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Further Applications of Lactone Syntheses on Glyceraldehyde Acetonide, and Attempts at a Safer Process for the Synthesis of Trimethylsilylketene

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Abstract

During this semester, ten reactions were carried out. The first was the synthesis of D-glyceraldehyde acetonide from D-mannitol. The next six reactions were involved with the synthesis of the corresponding γ-lactone of glyceraldehyde acetonide. The final three reactions were attempted syntheses of ethyl ethynyl ether, the key starting material in the synthesis of TMS ketene.

Introduction

In the area of lactone research, there are several key questions that need answered, and several key reactions that need run. One of the biggest questions involves the mechanism by which a β-lactone expands to a γ-lactone. It has been speculated that the dyotropic rearrangement that is responsible for the expansion is a concerted process. To shed more light on this, ring expansion reactions on optically active molecules is of interest. This is the one of the goals behind the glyceraldehyde acetonide γ-lactone project. Here, the optically active aldehyde would be converted to its corresponding γ-lactone using Black’s γ-lactone synthesis,\(^2\) and enantiomeric purity of that γ-lactone would be tested on a polarimeter, as well as with perhaps a series of NMR experiments like nOe. If a concerted process were to take place, then the optical purity of the product would remain intact. However, with glyceraldehyde acetonide, one of three theorized products will be obtained (Figure 2), each with intriguing possibilities for further lactone research. The glyceraldehyde acetonide molecule may produce as many as three chiral centers upon expansion to a γ-lactone.

Another hot area of lactone research involves not the products of various lactone synthetic protocols, but the reagents used to carry out those reactions. One of the most
interesting of these developments is the reagent trimethylsilylketene (TMS-ketene) (Figure 4). This reagent reacts with ketone or aldehyde functions in a [2+2] cycloaddition reaction to yield β-lactones without the need for β-hydroxy acid intermediates. This is a much simplified approach to lactone synthesis, except for the acquisition of the TMS-ketene itself. TMS-ketene can be purchased commercially, but at an extravagant price, and current reported syntheses involve the use of liquid ammonia and a very cold apparatus. However, our group is finding a solution to this problem. The key to the synthesis of TMS-ketene is the synthesis of ethyl ethynyl ether from chloroacetaldehyde diethylacetal. If this step were to be simplified, then the process as a whole would be much easier; thus making synthesis of lactones from TMS-ketene much more applicable. This reaction (Figure 3) involves use of three equivalents of a strong base to facilitate an E2 reaction of chloroacetaldehyde diethylacetal, a reaction in which a double elimination takes place, affording the alkyne-ether product.

Results and Discussion

The synthesis of D-glyceraldehyde acetonide (Figure 1) was accomplished from 50 g of D-mannitol in two steps, to yield 31.2 g of the aldehyde, giving an overall percent yield of 44%. The first step of this reaction was the formation of the bis-acetonide on the two far left and far right alcohols using 2,2-dimethoxypropane. The reaction was carried out in 1,2-dimethoxyethane as the solvent, with tin II) chloride as the catalyst. The product obtained from this reaction was characterized by IR spectroscopy, which showed an alcohol stretch at 3314 cm⁻¹, and a series of C-O stretches in between 1000 cm⁻¹ and 1300 cm⁻¹. However, there were two unexplained stretches at 2360 cm⁻¹ and 1610 cm⁻¹,
which were probably due to impurities, since it was not necessary to purify this product according to the publication used.¹

The second step of this reaction was the cleavage of the bond between the two hydroxyl substituted carbons to yield two equivalents of aldehyde. This was accomplished with sodium metaperiodate, with sodium bicarbonate as a catalyst.

![Chemical structures](https://via.placeholder.com/150)

**Figure 1 – Synthesis of D-glyceraldehyde acetonide from D-mannitol**

Upon the synthesis of this starting material, utilization of it in Black’s lactone synthesis² was made (Figure 2). This synthesis involves exposing an acetic acid derivative to the strong base lithium diisopropylamine (LDA), and then adding the D-glyceraldehyde acetonide to create a β-hydroxy acid. The β-hydroxy acid is then added with benzene sulfonyl chloride, which creates the β-cyclic ester, or β-lactone. The final step in the synthesis, and the one of the most interest with this particular substrate, is the Lewis acid catalyzed ring expansion from the β-lactone to the γ-lactone. As can be seen in Figure 2, there are three proposed pathways as to which this reaction might follow. Previous experience with lactones suggests that it will most probably follow only one
pathway, so all that must be determined is which way it went. Once this is discovered, we will gain a great deal of additional information as to how this reaction proceeds.

Of the three listed pathways, it is felt the most probable is the middle one, which yields the fused ring system. However, until the final product is actually characterized, there is not much information as to which pathway the reaction will follow. What it comes down to is how all of the oxygen atoms present in the molecule will interact with the magnesium ions that are present during this phase of the reaction. Whatever conformation results from metal ion interaction, the result of any different interaction places another function anti-periplanar from the lactone ring-oxygen, which will result in migration of a different group during the dyotropic rearrangement. This can be seen in Figure 2, with the arrows drawn showing which group is migrating. As mentioned earlier, if whatever product produced by this reaction still has its chirality intact after the dyotropic rearrangement, this will indicate a mechanism that is concerted. A concerted process for this mechanism means that when the bonds migrate from one position to the other, it happens fast enough that no true carbocation is formed, and thus no chance for free rotation about any of the bonds involved – which would compromise chirality.
The last project outlined in this report involves a new approach to the synthesis of TMS-ketene (see Figure 4 for structure). Though a proven synthesis soon to reach publication in *Synthetic Communications*, which was authored by Dr. T.H. Black and past members of this research group, works fine for making TMS-ketene; it is now desired to find a more simplistic route, and this current route requires the use of stringent conditions and liquid ammonia. To find this elusive, more simplistic route, several test reactions were carried out for the synthesis of the starting material, ethyl ethynyl ether (ethoxyacetylene) (Figure 3). Just as in the *Synthetic Communications* procedure, the ethyl ethynyl ether is made by treating one equivalent of chloroacetaldehyde diethylacetal.
with three equivalents of a strong base. The *Synthetic Communications* procedure uses the base sodium amide, which is made *in situ*; however, sodium amide has been recently made commercially available in a pellet form. To take advantage of this, modification on the known procedure is being attempted. Also, use of a different base is being tested to see if the reaction still takes place. Using the same test procedure used with the solid sodium amide, chloroacetaldehyde diethylacetal was also treated with butyllithium in a THF solvent.

In all of these reactions, the three equivalents of base are used to facilitate a double E2 reaction in which the tertiary proton from chloroacetaldehyde diethylacetal is abstracted, and a triple bond is created (Figure 3).

Outlined in this report is the attempted synthesis from two variations using sodium amide in dimethoxyethane, and one variation using butyllithium in THF. So far, none of the reactions has produced any of the desired product. However, some reaction is taking place, as exotherms and color changes were observed during both reactions. And there is still some hope for the sodium amide procedure, as it met its demise due to a malfunction in the water faucet suppling the water to the condensers.

Figure 3 – The first step in the synthesis of TMS-Ketene.
Conclusions

The project involving the lactone formation from glyceraldehyde acetonide is going quite smoothly. Soon, all kinds of characterization data will be compiled and analyzed. The same cannot be said, however, for the project involving the modification of the TMS-ketene procedure, though still in its early stages. The reactions attempted are not yet yielding any product, but much more work is planned for them in the future. The small systematic errors involved with the procedures in this report will be corrected, and new variations will be attempted in order to reach the goal of a synthesis that can be done under mild conditions, with less dangerous reagents.

Experimental

Synthesis of D-glyceraldehyde acetonide

A 500 mL 3-neck flask was obtained and fitted with a condenser w/drying tube, septum, stir bar, and sand bath. Then added to the flask was 50 g of D-mannitol (0.27 mol) was with 120 mL freshly distilled 1,2-dimethoxyethane, 80 mL of 2,2-dimethoxypropane (65.6 g 0.63 mol), and 0.06 g (0.26 mmol) of tin (II) chloride. This apparatus was placed on a hot plate and refluxed until the solution appeared clear, then, after an additional 30 min of stirring, the apparatus was allowed to cool. When the
mixture was cool, 0.2 mL of pyridine was added and the contents of the flask were vacuum filtered through a sintered glass funnel into a tared 500 mL round-bottom flask. The contents of this flask were then placed on a rotary evaporator, and IR analysis was done. The following peaks were observed: 3314, 2924, 2853, 1462, 1377, 1217, 1157, 1068, and 846 cm⁻¹. Comparison to literature values, and calculation of a percent yield for this step would be useless, as the intermediate was not purified.

Next, 430 mL of dichloromethane was added to the flask with a stir bar. A condenser and heating mantle were added, and vigorous stirring was begun. The flask was heated to reflux until all of the solids present were dissolved. The mantle was then removed, and the flask was allowed to cool below reflux. Then, 5 g of Celite® was added, and the mixture was stirred and allowed to cool to room temperature. At this point, the contents of the flask were vacuum filtered through a sintered glass funnel into a 500 mL 3-neck flask, which was equipped with a stir bar, and stirring was begun rapidly. Next, 18 mL of saturated aqueous sodium bicarbonate solution, and 42 g of sodium metaperiodate were added, adding the sodium metaperiodate portions over two minutes. Stirring was then continued for 2 hrs. After the stirring was completed, the contents of the flask were dried over magnesium sulfate, and vacuum filtered through a sintered glass funnel into a tared 500 mL round-bottom flask. Then, 50 mL of dichloromethane was then added back into the 3-neck vessel with the filter cake, and this was once again vacuum filtered into the same, tared 500 mL round-bottom flask. A distillation apparatus was then set up with a 10 cm Vigreux column, and the dichloromethane was distilled from the flask; the remaining oil in the flask was the pure product. An IR spectrum was taken immediately, and the pure product was stored in a freezer. IR analysis of the pure product
obtained showed the following peaks: 2989, 2938, 2891, 2821, 1735, 1374, 1255, 1220, 1151, 1073, and 842 cm$^{-1}$. All of these peaks corresponded to literature values. From this procedure, 31.2 g of the aldehyde was obtained, giving an overall percent yield of 44 %.

**Synthesis of the γ-Lactone from D-Glyceraldehyde Acetonide**

A 100 mL three-neck flask was fitted with a stirbar, septum, N$_2$ gas inlet, and a low-temperature thermometer, and was charged with 30 mL of freshly-distilled tetrahydrofuran (THF). Under a nitrogen atmosphere, 5.6 mL (4.05g 40 mmol) of diisopropylamine was injected into the flask via syringe. Upon completion of this addition, an ethyl acetate - liquid nitrogen bath was placed under the reaction flask, and the mixture was cooled to –78 ºC. When the desired temperature was reached, the drop-wise addition of 25 mL (40 mmol) of 1.6 M butyllithium (in hexanes) was begun, while the –78 ºC environment was maintained. When all of the butyllithium was added, the flask was allowed to warm to –40 ºC, and stirring was continued for 15 min. Next, 20 mL of a solution of 1 M phenylacetic acid in THF was added dropwise, and then the mixture was allowed to stir for 1 hr.

While the mixture was stirring, a 2.5 M solution of glyceraldehyde acetonide in THF was prepared. This was accomplished by placing the flask in which it was stored on a roto-vap, and bringing the gel-like substance to a near boil under vacuum, and using a hot-water bath. Doing this made the aldehyde much easier to work with. Next, 2 mL of the aldehyde was taken from the flask with a syringe, and added to 8 mL of fresh THF.

After the 1 hr stirring time, the aldehyde solution was injected into the flask, and the reaction was allowed to stir under nitrogen for 16 hrs. Once this was complete, the solution in the flask was poured over ca. 50 g of ice, and the layers were then separated,
discarding the organic layer. The aqueous layer was then washed two times with ether, and was then acidified using 6 N aqueous hydrochloric acid. Once it had been acidified, the aqueous solution was extracted three times with 15 mL of ether. The aqueous portions were then discarded. The combined organic extracts were then washed with brine and dried over magnesium sulfate. After vacuum filtration to remove the magnesium sulfate, the tared flask containing the crude product was placed on a rotary evaporator, and then on a vacuum rack to remove all of the solvents. The crude β-hydroxy acid crystals that were yielded were analyzed via melting point, TLC, and IR. The melting point of the crystals was 67 – 72 ºC. TLC analysis showed only one spot with an Rf value of 0.76. IR analysis showed peaks at 2922, 2736, 2656, 2559, 1697, 1496, 1450, 1407, 1338, 1229, 1186, 894, and 700 cm⁻¹.

Next, 500 mg (18.8 mmol) of the β-hydroxy acid was placed in a 50 mL Erlenmeyer flask already equipped with a septum, a stirbar, and containing 10 mL of pyridine. An ice bath was placed under the flask, and the solution was cooled to 0 ºC. When cool, 4.8 mL (6.6 g, 37.6 mmol) of benzene sulfonyl chloride was added dropwise to the flask with stirring, and the flask was then stored at 0 ºC for 16 hrs. When completed, the deep red solution was poured onto ca. 50 g of ice, and the layers were separated. The aqueous layer was extracted three times with 15 mL of methylene chloride, and was then discarded. The combined organic extracts were then washed sequentially with 15 mL of 10% HCl, saturated sodium carbonate, water, and brine. The organic layer was then dried over magnesium sulfate, and after the magnesium sulfate was removed via vacuum filtration, the crude β-lactone, which was in a tared flask, was
placed on a rotary evaporator, and a vacuum rack to yield 0.93 g (3.75 mmol) a deep-red oil in a 20 % yield. TLC, IR, and NMR analyses are yet to be done.

**Synthesis of Ethyl Ethynyl Ether using Sodium Amide as Base**

A clean, dry 100 mL three-neck flask was fitted with a septum, thermometer, N₂ gas inlet, and a stirbar. The flask was charged with 75 mL of fresh 1,2-dimethoxyethane, and placed in an ice bath. Once at 0 °C, 4.9 mL (5.0 g, 33 mmol) of chloroacetaldehyde diethylacetal was added via syringe.

Next, commercially available sodium amide pellets (95 %) were obtained and ground into a fine powder using a mortar and pestil; 4.08 g (95%, 104 mmol) of this powder was then collected and added slowly to the flask. Upon addition, the color of the solution changed slowly from yellow to light brown over a period of two minutes. The reaction was then allowed to stir under nitrogen for 24 hrs, and was then quenched using 10 mL of water. A still was then setup directly on the reaction flask, using a 10 cm Vigreux column, and an ice bath was placed under the collection flask. The desired fraction was that which distilled at 40 – 60 °C. Product collected at these temperatures was analyzed via IR, and showed none of the characteristics of ethyl ethynyl ether. The peaks present were characteristic of the starting material chloroacetaldehyde diethylacetal, which showed peaks at 3483, 2982, 2882, 2819, 1455, 1366, 1193, 1109, 1028, and 851 cm⁻¹.

A second attempt at this reaction was completed, with a few changes to procedure. The first alteration was sodium amide was added before the chloroacetaldehyde diethylacetal. The second alteration done was instead of letting the reaction sit for 24 hrs, two condensers (one on top of the other) were set up on the
reaction flask, and a gentle reflux was begun. However, a malfunction in the water-flow system to the condensers caused all of the solvent, as well as any product that may or may not have been present, to boil away.

**Synthesis of Ethyl Ethynyl Ether using Butyllithium as Base**

A clean, dry 250 mL three-neck flask was fitted with a septum, thermometer, N₂ gas inlet, an ice bath, and a stirbar. The flask was charged with 75 mL of freshly distilled tetrahydrofuran, and 61 mL (6.3 g, 98.0 mmol) of 1.6 M butyllithium (in hexanes). Once at 0 ºC, 4.9 mL (5.0 g, 33.0 mmol) of chloroacetaldehyde diethylacetal was added via syringe very slowly, taking care to not let the exotherms push the temperature too far above 40 ºC.

The reaction was then allowed to stir under nitrogen for 4 hrs, and was then stored in a cool, dark drawer for 3 days, due to the necessity of having to leave the lab for a weekend. The reaction was then quenched using 10 mL of water, and acidified with 5 mL of 1.5 N HCl. A still was then setup directly on the reaction flask, using a 10 cm Vigeux column, and an ice bath that resided under the collection flask. Two fractions were collected, one from under 50 ºC, and another from 50 to 55 ºC. Products collected at these temperatures was analyzed via IR, and showed none of the characteristics of ethyl ethynyl ether. The peaks observed in the IR were 2958, 2927, 2859, 1461, 1072, and 912 cm⁻¹.
References

