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Dihydropyran Formation by a Two Step Process

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Dihydropyran Formation by a Two Step Process

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James Zachary Wright

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Abstract

The 2, 6-disubstitued dihydropyran is produced by a two step process, involving a Suzuki Miyaura Cross Coupling reaction followed by an intramolecular ring closing Michael Addition reaction. In this project a vinyl boronic acid, 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole, was coupled with cis-ethyl-iodo-acrylate to yield ethyl 2E,4Z,8E-9-phenyl-7-hydroxy-2,4,8-nonatrienoate, which is capable of undergoing an intramolecular Michael addition to form the dihydropyran. The geometry of the cis enolate and the conjugated double bonds of the coupled product are such that under basic conditions a Michael addition is feasible. Throughout the project, the reaction conditions for high yields of Suzuki product were determined. Dihydropyrans were produced and verified by proton NMR. It was also established that dihydropyrans can be prepared in a single-pot synthesis, although this method is not yet optimized.

Acknowledgements

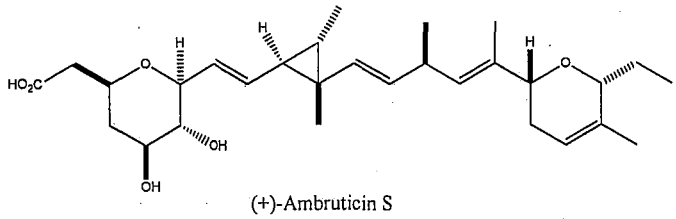
The material of this report was made possible by research which was supported by the National Science Foundation under Grant No. (0704050). I would also like to thank my research advisor Dr. LuAnne McNulty, as well as other students including Lindsey Fuller, Jeni Bishop, Stephanie Steele and Erica Hunt. I would also like to thank the Butler University Chemistry Department as well as the Butler University Honors Program for the great amount of support and resources made available for me throughout my undergraduate research and thesis writing process.

Abbreviations Used

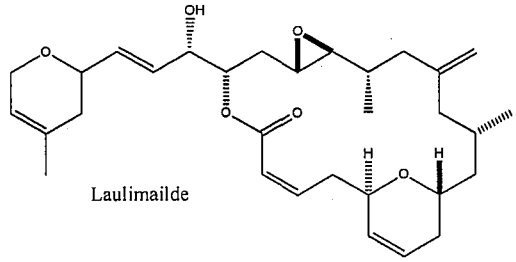
- Grams-g.
- Millimols-mmol
- Equivalents-eq
- Millimeters-mL
- Parts per million-ppm
- Celcius-C
- Minutes-min
- Pressure per Square Inch-PSI

Introduction

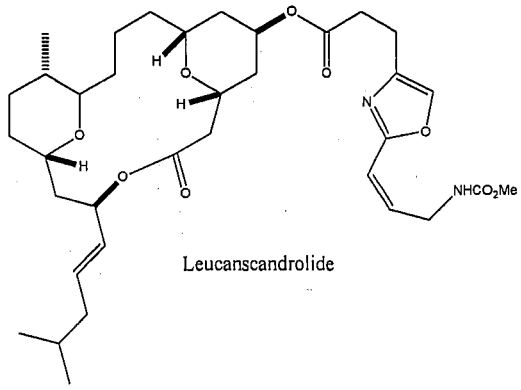
Dihydropyrans are found in a variety of biologically active natural products. The dihydropyrans are usually di- or tri-substituted, such as Laulimalide[1] and Ambruticin S[2]. Synthetic methods for the production of dihydropyrans can be extended to generate substituted tetrahydropyrans through hydrogenation, which could lead to the tetrahydropyran moiety of Leucanscandrolide[3].



(+)-Ambruticin S

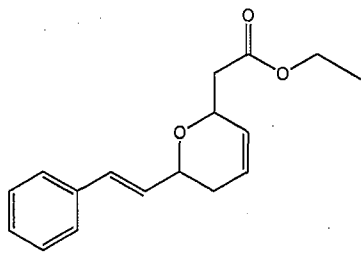


Laulimailde



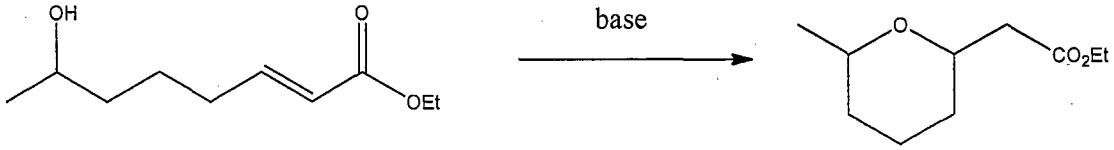
Leucanscandrolide

The goal of this project is to develop a simple two step synthesis of dihydropyrans. Although other synthetic methods are available, most involve complex starting materials as well as difficult reaction conditions. The proposed method differs in that the starting materials are simple and relatively easy to prepare, allowing for a convenient synthetic method.



2-(1-carboethoxymethyl)-6-(2-phenylethenyl)-3,4-dihydropyran

It is known that tetrahydropyran can be formed by way of an intramolecular Michael Addition[4] (shown below). However, the synthesis of dihydropyran molecules, using this type of procedure has not yet been reported.

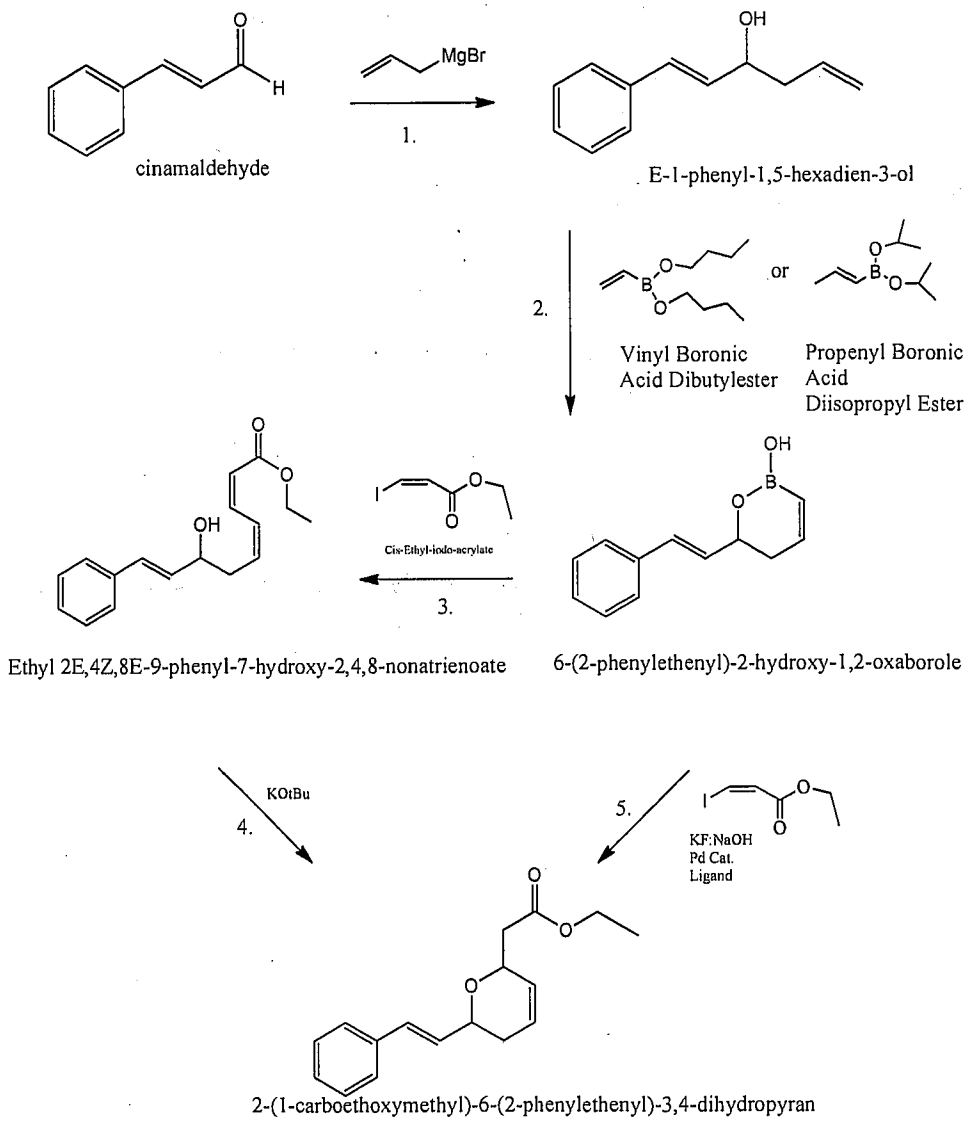


In order to use an intramolecular Michael addition in the formation of dihydropyran it is necessary to first make a substrate that is capable of undergoing this type of reaction. In the case of this project, I will use ethyl 2E,4Z,8E-9-phenyl-7-hydroxy-2,4,8-nonatrienoate. This molecule will be formed by doing a Suzuki Miyaura reaction. The Suzuki reaction is a common synthetic tool used in organic chemistry to create carbon-carbon bonds. This type of reaction involves the coupling of boronic acids and alkyl, aryl, or alkenyl halides. The Suzuki reaction in this experiment involves a cyclic boronic acid, a ligand *(BINAP and BH_4,), base, palladium catalyst, THF solvent, and an alkenyl halide. The alkenyl halide that will be used is *cis*-3-iodoacrylate (Sigma Aldrich), which should yield a product that is capable of undergoing an intramolecular Michael Addition reaction.

The reaction proceeds stereoselectively and yields a *cis* alkene at the location of the newly formed carbon-carbon bond. The *cis* conformation is significant because the orientation of the double bond and –OH functional groups are such that an intramolecular Michael Addition reaction can occur with the addition of a base, such as KOtBu (second step of dihydropyran

formation). It should be noted that intramolecular Michael Addition is not always possible, it depends on the identity of the alkyl, aryl, or alkenyl halide coupled with the boronic acid.

The approach to dihydropyrans in this project involves a Suzuki Miyaura coupling reaction of a cyclic vinylic boronic acid followed by an intramolecular Michael Addition reaction. The long term goal of this avenue of investigation is to accomplish both transformations in a tandem process in the same reaction vessel.



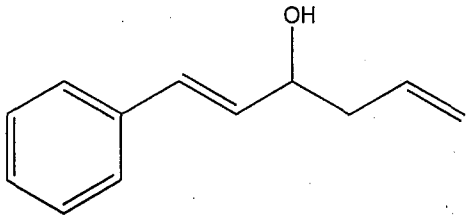
Scheme 1- The above reaction scheme indicates the reaction pathway that was followed throughout the project to prepare2-(1-carboethoxymethyl)-6-(2-phenylethenyl)-3,4-dihydropyran

As shown in the scheme, page 6, the project starts with a Grignard reaction in order to prepare a homoallylic alcohol, which will be used to form the starting material for the project. A critical part of this reaction sequence is the production of the boronic acid starting material. Vinyl boronic acids are very useful in the synthesis of organic molecules. Microwave synthesis of cyclic vinyl boronic acids has been accomplished in the McNulty laboratory. Boronic acids can be produced using both vinyl boronic acid dibutylester and 1-propenyl boronic acid diisopropyl ester. These two compounds react with a variety of homoallylic alcohols to form 6-membered cyclic vinyl boronc acids. The boronic acids formed are capable of undergoing cross coupling reactions, such as Suzuki reactions, which retain the *cis*-geometry of the alkene, as well as liberate the oxygen and allows for further reactions to take place. Once boronic acid is prepared it will be possible to perform the reactions of interest to this particular project, as 2-(1-carboethoxymethyl)-6-(2-phenylethenyl)-3,4-dihydropyran will be formed by a Suzuki Miyaura reaction followed by an intramolecular Michael addition.

It is important to note that although other methods exist for the preparation of dihydropyran molecules, DHPs have not been generated in this fashion previously. The results of this project will indicate the usefulness of this synthetic procedure for the production of dihydropyrans. It is the goal that this method will be found to be a relatively simple and quick way to create dihydropyran molecules.

Experimental

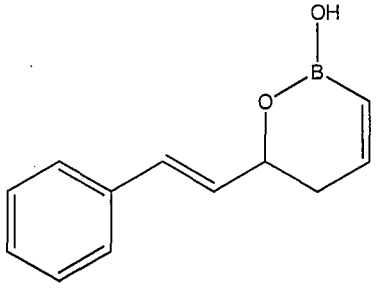
_E_-1-phenyl-1,5-hexadien-3-ol



To a stirred solution of cinnamaldehyde 0.4 g (30 mmols, 1eq) in 60 mL of THF, at 0 °C, Nitrogen gas was added allylmagnesium bromide 39.35 mL (39 mmols, 1.3 eq) was then added. Then 10 mL of HCl was added. The reaction mixture was stirred for an additional hour, and diluted with 20 mL of diethyl ether. The organic layer was washed with water (three times) and then 30 mL of brine. The aqueous washes were extracted with 10 mL of diethyl ether. The combined organic portion was dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the impure alcohol. The alcohol was purified by column chromatography to provide 2.62 g (50.3% yield) of alcohol.

^{1}H-NMR ($CdCl_3$) δ(ppm) 7.4-7.2 (m, 5H) aromatic hydrogen, 6.6-6.5 (d, 1H, C1-H) alkenyl hydrogen, 6.3-6.3 (dd, 1H, C2-H) alkenyl hydrogen, 5.8 (m, 1H, C5-H) terminal alkene hydrogen, 5.2-5.1 (m, 2H, C6-H) terminal alkene hydrogen, 4.4 (dd, 1H, C3-H) hydrogen near an electrophilic atom, 2.4 (m, 2H, C4-H) sp^3 hydrogen [Spectra A].

6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole



Procedure for 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole, formation with vinyl boronic acid dibutyl ester

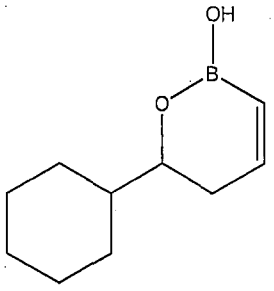
To a round bottom flask with 12 mL of CH_2Cl_2 under N_2, 0.37 g (0.46 mmols, 0.09 eq) of Grubbs First Generation catalyst was added. The stirred reaction mixture was degassed with nitrogen, then 1 g (5.7 mmols, 1 eq) of **alcohol* followed by 2.75 g (14 mmols, 2.5 eq) of vinylboronic acid dibutyl ester was added to the reaction mixture. The solution was degassed for two to three additional minutes, then was heated to reflux.

After 12 hours, the solution was concentrated. The resulting mixture was purified by column chromatography on silica gel with 90:10 hexanes to ethyl acetate as the elution solvent. As the purification process went on, the elution solvent was adjusted to increase the polarity of the solvent. The resulting 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole product had a yield of 84.2%, 1.07 g. ^{1}H-NMR ($CdCl_3$) δ (ppm) 7.5-7.2(m, 5H) aromatic hydrogens, 6.9(d, 1H) alkenyl hydrogen, 6.7-6.6(d, 1H) alkenyl hydrogen, 6.3 (dd, 1H) alkenyl hydrogen , 5.8(d, 1H) alcohol hydrogen, 4.7(m, 1H) alkenyl hydrogen, 4.2(s, 1H) alkenyl hydrogen, 2.4(m, 2H) sp^3 hydrogens

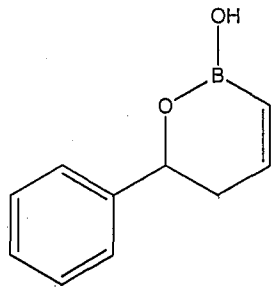
Spectra B

**The alcohols used in the synthesis dictated the final product. For instance E-1-phenyl-1,5-hexadien-3-ol was used to make 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole, however 1-phenyl-3-buten-1-ol and 1-cyclohexyl-3-buten-1-ol were used to make 6-phenyl-2-hydroxy-1,2-oxaborole and 6-cyclohexyl-2-hydroxy-1,2-oxaborole.*

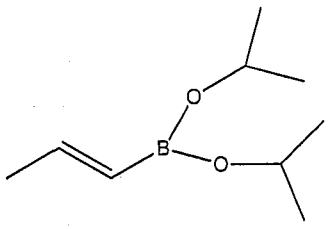
6-cyclohexyl-2-hydroxy-1,2-oxaborole



6-phenyl-2-hydroxy-1,2-oxaborole



Two additional cyclic boronic acids were prepared using the same method as described above. However the homoallylic alcohol, *E*-1-phenyl-1,5-hexadien-3-ol used in the procedure above, was replaced with 1-cyclohexyl-3-buten-1-ol and 1-phenyl-3-buten-1-ol to yield 6-cyclohexyl-2-hydroxy-1,2-oxaborole and 6-phenyl-2-hydroxy-1,2-oxaborole, respectively. These molecules were verified by ^{1}HNMR. The 6-cyclohexyl-2-hydroxy-1,2-oxaborole compound (yield of 52.4 %, 0.91 g), when analyzed by proton NMR exhibited the following splitting: ^{1}H-NMR ($CdCl_3$) δ(ppm) 6.6 (d, 1H, J=11.8 Hz) sp^3 hydrogen adjacent to electrophilic atom, 5.66 (d, 1H, J=12 Hz) alcohol hydrogen, 3.89 (br s, 1H) alkenyl hydrogen, 3.79 (q, 1H, J=7.3 Hz) alkenyl hydrogen, 2.2-2.15 (m, 2H) sp^3 hydrogen, 1.9-0.9 (m, 11H)sp^3 hydrogens attached to cyclohexyl group **Spectra C**. While, 6-phenyl-2-hydroxy-1,2-oxaborole (yield of 52.9%, 0.92g) compound showed the following splitting pattern: ^{1}H-NMR ($CdCl_3$) δ(ppm) 7.32-7.19 (m, 5H) aromatic hydrogen, 6.94-6.89 (m, 1H) sp^3 hydrogen adjacent to electronegative atom, 5.8 (d, J=11.25 Hz, 1H) alkenyl hydrogen, 5.11-5.04 (m, 1H) alkenyl hydrogen, 4.06 (s, 1H) alcohol hydrogen, 2.48-2.37 (m, 2H)sp^3 hydrogen **Spectra D**.

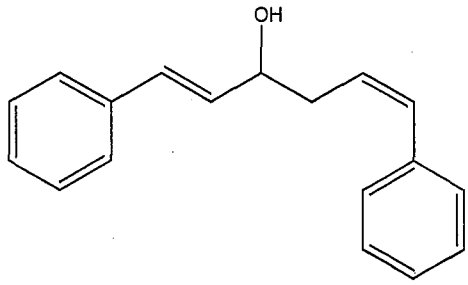


Procedure for the synthesis of Propenyl Boronic Acid diisopropyl ester

To a 500 mL round bottom flask with 50 mL of THF at -10 °C under N_2 was added trimethyl borate, 4.46 mL (40 mmols). Propenyl magnesium bromide, 100 mL (50 mmols), was addedto the reaction flask, using an addition funnel. The reaction mixture was stirred at -10 °C for an hour, then 10mL of 30% HCl was added. The solution was stirred for an additional hour.

The organic extracts were washed with water and brine. The aqueous layer was extracted three times with diethyl ether, and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give B-(1E)-propenyl boronic acid. Isopropyl alcohol, 1.1 g (40 mmols), was added to the flask. A Dean Stark trap and condenser were placed on top of the RBF. The reaction mixture was allowed to reflux for 8(+) hours, until no additional H_2O was collected. The solution was concentrated under reduced pressure to give 6.81 g of propenyl boronic acid diisopropyl ester. ^{1}H-NMR ($CdCl_3$) δ(ppm) 6.3 (m, 1H) alkenyl hydrogen, 5.5-5.4 (d, 1H) alkenyl hydrogen, 4.4 (m, 2H) sp^3 hydrogens, 1.9 (d, 3H) sp^3 hydrogens, 1.2 (m, 12H) sp^3 hydrogens [Spectra E].When pr openyl boronic acid diispropyl alcohol was used to prepare 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole the reaction resulted in 2.07g (79.8% yield) of product. The yield was very similar to the preparation of 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole when using vinyl boronic acid dibutyl ester, which means this was useful a secondary method

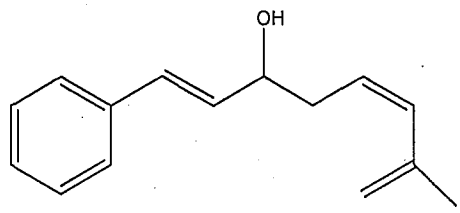
***E*, 5*Z*-1,6-diphenyl-1,5-hexadien-3-ol**



To a microwave vial containing a stir bar 0.095 g (0.477 mmols, 1.5 eq) of boronic acid; 0.21 g (0.636 mmols, 2.0 eq) of $CsCo_3$ and 0.11 g (0.0095 mmols, 0.03 eq) of $Pd(PPh_3)_4$ was added. The vial was capped and placed under nitrogen gas. THF, 1.6 mLs, and bromobenzene, 0.035 mL (0.318 mmols, 1 eq), were added. The reaction mixture was degassed with nitrogen for two to three minutes. The solution was heated to 90 °C, 100 watts, 200 PSI, and allowed to react for 20 minutes in the microwave.

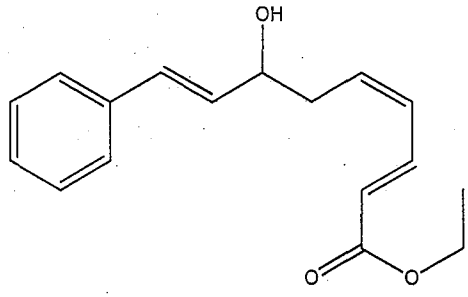
The organic layer was washed three times with water (10 mL) and once with brine(15 mL). The combined aqueous layers were extracted with ether. The combined organic products were dried over $MgSO_4$ and filtered, and concentrated under reduced pressure. The resulting product was purified by column chromatography to give 0.049 g (61.6% yield) of *E*, 5*Z*-1,6-diphenyl-1,5-hexadien-3-ol. ^{1}H-NMR splitting including the following peaks: ^{1}H-NMR ($CdCl_3$) δ (ppm) 7.3-7.1 (m, 5H) aromatic hydrogens, 6.5-6.6 (d, 2H, C1-H, C6-H) alkenyl hydrogens, 6.2 (dd, 1H, J=6.36Hz, 14.4Hz, C2-H) alkenyl hydrogen, 5.75 (dt, 1H, J = 6.9 Hz, 11.6 Hz) alkenyl hydrogen, 4.5-4.35 (m, 1H, C3-H) sp^3 hydrogen adjacent to an electrophilic atom, 2.75-2.65 (m, 2H, C4-H) sp^3 hydrogen, 1.73 (buried under Water, 1H, OH) alcohol hydrogen [Spectra F].

_E_, 5_Z_-7-methyl-1-phenyl-1,5,7-octatrien-3-ol



The same procedural method described above was used to prepare 1*E*, 5*Z*-7-methyl-1-phenyl-1,5,7-octatrien-3-ol (3). Instead of using bromobenzene as the aryl group, 2-bromopropene was used. The reaction resulted in 0.062 g (70% yield) of 1*E*, 5*Z*-7-methyl-1-phenyl-1,5,7-octatrien-3-ol, which was analyzed by proton NMR, ^{1}H-NMR ($CdCl_3$) ($CdCl_3$) δ(ppm) 7.5-7.2 (m, 5H) aromatic hydrogens, 6.7-6.6 (d, 1H, C1-H) alkenyl hydrogen, 6.3-6.1 (dd, 1H, C2-H) alkenyl hydrogen, 6 (d, 1H, C6-H) alkenyl hydrogen, 5.5 (m, 1H, C5-H) alkenyl hydrogen, 5-4.9 (d, 2H, C8-Hs) alkenyl hydrogen, 4.4 (s, 1H, C3-H) sp^3 hydrogen adjacent to an electrophilic atom, 2.7 (m, 2H, C4-Hs) sp^3 hydrogens, 1.8 (s, 1H, C7-H)alkenyl hydrogen [Spectra G].

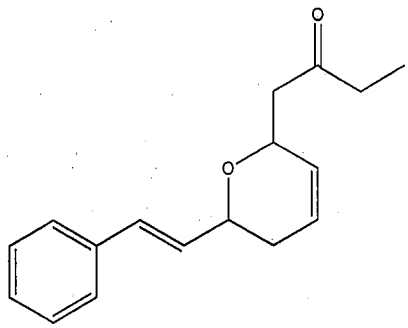
Ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate



To a microwave vial containing a stir bar, 0.05 g (0.25 mmols, 1.1 eq) of boronic acid, 0.046 g (0.007 mmols, 0.05 eq) of $Pd(OAc)_2$, 0.0042 g (0.007 mmols, 0.05 eq) of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), and THF (1mL) were added and the solution was degassed with Nitrogen gas. *Cis*-ethyl-iodo-acrylate, 0.052 g (0.23 mmols, 1 eq), and 2M sodium hydroxide, 0.46 mLs, were added. The solution was allowed to stir and degass for a few minutes. The reaction was run in the microwave for 60 min, at 90 °C and 150 watts.

The reaction mixture was diluted with diethyl ether, and then saturated ammonium chloride was added. The organic layer was washed three times with water (10 mL) and once with brine (15 mL). The aqueous layer was extracted with ether. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography to give 0.17 g (61.5% yield)of ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate. ^{1}H-NMR ($CdCl_3$) δ(ppm) 7.5 (dd, 1H, J = 8.75 Hz), 7.25-7.18 (m, 5H) aromatic hydrogen, 6.55 (d, 1H, J = 16 Hz) alkenyl hydrogen, 6.26-6.13, (m, 2H) sp^3 hydrogens, 5.9-5.81 (m, 2H) sp^3 hydrogens, 4.38-4.32 (m, 1H) alkenyl hydrogen, 4.14 (q, 2H, J = 7.25 Hz) sp^3 hydrogen, 2.64-2.58 (m, 2H) sp^3 hydrogens adjacent to an electrophilic atom, 1.2 (t, 3H, J = 7.25 Hz) sp^3 hydrogens [Spectra H].

2-(1-carboethoxymethyl)-6-(2-phenylethenyl)-3,4-dihydropyran



Procedure for Dihydropyran Synthesis by Two Steps

The first step of this method involves running the Suzuki reaction to produce ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate in the same fashion as described above. At the conclusion of the reaction, potassium *tert*-butoxide (0.07 g) was added to the Suzuki product, in 1 mL of THF. The reaction was run in the microwave for an additional 30 min, at 90 °C and 150 watts.

The reaction mixture was diluted with diethyl ether, and then saturated ammonium chloride was added. The organic layer was washed three times with water (10mL) and once with Brine (15mL). The aqueous layer was extracted with ether. The combined organic collections

were dried over magnesium sulfate, filtered and then the product was concentrated under reduced pressure. The residue was purified by column chromatography to give 2-(1-carboethoxymethyl)-6-(2-phenylethenyl)-3,4-dihydropyran, no weights or yields were recorded. ^{1}H-NMR ($CdCl_3$) δ(ppm) 7.5-7.2 (m, 5H) aromatic hydrogens, 6.7-6.6 (d, 1H) alkenyl hydrogen, 6.3-6.1 (dd, 1H) alkenyl hydrogen, 5.8 (d, 1H) alkenyl hydrogen, 5.7-5.6 (d, 1H) alkenyl hydrogen, 4.4 (m, 1H) sp^3 hydrogen attached to an electrophilic atom, 4.2-4.1 (m, 1H) sp^3 hydrogen adjacent to an electrophilic atom, 4.2-4.1 (br m, 2H) sp^3 hydrogens, 2.86 (br m, 2H)sp^3 hydrogens **Spectra I**.

Procedure for One-Pot synthesis of Dihydropyran

To a microwave vial containing a stir bar, 0.05 g (0.23 mmols, 1 eq) of boronic acid, 0.046 g (0.007 mmols, 0.05 eq) of $Pd(OAc)_2$, 0.0042 g (0.007 mmols, 0.05 eq)of BINAP and ***Potassium Flouride* were added. The vial was capped with a rubber septae and 1mL of THF was added. The solution was degassed with nitrogen. *Cis*-ethyl-iodo-acrylate, 0.052 g (0.25 mmols, 1 eq), and ***2M Sodium hydroxide* were added. The solution was allowed to stir and degass for a few minutes. The reaction vial was placed in the reaction microwave for 60 min, at 150 °C, 100 watts and 200 PSI. At the conclusion of the reaction time, the reaction mixture was worked up and purified in the same manner as described above. The formation of dihydropyran was verified by NMR. The compound exhibited the following chemical shift: ^{1}H-NMR ($CdCl_3$) δ(ppm) 7.5-7.2 (m, 5H) aromatic hydrogens, 6.7-6.6 (d, 1H) alkenyl hydrogens, 6.3-6.1 (dd, 1H) alkenyl hydrogens, 5.8 (d, 1H) alkenyl hydrogen, 5.7-5.6 (d, 1H) alkenyl hydrogen, 4.4 (m, 1H) sp^3 hydrogen adjacent to an electrophilic atom, 4.2-4.1 (m, 1H) sp^3 hydrogen adjacent to an electrophilic atom, 4.2-4.1 (br m, 2H) sp^3 hydrogens, 2.86 (br m, 2H) sp^3 hydrogens **Spectra J**.

** *The ratio of KF and NaOH varied from experiment to experiment. Various trials were preformed including 1:1, 1:2, 2:4, 1:3, 2:1, 4:2, and 3:1. Note, all ratios are KF:NaOH, relative to the number of mols of cis-ethyl-iodo-acrylate present in a given reaction.*

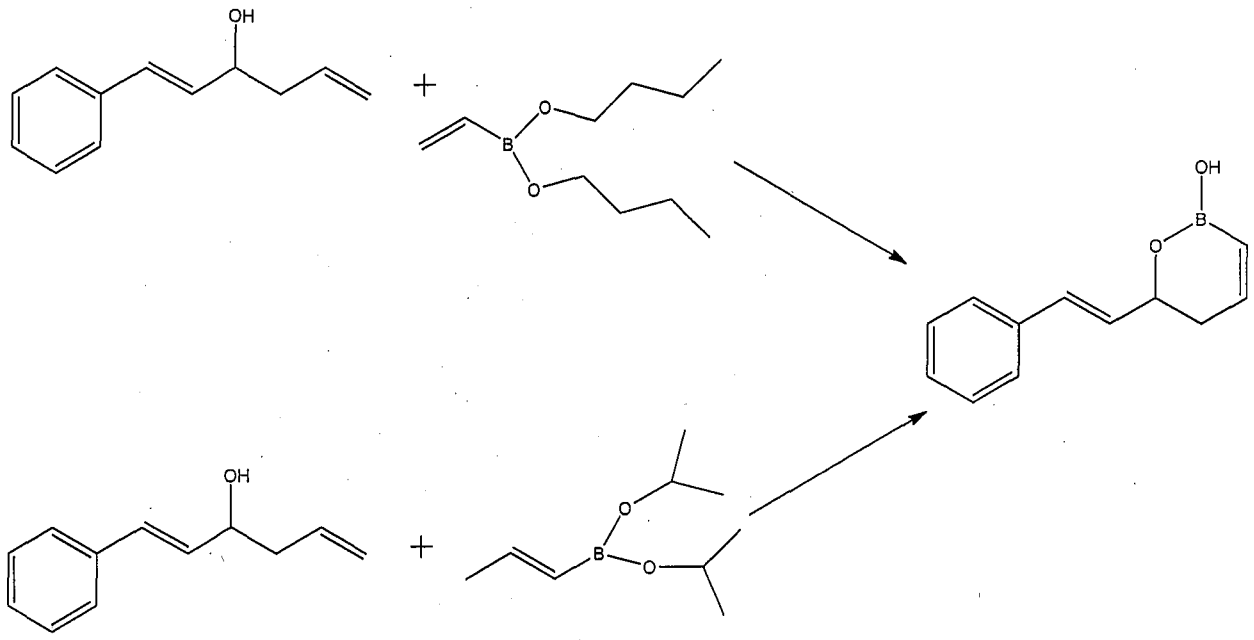
Results and Discussion

Alcohols

E-1-phenyl-1,5-hexadien-3-ol , was the necessary starting molecule for all subsequent reactions of this project; the molecule was synthesized by a Grignard Reaction. This alcohol could be prepared on a large scale without a loss of yield. Although it is not indicated in this particular project, a variety of other homoallylic alcohols can be prepared using this method. Such varying dienols could then be used to make different alkyl boronic acids. Analysis of proton NMR spectra verified the structure of the desired dienol. Key peaks exist at 5.2-5.1, which indicate the presence of a terminal alkene.

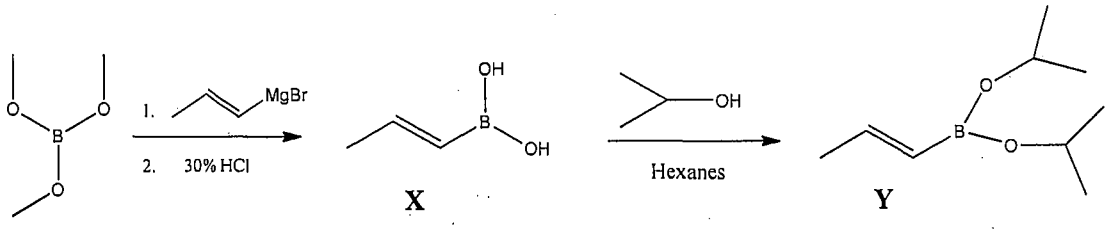
Boronic Acids

The desired cyclic boronic acids could be accessed from two boronic esters. As shown in Scheme 2 (page 17), both vinyl boronic acid dibutyl ester and propenyl boronic acid diispropyl ester were effective partners for the formation of the cyclic boronic acids. The use of vinyl boronic acid dibutyl ester required ordering the commercially available reagent, which was very expensive (>$100 per 5 g). Due to the cost of this reagent, as well as our rapid use of it throughout the project, a second method of synthesis was explored. This method involved the use of propenyl boronic acid diisopropyl ester instead of vinyl boronic acid dibutyl ester. This reagent is not commercially available, so it was necessary to make it in our lab.



Scheme 2- The Schematic above shows the two different methods used to make 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole, used for Suzuki cross-coupling reactions. The top method shows the use of vinyl boronic acid dibutly ester, while the bottom uses propenyl boronic acid diisopropyl ester.

The use of propenyl boronic acid diisopropyl ester for the synthesis of 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole was cost effective but required the use of lab time to prepare the reagent. The preparation of propenyl boronic acid diisopropyl ester required the addition of propenyl magnesium bromide to trimethyl borate, followed by hydrolysis to give the acid (**X**), which was esterified with isopropyl alcohol. Scheme 3 shows the pathway of synthesis used to make the propenyl boronic acid diisopropyl ester.



Scheme 3- The above schematic depicts the reaction pathway used for the synthesis of propenyl boronic acid diisopropyl ester.

After performing the synthesis of propenyl boronic acid diisopropyl ester (**Y**, from scheme above) the product was used for the formation of 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole. It was assumed that the reaction went to completion as no more water evolved. The

formation of propenyl boronic acid diisopropyl ester was verified by ^{1}HNMR. No yield was measured and the product was used in the synthesis of 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole without being purified.

After the synthesis of the 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole, the product was purified using column chromatography and analyzed by ^{1}H-NMR. The spectra showed the characteristic peaks of the boronic acid including peaks at 6.9 and 5.8 ppm, indicating the presence of an alkene next to boron of the six membered ring. The spectra also included some peaks that indicate the presence of other reagents and solvents, including a singlet at 4.2 ppm (vinyl boronic acid), a quartet at 3.5 ppm (diethyl ether) and two peaks at 2.7 and 0.9 ppm (1-butanol). The presence of the peak at 4.2 signifies that vinyl boronic acid dibutyl ester was used in the particular synthesis. A second spectra, for the same boronic acid synthesized using propenyl boronic acid dibutyl ester, had all corresponding peaks of the desired product however the singlet at 4.2ppm was absent.

This method was used to prepare two additional cyclic boronic acids using 1-cyclohexyl-3-buten-1-ol and 1-phenyl-3-buten-1-ol. Although the resulting boronic acids were not used in Suzuki coupling reactions, both products were analyzed by proton NMR. The chemical shifts associated with both 6-cyclohexyl-2-hydroxy-1,2-oxaborole and 6-phenyl-2-hydroxy-1,2-oxaborole contained peaks at 6.9 and 5.8, which indicate the double bond adjacent to the boron of the boronic acid. Along with the peaks that characterize the additional cyclic boronic acids, the proton NMR spectra show peaks indicating the presence of solvent.

Suzuki Coupling Reactions

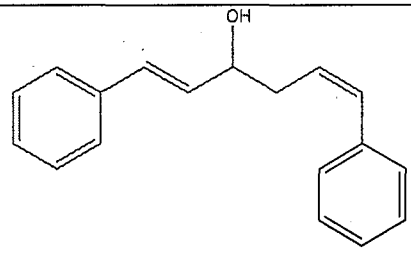
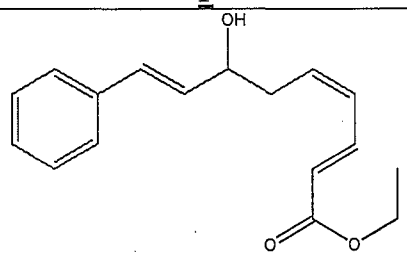
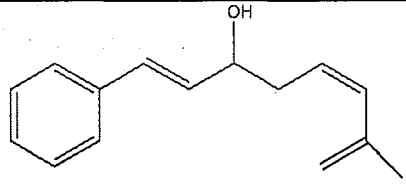
Compound Name	Structure	Yield
1*E*, 5*Z*-1,6-diphenyl-1,5-hexadien-3-ol	 ***1***	*61.6% *with Bromobenzene*
1*E*, 5*Z*-1,6-diphenyl-1,5-hexadien-3-ol	***1***	29.8% *with Iodobenzene*
Ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate	 ***2***	61.50%
1*E*, 5*Z*-7-methyl-1-phenyl-1,5,7-octatrien-3-ol	 ***3***	**52.4% *with $CsCO_4$*
1*E*, 5*Z*-7-methyl-1-phenyl-1,5,7-octatrien-3-ol	***3***	88% *with Na_2PO_4 tribasic*

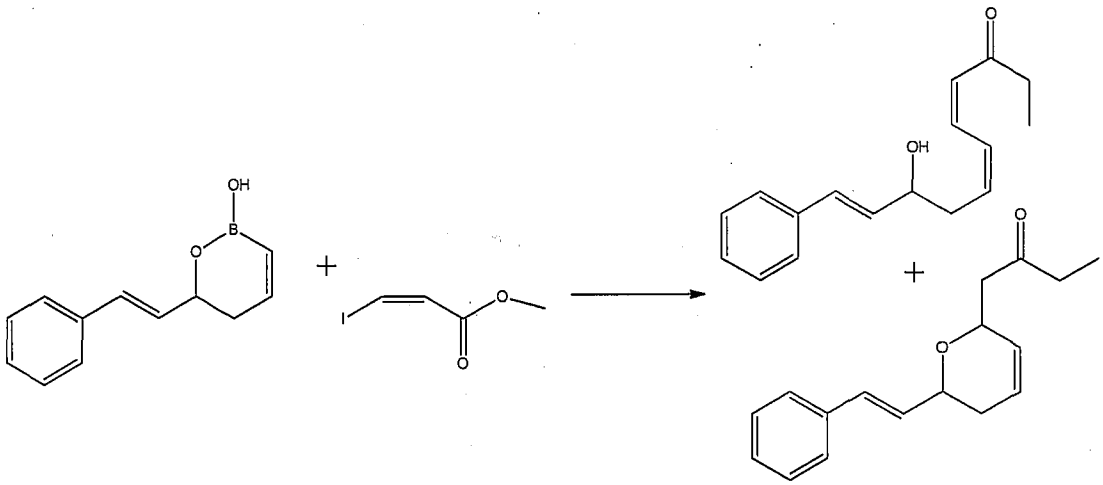
Table 1—The table above lists the products and yields of three Suzuki cross-coupling reactions.
*This product was formed using two different alkyl halides, Bromobenzene and Iodobenzene.
**This product was formed using two slightly different procedures, which varied by the bases used; one procedure included $CsCO_4$ while a better yield was obtained using Na_2PO_4 tribasic.

Using various alkyl halides three different dienol products were formed. The products were analyzed using proton Nuclear Magnetic Resonance (Bruker Avance 250 MHz NMR spectrometer with all shifts reported relative to TMS). Along with the peaks that are characteristic of product **1**, there are also peaks that indicate the presents of solvent as well as water. These peaks include a quartet at 3.5 ppm-Diethyl Ether as well as a singlet at 1.6ppm-Water. The second product listed, ethyl 2E,4Z,8E-9-phenyl-7-hydroxy-2,4,8-nonatrienoate (**2**), was created using boronic acid and cis-iodo ethyl acrylate. All three of the products listed above

exhibit the same chemical shifts from the hydrogens of the starting alcohols (depicted in above table with red atoms). Such peaks are located at 6.5, 6.3, 5.8, 4.3, and 2.5 ppm. The variable regions of these products(shown in black) were dictated by the halogentated R-group used in the particular reaction.

Dihydropyrans

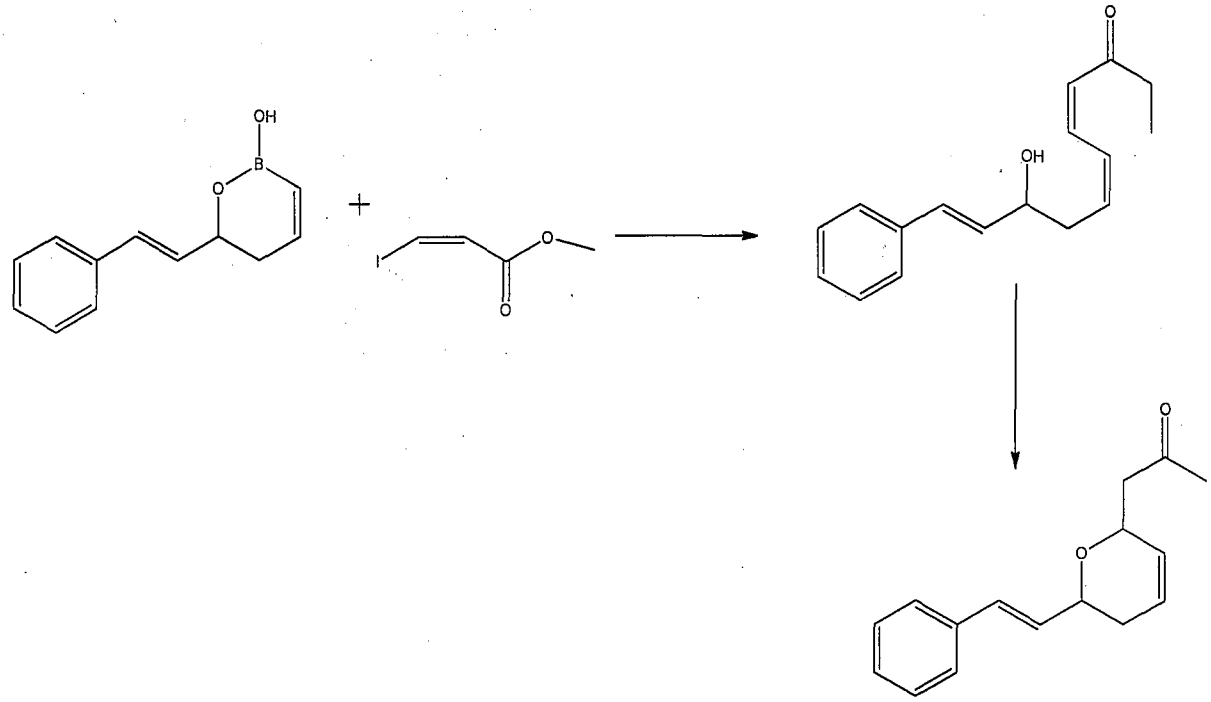
The resulting product of the Suzuki reaction, between 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole and *cis*-3-iodoacrylate, ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate has the correct geometry to undergo an intramolecular Michael addition. Ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate was treated with a base (KOtBu) and it was determined by proton NMR that the intramolecular Michael Addition took place to produce a cyclic 2,6-disubstituted dihydropyran (DHP). It was evident that the time frame of this two-step process was important, likely due to the instability of the *cis*, *cis*-diene that is present in ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate. In one example the cyclization reaction was attempted several weeks after running the Suzuki reaction, in which no reaction took place. The unwillingness of the molecule to cyclize was likely due to isomerization of the middle alkene of ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate.



Scheme 4- The reaction scheme above depicts the overall goal of this project which was a one pot synthesis of 2(1-carboethoxymethyl)-6-(2-phenylethenyl)-3,4-dihydropyran by way of a Suzuki coupling reaction between 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole and *cis*-Iodo Ethyl Acrylate. The desired dihydropyran is in bold, and Ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate is a side product of the reaction.

With significant success and good yields in the Suzuki cross-coupling reactions, it was the ultimate goal of this project to optimize a procedure for a one-pot synthesis. This one pot reaction involved a combination of NaOH and KF, which were added to a Suzuki reaction procedure (Part 3 above) with *cis*-3-iodoacrylate. The sodium hydroxide and potassium fluoride combination was necessary because it was learned from previous reactions that KF was a good base for cross coupling, but not for cyclization to occur; however, in the presence of NaOH, ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate had a tendency to undergo the intramolecular Michael Addition, forming the DHP. When attempting this one-pot synthesis, the reaction temperature was also increased (60 degrees increase; 90 to 150 °C).

Although the goal was a one step reaction, more success was had with a two step process going from 6-(2-phenylethenyl)-2-hydroxy-1,2-oxaborole and *cis*-iodo ethyl acrylate to ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate (via Suzuki reaction) and then adding a base to produce the 2,6-disubstituted dihydropyran.



Scheme 5- The two step reaction, shown in the scheme above, was successful in producing the desired 2-(1-carboethoxymethyl)-6-(2-phenylethenyl)-3,4-dihydropyran product.

At the conclusion of running the reactions described above, the products were analyzed by proton NMR. Adding various bases to ethyl 2*E*,4*Z*,8*E*-9-phenyl-7-hydroxy-2,4,8-nonatrienoate, resulted in ring closure and formation of dihydropryran. The two doublets at 5.8 and 5.7-5.6 are indicators of the presence of dihydropyran. It was previously known that this reaction produces cis/trans isomers of this dihydropyran product. It was determined by integration that the isomers were present in a 1:1 ratio[Spectra K]. There was one instance in which the two isomers were separated. The isolation was determined by proton NMR. Two samples were analyzed and the difference in the two spectra is exhibited in the difference between the distance between the two doublets (5.8 and 5.7-5.6). Also there is a slightly different splitting pattern in the peaks at 4.4 and 4.2-4.1 (compare spectra L and M). Unfortunately, although the individual isomers were isolated, the sample was contaminated.

Although when running the one-pot synthesis of dihydropyran some DHP was seen to have formed, determined by proton NMR, however we had a difficult time getting all of the Suzuki product to cyclize in one step. In most cases it was observed that the Suzuki coupling reaction would take place very effectively, and by adding KOtBu to the reaction mixture the cyclization would occur. When DHP was formed, it was determined to form as a mixture of cis and trans isomers. There was a single instance in which the mixture was separated and the two isomers were isolated. However, it was unfortunate that when the separation took place a contamination of our stock of Hexanes also occurred.

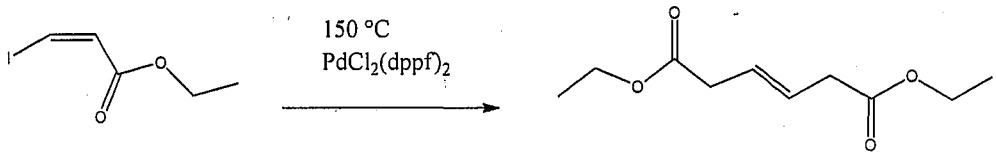
Due to the fact that we did not initially know what caused the contamination or where it came from, as well as it appeared to be in everything in the lab, it was pertinent to halt the main task at hand and focus on determining the culprit of the contamination. The presence of the contaminant was evident by characteristic peaks in proton NMR spectra, which included a singlet at 4.7 and quartet at 3.8-3.7. Through extensive investigation, lasting multiple weeks, it was eventually determined that there was a contamination in the lot of hexanes that was being used to

purify the products of reactions. Due to this unfortunate event, late into the summer of the research program, the recent advances that had been made with DHP formation was never finished.

Conclusion

In conclusion, it is evident that certain halogenated R-groups such as *cis*-iodo ethyl acrylate, when coupled with boronic acid yields a product that can undergo a second reaction, an intramolecular ring-closing Michael Addition reaction. This is possible due to the retention of the *cis* alkene, stereoselectivity of the Suzuki Miyaura coupling reaction.

It is also evident that it is possible to do both the coupling, Suzuki reaction, as well as the ring closing, Intramolecular Michael Addition reaction, in a one pot synthesis. NMR data confirms the formation of dihydropyran after this single step synthesis. Optimization of this method has not yet been completed, however it appears that the ratio of the two bases (KF:NaOH) has a significant impact on the success of producing dihydropyran in a single pot synthesis. It also appears that adding excess ethyl iodo acrylate to the reaction mixture results in the formation of dihydropyran in a single step synthesis. This could be due to the fact that we know that at 150 °C, and in the presence of $PdCl_2(dppf)_2$, *cis*-iodo ethyl acrylate has a tendency to decompose to a non reactive form; excess *cis*-iodo ethyl acrylate allows for sufficient reactive reagent to be present for the reaction to take place at this high temeperature. This was evident due to NMR data.



From the limited results of the one-pot synthesis it appears that the best results of dihydropyran formation in a single-step occurs when the ratio of KF:NaOH was 2:4 or 4:2 as well as excess *cis*-iodo ethyl acrylate in both cases, with yields of 15 and 10% dihydropyran respectively.

It was unfortunate that when I started to make progress on this variable of the reaction (the ratio of the two bases) that I had to deal with the contamination of solvents. This inconvenience detracted from further investigation of the reaction of interest, and did not allow for the completion of the project.

Future work in this particular pathway of research would be to develop a reaction procedure that optimizes the yields of dihdropyran by way of a one-step synthesis. In order to accomplish the optimization, the ratio of bases needs to be further investigated, as well as the attempt to run the reaction with other bases besides the two that have already been used. The optimal microwave setting for the reaction also needs to be determined. Temperature is especially critical due to the fact that at higher temperatures some of the starting materials used tend to decompose and lose their reactivity. Due to the decomposition of *cis*-iodo ethyl acrylate around 150 °C, discussed above, we tend to use the reagent in excess; in future experimentation the result of using excess boronic acid should also be investigated.

Once the reaction has been optimized, resulting in good yields of dihydropyran, the next step of research should be the development of a highly successful method for the isolation of individual dihydropyran isomers, as well as the side product produced.

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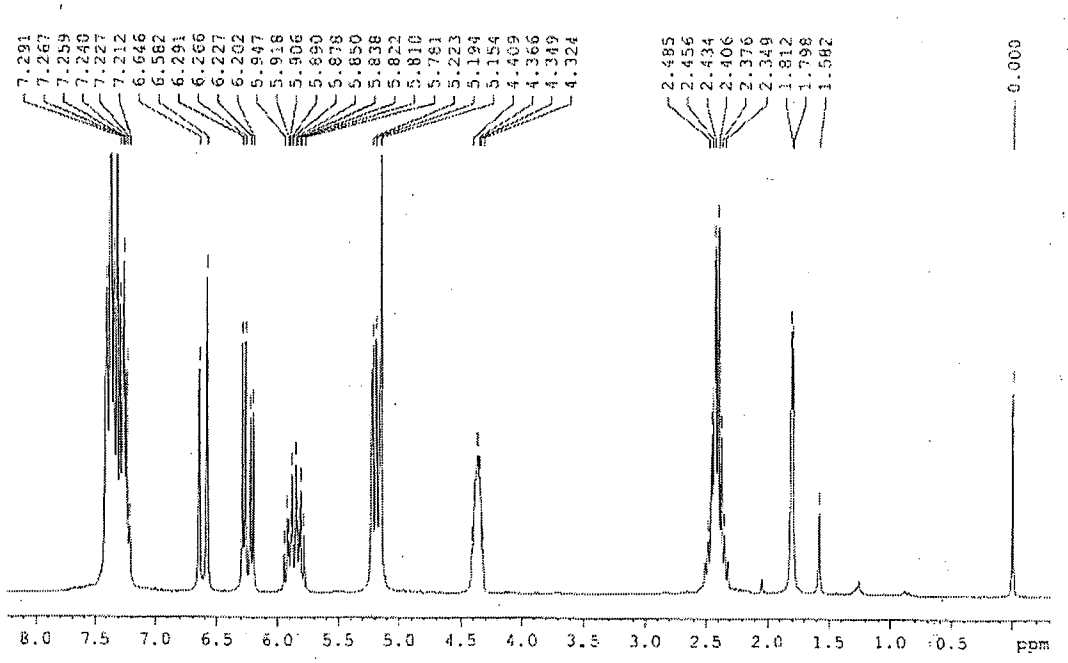
Appendix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1.798
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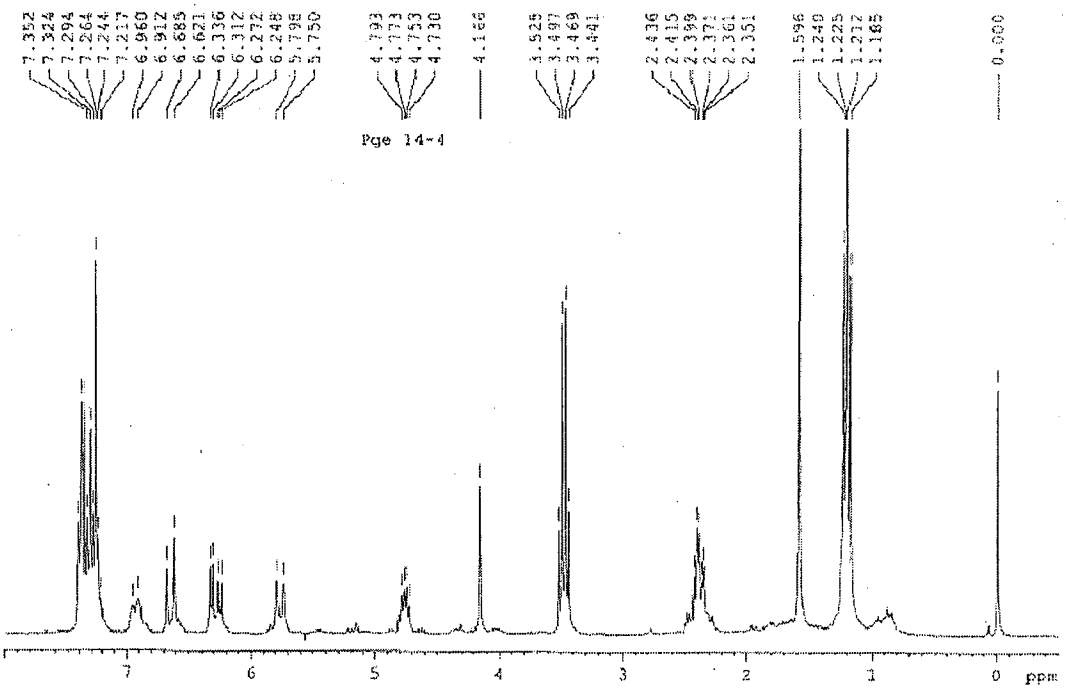
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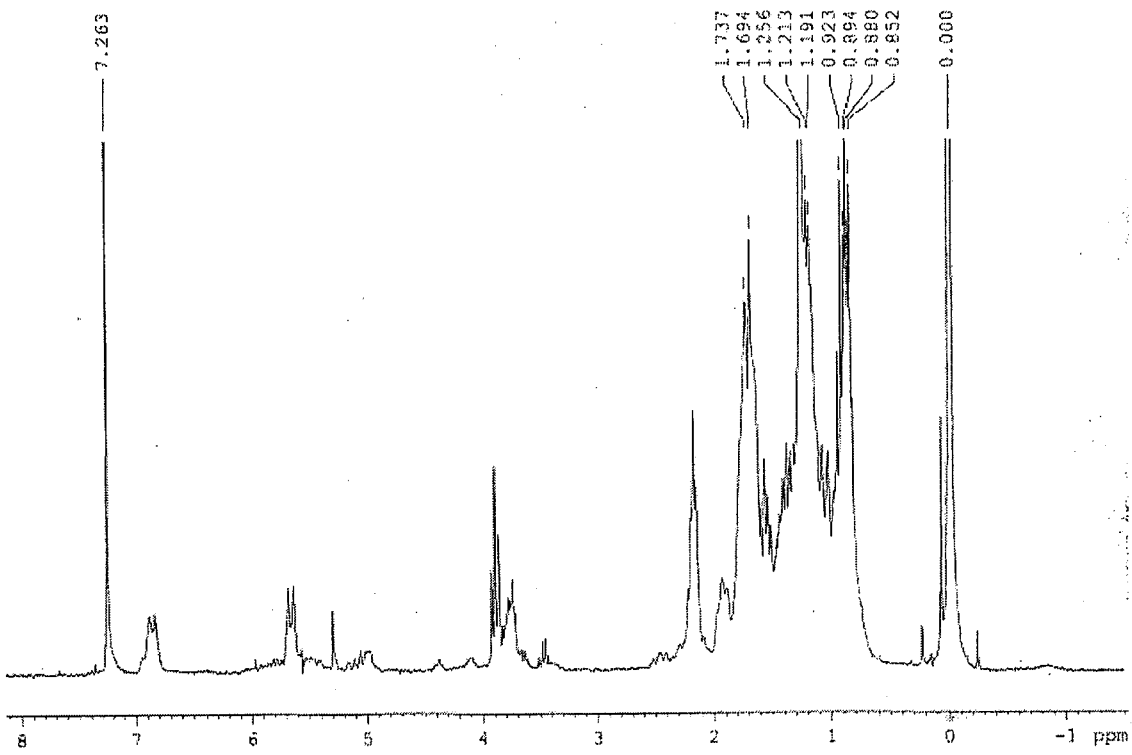
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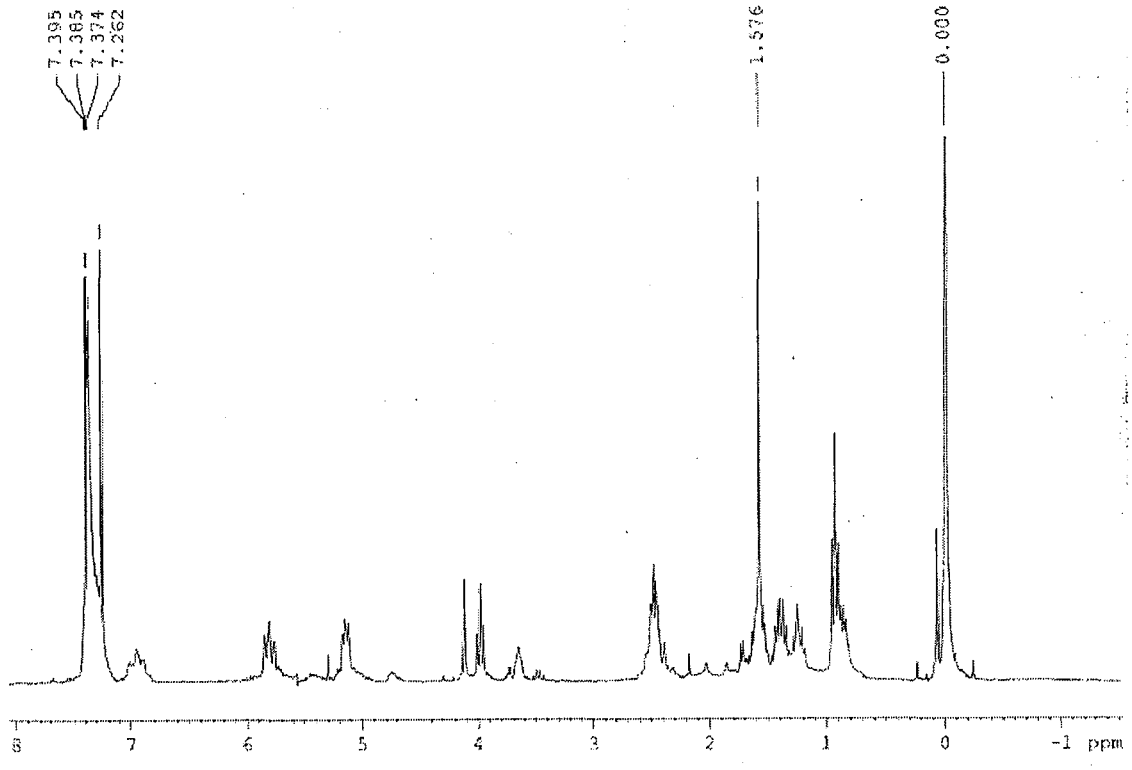
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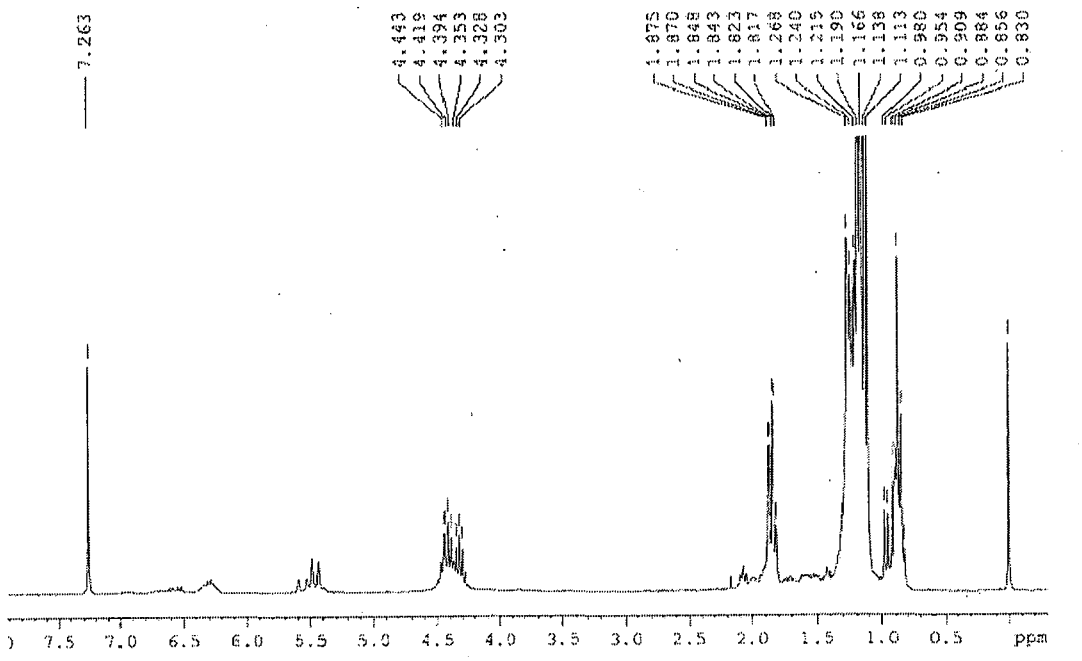
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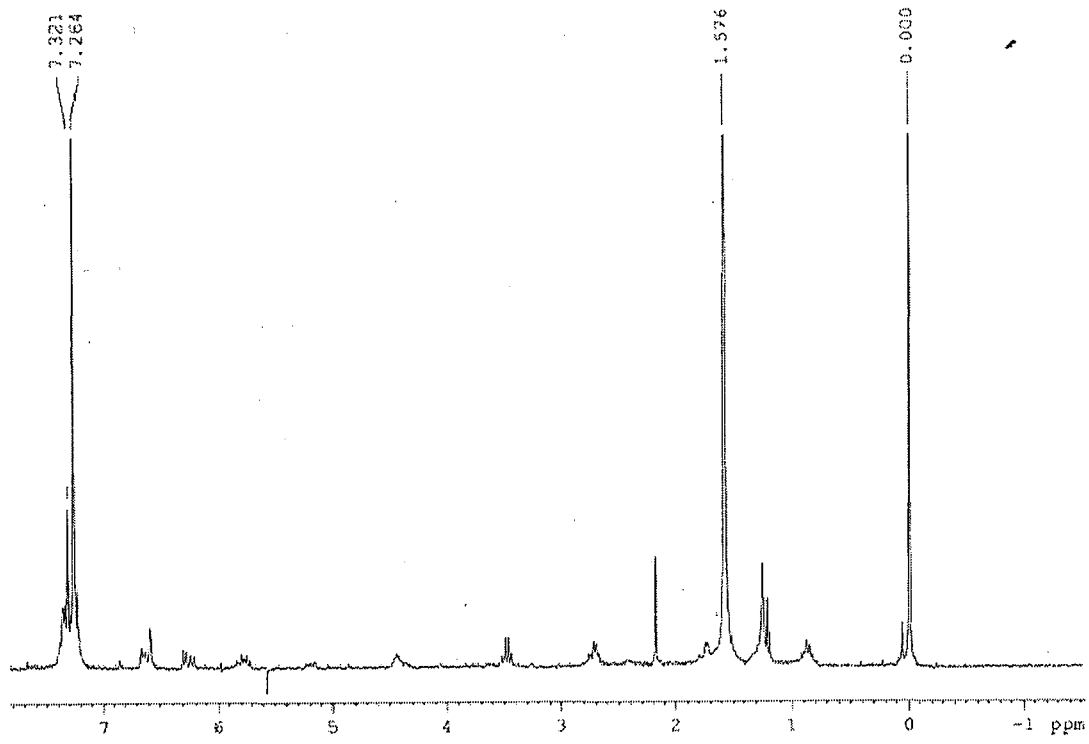
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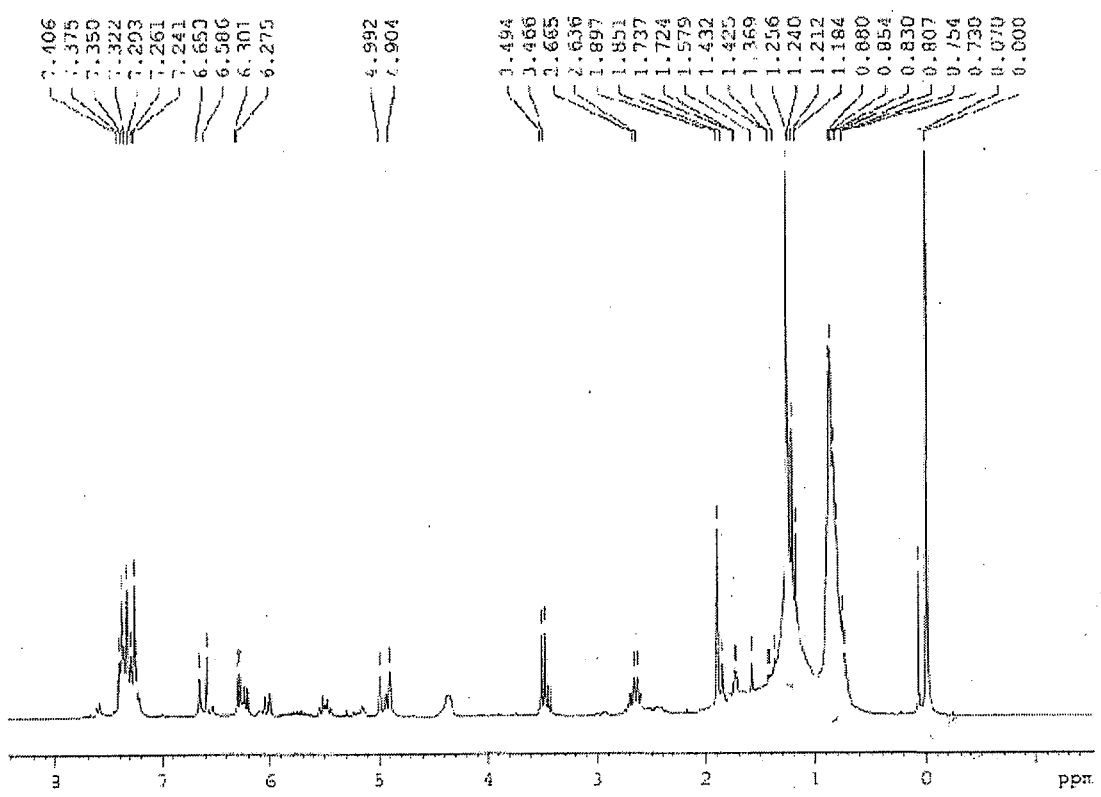
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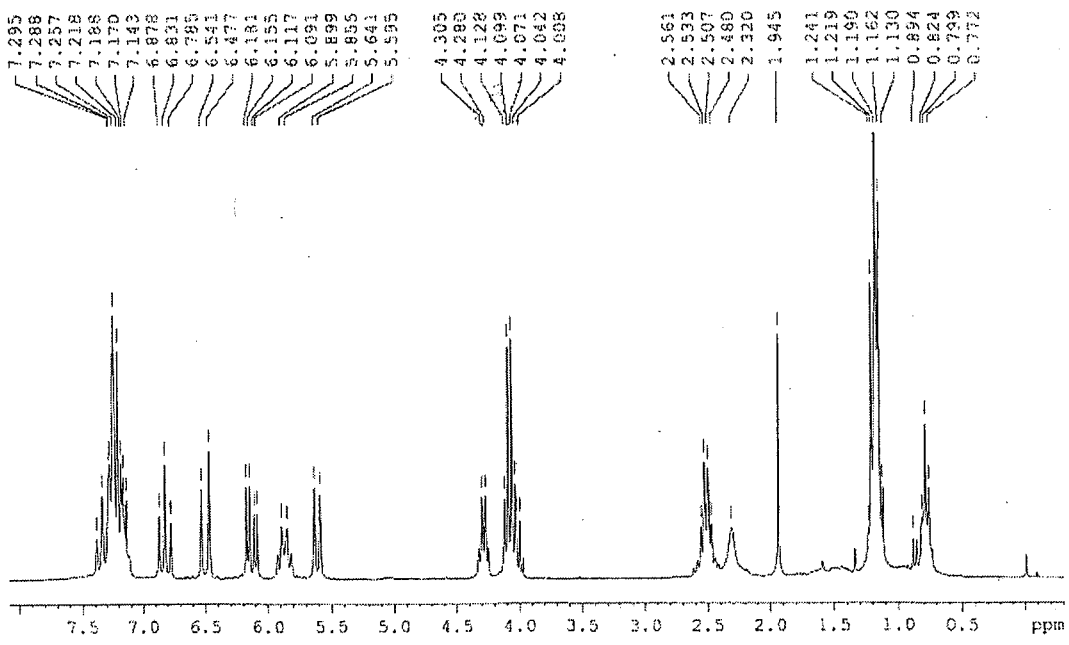
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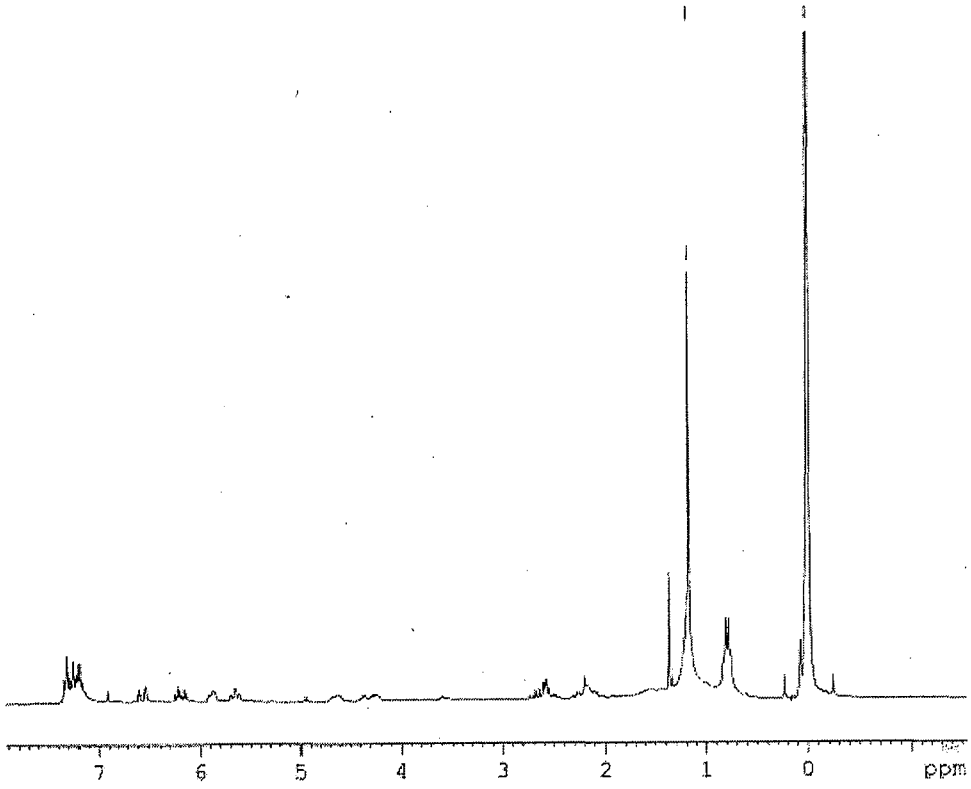
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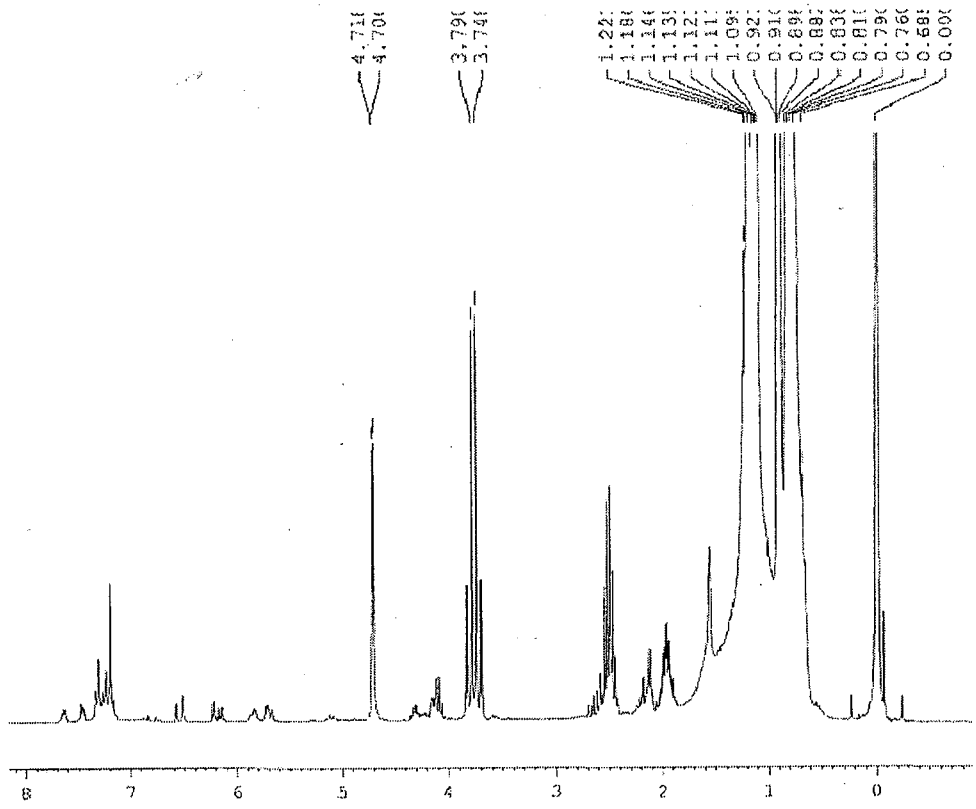
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6
5
4
3
2
1
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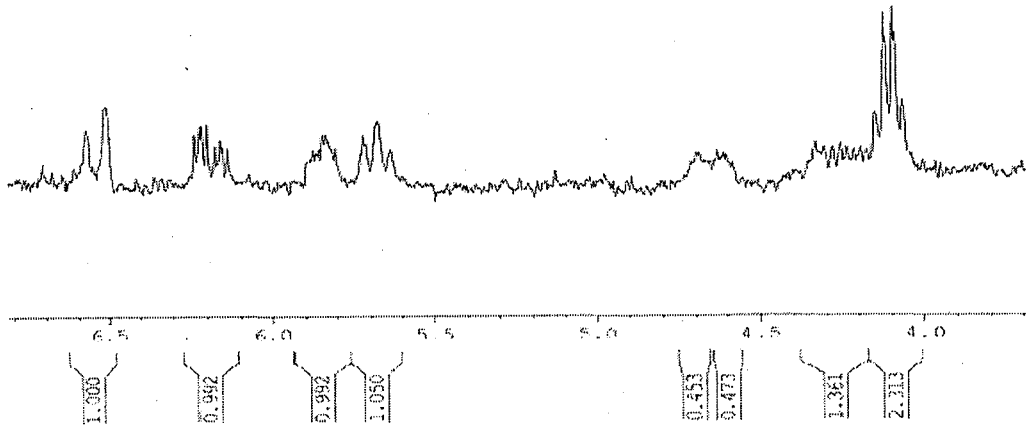
J.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6.0
5.5
5.0
4.5
4.0
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0.992
1.050
0.353
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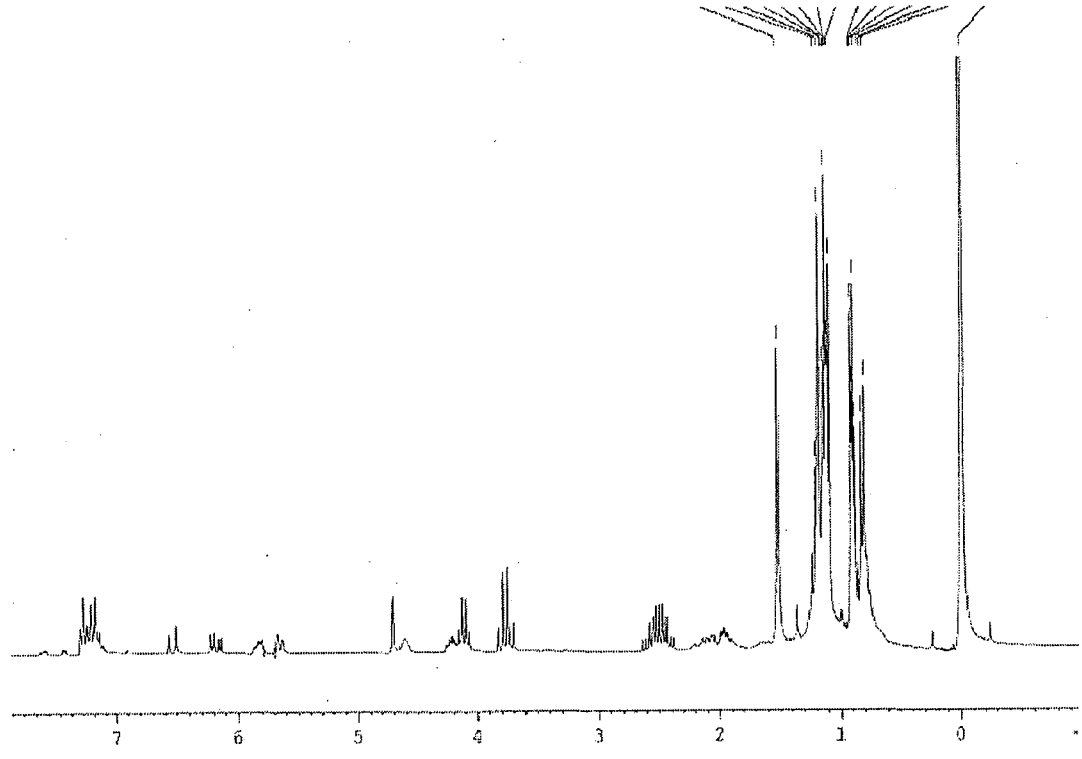
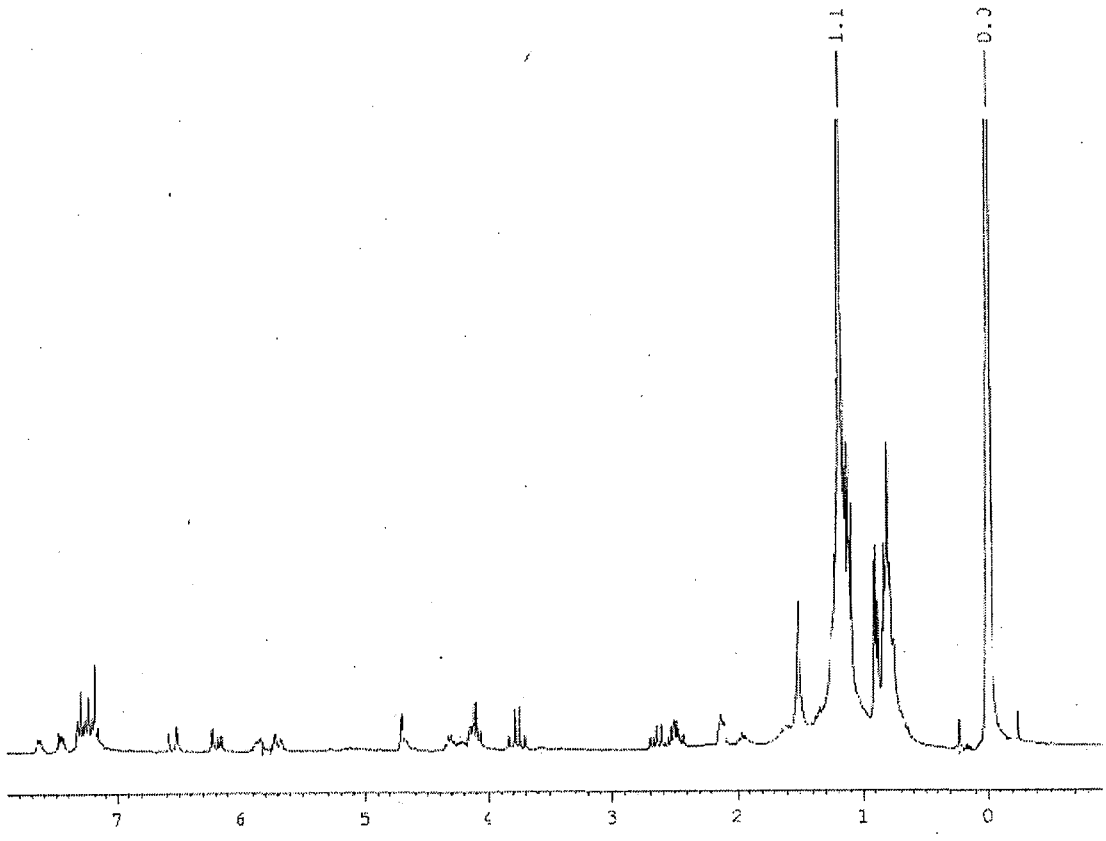
1.321
2.313

K.


7
6
5
4
3
2
1
0

L.



M.