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University of Nevada, Reno

Macrocyclic Polyamines and Their Metal Complexes Targeting HIV-1

A thesis submitted in partial fulfillment
of the requirements for the degree of

BACHELOR OF SCIENCE IN CHEMISTRY, PROFESSIONAL CHEMISTRY

by

ALEXANDRA RENE PEARCE

Thomas W. Bell, Ph.D., Thesis Advisor

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Synthesis of Macrocyclic Polyamines and Their Metal Complexes Targeting HIV-1

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M40401 is a well known antioxidant and as of late, it has been studied for anti-HIV properties. It was reported to reduce apoptosis of astrocytes caused by HIV-1 infected macrophages (M/M) supernatants, and in 2005, a poster presented at the International Conference for Antiviral Research claimed that HIV-1 replication was reduced in infected M/M when treated with M40401. Our goal is to synthesize M40403, a similar molecule, as well as other related molecules for further study. M40403 and previously synthesized related molecules have been shown to have anti-HIV properties. We will synthesize more related molecules in an attempt to maximize the ratio of potency to toxicity. Hopefully by tweaking the molecules, we will find one that can eventually be made into a drug to help the fight against HIV-1.

Introduction

Heterocycles (derived from *hetero* meaning "other or different" and *cycle* meaning "cyclic molecule") are a large division of organic chemistry defined by their ring-like structure that is composed of at least two different atoms. Heterocycles are known to be very important in biological and industrial applications. For example, penicillin, caffeine, nucleic acids, and many types of vitamins are all molecules that contain heterocycles.⁽¹⁾ (See Figure 1)

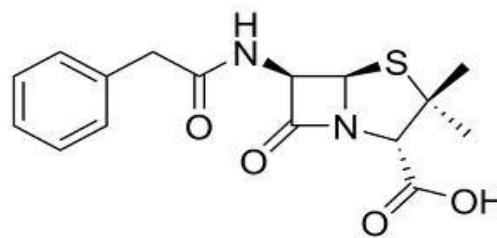


Figure 1: Penicillin

Macrocyclic polyamines are a specific division of heterocycles that are made up of large cyclic molecules containing more than one amine group. An amine is a functional group in organic chemistry consisting of a nitrogen atom bonded to three other atoms (usually

hydrogen or carbon). (See Figure 2) When an amine group is within a ring, it is bonded to two atoms, leaving one site free to bond to an atom outside the ring. Such an amine is referred to as a secondary amine. The availability of this secondary amine within the ring allows for other atoms, chains, or molecules to attach to the ring. This allows macrocyclic polyamines to be designed for specific functions depending on what is attached to the amine group.⁽²⁾

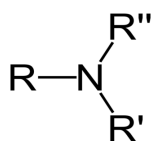


Figure 2: Amine group

Recently, interest in macrocyclic polyamines has grown tremendously, particularly in the medical field. These structures have been studied for a variety of uses including magnetic resonance imaging (MRI) agents and for their anti-tumor activity. The focus of this study is their anti-HIV properties.⁽²⁾

HIV (human immunodeficiency virus) is the cause of AIDS (acquired immunodeficiency syndrome), the transmissible disease of the immune system. HIV targets a special class of white blood cell called helper T cells, and in doing so, weakens the immune system leaving the host vulnerable to infections and diseases. These secondary infections are what actually cause fatalities for those infected with HIV.⁽³⁾

HIV is classified as a retrovirus, meaning that it is made up of RNA instead of DNA, and therefore, requires a host cell

in order to replicate. HIV enters the helper T cells via the CD4 receptor, a molecule on the cell's surface. A protein embedded in the membrane of the virus, called gp120, binds with the CD4 receptor. HIV also requires the participation of two other molecules, CCR5 and CXCR4, which are referred to as co-receptors. They work together with the CD4 receptor to allow the virus to gain entry into the cell and infect it with its genetic material.⁽³⁾ (See Figure 3)

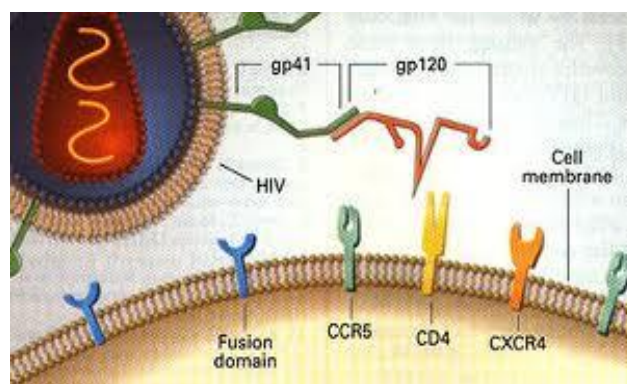


Figure 3: Depiction of HIV entering cell via receptor (CD4) and co-receptors (CCR5 and CXCR4)⁽⁴⁾

Once the virus has infected the cell, it converts its RNA into DNA which is then integrated into the DNA of the T cell. At this point, the cell is used to create copies of the virus's RNA which is sent out of the cell as new viruses ready to infect more T cells.⁽³⁾

Most anti-HIV drugs aim to inhibit the conversion of its RNA to DNA or they target it before it replicates. These methods, however, do not help the cells that have already been infected; they can only try and prevent the disease from spreading to more cells. Once a cell is infected with HIV, there is no hope of curing it, and it dies. The

ideal anti-HIV drug would, therefore, be one that stops the virus before it enters the cell. Some types of macrocyclic polyamines have been studied for this purpose and were found to be successful. Cyclams, cyclens, and multilayered macrocyclic polyamines are examples of the successful types.⁽²⁾ (See Figure 4)

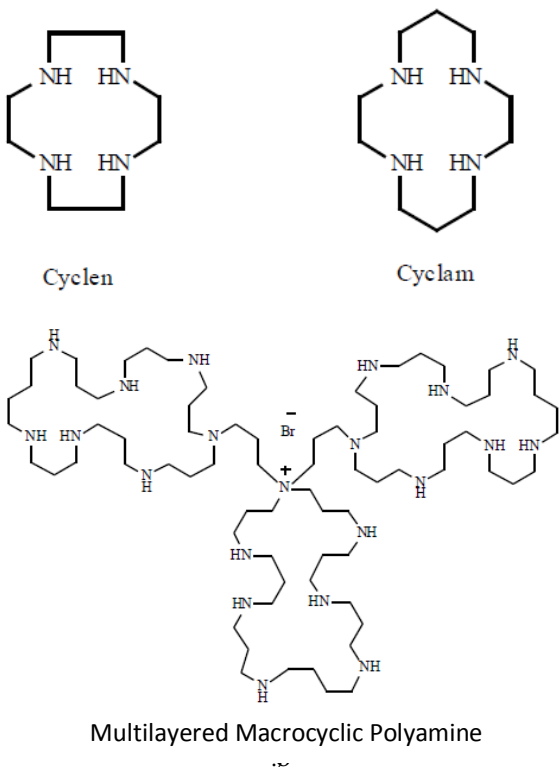


Figure 4: Example structures of cyclens, cyclams, and multi-layered macrocyclic polyamines⁽²⁾

M40401, a specific macrocyclic polyamine, is a known antioxidant. Evidence existed in the medical world that those infected with HIV-1 were constantly under excessive oxidative stress, which eventually leads to apoptosis (cell death). Studies done on astrocytes (star-shaped cells found in the brain) infected with HIV-1 showed that if the astrocytes were pretreated

with M40401, apoptosis was greatly reduced. This led to interest in M40401 and related compounds being used for their anti-HIV properties.⁽⁵⁾ (See Figure 5)

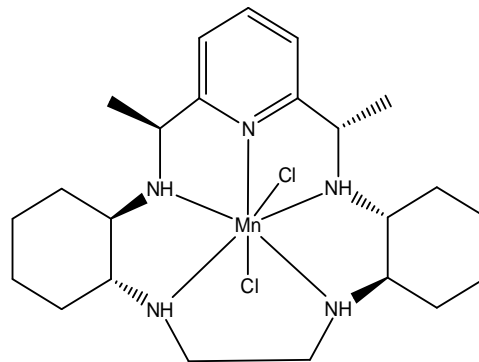


Figure 5: M40401

Sunil Hamal, a graduate student at the University of Nevada, Reno, has done a significant amount of work on a project to synthesize metal complexes of macrocyclic polyamines similar to M40401 to be sent away for testing against HIV. Two compounds in particular (SH04 and SH06) have proven very promising. It is believed they inhibit the entry of HIV-1 into cells by binding to one or both of the co-receptors (CCR5 and CXCR4).^{(6),(7)} (See Figure 6)

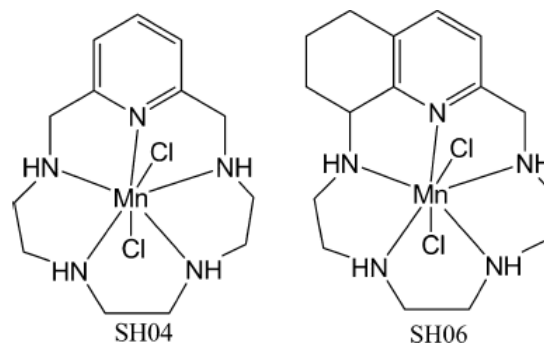


Figure 6: SH04 and SH06

This study will focus on synthesizing and testing M40403, a molecule very similar to M40401, and then proposing other similar

molecules to synthesize and test for their anti-HIV activity. (See Figure 7)

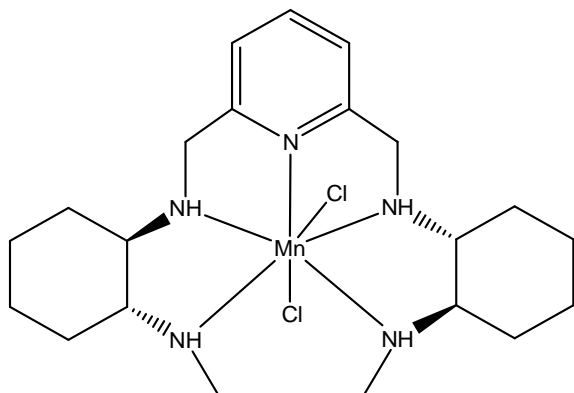


Figure 7: M40403

Methods

Retrosynthesis:

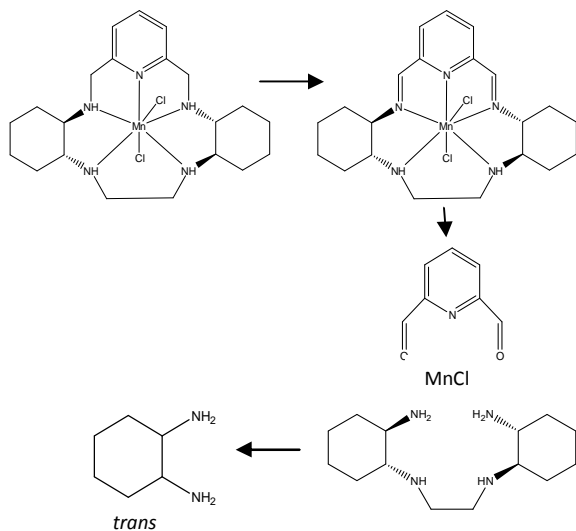


Diagram 1: Retrosynthesis of M40403

M40403 can be obtained from the reduction of the Schiff base, which is obtained from the metal-templated

condensation of the head group (prepared by Sunil Hamal), ϕ -Bis[(1R,2R)-(2-amino)cyclohexyl]-1,2-diaminoethane tetrachloride, and manganese chloride. ϕ -Bis[(1R,2R)-(2-amino)cyclohexyl]-1,2-diaminoethane tetrachloride is synthesized from 1,2-diaminocyclohexane. (See Diagram 1).

Synthesis:

Starting with a racemic mixture of *trans*-1,2-diaminocyclohexane, resolve with tartaric acid to yield (1R,2R)-1,2-diaminocyclohexane L-(+)-tartarate. Then react that with KOH and dry with sodium metal. Collect the newly formed (1R,2R)-1,2-diaminocyclohexane under nitrogen. Then mix the free amine with trityl chloride to yield *trans*-(triphenylmethyl)-(1R,2R)-1,2-diaminocyclohexane. Then mix with 40% (W/W) aqueous glyoxal, MeOH, and water to yield glyoxal bisimine of *trans*-(triphenylmethyl)-(1R,2R)-1,2-diaminocyclohexane. Reduce the product with LiBH_4 -THF to yield *trans*-(triphenylmethylamino)cyclohexyl]-1,2-diaminoethane. (See Diagram 2) Remove the trityl groups by adding acetone and HCl to yield *trans*-(2-amino)cyclohexyl]-1,2-diaminoethane tetrachloride. Perform metal-templated condensation with MnCl_2 and the head group synthesized by Sunil Hamal to yield the Schiff base. Then reduce the product to obtain the completed M40403.^{(8),(9),(10)} (See Diagram 2)

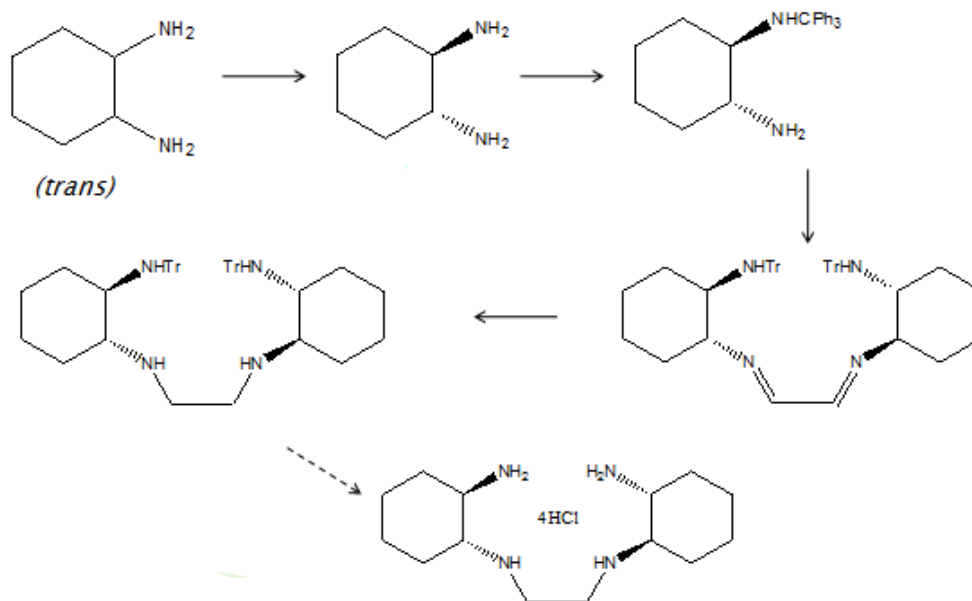


Diagram 2: Synthesis of *N, N'*-Bis[(1*R*,2*R*)-(2-amino)cyclohexyl]-1,2-diaminoethane tetrachloride

Experimental

Resolution of trans-1,2-diaminocyclohexane: Synthesis of (1*R*,2*R*)-1,2-diaminocyclohexane L-(+)-tartarate

A solution of 48 mL (400 mmol) of trans-1,2-diaminocyclohexane, 80 mL of water, and 640 mL of methanol (reagent grade) was stirred in a 2 L round bottom flask. While still stirring, 60 mL (520 mmol) glacial acetic acid was added dropwise using an addition funnel. A solution of 30.262 g (200 mmol) in 120 mL of methanol was added dropwise over a period of 2 ½ hours to the stirred solution. Then the resulting cloudy reaction mixture was refluxed for 24 hours. The solution was taken off heat and let cool overnight. The product was collected by filtration in a büchner funnel set up with a 2 L filter flask connected to a water aspirator. The product was rinsed three times with 75 mL of

methanol. The product was dried via water aspirator for 45 minutes and then transferred to a tared beaker to dry in an oven at 80• C for 24 hours. The product was placed in a tared brown product bottle and weighed in at 50.95 g (192.8 mmol).

Resolution of trans-1,2-diaminocyclohexane: Synthesis of (1*S*,2*S*)-1,2-diaminocyclohexane dihydrochloride

The filtrate from the resolution of trans-1,2-diaminocyclohexane the synthesis of (1*R*, 2*R*)-1,2-diamino-cyclohexane L-(+)-tartarate was transferred to a three-necked 5 L round bottom flask. 40 mL (0.5 mol) of concentrated hydrochloric acid was added in one portion to the filtrate while it was stirred. The solution was heated to reflux and 200 mL of reagent grade acetone was added dropwise from an addition funnel through the top of the condenser to the

refluxing mixture. The solution was refluxed for 28 hours allowing ample time for the acetone to add and mix in completely. The solution was allowed to cool to room temperature, and then concentrated to a volume of 150-200 mL by rotary evaporation. 1.5 L of reagent grade acetone was added to the newly concentrated solution while stirring, and grainy, tan precipitates formed instantly. The solution was stirred for 30 minutes and then refluxed for 14 hours. The reaction mixture was allowed to cool to room temperature and filtered through a büchner funnel set up to a 2 L filter flask connected to a water aspirator. The product was washed five times with 30 mL of acetone and allowed to air dry at room temperature for two days. The product was then transferred to a tared brown bottle and weighed in at 32.83 g (175.5 mmol).

Synthesis of (1R,2R)-1,2-diaminocyclohexane

14 mL of 25M aqueous potassium hydroxide was prepared by dissolving 19.94 g of potassium hydroxide in 14 mL of water. 22.96 g (86.9 mmol) of (1R,2R)-1,2-diaminocyclohexane L-(+)-tartarate was swirled with the 14 mL of 25M aqueous potassium hydroxide in a 125 mL separatory funnel. Two layers immediately formed; a dark organic layer on top and a clear aqueous layer with white precipitates on the bottom. The top layer was drawn off (approximately 20 mL in volume) using a pipette and was transferred to a 250 mL round bottom flask. 50 mL of diethyl ether (reagent grade) was added to the round

bottom flask. To dry the solution, small pieces of sodium metal (about $\frac{1}{4}$ cm³ in volume) were added 1-3 at a time, allowing time in between for the previously added pieces to fully react. When about thirty pieces of sodium metal had been added, the solution was no longer reacting much with the metal, indicating it was nearly dry. Ten extra pieces were added, and the flask was capped with a rubber septum, connected to a bubbler, and left overnight. Then the solution was transferred by cannula via nitrogen pressure to a 250 mL round bottom flask that was flushed with nitrogen and contained thirteen small pieces of sodium metal. The solution, which was a dark red color, was let stand overnight to ensure complete dryness. The solution was then transferred by cannula via nitrogen pressure to another 250 mL round bottom flask that had been flushed with nitrogen and contained some activated charcoal. The flask was allowed to stand for two hours being swirled occasionally. The solution was then transferred by cannula via nitrogen pressure to a Dannley pressure fritted funnel fitted with filter flask. The solution was filtered through celite in the Dannley funnel with nitrogen pressure. The solution was then transferred by cannula via nitrogen pressure into a 250 mL round bottom flask that was flushed with nitrogen. The solution was concentrated using a vacuum pump to a volume of approximately 15 mL, at which point the solution crystallized. After warming the crystals to room temperature in a water bath, they were dissolved. The solution was transferred by cannula via nitrogen pressure to a Dannley pressure fritted funnel that was sealed off with septa,

Teflon tape, and parafilm. It was placed in the freezer at -10• C for 72 hours. Peach-colored needle-shaped crystals formed and the filtrate was removed from the funnel using nitrogen pressure. The crystals were collected in a tared brown bottle flushed with nitrogen. The crystals weighed 3.00 g (26.3 mmol) and they were stored in the bottle inside a dessicator.

Synthesis of -(Triphenylmethyl)-(1R,2R)-1,2-diaminocyclohexane

A solution of 1.38 g (4.95 mmol) of trityl chloride in 10 mL of anhydrous dichloromethane (previously distilled over anhydrous calcium chloride) was poured into an addition funnel. Then a solution of 1.16 g (10.2 mmol) of (1R,2R)-1,2-diaminocyclohexane in 20 mL of anhydrous dichloromethane was made and stirred in a 50 mL round bottom flask under nitrogen at 0• C (via ice bath). The trityl chloride solution was added to the (1R,2R)-1,2-diaminocyclohexane solution dropwise over 60 minutes. Then the reaction mixture was allowed to warm to room temperature and was stirred for 17.5 hours. The reaction mixture was then heated to 35-40• C for 15 minutes and then allowed to cool back down to room temperature. The solution was transferred to a separatory funnel and was washed once with 5 mL of water to bring the pH of the water wash down to 10. Then the organic bottom layer was separated into an Erlenmeyer flask and dried with anhydrous sodium sulfate overnight. The product was obtained by gravity filtration and was then dried using rotary evaporation. Once the product was dry, it became white and

foamy. It was further dried under vacuum overnight and collected into a tared product bottle. The product weighed 1.61 g (4.52 mmol).

Synthesis of glyoxal bisimine of -(triphenylmethyl)-(1R,2R)-1,2-diaminocyclohexane

A solution of 0.92 g (2.6 mmol) of -(triphenylmethyl)-(1R,2R)-1,2-diaminocyclohexane in 16 mL of methanol was stirred in a 50 mL round bottom flask. 0.14 mL of 40% (W/W) aqueous glyoxal (172 mg, 1.2 mmol) was added dropwise. The solution was stirred for 26 hours at room temperature. The cloudy off-white reaction mixture was vacuum filtered in a büchner funnel via water aspirator. The white product was washed with 8 mL of cold methanol. The product was left to dry on the vacuum for 20 minutes, placed in a tared product vial and further dried under vacuum for 24 hours. The product weighed 0.69 g (0.94 mmol).

Synthesis of , ø-Bis[(1R,2R)-(2-triphenylmethylamino)cyclohexyl]-1,2-diaminoethane

A solution of 0.165 g (0.22 mmol) of the glyoxal bisimine of -(triphenylmethyl)-(1R,2R)-1,2-diaminocyclohexane in 2 mL of freshly distilled tetrahydrofuran (THF) was stirred under nitrogen in a 50 mL round bottom flask as a solution of 1.5 mL of 2M lithium borohydride in THF was added dropwise. The reaction mixture was stirred for 14 hours at room temperature, then for 4

hours at 40• C. Then the reaction mixture was cooled to 0• C using an ice water bath, and 1 mL of cold water was added dropwise using a Pasteur pipette. Most of the THF was evaporated using a rotary evaporator and the remaining mixture was swirled with 15 mL of dichloromethane in a separatory funnel. The mixture was gravity filtered into an Erlenmeyer flask and the filtrate was dried over anhydrous sodium sulfate overnight. It was then filtered, evaporated via rotary evaporator, and dried under vacuum in a tared round bottom flask. The resulting product was a white foamy solid that weighed 0.078 g (0.11 mmol).

Results

Resolution of trans-1,2-diaminocyclohexane: Synthesis of (1R,2R)-1,2-diaminocyclohexane L-(+)-tartarate

The experiment was conducted twice, the results of which are presented in Table 1. Because the starting material was a racemic mixture of both enantiomers, we expect there to be about 50% of each one present. Therefore, the yields listed in Table 1 are very high. In both cases, the product was tan to off-white in color and decomposed between 251-259• C, which is relatively close to the Aldrich literature value of 273• C.

Experiment number	Reactant (mL)	Product (g)	Percent yield
1	24	24.40	48.1%
2	48	50.45	48.2%

Table 1: Results of the synthesis of (1R,2R)-1,2-diaminocyclohexane L-(+)-tartarate

Resolution of trans-1,2-diaminocyclohexane: Synthesis of (1S,2S)-1,2-diaminocyclohexane dihydrochloride

The experiment was performed twice, and the results, which can be seen in Table 2, were consistently good for both trials. As with the previous experiment, 50% is the highest percent yield that could be expected for this enantiomer, therefore, the yields listed in Table 2 are more than satisfactory. The product obtained was a tan, powdery solid that decomposed at 301-304• C. Note that this product was not used in any further experiments.

Experiment number	Reactant (mL)	Product (g)	Percent yield
1	24	15.48	41.4%
2	48	32.83	43.9%

Table 2: Results of the synthesis of (1S,2S)-1,2-diaminocyclohexane dihydrochloride

Synthesis of (1R,2R)-1,2-diaminocyclohexane

The experiment was conducted four times, and the results are shown in Table 3. The first trial conducted resulted in the highest percent yield, however, it took over a week to complete because of the many stages of drying and transfers between flasks. The end product was very fine peach-colored needle-shaped crystals that melted at 43• C (Aldrich literature melting point: 45• C).

In the second trial, an attempt was made to cut out a couple steps by concentrating the solution in the Dannley

pressure fritted funnel instead of transferring it into a round bottom flask and then transferring it back into a Dannley funnel. However, while the solution was being concentrated via vacuum pump, a leak in the Dannley funnel was formed, exposing the moisture-sensitive product to the air. Even after re-drying the solution with sodium metal and attempting to crystallize the product, only a small amount of clumpy crystals formed with a melting point of 160• C. Clearly, the desired product was not obtained.

In the third trial, the scale was doubled, but it was carried out in the same way as the first trial, without skipping any steps. The percent yield was a little lower, but the crystals were needle-shaped and melted at 44• C.

The fourth trial is not complete, and the only variation is that the solution was not filtered through activated charcoal.

Experiment number	Reactant (g)	Product (g)	Percent yield
1	11.54	2.01	40.9%
2	10.57	0.11	2.5%
3	22.96	3.00	30.2%
4	23.0	In Progress	In Progress

Table 3: Results of the synthesis of (1R,2R)-1,2-diaminocyclohexane

Synthesis of -(Triphenylmethyl)-(1R,2R)-1,2-diaminocyclohexane

The experiment was conducted five times, the results of which are shown in Table 4. The first two trials were not

successful; as Table 4 shows, the first trial did not result in any product and the second trial resulted in an impure oil. The oil was analyzed via thin layer chromatography which showed that it consisted of mainly starting material.

During the third trial, it was discovered that a bottle of silica gel was mislabeled as sodium sulfate. Therefore, during the previous two trials, while the organic layer was thought to be drying over sodium sulfate, it was actually being left to sit with silica gel. Because of this, the product was being lost after gravity filtration. A new bottle of sodium sulfate was obtained and the third trial was successful. The fourth and fifth trials were performed similarly and were also successful. In all three trials, the product obtained after drying was a white foamy solid that melted at 50-60• C.

Experiment number	Reactant (g)	Product (g)	Percent yield
1	0.42	NA	NA
2	0.57	0.33 of impure oil	NA
3	0.58	0.68	77.0%
4	1.16	1.61	91.2%
5	0.57	0.73	82.0%

Table 4: Results of the synthesis of N-(triphenylmethyl)-(1R,2R)-1,2-diaminocyclohexane

Synthesis of glyoxal bisimine of -(triphenylmethyl)-(1R,2R)-1,2-diaminocyclohexane

The experiment was conducted three times, and the results can be seen in Table 5.

This experiment was by far the shortest as it only involved stirring the reactants at room temperature and then filtration and drying of the product. All three trials were successful and had satisfactory percent yields. The product collected was a white solid that melted at 204-214• C.

Experiment number	Reactant (g)	Product (g)	Percent yield
1	0.23	0.16	74.33%
2	0.92	0.69	78.3%
3	0.51	0.44	84.3%

Table 5: Results of the synthesis of glyoxal bisimine of N-(triphenylmethyl)-(1R,2R)-1,2-diaminocyclohexane

Synthesis of , øBis[(1R,2R)-(2-triphenylmethylamino)cyclohexyl]-1,2-diaminoethane

The experiment was only performed once and on a small scale. The results can be seen in Table 6. Note that there is not enough product to continue on with the experiments at this time.

Experiment number	Reactant (g)	Product (g)	Percent yield
1	0.17	0.078	47%

Table 6: Results of the synthesis of N,N'-bis[(1R,2R)- (2-triphenylmethylamino)-cyclohexyl]-1,2-diaminocyclohexane

Conclusions

The first six experiments that have been conducted have all yielded successful results. However, at this time there is not enough , øBis[(1R,2R)-(2-triphenyl-

methylamino)cyclohexyl]-1,2-diaminoethane to continue on to the synthesis of , 'Bis[(1R,2R)-(2-amino)cyclohexyl]-1,2-diaminoethane. Currently the synthesis of (1R,2R)-1,2-diaminocyclohexane is being repeated so that there is enough product to conduct the next three experiments with to result in at least 1 gram of , øBis[(1R,2R)-(2-triphenylmethylamino)-cyclohexyl]-1,2-diaminoethane. Once that is achieved, the experiments can continue on until M40403 is fully synthesized.

References

- (1) Heterocyclic Compound. *Encyclopedia Britannica*, Academic Edition [Online]; Encyclopedia Britannica, Posted 2011. <http://www.britannica.com/EBchecked/topic/264227/heterocyclic-compound> (accessed Apr 21, 2011).
- (2) Feng, L.; Shuhui, W.; Zheng, L., Xiaoqin, X.; Li, Y.; Xiang, Z.; Chengtai, W. Medical Applications of Macrocylic Polyamines, *Current Medicinal Chemistry*, **2006**, *13*, 711-727.
- (3) AIDS. *Encyclopædia Britannica*. Encyclopædia Britannica Online. Encyclopædia Britannica. Posted 2011. <http://0-www.britannica.com.innopac.library.unr.edu/EBchecked/topic/10414/AIDS> (accessed Apr 21, 2011).

- (4) Highleyman, L. *Maraviroc (Selzentry): 48-week Treatment-experienced Data, Failure and Lipids in Treatment-naive patients, and Possible Use for Prevention.* HIV and Hepatitis. Posted 2008. http://www.hivandhepatitis.com/2008/croi/docs/021208_a.html (accessed Apr 20, 2011).
- (5) Mollace, V.; Salvemini, D.; Riley, D. P.; Muscoli, C.; Iannone, M.; Granato, T.; *The contribution of oxidative stress in apoptosis of human cultured astroglial cells induced by supernatants of HIV-1-infected macrophages.* *J. Leukoc. Biol.* **2002**, *71*, 65-72.
- (6) Hamal, S.; Cui, L.; Thomas, B.; Stefano, A.; Huskens, D.; Schols, D. *Macrocyclic Polyamines Targeting the Cellular HIV Co-receptors, CXCR4 and CCR5.* *Antiviral Research*, **2009**, *82*, A58.
- (7) Hamal, Sunil; Huskens, Dana; Schols, Dominique; Bell, Thomas, *Metal Complexes of Macrocyclic Polyamines Targeting the Cellular HIV Co-receptors, CXCR4 and CCR5.* *J. Antiviral.* **2010**, *86*, A55-A56.
- (8) Schanz, Hans-Jörg; Linseis, Michael A.; Gilheany, Declan G., *Improved resolution methods for (R, R)- and (S,S)-cyclohexane-1,2-diamine and (R)- and (S)-BINOL.* *Tetrahedron: Asymmetry*, **2003**, *14*, 2763-2769.
- (9) Galsboel, F.; Steenboel, P.; Soerensen, B. S., *Preparation, Separation, and Characterization of the 1e13- and ob3-isomers of tris(trans-1,2-cyclohexanediamine)rhodium(III) complexes.* *Acta Chem. Scand.* **1972**, *26*, 3605-3611.
- (10) Riley, D. P.; Neumann, W. L.; Henke, S. L.; Lennon, P.; Aston, K. W.; Salvemini, D.; Sikorski, J. A.; Fobian, Y. M.; Grapperhaus, M. L.; Kusturin, C. L. *Substituted pyridine pentaazamacrocyclic complexes having superoxide dismutase activity as therapeutic agents.* U.S. Patent 6,214,817, 19990916, 2001.