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# Synthesis of Novel Sesquiterpene Lactones: Heritianin, Vallapianin and Vallapin

Kostas Gavardinas '99
*Illinois Wesleyan University*

# Synthesis of Novel Sesquiterpene Lactones: Heritianin, Vallapianin and Vallapin

By

Kostas Gavardinas

Advisor: Professor Ram. S. Mohan
Research Honors Senior Thesis
Illinois Wesleyan University
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This thesis is dedicated to my fiance Tara,
the sweetest and most wonderful person I know

Approval Page

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A PAPER SUBMITTED AS PART OF THE REQUIREMENTS FOR
CHEMISTRY 499 AND RESEARCH HONORS IN CHEMISTRY

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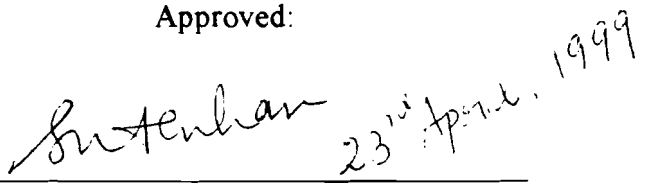

Ram S. Mohan, Ph. D., Research Advisor

Illinois Wesleyan University, 1998-1999

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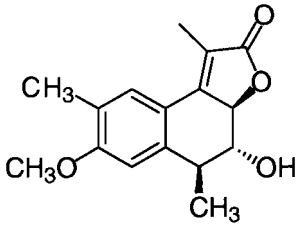
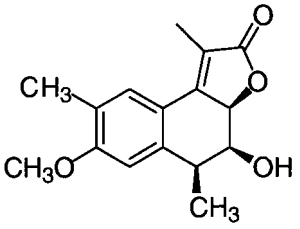
## ABSTRACT

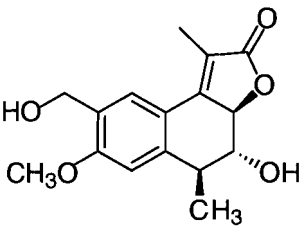
For decades considerable research has focused on improving the efficiency of crop protection. Many naturally occurring biodegradable compounds have often been used as pesticides and with increased environmental concerns, the identification of biologically active natural products has attracted significant attention. Fish toxicity has often been used as a measure of pesticidal activity. Several Southeast Asian mangrove species have been shown to possess ichthyotoxic properties. A bioassay of the extracts obtained from *Heritiera littoralis,* a Philippine mangrove plant, indicated toxicity toward fish thus suggesting the possibility of their use as pesticides. Three sesquiterpene lactones, Heritianin, Vallapin, and Vallapianin have been isolated from *H. littoralis*. Vallapin showed activity against the cotton boll weevils.



Heritianin



Vallapin



Vallapianin

The aim of this project is to attempt the total synthesis of these lactones. The key reaction in the total synthesis is the construction of the lactone moiety. Based on literature precedent it appeared that an intramolecular Reformatsky reaction is the method of choice to construct the lactone. Model studies were carried out successfully with 6-methoxy-1-tetralone. The total synthesis of the target molecules is now underway and seven steps in the proposed ten step synthesis have been completed in 27% overall yield. The asymmetric synthesis of the target molecules will also be carried out.

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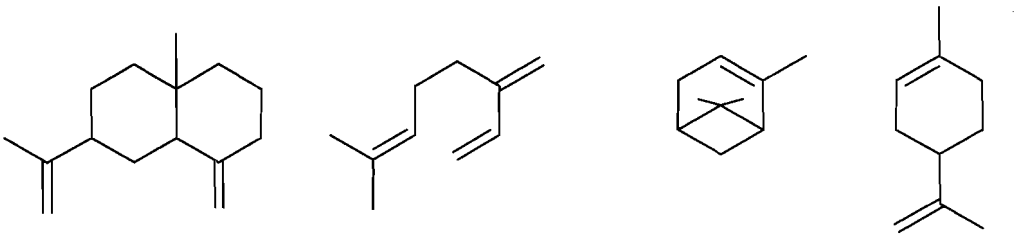
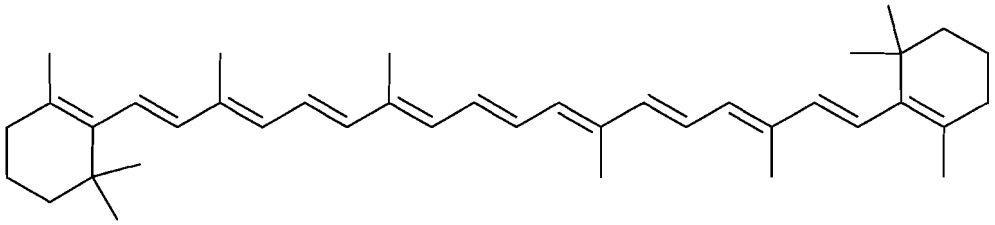
# I. INTRODUCTION

## A. Background

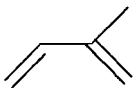
The chemistry of natural products has been extensively investigated in the second half of the century because of its great significance in understanding biological systems and the balances that govern them. Terpenes and terpenoids have been particularly interesting in that sense, because of the relative ease with which they can be isolated, as well as because of the many structural features that they possess, which affect their chemical behavior. Terpenes and terpenoids are the most abundant and widely distributed natural products formed in plants. Some examples include *β-carotene*, the terpene responsible for the pigmentation of carrots, tomatoes and squash, *limonene*, which is isolated from the oil of lemons, *myrcene*, which is extracted from the oil of bay leaves, *α-pinene*, a terpene found in the leaves of "white cedar" pine trees and *β-selinene*, which exists in the oil of celery[1] (Figure 1).

**FIGURE 1**



Many fragrant odors of plants have been associated with volatile liquids that can be extracted from leaves, fruit, flowers and occasionally from roots and other parts of the plants. These compounds were the first ones to be called *terpenes* or *terpenoids*, or *essential, ethereal,* or *volatile oils*, due to their association with the oil of turpentine.[2] Even though terpenes are structurally very diverse compounds with acyclic, alicyclic, aromatic, or heterocyclic skeletons, the vast majority appear to be head-to-tail combinations of the five-carbon compound *isoprene*. This *isoprene rule* was first proposed by O. Wallach[3] but it did not account for all the exceptions. In 1953, L. Ruzicka[4] proposed the *biogenetic isoprene rule*, according to which all terpenes consist of formal $C_5$ units and the initially formed hydrocarbon structure can undergo enzymatic modification. Incorporation of other functional groups can happen through enzymatic oxidations.



Isoprene

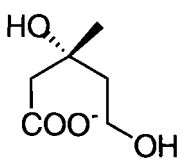
Several exceptions to the isoprene rule are known. For example, cholesterol is a $C_{27}$ terpene. Those exceptions are more broadly termed *terpenoids*, even though the terms *terpene* and *terpenoid* are used interchangeably in most cases. However, the term *terpene* is the most common one, since it originated first. Terpenes are classified according to the number of five-carbon units that they contain. Therefore, $C_{10}$ molecules are called monoterpenes (two isoprene units), $C_{15}$ molecules sesquiterpenes (three isoprene units), $C_{20}$ molecules diterpenes (four isoprene units), and so on.

The function of terpenes is as diverse are their structure. Monoterpenes act as agents for defense against insects.[2c] Steroidal hormones, vitamins, and plant growth regulators such as abscissic acid and the gibberillins have hormonal and regulatory functions.[2d] Also, various quinones and carotenoids are involved in electron transport and photosynthesis respectively.

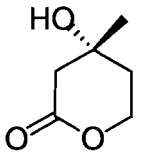
## B. Biosynthesis of Terpenes

One major complication with the theory that isoprene is the precursor to all terpenes and terpenoids is the fact that there is no account of biologically occurring isoprene. The first major breakthrough in the search for a naturally occurring "isoprene equivalent" unit came with the discovery[5] of (*R*)-mevalonate **1** as a growth factor for *Lactobacillus acidophilus*, from which it was isolated as the δ-lactone **2** (Figure 2).

**FIGURE 2**




**1**




**2**

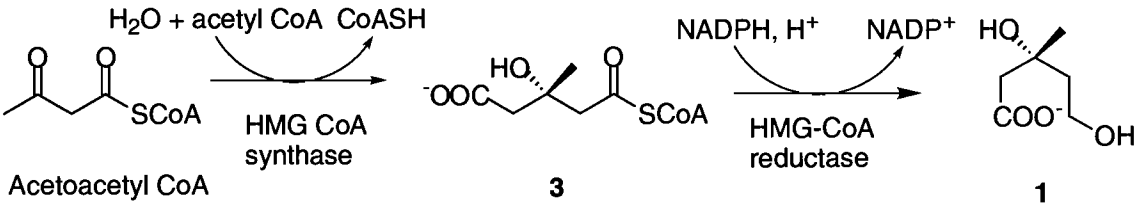
It was demonstrated that under anaerobic conditions radioactive 2-$^{14}$C- labeled mevalonate was incorporated into cholesterol after incubation with cell-free rat liver homogenate. Similar studies indicated that many terpenes and terpenoids contained

radioactive carbon when $^{14}C$-labeled mevalonate was used. Also, it was demonstrated that only the (*R*) enantiomer is biologically active.

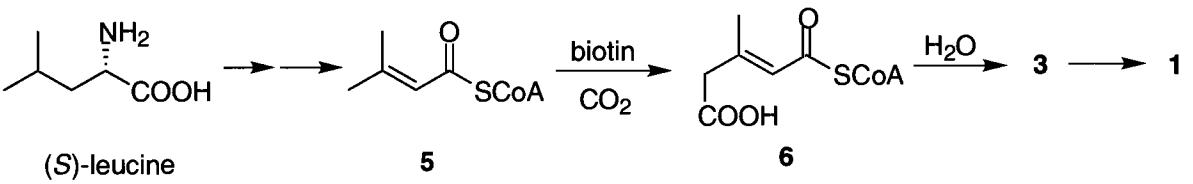
The current view[2a] is that (*R*)-mevalonate **1** is synthesized from acetyl coenzyme A, a key product of carbohydrate metabolism. According to this view, the biosynthesis of (*R*)-mevalonate **1**, which is shown in figure 3(a), starts with the aldol condensation of acetoacetylcoenzyme A with acetylcoenzyme A (acetyl CoA) to give (*S*)-3-hydroxy-3-methylglutaryl CoA (HMG CoA) **3**, which is reduced by NADPH to generate (*R*)-mevalonate **1**. An alternative pathway shown in figure 3(b) that is also supported by experimental data starts with the enzymatic conversion of the amino acid (*S*)-leucine **4** to 3-methylcrotonylcoenzyme A **5**, which is transformed to **6** after carboxylation in the presence of biotin as a cofactor. Carboxylate **6** undergoes then a hydration/reduction sequence to produce (*S*)-3-hydroxy-3-methylglutaryl CoA **3**.

**FIGURE 3**

(a) Generation of(*R*)-mevalonate **1** from acetoacetyl CoA.

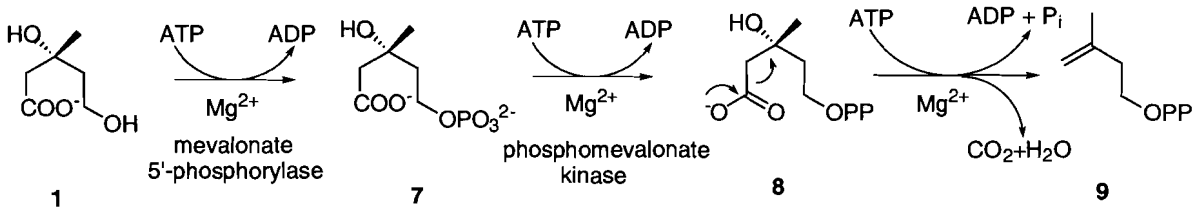



(b) Generation of(*R*)-mevalonate **1** from (*S*)-leucine.



Mevalonate **1** is phosphorylated twice by ATP (Figure 4) to give the corresponding pyrophosphate **8**, which undergoes a *trans*-concerted decarboxylation/dehydration process to form isopentenyl pyrophosphate **9**. Isopentenyl pyrophosphate (IPP) is considered to be the "true biological isoprene unit".[2a]

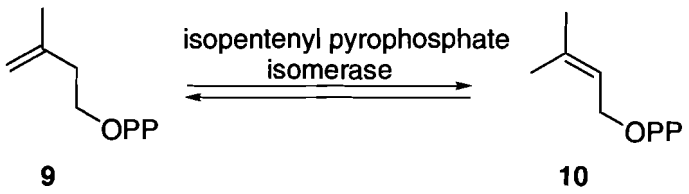
**FIGURE 4**



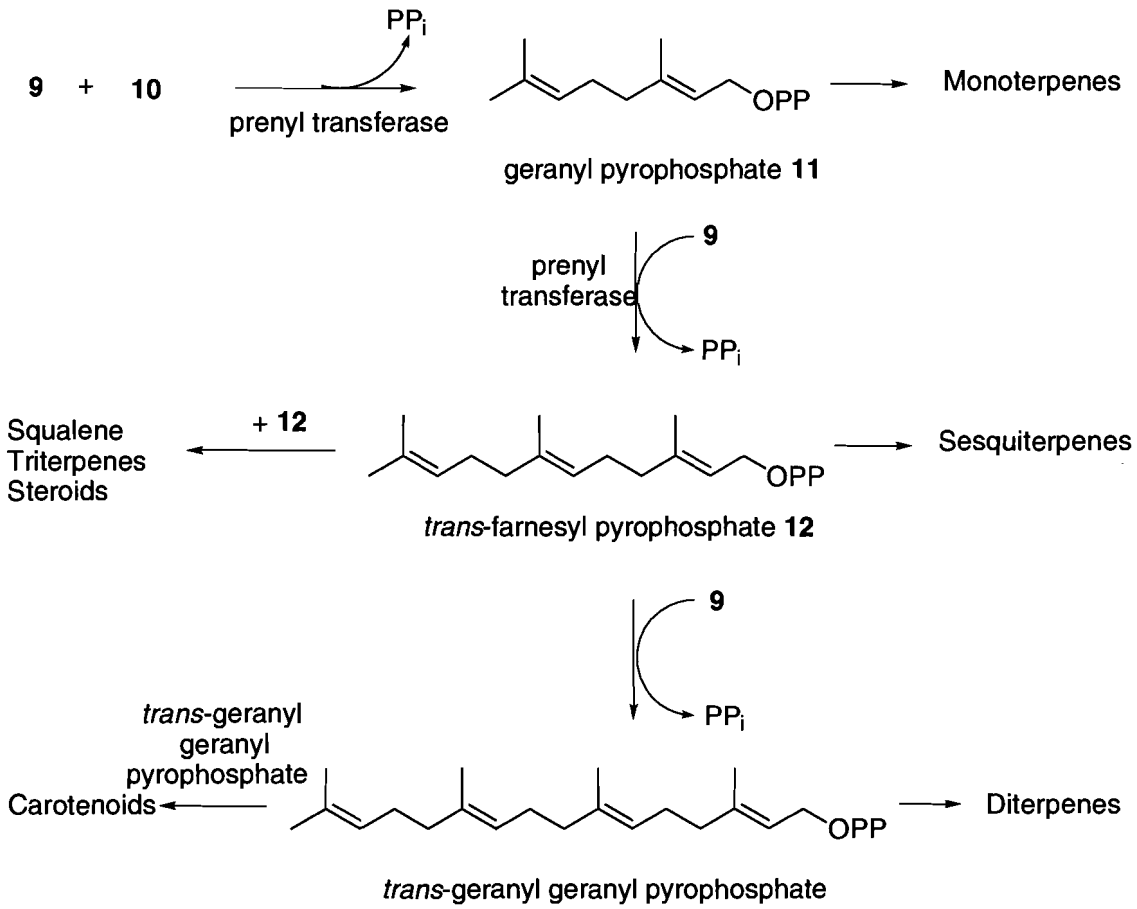

Isopentenyl pyrophosphate **9** can isomerize to dimethylallyl pyrophosphate **10** in the presence of isopentenyl pyrophosphate isomerase as shown in figure 5(a). A head-to-tail combination of **9** and **10** results in the formation of geranyl pyrophosphate **11**. After this point, head-to-tail and head-to-head combinations of **9** and **10** or among the newly formed intermediates generate all the different types of terpenes. Figure 5(b) outlines how the various terpenoids can be synthesized from geranyl pyrophosphate **11** and *trans*-farnesyl pyrophosphate **12**.

## FIGURE 5

(a) Isomerization of isopentenyl pyrophosphate **9** to dimethylallyl pyrophosphate **10**.



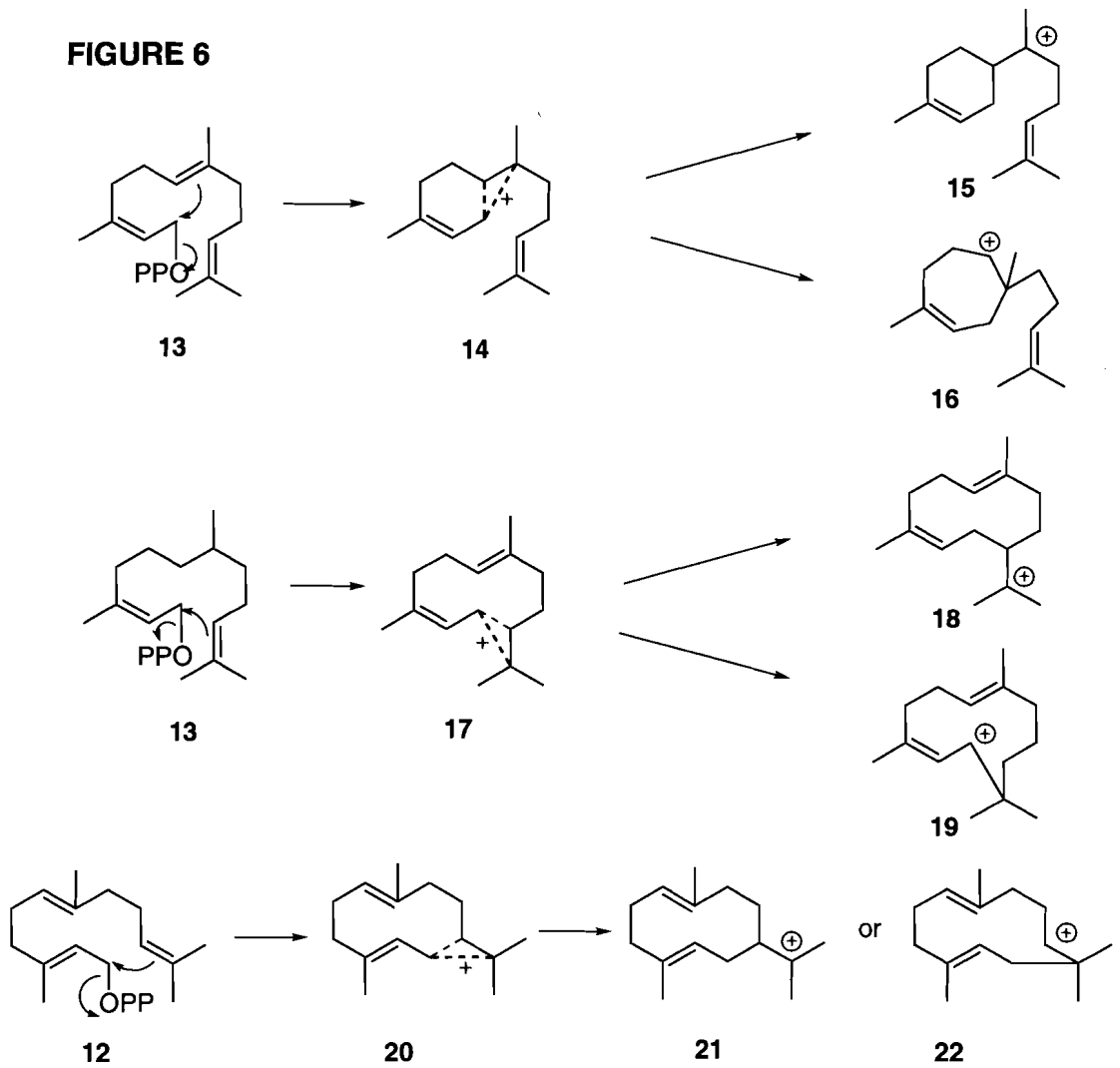

(b) Biosynthesis of terpenois from isopentenyl pyrophosphate **9** and dimethylallyl pyrophosphate **10**.



## C. Biosynthesis of Sesquiterpenes

Several hundred sesquiterpenes are known in the literature.[7] *trans*-Farnesyl pyrophosphate can give rise to *cis*-farnesyl pyrophosphate through enzymatic isomerization (Figure 6). *cis*-Farnesyl pyrophosphate **13** gives rise to carbocations **15**, **16**, **18**, and **19** via the non-classical carbocations **14** and **17**. Trans-Farnesyl pyrophosphate **12** forms carbocations **21** and **22** via the non-classical carbocation **20**. The biosynthesis of sesquiterpenes seems to proceed through carbocations **15**, **16**, **18**, **19**, **21**, and **22**. The conversion of **12** and **13** to various sesquiterpenes has been demonstrated by careful studies of tritium and $^{14}C$ labeled **13** and **12**.

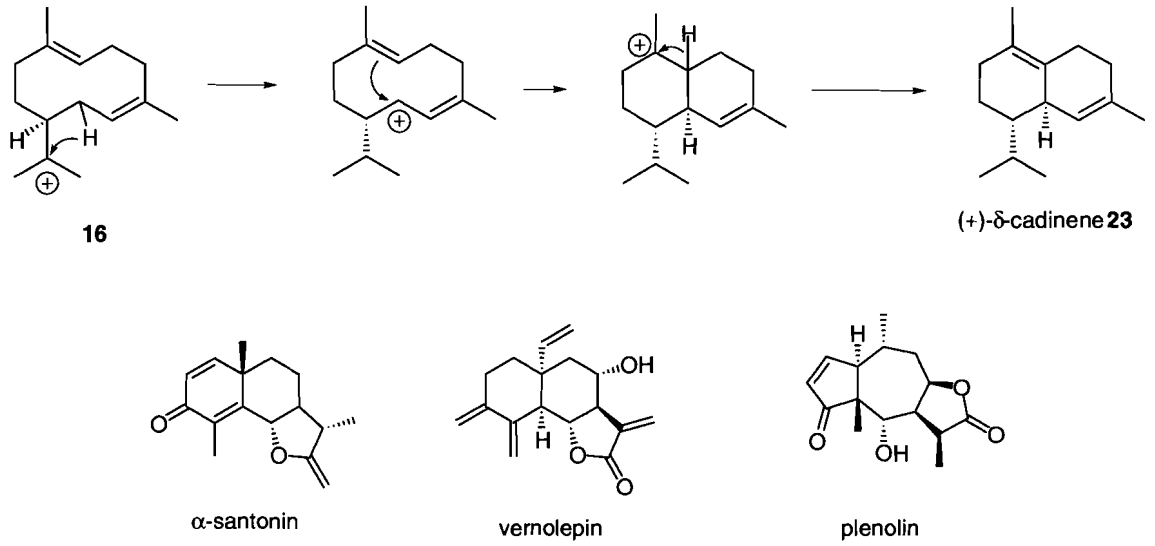
**FIGURE 6**



The research project described in the present paper focuses on the cadinane class of sesquiterpenes. Until 1972 about 600 sesquiterpenes had been isolated and characterized, but the number continues to grow at a quick pace.[2b] A number of sesquiterpenoids were initially grouped together according to their ability to undergo dehydrogenation to cadalene, but gradually a discrete class with respect to stereochemistry emerged, which is now referred to as the cadinane class. The parent compound (+)-δ-cadinene **23**, which was isolated from the oil of cubebs[2a] (a berry of a tropical shrub of the pepper family) is believed to arise from a hydride shift of carbocation **18** as shown in figure 7.[2a] A (+)-δ-cadinane synthase cDNA has been recently identified and it has been demonstrated that it encodes for the enzyme that converts farnesyl pyrophosphate to (+)-δ-cadinene.[8a] This is strong evidence that farnesyl pyrophosphate is the true precursor of (+)-δ-cadinene.

Some sesquiterpene lactones found in nature include α-santonin, and the very potent antitumor agents vernolepin and plenolin.[8b]

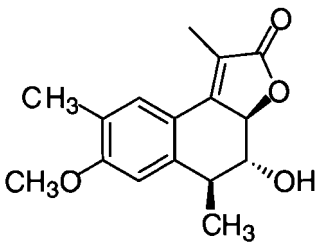
**FIGURE 7**



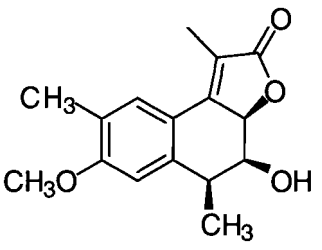
## D. Heritianin, Vallapin, and Vallapianin

Heritianin **24**, Vallapin **25**, and Vallapianin **26** (Figure 8) are sesquiterpene lactones belonging to the cadinane class described previously. They were isolated from the roots of the mangrove plant *Heritiera littoralis* that grows in the Philippines.[9] This plant drew the attention of scientists because it had been utilized by natives of the Philippine islands as a fish poison. Toxicity towards fish is often used as a measure of pesticidal activity.[10] A bioassay of Vallapin showed activity against boll weevils, pests of the cotton plant, at an inhibition level of 80% at a dose of 0.6 mg when administered by the Hedin method.[11]

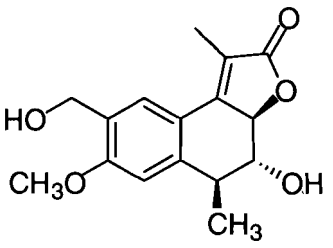
**FIGURE 8**




Heritianin **24**




Vallapin **25**




Vallapianin **26**

All three compounds contain a very unusual oxygenation pattern and an aromatic ring. The structures of the three compounds were elucidated by spectroscopic methods (HRMS, $^{1}H$ and $^{13}C$ NMR spectroscopy) and the relative configuration was assigned by X-ray crystallography. The absolute configuration is not known with certainty, but Miles et al.[9] speculate that the correct configuration around the stereocenters is *R*, since the main skeleton is analogous to other similar members of the cadinane class of

sesquiterpenes. To our knowledge, no report of a total synthesis of any of the three lactones exists in the literature.

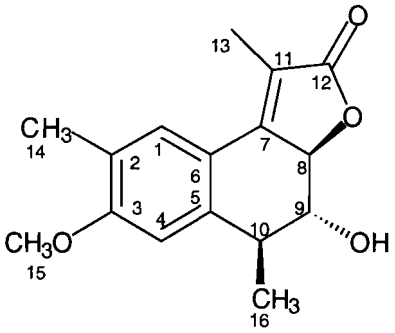
## E. Isolation of Vallapin and Vallapianin

The following is a summary of the procedure used by Miles et al. for the isolation of Vallapin and Vallapianin from the mangrove plant *Heritiera littoralis*.[8]

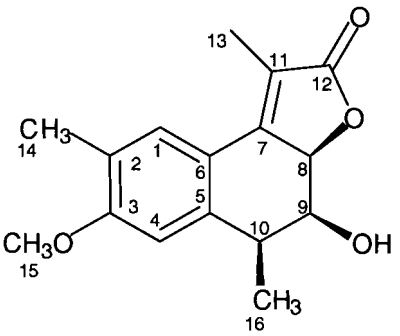
Chopped, air-dried roots of *H. littoralis* (21 kg) that were collected from the mangrove forest reserve in Pagbilao, Quezon, Philippines, were extracted with hexane (21 x 6 L) in a Soxhlet extractor for 16 hours to remove the fat. Evaporation of hexane gave 98.2 g of crude hexane extract (fat). The defatted roots were allowed to air-dry and were then extracted with 95% EtOH in a Soxhlet extractor for 16 hours. EtOH was concentrated in vacuo to give 524 g of crude extract, which was partitioned between $CHCl_3$ and water (1:1). $CHCl_3$ was removed in vacuo to yield 38.4 g of crude extract. The crude extract was partitioned between $CHCl_3$/MeOH and water to give 20 g after removal of $CHCl_3$/MeOH. The extract was chromatographed on an open column (Silica gel) using a hexane/$CHCl_3$/MeOH solvent system to yield 90 mg of vallapin as white crystals and 60 mg of vallapianin as a white powder.

Spectral data for Heritianin, Vallapin and Vallapianin are shown in the table below.

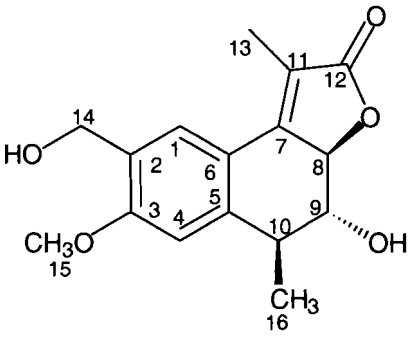
**TABLE 1.** $^{1}$H NMR Data for Heritianin **24**, Vallapin **25**, and Vallapianin **26**.[9]



Heritianin **24**



Vallapin **25**



Vallapianin **26**

| Proton | Chemical shift δ downfield from TMS (in ppm) | | |
|---|---|---|---|
| | Heritianin (**24**) | Vallapin (**25**) | Vallapianin (**26**) |
| H-2 | 6.85 (s) | 6.74 (s) | 6.89 (s) |
| H-5 | 7.40 (s) | 7.48 (s) | 7.58 (s) |
| H-8 | 4.80 (dd, *J* =1.8 Hz) | 5.22 (s) | 4.80 (dd, *J* =1.8 Hz) |
| H-9 | 3.49 (d, *J* =7 Hz) | 4.42 (s) | 3.49 (t, *J* =7 Hz) |
| H-10 | 3.01 (m) | 3.06 (m) | 3.01 (m) |
| H-13 | 2.15 (s) | 1.45 (d, *J* =10 Hz) | 2.15 (s) |
| H-14 | 2.25 (s) | 2.31 (s) | 4.71 (s) |
| 14-OH | - | - | 1.6 (s) |
| H-15 | 3.90 (s) | 3.95 (s) | 3.91 (s) |
| H-16 | 1.55 (d, *J* =7 Hz) | 1.55 (d, *J* =7 Hz) | 1.55 (d, *J* =7 Hz) |

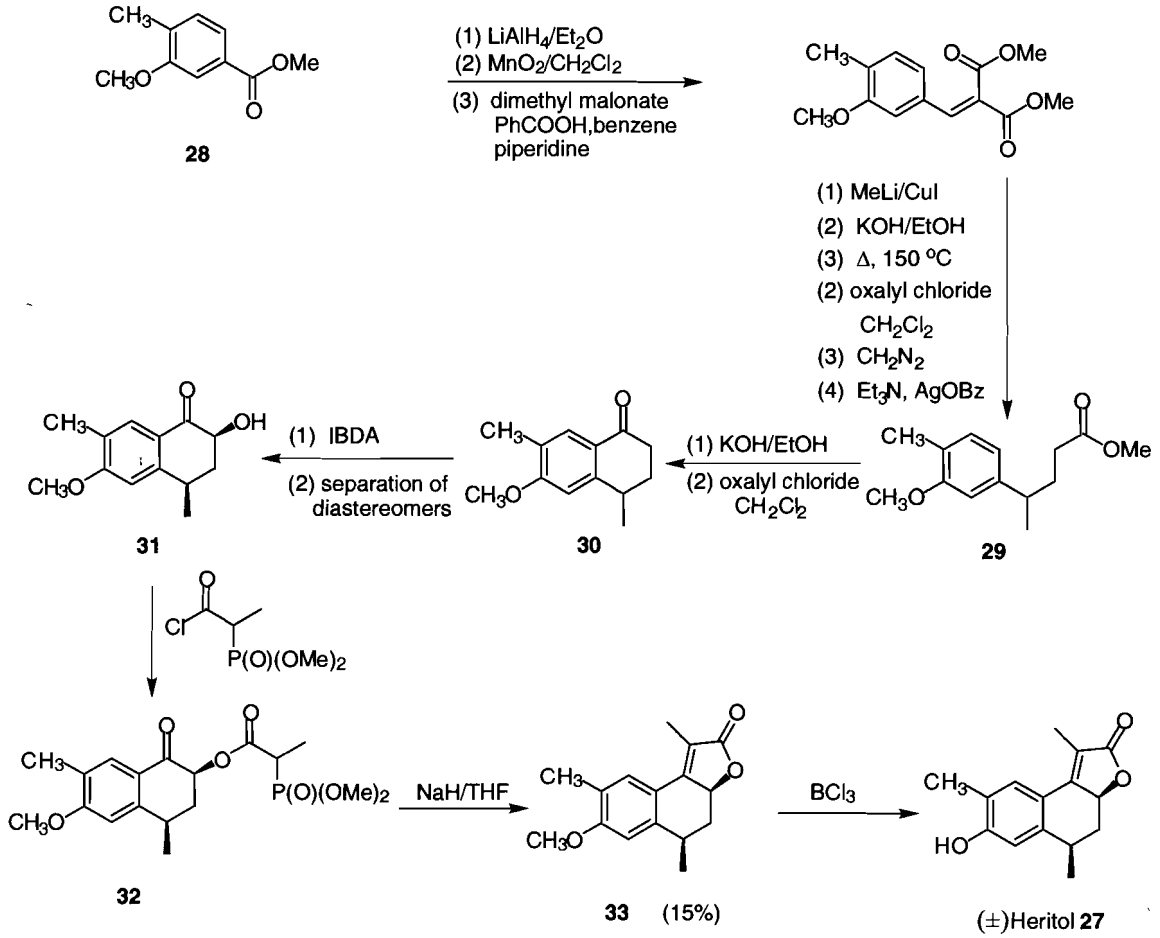
**TABLE 2.** Other Data for Heritianin **24**, Vallapin **25**, and Vallapianin **26**.[9]

| | Heritianin **24** | Vallapin **25** | Vallapianin **26** |
|---|---|---|---|
| mp (°C) | - | 269 | 182 |
| optical rotation $[\alpha]^{25}_{D}$ | - | -289.5° | 225° |
| IR data (KBr) ($cm^{-1}$) | - | 3450, 1750, 1660, 1620, 1320 | 3250-3350, 1750, 1640, 1600, 1440 |
| UV λ max (nm) | - | (cyclohexane) 216, 239, 286, 310 | (ethanol) 218, 239, 283, 296, 302 |
| HREIMS | - | 274.3158 | 290.1154 |

## F. Synthesis of Analogous Compounds

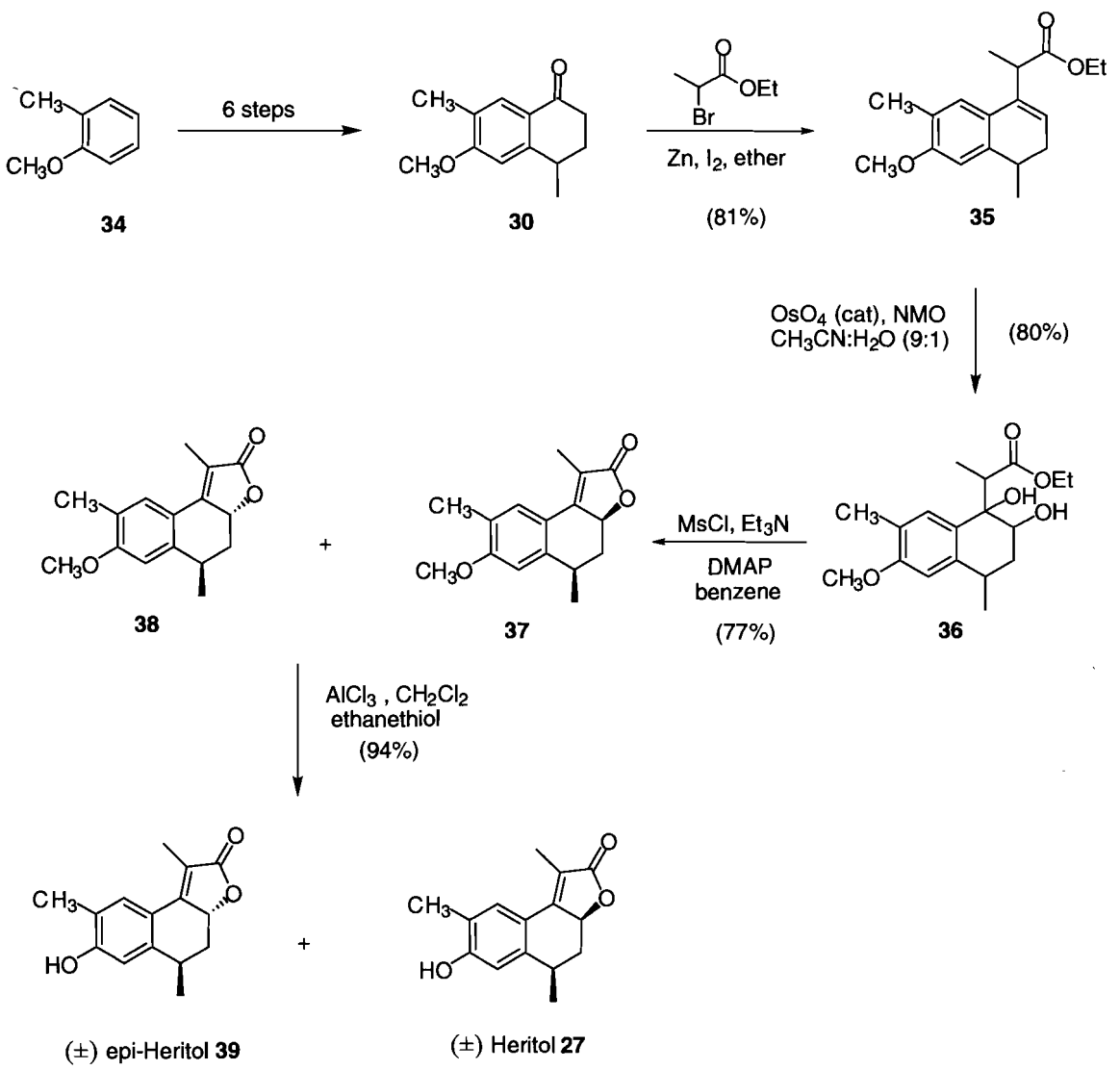
Not many examples of compounds similar to Heritianin, Vallapin, and Vallapianin can be found in the literature. In 1990 and 1991 two syntheses of the sesquiterpene lactone (±)-Heritol were reported by Irie[12] and Zubaidha[13] respectively. Scheme 9 outlines some of the highlights of Irie's synthesis. It should be pointed out that both Irie and Zubaidha employ tetralone **30** as the key synthetic intermediate in the construction of the butenolide moiety. The Irie synthesis generated tetralone **30** in seven steps from methyl 3-methoxy-4-methylbenzoate **28**. Hydroxylation of the α carbon in **30** with iodosobenzene diaacetate (IBDA) gave the corresponding α-hydroxyketone as a mixture of diastereomers. The desired diastereomer **31** was separated and acylated with α-(dimethylphosphono)propionyl chloride (DMPP-Cl). The crucial step in Irie's synthesis is the intramolecular Wittig reaction of **32** to construct the butenolide moiety of *O*-methylheritol **33**. Unfortunately, this step resulted in low yields (15%). Irie speculates that the reasons for this low yield could be attributed to a *peri* effect but they still remain unclear.

**SCHEME 9.** Synthesis of (±)-Heritol by Irie[12]




On the other hand, Zubaidha's synthesis[13] (Scheme 10) utilizes the Reformatsky reaction of tetralone **30** with ethyl α-bromopropionate to prepare the β,γ-unsaturated ester **35**. Osmium tetroxide catalyzed dihydroxylation of **35** gave diol **36**, which was lactonized and dehydrated in one step using methanesulfonyl chloride to give a mixture of lactones **37** and **38**, which were separated by fractional recrystallization. They were demethylated with aluminum trichloride to afford epi-Heritol **39** and Heritol **27** in racemic form. Zubaidha's synthesis is more efficient affording Heritol in 0.8% overall yield compared to 0.2% obtained by Irie.

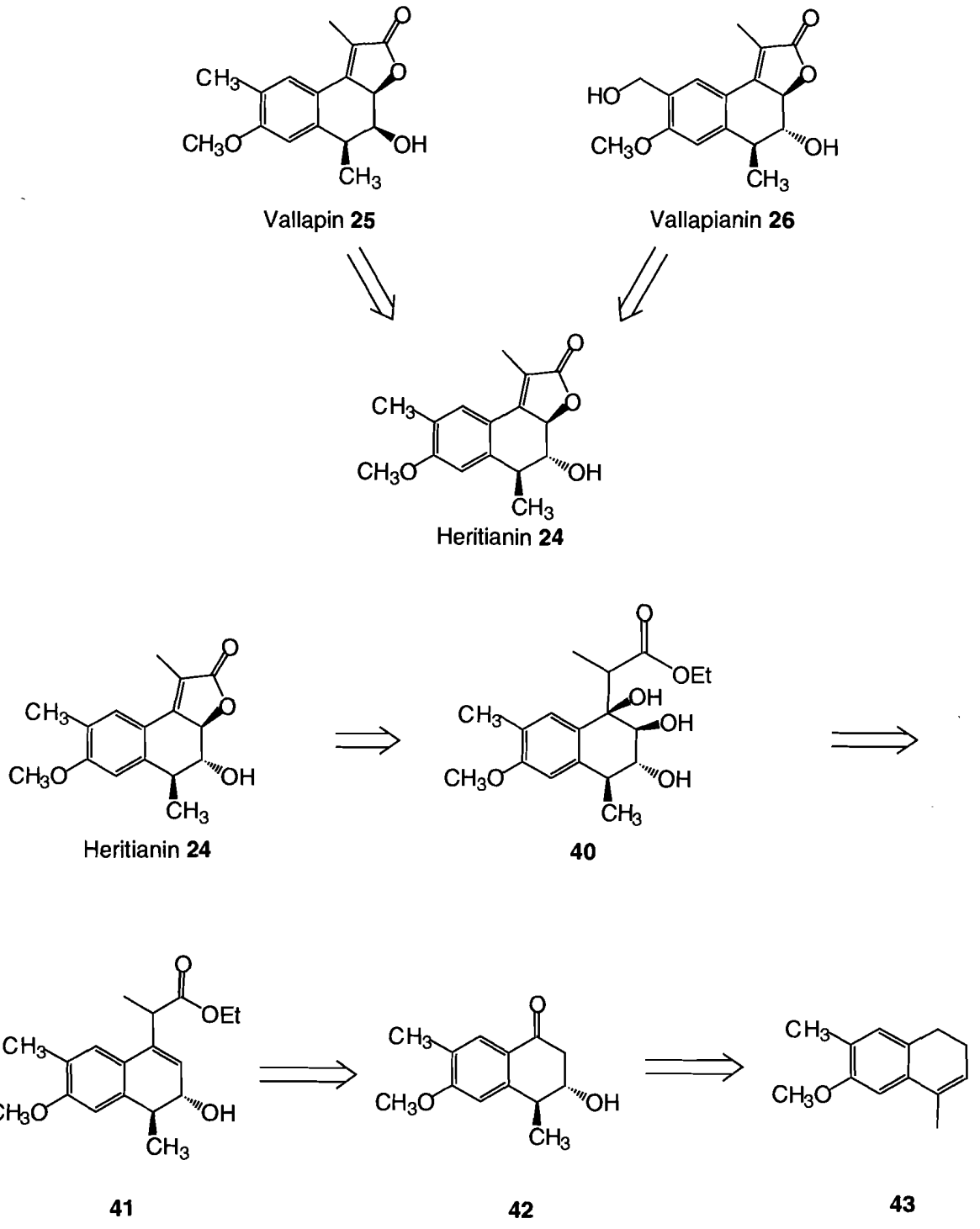
**SCHEME 10.** Synthesis of (±)-Heritol by Zubaidha[13]



# II. RETROSYNTHESIS

The retrosynthesis of Heritianin **24**, Vallapin **25**, and Vallapianin **26** is outlined in Scheme 11. Vallapin **25** can be generated from Heritianin **24** through an inversion of the configuration of the hydroxyl group (Mitsunobu reaction). Also, Vallapianin **26** can be synthesized from Heritianin **24** by oxidation of the methyl side chain on the aromatic ring to an aldehyde followed by hydride reduction. Following Zubaidha's approach it should be possible to synthesize the lactone moiety of **24** from diol **40**, which can be obtained by asymmetric dihydroxylation of β,γ-unsaturated ester **41**. Ester **41** can be synthesized from tetralone **42**, which can be obtained from olefin **43** via a hydroboration/oxidation and benzylic oxidation. In the synthetic direction, oxidation of the benzylic carbon would require protection of the alcohol in order to avoid oxidation of the hydroxyl group. Olefin **43** is one of Zubaidha's intermediates in the synthesis of Heritol and has been conveniently prepared from 2-methylanisole in four high yielding steps.

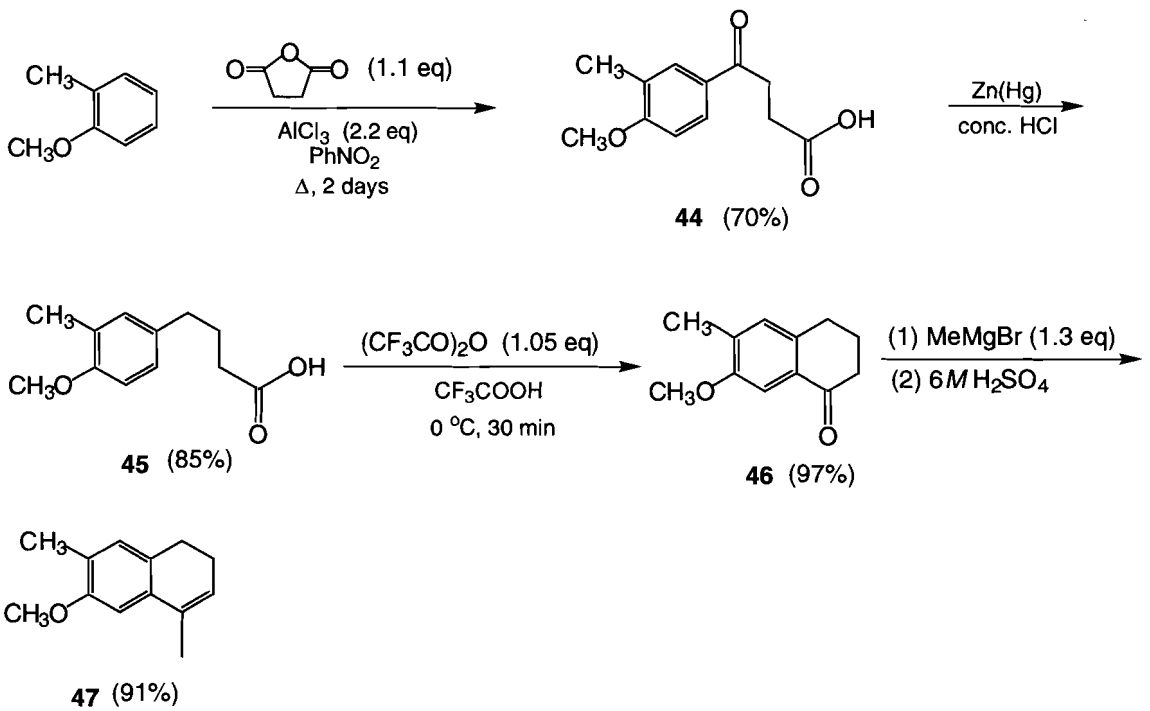
**SCHEME 11.** Retrosynthesis



# III. DISCUSSION

The synthesis of 6-methoxy-4,7-dimethyl-1,2-dihydronaphthalene **47** (Scheme 12) is described by Zubaidha at el.[13] Friedel-Crafts acylation of 2-methylanisole using a slight excess of succinic anhydride (1.1 equivalents) and aluminum trichloride (2.2 equivalents) as a Lewis acid in nitrobenzene afforded ketocarboxylic acid **44** in 70% crude yield. 2-Methylanisole was acylated *para* to the methoxy group as expected due to the strong *para* directing effect of the methoxy group. It was deemed unnecessary to further purify the crystalline product by recrystallization or chromatography since the observed melting point (147-149 °C) was in close agreement with the literature value (147 °C)[13] and the spectral data (Spectra 1 and 2) were consistent with literature data.

**SCHEME 12**



Ketocarboxylic acid **44** was reduced to butyric acid **45** (Spectra 3 and 4) using the Clemmensen reduction (zinc amalgam in refluxing concentrated hydrochloric acid) in 85% yield. Early unsuccessful attempts to reduce carboxylic acid **44** indicated that it is crucial that the heterogeneous reaction mixture is stirred very vigorously since the reaction appears to take place on the surface of the zinc amalgam. The ketocarboxylic acid **44** is not soluble in concentrated HCl, therefore, insufficient stirring will prevent the suspension of **44** from reacting with the amalgam at the bottom of the flask. Efficient mechanical stirring was found to be crucial for the success of the reaction. The zinc amalgam was prepared using $HgCl_2$ according to literature procedures.[14]

The preparation of tetralone **46** (Spectra 5 and 6) was achieved by reaction of **45** with a mixture of a slight excess of trifluoroacetic anhydride (1.05 equivalents) and trifluoroacetic acid. Butyric acid **45** forms a mixed anhydride with trifluoroacetic anhydride, which then undergoes an intramolecular cyclization to form tetralone **46**. The reaction was performed by slow addition of the trifluoroacetic anhydride/trifluoroacetic acid mixture to butyric acid **45** via syringe at 0 °C. The mixture gradually turned dark purple and the reaction was complete as soon as the butyric acid dissolved completely. In all preparations of **46** the reaction was complete (by TLC) within 30 minutes after the addition of the trifluoroacetic anhydride/trifluoroacetic acid mixture. Typical yields for this reaction were in the 80-90% range when the reaction was carried out on a medium scale (1.00 g of starting material), however, a larger scale preparation of **46** (9.00 g of

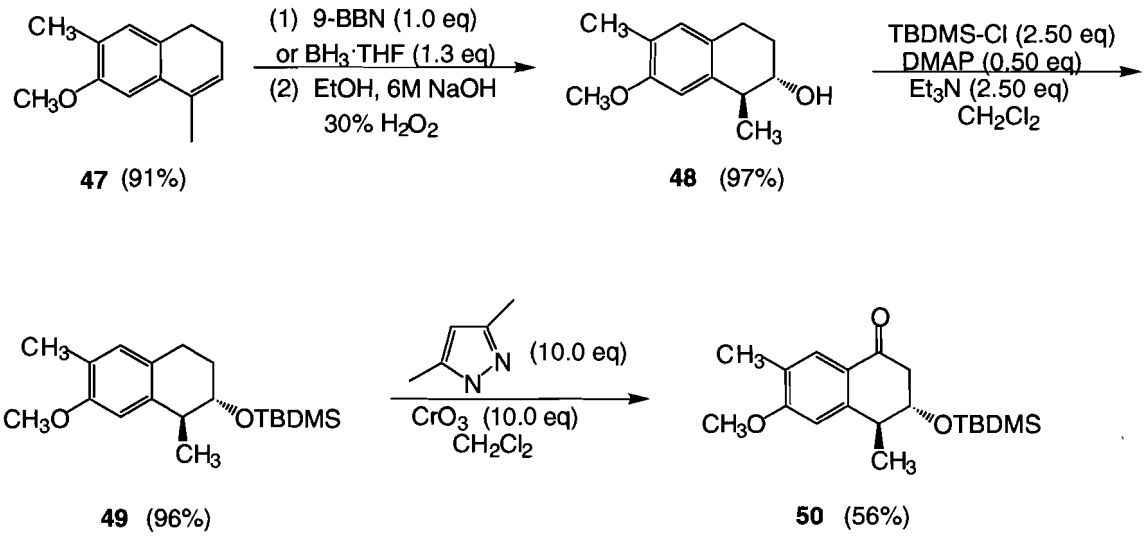
starting material) seemed to afford a better yield (97%). Also, adequate cooling of the reaction mixture with an ice-bath improved the yield. The crude tetralone **46** was found to be pure by NMR and hence it was used without further purification in the next step. A small sample of **46** was purified by bulb-to-bulb distillation (200 °C/6 mm Hg).

The Grignard reaction of methylmagnesium bromide with tetralone **46** was done with commercially available methylmagnesium bromide solution in ether (Aldrich). In Zubaidha's synthesis the Grignard reagent (methylmagnesium iodide) was prepared from magnesium metal and iodomethane instead. The commercial Grignard solution was standardized by titrating the preformed 1,10-phenanthroline-magnesium complex with dry *sec*-butanol.[15] 1,10-Phenanthroline forms a pink-pale red complex with organomagnesium and organozinc reagents. *sec*-Butanol reacts stoichiometrically to displace the metal ion from the complex. Once all the metal ions are displaced, the solution turns milky white indicating that the end point has been reached.

The Grignard reaction was carried by slowly adding a solution of tetralone **46** in anhydrous ether through a dropping funnel to the methylmagnesium bromide solution while maintaining a gentle reflux. During the Grignard reaction a buildup of the tertiary benzylic alcohol intermediate was observed by thin-layer-chromatography along with the dehydrated product **47** (NMR and mass spectra 7-9). Complete dehydration was achieved by acidic workup of the crude product with 6 M $H_2SO_4$. The residual brown oil appeared to be very clean by NMR and in most cases it was used in the next step without

further purification. An analytical sample was obtained by bulb-to-bulb distillation (105-110 °C/1 mm Hg). The Grignard reaction generally afforded alkene **47** in 80-95% yield. The molecular ion (m/z 188) of the mass spectrum of the product (spectrum 9) was also consistent with the expected molecular weight (188 g/mol) for olefin **47**.

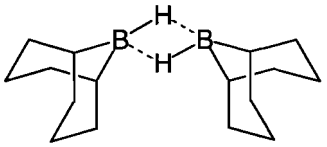
**SCHEME 13**




**47** (91%) **48** (97%)

**49** (96%) **50** (56%)

Scheme 13 outlines the conversion of olefin **47** to tetralone **50**. None of structures **48** through **50** have been reported in the literature. Alkene **47** was converted to alcohol **48** using either borane-tetrahydrofuran complex ($BH_3$·THF) or 9-borabicyclo[3.3.1]nonane (9-BBN) dimer (page 21) as the hydroborating agent followed by oxidation with 30% hydrogen peroxide. The hydroboration of alkenes using the above two reagents is very well documented in the literature.[16a-c]



9-borabicyclo[3.3.1]nonane (9-BBN)

It should also be pointed out that the hydroboration of **47** can also be carried out asymmetrically. The asymmetric hydroboration of alkenes has been thoroughly investigated with a variety of chiral boranes (mono- and diisopinocampheylborane and other chiral boranes[17a-d], chiral borolanes[18a], as well as catecholboranes combined with chiral rhodium-BINAP complexes[19]) resulting in moderate to excellent enantioselectivities (50-99%) for a broad range of olefins. Also, models exist in the literature that can be used to predict the stereochemistry of the hydroborated product.[20] At this point, the asymmetric hydroboration was not pursued and the rest of the synthesis was carried out with racemic alcohol **48**. As expected, the hydroboration using the bulky 9-BBN was significantly slower than when the borane-THF complex was used. When 9-BBN was used only 47% of the desired product was formed after 24 hours of refluxing. Unreacted starting material was also recovered in 50% yield after chromatography. In contrast, the hydroboration employing borane-THF was complete after two hours (by TLC) of refluxing and gave alcohol **48** in 97% yield. The regioselectivity of both reactions was excellent and only the anti-Markovnikov product was observed in both cases. It is possible though that a small amount of the tertiary benzylic alcohol

(Markovnikov product) formed also during the reaction, but it dehydrated immediately back to alkene **47** due to the harsh reaction conditions. The NMR and MS data are consistent with alcohol **48** (spectra 10, 11, and 12).

As mentioned earlier (see Retrosynthesis), it was necessary to protect the hydroxyl group of **48** in order to prevent its oxidation during the oxidation of the benzylic carbon to form tetralone **50**. Silyl ethers are considered excellent protecting groups for alcohols because they are stable to base hydrolysis and relatively stable to dilute acid. Also, they can survive high temperature reaction conditions and they can be cleaved easily under very mild conditions using tetrabutylammonium fluoride ($Bu_4NF$)[21]. Alcohol **48** was thus converted to the corresponding *tert*-butyldimethylsilyl ether using *tert*-butyldimethylsilyl chloride (TBDMS-Cl) (2.50 equivalents), triethylamine (2.50 equivalents) and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) (0.50 equivalents).[22] The reaction was carried out under very mild conditions at room temperature and after completion of the reaction (15 hours by TLC) the desired product **49** (spectra 13 and 14. Appendix I) was obtained in 96% yield after flash chromatography. The reaction can also be carried out using fewer equivalents of the TBDMS chloride, however, the rate of the reaction is extremely slow and the reaction is only approximately 50% complete after two days.

Oxidation of the benzylic carbon proved to be a difficult task. An initial attempt to oxidize the benzylic carbon of alcohol **48** employing selenium dioxide (1.1

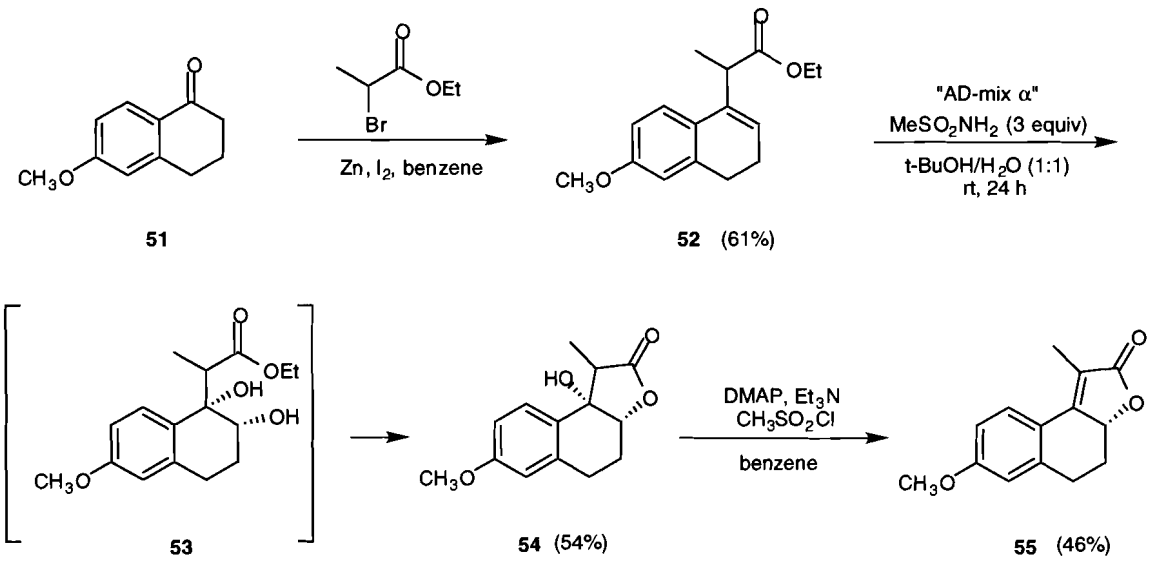
equivalents) in dioxane/water[15a,b] was unsuccessful and gave a mixture of unidentifiable products. Two singlets at 10.3 and 10.6 ppm of the $^1$H NMR spectrum suggested that a mixture of aldehydes possibly formed by oxidation of the methyl group on the aromatic ring. The reaction also gave a very low 15% mass recovery so it was not pursued any further. An attempt to oxidize the benzylic carbon of **47** with an excess (15 equivalents) of activated $MnO_2$[23] (prepared from $KMnO_4$ and $MnSO_4 \cdot H_2O$ under basic conditions[24]) in dry $CH_2Cl_2$ at room temperature only gave starting material after two days in 88% mass recovery.

Oxidation of silyl ether **49** was eventually achieved by the Corey procedure[25] using the $CrO_3$–3,5-dimethylpyrazole complex (10.0 equivalents) in dry $CH_2Cl_2$ at room temperature affording the desired tetralone **50** in 56% yield after chromatography. Typically, oxidations involving $CrO_3$ are carried out in refluxing acetic acid due to the poor solubility of $CrO_3$ in common organic solvents. Even then, the reaction often progresses very sluggishly requiring several days to reach completion and often results in moderate to very low yields. The Corey procedure avoids the extremely harsh acidic conditions and the long reaction times because the $CrO_3$-3,5-dimethylpyrazole complex is very soluble in $CH_2Cl_2$, which can result in a tremendous increase in the rate of the reaction. Furthermore, the reaction can be carried out at room temperature with a very satisfactory reaction rate. The oxidation of silyl ether **49** was complete after 24 hours (by TLC). One of the main problems was the irreproducible yields (45-76%) between the

different attempts to improve the yield of the reaction. It appears that reaction times that are longer than 24 hours result in a decrease in yield. Also, it was necessary to purify the product by flash chromatography to remove the $CrO_3$-3,5-dimethylpyrazole complex. As it is evident from the NMR spectra for tetralone **50** (spectra 15 and 16) the silyl ether was intact after the oxidation and the subsequent chromatographic purification.

After the synthesis of tetralone **50** it was desirable to practice the construction of the α,β-unsaturated lactone moiety with a model tetralone system. Scheme 14 outlines the synthesis of the butenolide ring using 6-methoxy-1-tetralone. The methodology is similar to Zubaidha's approach.[13] The main difference is the use of the commercially available "AD mix α" to achieve the asymmetric dihydroxylation of alkene **52**.

**SCHEME 14**

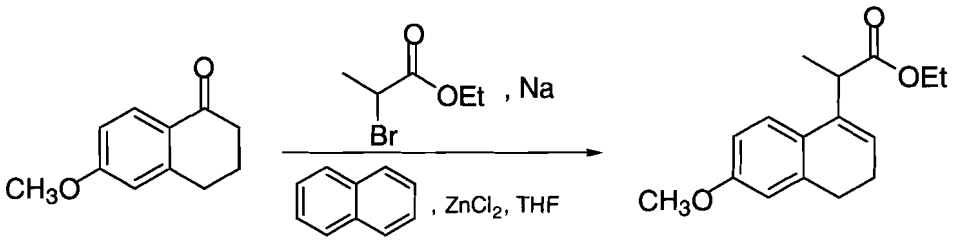


The conversion of 6-methoxy-1-tetralone **51** to alkene **52** was accomplished by the Reformatsky reaction using ethyl 2-bromopriopionate and activated Zn metal. The classical procedure by Reformatsky was first discovered in 1887[26] and has been the focus of many reviews[27a-f]. Even though the classical procedure uses Zn metal, in the last two decades the reaction has also been carried out with other metals such as bismuth[28], samarium[29], germanium[30], and chromium[31], Rieke nickel[32], tin[33], and indium[34] as well as in aqueous media[35] and with zinc-copper[36] and cerium-mercury couples[37]. The most common problem that is often encountered arises from the difficulty in activating Zn metal. Several purification/activation procedures exist in the literature.[38a-b] The zinc metal used in the reaction of **51** was activated by briefly washing it with 6M HCl, followed by several portions of deionized water, acetone, and ether. It was then dried in a vacuum oven for 20 minutes at 120 °C/25 Torr. Typically an excess of ethyl 2-bromoprionate and zinc (1.2 equivalents of each) was used. In early attempts the reaction was initiated with the addition of a catalytic or stoichiometric amount of iodine to the mixture of ethyl 2-bromopropionate, tetralone **51**, and zinc in a variety of solvents (dry THF, anhydrous ether, dry benzene). This procedure resulted in very irreproducible results. In many cases the reaction would not initiate at all, or it would yield between 40-85% of the desired product. The reaction times were also extremely irreproducible varying from two hours to several days. After numerous attempts, the best procedure that gave reproducible results was the following. Activated zinc (3.00 equivalents) was

suspended in dry benzene (distilled over Na/benzophenone) under nitrogen and was brought to a reflux with an oil bath. Ethyl 2-bromopropionate (0.30 equivalents) was added via syringe and the mixture was heated for approximately 10 minutes. Tetralone **51** and ethyl 2-bromopropionate (2.70 equivalents) in benzene were then added via syringe and the mixture was refluxed with vigorous stirring. The above procedure shortened the reaction time of the Reformatsky reaction to approximately 2 hours. While monitoring the progress of the reaction by TLC a buildup of the intermediate diastereomeric alcohols was observed ($R_f$ 0.29 and 0.24 with 20% EtOAc/Hex). They can be dehydrated to olefin **52** by acidic workup (2 M HCl). The excess bromoester can be removed at the end of the reaction either by rotary evaporation (approx. 50-60 °C/30 Torr) or by flash chromatography. Also, the above procedure avoids the use of iodine and the product **52** ($^1$H and $^{13}$C NMR spectra 17 and 18) is relatively clean. The isolated yield is typically very good (80-90%).

Another approach that was first developed by Rieke[39] makes use of activated zinc powders that are prepared *in situ.* by reacting anhydrous $ZnCl_2$ with K metal under anhydrous conditions. Alternatively, activated Rieke zinc powder can also be prepared from $ZnCl_2$ and Na/naphthalene[40] or from $ZnCl_2$ and Li metal[41].

## SCHEME 15




**51** **52** (100%)

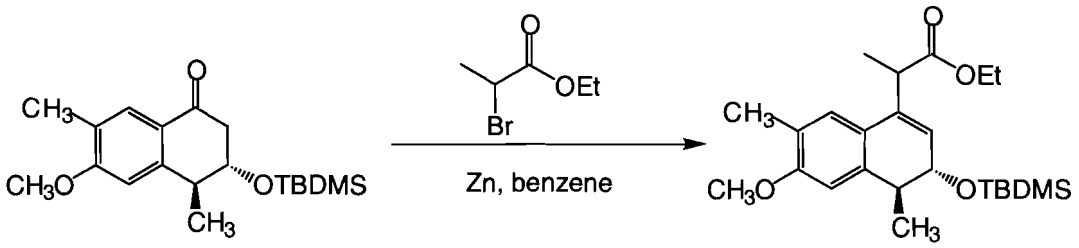
Scheme 15 depicts the conversion of tetralone **51** to alkene **52**. The sodium naphthalenide radical was prepared in a dry flask using freshly cut Na metal (4.50 equivalents of **51**) and naphthalene (5.00 equivalents of **51**) in THF (distilled over Na/benzophenone) under nitrogen at room temperature. After 3 hours, the dark green THF solution was added dropwise to a suspension of anhydrous $ZnCl_2$ (3.00 equivalents) in THF via syringe or cannula causing Zn metal to precipitate almost immediately as a fine gray powder. Ethyl 2-bromopropionate (2.00 equivalents) and tetralone **51** (1.00 equivalent) in THF were then added to the suspension via syringe and the mixture was stirred vigorously overnight at room temperature. The above procedure afforded olefin **52** in almost quantitative yield. The major disadvantage is that the product has to be separated chromatographically from naphthalene, while the classical procedure described earlier yields sufficiently clean product and the purification step by chromatography can be avoided.

Alkene **52** was dihydroxylated according to Sharpless' procedure[42] using commercially available "AD mix α" (1.4 g per mmol of **52**, 0.4 mol % of $OsO_4$), methanesulfonylamide ($MeSO_2NH_2$, 3.00 equivalents) in a 1:1 water/*t*-butanol solvent system. The recommended procedure that can be applied to most 1,2-disubstituted alkenes is usually carried out with 1.00 equivalent of $MeSO_2NH_2$, which results in a 50-fold decrease in reaction time. The dihydroxylation of **52** was very slow with 1.00 equivalent of $MeSO_2NH_2$ and at 0 °C. That was not surprising since it is reported that trisubstituted alkenes tend to undergo dihydroxylation very slowly.[42] The reaction was carried out at room temperature instead using 3.00 equivalents of $MeSO_2NH_2$ and with twice the recommended amount of "AD mix α" (0.8 mol % of $OsO_4$). Surprisingly, the expected diol **53** was not observed, but the β-hydroxy lactone **54** was obtained instead (Spectra 19 and 20). It is still not clear why diol **53** lactonized under the asymmetric dihydroxylation conditions. Lactone **54** was obtained at 54% isolated yield as a white crystalline solid. It was also surprising that the tertiary benzylic hydroxyl group of **54** did not spontaneously dehydrate to α,β-unsaturated lactone **55**. The dehydration of **54** was carried out using methanesulfonyl chloride (2.0 equivalents), triethylamine (2.1 equivalents), and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) in benzene. α,β-Unsaturated lactone **55** was thus obtained in 46% yield as a white solid (Spectra 21

and 22). The dehydration of **55** was also accomplished simply by acidic workup (2 M $H_2SO_4$) after the dihydroxylation step.

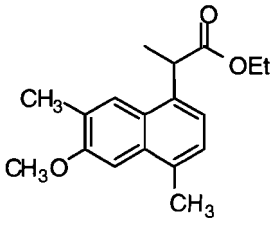
After studying the synthesis of the butenolide moiety on 6-methoxytetralone, the Reformatsky reaction using activated Zn and Rieke Zinc was attempted with tetralone **50**. The classical procedure using activated Zn did not give the expected adduct **56** (Scheme 16), but instead it gave a mixture of three products. The mixture was separated by chromatography to yield unreacted ethyl 2-bromopropionate (Compound A. $R_f$ 0.53), **58** (Compound B. 47%. $R_f$ 0.41 (30% hexanes/$CH_2Cl_2$) spectra 32 ($^1$H NMR), 33 ($^{13}$C NMR), 34 (MS) m/z 286 ($C_{18}H_{22}O_3$), 35 (HETCOR) and 36 (DEPT-90)), and **59** (Compound C. $R_f$ 0.2 (30% hexanes/$CH_2Cl_2$) spectra 37 ($^1$H NMR), 38 ($^{13}$C NMR), 39 (MS) m/z 202 ($C_{13}H_{14}O_2$)) respectively shown in Figure 17.

**SCHEME 16**

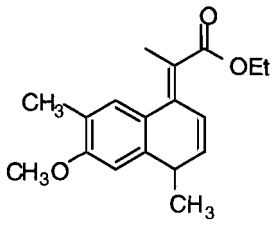



**50** **56**

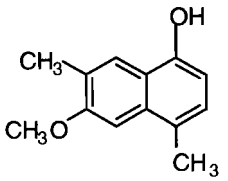
**FIGURE 17**




**57**




**58**




**59**

Compound B was assigned structure **58** instead of **57** because the IR spectrum gave a peak at 1725 $cm^{-1}$, a peak that is characteristic for the C=O vibration of α,β-unsaturated esters (1730-1715 $cm^{-1}$). The peak for the C=O vibration of aliphatic esters usually shows between 1750-1735 $cm^{-1}$.[44] Both **57** and **58** have a molecular weight of 286 g/mol.

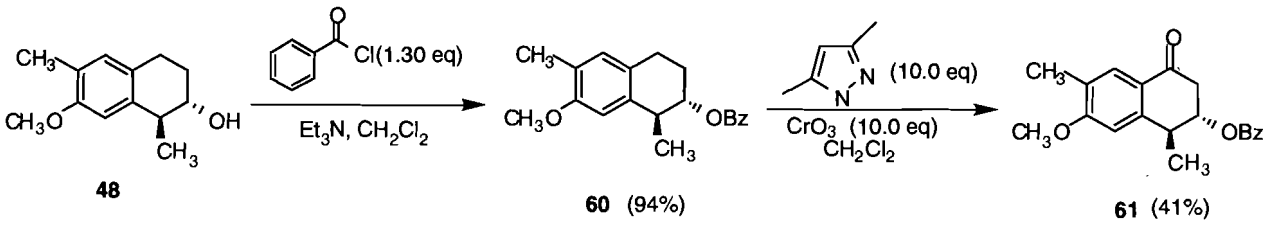
Compound C was assigned the structure of naphthol **59** (Mol. Wt. 202 g/mol), because a characteristic broad peak between 5.0 and 5.6 ppm (1H) was observed at the $^{1}H$ NMR spectrum (spectrum 37) that is characteristic of hydroxyl protons of naphthols. The same broad peak appears at the $^{1}H$ NMR spectrum of α-naphthol (spectrum 40)[45]. The $^{13}C$ and mass spectra (spectra 38 and 39 respectively) are also consistent with the assigned structure **59**.

On the other hand, the Reformatsky reaction using Rieke Zn gave one major product whose structure has not been elucidated yet. The IR spectrum (C=O vibration at 1750 $cm^{-1}$) suggests that an aliphatic ester is present. The mass spectrum (spectrum 29.

Appendix I. m/z 302 [$M^+$]) is consistent with the molecular formula $C_{18}H_{22}O_4$, suggesting that in addition to the two oxygen atoms from the ester and the one from the methoxy group there is one additional oxygen somewhere in the structure. No OH stretch appears in the IR spectrum. The $^1H$ NMR (spectrum 27), $^{13}C$ NMR (spectrum 28), COSY (spectrum 30) and HETCOR (spectrum 31) spectra were also obtained.

It was speculated that the TBDMS protecting group was not sufficiently stable to the Reformatsky reaction conditions, therefore alcohol **48** was protected as a benzoate ester instead according to Scheme 18.

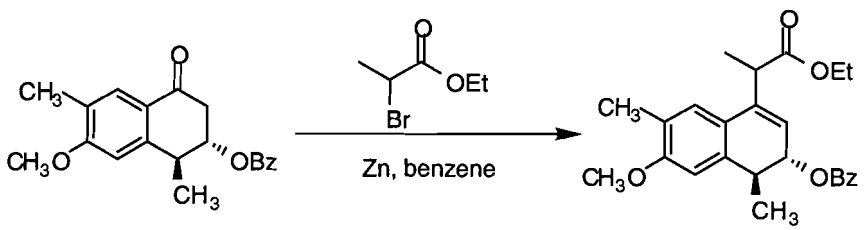
**SCHEME 18**




Alcohol **48** was first converted to ester **60** using benzoyl chloride (1.30 equivalents) in a mixture of triethylamine and dichloromethane. The reaction was carried out at room temperature and it required two days to go to completion. Benzoate ester **60** was isolated in 94% yield as a crystalline solid (spectra 23 and 24). It was then converted to tetralone **61** in 41% yield using Corey's procedure ($CrO_3$-3,5-dimethylpyrazole) described earlier (spectra 25 and 26).

The Reformatsky reaction of **61** with ethyl 2-bromopropionate using activated Zn did not give the expected olefin **62** (Scheme 19), but instead a compound with spectra identical to compound B (**58**) described earlier were obtained. It is noteworthy to mention that naphthol **59** was not observed (by TLC) or isolated. The aromatic protons of the benzoate ester were absent in the $^1$H NMR spectrum. The Reformatsky reaction of **61** with Rieke Zn was not attempted.

**SCHEME 19**




**61** **62**

# IV. FUTURE WORK

Future work includes the dihydroxylation of compound **58** in order to obtain Vallapin **25**. Also, the Reformatsky reaction needs to be attempted with other protective groups where elimination can be avoided. The butenolide moiety can be constructed then based on the methodology that was described earlier. Long-term plans include carrying out the asymmetric hydroboration step of **47** using chiral diisopinocampheylborane.

# V. EXPERIMENTAL SECTION

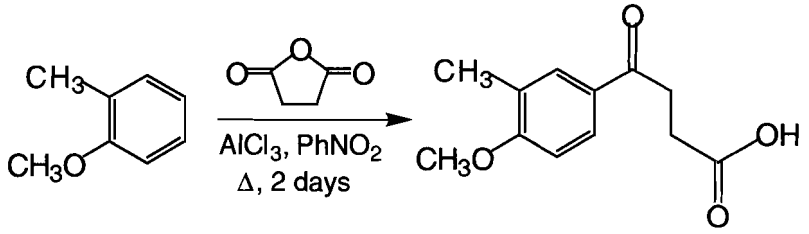
**General.** $^{1}H$ and $^{13}C$ NMR spectra were recorded on a JEOL Eclipse NMR spectrometer at 270 and 67.5 MHz in $CDCl_3$. Chemical shifts ($\delta$) are reported in parts per million (ppm); multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broadened). Coupling constants ($J$) are reported in Hz. Infrared spectra were recorded on a Mattson Series Fourier Transform IR spectrometer using NaCl pellets for liquid samples and KBr pellets for solid samples. Nujol IR spectra were recorded using mineral oil. IR peaks are reported as weak (w), strong (s) and broad (br). Mass spectra were obtained with a Hewlett Packard Model 6890 GC-MS (70 eV).

Boiling points (bp) refer to air bath temperatures (Kugelrohr) or distillation head temperatures and are uncorrected. Melting points (mp) were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. TLC was performed on Whatman aluminum backing Silica gel plates (250 μm layer thickness). Visualization was accomplished with phosphomolybdic acid (PMA) spray and/or UV light (254 nm).

All reactions were performed in flame-dried glassware under an inert atmosphere of dry $N_2$, unless water was used as solvent. Reagents were purchased from the indicated suppliers: 2-methylanisole (Acros), succinic anhydride (Acros), aluminum chloride

(Fisher), zinc metal (30 mesh) (Fisher), trifluoroacetic anhydride (Acros), methylmagnesium bromide solution in ether (Aldrich), 9-borabicyclo[3.3.1]nonane dimer (9-BBN) (Aldrich), t-butyldimethylsilyl chloride (TBDMS chloride) (Aldrich), and 4-dimethylaminopyridine (DMAP) (Aldrich), AD-mix $\alpha$ and $\beta$ (Aldrich), ethyl 2-bromopropionate (Aldrich), iodine (Aldrich), borane-THF (Acros), chromium trioxide (J. T. Baker), 3,5-dimethylpyrazole (Acros), methanesulfonyl chloride (Eastman), benzoyl chloride (Aldrich). Solvents were reagent grade and were distilled from the indicated drying agents: dichloromethane ($CaH_2$), tetrahydrofuran (THF) (sodium-benzophenone), benzene (sodium-benzophenone). Anhydrous diethyl ether (Fisher) was used as received. Flash chromatography was done according to the procedure of Still[43] using Merck silica gel (grade 9385, 230-400 mesh, 60Å) (Aldrich).

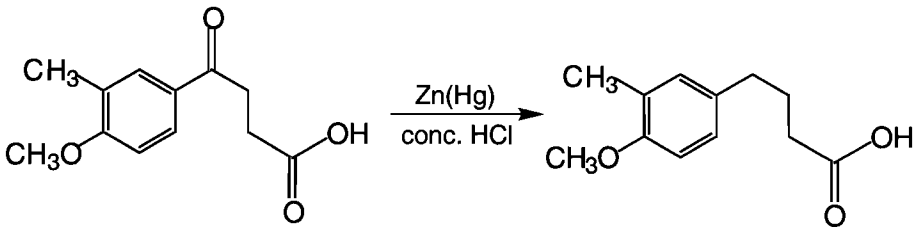
**4-(4-Methoxy-3-methylphenyl)-4-oxobutanoic acid (44, KG II/p. 36).**




**234** **44**

The following is a procedure by Zubaidha et al[13]. A solution of 2-methylanisole (29.42 g, 0.241 mol) and succinic anhydride (26.68 g, 0.267 mol, 1.10 equiv.) in nitrobenzene (100 ml) was mechanically stirred with cooling to –2 °C in a dry 1L three-neck flask. Aluminum chloride (72.0 g, 0.540 mol, 2.24 equiv.) was added slowly through a solid addition funnel while maintaining the internal temperature below 5 °C. The resulting red solution was then stirred at room temperature for 24 hours. Ice-cold 6 M HCl (150 ml) was added slowly and the resulting light gray solid was suction filtered, washed with ether and dried under vacuum to give 37.49 g (70%) of the desired product **44**. mp 147-149 °C. Lit. mp[13] 147 °C. $^1$H NMR ($CDCl_3$) **(KG II/p. 40A)** (Spectrum 1. Appendix I) δ 2.23 (s, 3H), 2.78 (t, 2H, *J*=6.7 Hz), 3.26 (t, 2H, *J*=6.7 Hz), 3.88 (s, 3H), 6.83 (d, 1H, *J*=8.7 Hz), 7.76-7.87 (m, 2H). $^{13}$C NMR ($CDCl_3$) **(KG II/p. 40B)** (Spectrum 2. Appendix I) δ 16.4, 28.2, 32.7, 55.6, 109.3, 126.9, 128.3, 129.0, 130.8, 162.0, 177.9, 196.8. IR (Nujol) ($cm^{-1}$) **(KG II/p. 40C)**: 3430 (br), 2960 (s), 1780 (s), 1570 (w), 1510 (s), 1380 (s), 1260 (s), 1180(s), 1040 (w), 810 (s).

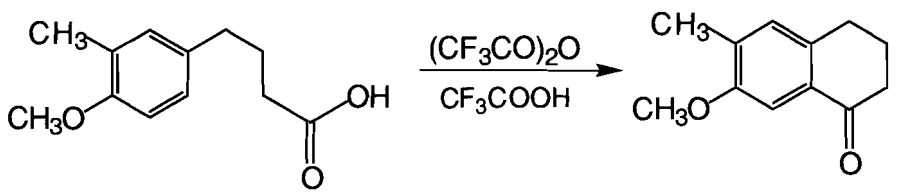
**4-(4-Methoxy-3-methylphenyl) butanoic acid (45, KG II/p. 70).**




**44** **45**

The following is a procedure by Zubaidha et al[13]. Granular Zn (300 g, 30 mesh, previously washed briefly with 6 M HCl), $HgCl_2$ (30.0 g, 0.111 mol), and concentrated HCl (20 ml) were mechanically stirred at room temperature for 30 minutes in a four-neck 2 L flask. Keto carboxylic acid **44** (49.14 g, 0.180 mol) and concentrated HCl (470 ml) were added and the reaction mixture was refluxed for 24 hours with vigorous stirring. The aqueous layer was then decanted and extracted with $CH_2Cl_2$ (3 x 200 ml), and the combined organic extracts were washed with water (2 x 200 ml), brine (200 ml) and dried ($Na_2SO_4$). Evaporation of the solvent under vacuum gave butyric acid **45** as a white crystalline solid (31.8 g, 85%). $^1H$ NMR ($CDCl_3$) **(KG II/p. 70)** (Spectrum 3. Appendix I) $\delta$ 1.91 (quintet, 2H, $J$=7.4 Hz), 2.18 (s, 3H), 2.35 (t, 2H, $J$=7.4 Hz), 2.57 (t, 2H), 3.79 (s, 3H), 6.7 (m, 1H), 6.9 (m, 2H). $^{13}C$ NMR ($CDCl_3$) **(KG II/p. 49B)** (Spectrum 4. Appendix I) $\delta$ 16.3, 26.6, 33.4, 34.2, 55.5, 110.0, 126.6, 130.9, 131.0, 132.9, 156.2, 179.8. IR (Nujol) ($cm^{-1}$) **(KG II/p. 49C)**: 2920 (br), 1710 (s), 1460 (w), 1380 (s), 1250 (s).

**7-Methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one (46, KG III/p. 10).**




**45** **46**

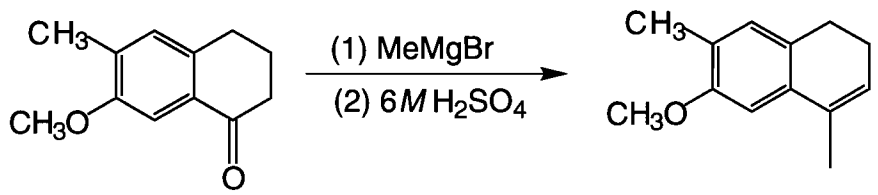
The following is a procedure by Zubaidha et al[13]. 4-(4-Methoxy-3-methylphenyl) butanoic acid **45** (9.02 g, 43.3 mmol) was cooled to 0 °C in a flame-dried three-neck 100 ml round-bottomed flask under nitrogen. A mixture of trifluoroacetic anhydride (9.52 g, 45.5 mmol, 1.05 equiv.) and trifluoroacetic acid (1.0 ml) was added dropwise and the purple mixture was stirred at 0 °C until the solid dissolved (30 min). The solution was poured over ice cold 10% sodium bicarbonate (50 ml) and stirred for 10 minutes. The mixture was extracted with ether (2 x 100 ml) and the combined extracts were washed with 10% sodium bicarbonate (3 x 100 ml), brine (100 ml) and dried ($Na_2SO_4$). The solvent was removed under vacuum to give an orange oil (8.02 g) which solidified in the freezer to afford tetralone **46** as white crystals (97%). TLC: $R_f$ 0.23 (10% EtOAc/Hex), 0.35 (20% EtOAc/Hex), 0.59 (40% EtOAc/Hex). $^1$H NMR ($CDCl_3$) **(KG II/p.69)** (Spectrum 5. Appendix I) δ 2.08 (q, 2H, *J*=6 Hz), 2.23 (s, 3H), 2.60 (t, 2H, *J*= 6 Hz), 2.84 (t, 2H, *J*=6 Hz), 3.84 (s, 3H), 7.00 (s, 1H), 7.43 (s, 1H). $^{13}$C NMR ($CDCl_3$) **(KG III/p. 10B)** (Spectrum 6. Appendix I) δ 16.7, 23.7, 28.9, 39.0, 55.6, 106.8, 130.9, 131.4,

133.9, 137.2, 156.6, 198.5. IR ($CDCl_3$) ($cm^{-1}$) **(KG II/p.69B)**: 2940 (s), 1740 (s), 1680 (s), 1610 (s), 1500 (s), 1460 (s), 1310 (s), 1270 (w), 1210 (s), 1130 (s), 1040 (s).

**Titration of methylmagnesium bromide solution in ether.**

The following is a modification of a procedure from Vogel.[15a] 3 M methylmagnesium bromide in ether (1.5 ml) was added to 1-10-phenanthroline (2-3 mg) in dry benzene (5 ml) in a two-neck 50 ml round-bottomed flask under nitrogen. The resulting turbid pink solution was titrated by injecting dry sec-butanol via syringe until the endpoint was reached (white turbid solution). The concentration was determined to be 3.2 M (average of two trials).

**6-Methoxy -4, 7-dimethyl-1, 2-dihydronaphthalene (47, KG III/p. 7).**

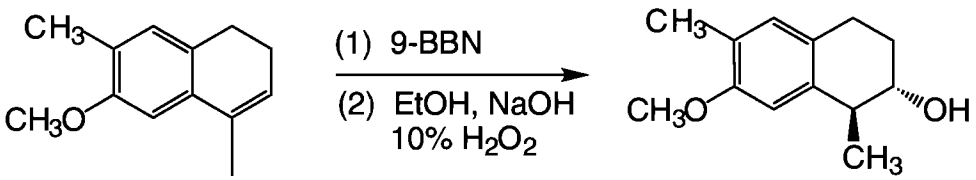



**46** **47**

A solution of tetralone **46** (3.06 g, 16.1 mmol) in dry ether (18.0 ml) was added drop wise through a dropping funnel to a 3.2 M methyl magnesium bromide solution in ether (6.96

ml, 20.9 mmol, 1.30 equiv.) in a flame dried three-neck 100 ml round-bottomed flask over 30 minutes while maintaining a gentle reflux. The resulting brown reaction mixture was stirred at room temperature for 2 hours and then was poured over ice-cold 6*M* $H_2SO_4$ (30 ml) and stirred for approximately 30 minutes. The mixture was extracted with petroleum ether (3 x 100 ml) and the combined organic extracts were washed with 10% sodium carbonate (2 x 100 ml), brine (100 ml) and dried ($Na_2SO_4$). The solvent was removed under vacuum and the residual oil was dried under high vacuum to afford 2.77 g of 6-methoxy -4, 7-dimethyl-1, 2-dihydronaphthalene **47** (91%). It was used in the next step without further purification. bp: 105-110 °C/1 mm Hg (air-bath temperature). Lit. bp: 110 °C/1 mm Hg. TLC: $R_f$ 0.60 (10% EtOAc/Hex), 0.63 (20% EtOAc/Hex). $^1$H NMR ($CDCl_3$) (**KG II/p.68A**) (Spectrum 7. Appendix I) δ 2.06 (q, 3H, *J*=1.7, 1.5 Hz), 2.20 (s, 3H), 2.19-2.28 (m, 3H), 2.66 (t, 2H, *J*=8 Hz), 3.84 (s, 3H), 5.82 (m, 1H, *J*=4.5, 1.2 Hz), 6.74 (s, 1H), 6.91 (s, 1H). $^{13}$C NMR ($CDCl_3$) (Spectrum 8. Appendix I) (**KG II/p.68B**) δ 15.9, 19.5, 23.6, 27.5, 55.7, 105.6, 124.7, 124.8, 128.1, 129.8, 132.2, 134.5, 156.3. IR (NaCl) ($cm^{-1}$) (**KG II/p.68C**): 2930 (br), 2830 (s), 1610 (s), 1570 (s), 1500 (s), 1270 (s), 1140 (s), 1050 (s). MS (EI) m/z (rel. intensity (%)) (**KG II/p. 9C-MS**) (Spectrum 9. Appendix I): 188 (84), 173 (100), 158 (49), 141 (17), 128 (28), 115 (26), 93 (10), 77 (10), 63 (9), 51 (10).

***trans*-7-Methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol using 9-BBN (48, KG III/p. 8).**

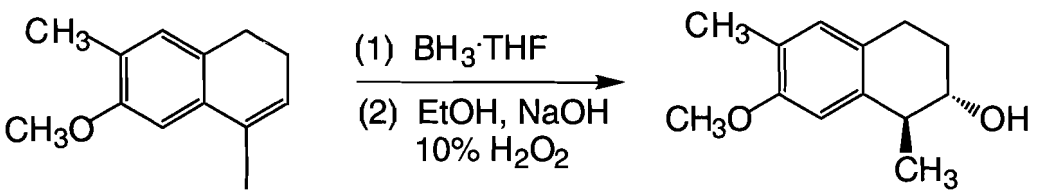



**47** **48**

The following is a modified procedure from Brown et al.[16] A 2M olefin **47** solution in THF (1.00 g, 5.32 mmol in 2.5 ml dry THF) was added via syringe to a refluxing solution of 9-borabicyclononane (9-BBN) (0.65 g, 5.32 mmol, 1.0 equiv.) in dry THF (10 ml) in a flame dried three-neck 50 ml round-bottomed flask and was refluxed with stirring for 17 hours. After allowing to cool to rt, absolute ethanol (3 ml), 6*M* NaOH (1 ml) and 30% $H_2O_2$ (2 ml) were added successively and the reaction mixture was heated at 45–50 °C for one hour. The reaction mixture was saturated with $K_2CO_3$ and the layers were allowed to separate. The aqueous layer was extracted with ether (10 ml) and the combined organic layers were dried ($Na_2SO_4$). The solvent was removed under vacuum to yield an orange oil, which was purified by flash chromatography (Silica gel, 100 g, 20% EtOAc/Hex) to afford 0.52 g of pure alcohol **48** (47%) (TLC: $R_f$ 0.36 (20% EtOAc/Hex)). Starting material **47** (0.50 g) was also recovered ($R_f$ 0.63 (20% EtOAc/Hex)). mp 44-48 °C. TLC: $R_f$ 0.36 (20% EtOAc/Hex). $^1$H NMR ($CDCl_3$) **(KG III/p. 9B)** (Spectrum 10.

Appendix I) δ 1.32 (d, 3H), 1.64 (br s, 1H), 1.8 (m, 3H), 2.0 (m, 1H), 2.18 (s, 3H), 2.6-2.9 (m, 3H), 3.80 (s, 3H), 3.7-3.8 (m, 1H), 6.63 (s, 1H), 6.85 (s, 1H). $^{13}C$ NMR ($CDCl_3$) **(KG III/p. 9B-C13)** (Spectrum 11. Appendix I) δ 15.8, 20.7,25.0, 28.3, 41.4, 55.5, 72.7, 110.1, 124.6, 126.7, 130.8, 137.5, 156.3. IR ($CH_2Cl_2$) ($cm^{-1}$) **(KG II/p. 9B-IR)**: 3600 (br), 3040 (w), 2930 (w), 1500 (s), 1470 (s), 1270 (s), 1210 (s), 1040 (s), 950 (s). MS (EI, 70 eV) m/z (rel. intensity (%)) **(KG II/p. 9B-MS)** (Spectrum 12. Appendix I): 206 (45), 188 (35), 173 (100), 162 (46), 147 (34), 131 (12), 115 (22), 105 (9), 91 (29), 77 (15), 65 (9), 51 (9).

***trans*-7-Methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol using borane-tetrahydrofuran complex (48, KG III/p. 22).**

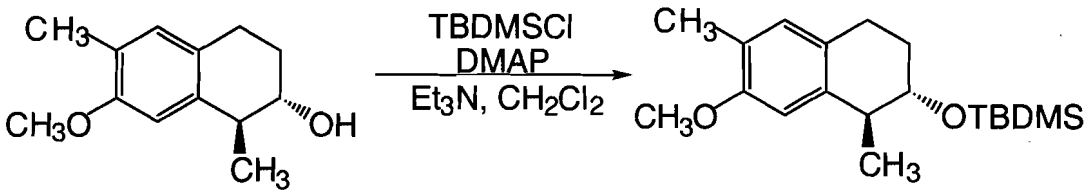



**47** **48**

The following is a modification of a procedure by Brown et al[16]. A 6-methoxy -4, 7-dimethyl-1, 2-dihydronaphthalene **47** solution in THF (1.76 g, 9.32 mmol in 2 ml dry THF) was added via syringe to a refluxing 1.0 M borane-THF solution (12.2 ml, 12.2 mmol, 1.3 equiv.) in a flame dried three-neck 50 ml round-bottomed flask and was refluxed with stirring for 2 hours. After allowing to cool to rt, absolute ethanol (5 ml), 6

M NaOH (2 ml) and 30% $H_2O_2$ (6 ml) were added successively and the reaction mixture was heated at 45 – 50 °C for one hour. The reaction mixture was saturated with $K_2CO_3$ and the aqueous and organic layers were allowed to separate. The aqueous layer was extracted with ether (20 ml) and the combined organic layers were dried ($Na_2SO_4$). The solvent was removed under vacuum to yield an orange oil, which was purified by flash chromatography (Silica gel, 110 g, 20% EtOAc/Hex) to afford 1.88 g of alcohol **48** (97%). The spectral data are identical with the spectra from the previous procedure.

***trans*- [(t-Butyldimethylsilyl) oxy]– 7-methoxy- 1,6-dimethyl- 1,2,3,4-tetrahydro naphthalene (49, KG III/p. 8).**

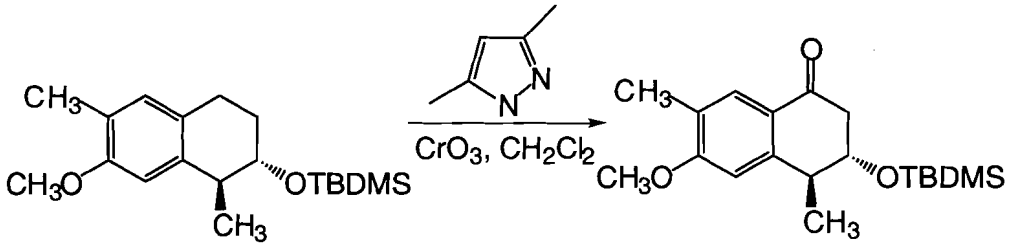



**48** **49**

The following is a modified procedure by Matt Mitchell.[22] A solution of TBDMS chloride (146 mg, 0.970 mmol, 2.00 equiv.), DMAP (61 mg, 0.43 mmol, 0.500 equiv.) and triethylamine (135 µl, 0.970 mmol, 2.00 equiv.) in dry $CH_2Cl_2$ (2 ml) in a flame dried three-neck 10 ml round-bottomed flask was stirred as alcohol **48** (100 mg, 0.485 mmol) was added and the resulting solution was stirred at rt for 24 hours. Additional TBDMS chloride (37 mg, 0.50 equiv.) and triethylamine (34 µl, 0.50 equiv.) were added and the

solution was stirred for 2 hours. It was then diluted with ether (20 ml), washed with 1 M HCl (20 ml), 10% sodium carbonate (10 ml), brine (20 ml) and dried ($Na_2SO_4$). Evaporation of the solvent under vacuum gave an oil, which was purified by flash chromatography (Silica gel, 10 g, 20% EtOAc/Hex) to afford silyl ether **49** as a clear colorless oil (149 mg, 96%). TLC: $R_f$ 0.74 (20% EtOAc/Hex). $^1H$ NMR ($CDCl_3$) **(KG III/p. 9B)** (Spectrum 13. Appendix I) δ 0.07 (d, 6H), 0.88 (s, 9H), 1.28 (d, 3H, *J*=7.2 Hz), 1.68-1.80 (m, 1H), 1.84-1.96 (m, 1H), 2.15 (s, 3H), 2.5-2.9 (m, 3H), 3.66-3.74 (m, 1H), 3.79 (s, 3H), 6.63 (s, 1H), 6.82 (s, 1H). $^{13}C$ NMR ($CDCl_3$) **(KG III/p. 14B)** (Spectrum 14. Appendix I) δ -4.60, -4.21, 15.8, 18.1, 20.3, 26.0, 29.6, 41.5, 55.3, 73.7, 109.8, 123.8, 127.5, 130.5, 138.4, 155.8.

***trans*-[(t-Butyldimethylsilyl)oxy]– 7-methoxy- 1,6-dimethyl- 3,4-dihydronaphthalen-1-(2*H*)-one (50, KG III/p. 25).**

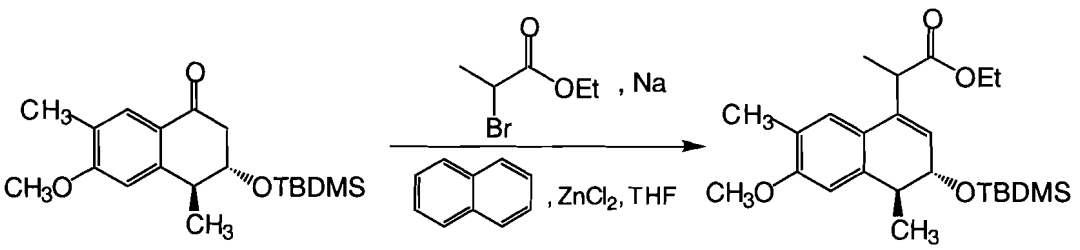



**49** **50**

The following is a modified procedure from Corey at el[25]. 3,5-Dimethylpyrazole (3.00 g, 31.2 mmol, 10.0 equiv.) was added to a suspension of chromium trioxide (3.12 g, 31.2

mmol, 10.0 equiv.) in dry $CH_2Cl_2$ (40 ml) under nitrogen in a flame dried three-neck 100 ml round-bottomed flask and the mixture was stirred at room temperature under nitrogen for 30 minutes. Silyl ether **49** (1.00 g, 3.12 mmol) in $CH_2Cl_2$ (10 ml) was added via syringe in one portion to the resulting brown mixture and was stirred at room temperature for 24 hours. The reaction mixture was concentrated, dissolved in ether (100 ml), filtered and dried ($Na_2SO_4$). Removal of the solvent gave a thick brown oil, which was purified by flash chromatography ($SiO_2$, 30 g, 10% EtOAc/Hex) to give tetralone **50** as a pale yellow oil that crystallized in the freezer to form a white solid (0.579 g, 56%). $R_f$ 0.26 (30% Hex/$CH_2Cl_2$). $^1$H NMR ($CDCl_3$) **(KG III/p. 21A)** (Spectrum 15. Appendix I) δ 0.05 (d, 6H, *J*=2.7 Hz), 0.83 (s, 9H), 1.37 (d, 3H, *J*=7.2 Hz), 2.18 (s, 3H), 2.54-2.66 (2d, 1H), 2.82-3.01 (m, 2H), 3.89 (s, 3H), 4.01 (m, 1H), 6.68 (s, 1H), 7.79 (s, 1H). $^{13}$C NMR ($CDCl_3$) **(KG III/p. 21B)** (Spectrum 16. Appendix I) δ -4.8, -4.5, 15.8, 18.0, 18.3, 25.8, 42.0, 45.2, 55.5, 72.9, 108.2, 124.7, 125.4, 129.1, 146.5, 162.6, 195.7. 15.9, 19.5, 23.6, 27.5, 55.7, 105.6, 124.7, 124.8, 128.1, 129.8, 132.2, 134.5, 156.3. IR ($CDCl_3$) ($cm^{-1}$) **(KG III/p.29C)**: 2960 (s), 2940 (s), 1670 (s), 1610 (s), 1500 (s), 1260 (s), 1140 (s), 1070 (s).

**Reformatsky Reaction of *trans*-[(t-Butyldimethylsilyl)oxy]– 7-methoxy- 1,6-dimethyl- 3,4-dihydronaphthalen-1-(2*H*)-one using Rieke Zn (KG III/ p.46)**

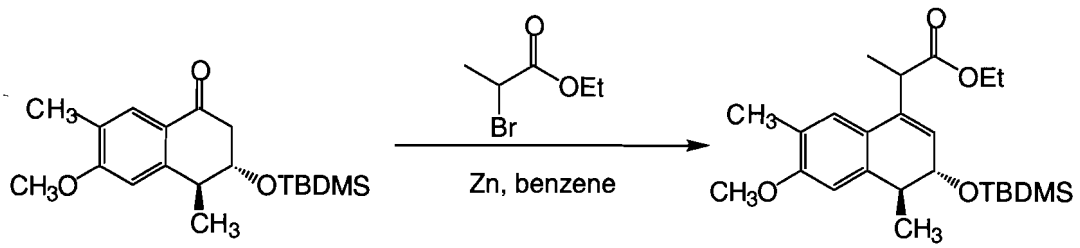



**50** **56**

A mixture of naphthalene (537 mg, 4.19 mmol, 7.00 equiv.) and Na metal (freshly cut and briefly washed in methanol) (100 mg, 4.07 mmol, 6.80 equiv.) in anhydrous THF (10 ml) in a 50 ml round-bottomed flask was stirred at room temperature for 3 hours. The resulting dark green sodium naphthalenide solution was added dropwise via syringe to a suspension of anhydrous $ZnCl_2$ (285 mg, 2.09 mmol, 3.50 equiv.) in THF (10 ml). The green color of the solution disappeared immediately and activated Zn precipitated as a fine black powder. Ethyl 2-bromopropionate (160 µl, 1.20 mmol, 2.00 equiv.) was added and stirred at room temperature for 30 minutes, followed by tetralone **50** (200 mg, 0.598 mmol, 1.00 equiv.). The dark brown reaction mixture was stirred at room temperature for 15 hours and was then heated at 65 °C for 6 days. It was poured over 2 M HCl (40 ml) and stirred for 15 minutes. The organic layer was separated, the aqueous layer was washed with ether (2 x 30 ml), the combined organic layers were then washed with 10% $Na_2CO_3$ (3 x 50 ml), brine (50 ml) and dried ($Na_2SO_4$). Removal of the solvent under

vacuum gave a mixture of naphthalene and one other major product that were separated by flash chromatography (Silica gel, 25 g, 20% EtOAc/Hex) to give 71 mg of a clear colorless oil. TLC: $R_f$ 0.52 ($CH_2Cl_2$). $^1$H NMR ($CDCl_3$) **(KG III/p. 46F)** (Spectrum 27. Appendix I) δ 1.23 (t, 3H, *J*=7 Hz), 1.72 (d, 3H, *J*=6.7 Hz), 2.40 (s, 3H), 2.54 (s, 3H), 3.95 (s, 3H), 4.14-4.28 (q, 2H, *J*=7 Hz), 4.80-4.92 (q, 1H, *J*=7 Hz), 6.45 (d, 1H, *J*=8Hz), 7.00-7.10 (m, 2H), 8.11 (s, 1H). $^{13}$C NMR ($CDCl_3$) **(KG III/p. 46F-C13)** (Spectrum 28. Appendix I) δ 14.2, 17.0, 18.8, 19.2, 55.3, 61.3, 73.1, 101.2, 103.6, 120.7, 123.9, 125.6, 125.7, 127.2, 13.7, 151.8, 157.3, 172.6. MS (70 eV) **(KG III/p. 46F-MS)** (Spectrum 29. Appendix I) m/z: 302 [$M^+$] ($C_{18}H_{22}O_4$). **(KG-III/p. 46F-IR)** ($CH_2Cl_2$) ($cm^{-1}$): 3000-2800 (b), 1750 (s), 1630 (w), 1460 (s), 1060 (w). The COSY and HETCOR spectra were also obtained (Appendix I. Spectra 30 and 31 respectively). Also, 395 mg of naphthalene were recovered.

**Reformatsky Reaction of *trans*-[(t-Butyldimethylsilyl)oxy]– 7-methoxy- 1,6-dimethyl- 3,4-dihydronaphthalen-1-(2*H*)-one using activated Zn in benzene (KG III/ p. 51)**

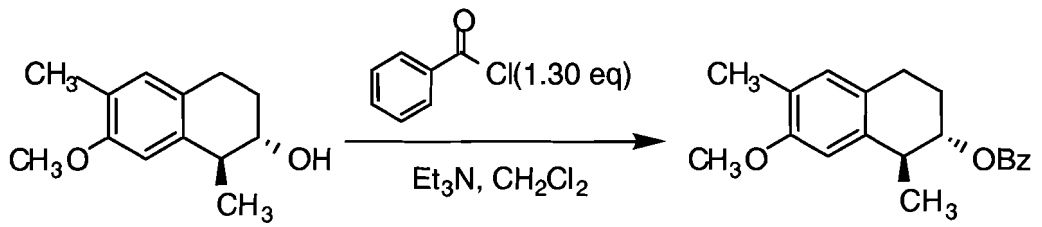



**50** **56**

To a refluxing suspension of activated Zn dust (100 mg, 1.50 mmol, 2.50 equiv.) in benzene (10 ml) was added ethyl 2-bromopropionate (30 µl) and one crystal of iodine and the mixture was refluxed for 10 minutes. Tetralone **50** (200 mg, 0.598 mmol, 1.00 equiv.) and ethyl 2-bromopropionate (170 µl) in benzene (10 ml) was added via syringe over 10 minutes and the reaction mixture was refluxed for 20 hours till the disappearance of starting material (by TLC). Three major components appeared by TLC ($R_f$0.53 (barely visible by UV, stains slightly with PMA), $R_f$ 0.41 (UV active, stains with PMA) and $R_f$0.20 (extremely UV, stains somewhat with PMA) 30% Hex/$CH_2Cl_2$). For tetralone **50**: $R_f$ 0.26 (30% Hex/$CH_2Cl_2$). The mixture was allowed to cool, 2M HCl (20 ml) was added and the mixture was stirred at room temperature for another 20 minutes. It was diluted with ether (10 ml) and the organic layer was washed with 2M HCl (2 x 20 ml), 10% $NaHCO_3$ (2 x 20 ml), 10% $Na_2S_2O_3$ (20 ml), brine (20 ml) and dried ($Na_2SO_4$).

Removal of the solvent under vacuum gave an orange oil (246 mg), whose components were separated by flash chromatography (Silica gel, 30 g, 30% Hex/$CH_2Cl_2$). Compound A: $R_f$ 0.53 (30% Hex/$CH_2Cl_2$). Ethyl 2-bromopropionate, 54.7 mg. $^1H$ NMR **(KG III/p.52A)** ($CDCl_3$) d 1.25 (t, 3H), 1.80 (d, 3H), 4.20 (q, 2H), 4.33 (q, 1H). Compound B: clear colorless oil (79.9 mg). $R_f$ 0.41(30% Hex/$CH_2Cl_2$). $^1H$ NMR ($CDCl_3$) **(KG III/p. 52B)** (Spectrum 32) δ 1.19 (t, 3H, *J*=7.2 Hz), 1.63 (d, 3H, *J*=7.2 Hz), 2.43 (d, 3H, *J*=0.5 Hz), 2.63 (s, 3H), 3.97 (s, 3H), 4.11-4.19 (q, 2H, *J*=7.2 Hz), 4.45 (q, 1H, *J*=7 Hz), 7.10-7.30 (m, 3H), 7.87 (s, 1H). $^{13}C$ NMR ($CDCl_3$) **(KG III/p. 52B-C13)** (Spectrum 33) δ 14.2, 17.3, 18.4, 19.9, 41.4, 55.3, 60.8, 102.0, 121.7, 124.9, 126.2, 126.5, 128.1, 132.0, 133.1, 134.5, 156.5, 175.3. MS (70 eV) **(KG III/p. 52B-MS)** (Spectrum 34) m/z: 286 [$M^+$] ($C_{18}H_{22}O_3$). **(KG-III/p. 52B-IR)** ($CH_2Cl_2$) ($cm^{-1}$): 3000-2800 (b), 1725 (s), 1630 (w), 1460 (w), 1270 (w), 1160 (w). HETCOR (Spectrum 35) and 90-DEPT (Spectrum 36) NMR data can also be found Appendix I. Compound C: 7-methoxy-4,8-dimethylnaphthalen-1-ol. White solid (92.6 mg). $R_f$ 0.20 (30% Hex/$CH_2Cl_2$). $^1H$ NMR ($CDCl_3$) **(KG III/p. 52D)** (Spectrum 37) δ 2.41 (s, 3H), 2.56 (s, 3H), 3.96 (s, 3H), 5.0-5.6 (broad s, 1H), 6.50-6.61 (m, 1H), 6.99-7.13 (m, 2H), 7.96 (s, 1H). $^{13}C$ NMR ($CDCl_3$) **(KG III/p. 52D-C13)** (Spectrum 38) δ 17.0, 19.1, 55.3, 101.4, 106.3, 119.5, 123.3, 125.1, 126.0, 127.3, 133.7, 149.6, 157.2. MS (70 eV) **(KG III/p. 52D-MS)** (Spectrum 39) m/z: 202 [$M^+$] ($C_{13}H_{14}O_2$).

***trans*-7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl benzoate (KG III/p. 57)**

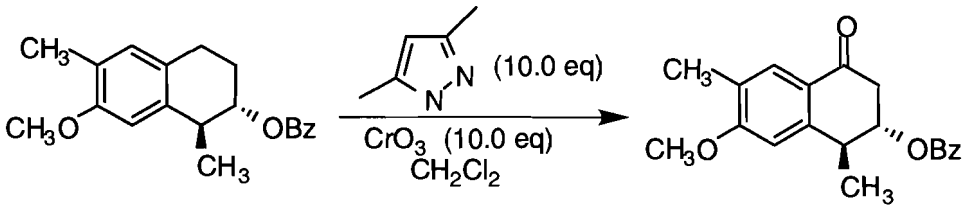



**48** **60**

The following is a modification of a procedure by Greene[21]. Benzoyl chloride (73 µl, 0.631 mmol, 1.30 equiv.) was added to a solution of alcohol **48** (100 mg, 0.485 mmol, 1.00 equiv.) in triethylamine (2 ml)/dichloromethane (2 ml) at room temperature under nitrogen in a flame dried 10 ml round bottomed flask and the resulting solution was stirred at room temperature for 15 hours. Additional benzoyl chloride (75 µl, 0.631 mmol) was added and the mixture was stirred for another two days after which it was diluted with ether (30 ml) and the organic layer was washed with 2 M HCl (3 x 30 ml), 1 M NaOH (3 x 30 ml), brine (30 ml) and dried ($Na_2SO_4$). Removal of the solvent gave 149 mg of an orange residue that was dissolved in dichloromethane and filtered through silica gel (1 g). Evaporation of the solvent under high vacuum gave an orange residue that was filtered through a short column (1 g silica gel, 10% EtOAc/Hex) to give 142 mg of benzoyl ester **60** as a pale yellow oil that crystallized in the freezer (94%). $R_f$ 0.58 (20% EtOAc/Hex) $^1H$ NMR ($CDCl_3$) **(KG III/p. 56)** (Spectrum 23. Appendix I) δ 1.38

(d, 3H, $J$=7.2 Hz), 2.0-2.2 (m, 2H), 2.20 (s, 3H), 2.71-3.01 (m, 2H), 3.09-3.20 (m, 1H), 3.81 (s, 3H), 5.19-5.28 (m, 1H), 6.64 (s, 1H), 6.91 (s, 1H), 7.35-7.62 (m, 3H), 7.95-8.12 (m, 2H). $^{13}C$ NMR ($CDCl_3$) **(KG III/p. 56C-C13)** (Spectrum 24. Appendix I) δ 15.9, 21.3, 24.8, 24.9, 38.0, 55.4, 75.5, 110.0, 124.6, 126.7, 128.4, 129.7, 130.8, 130.9, 132.9, 137.3, 156.2, 166.4.

***trans*-7-methoxy-1,6-dimethyl-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl benzoate (KG III/p. 58)**

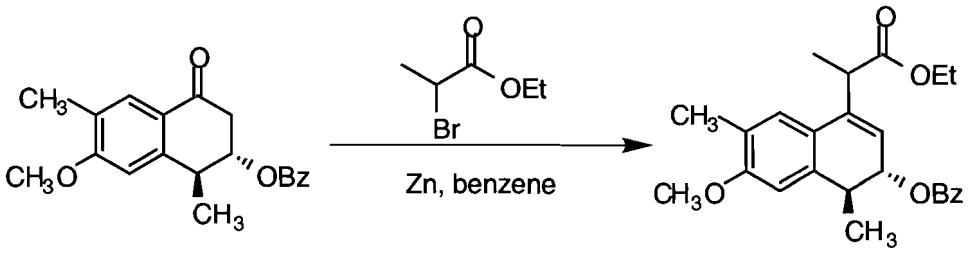



**60** **61**

The following is a modified procedure from Corey at el[25]. 3,5-Dimethylpyrazole (327 mg, 3.40 mmol, 10.0 equiv.) was added to a suspension of chromium trioxide (340 mg, 3.40 mmol, 10.0 equiv.) in dry $CH_2Cl_2$ (5 ml) under nitrogen in a flame dried three-neck 25 ml round-bottomed flask and the mixture was stirred at room temperature under nitrogen for 30 minutes. Benzoate **60** (100 mg, 0.340 mmol) was added to the resulting brown mixture and was stirred at room temperature for 20 hours. The reaction mixture was concentrated, dissolved in ether (10 ml), filtered and dried ($Na_2SO_4$). Removal of the solvent gave a residue, which was purified by flash chromatography (Silica gel, 5 g, 20%

EtOAc/Hex) to give tetralone **61** as a clear colorless oil (42 mg, 42%). TLC: $R_f$ 0.37 (20% EtOAc/Hex). $^1$H NMR ($CDCl_3$) **(KG III/p. 58)** (Spectrum 25. Appendix I) δ 1.45 (d, 3H, *J*=7.1 Hz), 2.20 (s, 3H), 2.80-2.91 (dd, 1H, *J*=4 Hz), 3.02-3.13 (dd, 1H, *J*=3.5 Hz), 3.28-3.41 (m, 1H), 3.87 (s, 3H), 5.47-5.56 (q (app), 1H), 6.62 (s, 1H), 7.27-7.58 (m, 3H), 7.78-7.92 (d, 3H). $^{13}$C NMR ($CDCl_3$) **(KG III/p. 58-C13)** (Spectrum 26. Appendix I) δ 15.9, 20.2, 38.2, 39.4, 55.6, 74.9, 108.8, 126.1, 128.4, 129.4, 129.7, 130.0, 133.2, 145.9, 162.9, 166.0, 193.6.

**Reformatsky Reaction of *trans*-7-methoxy- 1,6-dimethyl- 4-oxo- 1,2,3,4-tetrahydronaphthalen-2-yl benzoate using activated Zn in benzene (KG III/ p. 51)**

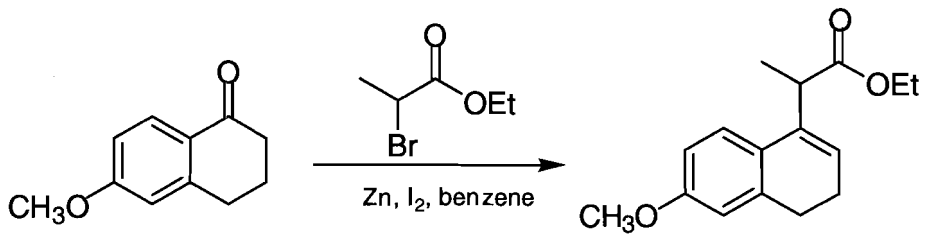



**61** **62**

To a refluxing suspension of activated Zn dust (25 mg, 0.388 mmol, 3.00 equiv.) in benzene (3 ml) in a dry 10 ml round bottomed flask was added ethyl 2-bromopropionate (10 µl) and the mixture was refluxed for 10 minutes. Tetralone **61** (42 mg, 0.129 mmol, 1.00 equiv.) and ethyl 2-bromopropionate (40 µl, mmol) in benzene (2 ml) were added via syringe over 5 minutes and the reaction mixture was refluxed for 20 hours till the

disappearance of starting material (by TLC). One major component appeared by TLC ($R_f$ 0.51 (10% EtOAc/Hex)). The mixture was allowed to cool, it was diluted with ether (20 ml) and the organic layer was washed with 2M HCl (4 x 40 ml), 10% $Na_2CO_3$ (3 x 20 ml), brine (30 ml) and dried ($Na_2SO_4$). Removal of the solvent under vacuum gave an orange oil (38.2 mg, 72%). TLC: $R_f$0.51 (10% EtOAc/Hex). $^1$H NMR ($CDCl_3$) **(KG III/p. 59)** δ 1.19 (t, 3H, *J*=7.2 Hz), 1.63 (d, 3H, *J*=7.2 Hz), 2.43 (d, 3H, *J*=0.5 Hz), 2.63 (s, 3H), 3.97 (s, 3H), 4.11-4.19 (q, 2H, *J*=7.2 Hz), 4.45 (q, 1H, *J*=7 Hz), 7.10-7.30 (m, 3H), 7.87 (s, 1H). $^{13}$C NMR ($CDCl_3$) **(KG III/p. 59-C13)** δ 14.2, 17.3, 18.4, 19.9, 41.4, 55.3, 60.8, 102.0, 121.7, 124.9, 126.2, 126.5, 128.1, 132.0, 133.1, 134.5, 156.5, 175.3. Product is identical with the product KG III/p.52B (Compound B)

**Ethyl 2-(6-methoxy-3,4-dihydronaphthalen-1-yl) propanoate. (52, KG III/p. 26).**

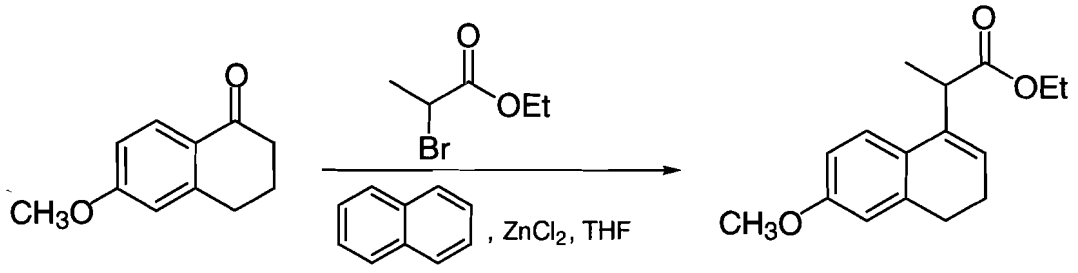



**51** **52**

To a stirred mixture of Zn dust (1.00 g, 15.3 mmol, 1.35 equiv.), 6-methoxytetralone **51** (2.00 g, 11.3 mmol, 1.00 equiv.) and ethyl 2-bromopropionate (1.77 ml, 13.6 mmol, 1.20 equiv.) in ether (40 ml) was added iodine (1.73 g, 13.6 mmol, 1.20 equiv.) over 30

minutes. Two scoops of activated 3Å molecular sieves (dust) were added and the reaction mixture was refluxed for 16 hours. The mixture was poured over 1:1 ice-6*M* HCl (100 ml). The organic layer was separated, the aqueous layer was washed with ether (2 x 100 ml), the combined organic layers were then washed with 10% $Na_2CO_3$ (2 x 100 ml), 10% $Na_2S_2O_3$ (100 ml), brine (100 ml) and dried ($Na_2SO_4$). Removal of the solvent under vacuum gave an oil, which was further purified by column chromatography (Silica gel, 70 g, 10% EtOAc/Hex) to furnish ester **52** as a clear colorless oil (1.80 g, 61%). Starting material (0.43 g) was also recovered. TLC: $R_f$ 0.21 (5% EtOAc/Hex), 0.32 (10% EtOAc/Hex), 0.49 (20% EtOAc/Hex). $^1$H NMR ($CDCl_3$) **(KG III/p. 27)** (Spectrum 17. Appendix I) δ 1.18 (t, 3H, *J*=7.2 Hz), 1.40 (d, 3H, *J*=6.9 Hz), 2.20-2.30 (m, 2H), 2.63-2.76 (t, 3H), 3.62-3.73 (m, 1H), 3.78 (1, 3H), 4.11 (q, 2H, *J*=7.2 Hz), 5.88 (t, 1H, *J*=4 Hz), 6.62-6.79 (m, 2H), 7.22-7.28 (m, 1H). $^{13}$C NMR ($CDCl_3$) **(KG III/p. 27B)** (Spectrum 18. Appendix I) δ 14.2, 17.0, 23.1, 28.8, 41.7, 55.3, 60.7, 110.9, 114.0, 123.3, 123.7, 127.4, 135.7, 138.7, 158.4, 175.3. IR ($CDCl_3$) ($cm^{-1}$) **(KG III/p. 27C)**: 2980 (s), 2940 (s), 2840 (s), 1730 (s), 1610 (s), 1500 (s), 1300 (s), 1250 (s), 1190 (s), 1040 (s).

**Ethyl 2-(6-methoxy-3,4-dihydronaphthalen-1-yl) propanoate using Rieke Zinc. (52, KG III/p. 45).**

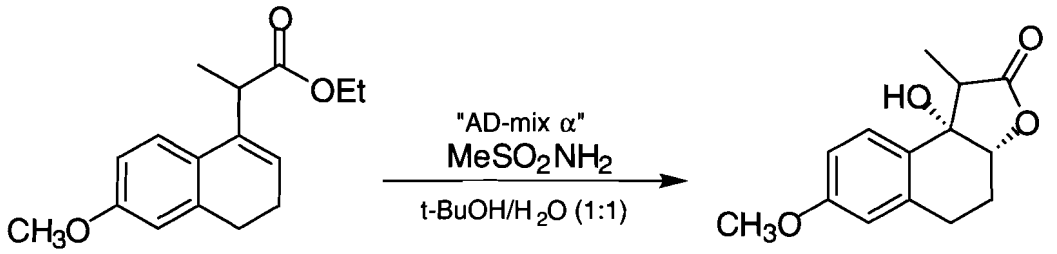



**51** **52**

A mixture of naphthalene (1.82 g, 14.2 mmol, 5.00 equiv.) and Na metal (freshly cut and briefly washed in methanol) (313 mg, 13.6 mmol, 4.80 equiv.) in anhydrous THF (20 ml) in a 50 ml round-bottomed flask was stirred at room temperature for 3 hours. The resulting dark green sodium naphthalide solution was added dropwise via syringe to a suspension of dry $ZnCl_2$ (1.16 g, 8.52 mmol, 3.00 equiv.) in THF (20 ml). The green color of the solution disappeared immediately and activated Zn precipitated as a fine black powder. Ethyl 2-bromopropionate (0.74 ml, 5.67 mmol, 2.00 equiv.) was added and stirred at room temperature for 30 minutes, followed by 6-methoxytetralone **51** (500 mg, 2.84 mmol, 1.00 equiv.). The dark brown reaction mixture was stirred at room temperature for 20 hours and was poured over 2 M HCl (40 ml) and stirred for 30 minutes. The organic layer was separated, the aqueous layer was washed with ether (3 x 50 ml), the combined organic layers were then washed with 10% $Na_2CO_3$ (2 x 50 ml), brine (50 ml) and dried ($Na_2SO_4$). Removal of the solvent under vacuum gave a mixture

of naphthalene and the desired product **52** (2.63 g, quantitative yield by NMR). The spectral data are identical with the spectra from the previous procedure.

**(3a*R*, 9b*R*)-Hydroxy-7-methoxy-1-methyl-3a, 4, 5, 9b-tetrahydronaphtho[2,1-*b*]furan-2-(1*H*)-one (54, KG III/p. 30).**

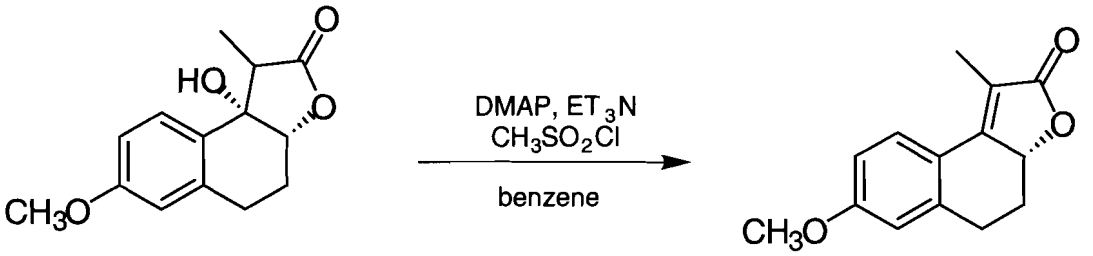



**52** **54**

To a solution of AD mix α (2.8 g) and methane sulfonamide (285 mg, 3.00 mmol, 3.00 equiv.) in *tert*-butanol/water (1:1, 10 ml) at 0 °C was added ester **52** (260 mg, 1.00 mmol, 1.00 equiv.) and the reaction mixture was stirred at room temperature under nitrogen for two days. The reaction mixture was extracted with $CH_2Cl_2$ (3 x 20 ml) and the combined organic layers were washed with 1 M KOH (2 x 20 ml), brine (20 ml) and dried ($Na_2SO_4$). Removal of the solvent gave 125 mg (54 %) of a white solid as the β-hydroxy lactone **54**. TLC: $R_f$ 0.06 (20% EtOAc/Hex). $^1$H NMR ($CDCl_3$) **(KG III/p. 28C)** (Spectrum 19. Appendix I) δ 1.68 (d, 3H), 2.20-2.48 (m, 2H), 2.88 (q, 1H), 2.99 (t, 1H), 3.15 (dd, 1H), 3.77 (s, 3H), 4.24 (dd, 1H), 6.62-6.78 (m, 2H), 7.18-7.30 (m, 1H). $^{13}$C NMR ($CDCl_3$) **(KG III/p. 28D)** (Spectrum 20. Appendix I) δ 9.5, 19.1, 26.7, 45.2, 55.4,

75.5, 81.8, 112.2, 114.9, 125.8, 129.6, 137.9, 160.1, 178.4. IR ($CDCl_3$) ($cm^{-1}$) **(KG III/p. 28E)**: 3610 (w), 2940 (w), 2840 (w), 1810 (s), 1740 (s), 1650 (w), 1610 (s), 1500 (s), 1460 (w), 1300 (s), 1280 (s), 1250 (w), 1100 (s).

**(3a*R*,)-7-Methoxy-1-methyl-3a, 4, 5, 9b-tetrahydronaphtho[2,1-*b*]furan-2-(1*H*)-one. (55, KG III/p. 30).**




**54** **55**

A solution of β-hydroxy lactone, triethylamine (60 µl, 0.42 mmol, 2.1 equiv.), methane sulfonyl chloride (31 µl, 0.40 mmol, 2.0 equiv.) and *N,N*-dimethylaminopyridine (DMAP) (3 mg) in benzene (5 ml) was stirred at room temperature under nitrogen for 2 hours. Additional methanesulfonyl chloride (150 µl) was added and the reaction mixture was refluxed for 15 hours. The reaction mixture was extracted with $CH_2Cl_2$ (2 x 20 ml) and the combined organic layers were washed with 10% $NaHCO_3$ (20 ml), brine (20 ml) and dried ($Na_2SO_4$). Removal of the solvent gave a dark brown residue, which was further purified by flash chromatography (Silica gel, 4 g, 20% EtOAc/Hex) to give the α, β-unsaturated lactone as pale pink crystalline needles (21 mg, 46%). mp 124-126°C.

TLC: $R_f$ 0.18 (20% EtOAc/Hex). $^1$H NMR ($CDCl_3$) **(KG III/p. 33B)** (Spectrum 21. Appendix I) δ 1.67-1.72 (m, 1H), 2.10 (d, 3H, *J*=1.7 Hz), 2.52-2.63 (m, 1H), 2.99-3.09 (m, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 4.84-4.96 (m, 1H), 6.80-6.93 (m, 2H), 7.58 (d, 1H). $^{13}$C NMR ($CDCl_3$) **(KG III/p. 33C)** (Spectrum 22. Appendix I) δ 10.0, 28.2, 29.9, 55.5, 78.7, 113.2, 114.0, 116.8, 121.8, 129.5, 140.0, 156.1, 161.0, 175.4. IR ($CDCl_3$) ($cm^{-1}$) **(KG III/p. 33D)**: 2960 (w), 2840 (w), 1740 (s), 1650 (w), 1610 (s), 1500 (w), 1460 (w), 1310 (s), 1280 (s), 1250 (w), 1090 (w).

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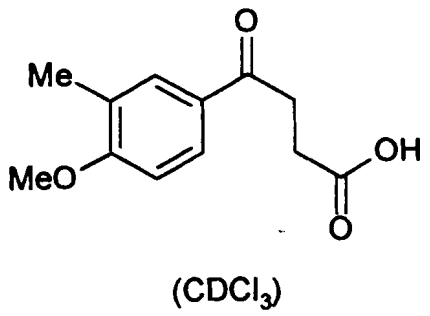
# VII. APPENDIX I. SPECTRAL DATA

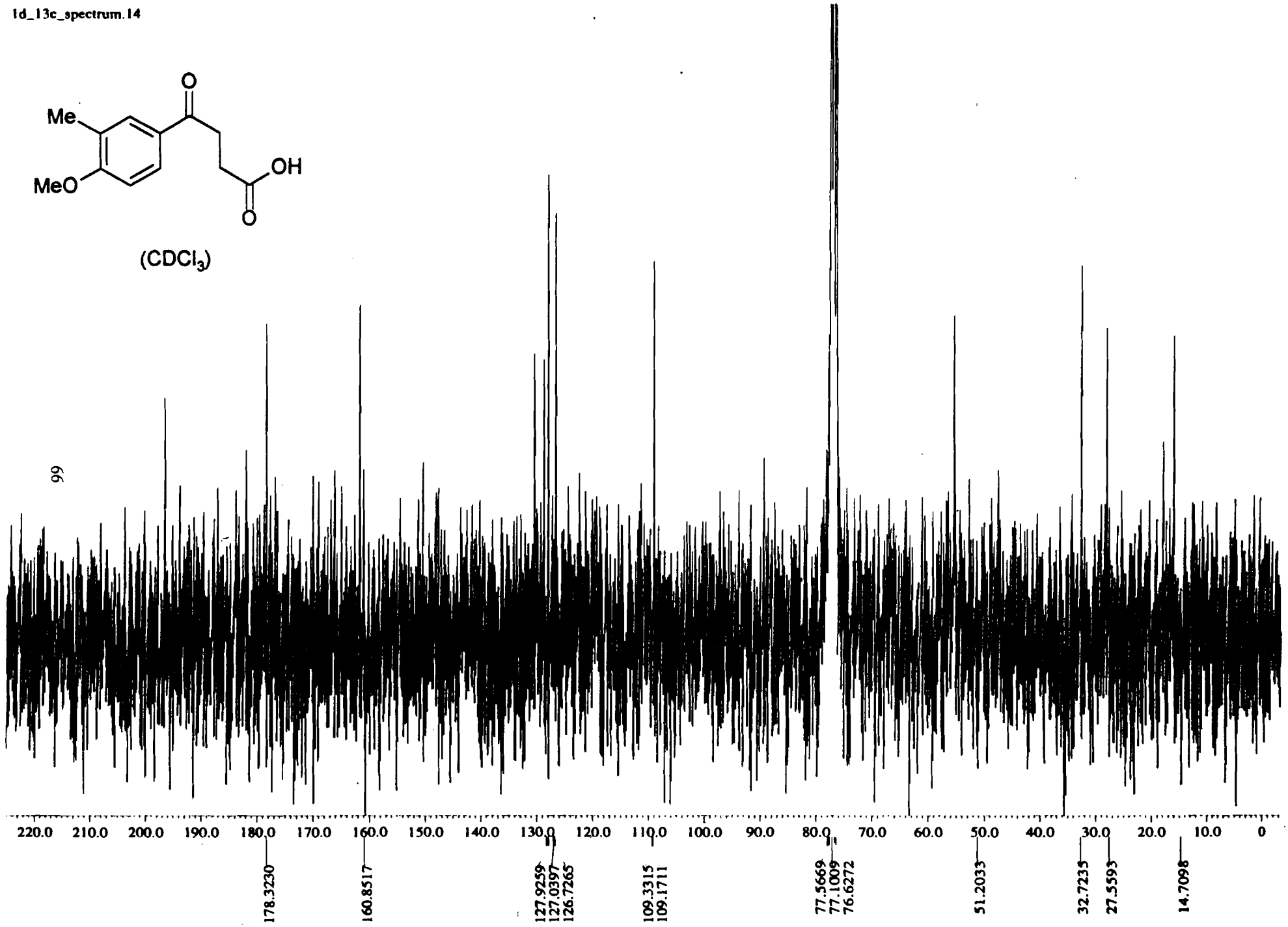
1d_spectrum.19




$(CDCl_3)$

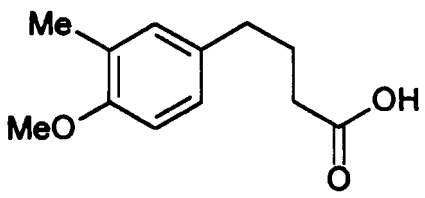



**SPECTRUM 1.** 270 MHz $^1$H NMR spectrum of 4-(4-methoxy-3-methyl phenyl)-4-oxobutanoic acid.




**SPECTRUM 2.** 67.5 MHz $^{13}C$ NMR spectrum of 4-(4-methoxy-3-methyl phenyl)-4-oxobutanoic acid.

KG–II–70.5




$(CDCl_3)$

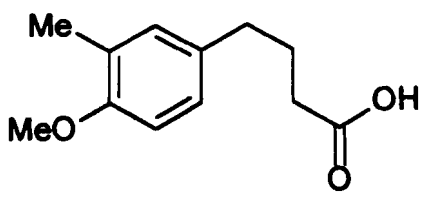
67




X : parts per Million : 1H

**SPECTRUM 3.** 270 MHz $^1$H NMR spectrum of 4-(4-methoxy-3-methylphenyl)butanoic acid.

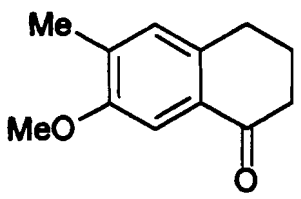
KG–II–70.3




$(CDCl_3)$




**SPECTRUM 4.** 67.5 MHz $^{13}C$ NMR spectrum of 4-(4-methoxy-3-methylphenyl)butanoic acid.

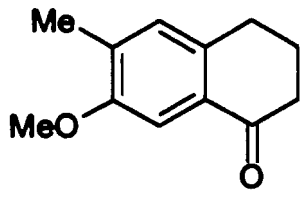



($CDCl_3$)






**SPECTRUM 5**. 270 MHz $^1$H NMR spectrum of 7-methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one.

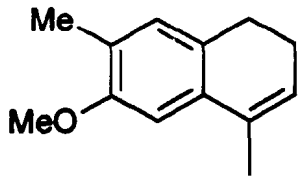



($CDCl_3$)




**SPECTRUM 6.** 67.5 MHz $^{13}C$ NMR spectrum of 7-methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one.

KG–III–42.10

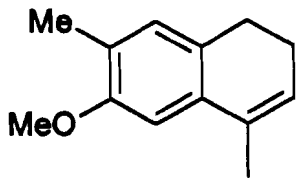



($CDCl_3$)




X : parts per Million : 1H

**SPECTRUM 7.** 270 MHz $^1$H NMR spectrum of 6-methoxy-4,7-dimethyl-1,2-dihydronaphthalene.



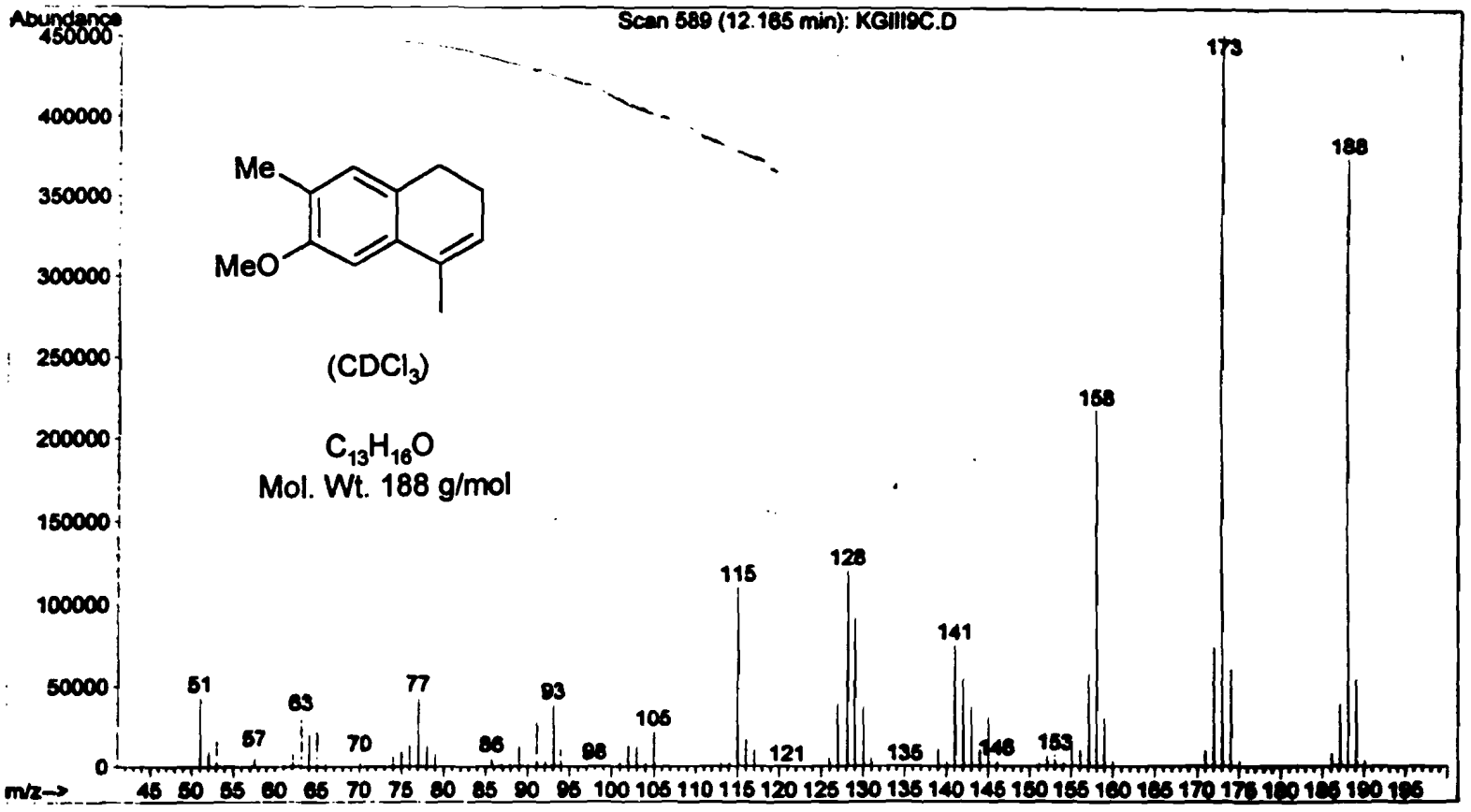

($CDCl_3$)



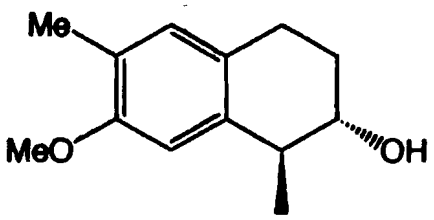



X : parts per Million : 13C

**SPECTRUM 8.** 67.5 MHz $^{13}C$ NMR spectrum of 6-methoxy-4,7-dimethyl-1,2-dihydronaphthalene.




**SPECTRUM 9.** Mass spectrum (MS) of 6-methoxy-4,7-dimethyl-1,2-dihydronaphthalene.

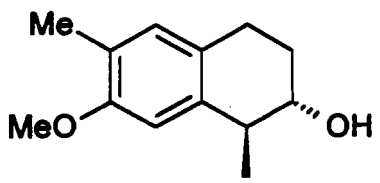



$(CDCl_3)$



X : parts per Million : 1H

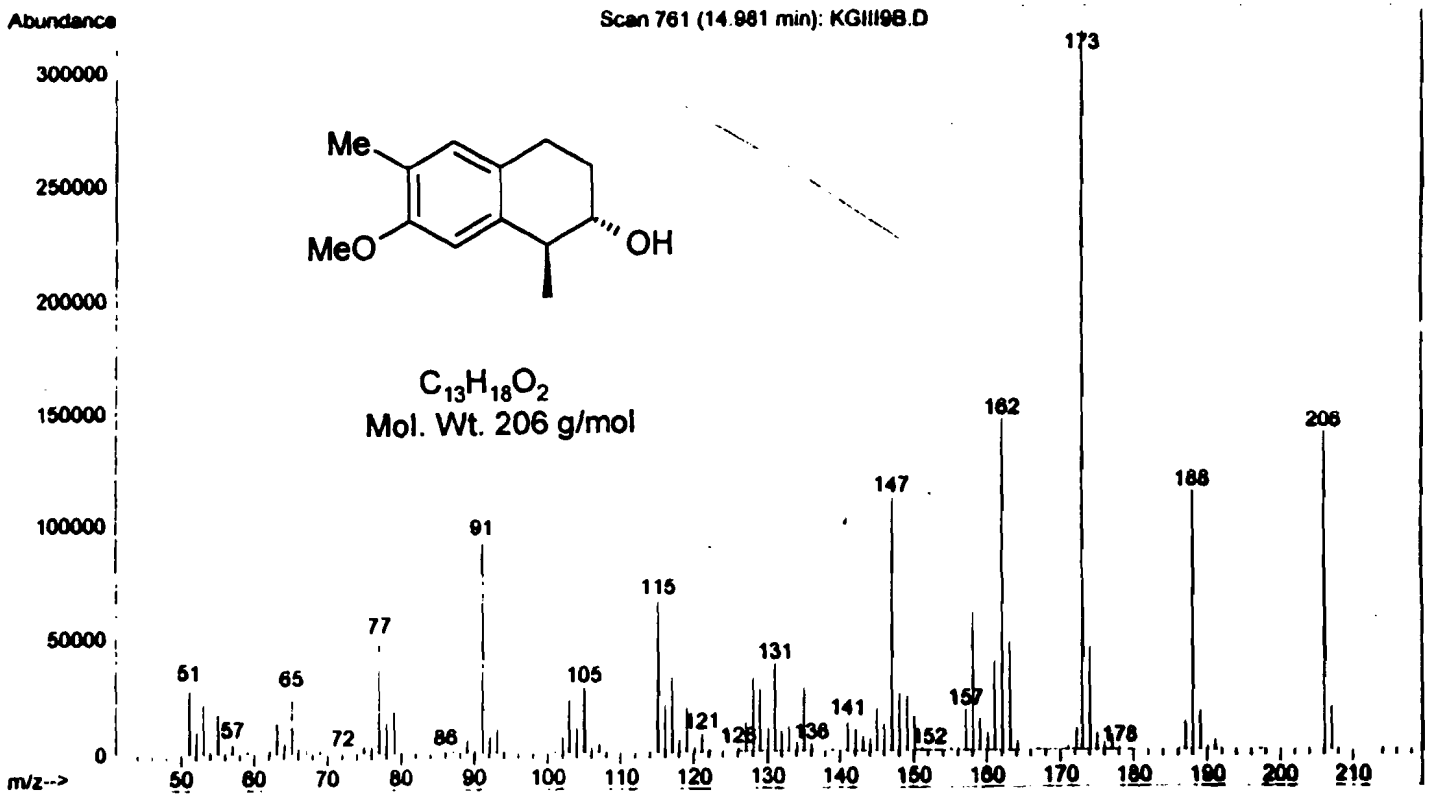
**SPECTRUM 10**. 1H NMR spectrum of 7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol.



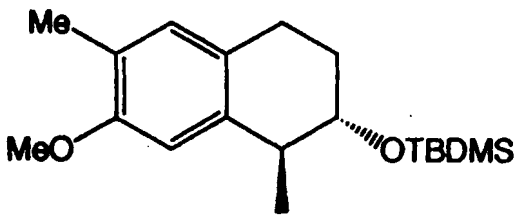

$(CDCl_3)$




**SPECTRUM 11.** $^{13}C$ NMR spectrum of 7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol.




**SPECTRUM 12.** Mass spectrum of 7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol.

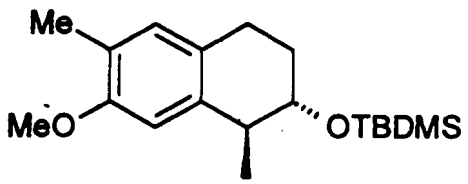



($CDCl_3$)






**SPECTRUM 13.** 270 MHz $^1H$ NMR spectrum of 2-[(t-butyldimethylsilyl)oxy]-7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalene.



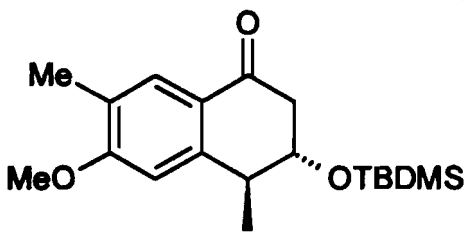

$(CDCl_3)$






X : parts per Million : 13C

**SPECTRUM 14.** 67.5 MHz $^{13}C$ NMR spectrum of 2-[(t-butyldimethylsilyl)oxy]-7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalene.

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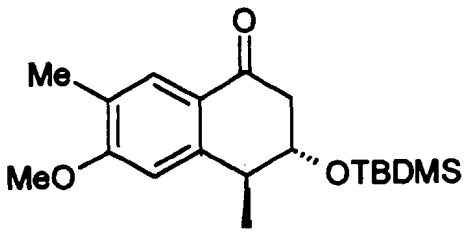
**SPECTRUM 15**. 270 MHz $^1$H NMR spectrum of 2-[(t-butyldimethylsilyl)oxy]-7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-1(2*H*)-one.

KG-III-21B-C13



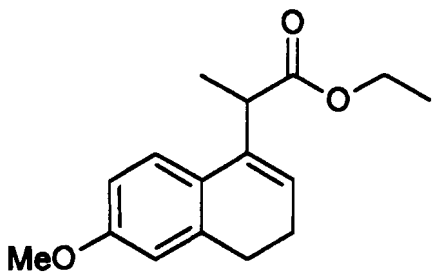

($CDCl_3$)

80




**SPECTRUM 16.** 67.5 MHz $^{13}C$ NMR spectrum of 2-[(t-butyldimethylsilyl)oxy]-7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-1(2*H*)-one.

KG-III-27.6




$(CDCl_3)$



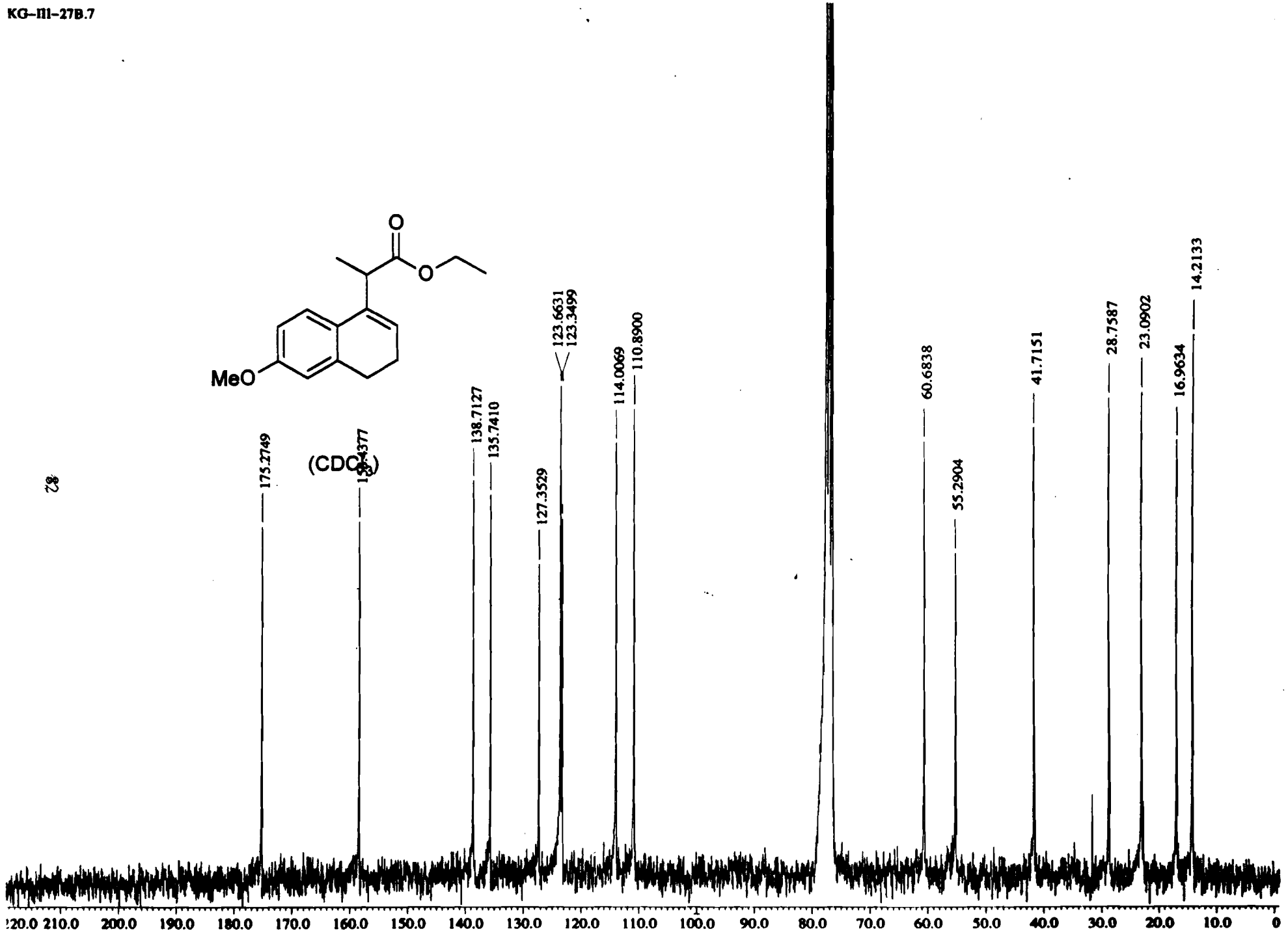
1H 2H 1H 3H 2H 2H 2H 3H 3H

11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0

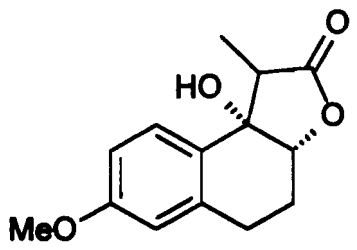
X : parts per Million : 1H

**SPECTRUM 17.** 270 MHz $^1$H NMR spectrum of ethyl 2-(6-methoxy-3,4-dihydronaphthalen-1-yl) propanoate.

KG-III-27B.7




**SPECTRUM 18.** $^{13}C$ NMR spectrum of ethyl 2-(6-methoxy-3,4-dihydronaphthalen-1-yl) propanoate.

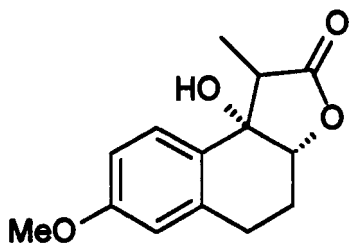



$(CDCl_3)$






**SPECTRUM 19.** $^1$H NMR spectrum of (3a*R*, 9b*R*)-hydroxy-7-methoxy-1-methyl-3a,4,5,9b-tetrahydronaphtho[2,1-*b*]furan-2(1*H*)-one.



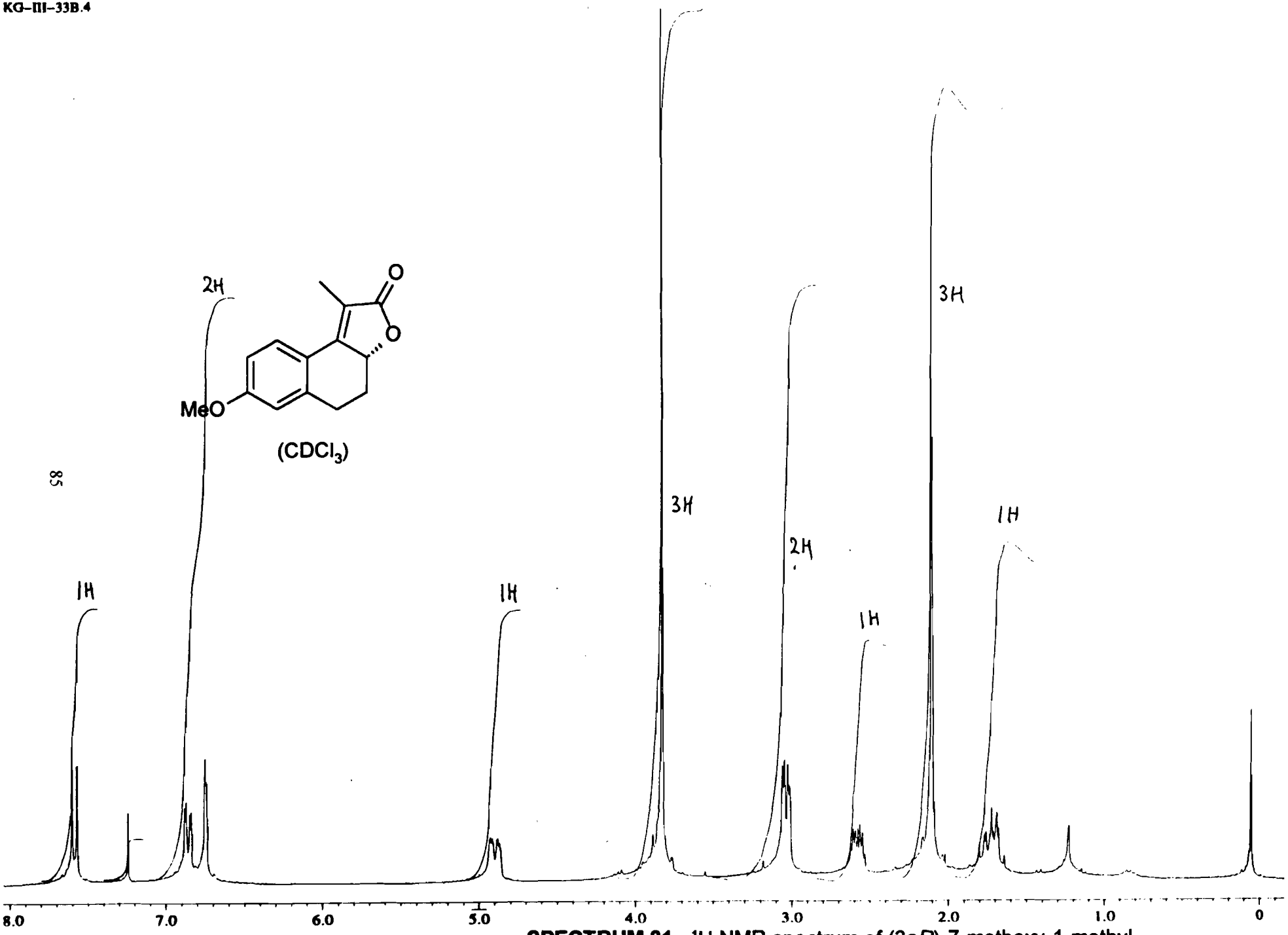

($CDCl_3$)




X : parts per Million : 13C

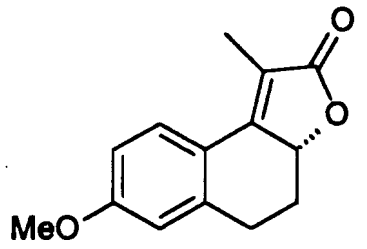
**SPECTRUM 20.** $^{13}C$ NMR spectrum of (3a*R*, 9b*R*)-hydroxy-7-methoxy-1-methyl-3a,4,5,9b-tetrahydronaphtho[2,1-*b*]furan-2(1*H*)-one.

KG-III-33B.4




**SPECTRUM 21**. $^1$H NMR spectrum of (3a*R*)-7-methoxy-1-methyl-4,5-dihydronaphtho[2,1-*b*]furan-2(3a*H*)-one.

KG-III-33C.3



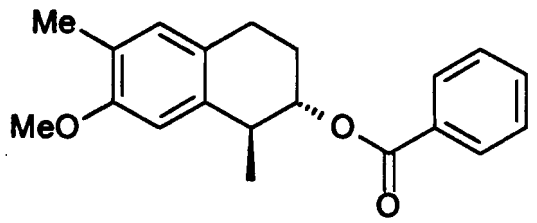

$(CDCl_3)$




X : parts per Million : 13C

**SPECTRUM 22.** $^{13}C$ NMR spectrum of (3a*R*)-7-methoxy-1-methyl-4,5-dihydronaphtho[2,1-*b*]furan-2(3a*H*)-one.

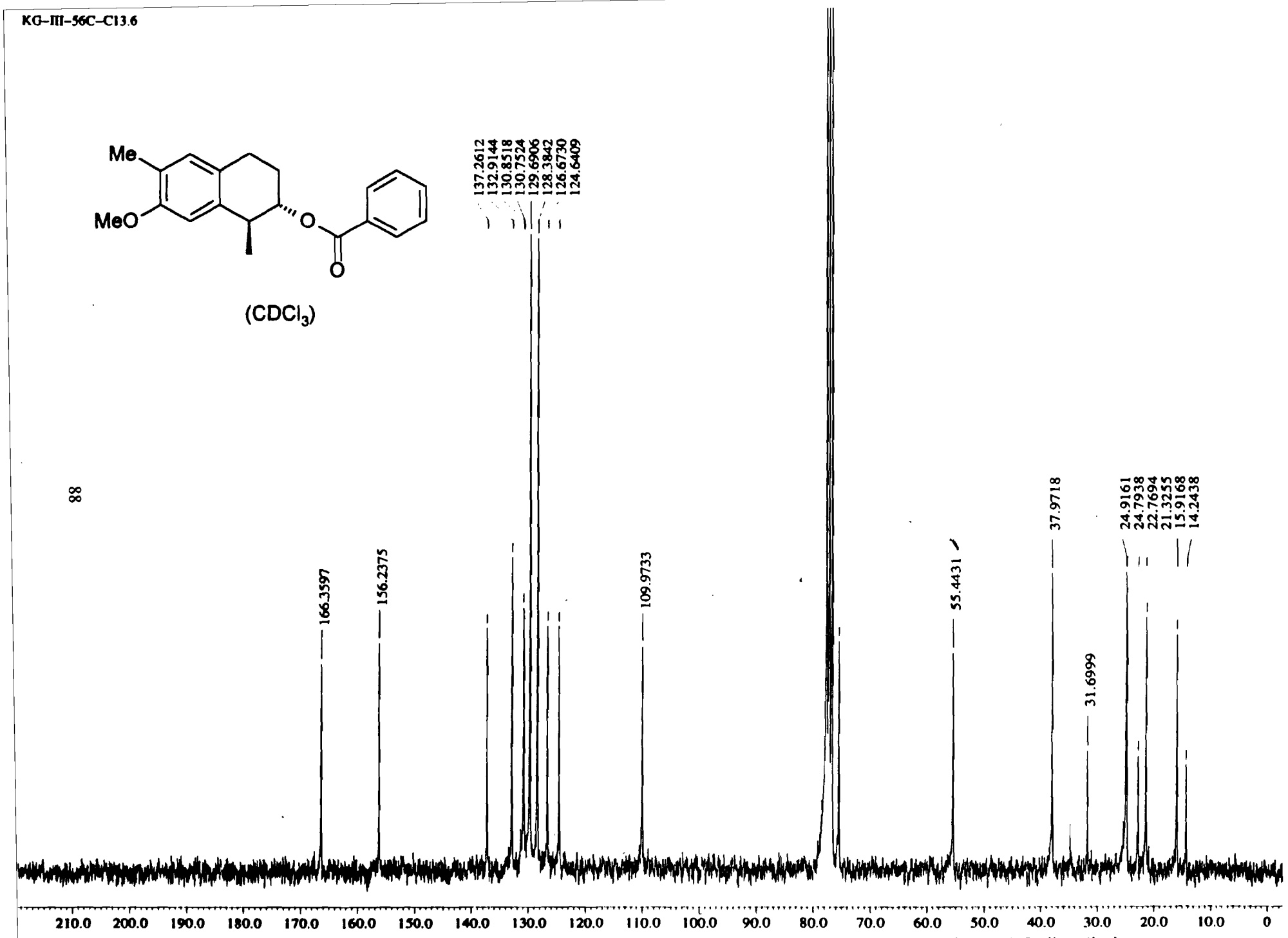
KG-III-56C.13




($CDCl_3$)

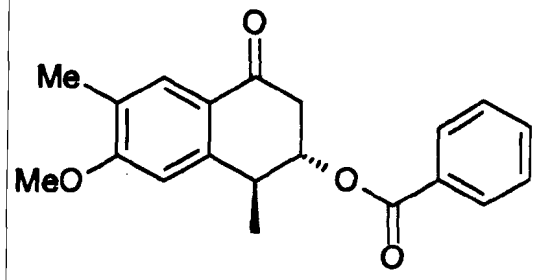



**SPECTRUM 23.** $^1H$ NMR spectrum of 7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl benzoate.




**SPECTRUM 24.** $^{13}C$ NMR spectrum of 7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl benzoate.

KG–III–58.4



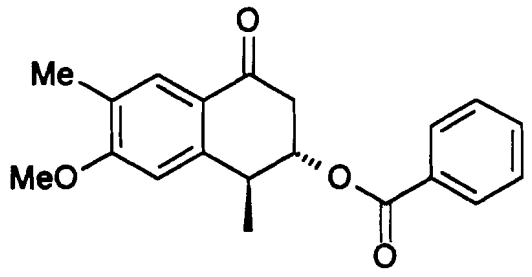

$(CDCl_3)$

68




**SPECTRUM 25.** $^1H$ NMR spectrum of 7-methoxy-1,6-dimethyl-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl benzoate.

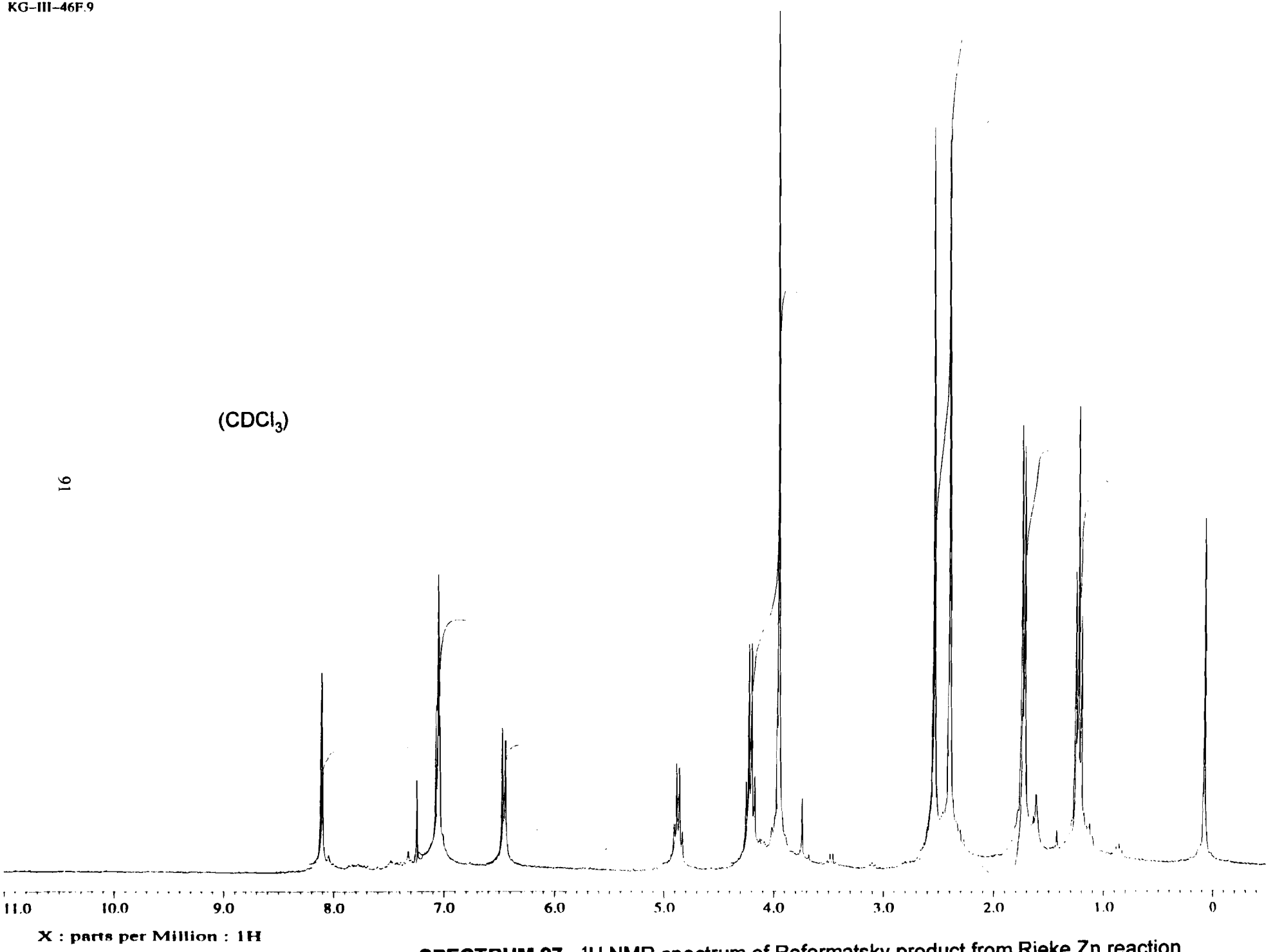
KG-III-58-C13.2



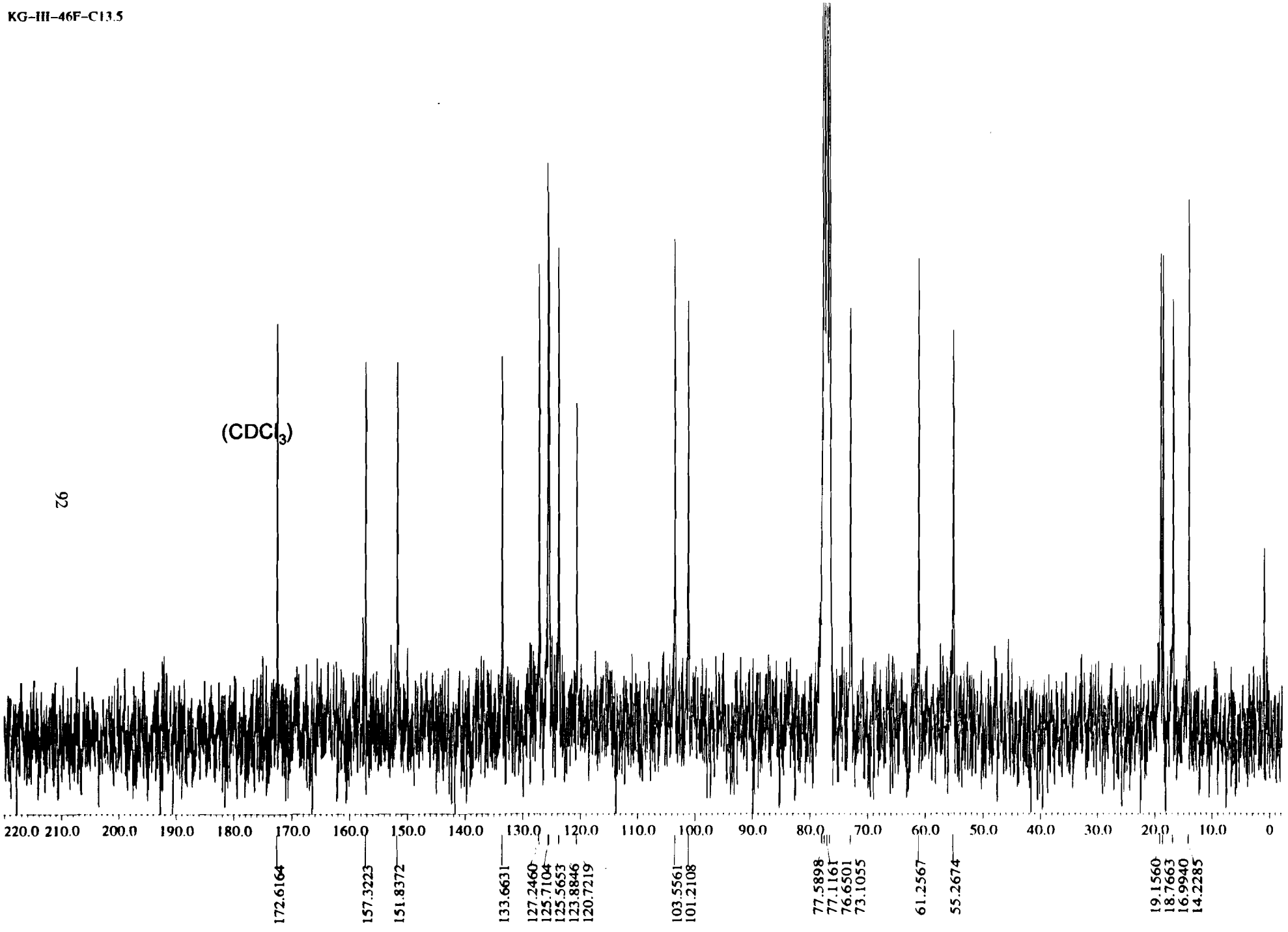

$(CDCl_3)$



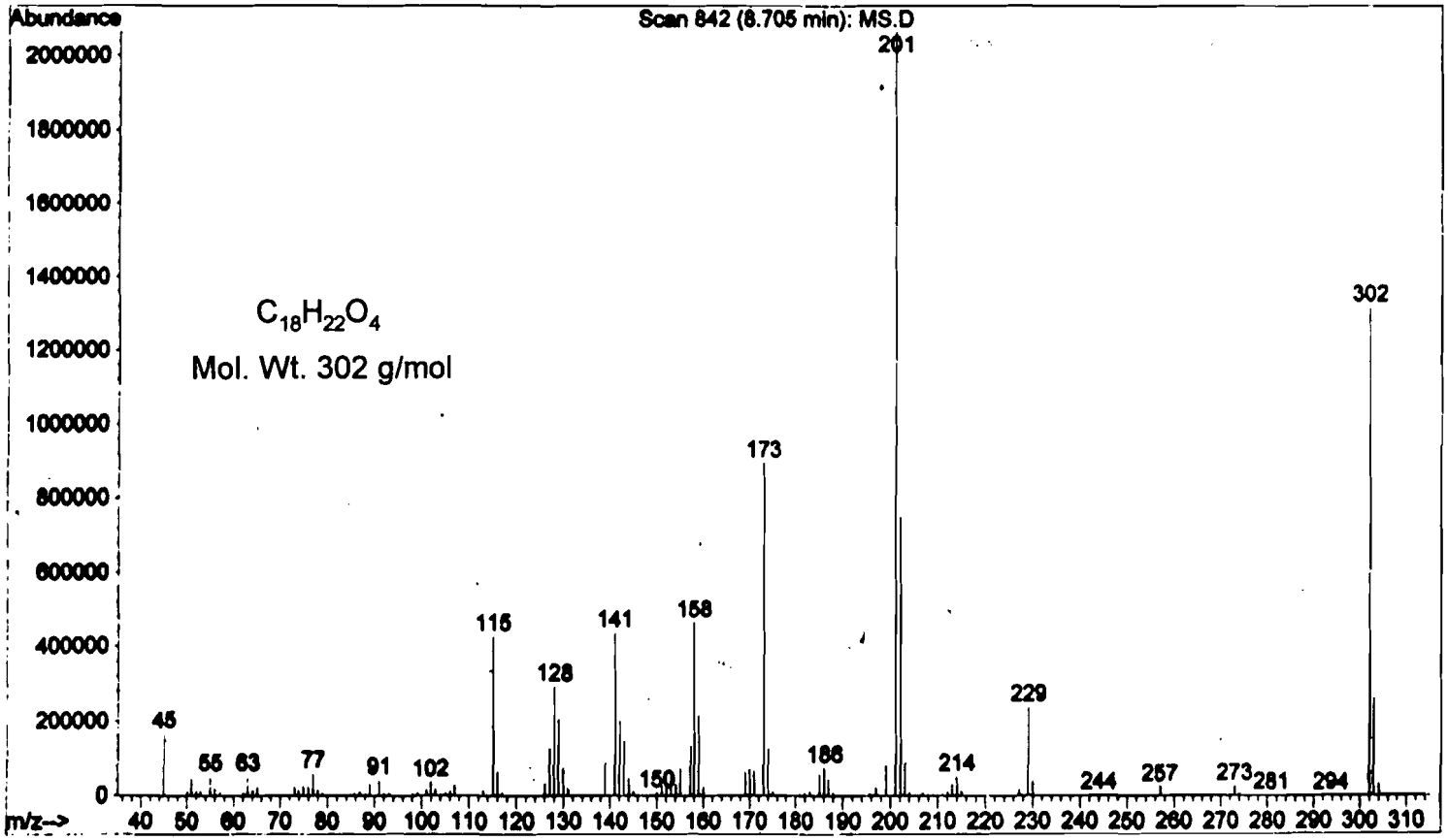

**SPECTRUM 26.** $^{13}C$ NMR spectrum of 7-methoxy-1,6-dimethyl-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl benzoate.



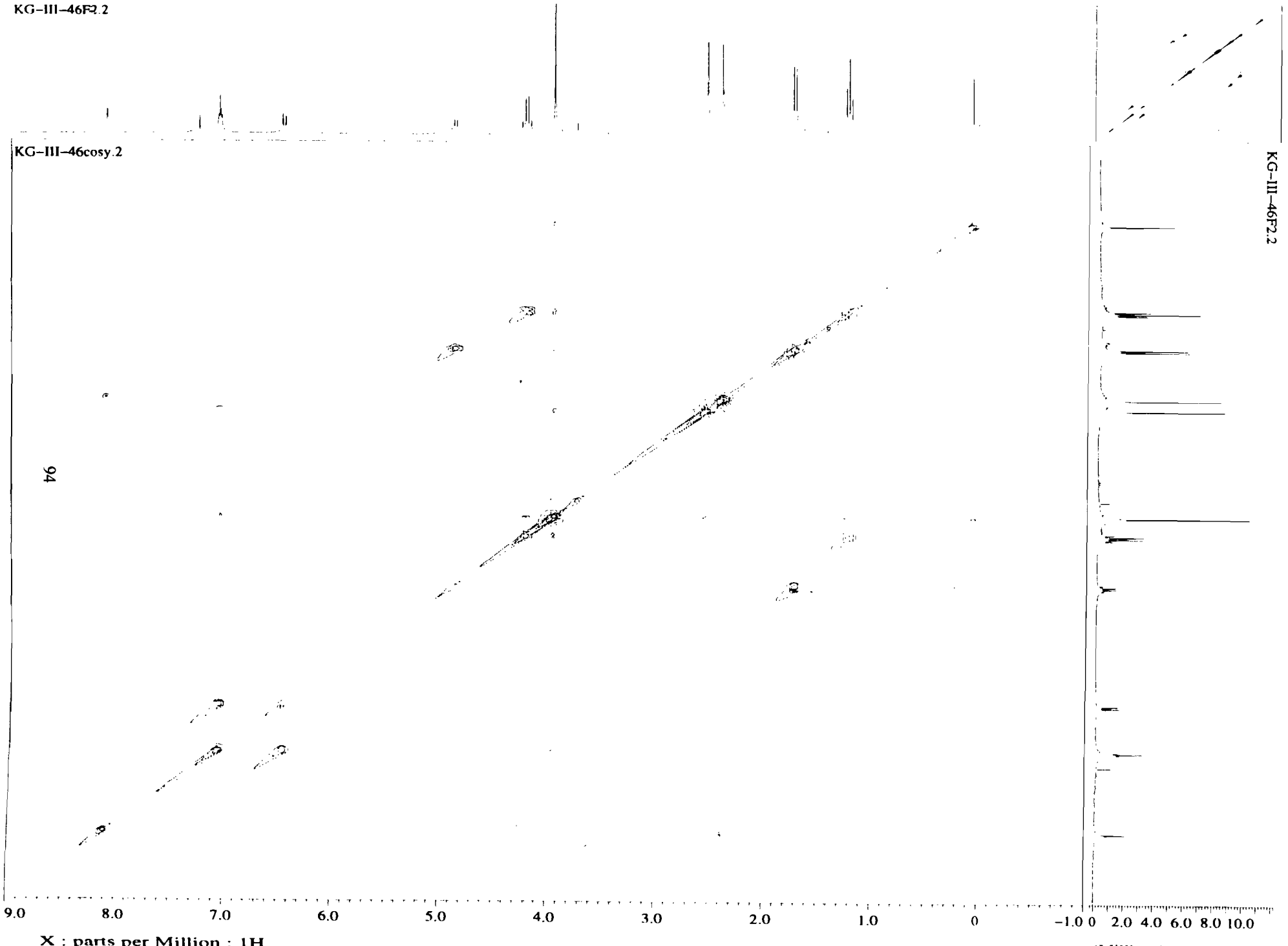

**SPECTRUM 27**. $^{1}H$ NMR spectrum of Reformatsky product from Rieke Zn reaction.



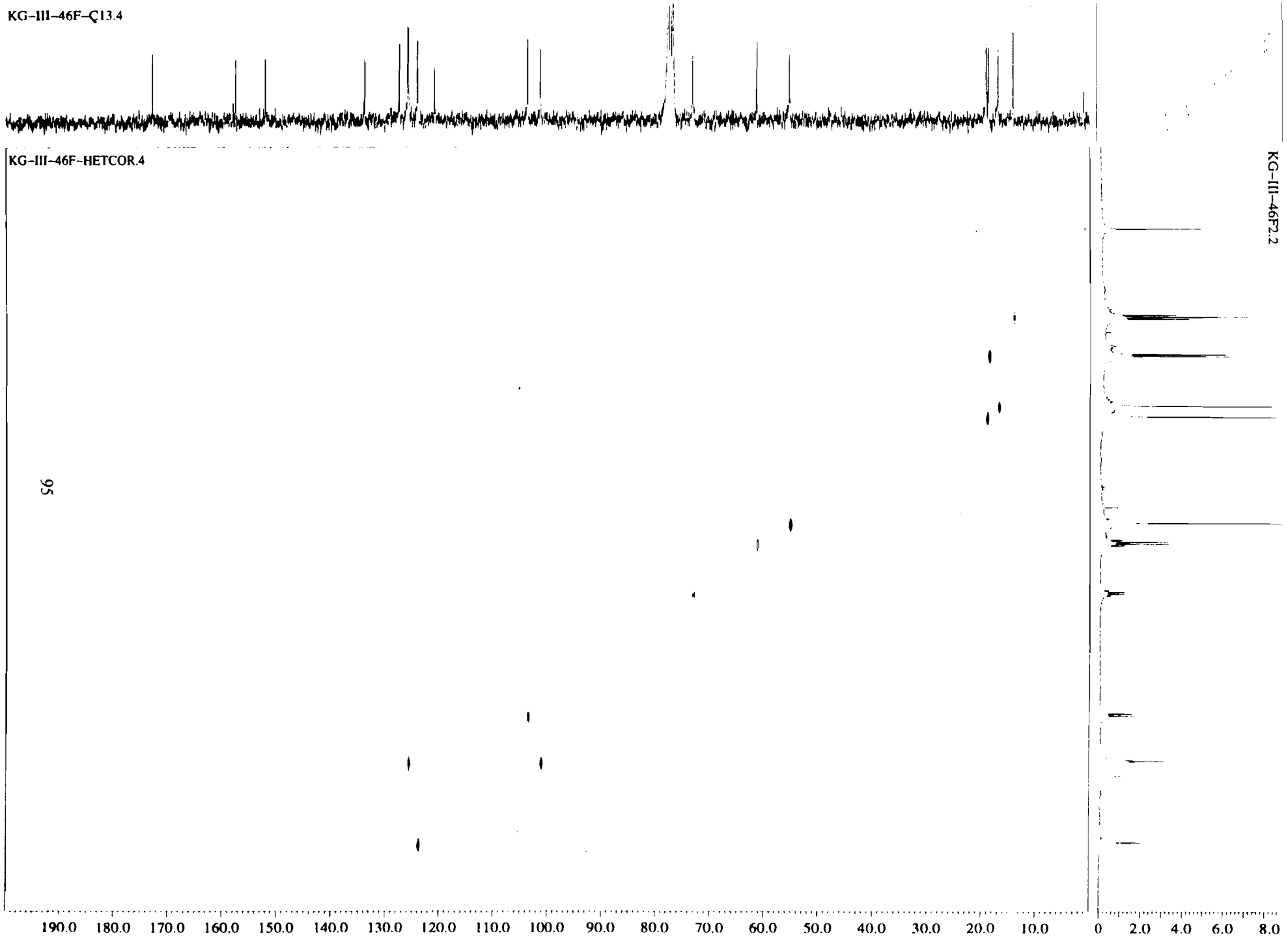

**SPECTRUM 28.** $^{13}C$ NMR spectrum of Reformatsky product from Rieke Zn reaction.



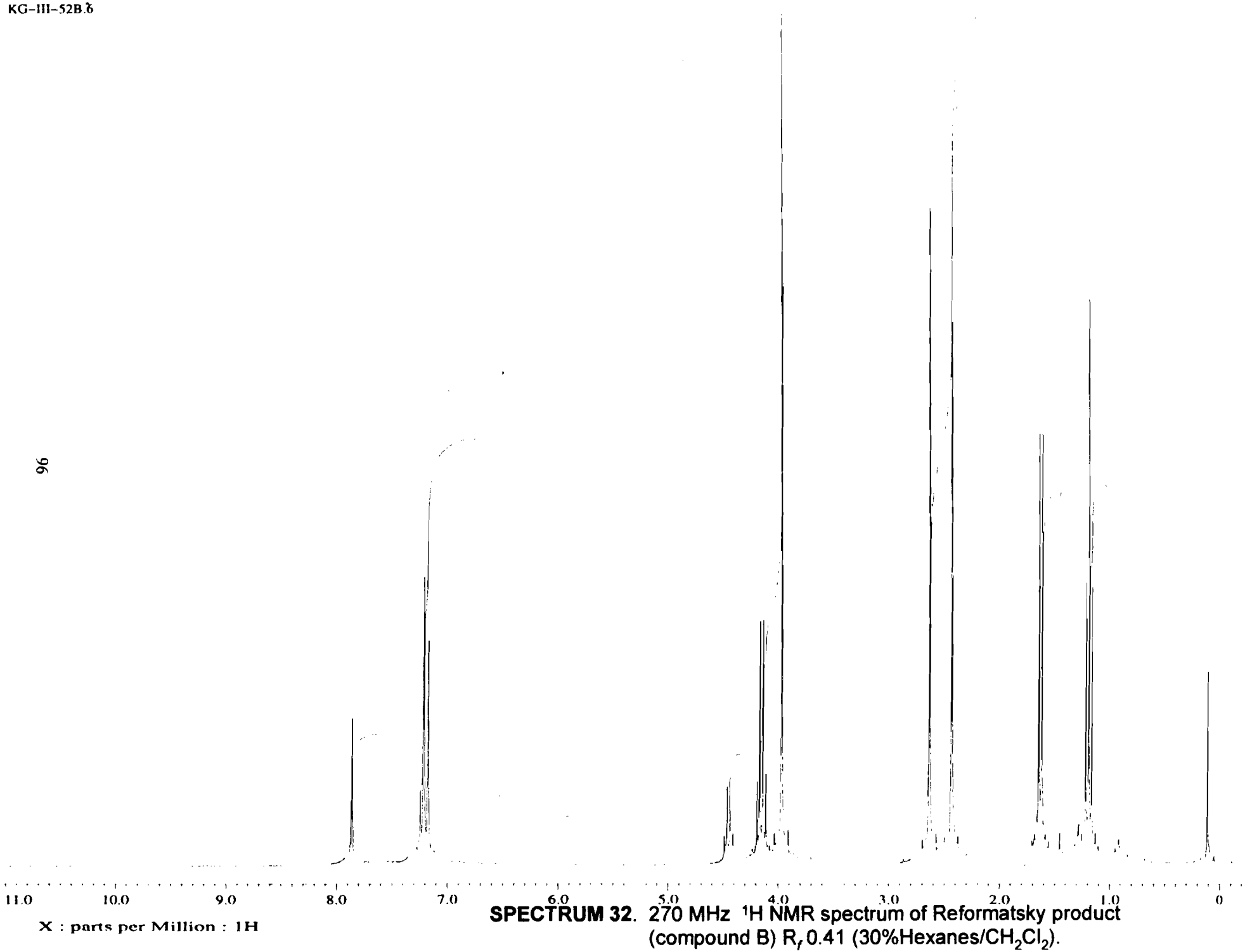

**SPECTRUM 29**. Mass spectrum of Reformatsky product from Rieke Zn reaction.



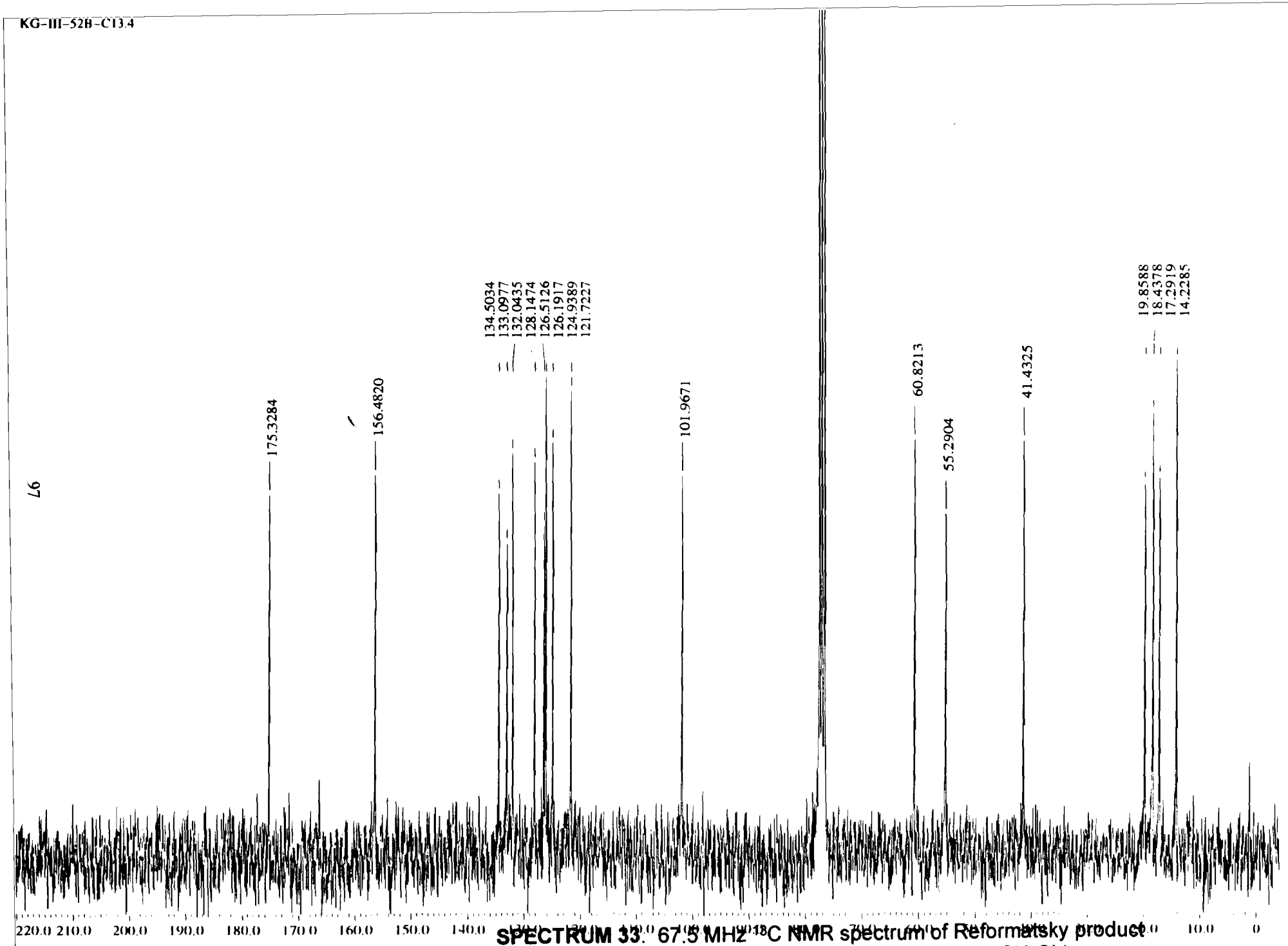

**SPECTRUM 30.** COSY spectrum of Reformatsky product from Rieke Zn reaction.



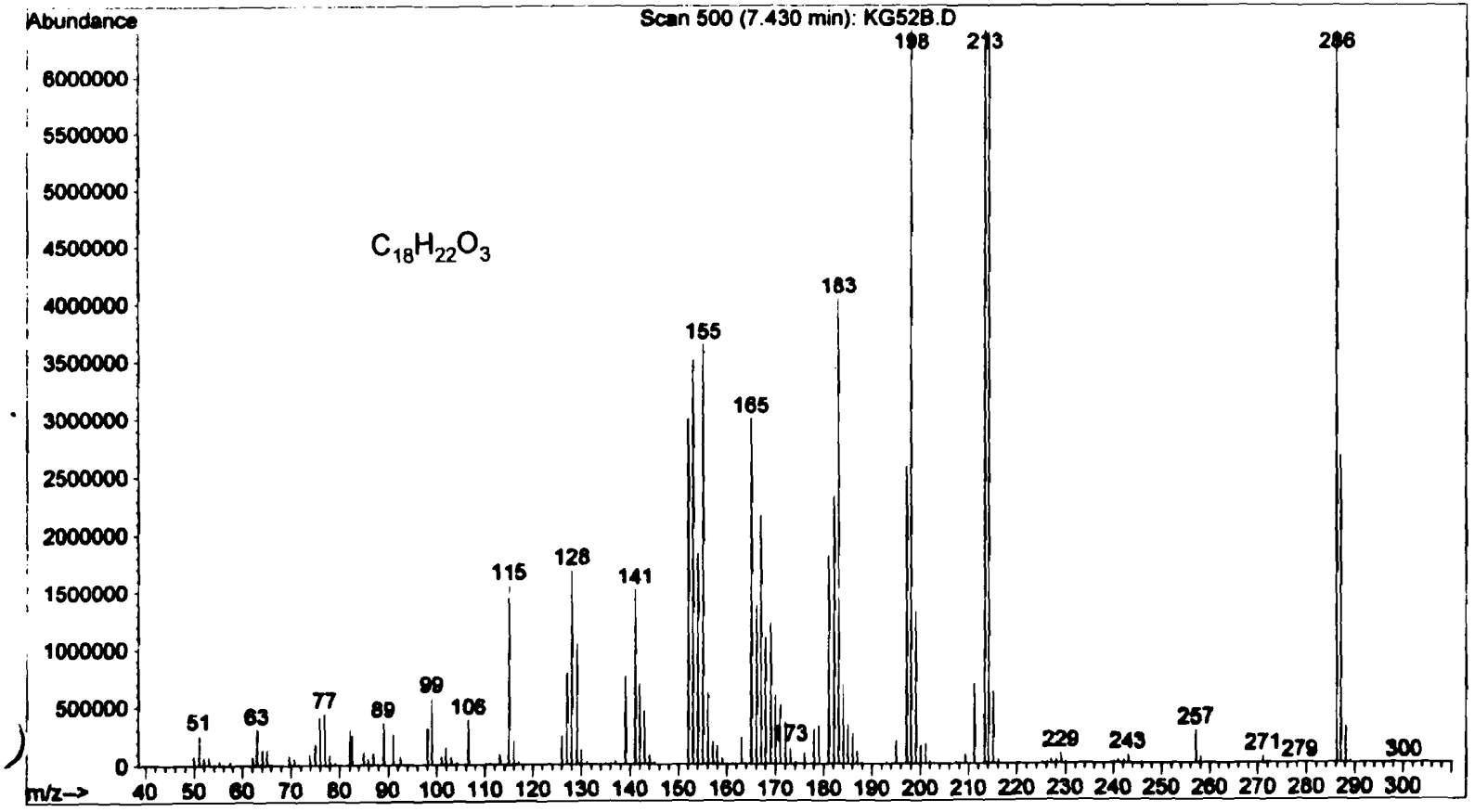

**SPECTRUM 31**. HETCOR spectrum of Reformatsky product from Rieke Zn reaction.



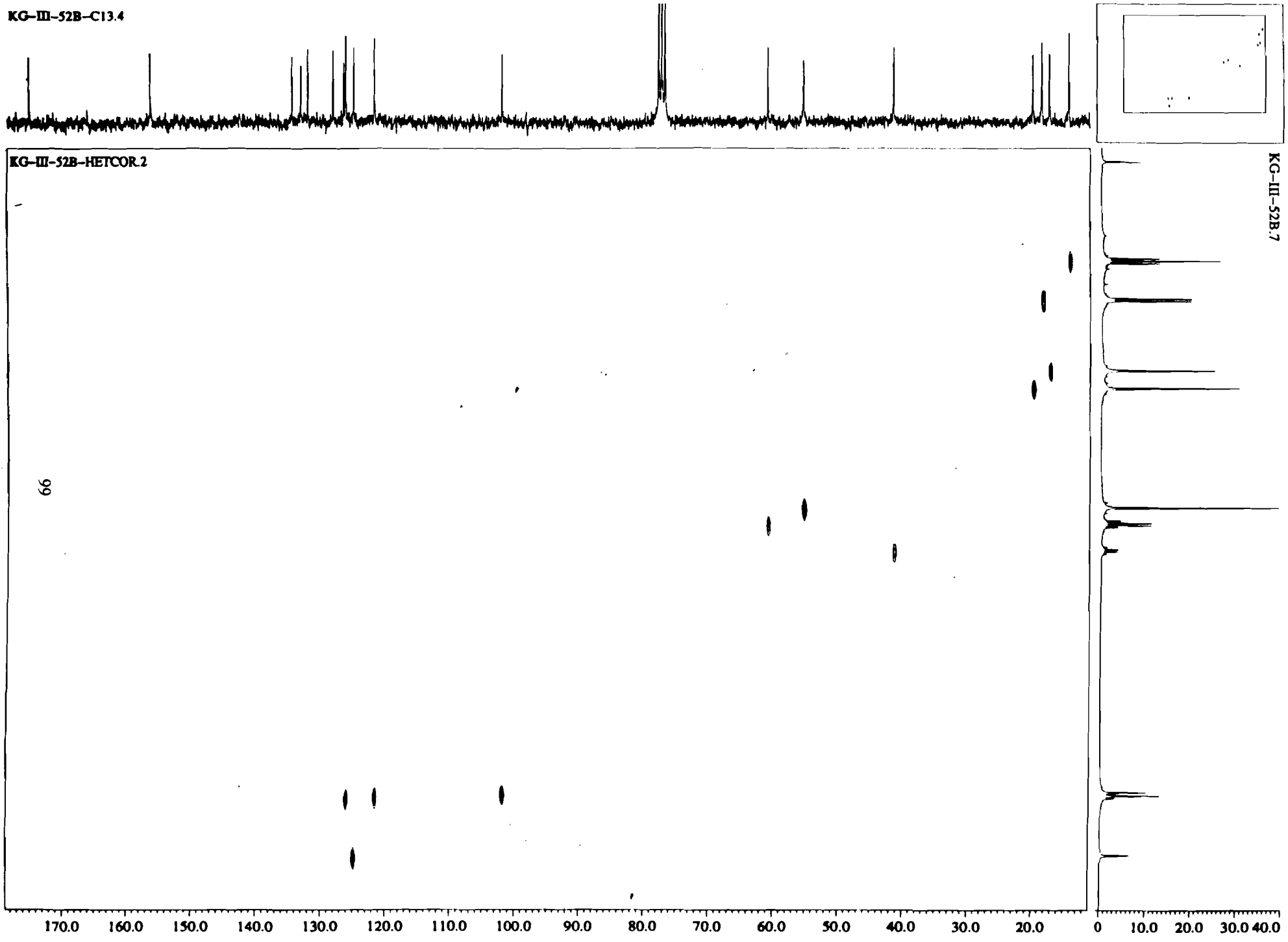

**SPECTRUM 32.** 270 MHz $^1$H NMR spectrum of Reformatsky product (compound B) $R_f$ 0.41 (30%Hexanes/$CH_2Cl_2$).




**SPECTRUM 33.** 67.5 MHz $^{13}C$ NMR spectrum of Reformatsky product (compound B) $R_f$ 0.41 (30%Hexanes/$CH_2Cl_2$).

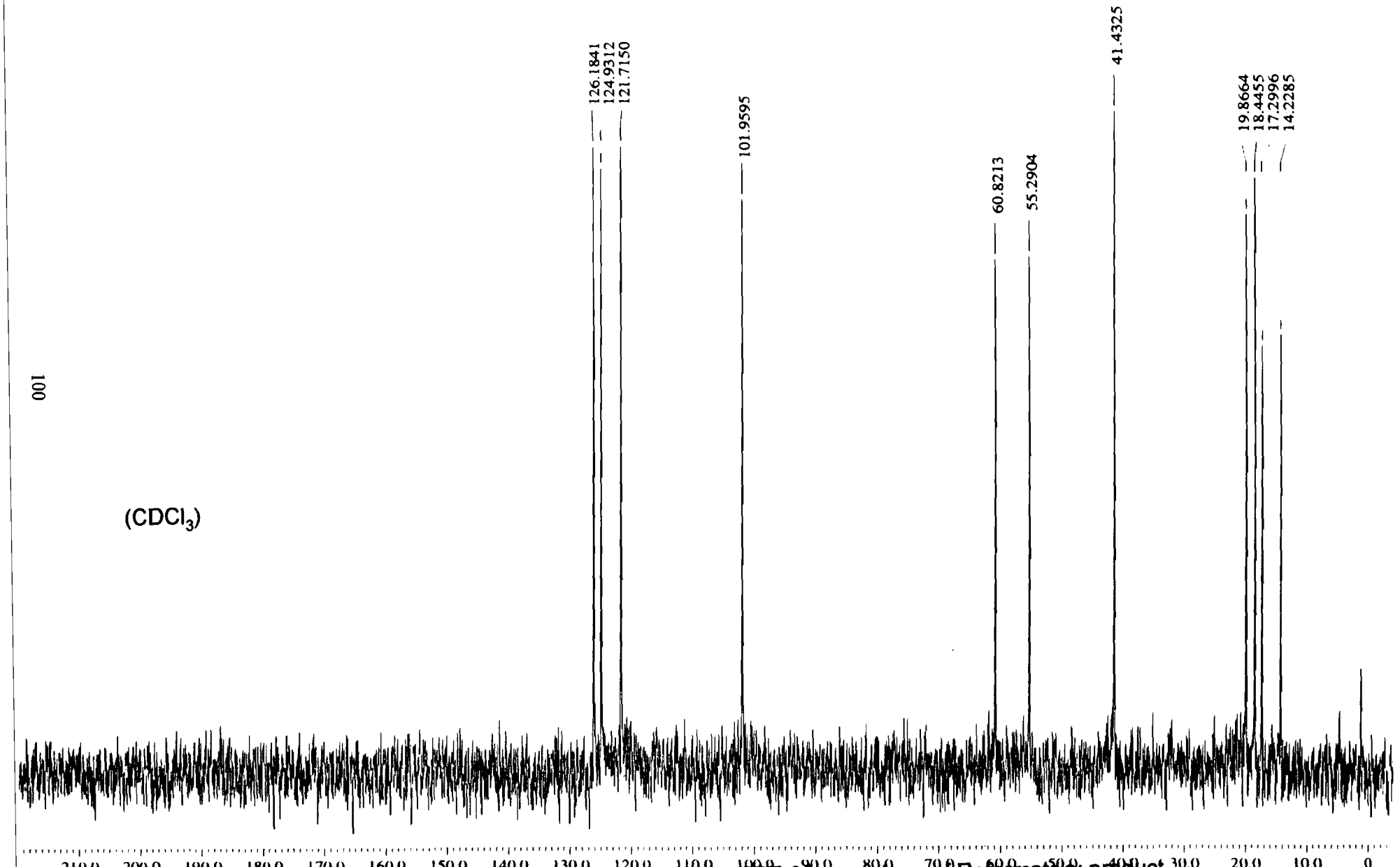



**SPECTRUM 34**. Mass spectrum of Reformatsky product (compound B)
$R_f$ 0.41 (30% Hexanes/$CH2Cl_2$)

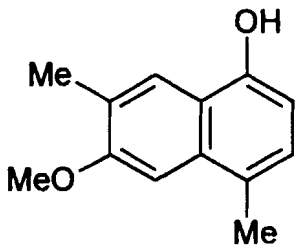



**SPECTRUM 35**. HETCOR spectrum of Reformatsky product (compound B) $R_f$ 0.41 (30%Hexanes/$CH_2Cl_2$).

KG-III-52B-DEPT.7




**SPECTRUM 36**. DEPT-90 spectrum of Reformatsky product (compound B) R, 0.41 (30%Hexanes/$CH_2Cl_2$).

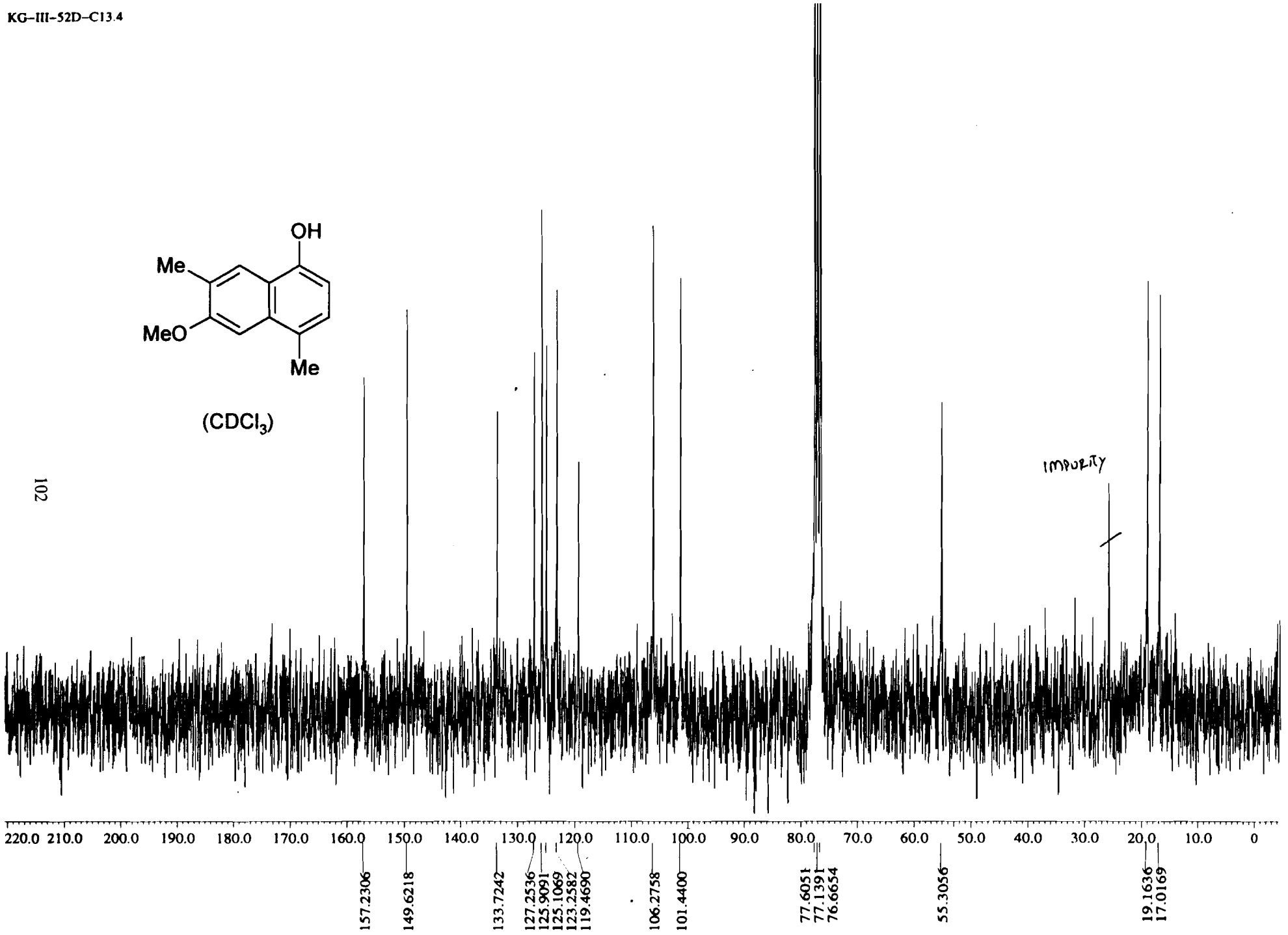



($CDCl_3$)

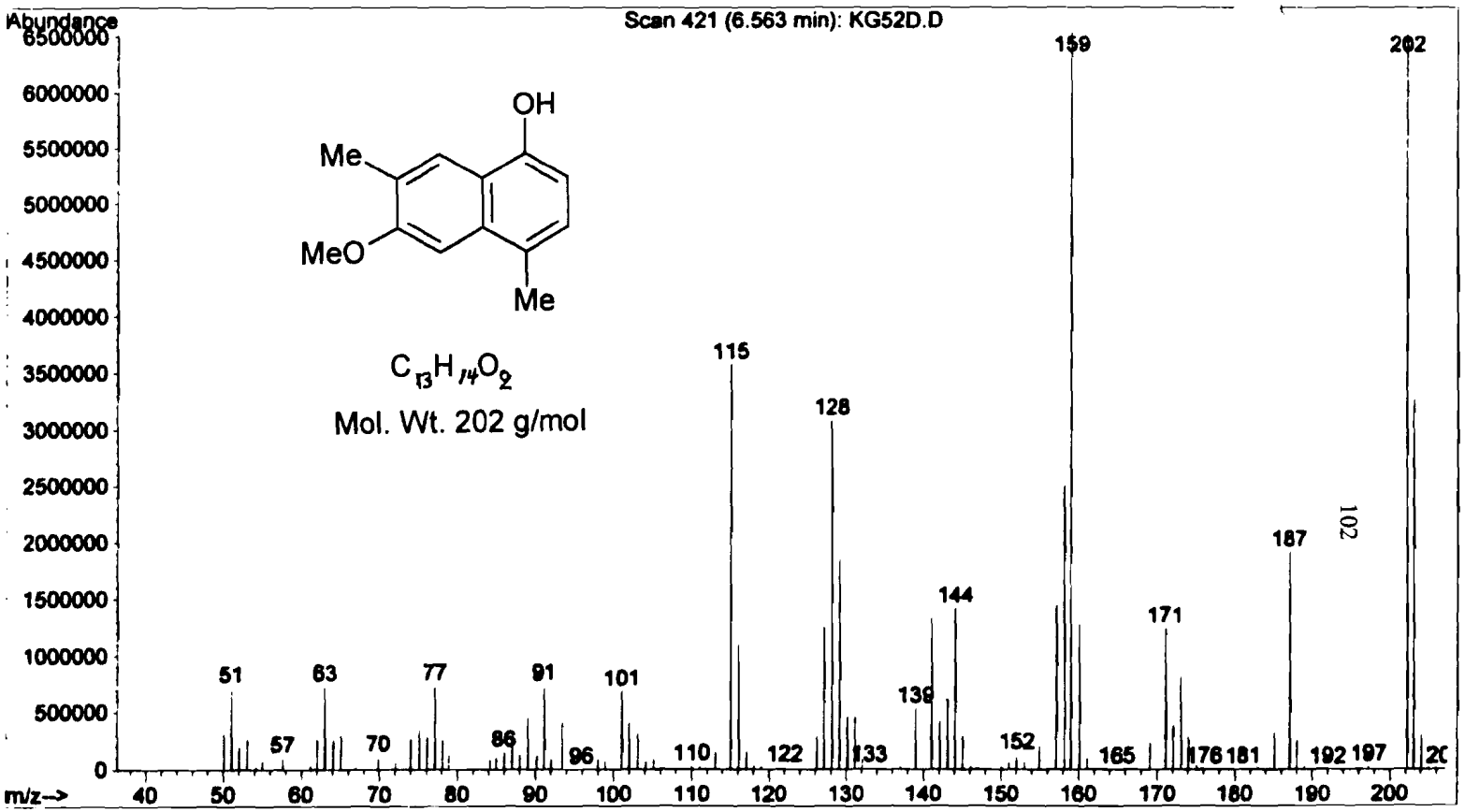





**SPECTRUM 37**. $^1H$ NMR spectrum of Reformatsky product (compound C) $R_f$ 0.2 (30%Hexanes/$CH_2Cl_2$).




**SPECTRUM 38**. $^{13}C$ NMR spectrum of Reformatsky product (compound C) R, 0.2 (30%Hexanes/$CH_2Cl_2$).




**SPECTRUM 39**. Mass spectrum of Reformatsky product (compound C)
~~$R_f$ 0.2 (30% Hexanes/$CH2Cl_2$)~~