Demonstrating Versatility of Green Chemistry Using the Cyclohexanol Cycle

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ABSTRACT

Part of the cyclohexanol cycle conducted to evaluate the tenets of green chemistry. Cyclohexanol underwent acid-catalyzed dehydration using a clay alternative to concentrated acid synthesizing cyclohexene in 43.4% yield. The cyclohexene was brominated using HBr and H_2O_2, forming Br_2 *in situ*. The product, *trans*-1,2-dibromocyclohexene, was then extracted in 3.73% yield. *trans*-1,2-Dibromocyclohexene underwent a debromination reaction using zinc metal as a reducing agent to recreate cyclohexene in 29.0% yield. The cyclohexene product was epoxidized, forming dimethyldioxirane *in situ* using Oxone® and acetone, to synthesize cyclohexene oxide in 37.9% yield. Cyclohexene oxide, once reduced using $LiBH_4$, recreated cyclohexanol in 70.6% yield. Proton NMR data for most products were consistent with literature values of each product.

INTRODUCTION

In the age of post-industrialization and global warming, chemists have a great deal of responsibility to synthesize desired products while adhering to environmentally friendly practices. Chemists working in lab have the ability to seek out sustainable, nontoxic, reusable, or otherwise harm-reduced reagents that can be used for a world running on mass production. Green chemistry is the practice of intentionally seeking out these reagents and processes in the laboratory to prevent harm to the environment.[1] It is

composed of 12 tenets, focusing particularly on the toxicity, efficiency, and renewability of chemical practices.

The cyclohexanol cycle (Scheme 1) can be used to illustrate many different reactions that can be completed while still demonstrating green chemistry practices. The cycle begins with dehydrating cyclohexanol to create cyclohexene, brominating cyclohexene to create *trans*-1,2-dibromocyclohexane, debrominating *trans*-1,2-dibromocyclohexane forming cyclohexene again to undergo epoxidation, reducing the cyclohexene oxide, to recreate cyclohexanol.[2] Synthesizing many of the products in the cycle originally required conventional procedures or materials, but can now be replaced with greener alternatives.

The dehydration reaction of cyclohexanol is acid-catalyzed and typically requires a concentrated acid like H_2SO_4, which is hazardous to both humans and the environment. Using green chemistry, however, this hazard was prevented by using Mont K-10, a natural clay, which acted as a Brønsted acid when reacting with cyclohexanol. Moreover, this clay is reusable, unlike the H_2SO_4, further adding to its green nature. Other components of the reaction were also green, including combining the separation and isolation steps and the use of cyclohexanol as the solvent. Solvents are particularly important to examine when practicing green chemistry because they are used in large quantity and are often volatile.[3] Using cyclohexanol as the solvent is efficient as it is the reacting compound and less harmful than other reagents.

Cyclohexene is brominated to *trans*-1,2-dibromocyclohexane through the process of halogenation. Typically, this reaction contains hazardous reagents, most notably, the bubbling in of elemental bromine in a gaseous state. Br_2 is corrosive, an acute toxin, and an environmental hazard.[4] Adding Br_2 manually would necessitate proper storage and a risky delivering process. This was avoided by creating Br_2 *in situ*, using HBr, water, and H_2O_2. Hydrogen bromide is still a harmful chemical, however not nearly as hazardous as elemental bromine.

Debromination of *trans*-1,2-dibromocyclohexane involves a reduction-oxidation reaction using zinc metal as a reducing agent, facilitating the reaction from the *trans*-1,2-dibromocyclohexane to the cyclohexene. In this process, water was used as the solvent, eliminating any risks from using a hazardous organic solvent.

Epoxidation of the cyclohexene product typically involves the use of meta-chloroperoxybenzoic acid (mCPBA), a strong and hazardous oxidizer, however, this reagent was substituted with the cheaper and less caustic Oxone®.

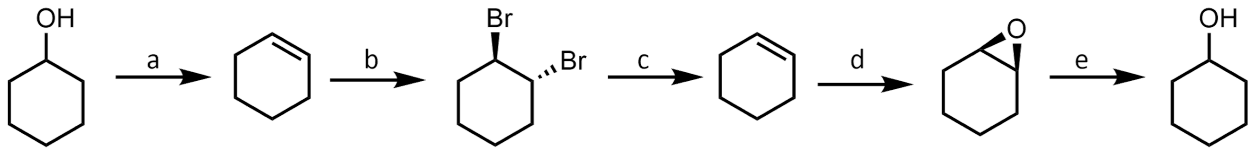
The reduction of cyclohexene necessitates a reducing agent, generally synthesized with the use of $LiAlH_4$. $LiAlH_4$ is a dangerous reducer that reacts violently with water and creates very flammable, hydrogen gas. With green chemistry methods, $LiBH_4$ was used as a safer alternative. Furthermore, this process regenerates cyclohexanol as a product, an obviously versatile compound.

The aforementioned reactions took place with relative ease while yielding desired products and reducing environmental risk. In addition, each of the products was utilized in the following step, eliminating waste, another green feature. Therefore it is clear that green chemistry does not implicate that originally hazardous reactions cannot be done, but rather that methods can be adapted to substitute hazardous features of reactions. Green chemistry can be (and is) as versatile as chemistry that does not take environmental wellbeing into consideration. Rather than “can chemistry be done in greener ways?”, the new question becomes, “can green methods prove themselves as useful to chemists by providing enough desired product?”. It is worth questioning whether these methods are of any use if they are either too expensive, too time consuming, or do not provide enough of the desired product (if they yield the product at all). Here, the yield and identity of each product within the cyclohexanol cycle was examined to answer this new question.

RESULTS & DISCUSSION

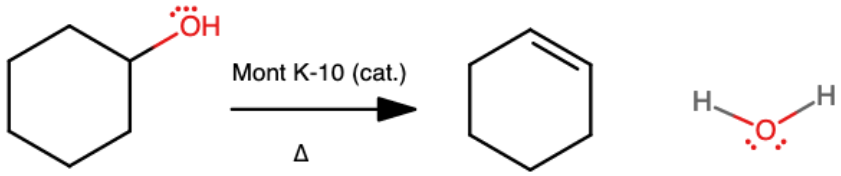
Each step of the cyclohexanol cycle was synthesized to answer whether reactions carried out using green practices can still deliver significant yield. The cyclohexanol cycle (Scheme 1) was characterized by five reactions: dehydration of cyclohexanol (Scheme 1a, 2), bromination of cyclohexane (Scheme 1b, 3), debromination of *trans*-1,2-cyclohexane (Scheme 1c, 4), epoxidation of cyclohexene (Scheme 1d, 5), and reduction of cyclohexene oxide (Scheme 1e, 6).

Scheme 1. Cyclohexanol cycle [9]



The dehydration of cyclohexanol catalyzed by Montmorillonite K-10 lead to the creation of cyclohexene in 43.4% yield (Scheme 1a, 2). This moderately low yield may be due to the reaction being cut off too soon. This reaction needs to be exposed to heat in order to isolate the cyclohexene product, however it is likely that the heat was removed early to avoid evaporating byproduct (H_2O) into the product flask. This could be improved upon by slowly heating the reaction and maintaining an appropriate heat (85-90°C) for an extended period.

Scheme 2. Clay-catalyzed dehydration of cyclohexanol reaction scheme

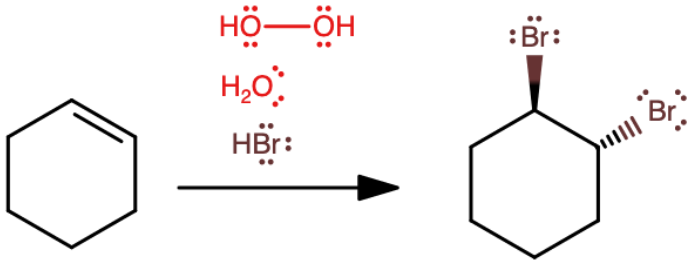


^{1}H NMR analysis of the dehydration product confirmed cyclohexene's identity. The product showed 3 peaks at δ = 1.61 (m), 1.99 (m), and 5.65 (t) ppm, consistent with the 3 unique hydrogens on cyclohexene. Literature data for cyclohexanol showed 3 peaks as well, at δ = 1.52 (m), 2.63 (d), and 3.58 (m) ppm, however these peaks were at

different locations.[5] The peak located at 1.52 ppm for cyclohexanol was broad, as it was composed of the different hydrogens further away from the hydroxy group. The location of the product peaks also matched the downshift shift associated with hydrogens near electronegative double bonds, particularly the 5.65 ppm peak, indicating vinylic hydrogens, which matched almost perfectly to the literature data for cyclohexene.[6]

The cyclohexene product was brominated to create *trans*-1,2-dibromocyclohexane, first reacting H_2O, 2 eq. HBr, and 30% H_2O_2 to form Br_2 *in situ* (Scheme 1b, 3). *trans*-1,2-Dibromocyclohexane was synthesized in a miniscule 3.73% yield. This low yield is possibly due to the age of the hydrogen peroxide. Hydrogen peroxide decomposes over time, which could be accelerated by contamination of a number of metal catalysts present in a laboratory setting.[7] Hydrogen peroxide decomposes to create water and oxygen gas, insufficient reagents for turning hydrogen bromide to molecular bromine. This can be avoided by using fresh H_2O_2. Otherwise, this reaction required several extraction, vacuum, and evaporating steps which allow for significant loss.

Scheme 3. Bromination of cyclohexene reaction scheme

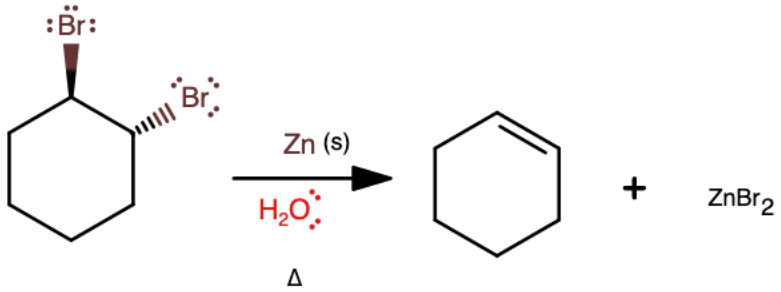


Despite its small yield, the ^{1}H NMR analysis of the product confirmed the compound's identity as *trans*-1,2-dibromocyclohexane. The ^{1}H NMR of the product showed five peaks at δ = 1.15 (m), 1.81 (m), 1.90 (m), 2.45 (m), and 4.45 (s) ppm. This was consistent with the 5 unique hydrogens on *trans*-1,2-dibromocyclohexane. Hydrogens on the same carbon atom in *trans*-1,2-dibromocyclohexane were considered different from one another because of their relation to the bromo substituents while in the chair

conformer. ^{1}H NMR for cyclohexene shows values shifted downfield because of the electronegative double bond. While bromine is somewhat electronegative, there were no hydrogens bonded directly to it like the hydrogens bound to the double bond. The ^{1}H NMR analysis of the product fit much better to the literature data for *trans*-1,2-dibromocyclohexane.[8]

trans-1,2-Dibromocyclohexane was debrominated using zinc dust to synthesize cyclohexene (Scheme 1c, 4). The reaction commenced with *trans*-1,2-dibromocyclohexane to yield cyclohexene in 28.96% yield. A significant portion of loss was likely due to the various delivery steps. Instead of measuring the product flask before the reaction began, the product was delivered into another container for massing. Furthermore, water got into the product flask and was pipetted out. This also contributed to the loss of product mass. This could have been avoided by both reducing the number of transfers of reagent or product and heating more consistently, preventing spikes in temperature that allow water to make its way into the product flask.

Scheme 4. Debromination of *trans*-1,2-dibromocyclohexane reaction scheme

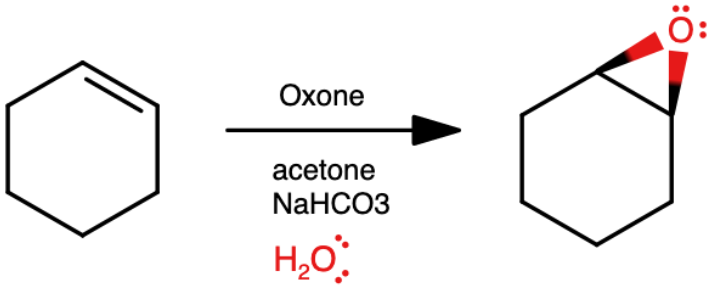


The ^{1}H NMR for the debromination product confirmed its identity as cyclohexene. The product showed 3 peaks at δ = 1.61 (m), 1.99 (m), and 5.66 (d) ppm. This was consistent with the literature data for cyclohexene ^{1}H NMR and was significantly different than the literature data for *trans*-1,2-dibromocyclohexane ^{1}H NMR. *trans*-1,2-Dibromocyclohexane had five unique hydrogens because of the chair conformer position; they were located at δ = 1.52 (m), 1.81 (m), 1.90 (m), 2.46 (m), and

4.46 (t) ppm. Again, the downfield shift of peaks in cyclohexene was due to the electronegative double bond, absent in *trans*-1,2-dibromocyclohexane, explaining more upfield values.

The cyclohexene product was epoxidized using Oxone®, acetone, and $NaHCO_3$. (Scheme 1d, 5). Oxone, acetone, and sodium bicarbonate created the oxidizing reagent, dimethyldioxirane, *in situ*. Dimethyldioxirane reacted with the cyclohexene to create the cyclohexene oxide product in 37.9% yield. Some of the loss found in this reaction may be due to the several transferring steps involved. It also could be due to failure to dissolve all of the Oxone® into the water.

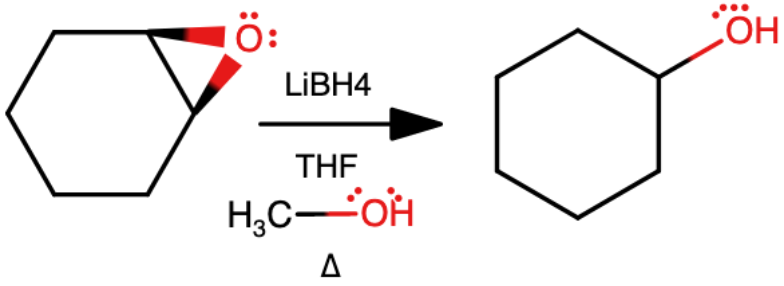
Scheme 5. Epoxidation of cyclohexene



The ^{1}H NMR for this product identified this product as cyclohexene oxide, though with notable contamination. The product showed six major peaks at δ = 1.25 (m), 1.43 (m), 1.81 (m), 1.91 (m), 2.15 (s), and 3.09 (s). The four smallest peaks were representative of hydrogens further from the epoxide group and were likely from cyclohexene oxide product. The peak located at 2.15, however, had an integration over six times the size of the other peaks. While the first four small peaks were consistent with literature NMR values, the largest peak, identifying the hydrogens closest to the epoxide group, was shifted further downfield (δ = 3.05) than what was recorded.[10] The last recorded peak (δ = 3.09) was also unaccounted for in the literature values. The low yield ultimately may have been due to the creation of the wrong product or contaminants. It is unlikely that the unknown peaks were from DCM, as DCM has one ^{1}H NMR peak at δ = 5.25.[11] Acetone's literature spectral data, however, does have a peak near 2.15 ppm (at 2.16), which may have contributed to the large peak.[12]

The cyclohexene oxide product was reduced using $LiBH_4$ as the reducing agent and THF as the solvent (Scheme 1e, 6). Cyclohexene oxide and $LiBH_4$ synthesized cyclohexanol in 70.6% yield. While this is a significantly larger yield than previous reactions, some of the loss may have been due to the contamination present in the those steps. There were also issues with transferring the product from reaction flask to measuring vial, in which there was some loss.

Scheme 6. Reduction of cyclohexene oxide



The ^1H NMR for this product identified this product as though with notable contamination. The product showed six major peaks δ = 1.10-1.32 (m), 1.70 (m), 1.82 (m), 3.41-3.59 (d), and 3.83 (m). The earlier of the peaks represented cyclohexanol well, particularly the first peak, broad like the literature spectral data depicts.[5] The later peaks, however, were characteristic of THF, the solvent in the reaction.[13]

Overall, it appears that green practices have a place within the field of chemistry. Many instances of low yield were not necessarily errors on behalf of the alternative reagents and each of the products was correctly identified as the desired result, albeit with some contamination. Some processes, however, were greener than others; the last two reactions had less green components than the reactions proceeding them. Investing in naturally occurring reagents however, like Mont K-10, seems to be a viable option because of how much less hazardous it is to operate in lab, how it is a reusable source, and how well the yield ended up being.

EXPERIMENTAL

General Methods

^{1}H NMR spectra measurements were conducted on a Bruker Fourier (300 MHz) transform spectrometer using $CDCl_3$ and TMS as a solvent. Separation was completed using a rotary evaporator.

Clay-catalyzed dehydration of cyclohexanol

The cyclohexanol was weighed by taring a balance and placing a graduated cylinder on top. Using a pipette, 102.61 mmols of cyclohexanol was delivered to the graduated cylinder. A simple distillation apparatus was set up and a 50 mL flask containing 5-10 boiling chips, a stir bar, and the two reagents was placed in a sand bath over the hot plate. A temperature probe was inserted above the pot flask. Before heating, all clumps of the 1.1980 g of Montmorillonite K-10 (“Mont K-10”) were broken to create a smooth mixture. The hot plate temperature was set to 200 °C and the condenser column was covered with aluminum foil. Refluxing began about 10-15 minutes into the reaction. The reaction was kept to a temperature range between 80-85 °C, maintaining a temperature under 90 °C. After an hour, there was a drop in temperature to 57 °C, indicating the reaction was complete. The heat was turned off and the apparatus was left to cool. The product appeared as a clear liquid, less dense than water. The end flask was removed and promptly sealed. There was no noticeable water in the flask, therefore use of a drying reagent nor extraction was necessary. The product was added via Pasteur pipette to a weighed glass vial, measuring 3.6383 g of cyclohexene in 43.42% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) for the product showed δ 5.65 (t, 1H), 1.99 (m, 2H), 1.61 (m, 2H).

Bromination of cyclohexene

In a clean and dry round-bottom flask, a stir bar and 2 equivalents of concentrated HBr (approx. 5.5 mL) were added. Over the flask, an addition funnel was added. The flask and addition funnel were clamped to a ring stand and placed over an ice bath. The flask

was let alone to stir over ice for 5 minutes. To the addition funnel, approximately 2.5 mL 30% H_2O_2 was added. This was added dropwise to the HBr solution, which immediately turned a red-brown color. After 2-3 minutes of H_2O_2 addition, the solution turned yellow. 24.60 mmol of cyclohexene were added dropwise to the flask and the reaction was let run until the color cleared. This reaction went on for about 15 minutes after the addition of cyclohexene.

The addition funnel was removed and washed down with soap and water. A final rinse of acetone was conducted and then the funnel was placed in the oven to dry. The stir bar was removed from the flask and the solution was transferred to a separatory funnel. The flask was washed with dichloromethane (DCM). In the separatory funnel, DCM was added, creating two layers: aqueous byproduct on the top and the desired product dissolved in DCM on the bottom. The separatory funnel was inverted and shaken, opening the stopcock while upside down to release pressure. The layers formed again and then the bottom layer was extracted by opening the stopcock and placing in another vial. More DCM was added to the remaining aqueous layer and the extraction process was repeated. The aqueous layer was saved in a separate vial.

The extracted organic layer was placed back into the separatory funnel and cleaned with $NaHSO_3$. Again, the desired product was in the bottom layer and extracted out using the stopcock. The organic product was dried of any excess water through the addition of $MgSO_4$, a drying reagent. After 5 minutes of allowing to dry, the solution underwent vacuum filtration. The desired product was extracted from the DCM solvent via rotary evaporator. The *trans*-1,2-dibromocyclohexane product was weighed out to be 0.2250 g, in 3.73% yield. The product was sealed with parafilm and refrigerated. ^1H NMR analysis for the product showed δ 4.45 (s, 1H), 2.45 (m, 1H), 1.90 (m, 1H), 1.81 (m, 1H), 1.15 (m, 1H).

Debromination of *trans*-1,2-dibromocyclohexane

Using a pipette, 8.4468 mmol of *trans*-1,2-dibromocyclohexane was delivered into a 25 mL round-bottom flask on a tared balance. In a 50 mL round-bottom flask, 2.744 g of

zinc dust and 10 mL of water were delivered. In the same flask, the dibromocyclohexane was added along with boiling chips and a stir bar. A reflux condenser was attached vertically above the flask with a thermometer probe at the very top. The heating mantle under the flask was switched on to 200 °C and the mixture began to reflux. After the first drop of liquid from the condensation falls back into the mixture, the reflux was allowed to run for 35 minutes further. After the 35 minutes, the water for the condenser was turned off and drained off. The apparatus was covered with aluminum foil. The cyclohexene was to be boiled off until the vapor stabilized at 100°C; this took approximately 45 minutes. The temperature first went down to 83-85 °C and then rapidly came back up to 90-92 °C. The heat was turned off and the apparatus was allowed to cool. The product was transferred to a vial. There was one significant bubble of water which was removed via pipette. The product was weighed to be 0.2006 g of cyclohexene in 28.96% yield. ^{1}H NMR analysis for the cyclohexene product showed δ 5.66 (d, 1H), 1.99 (m, 2H), 1.61 (m, 2H).

Epoxidation of cyclohexene

In an addition funnel, approximately 70 mL of water was added and shaken to dissolve 31.7 mmol of Oxone®. Under the addition funnel, a 250 mL round-bottom flask was placed with approximately 70 mL of acetone inside. In the same flask, 107 mmol of $NaCHO_3$ and 24.4 mmol of ice-cold cyclohexene was delivered. Once all of the Oxone® was completely dissolved in the funnel, the stopcock was opened to add the solution dropwise to the bottom flask. The reaction was run for 10 minutes and then given 30 minutes to sit untouched. Once the reaction was complete, the flask was removed and the vessel was decanted into a vacuum filter sealed with filter paper wet from water. Excess $NaCHO_3$ was left in the vacuum apparatus and the liquid remains were placed in a separatory funnel. DCM (25 mL) was added to the flask. The bottom layer was extracted first into a 500 mL beaker labelled “organic”. Fresh DCM (25 mL) was added into the separatory funnel and the extracting process was repeated into the same organic beaker. The remaining liquid was separated into a separate 500 mL beaker labelled “aqueous”. The contents of the organic beaker were placed back into the separatory funnel with 25 mL of water. The separating process was repeated one last

time, opening the stopcock to the bottom layer into the “organic” beaker. Enough $MgSO_4$ was added to the organic beaker to cover the bottom of the container and allowed to sit for 10 minutes. Excess $MgSO_4$ was filtered off using the same vacuum filtration process. The remaining liquid was placed in a rotary evaporator and the remaining product was weighed at 0.9062 g for a 37.9% yield. ^1H NMR analysis for the cyclohexene oxide product showed δ = 1.25 (m), 1.43 (m), 1.81 (m), 1.91 (m), 2.15 (s), and 3.09 (s).

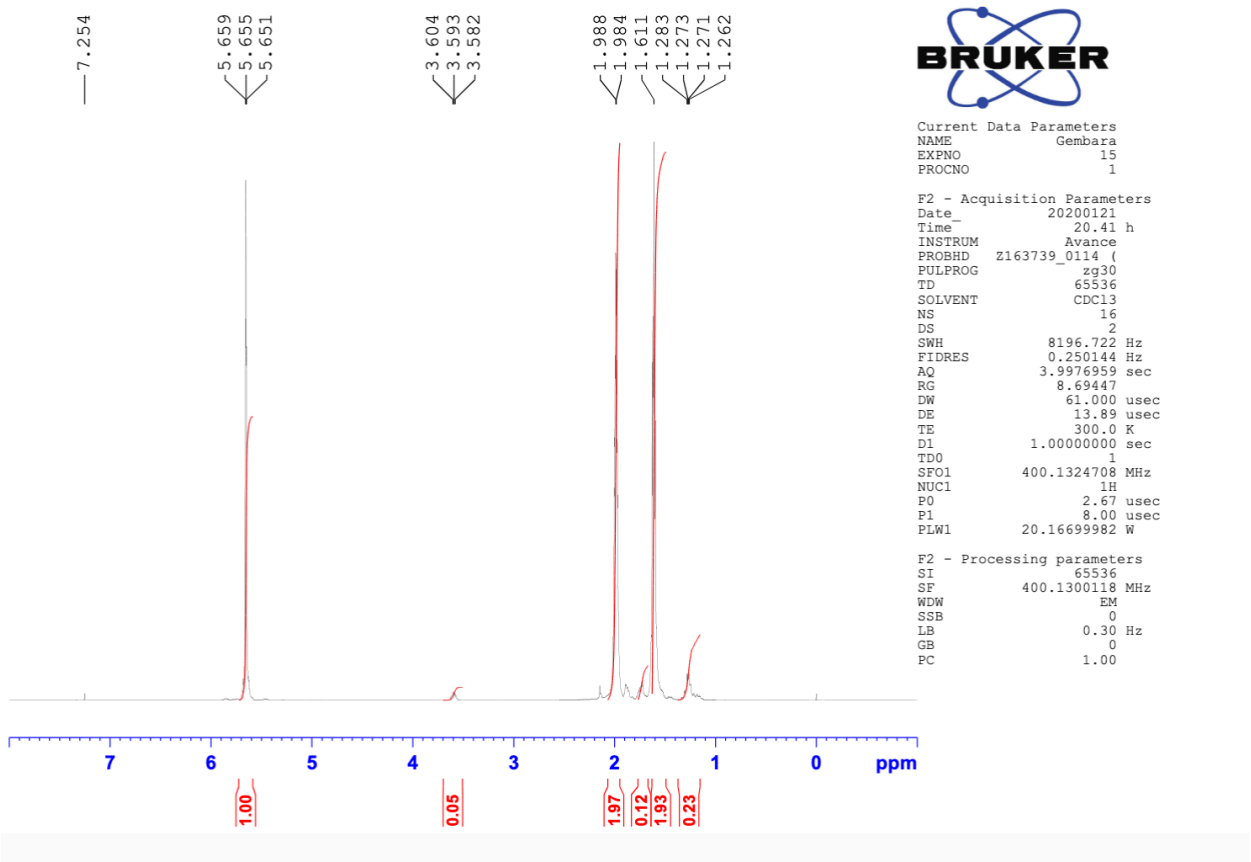
Reduction of cyclohexene oxide

To the inside an 100 mL round-bottom flask in a heated sand bath, a stir bar, 14.9 mL of THF, and 20.378 mmols of cyclohexene oxide product were added. The cyclohexene oxide dissolved into the THF. A pipette was then used to transfer 1.39 mL of methanol into a graduated cylinder. Once the cyclohexene oxide was dissolved, the methanol and 15 mL of $LiBH_4$, extracted via syringe, were added slowly to the flask. Tubing was added and a reflux apparatus was set up. The stirring was turned on and the apparatus was covered with aluminum foil. The refluxing portion of the reaction commenced for two hours after the first drop of condensation from the upper tubing back into the flask. After the two hours, the reaction was removed from the heat and left to cool to room temperature. A quenching solution of 15 mL 1:1 H_2O to methanol was prepared and added to the solution. A white foam formed and created Lithium salt. This solution was placed into an separatory funnel, adding approximately 15 mL of DCM. The funnel was shaken and the stopcock opened while upside down until all the pressure was released. The funnel was placed back into position and in a clean, 250 mL beaker labelled “organic”, the bottom layer was released. The addition of DCM and subsequent steps were repeated for a second organic washing of the solution. The remaining liquid was separated into a separate 500 mL beaker labelled “aqueous”. The contents of the organic beaker were placed back into the separatory funnel with approximately 15 mL of water. The separating process was repeated one last time, opening the stopcock to the bottom layer into the “organic” beaker. Enough $MgSO_4$ was added to the organic beaker to cover the bottom of the container and allowed to sit for 10 minutes. Excess $MgSO_4$ was filtered off using the same vacuum filtration process. The remaining liquid was

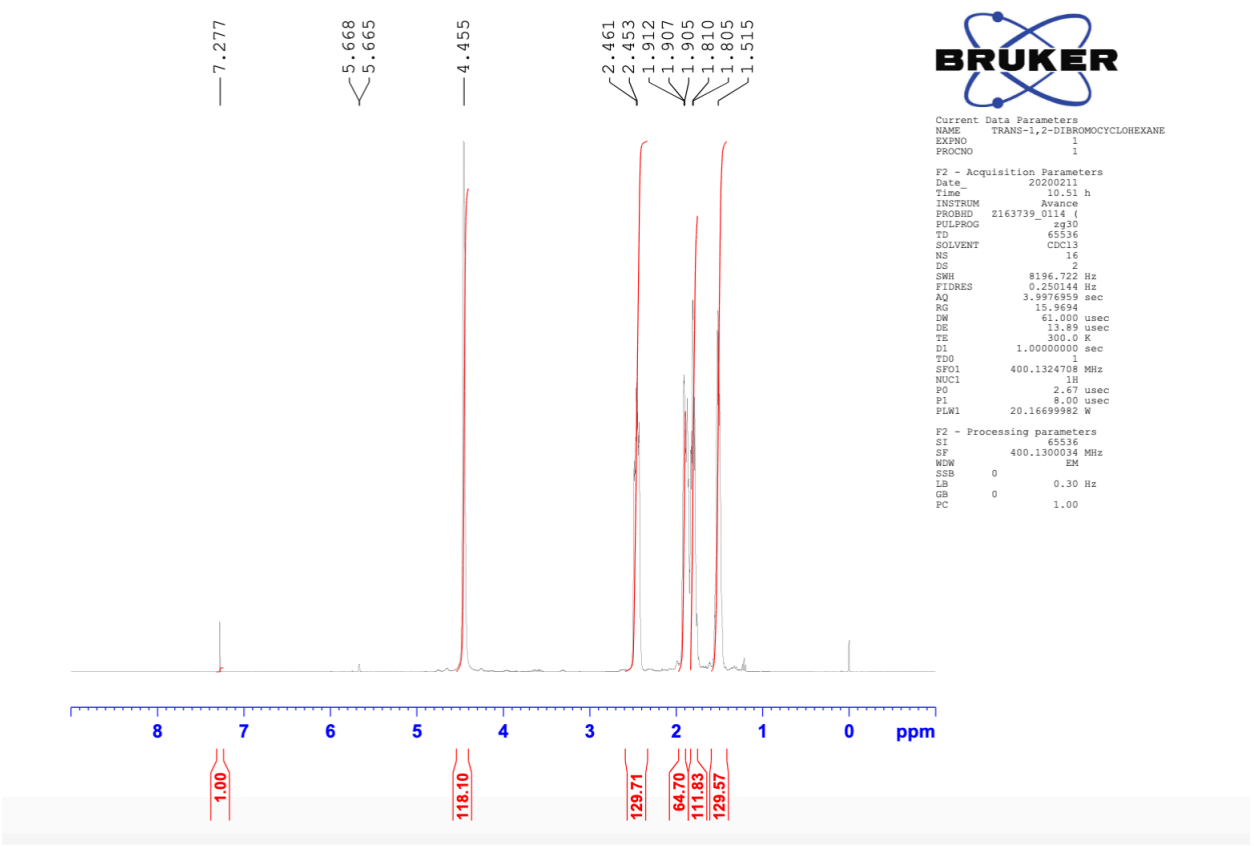
placed in a rotary evaporator and the remaining product was weighed at 1.4412 g for a 70.6% yield.

APPENDIX

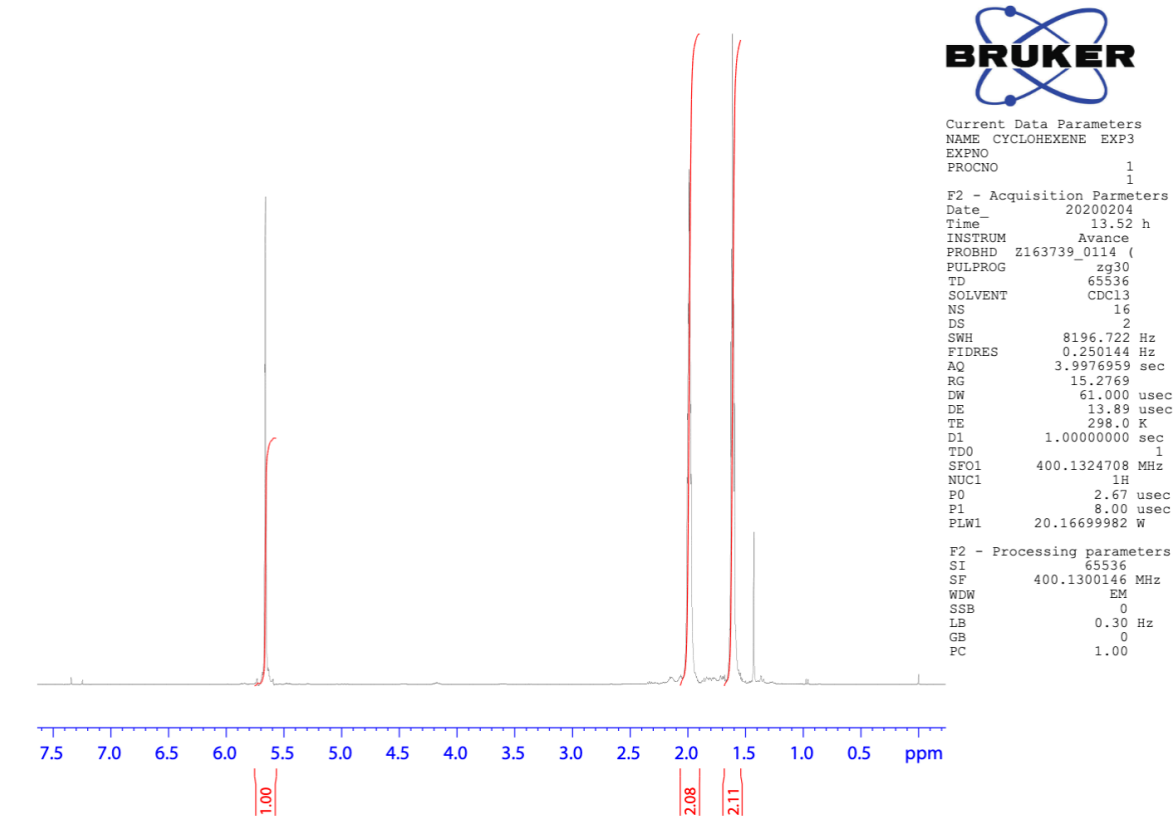
Spectra 1. Cyclohexanol ^{1}H NMR



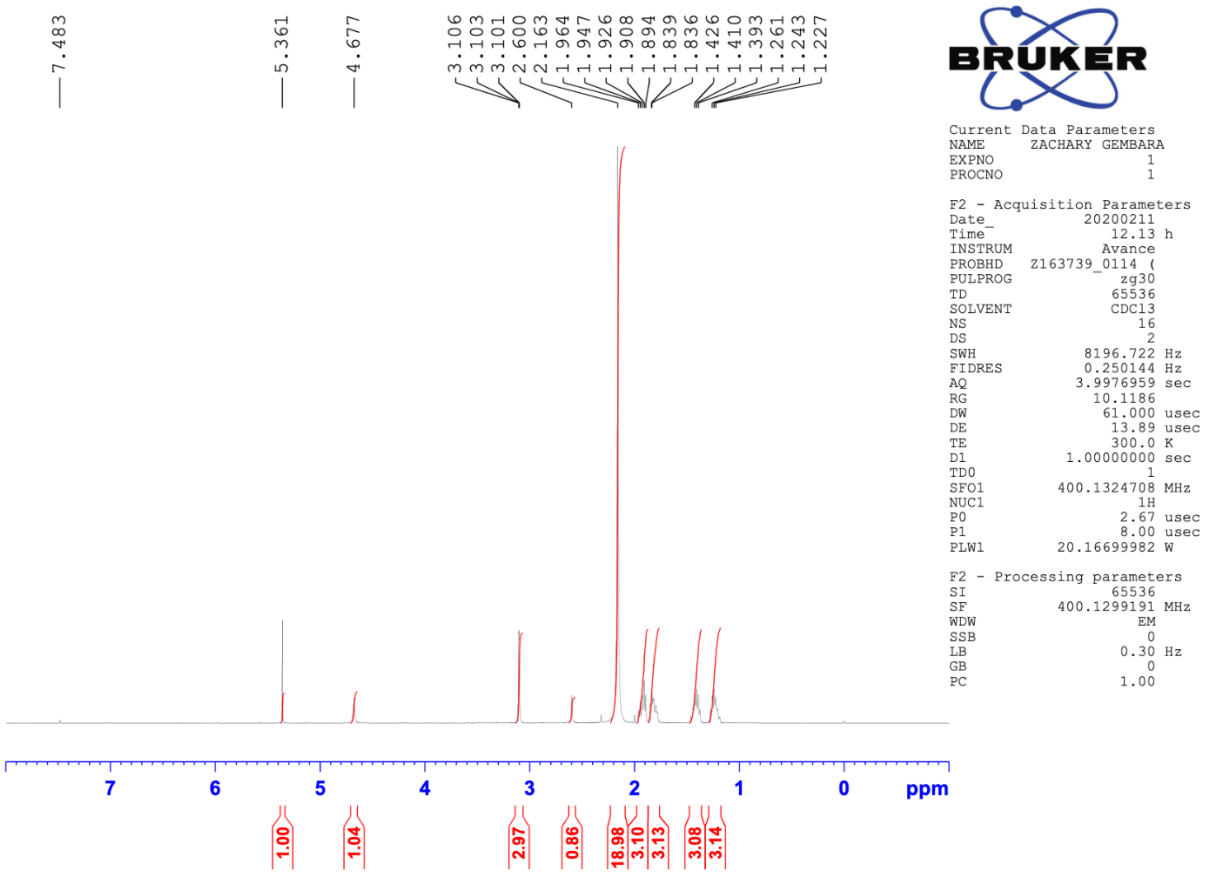
Spectra 2. Cyclohexene ^{1}H NMR



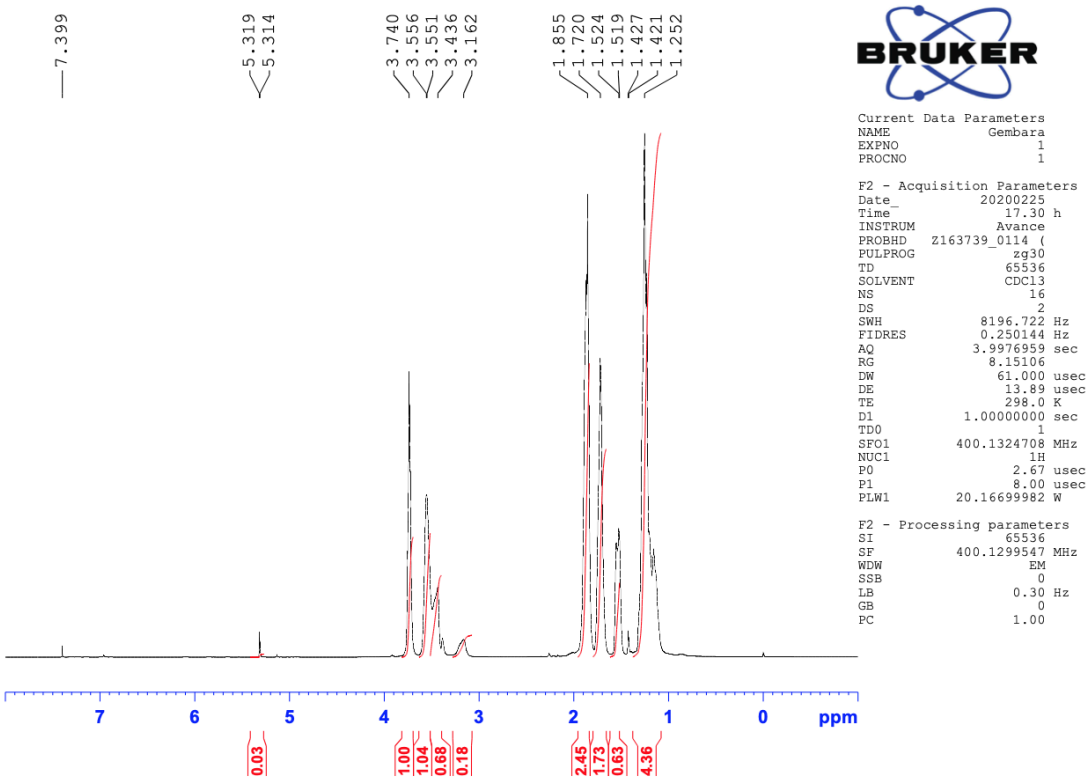
Spectra 3. *trans*-1,2-dibromocyclohexane ^{1}H NMR



Spectra 4. Cyclohexene oxide ^{1}H NMR



Spectra 5. Final cyclohexanol ^{1}H NMR



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