C h a p t e r 1

Investigations into a Two-Step Method to Access Aminosugars[34]

An Introduction to Organocatalytic Aldol Reactions

For the past 40 years, asymmetric synthesis has been a key focus in organic chemistry. This movement was christened by independent reports from Knowles and Noyori where chiral catalysts were used to produce chiral products from achiral substrates.[1] Since these reports, it has evolved into a multifaceted field of research involving the use of many different modes of catalysis.[2] Acknowledging the importance of asymmetric catalysis, the Nobel committee awarded the 2001 Nobel Prize to Knowles, Noyori, and Sharpless for their work in this field.[3]

Lewis acid catalysis has been extensively used in asymmetric synthesis to affect a range of organic transformations including oxidations, reductions, cycloadditions, conjugate additions, and π-bond activation reactions. A Lewis acid is considered to be an electron pair acceptor. Usually, a Lewis acid catalyst reversibly coordinates to the electrophilic substrate and lowers the energy of the lowest unoccupied molecular orbital (LUMO) of the electrophilic substrate to make it more susceptible to attack by the highest occupied molecular orbital (HOMO) of the nucleophile. Conversely, Lewis acids have also been shown to raise the HOMO of a nucleophilic substrate, which makes it more capable of attacking the LUMO of an electrophile (Figure 1.1). While these reactions are a staple in the chemist's toolbox, they are not without their drawbacks. Lewis acids can be

sensitive to air and water, so they require the use of anhydrous conditions and special handling. Also, the use of metals in the synthesis of human consumables such as pharmaceuticals has to be done judiciously to avoid metal contamination of the final products. In addition, many of these catalysts are costly to use on a large scale.[2]

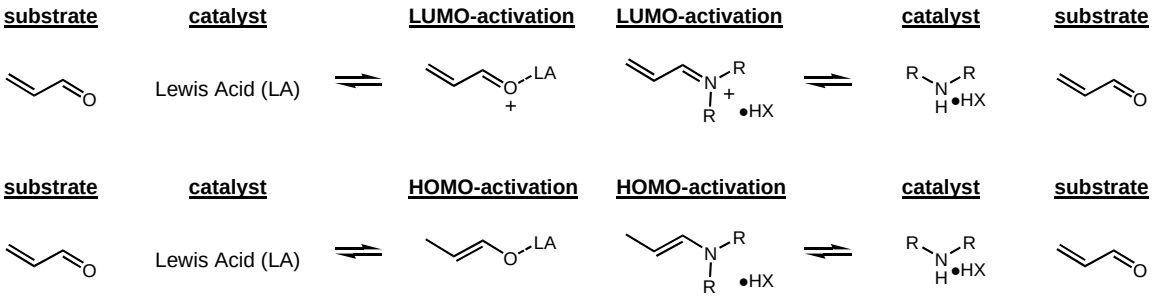
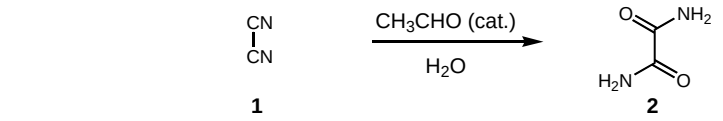


Figure 1.1: Secondary amines can behave like Lewis acids by performing both HOMO- and LUMO-activation.

Organocatalysts (that is, catalysts composed only of organic molecules) have been able to duplicate the reactivity of many Lewis acids. Furthermore, these catalysts do not possess many of the detrimental qualities of Lewis acids. Organic catalysts are typically air and water stable and are more cost-effective than their Lewis acid counterparts. [4]

The beginnings of the field of organocatalysis consist of a few unrelated reactions that peppered the early literature. The earliest reports of an organocatalytic reaction come in 1859 from Liebig who described the synthesis of oxamide from dicyan and water using acetaldehyde as a catalyst (Equation 1.1).[5] In 1912, Bredig and Friske described an alkaloid-catalyzed cyanohydrin methodology that afforded moderate enantioselectivities

(Equation 1.2).[6] In one example, using quinine as a catalyst, hydrogen cyanide was added to benzaldehyde to produce chiral cyanohydrin **4**. This methodology allowed access to both stereoisomers. While the enantioselectivities are low in both cases, these reactions represent the first enantioselective organocatalytic reactions described in the literature. The next report comes nearly half a century later when Pracejus describes an organocatalytic ketene methanolysis reaction to produce ester **6** (Equation 1.3).[7] In this reaction, the methanolysis of the ketene is catalyzed by strychnine (**7**). In the 1970's, two groups led by Hajos and Weichert described a proline-catalyzed Robinson annulation that now bears their name (the Hajos-Parrish-Eder-Sauer-Weichert reaction, Equation 1.4).[8] These results again lay dormant until the past decade when organocatalysis has become a defined field in organic chemistry. Since its awakening, organocatalysis has come to encompass a plethora of catalysts and activation methods that afford a variety of structural motifs.[4]



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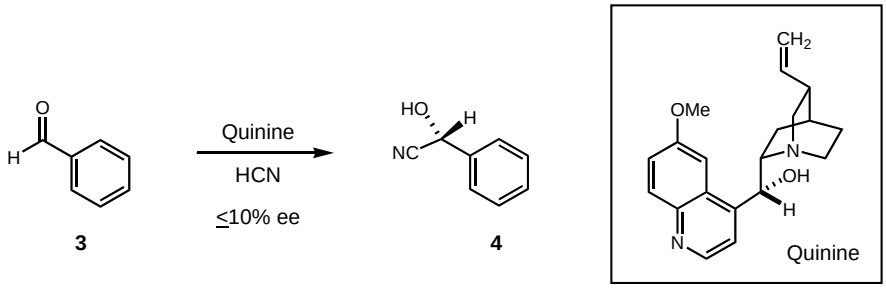

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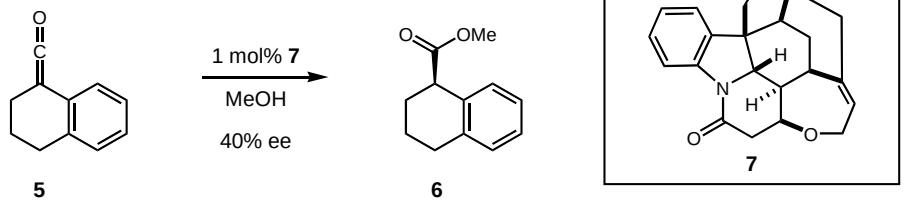

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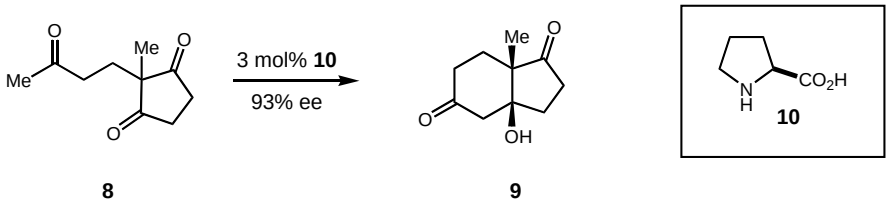


(1.4)

One of the first synthetic organocatalysts was the MacMillan imidazolidinone catalyst. This catalyst is capable of activating aldehydes and ketones in a fashion similar to Lewis acids and is both air and water stable (Figure 1.1). Its ability to impart chirality comes from the pendant groups on either side of the nitrogen that, when the substrate is bound to the catalyst, shield one face of the substrate while opening the other to attack (Figure 2.1).[4]

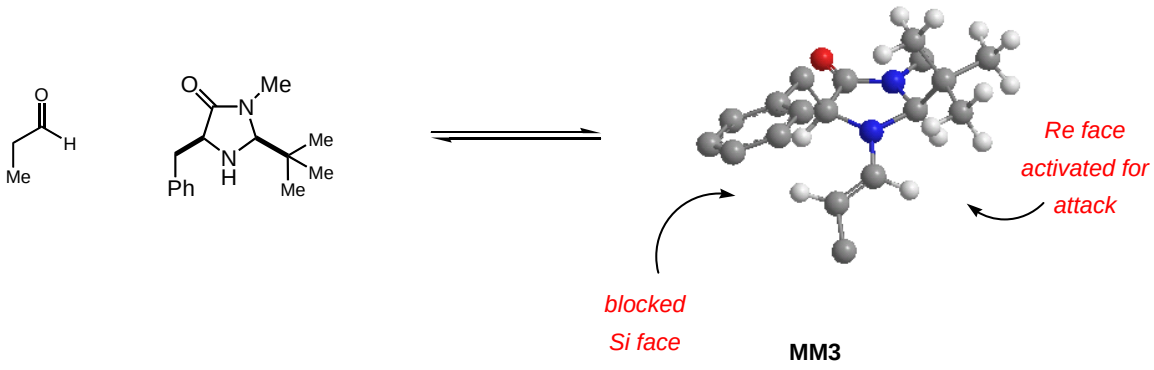


Figure 1.2: Chiral imidazolidinone catalysts allow enantiofacial discrimination.

This catalyst type has been used to affect iminium,[9] enamine,[10] and SOMO-activated[11] reactions (Figure 1.3), and both this catalyst and proline have been used by the MacMillan group to affect transformations such as the aldol reaction.[10b, 12]

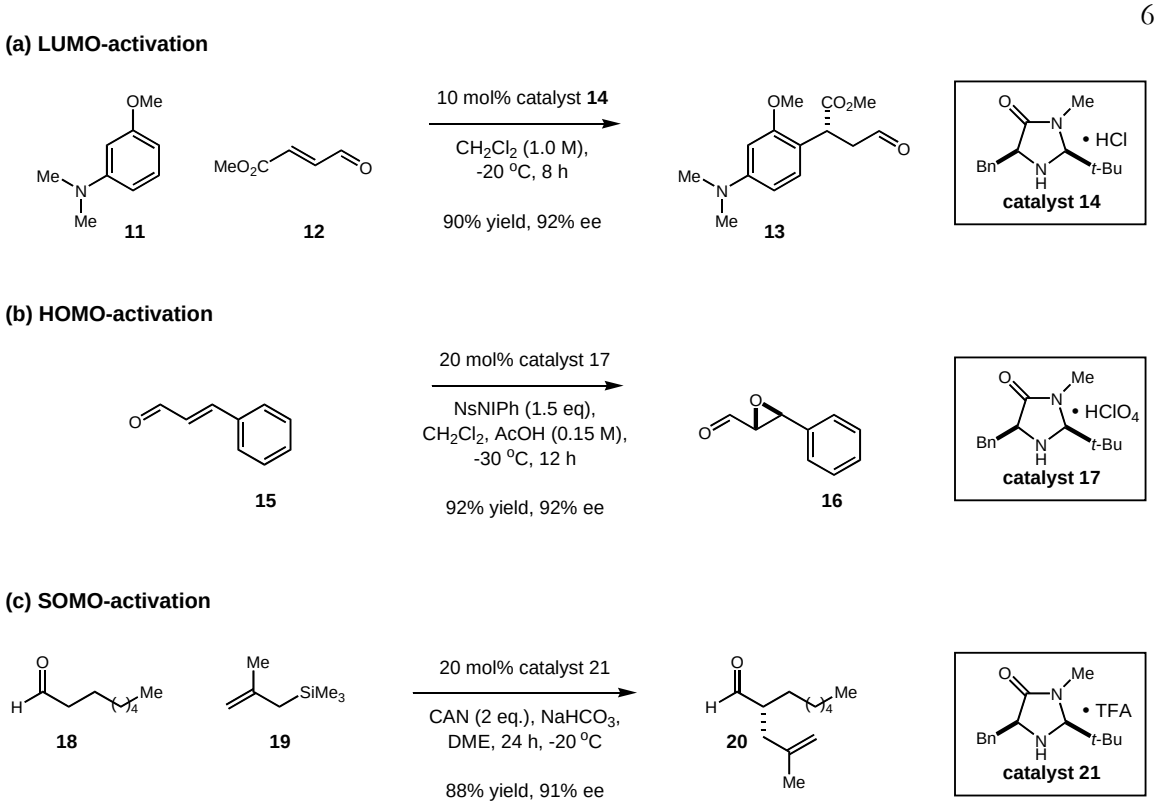


Figure 1.3: (a) Imidazolidinone **14** catalyzes the enantioselective 1,4-addition of substituted benzene **11** to α,β-unsaturated aldehyde **12**. (b) Imidazolidinone **17** catalyzes the epoxidation of α,β-unsaturated aldehyde **15** to epoxide **16**. (c) Single electron oxidation of the enamine formed between catalyst **21** and aldehyde **13** allows formation of aldehyde **20** through a radical pathway.

The aldol reaction is the general name for a reaction where an enolate nucleophile attacks an electrophilic carbonyl to form a new C-C bond (Figure 1.4). It was independently described by both Charles-Adolphe Wurtz and Alexander Borodin in 1872.[13] Since the discovery of the aldol reaction, numerous variants have been developed and it has

been employed in countless syntheses.[14] One challenge of the aldol reaction is controlling which reactant acts as the donor and which reactant acts as the acceptor (Figure 1.4).

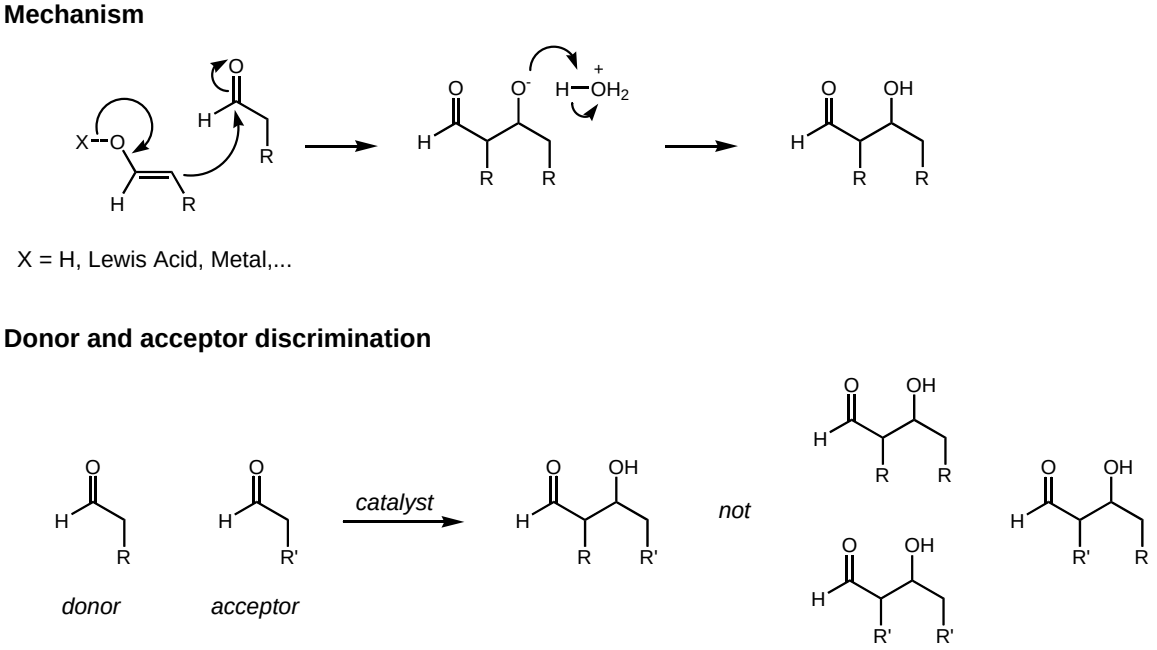
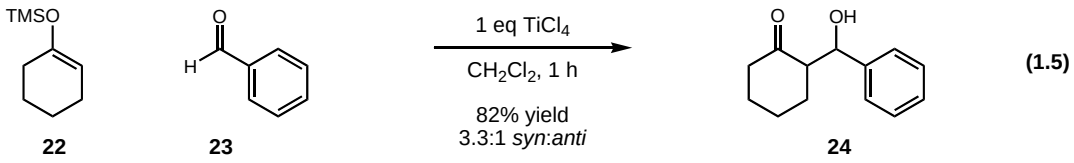


Figure 1.4: Mechanism and mechanistic challenges associated with the aldol reaction

One variant, known as the Mukaiyama aldol reaction, uses a preformed silyl enolate to help assign the role of donor and acceptor. Specifically, this reaction describes the

Lewis acid promoted or catalyzed addition of nucleophilic silyl enol ethers to aldehydes or ketones. The first description of this reaction was published by Mukaiyama in 1973 and described the titanium tetrachloride promoted addition of the silyl enol ether of cyclohexanone (**22**) into benzaldehyde (**23**) to produce the aldol product with an approximately 3:1 syn:anti relationship (**24**, Equation 1.5).[15]



22 **23** **24** **(1.5)**

Another variant on the aldol reaction that produces enantioenriched or enantiopure materials uses the Evans oxazolidinone, a chiral auxiliary that is appended to the aldehyde prior to enolization. This creates a chiral enolate for the purpose of the aldol reaction, and then the auxiliary can be cleaved to restore the aldehyde or provide other functional groups such as an acid or amide (Figure 1.5).[16] The Evans oxazolidinone has long been regarded as a major breakthrough in aldol technology, and countless natural products and pharmaceuticals owe their completion to this method. A drawback of this system is that the attachment and cleavage of the chiral auxiliary adds steps to the process of performing the aldol reaction, which ultimately decreases the overall yield.

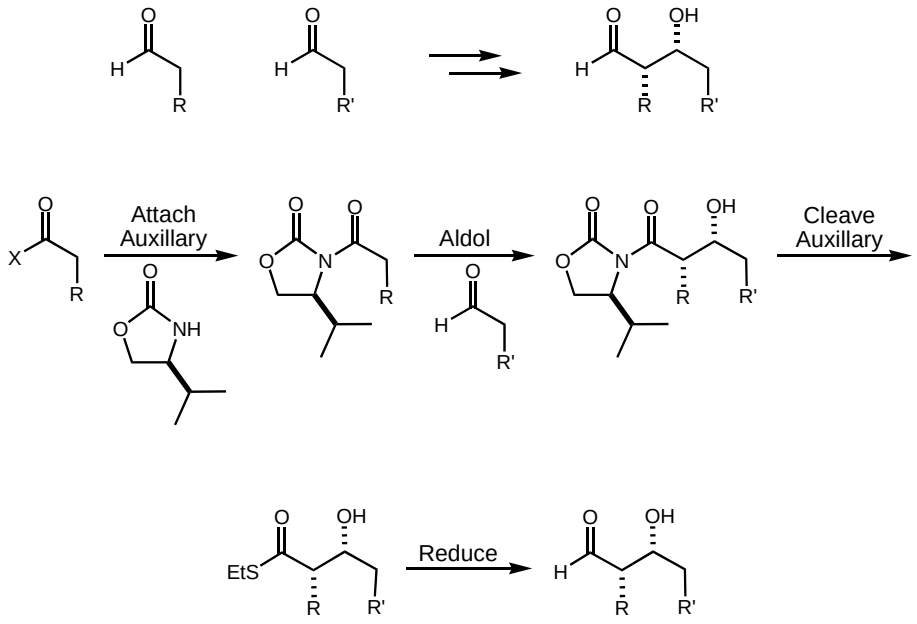


Figure 1.5: The Evans oxazolidinone methodology proceeds through the following steps: (a) attachment of the chiral auxiliary to the aldehyde, (b) aldol addition, (c) cleavage of the auxiliary, and (d) reduction of the cleaved product to the aldehyde. To add a second aldehyde to the aldol product, these steps would be repeated.

Therefore, the publication by Northrup and MacMillan in 2002 of a proline-catalyzed cross reaction of aldehydes produced considerable interest. This publication was followed by others detailing proline-catalyzed aldol reactions between α-oxyaldehydes and imidazolidinone-catalyzed aldol reactions to produce both syn- and anti-aldol products (Figure 1.6).[12] The catalytic cycles for the imidazolidinone and proline catalysts are believed to be similar. They both begin with the formation of an iminium ion that converts to the reactive enamine, and the aldol reaction takes place. However, the product of the imidazolidinone-catalyzed aldol reacts with another aldehyde in an acid-catalyzed acetal formation, while the proline-catalyzed reaction simply releases the product which does not

react further in the reaction media (Figure 1.7). The proline-catalyzed aldol reaction of α-oxyaldehydes provided a framework for the two-step synthesis of hexoses. Because both the imidazolidinone- and proline-catalyzed reactions failed to undergo multiple iterations, it was clear that a second aldol technology would have to be employed to produce hexoses.

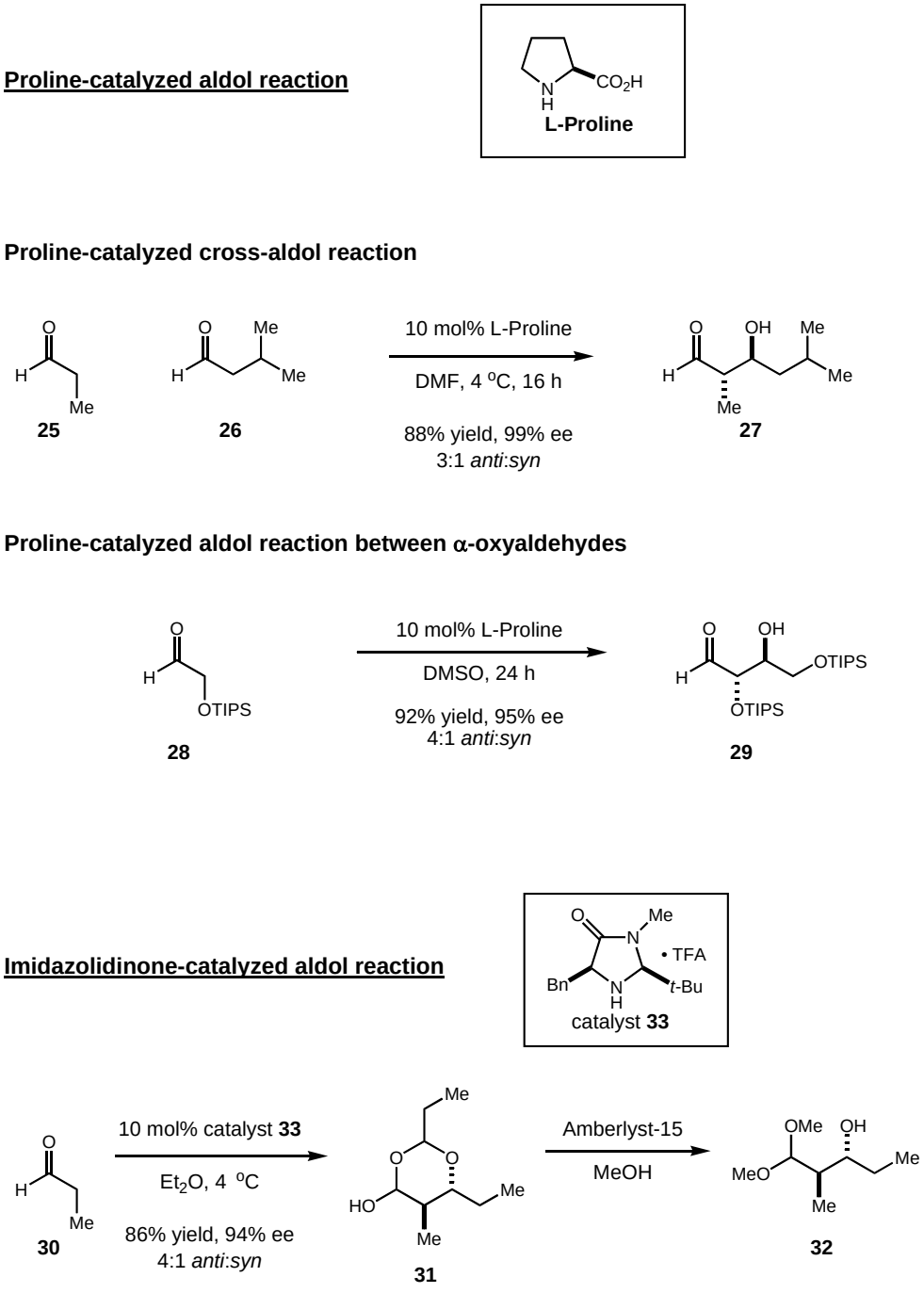


Figure 1.6: Both proline and imidazolidinone catalyst **35** can catalyze aldol additions.

A two-step synthesis of hexoses represented a great step forward for carbohydrate synthesis. Historically, the syntheses of hexose monomers have followed similar paths. One would begin with the natural hexose and elaborate it through a series of protections and deprotections to a usable saccharide for coupling. Protection motifs similar to the ones produced by the MacMillan methodology routinely took more than 15 steps to access.[17] This methodology also allowed the production of rare sugars: allose, L-sugars, and ^{13}C-labeled sugars. The most recent technology in selective glycoside protection was published by Wang, et al. and described a similar protection motif for glucose in four steps using a novel one-pot protection method.[18]

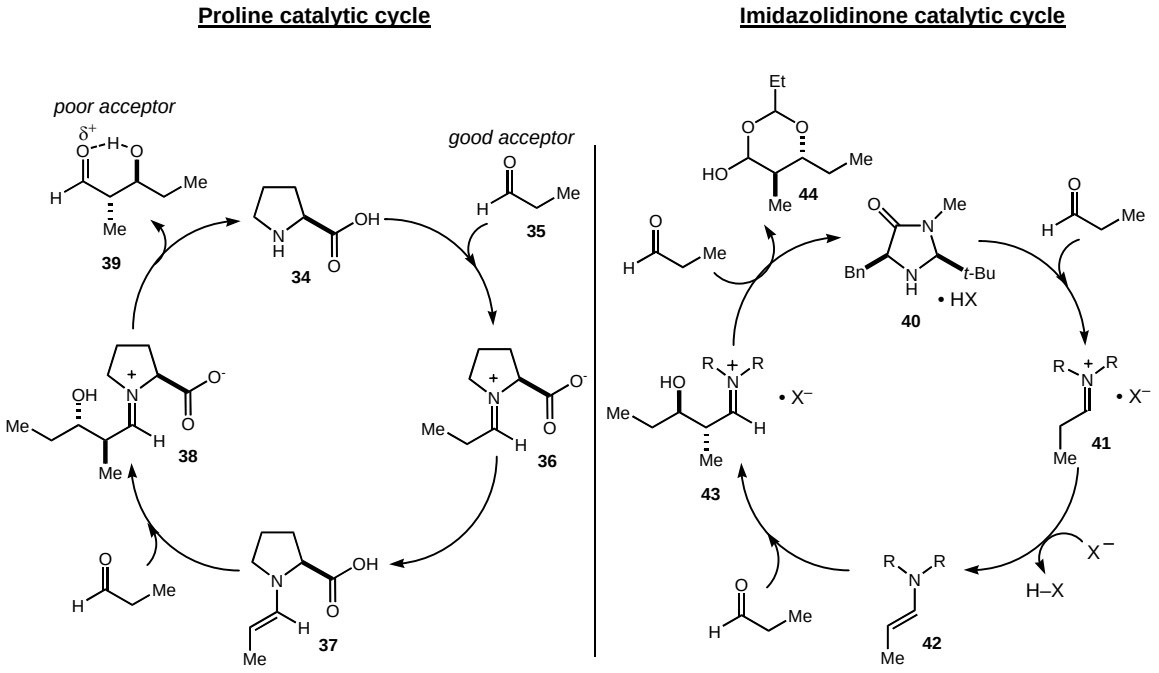
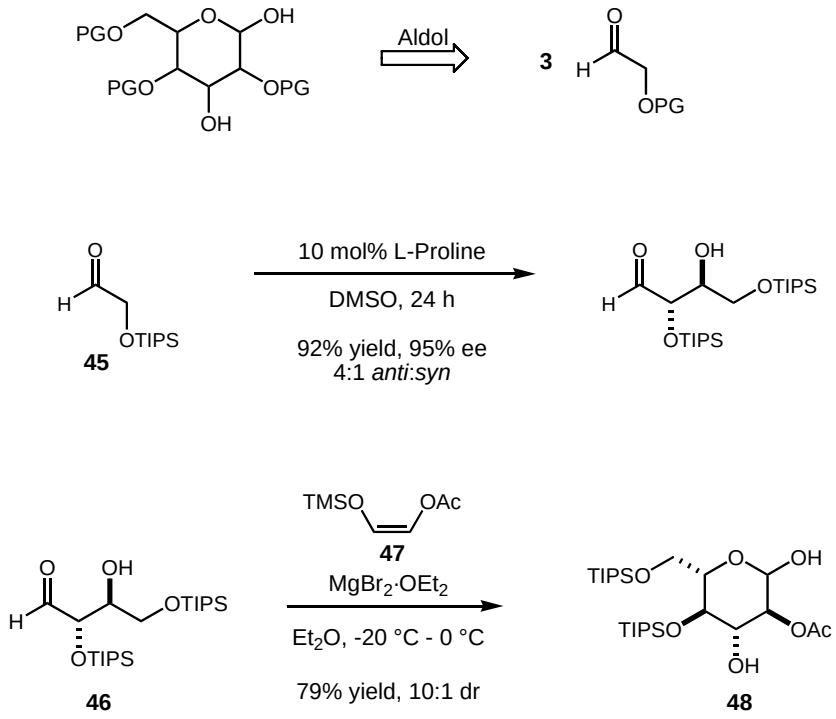


Figure 1.7: In both the proline and imidazolidinone catalytic cycles, the secondary amine condenses with the aldehyde to form an iminium ion which is converted to an enamine. This species adds into the second aldehyde to form the aldol product.

The concept behind the two-step synthesis is simple. A hexose can be thought of as the product of two aldol reactions combining three aldehydes. This two-step synthesis is the realization of this concept and relies on the combination of a proline-catalyzed aldol reaction between two protected α-oxyaldehydes, followed by a Mukaiyama aldol reaction between the resulting α,β,γ-oxyerythrose and a silyl enol ether. The aldol product cyclizes to form the hexose (Scheme 1.1).[20] This result was exciting because it was thought this reaction might produce a polymer instead of cyclizing (Figure 1.8).



Scheme 1.1: In the retrosynthetic sense, a hexose can be considered the product of two aldol reactions between three aldehydes. This has been achieved in the forward sense through a two-step procedure. First, TIPS-aldehyde **45** is dimerized through a proline-catalyzed aldol reaction to produce erythrose **46**. Then erythrose **46** and enolate **47** combine in a second aldol reaction to form protected glucose **48**.

The reagents used in this methodology were carefully chosen. The aldehyde used in the Mukiayama aldol reaction is the triisopropylsilyloxy-protected erythrose (TIPS-erythrose, **46**) produced by the proline-catalyzed reaction (Scheme 1.1). This aldehyde was selected for three reasons. First, the triisopropylsilyl (TIPS) protecting group is considered to be a very acid- and base-stable silyl protecting group and is useful in saccharide synthesis because it allows for other protecting groups to be installed and removed without

fear of removing the silyl group. Second, there are many ways reported in the literature to selectively remove a primary TIPS group in the presence of a secondary TIPS group.[20] Finally, the TIPS-erythrose could be prepared in good yield and diastereoselectivity (92% yield, 4:1 *anti*:*syn,* Scheme 1.1), and the diastereomers could be separated via column chromatography. The enolates were chosen to place a protecting group at the 2-position of the resulting hexose that would be compatible with the conditions used to remove the TIPS groups (hydrogen fluoride in pyridine or tetrabutylammonium fluoride (TBAF) can be used to remove a TIPS group).[20] In addition, the protecting groups on the enolate were chosen to allow the installation of either a participating or nonparticipating group (Figure 1.11). The choice of solvent and Lewis acid greatly affected the stereochemical outcome of the reaction. For example, when the TIPS dimer was combined with acetoxyenolate **47** in dichloromethane with titanium (VI) tetrachloride, the resulting saccharide was protected allose **49**. When the Lewis acid was changed to a magnesium bromide diethyl etherate complex, protected mannose **50** was produced. When the solvent of this reaction was changed to ether, the resulting saccharide was glucose **51** (Scheme 1.2).

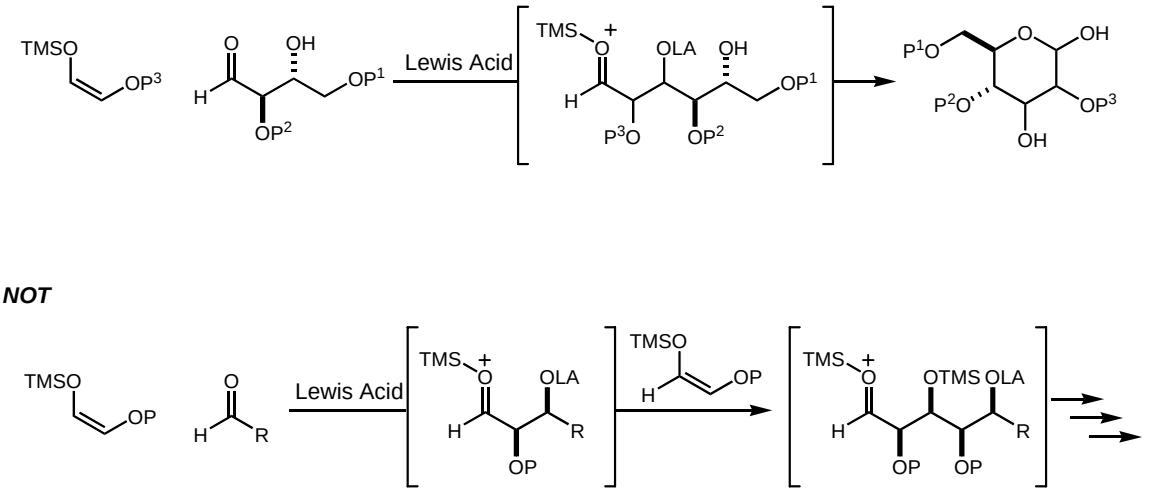
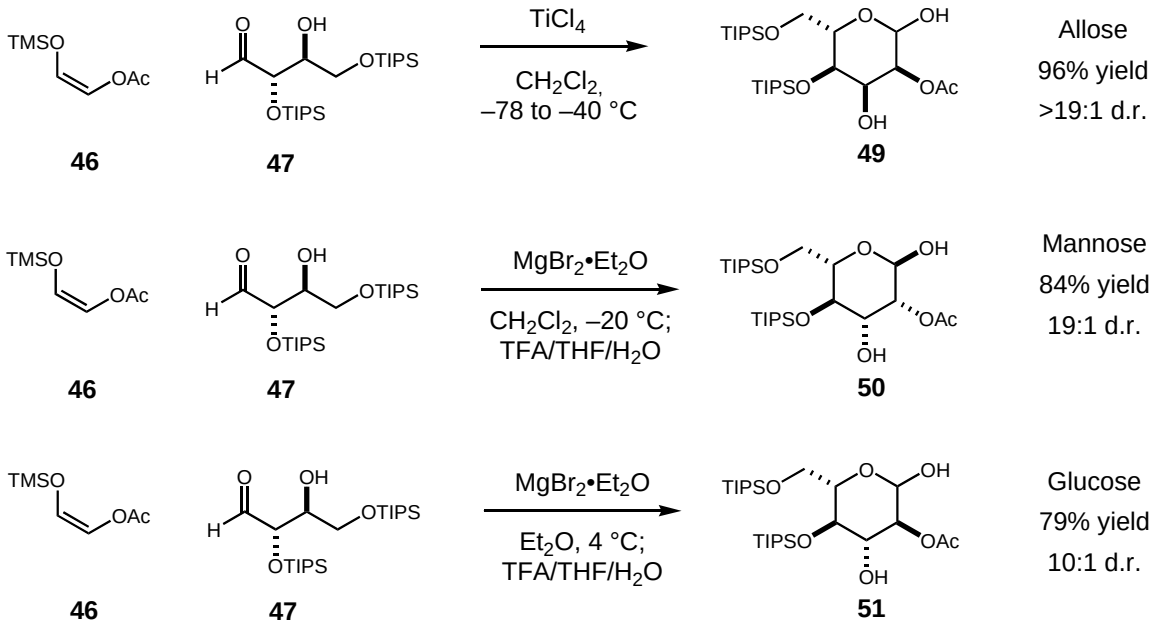


Figure 1.8: The δ-hydroxyaldehyde cyclizes to form a protected hexose, preventing subsequent aldol reaction which would produce a polymer.

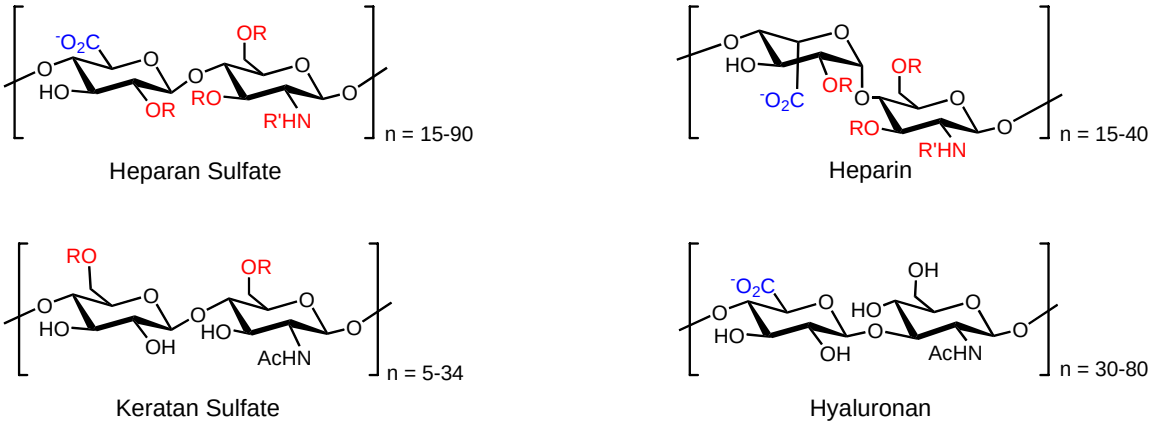
This methodology has been lauded for allowing chemists to efficiently access both natural and non-natural sugars. As the biological importance of glycosylation has become more apparent, the ability to rapidly synthesize saccharides becomes more and more necessary. For many biologically active polysaccharides, the ability to synthesize the saccharide of interest or non-natural saccharide probes has allowed scientists to better explore the biological roles that these sugars play.



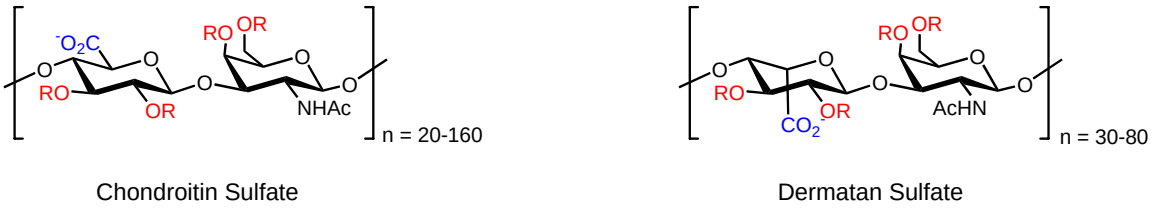
Scheme 1.2: By varying Lewis acid and solvent, acetoxyenolate **46** and TIPS-erythrose **47** can be combined to form a differentially-protected allose, mannose, and glucose.

For example, those studying glycosaminoglycans (GAGs) have relied heavily on synthesis to allow them to analyze the many biological roles these molecules play. Made up of alternating uronic acid and aminosugar residues, GAGs are polymeric and can consist of 2~200 disaccharide units. This broad class of molecules is commonly thought to have two subclasses (the glucosaminoglycan class and the galactosaminoglycan class). The glucosaminoglycan class is made up of four types: heparan sulfate, heparin, keratan sulfate, and hyaluronan. The galactosaminoglycan class consists of chondroitin sulfate and dermatan sulfate. These molecules can be sulfated at various positions around the ring, and they are given a letter designation to refer to each sulfation pattern (Figure 1.9).[21]

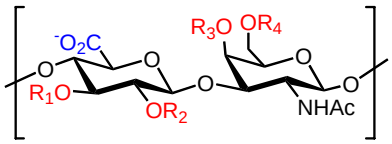
Glucosaminoglycan Class



Galactosaminoglycan Class



R = H or OSO_3^-
R' = Ac or OSO_3^-
n = average lengths



Chondroitin Sulfate-A: R_1, R_2, R_4=H; R_3=OSO_3^-
Chondroitin Sulfate-C: R_1, R_2, R_3=H; R_4=OSO_3^-
Chondroitin Sulfate-D: R_1, R_3=H; R_2, R_4=OSO_3^-
Chondroitin Sulfate-E: R_1, R_2=H; R_3, R_4=OSO_3^-

Figure 1.9: Glycosaminoglycans can be divided into two classes, glucosaminoglycans and galactosaminoglycans, based on the aminosugar residue present in the polysaccharide chain. These classes are further divided based on the uronic acid or glycosyl residue present in the polysaccharide backbone and the sulfation pattern displayed along the chain.

Glycosaminoglycans exist as heterogeneous polymeric chains that can consist of a mixture of glycosaminoglycan subtypes or one subtype, and the chain can display a variety of sulfation patterns. They usually reside on the cell surface and in the extracellular matrix where they are involved in numerous biological functions, ranging from cell growth to protein activity regulation. It is believed that the glycosaminoglycan conformation and sulfation pattern determines the biological activity. Synthetic glycosaminoglycans have been used to help determine the specific motif responsible for a biological event.[21]

For example, heparin is known to act as an anticoagulant, though the mechanism for this behavior was unclear. In the 1980s, the Sinay and Choay groups collaborated to synthesize a heparin pentasaccharide, and they used this synthetic pentasaccharide to determine how heparin inhibits coagulation. It was determined that a pentasaccharide expressing a specific sulfation pattern binds to antithrombin III, which induces a conformational change. This new complex binds an assortment of proteins and proteases involved in coagulation and inhibits clot formation (Figure 1.10).[21a]

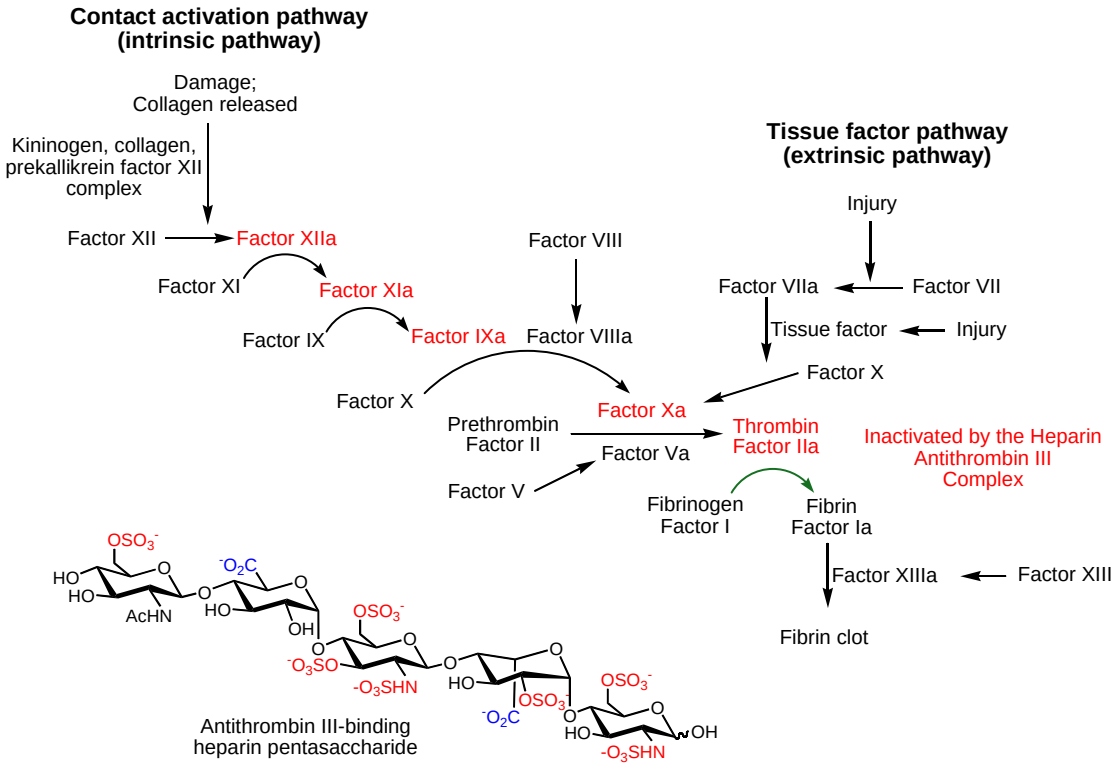


Figure 1.10: Heparin inhibits coagulation by binding and activating antithrombin III, which inhibits many factors along the coagulation pathway.

The synthesis of the heparin pentasaccharide by Sinay and Choay took 62 steps (33 in the longest linear sequence) and at least two years to complete.[21a] A more modern approach by Seeberger took 67 steps (with 28 in the longest linear sequence) to access a sulfated heparin tetrasaccharide.[22] The ability to access these molecules more quickly would be a great asset to glycobiologists.

The Synthesis of 2-Aminosugars Using a Two-Step Approach

The MacMillan sugar methodology allowed chemists to make many hexoses, but there were still sugars that needed to be accessed. For example, 2-aminosugars (sugars like glucosamine and galactosamine) are present in a plethora of glycoconjugates. It was believed that this technology should also allow an amine to be placed at the 2-position. To apply the same aldol technologies to 2-aminosugars, we first needed to find a way to make enolates of aminoaldehydes.

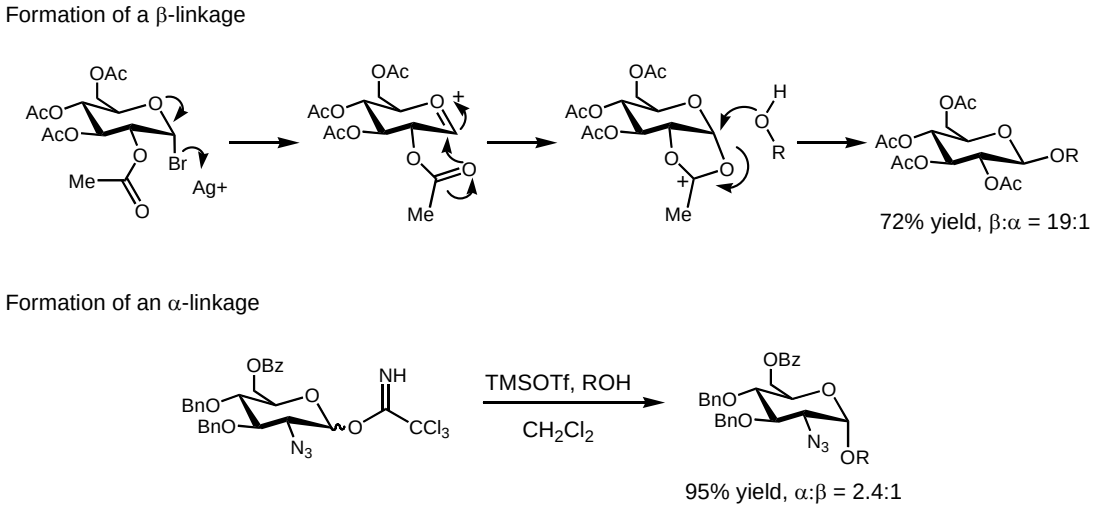
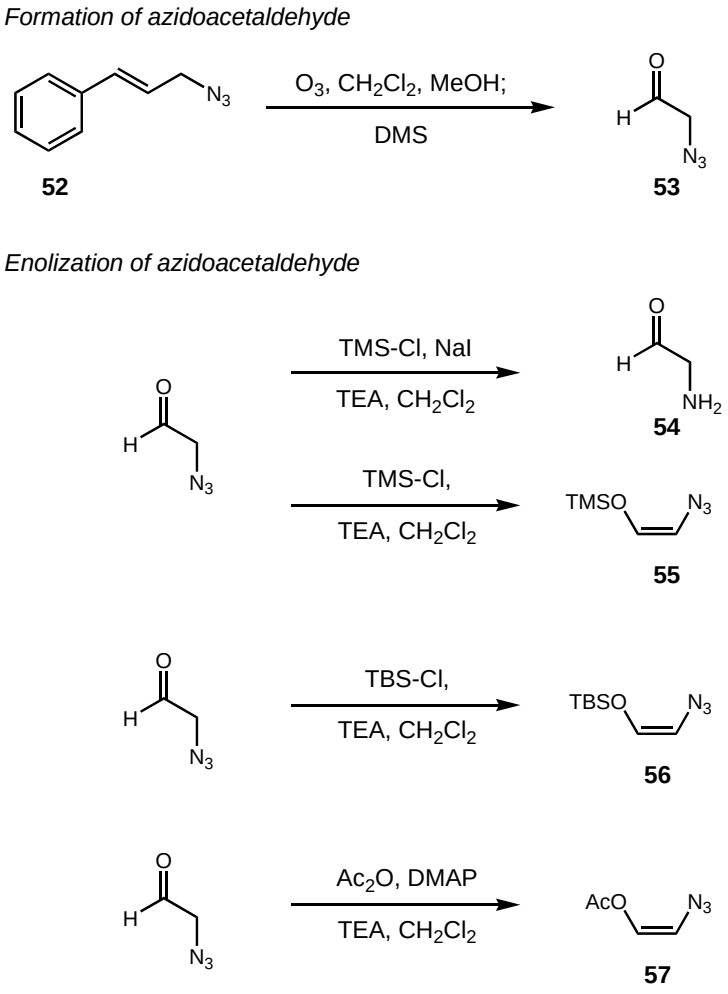


Figure 1.11: Participating groups refer to protecting groups that can block one face of the donor, forcing the acceptor to attack the unhindered face. Non-participating groups refer to protecting groups that do not perform in this manner.

Because any protecting group at the 2-position of a pyranose can affect the α:β ratio during coupling through the participating group effect (Figure 1.11), it was important to choose both protecting groups that participate in the coupling reaction and ones that do not participate. The first aldehyde chosen for enolization was azidoacetaldehyde (**53**, Scheme 1.3). The azide group does not participate in coupling reactions and can be converted to an amine via hydrogenation.[23]

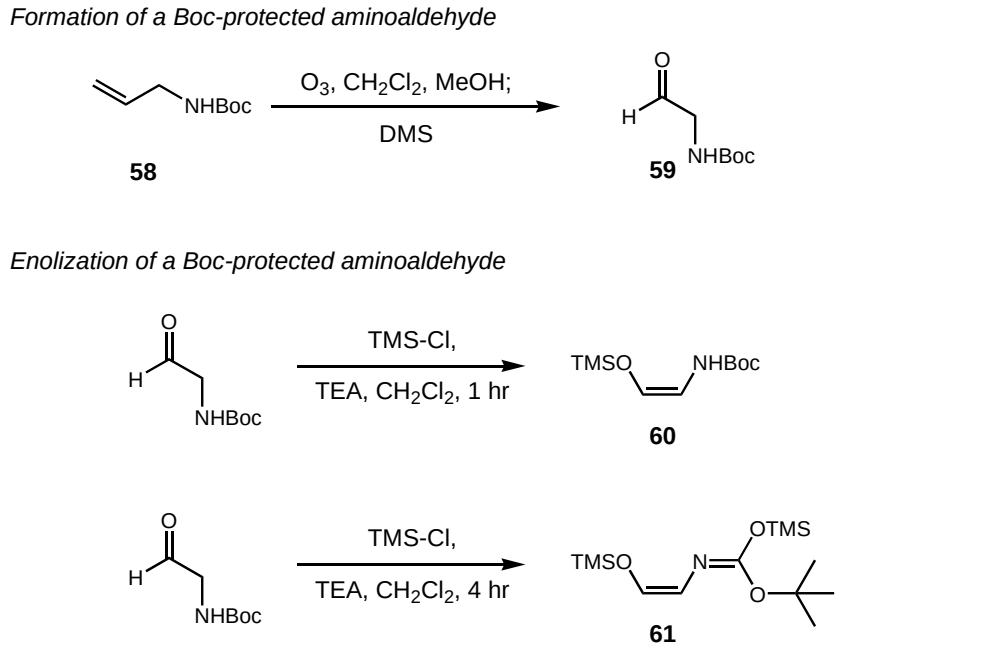
Forming the enolate of azidoacetaldehyde posed a few challenges. Aldehyde **53** was synthesized via the ozonolysis of cinnamylazide (**52**, Scheme 1.3).[32] Azidoacetaldehyde was not bench stable, and a trimer byproduct would begin to form when the azidoacetaldehyde was in concentrations greater than 0.5 M. This meant that isolation of the aldehyde and the conditions for its subsequent enolization had to be modified to allow for the purification and enolization to be performed on a 0.5 M solution of the aldehyde.



Scheme 1.3: Azidoacetaldehyde (**53**) was formed via ozonolysis of cinnamylazide (**52**) and enolized to form the TMS-, TBS-, and Ac-enolates.

Also, the aldehyde is typically distilled prior to enolization. However, there was a concern that the azidoacetaldehyde may be explosive when distilled. In addition, on the two occasions that the aldehyde was distilled, distillation was determined to be a low-yielding method for purification. Fortunately, experiments showed that the aldehyde could be enolized without being distilled.

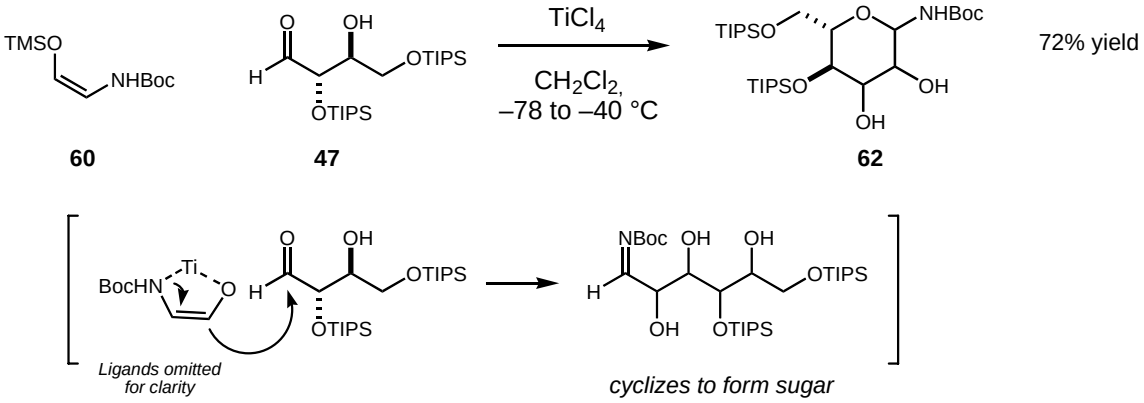
Next, the original conditions used for enolization were incompatible with the azide functionality. When the azidoacetaldehyde was exposed to the original enolization conditions (triethylamine, trimethylsilyl chloride, and NaI in acetonitrile), the azide was reduced to the amine. It was believed that the iodotrimethylsilane generated *in situ* was reducing the azide.[24] Accordingly, when the sodium iodide was omitted, the enolization reaction proceeded as desired (Scheme 1.3).



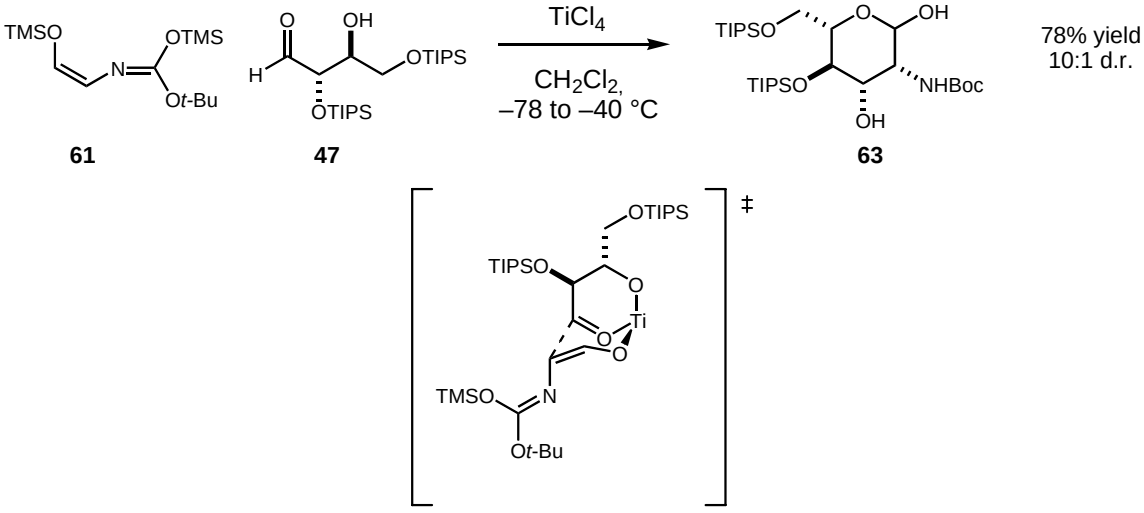
Scheme 1.4: Boc-protected aminoaldehyde **59** was synthesized via ozonolysis of Boc-protected allylamine **58.** Aldehyde **59** was elaborated to aminoenolate **60** and iminoenolate **61**.

Once formed, azidoenolate **55** was difficult to purify. Normally, to purify an enolate, the reaction is condensed and the residue is washed with dry ethyl ether. The ethereal extracts are then condensed and distilled. The enolate was unstable to distillation; ^{1}H NMR analysis of the distillate showed only the aldehyde. Column chromatography over triethylamine-treated silica also hydrolyzed the enolate. Consequently, the ethereal extracts were concentrated and used without distillation. The tributyldimethylsilyl-enolate (**56**) and the acetoxy-enolate (**57**) of azidoacetaldehyde were also synthesized with the hopes of creating a more stable enolate for purification, but both enolates proved unstable to distillation and column chromatography (Scheme 1.3).

Formation of a 1-aminosugar



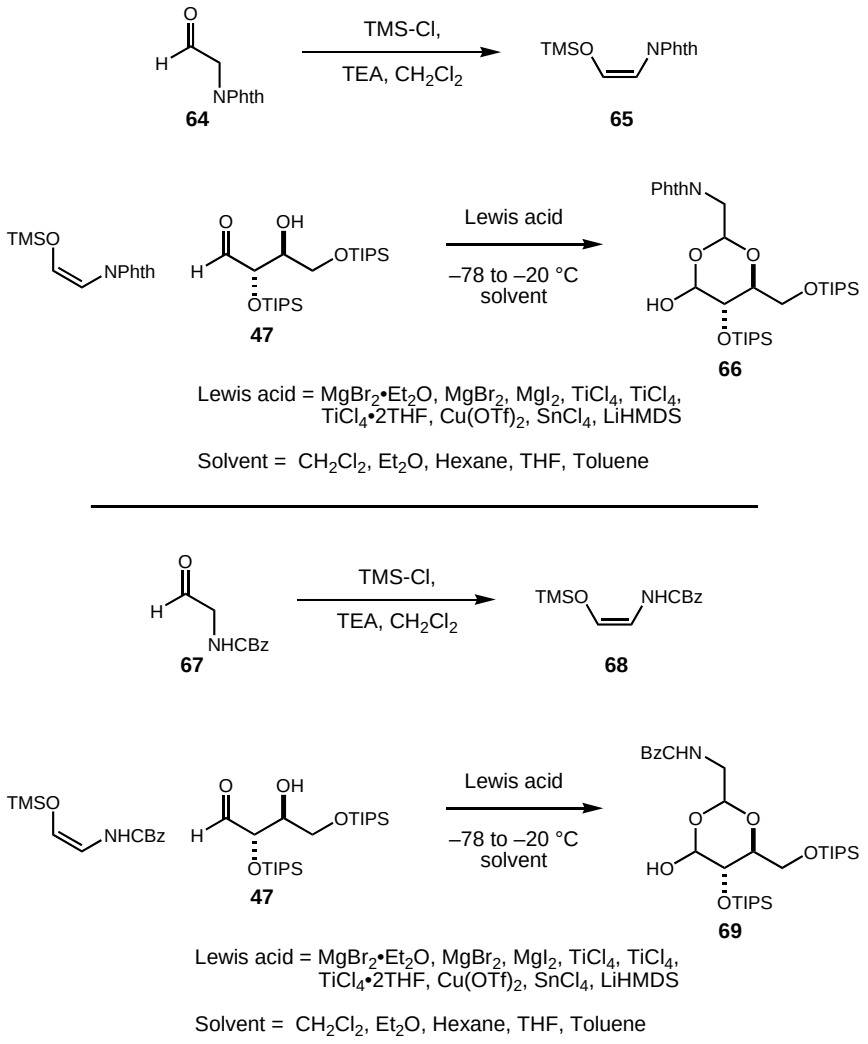
Formation of a 2-aminosugar



Anti-Felkin, *anti*-aldol

Figure 1.12: Aminoenolate **60** and TIPS-erythrose **47** combine to form 1-aminosugar **62**, while iminoenolate **61** and TIPS-erythrose **47** combine to form 2-aminosugar **63**.

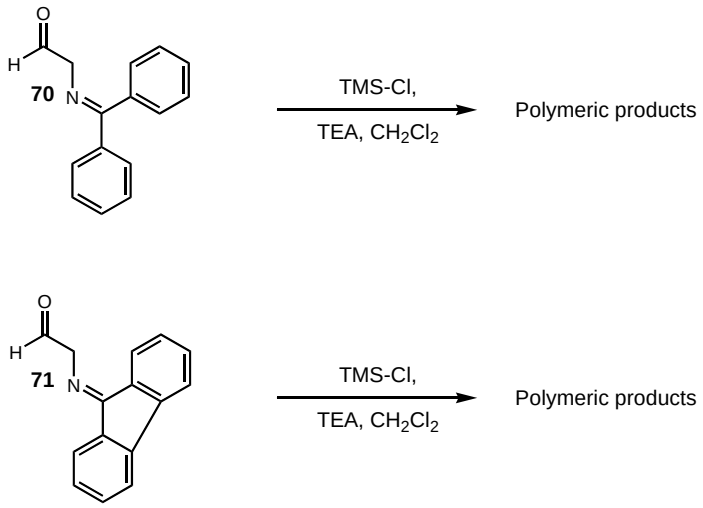
All three enolates were subjected to the aldol conditions with a variety of Lewis acids, though none afforded a 2-aminosugar product. Subjecting the azidoenolates to either tin (VI) tetrachloride or titanium (VI) tetrachloride reduced the azide to the amine, as shown by the isolation of aminoacetaldehyde from these reactions. Because of these complications, a different protecting group was chosen for installing an amine at the 2-position.



Scheme 1.5: Aminoenoates **64** and **67** did not participate in an aldol reaction with TIPS-erythrose **47.**

The *tert*-butylcarbamyl (Boc) protecting group is used frequently in carbohydrate chemistry because it functions as a good participating group in couplings and is stable to base and mild acids.[25] Though Boc-protected aminoaldehyde **59** is commercially available, it can also be easily prepared via an ozonolysis.[32] When the Boc-protected aminoaldehyde

was exposed to the enolization conditions for only an hour, the product was Boc-protected aminoenolate **60**. Surprisingly, exposing the Boc-protected aminoaldehyde to the enolization conditions for longer (3~5 hours) produced iminoenolate **61** (Scheme 1.4). Both enolates were tried in an aldol reaction with the TIPS-erythrose (using titanium (IV) tetrachloride and dichloromethane) with interesting results. The Boc-protected aminoenolate produced a 1-aminosugar (**62**). This implied that the nitrogen lone pair was donating into the π*-orbital of the enolate and initiating the reaction (Figure 1.12). We suspected that the iminoenolate would not react though this pathway because the nitrogen lone pair should be less active. Gratifyingly, iminoenolate **61** reacted as we expected, producing protected mannosamine **63** in 78% yield. We theorized that this originates from a closed, anti-Felkin transition state to give the *anti*-aldol product (Figure 1.12). Having established that an amine could be placed at the 2-position, the iminoenolate was tested with a variety of Lewis acids and solvents with the hope of accessing other stereochemistries, but none of these conditions produced usable yields of a 2-aminosugar.



Scheme 1.6: Exposure of aldehydes 70 and 71 to enolization conditions initiated polymerization of each aldehyde.

A variety of other aldehyde aminoenolates and iminoenolates were considered to access other 2-aminosugars. Aminoenolates **65** and **68** were made from their corresponding aldehydes. Interestingly, the CBz-protected aldehyde did not produce an iminoenolate despite varying the equivalents of TMS-Cl and reaction time. Use of aminoaldehyde enolates **65** and **68** did not provide access to the desired 2-aminosugar products. Instead, they both afforded a trimer-like product (Scheme 1.5). Iminoaldehydes **70** and **71**[33] were unable to be enolized, instead converting mostly to a polymeric material (Scheme 1.6). Also synthesized by a colleague, Dr. Akio Kayano, was thioester **72**, which can be converted to an enolate *in situ* via soft enolization techniques. This thioester provided access to a protected allosamine (**73**) when combined with the TIPS-erythrose in dichloromethane with titanium (VI) tetrachloride and Hunig's base (Figure 1.13). Having

determined that a stereochemistry other than mannose was accessible through this aldol technology, thioester **72** and the TIPS-erythrose were combined with a variety of Lewis acids, but none produced another stereochemistry or performed as well as titanium (VI) tetrachloride for the synthesis of the protected allosamine.

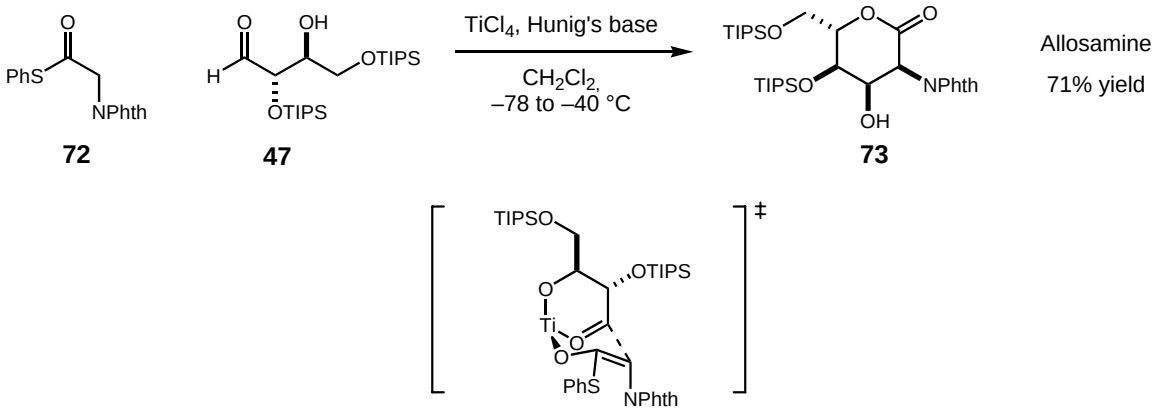


Figure 1.13: Titanium-mediated soft enolization of thioester **72** produced allosamine **73**.

The synthesis of protected mannosamine and allosamine were both exciting. Non-natural derivatives of mannosamine have been shown to have anti-tumor activity against T-cell lymphoma. Mannosamine has also implicated in the inhibition of proteoglycan breakdown, and derivatives of mannosamine are being investigated as anti-arthritics.[26] Allosamine, a rare aminosugar, is a key component of allosamidin, a chitinase inhibitor. Both asthma and allergies have been related to higher chitinase expression levels, and allosamidin and derivatives of allosamidin are being explored as a possible treatment

option for both conditions.[27] The ability to rapidly synthesize differentially-protected mannosamine and allosamine should accelerate the exploration of these molecules as treatment options.

Conclusions

Described above is the extension of the MacMillan sugar methodology to 2-aminosugars. Many enolates were not competent in this reaction, and a Boc-protected aminoenolate produced a protected 1-aminosugar. This methodology was successful at synthesizing a protected mannosamine using an iminoenolate. A protected allosamine was synthesized with a thioester using soft enolization conditions. Both products can serve as synthetic precursors for saccharides that are implicated as therapeutics for cancer, asthma, and arthritis.

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[28] All solvents were purified according to the method of Grubbs.[29] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile samples. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[30] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde, ceric ammonium molybdate, or $KMnO_4$ stain.

^{1}H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) or an Inova 500 (500 MHz and 125 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame

ionization detectors using a J&W Scientific DB-1701 (30 m x 0.25 mm) column as noted. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel OD-H column (25 cm) and OD-H guard (5 cm) as noted.

Preparation of Aldehyde Enolsilanes

Azidoacetaldehyde. (53) Previously prepared by Whitesides et al.,[31] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H, CHO); 4.03 (d, 2H, J = 1.2 Hz, CH_2N_3).

(*Z*)-Azido 2-(trimethylsilanyloxy)-vinyl ester. (55) Azidoacetaldehyde (0.3 g, 3.6 mmol) in dichloromethane (10 ml) was slowly added in a single portion to a 0° C solution of chlorotrimethylsilane (1.3 ml, 7.1 mmol), triethylamine (2.0 ml, 14.3 mmol), and dicloromethane (5 ml) in a flame-dried flask under an argon atmosphere. Within five minutes, the solution became a yellow suspension that continued to darken over time. The solution was allowed to warm to room temperature. Volatiles were removed *in vacuo* and the residue was extracted with three portions of anhydrous diethyl ether. The ether was removed *in vacuo* to afford the title compound (19:1 *Z*:*E*) in 70% yield as a translucent, red liquid. ^{1}H NMR (300 MHz, $CDCl_3$) *Z* isomer: δ 5.95 (d, 1H, J = 4.2 Hz, CHOTMS); 5.01

(d, 1H, J = 4.2 Hz, CHN_3); 0.16 (s, 9H, $Si(CH_3)_3$); *E* isomer: δ 6.41 (d, 1H, J = 10.8 Hz, CHOTMS); 5.94 (d, 1H, J = 10.8 Hz, CHN_3); 0.19 (s, 9H, $Si(CH_3)_3$).

(*Z*)-Azido 2-(tert-butyldimethylsilanyloxy)-vinyl ester. (56) Azidoacetaldehyde (0.3 g, 6.6 mmol) in dichloromethane (10 ml) was slowly added in a single portion to a 0 °C solution of *tert*-butyl dimethyl silyl chloride (1.1g, 7.2 mmol), triethylamine (2.0 ml, 14.3 mmol), and dicloromethane (5 ml) in a flame-dried flask under an argon atmosphere. Within five minutes, the solution became a yellow suspension that continued to darken over time. The solution was allowed to warm to room temperature. Volatiles were removed *in vacuo* and the residue was extracted with three portions of anhydrous diethyl ether. The ether was removed *in vacuo* to afford the title compound (16:1 *Z*:*E*) in 72% yield as a translucent, orange liquid. IR (film) 2955, 2930, 2858, 2360, 2382, 2108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *Z* isomer: δ 5.64 (d, 1H, J = 3.6 Hz, CHOTMS); 4.42 (d, 1H, J = 3.6 Hz, CHN_3); 0.93 (s, 9H, $CH_3)_3C$), 0.17 (s, 6H, $Si(CH_3)_2$); *E* isomer: δ 6.35 (d, 1H, J = 11.1 Hz, CHOTMS); 5.59 (d, 1H, J = 11.1 Hz, CHN_3); 0.87 (s, 9H, $CH_3)_3C$), 0.17 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) *Z* isomer: δ 139.1, 112.9, 51.5, 31.7, 23.9, 17.2; HRMS (Cl+) exact mass calcd for $[M + H]^+$ ($C_8H_{18}N_3OSi$) requires *m/z* 200.1219, found *m/z* 200.1212.

(*Z*)-Azido 2-(acetoxy)-vinyl ester. (57) Azidoacetaldehyde (0.61 g, 7.1 mmol) in dichloromethane (15 ml) was added dropwise over 15 minutes to a 0 °C solution of acetic anhydride (4.0 ml, 42.8 mmol), triethylamine (4.0 ml, 28.5 mmol), and 4-

dimethylaminopyridine (0.17 g, 1.4 mmol) in a flame-dried flask under an argon atmosphere. The solution was allowed to warm to room temperature. Volatiles were removed *in vacuo,* and the residue was extracted with three portions of anhydrous diethyl ether. The ether was removed *in vacuo* to afford the title compound (>19:1 *Z*:*E*) in ^{1}H NMR (300 MHz, $CDCl_3$) *Z* isomer: δ 6.83 (d, 1H, *J* = 4.8 Hz, CHOAc); 5.51 (d, 1H, *J* = 4.8 Hz, CHN_3); 2.13(s, 3H, $COCH_3$).

((*Z*)-[2-(Trimethylsilanyloxy)-vinyl]-carbamate. (60) (2-Oxo-ethyl)-carbamic acid *tert*-butyl ester (0.2 g, 1.2 mmol) was added in a single portion as a solution in 1 mL of acetonitrile to a room temperature solution of chlorotrimethylsilane (0.3 mL, 2.5 mmol), triethylamine (0.7 mL, 5.0 mmol), and acetonitrile (2 mL). In less than five minutes, the solution became a hot white suspension that turned into a rust-colored suspension within fifteen minutes. After stirring for 30 minutes, volatiles were removed *in vacuo* and the residue was extracted with three portions of anhydrous diethyl ether. Distillation of the ethereal extracts afforded the title compound (0.19 g, 0.82 mmol, b.p. 53-56 °C, 0.1 mmHg, 5:1 *Z*:*E*) in 68% yield as a clear, colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (bs, 1H, NH); 5.95 (d, 1H, *J* = 4.8 Hz, CHOTMS); 5.24 (d, 1H, *J* = 4.8 Hz, CHN); 1.46 (s, 9H, $C(CH_3)_3$); 0.21 (s, 9H, $Si(CH_3)_3$).

((*Z*)-[2-(Trimethylsilanyloxy)-vinyl]-carbamic acid *tert*-butyl ester)-trimethylsilyl-imidate. (61) (2-Oxo-ethyl)-carbamic acid *tert*-butyl ester (3.0 g, 18.8

mmol) was added in a single portion as a solution in 10 mL of acetonitrile to a room temperature solution of chlorotrimethylsilane (4.78 mL, 37.7 mmol), triethylamine (10.51 mL, 75.4 mmol), and acetonitrile (30 mL). In less than five minutes, the solution became a hot white suspension that turned into a rust-colored suspension within fifteen minutes. After stirring for 3 hours, volatiles were removed *in vacuo* and the residue was washed with anhydrous diethyl ether (3 x 20 mL). Distillation of the ethereal extracts afforded the title compound (3.67 g, 12.1 mmol, b.p. 66-68 °C, 0.25 mmHg, 13:1 *Z*:*E*) in 64% yield as a clear, colorless liquid. IR (film) 2977, 1709, 1689, 1482, 1392, 1367, 1313, 1251, 1170, 1086, 847.7, 784.3, 755.6 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (d, 1H, *J* = 2.7 Hz, CHOTMS); 5.25 (d, 1H, *J* = 2.7 Hz, CHN); 1.49 (s, 9H, $C(CH_3)_3$); 0.24 (s, 9H, $Si(CH_3)_3$); 0.20 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 134.7, 111.4, 80.1, 28.6, 0.74, –0.25; HRMS (FAB+) exact mass calcd for $[M + H]^+$ ($C_{13}H_{29}NO_3Si_2$) requires *m/z* 303.1686, found *m/z* 303.1695. The product ratios were determined by ^1H NMR integration of the crude reaction mixture.

(*Z*)-Phthalimido-2-(trimethylsilanyloxy)-vinyl ester. (65)

Phthalimidoacetaldehyde (0.50 g, 2.65 mmol) in acetonitrile (8 mL) was slowly added in a single portion to a 0° C solution of chlorotrimethylsilane (0.67 ml, 5.3 mmol), triethylamine (1.5 ml, 10.6 mmol), and acetonitrile (8 ml) in a flame-dried flask under an argon atmosphere. Within five minutes, the solution became a yellow suspension that continued to darken over time. The solution was allowed to warm to room temperature. Volatiles were removed *in vacuo* and the residue was extracted with three portions of

anhydrous diethyl ether. The ether was removed *in vacuo* to afford the title compound (1.5:1 *Z*:*E*) in 86% yield as a translucent, red liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ *Z* isomer: 7.91-7.78 (m, 2H) ArH, 7.72-7.65 (m, 2H) ArH, 6.47 (d, 1H, *J* = 4.8 Hz, C**H**OTMS); 5.43 (d, 1H, *J* = 4.8 Hz, CHN_3); 0.12 (s, 9H, $Si(CH_3)_3$); *E* isomer: δ 7.91-7.78 (m, 2H) ArH, 7.72-7.65 (m, 2H) ArH, 7.50 (d, 1H, *J* = 11.4 Hz, C**H**OTMS); 6.42 (d, 1H, *J* = 11.4 Hz, CHN_3); 0.11 (s, 9H, $Si(CH_3)_3$).

Preparation of Sugars

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde. (46) A suspension of triisopropylsilanoxy-acetaldehyde (5.00 g, 23.0 mmol) and L-proline (133 mg, 1.15 mmol) in methyl sulfoxide (50 mL) was stirred for 24 h at room temperature. The resulting solution was diluted with ethyl ether (150 mL) and washed with water (3x50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude ^{1}H NMR analysis indicated complete conversion to a mixture of 4:1 *anti*:*syn* diastereomers. Flash chromatography (3% ether in pentane) afforded the title compound as a clear, colorless oil that froze upon storage at –20 °C (1.86 g, 4.3 mmol, 37%) as well as a faster-eluting fraction of a mixture of *syn*- and *anti*-diastereomers (2.74 g, 6.3 mmol, 55%) in 92% combined yield, 95% ee (*anti*-diastereomer). IR (film) 3483, 2945, 2892, 2868, 1734, 1464, 1385, 1117, 1069, 883, 683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (d, 1H, *J* = 2.1 Hz, CHO); 4.25 (dd, 1H, *J* = 3.9, 2.1 Hz, C**H**CHO); 4.10-3.94 (m, 1H, C**H**OH); 3.84

(dd, 1H, J = 9.9, 6.6 Hz, CH_2OR); 3.79 (dd, 1H, J = 9.6, 6.3 Hz, CH_2OR); 2.40 (d, 1H, J = 5.4 Hz, OH); 1.16-1.00 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 78.9, 74.3, 62.7, 18.0 (12C), 12.4 (3C), 11.9 (3C); HRMS (CI+) exact mass calcd for $[M+H]^+$ ($C_{22}H_{49}O_4Si_2$) requires *m/z* 433.3169, found *m/z* 433.3176; $[\alpha]_D$ = –3.6 (c = 4.0, $CHCl_3$).

1-*tert*-Butylcarbamato-1-deoxy-4,6-bis-*O*-triisopropylsilyl-α,β-L-pyranose. (62) Titanium (IV) tetrachloride (38 μL, 0.35 mmol) was added dropwise to a stirring solution of (2*S,* 3*S*)-3-hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (50 mg, 0.12 mmol), ((*Z*)-[2-(Trimethylsilanyloxy)-vinyl]-carbamate (107 mg, 0.46 mmol) and dichloromethane (1.2 mL) at –78 °C. The solution turned dark red upon addition of $TiCl_4$ and was stirred at –78 °C for 5 hours. It was then allowed to warm gradually over 5 hours to –40 °C. After stirring for an additional 24 hours at –40 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl, extracted three times with ethyl acetate (4 mL), washed with 10% $NaHCO_3$ (2 x 5 mL)$_3$, brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (2:5 ether:hexanes) afforded the title compound as a clear, colorless oil (49 mg, 0.08 mmol, R_f = 0.3, stains teal blue in anisaldehyde) in 72% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (bs, 1H, NH); 4.91 (bd, 1H, J = 9.0 Hz, H1); 4.01 (dd, 1H, ,J = 2.4, 11.1 Hz, H6); 3.87 (dd, 1H, J = 2.4, 11.1 Hz, H6); 3.77 (dd, 1H, J = 9.0, 9.0 Hz, H2); 3.54 (dd, 1H, J = 9.0, 8.8 Hz, H3); 3.34 (m, 1H, H5); 3.21 (dd, 1H, J = 9.0, 8.8 Hz, H4); 2.57 (bs, 1H, OH); 2.54 (bs, 1H, OH); 1.16-1.00 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 77.4, 74.9, 73.6, 71.5, 71.2, 68.4, 65.3, 29.2, 18.6, 18.6,

13.5, 12.2,; 300 MHz COSY spectra support the above ^{1}H NMR assignments; HRMS (EI+) exact mass calcd for $[M+H]^{+}$ ($C_{29}H_{62}NO_7Si_2$) requires *m/z* 592.4065, found *m/z* 592.4066.

2-*tert*-Butylcarbamato-2-deoxy-4,6-bis-*O*-triisopropylsilyl-α,β-L-mannopyranose. (63) Titanium (IV) chloride (38 μL, 0.35 mmol) was added dropwise to a stirring –78 °C solution of (2*S*, 3*S*)-3-hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (50 mg, 0.12 mmol), ((*Z*)-[2-(trimethylsilanyloxy)-vinyl]-carbamic acid *tert*-butyl ester)-trimethylsilyl-imidate (175 mg, 0.58 mmol) and dichloromethane (2.3 mL). The resulting red solution was stirred at –78 °C for 5 hours, then allowed to warm gradually over 5 hours to –40 °C. After stirring for an additional 48 hours at –40 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl, extracted three times with ethyl acetate (5 mL), washed with 10% $NaHCO_3$ (2 x 7 mL), brine (7 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude ^{1}H and ^{13}C NMR analysis indicated complete conversion to a 10:1 mixture of mannose:allose-derived diastereomers as well as some minor acetal side-products. Flash chromatography (1:3 ether:hexanes, R_f = 0.4, stains red in anisaldehyde) afforded the title compound as a clear, colorless oil (51 mg, 0.09 mmol, 2:1 α:β, 74%). IR (film) 3436, 2943, 2893, 2867, 1699, 1510, 1464, 1368, 1248, 1151, 1122, 1066, 883.0, 763.3, 680.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, 1H, *J* = 9.0 Hz, OH); 7.59 (bs, 1H, NH); 5.13 (d, 1H, *J* = 3.0 Hz, H1); 4.95 (m, 1H, H3); 3.95 (m, 1H, H2); 4.10 (m, 1H, H4); 3.85 (m, 1H, H5); 3.96 (m, 2H, H6); 1.47 (d, 1H, *J* = 3.0 Hz, C3 OH); 1.45 (s, 9H, $C(CH_3)_3$); 1.22-1.06 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 163.1, 94.0, 80.5, 75.5, 71.2, 70.0 63.5, 54.5, 28.5, 18.5, 18.5, 18.2, 18.1, 13.0, 12.2; 500 MHz COSY spectra support the above ^1H NMR assignments; HRMS (EI+) exact mass calcd for $[M+H]^+$ ($C_{29}H_{62}NO_7Si_2$) requires *m/z* 592.4065, found *m/z* 592.4064; $[\alpha]_D$ = –27.1 (c = 2.00, $CHCl_3$, 2:1 α:β mixture). Stereochemistry was confirmed by comparison to an authentic 2-acetamido-2-dexoy-1,3,4,6-tetra-*O*-acetyl-α-mannopyranose.

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Chapter 2

A Novel Method to Access Hexoses[23]

Introduction

The methodologies described in the previous chapter explored the reactivity of the TIPS-erythrose (**1**) and allowed scientists to access a variety of hexoses (Figure 2.1), but the reactivity of the TIPS-threose (**7**) still remained to be investigated. It was thought that the threose may allow access to the syn-sugars: gulose, galactose, talose, and idose (Figure 2.2).

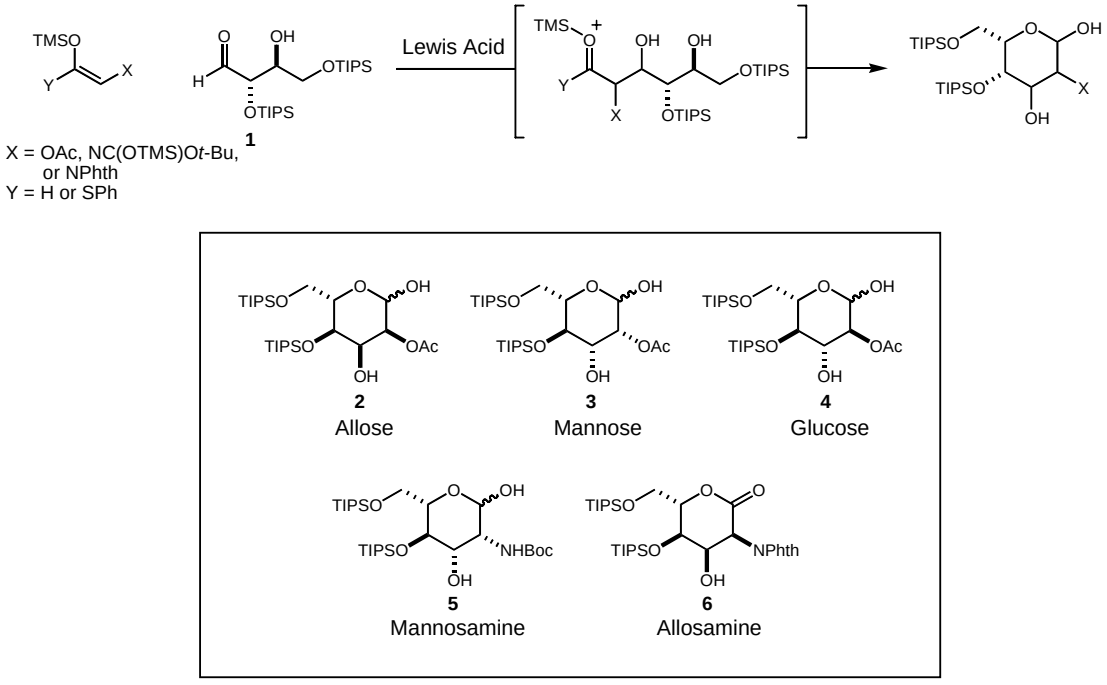


Figure 2.1: The TIPS-erythrose (**1**) has been elaborated to a differentially-protected allose, mannose, glucose, allosamine, and mannosamine.

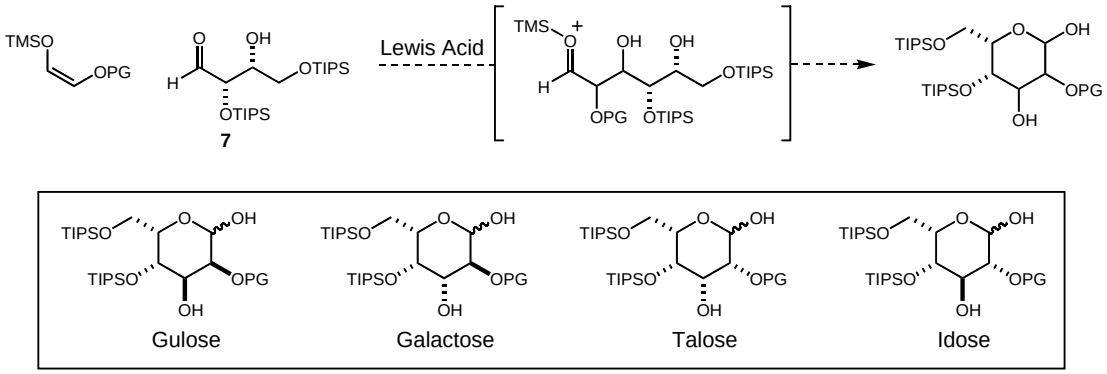


Figure 2.2: The TIPS-threose (**7**) may allow access to the syn-sugars, gulose, galactose, talose, and idose.

Many sugars are available in large quantities from natural sources. Syntheses often employ these sugars as starting materials because they can be easily obtained. In contrast, many of the syn-sugars are rare and are usually found as a component of a larger natural product.[2] In addition, many of these sugars often exist in modified forms, such as the uronic acid or a deoxygenated sugar. For example, free idose has not been isolated from nature even though iduronic acid is a key component of both heparin and dermatan sulfate (Figure 2.3). It is formed when heparan sulfate glucuronyl C5-epimerase (Hsepi) isomerizes D-glucuronic acid in heparan sulfate to L-iduronic acid.[3] Because of the impracticality or impossibility of isolating many of the syn-sugars from natural sources, methods for their synthesis have been explored.[2, 4]

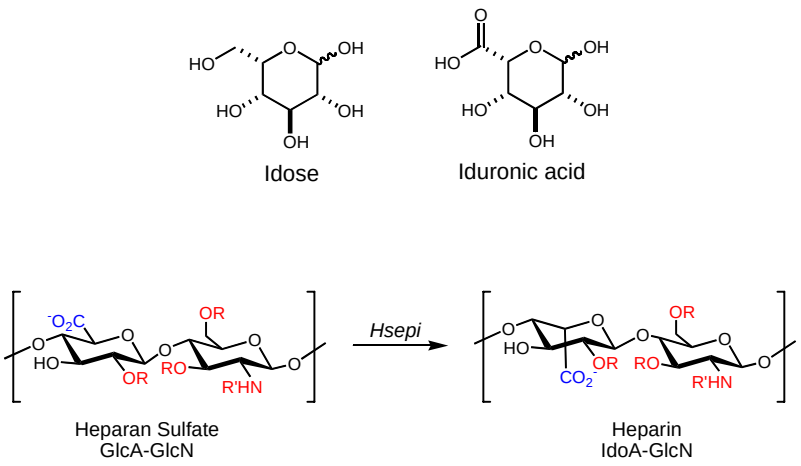
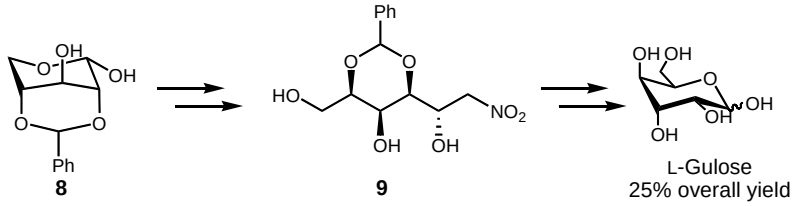


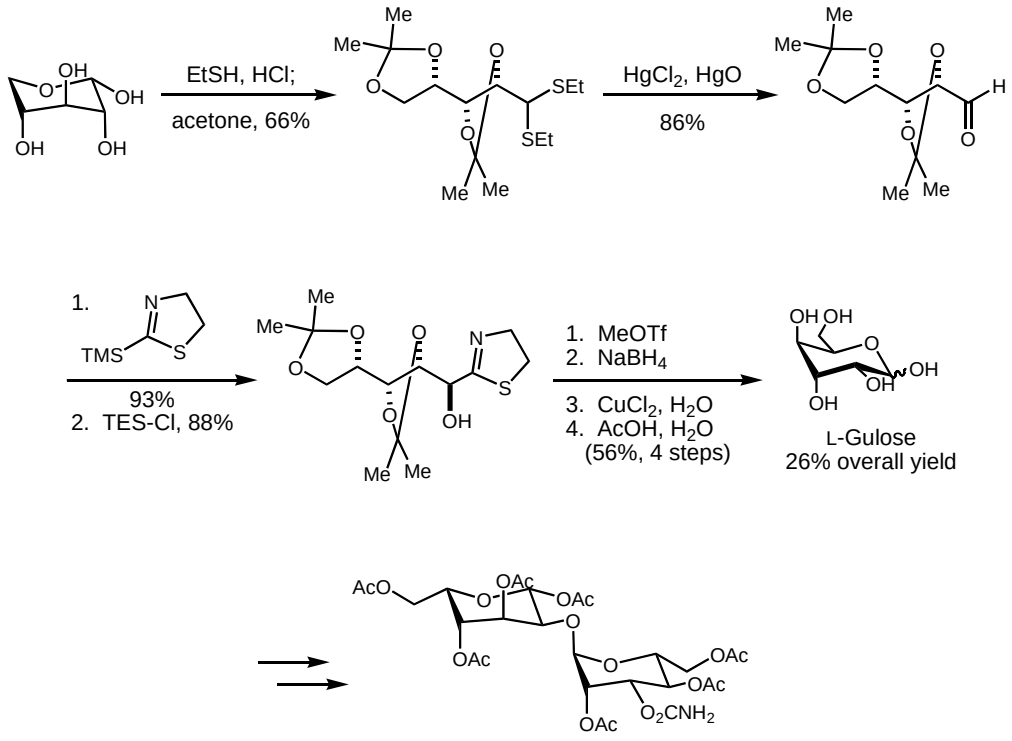
Figure 2.3: Glucuronic acid is epimerized to iduronic acid by heparan sulfate glucuronyl C5-epimerase (Hsepi).

Despite the ease with which nature prepares hexoses, they have posed a synthetic challenge for researchers. One method for synthesizing many rare sugars is to start with a commonly occurring sugar and then elaborate it to the desired syn-sugar.[4] For example, L-gulose has classically been synthesized from L-xylose. Sowden and Fischer used benzylidene L-xylose **8** to synthesize L-gulose in 25% overall yield (Scheme 2.1).[4a, b] While this method has seen extensive use, even the authors note that it is not a feasible method for large-scale synthesis.[4b] A more recent synthesis starts with commercially available L-xylose and synthesizes L-gulose in 8 steps and 26% overall yield.[4c] After converting xylose to gulose, Dondoni and coworkers used this saccharide to produce the gulose-mannose disaccharide moiety of Bleomycin A_2 (Scheme 2.2).



Scheme 2.1: Sowden and Fischer's method for accessing gulose

Though choosing starting materials from the chiral pool has long been a practice in synthesis, there are drawbacks to this method. Often effort must be spent modifying the chosen starting material before progress can begin towards the desired product. Because of the drawbacks of this method, researchers have looked for other ways to access hexoses. Even so, there are few methods for accessing hexoses from achiral starting materials. The methodologies that have been developed can be divided into four categories: asymmetric oxidation, allylation/oxidation, hetero-Diels-Alder, and aldol.



Scheme 2.2: Dondoni and Massi's method for accessing gulose

Asymmetric olefin oxidation technologies have been widely used to access carbohydrates due to their generality and the high enantioselectivities afforded by the chiral catalysts employed to set the vicinal oxygen stereocenters (Figure 2.4).[5]

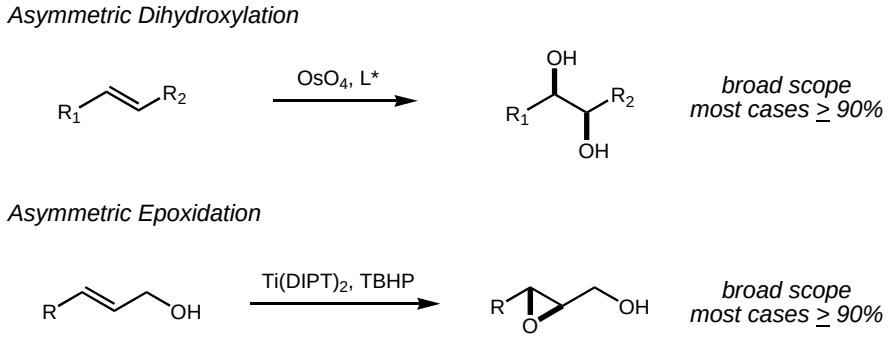


Figure 2.4: Asymmetric dihydroxylation and epoxidation strategies

Using these methodologies, Sharpless and coworkers were able to access all 8 of the L-hexoses. Through an iterative approach, they prepared each hexose in 20 steps (Figure 2.5).[6] Unfortunately, due to the requirement of acetonides as protecting groups for stereochemical purposes, this strategy cannot produce differentially-protected hexoses, and so further elaboration would be required for polysaccharide synthesis.

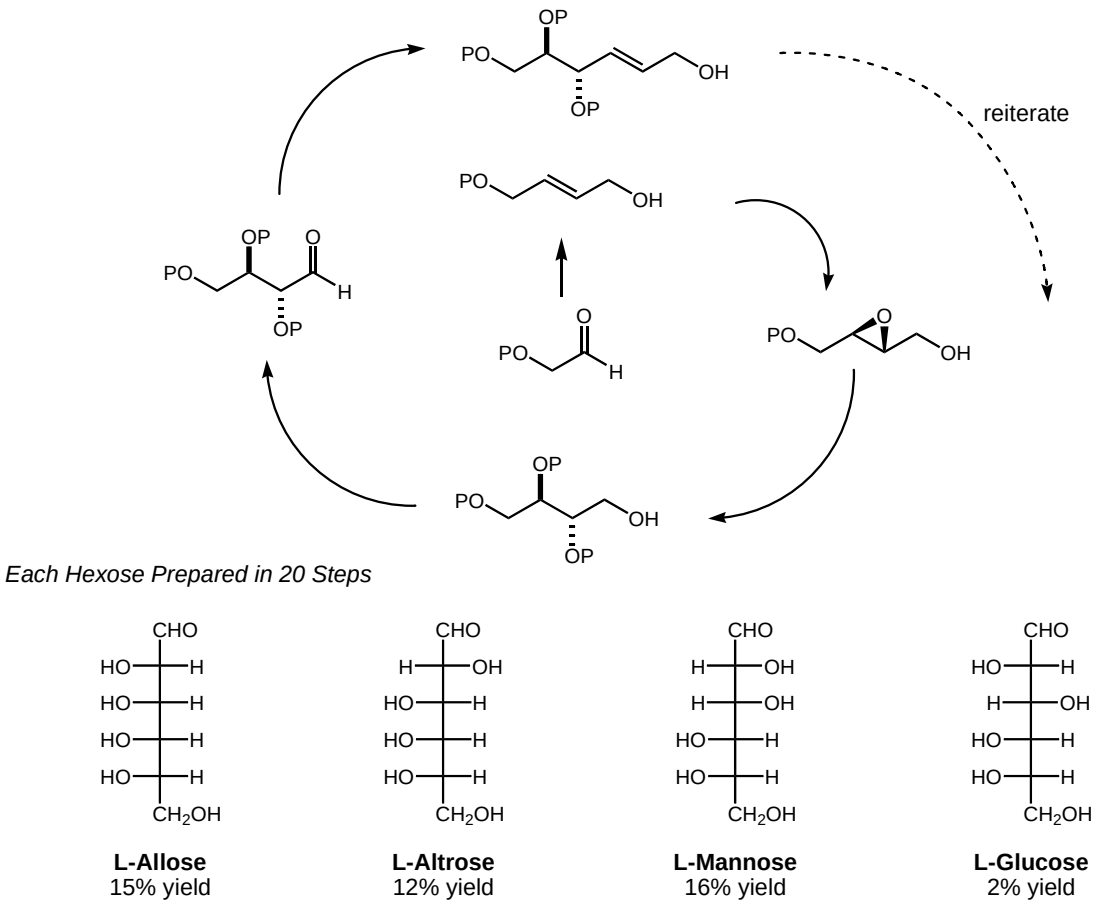


Figure 2.5: Asymmetric epoxidation has been used to synthesize the L-hexoses. It was noted that L-altrose was obtained as the 1,6-anhydro-β-L-altropyranose.

The allylation of aldehydes with chiral-metal reagents is another approach used for the construction of carbohydrates (Figure 2.6).[7] While this approach has been successfully used for natural and non-natural polysaccharides, the lengthy syntheses required to produce the chiral metal reagents, in addition to their toxicity and short shelf-lives, are drawbacks. In addition, this method again uses an iterative approach that lengthens the synthesis.

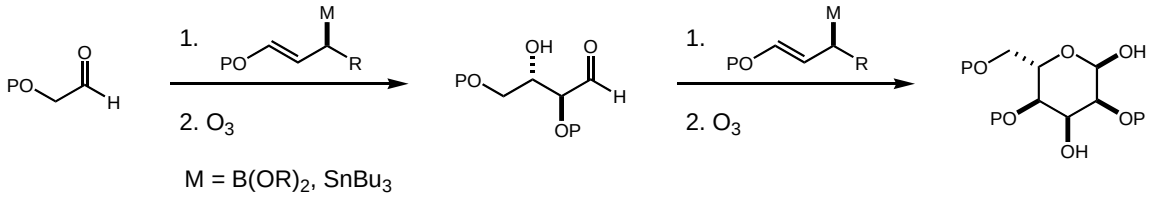


Figure 2.6: Allylmetal reagents have been used to synthesize carbohydrates.

Diels-Alder-based strategies have been employed for the synthesis of hexoses. For example, Danishefsky and coworkers have synthesized numerous natural and non-natural monosaccharides through the use of Danishefsky's diene (**10).** A Diels-Alder reaction between diene **10** and aldehyde **11** produces pyran **12**, which can be elaborated to form saccharides in the mannose, glucose, galactose, and talose families (Figure 2.7).[8] While this mode of synthesis is highly convergent, it cannot efficiently access all hexose stereochemistries since a large majority of Diels-Alder reactions favor the *endo* product.

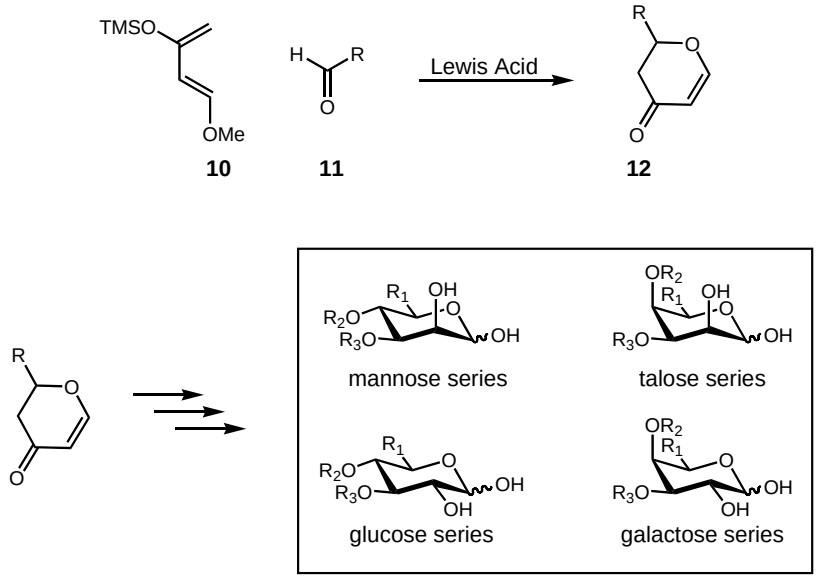


Figure 2.7: Diels-Alder chemistry has been used to access a variety of hexoses.

Another methodology applied to the synthesis of hexoses has been the aldol reaction. As described in Chapter 1, the aldol reaction is an important carbon-carbon bond-forming reaction that has been applied to the synthesis of many monosaccharides. One approach has involved the use of enzymes (such as kinase, aldolase, phosphatase, and isomerase enzymes) to form saccharides (Figure 2.8).[9] In addition to providing access to many useful natural monosaccharides, enzymatic aldol reactions have also allowed access to some non-natural monosaccharides. Unfortunately, the use of enzymes limits the substrate scope and limits or prevents the use of protecting groups. To circumvent this problem, other groups have used standard metal-catalyzed aldol technology to synthesize carbohydrates (Figure 2.9).[10] However, the use of standard aldol conditions required lengthy syntheses to access hexoses. Because of this, they have seen limited use in synthesis.

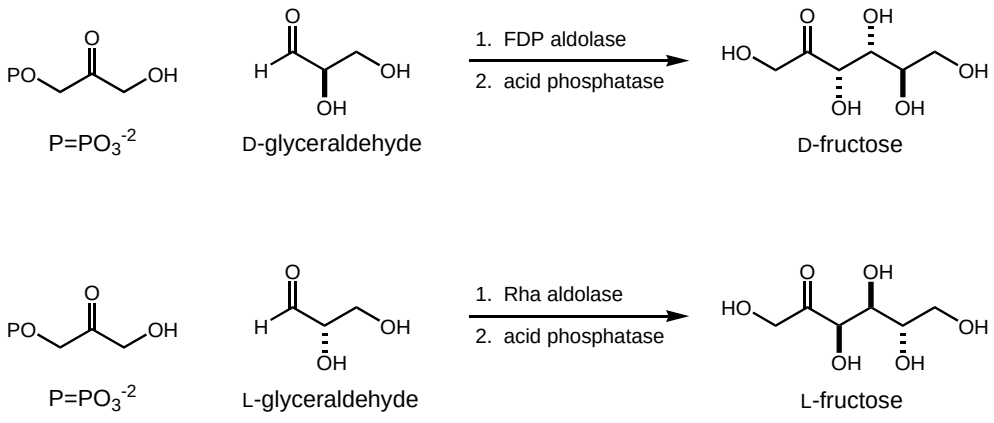


Figure 2.8: Aldolase enzymes have been applied to the synthesis of sugars.

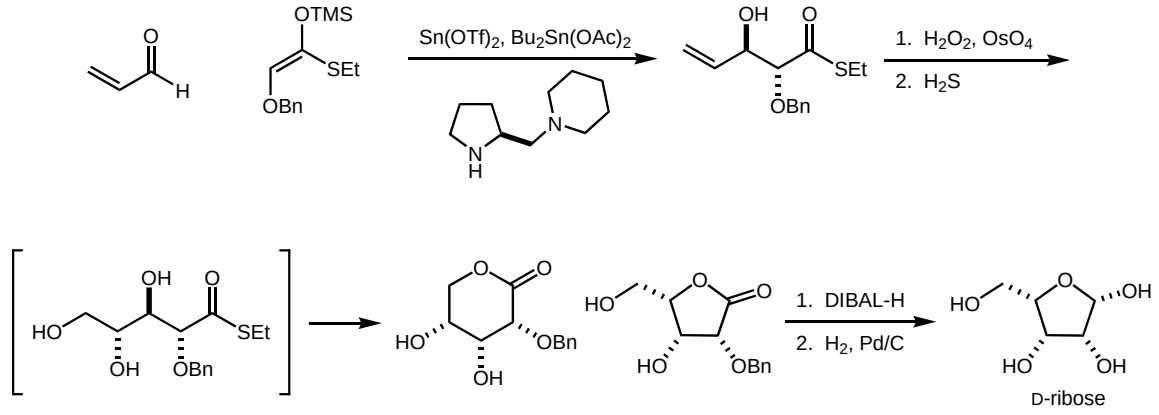
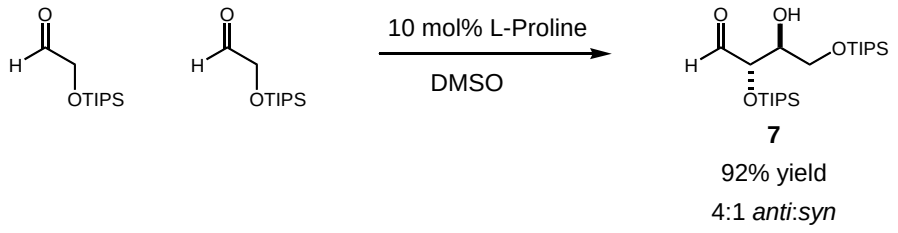


Figure 2.9: Enantioselective aldol chemistry has been applied to carbohydrate synthesis.

As described in Chapter 1, the MacMillan group has developed a new aldol methodology to access differentially-protected allose, mannose, and glucose from TIPS-erythrose **1** (Figure 2.1).[1] To extend this technology to the TIPS-threose (**7**), two reactions needed to be developed. Since the TIPS-threose is the minor product of the proline-catalyzed aldol reaction (Equation 2.1), a method needed to be developed to access it in larger quantities. Once the TIPS-threose could be readily accessed, conditions would have to be determined to promote the formation of the syn-hexoses.

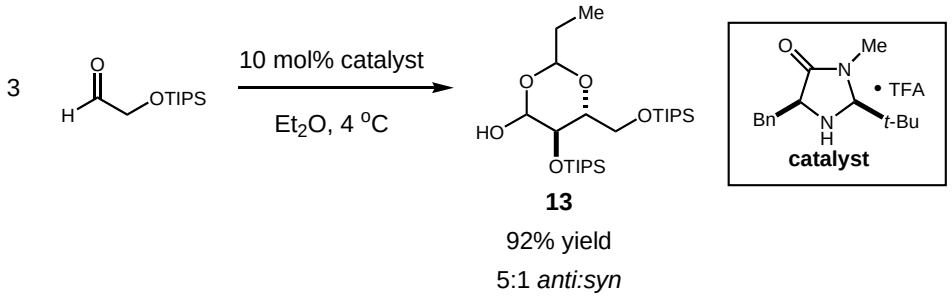


7
92% yield
4:1 *anti*:*syn*

(2.1)

Preparation of the TIPS-Threose

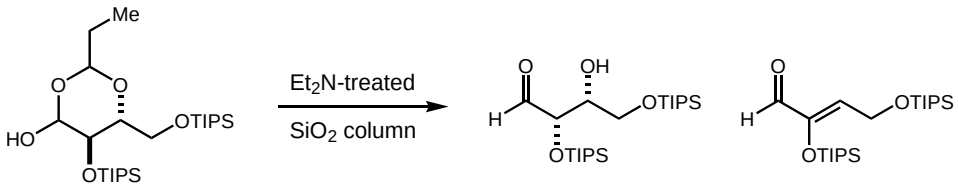
The TIPS-threose (**7**) is the minor product of a proline-catalyzed aldol reaction described in Chapter 1 (Equation 1).[1b] Because it constitutes only 20 percent of the product, a method was needed to access threose **7** more efficiently. Work in the MacMillan laboratory revealed that an imidazolidinone-catalyzed aldol reaction could produce TIPS-protected hemiacetal **13** (Equation 2.2). Furthermore, purification on a diethylamine-treated column produced the TIPS-threose from hemiacetal **13** in good yield.[11] However, this hydrolysis reaction was troublesome to reproduce. The diastereomeric ratio and overall yields would vary from column to column.



(2.2)

The first aim was to standardize the column conditions used to generate the threose. Half-gram samples of hemiacetal **13** were purified over 100, 150, 200, and 300 grams of silica gel treated initially with 800 mL of a 15% solution of diethylamine in pentane,

washed with 500 mL of pentane, and eluted with a 5% ether in pentane solution. While the 200 and 300 g columns produced the syn product, they also produced a β-elimination product **15**. The 100 g column did not completely hydrolyze the hemiacetal. The 150 g column effectively hydrolyzed the hemiacetal with minimal β-elimination product production (Table 2.1).



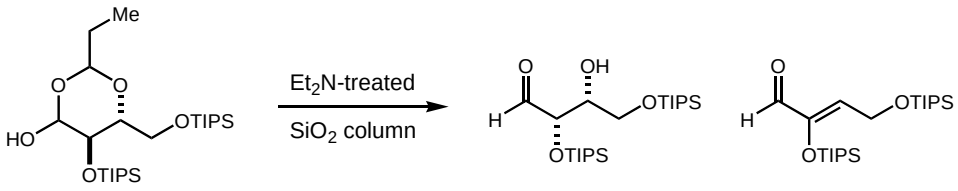
13 **14** **15**

entry	Amt. SiO_2 (g)	%**13**	%**14**	%**15**
1	100	32	41	0
2	150	0	52	14
3	200	0	39	23
4	300	0	37	27

Table 2.1: Column length affects the product ratio. Longer columns produced a larger amount of the β-elimination product (**15**) while a shorter column did not provide sufficient time for hydrolysis and separation.

It was suspected that excess diethylamine could be causing the β-elimination product to form, so the amount of diethylamine was evaluated next. Columns of 150 grams of silica were washed with 800 mL of a 5%, 10%, or 15% solution of diethylamine in pentane. Each column was washed with 500 mL of pentane and then a one gram sample of hemiacetal **13** was loaded onto each column. The 15% diethylamine/pentane treatment produced only 17% yield of the desired threose and while producing a 57% yield of the β-

elimination product. The 10 % diethylamine/pentane treatment produced 57% yield of the threose and only a 12% yield of the β-elimination product, and the 5% diethylamine/pentane treatment failed to completely open the hemiacetal product (Table 2.2).



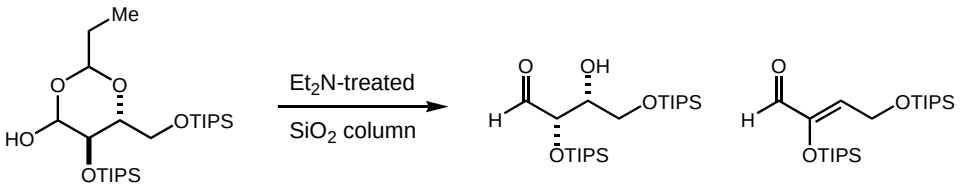
13 **14** **15**

entry	% Et_2N	%**13**	%**14**	%**15**
1	5	19	43	2
2	10	0	57	12
3	15	0	17	57

Table 2.2: The amount of β-elimination product formed correlates to the amount of Et_2N used to pretreat the column.

It was noticed that the amount of the β-elimination product formed seemed to correspond to the flow rate used for the column, so this was the next parameter examined. One-gram samples of hemiacetal **13** were chromatographed over 150 grams of silica gel treated with a 10% solution of diethylamine in pentane and washed with 500 mL of pentane. The samples were eluted in a 3% solution of diethyl ether in pentane with a flow rate of 52, 115, 196, or 273 mL/min. It was determined that a faster flow rate produced less of the β-elimination product (Table 2.3). When the flow rate was pushed to 273 mL/min,

the TIPS dimer was obtained in 92% yield and in 4:1 diastereomeric ratio with only a trace of the β-elimination product.



13 **14** **15**

entry	flow rate (mL/min)	%**13**	%**14**	%**15**
1	52	0	16	59
2	115	0	23	48
3	196	0	58	22
4	273	0	92	2

Table 2.3: Affect of flow rate on the yield of TIPS-threose. The flow rate was determined by collecting the void volume into a graduate cylinder for 30 seconds.

These results are consistent with the theory that the hemiacetal hydrolysis is equilibrium process that is driven by the chromatographic separation of the resulting aldehyde products. This idea is also supported by the observation that silica gel and diethylamine do not cause hydrolysis in solution. While there is no direct precedent for

this chemistry, the Rychnovsky laboratory has shown that the formation of β-hydroxy aldehydes from hemiacetals is facile in the presence of an amine base.[12]

The Reactivity of the TIPS-Threose

After the method for obtaining the TIPS-threose was determined, the reactivity of the threose could be explored. The TIPS-threose was first evaluated with benzyloxy- and acetoxyacetaldehyde enolates[1c] (**16** and **17**, Figure 2.10). Despite efforts to produce a reaction by varying Lewis acid, solvent, temperature, and concentration, the TIPS-threose was not competent in the aldol reaction. One theory for this observation is that the TIPS-threose may be less active due to unfavorable steric interactions between the enolate nucleophile and the axial TIPS group (Figure 2.11). It was determined in previous studies that the TIPS dimer assumes a chair conformation. While the TIPS groups on the erythrose are equatorial, the threose geometry places a TIPS group axial, hindering nucleophilic attack.

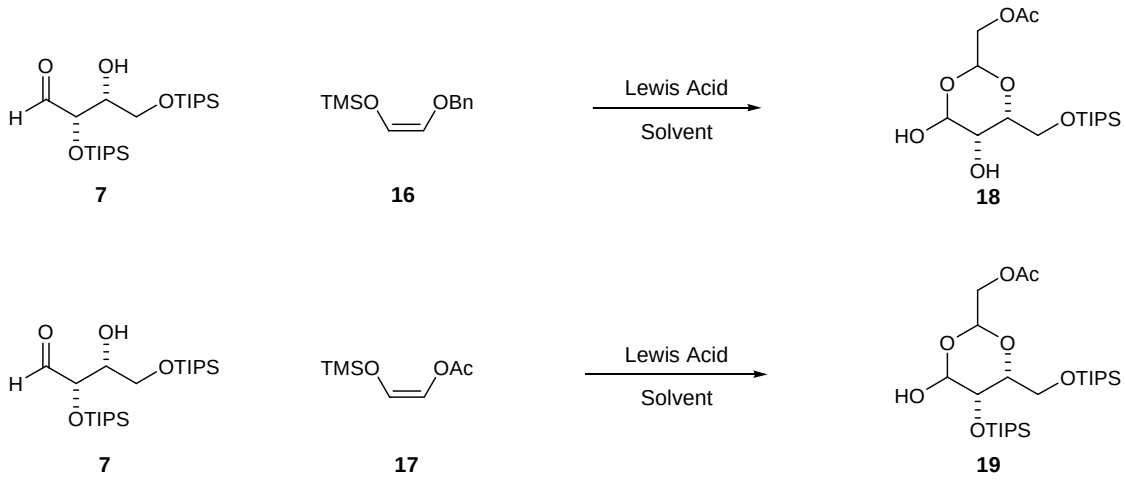
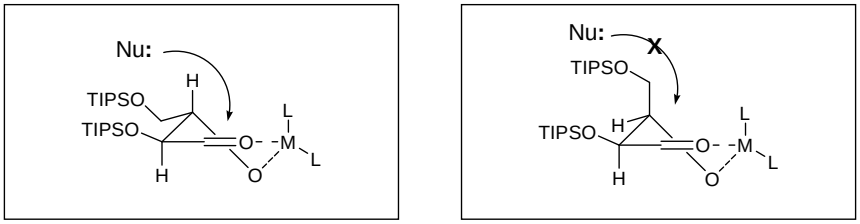


Figure 2.10: The TIPS-erythrose (**7**) did not produce the desired hexoses despite variations in Lewis acid, solvent, concentration, and temperature.



TIPS Erythrose TIPS Threose

Figure 2.11: The TIPS-threose may be less reactive due to an unfavorable steric interaction.

Further evidence that the TIPS-threose is less reactive than the erythrose was found when the threose was subjected to thioester soft-enolization reaction conditions. Thioester enolates are known to be more reactive than aldehyde enolates, so it was hoped these enolates would be better partners for the TIPS-threose.[13] Excitingly, when the TIPS-threose (**7**) was combined with benzyloxy thioester **20**, titanium tetrachloride, and Hunig's base in dichloromethane, it produced gulolactone **22**. However, it took 36 hours at 4 ^{o}C for this reaction to proceed. By comparison, when the TIPS-erythrose (**1**) was combined with benzyloxy thioester **20**, titanium tetrachloride, and Hunig's base in dichloromethane, it reacted in four hours at -40 ^{o}C to produce allolactone **21** (Figure 2.12).[20]

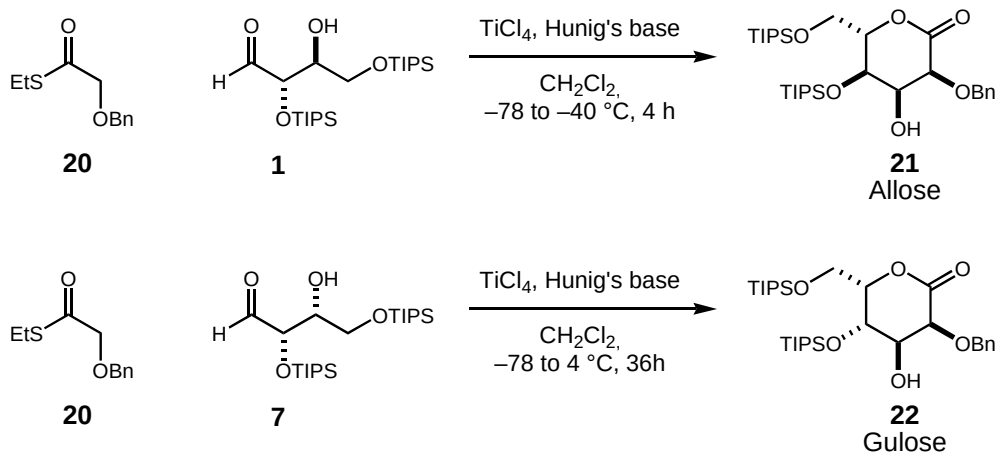


Figure 2.12: The TIPS-threose is less reactive than the TIPS-threose.

Efforts were then concentrated on accessing other stereochemistries through the use of benzyloxy thioester **20**, but the only hexose formed by these reactions was gulolactone **22.** Furthermore, none of the Lewis acids tried were as high yielding as $TiCl_4$, which produced gulolactone **22** in 75% yield. The production of gulolactone **22** represented a five-step synthesis (4 steps in the longest linear sequence) that produced a differentially-protected gulolactone in 48% overall yield from *cis*-butene diol. This was exciting because L-gulose has been found to be the key saccharide moiety of the pendant disaccharide on many anti-cancer therapeutics such as bleomycin A_2, bleomycin B_2, and phleomycin D_1. These drugs perform oxidative strand scission on double-stranded DNA. It is believed that the gulose moiety could be responsible for both entry into the cell and for stabilizing the iron (III) oxygen complex responsible for strand scission.[14] Furthermore, the presence of gulose in bacterial glycoproteins and glycolipids has been linked to higher virulence of the bacterial strain.[15] Because this sugar is rare, it can be costly to obtain (anywhere from $500~$3000 for 1g of either D- or L-gulose).[16] Furthermore, once purchased, the free

sugar still has to be modified before it can be used in polysaccharide synthesis. Therefore, it was pleasing to find a more efficient way to produce this saccharide.

Development of a One-Step Method to Access Hexoses

Because the thioester chemistry was unable to produce the other syn-hexose stereochemistries, different methods were sought to achieve this goal. It was considered that if an enolate was able to add to the TIPS dimer and cyclize to produce a hexose, then it should be possible to add two equivalents of an enolate to an aldehyde and it cyclize to form a hexose (Figure 2.13). To quickly evaluate this theory, acetoxyenolate **17** and TIPS-aldehyde **26** were combined with an assortment of Lewis acids and allowed to react until examination by thin layer chromatography (TLC) showed full consumption of the TIPS-aldehyde. The reaction was then extracted and the organic layer was filtered over silica. The organic layer was concentrated, and the residue was exposed to a 1:1 solution of TBAF and acetic acid in THF. After 1 hour, dichloromethane, triethylamine, and acetic anhydride were added, and the reactions were stirred for 8 hours. Previous work in the laboratory has shown that this sequence converts similar TIPS-protected hexoses to their pentaacetates.[1] Upon completion of this sequence, the reactions were extracted and purified. The isolated pentaacetates were then compared to known compounds to determine the stereochemical product of the aldol reaction. While we were able to isolate pentaacetates from a number of the reactions, only a few conditions selectively produced one hexose over another.

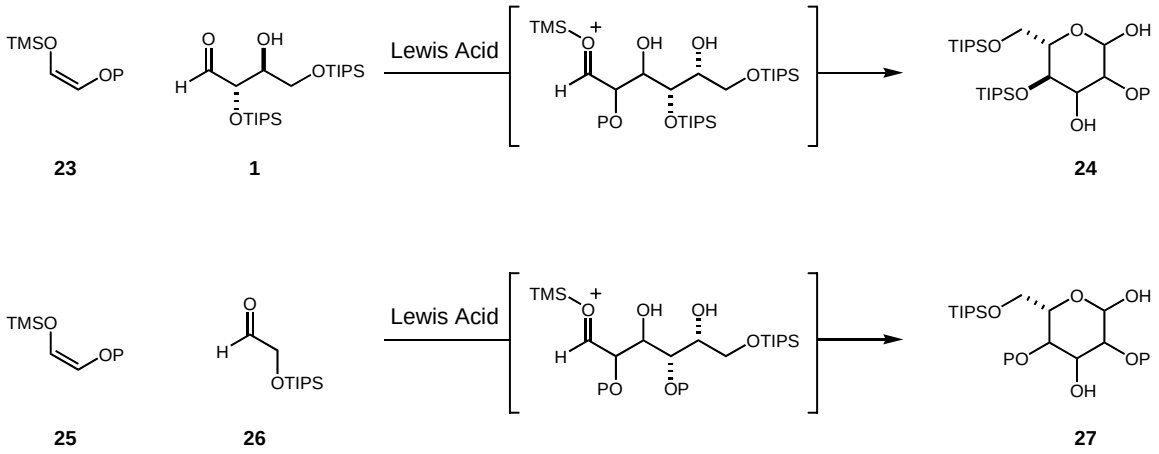


Figure 2.13: If the TIPS-erythrose (**1**) and enolate **23** are able to form a hexose instead of polymerizing, then it should be possible to form a hexose from TIPS-aldehyde **26**.

Specifically, both allose pentaacetate **28** and gulose pentaacetate **29** have been accessed through this chemistry. Using $TiCl_4 \cdot 2THF$ as the Lewis acid, we were able to isolate allose pentaacetate at the end of the reaction sequence. Similarly, when we used $MgBr_2 \cdot OEt_2$, we were able to access gulose pentaacetate. These results represented the first example of a one-step assembly of hexoses from achiral starting materials. Work is in progress to expand this technology to other stereochemistries. Studies are also underway to develop an asymmetric variant of this reaction.

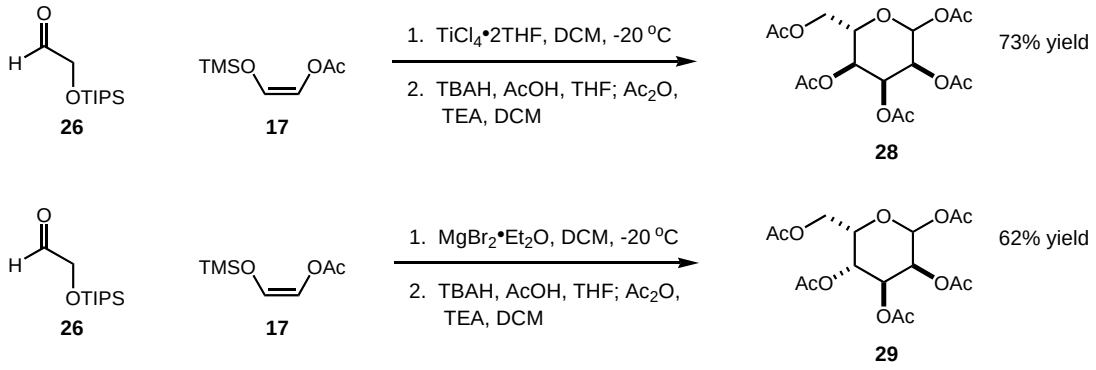


Figure 2.14: Both threo- and erytho-hexoses have been accessed through a one-step aldol reaction.

Conclusions

Described above are the efforts taken to access the syn hexoses. First developed was a method to efficiently access the TIPS-threose. This threose was tested in the two-step sugar methodology, and a protected gulolactone was formed via a thioester soft-enolization aldol reaction. Finally, a one-step method for synthesizing hexoses was developed and has produced a protected allose and gulose.

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[17] All solvents were purified according to the method of Grubbs.[18] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile samples. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[19] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde, ceric ammonium molybdate, or $KMnO_4$ stain.

^{1}H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) or an Inova 500 (500 MHz and 125 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame

ionization detectors using a J&W Scientific DB-1701 (30 m x 0.25 mm) column as noted. High-performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel OD-H column (25 cm) and OD-H guard (5 cm) as noted.

Preparation of the TIPS-threose

(2*S*, 3*R*)-3-Hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde. (14) A suspension of triisopropylsilanoxy-acetaldehyde (1.0 g, 4.6 mmol) and catalyst **1** (111 mg, 0.31 mmol) in diethyl ether (1.5 mL) was stirred for 40 h at 4° C. The resulting solution was diluted with ethyl acetate (10 mL) and washed successively with water (2 x 5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in pentane (5 ml) and flashed on a diethylamine treated silica column (3.0" diameter column was filled with 150 g silica that has been stirred with a 10% diethylamine: pentane solution, washed with 800 mLof pentane, loaded with a 5 mLsolution of 0.5 g of trimer in pentane, and eluted with a 3% ether in pentane solution at a flow rate of 273 mL/min) to afford the title compound as a clear, colorless liquid (306 mg, 0.71 mmol, 92% yield) as a mixture of *syn*- and *anti*-diastereomers (4:1, determined by ^{1}H NMR) IR (film) 3483, 2945, 2892, 2868, 1734, 1464, 1385, 1117, 1069, 883, 683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *syn*-isomer: δ 9.74 (d, 1H, *J* = 1.5 Hz, CHO); 4.28 (dd, 1H, *J* = 4.9, 1.5 Hz, C**H**CHO); 3.97 (dd, 1H, *J* = 9.9, 2.7 Hz, CH_2OR); 3.89 (m, 1H, C**H**OH); 3.77 (dd, 1H, *J* = 9.9, 4.5 Hz, CH_2OR); 2.73 (d, 1H, *J* = 9.9 Hz, OH); 1.16-1.00 (m, 42H, 6

$CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) *syn*-isomer: δ 203.8, 74.4, 62.2, 18.0 (12C), 12.3 (3C), 11.9 (3C), one signal obscured by solvent. HRMS (CI+) exact mass calcd for $[M+H]^+$ ($C_{22}H_{49}O_4Si_2$) requires *m/z* 433.3169, found *m/z* 433.3176.

Preparation of the Hexoses

2-*O*-Benzyl-4,6-bis-*O*-triisopropylsilyl-L-gulolactone. (22) To a solution of benzyloxyacetyl ethyl thioester (73.0 mg, 0.35 mmol)[21] in dichloromethane (1 ml) at –78 °C was added neat titanium (IV) chloride (23.0 μl, 0.35 mmol). The yellow solution was allowed to stir for 20 minutes before the addition of Hunig's Base (60.0 μl, 0.35 mmol). The resulting red solution was stirred for another hour before a solution of (2*S*, 3*R*)-3-hydroxy-2,3-bis-triisopropylsilanoxy-propionaldehyde (50.0 mg, 0.12 mmol)[1] in dichloromethane (0.7 ml) was added. The solution was stirred at –78 °C for an additional hour before being moved to 4 °C for an additional 36 hours. The reaction was quenched with saturated aqueous NH_4Cl and extracted twice with dichloromethane. The organic layers were combined and washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica to afford the title compound as a pale yellow oil (50.5 mg, 0.09 mmol, 10 % ethyl acetate in hexane, stains pale blue in anisaldehyde) in 75% yield. IR (film) 2922, 2340, 1756, 1732, 1682, 1456, 1372, 1223, 1101 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5H, ArH); 5.13 (d, *J* = 11.7 Hz, 1H, $ArCH_2$); 4.83 (d, 1H, *J*= 11.7 Hz, $ArCH_2$) 4.62-4.67 (m, 1H); 4.78 (dd, *J*= 1.7, 4.6, 1H); 4.12-4.20 (m, 2H); 3.84-4.02 (m, 2H); 2.82 (bs, 1H, OH); 0.97-1.15 (m,

42H, 6 $CH(CH_3)_2$);^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 137.0, 128.6, 128.5, 128.3, 79.4, 74.0, 72.5, 71.2, 68.4, 61.0, 18.1, 17.9, 12.7, 12.0. HRMS calcd for $[M+H]^+$ requires *m/z* 581.3615, found 581.3616 *m/z*. $[\alpha]_D$ = +28.98. Stereochemistry was confirmed by comparison to authentic gulose pentaacetate.

β-Allose pentaacetate. (28) To a stirring solution of $TiCl_4$-2THF (618 mg, 1.85 mmol) in dichloromethane (1.25 mL) at -78 ^oC was added triisopropylsilanoxy-acetaldehyde[1] (100 mg, 0.462 mmol) in dichloromethane (1 mL) and (*Z*)-acetic acid 2-(trimethyl-silanyloxy)-vinyl ester[1] (242 mg, 1.39 mmol). The solution was warmed to -20 ^oC and allowed to stir for 24 hours. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and extracted twice with dichloromethane (2 mL). The organic layers were combined and washed with saturated $NaHCO_3$ (2 x 3 mL) and brine (3 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in THF (1 mL), and to this was added a 2 M solution of TBAF and AcOH in THF (1 mL). The reaction was allowed to stir for 1 hour. Then dichloromethane (3 mL), triethylamine (1 mL, 7.2 mmol), and acetic anhydride (0.75 mL, 7.94 mmol) were added to the reaction mixture, and the reaction was allowed to stir for 8 hours. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with saturated aqueous NH_4Cl (7 mL), saturated $NaHCO_3$ (4 x 7 mL), and brine (7 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica to afford the title compound as a clear syrup that became a white solid upon standing (131 mg, 0.336 mmol, 50% ethyl acetate in hexane, stains green in anisaldehyde, R_f=0.47) in 73% yield. Identity of the product was determined by comparison with known β-allose pentaacetate.[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (d, *J* = 9.0 Hz, 1H, H-1); 5.68 (dd, 1H, *J*= 3.3, 3.0 Hz, H-

3) 5.01-4.95 (m, 2H) H-4, H-2; 4.27-4.12 (m, 3H) H-5, H-6, H-6; 2.15 (s, 3H) Ac; 2.10 (s, 3H) Ac, 2.06 (s, 3H) Ac, 2.00 (s, 3H) Ac, 1.99 (s, 3H) Ac. ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 169.5, 169.4, 169.2, 169.2, 90.2, 71.3, 68.5, 68.3, 65.9, 62.1, 21.3, 21.1, 21.1, 21.1, 20.9.

β-Gulose pentaacetate. (29) To a stirring solution of $MgBr_2$-OEt_2 (448 mg, 1.85 mmol) in dichloromethane (1.25 mL) at -78 ^oC was added triisopropylsilanoxy-acetaldehyde[1] (100 mg, 0.462 mmol) in dichloromethane (1 mL) and (*Z*)-acetic acid 2-(trimethyl-silanyloxy)-vinyl ester[1] (242 mg, 1.39 mmol). The solution was warmed to -20 ^oC and allowed to stir for 24 hours. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and extracted twice with dichloromethane (2 mL). The organic layers were combined and washed with saturated $NaHCO_3$ (2 x 3 mL) and brine (3 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in THF (1 mL), and to this was added a 2 M solution of TBAF and AcOH in THF (1 mL). The reaction was allowed to stir for 1 hour. Then dichloromethane (3 mL), triethylamine (1 mL, 7.2 mmol), and acetic anhydride (0.75 mL, 7.94 mmol) were added to the reaction mixture, and the reaction was allowed to stir for 8 hours. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with saturated aqueous NH_4Cl (7 mL), saturated $NaHCO_3$ (4 x 7 mL), and brine (7 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica to afford the title compound as a clear, colorless syrup (112 mg, 0.287 mmol, 50% ethyl acetate in hexane, stains dark green in anisaldehyde, R_f=0.47) in 62% yield and 4:1 d.r. Identity of the major product was determined by comparison with known β-gulose pentaacetate.[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, 1H, *J* = 8.7 Hz) H-1); 5.42 (dd, 1H, *J*= 3.3, 3.6 Hz) H-3,

5.12-5.08 (m, 1H) H-2, 4.99-4.97 (m, 1H) H-4, 4.38-4.33 (m, 1H) H-5, 4.20-4.05 (m, 2H) H-6, H-6; 2.16 (s, 3H) Ac; 2.15 (s, 3H) Ac, 2.13 (s, 3H) Ac, 2.05 (s, 3H) Ac, 2.00 (s, 3H) Ac. ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.6, 169.5, 169.3, 169.1, 90.1, 71.6, 67.8, 67.6, 67.5, 61.8, 21.3, 21.1, 21.1, 21.1, 21.0. The minor product was unable to be separated sufficiently from the major product for comparison to known pentaacetates.

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