Bicyclic Carbohydrate-Based Templates for the Asymmetric Synthesis of α-Amino Acids

By

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BICYCLIC CARBOHYDRATE-BASED TEMPLATES FOR THE ASYMMETRIC SYNTHESIS OF a-AMINO ACIDS

BY

MIKAELA NAHAMA KEYNES

A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

This thesis is dedicated to the memory of my grandparents,

Ethel and Samuel Shinoff.

Abstract

A novel bicyclic carbohydrate-based template **(39)** for the asymmetric synthesis of α-amino acids has been synthesized. This template has been prepared by two short, high yielding sequences. Methylation and allylation of the lithium enolate of the benzyl-protected template occurred with excellent and predictable diastereoselectivity. Preliminary investigation into the hydrolysis of the methylated template produced *L*-alanine in 87-93% enantiomeric excess.

Acknowledgments

I would like to express my sincere gratitude to Dr. P. G. Hultin for his never ending patience, guidance and support during the past two and a half years. Working for someone with such enthusiasm for chemistry has been a pleasure. Thanks are also due to Marion, Manjula, Sean, and Leah for their friendship, suggestions, encouragement and for their telephone answering services throughout this ordeal. A special thanks to Rick, Gregg and Dave for helping me channel my frustrations into fitness, and ensuring that life is not taken too seriously. Also thanks to Curtis for listening and lightening my dark moods with laughter and friendship. The technical assistance of Mr. T. Foniok, Mr. T. Wolowiec, and Dr. K. Marat of the nmr facility, and Mr. I. Ward of the glassblowing shop is greatly appreciated. I would also like to express my gratitude to Dr. A. Chow for supplying me with a computer which greatly facilitated writing this manuscript. The financial support of the University of Manitoba is acknowledged.

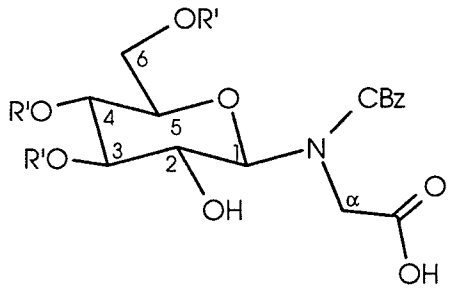
I would like to thank my mother, father and sister for all their love, support and encouragement during each and every endeavor I have undertaken...they are the best family one could ever ask for. Finally I would like to thank my chauffeur, who would drop anything at anytime to accommodate me, thanks dad.

Table of Contents

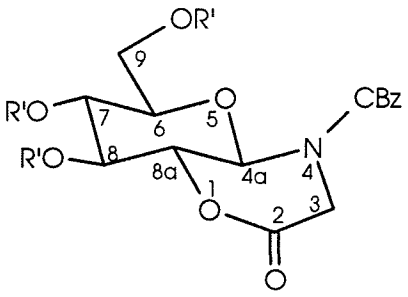
Abbreviations

tlc	thin layer chromatography
EtOH	Ethanol
MHz	megahertz
TMS	Tetramethylsilane
COSY	correlated off-resonance spectroscopy
nOe	nuclear Overhauser enhancement
h	hours
EtOAc	Ethyl acetate
DMSO-d6	Deuterated dimethyl sulfoxide
DMF	Dimethyl formamide
CBz	benzyloxycarbonyl
Bn	benzyl
Ac	acetyl
Ar	aryl
4°	quaternary
Σ	sum of
HMPA	Hexamethyl phosphoramide
LiHMDS	Lithium hexamethyldisilazide
THF	Tetrahydrofuran
TBDMS-OTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate

General structure for acyclic precursors



General structure for the bicyclic template



Introduction

General Introduction

This research has focused on an approach to the asymmetric synthesis of α-amino acids. Amino acids are compounds that have an amino and a carboxyl group within the same molecule, and α-amino acids have these groups α- to each other. These compounds are chiral molecules (except glycine), and occur in both enantiomeric forms, but the naturally occurring enantiomer is generally in the *L*-form. Amino acids are important biomolecules, that are involved in practically every living process. The 20 common naturally occurring α-amino acids are readily available by a wide variety of methods, however novel α-amino acids are generally obtained by chemical synthesis.[1] Since most biological receptors are chiral, they impose certain steric demands of other molecules that interact with them. These molecules must have a particular chirality in order to interact with their chiral targets, and the preferred isomer is generally in the *L*-form.

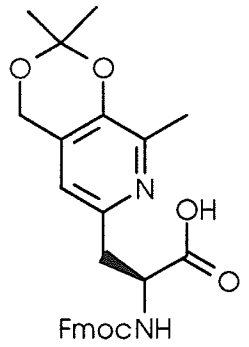
Chiral compounds may be prepared using racemic or asymmetric synthetic routes. Current trends in synthesis favor asymmetric syntheses where one enantiomer or diastereomer is produced preferentially. Asymmetric syntheses often employ chiral auxiliaries to achieve this goal. There are a wide variety of chiral compounds (both synthetic and natural) that may be employed as auxiliaries, but the following discussion of chiral auxiliaries will focus solely on carbohydrates.

Recently drug companies have targeted the area of peptide design, and as a result the demand for novel amino acids has flourished. A beneficial side effect of this demand is that these novel amino acids have led to a better understanding of the structure/ function relationship of proteins. This information has been obtained by

substitution or insertion of novel residues into peptides, and then monitoring changes in peptide folding and activity.

Amino acids are essential to all living forms. They are the basic building blocks of proteins, which are involved in practically every living process. Because proteins participate in signal transduction, enzyme activity, gene regulation, and immune responses,[2,3,4,5,6] it is important to understand their structure-function relationships. This can be achieved by performing site-specific insertions or substitutions of novel amino acids into proteins, followed by monitoring changes in catalysis, conformation/folding, pH, H-bonding and hydrophobic interactions.[2,6]

An example of this type of study has been performed by Imperiali et al.. This group has designed a novel amino acid, POL (**1**) (Figure 1), which can be incorporated into polypeptides. Once incorporated, it is converted into its active form, PAL (**2**), which is analogous, in structure, to the pyridoxyl-5'-phosphate coenzyme (PLP) (**3**). PLP is a coenzyme that can function in transamination, decarboxylation, and racemization reactions. PAL has also demonstrated ability to function as a cofactor for transamination reactions.[7,8]



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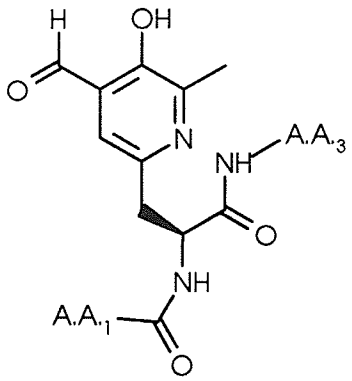

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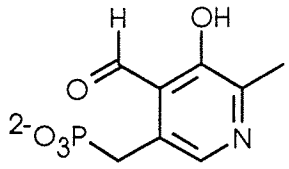
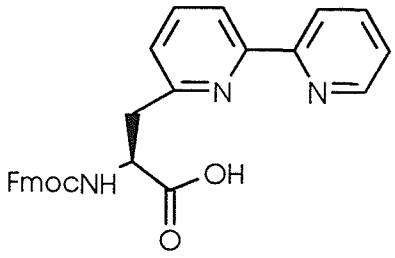


3

Figure 1

The most striking illustration of this activity has been evidenced by the attachment of a PAL-containing-fragment to the enzyme Rnase.[8] Here, Imperiali et al., synthesized a peptide fragment containing **1**, which was then attached to the enzyme. Next they deprotected this residue and oxidized to the phenolic aldehyde shown by structure **2**. This modified Rnase was seen to possess transaminase activity. This was significant since the enzyme was not capable of this activity prior to the attachment of this novel fragment.

Imperiali has also synthesized novel metalloproteins that may be employed as cofactors within the primary structure of enzymes. This may be achieved by using the novel amino acid (**4**) (Figure 2) which is able to coordinate with metal cations.[9,10] These examples illustrate how novel amino acids may be used to tailor proteins to perform specific functions, i.e., protein engineering.



4

Figure 2

Amino acids themselves or as a part of a larger molecule, can be used as inhibitors, which bind to receptors or to specific enzymes, and thus change the activities normally associated with those sites. An example of this is the anti-cancer drug methotrexate shown in Figure 3. This drug contains a glutamic acid residue within its structure. Methotrexate inhibits the enzyme dihydrofolate reductase. This enzyme is responsible for the generation of methylated tetrahydrofolate intermediates needed to sustain tumor cell growth. However methotrexate forms a tight complex with the enzyme so that its (enzyme) activity is impaired resulting in tumor cell death.[11]

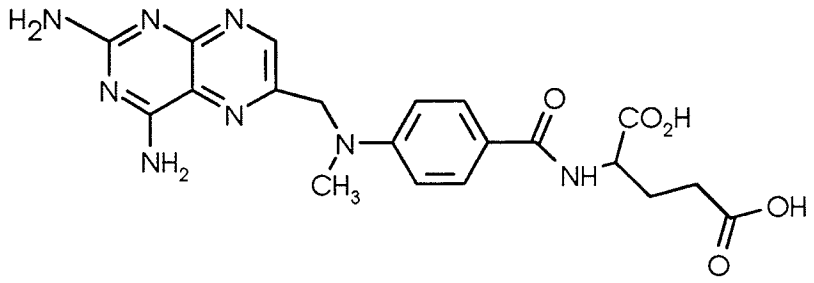
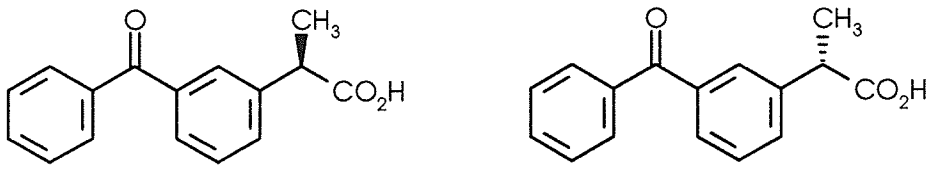


Figure 3

Recently the world wide impetus for syntheses that result in enantiomerically pure products has come in part from the Food and Drug Administration (FDA) which controls drug regulation in the United States. This agency is making it more difficult to obtain drug approval for racemates.[12] Since human enzymes and their active sites are chiral, they will interact differently with each enantiomer of a drug, and this can lead to differential rates of absorption, degradation, and activation. An example of how different enantiomers may be can be seen in (*S*)-(+) and (*R*)-(-) enantiomers of ketoprofen, shown in Figure 4. The (*S*)-(+)-form is an analgesic with anti-inflammatory ability, while the (*R*)-(-)-form is active against bone loss associated with periodontal disease.[12]

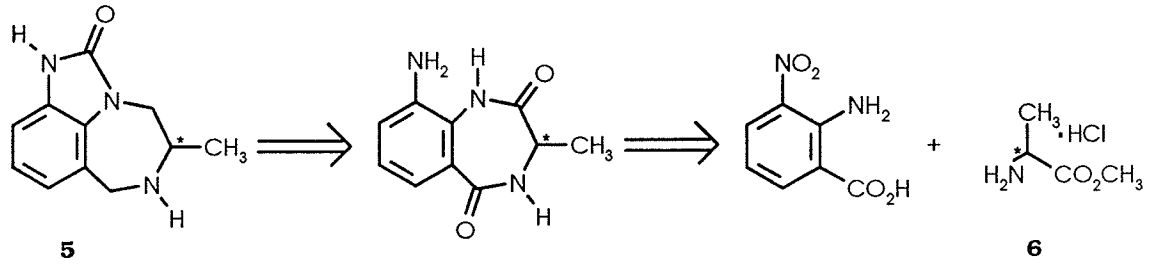


(R)-ketoprofen (S)-ketoprofen

Figure 4

Amino acids are often used as chiral starting materials in chemical synthesis, which undergo modification to give the desired product. Once this has been accomplished, it is often difficult to recognize the original α-amino acid. An example of this is

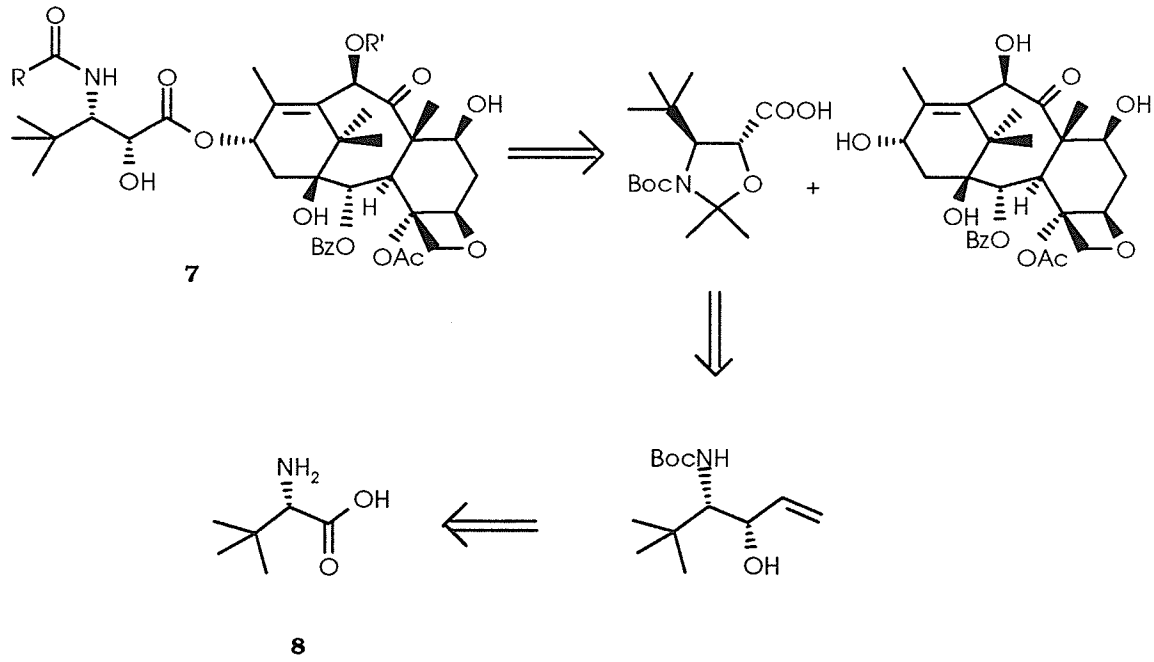
the anti-AIDS drug TIBO (**5**).[13] This drug may be synthesized from alanine methyl ester (**6**), as shown in Scheme 1.



5 **6**

Scheme 1

Other drugs synthesized using amino acid precursors are Paclitaxel (*R*=Ph, R'=Ac) and Docetaxel (*R*=*tert*-BuO, R'=H) (**7**).[14] These are used in the therapeutic treatment of ovarian and breast cancers. In this case the disconnections shown in Scheme 2 leads to a novel α-amino acid, *L*-*tert*-leucine (**8**), necessary for the synthesis of the *t*-butyliso-serine side chain of these two analogs.



7 **8**

Scheme 2

Methods for the Preparation of Amino Acids

Naturally occurring α-amino acids required for some of the above methods may be produced by several methods. These are extraction, fermentation, and chemical synthesis.

Extraction methods involve the digestion of proteins, followed by the selective separation of the desired amino acids based upon their solubility differences. This method is employed for those amino acids that cannot be efficiently obtained by alternative methods, e.g., tyrosine.[15]

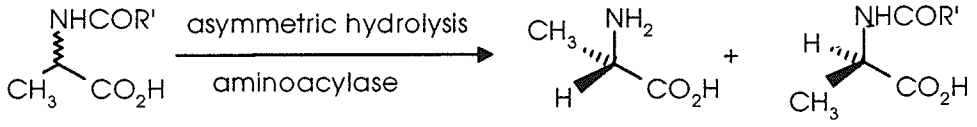
Many microorganisms can produce amino acids by fermentation.[15] This method allows for the production of amino acids from cheap carbon and nitrogen sources. For example, 1 tonne of glucose can be used to make 500 kg *L*-glutamic acid, by using the *Corneybacterium glutamicum* or *Brevibacterium flavum* microorganisms. Fermentation reactions used to generate a specific amino acid, generally produce only that one. As a result, the only purification required is the isolation of that amino acid from the carbon and nitrogen supply, and any salts present in the culture broth.[16]

Chemical synthesis may produce either racemic or enantiomerically enriched amino acids. If the product is a racemate, it is necessary to separate enantiomers to obtain pure products. This limits the maximum yield to 50%, although it is possible to enhance the yield of a particular enantiomer by racemization of the undesired enantiomer, followed by re-isolation of the desired form. Techniques for resolution include preferential crystallization, chromatography, or enzymatic methods.

Chromatography may be used to separate enantiomers, based on differences in their affinities for the column and/or the eluting solvent. Chiral stationary phases for this purpose are obtained from saccharides, amino acids or other chiral polymers.[17] In

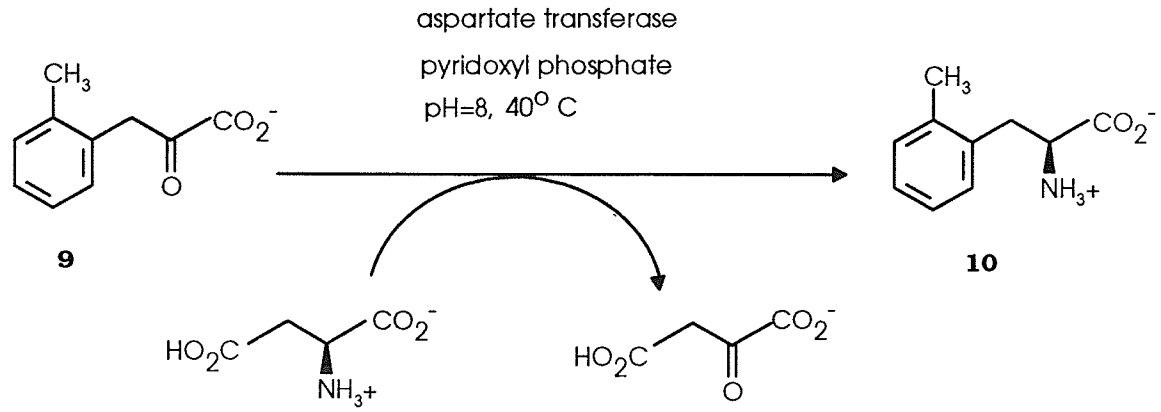
optimal cases chiral columns can provide high yields of both enantiomers of an amino acid in high enantiomeric excess. This method is rarely chosen by basic research chemists wanting to perform small scale resolution, because it is very expensive. The chiral packing can cost as much as $ 8000.00/kg, and the columns may require up to ten times more packing than traditional silica columns.[18]

Enzymes may be used to resolve racemic mixtures of amino acids. This may be achieved by using an enzyme to catalyze either the enantioselective derivatization of the racemate, or the enantioselective hydrolysis of a derivatized amino acid, to obtain the desired isomer.[17] The industrially preferred method of enzymatic resolution of racemic mixtures of amino acids involves asymmetric hydrolysis of acyl derivatives of *D/L*-amino acids using an aminoacylase, as seen in Scheme 3.[15,17]

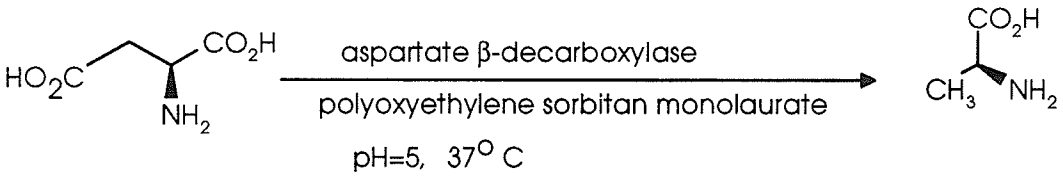


Scheme 3

Another form of chemical synthesis involves the use of enzymes, isolated from microorganisms or other enzyme sources, to produce amino acids. An example of this is seen in the production of the novel α-amino acid (**10**) in Scheme 4. Here the enzyme, aspartate transferase—when bound to the coenzyme, PLP—catalyzes the reversible transfer of the α-amino group of aspartic acid to an α-keto acid (**9**), resulting in the production of **10**.[19,20] Another example of an enzyme frequently used to make α-amino acids is *L*-aspartate β-decarboxylase. This enzyme can be used to convert *L*-aspartic acid to *L*-alanine, Scheme 5.[21] This method is excellent provided that suitable precursors to the desired amino acids are cheap and readily available.[17]



Scheme 4



Scheme 5

An alternative to the problems of racemic syntheses is an asymmetric route where one enantiomer is produced in considerable excess. This is the area of amino acid synthesis that is still growing. According to Schöllkopf,[22] there are several prerequisites that must be fulfilled in order to justify an asymmetric synthesis, and they are:

- It should be easily performed and give good chemical yields.
- It should proceed with d.e. or e.e., close to 100%.
- In a stoichiometric asymmetric synthesis the chiral auxiliary must be recoverable for recyclization.
- The chiral auxiliary should be readily available, if possible from nature's chiral pool and in both enantiomers.
- The configuration of the newly created asymmetric center should be predictable.

Recent interest in α-amino acid synthesis has focused on the preparation of novel amino acid residues. Currently there exist effective routes to the preparation of the naturally occurring α-amino acids, but the development of routes to novel amino acids is an area worth exploring. Novel amino acids cannot be generated via extraction or fermentation, but can be prepared by chemical synthesis. This is the area upon which my research has been based.

There are four possible disconnections of the basic structure of α-amino acids, as shown in Figure 5.[i] These operations represent the numerous routes to α-amino acid synthesis, and these reactions are only limited by the imagination of the chemist. A further limitation to chemical synthesis lies in the potentially high cost of the starting materials and reagents.

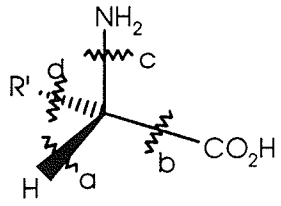
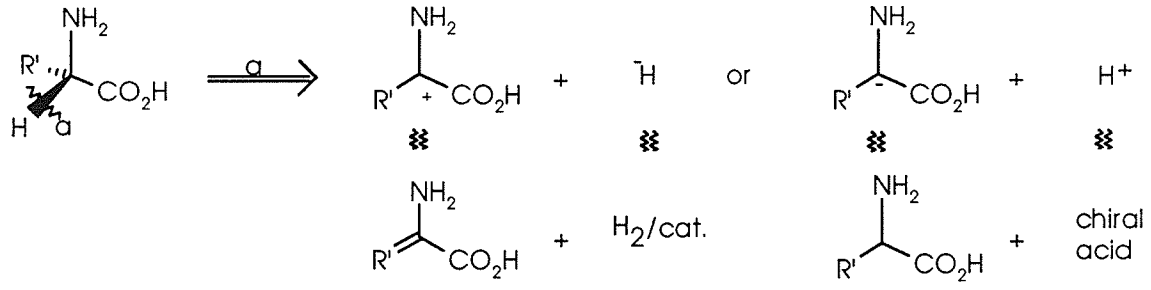


Figure 5

The first disconnection shown by pathway a is expanded upon in Scheme 6. This disconnection results in two sets of synthons leading to α-amino acids. The first set is an



Scheme 6

α,β-unsaturated α-amino acid which upon reduction provides α-amino acids and the second set involves the chiral protonation of an α-amino acid enolate equivalent.

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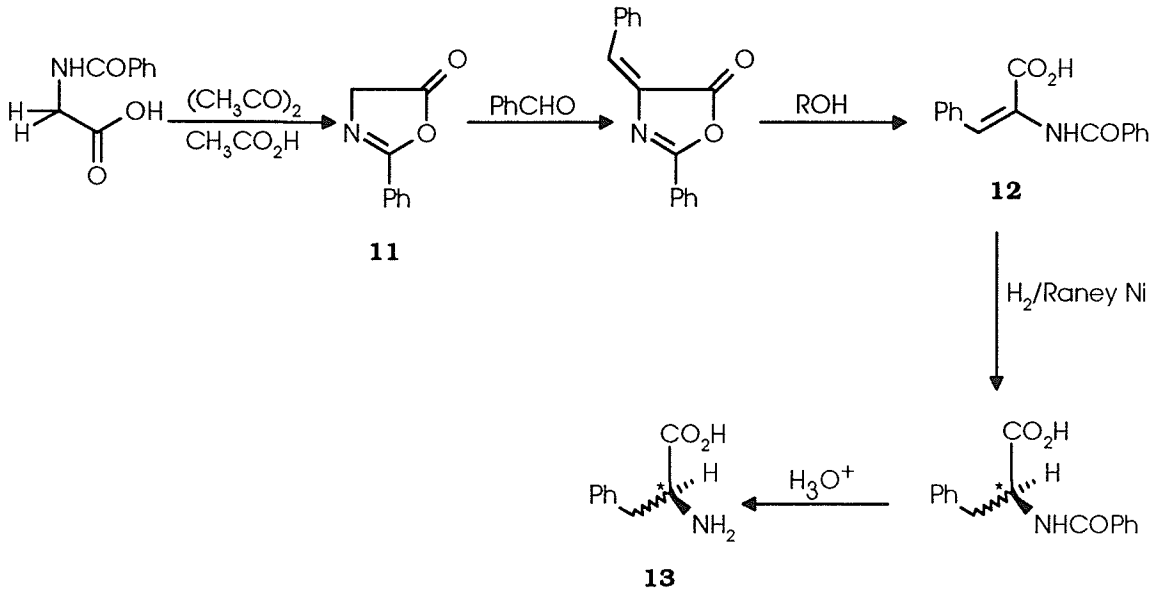
[i] The retrosynthetic pathways shown illustrate only one possible set of reagents corresponding to the indicated synthons.

Both Jones[23] and Jakubke et al.[24] refer to Erlenmeyer as one of the first to use catalytic hydrogenation of an α,β-unsaturated α-amino acid (**12**). He prepared **12**, starting with *N*-benzoyl glycine, via the oxazolone (**11**), as seen in Scheme 7. Catalytic hydrogenation of **12** resulted in a racemic mixture of phenylalanine (**13**).



R - and *S*- phenylalanine

Scheme 7

An asymmetric alternative to Erlenmeyer's racemic synthesis has been developed in Lubell's laboratory and is depicted in Scheme 8.[25] Using Wadsworth-Horner-Emmons chemistry, they generated an enamido diester (**14**) from the condensation of an aldehyde with phosphonyl glycine. Catalytic hydrogenation of **14**, with (*R*)-BINAP-Ru(II)$(OAc)_2$ (a chiral catalyst, shown in Figure 6), resulted in the production of

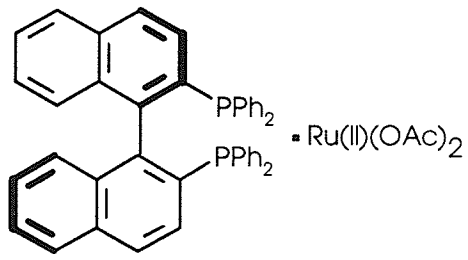
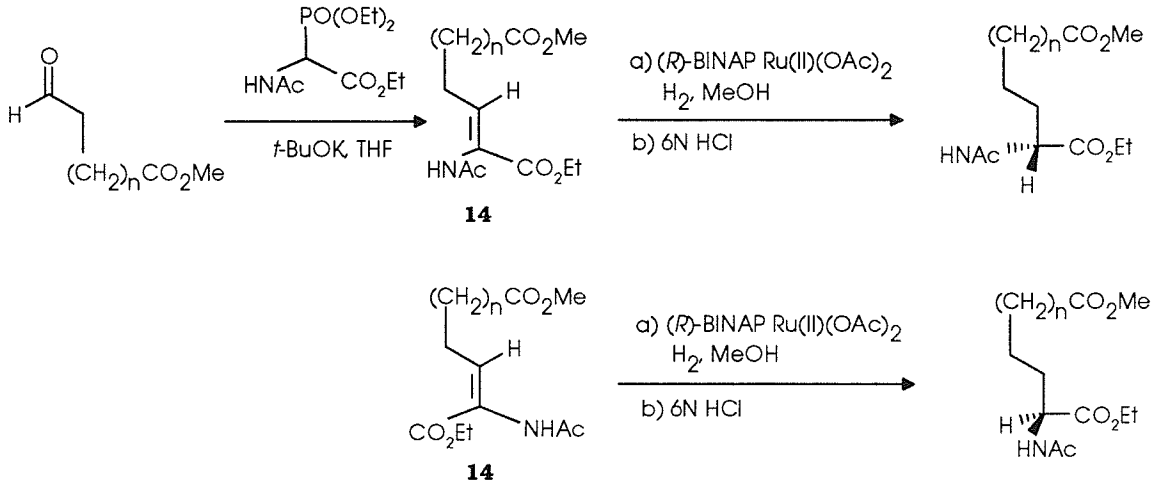


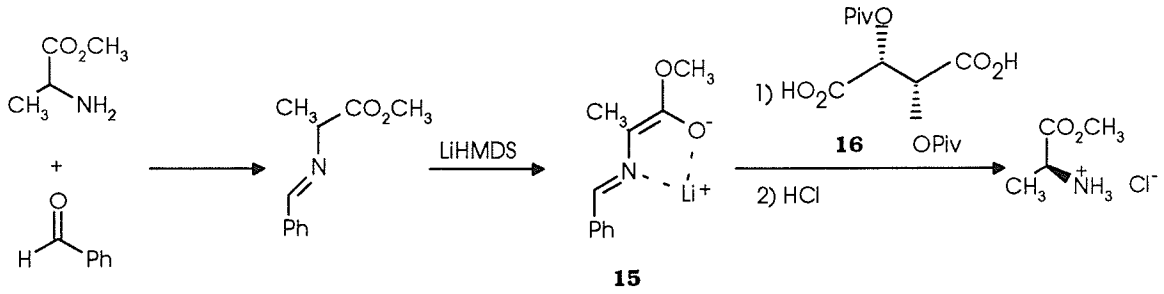
Figure 6

novel, chiral α-amino acids.[25] The geometry of the enamido ester determines the stereoselectivity for this step. If the olefin is in the *E*-configuration, then (*S*) α-amino acids result, but if it is in the *Z*-configuration, then (*R*) α- amino acids are produced. This method gives both excellent yields (quantitative reduction of enamido diester) and enantiomeric excesses (81-96%) of chiral amino acids.



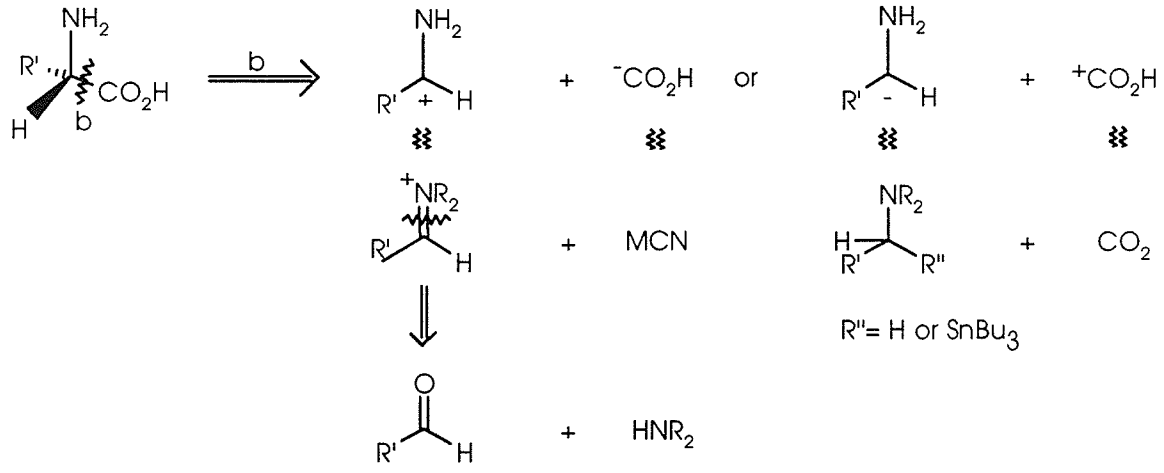
Scheme 8

Chiral protonation of an α-amino acid is similar to a resolution process, where the sequence begins with a racemate and ends with an enantiomerically enriched product (Scheme 9). Here, the lithium enolate (**15**) is generated from a racemic mixture of an α-amino acid. Once the enolate formed, it is asymmetrically protonated using the chiral proton source,(2*R*, 3S)-dipivaloyl-tartaric acid (**16**). This type of reaction is not the preferred route to optically pure α-amino acids. Although the yields are good (70-89%), the optical purities are only fair (35-70%).[26]



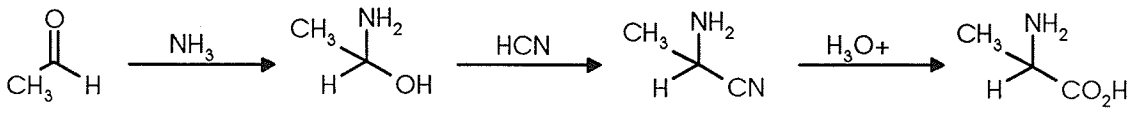
Scheme 9

Disconnection b, shown in Scheme 10, results in two sets of synthetic equivalents for the preparation α-amino acids. The first set involves an imine and cyanide source, and the second set involves an amine and an electrophilic carboxylate source.



Scheme 10

In 1850, Strecker inadvertently synthesized alanine while attempting to prepare lactic acid (Scheme 11).[27] He found that upon the addition of ammonia to acetaldehyde, an amino alcohol (**17**) was obtained. Addition of HCN led to the conversion of **17** to the amino nitrile (**18**). Following the hydrolysis of the nitrile, with aqueous acid, racemic alanine was obtained.

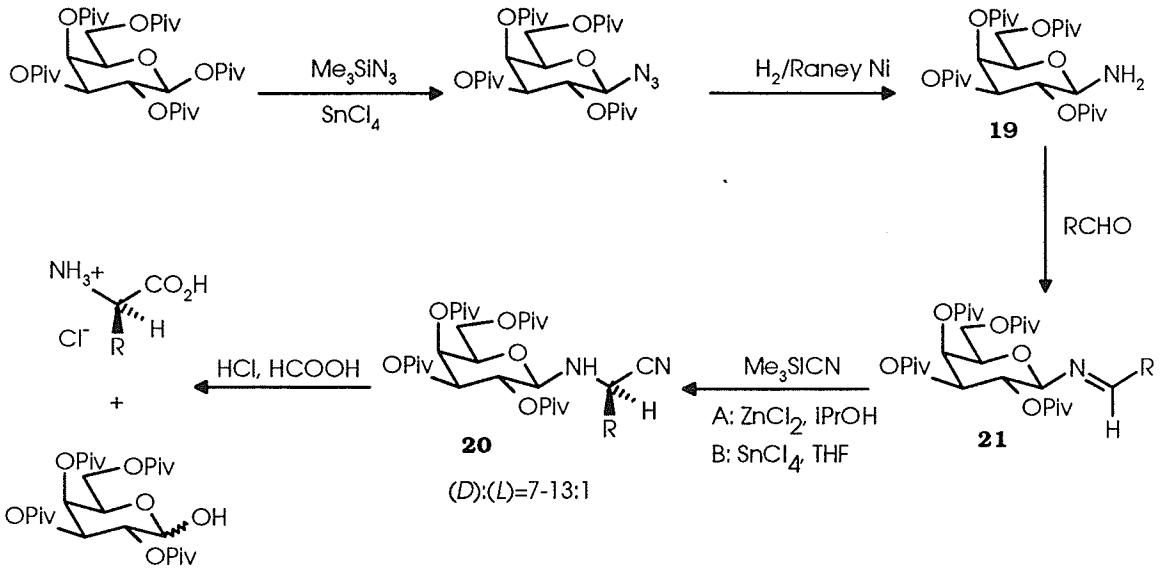


17 **18**

Scheme 11

The classic Strecker synthesis is not the preferred method for the synthesis of α-amino acids, due to the high toxicity of HCN, and the poor product yield (~10%). Zelinski and Stadnikoff[28] modified this method. They used NH_4Cl and KCN to provide α-amino nitriles, which upon hydrolysis gave α-amino acids in relatively good yields (~70%). The use of potassium cyanide to introduce the cyano group is preferable to hydrogen cyanide, since it is easier to handle and less toxic. The Strecker synthesis still plays a fundamental role in industrial syntheses of α-amino acids.[17]

Kunz and Rück have developed an asymmetric Strecker synthesis of α-amino acids,[29] using carbohydrates as chiral auxiliaries and trimethylsilylcyanide (TMSCN) as the cyanide source. This method is illustrated by Scheme 12. It employs a chiral amine (**19**) which is prepared from penta-*O*-pivaloyl-β-*D*-galactose and trimethylsilyl azide. This amine undergoes Schiff base formation with an aldehyde, which is converted to the amino nitrile (**20**) upon addition of TMSCN. Hydrolysis of **20** with HCl and formic acid proceeds without racemization to yield the free α-amino acid.[29] The chiral Strecker synthesis is able to produce α-amino acids in high yields, but only in fair to moderate selectivity (*D*:*L*=4-13:1). Consequently Kunz and Rück changed their approach from the Strecker synthesis to the Ugi synthesis. The classic Ugi four component synthesis uses an amine, an aldehyde, an isocyanide and an acid, to obtain racemic mixtures of amino acids. Kunz applied this type of chemistry to galactosamine. Amino acids produced by this method were obtained in high yields and excellent selectivities (*D*:*L*=~19:1).[29]



Scheme 12

The improved selectivity of the Ugi synthesis, when applied to Kunz's system, results from *si*-face addition of isocyanide to the imine (**21**) (Figure 7). Isocyanide must add from the *si*-face as the *re*-face of **21** is blocked by the Lewis acid which is coordinated to the amine, and the 2- and 3-*O*-pivaloyl substituents.[30] Both the modified Strecker and Ugi syntheses result in predominantly *D*-α-amino acids. In the modified Strecker synthesis, this selectivity was found to be dependent on solvent polarity. In polar solvents the cyanide source is completely ionized, resulting in cyanide attack from the face opposite to the Lewis acid. Conversely, in non-polar solvents the cyanide source is not completely ionized, and thus requires coordination to the Lewis acid to facilitate cyanide addition. This coordination results in attack from the same face as the Lewis

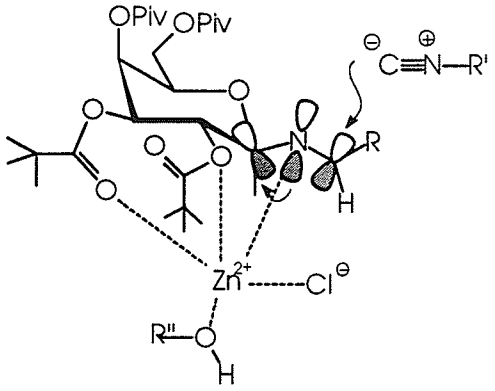
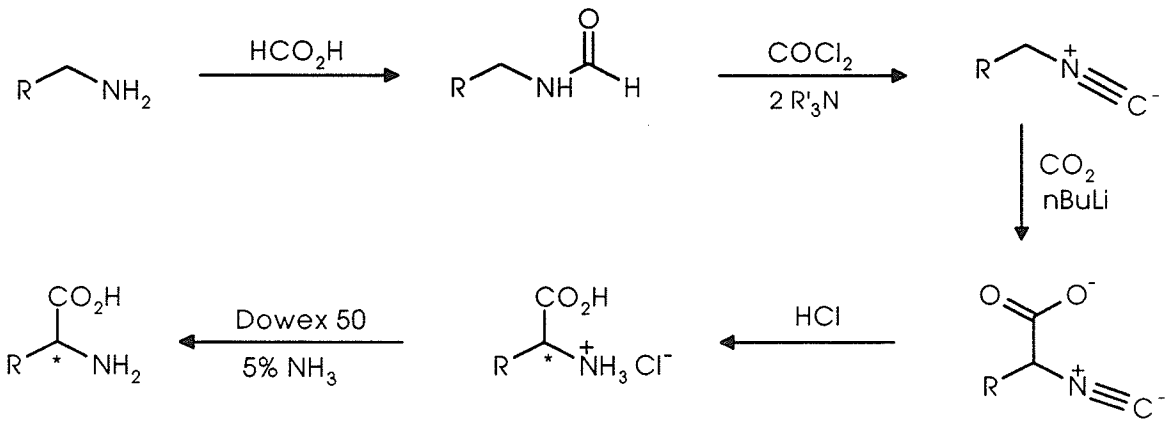


Figure 7

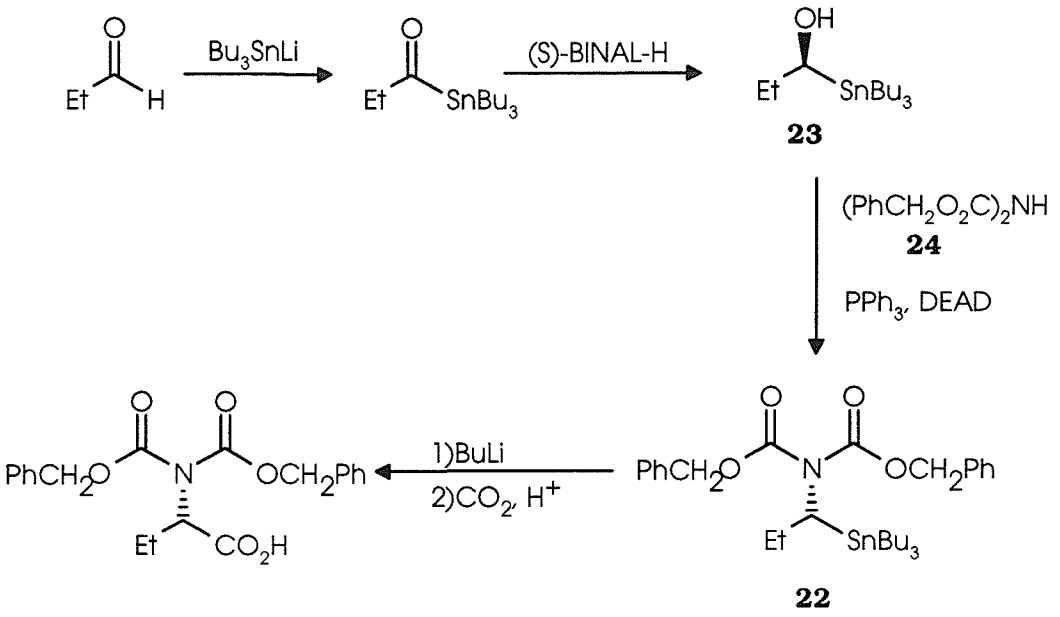
acid. These mechanistic differences make it possible to prepare both the *R* and *S* isomers from the same chiral template.[30]

Another method that may be used to introduce the carboxylate group to the α-carbon of an amine, was shown by Matsumoto et al.,[31] This method is illustrated in Scheme 13, and involves the substitution of carbon dioxide to an isocyanide, to prepare racemic mixtures of α-amino acids. Product yields were poor (35 %) when carbon dioxide was used as the carbonate source but when diethyl carbonate or dimethyl carbonate were used the yields improved to 70%.



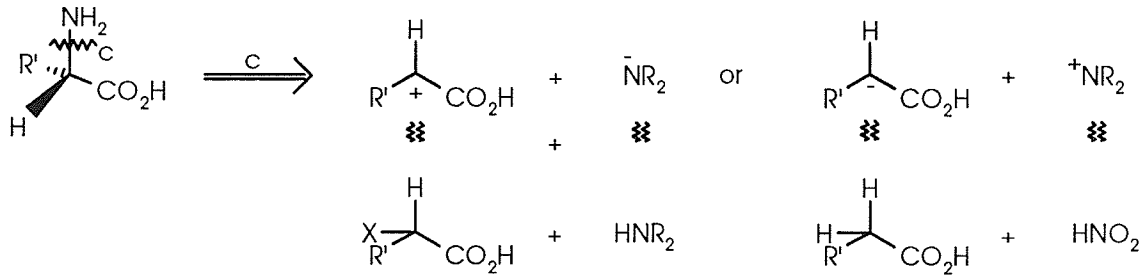
Scheme 13

Chong et al. have developed an asymmetric synthesis analogous to the above pioneering work in carboxylate additions to prepare α-amino acids, shown in Scheme 14.[32,33] They prepared an *N, N*-di(benzyloxycarbonyl)aminostannane (**22**) which underwent carboxylation by carbon dioxide via transmetalation with lithium, to give an α-amino acid stereoselectively, in high yield (45-60%) from the initial aldehyde. Stereoselectivity of this sequence results from S_N2 displacement of the chiral alcohol (**23**) by alkyl-*tert*-butyl iminodicarbonate (**24**), followed by carboxylation of **22** with retention of configuration.



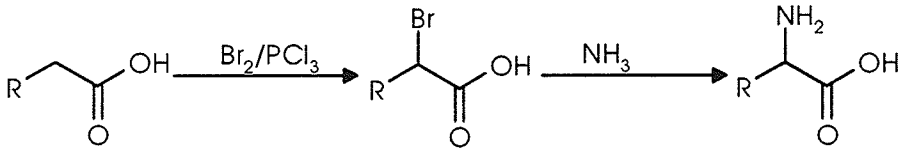
Scheme 14

Disconnection pathway c, seen in Scheme 15, results in two sets of synthetic equivalents that may combine to produce amino acids. One route begins with an α-haloacid and an amine, while the other begins with a carboxylic acid and an electrophilic nitrogen source.



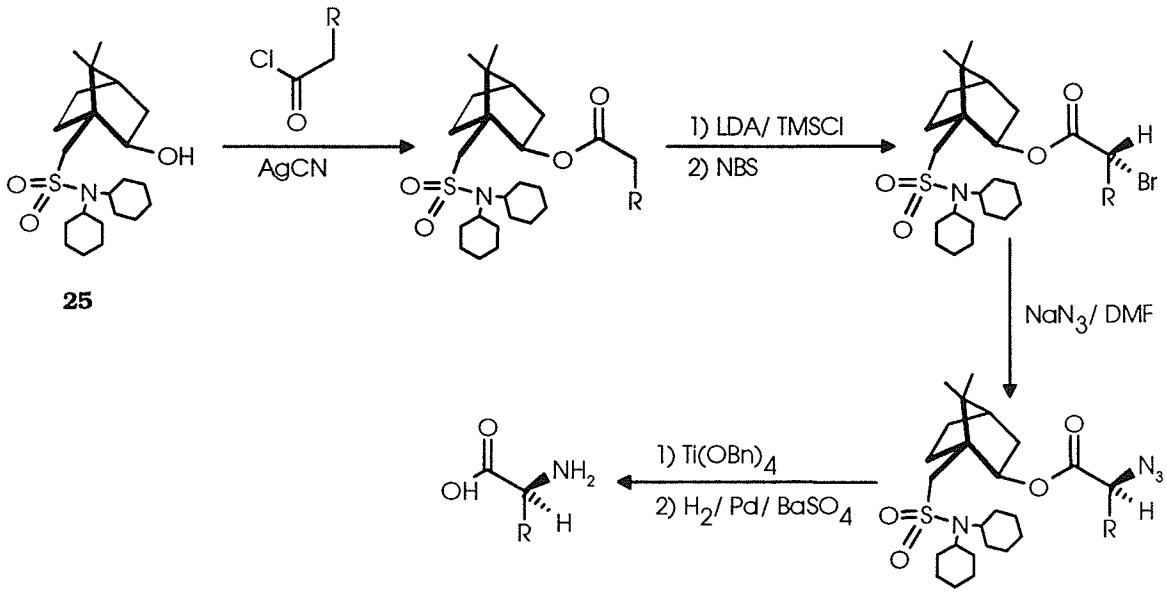
Scheme 15

The first route, amination of an α-haloacid, was performed by Cahours in 1858, when he prepared glycine using this method. Later work indicated that other chiral α-amino acids could be prepared by this method as seen in Scheme 16.[34] Cahours' method often resulted in poor product yields and the formation of secondary and tertiary amines (upon reaction with 2 or 3 α-haloacids, respectively).[27] The use of a large excess of ammonia resulted in improved product yields, provided the temperature was maintained between 40-60°C.



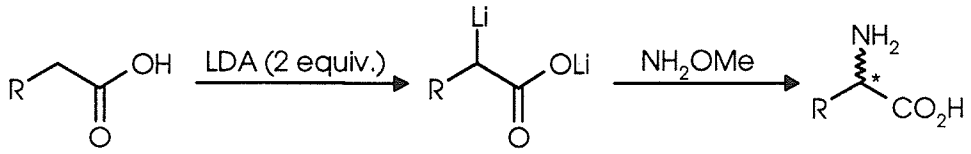
Scheme 16

Oppolzer et al. performed an excellent chiral rendition of the Cahours method, by using a 10-sulfonamido-isoborneol (**25**) as a chiral auxiliary attached to an acid chloride, as seen in Scheme 17.[35,36] The resulting ester was brominated using a strong base and NBS, to give the chiral α-bromoester with excellent stereoselectivity. This center underwent complete stereoinversion upon the nucleophilic addition of the azide function. Following saponification (from the chiral auxiliary) and reduction (of the azide), α-amino acids were obtained in high yields and excellent stereoselectivities. Furthermore this chiral auxiliary has been used to prepare α- and β-substituted amino acids with excellent stereoselectivity at both chiral centers.[35]



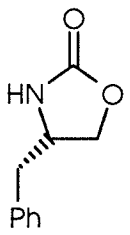
Scheme 17

The racemic preparation of α-amino acids by electrophilic amination of a carboxylic acid, has been performed by Yamada et al. Their method involved the preparation of an α-lithiated carboxylic acid salt which was aminated using an electrophilic *O*-alkylhydroxylamine, as seen in Scheme 18.[24,37] The α-amino acids produced by this method were obtained in good overall yield, but they found that amination depended on the O-alkyl group of the aminating species—as electron donation increased, the aminating ability decreased.[38]



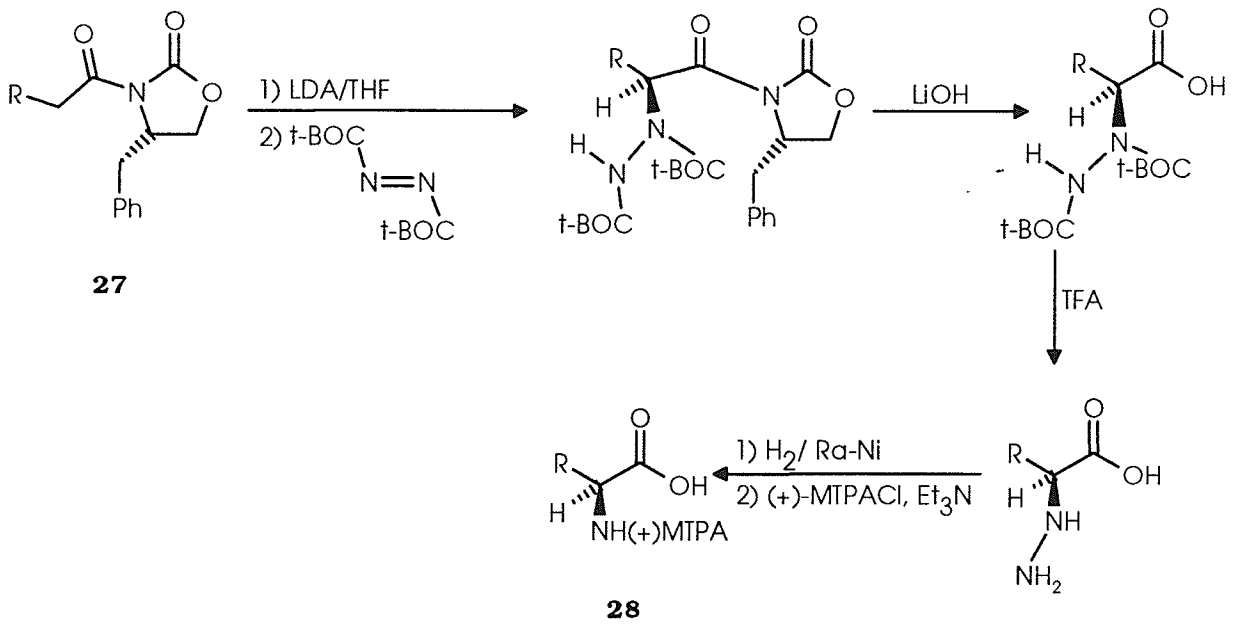
Scheme 18

The chiral version of this method was developed by Evans et al. They prepared α-amino acids with high enantioselectivity by using Evans' chiral auxiliary, (4*S*)-4-Phenylmethyl-2-oxazolidinone (**26**) (Figure 8). This auxiliary combines with an acid to produce a carboximide (**27**), which is the first compound in Scheme 19. Enolates of **27** undergo electrophilic amination with a variety of azo-dicarboxylates resulting in α-hydrazido adducts which upon reduction give α-amino acids.[1] An overview of this synthesis is shown in Scheme 19.[39] All steps proceeded



26

Figure 8



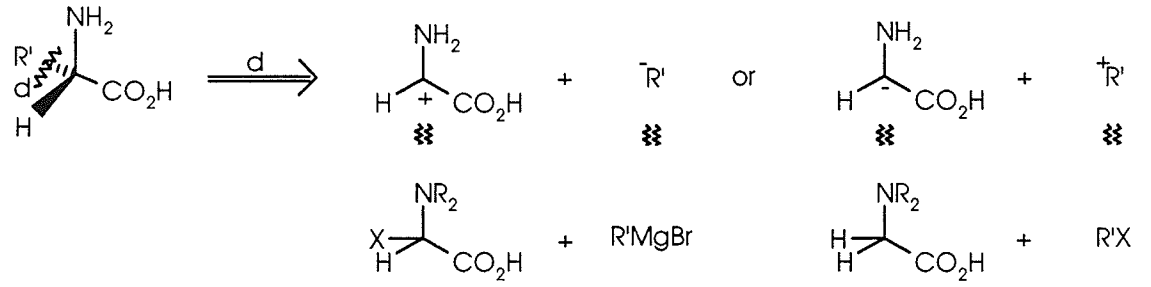
27

28

Scheme 19

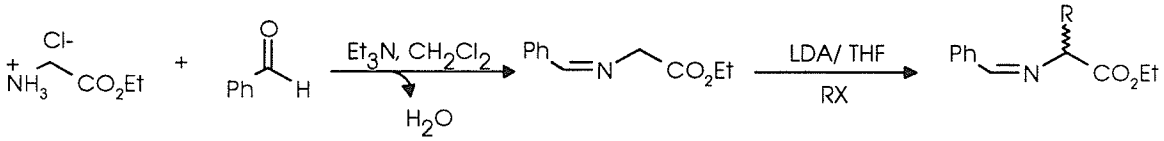
with good to excellent yields and enantiomeric excesses (both for the crude and recrystallized product). The purity of the product was determined by the preparation of the Mosher's amide derivatives (**28**), and analysis using capillary GLC.[40]

Disconnection pathway d, seen in Scheme 20, results in the synthetic equivalents of either an electrophilic or a nucleophilic R-group which upon addition to glycine produce α-amino acids.



Scheme 20

One of the simplest methods of preparing α-amino acids is by alkylation of glycine. Stork et al. found that alkylation of the benzylidine derivative of glycine ethyl ester afforded α-amino acids in high yields (Scheme 21).[41] He found that this method could be used to prepare both natural and novel α-amino acids, by using a wide variety of electrophiles.

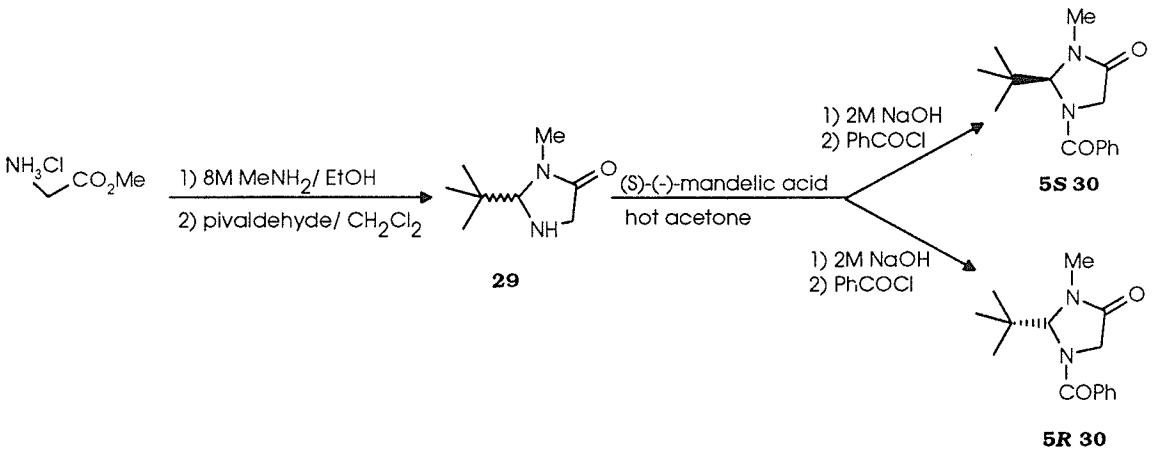


Scheme 21

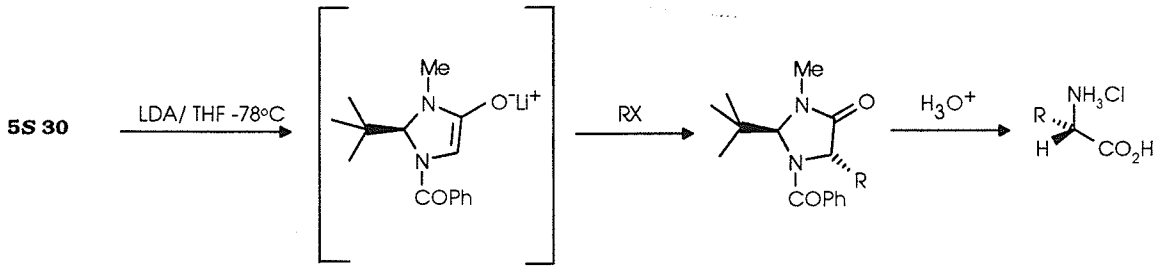
Others have taken the idea of racemic alkylation of glycine, and extended it to include asymmetric alkylation by employing chiral auxiliaries.[1] Three of the major influences in the area of α-amino acid production from chiral glycinates are Seebach,

Schöllkopf, and Williams. A chiral glycine is a compound that has a chiral auxiliary tethered to glycine, which (following asymmetric substitution at the α-carbon of glycine) is easily removed leaving a chiral amino acid in its wake. A description of these auxiliaries and methodologies follow.

Seebach et al. developed a chiral glycine equivalent using glycine, methylamine, and pivaldehyde, as seen in Scheme 22. The condensation of these reagents leads to a racemic mixture of the imidazolidinone (**29**) (chiral glycinate) which can be resolved by crystallization with (*S*)-mandelic acid or by chromatography on a chiral stationary phase. Deprotonation of imidazolidinone (**30**) affords an enolate which undergoes alkylation with various electrophiles, with high selectivity, as seen in Scheme 23.[42] Hydrolysis of the alkylated imidazolidinone results in α-amino acids in high yields, and with good-to-excellent enantiomeric excesses.[43]



Scheme 22



Scheme 23

Although it seems likely that the stereoselectivity of this system is determined by steric approach control, the authors have found evidence that this is not the sole factor controlling addition. They found that there was little change in facial selectivity for the electrophile when the smaller isopropyl group was substituted for *t*-butyl. This suggested another mechanism controlling facial selectivity in alkylation of the enolate, which is based on both steric and electronic factors.[44] In this case steric effects place the *t*-butyl substituent in a pseudoequatorial position, which consequently places the ring nitrogen atoms in a pyramidal conformation with their lone pair electrons occupying pseudoaxial orientations. As a result, the non-bonding electrons of nitrogen can interact with an anti-bonding orbital of the enolate. This orbital interaction will increase the electron density of the enolate on the opposite face (to the non-bonded electrons), resulting in preferential addition of the electrophile to that face. This type of interaction has been likened to that of an enamine system (see Figure 9).[1]

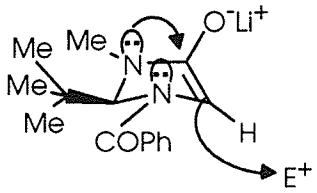


Figure 9

This chiral glycinate also can combine in both aldol condensation and Michael addition reactions with greater than 90% diastereoselectivity.[45] The high selectivity of these reactions is directed by two factors that govern enolate addition to an sp^2 electrophile. These are: (1) the electrophile must approach the enolate from the face opposite to the bulky *t*-butyl group, and (2) the enolate and the sp^2 bond of the electrophile must possess a synclinal orientation with respect to each other. This orientation places the transition state (for the addition) in a twist boat conformation when coordinated to the Li^+ counter ion, thus affording a high degree of selectivity (Figure 10).[45] The twist boat is the preferred conformation for this transition state as it places the R'-group of the electrophile in the equatorial position rather than the axial position found in the chair conformer.

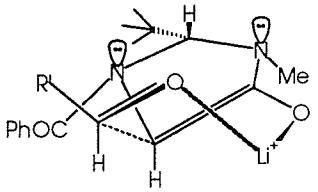


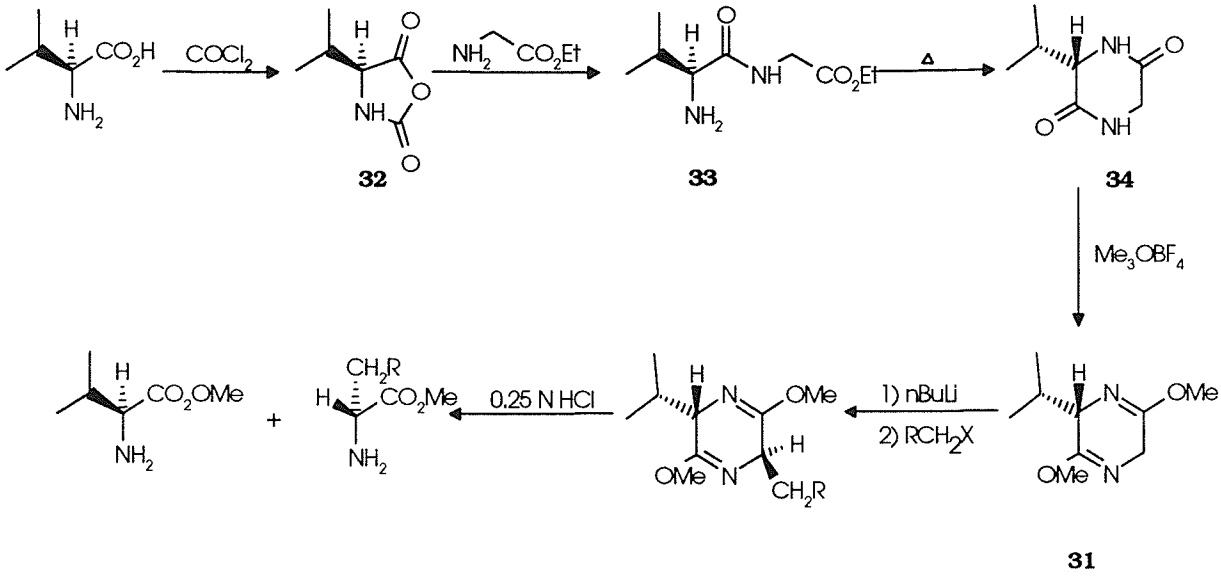
Figure 10

One advantage to this system is that upon hydrolysis of the α-amino acid from the imidazolidinone, the remaining by-products of the system are readily removable. The volatile materials are removed by evaporation and/or distillation and the non-volatile compounds are separated by extraction. Further purification of the amino acid is achieved by crystallization.[46]

Schöllkopf et al. have developed a bislactim ether (**31**) which undergoes alkylation with tremendous asymmetric induction at the α-carbon center.[22] This chiral glycine is constructed from α-amino acids found in the chiral pool. One of the α-amino acids used must be glycine while the other may be any available chiral α-amino acid.[47,48]

The synthesis, in Scheme 24, begins with the conversion of *L*-valine to the more reactive *N*-carboxyanhydride (**32**) which then condenses with glycine ethyl ester to

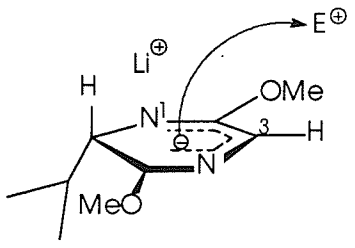
give **33**. Upon heating, **33** cyclizes to form the bislactam (**34**). This is converted to **31** with Meerwein's salt, and subsequently deprotonated with LDA. The free α-amino acid is obtained by alkylation of the lithium enolate, followed by hydrolysis of the bislactim ether.



Scheme 24

These bislactim ethers may be used in a variety of reactions, particularly alkylations, and aldol condensations.[47]

Alkylations of this system result in amino acids that have the opposite stereochemistry to the amino acid used to prepare **31**. This orientation is determined by the approach of the electrophile, which must approach the enolate (**35**) from the face opposite the isopropyl group (Figure 11).[47] It



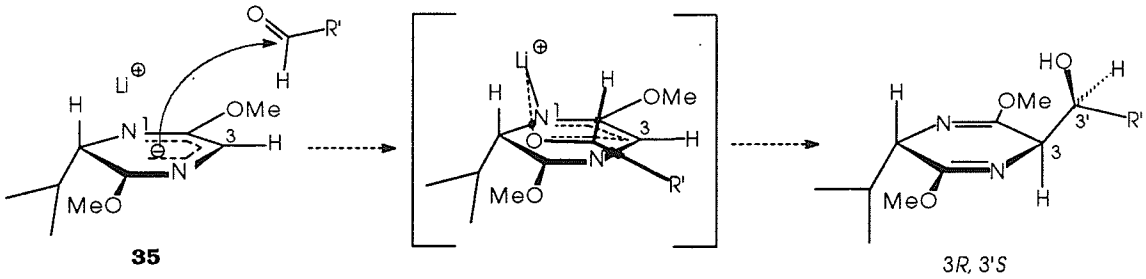
35

Figure 11

was found that asymmetric induction at the C-3 center improved as the steric bulk of the amino acid used to prepare the bislactim ether increased.[49]

Aldol condensations with **35** proceed with excellent asymmetric induction at the C-3 center (80->95%), and with variable induction at the C-3′ center (10-80%). The selectivity at the C-3 center results from the aldehyde addition to the face opposite to the isopropyl group of **35**. Asymmetric induction at the C-3′ center results from the transition state (Scheme 25) for the addition of an aldehyde to **35**. This transition state is favored due to the following three factors:

1. The carbonyl oxygen lies above the N-1 of **35**. This orientation places the system in a stable chair conformation upon coordination to the Li^+ counter ion.
2. The approach of the aldehyde places R′ in the favored, equatorial position within the chair conformer.
3. R′ is oriented near the hydrogen of **35** thus minimizing steric repulsion between the anion and the electrophile.[50]

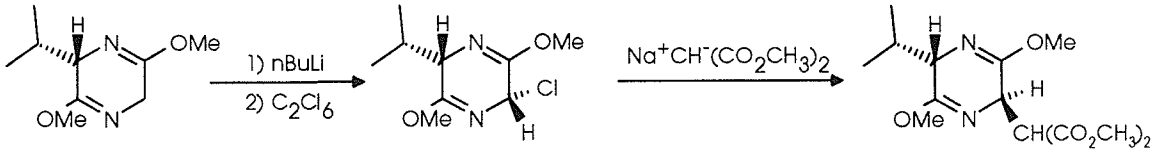


Scheme 25

This transition state predicts an aldol product having two chiral centers, 3 and 3′, of opposite stereochemistry. This prediction is supported by experimental observations where the α-amino acids produced have opposite chirality at the α- and β-centers.

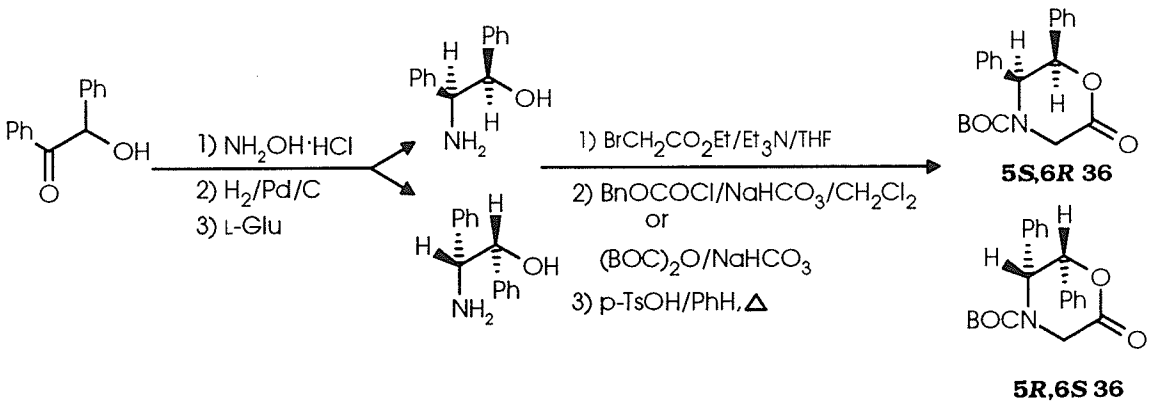
Schöllkopf's bislactim ether may also be employed in nucleophilic substitutions (Scheme 26). This is achieved by halogenation of the α-position of the glycine portion

of the bislactim ether, followed by displacement of the halide with a nucleophile. It is interesting to note that the halogenation of the bislactim ether occurred cis to the isopropyl group. Although one might expect this reaction to proceed via an ionic mechanism, the authors postulate that the addition of chlorine to the nucleophile is controlled by a radical mechanism.[51] The nucleophilic displacement of the halide occurs with complete stereo-inversion at that center. The authors found that the yields were good in only some cases. When "soft" nucleophiles such as thiolates, water, or resonance-stabilized anions of carbon acids were used, the yields tended to be low.[51,52]



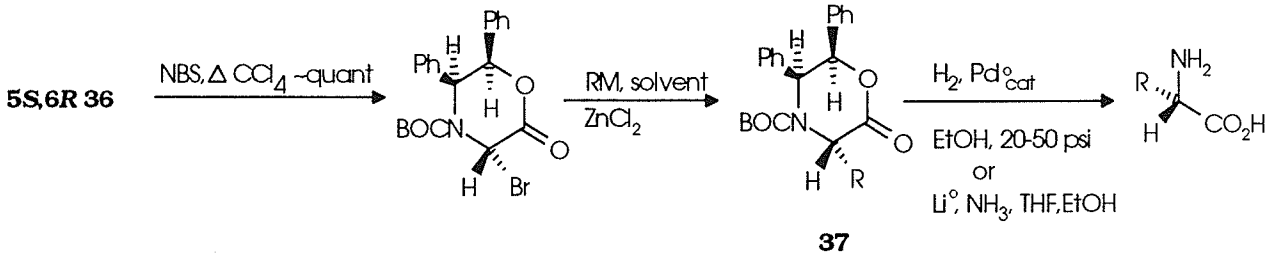
Scheme 26

The third well known chiral glycine (**36**) was introduced by Williams group, and its preparation from (±) benzoin is outlined in Scheme 27.[1]



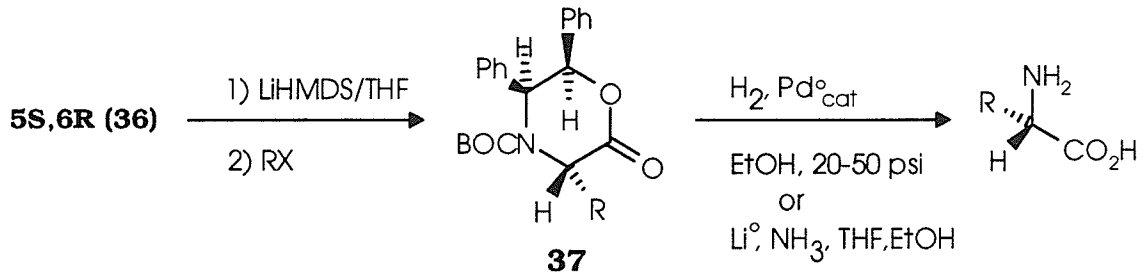
Scheme 27

Oxazinone (**36**) provides access to either α-amino acid enantiomer, by simply choosing electrophilic or nucleophilic modes of alkylation or by using the other enantiomer of the oxazinone.[53,54,55] These differences may be explained by their different modes of interaction with the chiral auxiliary. Nucleophilic alkylation (Scheme 28) of the oxazinone is a two-step process, which involves, first, halogenation of **36**, followed by alkylation, with retention of configuration, providing **37**. The retention of configuration is likely a consequence of zinc coordination with the halide. This



Scheme 28

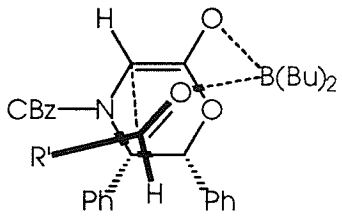
coordination may produce a reactive iminium intermediate which undergoes alkylation from the least hindered face (trans to the phenyl groups).[54] This sequence of events results in complete inversion of the stereochemistry at the center of addition. In contrast, electrophilic addition (Scheme 29) to the chiral enolate nucleophile is essentially a single step process, during which the electrophilic approach occurs from



Scheme 29

the least hindered face (of the enolate). The chemical yields of the alkylated lactone (**37**) are produced in good to excellent yields (85-100%) with excellent stereoselectivity (91->96%).[1] The chiral α-amino acids resulting from either method are separated by destructive cleavage of the chiral auxiliary using hydrogenation or dissolving metal reductions.

Although no aldol condensations using this chiral glycinate have been reported by Williams' group, Miller et al. have used it in aldol condensations, via the generation of the boron enolate.[56] These reactions produced the *L*-erythro diastereomers, resulting from the aldol addition anti to the bulky phenyl groups. The diastereoselectivities for these reactions were fair to good. The proposed rationale for this selectivity is that the addition proceeds through a chair transition state (**38**) which has the aldehyde approaching from the less hindered face of the enolate (Figure 12). Miller noted that the stereoselectivity of this system was opposite to that of Seebach, even though both proceed through the *E*-enolate.[56] He said this was likely due to the presence of the boron alkyl substituents which cause a chair conformation in the transition state, rather than the normally preferred twist-boat conformation. The chair conformation minimizes the 1,4-diaxial interaction of the bulky alkyl groups.



38

Figure 12

Our Proposal: a new carbohydrate-based chiral auxiliary

Three criteria should be fulfilled if one chooses to employ a chiral auxiliary to direct alkylations:

1. the synthesis should result in an enantiomerically pure product
2. isolation of the new chiral product should readily occur, without racemization
3. easy recovery of the chiral auxiliary.[57]

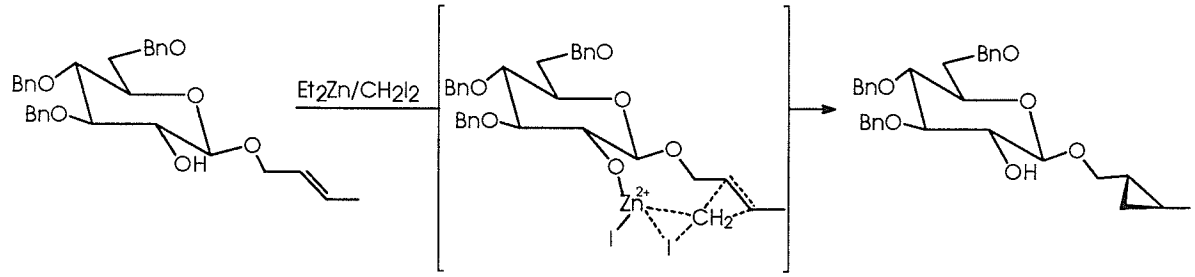
Furthermore all of these steps should be relatively easy and proceed in high yield.

We believe that carbohydrates should satisfy the above conditions. Carbohydrates are molecules that contain multiple chiral centers and more than one functional group. These characteristics have led to the postulate that they should be efficient chiral auxiliaries for enantioselective syntheses. Until recently, they were not widely used as chiral auxiliaries due to their complex structure.[29] This complexity is responsible for the uncertainty associated with the correlation of the structure of the auxiliary with that of the product.[30] Another deterrent was the requirement of multiple protection steps to preserve functionality within the carbohydrate. On the other hand, derivatives of carbohydrates are often crystalline, and thus purification is convenient.[58]

Carbohydrates have proven valuable as chiral auxiliaries in a wide variety of chemical reactions, e.g.: cyclopropanation reactions,[59] Diels Alder reactions,[60] nucleophilic addition to esters,[29] nucleophilic additions to electrophilc centers α-to the sugar,[61,62,63] Michael additions of organometallic reagents[29], cycloadditions {(4+2) and (2+2)},[64] reductions using carbohydrate-bound borohydrides[65], and aldol reactions involving chiral titanium enolate addition to simple aldehydes or ketones.[66]

Charette's cyclopropanation reaction is an excellent illustration of how effective carbohydrates can be as chiral auxiliaries, and it is outlined in Scheme 30. The

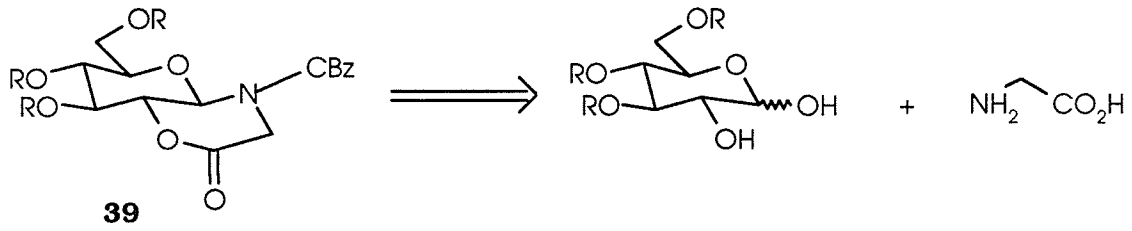
cyclopropanation reaction is highly selective due to the Lewis acid coordination with both the 2'-hydroxyl group and the carbene. This coordination ensures carbene delivery to the olefin from the same face as the Lewis acid. This reaction proceeds with greater than 50:1 diastereoselectivity, and in almost quantitative yields.[59]



Scheme 30

Further evidence supporting the value of carbohydrates as chiral auxiliaries has been illustrated in Scheme 12 and has been discussed in the section dealing with Kunz's methodology on page 22. He used galactosamine as a carbohydrate derivative in the asymmetric preparation of α-amino acids via the Ugi four component synthesis. As mentioned earlier his method gave chiral products in high yields and excellent enantiomeric excesses.

Considering the evidence supporting the use of carbohydrates as effective chiral auxiliaries, it should follow that our "chiral glycine" system too should be a success. Our chiral glycinate (**39**) should provide an alternative to the other chiral glycinates, because it starts from cheap, readily available starting materials.



Scheme 31

We believe that our system will fulfill Schöllkopf's criteria for asymmetric methods of synthesis involving chiral auxiliaries. Our system, **39**, is a bicyclic oxazinone, where one part is the cyclic sugar, and the other is glycine. Since the system is cyclic, it is consequently more rigid when compared to the open chain form of this system. This rigidity should result in a higher degree of asymmetric induction. Scheme 31 shows the retrosynthetic analysis of this system, and that it can be prepared from the simple and easily available starting materials of glycine and *D*-glucose. Following alkylation of **39**, the resulting amino acid should be easily obtained by removal of the amine protecting group, followed by simple hydrolysis, resulting in the free α-amino acid and the intact chiral auxiliary, 3, 4, 6-tri-*O*-benzyl-*D*-glucose starting material.

A related chiral glycine based on *L*-rhamnose might provide access to the α-amino acid enantiomer of the one generated from **39**. Figure 13 illustrates the structural similarity between *D*-glucose and *L*-rhamnose.[59]

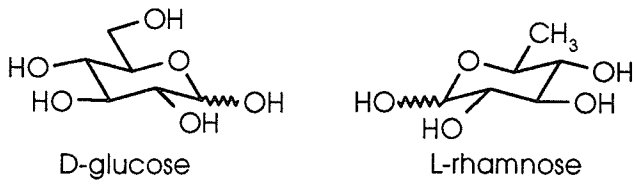


Figure 13

Although the "chiral glycine' systems of Schöllkopf, Seebach and Williams result in the production of α-amino acids with high optical purity, their methods do have some limitations, which might be alleviated in our system.

Schöllkopf's chiral glycine may require harsh acid conditions (up to 6N HCl) for hydrolysis of the bislactim ether, which may prevent the preparation of amino acids with acid sensitive R-groups. He also found that the best combination of amino acids for directing alkylations involved *L-tert*-leucine (an unnatural α-amino acid) and glycine. This would therefore necessitate the production of *L-tert*-leucine prior to bislactim preparation. The amino acids produced by this method require separation from the chiral auxiliary (the other amino acid) by either distillation, or chromatography. The final limitation of this method is that Schöllkopf's bislactim ether is no longer commercially available.

There appear to be two limitations to Seebach's system, they are: (1) resolution of the chiral auxiliary, and (2) harsh conditions frequently used for hydrolysis. The need to resolve the chiral auxiliary results in an extra step in this sequence that may be avoided by starting with chiral materials. The use of strong acid conditions to liberate the amino acid from the chiral auxiliary restricts the preparation of amino acids with acid sensitive R-groups. Furthermore the harsh conditions of hydrolysis destroy the chiral auxiliary. Seebach's "chiral glycine" is commercially available but is quite costly, and thus not suited to large scale syntheses.

Williams' method, like Seebach's, involves both resolution (of the amino alcohol), and the destructive removal of the chiral auxiliary. This "chiral glycine" is also commercially available. It is expensive, although not as expensive as Seebach's.

The use of enantiomerically pure starting materials avoids resolution of the "chiral glycine" prior to alkylation. Furthermore, hydrolysis of the anomeric linkage

between the chiral auxiliary and the amino acid should proceed under mild conditions. Consequently the amino acid should be obtained without destroying the chiral auxiliary.

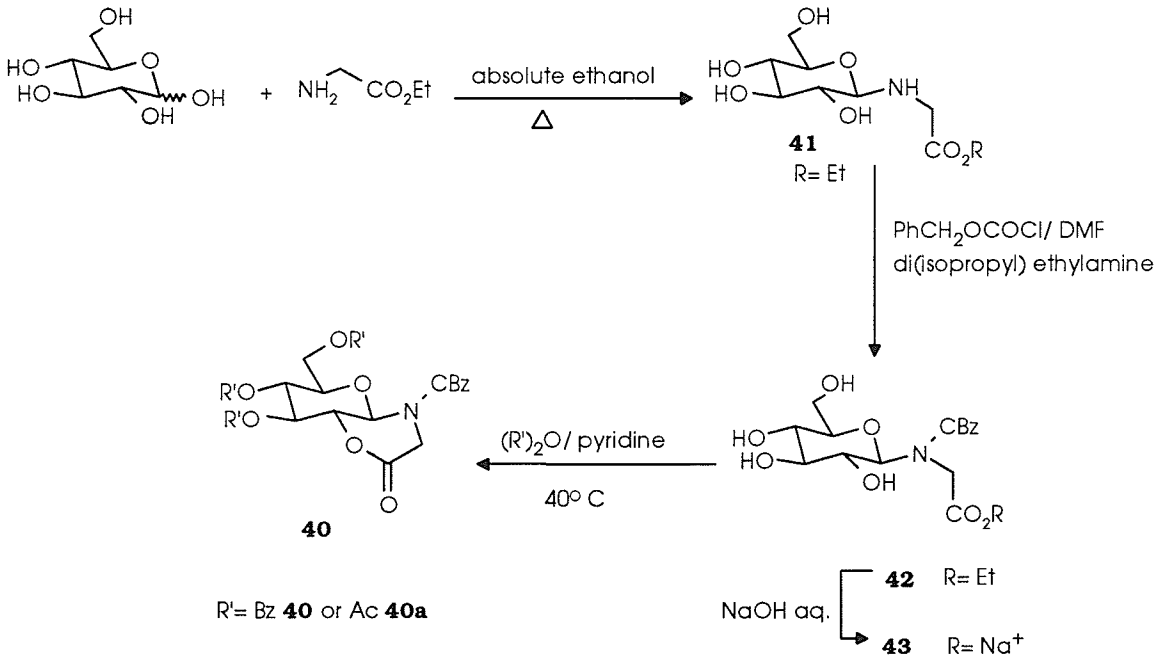
It is worthwhile to note that our method is not intended for multi-kilogram or industrial scale syntheses, since these syntheses would be better suited to catalytic methods. However this method should be well suited to the needs of the bench scale syntheses, where one needs predictable and rapid access to a variety of structurally diverse, optically active amino acids.

Since it is possible to differentially protect the sugar hydroxyl groups, this chiral glycinate may be tethered to a solid support[67] by either the C-3 or C-6 hydroxyl oxygen. This may be performed either at the beginning of the sequence or once the template has been prepared. Solid support syntheses provide some advantages over traditional solution phase chemistry in that those reagents that do not interact with the bound compound are simply washed away. This reduces the need for purification (chromatography, and recrystallization) between steps.[68]

Our chiral auxiliary need not be readily cleavable from the solid support because the target molecule is the amino acid produced, not the glucosylamino acid. This possibility may make our chiral glycine an excellent alternative for the preparation of α-amino acids.

Results

Our chiral glycine was obtained by two routes. The first route started with *D*-glucose, and resulted in (4aR, 6R, 7R, 8aR)-4-(benzyloxycarbonyl)-6-(benzyloxy)methyl-7, 8-bis(benzyloxy)-6H-pyrano(3, 2-b)1, 4-oxazin-2-one (**40**) (Scheme 32). This sequence began with the preparation of **41** from *D*-glucose and glycine ethyl ester according to the procedure of Wolfrom et al..[69] Following protection of **41** with carbobenzyloxy chloride (71%), the ester was converted to the carboxylic acid salt (**43**) under basic conditions. Treatment of **43** with benzoic anhydride produced the fully protected bicyclic template (**40**, 60%).

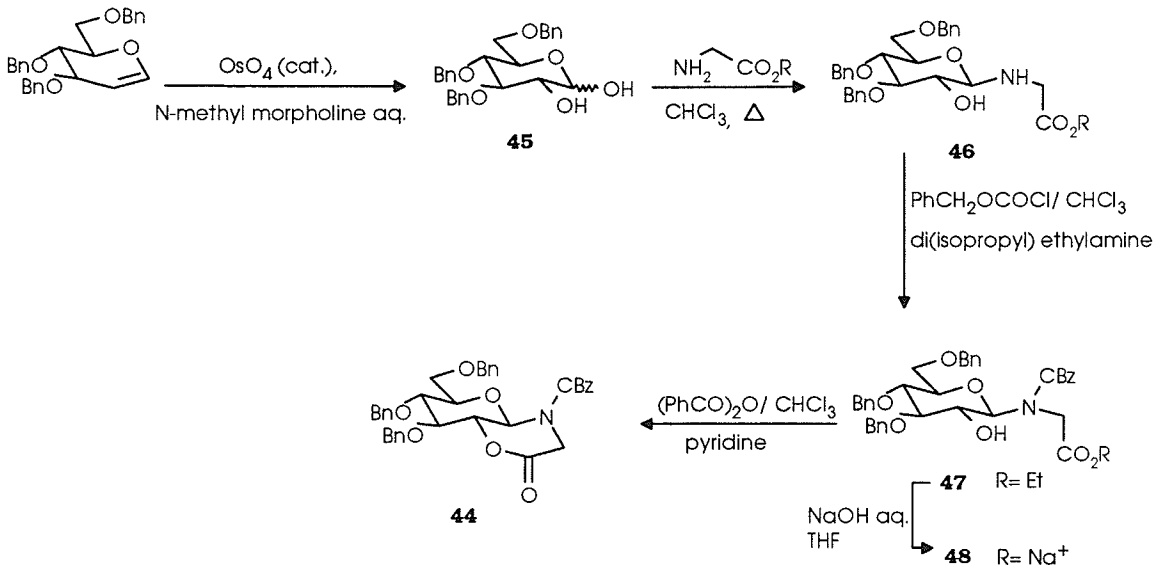


Scheme 32

The glycosidic bond of **41** is sensitive to aqueous conditions (reverts to the starting materials), and to acid catalysed rearrangements (the Amadori rearrangement). This prompted us to test the stability of the glycosidic bond of **42**. This

compound was tested under aqueous acid and base conditions (between pH 1 and 14), and at high temperature (110° C), and the glycosidic linkage was found to be stable in both environments.

Scheme 33 illustrates an alternate method for the preparation of the benzyl ether protected bicyclic template (**44**) beginning with the osmylation of 3,4,6-tri-*O*-benzyl-*D*-glucal, according to the procedure of Charette et al..[70] Once **45** is obtained, it undergoes condensation with glycine ethyl ester to produce **46** (70%), which is subsequently protected with carbobenzyloxy chloride (95%). Again, cyclization to the oxazinone (72%) was performed by treatment of the carboxylic acid salt (**48**) obtained from the hydrolysis of the carboxylic ester of **47**, with benzoic anhydride.



Scheme 33

Once **44** had been obtained, it was then possible to test whether this would be an effective template for the asymmetric synthesis of α-amino acids in high yields, and in high optical purities. This was done by preparing the enolate (**49**), followed by alkylation with the electrophiles listed in Table 1. This procedure is illustrated in Scheme 34.

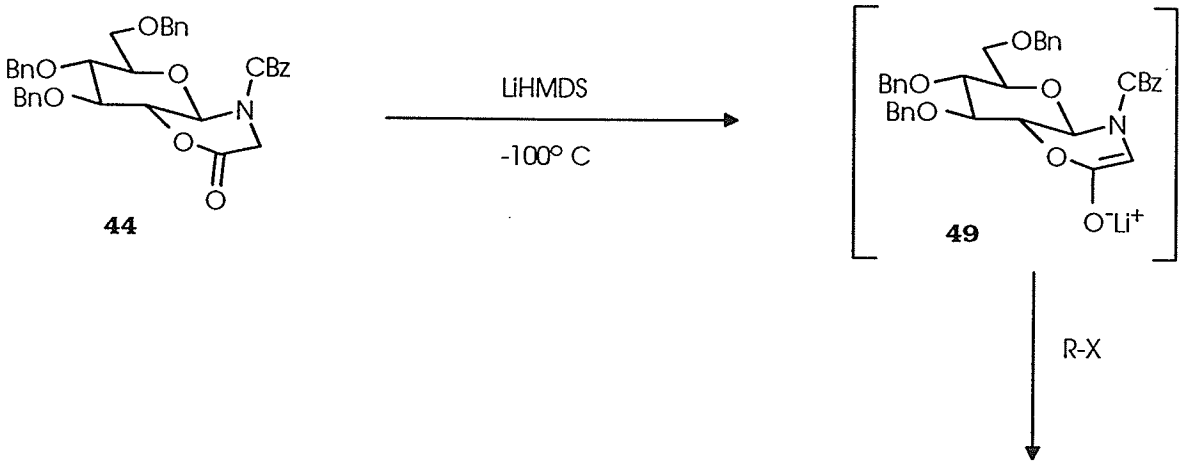


Table 1

R-X	Solvent	Monoalkyl yield		Dialkyl yield	
H_3C-I	THF	23%	**(50a)**	—	
	THF/HMPA[ii]	55%	**(50a)**	—	
CH_2CHCH_2-Br	THF	25%	**(50b)**	—	
	THF/HMPA[ii]	26%	**(50b)**	25%	**(51a)**
$C_6H_5CH_2$-Br	THF/HMPA[ii]	—[iii]		21%	**(51b)**

Scheme 34

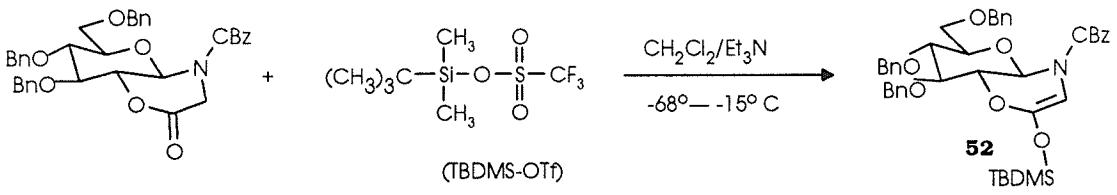
[ii] 20% solution of HMPA in THF

[iii] Observed by tlc, but not isolated.

The diastereomeric excesses of the monoalkylated products of (**50**) were determined by analysis of the 500 MHz ^1H nmr spectra (Figure 14 and Figure 15). The signals due to the methyl group of **50a** and the methine protons of the allyl group of **50b** were used as markers. The nmr data suggested that the diastereomeric excess of **50a** was 92% and for **50b** was >95%. Facial selectivity for the monoalkyl product was confirmed using nuclear Overhauser enhancement difference (nOe) experiments (Figure 16 and Figure 17).

Preliminary experiments were performed to obtain free *L*-alanine from **50a**. Free alanine was acquired according to the procedure of Seebach et al.,[71] and it was assessed for optical purity using a chiral HPLC column.[iv] Early results (Figure 18, Figure 19 and Figure 20) indicate that the sample was predominantly *L*-alanine (87-93% e.e.).

The *t*-butyldimethylsilylenol ether (**52**) was prepared according to the procedure of Rossi and Pecunioso[72] (Scheme 35). Attempts to alkylate **52** with allyl bromide in the presence of zinc chloride, according to the procedure of Patterson, were unsuccessful.[73]



Scheme 35

[iv] The HPLC experiments were performed by Chiral Technologies Incorporated.

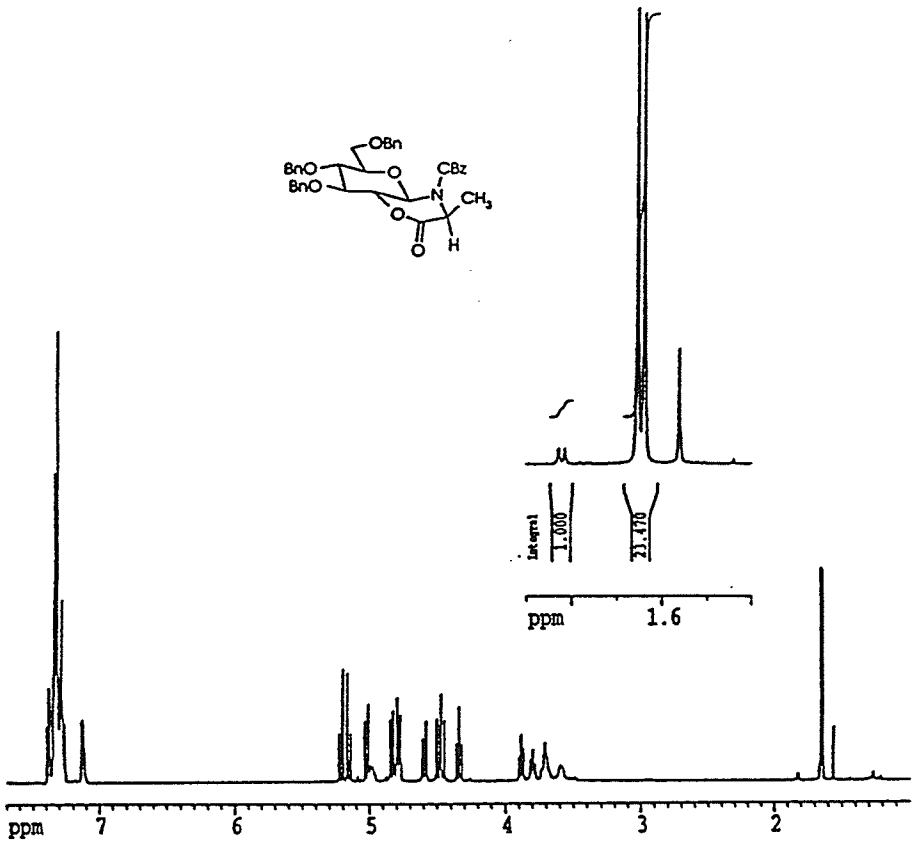


Figure 14: ^{1}H nmr spectrum for compound **50a**

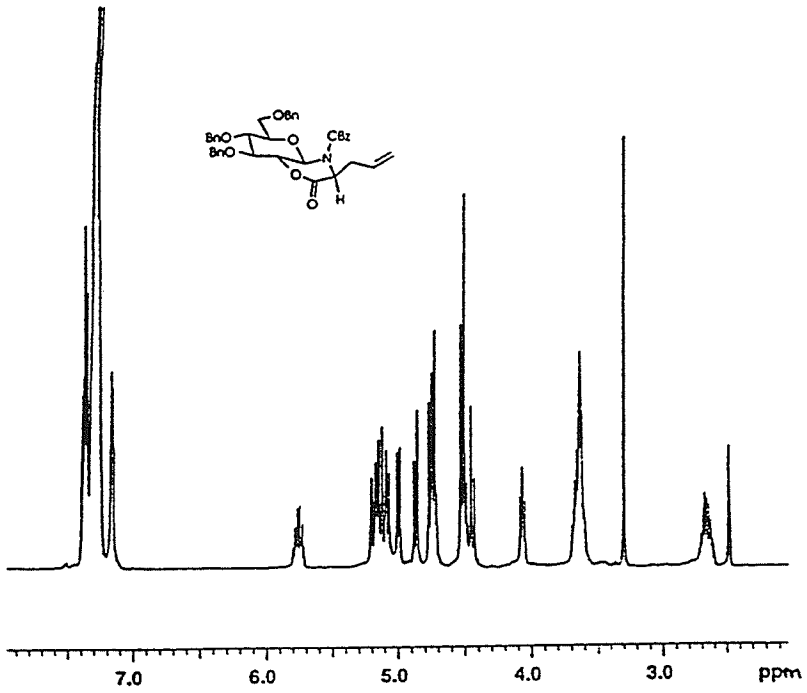


Figure 15: ^{1}H nmr spectrum for compound **50b**

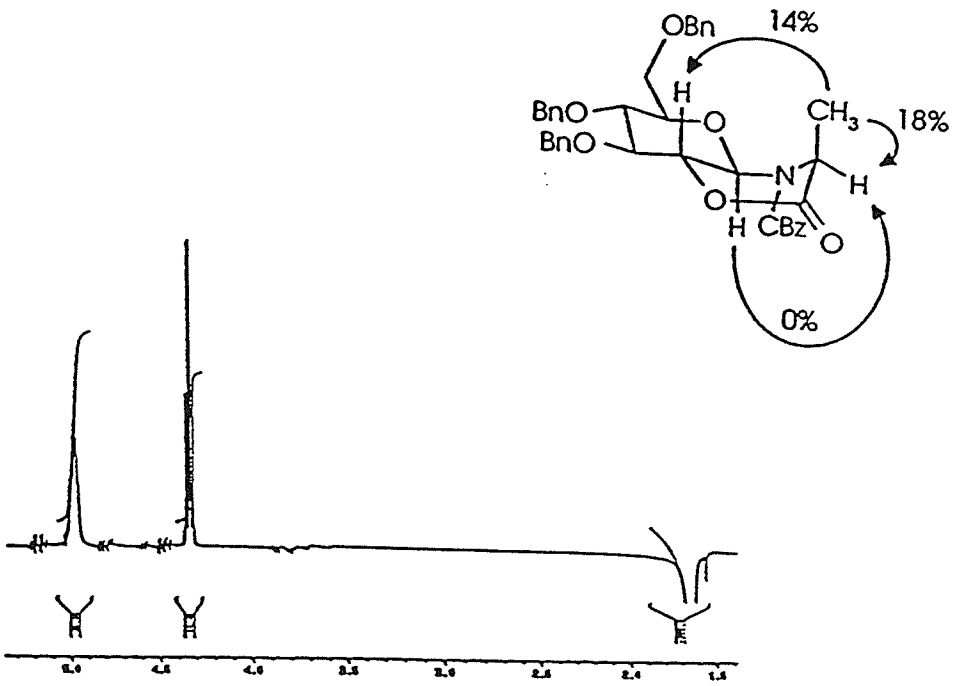


Figure 16: nOe difference spectrum for compound **50a**.

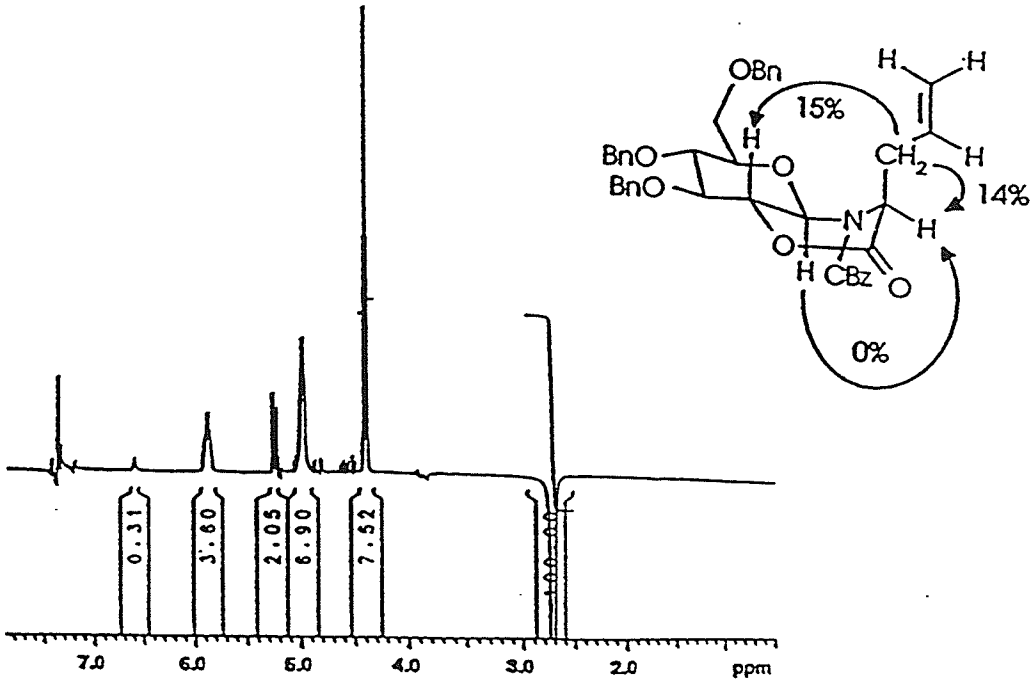
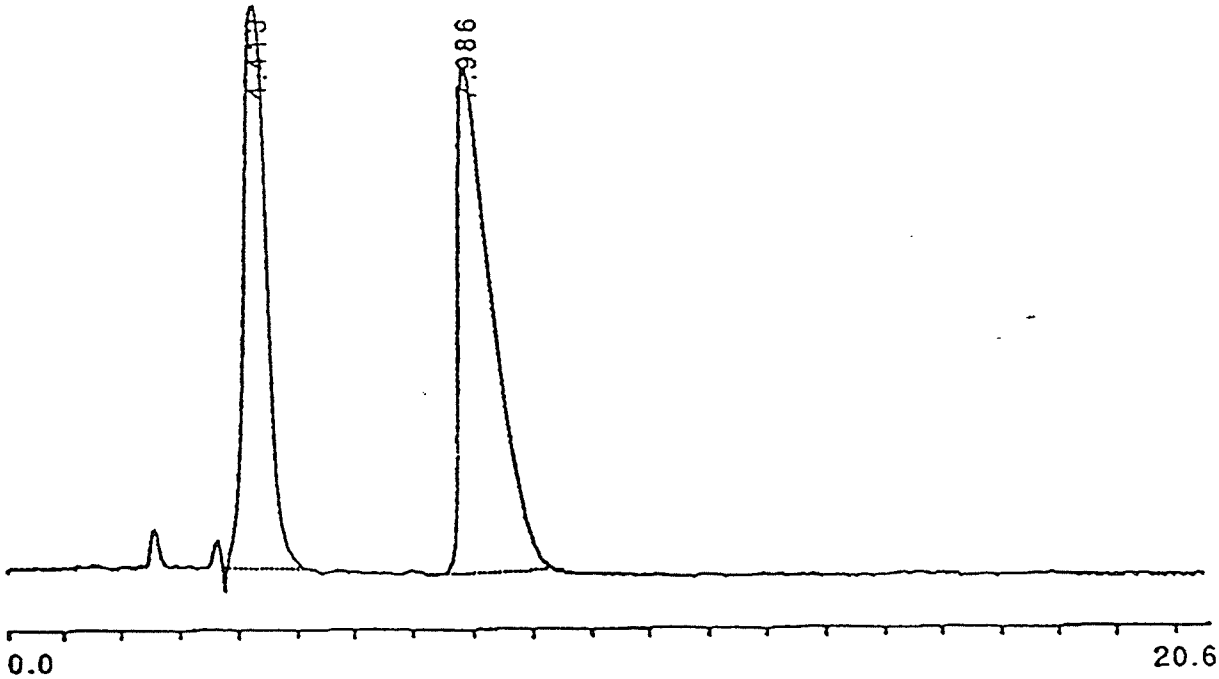


Figure 17: nOe difference spectrum for compound **50a**.

Eluent: PERCHLORIC ACID PH 1.5
Flowrate: 0.5 ml/min; 0 deg. C; UV 215 nm
Column: CROWNPAK CR(+) 4.6 I.D X 150 mm

Method: U2
Inject Vol: 20
Sampling Int: 0.4 Seconds

Data:



Analysis: Channel A

	Peak No.	Time	Type	Height(µV)	Area(µV-sec)	Area%
D →	1	4.413	N2	56796	1372850	41.906
L →	2	7.986	N	50726	1903148	58.093
	Total Area				3275998	99.999

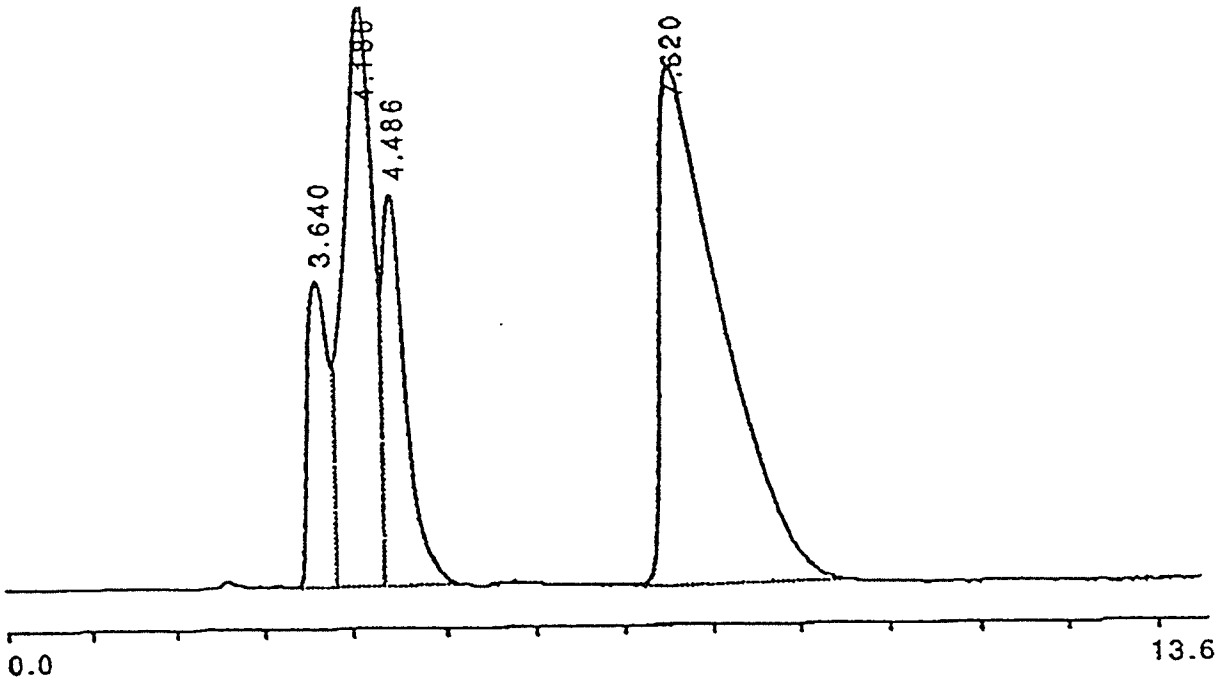
Peak No.	Time	Asymmetry	Efficiency
2	7.986	4.000	1075

Figure 18: HPLC analysis of a commercial sample of *D-/L-* Alanine.

Eluent: PERCHLORIC ACID PH 1.5
Flowrate: 0.5ml/min; 0 deg. C; UV 215 nm
Column: CROWNPAK CR(+) 4.6 I.D X 150 mm

Method: U2
Inject Vol: 20
Sampling Int: 0.4 Seconds

Data:



Analysis: Channel A

Peak No.	Time	Type	Height(µV)	Area(µV-sec)	Area%
1	3.640	N1	51679	783620	9.547
2	4.186	N2	98831	2248274	27.392
D→ 3	4.486	N3	66294	1063747	12.960
L→ 4	7.620	N	87872	4111936	50.099
Total Area				8207577	99.998

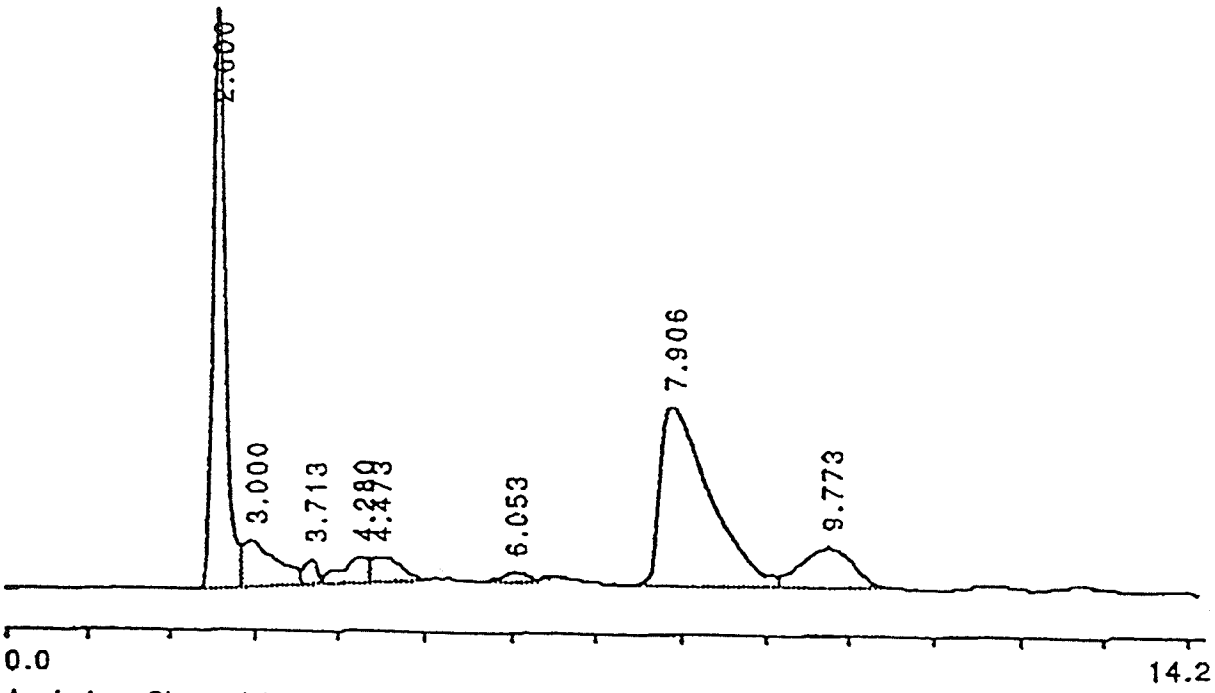
Peak No.	Time	Asymmetry	Efficiency
4	7.620	5.382	632

Figure 19: HPLC analysis of a commercial sample of partially racemized *L*- Alanine.

Eluent: PERCHLORIC ACID PH 1.5
Flowrate: 0.5 ml/min; 0 deg. C; UV 215 nm
Column: CROWNPAK CR(+) 4.6 I.D X 150 mm

Method: U2
Inject Vol: 20
Sampling Int: 0.4 Seconds

Data:



Analysis: Channel A

	Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
	1	2.600	N1	193541	1706383	31.101
	2	3.000	N2	14922	401192	7.312
	3	3.713	N3	8061	79319	1.445
D →	4	4.280	N4	7796	160537	2.926
	5	4.473	N5	7529	178927	3.261
	6	6.053	N1	3262	61484	1.120
L →	7	7.906	N1	59494	2337460	42.604
	8	9.773	N2	13143	561178	10.228
	Total Area				5486480	99.997

Peak No.	Time	Asymmetry	Efficiency

Figure 20: HPLC analysis of *L*-Alanine **(67)**.

Discussion

The syntheses of adducts **41** and **46** were accomplished by literature methods, and proceeded as expected. In both cases, only the β-anomer was formed. These results are contrary to the product predicted by the anomeric effect, however they are consistent with the "reverse" anomeric effect and/or steric effects.[74,75]

The anomeric effect is defined as the tendency of an electron withdrawing aglycon at the C-1 position of a tetrahydropyranyl (THP) derivative to occupy preferentially the axial conformation.[74,76] This effect is said to result from the electronic demands of the THP system rather than steric effects. If steric effects controlled aglycon substitution, the major conformer would have the aglycon in the equatorial position, as this minimizes steric repulsion between this group and the C-3 and C-5 hydrogens (Figure 21). The electronic effects said to be responsible for the anomeric effect have been rationalized according to two separate postulates: The first postulate states that dipole interactions are minimized when the charges associated with the dipoles are anti to each other ((**54**), Figure 22). These dipoles result from the lone pair electrons of the THP ring oxygen and the polar bond between the sugar and the aglycon. When the aglycon is in the equatorial position, as seen in **55**,

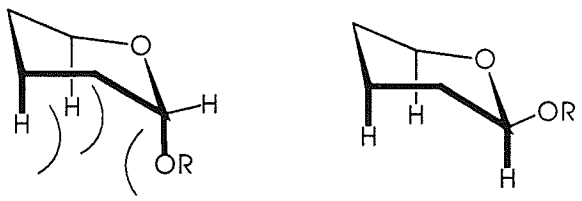
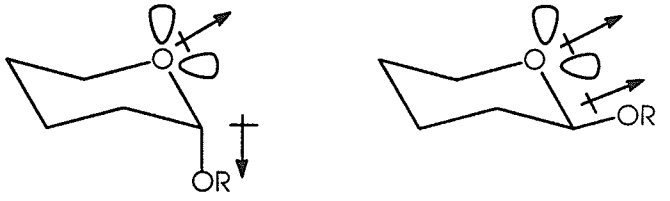


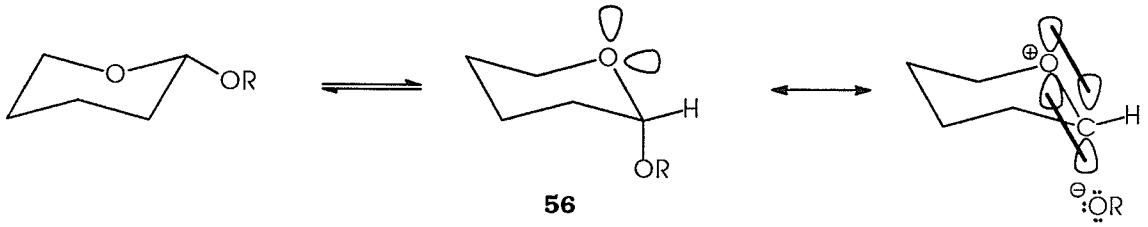
Figure 21



54 **55**

Figure 22

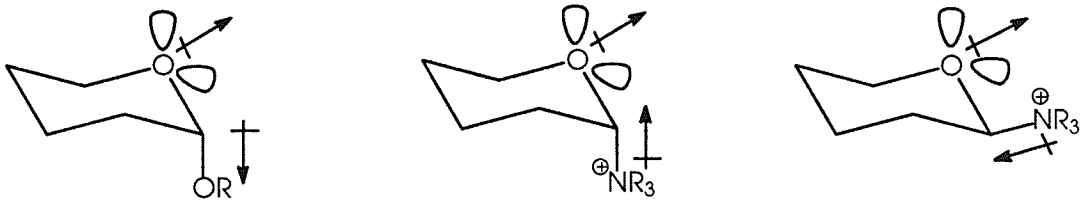
the dipoles are oriented gauche to each other and consequently the system is destabilized due to dipolar repulsion. The second, and favored,[76] postulate is based on molecular orbital interactions between a high energy donor orbital (*n* belonging to the nonbonded electrons of the ring oxygen) and an empty lower energy acceptor orbital (σ* of the C-1-aglycon bond). This interaction has been termed the "double bond/no bond model",[74,76] and is seen in Scheme 36. In this case orbital overlap is most effective in the system that has the electron donor (lone pair electrons of the THP oxygen) antiperiplanar to the electron acceptor (the electronegative aglycon) (**56**).[77,78] This orbital mixing accounts for the greater stability of the axial conformer in comparison with the equatorial where hyperconjugation of the system cannot occur.



56

Scheme 36

The tendency of a positively charged or a less electronegative substituent to occupy the equatorial position of the THP derivative has often been called the "reverse" anomeric effect.[78] The magnitude of this effect has been said to result from more than steric preferences, and has sometimes been attributed to electrostatic forces.[78] The dipolar interactions mentioned earlier reverse upon introduction of an electropositive substituent, as seen in Figure 23. This results in a favorable through space interaction between the dipoles when the aglycon is in the equatorial position (**57**).[74] Recently Perrin and Armstrong have questioned the validity of this hypothesis, and in response have asserted that the "reverse" anomeric effect is simply a steric effect.[75]



57

Figure 23

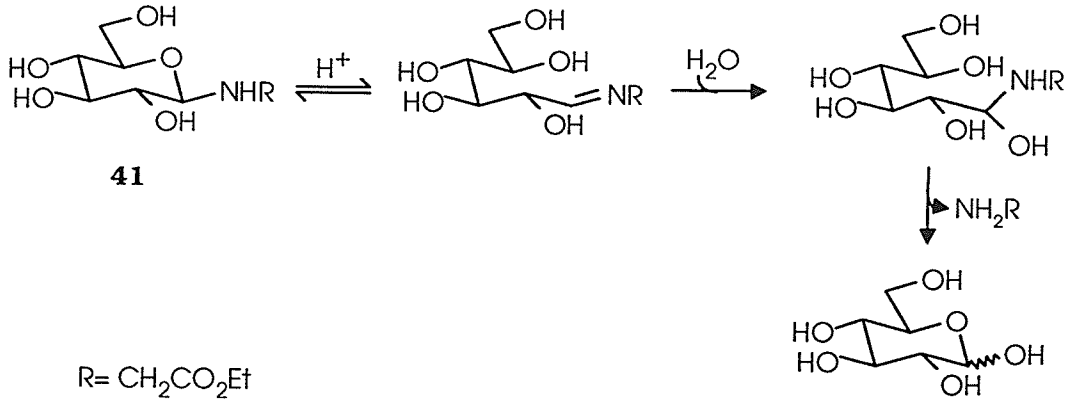
Perrin and Armstrong believe that there is no validity to the term "reverse" anomeric effect. In contrast, they believe that the preference for some substituents to occupy the equatorial position is strictly due to steric control.[75] In their studies, using a variety of substituted glucosamines, they found that the equatorial conformation was preferred for both cationic and neutral amines. Furthermore when they compared this preference to that seen in cyclohexanes, they found little difference between the A values of the substituents for both systems.[75] Since the A value measured in the cyclohexane system is a measure of the purely steric preference for the equatorial conformation, and since the values for these systems are close, it follows that the formation of *N*-glycosides under thermodynamic conditions is predominantly under steric control. If the "reverse" anomeric effect were operational in this system then one would expect the A value of the system to be significantly greater than that calculated for the cyclohexane system, however this was not observed.[75]

The exocyclic nitrogen substituent in our system likely occupies the equatorial conformation for the following reasons:

1. The condensation reaction is reversible, therefore the thermodynamically favored product will predominate.
2. Nitrogen is less electronegative than oxygen or a halide, so the anomeric effect is not operative in this system.

3. The C-N bond is shorter than the C-O, or C-X bond, and thus there is more steric interaction between the ring substituents and the exocyclic amine group.
4. There are more substituents associated with a nitrogen, than an oxygen or a halide, which also results in increased steric crowding.

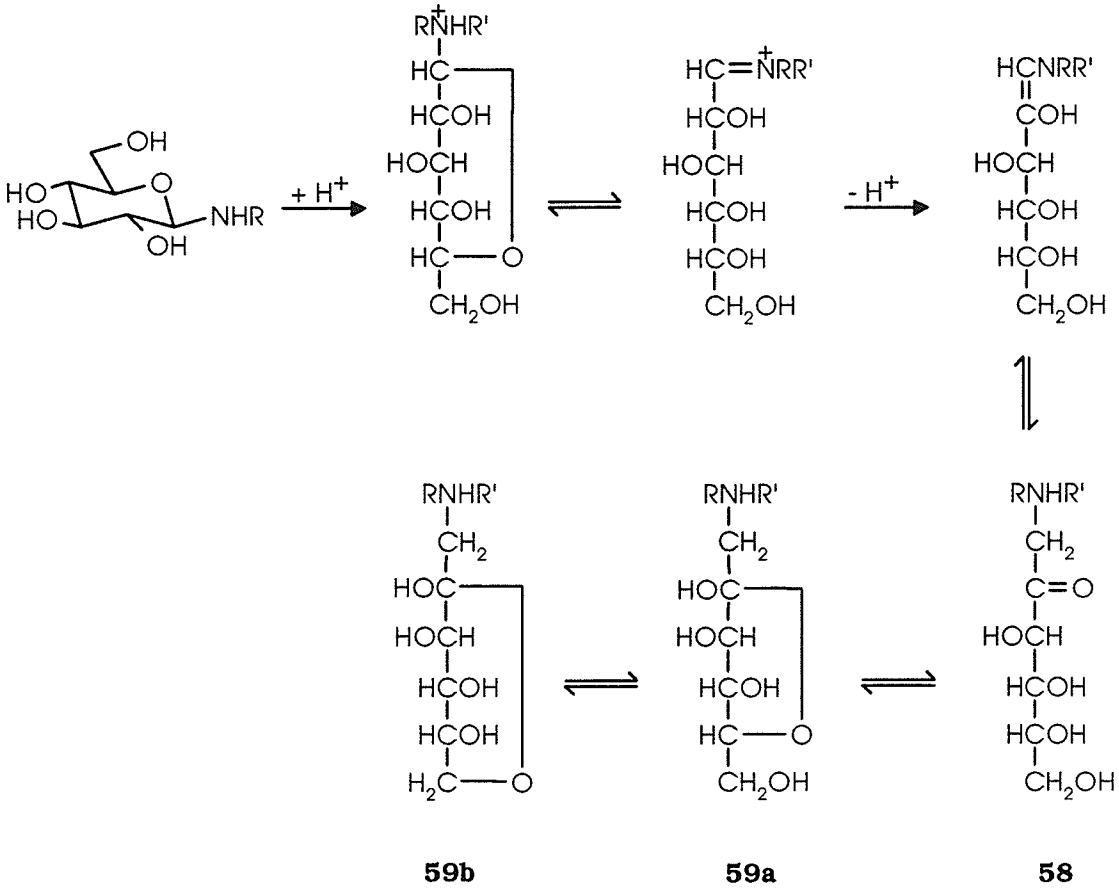
It is a well-known fact that the *N*-glycosidic linkage is readily cleaved under mild acid conditions.[79] This hydrolysis was evidenced by compound **41**, which when placed in D_2O, underwent rapid, partial hydrolysis to give *D*-glucose, glycine ethyl ester and adduct **41**. Hydrolysis of glucosamines occurs via the Schiff's base, and is under general acid catalysis (Scheme 37).[80] This mechanism clearly illustrates that the non-bonded electron pair of the amine plays an essential role in hydrolysis. Consequently we chose to protect the amine using carbobenzyloxy chloride. Carbamate **42** (see page 43) is stable to acid hydrolysis as there are no lone pair electrons available to



Scheme 37

participate in this reaction. Another drawback to unprotected glucosamines is that they are susceptible to rearrangement under acidic conditions. They commonly undergo what is called the Amadori rearrangement, (Scheme 38), in which an aldosylamine is converted to a 1-amino-1-deoxy-2-ketose (**58**).[81] Here too protection of the amine as an amide prevents this rearrangement for the same reasons discussed

earlier. The danger of the Amadori rearrangement is that the amino group is no longer at the anomeric position of the sugar (**59a/59b**), thus eliminating the potential to prepare the proposed bicyclic template (**39**).



59b **59a** **58**

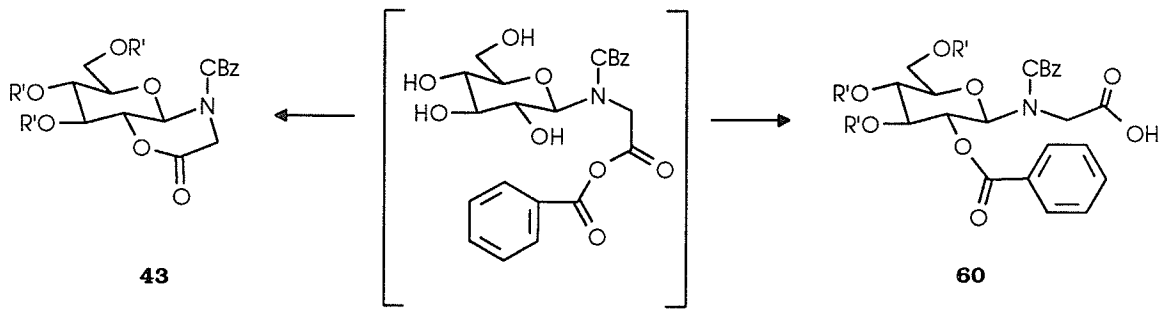
Scheme 38

The stability of carbamate protected **42** was tested in aqueous acid and base solutions ranging in pH from 0 to 14. These samples were monitored for changes over a 49 hour period by tlc. The only observable change was the hydrolysis of the ester group in the basic solutions between pH 12-14. Compound **42** was also found to be stable in DMSO at 110°C over a span of 26 hours. Again tlc showed no hydrolysis or rearrangement. This test was important since rotation of the C-N bond of the carbamate protecting group is slow on the nmr time scale at 300 K. This resulted in severe line

broadening in the ^1H spectra of **42**, which could be overcome by heating the sample to 383 K and acquiring the spectrum at that temperature.

Three different procedures were followed in the preparation of oxazinone **39** with varying degrees of success. The first method involved dicyclohexylcarbodiimide to activate the carboxylic acid, however this method was completely unsuccessful. A second route involving an excess of HCl in refluxing acetic acid, produced unprotected **39** which upon addition of Ac_2O yielded **39** (R=Ac). Although this method was effective, it required long reaction times, 72 hours, and the yields were ~50%. The third and most successful formation of the oxazinone was accomplished using benzoic anhydride (or acetic anhydride) in pyridine to give **43** (R'=Bz) in 60 % yield. Other researchers have used mixed anhydrides to prepare lactones, and some groups found that lactonization is sensitive to the ionic state of the carboxylic acid salt.[82] This group obtained a 1:1 mixture of the desired lactone and the acetylated alcohol products when the starting material was obtained from a solution at pH=3 (forming the protonated carboxyl), however when the solution was concentrated at pH 8 or 9 (forming the sodium salt), lactonization predominated. Since their experience indicated that the ionic state of the carboxyl group was important we performed the lactonization starting with the sodium carboxylate (**42**) isolated from aqueous solution at pH≈9.

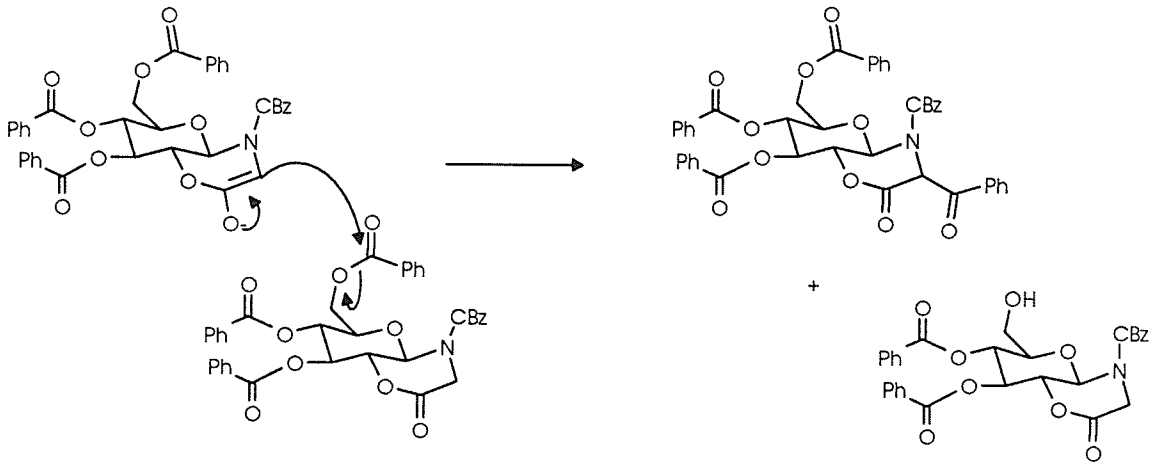
There are two possible products that can be obtained from the mixed anhydride intermediate, and they are shown in Scheme 39. We found that **43** was obtained exclusively, and no trace of the acylated alcohol (**60**) was observed. This is due to the fact that **43** passes through a "6-Exo-Trig transition state" which, according to Baldwin's rules, is favored, while the formation of **60** would necessitate an "8-Exo-Trig transition state" which according to Baldwin is disfavored.[83]



43 **60**

Scheme 39

Although the route to oxazinone **43** outlined in Scheme 32 resulted in the desired bicyclic template (**39**), this was not the optimal template for enolate chemistry as it contained benzoate protecting groups on the sugar hydroxyls. The presence of ester groups during alkylation will likely result in decreased yields of alkylated product due to the competing Claisen condensation reaction (Scheme 40). Furthermore, even if alkylations were successful benzoate ester groups protecting the alcohols would be susceptible to hydrolysis under the mild acid or base conditions that would likely be used separate the amino acid from the sugar. This would be undesirable as this would result in a partially unprotected sugar, whereas we would like to recycle the protected sugar for use as a chiral auxiliary in future syntheses.



Scheme 40

Based on this we thought that protecting the sugar hydroxyl groups as ether derivatives would be preferable, as these groups do not interfere with alkylation nor are they vulnerable to mild base hydrolysis. Although we were able to synthesize the unprotected template **39** (R=H), related work in our laboratory indicated that ether protection would be unsuccessful, as **39** would likely be unstable at the necessary reaction conditions.

These issues led to the route shown in Scheme 33 which began with tri-*O*-benzyl-*D*-glucal. Following catalytic osmylation to give **45**,[84] the remaining steps of the sequence involved the same reagents as those used in Scheme 32. This route is preferable to the first route since it begins with a protected sugar and it leads to crystalline intermediates which simplify purification. Although this method begins with a costly starting material, it is possible to reduce this cost by preparing tri-*O*-benzyl-*D*-glucal from glucose. We chose to begin with the protected glucal as we wished to determine as quickly as possible whether our template would in fact lead to a viable method for the production of α-amino acids.

Once the protected oxazinone (**44**) was obtained it was necessary to determine whether or not our "chiral glycine" was in fact able to undergo alkylations diastereoselectively. The enolate intermediate (**49**) was generated with lithium hexamethyldisilazide (LiHMDS) in THF. Work by Williams et al.[54,55] indicated that this base functioned to deprotonate oxazinones without the degradation seen when LDA was used. This may be a result of two factors associated with LiHMDS, the first being that this base is more sterically hindered, thus less nucleophilic than LDA, and the second being that it is less basic than LDA. The pK_a of the conjugate acid of LiHMDS is ~29.5 as compared to 35.7 for LDA (as measured in THF).[85]

We did however have some trouble with the alkylation reaction. We found that we were unable to obtain complete conversion of the oxazinone to product, and that there was some degradation that occurred during the alkylation reactions, even when performed at -100°C.

It is well known that lithium enolates form aggregates in THF.[86,87] These aggregates are most commonly found as tetramers, although dimers and hexamers have been seen to exist.[88] Studies of these tetramers have revealed that they often aggregate to form cubic structures in solution,[89] similar to those seen in Figure 24. The steric bulk surrounding lithium and the enolate likely hinder alkylation, which may account for the decreased product yields. Enolates generally prefer electrophilic approach from an angle of 109° with respect to the plane of the C=C bond (the Bürgi-Dunitz trajectory angle), but due to severe crowding in the aggregate, this may not be possible. It has also been postulated that the electrophile undergoes coordination with lithium[88b,90] prior to alkylation of the enolate, and this too may be inhibited due to excessive steric crowding of lithium aggregates. In a study, of the reactivity of

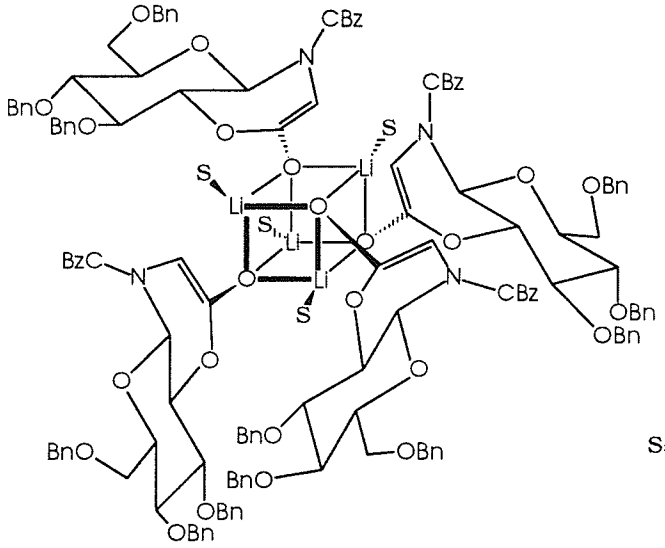
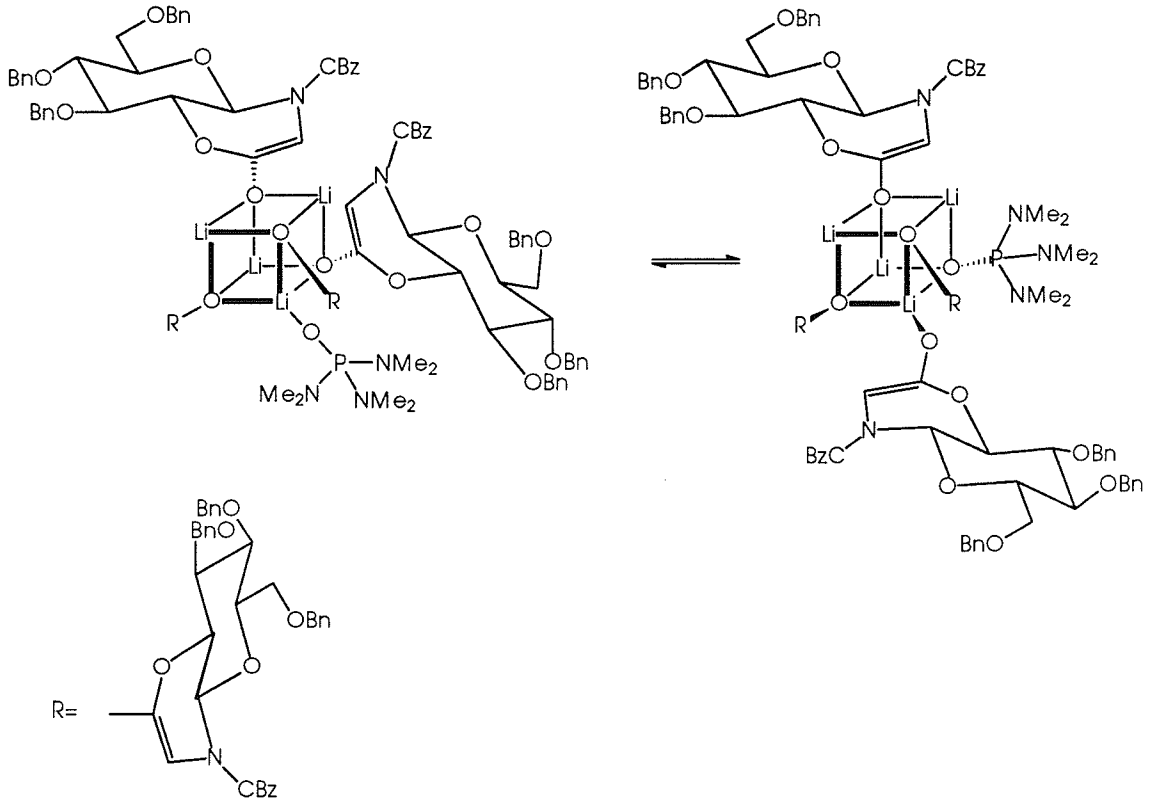


Figure 24

carbohydrate ester enolates, Kunz observed inertness toward electrophiles in cases where the counterion was strongly complexed with both the enolate and the sugar oxygens of the system.[90] He attributed this phenomenon to steric crowding of the lithium cation which is pivotal to electrophilic addition to enolates. He concluded that in order for alkylation to occur the electrophile must have access to both the nucleophilic site and the lithium counterion, and in the absence of one of these factors there would be no reaction.

House et al. studied the relationship between enolate reactivity and solvent polarity.[91] They found that slight increases in electron donating ability of the solvent resulted in stronger solvent-cation coordination, which in turn resulted in increased enolate reactivity. Based on their observations we attempted to methylate the oxazinone in DME. Although DME is a better electron donor than THF, it lead to increased degradation and decreased alkylation yield, thus we reverted to THF. HMPA was then added to the reaction solvent and it was seen that this polar aprotic co-solvent resulted in a significant increase in the yield of alkylation product **50a**, and a decrease in degradation. In the presence of HMPA, methylation to produce **50a** increased from 23% (in THF) to 55% (in THF/HMPA); allylation to produce **50b** and **51a** rose from 25% (THF) to 51% (THF/HMPA); and benzylation resulting in **51b** increased from 0% (THF) to 25% (THF/HMPA) (see Table 1, page 45). This increase in enolate reactivity may result from isomerization of the cubic structure of the aggregates as seen in Scheme 41. This isomerization results in the enolate being further removed from the cubic structure of the aggregate thus allowing the electrophile greater access. Although HMPA results in increased alkylation, it also results in the production of dialkylated products for allylation and benzylation. A review focusing on enolate reactivity stated that conditions favoring aggregation function to suppress

intermolecular proton transfer (between an enolate and an alkylated product), and hence reduce dialkylation.[88] This was observed in our system: when allylation was performed in THF (conditions which favor aggregation) strictly **50b** was obtained, yet in the presence of HMPA (conditions which favor disaggregation) both **50b** and **51a** were isolated.



Scheme 41

Williams and Im also experienced problems with dialkylation, however they were able to overcome these problems by altering the order of reagent addition.[55] Their alkylations were performed according to one of the two following sequences: The first sequence (sequence A) involved deprotonation of the oxazinone prior to the introduction of the electrophile, while the second sequence (sequence B) introduced the electrophile prior to deprotonation of the oxazinone. Sequence A resulted in

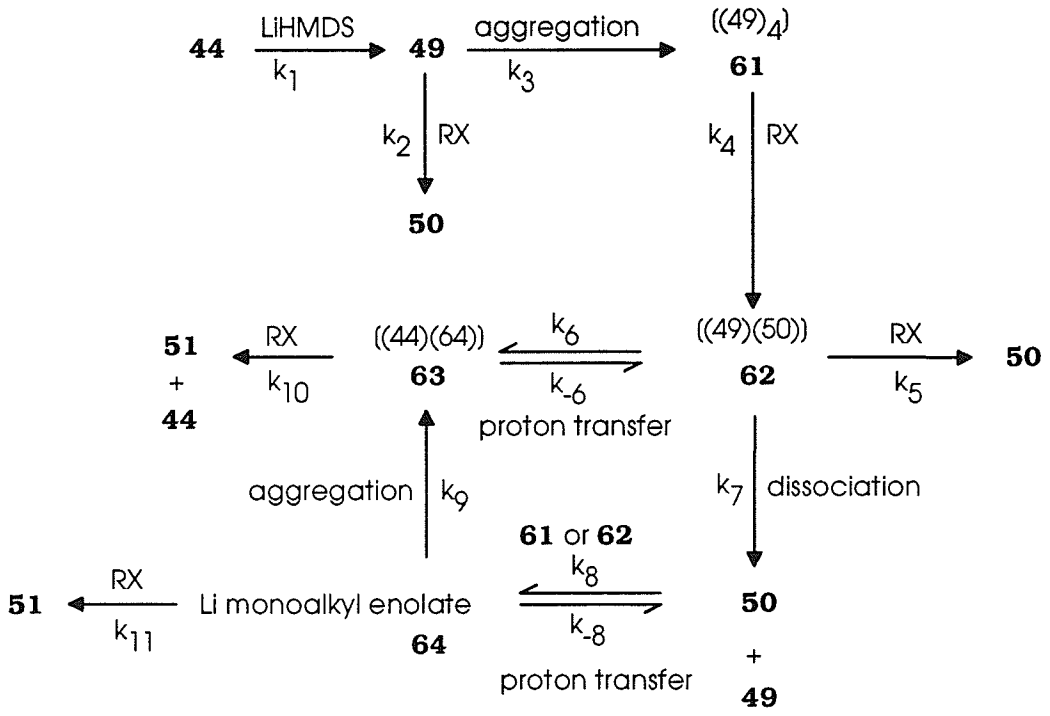
predominantly dialkylated products, while sequence B yielded mostly monoalkylated products. Dialkylation was rationalized based on an aggregation complex similar to the one illustrated in Figure 24. This aggregation complex is composed of both the enolate and the monoalkylated product placing them in close proximity, thus facilitating intermolecular proton transfer.[55] Should transfer occur, it would produce a substituted enolate which could undergo a second alkylation, resulting in dialkylated products. The successful monoalkylation sequence (sequence B) was explained by suggesting that the presence of the electrophile prior to deprotonation functions to competitively alkylate the enolate prior to aggregate formation. This reduces the opportunity for intermolecular proton transfer, and thus dialkylation is reduced.[55]

Based on these observations, we changed our procedure from sequence A to that illustrated in sequence B for the allylation of **44**. This change in sequence however did not result in a change in product yield. We still obtained a mixture of mono-and di-allylated product in nearly equal amounts, suggesting that our oxazinone behaves differently from Williams' oxazinone. This leaves us with a question as to why dialkylation occurs for allylation and benzylation and not for methylation. This may be rationalized by one of two theories: The first theory involves the relative rates of proton transfer vs. alkylation, and the second theory addresses the relative rates of alkylation vs. aggregation.

Proton transfer vs. alkylation:

Scheme 42 indicates that following deprotonation of **44**, enolate **49** can either undergo alkylation to the monoalkyl product (**50**), or it can form an aggregate (**61**). If **61** is formed, then it can undergo reaction to form a partially alkylated aggregate **62**. Further alkylation of **62** (k_5) must compete with two other processes. There may be an

intra-aggregate proton transfer to enolate **49**, producing aggregate **63**, made up of neutral oxazinone **44** and monoalkylated Li-enolate **64**. It may also dissociate without further reaction giving monoalkylated **50** and free enolate **49**. Alkylation of **63** or **64** will result in the production of dialkylated products (**51**).



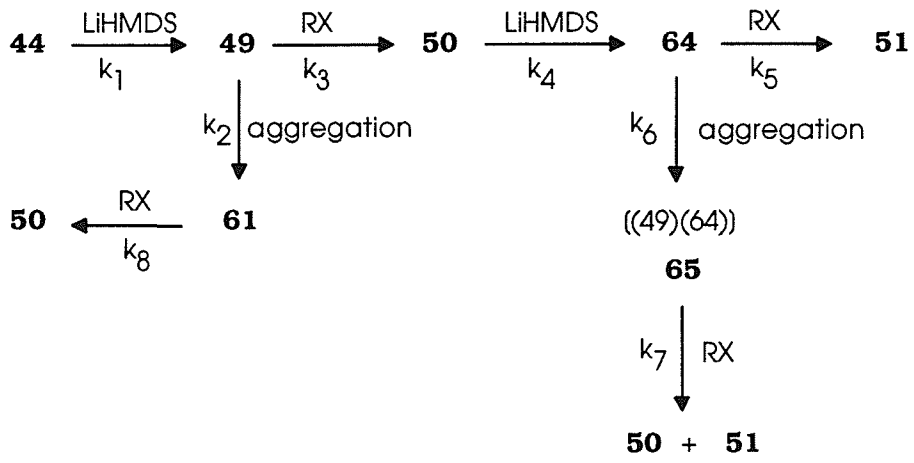
Scheme 42

This proposal has two possibilities to consider. The first assumes that proton transfer occurs prior to dissociation of **62** ($k_6 > k_5, k_7$). Based on this model our results suggest that methylation occurs faster than proton transfer between an enolate (**61** and **62**) and **50** (k_2 and $k_5 > k_6$ and $k_7 \cdot k_8$), as we obtain exclusively **50**. The allylation and benzylation results, indicating an equal mixture of products **50** and **51**, suggest that proton transfer occurs at a rate comparable to that of allylation and benzylation (k_2 and $k_5 \approx k_6$ and $k_7 \cdot k_8$). If these two observations are taken together it would appear that the rate of methylation is much faster than the rate of allylation and/or benzylation. However these rates have been studied for S_N2 reactions, and it is known that in general

this is not the case. In fact, the rate of benzylation is typically faster than the rate of allylation which in turn is faster than the rate of methylation.[92,93] Once the enolate has undergone alkylation, it is no longer charged resulting in a weak electrostatic interaction between the product and the metal, which would likely lead to deaggregation of that complex. Thus it seems reasonable that deaggregation occurs prior to proton transfer ($k_7 > k_6$). Then proton transfer would occur between a monoalkylated product (**50**) and an aggregated enolate (**61** or **62**), thus generating a monoalkyl enolate (**64**) which could then undergo a second alkylation to produce a dialkylated product (**51**). This method of proton transfer seems rather unlikely, because it would necessitate a proton transfer between a bulky proton donor (**50**) and a very sterically hindered proton acceptor (**61** or **62**). Although allyl bromide and benzyl bromide are bulkier than methyl iodide, they are still significantly smaller than **50**. This difference in steric bulk renders proton transfer between the aggregated enolates and the monoalkylated products unlikely in the presence of other more reactive and smaller electrophiles.

Rate of aggregation vs. rate of alkylation:

The proposal illustrated in Scheme 43 assumes deprotonation is slow ($k_1 < k_2$ and k_3) and that alkylation and aggregation are competitive processes ($k_2 \approx k_3$). Since it is known that allyl bromide and benzyl bromide are usually more reactive than methyl iodide in S_N2 reactions,[93] it is possible that these rates, in combination with the rate of aggregation, will explain the dialkylation results. If no proton transfer is involved then it is only a question of the rates of alkylation and aggregation. Substitution can occur between the electrophile and either the free or the aggregated enolate (**49** or **61** respectively).



Scheme 43

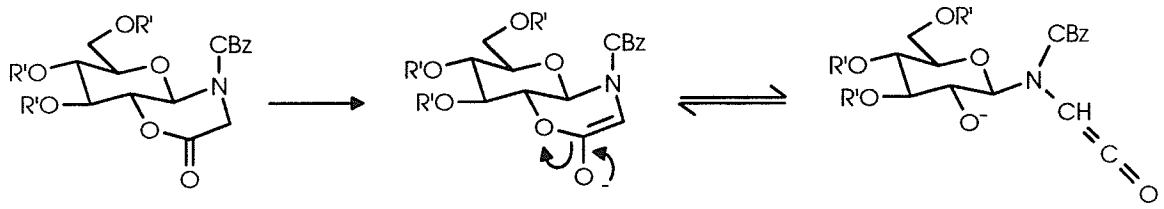
If deprotonation by LiHMDS is slow, then it is possible that this process has not gone to completion by the time the electrophile is introduced to the reaction. This would mean that some alkylation could occur and that these monoalkylated products (**50**) could be deprotonated by the base that has yet to react. This would lead to the possibility of an immediate second alkylation by the electrophile or to the formation of mixed aggregates (composed of substituted and unsubstituted enolates, **65**) which could then undergo alkylation to yield a mixture of products **50** and **51**. The production of mixtures of **50** and **51** would occur in cases involving highly reactive electrophiles, where the rate of electrophilic substitution is equal to or exceeds the rate of aggregation ($k_3 \geq k_2$). In cases where the rate of aggregation is faster than the rate of substitution ($k_2 > k_3$), then one would expect to obtain primarily the monoalkylated product. These conclusions appear consistent with our results since the less reactive electrophile (methyl iodide) resulted in monoalkyl products, while the more reactive electrophiles (allyl bromide and benzyl bromide) produced mixtures of mono- and di-alkylated products.

The validity of this hypothesis could be tested by adding an equimolar mixture of allyl bromide and methyl iodide to the deprotonated oxazinone followed by the isolation, characterization and the quantitation of the products obtained. If a majority of the products possessed an allyl substituent, (whether it be monoallyl, diallyl or both allyl and methyl) then it would support the proposal that allylation occurs competitively with aggregation, and that aggregation occurs prior to methylation.

Another factor that supports the theory based on alkylation occurring faster than proton transfer is that the monoalkylated products are produced in very high diastereomeric excesses. This suggests that if the monoalkylated enolate is formed, either free or aggregated, it alkylates rapidly to give the dialkyl product **51** and does not survive to epimerize.

A third factor responsible for disappointing alkylation yields may be degradation of the enolate. Evidence for this was the significant amount of polar baseline material observed on tlc monitoring of these reactions. The stability of the enolate was tested. The enolate was prepared (from **44**) using sodium hexamethyldisilazide (NaHMDS) in THF at -100°C. Samples for tlc were quenched with aqueous ammonium chloride and were extracted with EtOAc prior to analysis. These samples were taken at 15 minute intervals during a one hour period. After 15 minutes a significant amount original oxazinone **44** had decomposed to a more polar substance and baseline material and after 30 minutes none of the oxazinone remained. Degradation may be observed in this situation as the enolates of esters are considerably less stable than enolates of ketones, aldehydes and amides. Ester enolates can undergo elimination to produce a ketene and an alcoholate (**66**) (Scheme 44), although this typically requires temperatures of >-20°C.[94,95] Kunz and Mohr have shown that carbohydrate ester enolates may undergo this elimination even at temperatures below -70° C.[90] This

elimination may actually be facilitated by the formation of aggregates as illustrated in Figure 24. It is possible that lithium is coordinated to the ring oxygen of the enolate (rather than to the solvent), and it is this coordination that functions to stabilize the incipient alcoholate anion, thus assisting ketene formation. Another factor that may favor ketene formation from enolates of carbohydrate enolate esters arises from the enhanced acidity of the carbohydrate hydroxyl groups.[96] The pK_a of a hydroxyl group of a glucose derivative is ~12.5, where as the pK_a of an alcohol is approximately ~15-16 (depending on the R-group).[97,98]



44 **49** **66**

Scheme 44

The formation of a ketene and an alcoholate presents an opportunity for a variety of side reactions to occur under the existing conditions. They are:

- attack on the ketene by hexamethyldisilazane resulting in an amide
- the ketene could be attacked by other enolates
- the alkoxide will likely undergo alkylation upon addition of an electrophile
- an aqueous acid quench of the reaction would likely protonate the alkoxide and hydrolyze the ketene (to a carboxylic acid)

Although any of these side reactions may be the decomposition product, we did not isolate or investigate these products in any detail.

The diastereoselectivity of these alkylations was determined (for the monoalkylated compounds) by nmr analysis of both crude and purified samples of **50a** and **50b**. The spectrum for **50a** revealed that there were two signals at δ 1.65 (major isomer) and

1.83 (minor isomer) which corresponded to the methyl protons (Figure 14). The diastereomeric excess was calculated based on the integration of these two sets of signals, and the d.e. for methylation was 92%. It was not possible to calculate the d.e. for allylation as there were no signals corresponding to a minor diastereomer of **50b** visible in the nmr spectrum, therefore we can only estimate that the d.e. was >95%.

Once we had determined that alkylation proceeded with excellent diastereoselectivity, we then wanted to determine which face of the enolate was being alkylated. The facial selectivity of these reactions was determined using nuclear Overhauser effect (nOe) difference experiments on the monoalkylated products. These experiments are used to obtain information about the distances between nuclear spins.[99] The nOe is measured as a change in the intensity of the signal due to one resonance when the nmr transitions of another nucleus are saturated.[100] A large nOe corresponds to domination of the relaxation pathways by dipolar interactions. Since dipolar coupling is a very sensitive function of distance, nOe can be used to predict internuclear distances. The maximum homonuclear coupling (nOe=50%) is observed for ^{1}H nuclei that are separated by only their van der Waals' radius (~2.40 Å).[101] As this distance increases, the nOe decreases such that an nOe of less than 5% corresponds to an internuclear separation of greater than 3.4 Å.[101] The maximum nOe possible is calculated to be 50%, however this value is based on an ideal system where the nuclei in question exist in isolation. In real systems nuclei do not exist in isolation, and as a consequence a variety of relaxation pathways are usually present for any given nucleus. The presence of other protons within the molecule are very important as well as residual protons in the solvent and dissolved paramagnetic oxygen, all of which are able to participate in the dissipation of the magnetization induced by saturation of the system. Figure 16 shows the nOe difference spectrum for compound **50a**. Saturation of

the methyl signal resulted in a 14% increase in intensity of the H-8a proton signal and an 18% increase in the H-3 proton signal. It is important to note that these values might be even greater than their values indicate, had we taken care to remove oxygen from these samples prior to measuring the nOe, since paramagnetic oxygen can provide an alternate pathway of relaxation to the system, thus decreasing the observed nOe. The nOe observed between the methyl group and the H-8a proton suggests that these two nuclei are close, likely occupying the same face of the chiral template. The nOe spectrum for the saturation of the anomeric proton was obtained and no increase in signal intensity of the methyl protons nor of the H-3 proton was observed, suggesting that these nuclei are distant. Based on these results, we proposed the structure (possessing the configuration and the conformation) seen in Figure 16 as belonging to **50a**. This structure has the oxazinone portion of the template in a boat conformation with the methyl group occupying the axial position and the same face as the H-8a proton. This conformation and configuration are consistent with the nOe data as they place the CH_3 group and H-8a hydrogen in close proximity, while maximizing the distance between the anomeric hydrogen and the H-3 hydrogen.

Similar nOe studies were performed with compound **50b**. Saturation of the methylene signal of the allyl group increased the intensity of the H-8a signal by 15%, and the H-3 signal by 14%. No nOe was observed for the H-3 proton nor for any of the allyl protons upon saturation of the anomeric proton signal. The results obtained by nOe for **50b** compare favorably with those obtained for **50a**, therefore we believe that the allyl group occupies the same face as the methyl group, and that both structures have the same boat conformation (Figure 17). Once the diastereoselectivity for the alkylation of **44** was determined we wanted to understand the source of this facial bias.

This information was obtained from a combination of molecular modeling, nmr and nOe studies of **44**, **49**, and **50a**.

AM1 molecular modeling studies were performed using the Spartan program to find the lowest energy conformation for compound **50a**, the results of which are shown in Figure 25. The predicted structure indicated that the sugar portion of the template maintained a chair conformation, while the methylated oxazinone ring adopted a boat arrangement. These results were consistent with those obtained from the ^{1}H ^{3}J coupling constants for the sugar ring hydrogens and from nOe experiments which showed the H-3 methyl group and the H-8a proton in close proximity. The internuclear distance between these two groups was calculated by Spartan to be 2.88 Å.[v] The close correlation between these two experiments persuaded us to perform AM1 studies on the conformations of the oxazinone (**44**) and the enolate (**49**) the results of which are shown in Figure 26 and Figure 27 respectively. The stable conformation of **44**, as calculated by AM1, possessed the same boat geometry as **50a** and both structures placed the ring nitrogen in a slightly pyramidal geometry. It is likely that the nitrogen is pyramidalized in these conformations to reduce eclipsing between the carbamate protecting group and the sugar ring oxygen that would exist if nitrogen were planar. The boat conformation in these structures was predicted to be the only stable conformation by the modeling program. The chair conformation was not observed to be associated with an energy minimum according to AM1 calculations. In this structure there would be significant destabilization of this conformer due to Van der Waals interactions between the equatorial H-3 methyl group and the carbamate carbonyl.

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[v] This value corresponds to the distance between the carbon nucleus of the H-3 methyl group and the H-8a nucleus.

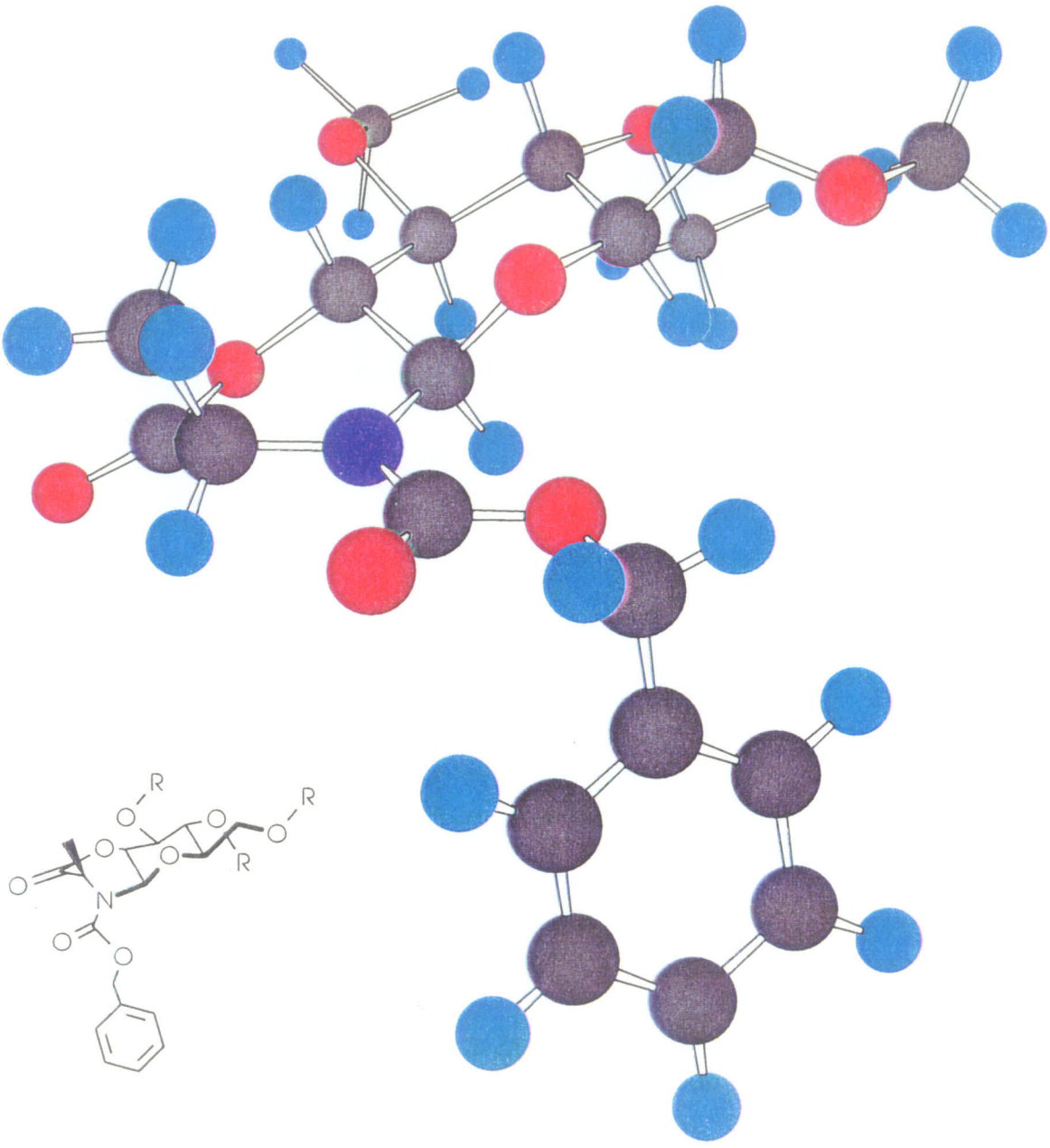


Figure 25: AM1 proposed structure for compound **50a**.

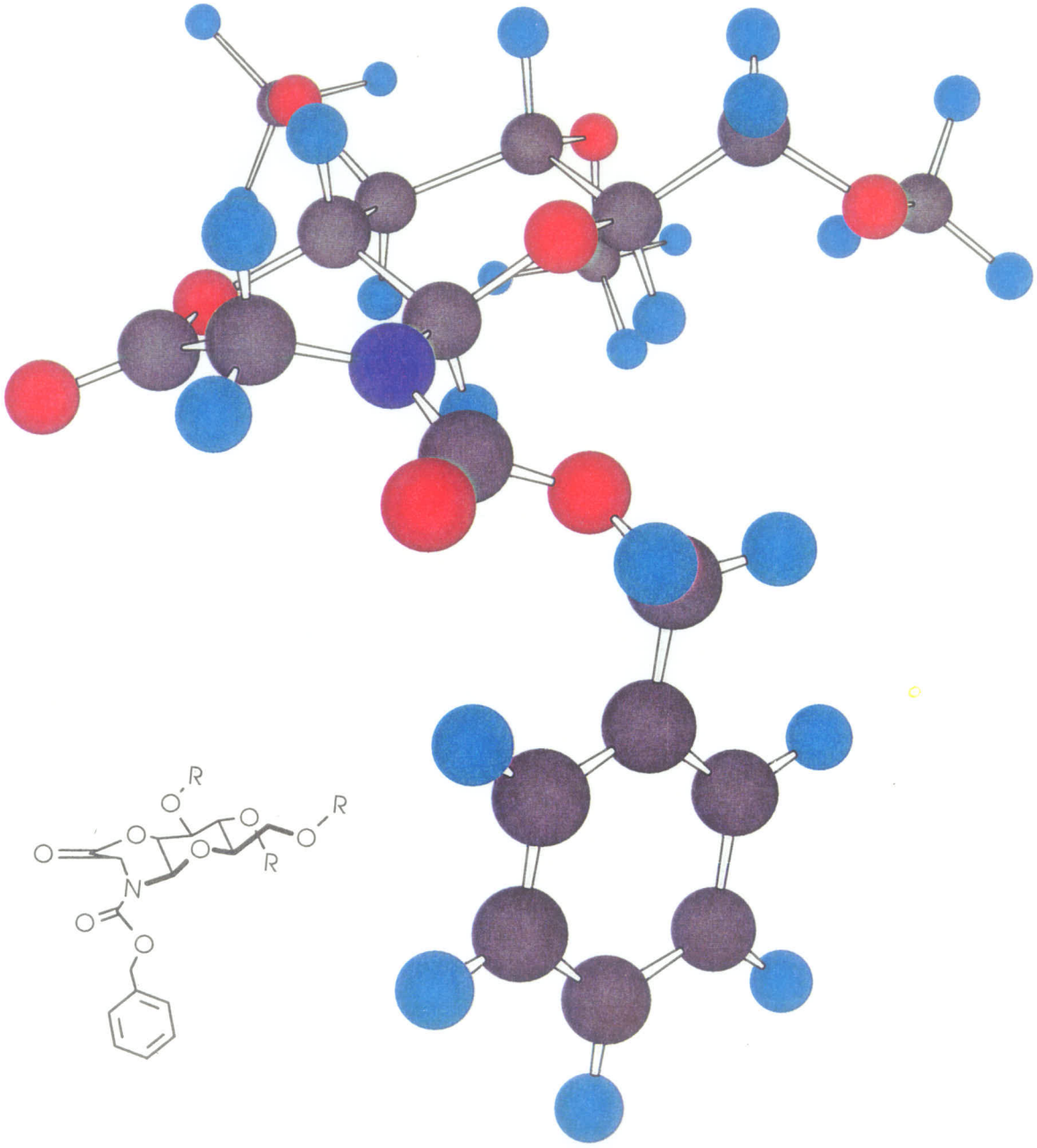


Figure 26: AM1 proposed structure for compound **44**.

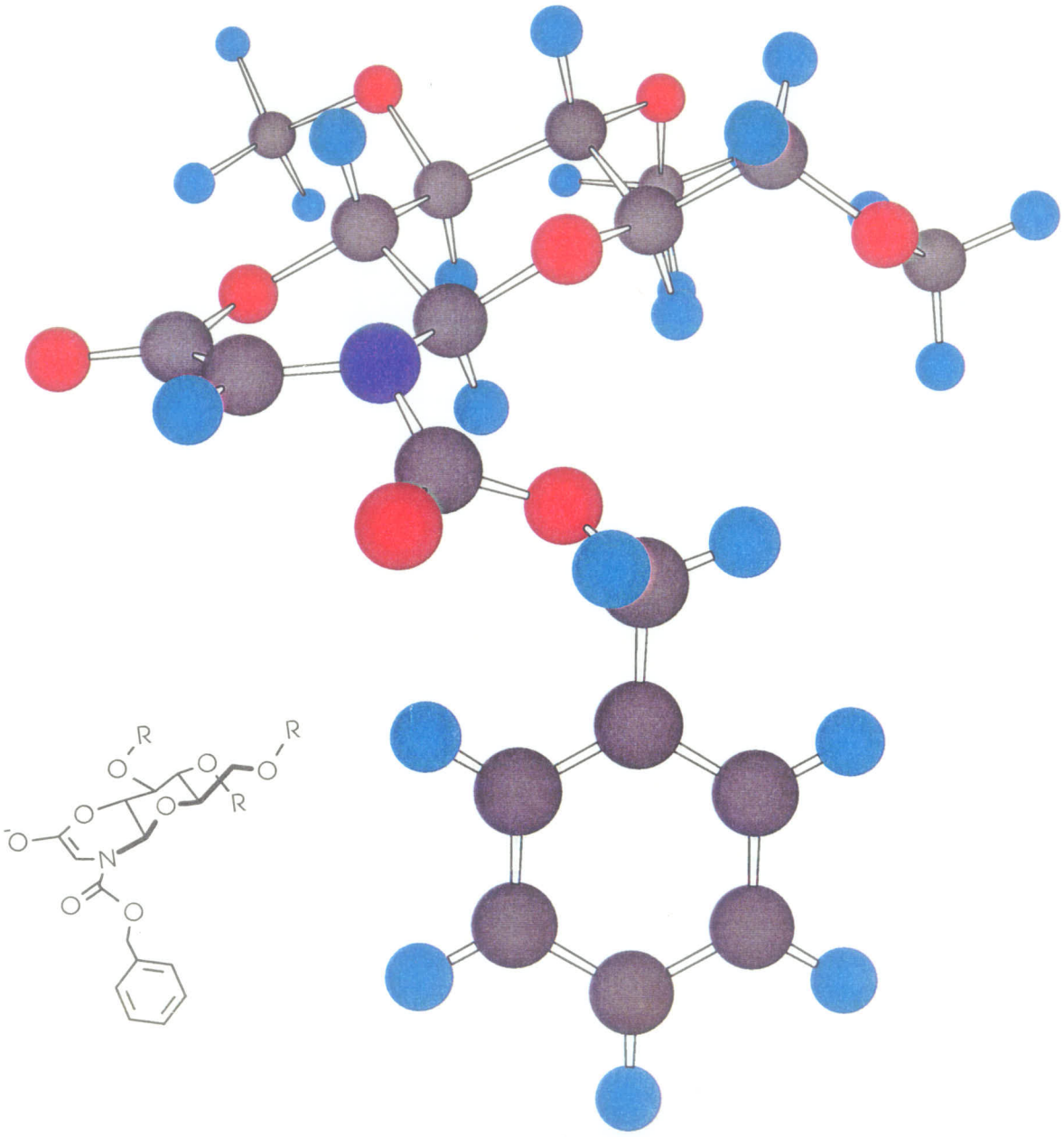
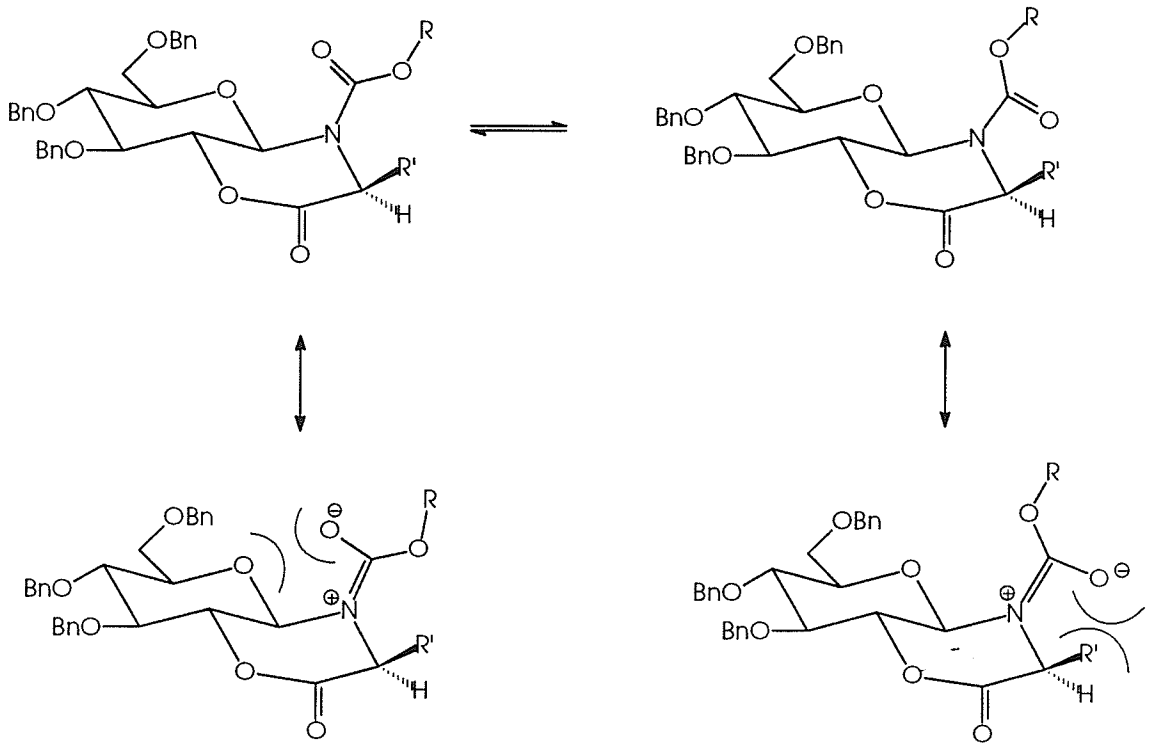


Figure 27: AM1 proposed structure for compound **49**.

The increased stability of the boat is due to a reduction of these interactions. These van der Waals interactions are similar to $A^{1,3}$ strain observed in allylic systems (Scheme 45).



Scheme 45

An alternative factor controlling the conformation of **44** and **50a** may arise from the oxazinone ester function. Ester groups have significant orbital overlap of the p-orbital of the alkoxyl oxygen and the carbonyl double bond which results in substantial double bond character of the alkoxy bond.[102] Ester groups prefer an eclipsed orientation of the carbonyl and the alkoxy groups. Eclipsing between these groups is preferred as it minimizes the steric interactions between the α-substituent of the carbonyl that arise in the trans conformation.[103] The energy difference between the cis (*Z*) and trans (*E*) isomers has been calculated to be 9.4 kcal/mol for methyl acetate, with the maximum barrier to rotation of 13 kcal/mol occurring when the carbonyl and the methoxy groups are between 90 and 120°. Small ringed lactones cannot achieve a

Z conformation. Some small ringed lactones may not be able to attain a perfect *E* conformation either. The conformation of these systems will possess a torsional angle involving varying degrees of destabilization of that system (Figure 28). For example an oxazinone may distort the angle between the carbonyl and the alkoxy group from 180°, but this will only happen if all other interactions in the ring are minimized.

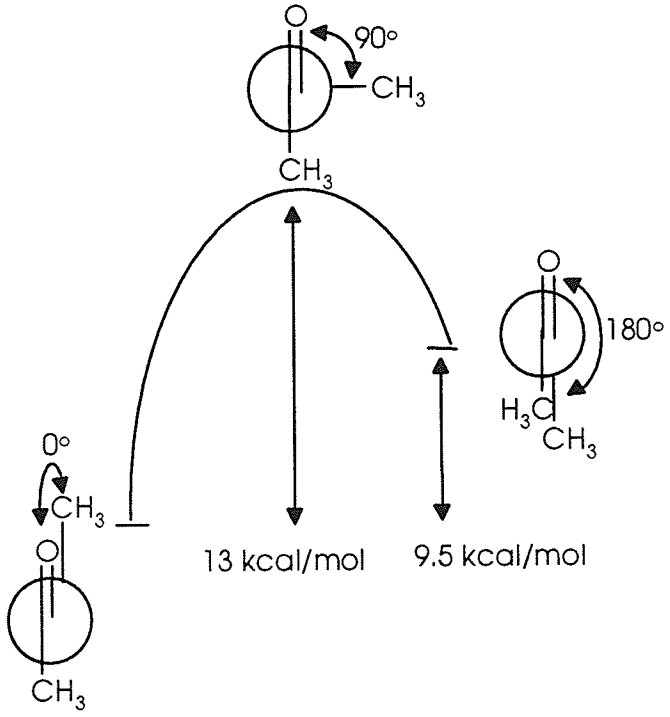


Figure 28

AM1 modeling of **44** predicts a flattened-boat conformation for the oxazinone (Figure 26), with the ester carbonyl trans (~180°) to the alkoxy substituent. In this conformation, $A^{1,3}$ strain between the carbamate and the sugar ring oxygen is minimized (Scheme 45). If the boat were to move towards the chair, rotation along the C-O bond would lead to a reduction in the angle between the carbonyl and the alkoxy groups, and it would also result in increased $A^{1,3}$ strain between the carbamate and the sugar

ring oxygen. Both of these factors would lead to a net destabilization of the system, thus no net gain in stabilization would likely result from the chair conformer.

The AM1 geometry of enolate **49** (Figure 27) had a flattened-half-chair conformation. The most striking observation of this structure was that the carbamate nitrogen was placed in a significantly pyramidalized conformation, which was calculated to be 0.36 Å out of the plane (as defined by C-3, C-4a and C=O of the carbamate). This conformation was not entirely unexpected, since Seebach et al. also observed pyramidalization of the ring nitrogen in the enolate of **30** (see Figure 9).[104] During an investigation into the crystal structures of five- and six-membered ring *N,N*-, and *N,O*-acetals they discovered that these systems underwent pyramidalization apparently to alleviate $A^{1,3}$ strain.[104] In compound **49**, if the nitrogen were planar, significant $A^{1,3}$ strain would arise between the carbamate carbonyl and either the sugar ring oxygen or the α-substituents. Pyramidalization of the nitrogen would relieve this strain. Our AM1 study indicates that the carbamate group is positioned below the oxazinone due to this pyramidalization. This orientation minimizes steric interactions between the sugar template and the carbamate. Had the carbamate pyramidalized such that it occupied the top face of the template, steric interactions between the carbamate and the sugar oxygen or the carbamate and the H-8a proton would be increased rather than decreased. Since the AM1 prediction of the enolate conformation seems reasonable, it will be used as the basis of my discussion of facial selectivity during alkylation.

Stereoelectronic effects and steric effects are two factors that influence diastereoselectivity in the kinetically controlled alkylation of enolates.

The transition state for the alkylation of an enolate is early, and as such is reactant-like in character.[105] Generally product stereochemistry for these reactions is determined by steric factors, which may yield to electronic factors when cyclic systems are involved.[106] Electrophilic addition to an enolate occurs along a trajectory close to perpendicular to the unsaturated system. Attack from this angle allows maximum overlap between the σ*-orbital of the electrophile and the π-orbital of the α-carbon of the enolate.[107] The electrophile may approach the enolate either from the top or the bottom face, therefore, along only the trajectories shown in Figure 29.

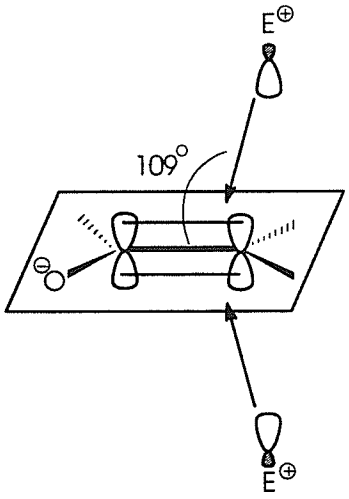
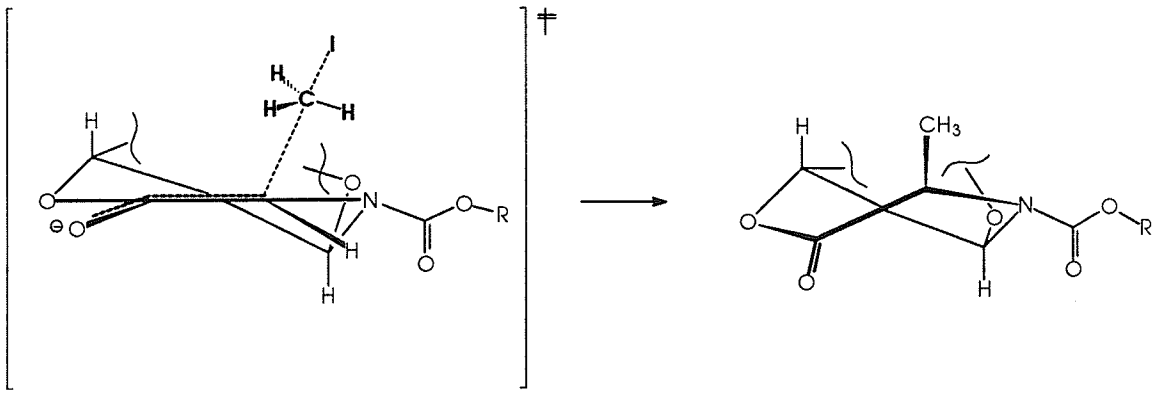


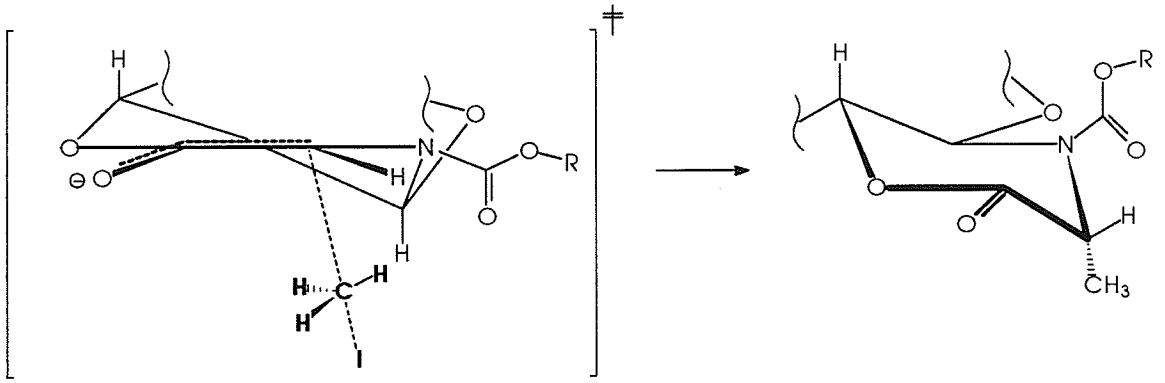
Figure 29

The principle of least motion states that reactions that involve the least change in atomic position and electronic configuration will be favored over those that involve drastic changes.[108] Attack at the top face of **49** leads to **50a** which is in accordance with this principle. The conformational change required to achieve the boat geometry



Scheme 46

of the product from the transition state is not severe, as this motion is along the reaction trajectory and essentially the only nucleus moving is the α-carbon of the oxazinone (Scheme 46). This motion does not require significant change in the rest of the template therefore requiring the least expenditure of energy to achieve the transition state. The same does not hold true for axial alkylation from the bottom face of the enolate. This approach necessitates a chair conformation to place the methyl group in an axial position. The only way that this is possible requires the enolate to undergo significant distortion as it moves toward the chair conformation (Scheme 47). Although the transition state for alkylation occurs early along the reaction coordinate some progression toward the geometry of the alkylated compound occurs. Any motion from the enolate to the chair will result in a reduction of the dihedral angle between the carbamate and the ring oxygen. This would cause increased Van der Waals interactions which would destabilize the transition state. Diastereoselectivity resulting from stereoelectronic control may be seen to favor top face approach since this path passes through a more stable transition state.



Scheme 47

As mentioned earlier, another feature controlling the alkylation of enolates is steric approach control. The conformation of the enolate proposed in Figure 27 lends itself well to a steric argument. Upon analysis of this conformation, it is obvious that the

carbamate group of the pyramidalized nitrogen hinders approach of the electrophile from the bottom face thus inducing alkylation to occur from the top face (Figure 30).

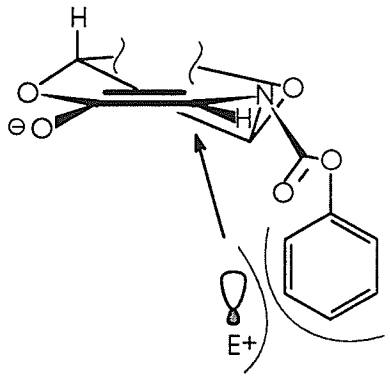


Figure 30

It is likely that alkylation of **49** is under both steric and stereoelectronic control, although since both effects favor the same product we cannot say with certainty which effect dominates.

Since our yields from the alkylation reactions were only moderate, we attempted alkylation *via* the silyl enol ether (**52**). We were able to prepare **52** with product yields between 52-58%. These reduced yields may be partially caused by Et_3NH^+-OTf produced during the reaction. Further loss of product likely resulted from chromatographic purification. Although Et_3N was added to buffer the tlc solvent, it was not added to the solvent used for chromatography, and as a result some degradation of the product arose due to the acidity of the silica gel. Following the isolation of **52** we attempted to effect alkylation with allyl bromide and $ZnCl_2$. These reactions strictly resulted in degradation of the starting material, and no visible trace of **51a**.

The final series of experiments involved the cleavage of alanine from the chiral auxiliary, **50a**. Two different methods were employed to achieve this goal. The first procedure used H_2/Pd, in the presence of an amine. Catalytic hydrogenation is a common method used to cleave benzyloxycarbonyl (CBz) and benzyl protecting groups from the substituents that they protect. Although both of these protecting groups are present in compound **50a**, it is only necessary to remove the CBz group from nitrogen to obtain free alanine. Preservation of the benzyl ether protecting groups is desirable as it conserves the chiral auxiliary so that it can be re-used in another

alkylation sequence. Amines have been employed for exactly this purpose. They have been used to selectively inhibit the hydrogenolysis of benzyl ethers in the presence of other hydrogenolytically sensitive groups like CBz.[109,110] We added pyridine to our reaction mixture to see whether we could prevent ether deprotection, while allowing deprotection of the amine. Even in the presence of an inhibitor, our system was completely deprotected, and the recovery of alanine was very low (~10-20%). The disappointing results obtained from hydrogenation led us to find another method for the removal of alanine from **50a**.

The second method used to cleave alanine from the template employed the harsh acid conditions often used by Seebach et al..[71] A mixture of concentrated HCl and HOAc at reflux cleaved the carbamate, and also the ester and *N*-glycosidic bonds to give free alanine. These conditions resulted in the destruction of the chiral auxiliary, but did liberate alanine in 60% yield. This quantity of free alanine allowed us to send it for HPLC analysis using a chiral column to separate the enantiomers. Analysis was performed by Chiral Technologies Inc.. They used a *CROWNPAK® CR+* column to effect separation of the isomers. HPLC analysis of the commercial sample of *D/L*-alanine proved it was not a racemate as it had an e.e. of 16% favoring the *L*-enantiomer (p. 44). The commercial sample of *L*-alanine used was also impure (p. 45). This sample appeared to contain some *D*-alanine among the impurities, however the retention time for the *L*-enantiomer was consistent with that seen for the "racemate". The e.e. for our sample was presented as a range, 87-93%, since the peak corresponding with the *D*-enantiomer was not baseline resolved (p. 46). The uncertainty associated with the e.e. cannot be assigned as our standard was not racemic. The results obtained from this analysis are consistent with the 92% d.e. calculated from the nmr data in Figure 14 (p. 42). The close agreement between the e.e. of the product (**67**)

and the d.e. of the reactant (**50a**) indicate that essentially no racemization occurred during hydrolysis.

Conclusion

The objective of my research project was to synthesize a bicyclic, carbohydrate based template (**39**) for the asymmetric synthesis of α-amino acids. Once this had been achieved I was to determine the diastereoselectivity of alkylation reactions of this template with various electrophiles. The final stage of my project was to determine conditions necessary to cleave the product from the template without racemization.

The first objective was achieved by two independent routes. Two short sequences were designed leading to the preparation of **39**, with each route producing a differentially protected sugar. The first route produced an ester-protected template (**40**) while the other resulted in an ether-protected template (**44**). Both sequences were short, and all intermediates were crystalline.

The diastereoselectivity was assessed to be both excellent (92% or greater), and predictable (resulting in top face alkylation).

Preliminary experiments dealing with the hydrolysis of the product from the chiral auxiliary were performed. The conditions used involved harsh acid to cleave the product from the template. Despite the strong acids used there was minimal racemization of the product which was obtained in 87-93% e.e..

Suggestions for future research

From the preceding discussion it is evident that there remain two areas of concern in the sequence leading to the asymmetric production of α-amino acids from

our carbohydrate based template. These areas are; (1) enolate stability, and (2) strongly acidic conditions necessary for hydrolysis.

Aggregation of the enolate appears to have led to both the decomposition of the template, and dialkylation. Perhaps the use of a non-nucleophilic, non-aggregating base such as Schwesinger's base (a *t*-butyl P4 base, pK_a=28)[111,112] would reduce decomposition and dialkylation, thus improving the yields associated with monoalkylation. The addition of LiCl,[89] crown ethers,[91] or other cation complexing reagents[113] to reactions involving lithium enolates has led to reduced aggregation. It is possible that the addition of one of these may reduce aggregation and increase yields.

The presence of similar protecting groups for both the amine and the alcohols necessitated harsh acid conditions for the deprotection and hydrolysis of the alkylated template. The use of orthogonal protecting groups would allow the deprotection of the amine without deprotection of the alcohols, and this may lead to mild (or milder) conditions for the hydrolysis of the product from the chiral auxiliary. Some potentially good combinations may be:

1. amine protection with CBz combined with the protection of the alcohols as pivaloate ester, or as an ether stable to hydrogenation conditions (ie: a methyl ether).[114]
2. protection of the alcohols as benzyl ethers and protection of the amine with p-nitrobenzyl carbamate (p-$NO_2C_6H_4CH_2OC(O)NR_2$), or as a p-methoxybenzyl carbamate (p-$MeOC_6H_4CH_2OC(O)NR_2$), both of these carbamates can be removed in the presence of a benzyl ether.[115]

Once the questions surrounding enolate stability and hydrolysis have been solved, it should be possible to synthesize novel α-amino acids in high yield and high diastereoselectivity.

Experimental

General methods

All chemical reagents were purchased from Aldrich and silica gel was obtained from Rose Scientific. Commercial reagents were purified prior to use, according to published methods.[116] Methyl iodide was distilled into a receiver containing a copper wire (1 cm). This was protected from light and moisture and stored at 0°C.

In all dry experiments, glassware was flame-dried then cooled under vacuum, and the reactions were performed under a positive pressure of nitrogen (unless otherwise stated).

All reactions were monitored by analytical thin layer chromatography (tlc), on precoated Machery-Nagel Alugram SIL G/UV_{254} plates (0.25 mm thickness). For visualization, the tlc plates were placed under ultraviolet light and/or stained using either a solution of 5% H_2SO_4/EtOH or ninhydrin. Reactions were deemed complete based on the disappearance of starting materials.

Flash column chromatography was performed according to the general procedure described by Still[117] using Machery-Nagel silica gel 60 (230-400 mesh).

The ^1H nmr spectra were recorded on a Bruker AMX-500 or AM-300 spectrometer at 500.140 or 300.135 MHz, respectively. The signals due to residual protons in the deuterated solvents indicated were used as internal standards. Chemical shifts are reported in ppm (δ) downfield from the position of tetramethylsilane (TMS). The symbols used to describe the multiplicity and shape of the signals are; s (singlet), d (doublet), dd (double doublet), ddd (double doublet of doublets), t (triplet), m (multiplet), and br (broadened). The ^{13}C nmr spectra were obtained at 125.769 or 75.469 MHz on the AMX-500 and AM-300 spectrometers, respectively. Chemical shifts in ppm (δ) downfield from the position of TMS were measured using the solvent signals as internal standards. Assignments in the ^1H spectra were made on the basis of homonuclear decoupling

experiments and/or $^{1}H/^{13}C$ correlation experiments and/or correlated off-resonance spectroscopy (COSY). Relative stereochemical assignments were made on the basis of observed nuclear Overhauser enhancements (nOe). All spectra were recorded at 300 K, unless otherwise stated.

Melting points were determined using an Electrothermal Melting Point Apparatus.

An Autopol III automatic polarimeter (cell length of 10 cm and concentrations measured in g/100 mL, at 25°C) was used to measure optical rotations.

Elemental analysis was performed by the Guelph Chemical Laboratories Ltd. (Guelph, Ontario).

Glycine ethyl ester

Glycine ethyl ester was prepared from glycine ethyl ester hydrochloride according to the procedure of Goodman and McGahren.[118]

N-(β–*D*-Glucopyranosyl)glycine ethyl ester (41)

N-(β–*D*-Glucopyranosyl)glycine ethyl ester was prepared from *D*-glucose and freshly distilled glycine ethyl ester, according to the procedure of Wolfrom et al.[69]

N-(β–*D*-Glucopyranosyl)-*N*-(benzyloxycarbonyl)glycine ethyl ester (42)

A solution of *N*-(β–*D*-glucopyranosyl)glycine ethyl ester (5.00 g, 18. 9 mmol) in dry DMF (25 mL) was dried over activated 4 Å molecular sieves, for 40 mins. This solution (along with a DMF (5 mL) rinse of the sieves) was then transferred to a fresh flask by syringe, and cooled to 0°C. Diisopropyl ethylamine (3.60 mL, 20.7 mmol) was added to the above mixture, followed by benzyl chloroformate (4.00 mL, 28.0 mmol). After 1.5 h, the solution was concentrated under reduced pressure. The last traces of DMF were removed from the residue by co-evaporation with toluene (2×15 mL). The residue was dried under high vacuum.

The residue was adsorbed onto a minimal amount of silica gel, and applied to the top of a short column of silica gel. Elution, using a gradient of hexanes:ethyl acetate (3:1→0:1), gave **42** (5.36 g, 71 %). The product was obtained as a white amorphous solid upon scratching.

tlc (5:3:2 EtOAc:95% EtOH:aqueous NH_4OH) R_f 0.55.

$(\alpha)_D^{25}$ +22.4° (c 1.24, ethanol).

^{1}H nmr (DMSO-d6, 300 MHz, 383 K) δ 1.18 (t, 3H, *J*= 7.1, CH_3), 3.14-3.36 (m, 4H, H-2, H-3, H-4, H-5), 3.51(ddd, 1H, J_{gem}= 11.6, $J_{5,6}$= 4.8, J_{OH}= 5.1, H-6), 3.69 (ddd, 1H, J_{gem}= 11.6, $J_{5,6'}$= 2.5, J_{OH}= 5.1, H'-6), 3.82 (dd, 1H, $J_{6,OH}$= 5.6, O*H*$_6$), 3.94 (d, 1H, J_{gem}= 17.5, H_α), 4.07 (d, 1H, J_{gem}= 18.9, H'_α), 4.12 (q, 2H, *J* =7.1, CH_2CH_3), 4.29 (d, 1H, *J*= 4.1, O*H*), 4.45 (d, 1H, *J*= 4.8, O*H*), 4.49 (d, 1H, *J*= 3.42, O*H*), 5.07 (d, 1H, *J*= 8.9, H-1), 5.14 (s, 2H, CH_{2CBz}), 7.35 (m, 5H, CH_{Ar}) ppm.

^{13}C nmr (DMSO-d6, 75 MHz, 383 K) δ 13.15 (CH_3), 43.36 (C_α), 60.02, 60.9 (2× CH_2), 66.28 (CH_{2CBz}), 69.72, 69.93, 76.41, 78.38 (C-2, C-3, C-4, C-5), 84.76 (C-1), 126.6, 127.04, 127.55 (3×C_{Ar}), 135.83 (4° C_{Ar}), 154.64 (C_{CBz} carbonyl), 169.56 (C_{ester} carbonyl) ppm.

Anal. calcd for $C_{18}H_{25}O_9N$: C, 54.13; H, 6.31; N, 3.51. Found: C, 54.06; H, 6.49; N, 3.50.

(4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-4-(Benzyloxycarbonyl)-6-(benzoyloxy)methyl-7, 8-bis-(benzoyloxy)-6H-pyrano(3, 2-b)-1, 4-oxazin-2-one (40)[vi]

Ester **42** (4.73 g, 11.83 mmol) dissolved in a minimum amount of 95% EtOH, was treated with 0.3 M aqueous NaOH (47 mL, 14.1 mmol). After stirring for 3 h, the solution was acidified to pH=3 using Amberlite IR-120 (H^+) resin. The resin was removed by filtration. The resulting solution was decolorized using charcoal, filtered and concentrated. The residue was dried under high vacuum to afford the carboxylic acid **43** as a white solid.

A sample of carboxylic acid **43** (0.10 g, 0.27 mmol) was dissolved in H_2O and the pH was adjusted to 9.0 with 1 M aqueous NaOH. The solution was concentrated and

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vi Note: there has been a change in nomenclature from that which is used for sugars to one that is based on derivatives of pyrano-(3,2-b)-oxazinones. The numbering of these molecules may be seen in the following diagram.

the residue was dried by evaporation with toluene. Traces of H_2O were removed from the residue by co-evaporation with toluene. Then the residue was dissolved in dry pyridine (5 mL), and benzoic anhydride (0.61 g, 2.7 mmol) was added. Diethyl ether (1 mL) was added when the solution began to crystallize. The reaction was stirred at 40°C for 19 h. The solution was partitioned between ethyl acetate and water, and the organic phase was washed with 1 M aqueous HCl (3×20 mL) and brine (20 mL), dried and concentrated. Chromatography of the residue (2:1 hexanes:EtOAc) afforded **40** as an oil (0.11g, 60%).

A separate experiment revealed that **40** could be recrystallized from a mixture of dichloromethane/hexanes to afford a white powder.

m.p. 181.5-182.5°C

tlc (2:1 hexanes:EtOAc) R_f 0.57

$(\alpha)_D^{25}$ +34.0° (c 0. 9, $CHCl_3$)

^{1}H nmr ($CDCl_3$, 300 MHz) δ 4.09 (d, 1H, J_{gem}= 17.0, H-3), 4.29 (br s,1H, H-6), 4.48 (ddd, 1H, J_{gem}= 12.3, $J_{6,9}$= 4.8, H-9), 4.54 (dd, 1H, ΣJ= 19.7, H-8a), 4.63 (ddd, 1H, J_{gem}= 12.3, $J_{6,9'}$= 2.8, H'-9), 4.89 (d, 1H, J_{gem}= 16.8, H-3), 5.14 (d, 1H, J_{gem}= 12.3, CH_{2CBz}), 5.20(br s, 1H, H-4a), 5.24 (d, 1H, J_{gem}= 12.3, CH_{2CBz}), 5.72 (dd, 1H, ΣJ= 19.0, H-7), 6.01 (dd, 1H, ΣJ= 19.0, H-8), 7.31-7.41 (m, 10 H, CH_{Ar}), 7.43-7.59 (m, 4H, CH_{Ar}), 7.89-8.11 (m, 6H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$, 75 MHz) δ 44.29 (C-3), 62.59 (C-9), 68.56 (CH_{2CBz}), 69.56 (C-7), 71.70 (C-8) 74.50 (C-8a), 74.53 (C-6), 81.38 (C-4a), 127.79, 128.16, 128.26, 128.32, 128.38, 128.56, 129.38, 129.65, 129.76, 130.02 (C_{Ar}), 133.08, 133.44, 133.55 (3×4° C_{Bn}), 135.12 (4° C_{CBz}), 154.44 (C_{CBz} carbonyl), 165.07, 165.20, 165.90, 166.30 (4×$C_{ester/lactone}$ carbonyls) ppm.

Anal. calcd for $C_{37}H_{31}O_{11}N$: C, 66.76; H, 4.69; N, 2.10. Found: C, 66.73; H, 4.66; N, 2.01.

(4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-4-(Benzyloxycarbonyl)-6-(acetoxy)methyl-7, 8- bis-(acetoxy)-6H-pyrano(3, 2- b)-1, 4-oxazin-2-one (40a)

A sample of the carboxylic acid **43** (0.20 g, 0.51 mmol) was converted to the sodium carboxylate salt, and dried, as described for **40**, above. The salt was dissolved in pyridine (10 mL), and acetic anhydride (0.24 mL, 2.54 mmol) was added. After 16 h, a second portion of acetic anhydride (0.24 mL, 2.54 mmol) was added. DMAP (ca. 5 mg) was added 24 h later, and after another 20 h, the reaction mixture was heated to 40°C. The reaction was worked up as described for **40**, after 24 h of heating. Chromatography (3:2 hexanes:EtOAc) provided **40a** (0.15 g, 60%).

tlc (2:1 hexanes:EtOAc) R_f 0.40

$(\alpha)_D^{25}$ +22.9° (c 0. 6, $CHCl_3$)

^{1}H nmr ($CDCl_3$, 300 MHz)[vii] δ 2.06 (t, 9H, CH_3), 3.87 (br s, 1H, H-6), 4.03 (d, 1H, J_{gem}= 17.1, H-3), 4.06-4.12 (br d, 1H, $J_{9,9'} \cong$ 12.7, H-9), 4.26 (dd, 1H, $J_{4a,8a}$= 9.5, $J_{8,8a}$= 10.1, H-8a), 4.30 (br dd, 1H, $J_{6,9'} \cong$ 4.5, $J_{9,9'} \cong$ 12.7, H-9'), 4.86 (d, 1H, J_{gem}= 17.4, H'-3), 4.96 (d, 1H, $J_{4a,8a}$= 9.5, H-4a), 5.12 (dd, 1H, $J_{6,7}$= 9.9, $J_{7,8}$= 9.0, H-7), 5.21 (dd, 2H, J_{gem}= 12.5, CH_{2CBz}), 5.43 (dd, 1H, $J_{7,8}$= 9.0, $J_{8,8a}$= 9.8, H-8), 7.37 (m, 5H, CH_{Ar}) ppm.

Anal. calcd for $C_{22}H_{25}O_{11}N$: C, 55.11; H, 5.26; N, 2.92. Found: C, 54.55; H, 5.46; N, 2.78.

Acid-catalyzed preparation of 40a

A sample of **43** (0.25 g, 0.67 mmol) was dissolved in acetic acid (10 mL) and a 1.22 M solution of HCl in HOAc (0.55 mL, 0.67 mmol) was added. The reaction was stirred over 3Å molecular sieves at 40°C. After 4.5 h, a second equivalent of 1.22 M

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vii This spectral assignment is based solely on the proton spectrum, as the ^{13}C, COSY, and the ^{1}H/^{13}C correlation spectra were not taken.

HCl/HOAc (0.55 mL. 0.67 mmol) was added, followed by a third equivalent at 27 h. At this time the temperature was increased to 80°C. A fourth equivalent of HCl was added after 48 h, along with the addition of more sieves, and the reaction was complete at 72 h. Celite was added to the suspension, and it was filtered through a celite plug, to remove the sieves. The reaction flask and celite plug were washed with ether. The ether washings and the filtrate were combined and concentrated. The residue was dissolved in pyridine (5 mL), and acetic anhydride (0.64 mL, 6.8 mmol) was added. After 20 h, the reaction mixture was poured into a crushed ice/H_2O slurry (60 mL), stirred for 1 h, and extracted with ether (3× 20 mL). The combined organic layers were washed with 1 M aqueous HCl (3× 20 mL), saturated aqueous sodium bicarbonate (20 mL), and brine (20 mL), dried and evaporated to give **40a** as a clear glass (0.16 g, 52%). The nmr spectrum was identical to that previously obtained.

3, 4, 6-Tri-*O*-benzyl-*D*-glucose (45)

This compound was prepared by the method of Charette et al.[119,viii]

N-(3, 4, 6-Tri-*O*-benzyl-β-*D*-glucopyranosyl)glycine ethyl ester (46)

A solution of 3, 4, 6-tri-*O*-benzyl-*D*-glucose (13.1 g, 29.1 mmol) in $CHCl_3$ (30 mL), and freshly distilled glycine ethyl ester (5.00 mL, 49.6 mmol) was heated at 70°C, for 16 h, under an argon atmosphere. It was then concentrated to afford a brown oil, which solidified on standing under reduced pressure. This solid was recrystallized using

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viii A.B. Charette, personal communication.

di(isopropyl)ether, to yield a white powder. A second crop of crystals was obtained from the mother liquor and the combined crops provided **46** (10.9 g, 70%).

tlc (1:1 Hexanes:Ether) R_f 0.67

m.p. 74-75°C

$(\alpha)_D^{25}$ +5.0° (c 0. 6, $CHCl_3$)[ix]

^1H nmr ($CDCl_3$, 300 MHz) δ 1.273 (t, 3H, *J* 7.2, CH_3), 2.27 (br s, 1H, N*H*), 3.07 (s, 1H, O*H*), 3.35-3.47(m, 2H), 3.52 (d, 1H, J_{gem} 17.4, H_α), 3.57-3.61 (m, 2H), 3.64-3.72 (m, 2H), 3.70 (d, 1H, J_{gem}17.4, H'_α), 3.87 (d, 1H, $J_{1,2}$ 8.7, H-1), 4.19 (q, 2H, CH_2CH_3), 4.51 (d, 1H, J_{gem} 12.2, CH_{2Bn}), 4.52 (d, 1H, J_{gem} 10.8, CH_{2Bn}), 4.59 (d, 1H, J_{gem} 12.2, CH_{2Bn}), 4.83 (d, 1H, J_{gem} 11.3, CH_{2Bn}), 4.85 (d, 1H, J_{gem} 10.8, CH_{2Bn}), 5.01 (d, 1H, J_{gem} 11.3, CH_{2Bn}), 7.10-7.40 (m, 15 H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$, 75 MHz) δ 14.19 (CH_3), 46.43 (C_α), 61.06 (CH_2CH_3), 69.04, 73.53, 74.31, 75.00, 76.28 (C-2,C-4, C-5, C-6 and 3xCH_{2Bn})[x], 85.51 (C-3), 89.71 (C-1),127.56, 127.62, 127.66, 127.79, 127.95, 128.34 (C_{Ar}), 138.05, 138.18, 138.80 (3x4° C_{Ar}), 172.39 (C_{ester} carbonyl) ppm.

Anal. calcd for $C_{31}H_{37}O_7N$: C, 69.51; H, 6.96; N, 2.61. Found: C, 69.27; H, 7.02; N, 2.59.

N-(3, 4, 6-Tri-*O*-benzyl-β-*D*-glucopyranosyl)-*N*-(benzyloxycarbonyl)glycine ethyl ester (47)

A solution of **46** (4.90 g, 9.16 mmol) and di(isopropyl) ethylamine (3.20 mL, 18.8 mmol) in $CHCl_3$ (10 mL), was cooled to 0°C. Benzyl chloroformate (2.00 mL, 14.0 mmol) was added dropwise over 10 min. The solution was allowed to warm to room temperature over 1 h. At 3 h, the reaction was quenched with H_2O (70 mL), and the product

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ix Melting point, optical rotation, NMR, and elemental analysis data all provided by P.G. Hultin.

x Two lines are obscured by the solvent.

was extracted into ether (265 mL). The organic phase was washed with 1 M aqueous HCl (2x35 mL), saturated aqueous sodium carbonate solution (35 mL), brine (35 mL), and dried. The residue obtained after concentration was dissolved in a minimum amount of 4:1 hexanes:EtOAc, and applied to a 4.5 cm x 8 cm silica column, and the product was eluted using a gradient of hexanes:EtOAC (1:0→2:1). After evaporation of the solvent the product **47** was obtained as an oil (5.85 g, 95%) which crystallized upon seeding and scratching.

tlc (2:1 hexanes:EtOAc) R_f 0.53

m.p. 75.5-77°C[xi]

$(\alpha)_D^{25}$ +15.7° (c 0. 6, $CHCl_3$)

^{1}H nmr ($CDCl_3$, 500 MHz) δ 1.15 (t, 3H, J= 7.1, CH_3), 3.45 (dd, 1H, J= 9.1, H-4), 3.54-3.59 (m, 2H, H-2, H-5), 3.61-3.69 (m, 3H, H-3, H-6, H'-6), 3.94 (d, 1H, J_{gem}= 17.6, H_α), 4.06-4.10 (m, 3H, J_{gem}= 17.2, H'_α, CH_2CH_3), 4.47 (d, 1H, J_{gem}= 12.3, CH_{2CBz}), 4.51 (d, 1H, J_{gem}= 12.3, CH_{2CBz}), 4.56 (d, 1H, J_{gem}= 11.3, CH_{2Bn}), 4.68 (d, 1H, J_{OH}= 5.0, O*H*), 4.74 (d, 1H, J_{gem}= 11.2, CH_{2Bn}), 4.76 (d, 1H, J_{gem}= 11.5, CH_{2Bn}), 4.94 (d, 1H, J_{gem}= 11.6, CH_{2Bn}), 5.13 (d, 1H, J_{gem}= 12.9, CH_{2Bn}), 5.15 (d, 1H, $J_{1,2}$= 9.1, H-1), 5.16 (d, 1H, J_{gem}= 12.9, CH_{2Bn}), 7.16 (m, 2H, CH_{Ar}) 7.30 (m, 15H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$, 125 MHz)[xii] δ 13.11 (CH_3), 43.42 (C_α), 60.01 (CH_2CH_3), 66.36 (CH_{2Bn}), 68.85 (C-6), 70.31 (C-2), 72.09, 73.02, 73.27(3xCH_{2Bn}), 76.20 (C-5), 76.81 (C-4), 84.41 (C-3), 84.89 (C-1), 126.42, 126.63, 126.71, 126.83, 127.07, 127.28, 127.36, 127.57 (C_{Ar}) ppm.

Anal. calcd for $C_{39}H_{43}O_9N$: C 69.94; H, 6.47; N, 2.09. Found: C, 69.81; H, 6.51; N, 2.07.

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xi Melting point, optical rotation and elemental analysis data provided by P. G. Hultin.

xii The ^{13}C shifts were taken from the ^{1}H/^{13}C correlation experiments, therefore the peak positions of the non-protonated carbons are absent.

(4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-4-(Benzyloxycarbonyl)-6-(benzyloxy)methyl-7, 8-bis-(benzyloxy)-6H-pyrano(3, 2-b)-1, 4-oxazin-2-one (44)

Ester **47** (5.85 g, 8.74 mmol) was dissolved in THF (50 mL) and 0.3 M aqueous NaOH (44.0 mL, 13.2 mmol) was added. The reaction was stirred for 2 h. The pH was adjusted to 9 using 1 M aqueous HCl. The solution was concentrated to a white powder **48**. Traces of H_2O were removed by co-evaporation with toluene, and the residue was then allowed to stand under reduced pressure for 3 days.

A portion of the acid salt **48** (1.21 g, 1.83 mmol) was dissolved in pyridine (36 mL), and a 0.5 M solution of benzoic anhydride in chloroform[xiii] (4.60 mL, 2.30 mmol) was added. The reaction was stirred under an argon atmosphere for 2 h, at room temperature. The solvent was removed and the product was allowed to stand under high vacuum for 16 h, to yield a crude oil **44** (0.82 g, 72%).[xiv]

tlc (3:1 hexanes:ether) R_f 0.30

m.p. 85-86°C

$[\alpha]_D^{25}$ +26.1° (c 0.66, $CHCl_3$)

^{1}H nmr (DMSO-d6, 383 K, 500 MHz) δ 3.63-3.72 (m, 4H, H-6, H-7, H-9, H'-9), 4.09 (dd, 1H, $J_{7,8}$= 9.5, $J_{8,8a}$= 8.0, H-8), 4.40 (d, 1H, J_{gem}= 16.5, H-3), 4.46 (dd. 1H, $J_{4a,8a}$= 9.5, $J_{8,8a}$= 8.1, H-8a), 4.47 (d, 1H, J_{gem}= 12.2, CH_{2Bn}), 4.49 (d, 1H, J_{gem}= 16.4, H-3), 4.51 (d, 1H, J_{gem}= 12.2, CH_{2Bn}), 4.59 (d, 1H, J_{gem}= 11.3, CH_{2Bn}), 4.77 (d, 2H, J_{gem}= 11.6, CH_{2Bn}), 4.88 (d, 1H, J_{gem}= 11.4,

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xiii In later experiments benzoic anhydride was added as a pyridine solution, for simplicity.

xiv In later experiments, the quench for the completed reaction proceeded as follows: H_2O was added (enough to afford a clear solution) and this was stirred 1 h. Ether was used to extract the product, and after separation, the organic layer was washed with 10% aqueous HCl (to remove all traces of pyridine), saturated sodium carbonate solution and brine. The crude product was then concentrated and could be recrystallized from di(isopropyl) ether and scratching, or from a mixture of diethyl ether/pentane.

CH_{2Bn}), 4.99 (d, 1H, $J_{4a,8a}$= 9.5, H-4a), 5.15 (d, 1H, J_{gem}= 12.7, CH_{2CBz}), 5.21 (d, 1H, J_{gem}= 12.7, CH_{2CBz}), 7.29 (m, 20H, CH_{Ar}) ppm.

^{13}C nmr (DMSO-d6, 383 K, 125 MHz) δ 43.66 (C-3), 66.77 (CH_{2CBz}), 68.35 (C-9), 72.02 (C_{Bn-9}), 73.19 (C_{Bn-8}), 73.36 (C_{Bn-7}), 76.17 (C-8a), 76.28 (C-6), 77.46 (C-7), 79.97 (C-4a), 80.74 (C-8), 126.69, 126.79, 126.93, 127.19, 127.46, 127.64 (C_{Ar}), 135.55 (4° C_{CBz}), 137.62, 137.69 (3×4° C_{Bn}), 154.06 (C_{CBz} carbonyl), 167.08 ($C_{oxazinone}$ carbonyl) ppm.

Anal. calcd for $C_{37}H_{37}O_8N$: C, 71.25; H, 5.98; N, 2.25. Found: C, 71.20; H, 5.96; N, 2.21.

(3*S*, 4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3-Methyl-4-(benzyloxycarbonyl)-6-(benzyloxy)-methyl-7,8-bis(benzyloxy)-6H-pyrano(3, 2-b)-1, 4-oxazin-2-one (50a)

Oxazinone **44** (1.00 g, 1.60 mmol) was dissolved in a 20% solution of HMPA in THF (5 mL), and cooled to -100 °C under an argon atmosphere. A 1 M solution of LiHMDS in THF (2.00 mL, 2.00 mmol) was added, followed two minutes later by methyl iodide (1.00 mL, 16.0 mmol). The reaction temperature was maintained between -100 and -70°C for 2.5 h. H_2O (50 mL) was used to quench the reaction. The product was extracted with ether (200 mL). The organic layer was washed with H_2O (5× 50 mL), and brine (50 mL), then dried and concentrated. Purification by chromatography, using a gradient of hexanes:ether (2:1→3:5), provided **50a** (0.56 g, 56%). A mixture of ether/pentane was used to recrystallize the chromatographed product. (NOTE: A sample of the chromatographed material was removed for nmr analysis and diastereomeric excess determination prior to recrystallization.)

tlc (2:1 hexanes:ether) R_f 0.32

m.p. 83-84.5°C

$(\alpha)_D^{25}$ +38.4° (c 0. 61, $CHCl_3$)

^{1}H nmr ($CDCl_3$, 500 MHz) δ 1.65 (d, 3H, J_{3,CH_2}= 7.6, CH_3 major isomer), 1.83 (d, 3H, CH_3 minor isomer), 3.60 (m, 1H, H-6), 3.71 (m, 2H, H-9, H'-9), 3.80 (dd, 1H, $J_{6,7}$= 10.0, $J_{7,8}$= 8.0, H-7), 3.88 (dd, 1H, $J_{7,8}$= 8.0, $J_{8,8a}$= 9.5, H-8), 4.34 (dd, 1H, $J_{4a,8a}$= 9.6, $J_{8,8a}$= 9.5, H-8a), 4.46 (d, 1H, J_{gem}= 12.1, CH_{2Bn}), 4.50 (d, 1H, J_{gem}= 10.8, CH_{2Bn}), 4.59 (d, 1H, J_{gem}= 12.1, CH_{2Bn}), 4.78 (m, 2H, $J_{4a,8a}$= 9.6, J_{gem}= 10.9, H-4a, CH_{2Bn}), 4.84 (d, 1H, J_{gem}= 10.8, CH_{2Bn}), 4.98 (br q, 1H, J_{3,CH_2}= 7.6, H-3), 5.02 (d, 1H, J_{gem}= 10.9, CH_{2Bn}), 5.16 (d, 1H, J_{gem}= 12.2, CH_{2CBz}), 5.21 (d, 1H, J_{gem}= 12.2, CH_{2CBz}), 7.33 (m, 20H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$, 125 MHz) δ 19.46 (CH_3), 52.29 (C-3), 67.73 (C-9), 68.20 (CH_{2CBz}), 73,38, 75.33, 75.45 (CH_{2Bn}), 76.28 (C-8a), 77.37 (C-6), 77.48 (C-7), 80.51 (C-4a), 82.47 (C-8), 127.72, 127.85, 127.87, 128.01, 128.26, 128.36, 128.41, 128.49, 128.57 (C_{Ar}), 135.39 (4° C_{CBz}), 137.50, 137.63, 137.78 (4° C_{Bn}), 154.76 (C_{CBz} carbonyl), 169.38 ($C_{oxazinone}$ carbonyl) ppm.

Anal. calcd for $C_{38}H_{39}O_8N$: C, 71.57; H, 6.16; N, 2.20. Found: C, 71.64; H, 6.16; N, 2.19.

(3*S*, 4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3-Allyl-4-(benzyloxycarbonyl)-6-(benzyloxy)methyl-7, 8-bis(benzyloxy)-6H-pyrano(3, 2-b)-1, 4-oxazin-2-one (50b)

Oxazinone **44** (0.25 g, 0.40 mmol) was dissolved in a 20% solution of HMPA in THF (5 mL), and cooled to -100°C, under an argon atmosphere. A 1 M solution of LiHMDS (0.54 mL, 0.54 mmol) was added, followed by allyl bromide (0.35 mL, 4.0 mmol) two minutes later. The reaction was allowed to gradually warm from -100 to -78°C. After 2.5 h the reaction was quenched with H_2O (15 mL), and the product was extracted into ether (50 mL). The organic phase was washed with H_2O (5x15 mL) and brine (15 mL), then dried and concentrated. The residual oil was chromatographed using 2:1 hexanes:ether to obtain **50b** (0.07 g, 26%), and a less polar product, identified as (4a*R*,

6*R*, 7*R*, 8*S*, 8a*R*)-3,3-Di(allyl)-4-(benzyloxycarbonyl)-6-(benzyloxy)methyl-7, 8-bis-(benzyloxy)-6H-pyrano(3, 2-b)-1, 4-oxazin-2-one **51a** (0.07 g, 25%).

tlc (1:1 hexanes:ether) R_f 0.43 (**50b**)

$(\alpha)_D^{25}$ +29.9° (c. 0.66, $CHCl_3$) (**50b**)

^{1}H nmr (**50b**) ($CDCl_3$, 500 MHz) δ 2.71 (dd, 2H, J_{3,CH_2}= 6.7, CH_2CHCH_2), 3.58-3.65 (br m, 1H, H-6), 3.71-3.78 (br m, 2H, $J_{6,9'}$= 3.4, H-9, H'-9), 3.84 (dd, 1H, $J_{6,7}$= 10.4, $J_{7,8}$= 7.7, H-7), 3.91 (d, 1H, $J_{7,8}$= 7.7, $J_{8,8a}$= 9.8, H-8), 4.40 (dd, 1H, $J_{4a,8a}$= 9.2, $J_{8,8a}$= 9.8, H-8a), 4.51 (d, 1H, J_{gem}= 12.1, CH_{2Bn}), 4.57 (d, 1H, J_{gem}= 10.7, CH_{2Bn}), 4.62 (d, 1H, J_{gem}= 12.1, CH_{2Bn}), 4.80 (d, 1H, J_{gem}= 10.9, CH_{2Bn}), 4.82 (d, 1H, $J_{4a,8a}$= 9.2, H-4a), 4.88 (d, 1H, J_{gem}= 10.8, CH_{2Bn}), 4.97 (br t, 1H, J_{3,CH_2}= 6.7, H-3), 5.05 (d, 1H, J_{gem}= 10.9, CH_{2Bn}), 5.19 (d, 1H, J_{gem}= 12.3, CH_{2CBz}), 5.23 (d, 1H, J_{gem}= 12.3, CH_{2CBz}), 5.25 (br m, 2H, CH_2CHCH_2), 5.83-5.92 (m, 1H, CH_2CHCH_2), 7.15-7.20 (m, 2H, CH_{2Ar}), 7.25-7.40 (m, 18H, CH_{2Ar}) ppm.

^{13}C nmr (**50b**) ($CDCl_3$, 125 MHz)[xv] δ 37.38 (CH_2CHCH_2), 56.37 (C-3), 68.01 (C-9), 68.2 (C_{CBz}), 72.73, 75.00, 76.95 (3xC_{Bn}), 76.14 (C-8a), 77.27 (C-6), 77.46 (C-7), 80.29 (C-4a), 81.99 (C-8), 119.36 (CH_2CHCH_2), 128.11 (C_{Ar}), 131.87(CH_2CHCH_2) ppm.

tlc (1:1 hexanes:ether) R_f 0.66 (**51a**)

$(\alpha)_D^{25}$ +30.2 (c 1.43, $CHCl_3$) (**51a**)

^{1}H nmr (**51a**) ($CDCl_3$, 300 MHz) δ 2.80 (br dd, 1H, β—CH_2CHCH_2), 2.93 (br dd, 1H, α—CH_2CHCH_2), 3.11 (br dd, 1H, β—CH_2CHCH_2), 3.38-3.52 93 (m, 3H, α—CH_2CHCH_2, H-6, H-9), 3.61 (dd, 1H, $J_{6,9'}$= 3.5, $J_{9,9'}$= 11.0, H'-9), 3.74-3.85 (m, 2H, H-7, H-8), 4.26 (dd, 1H, $J_{4a,8a}$= 9.3, $J_{8,8a}$= 9.0, H-8a), 4.41 (d, 1H, J_{gem}= 12.1, CH_{2Bn}), 4.52 (2xd, 2H, $J_{gem}\cong$ 10.8, 2xCH_{2Bn}), 4.65 (d, 1H, $J_{4a,8a}$= 9.2, H-4a), 4.75 (d, 1H, J_{gem}= 10.9, CH_{2CBz}), 4.82 (d, 1H, J_{gem}= 10.9, CH_{2CBz}), 5.01-5.10 (m, 5H, α—CH_2CHCH_2, 3xCH_{2Bn}), 5.20-6.26 (br m, 2H,

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xv The ^{13}C shifts were taken from the ^{1}H/^{13}C correlation experiments, therefore the peak positions of the non-protonated carbons are absent.

β—CH_2CHCH_2), 5.45-5.58 (m, 1H, α—CH_2CHCH_2), 5.84-5.98 (m, 1H, β—CH_2CHCH_2), 7.30 (m, 20H, CH_{Ar}) ppm.

^{13}C nmr (**51a**) ($CDCl_3$, 75 MHz) δ 41.39, 43.56 (α— and β—CH_2CHCH_2), 67.68 (C-9), 67.96 (CH_{2CBz}), 68.94 (C-3), 73.25, 75.23, 75.48 (3×CH_{2Bn}), 76.58 (C-8a), 77.18 (C-7). 7.52 (C-6), 80.44 (C-4a), 82.56 (C-8), 120.19 ,120.49 (α— and β—CH_2CHCH_2), 127.62, 127.82, 127.88, 128.17, 128.23, 128.27, 128.31, 128.36, 128.42, 128.44 (C_{Ar}), 131.76, 132.18 (α— and β—CH_2CHCH_2), 135.69 (4° C_{CBz}), 137.71, 137.87, 138.03 (3×4° C_{Bn}), 154.30 (C_{CBz} carbonyl), 170.08 ($C_{oxazinone}$ carbonyl) ppm.

Anal. calcd for (**50b**) $C_{40}H_{41}O_8N$: C, 72.38; H, 6.23; N, 2.11. Found: C, 72.61; H, 6.46; N, 2.24.

Anal. calcd for (**51a**) $C_{43}H_{45}O_8N$: C ,73.38; H, 6.45; N, 1.99. Found: C, 73.25; H, 6.38; N, 1.97.

(4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3, 3-Di(benzyl)-4-(benzyloxycarbonyl)-6-(benzyloxy)-methyl-7, 8-bis(benzyloxy)-6H-pyrano(3, 2-b)-1, 4-oxazin-2-one (51b)

Oxazinone **44** (0.25 g, 0.41 mmol) was dissolved in a 20% solution of HMPA in THF (5 mL) and cooled to -100 °C, under an argon atmosphere. A 1 M solution of LiHMDS (0.49 mL, 0.49 mmol) was added, followed by benzyl bromide (0.095 mL, 0.76 mmol), two minutes later. After 4 h, the reaction was quenched with H_2O (15 mL), and extracted with ether (50 mL). The organic phase was washed with H_2O (5×15 mL) and brine (15 mL), then dried and concentrated to an oil. Purification using flash chromatography (1:1 hexanes:ether) gave **51b** (0.07 g, 21%). After evaporation, **51b** was recrystallized from a mixture of ether/hexanes.

tlc (1:1 hexanes:ether) R_f 0.78

m.p. 106-108 °C

$(\alpha)_D^{25}$ +52.4° (c 1.8, $CHCl_3$)

^{1}H nmr (DMSO-d6, 383 K, 300 MHz) δ 2.41 (dd, 1H, $J_{4a,8a}$= 9.2, $J_{8,8a}$= 9.4, H-8a), 3.12 (dd, 1H, $J_{6,7}$= 9.6, $J_{7,8}$= 8.1, H-7), 3.20-3.31 (m, 1H, H-6), 3.28 (d, 1H, J_{gem}= 13.3, CH_{2Bn}), 3.37 (dd, 1H, $J_{6,9}$= 2.1, $J_{9,9'}$= 11.3, H-9), 3.46 (dd, 1H, $J_{6,9'}$= 4.3, $J_{9,9'}$= 11.3 H'-9), 3.56-3.62 (m, 2H, J_{gem}= 13.5, $J_{7,8}$= 8.1, $J_{8,8a}$= 9.5, CH_{2Bn}, H-8), 3.94 (d, 2H, J_{gem}= 13.3, CH_{2Bn}), 4.13 (d, 1H, $J_{4a,8a}$= 9.2, H-4a), 4.36-4.65 (m, 6H, J_{gem}= 11.5, J_{gem}= 11.4, J_{gem}= 11.5, J_{gem}= 12.5, J_{gem}= 11.8, J_{gem}= 12.3, CH_{2Bn}), 5.13 (d, 2H, J_{gem}= 12.3, CH_{2CBz}), 7.27 (m, 30H, CH_{Ar}) ppm.

^{13}C nmr (DMSO-d6, 75 MHz) δ 42.78, 44.32 (α and β CH_2), 66.88 (C-9), 67.61 (CH_{2CBz}), 71.46 (4° C-3), 71.97, 73.01, 73.70 (3×CH_{2Bn}), 73.89, 75.57, 76,82 (C-6, C-7, C-8), 78.40 (C-8a), 79.94 (C-4a), 126.91, 127.12, 127.19, 127.25, 127.30, 127.34, 127.41, 127.78, 127.93, 128.00, 128.04, 128.12, 128.28, 128.38, 129.26, 130.23 (C_{Ar}),135.15, 135.22 (α and β 4° C), 135.71 (4° C_{CBz}), 137.82, 138.01, 138.18 (3×4° C_{Bn}), 154.05 (C_{CBz} carbonyl), 170.34 ($C_{oxazinone}$ carbonyl) ppm.

Anal. calcd for $C_{51}H_{49}O_8N$: C, 76.19; H, 6.14; N, 1.74. Found: C, 76.06; H, 6.15; N, 1.73.

(4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-2-*t*-Butyldimethylsilyloxy-4-(benzyloxycarbonyl)-6-(benzyloxy)methyl-7, 8-bis(benzyloxy)-4H, 6H-(4a, 7, 8, 8a)-tetrahydro)-pyrano(3, 2-b)-1,4-oxazine (52)

Following the procedure of Rossi and Pecunioso,[120] oxazinone **44** (0.15 g, 0.24 mmol) and Et_3N (0.067 mL, 0.48 mmol) were dissolved in CH_2Cl_2 (1.0 mL). The solution was cooled to -15 °C followed by dropwise addition of TBDMS-OTf (0.066 mL, 0.29 mmol). After 1.5 h, the reaction was quenched by the addition of ether (5 mL). The solution was washed with saturated aqueous ammonium chloride (3 mL), and the organic phase was dried, concentrated, and allowed to stand under high vacuum for 16 h, to yield a

crude oil (0.17 g, 99%). Purification *via* chromatography (1:1 hexanes:ether with 10 drops Et_3N/10 mL), yielded **52** (0.10 g, 58%).

tlc (1:1 hexanes:ether with 10 drops Et_3N/10 mL) R_f 0.54

^1H nmr ($CDCl_3$, 500 MHz) δ 0.18 (s, 3H, CH_3), 0.19 (s, 3H, CH_3), 0.93 (s, 9H, CH_{3tBu}), 3.62, (br s, 1H, H-6), 3.71 (br m, 2H, J_{gem}= 13.1, $J_{6,9}$= 3.1, H-9, H'-9), 3.83-3.86 (m, 3H, H-7, H-8, H-8a), 4.46 (dd, 2H, J_{gem}= 12.1, J_{gem}= 10.6, CH_{2Bn}), 4.61-4.65 (m, 2H, J_{gem}= 12.1, $J_{4a,8a}$= 7.2, CH_{2Bn}, H-4a), 4.80 (dd, 2H, J_{gem}= 10.8, J_{gem}= 11.2, CH_{2Bn}), 5.00 (d, 1H, J_{gem}= 11.1, CH_{2Bn}), 5.14 (d, 1H, J_{gem}= 12.4, CH_{2CBz}), 5.23 (d, 1H, J_{gem}= 12.4, CH_{2CBz}), 5.81 (s, 1H, H-3), 7.27 (m, 20H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$, 125 MHz)[xvi] δ 67.61(CH_{2CBz}), 68.05 (C-9), 73.47, 75.15, 75.24 (3×CH_{2Bn}), 77.25 (C-6), 77.64 (C-7), 79.65 (C-8), 81.20 (C-4a), 82.69 (C-8a), 89.23 (C-3), 127.71, 127.83, 127.88, 128.00, 128.07, 128.35, 128.44 (C_{Ar}) ppm.

L-Alanine (67)

Following a procedure of Seebach et al.,[71] methyl oxazinone **50a** (0.10 g, 0.16 mmol) was dissolved in acetic acid (2.4 mL). Concentrated aqueous HCl[xvii] (2 mL) was added and the reaction was heated to reflux for 2.5 h. The reaction was quenched with H_2O (13 mL). The precipitate that formed was removed by centrifugation, and the supernatant was decanted. This was concentrated to dryness prior to purification by ion exchange chromatography. A column containing Dowex 50W X8 (1 g) was washed (H_2O), until the effluent was neutral, followed by the application of the crude product. Elution using 1.75 M aqueous ammonia gave *L*-alanine (14.9 mg, 60%).

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xvi The ^{13}C shifts were taken from the $^1H/^{13}C$ correlation experiments, therefore the peak positions of the non-protonated carbons are absent.

xvii Enough HCl was added so that the solution began to cloud, but no more than an equivalent volume to that of acetic acid.

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