs include a benzylic hydroxyl group bonded to a chiral carbon, and a nitrogen atom bonded to an achiral carbon (methylene group). All of the drugs in Figure 4, with the exception of levalbuterol, are sold as racemates. However, the current strategy in the pharmaceutical industry is to remarket racemic drugs as their single stereoisomer in order to make the drugs more therapeutically effective as discussed in Section 1.1. Remarketing a racemic drug as a single stereoisomer also allows a pharmaceutical company to sometimes acquire a new patent on an old drug. For example, the older racemic drug albuterol **41**, has been remarketed by Sepracor in 1999 as the single (R) enantiomer and is called levalbuterol **44**.[41]

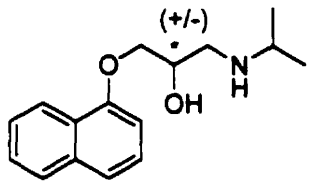
Figure 4. Examples of β-adrenoreceptor drugs.



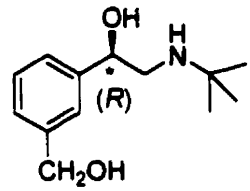
albuterol **41**
(bronchodilator)



denopamine **42**
(cardiotonic)



propranolol **43**
(antihypertensive)



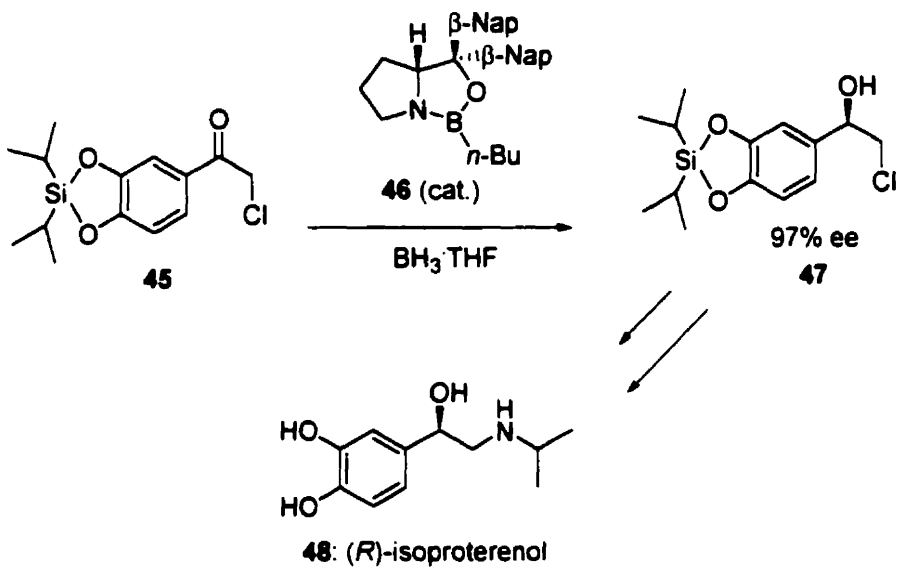
levalbuterol **44**
(bronchodilator)

The method employed by chemists at Sepracor to obtain levalbuterol as the exclusive R-isomer relies on a resolution step of diastereomeric tartrate salts.[41] An enzymatic resolution step in the synthesis of optically pure propranolol **43** has been proposed as well.[42] However, asymmetric syntheses can also provide viable alternative methods for obtaining β-blocker drugs of high optical purity.

Many examples exist for the asymmetric synthesis of β-blocker drugs and related compounds. One example has already been presented in Section 1.2.3 that involves the asymmetric addition of cyanide to an aldehyde. Other methods in the literature include asymmetric deprotonations of β-amino alcohol precursors,[43] asymmetric hydrogenations of α-amino ketones,[44] and the use of chiral boranes in the asymmetric reductions of α-halogenated ketones,[45] α-ketoimines,[46] α-amino ketones,[47] and enamines.[48] For instance, the α-chloro ketone **45** was reduced with the oxazaborolidine based CBS catalyst **46** in 97% ee to furnish the chlorohydrin **47** which was

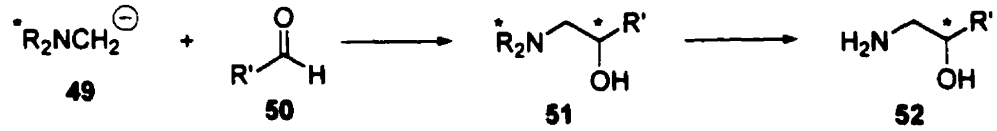
subsequently transformed to the β-adrenoreceptor drug (*R*)-isoproternol **48** in high optical purity (Scheme 15).[45a]

Scheme 15



Most of the methods mentioned above rely on asymmetric reduction methodology to arrive at β-adrenoreceptor drugs of high optical purity. An alternative method to form the chiral stereocenter selectively in β-adrenoreceptor drugs can be *via* carbon-carbon bond formation in the asymmetric addition of a nitrogen containing chiral α-heteroatom nucleophile (Scheme 16). A chiral auxiliary (R^*) bonded to the nitrogen in the α-heteroatom nucleophile **49** can direct the stereoselective addition onto aldehyde **50**, to form the addition product **51**. The chiral auxiliary should then be removed to form enantiomerically enriched β-adrenoreceptor drug precursors **52**. Literature examples that attempt to develop the type of methodology outlined in Scheme 16 will be presented in Section 1.3.4.2. The next section will discuss the generation and stability of α-heteroatom nucleophiles such as **49**.

Scheme 16



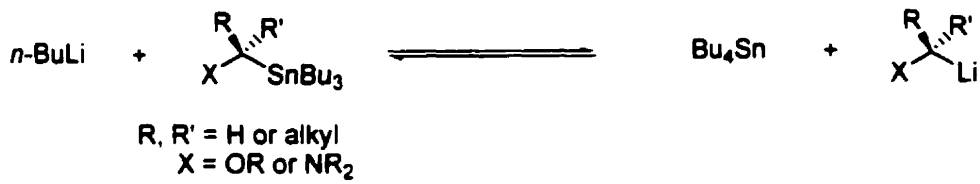
1.3.2 The Sn-Li Exchange Process for the Generation of α-Heteroatom Carbanions

The Sn-Li exchange process is a method employed to generate α-heteroatom carbanions from α-heteroatom substituted organostannane precursors.[49] Sn-Li exchange is also the method used to generate unsubstituted α-alkoxycarbanions throughout the work of this thesis. Other popular methods to generate α-heteroatom carbanions include the deprotonation of activated α-amino[50] and α-alkoxy compounds.[51] Enantioselective deprotonations can occur to generate α-amino[50b] and α-alkoxy[51] carbanions. α-Heteroatom carbanions can also be generated by reductive lithiations of chloromethyl ethers[52] and phenylthio ethers.[53] Many methods are also available for the synthesis of α-alkoxystannanes[54] and α-aminostannanes,[54a, 55] and enantioselective syntheses of chiral α-alkoxystannanes[54b] and chiral α-aminostannanes[55] are possible.

Sn-Li exchange occurs with retention of configuration,[56] and is an equilibrium reaction,[57] with the equilibrium being shifted towards the formation of the more stable (less basic) α-heteroatom substituted organolithium (Scheme 17). The α-heteroatom organolithium is more stable then the alkyllithium (i.e. *n*-BuLi) due to the inductive withdrawal of electron density from the carbanion by the heteroatom.[58] Also, stabilization can occur by lithium bridging to the heteroatom, through dipole stabilization of a carbonyl group present on the heteroatom, and by intramolecular chelation of the Li atom by a chelating group attached to the heteroatom.[58] An intramolecular chelating group also allows substituted α-amino and α-alkoxy organolithiums (possessing chirality

at the charged carbon) to be configurationally stable.[58] The configurational stability of substituted α-heteroatom carbanions allow the transfer of chirality from the nucleophile carbanionic center to an aldehyde in a process known as 1,2-induction (Section 1.3.4.1). Furthermore, it has been demonstrated that the chemical stability of the α-heteroatom carbanion decreases with increasing alkyl group substitution on the charged carbon atom.[56b]

Scheme 17



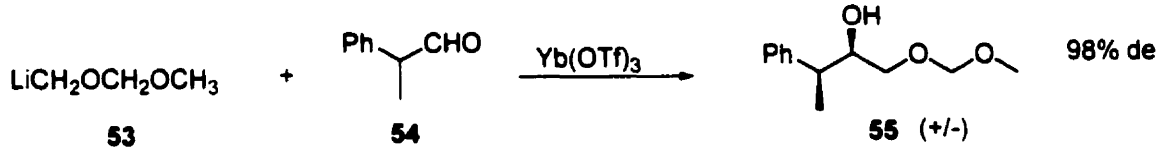
There has been considerable debate as to whether the mechanism of Sn-Li exchange is concerted or step-wise. A step-wise mechanism involves the formation of a stannylate species (Figure 5a) that has been observed by spectroscopic studies of tetraalkylstannane transmetalations.[59] On the other hand, there has been no evidence of such intermediates existing in similar spectroscopic studies involving transmetalation reactions of α-alkoxy[56b] and α-siloxy stannanes.[60] The absence of stannylate intermediate observations allows for the consideration of a concerted mechanism involving a four-centered transition state (Figure 5b).

Figure 5. The proposed stannylate intermediate (a) and the four-centered transition state (b)

1.3.3 Chiral induction from the aldehyde

One strategy that can be employed in the asymmetric 1,2-additions of α-heteroatom nucleophiles to aldehydes is to conduct reactions between an achiral α-heteroatom nucleophile and a chiral aldehyde. However, only one literature example exists where additions of achiral and hydroxyl protected $LiCH_2OR$ to a chiral aldehyde occurs.[61] For instance, the addition of $LiCH_2OCH_2OCH_3$ **53** to 2-phenylpropanal **54** in the presence of $Yb(OTf)_3$ as an additive results in the formation of the *syn* addition product **55** as predicted by the Felkin-Ahn model. in 98% de (Scheme 18).

Scheme 18



1.3.4 Chiral Induction from the Nucleophile

The asymmetric addition of a chiral α-heteroatom nucleophile to an achiral aldehyde or ketone is the second strategy employed in the asymmetric 1,2-addition of α-heteroatom nucleophiles to aldehydes and ketones. The chirality can be present on the charged carbon (Section 1.3.4.1) or can be present on a group or chiral auxiliary bonded to the oxygen or nitrogen atom (Section 1.3.4.2). The former method has been shown to be more successful in providing higher levels of selectivity perhaps due to the fact that chiral induction occurs more efficiently through shorter

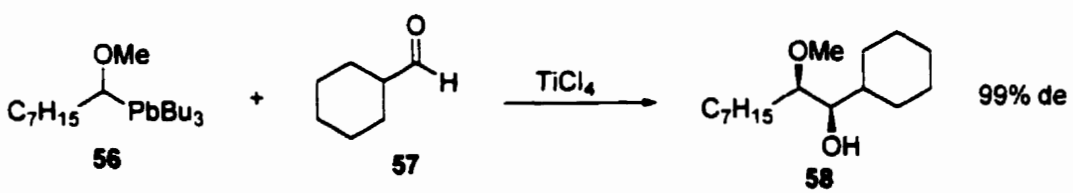
distances. The later method is largely undeveloped in the literature with low levels of selectivity being achieved.

1.3.4.1 Proximal Chiral (1,2)-Induction from the Nucleophile

The chiral center present on the charged carbon of substituted α-heteroatom nucleophiles allows for the transfer of chirality to occur from the nucleophile to the aldehyde. McGarvey and Kimura were able to investigate the stereoselectivity achieved in the additions of chiral α-alkoxyorganolithiums to aldehydes.[62] However, good to excellent levels of stereoinduction were only achieved with bulky alkyl R groups attached to the charged carbon.

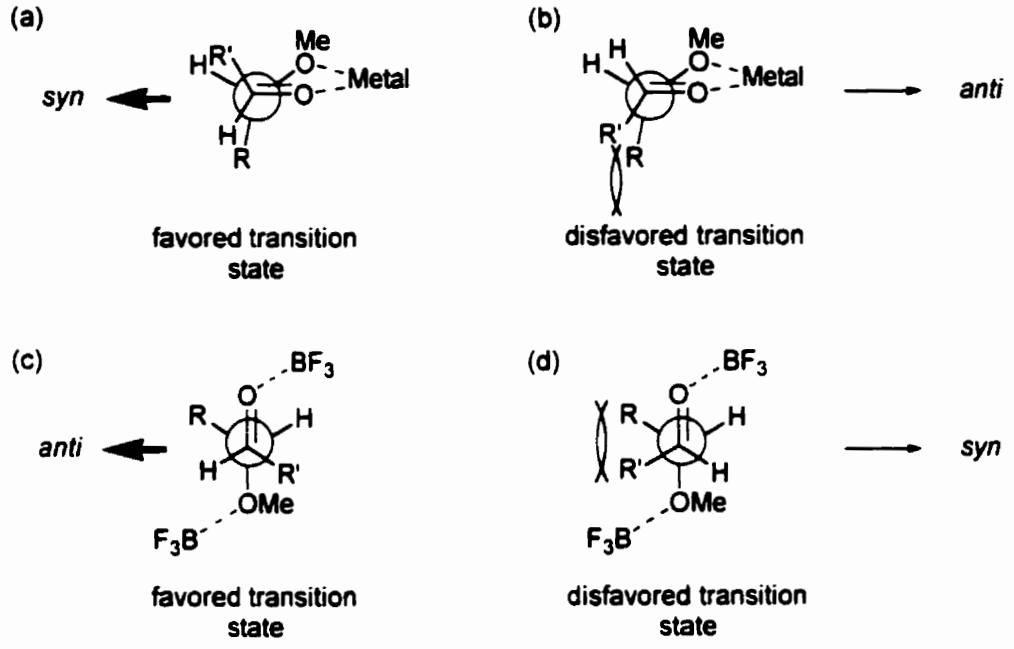
The use of α-alkoxyorganolead compounds offers higher levels of selectivity even with only primary alkyl groups present on the charged carbon.[63] For instance, the addition of the α-alkoxyorganolead compound **56** to cyclohexanecarboxaldehyde **57**, in the presence of the Lewis acid $TiCl_4$, allows for the formation of the *syn* α-hydroxyether **58** in 99% de (Scheme 19). The use of $BF_3{\bullet}OEt_2$ as a Lewis acid allows for the formation of *anti* relative stereochemistry in the product, however with lower levels of selectivity.

Scheme 19



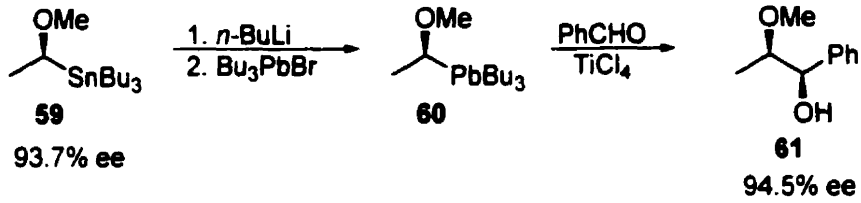
The transition states for 1,2 induction reactions are believed to occur through chelated structures in the presence of $TiCl_4$ for organolead additions or when organolithium or organomagnesium nucleophiles are used without Lewis acids (Figure 6 a, b). Non-chelated structures are believed to occur in the presence of $BF_3 \cdot OEt_2$ when organolead nucleophiles are employed (Figure 6 c, d). Chelation of the metal (Ti, Li, or Mg) between the α-oxygen of the nucleophile and the carbonyl oxygen allows the nucleophile to prefer the approach onto the prochiral face of the aldehyde where the R groups of both compounds would be the furthest apart (Figure 6a) as opposed to the more crowded transition state seen in Figure 6b. Therefore, a chelated transition state would allow the formation of diols with *syn* relative stereochemistry to predominate. In a non-chelated transition state seen in organolead nucleophile additions with $BF_3 \cdot OEt_2$ present, the carbonyl oxygen and nucleophile oxygen point away from each other and attack on the prochiral face is preferred where steric interactions are minimized between the R groups of both compounds (Figure 6c) as opposed to Figure 6d. As a result, a non-chelated transition state would allow the formation of diols with *anti* relative stereochemistry to predominate.

Figure 6. Chelation control (a,b) and non-chelation control (c,d) in 1,2-induction reactions.



Absolute stereochemistry can be transferred in 1,2-inductions as well, in order to form enantiomerically enriched hydroxyethers, if one starts out with enantiomerically enriched α-alkoxyorganostannanes.[63] For instance, the α-alkoxyorganostannane **59**, of 93.7% ee (*S*) was transformed to the α-alkoxyorganolead compound **60**, with retention of configuration, then treated with benzaldehyde and $TiCl_4$ to form the *syn* hydroxyether **61** over the *anti* in a 93:7 ratio, with the *syn* hydroxyether being formed in 94.5% ee (Scheme 20). The *syn* hydroxyether maintained the same configuration at the OMe substituted carbon as in the organolead compound and with no loss in ee. Therefore the nucleophile **60** maintains the same configuration with complete configurational stability in addition to benzaldehyde.

Scheme 20



Chiral α-alkoxyorganolead compounds have also been successfully employed in additions to chiral aldehydes to form 3-contiguous stereocenters,[64] and have been applied in a study towards the synthesis of the brassinosteroid side chain.[65] Similar examples of nucleophilic 1,2-induction in the diastereoselective formation of hydroxyethers have also been shown to occur in pinacol couplings.[66]

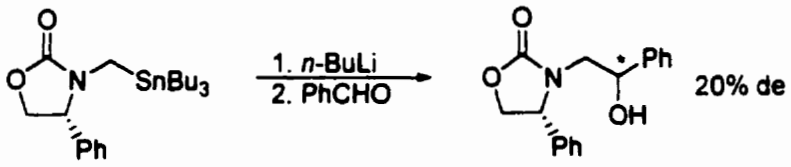
Examples involving chiral α-amino[53a] and α-thio[67] carbanions in stereoselective additions to aldehydes have also appeared in the literature. The direction of selectivity of chiral α-amino carbanion additions, with secondary and tertiary alkyl groups attached to the carbanion, was reversed (i.e. *anti* configuration predominates in the aminoalcohol) from what was observed with chiral α-alkoxy carbanion additions. Furthermore in another paper,[68] an example involving an α-aminoorganolithium attached to primary alkyl group at the charged carbanion did not show any reasonable 1,2-induction. Therefore, a big R group attached to the carbanion on the α-aminoorganolithium seems to be necessary in order for 1,2-induction to occur and correlates with explanations noted earlier by McGarvey and Kimura for α-alkoxycarbanions additions with exception to the direction of selectivity.[62]

1.3.4.2 Remote Chiral Induction from the Nucleophile

A chiral α-heteroatom nucleophile can have the source of chirality further removed from the charged carbon atom and still be able to promote stereoinduction in 1,2-additions to aldehydes. A general example for remote induction involving α-amino nucleophiles was given in Scheme 16, and showed the charged carbon atom on the nucleophile **49**, to be unsubstituted (i.e. a methylene group). If the chiral group is an auxiliary, it can be removed from an addition product such as **51**, to provide enantiomerically enriched β-amino alcohols **52**. Enantiomerically enriched hydroxyethers can also be formed in the process of remote induction if α-alkoxy nucleophiles are involved. The structure of the products **52**, (hydroxyl group bonded to a chiral carbon, and the nitrogen bonded to a methylene group) demonstrates common structural features present in β-adrenoreceptor drugs. Therefore, the method of remote induction for α-amino carbanions can be applied towards the enantioselective synthesis of β-adrenoreceptor drugs.

Only a few literature examples involve remote induction of α-heteroatom nucleophiles and levels of stereoselectivity are generally very low. For instance, the stereoselective 1,2-addition of α-amino nucleophiles to aldehydes has been attempted by employing various oxazolidinone chiral auxiliaries bonded to aminostannanes such as **62** (Scheme 21).[69] The transmetalation and trapping of the intermediate α-aminoorganolithium with benzaldehyde resulted in poor levels of diastereoselection: addition products such as **63**, were formed in only 5 to 20% de. The auxiliary that provided the largest level of diastereoselection is shown in Scheme 21. It was explained that the chiral center of the auxiliary was too remote to interact with the aldehyde in the transition state, and as a consequence low levels of stereoselectivity were achieved.

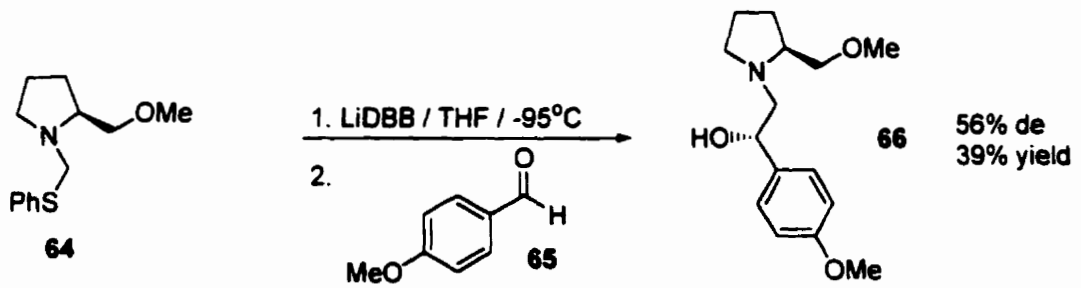
Scheme 21



62 **63**

A second example of remote induction by α-amino nucleophiles is through the use of proline-derived chiral auxiliaries.[53b] The sulfide **64**, underwent reductive lithiation with lithium 4,4'-di-*tert*-butylbiphenyl (LiDBB), and trapped with *p*-anisaldehyde **65** to afford the addition product **66**, in 56% de and in 39% yield (Scheme 22). Lower levels of diastereoselection were achieved with other aldehydes; however the yields were increased when Sn-Li exchange was used to form the α-aminoorganolithium intermediate. While higher yields were achieved with Sn-Li exchange, the addition product **66** was obtained in only 14% de when an α-aminoorganostannane precursor was employed.

Scheme 22

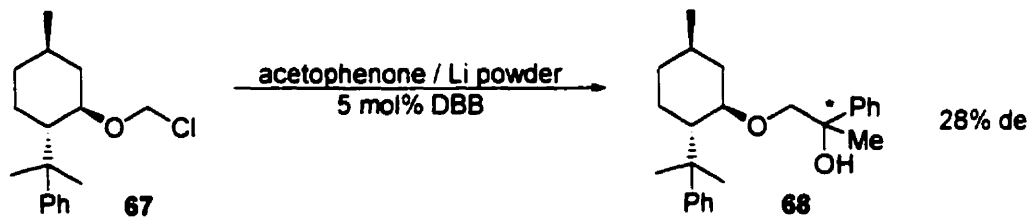


64 **65** **66**

Examples of remote induction involving chiral α-alkoxy carbanions have also appeared in the literature. The enantiomerically pure chloromethyl (-)-8-phenylmenthyl derivative **67**, was lithiated by DBB-mediated chlorine-lithium exchange and trapped with acetophenone to afford the

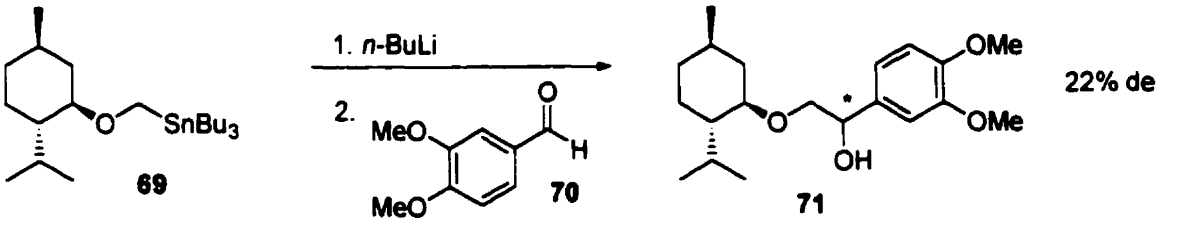
addition product **68** in 28% de (Scheme 23).[52] The reaction of **67** with pivaldehyde occurred in only 18% de. Further low levels of diasteroselectivity were also encountered by the same authors with (+) and (-) chloromethyl menthyl derivatives in similar addition reactions to pivaldehyde and to an imine.

Scheme 23



More results involving remote induction from chiral α-alkoxy carbanions have appeared in the work by Ponzo and Kaufman.[70] The Sn-Li exchange method was used to form the α-alkoxylithium intermediates. Two of the chiral auxiliaries employed by Ponzo and Kaufman are identical to the ones employed in the previous literature example discussed. Both literature examples employ (-)-8-phenyl-menthol and (-)-menthol as chiral auxiliaries. However, Ponzo and Kaufman also experimented with a (+)-isopinocampheol auxiliary and reactions were conducted with various oxygenated electron-rich aromatic aldehydes. The highest level of diastereoselectivity was achieved with the use of the (-)-menthol auxiliary **69**, and 3,4-dimethoxybenzaldehyde **70**, to form the addition product **71** in 22% de (Scheme 24).

Scheme 24



From the four examples shown in this sub-section, it is obvious that remote chiral induction from α-heteroatom nucleophiles has thus far provided low to modest levels of stereoselection. Most likely the chiral centers of the auxiliaries are too far away from the aldehyde in the transition state or the structure of the transition state is not rigid enough in order to have a significant stereodifferentiating process occurring. The chiral center of the nucleophile in proximal (1,2)-inductions as seen in the previous sub-section is able to interact with the aldehyde through chelation in the transition state (i.e. Scheme 19, Figure 6a,b) and generally produce higher levels of diastereoselectivity. Therefore, it would be advantageous to design an auxiliary that can have chiral groups interacting more closely with the aldehyde in a rigid transition state as through chelation. The remaining chapters of this thesis concentrate on such a chiral auxiliary design process.

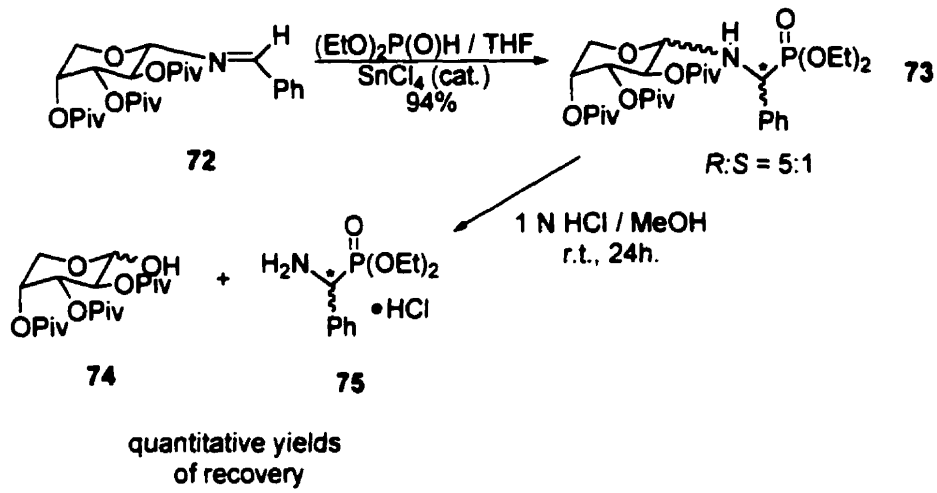
Furthermore, it must be stressed that for a chiral auxiliary to be practical, the auxiliary must be removable from the addition product, in order to isolate the enantiomerically enriched β-amino alcohols and 1,2-diols free from the auxiliary. Also if the auxiliary is expensive or difficult to make, it would also be advantageous to recover and reuse the auxiliary. The literature methods outlined in this sub-section fail to demonstrate that the auxiliary can be removed from any of the addition products **63**, **66**, **68**, or **71**. Therefore the other aim of this thesis is to develop an auxiliary that can be removed and recovered from an addition product. The exact nature of the auxiliary will be

discussed further in Section 1.5 and the relevance of carbohydrate-derived auxiliaries is presented in the next section.

1.4 Use of Carbohydrate-Derived Chiral Auxiliaries in Asymmetric Synthesis

It has been demonstrated extensively that carbohydrates can be transformed in order to function as efficient chiral auxiliaries in many asymmetric reactions.[71] Carbohydrates possess many oxygenated stereocenters that can be manipulated through metal chelation[72] to induce a stereodifferentiating process to occur. Furthermore, the oxygen atoms present on the carbohydrate cyclic framework offer convenient points of attachment for substrates undergoing asymmetric transformations. Bonding at non-anomeric oxygens can occur *via* ester linkages or ether linkages as was shown in Scheme 7 and 8 (Section 1.2.2.2), which can be easily cleaved to afford the recovery of both product and auxiliary. Also, if the point of attachment of the substrate occurs at the anomeric oxygen, the acetal linkage can be cleaved easily under acidic conditions. For example, in the asymmetric synthesis of α-aminophosphonic acid derivatives (Scheme 25),[73] the addition of diethyl phosphite to the galactosylamine **72** resulted in the stereoselective formation of the *R* chiral center α to the phosphonate group in **73** in a 5:1 ratio. The recovery of the auxiliary **74**, and the release of the enantiomerically enriched product **75**, was then accomplished by treating **73** with 1N HCl in methanol.

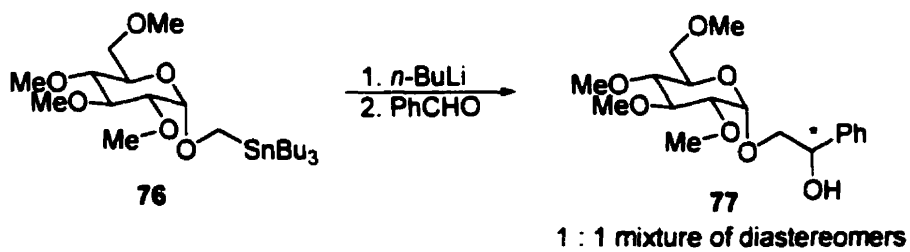
Scheme 25



72 73 74 75

An attempt has previously been made in our lab to utilize a carbohydrate-derived chiral auxiliary for the asymmetric 1,2-addition of α-alkoxymethylcarbanions to aldehydes (i.e. remote induction) (Scheme 26).[74] The α-alkoxymethylstannane was attached to the anomeric position of a glucose derived auxiliary to form compound **76**. Therefore, after Sn-Li exchange of **76** and the 1,2-addition of the organolithium intermediate to an aldehyde, it should be possible to recover both the auxiliary and 1,2-diol product from the addition product **77** under acidic conditions as was shown in Scheme 25. However, the addition product **77** was isolated as a 1 to 1 mixture of diastereomers in all experiments with benzaldehyde and the auxiliary / diol recovery was not attempted.

Scheme 26

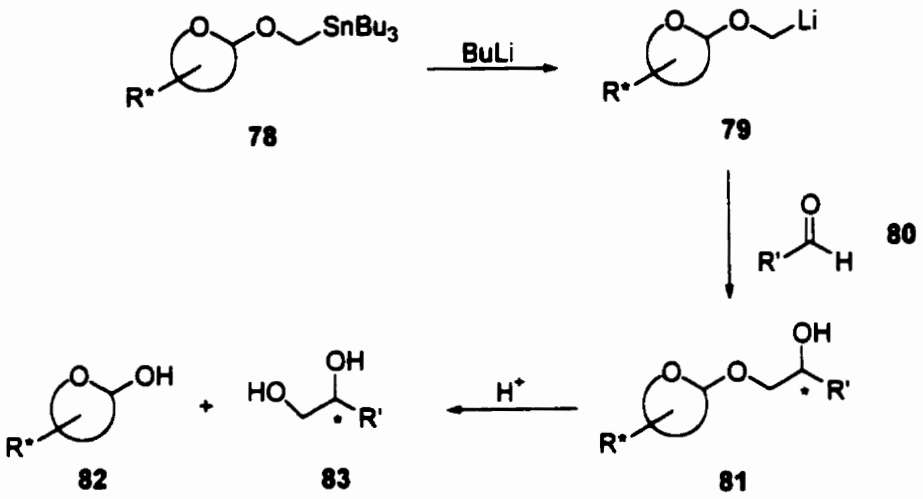


76 77

1.5 Goal of Thesis

This chapter has introduced various strategies that have been developed for the asymmetric 1,2-addition of carbon nucleophiles to aldehydes and ketones. The relevance of introducing heteroatoms to aldehydes by the addition of heteroatom containing nucleophiles in order to produce enantiomerically enriched biologically active compounds such as β-adrenoreceptor drugs has also been examined. However, effective methods for the asymmetric 1,2-additions of α-heteroatom carbanions to aldehydes are scarce in the literature. The lack of effective methods is especially true for the addition of α-heteroatom carbanions controlled by remote induction. Therefore the goal of this thesis work is to develop a method for the asymmetric addition of α-heteroatom nucleophiles to aldehydes and ketones by remote induction control. The chiral auxiliary approach initially taken as was seen in Scheme 26 will be modified. The use of α-alkoxy carbanions will also be pursued since difficulties in the synthesis of the α-amino analog of **76** were previously encountered.[74] The focus of this thesis work is therefore to design an α-alkoxystannane **78**, which contains a chiral auxiliary, so that it can be transmetalated to the organolithium **79**, and trapped with an aldehyde **80** with a high level of diastereoselectivity to give **81** (Scheme 27). Also the auxiliary **82** must be recovered along with the 1,2-diol **83** in order for the method to be practical. The next chapter outlines the first set of strategies employed in the chiral auxiliary design process that were taken.

Scheme 27



1.6 References

[1] Stinson, S. C. *Chem. and Engin. News* **1999**, *77*, nr. 41, Oct. 11, pp. 101-120.

[2] For current comprehensive reviews on asymmetric synthesis refer to: (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons Inc.: New York, 1995. (b) Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*; Elsevier Science Inc.: New York, 1996. (c) Proctor, G. *Asymmetric Synthesis*; Oxford University Press: New York, 1996. (d) Williams, J. M. J. *Catalysis in Asymmetric Synthesis*; Blackwell Science: Malden, MA, 1999.

[3] See reference 2a, p.xv and references therein.

[4] Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*: Permagon Press: New York, 1983.

[5] (a) see reference 2a, pp. 209-242. (b) see reference 2b, pp. 293-311. (c) see reference 2c, pp. 148-173. (d) see reference 2d, Chapter 3.

[6] (a) see reference 2a, pp. 306-345. (b) see reference 2b, pp. 171-197. (c) see reference 2c, pp. Chapter 5. (d) see reference 2d, pp.101-108.

[7] (a) see reference 2a, pp. 242-306. (b) see reference 2b. pp. 103-113. (c) see reference 2c, pp. Chapter 3. (d) see reference 2d, pp.85-97.

[8] (a) Reetz, M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556. (b) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

[9] Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

[10] (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199. (b) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

[11] (a) see reference 2a, pp. 17-19. (b) see reference 2b, pp. 123-124. (c) see reference 2c, pp. 15-16.

[12] (a) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153. (b) see reference 2b, pp. 124-126.

[13] Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1988**, *110*, 4826.

[14] (a) see reference 2a, pp. 27-28. (b) see reference 2b, pp. 130-136. (c) see reference 2c, pp.17-18.

[15] see reference 2c, pp. 15-18.

[16] (a) Veeresa, G.; Datta, A. *Tetrahedron* **1998**, *54*, 15673. (b) Veeresa, G.; Datta, A. *Tetrahedron Lett.* **1998**, *39*, 8503. (c) Abel, S.; Faber, D.; Hüter, O.; Giese, B. *Syntesis* **1999**, 188. (d) Kumar, K. K.; Datta, A. *Tetrahedron* **1999**, *55*, 13899. (e) Micalizio, G. C.; Roush, W. R. *Tetrahedron Lett.* **1999**, *40*, 3351.

[17] (a) Chandrasekhar, S.; Mohapatra, S.; Yadav, J. S. *Tetrahedron* **1999**, *55*, 4763. (b) Righi, G.; Chionne, A.; Bonini, C. *Eur. J. Org. Chem.* **2000**, 3127.

[18] (a) See reference 2a, p. 261-262. (b) See reference 2c, p.37-38. (c) For a review see: Alexakis, A.; Mangeney, P. *Teterahedron: Asymmetry* **1990**, *1*, 477. (d) Lindell, S. D.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 3947.

[19] (a) See reference 2a, p. 255-261. (b) See reference 2c, p.18-19.

[20] Ukaji, Y.; Yamamoto, K.; Fukui, M.; Fujisawa, T. *Tetrahedron Lett.* **1991**, *32*, 2119.

[21] (a) See reference 2a, p. 268-281. (b) See reference 2c, p.27-35.

[22] Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.

[23] (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J Am. Chem. Soc.* **1988**, *110*, 1535. (b) Coleman, R. S.; Kong, J.-S.; Richardson, T. E. *J. Am. Chem. Soc.* **1999**, *121*, 9088.

[24] (a) See reference 2a, p. 99, 247-248. (b) See reference 2c, p.21.

[25] (a) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028. (b) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.

[26] (a) See reference 2a, p. 254-255. (b) See reference 2c, p.20-21.

[27] Shing, T. K. M.; Li, L.-H. *J. Org. Chem.* **1997**, *62*, 1230.

[28] Hultin, P. G.; Earle, M. A.; Sudharshan, M. *Tetrahedron* **1997**, *53*, 14823.

[29] (a) Roush, W. R.; VanNieuwenze, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 8536. (b) Yamamoto, Y.; Kobayashi, K.; Okano, H.; Kadota, I. *J. Org. Chem.* **1992**, 57, 7003.

[30] Rochet, P.; Vatèle, J.-M.; Goré, J. *Synlett* **1993**, 105.

[31] Sakuraba, H.; Ushiki, S. *Tetrahedron Lett.* **1990**, *31*, 5349.

[32] (a) See reference 2a, p. 250-253. (b) See reference 2b, p. 137-140. (c) See reference 2c, p.21-27. (d) See reference 2d, p.85-89.

[33] Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.

[34] (a) Eisenberg, C.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 3760. (b) Ostwlad, R.; Chavant, P.-Y.; Stadmüller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143. (c) Lütjens, H.; Nowotny, S.; Knochel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 2675. (d) For a general review of functionalized organozinc

reagents in organic synthesis see: Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (e) For a more recent general review of functionalized organozinc reagents including other functionalized organometallic reagents see: Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.

[35] (a) See reference 2a, p. 242, 282-284. (b) See reference 2b, p. 140-141. (c) See reference 2c, p.36-37. (d) See reference 2d, p.89-97.

[36] Effenberger, F.; Jäger, J. *J. Org. Chem.* **1997**, *62*, 3867.

[37] Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001.

[38] Weber, B.; Seebach, D. *Tetrahedron* **1994**, 7473.

[39] Ager, D. J.; East, M. B. *Tetrahedron* **1992**, 2803.

[40] *The Merck Index*; 12th edition; Budavari, S., Ed.; Merck & Co., Inc.: Whitehouse Station, NJ, 1996.

[41] Gaudillière, B.; Berna, P. *Ann. Rep. Med. Chem.* **2000**, *35*, 331.

[42] Mohapatra, S. C.; Hsu, J. T. *Biotechnol. Bioeng.* **1999**, *64*, 213.

[43] Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.

[44] (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. (b) Takahashi, H.; Sakuraba, S.; Takeda, H.; Achiwa, K. *J. Am. Chem. Soc.* **1990**, *112*, 5876.

[45] (a) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1990**, *31*, 601. (b) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442. (c) Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 6631.

[46] Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 5551.

[47] Beardsley, D. A.; Fisher, G. B.; Goralski, C. T.; Nicolson, L. W.; Singaram, B. *Tetrahedron Lett.* **1994**, *35*, 1511.

[48] (a) Fisher, G. B.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 7693. (b) Fisher, G. B.; Goralski, C. T.; Nicholson, L. W.; Hasha, D. L.; Zakett, D. L.; Singaram, B. *J. Org. Chem.* **1995**, *60*, 2026.

[49] Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987; p. 149, 165-176.

[50] (a) Beak, P.; Zajdel, W. J. *Chem. Rev.* **1984**, *84*, 471. (b) See reference 2b, p. 109-112.

[51] See reference 2b, p. 107.

[52] Ortiz, J.; Guijarro, A.; Yus, M. *An. Quim. Int. Ed.* **1997**, *93*, 44.

[53] (a) Tsunoda, T.; Fujiwara, K.; Yamamoto, Y.; Shô, I. *Tetrahedron Lett.* **1991**, *32*, 1975. (b) Coldham, I.; Holman, S.; Lang-Anderson, M. M. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1481.

[54] (a) See reference 49, p. 19-20. (b) See reference 2b, p. 104.

[55] Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, 57, 2220.

[56] (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

[57] See reference 49, p. 149.

[58] See reference 2b, p. 103-104.

[59] Reich, H. J.; Phillips, W. H. *J. Am. Chem. Soc.* **1986**, *108*, 2102.

[60] Linderman, R. J.; Ghonan, A. *J. Am. Chem. Soc.* **1990**, *112*, 2392.

[61] Molander, G. A.; Estévez-Braun, A. M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 275.

[62] McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5422.

[63] Yamada, J.-I.; Abe, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6118.

[64] Furuta, T.; Yamamoto, Y. *J. Chem. Soc. Chem. Commun.* **1992**, 865.

[65] Furuta, T.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 2981.

[66] Askham, F. R.; Carroll, K. M. *J. Org. Chem.* **1993**, *58*, 7328.

[67] McDougal, P. G.; Condon, B. D.; Laffosse, Jr., M. D.; Lauro, A. M.; VanDerveer, D. *Tetrahedron Lett.* **1988**, *29*, 2547.

[68] Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763.

[69] Pearson, W. H.; Lindbeck, W. H.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622.

[70] Ponzo, V. L.; Kaufman, T. *Can. J. Chem.* **1998**, *76*, 1338.

[71] For reviews see: (a) Cintas, P. *Tetrahedron* **1991**, *47*, 6079. (b) Kunz, H.; Ruck, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 336. (c) Reissig, H.-U. *Angew. Chem. Int. Ed. Engl.* **1993**, *31*, 288. (d) Kunz, H. *Pure Appl. Chem.* **1995**, *67*, 1627. (e) see reference 28.

[72] Kishida, M.; Eguchi, T.; Kakinuma, K. *Tetrahedron Lett.* **1996**, *37*, 2061.

[73] Laschat, S.; Kunz, H. *Synthesis* **1992**, 90.

[74] Frese, P. *Diplome-Chimiker Thesis*; University of Waterloo, 1996.

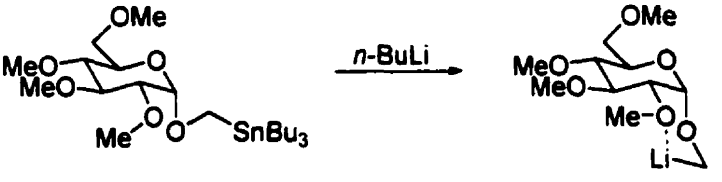
CHAPTER 2

GLUCOSE-DERIVED CHIRAL AUXILIARIES

2.1 Introduction

It was demonstrated in Chapter 1, Section 1.4 (Scheme 26) that a chiral auxiliary derived from glucose did not induce any diastereoselectivity in the addition of an α-alkoxycarbanion to benzaldehyde.[1] It was expected that the structure of the organolithium intermediate **84**, after being derived from the Sn-Li exchange of **76**, might consist of a *cis*-fused bicyclic system, due to possible intramolecular chelation of the C-2 oxygen to the lithium atom (Scheme 28).

Scheme 28

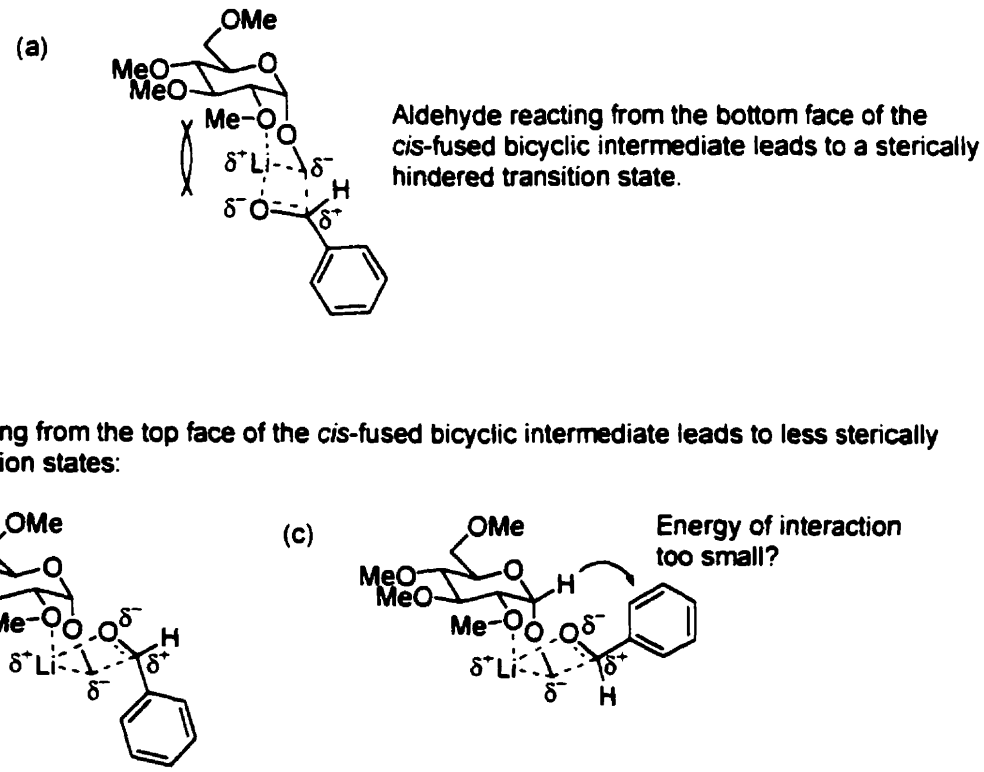


76 **84**

The hypothetical *cis*-fused bicyclic structure was expected to induce diastereoselectivity in the 1,2-addition to benzaldehyde. The internal chelation of the lithium atom can possibly create a conformationally constrained transition state so that a reaction where benzaldehyde reacts from the bottom concave face of the auxiliary *cis*-fused bicyclic system would be too sterically hindered to occur (Figure 7a). Therefore, it was believed that a transition state where the aldehyde reacts from the less hindered top convex face of the auxiliary *cis*-fused bicyclic system would be more likely to occur and provide diastereoselectivity. However, it was not expected at the time that transition

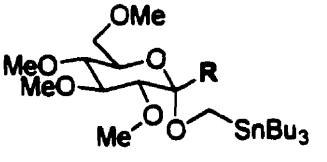
states occurring on either prochiral face of benzaldehyde could be equally probable (Figure 7b and c) from the top convex face of the auxiliary *cis*-fused bicyclic system. The phenyl group of the aldehyde could be pointing away from the auxiliary (Figure 7b), or be pointing towards the auxiliary (Figure 7c). The difference in energy ($\Delta\Delta G^{\ddagger}$) between the two possible transition states in Figure 7b and 7c could be too small to produce any observable amount of diastereoselectivity. The energy of the interaction between the R group of the aldehyde and the anomeric H of the auxiliary when the R group of the aldehyde is pointing towards the auxiliary may be insignificant (Figure 7c). Therefore, both proposed transition states seen in Figure 7b and 7c might occur with equal probability.

Figure 7. Proposed transition states (a-c) for the reaction of organolithium **84** with benzaldehyde.



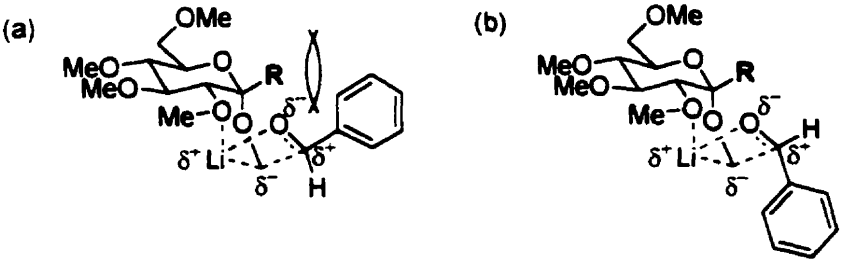
It was then decided to test the hypothesis that the anomeric H is too small to cause a significant amount of interaction with the R group of aldehydes to occur. The hypothesis was tested by designing and employing new auxiliary derivatives that have H replaced by different R groups at the equatorial anomeric position (Figure 8). Larger substituents then H present at the anomeric equatorial position may induce a greater steric interaction to occur with the R group of the aldehyde (Figure 9a). As a result, a transition state where the *Re* prochiral face of the aldehyde is trapped selectively may be more probable (Figure 9b). Therefore the introduction of the anomeric equatorial R groups represents the first structural modification during the chiral auxiliary design process taken in this thesis.

Figure 8. Glucose-derived auxiliaries with an anomeric axial alkoxymethyltributylstannane substrate and anomeric equatorial **R** groups.



R = alkyl, aryl, alkynyl

Figure 9. Possible transition states (a,b) for the transmetalated modified auxiliary derivatives with benzaldehyde.

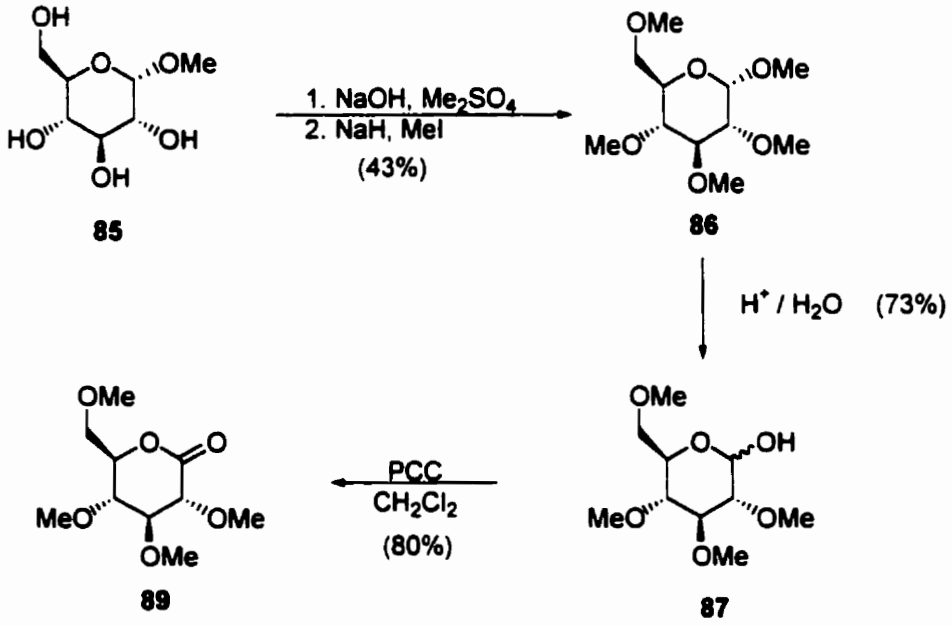


2.2 Results and Discussion

2.2.1 Synthesis of Glucose-Derived Chiral Auxiliaries

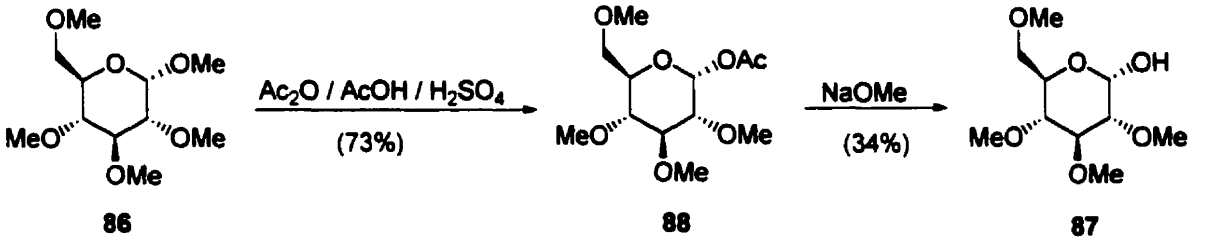
The starting material employed for the synthesis of glucose-derived chiral auxiliaries was methyl-α-D-glucopyranoside (**85**) (Scheme 29). Permethylation of **85**,[2] followed by hydrolysis of **86**,[3] afforded the lactol **87**. Direct hydrolysis of **86**, was discovered to be more efficient than transforming the methyl glycoside **86** to the acetate **88**,[4] and treating **88** with NaOMe in a second step to give **87** (Scheme 30). Oxidation of **87** with PCC[5] resulted in the formation of the lactone **89** (Scheme 29).

Scheme 29



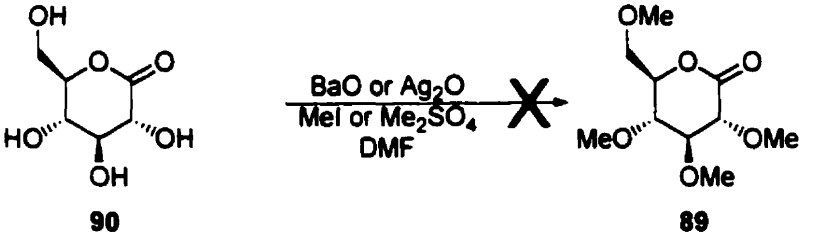
85 **86** **87** **89**

Scheme 30



A one step synthesis to the lactone **89** was attempted by using δ-gluconolactone **90** as the commercial starting material (Scheme 31). However, attempted permethylations of **90** did not result in the formation of the protected lactone **89** and instead resulted in the formation of a complex mixture of unidentified products.

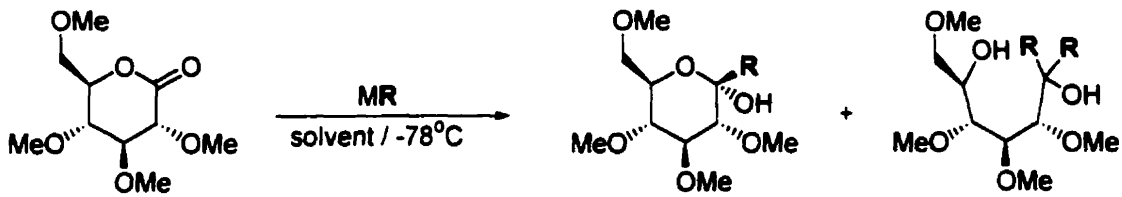
Scheme 31



The anomeric substituents were then introduced by the addition of various alkyl, aryl, and alkynyl groups to the lactone **89** (Table 2). Organolithium reagents (entries 2, 4-11) were more successful in producing the desired monosubstituted products **91-99**. When Grignard reagents were employed (entries 1 and 3), the unwanted disubstituted products **91a** and **92a** were formed. Provisional identifications were made for compounds **91a** and **92a**. Compound **91a** was identified by IR, ^{1}H NMR, ^{13}C NMR, and low resolution MS data, and the structural assignment for **92a** was

based on ^{1}H NMR data. The disubstituted product **91a** was formed as a minor by-product in entry 1; however the disubstitution product was the only product formed in entry 3. Therefore organolithium reagents were employed in the remaining entries and satisfactory to excellent yields were obtained for the desired monosubstituted compounds **91-99**, with no disubstituted products being detected or isolated.

Table 2. Introduction of anomeric substituents.

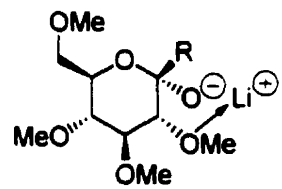


Entry	R	Metal (M)	Solvent	Yield of monosubstituted product (%) (#)	Yield of disubstituted product (%) (#)
1	**Me**	MgBr	THF	70 (**91**)	11 (**91a**)
2	**Me**	Li	THF	80 (**91**)	0
3	**Ph**	MgCl	Et_2O	0	78 (**92a**)
4	**Ph**	Li	Et_2O	63 (**92**)	0
5	***i*Pr**	Li	Et_2O	65 (**93**)	0
6	***t*Bu**	Li	Et_2O	49 (**94**)	0
7	**1-naphthyl**	Li	THF / Et_2O	86 (**95**)	0
8	**2-naphthyl**	Li	THF / Et_2O	100 (**96**)	0
9	**-C_6H_4-4-OMe**	Li	THF / Et_2O	94 (**97**)	0
10	**-C_6H_4-4-CF_3**	Li	THF / Et_2O	94 (**98**)	0
11	**—C≡C–Ph**	Li	Et_2O	75[a] (**99**)	0

a - formed as a 1:1 mixture of diastereomers.

These results are consistent with literature examples involving addition of organometallic reagents to esters and lactones. Carboxylic esters are well known to give disubstituted products (tertiary alcohols) when treated with Grignard reagents while monosubtituted products (ketones) have been obtained when using alkyllithium reagents at low temperatures.[6] Furthermore, monosubstitued products have been obtained when organolithium reagents are added to lactones such as δ-valerolactone[7] and to carbohydrate derived lactones.[8] Disubstitution onto δ-valerolactone[9] or on a sugar[10] is possible with the use of a Grignard reagent. A factor preventing the addition of a second equivalent of organolithium to carbohydrate-derived lactones such as **89** may be stabilization of the tetrahedral intermediate by internal chelation of the lithium atom by an α-alkoxy substituent (Figure 10).

Figure 10. Internal chelation of the tetrahedral intermediate derived from **89**.

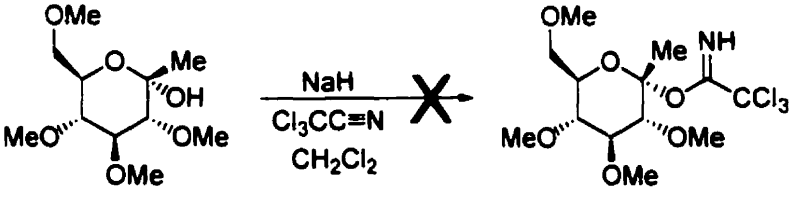


The compounds **91-99**, were formed as one diastereomer with the exception of **99** which was formed as a 1:1 mixture of diastereomers. It was not important to form the hemiketals **91-99** stereoselectively or to determine the stereochemistry at this stage since the next step involved carbocation formation at the anomeric carbon. The stereochemistry formed in **91-99** is represented as the one that allows for the larger substituent to adopt the equatorial position and for the smaller hydroxyl group to adopt the axial position on the ring. Furthermore, an anomeric hydroxyl group

prefers to be in the axial position in sugars due to the anomeric effect.[11] Therefore it is highly likely that compounds **91-99** possess the stereochemistry indicated.

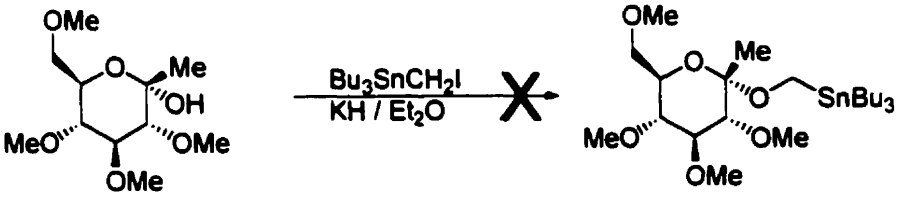
The final step involved the attachment of the α-alkoxymethylstannane fragment to the glucose-derived chiral auxiliaries. An attempt was made using the trichloroacetimidate method,[12] since the method worked previously for the glucose-derived auxiliary without the anomeric substituent present.[1] However, attempts to derivatize **91** to the trichloroacetamide **100** failed (Scheme 32). Furthermore, a reaction between **91** and Bu_3SnCH_2I / KI failed to produce the desired stannane **101** (Scheme 33). It was thought that a substitution reaction onto the tertiary oxyanion of **91** was too sterically hindered to occur.

Scheme 32



91 **100**

Scheme 33

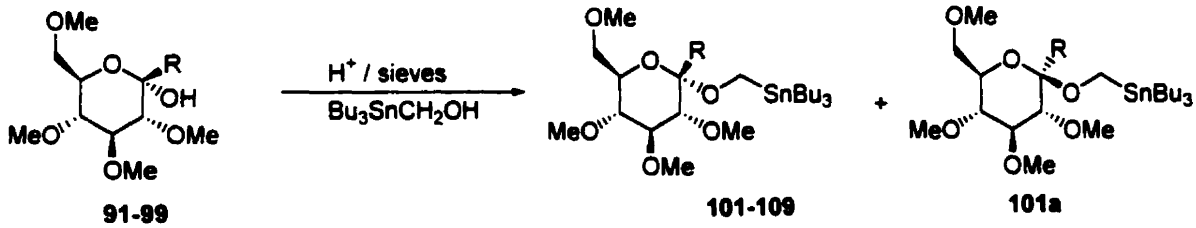


91 **101**

The acid catalyzed glycosylation method allowed for the attachment of the α-alkoxymethyltin group to anomeric position of the sugar (Table 3). Either HCl or TfOH were used

as the acidic catalysts in the glycosylation reactions involving the hemiketals **91-99** and Bu_3SnCH_2OH. Furthermore, 3 Å molecular sieves were used in both instances to soak up the water produced in the reaction and to drive the equilibrium toward the formation of the glycosides **101-109**. The method involving the use of TfOH was operationally simpler since HCl quickly escaped the refluxing Et_2O solvent and more HCl had to be frequently added during the course of the reaction. However, both methods provided similar yields (entries 2 vs. 3 and entries 4 vs. 5). Either Et_2O or CH_2Cl_2 were satisfactory solvents for the glycosylation reactions involving HCl. In general, low yields were observed. This may be because auxiliaries **91-99** decompose slowly under the acidic conditions, and therefore a lower reaction temperature (0 °C) was employed in reactions involving TfOH to minimize decomposition.

Table 3. Acid catalyzed glycosylations of auxiliaries **91-99** and Bu_3SnCH_2OH.



Entry	**Auxiliary**	R	H^+	Yield (%) of α-anomer product (#)	Yield (%) of β-anomer product (#)
1	**91**	Me	HCl	81 **(101)**	4 **(101a)**
2	**92**	Ph	HCl	59 **(102)**	0
3	**92**	Ph	TfOH	57 **(102)**	0
4	**93**	*i*Pr	HCl	35 **(103)**	0
5	**93**	*i*Pr	TfOH	44 **(103)**	0
6	**94**	*t*Bu	TfOH	41 **(104)**	0
7	**95**	1-naphthyl	TfOH	52 **(105)**	0
8	**96**	2-naphthyl	TfOH	55 **(106)**	0
9	**97**	4-OMe-C_6H_4	TfOH	46 **(107)**	0
10	**98**	4-CF_3-C_6H_4	TfOH	49 **(108)**	0
11	**99**	—C≡C—Ph	TfOH	42[a] **(109)**	14[b] **(109a)**

a - stereochemistry was unassigned and the yield refers to the major diastereomer.
b - stereochemistry was unassigned and the yield refers to the minor diastereomer.

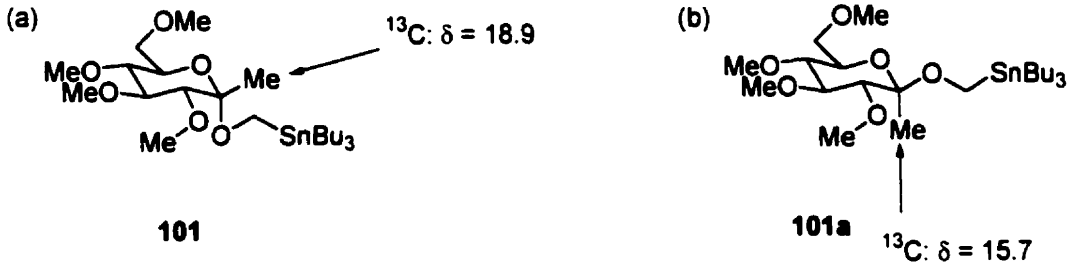
In order to form the *cis*-fused organolithium intermediate, the C-1 alkoxymethyltin and C-2 methoxy groups on the ring are required to be *syn* to each other. This requires the glycosylation reaction to produce the α-anomer stereoselectively. Based on theoretical considerations, the α-

anomer is expected to be formed preferentially. As discussed in the formation of the hemiketal synthetic intermediates **91-99**, the anomeric effect and steric effect of the C-glycoside substituent should in theory allow for the preferential formation of the α-anomer. Furthermore there are many literature examples involving glycosylation reactions between hemiketals similar to **91-99** and *O*-glycoside acceptors that result in the formation of the α-anomer preferentially or exclusively.[13] Examples include hemiketals with various C-glycoside substituents such as primary alkyl,[13b,c,g-i] methyl,[13a] vinyl,[13f,g,i] heteroaromatic,[13d,e] and alkynyl groups.[13i]

Experimental evidence for the stereoselective formation of the α-anomer in the case of an anomeric methyl group (entry 1) was obtained from C-13 NMR data (Figure 11). The difference in the chemical shift between the major isomer **101** (Figure 11a) and the minor isomer **101a** (Figure 11b) provides support for the stereoselective formation of the α-anomer. A provisional identification was made for **101a**, based on ^{1}H and ^{13}C NMR data. The equatorial methyl group in the α-anomer is less shielded and the ^{13}C chemical shift for the methyl group appears at higher ppm for the major isomer **101** than for the minor isomer **101a** due to the γ-gauche effect.[14] Therefore the major isomer **101** can be assigned as the α-anomer. This type of reasoning has been employed in a similar literature example to assign stereochemistry for an anomeric methyl group.[8d]

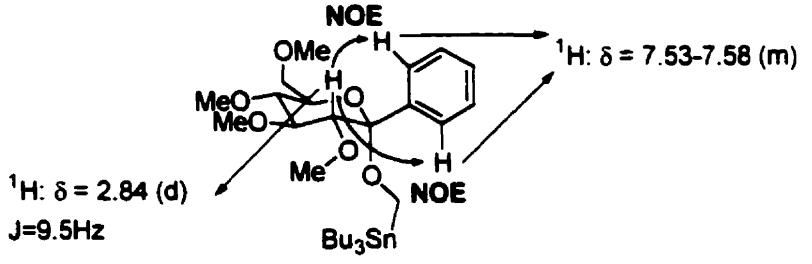
A stereochemical assignment could not be made for either **109** or **109a** since no literature precedent could be found involving assignments for anomeric alkynyl groups on the basis of C-13 chemical shifts. It was not important to assign stereochemistry for **109** or **109a** since the transmetalation/trapping chemistry of **109** was unsuccessful (*vide infra*) and other methods to determine the stereochemistry of **109** or **109a** were not attempted.

Figure 11. Anomeric methyl group C-13 chemical shifts for **101** (a) and **101a** (b).



For the other auxiliary derivatives that were formed, it was not possible to make NMR shift comparisons between major and minor isomers since only one isomer was detected and isolated (Table 3, entries 2-9). A 2-dimensional NMR NOESY experiment was conducted for the compound **102** in order to provide support for the formation of the α-anomer (Figure 12). An NOE was observed between the axial C-2 proton, which was assigned by an HMQC (Heteronuclear Multiple Quantum Coherence) NMR experiment, and aromatic protons. Therefore the C-2 proton and phenyl group must be in a *syn* stereochemical relationship to each other and is the stereochemical relationship present in the α-anomer.

Figure 12. NOE's visible form the NOESY spectrum of **102**.



With the experimental evidence presented for the compounds **101** and **102**, it is reasonable to assume the compounds **103-108** also are α-anomers. The formation of the β-anomer side products **101a** and **109a** indicate the steric importance of the C-glycoside substituent in inducing the formation of the α-anomer in the glycosylation reaction. The methyl group and alkynyl group are the smallest C-glycoside substituents studied on the auxiliary. Therefore, it was not too surprising that the β-anomer by-product was produced for the methyl and alkynyl auxiliary derivative analogs as the minor isomer. However compounds **103-108** possess larger alkyl groups and similar or larger aromatic groups than **102** present at the anomeric position. Therefore it is reasonable to assume that the α-anomer is formed in compounds **103-108** due to the preference for larger C-glycoside groups, as seen for the Ph group in **102**, to prefer the equatorial position and due to the anomeric effect.

2.2.2 1,2-Additions of Lithiated Glucose-Derived Chiral Auxiliary Derivatives to Benzaldehyde

All auxiliary derivatives were successfully transmetalated with *n*-BuLi to the α-alkoxyorganolithium and trapped with benzaldehyde with the exception of **109**. It was possible to transmetalate the auxiliary **109** since Bu_4Sn was formed; however no addition product to benzaldehyde was detected and only a complex mixture of unidentified products was isolated.

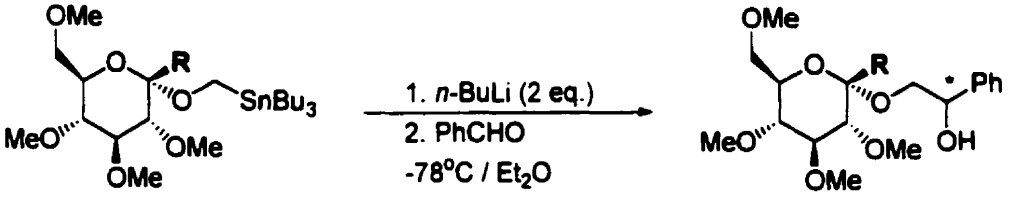
The hypothesis for achieving stereoselectivity made earlier is supported by the fact that C-glycoside substituents (Table 4) can induce a stereodifferentiating process in accordance with the proposed transition state model. However, improvements in selectivity were not observed with all C-glycoside substituents that were screened. For example, a methyl substituent (entry 1) did provide an improvement in selectivity from R=H, yet bulkier groups such as ^{i}Pr or ^{t}Bu offered none or only marginal improvements (entries 2, 3). Similarly, a 1-naphthyl substituent offered little improvement

in diastereoselectivity (entry 4). The set of results in entries 1-4 indicate that larger alkyl groups and aromatic groups introducing steric bulk towards the pyranoside ring system (i.e. 1-naphthyl vs. 2-naphthyl (*vide infra*)) were detrimental to stereoselectivity. The lack or low amount of stereoselectivity in entries 2-4 was surprising since it was expected that larger groups would offer better selectivity in accordance to the proposed transition state model. It was speculated that sterically demanding groups at the anomeric position had created greater strain in the chair conformation of the auxiliary. The auxiliary could have adopted a lower energy non-chair conformation to possibly relieve strain and preclude the formation of a *cis*- fused bicyclic intermediate. Therefore intramolecular chelation could have been prevented or a *cis*-fused bicyclic ring system with a non-chair conformation could have been formed but not able to induce a stereodifferentiating process. In order to minimize any possible ring strain, aryl groups that had connectivity to the auxiliary that placed steric bulk of the aromatic group further away from the auxiliary were further investigated. For instance, a 2-naphthyl group has connectivity to the auxiliary that places the aromatic ring, which is not directly bonded to the pyranoside ring system, further away from the pyranose ring. The change in connectivity of the naphthyl group to the 2-position resulted in a substantial improvement in stereoselectivity (entry 5). The large difference between a 1-naphthyl and 2-naphthyl group towards providing stereoselectivity gave support to the reasoning that C-glycoside groups pointing further away from the auxiliary would favor the formation of the lithium chelated *cis*-fused (decalin-like) bicyclic intermediate and provide a greater amount of stereoselectivity. A similar result was noted with a Ph group at the anomeric position (entry 6), so greater steric hindrance placed further away from the auxiliary as provided by the 2-naphthyl group did not offer any extra benefit.

Furthermore, stereoelectronic effects were investigated by altering the substituents on the aryl ring of the auxiliary in order to observe if any π type interactions were occurring between the Ph

ring of benzaldehyde and the auxiliary C-glycoside aromatic substituent. Neither electron rich (entry 7) nor electron poor (entry 8) substituents had any beneficial or detrimental effect on selectivity; therefore stereoelectronic effects such as π stacking or π repulsions from the auxiliary are of minimal importance in the transition state with benzaldehyde.

Table 4. Effect of auxiliary anomeric equatorial substituents on selectivity in 1,2-additions to benzaldehyde.



101-108 **110-117**

Entry	Stannane #	R	Yield of Product (%) (#)	Selectivity (% de)	Method of de determin-ation[b]
1[a]	**101**	Me	28 (**110**)	21	A
2	**103**	^{i}Pr	40 (**111**)	0	B
3	**104**	^{t}Bu	96 (**112**)	2	A
4	**105**	1-naphthyl	23 (**113**)	2	C
5	**106**	2-naphthyl	97 (**114**)	36	C
6	**102**	Ph	79 (**115**)	34	A
7	**107**	4-OMe-C_6H_4	80 (**116**)	34	D
8	**108**	4-CF_3- C_6H_4	67 (**117**)	35	B

[a]Reaction conducted in hexane and with 1.1 eq. of *n*-BuLi.
[b]Methods for de determination: A: Selectivity determined by chiral HPLC analysis of the recovered 1,2-diol product. B: Selectivity determined by proton NMR of the addition product. C: Selectivity determined by chiral HPLC analysis of the addition product. D: Selectivity determined by silica gel column HPLC analysis of the addition product.

2.2.3 Solvent Effects

It was demonstrated in Table 4, entry 1 that the reaction of **101** in hexane provided a low yield of the addition product, which is partly due to a low yield in the Sn-Li exchange step (*vide infra*). It was surprising that Sn-Li exchange occurred at all in hexane since Sn-Li exchange for α-heteroatomstannanes of non-carbohydrate systems usually only occur in polar solvents such as Et_2O and THF.[15] Intra- or intermolecular coordination (i.e. aggregation) of the lithium atom with the C-2 oxygen or other oxygens of the sugar-derived auxiliary may offer greater stabilization for the α-alkoxycarbanion.

The general trend observed for the yield of Sn-Li exchange was that a decrease in the polarity of solvent correlated with a decrease in yield of Sn-Li exchange (Table 5). The results for each auxiliary in Table 5 are presented in order of decreasing solvent polarity. THF generally provided the highest yield and hexane the lowest, with Et_2O and toluene providing the second and third best yields respectively. Therefore stabilization of the α-alkoxycarbanion by polar co-ordinating solvents also may occur to help shift the equilibrium in greater favor towards the α-alkoxyorganolithium or to increase the rate of the transmetalation reaction. However, a transmetalation attempt made in CH_2Cl_2 proved to be unsuccessful (entry 7).

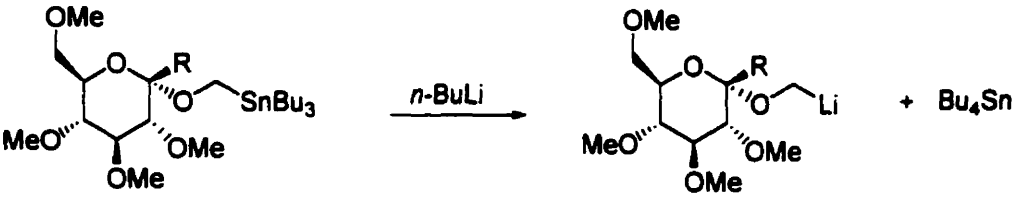
More then one equivalent of *n*-BuLi was sometimes necessary to maximize the yield of Sn-Li exchange. The benefit of employing more than one equivalent of *n*-BuLi was realized especially when the reaction was conducted in non-polar solvents. Utilizing 2.2 eq. in the non-polar solvent toluene (entry 3) actually led to a slightly higher yield than using only 1.1 equivalents in the polar solvent Et_2O (entry 2). Furthermore, with auxiliary **102** only a trace amount of Bu_4Sn was detected when the transmetalation reaction was conducted in hexane with 1.0 eq. of *n*-BuLi (entry 10).

However, when 2 eq. of *n*-BuLi was used under similar conditions for **102**, a 60% exchange yield was obtained (entry 9). It was thought that an extra equivalent of *n*-BuLi might be required to optimize the reaction since the first equivalent that is added to the reaction might be bound to any of the auxiliary oxygens. Nevertheless, even with the presence of excess benzaldehyde in the addition step, no *n*-BuLi addition product to benzaldehyde was detected. Therefore, binding of *n*-BuLi to the auxiliary oxygens may not occur and quenching of *n*-BuLi by trace amounts of water might have taken place since only a very small amount of *n*-BuLi was employed in the experiments (i.e. 1.0 eq. *n*-BuLi = 0.2 mmol approx.). Employing more than 2.0 eq. of *n*-BuLi did not generate a higher yield (entry 14).

The time for the Sn-Li exchange reaction also had an effect on the yield of the transmetalated product. For reactions conducted in non-polar solvents such as hexane where the reaction appeared to occur with small amount of conversion, extending the reaction time had a beneficial effect (entry 9 vs. entry 13).

Furthermore, a higher temperature for the exchange reaction allowed for almost a quantitative formation of Bu_4Sn (entry 12). However, the temperature of the reaction (-20 °C) was too high for the α-alkoxyorganolithium to be stable since the transmetalated product decomposed at the high temperature before it could be trapped with benzaldehyde. This observation is consistent with what has been reported in the literature for α-alkoxyorganolithium reagents,[16] where reagents were observed to be stable at -30 °C, but to decompose at 0 °C. Therefore, a temperature of -60 °C was sometimes employed in order to avoid decomposition of the α-alkoxyorganolithium while increasing the transmetalation yield.

Table 5. Yield of Sn-Li exchange.

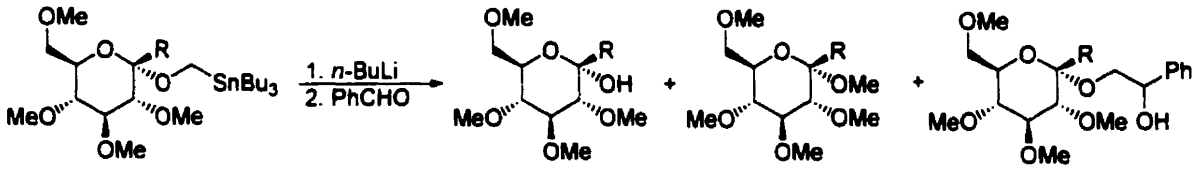


101-108

Entry	Stannane #	(R)	Solvent	*n*-BuLi (eq.)	Time (min.)	Temp. (°C)	Yield of $SnBu_4$ (%)
1	**101**	Me	THF	2.2	20	-78	100
2	**101**	Me	Et_2O	1.1	15	-78	81
3	**101**	Me	toluene	2.2	45	-78	100
4	**101**	Me	hexane	1.1	15	-78	67
5	**102**	Ph	THF	2.0	80	-60	98
6	**102**	Ph	Et_2O	2.0	80	-60	81
7	**102**	Ph	CH_2Cl_2	2.0	45	-78	trace
8	**102**	Ph	toluene	2.0	90	-60	75
9	**102**	Ph	hexane	2.0	100	-60	60
10	**102**	Ph	hexane	1.0	60	-78	trace
11	**102**	Ph	hexane	1.5	15	-78	46
12	**102**	Ph	hexane	1.5	35	-20	93
13	**102**	Ph	hexane	2.0	420	-60	85
14	**102**	Ph	hexane	4.4	100	-60	48
15	**103**	*i*Pr	Et_2O	2.0	60	-60	88
16	**103**	*i*Pr	toluene	2.0	65	-60	78
17	**104**	*t*Bu	THF	2.0	65	-60	89
18	**104**	*t*Bu	Et_2O	2.0	105	-60	86
19	**104**	*t*Bu	toluene	2.0	90	-60	54
20	**104**	*t*Bu	hexane	2.0	90	-60	89
21	**105**	1-naphthyl	Et_2O	2.0	60	-60	61
22	**105**	1-naphthyl	toluene	2.0	65	-60	48
23	**105**	1-naphthyl	hexane	2.0	60	-60	30
24	**106**	2-naphthyl	THF	2.0	70	-60	93
25	**106**	2-naphthyl	Et_2O	2.0	50	-60	88
26	**106**	2-naphthyl	toluene	2.0	70	-60	62
27	**106**	2-naphthyl	hexane	2.0	50	-60	34
28	**107**	4-OMe-C_6H_4	THF	2.0	60	-60	93
29	**107**	4-OMe-C_6H_4	Et_2O	2.0	60	-60	88
30	**107**	4-OMe-C_6H_4	toluene	2.0	60	-60	70
31	**107**	4-OMe-C_6H_4	hexane	2.0	60	-60	53
32	**108**	4-CF_3-C_6H_4	Et_2O	2.0	60	-78	84
33	**108**	4-CF_3-C_6H_4	toluene	2.2	60	-78	76

The transmetalation yield did not always translate into the yield of the addition product to benzaldehyde obtained. The formation of hemiketal by-products **91**, **94**, and **95** or protonated by-products **118-120** was often observed; their presence correlated with a decrease in the yield of the benzaldehyde addition products **110-113**, and **115** (Table 6). Provisional identifications were made for compounds **118** and **120**. The assigned structure for **118** was based on IR, ^{1}H NMR, ^{13}C NMR and low resolution MS data, and **120** was identified by ^{1}H NMR data. It is unknown how the by-products were formed. Protonation may result from aqueous quench if all the α-alkoxyorganolithium did not react with benzaldehyde or from decomposition of the α-alkoxyorganolithium. However, the source of protonation was not investigated in these cases since more effort was placed on optimizing the diastereoselectivity of the reaction.

Table 6. Formation of by-products.



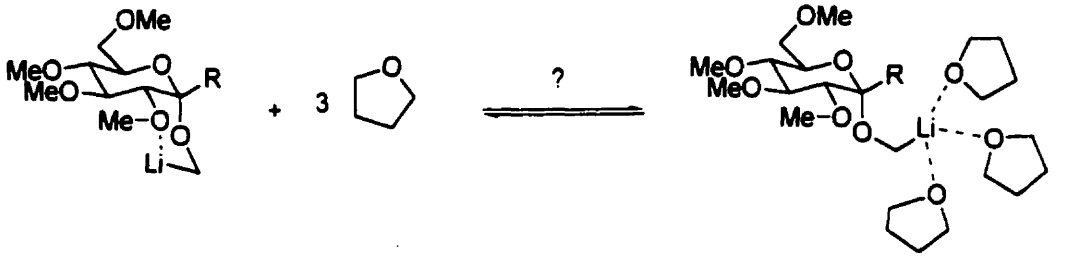
Entry	Stannane #	R	Solvent	Yield of Bu_4Sn (%)	Yield of hemiketal (%) (#)	Yield of H^+ product (%) (#)	Yield of addition product (%) (#)
1	**101**	Me	Et_2O	81	nd	42 (**118**)	53 (**110**)
2	**101**	Me	hexane	67	nd	46 (**118**)	28 (**110**)
3	**101**	Me	toluene	90	14 (**91**)	nd	34 (**110**)
4	**102**	Ph	hexane	62	nd	6 (**119**)	42 (**115**)
5	**103**	*i*Pr	Et_2O	85	nd	37 (**120**)	40 (**111**)
6	**104**	*t*Bu	toluene	54	41 (**94**)	nd	19 (**112**)
7	**105**	1-naphthyl	Et_2O	61	50 (**95**)	nd	23 (**113**)

nd-not determined

During the optimization process for increasing the amount of diastereoselectivity, it was considered that non-polar solvents such as hexane and toluene may have the potential to provide a higher amount of selectivity for the auxiliaries. Polar solvents such as THF and Et_2O may competitively coordinate to the lithium atom of the auxiliary lithiated intermediate, thus preventing intramolecular coordination with the C-2 oxygen of the auxiliary and formation of the *cis*-fused bicyclic ring system (Figure 13). An intermediate without intramolecular coordination results in the formation of a less-rigid transition state and the transfer of chiral induction would be less likely to

occur. Therefore, a non-polar / non-coordinating solvent such as toluene or hexane may have the potential to offer a greater level of selectivity by avoiding competitive coordination and favoring the formation of the *cis*-fused bicyclic intermediate.

Figure 13. Possible competitive coordination of polar solvent to the auxiliary lithium atom.

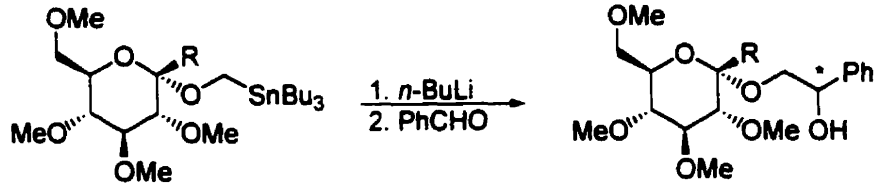


The level of diastereoselectivity achieved with auxiliary derivatives **101-108** in Et_2O has been outlined in Table 4. It also has been demonstrated that the transmetalation reaction for the auxiliary derivatives **101-108** can occur in THF, toluene and hexane (Tables 5 and 6). The level of stereoselectivity obtained in reactions with benzaldehyde in the other 3 solvents is outlined in the next table (Table 7) and comparisons are included with reactions conducted in Et_2O. The results for each auxiliary derivative are presented in order of decreasing solvent polarity.

For reactions involving auxiliary derivative **101** (entries 1-4), non-polar solvents as expected provided higher levels of diastereoselectivity. However, for auxiliary **102** (entries 5-8), it was surprising that the coordinating solvent Et_2O (entry 6), provided a similar level of stereoselectivity as hexane (entry 8). A non-polar solvent in a reaction involving auxiliary derivative **103** (entries 9 and 10), did not help to achieve any diastereoselectivity at all. Nevertheless, for auxiliary derivative **104** (entries 11-14), toluene provided a very significant improvement from reactions involving other solvents. Furthermore, for reactions involving auxiliary derivatives **106** (entries 18-21) and **107** (entries 22-25), coordinating solvents provided higher levels of diastereoselectivity than non-

coordinating solvents. Therefore, no general trend is visible on what effect solvents have on diastereoselectivity and many inconsistencies are present. The effect of solvent seems to be very particular to the auxiliary studied. Benefits of employing a non-polar solvent in perhaps promoting intramolecular coordination of the C-2 oxygen atom to lithium are only realized for reactions involving auxiliary derivatives **101**, **104**, and **105** and coordinating solvents are actually beneficial for selectivity for auxiliary derivatives **103**, **106**, and **107**. Also, both Et_2O and hexane can be used to optimize the level of selectivity for auxiliary derivative **102**. However, the level of difference in selectivity achieved between different solvents is only modest at best (i.e 10% to 18% de in difference for each auxiliary), with the exception of auxiliary derivative **104** (i.e. a 30% de difference). As a result, experimenting with different solvents can optimize levels of diastereoselectivity only slightly. Furthermore, employing different solvents for a particular auxiliary in most cases did not alter the direction of selectivity or configuration obtained in the addition product. The changes in the direction of selectivity observed when employing auxiliary derivatives **101**, **104**, and **105** are not very significant since the level of selectivity experienced was very low.

Table 7. Effects of Solvent on Diastereoselectivity



101-107 **110-116**

Entry	Auxiliary derivative	R	Solvent	Yield of addition product (%) (#)	de (%)	Method of de determin-ation[a]
1	**101**	Me	THF	60 (**110**)	8*	A
2	**101**	Me	Et_2O	53 (**110**)	4	A
3	**101**	Me	toluene	34 (**110**)	22	A
4	**101**	Me	hexane	28 (**110**)	21	A
5	**102**	Ph	THF	60 (**115**)	17	A
6	**102**	Ph	Et_2O	79 (**115**)	34	A
7	**102**	Ph	toluene	59 (**115**)	23	A
8	**102**	Ph	hexane	42 (**115**)	36	C
9	**103**	*i*Pr	Et_2O	40 (**111**)	0	B
10	**103**	*i*Pr	toluene	66 (**111**)	0	B
11	**104**	*t*Bu	THF	79 (**112**)	0	B
12	**104**	*t*Bu	Et_2O	96 (**112**)	2*	A
13	**104**	*t*Bu	toluene	19 (**112**)	30	A
14	**104**	*t*Bu	hexane	62 (**112**)	0	B
15	**105**	1-naphthyl	Et_2O	23 (**113**)	2*	C
16	**105**	1-naphthyl	toluene	53 (**113**)	12	C
17	**105**	1-naphthyl	hexane	28 (**113**)	10*	C
18	**106**	2-naphthyl	THF	nd (**114**)	35	C
19	**106**	2-naphthyl	Et_2O	97 (**114**)	36	C
20	**106**	2-naphthyl	toluene	58 (**114**)	22	C
21	**106**	2-naphthyl	hexane	34 (**114**)	29	C
22	**107**	4-OMe-C_6H_4	THF	50 (**116**)	35	D
23	**107**	4-OMe-C_6H_4	Et_2O	80 (**116**)	34	D
24	**107**	4-OMe-C_6H_4	toluene	58 (**116**)	20	D
25	**107**	4-OMe-C_6H_4	hexane	54 (**116**)	26	D

*Opposite sense of selectivity observed.

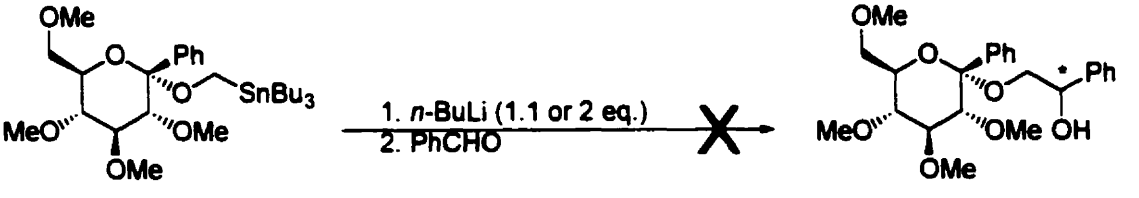
[a]Methods for de determination: A: Selectivity determined by chiral HPLC analysis of the recovered 1,2-diol product. B: Selectivity determined by proton NMR of the addition product. C: Selectivity determined by chiral HPLC analysis of the addition product. D: Selectivity determined by silica gel column HPLC analysis of the addition product.

It is possible that aggregation effects involving intermolecular coordination of the lithium atom between the oxygen atoms of two or more auxiliaries may reduce the probability of a *cis*-fused bicyclic system to be formed (Figure 14).

Figure 14. Possible aggregation.

A reaction was conducted in a more dilute reaction mixture (0.005 M vs. 0.05 M) that may reduce the chance of aggregation and increase the chance of a *cis*-fused bicyclic monomeric species to exist (Scheme 34). However it was not possible to transmetalate auxiliary derivative **102** using 1.1 or 2 equivalents of *n*-BuLi and the effect of diluted conditions on diastereoselectivity could not be determined. Trace amounts of water in the greater volume of Et_2O may have quenched the *n*-BuLi. More *n*-BuLi was not introduced since a greater amount of Li present in the reaction mixture may promote aggregation to occur and give inconclusive results.

Scheme 34

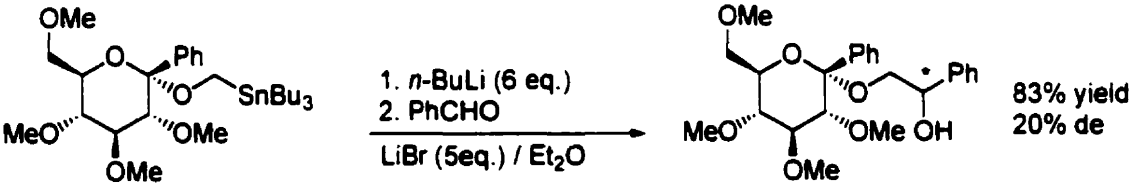


102 : 0.005 M in Et_2O

115

The aggregation study was conducted also under conditions that may induce aggregation to occur. The presence of excess Li^+ in the reaction mixture may induce aggregation to occur and may shed more light on what effect aggregation may have on diastereoselectivity. The use of 6 equivalents of *n*-BuLi and 5 equivalents of LiBr were used to transmetalate the auxiliary derivative **102** and to maintain a high concentration of Li^+ in the reaction mixture (Scheme 35). Diastereoselectivity was decreased slightly to 20% de from the 34% de experienced under the usual conditions. Therefore higher aggregation states may have a negative effect on achieving diastereoselectivity. More studies on aggregation and solvent effects were conducted in a reaction involving auxiliary derivative **102** and 3,4-dimethoxybenzaldehyde (Section 2.2.4) and also with other auxiliaries that are presented in other chapters of this thesis (Chapter 4, 5 and 6).

Scheme 35



102 **115**

*2.2.4 Transmetalation of **102** and Subsequent Trapping with Other Aldehydes and Ketones*

Further steric and stereoelectronic interactions between the auxiliary C-glycoside R group and aldehyde R group were probed by employing other aldehydes and ketones in the addition step (Table 8). The phenyl-C-glycoside auxiliary derivative **102** was used for the

transmetalation/addition experiments since other aryl C-glycoside groups present on the auxiliary as discussed earlier did not provide any substantial improvements in selectivity.

The results achieved with aliphatic aldehydes indicated that bulky branched aldehydes such as pivaldehyde did not react selectively with the auxiliary derivative **102** (entry 1). Again this was surprising since it was expected that bulkier groups on either aldehyde or auxiliary would promote greater selectivity due to greater steric interactions in the transition state. Straight chain aldehydes such as propionaldehyde provided selectivity at a level similar to benzaldehyde (entry 2).

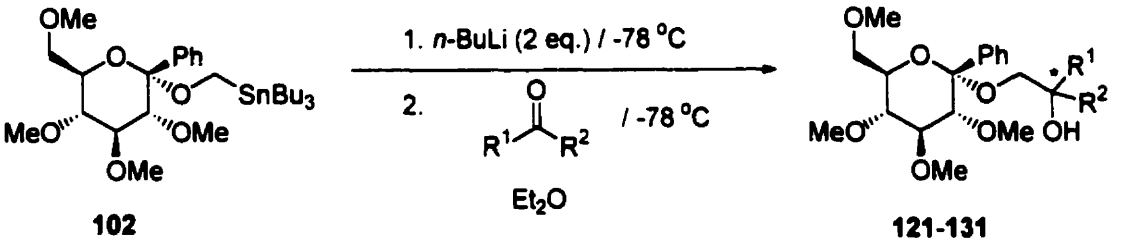
A greater level of success was achieved with other aryl aldehydes. For instance 1-naphthaldehyde, *p*-anisaldehyde and 3,4-dimethoxybenzaldehyde, all provided selectivities between 54-59% de (entries 3-5). It was speculated that this increase in selectivity was due to the electron rich nature of the aldehyde. Therefore, electron deficient aryl aldehydes were employed in another 2 experiments (entries 6 and 7). Selectivities were significantly reduced with these systems and were only marginally better than with benzaldehyde. Therefore, electron rich aryl aldehydes, possibly through stereoelectronic effects, promote higher levels of selectivity than electron deficient aldehydes. Stereoelectronic interactions between auxiliary and aldehyde were further investigated and the results of these studies are discussed in Section 2.2.7.

An electron rich aromatic substituent placed closer to the reaction site did not provide a higher level of selectivity (entry 8). A provisional identification was made for compound **128**, based on IR, ^{1}H NMR and ^{13}C NMR data. It was thought that the 2-OMe might have the potential to coordinate with the lithium atom in the transition state to favor an even more rigid transition state as shown in Figure 15a. Furthermore, it was considered that the 2-OMe group may be in close proximity to the anomeric phenyl group of the auxiliary in the transition state and therefore disfavor the alternate transition state shown in Figure 15b to a greater extent. However, since the de obtained

was not greater than from the reaction with *p*-anisaldehyde or 3,4-dimethoxybenzaldehyde, the above effects may not be operating in the transition state with *o*-anisaldehyde.

Furthermore, it was interesting to observe that α,β unsaturated aldehydes can react selectively with the auxiliary similar to the level achieved with benzaldehyde (entry 9). Success was achieved with ketones as well (entries 10 and 11) and proves that diastereoselective reactions with lithiated **102** are not limited only to aldehydes.

Table 8. Selectivities obtained with the lithiated auxiliary derivative **102** in additions to various aldehydes and ketones.

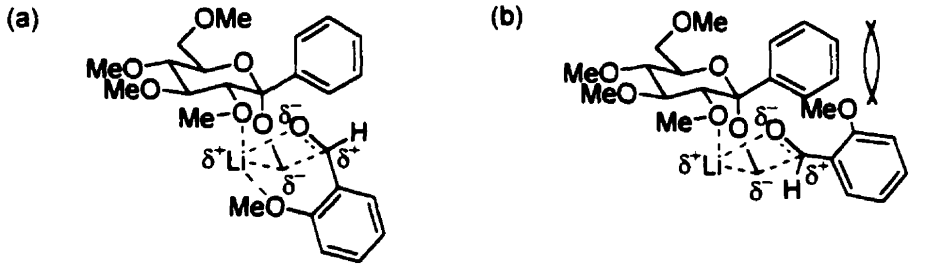


102 **121-131**

Entry	R^1	R^2	Product (#)	Yield of Product (%)	de (%)	Method for de determin-ation[a]
1	^{t}Bu	H	**121**	65	0	B
2	Et	H	**122**	45	33	B
3	1-naphthyl	H	**123**	77	54	D
4	4-OMe-C_6H_4	H	**124**	74	55	B
5	3,4-OMe-C_6H_4	H	**125**	68	59	C
6	4-Cl-C_6H_4	H	**126**	68	39	C
7	C_6F_5	H	**127**	76	44	C
8	2-OMe-C_6H_4	H	**128**	93	51	B
9	Cinnamyl	H	**129**	59	32	C
10	Me	Ph	**130**	60	56	A
11	Et	Ph	**131**	65	40	A

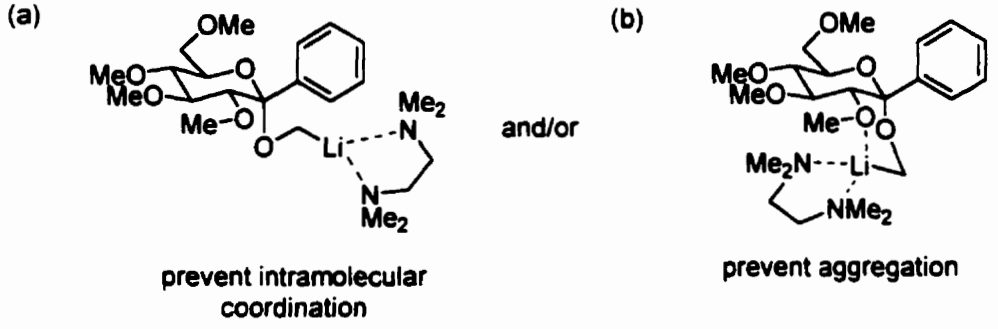
[a] Methods for de determination: A: Chiral HPLC analysis of the recovered 1,2-diol product. B: ^{1}H NMR analysis of the addition product. C: Chiral HPLC analysis of the addition product. D: Silica gel column HPLC analysis of the addition product.

Figure 15. Proposed transition states between lithiated auxiliary derivative **102** and *o*-anisaldehyde.



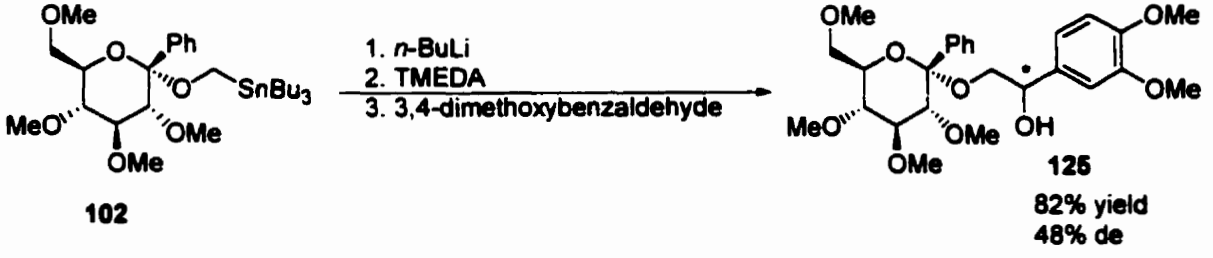
A further study on solvent/aggregation effects was conducted with stannane **102** and 3,4-dimethoxybenzaldehyde. In order to study the effect of solvent in competitive coordination for the lithium atom with the C-2 oxygen of the auxiliary, TMEDA was used as a solvent additive. TMEDA was expected to have stronger coordination ability towards the lithium atom than other polar solvents presented thus far. Therefore, it was anticipated that a lithiated auxiliary derivative in the presence of TMEDA would not be able to form the intramolecularly coordinated *cis*-fused bicyclic system since TMEDA could compete with the C-2 oxygen of the auxiliary for coordination (Figure 16a). Consequently, a large drop in selectivity was expected to occur with a reaction in the presence of TMEDA. Furthermore, aggregation between other auxiliary molecules for the lithium atom can possibly be prevented if TMEDA out-competes the other auxiliary molecules for coordination onto the lithium atom, while still maintaining intramolecular coordination (Figure 16b). Therefore, the effect of possibly breaking up aggregation on selectivity can be studied as well.

Figure 16. Possible potential effects of TMEDA in the presence of lithiated auxiliary derivative **102**.



When compound **102** was transmetalated and trapped with 3,4-dimethoxybenzaldehyde in the presence of TMEDA, the addition product **125** was formed in 48% de (Scheme 36). Under the usual conditions the addition product **125** was formed in 59% de, and therefore only a small drop in selectivity occurs when the reaction was conducted in the presence of TMEDA. It could have been possible that TMEDA was too weak a coordinating agent relative to the auxiliary oxygens in order to cause any drastic changes to aggregation states or to out compete the proposed C-2 oxygen's intramolecular lithium coordination. Another strategy was taken to study the effect of aggregation, which required making major structural changes to the auxiliary framework and results are presented in Chapter 4, 5 and 6.

Scheme 36



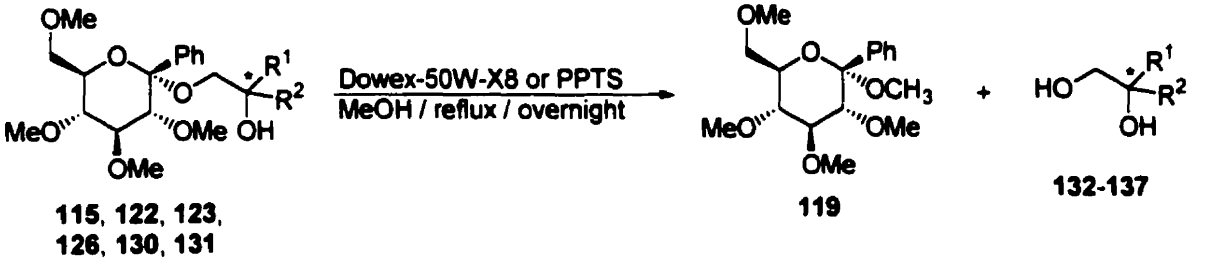
2.2.5 Recovery of Chiral Auxiliaries and Enantiomerically Enriched 1,2-Diols

In order for the auxiliary directed stereoselective addition of α-alkoxycarbanions to aldehydes to be practical, both the chiral auxiliary and the enantiomerically enriched 1,2-diol product must be recovered. Methods that accomplish the recovery of product and auxiliary from auxiliary directed stereoselective additions of α-heteroatomcarbanions are absent in the literature. This thesis demonstrates the first known examples where a chiral auxiliary directed stereoselective addition of an α-alkoxycarbanion to aldehydes and ketones results in the subsequent recovery of the chiral auxiliary and enantiomerically enriched 1,2-diol products. The recovery method employed in this thesis has already been indicated in Tables 4, 7 and 8 as one of the means to determine the de of addition to benzaldehyde and to other aldehydes and ketones. This section presents the recovery process in greater detail.

Another important reason to recover the 1,2-diol was to determine the absolute configuration of the stereocenter formed in excess and observe if it was the one predicted by the proposed transition state model. Attempts were made to cleave off products that have absolute configurations cited in the literature (Table 9). The recovery of both chiral auxiliary and 1,2-diol was accomplished by refluxing the addition products in methanol for 24 h in the presence of Dowex-50W-X8 resin (H^+ form) or with a catalytic amount of PPTS. The yields of the auxiliary as the methyl glycoside **119** and 1,2 diols **132-137** were good in most cases (Table 9). Most importantly, all examples in Table 9 show that all diols have the *S* configuration when comparing to literature values, and are in accordance with the proposed transition state model where the *Re* face of the aldehyde or ketone is preferentially attacked. Furthermore the de of the addition product translates to the ee of the diol

within the experimental error of analysis. Therefore, stereochemical integrity is maintained in the transformation from the addition product to the 1,2-diol.

Table 9. Recovery of the auxiliary and enantiomerically enriched 1,2-diols.



115, 122, 123, 126, 130, 131 → **119** + **132-137**

Entry	Addition product #	R^1	R^2	Yield of auxiliary (%)	Yield of diol (%) (#)	de (%) of addition product	ee (%) of diol	Con-fig.
1	**115**	Ph	H	65	68 (**132**)	30[b]	34[a]	*S*
2	**122**	Et	H	83	45 (**133**)	33[b]	27[c]	*S*
3	**123**	1-naphthyl	H	92	98 (**134**)	54[d]	68[c]	*S*
4	**126**	4-Cl-C_6H_4	H	90	86 (**135**)	39[c]	43[a]	*S*
5	**130**	Ph	Me	94	76 (**136**)	64[b]	56[a]	*S*
6	**131**	Ph	Et	85	69 (**137**)	43[b]	40[a]	*S*

[a] Determined by chiral HPLC analysis of the recovered 1,2-diol product.
[b] Determined by proton NMR of the addition product.
[c] Determined by chiral HPLC analysis of the addition product.
[d] Determined by silica gel column HPLC analysis of the addition product.
[e] Determined by an optical rotation comparison with a literature value.

To further check if stereochemical integrity is maintained under the acidic conditions, the diol **132** commercially available in pure *R* form, was subjected to the usual acidic conditions (Scheme 37). After overnight reflux the diol was isolated as usual and chiral HPLC analysis

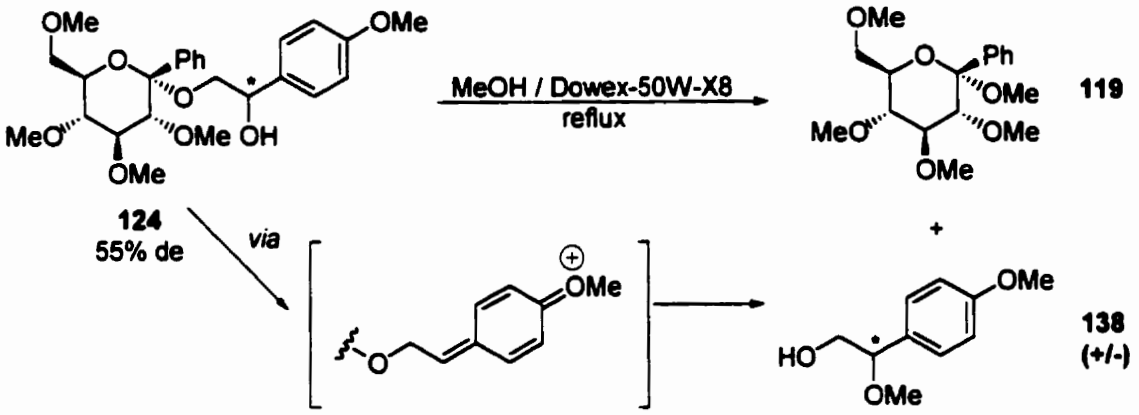
indicated no detectable *S* enantiomer. Therefore, stereochemistry is maintained for diol **132** under the acidic conditions used for its recovery from the addition product **115**.

Scheme 37

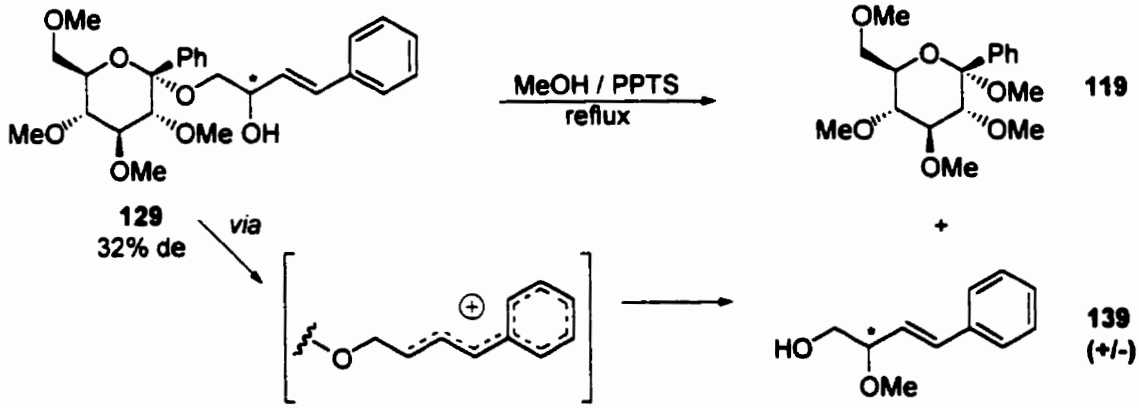
Furthermore, the mechanism of racemization most likely would involve the formation of a benzylic cation being trapped by the solvent methanol to form racemic methyl ether products (*vide infra*). Another reason for believing that racemization does not occur for the examples presented in Table 9 is that methyl ether products were not detected or isolated in these cases.

However, certain diols cannot be recovered with stereochemical integrity being maintained. Adducts that can form stable benzylic cations have been observed to racemize. For instance treatment of the addition product derived from *p*-anisaldehyde **124** under acidic conditions yielded the auxiliary **119**; however the 1,2 diol was not recovered and only the methyl ether **138** was isolated (Scheme 38). Formation of the methyl ether presumably occurs through the formation of a benzylic cation stabilized by the *p*-OMe substituent, followed by trapping with methanol. Similarly, the addition product derived from cinnamaldehyde **129** is problematic under these conditions since it forms a stable allyl benzylic cation, which is subject to racemization under the acidic conditions to form the methyl ether **139** (Scheme 39). Therefore, the acidic conditions of the recovery method are inappropriate for diols that have the potential to form benzylic cations stabilized by extra conjugation or by electron rich aromatic groups.

Scheme 38



Scheme 39

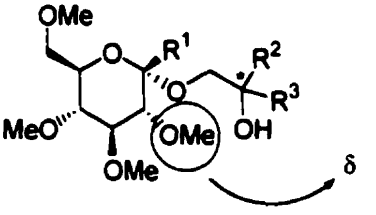


2.2.6 Correlation of Absolute Configuration

The absolute configuration obtained from the reaction of the lithiated auxiliary derivative **102** to various aldehydes has been demonstrated in 6 examples (Table 9). The diols cleaved from the addition products **115**, **122**, **123**, **126**, **130**, and **131** have known absolute configurations in the literature and therefore optical rotation comparison made it possible to assign absolute

stereochemistry for the diols **132-137** derived from the auxiliary addition products. However, it was not possible to cleave off enantiomerically enriched diols obtained from addition adducts derived from reactions with *p*-anisaldehyde or from cinnamaldehyde. Furthermore the absolute configuration of the diol that can be derived from the lithiated auxiliary derivative addition to pentafluorobenzaldehyde is unknown. Due to the above limitations, the absolute configurations for the remainder of the addition products were assigned by correlating ^{1}H NMR data of the addition products with known configuration (Table 10, entries 1-6) to those of unknown configuration (entries 7-16). The furthest upfield OMe singlets for both diastereomers are well separated from the other 3 pairs of downfield OMe singlets in all the addition products studied. The upfield OMe singlet pair has also been assigned to be in the 2-position of the auxiliary since it experiences the greatest $\Delta\delta$ between diastereomers due to the fact it is the closest OMe group to the variable stereocenter. Since the 2-OMe singlet is readily identifiable for all addition products it was used for absolute configuration comparisons. The addition products of known configuration follow the same pattern where the 2-OMe singlet for the auxiliary exhibits a signal for the major diastereomer that is downfield from the minor diastereomer. Therefore, the diastereomer with the *S* configuration at the carbinol carbon exhibits a signal for the 2-OMe singlet downfield from the diastereomer with the *R* configuration at the carbinol carbon. This NMR shift pattern can be correlated to the addition products of unknown configuration that could not be determined (entries 7-9), or from which diols were not recovered (entries 8-16). The same pattern continues for the addition products of unassigned configuration where the 2-OMe singlet for the major diastereomer is downfield from the minor diastereomer, with only one exception (entry 9, $R_2 = C_6F_5$). Since all examples with only one exception display the identical ^{1}H NMR shift pattern, it is reasonable to expect that all addition products except the product derived from pentafluorobenzaldehyde exhibit the *S* configuration preferentially at the carbinol carbon.

Table 10. Proton NMR shifts of 2-OMe resonances of minor and major diastereomer peaks of addition products.

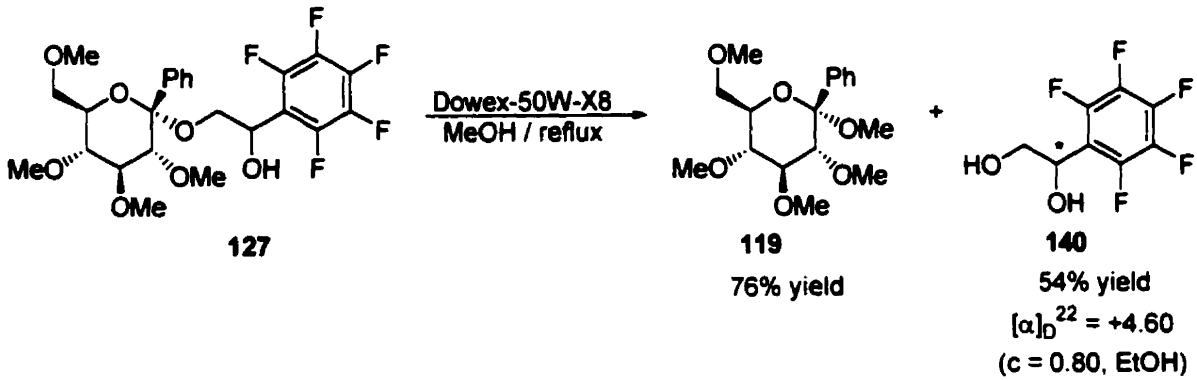


Entry	Cmpd #	R^1	R^2	R^3	Major δ (config.)	Minor δ (config.)
1	**115**	Ph	Ph	H	3.13 (*S*)	3.10 (*R*)
2	**122**	Ph	Et	H	3.08 (*S*)	3.06 (*R*)
3	**123**	Ph	1-naphthyl	H	3.18 (*S*)	3.13 (*R*)
4	**126**	Ph	4-Cl-C_6H_4	H	3.12 (*S*)	3.09 (*R*)
5	**130**	Ph	Ph	Me	3.06 (*S*)	3.04 (*R*)
6	**131**	Ph	Ph	Et	3.06 (*S*)	3.03 (*R*)
7	**124**	Ph	4-OMe-C_6H_4	H	3.12	3.08
8	**129**	Ph	Cinnamyl	H	3.12	3.09
9	**127**	**Ph**	**C_6F_5**	**H**	**3.09**	**3.12**
10[a]	**125**	Ph	3,4-OMe-C_6H_4	H	3.11	3.08
11	**128**	Ph	2-OMe-C_6H_4	H	3.10	3.08
11	**110**	Me	Ph	H	3.40	3.37
12	**116**	4-OMe-C_6H_4	Ph	H	3.17	3.13
13	**117**	4-CF_3-C_6H_4	Ph	H	3.15	3.11
14	**114**	2-naphthyl	Ph	H	3.12	3.08
15[b]	**113**	1-naphthyl	Ph	H	2.76	2.73
16[c]	**112**	*t*-Bu	Ph	H	3.42	3.39

[a]opposite sense of diastereoselectivity observed when the product was obtained from a reaction conducted in THF.
[b]opposite sense of diastereoselectivity observed when the product was obtained from reactions conducted in THF or hexane.
[c]product obtained from a reaction conducted in toluene.

In order to determine the configuration of the carbinol carbon of the addition product derived from pentafluorobenzaldehyde, the diol **140** was first cleaved from the addition product **127** so that the optical rotation of **140** could be determined (Scheme 40).

Scheme 40



127

119

76% yield

140

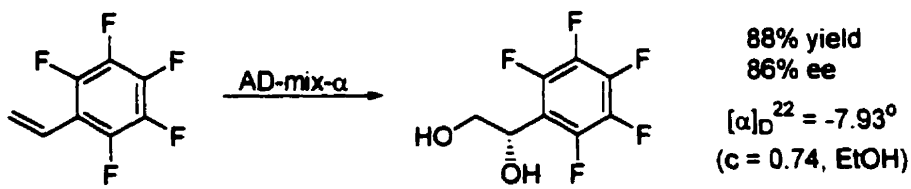
54% yield

$[\alpha]_D^{22}$ = +4.60

(c = 0.80, EtOH)

Next, enantiomerically enriched **140** was synthesized by using a method where the configuration of the product diol can be reliably predicted based on the configuration of the chiral ligand that induces the asymmetric transformation. For instance, the Sharpless asymmetric dihydroxylation (AD) reaction can form a diol of known configuration based on the Sharpless model of the AD reaction,[17] and an optical rotation comparison can be made with the diol derived from the addition product **127**. Therefore the AD reaction with pentafluorostyrene was conducted with the AD-mix-α reagent to generate the diol **140** with the *S* configuration according to the Sharpless model in 86% ee and with a negative sign of rotation (Scheme 41). Since the diol derived from the AD reaction differed in sign of optical rotation from the diol derived from the addition product **127**, the addition product **127** must have the *R* configuration at the carbinol carbon.

Scheme 41



140-*S*

88% yield

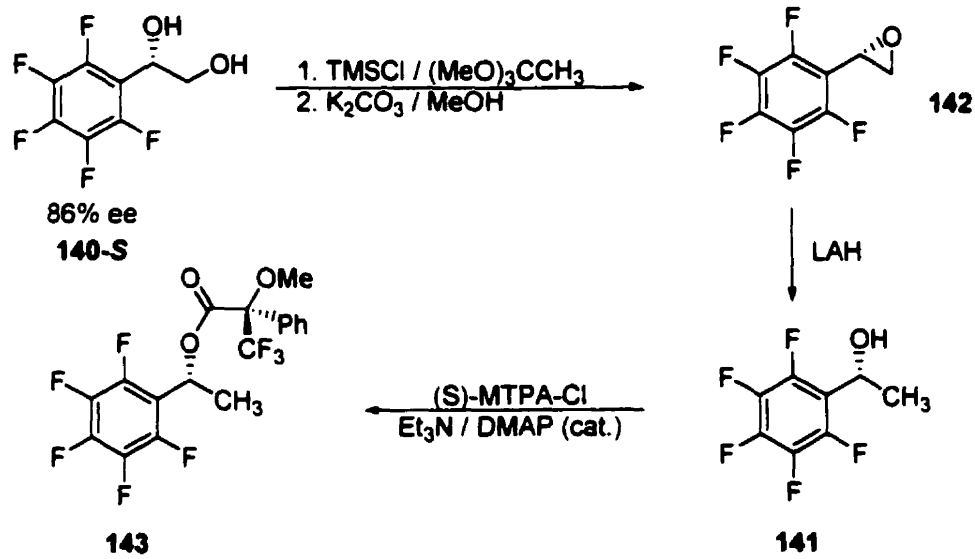
86% ee

$[\alpha]_D^{22}$ = -7.93°

(c = 0.74, EtOH)

In order to verify the configuration determined by the Sharpless model, the configuration of the diol **140-*S*** was further confirmed by the Mosher ester method.[18] To employ the Mosher ester analysis for absolute configuration determination it was necessary to transform the diol **140-*S*** into the secondary alcohol **141** (Scheme 42). This was accomplished by first forming the epoxide **142** from the diol **140-*S*** by following a known literature procedure.[19] The epoxide **142** was then reduced to the secondary alcohol **141** followed by forming the Mosher ester derivative **143** with (*S*)-MTPA-Cl (from (*R*)-MTPA). A provisional identification was made for compound **143**, based on ^{1}H NMR data.

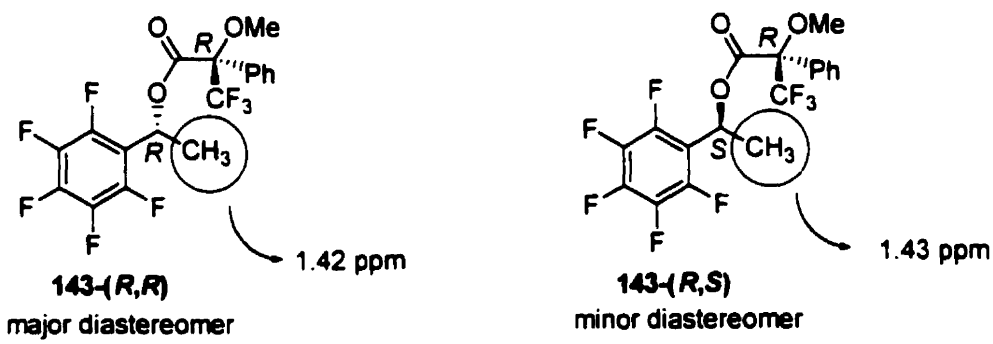
Scheme 42



Proton NMR analysis revealed that the methyl group from the alcohol in the major diastereomer of **143** to be upfield by 0.01 ppm from the methyl group signal from the alcohol in the minor diastereomer **143** (Figure 17). The Mosher ester model indicates that esters formed with (*S*)-MTPA-Cl and a (*R*)-secondary alcohol with aryl and methyl groups would have a signal for a methyl group from the secondary alcohol in the (*R*, *R*) diastereomer upfield from the (*R*, *S*) diastereomer. Therefore, the major isomer of the secondary alcohol **141** must have the *R* configuration and the diol

140-*S* the opposite *S* configuration due to changes in group priorities. As a result, the Mosher model predicts the same stereochemistry for the diol **140-*S*** as predicted by the Sharpless model and provides further proof that the major diol **140** derived from the addition product **127** has the *R* configuration. Furthermore, the ^{1}H NMR data in Table 10 are consistent in indicating a reversal in sense of selectivity due to a reversal in chemical shift pattern observed for **127** and further support the formation of the *S* stereocenter in the major diastereomer for other adducts.

Figure 17. Chemical shift differences between (*R*,*R*) and (*R*,*S*) diastereomers of Mosher ester derivative **143**.



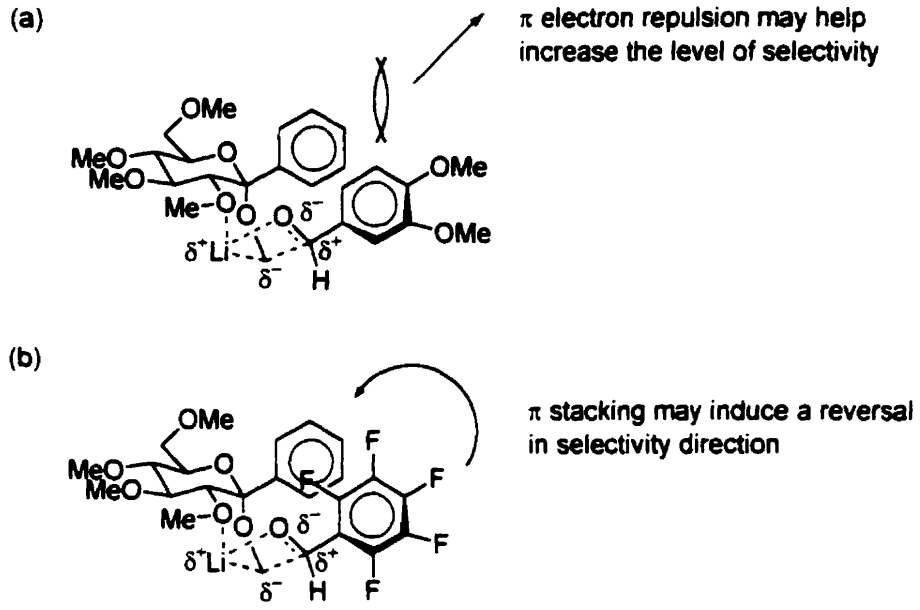
Therefore, a major deviation with respect to direction of stereoselectivity was encountered with the auxiliary addition reaction to pentafluorobenzaldehyde. All other examples where significant levels of stereoselectivity were achieved had the *S* stereocenter formed preferentially at the carbinol carbon. The formation of the *S* stereocenter preferentially also agrees with the proposed transition state model where the *Re* face of the aldehyde is trapped stereoselectively.

A reversal in the sense of chiral induction upon fluorine substitution for a chiral ligand has also been documented in the literature.[20] It was speculated that a change in aggregation might be the cause for the observed change in enantioselectivity.

2.2.7 Optimization of Stereoelectronic Interactions

It was noted in Section 2.2.4 that electron rich aldehydes provide higher levels of selectivity than benzaldehyde or electron poor aldehydes. It could be possible that in the transition state π-electron repulsion occurs in tandem with steric repulsion between two π-base groups such as the auxiliary anomeric phenyl group and an electron rich aldehyde aromatic group to provide a greater level of diastereoselectivity (Figure 18a). Furthermore, it may be feasible for a highly electron deficient aromatic group or π-acid of an aldehyde to participate in a π stacking interaction with the π-base auxiliary anomeric phenyl group (Figure 18b). The π stacking interaction theory is supported by the fact that reactions with pentafluorobenzaldehyde provide the *R* configuration preferentially in the diol product. In order to form the *R* configuration preferentially, a transition state structure would have to be favored where the aromatic groups of pentafluorobenzaldehyde and the auxiliary are both pointing towards each other as seen in Figure 18b. Therefore, the unfavorable steric interaction between both aromatic groups may be overridden by a favorable π stacking interaction. As a result the $\Delta G^{\ddagger}$ for the transition state leading to the *R* configuration may be decreased by π-stacking to be even lower then the $\Delta G^{\ddagger}$ for the transition state leading to the *S* configuration.

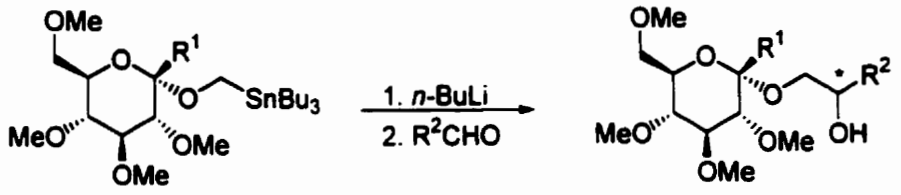
Figure 18. Possible stereoelectronic interactions in the transition state.



Attempts were made to increase both π stacking and π repulsion interactions in order to increase the level of diastereoselectivity (Table 11). A reaction with a lithiated auxiliary derivative containing an anomeric aromatic group with greater π electron density than a phenyl group may induce greater π repulsion to occur in reactions with π electron rich aromatic aldehydes and hence induce a greater level of selectivity. Similarly, a π electron rich auxiliary anomeric aromatic group with greater π electron density than a phenyl group, may donate a greater amount of electron density to promote the π stacking interaction to a greater extent with highly electron deficient π acid aromatic aldehydes such as pentafluorobenzaldehyde. Therefore, the level of selectivity in a reaction between a lithiated auxiliary derivative with an electron rich anomeric aromatic group and pentafluorobenzaldehyde may also be increased.

The transmetalation of auxiliary derivative **107**, which contains the electron rich 4-OMe-C_6H_4 anomeric group, and trapping with 3,4-dimethoxybenzaldehyde resulted in only 56% de (entry 1). This was no improvement over the reaction between lithiated auxiliary derivative **102** with the Ph anomeric group where 59% de was achieved in the addition to 3,4-dimethoxybenzaldehyde. Therefore, extra π electron density on the auxiliary anomeric group did not provide extra selectivity as was previously believed. In another reaction between the lithiated auxiliary derivative **107** containing electron rich 4-OMe-C_6H_4 anomeric group and pentafluorobenzaldehyde resulted in only achieving 39% de (entry 2). Again this was no improvement over the reaction involving the lithiated auxiliary derivative with the Ph anomeric group **102** where 44% de was achieved in the addition to pentafluorobenzaldehyde. As a result, a greater π stacking interaction may not be induced with the 4-OMe-C_6H_4 group. A further investigation was conducted to study the π stacking interaction by having a π acid group at the anomeric position of the auxiliary in a reaction with a π base aromatic aldehyde (entry 3). A reaction with the lithiated auxiliary derivative **108** possessing the anomeric 4-CF_3-C_6H_4 group and 3,4-dimethoxybenzaldehyde led to a decrease in selectivity as expected to 39% de, yet still maintaining the *S* configuration in the major product. Therefore, the 4-CF_3-C_6H_4 group on the auxiliary may influence a π stacking transition state to occur; however the interaction is still weaker then the steric repulsion interaction since the *S* configuration dominates in the product.

Table 11. Attempted optimization of stereoelectronic interactions.



107, 108 **144-146**

Entry	Stannane: R^1 (#)	Aldehyde: R^2	Yield of product (%) (#)	Product (%de)	major config.
1	4-OMe-C_6H_4 (**107**)	3,4-OMe-C_6H_3	69 (**144**)	56[a]	*S*
2	4-OMe-C_6H_4 (**107**)	C_6F_5	80 (**145**)	39[a]	*R*
3	4-CF_3-C_6H_4 (**108**)	3,4-OMe-C_6H_3	49 (**146**)	39[b]	*S*

[a] Determined by chiral HPLC analysis of the addition product.
[b] Determined by silica gel column HPLC analysis of the addition product.

Thus, employing conditions that would favor an electron repulsion or attraction interaction between auxiliary and aldehyde did not increase the level of diastereoselectivity. Another unrelated limiting factor may be reducing the potential for achieving a greater level of diastereoselectivity and is discussed in the next section.

2.2.8 Effect of Metals on Diastereoselectivity

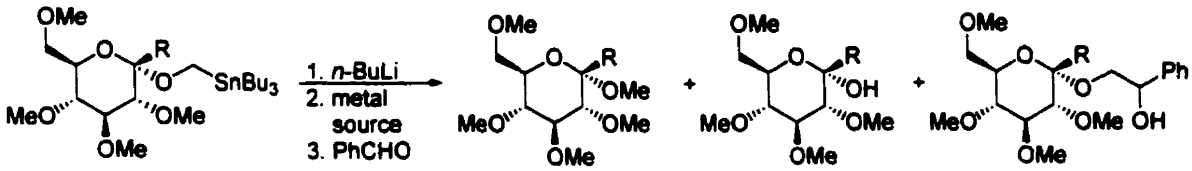
Further efforts were made to favor the formation of the *cis*-fused bicyclic intermediate by transmetalating the Sn-auxiliaries to metals other than Li. Other metals may have the potential to coordinate better than Li. For instance, it was considered that by transmetalating the glucose-derived chiral auxiliaries to Mg, a greater level of diastereoselectivity may be achieved, perhaps due to a greater likelihood for the formation of the proposed *cis*-fused bicyclic intermediate. Other metals

such as Zn, Ce, Ti, and Al may also have the potential to coordinate better than Li, and also may have the potential as Mg to induce greater levels of diastereoselectivity.

The stannanes **101** and **107** were transmetalated to metals other than Li (Table 12). The reaction sequence involved 3 steps: the first involving Sn-Li exchange, the second transmetalation from Li to the secondary metal, then trapping with benzaldehyde in the third step. In general, yields of the benzaldehyde addition products (**110** or **116**) were low due to the formation of protonated (**118** or **147**) and hemiketal (**91** or **97**) by-products to even a greater extent then seen previously in addition reactions involving only the organolithium species (*vide supra*: Table 6). A provisional identification was made for compound **147**, based on ^{1}H NMR data. For reactions where the amount of protonated product was not determined, the yield can be assumed to consist of the remainder of the Sn-Li exchange yield since no other by-products originating from the auxiliary other then the ones mentioned were formed in all the reactions. The level of diastereoselectivity experienced was also low in most examples. For instance, in the transmetalation involving **101** to the organomagnesium species (entries 1-3), the protonated product dominated as the major product. No significant increase in diastereoselectivity was experienced from the case where the organolithium of **101** is trapped with benzaldehyde (i.e. 21% de). Furthermore, transmetalations to the organozinc compound involving the use of $ZnCl_2$•(OEt_2) (entries 4-7), did not result in the formation of the addition product with the exception of a low yield obtained from a reaction conducted in hexane (entry 7). Very low levels of selectivity were obtained in cerium transmetalations (entries 8 and 9), and the protonated product presumably formed as the major product in aluminum transmetalations (entries 10-11). The only notable result in Table 12 includes the experiment involving the titanium transmetalation where a relatively high level of diastereoselectivity was achieved with the unexpected *R* configuration being formed preferentially (entry 12). Attempts were later made to optimize the almost non-existent yield of addition product

in the organotitanium addition (*vide infra*). Transmetalation of auxiliary derivative **107** (entries 13-18), also resulted in low yields of addition product with no significant increase in diastereoselectivity from the organolithium additions to benzaldehyde. The only notable exception is entry 15 where the direction of selectivity is reversed when toluene was used as the solvent.

Table 12. Effect of metals on yield and diastereoselectivity in additions to benzaldehyde.



101, 107 **118, 147** **91, 97** **110, 116**

Entry	Stann-ane	Metal[a]	Solvent	Yield of Sn-Li ex-change (%)	Yield of H^+ product (%) (#)	Yield of hemiketal product (%) (#)	Yield of addition product (%) (#)	de[a] (%)	Con-fig.
1	**101**	Mg	Et_2O	78	67 (**118**)	tr (**91**)	0	-	-
2	**101**	Mg	toluene	90	nd	11 (**91**)	2 (**110**)	29	S
3	**101**	Mg	hexane	nd	48 (**118**)	20 (**91**)	31 (**110**)	12	R
4	**101**	Zn	THF	100	32 (**118**)	68 (**91**)	0	-	-
5	**101**	Zn	Et_2O	100	28 (**118**)	72 (**91**)	0	-	-
6	**101**	Zn	toluene	84	nd	16 (**91**)	0	-	-
7	**101**	Zn	hexane	83	nd	12 (**91**)	25 (**110**)	17	R
8	**101**	Ce	toluene	100	nd	36 (**91**)	64 (**110**)	7	S
9	**101**	Ce	hexane	100	nd	58 (**91**)	6 (**110**)	10	S
10	**101**	Al	toluene	64	nd	1 (**91**)	2 (**110**)	2	S
11	**101**	Al	hexane	50	nd	3 (**91**)	3 (**110**)	30	S
12	**101**	Ti	hexane	88	nd	16 (**91**)	tr (**110**)	75	R
13	**107**	Mg	THF	94	nd	nd	39 (**116**)	33	S
14	**107**	Mg	Et_2O	82	82 (**147**)	nd	11 (**116**)	21	S
15	**107**	Mg	toluene	55	24 (**147**)	nd	7 (**116**)	38	R
16	**107**	Mg	hexane	41	nd	nd	24 (**116**)	22	S
17	**107**	Zn	Et_2O	84	nd	51 (**97**)	0	-	-
18	**107**	Zn	hexane	46	nd	7 (**97**)	22 (**116**)	0	-

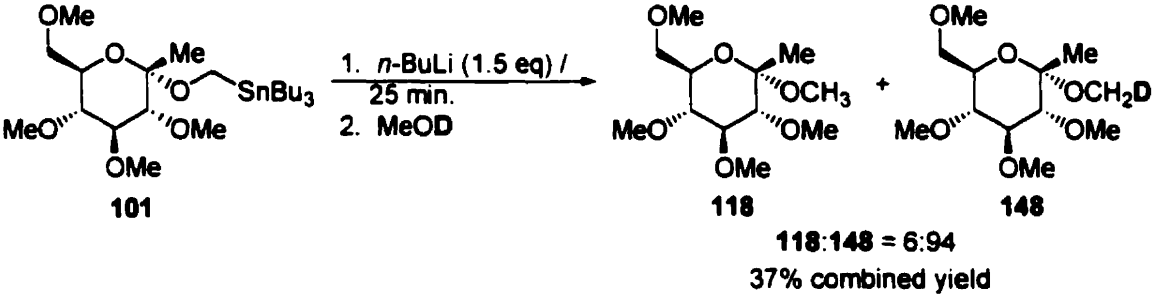
a - Metal sources employed were as follows: entries 1-3 and entries 13-16: $MgBr_2 \cdot OEt_2$; entries 4-7: $ZnCl_2 \cdot OEt_2$; entries 8 and 9: $CeCl_3$; entries 10 and 11: Et_2AlCl; entry 12: $Ti(O^iPr)_3Cl$; entries 17 and 18: $ZnCl_2 \cdot TMEDA$.
b - Selectivity for entries 1-12, determined by chiral HPLC analysis of the recovered 1,2-diol product and entries 13-18 by silica gel column HPLC analysis of the addition product.
nd - not determined
tr - trace yield

As was mentioned in the reactions involving α-alkoxyorganolithium species with benzaldehyde, protonation may result from aqueous quench if all the α-alkoxyorganometallic did not

react with benzaldehyde, or from decomposition of the α-alkoxyorganometallic. Furthermore, protonation may come from wet reagents and may be possible for solutions of $MgBr_2 \cdot (OEt_2)$ and $ZnCl_2 \cdot (OEt_2)$ or for solid $CeCl_3$ since they are highly hygroscopic. However, $ZnCl_2 \cdot$TMEDA is not hygroscopic and protonation nevertheless resulted in the use of this reagent as well. The source of protonation was investigated for reactions involving organotitanium auxiliaries in order to optimize the yield since the amount of diastereoselectivity achieved was relatively high.

A series of deuterium quenching experiments were conducted in order to determine if the α-alkoxyorganotitanium intermediate does not react with benzaldehyde or if it decomposes. First, the stability of the organolithium derived from **101** was investigated by quenching with MeOD after the usual transmetalation with *n*-BuLi (Scheme 43). The organolithium was observed to have good stability since protonated material **118** was only detected in a 6:94 ratio to deuterated material **148** from ^{1}H NMR data.

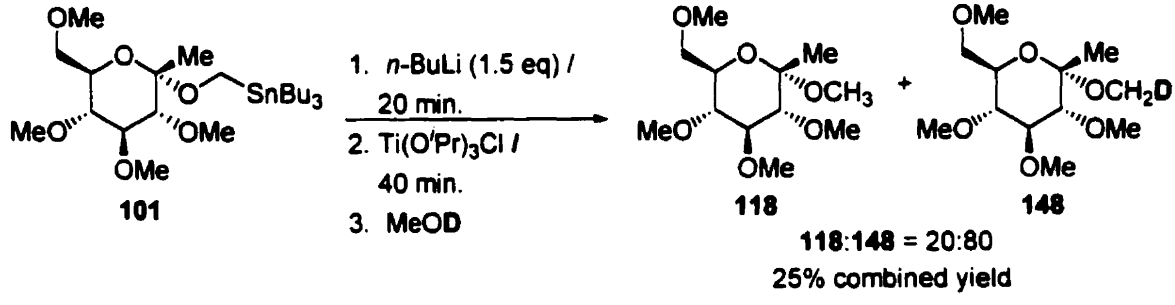
Scheme 43



Another experiment was conducted to test the stability of the organotitanium intermediate derived from **101** by adding MeOD 40 minutes after the addition of $Ti(O^iPr)_3Cl$ (Scheme 44). This time protonated material **118** was detected in a 19:81 ratio to dueterated material. Therefore, additional protonation is most likely derived from the decomposition of the organotitanium intermediate. It is unlikely that the proton source can come from a wet $Ti(O^iPr)_3Cl$ solution since in

another experiment the $Ti(O^iPr)_3Cl$ solution was predried with CaH_2 before use and no reduction in protonation was observed. As a result, the instability of the organotitanium intermediate is a minor problem in the formation of the protonated product since deuterated product was detected as the major product in the MeOD quench of the organotitanium intermediate. Consequently, the majority of protonation observed from the previous experiment (Table 12, entry 12) when benzaldehyde was present most likely results from protonation on work-up due to the lack of reactivity of the organotitanium intermediate with benzaldehyde.

Scheme 44

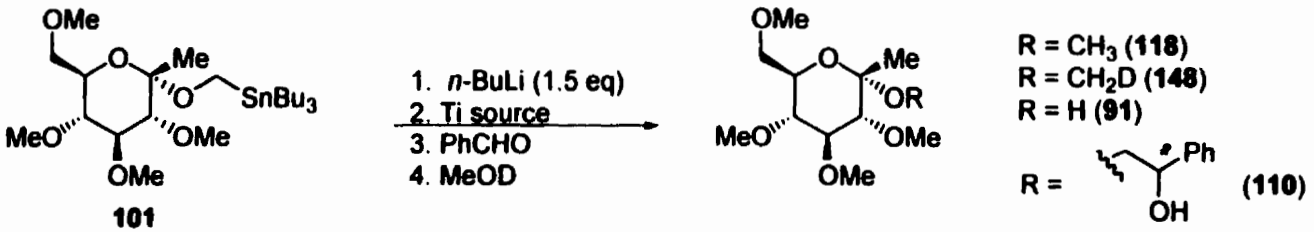


In order to optimize the yield in the reaction of the organotitanium intermediate with benzaldehyde many reaction variables were changed (Table 13). For instance, in order to promote the reaction of the organotitanium intermediate with benzaldehyde, longer reaction times and higher temperatures were employed in step 3 of the reaction sequence. The previous experiment (Table 12, entry 12) consisted of a reaction time of only 15 min with benzaldehyde at -78 °C. Longer reaction times and higher temperatures for the addition step to benzaldehyde were employed in entries 1-4. A provisional identification was made for compound **148**, based on IR, ^1H NMR, ^{13}C NMR, and low resolution MS data. Very low yields were achieved with protonated material **118** still dominating as the major product. Furthermore, the amount of diastereoselectivity was reduced as well. Warming

the reaction mixture to rt (entry 3), most likely resulted in the complete decomposition of the organotitanium since deuterated compound **148** was not detected. An overnight reaction with benzaldehyde (entry 4) also failed to improve the yield and a substantial portion of the organotitanium intermediate was left unreacted with the amount of diastereoselectivity further reduced. In order to reduce the amount of decomposition of the organotitanium intermediate, a shorter Li-Ti exchange time was used and a lower temperature as well (entry 5). The amount of protonation was substantially reduced with the yield being increased, however the diastereoselectivity was almost non-existent. Most likely very little transmetalation to the organotitanium had taken place and benzaldehyde mostly reacted with the organolithium species, which preferentially gave the *S* configuration, to provide the lower amount of diastereoselectivity. Therefore, the time for Li-Ti exchange was increased slightly along with the temperature (entry 6); however no significant improvements were noted. To further increase the reactivity of the organotitanium intermediate, a titanium source with a second chlorine atom was employed in entry 7. Unfortunately the reaction of the organotitanium intermediate derived from $Ti(O^iPr)_2Cl_2$ resembled the reactions involving the use of $Ti(O^iPr)_3Cl$ with very little diastereoselectivity being observed. Furthermore it was thought that the organotitanium intermediate might be more stable if an ate complex could be formed with $Ti(O^iPr)_4$ (entry 8). However, the yield proved to be very low with a significant reversal in the direction of stereoselectivity.

The important conclusion to be drawn from the set of organotitanium experiments is that the $\Delta G^{\ddagger}$ for decomposition pathway of the organotitanium intermediate must be lower than for the $\Delta G^{\ddagger}$ for the addition reaction to benzaldehyde. As a result, any increase in reaction time or temperature, always favored decomposition of the organotitanium while not overcoming the higher energy barrier for the reaction with benzaldehyde.

Table 13. Attempted yield optimization for the organotitanium reaction.



Entry	Ti source	Yield of Sn-Li ex-change (%)	Time for Li-Ti ex-change (min.)	Temp. for Li-Ti ex-change (°C)	Time for add-ition (min.)	Temp. for addition (°C)	Yield of H^+ and D^+ products (%) (**118** and **148**)	Ratio[b] of H^+:D^+ products (**118**:**148**)	Yield of hemi-ketal (**91**)(%)	Yield of add-ition product (**110**)	de[c] (%)	conf.
1	$Ti(O^iPr)_3Cl$	73	30	-40	60	-40	26	nd	2	7	40	R
2	$Ti(O^iPr)_3Cl$	65	30	-40	60	-40 to 0	10	nd	10	5	63	R
3[a]	$Ti(O^iPr)_3Cl$	59	40	-40	O/N	-31 to rt	32	100:0	7	5	50	R
4	$Ti(O^iPr)_3Cl$	56	40	-40	O/N	-78 to -45	22	39:61	6	4	36	R
5	$Ti(O^iPr)_3Cl$	55	5	-78	O/N	-78 to -45	16	70:30	6	15	6	R
6	$Ti(O^iPr)_3Cl$	44	10	-60	60	-55	47	19:81	24	7	26	R
7	$Ti(O^iPr)_2Cl_2$	nd	5	-78	90	-78	30	25:75	17	9	10	S
8	$Ti(O^iPr)_4$	nd	35	-35	90	-40	nd	-	13	2	29	S

nd - not determined; a - Reaction quenched with D_2O; b - H^+:D^+ Ratio determined by ^1H NMR; c - Determined by proton NMR of the addition product.

2.2.9 Summary and Conclusions

The incorporation of various anomeric equatorial substituents in a glucose-derived chiral auxiliary allows for the stereoselective addition of α-alkoxyanions to aldehydes and ketones in practical yields and in up to 59% de. Previous attempts made with a similar auxiliary with a hydrogen as an anomeric equatorial substituent, were unsuccessful in achieving any diastereoselectivity.[1] The level of selectivity is rather modest and similar to the level achieved in the literature with α-aminoanions (56% de);[21] however it exceeds the level of selectivity achieved in the literature for α-alkoxyanions (28 % de).[22] Most importantly this work has demonstrated that the recovery of enantiomerically enriched diol and chiral auxiliary is possible in several examples. Methods that allow for the product to be cleaved off from the auxiliary are absent in the literature.

The level of selectivity could not be increased by experimenting with certain reaction parameters such as solvent or metal without sacrificing the yield drastically (i.e. organotitanium experiments). The level of selectivity could only be maximized with an aromatic group present at the anomeric position of the auxiliary (excluding 1-naphthyl) and with reactions involving electron rich aldehydes. The sense of selectivity can also be reversed in reactions with pentafluorobenzaldehyde. The remaining chapters of this thesis will focus on the chiral auxiliary design process away from the anomeric carbon for the purpose of increasing the level of diastereoselectivity.

2.3 Experimental

2.3.1 General

All reactions were carried out with dry glassware under an atmosphere of argon unless otherwise noted. Low temperature baths were prepared as follows: -78 °C, dry ice/acetone; -40 °C, dry ice/ethylene glycol-water 50:50 (v/v); -20 °C, dry ice/ethylene glycol-water 30:70 (v/v); 0 °C, ice-water. Diethyl ether, tetrahydrofuran and toluene were distilled from sodium/benzophenone ketyl; CH_2Cl_2 and hexane were distilled from CaH_2. Tributyltinmethanol was prepared according to Seitz *et al.*[23] Other reagents were purchased (Aldrich) or prepared by modification of literature methods. All liquid aldehydes with exception of propionaldehyde were purified through a Pasteur pipette column of basic alumina immediately before use. Propionaldehyde was distilled before use. Other reagents were used without further purification. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter equipped with a sodium lamp. Infrared spectra of neat liquids were recorded on NaCl plates and solids in KBr disks. ^{13}C and ^{1}H NMR spectra were recorded at 62.9 MHz and 250MHz, respectively, using $CDCl_3$ (pretreated with anhydrous K_2CO_3 and 4 Å molecular sieves) as solvent unless otherwise noted, with $CDCl_3$ (^{13}C, δ 77.0) or tetramethylsilane (^{1}H, δ 0.0) being used as internal references. ^{1}H NMR data are presented as follows: chemical shift (multiplicity, integration, coupling constant(s), peak assignment). For ^{13}C NMR signals, coupling constants for satellites due to $^{117/119}Sn$ (where discernible) are reported. An asterisk (*) indicates signals that could be unequivocally attributed to the minor isomer in an uneven mixture of diastereomers or indicating a signal for the alternate diastereomer in a 1:1 mixture of diastereomers. ^{19}F NMR data were recorded at 188.3 MHz in $CDCl_3$, using trifluoroacetic acid (δ -76.53) as an external reference.

Mass spectra were recorded in CH_3CN using electrospray ionization in positive ion mode unless otherwise noted; for compounds containing Sn, data are reported for the most abundant isotope, ^{120}Sn. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Az.

2.3.2 Determination of Stereoselectivities

Method A: The addition product was subjected to the experimental conditions outlined in Section 2.3.57 in order to recover the 1,2-diol. Analysis of the 1,2-diol then occurred by chiral high performance liquid chromatography (HPLC) (*i*PrOH/hexane, 1.0 mL/min) on a Waters 600E instrument using a Waters 486 UV-visible detector at 254 nm, a Waters recording integrator, and a 4.6 mm x 150 mm Chiralcel OD column. The determined level of ee was then extrapolated to the de of the addition product as discussed in Section 2.2.5.

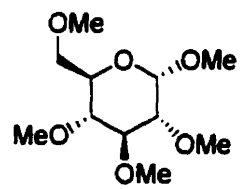
Method B: The integral values of the C-2 OMe peak for each diastereomer (see Table 10) were compared. Also the integral values of the carbinol proton resonance for each diastereomer were compared in instances where the carbinol signals for both isomers did not overlap with each other or from other peaks in the spectrum. In cases where both carbinol and C-2 OMe peaks were used for comparisons, the de was taken as the average from both determinations.

Method C: Analysis of the addition product occurred by chiral HPLC (*i*PrOH/hexane, 1.0 mL/min) on a Waters 600E instrument using a Waters 486 UV-visible detector at 254 nm, a Waters recording integrator, and a 4.6 mm x 150 mm Chiralcel OD column.

Method D: Analysis of the addition product occurred by HPLC (*i*PrOH/hexane, 2 mL/min) on a Waters 600E instrument using a Waters 486 UV-visible detector at 254 nm, a Waters recording integrator, and a 4.6 mm x 150 mm CSC silica (5 μm) column.

Method E: Analysis of the 1,2-diol occurred by measuring the optical rotation with a Perkin-Elmer 241 polarimeter equipped with a sodium lamp followed by comparing the optical rotation to literature values noted in Section 2.3.59 to 2.3.64.

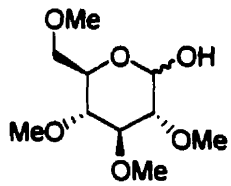
2.3.3 Methyl(2,3,4,6-tetra-O-methyl)-α-D-glucopyranoside **86**



This known compound[24] was prepared by a procedure modified from that described by Vogel.[2] A solution of methyl α-D-glucopyranoside **85** (250 g, 1.29 mol) in 250 mL of H_2O in a 3 L 3-neck round bottom flask equipped with a reflux condenser, overhead stirrer, and two dropping funnels, one with 1.55 L of a 60% NaOH solution (23.2 mol) and another containing 980 mL of Me_2SO_4 (10.3 mol), was heated to 60 °C. To the sugar solution 100 mL of Me_2SO_4 was first added followed by adding the NaOH solution and remainder of Me_2SO_4 dropwise at the same time and at approximately the same rates. The reaction became exothermic quickly and turned dark yellow after 10 min and dark brown after 25 min. When the additions were complete the reaction mixture was refluxed for 90 min then cooled to rt. The mixture was then extracted with Et_2O (3 x 2 L), the

combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo* to give 142 g of crude tetra- and penta- methylated glucoside. To a suspension of NaH (26.4 g, 1.1 mol) and MeI (62.3 mL, 1.0 mol) in 600 mL THF in another 3-neck round bottom flask was added the crude tetra- and penta- methylated glucoside in 400 mL of THF dropwise over 1 h at 0 °C. The reaction was stirred for 1 h after which it was slowly quenched with 100 mL of H_2O. The layers were then separated and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic layers were then dried over Na_2SO_4, and concentrated *in vacuo* to give 140 g (43% yield) of **86** as a yellow oil which was used without further purification: ^{1}H NMR δ 4.83 (d, 1H, J = 3.6 Hz, anomeric-H), 3.35-3.65 (m, 5H, OCH_2 + OCH), 3.63 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.21 (dd, 1H,' J = 3.6, 9.5 Hz, OCH).

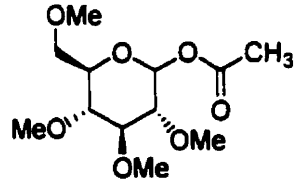
2.3.4 (2,3,4,6-Tetra-O-methyl)-D-glucopyranose **87**



Method A: NaOMe was first generated by adding Na (0.3 g) to anhydrous MeOH (60 mL) at 0° C. The acetate **88** (3.07 g, 11.0 mmol) in 11 mL of anhydrous MeOH was then added dropwise to the NaOMe solution. After 4 h of stirring the reaction was quenched with a saturated NH_4Cl solution (100 mL), then extracted with Et_2O (2 x 150 mL), washed with brine (100 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was then purified by silica gel chromatography using gradient elution (60% EtOAc/hexane to neat EtOAc) to afford 7.50 g of the known compound[3] **87** (34% yield) as 3:1 mixture of α:β diastereomers.

Method B: Compound **87** was also prepared by a procedure modified from that described by Hultman *et al.*[3] To a 2M solution of HCl (1.4 L) was added crude **86** (138 g, 0.56 mol) and the mixture was then set to reflux for 3 hrs. The reaction was then cooled to 0° C and slowly quenched with solid Na_2CO_3 until slightly basic by pH paper, then extracted with $CHCl_3$ (5 x 700 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude was then recrystallized from hexane (300 mL) to afford 96.3 g (73% yield) of **87** as 3:1 mixture of α:β diastereomers as a white solid: mp 82-90 °C; lit.[3] mp 94-97 °C; ^{1}H NMR δ 5.33 (t, 1H, J = 3.1 Hz, anomeric-H), 4.58* (dd, 1H, anomeric-H), 3.89 (dt, 1H, J = 5.4, 7.7 Hz, $CH_3OCH_2C\underline{H}O$), 3.03-3.75 (m, 5H, OCH_2 + OCH), 3.64 (s, 3H, OCH_3), 3.63* (s, 3H, OCH_3), 3.62* (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.53* (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.40* (s, 3H, OCH_3), 2.96* (dd, 1H, J = 7.7, 8.7 Hz).

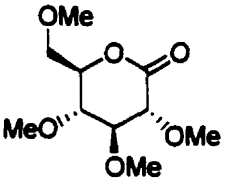
2.3.5 Acetyl(2,3,4,6-tetra-O-methyl)-D-glucopyranose **88**



This known compound[25] was prepared by a procedure modified from that described by Mikake *et* al.[4] To a pre-cooled (0 °C) mixture of Ac_2O (11 mL), AcOH (11 mL) and H_2SO_4 (1.1 mL), 7.04 g (28.1 mmol) of **86** was added dropwise. The mixture was stirred for 2½ hours after which CH_2Cl_2 (35 mL) was added followed by portions of a $NaHCO_3$ saturated solution (600 mL) in order to neutralize the reaction mixture. The aqueous layer was then separated and the organic layer was washed with water followed by brine, then dried over Na_2SO_4 and concentrated in *vacuo*. The

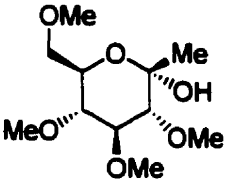
crude material was then purified by silica gel chromatography using gradient elution (25% to 50% EtOAc/hexane to neat EtOAc) to afford 5.70 g of **88** (73% yield) as a 3:1 mixture of α:β diastereomers and as an oil: ^{1}H NMR δ 6.31 (d, 1H, J = 3.5 Hz, anomeric-H), 5.44* (d, 1H, J = 7.9 Hz, anomeric-H), 3.10-3.73 (m, 6H, OCH_2 + OCH), 3.64 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 2.13 (s, 3H, CH_3CO_2).

2.3.6 (2,3,4,6-Tetra-O-methyl)-δ-gluconolactone **89**



This known compound[8d] was prepared by a procedure modified from that described by Corey and Suggs.[5] A mixture of hemiacetal **87** (95.2 g, 0.40 mol), PCC (174 g, 0.81 mol), neutral alumina (100 g) and crushed 3 Å molecular sieves (100 g) in CH_2Cl_2 (1.5 L) was stirred with an overhead stirrer and refluxed for 4 h. After cooling to rt the reaction mixture was diluted with anhydrous Et_2O (4 L) then filtered through a pad of Florisil. The filtrate was then concentrated *in vacuo* followed by kugelrohr distillation of the crude material (100-110 °C, 0.2 mm Hg) to afford 75.8 g (80% yield) of **89** as a colorless oil: IR (neat film) 2923, 2832, 1754 (C=O stretch), 1458, 1354, 1142 (C-O stretch), 981 (C-O stretch), 787cm^{-1}; ^{1}H NMR δ 4.34-4.45 (m, 1H, OCH), 3.81-3.88 (m, 1H, OCH), 3.39-3.66 (m, 4H, OCH_2 + OCH), 3.58 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3); ^{13}C NMR (C_6D_6) δ 168.5 (C=O), 82.7 (OCH), 79.8 (OCH), 78.0 (OCH), 77.6 (OCH), 71.1 (OCH_2), 58.8 (OCH_3), 58.7 (OCH_3), 58.4 (OCH_3), 58.3 (OCH_3).

2.3.7 (2R,3S,4S,5R,6R)-3,4,5-Trimethoxy-6-(methoxymethyl)-2-methyltetrahydro-2H-2-pyranol **91**

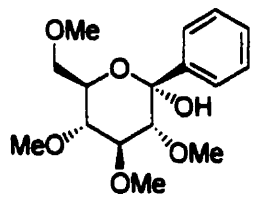


Two experimental procedures are given for the preparation of this compound. The following procedure provided the result reported in Table 2, entry 2: To a cooled solution (-78 °C) of δ-lactone **89** (5.28 g, 22.5 mmol) in THF (50 mL), a solution of 1.4 M MeLi (17.7 mL, 24.8 mmol) was added dropwise and the resulting solution was stirred for 10 minutes. The mixture was then quenched with an aqueous saturated NH_4Cl solution (5 mL) and diluted with Et_2O (100 mL). The aqueous layer was then separated and extracted with Et_2O (2 x 200 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (60% EtOAc/hexane) to obtain 4.51 g (80% yield) of known[8d] **91** as a thick syrup: ^{1}H NMR δ 3.82 (dt, 1H, J = 10.0 Hz, $CH_3OCH_2C\underline{H}O$), 3.3-3.7 (m, 3H, OCH_2 + OCH), 3.64 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.16 (t, 1H, J = 9.5 Hz, OCH), 2.92 (d, 1H, J = 9.1 Hz, OCH), 1.48 (s, 3H, CCH_3); ^{13}C NMR δ 96.9 (anomeric C), 85.6 (OCH), 85.0 (OCH), 80.0 (OCH), 71.4 (OCH), 70.5 (OCH_2), 61.1 (OCH_3), 60.5 (OCH_3), 60.0 (OCH_3), 58.9 (OCH_3), 25.7 (CCH_3).

Furthermore, compound **91** was formed along with unreported by-product (2*R*,3*S*,4*S*,5*S*)-1,3,4,5-tetramethoxy-6-methylheptane-2,6-diol (**91a**) by employing an alternative procedure as reported in Table 2, entry 1: To a cooled solution (-78 °C) of δ-lactone **89** (1.71 g, 7.28 mmol) in THF (70 mL), a solution of 3.0 M MeMgBr (2.67 mL, 8.01 mmol) was added dropwise and the

resulting solution was stirred for 1 h. The mixture was then quenched with an aqueous saturated NH_4Cl solution (5 mL) and diluted with Et_2O (100 mL). The aqueous layer was then separated and extracted with Et_2O (2 x 200 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (gradient elution: 45% EtOAc/hexane to neat EtOAc) to obtain 1.27 g (70% yield) of **91** and 210 mg (11 % yield) of upper R_f by-product **91a**. Compound **91a** exhibited the following spectral data: $[\alpha]_D^{22}$ = + 6.6 (c = 0.81, $CHCl_3$); IR (neat film) 3449 (O-H stretch), 2829, 1450, 1377, 1096 (C-O stretch) cm^{-1}; ^1H NMR δ 3.87-4.07 (br m, 1H, OCH), 3.30-3.75 (m, 3H, OCH_2 + OCH), 3.59 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.05-3.22 (m, 2H, OCH), 2.67 (br s, 1H, OH), 1.26 (s, 3H, $C(C\underline{H}_3)(CH_3)$), 1.23 (s, 3H, $C(CH_3)(C\underline{H}_3)$). ^{13}C NMR (75.47 MHz) δ 85.9 ($\underline{C}(CH_3)(OH)$), 80.4 (OCH), 79.8 (OCH), 73.5 (OCH), 73.0 (OCH), 70.4 (OCH_2), 61.2 (OCH_3), 59.9 (OCH_3), 59.5 (OCH_3), 59.0 (OCH_3), 26.7 ($C(\underline{C}H_3)(CH_3)(OH)$), 25.9 ($C(\underline{C}H_3)(CH_3)(OH)$); MS (EI) *m/z* 101 (100), 234 (M^+ - CH_3OH, 6), 235 (M^+ - CH_3O, 8), 249 (M^+ - OH, 0.1), 251 (M^+ - CH_3, 0.4), 265 (M^+ - 1, 3), 266 (M^+, 2), 267 (M^+ + 1, 0.1).

2.3.8 *(2R,3S,4S,5R,6R)-3,4,5-Trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranol* **92**

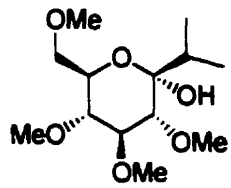


Two experimental procedures are given for the preparation and attempted preparation of this compound. The following procedure provided the result reported in Table 2, entry 4: Phenyllithium was first prepared according to a literature procedure.[26] The remainder of the procedure then occurred as follows: To a cooled solution (-78 °C) of δ-lactone **89** (4.85 g, 20.7 mmol) in Et_2O (150 mL), a solution of 1.0 M PhLi (21.0 mL, 21.0 mmol) was added dropwise and the resulting solution was stirred for 15 minutes. The mixture was then quenched with an aqueous saturated NH_4Cl solution (50 mL) and diluted with H_2O (75 mL) and Et_2O (50 mL). The aqueous layer was then separated and extracted with Et_2O (2 x 200 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was recrystallized from hexane to give 4.07 g of the unreported compound **92** (63% yield) as a white solid: mp 119-122 °C; $[\alpha]_D^{22} = +$ 38.4 (c = 1.02, $CHCl_3$); IR (KBr disk) 3432 (O-H stretch), 3035, 2834, 1081 (C-O stretch), 1051 (C-O stretch), 773, 717, 699 cm^{-1}; ^1H NMR δ 7.55-7.65 (m, 2H, Ar-H), 7.30-7.40 (m, 3H, Ar-H), 3.55-4.05 (m, 1H, OCH), 3.55-3.7 (m, 2H, OCH), 3.65 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.28 (dd, 1H, J = 9.3, 10.0 Hz, OCH), 3.0-3.1 (m, 2H, OCH), 3.04 (s, 3H, OCH_3), 1.77 (s, 1H, OH); ^{13}C NMR δ 142.4 (Ar-C), 128.1 (Ar-C), 127.9 (Ar-C), 126.0 (Ar-C), 97.4 (anomeric-C), 87.1 (OCH), 85.1 (OCH), 79.8 (OCH), 71.6 (OCH), 71.4 (OCH_2), 60.1 (OCH_3), 60.8 (OCH_3), 60.2

(OCH_3), 59.3 (OCH_3); MS (FAB) *m/z* 295.2 (M^+ - OH, 100), 313 (M^+ + 1, 4). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.36; H, 7.75.

Furthermore, unreported and undesired product (2*S*,3*S*,4*S*,5*R*)-2,3,4,6-tetramethoxy-1,1-diphenylhexane-1,5-diol (**92a**) was formed exclusively when an alternative procedure was employed as reported in Table 2, entry 3: To a cooled solution (-78 °C) of δ-lactone **89** (104 mg, 0.443 mmol) in Et_2O (3 mL), a solution of 2.0 M PhMgCl (0.22 mL, 0.44 mmol) was added dropwise and the resulting solution was stirred for 15 minutes. A reaction was not observed to have occurred by TLC, so the mixture was then warmed slowly to rt and an additional amount of 2.0 M PhMgCl (0.44 mL, 0.88 mmol) was added . The reaction was quenched with an aqueous saturated NH_4Cl solution (5 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were combined and washed with brine (10 mL), then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: 10% to 50% EtOAc/hexane) to obtain 135 mg (78% yield) of **92a** as an oil: ^1H NMR δ 7.51-7.70 (m, 4H, Ar-H), 7.14-7.49 (m, 6H, Ar-H), 4.41 (d, 1H, J = 3.1 Hz), 3.70-3.85 (m, 2H, OCH), 3.30-3.50 (m, 2H, OCH), 3.38 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.10 (s, 3H, OCH_3), 2.95-3.05 (m, 1H, OCH).

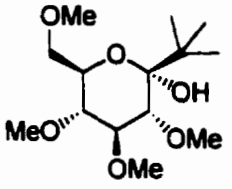
2.3.9 (2R,3S,4S,5R,6R)-2-Isopropyl-3,4,5-trimethoxy-6-(methoxymethyl)tetrahydro-2H-2-pyranol 93



Isopropyllithium was first prepared according to a literature procedure.[27] The remainder of the procedure then occurred as follows: To a cooled solution (-78 °C) of δ-lactone **89** (2.63 g, 11.2 mmol) in Et_2O (80 mL), a solution of 0.13 M ^iPrLi in hexane (86.0 mL, 11.2 mmol) was added dropwise and the resulting solution was stirred for 15 minutes. The mixture was then quenched with an aqueous saturated NH_4Cl solution (5 mL). The aqueous layer was then separated and extracted with Et_2O (2 x 40 mL), followed by extracting with CH_2Cl_2 (50 mL) and then with EtOAc (50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford 2.03 g (65% yield) of the unreported compound **93** as a thick syrup. The crude product was sufficiently pure and was employed in the next step without further purification: $[\alpha]_D^{22}$ = + 53.7 (c = 0.92, $CHCl_3$); IR (neat film) 3433 (O-H stretch), 2832, 1075 (C-O stretch) cm^{-1}; ^1H NMR δ 3.75 (ddd, 1H, J = 2.1, 4.1, 10.1 Hz, $CH_3OCH_2C\underline{H}O$), 3.4-3.7 (m, 3H, OCH), 3.65 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.05-3.2 (m, 2H, OCH), 2.5 (s, 1H, OH), 2.01 (spt, 1H, J = 6.9 Hz, $C\underline{H}CH_3$), 0.99 (d, 3H, J = 6.9 Hz, $CH(C\underline{H_3})_2$), 0.98 (d, 3H, J = 6.9 Hz, $CH(C\underline{H_3})_2$); ^{13}C NMR δ 99.0 (anomeric C), 85.9 (OCH), 81.4 (OCH), 79.9 (OCH), 71.4 (OCH), 71.1 (OCH_2), 60.4 (OCH_3), 60.3 (OCH_3), 59.9 (OCH_3), 59.2 (OCH_3), 34.2 ($\underline{C}H(CH_3)_2$), 17.1

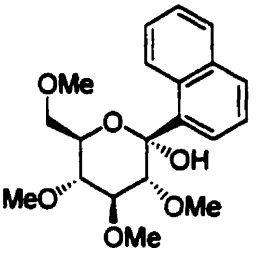
($CH\underline{C}H_3$), 15.3 ($CH\underline{C}H_3$); MS (EI) *m/z* 101 (100), 260 (M^+ - H_2O, 1). Anal. Calcd for $C_{13}H_{26}O_6$: C, 56.10; H, 9.42. Found: C, 56.18; H, 9.19.

2.3.10 (2R,3S,4S,5R,6R)-2-(Tert-butyl)-3,4,5-trimethoxy-6-(methoxymethyl)tetrahydro-2H-2-pyranol ***94***



To a cooled solution (-78 °C) of δ-lactone **89** (4.45 g, 19.0 mmol) in Et_2O (100 mL), a solution of 1.67 M ^{t}BuLi in pentane (11.4 mL, 19.0 mmol) was added dropwise and the resulting solution was stirred for 10 minutes. The mixture was then quenched with H_2O (0.5 mL. 28.5 mmol), and then filtered through Celite, and the filtrate was concentrated *in vacuo*. Purification was performed by recrystallizing the crude material from hexane to afford 2.70 g (49% yield) of the unreported compound **94** as a white solid powder: mp 62-65 °C; $[\alpha]_D^{22}$ = + 44.7 (c = 1.06, $CHCl_3$); IR (neat film) 3472 (O-H stretch), 1107 (C-O stretch), 1015 (C-O stretch) cm^{-1}; ^{1}H NMR δ 3.71 (ddd, 1H, J = 1.9, 4.1, 9.9 Hz, $CH_3OCH_2C\underline{H}O$), 3.4-3.7 (m, 3H, OCH), 3.65 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.28 (d, 1H, J = 8.7 Hz, OCH), 3.09 (t, 1H, J = 9.6 Hz, OCH), 1.01 (s, 9H, $C(C\underline{H}_3)_3$); ^{13}C NMR δ 99.8 (anomeric-C), 87.0 (OCH), 81.1 (OCH), 79.7 (OCH), 71.2 (OCH), 70.7 (OCH_2), 60.2 (OCH_3), 59.6 (OCH_3), 59.3 (OCH_3), 59.1 (OCH_3), 38.8 ($\underline{C}(CH_3)_3$), 25.2 ($C(\underline{C}H_3)_3$); MS (EI) *m/z* 101 (100), 275 (M^+ - OH, 1). Anal. Calcd for $C_{14}H_{28}O_6$: C, 57.51; 9.65. Found: C, 57.70; H, 9.39.

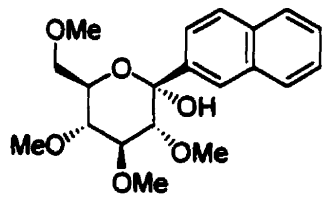
2.3.11 (2R,3S,4S,5R,6R)-3,4,5-Trimethoxy-6-(methoxymethyl)-2-(1-naphthyl)tetrahydro-2H-2-pyranol ***95***



1-Naphthyllithium was first prepared as follows: To a -78 °C solution of 1-bromonaphthalene (1.78 mL, 12.8 mmol) in THF (100 mL) was added a solution of 1.30 M *n*-BuLi in hexane (9.87 mL, 12.8 mmol) dropwise. The mixture was stirred for 10 minutes after which the solution was transferred by cannula to a -78 °C solution of δ-lactone **89** (2.73 g, 11.7 mmol) in Et_2O (200 mL). The resulting mixture was stirred for 10 minutes, and then quenched with an aqueous saturated NH_4Cl solution (15 mL). The aqueous layer was then separated and extracted with Et_2O (2 x 40 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Colored impurities were removed by washing the crude solid product with cold hexanes (100 mL) to give 3.64 g (86% yield) of the unreported compound **95** as a white powder: mp 133-135 °C; $[\alpha]_D^{22}$ = + 20.3 (c = 1.00, $CHCl_3$); IR (neat film) 3410 (O-H stretch), 1101 (C-O stretch), 1067 (C-O stretch), 990 (C-O stretch), 808, 786, 746, 723 cm^{-1}; ^1H NMR δ 8.6-8.65 (m, 1H, Ar-H), 7.85-7.95 (m, 3H, Ar-H), 7.4-7.6 (m, 3H, Ar-H), 4.05-4.20 (m, 1H, OCH, $CH_3OCH_2C\underline{H}O$), 3.3-4.0 (m, 5H, OCH + OCH_2), 3.66 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 2.74 (s, 3H, OCH_3); ^{13}C NMR δ 137.0 (Ar-C), 134.3 (Ar-C), 130.3 (Ar-C), 129.6 (Ar-C), 128.6 (Ar-C), 126.5 (Ar-C), 125.7 (Ar-C), 125.4 (Ar-C), 125.1 (Ar-C), 124.5 (Ar-C), 98.8 (anomeric-C), 85.4 (OCH), 85.1 (OCH), 79.4 (OCH), 71.9 (OCH), 71.2 (OCH_2), 60.7 (OCH_3), 60.3 (OCH_3), 60.2 (OCH_3), 59.2

(OCH_3); MS *m/z* 229 (100), 345 (M^+ - OH, 83), 363 (M + H^+, 11). Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; 7.23. Found: C, 66.04; H, 7.19.

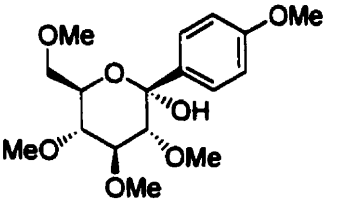
2.3.12 (2R,3S,4S,5R,6R)-3,4,5-Trimethoxy-6-(methoxymethyl)-2-(2-naphthyl)tetrahydro-2H-2-pyranol **96**



2-Naphthyllithium was first prepared as follows: To a -78 °C solution of 2-bromonaphthalene (1.77 g, 8.55 mmol) in THF (70 mL) was added a solution of 1.3 M *n*-BuLi (6.57 mL, 8.55 mmol) in hexane dropwise. The mixture was stirred for 13 minutes after which the solution was transferred by cannula to a -78 °C solution of δ-lactone **89** (1.82 g, 7.77 mmol) in Et_2O (80 mL). The resulting mixture was stirred for 5 minutes, and then quenched with an aqueous saturated NH_4Cl solution (15 mL). The aqueous layer was then separated and extracted with Et_2O (2 x 40 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford 3.00 g (100% yield) of the unreported compound **96** as thick syrup. The crude product was sufficiently pure and was employed in the next step without further purification: $[\alpha]_D^{22}$ = + 21.8 (c = 1.02, $CHCl_3$); IR (neat film) 3361 (O-H stretch), 3057, 2833, 1112 (C-O stretch), 791, 752, 730 cm^{-1}; ^1H NMR δ 8.10 (br, 1H, Ar-H), 7.8-7.9 (m, 3H, Ar-H), 7.71 (dd, 1H, J = 1.8, 8.6 Hz, Ar-H), 7.4-7.55 (m, 2H, Ar-H), 4.05 (ddd, 1H, J = 2.1, 4.3, 10.1, $CH_3OCH_2C\underline{H}O$), 3.1-3.8 (m, 5H), 3.66 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.00 (s, 3H, OCH_3); ^{13}C NMR δ 139.7

(Ar-C), 132.9 (Ar-C), 132.6 (Ar-C), 128.3 (Ar-C), 127.3 (Ar-C), 127.2 (Ar-C), 125.9 (Ar-C), 125.7 (Ar-C), 125.3 (Ar-C), 124.1 (Ar-C), 97.3 (anomeric-C), 86.9 (OCH), 85.0 (OCH), 79.7 (OCH), 71.4 (OCH), 71.2 (OCH_2), 60.7 (OCH_3), 60.5 (OCH_3), 59.9 (OCH_3), 59.0 (OCH_3); MS *m/z* 345 (M^+ - OH, 24), 385 (M + Na^+, 100). Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.02; H, 7.33.

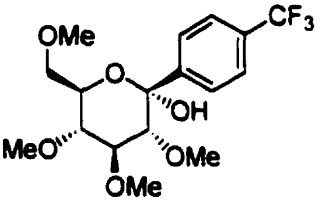
2.3.13 (2R,3S,4S,5R,6R)-3,4,5-Trimethoxy-6-(methoxymethyl)-2-(4-methoxyphenyl)tetrahydro-2H-2-pyranol **97**



4-OMe-C_6H_4-Li was first prepared as follows: To a -78 °C solution of 4-bromoanisole (1.72 g, 9.17 mmol) in THF (50 mL) was added a solution of 1.67 M ^{t}BuLi (11.0 mL, 18.3 mmol) in pentane dropwise. The mixture was stirred for 15 minutes after which the solution was transferred by cannula to a -78 °C solution of δ-lactone **89** (2.05 g, 8.73 mmol) in Et_2O (50 mL). The resulting mixture was stirred for 5 minutes, and then quenched with an aqueous saturated NH_4Cl solution (15 mL). The aqueous layer was then separated and extracted with Et_2O (2 x 40 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford 2.80 g (94% yield) of the unreported compound **97** as a thick syrup. The crude product was sufficiently pure and was employed in the next step without further purification: $[\alpha]_D^{22}$ = + 25.5 (c = 1.14, $CHCl_3$); IR (neat film) 3375 (O-H stretch), 2833, 1106 (C-O stretch), 827, 784, 734 cm^{-1}; ^{1}H NMR δ 7.52 (AA' of AA'XX', 2H, *m*-Ph-H), 6.87 (XX' of AA'XX', 2H, *o*-Ph-H), 3.98 (ddd, 1H, J = 2.1,

4.2, 10.0, $CH_3OCH_2\underline{C}HO$), 2.95-3.95 (m, 5H, OCH + OCH_2), 3.81 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.07 (s, 3H, OCH_3); ^{13}C NMR δ 159.1 (Ar-C), 134.6 (Ar-C), 127.1 (Ar-C), 112.7 (Ar-C), 96.9 (anomeric C), 87.0 (OCH), 84.8 (OCH), 79.6 (OCH), 71.3 (OCH), 70.9 (OCH_2), 60.5 (OCH_3), 60.3 (OCH_3), 59.7 (OCH_3), 58.9 (OCH_3), 54.7 (OCH_3); MS *m/z* 325 (M^+ - OH, 100), 343 (M + H^+, 14). Anal. Calcd for $C_{17}H_{26}O_7$: C, 59.64; 7.65. Found: C, 59.60; H, 7.78.

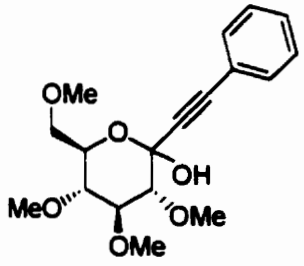
2.3.14 (2R,3S,4S,5R,6R)-3,4,5-Trimethoxy-6-(methoxymethyl)-2-[4-(trifluoromethyl)phenyl]tetrahydro-2H-2-pyranol **98**



4-CF_3-C_6H_4-Li was first prepared as follows: To a -78 °C solution of 4-bromobenzotrifluoride (0.94 mL, 6.72 mmol) in THF (50 mL) was added a solution of 1.41 M *n*-BuLi (4.77 mL, 6.72 mmol) in hexane dropwise. The mixture was stirred for 15 minutes after which the solution was transferred by cannula to a -78 °C solution of δ-lactone **89** (1.50 g, 6.40 mmol) in THF (50 mL). The resulting mixture was stirred for 5 minutes, and then quenched with an aqueous saturated NH_4Cl solution (15 mL). The aqueous layer was then separated and extracted with Et_2O (2 x 40 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford 2.30 g (94% yield) of the unreported compound **98** as a thick syrup. The crude product was sufficiently pure and was employed in the next step without further purification: $[\alpha]_D^{22}$ =

+ 31.1 (c = 0.85, $CHCl_3$); IR (neat film) 3357 (O-H stretch), 2835, 1109 (C-O stretch), 997, 772, 725, 685 cm^{-1}; ^1H NMR δ 7.74 (AA' of AA'XX, 2H, Ar-H), 7.62 (d, 2H, XX' of AA'XX', Ar-H), 3.99 (ddd, 1H, J = 2.1, 4.4, 10.0 Hz, $CH_3OCH_2C\underline{H}O$), 3.0-3.9 (m, 4H, OCH + OCH_2), 3.65 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.08 (s, 3H, OCH_3), 3.03 (d, 1H, J = 9.2 Hz, OCH); ^{13}C NMR δ 146.3 (Ar-C), 130.3 (q, ^2J = 33 Hz, Ar-C), 126.7 (Ar-C), 124.6 (q, ^3J = 3 Hz, Ar-C), 124.0 (q, ^1J = 272 Hz, CF_3), 96.9 (anomeric-C), 86.8 (OCH), 85.0 (OCH), 79.8 (OCH), 71.5 (OCH), 71.3 (OCH_2), 60.7 (OCH_3), 60.4 (OCH_3), 59.9 (OCH_3), 58.8 (OCH_3); ^{19}F NMR δ -63.53; MS *m/z* 363.1 (M^+ - OH, 100), 381.0 ($M^+ + H^+$, 8). Anal. Calcd for $C_{17}H_{23}O_6F_3$: C, 53.68; H, 6.10. Found: C, 53.79; H, 6.22.

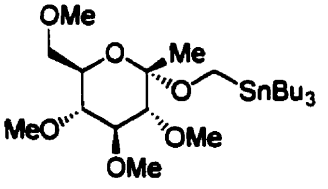
2.3.15 (2R,3S,4S,5R,6R)-3,4,5-Trimethoxy-6-(methoxymethyl)-2-(2-phenyl-1-ethynyl)tetrahydro-2H-2-pyranol ***99***



Phenylethynyllithium was first prepared as follows: To a -78 °C solution of freshly distilled phenylacetylene (1.24 mL, 11.3 mmol) in Et_2O (80 mL) was added a solution of 1.15 M *n*-BuLi (9.83 mL, 11.3 mmol) in hexane dropwise. The mixture was stirred for 15 minutes after which the solution was transferred by cannula to a -78 °C solution of δ-lactone **89** (2.52 g, 10.8 mmol) in Et_2O (80 mL). The resulting mixture was stirred for 15 minutes, and then quenched with an aqueous saturated NH_4Cl solution (15 mL). The aqueous layer was then separated and extracted with Et_2O (2

x 40 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford 2.73 g (75% yield) of the unreported compound **99** as a thick syrup produced as an approximate 1:1 mixture of diastereomers. The crude product was sufficiently pure and was employed in the next step without further purification: IR (neat film) 3323 (O-H stretch), 2232 (C≡C stretch), 1104 (C-O stretch), 760, 692 cm^{-1}; ^1H NMR δ 7.3-7.5 (m, 5H, Ar-H), 3.1-3.9 (m, 6H, OCH + OCH_2), 3.75 (s, 3H, OCH_3), 3.69* (s, 3H, OCH_3), 3.67* (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3) ; ^{13}C NMR δ 132.0* (Ar-C), 131.7 (Ar-C), 128.8* (Ar-C), 128.7 (Ar-C), 128.1 (Ar-C), 128.0* (Ar-C), 121.7 (Ar-C), 121.4* (Ar-C), 95.5* (anomeric-C, β-anomer), 91.7 (anomeric-C, α-anomer), 80.0* (OCH), 87.5 (OCH), 86.2* (OCH), 86.1 (OCH), 85.5 (OCH), 84.6* (OCH), 84.0 (OCH), 83.2 (OCH), 79.3 (OCH), 79.3* (OCH), 71.3* (OCH_2), 71.1 (OCH_2), 61.3 (OCH_3), 60.8* (OCH_3), 60.7 (OCH_3), 60.2* (OCH_3), 60.2 (OCH_3), 59.0 (OCH_3), 58.9* (OCH_3); MS *m/z* 319.0 (M^+ - OH, 30), 359 (M + Na^+, 49); Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.18; H, 7.15.

2.3.16 Tributyl([(2S,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-methyltetrahydro-2H-2-pyranyl]oxymethyl)stannane ***101***



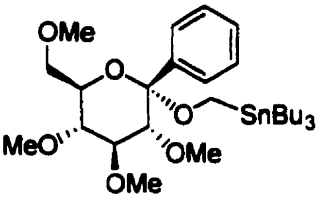
An addition funnel (50 mL) equipped with a side arm was filled with 3 Å molecular sieves and attached to a reflux condenser and a 2-neck round bottom flask (100 mL). The stopcock on the addition funnel was left open and Et_2O (30 mL) was then transferred to the round bottom flask

followed by the hemiketal **91** (485 mg, 1.94 mmol) and Bu_3SnCH_2OH (1.57 mL, 5.82 mmol). An anhydrous solution of 0.95 M HCl (2.04 mL, 1.94 mmol) in ether was then transferred to the round bottom flask and the mixture was then set to reflux. The reaction mixture was monitored periodically for the presence of HCl by litmus paper and additional 0.95 M HCl solution (2.04 mL, 1.94 mmol) was added if the reaction mixture had ceased to be acidic. The reaction was observed to be complete by TLC after 24 h, and the reaction mixture was then neutralized with anhydrous $NaHCO_3$, followed by filtration of the solid material. The filtrate was then concentrated *in vacuo* and the crude material was purified by silica gel chromatography (gradient elution: 9% EtOAc/hexane to 14% EtOAc/hexane) to isolate 869 mg of unknown **101** (81% yield) as a colorless oil: $[\alpha]_D^{22}$ = + 47.2 (c = 1.15, $CHCl_3$); IR (neat film) 2872, 1107 (C-O stretch), 1095 (C-O stretch) cm^{-1}; ^1H NMR δ 3.4-3.6 (m, 5H, OCH_2 + OCH), 3.61 (s, 3H, OMe), 3.55 (s, 3H, OMe), 3.52 (s, 3H, OMe), 3.40 (s, 3H, OMe), 3.31 (dt, 1H, J = 3.1, 10.0 Hz, $CH_3OCH_2C\underline{H}O$), 3.13 (dd, 1H, J = 8.9, 9.9 Hz, OCH), 2.93 (d, 1H, J = 9.5 Hz, OCH), 1.15-1.70 (m, 12 H, $Sn(CH_2C\underline{H}_2C\underline{H}_2CH_3)_3$), 1.40 (s, 3H, CMe), 0.75-1.05 (m, 15H($C\underline{H}_2CH_2CH_2C\underline{H}_3$)$_3$); ^{13}C NMR δ 101.4 (^3J = 38 Hz, anomeric-C), 86.5 (OCH), 84.5 (OCH), 79.9 (OCH), 71.3 (OCH), 71.2 ($O\underline{C}H_2CHO$), 60.8 (OCH_3), 60.2 (OCH_3), 59.9 (OCH_3), 59.0 (OCH_3), 48.9 (^1J = 354, 370 Hz, $O\underline{C}H_2SnBu_3$), 29.0 (^2J = 22 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.2 ($^3J$ = 54 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 18.9 ($C\underline{C}H_3$), 13.3 ($Sn(CH_2)_3\underline{C}H_3$), 9.0 ($^1J$ = 310, 326 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$); MS (FAB) *m/z* 383.1 (M^+ - 3 C_4H_7, 4), 440.1 (M^+ - 2 C_4H_9, 2), 497.2 (M^+ - C_4H_9, 24), 553.1 (M^+ - H, 1). Anal. Calcd for $C_{24}H_{50}O_6Sn$: C, 52.09; H, 9.11. Found: C, 52.11, 8.94.

Furthermore, the unreported minor by-product tributyl([(2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-trimethoxy-6-(methoxymethyl)-2-methyltetrahydro-2H-2-pyranyl]oxymethyl)stannane (**101a**) was isolated as the upper R_f material and as a colorless oil: ^1H NMR δ 3.05-3.75 (m, 8H, OCH_2 + OCH), 3.61 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 1.15-1.75 (m, 12 H,

$Sn(CH_2C\underline{H}_2C\underline{H}_2CH_3)_3$), 1.30 (s, 3H, CMe), 0.75-1.05 (m, 15H, $Sn(C\underline{H}_2CH_2CH_2C\underline{H}_3)_3$); ^{13}C NMR δ 102.4 (anomeric-C), 85.9 (OCH), 84.4 (OCH), 80.1 (OCH), 73.2 (OCH), 72.1 (OCH_2), 60.6 (OCH_3), 60.3 (OCH_3), 60.0 (OCH_3), 59.5 (OCH_3), 49.5 ($O\underline{C}H_2SnBu_3$), 29.1 (^2J = 22 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($^3J$ = 62 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 15.7 ($C\underline{C}H_3$), 13.7 ($Sn(CH_2)_3\underline{C}H_3$), 8.9 ($^1J$ = 310, 326 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$).

2.3.17 Tributyl([(2S,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxymethyl)stannane ***102***



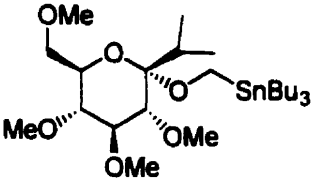
Two experimental procedures are given for the preparation of this unreported compound. The following procedure provided the result reported in Table 3, entry 2: An addition funnel (125 mL) equipped with a side arm was filled with 3 Å molecular sieves and attached to a reflux condenser and a 2-neck round bottom flask (250 mL). The stopcock on the addition funnel was left open and Et_2O (150 mL) was then transferred to the round bottom flask followed by the hemiketal **92** (4.05 g, 13.0 mmol) and Bu_3SnCH_2OH (4.17 g, 13.0 mmol). An anhydrous solution of 4.17 M HCl (3.20 mL, 13.0 mmol) in ether was then transferred to the round bottom flask and the mixture was then set to reflux. The reaction mixture was monitored periodically for the presence of HCl by litmus paper and additional 4.17 M HCl solution (3.20 mL, 13.0 mmol) was added if the reaction mixture had ceased to be acidic. The reaction was observed to be complete by TLC after 2 days, and the reaction mixture was then neutralized with anhydrous $NaHCO_3$, followed by filtration of the

solid material. The filtrate was then concentrated *in vacuo* and the crude material was purified by silica gel chromatography (gradient elution: hexane to 3.5% to 5% EtOAc/hexane) to isolate 4.71 g of **102** (59% yield) as a colorless oil.

The following procedure provided the result reported in Table 3, entry 3: To a cooled mixture (0°C) of hemiketal **92** (6.20 g, 19.8 mmol) and Bu_3SnCH_2OH (5.00 g, 15.6 mmol) in the presence of 3 Å crushed molecular sieves (30 g) in CH_2Cl_2 (200 mL) was added triflic acid (0.45 mL, 5.09 mmol) dropwise. The mixture was stirred for 5 minutes, after which the reaction was quenched with dry Et_3N (1 mL), followed by removing all solid material by filtration. The crude product was then purified by silica gel chromatography as noted above to afford 6.90 g of **102** (57% yield, based on hemi-ketal **92**) as a colorless oil.

Compound **102** exhibited the following spectral data: $[\alpha]_D^{22}$ = + 54.2 (c = 1.04, $CHCl_3$); IR (neat film) 3061, 2848, 1079 (C-O stretch), 1006 (C-O stretch), 728, 700 cm^{-1}; ^1H NMR δ 7.5-7.6 (m, 2H, Ar-H), 7.3-7.4 (m, 3H, Ar-H), 3.2-3.8 (m, 7H, OCH_2 + OCH), 3.63 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.01 (s, 3H, OCH_3), 2.84 (d, 1H, J = 9.5 Hz, OCH (2-position)), 1.2-1.6 (m, 12 H, $SnCH_2C\underline{H}_2C\underline{H}_2CH_3$), 0.75-1.1 (m, 15H, $(SnC\underline{H}_2CH_2CH_2C\underline{H}_3)_3$); ^{13}C NMR δ 138.5 (Ar-C), 127.7 (Ar-C), 127.6 (Ar-C), 102.1 (anomeric-C), 87.8 (OCH), 85.0 (OCH), 80.0 (OCH), 71.8 (OCH), 71.6 (OCH_2), 61.0 (OCH_3), 60.6 (OCH_3), 60.2 (OCH_3), 59.5 (OCH_3), 50.3 ($O\underline{C}H_2SnBu_3$), 29.1 (^2J = 20 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.4 ($^3J$ = 54 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 13.7 ($Sn(CH_2)_3\underline{C}H_3$), 9.1 ($^1J$ = 312, 326 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$); MS (FAB) *m/z* 105 (100), 295.1 (M^+ - OCH_2SnBu_3, 67), 445.0 (M^+ - 3 C_4H_9, 3), 559.1 (M^+ - C_4H_9, 10). Anal. Calcd for $C_{29}H_{52}O_6Sn$: C, 56.60; H, 8.52. Found: C, 56.37, 8.35.

2.3.18 Tributyl([(2S,3S,4S,5R,6R)-2-isopropyl-3,4,5-trimethoxy-6-(methoxymethyl)tetrahydro-2H-2-pyranyl]oxymethyl)stannane ***103***



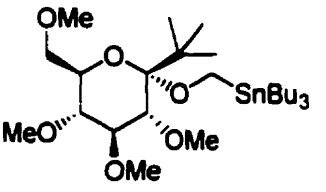
Two experimental procedures are given for the preparation of this unreported compound. The following procedure provided the result reported in Table 3, entry 4: An addition funnel (50 mL) equipped with a side arm was filled with 3 Å molecular sieves and attached to a reflux condenser and a 2-neck round bottom flask (25 mL). The stopcock on the addition funnel was left open and Et_2O (15 mL) was then transferred to the round bottom flask followed by the hemiketal **93** (91 mg, 0.327 mmol) and Bu_3SnCH_2OH (105 mg, 0.327 mmol). An anhydrous solution of 2.70 M HCl (0.12 mL, 0.327 mmol) in ether was then transferred to the round bottom flask and the mixture was then set to reflux. The reaction mixture was monitored periodically for the presence of HCl by litmus paper and additional 2.70 M HCl solution (0.12 mL, 0.327 mmol) was added if the reaction mixture had ceased to be acidic. The reaction was observed to be complete by TLC after 24 h, and the reaction mixture was then neutralized with anhydrous $NaHCO_3$, followed by filtration of the solid material. The filtrate was then concentrated *in vacuo* and the crude material was purified by silica gel chromatography (gradient elution: 5% to 7% to 9% EtOAc/hexane) to isolate 67 mg (35% yield) of **103**.

The following procedure provided the result reported in Table 3, entry 5: To a cooled mixture (0°C) of hemiketal **93** (77 mg, 0.277 mmol) and Bu_3SnCH_2OH (85 mg, 0.264 mmol) in the presence of 3 Å crushed molecular sieves (2 g) in Et_2O (10 mL) was added triflic acid (19 μL, 0.215 mmol)

dropwise. The mixture was stirred for 1 h, after which the reaction was quenched with a 6 M solution of NaOH (1 mL). The mixture was then diluted with H_2O (10 mL), and the molecular sieves were filtered off. The aqueous layer was separated, and then extracted with Et_2O. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was then purified as noted above to afford 68 mg (44% yield) of **103** as a colorless oil.

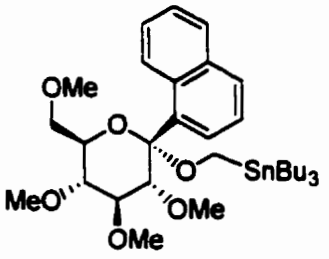
Compound **103** exhibited the following spectral data: $[\alpha]_D^{22}$ = + 40.3 (c = 0.94, $CHCl_3$); IR (neat film) 1071 (C-O stretch), 999 (C-O stretch) cm^{-1}; ^1H NMR δ 3.2-3.8 (m, 6H, OCH_2 + OCH), 3.61 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.20 (d, 1H, J = 9.4 Hz, OCH), 3.00 (t, 1H, J = 9.5 Hz, OCH), 2.26 (spt, 1H, J = 7.2 Hz, C<u>H</u>$(CH_3)_2$), 0.8-1.6 (m, 33H $Sn((C\underline{H}_2)_3C\underline{H}_3)_3$ + $CH(C\underline{H}_3)_2$); ^{13}C NMR δ 103.9 (anomeric-C), 85.6 (OCH), 81.4 (OCH), 80.4 (OCH), 71.8 (OCH), 71.7 (OCH_2), 60.3 (OCH_3), 59.9 (OCH_3), 59.3 (OCH_3), 59.2 (OCH_3), 47.9 (^1J = 385, 374 Hz, $O\underline{C}H_2SnBu_3$), 31.1 ($\underline{C}H(CH_3)_2$), 29.1 (^2J = 20 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($^3J$ = 54 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 17.9 ($CH(\underline{C}H_3)$), 17.1 ($CH(\underline{C}H_3)$), 13.5 ($Sn(CH_2)_3\underline{C}H_3$), 9.1 ($^1J$ = 310, 326 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$); MS *m/z* 525 ($M^+$ - C_4H_9, 23). Anal. Calcd for $C_{26}H_{54}O_6Sn$: C, 53.71; H, 9.37. Found: C, 53.57, 9.40.

*2.3.19 Tributyl([(2S,3S,4S,5R,6R)-2-(tert-butyl)-3,4,5-trimethoxy-6-(methoxymethyl)tetrahydro-2H-2-pyranyl]oxymethyl)stannane **104***



To a cooled mixture (0°C) of hemiketal **94** (2.13 g, 7.29 mmol) and Bu_3SnCH_2OH (3.51 g, 10.93 mmol) in the presence of 3 Å crushed molecular sieves (25 g) in CH_2Cl_2 (150 mL) was added triflic acid (0.32 mL, 3.65 mmol) dropwise. The mixture was stirred for 21 h, after which the reaction was quenched with a 6 M solution of NaOH (5 mL). The molecular sieves were filtered off and the filtrate was concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (gradient elution: 2% to 3% to 4% EtOAc/hexane) to isolate 1.77 g (41% yield) of unreported compound **104** as a colorless oil: $[\alpha]_D^{22}$ = + 29.7 (c = 1.16, $CHCl_3$); IR (neat film) 1104 (C-O stretch), 1058 (C-O stretch) cm^{-1}; ^1H NMR δ 3.5-3.8 (m, 5H, OCH_2 + OCH), 3.61 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.26 (d, 1H, J = 9.4 Hz, OCH), 3.15-3.25 (m, 1H, OCH), 3.03 (t, 1H, J = 9.5 Hz, OCH), 0.8-1.6 (m, 27H $Sn((C\underline{H}_2)_3C\underline{H}_3)_3$), 1.12 (s, 9H, $(C(C\underline{H}_3)_3)$; ^{13}C NMR δ 104.1 (anomeric-C), 85.9 (OCH), 83.3 (OCH), 80.4 (OCH), 73.0 (OCH), 71.6 (OCH_2), 60.1 (OCH_3), 60.0 (OCH_3), 59.6 (OCH_3), 58.7 (OCH_3), 53.6 ($\underline{C}(CH_3)_3$), 39.0 ($O\underline{C}H_2SnBu_3$), 29.1 (^2J = 30 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.9 ($C(\underline{C}H_3)_3$), 27.4 ($^3J$ = 80 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 13.5 ($Sn(CH_2)_3\underline{C}H_3$), 9.1 ($^1J$ = 308, 320 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$); MS *m/z* 311 (100), 539 (M^+ - C_4H_7, 39). Anal. Calcd for $C_{27}H_{56}O_6Sn$: C, 54.46; H, 9.48. Found: C, 54.33, 9.51.

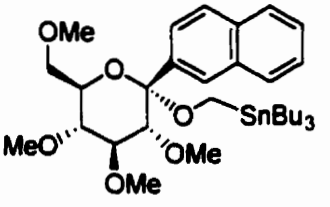
2.3.20 Tributyl([(2S,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-(1-naphthyl)tetrahydro-2H-2-pyranyl]oxymethyl)stannane ***105***



To a cooled mixture (0°C) of hemiketal **95** (3.28 g, 9.04 mmol) and Bu_3SnCH_2OH (2.76 g, 8.61 mmol) in the presence of 3 Å crushed molecular sieves (10 g) in CH_2Cl_2 (200 mL) was added triflic acid (320 μL, 3.62 mmol) dropwise. The mixture was stirred for 20 minutes, after which the reaction was quenched with dry Et_3N (2 mL). The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (gradient elution: 3% to 4% to 5% EtOAc/hexane) to isolate 2.98 g (52% yield) of the unreported compound **105** as a colorless oil: $[\alpha]_D^{22} = +64.3$ (c = 1.15, $CHCl_3$); IR (neat film) 1106 (C-O stretch), 1000 (C-O stretch), 780, 749, 668 cm^{-1}; ^1H NMR δ 8.99 (m, 1H, Ar-H), 7.75-7.95 (m, 3H, Ar-H), 7.4-7.55 (m, 3H, Ar-H), 2.9-3.9 (m, 8H, OCH_2 + OCH), 3.65 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 2.64 (s, 3H, OMe), 0.75-1.65 (m, 27H, $Sn((C\underline{H}_2)_3C\underline{H}_3)_3$); ^{13}C NMR (DMSO, 140°C) δ 133.7 (Ar-C), 133.3 (Ar-C), 130.8 (Ar-C), 128.3 (br, Ar-C), 127.1 (br, Ar-C), 126.4 (br, Ar-C), 126.2 (br, Ar-C), 124.2 (br, Ar-C), 124.0 (br, Ar-C), 123.7 (br, Ar-C), 102.9 (anomeric-C), 87.6 (OCH), 84.0 (OCH), 79.4 (OCH), 71.2 (OCH), 71.1 (OCH_2), 58.9 (OCH_3), 58.6 (OCH_3), 58.3 (OCH_3), 58.0 (OCH_3), 49.9 ($O\underline{C}H_2SnBu_3$), 27.7 (^2J = 22 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 25.7 ($^3J$ = 50 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 12.1 ($Sn(CH_2)_3\underline{C}H_3$), 8.3 ($^1J$ = 312, 326 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$); MS *m/z* 345

(M^+ - OCH_2SnBu_3, 100), 609 (M^+ - C_4H_9, 20). Anal. Calcd for $C_{33}H_{54}O_6Sn$: C, 59.56; H, 8.18. Found: C, 59.39, 7.91.

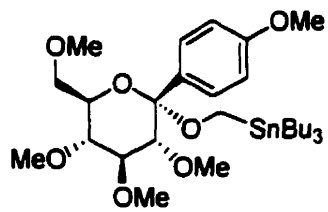
2.3.21 Tributyl([(2S,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-(2-naphthyl)tetrahydro-2H-2-pyranyl]oxymethyl)stannane ***106***



To a cooled mixture (0°C) of hemiketal **96** (2.45 g, 6.76 mmol) and Bu_3SnCH_2OH (2.17 g, 6.76 mmol) in the presence of 3 Å crushed molecular sieves (13 g) in CH_2Cl_2 (130 mL) was added triflic acid (240 μL, 2.70 mmol) dropwise. The mixture was stirred for 20 minutes, after which the reaction was quenched with Et_2NH (2 mL). The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (gradient elution: 2% to 4% to 5% to 6% EtOAc/hexane) to isolate 2.47 g (55% yield) of the unreported compound **106** as a colorless oil: $[\alpha]_D^{22}$ = + 46.9 (c = 1.04, $CHCl_3$); IR (neat film) 3059, 1073 (C-O stretch), 1005 (C-O stretch), 775, 756 cm^{-1}; ^1H NMR δ 8.05 (br, 1H, Ar-H), 7.65-7.95 (m, 4H, Ar-H), 7.4-7.5 (m, 2H, Ar-H), 3.2-3.9 (m, 6H, OCH_2 + OCH), 3.65 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 2.9-3.1 (m, 2H, OCH), 3.00 (s, 3H, OCH_3), 1.2-1.7 (m, 12H, $SnCH_2C\underline{H}_2C\underline{H}_2CH_3$), 0.7-1.1 (m, 15 H, $(SnC\underline{H}_2CH_2CH_2C\underline{H}_3)_3$); ^{13}C NMR δ 136.2 (Ar-C), 133.0 (Ar-C), 128.3 (Ar-C), 127.3 (Ar-C), 127.0 (Ar-C), 126.8 (Ar-C), 125.8 (Ar-C), 125.5 (Ar-C), 102.1 (anomeric-C), 87.9 (OCH), 85.1 (OCH), 80.0 (OCH), 71.9 (OCH), 71.7 (OCH_2), 60.9 (OCH_3), 60.4

(OCH_3), 60.0 (OCH_3), 59.3 (OCH_3), 50.4 ($O\underline{C}H_2SnBu_3$), 29.1 (^2J = 20 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($^3J$ = 54 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 13.5 ($Sn(CH_2)_3\underline{C}H_3$), 9.0 ($^1J$ = 312, 326 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$); MS *m/z* 345 ($M^+$ - OCH_2SnBu_3, 100), 609 (M^+ - C_4H_9, 9). Anal. Calcd for $C_{33}H_{54}O_6Sn$: C, 59.56; H, 8.18. Found: C, 59.56, 8.35.

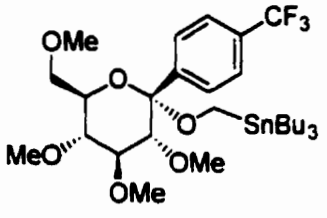
2.3.22 Tributyl([(2S,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-(4-methoxyphenyl)tetrahydro-2H-2-pyranyl]oxymethyl)stannane ***107***



To a cooled mixture (0°C) of hemiketal **97** (2.05 g, 5.99 mmol) and Bu_3SnCH_2OH (1.92 g, 5.99 mmol) in the presence of 3 Å crushed molecular sieves (6 g) in CH_2Cl_2 (100 mL) was added triflic acid (0.21 mL, 2.40 mmol) dropwise. The mixture was stirred for 20 minutes, after which the reaction was quenched with Et_2NH (2 mL). The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (gradient elution: 4% to 6% to 8% to 10% EtOAc/hexane) to isolate 1.77 g (46% yield) of the unreported compound **107** as a colorless oil: $[\alpha]_D^{22}$ = + 50.7 (c = 1.27, $CHCl_3$); IR (neat film) 2843, 1081 (C-O stretch), 803, 771, 758 cm^{-1}; ^1H NMR δ 7.46 (AA' of AA'XX', 2H, *m*-Ph-H), 6.88 (XX' of AA'XX', 2H, *p*-Ph-H), 3.82 (s, 3H, OCH_3), 3.1-3.8 (m, 7H, OCH_2 + OCH), 3.62 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.05 (s, 3H, OCH_3), 2.82 (d, 1H, J = 9.6 Hz, OCH), 1.15-1.7 (m, 12H, $SnCH_2C\underline{H}_2C\underline{H}_2CH_3$), 0.75-1.1 (m, 15H, $(SnC\underline{H}_2CH_2CH_2C\underline{H}_3)_3$); ^{13}C NMR δ 159.2 (Ar-C), 130.6

(Ar-C), 128.7 (Ar-C), 112.9 (Ar-C), 101.9 (anomeric-C), 87.9 (OCH), 85.0 (OCH), 80.0 (OCH), 71.7 (OCH), 71.6 (OCH_2), 60.8 (OCH_3), 60.3 (OCH_3), 59.9 (OCH_3), 59.3 (OCH_3), 54.8 (OCH_3), 50.0 ($O\underline{C}H_2SnBu_3$), 29.0 (^2J = 22 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.2 ($^3J$ = 54 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 13.5 ($Sn(CH_2)_3\underline{C}H_3$), 9.0 ($^1J$ = 312, 326 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$); MS *m/z* 325 ($M^+$ - OCH_2SnBu_3, 100), 589 (M^+ - C_4H_9, 12). Anal. Calcd for $C_{30}H_{54}O_7Sn$: C, 55.83; H, 8.43. Found: C, 55.97, 8.33.

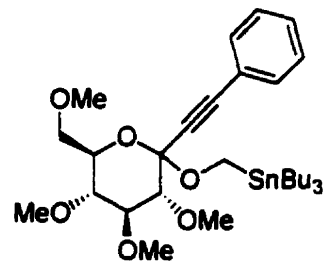
2.3.23 Tributyl[((2S,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-[4-(trifluoromethyl)phenyl]tetrahydro-2H-2-pyranyloxy)methyl]stannane ***108***



To a cooled mixture (0°C) of hemiketal **98** (1.78 g, 4.69 mmol) and Bu_3SnCH_2OH (1.50 g, 4.69 mmol) in the presence of 3 Å crushed molecular sieves (19 g) in CH_2Cl_2 (80 mL) was added triflic acid (266 μL, 3.01 mmol) dropwise. The mixture was stirred for 20 minutes, after which the reaction was quenched with Et_3N (2 mL). The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (gradient elution: 4% to 5% to 6% EtOAc/hexane) to isolate 1.58 g (49% yield) of the unreported compound **108** as a colorless oil: $[\alpha]_D^{22}$ = + 46.8 (c = 1.13, $CHCl_3$); IR (neat film) 2854, 1068 (C-O stretch), 1010 (C-O stretch), 768, 724, 688 cm^{-1}; ^1H NMR δ 7.68 (d, 2H, 8.4 Hz, Ar-H), 7.61 (d, 2H, 8.4 Hz, Ar-H), 3.0-3.8 (m, 7H), 3.63 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.04 (s, 3H, OCH_3), 2.83 (d, 1H, J = 9.5 Hz, OCH). 1.15-1.65 (m, 12 H, $SnCH_2C\underline{H}_2C\underline{H}_2CH_3$), 0.75-1.1 (m, 15H,

($SnC\underline{H}_2CH_2CH_2C\underline{H}_3)_3$); ^{13}C NMR δ 142.7 (Ar-C), 130.1 (q, ^2J = 32 Hz, Ar-C), 128.1 (Ar-C), 124.6 (q, ^3J = 4 Hz, Ar-C), 123.8 (q, ^1J = 272 Hz, Ar-C), 101.8 (anomeric-C), 87.5 (OCH), 85.1 (OCH), 80.1 (OCH), 72.1 (OCH), 71.6 (OCH_2), 61.0 (OCH_3), 60.5 (OCH_3), 60.1 (OCH_3), 59.3 (OCH_3), 50.6 (^1J = 348, 362 Hz, $O\underline{C}H_2SnBu_3$), 29.1 (^2J = 20 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($^3J$ = 54 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 13.5 ($Sn(CH_2)_3\underline{C}H_3$), 9.1 ($^1J$ = 314, 328 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$); ^{19}F NMR δ -63.40; MS *m/z* 331.1 (100), 363.1 (M^+ - OCH_2SnBu_3, 76), 626.9 (M^+ - C_4H_9, 7). Anal. Calcd for $C_{30}H_{51}F_3O_6Sn$: C, 52.72; H, 7.52 Found: C, 52.61, 7.50.

2.3.24 Tributyl([(3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-(2-phenyl-1-ethynyl)tetrahydro-2H-2-pyranyl]oxymethyl)stannane ***109/109a***



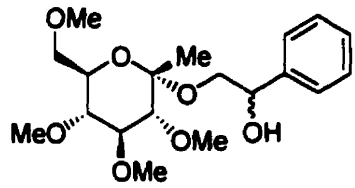
To a cooled mixture (0°C) of hemiketal **99** (2.63 g, 7.82 mmol) and Bu_3SnCH_2OH (2.09 g, 6.52 mmol) in the presence of 3 Å crushed molecular sieves (11 g) in CH_2Cl_2 (150 mL) was added triflic acid (230 μL, 2.61 mmol) dropwise. The mixture was stirred for 10 minutes, after which the reaction was quenched with Et_3N (2 mL). The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (gradient elution: 4% to 5% to 6% to 7% EtOAc/hexane) to isolate 2.80 g (56% yield) of the unreported compounds **109** and **109a** as colorless oils and as an approximate 3:1 (**109**:**109a**) mixture of diastereomers.

The major isomer (higher R_f) **109** exhibited the following data: IR (neat film) 2232 (C≡C stretch), 1070 (C-O stretch), 1042 (C-O stretch), 757, 691 cm^{-1}; ^1H NMR δ 7.2-7.6 (m, 5H, Ar-H), 4.00 (d, 1H, J = 10.3 Hz, OCH), 3.77 (d, 1H, J = 10.3 Hz, OCH), 3.3-3.8 (m, 5H, OCH_2 + OCH), 3.68 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.22 (t, 1H, J = 9.3 Hz, OCH), 1.15-1.7 (m, 15H, $SnCH_2C\underline{H}_2C\underline{H}_2CH_3$), 0.75-1.1 (m, 12H, $(SnC\underline{H}_2CH_2CH_2C\underline{H}_3)_3$).

The minor isomer (lower R_f) **109a** exhibited the following data: ^1H NMR δ 7.4-7.6 (m, 2H, Ar-H), 7.2-7.4 (m, 3H, Ar-H), 4.0-4.1 (m, 2H, OCH), 3.75 (dt, 1H, J = 2.9, 10.0 Hz, $CH_3OCH_2C\underline{H}O$), 3.3-3.7 (m, 3H, OCH_2 + OCH), 3.64 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.21 (t, 1H, J = 9.2 Hz, OCH), 3.06 (d, 1H, J = 9.5 Hz, OCH), 1.15-1.7 (m, 15H, $SnCH_2C\underline{H}_2C\underline{H}_2CH_3$), 0.7-1.1 (m, 12H, $(SnC\underline{H}_2CH_2CH_2C\underline{H}_3)_3$).

A mixture of **109** and **109a** exhibited the following data: ^{13}C NMR δ 131.8* (Ar-C), 131.6 (Ar-C), 128.5* (Ar-C), 128.4 (Ar-C), 128.0 (Ar-C), 121.9 (Ar-C), 101.4* (anomeric-C), 98.2 (anomeric-C), 86.3 (OCH), 85.5* (OCH), 85.4 (OCH), 85.1* (OCH), 84.0 (OCH), 79.3 (OCH), 79.2* (OCH), 73.6 (OCH), 71.3 (OCH_2), 71.2* (OCH_2), 71.0 (OCH_2), 60.9 (OCH_3), 60.5* (OCH_3), 60.4* (OCH_3), 60.3 (OCH_3), 59.9 (OCH_3), 59.0* (OCH_3), 58.9 (OCH_3), 53.7* ($O\underline{C}H_2SnBu_3$) 52.6, ($O\underline{C}H_2SnBu_3$), 28.9 (^2J = 22 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 28.8* ($SnCH_2\underline{C}H_2CH_2CH_3$), 27.1 ($^3J$ = 54 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 27.0* ($Sn(CH_2)_2\underline{C}H_2CH_3$), 13.4 ($Sn(CH_2)_3\underline{C}H_3$), 9.0 ($^1J$ = 314, 328 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$); MS *m/z* 319.1 ($M^+$ - OCH_2SnBu_3, 100), 583.0 (M^+ - C_4H_9, 50), 663.1 ($M + Na^+$, 26). Anal. Calcd for $C_{31}H_{52}O_6Sn$: C, 58.23; H, 8.20. Found: C, 58.33; H, 7.97.

2.3.25 1-Phenyl-2-[(2S,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-methyltetrahydro-2H-2-pyranyl]oxy-1-ethanol ***110***



This unreported compound was prepared or attempted to be prepared in 26 different experimental procedures and all experiments are described below. Also included in this section are spectral data for unreported by-products **118** and **149**, which were formed in some of the experimental procedures.

Experiment 1 (results reported in Table 4, entry 1; Table 5, entry 4; Table 6, entry 2; and Table 7, entry 4): To a cooled solution (-78 °C) of **101** (149 mg, 0.269 mmol) in hexane (2 mL) was added a solution of 1.73 M *n*-BuLi in hexane (0.17 mL, 0.296 mmol) dropwise and the resulting solution was stirred for 15 minutes. Benzaldehyde (30 μL, 0.296 mmol) was next added dropwise and the resulting solution was stirred for an additional 20 min after which an aqueous saturated solution of NH_4Cl (1 mL) was added. The mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 63 mg (67 % yield) of Bu_4Sn, 33 mg (46% yield) of protonated by-product **118**, and 28 mg (28% yield) of addition adduct **110**, formed in 21% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Experiment 2 (results reported in Table 5, entry 1; and Table 7, entry 1): To a cooled solution (-78 °C) of **101** (157 mg, 0.284 mmol) in THF (2 mL) was added a solution of 1.10 M *n*-BuLi in hexane (0.28 mL, 0.310 mmol) dropwise and the resulting solution was stirred for 10 minutes. The Sn-Li exchange reaction did not appear to be complete by TLC and an additional amount of 1.10 M *n*-BuLi in hexane (0.28 mL, 0.310 mmol) was added dropwise and the reaction stirred for an additional 10 minutes. The Sn-Li exchange reaction then appeared to be complete by TLC and benzaldehyde (30 μL, 0.296 mmol) was added dropwise, and the resulting solution was stirred for an additional 20 min, after which an aqueous saturated solution of NH_4Cl (1 mL) was added. The mixture was then extracted with Et_2O (3 x 20 mL), followed by washing the combined organic extracts with brine (5 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 111 mg (100 % yield) of Bu_4Sn, and 63 mg (60% yield) of addition adduct **110**, formed in 8% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 3 (results reported in Table 5, entry 2; Table 6, entry 1; and Table 7, entry 2): To a cooled solution (-78 °C) of **101** (151 mg, 0.273 mmol) in Et_2O (2 mL) was added a solution of 1.73 M *n*-BuLi in hexane (0.17 mL, 0.30 mmol) dropwise and the resulting solution was stirred for 15 minutes. Benzaldehyde (30 μL, 0.30 mmol) was next added dropwise and the resulting solution was stirred for an additional 20 min after which an aqueous saturated solution of NH_4Cl (1 mL) was added. The mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient

elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 77 mg (81 % yield) of Bu_4Sn, 30 mg (42% yield) of protonated by-product **118**, and 50 mg (53% yield) of addition adduct **110**, formed in 4% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Experiment 4 (results reported in Table 5, entry 3; Table 6, entry 3; and Table 7, entry 3): To a cooled solution (-78 °C) of **101** (200 mg, 0.361 mmol) in toluene (6 mL) was added a solution of 1.60 M *n*-BuLi in hexane (0.25 mL, 0.397 mmol) dropwise and the resulting solution was stirred for 30 minutes. The Sn-Li exchange reaction did not appear to be complete by TLC and an additional amount of 1.60 M *n*-BuLi in hexane (0.25 mL, 0.397 mmol) was added dropwise and the reaction was stirred for an additional 15 minutes. Benzaldehyde (40 μL, 0.397 mmol) was next added dropwise and the resulting solution was stirred for an additional 15 min after which an aqueous saturated solution of NH_4Cl (1 mL) was added. The mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 135 mg (100 % yield) of Bu_4Sn, and a 58 mg mixture of hemi-ketal **91** (29% yield) with addition adduct **110** (14% yield). Compound **110** was formed in 22% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Experiment 5 (results reported in Table 12, entry 1): To a cooled solution (-78 °C) of **101** (127 mg, 0.230 mmol) in Et_2O (3 mL) was added a 1.60 M solution of *n*-BuLi in hexane (0.16 mL, 0.256 mmol) dropwise and the resulting solution was stirred for 15 minutes. The Sn-Li exchange reaction did not appear to be complete by TLC and an additional amount of 1.60 M *n*-BuLi in

hexane (0.13 mL, 0.207 mmol) was added dropwise and the reaction stirred for an additional 15 minutes. The Sn-Li exchange reaction then appeared to be complete by TLC. Next a 2.0 M solution of freshly generated $MgBr_2 \cdot (OEt_2)$[28] (0.13 mL, 0.256 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. After 30 min the flask was placed in a -78 °C bath and cooled for 10 minutes after which benzaldehyde (26 μL, 0.256 mmol) was added dropwise and the resulting solution was stirred for an additional 15 minutes. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the mixture was then extracted with Et_2O (2 x 20 mL), followed by washing the combined organic extracts with brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 62 mg (78 % yield) of Bu_4Sn, 41 mg (67% yield) of protonated by-product **118**, and a trace amount of hemi-ketal **91**. Addition adduct **110** was not formed in this experiment.

Experiment 6 (results reported in Table 12, entry 2): To a cooled solution (-78 °C) of **101** (210 mg, 0.379 mmol) in toluene (6 mL) was added a 1.60 M solution of *n*-BuLi in hexane (0.26 mL, 0.417 mmol) dropwise and the resulting solution was stirred for 30 minutes. The Sn-Li exchange reaction did not appear to be complete by TLC and an additional amount of 1.60 M *n*-BuLi in hexane (0.26 mL, 0.417 mmol) was added dropwise and the reaction was stirred for an additional 15 minutes. Next a 2.0 M solution of freshly generated $MgBr_2 \cdot (OEt_2)$[28] (0.13 mL, 0.256 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. After 30 min the flask was placed in a -78 °C bath and cooled for 10 minutes after which benzaldehyde (42 μL, 0.417 mmol) was added dropwise and the resulting solution was stirred for an additional 15 minutes. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the mixture was then extracted with Et_2O (2 x 20 mL), followed by washing the combined organic extracts with brine (10 mL). The organic layer was

then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 142 mg (100 % yield) of Bu_4Sn, and a 18 mg mixture of hemi-ketal **91** (11% yield) with addition adduct **110** (2% yield). Compound **110** was formed in 29% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Experiment 7 (results reported in Table 12, entry 7): To a cooled solution (-78 °C) of **101** (163 mg, 0.295 mmol) in hexane (5 mL) was added a 1.61 M solution of *n*-BuLi in hexane (0.20 mL, 0.325 mmol) dropwise and the resulting solution was stirred for 25 minutes. The Sn-Li exchange reaction did not appear to be complete by TLC and an additional amount of 1.61 M *n*-BuLi in hexane (0.18 mL, 0.295 mmol) was added dropwise and the reaction was stirred for an additional 25 minutes. Next a 2.0 M solution of freshly generated $MgBr_2 \cdot (OEt_2)$[28] (0.16 mL, 0.325 mmol) was added to the reaction mixture, after which a white precipitate had formed in the reaction, and the flask was placed in a -40 °C bath. After 30 min the flask was placed in a -78 °C bath and cooled for 10 minutes after which benzaldehyde (33 μL, 0.325 mmol) was added dropwise and the resulting solution was stirred for an additional 15 minutes. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 38 mg (48% yield) of protonated by-product **118**, a 56 mg mixture of hemi-ketal **91** (20% yield) with addition adduct **110** (31% yield). Compound **110** was formed in 12% de (de determined

by Method A, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 8 (results reported in Table 12, entry 4): To a cooled solution (-78 °C) of **101** (180 mg, 0.325 mmol) in THF (5 mL) was added a 1.40 M solution of *n*-BuLi in hexane (0.35 mL, 0.488 mmol) dropwise and the resulting solution was stirred for 30 minutes. Next a 0.7 M solution of freshly generated $ZnCl_2 \bullet (OEt_2)$[29] (0.65 mL, 0.488 mmol) was added to the reaction mixture and the flask was placed in a -30 °C bath. A precipitate was not observed to be formed during this time. After 30 min the flask was placed in a -78 °C bath and cooled for 10 min after which benzaldehyde (36 μL, 0.358 mmol) was added dropwise and the resulting solution was stirred for an additional 15 min. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 139 mg (100% yield) of Bu_4Sn, 28 mg (32% yield) of protonated by-product **118**, and 55 mg (68% yield) of hemi-ketal **91**. Addition adduct **110** was not formed in this experiment.

Experiment 9 (results reported in Table 12, entry 5): To a cooled solution (-78 °C) of 1-*O*-tributylstannylmethyl derivative **101** (140 mg, 0.253 mmol) in Et_2O (5 mL) was added a 1.40 M solution of *n*-BuLi in hexane (0.27 mL, 0.380 mmol) dropwise and the resulting solution was stirred for 30 minutes. Next a 0.7 M solution of freshly generated $ZnCl_2 \bullet (OEt_2)$[29] (0.54 mL, 0.380 mmol) was added to the reaction mixture and the flask was placed in a -30 °C bath. A precipitate was then observed to be formed. After 30 min the flask was placed in a -78 °C bath and cooled for 10 min after which benzaldehyde (34 μL, 0.338 mmol) was added dropwise and the resulting solution was

stirred for an additional 15 min. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 95 mg (100% yield) of Bu_4Sn, 19 mg (28% yield) of protonated by-product **118**, and 46 mg (72% yield) of hemi-ketal **91**. Addition adduct **110** was not formed in this experiment.

Experiment 10 (results reported in Table 12, entry 6): To a cooled solution (-78 °C) of 1-*O*-tributylstannylmethyl derivative **101** (170 mg, 0.307 mmol) in toluene (10 mL) was added a 1.40 M solution of *n*-BuLi in hexane (0.33 mL, 0.461 mmol) dropwise and the resulting solution was stirred for 30 minutes. Next a 0.7 M solution of freshly generated $ZnCl_2{\bullet}(OEt_2)$[29] (0.66 mL, 0.461 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. After 30 min the flask was placed in a -78 °C bath and cooled for 10 min after which benzaldehyde (34 μL, 0.338 mmol) was added dropwise and the resulting solution was stirred for an additional 15 min. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 90 mg (84% yield) of Bu_4Sn, and 12 mg (16% yield) of hemi-ketal **91**. Addition adduct **110** was not formed in this experiment.

Experiment 11 (results reported in Table 12, entry 7): To a cooled solution (-78 °C) of 1-*O*-tributylstannylmethyl derivative **101** (330 mg, 0.596 mmol) in hexane (10 mL) was added a 1.40 M solution of *n*-BuLi in hexane (0.64 mL, 0.894 mmol) dropwise and the resulting solution was stirred

for 30 minutes. A precipitate was observed to be formed after the addition of *n*-BuLi. Next a 0.7 M solution of freshly generated $ZnCl_2 \cdot (OEt_2)$[29] (1.28 mL, 0.894 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. After 30 min the flask was placed in a -78 °C bath and cooled for 10 min after which benzaldehyde (67 μL, 0.656 mmol) was added dropwise and the resulting solution was stirred for an additional 15 min. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 172 mg (83% yield) of Bu_4Sn, and a 80 mg mixture containing hemi-ketal **91** (12% yield) and addition adduct **110** (25% yield). Compound **110** was formed in 17% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 12 (results reported in Table 12, entry 8): To a cooled solution (-78 °C) of **101** (220 mg, 0.398 mmol) in toluene (8 mL) was added a 1.40 M solution of *n*-BuLi in hexane (0.43 mL, 0.596 mmol) dropwise and the resulting solution was stirred for 30 minutes. Next solid anhydrous $CeCl_3$[30] (147 mg, 0.596 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. After 30 minutes the flask was placed in a -78 °C bath and cooled for 10 min after which benzaldehyde (45 μL, 0.438 mmol) was added dropwise and the resulting solution was stirred for an additional 15 min. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient

elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 147 mg (100% yield) of Bu_4Sn, and a 180 mg mixture containing hemi-ketal **91** (36% yield) and addition adduct **110** (64% yield). Compound **110** was formed in 7% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Experiment 13 (results reported in Table 12, entry 9): To a cooled solution (-78 °C) of **101** (420 mg, 0.759 mmol) in hexane (5 mL) was added a 1.40 M solution of *n*-BuLi in hexane (0.81 mL, 1.14 mmol) dropwise and the resulting solution was stirred for 30 minutes. Next solid anhydrous $CeCl_3$[30] (281 mg, 1.14 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. After 30 minutes the flask was placed in a -78 °C bath and cooled for 10 min after which benzaldehyde (85 μL, 0.835 mmol) was added dropwise and the resulting solution was stirred for an additional 15 min. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 298 mg (100% yield) of Bu_4Sn, and a 128 mg mixture containing hemi-ketal **91** (58% yield) and addition adduct **110** (6% yield). Compound **110** was formed in 10% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Experiment 14 (results reported in Table 12, entry 10): To a cooled solution (-78 °C) of **101** (155 mg, 0.280 mmol) in toluene (5 mL) was added a 1.40 M solution of *n*-BuLi in hexane (0.30 mL, 0.420 mmol) dropwise and the resulting solution was stirred for 25 minutes. Next a 1.0 M solution of Et_2AlCl (0.31 mL, 0.308 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. After 30 min the flask was placed in a -78 °C bath and cooled for 10 min,

after which benzaldehyde (31 μL, 0.308 mmol) was added dropwise and the resulting solution was stirred for an additional 15 minutes. An aqueous saturated solution NH_4Cl (1 mL) was added, after which a thick precipitate of Al salts was formed. The mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 62 mg (64% yield) of Bu_4Sn, and a 2 mg mixture containing hemi-ketal **91** (1% yield) and addition adduct **110** (2% yield). Compound **110** was formed in 2% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Experiment 15 (results reported in Table 12, entry 11): To a cooled solution (-78 °C) of **101** (340 mg, 0.614 mmol) in hexane (5 mL) was added a 1.40 M solution of *n*-BuLi in hexane (0.66 mL, 0.922 mmol) dropwise and the resulting solution was stirred for 25 minutes. A precipitate was observed to be formed after *n*-BuLi was added. Next a 1.0 M solution of Et_2AlCl (0.68 mL, 0.675 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. After 30 min the flask was placed in a -78 °C bath and cooled for 10 min, after which benzaldehyde (69 μL, 0.675 mmol) was added dropwise and the resulting solution was stirred for an additional 15 minutes. An aqueous saturated solution of NH_4Cl (1 mL) was added, after which a thick precipitate of Al salts was formed. The mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 106 mg (50% yield) of Bu_4Sn, and a 10 mg mixture containing hemi-ketal **91** (3% yield) and

addition adduct **110** (3% yield). Compound **110** was formed in 10% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Experiment 16 (results reported in Table 12, entry 12): To a cooled solution (-78 °C) of **101** (200 mg, 0.361 mmol) in hexane (5 mL) was added a 1.40 M solution of *n*-BuLi (0.39 mL, 0.542 mmol) dropwise and the resulting solution was stirred for 25 minutes. A precipitate was observed to be formed after the addition of *n*-BuLi. Next a 1.0 M solution $Ti(O^iPr)_3Cl$ (0.40 mL, 0.397 mmol) was added to the reaction mixture and the flask was placed in a -40°C bath. A dark red/brown precipitate was observed to be formed after the addition of $Ti(O^iPr)_3Cl$. After allowing 30 min for Li-Ti exchange to occur, the flask was placed in a -78 °C bath and cooled for 10 minutes after which benzaldehyde (40 μL, 0.397 mmol) was added dropwise. The mixture appeared to turn to a darker color during the addition of benzaldehyde, and the resulting solution was then stirred for 15 minutes. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (1 mL) and the mixture was brought to rt. The mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with brine (15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 110 mg (88% yield) of Bu_4Sn, and a 7 mg mixture containing hemi-ketal **91** (16% yield) and addition adduct **110** (trace yield). Compound **110** was formed in 75% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 17 (results reported in Scheme 43): To a cooled solution (-78 °C) of **101** (350 mg, 0.632 mmol) in hexane (12 mL) was added a 1.20 M solution of *n*-BuLi (0.79 mL, 0.948 mmol) dropwise and the resulting solution was stirred for 25 minutes. MeOD (1 mL) was then added, and

the mixture was slowly warmed to rt. An aqueous saturated solution of NH_4Cl (1 mL) was added, followed by extracting the mixture with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), and the organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc) to isolate in order of elution: 98 mg (55% yield) of Bu_4Sn, and a 62 mg mixture containing protonated product **118** (2% yield) and deuterated product **148** (35% yield) (6:94 ratio of **118**:**148**).

Experiment 18 (result reported in Scheme 44): To a cooled solution (-78 °C) of **101** (300 mg, 0.542 mmol) in hexane (12 mL) was added a 1.20 M solution of *n*-BuLi (0.68 mL, 0.813 mmol) dropwise and the resulting solution was stirred for 15 minutes. A precipitate was observed to be formed after the addition of *n*-BuLi. Next a 1.0 M solution $Ti(O^iPr)_3Cl$ (0.40 mL, 0.397 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. A dark red/brown precipitate was observed to be formed after the addition of $Ti(O^iPr)_3Cl$. After allowing 40 min for Li-Ti exchange to occur, MeOD (1 mL) was added dropwise, and the mixture was brought to rt. Water was then added (5 mL), and the mixture was extracted with Et_2O (2 x 15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane) to isolate in order of elution: 109 mg (58% yield) of Bu_4Sn, a 36 mg mixture containing protonated product **118** (5% yield) and deuterated product **148** (20% yield) (20:80 ratio of **118**:**148**), and 6 mg (4% yield) of hemi-ketal **91**.

Experiment 19 (results reported in Table 13, entry 1): To a cooled solution (-78 °C) of **101** (225 mg, 0.407 mmol) in hexane (5 mL) was added a 1.20 M solution of *n*-BuLi (0.51 mL, 0.611 mmol) dropwise and the resulting solution was stirred for 25 minutes. Next a 1.0 M solution $Ti(O^iPr)_3Cl$ (0.45 mL, 0.448 mmol) was added to the reaction mixture and the flask was placed in a

-40 °C bath. A dark red/brown precipitate was observed to be formed after the addition of $Ti(O^iPr)_3Cl$. After allowing 30 min for Li-Ti exchange to occur, benzaldehyde (46 μL, 0.448 mmol) was added dropwise and the mixture was stirred for 1 h. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (1 mL) and the mixture was brought to rt. The mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with water (2 x 15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to obtain 250 mg of crude material. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 97 mg (73% yield) of Bu_4Sn, 28 mg (26% yield) of protonated by-product **118**, 2 mg (2% yield) of hemi-ketal **91**, and 11 mg of addition adduct **110** (7% yield). Compound **110** was formed in 40% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 20 (results presented in Table 13, entry 2): To a cooled solution (-78 °C) of **101** (240 mg, 0.434 mmol) in hexane (5 mL) was added a 1.20 M solution of *n*-BuLi (0.54 mL, 0.651 mmol) dropwise and the resulting solution was stirred for 25 minutes. Next a 1.0 M solution $Ti(O^iPr)_3Cl$ (0.45 mL, 0.448 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. A dark red/brown precipitate was observed to be formed after the addition of $Ti(O^iPr)_3Cl$. After allowing 30 min for Li-Ti exchange to occur, benzaldehyde (46 μL, 0.448 mmol) was added dropwise and the mixture was placed in a 0 °C bath and stirred for an additional 1 h. The mixture was observed to turn to a bright yellow colour when warmed to 0 °C. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (1 mL) and the mixture was brought to rt. The mixture was then extracted with Et_2O (3 x 15 mL), followed by washing the combined organic extracts with water (2 x 15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and

concentrated *in vacuo* to obtain 265 mg of crude material. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 98 mg (65% yield) of Bu_4Sn, 11 mg (10% yield) of protonated by-product **118**, 11 mg (10% yield) of hemi-ketal **91**, and 8 mg of addition adduct **110** (5% yield). Compound **110** was formed in 63% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 21 (results reported in Table 12, entry 3): To a cooled solution (-78 °C) of **101** (310 mg, 0.560 mmol) in hexane (10 mL) was added a 1.20 M solution of *n*-BuLi (0.70 mL, 0.840 mmol) dropwise and the resulting solution was stirred for 30 minutes. Next a 1.0 M solution $Ti(O^iPr)_3Cl$ (0.62 mL, 0.616 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. An orange precipitate formed initially after the addition of $Ti(O^iPr)_3Cl$, then quickly turned to a dark green/brown colour. After allowing 40 minutes for Li-Ti exchange to occur, benzaldehyde (63 μL, 0.616 mmol) was added dropwise at -31 °C and the mixture was allowed to reach rt. The mixture was observed to turn from a light yellow/green colour to a bright yellow colour, then to a light yellow colour when warmed to rt. After stirring overnight, the reaction was quenched with D_2O (4 mL), then filtered through a frit. The filtrate was then diluted with H_2O (5 mL), and extracted with Et_2O (3 x 15 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to obtain 325 mg of crude material. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc to 5% MeOH/EtOAc) to isolate in order of elution: 114 mg (59% yield) of Bu_4Sn, 47 mg (32% yield) of protonated by-product **118**, 10 mg (7% yield) of hemi-ketal **91**, and 10 mg of addition adduct **110** (5% yield). Compound **110** was formed in 50% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 22 (results reported in Table 13, entry 4): To a cooled solution (-78 °C) of **101** (280 mg, 0.506 mmol) in hexane (10 mL) was added a 1.70 M solution of *n*-BuLi (0.45 mL, 0.759 mmol) dropwise and the resulting solution was stirred for 20 minutes. Next a 1.0 M solution $Ti(O^iPr)_3Cl$ (0.56 mL, 0.557 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. A yellow precipitate formed initially after the addition of $Ti(O^iPr)_3Cl$, then quickly turned to a dark green/brown colour. After allowing 40 minutes for Li-Ti exchange to occur, the reaction was placed in a -78 °C, and cooled for 10 minutes. Next, benzaldehyde (57 μL, 0.557 mmol) was added dropwise at -78 °C and the mixture was allowed to reach -45 °C, and stirred overnight. The mixture was observed to turn yellow when reaching -45 °C. After stirring overnight, the reaction mixture was observed to be pale yellow, and was quenched with MeOD (4 mL), then filtered through Celite. The filtrate was dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to obtain 370 mg of crude material. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc to 5% MeOH/EtOAc) to isolate in order of elution: 99 mg (56% yield) of Bu_4Sn, 30 mg of a 39:61 mixture of protonated product **118** (9% yield) to deuterated product **148** (13% yield), 8 mg (6% yield) of hemi-ketal **91**, and 6.5 mg of addition adduct **110** (4% yield). Compound **110** was formed in 36% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 23 (results reported in Table 12, entry 5): To a cooled solution (-78 °C) of **101** (180 mg, 0.325 mmol) in hexane (10 mL) was added a 1.70 M solution of *n*-BuLi (0.29 mL, 0.488 mmol) dropwise and the resulting solution was stirred for 30 minutes. Next a 1.0 M solution $Ti(O^iPr)_3Cl$ (0.36 mL, 0.360 mmol) was added to the reaction mixture and a yellow precipitate formed. After allowing 5 minutes for Li-Ti exchange to occur, benzaldehyde (36 μL, 0.358 mmol)

was added dropwise and the mixture was allowed to reach -45 °C, and stirred overnight. After stirring overnight, the reaction mixture was observed to be pale yellow, and was quenched with MeOD (4 mL), then filtered through Celite. The filtrate was dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to obtain 240 mg of crude material. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc to 5% MeOH/EtOAc) to isolate in order of elution: 62 mg (55% yield) of Bu_4Sn, 14 mg of a 70:30 mixture of protonated product **118** (11% yield) to deuterated product **148** (5% yield), 5 mg (6% yield) of hemi-ketal **91**, and 17.9 mg of addition adduct **110** (15% yield). Compound **110** was formed in 6% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 24 (results presented in Table 12, entry 6): To a cooled solution (-78 °C) of **101** (260 mg, 0.469 mmol) in hexane (10 mL) was added a 1.56 M solution of *n*-BuLi (0.45 mL, 0.705 mmol) dropwise and the resulting solution was stirred for 15 minutes. Next a 1.0 M solution $Ti(O^iPr)_3Cl$ (0.52 mL, 0.520 mmol) was added to the reaction mixture and an orange precipitate formed. The reaction was then placed in a -60 °C bath and stirred for 10 minutes, and the precipitate had turned to a dark brown/green colour by this time. Next, benzaldehyde (52 μL, 0.516 mmol) was added dropwise and the mixture was stirred at -55 °C for 1 h. The reaction mixture was observed to stay the same colour, and was quenched with MeOD (4 mL). The reaction mixture was brought to rt, and H_2O (5 mL) was added. The mixture was then filtered through Celite, and the aqueous layer was separated. The organic layer was then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc to 5% MeOH/EtOAc) to isolate in order of elution: 72 mg (44% yield) of Bu_4Sn, 59 mg of a 19:81 mixture of protonated product **118** (5% yield) to deuterated product **148** (19% yield), 28 mg (24% yield) of hemi-ketal **91**, and 12.8 mg of addition

adduct **110** (7% yield). Compound **110** was formed in 26% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 25 (results presented in Table 12, entry 7): First, a 1 M solution of $Ti(O^iPr)_2Cl_2$ was prepared by mixing equimolar amounts of $Ti(O^iPr)_4$ (3.72 mL, 12.5 mmol) and $TiCl_4$ (1.37 mL, 12.5 mmol) in hexane (19.9 mL) for 30 minutes. The experiment then continued as follows: To a cooled solution (-78 °C) of **101** (175 mg, 0.316 mmol) in hexane (7 mL) was added a 1.50 M solution of *n*-BuLi (0.32 mL, 0.474 mmol) dropwise and the resulting solution was stirred for 20 minutes. Next, the 1.0 M solution of $Ti(O^iPr)_2Cl_2$ (0.35 mL, 0.350 mmol) was added to the reaction mixture and a dark brown/green precipitate formed. The mixture was stirred for 5 minutes, and benzaldehyde (35 μL, 0.348 mmol) was added dropwise, and the mixture was stirred for 1.5 h. The reaction mixture was observed to stay the same colour, and was quenched with MeOD (4 mL). The reaction mixture was brought to rt, and then the mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc to 5% MeOH/EtOAc) to isolate in order of elution: 25 mg of a 25:75 mixture of protonted product **118** (8% yield) to deuterated product **148** (22% yield), and 45 mg of mixture consisting of hemi-ketal **91** (17% yield) and of addition adduct **110** (9% yield). Compound **110** was formed in 10% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Experiment 26 (results presented in Table 13, entry 8): To a cooled solution (-60 °C) of **101** (195 mg, 0.352 mmol) in hexane (7 mL) was added a 1.50 M solution of *n*-BuLi in hexane (0.35 mL, 0.528 mmol) dropwise and the resulting solution was stirred for 25 minutes. Next, $Ti(O^iPr)_4$ (115 μL, 0.387 mmol) was added to the reaction mixture and a pale yellow precipitate formed. The

reaction was then placed in a -40 °C bath and stirred for 35 minutes. When warming the mixture to -40 °C, the precipitate changed to an orange colour. Benzaldehyde (39 μL, 0.387 mmol) was then added dropwise and the mixture was stirred for 1.5 h. Quenching then occurred with MeOD (4 mL), and the mixture was brought to rt. Filtration of the mixture then occurred through Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc to 5% MeOH/EtOAc) to isolate in order of elution: 11 mg (13% yield) of hemi-ketal **91**, and 3 mg of addition adduct **110** (2% yield). Compound **110** was formed in 29% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

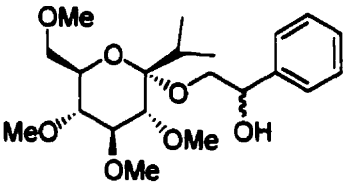
Compound **110** was isolated as a thick syrup in all experiments and exhibited the following characterization data: IR (neat film) 3428 (O-H stretch), 1106 (C-O stretch), 759, 702 cm^{-1}; ^1H NMR (benzylic *S* configuration diastereomer) δ 7.25-7.40 (m, 5H, Ar-H), 4.97 (dd, 1H, J = 3.1, 5.7 Hz, Bn-H), 3.3-3.75 (m, 6H, OCH_2 + OCH), 3.66 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.1-3.2 (m, 1H, OCH), 2.95 (d, 1H, J = 9.5 Hz, OCH), 1.45 (s, 3H, CCH_3); ^1H NMR (benzylic *R* configuration diastereomer) δ 7.25-7.40 (m, 5H, Ar-H), 4.87 (dd, 1H, J = 4.0, 8.6 Hz, Bn-H), 3.2-3.7 (m, 6H, OCH_2 + OCH), 3.66 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.14 (dd, 1H, J = 9.0, 9.9 Hz, OCH), 2.93 (d, 1H, J = 9.5 Hz, OCH), 1.44 (s, 3H, CCH_3); ^{13}C NMR (benzylic *S* configuration diastereomer) δ 140.8 (Ar-C), 128.3 (Ar-C), 127.7 (Ar-C), 126.1 (Ar-C), 100.3 (anomeric-C), 86.8 (OCH), 84.6 (OCH), 79.9 (OCH), 72.8 (OCH), 71.2 (OCH), 70.8 (OCH_2), 67.0 (OCH_2), 61.6 (OCH_3), 60.6 (OCH_3), 60.2 (OCH_3), 59.2 (OCH_3), 20.8 ($C\underline{C}H_3$); ^{13}C NMR (benzylic *R* configuration diastereomer) δ 140.4 (Ar-C), 128.4 (Ar-C), 127.8 (Ar-C), 126.2 (Ar-C), 100.6 (anomeric-C), 86.8 (OCH), 84.6 (OCH), 80.0 (OCH), 72.9 (OCH), 71.4 (OCH), 71.2 (OCH_2), 67.0 (OCH_2), 61.5 (OCH_3), 60.7 (OCH_3), 60.3 (OCH_3), 59.3

(OCH_3), 20.9 ($C\underline{C}H_3$); MS (FAB) *m/z* 103.1 (100), 233.3 (M^+-$OCH_2CH(OH)Ph$, 7). Anal. Calcd for $C_{19}H_{30}O_7$: C, 61.60; H, 8.16 Found: C, 61.41; H, 8.16.

Compound **118** was formed as a thick syrup and exhibited the following spectral data: $[\alpha]_D^{22}$ = + 94.6 (c = 1.25, $CHCl_3$); IR (neat film) 2833, 1452, 1374, 1093 (C-O stretch), 957 cm^{-1}; ^1H NMR δ 3.39-3.70 (m, 4H, OCH_2 + OCH), 3.64 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 3.15 (t, 1H, J = 9.9 Hz, OCH), 2.92 (d, 1H, J = 9.5 Hz, OCH), 1.41 (s, 3H, CCH_3); ^{13}C NMR (75.47 MHz) δ 100.2 (anomeric-C), 86.5 (OCH), 84.8 (OCH), 79.9 (OCH), 71.3 (OCH), 71.1 (OCH_2), 61.6 (OCH_3), 60.7 (OCH_3), 60.3 (OCH_3), 59.3 (OCH_3), 47.9 (OCH_3), 19.7 ($C\underline{C}H_3$); MS (EI) *m/z* 88 (100), 101 (40), 155 (25), 233 (M^+ - CH_3O, 2), 249 (M^+ - CH_3, 0.5), 263 (M^+ - 1, 2), 264 (M^+, 1), 265 (M^+ + 1, 2).

Compound **148** was formed as a thick syrup and exhibited the following spectral data: $[\alpha]_D^{22}$ = + 100.3 (c = 1.75, $CHCl_3$); IR (neat film) 2833, 2160 (C-D stretch), 1450, 1374, 1092 (C-O stretch), 958, 859 cm^{-1}; ^1H NMR δ 3.39-3.70 (m, 4H, OCH_2 + OCH), 3.64 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.20 (3 lines (1:1:1), 2H, J = 1.5 Hz, OCH_2D), 3.15 (t, 1H, J = 9.9 Hz, OCH), 2.92 (d, 1H, J = 9.5 Hz, OCH), 1.41 (s, 3H, CCH_3); ^{13}C NMR (75.47 MHz) δ 100.1 (anomeric-C), 86.5 (OCH), 84.8 (OCH), 79.9 (OCH), 71.3 (OCH), 71.1 (OCH_2), 61.5 (OCH_3), 60.7 (OCH_3), 60.3 (OCH_3), 59.3 (OCH_3), 47.7 (3 lines, J = 22 Hz, OCH_2D), 19.7 ($C\underline{C}H_3$); MS (EI) *m/z* 88 (100), 101 (46), 155 (43), 232 (M^+ - CH_2DOH, 0.2), 233 (M^+ - CH_2DO, 1), 250 (M^+ - CH_3, 0.09), 264 (M^+ - 1, 1), 265 (M^+, 2), 266 (M^+ + 1, 2).

2.3.26 2-[(2R,3S,4S,5R,6R)-2-Isopropyl-3,4,5-trimethoxy-6-(methoxymethyl)tetrahydro-2H-2-pyranyl]oxy-1-phenyl-1-ethanol ***111***



This unreported compound was prepared in 2 experimental procedures outlined below. Also reported in this section is partial spectral data for protonated by-product **120**.

Experiment 1 (results reported in Table 4, entry 2; Table 5, entry 15; Table 6, entry 5; and Table 7, entry 9): To a cooled solution (-60 °C) of **103** (87 mg, 0.150 mmol) in Et_2O (5 mL) was added a solution of 1.30 M *n*-BuLi in hexane (0.23 mL, 0.300 mmol) dropwise and the resulting solution was stirred for 1 h. The reaction mixture turned to a slight yellow colour during the transmetalation. Benzaldehyde (46 μL, 0.450 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to isolate 175 mg of crude material. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 46 mg (88% yield) of Bu_4Sn, 17 mg (37% yield) of protonated by-product **120**, and 24 mg (40% yield) of addition adduct **111**. Compound **111** was formed as a 1:1 mixture of diastereomers (determined by Method B, described in Section 2.3.2).

Experiment 2 (results reported in Table 5, entry 16; and Table 7, entry 10): To a cooled solution (-60 °C) of **103** (72.5 mg, 0.125 mmol) in toluene (4 mL) was added a solution of 1.30 M *n*-

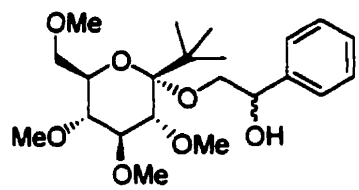
BuLi in hexane (0.19 mL, 0.249 mmol) dropwise and the resulting solution was stirred for 65 min. Benzaldehyde (38 μL, 0.375 mmol) was next added dropwise and the resulting solution was stirred for an additional 45 min after which an aquwous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 34 mg (78% yield) of Bu_4Sn, 11 mg (15% yield) of recovered starting material **103**, and 33 mg (66% yield) of addition adduct **111**. Compound **111** was formed as a 1:1 mixture of diastereomers (determined by Method B, described in Section 2.3.2).

Compound **111** was formed as a thick syrup in both experiments and exhibited the following characterization data: IR (neat film) 3426 (O-H stretch), 2833, 1068 (C-O stretch), 1030 (C-O stretch), 760, 702 cm^{-1}; ^1H NMR δ 7.2-7.4 (m, 5H, Ar-H), 5.03 (dd, 1H, J = 3.8, 8.1 Hz, Bn-H), 4.90* (dd, 1H, J = 3.5, 8.9 Hz, Bn-H), 3.4-3.8 (m, 6H, OCH_2 + OCH), 3.66 (s, 3H, OCH_3), 3.65* (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.57* (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.52* (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.37* (s, 3H, OCH_3), 3.20-3.27 (m,1H, OCH), 2.97-3.08 (m,1H, OCH), 2.07 (spt, 1H, J = 7.0 Hz, C<u>H</u>$(CH_3)_2$), 1.08 (d, 3H, J = 7.2 Hz, CH(C<u>H</u>$_3$)(CH_3)), 1.06 (d, 3H, J = 7.2 Hz, CH(C<u>H</u>$_3$)(CH_3)), 1.02 (d, 3H, J = 6.9 Hz, CH(CH_3)(C<u>H</u>$_3$)), 1.00 (d, 3H, J = 6.9 Hz, CH(CH_3)(C<u>H</u>$_3$)); ^{13}C NMR δ 141.1* (Ar-C), 140.9 (Ar-C), 128.3 (Ar-C), 128.2* (Ar-C), 127.6 (Ar-C), 126.2* (Ar-C), 127.6 (Ar-C), 126.2 (Ar-C), 126.1* (Ar-C), 102.8* (anomeric-C), 102.6 (anomeric-C), 85.8 (OCH), 81.5 (OCH), 81.4* (OCH), 80.1 (OCH), 80.1* (OCH), 73.0* (OCH), 72.8 (OCH), 71.7 (OCH), 71.5* (OCH), 71.4 (OCH), 71.0* (OCH_2), 65.9* (OCH_2), 65.7 (OCH_2), 60.6 (OCH_3), 60.3* (OCH_3), 60.1 (OCH_3), 60.0 (OCH_3), 59.4 (OCH_3), 59.3* (OCH_3), 32.7* (<u>C</u>H$(CH_3)_2$), 32.5 (<u>C</u>H$(CH_3)_2$), 18.1 (CH(<u>C</u>H$_3$)(CH_3)), 17.1* (CH(<u>C</u>H$_3$)(CH_3)), 17.0 (CH(CH_3)(<u>C</u>H$_3$)); MS *m/z* 261 (M^+-

$OCH_2CH(OH)Ph$, 87), 421 ($M^+ + Na^+$, 100). Anal. Calcd for $C_{21}H_{34}O_7$: C, 63.30; H, 8.60. Found: C, 63.19; H, 8.87.

Protonated by-product **120** was formed as a thick syrup and exhibited the following spectral data: ^1H NMR δ 3.15-3.69 (m, 5H, OCH_2 + OCH), 3.64 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 3.02 (dd, 1H, J = 9.2, 9.9 Hz, OCH), 2.14 (spt, 1H, J = 7.1 Hz, $C\underline{H}(CH_3)_2$), 1.04 (t, 6H, J = 7.1 Hz, $CH(C\underline{H}_3)_2$).

2.3.27 2-[(2R,3S,4S,5R,6R)-2-(Tert-butyl)-3,4,5-trimethoxy-6-(methoxymethyl)tetrahydro-2H-2-pyranyl]oxy-1-phenyl-1-ethanol ***112***



This unreported compound was prepared in 4 experimental procedures outlined below.

Experiment 1 (results reported in Table 4, entry 3; Table 5, entry 18; and Table 7, entry 12): To a cooled solution (-60 °C) of **104** (104 mg, 0.175 mmol) in Et_2O (10 mL) was added a solution of 1.30 M *n*-BuLi in hexane (0.27 mL, 0.349 mmol) dropwise and the resulting solution was stirred for 105 min. Benzaldehyde (53 μL, 0.527 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min after which an aqueous solution of saturated NH_4Cl (5 mL) was added, followed by H_2O (5 mL). The aqueous layer was then separated and extracted with Et_2O (20 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to

10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 52 mg (86% yield) of Bu_4Sn, and 69 mg (96% yield) of addition adduct **112**. Compound **112** was formed in 2% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

Experiment 2 (results reported in Table 5, entry 17; and Table 7, entry 11): To a cooled solution (-60 °C) of **104** (503 mg, 0.845 mmol) in THF (20 mL) was added a solution of 1.30 M *n*-BuLi in hexane (1.30 mL, 1.69 mmol) dropwise and the resulting solution was stirred for 65 minutes. Benzaldehyde (258 μL, 2.54 mmol) was next added dropwise and the resulting solution was stirred for an additional 40 min after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to isolate 0.9 g of crude material. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 261 mg (89% yield) of Bu_4Sn, and 276 mg (79% yield) of addition adduct **112**. Compound **112** was formed as a 1:1 mixture of diastereomers (determined by Method B, described in Section 2.3.2).

Experiment 3 (results reported in Table 5, entry 19; Table 6, entry 6; and Table 7, entry 13): To a cooled solution (-60 °C) of **104** (101 mg, 0.170 mmol) in toluene (10 mL) was added a solution of 1.30 M *n*-BuLi in hexane (0.26 mL, 0.340 mmol) dropwise and the resulting solution was stirred for 90 minutes. Benzaldehyde (52 μL, 0.510 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min after which an aqueous solution of saturated NH_4Cl (5 mL) was added. The aqueous layer was then separated and extracted with Et_2O (15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to isolate 140 mg of crude material. The crude product was purified by silica gel chromatography

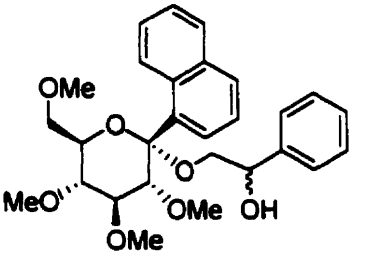
(gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 32 mg (54% yield) of Bu_4Sn, 21 mg (41% yield) of hemi-ketal **94**, and 13 mg (19% yield) of addition product **112**. Compound **112** was formed in 30% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Experiment 4 (results reported in Table 5, entry 20; and Table 7, entry 14): To a cooled solution (-60 °C) of **104** (96 mg, 0.161 mmol) in hexane (10 mL) was added a solution of 1.30 M *n*-BuLi in hexane (0.25 mL, 0.322 mmol) dropwise and the resulting solution was stirred for 90 minutes. Benzaldehyde (49 μL, 0.483 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated $NaHCO_3$ (5 mL) was added, followed by H_2O (5 mL). The aqueous layer was then separated and extracted with Et_2O (20 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to isolate 150 mg of crude material. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 50 mg (89% yield) of Bu_4Sn, and 41 mg (62% yield) of addition product **112**. Compound **112** was formed as a 1:1 diastereomeric mixture (determined by Method A, described in Section 2.3.2).

Compound **112** was formed as a thick syrup in all experiments and exhibited the following characterization data (refers to sample derived from Experiment 1): IR (neat film) 3421 (O-H stretch), 2833, 1092 (C-O stretch), 758, 733, 702 cm^{-1}; ^1H NMR δ 7.25-7.45 (m, 5H, Ar-H), 5.03* (dd, 1H, J = 3.0, 9.0 Hz, Bn-H), 4.85 (dd, 1H, J = 3.3, 8.8 Hz, Bn-H), 3.88* (ddd, 1H, J = 1.8, 4.4, 10.2 Hz, $CH_3OCH_2C\underline{H}O$), 3.25-3.75 (m, 6H, OCH_2 + OCH), 3.66 (s, 3H, OCH_3), 3.65* (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.42* (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 3.32* (d,

1H, J = 8.5 Hz, OCH), 3.30 (d, 1H, J = 9.2 Hz. OCH), 3.08* (t, 1H, J = 9.6 Hz, OCH), 3.04 (t, 1H, J = 9.6 Hz, OCH), 1.09* (s, 9H, C(C$\underline{H}_3$)$_3$), 1.08 (s, 9H, C(C$\underline{H}_3$)$_3$); ^{13}C NMR δ 141.8* (Ar-C), 141.0 (Ar-C), 128.0* (Ar-C), 127.9 (Ar-C), 127.2* (Ar-C), 127.2 (Ar-C), 126.0* (Ar-C), 125.9 (Ar-C), 103.1* (anomeric-C), 102.8 (anomeric-C), 85.9* (OCH), 85.7 (OCH), 83.5 (OCH), 83.2* (OCH), 79.9 (OCH), 73.3* (OCH), 73.1 (OCH), 72.2 (OCH), 71.3 (OCH_2), 71.2* (OCH_2), 69.1* (OCH_2), 68.7 (OCH_2), 60.1 (OCH_3), 59.7 (OCH_3), 59.6* (OCH_3), 59.5 (OCH_3), 59.4* (OCH_3), 59.3 (OCH_3), 59.2* (OCH_3), 39.3 ($\underline{C}(CH_3)_3$), 39.2* ($\underline{C}(CH_3)_3$), 27.4 (C($\underline{C}H_3$)$_3$); MS *m/z* 275 (M^+-$OCH_2CH(OH)Ph$, 100). Anal. Calcd for $C_{22}H_{36}O_7$: C, 64.09; H, 8.80. Found: C, 63.96; H, 8.80.

2.3.28 1-Phenyl-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-(1-naphthyl)tetrahydro-2H-2-pyranyl]oxy-1-ethanol ***113***



This unreported compound was prepared by Sn-Li exchange of **105**, followed by trapping with benzaldehyde. Reactions were conducted in Et_2O (results presented in Table 4, entry 4; Table 5, entry 21; Table 6, entry 7; and Table 7, entry 15), toluene (results presented in Table 5, entry 22; and Table 7, entry 16), or hexane (results presented in Table 5, entry 23; and Table 7, entry 17). A representative procedure (reaction conducted in toluene) is included below.

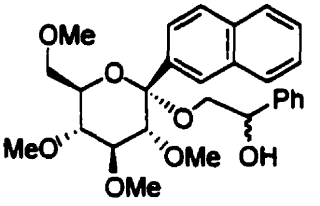
To a cooled solution (-60 °C) of **105** (617 mg, 0.927 mmol) in toluene (20 mL) was added a solution of 1.30 M *n*-BuLi in hexane (1.43 mL, 1.85 mmol) dropwise and the resulting solution was

stirred for 65 minutes. Benzaldehyde (283 μL, 2.78 mmol) was next added dropwise and the resulting solution was stirred for an additional 40 min, after which an aqueous solution of saturated NH_4Cl (5 mL) was added. The aqueous layer was then separated and extracted with Et_2O (20 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to isolate 1.1 g of crude material. The crude product was purified by silica gel chromatography (gradient elution: hexane to 20% to 30% to 40% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 156 mg (48% yield) of Bu_4Sn, and 202 mg (53% yield) of addition adduct **113**. Compound **113** was formed in 12% de (de determined by Method C, described in Section 2.3.2; HPLC solvent system and retention times: 5% ^iPrOH/hexane, 5.98 min (*S*), 6.96 min (R)), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Compound **113** was formed as a thick syrup in all experiments and exhibited the following characterization data (sample from the reaction conducted in toluene): IR (neat film) 3422 (O-H stretch), 1106 (C-O stretch), 1070 (C-O stretch), 807, 781, 760, 701 cm^{-1}; ^1H NMR δ 8.8-9.1 (br, 1H, Ar-H), 7.75-7.95 (m, 3H, Ar-H), 7.1-7.6 (m,8H, Ar-H), 5.05-5.15 (br, 1H, Bn-H), 5.0* (m, 1H, Bn-H), 3.9-4.0* (m, 1H, OCH), 2.9-3.85 (m, 8H, OCH_2 + OCH), 3.70 (s, 3H, OCH_3), 3.69* (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.62* (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.46* (s, 3H, OCH_3), 2.76 (s, 3H, OCH_3), 2.73* (s, 3H, OCH_3); ^{13}C NMR δ 140.9 (Ar-C), 139.7 (br, Ar-C), 137.1 (br, Ar-C), 134.3 (br, Ar-C), 131.1 (Ar-C), 131.0* (Ar-C), 130.4 (br, Ar-C), 129.6 (br, Ar-C), 128.3* (br, Ar-C), 128.0 (Ar-C), 127.4* (Ar-C), 127.4 (Ar-C), 126.9* (br, Ar-C), 126.2* (Ar-C), 125.9 (Ar-C), 125.8 (Ar-C), 125.7* (Ar-C), 125.4 (br, Ar-C), 125.1 (Ar-C), 124.7* (Ar-C), 102.4* (br, anomeric-C), 98.9 (anomeric-C), 89.2* (br, OCH), 86.9 (br, OCH), 85.6 (OCH), 85.2* (OCH), 84.7 (OCH), 79.5 (OCH), 72.8 (OCH), 72.7* (OCH), 72.0* (br, OCH), 71.2 (br, OCH_2), 67.3* (OCH_2), 67.0 (OCH_2), 60.9* (OCH_3), 60.8 (OCH_3), 60.6 (OCH_3), 60.1* (OCH_3), 60.0 (OCH_3), 59.3* (OCH_3), 59.2 (OCH_3);

MS *m/z* 345 (M^+-$OCH_2CH(OH)Ph$, 100). Anal. Calcd for $C_{28}H_{34}O_7$: C, 69.69; H, 7.10. Found: C, 69.31; H, 7.10.

2.3.29 1-Phenyl-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-(2-naphthyl)tetrahydro-2H-2-pyranyl]oxy-1-ethanol ***114***



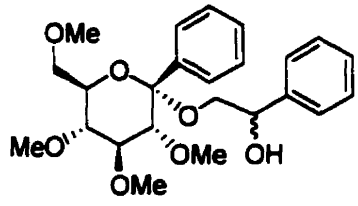
This unreported compound was prepared by Sn-Li exchange of **106**, and trapping with benzaldehyde. Reactions were conducted in Et_2O (results presented in Table 4, entry 5; Table 5, entry 25; and Table 7, entry 19), THF (results presented in Table 5, entry 24; and Table 7, entry 18), toluene (results presented in Table 5, entry 26; and Table 7, entry 20), or hexane (results presented in Table 5, entry 27; and Table 7, entry 21). A representative procedure (reaction conducted in Et_2O) is included below.

To a cooled solution (-60 °C) of **106** (120 mg, 0.180 mmol) in Et_2O (5 mL) was added a solution of 1.30 M *n*-BuLi in hexane (0.28 mL, 0.360 mmol) dropwise and the resulting solution was stirred for 50 minutes. Benzaldehyde (55 μL, 0.540 mmol) was next added dropwise and the resulting solution was stirred for an additional 20 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to isolate 190 mg of crude material. The crude product was purified by silica gel chromatography (gradient elution: hexane to 20% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 55 mg

(88% yield) of Bu_4Sn, and 70 mg (97% yield) of addition adduct **114**. Compound **114** was formed in 36% de (de determined by Method C, described in Section 2.3.2; HPLC solvent system and retention times: 5% ^{i}PrOH/hexane, retention times: 6.31 min (*S*), 6.98 min (*R*)), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Compound **114** was formed as a thick syrup in all experiments and exhibited the following characterization data: IR (neat film) 3424 (O-H stretch), 1100 (C-O stretch), 755, 733, 702 cm^{-1}; ^1H NMR δ 8.08 (br, 1H, Ar-H), 7.7-7.95 (m, 4H, Ar-H), 7.4-7.5 (m, 2H, Ar-H), 7.15-7.35 (m, 5H, Ar-H), 5.06 (dd, 1H, J = 5.2, 6.7 Hz, Bn-H), 4.97* (dd, 1H, J = 3.4, 9.0 Hz, Bn-H), 3.98 (ddd, 1H, J = 2.0, 4.2, 10.1 Hz, $CH_3OCH_2C\underline{H}O$), 3.2-3.85 (m, 6H, OCH_2 + OCH), 3.70 (s, 3H, OCH_3), 3.69* (s, 3H, OCH_3), 3.61* (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.49* (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 3.08* (s, 3H, OCH_3), 3.00 (d, 1H, J = 9.5 Hz, OCH), 2.98* (d, 1H, J = 9.5 Hz, OCH); ^{13}C NMR δ 140.9 (Ar-C), 140.7* (Ar-C), 136.0 (Ar-C), 135.7* (Ar-C), 133.0 (Ar-C), 132.9* (Ar-C), 128.5* (Ar-C), 128.4 (Ar-C), 128.1 (Ar-C), 127.5* (Ar-C), 127.5 (Ar-C), 127.4* (Ar-C), 127.3 (Ar-C), 126.6* (Ar-C), 126.5 (Ar-C), 126.2 (Ar-C), 126.0 (Ar-C), 125.8 (Ar-C), 125.7* (Ar-C), 125.0* (Ar-C), 124.9 (Ar-C), 100.6* (anomeric-C), 100.4 (anomeric-C), 87.8 (OCH), 85.0 (OCH), 84.9* (OCH), 79.9* (OCH), 79.8 (OCH), 72.8 (OCH), 71.9 (OCH_2), 71.4 (OCH_2), 67.6 (OCH_2), 61.4 (OCH_3), 61.3* (OCH_3), 60.7 (OCH_3), 60.2* (OCH_3), 60.1 (OCH_3), 59.4* (OCH_3), 59.3 (OCH_3); MS *m/z* 345 (M^+-$OCH_2CH(OH)Ph$, 100), 505 (M + Na^+, 14). Anal. Calcd for $C_{28}H_{34}O_7$: C, 69.69; H, 7.10. Found: C, 69.43; H, 7.31.

2.3.30 1-Phenyl-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-ethanol 115



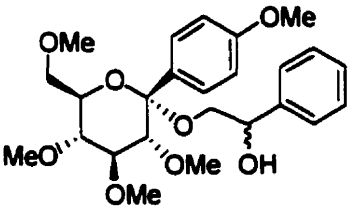
This unreported compound was prepared by Sn-Li exchange of **102**, and trapping with benzaldehyde. Reactions were conducted in Et_2O (results presented in Table 4, entry 6; Table 5, entry 6; and Table 7, entry 6), THF (results presented in Table 5, entry 5; and Table 7, entry 5), CH_2Cl_2 (result presented in Table 5, entry 7), toluene (results presented in Table 5, entry 8; and Table 7, entry 7), or hexane (results presented in Table 5, entries 9-14; Table 6, entry 4; and Table 7. entry 8). A representative procedure (reaction conducted in Et_2O) is included below.

To a cooled solution (-60 °C) of **102** (162 mg, 0.263 mmol) in Et_2O (10 mL) was added a solution of 1.50 M *n*-BuLi in hexane (0.35 mL, 0.526 mmol) dropwise and the resulting solution was stirred for 80 minutes. Benzaldehyde (59 μL, 0.579 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqeous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 50% to 75% EtOAc/hexane) to isolate in order of elution: 74 mg (81% yield) of Bu_4Sn, and 90 mg (79% yield) of addition adduct **115**. Compound **115** was formed in 34% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at

the carbinol carbon. HPLC analysis of this compound (i.e. different samples) was also possible by Method C, described in Section 2.3.2; solvent system and retention times: 5% ^{i}PrOH/hexane: 5.47 min (*S*), 6.32 min (*R*).

Compound **115** was formed as a thick syrup in all experiments and exhibited the following characterization data: IR (neat film) 3424 (O-H stretch), 2834, 1094 (C-O stretch), 763, 703 cm^{-1}; ^{1}H NMR δ 7.58-7.62 (m, 2H, Ar-H), 7.2-7.4 (m, 8H, Ar-H), 5.02 (dd, 1H, J = 5.1, 6.9 Hz, Bn-H), 4.94* (dd, 1H, J = 3.5, 9.0 Hz, Bn-H), 3.92 (ddd, 1H, J = 2.0, 4.2, 10.1 Hz, $CH_3OCH_2C\underline{H}O$), 3.0-3.75 (m, 6H, OCH_2 + OCH), 3.69 (s, 3H, OCH_3), 3.59* (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.45* (s, 3H, OCH_3), 3.13 (s, 3H, OCH_3), 3.10* (s, 3H, OCH_3), 2.91 (d, 1H, J = 9.5 Hz, OCH), 2.89* (d, 1H, J = 9.5 Hz, OCH); ^{13}C NMR δ 141.0 (Ar-C), 140.8* (Ar-C), 138.3 (Ar-C), 137.9* (Ar-C), 128.0 (Ar-C), 127.8 (Ar-C), 127.4* (Ar-C), 127.4* (Ar-C), 127.1 (Ar-C), 127.0 (Ar-C), 126.1 (Ar-C), 125.9 (Ar-C), 100.4* (anomeric-C), 100.2 (anomeric-C), 87.6 (OCH), 84.7 (OCH), 84.7* (OCH), 79.6 (OCH), 72.7 (OCH), 72.6* (OCH), 71.7* (OCH_2), 71.2 (OCH_2), 67.4 (OCH_2), 61.4 (OCH_3), 61.3* (OCH_3), 60.6* (OCH_3), 60.6 (OCH_3), 60.1* (OCH_3), 60.1 (OCH_3), 59.4* (OCH_3), 59.2 (OCH_3); MS *m/z* 295.1 (M-$OCH_2CH(OH)Ph$, 81), 263.1 (34), 185.1 (47), 121.0 (51), 105.0 (100). Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.39; H, 7.46.

2.3.31 1-Phenyl-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-(4-methoxyphenyl)tetrahydro-2H-2-pyranyl]oxy-1-ethanol **116**



This unreported compound was prepared by Sn-Li exchange of **107**, and trapping with benzaldehyde, or by Sn-Li exchange of **107**, followed by Li-Mg or Li-Zn exchange, followed by trapping with benzaldehyde. Reactions of the organolithium species with benzaldehyde were conducted in Et_2O (results presented in Table 4, entry 7; Table 5, entry 29; and Table 7, entry 23), THF (results presented in Table 5, entry 28; and Table 7, entry 22), toluene (results presented in Table 5, entry 30; and Table 7, entry 24), or hexane (results presented in Table 5, entry 31; and Table 7, entry 25). Reactions of the organomagnesium species with benzaldehyde were conducted in THF (results presented in Table 12, entry 13), Et_2O (results presented in Table 12, entry 14), toluene (results presented in Table 12, entry 15), and hexane (results presented in Table 12, entry 16). Reactions of the organozinc species with benzaldehyde were conducted in Et_2O (results presented in Table 12, entry 17) and hexane (results presented in Table 12, entry 18). Representative procedures are included below. Spectral data for unreported protonated by-product **147** is also presented in this section.

Reaction of the organolithium species with benzaldehyde (reaction conducted in Et_2O): To a cooled solution (-60 °C) of **107** (131 mg, 0.203 mmol) in Et_2O (5 mL) was added a solution of 1.60 M *n*-BuLi in hexane (0.25 mL, 0.406 mmol) dropwise and the resulting solution was stirred for 1 h.

Benzaldehyde (62 μL, 0.609 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 50% to 75% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 62 mg (88% yield) of Bu_4Sn, and 75 mg (80% yield) of addition adduct **116**. Compound **116** was formed in 34% de (de determined by Method D, described in Section 2.3.2: solvent system and retention times: 1% ^{i}PrOH/hexane, retention times: 19.32 min (*R*), 21.53 min (*S*)), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Reaction of the organomagnesium species with benzaldehyde (reaction conducted in toluene): To a cooled solution (-78 °C) of **107** (122 mg, 0.189 mmol) in toluene (5 mL) was added a solution of 1.60 M *n*-BuLi in hexane (0.24 mL, 0.378 mmol) dropwise and the resulting solution was stirred for 1 h. Next a 1.0 M solution of freshly generated $MgBr_2 \bullet (OEt_2)$[28] (0.42 mL, 0.416 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. After 30 min the flask was placed in a -78 °C bath and cooled for 10 minutes after which benzaldehyde (58 μL, 0.567 mmol) was added dropwise and the resulting solution was stirred for an additional 30 minutes. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the aqueous layer was then separated, and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 50% to 75% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 36 mg (55% yield) of Bu_4Sn, 16 mg (24% yield) of protonated by-product **147**, and 6 mg (7% yield) of addition adduct **116**. Compound **116** was formed in 38% de (de determined by

Method D, described in Section 2.3.2: solvent system and retention times: 1% ^{i}PrOH/hexane, retention times: 19.32 min (*R*), 21.53 min (*S*)), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

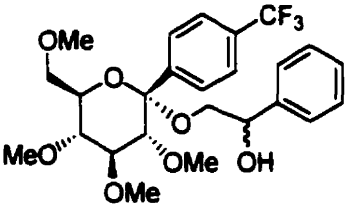
Reaction of the organozinc species with benzaldehyde (reaction conducted in hexane): To a cooled solution (-60°C) of **107** (121 mg, 0.187 mmol) was added a 1.15 M solution of *n*-BuLi in hexane (0.33 mL, 0.374 mmol) dropwise and the resulting solution was stirred for 1 h. Next $ZnCl_2$•TMEDA[31] (115 mg, 0.468 mmol) was added to the reaction mixture and the flask was placed in a -40 °C bath. A light pink precipitate formed after the addition of $ZnCl_2$•TMEDA that turned gradually darker as the Li-Zn exchange progressed. After 15 min the flask was placed in a -78 °C bath and cooled for 10 min after which benzaldehyde (60 μL, 0.561 mmol) was added dropwise and the resulting solution was stirred for an additional 30 min. An aqueous saturated solution of NH_4Cl (1 mL) was added, and the aqueous layer was then separated, and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 50% to 75% EtOAc/hexane to neat EtOAc) to isolate in order of elution: 30 mg (46% yield) of Bu_4Sn, and a 24 mg mixture of hemi-ketal by-product **97** (7% yield) and addition adduct **116** (22% yield). Compound **116** was formed as a 1:1 diastereomeric mixture (de determined by Method B, described in Section 2.3.2).

Compound **116** (diastereomeric mixture with the *S* configuration of carbinol carbon in excess), was formed as a thick syrup in all experiments and exhibited the following characterization data: IR (neat film) 3417 (O-H stretch), 2835, 1096 (C-O stretch), 837, 702 cm^{-1}; ^{1}H NMR δ 7.51 (d, 2H, J = 8.7 Hz, *m*-Ph-H), 7.15-7.4 (m, 5H, Ar-H), 6.87 (d, 2H, J = 8.7 Hz, *o*-Ph-H), 5.00 (dd, 1H, J = 4.0, 7.9 Hz, Bn-H), 4.93* (dd, 1H, J = 3.5, 9.1 Hz, Bn-H), 3.1-4.0 (m, 7H), 3.80 (s, 3H, OCH_3),

3.68 (s, 3H, OCH_3), 3.67* (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.44* (s, 3H, OCH_3), 3.17 (s, 3H, OCH_3), 3.13* (s, 3H, OCH_3), 2.89 (d, 1H, J = 9.6 Hz, OCH), 2.87* (d, 1H, J = 9.5 Hz, OCH); ^{13}C NMR δ 159.3 (Ar-C), 141.1 (Ar-C), 140.8* (Ar-C), 130.5 (Ar-C), 130.1* (Ar-C), 128.4* (Ar-C), 128.3 (Ar-C), 128.0 (Ar-C), 127.4* (Ar-C), 127.3 (Ar-C), 126.1* (Ar-C), 125.9 (Ar-C), 113.2* (Ar-C), 113.1 (Ar-C), 100.3* (anomeric-C), 100.2 (anomeric-C), 87.8 (OCH), 84.7 (OCH), 79.8* (OCH), 79.7 (OCH), 72.6 (OCH), 72.6* (OCH), 71.7 (OCH), 71.6* (OCH), 71.3 (OCH_2), 71.2* (OCH_2), 67.3 (OCH_2), 61.3 (OCH_3), 61.2* (OCH_3), 60.5* (OCH_3), 60.5 (OCH_3), 60.0* (OCH_3), 59.9 (OCH_3), 59.3* (OCH_3), 59.2 (OCH_3), 54.9 (OCH_3); MS *m/z* 325 (M^+-$OCH_2CH(OH)Ph$, 100), 485 ($M + Na^+$, 42). Anal. Calcd for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41. Found: C, 65.02; H, 7.53.

Protonated by-product **147**: (2*R*,3*S*,4*S*,5*R*,6*R*)-2,3,4,5-Tetramethoxy-6-(methoxymethyl)-2-(4-methoxyphenyl)tetrahydro-2H-pyran, was formed as a thick syrup and exhibited the following spectral data: ^1H NMR δ 7.42-7.57 (AA'XX', 2H, *m*-Ph-H), 6.83-6.98 (AA'XX', 2H, *m*-Ph-H), 3.82 (s, 3H, OCH_3), 3.55-3.79 (m, 4H, OCH + OCH_2), 3.65 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.24 (dd, 1H, J = 9.2, 9.7 Hz, OCH), 3.12 (s, 3H, OCH_3), 3.08 (s, 3H, OCH_3), 2.86 (d, 1H, OCH, J = 9.5 Hz).

2.3.32 1-Phenyl-2-((2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-[4-(trifluoromethyl)phenyl]tetrahydro-2H-2-pyranyloxy)-1-ethanol 117

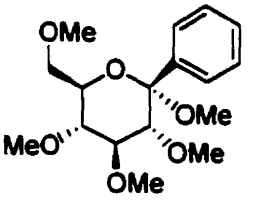


To a cooled solution (-78 °C) of **108** (153 mg, 0.224 mmol) in Et_2O (5 mL) was added a solution of 1.41 M *n*-BuLi in hexane (0.32 mL, 0.448 mmol) dropwise and the resulting solution was stirred for 1 h. Benzaldehyde (68 μL, 0.672 mmol) was next added dropwise and the resulting solution was stirred for an additional 20 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 20% to 50% to 60% EtOAc/hexane) to isolate 75 mg (67% yield) of addition adduct **116**. Compound **116** was formed in 35% de (de determined by Method B), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Compound **116** was formed as a thick syrup and exhibited the following characterization data: IR (neat film) 3422 (O-H stretch), 2836, 1082 (C-O stretch), 1000 (C-O stretch), 760, 733, 701 cm^{-1}; ^1H NMR δ 7.55-7.75 (m, 4H, Ar-H), 7.15-7.4 (m, 5H, Ar-H), 5.02 (d, 1H, J = 8.8 Hz, Bn-H), 4.95* (dd, 1H, J = 3.7, 9.5 Hz, Bn-H), 3.95 (ddd, 1H, J = 2.2, 4.4, 10.0 Hz, $CH_3OCH_2C\underline{H}O$), 3.0-3.8 (m, 6H), 3.67 (s, 3H, OCH_3), 3.66* (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.44* (s, 3H, OCH_3), 3.16 (s, 3H, OCH_3), 3.10* (s, 3H, OCH_3), 2.88 (d, 1H, J = 9.5 Hz, OCH), 2.86* (d, 1H, J

= 9.5 Hz, OCH); ^{13}C NMR δ 142.3 (Ar-C), 142.0* (Ar-C), 140.7 (Ar-C), 140.5* (Ar-C), 130.4 (q, ^{2}J = 32 Hz, Ar-C), 128.3 (Ar-C), 128.3* (Ar-C), 127.8* (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 126.2* (Ar-C), 126.0 (Ar-C), 124.9 (q, ^{3}J = 4 Hz, Ar-C), 124.1* (q, ^{1}J = 272 Hz, Ar-C), 124.1 (q, ^{1}J = 272 Hz, Ar-C), 100.2* (anomeric-C), 100.0 (anomeric-C), 87.3* (OCH), 87.2 (OCH), 84.9 (OCH), 84.8* (OCH), 79.7* (OCH), 79.7 (OCH), 72.8 (OCH), 72.7* (OCH), 72.0* (OCH), 71.5 (OCH), 71.3 (OCH_2), 71.2* (OCH_2), 67.7* (OCH_2), 67.6 (OCH_2), 61.6 (OCH_3), 61.5* (OCH_3), 60.8 (OCH_3), 60.8* (OCH_3), 60.4* (OCH_3), 60.3 (OCH_3), 59.4* (OCH_3), 59.4 (OCH_3); ^{19}F NMR δ -63.53; MS *m/z* 363.1 (M^+ - $OCH_2CH(OH)Ph$, 100), 501.0 (M + H^+, 10), 518.1 (M + NH_4^+, 40). Anal. Calcd for $C_{25}H_{31}F_3O_7$: C, 59.99; H, 6.24. Found: C, 59.96; H, 6.35.

2.3.33 (2R,3S,4S,5R,6R)-2,3,4,5-Tetramethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-pyran ***119***

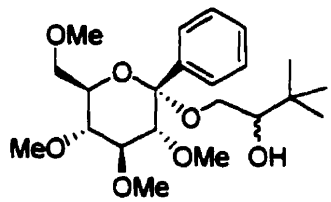


This unreported compound was formed in the auxiliary/diol recovery procedures outlined in Section 2.3.45 to Section 2.3.53, as the recovered chiral auxiliary in the methyl glycoside form. Furthermore, **119** was formed as a protonated by-product according to a representative procedure given in Section 2.3.30, under the experimental conditions presented in Table 4, entry 4.

The following characterization data was obtained for **119**: IR (neat film) 2832 (OCH_2-H stretch), 1100 (C-O stretch), 765, 726, 707 cm^{-1}; ^{1}H NMR δ 7.55-7.65 (m, 2H, Ar-H), 7.25-7.45 (m,

3H, Ar-H), 3.55-3.85 (m, 4H, OCH_2 + OCH), 3.66 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.25 (t, 1H, J = 9.3 Hz, OCH), 3.11 (s, 3H, OCH_3), 3.08 (s, 3H, OCH_3), 2.89 (d, 1H, J = 9.5 Hz, OCH); ^{13}C NMR δ 138.1 (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 127.0 (Ar-C), 100.6 (anomeric-C), 87.5 (OCH), 85.0 (OCH), 79.8 (OCH), 71.6 (OCH), 71.4 (OCH_2), 61.0 (OCH_3), 60.4 (OCH_3), 60.0 (OCH_3), 59.2 (OCH_3), 48.9 (OCH_3); MS *m/z* (EI) 88.1 (100), 295.1 (M^+ -OMe, 1); Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.70; H, 7.91.

2.3.34 3,3-Dimethyl-1-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-2-butanol **121**

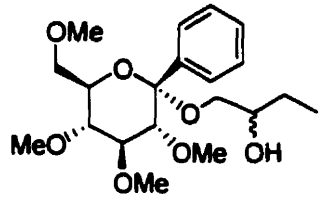


To a cooled solution (-78 °C) of **102** (112 mg, 0.182 mmol) in Et_2O (5 mL) was added a solution of 1.40 M *n*-BuLi in hexane (0.26 mL, 0.364 mmol) dropwise and the resulting solution was stirred for 1 h. Pivaldehyde (59 μL, 0.546 mmol) was next added dropwise and the resulting solution was stirred for an additional 90 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 15% to 35% to 50% EtOAc/hexane) to isolate in order of elution: 47 mg (74% yield) of Bu_4Sn, and 49 mg (65% yield) of addition adduct **121**. Compound **121** was formed as a 1:1 mixture of diastereomers (de

determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

Compound **121** is unreported and was formed as a thick syrup, and exhibited the following spectral data: IR (neat film) 3452 (O-H stretch), 1098 (C-O stretch), 1033 (C-O stretch), 706, 670 cm^{-1}; ^1H NMR δ 7.25-7.65 (m, 5H, Ar-H), 3.85-3.95* (m, 1H, OCH), 3.0-3.8 (m, 8H, OCH_2 + OCH), 3.65 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.57* (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.46* (s, 3H, OCH_3), 3.07 (s, 3H, OCH_3), 3.04* (s, 3H, OCH_3), 2.88 (d, 1H, J = 9.5 Hz, OCH), 2.87* (d, 1H, J = 9.5 Hz, OCH), 0.84 (s, 9H, $C(CH_3)_3$), 0.82* (s, 9H, $C(CH_3)_3$); ^{13}C NMR δ 138.5 (Ar-C), 138.2* (Ar-C), 128.0* (Ar-C), 127.9 (Ar-C), 127.3 (Ar-C), 127.1* (Ar-C), 126.2 (Ar-C), 100.7* (anomeric-C), 100.5 (anomeric-C), 87.9 (OCH), 85.0 (OCH), 85.0* (OCH), 80.1* (OCH), 80.0 (OCH), 77.8* (OCH), 77.5 (OCH), 71.9* (OCH), 71.5 (OCH_2), 71.4 (OCH_2), 63.0 (OCH_3), 62.8* (OCH_3), 61.4* (OCH_3), 61.3 (OCH_3), 60.7 (OCH_3), 60.3* (OCH_3), 60.2 (OCH_3), 59.4 (OCH_3), 59.3* (OCH_3), 33.6 ($\underline{C}(CH_3)_3$), 33.4* ($\underline{C}(CH_3)_3$), 25.8 ($C(\underline{C}H_3)_3$), 25.8* ($C(\underline{C}H_3)_3$); MS *m/z* 295.1 (M^+-$OCH_2CH(OH)^tBu$. 50), 435.2 (M + Na^+, 100). Anal. Calcd for $C_{22}H_{36}O_7$: C, 64.06; H, 8.80. Found: C, 63.82; H, 8.87.

2.3.35 1-[(2R,3S,4S,5R,6R)-3,4,5-Trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-2-butanol 122

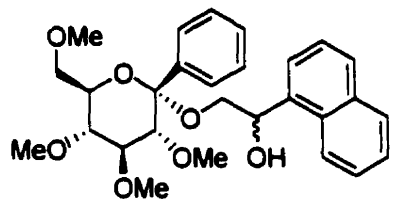


To a cooled solution (-78 °C) of **102** (138 mg, 0.224 mmol) in Et_2O (5 mL) was added a solution of 1.08 M *n*-BuLi in hexane (0.41 mL, 0.448 mmol) dropwise and the resulting solution was stirred for 1 h. Propionaldehyde (48 μL, 0.672 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 60% EtOAc/ hexane) to isolate 39 mg (45% yield) of unreported addition adduct **122** as a thick syrup. Compound **122** was formed in 33% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **122**: IR (neat film) 3445 (O-H stretch), 2928, 2835, 1049 (C-O stretch), 998 (C-O stretch), 773, 725, 707 cm^{-1}; ^1H NMR δ 7.55-7.65 (m, 2H, Ar-H), 7.3-7.4 (m, 3H, Ar-H), 3.0-3.9 (m, 8H, OCH_2 + OCH), 3.66 (s, 3H, OCH_3), 3.59* (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.47* (s, 3H, OCH_3), 3.09 (s, 3H, OCH_3), 3.06* (s, 3H, OCH_3), 2.89 (d, 1H, J = 9.6 Hz, OCH), 2.88* (d, 1H, J = 9.5 Hz, OCH), 1.2-1.5 (m, 2H, $C\underline{H}_2CH_3$), 0.85-1.0 (m, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR δ 138.5 (Ar-C), 138.4* (Ar-C), 128.1* (Ar-C),

128.0 (Ar-C), 127.3 (Ar-C), 127.2 (Ar-C), 100.5* (anomeric-C), 100.4 (anomeric-C), 87.8 (OCH), 85.1 (OCH), 85.0* (OCH), 80.1* (OCH), 80.0 (OCH), 71.9* (OCH), 71.7 (OCH), 71.6 (OCH), 65.8 (OCH_2), 65.8* (OCH_2), 65.6 (OCH_2), 61.5 (OCH_3), 61.4* (OCH_3), 60.8 (OCH_3), 60.4* (OCH_3), 60.3 (OCH_3), 59.5* (OCH_3), 59.5 (OCH_3), 26.4 ($\underline{C}H_2CH_3$), 26.2* ($\underline{C}H_2CH_3$), 9.8 ($CH_2\underline{C}H_3$); MS *m/z* 295.1 (M^+ - $CH_2CH(OH)Et$, 100), 402.2 (M + NH_4^+, 7). Anal. Calcd for $C_{28}H_{32}O_7$: C, 62.48; H, 8.39. Found C, 62.60; H, 8.29.

2.3.36 1-(1-Naphthyl)-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-ethanol ***123***

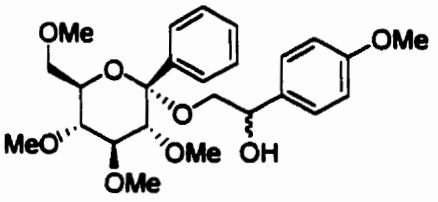


To a cooled solution (-78 °C) of **102** (116 mg, 0.188 mmol) in Et_2O (5 mL) was added a solution of 1.40 M *n*-BuLi in hexane (0.27 mL, 0.377 mmol) dropwise and the resulting solution was stirred for 1 h. 1-naphthaldehyde (77 μL, 0.564 mmol) was next added dropwise and the resulting solution was stirred for an additional 90 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: EtOAc/hexane) to isolate 70 mg (77% yield) of unreported addition adduct **123** as a thick syrup. Compound **123** was formed in 54% de (de determined by Method D, described in Section 2.3.2; HPLC solvent system and

retention times: 1% ^{i}PrOH/hexane, 12.77 min (*R*), 14.41 min (*S*)), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **123**: IR (neat film) 3426 (O-H stretch), 3057 (C-H aromatic stretch), 2926, 2836, 1027, 778, 726, 705cm^{-1}; ^{1}H NMR δ 7.55-7.95 (m, 6H, Ar-H), 7.25-7.5 (m, 6H, Ar-H), 5.7-5.8 (m, 1H, Bn-H), 2.8-3.9 (m, 8H, OCH_2 + OCH), 3.70 (s, 3H, OCH_3), 3.69* (s, 3H, OCH_3), 3.61* (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.41* (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 3.13* (s, 3H, OCH_3); ^{13}C NMR δ 138.7 (Ar-C), 136.3 (Ar-C), 133.5 (Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 127.9 (Ar-C), 127.3 (Ar-C), 127.2 (Ar-C), 125.8 (Ar-C), 125.8 (Ar-C), 125.3 (Ar-C), 125.2 (Ar-C), 123.9 (Ar-C), 123.6 (Ar-C), 123.0 (Ar-C), 122.8 (Ar-C), 100.4 (anomeric-C), 87.7 (OCH), 85.0 (OCH), 79.9* (OCH), 79.8 (OCH), 71.6 (OCH), 71.3 (OCH), 70.0 (OCH_2), 67.3* (OCH_2), 67.1 (OCH_2), 65.7* (OCH_2), 61.5 (OCH_3), 61.4* (OCH_3), 60.7 (OCH_3), 60.1 (OCH_3), 59.5* (OCH_3), 59.3 (OCH_3); MS *m/z* 295.1 (M^+-OCH_2CH(OH)-1-naphthyl, 100), 500.2 (98), 505.1 ($M^+ + Na^+$, 48); HRMS (FAB) calcd for $C_{28}H_{34}NaO_7$ 505.2202, found 505.2231.

2.3.37 1-(4-Methoxyphenyl)-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-ethanol ***124***

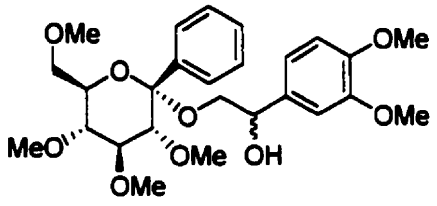


To a cooled solution (-78 °C) of **102** (110 mg, 0.179 mmol) in Et_2O (5 mL) was added a solution of 1.40 M *n*-BuLi in hexane (0.26 mL, 0.357 mmol) dropwise and the resulting solution was

stirred for 50 min. *p*-Anisaldehyde (65 μL, 0.537 mmol) was next added dropwise and the resulting solution was stirred for an additional 20 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 20% to 50% EtOAc/hexane to neat EtOAc to 15% MeOH/EtOAc) to isolate 60 mg (74% yield) of unreported addition adduct **124** as a thick syrup. Compound **124** was formed in 55% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **124**: IR (neat film) 3431 (O-H stretch), 2836, 1095 (C-O stretch), 1031 (C-O stretch), 828, 715cm^{-1}; ^{1}H NMR δ 7.55-7.65 (m, 2H, *m*-Ph-H), 7.15-7.45 (m, 5H, Ar-H), 6.75-6.9 (m, 2H, *o*-Ph-H), 4.94-5.00 (m, 1H, Bn-H), 4.89* (dd, 1H, J = 4.4, 8.2 Hz, Bn-H), 3.2-4.0 (m, 7H, OCH_2 + OCH), 3.75 (s, 3H, OCH_3), 3.72* (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.66* (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.44* (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 3.08* (s, 3H, OCH_3), 2.90 (d, 1H, J = 9.5 Hz, OCH), 2.87* (d, 1H, J = 9.5 Hz, OCH); ^{13}C NMR δ 159.1 (Ar-C), 138.5 (Ar-C), 133.0 (Ar-C), 128.1 (Ar-C), 127.9 (Ar-C), 127.4 (Ar-C), 127.2 (Ar-C), 127.1 (Ar-C), 113.7 (Ar-C), 100.4 (anomeric-C), 87.7 (OCH), 84.9 (OCH), 79.9 (OCH), 72.4 (OCH), 71.5 (OCH), 71.4 (OCH_2), 67.5 (OCH_2), 61.4 (OCH_3), 61.3* (OCH_3), 60.7 (OCH_3), 60.1* (OCH_3), 60.1 (OCH_3), 59.4* (OCH_3), 59.4 (OCH_3), 55.1 (OCH_3); MS *m/z* 295.1 (M^+-$OCH_2CH(OH)C_6H_4$-4-OMe, 41), 485.1 (M^+ + Na^+, 100). Anal. Calcd for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41. Found: C, 64.78; H, 7.60.

2.3.38 1-(3,4-Dimethoxyphenyl)-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-ethanol ***125***

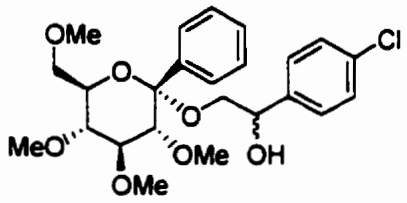


To a cooled solution (-78 °C) of **102** (297 mg, 0.483 mmol) in Et_2O (10 mL) was added a solution of 1.40 M *n*-BuLi in hexane (0.69 mL, 0.965 mmol) dropwise and the resulting solution was stirred for 1 h. 3,4-Dimethoxybenzaldehyde (241 mg, 1.45 mmol) was added next, and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (20 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 20% to 50% to 80% EtOAc/hexane to neat EtOAc) to isolate 156 mg (68% yield) of unreported addition adduct **125** as a thick syrup. Compound **125** was formed in 59% de (de determined by Method C, described in Section 2.3.2; HPLC solvent system and retention times: 12% ^{i}PrOH/hexane, 8.07 min (*R*), 11.81 min (*S*)), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **125**: IR (neat film) 3435 (O-H stretch), 2835, 1096 (C-O stretch), 1029 (C-O stretch), 811, 769, 719 cm^{-1}; ^1H NMR δ 7.55-7.65 (m, 2H, Ar-H), 7.25-7.45 (m, 3H, Ar-H), 6.7-6.9 (m, 3H, 3,4-OMe-Ph-H), 4.9-5.0 (m, 1H, Bn-H), 2.8-4.0 (m, 8H, OCH_2 + OCH), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.11 (s, 3H, OCH_3); ^{13}C NMR δ 148.7 (Ar-C), 148.4* (Ar-C), 148.3

(Ar-C), 138.2 (Ar-C), 137.9* (Ar-C), 134.0* (Ar-C), 133.9 (Ar-C), 127.8 (Ar-C), 127.6 (Ar-C), 127.0* (Ar-C), 126.9 (Ar-C), 118.4* (Ar-C), 118.1 (Ar-C), 110.9 (Ar-C), 109.4 (Ar-C), 100.2 (anomeric-C), 87.5 (OCH), 84.7 (OCH), 84.6* (OCH), 79.6 (OCH), 72.3 (OCH), 71.2 (OCH_2), 67.3 (OCH_2), 67.1* (OCH_2), 61.1 (OCH_3), 60.3 (OCH_3), 59.8 (OCH_3), 59.2* (OCH_3), 59.1 (OCH_3), 55.7 (OCH_3), 55.5 (OCH_3); MS *m/z* 295.2 (M^+-$OCH_2CH(OH)C_6H_4$-3,4-OMe, 4), 515.1 (M + Na^+, 100). Anal. Calcd for $C_{26}H_{36}O_9$: C, 63.40; H, 7.37. Found: C, 63.16; H, 7.12.

2.3.39 1-(4-Chlorophenyl)-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-ethanol **126**

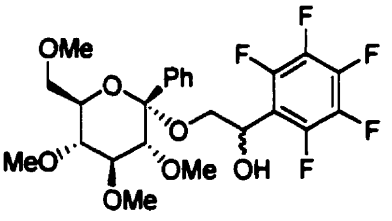


To a cooled solution (-78 °C) of **102** (112 mg, 0.182 mmol) in Et_2O (5 mL) was added a solution of 1.40 M *n*-BuLi in hexane (0.26 mL, 0.364 mmol) dropwise and the resulting solution was stirred for 50 min. 4-Chlorobenzaldehyde (77 mg, 0.546 mmol) was next added dropwise and the resulting solution was stirred for an additional 20 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: EtOAc/hexane) to isolate 58 mg (68% yield) of unreported addition adduct **126** as a thick syrup. Compound **126** was formed in 39% de (de determined by Method C, described in Section 2.3.2; HPLC solvent system

and retention times: 2% ^{i}PrOH/hexane, 8.60 min (*R*), 9.25 min (*S*)), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **126**: IR (neat film) 3417 (O-H stretch), 2836, 1030 (C-O stretch), 1014 (C-O stretch), 773, 729, 709 cm^{-1}; ^{1}H NMR δ 7.58 (dd, 2H, J = 1.8, 8.0 Hz, Ar-H), 7.15-7.4 (m, 7H, Ar-H), 4.97 (dd, 1H, J = 4.0, 7.7 Hz, Bn-H), 4.92* (dd, 1H, J = 3.5, 9.0 Hz, Bn-H), 3.0-3.9 (m, 7H, OCH_2 + OCH), 3.67 (s, 3H, OCH_3), 3.65* (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.44* (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 3.09* (s, 3H, OCH_3), 2.90 (d, 1H, J = 9.5 Hz, OCH), 2.88* (d, 1H, J = 9.5 Hz, OCH); ^{13}C NMR δ 139.4 (Ar-C), 139.3* (Ar-C), 138.3 (Ar-C), 138.0* (Ar-C), 133.3 (Ar-C), 128.3 (Ar-C), 128.2* (Ar-C), 128.0 (Ar-C), 127.6* (Ar-C), 127.4 (Ar-C), 127.2* (Ar-C), 127.1 (Ar-C), 126.1 (Ar-C), 100.6* (anomeric-C), 100.4 (anomeric-C), 87.7 (OCH), 84.9 (OCH), 80.0* (OCH), 79.9 (OCH), 72.2 (OCH), 72.0* (OCH), 71.6 (OCH), 71.5 (OCH_2), 67.3 (OCH_2), 61.5 (OCH_3), 61.4* (OCH_3), 60.7 (OCH_3), 60.2* (OCH_3), 60.1 (OCH_3), 59.5* (OCH_3), 59.4 (OCH_3); MS *m/z* 295.1 (M^{+}-$OCH_2CH(OH)C_6H_4$-4-Cl, 100), 489.1 ((^{35}Cl) M + Na^{+}, 48), 491.0 ((^{37}Cl) M + Na^{+}, 16). Anal. Calcd for $C_{24}H_{31}ClO_7$: C, 61.73; H, 6.69. Found: C, 61.66; H, 7.00.

2.3.40 1-(2,3,4,5,6-Pentafluorophenyl)-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-ethanol **127**

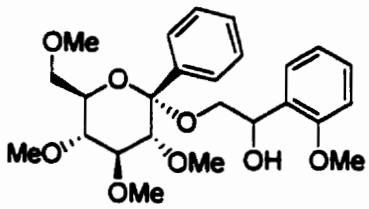


To a cooled solution (-78 °C) of **102** (179 mg, 0.291 mmol) in Et_2O (5 mL) was added a solution of 1.40 M *n*-BuLi in hexane (0.42 mL, 0.582 mmol) dropwise and the resulting solution was stirred for 1 h. Pentafluorobenzaldehyde (108 μL, 0.873 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 20% to 30% to 40% EtOAc/hexane) to isolate 115 mg (76% yield) of unreported addition adduct **127** as a thick syrup. Compound **127** was formed in 44% de (de determined by Method C, described in Section 2.3.2; HPLC solvent system and retention times: 5.5% ^{i}PrOH/hexane, retention times: 4.23 min (*S*), 9.96 min (*R*)) with the major diastereomer possessing the *R* configuration at the carbinol carbon.

The following characterization data was obtained for **127**: IR (neat film) 3408 (O-H stretch), 2837, 1035 (C-O stretch), 996 (C-O stretch), 777, 723, 710 cm^{-1}; ^1H NMR δ 7.25-7.45 (m, 3H, Ar-H), 7.5-7.65 (m, 2H, Ar-H), 5.36* (dd, 1H, J = 2.3, 8.2 Hz, Bn-H), 5.31 (dd, 1H, J = 4.3, 8.3 Hz, Bn-H), 3.0-3.9 (m, 7H, OCH_2 + OCH), 3.66* (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3),

3.46* (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.12* (s, 3H, OCH_3), 3.09 (s, 3H, OCH_3), 2.90* (d, 1H, J = 9.5 Hz, OCH), 2.88 (d, 1H, J = 9.5 Hz, OCH); ^{13}C NMR δ 145.1 (br d, ^1J = 248 Hz, Ar-C), 141.4 (br d, ^1J = 226 Hz, Ar-C), 137.9 (Ar-C), 137.5 (Ar-C), 137.5 (br d, ^1J = 253 Hz, Ar-C), 128.3 (Ar-C), 128.0 (Ar-C), 127.8 (Ar-C), 127.1 (Ar-C), 127.0 (Ar-C), 126.2 (Ar-C), 114.4 (br m, Ar-C), 100.6 (anomeric-C), 100.4* (anomeric-C), 87.5 (OCH), 85.0* (OCH), 84.8 (OCH), 79.8* (OCH), 79.7 (OCH), 72.0 (OCH), 71.6* (OCH), 71.5* (OCH), 71.4 (OCH), 65.4* (OCH_2), 65.0 (OCH_2), 64.4* (OCH_2), 64.2 (OCH_2), 61.4* (OCH_3), 61.3 (OCH_3), 60.6 (OCH_3), 60.2 (OCH_3), 60.1* (OCH_3), 59.4 (OCH_3), 59.3* (OCH_3); ^{19}F NMR δ -142.9 to – 143.5 (m, 2F), -154.9 to –155.9 (m, 1F), -162.3 to – 163.1 (m, 2F); MS *m/z* 295.1 (M^+ - $OCH_2CH(OH)C_6F_5$, 100), 545.0 (M + Na^+, 17). Anal. Calcd for $C_{24}H_{27}F_5O_7$: C, 55.17; H, 5.21. Found: C, 55.20; H, 5.37.

2.3.41 1-(2-Methoxyphenyl)-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-ethanol ***128***

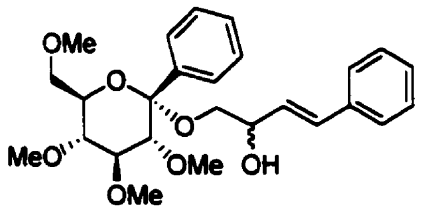


To a cooled solution (-78 °C) of **102** (164 mg, 0.266 mmol) in Et_2O (5 mL) was added a solution of 1.64 M *n*-BuLi in hexane (0.32 mL, 0.532 mmol) dropwise and the resulting solution was stirred for 1 h. *o*-Anisaldehyde (96 μL, 0.798 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The

combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 20% to 50% to 75% EtOAc/hexane to neat EtOAc) to isolate 114 mg (93% yield) of unreported addition adduct **128** as a thick syrup. Compound **128** was formed in 51% de (de determined by Method B, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following partial characterization data was obtained for **128**: IR (neat film) 3435 (O-H stretch), 1492, 1448, 1241, 1095 (C-O stretch), 801 cm^{-1}; ^1H NMR δ 7.52-7.65 (m, 2H, Ar-H), 7.11-7.46 (m, 5H, Ar-H), 6.91 (t, 1H, J = 7.5 Hz, Ar-H), 6.76 (t, 1H, J = 7.8 Hz, Ar-H), 5.28-5.40 (br m, 1H, Bn-H), 5.23* (dd, 1H, J = 3.0, 8.8 Hz, Bn-H), 3.89 (ddd, 1H, J = 1.9, 4.1, 10.1 Hz, $CH_3OCH_2C\underline{H}O$), 3.02-3.80 (m, 7H, OCH_2 + OCH), 3.74* (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.60* (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.10 (s, 3H, OCH_3), 3.08* (s, 3H, OCH_3); ^{13}C NMR (75.47 MHz) δ 156.0* (Ar-C), 155.9 (Ar-C), 138.5 (Ar-C), 138.2* (Ar-C), 128.8 (Ar-C), 128.5 (Ar-C), 128.3* (Ar-C), 128.3 (Ar-C), 128.0* (Ar-C), 127.9 (Ar-C), 127.9 (Ar-C), 127.8 (Ar-C), 127.3 (Ar-C), 127.0 (Ar-C), 126.8 (Ar-C), 120.5* (Ar-C), 120.5 (Ar-C), 109.9 (Ar-C), 100.5* (anomeric-C), 100.4 (anomeric-C), 87.8 (OCH), 87.7* (OCH), 84.8 (OCH), 84.8* (OCH), 79.8 (OCH), 71.1 (OCH), 71.4 (OCH), 71.3 (OCH), 68.3 (OCH_2), 66.3 (OCH_2), 66.0* (OCH_2), 61.5 (OCH_3), 61.4* (OCH_3), 60.8 (OCH_3), 60.8* (OCH_3), 60.3* (OCH_3), 60.2 (OCH_3), 59.5* (OCH_3), 59.4 (OCH_3), 55.0* (OCH_3), 54.9 (OCH_3).

2.3.42 (E)-4-Phenyl-1-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-3-buten-2-ol ***129***

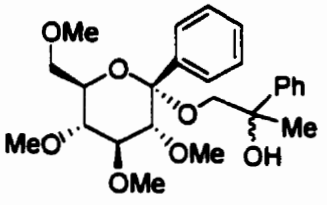


To a cooled solution (-78 °C) of **102** (120 mg, 0.195 mmol) in Et_2O (5 mL) was added a solution of 1.08 M *n*-BuLi in hexane (0.36 mL, 0.390 mmol) dropwise and the resulting solution was stirred for 1 h. Cinnamaldehyde (74 μL, 0.585 mmol) was next added dropwise and the resulting solution was stirred for an additional 20 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 15% to 30% to 50% EtOAc/hexane) to isolate 53 mg (59% yield) of unreported addition adduct **129** as a thick syrup. Compound **129** was formed in 32% de (de determined by Method C, described in Section 2.3.2; HPLC solvent system and retention times: 4% ^{i}PrOH/hexane, retention times: 13.83 min (*S*), 32.79 min (*R*)), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **129**: IR (neat film) 3424 (O-H stretch), 2835, 1029 (C-O stretch), 749, 725, 697 cm^{-1}; ^1H NMR δ 7.55-7.65 (m, 2H, Ar-H), 7.15-7.45 (m, 8H, Ar-H), 6.65* (dd, 1H, J = 1.2, 16.0 Hz, vinyl-H), 6.63 (dd, 1H, J = 1.3, 16.0 Hz, vinyl-H), 6.09* (dd, 1H, J = 6.1, 16.0 Hz, vinyl-H), 6.07 (dd, 1H, J = 6.1, 16.0 Hz, vinyl-H), 4.5-4.7 (m, 1H, allylic-H), 3.91 (ddd, 1H, J = 2.1, 4.2, 10.0 Hz, $CH_3OCH_2C\underline{H}O$), 3.15-3.8 (m, 6H, OCH_2 + OCH), 3.67 (s,

3H, OCH_3), 3.67* (s, 3H, OCH_3), 3.59* (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.47* (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 3.09* (s, 3H, OCH_3), 2.91 (d, 1H, J = 9.6 Hz, OCH), 2.89* (d, 1H, J = 9.5 Hz, OCH); ^{13}C NMR δ 138.4 (Ar-C), 138.1* (Ar-C), 136.7* (Ar-C), 136.6 (Ar-C), 131.5* (Ar-C), 131.3 (Ar-C), 128.4 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.5 (Ar-C), 127.3* (Ar-C), 127.2 (Ar-C), 126.4 (Ar-C), 100.6* (anomeric-C), 100.4 (anomeric-C), 87.7 (OCH), 85.0 (OCH), 84.9* (OCH), 80.0* (OCH), 79.9 (OCH), 72.0* (OCH), 71.6 (OCH), 71.5 (OCH), 71.2 (OCH_2), 66.0 (OCH_2), 65.8* (OCH_2), 61.5 (OCH_3), 61.4* (OCH_3), 60.7 (OCH_3), 60.2* (OCH_3), 60.1 (OCH_3), 59.5* (OCH_3), 59.4 (OCH_3); MS *m/z* 295.1 (M^+ - $OCH_2CH(OH)CHCHPh$, 100), 476.2 (M + NH_4^+, 10), 481.0 (M + Na^+, 8). Anal. Calcd for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 68.05; H, 7.59.

2.3.43 2-Phenyl-1-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-2-propanol ***130***

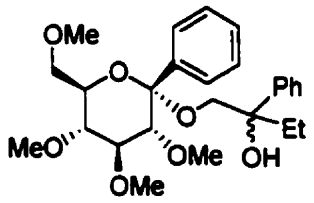


To a cooled solution (-78 °C) of **102** (126 mg, 0.205 mmol) in Et_2O (5 mL) was added a solution of 1.08 M *n*-BuLi in hexane (0.38 mL, 0.409 mmol) dropwise and the resulting solution was stirred for 1 h. Acetophenone (72 μL, 0.615 mmol) was next added dropwise and the resulting solution was stirred for an additional 20 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The

combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 15% to 30% to 50% EtOAc/hexane) to isolate 55 mg (60% yield) of unreported addition adduct **130** as a thick syrup. Compound **130** was formed in 56% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **130**: IR (neat film) 3421 (O-H stretch), 1039 (C-O stretch), 765, 703 cm^{-1}; ^1H NMR δ 7.15-7.6 (m, 10H, Ar-H), 3.0-3.8 (m, 7H, OCH_2 + OCH), 3.60 (s, 3H, OCH_3), 3.58* (s, 3H, OCH_3), 3.47* (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.06 (s, 3H, OCH_3), 3.04* (s, 3H, OCH_3), 2.87* (d, 1H, J = 9.5 Hz), 2.80 (d, 1H, J = 9.5 Hz), 1.65* (s, 3H), 1.56 (s, 3H); ^{13}C NMR δ 145.7 (Ar-C), 138.2 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 127.3 (Ar-C), 126.9* (Ar-C), 126.8 (Ar-C), 125.1* (Ar-C), 125.0 (Ar-C), 100.2 (anomeric-C), 87.8* (OCH), 87.7 (OCH), 85.0* (OCH), 84.5 (OCH), 80.1* (OCH), 79.6 (OCH), 73.8 (OCH), 73.6* (OCH), 71.9* (OCH), 71.6* (OCH), 71.5 (OCH), 71.3 (OCH_2), 69.6 (OCH_2), 69.2* (OCH_2), 61.3 (OCH_3), 61.3* (OCH_3), 60.7* (OCH_3), 60.6 (OCH_3), 60.2* (OCH_3), 59.7 (OCH_3), 59.6* (OCH_3), 59.5 (OCH_3), 26.9*, 26.5; MS *m/z* 295.1 (M^+ - $OCH_2C(OH)(Ph)Me$, 100), 464.2 (M + NH_4^+); HRMS (FAB) calcd for $C_{25}H_{34}NaO_7$ 469.2202, found 469.2184.

2.3.44 2-Phenyl-1-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-2-pyranyl]oxy-2-butanol ***131***

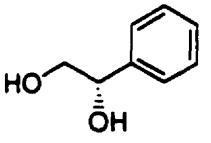


To a cooled solution (-78 °C) of **102** (132.5 mg, 0.215 mmol) in Et_2O (5 mL) was added a solution of 1.08 M *n*-BuLi in hexane (0.40 mL, 0.431 mmol) dropwise and the resulting solution was stirred for 1 h. Propiophenone (86 μL, 0.645 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 10% to 30% EtOAc/hexane) to isolate 64 mg (65% yield) of unreported addition adduct **131** as a thick syrup. Compound **131** was formed in 40% de (de determined by Method A, described in Section 2.3.2), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **131**: IR (neat film) 3439 (O-H stretch), 2835, 1046 (C-O stretch), 1000 (C-O stretch), 764, 731, 703 cm^{-1}; ^1H NMR δ 7.15-7.7 (m, 10H, Ar-H), 3.0-3.7 (m, 7H), 3.59 (s, 3H, OCH_3), 3.59* (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.06 (s, 3H, OCH_3), 3.03* (s, 3H, OCH_3), 2.86* (d, 1H, J = 9.5 Hz, OCH), 2.80 (d, 1H, J = 9.5 Hz, OCH), 1.7-2.2 (m, 2H, $C\underline{H}_2CH_3$), 0.7-0.8 (m, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR δ 143.9 (Ar-C), 143.1* (Ar-C), 138.2 (Ar-C), 138.0* (Ar-C), 128.1 (Ar-C), 128.0* (Ar-C), 127.9 (Ar-C), 127.9 (Ar-

C), 127.3 (Ar-C), 126.6* (Ar-C), 126.6 (Ar-C), 125.5 (Ar-C), 100.3* (anomeric-C), 100.1 (anomeric-C), 87.8 (OCH), 87.2* (OCH), 85.0* (OCH), 84.5 (OCH), 80.1* (OCH), 79.6 (OCH), 76.3 (OCH), 76.1* (OCH), 71.9* (OCH), 71.6* (OCH), 71.4 (OCH), 71.3 (OCH_2), 69.0 (OCH_2), 68.7* (OCH_2), 61.4 (OCH_3), 61.3* (OCH_3), 60.7* (OCH_3), 60.5 (OCH_3), 60.3* (OCH_3), 59.6 (OCH_3), 59.5* (OCH_3), 59.4 (OCH_3), 31.6* ($\underline{C}H_2CH_3$), 31.4 ($\underline{C}H_2CH_3$), 7.5* ($CH_2\underline{C}H_3$), 7.4 ($CH_2\underline{C}H_3$); MS *m/z* 295.1 (M^+ - $OCH_2C(OH)(Et)Ph$, 100), 483.1 (M + Na^+, 4). Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.68; H, 7.68.

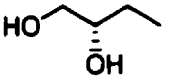
2.3.45 (S)-1-Phenyl-1,2-ethanediol ***132***



To a stirred solution of addition product **115** (30% de, determined by Method B described in Section 2.3.2), (116 mg, 0.268 mmol) in MeOH (10 mL) was added Dowex 50W-X8 resin (270 mg) (acidic form) and the resulting mixture was refluxed for 4 h, then stirred at rt overnight. The resin was then filtered off, and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: hexane to 10% to 15% to 40% EtOAc/hexane) to isolate in order of elution: 57 mg (65% yield) of **119** as a colourless oil, and 25 mg (68% yield) of known diol[32] **132** as a white solid. Compound **132** was also determined to exist in 34% ee (ee determined by Method A, described in Section 2.3.2: HPLC solvent system and retention times: 5% ^{i}PrOH/hexane, 19.80 min (*R*), 21.33 min (*S*)), with the major enantiomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **132**: mp 61-62 °C; lit.[32] mp (for a racemic sample) 64.5-65.5 °C; $[\alpha]_D^{22}$ +20.0 (c = 0.5, $CHCl_3$); lit.[33] (for a sample of 99% ee, *S* configuration) $[\alpha]_D^{22}$ +38.90 (c = 3.61, EtOH),; ^{1}H NMR δ 7.25-7.45 (m, 5H, Ar-H), 4.79 (dd, 1H, J = 3.6, 8.0 Hz, Bn-H), 3.55-3.80 (m, 2H, $C\underline{H}_2OH$), 2.85 (br s, 2H, OH).

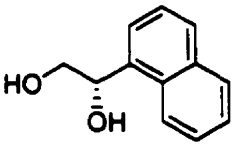
*2.3.46 (S)-1,2-butanediol **133***



To a stirred solution of addition product **122** (33% de, determined by Method B described in Section 2.3.2), (77 mg, 0.200 mmol) in MeOH (10 mL) was added Dowex 50W-X8 resin (200 mg) (acidic form) and the resulting mixture was refluxed for 4 h, then stirred at rt overnight. The resin was then filtered off, and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: 20% to 75% EtOAc/hexane) to isolate in order of elution: 54 mg (83% yield) of **119** as a colourless oil, and 8.1 mg (45% yield) of known diol[33] **133** as a colourless oil. Compound **133** was also determined to exist in 27% ee (ee determined by Method E, described in Section 2.3.2, by an optical rotation comparison to the literature value given below), with the major enantiomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **133**: $[\alpha]_D^{22}$ –3.46 (c = 0.81, EtOH); lit.[33] (for a sample of 77% ee, *S* configuration) $[\alpha]_D^{22}$ –9.40 (c = 2.59, EtOH); ^{1}H NMR δ 3.6-3.75 (m, 2H, $C\underline{H}_2OH$), 3.45 (dd, 1H, J = 8.2, 11.5 Hz, $C\underline{H}OH$), 2.31 (br s, 2H, OH), 1.4-1.6 (m, 2H, $C\underline{H}_2CH_3$), 0.97 (t, 3H, J = 7.5 Hz, $CH_2C\underline{H}_3$).

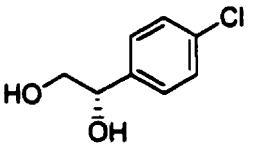
*2.3.47 (S)-1-(1-naphthyl)-1,2-ethanediol **134***



To a stirred solution of addition product **123** (54% de, determined by Method D described in Section 2.3.2), (106 mg, 0.220 mmol) in MeOH (4 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (8 mg, 0.032 mmol) and the resulting mixture was refluxed for 24 h. The solvent was then removed *in vacuo* and the resulting crude mixture was purified by silica gel chromatography (EtOAc/hexane) to isolate in order of elution: 66 mg (92% yield) of **119** as a colourless oil, and 41 mg (98% yield) of known diol[34] **134** as a white solid. Compound **134** was also determined to exist in 68% ee (ee determined by Method E, described in Section 2.3.2, by an optical rotation comparison to the literature value given below), with the major enantiomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **134**: mp 124-130 °C; lit.[35] mp 146-147 °C (for a racemic mixture); $[\alpha]_D^{22}$ +51.9 (c = 0.57, MeOH); lit.[34] (value given for *R* enantiomer) $[\alpha]_D^{22}$ –76.8 (c = 1.00, MeOH); ^{1}H NMR δ 7.3-8.1 (m, 7H, Ar-H), 5.61 (dd, 1H, J = 2.9, 8.2 Hz, Bn-H), 3.6-4.1 (m, 2H, C<u>H</u>$_2$OH), 3.1 (br s, 1H, OH), 2.7 (br s, 1H, OH).

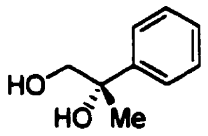
*2.3.48 (S)-1-(4-chlorophenyl)-1,2-ethanediol **135***



To a stirred solution of addition product **126** (39% de, determined by Method C described in Section 2.3.2), (114 mg, 0.244 mmol) in MeOH (10 mL) was added Dowex 50W-X8 resin (244 mg) (acidic form) and the resulting mixture was refluxed for 6 h, then stirred at rt for 12 h. The resin was then filtered off, and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: 20% to 50% EtOAc/hexane) to isolate in order of elution: 72 mg (90% yield) of **119** as a colourless oil, and 36 mg (86% yield) of known diol[36] **135** as a white solid. Compound **135** was also determined to exist in 43% ee (ee determined by Method A, described in Section 2.3.2, HPLC solvent system and retention times: 5% ^{i}PrOH/hexane, 20.34 min (*R*), 22.13 min (*S*)), with the major enantiomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **135**: mp 76-78 °C; lit.[37] mp (for a racemic sample) 83-84 °C; $[\alpha]_D^{22}$ +12.1 (c = 2.08, EtOH); lit.[36] (value given for *R* enantiomer) $[\alpha]_D^{22}$ –38.2 (c = 1.81, EtOH); ^{1}H NMR δ 7.25-7.45 (m, 4H, Ar-H), 4.78 (dd, 1H, J = 3.7, 8.1 Hz, Bn-H), 3.5-3.8 (m, 2H, C$\underline{H_2}$OH), 2.61 (br s, 2H, OH).

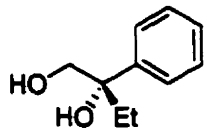
2.3.49 (S)-2-Phenyl-1,2-propanediol ***136***



To a stirred solution of addition product **130** (64% de, determined by Method B described in Section 2.3.2), (53.6 mg, 0.121 mmol) in MeOH (2 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (10 mg, 0.040 mmol) and the resulting mixture was refluxed for 17 h, then stirred at rt for 5 h, then refluxed for an additional 18 h. The solvent was then removed *in vacuo* and the resulting crude mixture was purified by silica gel chromatography (gradient elution: 20% to 30% to 40% to 50% EtOAc/hexane) to isolate in order of elution: 37.2 mg (94% yield) of **119** as a colourless oil, and 14 mg (76% yield) of known diol[38] **136** as a colourless oil. Compound **136** was also determined to exist in 56% ee (ee determined by Method A, described in Section 2.3.2, HPLC solvent system and retention times: 3% ^{i}PrOH/hexane, 22.18 min (*R*), 23.56 min (*S*)), with the major enantiomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **136**: $[\alpha]_D^{22}$ +2.92 (c = 0.6, EtOH); lit.[38] (for a sample of >96% ee, *S* configuration) $[\alpha]_D^{22}$ +4.76 (c = 4.2, EtOH); ^{1}H NMR δ 7.2-7.5 (m, 5H, Ar-H), 3.81 (d, 1H, 11.1 Hz, C<u>H</u>HOH), 3.64 (d, 1H, J = 11.1 Hz, CH<u>H</u>OH), 2.15 (br s, 2H, OH), 1.54 (s, 3H, CH_3).

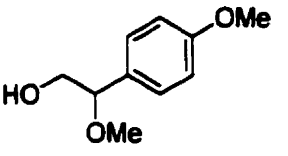
2.3.50 (S)-2-Phenyl-1,2-butanediol 137



To a stirred solution of addition product **131** (43% de, determined by Method B described in Section 2.3.2), (40 mg, 0.087 mmol) in MeOH (1 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (5 mg, 0.020 mmol) and the resulting mixture was refluxed for 7 h, then stirred at rt for 18 h, then refluxed for additional 6 h, and once again stirred at rt overnight. The solvent was then removed *in vacuo* and the resulting crude mixture was purified by silica gel chromatography (gradient elution: 15% to 20% to 25% EtOAc/hexane) to isolate in order of elution: 24 mg (85% yield) of **119** as a colourless oil, and 10.0 mg (69% yield) of known diol[38] **137** as a white solid. Compound **137** was also determined to exist in 40% ee (ee determined by Method A, described in Section 2.3.2, HPLC solvent system and retention times: 3% ^{i}PrOH/hexane, retention times: 18.05 min (*R*), 19.72 min (*S*)), with the major enantiomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **137**: mp 46-49 °C; $[\alpha]_D^{22}$ –2.55 (c = 0.94, EtOH); lit.[38] (value given for a sample of >96% ee, *S* configuration) $[\alpha]_D^{22}$ –13.95 (c = 0.6, EtOH), (>96% ee, *S*); ^{1}H NMR δ 7.2-7.5 (m, 5H, Ar-H), 3.84 (d, 1H, J = 11.1 Hz, C<u>H</u>HOH), 3.68 (d, 1H, J = 11.1 Hz, CH<u>H</u>OH), 2.6 (br s, 1H, OH), 1.85 (br s, 1H, OH), 1.7-1.9 (q, 2H, J = 7.4 Hz, C<u>H</u>$_2$CH$_3$), 0.77 (t, 3H, J = 7.4 Hz, CH$_2$C<u>H</u>$_3$).

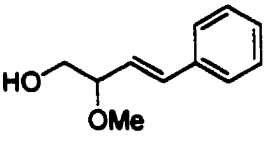
*2.3.51 (+/-)-2-Methoxy-2-(4-methoxy-phenyl)-ethanol **138***



To a stirred solution of addition product **124** (55% de, determined by Method B described in Section 2.3.2), (280 mg, 0.605 mmol) in MeOH (12 mL) was added Dowex 50W-X8 resin (600 mg) (acidic form) and the resulting mixture was refluxed overnight. The mixture was cooled to rt, and the resin was filtered off, then the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: EtOAc/hexane) to isolate in order of elution: 52 mg (26% yield) of **119** as a colourless oil, and 35 mg (32% yield) of known[39] **138** as a white solid.

The following characterization data was obtained for **138**: mp 64-66 °C; ^{1}H NMR δ 7.23 (d, 2H, J = 8.5 Hz, *m*-Ph-H), 6.90 (d, 2H, J = 8.6 Hz, *o*-Ph-H), 4.25 (dd, 1H, J = 3.9, 8.3 Hz, OCH), 3.81 (s, 3H, OMe), 3.45-3.75 (m, 2H, CH_2OH), 3.28 (s, 3H, OMe), 2.34 (br s, 1H, OH).

*2.3.52 (+/-)-3(E)-2-Methoxy-4-phenyl-but-3-en-1-ol **139***

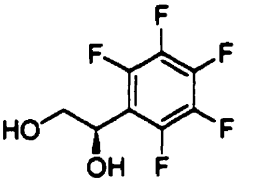


To a stirred solution of addition product **129** (32% de, determined by Method B described in Section 2.3.2), (113 mg, 0.246 mmol) in MeOH (10 mL) was added Dowex 50W-X8 resin (250 mg)

(acidic form) and the resulting mixture was refluxed for 3 h. The mixture was cooled to rt, and the resin was filtered off, then the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: EtOAc/hexane) to isolate in order of elution: 73 mg (91% yield) of **119** as a colourless oil, and 26 mg (59% yield) of known[40] **139** as a colourless oil.

The following characterization data was obtained for **139**: ^{1}H NMR δ 7.21-7.45 (m, 5H, Ar-H), 6.65 (d, 1H, J = 16.0 Hz, vinyl-H), 6.05 (dd, 1H, J = 7.8, 16.0 Hz, vinyl-H), 3.82-3.95 (m, 1H, C<u>H</u>OCH$_3$), 3.58-3.72 (m, 2H, C<u>H$_2$</u>OH), 3.39 (s, 3H, OMe), 2.17 (br s, 1H, OH).

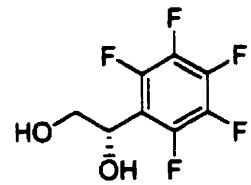
*2.3.53 (R)-1-Pentafluorophenylethane-1,2-diol **140***



To a stirred solution of addition product **127** (44% de, determined by Method C described in Section 2.3.2), (127 mg, 0.243 mmol) in MeOH (5 mL) was added Dowex 50W-X8 resin (243 mg) (acidic form) and the resulting mixture was refluxed for 3 h, then stirred at rt overnight. The resin was then filtered off, and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: EtOAc/hexane) to isolate in order of elution: 60 mg (76% yield) of **119** as a colourless oil, and 30 mg (54% yield) of known diol (reported in racemic form)[41] **140** as a white solid. Compound **140** was also determined to exist in 27% ee (ee determined by Method A, described in Section 2.3.2, HPLC solvent system and retention times: 5% ^{i}PrOH/hexane, 15.89 min (*R*), 16.80 min (*S*)), with the major enantiomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **140**: mp 74-87 °C; $[\alpha]_D^{22}$ +4.60 (c = 0.80, EtOH); ^{1}H NMR δ 5.20 (dd, 1H, J = 4.0, 7.9 Hz, OCH), 3.99 (dd, 1H, J = 7.9, 11.2 Hz, CHHOH), 3.82 (dd, 1H, J = 4.0, 11.2 Hz, CHHOH), 2.92 (br s, 1H, OH), 2.30 (br s, 1H, OH).

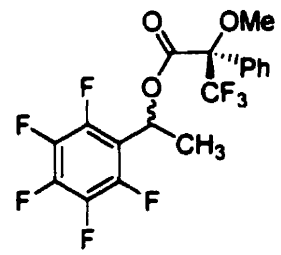
2.3.54 (S)-1-Pentafluorophenylethane-1,2-diol ***140-S***



This compound has only been reported in its racemic form[41] was prepared by following the general procedure for the Sharpless asymmetric dihydroxylation reaction[17] of pentafluorostyrene (138 μL, 1.00 mmol) and AD-mix-α (1.40 g) in *t*-BuOH (5 mL)/H_2O (5 mL). Purification of crude material (250 mg) occurred by silica gel chromatography (gradient elution: EtOAc/hexane) to afford 200 mg (88% yield) of **140-*S*** as a white solid. Compound **140-*S*** was also determined to be formed in 86% ee (ee determined by Method A: HPLC solvent system and retention times: 5% ^{i}PrOH/hexane, 15.94 min (*R*), 16.77 min (*S*)), with the major enantiomer determined to possess the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **140-*S***: mp 69-70 °C; $[\alpha]_D^{22}$ -7.93 (c = 0.74, EtOH); ^{1}H NMR δ 5.20 (dd, 1H, J = 4.0, 7.9 Hz, OCH), 3.99 (dd, 1H, J = 7.9, 11.2 Hz, CHHOH), 3.82 (dd, 1H, J = 4.0, 11.2 Hz, CHHOH), 2.92 (br s, 1H, OH), 2.30 (br s, 1H, OH).

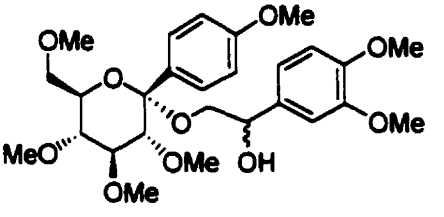
2.3.55 (1S/R)-1-Pentafluorophenylethyl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ***143***



This unknown compound was prepared following a procedure modified from that described by Kolb and Sharpless.[19] Trimethylsilyl chloride (216 μL, 1.70 mmol) was added to a solution of diol **140-*S*** (86% ee, 258 mg, 1.13 mmol) and trimethyl orthoacetate (216 μL, 1.70 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The solution was stirred for 90 min and then evaporated. The residue was dissolved in anhydrous MeOH (5 mL), then K_2CO_3 (469 mg, 3.39 mmol) was added. The suspension was stirred for 90 min, then H_2O (5 mL) and hexane (20 mL) were added. The layers were separated and the aqueous layer was extracted with hexane (20 mL). The combined organic layers were then dried over anhydrous Na_2SO_4 and filtered. One-third the volume (25 mL) of the combined dried organic layers was then cooled to 0 °C and THF (25 mL) was added followed by a 1 M solution of $LiAlH_4$ in THF (1.13 mL, 1.13 mmol). The mixture was stirred for 30 min after which the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, with the resulting salts being filtered off. (*S*)-MTPA-Cl (93 μL, 0.5 mmol) (from *R*-MTPA), Et_3N (139 μL, 1.0 mmol) and a catalytic amount of DMAP were then added to the filtrate. A thick white precipitate formed quickly and the mixture was stirred for 90 min. The mixture was then partitioned between H_2O (25 mL) and EtOAc (25 mL) followed by separating the two layers. The aqueous layer was then extracted with EtOAc, and the organic layers were combined, and dried over anhydrous Na_2SO_4. The solvent was then removed *in vacuo*, and the resulting crude material was purified by silica gel chromatography (EtOAc/hexane) to afford 11 mg

(9% overall yield from the diol **140-*S***) of the Mosher ester derivative **143** as an oil and as an approximate 3:1 mixture of (*R*:*R*):(*R*:*S*) diastereomers: ^{1}H NMR δ 7.30-7.60 (m, 5H, Ar-H), 5.45 (q, 1H, J = 5.5 Hz, OCH), 5.29* (q, 1H, J = 5.5 Hz, OCH), 3.53 (q, 3H, ^{5}J = 1.2 Hz, OMe), 1.43* (d, 1H, J = 5.5 Hz, CCH_3), 1.42 (d, 1H, J = 5.5 Hz, CCH_3).

2.3.56 1-(3,4-Dimethoxyphenyl)-2-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-(4-methoxyphenyl)tetrahydro-2H-2-pyranyl]oxy-1-ethanol ***144***

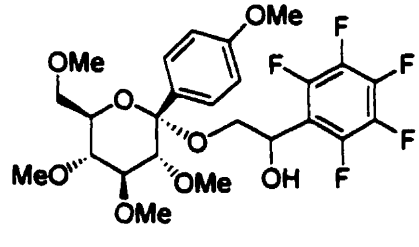


To a cooled solution (-78 °C) of **107** (132 mg, 0.205 mmol) in Et_2O (5 mL) was added a solution of 1.40 M *n*-BuLi in hexane (0.29 mL, 0.409 mmol) dropwise and the resulting solution was stirred for 1 h. 3,4-Dimethoxybenzaldehyde (102 mg, 0.615 mmol) was added next, and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: 50% to 75% EtOAc/hexane to neat EtOAc then 10% MeOH/EtOAc) to isolate 74 mg (69% yield) of unreported addition adduct **144** as a thick syrup. Compound **144** was formed in 56% de (de determined by Method C, described in Section 2.3.2; HPLC solvent system and retention times: 20%

'PrOH/hexane, 6.35 min (*R*), 8.75 min (*S*)), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **144**: IR (neat film) 3432 (O-H stretch), 1095 (C-O stretch), 1030 (C-O stretch), 827 cm^{-1}; ^1H NMR δ 7.73 (d, 2H, J = 8.9 Hz, 4-OMe-Ph-*m*-H), 6.7-7.0 (m, 5H, 3,4-OMe-Ph-H + 4-OMe-*o*-Ph-H), 4.85-5.0 (m, 1H, Bn-H), 3.1-4.0 (m, 7H, OCH_2 + OCH), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.16 (s, 3H, OCH_3), 2.88 (d, 1H, J = 9.6 Hz, OCH), 2.86* (d, 1H, J = 9.5 Hz, OCH); ^{13}C NMR δ 159.4 (Ar-C), 148.9 (Ar-C), 148.4 (Ar-C), 133.8 (Ar-C), 130.6 (Ar-C), 130.3* (Ar-C), 128.4* (Ar-C), 128.3 (Ar-C), 118.5* (Ar-C), 118.2 (Ar-C), 113.1 (Ar-C), 111.0 (Ar-C), 109.6* (Ar-C), 109.5 (Ar-C), 100.3* (anomeric-C), 100.2 (anomeric-C), 87.8 (OCH), 84.8 (OCH), 79.8 (OCH), 72.5 (OCH), 71.7* (OCH), 71.4 (OCH), 71.3 (OCH_2), 67.3 (OCH_2), 67.2* (OCH_2), 61.3 (OCH_3), 60.5 (OCH_3), 60.0 (OCH_3), 59.3* (OCH_3), 59.3 (OCH_3), 55.8 (OCH_3), 55.7 (OCH_3), 55.0 (OCH_3); MS *m/z* 325.1 (M^+ - $OCH_2CH(OH)C_6H_3$-3,4-OMe, 19), 540.2 (M + NH_4^+, 9), 545 (M + Na^+, 100); HRMS (FAB) calcd for $C_{27}H_{39}O_{10}$ 523.2543, found 523.2567.

2.3.57 2-(2,3,4,5,6-Pentafluorophenyl)-1-[(2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-(4-methoxyphenyl)tetrahydro-2H-2-pyranyl]oxy-1-ethanol ***145***



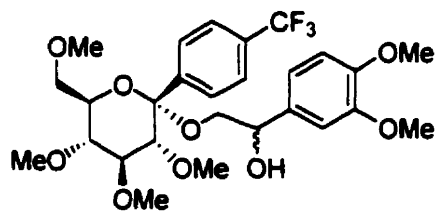
To a cooled solution (-78 °C) of **107** (106 mg, 0.164 mmol) in Et_2O (5 mL) was added a solution of 1.40 M *n*-BuLi in hexane (0.23 mL, 0.328 mmol) dropwise and the resulting solution was

stirred for 1 h. Pentafluorobenzaldehyde (61 μL, 0.493 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 20% to 30% to 40% to 50% to 60% EtOAc/hexane) to isolate 72 mg (80% yield) of unreported addition adduct **145** as a thick syrup. Compound **145** was formed in 39% de (de determined by Method C, described in Section 2.3.2; HPLC solvent system and retention times: 3% ^{i}PrOH/hexane, 5.43 min (*S*), 6.13 min (*R*)), with the major diastereomer possessing the *R* configuration at the carbinol carbon.

The following characterization data was obtained for **145**: IR (neat film) 3410 (O-H stretch), 1510, 1249, 1096 (C-O stretch), 838, 815 cm^{-1}; ^1H NMR δ 7.45-7.55 (m, 2H, Ar-H), 6.8-7.0 (m, 2H, Ar-H), 5.15-5.4 (m, 1H, Ar-H), 3.0-4.0 (m, 7H, Ar-H), 3.82 (s, 3H, OCH_3), 3.80* (s, 3H, OCH_3), 3.66* (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.45* (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.16* (s, 3H, OCH_3), 3.13 (s, 3H, OCH_3), 2.88* (d, 1H, J = 9.6 Hz, OCH), 2.86 (d, 1H, J = 9.6 Hz, OCH); ^{13}C NMR δ 159.7 (Ar-H), 145.0 (br d, ^1J = 255 Hz, Ar-H), 141.3 (br d, ^1J = 210 Hz, Ar-H), 137.6 (br d, ^1J = 253 Hz, Ar-H), 130.2 (Ar-H), 129.8 (Ar-H), 128.5 (Ar-H), 128.3 (Ar-H), 114.5 (br m, Ar-H), 113.4 (Ar-H), 100.6 (anomeric-H), 100.4* (anomeric-H), 87.7 (OCH), 85.1* (OCH), 84.9 (OCH), 79.9* (OCH), 79.8 (OCH), 72.0 (OCH), 71.6* (OCH), 71.5* (OCH), 71.5 (OCH), 65.7* (OCH_2), 65.5* (OCH_2), 65.1 (OCH_2), 64.4* (OCH_3), 64.2 (OCH_3), 61.5* (OCH_3), 61.4 (OCH_3), 60.7 (OCH_3), 60.2 (OCH_3), 60.2* (OCH_3), 59.4 (OCH_3), 59.3* (OCH_3), 55.1 (OCH_3); ^{19}F NMR δ -142.8 to –143.6 (m, 2F), -154.9 to –156.4 (m, 1F), -162.3 to –163.6 (m, 2F); MS *m/z* 325.1

(M^+ - $OCH_2CH(OH)C_6F_5$, 100), 570.0 (21), 575.0 (M + Na^+, 15). Anal. Calcd for $C_{25}H_{29}F_5O_8$: C, 54.35; H, 5.29. Found: C, 54.44; H, 5.40.

2.3.58 1-(3,4-Dimethoxyphenyl)-2-((2R,3S,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)-2-[4-(trifluoromethyl)phenyl]tetrahydro-2H-2-pyranyloxy)-1-ethanol ***146***



To a cooled solution (-78 °C) of **108** (153 mg, 0.224 mmol) in Et_2O (5 mL) was added a solution of 1.40 M *n*-BuLi in hexane (0.32 mL, 0.448 mmol) dropwise and the resulting solution was stirred for 1 h. 3,4-Dimethoxybenzaldehyde (112 mg, 0.672 mmol) was added next, and the resulting solution was stirred for an additional 20 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution: hexane to 30% to 50% to 60% to 80% EtOAc/hexane to neat EtOAc) to isolate 62 mg (49% yield) of unreported addition adduct **146** as a thick syrup. Compound **146** was formed in 39% de (de determined by Method D, described in Section 2.3.2; HPLC solvent system and retention times: 20% ^{i}PrOH/hexane: 5.75 min (*R*), 7.86 min (*S*)), with the major diastereomer possessing the *S* configuration at the carbinol carbon.

The following characterization data was obtained for **146**: IR (neat film) 3429 (O-H stretch), 1091 (C-O stretch), 1067 (C-O stretch), 766, 687 cm^{-1}; ^1H NMR δ 7.73* (d, 2H, J = 8.7 Hz, Ar-H), 7.72 (d, 2H, J = 8.2 Hz, Ar-H), 7.62* (d, 2H, J = 8.7 Hz, Ar-H), 7.61 (d, 2H, J = 8.2 Hz, Ar-H), 6.7-6.9 (m, 3H, 3,4-OMe-Ph-H), 4.85-5.0 (m, 1H, Bn-H), 3.93 (ddd, 1H, J = 2.1, 4.2, 10.1 Hz, CH_3OCH_2CHO), 3.85* (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.66* (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.58* (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.43* (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 3.11* (s, 3H, OCH_3), 3.0-3.8 (m, 6H, OCH_2 + OCH), 2.88 (d, 1H, J = 9.5 Hz, OCH), 2.86* (s, 1H, J = 9.5 Hz, OCH); ^{13}C NMR (75.5 MHz) δ 148.9 (Ar-C), 148.6* (Ar-C), 142.3 (Ar-C), 142.0* (Ar-C), 133.3 (Ar-C), 133.3* (Ar-C), 130.4 (q, ^2J = 32 Hz, Ar-C), 127.8* (Ar-C), 127.7 (Ar-C), 124.9 (Ar-C), 124.9* (Ar-C), 124.1* (q, ^1J = 272 Hz, Ar-C), 124.0 (q, ^1J = 272 Hz, Ar-C), 118.5* (Ar-C), 118.3 (Ar-C), 110.9 (Ar-C), 109.3* (Ar-C), 109.2 (Ar-C), 100.1* (anomeric-C), 100.0 (anomeric-C), 87.2* (OCH), 87.2 (OCH), 84.9 (OCH), 84.8* (OCH), 79.7* (OCH), 79.7 (OCH), 72.5 (OCH), 72.5* (OCH), 72.0* (OCH), 71.6 (OCH), 71.3 (OCH), 67.6 (OCH_2), 67.5 (OCH_2), 61.6 (OCH_3), 61.5* (OCH_3), 60.8 (OCH_3), 60.4* (OCH_3), 60.3 (OCH_3), 59.4* (OCH_3), 59.4 (OCH_3), 55.8 (OCH_3), 55.7 (OCH_3); ^{19}F NMR δ -63.52*, -63.53; MS *m/z* 331.1 (100), 363.0 (M^+ - $OCH_2CH(OH)C_6H_3$-3,4-OMe, 96); HRMS (FAB) calcd for $C_{27}H_{35}F_3NaO_9$: 583.2131, found 583.2145.

2.4 References

[1] Frese, P. *Diplome-Chemiker Thesis*, University of Waterloo, **1996**.

[2] Vogel, A.I. *Vogel's Textbook of Practical Organic Chemistry*; 5th edition; revised by: Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R.; John Wiley & Sons Inc.: New York, 1989; pp. 663-664.

[3] Hultman, D. P.; Schroeder, L. R.; Haigh, F. C. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1525.

[4] Mikake, T.; Tsuchiya, T.; Umezasawa, S.; Saito, S.; Umezawa, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1387.

[5] Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

[6] March, J. *Advanced Organic Chemistry*; 4th edition; John Wiley & Sons, Inc.: New York, 1992; pp. 488-490, 932.

[7] (a) Audin, P.; Doutheau, A.; Gore, J. *Tetrahedron Lett.* **1982**, *23*, 4337. (b) Hernández, J. E.; Cisneros, A.; Fernández, S. *Synth. Commun.* **1983**, *13*, 191. (c) Burke, S. D.; Deaton, D. N. *Tetrahedron Lett.* **1991**, *32*, 4651. (d) Martin, S. F.; Anderson, B. G.; Daniel, D.; Gauchen, A. *Tetrahedron* **1997**, *53*, 8997. (e) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700.

[8] (a) Asbun, W.; Binkley, S.B. *J. Org. Chem.* **1968**, *33*, 140. (b) Ogura, H.; Takahashi, H. *J. Org. Chem.* **1974**, *39*, 1374. (c) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (d) Bihovsky, R.; Selick, C.; Giusti, I. *J. Org. Chem.* **1988**, *53*, 4026. (e) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752. (f) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610. (g) Rosenblum, S. B.; Bihovsky, R. *J. Am. Chem. Soc.* **1990**, *112*, 2746. (h) Lay, L.; Nicotra, F.; Panza, L.; Russo, G.; Caneva, E. *J. Org. Chem.* **1992**, *57*, 1304. (i) Martin, O. R.; Saavedra, O. M. *Tetrahedron Lett.* **1995**, *36*, 799. (j) McDonald, F. E.; Zhu, H. Y. H.; Holmquist, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 6605.

[9] (a) Biellmann, J. F; Ducep, J. B.; Schmitt, J. L.; Vicens, J. J. *Tetrahedron* **1976**, *32*, 1061. (b) Zahorszky, U. I.; Uwe, I. *J. Chem. Soc. Perkin Trans. 2* **1983**, 1655. (c) Doherty, A. M.; Ley, S. V.; Lygo, B.; Williams, D. J. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1371. (d) Niwa, H.; Yoshida, Y.; Hasegawa, T.; Yamada, K. *Chem. Lett.* **1985**, 1687. (e) Snowden, R.L.; Linder, S. M.; Muller, B. L.; Schulte, K. H. *Helv. Chim. Acta.* **1987**, *70*, 1879. (f) Lehmann, J.; Marquardt, N. *Liebigs Ann. Chem.* **1988**, 827.

[10] Best, W. M.; Ferro, V.; Harle, J.; Stick, R. V. *Aust. J. Chem.* **1997**, *50*, 463.

[11] Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp. 5-20.

[12] (a) Schmidt, R. R. *Comprehensive Organic Synthesis*; Trost, B.M.; Paquette, L.A., Eds.; Pergamon Press: Oxford, 1991; volume 6, pp. 49-54. (b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.

[13] (a) Weber, G. F.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 364. (b) Shiozaki, M. *J. Org. Chem.* **1991**, *56*, 528. (c) Heskamp, B. M.; Veeneman, G. H.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron* **1995**, *51*, 5657. (d) Crich, D.; Hwang, J.-T.; Yuan, H. *J. Org. Chem.* **1996**, *61*, 6189. (e) Dondoni, A.; Marra, A.; Rojo, I.; Scherrmann, M.-C. *Tetrahedron* **1996**, *52*, 3057. (f) Lay, L.; Meldal, M.; Nicotra, F.; Panza, L.; Russo, G. *Chem. Commun.* **1997**, 1469. (g) van Hooft, P. A. V.; Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 6061. (h) Borbas, A.; Szabovik, G.; Antal, Z.; Feher, K.; Csavas, M.; Szilagyi, L.; Herczegh, P.; Liptak, A. *Tetrahedron: Asymmetry* **2000**, *11*, 549. (i) Leeuwenburgh, M. A.; Appeldoorn, C. C. M.; van Hooft, P. A. V.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Eur. J. Org. Chem.* **2000**, 873.

[14] Silverstein, R. M.; Bassler, G. C.; Morill, T. C. *Spectrometric Identification of Organic Compounds*; 5th edition; John Wiley & Sons, Inc.: New York, 1991; p.237.

[15] Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987; pp. 149, 165-176.

[16] Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201.

[17] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

[18] Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

[19] Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.

[20] Martyn, L. J. P.; Pandiaraju, S.; Yudin, A. K. *J. Organomet. Chem.* **2000**, *603*, 98.

[21] Coldham, I., Holman, S.; Lang-Anderson, M. M. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1481.

[22] Ortiz, J.; Guijarro, A.; Yus, M. *An. Quim. Int. Ed.* **1997**, *93*, 44.

[23] Seitz, D. E.; Carroll, J. J.; Cartaya M., C. P.; Lee, S.-H.; Zapata, A. *Synth. Commun.* **1983**, *13*, 129.

[24] Lee, C. K.; Kim, E. J.; Lee, I.-S. H. *Carbohydrate Res.* **1993**, *240*, 197.

[25] Wolfrom, H. *J. Am. Chem. Soc.* **1937**, *59*, 2559.

[26] Wakefield, B. J. *Organolithiums in Organic Synthesis*; Academic Press: Toronto, 1988; p. 24.

[27] Gilman, H.; Moore, F.; Baine, O. *J. Am. Chem. Soc.* **1941**, *63*, 2479.

[28] Pohmakotr, M.; Geiss, K.-H.; Seebach, D. *Chem. Ber.* **1979**, *112*, 1420.

[29] *Organic Syntheses Collective Volume VI*; Noland, W. E., Ed.; John Wiley & Sons: New York, 1988; p. 695.

[30] *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; volume 2, pp. 1031-1034.

[31] Kjohaas, R. A.; Vawter, E. J.; *J. Org. Chem.* **1986**, *51*, 3993.

[32] Cohen, T.; Dughi, M.; Notaro, V. A.; Pinkus, G. *J. Org. Chem.* **1962**, *27*, 814.

[33] Cho, B. T.; Chun, Y. S. *J. Org. Chem.* **1998**, 5280.

[34] Miao, G.; Rossiter, B. *J. Org. Chem.* **1995**, *60*, 8424.

[35] Russell, G. A.; Mikol, G. J. *J. Am. Chem. Soc.* **1966**, *88*, 5498.

[36] Kawasaki, K.-I.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337.

[37] Pedragosa-Moreau, S.; Morisseau, C.; Zylber, J.; Archelas, A.; Baratti, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 7402.

[38] Colombo, L.; Di Giacomo, M.; Brusotti, G.; Milano, E. *Tetrahedron Lett.* **1995**, *36*, 2863.

[39] Kojima, M.; Kuriyama, Y.; Sakuragi, H.; Katsumi, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2724.

[40] Cotterill, I. C.; Shelton, M. C.; Machemer, D. E. W.; Henderson, D. P.; Toone, E. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1335.

[41] Hermann, W. A.; Eder, S. J. *Chem. Ber.* **1993**, *126*, 31.

CHAPTER 3

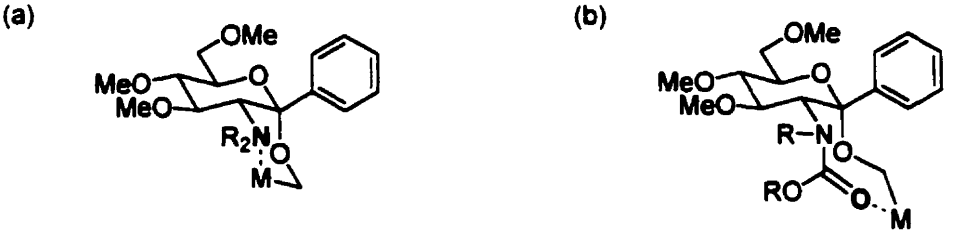
A GLUCOSAMINE-DERIVED CHIRAL AUXILIARY

3.1 Introduction

It was discussed in Chapter 2 that attempts were made to increase the likelihood of intramolecular coordination of the metal to the C-2 oxygen of the auxiliary by experimenting with different solvents and metals. This chapter discusses the efforts made to increase the chance for intramolecular coordination of the metal to the C-2 position of the auxiliary by changing the nature of the C-2 substituent on the auxiliary.

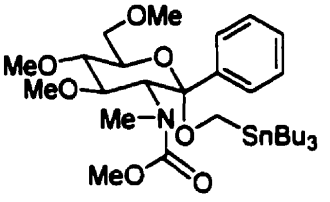
A nitrogen atom at the C-2 site of the auxiliary may have a greater potential to coordinate to the metal in the transmetalated intermediate (Figure 19a). Furthermore, a carbamate protecting group on the nitrogen may also have the potential to coordinate to the metal (Figure 19b).

Figure 19. (a) Intramolecular coordination involving the C-2 nitrogen atom or (b) the carbamate group.



Therefore, this chapter discusses the synthesis of a sugar-derived chiral reagent, containing the tributylstannylmethoxy substituent and a carbamate protected nitrogen atom at the C-2 position (compound **149**) (Figure 20), from glucosamine. The result obtained in the transmetalation of stannane **149** and subsequent addition to benzaldehyde will also be discussed. The introduction of a different heteroatom at the C-2 position represents the second structural modification studied during the chiral auxiliary design process in this thesis.

Figure 20. A glucosamine-derived stannane.



149

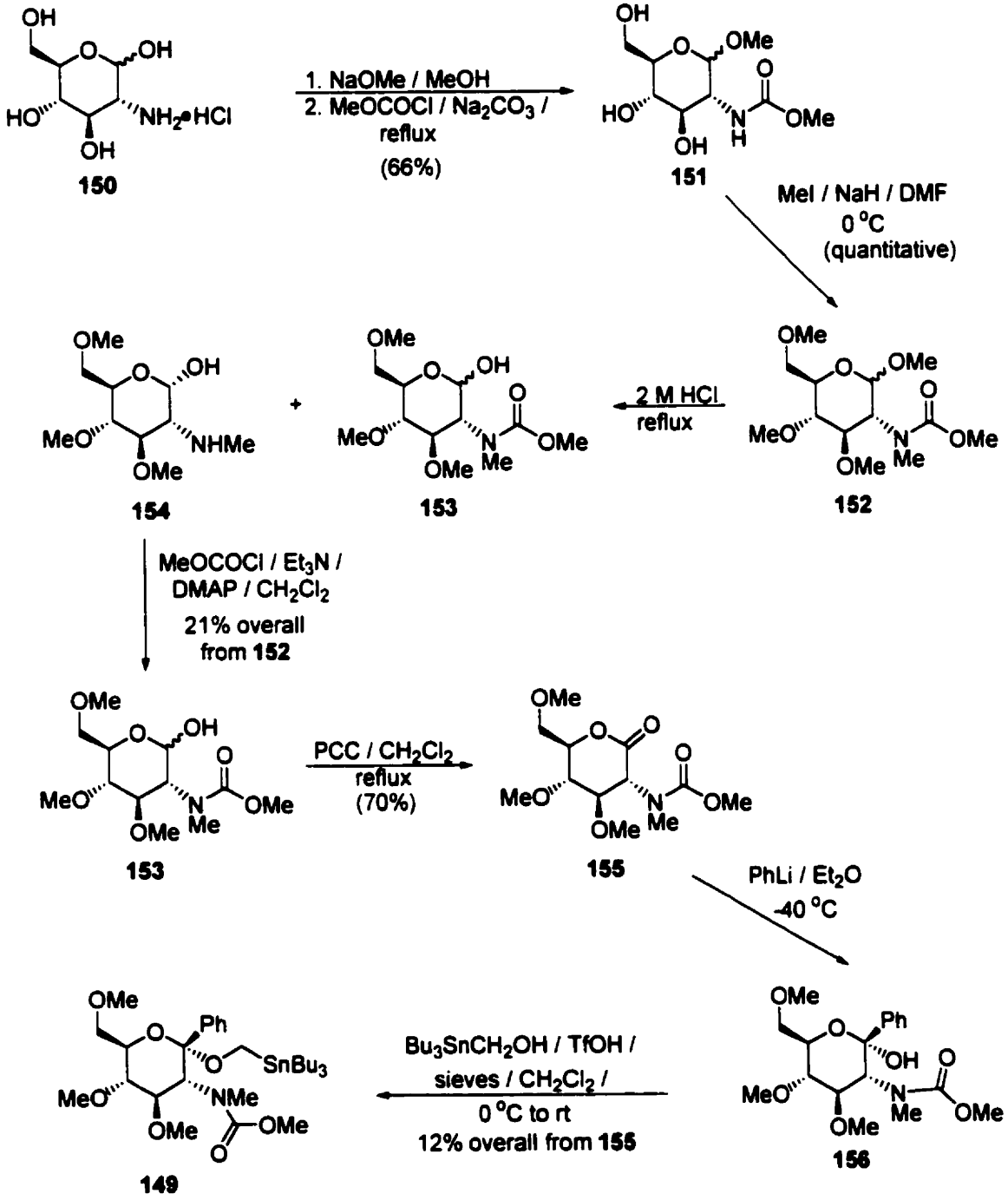
3.2 Results and Discussion

*3.2.1 Synthesis of the Glucosamine-Derived Compound **149***

The structure of glucosamine is identical to glucose with the exception that the 2-hydroxy group is replaced with a 2-amino substituent. Therefore glucosamine was an appropriate starting material to employ in the study of substituting an oxygen atom for a nitrogen atom at the C-2 position. The carbamate group was first introduced by treating glucosamine•HCl **150** with NaOMe and methyl chloroformate to form **151** (Scheme 45).[1] The compound **151** was then permethylated to

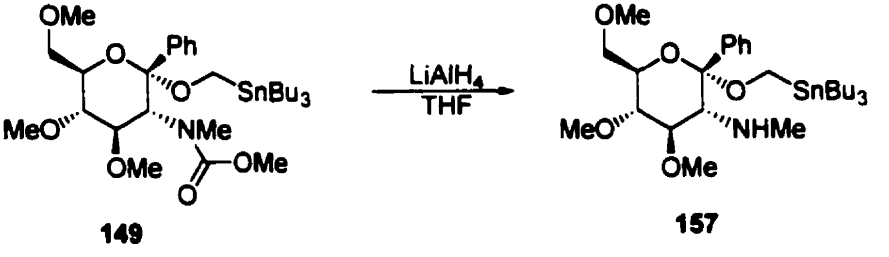
afford **152** in a quantitative yield. A provisional identification was made for **152** based on IR, low resolution MS, and by ^{1}H and ^{13}C NMR data. Deprotection of the anomeric oxygen was problematic since conversion to the lactol **153** was slow with decomposition of the starting material occurring at the same time. A provisional identification was also made for **153** based on IR, and by ^{1}H and ^{13}C NMR data. Furthermore the carbamate protecting group was cleaved off under the acidic conditions to give **154** along with the desired product **153**. However it was possible to convert **154** to the carbamate protected lactol **153** by treating the crude reaction mixture with methyl chloroformate to afford **153** in a 21% yield from **152**. The lactol **153** was then oxidized with PCC[2] to afford the lactone **155** in a 70% yield. Introduction of the phenyl group was effected with PhLi to form **156** followed by glycosylation of the crude reaction mixture with Bu_3SnCH_2OH to afford the stannane **149** in only a 12% yield from the lactone **155**. Compound **156** was provisionally identified based on IR, low resolution MS, and by ^{1}H and ^{13}C NMR data. A low overall yield was encountered for the last two steps since only about 40 to 50% of the lactone **155** was converted to **156** in the PhLi addition step and a low recovery of crude material also occurred (72% crude recovery).

Scheme 45


1. NaOMe / MeOH
2. MeOCOCl / Na2CO3 / reflux
(66%)
MeI / NaH / DMF
0 °C
(quantitative)
2 M HCl
reflux
MeOCOCl / Et3N / DMAP / CH2Cl2
21% overall from 152
PCC / CH2Cl2
reflux
(70%)
PhLi / Et2O
-40 °C
Bu3SnCH2OH / TfOH / sieves / CH2Cl2 /
0 °C to rt
12% overall from 155
150
151
152
153
154
155
156
149

The ^{1}H and ^{13}C NMR spectra of **149** showed 2 sets of signals in an approximate 2:1 ratio. This doubling of signals could be due to hindered rotation of the carbamate group (i.e. 2 rotamers) or to 2 diastereomers. To disprove the possibility of 2 diastereomers, **149** was treated with $LiAlH_4$ to form the unexpected secondary amine **157** (Scheme 46). It was expected that the tertiary amine (*N*, *N*-dimethyl compound) would form; however, the presence of hydroxides in the solution of $LiAlH_4$ may have caused the formation of **157** instead. Nevertheless, the ^{1}H NMR spectrum of **157** displayed only one set of signals. Therefore, only one diastereomer was formed in the glycosylation reaction between **156** and Bu_3SnCH_2OH.

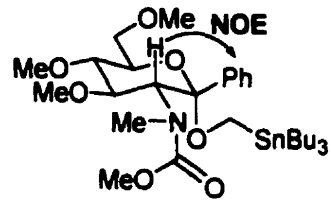
Scheme 46



149 **157**

In order to provide support for the α-glycoside stereochemistry in **149** a NOESY spectrum of **149** was taken. An NOE was visible between the C-2 proton and aromatic protons (Figure 21), while an NOE was absent between the C-2 proton and the protons on the methylene group connected to the Sn atom or to the protons in the Bu_3Sn group. Thus, it is reasonable to assign a *syn* relationship between the C-2 proton and phenyl group.

Figure 21. NOE correlation observed in a NOESY spectrum of **149**.

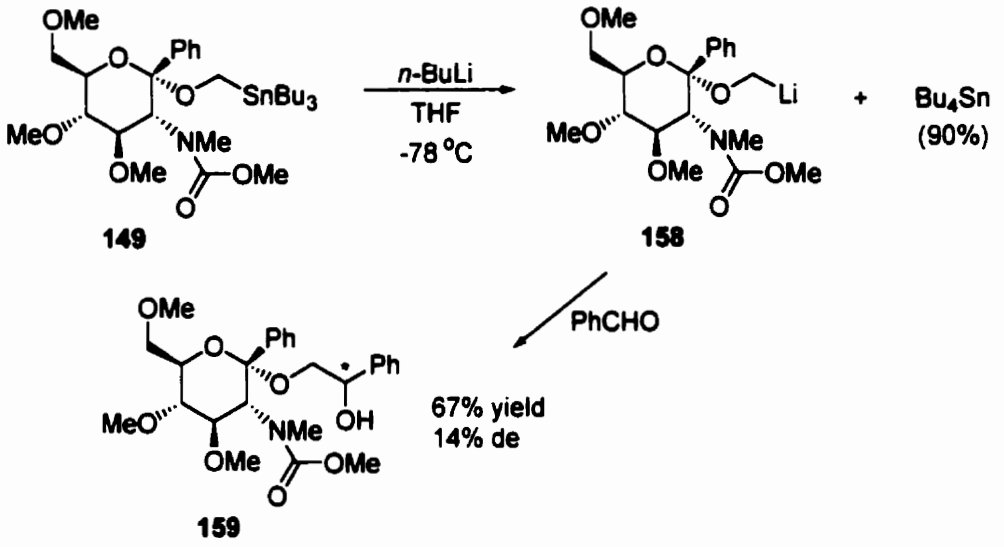


149

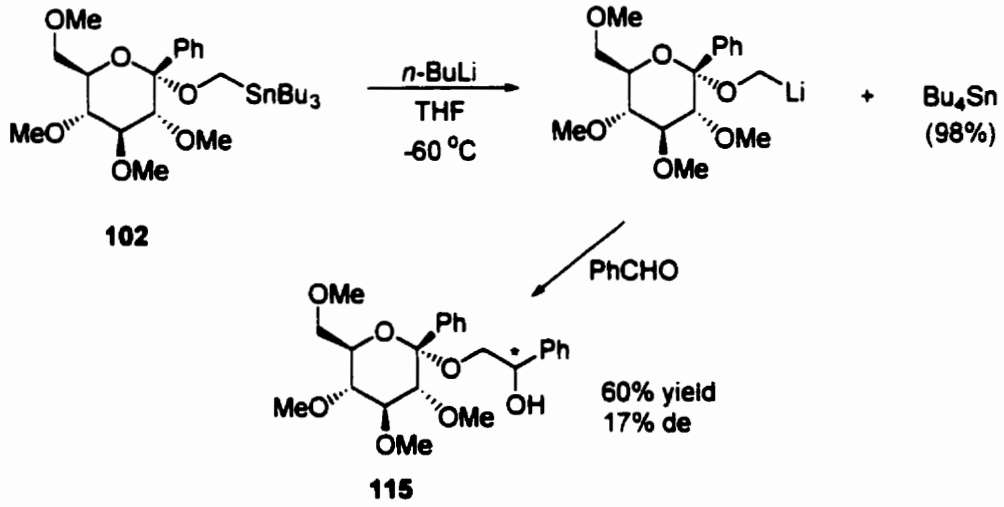
*3.2.2 Transmetalation of Stannane **149** and Subsequent Trapping with Benzaldehyde*

An attempt was first made to transmetalate the stannane **149** with *n*-BuLi in Et_2O; however, transmetalation did not occur and an addition to benzaldehyde was not possible. On the other hand, transmetalation occurred readily in THF to form the organolithium **158** with Bu_4Sn being formed in a 90% yield (Scheme 47). The addition step to benzaldehyde occurred to form **159** in a 67% yield though the selectivity achieved was very low at 14% de. A provisional identification was made for **159**, based on IR, low resolution MS, and by ^1H and ^{13}C NMR data. The lithiated glucose-derived stannane **102** with a phenyl anomeric group (Chapter 2) (Scheme 48), reacted with benzaldehyde in only 17% de when the reaction was conducted in THF.

Scheme 47



Scheme 48



The factor that may be reducing the potential for achieving higher levels of selectivity may be due to intermolecular coordination of the metal between two or more molecules of the metalated intermediate (i.e. aggregation) as was discussed in Chapter 2 and thus preventing the formation of the *cis*-fused bicyclic intermediate that is speculated to induce diastereoselectivity. As a result the

introduction of a group at the C-2 position that may have the potential for greater coordination ability would be futile if intermolecular coordination is occurring between the C-2 group and the metal of another molecule.

3.2.3 Summary and Conclusion

The introduction of a nitrogen atom at the C-2 position using a glucosamine-derived chiral auxiliary did not induce a greater level of diastereoselectivity to occur over the glucose-derived analog. Furthermore, the synthesis of the glucosamine-derived stannane **149** was difficult since very low yields were experienced in two steps.

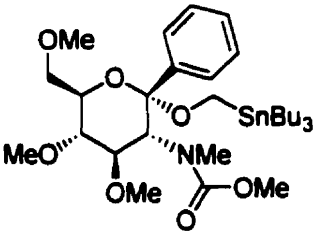
It was speculated that aggregation might reduce the amount of diastereoselectivity that could be possibly achieved with the auxiliaries designed so far. Further efforts were made to introduce structural features on other auxiliaries that would possibly reduce aggregation from occurring. The results of introducing additional structural modifications on other auxiliaries are discussed in the remaining chapters of this thesis.

3.3 Experimental

3.3.1 General

The general procedures described in Section 2.3.1 are applicable here with the following additions. In the instances were rotamers were characterized, an asterisk (*) indicates signals that could be unequivocally attributed to the minor rotamer. Signals for minor diastereomers are also noted with an asterisk. PhLi was obtained as indicated in Section 2.3.10.

3.3.2 Methyl N-(2S,3S,4R,5R,6R)-4,5-dimethoxy-6-(methoxymethyl)-2-phenyl-2-[(1,1,1-tributylstannyl)methoxy]tetrahydro-2H-3-pyranyl-N-methylcarbamate ***149***



This section describes the synthesis of unreported **149** from **155**, *via* unreported and not fully characterized synthetic intermediate methyl *N*-[(2*R*,3*S*,4*R*,5*R*,6*R*)-2-hydroxy-4,5-dimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2*H*-3-pyranyl]-*N*-methylcarbamate (**156**).

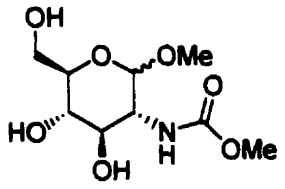
Synthetic intermediate **156** was first prepared as follows: To a -40 °C solution of lactone **155** (1.10 g, 3.77 mmol) in Et_2O (38 mL) was added a 0.83 M solution of PhLi in Et_2O (4.77 mL, 3.96 mmol) dropwise. The mixture was stirred for 75 minutes after which the reaction was quenched with methanol (1 mL) and stirred for another 5 minutes. A pH 8 buffer solution (1.5% NH_3 in an

aqueous saturated solution of NH_4Cl) (10 mL) was added to the mixture and the mixture was then allowed to reach rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, filtered, then concentrated *in vacuo* to afford 1.00 g of crude material (72% crude recovery, approximate 45% conversion by ^1H NMR spectroscopy) which was employed in the next step without any purification. Pure **156** was obtained for characterization purposes as a white solid by silica gel chromatography (gradient elution: 30% to 35% EtOAc/hexane) and as an approximate 1:1 mixture of rotamers: mp 144-146 °C; $[\alpha]_D^{22}$ = - 83.1 (c = 0.41, $CHCl_3$); IR (KBr) 3398 (O-H stretch), 2820, 1700 (C=O stretch), 1081 (C-O stretch), 769, 706 cm^{-1}; ^1H NMR δ 7.18-7.80 (m, 5H, Ar-H), 4.37 (dd, 1H, J = 8.7, 10.9 Hz, OCH), 3.30-4.20 (m, 5H, OCH_2 + OCH + NCH), 3.75 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.59* (s, 3H, OCH_3), 3.55* (s, 3H, OCH_3), 3.53* (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 3.41* (s, 3H, OCH_3), 3.06* (s, 3H, OCH_3), 3.00 (s, 3H, OCH_3), 2.95* (s, 3H, OCH_3), 2.34 (s, 1H, OH); ^{13}C NMR (75.47 MHz) δ 159.1 (C=O), 157.1* (C=O), 142.4 (Ar-C), 141.8* (Ar-C), 128.3* (Ar-C), 128.0 (Ar-C), 128.0 (Ar-C), 127.8* (Ar-C), 125.9 (Ar-C), 125.6* (Ar-C), 99.5* (anomeric-C), 98.7 (anomeric-C), 81.4 (OCH), 81.2* (OCH), 79.1* (OCH) 79.7 (OCH), 73.7 (OCH), 71.6* (OCH), 71.4 (OCH), 71.0* (OCH), 62.3 (NCH), 61.4* (NCH), 60.4 (OCH_3), 60.3 (OCH_3), 60.3* (OCH_3), 59.5* (OCH_3), 59.4 (OCH_3), 59.4* (OCH_3), 53.4 (OCH_3), 52.1* (OCH_3), 39.7 (NCH_3), 30.7 (NCH_3).

The titled compound was then prepared as follows: To a 0 °C solution of the crude reaction mixture (523 mg) isolated in Section 3.3.7 in CH_2Cl_2 (14 mL), was added 4 Å crushed molecular sieves (1.4 g), Bu_3SnCH_2OH (479 mg, 1.49 mmol), followed by TfOH (70 μL, 0.8 mmol). The mixture was then brought to rt and stirred for 4 days. The reaction was then quenched with Et_3N (1 mL) followed by filtering off all solid material. The filtrate was then concentrated *in vacuo* and the

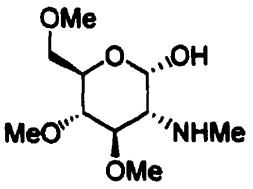
resulting crude material was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 25% EtOAc/hexane) to obtain 155 mg of the unreported compound **149** (12% overall yield from **155**) as a colorless oil and as an approximate 2:1 mixture of rotamers: $[\alpha]_D^{22}$ = + 44.1 (c = 0.68, $CHCl_3$); IR (neat film) 2854, 1708 (C=O stretch), 1453, 1126 (C-O stretch), 1001 (C-O stretch), 769, 705 cm^{-1}; ^1H NMR δ 7.18-7.49 (m, 5H, Ar-H), 4.20* (d, 1H, J = 11.1 Hz, NCH), 3.94 (d, 1H, J = 10.9 Hz, NCH), 3.13-3.85 (m, 6H, OCH_2 + OCH), 3.59 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.42* (s, 3H, OCH_3), 3.23 (d, 1H, J = 10.5 Hz, $OC\underline{H}HSnBu_3$), 3.06 (s, 3H, NCH_3), 3.01* (s, 3H, NCH_3), 2.96 (s, 3H, OCH_3), 1.11-1.67 (m, 12H, $Sn(CH_2C\underline{H_2}C\underline{H_2}CH_3)_3$), 0.70-1.08 (m, 15H, $Sn(C\underline{H_2}CH_2CH_2C\underline{H_3})_3$); ^{13}C NMR (50.32 MHz) δ 157.3* (C=O), 157.1 (C=O), 137.9 (Ar-C), 137.6* (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 126.7 (Ar-C), 104.1 (^3J = 20 Hz, anomeric-C), 80.7 (OCH), 80.4* (OCH), 79.1 (OCH), 78.6* (OCH), 72.4* (OCH), 72.0 (OCH), 71.4* (OCH_2), 71.2 (OCH_2), 62.8 (NCH), 62.1* (NCH), 60.0 (OCH_3), 59.4 (OCH_3), 59.0* (OCH_3), 58.3* (OCH_3), 52.4* (OCH_3), 51.9 (OCH_3), 50.0 ($O\underline{C}H_2SnBu_3$), 33.8* (NCH_3), 32.7* (NCH_3), 31.7 (NCH_3), 30.8 (NCH_3), 30.4* (NCH_3), 29.1 (^2J = 10 Hz, $SnCH_2\underline{C}H_2CH_2CH_3$), 27.3 ($^3J$ = 27 Hz, $Sn(CH_2)_2\underline{C}H_2CH_3$), 13.5 ($Sn(CH_2)_3\underline{C}H_3$), 8.8 ($^1J$ = 157, 162 Hz, $Sn\underline{C}H_2(CH_2)_2CH_3$). Anal. Calcd for $C_{31}H_{55}NO_7Sn$: C, 55.38; H, 8.24; N, 2.08. Found: C, 55.52; H, 8.08; N, 2.09.

3.3.3 Methyl 2-deoxy-2-methoxycarbonylamino-α/β-D-glucopyranoside **151**



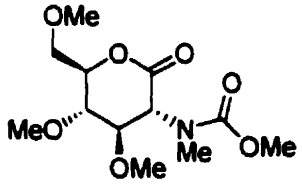
This known compound[1] was prepared by a procedure modified from that described by Otani.[1] To 1.3 L of anhydrous MeOH at 0 °C in a 3-neck 3 L flask equipped with an overhead stirrer was added Na (12.7 g, 0.55 mol) slowly followed by D-glucosamine•HCl (108 g, 0.5 mol) and anhydrous Na_2CO_3 (53.1 g, 0.5 mol). An addition funnel with 324 mL of methyl chloroformate (4.2 mol) was attached to the flask and the methyl chloroformate was added dropwise. After the addition was complete the reaction mixture was refluxed overnight. The reaction mixture was then cooled to 0 °C and Na_2CO_3 (approximately 250 g) was added slowly with stirring until the solution was slightly basic by pH paper. The mixture was then concentrated *in vacuo*, followed by removing salts by filtering the concentrated crude salt mixture through a plug of silica and washing the residue with a 15% solution of MeOH in EtOAc. The salt free filtrate was then concentrated *in vacuo* to afford 83 g of **151** (66% yield) as a white solid in an approximate 10:1 mixture of α- and β-anomers respectively: mp 119-121 °C;[1] lit. mp 150-151 °C (α anomer),[1] 197-198 °C (β anomer);[1] ^{1}H NMR (D_2O) δ 4.58-4.69 (br s, 1H, anomeric-H), 4.26* (d, 1H, J = 8.5 Hz, anomeric-H), 3.16-3.82 (m, 6H, OCH + NCH + OCH_2), 3.52 (s, 3H, $COOCH_3$), 3.23 (s, 3H, OCH_3).

3.3.4 2-Deoxy-2-N-methylamino-3,4,6-tri-O-methyl-α-D-glucopyranose 154



The above known compound[3] was isolated as a thick syrup, as a by-product during the preparation of **153**: ^{1}H NMR δ 5.26 (d, 1H, J = 3.5 Hz, anomeric-H), 3.18-3.95 (m, 4H, OCH + OCH_2), 3.62 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 2.92-3.05 (m, 1H, OCH), 2.50-2.61 (m, 1H, NCH), 2.42 (s, 3H, NCH_3).

3.3.5 2-Deoxy-2-(N-methoxycarbonyl-N-methylamino)-3,4,6-tri-O-methyl-D-glucono-1,5-lactone 155



This section describes the synthesis of unreported compound **155**, starting from known compound **151**, and *via* unreported and not fully characterized synthetic intermediates methyl 2-deoxy-2-(*N*-methoxycarbonyl-*N*-methylamino)-3,4,6-tri-*O*-methyl-α/β-D-glucopyranoside (**152**), and 2-deoxy-2-(*N*-methoxycarbonyl-*N*-methylamino)-3,4,6-tri-*O*-methyl-α/β-D-glucopyranose (**153**).

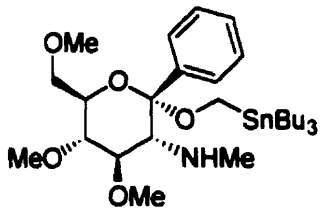
Synthetic intermediate **152** was first prepared as follows: To a solution of **151** (83 g, 0.33 mol) and MeI (103 mL, 1.65 mol) in dry DMF (2 L) at 0 °C was added NaH (66 g, 1.65 mol) slowly over a period of one hour. The reaction was over after the NaH addition was complete as judged by TLC. The excess NaH was quenched by adding H_2O (50 mL) slowly to the reaction mixture at 0 °C while stirring. The mixture was then concentrated *in vacuo* followed by dissolving the crude residue in H_2O (600 mL). The solution was then extracted with EtOAc (8 x 500 mL) followed by drying the combined organic layers with anhydrous Na_2SO_4. The dried mixture was then filtered and concentrated the in *vacuo* to afford 115.4 g of the unreported compound **152** (100% yield) as a light yellow oil and as an approximate 2:1 mixture of α:β anomers: IR (neat film) 2929, 2837, 1770, 1702, (C=O stretch), 1062 (C-O stretch) cm^{-1}; ^1H NMR δ 4.67 (dd, 1H, J = 3.2, 10.8 Hz, anomeric-H), 4.29* (dd, 1H, J = 3.2, 11.3 Hz, anomeric-H), 4.08 (dd, 1H, J = 3.2, 10.9 Hz, NCH), 3.28-3.78 (m, 5H, OCH + OCH_2), 3.55 (s, 6H, 2 OCH_3), 3.43 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 2.95 (s, 3H, NCH_3), 2.90* (s, 3H, NCH_3); ^{13}C NMR δ 157.7 (C=O), 100.4 (anomeric-C), 100.0* (anomeric-C), 80.8 (OCH), 80.5* (OCH), 78.1 (OCH), 77.8* (OCH), 71.1* (OCH), 70.8 (OCH), 70.1 (OCH_2), 60.0 (NCH), 59.1 (OCH_3), 58.1* (OCH_3), 57.6 (OCH_3), 57.2* (OCH_3), 54.8 (OCH_3), 52.6 (OCH_3), 30.5 (NCH_3), 30.3* (NCH_3); MS (ES) *m/z* 244.1 (M^+ - 2 CH_3OH, 17), 276.2 (M^+ - CH_3OH, 100), 277.1 (M^+ - OCH_3), 308.2 (M + H^+, 100).

Synthetic intermediate **153** was then prepared as follows: A solution of **152** (115.4 g, 0.38 mol) in 2 M HCl (2 L) was refluxed for 12 hours by which time all starting material had disappeared as judged by TLC. The reaction mixture was then cooled to 0 °C and solid $NaHCO_3$ (approximately 350 g) was slowly added (**Caution: vigorous bubbling occurs !**) until the solution was slightly basic by pH paper. The mixture was then extracted once with hexane (500 mL) to remove non-polar impurities. The aqueous layer was then concentrated to a volume of 600 mL and saturated with

$NaHCO_3$. This was followed by extracting the aqueous layer with EtOAc (7 x 600 mL), drying the combined EtOAc extracts over anhydrous Na_2SO_4 and concentrating the extracts *in vacuo* to afford 55.5 g of a crude mixture of **153** and **154**. The crude mixture was then dissolved in CH_2Cl_2 and cooled to 0 °C. A few crystals of DMAP were then added to the mixture followed by Et_3N (57 mL, 0.41 mol). Methyl chloroformate was then added dropwise and the mixture was stirred overnight. The reaction mixture was then concentrated *in vacuo* followed by purification of the crude material by silica gel chromatography (40% to 50% EtOAc/hexane) to afford 23.1 g (21% yield) of the unreported compound **153** as a thick syrup and as an approximate 1:1 mixture of α:β anomers and an approximate 2:1 mixture of rotamers: IR (neat film) 3386 (O-H stretch), 1702 (C=O stretch), 1459, 1135 (C-O stretch) cm^{-1}; ^1H NMR δ 5.83 (d, 1H, J = 6.9 Hz, β-anomer-anomeric-H), 5.74* (d, 1H, J = 6.8 Hz, β-anomer-anomeric-H), 5.27* (br t, 1H, J = 3.1 Hz, α-anomer-anomeric-H), 5.19* (br t, 1H, J = 3.6 Hz, α-anomer-anomeric-H), 3.19-4.10 (m, 5H, OCH_2 + OCH + NCH), 3.60* (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.54* (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.29 (t, 1H, J = 9.3 Hz, OCH), 3.00* (s, 3H, NCH_3), 2.98 (s, 3H, NCH_3), 2.96* (s, 3H, NCH_3); ^{13}C NMR (75.47 MHz) δ 158.1* (C=O), 157.2* (C=O), 157.1* (C=O), 156.8 (C=O), 94.8* (anomeric-C), 94.3 (anomeric-C), 93.1* (anomeric-C), 92.9* (anomeric-C), 81.1* (OCH), 80.8* (OCH), 79.1* (OCH), 77.7* (OCH), 77.5* (OCH), 77.2* (OCH), 76.6 (OCH), 75.9* (OCH), 75.4 (OCH), 73.2* (OCH), 71.7* (OCH), 71.6 (OCH), 71.1* (OCH_2), 71.0* (OCH_2), 70.1 (OCH_2), 69.7* (OCH_2), 60.2* (NCH), 60.0 (NCH), 59.8* (NCH), 59.5* (NCH), 59.1* (OCH_3), 59.0* (OCH_3), 59.0 (OCH_3), 59.0* (OCH_3), 58.9* (OCH_3), 58.8* (OCH_3), 58.7* (OCH_3), 58.0 (OCH_3), 58.0 (OCH_3), 57.7* (OCH_3), 57.6* (OCH_3), 57.3 (OCH_3), 56.8* (OCH_3), 54.6* (OCH_3), 52.7* (OCH_3), 52.6* (OCH_3), 31.2* (NCH_3), 30.5* (NCH_3), 29.0 (NCH_3).

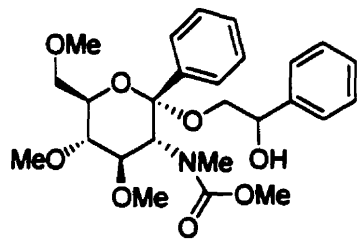
Compound **155** was then prepared by a procedure modified from that described by Corey and Suggs.[2] To a solution of lactol **153** (1.68 g, 5.73 mmol) in CH_2Cl_2 (100 mL) was added PCC (1.85 g, 8.59 mmol) and the mixture was refluxed for 5 hours. After cooling to rt the reaction mixture was diluted with anhydrous Et_2O (400 mL) then filtered through a pad of Florisil, followed by washing the residue with EtOAc (400 mL). The filtrate was concentrated *in vacuo* and the resulting crude material was purified by silica gel chromatography (gradient elution: hexane to 40% to 50% EtOAc/hexane) in order to isolate 1.17 g of **155** (70% yield) as a white solid and as an approximate 2:1 mixture of rotamers: mp 62-64 °C; $[\alpha]_D^{22}$ = + 124.0 (c = 1.16, $CHCl_3$); IR (neat film) 1747 (C=O lactone stretch), 1686 (C=O carbamate stretch), 1492, 1074 (C-O stretch), 996 (C-O stretch), 780, 690, 657, 604 cm^{-1}; ^1H NMR δ 4.24 (dt, 1H, J = 2.5, 9.2 Hz, $CH_3OCH_2C\underline{H}O$), 4.00-4.14* (m, 1H, NCH), 3.30-3.90 (m, 4H, OCH + OCH_2), 3.74 (s, 3H, OCH_3), 3.58 (s, 6H, 2 OCH_3), 3.41 (s, 3H, OCH_3), 3.10 (s, 3H, NCH_3), 3.06* (s, 3H, NCH_3); ^{13}C NMR δ 167.1 (lactone C=O), 156.1 (carbamate C=O), 80.9 (OCH), 77.1 (OCH), 76.9* (OCH), 76.8 (OCH), 75.9* (OCH), 69.6* (OCH), 69.3 (OCH_2), 63.8 (NCH), 62.3* (NCH), 59.3 (OCH_3), 59.2 (OCH_3), 58.3 (OCH_3), 54.8* (OCH_3), 52.1 (OCH_3), 52.0* (OCH_3), 35.5 (NCH_3), 34.9* (NCH_3). Anal. Calcd for $C_{12}H_{21}NO_7$: C, 49.48; H, 7.27; N, 4.81. Found: C, 49.33; H, 7.04; N, 4.76.

3.3.6 *N-(2S,3S,4R,5R,6R)-4,5-Dimethoxy-6-(methoxymethyl)-2-phenyl-2-[(1,1,1-tributylstannyl)methoxy]tetrahydro-2H-3-pyranyl-N-methylamine* **157**



To a solution of **149** (17 mg, 0.025 mmol) in THF (1 mL) was added a 1 M solution of $LiAlH_4$ in THF (25 μL, 0.025 mmol) and the mixture was stirred for one hour. The reaction was then quenched with $Na_2SO_4 \cdot 10\ H_2O$ (20 mg) and filtered through a small plug of Celite to afford the unreported compound **157** as a clear oil: IR (neat film) 2854, 1448, 1106 (C-O stretch), 1002 (C-O stretch), 700; ^1H NMR δ 7.24-7.60 (m, 5H, Ar-H), 3.18-3.93 (m, 7H, OCH_2 + OCH), 3.65 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 2.23-2.40 (m, 1H, NCH), 2.06 (s, 3H, NCH_3), 1.18-1.78 (m, 12 H, $Sn(CH_2C\underline{H}_2C\underline{H}_2CH_3)_3$), 0.70-1.12 (m, 15H, $Sn(C\underline{H}_2CH_2CH_2C\underline{H}_3)_3$); MS (FAB) *m/z* 105 (28), 294 (M^+ - OCH_2SnBu_3, 100), 558 (M^+ - C_4H_9, 5); HRMS (FAB) calcd for $C_{25}H_{44}NO_5Sn$ (M^+ - C_4H_9) 558.2241, found 558.2252.

3.3.7 *Methyl N-[(2R,3S,4R,5R,6R)-2-(2-hydroxy-2-phenylethoxy)-4,5-dimethoxy-6-(methoxymethyl)-2-phenyltetrahydro-2H-3-pyranyl]-N-methylcarbamate* **159**



To a cooled solution (-78 °C) of **149** (151 mg, 0.225 mmol) in THF (5 mL) was added a 1.53 M solution of *n*-BuLi in hexane (0.29 mL, 0.449 mmol) and the resulting mixture was stirred for 25 minutes. Benzaldehyde (69 μL, 0.675 mmol) was then added and the mixture was stirred for an additional 15 minutes after which the reaction was quenched with a saturated aqueous NH_4Cl solution (5 mL). The mixture was diluted with EtOAc (5 mL) followed by separating the aqueous layer. The aqueous layer was then extracted with EtOAc (3 x 25 mL), the organic layers were combined, dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The crude product was then purified by silica gel chromatography (gradient elution: hexane to 20% to 40% to 60% to 80% Et_2O/hexane to neat Et_2O) to isolate 70 mg of Bu_4Sn (90% yield) and 74 mg of the unreported compound **159** (67 % yield) as a white solid in 14% de (de determined by Method C outlined in Section 2.3.2; 50% ^{i}PrOH/hexane, retention times: 4.95 min (major diastereomer), 5.48 min (minor diastereomer)) and as an approximate 2:1 mixture of rotamers: mp 111-114 °C; IR (KBr disk) 3447 (O-H stretch), 2877, 1686 (C=O stretch), 1465, 1357, 1138 (C-O stretch),1081 (C-O stretch), 1054 (C-O stretch), 704 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.16-7.39 (m, 10H, Ar-H), 4.83-4.95 (m, 1H, Bn-H), 4.18* (d, 1H, J = 11.3 Hz, NCH), 4.18* (d, 1H, J = 11.1 Hz, NCH), 3.91* (d, 1H, J = 11.0 Hz, NCH), 3.91 (d, 1H, J = 11.0 Hz, NCH), 3.32-3.86 (m, 7H, OCH_2 + OCH), 3.58* (s, 3H, OCH_3), 3.58 (s, 3H,

OCH_3), 3.54 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.47* (s, 3H, OCH_3), 3.41* (s, 3H, OCH_3), 2.99 (s, 3H, NCH_3), 2.97* (s, 3H, NCH_3), 2.95 (s, 3H, OCH_3), 2.94* (s, 3H, OCH_3); ^{13}C (125.8 MHz) δ 157.3* (C=O), 157.1 (C=O), 141.1* (Ar-C), 141.0 (Ar-C), 140.9 (Ar-C), 140.8* (Ar-C), 137.7 (Ar-C), 137.6* (Ar-C), 137.4 (Ar-C), 137.3* (Ar-C), 128.3 (Ar-C), 128.3 (Ar-C), 128.2 (Ar-C), 128.2 (Ar-C), 128.0 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 127.8 (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 126.5 (Ar-C), 126.4 (Ar-C), 126.4 (Ar-C), 126.2 (Ar-C), 126.1 (Ar-C), 126.0 (Ar-C), 102.5* (anomeric-C), 102.4 (anomeric-C), 80.7* (OCH), 80.6 (OCH), 80.4* (OCH), 80.2* (OCH), 78.9* (OCH), 78.8 (OCH), 78.5* (OCH), 78.4* (OCH), 73.1 (OCH), 72.8* (OCH), 72.8* (OCH), 72.1* (OCH), 71.9* (OCH), 71.8* (OCH), 71.6 (OCH), 71.5* (OCH_2), 71.4* (OCH_2), 71.2* (OCH_2), 71.2 (OCH_2), 66.8* (OCH_2), 66.7 (OCH_2), 66.6* (OCH_2), 62.8* (NCH), 62.8 (NCH), 62.0* (NCH), 62.0* (NCH), 60.2* (OCH_3), 60.1 (OCH_3), 60.0* (OCH_3), 59.5* (OCH_3), 59.5* (OCH_3), 59.5* (OCH_3), 59.4 (OCH_3), 59.2* (OCH_3), 59.2 (OCH_3), 58.4* (OCH_3), 58.4* (OCH_3), 52.5* (OCH_3), 52.0 (OCH_3), 30.9* (NMe), 30.9 (NMe), 30.5* (NMe), 30.5* (NMe), 30.5* (NMe), 29.6* (NMe); MS (CI) (OH^-) *m/z* 145 (100), 158 (37), 255 (44), 352 (M^+ - $OCH_2CH(OH)Ph$, 3).

3.4 References

[1] Otani, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 781.

[2] Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

[3] Stoffyn, A.; Stoffyn, P.; Orr, J. C. *Carbohyd. Res.* **1972**, *23*, 251.

CHAPTER 4

A 3-METHOXY-TETRAHYDROPYRAN CHIRAL AUXILIARY

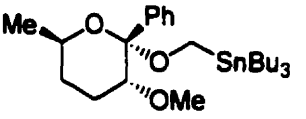
4.1 Introduction

It has been shown that the level of diastereoselectivity in additions of α-alkoxycarbanions to aldehydes could not be increased by experimenting with different metals or solvents (Chapter 2), or by changing the nature of the C-2 group on the auxiliary (Chapter 3). The factor reducing the potential for achieving a higher level of diastereoselectivity was believed to be aggregation occurring between the metalated intermediates to possibly prevent intramolecular coordination between the C-2 heteroatom of the auxiliary and metal from taking place.

Sugars are polyoxygenated compounds and therefore have great potential to participate in multiple coordination states with a metal. A possible strategy to avoid aggregation from taking place would be to design auxiliaries that are less "sugar-like" in structure. This entails synthesizing auxiliaries that possess only the oxygen atoms necessary for intramolecular coordination in the metalated intermediate (C-2 oxygen) and for maintaining the anomeric functionality (ring oxygen) linking the substrate so auxiliary/product recovery could still be possible.

Therefore, a new alkoxymethyltributyltin substrate containing auxiliary **160** was synthesized incorporating the only above required structural features in the form of a chiral 3-methoxy-tetrahydropyran ring (Figure 22). The synthesis of stannane **160** is presented in this chapter along with the results obtained in the transmetalation of **160** and subsequent trapping with aldehydes.

Figure 22. A 3-methoxy-tetrahydropyran chiral auxiliary bonded to the alkoxymethyltin substrate (**160**).



160

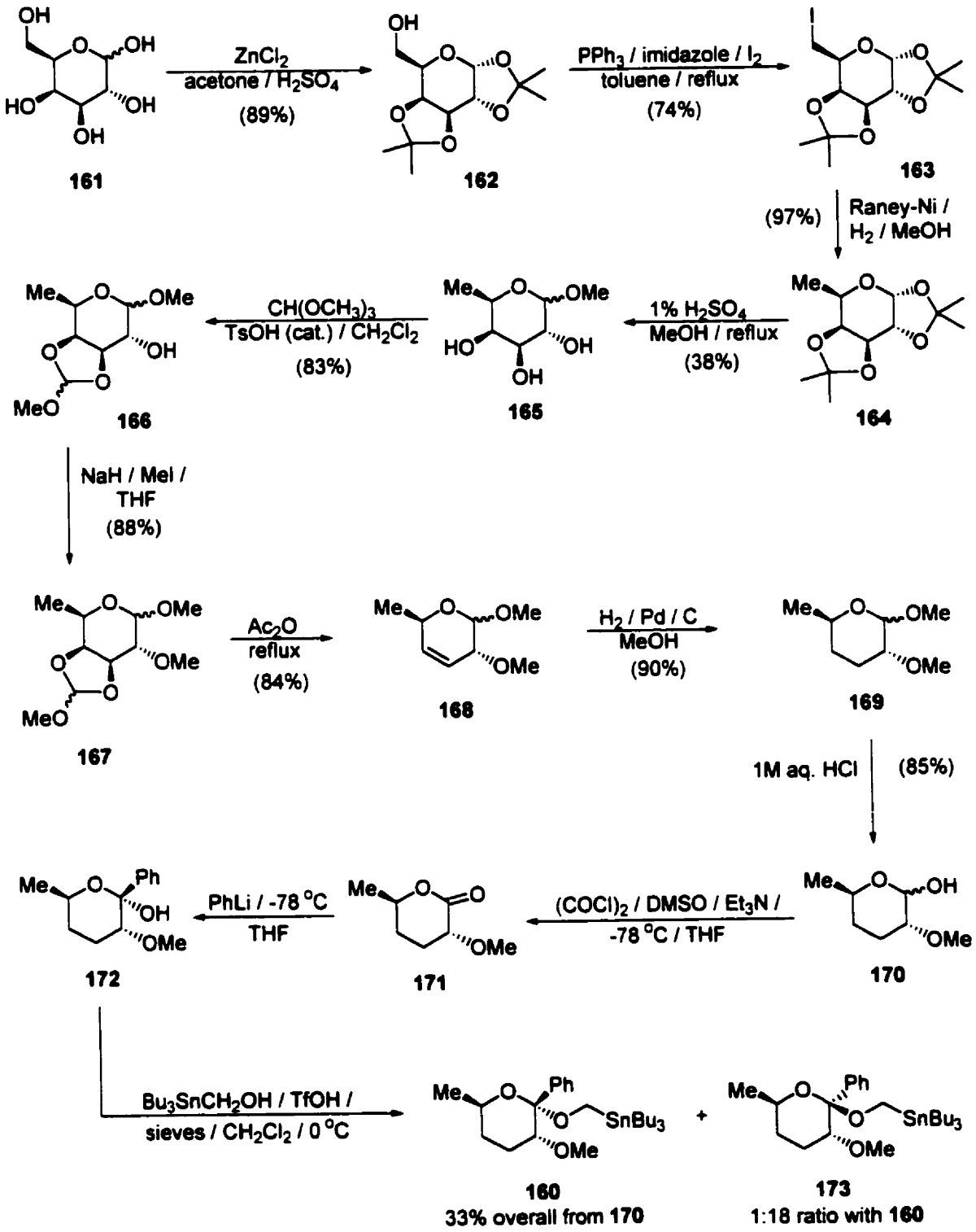
4.2 Results and Discussion

*4.2.1 Synthesis of the 3-Methoxy-Tetrahydropyran Alkoxymethyltin Derivative **160***

The synthesis of the stannane **160** involved removing the 3, 4 and 6-position oxygens of D-galactose followed by introduction of the phenyl and alkoxymethyltin groups (Scheme 49). The 6-position oxygen was removed first by protecting the other oxygens of D-galactose **161** as isopropylidene ketals[1] to form **162**. The 6-hydroxyl group was then transformed to the iodide[2] **163** followed by reduction with Raney-Ni[3] to form **164** in a 97% yield. The isopropylidene protecting groups were then removed to form **165**, which is the methyl glycoside of the naturally occurring sugar D-fucose. The next part of the synthesis involved removing the 3 and 4-position oxygens of the sugar backbone, and first involved incorporating the 3 and 4-position oxygens into an ortho ester[4] to form **166**. The C-2 oxygen was then protected with MeI to form the methyl ether in **167**. Provisional identifications were made for unreported compounds **166** and **167**, based on ^{1}H and ^{13}C NMR data. The C-3 and C-4 position oxygens were then removed in a reaction,[5] which involved refluxing **167** in Ac_2O to form the alkene **168**. The alkene **168** was then subjected to hydrogenation

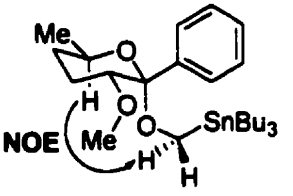
to afford **169** (provisionally identified by low resolution MS and by ^{1}H and ^{13}C NMR data), in which the C-4, 5, 6 oxygens have been removed. The lactol **170** (provisionally identified by IR, low resolution MS and by ^{1}H and ^{13}C NMR data) was then formed in a 85% yield by hydrolyzing the glycoside bond present in **169**. The lactol **170** then underwent a Swern oxidation in THF to form the lactone **171** *in situ*,[6] to which PhLi was added immediately to form the auxiliary **172**. A provisional identification was made for **172** based on low resolution MS data. The lactone **171** was not isolated since it was suspected to decompose during aqueous work-up and by silica gel chromatography. Furthermore, PCC oxidation[7] of **170** resulted in only a 21% yield of **171**; this may be due to decomposition during silica gel chromatography and to the product sticking to chromium salts leading to low crude recovery. However isolation of **171** allowed for its provisional identification based on IR, low resolution MS, and ^{1}H NMR data. Also, the auxiliary **172** was believed to be unstable and was used in the next step as the crude form. The final product **160** was then formed under the usual glycosylation conditions employed in Chapter 2 and 3, in an overall yield of 33 % from lactol **170**. Along with the desired product **160**, a minor by-product **173** was formed, which was provisionally identified to be an isomer of **160** (based on IR and by ^{1}H and ^{13}C NMR data). Compound **173** was formed in a 1:18 ratio to **160** and was easily separated by silica gel chromatography.

Scheme 49


ZnCl2
acetone / H2SO4
(89%)
PPh3 / imidazole / I2
toluene / reflux
(74%)
(97%)
Raney-Ni /
H2 / MeOH
1% H2SO4
MeOH / reflux
(38%)
CH(OCH3)3
TsOH (cat.) / CH2Cl2
(83%)
NaH / MeI /
THF
(88%)
Ac2O
reflux
(84%)
H2 / Pd / C
MeOH
(90%)
1M aq. HCl
(85%)
(COCl)2 / DMSO / Et3N /
-78 °C / THF
PhLi / -78 °C
THF
Bu3SnCH2OH / TfOH /
sieves / CH2Cl2 / 0 °C
161
162
163
164
165
166
167
168
169
170
171
172
160
33% overall from 170
173
1:18 ratio with 160

The stereochemistry of **160** was confirmed by a NOESY NMR experiment. An NOE was visible between the C-5 position proton and one of the methylene protons adjacent to the $SnBu_3$ group (Figure 23). Therefore, the methyl and phenyl groups of **160** must be *syn* to each other as expected due to sterics and the anomeric effect, since the largest ring substituents would prefer to be diequatorial and the anomeric position oxygen would prefer the axial position.

Figure 23. NOE correlation observed in **160**.



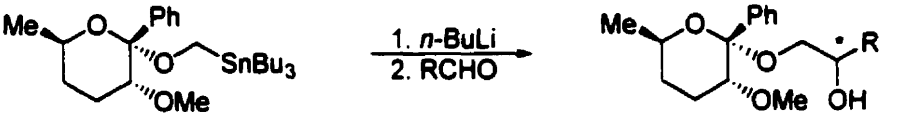
160

*4.2.2 Transmetalation of Stannane **160** and Subsequent Trapping with Aldehydes*

The stannane **160** was transmetalated to the organolithium species in a variety of solvents and trapped with either benzaldehyde or 3,4-dimethoxybenzaldehyde (Table 14). The yield of addition product **174** was low in toluene and hexane (entries 3 and 4) since Sn-Li exchange occurred in a low yield. The level of diastereoselectivity induced with the 3-methoxy-tetrahydropyran auxiliary was no better then levels of diastereoselectivity obtained with glucose-derived chiral auxiliaries (Chapter 2, up to 59% de) and only slightly better then the glucosamine-derived chiral auxiliary (Chapter 3, 14% de). Furthermore, addition to an electron rich aldehyde did not result in a big improvement in diastereoselectivity (entry 5) as was observed when employing glucose-derived chiral auxiliaries. Since aggregation was believed to be less of a problem with the 3-methoxy-tetrahydropyran auxiliary, it was thought that intramolecular coordination of the lithium atom to the

3-position oxygen of the THP ring may not be occurring. Therefore, the strategy involving transmetalation to metals with better coordinating abilities than lithium was adopted next.

Table 14. Selectivities obtained after Sn-Li exchange of **160** and subsequent trapping with benzaldehyde or 3,4-dimethoxybenzaldehyde.



160

174: R = Ph
175: R = 3,4-OMe-C_6H_3

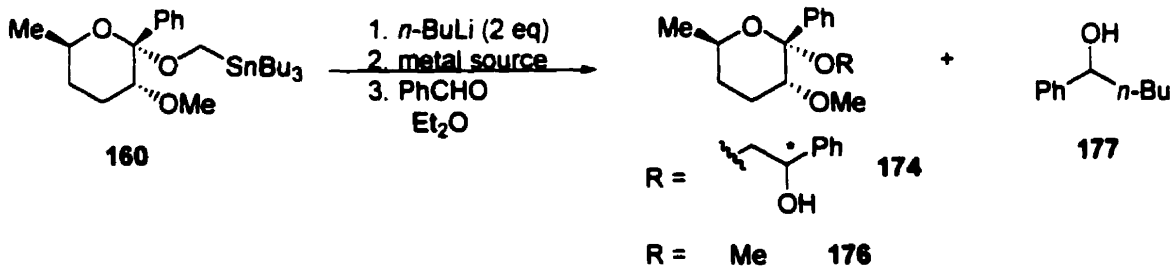
Entry	Aldehyde (R)	Solvent	Yield (%)	De[a] (%)
1	Ph	THF	77	22
2	Ph	Et_2O	98	29
3	Ph	toluene	26	18
4	Ph	hexane	16	15
5	3,4-OMe-C_6H_3	Et_2O	73	31

a - Determined by chiral HPLC analysis of the addition product.

Table 15 indicates the results achieved when Li from the organolithium intermediate was exchanged for Mg or Zn and then trapped with benzaldehyde. The yield of addition product **174** was noticeably decreased when Mg was exchanged for Li (entries 1 and 2). The decrease in yield can be attributable to the formation of protonated by-product **176**, which co-spotted on TLC with the *n*-BuLi addition product to benzaldehyde (**177**). A provisional identification was made for unreported

compound **176** based on ^{1}H NMR data. An interesting effect on diastereoselectivity occurred when the amount of $MgBr_2 \cdot OEt_2$ was varied. A nearly stoichiometric amount of Mg to organolithium species in the reaction gives an increase in diastereoselectivity over the auxiliary organolithium derivative (entry 1). However, a large excess of $MgBr_2 \cdot OEt_2$ actually results in a decrease in the level of diastereoselectivity (entry 2). Perhaps aggregation can be occurring since the transmetalated derivative still contains 3 oxygen coordination sites and a greater amount of Mg may promote aggregation to a greater extent to lower the level of diastereoselectivity. Furthermore, addition product **174** could not be obtained in the Li-Zn exchange reaction (entry 3), and it was believed that only protonated by-product **176** was formed along with **177** and Bu_4Sn.

Table 15. Formation of organomagnesium and organozinc intermediates followed by trapping with benzaldehyde.

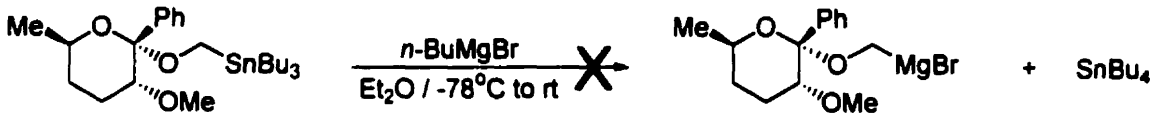


Entry	Metal source	Eq of metal source	Yield of **176** (%)	Yield of **174** (%)	De[a] (%)
1	$MgBr_2 \cdot OEt_2$	2.1	nd	41	42
2	$MgBr_2 \cdot OEt_2$	8	53	34	12
3	$ZnCl_2$•TMEDA	3	nd	0	-

a - Determined by chiral HPLC analysis of the addition product.

It was thought that the low level of diastereoselectivity experienced in the Li-Mg exchange reaction was due to the inability for the Li-Mg exchange process to proceed to completion. Therefore, a direct formation of the organomagnesium intermediate **178** was attempted by Sn-Mg exchange (Scheme 50). Treating the stannane **160** with 2 equivalents of *n*-BuMgBr did not result in the formation of Bu_4Sn or the organomagnesium intermediate **178** even when the reaction mixture was brought to room temperature.

Scheme 50



160 **178**

4.2.3 Summary and Conclusion

A lengthy 12 step synthesis was used to form the stannane derivative **160** containing the 3-methoxy-tetrahydropyran auxiliary. This effort was disappointing in the end since no significant improvements in diastereoselectivity were achieved with the less oxygenated chiral auxiliary over glucose or glucosamine-derived chiral auxiliaries. It was believed that an alternative intramolecular coordination mode might be operating in the transmetalated intermediate (Figure 24). The expected structure represented by **179** (Figure 24a) may not form and the structure represented by **180** (Figure 24b), which has the metal intramolecularly coordinated to the ring oxygen, may be the actual structure of the transmetalated intermediate. One of the structures may induce a lower level of diastereoselectivity over the other in additions to aldehydes and therefore reduce the potential for achieving a high level of diastereoselectivity with the 3-methoxy-tetrahydropyran chiral auxiliary.

Furthermore, the coordination mode represented by **179** would react with aldehydes with opposite facial selectivity than **180**, assuming that the aldehyde reacts on the top face of the *cis*-fused bicyclic system. Therefore, one structure can possibly negate the selectivity produced by the other due to opposite facial selectivity, if both intermediates are present in solution. This dual coordination theory was tested with the use of an auxiliary without the tetrahydropyran 3-oxygen substituent and is further discussed in Chapter 6. The next chapter discusses the results obtained with auxiliaries prepared by considerably shorter synthetic routes than the one presented in this chapter in order to evaluate the effect of a 5-membered ring auxiliary on diastereoselectivity.

Figure 24. Two possible coordination modes for the transmetalated intermediate.

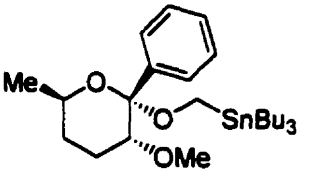
179 **180**

4.3 Experimental

4.3.1 General

The general procedures described in Section 2.3.1 and Section 3.3.1 are applicable here with the following additions. Mass spectral data were obtained by GC/MS analysis on a Hewlett Packard G1800A GCD system equipped with a HP-5 column (crosslinked 5% Ph Me silicone) (30 m x 0.25 mm x 0.25 μm (film thickness)), with ionization occurring by electron impact. The GC retention times that are quoted were also obtained on the above GC/MS instrument and column with the following temperature program being employed: initial conditions: (50 °C for 3 min), ramp: (15 °C/min), final conditions: (220 °C for 10 min).

*4.3.2 Tributyl([(2S,3S,6R)-3-methoxy-6-methyl-2-phenyltetrahydro-2H-2-pyranyl]oxymethyl)stannane **160***



This section describes the preparation of **160** from known synthetic intermediate[8] **168**, and the formation of not fully characterized and unreported synthetic intermediates (3*S*,6*R*)-2,3-dimethoxy-6-methyltetrahydro-2*H*-pyran (**169**), (3*S*,6*R*)-3-methoxy-6-methyltetrahydro-2*H*-2-pyranol (**170**), (3*S*,6*R*)-3-methoxy-6-methyltetrahydro-2*H*-2-pyranone (**171**), and (2*R*,3*S*,6*R*)-3-methoxy-6-methyl-2-phenyltetrahydro-2*H*-2-pyranol (**172**). Partial characterization data for

unreported by-product tributyl([(2*R*,3*S*,6*R*)-3-methoxy-6-methyl-2-phenyltetrahydro-2*H*-2-pyranyl]oxymethyl)stannane (**173**), is also presented in this section.

A solution of **168** (1.3 g, 8.22 mmol) in MeOH (80 mL) was hydrogenated with H_2 using 10% Pd/C (873 mg, 0.82 mmol) at room temperature and atmospheric pressure for 2 h. The mixture was then filtered and the filtrate was concentrated *in vacuo* (bath temperature: 0 °C). The crude material was then purified by silica gel chromatography (gradient elution: petroleum ether (bp 30-60 °C) to 10% to 15% to 20% to 30% Et_2O/petroleum ether (bp 30-60 °C)) to afford 1.2 g of the unreported compound **169** (90% yield) as a colourless oil and as a mixture of 2 diastereomers: GC retention times: 7.22 min. (β anomer), 7.58 min. (α anomer); ^{1}H NMR (α anomer) (300 MHz, $CDCl_3$) δ 4.76 (d, 1H, J = 3.3Hz, anomeric-H), 3.75-3.9 (m, 1H, OCH), 3.1-3.5 (m, 1H, OCH), 3.44 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 1.55-2.0 (m, 3H, CC<u>H</u><u>H</u>C<u>H</u>HC), 1.1-1.5 (m, 1H, CCHHCH<u>H</u>C), 1.15 (d, 3H, J = 6.4 Hz, OCHC<u>H</u>$_3$); ^{1}H NMR (β anomer) (300 MHz, $CDCl_3$) δ 4.15 (d, 1H, J = 7.5 Hz, anomeric-H), 3.35-3.6 (m, 1H, OCH), 3.53 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 2.95-3.05 (m, 1H, OCH), 2.1-2.2 (m, 1H, CH_2C<u>H</u>H), 1.6-1.75 (m, 1H, CH_2C<u>H</u>H), 1.15-1.45 (m ,2H, 2 CH_2C<u>H</u>H), 1.22 (d, 3H, J = 6.1 Hz, OCHC<u>H</u>$_3$); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 105.2* (anomeric-H), 97.1 (anomeric-H), 77.6 (OCH), 70.9 (OCH), 63.5 (OCH_3), 55.4 (OCH_3), 55.3* (OCH_3), 53.9 (OCH_3), 31.6 (<u>C</u>H_2CH_2), 31.5* (<u>C</u>H_2CH_2), 27.7 (CH_2<u>C</u>H_2), 22.8 (OCH<u>C</u>H_3), 20.2* (OCH<u>C</u>H_3); MS (EI) *m/z* 58 (100), 128 (M^+ - CH_3OH, 1), 129 (M^+ - OCH_3, 1), 159 (M^+- H, 1), 160 (M^+, 1).

A solution of **169** (673 mg, 4.20 mmol) in aqueous 1 M HCl (30 mL) was heated to 70 °C for 1 h, then cooled to rt after which $NaHCO_3$ was added until the mixture was slightly basic. The mixture was then saturated with NaCl and placed in a continuous extractor and extracted with Et_2O for 2 days. The organic layer was then separated, dried over anhydrous Na_2SO_4, filtered, then concentrated *in vacuo* (bath temperature: 0 °C). The crude material was purified by silica gel

chromatography (gradient elution: petroleum ether (bp 30-60 °C) to 30% to 40% to 50% Et_2O/petroleum ether (bp 30-60 °C)) in order to isolate 522 mg of the unreported compound **170** (85% yield) as a colourless oil and as a mixture of 2 diastereomers: GC retention time: 8.09 min; IR (neat) 3401 (O-H stretch), 1457, 1082 (C-O stretch); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.25-5.35 (br, 1H, α-anomer-anomeric-H), 4.56 (dd, 1H, J = 4.4, 7.4 Hz, β-anomer-anomeric-H), 3.95-4.15 (m, 1H, α anomer-OCH), 3.25-3.7 (m, 2H, OCH), 3.48 (s, 3H, β-anomer-OCH_3), 3.40 (s, 3H, α-anomer-OCH_3), 2.9-3.05 (m, 1H, OCH), 2.1-2.25 (m, 1H, β-anomer-OCH), 1.65-2.0 (m, 3H, $CC\underline{H_2}CH_2C$ + OH), 1.15-1.5 (m, 2H, $CC\underline{H_2}CH_2C$), 1.23 (d, 3H, J = 6.2 Hz, β-anomer-$OCHC\underline{H_3}$), 1.15 (d, 3H, J = 6.3 Hz, α anomer-$OCHC\underline{H_3}$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 98.0 (anomeric-C), 90.0* (anomeric-C), 79.3 (OCH), 76.9* (OCH), 71.6 (OCH), 63.9 (OCH), 57.3* (OCH_3), 55.7* (OCH_3), 31.8 ($\underline{C}H_2CH_2$), 31.6* ($\underline{C}H_2CH_2$), 27.6 ($\underline{C}H_2CH_2$), 22.3* ($\underline{C}H_2CH_2$), 20.6 ($OCH\underline{C}H_3$), 20.6* ($OCH\underline{C}H_3$); MS (EI) *m/z* 58 (100), 115 (M^+ - OCH_3, 3), 128 (M^+ - H_2O, 1), 129 (M^+ - OH, 1), 146 (M^+, 1).

The next 3 steps to prepare the unreported compound **160** involved a procedure modified from that described by Ireland and Norbeck.[6] To a stirred solution of oxalyl chloride (132 μL, 1.51 mmol) in THF (3 mL) at -78 °C was added dimethyl sulfoxide (113 μL, 1.59 mmol). The solution was allowed to warm to -35 °C for 3 min and was then recooled to -78 °C for 15 min. A solution of lactol **170** (220 mg, 1.51 mmol) in THF (3 mL) was added to the reaction mixture. The resulting solution was allowed to warm to -35 °C and after 15 min was treated with Et_3N (1.1 mL, 7.55 mmol). The reaction mixture was then allowed to warm to rt for 10 min to form the lactone **171** *in situ*.

Lactone **171** was also prepared by a PCC oxidation[7] in low yield as outlined in this paragraph: A mixture of lactol **170** (80 mg, 0.547 mmol), PCC (242 mg, 1.09 mmol), sodium acetate (13 mg, 0.164 mmol) and 4 Å molecular sieves (200 mg) in CH_2Cl_2 (5 mL) was refluxed for 45 min.

The mixture was then cooled to rt, then diluted with anhydrous Et_2O (20 mL) followed by filtration through Florisil. The filtrate was then concentrated *in vacuo* (bath temperature: 0 °C) followed by purifying the crude by silica gel chromatography (gradient elution: petroleum ether (bp 30-60 °C) to 10% to 15% to 20% to 30% to 35% Et_2O/petroleum ether (bp 30-60 °C)) in order to isolate 21 mg of **171** (27% yield) as a colourless oil: GC retention time: 8.54 min; IR (neat film) 2832, 1742 (C=O stretch), 1452, 1379, 1196 (C-O stretch), 1126 (C-O stretch), 1005 (C-O stretch), 847 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.52-4.72 (m, 1H, $CH_3CHOC{=}O$), 3.79 (dd, 1H, J = 5.9, 7.6 Hz), 3.54 (s, 3H, OCH_3), 1.85-2.27 (m, 3H, $C\underline{H}_2C\underline{H}H$), 1.50-1.78 (m, 1H, $CH_2CH\underline{H}$), 1.36 (d, 3H, J = 6.3 Hz, $CH_3CHOC{=}O$); MS (EI) *m/e* 58 (100), 114 (M^+ - CH_2O, 14), 129 (M^+ - CH_3, 1).

After lactone **171** was generated *in situ*, the reaction mixture was cooled to -78 °C, after which a 0.82 M solution of PhLi in Et_2O (2.8 mL, 2.27 mmol) was added. The reaction was stirred for 20 min then quenched with a saturated aqueous NH_4Cl solution (1 mL). The mixture was then brought to rt and extracted with Et_2O (3 x 10 mL), followed by drying the combined organic extracts over anhydrous Na_2SO_4, then filtering. The filtrate was then concentrated *in vacuo* to give 333 mg of crude material containing **172**, which was used in the next step without purification. GC/MS data of the crude material indicated a 3:1 mixture of auxiliary **172** and lactol **170**. Purification of **172** was not attempted since it was suspected to be unstable to silica gel chromatography; therefore adequate NMR data could not be obtained. However GC/MS data was satisfactory and indicated **172** to be 79% pure: GC retention time: 13.54 min; MS *m/z* (EI) 115 (100), 204 (M^+ - H_2O, 0.5), 205 (M^+ - OH, 0.1), 207 (M^+ - CH_3, 0.1).

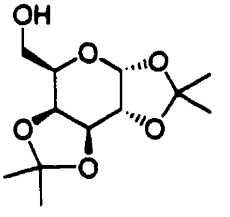
To a cooled solution (0 °C) of crude auxiliary **172** (333 mg) and Bu_3SnCH_2OH (480 mg, 1.50 mmol) in CH_2Cl_2 (25 mL) and in the presence of crushed 4 Å molecular sieves (6 g) was added triflic acid (53 μL, 0.60 mmol). The mixture was stirred for 30 minutes after which it was quenched

with Et_3N (1 mL), then filtered, followed by concentrating the filtrate *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: hexane to 0.5% to 1% to 2% to 3% to 4% Et_2O/hexane) to afford 262 mg of **160** (33% overall yield from **170**) as a colourless oil: $[\alpha]_D^{22}$ = + 30.1 (c = 0.92, EtOH); GC retention time: 19.11 min; IR (neat) 3059, 3028, 2852, 1950, 1448, 1107 (C-O stretch), 1011 (C-O stretch), 862; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.5-7.65 (m, 2H, Ar-H), 7.25-7.4 (m, 2H, Ar-H), 3.7-3.9 (m, 1H, OCH), 3.44 (d, 1H, 10.5 Hz, $^2J_{Sn-H}$ = 30.1 Hz) OCHHSnBu_3), 3.24 (d, 1H, 10.5 Hz, $^2J_{Sn-H}$ = 26.8 Hz) OCHHSnBu_3), 2.9-3.1 (m, 1H, OCH), 2.99 (s, 3H, OCH_3), 1.7-2.1 (m, 3H, CH_2CHH), 1.15-1.7 (m, 16H, CH_2CHH + $Sn(CH_2CH_2CH_2CH_3)_3$ + $OCHCH_3$), 0.75-1.1 (m, 15H, $Sn(CH_2(CH_2)_2CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 140.1 (Ar-C), 127.8 (Ar-C), 127.4 (Ar-C), 127.4 (Ar-C), 101.2 (^3J = 42 Hz, anomeric-C), 83.5 (OCH), 69.6 (OCH), 57.6 (OCH_3), 49.8 (^1J = 362, 378 Hz, OCH_2SnBu_3), 33.2 (CH_2CH_2), 29.2 (^2J = 20 Hz, $Sn(CH_2CH_2CH_2CH_3)_3$), 27.4 (^3J = 52, 54 Hz, $Sn((CH_2)_2CH_2CH_3)_3$), 24.3 (CH_2CH_2), 21.2 ($OCHCH_3$), 13.7 ($Sn((CH_2)_3CH_3)_3$), 9.0 (^1J = 310, 324 Hz, $Sn(CH_2(CH_2)_2CH_3)_3$); MS (EI) *m/e* 205 (M^+ - OCH_2SnBu_3, 100). Anal. Calcd for $C_{26}H_{46}O_3Sn$: C, 59.46; H, 8.83. Found: C, 59.63; H, 8.85.

Also formed in the reaction involving the preparation of **160** was the by-product and minor diastereomer **173** in a 1:18 ratio with **160**. Compound **173** also has a slightly lower R_f value then **160** and displayed the following characterization data: $[\alpha]_D^{22}$ = + 21.0 (c = 0.61, $CHCl_3$); IR (neat film) 2823, 1449, 1379, 1259, 1118 (C-O stretch), 1085 (C-O stretch), 1011 (C-O stretch), 763, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.55 (m, 2H, Ar-H), 7.22-7.39 (m, 3H, Ar-H), 3.73-3.90 (m, 1H, OCH), 3.37 (d, 1H, J = 10.0 Hz, $^2J_{Sn-H}$ = 28.3 Hz, OCHHSnBu_3), 3.23 (t, 1H, J = 2.6 Hz, OCH), 3.02 (d, 1H, J = 10.3 Hz, $^2J_{Sn-H}$ = 28.8 Hz, OCHHSnBu_3), 1.98-2.12 (m, 1H, $CHHCH_2$), 1.80-1.94 (m, 1H, $CHHCH_2$), 1.10-1.72 (m, 17H, CH_2CH_2 + $Sn(CH_2CH_2CH_2CH_3)_3$ + $OCHCH_3$), 0.70-1.00 (m, 15H, $Sn(CH_2(CH_2)_2CH_3)_3$). ^{13}C NMR (75.47 MHz) δ 140.5 (Ar-C), 127.6 (Ar-C), 127.3

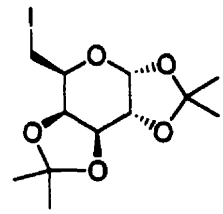
(Ar-C), 127.0 (Ar-C), 101.7 (anomeric-C), 78.5 (OCH), 66.4 (OCH), 57.6 (OCH), 49.2 (OCH_2SnBu_3), 29.3 (^2J = 21 Hz, $Sn(CH_2\underline{C}H_2CH_2CH_3)_3$), 27.3 ($^3J$ = 51 Hz, $Sn((CH_2)_2\underline{C}H_2CH_3)_3$), 26.5 ($C\underline{C}H_2CH_2C$), 23.3 ($CCH_2\underline{C}H_2$), 21.6 ($C\underline{C}H_3$), 13.7 ($Sn((CH_2)_3\underline{C}H_3)_3$), 8.9 ($^1J$ = 311, 325 Hz, $Sn(\underline{C}H_2(CH_2)_2CH_3)_3$).

4.3.3 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose **162**



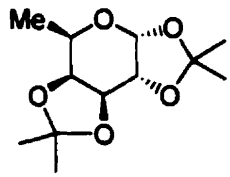
This known compound[1] was prepared by a procedure modified from that described by Tipson.[1] To a solution of anhydrous zinc chloride[9] (59.5 g, 0.437 mol) in anhydrous acetone (500 mL) was added concentrated sulphuric acid (2 mL, 0.036 mol) followed by D-galactose (**161**) (49 g, 0.273 mol). The mixture was stirred for 4 h after which Na_2CO_3 (81 g, 0.976 mol) in H_2O (143 mL) was added dropwise. Next the mixture was partitioned between H_2O (500 mL) and EtOAc (500 mL), followed by separating the organic layer. The aqueous layer was then extracted with EtOAc (4 x 500 mL), followed by combining the organic layers and drying over anhydrous Na_2SO_4. The dried solution was then filtered and concentrated *in vacuo* to afford 63.3 g of crude **162** (89% yield) as a thick syrup which was used without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.57 (d, 1H, J = 5.0 Hz, anomeric-H), 4.61 (dd, 1H, J = 2.4, 7.9 Hz, OCH), 4.34 (dd, 1H, J = 2.4, 5.1 Hz, OCH), 4.28 (dd, 1H, J = 1.6, 7.9 Hz, OCH), 3.70-3.95 (m, 3H, OCH + OCH_2), 1.54 (s, 3H, CCH_3), 1.46 (s, 3H, CCH_3), 1.34 (s, 6H, 2 CCH_3).

4.3.4 6-Deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galactose ***163***



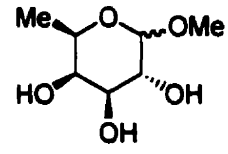
This known compound[2] was prepared by a procedure modified from that described by Durette.[2] A mixture of crude **162** (63.3 g, 243 mmol), imidazole (48 g, 730 mmol), iodine (123 g, 486 mmol), and triphenylphosphine (191 g, 730 mmol) in toluene (2 L) was refluxed for 2 h. The mixture was then cooled to rt, then washed with a saturated solution of $NaHCO_3$ (500 mL), then with a saturated solution of sodium thiosulfate (500 mL), and finally with H_2O (500 mL). The organic layer was dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The crude oil was then triturated with anhydrous Et_2O to precipitate triphenylphosphine oxide, which was filtered off. The filtrate was then concentrated *in vacuo* and the crude material purified by silica gel chromatography (gradient elution: hexane to 2% to 10% EtOAc/hexane) to afford 66.5 g of **163** (74% yield) as a white solid: mp 58-59 °C; lit.[3] mp 72 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.55 (d, 1H, J = 5.0 Hz, anomeric-H), 4.62 (dd, 1H, J = 2.5, 7.8 Hz, OCH), 4.41(dd, 1H, J = 1.9, 7.9 Hz, OCH), 4.31 (dd, 1H, J = 2.5, 5.1 Hz, OCH), 3.95 (td, 1H, J = 1.8, 7.0 Hz, OC<u>H</u>CH_2I), 3.15-3.4 (m, 2H, CH_2I), 1.55 (s, 3H, CCH_3), 1.45 (s, 3H, CCH_3), 1.36 (s, 3H, CCH_3), 1.34 (s, 3H, CCH_3).

4.3.5 1,2:3,4-Di-O-isopropylidene-α-D-fucose ***164***



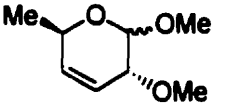
This known compound[3] was prepared by a procedure modified from that described by Shafizadeh.[3] The iodo compound **163** (66 g, 178 mmol) was dissolved in MeOH (700 mL), then hydrogenated at room temperature and atmospheric pressure with Raney nickel (500 g) (**Caution: Fire Hazard:** Raney nickel has the potential to ignite spontaneously in air when dry) for 2 days. The Raney nickel was allowed to settle and the MeOH solution was decanted, the Raney nickel slurry was then washed with MeOH (3 x 500 mL) followed by additional decantation. The MeOH solutions were then combined and concentrate *in vacuo* to afford 42.3 g of crude **164** (97% yield) which was used without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.52 (d, 1H, J = 5.1 Hz, anomeric-H), 4.59 (dd, 1H, J = 2.4, 7.9 Hz, OCH), 4.29(dd, 1H, J = 2.2, 5.1 Hz, OCH), 4.08 (dd, 1H, J = 1.9, 7.9 Hz, OCH), 3.92 (qd, 1H, J = 1.8, 6.5 Hz, OC<u>H</u>CH_3), 1.53 (s, 3H, CCH_3), 1.47 (s, 3H, CCH_3), 1.36 (s, 3H, CCH_3), 1.33 (s, 3H, CCH_3), 1.26 (d, 3H, J = 6.6 Hz, OCHC<u>H</u>$_3$).

*4.3.6 Methyl α/β-D-fucoside **165***



This known compound[10] was prepared by a procedure modified from that described by Shafizadeh.[3] Compound **164** (10.7 g, 43.8 mmol) was refluxed in 1% H_2SO_4/MeOH (210 ml) for 30 min. The reaction was then cooled to 0 °C and $NaHCO_3$ (approximately 4 g) was added until the mixture was slightly basic by pH paper. The mixture was then filtered through Celite and the resulting filtrate concentrated *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: EtOAc to 1% to 2% to 3% to 5% to 7.5% to 10% to 15% MeOH/EtOAc) to afford 3.0 g of **165** (38% yield) as a white solid and as a mixture of anomers: mp 138-143 °C; lit. mp 146-147 °C (α-anomer),[11] 121-122 °C (β-anomer);[12] ^{1}H NMR (200 MHz, D_2O) δ 4.82 (m, 1H, anomeric-H), 4.34* (d, 1H, J = 7.9 Hz, anomeric-H), 4.09 (q, 1H, J = 6.6 Hz, OCH), 3.35-3.9 (m, 3H, OCH), 3.44 (s, 3H, OCH_3), 1.31* (d, 3H, J = 6.5 Hz, $OCHC\underline{H}_3$), 1.27 (d, 3H, J = 6.5 Hz, $OCHC\underline{H}_3$).

*4.3.7 (3S,6R)-2,3-Dimethoxy-6-methyl-3,6-dihydro-2H-pyran **168***



The preparation of known[8] **168** is described in this section starting from known compound **165** *via* the formation of unreported synthetic intermediates (3a*S*,4*R*,7*S*,7a*R*)-2,6-dimethoxy-4-methylperhydro[1,3]dioxolo[4,5-*c*]pyran-7-ol (**166**), (3a*S*,4*R*,7*S*,7a*R*)-2,6,7-trimethoxy-4-methylperhydro[1,3]dioxolo[4,5-*c*]pyran (**167**), which were not fully characterized.

Unreported synthetic intermediate **166** was prepared by a procedure modified from that described by Tanaka *et al.*:[4] To a solution of **165** (4.9 g, 27.5 mmol) in CH_2Cl_2 (250 mL) was added trimethylorthoformate (18.1 mL, 165 mmol) followed by a catalytic amount of TsOH (523 mg, 2.75 mmol). The mixture was stirred for 1 h after which the reaction was quenched with Et_3N (5 mL). The solvent was then removed *in vacuo* to afford the crude material which was purified by silica gel chromatography (gradient elution: 30% to 40% to 50% EtOAc/hexane) to provide 5.0 g of **166** (83% yield) as a colourless oil and as a mixture of 4 diastereomers: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.83* (s, 1H, $(RO)_3C\underline{H}$), 5.81 (s, 1H, $(RO)_3C\underline{H}$), 5.80* (s, 1H, $(RO)_3C\underline{H}$), 5.78* (s, 1H, $(RO)_3C\underline{H}$), 4.74* (d, 1H, J = 3.8 Hz, α-anomer-anomeric-H), 4.71 (d, 1H, J = 3.9 Hz, α-anomer-anomeric-H), 4.38* (d, 1H, J = 6.3 Hz, β-anomer-anomeric-H), 4.36* (d, 1H, J = 6.3 Hz, β-anomer-anomeric-H), 4.00-4.30 (m, 3H, OCH), 3.70-3.93 (m, 1H, OCH), 3.54* (s, 3H, OCH_3), 3.54* (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.44* (s, 3H, OCH_3), 3.42* (s, 3H, OCH_3), 3.37* (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 1.45* (d, 3H, J = 6.6 Hz, $OCHC\underline{H}_3$), 1.38* (d, 3H, J = 5.6 Hz, $OCHC\underline{H}_3$), 1.35 (d, 3H, J = 6.6 Hz, $OCHC\underline{H}_3$); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 117.1* ($(RO)_3\underline{C}H$), 116.8* ($(RO)_3\underline{C}H$), 115.7

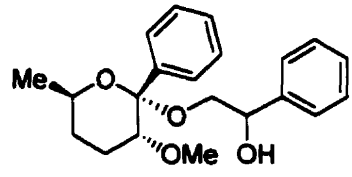
((RO)$_3$C<u>H</u>), 115.3* ((RO)$_3$C<u>H</u>), 103.2* (anomeric-C), 102.7 (anomeric-C), 99.0* (anomeric-C), 98.4* (anomeric-C), 79.2 (OCH), 77.9* (OCH), 77.8* (OCH), 77.3* (OCH), 76.3* (OCH), 75.9* (OCH), 75.1 (OCH), 74.8* (OCH), 72.8 (OCH), 72.5* (OCH), 69.2* (OCH), 68.8* (OCH), 68.7 (OCH), 68.5* (OCH), 63.0* (OCH_3), 62.9* (OCH_3), 56.7* (OCH_3), 56.7* (OCH_3), 55.3 (OCH_3), 52.7* (OCH_3), 52.5* (OCH_3), 51.9 (OCH_3), 51.8* (OCH_3), 16.3 (OCH<u>C</u>H$_3$), 16.1* (OCH<u>C</u>H$_3$), 16.0* (OCH<u>C</u>H$_3$).

Unreported synthetic intermediate **167** was then prepared by the following procedure: To a cooled (0 °C) solution of **166** (4.9 g, 22.3 mmol) in THF added MeI (5.6 mL, 89.2 mmol) followed by adding NaH (2.7 g (60% suspension in mineral oil), 66.8 mmol) slowly. The mixture was then allowed to reach rt and was stirred for 2 h after which the reaction was quenched with H_2O (10 mL). The solvent was then removed *in vacuo* followed by partitioning the crude salt mixture between brine (45 mL) and EtOAc (150 mL). The layers were then separated and the aqueous layer was extracted with EtOAc (3 x 150 mL), followed by drying the combined organic layers over anhydrous Na_2SO_4. The solvent was then removed *in vacuo* and the crude material was purified by silica gel chromatography (gradient elution: hexane to 20% to 25% to 30% to 35% to 40% EtOAc/hexane) to isolate 4.6 g of the unreported compound **167** (88% yield) as colourless oil and as a mixture of 4 diastereomers: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.84* (s, 1H, (RO)$_3$C<u>H</u>), 5.82 (s, 1H, (RO)$_3$C<u>H</u>), 5.79* (s, 1H, (RO)$_3$C<u>H</u>), 5.76* (s, 1H, (RO)$_3$C<u>H</u>), 4.79 (d, 1H, J = 3.5 Hz, α-anomer-anomeric-H), 4.44 (d, 1H, J = 7.7 Hz, α-anomer-anomeric-H), 4.41* (d, 1H, J = 7.7 Hz, β-anomer-anomeric-H), 4.27* (t, 1H, J = 6.2 Hz, β-anomer-anomeric-H), 3.97-4.19 (m, 2H, OCH), 3.69-3.89 (m, 1H, OCH), 3.59* (s, 3H, OCH_3), 3.57* (s, 3H, OCH_3), 3.56* (s, 3H, OCH_3), 3.55* (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.53* (s, 3H, OCH_3), 3.52* (s, 3H, OCH_3), 3.45* (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.41* (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.36* (s, 3H, OCH_3), 3.27 (dd, 1H, J = 3.6, 7.7 Hz, OCH), 3.09* (dd, 1H, J = 6.5, 7.7 Hz, OCH), 1.43* (d, 3H, J = 6.6 Hz, OCHC<u>H</u>$_3$), 1.39 (d, 3H, J = 6.6 Hz,

$OCHC\underline{H}_3$); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 116.8* ($(RO)_3\underline{C}H$), 115.4* ($(RO)_3\underline{C}H$), 115.0 ($(RO)_3\underline{C}H$), 103.2* (anomeric-C), 102.7* (anomeric-C), 97.6* (anomeric-C), 97.2 (anomeric-C), 81.2 (OCH), 81.1* (OCH), 78.9* (OCH), 78.3 (OCH), 78.1* (OCH), 77.6* (OCH), 76.2 (OCH), 75.0* (OCH), 74.9* (OCH), 74.6 (OCH), 68.4* (OCH), 68.0* (OCH), 62.3* (OCH_3), 62.1 (OCH_3), 59.1* (OCH_3), 58.3* (OCH_3), 58.1 (OCH_3), 56.0* (OCH_3), 55.1 (OCH_3), 52.4* (OCH_3), 51.8* (OCH_3), 51.4* (OCH_3), 16.0* ($OCH\underline{C}H_3$), 15.8 ($OCH\underline{C}H_3$).

Compound **168** was then prepared by a procedure modified from that described by Ando *et al.*[5] Compound **167** (2.3 g, 9.8 mmol) was dissolved in acetic anhydride (30 mL) and the solution was heated at reflux overnight. Work-up of the reaction mixture then followed by slowly adding a saturated aqueous solution of K_2CO_3 until the solution was slightly basic (pH 8-9) and all bubbling had ceased. The mixture was then extracted with Et_2O (3 x 100 mL), followed by drying the combined organic extracts over anhydrous Na_2SO_4, and removing the solvent *in vacuo* (bath temperature: 0°C). The crude material was then purified by silica gel chromatography (gradient elution: petroleum ether (bp 30-60 °C) to 5% to 10% to 15% to 20% to 25% Et_2O/petroleum ether (bp 30-60 °C)) to afford 1.3 g of **168** as a colourless oil and as a mixture of 2 diastereomers: GC retention times: 7.21 min. (β anomer), 7.73 min. (α anomer); ^1H NMR (α anomer) (250 MHz, $CDCl_3$) δ 5.65-5.8 (m, 2H, alkenyl-H), 4.96 (d, 1H, J = 4.0 Hz, anomeric-H), 4.15-4.35 (m, 1H, OCH), 3.9-4.0 (m, 1H, OCH), 3.52 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 1.24 (d, 3H, J = 6.8 Hz, $OCHC\underline{H}_3$); ^1H NMR (β anomer) (250 MHz, $CDCl_3$) δ 5.65-5.8 (m, 2H, alkenyl-H), 4.40 (d, 1H, J = 6.2 Hz, anomeric-H), 4.25-4.4 (m, 1H, OCH), 3.6-3.7 (m, 1H, OCH), 3.55 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 1.28 (d, 3H, J = 6.8 Hz, $OCHC\underline{H}_3$); MS (EI) *m/z* 98(100), 127 (M^+ - OCH_3, 4), 143 (M^+ - CH_3, 1), 158 (M^+, 1).

*4.3.8 2-[(2R,3S,6R)-3-methoxy-6-methyl-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-phenyl-1-ethanol **174***



This unreported compound was prepared by Sn-Li exchange of **160**, followed by trapping with benzaldehyde. Reactions were conducted in THF (results presented in Table 14, entry 1), Et_2O (results presented in Table 14, entry 2), toluene (results presented in Table 14, entry 3) and hexane (results presented in Table 14, entry 4). The transmetalation step was conducted at -50 °C when hexane and toluene were used as solvents and at -78 °C when THF and Et_2O were employed. Furthermore, Li-Mg exchange was also used to generate **160** (results presented in Table 15, entries 1-2). Representative procedures are included for the generation/trapping of both the organolithium and the orangomagnesium species.

A representative procedure for a reaction conducted in Et_2O, and trapping with the organolithium species follows: To a cooled solution (-78 °C) of **160** (125.6 mg, 0.239 mmol) in Et_2O (5 mL) was added a solution of 1.56 M *n*-BuLi in hexane (0.31 mL, 0.478 mmol) dropwise and the resulting solution was stirred for 50 minutes. Benzaldehyde (73 μL, 0.717 mmol) was next added dropwise and the resulting solution was stirred for an additional 25 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude material occurred by silica gel

chromatography (gradient elution: hexane to 30% to 50% to 60% to 80% Et_2O/hexane to neat Et_2O), to afford 80 mg (98% yield) of **174** in 29% de (de determined by Method C outlined in Section 2.3.2: 2% ^{i}PrOH/hexane, retention times: 9.24 min (major diastereomer), 13.46 min (minor diastereomer).

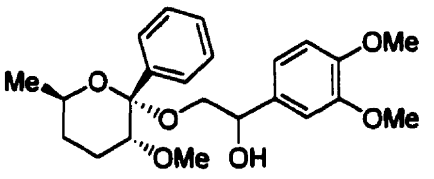
A representative procedure for a reaction conducted in Et_2O, and trapping with the organomagnesium species follows: To a cooled solution (-78 °C) of **160** (112.9 mg, 0.215 mmol) in Et_2O (5 mL) was added a solution of 1.56 M *n*-BuLi in hexane (0.28 mL, 0.430 mmol) dropwise and the resulting solution was stirred for 20 minutes. Next, freshly generated $MgBr_2 \bullet (OEt_2)$[13] (104 mg, 0.452 mmol) in Et_2O (2 mL) was added to the reaction mixture and the flask was placed in a -40 °C bath. After 45 min the flask was placed in a -78 °C bath and cooled for 10 minutes, after which benzaldehyde (66 μL, 0.645 mmol) was added dropwise and the resulting solution was stirred for an additional 20 minutes. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (1 mL). The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude material occurred by silica gel chromatography (gradient elution: hexane to 30% to 50% to 60% to 80% Et_2O/hexane to neat Et_2O), to afford 30.5 mg (41% yield) of **174** in 42% de (de determined by Method C outlined in Section 2.3.2: 2% ^{i}PrOH/hexane, retention times: 9.24 min (major diastereomer), 13.46 min (minor diastereomer).

Compound **174** was isolated as a white solid in all experiments and exhibited the following characterization data: GC retention time: 17.86 min; mp 84-89 °C; IR (KBr) 3435 (O-H stretch), 1094 (C-O stretch), 768, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.65 (m, 2H, Ar-H), 7.15-7.4 (m, 8H, Ar-H), 4.95-5.05 (m,1H, Bn-H), 3.85-3.95 (m, 1H, OCH), 3.6-3.8* (m, 1H, OCH), 3.2-3.5 (m, 2H, OCH_2), 3.05 (s, 3H, OCH_3), 3.03* (s, 3H, OCH_3), 2.9-3.1 (m, 1H, OCH), 1.9-2.0 (m,

2H, CC$\underline{H}_2$CH$_2$C), 1.75-1.85 (m, 1H, CCH$_2$C$\underline{H}$HC), 1.35-1.5 (m, 1H, CCH$_2$CH$\underline{H}$C), 1.21 (d, 3H, J = 6.2 Hz, OCHC$\underline{H}_3$), 1.19* (d, 3H, J = 6.0, OCHC$\underline{H}_3$) ; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 141.0 (Ar-H), 140.7* (Ar-H) , 139.9 (Ar-H), 139.7* (Ar-H), 128.1* (Ar-H), 128.1 (Ar-H), 127.8* (Ar-H), 127.6 (Ar-H), 127.6 (Ar-H), 127.5* (Ar-H), 127.5 (Ar-H), 127.3 (Ar-H), 126.3* (Ar-H), 126.1 (Ar-H), 99.5* (anomeric-H), 99.4 (anomeric-H), 83.5 (OCH), 73.0* (OCH) , 72.9 (OCH), 67.0* (OCH), 66.9 (OCH), 66.2* (OCH_2), 66.1 (OCH_2), 58.0 (OCH_3) , 32.7* ($\underline{C}H_2CH_2$), 32.7 ($\underline{C}H_2CH_2$), 24.3 ($CH_2\underline{C}H_2$), 24.3* ($CH_2\underline{C}H_2$) , 21.1 (OCH$\underline{C}H_3$); MS (EI) ***m/e*** 58 (100), 205 (M^+ - $OCH_2CH(OH)Ph$, 17). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.88; H, 7.72.

Unreported compound (2*R*,3*S*,6*R*)-2,3-Dimethoxy-6-methyl-2-phenyltetrahydro-2*H*-pyran (**176**) was formed as a protonated by-product in 53% yield (yield determined by ^{1}H NMR) and characterized to be present in a mixture with known compound[14] **177** when 8 equivalents of $MgBr_2$•OEt_2 was employed in a typical Li-Mg exchange procedure. The following data was assigned to **176**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.65 (m, 2H, Ar-H), 7.22-7.44 (m, 3H, Ar-H), 3.82-3.97 (m, 1H, OC$\underline{H}$CH$_3$), 3.12 (s, 3H, OCH_3), 3.05 (s, 3H, OCH_3), 2.98 (dd, 1H, J = 5.3, 10.8 Hz, C$\underline{H}$OCH$_3$), 1.65-2.00 (m, 3H, C$\underline{H}_2$C$\underline{H}$H), 1.30-1.50 (m, 1H, CH$_2$CH$\underline{H}$), 1.27 (d, 3H, J = 6.3 Hz, OCHC$\underline{H}_3$).

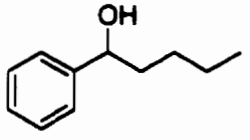
4.3.9 1-(3,4-dimethoxyphenyl)-2-[(2R,3S,6R)-3-methoxy-6-methyl-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-ethanol 175



To a cooled solution (-78 °C) of **160** (110.2 mg, 0.210 mmol) in Et_2O (5 mL) was added a solution of 1.56 M *n*-BuLi in hexane (0.27 mL, 0.420 mmol) dropwise and the resulting solution was stirred for 30 minutes. 3,4-Dimethoxybenzaldehyde (105 mg, 0.630 mmol) was next added dropwise and the resulting solution was stirred for an additional 25 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude material occurred by silica gel chromatography (gradient elution: hexane to 10% to 20% to 30% to 40% to 50% to 60% EtOAc/hexane to neat EtOAc) to afford 62 mg (73% yield) of **175** as a thick syrup in 31% de (de determined by Method C outlined in Section 2.3.2: 20% ^{i}PrOH/hexane, retention times: 6.04 min (minor diastereomer), 7.35 min (major diastereomer): IR (neat film) 3411 (O-H stretch), 1516, 1263, 1096 (C-O stretch), 1028 (C-O stretch), 764, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.22-7.41 (m, 3H, Ar-H), 6.61-6.98 (m, 3H, Ar-H), 4.85-5.01 (m, 1H, Bn-H), 3.63-4.00 (m, 1H, OCH), 3.85* (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.12-3.50 (m, 2H, OCH), 2.90-3.08 (m, 1H, OCH), 3.06 (s, 3H, OCH_3), 3.04* (s, 3H, OCH_3), 1.71-2.06 (m, 3H, $CC\underline{H}_2C\underline{H}HC$), 1.34-1.58 (m, 1H, $CCH_2CH\underline{H}C$), 1.23 (d, 3H, J = 6.0 Hz, $OCHC\underline{H}_3$), 1.20* (d, 3H, J = 5.8 Hz, $OCHC\underline{H}_3$); ^{13}C (75.47 MHz, $CDCl_3$) δ 148.8* (Ar-C), 148.7 (Ar-C), 148.4* (Ar-C), 148.3 (Ar-C), 139.8 (Ar-C), 139.7* (Ar-C), 133.8* (Ar-C), 133.3

(Ar-C), 127.7 (Ar-C), 127.6 (Ar-C), 127.6 (Ar-C), 127.4 (Ar-C), 127.3 (Ar-C), 118.7* (Ar-C), 118.3 (Ar-C), 110.7 (Ar-C), 109.5* (Ar-C), 109.2 (Ar-C), 99.5* (anomeric-C), 99.4 (anomeric-C), 83.4 (OCH), 72.8* (OCH), 72.6 (OCH), 67.0 (OCH), 66.9* (OCH), 66.2 (OCH_2), 66.2* (OCH_2), 58.1 (OCH_3), 58.0* (OCH_3), 55.9* (OCH_3), 55.8 (OCH_3), 55.8 (OCH_3), 32.7* ($\underline{C}H_2CH_2$), 32.6 ($\underline{C}H_2CH_2$), 24.4 ($CH_2\underline{C}H_2$), 24.3* ($CH_2\underline{C}H_2$), 21.1 ($OCH\underline{C}H_3$), 21.0* ($OCH\underline{C}H_3$). Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.75; H, 7.75.

4.3.10 1-phenyl-1-pentanol 177



This known compound[14] was formed in 48% yield (yield determined by ^{1}H NMR and based on *n*-BuLi employed) and characterized to be present in a mixture with **176** as a by-product from the procedure followed in Section 4.3.15 involving the use of $MgBr_2 \cdot OEt_2$ (8 eq). The following data was assigned for **177**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.50 (m, 5H, Ar-H), 4.60-4.71 (m, 1H, Bn-H), 1.61-1.88 (m, 2H, $PhCH(OH)C\underline{H}_2(CH_2)_2CH_3$), 1.18-1.47 (m, 4H, $PhCH(OH)CH_2(C\underline{H}_2)_2CH_3$), 0.89 (t, 3H, J = 7.0 Hz, $PhCH(OH)(CH_2)_3C\underline{H}_3$).

4.4 References

[1] Tipson, R. S. *Methods in Carbohydrate Chemistry*; volume 2; Whistler, R. L.; Wolfrom, M. L., BeMiller, J. N., Eds.; Academic Press Inc.: New York, 1963; pp. 246-250.

[2] Durette, P. L. *Synthesis* **1980**, 1037.

[3] Shafizadeh, F. *Methods in Carbohydrate Chemistry*; volume 1; Whistler, R. L.; Wolfrom, M. L.; BeMiller, J. N.; Shafizadeh, F., Eds.; Academic Press Inc.: New York; 1962; pp. 190-194.

[4] Tanaka, D.; Yoshino, T.; Kouno, I.; Miyashita, M.; Irie, I. *Tetrahedron* **1993**, *49*, 10253.

[5] Ando, M.; Ohhara, H.; Takase, K. *Chem. Lett.* **1986**, 879.

[6] Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2199.

[7] Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

[8] Banaszek, A. *Bull. Acad. Pol. Sci., Ser. Sci.* **1975**, *23*, 585.

[9] *Organic Syntheses Collective Volume VI*; Nowland, W. E., Ed.; John Wiley & Sons: New York, 1988; p. 695.

[10] Thøgersen, H.; Lemieux, R. U.; Block, K.; Meyer, B. *Can. J. Chem.* **1982**, *60*, 44.

[11] Choudhury, A. K.; Ray, A. K.; Roy, N. *J. Carbohydr. Chem.* **1995**, *14*, 1153.

[12] Baer, H. H.; Mateo, F. H.; Siemsen, L. *Carbohydr. Res.* **1989**, *187*, 67.

[13] Pohmakotr, M.; Geiss, K.-H.; Seebach, D. *Chem. Ber.* **1979**, *112*, 1420.

[14] Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605.

CHAPTER 5

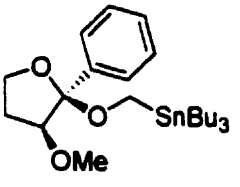
5-MEMBERED-RING AUXILIARIES

5.1 Introduction

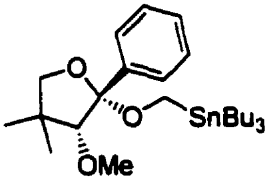
The results obtained that were presented in Chapter 4 were disappointing especially after a lengthy 12 step synthesis to form the auxiliary-substrate compound. Therefore, shorter synthetic routes were examined to synthesize other chiral auxiliaries.

The prospect of synthesizing in relatively few steps a new class of chiral auxiliaries that incorporate a 5-membered ring became very appealing. This chapter presents routes towards the 5-membered ring auxiliary containing derivatives **181** and **182** (Figure 25) and the results obtained in the transmetalation/trapping chemistry with benzaldehyde.

Figure 25. 5-membered ring auxiliary derivatives **181** and **182**.



181



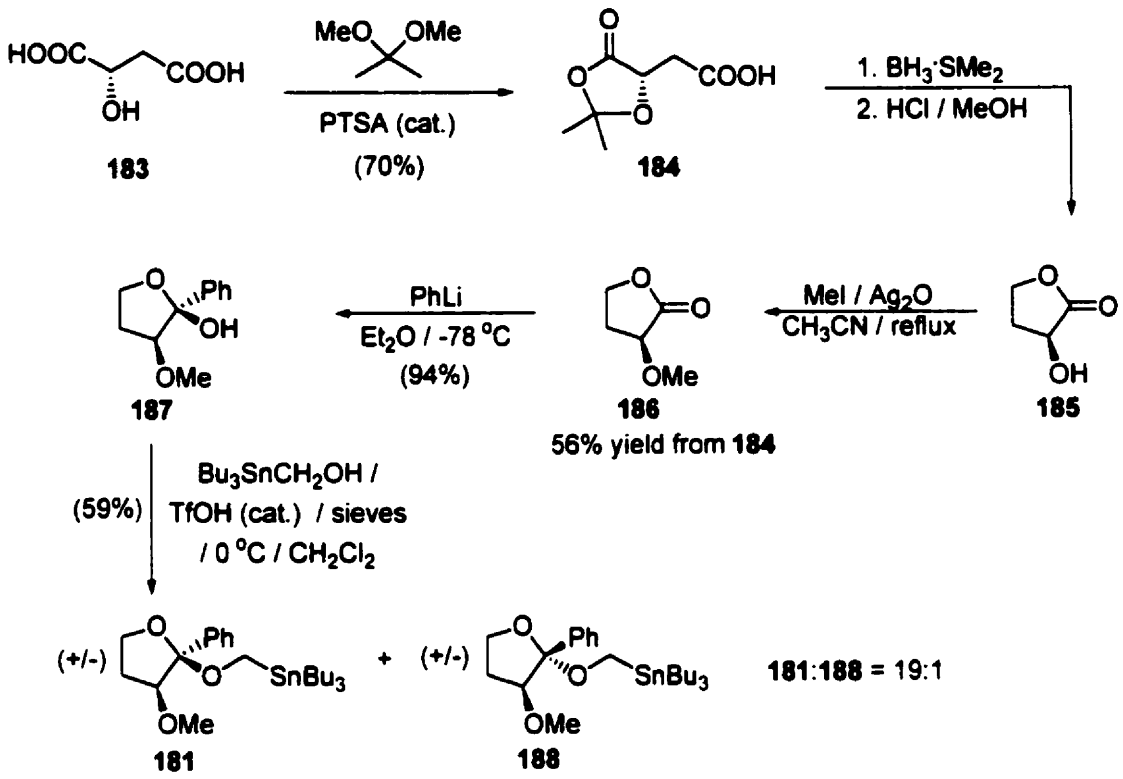
182

5.2 Results and Discussion

*5.2.1 Synthesis of Auxiliary Derivatives **181** and **182***

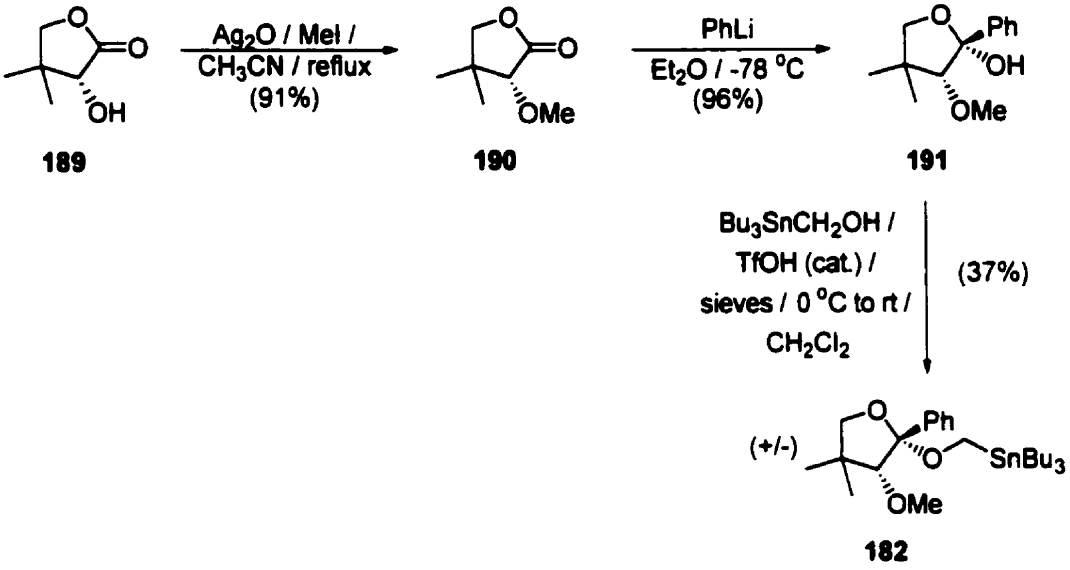
The route towards the auxiliary derivative **181** began with readily available (*S*)-malic acid (**183**) (Scheme 51). The hydroxyl group and one carboxylate group of **183** were protected in a dioxolane ring with the use of 2,2-dimethoxypropane and a catalytic amount of PTSA to form **184**.[1] The unprotected carboxylate group of **184** was then reduced with BH_3•SMe_2 followed by deprotection of the acetal group and subsequent lactonization during the acidic work-up step to form **185**.[2] Crude **185** was then methylated[3] to form **186** in an overall yield of 56% from **184**. Introduction of the Ph group then occurred as usual to form the auxiliary **187** in a 94% yield. The unreported compound **187** was identified provisionally by IR, low resolution MS, and by ^1H and ^{13}C NMR data. The α-alkoxymethyltin substrate was then attached to the auxiliary under the usual acid-catalyzed glycosylation conditions to from the desired product **181** and the undesired diastereomer **188**, which were easily separated by silica gel chromatography, in a combined 59% yield and in a 19:1 ratio of **181**:**188**. The biggest surprise in the synthesis of **181** and **188** is that both compounds racemized during the acid-catalyzed glycosylation step. Racemization occurring in the type of system exemplified by the chiral auxiliary **187** under acidic conditions is unprecedented and a possible mechanism for the racemization process will be presented later in this section.

Scheme 51



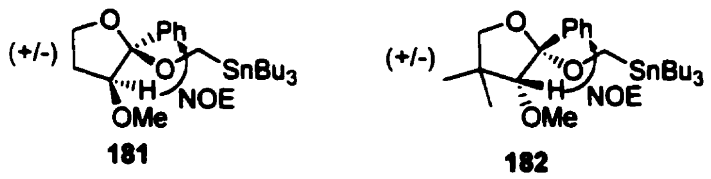
The other auxiliary derivative **182** was accessible in even fewer steps than **181** (Scheme 52). Commercially available (*R*)-pantolactone **189** was methylated to form **190** in a 91% yield. The auxiliary **191** was then formed in a 96% yield by adding PhLi to **190**. The unreported compound **191** was identified provisionally by IR, low resolution MS, and by ^{1}H and ^{13}C NMR data. Once again as seen during the synthesis of **181**, the glycoside **182** was formed as a racemate in a 37% yield and this time as only one diastereomer.

Scheme 52



The assigned relative stereochemistries of **181** and **182** where the 2 and 3 position oxygens of the tetrahydrofuran ring are *syn* to each other are supported by NOE data obtained from NOESY spectra (Figure 26). In both cases an NOE was visible between the 3 position hydrogen and aromatic hydrogens. On the other hand, an NOE between the methoxy group and phenyl group was not visible in either compound. Therefore, support is given for the relative stereochemistry that was assigned for **181** and **182**.

Figure 26. NOE correlations of **181** and **182** from NOESY spectra.

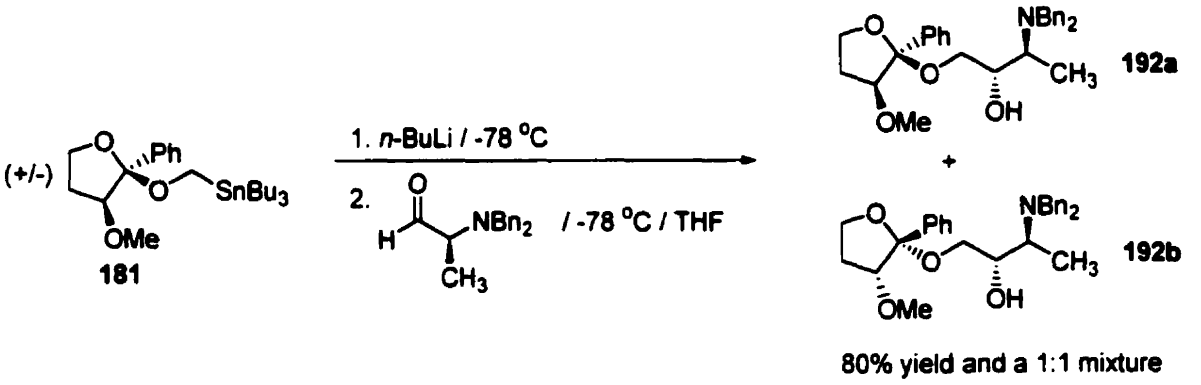


181 **182**

It was difficult to comprehend that compounds **181** and **182** could have racemized. Optical rotations of both compounds were initially taken in $CHCl_3$ (c = 1.15 and 1.05, respectively, for **181** and **182**), and found to be 0 at 589 nm (the D line of Na). Additional proof was desired to confirm that compounds **181** and **182** had actually racemized. It was considered that the non-existent optical rotation might be due to the function of wavelength that the optical rotation readings were taken. Therefore, additional readings for both compounds were taken at 578, 546, 436 and 365 nm in $CHCl_3$; however no rotation was observed at these other wavelengths. Readings for **182** were also taken in different solvents (i.e. methanol, THF, toluene, and hexane) and at similar concentrations as was obtained in $CHCl_3$ with the result of not observing any significant differences from what was observed in $CHCl_3$. Furthermore, a neat sample of **181** did not provide significant optical rotations at either 589, 578, 546, 436 or 365 nm.

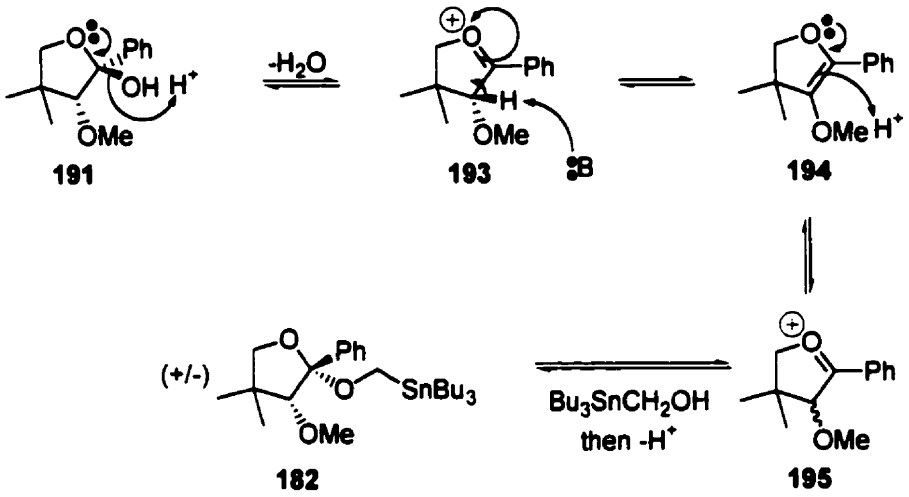
Additional proof that both **181** and **182** were formed as racemates included a derivatization experiment where **181** was transmetalated and trapped with (*S*)-2-*N*,*N*-dibenzylaminopropanal (Scheme 53). The ^1H NMR analysis of the product had revealed that a mixture of 2 diastereomers **192a** and **192b** were formed in a 1:1 ratio. A provisional identification was made for compounds **192a** and **192b**, by IR, and by ^1H and ^{13}C NMR data. According to the literature,[4] the β-amino alcohol functionality is formed in a *anti* stereochemical relationship in additions of organolithium reagents to (*S*)-2-*N*,*N*-dibenzylaminopropanal. Therefore, the formation of 2 diastereomers in a 1:1 ratio can be attributed to the racemic nature of the Sn derivative **181** since a reaction with **181** and (+/-)-2-*N*,*N*-dibenzylaminopropanal gave the identical ^1H NMR spectrum as with (*S*)-2-*N*,*N*-dibenzylaminopropanal.

Scheme 53



There is little doubt that **181** and **182** were formed as racemates due to the mentioned optical rotation data and derivatization experiment. How could such a racemization process happen? It could be possible that the chiral auxiliaries **187** and **191** undergo a process where the oxonium intermediate **193** that is formed during the glycosylation reaction as shown for **191** in Scheme 54, undergoes proton abstraction at the C-3 site of the tetrahydrofuran ring to form an alkene intermediate **194**. The alkene can then be reprotonated at the same site in order to effect racemization at the C-3 stereocenter. The racemic oxonium intermediate **195** can then be trapped with Bu_3SnCH_2OH to form the racemic glycoside **182**.

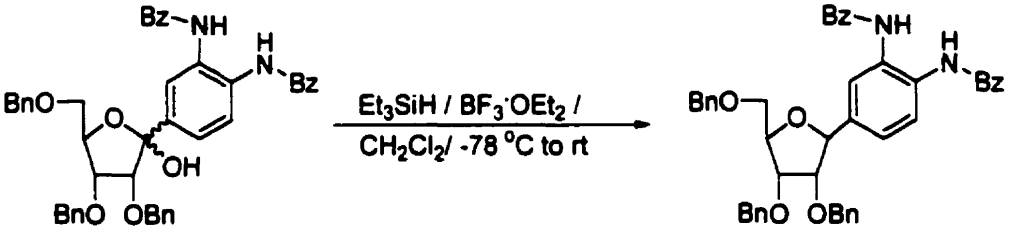
Scheme 54



This type of racemization is unusual for furanoside systems since nitrogen glycosylation reactions involving pyrimidine and purine nucleosides bases with furanosides do not proceed with racemization.[5] Furthermore, furanoses with anomeric C-substituents do not undergo racemization in acidic glycosylation reactions,[6] in BF_3•OEt_2 promoted Et_3SiH reductions,[7] or in another reaction involving oxonium ion formation at the anomeric carbon.[8] For example, a compound in the literature (**196**),[7b] closely related to **187/191**, possessing an aryl anomeric substituent underwent reduction with Et_3SiH/BF_3•OEt_2 to afford **197** without racemization (Scheme 55). The BF_3•OEt_2 promoted Et_3SiH reductions of anomeric carbons are believed to occur *via* a carbocation intermediate.[9] Perhaps a discrete carbocation intermediate is formed from **187/191** under the acidic conditions resulting from the use of TfOH and a discrete carbocation intermediate may not form in reactions involving the use of BF_3•OEt_2. There are no examples in the literature for a glycosylation reaction under protic acid conditions involving a furanose/furanoside glycoside bond donor possessing an anomeric aryl group. Therefore, the carbocation formed from **187/191** also may have

greater stability due to resonance stabilization by the aromatic group. As a result, two requirements may be required for racemization to occur: the presence of an anomeric aryl group (along with a 3-OR group) for the furanose glycoside bond donor and reactions involving the use of protic acids.

Scheme 55

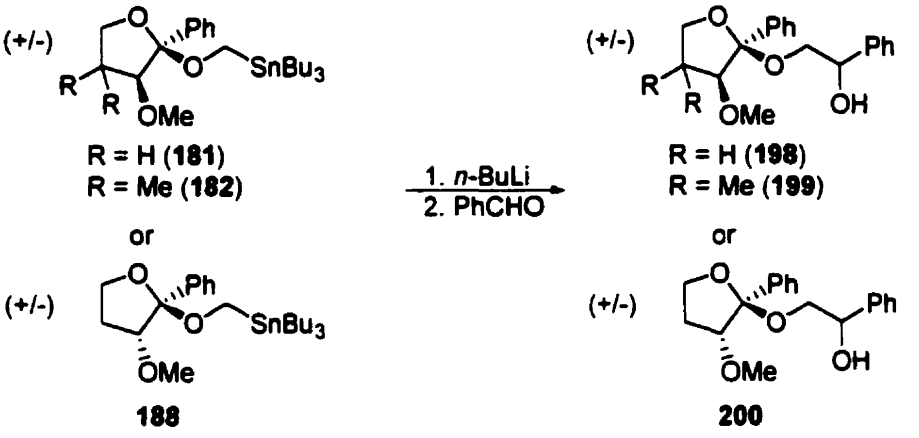


196 **197**

*5.2.2 Transmetalation of Auxiliary Derivatives **181**, **182**, and **188** and Subsequent Trapping with Benzaldehyde*

Both auxiliary derivatives **181** and **182** and also **188**, which is the minor diastereomer formed in the synthesis of **181**, were transmetalated then trapped with benzaldehyde (Table 16). Sn-Li exchange was observed to occur more favorably in THF rather than in Et_2O (entry 1 vs. 2 and entry 3 vs. 4), and addition products were only isolated in reactions conducted in THF. However, addition products were formed as 1 to 1 mixtures in all cases studied. The *anti* relative configuration of the C-2 and C-3 oxygens on the tetrahydrofuran ring in **188** (entry 5) produced no difference in stereoselectivity over the *syn* relative configuration in **181** and **182**. Provisional identifications were made for addition products **198-200**, based on IR, low resolution MS, and by ^1H and ^{13}C NMR data.

Table 16. Transmetalation and trapping of 5-membered ring auxiliaries **181**, **182**, and **188**.



Entry	Auxiliary derivative #	Solvent	Yield: $SnBu_4$ (%)	Yield: addition product (%) (#)	De[a] (%)
1	**181**	THF	96	84	0
2	**181**	Et_2O	3	0	-
3	**182**	THF	75	63	0
4	**182**	Et_2O	18	0	-
5	**188**	THF	nd	64	0

a – de determined by ^1H NMR
nd – not determined

It could be possible that a *cis*-fused-(5,5)-bicyclic system intermediate if formed may not form a template that would allow a stereodifferentiating process to occur. The aldehyde may react from either the top or bottom face of the organolithium intermediate with equal probability.

5.2.3 Summary and Conclusions

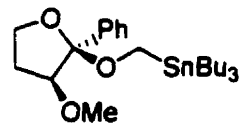
The effect that 5-membered ring auxiliaries have on diastereoselectivity in additions to benzaldehyde have been studied and found to be unable to induce a stereodifferentiating process. The synthetic routes towards the auxiliaries were relatively short; however racemization in the last step had occurred in all cases. This racemization process has been discovered for the first time for compounds posessing a phenyl group as a C-glycoside and a 2-OR group in a furanose ring system.

5.3 Experimental

5.3.1 General

The general procedures described in Section 2.3.1, Section 3.3.1 and Section 4.3.1 are applicable here with the following additions. The known compounds[4] (*S*) and (+/-)-2-*N*,*N*-dibenzylaminopropanal were prepared by following the procedure of Reetz *et* al.[10] with the exception to using L- and (+/-)-alanine as starting materials instead of L-phenylalanine. Ag_2O was also prepared according to a literature procedure.[11]

5.3.2 Tributyl([(2S,3S*)-3-methoxy-2-phenyltetrahydro-2-furanyl]oxymethyl)stannane* ***181***



This section presents the synthesis of **181** from the known compound **186**,[12] *via* unreported synthetic intermediate (2*R*,3*S*)-3-Methoxy-2-phenyltetrahydro-2-furanol (**187**), which was not fully characterized.

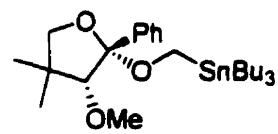
Synthetic intermediate **187** was first prepared as follows: To a cooled (-78 °C) solution of **186** (3.83 g, 33.0 mmol) in Et_2O (330 mL) was added a 1.03 M solution of PhLi in Et_2O (33.6 mL, 34.6 mmol). The mixture was stirred for 20 min after which the reaction was quenched by adding a saturated solution of NH_4Cl (125 mL) and the mixture was then brought to rt. The aqueous layer was then separated and extracted with Et_2O (2 x 200 mL). The combined organic layers were then

dried over anhydrous Na_2SO_4 and filtered, followed by removing the solvent *in vacuo*. Purification of the crude material then occurred by silica gel chromatography (gradient elution: 25% to 50% to 75% Et_2O/hexane to neat Et_2O) to isolate 6.02 g of the unreported compound **187** (94% yield) as a colorless oil: GC retention time: 12.45 min; IR (neat film) 3435 (O-H stretch), 3063, 2830, 1973, 1690, 1118 (C-O stretch), 765, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.03-8.09 (m, 2H, Ar-H), 7.32-7.65 (m, 3H, Ar-H), 4.80 (dd, 1H, J = 4.8, 7.9 Hz, OCH), 3.75-3.88 (m, 2H, OCH_2), 3.41 (s, 3H, OCH_3), 1.92-2.28 (m, 2H, CCH_2C); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 133.4 (Ar-C), 128.6 (Ar-C), 128.6 (Ar-C), 128.0 (Ar-C), 103.4 (anomeric-C), 82.5 (OCH), 59.5 (OCH_2), 57.5 (OCH_3), 35.4 ($C\underline{C}H_2C$); MS (EI) *m/z* 176 (M^+ - H_2O, 3), 177 (M^+ - OH, 1).

Compound **181** was then prepared by the following procedure: To a cooled (0 °C) solution of **187** (2.84 g, 14.6 mmol) and Bu_3SnCH_2OH (4.93 g, 15.4 mmol) in CH_2Cl_2 (150 mL) and in the presence of crushed 4 Å molecular sieves (15 g) was added triflic acid (0.52 mL, 5.84 mmol). The mixture was stirred for 90 min after which the reaction was quenched by adding Et_3N (2 mL) and the mixture was then brought to rt. The mixture was then filtered, followed concentrating the filtrate *in vacuo*. Purification of the crude material then occurred by silica gel chromatography (gradient elution: 25% to 50% to 75% CH_2Cl_2/hexane to neat CH_2Cl_2) to isolate 4.26 g of the major isomer **181** and minor isomer **188** in a 19:1 ratio as oils (59% combined yield) (minor isomer elutes in 50% CH_2Cl_2/hexane, major isomer elutes in 75% CH_2Cl_2/hexane to neat CH_2Cl_2). Data obtained for **181**: $[\alpha]_D^{22} = 0$ (c = 1.15, $CHCl_3$); $[\alpha]_{578}^{22} = 0$ (c = 1.15, $CHCl_3$); $[\alpha]_{546}^{22} = 0$ (c = 1.15, $CHCl_3$); $[\alpha]_{436}^{22} = 0$ (c = 1.15, $CHCl_3$); $[\alpha]_{365}^{22} = 0$ (c = 1.15, $CHCl_3$); $[\alpha]_D^{22} = +0.11$ (c = 114, neat); $[\alpha]_{578}^{22} = +0.10$ (c = 114, neat); $[\alpha]_{546}^{22} = +0.12$ (c = 114, neat); $[\alpha]_{436}^{22} = +0.21$ (c = 114, neat); $[\alpha]_{365}^{22} = 0$ (c = 114, neat); IR (neat film) 2832, 1950, 1108 (C-O stretch), 1017 (C-O stretch), 864 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.52 (m, 2H, Ar-H), 7.25-7.39 (m, 3H, Ar-H), 4.23 (q, 1H, J = 7.9 Hz,

OCHH), 3.92-4.04 (m, 1H, OCHH), 3.72 (dd, 1H, J = 0.9, 5.6 Hz, OCH), 3.53 (d, 1H, J = 10.1 Hz, $^2J_{Sn-H}$ = 29.3 Hz, OCHHSnBu$_3$), 3.11 (d, 1H, J = 10.1 Hz, $^2J_{Sn-H}$ = 27.9 Hz, OCHHSnBu$_3$), 2.88 (s, 3H, OCH$_3$), 2.31-2.43 (m, 1H, CCHHC), 1.98-2.06 (m, 1H, CCHHC), 1.23-1.60 (m, 12H, Sn(CH$_2$CH$_2$CH$_2$CH$_3$)$_3$), 0.65-1.11 (m, 15H, Sn(CH$_2$(CH$_2$)$_2$CH$_3$)$_3$); ^{13}C NMR (75.47 MHz) δ 137.0 (Ar-C), 127.9 (Ar-C), 127.7 (Ar-C), 127.6 (Ar-C), 111.3 (^{3}J = 41 Hz, anomeric-C), 87.0 (OCH), 65.9 (OCH$_2$), 57.3 (OCH$_3$), 49.5 (^{1}J = 363, 380 Hz, OCH$_2$SnBu$_3$), 30.8 (CCH$_2$C), 29.1 (^{2}J = 21 Hz, Sn(CH$_2$CH$_2$CH$_2$CH$_3$)$_3$), 27.2 (^{3}J = 51 Hz, Sn((CH$_2$)$_2$CH$_2$CH$_3$)$_3$), 13.6 (Sn((CH$_2$)$_3$CH$_3$)$_3$), 8.8 (^{1}J = 311, 325 Hz, Sn(CH$_2$(CH$_2$)$_2$CH$_3$)$_3$); MS (FAB) *m/z* 146 (26), 177 (M$^+$ - OCH$_2$SnBu$_3$, 100), 291 (30), 441 (M$^+$ - C$_4$H$_9$, 12); HRMS (FAB) calcd for C$_{20}$H$_{33}$O$_3$Sn (M$^+$ - C$_4$H$_9$) 441.1452, found 441.1465.

5.3.3 Tributyl([(2R,3R*)-3-methoxy-4,4-dimethyl-2-phenyltetrahydro-2-furanyl]oxymethyl)stannane* **182**



This section describes the synthesis of **182** from known compound **190**,[13] *via* unreported synthetic intermediate (2*S*,3*R*)-3-methoxy-4,4-dimethyl-2-phenyltetrahydro-2-furanol (**191**), which was not fully characterized.

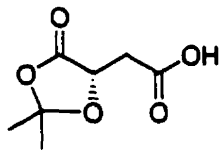
To a cooled (-78 °C) solution of **190** (1.07 g, 7.42 mmol) in Et$_2$O (75 mL) was added a 1.07 M solution of PhLi in Et$_2$O (7.28 mL, 7.42 mmol). The mixture was stirred for 15 min after which the reaction was quenched by adding a saturated solution of NH$_4$Cl (30 mL) and the mixture was then brought to rt. The aqueous layer was then separated and extracted with Et$_2$O (3 x 50 mL). The

combined organic layers were then dried over anhydrous Na_2SO_4 and filtered, followed by removing the solvent *in vacuo*. Purification of the crude material then occurred by silica gel chromatography (gradient elution: hexane to 10% to 20% to 30% to 40% Et_2O/hexane) to isolate 1.58 g of the unreported compound **191** (96% yield) as a colorless oil: GC retention time: 12.76 min; $[\alpha]_D^{22}$ = +21.9 (c = 1.68, $CHCl_3$); IR (neat film) 3368 (O-H stretch), 2828, 1460, 1448, 1112 (C-O stretch), 975 (C-O stretch), 757, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.21-7.63 (m, 5H, Ar-H), 3.86 (d, 1H, J = 8.5 Hz, OC<u>H</u>H), 3.68 (d, 1H, J = 8.5 Hz, OCH<u>H</u>), 3.43 (s, 3H, OCH_3), 3.33 (s, 1H, OCH), 1.15 (s, 3H, CCH_3), 1.11 (s, 3H, CCH_3); ^{13}C NMR δ 137.9 (Ar-C), 127.9 (Ar-C), 127.6 (Ar-C), 125.5 (Ar-C), 94.2 (anomeric-C), 77.7 (OCH), 60.1 (OCH_2), 58.3 (OCH_3), 41.2 (<u>C</u>$(CH_3)_2$), 27.7 (C<u>C</u>H_3), 20.2 (C<u>C</u>H_3); MS (EI) *m/z* 85 (100), 204 (M^+ - H_2O, 2), 205 (M^+ - OH, 1).

Compound **182** was then prepared as follows: To a cooled (0 °C) solution of **191** (3.33 g, 15.0 mmol) and Bu_3SnCH_2OH (4.82 g, 15.0 mmol) in CH_2Cl_2 (150 mL) and in the presence of crushed 4 Å molecular sieves (15 g) was added triflic acid (0.53 mL, 5.99 mmol). The mixture was stirred for 2 h at 0 °C then brought to rt and stirred for an additional 1 h after which the reaction was quenched by adding Et_3N (2 mL). The mixture was then filtered, followed concentrating the filtrate *in vacuo*. Purification of the crude material then occurred by silica gel chromatography (gradient elution: 20% to 30% to 40% to 50% CH_2Cl_2/hexane) to isolate 2.95 g of the unreported compound **182** (37% yield) as a colorless oil: GC retention time: 19.24 min; $[\alpha]_D^{22}$ = 0 (c = 1.05, $CHCl_3$); $[\alpha]_D^{22}$ = 0 (c = 1.06, MeOH); $[\alpha]_D^{22}$ = 0 (c = 1.52, THF); $[\alpha]_D^{22}$ = 0 (c = 1.34, toluene); $[\alpha]_D^{22}$ = + 0.6 (c = 1.51, hexane); $[\alpha]_{578}^{22}$ = 0 (c = 1.37, $CHCl_3$); $[\alpha]_{546}^{22}$ = 0 (c = 1.37, $CHCl_3$); $[\alpha]_{436}^{22}$ = 0 (c = 1.37, $CHCl_3$); $[\alpha]_{365}^{22}$ = 0 (c = 1.37, $CHCl_3$); IR (neat film) 1580, 1465, 1107 (C-O stretch), 1058 (C-O stretch), 1028 (C-O stretch), 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.50 (m, 5H, Ar-H), 3.76 (d, 1H, J = 8.2 Hz, OCH_2), 3.68 (d, 1H, 8.2 Hz, OCH_2), 3.53 (d, 1H, J = 10.2 Hz, $^2J_{H\text{-}Sn}$

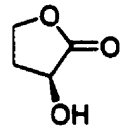
= 28.1 Hz, OC<u>H</u>HSnBu$_3$), 3.38 (s, 1H, OCH), 3.12 (d, 1H, J = 10.2 Hz, $^2J_{H\text{-}Sn}$ = 27.4 Hz, OCH<u>H</u>SnBu$_3$), 3.04 (s, 3H, OCH$_3$), 1.10-1.68 (m, 12H, Sn(CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$)$_3$)), 1.24 (s, 3H, CCH$_3$), 1.05 (s, 3H, CCH$_3$), 0.75-1.00 (m, 15H, Sn(C<u>H</u>$_2$(CH$_2$)$_2$C<u>H</u>$_3$)$_3$); ^{13}C NMR δ 138.0 (Ar-C), 127.8 (Ar-C), 127.6 (Ar-C), 127.5 (Ar-C), 96.7 (anomeric-C), 78.1 (OCH), 59.9 (OCH$_2$), 59.9 (OCH$_3$), 50.0 (O<u>C</u>H$_2$SnBu$_3$), 42.7 (<u>C</u>(CH$_3$)$_2$), 29.1 (^{2}J = 21 Hz, Sn(CH$_2$<u>C</u>H$_2$CH$_2$CH$_3$)$_3$), 27.3 (^{3}J = 52 Hz, Sn((CH$_2$)$_2$<u>C</u>H$_2$CH$_3$)$_3$), 26.4 (CCH$_3$), 21.7 (CCH$_3$), 13.7 (Sn((CH$_2$)$_3$<u>C</u>H$_3$)$_3$), 8.8 (^{1}J = 310, 324 Hz, Sn(<u>C</u>H$_2$(CH$_2$)$_2$CH$_3$)$_3$); MS (FAB) *m/z* 105 (43), 159 (33), 174 (45), 205 (M$^+$ - OCH$_2$SnBu$_3$, 100), 469 (M$^+$ - C$_4$H$_9$, 9); HRMS (FAB) calcd for C$_{22}$H$_{37}$O$_3$Sn (M$^+$ - C$_4$H$_9$) 469.1765, found 469.1789.

5.3.4 (S)-(2,2-Dimethyl-1,3-dioxolan-4-one)-5-ethanoic acid ***184***



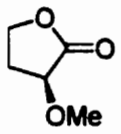
This known compound[1] was prepared by following the literature procedure given by Green *et al.*[1] with the following modification. The crude material was recrystallized from CHCl$_3$ / hexane (1:1) to afford 9.1 g of **184** (70% yield) as a white solid: GC retention time: 10.58 min; ^{1}H NMR (200 MHz, CDCl$_3$) δ 9.0-9.5 (br s, 1 H, COOH), 4.70-4.75 (X of ABX, 1H, OCH), 2.80-3.07 (AB of ABX, 2H, CH$_2$), 1.63 (s, 3H, CH$_3$), 1.58 (s, 3H, CH$_3$); MS (EI) *m/z* 59 (100), 175 (M + H$^+$, 1).

*5.3.5 (S)-3-Hydroxybutyrolactone **185***



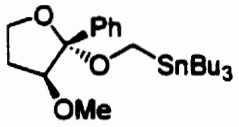
This known compound[2] was prepared by a procedure modified from that described by Shioiri *et al.*[2] To a cooled (-10 °C) solution of **184** (11.5 g, 66.0 mmol) in THF (200 ml) was added a 10 M solution of BH_3•SMe_2 (10.6 mL, 106 mmol) (**Caution: stench!**). The mixture was then brought to rt and stirred overnight after which the reaction was cooled to 0 °C and quenched with MeOH (20 mL). The solvent was then removed *in vacuo*, followed by redissolving the crude material in MeOH (90 mL) and cooling to 0 °C, after which concentrated HCl (30 mL) was added. The mixture was stirred for 90 min, then benzene-EtOH was added (1:1, 300 mL) and the solvent was removed *in vacuo* to afford 6.9 g of crude **185**, which was used without further purification: GC retention time: 6.85 min; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.37-4.60 (m, 2H, OCH_2), 4.18-4.34 (m, 1H, OCH), 3.39 (s, 1H, OH), 2.54-2.71 (m, 1H, CC<u>H</u>HC), 2.17-2.41 (m, 1H, CCH<u>H</u>C); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 178.3 (C=O), 67.0 (OCH), 65.1 (OCH_2), 30.6 (C<u>C</u>H_2C); MS (EI) *m/z* 57 (100), 84 (M^+ - H_2O, 1), 85 (M^+ - OH), 102 (M^+, 1), 103 (M + H^+, 1).

*5.3.6 (S)-3-Methoxybutyrolactone **186***



This known compound[12] was prepared by a procedure modified from that described by Finch *et al.*[3] To a stirred solution of crude **185** (6.7 g, 65.6 mmol) in CH_3CN (160 mL) was added MeI (33 mL, 525 mmol), followed by Ag_2O (18.2 g, 78.7 mmol). The mixture was refluxed for 2 h after which the mixture was cooled and the solids were removed by filtration through Celite. The filtrate was concentrated *in vacuo* followed by purifying the crude material by silica gel chromatography (60% Et_2O/hexane) to afford 4.30 g of **186** (56% yield from **184**) as an oil: GC retention time: 6.78 min; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.37-4.48 (m, 1H, OC<u>H</u>H), 4.19-4.31 (m, 1H, OCH<u>H</u>), 4.03 (t, 1H, J = 7.6 Hz, OCH), 3.58 (s, 3H, OCH_3), 2.45-2.61 (m, 1H, CC<u>H</u>HC), 2.15-2.34 (m, 1H, CCH<u>H</u>C); MS (EI) *m/z* 86 (M^+ -CH_2O, 100), 116 (M^+, 6).

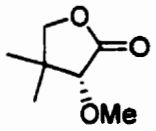
5.3.7 Tributyl([(2R,3S*)-3-methoxy-2-phenyltetrahydro-2-furanyl]oxymethyl)stannane **188***



This unreported compound was obtained as outlined in Section 5.3.2 as the minor isomer: IR (neat film) 2855, 1581, 1450, 1273, 1118 (C-O stretch), 1026 (C-O stretch), 1014 (C-O stretch), 876, 764, 702 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.52-7.55 (m, 2H, Ar-H), 7.30-7.36 (m, 3H, Ar-H), 4.08 (d,

1H, J = 8.4 Hz, OC<u>H</u>H), 4.06 (dd, 1H, J = 2.3, 9.3 Hz, OCH), 3.57-3.64 (m, 1H, OCH<u>H</u>), 3.60 (d, 1H, J = 10.6 Hz, OC<u>H</u>HSnBu$_3$), 3.31 (s, 3H, OCH$_3$), 3.27 (d, 1H, J = 10.6 Hz, OCH<u>H</u>SnBu$_3$), 2.03-2.34 (m, 2H, CC<u>H</u>$_2$C), 1.20-1.65 (m, 12H, Sn(CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$)$_3$), 0.75-1.03 (m, 15H, Sn(C<u>H</u>$_2$(CH$_2$)$_2$C<u>H</u>$_3$)$_3$); ^{13}C NMR (75.47 MHz, CDCl$_3$) δ 139.9 (Ar-C), 128.0 (Ar-C), 127.8 (Ar-C), 126.8 (Ar-C), 105.8 (anomeric-C), 87.3 (OCH), 64.5(OCH$_2$), 58.4 (OCH$_3$), 50.9 (^{1}J = 381 Hz, O<u>C</u>H$_2$SnBu$_3$), 29.1 (^{2}J = 20 Hz, Sn(CH$_2$<u>C</u>H$_2$CH$_2$CH$_3$)$_3$), 29.0 (C<u>C</u>H$_2$C), 27.4 (^{3}J = 53 Hz, Sn((CH$_2$)$_2$<u>C</u>H$_2$CH$_3$)$_3$), 13.7 (Sn((CH$_2$)$_3$<u>C</u>H$_3$)$_3$), 9.0 (^{1}J = 308, 323 Hz, Sn(<u>C</u>H$_2$(CH$_2$)$_2$CH$_3$)$_3$); MS (FAB) *m/z* 177 (M$^+$ - OCH$_2$SnBu$_3$, 100), 277 (58), 279 (71), 441 (M$^+$ - C$_4$H$_9$, 16); HRMS (FAB) calcd for C$_{20}$H$_{33}$O$_3$Sn (M$^+$ - C$_4$H$_9$) 441.1452, found 441.1456.

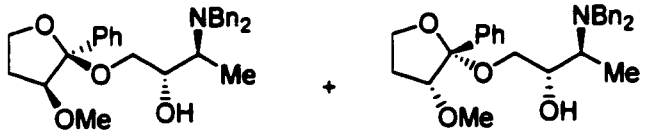
5.3.8 (3R)-3-Methoxy-4,4-dimethyltetrahydro-2-furanone ***190***



This known compound[12] was prepared by a procedure modified from that described by Finch *et al.*[3] To a stirred solution of (*R*)-pantolactone **189** (7.0 g, 53.7 mmol) in CH$_3$CN (31 mL) was added MeI (26.8 mL, 430 mmol), followed by Ag$_2$O (13.7 g, 59.1 mmol). The mixture was refluxed overnight after which the mixture was cooled and the solids were removed by filtering through Celite. The filtrate was concentrated *in vacuo* followed by purifying the crude material by silica gel chromatography (gradient elution: hexane to 10% to 30% Et$_2$O/hexane) to afford 7.05 g of **190** (91% yield) as a colorless oil: $[\alpha]_D^{22}$ = +58.5 (c = 1.25, CHCl$_3$), lit[8] $[\alpha]_D^{25}$ = +48.5 (c = 3.4, CHCl$_3$); ^{1}H

NMR (200 MHz, $CDCl_3$) δ 3.99 (d, 1H, J = 8.8 Hz, OCHH), 3.89 (d, 1H, J = 8.8 Hz, OCHH), 3.65 (s, 3H, OCH_3), 3.58 (s, 1H, OCH), 1.21 (s, 3H, CCH_3), 1.09 (s, 3H, CCH_3).

5.3.9 (2R,3S)-3-(dibenzylamino)-1-[((2S,3S*)-3-methoxy-2-phenyltetrahydro-2-furanyl)oxy]butan-2-ol* ***192a*** *and* ***192b***

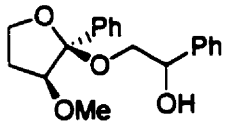


192a **192b**

To a cooled (-78 °C) solution of **181** (110 mg, 0.223 mmol) in THF (5 mL) was added a 1.53 M solution of *n*-BuLi in hexane (0.29 mL, 0.446 mmol). The mixture was stirred for 20 min after which (*S*)-2-*N*,*N*-dibenzylaminopropanal (170 mg, 0.671 mmol) was added and stirring was continued for an additional 30 min. The reaction was then quenched by adding a saturated solution of NH_4Cl (2 mL) and the mixture was then brought to rt. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4 and filtered, followed by removing the solvent *in vacuo*. Purification of the crude material then occurred by silica gel chromatography (gradient elution: 20% to 30% to 40% to 50% Et_2O/hexane) to isolate 98 mg of the unreported compounds **192a** and **192b** as a 1:1 mixture (80% yield) and as an oil (The above reaction with (+/-)-2-*N*,*N*-dibenzylaminopropanal also provided identical spectral characteristics): IR (neat film) 3458 (O-H stretch), 3062 (O-H stretch), 2826, 1952, 1669, 1451, 1112 (C-O stretch), 1029 (C-O stretch), 748, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.03-7.56 (m, 15H, Ar-H), 4.23* (q, 1H, J = 8.0 Hz, HOCH), 3.88-4.05 (m, 1H, HOCH), 3.51-3.86 (m, 4H, 2 OCH_2), 3.37* (d, 2H, J = 13.7 Hz, Bn-H), 3.33 (d, 2H, J = 13.7 Hz, Bn-H), 3.00 (dd, 1H, J

= 9.0, 10.5 Hz, $CH_3OC\underline{H}$), 2.93 (s, 3H, OCH_3), 2.91* (s, 3H, OCH_3), 2.47-2.68 (m, 1H, NCH), 2.18-2.42 (m, 1H, $CC\underline{H}HC$), 1.92-2.12 (m, 1H, $CCH\underline{H}C$), 1.09* (d, 3H, J = 6.6 Hz, CCH_3), 1.06 (d, 3H, J = 6.7 Hz, CCH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 140.2* (Ar-C), 139.9 (Ar-C), 139.8 (Ar-C), 137.0 (Ar-C), 137.0* (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 128.3 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 128.0* (Ar-C), 127.8 (Ar-C), 127.8* (Ar-C), 127.7* (Ar-C), 127.6 (Ar-C), 126.9 (Ar-C), 126.7 (Ar-C), 110.5* (anomeric-C), 110.3 (anomeric-C), 86.8* (OCH), 86.7 (OCH), 72.6* (OCH), 72.1 (OCH), 66.5* (OCH_2), 66.3 (OCH_2), 65.3 (OCH_2), 65.0* (OCH_2), 57.4* (OCH_3), 54.8 (OCH_3), 54.3* (NCH), 54.2 (NCH), 53.0 ($Bn_2N\underline{C}H_2$), 30.6 ($C\underline{C}H_2C$), 30.5* ($C\underline{C}H_2C$), 8.3 ($C\underline{C}H_3$).

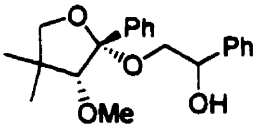
5.3.10 2-[(2S,3S*)-3-Methoxy-2-phenyltetrahydro-2-furanyl]oxy-1-phenyl-1-ethanol* ***198***



To a cooled solution (-78 °C) of **181** (146 mg, 0.294 mmol) in THF (5 mL) was added a solution of 1.56 M *n*-BuLi in hexane (0.38 mL, 0.588 mmol) dropwise and the resulting solution was stirred for 1 h. Benzaldehyde (90 μL, 0.882 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude material occurred by silica gel chromatography (gradient elution: hexane to 20% to 30% to 50% Et_2O/hexane) to isolate in order of elution: 98 mg (96% yield) of $SnBu_4$ and 78 mg (84% yield) of unreported compound **198** as a colorless oil and as a 1:1 mixture of diastereomers

(de determined by Method B, described in Section 2.3.2). Compound **198** displayed the following characterization data: IR (neat film) 3428 (O-H stretch), 2828, 1959, 1112 (C-O stretch), 1029 (C-O stretch), 856 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.52 (m, 2H, Ar-H), 7.19-7.38 (m, 8H, Ar-H), 4.74-4.82 (m, 1H, Bn-H), 4.18-4.28 (m, 1H, $OC\underline{H}HCH_2$), 3.92-4.01 (m, 1H, $OCH\underline{H}CH_2$), 3.85-3.88 (m, 1H, $CH_3OC\underline{H}$), 3.20-3.58 (m, 2H, $OC\underline{H}_2CH(OH)$), 2.91 (s, 3H, OCH_3), 2.89* (s, 3H, OCH_3), 2.32-2.46 (m, 1H, $CC\underline{H}HC$), 2.02-2.11 (m, 1H, $CCH\underline{H}C$); ^{13}C NMR (75.47 MHz) δ 140.5 (Ar-C), 140.5* (Ar-C), 133.6 (Ar-C), 133.4* (Ar-C), 128.8 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 127.9 (Ar-C), 127.9 (Ar-C), 127.9 (Ar-C), 127.6 (Ar-C), 127.6 (Ar-C), 126.1 (Ar-C), 126.1 (Ar-C), 126.1 (Ar-C), 110.5 (anomeric-C), 110.4* (anomeric-C), 86.7* (OCH), 86.7 (OCH), 74.6 (OCH), 73.3 (OCH), 73.1 (OCH_2), 68.1 (OCH_2), 67.0 (OCH_2), 66.6 (OCH_2), 58.9* (OCH_3), 57.5 (OCH_3), 35.3 ($C\underline{C}H_2C$), 30.6 ($C\underline{C}H_2C$); MS (CI) (OH^-) *m/z* 77 ($C_6H_5^+$, 68), 79 (67), 89 (58), 105 (62), 107 (100), 177 (M^+ - $HOCH_2CH(OH)Ph$, 32).

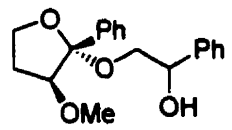
5.3.11 2-[(2R,3R*)-3-Methoxy-4,4-dimethyl-2-phenyltetrahydro-2-furanyl]oxy-1-phenyl-1-ethanol* ***199***



To a cooled solution (-78 °C) of **182** (134 mg, 0.255 mmol) in THF (5 mL) was added a solution of 1.64 M *n*-BuLi in hexane (0.31 mL, 0.508 mmol) dropwise and the resulting solution was stirred for 2 h. Benzaldehyde (78 μL, 0.767 mmol) was next added dropwise and the resulting solution was stirred for an additional 1 h, after which an aqueous solution of saturated NH_4Cl (1 mL)

was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude material occurred by silica gel chromatography (gradient elution: hexane to 10% to 20% to 50% to 75% Et_2O/hexane) to isolate in order of elution: 66 mg (75% yield) of $SnBu_4$ and 55 mg (63% yield) of unreported compound **199** as a colorless oil and as a 1:1 mixture of diastereomers (de determined by Method B, described in Section 2.3.2). Compound **199** displayed the following characterization data: IR (neat film): 3448 (O-H stretch), 1449, 1110 (C-O stretch), 1028 (C-O stretch), 759, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.65 (m, 10H, Ar-H), 4.79-4.90 (m, 1H, Bn-H), 3.05-3.97 (m, 4H, 2 OCH_2), 3.46 (s, 1H, $CH_3OC\underline{H}$), 3.14* (s, 3H, OCH_3), 3.10 (s, 3H, OCH_3), 1.26 (s, 3H, CCH_3), 1.04 (s, 3H, CCH_3), 1.03* (s, 3H, CCH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 140.6* (Ar-C), 140.5 (Ar-C), 137.9* (Ar-C), 137.8* (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 127.6 (Ar-C), 126.2 (Ar-C), 126.1 (Ar-C), 126.0 (Ar-C), 125.7 (Ar-C), 96.5 (anomeric-C), 94.4* (anomeric-C), 78.5 (OCH), 78.4* (OCH), 77.9 (OCH), 77.2 (OCH), 73.5 (OCH_2), 73.3 (OCH_2), 68.9 (OCH_2), 67.7 (OCH_2), 60.2 (OCH_3), 42.9 ($\underline{C}(CH_3)_2$) 42.8* ($\underline{C}(CH_3)_2$), 26.2 ($C\underline{C}H_3$), 26.0* ($C\underline{C}H_3$), 21.4 ($C\underline{C}H_3$), 21.2* ($C\underline{C}H_3$); MS (CI) (OH^-) *m/z* 77 ($C_6H_5^+$, 50), 85 (88), 100 (58), 105 (100), 205 (M^+ - $OCH_2CH(OH)Ph$, 84).

5.3.12 2-[(2R,3S*)-3-Methoxy-2-phenyltetrahydro-2-furanyl]oxy-1-phenyl-1-ethanol* ***200***



To a cooled solution (-78 °C) of **188** (74 mg, 0.149 mmol) in THF (3 mL) was added a solution of 1.56 M *n*-BuLi in hexane (0.19 mL, 0.298 mmol) dropwise and the resulting solution was stirred for 30 min. Benzaldehyde (45 μL, 0.447 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude material occurred by silica gel chromatography (gradient elution: hexane to 20% to 60% to 80% Et_2O/hexane to neat Et_2O to 5% to 10% MeOH/Et_2O) to isolate 30 mg (64% yield) of unreported compound **200** as a colorless oil and as a 1:1 mixture of diastereomers (de determined by Method B, described in Section 2.3.2). Compound **200** displayed the following characterization data: IR (neat film) 3431 (O-H stretch), 2897, 1494, 1449, 1116 (C-O stretch), 1027 (C-O stretch), 1006 (C-O stretch), 762, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.49-7.58 (m, 2H, Ar-H), 7.17-7.39 (m, 8H, Ar-H), 4.88-4.94 (m, 1H, Bn-H), 4.00-4.25 (m, 2H, $OC\underline{H_2}CH_2$), 3.26-3.73 (m, 3H, $CH_3OC\underline{H}$ + , $OC\underline{H_2}CH(OH)$), 3.38 (s, 3H, OCH_3), 3.35* (s, 3H, OCH_3), 2.05-2.46 (m, 2H, $CC\underline{H_2}C$); ^{13}C NMR (75.47 MHz) δ 140.7* (Ar-C), 140.5 (Ar-C), 136.7 (Ar-C), 133.4* (Ar-C), 128.5 (Ar-C), 128.3 (Ar-C), 128.2 (Ar-C), 128.2 (Ar-C), 128.2 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 127.6 (Ar-C), 127.6 (Ar-C), 126.1 (Ar-C), 126.1 (Ar-C), 126.0 (Ar-C), 110.5* (anomeric-C), 110.4 (anomeric-C), 86.9* (OCH), 86.9 (OCH), 74.7* (OCH), 68.1 (OCH), 67.6 (OCH_2), 67.0 (OCH_2),

66.7 (OCH_2), 66.7 (OCH_2), 57.6 (OCH_3), 30.7$^{\bullet}$ (CCH_2C), 30.7 (CCH_2C); MS (CI) (OH^-) ***m/z*** 105 (44), 121 (50), 177 (M^+ - $OCH_2CH(OH)Ph$, 100), 178 (33), 193 (M^+ - $CH_2CH(OH)Ph$, 8).

5.4 References

[1] Green, D. L. C.; Kiddle, J. J.; Thompson, C. M. *Tetrahedron* **1995**, *51*, 2865.

[2] Shioiri, T.; Irako, N.; Sakakibara, S.; Matsuura, F.; Hamada, Y. *Heterocycles* **1997**, *44*, 519.

[3] Finch, N.; Fitt, J. J.; Hsu, I. H. S. *J. Org. Chem.* **1975**, *40*, 206.

[4] Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141.

[5] For a review on nitrogen glycosylation reactions involving pyrimidine and purine nucleoside bases with furanoside sugars see: Wilson, L. J; Hager, M. W.; El-Kattan- Y. A.; Liotta, D. C. *Synthesis* **1995**, 1465.

[6] (a) Guthrie, R. D.; Jenkins, I. D.; Yamasaki, R. *Aust. J. Chem.* **1982**, *35*, 1003. (b) Li, Y.-L.; Wu, Y.-L. *Tetrahedron Lett.* **1996**, *37*, 7413. (c) Tomooka, K.; Kikuchi, M.; Igawa, K.; Keong, P.-H.; Nakai, T. *Tetrahedron Lett.* **1999**, *40*, 1917.

[7] (a) Krohn, K.; Heins, H.; Wielckens, K. *J. Med. Chem.* **1992**, *35*, 511. (b) Tanaka, K.; Shionoya, M. *J. Org. Chem.* **1999**, *64*, 5002. (c) Yoda, H.; Shimojo, T.; Takabe, K. *Synlett* **1999**, 1969. (d) Ooi, T.; Uraguchi, D.; Morikawa, J.; Maruoka, K. *Org. Lett.* **2000**, *2*, 2015.

[8] Lay, L.; Nicotra, F.; Panza, L.; Russo, G.; Caneva, E. *J. Org. Chem.* **1992**, *57*, 1304.

[9] Czernecki, S. Ville, G. *J. Org. Chem.* **1989**, *54*, 610.

[10] Reetz, M. T.; Drewes, M. W.; Schwickardi, R. *Organic Syntheses*; volume 76; Martin, S. F., Ed.; John Wiley & Sons: New York, 1998; pp. 110-122.

[11] Pearl, I. A. *Organic Syntheses*; collective volume IV; Rabjohn, N., Ed.; John Wiley & Sons: New York, 1963; pp. 972-977.

[12] Fujimoto, Y.; Ukita, T.; Miyagawa, H.; Tsurushima, T.; Irie, H.; Nishimura, K.; Ueno, T. *Biosci. Biotech. Biochem.* **1994**, *58*, 1627.

[13] (a) Dang, H.-S.; Diart, V.; Roberts, B. P. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1033. (b) Hasse, L; Klemm, E. *J. Prakt. Chem.* **1985**, *327*, 174.

CHAPTER 6

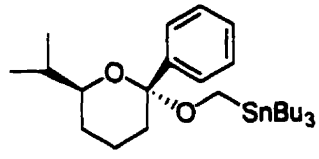
A TETRAHYDROPYRAN CHIRAL AUXILIARY

6.1 Introduction

Employing a tetrahydropyran chiral auxiliary with a methoxy group in the 3-position (Chapter 4) did not lead to improvements in diastereoselectivity of α-alkoxycarbanion additions to aldehydes over other auxiliaries. With fewer oxygen atoms on the auxiliary, it was believed that aggregation of the transmetalated intermediate might be reduced to enhance intramolecular coordination at the C-3 position and result in an increase in the level of diastereoselectivity. However, two oxygen atoms still remained on the auxiliary and intramolecular coordination to the Li atom of the transmetalated intermediate by either ring oxygen or C-3 position oxygen may occur. One or possibly both of the coordination modes may exist and react with aldehydes, with one structure possibly inducing a lower level or opposite sense of diastereoselectivity over the other.

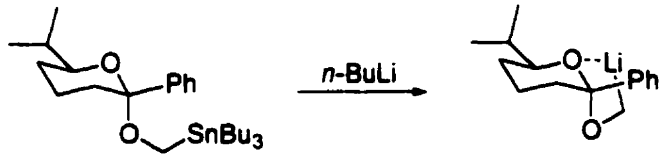
It was desirable to construct an auxiliary with only one coordination mode possible in order to probe the role of two different coordination modes possibly occurring in the 3-methoxytetrahydropyran auxiliary. An auxiliary possessing only a ring oxygen and connected to an alkoxymethyltin substrate (**201**) (Figure 27) was synthesized so that the acetal functionality required for auxiliary/product recovery can be maintained. Furthermore, an isopropyl group was chosen to be included at the 5-position so that a chair conformation could predominate. Transmetalation of **201** to the organolithium **202** can result in only one possible intramolecular coordination mode (Scheme 56). This chapter presents the synthesis of **201** and the results obtained in the transmetalation/trapping chemistry with aldehydes.

Figure 27. An auxiliary derivative (**201**) containing a single oxygen atom in the ring position.



201

Scheme 56



201 **202**

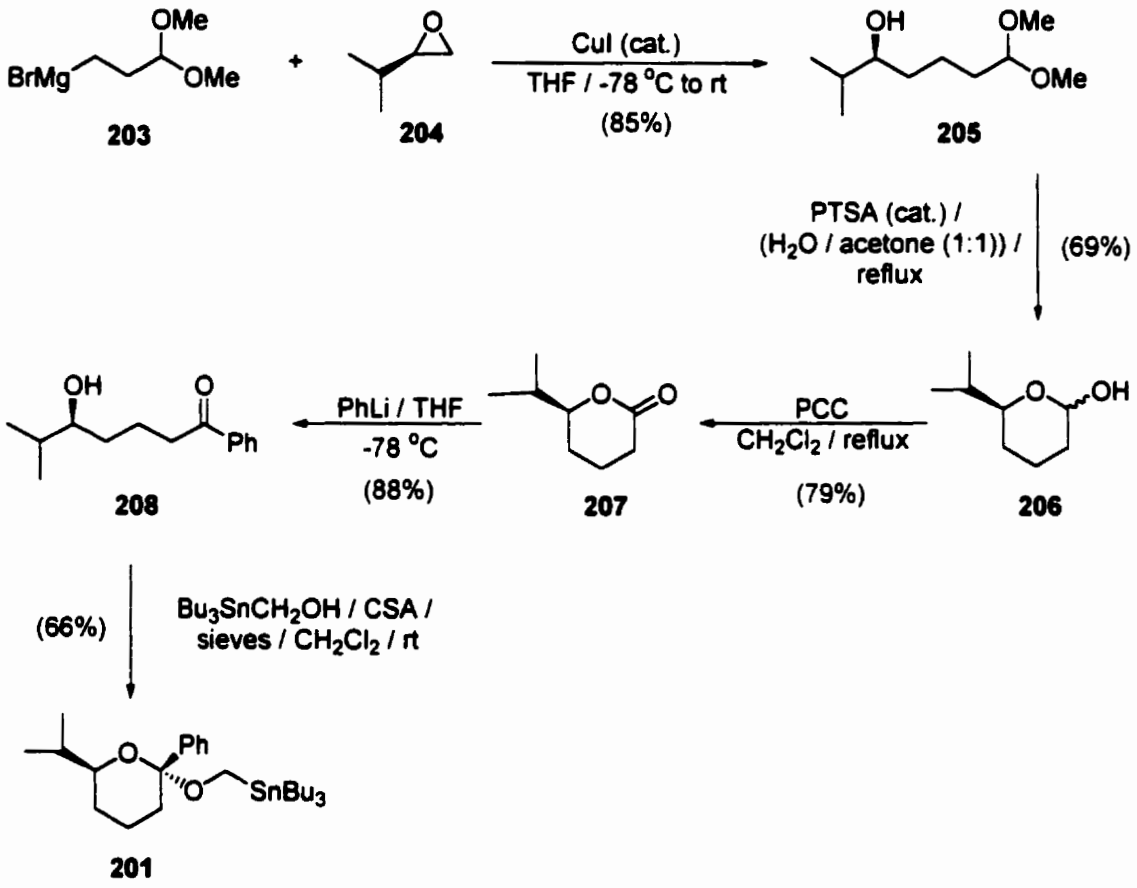
6.2 Results and Discussion

6.2.1 Synthesis of Auxiliary Derivative 201

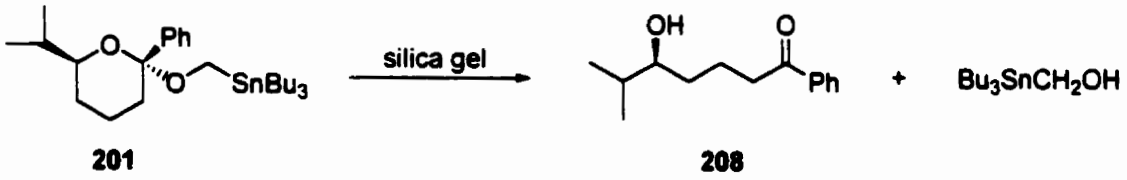
The synthesis of **201** first involved the copper-catalyzed addition of Grignard reagent **203** to the known epoxide **204**,[1] to obtain **205** in a 85% yield (Scheme 57). Deprotection of the dimethylacetal and subsequent cyclization to the lactol **206** then occurred under acidic conditions. PCC oxidation[2] of **206** then furnished the lactone **207**, to which PhLi was added to afford **208**. The expected cyclic hemiketal was not formed in this case and instead the PhLi addition product was characterized as being in the open chain form. The open chain form may be thermodynamically more stable than the ring form.[3] An addition product resulting from a second equivalent of PhLi adding to the ketone **208** was not detected. The glycosylation reaction with **208** was successful in producing the auxiliary derivative **201** in a 66% yield. Compound **201** was found to be extremely

sensitive to acid; therefore purification was performed quickly on Et_3N-deactivated silica gel. When purification of crude **201** was attempted on active silica gel, isolated yields of **201** where very low since **201** slowly broke down to **208** and Bu_3SnCH_2OH (Scheme 58).

Scheme 57

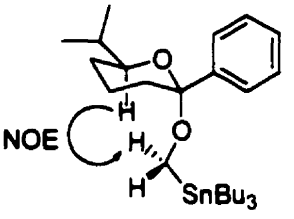


Scheme 58



The relative stereochemistry of **201** was confirmed by a NOESY spectrum (500 ms mixing time) in C_6D_6. An NOE was visible between the C-5 position proton and one of the methylene protons adjacent to the $SnBu_3$ group (Figure 28). An NOE was not visible between the C-5 proton and aromatic protons. Therefore, the isopropyl and phenyl groups of **201** must be *syn* to each other as expected due to sterics and the anomeric effect; hence the largest ring substituents would prefer to be diequatorial and the oxygen substituent would prefer to be in the axial position.

Figure 28. NOE correlation observed in **201**.



201

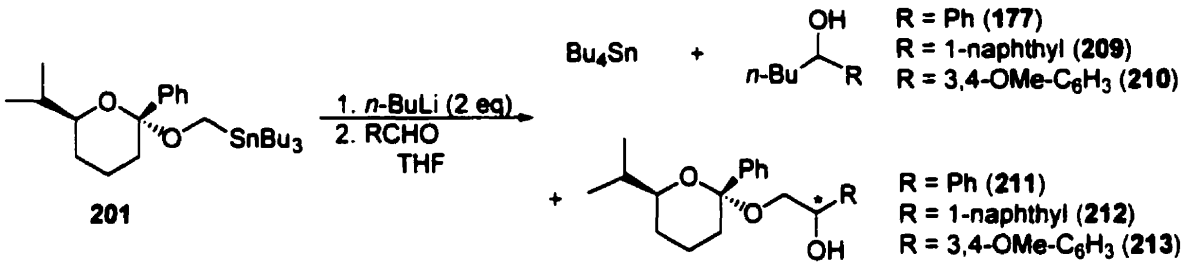
*6.2.2 Transmetalation of **201** and Subsequent Trapping with Aldehydes*

Many experimental variables and their effect on diastereoselectivity were studied in the transmetalation of **201** and subsequent trapping with aldehydes. Each variable will be discussed separately with the effect of the structure of the aldehydes being discussed first (Section 6.2.2.1), followed by metals (Section 6.2.2.2), alkyllithiums (Section 6.2.2.3), solvent (Section 6.2.2.4) and coordinating agents (Section 6.2.2.5). A discussion of the direction of selectivity and the implications of this on a proposed transition state model is also included (Section 6.2.2.6).

6.2.2.1 Effect of Aldehyde Structure

Sn-Li exchange of **201** occurred readily in THF (Table 17); however additions to various aldehydes always led to an inseparable mixture of *n*-BuLi addition products **177**, **209**, **210**, and α-alkoxymethyllithium addition products **211-213**. Unreported addition products **211-213**, were identified provisionally based on ^{1}H NMR data of the mixtures containing the known *n*-BuLi addition compounds. Furthermore, low yields for addition products **211-213** were encountered since they were extremely sensitive to acid as was observed for auxiliary derivative **201**. Therefore, during purification by silica gel chromatography and also during TLC analysis a portion of the addition products **211-213** broke down to the auxiliary **208** and diols **132** and **134** (Scheme 59). The addition product **213** did not result in the formation of **208** during TLC analysis and instead a different lower R_f by-product was formed that was not isolated or identified.

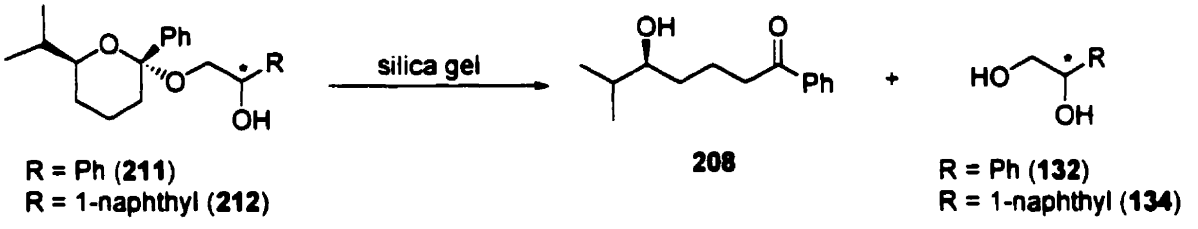
Table 17. Effect of aldehyde structure on diastereoselectivity.



Entry	R	Yield: Bu_4Sn (%)	Yield[a]: *n*-BuLi addition products (**177**, **209**, **210**) (%) (#)	Yield[b]: Addition products (**211**-**213**) (%) (#)	De[c] (%)
1	Ph	93	17 (**177**)	80 (**211**)	46
2	1-naphthyl	84	35 (**209**)	35 (**212**)	39
3	3,4-OMe-C_6H_3	nd	17 (**210**)	19 (**213**)	41

nd - not determined.
a - yield determined by ^{1}H NMR and based on *n*-BuLi employed.
b - yield determined by ^{1}H NMR and based on **201**.
c - de determined by ^{1}H NMR.

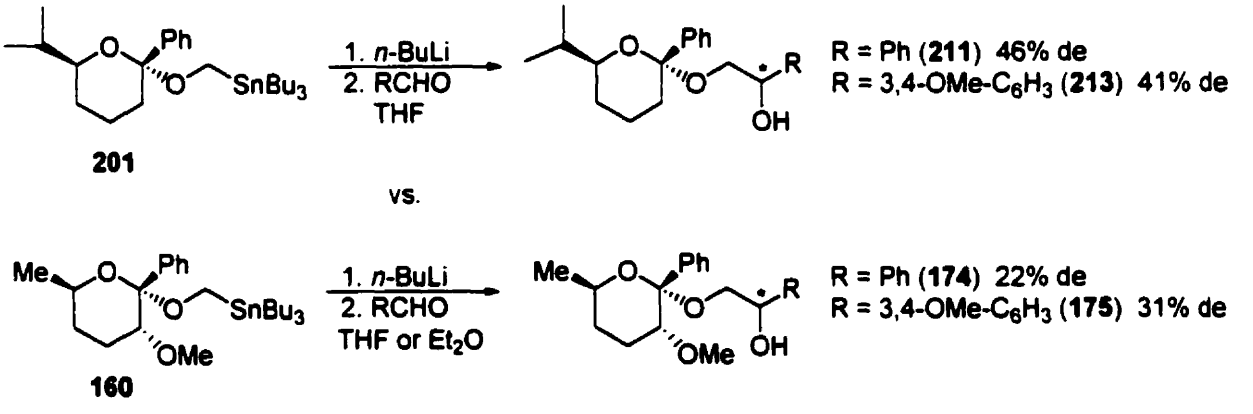
Scheme 59



The most important result and conclusion to be drawn from Table 17 is that diastereoselectivity was achieved with lithiated auxiliary **201** and suggests that an intramolecular coordination mode of the lithium atom to the ring oxygen of the auxiliary is a possible coordination mode for achieving diastereoselectivity. A remarkable improvement to 46% de (entry 1) occurred in an addition to benzaldehyde when comparing to the 22% de experienced with the lithiated 3-

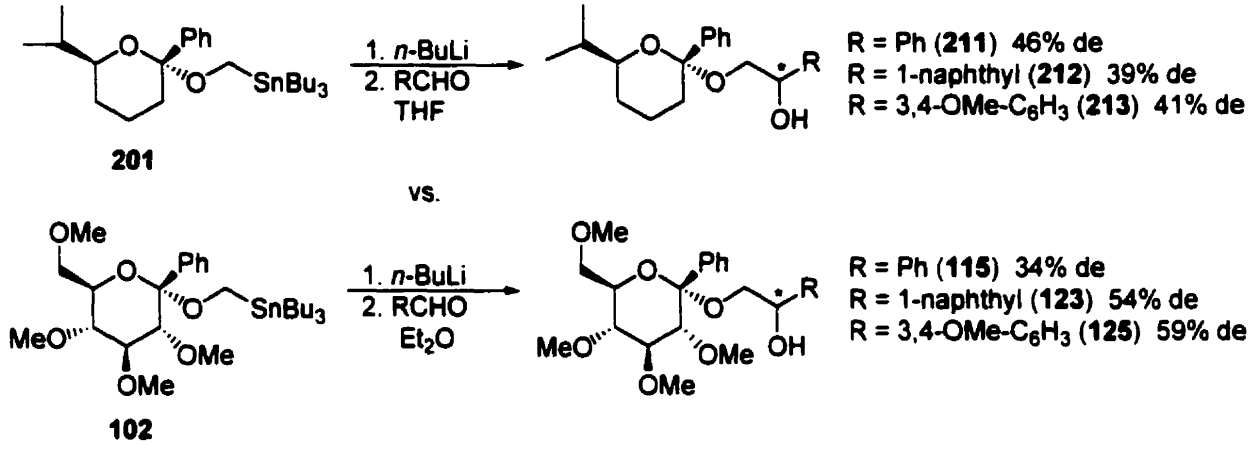
methoxytetrahydropyran chiral auxiliary derivative **160** (Chapter 4) (Scheme 60). Also, a slight improvement was noted for the result obtained with 3,4-dimethoxybenzaldehyde (41% de) (entry 3) up from the 31% de obtained with the lithiated 3-methoxytetrahypropyran chiral auxiliary derivative **160** in a reaction conducted in Et_2O (Scheme 60). Therefore, the hypothetical structure of the 3-methoxytetrahydropyran chiral auxiliary lithiated intermediate, where the ring oxygen is coordinated to the lithium atom may in fact provide the greatest amount of diastereoselectivity. A speculative intermediate with coordination to the C-3 oxygen may in fact provide a lower amount of diastereoselectivity and perhaps with a direction reversal.

Scheme 60



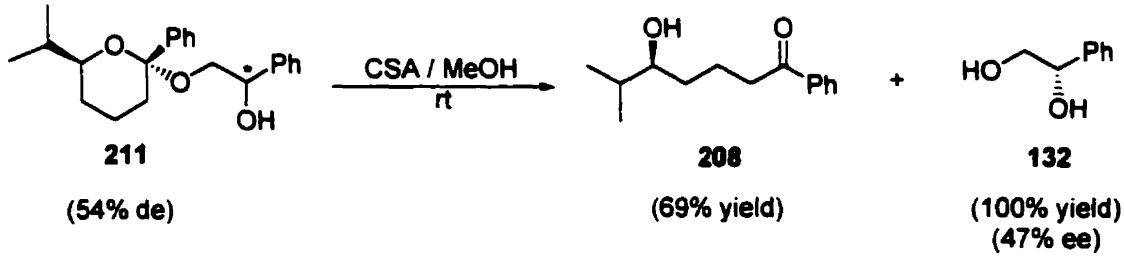
When comparisons are made between the results in Table 17 and the lithiated glucose-derived chiral auxiliary derivative **102** (Chapter 2), another impressive improvement is noted for the reaction involving benzaldehyde and lithiated **201** (46% de vs. 34% de (for a reaction conducted in Et_2O)) (Scheme 61). However reactions with lithiated **201** and 1-naphthaldehyde or 3,4-dimethoxybenzaldehyde provide lower levels of diastereoselectivities than those achieved with the lithiated glucose-derived chiral auxiliary derivative **102** (39% vs. 54% de and 41% vs. 59% de respectively) (Scheme 61).

Scheme 61



The acid-labile nature of the addition products were once again beneficial towards product and auxiliary recovery. The addition product **211** obtained from the reaction noted in Table 17 was readily cleaved to the enantiomerically enriched diol **132** and auxiliary **208** in 100% and 69% yields, respectively, by treatment with camphorsulfonic acid (CSA) in methanol (Scheme 62). The expected auxiliary methyl glycoside was not obtained but instead **208** was isolated, this may be due to hydrolysis during silica gel chromatography. The stereocenter in the addition product was conserved in the diol **132** since chiral HPLC analysis revealed **132** to be present in 47% ee with the *S* enantiomer being the major isomer. A discussion on the direction of selectivity will be included in Section 6.2.2.6.

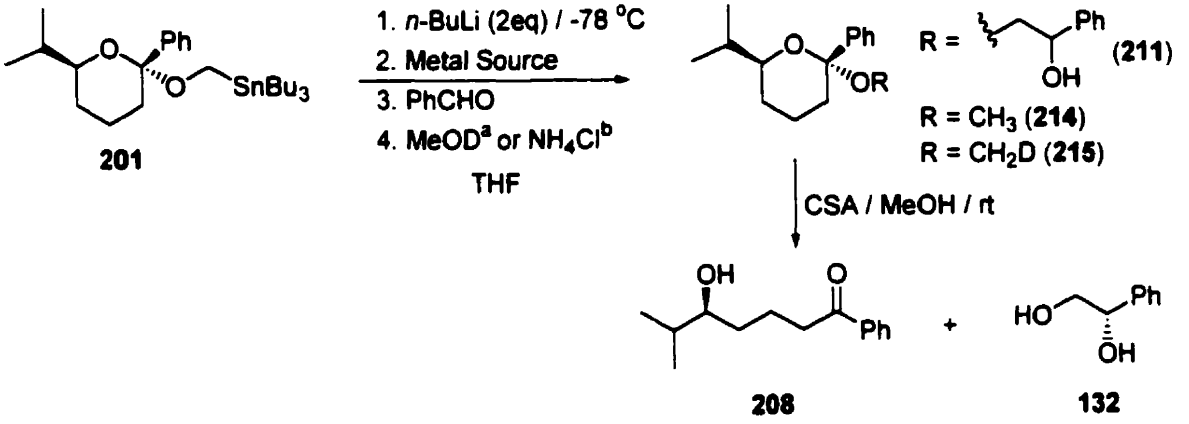
Scheme 62



6.2.2.2 Coordination Optimization Trials

With support for intramolecular coordination by the ring oxygen mode, attempts were made to optimize coordination by employing the same strategy presented in previous chapters (Chapter 2 and 4) involving transmetalation to metals other than lithium (Table 18). When Li-Ce exchange occurred at -40 °C (entry 1) the diol **132** was formed in 54% ee, which is approximately the same level of selectivity achieved with the organolithium species. Therefore, it was believed that Li-Ce exchange did not take place and trapping with benzaldehyde possibly occurred with the organolithium species. Another attempt was made to perform the Li-Ce exchange at a higher temperature (-20 °C) (entry 2) in order to favor the exchange process; however a complex mixture of unidentified products was produced with only a trace amount of protonated material **214** without any deuterated compound **215**. ^{1}H NMR and low resolution MS data provisionally identified the unreported deuterated compound **215**. Most likely either the organolithium or organocerium species if formed decomposed at this higher temperature. Further attempts were made to transmetalate to Zn (entry 3) with the result of not producing any diol and protonated/deuterated material was isolated in a 72% yield and in a 73:27 ratio respectively. Thus, it seems that the Zn species must be unreactive with benzaldehyde and is also unstable. This unreactivity/instability problem was documented in Chapter 2 for organotitanium species. Transmetalation to the Mg species (entry 4) was successful in forming the diol **132** in a 60% yield however in only 5% ee. In another experiment, an attempt was made to form and trap an organoboron species (entry 5). However, once again decomposition was suspected as a complex mixture of unidentified products was produced.

Table 18. Transmetalation to other metals.



Entry	Metal Source	Temp. for Li-M exchange (°C)	Yield of H^+ and D^+ material (**214** and **215**) (%)	H^+ : D^+ ratio (**214**:**215**)	Yield: diol (**132**) (%)	ee (%)
1	$CeCl_3$	-40	nd	-	51	54
2	$CeCl_3$	-20	trace	100:0	0	-
3	$ZnCl_2$•TMEDA	-40	72	73:27	0	-
4	$MgBr_2$•OEt_2	-40	nd	-	60	5
5	BF_3•OEt_2	-40	0	-	0	-

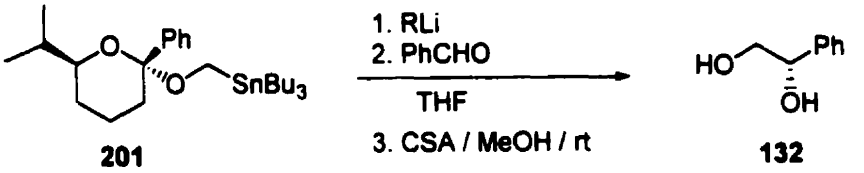
nd - not determined.
a - quench occurred with MeOD for entries 2 and 3 and 5.
b - quench occurred with an aqueous 1.5% NH_3 / $NHCl_4$ saturated solution for entry 1 and with an aqueous NH_4Cl saturated solution for entry 4.

6.2.2.3 Role of Alkyllithium

The primary function of the alkyllithium is to convert the alkoxymethylstannane into the alkoxymethyllithium. Throughout most of the work in this thesis it was routine to employ 2

equivalents of *n*-BuLi since this amount provided a higher yield of transmetalated product (Chapter 2). It was not clear whether the extra equivalent played an important coordination role onto the chiral auxiliary derivative organolithium intermediate to induce diastereoselectivity. Therefore, the amount and nature of alkyllithium employed was studied further (Table 19). Reducing the amount of *n*-BuLi to one equivalent resulted in a very significant drop in selectivity (entry 1 vs. 2). Therefore *n*-BuLi may play an important role in coordinating to the chiral auxiliary derivative organolithium intermediate to induce a greater level of selectivity. This effect could be increased by employing even more *n*-BuLi (4 eq.) (entry 3). Bulkier alkyllithiums were then employed (entries 4 and 5) in hopes of increasing the beneficial steric interaction induced by *n*-BuLi. Selectivity dropped with the use of *s*-BuLi or *t*-BuLi and it was believed that these larger alkyllithiums might be too big to coordinate onto the chiral auxiliary derivative organolithium intermediate. Furthermore, the yield of diol **132** dropped significantly with the use of *t*-BuLi (entry 5) since Sn-Li exchange occurred to a smaller extent. The drop in yield can be attributed to greater steric crowding for the larger alkyllithium occurring in the transition state for Sn-Li exchange.

Table 19. Effect of Alkyllithium.



201 **132**

Entry	Alkyllithium (R)	eq.	Yield: diol (**132**) (%)	ee[a] (%)
1	*n*-Bu	2	85	47
2	*n*-Bu	1	56	32
3	*n*-Bu	4	90	60
4	*s*-Bu	2	56	44
5	*t*-Bu	2	21	46

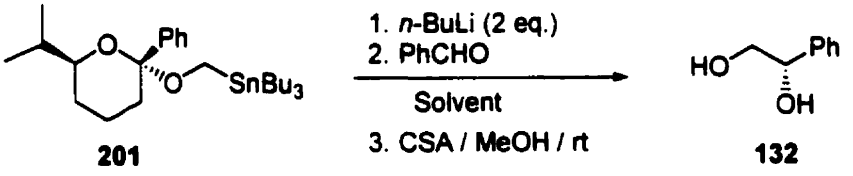
a - ee determined by chiral HPLC analysis of **132**

6.2.2.4 Solvent Effects

Other solvents than THF were studied (Table 20) in an attempt to optimize intramolecular coordination as was discussed in Chapter 2. Unfortunately, selectivity in toluene (entry 2) could not be studied since Sn-Li exchange did not occur in this solvent. However, transmetalation did occur in Et_2O (entry 3) although rather sluggishly, and a remarkable drop in selectivity occurred (entry 1 vs. entry 3). Therefore, less polar solvents than THF did not promote greater intramolecular coordination as was previously considered and THF may be playing a beneficial role towards selectivity. A mixed solvent system (15% THF/Et_2O) (entry 4) was studied originally for the purpose of increasing the yield of diol. However the observation that an increase in selectivity (entry 1 vs. entry 4) occurred with the use of 15% THF in Et_2O was totally unexpected. A solvent

system including a solvent with less coordinating ability than Et_2O (TBME) (entry 5) was also studied with the result of not observing any significant changes (entry 4 vs. entry 5). Furthermore, a solvent with greater coordinating ability than THF was studied (DME) (entry 6), and selectivity dropped significantly (entry 1 vs. entry 6).

Table 20. Effect of solvent on selectivity.



201 **132**

Entry	Solvent	Yield: diol (**132**) (%)	ee[a] (%)
1	THF	85	47
2	toluene	0	-
3[b]	Et_2O	49	26
4	15% THF/Et_2O	59	74
5	15% THF/TBME	52	70
6	DME	97	39

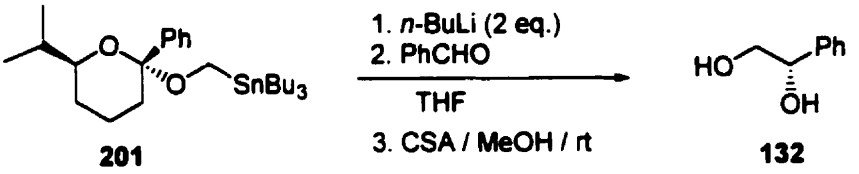
a - ee determined by chiral HPLC analysis of **132**
b - transmetalation conducted with 2 eq. of *n*-BuLi plus 2 eq. of *t*-BuLi and at -40 °C.

From the results presented in Table 20, it can be postulated that THF may act as a coordinating agent as seen for alkyllithiums (Section 6.2.2.3). Coordination of THF to the chiral auxiliary derivative organolithium intermediate lithium atom may also create a beneficial steric

interaction in the transition state to induce a greater level of selectivity. Weaker coordinating agents such as Et_2O or TBME may not coordinate at all or create the necessary steric environment as THF for inducing a higher level of selectivity. DME on the other hand most likely competes with the chiral auxiliary derivative organolithium intermediate ring oxygen for coordination for the α-alkoxy lithium atom to reduce the chance for a *cis*-fused bicyclic system to be formed. THF may also compete with the chiral auxiliary derivative organolithium intermediate ring oxygen to a smaller extent than DME for coordination for the α-alkoxy lithium atom since a reaction conducted in neat THF results in a lower level of selectivity (47% ee) when comparing with the 74% ee achieved with the use of 15% THF in Et_2O. The next section further discusses the use of THF and other potential coordination additives in order to optimize possible steric interactions.

Concentration effects in THF were also studied (Table 21) since a reaction conducted in a concentrated solution may have aggregation occurring to a larger extent than in a dilute solution and different aggregation states may have different effects on selectivity. The result in entry 2 represents the standard concentration (0.05 M) employed for all auxiliary derivatives in this thesis. A very significant drop in selectivity occurs when the reaction is conducted in a more dilute solution (0.005 M) (entry 1); therefore aggregation may also play an important role in achieving selectivity. The selectivity was further enhanced by conducting a reaction in a more concentrated solution (0.5 M) (entry 3).

Table 21. Study of concentration effects in THF.



201 **132**

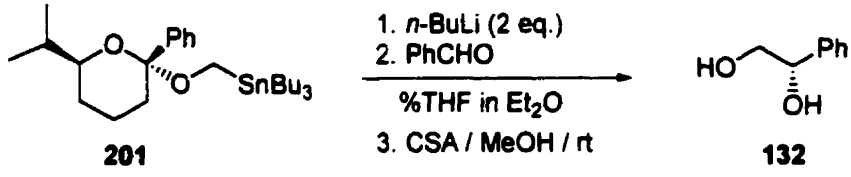
Entry	Concentration of **201** in THF (M)	Yield of diol **132** (%)	ee[a] (%)
1	0.005	62	32
2	0.05	85	47
3	0.5[b]	34	65

a - ee determined by chiral HPLC analysis of **132**.
b - represents the concentration in combined THF (35%) and hexane (65%) from the *n*-BuLi solution.

6.2.2.5 Study of Coordinating Agents

Other concentrations of THF in Et_2O were employed (Table 22 and see graph in Figure 29) in order to find the optimal conditions for THF coordination onto the lithium atom of the chiral auxiliary derivative organolithium intermediate while still maintaining the intramolecular coordination of the lithium atom to the ring oxygen. Only 0.9 % of THF (entry 2), which equates to one equivalent of THF to organolithium species present in solution, was required to cause a very significant increase in selectivity from no THF at all (entry 1 vs. entry 2). Increasing the amount of THF to 7% (entry 3) resulted in another increase and the level of selectivity was maximized between 15% and 30% THF (entries 4 and 5), after which a slow decline in selectivity must occur to 100% THF (entry 6). Employing 30% THF in Et_2O is the ideal condition since it affords the highest yield of diol **132** (91 % yield) because the yield of Sn-Li exchange is maximized and the level of selectivity is maximized as well.

Table 22. Effect of % THF in Et_2O on selectivity.

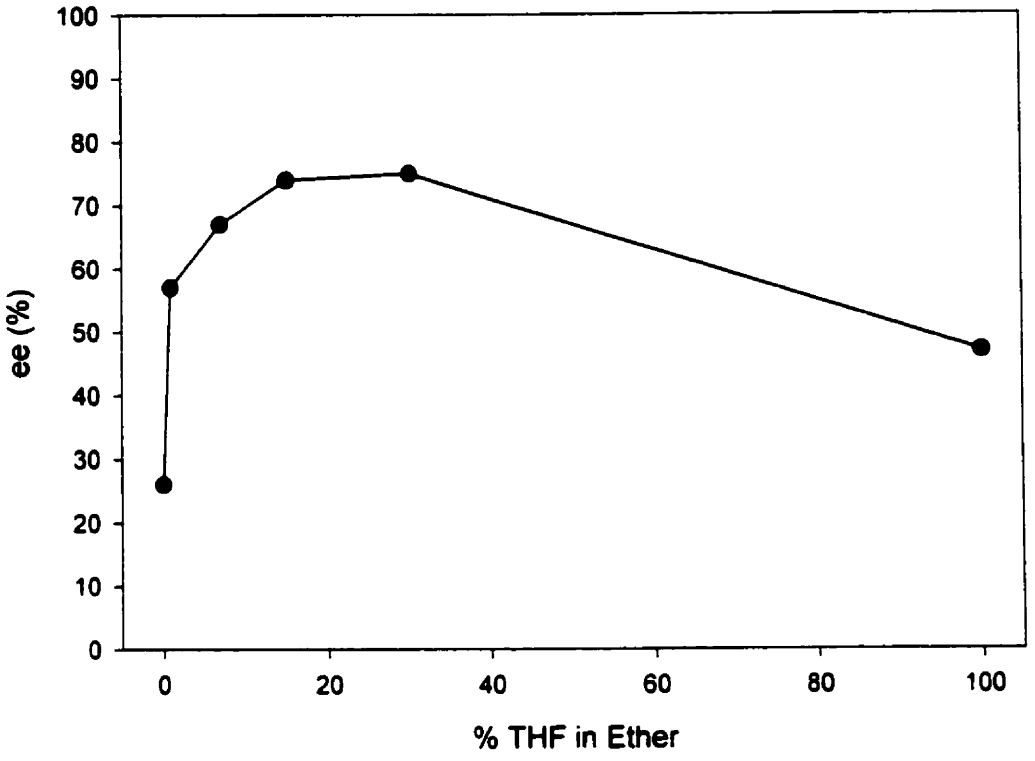


201 **132**

Entry	% THF in Et_2O	Yield of diol **132** (%)	ee[a] (%)
1	0[b]	49	26
2	0.9[c]	28	57
3	7	38	67
4	15	59	74
5	30	91	75
6	100	85	47

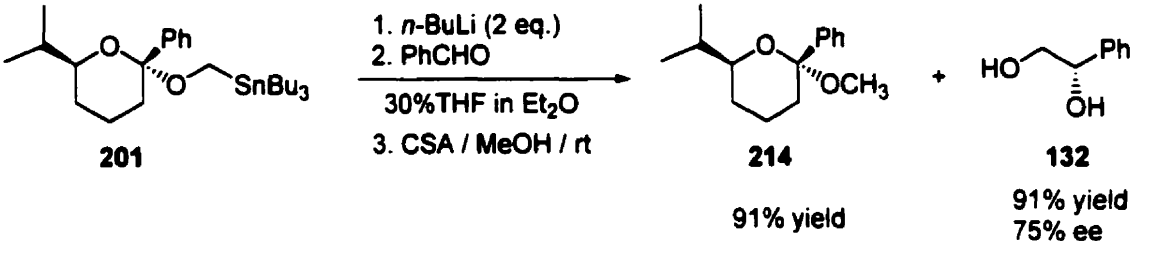
a - ee determined by chiral HPLC analysis of **132**.
b - transmetalation conducted with 2 eq. of *n*-BuLi plus 2 eq. of *t*-BuLi and at -40 °C.
c - transmetalation conducted with 2 eq. of *t*-BuLi and at -40 °C.

Figure 29. Plot of % THF in Et_2O vs. ee (%) of diol **132**.



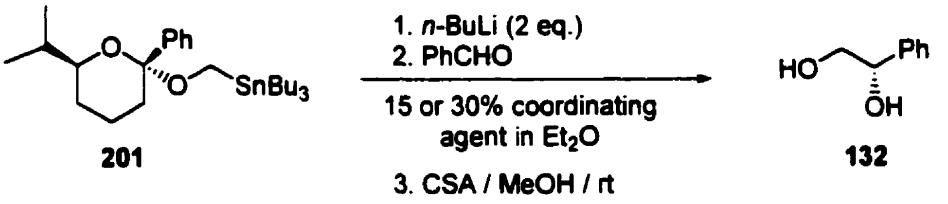
Recovery of the auxiliary as the methyl glycoside **214** occurred in a 91% yield from the reaction involving the use of 30% THF in Et_2O (Scheme 63). Isolation of **214** was possible by chromatography on Et_3N-deactivated silica. Therefore, isolation of the auxiliary as the methyl glycoside is more effective than isolation of the auxiliary in the open chain form **208** as was seen in Scheme 62 where only a 69% yield of **208** was obtained from the addition adduct **211**.

Scheme 63



Coordinating agents other than THF were further studied (Table 23). Nitrogen containing coordinating agents (entries 2 and 3) had the effect of reducing selectivity substantially. Et_3N and TMEDA are too strong as coordinating agents just as was suggested for DME previously, and were perhaps competing with the chiral auxiliary derivative organolithium intermediate ring oxygen for coordination onto the α-alkoxy lithium atom. THP is slightly larger than THF and the use of THP resulted in a slight increase in the level of selectivity (entry 1 vs. entry 4). The slightly higher level of selectivity in entry 4 was reproduced with the use of 30% THP in Et_2O (entry 5). Therefore, a slightly greater steric interaction may occur with the use of THP over THF. A bulkier coordinating agent was then used (2,5-dimethyltetrahydrofuran) (entry 6) with the hope of increasing a steric interaction. Unfortunately, the effect on selectivity could not be studied since transmetalation occurred to only a very small extent even with the use of 8 eq. of *n*-BuLi, and diol **132** was not isolated.

Table 23. Effect of other coordinating agents on selectivity.

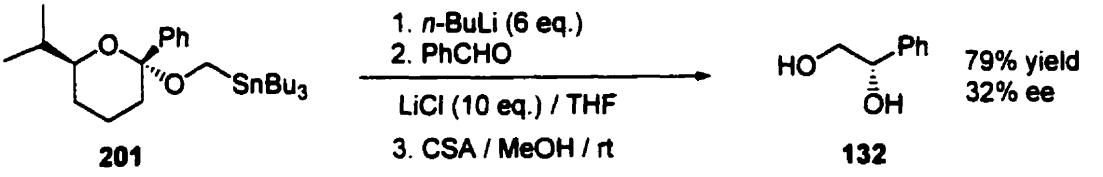


Entry	Coordinating agent	Yield of diol **132** (%)	ee[a] (%)
1	30% THF	91	75
2	15% Et_3N	26	6
3	15% TMEDA	18	44
4	15% THP	19	78
5	30% THP	24	81
6	30% 2,5-dimethyltetrahydrofuran	0	-

a - ee determined by chiral HPLC analysis of **132**.
b - 8 eq. of *n*-BuLi was employed in the transmetalation step. *n*-BuLi addition product to benzaldehyde **177** was detected.

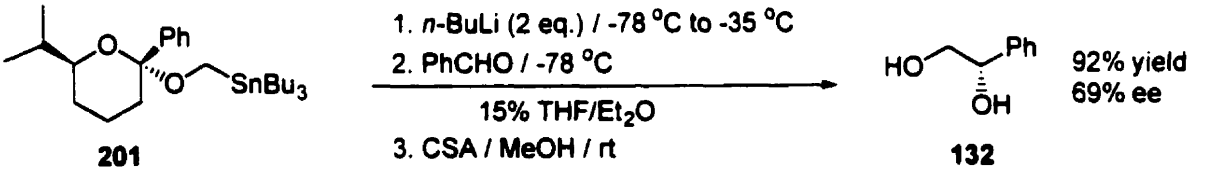
LiCl was used as a coordinating agent to further study the effect of aggregation (Scheme 64). It was seen earlier (Table 21) that a reaction conducted in a diluted solution resulted in the loss of stereoselectivity possibly due to lower aggregation states. It was believed that LiCl might promote higher aggregation states to occur and possibly increase stereoselectivity. However, this was not the case as the diol **132** was isolated in only 32% ee. It was speculated that the aggregation states created with the use of LiCl might have a negative effect on stereoselectivity.

Scheme 64



Furthermore the effect of temperature on selectivity in the transmetalation step was studied (Scheme 65). Conducting the transmetalation from -78 °C to -35 °C resulted in only a small loss of selectivity (69% ee from 74% ee), when the reactions were conducted in 15% THF/Et_2O. Therefore, the structure of the organolithium species responsible for inducing the high level of selectivity stays mostly intact at a higher temperature.

Scheme 65

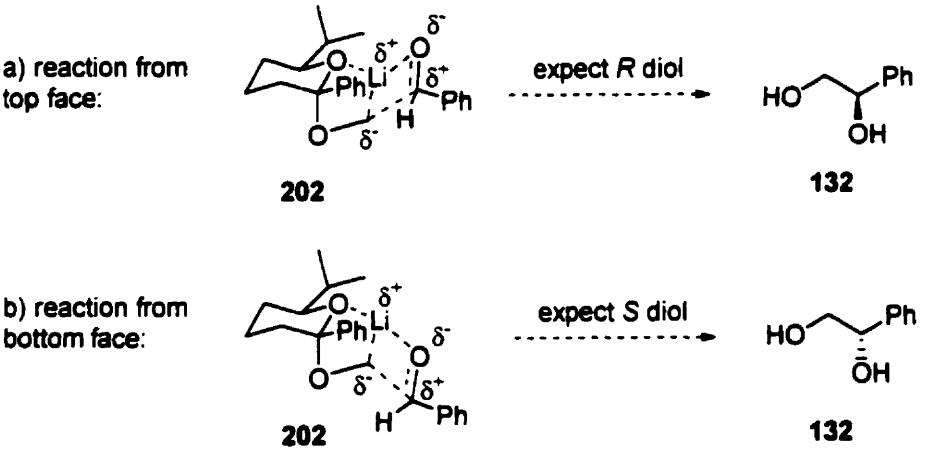


6.2.2.6 Interpretation of the Direction of Selectivity

The transition state model proposed in Chapter 2 for a *cis*-fused 6,6-bicyclic system predicts the formation of the *S* stereocenter in the addition product. The results obtained in Chapter 2 with only one exception consisted of isolating addition products with the *S* stereocenter formed preferentially. Therefore, most of the results agreed with the transition state model where the aldehyde reacts from the top face of the *cis* fused 6,6-bicyclic system and with the R group of the aldehyde pointing away from the anomeric equatorial R group.

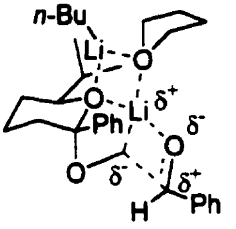
For the lithiated auxiliary derivative **202**, it was originally believed as in Chapter 2 that attack of the aldehyde would occur from the top face the *cis*-fused 5,6-bicyclic system (Figure 30a) since the top convex face was believed to be less sterically hindered. However, the transition state model in Figure 30a predicts the formation of the diol **132** with *R* stereochemistry, opposite from the results achieved in all examples in this chapter. Therefore, attack of the aldehyde may occur from the bottom face of the *cis*-fused 5,6-bicyclic system (Figure 30b) to form the *S* configuration in the diol **132**.

Figure 30. Transition state models (a, b) for lithiated auxiliary derivative **202** and benzaldehyde.



The equatorial isopropyl and phenyl groups may block the top face of the *cis*-fused 5,6-bicyclic system intermediate towards attack. Furthermore, *n*-BuLi and other coordinating agents have been shown to increase the level of selectivity and therefore, may coordinate to the top face of the *cis*-fused 5,6-bicyclic system intermediate to enhance the steric hindrance created by the isopropyl and phenyl groups (Figure 31).

Figure 31. Coordination of *n*-BuLi and THF to **202** in the transition state with benzaldehyde.



6.2.3 Summary and Conclusions

A tetrahydropyran chiral auxiliary without a 3-methoxy substituent was able to induce the stereoselective addition of α-alkoxymethylcarbanions to aldehydes in up to 81% de. This suggests that an intramolecular coordination mode of the α-alkoxymethylcarbanion lithium atom to the ring oxygen of the auxiliary is a possible coordination mode for achieving diastereoselectivity in tetrahydropyran chiral auxiliary systems. A bottom face attack of the aldehyde onto the *cis*-fused 5,6-bicyclic system intermediate was believed to occur since the *S* configuration was formed preferentially in all examples for the diol **132**. Coordinating agents have also been implicated to enhance the steric hindrance created by the isopropyl and phenyl substituents of the auxiliary.

Future work can be aimed toward designing an auxiliary that would further prevent reactions occurring from the top face. The simplest modification would be to study other groups at the 2-position of the tetrahydropyran ring as was studied in Chapter 2 for glucose-derived chiral auxiliaries. Different effects may be observed this time since a totally different transition state structure may be occurring. Also different groups at the 5-position can be studied if one starts out with different mono-substituted chiral epoxides in the synthetic route employed for **201**. The effect of introducing other groups onto the top face of the auxiliary at other positions may also be studied;

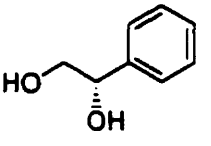
however the synthesis of such auxiliaries may be more difficult. Future work may also be extended to include stereoselective additions of α-aminomethylcarbanions.

6.3 Experimental

6.3.1 General

The general procedures described in Section 2.3.1, Section 3.3.1 and Section 4.3.1 are applicable here with the following additions. 1-Bromo-3,3-dimethoxypropane was prepared according to the procedure of Lee and Porter,[4] except that a 0.35 M solution of HBr was used instead of a 0.81 M solution. (*R*)-Isopropyloxirane (**204**) was also prepared according to a literature procedure.[1] $BF_3 \bullet (OEt)_2$ was distilled from CaH_2 under reduced pressure (aspirator) immediately before use.

6.3.2 (S)-1-Phenyl-1,2-ethanediol 132



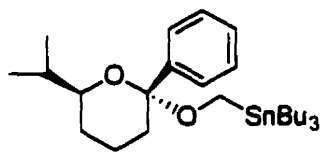
Characterization data for this known compound[5] was presented in Section 2.3.45. This section describes 2 procedures, where **132** was isolated. The first procedure (procedure 1), describes a representative transmetalation/trapping procedure with benzaldehyde (without purification of addition adduct **211**), followed by the recovery of the auxiliary **208** and diol **132**. The second procedure (procedure 2) is identical to procedure 1, except the auxiliary is isolated as the methyl glycoside **214**.

Procedure 1: To a cooled solution (-78 °C) of **201** (108 mg, 0.206 mmol) in THF (4 mL) was added a solution of 1.57 M *n*-BuLi in hexane (0.27 mL, 0.424 mmol) dropwise and the resulting solution was stirred for 1 h. Benzaldehyde (63 μL, 0.620 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to obtain 172 mg of crude material. The crude material containing the addition adduct **211** was then dissolved in MeOH (4 mL) and CSA (30 mg) was added. The mixture was stirred overnight at rt and the reaction was quenched with Et_3N (1 mL). The solvent was then removed *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: hexane to 10% to 25% to 50% Et_2O/hexane to neat Et_2O to 10% MeOH/Et_2O) to isolate 25.0 mg (55% yield based on **201**) of auxiliary **208** (eluting in 50% Et_2O/hexane) and 24.2 mg (85% yield based on **201**) of diol **132** (eluting from neat Et_2O to 10% MeOH/Et_2O). The diol **132** was determined to be formed in 47% ee (determined by chiral HPLC (elution: 5% ^{i}PrOH/hexane, 1.0 mL/min), on a Waters 600E instrument using a Waters 486 UV-visible detector at 254 nm, a Waters recording integrator, and a 4.6 mm x 150 mm Chiralcel OD column), with the *S* configuration present in the major isomer. Order of elution was determined using commercially available (+/-)-**132** (Aldrich # P2.405-5) and (*R*)-**132** (Aldrich # 30,216-3). Retention times of **132**: 19.80 min (*R*), 21.33 min (*S*). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25-7.45 (m, 5H, Ar-H), 4.79 (dd, 1H, J = 3.6, 8.0 Hz, Bn-H), 3.55-3.80 (m, 2H, C$\underline{H_2}$OH), 2.85 (br s, 2H, OH).

Procedure 2: To a cooled solution (-78 °C) of **201** (110 mg, 0.210 mmol) in THF (1.42 mL) and Et_2O (3.32 mL) (i.e. 30% THF in Et_2O) was added a solution of 1.51 M *n*-BuLi in hexane (0.28 mL, 0.420 mmol) dropwise and the resulting solution was stirred for 1 h. Benzaldehyde (64 μL,

0.630 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material containing the addition adduct **211** was then dissolved in MeOH (4 mL) and CSA (30 mg) was added. The mixture was stirred overnight at rt and the reaction was quenched with Et_3N (1 mL). The solvent was then removed *in vacuo*. Compound **214** is sensitive to acid, therefore purification of the crude material occurred by silica gel chromatography with deactivated silica gel (deactivated with 1% Et_3N/hexane), employing gradient elution (all eluent containing 1% Et_3N): hexane to 1% to 2% CH_2Cl_2/hexane to isolate 44.9 mg (91% yield) of recovered methyl glycoside auxiliary **214**, followed by elution with 10% to 25% to 50% Et_2O/hexane to neat Et_2O to 10% MeOH/Et_2O to isolate 26.4 mg (91% yield) of the diol **132**. The diol **132** was determined to exist in 75% ee. with the *S* configuration present in the major isomer (ee determined as in procedure above).

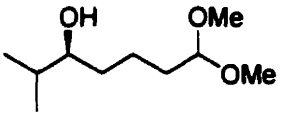
6.3.3 Tributyl([(2R,6S)-6-isopropyl-2-phenyltetrahydro-2H-2-pyranyl]oxymethyl)stannane **201**



To a mixture of **208** (1.29 g, 5.86 mmol) and Bu_3SnCH_2OH (3.77 g, 11.73 mmol) in CH_2Cl_2 (120 mL) and in the presence of crushed 4 Å molecular sieves (23 g) was added camphorsulfonic acid (CSA) (1.09 g, 4.69 mmol). The mixture was stirred for 4 h after which the reaction was quenched with Et_3N (2 mL) then filtered. The filtrate was concentrated *in vacuo* and the crude

material was quickly purified by silica gel chromatography (silica gel first deactivated with 0.1% Et_3N/hexane)(gradient elution: hexane to 1% CH_2Cl_2/hexane (all eluent contained 0.1% Et_3N)) to afford 2.03 g of the unreported compound **201** (66% yield) as a colorless oil: $[\alpha]_D^{22}$ = + 58.9 (c = 1.06, $CHCl_3$); IR (neat film) 2871, 2853, 1464, 1449, 1255, 1050 (C-O stretch), 1029 (C-O stretch), 1003 (C-O stretch), 864, 767, 753, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.49 (m, 2H, Ar-H), 7.20-7.35 (m, 3H, Ar-H), 3.38-3.47 (m, 1H, OC<u>H</u>(^{i}Pr)), 3.42 (d, 1H, J = 10.1 Hz, $^2J_{Sn-H}$ = 29.0 Hz, OC<u>H</u>HSnBu_3), 2.99 (d, 1H, J = 10.2 Hz, $^2J_{Sn-H}$ = 28.6 Hz, OCH<u>H</u>SnBu_3), 1.86-2.03 (m, 2H, CCH_2C), 1.79 (oct, 1H, J = 6.7 Hz, C<u>H</u>(CH_3)), 1.19-1.67 (m, 16H, 2 CCH_2C + Sn(CH_2(C<u>H</u>$_2$)$_2CH_3$)$_3$), 1.05 (d, 3H, J = 6.8 Hz, CH(C<u>H</u>$_3$)(CH_3)), 1.00 (d, 3H, J = 6.8 Hz, CH(CH_3)(C<u>H</u>$_3$)), 0.70-0.98 (m, 15H, Sn(C<u>H</u>$_2$(CH_2)$_2$C<u>H</u>$_3$)$_3$); ^1H NMR (C_6D_6) δ 7.68-7.78 (m, 2H, Ar-H), 7.24-7.35 (m, 2H, Ar-H), 7.05-7.20 (m ,1H, Ar-H), 3.69 (d, 1H, J = 10.3 Hz, $^2J_{Sn-H}$ = 28.3 Hz, OC<u>H</u>HSnBu_3), 3.58 (br dd, 1H, J = 6.1, 9.9 Hz, OC<u>H</u>(^{i}Pr)), 3.31 (d, 1H, J = 10.3 Hz, $^2J_{Sn-H}$ = 28.6 Hz, OCH<u>H</u>SnBu_3) 1.92-2.19 (m, 2H, CCH_2C), 1.83 (oct, 1H, J = 6.6 Hz, C<u>H</u>(CH_3)$_2$), 1.22-1.71 (m, 16H, 2 CCH_2C + Sn(CH_2(C<u>H</u>$_2$)$_2CH_3$)$_3$), 1.17 (d, 3H, J = 6.7 Hz, CH(C<u>H</u>$_3$)(CH_3)), 0.78-1.09 (m, 15H, Sn(C<u>H</u>$_2$(CH_2)$_2$C<u>H</u>$_3$)$_3$), 1.05 (d, 3H, J = 6.8 Hz, CH(CH_3)(C<u>H</u>$_3$)); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 144.0 (Ar-C), 127.8 (Ar-C), 127.1 (Ar-C), 126.2 (Ar-C), 100.5 (^3J = 45 Hz, anomeric-C), 74.8 (O<u>C</u>H(^{i}Pr), 49.6 (^1J = 371, 388 Hz, O<u>C</u>H_2SnBu_3), 37.7 (C<u>C</u>H_2C), 33.3 (C<u>C</u>H_2C), 29.3 (^2J = 21 Hz, Sn(CH_2<u>C</u>$H_2CH_2CH_3$)$_3$), 27.4 (^3J = 52 Hz, Sn(CH_2)$_2$<u>C</u>H_2CH_3)$_3$, 27.2 (C<u>C</u>H_2C), 19.8 (<u>C</u>H(CH_3)$_2$), 18.8 (CH(<u>C</u>H_3)(CH_3)), 18.4 (CH(CH_3)(<u>C</u>H_3)), 13.7 (Sn(CH_2)$_3$<u>C</u>H_3)$_3$, 8.9 (^1J = 309, 323 Hz, Sn(<u>C</u>H_2(CH_2)$_2CH_3$)$_3$); MS (FAB) *m/z* 105 (23), 145 (22), 203 (M^+ - $OCH_2Sn Bu_3$, 100), 467 (M^+ - C_4H_9, 2); Anal. Calcd for $C_{27}H_{48}O_2Sn$: C, 61.97; H, 9.25. Found C, 61.78; H, 9.13.

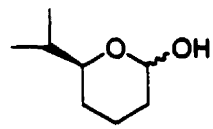
6.3.4 (S)-7,7-Dimethoxy-2-methylheptan-3-ol ***205***



This unreported compound was prepared by a procedure modified from that described by Johannsen.[6] Mg turnings (2.19 g, 90.1 mmol) together with 2 small crystals of I_2 were heated for 20 min while stirring until the purple I_2 vapors had disappeared. The mixture was then allowed to cool to rt after which THF was added (20 mL) and 1,2-dibromoethane (0.52 mL, 6.03 mmol). After initiation had taken place 1-bromo-3,3-dimethoxypropane (11 g, 6.01 mmol) in THF (80 mL) was added dropwise. The mixture was then cooled to an internal temperature of -71 °C and CuI (1.14 g, 5.99 mmol) was added and stirred for 15 min. (*R*)-Isopropyloxirane (**204**) (4.31 g, 50.0 mmol) was then added and the mixture was allowed to slowly reach rt and was stirred overnight. The reaction was then cooled (0 °C) and slowly quenched with an aqueous 1.5% solution of NH_3 in saturated NH_4Cl (pH 8 buffer) (50 mL) and stirred until all solid material had dissolved and bubbling had stopped. The layers were then separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic extracts were then dried over anhydrous Na_2SO_4 and filtered. The filtrate was then concentrated *in vacuo* (bath temperature: 30 °C) and the crude material was purified by silica gel chromatography (gradient elution: hexane to 15% to 30% to 50% Et_2O in hexane) to afford 8.12 g of **205** (85% yield (based on **204**)) as a colorless oil: GC retention time: 10.22 min; $[\alpha]_D^{22}$ = - 19.2 (c = 0.60, $CHCl_3$); IR (neat film) 3436 (O-H stretch), 2832, 1463, 1386, 1367, 1127 (C-O stretch), 1068 (C-O stretch), 982 (C-O stretch), 947 (C-O stretch), 839, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.38 (t, 1H, J = 5.6 Hz, C<u>H</u>$(OCH_3)_2$), 3.24-3.42 (m, 1H, C<u>H</u>(OH)), 3.33 (s, 3H,

OCH_3), 3.32 (s, 3H, OCH_3), 1.30-1.75 (m, 7H, 3 CH_2 + C<u>H</u>CH_3), 0.92 (d, 3H, J = 6.9 Hz, CH(C<u>H</u>$_3$)(CH_3)), 0.91 (d, 3H, J = 6.7 Hz, CH(CH_3)(C<u>H</u>$_3$)); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 104.1 (<u>C</u>H(OCH_3)$_2$), 75.8 (<u>C</u>H(OH), 52.2 (OCH_3), 52.1 (OCH_3), 33.4 (CH_2), 33.2 (CH_2), 32.1 (CH_2), 20.8 (CH), 18.5 (CH_3), 17.0 (CH_3); MS (EI) *m/z* 75 (100), 159 (M^+ - OCH_3, 2), 189 (M^+ - 1, 0.1), 190 (M^+, 0.02). Anal. Calcd for $C_{10}H_{22}O_3$: C, 63.12; H, 11.65. Found: C, 62.88; H, 11.38.

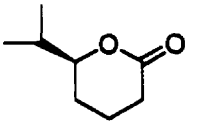
6.3.5 (S)-6-isopropyl-tetrahydro-pyran-2-ol ***206***



This compound has been reported in racemic form[7] and **206** was prepared as follows: A mixture of **205** (7.93 g, 41.7 mmol) and *p*-toluenesulfonic acid (793 mg, 4.17 mmol) in H_2O/acetone (1:1) (200 mL) was stirred at rt for 1 h then refluxed for 1 h. A saturated solution of $NaHCO_3$ was then added until the mixture was slightly basic by pH paper. The mixture was then extracted with Et_2O (3 x 300 mL) followed by drying the combined organic extracts over anhydrous Na_2SO_4. The solution was then filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography (gradient elution: hexane to 10% to 20% to 30% Et_2O/hexane) to afford 4.83 g (69% yield) of **206** as a colorless oil and as an approximate 2:1 ratio of β:α anomers: GC retention time: 7.74 min (both isomers). Mutarotation was observed for **9**, so that 5 min after a solution of **9** (c = 1.06, $CHCl_3$) was made the following rotation was observed: $[\alpha]_D^{22}$ = +52.4, which increased 2 min later to $[\alpha]_D^{22}$ = +59.9. The rotation increased further over time and a steady reading ($[\alpha]_D^{22}$ = +89.9) was obtained after 80 min from the time the solution was made.; ^{1}H NMR

(200 MHz, $CDCl_3$) δ 5.27-5.38* (br m, 1H, anomeric-H), 4.61-4.76 (m, 1H, anomeric-H), 3.66* (ddd, 1H, J = 2.0, 6.3, 11.2 Hz, OC<u>H</u>('Pr)) 3.13 (ddd, 1H, J = 1.9, 6.4, 11.1 Hz, OC<u>H</u>('Pr)), 3.00 (d, 1H, J = 6.2 Hz, OH), 2.43* (dd, 1H, J = 1.7, 3.0 Hz, OH), 1.05-1.97 (m, 7H, 3 CH_2 + C<u>H</u>$(CH_3)_2$), 0.96 (d, 3H, J = 6.8 Hz, CH(C<u>H</u>$_3$)(CH_3)), 0.92* (d, 3H, J = 6.7 Hz, CH(C<u>H</u>$_3$)(CH_3)), 0.91 (d, 3H, J = 6.8 Hz, CH(CH_3)(C<u>H</u>$_3$)), 0.88* (d, 3H, J = 6.8 Hz, CH(CH_3)(C<u>H</u>$_3$)); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 96.5 (anomeric-C), 91.6* (anomeric-C), 81.4 (OC<u>H</u>('Pr)), 73.3* (OC<u>H</u>('Pr)), 32.6 (CH_2), 32.4* (CH_2), 29.8 (CH_2), 27.1* (CH_2), 26.5 (CH_2), 22.0 (<u>C</u>H('Pr)), 18.6 (CH(<u>C</u>H$_3$)(CH_3)), 18.4* (CH(<u>C</u>H$_3$)(CH_3)), 18.1* (CH(CH_3)(<u>C</u>H$_3$)), 17.8 (CH(CH_3)(<u>C</u>H$_3$)); MS (EI) *m/z* 55 (100), 101 (M^+ - 'Pr, 69), 126 (M^+ - H_2O, 12), 143 (M^+ - 1, 0.4), 144 (M^+, 0.2).

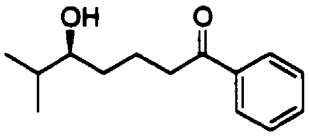
*6.3.6 (S)-6-isopropyl-tetrahydro-pyran-2-one **207***



This compound has been reported in racemic form[6] and **207** was prepared by a procedure modified from that described by Corey and Suggs.[2] A mixture of lactol **206** (4.83 g, 33.5 mmol) and PCC (14.8 g, 67.0 mmol) in CH_2Cl_2 (330 mL) and in the presence of crushed 4 Å molecular sieves (33 g) was refluxed for 2.5 h. The reaction was then diluted with anhydrous Et_2O (1 L) and filtered through Florisil. All solid material that was filtered, along with the Florisil that was employed, was extracted with Et_2O (4 x 300 mL) and the combined organic extracts were filtered once again through Florisil. The filtrate was then concentrated *in vacuo* and the crude material was purified by silica gel chromatography (gradient elution: 10% to 25% to 50% to 75% Et_2O/hexane) to afford 3.77

g (79% yield) of **207** as a colorless oil: GC retention time: 9.49 min; $[\alpha]_D^{22}$ = + 4.0 (c = 1.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.06 (ddd, 1H, J = 2.9, 5.7, 11.3 Hz, (OC<u>H</u>(^{i}Pr)), 2.51-2.68 (m, 1H, C<u>H</u>HC=O), 2.35-2.50 (m, 1H, CH<u>H</u>C=O), 1.73-2.00 (m, 4H, CH_2 + C<u>H</u>H + C<u>H</u>$(CH_3)_2$), 1.45-1.51 (m, 1H, CH<u>H</u>), 1.01 (d, 3H, J = 6.8 Hz, CH(C<u>H</u>$_3$)(CH_3)), 0.97 (d, 3H, J = 6.9 Hz, CH(CH_3)(C<u>H</u>$_3$)); ^{13}C NMR δ 172.0 (C=O), 85.1 (OC<u>H</u>(^{i}Pr)), 33.3 (CH_2), 32.5 (CH_2), 29.3 (CH_2), 24.4 (<u>C</u>H$(CH_3)_2$), 17.7 (CH(<u>C</u>H$_3$)(CH_3), 17.5 (CH(CH_3)(<u>C</u>H$_3$); MS (EI) *m/z* 99 (M^+ - ^{i}Pr, 100), 142 (M^+, 5), 143 (M^+ + 1, 0.4).

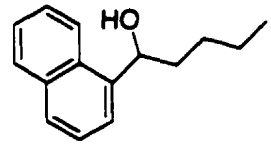
6.3.7 (S)-5-Hydroxy-6-methyl-1-phenylheptan-1-one ***208***



This compound has been reported in racemic form[8] and **208** was prepared as follows: To a cooled (-78 °C) solution of lactone **207** (3.77 g, 26.5 mmol) in THF (265 mL) was added a 0.64 M solution of PhLi in Et_2O (43.5 mL, 27.8 mmol). The mixture was stirred for 30 min after which the reaction was quenched with a saturated aqueous solution of NH_4Cl (30 mL). The mixture was then allowed to reach rt and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. The solution was then filtered and the filtrate was concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (silica gel first deactivated with 1% Et_3N/hexane)(gradient elution: 5% to 20% to 40% to 50% Et_2O/hexane (all eluent contained 1% Et_3N)) to afford 5.13 g of **208** (88% yield) as a colorless oil: $[\alpha]_D^{22}$ = - 8.27 (c = 1.21, $CHCl_3$); IR (neat film) 3436 (O-H stretch), 1682

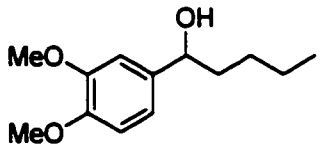
(C=O stretch), 1449, 691 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.90-8.03 (m, 2H, Ar-H), 7.30-7.66 (m, 3H, Ar-H), 3.30-3.46 (br m, 1H, C<u>H</u>(OH)), 3.03 (t, 2H, J = 7.0 Hz, CH_2C=O), 1.38-2.09 (m, 5H, 2 CH_2 + C<u>H</u>$(CH_3)_2$), 0.92 (d, 6H, J = 6.8 Hz, CH(C<u>H</u>$_3)_2$); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 200.4 (C=O), 136.8 (Ar-C), 132.8 (Ar-C), 128.4 (Ar-C), 127.9 (Ar-C), 76.1 (CHOH), 38.2 (C<u>H</u>$_2$C=O), 33.4 (2 CH_2), 20.5 (<u>C</u>H$(CH_3)_2$), 18.7 (CH(<u>C</u>H$_3$)(CH_3)), 17.1 (CH(CH_3)(<u>C</u>H$_3$)); MS (EI) 82 (100), 105 (90), 133 (71), 202 (M^+ - H_2O, 33), 203 (M^+ - OH, 5).

6.3.8 1-(1-naphthyl)-1-pentanol ***209***



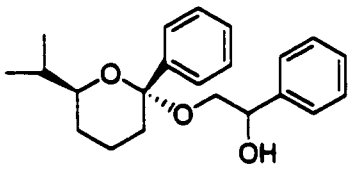
This known compound[9] was obtained in a mixture with **212** as described in Section 6.3.11 and the following data was assigned to **209**: ^1H NMR (200 MHz, $CDCl_3$) δ 8.05-8.20 (m, 1H, Ar-H), 7.71-7.93 (m, 2H, Ar-H), 7.59-7.68 (m, 1H, Ar-H), 7.39-7.57 (m, 3H, Ar-H), 5.46 (dd, 1H, J = 5.3, 7.3 Hz, Bn-H), 1.70-2.08 (m, 2H, C<u>H</u>$_2$CH(OH)), 1.21-1.63 (m, 4H, C<u>H</u>$_2$C<u>H</u>$_2CH_3$), 0.90 (t, 3H, J = 7.1 Hz, CH_3).

6.3.9 1-(3,4-dimethoxyphenyl)-1-pentanol ***210***



This known compound[10] was obtained in a mixture with **213** as described in Section 6.3.12, and the following data was assigned to **210**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.78-6.96 (m, 3H, Ar-H), 4.60 (t, 1H, J = 6.7 Hz, Bn-H), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 1.63-1.89 (m, 2H, $C\underline{H}_2CH(OH)$), 1.14-1.45 (m, 4H, $C\underline{H}_2C\underline{H}_2CH_3$), 0.89 (t, 3H, J = 6.8 Hz, CH_3).

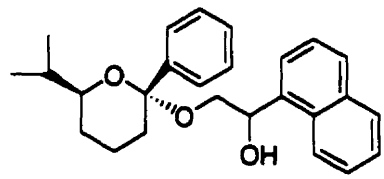
6.3.10 2-[(2S,6S)-6-isopropyl-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-phenyl-1-ethanol ***211***



To a cooled solution (-78 °C) of **201** (112 mg, 0.214 mmol) in THF (4 mL) was added a solution of 1.57 M *n*-BuLi in hexane (0.28 mL, 0.440 mmol) dropwise and the resulting solution was stirred for 1 h. Benzaldehyde (65 μL, 0.639 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to obtain 178 mg of crude material. The addition adduct **211** is sensitive to acid, therefore purification

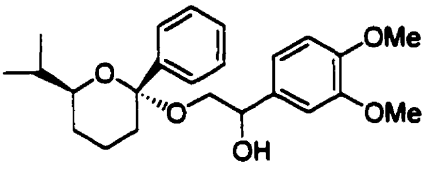
of the crude material occurred by silica gel chromatography with deactivated silica gel (deactivated with 1% Et_3N/hexane), employing gradient elution (all eluent containing 1% Et_3N): (gradient elution: hexane to 5% to 10% to 15% to 20% Et_2O/hexane) to obtain in order of elution: 67 mg (93% yield) of Bu_4Sn, and a 70 mg mixture of unreported addition adduct **211** (58 mg, 80% yield, based on **201**), and 1-phenyl-1-pentanol (12 mg, 17% yield, based on *n*-BuLi), (yields for **211** and 1-phenyl-1-pentanol determined by ^1H NMR integration of benzylic-H) as a colourless oil. Furthermore, **211** was determined to be formed in 46% de (de determined by ^1H NMR integration of benzylic-H). The following data was assigned to **211**: GC retention time: 13.45 min; IR (neat film) 3436 (O-H stretch), 2873, 1449, 1249, 1027 (C-O stretch), 1012 (C-O stretch), 760, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.17-7.56 (m, 5H, Ar-H), 4.83-4.96* (m, 1H, Bn-H), 4.71-4.81 (m, 1H, Bn-H), 3.25-3.54 (m, 2H, OC<u>H</u>(^{i}Pr) + OC<u>H</u><u>H</u>), 2.94-3.20 (m, 1H, OCH<u>H</u>), 2.85 (br d, 1H, J = 2.5 Hz, OH), 2.74 (br s, 1H, OH), 1.13-2.17 (m, 7H, $CCH_2CH_2CH_2C$ + C<u>H</u>$(CH_3)_2$), 0.99 (d, 3H, J = 6.7 Hz, CH(C<u>H</u>$_3$)(CH_3)), 0.98* (d, 3H, J = 6.2 Hz, CH(C<u>H</u>$_3$)(CH_3)), 0.95 (d, 3H, J = 6.8 Hz, CH(CH_3)(C<u>H</u>$_3$)), 0.91* (d, 3H, J = 6.8 Hz, CH(CH_3)(C<u>H</u>$_3$)); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 143.4 (Ar-C), 143.3* (Ar-C), 140.7 (Ar-C), 128.2 (Ar-C), 128.0 (Ar-C), 127.6 (Ar-C), 126.0 (Ar-C), 125.5 (Ar-C), 99.4* (anomeric-C), 99.1 (anomeric-C), 75.2 (OCH), 74.7 (OCH), 73.3 (OCH), 73.1 (OCH), 66.3 (OCH_2), 37.3 (<u>C</u>H$(CH_3)_2$), 33.4 (C<u>C</u>H_2C), 32.8 (C<u>C</u>H_2C), 27.1 (C<u>C</u>H_2C), 19.7 (C<u>C</u>H_2C), 19.2 (C<u>C</u>H_2C), 19.0 (CH(<u>C</u>H_3)(CH_3)), 18.5 (CH(<u>C</u>H_3)(CH_3)), 18.4 (CH(<u>C</u>H_3)(CH_3)), 17.9 (CH(<u>C</u>H_3)(CH_3)); MS (EI) 55 (60), 77 ($C_6H_5^+$, 49), 82 (100), 105 (72), 120 (49), 133 (44), 202 (M^+ - $HOCH_2CH(OH)Ph$, 21), 203 (M^+ - $OCH_2CH(OH)Ph$, 3).

6.3.11 2-[(2S,6S)-6-isopropyl-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-(1-naphthyl)-1-ethanol **212**



To a cooled solution (-78 °C) of **201** (100 mg, 0.191 mmol) in THF (4 mL) was added a solution of 1.50 M *n*-BuLi in hexane (0.25 mL, 0.382 mmol) dropwise and the resulting solution was stirred for 45 minutes. 1-Naphthaldehyde (78 μL, 0.573 mmol) was next added dropwise and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude material occurred by silica gel chromatography (gradient elution: hexane to 5% to 10% to 15% to 20% Et_2O/hexane) to obtain in order of elution: 56 mg (84% yield) of Bu_4Sn, 18 mg of known by-product **209**,[9] and a 37 mg mixture of **209** (35% combined yield, based on *n*-BuLi) and unreported addition adduct **212** (35% yield, based on **201**), (yields for **209** and **212** determined by ^1H NMR). Furthermore, **209** was determined to be formed in 39% de (de determined by Method B outlined in Section 2.3.2). The following data was assigned to **212**: ^1H NMR (200 MHz, C_6D_6) δ 7.00-8.23 (m, 12H, Ar-H), 5.66-5.84* (m, 1H, Bn-H), 5.48-5.65 (m, 1H, Bn-H), 3.08-3.88 (m, 3H, OC<u>H</u>(^{i}Pr) + OCH_2), 2.72-3.05 (br s, 1H, OH), 0.67-2.21 (m, 13H, $CCH_2CH_2CH_2C + CH(CH_3)_2$).

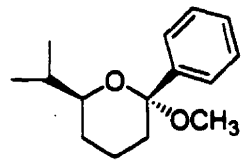
6.3.12 1-(3,4-dimethoxyphenyl)-2-[(2S,6S)-6-isopropyl-2-phenyltetrahydro-2H-2-pyranyl]oxy-1-ethanol ***213***



To a cooled solution (-78 °C) of **201** (100 mg, 0.191 mmol) in THF (4 mL) was added a solution of 1.50 M *n*-BuLi in hexane (0.25 mL, 0.382 mmol) dropwise and the resulting solution was stirred for 45 minutes. 3,4-Dimethoxybenzaldehyde (95 mg, 0.573 mmol) was next added, and the resulting solution was stirred for an additional 30 min, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude material occurred by silica gel chromatography (gradient elution: hexane to 5% to 30% to 40% to 50% to 60% Et_2O/hexane) to obtain in order of elution: 84 mg of recovered 3,4-dimethoxybenzaldehyde, 32 mg of a mixed fraction including: 3,4-dimethoxybenzaldehyde, known by-product **210**,[10] and unreported addition adduct **213** (19% yield, based on **201**), followed by a 2 mg fraction containing pure **210** (17% combined yield, based on *n*-BuLi), (yields for **210** and **213** determined by ^{1}H NMR). Furthermore, **213** was determined to be formed in 41% de (de determined by Method B outlined in Section 2.3.2). The following data was assigned to **213**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.60 (m, 2H, Ar-H), 7.13-7.34 (m, 3H, Ar-H), 6.70-7.00 (m, 3H, Ar-H), 4.85* (dd, 1H, J = 3.6, 8.6 Hz, Bn-H), 4.72 (dd, 1H, J = 3.3, 8.6 Hz, Bn-H), 3.25-3.52 (m, 2H, OC<u>H</u>(^{i}Pr) + OC<u>H</u>H), 2.92-3.11 (m, 1H, OCH<u>H</u>), 2.86 (br s, 1H, OH), 2.71* (br s, 1H, OH), 1.13-2.19 (m, 7H, $CCH_2CH_2CH_2C$ + C<u>H</u>$(CH_3)_2$), 1.01 (d, 3H, J = 6.7 Hz, CH(C<u>H</u>$_3$)(CH_3)),

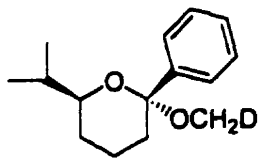
1.00* (d, 3H, J = 6.5 Hz, CH(C<u>H</u>$_3$)(CH$_3$)), 0.98 (d, 3H, J = 6.8 Hz, CH(CH$_3$)(C<u>H</u>$_3$)), 0.97* (d, 3H, J = 6.8 Hz, CH(CH$_3$)(C<u>H</u>$_3$)).

6.3.13 (2S,6S)-6-isopropyl-2-methoxy-2-phenyltetrahydro-2H-pyran ***214***



This unreported compound was formed and isolated as a colorless oil according to the representative procedure given in Section 6.3.2 as the recovered methyl glycoside auxiliary. Compound **214** was also formed as a by-product as described in Table 18 and displayed the following characterization data: $[\alpha]_D^{22}$ = + 62.3 (c = 0.58, $CHCl_3$); IR (neat film) 2872, 2829, 1494, 1256, 1155 (C-O stretch), 1039 (C-O stretch), 1015 (C-O stretch), 866, 762, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 7.45-7.55 (m, 2H, Ar-H), 7.23-7.38 (m, 3H, Ar-H), 3.49 (ddd, 1H, J = 2.1, 6.0, 11.6 Hz, OC<u>H</u>('Pr)), 2.97 (s, 3H, OCH_3), 1.88-2.06 (m, 2H, CC<u>H$_2$</u>C), 1.79 (oct, 1H, J = 6.7 Hz, C<u>H</u>(CH$_3$)$_2$), 1.60-1.75 (m, 2H, CC<u>H$_2$</u>C), 1.21-1.52 (m, 2H, CC<u>H$_2$</u>C), 1.05 (d, 3H, J = 6.7 Hz, CH(C<u>H</u>$_3$)(CH$_3$)), 1.00 (d, 3H, J = 6.8 Hz, CH(CH$_3$)(C<u>H</u>$_3$)); ^{13}C NMR (75.47 MHz) δ 143.7 (Ar-C), 128.0 (Ar-C), 127.4 (Ar-C), 125.9 (Ar-C), 99.4 (anomeric-C), 74.9 (OCH), 48.8 (OCH_3), 37.5 (C<u>C</u>H$_2$C), 33.2 (C<u>C</u>H$_2$C), 27.2 (C<u>C</u>H$_2$C), 19.7 (<u>C</u>H(CH$_3$)$_2$), 18.8 (CH(<u>C</u>H$_3$)(CH$_3$)), 18.2 (CH(CH$_3$)(<u>C</u>H$_3$)); MS (EI) *m/z* 105 (100), 133 (60), 191 (M^+ - CH(CH$_3$)$_2$, 0.1), 202 (M^+ - CH_3OH, 38), 203 (M^+ - CH_3O, 7), 233 (M^+ - 1, 0.03), 234 (M^+, 0.05), 235 (M^+ + 1, 0.07); HRMS (FAB) calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1632.

6.3.14 (2S,6S)-6-isopropyl-2-deuteriomethoxy-2-phenyltetrahydro-2H-pyran ***215***



To a cooled solution (-78 °C) of **201** (110 mg, 0.210 mmol) in THF (4 mL) was added a solution of 1.56 M *n*-BuLi in hexane (0.27 mL, 0.420 mmol) dropwise and the resulting solution was stirred for 40 minutes. MeOD (0.1 mL, 2.46 mmol) was next added dropwise and the resulting solution was slowly warmed to 0 °C, after which an aqueous solution of saturated NH_4Cl (1 mL) was added. The aqueous layer was then separated and extracted with Et_2O (2 x 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude material occurred by silica gel chromatography with deactivated silica gel (deactivated with 1% Et_3N/hexane), employing gradient elution (all eluent containing 1% Et_3N): hexane to 2% CH_2Cl_2/hexane to 10% Et_2O/hexane to isolate 34 mg (69% yield) of unreported compound **215**. Compound **215** was also formed as a by-product in a reaction described in Table 18 and was obtained in a mixture with **214**. The following data obtained for **215**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.40-7.52 (m, 2H, Ar-H), 7.18-7.39 (m, 3H, Ar-H), 3.49 (ddd, 1H, J = 2.1, 6.1, 11.6 Hz, OCH(^{i}Pr)), 2.95 (3 lines, 2H, J = 1.6 Hz, OCH_2D), 1.54-2.10 (m, 5H, 2 CCH_2C + $C\underline{H}(CH_3)_2$), 1.18-1.53 (m, 2H, CCH_2C), 1.05 (d, 3H, J = 6.8 Hz, $CH(C\underline{H}_3)(CH_3)$), 1.00 (d, 3H, J = 7.0 Hz, $CH(CH_3)(C\underline{H}_3)$); MS (EI) *m/z* 77 ($C_6H_5^+$, 30), 105 (100), 112 (25), 235 (M^+, 2).

6.4 References

[1] Koppenhoefer, B.; Schurig, V. *Organic Syntheses*; volume 66; Heathcock, C. H., Ed.; John Wiley & Sons: New York, 1988; pp.160-172.

[2] Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

[3] For more information on this topic refer to: Valters, R. E.; Flitsch, W. *Ring-Chain Tautomerism*; Katritzky, A. R., Ed.; Plenum Press: New York, 1985.

[4] Lee, T. V.; Porter, J. R. *Organic Syntheses*; volume 72; Coffen, D. L., Ed.; John Wiley & Sons: New York, 1994; pp. 189-198.

[5] Cho, B. T.; Chun, Y. S. *J. Org. Chem.* **1998**, 5280.

[6] Johannsen, J. A. *M.Sc. Thesis*, 1994, University of Waterloo, p.195.

[7] Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **1990**, *31*, 3767.

[8] Warnhoff, E. W.; Wong, M. Y. H.; Raman, P. S. *Can. J. Chem.* **1981**, *59*, 688.

[9] Li, N.-S.; Yu, S.; Kabalka, G. W. *J. Organomet. Chem.* **1997**, *531*, 101.

[10] Witiak, D. T.; Kakodkar, S. V.; Brunst, G. E.; Baldwin, J. R.; Rahwan. R. G. *J. Med. Chem.* **1978**, *21*, 1313.

CHAPTER 7

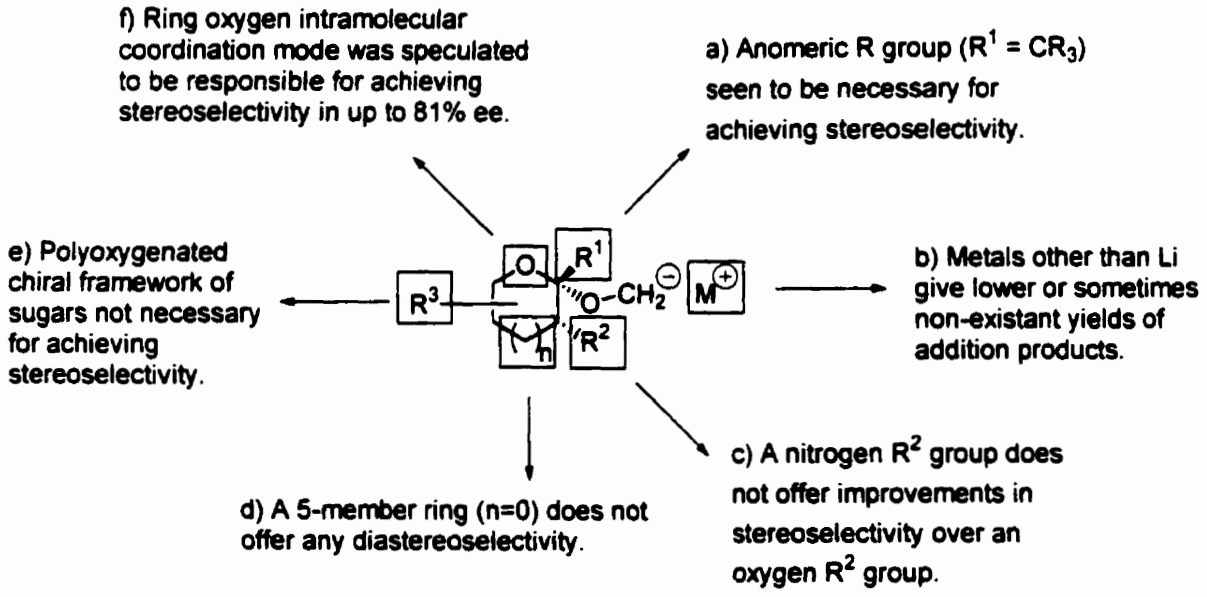
OVERALL SUMMARY

It has been shown for the first time that an α-heteroatom chiral nucleophile can be added to an aldehyde stereoselectively *with* recovery of the chiral auxiliary and enantiomerically enriched product being possible. The asymmetric addition of α-alkoxymethyl carbanions to aldehydes has resulted in the formation of diol products in up to 81% ee (Chapter 6). The best examples in the current literature include the addition of an α-alkoxymethyl carbanion in 28% de[1] and an α-aminomethyl carbanion in 56% de.[2] However, none of the literature examples allow for the recovery of the chiral auxiliary and enantiomerically enriched product.

The achievement in this thesis has been realized through the chiral auxiliary design process that was followed and is summarized in Figure 32 (a-f). The design centered on a sugar-like core structure with substrate attachment occurring to the anomeric carbon of the auxiliary so that product and auxiliary recovery can be possible. The first important finding was the realization that having H replaced by different R groups at the equatorial anomeric position was necessary for achieving diastereoselectivity in up to 59% de (Chapter 2) (Figure 32a). Most aryl R groups and additions to electron rich aldehydes had provided the optimal level of diastereoselectivity. Throughout many examples in this thesis, employing metals other than Li almost always led to lower or non-existent yields of addition products and in most cases not offering any improvements in stereoselectivity (Figure 32b). Ti based reagents were seen to have potential for achieving a high level of diastereoselectivity (Chapter 2); however practical yields could not be obtained. Next the nature of the C-2 group of the pyranose ring system was studied (Chapter 3) (Figure 32c) by employing a glucosamine-derived chiral auxiliary. A carbamate protected nitrogen group did not offer any

improvement over a methyl ether group at the same position (14% de vs. 17% de). Furthermore 5-membered ring auxiliaries did not offer any diastereoselectivity and racemization occurred in the synthesis of the auxiliary derivatives (Chapter 5) (Figure 32d). Auxiliaries that were less sugar-like in structure (Chapter 4 and 6) (Figure 32e) were also able to induce stereoselectivity and indicates that the chiral polyoxygenated framework of sugars is not necessary. Lastly, it was speculated that a ring oxygen intramolecular coordination mode might be responsible for achieving the highest levels of stereoselectivity in this thesis (up to 81% ee) (Chapter 6) (Figure 32f).

Figure 32. Structural features studied and findings obtained from the chiral auxiliary design process.



Future work can possibly be aimed towards the optimization of structural features outlined in Chapter 6 (Section 6.2.3).

References

[1] Ortiz, J.; Guijarro, A.; Yus, M. *An. Quim. Int. Ed.* **1997**, *93*, 44.

[2] Coldham, I.; Holman, S.; Lang-Anderson, M. M. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1481.