Using Organo-Catalysis to Synthesize One Side of Lipitor

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Abstract - For this project, a new synthesis of the key precursor for Lipitor (as well as other statin drugs) was attempted. This involved a series of reactions, some of which were to create materials which were not present in the lab, and some of which were essential to the production of the compound. First, we carried out an acylation reaction between 2-naphthoyl chloride and aminoacetaldehyde dimethyl acetal with triethylamine to act as a base and ethyl acetate as a solvent. Then, that product underwent a hydrolysis using THF and 2M HCl to convert the acetal to an aldehyde which went in about 80% yield. Next, L-proline was used to catalyze a reaction in conjunction with DMSO to add 2 equivalents of acetaldehyde to the aldehyde product, which should result in two hydroxyl groups facing forward due to syn addition. L-proline acts to add the hydroxyl groups in a stereochemically-specific way, which should be the syn conformation. That reaction was based on a publishing in the Journal of the American Chemical Society by Carlos F. Barbas III, et al. The product of this reaction can cyclize, which was seen in this case. The next reaction involved protecting the hydroxyl groups before an oxidation reaction to convert the aldehyde to a carboxylic acid. This is where research ended for this project and where future researchers can pick up at.

Introduction

Current production methods for this key side-chain of Lipitor are lengthy and outdated. They were developed in the late 1980s using the methods available at the time. It is 2016 now and Dr. Brian Lavey has proposed an alternate route for synthesis. This has the potential to cut 4-5 steps from traditional methods of production. There are many benefits to this. Some benefits are reduced production cost, greater yield in a lesser amount of time, and a backup plan in case materials needed for traditional synthesis become unavailable. The most important reaction is the L-proline catalyzed reaction, as the Lipitor side-chain has R,R stereochemistry, which results from **syn addition** of hydroxyl groups. **This stereochemistry is what makes the compound biologically active, so syn addition must be seen in the synthesis.** The goal of this project was to produce a stereochemically-correct molecule similar to the precursor of Lipitor exhibiting syn addition during the L-proline catalyzed reaction.

Experimental Section

In order to achieve the goals of this experiment, a series of reactions were performed in this order. All reagents were purchased from Sigma-Aldrich, some of which were already available in the lab. NMR was taken of each product on a NMReady^{TM}60 Nanalysis NMR Machine.

Acylation – N-(2,2-Dimethoxyethyl)-2-naphthamide was synthesized through an acylation reaction involving 2-naphthoyl chloride (1.00 eq) and aminoacetaldehyde dimethyl acetal (1.20 eq). Triethylamine (1.03 eq) acted as a base to push this reaction towards the product side. To begin, 2-naphthoyl chloride was added to a round bottom flask followed by ethyl acetate to dissolve the compound. Then aminoacetaldehyde dimethyl acetal and

triethyl amine were added in their respective amounts. This reaction was stirred under reflux for 1 hour and monitored via TLC. The reaction mixture then underwent a routine workup to extract the product. It was first quenched with aq. NH_4Cl and then washed 3 times with EtOAc. The organic layer was dried with Na_2SO_4. A rotary evaporator was used to remove any solvent and the remaining product was left on the vacuum pump for 15 minutes prior to taking a NMR.

Hydrolysis – The acetal product (1.00 eq.) from the previous reaction then underwent a hydrolysis using 4 mL of THF (approx. 25 eq.) and 4 mL of 2M HCl (4.00 eq.) to convert the acetal group to an aldehyde. All components were added to a RB flask and stirred at room temp. The reaction was monitored via TLC and ran for about 1 hour. The reaction was then neutralized with $NaHCO_3$ and checked with pH paper. It was then worked up with 20 mL of brine and 3x15 mL of EtOAc. (Note: After first wash of EtOAc, aqueous layer was drained and organic layer was decanted into separate beaker. Aqueous layer was washed with fresh EtOAc again repeating previous step and decanting organic layer into beaker. This was done to remove any product that may have been trapped in the aqueous layer). The organic layer was dried with Na_2SO_4. A rotary evaporator was used to remove any solvent and the remaining product was left on the vacuum pump for 15 minutes prior to taking a NMR.

L-Proline Catalyzed Reaction – After successful conversion to the aldehyde product, this stereochemically-specific reaction was performed to attach 2 equivalents of acetaldehyde to the compound, forming a diol, exhibiting syn addition. This reaction is based on the publishing of *Barbas III, et. al.*[1] L-proline (0.2 eq.) was added to the RB flask containing the aldehyde product, followed by 4 mL of DMSO (approx. 30 eq.) and 1 mL of acetaldehyde (approx. 10 eq.). This reaction was stirred at room temp and monitored via TLC. It underwent a routine workup with aqueous NH_4Cl and EtOAc, followed by drying with Na_2SO_4 and evaporation of solvent with rotavap and vacuum pump. NMR results showed a mixture of products. To isolate the pure product, it was subjected to flash chromatography. One pure compound was isolated using 15% EtOAc in n-hexanes. The remainder was pushed through the column using a 25% EtOAc in n-hexanes solution. The fractions were then rotavapped and vacuum pumped prior to NMRs.

Scheme 1. Proposed Enamine Mechanism of the Proline-Catalyzed Asymmetric Aldol Reaction

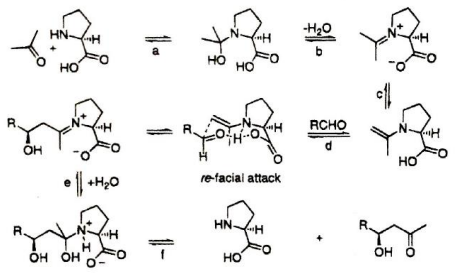


Figure 1: Carlos F. Barbas III, et. al. proposed L-proline catalyzed mechanism. Product exhibits syn addition when multiple additions occur.

Protection and Pinnick Oxidation – After the double addition product was isolated from the cyclization product in the previous step, the hydroxyl groups of the diol needed to be protected in preparation for a Pinnick oxidation to convert the aldehyde to a carboxylic acid. Only one method of protection was tried, which proved to be

[1]Carlos F. Barbas III, et. al, "Proposed Mechanism of the L-Proline Catalyzed Asymmetric Aldol Reaction," *J. Amer. Chem. Soc.*, **122,** pp 2395-2396 (2000)

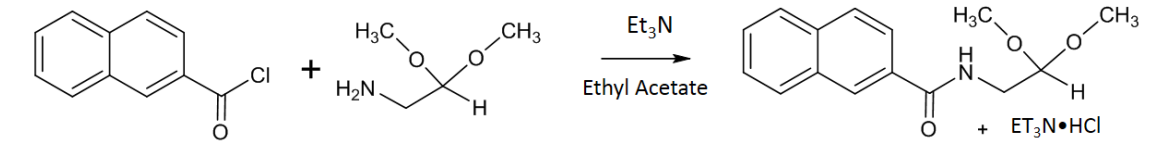
unsuccessful. The procedure called for adding the double addition product (1.00 eq.), acetic anhydride (2.1 eq.), DMAP (0.1 eq.), triethylamine (2.1 eq.) and 3 mL of diethyl ether (approx. 385 eq.). This reaction was stirred at room temp in a small RB flask. This was a very small scale reaction and the addition of 3 mL of diethyl ether made it very dilute. After 24 hours, TLC showed the reaction was not near completion, so 50 uL of acetic anhydride (approx. 5 eq.) were added to push it along. After 72 hours, the reaction had gone to completion and was worked up by first diluting with EtOAc and then transferring to a separatory funnel. The organic layer was washed with DI H_2O, then brine. The organic layer was then dried with Na_2SO_4. A rotary evaporator was used to remove any solvent and the remaining product was left on the vacuum pump for 15 minutes prior to taking a NMR. The NMR showed no aldehyde peak present, meaning that the product must have cyclized during the reaction. Because there was not an aldehyde present, it could not undergo the Pinnick oxidation to form the carboxylic acid. This is where research came to a halt.

Results and Discussion

The first three reactions in the synthesis went in good yield and can be easily reproduced. The protection reaction was not successful due to cyclization, so an alternate method of protection must be considered so the remainder of the synthesis can be carried out. This is where future researchers must pick up the work. Following are the results of each reaction.

Acylation Results –

After comparing an NMR of the product to a predicted NMR from ChemDraw Professional software, it was clear that the expected product was formed during the reaction. The NMR was taken in $CDCl_3$ on a 60 MHz machine, while the predicted NMR is on a 300 MHz machine using d^6DMSO as a solvent, so chemical shifts may differ.



2-naphthoyl chloride Aminoacetaldehyde dimethyl acetal N-(2,2-Dimethoxyethyl)-2-naphthamide

Figure 2: Acylation reaction scheme

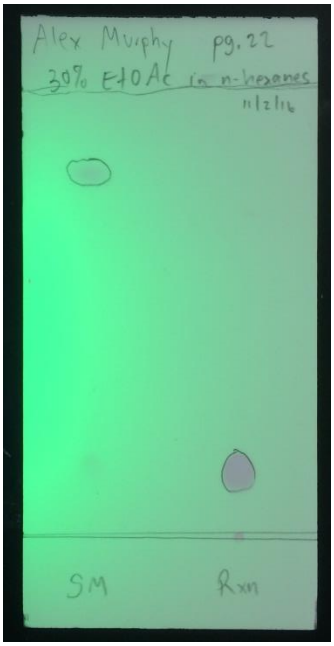


Figure 3: TLC of starting material (left) vs Reaction mixture (right) in 30% EtOAc in n-hexanes

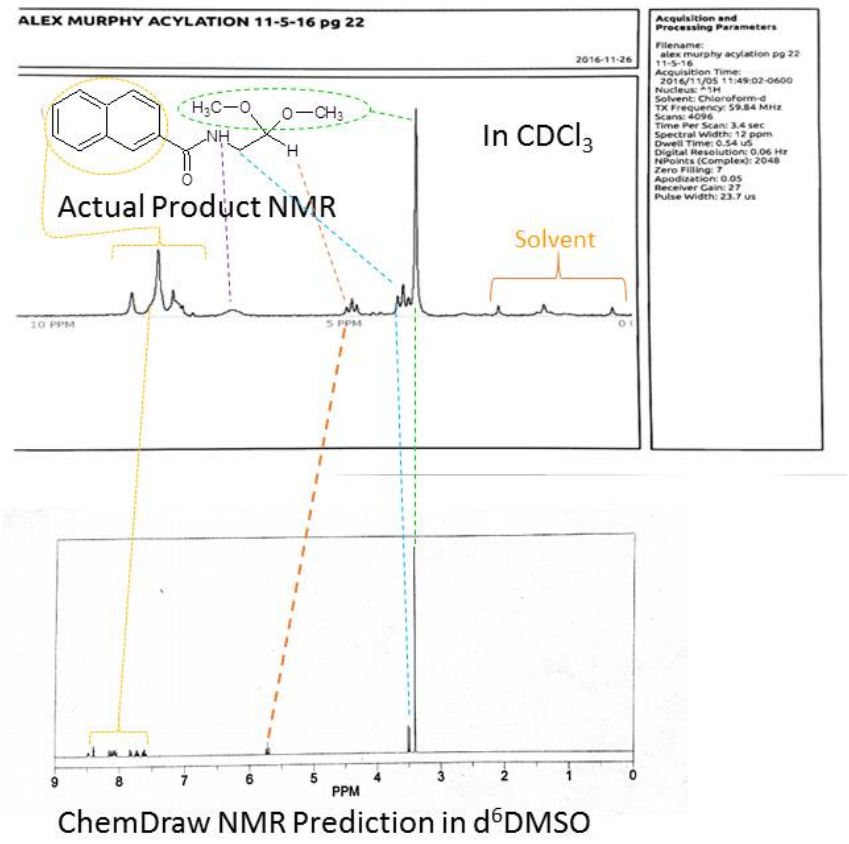


Figure 4: NMR of product compared with NMR prediction of product

Hydrolysis –

Again, comparing the NMR of the product to the prediction, it is clear that the expected product was formed during the reaction. A distinct aldehyde peak around 10 ppm in a good indicator of product formation.

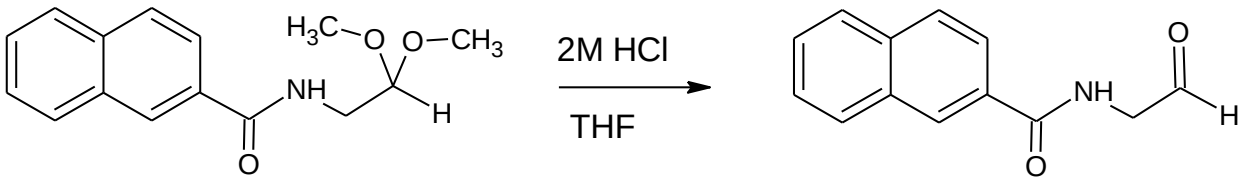


Figure 5: Hydrolysis reaction scheme

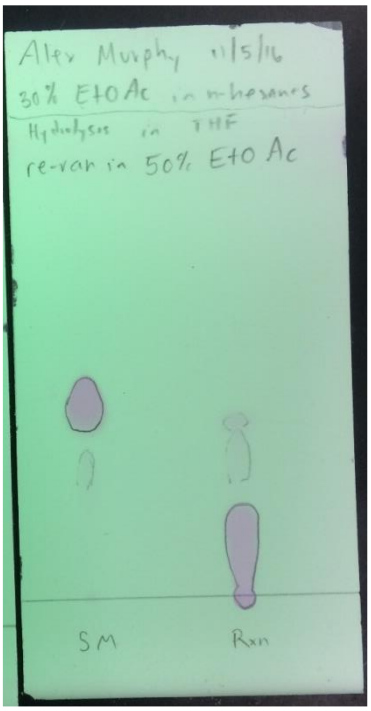
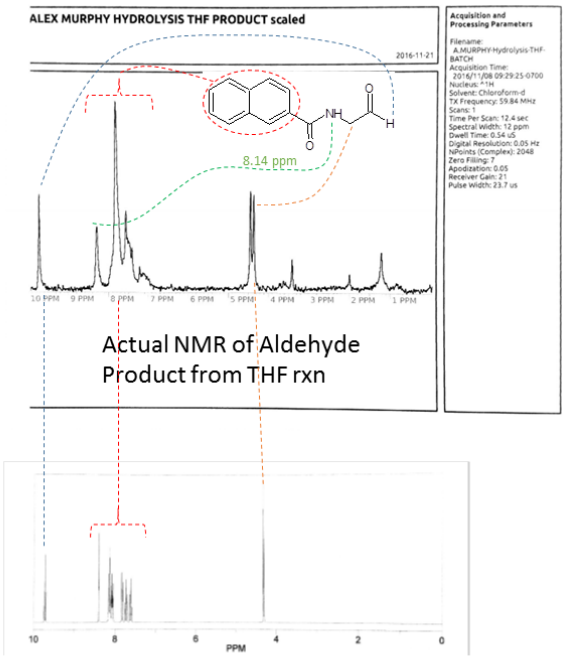


Figure 6: TLC of starting material (left) vs reaction mixture (right) after 1 hour in 50% EtOAc in n-hexanes.



Predicted NMR from ChemDraw software

Figure 7: NMR of product compared to NMR prediction of product.

L-Proline Catalyzed Reaction Results –

This reaction gave a mixture of the cyclization product and double addition (diol) product. This is known because in the NMR predictions, only the double addition and cyclization products showed peaks before 2 ppm and the NMRs of the products show peaks before 2 ppm as well as other characteristic peaks. Flash chromatography was performed to separate these products. It was found that 5% and 10% EtOAc in n-hexanes did not elute any compounds after 23 fractions. Polarity was increased to 15% EtOAc in n-hexanes and a compound eluted starting at fraction 30. After separation, the NMRs of both products show a quartet, which has not been accounted for in the predicted NMRs. It is possible that, although purified through column chromatography, there is still byproduct present.

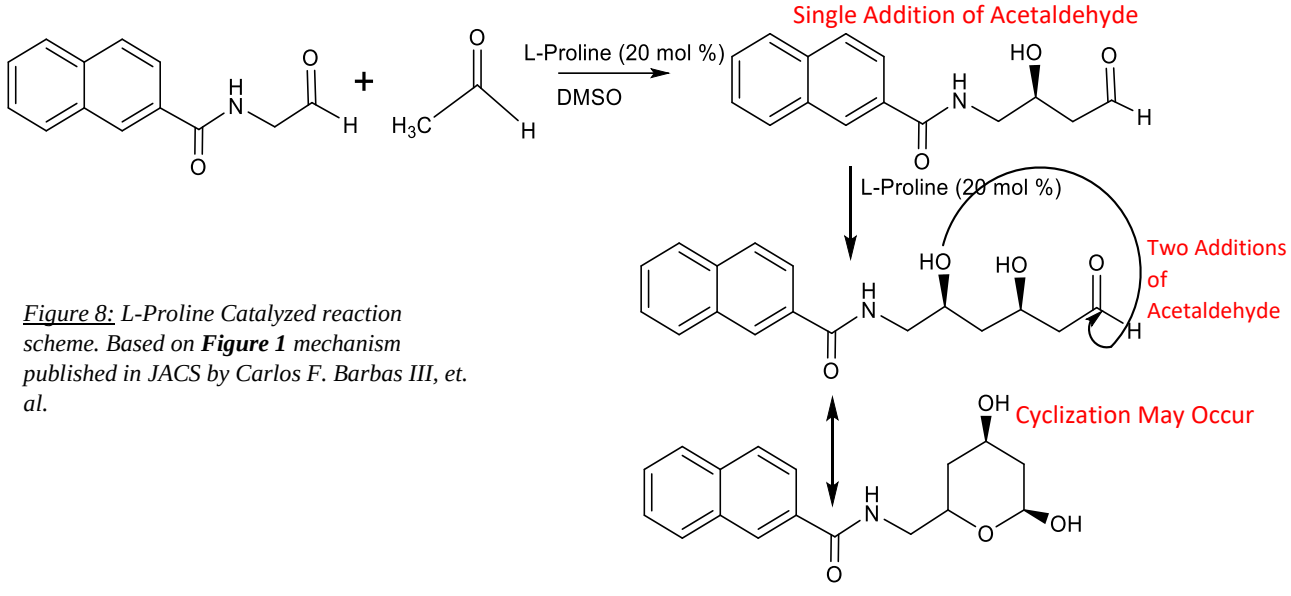
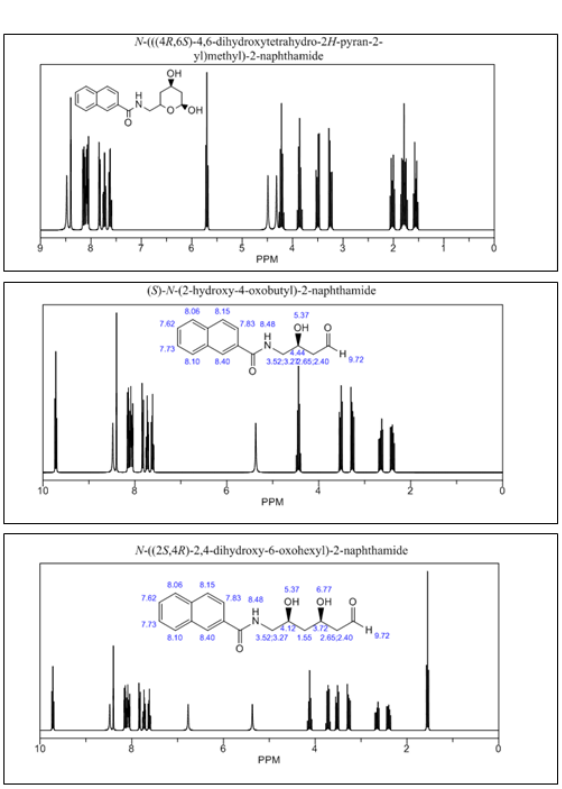


*Figure 8: L-Proline Catalyzed reaction scheme. Based on **Figure 1** mechanism published in JACS by Carlos F. Barbas III, et. al.*



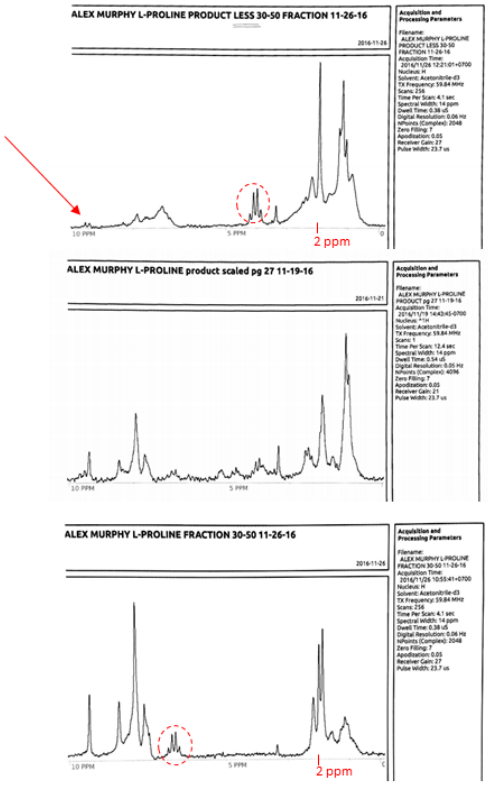


Figure 9: ***Top Right:*** *NMR of product mixture less 30-50 Fraction. No aldehyde peak present near 10 ppm indicating cyclization.* ***Middle Right:*** *Product before chromatography.* ***Bottom Right:*** *Product from 30-50 fraction. Aldehyde peak present near 10 ppm.* ***Left:*** *Predicted NMRs for molecules shown.*

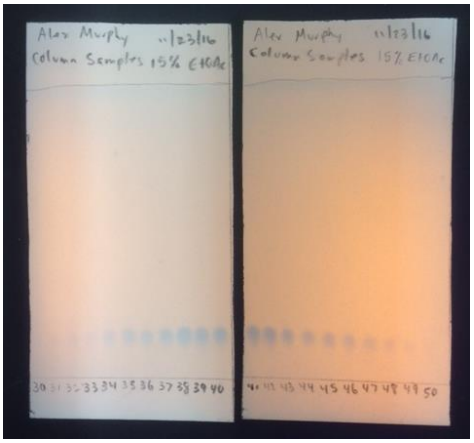


Figure 10: Fractions 30-50 show same Rf value. Fractions were collected and rotavapped, then placed on the vacuum pump prior to NMR.

Protection Reaction and Pinnick Oxidation Results –

The protection reaction performed was not successful. The NMR results show an absence of aldehyde, indicating that the product has cyclized. If there is no aldehyde present, then it cannot be oxidized to a carboxylic acid in the next step. Future experiments must utilize a different method of protection to prevent cyclization.

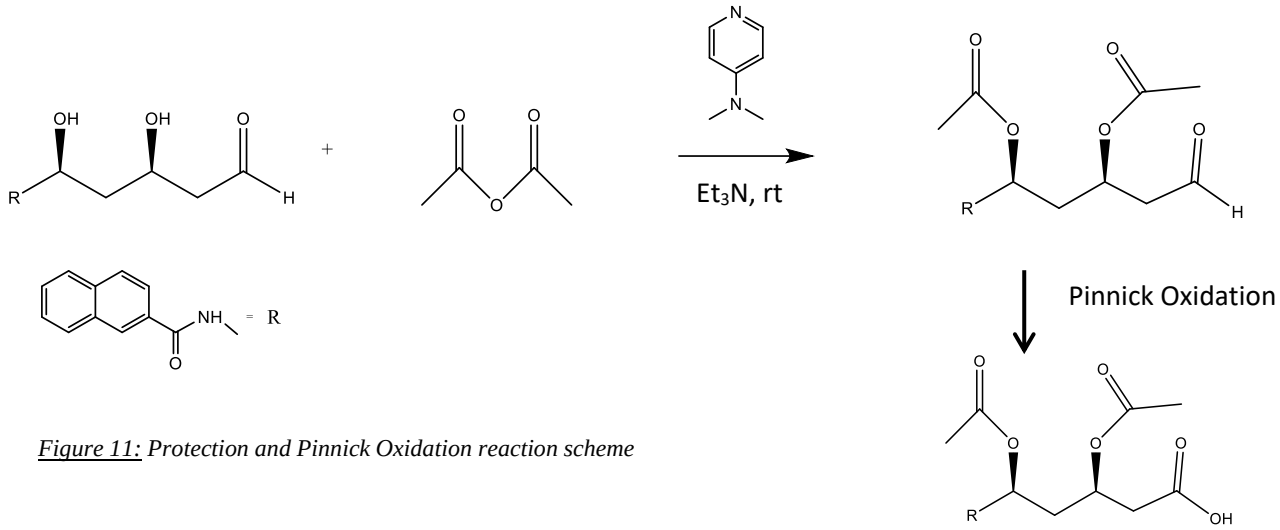
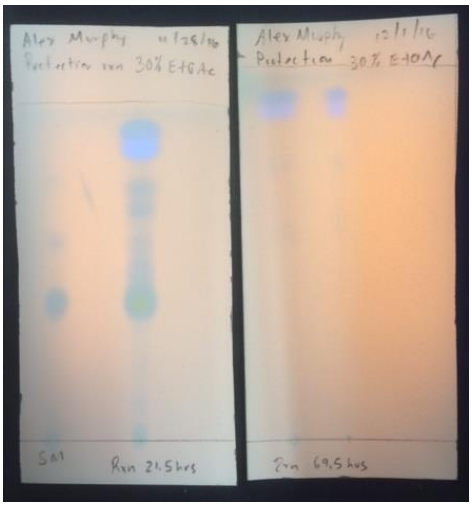


Figure 11: Protection and Pinnick Oxidation reaction scheme



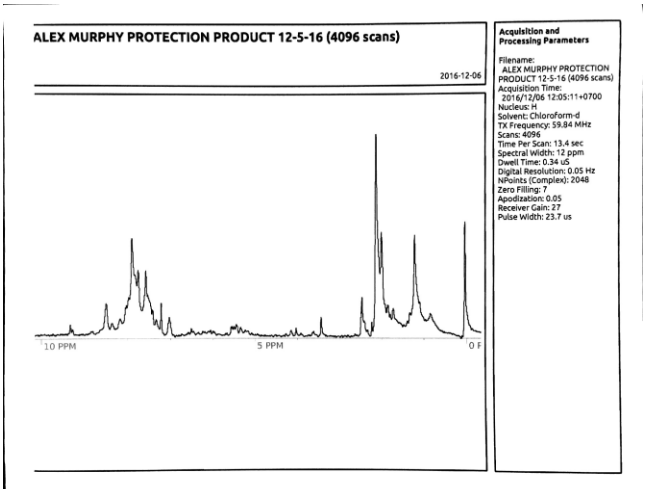


*Figure 12: **Left Plate:** Starting material on left, Rxn mixture after 24 hours on right. **Right Plate:** Rxn mixture only after 72 hours (spotted twice by mistake)*

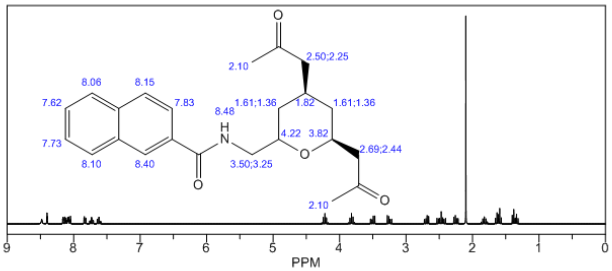


Figure 13: Actual NMR on top shows no peak at 10 ppm, meaning there is no aldehyde. Resembles cyclization prediction on bottom.

Acknowledgments:

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