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A Catechol Approach to Natural Product Synthesis

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A thesis submitted to the chemistry department
in partial fulfillment of the requirement for
graduation with honors in chemistry.

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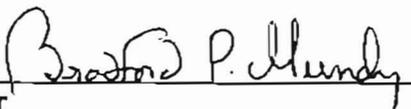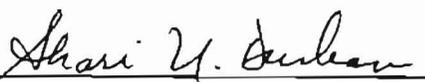
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May, 2000

Vita

Michelle Weber was born in Edina, MN to parents Gerry and Linda Weber on September 21, 1978. Her sister, Jen, followed two years later and Ali two years after that. When Michelle was four, she moved from Minnesota to Salt Lake City where she lived until she was eight. In 1987, her family moved to Wellesley, MA. Michelle graduated from Wellesley High School in June, 1996.

Entering Colby College in Waterville, ME in the fall of 1996, Michelle began working with Professor Brad Mundy during her sophomore year. During her two and a half years of undergraduate research, she worked on many projects involving natural products.

In the summer of 1998, Michelle was awarded a fellowship by the Department of Energy to participate in The Summer School for Nuclear and Radiochemistry in San Jose, CA. The following summer she returned to California with an internship at Lawrence Livermore National Laboratory, sponsored by the Glenn T. Seaborg Institute for Transactinium Science. She will be pursuing her Ph.D. at Washington University in St. Louis in bioorganic chemistry.

Acknowledgements

I have to start by thanking my family, especially my parents, for supporting me in every way possible over the last 21 years. Their belief in me has been my greatest motivation and without them, I would not have made it this far. I dedicate this thesis to them.

I need also to thank Professor Brad Mundy for his guidance and patience throughout my time working with him. The knowledge I have gained working for him has been immeasurable and the experience invaluable. His enthusiasm and love of chemistry are truly an inspiration to all. Thanks for everything Professor Mundy.

My lab partner, Sean Neville, might possibly be the best lab partner ever. I cannot write this without thanking him for all of his help both in and out of lab. Thanks, Sean. Good luck!

Organic chemistry just now is enough to drive one mad. It gives me the impression of a primeval tropical forest, full of the most remarkable things, a monstrous and boundless thicket, with no way of escape, into which one may well dread to enter.

--Fredrich Wöhler, 1835

Scientific developments are very often the result of human efforts either to mimic Nature or to "create the unnatural," whether in the field of human flight or chemistry. For example, Icarus's attempt to mimic Nature is part of Greek mythology; Wilbur and Orville Wright successfully created the unnatural at Kitty Hawk, N.C., December 17, 1903. In chemistry, along with synthesizing new compounds—an enormous effort has been devoted to synthesizing naturally occurring compounds—copying Nature.

--Giovanni Desmoni, et al
Natural Product Synthesis through Pericyclic Reactions

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Figures, Schemes and Tables

Abstract

This research has focused on the total synthesis of the iron–chelating natural product 1–(2,3–hydroxyphenyl)–4–methoxy–1–butanone. An extract of the iron–deficient fungus *Gleophyllum traebeum*, this molecule is thought to bind to Fe^{3+} in a hexacoordinate system to aid in transport through cell walls in order to help regulate iron levels in such iron–deficient fungi. Since the proposed structure of the molecule is based only on the spectral data of a very small sample, our hope is to synthesize and confirm its structure as the extract of the brown rot fungus.
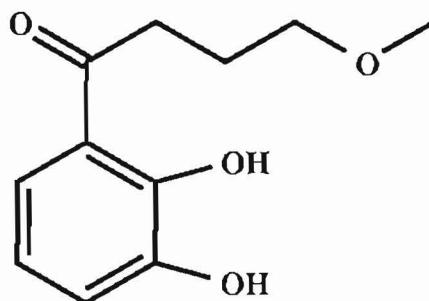
1–(2,3–dihydroxyphenyl)–4–methoxy–1–butanone

We have developed a relatively short retrosynthesis for our work on this molecule. Our approach relies on an electrophilic aromatic substitution of the side chain onto the aromatic ring of the catechol. By building up the ether side chain in the first few steps of the synthesis, we will be able to add it to the catechol as an acid chloride through a Friedel–Crafts acylation. This approach will allow us to avoid the use of protecting groups for the reactive diol system; such methods have proved problematic in past work done by our group.

Introduction

The extraction of natural products for human benefit is not new. In the ancient worlds, extracts from plants, flowers, minerals, and insects provided the luxuries of perfume oils and dyes used on clothing and in art. Primitive societies used various plants for their magical healing capabilities, many of which are still used in natural medicines today. These uses were no mistake. People were quick to realize the aesthetic appeal associated with the coloring of houses, pictures, and clothing, as well as the medicinal benefit of many plants. But it was not until Friedrich Wilhelm Sertürner's 1805 morphine isolation that a single active component from a pain–relieving plant was separated for use.[1] The next 50 years yielded the isolation of five other major alkaloids (strychnine, caffeine, nicotine, atropine, and cocaine)[2] and launched a massive search for more natural products.

Marcelin Berthelot, a French chemist whose contributions to chemistry range from organic synthesis to thermochemistry to documenting the history of chemistry, believed that the fundamental problem of all organic chemistry was "to prove beyond all question that compounds identical with those produced by plants and animals can be synthesized from inorganic or mineral matter."[1] In the early years of chemistry it was thought that there was a "vital force" necessary for the production of organic compounds, and that this force was found only in naturally occurring biological systems. In 1828 Fredrich Wöhler shocked the world with his synthesis of urea,[3] the first natural product made from inorganic compounds outside of a living organism, a compound made without the aid of a "vital force." Of his accomplishment, Wöhler wrote, "I can no longer, as it were, hold back my chemical urine; and I have to let out that I can make urea without needing a kidney, whether of man or dog; the ammonium salt of cyanic acid is urea."[4]

Wöhler's accomplishment was no small feat. It established the first stepping stones for the development of synthetic organic chemistry.

Before the late 19th century, dyes had been made exclusively from natural products extracted from plants and imported into Europe from India at high costs. Realizing the economic potential of this market, which was rapidly growing as the demand for consumer goods increased, German scientists worked towards developing syntheses for the active materials of the extracts. Chemist Adolf Baeyer led the field, developing the first synthesis of indigo in 1880, a project that he had been working on since the age of 13. In 1860, Germany had no dye exports; by 1914, they had a virtual world monopoly on synthetic dyes, controlling 90% of the world's dye market.[4]

The probing of natural products began to grow even faster after 1884, when Emil Fischer, a student of Adolf Baeyer, announced to the world that he had determined the structure of glucose. In 1887, Fischer succeeded in synthesizing fructose, the first artificially produced carbohydrate, and in 1902 won the second ever Nobel Prize in chemistry for his work in characterizing and synthesizing natural products.[1]

Today, the total synthesis of complex natural products has become an essential piece in the development of many pharmaceuticals. Natural products, along with their analogs and derivatives, make up more than half of all drugs currently in clinical use.[5] One of the most common over–the–counter pain relievers, aspirin, is a derivative of salicin, a component of willow juice that had been used to treat gout for over 2,000 years.[2] A relatively simple compound, acetylsalicylic acid (**figure 1**) was first prepared by German chemists in 1899.

Figure 1: Structure of acetylsalicylic acid

On the other end of the pharmaceutical spectrum are much more complicated molecules that contain several chiral centers. These multiple chiral centers make syntheses extremely difficult. One such compound is taxol **(figure 2)**, an extract of the Pacific yew tree *Taxus brevifolia*. Found to have potent activity in fighting breast and ovarian cancers, it has been estimated that one century-old tree is needed to extract enough of the compound to treat one cancer patient.[2]

Figure 2: Structure of taxol

As taxol is environmentally unfriendly to isolate in large quantities, a synthetic route to the drug is a necessity in the fight against cancer. By 1995, three separate groups had reported syntheses[7,8,9] for the complex molecule, with a fourth, shorter protocol[10] reported in 1997.

Natural products have become vital in today's world for everything from economic growth to medicine to the ever–strong desire to understand the workings of the world in which we live.

> [N]atural products continue to hold a unique fascination not only because of their relationships to the organisms from which they are derived, not only because plants that can photosynthesize possess synthetic power that far surpasses that of man, not only because of their potential usefulness to man in their natural form or as templates for synthetic analogs, but chiefly because each new structural type reveals something of nature's molecular architecture and passes new questions of how and why these compounds are being produced.[4]

The search for biologically active natural products continues to expand as mankind needs and desires these products more and more. But there still remain millions of unexplored species still waiting to be found. The chemistry of natural products is a vibrant and exciting area for study. In the pages that follow, we will describe our part in this continuing story.

Background

This research has focused primarily on the natural product 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone, (that we will hereafter refer to as the methoxy ketone) a potential iron–binding compound isolated from a crude extract of the iron–deficient fungus *Gloeophyllum trabeum* (**figure 3**). The extract was isolated by Dr. Frank A. Fekete of the Colby College Biology Department in conjunction with colleagues in the Forest Biology Department at the University of Maine, Orono.[11] The proposed structure (**figure 4**) of the iron–binding compound is based only on the spectral data of a small amount of isolated material and has not been reported in the literature. Our goal is to synthesize the proposed structure to confirm the identity of the extract.
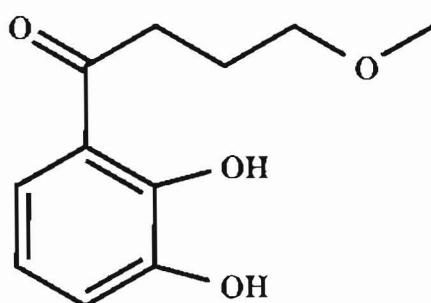
Figure 4: 1–(2,3–dihyroxyphenyl)–4–methoxy–1–butanone (methoxy ketone)

Iron is an element that is essential for microbial growth, as well as for normal human development. It is mobilized intracellularly by organisms in its Fe(II) oxidation state, but is found in aerobic environments in the insoluble Fe(III) state. It is necessary for organisms to have the ability to scavenge and absorb Fe(III) and then reduce it to the usable Fe(II) oxidation state. The potential iron chelator formed by *G. trabeum*, should to have the ability to bind to Fe(III) in a hexacoordinate system. In this complexed form,
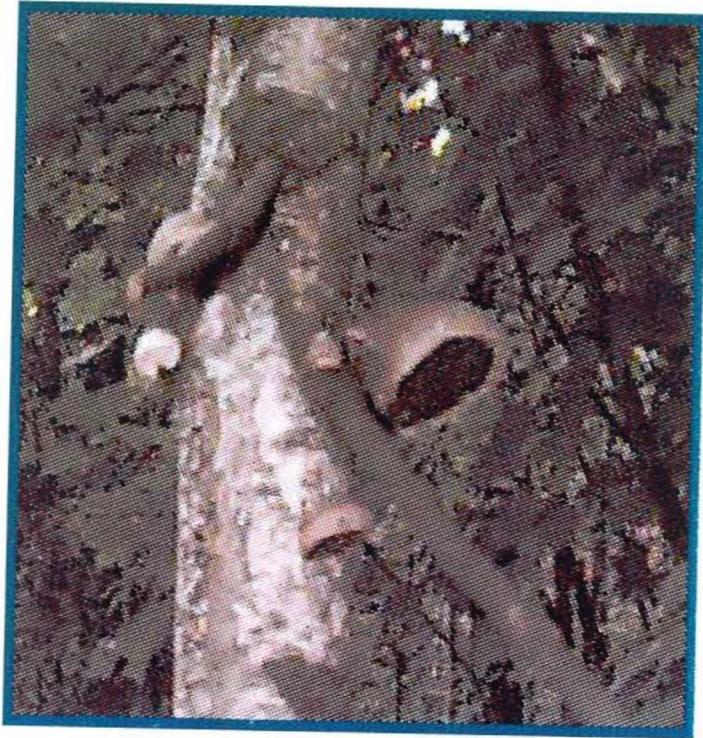
Figure 3: An example of the shelf-like brown rot fungus

Fe(III) could putatively be transported into cells and be reduced intracellularly. Although the exact binding mechanism is unknown, there are two proposed schemes. In one (figure 5a), Fe(III) is bound to the two hydroxyl groups of the aromatic ring. The other proposed chelate (figure 5b) has Fe(II) bound to only one of the aromatic hydroxyl groups and to the carbonyl oxygen.

It has been postulated that the methoxy ketone is involved in wood degradation. This degradative process is dependent on the generation of oxygen and hydroxy free-radicals. Iron is believed to play an essential role in a nonenzymatic iron-hydrogen peroxide catalysis of lignocellulose degradation, making the sequestering of iron from the surrounding environment a necessity for this fungus.[16] One possible pathway through which iron levels in such fungi may be regulated is through iron chelated complexes with organic substrates methoxy ketone.

There have been several earlier synthetic attempts made by our research group to prepare 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone. The earliest attempt utilized organometallic chemistry, specifically organolithium reagents, in preparation of ketones from carboxylic acids.[12] The hope was to build the ether side chain from the resulting ketone. Using 2,3-dihyroxybenzoic acid, a hydrocarbon chain was successfully added on in a model reaction (scheme 1).
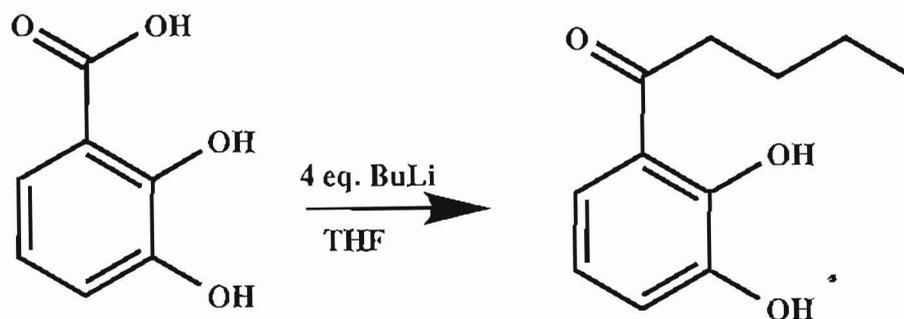
Scheme 1: Early model reaction to synthesize the methoxy ketone
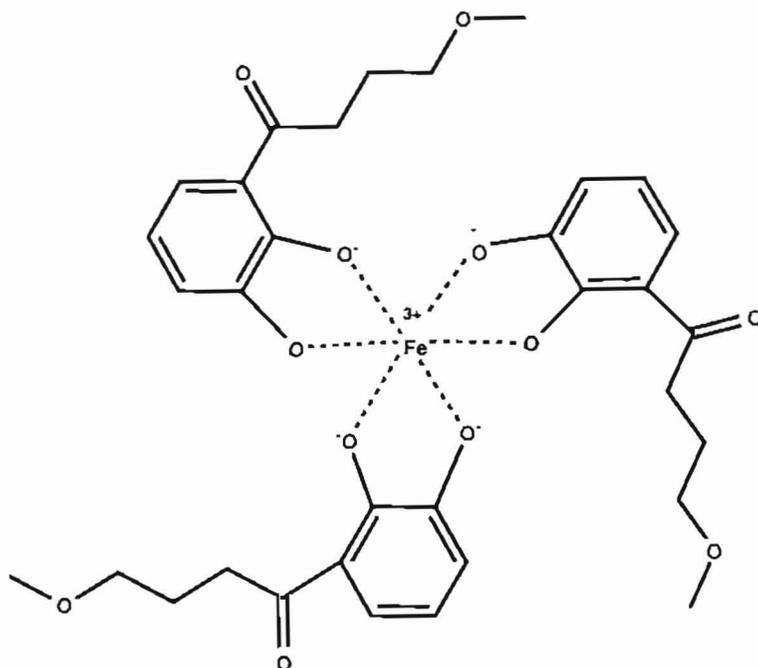
Figure 5a: Proposed binding scheme for Fe^{3+} to the two hydroxy groups of
1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone
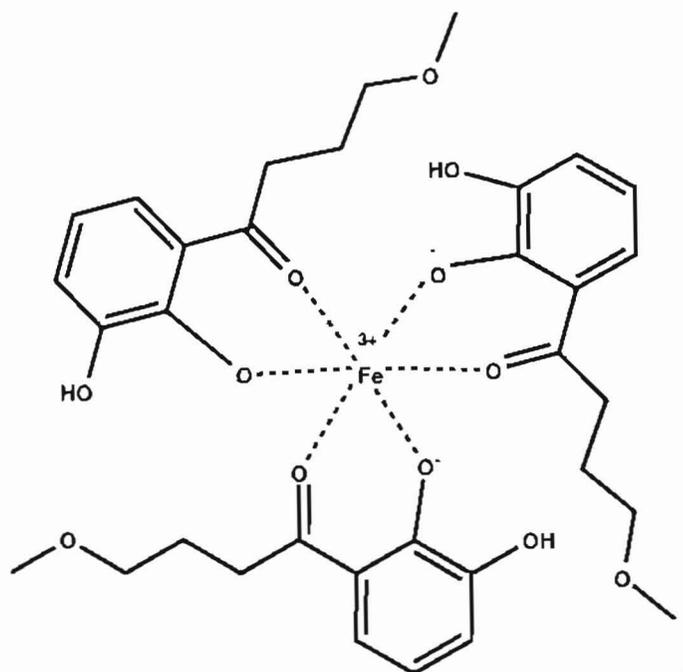
Figure 5b: Proposed binding of Fe^{3+} to the hydroxy and the carbonyl groups of
1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone

The next step in this route was to synthesize the appropriate R–Li side chain (1) for nucleophilic addition to 2,3–dihyroxybenzoic acid.

(1)
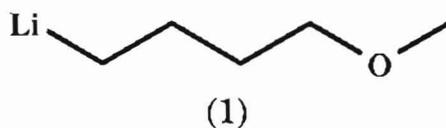
Using methyl propargyl ether (2) to make the side chain would allow for a three step synthesis of 1–(2,3–dihydroxyphenyl)–4–methoxy–1–butanone (**scheme 2**).
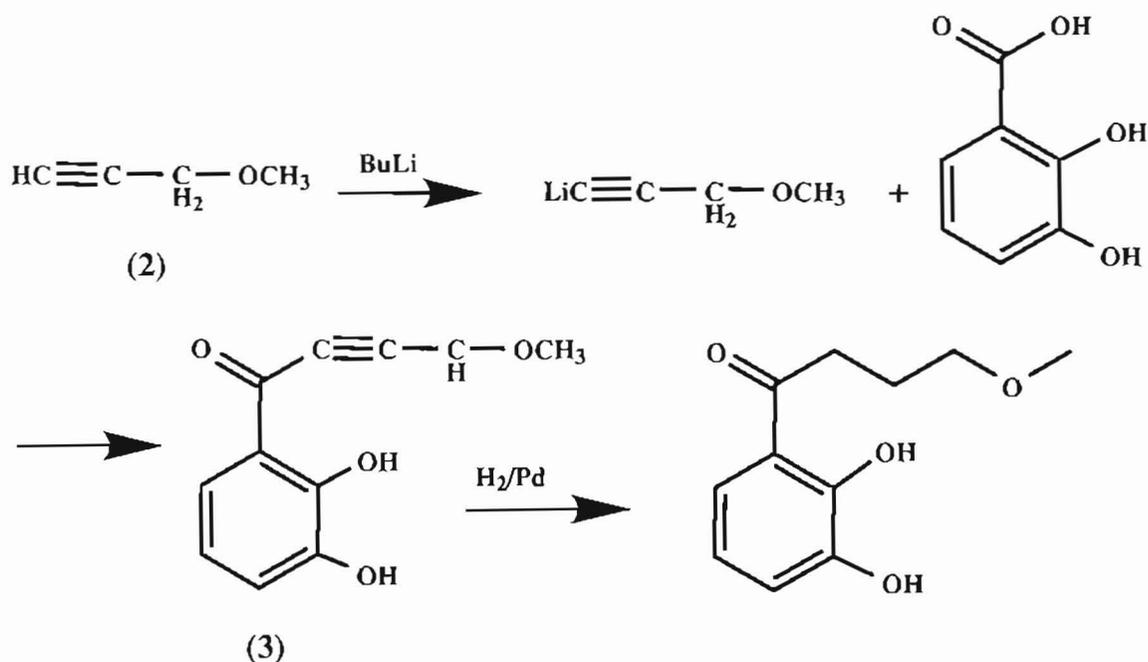
Scheme 2: Early projected synthesis for the methoxy ketone

Although the addition of the R–Li chain (3) was successful, model reactions using salicylic acid were unable to reduce the triple bond in the next step and this approach was abandoned.

The failure of the reduction reaction in **scheme 2** is likely attributed to an electronic difference between carrying the negative charge of the anion on an sp^3-hybridized carbon, as in the case of BuLi (**scheme 1**), as opposed to an sp-hybridized carbon of the methyl propargyl ether. The low reactivity of the lithium chain with the carboxylic acid may be rationalized by this difference.

In a second synthesis attempt, the aim was to build a brominated ether side chain (**4**) before attaching it to 2,3-dihyroxybenzoic acid (**scheme 3**).

(4)
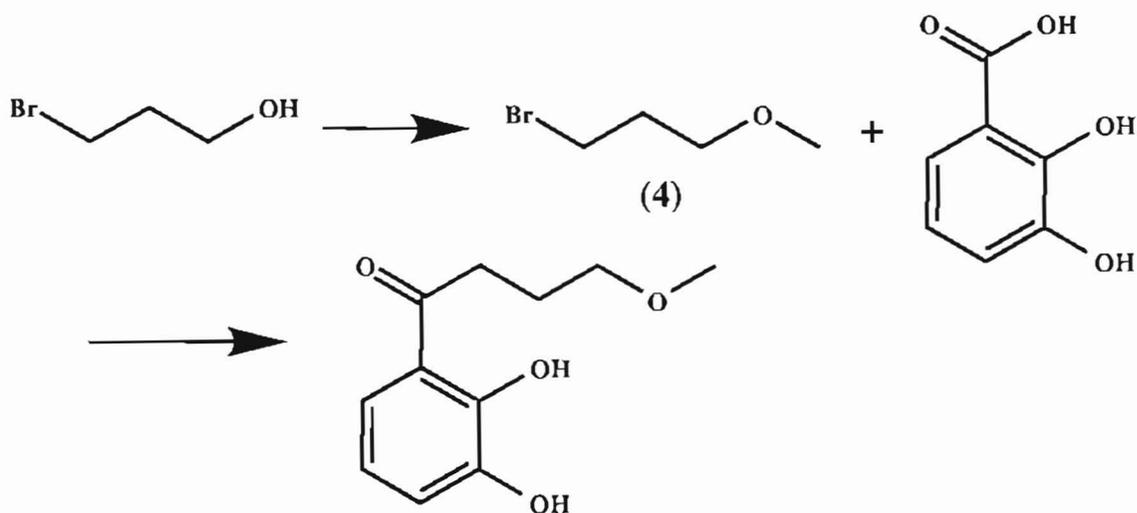
Scheme 3: Early proposed synthesis for the methoxy ketone

Analysis of the model reaction (**scheme 4**) was never completed as the brominated ether side chain (**4**) for the methoxy ketone could not be synthesized.
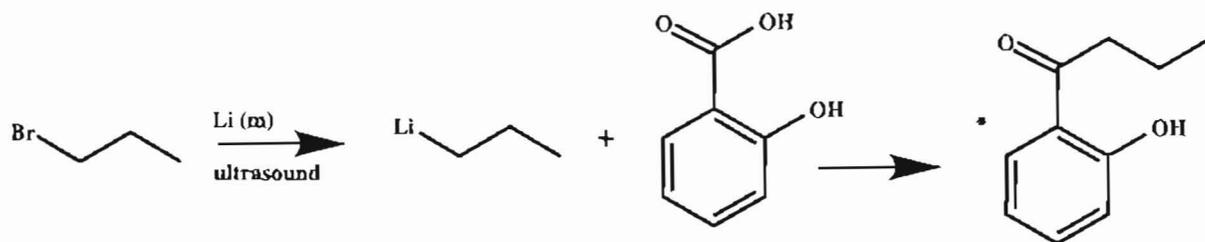
Scheme 4: Model reaction for the synthesis via scheme 3

More recently, several synthesis attempts by our group have been made using protection of the 1,2–diol system.[13] **Scheme 5** shows a retrosynthetic analysis for the methoxy ketone that includes the oxidation of a secondary alcohol on the side chain. The high reactivity of the diol system would hinder a selective reduction of the secondary alcohol without first protecting the diols.

(5)
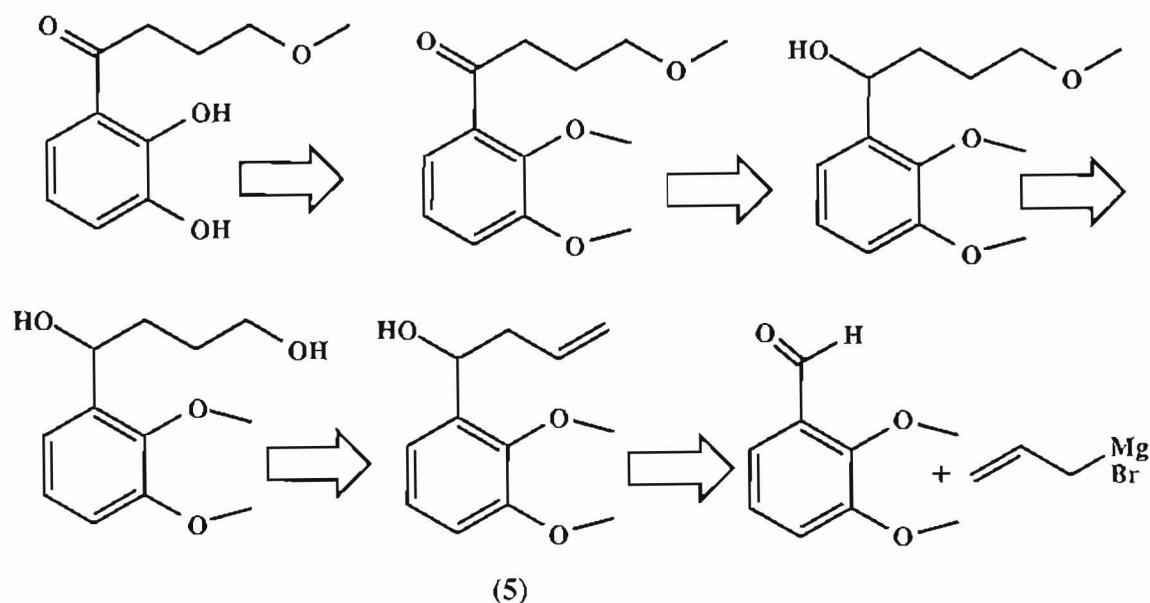
Scheme 5: An early retrosynthesis for the complete synthesis of the methoxy ketone

This scheme utilizes methoxy groups as protecting groups, followed by a Grignard reaction of 1–propenylmagnesium bromide to yield the secondary alcohol.

Both the protection of the diol system and the formation of the secondary alcohol (5) were successfully completed, but purification of 5 could not be achieved.
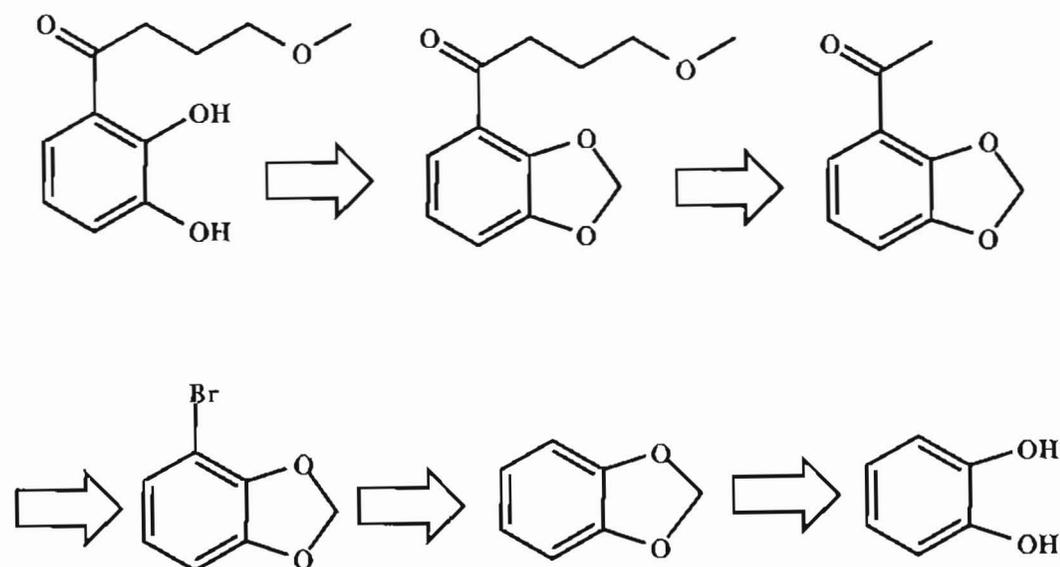
Scheme 6: A second early retrosynthesis utilizing protecting groups

A second attempt at utilizing protecting groups is shown in **scheme 6**. The hydroxy groups of the catechol starting material were protected in high yield using KF, distilled DMF and dibromomethane. The next step was bromination of the aromatic ring in order to add the carbonyl, but here this procedure was abandoned. Although only one equivalent of bromine was used, the reaction repeatedly formed a dibrominated species (**scheme 7**).
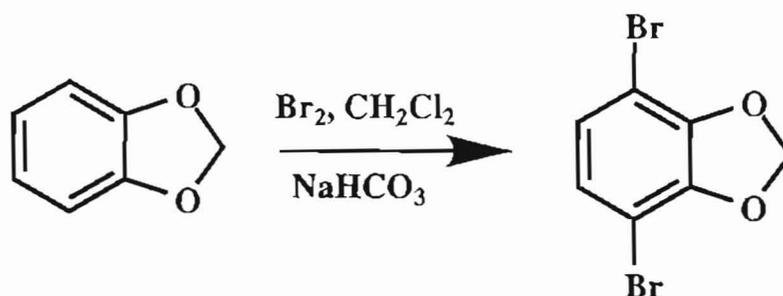
Scheme 7: Bromination of the protected catechol

A way around the bromination step was developed and is shown in **scheme 8**. This method was successful until purification of **6** was attempted. Distillation of the reaction product left some residual starting material and the use of TLC plates could not find an appropriate solvent in which to run a column. Model reactions for the remaining steps of **scheme 8** were successfully completed, but purification of **6** was never obtained and this synthetic route was never completed.
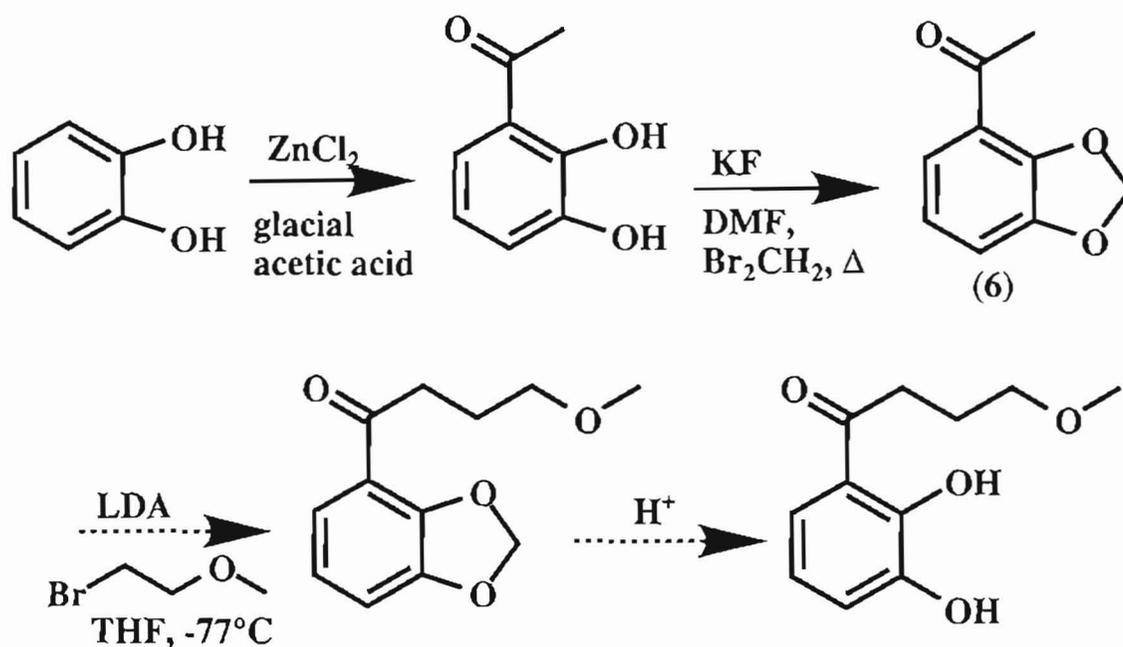
Scheme 8: Complete synthesis attempt for the methoxy ketone

Problems with the purification of these reaction products led our group to abandon these attempts. A new methodology was developed to synthesize the ether side chain first and then add it to catechol using a Friedel–Crafts acylation.

Retrosynthetic Analysis

Our current work on 1–(2,3–dihydroxyphenyl)–4–methoxy–1–butanone entails the use of catechol (1,2–benzene diol) for an electrophilic attack by a tertiary carbocation. Once the appropriate acid chloride side chain is made, it can be attached to the aromatic ring using a Friedel–Crafts acylation. This retrosynthetic route **(scheme 9)**, which builds the side chain in its entirety before addition of the diol, does not require the use of protecting groups as did previous work. Since the highly reactive diol system is not added until the final step of the synthesis, it will not be affected either by early synthetic steps or the acylation reaction.
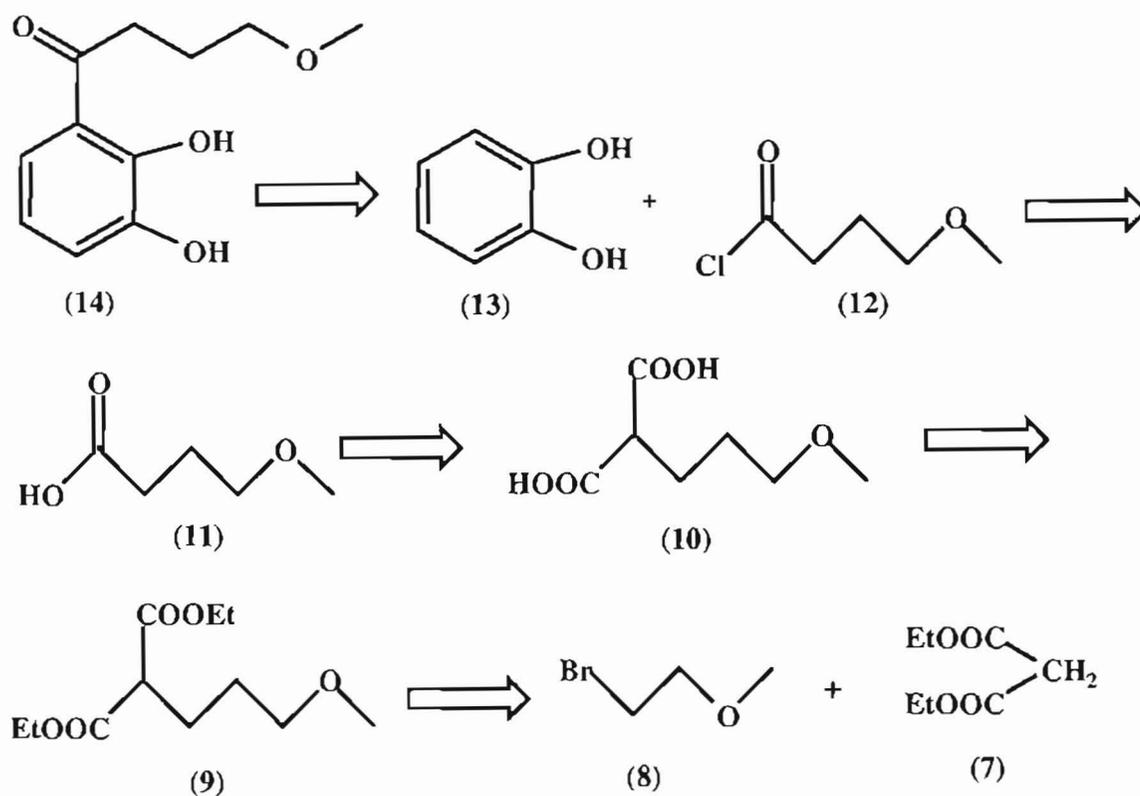
Scheme 9: Current retrosynthesis of
1–(2,3–dihydroxyphenyl)–4–methoxy–1–butanone

Alkylation of diethyl malonate (7) with bromoethyl methyl ether (8) gives a diester (9), which can then be hydrolyzed to give the diacid (10). The monoacid (11) can then be obtained through decarboxylation. The necessary acid chloride (12) can be made from the reaction of the monoacid and thionyl chloride and can then be attached to the catechol (13) using any of a variety of Lewis acids (AlCl$_3$, TiCl$_4$, H$_2$SO$_4$) to give our target molecule (14).
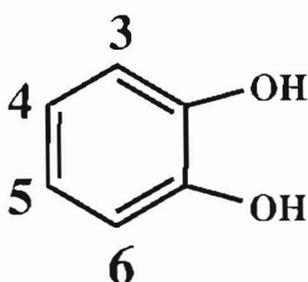
Figure 6: Positions of 1,2-benzene diol (catechol)

We expected to obtain a mixture of isomers of the final product since the hydroxy groups are ortho/para directors. Basic steric hindrance arguments favor the undesired isomer, as the 4 and 5 positions of the catechol are less blocked by the bulky hydroxy groups (figure 7).
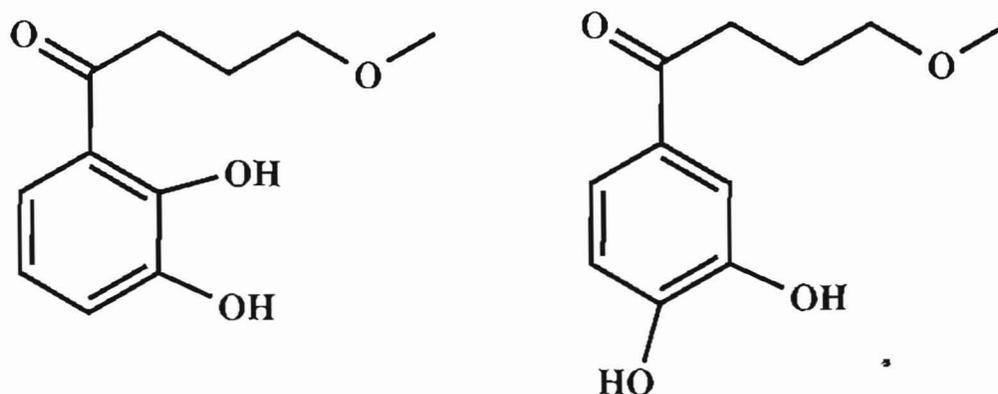
Figure 7: Structures of the expected isomers

A semi-empirical PM3 calculation of the HOMO reactivity of these two positions was performed **(figure 8)** and confirmed our suspicions that the 3 and 6 positions of 1,2-benzene diol are less reactive than the more open 5 and 6 positions.

We were able to find a literature precedence reported by Wähälä and Hase[14] that suggests that the desired isomer can be obtained in small yield. With this understanding we decided to continue with this synthetic route, as only a small amount (50-100 mg) of the methoxy ketone is needed to confirm the structure of the brown rot extract.
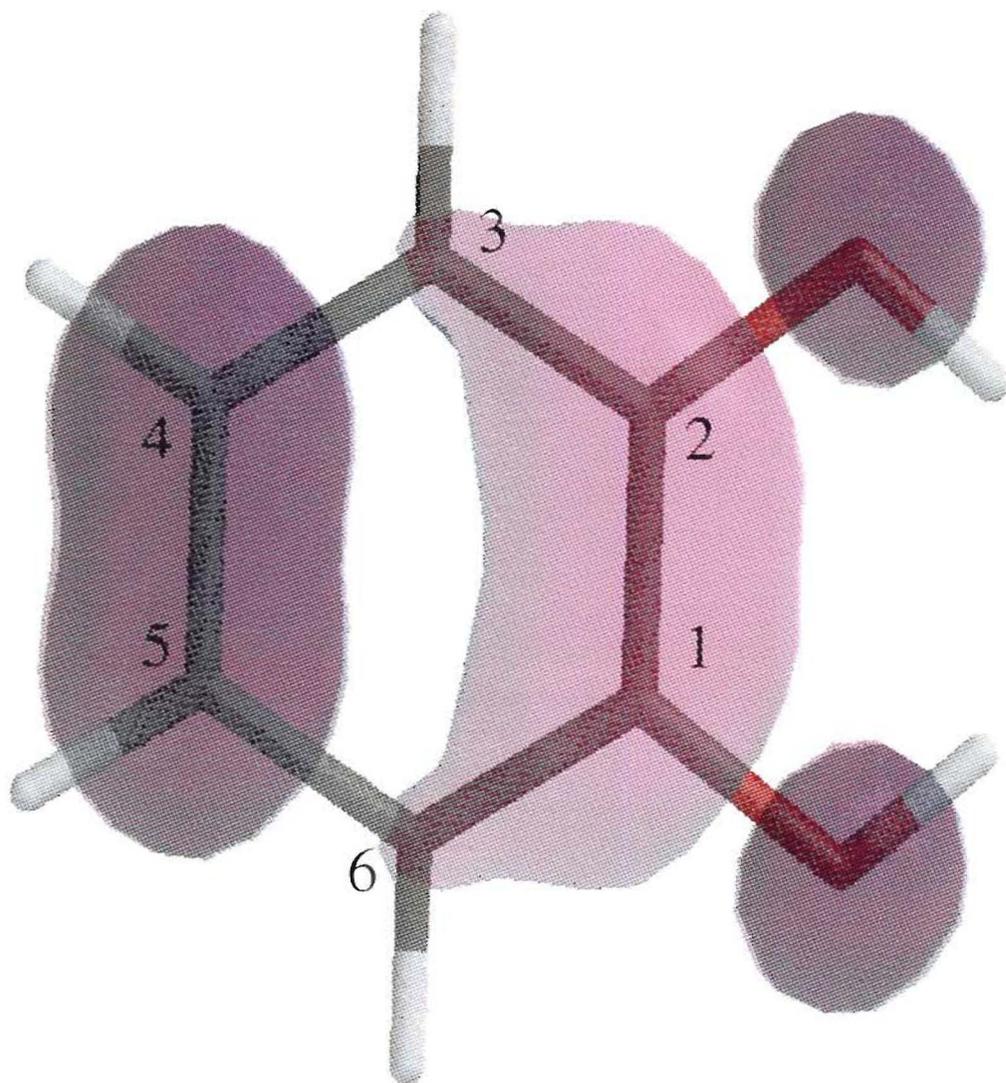
Figure 8: Potential HOMO reactivity of catechol
based on a semi-empirical PM3 calculation

Results/Discussion

The first step in our synthesis was the reaction of diethyl malonate and bromoethyl methyl ether. Due to the high cost of the ether starting material, several model reactions were run in order to find optimal conditions.

The first test (scheme 10) used dimethyl malonate (14) and butyl bromide (15) with NaH to give the diester dimethyl butyl malonate (16).
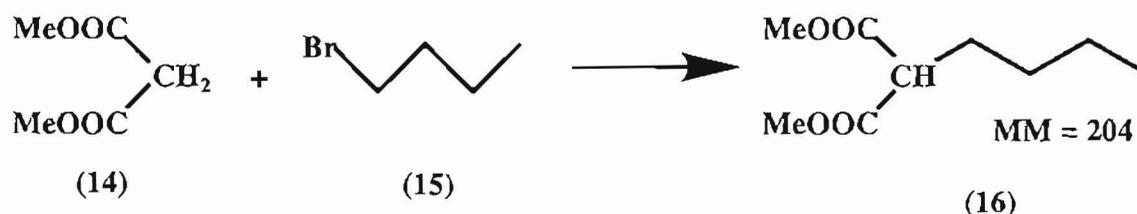
Scheme 10: Model reaction for the alkylation step

Unfortunately, GC/MS analysis showed no indication of a successful reaction under these conditions. The same reaction was run using a stronger base, MeO^-, and again no evidence of the diester products was observed.

A literature search of similar reactions yielded a procedure reported by Rastetter[15] using NaH in THF as the solvent for the alkylation. Using dimethyl malonate (14) and bromoethyl ethyl ether (16) (scheme 11), we followed the procedure of Rastetter and added the reactants at 0°C before heating to reflux. Under these reaction conditions, the ester synthesis was successful and the product (17) was synthesized.
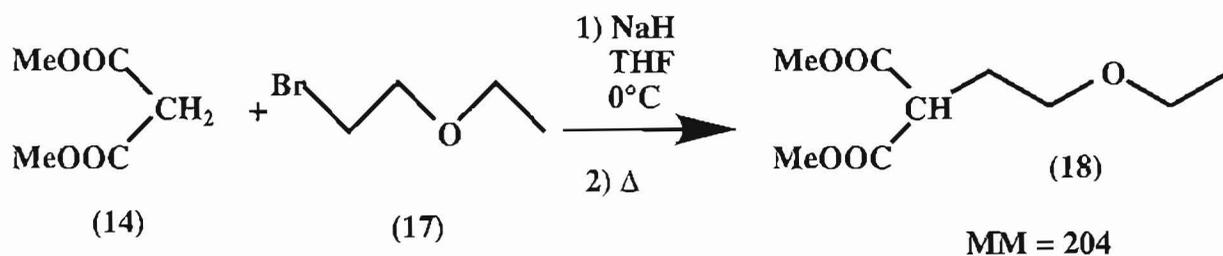
Scheme 11: Successful alkylation model reaction of the mthoxy ketone synthesis

However, the GC/MS of the reaction product shows only a small peak corresponding to the desired diester, with mostly starting material remaining.

We thought it necessary to improve on this yield. Using diethylmalonate, the alkylation was attempted again (scheme 12) using a procedure reported by Adams and Marvel.[16]
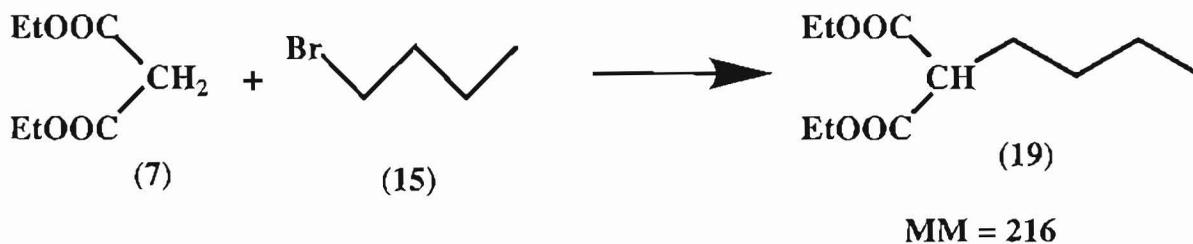
Scheme 12: Alkylation of diethyl malonate and butyl bromide

After several attempts under various reaction conditions, the GC/MS showed no evidence of a $m/z = 216$ peak for the synthesis of diethyl butyl malonate (19).

Troubled by the lack of evidence for our product of the alkylation reaction, we turned to the characterization method being used. Mass spectra of esters are generally characterized by two different peaks. The fragmentation peak resulting from the

McLafferty Rearrangement, whose mechanism is shown in **figure 9**, tends to dominate the mass spectrum of an ester.[17] This rearrangement results from the transfer of a γ–hydrogen to the carbonyl oxygen to produce an alkene as the neutral product and the radical cation detected by the mass spectrometer. The peak of the radical cation is almost always found in mass spectra of many carbonyl compounds.
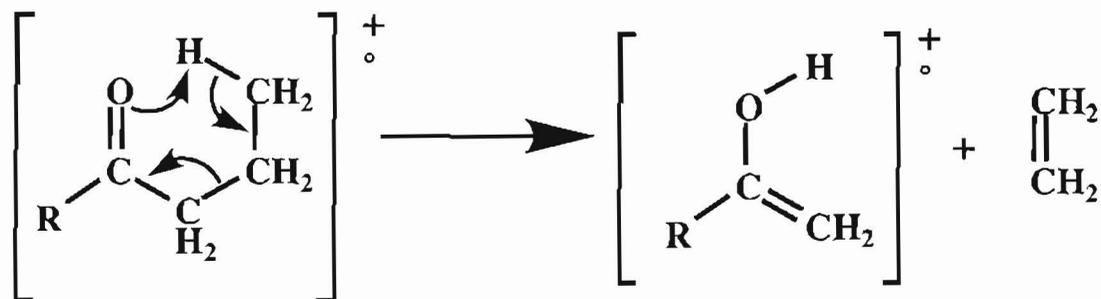
Figure 9: The mechanism for the McLafferty Rearrangement

For the diester used in our model reactions, the peak resulting from the McLafferty Rearrangement should be found at $m/z = 158$. None of our spectra contained this peak.

Looking further into peaks that should be found for esters, a set of six peaks resulting from α–cleavage should also be fairly prominent: R^+, RCO^+, RCO_2^+, R'^+, $R'O^+$, and $R'OCO^+$.[17] Of this set of six, the peak with the largest intensity should be the RCO^+ peak. Since we are working with a diester, the α–cleavage peaks become a bit more difficult to predict because there are two sites for cleavage. **Table 1** outlines the peaks expected from the α–cleavage of our model compound due to the cleavage of the ester groups.
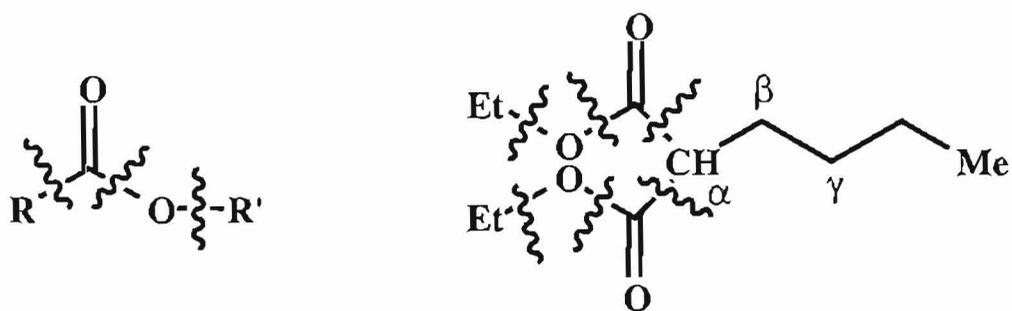
Figure 10: Potential sites of α–cleavage, generically and in our diester

Table 1: Expected α–cleavage peaks of diethyl butyl malonate

	R^+	RCO^+	RCO_2^+	R'^+	$R'O^+$	$R'OCO^+$
one ester	$[C_8H_{16}O_2]^+$	$[C_9H_{16}O_3]^+$	$[C_9H_{16}O_4]^+$	$[C_2H_5]^+$	$[C_2H_5O]^+$	$[C_2H_5O_2]^+$
m/z peak	144	172	188	29	45	61
two esters	$[C_5H_{11}]^{2+}$	$[C_6H_{11}O]^{2+}$	$[C_6H_{11}O_2]^{2+}$	$[C_2H_5]^-$	$[C_2H_5O]^+$	$[C_2H_5O_2]^+$
m/z peak	35.5	49.5	57.5	29	45	61

The spectra of our reactions showed only two of these α–cleavage peaks, at $m/z = 29$ and $m/z = 45$. Since both of these peaks would also be present in the mass spectrum of our starting material, we wanted to have a better characterization for this alkylation step. Looking at the higher m/z peaks, were able to find was a $m/z = 173$ peak (**Appendix, spectrum 1**), the largest in each of our spectra for this reaction. This corresponds to the resonance stabilized γ–cleavage of our diester (**figure 11**), another less probable possibility of cleavage in the mass spectrum.[18] Using this $m/z = 173$ peak and the peaks

-28-

of smaller m/z, we were finally able to characterize the product of our model reactions as the desired diethyl butyl malonate (19).
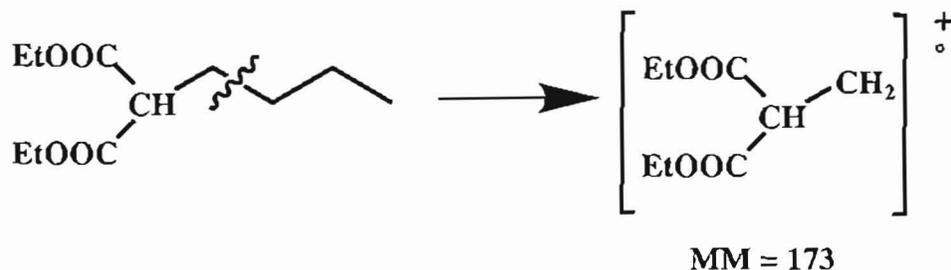
Figure 11: γ–cleavage of diethyl butyl malonate

Interestingly, when a pure sample of diethyl butyl malonate from Acros was run through the GC/MS as a comparison (**Appendix, spectrum 2**), we were further baffled to find that the fragmentation pattern of this pure sample did not correlate to the peak we had identified from the spectrum of the reaction. To make it even more confusing, a ^{1}H NMR was taken of both the pure sample and the reaction peak as collected by gas chromatography; they were very similar and confirmed both as diethyl butyl malonate.

After realizing that the alkylation product was likely to be the desired ester, the next step was to test the hydrolysis of the diester to give the diacid (**scheme 13**). Using a distilled sample of diethyl butyl malonate, two equivalents of base were added. We expected to obtain the diacid product (20).

EtOOC
    CH
EtOOC   (19)

1) OH⁻
2) H₃O⁺

HOOC
    CH
HOOC   (20)

MM = 164
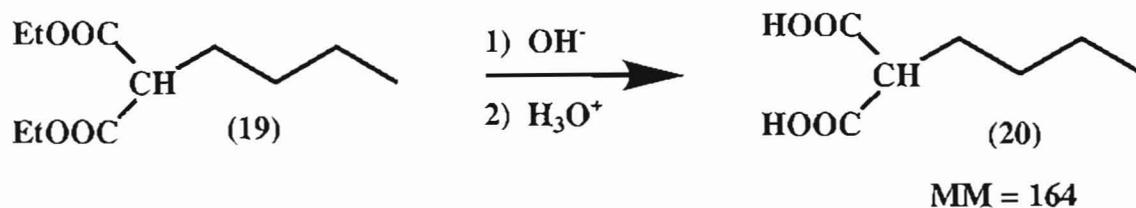
Scheme 13A: Expected hydrolysis product

However, upon work–up of the reaction, we obtained hexanoic acid (21) (**Appendix, spectrum 3**).

EtOOC
    CH
EtOOC   (19)

1) OH⁻
2) H₃O⁺

O

HO   (21)

MM = 116
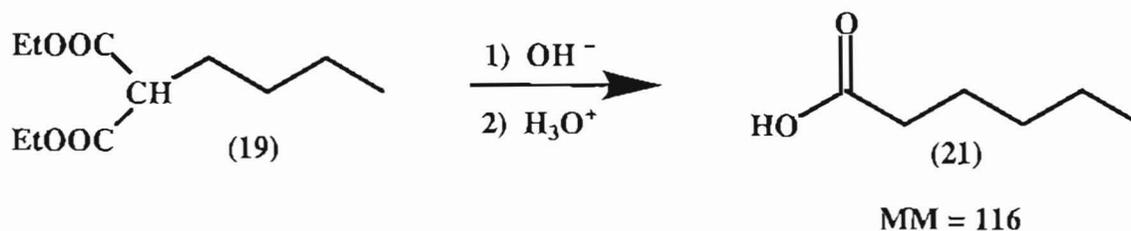
Scheme 13B: Actual hydrolysis product

The product that was actually made by this reaction was the monoacid (21). The diester was not only hydrolyzed, but also decarboxylated in this reaction to give a transparent liquid that can be purified from residual starting material by distillation. This means that we had one less reaction step to do in our synthesis.

After optimizing the alkylation and hydrolysis steps, the next reaction in our synthesis of 1–(2,3–dihydroxyphenyl)–4–methoxy–1–butanone was to make the acid chloride (22) to then undergo the Friedel–Crafts acylation to attach the catechol. We used the purified hydrolysis product from **scheme 13B** to run the model reaction using thionyl chloride (**scheme 14**).
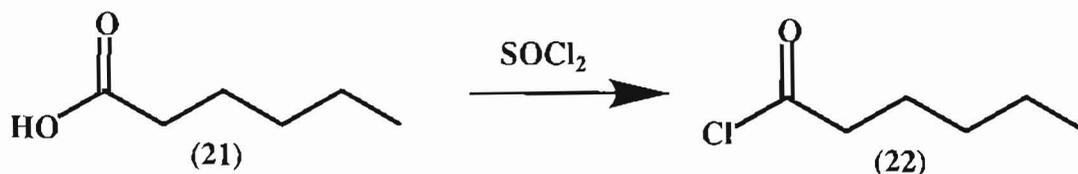
Scheme 14: The synthesis of the desired acid chloride

We then tested the unpurified acid chloride product (22) with the previously tested Friedel–Crafts reaction. Using TiCl₄ as the Lewis acid, we attempted to complete our model reaction to give 23 (scheme 15). However, the GC/MS of the reaction product gave no indication that we had successfully made our product. We believe that any unreacted thionyl chloride may have hindered the reactivity of the acid carbocation which is essential to obtaining our desired product.
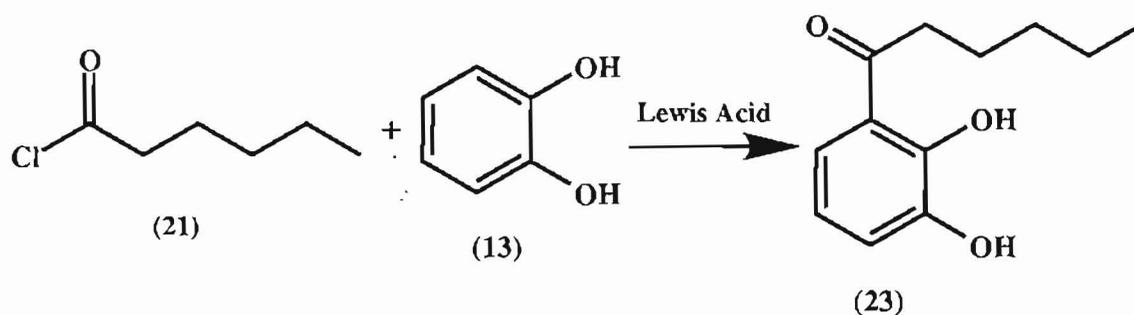
Scheme 15: Expected outcome of the Friedel–Crafts acylation

Model reactions of this step had been extremely successful both in attaching the side chain and in obtaining the desired isomer (scheme 16). Early tests used AlCl₃ and TiCl₄ to determine whether varying strength of the Lewis acid made a difference. We

had expected that the stronger acid, AlCl₃, would give a greater yield of the acylated molecule. However, it was TiCl₄ that gave a greater product yield, as well as a much cleaner final product as shown by the GC/MS spectrum. Some surprising results about the product ratios were also obtained.
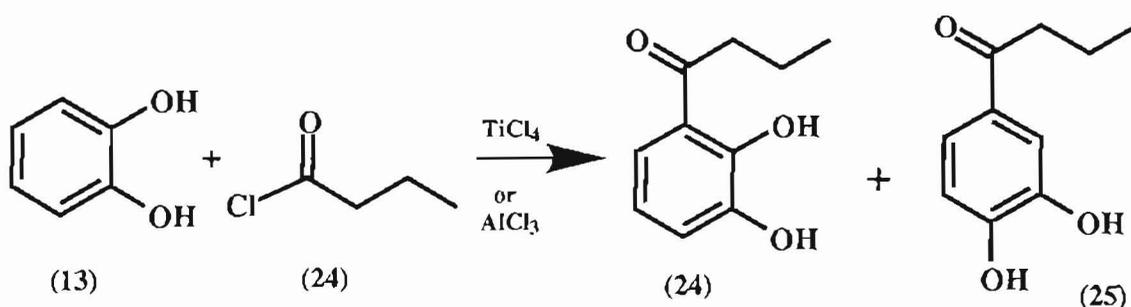
Scheme 16: Comparision of lewis acid affects on model reactions

The model reactions of catechol **(13)** and butryl chloride **(24)** in the presence of either acid yielded both isomers **(24 and 25)**, as expected, but the major product changed depending on the acid. In the case of the AlCl₃, the GC/MS spectrum **(Appendix, spectra 4A and 4B)** of the product showed two major peaks in a ratio of 2.5 to 1. The spectrum of the TiCl₄ reaction **(Appendix, spectra 5A and 5B)** showed the same two peaks, but in a ratio of 1 to 4. Attempts made to separate the isomers to determine their identity (and thus which was our desired isomer) were made by gas chromatography and TLC, but no suitable solvent could be found for separation. The packed column of the preparative GC was unable to give a separation as the longer capillary column of the GC/MS did. The differences in the polarities of the columns were source of the separation difficulties here. The GC column has a non–polar stationary phase, compared to the very polar polyethlylene glycol column of the preparative GC. If this separation

can be achieved and the isomers identified, we can maximize the yield of our isomer depending on which Lewis acid is used.

To further investigate the product isomers and try to ascertain their identities, another model reaction using t-butyl alcohol (26) was tested. The Lewis acids tested were $TiCl_4$ (Appendix, spectrum 6), $AlCl_3$ (Appendix, spectrum 7), and H_2SO_4 (Appendix, spectrum 8). Catechol was reacted with the alcohol in each of these acids to give a mixture of the isomer products (scheme 17).
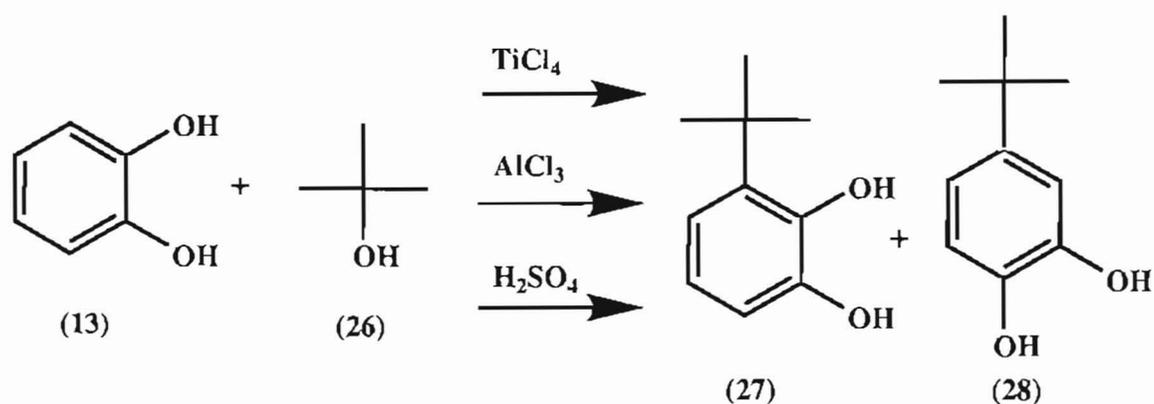
Scheme 17: Lewis Acid test reactions with *t*-butyl alcohol

As these products are known compounds, we were able to use the GC/MS library of compounds, to identify the major product of the H_2SO_4 reaction as 1,1–dimethylethyl–1,2–benzene diol (27) with substitution in the desired position. The undesired isomer, 4–(1,1–dimethylethyl)–1,2–benzene diol (28), was identified as a minor product. Comparing the spectra of the isomers, there are small, but definite differences in the spectra of the different positions of the t–butyl group on the catechol;

the fragmentation pattern of our major product matches better with the desired isomer, as confirmed by the library. The tests with $TiCl_4$ and $AlCl_3$ showed only one product peak, though much smaller, also identified as the desired isomer both by the library and by the retention time of the peak on the chromatograph.

Having optimized all of our model reaction conditions, it was time to proceed with our planned synthetic route (**scheme 18**).
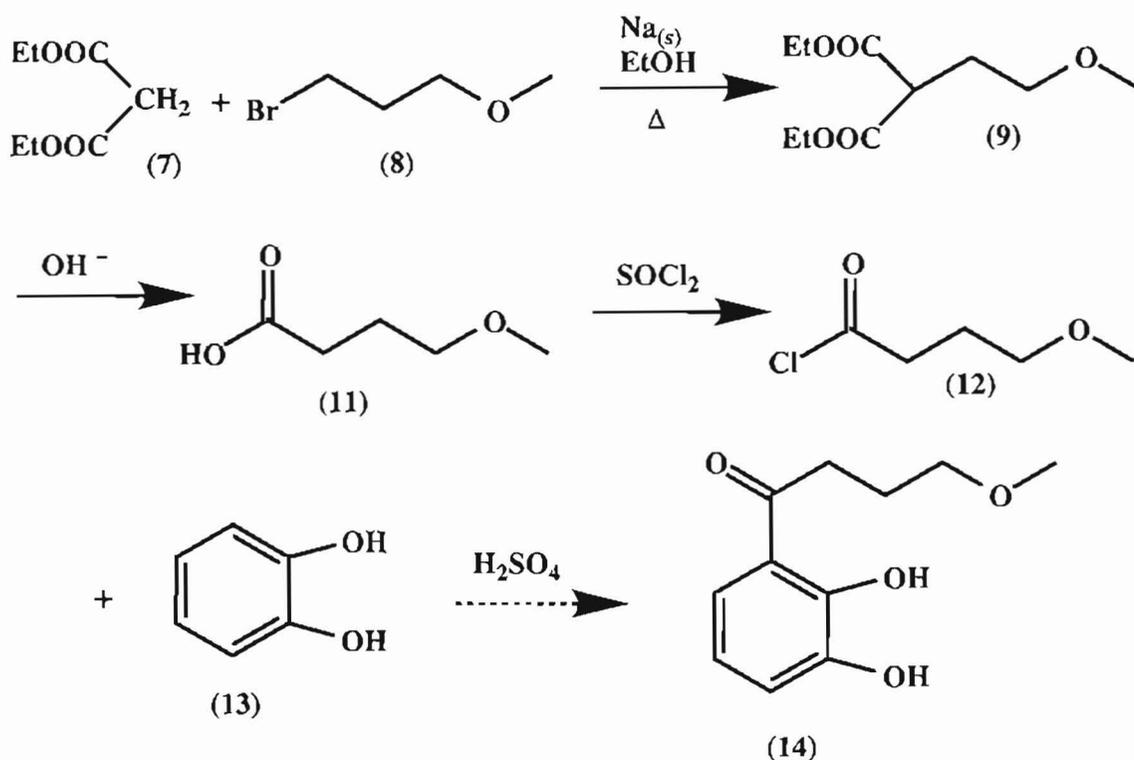
Scheme 18: Working synthetic route to
1–(2,3–dihydroxyphenyl)–4–methoxy–1–butanone

We began with the alkylation step using the procedure reported by Adams and Marvel ,[16] as it was the one that we had the most success with in our model reactions. Using diethyl

malonate and bromoethyl methyl ether, the alkylation was carried out with sodium metal in ethanol (**scheme 19**).
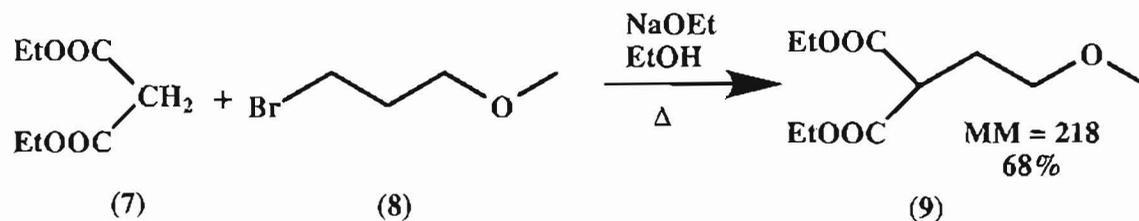
Scheme 19: Alkylation step of the synthesis of the methoxy ketone

The mass spectrum of the product resulting from **scheme 19 (Appendix, spectrum 9)** was somewhat puzzling due to the aforementioned fragmentation of these types of compounds. Although the fragmentation pattern fit well, we wanted an absolute confirmation that this was our product. A pure fraction of the product was collected by gas chromatography and a ^{1}H NMR spectrum (**Appendix, spectrum 10**) was taken. The NMR fit exactly our diester and we were able to continue to the hydrolysis step (**scheme 20**).
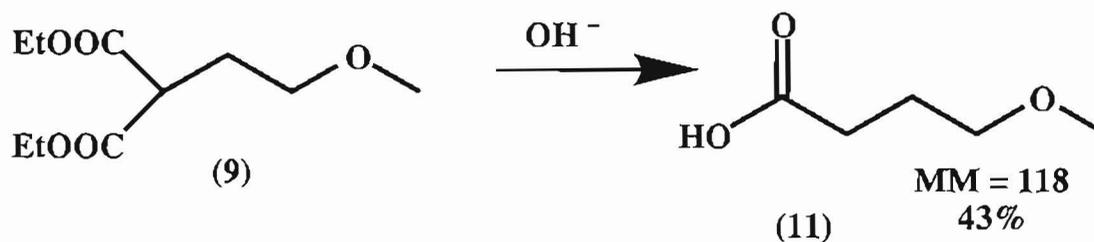
Scheme 20: Hydrolysis of the diester to the mono acid

Addition of base to the diester resulted in a product that the GC/MS spectrum (**Appendix, spectrum 11**) confirmed to be 4-methoxy butanoic acid (**11**). Unfortunately the yield of this reaction was low, only 43%.

Having taken a much larger hit on the yield of our product than we expected, we again turned to the literature hoping for a way in which we could avoid the problematic acid chloride step. Wähälä and Hase[14] report using BF_3 to react a mono acid directly with catechol to obtain an isomeric mixture of products, with substitution in our desired position with a 15% yield. Although this was a smaller yield than desired, it is likely enough to confirm our product. Following Wähälä and Hase's procedure, we reacted the monoacid (**11**) with BF_3 (**scheme 21**) in an attempt to complete our synthesis of 1-(2,3-dihyroxyphenyl)-4-methoxy-1-butanone.
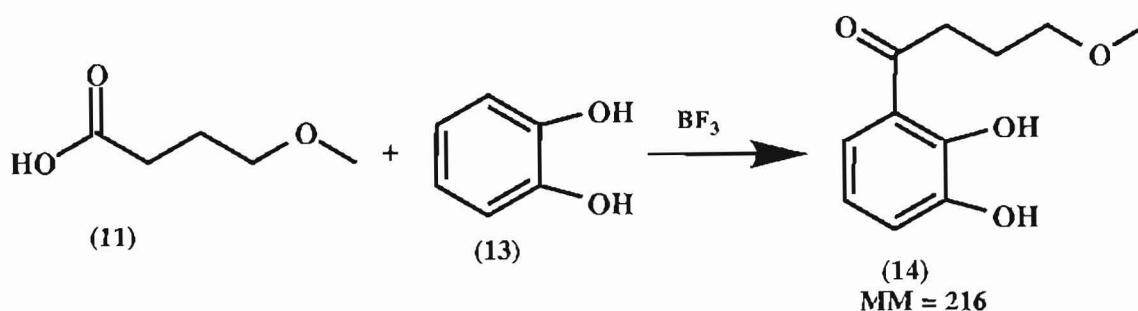
Scheme 21: Attempted BF_3 reaction of the acid with catechol

The GC/MS spectrum of this reaction product (**Appendix, spectrum 12**) showed a single peak with M/Z = 198. Although this is not the mass of our product, it is interesting to note that this could correspond to the loss of water from the molecule. In previous, unpublished work done by the Mundy group, systems such as these ether systems have been shown to lose water in the mass spectrometer and this M-18 peak often dominates the fragmentation spectrum of such compounds.[19] Since mass spec was

-36-

unable to confirm our product, a ^{1}H NMR was taken of the remaining black solid but it was in too low of a concentration to see any peaks above the noise of the NMR.

Returning to the acylation with the acid chloride to complete our synthesis, we reacted the remaining monoacid with thionyl chloride to make the acid chloride (**scheme 22A**).
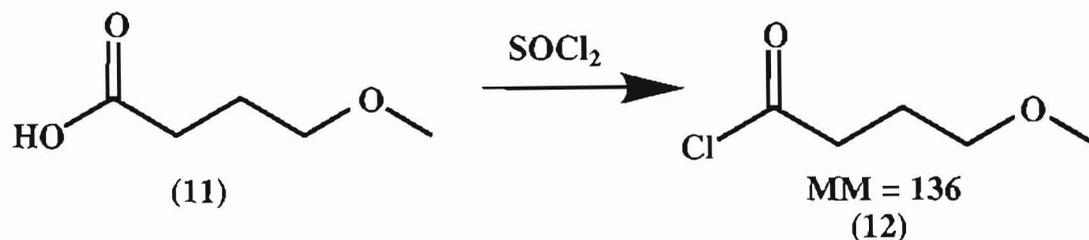
Scheme 22A: Anticipated reaction of 4–methoxy butanoic acid with thionyl chloride

The GC/MS of the crude product (**Appendix, spectrum 13 A and B**) of this reaction had several peaks. A small amount of a $m/z = 136$ peak was present, corresponding to the expected acid chloride product. However the major peak in the spectrum was $m/z = 158$. This corresponds to the reaction of the diacid (**10**) with one equivalent of thionyl chloride to generate the acid/acid chloride product (**29**) seen in scheme 22B.
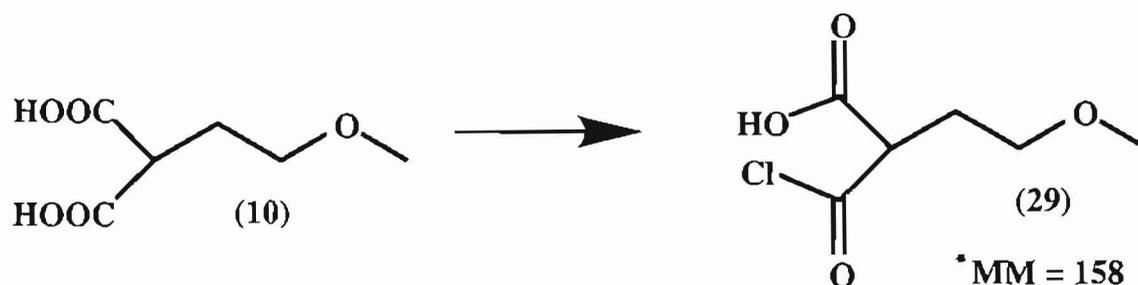
Scheme 22B: Main product of the acid chloride reaction

Apparently the hydrolysis did not result in a complete decarboxylation of the product as seen in model reactions. It is possible that while some decarboxylation took place as the reaction progressed, that decarboxylation was also occurring in the GC column as we were trying to characterize our product. The consequence of this would be the appearance of a m/z peak corresponding to the monoacid, as was detected after CO_2 was lost in the column.

Correcting this problem was straightforward: heat the product to decarboxylate it fully through the mechanism in **figure 12**.
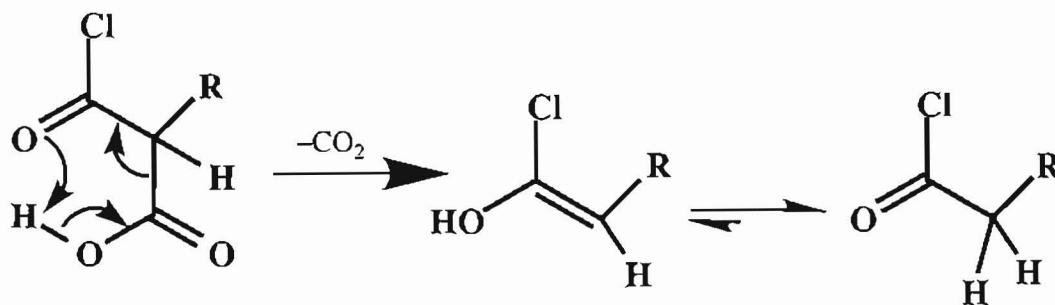
Figure 12: Decarboxylation mechanism for the acid/acid chloride product

Unfortunately, heating resulted in a thick intractable black. As the acid chloride must be completely pure for the acylation reaction to be successful, we were unable to continue.

If isolating the purified acid chloride had been successful, the next step would be to complete the synthesis using H_2SO_4 as the Lewis acid to do the Friedel–Crafts acylation (**scheme 23**) with the catechol.
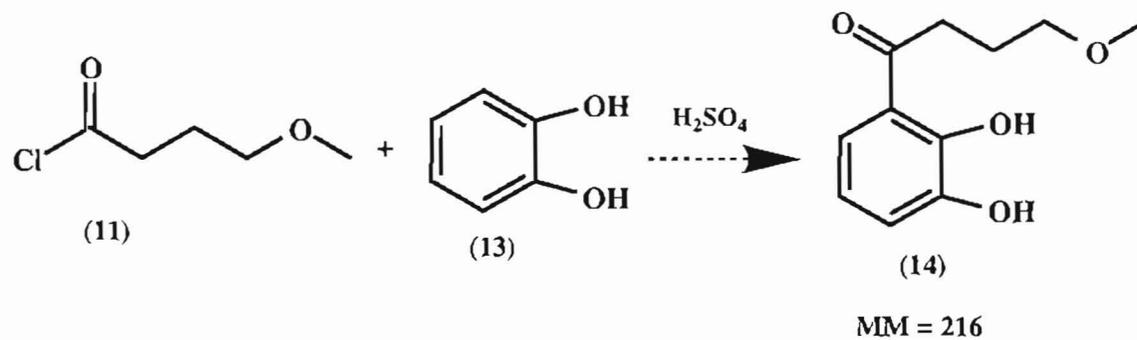
Scheme 23: The projected final step in the synthesis for scheme 18

A mixture of isomers would be obtained and the desired isomer (14) would need to be isolated, possibly by HPLC.

Conclusions

The goal of this project was the total synthesis and purification of 1-(2,3-dihydroxyphenyl)-4-methoxy-1-butanone **(14)** . Had we been able to complete this synthesis, structural data for our product would have been compared to that of the extract of the brown rot fungus *Gleophyllum traebeum* as a structural confirmation for the iron-chelating extract. Unfortunately, this synthetic route has not yielded our desired product, though model reactions for each of the procedural steps were successful.

There are several directions in which future focus of this project should be directed. The most important would be finding an efficient separation of the isomers obtained by the Friedel-Crafts acylation in order to better determine which of the Lewis acids studied will result in the maximum yield of our desired isomer. One such separation attempt may be using HPLC. Examination of the BF_3 reaction with the monoacid also needs to be done. The possible loss of water from our ether system is an interesting possibility that is without a good explanation. By increasing the scale of this reaction, an NMR spectrum could likely be taken to help determine the structure of the resulting product. If this reaction is found not to yield our product, further research needs to be done on either the purification of the acid chloride or on a more efficient way in which to make it. It would be terrific if this problematic step could be avoided altogether, but this may not be possible.

Experimental

General Procedures

^{1}H NMR spectra at 400 MHz were determined in CDCl$_3$ solutions containing *ca.* 1% TMS as an internal standard with a JEOL GSX–400/54 high resolution NMR spectrometer. GC/MS analyses were performed on a Hewlett–Packard 5890 gas chromatograph coupled to a 5970 series mass selective detector using Supelco 2–4026 15m x 0.25 capillary column packed with SPBM–1 (0.25 μm). Preparative GC separations were performed on a Gow–Mac Series 350 gas chromatograph using 8' x 0.25" 20% Carbowax 20M on Chrom–P 80/100 mesh column (injector port and detector set to 50°C, column temperature of 45°C; He flow rate = 8 mL/min). Thin layer chromatography (TLC) was done using Baker Flex IB–F silica gel plates using UV absorption. Dichloromethane, toluene, and ethyl acetate were used as purchased from Acros; anhydrous ether was purchased from Fischer. Absolute ethanol was purchased from Aaper and distilled with Na$_{(s)}$ prior to use.

Preparation of 18: Hexane (40 mL) was mixed with NaH (6.3 g, 60% dispersion in oil). After 15 minutes of mixing, the liquid was decanted from the solid NaH in order to remove the oil residue. Distilled THF (30 mL) was used as the solvent to react dimethyl malonate (23.0 mL, 0.2 mol) and bromoethyl ethyl ether (12.0 mL, 0.1 mol). The ether was added to the system before adding the malonate dropwise at 0°C. The reaction mixture was stirred and heated to reflux for 4 hours with a CaCl$_2$ drying tube to keep the system dry. Once the reaction was complete, water was added to the system to quench the reaction. The product was extracted three times with CH$_2$Cl$_2$. The organic layer was

dried with Na_2SO_4 (anhydrous) and the diester product was collected by removing the remaining solvent by rotary evaporation. Reaction was analyzed by GC/MS.

Preparation of 19: Absolute ethanol (250 mL) distilled with Na metal was used as the solvent to react diethyl malonate (3.2 mL, 0.02 mol) and butyl bromide (2.2 mL, 0.02 mol) in a round–bottom flask fitted with a $CaCl_2$ drying tube. Sodium metal (0.5 g, 0.02 mol) was added and stirred for 30 minutes. The reaction was refluxed for 2 hours. Once the reaction was complete (pH was basic), the volume was reduced by rotary evaporation. The product was acidified with 1M HCl before extracting three times with Et_2O. The ether layer was dried with Na_2SO_4 (anhydrous) and the diester product was collected by removing the solvent by rotary evaporation. A 71.4% (0.011 mol) yield of crude diethyl butyl malonate was obtained. Reaction was analyzed by GC/MS (**Appendix, spectrum 1 and 2**).

Preparation of 20 from 19: Under Ar, in a 50/50 water/ethanol mixture, distilled diethyl butyl malonate (1 mL, 4.54 mmol) and allowed to stir for five minutes to obtain a uniform solution. Two equivalents of NaOH (0.365 g, 10.0 mmol) were added and dissolved. The reaction was heated to reflux for two hours and then cooled. The pH was strongly basic. Solvent was removed by rotary evaporation to give a white solid that dissolved upon addition of 1M HCl used to acidify the product. The product was extracted three times with CH_2Cl_2 and the organic layer was dried using anhydrous Na_2SO_4. After filtering to remove the Na_2SO_4, the solvent was again removed using rotary evaporation to give the monoacid. The product was analyzed by GC/MS (**Appendix, spectrum 3**).

Preparation of 22: In an inert Ar atmosphere, 1 equivalent of thionyl chloride (0.58 mL, 4.9 mmol) was added to 10 mL of CH_2Cl_2. The acid from **scheme 15** was then added and the reaction was gently heated for 30 minutes. Once cool, the CH_2Cl_2 solvent was removed using rotary evaporation to obtain the acid chloride product. The reaction product was analyzed by GC/MS.

Preparation of 25 with $AlCl_3$: Under Ar and using excess toluene (10 mL) as the solvent, catechol (0.1 g, 0.9 mmol) was dissolved. Butryl chloride (0.1 mL, 0.9 mmol) was added to the reaction flask followed by one equivalent of $AlCl_3$ (0.12 g, 0.9 mmol) and the reaction stirred without heat. After 12 hours, the reaction was quenched with deionized H_2O. Extraction was done using Et_2O and the organic layer was dried with Na_2SO_4. The solvent was removed by rotary evaporation to obtain the product which was then analyzed by GC/MS **(Appendix, spectrum 4A and 4B)**.

Preparation of 25 with $TiCl_4$: Under Ar and using toluene (10 mL) as the solvent, catechol (0.1 g, 0.9 mmol) was dissolved. Butryl chloride (0.1 mL, 0.9 mmol) was added to the reaction flask followed by one equivalent of $TiCl_4$ (0.1 mL, 0.9 mmol) and the reaction stirred without heat. After 12 hours, the reaction was quenched with deionized H_2O. Extraction was done using Et_2O and the organic layer was dried with Na_2SO_4. The solvent was removed by rotary evaporation. The resulting product was analyzed by GC/MS **(Appendix, spectrum 5A and 5B)**.

Preparation of 27 and 28 using TiCl₄: Catechol (1.15 g, 10.4 mmol) was dissolved with stirring in excess toluene (10 mL). I–Butyl alcohol (1.0 mL, 10.4 mmol) was added and the reaction flask was capped and put under Ar. The Lewis acid $TiCl_4$ (1.15 mL, 10.4 mmol) was injected into the reaction vessel and left to react for 12 hours. Once complete, H_2O was used to quench the reaction and the product was extracted three times in CH_2Cl_2. This organic layer was dried using Na_2SO_4 and the solvent was removed by rotary evaporation to obtain the product, which was then analyzed by GC/MS **(Appendix, spectrum 6)**.

Preparation of 27 and 28 with AlCl₃: Catechol (1.15 g, 10.4 mmol) was dissolved with stirring in excess toluene (15 mL). t–Butyl alcohol (1.0 mL, 10.4 mmol) and $AlCl_3$ (1.39 g, 10.4 mmol) were added. The reaction flask was capped and put under Ar then left to react for 12 hours. Once complete, H_2O was used to quench the reaction and the product was extracted three times in Et_2O. The ether layer was dried using Na_2SO_4 and the solvent was removed by rotary evaporation to obtain the product. GC/MS was used for product analysis **(Appendix, spectrum 7)**.

Preparation of 27 and 28 with H₂SO₄: Using stirring, catechol (1.15 g, 10.4 mmol) was dissolved in excess toluene (10 mL). t–butyl alcohol (1.0 mL, 10.4 mmol) was added and the reaction flask was capped and put under Ar. Concentrated H_2SO_4 (0.55 mL, 10.4 mmol) was injected into the reaction vessel and left to react for 12 hours. Once complete, H_2O was used to quench the reaction and the product was extracted three times in CH_2Cl_2. This organic layer was dried using Na_2SO_4 and the solvent was removed by rotary evaporation to obtain the product. The resulting product was analyzed by GC/MS **(Appendix, spectrum 7)**.

Preparation of 9: Absolute EtOH was distilled with Na metal to give an anhydrous solvent. Absolute EtOH (150 mL) was put into a round–bottom flask with a stir bar fit with a CaCl$_2$ drying tube. Na metal (3.28 g, 72.0 mmol) was added and stirred until dissolved. Diethyl malonate (11.0 mL, 72.0 mmol) was added and stirred for 20 minutes before bromoethyl methyl ether (6.8 mL, 72.0 mmol) was added dropwise at 0°C. The ice bath was removed and the reaction was refluxed. After 4 hours, the pH was checked and confirmed to be basic. The volume of the reaction was reduced to give a white solid that dissolved upon addition of cold H$_2$O. The product was extracted three times with anhydrous Et$_2$O. The ether layer was dried with Na$_2$SO$_4$ (anhydrous) and the solvent was removed. Analysis of the product was done by GC/MS. The diester was distilled to purify. The liquid diester product has an approximate boiling point of 175°C at a pressure of 4 mm Hg. The purified diester product was obtained in a 68% yield after purification by distillation. GC/MS and ^{1}H NMR spectra were taken for identification of the resulting product. (**Appendix, spectra 9 and 10**). 1H NMR (CDCl$_3$–d) δ: 1.28 (6 H, t), 2.17 (2 H, q), 3.31 (3 H, s), 3.43 (2 H, t), 3.55 (1 H, t), 4.20 (4 H, q).

Preparation of 11 from 9: A portion of the purified diester product **9** (3.25 g, 15 mmol) was added to 100 mL of 50/50 EtOH/H$_2$O solution. Two equivalents of NaOH pellets (1.2 g, 30.0 mmol) were stirred until dissolved. The reaction was refluxed for 12 hours, during which time there was evolution of gas. The pH was checked to be basic before work–up. Excess solvent was removed by rotary evaporation until near dryness. A small amount of water (5 mL) was added to the reaction flask before the product was acidified with 1M HCl. Extraction was done three times in Et$_2$O and the organic layer was dried

with anhydrous Na_2SO_4. The ether was removed via rotary distillation and the product analyzed by GC/MS (**Appendix, spectrum 11**). A 43% product yield was obtained.

Preparation of 14 via BF$_3$: The monoacid product **11** (0.39 g , 3.3 mmol) from **scheme 20** was added under Ar to 20 equivalents of BF_3*2Et_2O (8.13 mL, 66.1 mmol). Heat was added. After 7 hours of refluxing, the reaction was cooled to room temperature and an aqueous solution of NaOAc (12 g/100 mL) was added to crystallize the solid product. A thick smoke evolved but cleared upon addition of Et_2O. The small amount of solid was filtered and rinsed with a small amount of cold water. Analysis of the product was done by GC/MS.

Scheme 22, acid chloride from the acid (11): In excess CH_2Cl_2 a portion of the acid product **11** (1.63 g, 13.8 mmol) was reacted with one equivalent of thionyl chloride, $SOCl_2$, (1.0 mL, 13.8 mmol). Upon addition of the thionyl chloride, the solution turned bright blue. Reflux was started and continued for 2 hours. GC/MS was used to analyze the product (**Appendix, spectrum 12**). Distillation was attempted for purification but was unsuccessful.

Appendix: Supporting Spectra

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Vial Number: 1

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3e+07

2.5e+07

2e+07

1.5e+07   MM = 216

1e+07

5000000

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                                                    β cleavage

                   29   α cleavage D'

1500000

                        α cleavage [R O]

1000000
                        55

                        69
                   42
500000   127
                        83   99   142 157
              18   115   199 216
                                                                  227
                                                                       243
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m/z-->   20   40   60   80 100 120 140 160 180 200 220 240

-48-
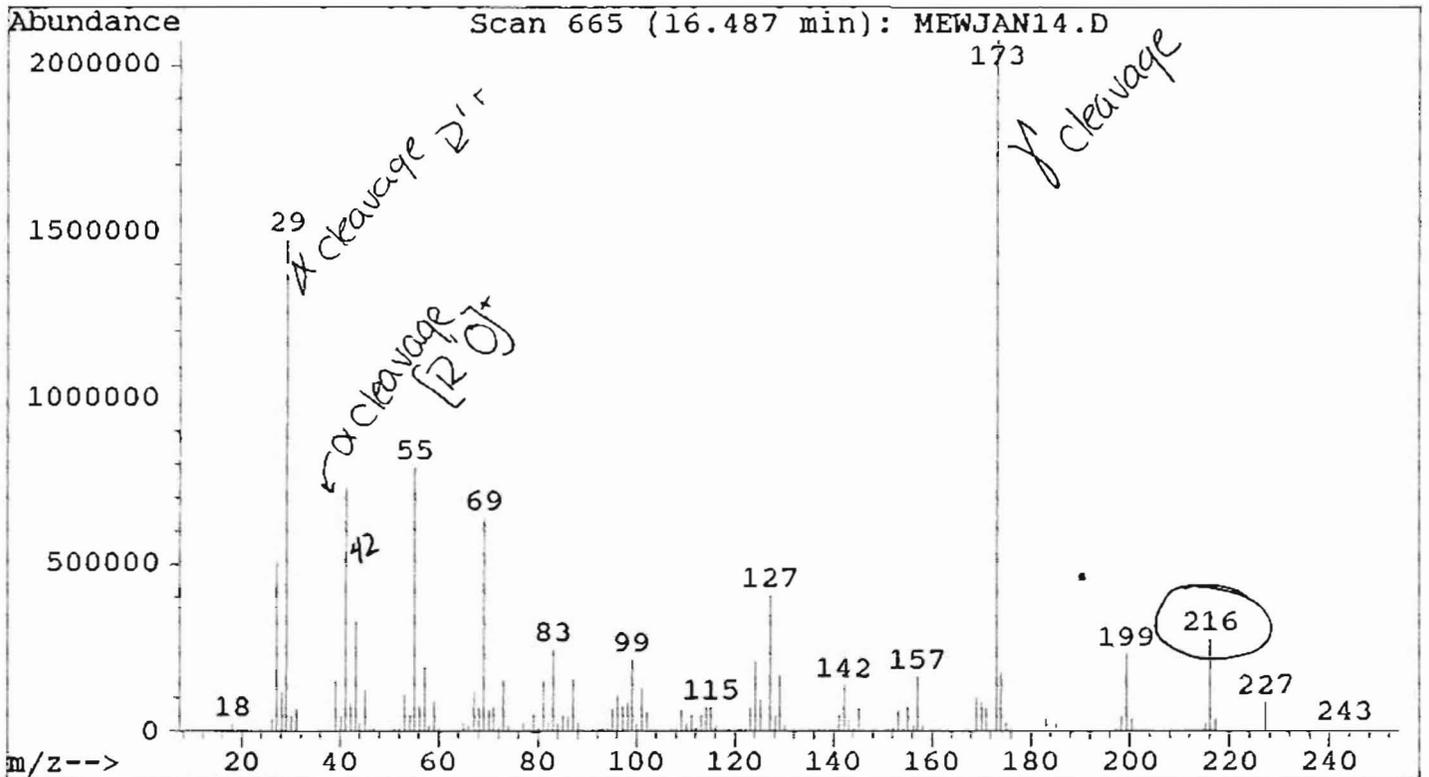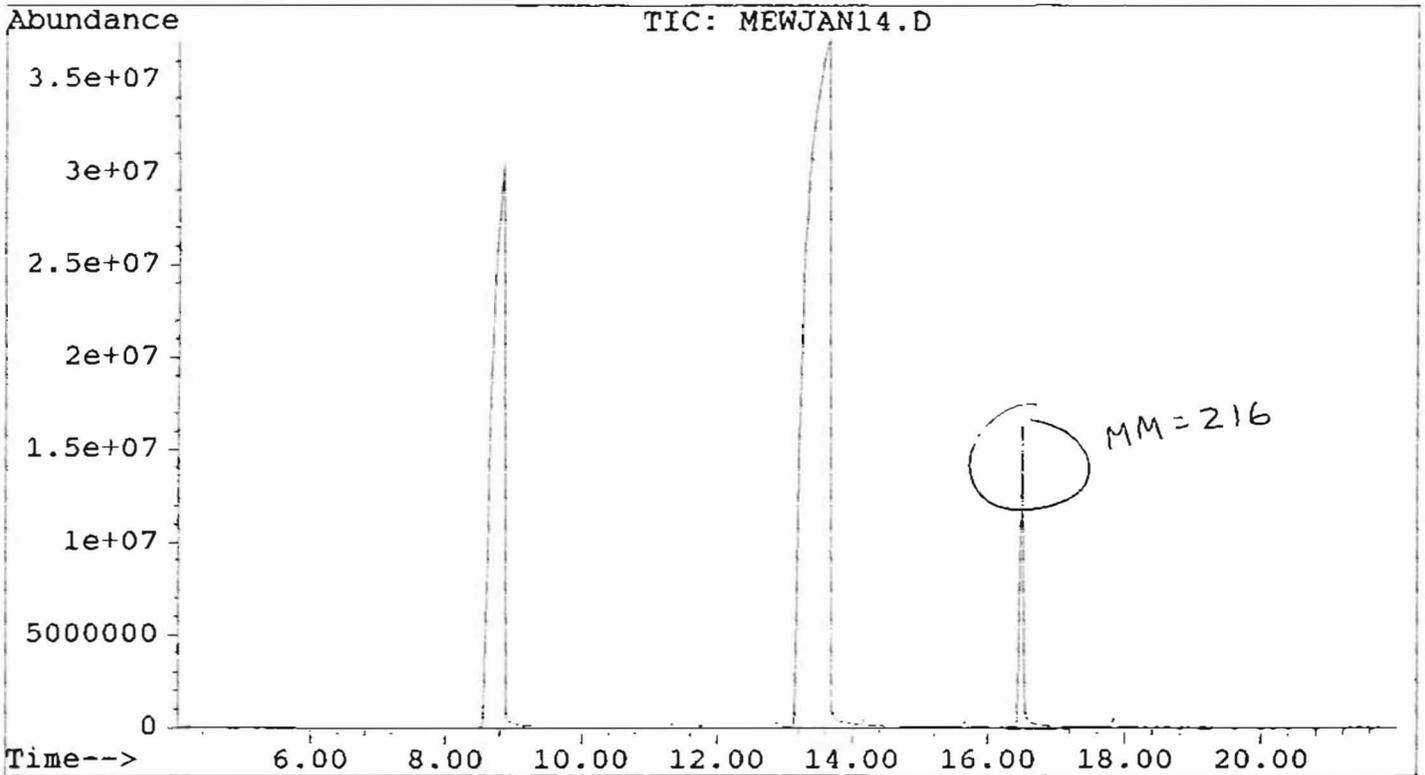
File   : C:\HPCHEM\1\DATA\MEWJAN10.D
Operator   : Michelle
Acquired   : 4 Jan 80   4:02 pm using AcqMethod _OCHEM
Instrument :   5970B
Sample Name: diethyl butyl malonate
Misc Info   : pure sample test run
Vial Number: 1

TIC: MEWJAN10.D

pure sample

$$EtOOC \atop EtOOC } CH-CH_2 \ CH_2-CH_2-CH_3$$

MM = 216

Scan 506 (13.499 min): MEWJAN10.D - CORRUPT

29 ✓

C_2H_5

217-57 = 160
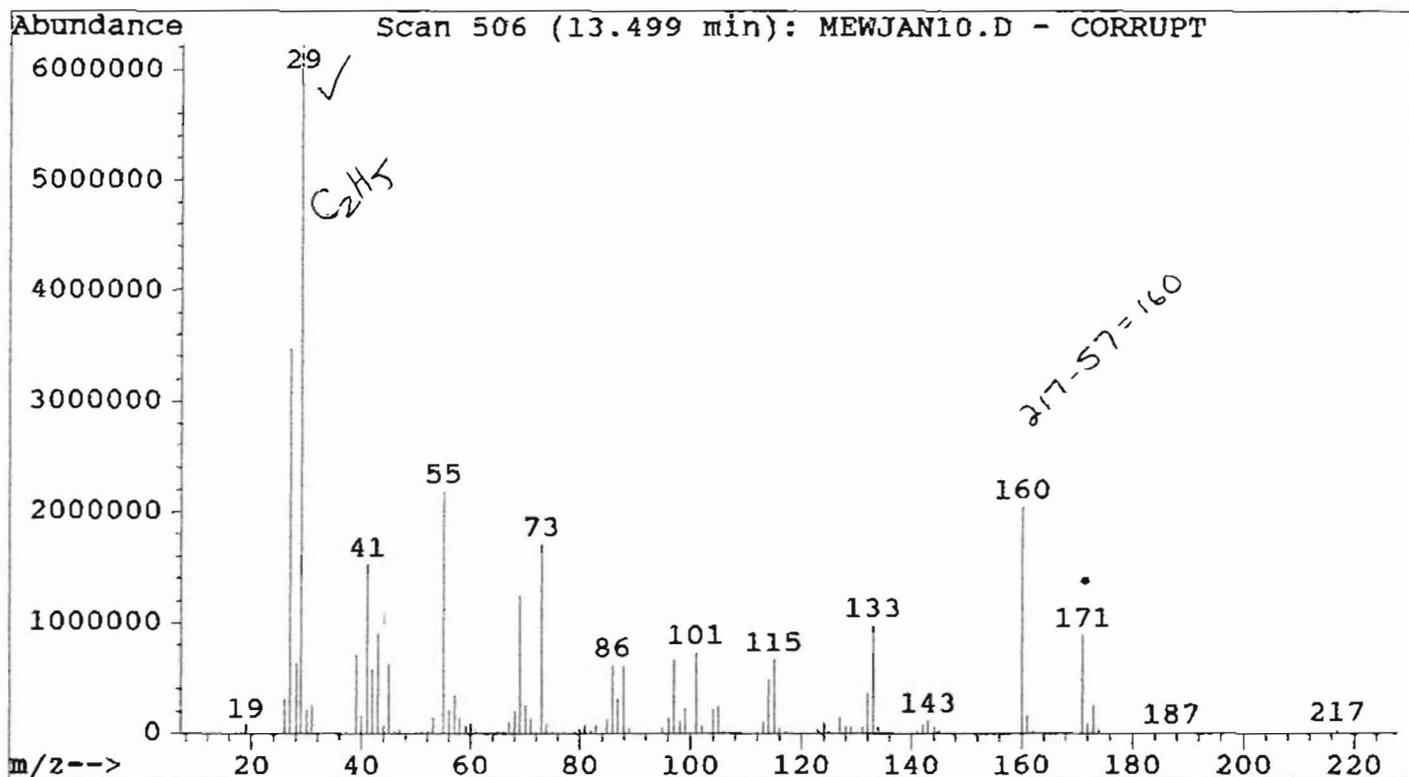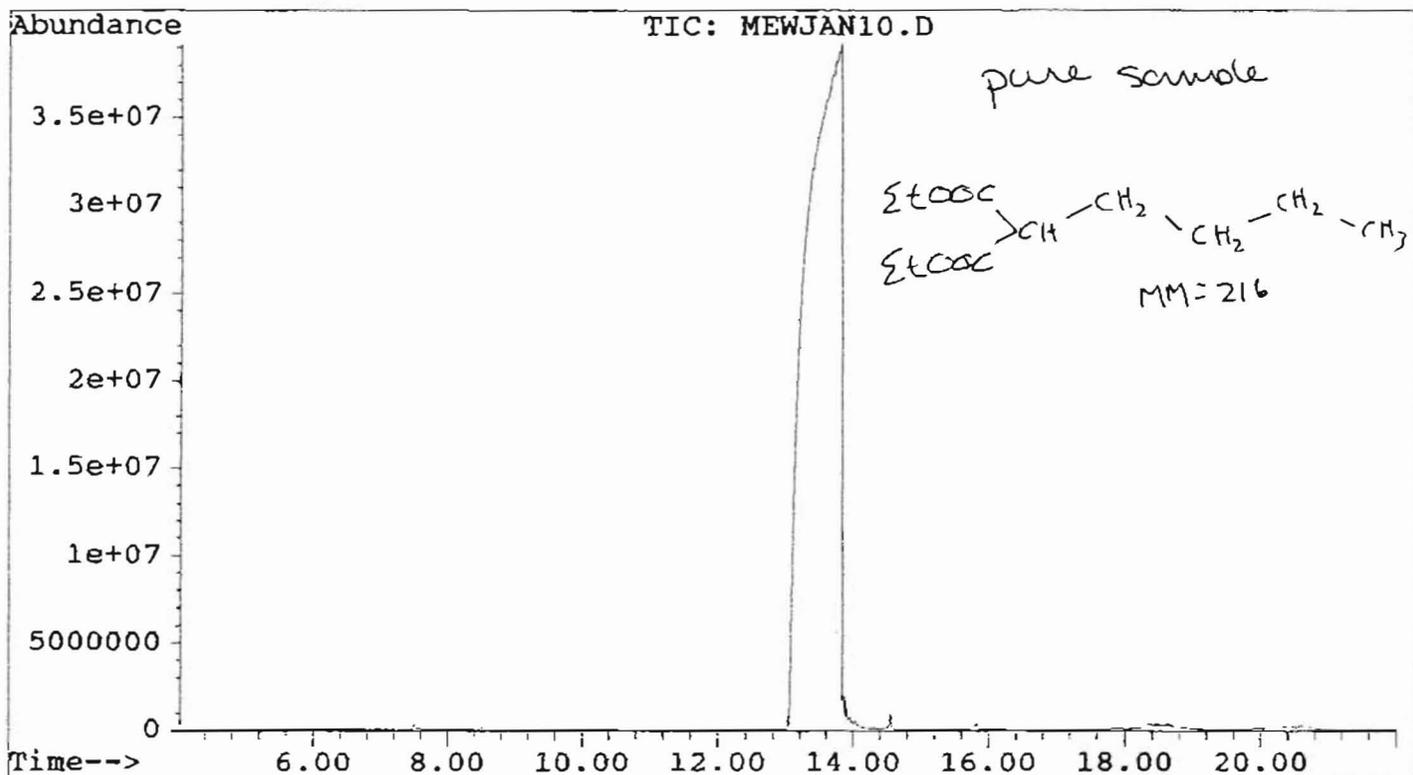
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Operator   : Michelle
Acquired   : 4 Jan 80   3:54 pm using AcqMethod _OCHEM
Instrument :   5970B
Sample Name : hydrolysis 1/17
Misc Info   : in CH2Cl2
Vial Number : 1

Abundance   TIC: MEWJAN13.D

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3.5e+07 -

3e+07 -

2.5e+07 -

2e+07 -

1.5e+07 -

1e+07 -

5000000 -

0 -

Time-->   5.00   6.00   7.00   8.00   9.00

hexanoic acid
MM = 116

Abundance   Scan 186 (7.497 min): MEWJAN13.D
4500000 -   29
4000000 -   43
3500000 -   88
3000000 -
2500000 -
2000000 -   60
1500000 -   99
1000000 -   39   55   70 73
500000 -   87   115
0 -   19
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-50-
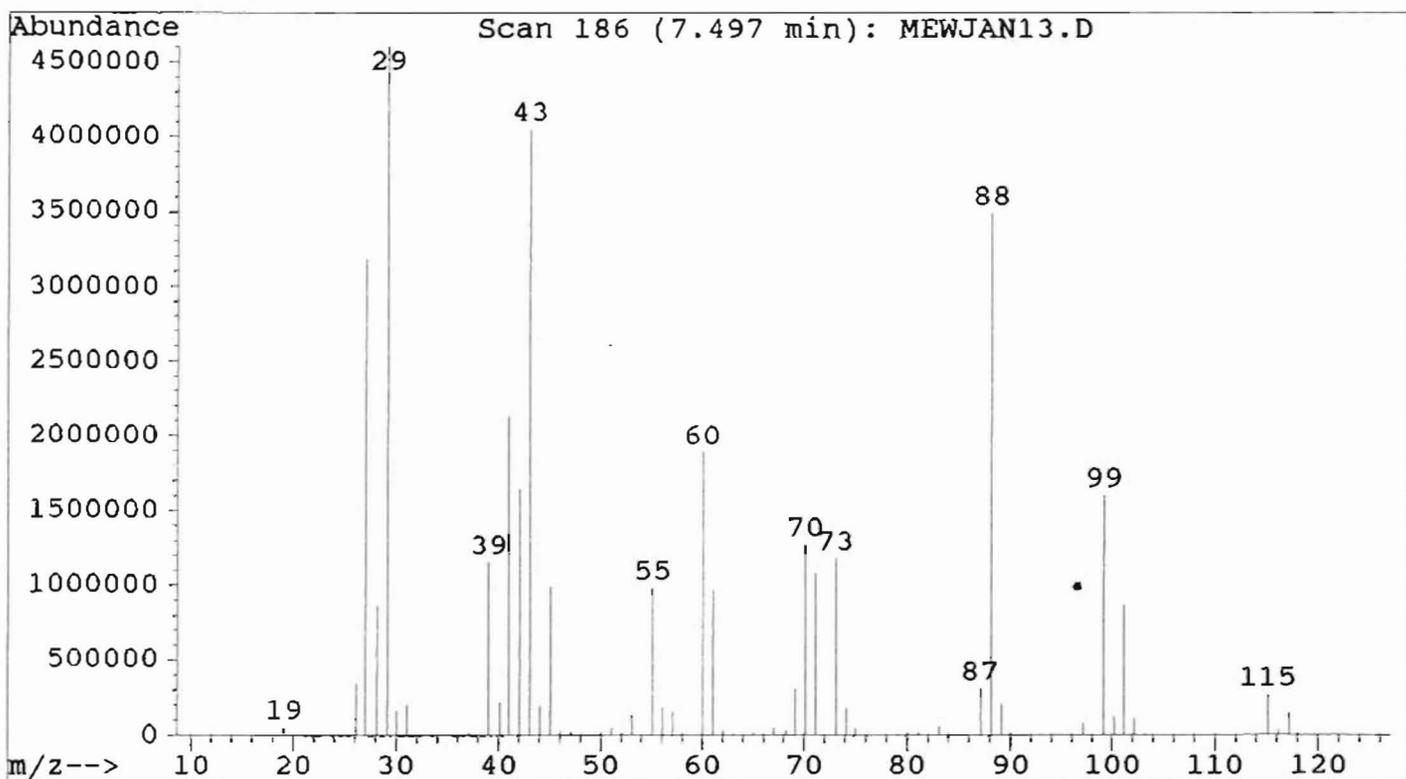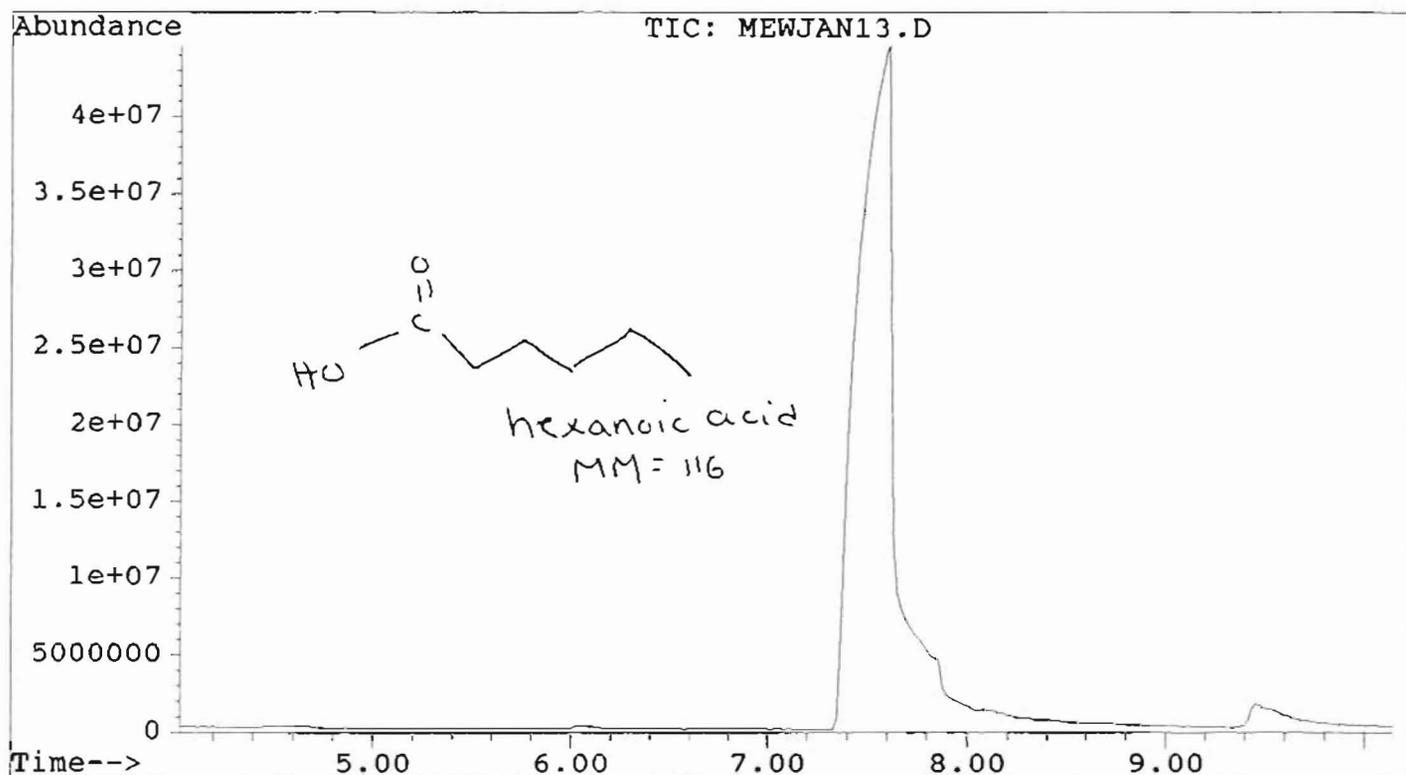
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Operator   : Michelle
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Sample Name: catechol/ACl test
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Vial Number: 1

AlCl₃

TIC: MEWJAN2.D

MM = 180

Scan 539 (14.112 min): MEWJAN2.D

File   : C:\...M\1\DATA\MEWJAN2.D
Operator   : Mic...
Acquired   : 4 ... 80   10:53 am using AcqMethod _OCHEM
Instrument : ...OB
Sample Name: catechol/ACl test
Misc Info   : AlCl3
Vial Number: 1

AlCl3

TIC: MEWJAN2.D

Scan 762 (18.293 min): MEWJAN2.D

le   : C:\HPCHEM\1\DATA\MEWJAN1.D
erator   : Michelle
quired   : 4 Jan 80 11:27 am using AcqMethod _OCHEM
strument :   5970B
mple Name: catechol/ACl test
sc Info : TiCl4
al Number: 1

T:Cl4

undance   TIC: MEWJAN1.D

2e+07 -

.5e+07 -

1e+07 -

000000 -

0

ne-->   6.00   8.00   10.00   12.00   14.00   16.00   18.00   20.00

MM=180

undance   Scan 537 (14.051 min): MEWJAN1.D

                43   110

000000 -

600000 -

                        71

400000 -

        27

600000 -
                                                                      180

                    53   81
            18   64   94   121   137 147   177

0

-->   20   40   60   80   100   120   140   160   180

-53-
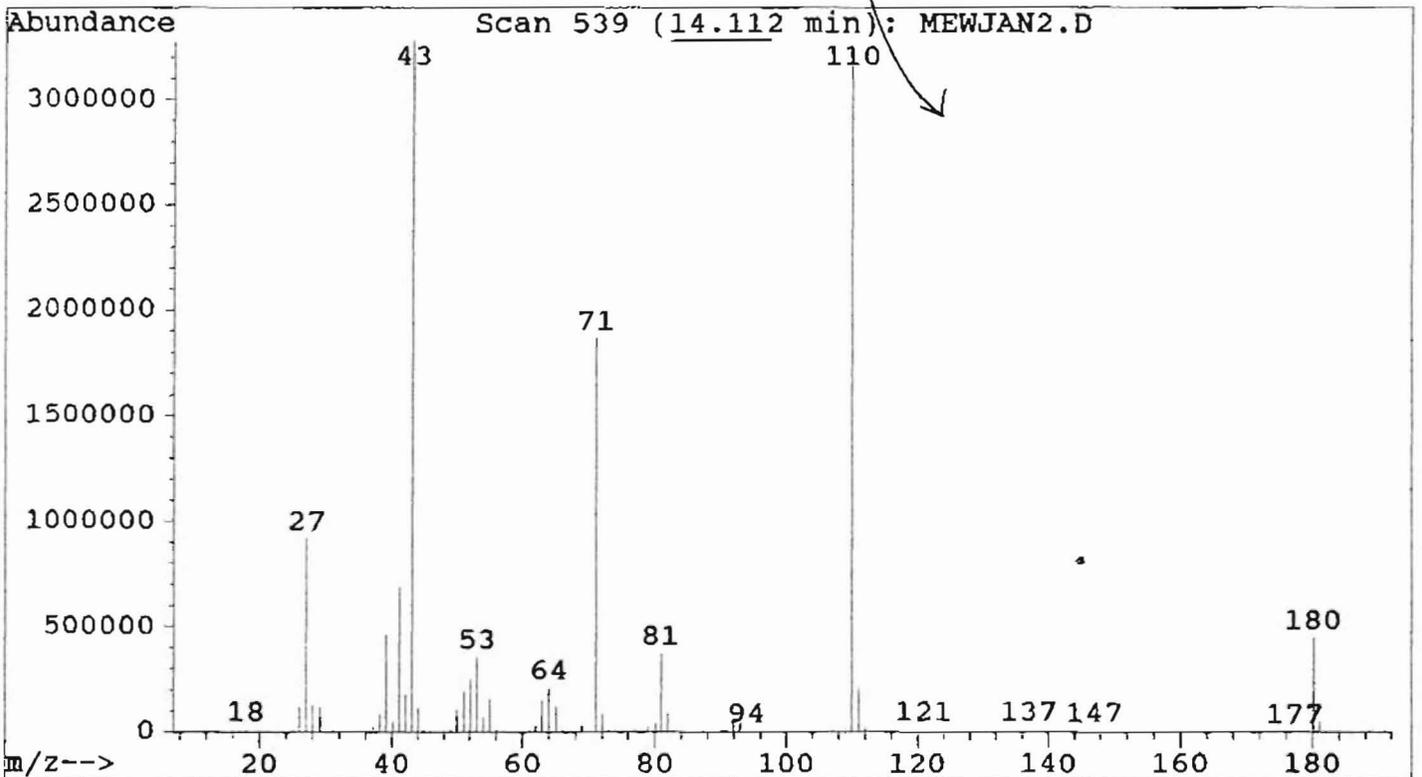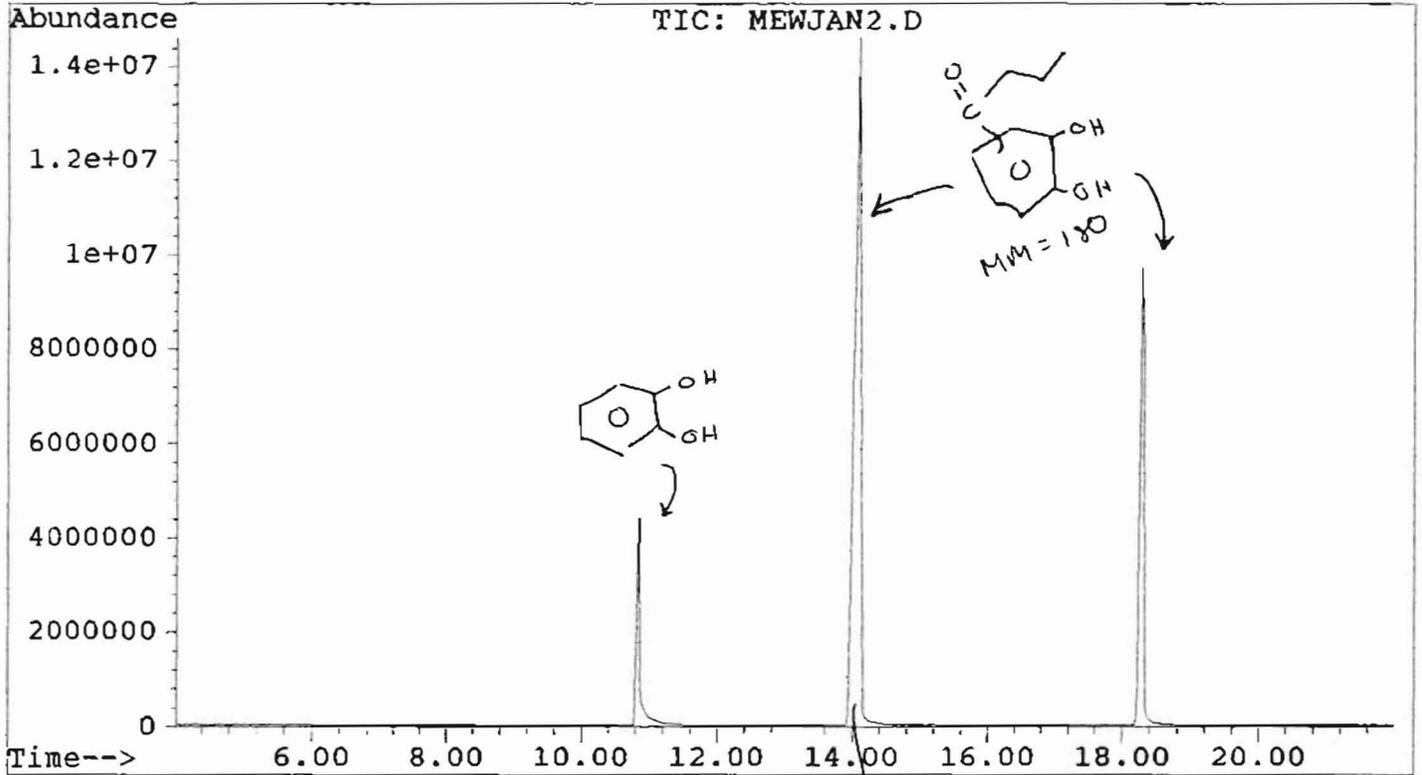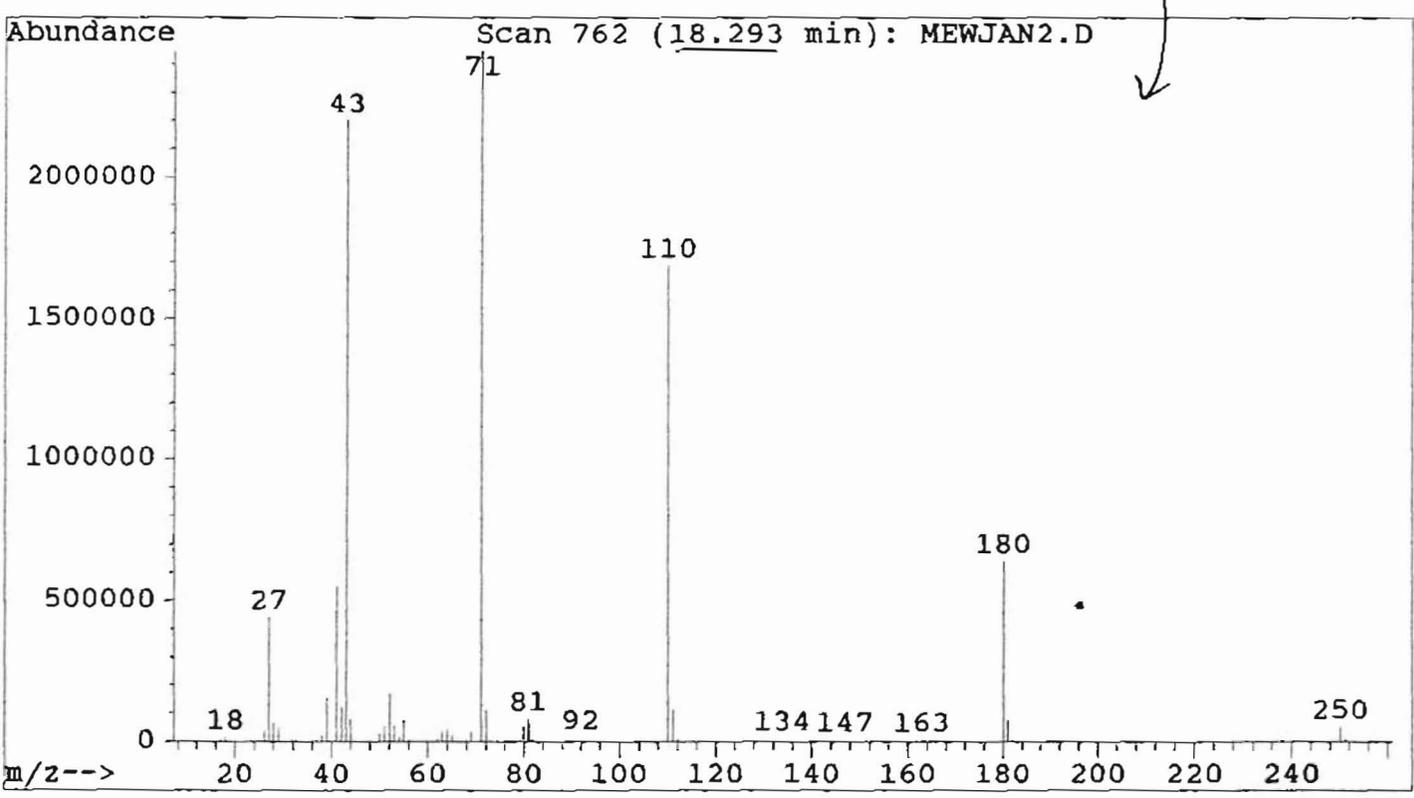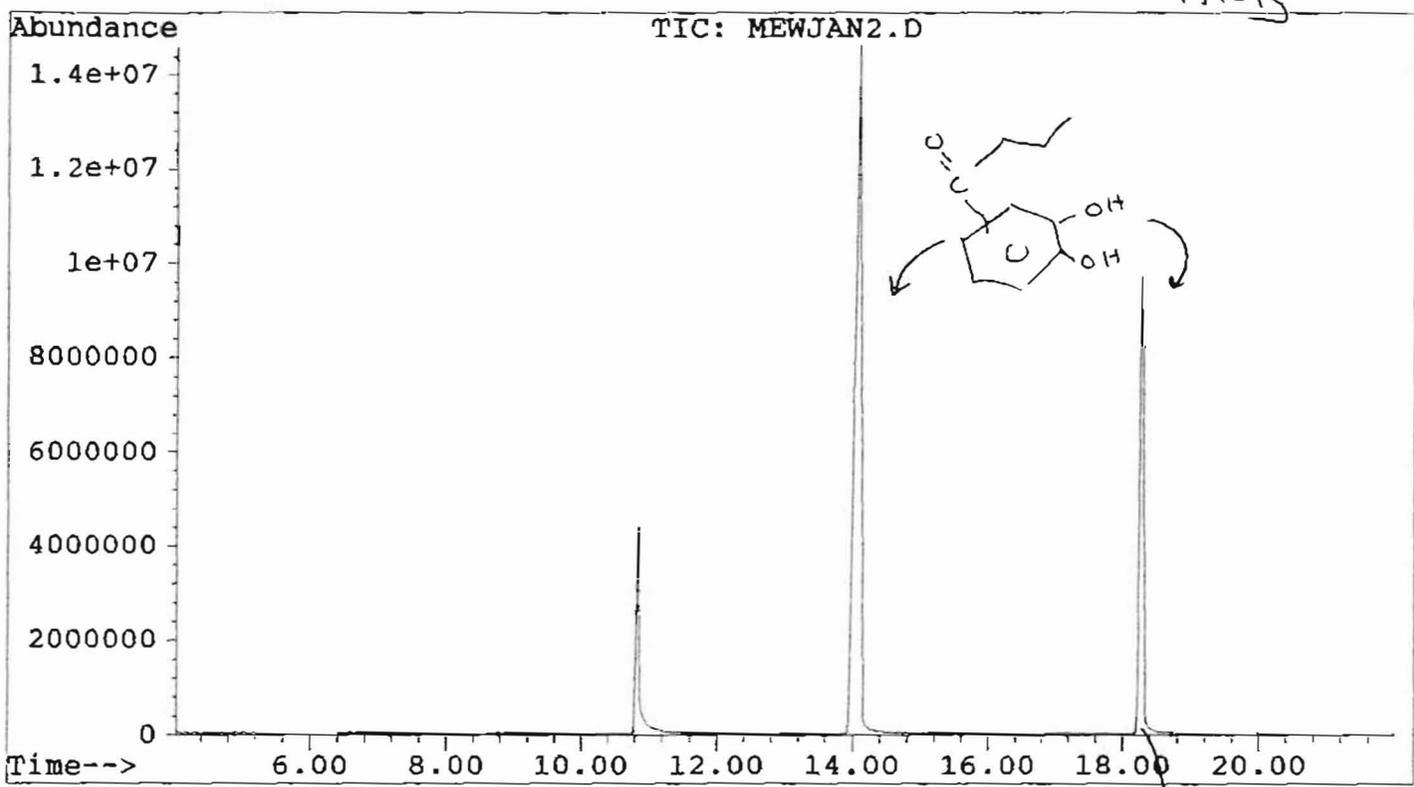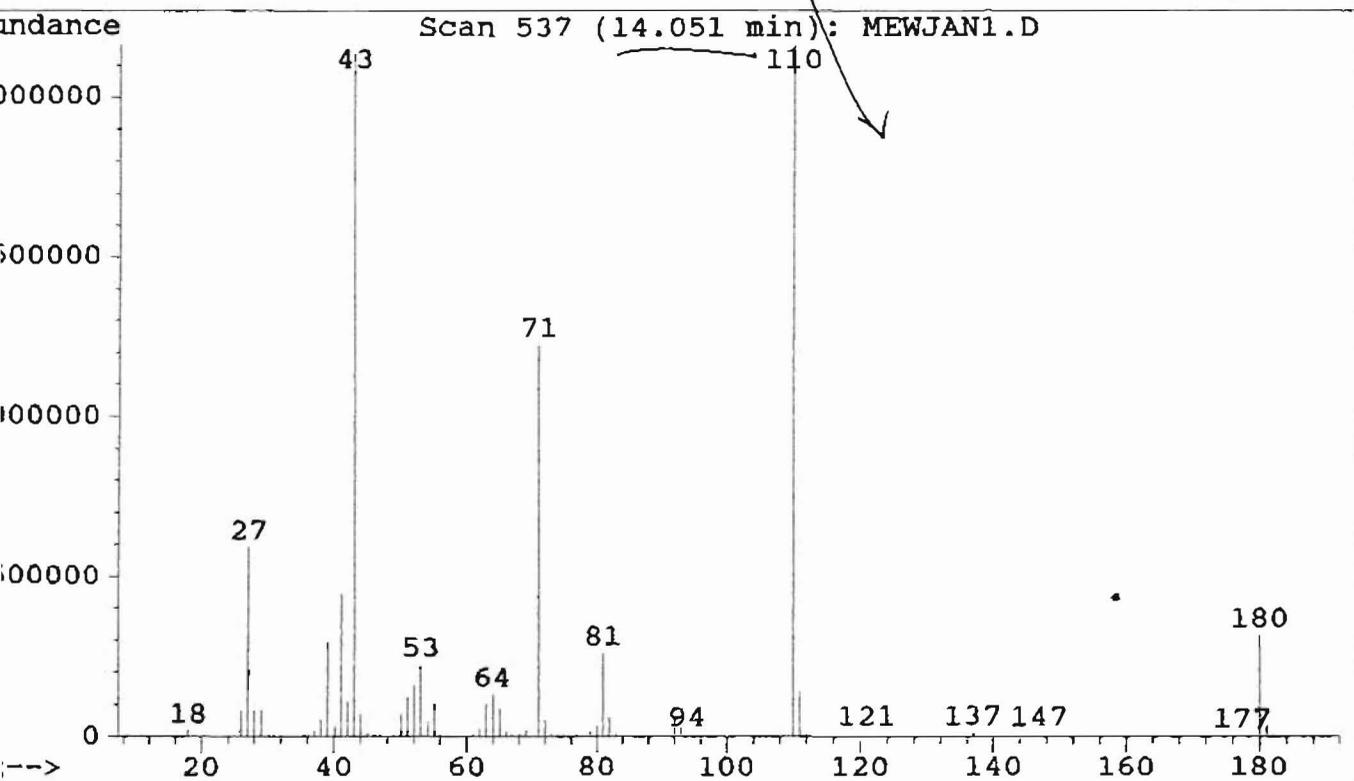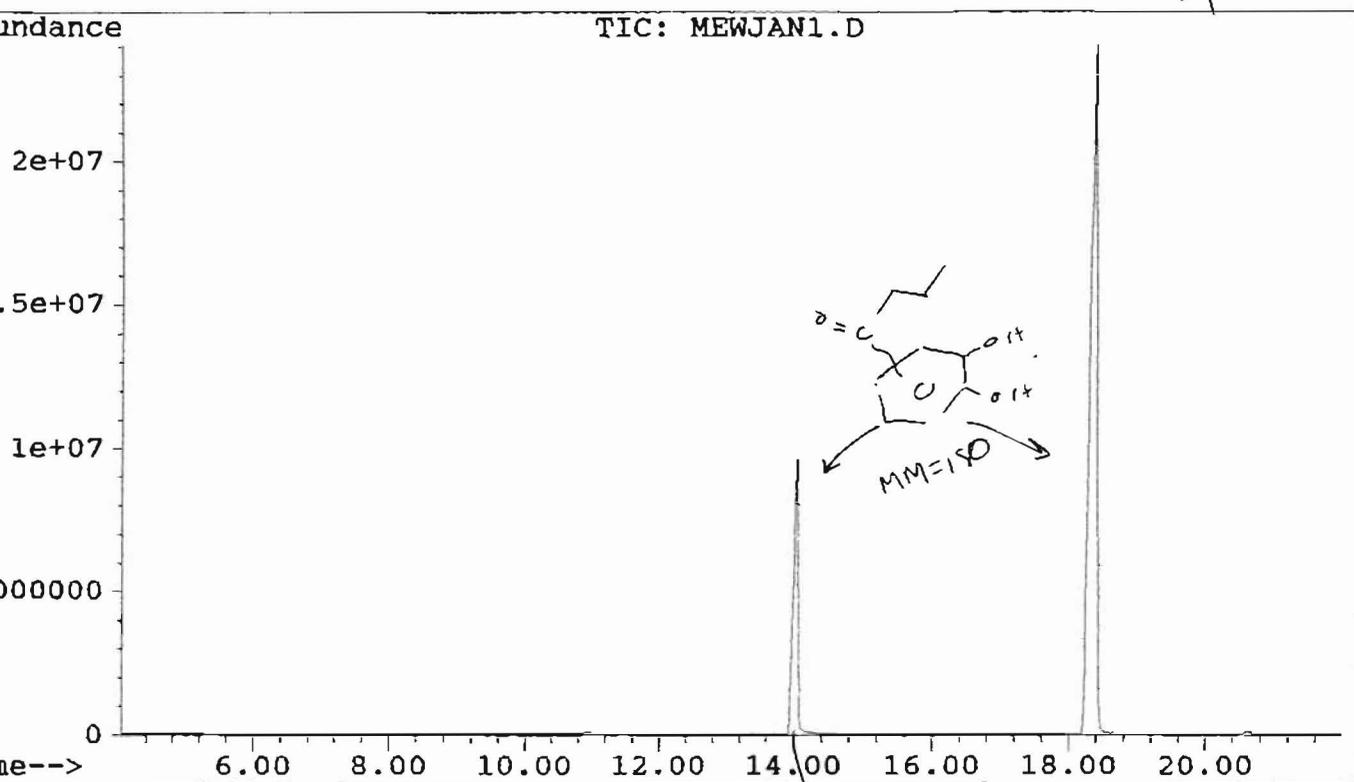
File   : C:\HPCHEM\1\DATA\MEWJAN1.D
Operator : Michelle
Acquired : 4 Jan 80 11:27 am using AcqMethod _OCHEM
Instrument :   5970B
Sample Name: catechol/ACl test
Misc Info : TiCl4
Vial Number: 1

TiCl4

Abundance   TIC: MEWJAN1.D

$O=CCH_2CH_2CH_3$

OH
OH

MM=180

Abundance   Scan 774 (18.495 min): MEWJAN1.D

43 71

110

28

18

44

64

81

180
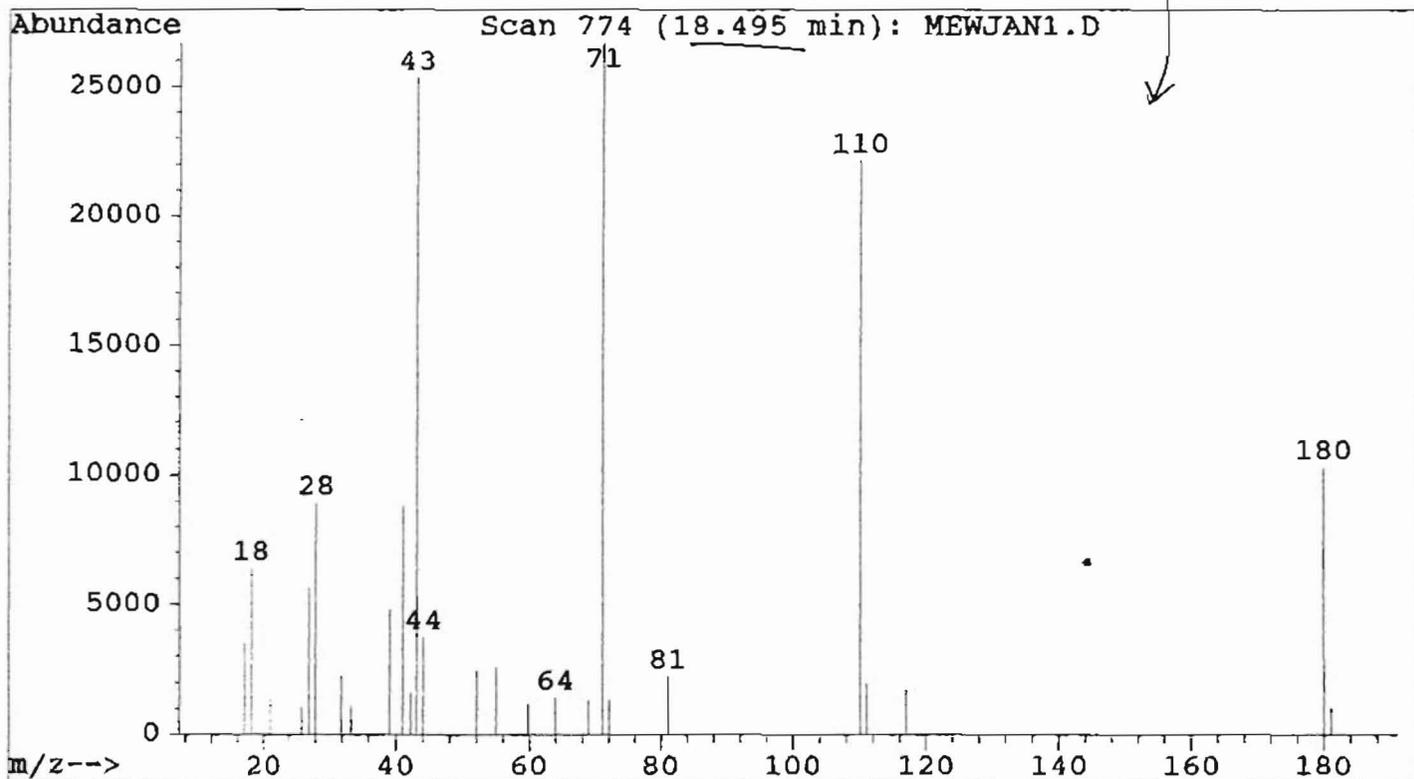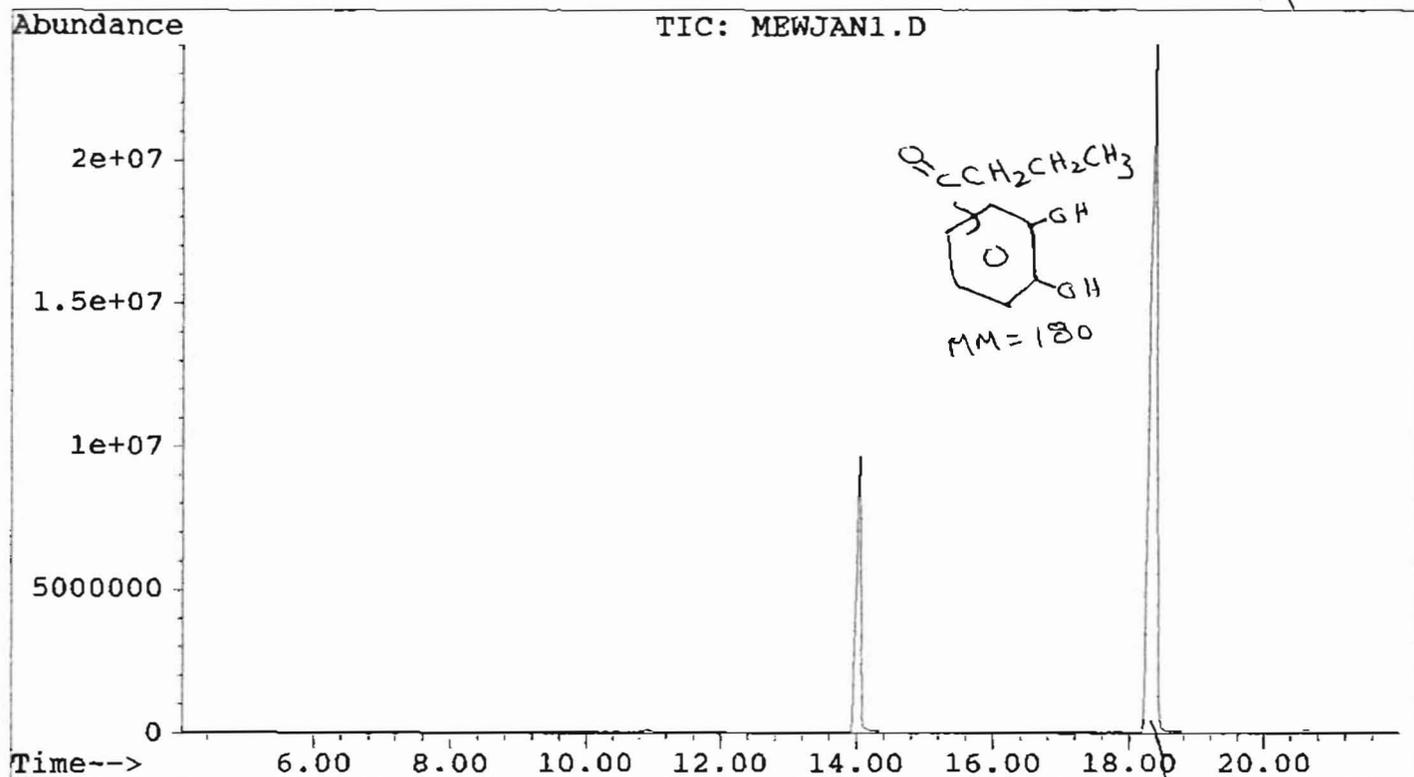
File   : C:\HPCHEM\1\DATA\MEWJAN19.D
Operator   : Michelle
Acquired   : 4 Jan 80   1:39 pm using AcqMethod _OCHEM
Instrument :   5970B
Sample Name: lewis acid test--TiCl4
Misc Info   :
Vial Number: 1

TiCl₄

Abundance   TIC: MEWJAN19.D

2e+07

1.5e+07

1e+07

5000000   product

0
Time-->   6.00   8.00   10.00 12.00 14.00 16.00 18.00 20.00

MM=166

Abundance   Scan 609 (15.433 min): MEWJAN19.D
                                              151

1200000

1000000

800000

600000
                                      123

400000   166

                41   105
200000   27   51   77
         18   79   133   187   207

0
m/z-->   20   40   60   80   100   120   140   160   180   200

-55-
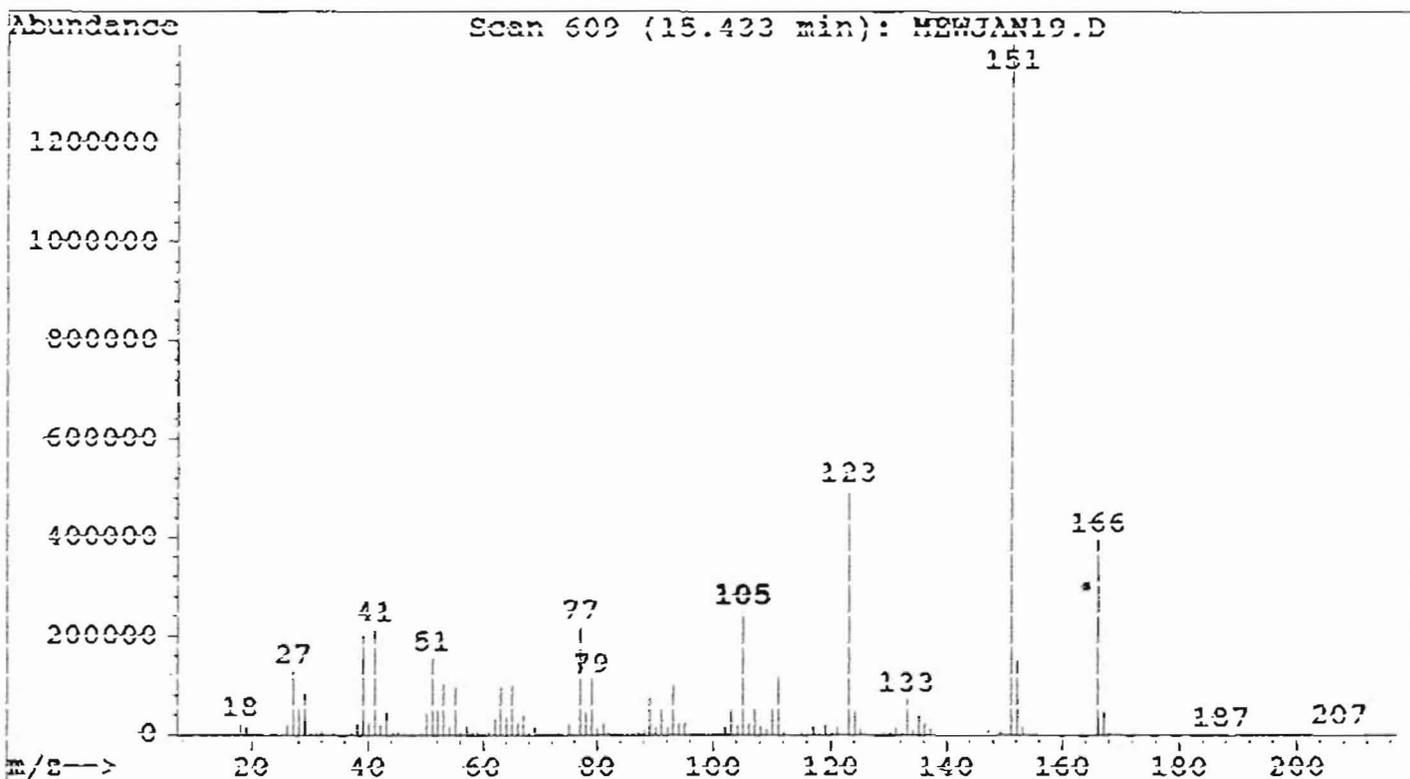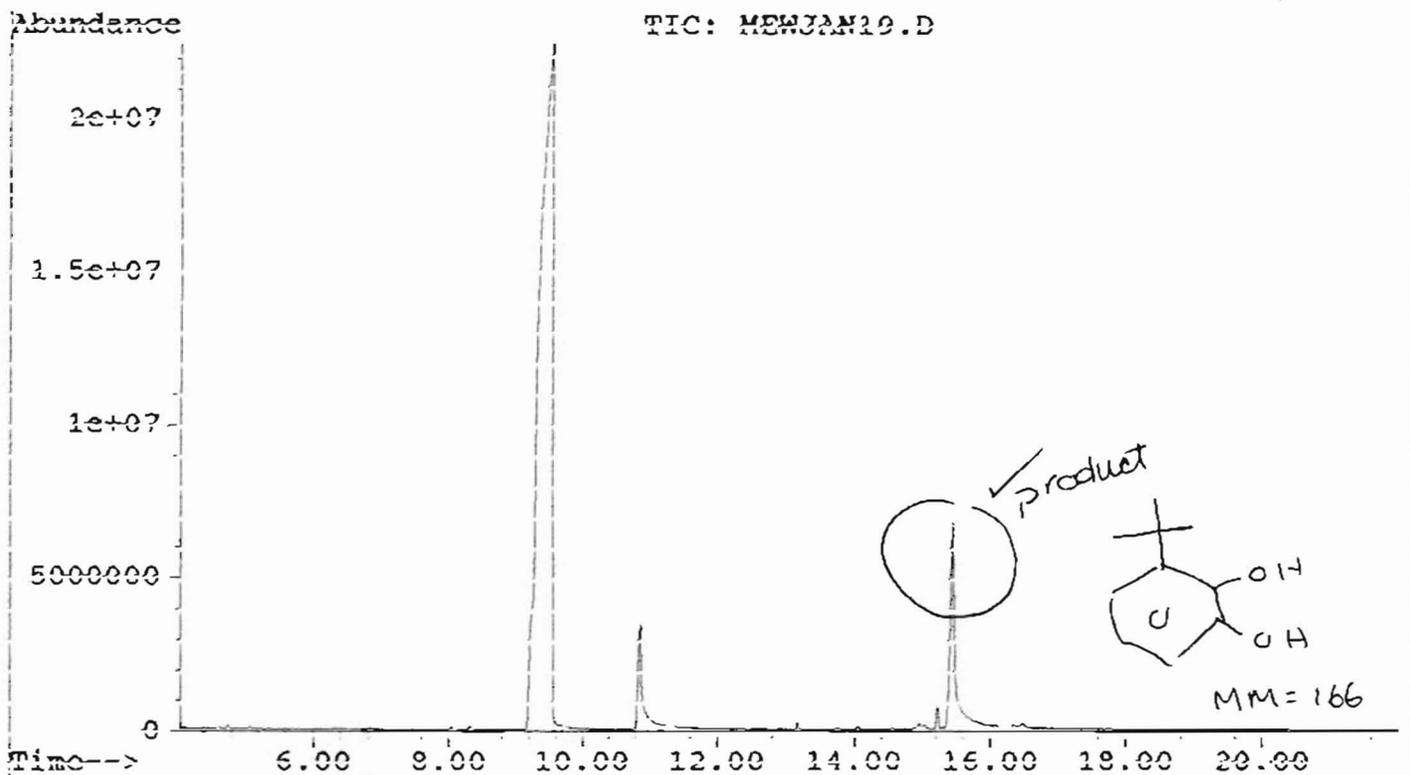
File   : D:\MEWJAN20.D
Operator : Michelle
Acquired : 4 Jan 80   2:34 pm using AcqMethod _OCHEM
Instrument :   5970B
Sample Name: lewis acid test--AlCl3
Misc Info : re-extracted in ether
Vial Number: 1

AlCl3

TIC: MEWJAN20.D

Abundance

2e+07 –

1.5e+07 –

1e+07 –

5000000 –

0 –

MM=166

Time-->   6.00   8.00   10.00   12.00   14.00   16.00   18.00   20.00

Abundance   Scan 612 (15.493 min): MEWJAN20.D
                                                    151
2000000 –

1500000 –

1000000 –
                                            123
                                                      166
500000 –   77   105
              41   51   79   133
        19 27   207

m/z-->   20   40   60   80   100   120   140   160   180   200

-56-
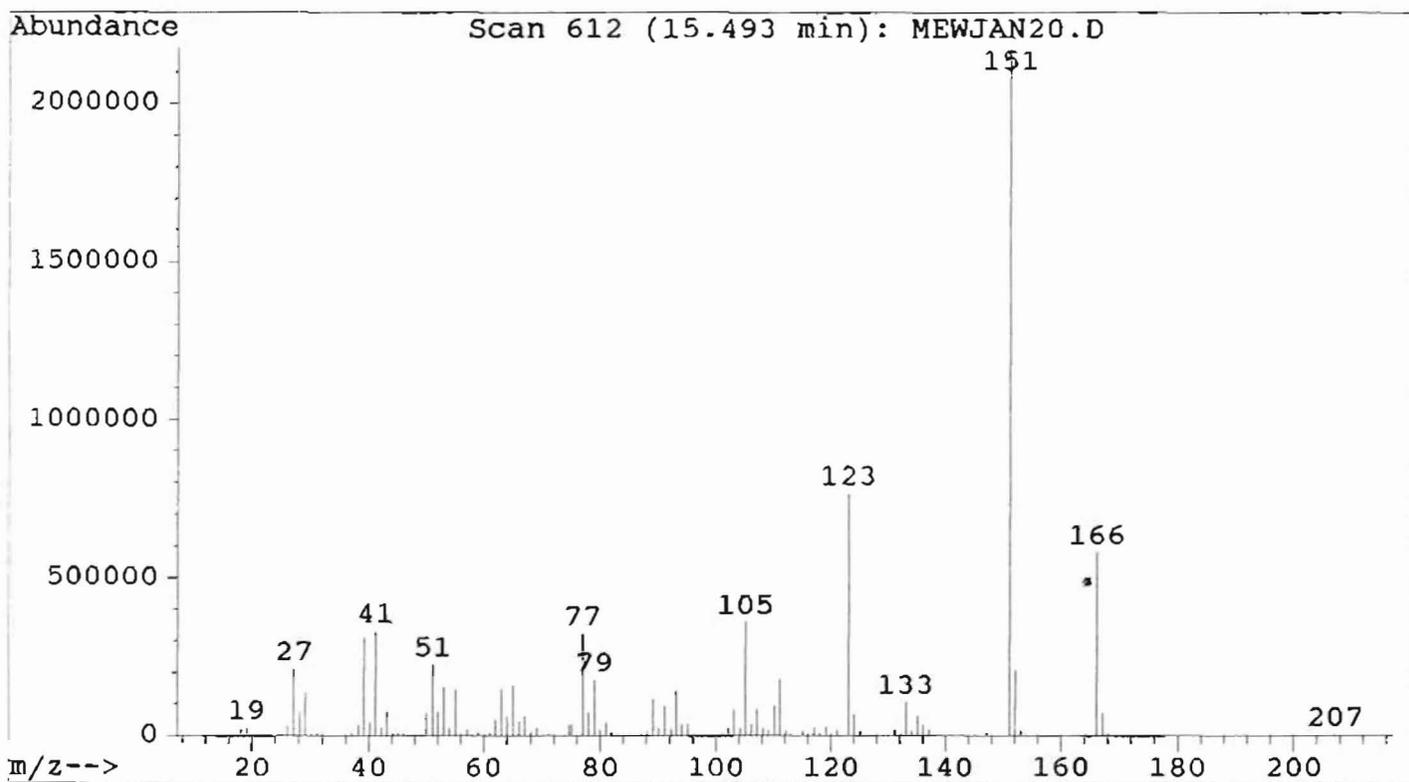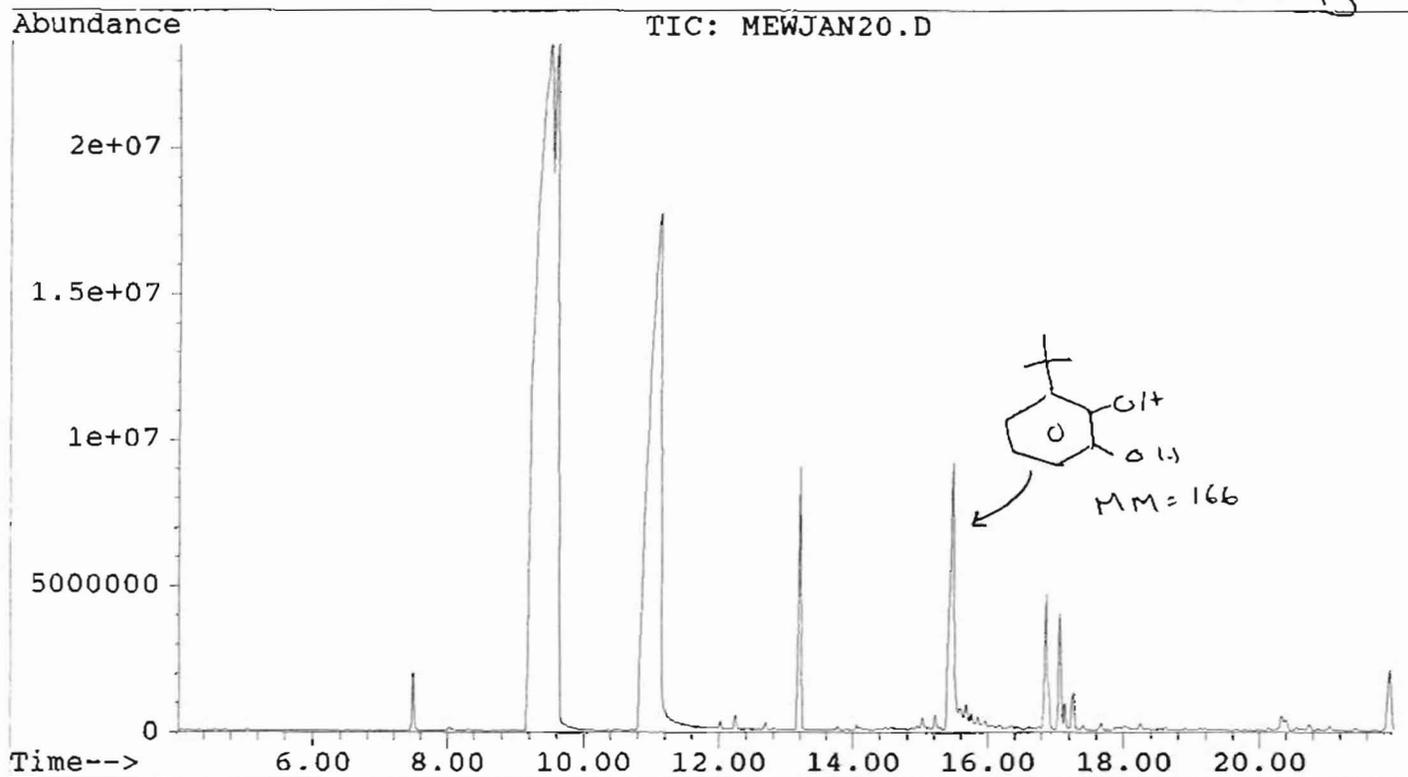
```
File        : D:\MEWJAN18.D
Operator    : Michelle
Acquired    : 4 Jan 80   11:14 am using AcqMethod _OCHEM
Instrument  :    5970B
Sample Name: lewis acid test--H2SO4
Misc Info   :
Vial Number: 1
```

H_2SO_4

Abundance   TIC: MEWJAN18.D

$MM = 166$

Abundance   Scan 624 (15.723 min): MEWJAN18.D
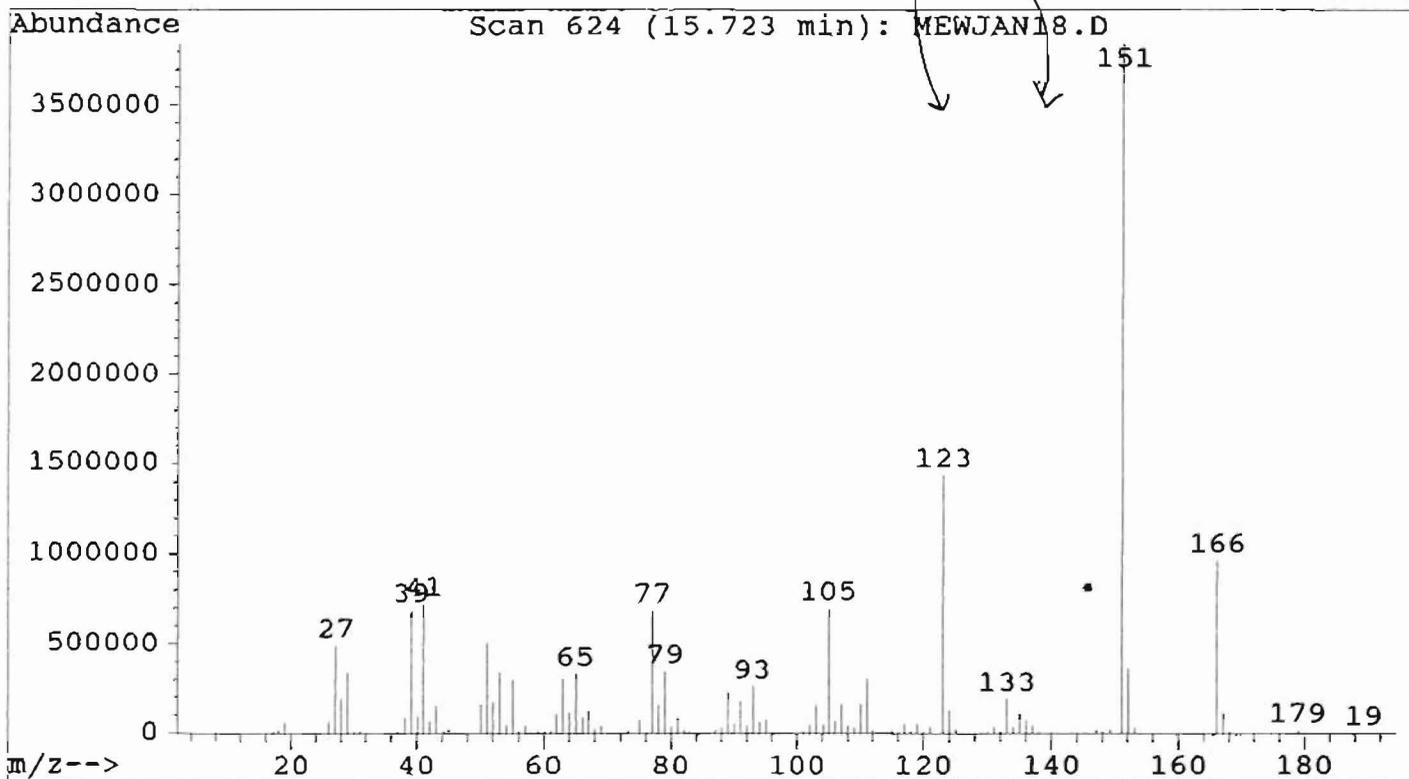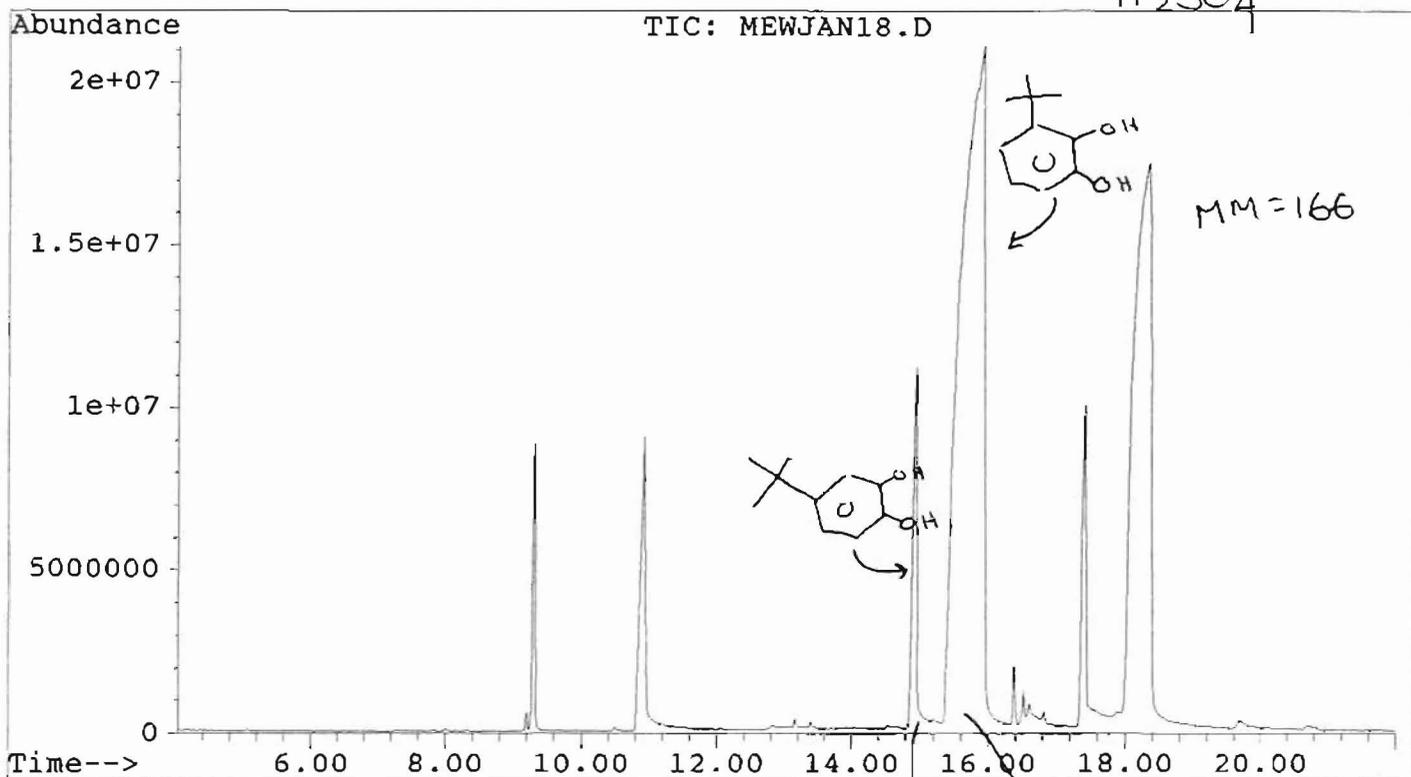
Library Searched : C:\DATABASE\NBS75K.L
Quality   : 91
ID   : 1,2-Benzenediol, (1,1-dimethylethyl)-

Abundance   Scan 629 (15.817 min): MEWJAN18.D (*)

8000

6000

4000

2000

0

m/z-->   20   40   60   80   100   120   140   160   180   200   220

Peaks labeled: 18, 27, 41, 51, 77, 79, 105, 111, 123, 151, 166, 167, 191, 207, 22

Abundance   #14046: 1,2-Benzenediol, (1,1-dimethylethyl)- (*)

151

91% match

8000

6000

4000

2000

0

m/z-->   20   40   60   80   100   120   140   160   180   200   220

Peaks labeled: 27, 41, 51, 77, 79, 105, 111, 123, 151, 166, 167

Abundance   #68000: 1,2-Benzenediol, 4-(1,1-dimethylethyl)- (*)

151

74% match

8000

6000

4000

2000

0

m/z-->   20   40   60   80   100   120   140   160   180   200

Peaks labeled: 41, 51, 63, 77, 93, 105, 123, 135, 151, 166

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File   : C:\HPCHEM\1\DATA\MEWSTEP1.D
Operator   : Michelle
Acquired   : 7 Mar 100   8:59 am using AcqMethod _OCHEM
Instrument   :   5970B
Sample Name: step 1 alkylation, GC separated
Misc Info   : in CHCL3
Vial Number: 1
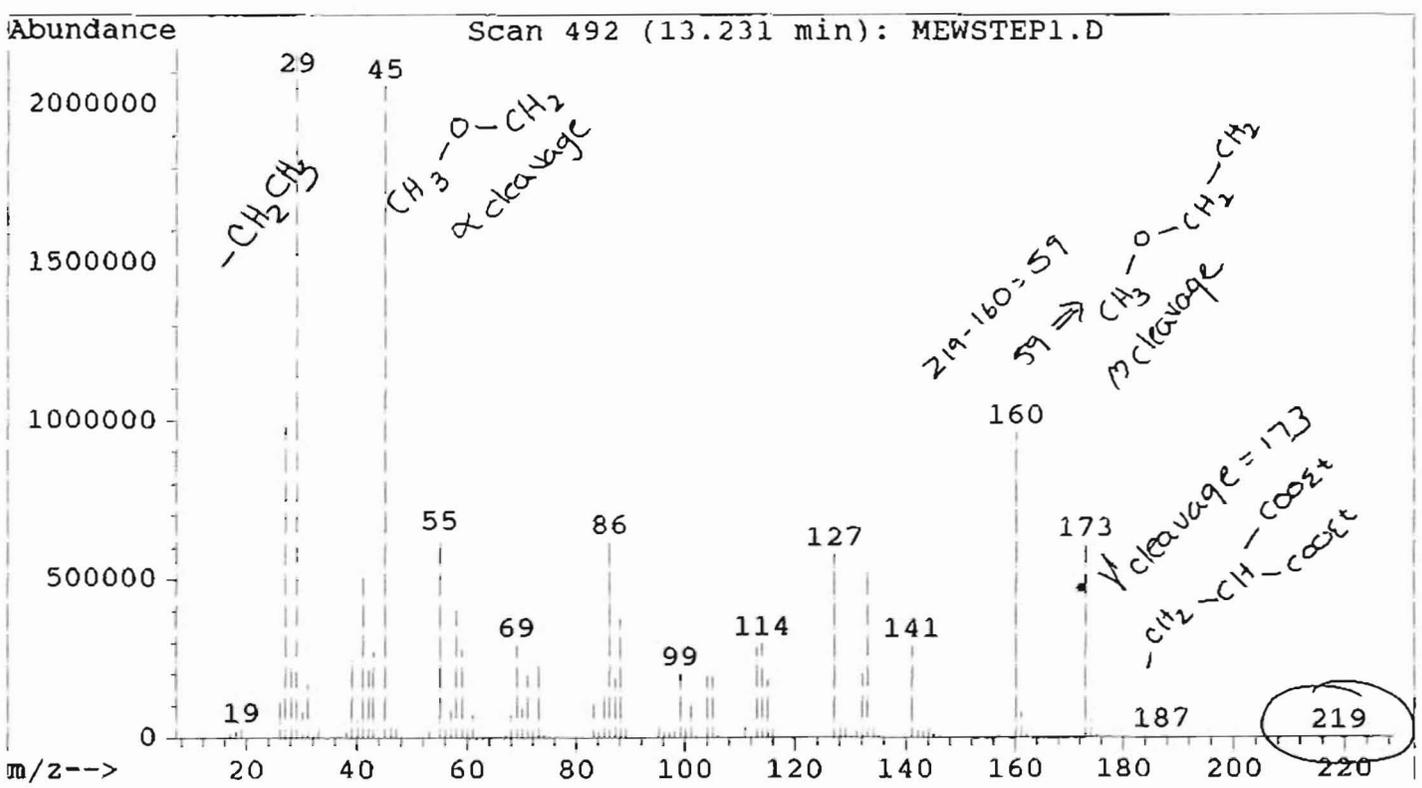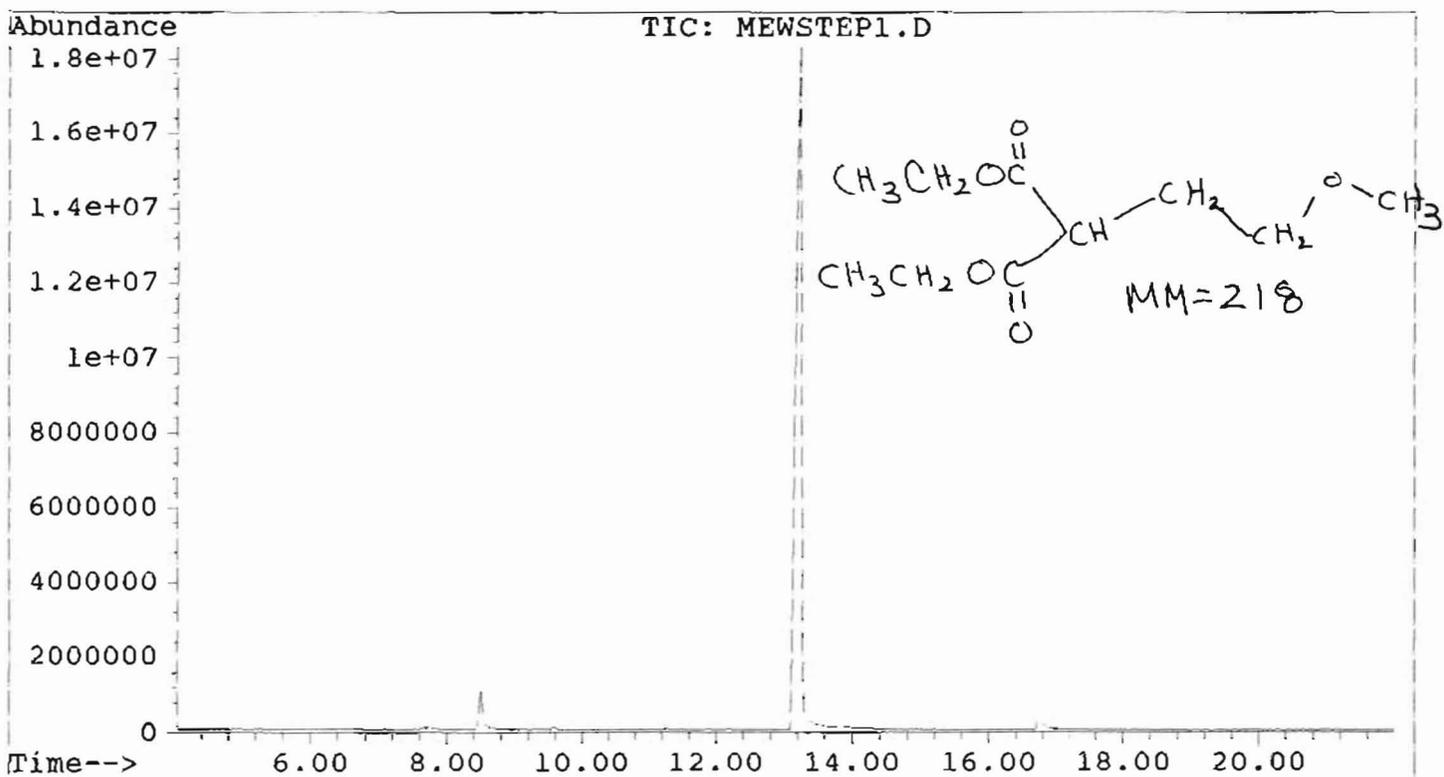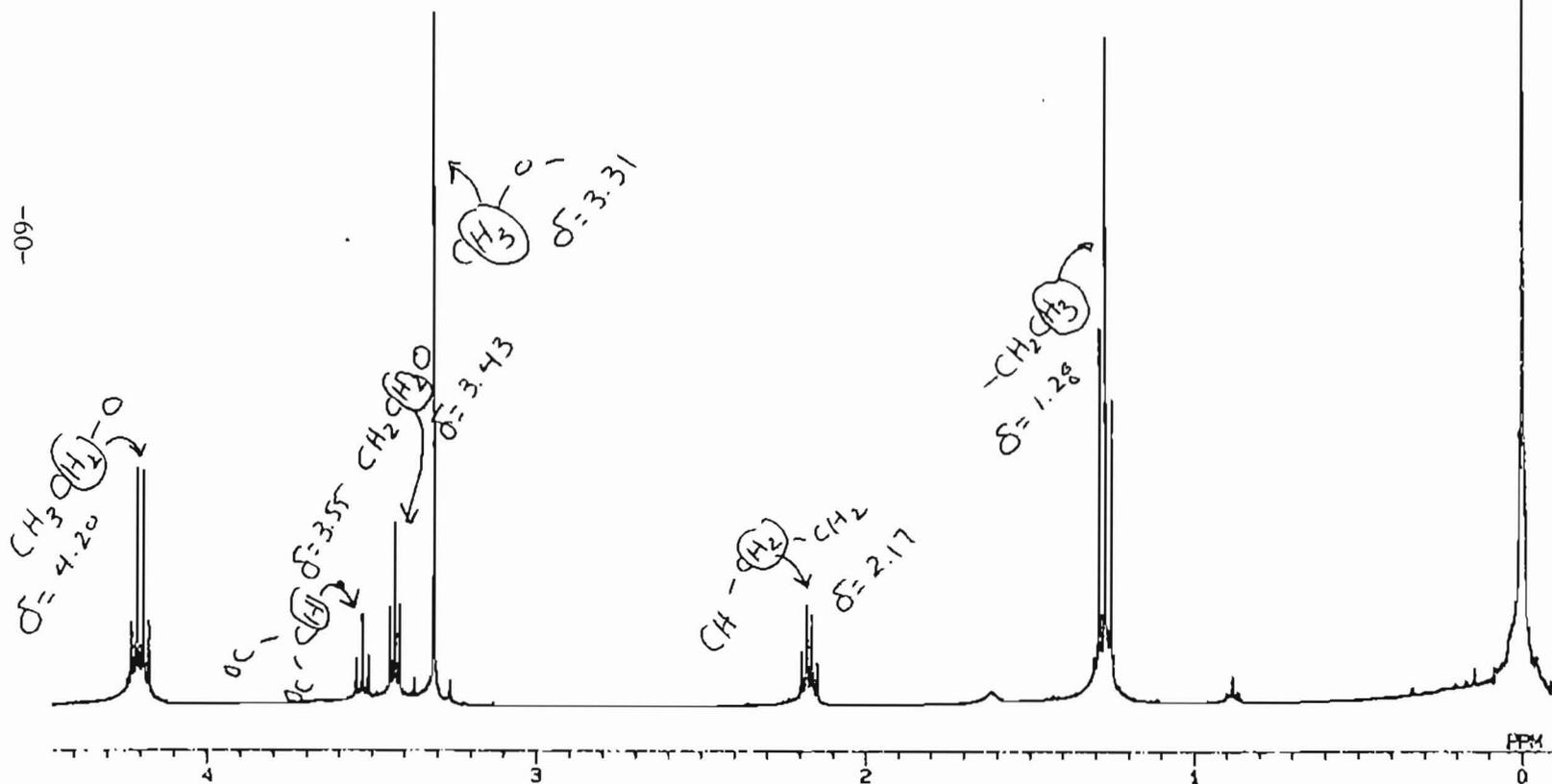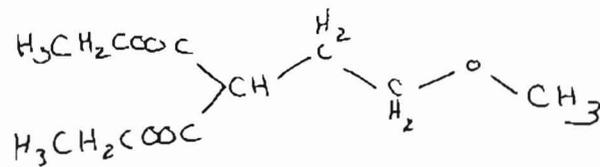
TIC: MEWSTEP1.D

CH_3CH_2OC, CH_3CH_2OC ... CH — CH_2 — CH_2 — O — CH_3

MM = 218

Scan 492 (13.231 min): MEWSTEP1.D

29
45
55
69
86
99
114
127
141
160
173
187
219
19

$-CH_2CH_3$

CH_3-O-CH_2 α cleavage

219-160=59   59 ⟹ $CH_3-O-CH_2-CH_2$ m cleavage

γ cleavage = 173
$CH_2-CH-COOEt$

MEW_ALKYLATION

H_3CH_2COOC—CH—CH_2—CH_2—O—CH_3 (structure as drawn)

H_3CH_2COOC

CH₃ δ=3.31

CH₂(H)O δ=3.43

CH₃(H₂)—O δ=4.20

OC—(H) δ=3.55 CH₂

CH—(H₂)—CH₂ δ=2.17

—CH₂C(H₃) δ=1.28

-09-

4   3   2   1   0   PPM

File   : C:\HPCHEM\1\DATA\MEWHYF1.D
Operator   : Michelle
Acquired   : 10 Apr 100   9:33 am using AcqMethod _OCHEM
Instrument :   5970B
Sample Name: hydrolysis product, fraction 1
Misc Info   : in CH2Cl2
Vial Number: 1
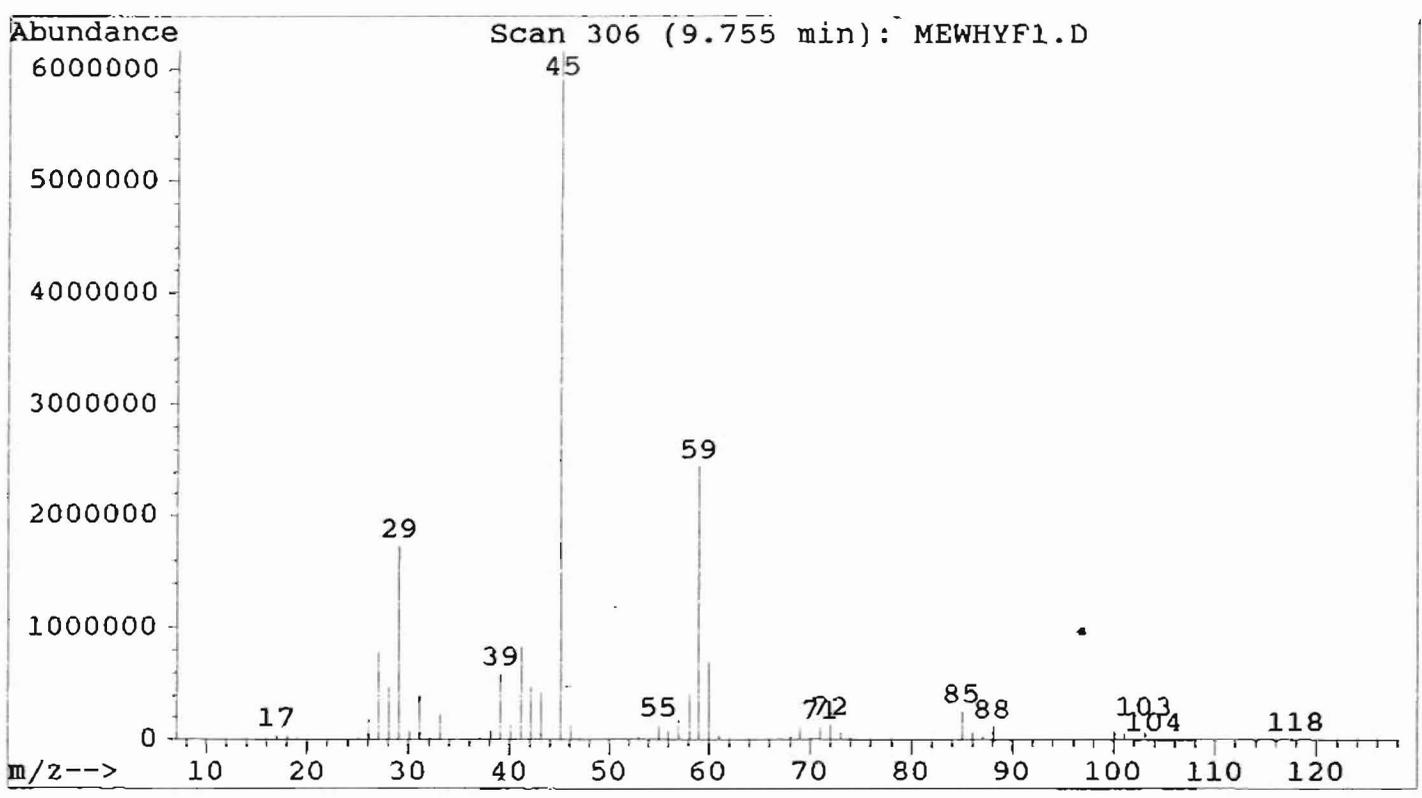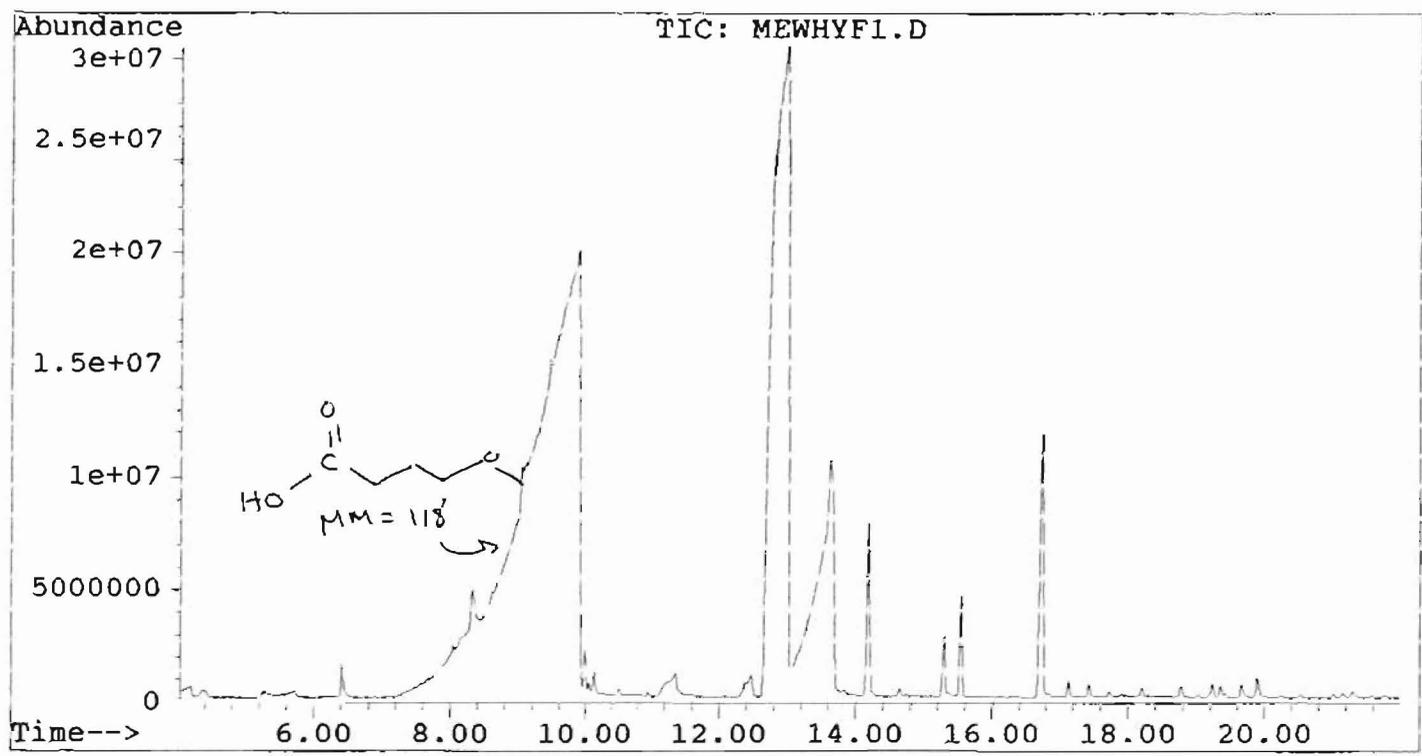
Library Searched : C:\DATABASE\NBS75K.L
Quality : 83
ID : Butanoic acid, 4-methoxy-

Comparison

Abundance   Scan 306 (9.755 min): MEWHYF1.D (*)

```
8000 -

6000 -

4000 -

2000 -

   0
m/z-->   10   20   30   40   50   60   70   80   90   100  110  120
```

45
59
29
39
17
55
712
85 88
103 104
118

Abundance   #3507: Butanoic acid, 4-methoxy- (*)

```
8000 -

6000 -

4000 -

2000 -

   0
m/z-->   10   20   30   40   50   60   70   80   90   100  110  120
```

45
59
55
712
85 88
103

MM = 110

-62-
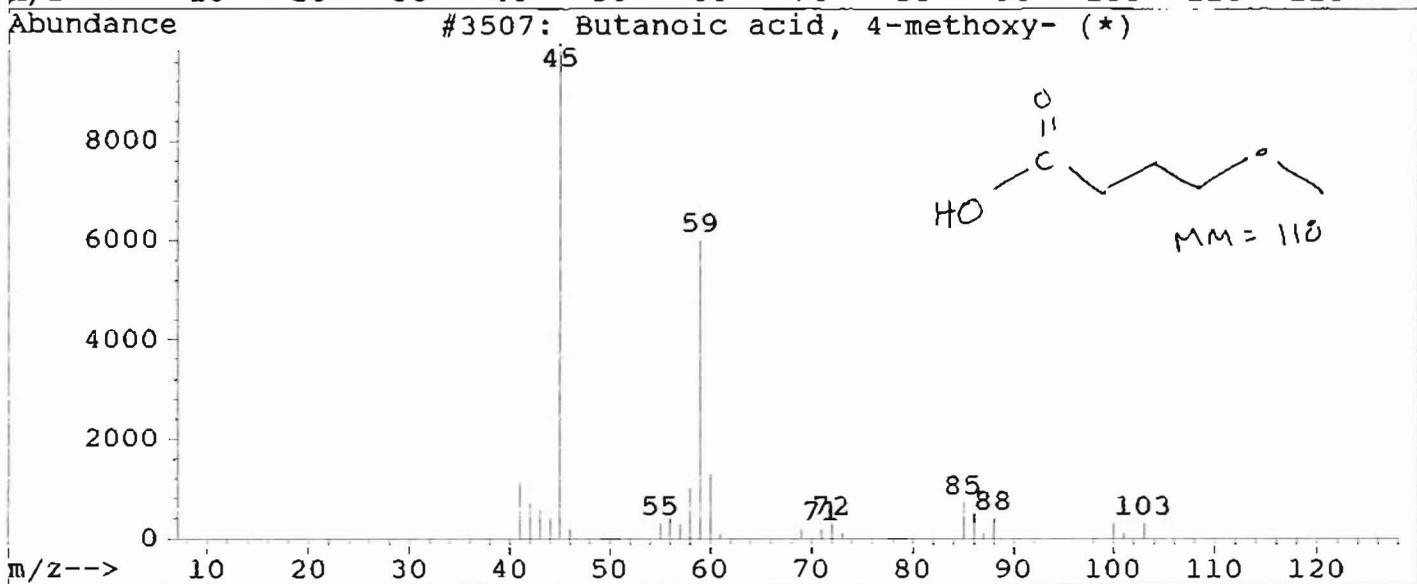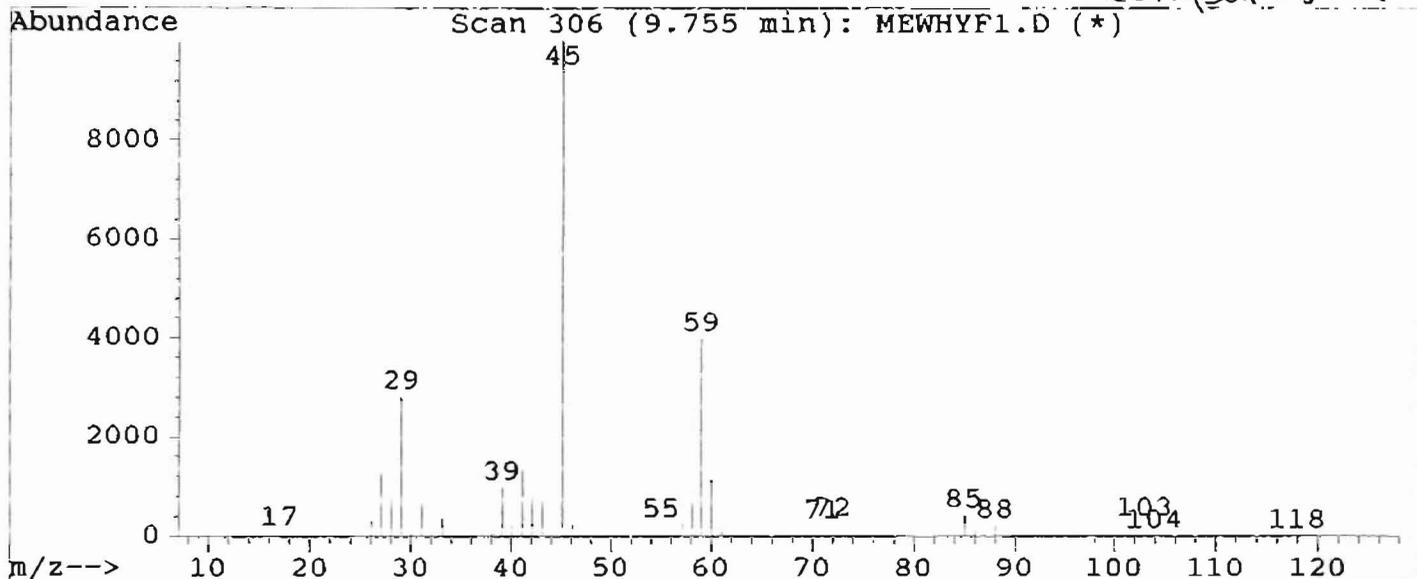
File   : C:\HPCHEM\1\DATA\MEWBF32.D
Operator   : Michelle
Acquired   : 15 Mar 100   1:32 pm using AcqMethod _OCHEM
Instrument :   5970B
Sample Name: catechol + BF3, solid fraction
Misc Info   : in CH2Cl2
Vial Number: 1

BF₃ reaction

TIC: MEWBF32.D

Scan 669 (16.552 min): MEWBF32.D
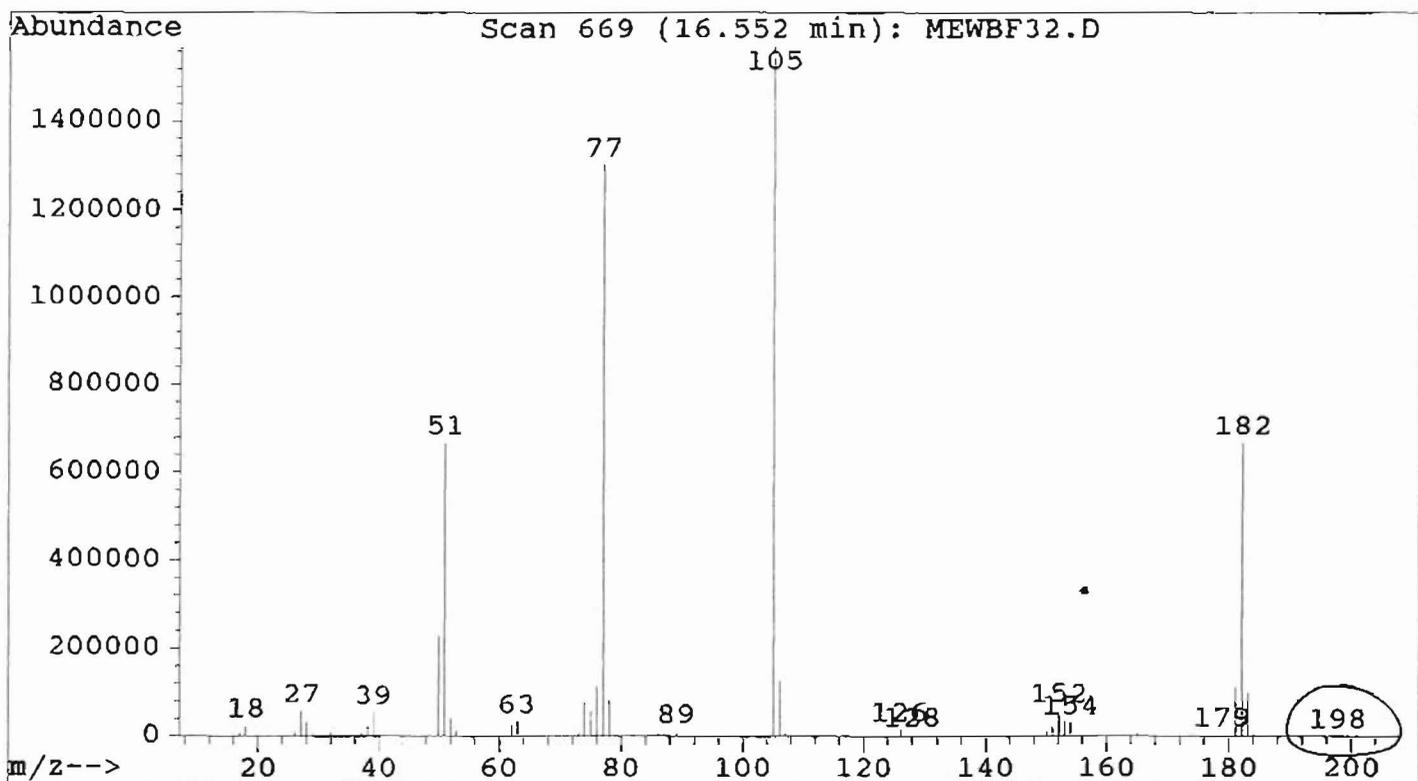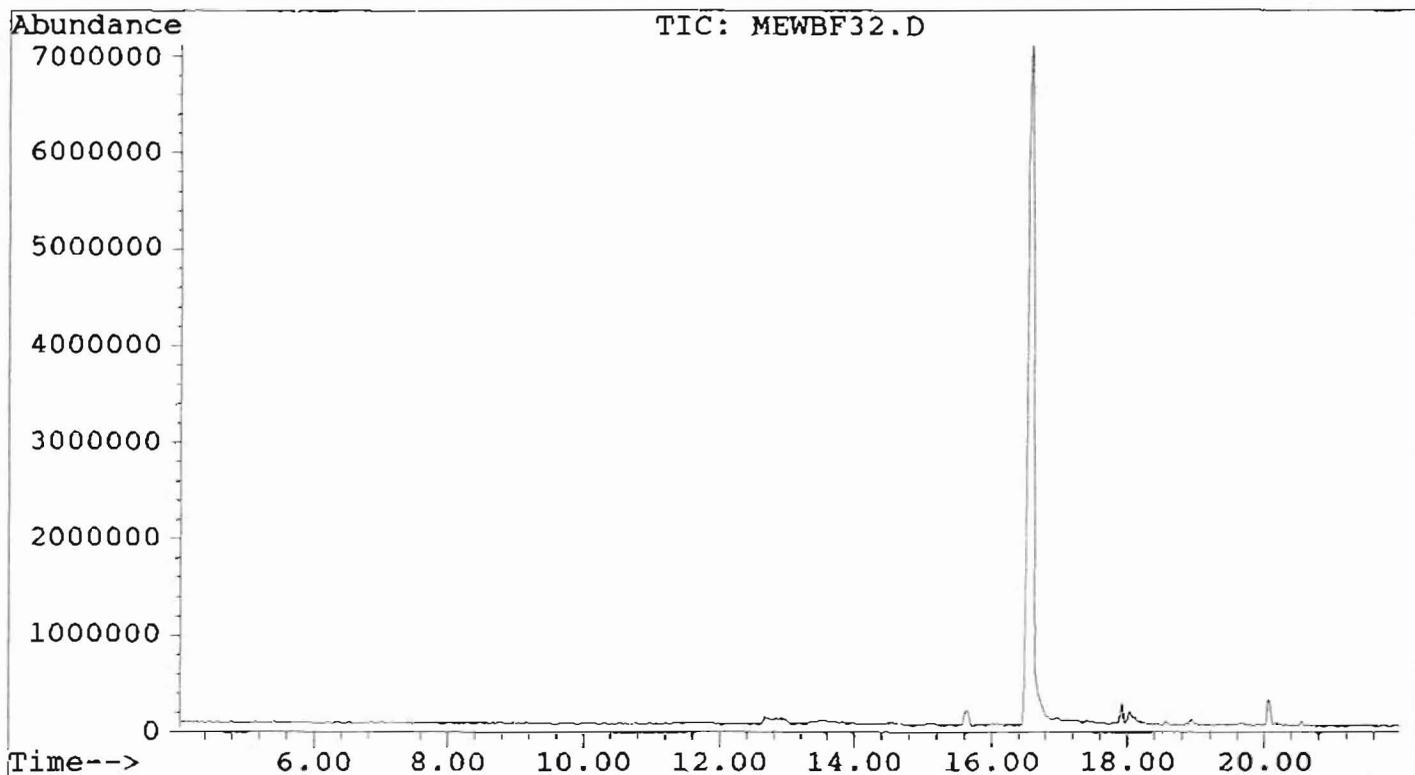
216 - 198 = 18
loss of H₂O (?)

-63-

File   : C:\HPCHEM\1\DATA\MEWAC.D
Operator : Michelle
Acquired : 12 Apr 100   5:45 pm using AcqMethod _OCHEM
Instrument :   5970B
Sample Name: acid chloride, crude product
Misc Info : in CH2Cl2
Vial Number: 1

TIC: MEWAC.D

MM = 136.5

Scan 421 (11.905 min): MEWAC.D
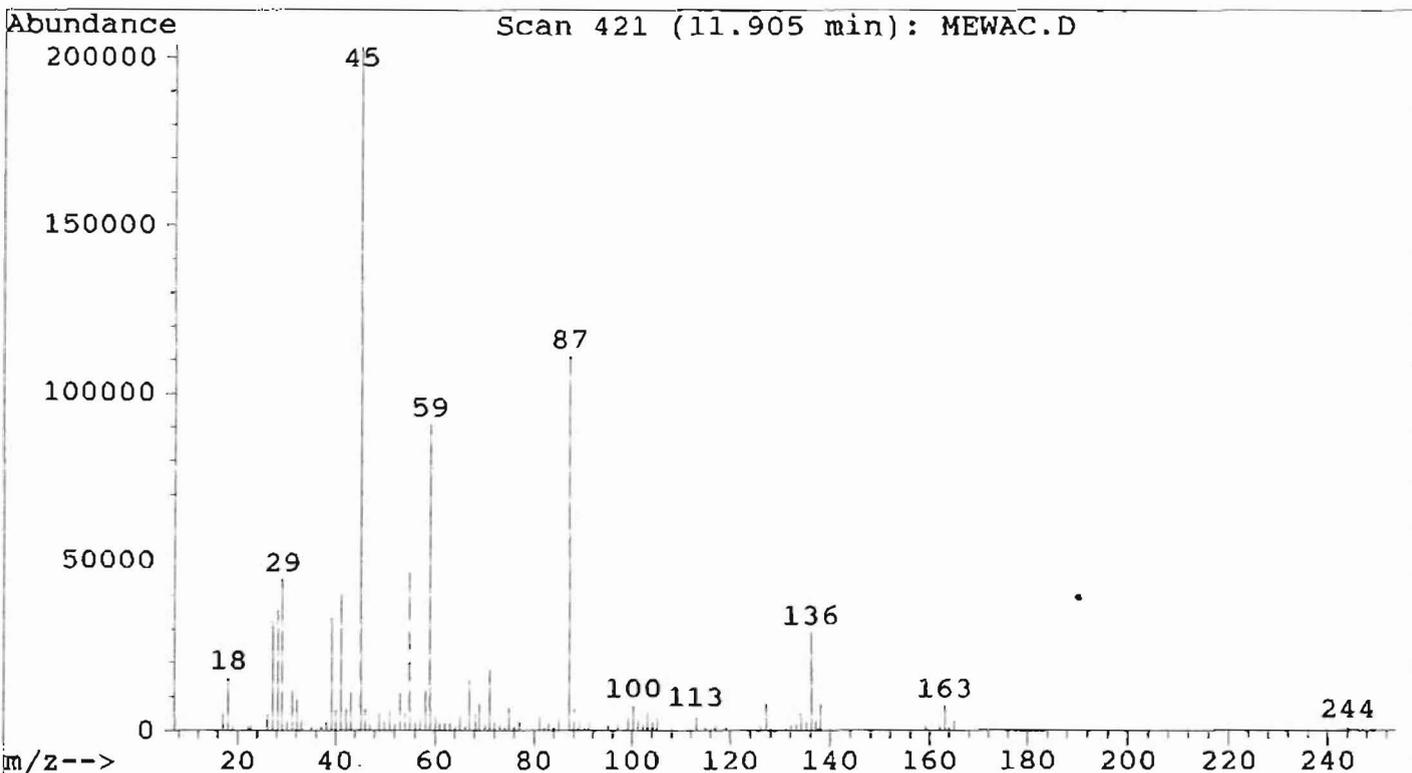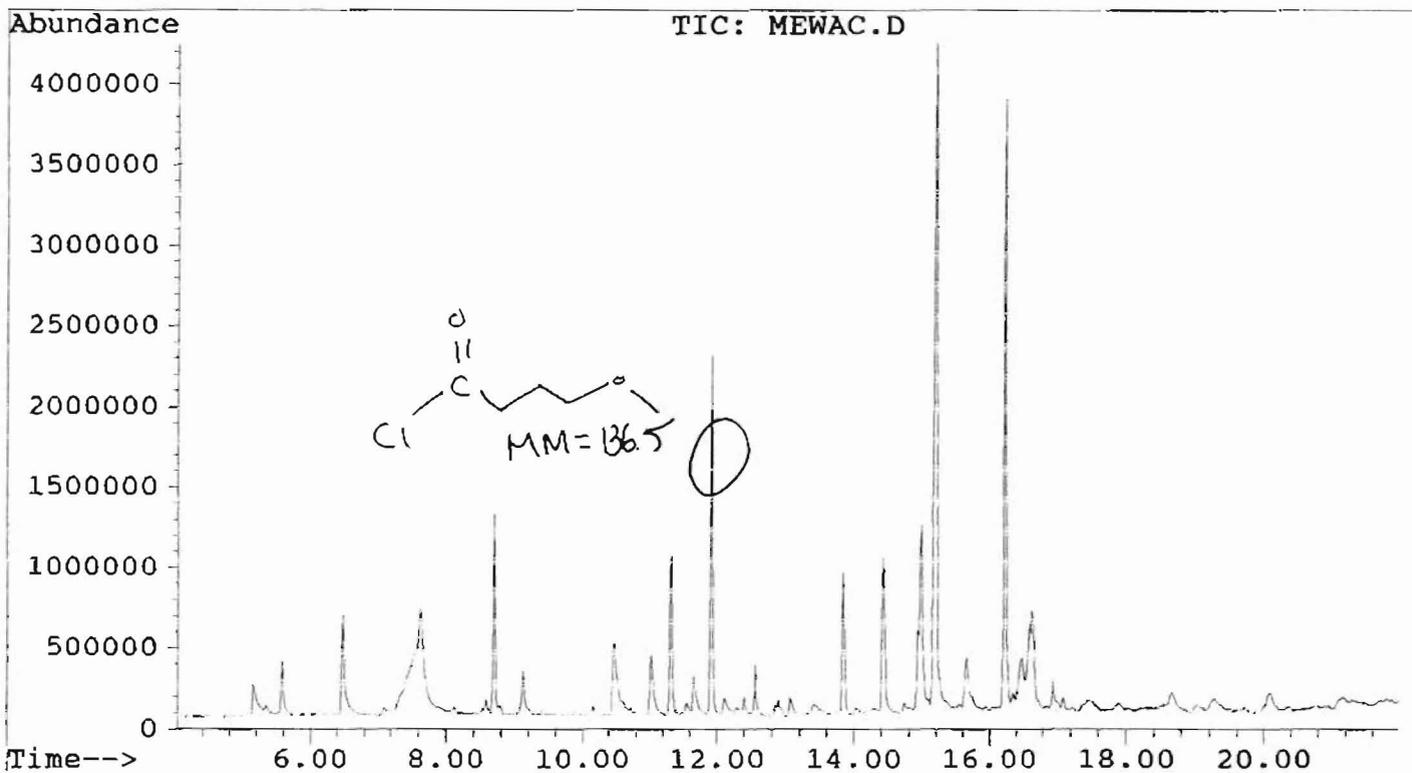
File   : D:\MICHELLE\MEWAC.D
Operator   : Michelle
Acquired   : 12 Apr 100   5:45 pm using AcqMethod _OCHEM
Instrument :   5970B
Sample Name: acid chloride, crude product
Misc Info   : in CH2Cl2
Vial Number: 1
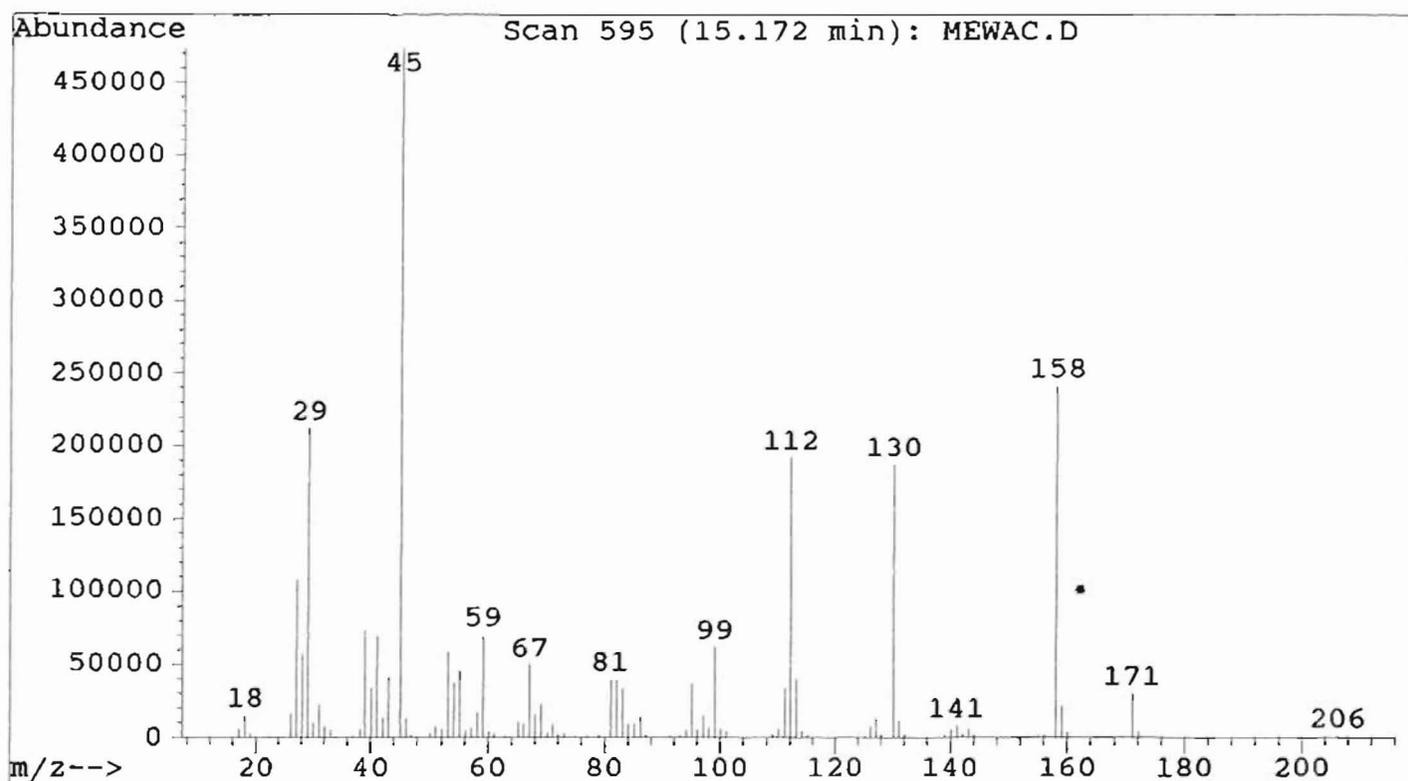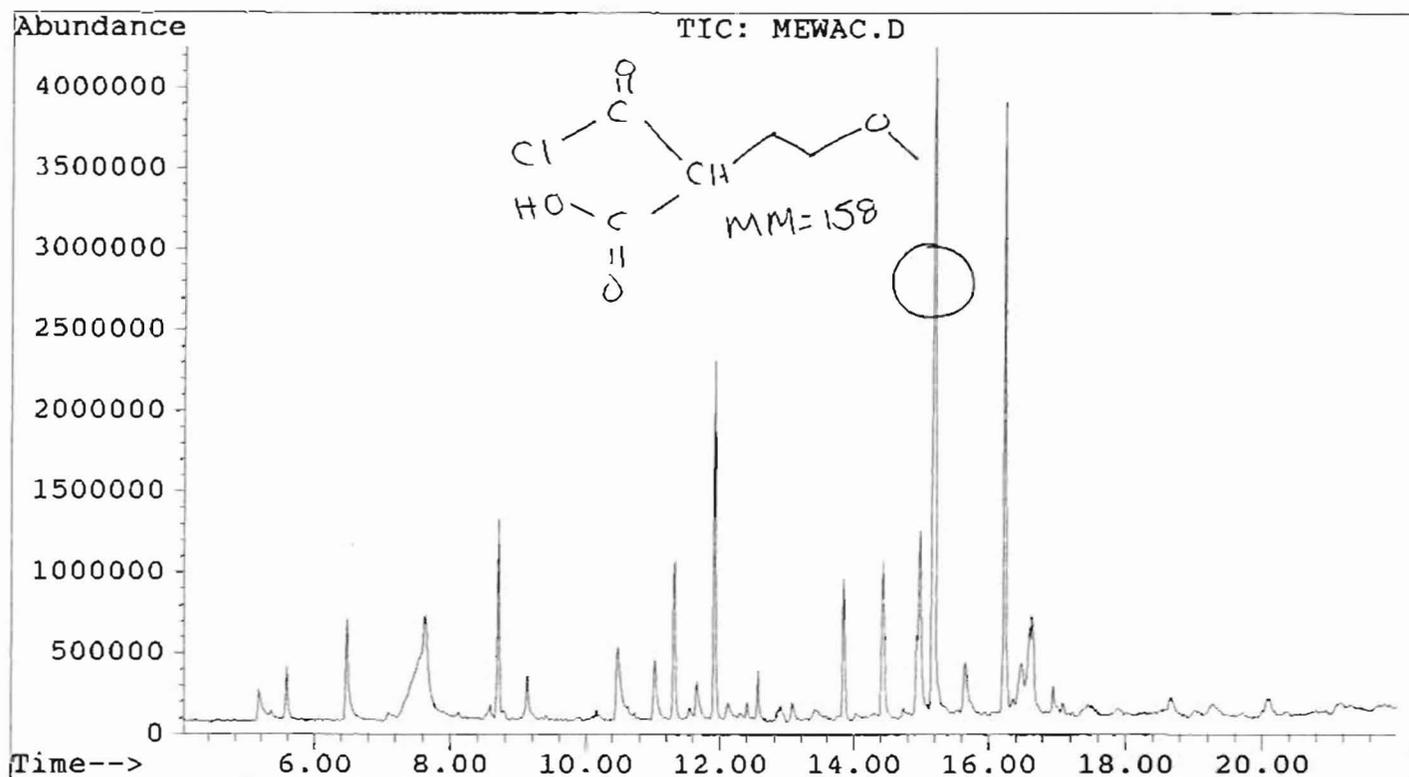
References

1. Findlay, Alexander. *A Hundred Years of Chemistry*. Kemp Hall Press Ltd.: Great Britain, 1938.

2. Joyce, C. *Earthly Goods: Medicine–Hunting in the Rainforest*. Little, Brown & Co.: Boston, MA, 1994.

3. http://dbhs.wvusd.k12.ca.us/Chem-History/Wohler-article.html Accessed May, 2000.

4. Cobb, C.; Goldwhite, H. *Creations of Fire: Chemistry's Lively History from Alchemy to the Atomic Age*. Plenum Press: New York.

5. Balandrin, M.F.; Kinghorn, A.D.; Farnsworth, N.R. *Plant Derived Natural Products in Drug Discovery and Development: An Overview*. In *Human Medicinal Agents from Plants*. A.D. Kinghorn, M.F. Balandrin, Eds. American Chemical Society: Washington D.C., 1993.

6. Scheuer, Paul J. *Chemistry of Marine Natural Products*. Academic Press: New York, NY, 1973.

7. Nicalaou, K.C., et al. *Nature* **1994** *367*, 630-4.

8. Danishefsky, S., et al. *Angew. Chem., Int. Ed. Engl.* **1995** *34*, 1723-6.

9. Holton, Robert A. Total Synthesis of taxusin: An Initial Step Toward Taxol Synthesis. In *Strategies and Tactics in Organic Synthesis*. Lindberg, Thomas, Ed.; Academic Press: New York, 1991; 3, pp 165-197.

10. Wender, P.A.; Badham, N.F.; Conway, S.P.; et al *J. Am. Chem. Soc.* **1997** *119*, 2757-2758.

11. Fekete, F.A.; Chandhoke, V.; Jellison, J. *Appl. And Env. Microb.* **1989**•*55*, 2720-2722.

12. Salman, Sarri S. *Studies Directed Toward the Synthesis of Natural Products*. Honors Thesis: Colby College, Waterville, ME 1994.

13. Goudreau, Christina A. *Approaches and Methodologies for the Synthesis of Aromatic Natural Products.* Honors Thesis: Colby College, Waterville, ME 1998.

14. Wähälä, K.; Hase T. *J. Chem. Soc., Perkin Trans. 1* **1991** *12,* 3005-3008.

15. Rastetter, W.H.; Phillion, D.P. *J. Org. Chem.* **1981** *46,* 3204-3208.

16. Adams,R.; Marvel, C.S. *J. Am. Chem. Soc.* **1920** *42,* 316-317.

17. Lee, Terrance A. *A Beginner's Guide to Mass Spectral Interpretation.* John Wiley & Sons, Inc.: New York, NY, 1998.

18. Budzikiewicz, H; Djerassi, C.; Williams D.H. *Interpretation of Mass Spectra of Organic Compounds.* Holden-Day, Inc.: San Francisco, CA, 1964.

19. Lee, Changjoo. *Heterocyclic Chemistry: The Unique Role of Heteroatoms in Structure and Reactivity.* Ph.D. Thesis: Montana State University, Bozeman, MT 1991.