Synthesis of Ambrox from Abietic Acid Isolated from Pine Rosin

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The Synthesis of Ambrox from Abietic Acid Isolated from Pine Rosin

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2006 Senior Honors Thesis

Introduction

Perfumes have been a mainstay in different cultures for centuries. They have had many uses, depending on cultural practices. Today the perfume industry is a multi-billion dollar industry that attracts a worldwide consumer base. However, in the past fifty years the perfume industry had to revert to synthetic means to produce fragrances. Environmental concerns have shifted the way the industry manufacture perfumes that are in high demand all over the world.

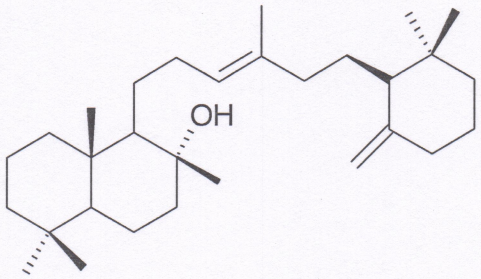
For many years, the main fixative in perfumes was ambergris. Ambergris is a by-product from the sperm whale (*Physeter macrocephalus*). The main function of ambergris is to assist in the digestion of the sperm whale's main food source, the giant squid. The beaks from the giant squid have been found in ambergris, leading scientists to believe that ambergris aids in the digestion of hard sharp objects[4].

When first secreted by the sperm whale, ambergris appears as a soft pale white mass with a strong fecal smell. While floating on the surface of the ocean, ambergris undergoes photo-degradation and oxidation. After years of undergoing these two processes, ambergris develops into a hard, grey, waxy mass. This mass has a sweet and musky odor, which has been compared to isopropanol.

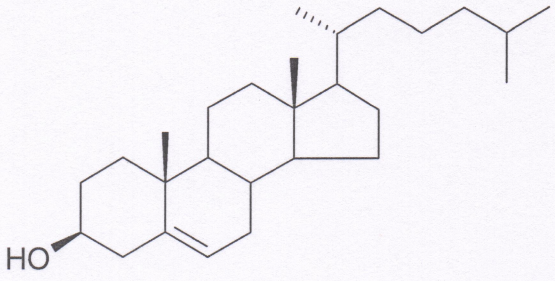
Ambergris has a high market value due to its global demand. A good piece of ambergris could sell for $20 (U.S.) a gram. For example, a recent news story on BBC News[4], featured a story on an Australian couple who recently found a 14.75 kg lump of ambergris that washed up on the shoreline of the beach they were visiting. They discovered that the lump of ambergris that they found was worth over $295,000. (U.S.)

Ambergris is a natural starting material for the fixative, Ambrox®. The chief chemical component of ambergris is ambrein, which bears some resemblance to cholesterin. Figure 1 shows the comparison between ambrein and cholesterol. Ambrox® is synthesized from ambrein by autoxidative decomposition. Figure 2 shows the reaction that occurs in the production of Ambrox®.

Figure 1

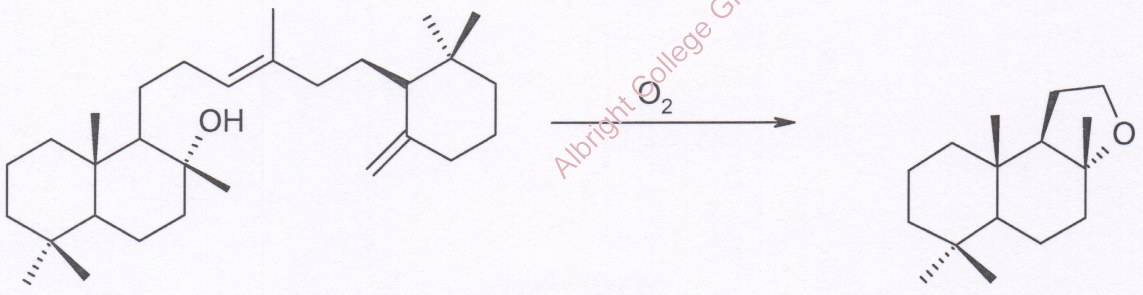


Ambrein



Cholesterol

Figure 2



Ambrein

Ambrox

This "floating gold" can be found in the oceans all around the world. It would be viable for the perfume industry to use this natural fixative, instead of trying to provide a synthetic approach. However, the amount of ambergris that is found does not meet the world demand for perfumes with the fixative present. In addition, since the sperm whale is an endangered species, most industrialized countries do not permit the use of any part of the species. The Endangered Species Act of 1978[4] prohibits the use of any part of an endangered species. The perfume industry had to come up with a synthetic method to create this fixative.

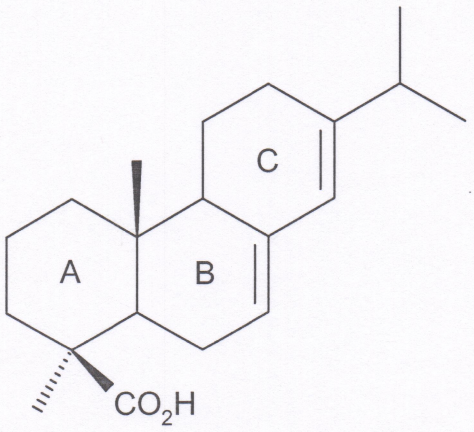
The original synthesis of Ambrox® was prepared in 1950 by Stoll and Hinder from (-)-sclareol[5]. This synthetic approach is still the only method currently used by the fragrance industry. (-)-Sclareol is a diterpenic alcohol that is extracted from the clary sage (*Salvia sclarea L.*) plant[1]. This particular natural product is very expensive to obtain.

To offset the cost, cheap and abundant natural starting materials are currently being explored to synthesize Ambrox®. One approach that has been explored is the synthesis of Ambrox® from labdanolic acid[1]. Labdanolic acid is a diterpene that is extracted from *C. ladaniferus*, which is a plant that is found in abundant amounts in the Iberian Peninsula[1]. Other approaches of synthesizing Ambrox® include: (-)-manoyl oxide, (-)-levopimaric acid, and (-)-abietic acid[1]. This research will focus on the synthesis of Ambrox® from (-)-abietic acid.

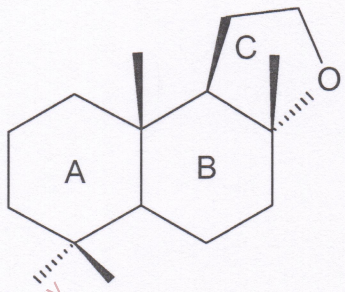
Abietic acid is a natural product that is easily extracted from pine rosin. Pine rosin has many practical industrial uses. Pine rosin is used for "rosin" for string instrumentalists, used in the manufacturing of soaps, and it is used in waxes. Abietic acid

would be a viable natural product to use as a starting material for the synthesis of Ambrox® due to its availability and abundance.

The figure below shows the chemical comparison of the starting material and desired product. Abeitc acid has a three ring fused backbone, with a conjugated double bond system between the B and C rings. Abietic acid also has a carboxylic acid functional group on the A ring. Ambrox® has the same three-ringed backbone, with major differences. The major difference is the 5-membered cyclic ether, which has a specific stereochemistry. The conjugated double bond system is also not present. The carboxylic functional group is replaced with a methyl group.



Abietic Acid



Ambrox

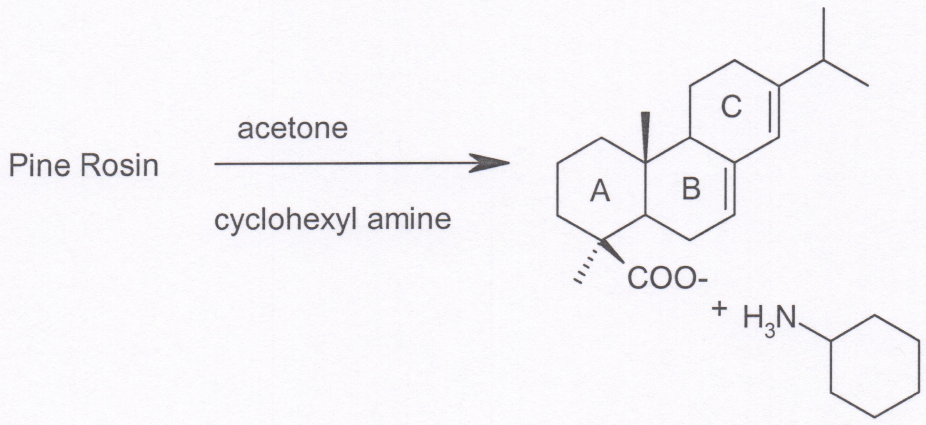
The research starts with the isolation of the abietic acid salt from the pine rosin. Abietic acid will then be isolated from the salt by acidification. Abietic acid will be methylated to the methyl ester, which makes the molecule more feasible to work with. The double bond on the B-ring is then oxidized to a ketone. A Wolff-Kishner reduction is preformed to reduce the ketone to a methylene group[2].

Objective

The objective of this project is to design a synthesis of Ambrox® starting with abietic acid isolated from pine rosin.

Experimental Procedure

Isolation of Abietic Salt from Pine Rosin



abietic acid cyclohexyl amine salt

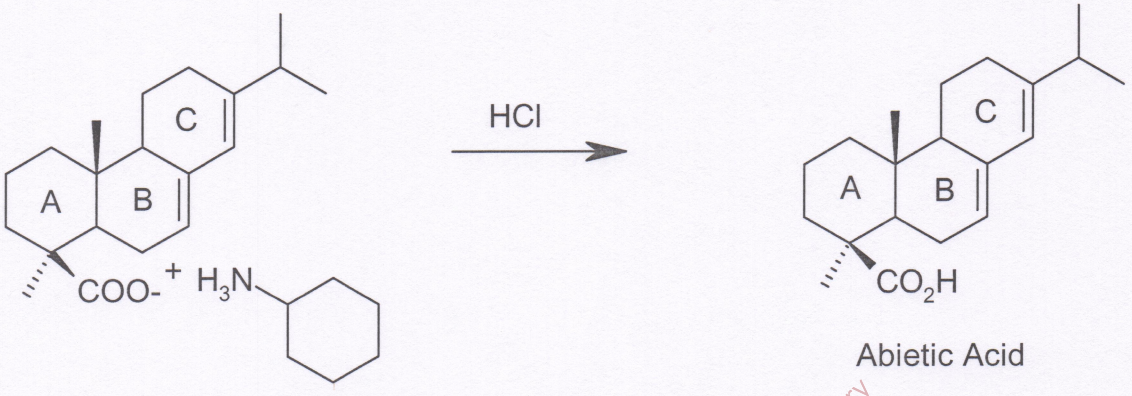
The research started with the isolation of the abietic acid salt from the pine rosin. 10 g (33 mmol) of pine rosin was first dissolved in 50 ml of acetone. Next 7.58 ml (66 mmol) of cyclohexyl amine in 15 ml of acetone was added to the dissolved pine rosin solution. A precipitate immediately formed and was cooled in an ice bath. The salt was collected and washed several times with a total of 25 ml of cold acetone.

To further purify the cyclohexyl amine salt, the solid was dispersed in 100 ml of acetone and heated to boiling. While the mixture was at the boiling point, 30 ml of methanol was added drop-wise. The flask was allowed to cool to room temperature, and

then the flask was put in an ice bath and covered for about 30 minutes. During this time, white crystals formed. The crystals were collected and allowed to dry.

The impure abietic acid cylohexyl amine salt was recrystallized. The sample was suspended in 50 ml of acetone and heated to boiling. 25 ml of methanol was then added drop-wise to dissolve the salt. The solution was allowed to cool to room temperature then put in an ice bath for 30 minutes. After the crystals were collected and allowed to air dry, a melting point was taken to determine the purity of the salt. A melting point range of 197-198 °C indicated the salt crystals were pure.

Isolation of Abietic Acid



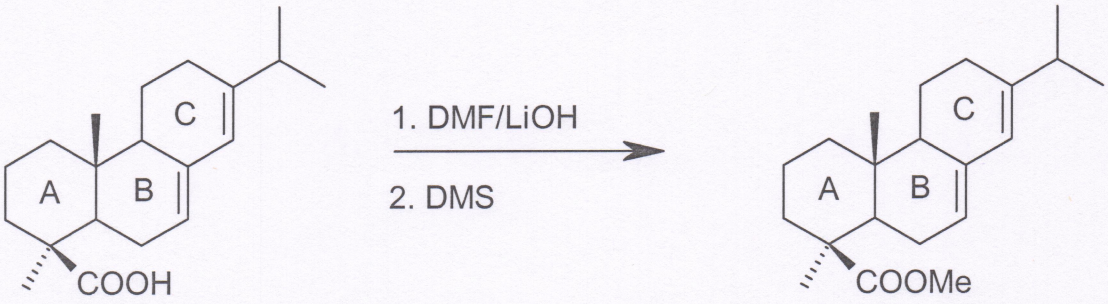
abietic acid cyclohexyl amine salt

Abietic Acid

The next step in isolating abietic acid was to recover the abietic acid from the cyclohexyl amine salt. 5.00 g (12.5 mmol) of the pure salt was dispersed in 80 ml of water and concentrated hydrochloric acid (HCl) was added drop-wise to adjust the pH to 1. The dispersion was then extracted five times using the following amounts of chloroform: 50 ml, 25 ml, and 3x10 ml. The extracts that were collected were combined and washed with 2 x 15 ml of 6 M hydrochloric acid followed by one wash with 25 ml of

water. The chloroform layer was dried over anhydrous magnesium sulfate and evaporated to yield a yellow viscous oil. The oil was then dissolved in 75 ml of 95% ethanol and heated to boiling. When the solution reached the boiling point, water was added to the cloud point. Approximately 35 ml of water was required. The cloudy solution was allowed to cool to room temperature overnight, during which crystallization occurred. A better yield of crystals was obtained if the suspension was placed in the freezer overnight.

Methylation of Abietic Acid



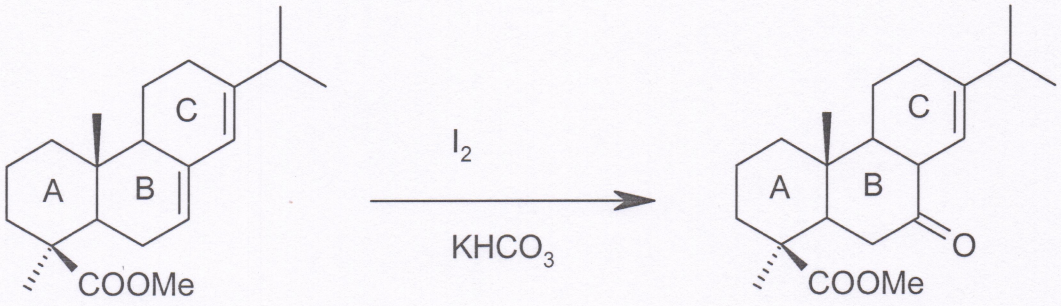
Abietic Acid

Methyl Abietate

After the recovery of the acid, the next step was to esterfiy the acid to the methyl ester. In a small vial, that contained 200 mg (0.66 mmol) of the abietic acid crystals, 0.800 ml of *N,N*-dimethyl foramide (DMF) and 52.4 mg (1.25 mmol) of lithium hydroxide monohydrate ($LiOH \cdot H_2O$) was added. The mixture was then stirred overnight at room temperature during which a white semisolid mass formed. The vial was then placed in an ice bath for 15 min then 0.188 ml (1.98 mmol) of dimethyl sulfate (DMS) was added. The mixture was then stirred at room temperature for 15 min during which a clear light brown solution formed. While stirring, the light brown solution was poured

into 20 ml of water. The emulsion that formed was extracted using 8 x 10 ml of hexane. To facilitate the separation of the hexane phase, a small amount of sodium chloride was added to the aqueous phase. The hexane extracts were then combined and washed with the following: 15 ml of 15% hydrochloric acid, 15 ml of 10% sodium bicarbonate and 15 ml of brine. The hexane solution was dried over anhydrous magnesium sulfate and evaporated to yield a cloudy, yellow colored oil. The product was then purified using a silica gel column (5:1 Cyclohexane/Ethyl Acetate).

Oxidation of Methyl Abietate

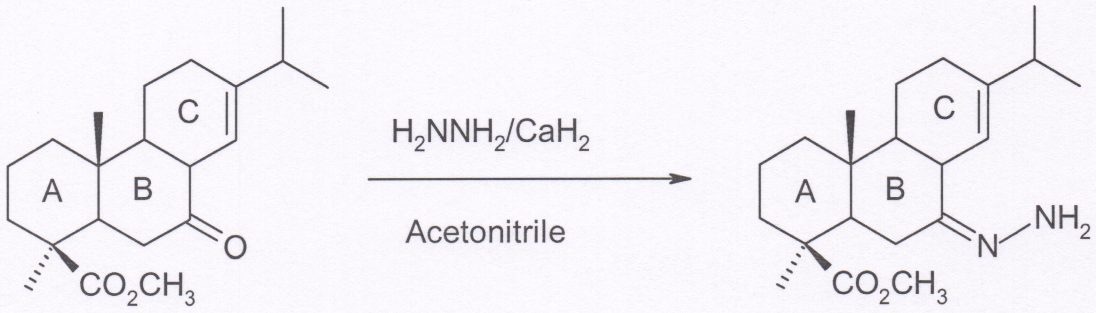


Methyl Abietate Ketone

The next step in the synthesis yields an oxidized B-ring, which breaks the double bond on the B-ring and yields a ketone[3]. 157 mg (0.496 mmol) of methyl abietate was placed into 42.73 ml of ethyl ether and 0.92 ml of water. 1.026 g of potassium bicarbonate ($KHCO_3$) (10.26 mmol) and 0.488 g (1.92 mmol) of iodine (I_2) was then added to the solution. The mixture was allowed to stir for 4 hours at 30°C. After 4 hours, the mixture was washed twice with 15 ml of water followed by 15 ml of 2 N sodium thiosulfate and again with 3 x 15 ml of water. The organic solution that was

collected was dried over anhydrous sodium sulfate and evaporated to yield a cloudy yellow oil. The product was purified on a silica gel column (5:1 Cyclohexane/Ethyl Acetate) to yield a colorless oil.

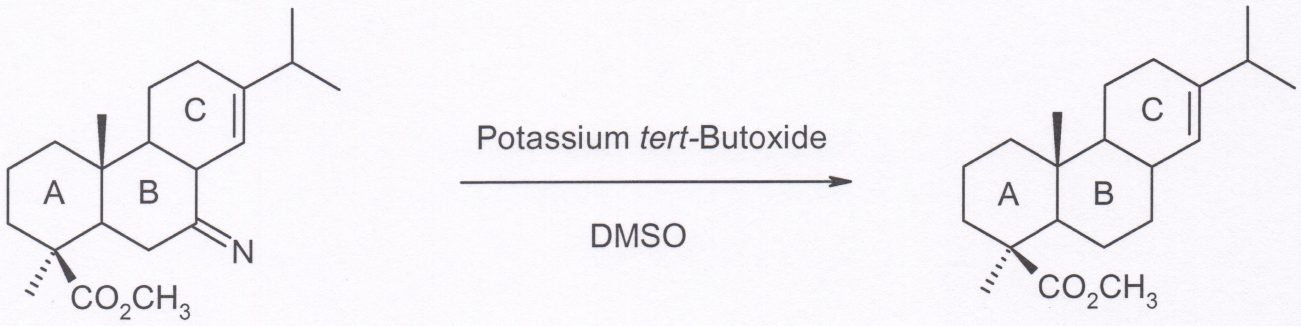
Formation of Hydrazone



Ketone Hydrazone

This is the first step in the Wolff-Kisner reduction of a ketone to a methylene group. The first step involves converting the ketone to a hydrazone. To 0.500 g of calcium hydride (CaH_2), 5 ml of anhydrous acetonitrile was added. The flask was cooled in an ice bath. 1 ml of hydrazine monohydrate was added to the flask. When the reaction was done, the solid was filtered off using a milipore filter. The liquid was then added to 250 mg of the ketone. The reaction was stirred for 7 days at room temperature, and evaporated to give the hydrazone, which appears as orange crystals.

Reduction of Hydrazone



Hydrazone

The second and final step of the Wolff-Kishner Reduction involves converting the hydrazone into a methylene group. 0.250 g of potassium *tert*-butoxide was added to 5 ml of dimethyl sulfoxide (DMSO) at room temperature. After the potassium *tert*-butoxide was dissolved in the DMSO, the hydrazone was added very slowly over a 6-hour period. This was to prevent the formation of the azine, which is a side product of the reaction. After the first couple of additions, the solution turned deep red, indicating the release of nitrogen gas (N_2). After a few minutes, the solution turned back to orange. After a couple of hours however, the solution remained deep red. After the all the additions were made, the reaction was stirred overnight.

After stirring overnight, the reaction suspension was diluted with 50 ml of methylene chloride. The suspension was washed with 20 ml of water and the aqueous layer was separated. The organic layer was then washed again with 20 ml of water and with 10 ml of saturated brine solution. The organic layer was then dried over magnesium sulfate and evaporated to yield a yellow oil.

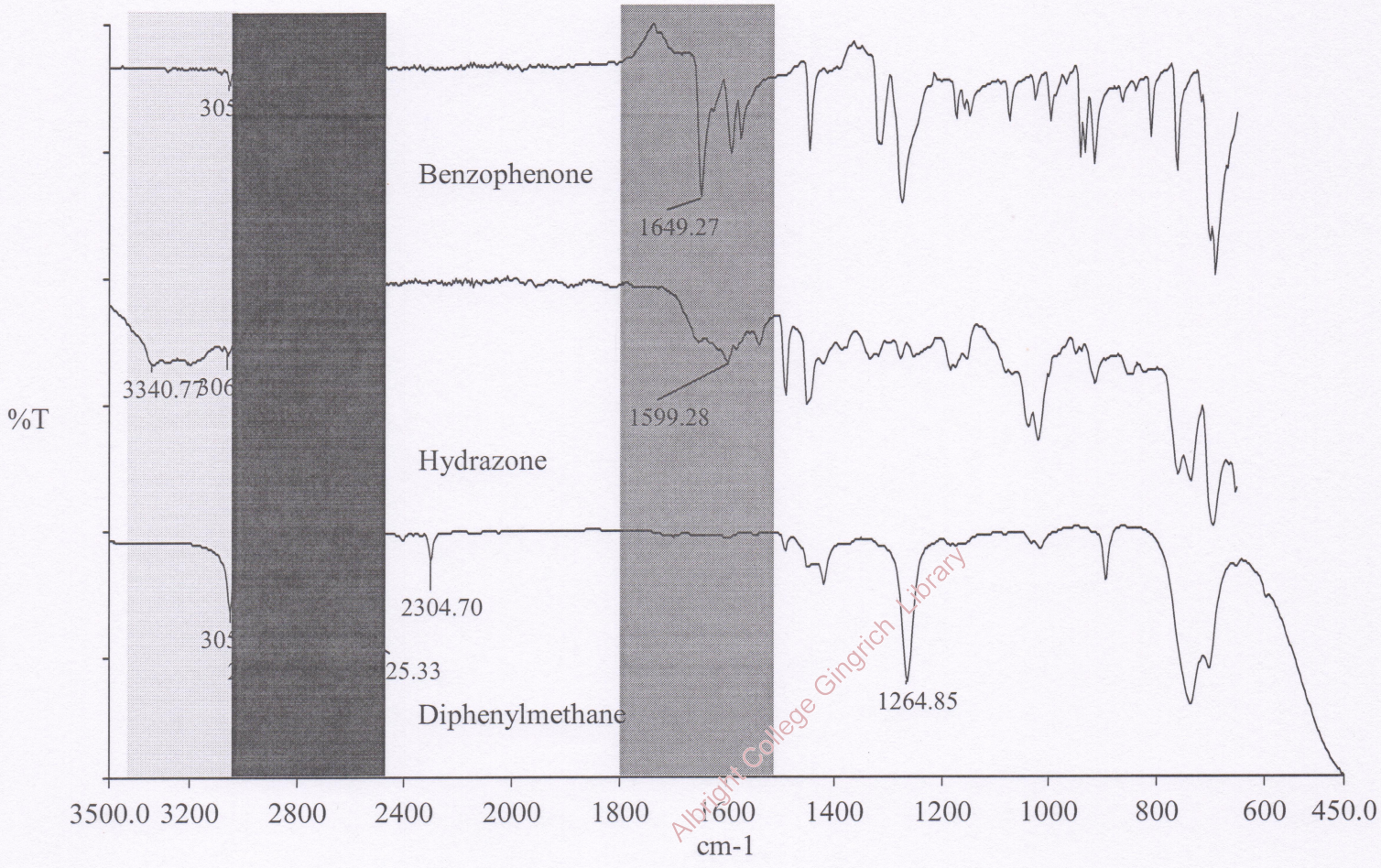
Data and Results

To confirm that the reaction produced the desired product, numerous instruments and techniques were used. These techniques included infrared spectroscopy, nuclear magnetic resonance, and melting point (when applicable). The infrared spectra will discern the different functional groups present in the molecule. The ^{13}C nuclear magnetic resonance spectra will discern the different carbon environments present in the molecule. Correlation tables will be used to assign peaks and functional groups[7]. The melting point techniques apply for the crystal solids that are formed. The melting point of crystal tells about the purity of the crystals and is specific for the compound. This technique helps identify compounds that are solids.

The specific data for the first four steps in the synthetic pathway is presented in the appendix. The appendix includes the yield data, melting point (when applicable), and IR analysis. The first four steps in the synthetic pathway have been optimized pertaining to yields, purity, etc. The individual spectra are presented as attachments 1-3

The major part of the research focused on the Wolff-Kishner reduction of the advanced intermediate. The reaction is two separate steps, the first being the formation of a hydrazone intermediate. Using a strong base, the hydrazone can then be reduced to a methylene group. The reaction can be followed by infrared spectroscopy. The disappearance of the carbonyl group and the appearance of an N-H stretch around 3300 cm^{-1} discerns the starting material from the hydrazone intermediate. The intermediate and the product of the reaction can be differentiated by the disappearance of the N-H stretch and the formation of a new C-H peak in the C-H stretch region[7].

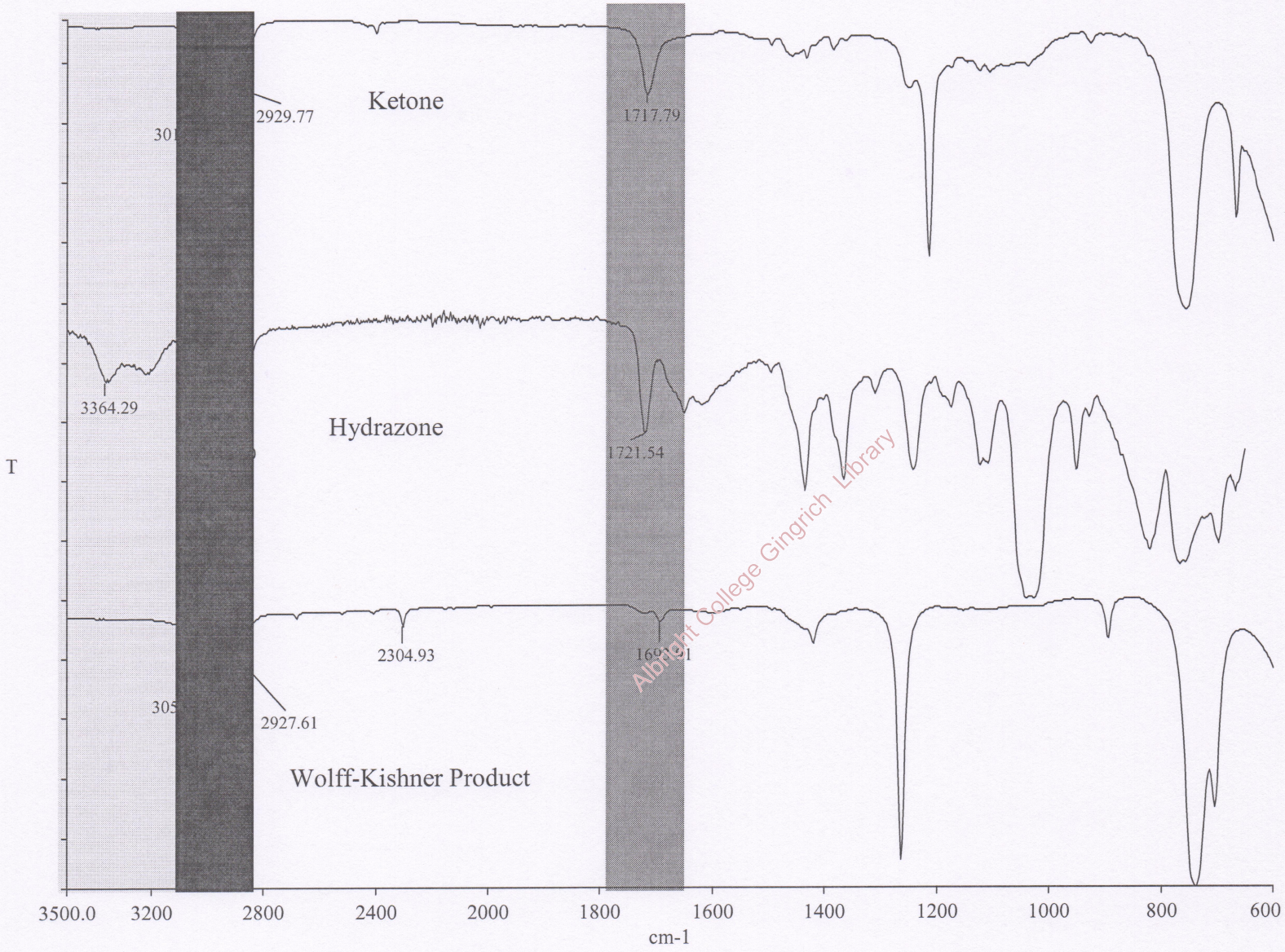
Before the Wolff-Kishner Reduction was preformed on the advanced intermediate, a model compound was studied. This was done to test the procedure in order to find any problems with the procedure[8]. This avoids the loss of the intermediate. The compound that was chosen was benzophenone. We chose benzophenone due to the availability and cost of the compound. The results are given in Figure 4. The individual spectrum of each compound is attached as attachments 4-6.



(Figure 4)

The shaded boxes indicate the specific region based on correlation tables[7]. The yellow region highlights the N-H stretch region, the green region highlights the C-H

stretch region, and the red region highlights the C=O region. The starting material does not have the presence of the N-H stretch, but is present in the hydrazone intermediate at 3341 cm^{-1}. It can then be discerned that the hydrazone was formed in the intermediate. In addition, the carbonyl present at 1649 cm^{-1} in benzophenone disappeared in the hydrazone intermediate and in the spectra for diphenylmethane. This is consistent with the reduction of the carbonyl group. These spectra are consistent with the reduction of a ketone to a methlylene group with a hyrdazone intermediate.



(Figure 5)

Figure 5 shows the IR spectra for the advanced intermediate, hyrdazone, and Wolff-Kishner product. The same correlation table and color scheme is used in Figure 5 as in Figure 4. Again, the appearance of an N-H stretch in the hydrazone and disappearance of the stretch in the product discerns the presence of a hydrazone. The carbonyl region is harder to follow, due to the presence of two carbonyls in the ketone. The individual spectra are attached as attachments 7-8

^{13}CNMR spectra were also obtained for the benzophenone series and for my advanced intermediate. Table 1 shows the ^{13}C peaks for the central carbon. The carbon of interest is marked by an (*). Correlation tables were used to assign the peaks[7]. To assign the C=N present in the hydrazone another correlation was used[9]. Table 2 shows the ^{13}C spectra for the advanced intermediate. The carbonyl carbon is the highlighted carbon marked by an (*).

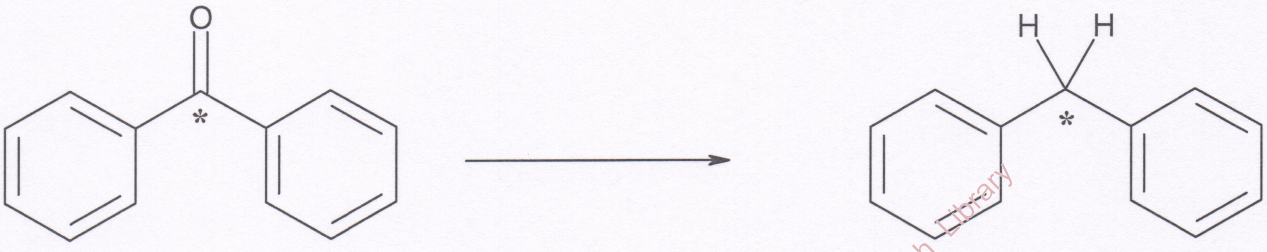


Table 1

Compound	Signal (ppm)	Structure
Benzophenone	197	C=O
Hydrazone	145	C=N
Diphenylmethane	30	C-H

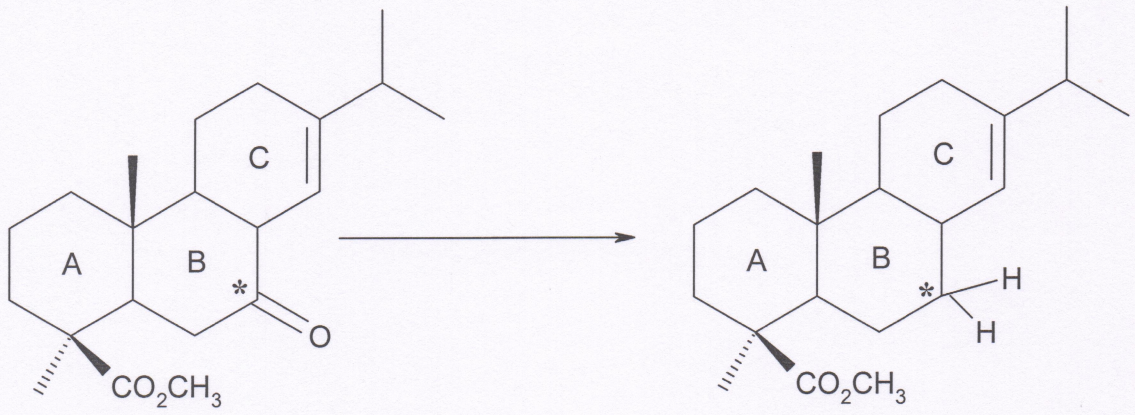


Table 2

Compound	Signal (ppm)	Structure
Ketone	178	C=O
Hydrazone	145	C=N
Wolff-Kishner Product	43	C-H

Conclusions and Future Work

The first four steps in the synthetic pathway have been confirmed and optimized. Various instrumental techniques have been used to analyze these products. These techniques include melting point, IR, and thin-layer chromatography (TLC). Notice in appendix 1, the changes in the IR spectra from the abietic acid to the ketone intermediate. The melting points taken on the abietic acid salt and abietic acid indicate pure crystals. Thin-layer chromatography also indicates purity in the column-purified ester and ketone.

The focus of the research that was conducted was the Wolff-Kishner reduction of the ketone. These reaction conditions have not been optimized, thus yield data is not presented. The primary focus was on performing and analyzing the reaction on a model

compound and the advanced intermediate. The next step in the research is to analyze the reaction conditions of the Wolff-Kishner reduction and devise conditions that will produce the highest possible yield.

Based on the spectra data for the model compound, it can be discerned that the reduction has occurred. The presence of an N-H stretch and the disappearance of the carbonyl group in the intermediate, indicate the formation of the hydrazone. The disappearance of the N-H stretch and the presence of only C-H stretch in the functional group region in the product, it can be discerned that the desired product was obtained. ^{13}CNMR spectra complement the IR data obtained as shown in Table 1.

The data for the advanced intermediate made it more difficult to come to a specific conclusion. The presence of the ester carbonyl makes the reaction more difficult to follow. It can be discerned based on the IR data that an N-H stretch was formed in the hydrazone. It can be questioned though as to which carbonyl they hydrazine reacted with. It is possible that the hydrazone could have reacted with the ester carbonyl instead of the ketone. The IR data also shows the reduction of the hydrazone, and a shift in the carbonyl peak in the product.

The ^{13}CNMR data is as questionable as the IR data. The number of nearly equivalent carbons makes it difficult to follow where the new C-H peak lies in the spectrum. The presence of another carbonyl also poses a challenge as to assigning the carbonyl that undergoes the reduction.

The next step in the research is a complete analysis of the hydrazone intermediate and the product of the Wolff-Kishner reduction. ^{1}HNMR studies can also be conducted

as a complement to the ^{13}CNMR and IR data. An HPLC experiment could possibly be used to further characterize the hyrdazone and product.

After the completion of the Wolff-Kishner reduction, the next step in the synthesis is the opening of the C-ring using ozonolysis. This will open the C-ring and allow for future reactions that will lead to the closing of the 5-membered cyclic ether ring.

Physical Properties of Chemicals used

The following list contains all the chemicals used during the research and their physical properties. The data was obtained from the Merck Index[6] and the Arcos Catalog[10]. The abbreviations are as followed: mp- melting point, bp- boiling point, and d- density at a given temperature.

abietic acid- $C_{20}H_{30}O_2$, 302.46 g/mol, mp 172-175 ºC, insoluble in water, soluble in benzene, chloroform, ether, acetone, carbon disulfide, and dilute sodium hydroxide solution

methyl abietate- $C_{21}H_{32}O_2$, 316.48 g/mol, colorless to yellow thick liquid, d^{20} 1.040 g/ml, bp 360-365 ºC, index of refraction @ 20 ºC 1.530, insoluble in water, soluble in usual organic solvents

cyclohexylamine- $C_6H_{13}N$, 98.18 g/mol, liquid strong amine odor, d^{20} 0.8647 g/ml, mp -17.7 ºC, bp 134.5 ºC, index of refraction @ 25 ºC 1.4565, miscible in water and organic solvents

acetone (2-propanone)- C_3H_6O, 58.08 g/mol d^{25} 0.788 g/ml, bp 56.5 ºC, mp -94 ºC, index of refraction @ 20ºC 1.3591, miscible with water and organic solvents

methanol (wood alcohol)- CH_4O, 32.04 g/mol, d^{20} 0.7915 g/ml, mp -97.8 ºC, bp 64.7 ºC, miscible with water and most organic solvents

hydrochloric acid- HCl, 36.46 g/mol, d 1.268 g/ml, mp -114.22 ºC, bp 85.05 ºC

chloroform (trichloromethane)- $CHCl_3$, 119.38 g/mol d^{20} 1.484 g/ml, bp 61-62 ºC, mp -63.5 ºC index of refraction @ 20 ºC 1.4476

magnesium sulfate – $MgSO_4$, 120.37 g/mol

lithium hydroxide monohydrate- $LiOH * H_2O$, LiOH 23.95 g/mol, d 2.54, mp 471 ºC

dimethyl formamide (DMF)- C_3H_7NO, 73.09 g/mol, mp -61ºC, bp 53 ºC, d^{25} 0.9445 g/ml, index of refraction @ 20 ºC 1.42803

dimethyl sulfate (DMS)- $C_2H_6O_4S$, 126.13 g/mol, bp 188 ºC, mp -27ºC d^{20} 1.3322 g/ml, index of refraction @ 20 ºC 1.3874

n-hexane- C_6H_{14}, 86.18 g/mol, bp 64 ºC, mp -100 ºC, index of refraction @ 20 ºC 1.375.

sodium bicarbonate- $CHNaO_3$, 84.01 g/mol

ethyl acetate- $C_4H_8O_2$, 88.10 g/mol, bp 77 ºC, mp -83 ºC, index of refraction @ 20 ºC 1.3719

methlylene chloride- CH_2Cl_2, 84.94 g/mol, bp 39.75 ºC, d^{20} 1.3255

hydrazine hydrate- H_6N_2O, 50.06 g/mol, bp 118-119 ºC, d^{21} 1.03

benzophenone- $C_{13}H_{10}O$, 182.22 g/mol, mp 48.5 ºC

potassium *tert*-butoxide- C_4H_9OK, 112 g/mol, mp 256-258 ºC

dimethyl sulfoxide- C_2H_6OS, 78.13 g/mol, d^{20} 1.11, mp 18.55 ºC, bp 189 ºC, index of refraction at 20 ºC 1.478

calcium hydride- CaH_2, 42.09 g/mol

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Appendix

Isolation of Salt

Yield: 80%

Mp (ºC): 197-198

Isolation of Abietic Acid

Yield: 59%

Mp (ºC): 149.0-149.5

IR Analysis (attachment 1)

Peak (cm^{-1})	Structure Assignment
2931	O-H stretch
2775	C-H stretch
1686	C=O (carboxylic acid)

Methylation of Abietic Acid

Yield: 90%

IR Analysis (attachment 2)

Peak (cm^{-1})	Structure Assignment
2925	C-H stretch
2850	C-H stretch
1728	C=O (ester)

Oxidation of Methyl Abietate

Yield: 50%

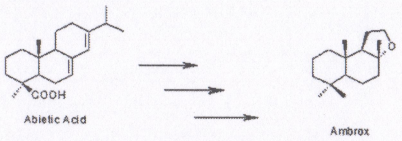
IR Analysis (Attachment 3)

Peak (cm^{-1})	Structure Assignment
2924	O-H stretch
2851	C-H stretch
1717	C=O (ketone/ester)

The Synthesis of Ambrox from Chinese Pine Rosin

by Gary Willman and Dr. Christian Hamann
Albright College, Reading PA

Objective



The Importance of This Synthesis

Find a "cheap and easy" way of making Ambrox

Use a natural starting material that is a abundant and easily accessible in nature

Give the perfume industry a cheaper way synthesizing Ambrox, which in turn may lower the cost of perfumes containing Ambrox

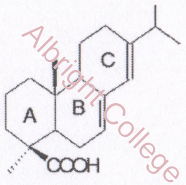
Gain a better understanding of the chemistry of terpenes

Abietic Acid

Abietic acid is my starting material for this synthesis

Abietic acid is easily isolated from pine rosin

Abietic acid is a member of a class of compounds called terpenes



Terpenes

Terpenes are a class of compounds with units of 10 carbon atoms in the molecule

Diterpenes are compounds with 20 carbon atoms

Abietic acid is a diterpene

Terpenes are found abundantly in nature

Carvones are terpenes that are responsible for caraway, spearmint, and dill odors

Other familiar terpene odorants are camphor, menthol, and farmesol (lilly-of-the-valley)

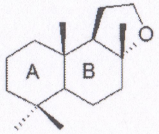
Vitamin A is a terpene that is vital in human biochemistry (eyesight)

Ambrox

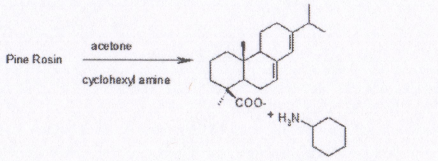
Used by the perfume industry as a fixative

Very expensive chemical and is in very high demand

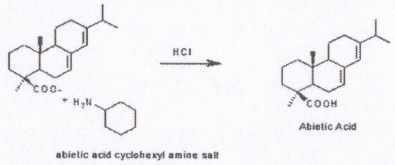
The synthesis of ambrox from (-)-scareol is the only synthesis currently used by industry



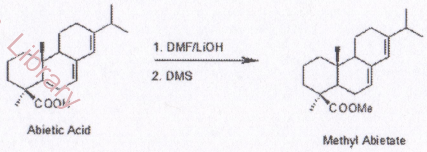
Isolation of Abietic Acid Salt



Acidification of Abietic Acid Salt

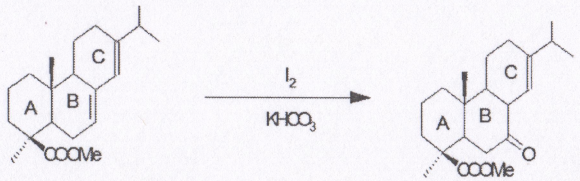


Methylation of Abietic Acid



DMF: N,N-dimethyl formamide
DMS: dimethyl sulfate

Oxidation of B-Ring



Progress Report

Successfully isolated abietic acid from pine rosin

Successfully executed the first four steps in the synthetic pathway

Have verified each step along synthetic pathway by various instrumental techniques; Infrared Spectrometry and Nuclear Magnetic Resonance are examples

Conclusions

Was able to purify the products of each step using column chromatography on silica gel

Overall yield data was acceptable, which confirms the effectiveness of each step

Have not been able to verify the product of the ketone in the oxidation step with Infrared Spectrometry and Nuclear Magnetic Resonance.

More investigations have to be preformed to confirm the oxidized product before the next step in the synthetic pathway can be explored

Acknowledgments

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