A NEW ROUTE TO SUGAR ALCOHOLS

by

Tyler Ford

Submitted in partial fulfillment of the

requirements for Departmental Honors in

the Department of Chemistry

Texas Christian University

Fort Worth, Texas

May 8, 2017

A NEW ROUTE TO SUGAR ALCOHOLS

Project Approved:

Supervising Professor: David Minter, Ph.D.

Department of Chemistry

Sergei Dzyuba, Ph.D.

Department of Chemistry

Matt Chumchal, Ph.D.

Department of Biology

ABSTRACT

Sugar alcohols have long been utilized in many commercial products as sugar alternatives that can present fewer health problems while retaining nearly the same sweetness. Sugar alcohol alternatives do not raise blood sugar nor do they cause tooth decay. Sugar alcohols contain vastly fewer calories than natural sugars due to their low digestibility, which at the same time is the basis of their negative effects. The non-digestible portion of the sugar alcohol can undergo fermentation by small bowel flora thus creating unwanted bloating and diarrhea. Reducing these side effects is an important motive for exploring new sugar alcohol isomers as well as inexpensive approaches to their laboratory synthesis.

Sugar alcohols are currently synthesized by the reduction of natural sugars, but this process does not allow for controlling specific stereochemistry; and this could be the basis for their problematic digestibility. Using a different synthetic pathway that allows the control of stereochemistry of the sugar alcohol hydroxyl groups may produce new sugar alcohols that are resistant to fermentation. A methodological approach using aldol additions to cyclic ketones to produce higher order sugar alcohols will be investigated. Double aldol reactions would be expected to produce 7, 8 or 9-carbon sugar alcohols with specific isomers that have yet to be studied. Expanding this investigation to include cyclic ketones with bulky R-groups introduces another possibility for controlling stereochemistry. The ultimate result of this synthetic project would be a sugar alcohol homolog that can act as a viable low-calorie sweetener without gastrointestinal setbacks.

ACKNOWLEDGEMENTS

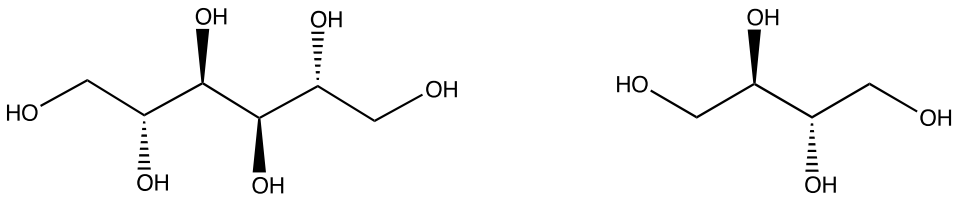
I would like to thank Dr. Minter for giving me the opportunity to work in his lab on this honors thesis project. Also, I thank him for his assistance throughout this research project and guidance in an organic synthesis lab setting at large. I would also like to thank Charles Ochoa and Adam Montoya for aiding me in any technical or theoretical manner in times that required help. The TCU Honors Research grant and TCU SERC provided support for this project.

TABLE OF CONTENTS

INTRODUCTION

Sugar alcohols represent derivatives of natural sugars and are structurally similar in several aspects. The most common natural monosaccharides contain 4, 5 or 6 carbon atoms in a straight chain. There is one carbonyl group—either an aldehyde or a ketone—and hydroxyl groups on the remaining carbons. Sugars exist naturally as cyclic hemiacetals or hemiketals rather than as linear structures. Currently, the standard synthesis for sugar alcohols is a hydrogenation procedure which is used to convert glucose into sorbitol and mannose into mannitol. These are only two examples of sugar alcohol production, and a number of other sugars can be hydrogenated in order to create sugar alcohols that differ in chain length and stereochemistry. In an industrial setting, pentoses and hexoses are the usual starting materials in the process to generate commercially available sweeteners.

The structure of a sugar alcohol is fairly simple. All sugar alcohols are straight chained hydrocarbons of varying length with hydroxyl groups attached on each carbon atom as illustrated by the structures of sorbitol and erythritol (Figure 1). As mentioned earlier, sorbitol is the reduction product of glucose. Erythritol is a short-chained four-carbon sugar alcohol that comes from a fermentation process. Erythritol is present in very large amounts in commercial products such as "no sugar added" health bars.



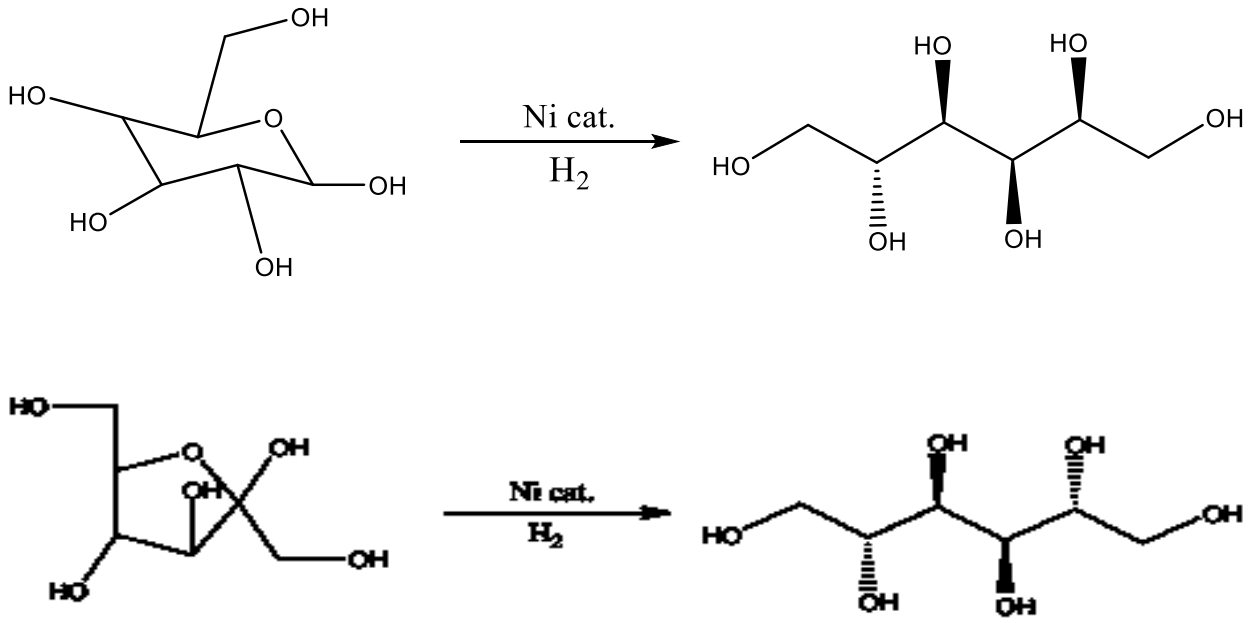
Sorbitol Erythritol

Figure 1. Structures for sorbitol and erythritol.

Previous Synthetic Approaches to Sugar Alcohols

The syntheses of sugar alcohols in general are not new procedures having roots dating back to the 1980s. There are currently two primary methods of synthesis with one greatly predominating over the other due mainly to cost. The majority of sugar alcohols are created commercially by the hydrogenation of readily available sugars like glucose and maltose. The most commonly used alternative route is through a fermentation reaction. Both of these current methods present their own sets of problems thus giving reason to investigate new routes to these compounds.

a. Synthesis of Sugar Alcohols using Reduction by Catalytic Hydrogenation

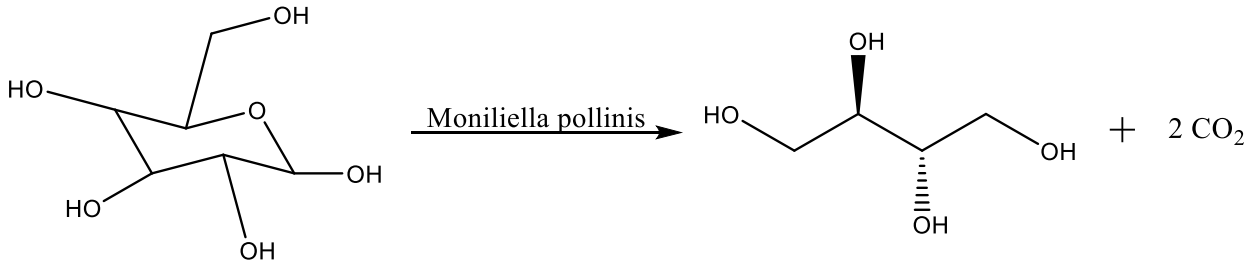


Scheme 1. Catalytic hydrogenation reactions produce sugar alcohols.

The fundamental difference between sugars and sugar alcohols is the presence of an aldehyde or ketone carbonyl group, which is observable only in the non-cyclic structure of the sugar. The hydrogenation reaction reduces the carbonyl function to an alcohol and depends on

the equilibrium between the cyclic and the non-cyclic structures of the sugar. The stereochemical configurations of the hydroxyl groups in the original sugar are preserved in this reaction. For example, the products of the reactions shown in Scheme 1 have the same absolute configuration for the chiral centers with hydroxyl groups as in the starting sugar. These reactions are relatively inexpensive and produce near quantitative yields of product.

b. Synthesis of Sugar Alcohols using Fermentation



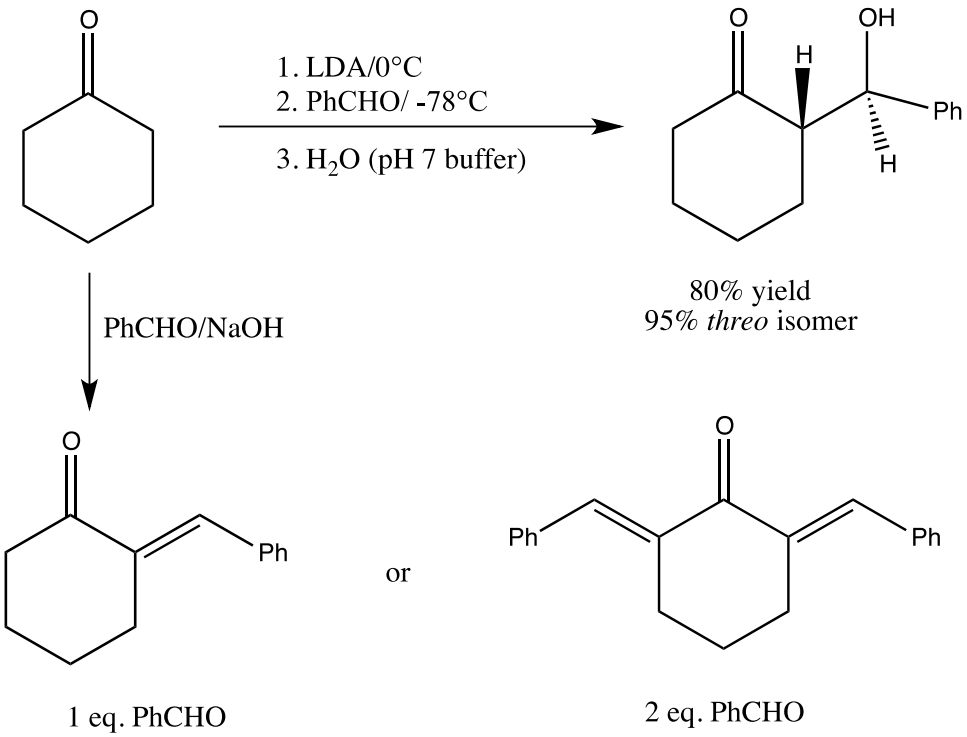
Scheme 2. Synthesis of erythritol using fermentation.

A less common means of sugar alcohol synthesis is through fermentation. The procedure is very expensive and requires the use of a bacterium, mainly Moniliella pollinis, for the best fermentation conditions. This method of synthesis has a very narrow range of application and is currently being used solely for the production of erythritol from glucose or sucrose. Erythritol is in high demand since it causes fewer digestive problems than any other sugar alcohol. It is not available by the reduction method since erythrose is a rare sugar with a cost that makes its use prohibitive. Thus the more expensive fermentation method is the only practical source for erythritol.

Novel Synthetic Approaches to Sugar Alcohols

a. A New Synthesis of Sugar Alcohols using the Aldol Addition Reaction

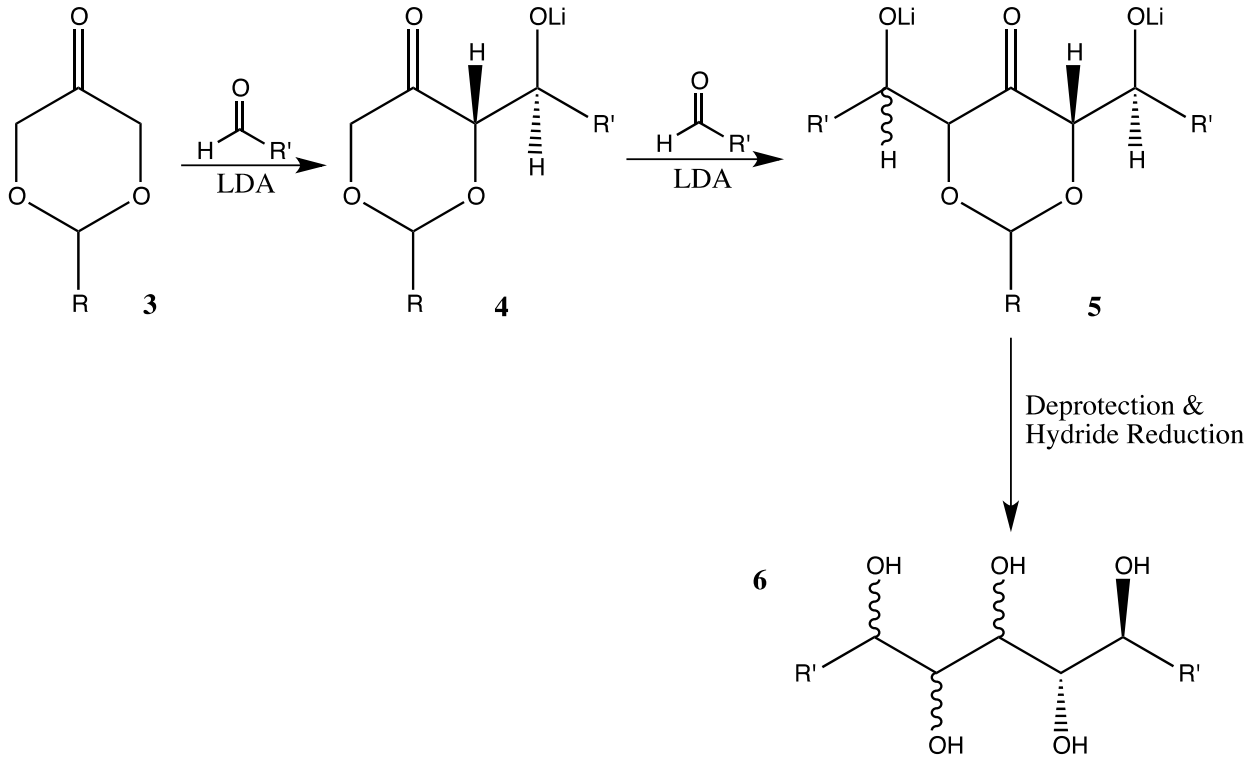
The basis of our new approach to sugar alcohols is a model study completed several years ago which showed that the aldol addition reaction can be controlled to give a single diastereoisomer of the product (Scheme 3). The reaction was done using LDA as a base to



Scheme 3. A model study of the aldol addition reaction.

form cyclohexanone enolate followed by the reaction of this enolate with benzaldehyde under conditions of kinetic control. This reaction gave a product mixture that was 95% threo isomer with only 5% erythro isomer. This degree of control is absolutely critical in the development of a synthetic pathway that requires predictable stereochemistry for the hydroxyl functions. Using this model study as a guide, we have proposed a synthetic route to sugar alcohols as depicted in

Scheme 4. The starting ketone with two oxygen atoms in the ring will be used in the place of cyclohexanone, and the group R can be varied to help control the stereochemistry of the aldol addition reaction. By performing two consecutive aldol addition reactions, sugar alcohols as large as nine carbon atoms in the chain can be generated conveniently.

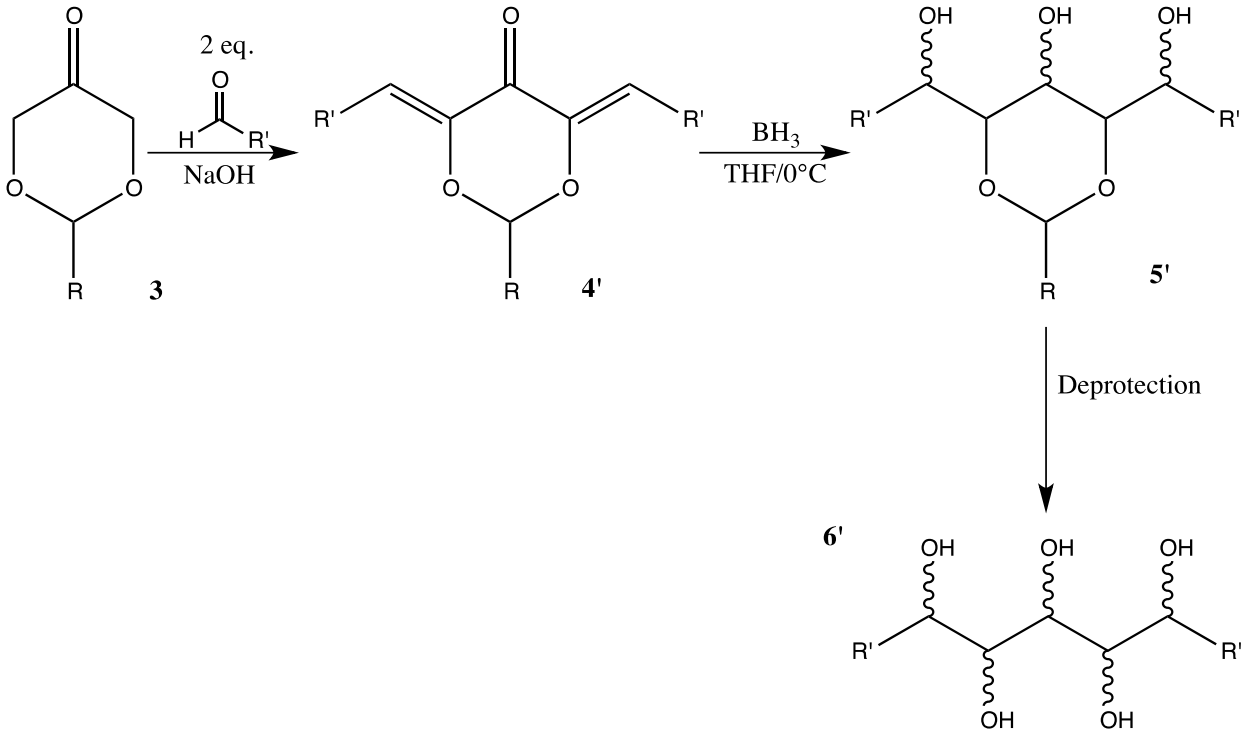


Scheme 4. A proposed route to sugar alcohols using an aldol addition approach.

The advantages of this route are numerous and provide the potential for making sugar alcohols that are impractical to produce from natural sugars as starting materials. Our proposed synthetic route takes advantage of the high diastereoselectivity of aldol addition reactions between lithium enolates derived from cyclic ketones and aldehydes carried out at low reaction temperature (kinetic conditions). As shown in Scheme 4, we will also investigate a double substitution (two consecutive aldol addition reactions) by repeating the process using the

acidic hydrogen at the α'-position. A hydride reduction of the remaining carbonyl group would be necessary to allow for only alcohol functional groups to be present in the final product. Hydrolysis of the acetal is the last step and will remove the protecting group to yield the sugar alcohol product. On the basis of the model study, we can predict the stereochemistry of the initial aldol reaction. However, the second addition reaction has never been carried out. This makes it difficult to predict not only the diastereoselectivity of this aldol reaction but also the final hydride reduction of the original ketone carbonyl group.

b. An Alternative Synthesis using the Aldol Condensation Reaction

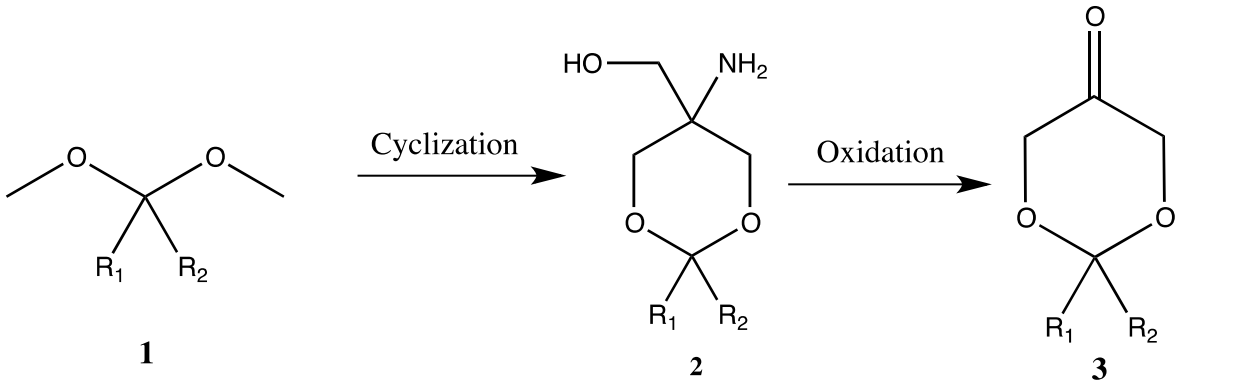


Scheme 5. A proposed route to sugar alcohols using an aldol condensation approach.

After encountering some difficulties in repeating the aldol addition reaction shown in Scheme 3 (described in the discussion section), an alternative route was also formulated using an

aldol condensation reaction as a basis. Aldol condensation reactions are much easier to carry out since they do not require strong bases or strictly anhydrous, anaerobic conditions. The strong base LDA can be replaced with NaOH and the reaction can be done in the presence of air with aqueous alcohol solvent or with no solvent at all. The double aldol condensation can also be carried out easily by simply using two molar equivalents of the aldehyde. As indicated in Scheme 5, this plan would use hydroboration of the alkene to introduce hydroxyl groups and a hydride reduction of the ketone carbonyl to create an additional alcohol function. It is possible that borane alone will accomplish both steps, but these details cannot be predicted without experimental evidence. As in the original proposal (Scheme 4), hydrolysis of the acetal would be the final step to remove the protecting group and yield the sugar alcohol product.

Synthetic Approach for Cyclic Ketones



a: R_1-Me R_2-Me
b: R_1-H R_2-Ph
c: R_1-H R_2-tert butyl
d: cyclohexanone

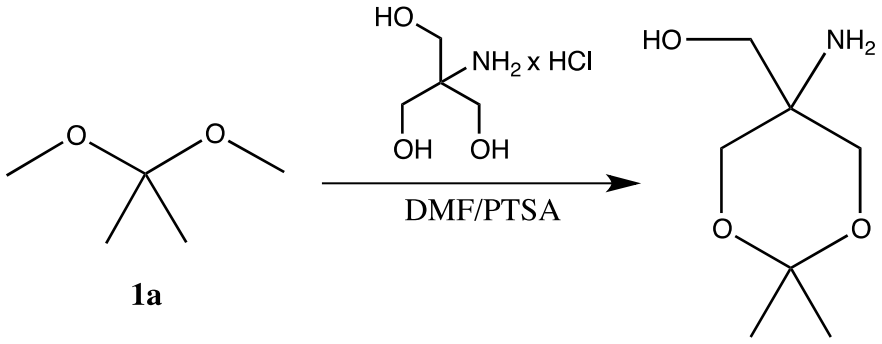
Scheme 6. A proposed route to cyclic ketones by cyclization followed by oxidation.

The cyclic ketones that will act as the backbone for the sugar alcohol synthesis will be formed through processes of cyclization to obtain the closed ring portion of the structure

followed by oxidation to allow for the necessary ketone group. These particular compounds are structurally similar to the cyclohexanone giving the impression that an aldol addition reaction can be controlled to give a single diastereoisomer just as the reaction using cyclohexanone previously had displayed. The key similarity is that the have the α-H that can be readily removed to form the enolate for the aldol reactions. The R groups attached to the starting materials will vary, but the same general process will remain the same as seen in Scheme 6. Cyclohexanone will be grouped together with these cyclic ketones and referred to as 3d even though it does not have the two oxygens within its ring structure.

EXPERIMENTAL SECTION

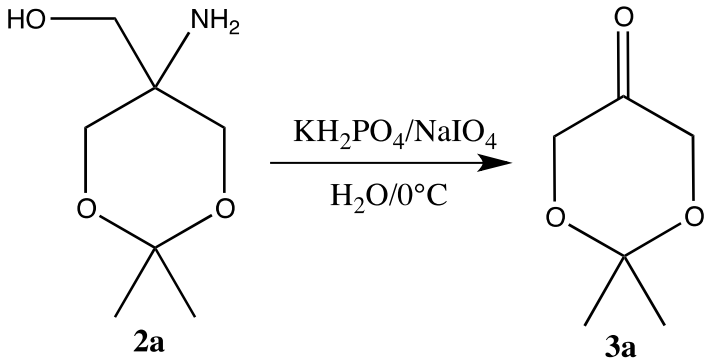
Preparation of 5- amino-(2,2-dimethyl-1,3-dioxan-5-yl)methanol



1a **2a**

2-amino-2-(hydroxymethyl)-1,3-propandiol hydrochloride (17.5 g, 111.11 mmol) was dissolved in DMF (155 mL), along with p-Toulenesulfonic acid (0.913 g) and 2,2-dimethoxypropane (14.70 mL, 120.00 mmol) in a 250 mL round bottom flask. This mixture was allowed to stir for 24 hr. To the colorless, homogeneous solution, triethylamine (1.22 mL) was added. At this point, the original solvent was removed in vacuo. After removal of the solvent, resulting gel was then stirred with additional triethylamine (19.53 mL) until the all the triethylamine had reacted. This was followed by a wash with EtOAc (305 mL). The white precipitate that formed was removed by vacuum filtration and the filtrate was distilled in vacuo (125°C/0.3 Torr) to give a white crystalline product (14.50 g, 89.85 mmol, 82%) of **2a** that was shown to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 3H), 1.44 (s, 3H), 2.36 (br, s, 3H), 3.50 (s, 2H), 3.53 (d, *J*=11.4 Hz, 2H), 3.81 (d, *J*=11.9 Hz, 2H).

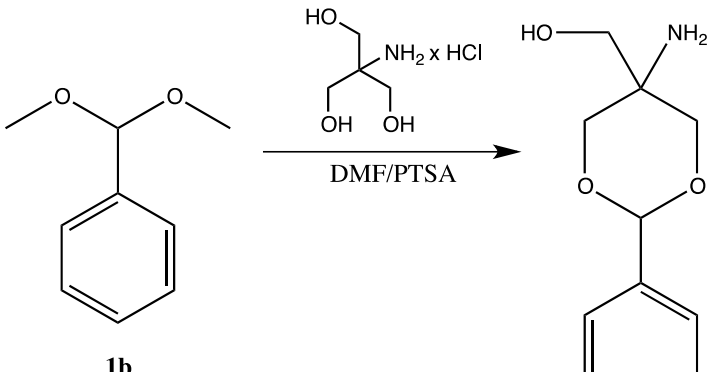
Preparation of 2,2,-Dimethyl-1,3-dioxan-5-one



2a **3a**

In a three neck flask, 5- amino-(2,2-dimethyl-1,3-dioxan-5-yl)methanol (11.01 g, 68.87 mmol) and KH_2PO_4 (9.36 g, 68.90 mmol) were dissolved in water (250 mL) and brought down to 0°C. A 0.5 M $NaIO_4$ and water solution (100 mL) was added dropwise to the initial three neck flask at 0°C over a period of 2.5 hr. After completion of the addition, the mixture was allowed to stir at 0°C for 1 hour then at room temperature for an additional 5 hours. The solution was then extracted with DCM (10 x 30 mL), dried with $MgSO_4$, and distilled under reduced pressure (67°C/20 Torr) to give a sweet smelling clear liquid product (7.98 g, 61.34 mmol, 90%) of **3a** that was shown to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.45 (s, 6H), 4.15 (s 4H).

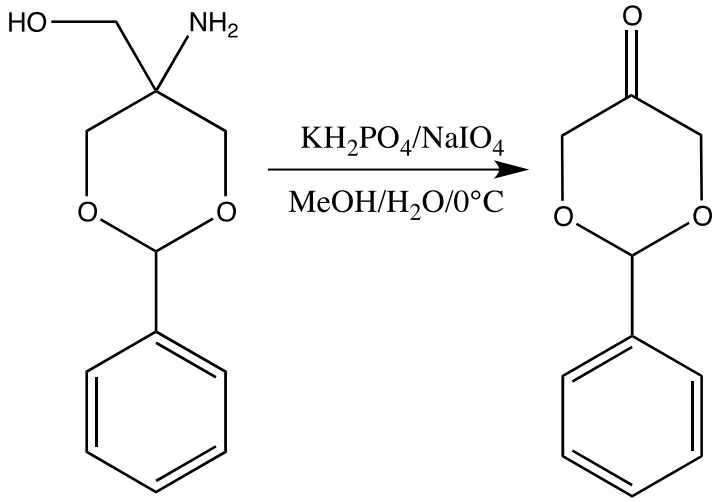
Preparation of 5-Amino-5-hydroxymethyl-2-phenyl-1,3-dioxane



1b **2b**

In a 100 mL round bottom, a mixture of 2-amino-2-(hydroxymethyl)-1,3-propandiol hydrochloride (3.00 g, 19.05 mmol), PTSA (0.183 g, 0.96 mmol), and benzaldehyde dimethylacetal (3.12 mL, 20.85 mmol) was dissolved in DMF (22.5 mL). The reaction mixture was stirred for 18 hr. Triethylamine (0.33 mL, 2.39 mmol) was allowed to stir for 10 min in the reaction mixture prior to removing the solvent in vacuo. Excess triethylamine (2.20 mL, 15.97 mmol) was added followed by the addition of EtOAc (60 mL). The solvent was removed in a rotary evaporator and the product was obtained as an opaque oil (2.60 g, 15.42 mmol, 81%) of **2b** that was shown to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ3.03 (br, s, 3H), 3.93 (s, 2H), 3.81 (d, *J*=11.4 Hz, 2H), 3.97 (d, *J*=11.4 Hz, 2H), 5.41 (s, 1H), 7.36-7.52 (m, 5H).

Preparation of 5-Oxo-2-phenyl-1,3-dioxane

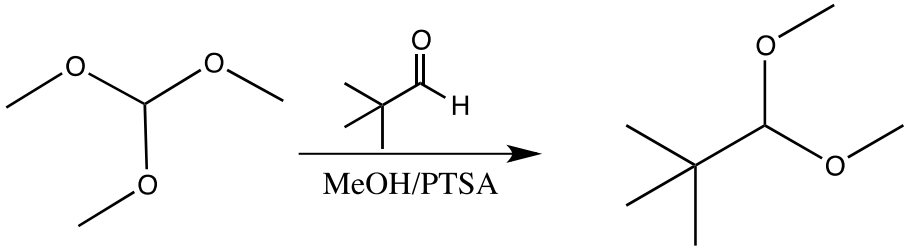


2b **3b**

In a three-necked round bottom flask, 5-Amino-5-hydroxymethyl-2-phenyl-1,3-dioxane (2.0 g, 9.48 mmol) and KH_2PO4 (1.50 g, 9.54 mmol) was dissolved in water (25 mL) and methanol (10 mL) then brought to 0°C. A solution of $NaIO_4$ (2.03 g, 9.54 mmol) in water (30 mL) was added dropwise via addition funnel over 30 min. The mixture was allowed to stir for an additional hour at 0°C and then for 5 h at room temperature. $Na_2S_2O_3$ (2.40 g, 9.70 mmol)

was next added, and the resulting solution was allowed to stir for approximately 15 min at which time it was extracted with CH_2Cl_2 (5 x 15 mL). The combined organic phases were dried with $MgSO_4$, filtered, then purified by distillation under reduced pressure (85°C/20 Torr) to afford 1.04 g (8.06 mmol, 85% yield) of clear and colorless oil of **3b** that was shown to be pure by NMR analysis. ^{1}H NMR (C_6D_6, 300 MHz): δ4.03 (d, *J*=17.4 Hz, 2H), 5.28 (s, 1H), 7.16-7.45 (m, 5H).

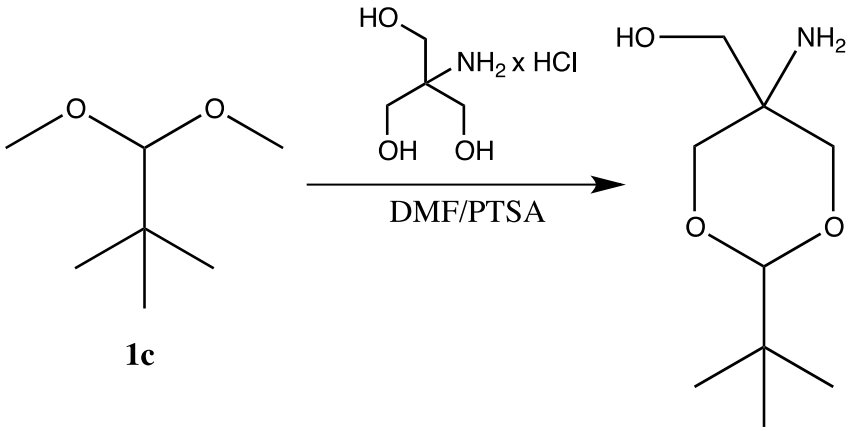
Preparation of 1,1-Dimethoxy-2,2-dimethylpropane



1c

To a solution of pivaldehyde (3.88 g, 45.04 mmol) in 400 mL methanol, trimethyl orthoformate (4.29 g, 40.43 mmol) was added with a trace amount of PTSA. This mixture was allowed to stir for 6 hours at which point the solution was poured into 800 mL of water. This aqueous solution was extracted with 1:1 pentane & petroleum ether (3 x 200 mL), dried over $NaSO_4$, and the solvent was removed via distillation. The resulting product was a colorless, sweet smelling liquid of 4.86 g (36.80 mmol, 91% yield) of **1c** that was shown to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (s, 9H), 3.48 (s, 6H), 3.66 (s, 1H).

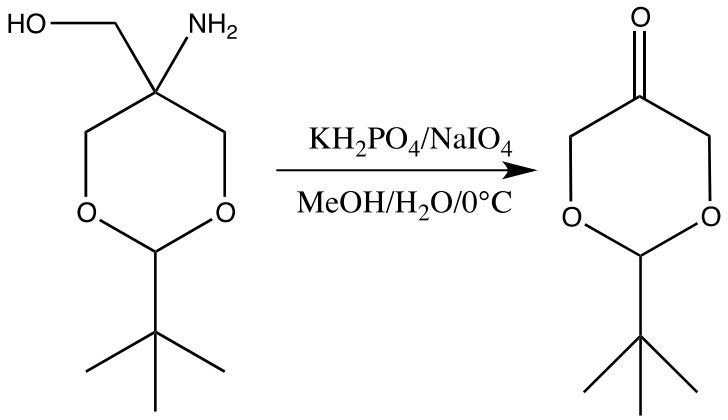
Preparation of 5-Amino-2-*tert*-butyl-5-hydroxymethyl-1,3-dioxane



1c **2c**

In a 100 mL round bottom, a mixture of 2-amino-2-(hydroxymethyl)-1,3-propandiol hydrochloride (3.00 g, 19.05 mmol), PTSA (0.183 g, 0.96 mmol), and 1,1-Dimethoxy-2,2-dimethylpropane (2.64 g, 20.85 mmol) was dissolved in DMF (22.5 mL). The reaction mixture was stirred for 18 hr at which point the reaction mixture has a teal appearance. Triethylamine (0.33 mL, 2.39 mmol) was allowed to stir for 10 min in the reaction mixture prior to removing the solvent in vacuo. Excess triethylamine (2.20 mL, 15.97 mmol) was added followed by the addition of EtOAc (60 mL). The solvent was removed in a rotary evaporator and the product was obtained as an oil (2.75 g, 12.38 mmol, 65%) of **2c** that was tested for purity by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93 (s, 9H), 2.29 (br, s, 3H), 3.61 (d, *J*=11.3 Hz, 2H), 3.88 (d, *J*=11.3 Hz, 2H), 4.06 (s, 1H).

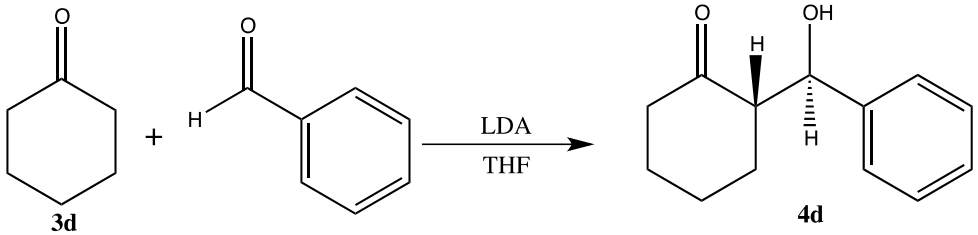
Preparation of 2-tert-Butyl-5-oxo-1,3-dioxane



2c **3c**

In a three-necked round bottom flask, of 5-Amino-2-tert-butyl-5-hydroxymethyl-1,3-dioxane (2.0 g, 10.64 mmol) and KH_2PO_4 (1.74 g, 11.04 mmol) in water (25 mL) and methanol (10 mL). A solution of $NaIO_4$ (2.03 g, 9.54 mmol) in water (30 mL) was added dropwise via addition funnel over 30 min. The mixture was allowed to stir for an additional hour at 0°C and then 5 h at room temperature. $Na_2S_2O_3$ (2.40 g, 9.70 mmol) was next added, and the resulting solution was allowed to stir for approximately 15 min at which time it was extracted with CH_2Cl_2 (5 x 15 mL). The combined organic phases were dried with $MgSO_4$, filtered, then purified by distillation under reduced pressure (60°C/30 Torr) to afford 1.04 g (6.49 mmol, 61% yield) of pale yellow solid of **3c** that was tested to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.98 (s, 9H), 4.25 (dd, *J*=17.9 Hz, 1.0 Hz, 2H), 5.28 (s, 1H), 4.40 (s, 1H), 4.43 (dd, *J*=17.9 Hz, 1.0 Hz, 2H).

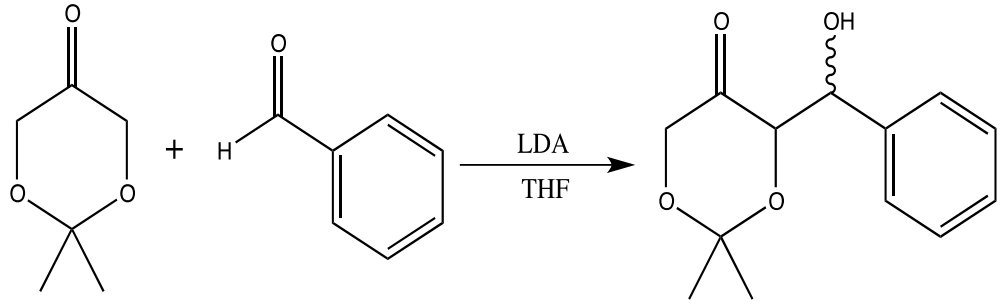
Preparation of 2-(phenylmethylene)-cyclohexanone



3d **4d**

In a 50 mL three necked round bottom flask, cyclohexanone (0.40 g, 4.08 mmol) and LDA (0.42 g, 4.00 mmol) was placed in 40 mL of dry THF and allowed to stir while at -78°C for 30 minutes. The solution was brought to 0°C and benzaldehyde (0.40 mL, 4.02 mmol) was added. After being stirred for 30 seconds, a trace of acetic acid (0.40mL, 4.00 mmol) was added to the round bottom and the resulting solution was placed into a buffer solution consisting of 6.80 g potassium monobasic phosphate and 1.16 g sodium hydroxide in 80 mL water. The solution was extracted with DCM (3 x 20mL), dried over $NaSO_4$, and the solvent was then removed by means of rotary evaporation. The resulting gel-like product gave a crude product (0.27 g) that was unidentifiable by NMR spectrum. Starting material was prominent in the spectrum indicating the lack of a desired reaction.

Preparation of 4,4-dimethyl-2-(phenylmethylene)-cyclohexanone

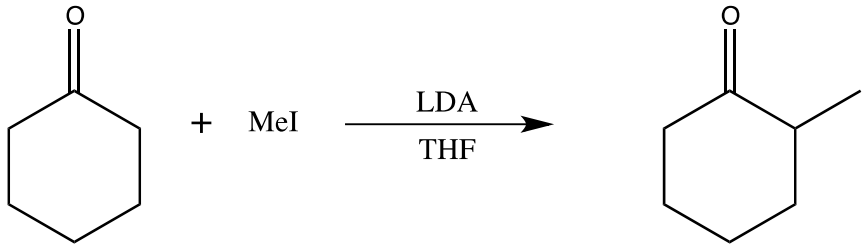


3a **4a**

In a 50 mL three necked round bottom flask, 2,2,-Dimethyl-1,3-dioxan-5-one (0.13 g, 1.01 mmol) was dissolved in 10 mL of dry THF at which point LDA (0.21 g, 2.00 mmol) and allowed to stir while at -78°C for 30 minutes. The solution was brought to 0°C and benzaldehyde (0.10 mL, 1.00 mmol) was added and allowed to react for 30 s. Trace acetic acid (0.06 g, 1.00 mmol) was added to the round bottom to quench the reaction and the resulting solution was placed into a buffer solution consisting of 3.40 g potassium monobasic phosphate

and 0.58 g sodium hydroxide dissolved in 40 mL water. The solution was extracted with DCM (3 x 20mL), dried over $NaSO_4$, and the solvent was then removed by rotary evaporation. The resulting gel-like product gave a crude product (0.18 g) that was unidentifiable by NMR spectrum. Starting material was prominent in the spectrum indicating the lack of the desired reaction. By means of TLC, a trace amount of an unintentionally made product was recovered and tested by NMR analysis. This product was later discovered to be **4d'**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.85 (s, 6H), 7.32-7.55 (m, 10 H), 7.80 (s, 2H).

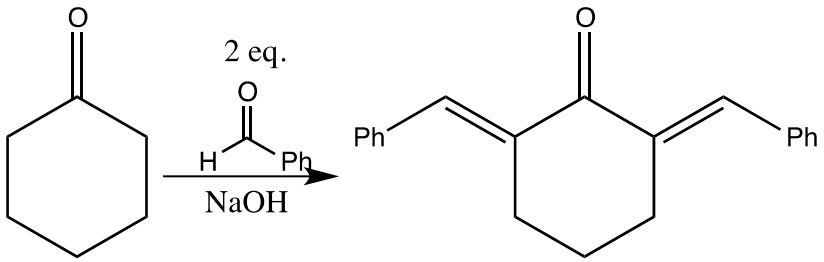
Preparation of 2-methylcyclohexanone



3d **7d**

In a 50 mL three necked round bottom flask, cyclohexanone (0.40 g, 4.08 mmol) was placed in 30 mL of dry THF with LDA (0.42 g, 4.00 mmol) and allowed to stir while at -78°C for 30 minutes. The solution was brought to 0°C and methyl iodide (0.59 g, 4.05 mmol) was added. After being stirred for 30 seconds, acetic acid (0.40 mL, 4.00 mmol) was added to the round bottom and the resulting solution was placed into a buffer solution consisting of 6.80 g potassium monobasic phosphate and 1.16 g sodium hydroxide in 80 mL water. The solution was extracted with DCM (3 x 20 mL), dried over $NaSO_4$, and the solvent was then removed. The colorless, liquid product (0.17 g) was unidentifiable of a single product by NMR analysis, but showed appearance of starting materials.

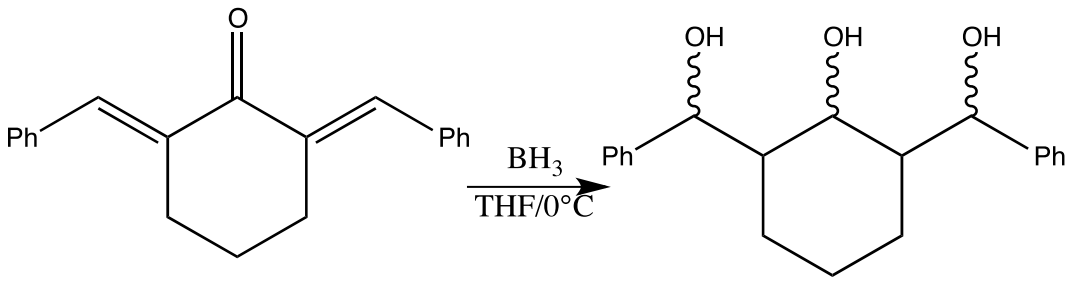
Preparation of 2,6-dibenzalidenecyclohexanone



3d **4d'**

Cyclohexanone (0.20 g, 2.00 mmol) along with NaOH pellets (0.06 g, 1.60 mmol) were placed in a mortar and benzaldehyde (0.42 g, 4.00 mmol) was then added. The mixture was ground together with a pestle for 5 minutes as a yellow solid appeared. To remove any excess base, a solution of 2 M HCl (12 mL) is added to the mortar and mixed with the solid. The resulting yellow solid is removed from the mortar and recrystallized with 95% ethanol. The post-recrystallized needles of 1.01 g (2.00 mmol, quantitative yield) of **4d'** was proven to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.82 (q, 2H), 2.96 (t, 4H), 7.36-7.50 (m, 10 H), 7.83 (s, 2H). MP: 97.1°C.

Preparation of 2,6-dihydroxyphenylcyclohexanol

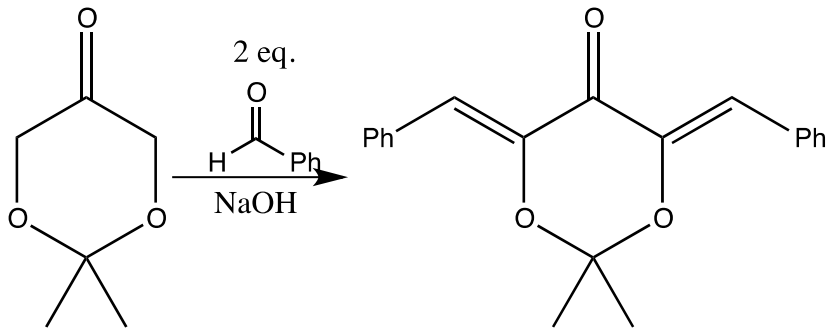


4d' **5d'**

In a 50-mL three neck round bottom flask, 2,6-Dibenzalidenecyclohexanone (1.01 g, 1.97 mmol) was dissolved in 10 mL of dry THF. The flask was cooled to 0 °C using an ice bath and a 1.0 M borane/THF complex (2.0 mL, 2.00 mmol) was slowly added to the round bottom from a syringe. The ice bath was removed and reaction mixture was stirred at room temperature for 1.5

hours. The flask was then again cooled to 0 °C and 0.5 mL of water was added to destroy excess borane. An alkaline solution of hydrogen peroxide made from 3 mL of 30% hydrogen peroxide with 6 mL of 2 M sodium hydroxide solution, is then slowly added to the initial round bottom. The ice bath was then removed and the solution was stirred for 5 minutes. The reaction mixture was then extracted with ether (3 × 10 mL). The combined organic layers were then washed with 10 mL of water and 10 mL each of brine. The organic solution was dried over $NaSO_4$ and the solvent was removed by rotary evaporation. This allotted a clear, whitish gel (0.56 g). The NMR spectra indicated that there was most likely not a single product and the specific stereochemistry of the product was unable to be determined.

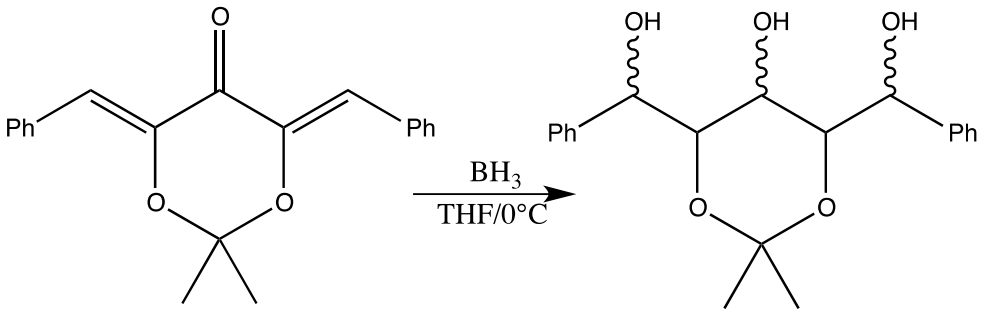
Preparation of 2,2-dimethyl-4,6-bis(phenylmethylene)-1,3-dioxanone



3a **4a'**

A mixture of 2,2,-Dimethyl-1,3-dioxan-5-one (0.40 g, 4.00 mmol) along with NaOH pellets (0.12 g, 3.20 mmol) were placed in a mortar and benzaldehyde (0.84 g, 8.00 mmol) was then added. The mixture was ground together with a pestle for 5 minutes as a yellow solid appeared. To remove any excess base, a solution of 2 M HCl (24 mL) is added to the mortar and mixed with the solid. The resulting yellow solid is removed from the mortar and recrystallized with 95% ethanol. The post-recrystallized product of 2.02 g (4.00 mmol, quantitative yield) of **4a'** was proven to be pure by NMR analysis. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.85 (s, 6H), 7.32-7.55 (m, 10 H), 7.80 (s, 2H). MP: 80.2°C.

Preparation of 2,2-dimethyl-4,6-bis(dihydroxyphenyl)-1,3-dioxanol



4a' **5a'**

In a 50-mL three neck round bottom flask, 2,2-dimethyl-4,6-bis(phenylmethylene)-1,3-dioxanone (2.02 g, 4.00 mmol) was dissolved in 10 mL of dry THF. The flask was cooled to 0 °C using an ice bath and a 1.0 M borane/THF complex (4.0 mL, 4.00 mmol) was slowly added to the round bottom from a syringe. The ice bath was removed and reaction mixture was stirred at room temperature for 1.5 hours. The flask was then again cooled to 0 °C and 0.5 mL of water was added to destroy excess borane. An alkaline solution of hydrogen peroxide made from 3 mL of 30% hydrogen peroxide with 6 mL of 2 M sodium hydroxide solution, is then slowly added to the initial round bottom. The ice bath was then removed and the solution was stirred for 5 minutes. The reaction mixture was then extracted with ether (3 × 10 mL). The combined organic layers were then washed with 10 mL of water and 10 mL each of brine. The organic solution was dried over $NaSO_4$ and the solvent was removed by rotary evaporation. This allotted a clear, whitish gel (1.34 g). The NMR spectra indicated that there was most likely not a single product and the specific stereochemistry of the product was unable to be determined.

DISCUSSION AND CONCLUSION

The first portion of this research was dedicated to finding efficient syntheses of the cyclic ketones that would serve as starting materials for the aldol addition reactions. Three cyclic ketones with differing R groups at the ketal or acetal carbon were chosen; namely, 2,2-dimethyl-1,3-dioxane-5-one, 2-phenyl-1,3-dioxane-5-one and 2-*t*-butyl-1,3-dioxane-5-one. These R groups represent differing levels of steric bulk, which could alter the conformation of the cyclic enolate thereby impacting the diastereoselectivity of the product in the aldol addition reaction. This portion of the research was very successful providing acceptable to excellent yields for all three cyclic ketones.

For the dimethyl compound, an acid-catalyzed ketal exchange between TRIS hydrochloride and dimethoxypropane provided a substituted dioxane in the first step. The ketone carbonyl group was created by an oxidative cleavage of the diol (or epoxide) formed in situ under acidic conditions from the aminoalcohol function. Similarly, the phenyl substituted ketone was synthesized from the dimethyl acetal of benzaldehyde. Since the dimethyl acetal of pivaldehyde is not commercially available, it was synthesized from the aldehyde and trimethyl orthoformate. This was used to generate the cyclic ketone with a *t*-butyl substituent at position 2 albeit in lower yield than the other two ketones. This is an area that will require further research to improve the overall yield in order for this ketone to be available as a viable synthetic intermediate.

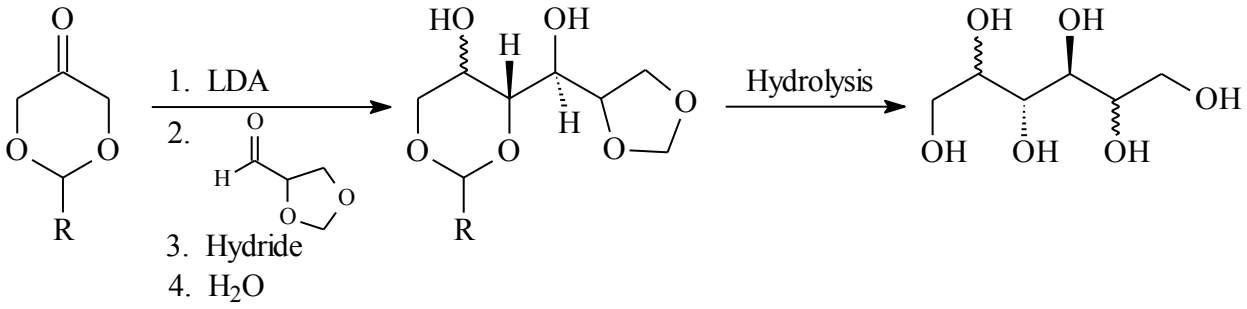
Next, we attempted to reproduce the data from the model system shown in Scheme 3 by generating the lithium enolate of cyclohexanone and adding it to benzaldehyde at low temperature. This proved to be extremely difficult for an inexplicable reason since the reaction had been carried out successfully numerous times before. Our troubleshooting attempts included

variations in the reaction temperature, reaction time, concentration and electrophile; but none of these changes produced a positive result. Analyses of the reaction mixtures revealed that a substantial amount of benzaldehyde was recovered in all of these trials. This led to the speculation that the source of the problem was in the generation of the enolate, but the cause remained a mystery until much later when there was insufficient time to solve the problem and investigate this pathway further. The culprit turned out to be the presence of trace water in the nitrogen supply that was used to assure that the reaction was carried out under anaerobic conditions. This was caused by using nitrogen from a different vendor without confirming that the quality of the gas was the same as before. (Other people in the chemistry department were affected as well.)

In the meantime, the alternate approach depicted in Scheme 5 was investigated using cyclohexanone as a model ketone and benzaldehyde as a model aldehyde. The single aldol condensation and the double aldol condensation were carried out in high yield to prepare for the alternate pathway if needed. Cyclohexanone and benzaldehyde were triturated with solid NaOH using a mortar and pestle. This novel solventless technique is a "green" procedure that worked exceedingly well to produce the enone and the dienone using one equivalent of benzaldehyde and two equivalents of benzaldehyde, respectively. Attempts to carry out the hydroboration procedure on the dienone led to extremely complex mixtures of products in which both the double bonds and the ketone function were absent. This indicated that the alkenes were successfully hydroborated and that borane had also reduced the ketone carbonyl. It was not possible to determine which reaction occurred faster. On the basis of this evidence, we assume that these products are triols of unknown stereochemistry. In retrospect, it would have been

more logical to use the enone instead of the dienone since this would have produced a simpler reaction mixture.

Future researchers on this project must repeat the model chemistry shown in Scheme 3 using ultrapure nitrogen. The original approach to making sugar alcohols depicted in Scheme 4 is better by far than the aldol condensation approach since it will likely allow the control of all the stereochemical centers. This could be verified by carrying out the chemistry shown in Scheme 5.



Scheme 5. Future research.

REFERENCES

1. Crezee, E.; Devred, F.; Hoffer, B.W.; Kapteijn, F.; Kooyman, P.J.; Mooijman, P.R.M.; Moulijn, J.A.; Sloof, W.G.; van Langeveld, A.D. Synthesis, Characterization, and Catalytic Performance of Highly Dispersed Supported Nickel Catalysts from Ni-Al Layered Double Hydroxides. *Applied Catalysis A: General* **2003**, *253* (2), 437-452.
2. Aebi, Johannes D.; Seebach, Dieter; Gander-Coquoz, Marlyse; Naef, Reto. A Convenient Route to Enantiomerically Pure 2-Substituted Methyl Glycerate Derivatives. *Helvetica Chimica Acta*. **1987**, *70* (4), 1194-216.
3. Blanc, B.; Cerino, P.J.; Flèche, F.; Fuertes, P.; Gallezot, P. Evaluation of D-glucose hydrogenation catalysts stability in different reactor systems. *Journal of Catalysts* **1994**, *146* (1), 93-102.
4. Amadò, R.; Arrigoni, E.; Brouns, F. Human gut microbiota does not ferment erythritol. *British Journal of Nutrition*. **2005**, *94* (5), 643-6.
5. Mahrwald, R.; Markert, R. Asymmetric assembly of aldose carbohydrates from formaldehyde and glycolaldehyde by tandem biocatalytic aldol reactions. *Chem. Eur. J.* **2008**, *14*, 40-48.
6. Obora, Yasushi; Nakamura, Kazuhiro; Hatanaka, Shintaro. Iridium-catalyzed reaction of enones with alcohols affording 1,3-diketones. *Chem. Commun.* **2012,** *48,* 6720-6722.
7. Schmid, C. R.; Bryant, J. D.; Dowlatezdah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear N. L.; Vianco, C. S. Synthesis of 2,3- O-isopropylidene-D-glyceraldehyde in High Chemical and Optical Purity: Observations on the Development of a Practical Bulk Process. *J. Org. Chem*. **1991**, *56*, 4056-4058
8. Forbes, David C.; Doyle, Michael P.; Ene, Doina G. Stereoselective Synthesis of Subtittuted 5-Hydroxy-1,3-dioxanes. *Synthesis* **1998,** 879-882.

9. Hoppe, D.; Schmicke, H.; Kleemann, H.W. Studies toward the total synthesis of 1-oxacephalosporins 1: 3-amino-4-thio-2-azetidinones with protected γ.γ'-dihydroxyalkenoate side chain. *Tetrahedron* **1989**, *45* (3), 687-694.
10. Bartlett, N.; Gross, L.; Peron, F.; Asby, D.J.; Selby, M.D.; Tavassoli, A.; Linclau, B. Stereocontrol by Quaternary Centres: A Stereoselective Synthesis of (−)Luminacin D. *Chemistry - A European Journal* **2014,** *20* (11), 3306-3310.
11. Díez, Elena; Dixon, Darren J.; Ley, Steven V. Butane-2,3-Diacetal-Desymmetrized Glycolic Acid—A New Building Block for the Stereoselective Synthesis of Enantiopure *α*-Hydroxy Acids**.** *Angew. Chem. Int. Ed.* **2001,** *40* (11), 2906-09.
12. Rahman, A.F.M.M.; Ali, R.; Jahng, Y.; Kadi, A.A. A Facile Solvent Free Claisen-Schmidt Reaction: Synthesis of α,α′-bis-(Substituted-benzylidene)cycloalkanones and α,α′-bis-(Substituted-alkylidene)cycloalkanones. *Molecules* **2012**, *17*, 571-583.
13. Brown, H. C.; Zweifel, G. HYDROBORATION AS A CONVENIENT PROCEDURE FOR THE ASYMMETRIC SYNTHESIS OF ALCOHOLS OF HIGH OPTICAL PURITY. *J. Am. Chem. Soc.* **1961**, *83* (2), 486–487.