

**SYNTHESIS OF A DOUBLE-HEADED NUCLEOSIDE
THROUGH A
KNOEVENAGEL/ALDOL PATHWAY**

Thesis

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By

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LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
AZT	Azidothymidine
DEPT	Distortionless enhancement by polarization transfer
DHN	Double-headed nucleoside
DMF	Dimethylformamide
DMP	Dimethoxypropane
DNA	Deoxyribonucleic acid
HETCOR	Heteronuclear correlation experiment (2D NMR)
HIV	Human immunodeficiency virus
HPLC	High pressure liquid chromatography
NMR	Nuclear Magnetic Resonance
TCCA	Trichloroisocyanuric acid
TEMPO	2,2,6,6-tetramethyl-1-piperinyloxy, free radical
TLC	Thin layer chromatography
TsOH	p-toluenesulfonic acid
SO ₂	sulfur dioxide

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INTRODUCTION

Dideoxynucleosides (ddN) have been shown to be powerful antiviral agents⁷. Antiviral agents are an area of great interest due to the number of people affected worldwide by the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). HIV is a retrovirus and uses a viral specified enzyme called reverse transcriptase to build its DNA. Reverse transcriptase has been found to be inhibited by nucleoside analogs like AZT, which was the first approved drug for treatment of AIDS⁶.

Nucleoside analogs, like AZT and dideoxyadenosine, function as antiviral agents by becoming incorporated into viral DNA and serving as chain terminators as a result of the missing 3' hydroxyl group⁸. These molecules work well to prevent viral replication; however, other complications occur which prevent them from being used for long-term treatment. One complication results from the fact that these are incorporated into the bone marrow and become very toxic to the patient over time⁴. In addition, when taken orally, the acidic conditions of the stomach greatly weaken the glycosidic bond, and the molecule is broken down before being incorporated into the DNA³.

Efforts have been made to find analogs which do not pose these problems. Many attempts have been made with isomeric sugars, which provide an advantage over ddN because the elimination of the glycosidic bond stabilizes the molecule. Isodideoxynucleosides (iso-ddN) transpose the 3' carbon and ring oxygen, so that the critical distance between the base and phosphate attachment site remains unchanged. Frank³ has shown that these iso-ddNs are much more stable at low pH's and demonstrate antiviral activity, but these molecules are still incorporated into the bone marrow and have been found to be even more toxic than the ddNs.

A double-headed nucleoside could be created by combining the structure of the ddN and iso-ddN as shown in **Figure 1**. This molecule will possess the characteristics of the nucleosides known to be active antiviral agents, but would differ slightly in structure from previously tested nucleosides.

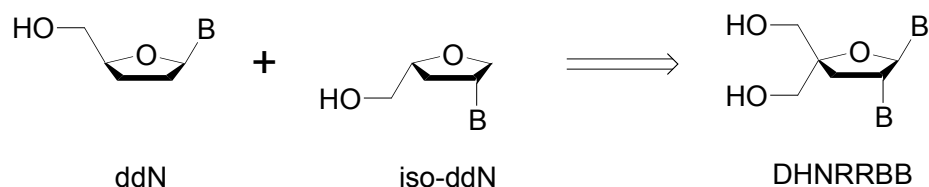


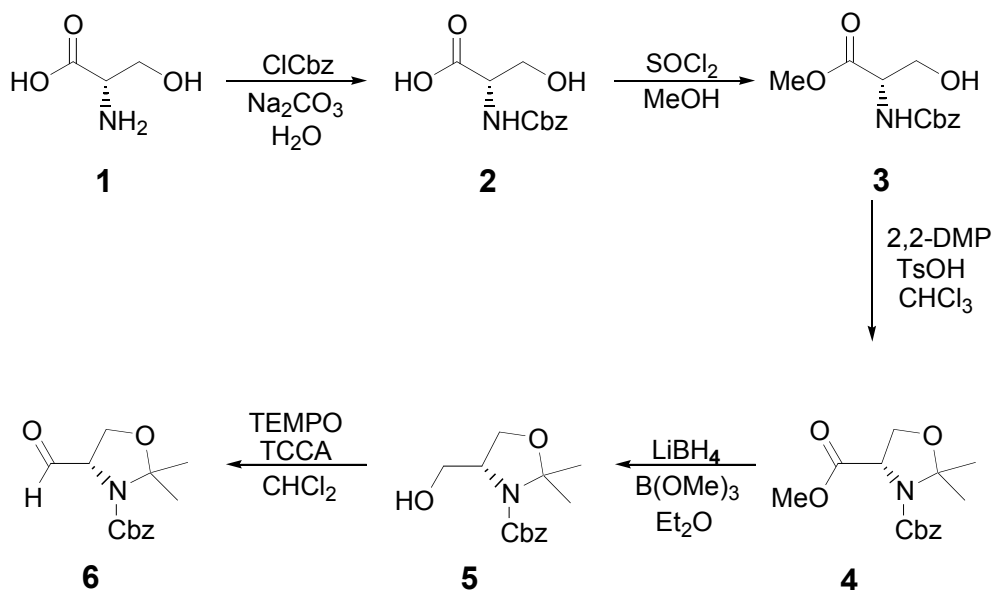
Figure 1. Combination of ddN and iso-ddN, to produce DHNRRBB with similar structure.

Synthesis of the double headed nucleoside will take many years of research, and so the goal of this procedure was to create a key carbohydrate intermediate, as depicted in the retrosynthesis **Scheme 1**, to the double headed nucleoside. This molecule would only need slight modifications to obtain the desired DHN. A similar carbohydrate using different protecting groups has been prepared by Smreina⁹; however, the carbohydrate in that preparation was not intended for an intermediate to the DHN, but was transformed through decarboxylation toward specific amino acids.

DISCUSSION

The procedure used to create the Garner's aldehyde, **6**, is shown in **Scheme 2**. This procedure⁵ was used for preparation of the aldehyde due to the expense of purchasing this molecule.

Scheme 2. Synthesis of Garner's aldehyde, 6.



The first step of the process, which was to protect the nitrogen with a Cbz protecting group to create **2**, was easily accomplished. The reaction took place in water, which is a convenient and inexpensive solvent to use. The product was filtered from the water and extracted into ethyl acetate; chromatography was unnecessary. The product formed large white solid particles in yields of up to 90%.

Producing the methyl ester **3** proved to be another problem free reaction. The most difficult part of this reaction was keeping the reaction in an inert environment, but this was accomplished using argon. The product was purified by extraction to remove the inorganic SO₂ and HCl. This reaction had a yield of 70%.

The production of the oxazolidine **4** was slow, requiring five hours of reflux to collect the desired product. When the solution turned a dark red color, the desired product had been produced. Methanol-chloroform azeotropes were slowly removed from the solution at 53-60 °C to drive the reaction using Le Chatlier's principle. The crude product was purified by vacuum distillation (0.96-1.00 torr at 158-159 °C) to a thick golden liquid in 74.4% yields.

Reduction of the ester was another fairly easy process. This reaction requires care in the handling of the lithium borohydride because lithium borohydride absorbs water from the atmosphere and becomes flammable in the process, so the reagents were added quickly to the reaction vessel to minimize adsorption. Purification was accomplished through aqueous washing, and the reaction yielded nearly 100%.

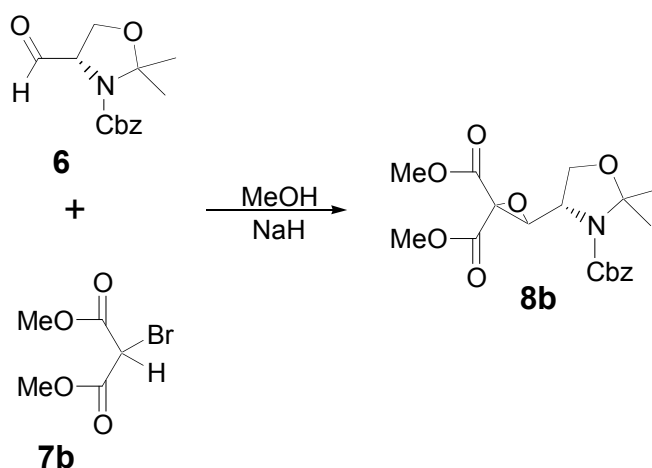
Several problems occurred while preparing the Garner's aldehyde. It is believed that during initial trials, the alcohol may have been overoxidized to the carboxylic acid form. This is due to evidence in the literature² that most of the oxidations with this type of molecule react quickly, usually taking only about twenty minutes. Initially, the reaction was allowed to react for several hours and, in these attempts, very little to no aldehyde was detected.

Another problem encountered resulted from the molecule not being stable in its oxidative environment. Much greater success was experienced when the molecule was stored in the refrigerator. During column chromatography the aldehyde would perform a Cannizzaro redox reaction with itself, so that every time purification was attempted, the molecule would be gone by the time the purification was completed. In literature preparations of this molecule, HPLC was used so that the Cannizzaro reaction is

minimized, and directly used to minimize the degradation. Cold temperature storage of the molecule slows down the rate at which the Cannizzaro reaction takes place. It was found that by using the procedure with multiple aqueous washes the compound was pure enough to proceed to the next step. Although the yield on this reaction was inconsistent, this reaction did produce the desired aldehyde, which is verified by NMR data found in Figure 4 of the Appendix. Under cold conditions with short reaction times, it yielded as high as 87%. Further investigation is needed to determine whether the remaining reactions of the scheme are successful in creating the double headed nucleoside. The resources available were not sufficient to determine whether or not this procedure could work.

After obtaining the aldehyde, the next step of the procedure was to perform an aldol condensation between **6** and another starting material dimethylbromomalonate, **7b**. This condensation is shown in **Scheme 3**.

Scheme 3. Attempted condensation between Garner's aldehyde and the malonate.

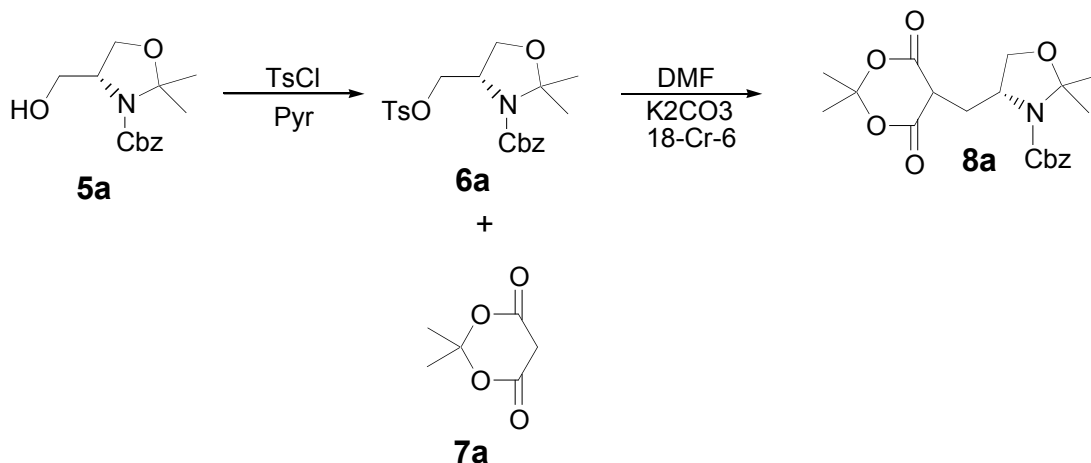


The aldol reaction, which would create **8b**, was difficult because the sodium hydride was highly sensitive, and as a result, it had to be kept completely dry. The main problem involved in this reaction was achieving the desired -78°C necessary to prevent

the malonate from reacting with itself. In addition, the aldehyde had undergone the Cannizzaro reaction, so that only its alcohol and acid were present. The malonate will not react with either of these functional groups, so in the presence of the strong base, it reacted with itself. After each purification, either starting material or polymer was found.

An alternate method (**Scheme 4**) of creating the key carbohydrate was tested in addition to the aldol pathway. This method used a tosylated form of the aldehyde, **5a**, and combined it with the structure of Meldrum's acid, **7a**, to yield a reduced form of the epoxide, **8a**.

Scheme 4. Attempted nucleophilic substitution of Meldrum's acid with the tosylate.



The tosylate molecule, **6a**, was readily produced, yielding 83%; however, the subsequent reaction to yield **8a** proved unsuccessful. The tosylate was purified by aqueous wash, and combined with Meldrum's acid to attempt a Knoevenagel reaction. This reaction was tested using microwaves to catalyze the reaction. Previous research by Bogdal demonstrated hope for this procedure using the microwave¹, but did not produce the desired compound. Based on success of the Knoevenagel reaction, this approach to creating the double headed nucleoside is not likely to be successful.

EXPERIMENTAL

(S)-2-benzyloxycarbonylamino-3-hydroxypropanoic acid (2). L-Serine (**1**) (2.50g, 19.5mmol) was dissolved in 20mL water and cooled in an ice bath as sodium bicarbonate (3.43g, 40.8mmol) was added over 15 minutes. The cool solution was treated with benzylchloroformate (CbzCl; 3mL, 21mmol) and stirred until CO₂ evolution stopped. The aqueous solution was washed with ether (4 x 20mL) and acidified (pH=2) with concentrated hydrochloric acid in an ice bath. The milky-white solution was filtered to collect pure product. The aqueous layer was extracted with ethyl acetate, dried over MgSO₄, filtered and concentrated to collect additional product (3.83 g total, 90% yield) as a white solid. ¹H NMR (DMSO) δ 7.3 (s, 5H), 5.1 (s, 2H), 4.1 (m, 1H), 3.8 (d, 2H).

Methyl-(3)-2-benzyloxycarbonylamino-3-hydroxypropanoate (3). A dry 500 mL round bottom flask was treated with N-Cbz-L-Serine (**2**) (10.032 g, 41.935 mmol) and methanol (200.00 mL, 5591.1 mmol). Thionyl chloride (3.0 mL, 41.128 mmol) was added dropwise under argon and in an ice bath. The solution was stirred overnight at room temperature.

The solution was evaporated and diluted with dichloromethane. The solution was then washed with water and sodium carbonate and brought to pH of 7 using sodium carbonate. The solution was dried over sodium sulfate and concentrated. ¹H NMR data showed a very clean desired product. This reaction yielded 7.539 g, for a 70% yield.

¹H NMR (CDCl₃) δ 7.4 (s, 5H), 5.8 (d, 1H), 5.2 (d, 4H), 4.4 (m, 1H), 3.9 (m, 5H), 2.3 (s, 1H).

(4S)-3-benzyl-2,2,4-trimethyl-3,4-oxazolidine dicarboxylate (4). A solution of methyl-(3)-2-benzyloxycarbonylamino-3-hydroxypropanoate **(3)** (7.539 g, 31.514 mmol) in chloroform (23.0 mL, 288.993 mmol) was treated with 2,2-DMP (5.0 mL, 40.663 mmol) and TsOH (0.320 g, 1.682 mmol) in a dry 500 mL round bottom flask. The solution was heated to reflux for five hours. The solution was changing into desired color so 100.0 mL of chloroform were added.

The solution was distilled to remove methanol-chloroform azeotropes (53-60°C). During distillation, the solution began turning a dark red color, which showed the production of the desired product. The product was then diluted into dichloromethane and washed with 20.0 mL of a saturated sodium hydrogen carbonate solution. The solution was then dried and evaporated. Both H^1 and C^{13} NMR data showed desired product with a yield of 74.7 %. DEPT and HETCOR experiments were also performed to further characterize the product. NMR data is shown in Figures 2 and 3 found in the Appendix.

1H NMR ($CDCl_3$) δ 7.3 (s, 5H), 5.1 (t, 2H), 4.5 (m, 1H), 4.05 (m, 2H), 3.7 (d, 3H), 1.6 (m, 6H).

^{13}C NMR ($CDCl_3$) δ 136.35, 127.97, 95.36, 77.16, 68.70, 59.54, 52.29, 25.14.

(4R)-3-benzyl-2,2-dimethyl-4-hydroxymethyl-3-oxazolidinecarboxylate (5). A dry 250 mL round bottom flask was treated with (4S)-3-benzyl-2,2,4-trimethyl-3,4-oxazolidine dicarboxylate **(4)** (10.014 g, 34.14 mmol), trimethyl borate (0.35 mL, 3.08 mmol), and ether (130.0 mL, 1241.77 mmol). The flask was filled with nitrogen gas, and then lithium borohydride (0.828 g, 38.02 mmol) was added to the stirring solution. The solution formed a sticky yellow solid on the surface of the glass.

After stirring overnight, 3 equivalents of methanol were added slowly throughout eight hours. The solution was then diluted in 50.0 mL ether and 50.0 mL of methanol, evaporated, and diluted in dichloromethane. Concentrated hydrochloric acid was added to bring the solution to pH 6-7. The solution was then washed with 75.0 mL of water, and the water extract was washed with dichloromethane (3 x 25 mL). The solution was then dried over sodium sulfate and concentrated. ^1H data NMR verified desired product. 11.603 g of product were collected for over 100% yield; however, this product contained solvent. The yield was very high.

^1H NMR (CDCl_3) δ 7.3 (s, 5H), 5.2 (d, 3H), 4.0 (m, 3H), 3.7 (m, 2H), 1.5 (d, 6H).

^{13}C NMR (CDCl_3) δ 127.24, 93.06, 75.83, 64.08, 58.30, 23.42.

(4S)-3-benzyl-4-formyl-2,2-dimethyl-3-oxazolidine carboxylate (6).

Method A. A dry 25 mL round bottom flask was treated with (4R)-3-benzyl-2,2-dimethyl-4-hydroxymethyl-3-oxazolidinecarboxylate (**5**) (1.009 g, 3.861 mmol), pyridium chlorochromate (1.237 g, 5.738 mmol), and dichloromethane (5.0 mL, 70.44 mmol). The solution was stirred at room temperature overnight and turned a dark brown color. After 48 hours, the solution was diluted in ether, and filtered to remove solids. The solution was concentrated and stored in the refrigerator.

^1H NMR showed that product was very impure and not the desired product.

Method B. A solution of (4R)-3-benzyl-2,2-dimethyl-4-hydroxymethyl-3-oxazolidinecarboxylate (**5**) (0.164 g, 0.632 mmol) in dichloromethane (1.0 mL) was cooled to 0°C using an ice bath in a small dry test tube. TCCA (0.100 g, 0.430 mmol) and TEMPO (0.004 g, 0.026 mmol) were added to the cooled solution. The solution was brought to room temperature and allowed to react for

two hours. The reaction was diluted into dichloromethane and was washed with 5.0 mL of sodium hydrogen carbonate, 5.0 mL of HCl, and 5.0 mL of brine. The solution was dried and prepared for NMR.

This reaction was unsuccessful; only a very small amount of aldehyde was detected but not isolated.

Method C. A dry 250 mL round bottom flask was treated with (4R)-3-benzyl-2,2-dimethyl-4-hydroxymethyl-3-oxazolidinecarboxylate (**5**) (2.014g, 7.767 mmol), TCCA (2.002g, 8.614 mmol), TEMPO (0.125g, 0.800 mmol), and dichloromethane (35 mL). The solution was stirred for thirty minutes, and imidazole (0.797g, 11.707 mmol) was added with additional dichloromethane (25 mL). Upon addition of the imidazole, the solution became a thick, milky orange color. TLC showed a new spot, so the product was purified by column chromatography. The desired product was not isolated. $^1\text{H NMR}$ (CDCl_3) δ 7.4 (s, 4H), 4.3 (m, 4H), 2.5 (m, 2H), 1.1(m, 3H).

Method D. A dry 50 mL round bottom flask equipped with a stir bar was treated with (4R)-3-benzyl-2,2-dimethyl-4-hydroxymethyl-3-oxazolidinecarboxylate (**5**) (2.001 g, 7.713 mmol) and dichloromethane (20 mL, 304.773 mmol). The solution was stirred and cooled to 0°C in an ice bath for 7 minutes. The solution was then treated with TCCA (1.791 g, 7.706 mmol) and stirred for 5 minutes. TEMPO (0.077 g, 0.493 mmol) was added the solution, and the solution was removed from the ice bath. The solution was stirred at room temperature for a couple of hours.

The solution was then filtered on 20-25 mL of Celite using dichloromethane to wash the product through the filter. The solution was then washed with 15-20 mL of Na₂CO₃, HCl and NaCl. The solution was then dried with sodium sulfate and concentrated *in vacuo*. The product was not completely pure, and so the it was purified by column chromatography. Three products were isolated and one product was the desired aldehyde: ¹H NMR (CDCl₃) δ 9.56 (s, 1H), 7.33 (s, 5H), 5.14 (s, 2H), 4.14 (m, 3H), 1.58 (s, 6H). ¹³C NMR (CDCl₃) δ 198.39, 151.53, 135.55, 128.02, 95.07, 66.70, 25.26.

Method E. A dry 100 mL round bottom flask equipped with a stir bar and ice bath was treated with (4R)-3-benzyl-2,2-dimethyl-4-hydroxymethyl-3-oxazolidinecarboxylate (**5**) (1.991 g, 7.619 mmol) and dichloromethane (20.00 mL, 304.773 mmol). The solution was stirred and cooled for 7 minutes. The solution was then treated with TCCA (1.772 g, 7.624 mmol) and stirred for 5 minutes. TEMPO (0.079 g, 0.506 mmol) was added the solution, and the solution was removed from the ice bath. The solution was stirred at room temperature for about 45 minutes.

The solution was then filtered on 20-25 mL of Celite using dichloromethane to wash the product through the filter. The solution was then washed with 15-20 mL of Na₂CO₃, HCl and NaCl. The solution was then dried with sodium sulfate and concentrated in vacuo. The product was not completely pure, but gave an excellent yield of 87%. The desired product was confirmed by ¹H NMR.

¹H NMR δ 9.6 (s, 1H), 7.3 (s, 5H), 5.2 (s, 2H), 4.1 (m, 3H), 2.9 (d, 1H), 1.6 (m, 6H).

3-benzyl-4-p-toluenesulfonyloxymethyl-(S)-2,2-dimethyl-3-oxazolidine carboxylate (6a). A dry 25 mL round bottom flask was treated with 3-benzyl-4-hydroxy-(R)-2,2-dimethyl-3-oxazolidine carboxylate (2.004 g, 7.669 mmol) and dichloromethane (10.0 mL). The solution was cooled to 0°C. Pyridine (1.2 mL, 14.842 mmol) and tosyl chloride (2.179 g, 11.429 mmol) were added to the cooled solution. The solution was warmed to room temperature and stirred overnight.

The solution was diluted in diethyl ether and washed with saturated sodium carbonate several times until the aqueous layer became basic. TLC showed that pyridine was still present in the solution so it was washed again with HCl (2 x 50 mL). The solution was dried over sodium sulfate and concentrated. ^1H NMR data showed the desired product with a small amount of ether still present. This reaction yielded 2.644g for nearly 100% yield.

^1H NMR (CDCl_3) δ 7.5 (s, 9H), 5.1 (m, 2H), 4.0 (m, 4H), 3.5 (t, 1H), 2.4 (d, 3H), 1.5 (s, 6), 1.2 (t, 1H).

^{13}C NMR (CDCl_3) δ 144.87, 135.88, 128.43, 94.42, 76.96, 66.76, 55.07, 26.30, 15.09.

(R) -5-[(3-benzyl-2,2-dimethyl-3-oxazolidenecarboxylate)-4-methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (8a) . A dry 5.0 mL round bottom flask was treated with the tosylate (6) (0.199g, 0.479 mmol), Meldrum's acid (0.089g, 0.617 mmol), K_2CO_3 (0.086g, 0.622 mmol), 18-Crown-6 (0.015g, 0.057 mmol), and DMF (3.0 mL). The solution was stirred overnight at room temperature.

The solution had turned a cloudy orange color overnight and was diluted in dichloromethane. The solution was washed with 1N hydrochloric acid (15.0 mL), dried over sodium sulfate and concentrated. A TLC showed that some starting material was

still present, so the solution was transferred into a 10 mL round bottom flask, a half equivalent of the base (0.032g) was added, and the solution was pulsed in the microwave at 10% power for 10 seconds. This heated the DMF drastically, so it was then heated at 10% power for 5 seconds for three rounds, with cooling time between each pulse. TLC showed no change in material, so another equivalent of Meldrum's acid (0.073g) was added. After switching TLC solvents from dichloromethane to ethyl acetate and hexanes, the reaction seemed almost complete. Another half equivalent of Meldrum's acid (0.044 g) and one equivalent of base (0.078g) were added to the solution and pulsed for 6 x 5 seconds in the microwave.

The solution was purified by plate chromatography and all three layers showed none of the desired product. Fraction 1 (0.036 g) showed to be the tosylate by ^1H NMR. ^1H NMR (CDCl_3) δ 7.4 (s, 7H), 5.1 (s, 2H), 4.0 (m, 4H), 2.4 (d, 2H), 1.5 (s, 6).

Fraction 2 showed to be Meldrum's acid, and Fraction 3 was mostly ethyl acetate and some other impurities. ^1H NMR (CDCl_3) δ 7.3 (s, 1H), 4.1 (m, 2H), 3.0 (d, 3), 1.5 (m, 12).

(R) -5-[(3-benzyl-2,2-dimethyl-3oxazolidenecarboxylate)-4-methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (8a). A dry test tube was treated with Meldrum's acid (0.100g, 0.241 mmol) and DMF (2.0 mL, 45.21 mmol). The solution was stirred and cooled to -78°C using a dry ice/acetone bath. Lithium hydride (0.0025g, 0.314 mmol) and more DMF (1.5 mL) were then added. The tosylate was then added and the solution was removed from the dry ice bath. The reaction was stirred overnight.

The product was purified by TLC and the product again showed to be starting material by ^1H NMR.

(R) -5-[(3-benzyl-2,2-dimethyl-3-oxazolidenecarboxylate)-4-methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (8a). A dry test tube was treated with (6) (0.048g, 0.185 mmol), Meldrum's Acid (0.029 g, 0.201 mmol), pyridine (0.016 g, 0.202 mmol), and deuterated chloroform (3 mL). The solution was stirred at room temperature for 30 minutes and monitored by NMR to determine reaction completion.

The solution was then microwaved for 4x5 seconds at 10% power in an ice bath. No change was observed so heating was continued for 8 seconds at 50%, 3 seconds at 100% followed by 2x5 second at 100%. No reaction had taken place, so a catalytic amount of pyridine (3 drops) was added. The solution was heated for 3x5 at 100%, and then 4x3 seconds at 100% without ice bath. The solution was allowed to react over the weekend at room temperature.

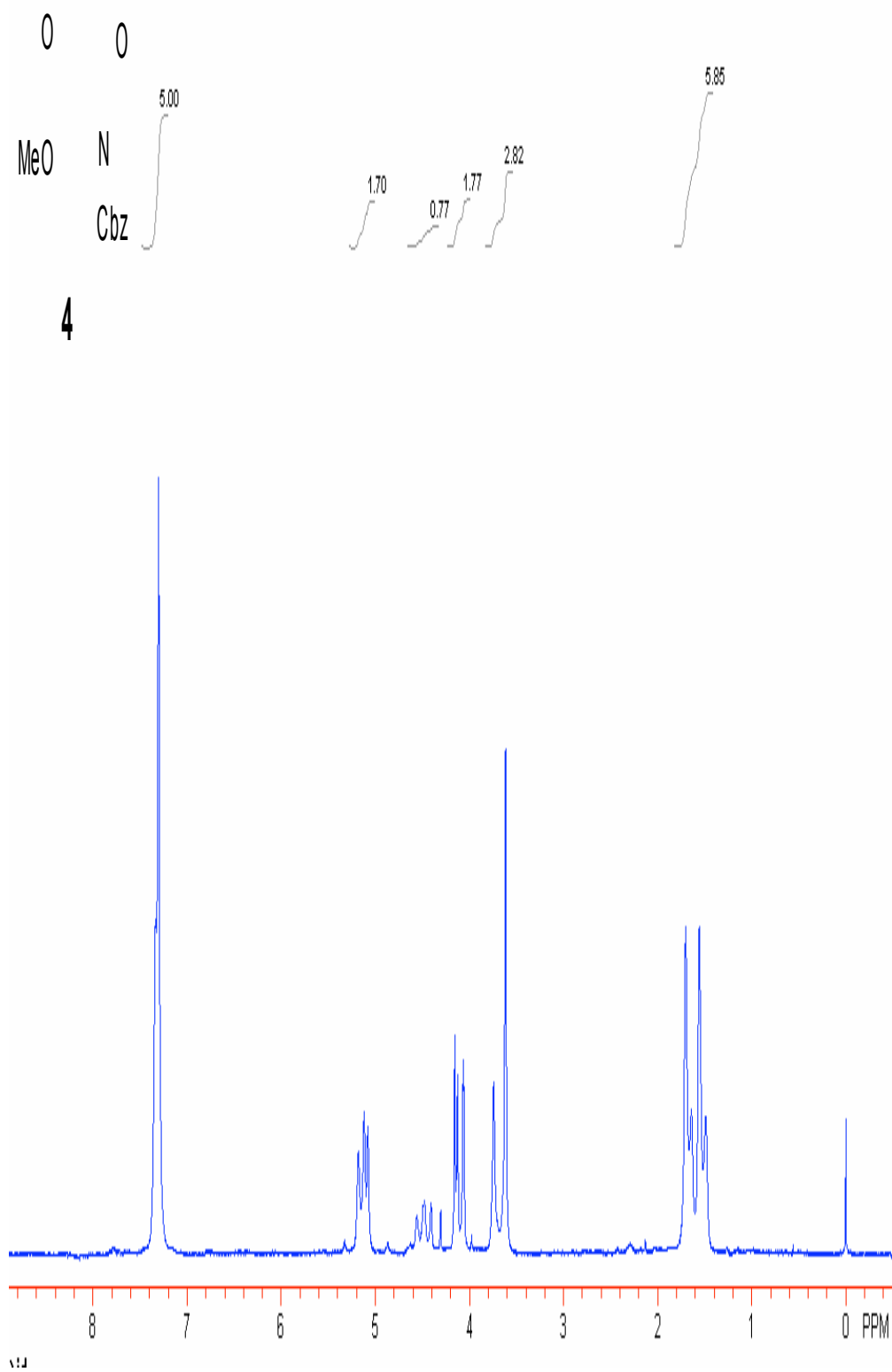
¹H NMR showed no desired product.

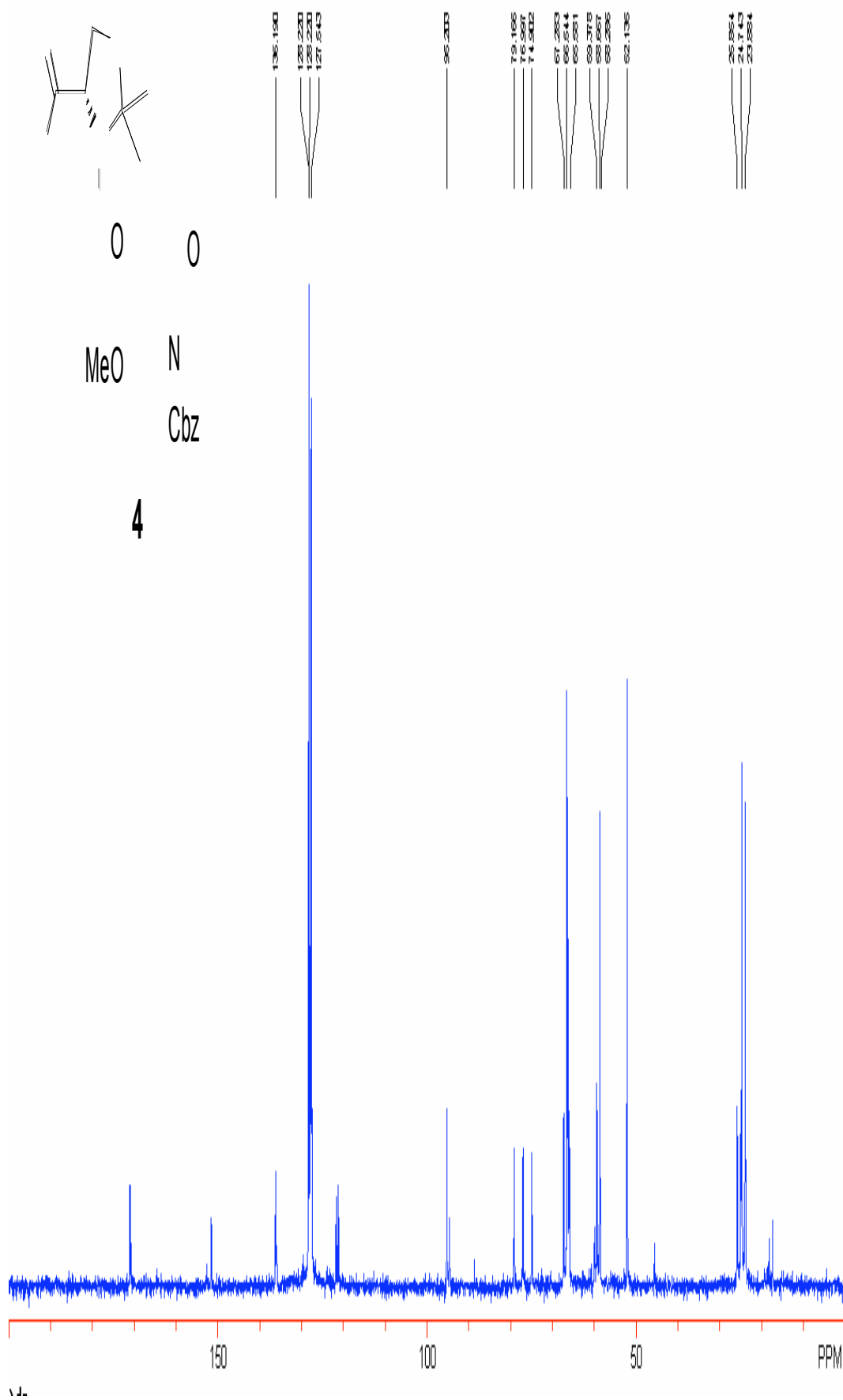
3-benzyl-(4S)-4-(dimethoxy-2,2-dicarbonylepoxy)-2,2-dimethyl-3-oxazolidinecarboxylate (8b). A small dry test tube was treated with 60 % wt NaH (0.10 g, 2.55 mmol) and DMF (7.0 mL). The solution was stirred for 20 minutes. Another small dry test tube was treated with the 90 % wt dimethyl-bromo-malonate (0.564 g, 2.105 mmol) and 3-benzyl-4-formal-(S)-2,2 dimethyl-3-oxazolidine carboxylate (6) (0.524 g, 2.021 mmol) with a small amount of DMF. The malonate solution was stirred for a few minutes and then transferred into a large test with the sodium hydride solution. The solution was stirred overnight at room temperature.

Characterization by H¹ NMR revealed presence of malonate polymer.

¹H δ 7.3 (m, 2H), 5.1 (s, 1H) 3.9 (m, 41H), 3.4 (s, 2H), 1.6 (m, 6H).

APPENDIX
SELECTED NMR SPECTRA

Figure 2. ^1H NMR of 4 in CDCl_3

Figure 3. ^{13}C NMR of 4 in CDCl_3

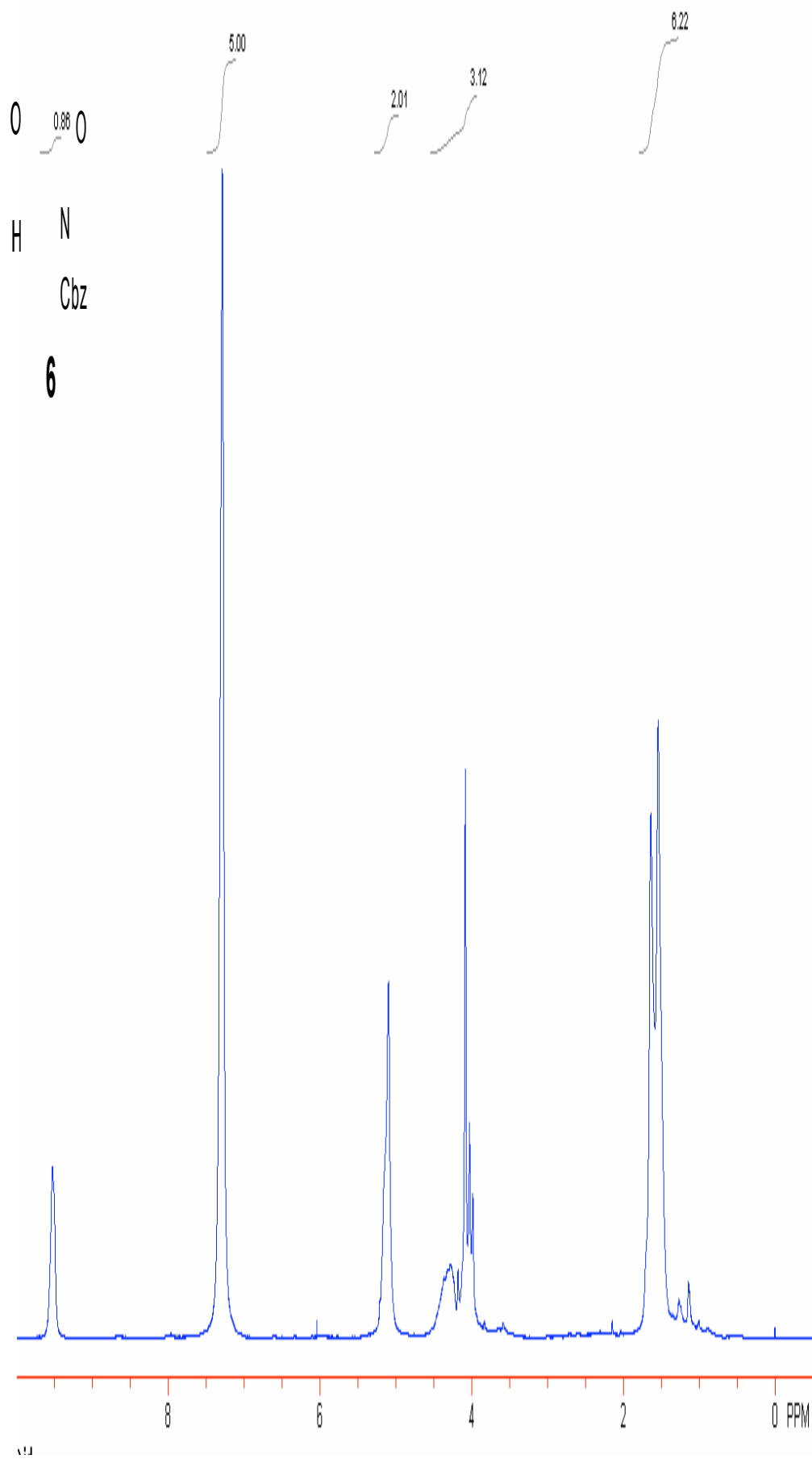


Figure 4. ¹H NMR of 6 in CDCl₃

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Curriculum Vitae

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