PREPARATION AND ADDITION REACTIONS OF CARBANIONS

BY

BITA MIRZAI

A Thesis

Submitted to the Faculty of Graduate Studies

in Partial Fulfillment of the Requirements

for the Degree of

MASTER OF SCIENCE

Department of Chemistry

University of Manitoba

Winnipeg, Manitoba

September, 1991

ISBN 0-315-76875-4

PREPARATION AND ADDITION REACTIONS OF CARBANIONS

BY

BITA MIRZAI

A thesis submitted to the Faculty of Graduate Studies of
the University of Manitoba in partial fulfillment of the requirements
of the degree of

MASTER OF SCIENCE

ACKNOWLEGEMENTS

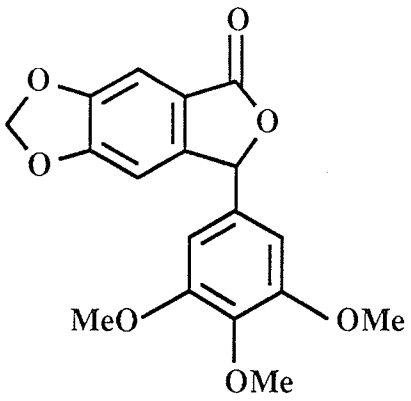
I would like to dedicate this thesis and many thanks to my parents Victoria Mirzai and Ali Mirzai. Your support, encouragement and love made this work possible.

I would also like to take this opportunity to thank the following persons: my supervisor Dr. J.L. Charlton for his patience and guidance throughout the course of the program, the other memebers of my examining committee, Dr. A. Queen and Dr. B. Hasinoff.

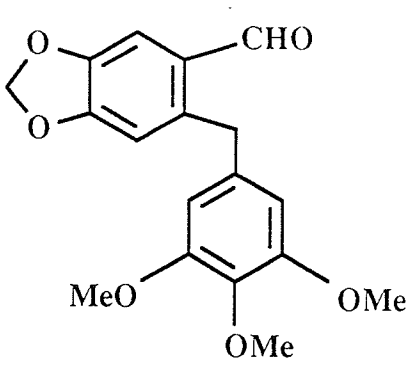
Thanks to the University of Manitoba for the financial assistance provided in the form of a Manitoba Graduate Fellowship.

ABSTRACT

Modifications to the previous synthesis of phthalide **30**, an intermediate used in the synthesis of aldehyde **24,** via halogen-metal (bromine-lithium) exchange of 6-bromopiperonylic acid and 6-bromopiperonal ethylene acetal afforded **30** in 30% and 42% overall yield respectively. The use of 6-bromopiperonal ethylene acetal as starting material was found to be a more satisfactory as it avoided problems of autometallation. Since improvements in the synthesis of **30** were modest a totally new route to aldehyde **24** was developed which resulted in a three step synthesis of **24** in an overall yield of 46%.



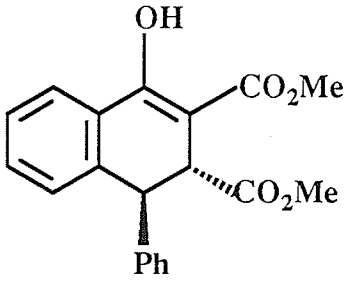
30



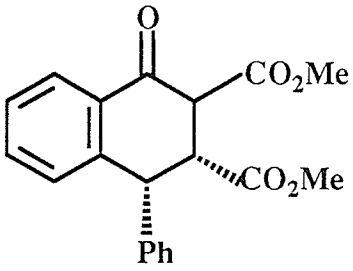
24

As a variation on the general strategy of using *o*-quinodimethanes (*o*-QDMs) for the synthesis of aryltetralin lignans, the application of an anionic α-oxy-*o*-QDM generated by benzylic hydrogen abstraction from methyl *o*-benzylbenzoate was investigated. The generated α-oxy-*o*-QDM underwent a cycloaddition reaction with dimethyl fumarate and the fumarate of (S)-methyl lactate. The reaction with dimethyl fumarate gave **56** and **57** in 42% and 10% yield respectively, whereas the cycloaddition with the fumarate (S)-methyl lactate gave **58** in 14%. The relative stereochemistry of products was assigned by

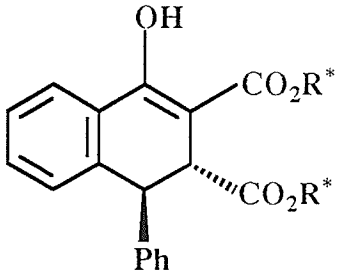
comparison with similar compounds in the literature.



56

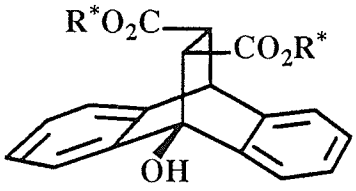


57

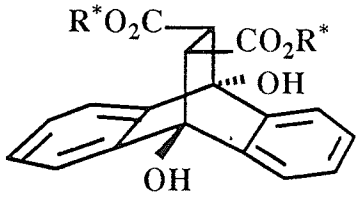


58

An analogue of the anionic α-oxy-*o*-QDM, namely the 1-oxido diene generated by base treatment of anthrone underwent an asymmetric cycloaddition with the fumarate of (S)-methyl lactate with high diastereoselectivity. The cycloadduct, which was assigned structure **45**, was obtained as the only isomer in 77% yield. In a similar manner 9,10-anthracenediol reacted with the fumarate of (S)-methyl lactate to give the cycloadduct **67** in 61% yield.



45



67

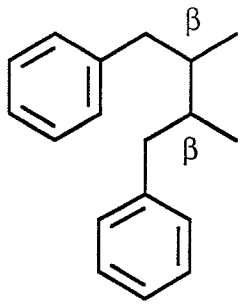
TABLE OF CONTENTS

Chapter 1

INTRODUCTION

1.1 Application of benzylic anions in cycloaddition reactions

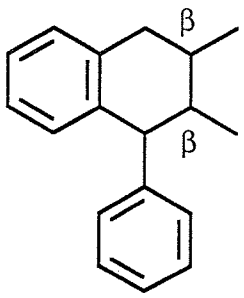
Lignans and neolignans have attracted much interest over the years on account of their widespread occurrence in nature, and on account of their broad range of biological activity. Thus, several lignans and neolignans are known to exhibit anti-tumour activity, while others function as growth inhibitors and anti-fungal agents. Traditionally the term lignan is reserved for compounds in which two phenylpropyl units are linked by a bond connecting the central β-carbon atoms of each side chain such that the end result is the formation of the 2,3-dibenzylbutane skeleton **1**[1].



1

The term neolignan was introduced to designate compounds in which the two phenylpropyl units are linked by other than a β-β bond[2]. Lignans having a side chain fused with the aromatic ring can be classified into two groups according to their structure. One of these groups is the class of compounds known as the aryltetralin lignans. Their

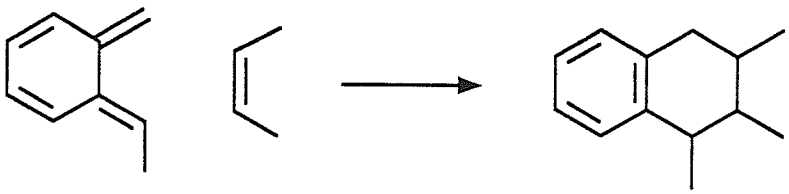
basic skeleton is shown in structure **2**.



2

The many varied types of structure that lignans and neolignans can possess have presented a considerable challenge to organic chemists over the years. Most syntheses that have been carried out depend in fact upon a limited number of key reactions, which have been used to construct the basic 18-carbon skeleton.

One strategy in the synthesis of aryltetralin lignans is to synthesize the basic skeleton via a Diels-Alder reaction of an *ortho*-quinodimethane (*o*-QDM) as shown schematically below.

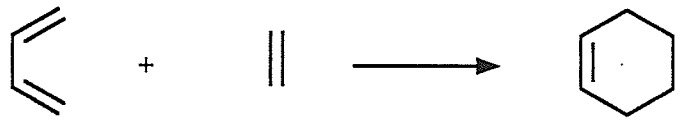


***o*-QDM**

The discovery, characterization and reactivity of *o*-QDMs will not be discussed here and the reader is referred to a recent review article for further reading material on this subject[3].

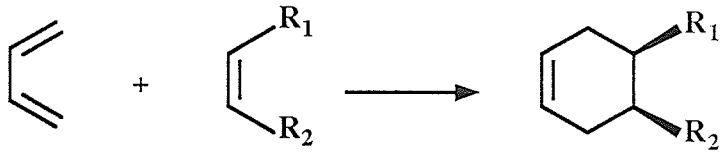
Many ways have been developed in the past to generate various substituted and unsubstituted *o*-quinodimethanes. They include: (1) thermolysis of benzocyclobutenes and benzocyclobutenols; (2) 1,4-elimination processes; (3) thermal elimination of sulfur dioxide from sultines and sulfones; (4) Diels-Alder cycloreversion; (5) photochemical expulsion of carbon monoxide or nitrogen; and (6) photoenolization and photorearrangement. These methods have been reviewed by Charlton and Alauddin and will not be discussed here.

In the Diels-Alder reaction a double bond adds 1,4 to a conjugated diene (4+2 cycloaddition), so that the product is always a six-membered ring. The double bond compound is called a *dienophile*.

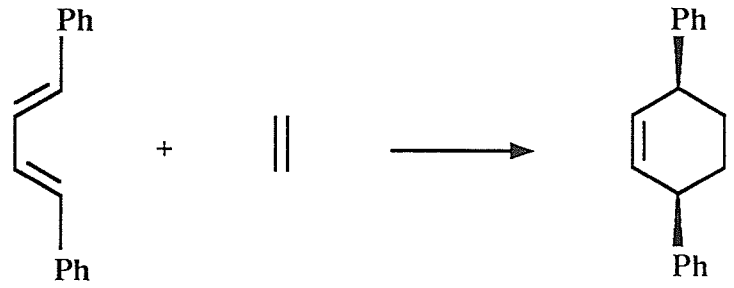


The stereochemistry of the Diels-Alder reaction can be considered from several aspects[4]:

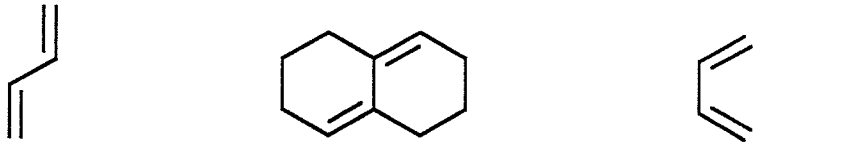
(1) With respect to the dienophile, the addition is stereospecifically *syn*. This means that groups that are *cis* in the olefin will be *cis* in the cyclohexene ring.



(2) With respect to 1,4-disubstituted dienes, the reaction is stereospecific and *syn*. Thus, *trans*,*trans*-1,4-diphenylbutane gives *cis*-1,4-diphenylcyclohexene derivatives.

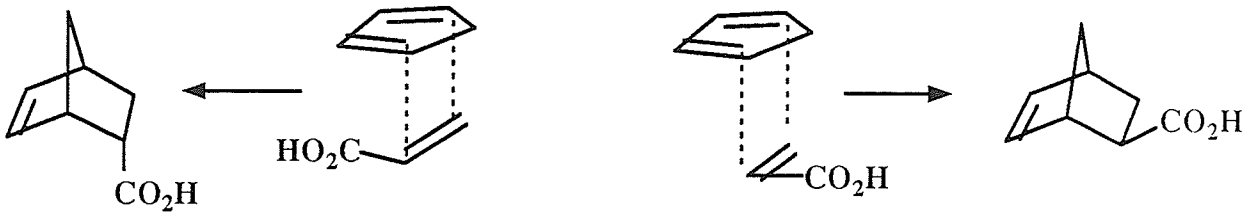


(3) The diene must be in the *cisoid* conformation. If it is frozen into the *transoid* conformation, the reaction does not take place. The diene either must be frozen into the *cisoid* conformation or must be able to achieve it during the reaction.



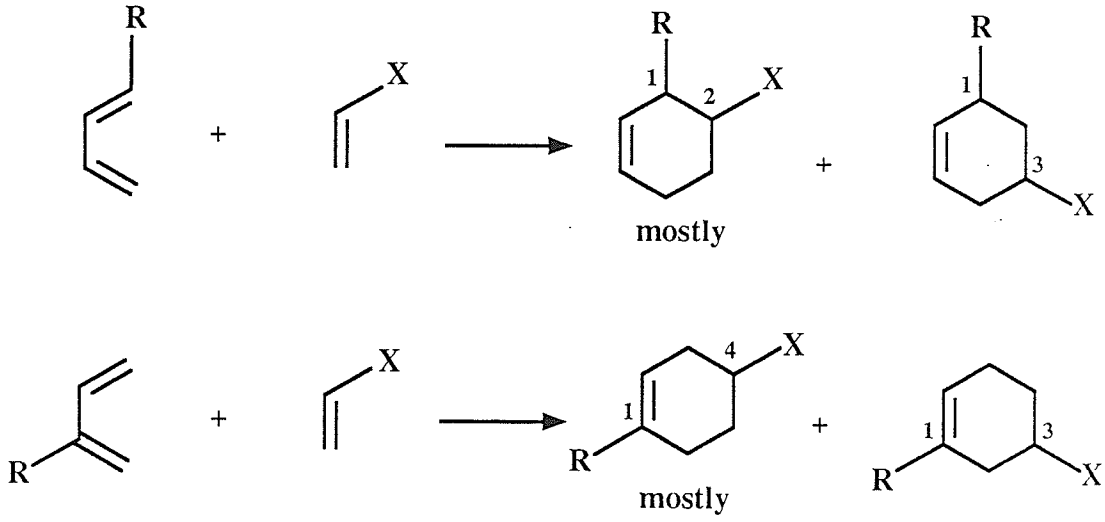
transoid conformation **frozen into transoid conformation** **cisoid conformation**

(4) When a 1-substituted diene, such as a cyclic diene, is reacting with an unsymmetrical dienophile, there are two possible ways in which addition can occur. If the substituent on the dienophile is located under carbon 2 of the diene, the addition is referred to as *endo*. However, when the substituent on the dienophile is extending away from the diene it is referred to as an *exo* addition. Most of the time, the addition is predominantly *endo*.

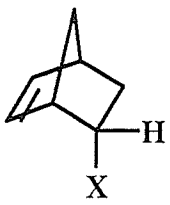


Endo addition **Exo addition**

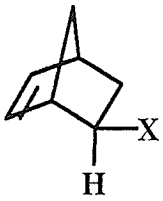
(5) When an usymmetrical diene adds to an unsymmetrical dienophile, there are two possible regioisomeric products. Normally the reactions are quite regioselective and one product predominates over the other.



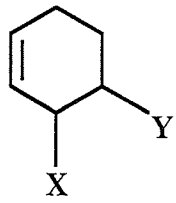
Since the reaction was first discovered in 1928 by Diels and Alder[5,6], several explanations have been given to account for: (a) the formation of crowded *endo* adducts such as **I** instead of the less hindered *exo* alternatives **II** and (b) the formation of *ortho* products such as **III** in preference to the corresponding *meta* adducts **IV**.



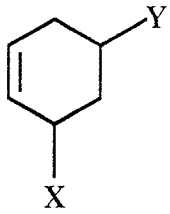
I



II

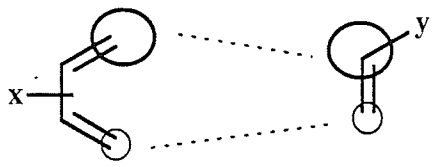


III



IV

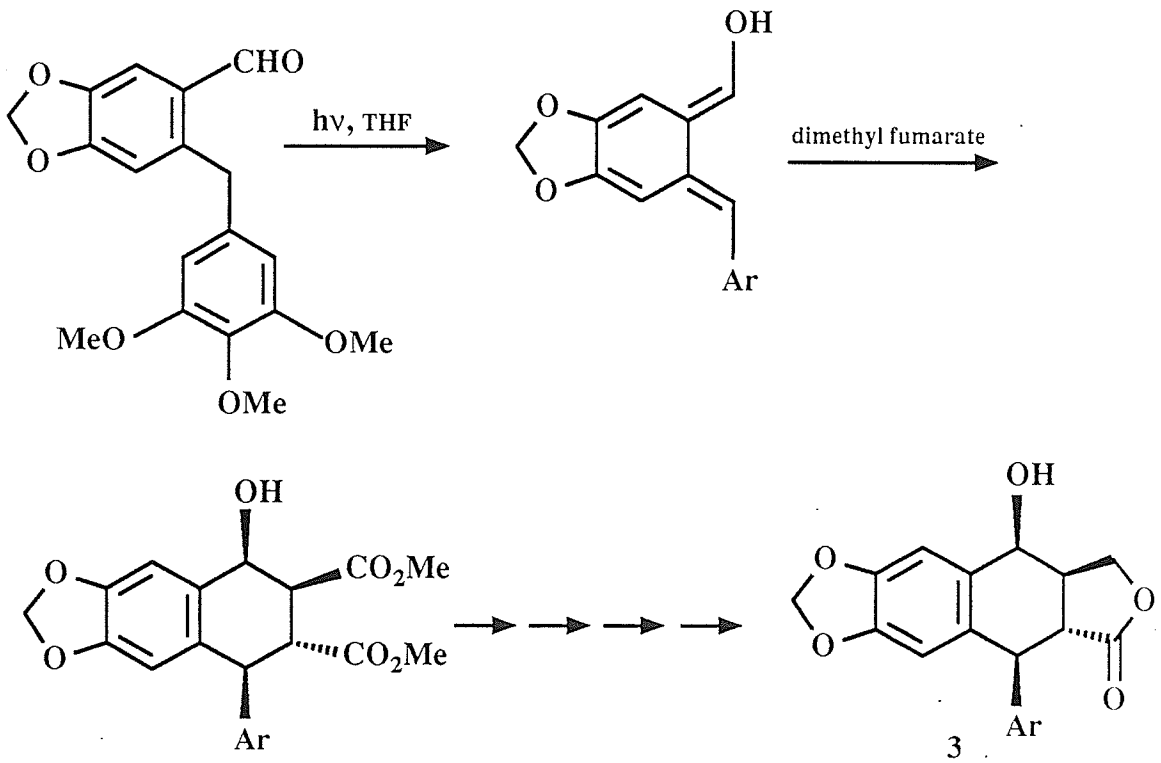
It is generally believed that under conditions of kinetic control, Diels-Alder regio- and stereochemistry is not directed (entirely) by steric factors but rather influenced primarily by interactions between valence orbitals on the diene and dienophile fragments[7]. Furthermore, it has come to be accepted that only frontier interactions, i.e., those involving the highest occupied and lowest unoccupied orbitals (**HOMO** and **LUMO**) on the diene and the dienophile, are important in dictating kinetic product distributions. From the synthetic point of view, usually Diels-Alder reactions are considered to proceed by the interaction of the highest occupied molecular orbital (**HOMO**) of electron-rich dienes with the lowest unoccupied molecular orbital (**LUMO**) of electron deficient dienophiles. For combinations involving both asymmetrically substituted dienes and dienophiles, the extent of overlap will depend on orbital coefficients and the regiochemistry of approach of diene and dienophile. The favoured cycloadduct will result from a transition state in which **HOMO/LUMO** overlap is a maximum.



When both diene and dienophile are substituted, the *endo* principle applies. Frontier orbital theory also explains the *endo* principle. This time secondary interactions are

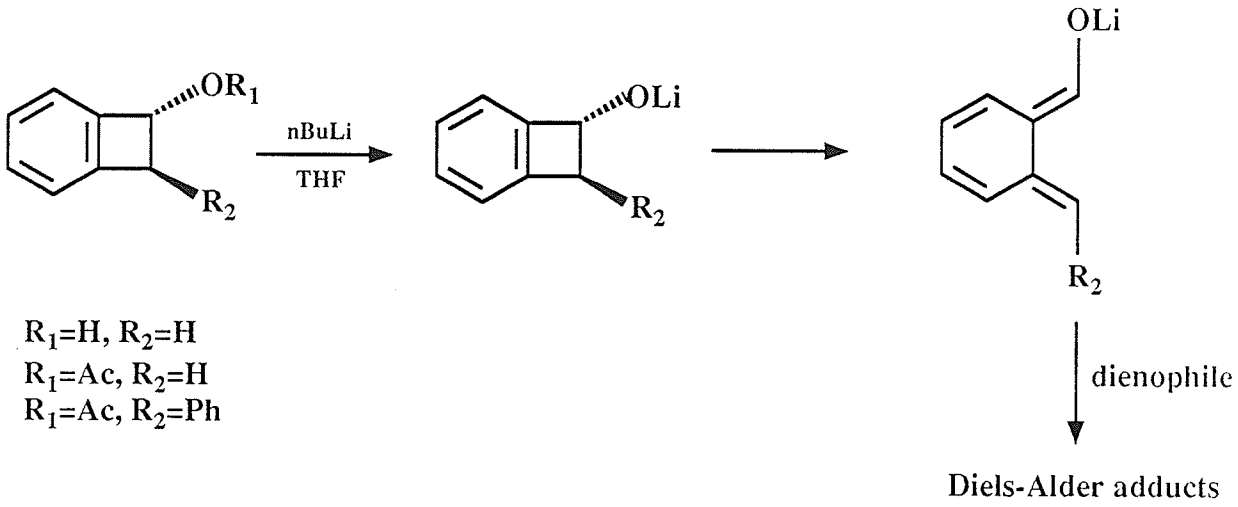
important. These are interactions between atoms not directly involved in the formation of new σ bonds.

The synthesis of (±)-epiisopodophyllotoxin, **3** (Durst & Glinski) shown below, illustrates the use of a Diels-Alder reaction of an *o*-QDM in an aryltetralin synthesis[8].



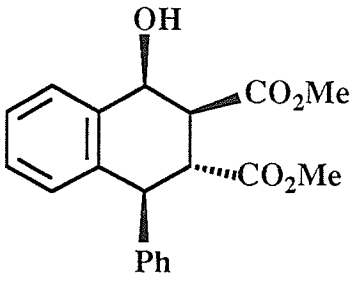
In this synthesis, and others in the literature[9,10], the 18-carbon skeleton is created from an α-alkoxy or α-hydroxy-α'-aryl-*o*-QDM and a four carbon dienophile. Unfortunately the above method is not always successful. When Plourde generated an α-hydroxy-α'-phenyl-*o*-quinodimethane via photolysis of *o*-benzylbenzaldehyde in order to react it with the chiral dienophile dilactyl fumarate, he obtained only a very small amount of cycloadduct[11].

As a variation on the general strategy of using *o*-QDMs in synthesis, Choy and Yang investigated the formation and cycloaddition reactions of anionic α-oxy-*o*-QDMs[12a]. They reported that the treatment of benzocyclobutenols or their acetates with *n*-butyllithium at 0°C or less could generate the corresponding anionic α-oxy-*o*-QDM, which readily underwent Diels-Alder reactions.



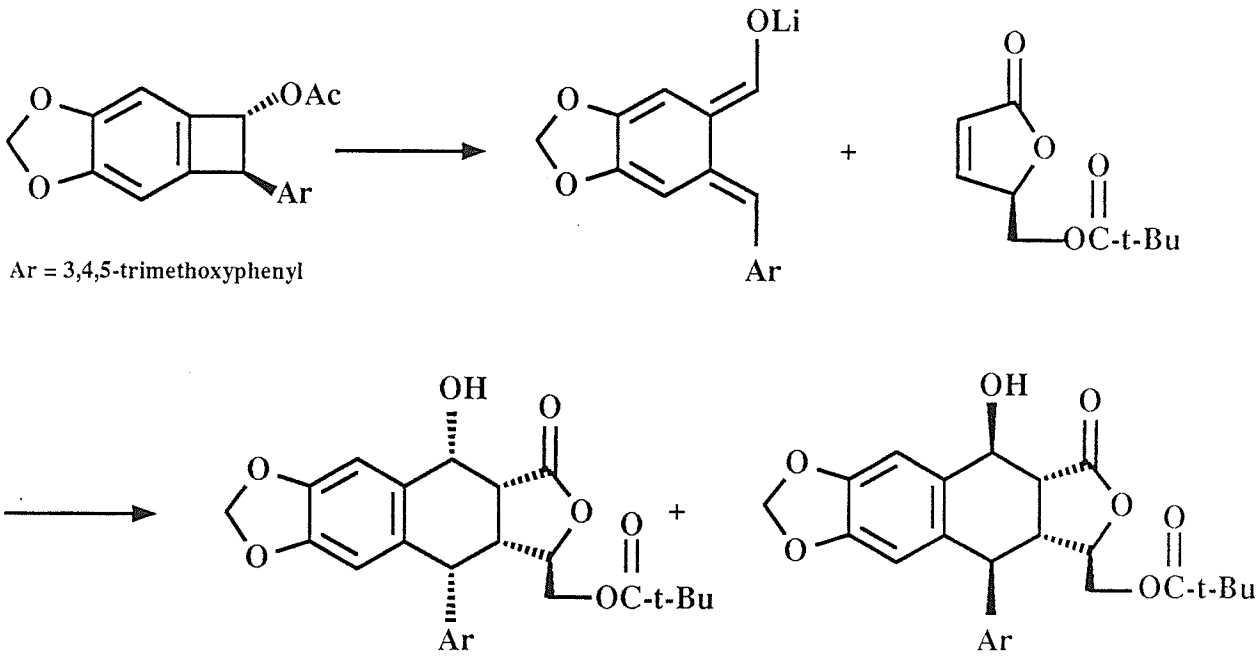
dienophile: dimethyl maleate, dimethyl fumarate

The addition of the anionic α-oxy-*o*-QDM to dimethyl fumarate gave the *endo* cycloadduct **4**.



4

Choy later reported an asymmetric Diels-Alder reaction between a chiral butenolide and an α-oxy-*o*-QDM. The ratio of *endo* to *exo* was found to be 6.2, with greater than 95% d.e. in each adduct[12b].

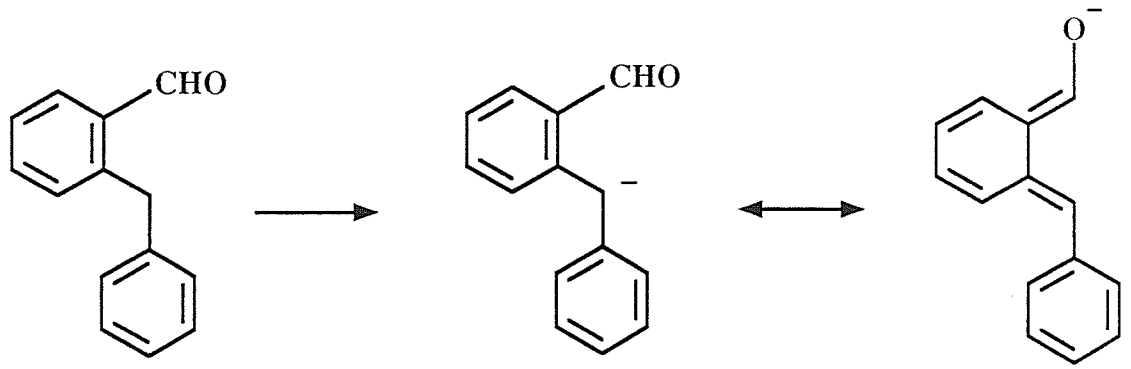


endo *exo*

The author claimed that the combination of the lower temperature and Li cation significantly increased the *endo* selectivity. The Li cation can act as a Lewis acid complexing the carbonyl oxygen of the enone thereby lowering the energy of the LUMO

of dienophile and increasing the rate of reaction.

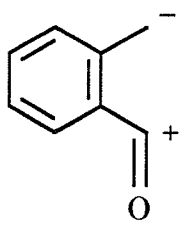
It is of interest to investigate other starting points for the formation of α-oxy-*o*-QDMs as reactive intermediates for the synthesis of lignans. For instance, one could consider the possibility of formation of α-oxy-*o*-QDMs from *o*-benzylbenzaldehyde, via abstraction of a benzylic hydrogen.



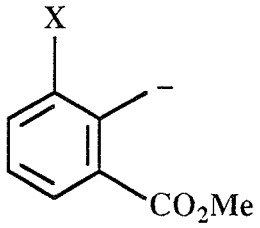
5 **6**

One could also consider the generation of the α-oxy-*o*-QDMs from the corresponding ester of the *o*-benzylbenzoic acid, via the generation of a benzylic carbanion.

Previous workers have shown that anions generated by benzylic hydrogen abstraction from toluic acid esters can be used in the synthesis of linear polycyclic aromatic systems. These anions provide a synthon with reactivity as shown in **7**. This synthon is effectively present in toluate anions such as **8** or **9**.

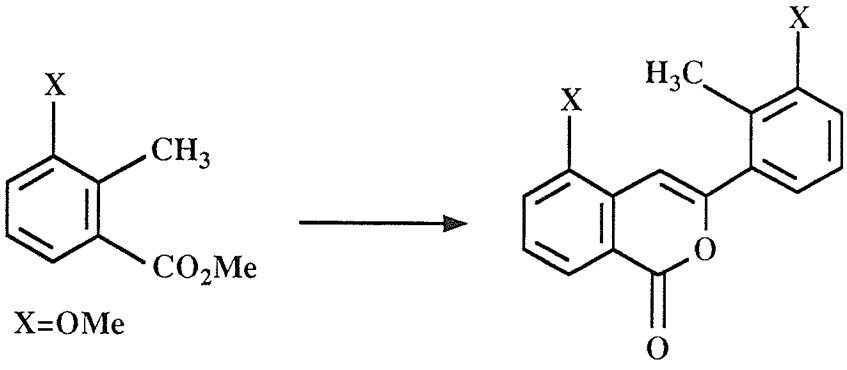


7



8 X=H
9 X=OMe

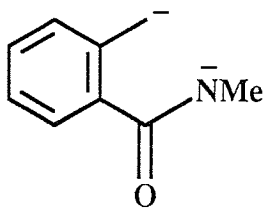
However, Hauser and Rhee have reported that the anion **8** dimerizes very rapidly and cannot be used synthetically[13]. The same result has been observed for the substituted *o*-toluate **9**. The anion derived was unstable and underwent rapid coupling to furnish isocoumarin[14].



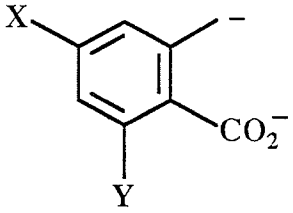
X=OMe

9 **10**

As a result many modifications have been adopted. The dianions **11**[15] and **12**[16] are reasonably stable and the substituted dianions **13**[17] and **14**[18] have been used synthetically.

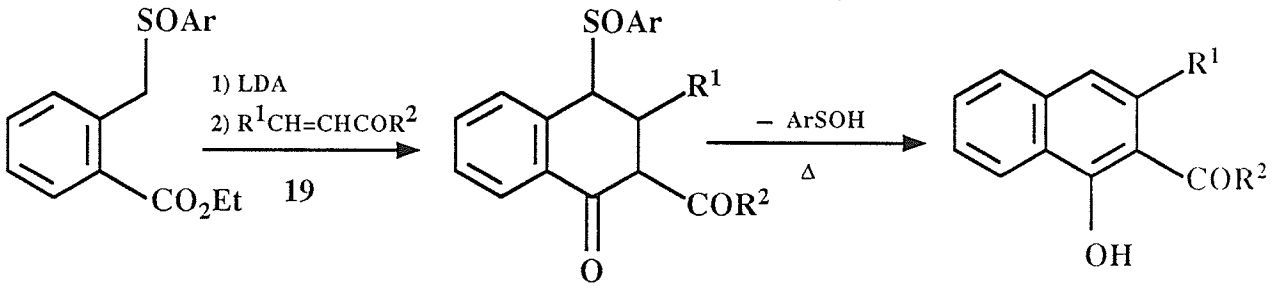


11



12 X=Y=H
13 X=H, Y=OMe
14 X=Y=OMe

Another method that has been used to stabilize *o*-toluate anions employs an electron-withdrawing substituent on the methyl group. Thus suphides[19], sulphoxides[13], and sulphones[20] have all been used, as well as methoxycarbonyl[21] and cyano[20] groups. Hauser and Rhee made use of sulphoxides to stabilize *o*-toluate anions to devise a route for the preparation of 1-hydroxy-2,3-disubstituted naphthalenes **21**[13].

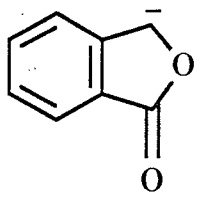


18 20 21

Ethyl 2-carboxybenzyl phenyl sulphoxide **18** was converted to an anion using lithium

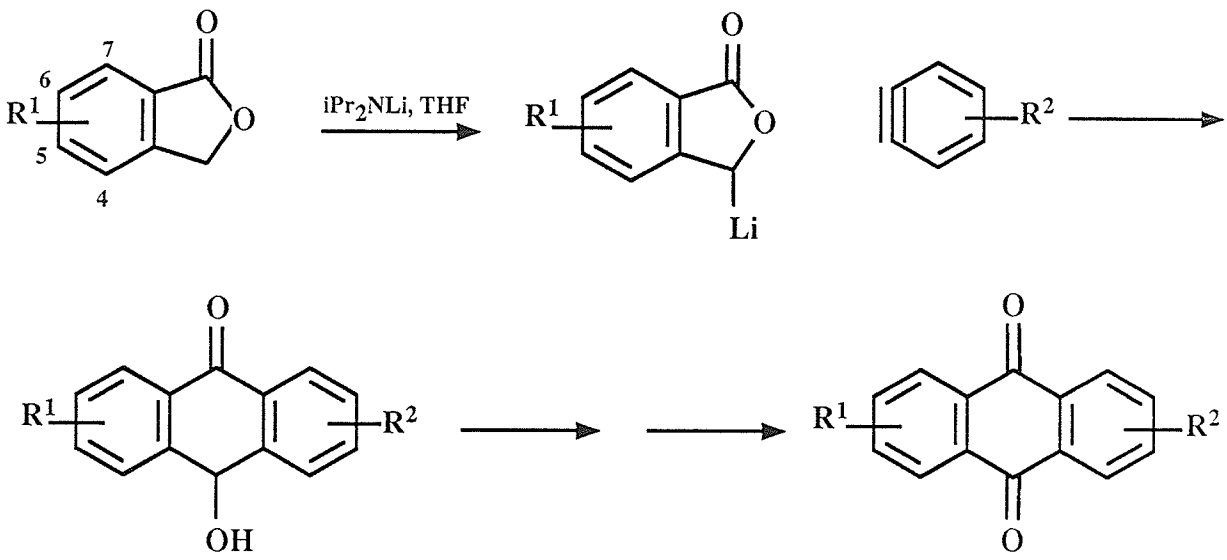
diisopropylamide (LDA) in tetrahydrofuran at -78°C, then allowed to react with various Michael acceptors **19**. The initially formed conjugate addition product underwent intramolecular condensation to yield a tetralone. In this scheme, the sulfoxide group not only serves as a good leaving group allowing aromatization but also it provides essential stabilization for the carbanion generated on the benzylic carbon. As previously mentioned the generation of the anion of the parent ethyl *o*-toluate (without the benzylic sulfoxide) and reaction with ethyl crotonate resulted in only the formation of the ethyl *o*-toluate dimer.

The unsubstituted and substituted phthalide anions, such as **15**, generated by benzylic hydrogen abstraction, have also received considerable attention for the preparation of polycyclic system such as quinones, naphthols and anthraquinones[22,23].

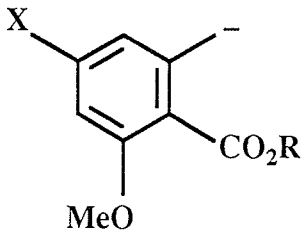


15

Sammes *et al.* reported that the carbanion reacted at position 3 with arynes to form adducts, which, upon air oxidation, produced anthraquinones in moderate to good yields[24]:

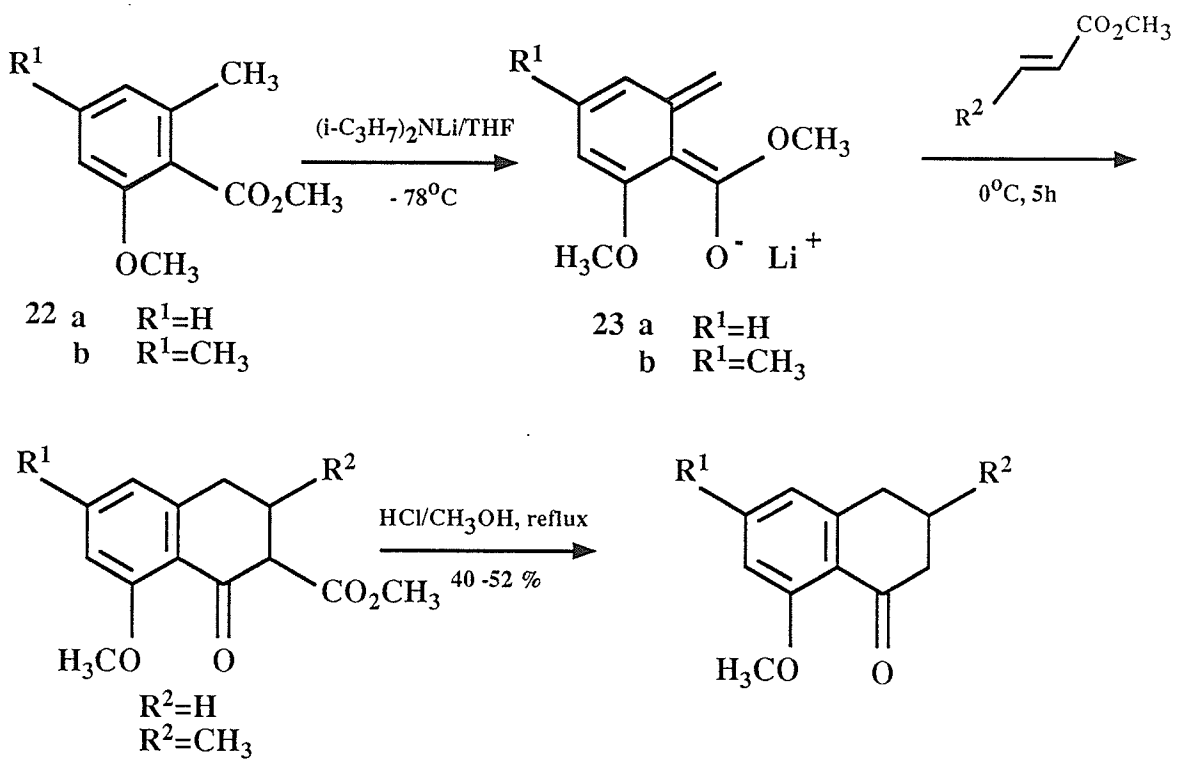


It has been found that the methoxy substituted *o*-toluate anions **16** and **17** are sufficiently stable at low temperatures to be synthetically useful without stabilizing groups and furthermore it has been concluded that an oxygen substituent *ortho* to the ester group is necessary to decrease the carbonyl electrophilicity (by both steric and electronic effects) enough to prevent rapid coupling, thus allowing time for reaction with electrophiles.



16 X=H
17 X=OMe

Based on these results a synthesis was developed for the preparation of 8-methoxy-1-tetralones[25].

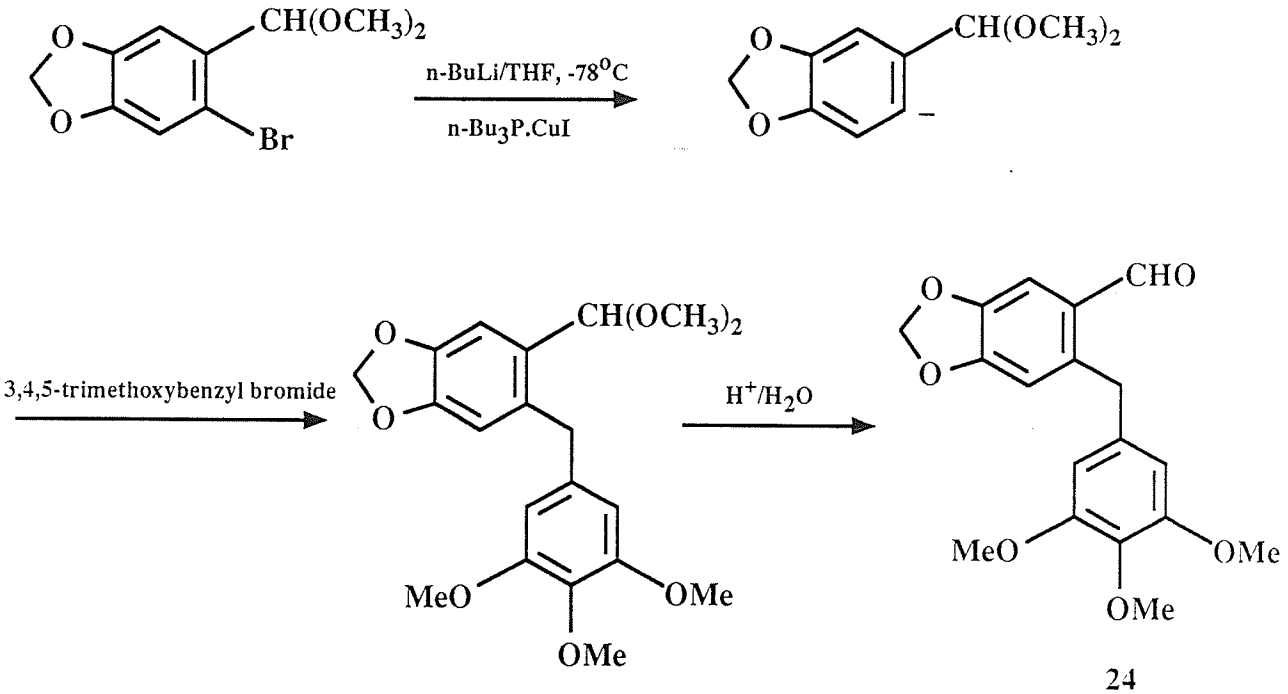


The synthesis was based on the work by Staunton who observed that anion **23a** derived from **22a**, was sufficiently stable in solution to be used in further reactions[26]. The course of reaction is explained as involving tandem Michael addition-Dieckmann condensation between anion **23a** and the acrylate Michael acceptor.

2.2 Synthesis of ortho-substituted benzaldehyde

Sammes and co-workers have shown that in general, *ortho*-substituted benzaldehydes in solvents such as benzene, acetone, or THF undergo isomerization to *o*-quinodimethanes when irradiated. The idea of generation of this type of dienol has led to syntheses of many *ortho*-substituted aromatic aldehydes especially in the area of lignan synthesis.

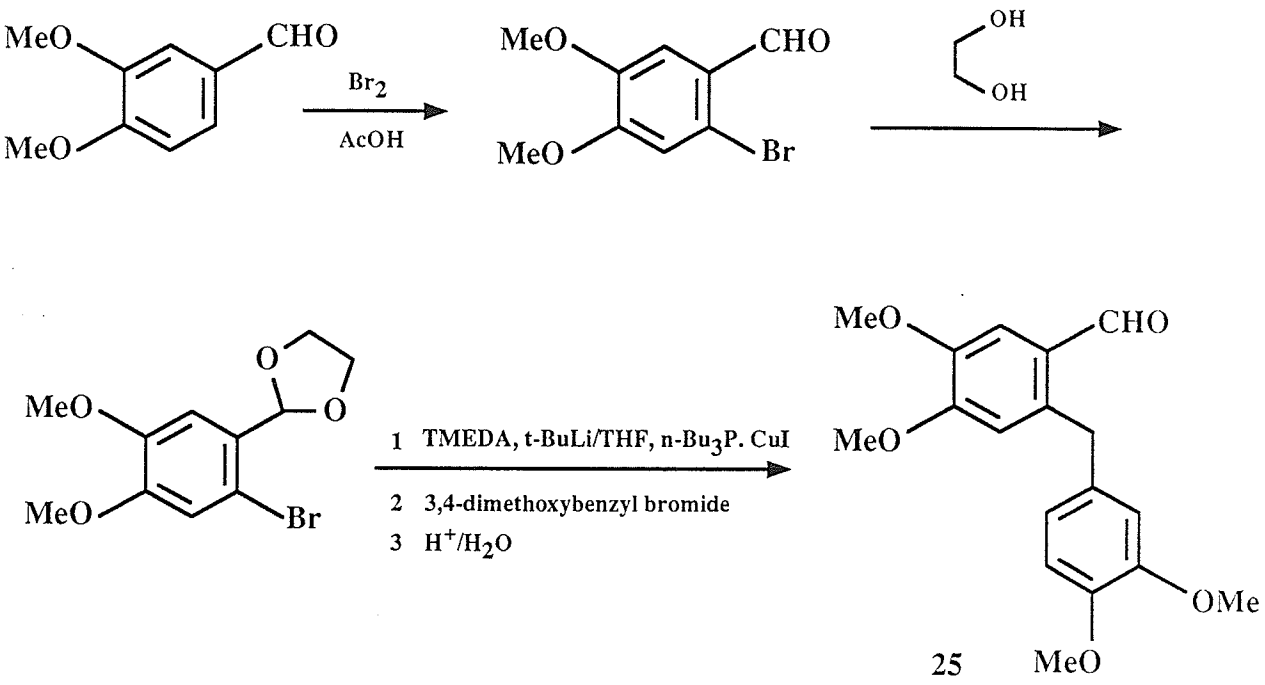
The α-hydroxy-*o*-quinodimethane required as an intermediate for the synthesis of (±)-epiisopodophyllotoxin **3** was generated photochemically from *6-(3,4,5-trimethoxybenzyl)piperonal* **24**. Durst *et al.* synthesized the required *ortho*-substituted benzaldehyde from 6-bromopiperonal dimethyl acetal and the synthesis is shown in the scheme below[8].



24

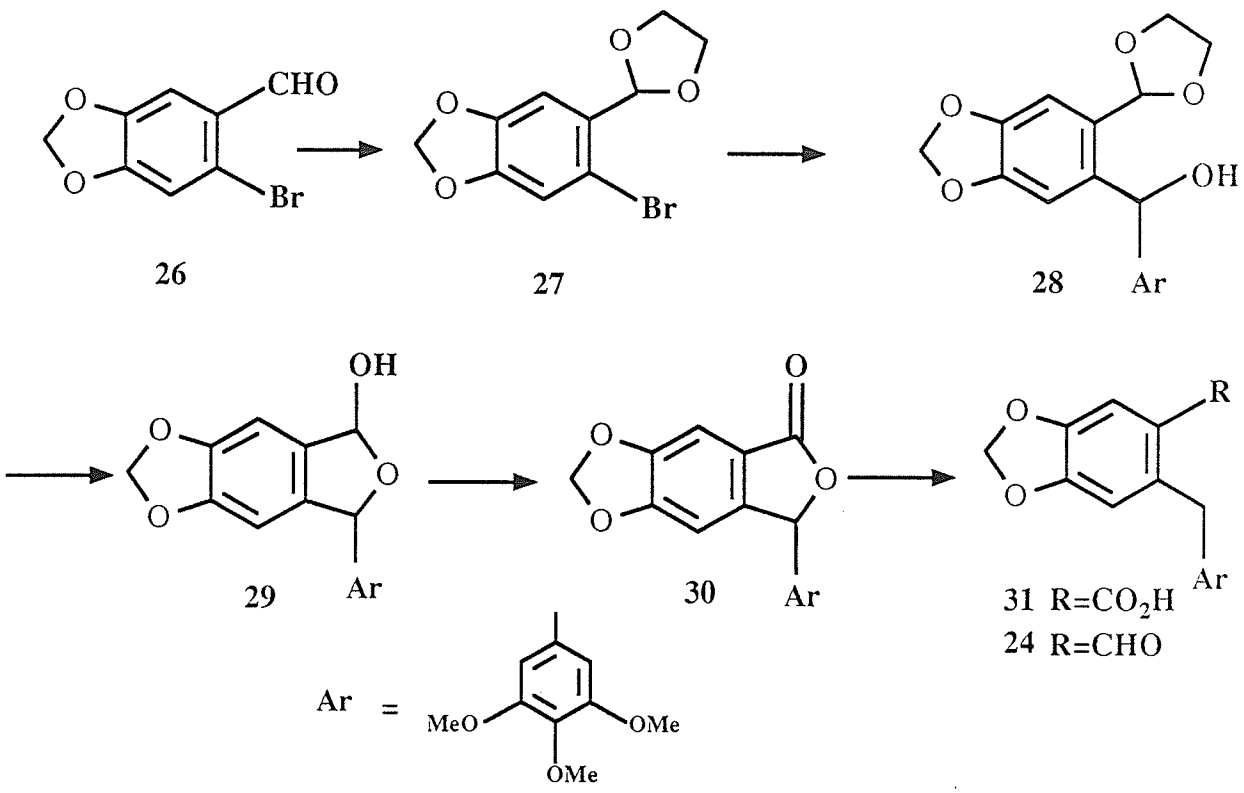
The authors have reported that it is possible to synthesize **24** in 84% yield from 6-bromopiperonal dimethyl acetal, by treatment with *n*-BuLi, *n*-Bu_3P.CuI, and 3,4,5-trimethoxybenzyl bromide. They also concluded that the presence of *n*-Bu_3P.CuI was crucial for the coupling reaction.

Alauddin used a similar procedure for the preparation of *ortho*-substituted benzaldehyde **25** which was required for the synthesis of isolariciresinol dimethyl ether[10].



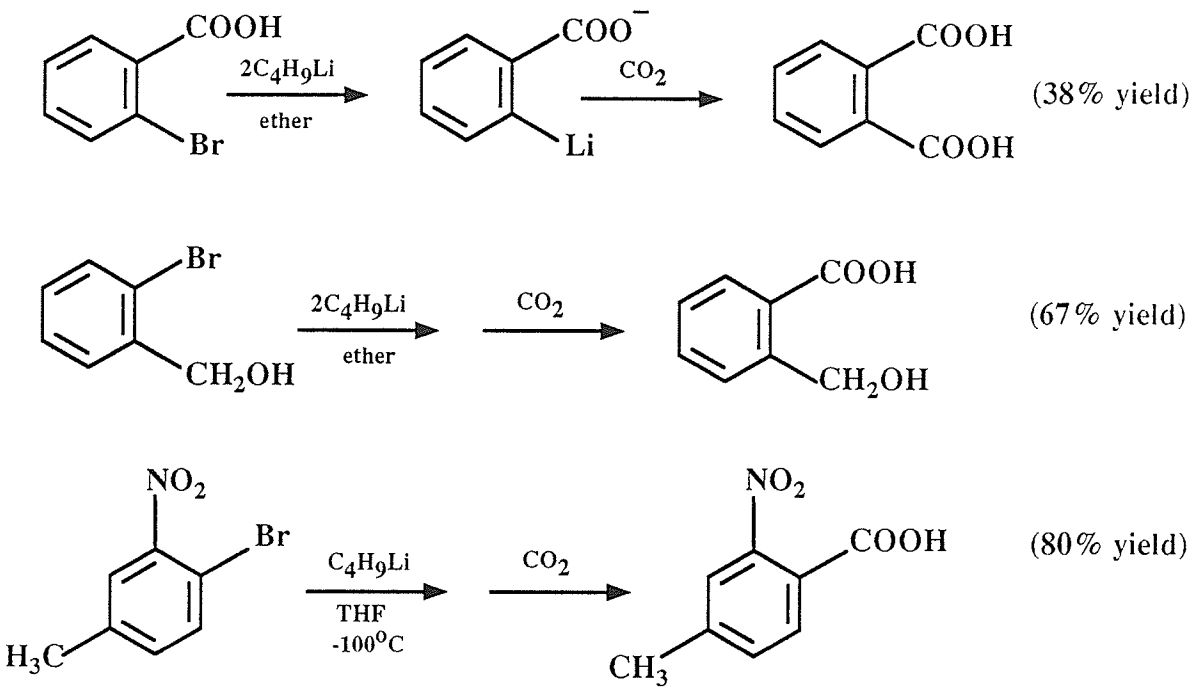
25

In 1978 Sammes *et al.* devised a route for the synthesis of *ortho*-substituted benzaldehyde **24** which is shown in the following scheme[27].

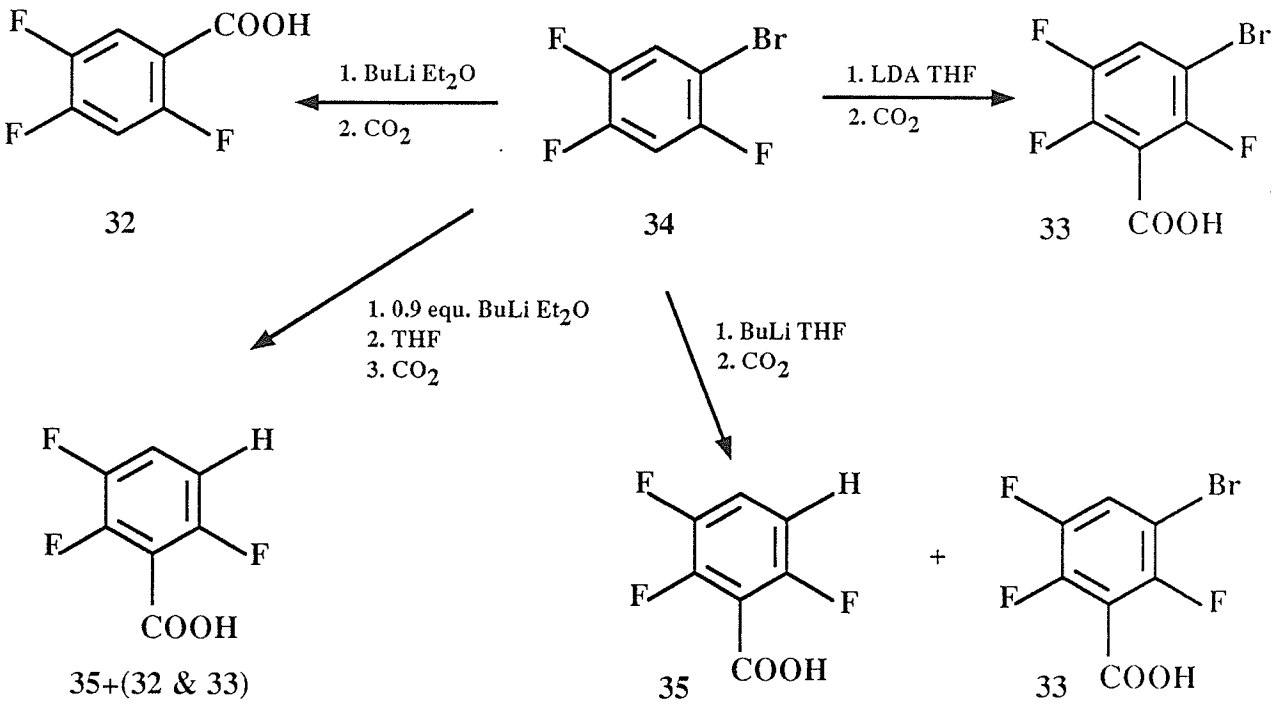


6-Bromopiperonal was obtained by bromination of piperonal in acetic acid. The aldehyde group was then protected by formation of its ethylene acetal in order to allow preparation of the aromatic Grignard. This Grignard reagent was then added to 3,4,5-trimethoxybenzaldehyde to give the alcohol **28**. Hydrolysis of the acetal gave the hemiacetal **29**, which was oxidised to the phthalide **30** with chromic acid in acetone. Selective hydrogenolysis of the diphenylcarbinol group was possible in the case of phthalide **30** giving the acid, itself readily converted into the required aldehyde.

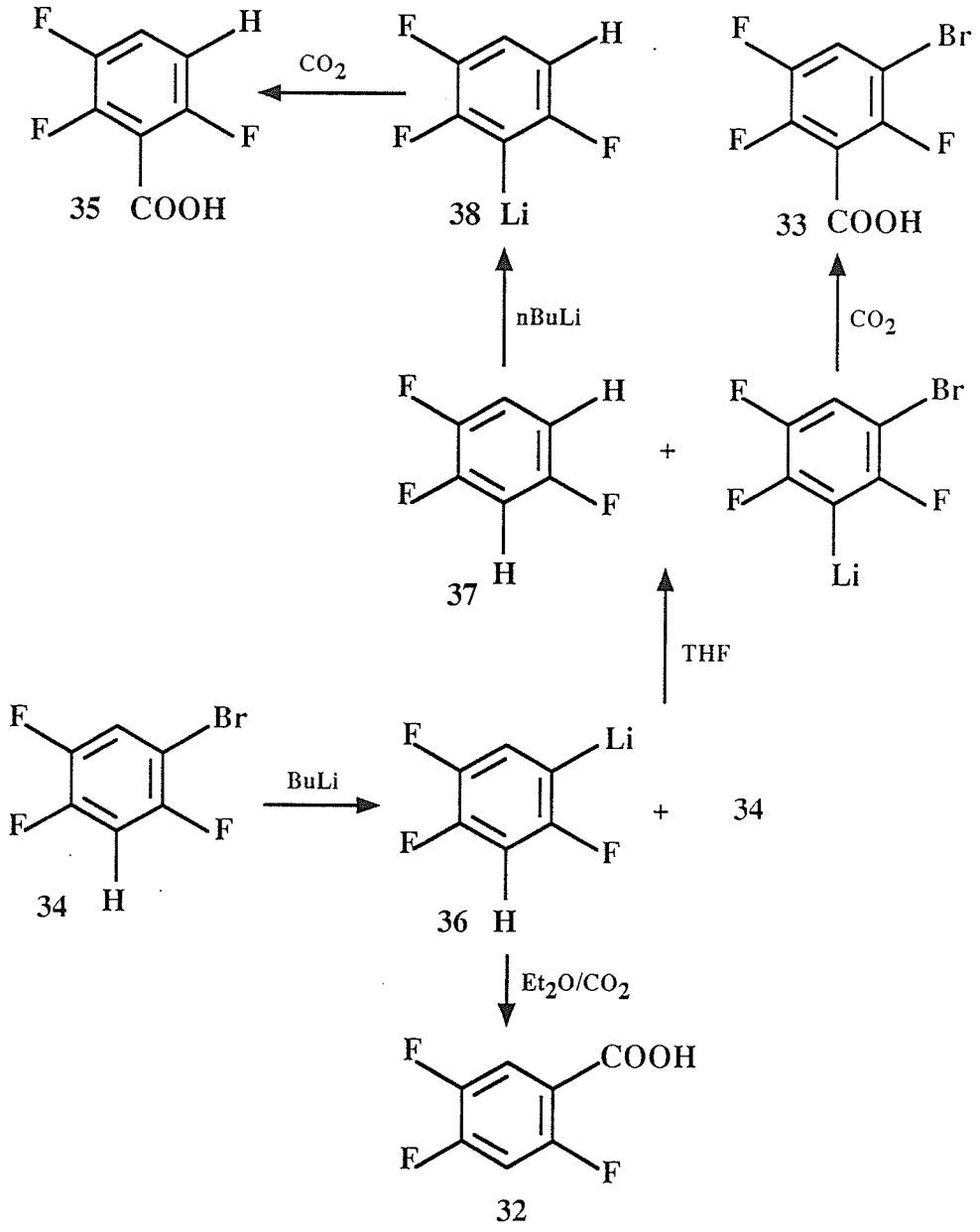
It was of interest to determine if one could modify the above synthesis, namely replacing the difficult Grignard preparation by a metal-halogen exchange reaction. In his pioneering work in organometallic chemistry, Gilman and his co-workers established that halogen-metal interchange could be achieved with substituted halobenzene derivatives, and that the derived anions could be used as intermediates in syntheses[28].



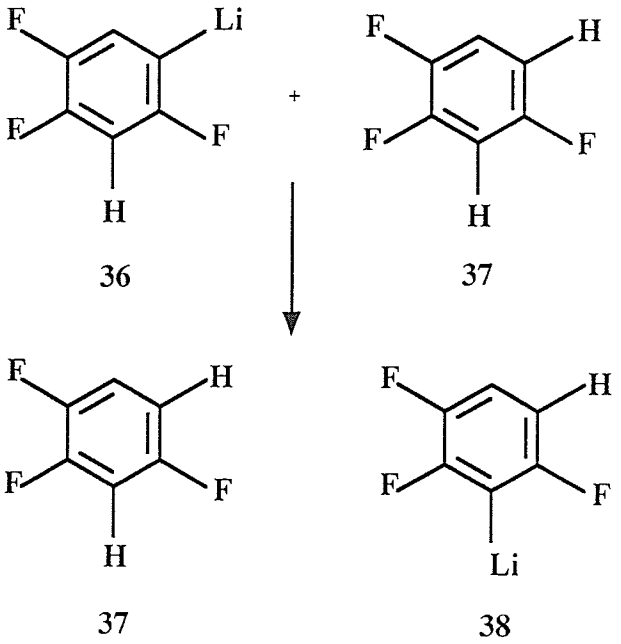
It has been shown that the fate of the anions derived from aromatic halogen metal exchange is dependent upon the solvent and the temperature. The effect of solvent during halogen-metal exchanges was illustrated recently by Bridges *et al.* during the preparation of **32** and **33** from **34** as shown in the following Scheme[29].



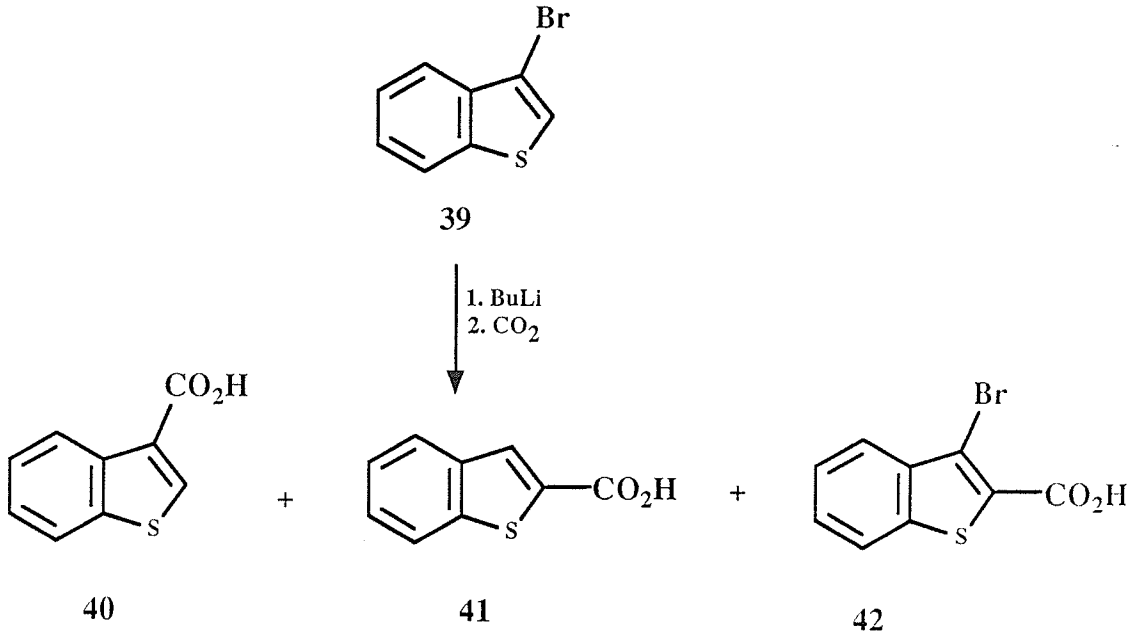
It was observed that bromide **34** was metalated by LDA at the more acidic *meta* position, and that carboxylation gave acid **33**. Acid **32** could be prepared from **34** by halogen-metal exchange in ether using BuLi. In THF, reaction with BuLi and CO_2 gave a mixture of **32**, **33** and **35**, which illustrates the effect of solvents on this type of reaction. It was argued that the mechanism of formation of **33** and **35**, involved *autometalation*, a process which was first described by Gilman. In autometalation the initially formed organolithium **36** can serve as a base toward unlithiated substrate.



The product **37** can also function as a relay compound, converting **36** to **38**.



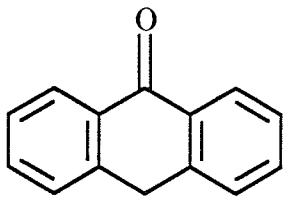
The effect of temperature on lithiation can be seen in the work of Dickenson and Iddon, shown below[30].



In ether at -70°C lithiation-carboxylation gave only one acid, the expected **40**. However upon holding the initial anion at 20°C prior to carboxylation, or by running the reaction at -70°C in THF, compounds **41** and **42** were formed along with compound **40**.

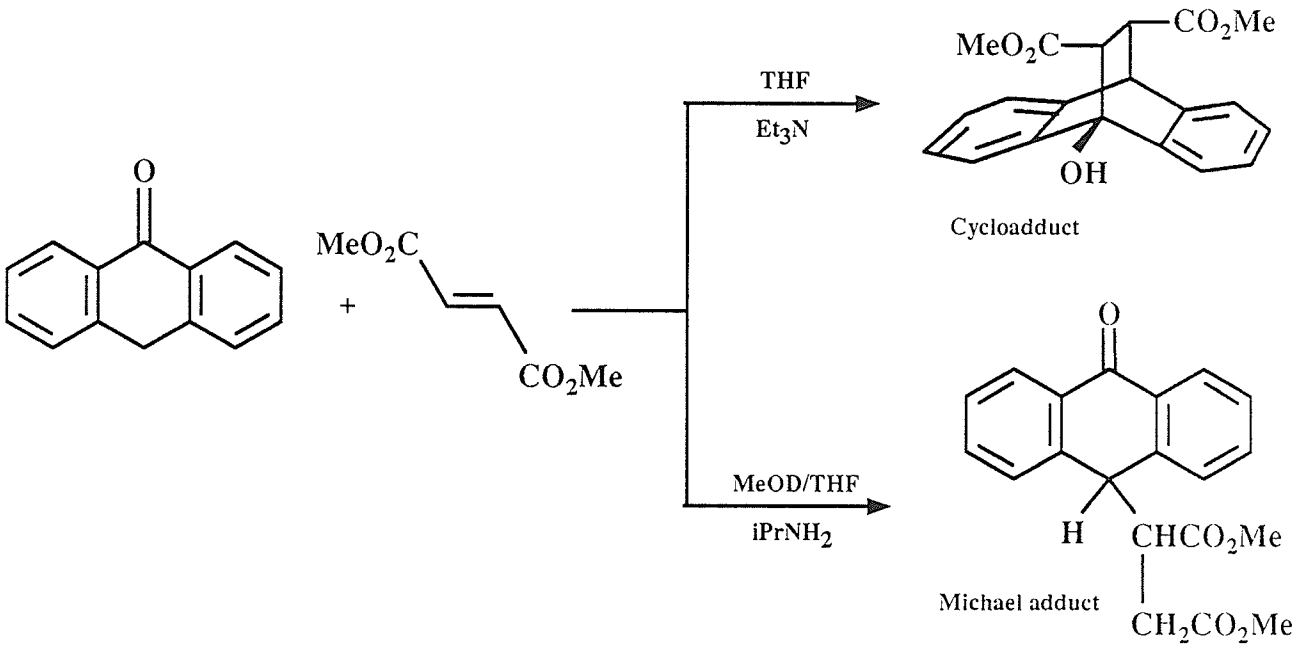
2.3 Anthrones as reactive dienes in Diels-Alder reactions:

The anion of anthrone ((9-(10H)-anthracenone, **43**) is an analogue of the anionic α-oxy-*o*-QDM and is also known to undergo Diels-Alder cycloaddition reactions[31].

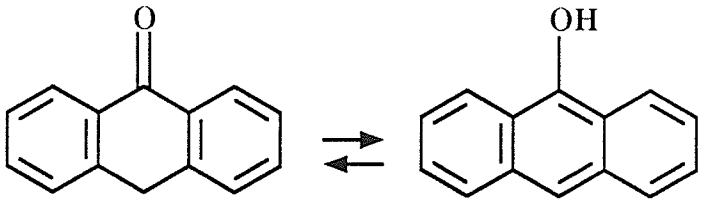


43

In the presence of an amine, anthrone functions as a reactive diene in (4+2) cycloadditions. Weak base treatment of anthrones gives "1-oxido dienes" as reactive intermediates, leading to base-catalyzed Diels-Alder reactions. Variation of base, solvent, dienophile, and substrate can result in the exclusive formation or either cycloadduct or Michael adduct. The example given below shows the products which Rickborn and Koerner obtained using dimethyl fumarate as dienophile in both THF solvent and alcoholic solvent[32].

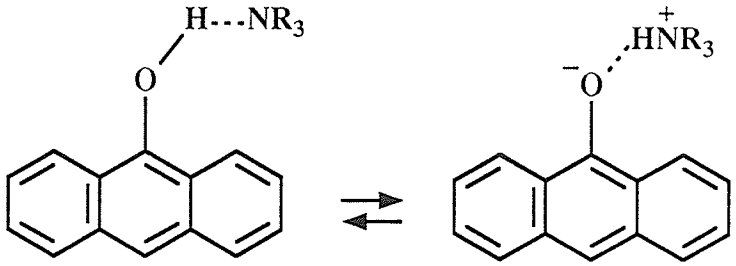


The phenolic tautomer 9-anthracenol **44** is known to be in equilibrium with anthrone **43**. The equilbrium position is known to be very much solvent dependent, with the keto form heavily favoured in relatively nonpolar solvents, and the enol form **44** slightly favoured in hydrogen bond acceptor solvents.



43 **44**

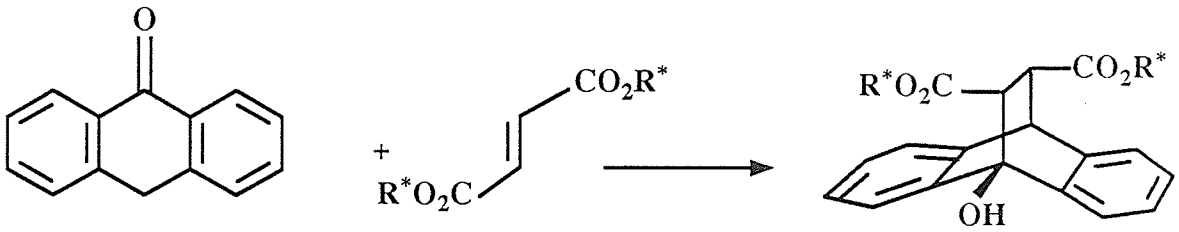
Koerner and Rickborn assumed, that hydrogen bonded species such as those shown below are formed, and proposed that an "*oxyanion*" complex of this kind was involved in cycloaddition reactions.



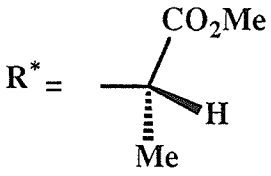
At this stage, it is useful to divide oxyanion processes into two categories, base *induced* and base *catalyzed.* For base-*induced* reactions, the relevant starting and product states are the oxyanions themselves. For base-*catalyzed* reactions, it is the neutral species, typically the conjugate acid of the oxyanion or a keto tautomer, which is hydrogen bonded to the base that enters into the reaction. The outcome of a reaction can be controlled by this difference. Thus for a cycloaddition the anionic starting material may be more stable than the anionic adduct, while the opposite may be true for the corresponding neutrals.

Regardless of mechanistic details, cycloadducts of anthrone and related species are more stable than the educts (starting materials) under the mild base conditions. Knapp *et al.* showed that strong base can cause a cycloadduct to cleave to form anionic starting material[33]. Furthermore, there is the question of whether the cycloadducts of an anthrone system are formed by stepwise (Michael+Aldol) reactions, or by oxyanion accelerated concerted Diels-Alder reactions. Arguments favoring the latter mechanism will be given in the results and discussion section of this thesis.

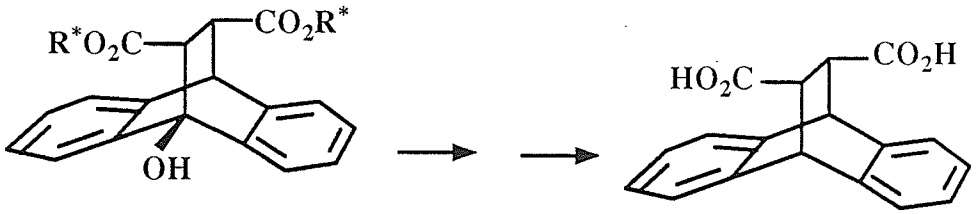
It is also of interest to investigate whether anthrone, when treated by weak base, can undergo a reaction with a chiral dienophile such as the fumarate of (S)-methyl lactate analogous to the reactions of α-oxy-*o*-QDM.



45



Such a reaction might provide an optically pure cycloadduct (of one absolute configuration) which could be converted to a chiral C_2 symmetric molecule **46** as shown below.



46

C_2 symmetric molecules are very popular as chiral auxiliaries since the presence of the C_2 symmetry axis within the chiral auxiliary can serve the very important function of dramatically reducing the number of possible competing diastereomeric transition states (stereochemical control).

The reader is referred to a recent review by Whitesell for further information on this subject[34]. While synthesis of the C_2 symmetric molecule shown above has already been reported by Helmchen *et al*[35] (via a Diels-Alder reaction between anthracene and the fumarate of (S)-ethyl lactate), the anthrone approach might provide a more efficient route to this interesting compound.

Chapter 2

RESULTS AND DISCUSSION

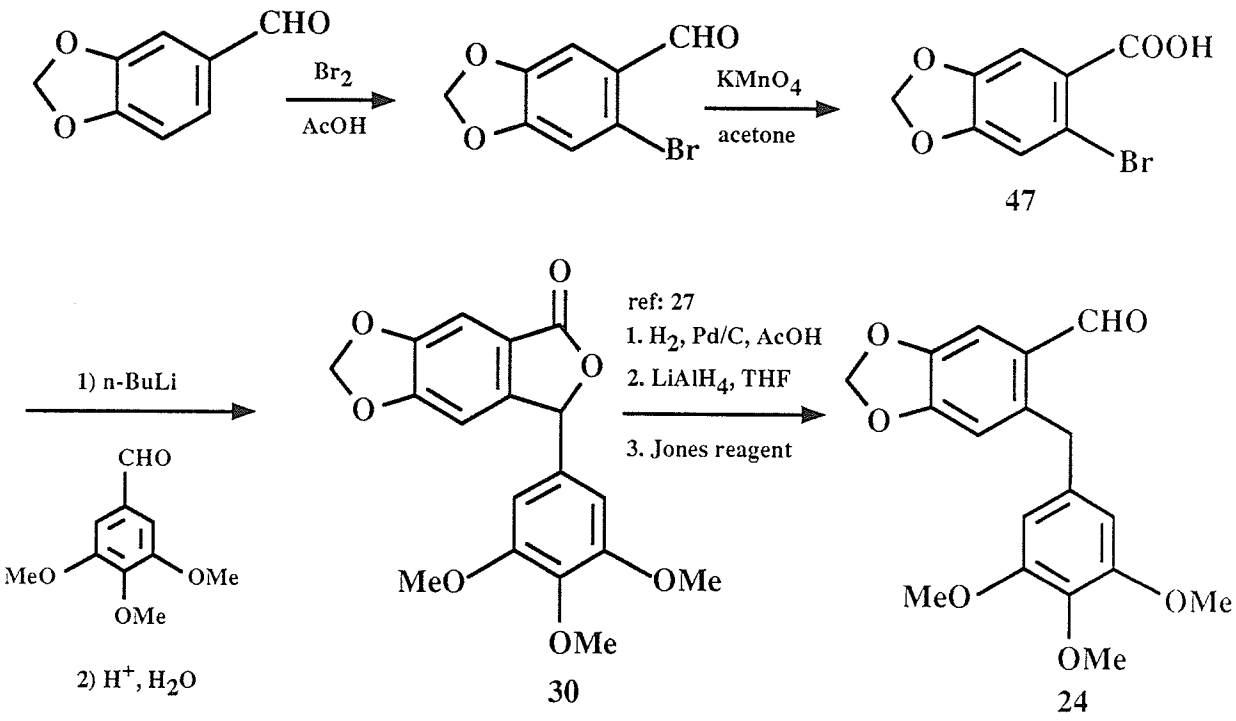
This chapter consists of three sections and covers the results accomplished during the course of the thesis work. The first section explains the modified and new synthetic route to the synthesis of 6-(3,4,5-trimethoxybenzyl)piperonal via halogen-metal exchange. The second and third sections describe the cycloaddition reactions of anionic α-oxy-*o*-QDMs generated from methyl *o*-benzylbenzoate and from anthrone, with the fumarate of (S)-methyl lactate.

2.1 Synthesis of 6-(3,4,5-Trimethoxybenzyl)piperonal

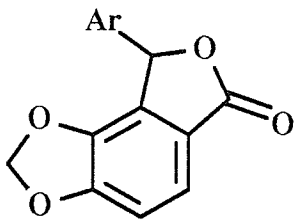
In the introduction section of this thesis the use and synthesis of the titled aldehyde was described. Furthermore, it was mentioned that Sammes *et al.* had devised a route to its synthesis via formation of the Grignard reagent from the ethylene acetal of *o*-bromopiperonal. The aim of this work was to investigate whether one could avoid the difficult preparation of the Grignard reagent and replace it by a halogen-metal (Br-Li) exchange. Br-Li exchange is a very useful technique for the regiospecific generation of aromatic anions. Because aromatic bromine-lithium exchange is very rapid, it allows for lithiation to be carried out at positions in the molecule not normally accessible by simple deprotonation due to the presence of kinetically or thermodynamically more acidic sites.

In the present work on improving Sammes synthesis of 6-(3,4,5-trimethoxybenzyl)piperonal the key intermediate phthalide **30**, was obtained via two different halogen-metal exchange routes (Path A & Path B).

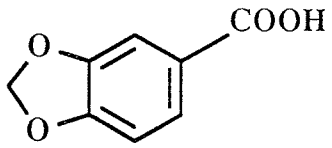
Path A:



Previously the phthalide **30** was synthesized in six steps and it involved the formation of the Grignard reagent. The proposed design for the synthesis of **30** not only eliminated the use of the Grignard reagent but also it reduced the number of steps to three. The idea was to metalate the bromopiperonylic acid and couple the dianion formed with 3,4,5-trimethoxybenzaldehyde to yield the phthalide **30**. Bromopiperonylic acid **47** was prepared by oxidation of bromopiperonal with potassium permanganate because direct bromination of piperonylic acid was not successful. The bromo acid was then metalated with two equivalents of *n*-BuLi at -78°C in THF and 3,4,5-trimethoxybenzaldehyde added to yield **30**. However, workup and chromatography showed that the phthalide (46 %) was contaminated with both **48** and piperonylic acid, **49** , along with in some cases traces of the starting 6-bromopiperonylic acid.

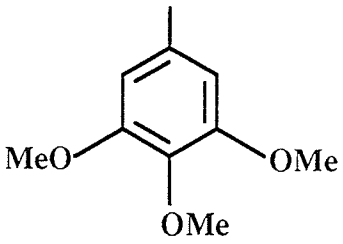


48

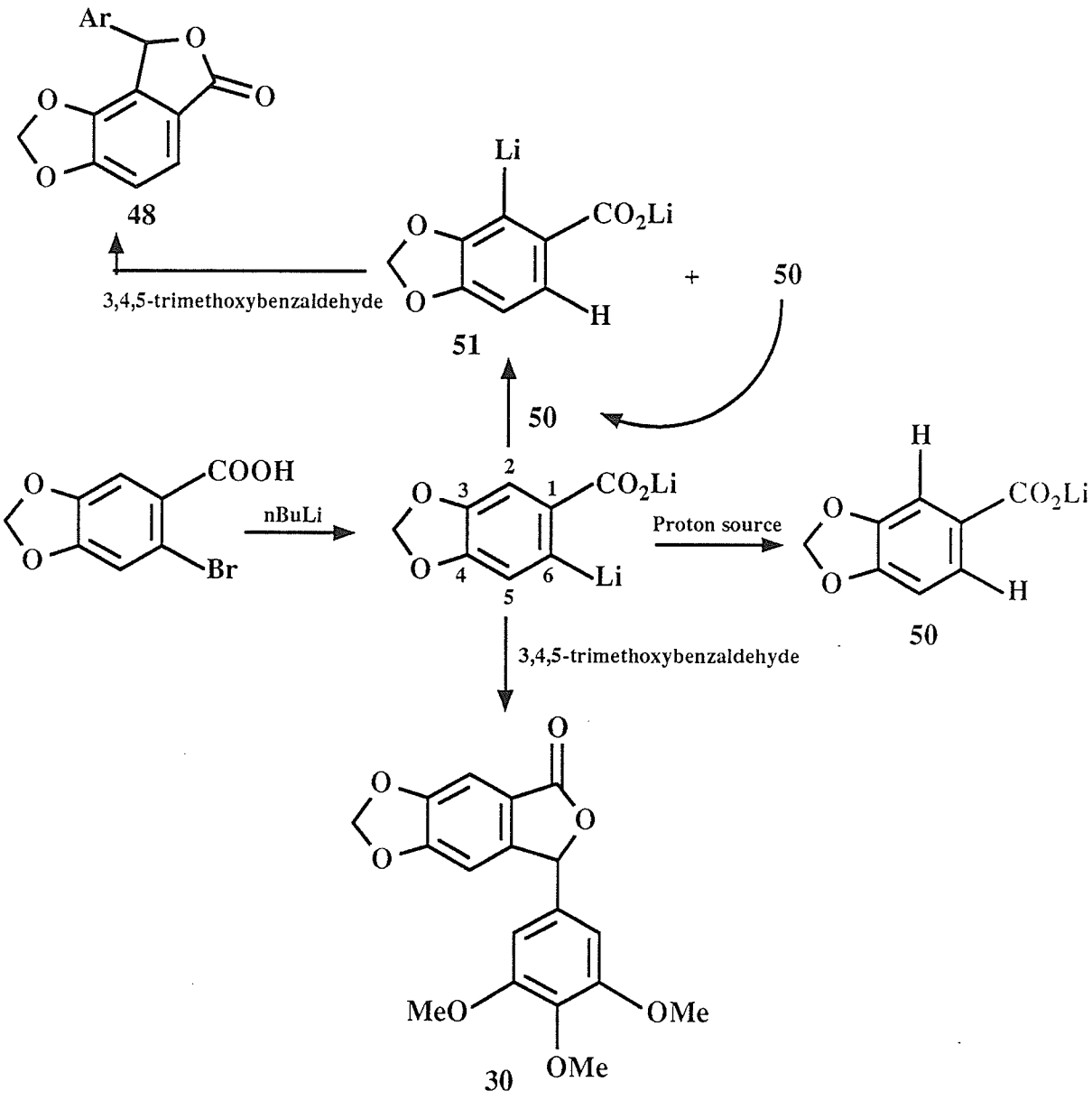


49

Ar =



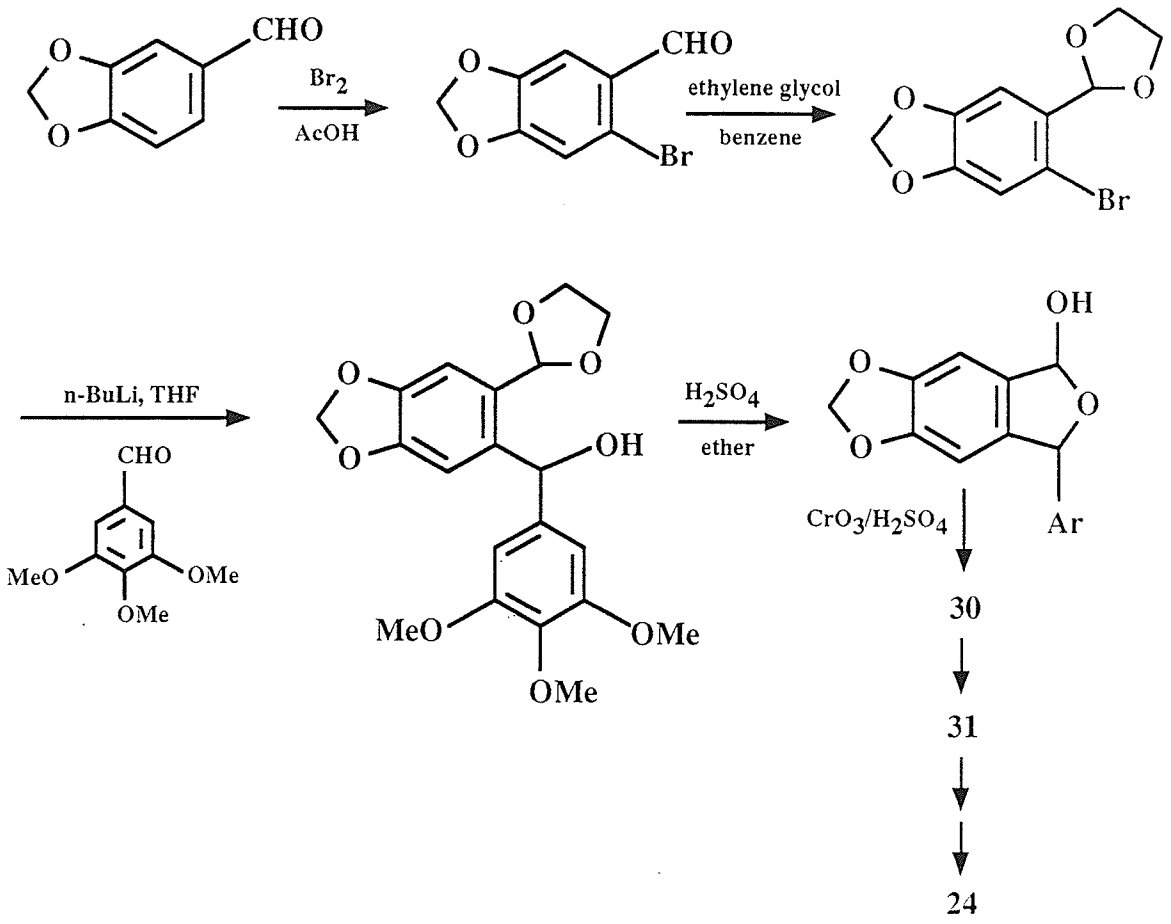
One could explain the results in the context of autometalation. The likely mechanism of formation of all these products is shown in the following Scheme.



The "proton source" could be the acid group on the starting material, the *ortho* hydrogen of the bromopiperonylic acid or traces of moisture. Regardless of its source the formation of lithium piperonylate **50**, provides a relay catalyst for the conversion of the lithium 6-lithiopiperonylate to lithium 2-lithiopiperonylate **51**. Although the experimental procedure was varied, including inverse addition of the *n*-BuLi, little progress was made in decreasing the amount of product arising from the lithium 2-lithiopiperonylate.

A much more satisfactory route **path B** to phthalide **30** was afforded by addition of 1 equivalent of *n*-butyllithium to the ethylene acetal of 6-bromopiperonal.

Path B:

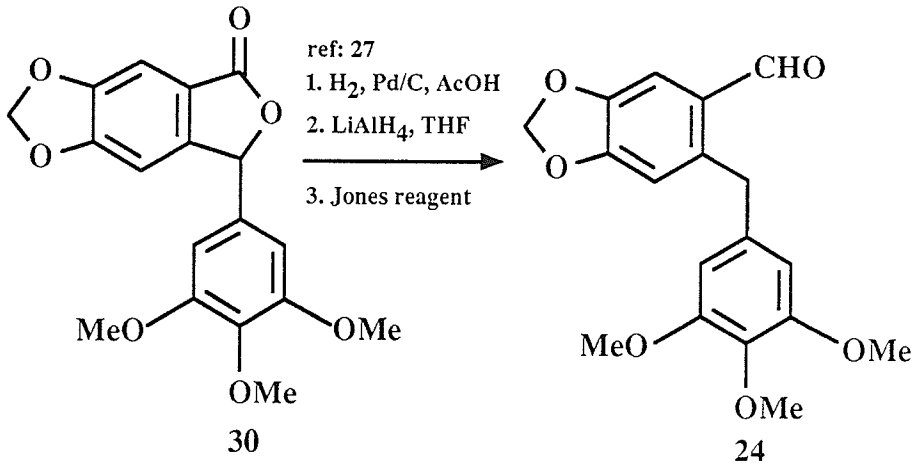


In a one pot synthesis, 3,4,5-trimethoxybenzaldehyde was added to the lithiated acetal to give the alcohol, followed directly by hydrolysis and oxidation to yield the phthalide **30** (57%). In this pathway the formation of 2-lithiopiperonal acetal, which leads to the formation of the undesired lactone **48**, was not observed. The reason for this is unknown but it may be due to a lower pKa for the potential relay catalyst piperonal acetal. The following table shows the comparison between the three methods: Sammes, path A and

path B.

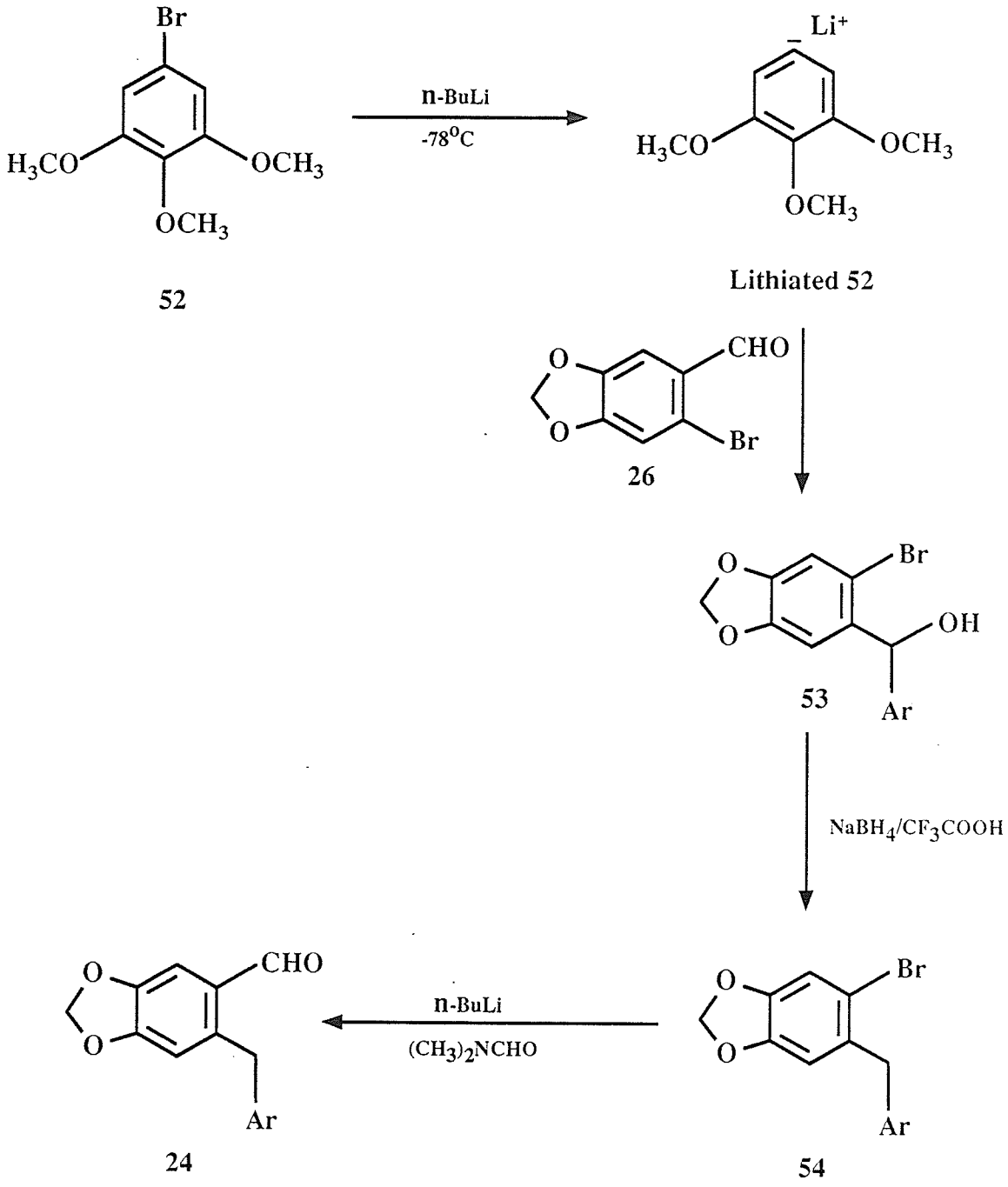
METHOD	NUMBER OF STEPS TO 30	%YIELD
Sammes	6	46.8
Path A	3	30
Path B	5	42

As mentioned previously, phthalide **30** prepared by any of the three methods explained above is the key intermediate in the synthesis of 6-(3,4,5-trimethoxybenzyl)piperonal **24**.



30 **24**

Although paths A and B are preferred to Sammes' original procedure, as they reduce the number of steps required, there was no improvement in yield for phthalide **30**. In a search for a more efficient route to aldehyde **24** a new aryl carbanion scheme was developed which is summarized below.



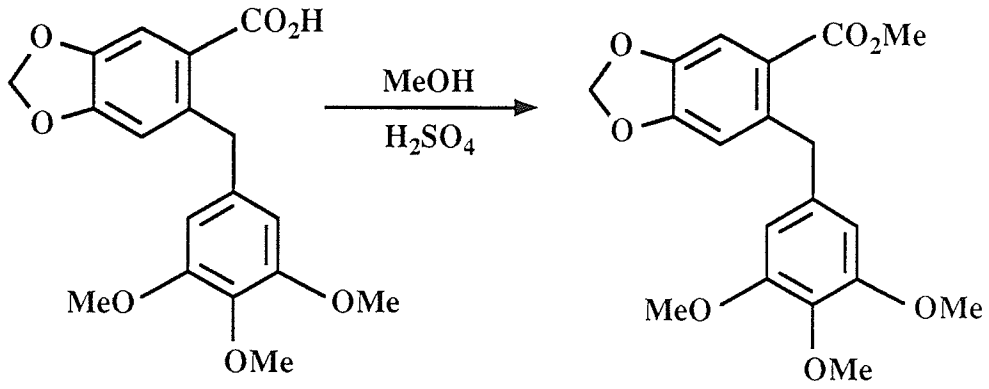
Alcohol **53** was prepared by the reaction of 6-bromopiperonal **26** with lithiated **52** at -78°C in 73% yield. Reduction of the alcohol **53** by the use of sodium borohydride/trifluoroacetic acid yielded the bromo compound **54** in 89% yield.

Halogen-metal exchange (Li-Br exchange) of **54** followed by coupling with N,N-dimethylformamide gave the desired aldehyde **24** in 71% yield. The yields for each step are those obtained after chromatography.

This new procedure was far superior to the routes previously investigated as it involved only three steps and yielded the aldehyde **24** in an overall yield of 46%. In addition, the halogen-metal exchange of **52** and **54** was uncomplicated by isomerization to alternate aryl anions, a problem which occurred in path A discussed above. Each step of the synthesis proceeded in high yield with only routine chromatography needed for purification of the products.

2.2 Synthesis of Aryltetralin Lignan Analogs

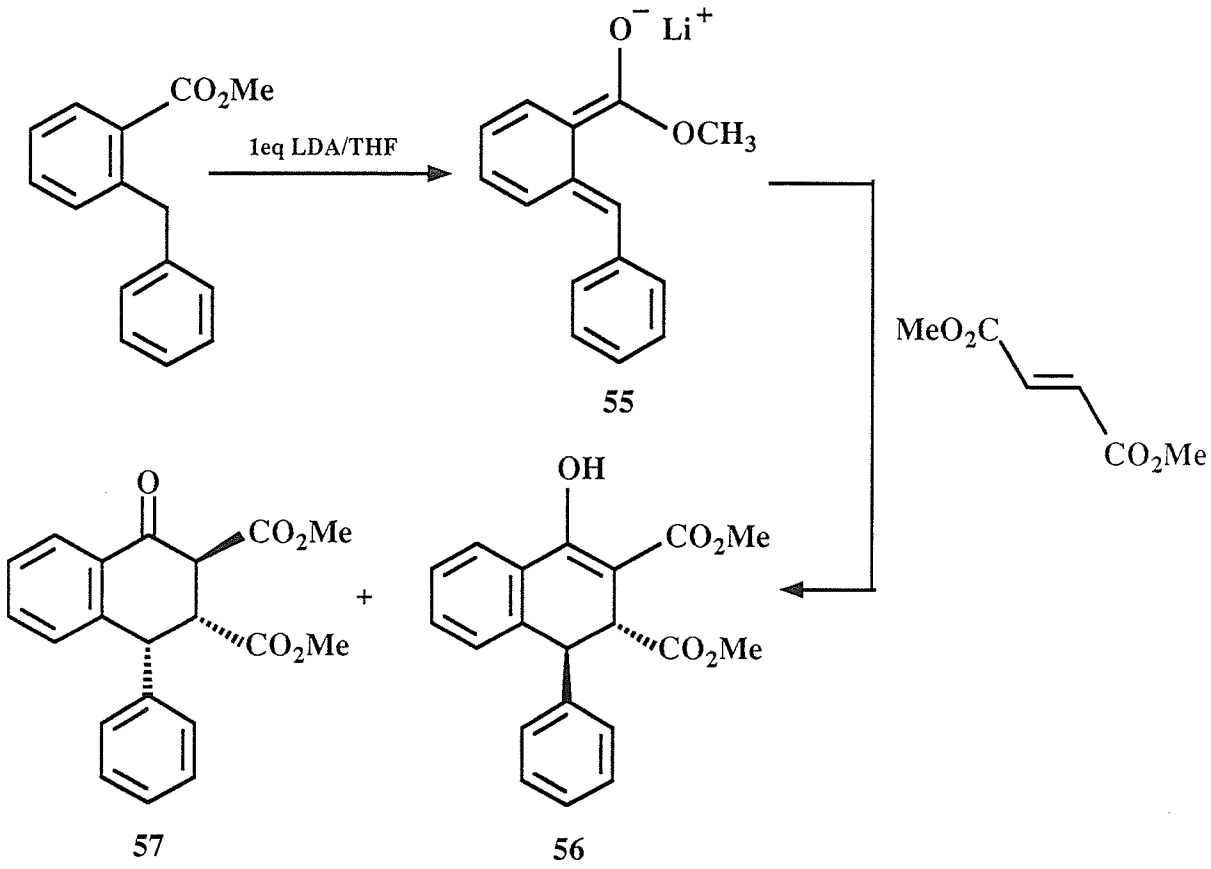
As previously explained, one strategy for the synthesis of aryltetralin lignans is via a Diels-Alder reaction of an *o*-QDM. Photoenolization of *ortho*-substituted benzaldehydes as a tool for generation of α-hydroxy-*o*-QDMs followed by trapping of the reactive intermediate with various dienophiles has been a very attractive concept to organic chemists. A complication that can arise in these photochemical reactions is the possibility that the dienophile itself is photoreactive as seen in photoisomerization of fumarate to maleate. As a result, as mentioned in the introduction, it was of interest to investigate if one could generate dienolates such as **6** (on page 10) having a reactivity in addition reactions similar to *o*-QDMs, by base abstraction of the benzylic hydrogen from *o*-alkyl benzaldehyde or the corresponding ester of the *o*-alkyl toluic acid. Furthermore, if this new strategy were indeed successful, one might apply it to the corresponding ester (**31 E**) of the acid **31** whose synthesis was described in the previous chapter.



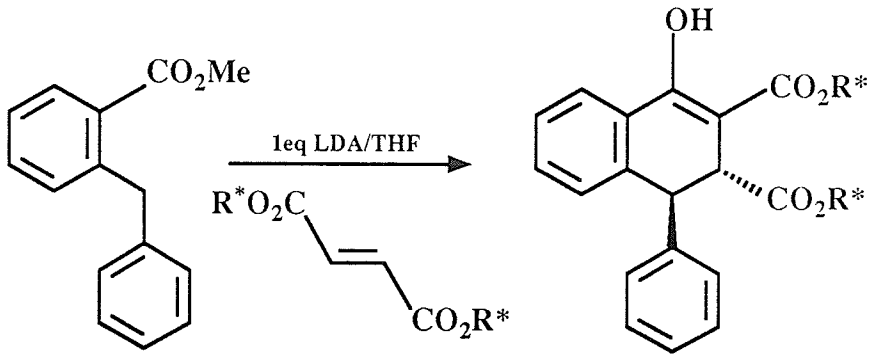
31 **31 E**

The ester **31 E** (81%) was prepared by refuxing the acid **31** in methanol and traces of concentrated sulfuric acid .

As a starting point for the study of anionic α-oxy-*o*-QDMs, the deprotonation of *o*-benzylbenzaldehyde was considered. Attempts to abstract the benzylic proton using lithium tetramethylpiperidide followed by reaction with methyl iodide or dimethyl fumarate were unsuccessful, yielding only recovered starting materials. This lack of success in forming the benzylic anion directed attention towards the ester of the *o*-benzylbenzoic acid. Fortunately it was possible to abstract a hydrogen from the benzylic position by use of 1 equivalent of lithium diisopropylamide in THF at -78°C. Thus dimethyl fumarate was added to a tetrahydrofuran solution of anion **55** (obtained from the reaction of lithium diisopropylamide (LDA) with methyl *o*-benzylbenzoate) and the resulting solution left to stir overnight. Following the usual ammonium chloride work up, the residue was chromatographed to afford a solid, **56** (42%) and an oil, tentatively assigned structure **57** (10%).

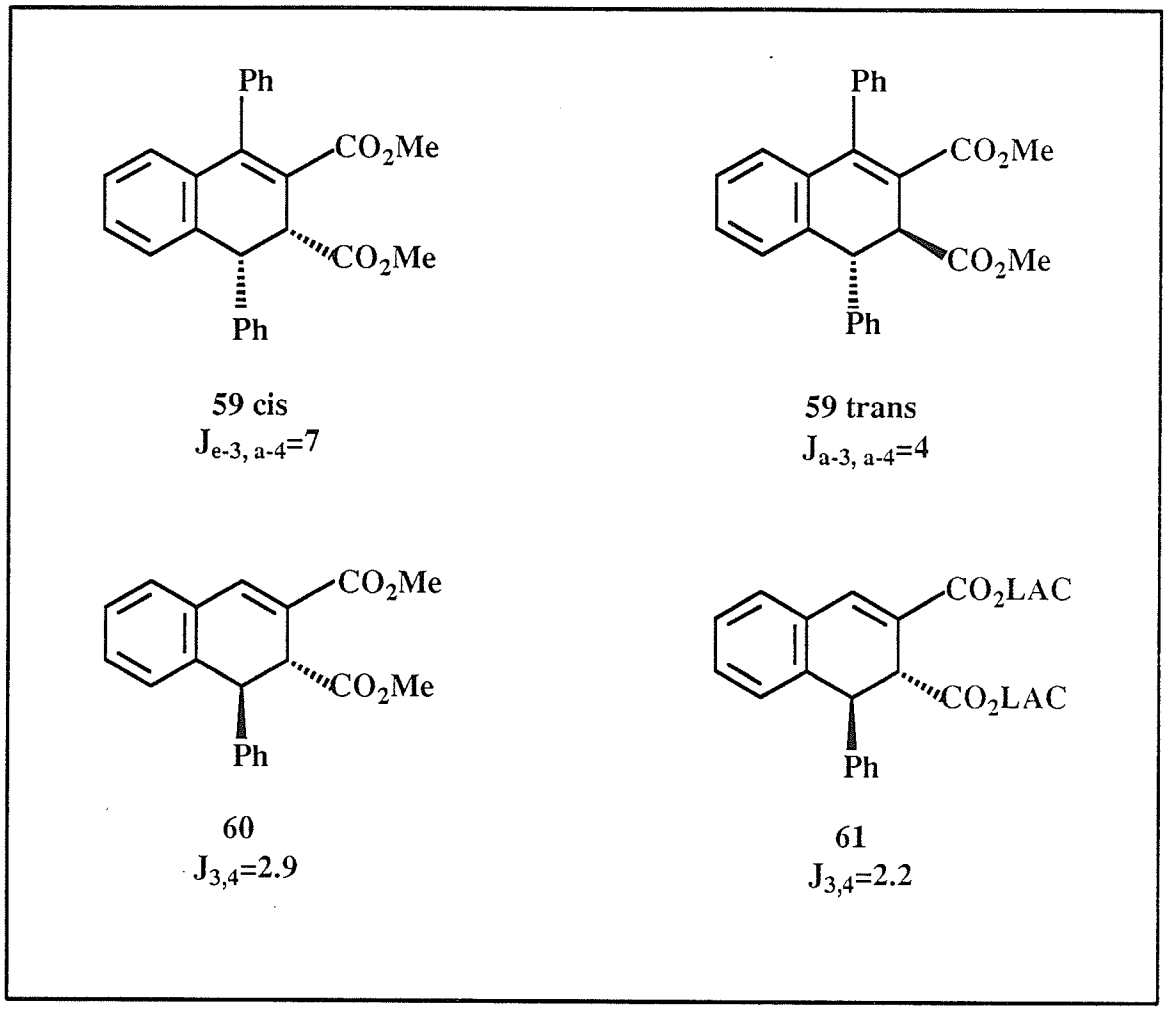


The same reaction was carried out using dilactyl fumarate as the Michael acceptor and on the basis of ^{1}H-nmr analysis it was identified as compound **58** (14%).



R^{*}= -$CH(CH_3)CO_2CH_3$ **58**

Compound **56** and **58** exhibit a $J_{3,4}$ of 1.86 and 1.95 Hz respectively. These data are in agreement with Pfau who found a $J_{3,4}$ of 4 Hz for the similar compound **59 trans** and 7 Hz for the corresponding cis isomer **59 cis**[36]. Other examples of *trans* coupling constants are given in the work of Charlton *et al.* who found a $J_{3,4}$ of 2.9 Hz for compound **60**[37] and in the work of Plourde who found a $J_{3,4}$ of 2.2 Hz for compound **61**[11]. Compound **57** exhibits a $J_{2,3}$ of 12.9 Hz establishing the *trans* diequatorial stereochemistry of the two ester groups. A $J_{3,4}$ of 7 Hz would be most consistent with a *cis* stereochemistry for the phenyl and the neighboring ester group.

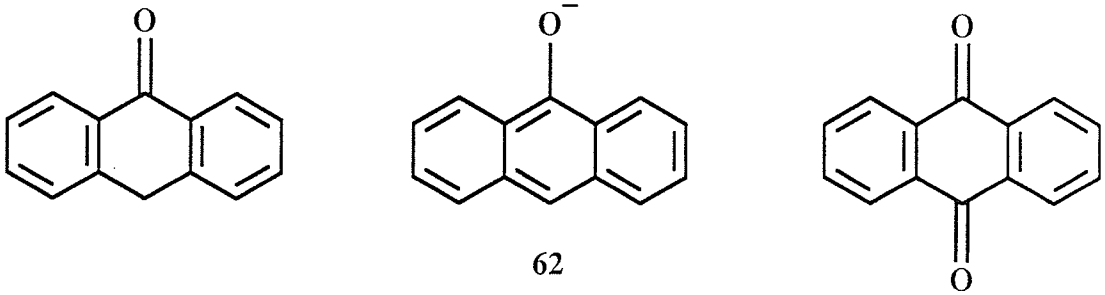


The relative stereochemistry of the products **56** and **58** can be accounted for by either a concerted Diels-Alder reaction or a conjugate addition (tandem Michael addition-Dieckmann condensation) between anion **55** and the fumarate Michael acceptor via the *endo* mode transition state in which the oxygens of the diene and dienophile may be coordinated to the metal cation. As was mentioned in chapter 1, Li^+ may act as a Lewis acid, and by coordinating to the dienophile it lowers the energy of the LUMO. As a consequence the value of $E_{LUMO(dienophile)}$-$E_{HOMO(diene)}$ decreases, resulting in an increase in the rate of reaction. Furthermore, the LUMO coefficent on the carbonyl carbon increases compared to the non-catalyzed case and this in turn makes the secondary orbital

interaction greater which would result in greater *endo* selectivity[7].

2.3 Base-Catalyzed Reactions of Anthrones with Dienophiles

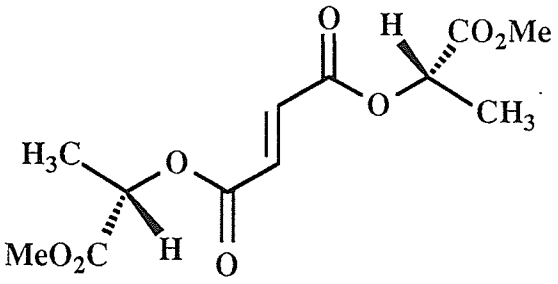
Anthrone in the presence of an amine forms an anion which is an analogue of the anionic α-oxy-*o*-QDM. The generated "1-oxido diene" **62** undergoes Diels-Alder reactions with various dienophiles. In the present study the asymmetric reaction of anthrone with the fumarate of (S)-methyl lactate was investigated. Dilactyl fumarate was added to a solution of anthrone and triethylamine in THF and the mixture stirred for 3 hours at room temperature. Upon evaporation a yellow viscous oil was obtained. Column chromatography afforded a single cycloadduct in 77% yield. The nmr (300 MHz) of the crude product exhibited no signals consistent with the presence of the other diastereomeric cycloadducts. The only other product was anthraquinone, which probably arises from air oxidation of the anthrone or the oxyanion.



62

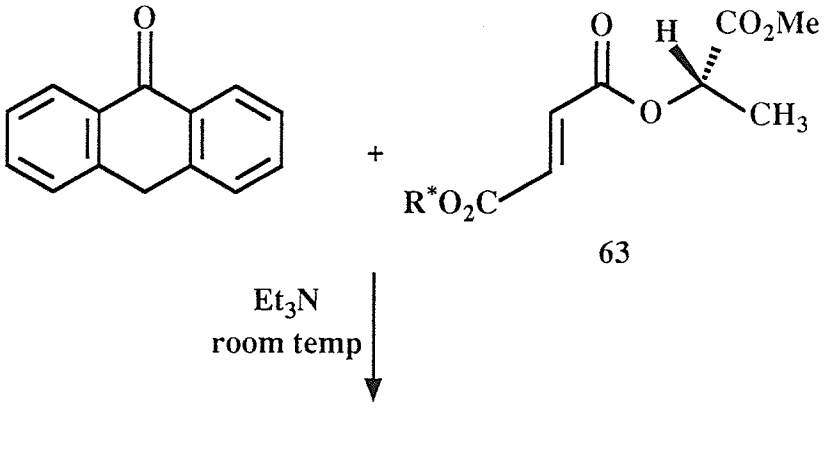
Anthrone **Anthrone anion** **Anthraquinone**

According to Helmchen *et al.* the most stable conformation of the fumarate of S-methyl lactate is that shown in structure **63**, and addition of dienes to this dienophile occurs to the less hindered top (*re*) face[35].



63

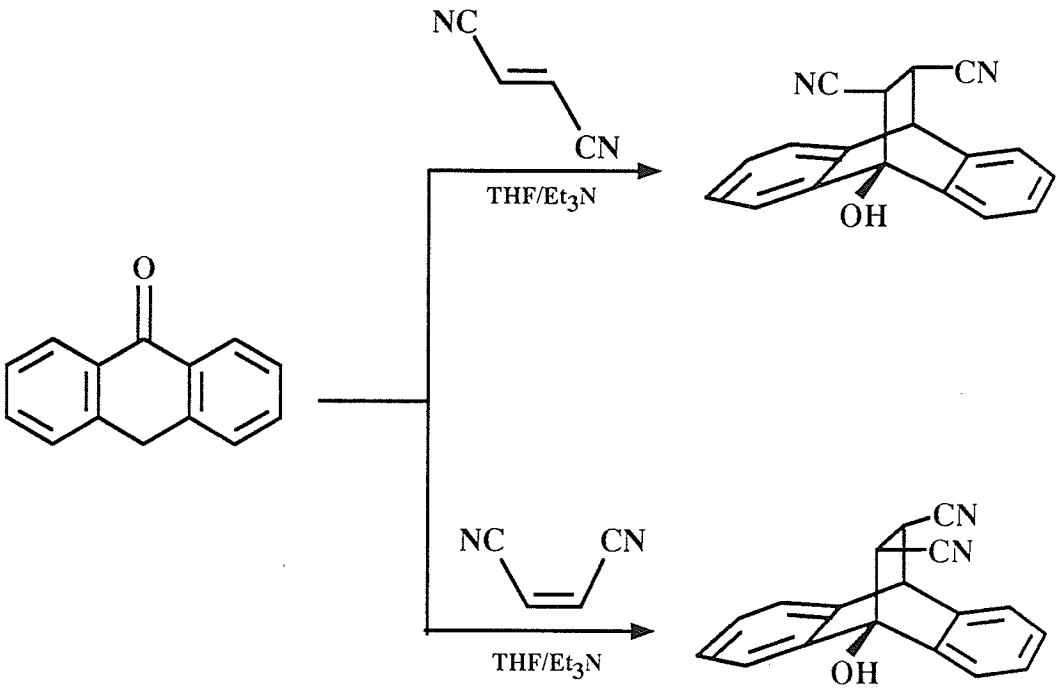
The absolute configuration of the cycloadduct was assigned structure **45**, assuming that addition to the fumarate occurred to the *re* face as has been found in other asymmetric additions to this compound[38].



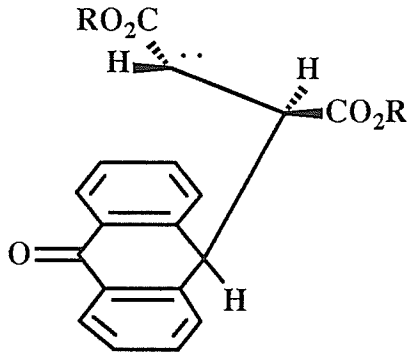
63

45

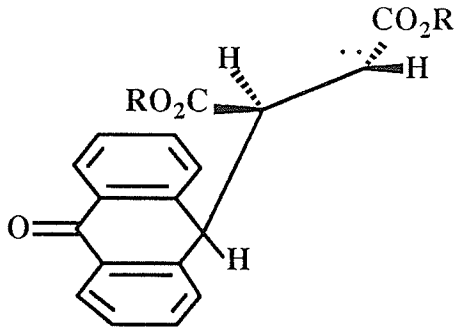
The retention of dienophile geometry was consistent with the work of Koerner and Rickborn who found that the formation of cycloadducts from anthrone and disubstituted dienophiles is stereospecific as is shown in the following example[32].



The stereospecificity of cycloaddition requires either a concerted Diels-Alder mechanism, or a stepwise process in which the second (ring closure) step is much faster than rotation about the single bond (former double bond) generated by Michael addition to the dienophile. This outcome would seem to require that the Michael addition occur to give the *syn* intermediate rather than the *anti* intermediate.



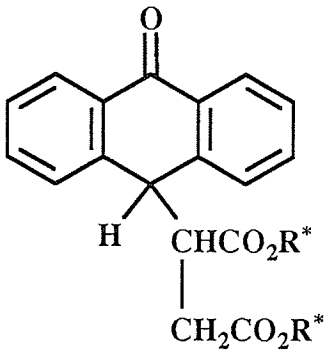
Syn



Anti

In order for the *anti* intermediate to undergo ring closure, 180° rotation about the C(10)-dienophile bond must occur. Previous workers have often discussed the sequential Michael reaction in those cases where a metal cation such as lithium is present to which the oxygens of the diene and the dienophile are chelated. In the present study triethylammonium ion does not fall under the same interpretation and shows that a stereospecific reaction is also possible in the absence of an oxygen chelator. Although this stereospecific reaction could be regarded as an anion-accelerated Diels-Alder reaction, the stepwise (Michael+aldol) could not be ruled out.

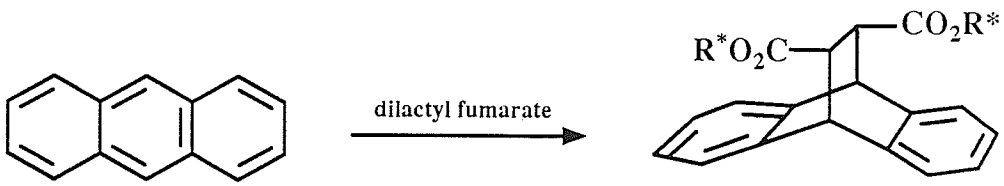
The reaction of anthrone and dilactyl fumarate was also performed at 85°C. The crude product was a brown viscous oil and upon purification it afforded a colorless oil in 68% yield. The product was assigned the structure **64**. The ^{1}H-nmr showed the presence of two sets of double doublets which would correspond to the two diastereotopic protons in the Michael adduct **64**.



64

The Michael adduct **64** probably arises from a retro Claisen reaction of the cycloadduct **45**. It was subsequently shown that **45** converts to **64** upon heating.

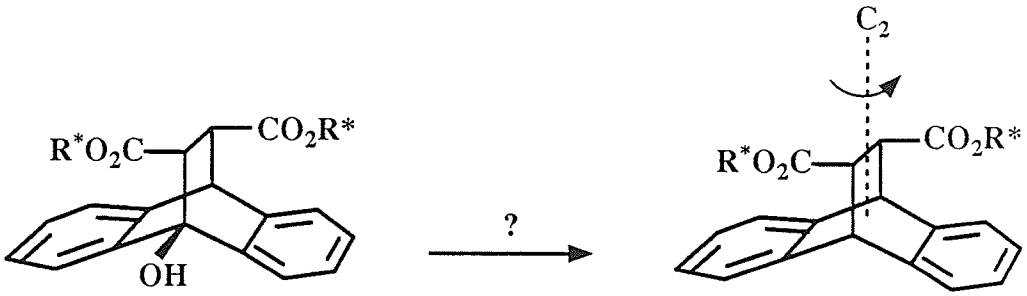
Previously Helmchen *et al.* reported high diastereoselectivity in the Diels-Alder reaction of anthracene and the fumarate of (S)-ethyl lactate[35]. In the present work the same procedure was applied and anthracene and the fumarate of (S)-methyl lactate were refluxed in xylene for 6 days. Upon evaporation of solvent, followed by a combination of chromatography and recrystallization a yellow solid was obtained (58%) which was assigned structure **65**.



65

The high asymmetric induction which was seen in the cycloaddition reaction of anthrone and the fumarate of (S)-methyl lactate stimulated an interest in the possibility of

generating the anthracene cycloadduct **65** by hydrogenolysis of **45**. Anthracenes as compared to anthrones have modest activity as dienes, and they would normally require higher temperatures for Diels-Alder reactions. These higher temperatures are undesirable in asymmetric reactions since diastereoselectivity decreases with increasing temperature.

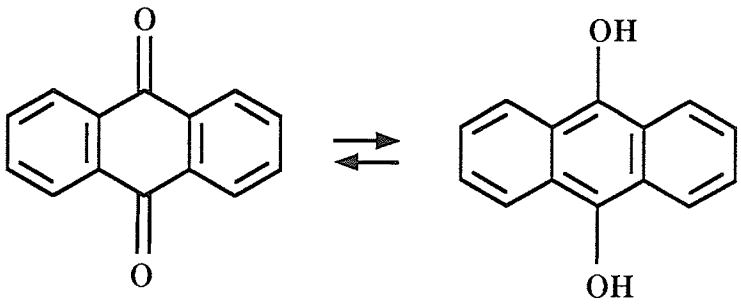


45 **65**

Optically pure molecules such as the cycloadduct **65** which possess a C_2 symmetry axis might have a potential as chiral auxiliaries in other asymmetric reactions. In general, the presence of a symmetry element such as a C_2 axis in a chiral auxiliary increases asymmetric induction by reducing the number of competing diastereomeric transition states.

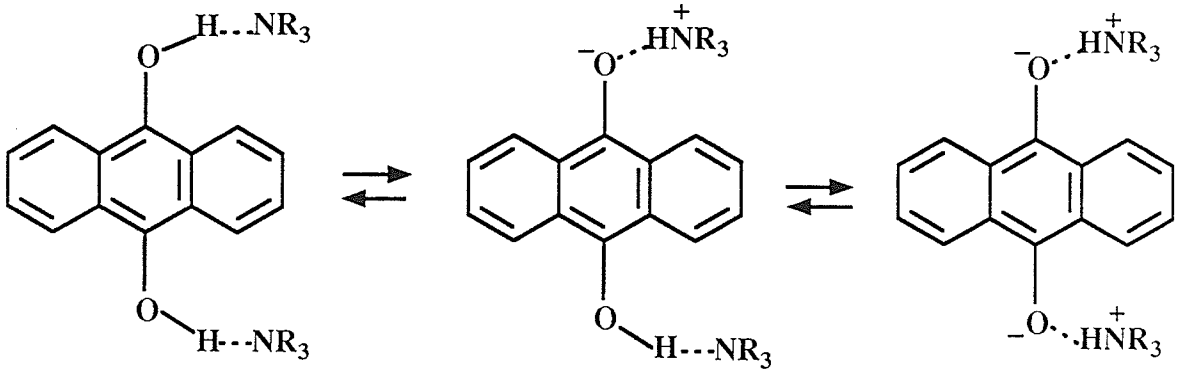
Hydrogenolysis of **45** with palladised charcoal as catalyst in 50% acetic acid/methanol at room temperature was not successful and only starting material was recovered. Repeating the experiment in glacial acetic acid and at higher temperatures was also unsuccessful. Attempts to remove the hydroxy group by use of $NaBH_4/CF_3COOH$ did not change the outcome of the reaction, and again the starting material was recovered.

Recently, it has been found that anthraquinone is readily reduced to the hydroquinone (9,10-anthracenediol) **66**, which under basic conditions serves as a reactive diene for cycloaddition purposes[39].



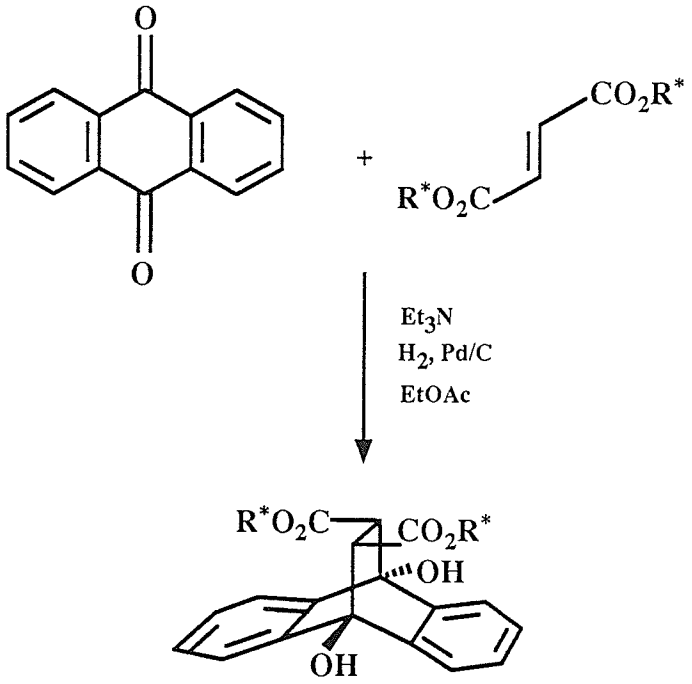
66

The catalytic reduction of anthraquinone in pyridine was assumed by Koerner and Rickborn to be analogous to the base-catalyzed reactions of anthrone and that hydrogen bonded species such as below are formed.



The lack of success in the preparation of a C_2 symmetric chiral molecule via the anthrone cycloaddition reaction directed attention towards the anthraquinone route. Hence, anthraquinone was hydrogenated at room temperature with palladised charcoal as catalyst and triethylamine in ethyl acetate. The quinone was stirred under H_2 for 0.5 h, after which the atmosphere was replaced by N_2, and then the fumarate of (S)-methyl lactate was introduced. The separation of the reduction and cycloaddition steps avoided the possibility of competitive reduction of the dienophile. The reaction was followed by tlc, at the end of which the mixture was suction filtered and the filtrate was evaporated

under vaccum to obtain a yellowish oil. Column chromatography afforded a single cycloadduct in 61% yield. The nmr of the crude product exhibited no signals consistent with the presence of the other diastereomeric cycloadducts. The absolute configuration of the cycloadduct was assigned structure **67**, assuming as before that addition of the fumarate occurred to the *re* face.



67

Molecule **67** should be an interesting candidate as a starting material for C_2-symmetric catalysts and/or reagents. The OH groups may have to be converted to OMe to avoid the possibility of retro-aldol reactions before further functional group modification of the ester groups is attempted.

Chapter 3

EXPERIMENTAL

Melting points were determined on a hot stage instrument and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer 881 spectrometer. ^{1}H-nmr spectra were recorded on a Bruker AM-300 instrument using tetramethylsilane as internal standard. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broadened. Exact mass/mass spectra were obtained on an Analytical V6 7070E-HF instrument. Analytical thin layer chromatography (tlc) were carried out on precoated silica gel sheets, 60 F_{254} (EM reagents) of 0.2 mm thickness. Merck Kieselgel 60 or Aldrich (230-400 mesh, 60Å) silica gel was used for all column chromatography.

o-Benzylbenzaldehyde **5**:

This compound was prepared according to the literature procedure[43].
To a suspension of $LiAlH_4$ (1.8 g, 47 mmol) in diethyl ether (50 mL) was slowly added at 0°C a solution of α-phenyl-o-toluic acid (10 g, 47 mmol). The solution was then refluxed for one hour, cooled, and water (1.8 mL) was added followed by 15% aqueous sodium hydroxide (1.8 mL) and water (5.4 mL). The white precipitate was filtered, washed with ethyl acetate and the combined filtrates evaporated to afford a colorless oil (8.7 g). The oil was dissolved in diethyl ether (65 mL) and a solution of chromium trioxide (5%) in 10% H_2SO_4 was slowly added at 0°C. The mixture was vigourously stirred for 30 minutes. Organic and aqueous layers were separated and the aqueous layer was extracted

with diethyl ether. The organic fractions were combined, washed with aqueous sodium bicarbonate (5%), dried ($MgSO_4$) and evaporated to afford a yellow oil (7.6 g, 82%) IR (CH_2Cl_2) cm^{-1}: 1698 (CO). ^{1}H-nmr ($CDCl_3$) δ: 10.24 (s,1H, CHO), 7.1-7.8 (m, 9H, aromatics), 4.44 (s, 2H, CH_2). The ^{1}H-nmr spectrum is shown in Appendix 1.

Methyl o-benzylbenzoate:

α-Phenyl-o-toluic acid (0.369 g, 1.73 mmol) was refluxed in methanol (50 mL) with concentrated sulfuric acid (few drops) for 2 days. The bulk of the methanol was evaporated to afford a brownish oil. The product was dissolved in methylene chloride and was washed with aqueous sodium bicarbonate (5%). The organic layer was dried ($MgSO_4$) and solvent was evaporated to afford a colourless oil (0.287 g, 73%). IR (CH_2Cl_2) cm^{-1}: 1726 (CO). ^{1}H-nmr ($CDCl_3$) δ: 7.1-7.8 (m, 9H, aromatics), 4.37 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3). The ^{1}H-nmr spectrum is shown in Appendix 1.

6-Bromopiperonal **26***:*

This compound was prepared according to the literature procedure[40].
To a solution of piperonal (5.23 g, 34.8 mmol) in acetic acid (40 mL) was added Br_2 (11.1 g, 69.4 mmol). The solution was stirred overnight at room temperature. An equal volume of water was added to the reaction mixture and the solution was cooled for four hours. The solution was filtered, the precipitate washed with 60% water/acetic acid and then recrystallized from ethyl acetate/hexane to give colourless needles (6.34 g, 80%, mp: 127-129°C).
^{1}H-nmr ($CDCl_3$) δ: 10.18 (s, 1H, CHO), 7.36 (s, 1H, aromatic), 7.06 (s, 1H, aromatic), 6.08 (s, 2H, O-CH_2-O). The ^{1}H-nmr spectrum is shown in Appendix 1.

6-Bromopiperonal Ethylene Acetal **27***:*

This compound was prepared according to the literature procedure[27]. 6-Bromopiperonal (7.68 g, 33.5 mmol) and ethylene glycol (4.60 g, 74.0 mmol) were heated in refluxing benzene (80 mL) containing a trace of *p*-toluenesulphonic acid, under a Dean-Stark trap. After 24 h the mixture was cooled, and filtered through a short silica gel column using 15% ethyl acetate/hexane as eluant. The solvent was evaporated to afford crystals of the acetal (8.43 g, 92%, mp: 68-69°C).

^{1}H-nmr ($CDCl_3$) δ: 7.1 (s, 1H, aromatic), 7.03 (s, 1H, aromatic), 5.96 (s, 2H, O-CH_2-O), 5.86 (s, 1H, acetal), 4.1 (s, 4H, O-CH_2-CH_2-O).

5,6-Methylenedioxy-3-(3,4,5-trimethoxyphenyl)phthalide **30**:

METHOD A:

To a solution of tetramethylethylenediamine (0.125 mL, 0.828 mmol) in tetrahydrofuran (2 mL) was added *n*-butyllithium in hexanes (2.4 M, 0.43 mL, 1.03 mmol) at -78°C under N_2(g). 6-Bromopiperonylic acid (0.102 g, 0.416 mmol) in tetrahydrofuran (4 mL) was added followed by addition of 3,4,5-trimethoxybenzaldehyde (0.082 g, 0.419 mmol) in tetrahydrofuran (3 mL). The solution was stirred at -78°C for 1/2 hour then at room temperature for 3 hours. 5% aqueous ammonium chloride (10 mL) was added followed by enough 10% HCl to lower the pH to 2. The solution was stirred overnight, extracted with methylene chloride, dried ($MgSO_4$), and evaporated to afford a yellowish solid. Trituration with 50% ethyl acetate/hexane afforded colourless crystals of the pure lactone (0.066 g, 46%, mp: 217-223°C).

IR (Nujol) cm^{-1}: 1764 (CO). ^{1}H-nmr ($CDCl_3$) δ: 7.24 (s, 1H, aromatic), 6.68 (s, 1H, aromatic), 6.45 (s, 2H, aromatics), 6.16 (s, 1H, benzylic H), 6.11 (s, 2H, O-CH_2-O), 3.83 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3). The ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): exact mass calculated for $C_{18}H_{16}O_7$: 344.0896, found: 344.0895. Spectral details are identical to those reported in the literature[27].

METHOD B:

To a solution of 6-bromopiperonal ethylene acetal (0.133 g, 0.487 mmol) and tetramethylethylenediamine (0.15 mL, 0.994 mmol) in tetrahydrofuran was added *n*-butyllithium in hexanes (2.4 M, 0.243 mL, 0.583 mmol), at -78°C under nitrogen, over a period of 2 min. After a further 2 min, a solution of 3,4,5-trimethoxybenzaldeyde (0.115 g, 0.584 mmol) in tetrahydrofuran was added dropwise at -78°C and the reaction mixture stirred for 30 min at that temperature. The reaction mixture was then allowed to warm to room temperature while stirring overnight. Ether (15 mL) and 10% H_2SO_4 (15 mL) was added and the solution was stirred for an additional 15 minutes. A solution of chromium trioxide (5%) in 10% aqueous H_2SO_4 was slowly added at 0°C and the reaction mixture stirred for an additional 1/2 hour. The layers were separated and the aqueous phase was extracted with ether. The organic fractions were combined, dried ($MgSO_4$) and evaporated to give a red oil. Recrystallization from ethyl acetate/hexane afforded a colorless solid (0.095g, 57%, mp: 217-223°C).

6-(3,4,5-Trimethoxybenzyl)piperonylic acid **31**:

This compound was prepared according to the literature procedure[27].
The phthalide (2.90 g, 8.41 mmol) in acetic acid (100 mL) was hydrogenolysed over 5% palladium-charcoal (1 g) at atmospheric pressure at 110°C for 2 days. The solution was filtered and the solvent evaporated to give a yellowish oil. The product was dissolved in methylene chloride and washed with aqueous sodium bicarbonate (5%). The aqueous layer was acidified with 10% HCl and was extracted with methylene chloride. The organic layer was dried ($MgSO_4$) and the sovent evaporated to afford a colourless solid (2.19 g, 75%, mp: 98-99°C).

IR (CH_2Cl_2) cm^{-1}: 1695 (CO). ^{1}H-nmr ($CDCl_3$) δ: 11.9 (br, 1H,CO_2H), 7.53 (s, 1H,

aromatic), 6.65 (s, 1H, aromatic), 6.39(s, 2H, aromatic), 6.02 (s, 2H, O-CH_2-O), 4.32 (s, 2H, benzylic H), 3.82 (s, 3H, OCH_3), 3.80 (s, 6H, OCH_3). The ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): exact mass calculated for $C_{18}H_{18}O_7$: 346.1052, found: 346.1046.

Methyl 6-(3,4,5-trimethoxybenzyl)piperonylate **31 E**:

This compound was prepared according to the literature procedure[27]. 6-(3,4,5-Trimethoxybenzyl)piperonylic acid (2.01 g, 5.81 mmol) was refluxed in methanol (100 mL) with concentrated sulfuric acid (0.5 mL) for 3 days. The bulk of the methanol was evaporated to afford a yellowish solid. The product was dissolved in methylene chloride and was washed with aqueous sodium bicarbonate (5%). The organic layer was dried ($MgSO_4$) and solvent was evaporated to afford a yellowish solid (1.77 g, 85%). Recrystallization from methylene chloride gave colourless crystals (mp: 97-99°C). IR (Nujol) cm^{-1}: 1714 (CO). ^{1}H-nmr ($CDCl_3$) δ: 7.40 (s, 1H, aromatic), 6.62 (s, 1H, aromatic), 6.39 (s, 2H, aromatic), 5.99 (s, 2H, O-CH_2-O), 4.27 (s, 2H, benzylic H), 3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.80 (s, 6H, OCH_3). The ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 360(100), 345(7), 328(25), 313(42), 297(90), 285(14), 270(19), 254(10), 242(11), 227(11), 199(6), 177(15), exact mass calculated for $C_{19}H_{20}O_7$: 360.1209, found: 360.1185.

Anthrone Cycloadduct **45**:

To a solution of anthrone (0.509 g, 2.62 mmol) in dry tetrahydrofuran (30 mL) was added at room temperature, dilactyl fumarate (0.830 g, 2.88 mmol) in tetrahydrofuran and triethylamine (1.2 mL, 8.6 mmol) under N_2(g). The solution was stirred for 5 hrs. The solvent was evaporated and the crude product was purified by chromatography on silica gel using 20% ethyl acetate/hexane as eluant to afford a colourless solid (0.973 g, 77%).

Recrystallization from ethyl acetate/hexane gave colourless needles (mp: 114-117°C). $[\alpha]_D$=-41.4° (c: 1.13, $CHCl_3$). IR (Nujol) cm^{-1}: 3459 (OH), 1730 (CO). ^{1}H-nmr ($CDCl_3$) δ: 7.1-7.7 (m, 8H, aromatic), 5.71 (s, 1H; OH), 5.18 (q, 1H, J=7.1, CH), 5.01 (q, 1H, J=7.1, CH), 4.77 (br s, 1H, benzylic H), 3.82 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.44 (br s, 2H), 1.51 (d, 3H, J=7.1, CH_3), 1.43 (d, 3H, J=7.1, CH_3). The ^{1}H-nmr specrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 482(1), 194(100), 185(50), 165(43), 149(4), 140(7), 129(8), 113(15), 99(16), 87(89), 69(16), 55(32), exact mass calculated for $C_{26}H_{26}O_9$: 482.1576, found: 482.1563.

6-Bromopiperonylic acid **47**:

This compound was prepared according to the literature procedure[40].
To a solution of 6-bromopiperonal (0.06 g, 0.28 mmol) in acetone (2 mL) and water (7 mL) was added potassium permanganate (0.06 g). The solution was refluxed for three hours, and then decolorized by addition of saturated aqueous sodium bisulfite. The acetone was evaporated on a rotary evaporator, the solution made basic by addition of concentrated sodium hydroxide (aq) and then extracted with methylene chloride. The aqueous layer was acidified with 10% HCl and again extracted with methylene chloride. The organic layer was dried ($MgSO_4$) and solvent evaporated to afford a white solid (0.055 g, 81%, m.p: 199-200°C).
^{1}H-nmr ($CDCl_3$) δ: 7.37 (s, 1H, aromatic), 7.18 (s, 1H, aromatic), 6.16 (s, 2H, O-CH_2-O).

α-*(3,4,5-Trimethoxyphenyl)-6-bromobenzo-1,3-dioxole-5-methanol* **53**:

A solution of arylbromide (0.608 g, 2.46 mmol) in dried tetrahydrofuran (20 mL) was cooled to -78°C under nitrogen and *n*-butyllithium (1.735 M, 1.43 mL) was added dropwise. The solution was allowed to stir for another 5 minutes at -78°C and a solution of 6-bromopiperonal (0.834 g, 3.64 mmol) in dried tetrahydrofuran (20 mL) was added at

a fast rate. After stirring at -78°C for one hour, the solution was allowed to warm to room temperature while stirring. The solution was quenched with saturated ammonium chloride solution. The mixture was saturated with sodium chloride and the organic phase was separated. The aqueous phase was extracted with methylene chloride. The combined organic phase were dried ($MgSO_4$) and evaporated to afford a yellow oil. The crude oil was chromatographed on silica gel using 20% ethyl acetate/hexane as eluant to afford a yellow oil (0.712 g, 73%).

^{1}H-nmr ($CDCl_3$) δ: 6.95 (s, 1H, aromatic), 6.93 (s, 1H, aromatic), 6.61 (s, 2H, aromatic), 6.02 (s, 1H, benzylic), 5.91-5.93 (ABq, 2H, J=1.2, O-CH_2-O), 3.80 (s, 9H, OCH_3), 3.05 (brs, 1H, OH). ^{1}H-nmr spectrum is shown in Appendix 1 and is identical to those reported in the literature[42].

Compound **54**:

A mixture of alcohol **53** (0.584 g, 1.46 mg) in dry methylene chloride (15 mL) and powdered sodium borohydride (18 eq) was added in portions to trifluoroacetic acid (20 mL) at 0°C under a stream of nitrogen with vigorous stirring. After stirring for 15 minutes at 0°C, saturated sodium bicarbonate solution was added and the organic phase was separated. The aqueous phase was saturated (NaCl) and extracted with methylene chloride. The combined organics were dried ($MgSO_4$) and solvent evaporated to yield a pale yellow solid. The crude solid was purified by chromatography on silica gel using 20% ethyl acetate/hexane as eluant to afford white crystals (0.496 g, 89%, mp: 124-128^{O}C).

^{1}H-nmr ($CDCl_3$) δ: 7.03 (s, 1H, aromatic), 6.60 (s, 1H, aromatic), 6.40 (s, 2H, aromatic), 5.94 (s, 2H, O-CH_2-O), 3.94 (s, 2H, benzylic), 3.83 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3). The ^{1}H-nmr spectrum is shown in Appendix 1. Mass spectrum, *m/e* (rel %): 382(12) 380(14), 270(29), 208(48), 185(54), 152(37), 135(21), 87(100), exact mass calculated for

$C_{17}H_{17}O_5{}^{79}Br$: 380.0259, found: 380.0234.

6-(3,4,5-Trimethoxybenzyl)piperonal **24**:

Bromide **54** (0.206 g, 0.541 mmol) in dry tetrahydrofuran (20 mL) was cooled to -78°C under nitrogen. *n*-Butyllithium in hexanes (1.73 M, 0.35 mL) was added dropwise over a period of five minutes followed by addition of N,N-dimethylformamide (0.13 mL) and the mixture was stirred at -78°C for half hour. The mixture was removed from the cold bath and stirred at room temperature for five minutes, at the end of which saturated ammonium chloride solution was added. The organic phase was separated and the aqueous phase was extracted with methylene chloride. The combined organics were dried ($MgSO_4$) and solvent evaporated to afford a yellow oil. The crude oil was chromatographed on silica gel using 35% ethyl acetate/hexane as eluant to afford a colorless oil (0.126 g, 71%).

^{1}H-nmr ($CDCl_3$) δ: 10.15 (s, 1H, CHO), 7.34 (s, 1H, aromatic), 6.69 (s, 1H, aromatic), 6.33 (s, 2H, aromatic), 6.04 (s, 2H, O-CH_2-O), 4.29 (s, 2H, benzylic), 3.80 (s, 3H, OCH_3), 3.79 (s, 6H, OCH_3). ^{1}H-nmr spectrum is shown in Appendix 1 and is identical to those reported in the literature[27].

Methyl o-benzylbenzoate Cycloadduct:

Methyl *o*-benzylbenzoate (0.248 g, 1.10 mmol), in tetrahydrofuran was added under nitrogen to a stirred solution of lithium di-isopropylamide in tetrahydrofuran cooled to -78°C, the latter being prepared by addition of *n*-butyllithium in hexanes (2.03 M, 0.54 mL, 1.09 mmol) to an equivalent amount of dry, redistilled di-isopropylamine in tetrahydrofuran at -78°C. The black anion solution was stirred for 10 minutes. Dimethyl fumarate (0.237 g, 1.64 mmol) was then added at -78°C and the reaction mixture stirred overnight, while gradually being warmed to room temperature. Saturated aqueous

ammonium chloride (20 mL) solution was added and the mixture extracted with methylene chloride. The organic phase was successively washed with 10% HCl, and 5% aqueous sodium bicarbonate, then dried ($MgSO_4$), and evaporated to afford a brownish oil. The residue was chromatographed on silica using 15% ethyl acetate/hexane as eluant to afford a white solid (corresponding to the enol form, 0.156 g, 42%), and traces of a colorless oil (corresponding to the keto form, 0.041 g, 11%).

***Enol* 56:**

^{1}H-nmr ($CDCl_3$) δ: 12.62 (br, 1H, OH), 7.00-7.99 (m, 9H, aromatics), 4.67 (d, 1H, J=1.46, H-4), 3.96 (d, 1H, J=1.86, H-3), 3.72 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3). The ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 338(6), 279(37), 247(100), 219(13), 191(14), 165(15), 149(40), 129(9), 57(23), exact mass calculated for $C_{20}H_{18}O_5$: 338.1154, found, 338.1149.

***Keto* 57:**

^{1}H-nmr ($CDCl_3$) δ: 6.43-8.27 (m, 9H, aromatics), 4.78 (d, J=6.26, H-4), 4.05-4.12 (dd, 1H, $J_{3,4}$=7, $J_{3,2}$= 12.9, H-3), 3.87 (d, 1H, J=12.9, H-2), 3.36 (s, 3H, OCH_3), 2.97 (s, 3H, OCH_3). The ^{1}H-nmr spectrum is shown in Appendix 1.

Methyl o-benzylbenzoate Cycloadduct:

A solution of methyl o-benzylbenzoate (0.154 g, 0.680 mmol) in tetrahydrofuran was introduced into a solution of lithium diisopropylamide (1 eq) in tetrahydrofuran at -78°C over a period of 10 min. Dilacthyl fumarate (0.246 g, 0.851 mmol) was then added and the reaction gradually warmed to room temperature and stirred overnight. Satuarated ammonium chloride (20 mL) was added followed by extraction of the organic layer with dichloromethane, drying ($MgSO_4$) and evaporation to dryness to leave a brownish oil. The oil was chromatographed on silica using 15% ethyl acetate/hexane as eluant to afford a colourless oil (0.046 g, 14%).

***Enol* 58:**

^{1}H-nmr ($CDCl_3$, obtained from crude reaction mixture) δ: 12.37 (s, 1H, OH), 7.12-7.99 (m, 9H, aromatics), 5.23 (q, 1H, J=7.1, CH), 5.03 (q, 1H, J=7.1, CH), 4.67 (br s, 1H, H-4), 4.21 (d, 1H, J=1.95, H-3), 3.64 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 1.50 (d, 3H, J=7.1, CH_3), 1.40 (d, 3H, J=7.1, CH_3). (Mass Spectrum, *m/e* (rel %): 482(2), 351(12), 247(100), 219(12), 191(11), 165(9), 149(5), 97(6), 84(13), 69(13), 57(14), exact mass calculated for $C_{26}H_{26}O_9$: 482.1576, found: 482.1567.

Fumarate of (S)-methyl lactate **63**:

This compound was prepared according to the literature procedure[35].
To (S)-methyl lactate (3.26 g, 31.4 mmol) was added fumaryl chloride (2.43 g, 15.9 mmol) and the resulting mixture heated at 110°C for 17 hrs. The mixture was then diluted with ethyl acetate and washed with aqueous sodium bicarbonate (5%), dried ($MgSO_4$) and evaporated to give a yellowish oil (3.91 g, 85%).
IR (CH_2Cl_2) cm^{-1}: 1733 (CO). ^{1}H-nmr ($CDCl_3$) δ: 6.97 (s, 1H, alkene CH), 5.21 (q, 1H, J=7.1, CH), 3.77 (s, 3H, OCH_3), 1.56 (d, 3H, J=7.1, CH_3). The ^{1}H-nmr spectrum is shown in Appendix 1.

Anthrone Michael Adduct **64**:

To a solution of anthrone (0.150 g, 0.77 mmol) in dry tetrahydrofuran (10 mL) was added dilactyl fumarate (0.242 g, 0.84 mmol) in tetrahydrofuran and triethylamine (0.35 mL, 2.5 mmol). The solution was refluxed overnight, cooled and the solvent evaporated. The crude product was purified by chromatography on silica gel using 30% ethyl acetate/hexane as eluant to afford a yellowish oil (0.253 g, 68%).
IR (CH_2Cl_2) cm^{-1}: 1744 (CO). ^{1}H-nmr ($CDCl_3$) δ: 7.5-8.2 (m, 8H, aromatics), 5.22 (q, 1H, J=7.1, CH), 5.03 (d, 1H, J=2.61, benzylic H), 4.90 (q, 1H, J=7.1, CH), 3.81 (s, 3H,

OCH_3), 3.63 (s, 3H, OCH_3), 3.51-3.57 (m, 1H), 2.05 (dd, 1H, J=11.24), 1.88 (dd, 1H, J=3.89), 1.53 (d, 3H, J=7.1, CH_3), 1.34 (d, 3H, J=7.1, CH_3). The ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 482(7), 257(6), 246(7), 208(7), 193(59), 165(7), 111(7), 84(100), 71(41), 55(11), exact mass calculated for $C_{26}H_{26}O_9$: 482.1576, found: 482.1571.

Anthracene Cycloadduct **65**:

A solution of anthracene (0.473 g, 2.65 mmol) and dilactyl fumarate (0.370 g, 1.28 mmol) in xylene (30 mL) was refluxed for 6 days at 139°C. The solution was concentrated by evaporation to afford a pale orange solid. The crude solid was purified by chromatography on silica gel using 20% ethyl acetate\hexane as eluant to afford a colourless solid (0.347 g, 58%). Recrystallization from ethyl acetate/hexane gave colourless crystals (mp: 109-111°C).

IR (Nujol) cm^{-1}: 1742 (CO). ^{1}H-nmr ($CDCl_3$) δ: 7.10-7.35 (m, 4H, aromatics), 5.04 (q, 1H, J=7.1, CH), 4.81 (br s, 1H), 3.73 (s, 3H, OCH_3), 3.40 (br s, 1H), 1.46 (d, 3H, J=7.1, CH_3). The ^{1}H-nmr spectrum is shown in Appendix 1.

Anthraquinone Cycloadduct **67**:

A suspension of anthraquinone (0.218 g, 1.04 mmol) and 5% Pd/C (30 mg) in ethyl acetate (30 mL) was vigorously stirred while H_2 gas was introduced at room temperature. After 0.5 h, triethylamine (1 mL) was added and the mixture stirred for additional 5 minutes. The H_2 atmosphere was replaced by N_2, followed by addition of dilactyl fumarate (0.287 g, 0.998 mmol) in ethylacetate (15 mL). The mixture was stirred for one hour, filtered and the filtrate was evaporated under vaccum to afford a yellowish oil. The crude oil was purified by chromatography on silica gel using 20% ethyl acetate\hexane as eluant to afford a colourless solid (0.304 g, 61%). Recrystallization from isopropanol

gave colourless crystals (mp: 118-120°C).

$[\alpha]_D$=-33.5° (c: 1.01, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3439 (OH), 1736 (CO). ^{1}H-nmr ($CDCl_3$) δ: 7.1-7.7 (m, 4H, aromatics), 5.71 (s, 1H, OH), 5.17 (q, 1H, J=7.1, CH), 3.80 (s, 3H, OCH_3), 3.50 (s, 1H, bridgehead), 1.47-1.50 (d, 3H, J=7.1, CH_3). Mass spectrum, *m/e* (rel %): 257(1), 208(20.4), 185(53), 165(3.9), 152(13.6), 140(5.5), 126(2.6), 113(16), 99(19.2), 87(100), 76(8.6), 69(2.7), 59(31.3). Found: C, 62.27; H, 5.63. $C_{26}H_{26}O_{10}$ requires C, 62.63; H, 5.26%.

REFERENCES

1. R.D. Haworth, *J. Chem. Soc.*, 448 (1942).
2. O.R. Gottlieb, *Phytochemistry* **11**, 1537 (1972).
3. J.L. Charlton, M.M. Alauddin, *Tetrahedron* **43**, 2873 (1987).
4. J. March, Advanced Organic Chemistry (3rd edition), pp. 745-753. John Wiley and Sons, New York (1985).
5. Otto Diels (1876-1954), Ph.D. Berlin (E. Fisher), Kiel, Nobel Prize 1950.
6. Kurt Alder (1902-1958), Ph.D. Kiel (O. Diels), Cologne, Nobel Prize 1950.
7. I. Fleming, Frontier Orbitals and Organic Chemical Reactions, John Wiley and Sons, New York (1976).
8. M.B. Glinski, T. Durst, *Can. J. Chem.* **61**, 573 (1983).
9. J.L. Charlton, G.L. Plourde, K. Koh, A.S. Secco, *Can. J. Chem.* **68**, 2022 (1990).
10. J.L. Charlton, M.M. Alauddin, *J. Org. Chem.* **51**, No. 18, 3490 (1986).
11. G.L. Plourde, Ph.D. thesis entitled: Asymmetric synthesis using *o*-QDMs, The University of Manitoba, 1990.
12. a) W. Choy, H. Yang, *J. Org. Chem.* **53**, 5796 (1988).
    b) W. Choy, *Tetrahedron* **46**, No. 7, 2281 (1990).
13. F.M. Hauser, R.P. Rhee, *J. Org. Chem.* **43**, 178 (1978).
14. F.M. Hauser, R.P. Rhee, S. Prasanna, S.M. Weinreb, J.M. Dodd, *Synthesis*, 72 (1980).
15. R.L. Vaulx, W.M. Puterbaugh, C.R. Hauser, *J. Org. Chem.* **29**, 3514 (1964).
16. P.L. Creger, *J. Am. Chem. Soc.* **92**, 1396 (1970); P.L. Creger, P.E. Pfeffer, L.S. Silbert, J.M. Chirinko Jr., *J. Org. Chem.* **37**, 451 (1972).
17. F.M. Hauser, R.P. Rhee, *J. Am. Chem. Soc.* **99**, 4533 (1977); *Synthesis*, 245 (1977).

18. F.M. Hauser, R.P. Rhee, *J. Org. Chem.* **42**, 4155 (1977).

19. T. Takahashi, K. Kasguga, M. Takahashi, J. Tsuji, *J. Am. Chem. Soc.* **101**, 5072 (1979).

20. J. Wildeman, P.C. Borgen, H. Pluim, P.H.F.M. Rouwette, A.M. Van Leusen, *Tetrahedron Lett.*, 2213 (1978).

21. B.L. Chenard, D.K. Anderson, J.S. Swenton, *J. Chem. Soc., Chem Commun.*, 932 (1980).

22. G.A. Kraus, H. Sugimoto, *Tetrahedron Lett.*, 2263 (1978).

23. W. Trueb, C.H. Eugester, *Helv. Chim. Acta.* **55**, 969 (1972); N.J.P. Broom, P.G. Sammes, *J. Chem. Soc., Chem Commun.*, 162 (1978); *J. Chem. Soc. Perkin Trans.* I, 465 (1981); P.G. Sammes, D.J. Dodsworth, *J. Chem. Soc., Chem. Commun.*, 33 (1979).

24. D.J. Dodsworth, M. Calcagno, E.U. Ehrmann, B. Devadas, P.G. Sammes, *J. Chem. Soc. Perkin Trans.* I, 2120 (1981).

25. B. Tarnchompoo, C. Thebtaranonth, Y. Thebtaranonth, *Synthesis*, 785 (1986).

26. T.A. Carpenter, G.E. Evans, F.J. Leeper, J. Staunton, M.R. Wilkinson, *J. Chem. Soc. Perkin Trans.* I, 1043 (1984).

27. B.J. Arnold, S.M. Mellows, P.G. Sammes, *J. Chem. Soc. Perkin Trans.* I, 1266 (1973).

28. (a) H. Gilman, C. Arntzen, *J. Amer. Chem. Soc.* **70**, 4178 (1948); (b) *ibid.* **70**, 2844 (1948); (c) H. Gilman, D.S. Melstrom, *ibid.* **63**, 2844 (1941).

29. A.J. Bridges, W.C. Patt, T.M. Stickney, *J. Org. Chem.* **55**, 773 (1990).

30. R.P. Dickinson, B. Iddon, *J. Chem. Soc.* C, 3447 (1971).

31. M. Koerner, B. Rickborn, *J. Org. Chem.* **54**, 9 (1989).

32. M. Koerner, B. Rickborn, *J. Org. Chem.* **55**, 2662 (1990).

33. S. Knapp, R.M. Ornaf, K.E. Rodrigues, *J. Am. Chem. Soc.* **105**, 5494 (1983).

34. J.K. Whitesell, *Chem. Rev.* **89**, No. 7, 1581 (1989).

35. H. Hartmann, A.F.A. Hady, K. Sartor, J. Weetman, G. Helmchen, *Angew. Chem. Int. Ed. Engl.* **26**, No. 11, 1143 (1987).

36. M. Pfau, S. Combrisson, J.E. Rowe, N.D. Heindel, *Tetrahedron* **34**, 3459 and 3469 (1978).

37. T. Durst, E.C. Kozma, J.L. Charlton, *J. Org. Chem.* **50**, No. 24, 4829 (1985).

38. J.L. Charlton, G.L Plourde, K. KoH, A.S. Secco, *Can. J. Chem.* **67**, 574 (1989).

39. M. Koerner, B. Rickborn, *J. Org. Chem.* **56**, 1373 (1991).

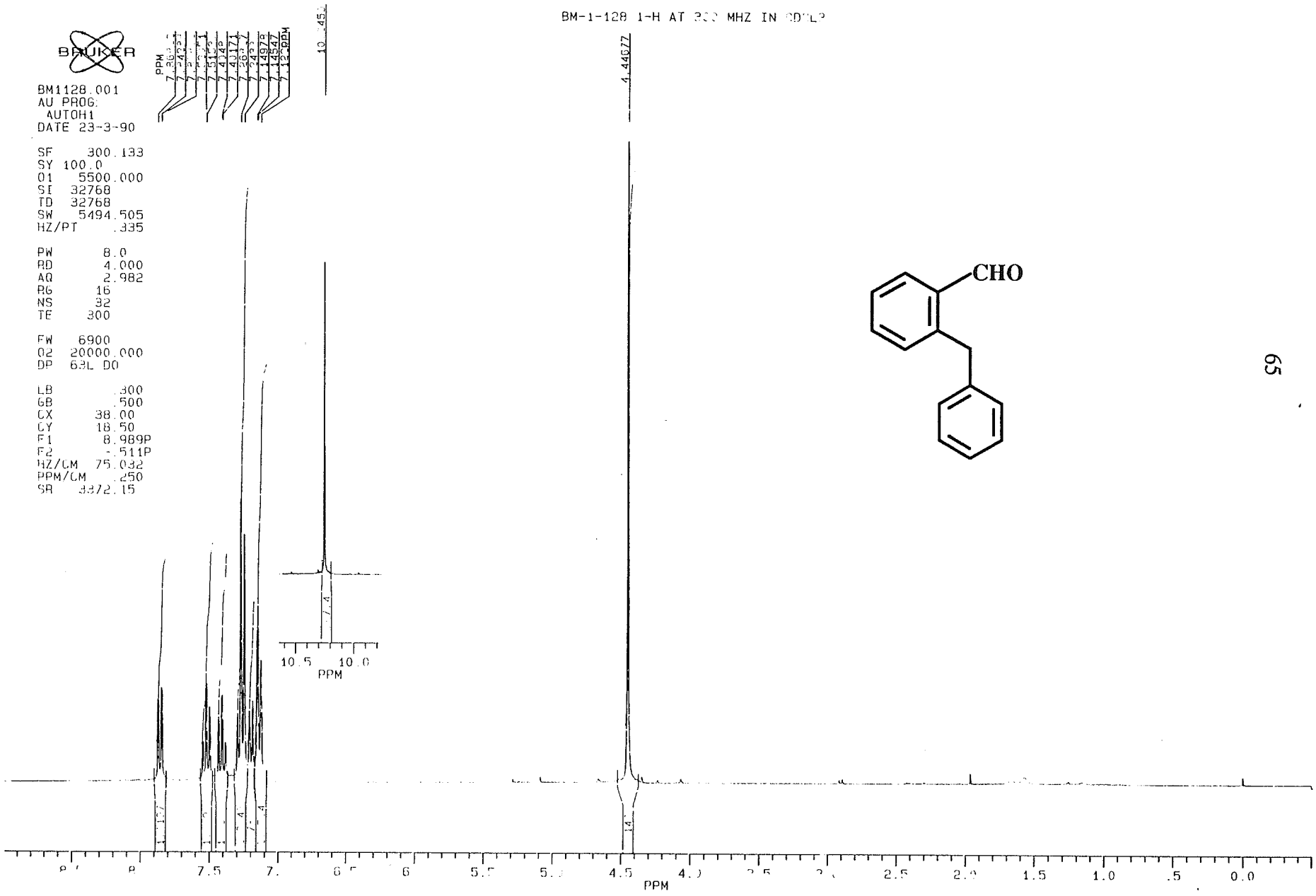
40. F. Dallacker, *Liebigs Ann. Chem.* Bd. 633, 14 (1960).

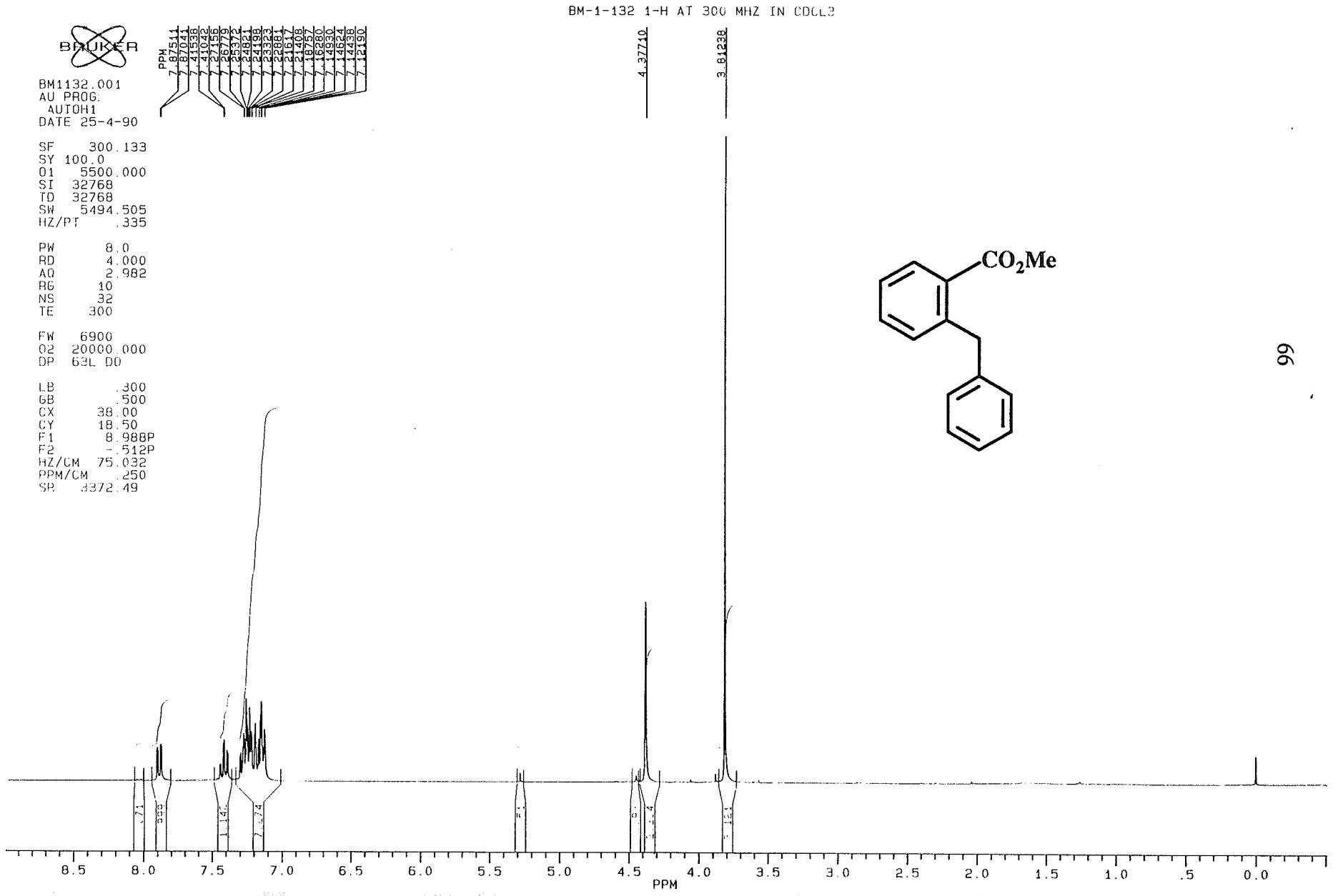
41. B.J. Arnold, S.M. Mellows, P.G. Sammes, T.W. Wallace, *J. Chem. Soc., Perkin Trans.* I, 401 (1974).

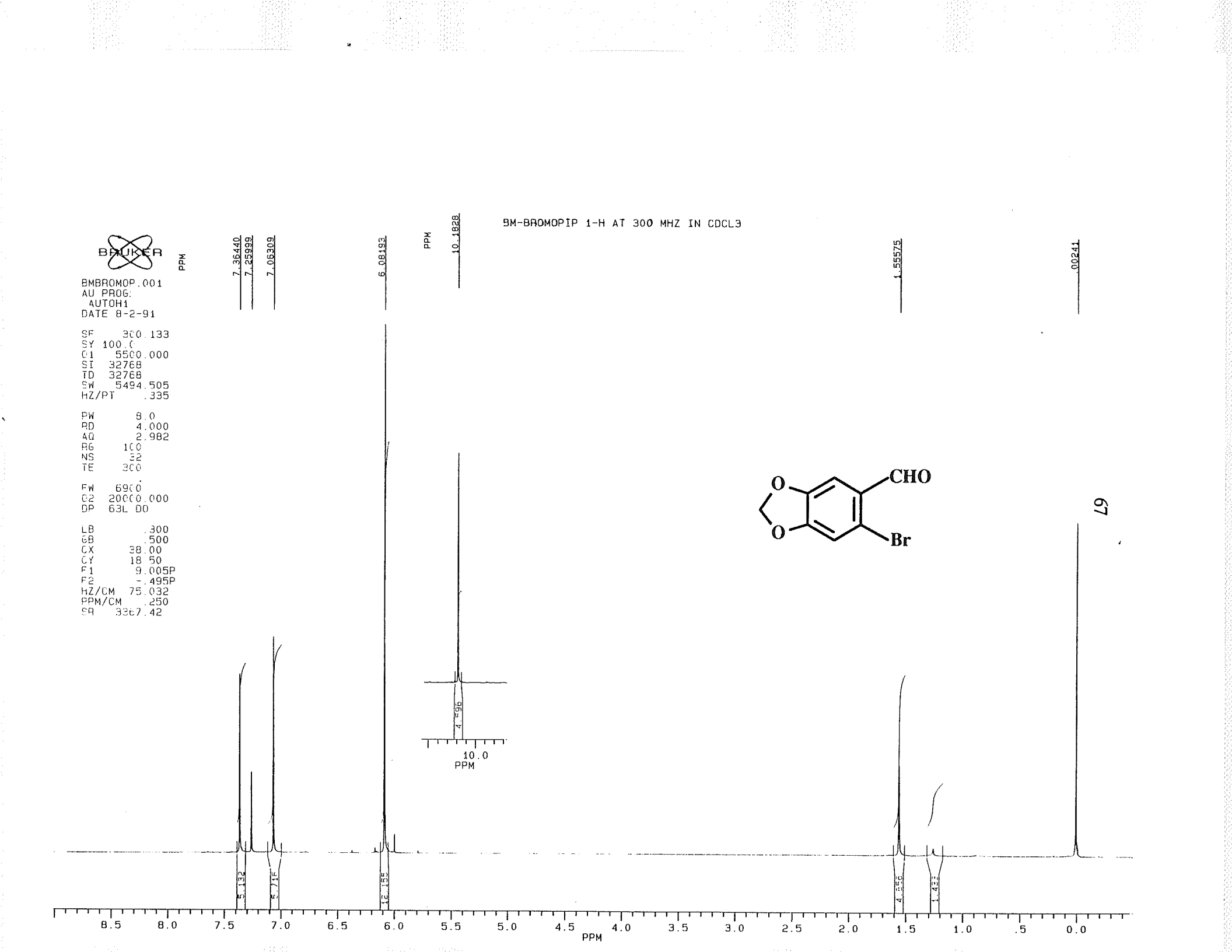
42. M.E. Jung, P.W. Lam, M.M. Mansuri, L.M. Spetz, *J. Org. Chem.* **50**, 1087 (1985).

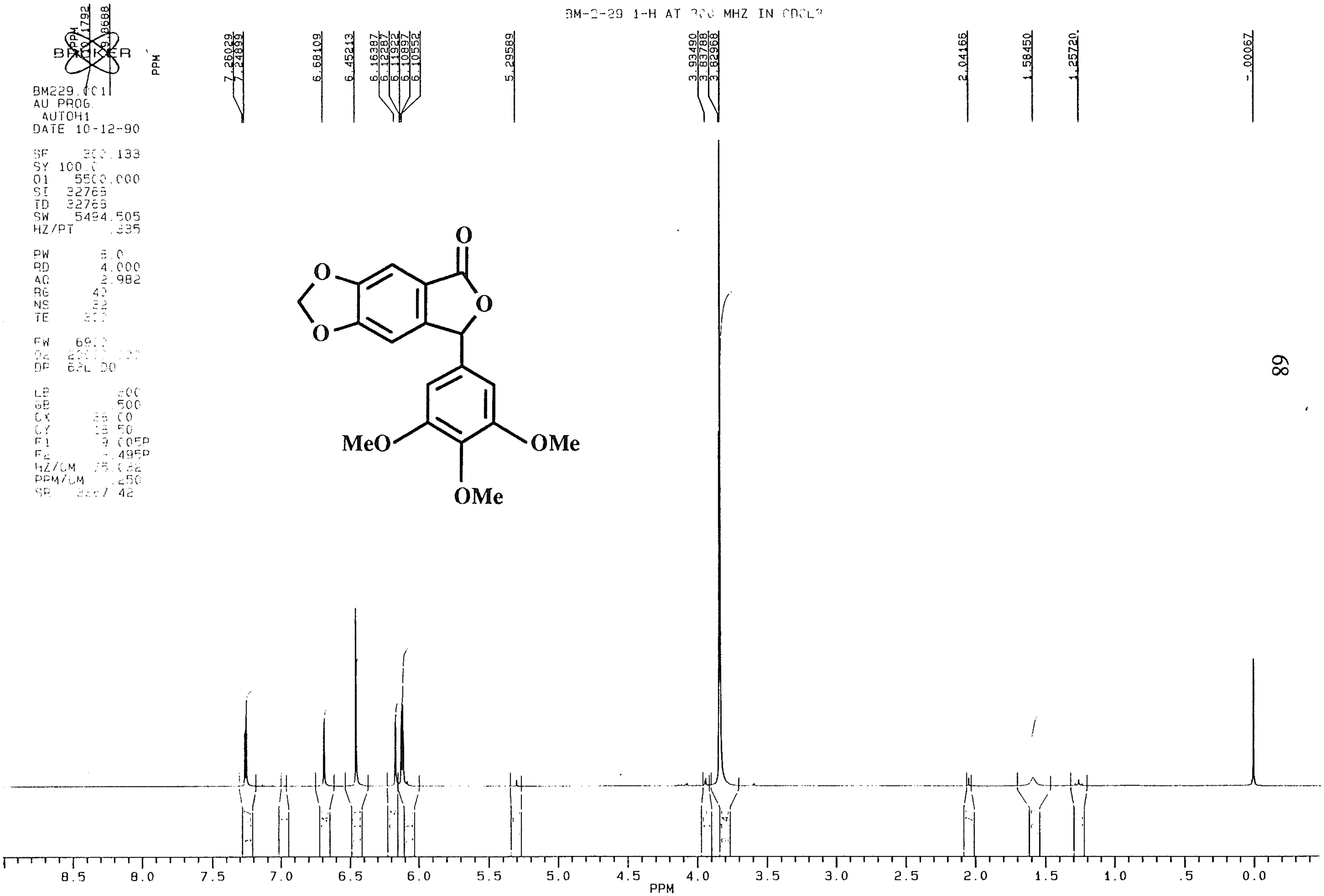
APPENDIX 1

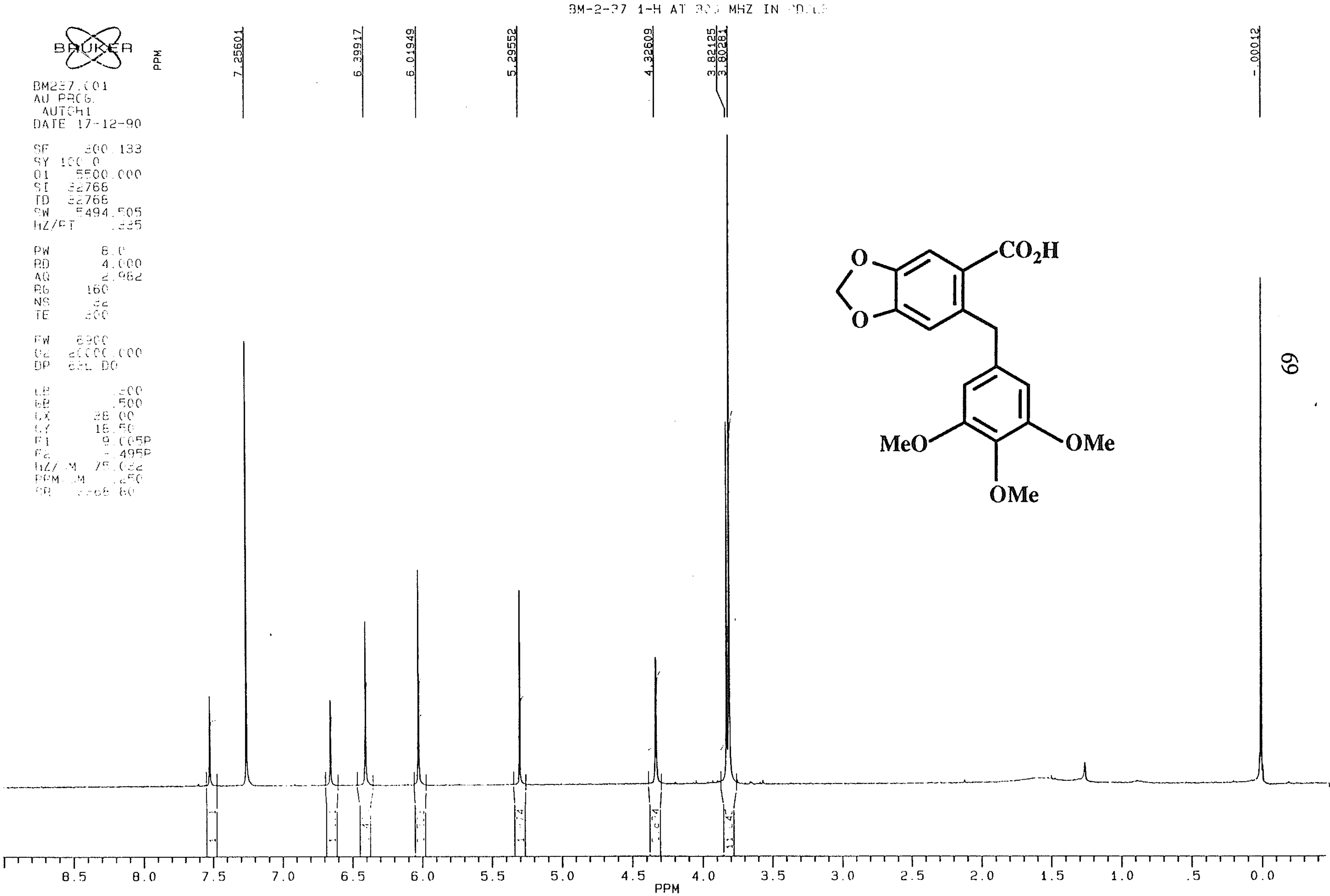
^{1}H-nmr Spectra


BM-1-128 1-H AT 300 MHZ IN CDCL3
BRUKER
BM1128.001
AU PROG:
AUTOH1
DATE 23-3-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 16
NS 32
TE 300
FW 6900
O2 20000.000
DP 68L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.989P
F2 -.511P
HZ/CM 75.032
PPM/CM .250
SR 3372.15
PPM
4.44677
CHO
10.5
10.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0


BM-1-132 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
7.87511
7.87041
7.41538
7.41042
7.27156
7.26779
7.26372
7.24821
7.24194
7.23323
7.22881
7.21617
7.21409
7.18257
7.16280
7.14930
7.14624
7.14436
7.12190
4.37710
3.81238
BM1132.001
AU PROG:
AUTOH1
DATE 25-4-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 10
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.988P
F2 -.512P
HZ/CM 75.032
PPM/CM .250
SR -372.49
CO2Me
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

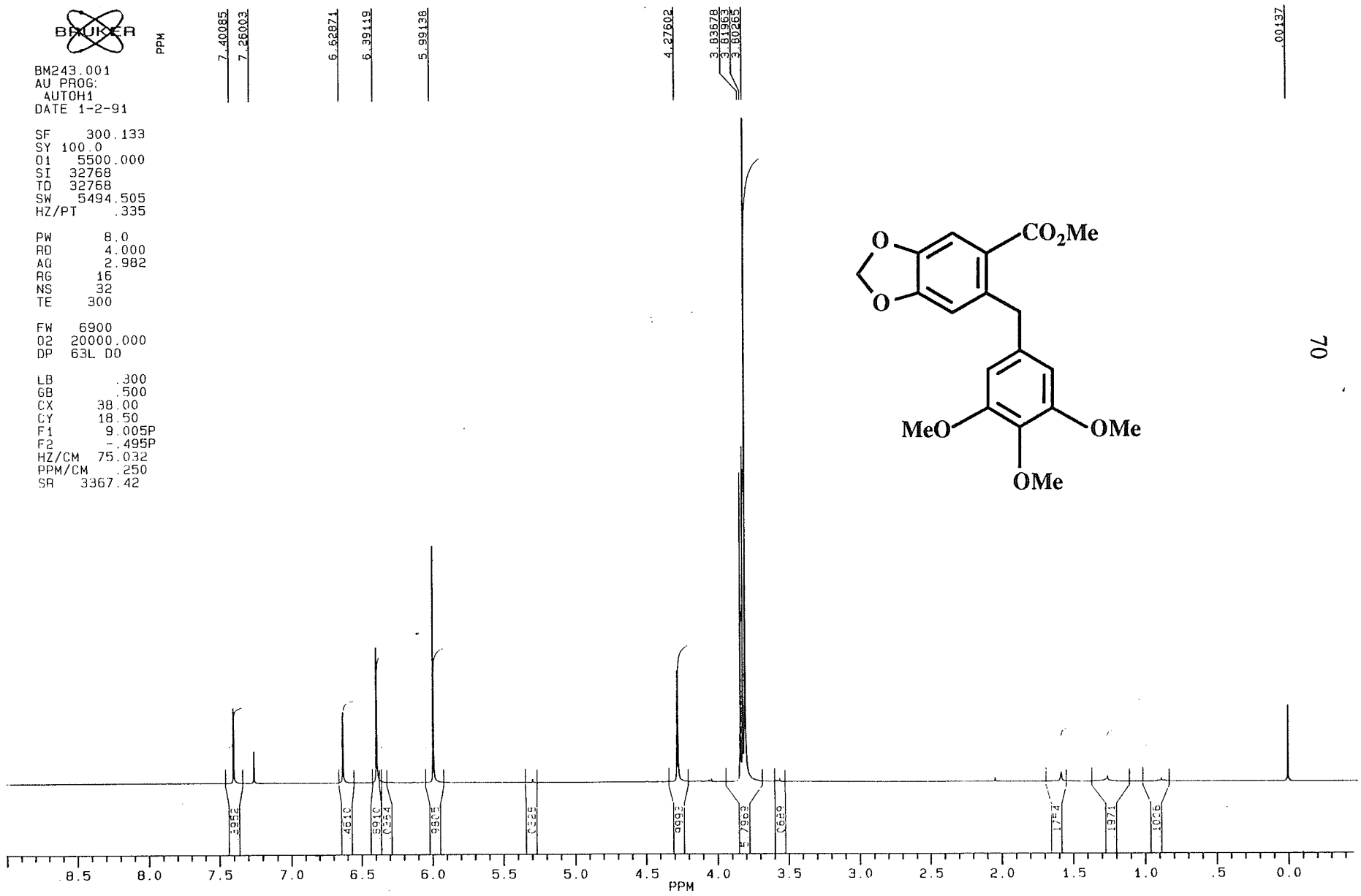

9M-BROMOPIP 1-H AT 300 MHZ IN CDCL3
BMBROMOP.001
AU PROG:
AUTOH1
DATE 8-2-91
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 100
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3367.42
7.36440
7.25999
7.06309
6.08193
10.1828
1.55575
.00241
CHO
O
O
Br
5.132
8.716
12.155
4.596
4.256
1.433
10.0
PPM
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0


BM-2-29 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
BM229.001
AU PROG.
AUTOH1
DATE 10-12-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 6.0
RD 4.000
AQ 2.982
7.26029
7.24899
6.68109
6.45213
6.16387
6.12287
6.11922
6.10897
6.10552
5.29589
3.93490
3.83788
3.82968
2.04166
1.58450
1.25720
-.00067
O
O
O
O
MeO
OMe
OMe
PPM

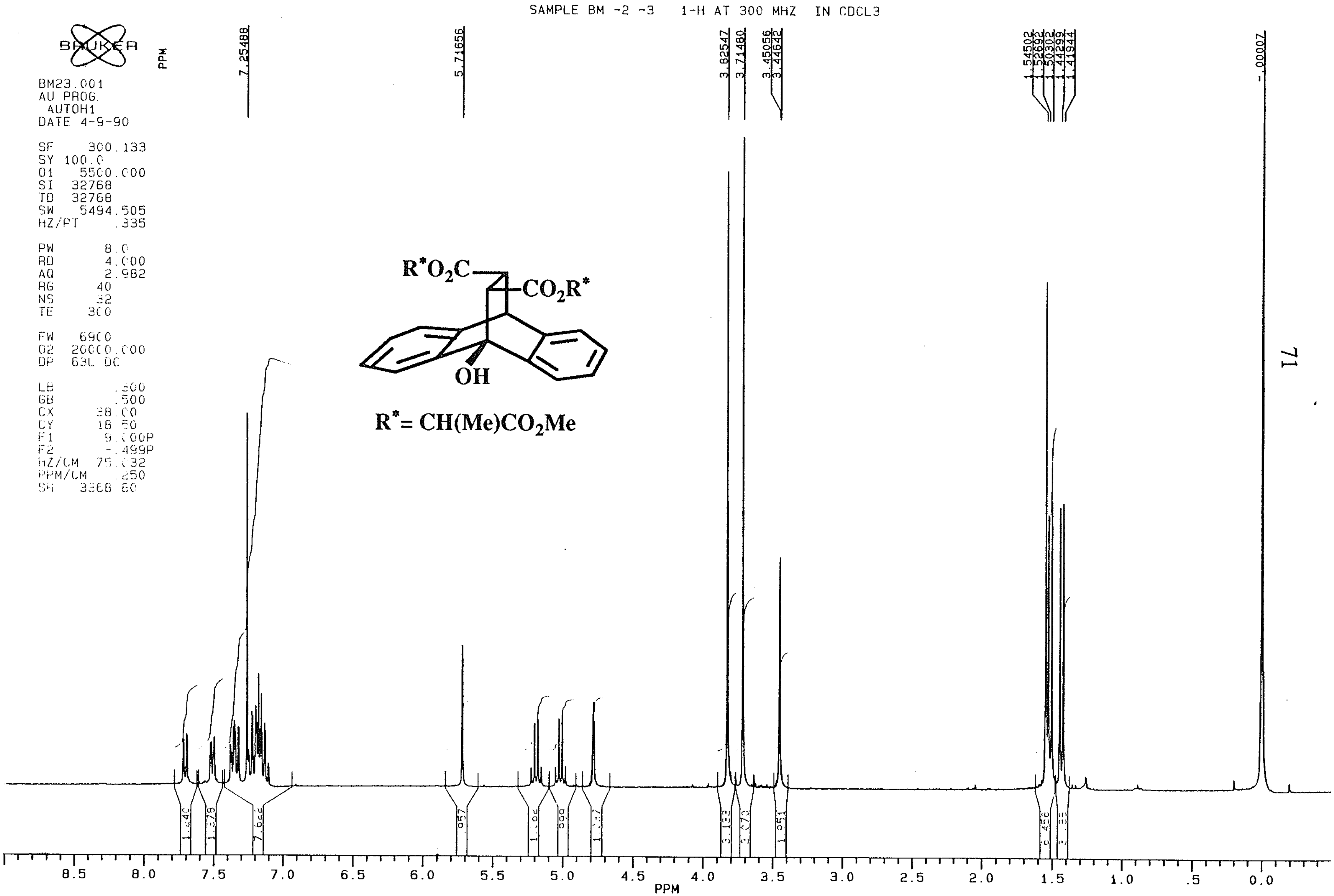

BM-2-37 1-H AT 30_ MHZ IN
BRUKER
PPM
7.25601
6.39917
6.01949
5.29552
4.32609
3.82125
3.80281
-.00012
BM237.001
AU PROG.
AUTOH1
DATE 17-12-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
PW 8.0
RD 4.000
AQ 2.982
RG 160
TE 300
GB .500
CX 38.00
CY 18.50
F1 9.005P
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM
CO2H
MeO
OMe
OMe

69

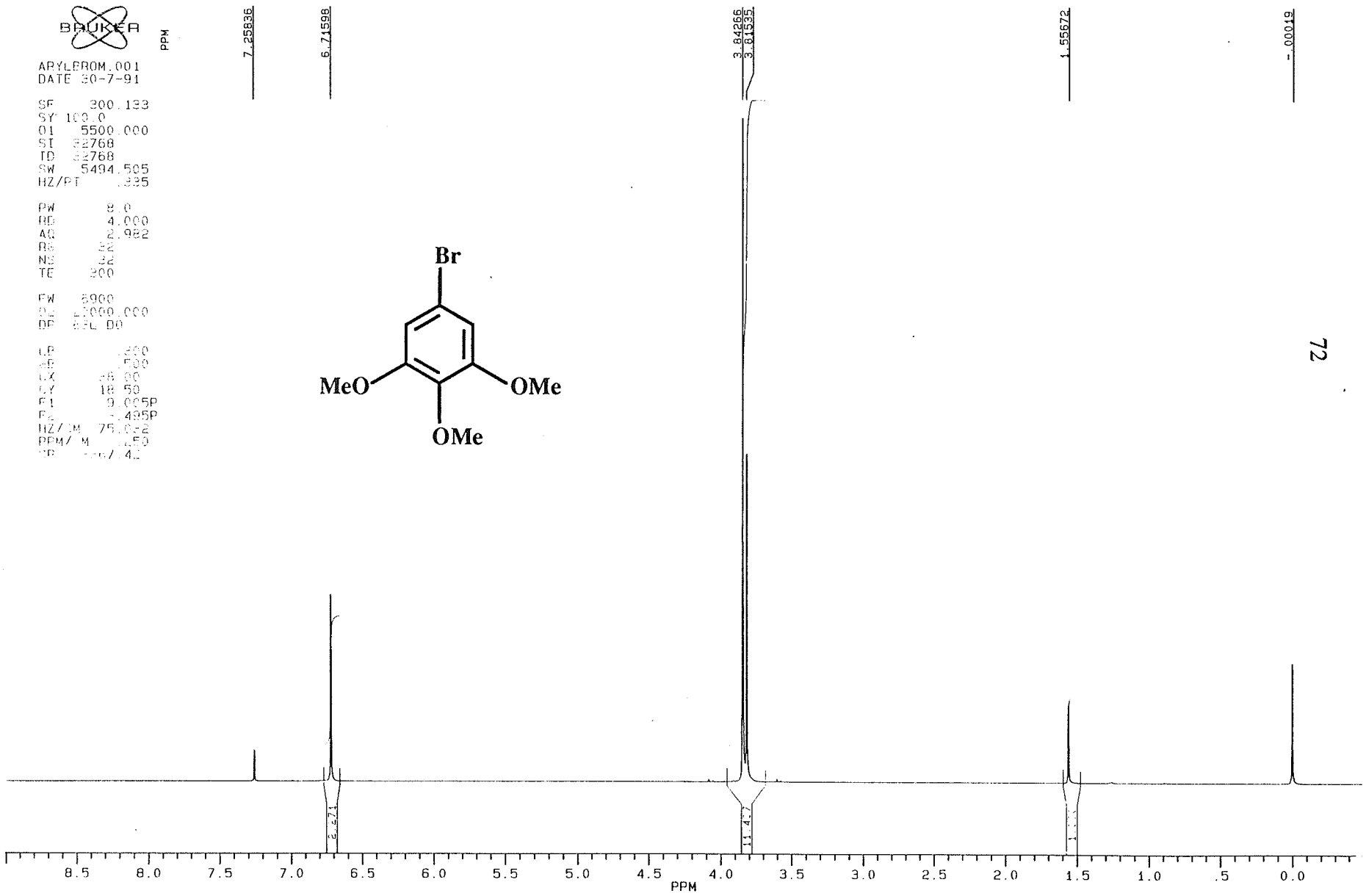
BM-2-43 1-H AT 300 MHZ IN CDCL3



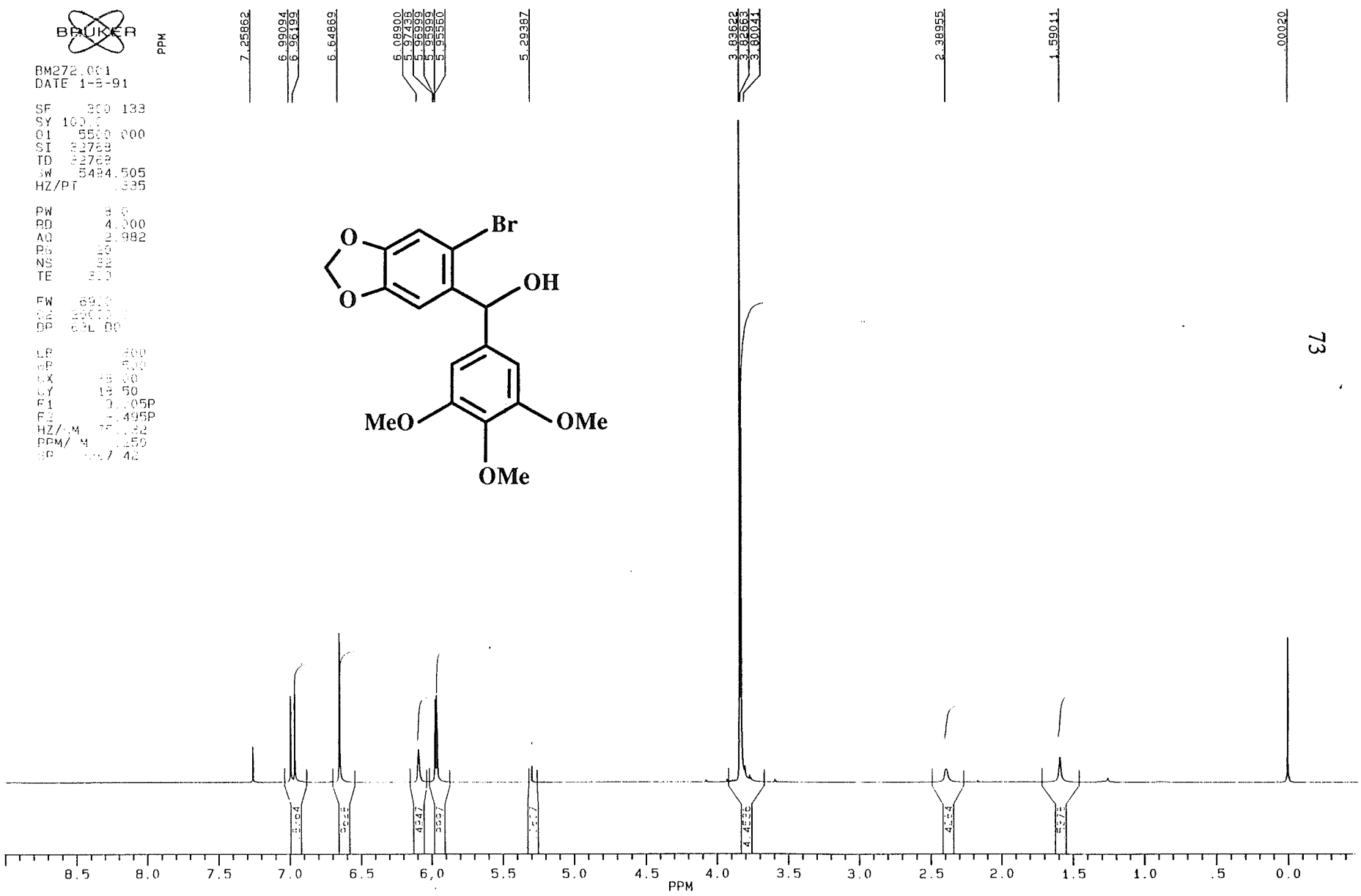
70


SAMPLE BM -2 -3 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
BM23.001
AU PROG.
AUTOH1
DATE 4-9-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DC
LB .500
GB .500
CX 28.00
CY 16.50
F1 9.000P
F2 -.499P
HZ/CM 75.032
PPM/CM .250
SR 3368.60
7.25488
5.71656
3.82547
3.71480
3.45056
3.44642
1.54502
1.52692
1.50302
1.44299
1.41944
-.00007
R*O2C
CO2R*
OH
R*= CH(Me)CO2Me
PPM

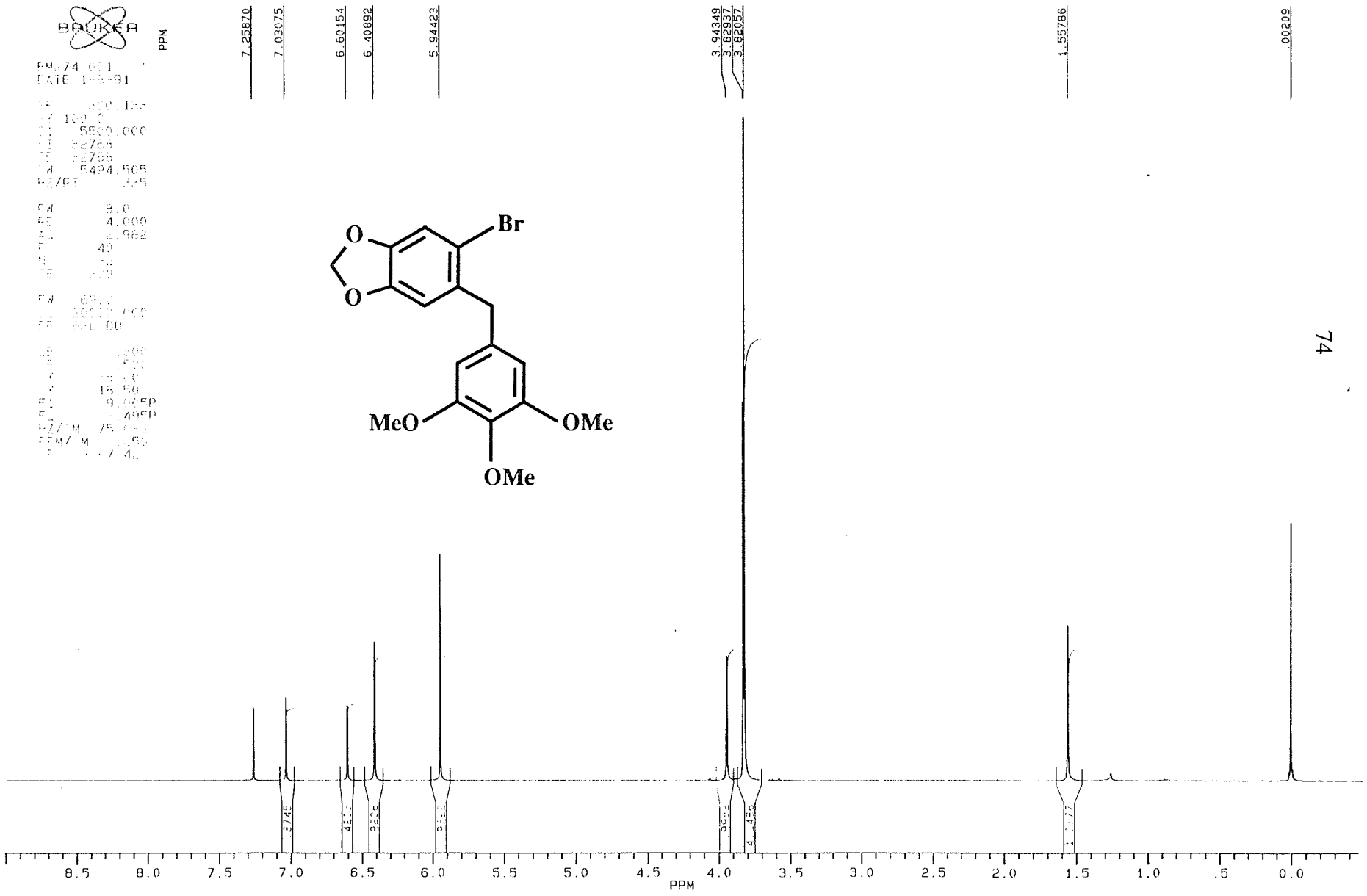
ARYLBROMIDE 1-H AT 300 MHZ IN CDCL3



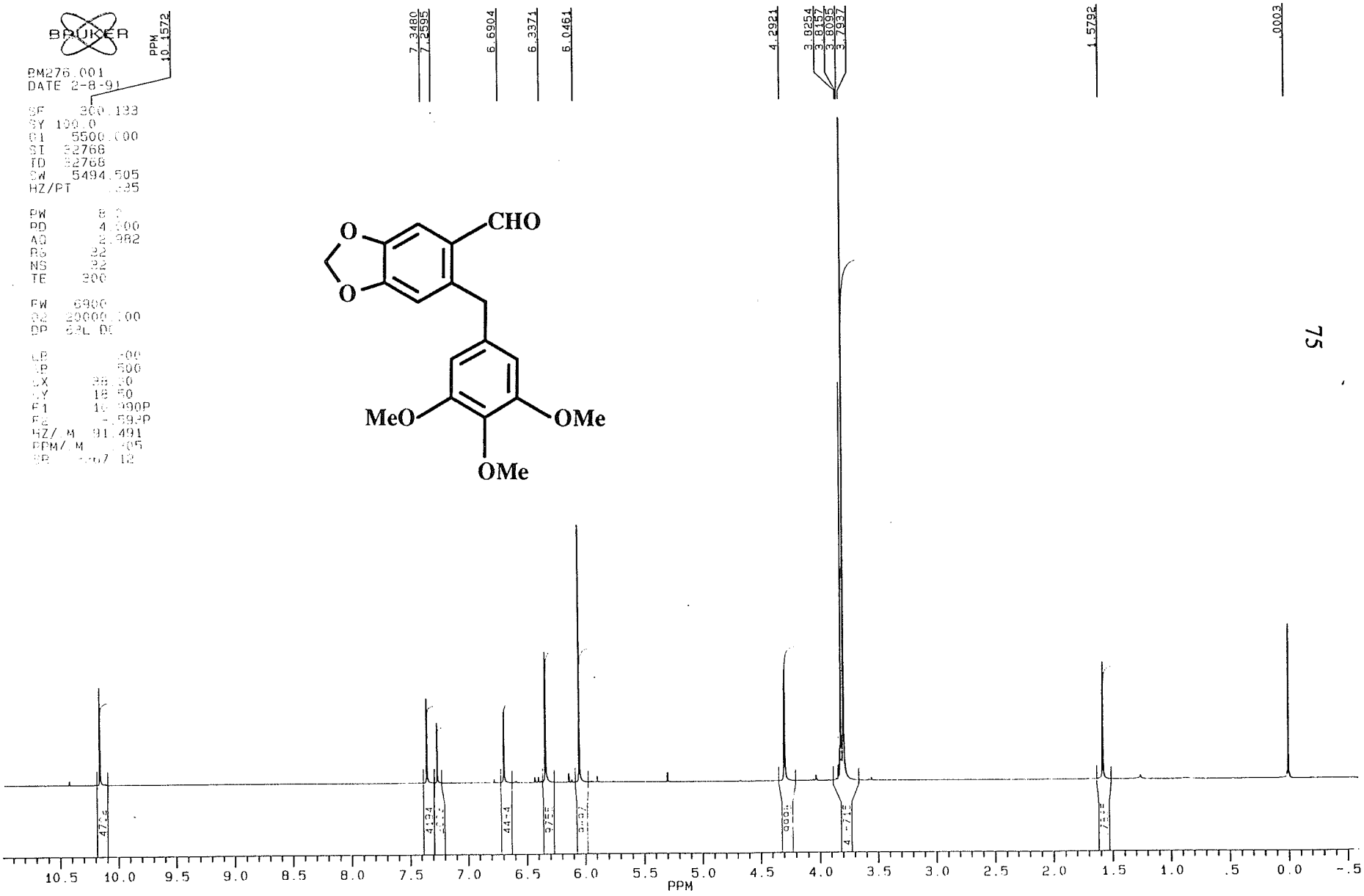
SAMPLE # BM-2-72 1-H AT 300 MHZ IN CDCL3

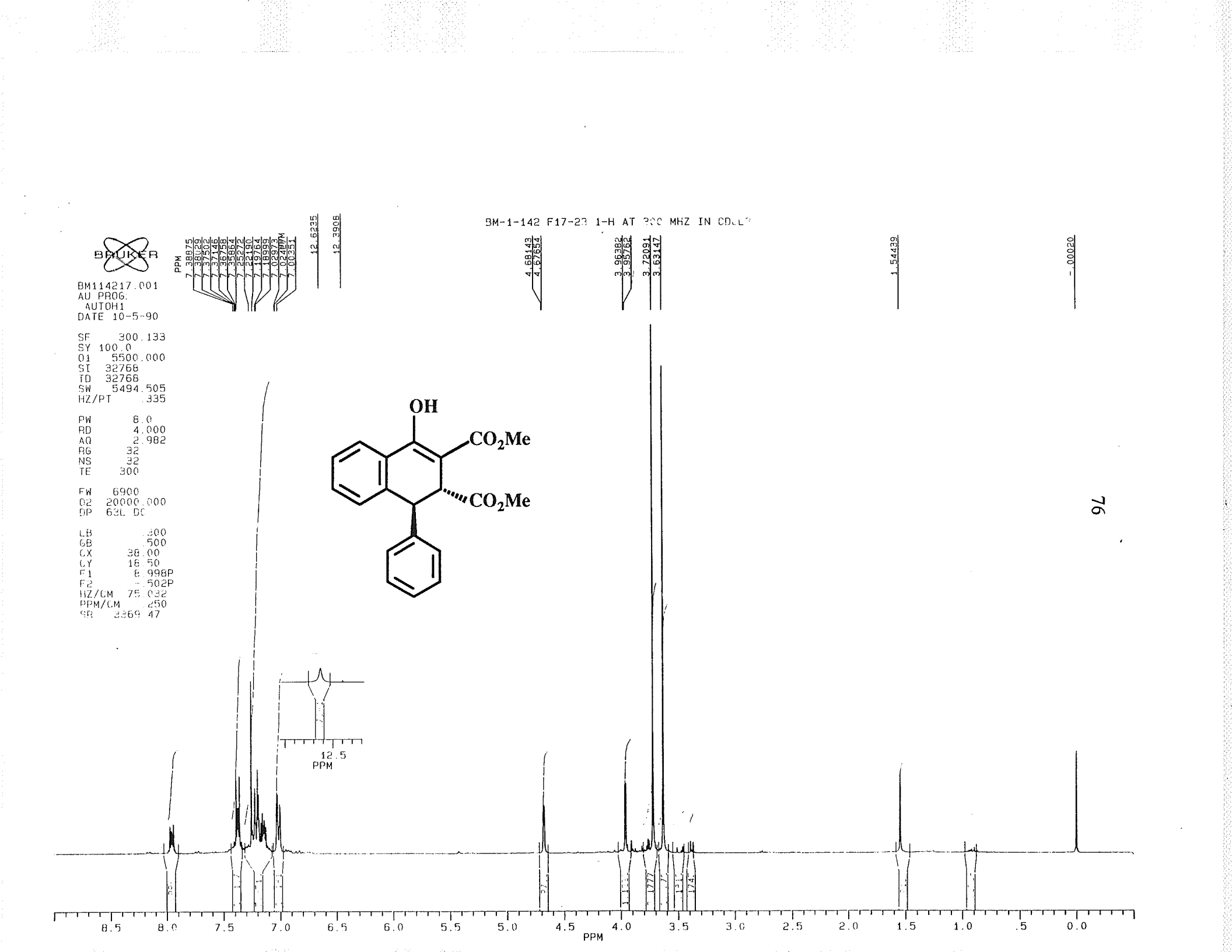


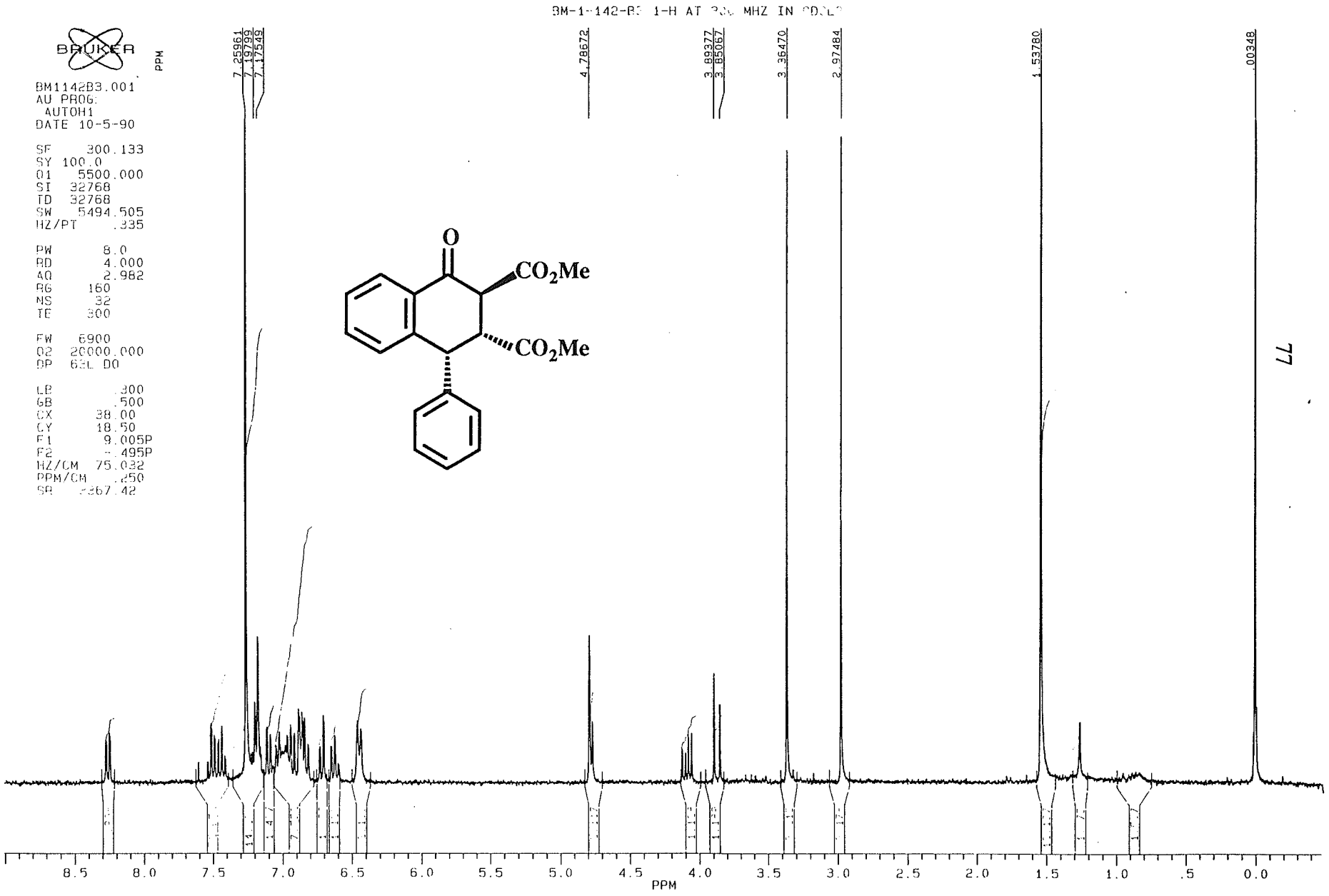
SAMPLE # BM-2-74 1-H AT 300 MHZ IN CDCL3



SAMPLE # BM-2-76 1-H AT 300 MHZ IN CDCL3




BM-1-142 F17-23 1-H AT 300 MHZ IN CDCL3
BRUKER
BM114217.001
AU PROG.
AUTOH1
DATE 10-5-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 32
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 16.50
F1 8.998P
F2 -.502P
HZ/CM 75.032
PPM/CM .250
SR 3369.47
PPM
7.38875
7.38029
7.37502
7.37146
7.36758
7.35864
7.25272
7.22190
7.19764
7.18999
7.02973
7.02478PPM
7.00351
12.6225
12.3908
4.68143
4.67654
3.96382
3.95762
3.72091
3.63147
1.54439
-.00020
OH
CO2Me
CO2Me
12.5
PPM
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


BM-1-142-B3 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
BM1142B3.001
AU PROG:
AUTOH1
DATE 10-5-90
SF 300.133
SY 100.0
01 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 160
NS 32
TE 300
FW 6900
02 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR -367.42
7.25961
7.19799
7.17549
4.78672
3.89377
3.85067
3.36470
2.97484
1.53780
.00348
O
CO2Me
CO2Me
77
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

BM-1-148 1-H AT 300 MHZ IN CDCL3

BRUKER

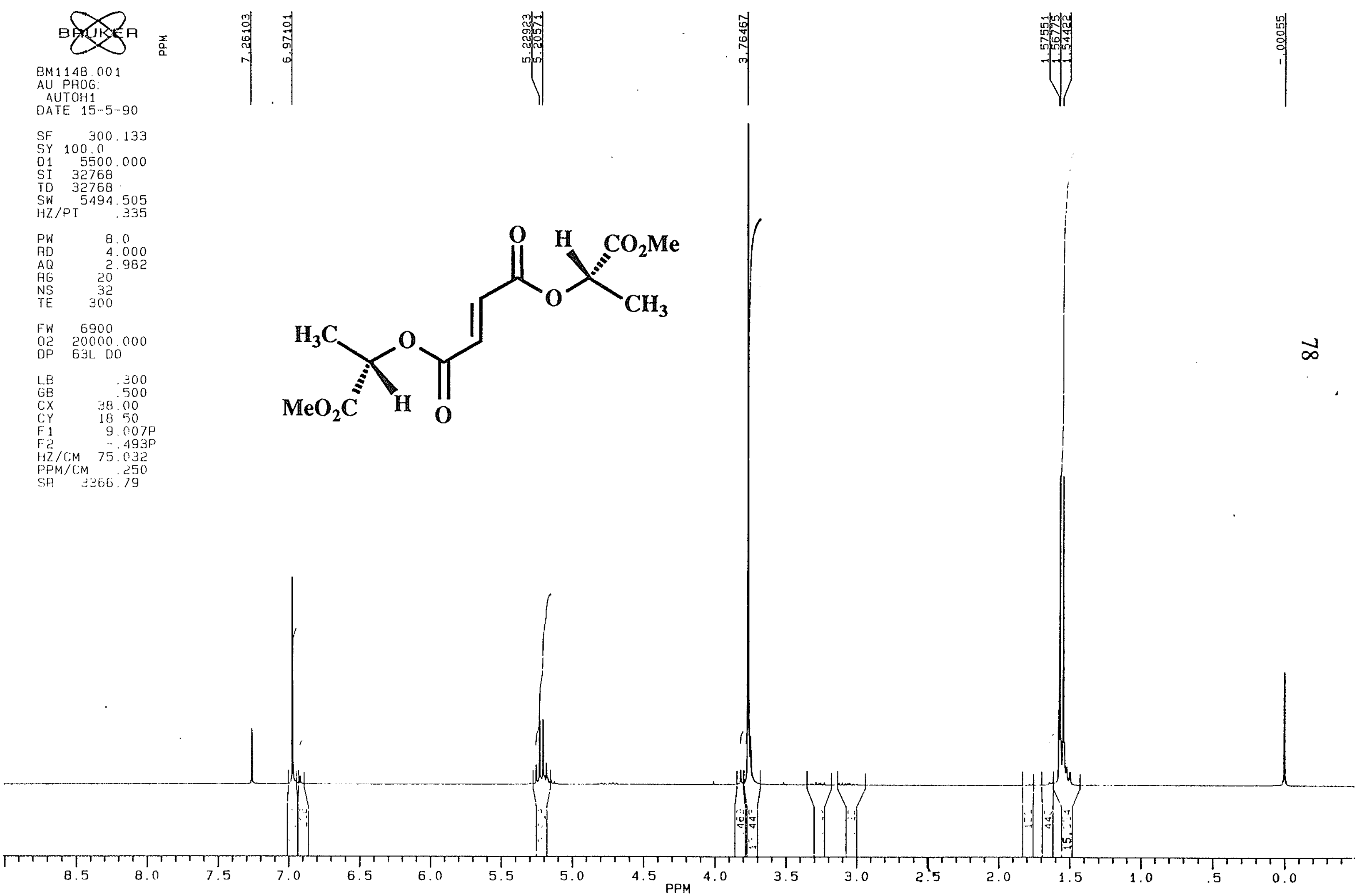
BM1148.001
AU PROG:
AUTOH1
DATE 15-5-90

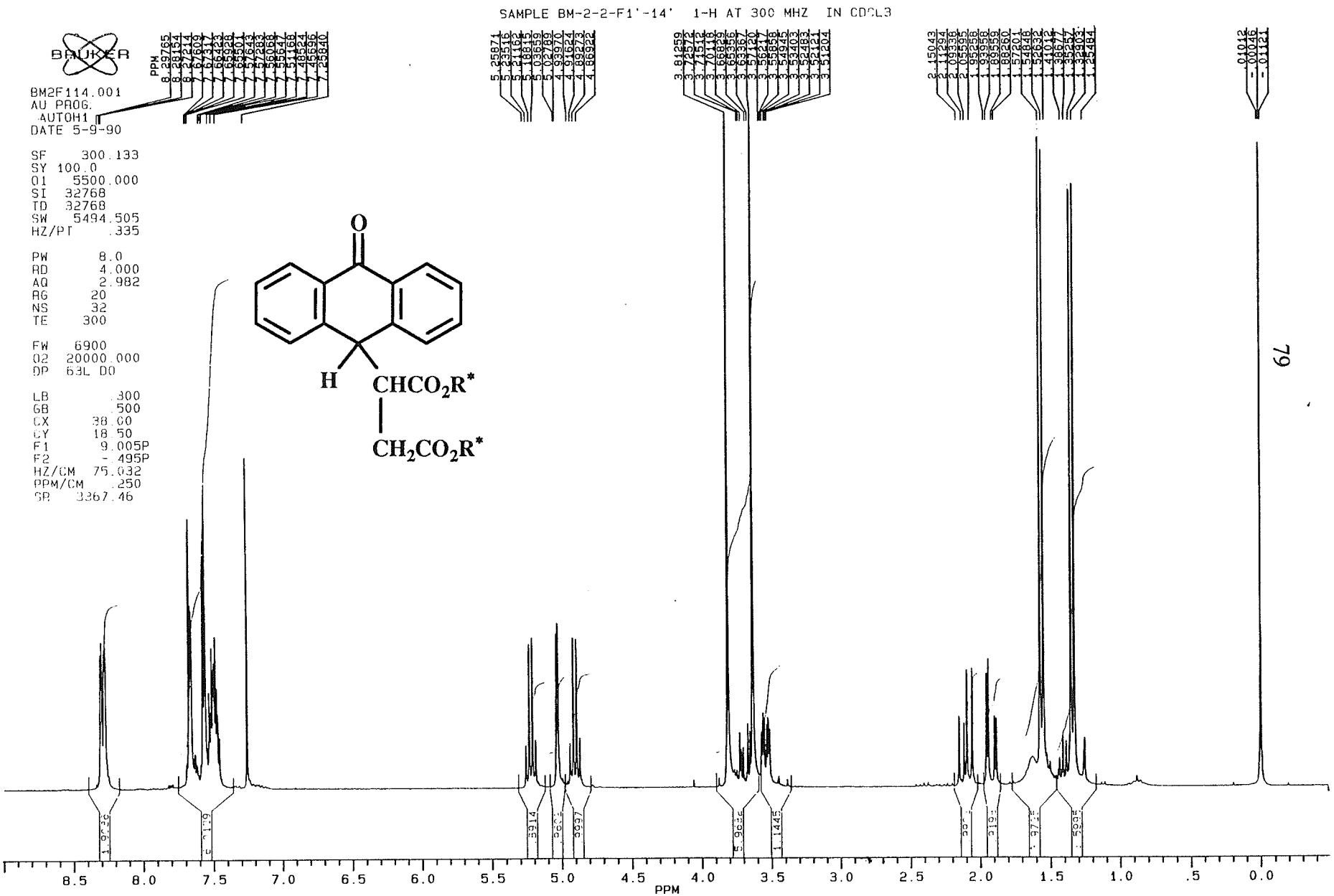
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335

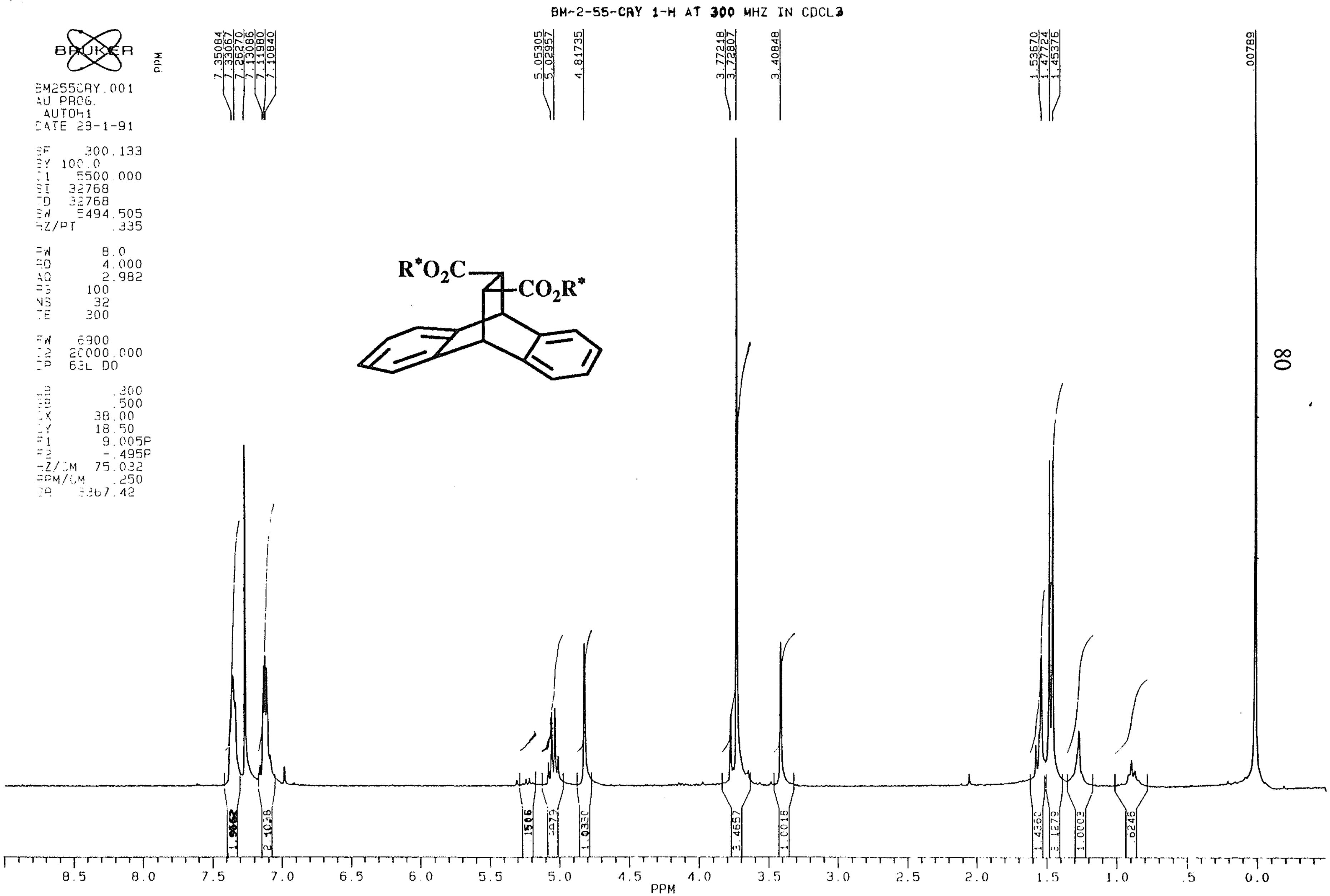
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300

FW 6900
O2 20000.000
DP 63L DO

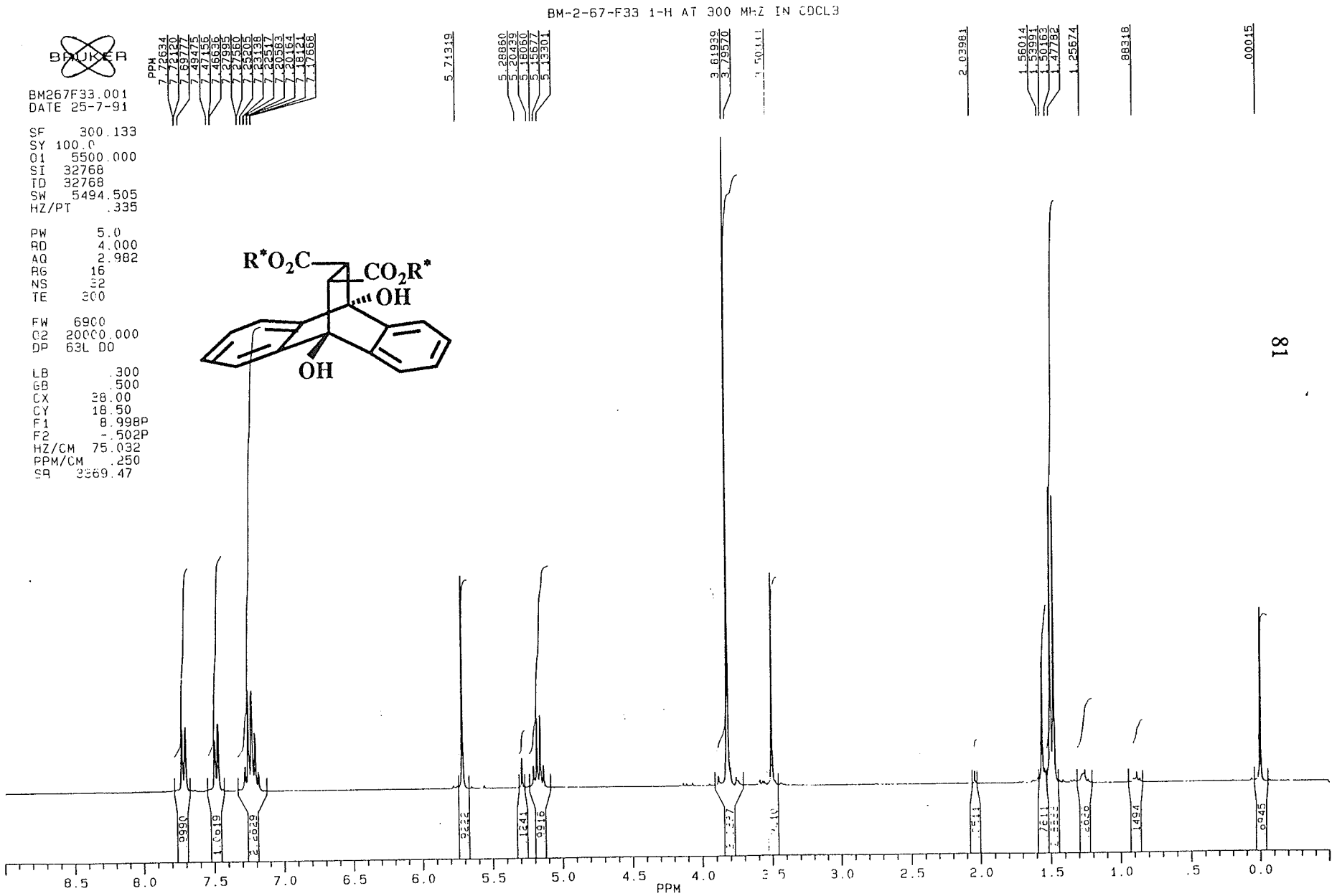
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.007P
F2 -.493P
HZ/CM 75.032
PPM/CM .250
SR 3366.79




SAMPLE BM-2-2-F1'-14' 1-H AT 300 MHZ IN CDCL3
BRUKER
BM2F114.001
AU PROG.
AUTOH1
DATE 5-9-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP 68L D0
LB .300
GB .500
CX 38.60
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3367.46
O
H
CHCO2R*
CH2CO2R*
PPM
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0


BM-2-55-CRY 1-H AT 300 MHZ IN CDCL3
BRUKER
BM255CRY.001
AU PROG.
AUTOH1
DATE 28-1-91
300.133
5500.000
32768
5494.505
8.0
4.000
2.982
100
32
300
6900
20000.000
38.00
18.50
9.005P
75.032
R*O2C
CO2R*
7.35084
7.33067
7.26270
7.13086
7.11980
7.10840
5.05305
5.02957
4.81735
3.77218
3.72807
3.40848
1.53670
1.47724
1.45376
.00789
PPM

80


BM-2-67-F33 1-H AT 300 MHZ IN CDCL3
BRUKER
BM267F33.001
DATE 25-7-91
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 5.0
RD 4.000
AQ 2.982
RG 16
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.998P
F2 -.502P
HZ/CM 75.032
PPM/CM .250
SR 3569.47
PPM
7.72634
7.72120
7.69777
7.49475
7.47156
7.46636
7.27995
7.27560
7.25205
7.23136
7.22517
7.20583
7.20164
7.18121
7.17668
5.71319
5.28860
5.20429
5.18060
5.15677
5.13301
3.61939
3.79570
2.03981
1.56014
1.53991
1.50163
1.47782
1.25674
.88318
.00015
R*O2C
CO2R*
OH
OH
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0