The Synthesis of Lignans and Lignan Analogs

by

Brigitte L. Yvon

a thesis

submitted to the Faculty of Graduate Studies

of the University of Manitoba in partial fulfillment

of the requirements for the Degree of

Master of Science

University of Manitoba

Winnipeg, Manitoba, Canada

THE UNIVERSITY OF MANITOBA

FACULTY OF GRADUATE STUDIES

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Table of Contents

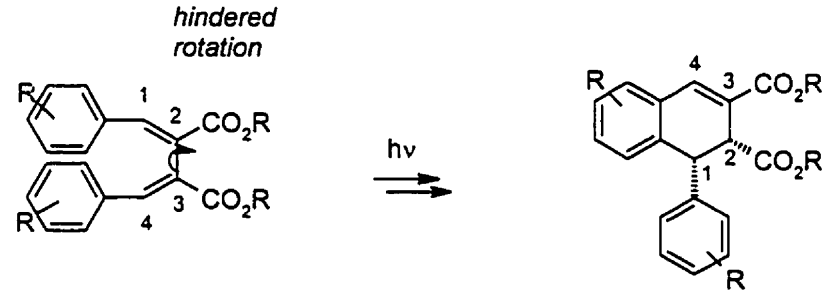
Abbreviations

Ac	acetyl
AcCl	acetyl chloride
Ar	aryl
t-Bu	*tert*-butyl
calcd.	calculated
d	doublet (spectral)
DCC	dicyclohexylcarbodiimide
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethyformamide
DMSO	dimethylsulfoxide
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
HMPA	hexamethylphosphorotriamide
HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
J	coupling constant (in NMR)
k	kilo
LDA	lithium diisopropylamide
m	multiplet (spectral)
μ	micro
MHz	megahertz
Me	methyl
MeOH	methanol
mp	melting point
m/z	mass to charge ratio (in mass spectrometry)
NMR	nuclear magnetic resonance
o-QDM	*ortho*-quinodimethane
p-TsOH	*para*-toluenesulfonic acid
rt	room temperature
S_N2	bimolecular nucleophilic substitution
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
vis	visible

Abstract

In this thesis *E,E*-dibenzylidenesuccinates were shown to exhibit atropisomerism, enantiomerism that originates from hindered rotation about the butadiene carbon - carbon single bond. It was found that the introduction of a bulky chiral auxiliary into an *E,E*-dibenzylidenesuccinate did not lead to the prejudicial formation of one atropisomer and did not raise the rotational barrier sufficiently to slow the interconversion between the two atropisomeric forms to the extent that they could be separated at room temperature.

In addition, the *E,E*-dibenzylidenesuccinates were found to undergo photochemical electrocyclic reactions and thermal 1,5-sigmatropic hydrogen shifts to give *cis*-1,2-dihydronaphthalenes.



E,E-Dibenzylidenesuccinate *cis*-1,2-Dihydronaphthalene

One of the photochemical electrocyclic reactions of the *E,E*-dibenzylidenesuccinates was studied for its application to photodynamic therapy, a therapy in which a photoactive compound is used to photochemically produce a medically therapeutic benefit. Another one of these photocyclic reactions was explored as a general method for the synthesis of the *trans*-1,2-dihydronaphthalene lignan, magnoshinin. Although the photochemical step in this reaction was ineffective, magnoshinin was successfully prepared by a more classical route.

The possibility of substantially increasing the barrier to rotation about the carbon-carbon butadiene single bond and/or prejudicing the formation of one atropisomer of an *E,E*-dibenzylidenesuccinate by linking the two carboxyl groups with a rigid chiral auxiliary was investigated with the idea that the photochemical cyclization of a single atropisomer could lead to the formation of an optically active *cis*-1,2-dihydronaphthalene. The strategy adopted, in order to obtain individual atropisomers, involved the introduction of a *trans*-1,2-cyclohexyl ring into the molecule to give an eight-membered dilactone. Several attempts were made to achieve this goal, but it was found that formation of dilactone was not possible using these methods.

Chapter 1

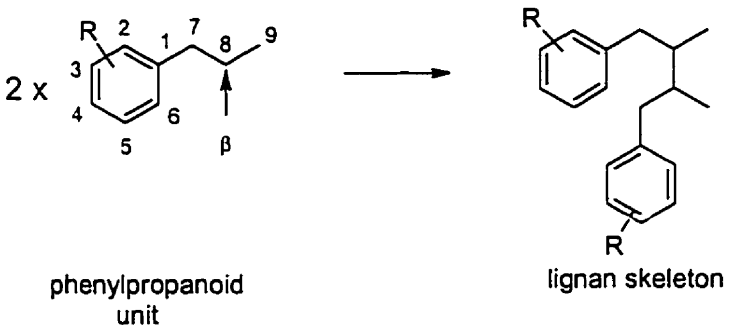
Introduction

Lignans form a class of natural products that are widely dispersed throughout the plant kingdom. Several lignans have also been detected in mammals but evidence suggests that these compounds arise from the microbial action on plant lignans in the gut.[1] The term "lignan" was introduced in 1936 by R. D. Haworth to denote structures that are comprised of two phenylpropanoid units linked by the central carbons of their side chain.[2] Lignans have long been of interest to organic chemists due to the challenges that accompany their synthesis and their diverse biological properties. Some members of this class of compounds possess a variety of intriguing photochemical properties. Some also exhibit a phenomenon referred to as atropisomerism, enantiomerism that originates from hindered rotation about carbon - carbon single bonds. It may be possible to exploit these chemical and physical properties in asymmetric lignan synthesis and/or photodynamic therapy. The introduction will give a brief review of lignans, lignan synthesis and the various biological properties that lignans possess. The subject of photodynamic therapy will also be reviewed. Included are discussions of the previously mentioned photochemical and physical properties, since these attributes may have applications in the asymmetric synthesis of lignans and lignan analogs.

1.1 Definition of Lignans

Lignans are a group of naturally occurring products found in plant material that are characterized by the union of two phenylpropanoid (C_6C_3) units with β-β' or C_8-C_8' linkages as shown in Scheme 1. The term "lignan" was introduced in 1936 by Haworth[1]

to encompass all phenylpropanoid dimers joined at the beta carbon. They are often found in woody plants and shrubs.

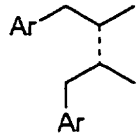


Scheme 1

1.2 Classification of Lignans

The phenylpropanoid dimer can be post-processed in the plant to varying degrees of oxidation. Further cyclization can also arise via the introduction of a C_6-C_7' or C_6-C_6' linkage. Accordingly, lignans can be divided into several subgroups based on their general structure as shown in Scheme 2, where the β-β' linkages are indicated with dashed lines. The dibenzylbutanes (**1**) are phenylpropanoid dimers that are joined only by β-β' bonds, while all the other lignan subgroups (**2-13**) have additional linkages. The more common subclasses of lignans are the dibenzylbutanes, diaryl or dibenzyl furans, butyrolactones, aryltetralins, and dibenzocyclooctadienes. Close relatives of the aryltetralin lignans are the aryl dihydronaphthalenes and arylnaphthalenes, which differ from each other and the aryltetralins in their degree of oxidation. There are many common variations in the substitution pattern on the aryl rings that occur in nature, including methylenedioxy, methoxy and hydroxy groups.[3] The position of substitution

on the aromatic ring also varies, but no lignan has ever been isolated with an unsubstituted phenyl ring.[3]



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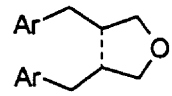
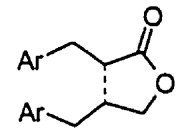
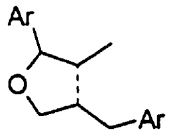
Dibenzylbutane



2
3,4-Dibenzylfuran



3
Dibenzylbutyrolactone



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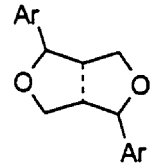
Arylbenzylfuran



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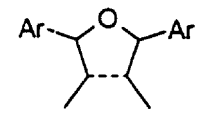
Diarylfurofuran



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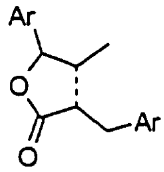
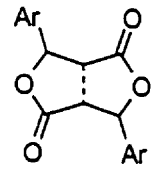
Diarylfuran



7
Arylbenzyllactone



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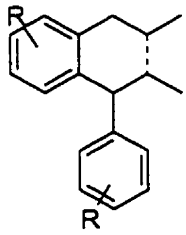
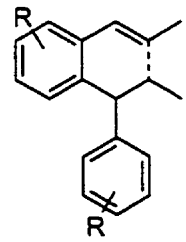
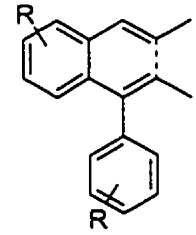
Diaryldilactone



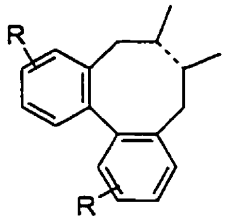
9
Aryltetralin



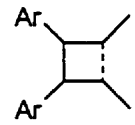
10
Aryldihydronaphthalene



11
Arylnaphthalene



12
Dibenzocyclooctadiene



13
Diarylcyclobutane

Scheme 2

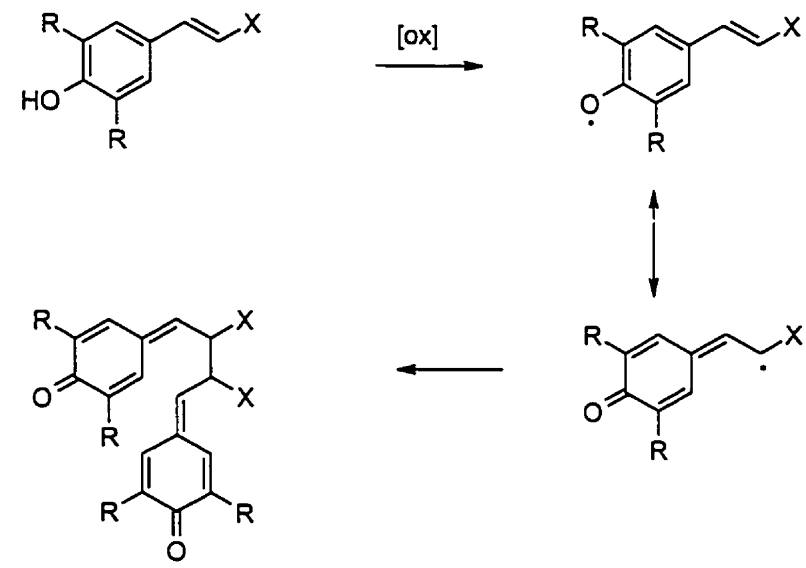
Thus there is an incredible diversity in lignan structure that arises from the construction of the lignan skeleton, the substitutions on the aryl rings and the various states of oxidation of the terminal groups. More than 200 members of this class of natural products have been identified[4] and there are several reviews available that catalog many of the known compounds.[5-10] Naturally occurring phenylpropanoid dimers with linkages other than β-β' are known and members of this class of compounds are referred to as neolignans.[11] These structural analogs are not as numerous or widely spread as lignans throughout the plant kingdom. A uniform system of nomenclature and numbering for lignans and neolignans has not yet been widely adopted. In fact, there is still controversy over the very definition of these two groups of compounds. Most authors prefer the definitions given here as they depict lignans and neolignans as having a fundamental chemical difference. Trivial names of old and newly discovered lignans are in common use. Typically, lignans are assigned names based on the plant species from which they are isolated. This convention will be retained throughout the introduction.

1. 3 Lignans in Nature

1.3.1 Lignans in Plants

Lignans have a widespread distribution within plants and have been isolated from all different parts of the plant including the wood, roots, leaves, flowers, fruit and seeds.[4] As for the biosynthetic origin of lignans, they are formed via the shikimate pathway.[5] It is hypothesized that the union of the phenylpropanoid units is enzyme catalyzed and occurs through free radical prompted dimerization of various *p*-hydroxyphenols

(cinnamyl alcohols, cinnamic acids, propenylphenols or allyl phenols), as shown in Scheme 3, although to date, there is little experimental evidence that supports this theory.



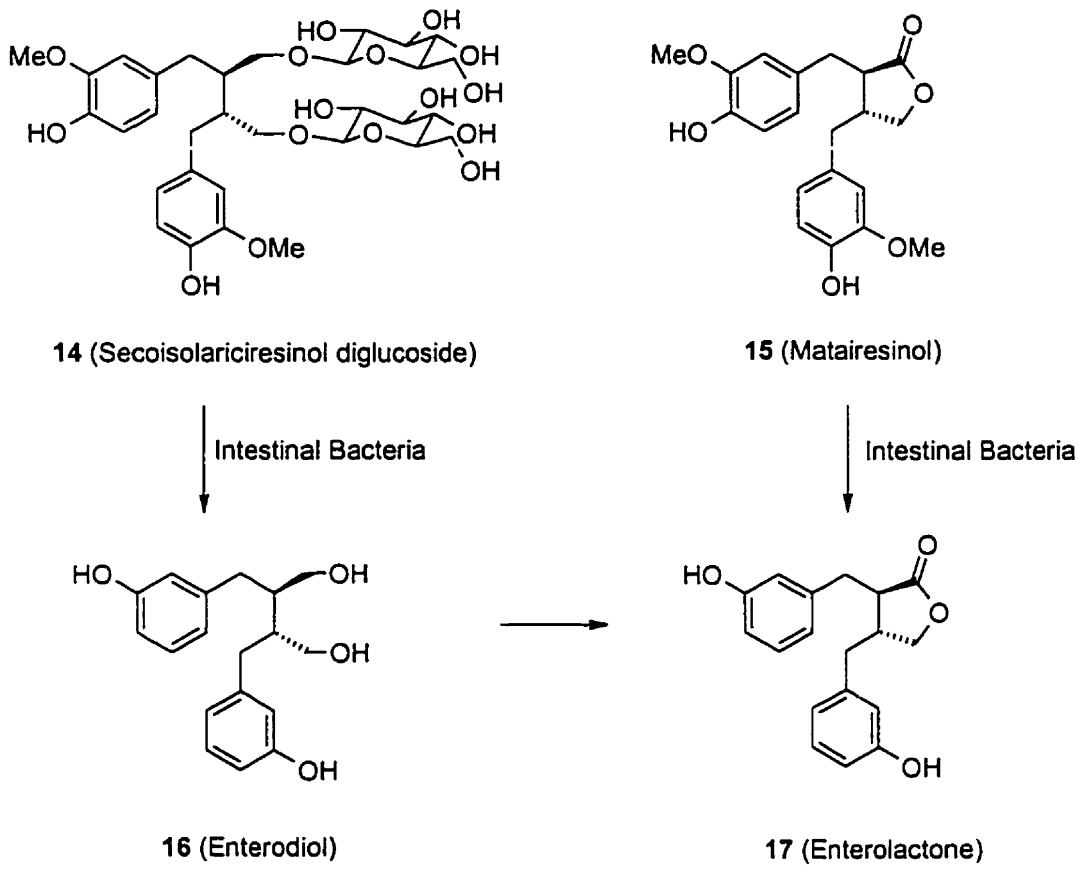
Scheme 3

1.3.2 Lignans in Animals

It is important to note that lignans have been found in man and primates. In particular, enterodiol (**16**) and enterolactone (**17**) have been detected in the urine of humans, baboons, vervet monkeys and rats. [12-14] These two lignans are not produced in plants and have been dubbed "mammalian lignans".

The presence of lignans in mammals does not necessarily indicate that they play an important role in mammalian biochemistry. In fact, there is evidence that suggests that mammalian lignans are simply the metabolic products from bacterial action in the gut of mammals that have consumed a diet rich in fiber. Secoisolariciresinol diglucoside (**14**) (SDG) and matairesinol (**15**), two lignans found in plant products, when consumed

by mammals are converted to their mammalian lignan counterparts by microbial processes in the gut[1] as shown in Scheme 4.



Scheme 4

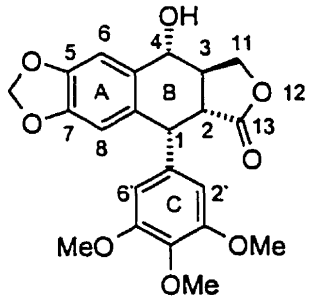
1.4 Biological Activity of Lignans

Lignans have long been well known for their many and varied biological activities in living organisms and have thus been the subject of several extensive reviews dealing with their biological properties.[3,4,16,17] Lignans have been found to exhibit antitumor, antiviral, antimitotic, antibacterial and antifungal properties as well as a host of physiological effects in man, insects and plants. Lignans have also been shown to exhibit

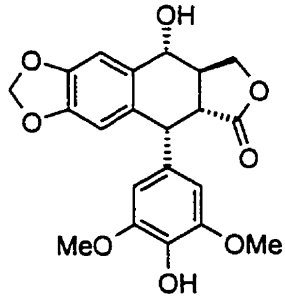
enzyme inhibition and have interesting effects on nucleic acids. More recently, lignans have found use as preservatives in the agriculture, food, rubber and pharmaceutical industries and as stabilizing agents for lubricants and polymers such as adhesives and plastics. The biological activity of lignans is widespread and varied, thus only a few examples of the more important biological properties will be discussed in detail here as they pertain to the treatment of human disease.

1.4.1 Antitumor and Antimitotic Activity of Lignans

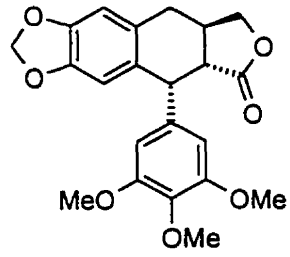
Lignans have gained importance since their discovery in 1936 because of the numerous biological properties that they possess. Amongst the most important of these properties is the ability of some lignans to arrest the rapid proliferation of cancer cells. About fifty years ago, researchers found that the alcoholic extracts of two closely related *Podophyllum* plant species containing lignans exhibited destructive effects towards cancerous cell growths in animals.[18] The group of lignans derived from the two *Podophyllum* plant species that are responsible for the antitumor activity of the extracts have been identified and have the aryltetralin general structure. Some examples of aryltetralin lignans exhibiting antitumor activity are given in Scheme 5. In an attempt to determine the mechanism of action against cancer cells and correlate activity with structure in podophyllotoxin type lignans, structure-activity relationship studies have been conducted.[19] Although certain features of aryltetralin lignans (and other lignan classes) have been implicated as being important or essential to the biological activity of the compound, few generalizations can be made based on the available information to date.



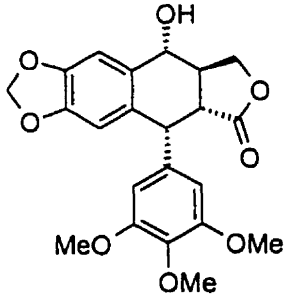
18 (Podophyllotoxin)



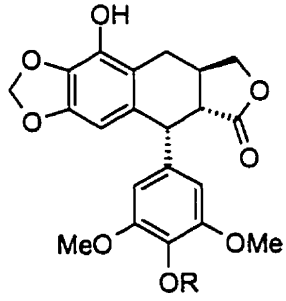
19 (4'-demethylpodophyllotoxin)



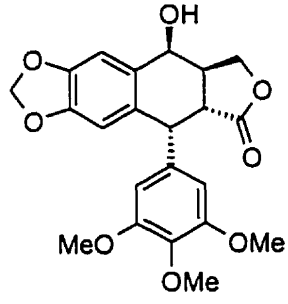
20 (Deoxypodophyllotoxin)



21 (Picropodophyllotoxin)



22 (alpha-Peltatin): R=H
23 (beta-Peltatin): R=CH_3



24 (Epipodophyllotoxin)

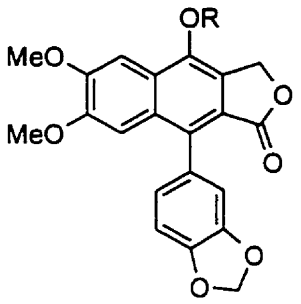
Scheme 5

It is evident that the configuration of C-4 affects antitumor activity in podophyllotoxin lignans. Epipodophyllotoxin and podophyllotoxin are diastereomers and differ only in the configuration at the C-4 position, yet epipodophyllotoxin is an order of magnitude less effective in its antitumor activity. The situation is complex, however, and not well understood. For example, positioning the hydroxyl substituent elsewhere on the molecule has surprising results. β-peltatin, which has the hydroxyl group at the C-5 position, has increased antitumor activity and deoxypodophyllotoxin is as potent an antitumor agent as podophyllotoxin itself. The configuration about the C-2 carbon also seems to be of importance in determining the antitumor activity of podophyllotoxins.

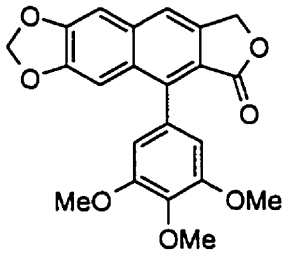
Picropodophyllotoxin, which differs from podophyllotoxin only in configuration at this center, shows a much lower activity as a direct result.

The mammalian lignans, enterodiol (**16**) and enterolactone (**17**), have also been implicated as anticancer agents.[20, 21] It has long been known that there is a significantly lower incidence of hormone-dependent cancers, such as breast and prostate cancer, in persons consuming a vegetarian diet rich in soybean and flaxseed. Studies have been conducted to assess the relative amounts of lignans produced from various plant foods by *in vitro* fermentation with human fecal microbiota.[10] The results showed that oilseeds, such as flaxseed and soybean, were the highest producers of lignans. Furthermore, the urinary levels of mammalian lignans were found to be significantly higher following periods of increased flaxseed consumption. It is hypothesized that the dietary plant lignans, secoisolariciresinol diglucoside (**14**) and matairesinol (**15**), which are converted to mammalian lignans enterodiol and enterolactone (Scheme 4), by the action of intestinal bacteria act as cancer-protective agents by an antiestrogenic action in persons consuming them.

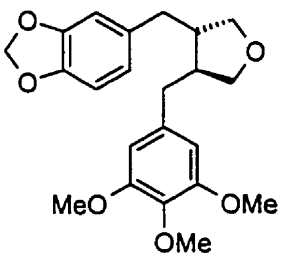
Although the aryltetralins are the best represented class of lignans with antitumor activity, members of other subgroups are also known to have antitumor activity[22-27] but they are not as effective as podophyllotoxin. Examples of other subclasses of lignans exhibiting antitumor properties are given in Scheme 6. These compounds and the podophyllotoxin derivatives have such structural diversity that it is difficult to find



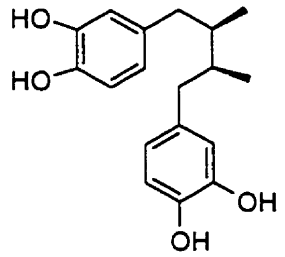
25 (Diphyllin): R=H
26 (Justicidin A): R=CH_3



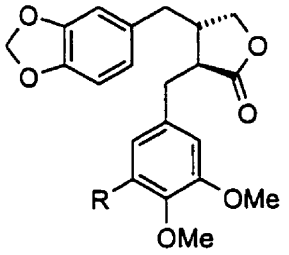
27 (Dehydroanhydropicro-podophyllotoxin)



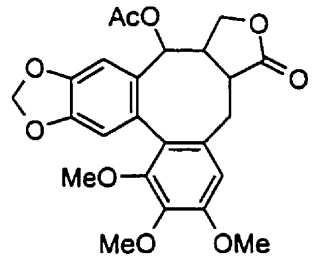
28 (Burseran)



29 (Nordihydroguaiaretic acid)



30 ((-)-trans-2-(3``,4``-Dimethoxybenzyl)-
-3-(3`,4`-methylenedioxybenzyl)butyrolactone
,R=H
31 ((-)-trans-2-(3``,4``,5``-Trimethoxybenzyl)-
-3-(3`,4`-methylenedioxybenzyl)butyrolactone
, R=CH_3



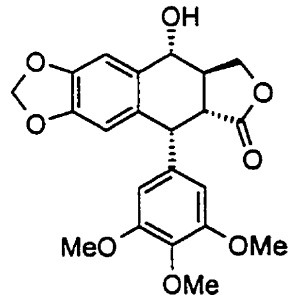
32 (Stegnacin)

Scheme 6

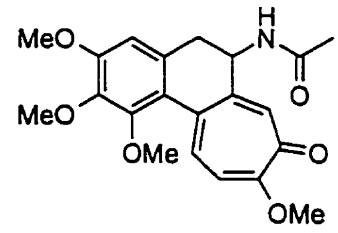
even a single unique underlying characteristic that may account for their antitumor activity. A common feature of antitumor lignans is the presence of a methylenedioxyphenyl group. Although this feature must have an important role in eliciting a response, it is clearly not an absolute requirement. The only conclusion that can be drawn from the large variation in structure amongst these lignans is that there are probably several different modes of action for different structures.

Many lignans of the podophyllotoxin type also have demonstrated antimitotic activity in that they are able to arrest cell growth at the metaphase stage of the growth cycle. Podophyllotoxin type lignans have been shown to bind to purified tubulin

preparations.[19] These compounds have destructive behavior towards cells as they inhibit the assembly of microtubule subunits or tubulin monomers to form microtubules or tubulin polymers. Tubulin polymerization is an integral part of cell division and microtubules in the cellular cytoskeleton have been implicated in vital cellular activities and processes such as cell wall synthesis. Interference with these processes is disastrous, as it not only interferes with cell division but also the structural integrity of the cell. This inevitably leads to cell death. Podophyllotoxin disrupts the dynamic equilibrium between the tubule monomers and tubulin polymers, which results in the disassembly of microtubules. It has been suggested that podophyllotoxin (**18**) competes for the same binding site on tubulin as colchicine (**33**). [4, 28] In fact, podophyllotoxin has been shown to have twice the affinity for tubulin as colchicine. Colchicine is a known microtubule poison that prevents the assembly of microtubules and promotes microtubule disassembly thereby arresting mitosis in cells.[29, 30] Colchicine and podophyllotoxin both have two sites of contact, but only one site in common, that being the 3,4,5-trimethoxyphenyl moiety.[31]



18 (Podophyllotoxin)

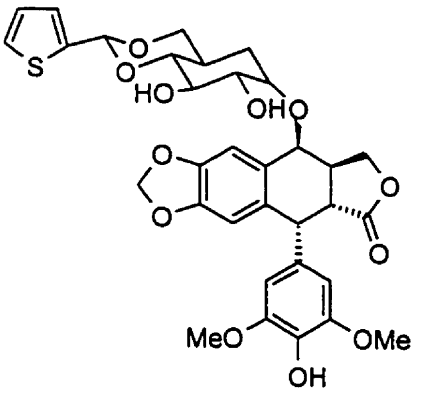


33 (Colchicine)

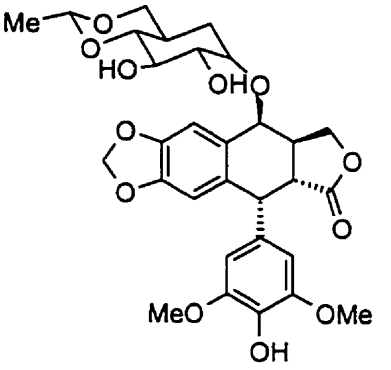
Scheme 7

Although it is of paramount importance to the antimitotic activity of podophyllotoxin, the 3,4,5-trimethoxyphenyl group is not a prerequisite to antitumor activity of podophyllotoxin analogs and lignans in general. This is exemplified by the fact that 4'-demethylpodophyllotoxin, which lacks this feature, has an antitumor activity comparable to that of podophyllotoxin.[19]

Not surprisingly, podophyllotoxin and some podophyllotoxin analogs, like other chemotherapeutic agents, are extremely toxic, leading not only to the death of cancer cells, but healthy cells as well. This has limited the use of podophyllotoxin as a chemotherapeutic agent for the treatment of cancer. Two semisynthetic derivatives of podophyllotoxin, teniposide (**34**) and etoposide (**35**), were developed to overcome the problem of non-selectivity of podophyllotoxin towards healthy cells versus cancer cells. The endeavor was successful and the derivatives (Scheme 8) are currently used for the clinical treatment of several varieties of leukemia, lymphoma, small cell lung cancer and germinal testicular cancer.[32] Unlike podophyllotoxin, etoposide and teniposide function by inhibiting the enzyme topoisomerase II, an enzyme that is responsible for the uncoiling of double-stranded DNA during cell replication. Topoisomerase II clips super-coiled DNA and allows it to relax in order for replication to occur, then reseals it. Etoposide and teniposide stabilize the topoisomerase-DNA complex, which promotes excessive breakage and inadequate reattachment of DNA fragments and the end result is cell death. Etoposide and teniposide are selective for cancer cells due to their interaction with topoisomerase II, which is abundant in the rapidly proliferating cancer cells.



34 Teniposide (VM-26)



35 Etoposide (VP-16-213)

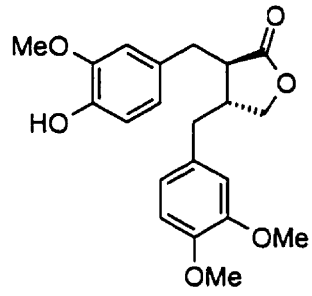
Scheme 8

1.4.2 Antiviral Activity of Lignans

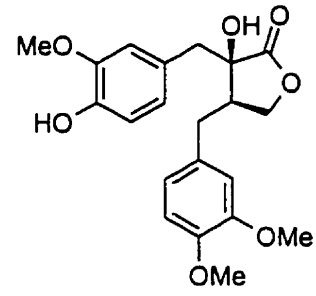
In addition to their antitumor and antimitotic properties, the extracts of several *Podophyllum* species have been known for their antiviral effects for many years. A crude extract of *Podophyllum peltatum* has been shown to have antiviral activity towards herpes symplex II, influenza A and vaccinia viruses.[33] Podophyllotoxin (**18**), deoxypodophyllotoxin (**20**), picropodophyllotoxin (**21**) and α-peltatin (**23**) have been shown to be effective against herpes symplex I.[34] Podophyllotoxin is used for the clinical treatment of condyloma acuminata (venereal warts), a disease which is caused by the human papilloma virus. The herpes symplex II and human papilloma viruses are especially harmful towards humans, as they have been implicated in cervical cancer. Although the mechanisms leading to the antitumor activity of podophyllotoxin derivatives has been extensively studied and is fairly well understood, the mode of action of podophyllotoxins exhibiting antiviral properties is still subject to conjecture. One hypothesis is that these lignans elicit the observed response in the same way they function as antimitotic agents.[4] In other words, podophyllotoxin type lignans are thought to

inhibit viral release owing to their interference with microtubule formation and as a result reduce the production of viruses by infected cells.

Lignans from subclasses other than the aryltetralins have also shown antiviral activity. Of particular importance are the benzylbutyrolactones (-)-arctigenin (**36**) and (-)-trachelogenin (**37**), isolated from the tropical climbing shrub *Ipomoea cairica*, which have been shown *in vitro* to strongly inhibit replication of the human immunodeficiency virus (HIV-1).[10] It is thought that these two compounds function by enzyme inhibition of topoisomerase II which is involved in viral replication after cellular infection by HIV-1.



36 (-)-Arctigenin



37(-)-Trachelogenin

Scheme 9

1.4.3 Miscellaneous Physiological Effects of Lignans

Lignans possess a myriad of biological properties and amongst these are a host of interesting physiological effects that are exhibited in a wide variety of living organisms. Lignans have been known to have cathartic, antimicrobial and antifungal activity, in addition to their roles as allergens and insecticides. Lignans have also been found to possess stress-reducing activity and have profound effects on the cardiovascular and central nervous systems in mammals. Plants containing lignans have been used as

therapeutic agents in Chinese herbal preparations for the treatment of various human ailments for more than 2000 years.

The magnitude and diversity of biological properties that lignans exhibit in humans and other living organisms is remarkable. Many of the members of this general class of compounds could prove to be excellent candidates for the treatment of human disease. Unfortunately, in most cases the structural features that govern lignan behavior in living organisms is poorly understood. New methods to facilitate the expedient synthesis of lignans are required in order to facilitate more systematic investigations of their biological activities. Insight into the factors which modulate the many biological properties of lignans may lead to the development of new treatments for human disease and will certainly further an understanding of their biological effects.

1.5 Synthesis of Lignans

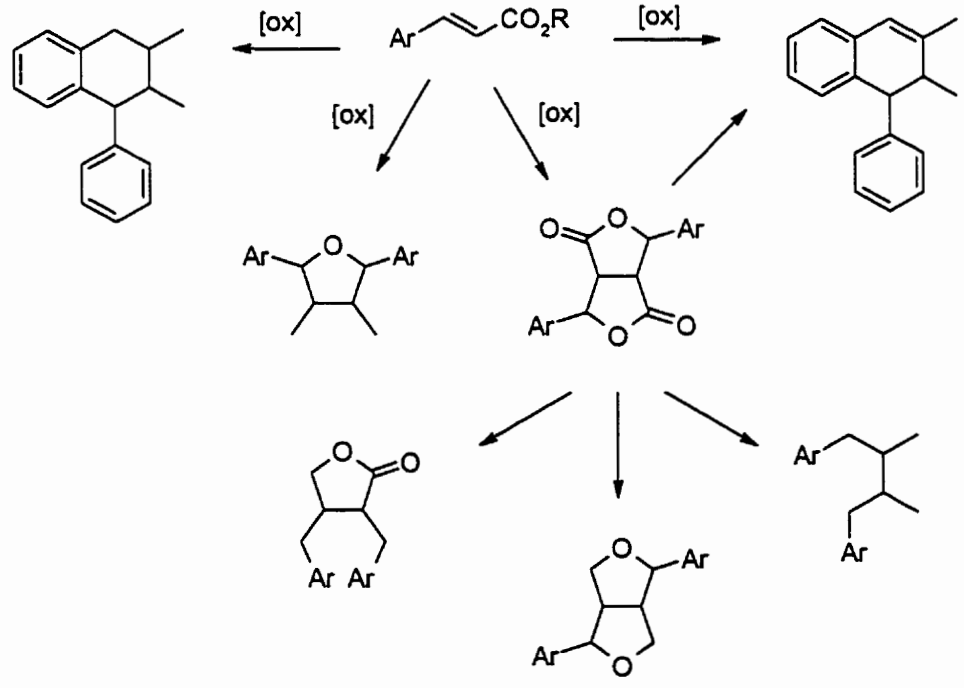
As a result of their staggering number of biological properties and incredible structural diversity, lignans have long been of interest to synthetic organic chemists. The potential of lignans as effective drugs and their prospective value to the pharmaceutical industry have made them the target for innumerable synthetic endeavors. There has been a cornucopia of accounts of lignan syntheses given in the literature[3, 5-10, 35-38], a few of which will be given here. The various methods that have been used for the preparation of lignans discussed in this section will be classed by reaction type rather than lignan structure in order to provide a brief overview of lignan synthesis.

Lignan synthesis fundamentally relies on a limited number of integral reactions that are required for the construction of the basic 18-carbon skeleton whose modification

(e.g. cyclization, reduction, oxidation, hydration) generates the entire set of lignan compounds.

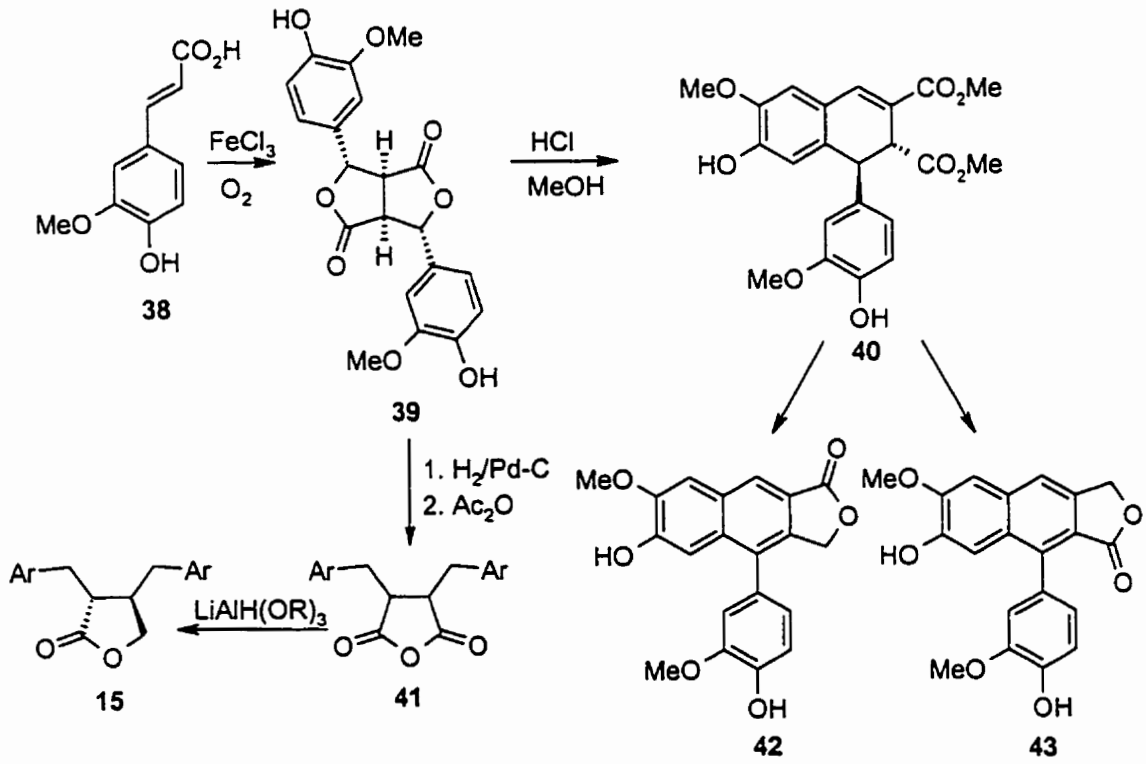
1.5.1 Oxidative Coupling

Some lignans can be synthesized directly from cinnamic acid derivatives through the use of conventional oxidizing agents. The phenolic oxidative coupling reactions of cinnamic acids is an efficient route that has been used to obtain a number of the general lignan structures as shown in Scheme 10. This method has been used to prepare a variety of lignans such as the diarylfurans, diaryldilactones, aryldihydronaphthalenes and aryltetralins. Synthesis of the diaryldilactone structure provides a convenient means to a variety of lignans. The diaryldilactones can undergo a range of structural modifications and have been converted to diarylfurofurans, dibenzylbutyrolactones, diarylfurans, dibenzylbutanes and aryldihydronaphthalenes.



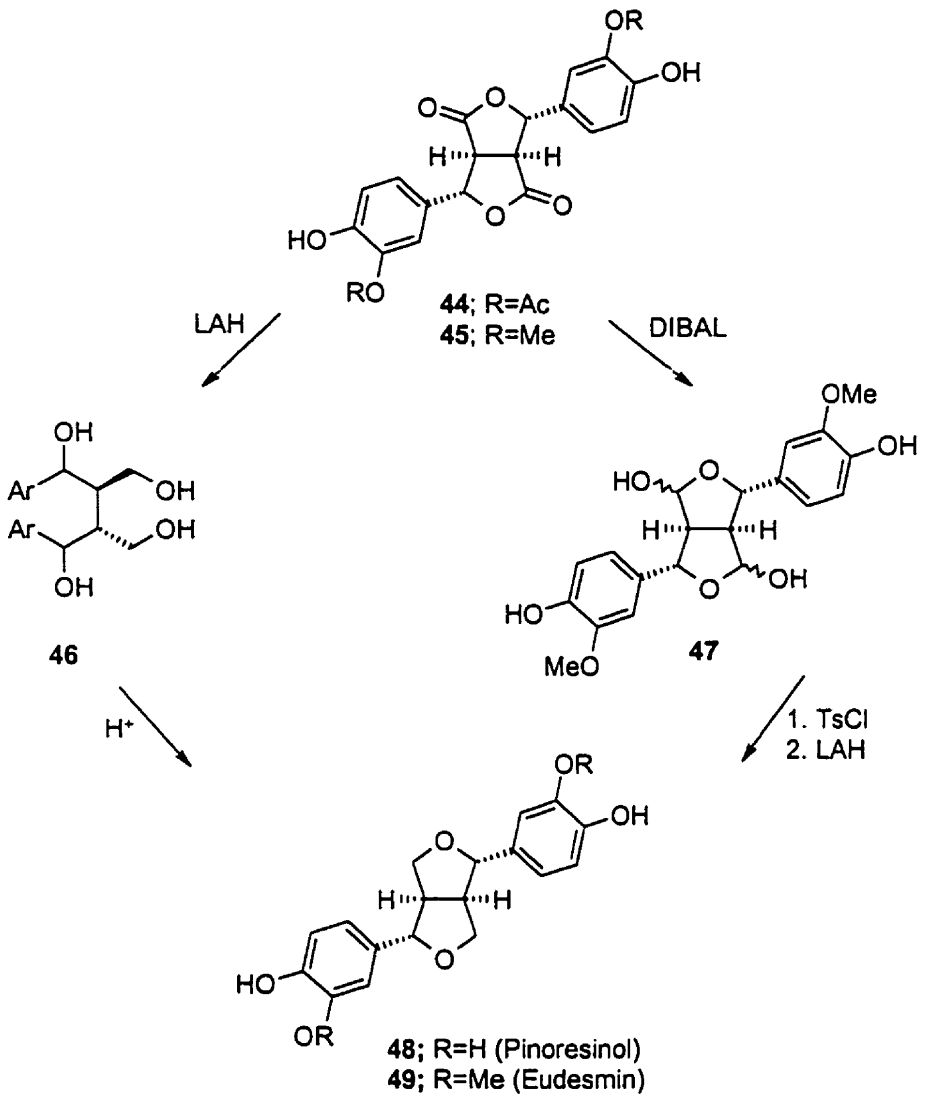
Scheme 10

The synthesis of the dibenzylbutyrolactone matairesinol (**15**) was achieved via the phenolic oxidative coupling of ferulic acid **38** through a diaryldilactone precursor as shown in Scheme 11.[39] The dilactone was converted to **41** by hydrogenation followed by dehydration. **41** was then further reduced to afford matairesinol. Dilactone **39** was also converted to the corresponding aryldihydronaphthalene by treatment with methanolic HCl. Arylnaphthalenes **42** and **43** were prepared from aryldihydronaphthalene **39** in several steps including oxidation, hydrolysis, reduction and lactonization.



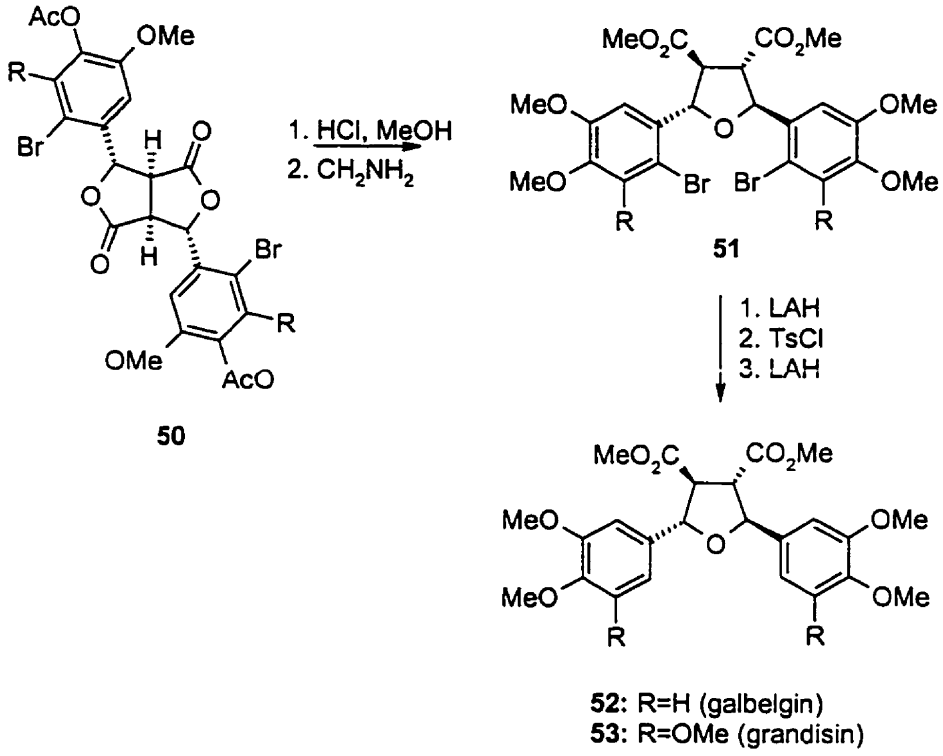
Scheme 11

Two derivatives of dilactone **39** were used in the preparation of diarylfurofuran lignans pinoresinol and eudesmin[39] by selective reduction of the acetylated lactone **44** or methylated derivative **45**.



Scheme 12

Dilactones are useful for the preparation of diarylfuran lignans.[40,41] In the usual manner, dilactone **50** was treated with methanolic HCl, but in this case, the presence of a halogen in the *ortho* position of the aromatic ring diverted the normal course of cyclization. Thus, diarylfuran **51** was obtained rather than the expected aryldihydronaphthalene product. Reduction of the aromatic bromide and carboxy-ethyl groups afforded lignans galbelgin (**52**) and grandisin (**53**) (see Scheme 13).

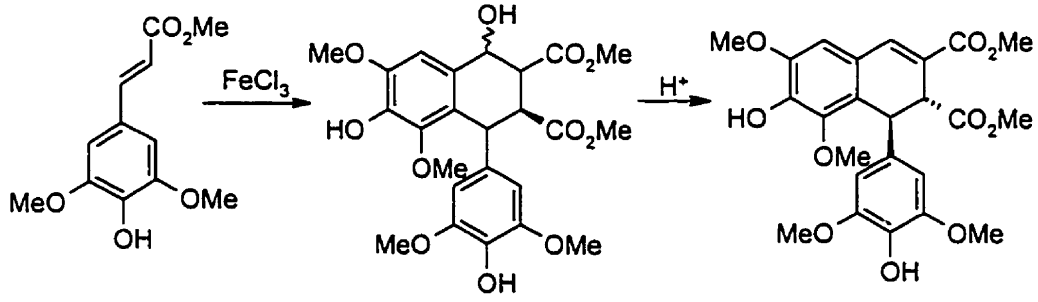


50 **51**

52: R=H (galbelgin)
53: R=OMe (grandisin)

Scheme 13

Phenolic oxidative coupling can also be used to prepare various aryltetralin lignans directly.[42] For example, methyl sinapate (**54**), upon treatment with ferric chloride, yielded 4-hydroxyaryltetralin **55** as the major product (61%). Acid catalyzed dehydration afforded the dimethyl ester of thomasadioic acid (**56**).

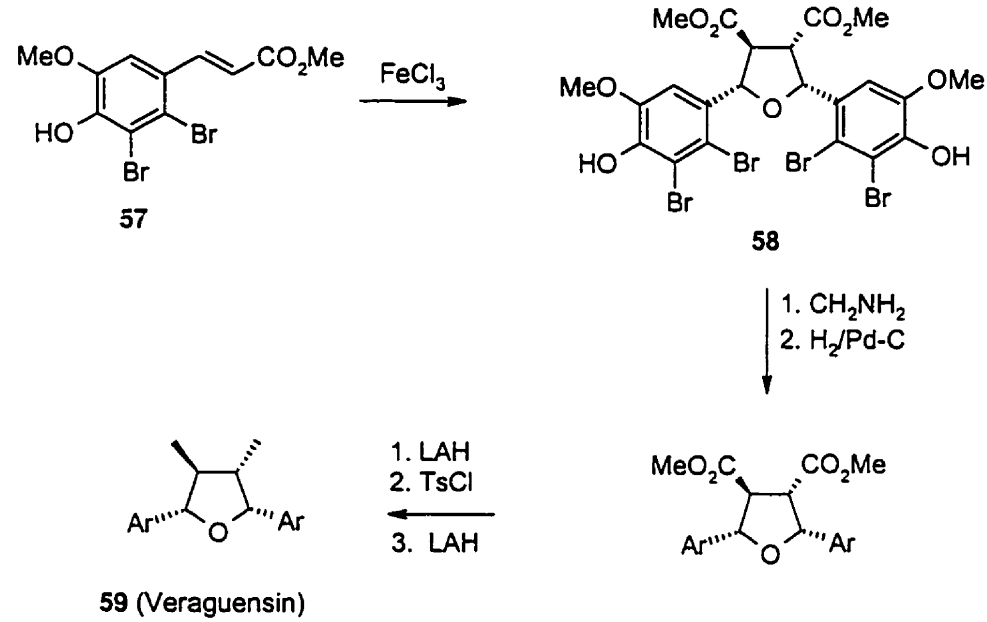


54 **55** **56**

Scheme 14

Phenolic oxidation of certain ferulate ester derivatives has led to the formation of the corresponding diarylfuran lignans[42] as illustrated in Scheme 15. Oxidative coupling

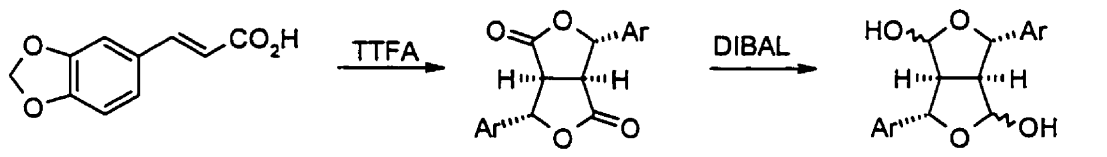
of dibromoferulate (**57**) afforded the diarylfuran derivative **58**. Subsequent reduction of the arylbromides and carboxy-ethyl groups gave verguensin (**59**).



57 **58** **59** (Veraguensin)

Scheme 15

Non-phenolic oxidative coupling to prepare lignans is also possible with the use of relatively new reagents such as thalium(III) trifluoroacetate. Non-phenolic coupling can be used to generate the useful diarylactone structures as shown in Scheme 16. The preparation of dilactone (**60**) was effected via oxidative coupling. Subsequent reduction afforded 4, 8-dihydroxysesamin (**61**).[39]

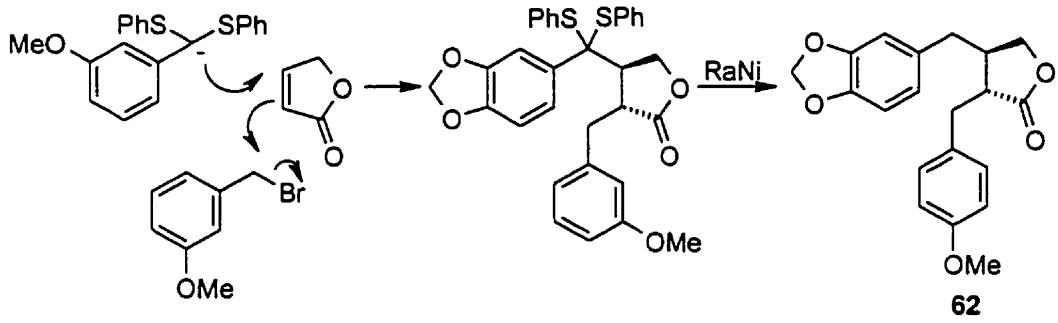


60 **61** (4, 8-Dihydroxysesamin)

Scheme 16

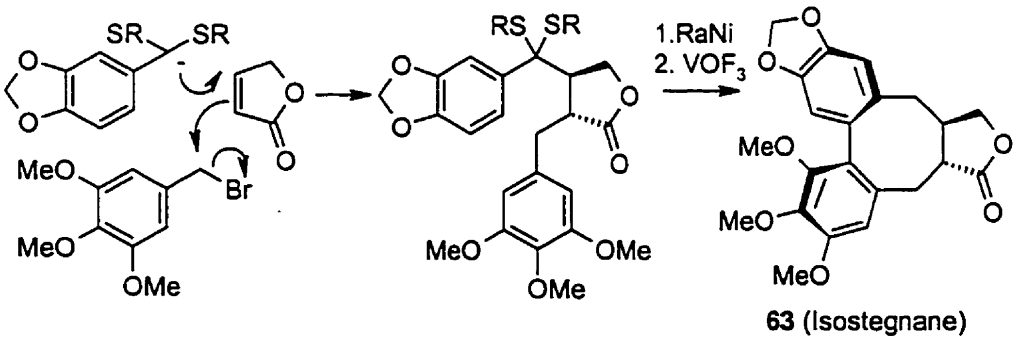
1.5.2 Tandem Conjugate Addition

The conjugate addition of a thioacetal carbanion to butenolide and subsequent trapping of the ensuing enolate carbanion with an appropriate electrophile has been used for the synthesis of many lignan compounds. Conjugate addition provides an efficient and convenient means for the asymmetric synthesis of optically active dibenzylbutyrolactone lignans as shown in Scheme 17.[43] Once the basic lignan skeleton has been constructed, it can then be modified to generate a variety of general lignan structures.



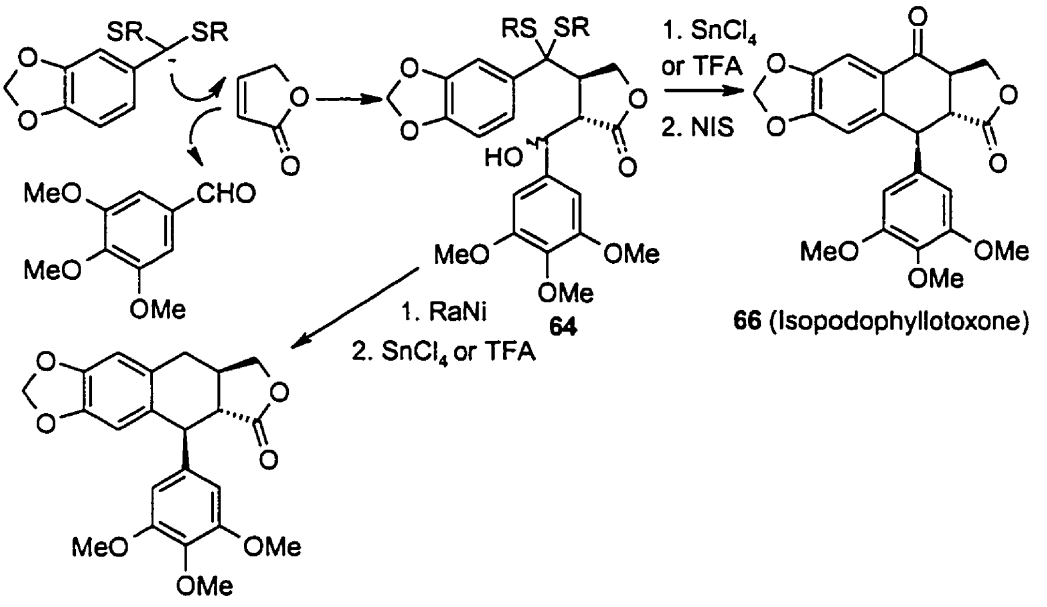
Scheme 17

Conjugate addition has been used in the synthesis of isostegnane (**63**), a benzocyclooctadiene.[44] Treatment of the butyrolactone structure with vanadium oxyfluoride results in the formation of the required 8-membered ring.



Scheme 18

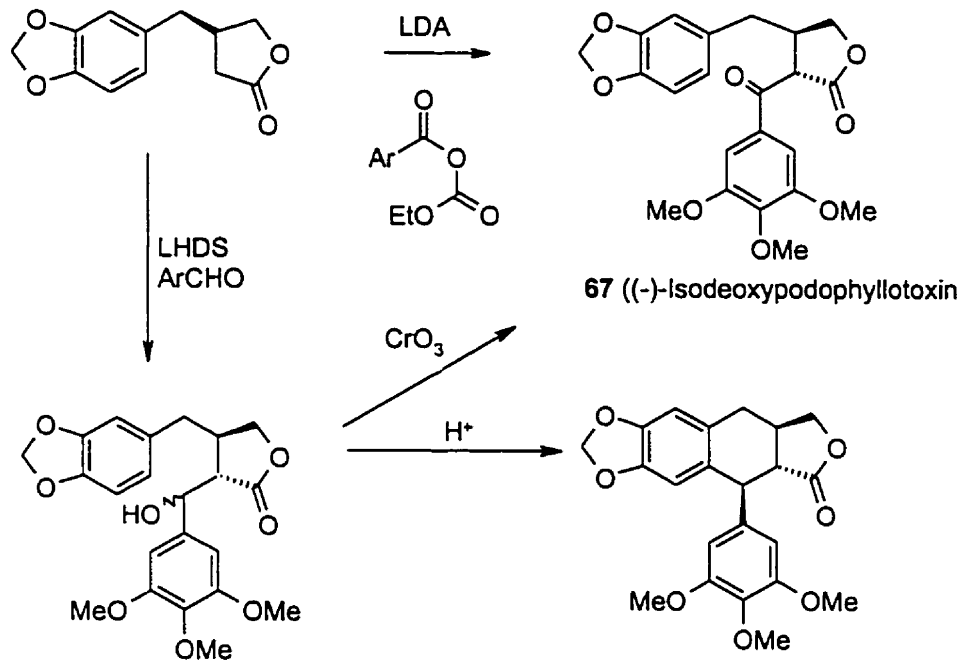
This reaction type is also useful for the preparation a variety of podophyllotoxin lignans. For example, deoxypodophyllotoxin (**65**) and isopodophyllotoxone (**66**) were prepared from a common butyrolactone precursor.[45]



Scheme 19

1.5.3 Alkylation of Benzylbutyrolactones

This reaction type is closely related to the reactions described above. Tandem conjugate addition and the alkylation of butyrolactones both generate the dibenzylbutyrolactone skeleton by trapping an intermediate enolate carbanion with a suitable electrophile. As above, the dibenzylbutyrolactone can then be cyclized to afford a range of aryltetralin lignans. Tomioka *et al.*[46,47] have reported the asymmetric syntheses of several lignans including, (-)-isodeoxypodophyllotoxin (**67**), (+)-podorhizon (**68**) and (-)-podorhizol (**69**) by employing chiral butyrolactones (Scheme 20).



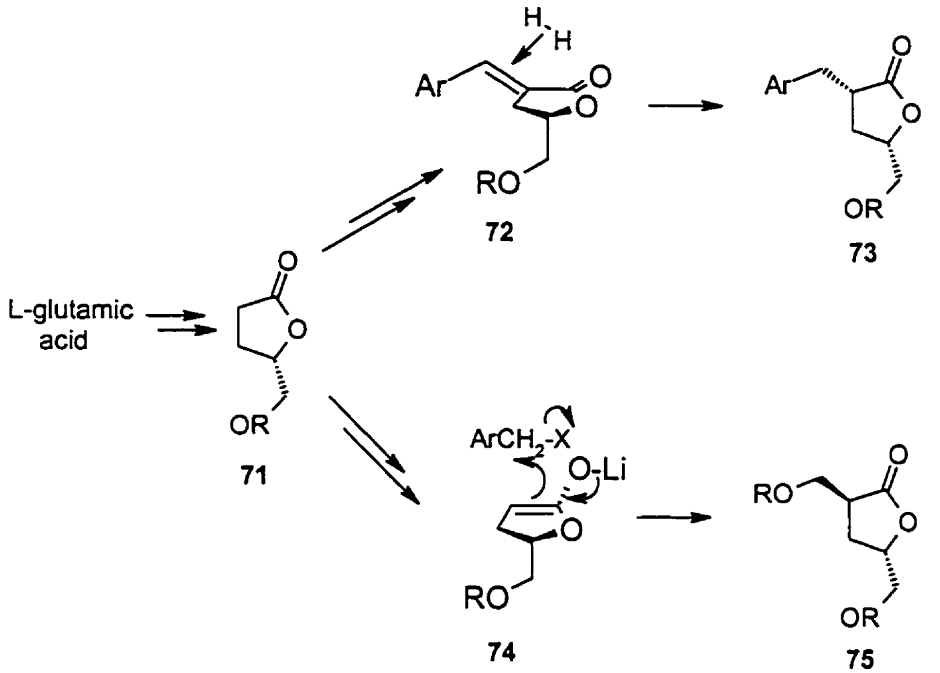
67 ((-)-Isodeoxypodophyllotoxin)

69 ((-)-Podorhizol)
70 ((-)-Epipodorhizol)

68 ((+)-Podorhizon)

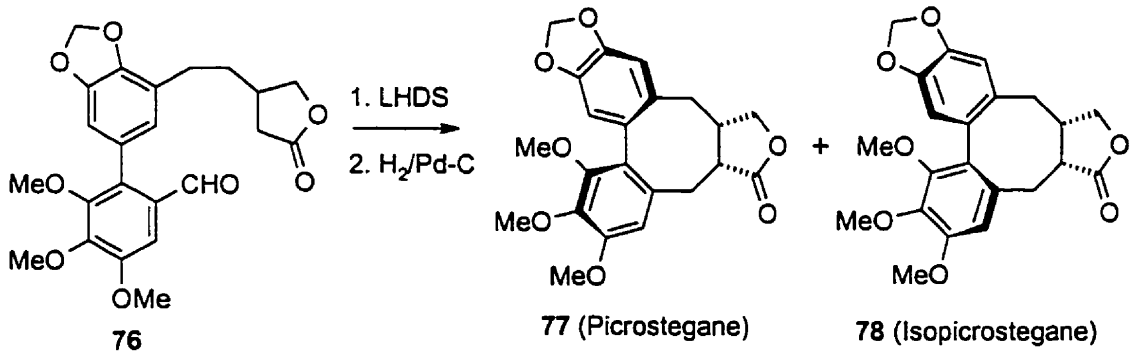
Scheme 20

The same authors have devised a method for the synthesis of chiral benzylbutyrolactones as illustrated in Scheme 21. Optically active benzylbutyrolactones **73** and **75** were prepared from a common precursor, lactone **71**. Lactone **71** was in turn prepared from L-glutamic acid in a multistep sequence. Asymmetric reduction of alkene **72** afforded benzylbutyrolactone **73**. In contrast, asymmetric alkylation of enolate **74** gave, after additional reactions, chiral benzylbutyrolactone **75**.



Scheme 21

Benzylbutyrolactones have also been used for the synthesis of lignans with the dibenzocyclooctadiene general structure.[46-51] For example, the intramolecular aldol reaction of biaryl derivative **76** afforded the basic lignan skeleton which after further modification gave picrostegane (**77**) and isopicrostegane (**78**) as shown in Scheme 22.

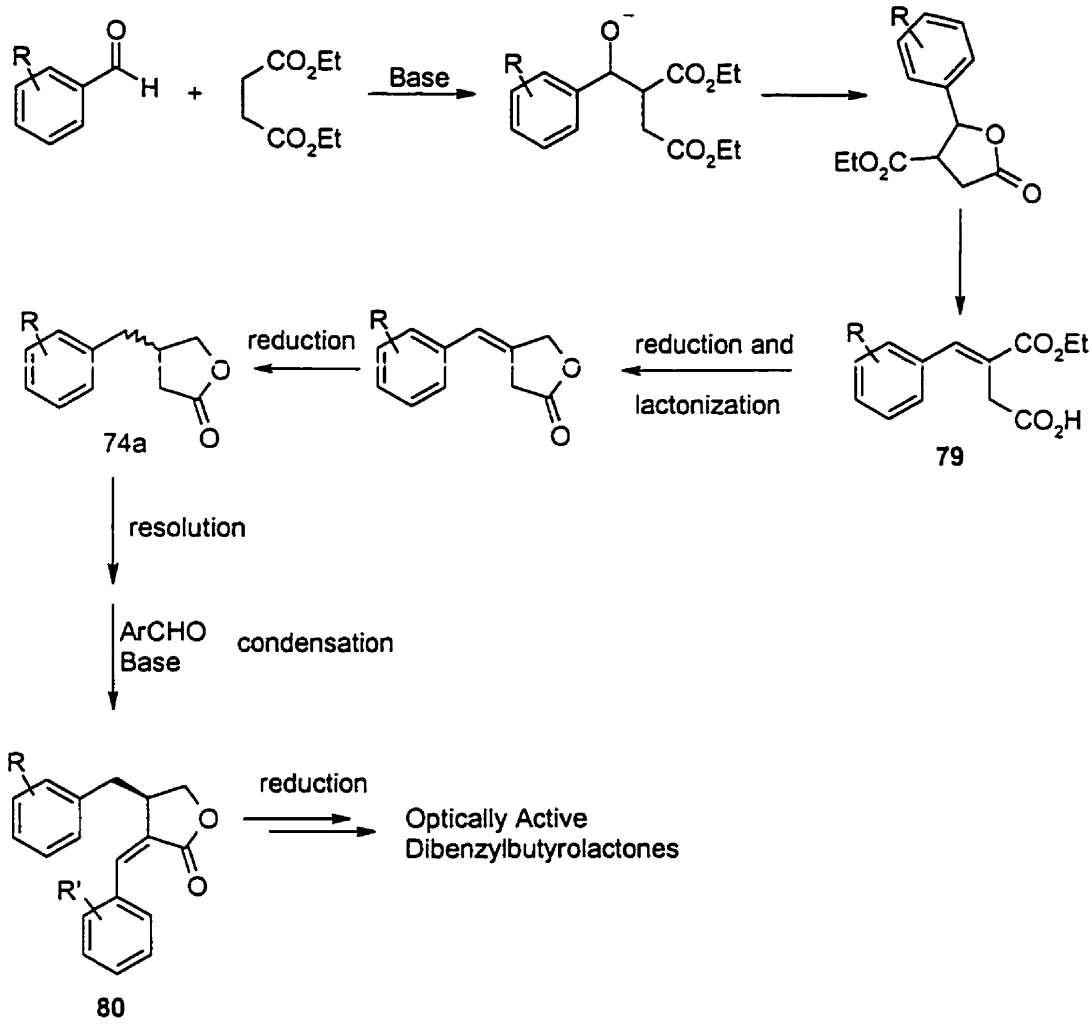


Scheme 22

1.5.4 Stobbe Condensation

This extremely versatile reaction is commonly used for the construction of the basic lignan skeleton.[52-56] The Stobbe condensation is the reaction of an aromatic aldehyde with a succinate ester to give *trans*-benzylidene succinate monoester **79**.[57,58a] This reaction has also been used for the preparation of chiral dibenzylbutyrolactone lignans and a general example is given in Scheme 23. The mechanism illustrates why the monoester is the product of the reaction. The carboxyethyl group can be selectively reduced. Subsequent lactonization and hydrogenation affords the racemic saturated lactone **74a**. Lactone **74a** can be resolved and condensed with a second equivalent of aromatic aldehyde to give the general lignan skeleton. Asymmetric reduction of the double bond leads to optically active dibenzylbutyrolactone **80**.

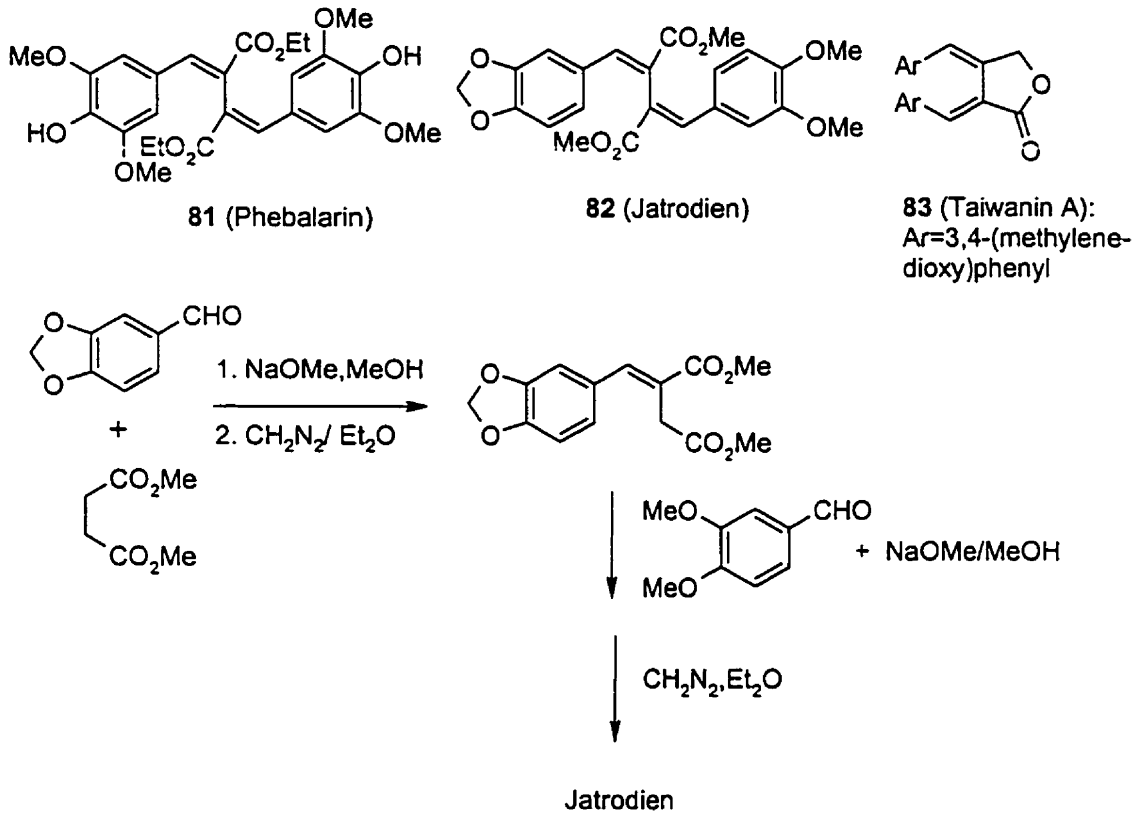
The stereochemistry of the *trans*-benzylidene generated by the Stobbe condensation of an aromatic aldehyde and succinate ester has been assigned based on NMR studies.[58a] The olefinic proton in the *trans*-arrangement gives a signal at a lower field than the corresponding *cis*-arrangement owing to the diamagnetic anisotropic deshielding effect of the adjacent carbonyl group.



Scheme 23

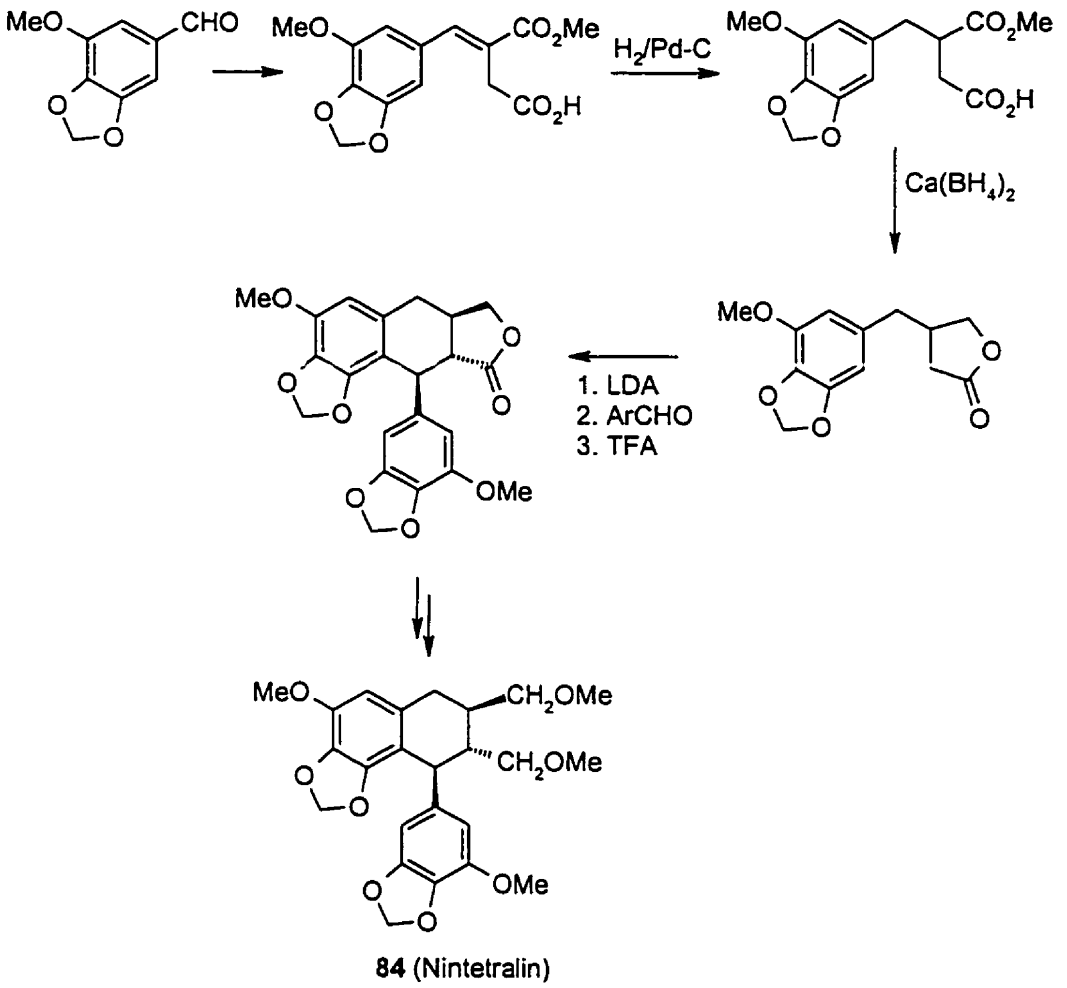
The successive Stobbe condensation of a *trans*-benzylidene succinate with another equivalent of aldehyde in refluxing alcohol/alkoxide affords a dibenzylidene succinate or diarylbutadiene structure. The dibenzylidene structures generated by two successive Stobbe condensations have a *trans, trans*-arrangement about the two double bonds, as do the three naturally occurring diarylbutadiene lignans, phebalarin (**81**),[58b] jatrodien (**82**)[58c] and taiwanin A (**83**),[58d] as shown in Scheme 24. The stereochemistry of the *E,E*-isomers have been unequivocally established by numerous NMR and x-ray crystallographic studies.[58a,c-i] Thus, the Stobbe condensation is ideally suited to the

synthesis of diarylbutadiene lignans and has been applied to the synthesis of jatrodien (**82**).[58c]



Scheme 24

The Stobbe condensation has also been used for the preparation of aryltetralin lignans[59,60] as illustrated in Scheme 25. The butyrolactone skeleton was prepared in the usual manner and subsequent condensation with another equivalent of aldehyde gave the diarylbutadiene skeleton, which after intramolecular Friedel-Crafts alkylation and further modification, afforded nintetralin (**84**).

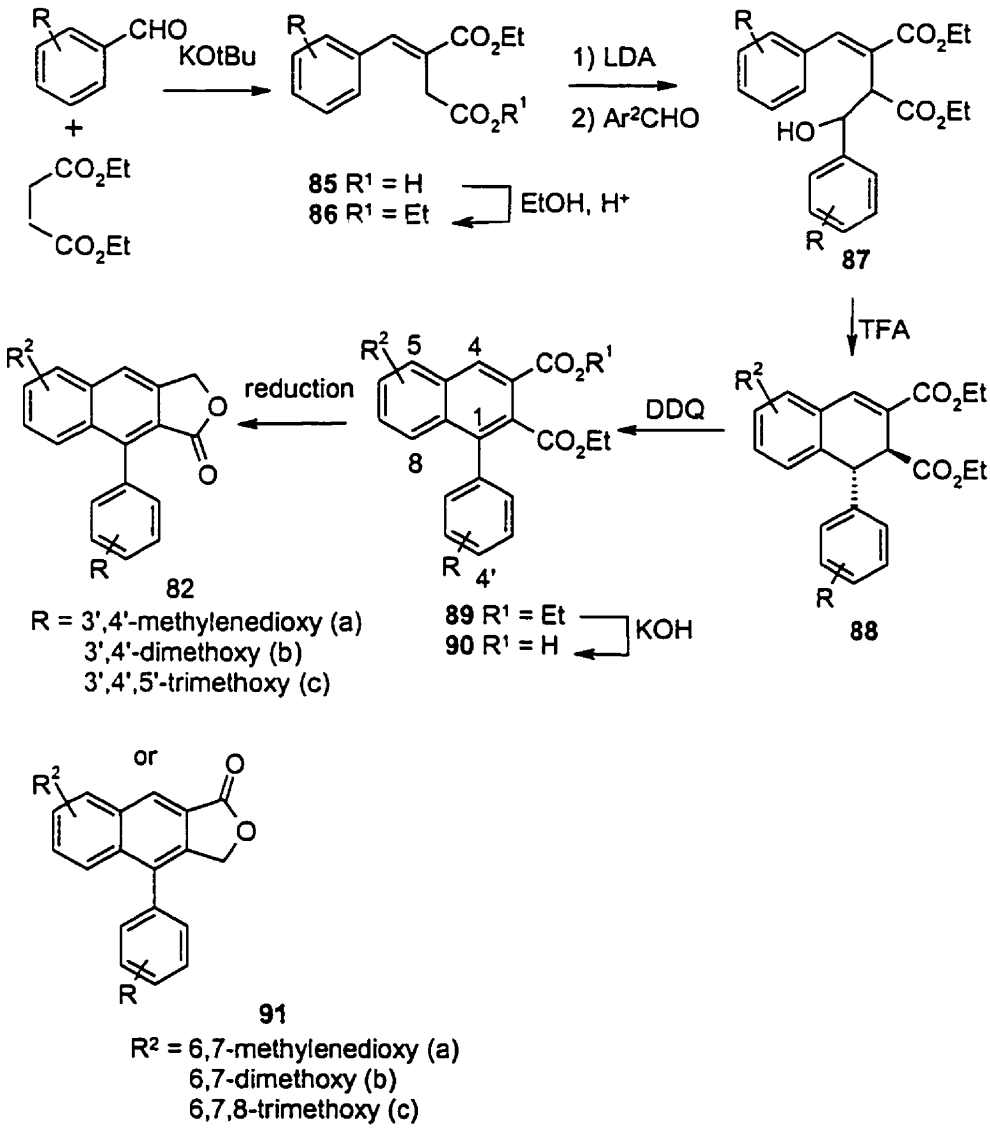


84 (Nintetralin)

Scheme 25

Charlton *et al.*[61] reported that the condensation of the Stobbe benzylidene diester with an equivalent of aromatic aldehyde could be prevented from eliminating to form the diarylbutadiene and instead be made to form alcohol **87**. This could be accomplished by employing LDA as a base thereby making the second Stobbe reaction irreversible, and quenching the reaction at low temperatures. Immediate treatment of the alcohol **87** with TFA promoted cyclization and afforded the dihydronaphthalene lignan **88**. Subsequent oxidation of **88** with DDQ gave the fully aromatic products. The aromatic diesters were selectively hydrolyzed at the C-3 position owing to steric hindrance by the phenyl ring

adjacent to C-2. Selective reduction and lactonization gave a variety of lignan lactones and retro lactone structures as illustrated in Scheme 26.



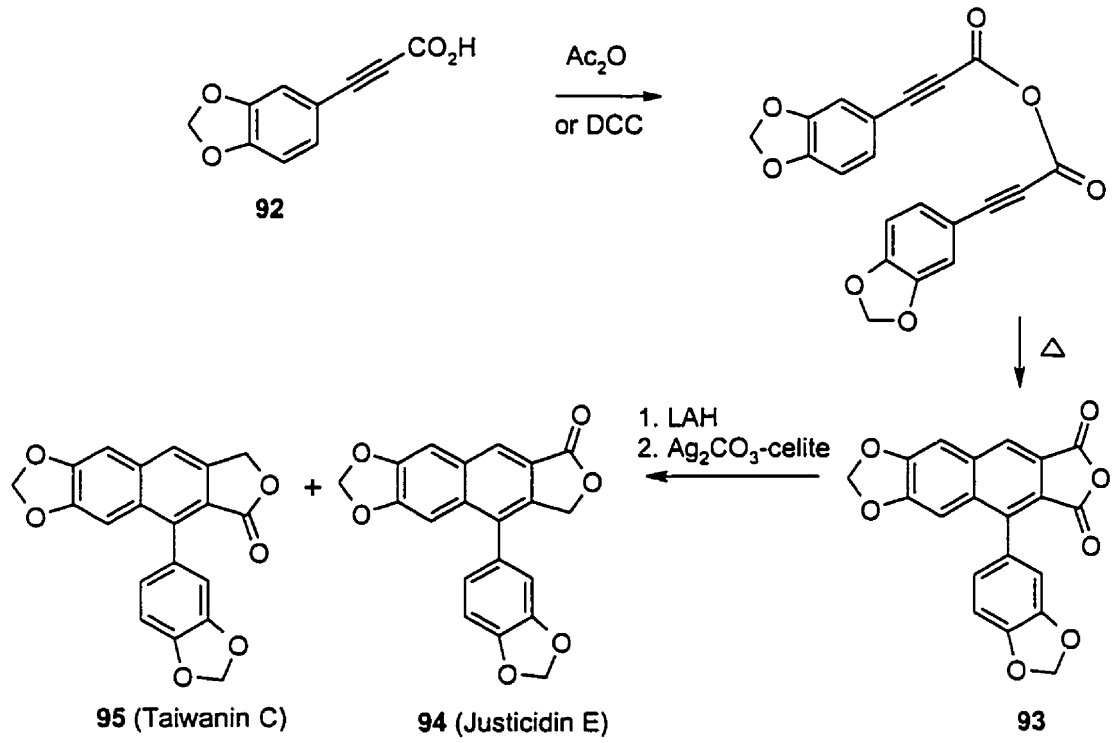
Scheme 26

1.5.5 Pericyclic Reactions

Pericyclic reactions have been used extensively for the preparation of a wide variety of arylnapthalene, dihydroarylnaphthalene and aryltetralin lignans.

1.5.5.1 Diels-Alder Reactions

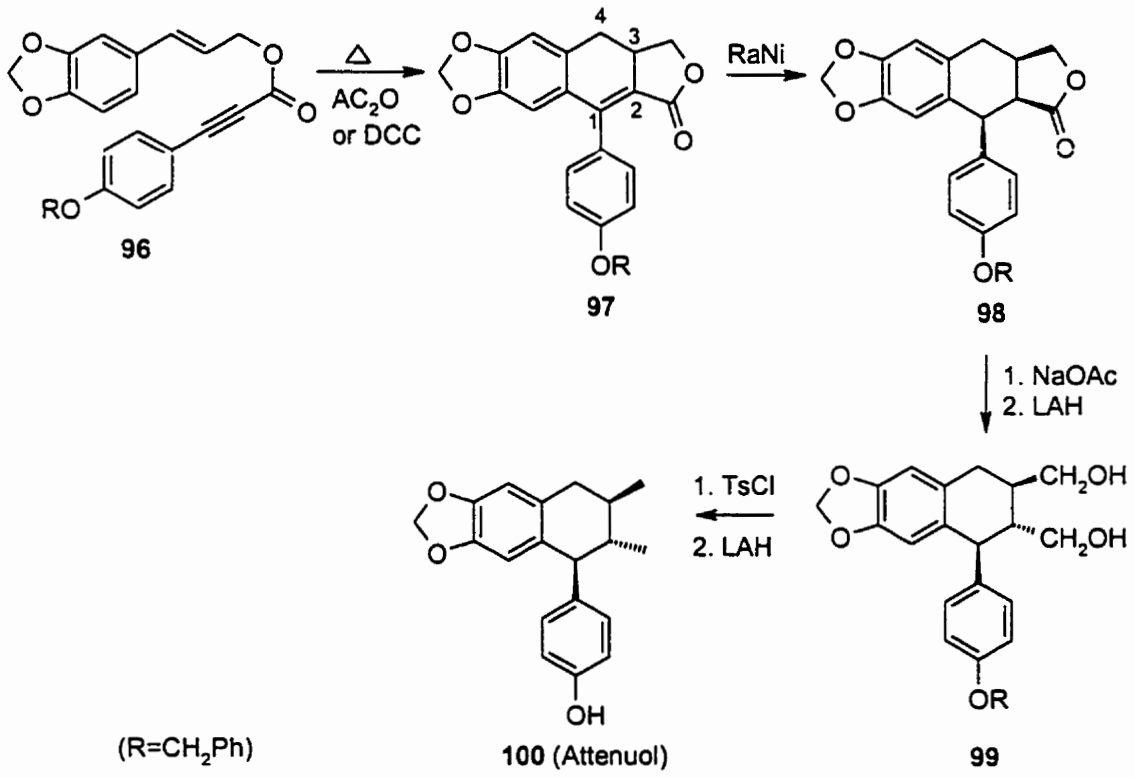
The Diels-Alder cycloaddition of cis-(arylpropiolyl) derivatives such as **92** has been used for the preparation of arylnapthalene lignans[62-64] as illustrated in Scheme 27.[62,63] The cycloaddition affords arylnaphthalene anhydride **93**, which was subsequently reduced and oxidized with Fetizon's reagent to give a mixture of two products justicidin E (**94**) and taiwanin C (**95**).



Scheme 27

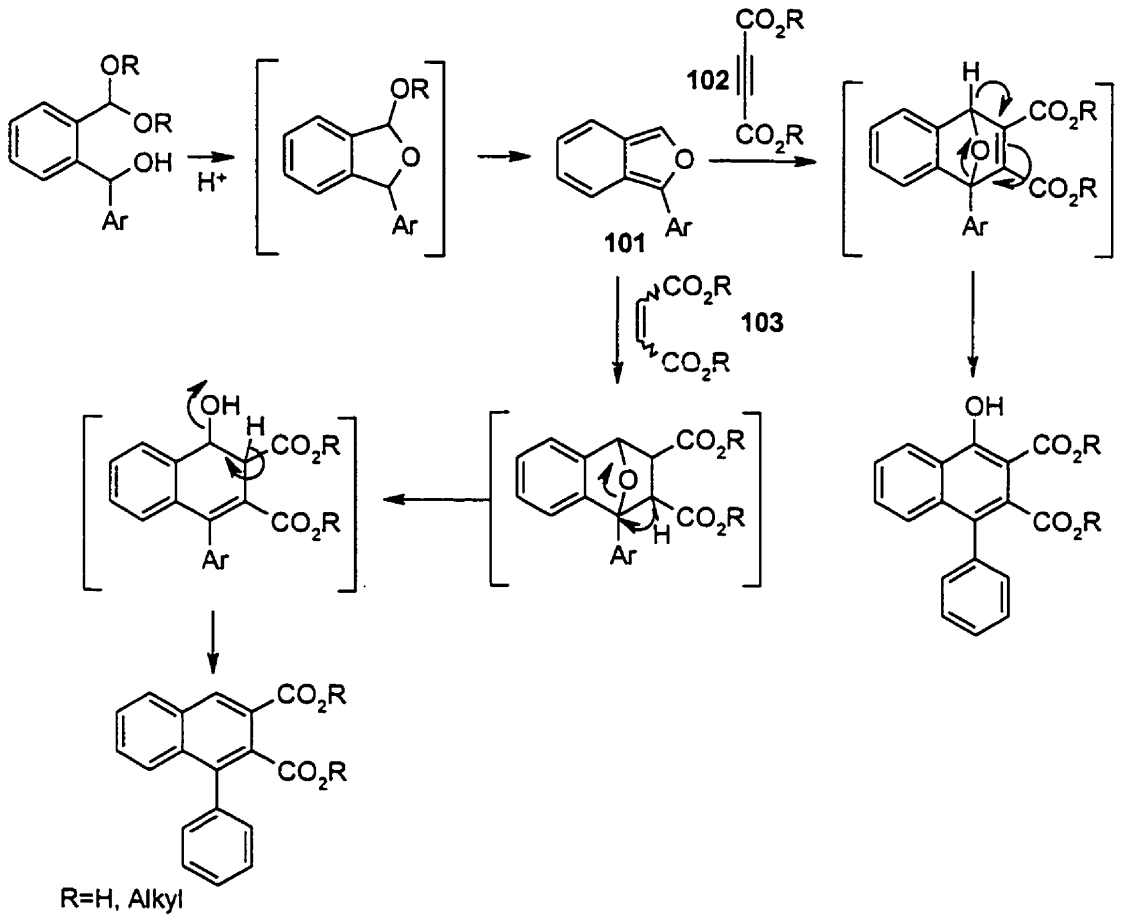
Doubly unsaturated esters have also been successfully used for the preparation of a variety of aryltetralin lignans,[65-69] aryldihydro- and arylnaphthalene lignans[70,71]. In each of these syntheses, intramolecular Diels-Alder cycloaddition results in a 3,4-dihydronaphthalene cycloadduct, which can be then further modified to afford the desired lignan. As shown in Scheme 28, intramolecular Diels-Alder cycloaddition of **96** affords the 3,4-dihydronaphthalene **97**. Dihydronaphthalene **97** can be subsequently reduced

with Raney Nickel to afford the aryltetralin general structure **98**. Reduction and epimerization of the C-2 position gives the diol **99** which can be further reduced to yield attenuol (**100**).[69]



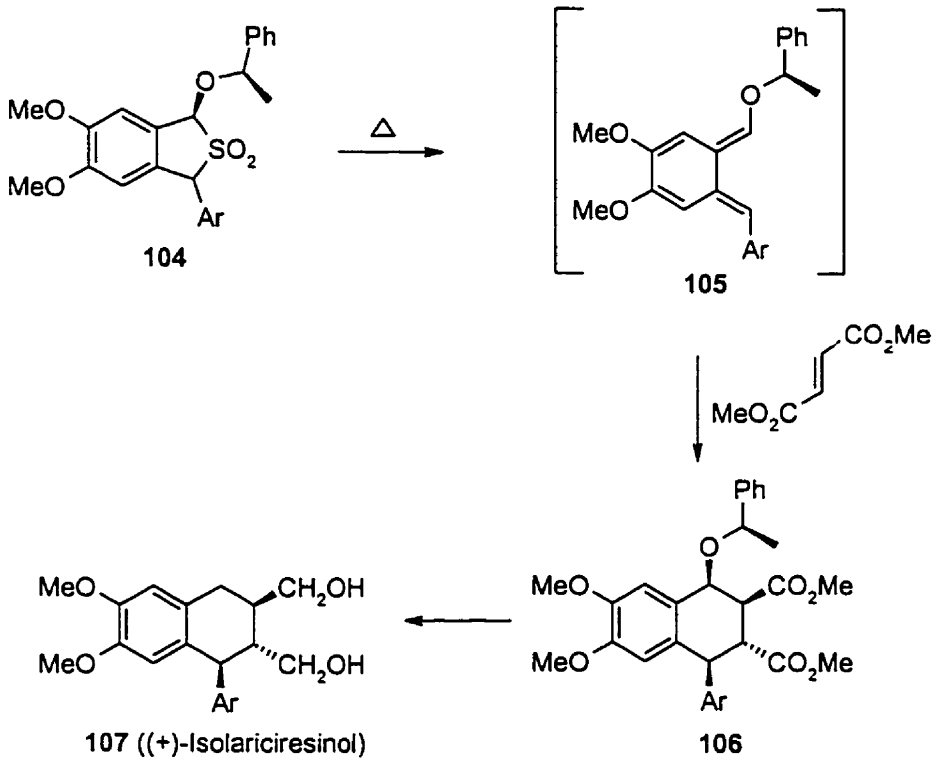
Scheme 28

The Diels-Alder reaction of an isobenzofuran diene with a suitable dienophile has proved to be a convenient method for the synthesis of phenolic and non-phenolic arylnapthalene lignans.[72] As illustrated in Scheme 29, the isobenzofuran needed for these reactions is normally prepared from a hydroxyacetal precursor,[55] such as **101**, and reacted *in situ* with a dienophile, such as fumarate, maleate (**102**) or acetylene dicarboxylate (**103**). The syntheses of many arylnapthalene lignans have been based on this approach.[55,72-77]



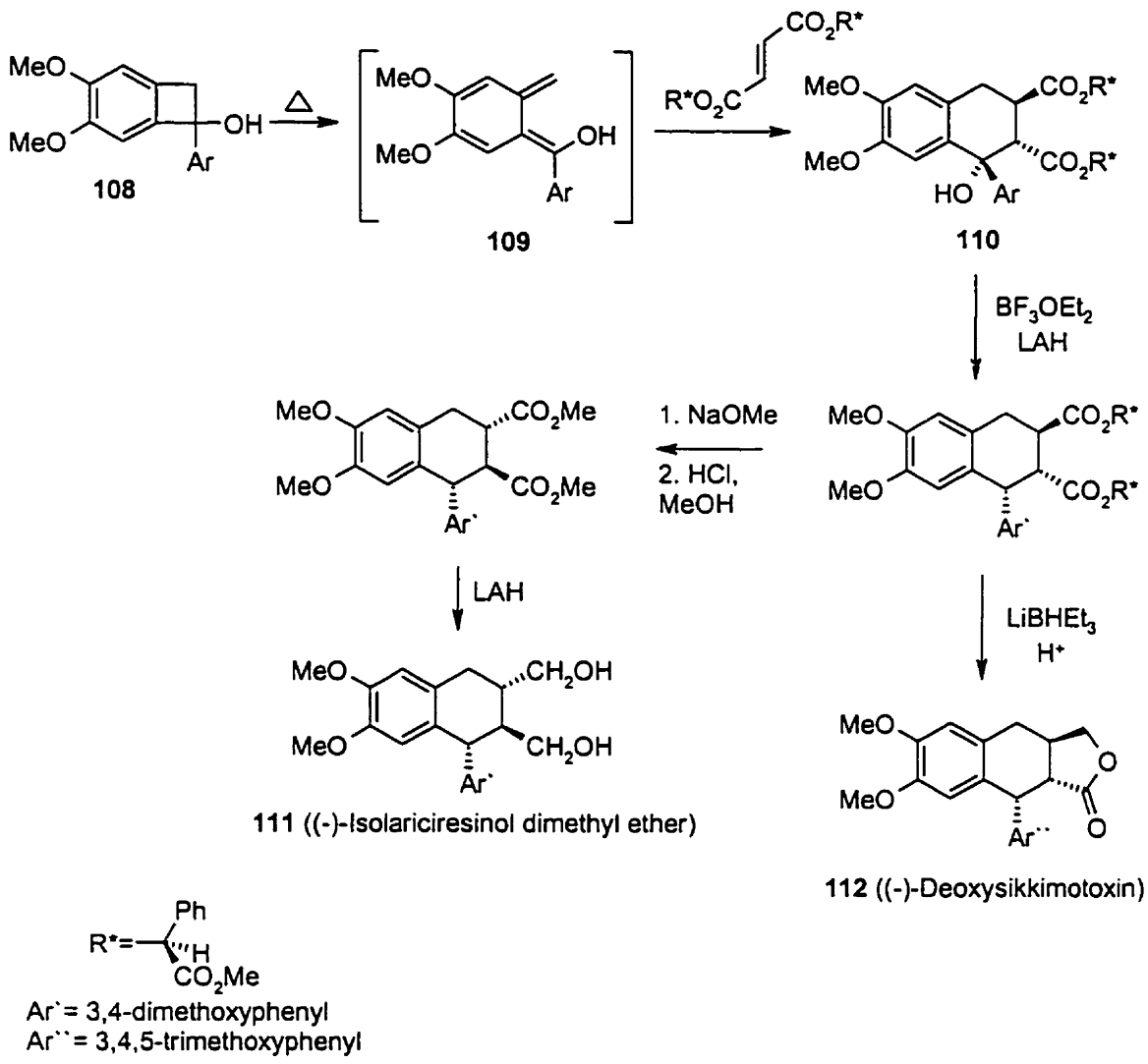
Scheme 29

The use of the Diels-Alder cycloaddition reaction of *ortho*-quinodimethanes (o-QDM) for the asymmetric synthesis of optically active aryltetralin lignans has been extensively studied by Charlton et al..[78-82] The synthesis of (+)-isolariciresinol dimethyl ether was accomplished by using this method. Thermolysis of sulfone **104** generated an *o*-QDM intermediate **105**,[78] which subsequently underwent cycloaddition with methyl fumarate to give **106** as the major product. Removal of the chiral auxiliary by hydrogenolysis followed by reduction of the carboxy-methyl groups gave (+)-isolariciresinol dimethyl ether **107**.



Scheme 30

The cycloaddition approach has also been used for the asymmetric synthesis of lignans having a *cis*-1,2 stereochemistry similar to that found in podophyllotoxin (podophyllotoxin type lignans).[81,82] The *o*-QDM intermediate **109** used the for the Diels-Alder asymmetric syntheses of (-)-isolariciresinol dimethyl ether (**111**) and (-)-deoxysikkimotoxin (**112**) was generated via the thermally induced ring opening of a benzocyclobutenol derivative **108**. The *o*-QDM diene so generated was then trapped by the fumarate of methyl (*R*)-mandelate to afford the aryltetralin cycloadduct **110** as illustrated in Scheme 31. Further modification of the cycloadduct **110** afforded aryltetralin lignans **111** and **112**.

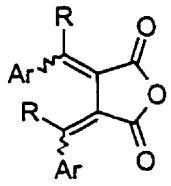


Scheme 31

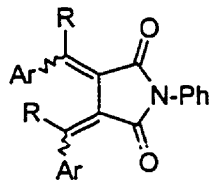
1.5.5.2 Electrocyclic Reactions and Sigmatropic Rearrangements

The intramolecular thermal and photochemical reactions of the dibenzylidenesuccinic anhydrides, known as diarylfulgides, dibenzylidenesuccinimides, known as diarylfulgimides **114**, and dibenzylidenebutyrolactones **115**, have been studied extensively by Heller[58f,83-86] *et al.* and others.[35,57e,87] These compounds have been found

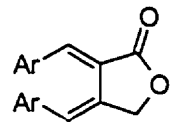
to undergo photochemical and thermal electrocyclic reactions and thermal sigmatropic rearrangements to give various dihydronaphthalene derivatives which can be modified to give dihydronaphthalene, arylnaphthalene or aryltetralin lignans.



113 (Dibenzylidene Fulgides)



114 (Dibenzylidene Fulgimides)



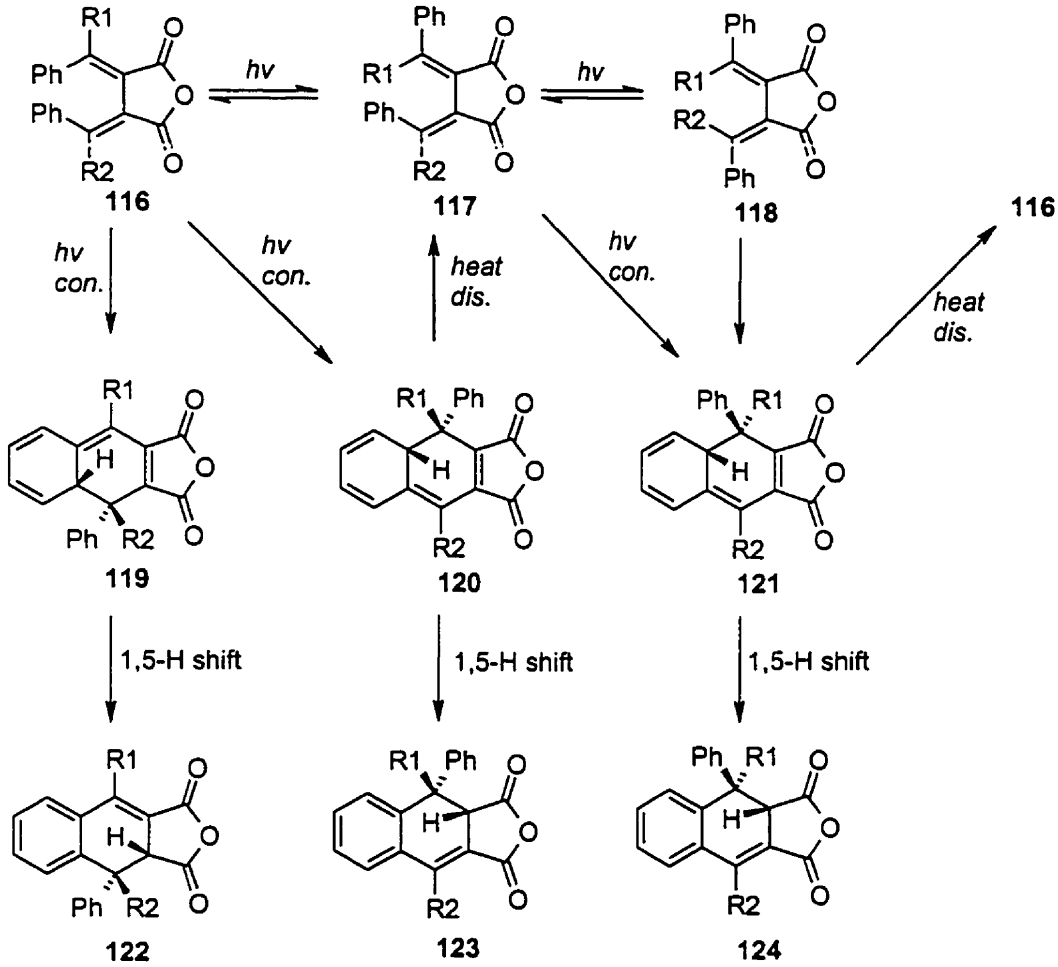
115 (Dibenzylidene-butyrolactones)

R=Aryl, Alkyl. H

Scheme 32

Heller *et al.* found that the reactions and product distribution of the diaryl fulgides and fulgimides under investigation were dependent on the nature of the substituents on the double bonds and their stereochemistry about the double bonds. For example, as illustrated in Scheme 33, fulgides **116a** and **116b** underwent photochemical conrotatory ring closure to afford intermediate 1,8-dihydronaphthalenes **120a** and **120b**, respectively. In both cases, photochemical ring closure occurred exclusively on the phenyl of the more substituted double bond, the diphenylidene and α-ethylphenylidene phenyl groups, and not the benzylidene phenyl group. 1,8-dihydronaphthalenes **120a** and **120b** were subject to two competing thermal processes, those being a 1,5-sigmatropic hydrogen shift to afford 1,2-dihydronaphthalenes **123a** and **123b** and thermal disrotatory ring opening to give fulgides **117a** and **117b**. Thus fulgides **116a** and **116b** were found to *cis,trans*-isomerize or cyclize to form a 1,2-dihydronaphthalene via a 1,8-dihydronaphthalene intermediate. Similarly, fulgides **117a** and **117b** were shown to undergo conrotatory photochemical cyclization to give 1,8-dihydronaphthalenes **121a** and **121b** which in turn

underwent either thermal disrotatory ring opening to afford the initial fulgides **116a** and **116b** or a thermal 1,5-hydrogen shift to give corresponding 1,2-dihydronaphthalenes **124a** and **124b**.



a: R1=H; R2=Ph
b: R1=H; R2=Me
c: R1=Me; R2=H
d: R1=Me; R2=Ph

Scheme 33

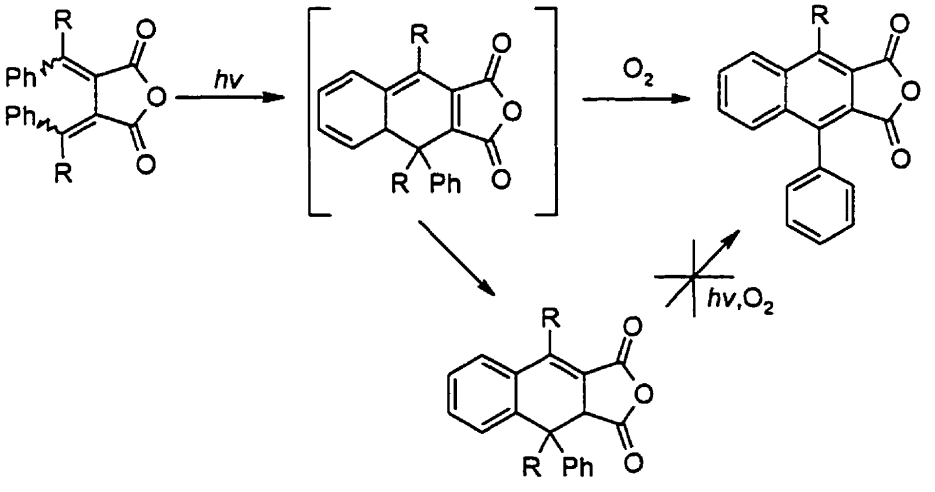
The activation energy for the 1,5-hydrogen shift was found to be lower than that for the competing thermal disrotatory ring opening, as evidenced by a variation in product distribution with temperature. Fulgide **116e** underwent a similar photo-induced process i.e. photochemical cyclization followed by either a 1,5-hydrogen shift or thermal ring

opening to afford the 1,2-dihydronaphthalene **123e**. Interestingly, photochemical cyclization onto the phenyl of the α-phenylethylidene of the *E*-fulgide **116e** did occur to some extent to form 1,8-dihydronaphthalene **119e** followed by a 1,5-hydrogen shift to afford 1,2-dihydronaphthalene **122e**. However, cyclization onto the phenyl of the diphenylidene phenyl was preferential as indicated by a 25:75 product distribution of 1,2-dihydronaphthalenes **122e** and **123e** respectively. Although the 1,8-dihydronaphthalene **120e** was formed as evidenced by the presence of the corresponding 1,2-dihydronaphthalene, **120e** did not undergo thermal disrotatory ring opening to give Z-fulgide **117e**.

As expected, fulgide **117c** did not undergo photochemical ring closure onto the phenyl of the benzylidene group and did not form the 1,8-dihydronaphthalene intermediate **121c** as indicated by the absence of the corresponding 1,2-dihydronaphthalene. The occurrence of **116b** was attributed to *Z-E* photo-isomerization of the α-phenylethylidene bond and not to formation of the corresponding 1,8-dihydronaphthalene intermediate **121c** as in the previous cases. Furthermore, *E,Z*-succinic anhydride was observed to photoisomerize to afford the three other possible stereoisomers, *E,E*-, *Z,E*- and *Z,Z*-succinic anhydrides **116b, 117b** and **118b** respectively. The photo-isomerization of **117c** to **116b** may be ascribed to steric strain in **117c** rather than to the reluctance of the benzylidene group to enter into the pericyclic ring closure. The *E*-fulgide **116e** also did not *E-Z* photo-isomerize, nor did the corresponding 1,8-dihydronaphthalene **120e** undergo thermal disrotatory ring opening as indicated by the complete absence of Z-fulgide **117e**.

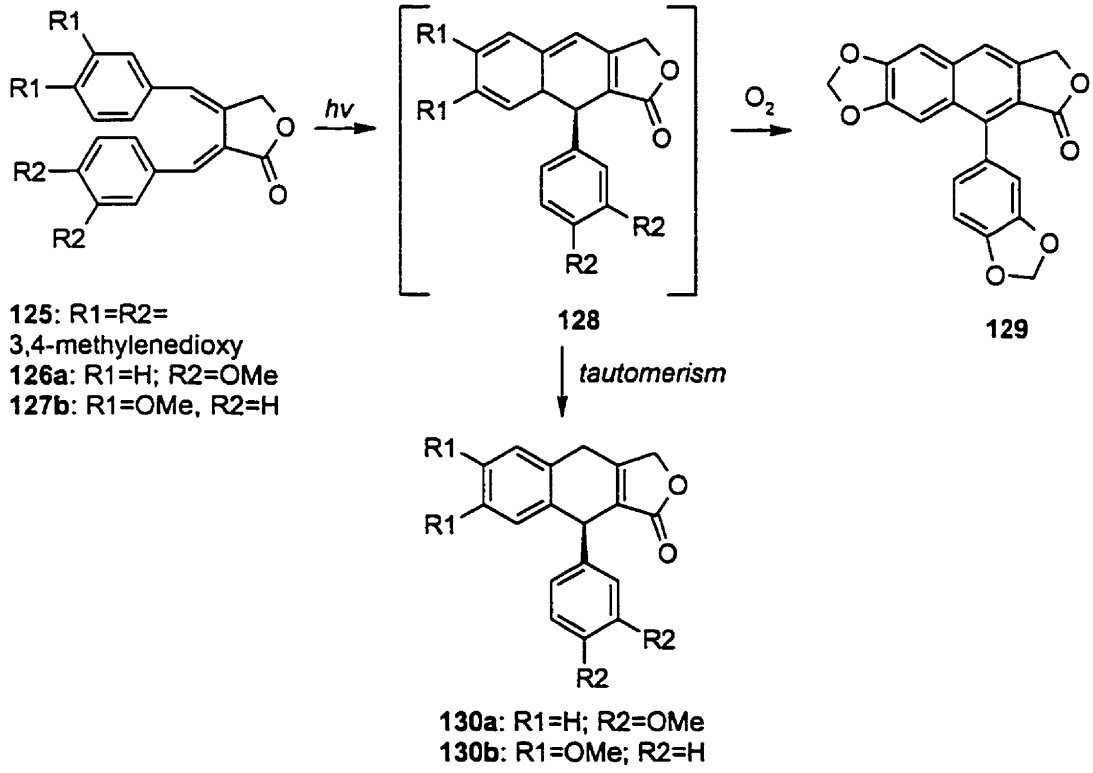
Heller found that *E*-fulgide **116a** and *Z*-fulgide **117a** both underwent thermal rearrangement on strong heating to afford high yields of *cis*-1,2-dihydronaphthalene **123a** via 1,8-dihydronaphthalene intermediate **120a**. This indicated that Z-fulgide **117a** underwent thermal disrotatory electrocyclic ring closure followed by a 1,5-hydrogen shift to afford 1,2-dihydronaphthalene **123a**, but that the overcrowded thermodynamically unstable E-fulgide **116a** isomerized to the Z-isomer at high temperatures. Thus, thermal disrotatory ring closure occurred predominantly through the *Z*-isomers.

The fulgides were converted into the corresponding 1,2-dihydronaphthalenes by the sequence of reactions describes above by the careful exclusion of oxygen. In the presence of oxygen, the formation of the corresponding arylnapthalene products occurred. Heller found that 1,2-dihydronaphthalenes did not undergo similar oxidation on prolonged irradiation, and therefore proposed that the arylnaphthalene compounds were formed by oxidation of the corresponding 1,8-dihydronaphthalene intermediates by the action of oxygen.



Scheme 34

By analogy to the fulgides, dibenzylidenebutyrolactones have been found to undergo conrotatory photochemical ring closure to afford 1,8-dihydronaphthalene intermediates. The photoproducts of taiwanin A (**125**) indicated that the photocyclization of this dibenzylidenebutyrolactone is regiospecific and ring closure occurs exclusively onto the aryl ring not in conjugation with the carbonyl group to afford 1,8-dihydronaphthalene intermediate **128** which subsequently could be oxidized to yield retrohelioxanthin (**129**),[35,85] as illustrated in Scheme 35. Moreover, in the absence of oxygen, dibenzylidenebutyrolactones **125a** and **125b** underwent conrotatory photocyclization to afford a 1,8-dihydronaphthalene intermediate followed by tautomerism and thus were converted to their corresponding 1,4-dihydronaphthalene structures[35] **130a and 130b**.



Scheme 35

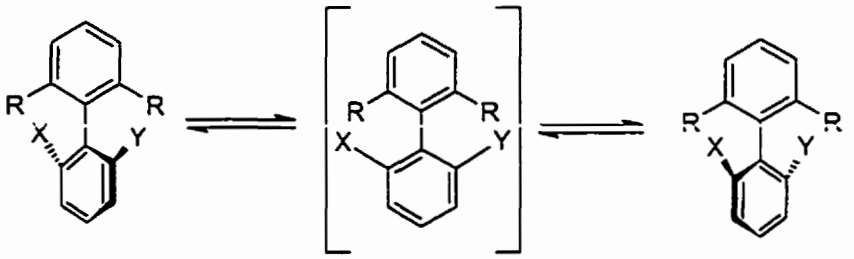
1.6 Atropisomerism and Hindered Rotation in Lignans

The term atropisomerism was introduced in 1933 by Kuhn[88] and refers to molecules that exhibit chirality solely on account of hindered rotation about a carbon-carbon single bond in the molecule. Such molecules can exist in two enantiomeric forms that are actually conformational isomers or rotamers. In order to distinguish between classical conformational isomers and atropisomers, the term atropisomerism was introduced to denote conformational isomers that can be isolated. However, the isolation temperature of the rotamers was not defined and the term atropisomerism is not conditional on a temperature range but is commonly used to designate conformational isomers that are isolable at technically achievable temperatures.

Molecules exhibiting atropisomerism exist in enantiomeric forms only in the absence of stereogenic centers in the molecule. In the event that the molecule exhibiting atropisomerism contains classical stereogenic centres, the rotamers will exist in diastereomeric forms. The term atropisomerism in its current use is not restricted to enantiomers but also denotes chiral rotamers that are diastereomeric.

A barrier to rotation may arise from any combination of steric, coulombic and stereoelectronic effects. In some cases, steric effects are the primary factors that determine the magnitude of the rotational hindrance in a molecule, as is the case with atropisomeric biphenyl derivatives, the class of compounds for which the term atropisomerism was introduced.[88] As illustrated in Scheme 36, these compounds exhibit atropisomerism due to hindered rotation about the carbon-carbon bond joining the aryl rings. Increasing the bulk of the ortho-substituents on either ring does not increase the steric interactions of the molecule as the two aryl rings lie in normal planes. As the

bulkiness of the ortho-substituents increases, however, so does the barrier to rotation as the transition state for the interconversion of the two enantiomers has both aryl rings coplanar.

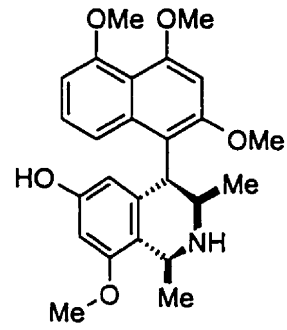


Scheme 36

In order for atropisomers to be isolable at room temperature, the barrier to rotation, which can be measured by dynamic NMR techniques, about the carbon-carbon single bond must be at least 22 kcal/mol.[37] Compounds with barriers to rotation greater than 22 kcal/mol are normally separable by conventional methods such as chromatography.

Atropisomers that exist in enantiomeric or diasteromeric forms at room temperature are interesting from a synthetic standpoint as they may be used as chiral reagents or catalysts for asymmetric synthesis as is the case with biaryl derivatives. Biaryl derivatives are employed as chiral ligands in asymmetric metal-catalyzed organic reactions.

Given that atropisomers can be related by enantiomerism, a difference in the pharmacological properties of the two enantiomeric forms may be anticipated. One enantiomeric form may show activity while the other does not. This is in fact the case as is illustrated by the biphenyl derivative, ancistrocladine (**131**) where only the (-)-enantiomer is naturally occurring and has biological activity[89] (Scheme 37).



131 ((-)-Ancistrocladine)

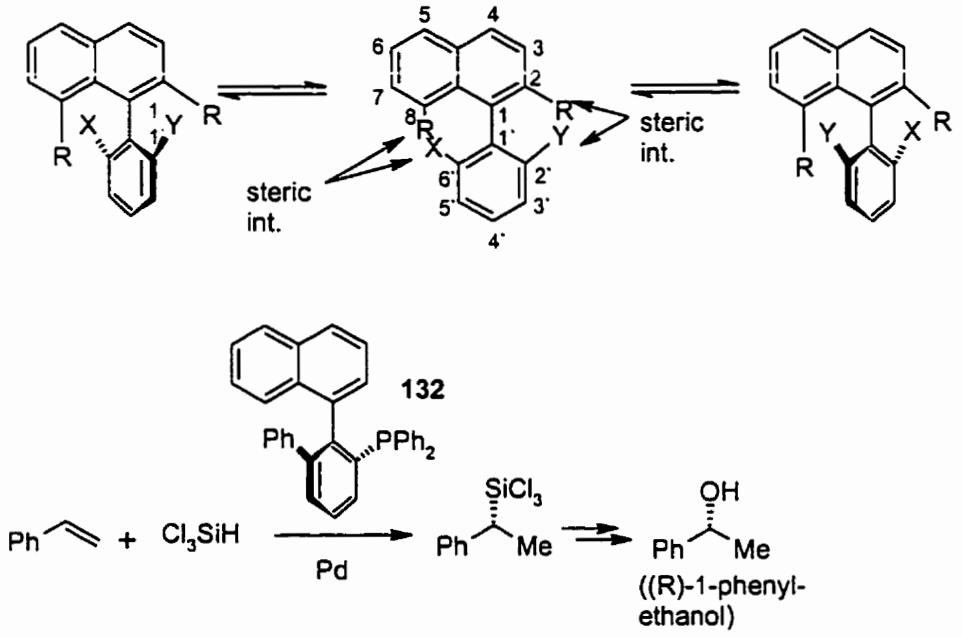
Scheme 37

1.6.1 Atropisomerism in Arylnaphthalenes

Arylnaphthalene lignans possess the biphenyl skeleton and thus exhibit atropisomerism as a result of hindered rotation about the C1-C1` bond. The barrier to rotation about the bond that unites the naphthalene and phenyl moieties is primarily due to steric interactions between the substituents at positions 2 and 8 on the naphthalene system and the *ortho*-substituents (at positions 2` and 6`) on the phenyl group (see Scheme 38). The naphthalene system lies in a plane normal to the phenyl ring and interconversion between the two isomeric forms occurs through a planar intermediate in which the steric interactions are the highest. Obviously the magnitude of the barrier to rotation depends on the bulk of the substituents at the C-2`, C-6`, C-2 and C-8 positions. Substituents at the C-3, C-7, C-3` or C-5` positions also have an effect on rotational hindrance,[37] as bulky substituents at these positions will render the entire the molecule more rigid.

Even for those arylnaphthalenes with the highest barriers to rotation, the interconversion is fast at room temperature.[90] Natural arylnaphthalene lignans appear to always be a mixture of the two rotamers. An example of an extremely stable synthetic

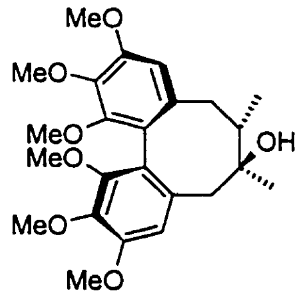
atropisomeric arylnaphthalene is the diphenyphosphino-substituted arylnaphthalene **132**, which does not undergo isomerization even after reflux for 36 hours in toluene. It has been used effectively as a chiral ligand for the palladium catalyzed asymmetric hydrosilylation of styrene with trichlorosilane to afford (*R*)-1-phenylethanol.[91]



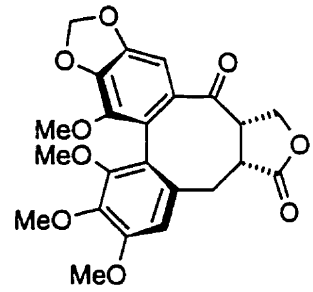
Scheme 38

1.6.2 Atropisomerism in Dibenzocyclooctadiene Lignans

The dibenzocyclooctadienes, like the arylnaphthalenes, exhibit atropisomerism as a result of the inclusion of a biaryl moiety in their lignan skeleton.[3,5] Atropisomerism in these compounds also arises due to the restriction of rotation in the biphenyl unit. The dibenzocyclooctadienes have relatively high barriers to rotation as evidenced by the fact that lignans schizandrin (**133**) and the anti-tumor compound (-)-steganone (**134**) exist as isolable atropisomers in which the biaryls are in the *R*-configuration and the *S*-configuration, respectively.



133 (Schizandrin)

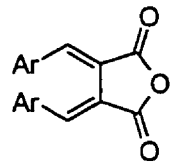


134 ((-)-Steganone)

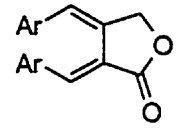
Scheme 39

1.6.3 Atropisomerism in Diarylbutadiene Lignans

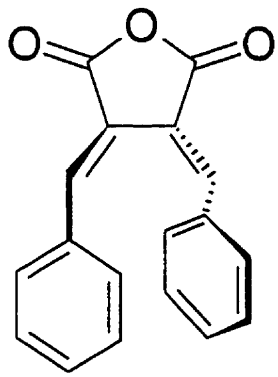
The *E,E*-dibenzylidenesuccinic anhydrides (diarylfulgides) (**135**) and related compounds have fascinated chemists since their discovery by Stobbe in 1911[92] because of their interesting photochemical and thermal properties. As a result, they have been the subject of numerous NMR and x-ray crystallographic studies.[58c,g-i,93] They have been shown to bend out of plane because of to the steric overcrowding brought about by the stereochemistry about the two double bonds. The *E,E*-diarylfulgides are not planar as expected, but rather the two aryl rings are stacked one on top of the other thereby giving the molecule helical chirality and leading to the formation of two enantiomeric structures.

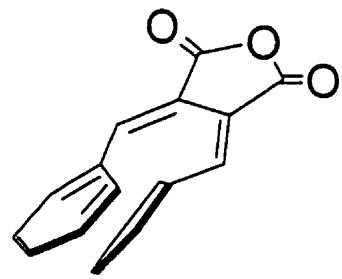


135
E,E-Dibenzylidene
Succinic Anhydride



136
(Taiwanin A):
Ar_1=3,4-methylene-



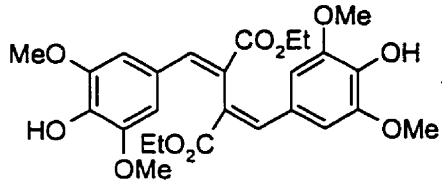


Scheme 40

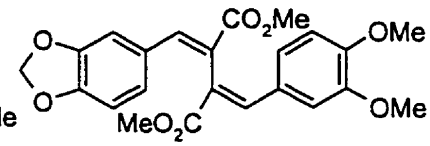
Moreover, the aryl rings are not in a coplanar arrangement[58e,g] as illustrated in Scheme 40. These compounds are extremely labile owing to interference between the aryl rings and the fact that they are forced to lie above and below the plane of the anhydride ring. The *E,E*-dibenzylidenesuccinic anhydrides behave chemically as two isolated cinnamic acid residues and not as a fully conjugated molecule. Taiwanin A (**136**), a dibenzylidenebutyrolactone has also been reported to have the distorted structure illustrated in Scheme 40.

Closely related to the *E,E*-diaryl fulgides are the *E,E*-dibenzylidenesuccinic acid derivatives (**139**) and the naturally occurring lignans phebalarin (**137**) and jatrodien (**138**). Some compounds having this general structure have also been reported to exhibit

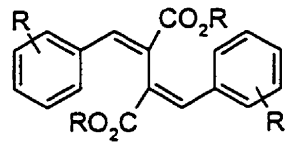
atropisomerism,[58g,94,95] existing as helical enantiomers analogous to the *E,E*-dibenzylidene fulgides.



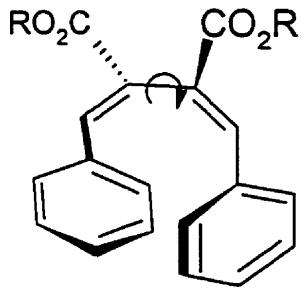
137 (Phebalarin)



138 (Jatrodien)



139
E, E-Dibenzylidene-succinic Acid Derivative



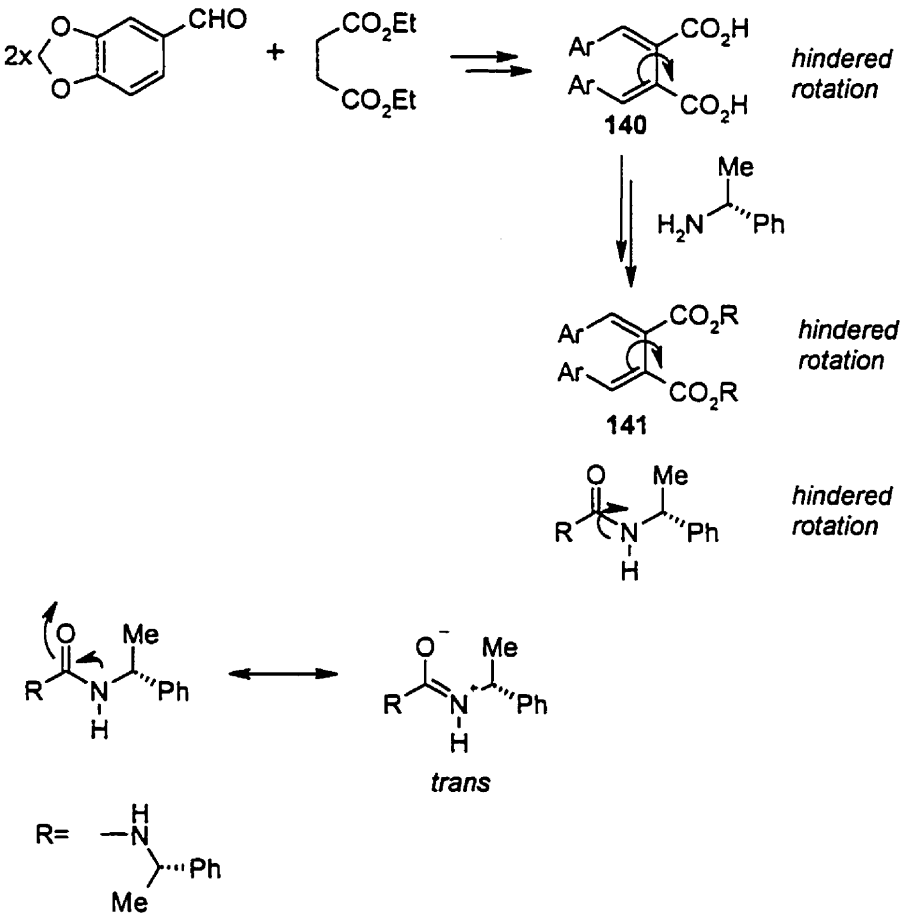
hindered rotation

Scheme 41

The NMR spectra of *E,E*-dibenzylidenesuccinic acids that were prepared via the Stobbe condensation by Charlton *et al.*[95] had anomalies that could only be explained by hindered rotation about the carbon-carbon single bond linking the two cinnamic acid residues. For example, nominally identical hydrogens in *E,E*-dibenzylidenesuccinic acid **140** were diastereotopic at room temperature and appeared as separate signals since rotation was slow. In the case of *E,E*-dibenzylidenesuccinic acid derivatives bearing classical chiral groups such as (*E,E*)-2,3-dipiperonylidenesuccinamide **141**, the whole spectrum of the compound was doubled due to the presence of two diastereomeric forms. At higher temperatures, the rotation was faster and the anomalies disappeared. From the temperature dependence of the spectra, the barrier to rotation of succinimide **141** was calculated and found to be *ca.* 17 kcal/mol.[95] This value is not unambiguously indicative

of the magnitude of the barrier to rotation about the carbon-carbon single bond of the butadiene moiety, since there is also hindered rotation about the N-C=O amide bond and this possibly contributed to the errors in determining the barrier (Scheme 42).

Presumably, the nature of the carboxyalkyl group would determine the magnitude of the barrier to rotation in *E,E*-dibenzylidenesuccinates and one would expect higher barriers for dibenzylidenesuccinates with bulky acid derivatized groups. The barriers to rotation in *E,E*-dibenzylidenesuccinates catalogued to date are not significant and are likely less than 22 kcal/mol as there is presently no report of the isolation of diarylbutadiene atropisomers.

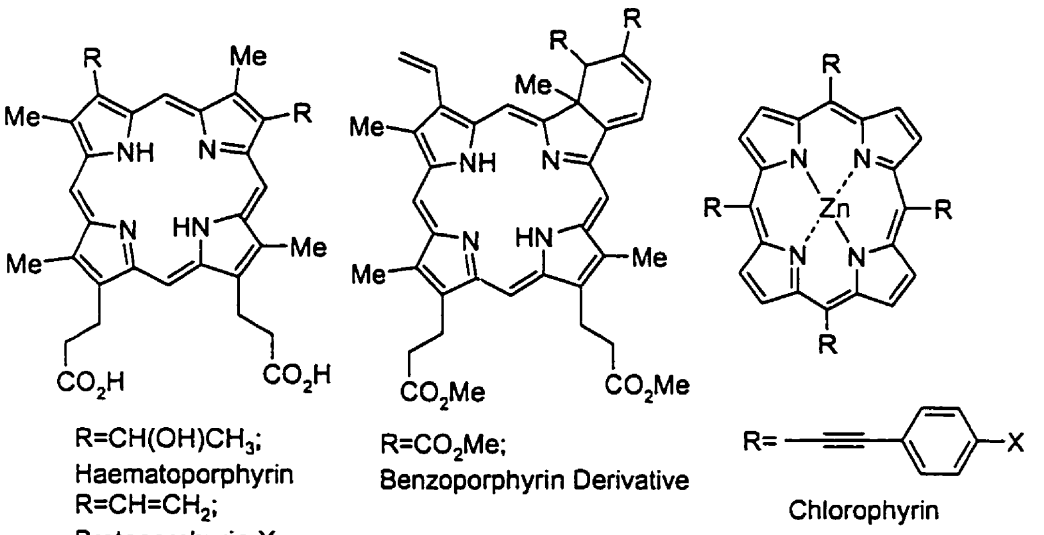


Scheme 42

Although atropisomerism has been detected in *E,E*-dibenzylidenesuccinates they have not been subject to as much scrutiny as the *E,E*-dibenzylidenesuccinic anhydrides and not much is known about the factors that influence rotational barriers. These compounds merit careful examination as the discovery of isolable atropisomeric *E,E*-benzylidenesuccinic acid derivatives may be of use in asymmetric organic synthesis.

1.7 Photodynamic Therapy

Photodynamic therapy (PDT) is a medical treatment that consists of the administration of a tissue selective photosensitizing agent, usually a tetrapyrrolic macrocycle such as porphyrin (see Scheme 43), followed by activation of the agent by light of a specific wavelength which then elicits a desired therapeutic effect.[96-100]

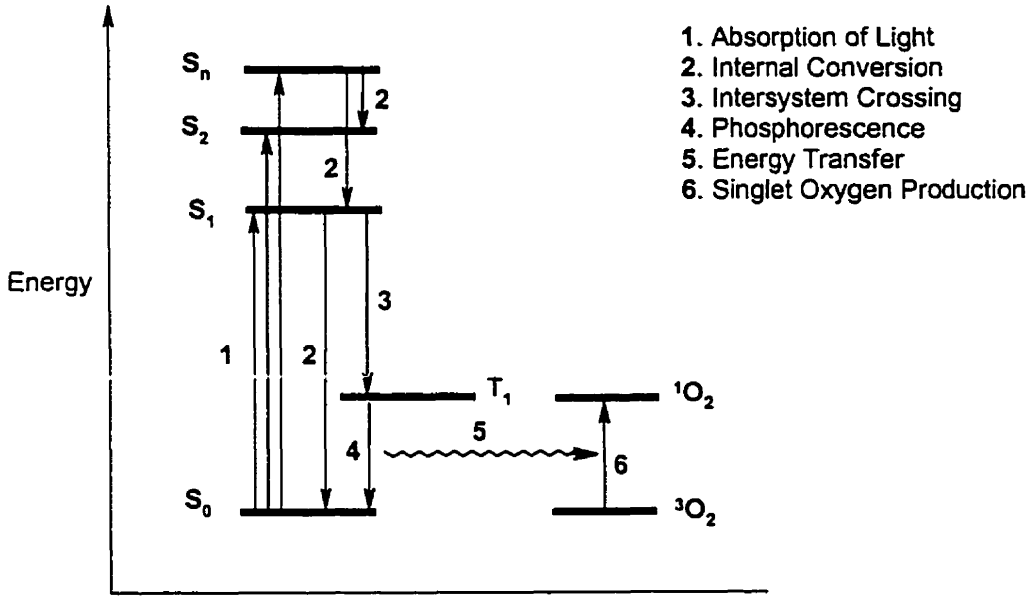


Scheme 43

The tissue selectivity of photosensitizing agents for neoplastic and other abnormal tissues, has been ascribed to the increased metabolism, increased permeability and decreased lymphatic drainage that is characteristic of these tissues.[96] The selectivity for

tumor cells compared with normal cells can be as high as 3:1 for extracranial tumors and 50:1 for tumors found in the brain.[98]

The photophysical processes that govern PDT are well understood and it is known to depend on the presence of molecular oxygen. The photosensitizer is administered to a patient and allowed to equilibrate within the body (*ca.* 3 – 96 hours). The photosensitizer is then promoted by light into its singlet excited state and can then return to its ground state via vibrational cascade and radiative decay, or can undergo the non-radiative process of intersystem crossing to the excited triplet state (Scheme 44). Effective photosensitizers undergo intersystem crossing to a triplet state with high efficiency and the triplet states have much longer lifetimes than their singlet state counterparts as they can only relax unimolecularly by the spin forbidden, radiative process of phosphorescence, or non-radiatively by intersystem crossing to the singlet ground state. The long lifetime of the triplet state sensitizer allows it to undergo energy transfer with appropriate acceptor molecules. Molecular oxygen, which is abundant in cells, is a triplet state quencher and is an ideal candidate for energy transfer from the excited photosensitizer. Molecular oxygen is promoted to an excited singlet state (singlet oxygen) by the excited photosensitizer, which in turn relaxes to its ground state.

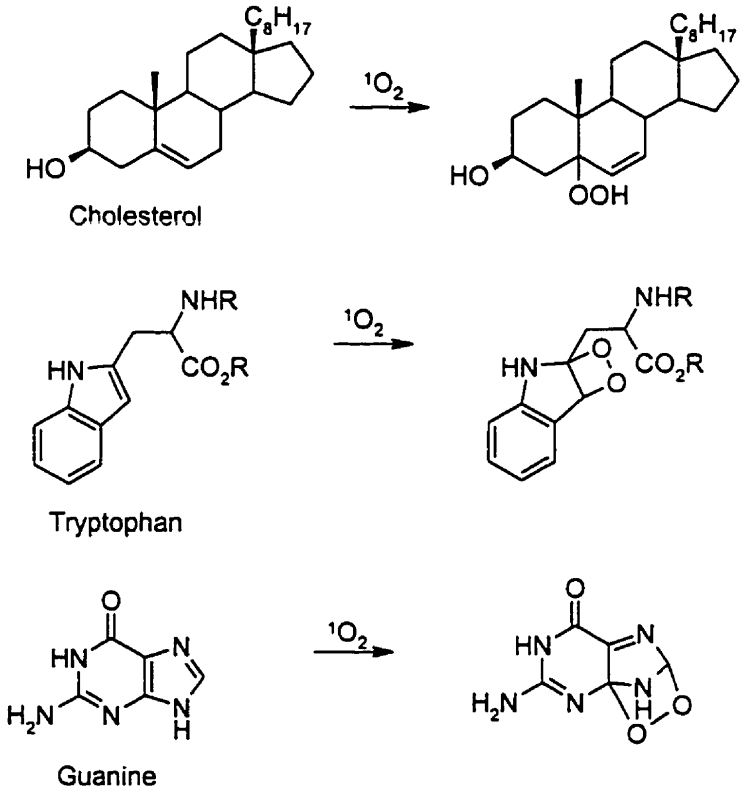


Modified Jablonski diagram for a typical photosensitizer

Scheme 44

Singlet state oxygen is an extremely reactive species with a lifetime in aqueous solution of several microseconds. Biological substrates containing double bonds such as unsaturated lipids and proteins (the main constituents of cell membranes) are especially susceptible to attack and undergo several reactions with singlet state oxygen including, cycloaddition and oxidation, which are disruptive to normal biological processes (see Scheme 45).[100] For example, the imidazole- and indole-containing amino acids, histidine and tryptophan, react with singlet oxygen to produce endoperoxides, and sulfur containing amino acids, including methionine, are likewise oxidized to sulfoxides. The endoperoxides subsequently release hydroxy radicals that can further react with cellular components, such as DNA. DNA is also subject to direct attack, as DNA bases, such as guanine, are degraded by singlet oxygen.[98] Thus singlet oxygen is the photodynamic agent in PDT and is produced by the action of a photosensitizing agent. Given that the photosensitizer is returned to its ground state, one molecule of the photosensitizing agent

is capable of efficiently generating many singlet oxygen molecules before undergoing degradation.



Scheme 45

The use of PDT has been proposed for the treatment of cancers, pre-cancers, non-cancerous dysplasias, inflammatory conditions, viral and bacterial infections such as gum disease, wound infections, and stomach ulcers, and arthritis.[96-100] and is under active investigation. PDT is particularly promising for the treatment of hollow-organ and skin cancers and has been approved for the treatment of obstructive esophageal cancer,[96] that has extremely high mortality rates. The porphyrin drug Photofrin®, is currently in phase III clinical trials for the treatment of esophageal cancer and has also been approved for

the treatment of early- and advanced-stage cancers of the lung, and digestive and genitourinary tracts.

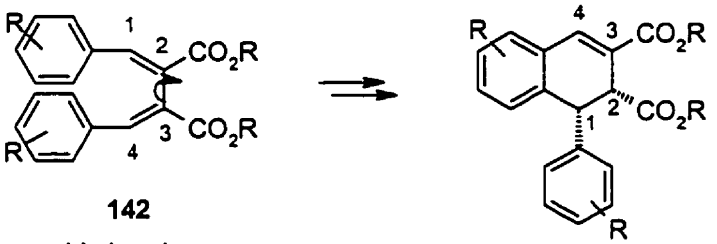
PDT is an attractive alternative to the traditional treatments for cancer, such as tumor excision and chemotherapy, due to its superior efficacy and non-invasive nature. It also has immense potential as a fulfillment for the critical need for new methods for combating bacterial infections. Thus the development of new drug candidates for use as sensitizers in PDT has become a subject of interest to many chemists. There are several limitations on the use of photosensitizers as drugs in PDT and there are requirements that must be met.[98,100] The light that is required to excite the photosensitizer for PDT must first pass through living tissue, which is laden with endogenous chromophores such as hemoglobin. Light at the red end of the spectrum (620-680 nM) is much less attenuated by tissue and is thus ideal for use in PDT. It is preferable that the photosensitizer be capable of absorbing tissue-penetrating red light.

The photosensitizer also must be non-toxic in the absence of light, must be orally bioavailable or be capable of being administered by injection. The triplet excited state of the photosensitizer must be sufficiently long-lived in order to allow for the production of singlet oxygen. Furthermore, the photosensitizer must, not only have specificity for localization in the abnormal tissue, but must also be rapidly expelled from the body once it has completed its task so as to reduce undue photosensitivity. This final criterion is also a major challenge in PDT as a high degree and duration of general photosensitivity is a side effect of current treatments.[96]

Chapter 2

Thesis Objectives

The ultimate objective of the research described in this thesis was to develop new methods for the asymmetric synthesis of 1,2-aryldihydronaphthalene lignans (**143**) starting from dibenzylidenesuccinates (**142**) (Scheme 46). If the dibenzylidenesuccinates (**142**) could be coerced to adopt one of the two helical atropisomeric forms, or if the two forms could be separated, then the subsequent photochemical ring closure of the single atropisomer to dihydronaphthalene **143** would result in the formation of a single absolute stereochemistry for **143** (an asymmetric synthesis). The work towards achieving this goal was divided into three parts. In the first part the barrier to interconversion of dibenzylidenesuccinate atropisomers was studied, as was the effect of a chiral auxiliary on the atropisomer populations. In the second part, the photochemical cyclization of dibenzylidenesuccinate diesters was studied. In the third part, attempts were made to introduce more rigid chiral auxiliaries in order to prejudice the atropisomer populations of the dibenzylidenesuccinates.



Scheme 46

I. A Study of the Hindered Rotation in Diarylbutadiene Lignans

Diarylbutadienes **142** have been found to exhibit atropisomerism due to hindered rotation about the C2-C3 single bond of the butadiene. Compounds having this general

structure exhibit helical chirality and exist in stereoisomeric forms. The structure of the diarylbutadienes and related compounds has been established on the basis of x-ray crystallographic and NMR studies. These studies have indicated that these compounds are not planar but have their aryl rings stacked (one on top of the other) in a non-parallel arrangement.

Some preliminary experiments hinted that the barrier to rotation in these compounds is not sufficiently high to allow for their isolation and that their interconversion is rapid at room temperature (< 22 kcal/mol). However, the results were ambiguous as the model compound used in these studies contained an amide functional group, which is known to suffer hindered rotation in its own right owing to the partial double bond character of the N-C=O amide bond.

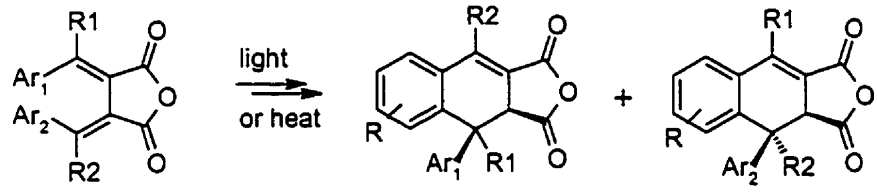
It would be interesting to see if the barrier to rotation increases as the bulk of the R group increases (**142**, Scheme 46) and the question of the possible existence of these compounds as stable atropisomers was raised. High barriers to rotation in diarylbutadienes would be beneficial from a synthetic standpoint as the stable atropisomers of these compounds could be used for asymmetric induction in organic synthesis. Furthermore, if a chiral substituent were introduced into the molecule it might prejudice the conformation and lead to the preponderance of one atropisomer. This single atropisomer could then also be used in asymmetric organic synthesis.

The study of atropisomerism in diarylbutadiene and related compounds has been neglected and the factors that modulate the barrier to rotation in these compounds await elucidation.

II. A Study of the Photochemical and Thermal Reactions of Diarylbutadiene Lignans

Heller *et al.* has shown that the diarylbutadienesuccinic anhydrides are photochemically and thermally labile. These compounds undergo photo-isomerization of the double bonds in addition to a variety of thermal and photochemical pericyclic reactions to afford mainly 1,2-aryldihydronaphthalene anhydrides in the absence of molecular oxygen.

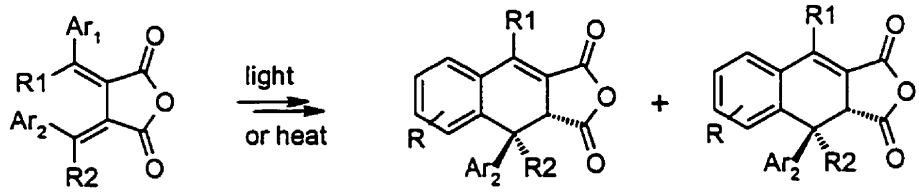
Different electrocyclic reactions (conrotatory versus disrotatory ring closure) result in the formation of diastereomeric 1,2-aryldihronaphthalenes as does different configurations about the double bonds. Furthermore, if the diarylbutadienesuccinic anhydride is unsymmetrical, different 1,2-dihydronaphthalenes are obtained if ring closure onto one of the double bond is not exclusive (see Scheme 47).



E,E-stereochemistry about the double bonds

cis-1,2 relative stereochemistry

E,E-arrangement leads to *cis*-1,2 relative stereochemistry but closure onto different rings leads to different dihydronaphthalenes.



Z,E-stereochemistry about the double bonds

trans-1,2 relative stereochemistry

Z,E-arrangement leads to *trans*-1,2 relative stereochemistry but closure onto different rings leads to different dihydronaphthalenes.

Scheme 47

Heller found that the pericyclic reactions of the diarylbutadienesuccinic anhydrides that give 1,2-aryldihydronaphthalenes were very sensitive to factors such as the *cis*- or *trans*-arrangement and the degree of substitution about the double bonds that was manifest in the product distribution.

The diarylbutadienesuccinate acid derivatives **142** are structurally analogous to the diarylbutadienesuccinic anhydrides and some cursory investigations have shown that they are subject to the same photochemical processes as the diarylbutadienesuccinic anhydrides.

Although the diarylbutadienesuccinate acid derivatives are potential precursors to the 1,2-aryldihydronaphthalene lignans, their photochemical properties have not previously been examined. Determination of the factors that govern the photochemical behavior of the diarylbutadienesuccinate acid derivatives could lead to efficient methods for the preparation of a variety 1,2-aryldihydronaphthalene lignans. It is possible that the stereochemistry of the products could be controlled by judicious selection of the appropriate stereoisomeric reactants by analogy to the diarylbutadienesuccinic anhydrides. For example, the photochemical ring closure of *E,E*-diarylbutadienesuccinate acid derivatives should lead to the synthesis of lignans having a *cis*-1,2 stereochemistry similar to that found in the lignan podophyllotoxin, which is very difficult to achieve by other synthetic methods.

III. Chiral Dibenzylidenesuccinates as Precursors to Optically Active 1,2-Dihydronaphthalene Lignans

The work in this part derives from the idea that the atropisomeric and photochemical properties of dibenzylidinesuccinic acid derivatives could be used as tools for the asymmetric synthesis of 1,2-aryldihydronaphthalene derivatives. Attempts were made to introduce a chiral dilactone functionality into the dibenzylidenesuccinate in order to lock the atropisomers into a particular conformation. The introduction of a ring system into the molecule would increase rigidity and better bias the conformational form.

If the introduction of the more rigid chiral auxiliaries were successful, the resulting products could be used in conjunction with the photochemical reactions of the symmetrical diarylbutadiene compounds, described above, to lead to enantiomerically enriched 1,2-dihydronaphthalenes.

Chapter 3

Results and Discussion

The research presented in this chapter is divided into three sections. The first section addresses a study on hindered rotation in dibenzylidenesuccinic acid derivatives. The purpose of this project was to unambiguously determine the magnitude of the barrier to rotation about the central single bond in these compounds. The possibility of prejudicing the conformational equilibrium by the introduction of a chiral group into the molecule resulting in the preferential formation of one atropisomer was also investigated.

In the second section, an investigation of the photochemical and thermal properties of dibenzylidenesuccinic acid derivatives was conducted. The product distribution generated by the photochemical reactions of dibenzylidenesuccinate diesters under a variety of reaction conditions was carefully inspected.

Finally, the third section discloses the details of a study that is based on the idea of exploiting the hindered rotation and photochemical behavior of dibenzylidenesuccinic acid derivatives for the asymmetric synthesis of 1,2-dihydronaphthalene lignans. Several approaches were taken in an attempt to stabilize diarylbutadiene atropisomers by introducing functional groups into the molecule that would prevent free rotation about the carbon-carbon single bond of the butadiene moiety or ideally lock them into one preferential conformation.

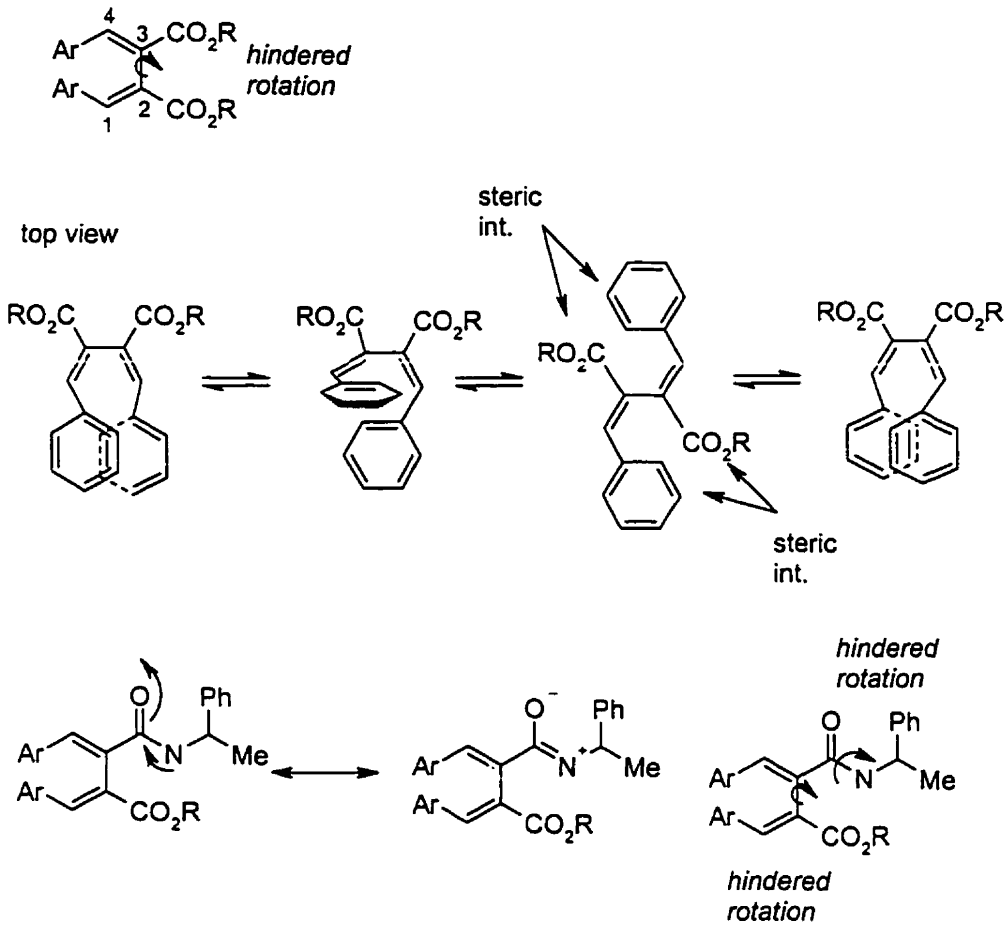
3.1 A Study of the Hindered Rotation in Dibenzylidenesuccinates

As stated previously, the purpose of studying the hindered rotation in dibenzylidenesuccinates is to determine if the barriers to rotation are sufficiently high to

give rise to stable atropisomers that are isolable at room temperature. If so, the individual atropisomers could be used for the asymmetric synthesis of 1,2-aryldihydronaphthalene lignans. The 1,2-dihydronaphthalenes in turn could be tested for biological activity directly or could be used as intermediates to various aryltetralin lignans. The aryltetralin lignans are an extremely well represented subclass of lignans exhibiting biological effects as discussed in Chapter 1. Developing efficient methods for the synthesis of 1,2-dihydronaphthalene and aryltetralin lignans would facilitate systematic investigations of the factors that modulate biological activity in these compounds and would, ideally, lead to new treatments for human disease.

For individual rotamers of dibenzylidenesuccinates to exist at room temperature, that is, in order to have stable atropisomers, the barrier to rotation must be at least 22 kcal/mol. To assess the stability of atropisomers, the barrier to the rotation that interconverts the two rotamers must be determined. A discussion of hindered rotation and atropisomerism in diarylbutadiene, dibenzocyclooctadiene and arylnaphthalene lignans was presented in Chapter 1.

Dibenzylidenesuccinic acid derivatives purportedly exhibit atropisomerism,[94,95] arising from hindered rotation about the C2-C3 butadiene double bond (see Scheme 48). The relatively high barrier to rotation in dibenzylidenesuccinates likely arises from a combination of factors. The hindered rotation may be ascribed to steric interactions between the carboxyl groups and aryl rings as they brush past one another. This would be especially true for very bulky R groups and as the bulk of the R group increases, the barrier to rotation would be expected to increase in response.



Scheme 48

In addition, as the butadiene derivative rotates about the carbon-carbon single bond, the conjugation throughout the entire molecule is gradually lost as it approaches 90° and this would be a high-energy conformation as a result. The magnitude of the rotational hindrance about the carbon-carbon butadiene single bond is likely a result of stereoelectronic effect and steric effects and both factors are important. In order to interconvert between the two rotamers, the butadiene molecule must rotate through one of the two high energy, planar butadiene forms likely the *s*-trans conformer. As the barrier to rotation increases, so does the stability of the individual atropisomers. A preliminary investigation[95] of the hindered rotation of dibenzylidenesuccinates has

indicated that the barrier to rotation in these compounds is small, thereby making the isolation of atropisomers at room temperature impossible as they are rapidly equilibrating. The measured barrier obtained in the previous study[95] was ambiguous as a diarylbutadiene containing amide functionalities was used in that study. Amides exhibit hindered rotation about the N-C=O single bond owing to partial double bond character, thus the numbers generated in the previous study might be ascribed to the barrier to rotation in the amide groups. The rotational barrier found was in fact typical of the barrier expected for hindered rotation of an amide group.

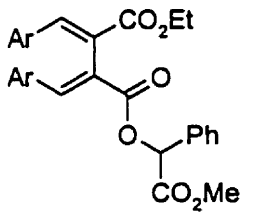
The study of the barrier to rotation in dibenzylidenesuccinates was revisited and an attempt was made to prepare a dibenzylidenesuccinic acid derivative with a relatively high barrier to rotation with the expectation that the ensuing atropisomers would be stable at room temperature. It was also believed that the introduction of a bulky chiral group into a diarylbutadiene would increase the prospects of preferentially obtaining one diastereomeric form of the atropisomers by prejudicing the conformation of the molecule.

Furthermore, by introducing a functional group into the molecule that did not exhibit hindered rotation itself, a more reliable representation of the barrier to rotation in these dibenzylidenesuccinates could be obtained.

In this project, dynamic NMR spectroscopy was used as a means to measure the barrier to rotation. Dynamic NMR spectroscopy is the study of signal variations in NMR spectra that are associated with exchange processes.[37,101] Dynamic NMR techniques can be used for the investigation of intramolecular exchange processes such as conformational interconversions including rotational isomerization. NMR spectroscopy is amenable to the study of rotational isomerization, as the NMR time scale is long

enough to detect the slow internal rotation in atropisomers. The changes in the NMR spectra caused by rotational isomerization (and other exchange processes) arise because the nuclei being observed by NMR spectroscopy are rapidly alternating between chemical environments and the chemical shifts or coupling constants of the exchanging nuclei are different. Rotational isomerization can be studied as a function of temperature using dynamic NMR spectroscopy in order to obtain information about the rate constants associated with the barrier to rotation.

A decision was made to study the temperature dependent NMR spectrum of the racemic ethyl (methyl mandelyl) *E,E*-dibenzylidenesuccinate **144** (scheme 49).



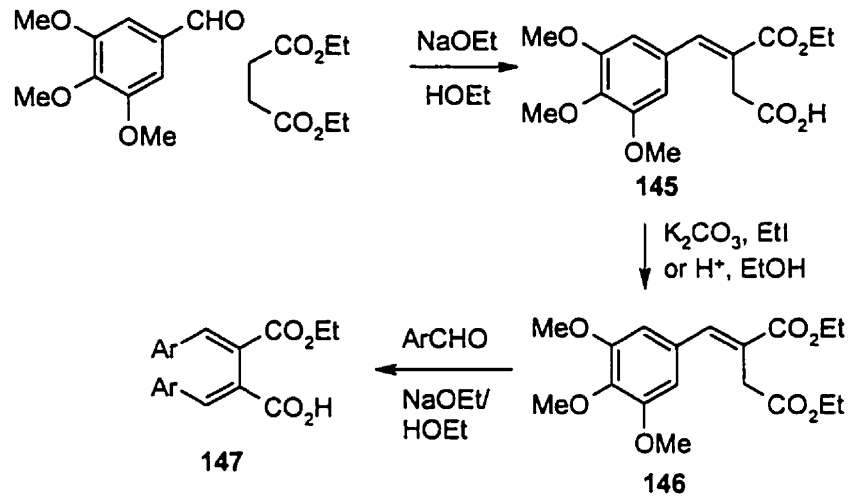
144

Ar = 3,4,5-Trimethoxyphenyl

Scheme 49

Rotamers of this compound would exist as diastereomers since the molecule contains a classical stereogenic center in the mandelyl group. The dibenzylidenesuccinate monoester-acid **147** was required as a precursor to this compound. The dibenzylidenesuccinate monoester-acid **147** was prepared via two successive Stobbe condensation reactions as follows (Scheme 50). The Stobbe condensation of 3,4,5-trimethoxybenzaldehye with diethyl succinate in the presence of sodium ethoxide afforded the *trans*-benzylidenesuccinate monoester-acid **145**. Isolation of monoester-acid **145** from the basic reaction mixture was attempted in several ways. In a first attempt at

isolation of the acid, the reaction mixture was acidified with aqueous HCl, evaporated to remove ethanol, and the monoester-acid **145** extracted with ethyl acetate.



Ar = 3,4,5-Trimethoxyphenyl

Scheme 50

However, the final product was contaminated with aldehyde starting material and would have required further purification. In a second attempt at the reaction, the basic reaction mixture was added to brine and extracted with ethyl acetate to remove any unreacted aldehyde. The aqueous solution was then acidified and the monoester-acid **145** was extracted with ethyl acetate. The crude yield of acid was very low possibly due to the presence of ethanol in the first extraction solvent used to remove neutral aldehyde. This may have made the organic layer sufficiently polar such that the sodium salt of the monoester-acid **145** was appreciably soluble in the organic layer. Subsequent removal and disposal of the organic layer at this point may have resulted in product loss. The most successful procedure involved the addition of water to the crude reaction mixture followed by evaporation to remove ethanol and extraction with ethyl acetate to remove unwanted neutral aldehyde starting material. The aqueous solution was then acidified and the monoacid-ester **145** was extracted with ethyl acetate. By using this approach, the

desired product was obtained in higher yield and purity and the only other contaminants were a small amount of the *cis*-benzylidenesuccinate monoester-acid and monoethyl succinate acid, which could not be avoided.

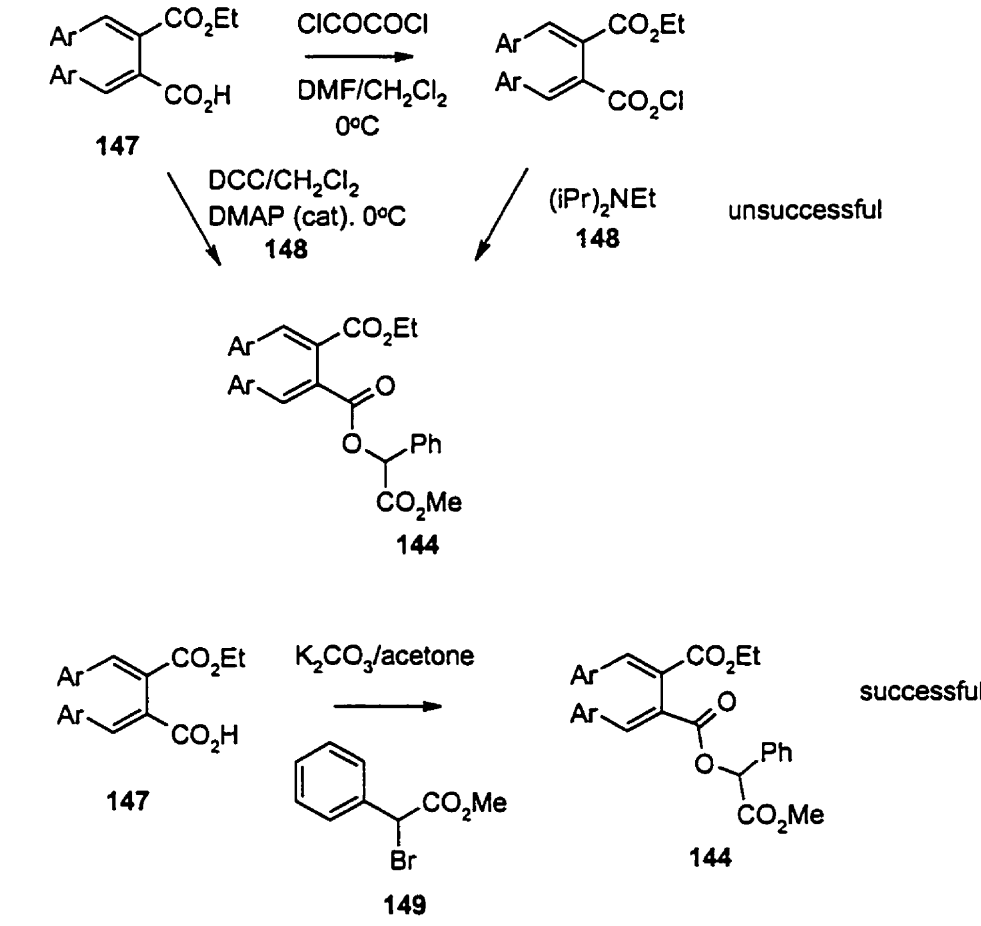
The stereochemistry of the acid **145,** having the *trans* arrangement of the carbonyl and aryl ring, was confirmed by proton NMR spectroscopy on the basis of the deshielding effect of the carbonyl on the adjacent vinyl proton.

The *trans*-benzylidenesuccinate monoester-acid **145** was subsequently esterified to give the corresponding diethylester **146.** The esterification of acid **145** was accomplished initially by treating the benzylidenesuccinate monoester with a 3% solution of ethanolic HCl. However, later work revealed that better yields of the benzylidenesuccinate diester **146** could be obtained by employing the S_N2 displacement reaction between the potassium salt of the benzylidenesuccinate monoester **145** and ethyl iodide. The diethyl ester **146** was purified by high vacuum, short path distillation and was obtained in high purity as confirmed by proton NMR spectroscopy.

The *trans*-benzylidenesuccinate diester **146** was condensed with another equivalent of 3,4,5-trimethoxybenzyaldehyde and afforded the *E,E*-dibenzylidenesuccinate monoester-acid **147.** The proton NMR spectrum of this compound gave rise to anomalies that could only be explained by hindered rotation about the butadiene carbon-carbon single bond. The methylene hydrogens on the carboxyethyl group were diastereotopic and appeared as a complex pattern of overlapping multiplets due to second order AB coupling.

The *E,E*-dibenzylidenesuccinate monoester-acid **147** was used as a precursor to the ethyl (methyl mandelyl) *E,E*-dibenzylidenesuccinate diester **144** needed for the

dynamic proton NMR study for determination of the barrier to rotation. Several attempts were made to couple methyl mandelate to the *E,E*-dibenzylidenesuccinate monoester-acid **147** (see Scheme 51). In a first approach, the acid chloride of monoester-acid **147** was prepared several times and reacted immediately with methyl mandelate (**148**) in the presence of a catalytic amount of Hunig's base (ethyldiisopropylamine). These attempts all met with failure. NMR spectral analysis of the intermediate acid chloride revealed that the formation of the acid chloride (oxalyl chloride, dichloromethane, DMF) had been unsuccessful. The reason for this failure is unknown.



Ar = 3,4,5-Trimethoxyphenyl

Scheme 51

With the expectation that a condensing reagent might give better results, DCC was employed in an attempt to prepare the desired diester **144**. DCC in the presence of catalytic amounts of DMAP converts carboxyl groups into powerful acylating agents that couple readily with alcohols.[102] Nevertheless, the reaction of ester-acid **147**, methyl mandelate and DCC led to a mixture of products that did not contain the desired *E,E*-dibenzylidenesuccinate diester **144**.

The failed attempts at the formation of the desired diester by activation of the carboxyl groups were conjectured to be a result of the insufficient reactivity of methyl mandelate. The bulky methyl mandelate may have been prevented from approaching the reactive carbonyl due to steric hindrance.

The S_N2 reaction of monoacid-ester **147** with racemic methyl α-bromophenylacetate **149** proved to be a highly successful method for the preparation of diester **144**. Treatment of the ester-acid **147** with potassium carbonate in acetone, in the presence of methyl α-bromophenylacetate afforded the desired *E,E*-dibenzylidenesuccinate diester **144** in 77% yield. The diester **144** was identified on the basis of its proton NMR spectrum.

The possibility that there was hindered rotation in the *E,E*-dibenzylidenesuccinate methylmandelylethyl ester **144** was first investigated by examining its proton NMR spectrum obtained at room temperature. A doubling of signals in the NMR spectra of this compound was observed, which indicated that there was slow rotation about the butadiene carbon-carbon single bond on the NMR time scale. The presence of the stereogenic center of the chiral methyl mandelyl ester group and the stereogenic center due to the hindered rotation about the central bond of the butadiene gives rise to two

diastereomers. Had there been rapid rotation about the central bond of the butadiene, only a single time averaged spectrum would have been observed.

The rotational isomerization of *E,E*-dibenzylidenesuccinate diester **144** was further studied by analyzing its temperature dependent proton NMR spectra at various temperatures above 303 K in the high boiling solvent, DMSO-d_6. The rate constant for the rotation about the butadiene carbon-carbon single bond increases with an increase in temperature, which increases the rate of interconversion of the diastereomers. The rapid interconversion of atropisomers was manifested in the variable temperature NMR spectra of the *E,E*-dibenzylidenesuccinate methyl mandelyl ethyl ester. As rotation became more rapid, the signals began to broaden and eventually coalesced.

The proton NMR signals of the methyl mandelyl ester that showed peak broadening and coalescence were simulated using the computer program Xsim.[103] Required input parameters for this program included the chemical shifts (δ) of the nuclei being monitored for exchange, the coupling constants among the nuclei (J), the populations of the exchanging species and the rate constant for the exchange (k). The process was iterative and the input parameters were manually adjusted until the simulated spectra closely matched the experimental spectra. In this way, the rate constants for atropisomer interconversion at various temperatures were obtained.

The observed and simulated spectra are given in Figures 1 and 2. Six nuclei were used in the simulation experiment. The rate constants associated with the barriers to rotation as well the chemical shifts for the exchanging protons that were monitored are given as a function of temperature in Table 1.

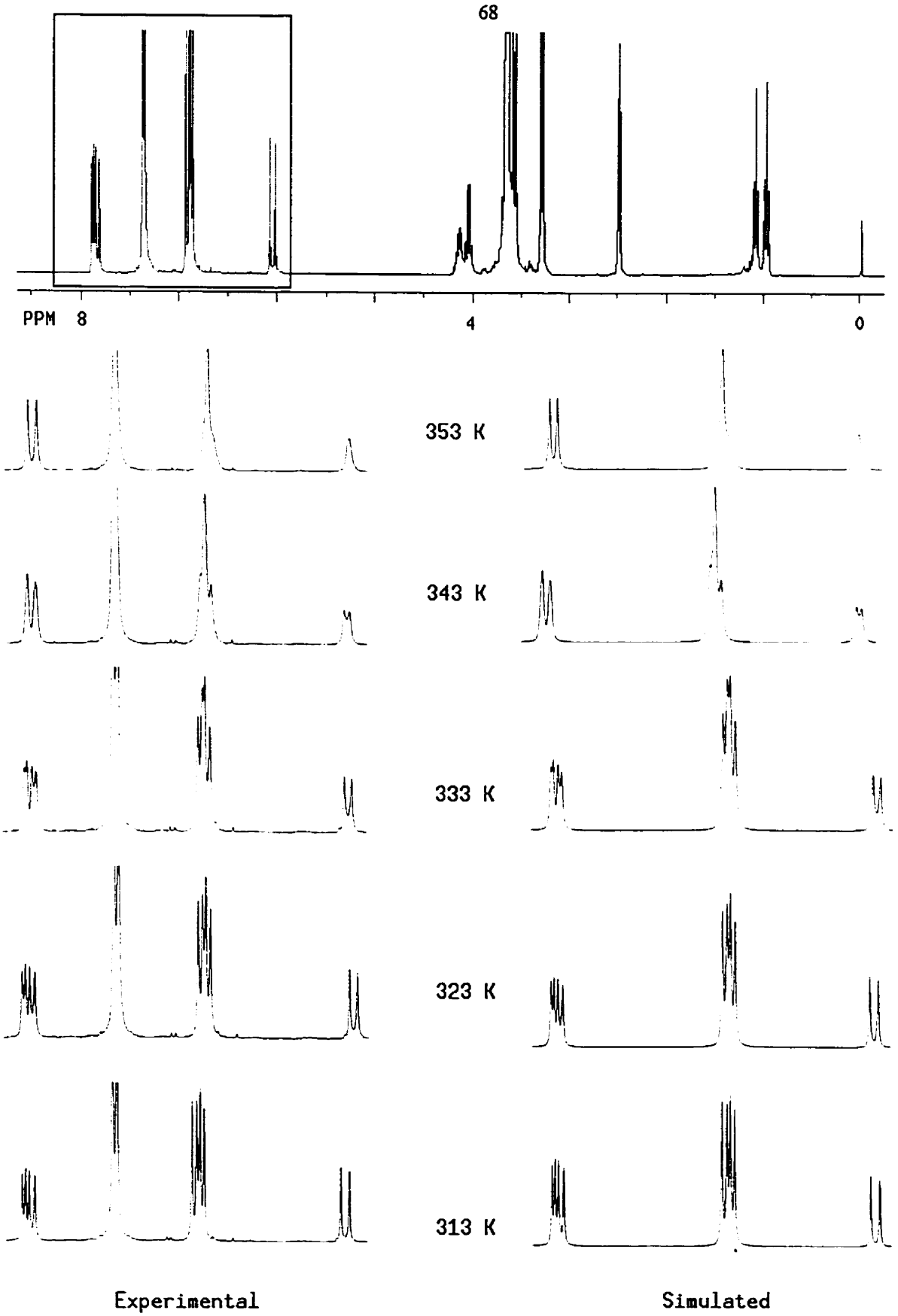


Figure 1. Simulated and Experimental Temperature Dependent Spectra of Diester 144

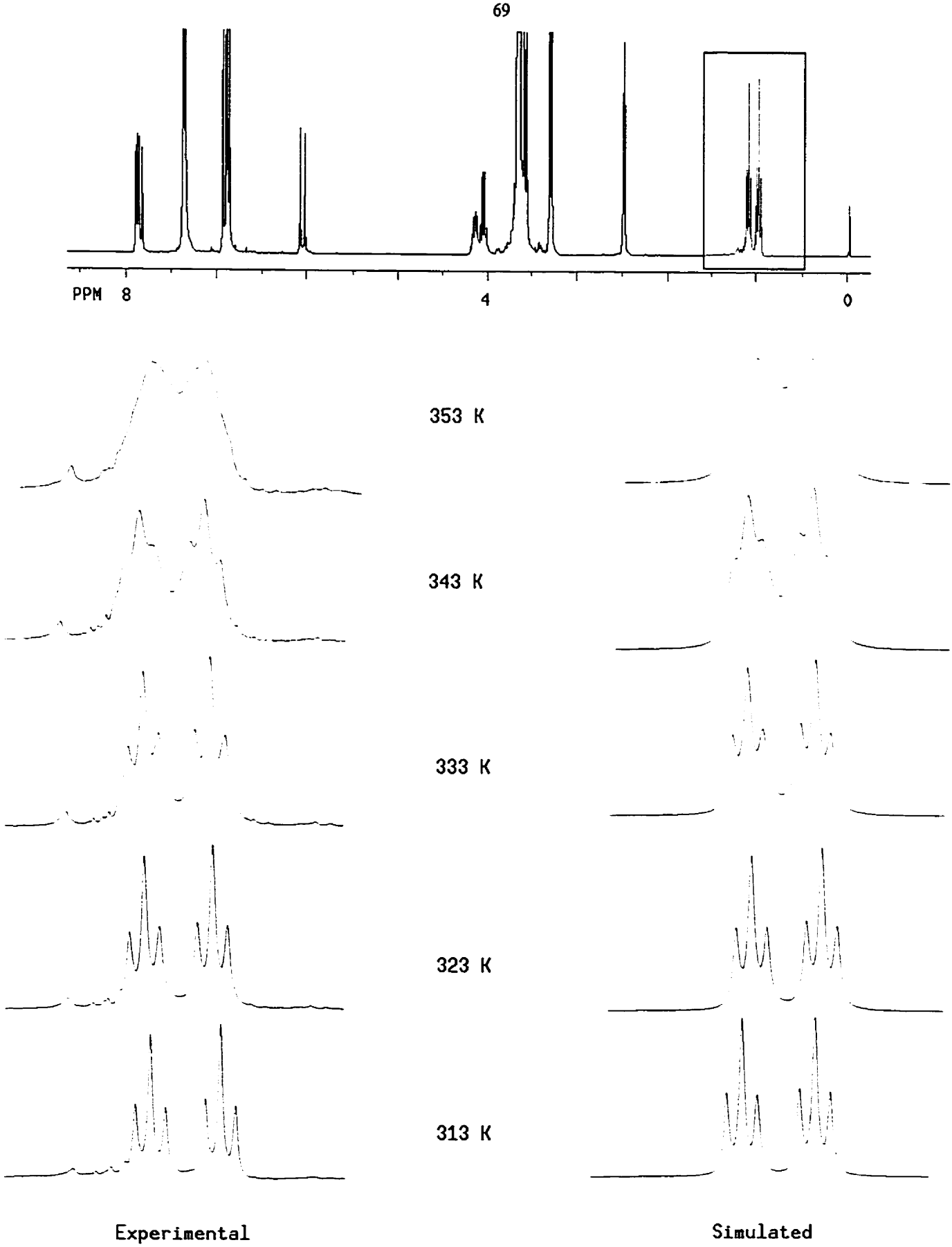


Figure 2. Simulated and Experimental Temperature Dependent Spectra of Diester 144

Table 1. Exchange Rate Constants (k) and Chemical Shifts of Exchanging Signals (δ) as a Function of Temperature for Diester 144.

Temp, °K	Exchanging signals – isomer 1, isomer 2 (δ ppm)	k, s^{-1}
313	7.88, 7.90 vinyl protons	0.3
	7.86, 7.83 vinyl protons	
	6.93, 6.90 aromatic protons	
	6.88, 6.86 aromatic protons	
	6.08, 6.03 methyne protons	
	1.00, 1.10 methyl (on the ethyl ester)	
323	7.87, 7.89 vinyl protons	2.3
	7.85, 7.82 vinyl protons	
	6.92, 6.89 aromatic protons	
	6.87, 6.85 aromatic protons	
	6.08, 6.03 methyne protons	
	1.01, 1.11 methyl (on the ethyl ester)	
333	7.86, 7.88 vinyl protons	6.0
	7.84, 7.81 vinyl protons	
	6.91, 6.89 aromatic protons	
	6.86, 6.84 aromatic protons	
	6.08, 6.04 methyne protons	
	1.02, 1.12 methyl (on the ethyl ester)	
343	7.86, 7.87 vinyl protons	14.0
	7.83, 7.81 vinyl protons	
	6.90, 6.88 aromatic protons	
	6.85, 6.82 aromatic protons	
	6.08, 6.04 methyne protons	
	1.03, 1.13 methyl (on the ethyl ester)	
353	7.85, 7.87 vinyl protons	30.5
	7.82, 7.80 vinyl protons	
	6.88, 6.87 aromatic protons	
	6.84, 6.81 aromatic protons	
	6.08, 6.05 methyne protons	
	1.04, 1.14 methyl (on the ethyl ester)	

At low temperature, the proton NMR spectrum of diester **144** exhibits four separate singlets for the olefinic protons and four separate singlets for the aryl protons. The methyl mandelyl methyne protons on each diastereomeric form of the molecule have different chemical shifts and thus give rise to two separate singlets. Similarly, the methyl protons on the carboxyethyl group give rise to two separate triplets, one for each

diastereomer. As the temperature increased, the four separate singlets arising from the vinyl protons and those arising from the aryl protons, collapse to two sets of two singlets. Likewise, the two singlets for the methyne protons on the methyl mandelyl groups and the methyl protons on the carboxyethyl group coalesce to form one singlet and one triplet, respectively.

Having determined the rate constants for the barrier to rotation at several different temperatures, by the iterative procedure described above, an Eyring plot of *-ln(k/T)* versus temperature (*1/T*) was constructed (Figure 3).

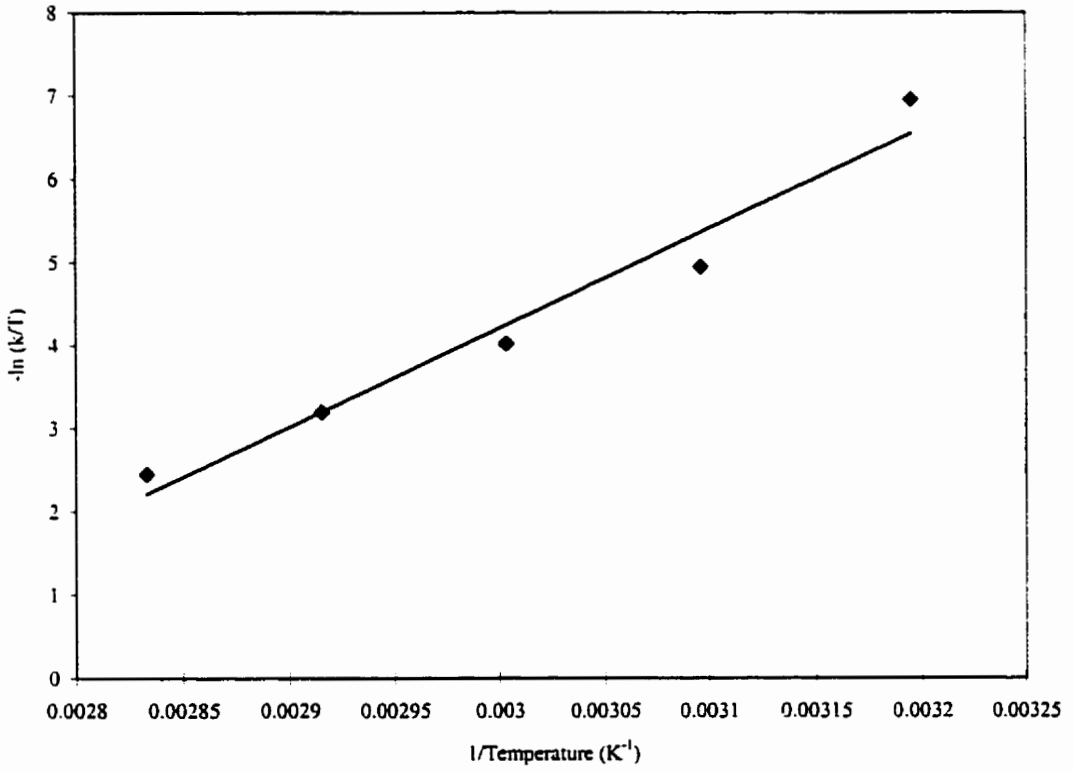


Figure 3. Eyring Plot of Rate Constants Obtained from the Dynamic NMR Analysis of Diester 144 as a Function of Temperature

The enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation for the rotational process were then obtained from the logarithmic form of the Eyring equation (1):

$$\ln(k/T) = \ln(k_B/h) - \Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R \quad (1)$$

(where k is the rate constant (s^{-1}), k_B is the Boltzmann constant (3.29986 x 10^{-27} kcal K^{-1}), h is Planck's constant (1.58369 x 10^{-37} kcal s), R is the universal gas constant (1.98719 x 10^{-3} kcal mol^{-1} K^{-1}). The enthalpy and entropy of activation ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) are derived from the slope and intercept, respectively, of the best-fit straight line obtained from a plot of -ln *(k/t)* versus *1/T* as follows:

$$\Delta H^{\ddagger} = \text{slope} \times R \quad (3)$$

$$\Delta S^{\ddagger} = R[-\text{intercept} - \ln(k_B/h)] \quad (4)$$

The free energy of activation ($\Delta G^{\ddagger}$), the energy barrier to rotation, can be calculated from equation (**5**):

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \quad (5)$$

The half-life for a dynamic interconversion process is defined as the reciprocal of the rate constant k (**6**):

$$\tau = 1/k \quad (6)$$

The energy of activation (barrier to rotation) and the half-life for isomer interconversion were calculated for diester **144** from equations (**5**) and (**6**), respectively (see Table 2).

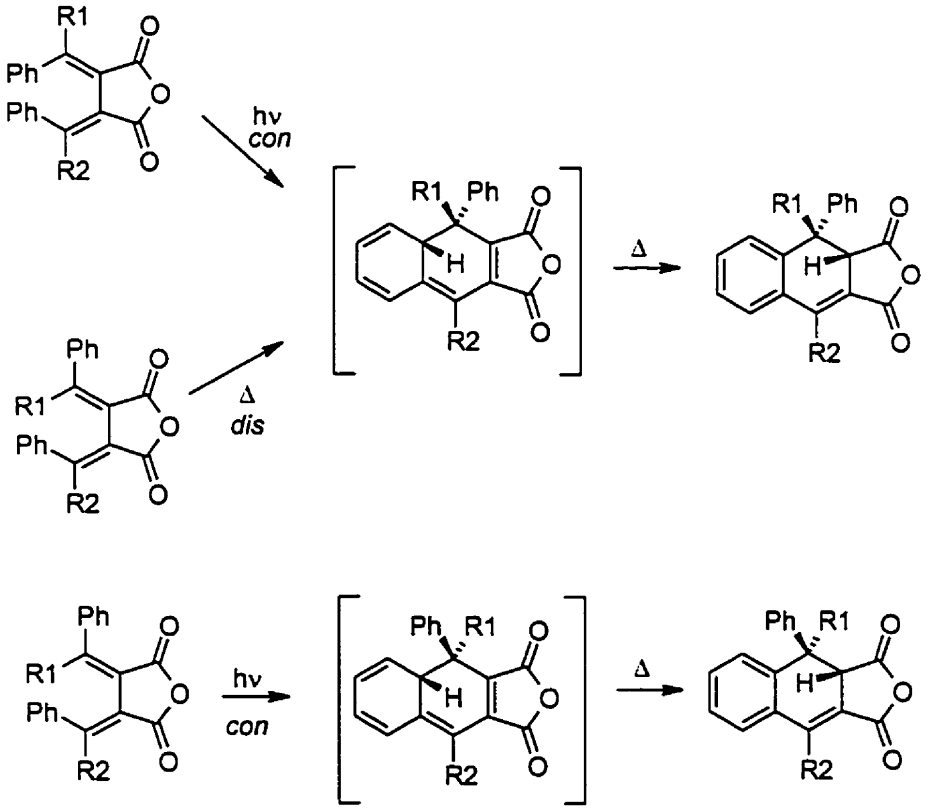
Table 2. Thermodynamic Parameters for Hindered Rotation in Diester 144

$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (cal/mol K^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)	τ (sec)
23.8(1.3)	15.7(4.1)	19.1	20.8

In conclusion, the barrier to rotation measured for diester **144** was found to be too small for this compound to exist as stable atropisomers at room temperature. The factors that determine the magnitude of the barrier to rotation in dibenzylidenesuccinates could not be elucidated based on this study. A more systematic approach involving the dynamic NMR study of a variety of substituted dibenzylidenesuccinates is required in order to gain insight as to what factors affect the barrier to rotation. Such a study would establish if the rotational hindrance could be increased and how this could be accomplished so that the atropisomers of these compounds would be isolable at room temperature. The fact that the introduction of methyl mandelate into the diarylbutadiene system did not sufficiently raise the barrier to rotation to afford stable atropisomers is surprising, given the bulk of this substituent. The atropisomers were also present in nearly equal amounts as estimated from the integration of the methyne NMR signals arising from the individual rotamers. It is unlikely that a bulkier substituent could be found that would significantly increase the rotational hindrance in this system. A different approach for the isolation of individual atropisomers is required.

3.2 A Study of the Photochemical and Thermal Reactions of Diarylbutadiene Lignans

The research described in this section is based on the results of Heller *et al.*[53,84-86] who found that the dibenzylidenesuccinic anhydrides (diarylfulgides) undergo photochemical and thermal electrocyclic ring closure followed by 1,5-sigmatropic shifts of hydrogen to afford 1,2-dihydroarylnaphthalene compounds via 1,8-dihydronaphthalene intermediates. The product distributions generated by the electrocyclic reactions of the diarylfulgides were found to be extremely sensitive to the substitution and stereochemistry of the double bonds in the butadiene system.

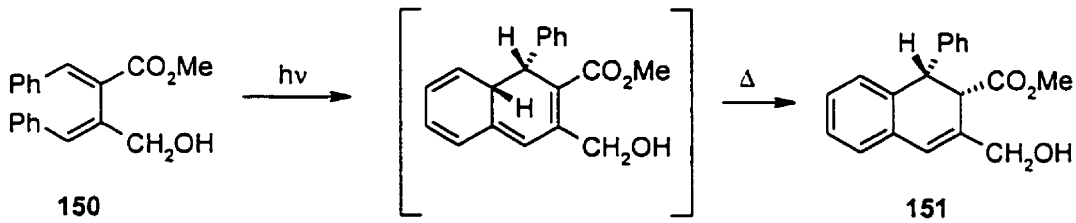


Scheme 52

The relative 1,2-stereochemistry of the 1,2-dihydronaphthalenes was determined by the direction of ring closure, conrotatory for photo-induced reactions and disrotatory

for thermal reactions, and by the configuration about the double bonds. In the presence of oxygen, fully aromatic compounds were obtained and this was attributed to oxidation of the 1,8-dihydronaphthalene intermediate since irradiation of the 1,2-dihydronaphthalenes did not lead to the formation of the corresponding arylnaphthalene compounds. A detailed description of photochemical and thermal properties of diarylbutadiene fulgides and related compounds is presented in Chapter 1.

Although the photochemical and thermal reactions of the diarylfulgides have been thoroughly investigated, their structural relatives have been largely neglected. There has been one study reported in the literature on the irradiation of an acyclic diarylbutadiene derivative that reports results similar to those obtained with the fulgides.[85] Irradiation of the alcohol/ester **150** in this case also led to the formation of a 1,2-dihydronaphthalene **151** via a 1,8-dihydronaphthalene intermediate and ring closure was exclusive onto the aryl group not in conjugation with the carbonyl group.



150 **151**

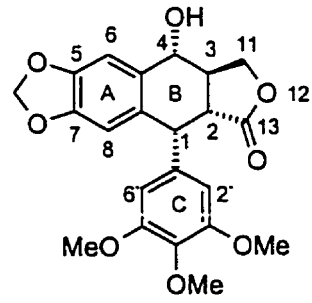
Scheme 53

It would be interesting to see if the diarylfulgides undergo electrocyclic ring closure and isomerization only because of the steric crowding of the pi system. The fulgides are not capable of freely rotating about the butadiene carbon-carbon single bond due to the anhydride ring system and one would expect them to be particularly strained and reactive as a result. In addition, the anhydride ring forces the system to be perfectly

poised for an electrocyclic reaction to occur. An investigation of the photochemical and thermal properties of open diarylbutadiene systems would provide insight as to whether they too would undergo the same reactions despite the lack of steric crowding. More importantly, if the open form dibenzylidenesuccinates are prone to the same photo-induced and thermal reactions as the fulgides, this could prove to be a facile and convenient new method for the synthesis of 1,2-dihydronaphthalene lignans. The diarylbutadiene precursors could be customized to afford 1,2-dihydronaphthalenes with a particular 1,2-configuration, such as the *cis*-1,2 configuration in podophyllotoxin which is very difficult and cumbersome to achieve by other synthetic methods. This is highly desirable since new efficient methods for the synthesis of lignans are required for more systematic investigations of factors that modulate their biological activity. This is especially true of the aryltetralin lignans, the class of lignans most often associated with biological activity, which are closely related to the dihydronaphthalene lignans. Moreover, if the dibenzylidenesuccinates could be constructed so as to afford stable atropisomers, the photochemical and thermal electrocyclization of these individual atropisomers could be exploited to asymmetrically prepare 1,2-dihydronaphthalene lignans. Thus it is highly desirable to ascertain whether or not the open dibenzylidenesuccinates are subject to the same photochemical and thermal reactions as the fulgides.

There are many examples of aryltetralin lignans exhibiting biological activity. Although the mechanism of action is unknown in most cases, a common feature amongst the aryltetralin lignans that possess the strongest biological activity is that they have the same *cis*-1,2 configuration as podophyllotoxin. Podophyllotoxin is a potent antimitotic,

antiviral and antitumor agent. Unfortunately, podophyllotoxin is non-selective and is as cytotoxic towards healthy cells as it is to infected or abnormal cells and therefore cannot



18 (Podophyllotoxin)

Scheme 54

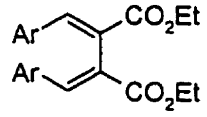
be used as a therapeutic agent for the treatment of cancers and viral infections in most cases. A discussion of the biological properties and different modes of action of podophyllotoxin type lignans was presented in Chapter 1. The *cis*-1,2-dihydronaphthalenes that are structurally similar to podophyllotoxin type lignans may also exhibit similar biological activity. These same *cis*-1,2-dihydronaphthalenes were prepared by Heller *et al.* by photocyclization of *E,E*-diarylfulgides. The possibility that the *E,E*-dibenzylidenesuccinates may also undergo photochemical cyclization to give *cis*-1,2-dihydronaphthalenes is being explored in this section. If the *E,E*-dibenzylidenesuccinates can be photochemically converted to *cis*-1,2-dihydronaphthalenes then it might be possible to exploit these photoreactions for the treatment of cancers or viral infections in a manner analogous to photodynamic therapy. The idea is that the *E,E*-dibenzylidene compounds could be administered to a patient, analogous to a photosensitizer, and allowed to equilibrate within the body. Irradiation of the infected area would convert the *E,E*-dibenzylidenesuccinate to the corresponding cytotoxic *cis*-1,2-dihydronaphthalene compound which would then eradicate the cells in

the diseased area . The classic definition of photodynamic therapy (discussed at length in Chapter 1) is that the absorption of light by a tissue selective photosensitizer subsequently leads to the production of singlet oxygen, which then elicits the cytotoxic effect. The absorption of light by a prodrug, which leads to the production of a photodynamic agent is very similar in principle. A criterion that must be met for the use of lignans and lignans analogs in photodynamic therapy is that the *E,E*-dibenzylidenesuccinate must exhibit less cytotoxicity than the *cis*-1,2-dihydronaphthalene photodynamic agent. In this way, the use of photodynamic therapy to photochemically convert *E,E*-dibenzylidenesuccinates to podophyllotoxin type lignans could be used to circumvent the problem of non-selectivity of the *cis*-1,2-aryltetralin lignans by exclusive irradiation of the infected site. One conceivable problem with using lignans in this capacity would be that near ultraviolet-visible light is required for the photochemical conversion of the prodrug to the photodynamic agent. However, light in this region of the electromagnetic spectrum is highly attenuated by chromophores in normal tissue. In addition, the non-selectivity of the *E,E*-dibenzylidenesuccinates compared to traditional photosensitizers would likely result in effects to large areas of tissue which would be a major side-effect of this treatment.

To determine whether or not dibenzylidenesuccinates would undergo photochemical and thermally induced ring closure and isomerization analogous to the fulgides, it was necessary to prepare a model compound for the study. A compound that was symmetrical was chosen so as to limit the number of different products formed and to avoid a complex reaction mixture arising from nonexclusive ring closure. Such a compound would enable us to easily assess the feasibility of using the photochemical or

thermal ring closure of dibenzylidenesuccinates as a synthetic route to 1,2-dihydronaphthalene lignans.

With these considerations in mind, *E,E*-bis(3,4,5-trimethoxy)benzylidenesuccinic acid diethyl ester (**152**) was chosen as the subject of the photochemical and thermal study. Two methods were used to prepare the dibenzylidenesuccinate diester **152**.

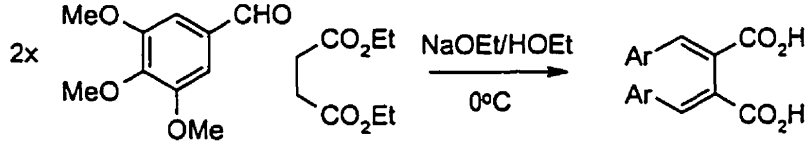


Ar = 3,4,5-Trimethoxyphenyl

152

Scheme 55

The quickest and most convenient route was thought be the Stobbe condensation of two equivalents of 3,4,5-trimethoxybenzaldehyde with diethyl succinate to afford the bis(3,4,5-trimethoxy)benzylidenesuccinic diacid **153**.

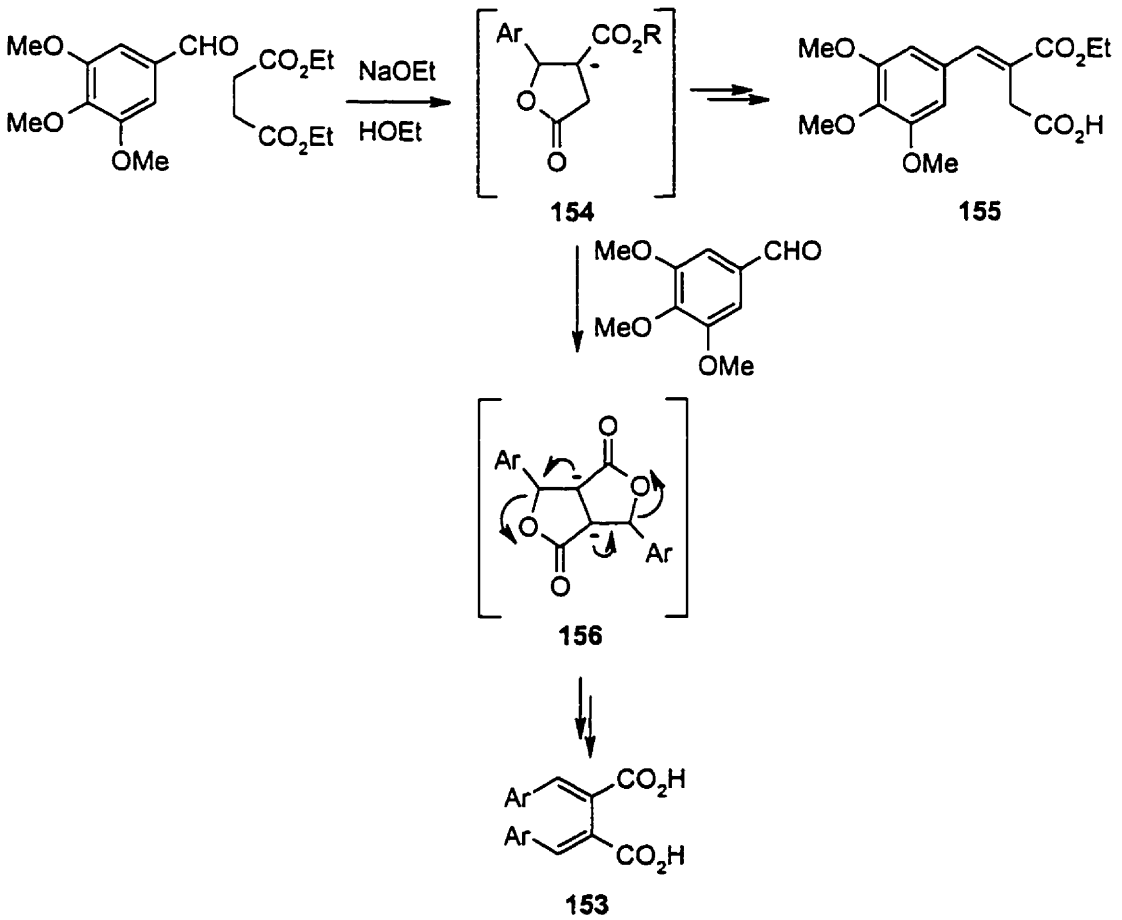


153

Scheme 56

Diacids, such as **153** is often present as a contaminant in the Stobbe condensation of one equivalent of aldehyde with a succinate ester. The amount of diacid produced during a classic Stobbe condensation reaction is reported to be dependent on the temperature at which the reaction takes place. Low temperatures are reported to increase production of the diacid.[57] It is believed that the intermediate lactone **154** has a longer existence at lower temperatures and condenses with another equivalent of aldehyde to form an extremely unstable dilactone **156**, which then undergoes elimination to afford the

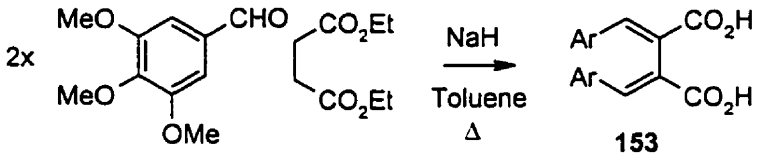
diacid.[57] At higher reaction temperatures, the intermediate lactone eliminates to form the benzylidenesuccinate monoester-acid **155**, which does not undergo further condensation as it has a less reactive methylene group being adjacent to a carboxylate anion.[57] Thus the condensation of two equivalents of aromatic aldehyde and diethyl succinate at zero degrees was executed with the expectation that the diacid would ensue. The proton NMR



Scheme 57

spectrum showed that only the typical Stobbe benzylidenesuccinate monoester-acid **155** was produced during the reaction. In another approach, the dianion of diethyl succinate was condensed with two equivalents of 3,4,5-trimethoxybenzaldehyde. Tandem addition to two equivalents of aromatic aldehyde should form the dilactone intermediate directly,

which would then undergo elimination to afford the diacid. The use of LDA to form dienolate structures has been reported[104] and therefore LDA was used in an attempt to form the diethyl succinate dianion. Unfortunately, condensation of this dianion with the aldehyde did not produce the desired diacid. The synthesis of the diacid from diethyl succinate and 3,4,5-trimethoxybenzaldehyde was also attempted by employing sodium hydride as a base in refluxing toluene. This method had reportedly been successful for the preparation of similar diacids.[105] Application of the method to the present case was also successful and led to formation of the desired diacid **153**.

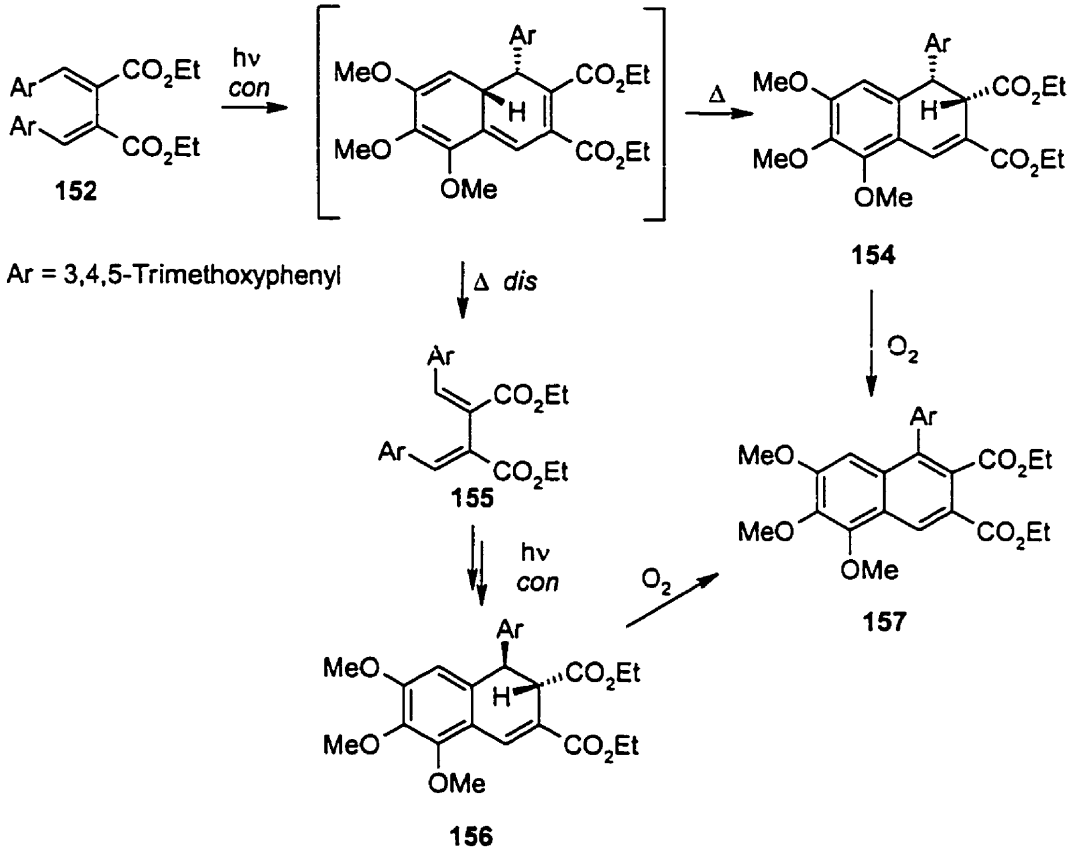


153

Scheme 58

The diacid, which was found to crystallize out of aqueous and alcoholic solutions, was used to prepare the diethyl diester. Reaction of the potassium dicarboxylate salt of the acid with ethyl iodide in acetone was attempted. This procedure was unsuccessful. This may be due to the poor solubility of the dipotassium salt of the acid, as it appeared to be very insoluble in acetone. Dimethylformamide, a polar solvent was added, in small amounts, to the reaction in order to solubilize the diacid salt. This improved the situation and the diester was obtained in 30% yield after heating the reaction mixture at reflux temperatures for 24 hours. The diethyl ester was also prepared from the monoethyl ester of the diacid by refluxing the monoethyl ester in acetone with potassium carbonate and ethyl iodide. Unlike the diacid, this reaction produced the diester in good yields. The diethyl diester could be recrystallized from a solvent mixture of methylene chloride and hexanes.

The thermal properties of the diarylbutadiene diester **152** were investigated. A solution of the compound in hexachlorobutadiene, was heated to reflux (215°C) over a flame for *ca.* 10 minutes. The proton NMR spectrum of the mixture showed only the presence of starting material. Refluxing a further 10 minutes also did not result in any change. It appears that the diester is thermodynamically stable. The photochemical properties of diester **152** were investigated by irradiation in a variety of solvents, with and without added acid and base. The goal of these studies was to determine if these differences in the reaction medium would have an effect on the product distribution. Irradiation of the diester in ethyl acetate led to a complex reaction mixture. The formation of at least four distinct products was discerned on the basis of proton NMR spectroscopy and thin layer chromatography (TLC) analyses of the reaction mixture. The structures of the compounds comprising the reaction mixture were not elucidated. The interesting observation was made that diester **152** exhibited photochromism, formation of a transient orange color on irradiation, both in solution and on TLC plates. This was interpreted to indicate that the 1,8-dihydronaphthalene intermediate was being formed upon irradiation but that its lifetime was relatively short. The 1,8-dihydronaphthalene would arise from the photoelectrocyclic ring closure. The photochemical electrocyclic reaction would only be an allowed process if the ring closure occurred in a conrotatory fashion. Conrotatory electrocyclic ring closure would afford a *cis*-1,8-dihydronaphthalene intermediate that would then be expected to undergo thermal suprafacial a 1,5-sigmatropic shift of hydrogen to give a *cis*-1,2-dihydronaphthalene **154**. Alternatively it could revert to the *E,Z*- isomer of the starting material **155** by a disrotatory ring opening.



Scheme 59

The diester was irradiated in a methanol solution and was, by inspection of the proton NMR spectrum, found to give rise to a mixture of compounds. The mixture was also analyzed by TLC and three distinct spots were detected when a solution of 30% ethyl acetate in hexanes was used as the mobile phase. Based on the proton NMR spectrum and TLC of the crude reaction mixture, the compounds were thought to be a mixture of the *cis*-and *trans*-1,2-dihydronaphthalene compounds **154** and **156**, respectively, in addition to the corresponding fully oxidized arylnaphthalene **157**. The *cis*-1,2-dihydronaphthalene **154** appeared to be the major product of the reaction and this assessment was based on integration of the peaks in the proton NMR spectrum attributed to this compound in comparison to those arising from the other minor compounds. An

indication that photocyclization had occurred was an apparent loss of symmetry in the molecule. Where there were formerly two methoxy peaks in the proton NMR spectrum of the symmetric starting material, there were now more than five methoxy signals in the proton NMR spectrum of the product mixture. Furthermore, there were two sets of doublets, one at 7.4 ppm and the other at 4.8 ppm which were strongly suggestive of *cis*-1,2-dihydronaphthalene olefinic and benzylic protons, respectively.

The product mixture was analyzed by high performance liquid chromatography (HPLC) and, after optimization of the solvent system, was found to contain three ultraviolet (UV) active compounds. The HPLC was fairly deceptive in that all three compounds appeared to be present in significant amounts, whereas the proton NMR indicated the presence of mainly one compound and very small amounts of two others. The discrepancy between the HPLC and NMR results is probably due to differences in the absorption coefficients of the three compounds, which skews the relative responses to detection in the HPLC. Optimization of the HPLC solvent system led to resolution of the peaks, which had fairly close retention times. This enabled the progress of the photochemical reaction to be monitored by HPLC (Figure 4). A solution of diester **152** in ethanol was prepared, purged with nitrogen and irradiated until the reaction had gone to completion (disappearance of starting material) as assessed by HPLC (*ca.* 30 minutes). A sample of the reaction mixture was removed every minute and kept in the dark until it was analyzed by HPLC.

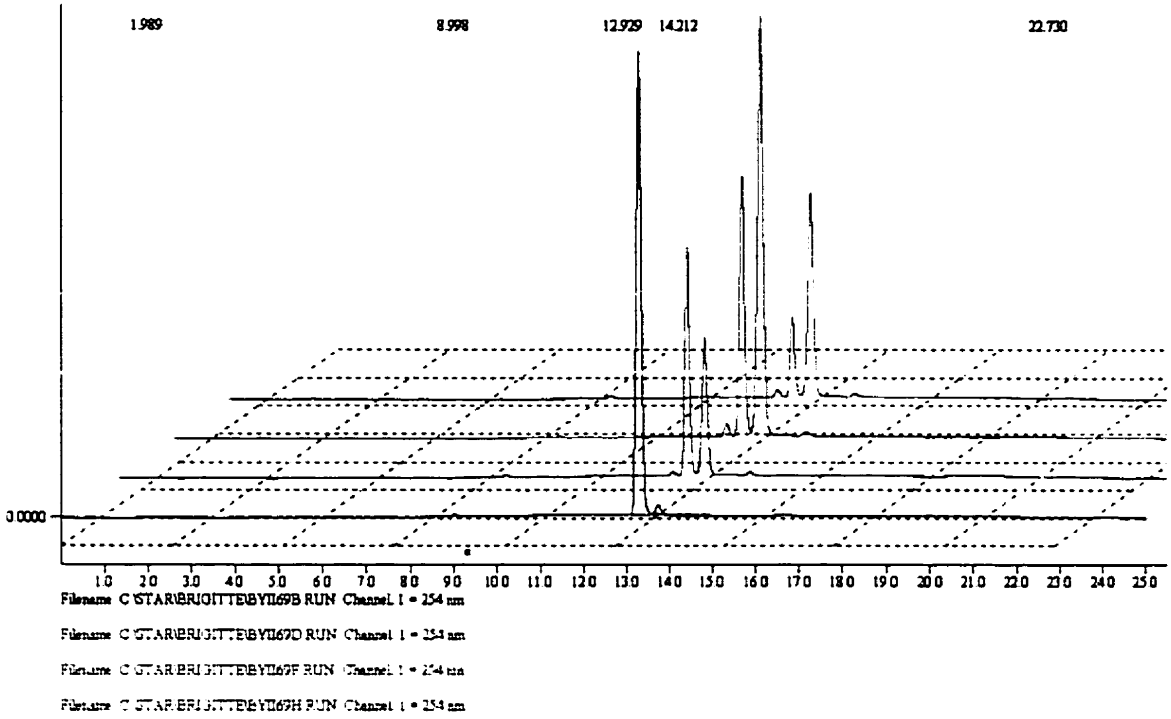


Figure 4. HPLC Chromatogram of the Photoreaction Progress of Diester 152

The fact that the solution turned vibrant yellow upon irradiation and then became colorless again was taken as an indication of the transient formation of the 1,8-dihydronaphthalene intermediate. The three product peaks in the HPLC chromatogram were thought to arise from the *cis*- and *trans*-1,2-dihydronaphthalenes and the arylnaphthalene. NMR spectral analysis of the products, described below, allowed the assignment of structures to the HPLC peaks. The *trans*-dihydronaphthalene **156** eluted first followed by the *cis*-compound **154** and then the arylnaphthalene **157**, which had the longest retention time.

The diester **152** was irradiated on a preparative scale and the product mixture was chromatographed on silica gel using 30% ethyl acetate in hexanes as the solvent system. Two compounds could be purified in this way. A small amount (*ca.* 2% yield) of the *trans*-dihydronaphthalene **156** was isolated and was identified by comparison to a sample

previously prepared by an alternate method by a colleague previously published.[61] The proton NMR spectra were identical. The second compound, isolated in *ca.* 34% yield, was assigned the *cis*-1,2-dihydronaphthalene structure (**154**) on the basis of its proton NMR spectrum. In addition, when a small amount of this compound was treated with dimethylaminopyridine (DMAP) in ethanol at reflux, it was quantitatively converted to the *trans*-dihydronaphthalene **156**. The *cis* and *trans*-dihydronaphthalenes isolated by silica gel chromatography were correlated to the first two peaks eluted on HPLC. No compound corresponding the third peak observed by HPLC could be isolated by silica gel chromatography. However, it was noted that continued irradiation of the reaction beyond that needed to completely convert the starting material to products resulted in a steady increase of this third HPLC peak at the expense of the other products. The conversion was accelerated by the presence of oxygen. This suggested that the dihydronaphthalene compounds were being oxidized to the corresponding fully aromatic arylnaphthalene **157**.

There were some interesting differences between the proton NMR spectra of the *cis*- and *trans*-dihydronaphthalenes. The *cis*-compound showed a doublet at *ca.* 4.8 ppm for the benzylic proton whereas the corresponding signal in the *trans*-compound appeared as a broadened singlet. The protons giving rise to these signals are spin coupled to the neighboring allylic protons and the difference in the coupling constants for the *cis* and *trans*-compound can be explained by the difference in the dihedral angles between the coupled protons. The coupling constants can be predicted using the Karplus equation.[106] Model studies indicate that the *trans*-compound has the adjacent protons in question at an angle close to 90°, resulting in a very small coupling constant. On the other hand, in the *cis*-compound the dihedral angle between the two protons is smaller resulting in a larger

coupling constant. The observed long range coupling between the allylic and vinylic protons in the *cis*-compound gives rise to a doublet at 7.4 ppm and a doublet of doublets at 4.0 ppm. The *cis*-compound exhibits long range allylic coupling, as the saturated C-H bond is parallel to the pi orbital of the double bond, which allows the coupling to be transmitted more effectively. In contrast, the *trans*-compound has the saturated C-H bond and the pi orbitals of the double bond more nearly orthogonal to one another and no apparent allylic coupling results.

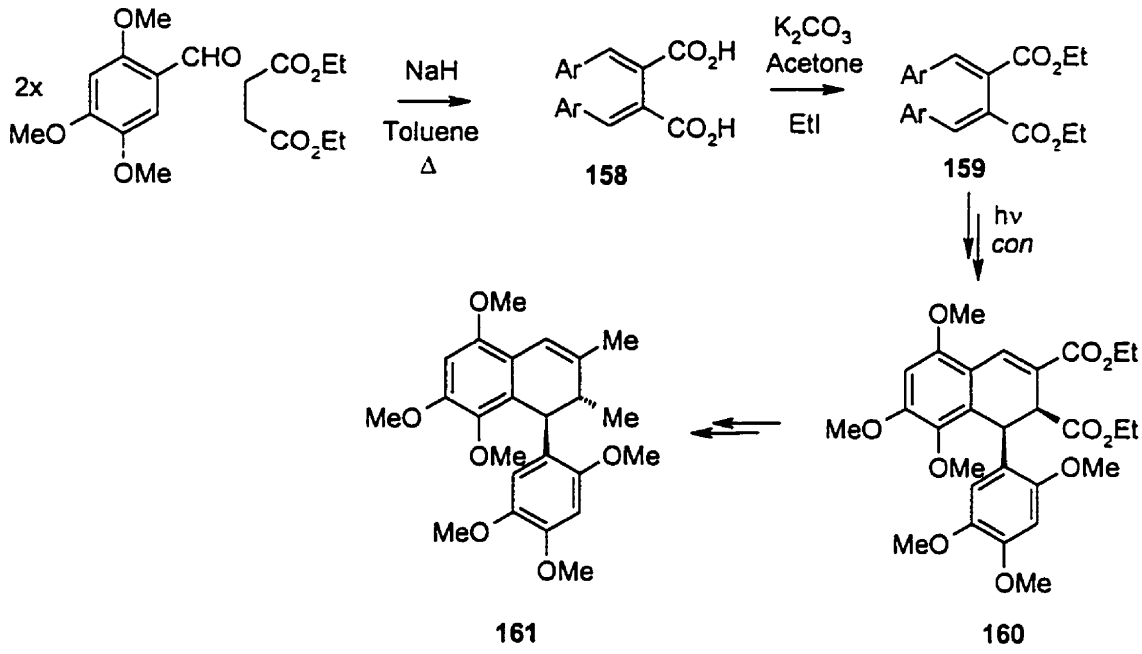
Irradiation of diester **152** was also carried out in ethanol in the presence of trifluoroacetic acid and then potassium carbonate in order to see what effects, if any, acid and base would have on the product distribution. It was thought that acid or base might act as catalysts (by protonation/deprotonation or *vice versa*) for the conversion of the 1,8-dihydronaphthalene intermediate to the corresponding *trans*-1,2-dihydronaphthalene. However, the same product distribution was obtained from the irradiation of diester **152** in neutral, acidic and basic media. Presumably, only a 1,5-hydrogen shift intramolecularly converts the 1,8-dihydronaphthalene to the *cis*-1,2-dihydronaphthalene.

In view of the fact that the *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate diethyl ester **152** could be photochemically converted to a *cis*-1,2-dihydronaphthalene structure in high yield, the possibility of using these compounds as agents for photodynamic therapy was explored. Ideally the starting material should be non-toxic and the product very cytotoxic. Both the starting material and product were tested for cytotoxicity at Boehringer Ingelheim (Canada) Ltd. (Montreal Canada). The cytotoxicities were measured using a tetrazolium salt MTT.[107] The results from these tests indicated that the prodrug, *E,E*-bis(3,4,5-trimethoxybenzylidene)succinate diethyl

ester (**152**), exhibited a 40% cytotoxicity towards human Hep-2 cells at 45 μM. On the other hand, the potential photodynamic product, *cis*-1,2-dihydronapthalene **154,** only exhibited a 30% cytotoxicity at 70 μM concentration. Thus neither the starting material nor the photoproduct exhibited very significant cytotoxicity. The cytotoxicity of the starting material was in an appropriate range for its use as a photodynamic agent. Disappointingly and surprisingly, the photoproduct was insufficiently toxic for it to be effective. Thus, the idea that these compounds could be used in photodynamic therapy did not materialize.

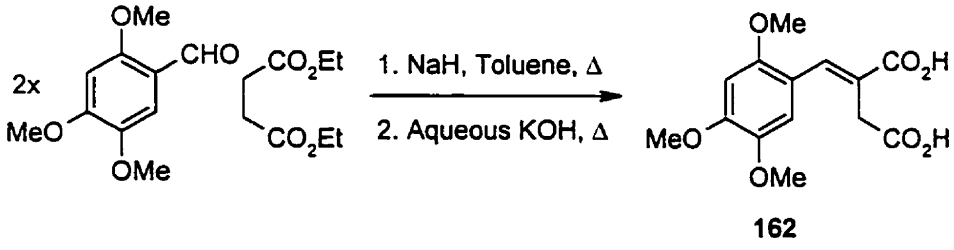
The *E,E*-bis(3,4,5-trimethoxybenzylidene)succinate diethyl ester served as a test compound for the photochemical behavior of diarylbutadiene lignans. The study of the photochemical properties of this compound, as described above, indicated that the photo-induced sequence of events described by Heller *et al.* for fulgides also occurred with acyclic dibenzylidenesuccinate diesters. Thus it was decided to apply the above principles to the synthesis of magnoshinin **161**, a naturally occurring *trans*-1,2-dihydronaphthalene lignan derived from the dry buds of *Magnolia salicifolia.* Magnoshinin is reported to have anti-inflammatory effects.[108] The synthesis of this compound has been reported in the literature twice.[108,109] One of the synthetic routes was based on an inefficient photochemical dimerization with numerous by-products[109] and the other was an eight-step synthesis.[108] We proposed a seven-step synthesis for the synthesis of magnoshinin. The first step en route to magnoshinin would involve preparation of the diacid **158** via the Stobbe condensation of two equivalents of 2,4,5-trimethoxybenzaldehyde with diethyl succinate in the presence of sodium hydride. Esterification of the diacid to its diethyl diester **159** and subsequent photochemical ring

closure should conveniently afford the basic *cis*-1,2-dihydronaphthalene lignan skeleton **160**. Epimerization of the C-2 position followed by reduction of the carboxyethyl groups to methyl groups should give magnoshinin.



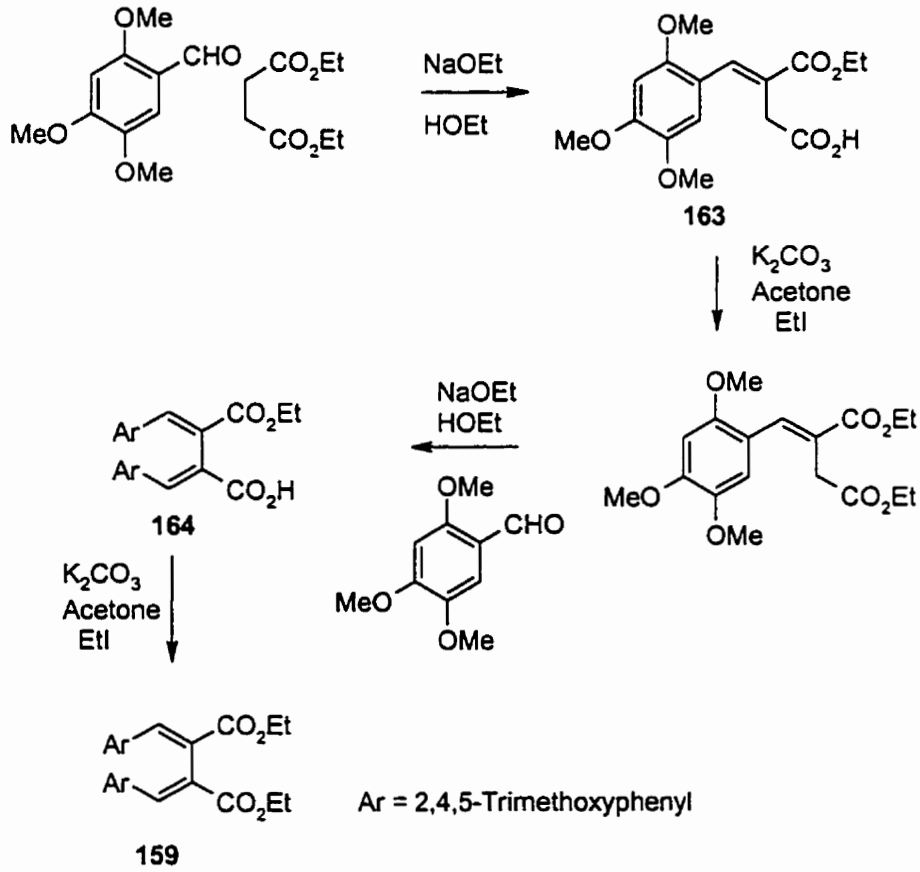
Scheme 60

An attempt was made to prepare the diacid **158** by condensing diethyl succinate with two equivalents of 2,4,5-trimethoxybenzaldehyde using sodium hydride as base, followed by base hydrolysis. Unfortunately, the major product of this reaction was the mono-benzylidenesuccinate diacid **162** and not the desired *E,E*-bis(2,4,5-trimethoxybenzylidene)succinic acid (**161**).



Scheme 61

The desired *E,E*-bis(2,4,5-trimethoxybenzylidene)succinic acid diethyl ester (**159**) was prepared via two successive Stobbe condensations as shown in Scheme 62. The first Stobbe condensation of 2,4,5-trimethoxybenzaldehye with diethyl succinate, which required long reaction times in comparison with 3,4,5-trimethoxybenzaldehyde, afforded the dibenzylidenesuccinate monoester-acid **163**. The monoester-acid was esterified using potassium carbonate and ethyl iodide in acetone and then condensed with another equivalent of 2,4,5-trimethoxybenzaldehyde to give the corresponding dibenzylidenesuccinate monoester-acid **164**. This was converted to the diethyl ester **159** as shown in Scheme 62.

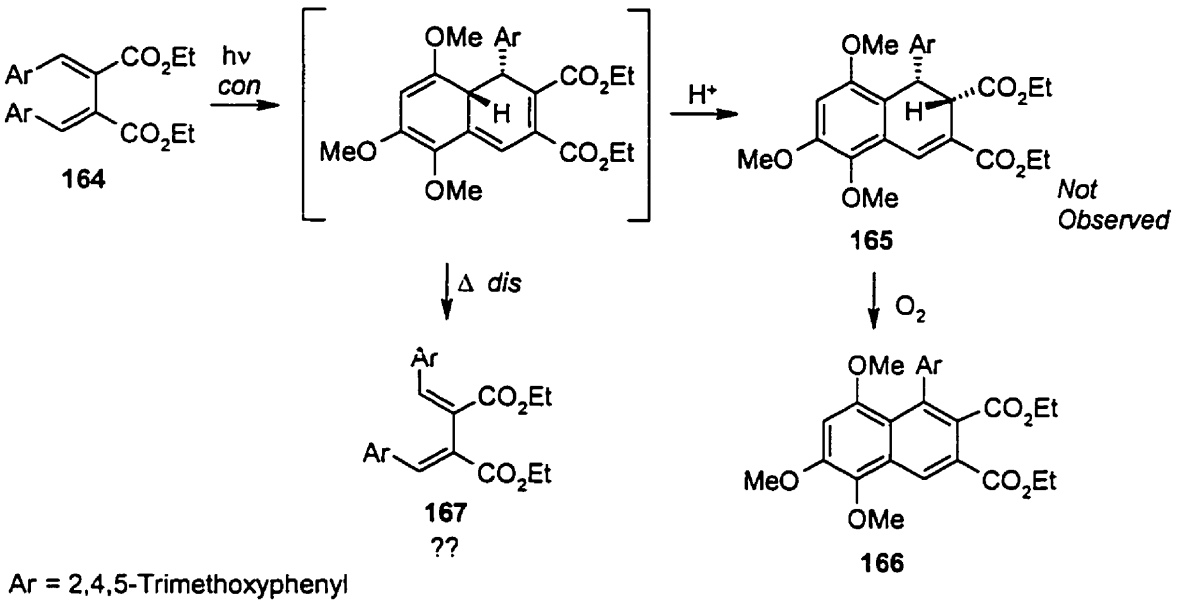


Scheme 62

The resulting diester **164** was irradiated in a solution of in ethanol under nitrogen. After relatively long irradiation times a complex mixture of products was obtained. Whereas the photochemical conversion of diethyl *E,E*-bis(3,4,5-trimethoxybenzylidene)succinate (**152**) went to completion in *ca.* two hours (Scheme 64), irradiation of the *E,E*-diethyl bis(2,4,5-trimethoxybenzylidene)succinate (**164**) under the same conditions gave little or no reaction even after five hours. The proton NMR spectrum of the crude reaction mixture, obtained after much longer irradiation times, suggested that the product mixture was comprised of mainly starting material and possibly a small amount of *E,Z*-isomer **167** of the starting material. The conclusion that a small amount of *E,Z*-isomer **167** might be present was based on the observation of a new vinylic peaks at 8.0 ppm and 7.3 ppm. More importantly, there were no peaks in the 4.5 – 5.5 ppm range, characteristic of the 1,2-dihydronaphthalene compounds. Irradiation of the diester in ethyl acetate also led to the same complex mixture of products, again with no signal in the proton NMR spectrum of the crude reaction mixture in the 4.5 - 5.5 ppm range. When the solution was irradiated for *ca.* 5 hours in a solution of 3% TFA in ethanol, a peak at 8.9 ppm appeared that suggested the arylnaphthalene **166** had been produced and was the main component of the reaction mixture. The TLC indicated there were three components in the reaction mixture. The reaction mixture was chromatographed to give two major fractions. The second, major component was obtained in *ca.* 17% yield in at least 90% purity, as there were no contaminant peaks in its proton NMR spectrum. The proton NMR spectrum of this fraction had four signals in the 6.5-8.9 ppm range that were of equal intensity. This implied that the major fraction was the arylnaphthalene compound **166** and that the signal at *ca.* 8.9 ppm was the highly deshielded naphthalene proton adjacent to the ester group.

The other three signals in this range were attributed to the remaining three aryl protons. Furthermore, there were six peaks in the 3 – 4 ppm range ascribed to the six methoxy groups on the aryl two rings and two triplets at *ca.* 1.4 ppm and *ca.* 1.1 ppm thought to arise from the two carboxyethyl groups on the arylnaphthalene.

The current information suggested that the *bis*-(2,4,5-trimethoxybenzylidene)succinate diethyl ester was *cis-trans* isomerizing, either through a 1,8-dihydronaphthalene intermediate or via direct photo-isomerization. A 1,8-dihydronaphthalene intermediate is capable of undergoing one of two competing reactions, a 1,5-sigmatropic shift of hydrogen to produce a dihydronaphthalene or disrotatory ring opening to afford the *cis-trans* isomer of the starting material. Since no signals corresponding to dihydronaphthalenes could be detected then the activation barrier for the thermal 1,5-sigmatropic shift must have been higher than the thermal disrotatory ring opening for this compound. The fact that the arylnaphthalene appeared to be the major product of the photoreaction in the presence of acid is suggestive of the transient formation of a 1,8-dihydronaphthalene intermediate. The intermediate could be oxidized to the fully aromatic product in competition with electrocyclic opening to the isomerized starting material.

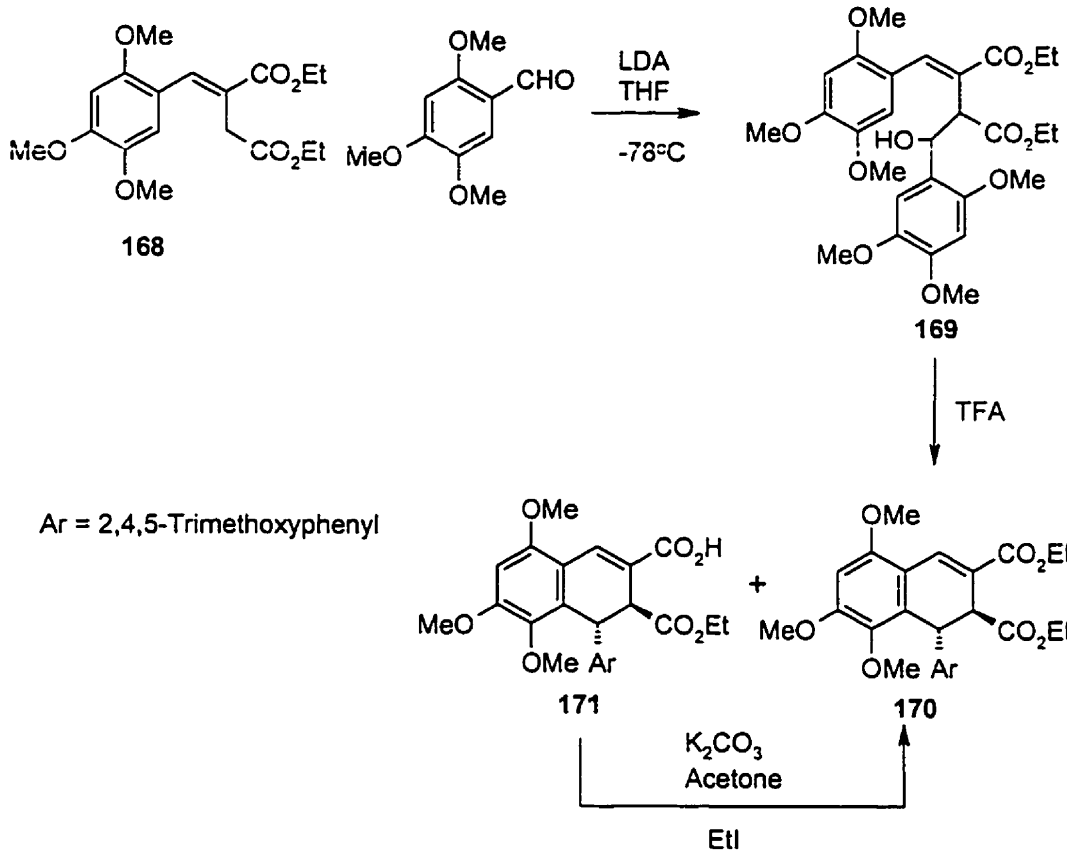


Scheme 63

In parallel with the work above a non-photochemical synthesis of magnoshinin was undertaken. An alternate synthesis passing through common intermediates would allow for easy confirmation of the structures expected from the photochemical cyclization-epimerization sequence proposed above. The alternate synthesis would also provide material for developing the functional group transformations needed to complete the synthesis of magnoshinin.

The procedure employed for the alternate synthesis was a modified version of the Stobbe condensation method, described in Chapter 1, that had been used by Charlton *et al.*[61] for the synthesis of a wide variety of *trans*-1,2-dihydronaphthalene lignans. One equivalent of 2,4,5-trimethoxybenzaldehyde was condensed with diethyl 2,4,5-trimethoxybenzylidenesuccinate **168** (see above) in the presence of lithium diisopropylamide to afford the corresponding alcohol **169**. The crude alcohol was immediately treated with TFA to afford a 50:50 mixture of the *trans*-1,2-

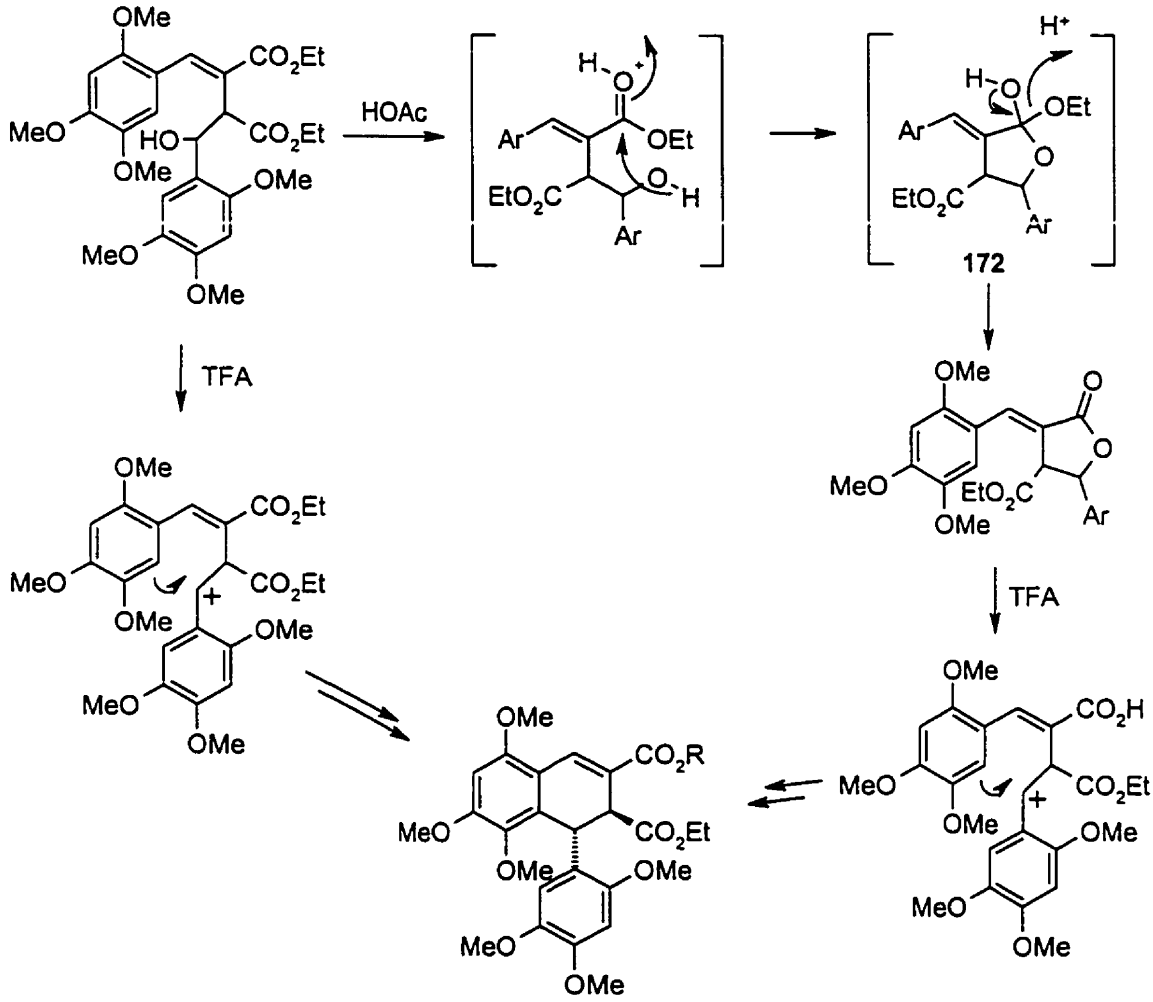
dihydronaphthalene diester **170** and monoester-acid **171**. Both components in the product mixture were fully characterized and the monoester-acid was converted to the diester by treatment with potassium carbonate and ethyl iodide in acetone.



Scheme 64

Only the diethyl diester was expected under these conditions, however, each time the procedure was repeated, a 50:50 mixture of the diethyl ester **170** and the monoethyl ester-acid **171** was obtained. The likely explanation for the presence of the monoester-acid is that lactonization of the alcohol **169** occurs when the reaction was quenched with glacial acetic acid. When a mixture of the lactone **172** and alcohol **169** was treated with TFA, loss of water from the alcohol and acid induced opening of the lactone resulting in formation of the monoester-acid and diester carbocations, which then both underwent

Friedel-Crafts cyclization to afford the observed mixture of *trans*-1,2-dihydronaphthalenes **170** and **171**.



Scheme 65

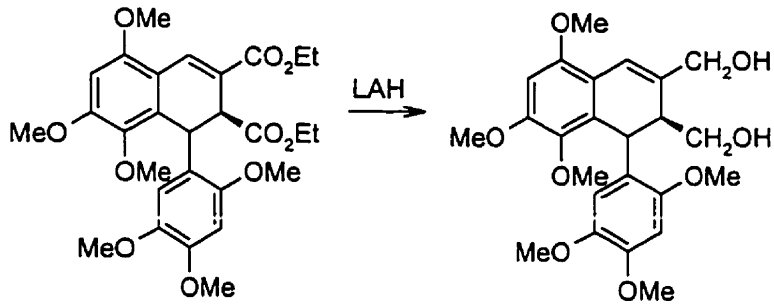
The proton NMR spectrum of the *trans*-1,2-dihydronaphthalene diester **170** indicates that the signal from the benzylic proton occurs as a singlet at 5.5 ppm, slightly more downfield than usual. Comparison of this spectrum to that obtained from the product of the irradiation of the corresponding diethyl *E,E*-dibenzylidenesuccinate **152** (see above) clearly confirmed that the irradiation had not produced any of this *trans*-dihydronaphthalene **170**. Furthermore, since the benzylic proton in the corresponding

cis-compound usually occurs slightly upfield from the trans-compound (*ca.* 0.25 ppm), it is unlikely that the *cis*-1,2-dihydronaphthalene was a product of the photoreactions either, as no peaks were observed in the 4.5 – 5.5 ppm range. As expected, the *trans*-benzylic and olefinic protons are singlets, analogous to the *trans*-1,2-dihydronapthalene compound prepared from diethyl *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate **152**.

In order to prepare magnoshinin from the diester **170** it was necessary to establish a protocol for the reduction of the carboxyethyl groups on the *trans*-1,2-dihydronaphthalene compound to methyl groups. This conversion had been reported in the literature for aryltetralin lignans, but not dihydronaphthalene lignans. Typically, the carboxyethyl groups were first reduced with lithium aluminum hydride (LAH) and then converted to the mesylates or tosylates, which were in turn reduced with LAH. One concern in using this approach was that furan formation could occur upon reduction of the carboxyethyl groups. This has reportedly been a problem with certain aryltetralin lignans. Another legitimate concern was that the intermediate allylic tosylate or mesylate would be extremely susceptible to hydrolysis.

The carboxyethyl groups were easily reduced with LAH in tetrahydrofuran under nitrogen. Fieser workup gave the resulting diol **173** but it proved to be rather unstable and slowly decomposed at room temperature (12 hours) to give several compounds. It also decomposed when column chromatography on silica gel was attempted. For this reason the diol **173** had to be used immediately in following reaction without purification. Numerous attempts were made to convert the diol **173** to the corresponding ditosylates or dimesylates. These attempts led to complex mixtures of products and it was not certain if

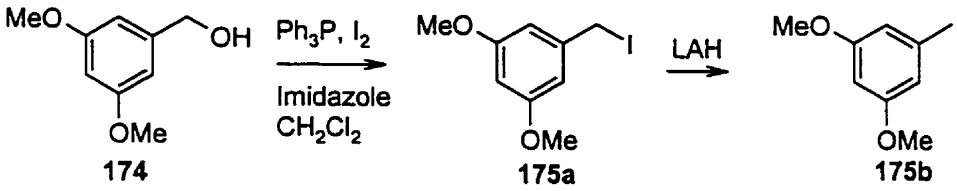
this was due to the thermal instability of the diol starting material or the instability of the products.



170 173

Scheme 66

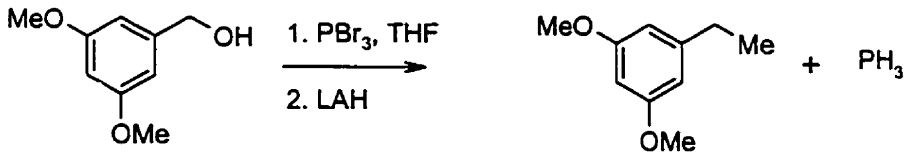
A search of the literature for methods for deoxygenating benzylic and allylic alcohols led to an article in which the authors boasted[110] of the ease with which the preparation of benzylic and allylic iodides could be accomplished. Subsequent treatment of the iodides with LAH gave the deoxygenated compounds. It was possible that this procedure would be more successful since alkyl iodides are slightly more stable than the corresponding mesylates or tosylates. The hypothesis was tested on a model compound, 3,5-dimethoxybenzylalcohol (**174**). This compound was suitable since benzylic alcohols and allylic alcohols are comparable in reactivity, the resulting hydrocarbon would not be unduly volatile and the reaction progress could be monitored via TLC. Treatment of the 3,5-dimethoxybenzyl alcohol with imidazole, triphenylphosphine and iodine easily provided the corresponding iodide **175a**, which could be readily reduced with LAH. Deoxygenation of the *trans*-1,2-dihydronaphthalene diol **173** was attempted using this procedure but no trace of magnoshinin could be detected in the complex mixture of products.



Scheme 67

Simultaneous bromination of both hydroxyls of diol **173** with PBr_3 was attempted on a small amount of material (*ca.* 8 mg). TLC was used to monitor the reaction progress. There was no indication of the formation of a less polar compound, which would have been expected if the dibromide had formed. Only products more polar than starting material appeared on TLC. Another experiment was carried out on a similar scale (*ca.* 9 mg) in which the diol was treated with PBr_3 in methylene chloride at room temperature for *ca.* two hours and then quickly passed through a plug of silica gel. The methylene chloride was evaporated and a THF solution of the crude product was immediately added to a LAH/THF slurry. Workup of this reaction also gave a complex mixture of products and NMR analysis showed no trace of magnoshinin.

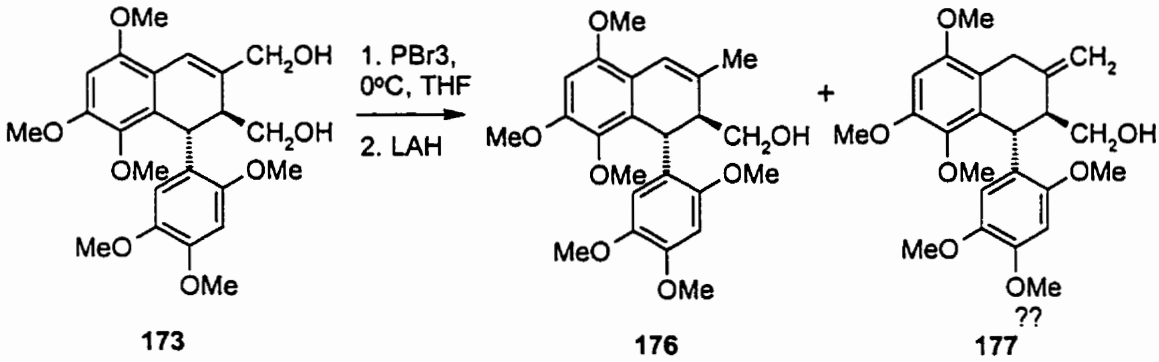
Another test reaction was attempted using 3,5-dimethoxybenzyl alcohol as a model compound. In this reaction, an attempt was made to prepare the benzylic bromide using PBr_3 in THF followed by immediate reduction by LAH in the same solution. The purpose of this test procedure was to avoid the possible decomposition of the intermediate bromide that might have occurred had its isolation been attempted.



Scheme 68

The success of the test reaction suggested that conversion of the allylic alcohol to the corresponding bromide and direct reduction should work. One major disadvantage of this procedure was the formation of phosphine as a bi-product of the reaction. Phosphine is soluble in organic solvents, spontaneously combustible in air and has a putrid stench.

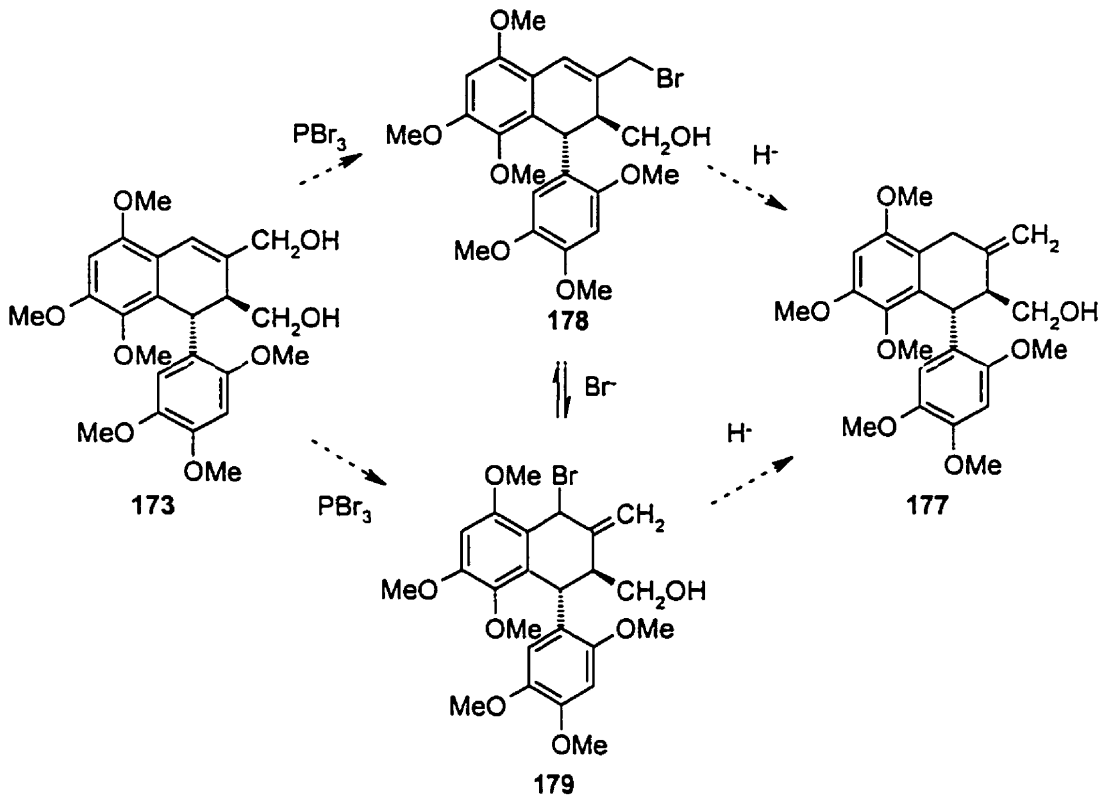
Bromination of the allylic alcohol at zero degrees with PBr_3 in THF followed by immediate treatment with LAH afforded a single major product in 78% yield. Proton NMR and mass spectral analysis clearly indicated that this product was the mono-alcohol **176** resulting from bromination and reduction at the allylic position only. The reaction was repeated three times and TLC indicated that a second faster running compound was also present in amounts that varied with the experiment. Proton NMR spectra of a product mixture rich in the minor component indicated that the second component was arising from double bond isomerization to give exocyclic alkene **177**.



173 **176** **177**

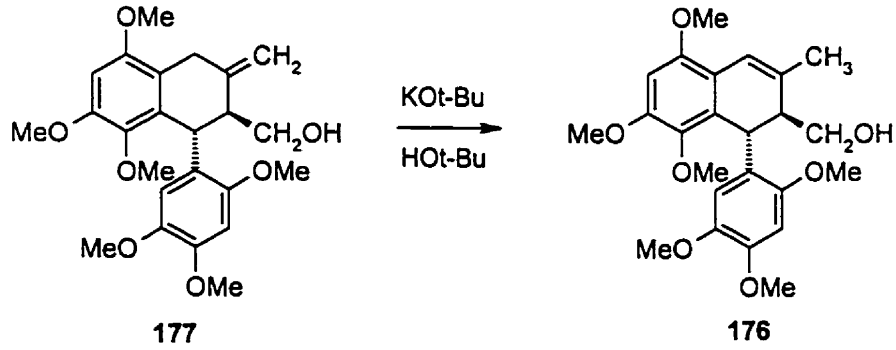
Scheme 69

Explanations include the possibility that both allylic and benzylic bromides form from the diol **173**, that the initially formed allylic bromide **178** isomerizes to the benzylic bromide **179**, or that the initially formed bromide is reduced by hydride ion to give the mixture of alcohols **176** and **177**.



Scheme 70

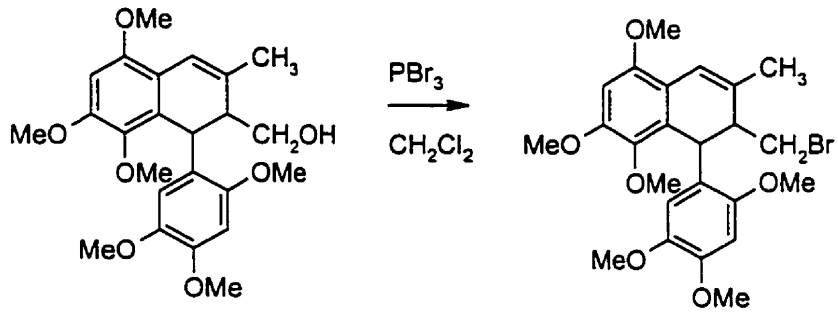
The two alcohols **176** and **177** could be separated by HPLC. When a mixture of the two alcohols was dissolved in a solution of potassium t-butoxide in t-butyl alcohol and stirred at room temperature an isomerization of the minor product **177** to the major product **176** was observed by HPLC.



Scheme 71

This conversion served to confirm the structure of the uncharacterized minor product.

The deoxygenation of the mono-alcohol **176** was achieved by conversion to the corresponding bromide **180** with PBr_3 in a separate reaction followed by reduction. The isolated yield obtained from the bromination step was poor (22%) although no other major products could be observed on TLC.



176 **180**

Scheme 72

The problem may have been attributable to the work up procedure. Aqueous 5% $NaHCO_3$ was used to destroy the remaining PBr_3 and this may have led to the hydrolysis of the bromide product. In addition, emulsions that formed during extraction of the bromide may have resulted in product loss into the emulsion layer. Another workup method was attempted in which the crude reaction mixture was rapidly filtered through a short plug of silica gel. This was slightly more effective in terms of yield, but the silica gel was not dried in an oven prior to its use, thus there was the distinct possibility of hydrolysis during filtration.

Although there have been reports in the literature stating that it is possible to reduce a saturated bromide with LAH to produce the corresponding hydrocarbon in excellent yields,[111] our use of this method for the reduction of the *trans*-1,2-

dihydronaphthalene bromide met with only limited success. Reduction of the bromide using LAH in THF at reflux gave a complicated mixture of products. Proton NMR analysis indicated the presence of signals corresponding to those given in the literature for magnoshinin (**161**). The amounts were too small to allow isolation of the product.

Despite the low yield, the observation of NMR signals consistent with magnoshinin validates the method and verifies the intermediate structures leading to magnoshinin. However, to establish the method as a practical synthesis of magnoshinin a better method for the reduction of the bromide must be developed. Other possible methods for reduction of the bromide include zinc in acetic acid, magnesium in methanol or tributyl tin hydride.

While the chemical route to magnoshinin was successful, the photochemical route involving photoconversion of the diethyl *E,E-bis*-(2,4,5-trimethoxybenzylidene) succinate to the *cis*-dihydronaphthalene intermediate **160** failed. The failure of this reaction was surprising in view of the success for the very similar 3,4,5-trimethoxy derivative. It appears that photocyclization reactions of dibenzylidenesuccinate substrates are not a general method for the preparation of 1,2-dihydronaphthalenes. At this point, no firm predictions can be made regarding potential or likely product distributions from the photochemical reactions of different dibenzylidenesuccinate substrates. A more controlled and systematic investigation is required, using a wide variety of dibenzylidenesuccinates, for the determination of the structural parameters that govern the photochemical behavior of these compounds.

3.3 Chiral Dibenzylidenesuccinates as Precursors to Optically Active 1,2-Dihydronaphthalene Lignans

The goal of the third phase of this endeavor was to exploit the photochemical behavior and rotational hindrance of dibenzylidenesuccinates for the asymmetric synthesis of 1,2-dihydronaphthalene lignans.

Lignans with the *cis*-1,2-tetrahydronaphthalene structure, such as podophyllotoxin, exist as enantiomers and the two enantiomers have different biological activities. It is preferable that synthetic methods leading to such structures be specific for one of the two possible enantiomers. The irradiation of *E,E*-diarylfulgides has been shown by Heller *et al.* to induce conrotatory electrocyclization to afford *cis*-1,8-dihydronaphthalenes that further isomerize to *cis*-1,2-dihydronaphthalenes, but this process yields a racemic product that is an equal mixture of both enantiomers. The method will be very useful for the synthesis of aryltetralin or aryl dihydronaphthalene lignans as it provides a route to the *cis*-1,2-dihydronaphthalenes that are difficult to prepare by other methods. However, the method would be much more useful if it could be controlled to produce a single enantiomer of the cyclized product. A discussion of other methods for the asymmetric synthesis of lignans was reviewed in Chapter 1.

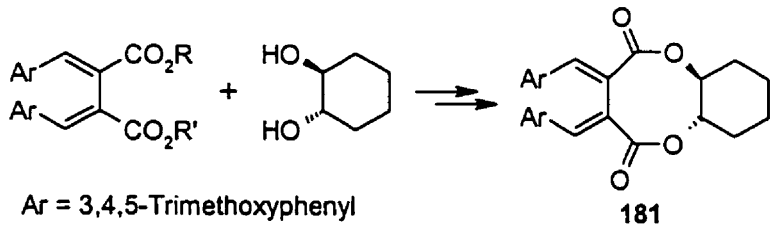
When *E,E*-1,4-diaryl-1,3-butadiene-2,3-dicarboxylates (*E,E*-dibenzylidene-succinates) undergo photochemical cyclization, the terminal carbons of the butadiene pi system are required to rotate in concert in the same direction (conrotatory closure). All other considerations aside, this would conceivably give rise to two possible modes for ring closure, one in which both terminal carbons rotate in a clockwise fashion and one in which both terminal carbons rotate in a counterclockwise fashion. One mode of ring

closure would lead to the formation of a *cis*-1,8-dihydronaphthalene having one absolute configuration and the opposite mode of ring closure would lead to the mirror image *cis*-1,8-dihydronaphthalene. The dibenzylidenesuccinates have been shown to exhibit atropisomerism and exist as rotamers owing to hindered rotation about the butadiene carbon-carbon single bond. Inspection of models shows that each atropisomer is capable of only one mode of ring closure. In other words, one individual atropisomer will give rise to a specific enantiomeric *cis*-1,8-dihydronaphthalene since the photochemical ring closure of dibenzylidenesuccinates would be 100% stereoselective. If the individual enantiomeric *E,E*-dibenzylidenesuccinates atropisomers could be isolated, then it would be possible to use their conrotatory electrocyclic ring closure to prepare optically active *cis*-1,2-dihydronaphthalenes. As described before, photochemical electrocyclic ring closure leads to the formation of a *cis*-1,8-dihydronaphthalene intermediate which undergoes a 1,5-hydrogen shift to form a *cis*-1,2-dihydronaphthalene structure. The hydrogen shift is suprafacial, that is, the hydrogen atom slides across one face of the molecule and therefore, the configurational integrity of the molecule is maintained.

One major obstacle to the exploitation of dibenzylidenesuccinates in asymmetric synthesis is the small barrier to rotation observed in these compounds. This prevents their isolation as stable enantiomeric atropisomers. Earlier work showed that the introduction of bulky chiral substituents into these molecules did not increase the barrier to rotation sufficiently to allow for the separation of atropisomers at room temperature (see section 2.1). The presence of a chiral mandelyl ester group also did not prejudice the molecule into adopting one preferential atropisomer.

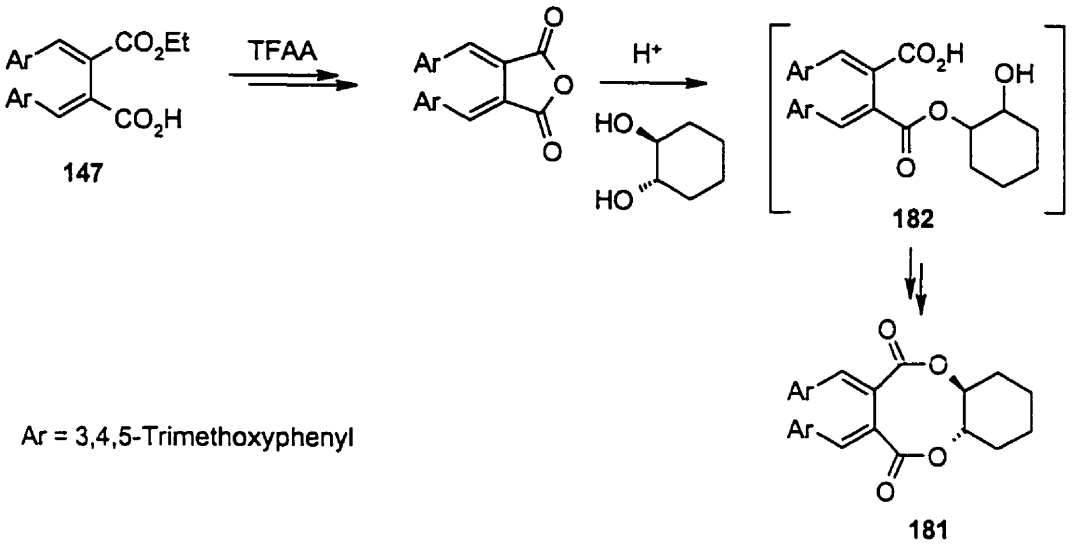
Other structural modifications were considered that would lead to higher barriers to atropsiomer interconversion and/or prejudice the molecule into one atropisomeric form. It was proposed that linking the two ester groups of the dibenzylidenesuccinate would substantially raise the barrier to interconversion of atropisomers. In addition, making this linkage chiral might bias the molecule into adopting one atropisomeric form.

A synthetic strategy was adopted that involved the introduction of a *trans*-1,2-cyclohexanediol into an *E,E*-dibenzylidenesuccinate in order to form the eight-membered dilactone **181**. In addition to preventing free rotation about the butadiene carbon-carbon single bond and forcing atropisomeric stability, it was conjectured that the chirality and rigidity of the *trans*-cyclohexyl ring system might influence the molecule to adopt one preferential conformation.



Scheme 73

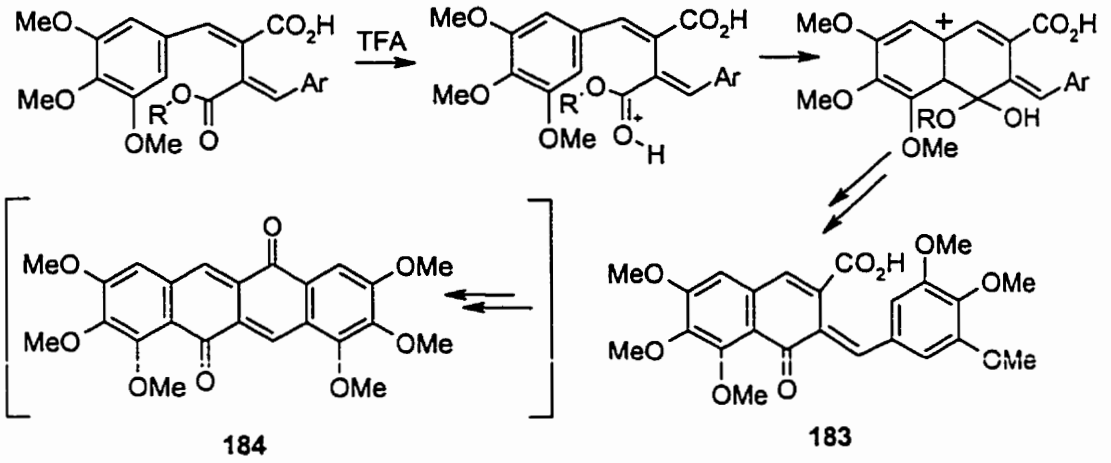
The first effort to introduce the *trans*-cyclohexyl ring into *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate **181** involved first preparing the fulgide and reacting it with *trans*-1,2-cyclohexanediol to form the first ester bond.



Scheme 74

This would result in the formation of the alcohol-acid bifunctional molecule **182** that would conceivably cyclize upon treatment with acid to form the second ester bond in the eight-membered lactone **181**.

The preparation of *E,E*-diarylbutadiene fulgides has previously been accomplished by treating the corresponding succinic acids with acetyl chloride. It was thought that treatment of the *E,E*-bis(3,4,5-trimethoxy)benzylidenesuccinate monoester-acid (**147**) with trifluoroacetic anhydride (TFAA) would be equally as effective. Thus the acid was dissolved in TFAA and heated to reflux temperature for one hour to afford a mixture of products, as evidenced by proton NMR spectroscopy and TLC. The product mixture, which was chromatographed using 30% ethyl acetate in hexanes as the mobile phase, resolved into many colored bands. The main fraction, a yellow band, was partially characterized by proton NMR spectroscopy and was found to exhibit some peculiarities that indicated it could not be the expected fulgide. Close inspection of the proton NMR spectrum led to the conclusion that the starting material had been converted to the compound **183**.



184 183

Ar = 3,4,5-Trimethoxyphenyl

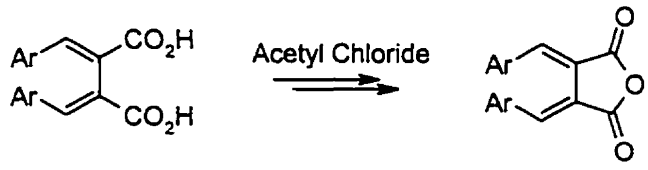
Scheme 75

There were five methoxy peaks apparent in the spectrum of this compound as well as two olefinic peaks at 7.9 ppm and 7.1 ppm. Two aromatic proton signals occurred in a 2:1 ratio and there was also a signal far downfield at 9.8 ppm.

It was surmised that an acid promoted cyclization product resulted from Friedel-Crafts acylation of one of the aromatic rings. The acid catalyst for the reaction could have been TFA, generated by hydrolysis of TFAA. Compounds similar to **184** had been previously reported in the literature as arising from acid catalyzed ring closure of dibenzylidenesuccinate monoester-acid compounds.

The mass spectrum of compound **183** was obtained and had a parent ion at 456 atomic mass units. This provided further evidence as to the identity of the isolated fraction and suggested that it was indeed the suspected cyclized product. The compound was not fully characterized owing to the small amount of material available (*ca.* 5 mg).

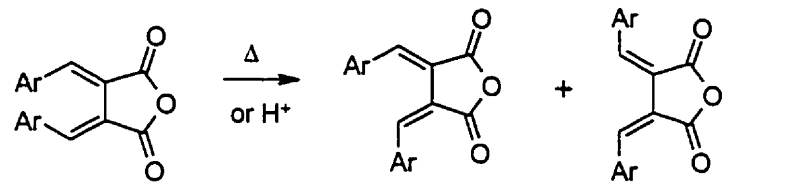
Another attempt was made to prepare the *E,E*-diarylfulgide **185** which involved treatment of the *E,E*-bis(3,4,5-trimethoxybenzylidene)succinic diacid (**153**) with acetyl chloride.



153 **185**

Scheme 76

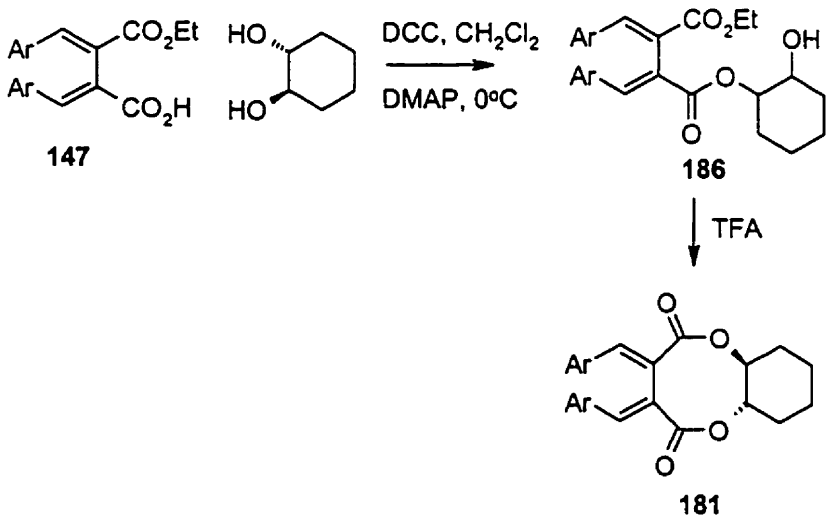
The crude reaction mixture was analyzed by TLC and proton NMR spectroscopy and was shown to be a complex mixture of products, the components of which were not identified. The TLC of the reaction mixture indicated that there were three yellow colored components in addition to several UV active components comprising the mixture. The diacid was next treated with TFAA and found to give rise to a mixture of products that had features in the proton NMR spectrum and TLC similar to the product mixture from acetyl chloride treatment. The fulgides are reported to be highly colored, and the fact that there were yellow compounds in both of the reaction mixtures was encouraging. The crude product mixture from the reaction from treating the diacid with acetyl chloride was therefore chromatographed. Based on the TLC analysis, the yellow compounds in the product mixture should have been easily resolvable by column chromatography. Unfortunately, repeated chromatography was unsuccessful and it appeared that the reactions products were slowly interconverting or decomposing. The thermal and photochemical *cis-trans* isomerization of fulgides is well known, and it was surmised that the *E,E*-diarylfulgide fulgide **185** had been successfully prepared but that it was undergoing isomerization to afford a mixture of the *E,E*-, *E,Z*-, and *Z,Z*- diaryfulgides.



E,E-Diarylfulgide *E,Z*-Diarylfulgide *Z,Z*-Diarylfulgide

Scheme 77

The fact that the *E,E*-fulgide **185** was unstable meant that a new approach had to be used for the synthesis of the cyclohexyl dilactone **181**. An attempt was made to cyclize the cyclohexyl ethyl *E,E*-bis(3,4,5-trimethoxy)benzylidenesuccinate **186** via a transesterification reaction between the hydroxy group on the cylcohexyl moiety and the carboxylethyl group to give dilactone **181**. The cyclohexyl ethyl *E,E*-bis(3,4,5-trimethoxy)benzylidenesuccinate **186** monoester-acid was prepared by treating monoester-acid **147** with DCC and racemic *trans*-1,2-cyclohexanediol.



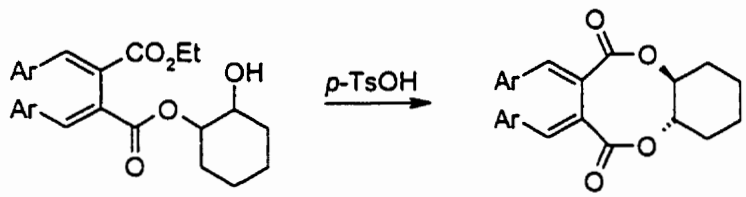
147 **186** **181**

Scheme 78

The proton NMR spectrum of the cyclohexyl ester **186** was similar to the methyl mandelyl ester from the hindered rotation study. The presence of two diastereomeric forms of the atropisomers could be detected in equal amounts as the spectrum of the

cyclohexyl ethyl diester was doubled. One of the major disadvantages of using DCC as a condensing agent was the persistence of the dicyclohexyl urea by-product in the reaction mixture, even after purification by column chromatography. Dicyclohexyl urea was very difficult to remove from product mixtures and it was especially troublesome as it obscured the signals from the cyclohexyl moiety of the diester in the proton NMR spectrum.

The purified diester **186** was treated with *para*-toluenesulfonic acid (*p*-TsOH) and heated in toluene at reflux temperatures in order to promote *trans*-esterification between the hydroxyl on the cyclohexyl group and the ethyl group to yield the desired dilactone **181**.



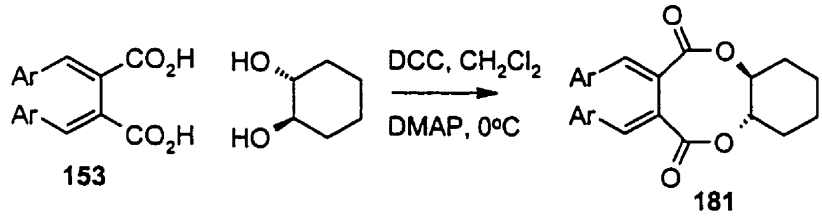
186 **181**

Scheme 79

The proton NMR spectrum of the reaction mixture indicated that the starting material had reacted to give a complex mixture of products that were not identifiable. The diester was next dissolved in TFA and stirred at room temperature. Analysis by TLC indicated the presence of mainly one compound, but the proton NMR spectrum of the reaction mixture was not consistent with that expected for the dilactone. It was clear that the attempted *trans*-esterification reaction of the cyclohexylethyl diester with TFA and p-TsOH had failed, as the presence of the dilactone could not be detected in the proton NMR spectra of the products of either reaction. The reason for the failure in both

cases may be due to the fact that the trans-esterification reaction equilibrium favors the reactants.

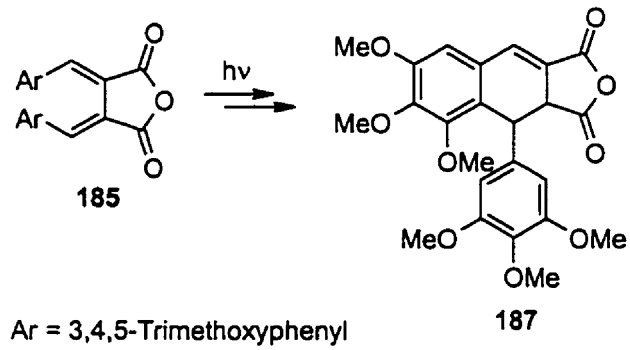
Since DCC had been used with success for the preparation of the cyclohexylethyl diester, it was employed once more in an attempt to generate the dilactone by tandem coupling of racemic *trans*-1,2-cyclohexanediol and the *E,E*-dibenzylidenesuccinic diacid.



Scheme 80

The proton NMR spectrum of the crude reaction mixture indicated that one product had been formed in *ca.* 90% purity, which appeared to be the desired lactone **181**. Furthermore, the spectrum suggested that only one enantiomeric pair of atropisomers (one diastereomer) was present. The proton NMR spectrum showed a signal at 7.8 ppm, attributed to the olefinic protons, a signal with twice the intensity at 6.3 ppm, attributed to the aryl protons, and two peaks between 3.8 and 3.6 ppm in a 3:9 ratio, ascribed to the methoxy protons. The only discrepancy arose from integration of the peaks ascribed to the cyclohexyl ester group, which appeared to be in a 1:36 ratio with the olefinic protons. This discrepancy was thought to arise due to the presence of dicyclohexyl urea in the crude product. The crude product was chromatographed but purification was difficult and repeated chromatography seemed to produce a mixture of compounds. It was conjectured that the dilactone **181** compound was unstable and was possibly undergoing photochemical reaction from exposure to daylight. Thus, instead of attempting to purify the product, the crude reaction mixture was irradiated in ethanol. The irradiation

appeared to produce a single compound as evidenced by proton NMR spectroscopy. The spectrum was very similar to that of the *cis*-1,2-dihydronaphthalene diester produced from irradiation of the corresponding diethyl *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate. A doublet was observed at 7.6 ppm that was ascribed to the olefinic protons of the suspected dilactone dihydronaphthalene, and two peaks at 6.8 and 6.3 ppm, in a 1:2 ratio, were ascribed to the aryl protons. A signal for a single proton at 5 ppm was also attributed to the expected benzylic proton. Regrettably, a close inspection of the aliphatic region of the spectrum showed it to be inconsistent with the expected dilactone structure. A lack of sufficient signal intensity in the aliphatic region finally led to the conclusion that the photoproduct was more likely that produced from irradiation of the *E,E-bis*-(3,4,5-trimethoxybenzylidene) fulgide.



185

Ar = 3,4,5-Trimethoxyphenyl

187

Scheme 81

This would mean that the attempted synthesis of the dilactone had actually given the *E,E*-diaryfulgide **185** and that it had been mistaken for the lactone due to the presence of dicyclohexyl urea.

Comparison of the product of the purported dilactone synthesis, now believed to be fulgide, with fulgide produced in earlier reactions (see above), showed that there were similarities. Indeed, closer inspection by TLC and proton NMR showed that the product

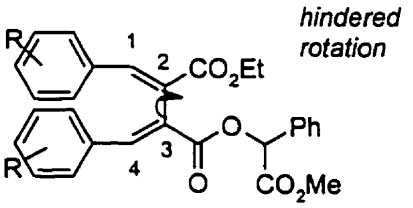
mixtures were identical. Thus the *E,E*-diarylfulgide **185** had been formed upon carboxyl group activation and the desired diarylbutadiene dilactone had not been formed. The reason for the failure may be due to the difficulty of forming an eight-membered dilactone. Only one report of the synthesis of an eight-membered dilactone was found in the literature. Medium sized rings are difficult to form owing to torsional strain in the molecule. The formation of this eight-membered dilactone may be especially difficult owing to ring strain from the presence of four sp^2 hybridized centers and from a *trans*-fused cyclohexyl ring since eight-membered rings prefer to adopt *cis*-conformations as they are inherently less strained.

Chapter 4

Conclusions

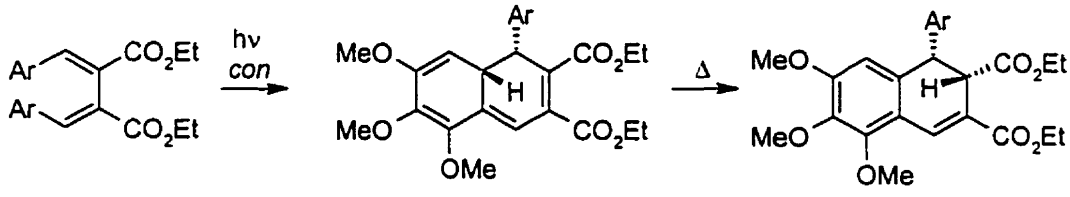
The research described in this thesis can be divided into three parts.

(i) The first part of the thesis involved a study of the rotational hindrance about the butadiene carbon-carbon single bond in racemic ethyl (methyl mandelyl) *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate.



The synthesis of racemic ethyl (methyl mandelyl) *E,E*-dibenzylidenesuccinate was successfully executed and this compound was shown to exhibit atropisomerism. The rotational isomerism of the ethyl (methyl mandelyl) *E,E*-dibenzylidenesuccinate was studied by analyzing its temperature dependent proton NMR spectra at various temperatures above 303 K. The barrier to rotation was successfully measured and found to be *ca.* 19 kcal/mol. The conclusion was reached that the introduction of a chiral methyl mandelyl ester group into ethyl *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate was insufficient to stop the interconversion of the atropisomers at room temperature. In addition, it was found that the chirality of the methyl mandelyl substituent group was not able to coerce the molecule into a single conformation. It is doubtful that a bulkier substituent would be more effective at producing isolable atropisomers, however, the introduction of a different chiral auxiliary may succeed in driving the equilibrium between atropisomers to favor one isomer.

(ii) The second part of this thesis was a study of the photochemical behavior of two *E,E*-dibenzylidenesuccinates. Diethyl *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate was successfully prepared and was shown to undergo conrotatory photochemical electrocyclization followed by a 1,5-hydrogen shift to afford the corresponding *cis*-1,2-dihydronaphthalene as the major product. This reaction has not been reported previously in the literature.



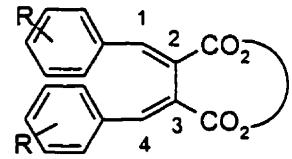
Ar = 3,4,5-Trimethoxyphenyl

The possibility of using the photochemical conversion of diethyl *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate to the *cis*-1,2-dihydronaphthalene for photodynamic therapy was explored and both of the compounds were tested for cytotoxicity. It was found that the photoproduct was insufficiently toxic for it to be effective as a photodynamic agent.

The preparation of diethyl *E,E-bis*-(2,4,5-trimethoxybenzylidene)succinate was successfully carried out so that its photochemical electrocyclization could be applied to the synthesis of the naturally occurring 1,2-dihydronaphthalene lignan, magnoshinin. The photochemical behavior of the diethyl *E,E-bis*-(2,4,5-trimethoxybenzylidene)succinate was studied and this compound was shown to give rise to a different photochemical product distribution than its counterpart, the diethyl *E,E-bis*-(3,4,5-trimethoxybenzyl-idene)succinate. It was found that irradiation of diethyl *E,E-bis*-(2,4,5-trimethoxybenzylidene)succinate did not lead to the formation of the corresponding 1,2-dihydronaphthalene. The synthesis of the *trans*-1,2-

dihydronaphthalene precursor for magnoshinin was successfully carried out using a modified version of a classical method, the Stobbe condensation. Magnoshinin was prepared in a small amount from the *trans*-1,2-dihydronaphthalene intermediate. The development of a better method for the reduction of the bromide in the last step would enable this method to be established as a practical synthesis of magnoshinin.

(iii) The last part of this thesis work was an aggressive attempt to link the two ester groups of an *E,E*-bis(3,4,5-trimethoxybenzylidene)succinate in order to stabilize individual *E,E*-dibenzylidenesuccinate atropisomers.



The synthesis of ethyl (2-hydroxycyclohexyl) *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate was successfully carried out and this compound was shown to exhibit atropisomerism. It was found that introduction of the *trans*-1,2-cyclohexanediol chiral auxiliary into ethyl *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate did not coerce the molecule into a preferential conformation. It was shown that the formation of an eight-membered dilactone to bind the ester groups together could not be accomplished by a trans-esterification reaction. Additionally, the *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinic anhydride was found to be too labile to serve as a precursor to the bis-cyclohexyl *E,E-bis*-(3,4,5-trimethoxybenzylidene)succinate. The failure of this endeavor may be due to the difficulty of preparing medium sized rings, which are inherently strained. Further attempts to introduce a different rigid cyclic system into an *E,E*-dibenzylidenesuccinate to stabilize atropisomers may yet prove fruitful.

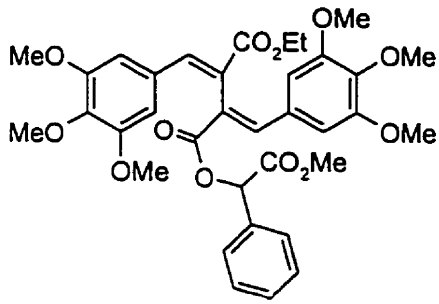
Chapter 5

Experimental

^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AM-300 FT instrument using chloroform as internal standard, unless otherwise specified. Silicycle silica gel was used for all chromatography. HRMS/mass spectra were obtained on a VG Analytical 7070E-HF instrument. Optical rotations were recorded on a Rudolf Research Corporation Autopol III instrument. Melting points were measured on a hot stage instrument and are uncorrected. High pressure liquid chromatography was performed on a C-18 reverse phase column with a Varian 9010 Solvent Delivery instrument with detection by a Varian 9050 Variable Wavelength UV-Vis Detector. The mobile phase employed for the separation of all components was 50% water in methanol for 10 minutes, then increasing to 20% water in methanol over a 5 minute period, and finally holding at 20% water in methanol for 5 minutes. THF was distilled from sodium and benzophenone under nitrogen. A 450 watt Hanovia medium pressure mercury lamp (1 mm Pyrex filter) equipped with a cooling jacket was used in irradiation experiments. "Room temperature" indicates a temperature range of 23°C to 26°C.

The NMR spectrometer used to perform the dynamic NMR studies was the same as described above. Simulation of the experimental dynamic NMR spectra were performed using a computer program (Marat, K. *XSIM*, copyright 1995).

Ethyl (methyl mandelyl) *E,E*-dibenzylidenesuccinate 144



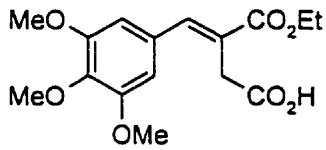
Methyl alpha-bromophenylacetate (0.29 mL, 1.84 mmol) was added to a stirred solution of bis(3,4,5-trimethoxybenzylidene)succinate monoacid-ester **147** (see below) (0.841 g, 1.67 mmol) and K_2CO_3 (1.17 g, 8.46 mmol) in acetone (10 mL) and the solution was stirred at reflux for 14 hours. The reaction mixture was filtered, the precipitate washed with acetone and the filtrate evaporated. The residue was dissolved in CH_2Cl_2, dried over anhydrous magnesium sulfate and stripped of solvent under reduced pressure to give an orange oil as crude product (0.986 g, 91%). The diester was purified by flash column chromatography on silica gel (50 mL) using 30% EtOAc/Hexanes as the eluent to afford a cream colored amorphous solid (0.367 g, 34%) which was used in the temperature dependent dynamic NMR experiment: ^{1}H NMR ($CDCl_3$) (a mixture of diasteromers) δ 1.00 (t, 3H, J = 7.1), 1.11 (t, 3H, J = 7.1), 3.59 (s, 3H), 3.63 (s, 3H), 3.69 (s, 6H), 3.71 (s, 6H), 3.74 (s, 12H), 3.81 (s, 12H), 4.07 (m, 2H), 4.17 (m, 2H), 5.91 (s, 1H), 5.98 (s, 1H), 6.68 (s, 2H), 6.73 (s, 2H), 6.76 (s, 2H), 6.79 (s, 2H), 7.32 (m, 10H), 7.83 (s, 1H), 7.87 (s, 1H), 7.88 (s, 1H), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$) (a mixture of two diastereomers) δ 14.0 (CH_3), 14.1 (CH_3), 52.5 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 60.8 (CH_3), 60.9 (CH_3) , 61.2 (CH_2), 61.3 (CH_2), 75.0 (2 x CH), 107.0 (CH), 107.3 (CH), 125.8 (C), 126.2 (2 x C), 127.4 (2 x CH), 128.7 (2 x CH), 129.1 (2 x CH), 129.9 (C), 130.0 (C), 130.1 (C), 133.8 (C), 139.4 (C), 139.5 (C), 139.7 (C), 139.8 (C), 142.8 (CH),

143.2 (CH), 143.5 (CH), 153.1 (2 x CH), 166.1 (C), 166.2 (C), 166.7 (C), 168.9 (C); mass spectrum *m/z* (relative intensity) 650 (M^+, 11), 501 (21), 411 (37), 195 (100), 181 (72), 91 (52), 77 (18); HRMS calcd. for $C_{35}H_{38}O_{12}$ 650.2363, found 650.2356.

Dynamic ^{1}H NMR Experiment

3,4,5-Trimethoxybenzylidenesuccinate methyl mandelyl ethyl ester **144** (0.042 g, 0.065 mmol) was dissolved in DMSO-d^6 (ca. 1 mL) and nine variable temperature spectra were collected. The first spectrum was obtained at 303 K and successive spectra were acquired at increasing 10-degree intervals, with the final spectrum at 383 K. Spectra are reproduced in the discussion section.

3,4,5-Trimethoxybenzylidenesuccinate monoester 145

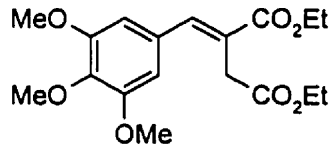


A modified literature procedure was used.[61] Sodium metal (0.587 g, 25.6 mmol) was added to anhydrous ethanol (25 mL) under N_2 and stirred at reflux until the sodium had completely reacted (ca. 30 minutes). The solution was cooled to room temperature and a solution of 3,4,5-trimethoxybenzaldehyde (5.03 g, 25.6 mmol) and diethyl succinate (4.3 mL, 25.8 mmol) in anhydrous ethanol (25 mL) was added dropwise over the course of an hour via a dropping funnel. The dropping funnel was rinsed with ethanol (10 mL) and the solution was refluxed for 5 hours.

The solution was acidified with 20% aqueous HCl, concentrated under reduced pressure and extracted with EtOAc (3 x 30 mL). The combined organic layers were

washed with 20% aqueous HCl (2 x 20 mL) and water (10 mL), dried over anhydrous magnesium sulfate and evaporated to yield a brown syrup (7.98 g, 96%) as the crude product which was reacted in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.1), 3.58 (s, 2H), 3.81 (s, 6H), 3.83 (s, 3H), 4.26 (q, 2H, J = 7.1), 6.6 (s, 2H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 33.9 (CH_2), 56.1 (2 X CH_3), 60.9 (CH_3), 61.5 (CH_2), 106.5 (CH), 124.9 (C), 130.2 (C), 138.9 (C), 142.5 (CH), 153.3 (2 x C), 167.6 (C), 176.7 (C); mass spectrum *m/z* (relative intensity) 240 (9), 129 (24), 128 (19), 101 (100). Spectral data were consistent with those previously reported.[61]

3,4,5-Trimethoxybenzylidenesuccinate diester 146

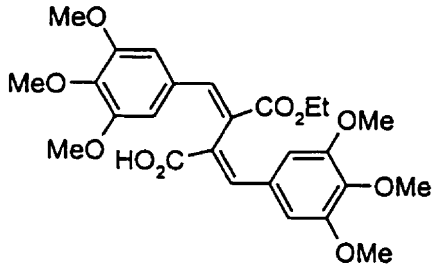


K_2CO_3 (16.6 g, 120 mmol) was added to a solution of benzylidenesuccinate monoacid-ester **2** (7.64 g, 23.6 mmol) in acetone (50 mL). The solution was stirred at room temperature for several minutes and ethyl iodide (2.1 mL, 26.3 mmol) was added. The reaction mixture was refluxed for 6 hours.

The reaction mixture was filtered, the precipitate rinsed several times with acetone and the filtrate evaporated. The brown residue was taken up in CH_2Cl_2, dried over anhydrous magnesium sulfate, filtered and evaporated to give a brown oil (6.48 g, 78%) as the crude product. The benzylidenesuccinate diester was purified by short path, high vacuum (0.01 mm Hg) distillation to yield a pale yellow oil (3.36 g, 41%). ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H, J = 7.2), 1.22 (t, 3H, J = 7.2), 3.46 (s, 2H), 3.73 (s, 6H), 3.75 (s, 3H), 4.07 (q, 2H, J = 7.2), 4.16 (q, 2H, J = 7.2), 6.53 (s, 2H), 7.71 (s, 1H); ^{13}C NMR

($CDCl_3$) δ 14.0 (2 x CH_3), 33.8 (CH_2), 55.9 (2 x CH_3), 60.6 (CH_2), 60.8 (CH_3), 60.9 (CH_2), 106.2 (CH), 125.6 (C), 130.3 (CH), 138.5 (C), 141.6 (CH), 153.0 (C), 167.1 (C), 171.1 (C); mass spectrum *m/z* (relative intensity) 352 (M^+, 4), 196 (13), 129 (50), 101 (100), 73 (17), 55 (19); HRMS calcd. for $C_{18}H_{24}O_7$ 352.1522. found 352.1503. Spectral data were consistent with those previously reported.[61]

_E,E_-bis-(3,4,5-trimethoxybenzylidene)succinate monoacid-ester 147

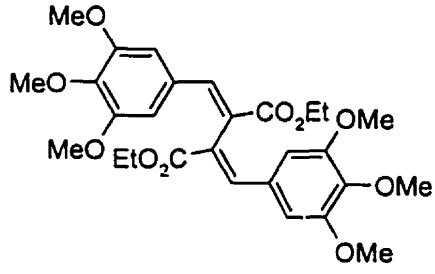


Sodium metal (0.334 g, 14.5 mmol) was added to anhydrous ethanol (15 mL) under N_2 and refluxed until the sodium had completely reacted. The solution was cooled to room temperature and a solution of 3,4,5-trimethoxybenzaldehyde (2.83 g, 14.4 mmol) and benzylidenesuccinate diester **2** (5.09 g, 14.4 mmol) in ethanol (20 mL) was added dropwise via a dropping funnel over the course of an hour. The solution was refluxed for 3 hours.

Water (20 mL) was added and the reaction mixture stripped of ethanol under reduced pressure. The solution was poured into water (20 mL) in a separatory funnel and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with 20% aqueous HCl (2 x 25 mL) and water (10 mL), dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford a brown syrup (7.26 g, 95%) which was reacted in the next step without further purification: ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, *J* =

7.0), 3.74 (s, 6H), 3.75 (s, 6H), 3.82 (s, 6H), 4.17 (m, 2H) 6.77 (s, 2H), 6.78 (s, 2H), 7.85 (s, 1H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 56.1 (4 x CH_3), 61.0 (2 x CH_3), 61.4 (CH_2), 107.4 (2 x CH), 107.5 (2 x CH), 125.7 (C), 126.0 (C), 129.8 (C), 129.9 (C), 139.7 (C), 140.1 (C), 142.6 (CH), 144.3 (CH), 153.2 (4 x C), 166.7 (C), 172.1 (C); mass spectrum *m/z* (relative intensity) 502 (M^+, 1), 458 (16), 212 (46), 197 (31), 168 (62), 62 (100); HRMS calcd. for $C_{26}H_{30}O_{10}$ 502.1838, found 502.1841.

Diethyl E,E-bis-(3,4,5-trimethoxybenzylidene)succinate 152



Method A: K_2CO_3 (3.68 g, 26.6 mmol) was added to a solution of bis(3,4,5-trimethoxybenzylidene)succinate monoacid-ester (2.60 g, 5.18 mmol) followed by ethyl iodide (0.85 mL, 10.6 mmol) and the reaction mixture was stirred at reflux for 2.5 hours.

The solution was filtered, the precipitate rinsed several times with acetone and the filtrate was evaporated. The residue was taken up in CH_2Cl_2, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford a pale green solid (1.56 g, 57%). The solid was recrystallized from CH_2Cl_2-Hexanes to yield the bis(3,4,5-trimethoxybenzylidene)succinate diethyl ester as fluffy, colorless crystals (0.933 g, 34%).

Method B: To a solution of bis(3,4,5-trimethoxybenzylidene)succinic acid (0.403 g, 0.849 mmol) in acetone (8 mL) was added K_2CO_3 (0.369 g, 2.67 mmol) and the solution was refluxed for 30 minutes to form the dianion. A white gelatinous material

formed and the solution was cooled to room temperature. Ethyl iodide (0.8 mL, 1:10 acetone) was added to the reaction mixture followed by DMF (2 mL) in order to solubilize the solid. The reaction mixture, which became much more fluid upon the addition of DMF, was refluxed for 33 hours. The reaction mixture was filtered and the precipitate was washed with acetone. The filtrate was evaporated to afford a brown residue that was taken up in EtOAc (10 mL) and poured into water (10 mL) in a separatory funnel. The reaction mixture was extracted into EtOAc (3 x 10 mL) and the combined organic layers were washed with 5% aqueous $NaHCO_3$ (2 x 10 mL), dried over anhydrous magnesium sulfate and evaporated to afford the diester (0.131 g, 29%).

Both procedures gave material that was essentially identical: mp 144-146°C; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3H, J = 7.2), 3.74 (s, 6H), 3.81 (s, 3H), 4.12 (m, 2H), 6.75 (s, 2H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (2 x CH_3), 56.0 (4 x CH_3), 60.9 (2 x CH_3), 61.2 (2 x CH_2), 107.2 (4 x CH), 126.9 (2 x C), 130.3 (2 x C), 139.5 (2 x C), 142.2 (2 x CH), 153.1 (4 x C), 166.9 (2 x C); mass spectrum *m/z* (relative intensity) 530 (M^+, 6), 317 (17), 289 (13), 181 (100); HRMS calcd. for $C_{28}H_{34}O_{10}$ 530.2151, found 530.2146.

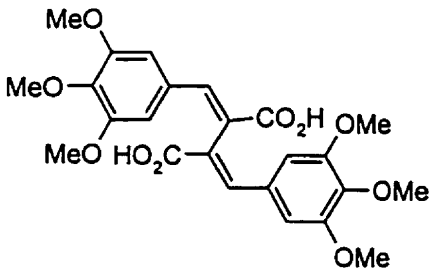
Photoreaction of the bis-(3,4,5-trimethoxybenzylidene)succinate 152

A solution of the diethyl ester (0.202 g, 0.381 mmol) in a 0.01 M solution of TFA in anhydrous ethanol (60 mL) was purged vigorously with N_2 for 5 minutes (the nitrogen atmosphere was maintained for the duration of the reaction), stoppered and irradiated for 3 hours. Aliquots of the reaction solution were obtained periodically and analyzed by HPLC in order to monitor the reaction progress. The solution was evaporated and the residue was redissolved in CH_2Cl_2, dried over anhydrous magnesium sulfate and

concentrated under vacuum to afford a pale yellow oil (0.213 g). The reaction mixture was purified by flash column chromatography on silica gel (100 mL) using 30% EtOAc/Hexanes as the solvent system to afford two fractions. The first chromatography fraction (0.004 g, 2%): ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, J = 7.1), 1.31 (t, 3H, J = 7.1), 3.67 (s, 3H), 3.73 (s, 6H), 3.77 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.05 (d, 1H, J = 1.0), 4.11 (m, 2H), 4.23 (m, 2H), 4.98 (s, 1H), 6.28 (s, 2H), 6.72 (s, 1H), 7.62 (s, 1H). This was identified as the trans-dihydronaphthalene by comparison of its ^{1}H NMR spectrum to that in the literature.[61]

The second eluted fraction (0.070 g, 34%) was a colorless and cloudy wax: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.2), 1.24 (t, 3H, J = 7.2), 3.46 (s, 3H), 3.71 (s, 3H), 3.72 (s, 6H), 3.82 (s, 3H), 3.86 (s, 3H), 4.08 (dd, 1H, J = 2.8, 9.1), 4.17 (m, 2H), 4.76 (d, 1H, J = 9.1), 6.32 (s, 2H), 6.63 (s, 1H), 7.36 (d, 1H, J = 2.8); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 14.3 (CH_3), 40.5 (CH), 48.1 (CH), 56.2 (4 x CH_3), 60.5 (CH_2), 60.6 (CH_2), 60.7 (CH_3), 60.8 (CH_3), 106.4 (CH), 108.0 (CH), 123.7 (C), 126.2 (C), 127.1 (C), 135.4 (CH), 136.4 (C), 137.2 (C), 144.2 (C), 151.1 (C), 152.6 (C), 152.9 (C), 167.3 (C), 171.5 (C); mass spectrum *m/z* (relative intensity) 530 (M^+, 100), 484 (44), 456 (62), 411 (65), 384 (33), 358 (69); HRMS calcd. for $C_{28}H_{34}O_{10}$ 530.2151, found

E,E-bis(3,4,5-trimethoxybenzylidene)succinic acid 153



A solution of diethyl succinate (3.4 mL, 20.4 mmol) and 3,4,5-trimethoxybenzaldehyde (8.63 g, 44.0 mmol) in dry toluene (50 mL) was added dropwise to a slurry of sodium hydride (57% in oil) (1.89 g, 44.9 mmol) in toluene via a dropping funnel over a period of an hour. The dropping funnel was rinsed with toluene (10 mL) and the reaction mixture was refluxed for 3.5 hours.

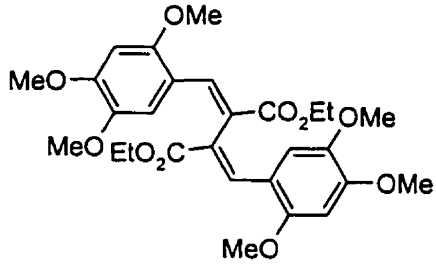
Water (50 mL) was added and the solution then evaporated under reduced pressure. The dark brown residue was dissolved in 0.1 M aqueous KOH solution (20 mL), heated at reflux for 2 hours and acidified with 0.5 N aqueous HCl solution (to ca. pH 2). A deep yellow precipitate formed on standing at room temperature after several days. The solid was recrystallized from the minimum amount of iso-propyl alcohol to afford small pale yellow crystals (2.91 g, 30%): mp 189-191°C; ^{1}H NMR (CD_3OD) δ 3.73 (s, 6H), 3.74 (s, 3H), 4.94 (s, 2H), 6.83 (s, 2H), 7.85 (s, 1H); ^{13}C NMR (CD_3OD) δ 56.5 (4 x CH_3), 61.1 (2 x CH_3), 108.4 (4 x CH), 129.0 (2 x C), 131.9 (2 x C), 140.4 (2 x C), 143.2 (2 x CH), 154.3 (4 x C), 170.2 (2 x C); mass spectrum *m/z* (relative intensity) 454 (M^+, 100), 439 (27), 392 (28), 168 (34), 156 (23); HRMS calcd. for (M+-18) $C_{24}H_{24}O_9$ 456.1420, found 456.1539.

Epimerization of *cis*-transdihydronaphthalene 154

DMAP (0.225 g, 1.84 mmol) was added to a solution of the cis-dihydronaphthalene (0.010 g, 0.019 mmol) in anhydrous ethanol (11 mL) and the solution was refluxed for 12 hours. The reaction mixture was evaporated, dissolved in EtOAc and washed with 10% HCl (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (2 x 10 mL) and the combined organic layers were dried over

anhydrous magnesium sulfate and concentrated under vacuum to afford the trans-dihydronaphthalene as the major product (0.007 g, 68%). Spectral data are identical with those previously reported above.

***E,E-bis*-(2,4,5-trimethoxybenzylidene)succinate 159**



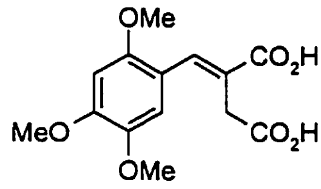
Method A: K_2CO_3 (4.04 g, 29.2 mmol) was added to a solution of bis(2,4,5-trimethoxybenzylidene)succinate monoacid-ester **164** (see below) (2.93 g, 5.83 mmol) in acetone (50 mL) and the solution was stirred at room temperature for several minutes before ethyl iodide (1 mL, 12.5 mmol) was added. The solution was stirred at reflux for 7 hours. The reaction mixture was filtered and the precipitate was washed with acetone. The filtrate was evaporated to dryness, taken up in CH_2Cl_2, dried over anhydrous magnesium sulfate and stripped of solvent under reduced pressure to give a brown oil as crude product (2.39 g, 77%). The diethyl ester was recrystallized from CH_2Cl_2-Hexanes to afford yellow crystals (1.105 g, 36%): mp 159-161°C; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7.1), 3.64 (s, 3H), 3.74 (s, 3H), 3.83 (s, 3H), 4.16 (q, 2H, J = 7.1), 6.35 (s, 1H), 7.08 (s, 1H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3 (2 x CH_3), 56.0 (4 x CH_3), 56.3 (2 x CH_3), 60.8 (2 x CH_2), 96.5 (2 x CH), 111.7 (2 x CH), 115.7 (2 x C), 125.3 (2 x C), 136.0 (2 x CH), 142.7 (2 x C), 151.1 (2 x C), 153.4 (2 x C), 167.7 (2 x C); mass spectrum *m/z*

(relative intensity) 530 (M^+, 100), 456 (30), 425 (43), 411 (45), 362 (47), 347 (51), 225 (26), 195 (38); HRMS calcd. for $C_{28}H_{34}O_{10}$ 530.2151, found 530.2169.

Photoreaction of bis(2,4,5-trimethoxybenzylidene)succinate diethyl ester 159

A solution of bis(2,4,5-trimethoxybenzylidene)succinate diethyl ester (0.101 g, 0.191 mmol) in 3% TFA in anhydrous ethanol (60 mL) was purged vigorously with N_2 for 10 minutes and irradiated for 6 hours to afford a gold colored solution. The solution was evaporated, dissolved in EtOAc, dried over anhydrous magnesium sulfate and evaporated to afford crude product (0.098 g). The reaction mixture was purified by flash column chromatography on silica gel using 30% EtOAc/Hexanes as eluent to give a clear colorless oil, as the major product: ^{1}H NMR ($CDCl_3$) δ 1.04 (t, 3H, J=7.2), 1.38 (t, 3H, J = 7.2), 3.18 (s, 3H), 3.64 (s, 3H), 3.80 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 4.04 (s, 3H), 4.37 (q, 2H, J = 7.1), 6.55 (s, 1H), 6.73 (s, 1H), 6.82 (s, 1H), 8.98 (s, 1H).

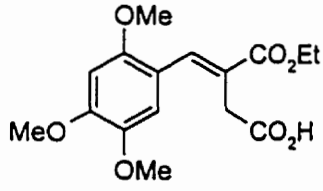
2,4,5-Trimethoxybenzylidenesuccinic acid 162



A solution 2,4,5-trimethoxybenzyaldehyde (3.19 g, 16.3 mmol) and diethyl succinate (1.35 mL, 8.13 mmol) in dry toluene (25 mL) was added dropwise over a period of 15 minutes to a slurry of sodium hydride (0.686 g, 16.3 mmol) in toluene (10 mL) and refluxed for 3 hours. The reaction mixture was evaporated and the brown residue was taken up in aqueous KOH (45 mL, 0.1 M) and refluxed for 2 hours. The

solution was acidified with 20% aqueous HCl and extracted into diethyl ether (3 x 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to afford a yellow amorphous solid as the crude product (0.264 g, 6.84%). This was recrystallized from CH_2Cl_2 to give bright yellow flakes (0.095g, 2.5%): mp 154-156°C; ^{1}H NMR (CD_3OD) δ 3.45 (s, 2H), 3.76 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 4.89 (s, 2H), 6.69 (s, 1H), 6.97 (s, 1H), 7.96 (s, 1H); ^{13}C NMR (CD_3OD) δ 34.9 (CH_2), 56.6 (CH_3), 56.8 (CH_3), 57.1 (CH_3), 98.6 (CH), 114.9 (CH), 116.5 (C), 125.6 (C), 138.9 (CH), 144.1 (C), 152.7 (C), 154.6 (C), 171.2 (C), 175.5 (C); mass spectrum *m/z* (relative intensity) 278 (M^+-18, 100), 263 (23), 235 (25), 191 (45); HRMS calcd. for (M^+-18) $C_{14}H_{14}O_6$ 278.0790, found 278.0801.

Benzylidenesuccinate monoester 163

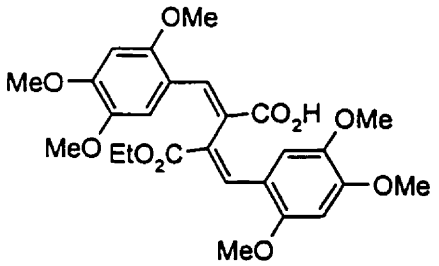


Sodium metal (0.432 g, 18.8 mmol) was added to anhydrous ethanol (20 mL) and heated at reflux under nitrogen until the sodium had completely reacted (ca. 30 minutes). The mixture was cooled to room temperature and a solution of diethyl succinate (3.1 mL, 18.6 mmol) and 2,4,5-trimethoxybenzaldehyde (3.23 g, 16.5 mmol) in anhydrous ethanol (15 mL) was added quickly, with stirring. The reaction mixture was stirred at reflux for 21 hours.

Distilled water (20 mL) was added to the reaction mixture, which was subsequently stripped of ethanol under reduced pressure. The mixture was poured into

water (20 mL) in a separatory funnel and then extracted with EtOAc (3 x 20 mL). The organic layers were combined and washed with 5% aqueous $NaHCO_3$ (3 x 20 mL). The basic extracts were combined and acidified with 10% HCl and extracted with fresh EtOAc (3 x 20 mL). This second organic extract was washed with water (10 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to give crude product, a brown syrup (5.08 g, 95%), which was reacted in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.1), 3.51 (s, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 4.26 (q, 2H, J = 7.1), 6.50 (s, 1H), 6.91 (s, 1H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 34.4 (CH_2), 56.1 (CH_3), 56.3 (CH_3), 56.5 (CH_3), 61.3 (CH_2), 97.0 (CH), 113.2 (CH), 115.0 (C), 123.7 (C), 138.4 (CH), 142.9 (C), 151.1 (C), 152.7 (C), 167.9 (C), 177.3 (C); mass spectrum *m/z* (relative intensity) 278 (31), 128 (16), 101 (100), 73 (26); HRMS calcd. for $C_{16}H_{20}O_7$ 324.1209, found 324.1210.

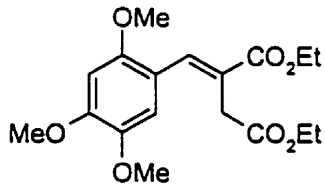
***E,E-bis*-(2,4,5-trimethoxybenzylidene)succinate monoacid-ester 164**



Sodium metal (0.434 g, 18.9 mmol) was added to anhydrous ethanol (15 mL) and refluxed until the sodium had completely reacted. The solution was cooled to room temperature and a solution of benzylidenesuccinate diester 4 (5.70 g, 16.2 mmol) and 2,4,5-trimethoxybenzaldehyde (3.18 g, 16.2 mmol) in ethanol (40 mL) was added. The reaction mixture was stirred at reflux for 4 hours. The solution was acidified with 20%

aqueous HCl and partially evaporated under reduced pressure to afford a dark green solution. The reaction mixture was poured into water (40 mL) in a separatory funnel and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with 20% aqueous HCl (2 x 20 mL), dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a brown tar (8.02 g, 99%) which was reacted in the next step without further purification; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3H, J = 7.1), 3.62 (s, 3H), 3.64 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.19 (m, 2H), 7.07 (s, 1H), 7.13 (s, 1H), 8.17 (s, 1H), 8.26 (s, 1H); ^{13}C NMR δ ($CDCl_3$) δ 14.3 (CH_3), 56.0 (4 x CH_3), 56.4 (2 x CH_3), 61.0 (CH_2), 96.3 (CH), 96.5 (CH), 111.6 (CH), 115.2 (C), 115.4 (C), 123.8 (C), 124.6 (C), 136.4 (C), 137.8 (C), 142.7 (C), 151.3 (C), 151.7 (C), 153.5 (C), 153.9 (C), 167.6 (C), 173.2 (C); mass spectrum *m/z* (relative intensity) 502 (M^+, 6), 456 (46), 454 (42), 424 (81), 278 (43), 191 (50), 168 (100); HRMS calcd. for $C_{26}H_{30}O_{10}$ 502.1838, found 502.1810.

Benzylidenesuccinate diester 168



To a solution of the crude benzylidenesuccinate acid-ester (4.91 g, 15.1 mmol) in acetone (30 mL) was added K_2CO_3 (10.5 g, 75.7 mmol) The solution turned bright orange. After stirring the solution at room temperature for several minutes, ethyl iodide (2.4 mL, 30 mmol) was added and the solution was refluxed for 20 hours.

The solution was filtered and the precipitate was rinsed several times with acetone. The filtrate was evaporated to yield an orange oil, which was taken up in CH_2Cl_2 and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield an orange oil (4.80 g, 90%) as the crude product. The diester was purified by short path, high vacuum (0.1 mm Hg) distillation to give a viscous yellow oil (3.16 g, 59%): ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, J = 7.1), 1.30 (t, 3H, J = 7.1), 3.47 (s, 2H), 3.77 (s, 3H), 3.80 (s, 3H), 3.89 (s, 3H), 4.15 (q, 2H, J = 7.1), 4.24 (q, 2H, J = 7.1), 6.50 (s, 1H), 6.91 (s, 1H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3 (2 x CH_3), 34.4 (CH_2), 56.1 (CH_3), 56.4 (2 x CH_3), 60.9 (CH_2), 61.0 (CH_2), 97.0 (CH), 113.2 (CH), 115.4 (C), 124.7 (C), 137.8 (CH), 142.8 (C), 150.9 (C), 152.7 (C), 167.6 (C), 171.8 (C); mass spectrum *m/z* (relative intensity) 352 (M^+, 100), 279 (23), 205 (70), 191 (28), 175 (21); HRMS calcd. for $C_{18}H_{24}O_7$ 352.1522, found 352.1529.

Dihydronaphthalene diester 170 and monoester-acid 171

In a dry, round bottom flask that had been flushed with N_2 (the nitrogen atmosphere was maintained throughout the reaction), diisopropylamine (0.49 mL, 3.5 mmol) was dissolved in freshly distilled THF (4 mL) and cooled to –70°C. n-BuLi (1.1 mL, 2.5 M in hexanes) was added with stirring and the solution was warmed to 0°C briefly and then recooled to –70°C. The benzylidenesuccinate diester (0.947 g, 2.69

mmol) was dissolved in dry THF (5 mL), and added to the lithium diisopropylamide solution through a plug of activated alumina (1.01 g) rinsing with THF (2.5 mL). Upon addition of the diester, the solution turned dark orange in color. This color persisted until the reaction was quenched. The solution was stirred for 10 minutes. 2,4,5-trimethoxybenzaldehyde (1.04 g, 5.28 mmol) was dissolved in dry THF (10 mL) with heating and added quickly, through a plug of activated alumina (1.07 g), to the reaction mixture. The alumina was rinsed with THF (5 mL) and the solution was stirred at $-70^{\circ}C$ for 1 hour. The reaction was quenched at $-70^{\circ}C$ with glacial acetic acid (1 mL) at which point the solution turned pale yellow. The solution was allowed to warm slowly to room temperature.

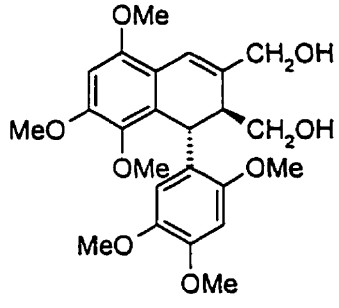
Distilled water (20 mL) was added to the reaction mixture, which was then extracted with EtOAc (3 x 25 mL). The combined organic layers were extracted with 20% aqueous HCl (2 x 25 mL), 5% aqueous $NaHCO_3$ (2 x 25 mL) and finally washed with water (10 mL). The organic layers were then dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give an orange oil (2.66 g), which was immediately dissolved in TFA (4 mL) and stirred at room temperature for 1 hour. The reaction mixture was poured into 5% aqueous $NaHCO_3$ and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ (3x 10 mL) and water (10 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The product was subjected to high vacuum overnight to leave 2.12 g, which contained some solvent. NMR spectroscopy indicated the presence of at least three compounds. A portion (0.258 g) was purified by flash column chromatography on silica gel (100 mL) using 30% EtOAc/Hexanes as the eluent (300

mL), then 40% EtOAc/Hexanes (600 mL) to afford first 2,4,5-trimethoxybenzaldehyde, followed by the dihydronaphthalene diester. The dihydronaphthalene diester was obtained as a yellow amorphous solid (0.039 g, 22%): ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3H, J = 7.1), 1.27 (t, 3H, J = 7.1), 3.50 (s, 3H), 3.51 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 3.97 (d, 1H, J = 1.2), 4.06 (m, 2H), 4.17 (m, 2H), 5.45 (d, 1H, J = 1.0), 6.02 (s, 1H), 6.40 (s, 1H), 6.51 (s, 1H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 14.4 (CH_3), 33.0 (CH), 44.5 (CH), 55.9 (CH_3), 56.1 (CH_3), 56.2 (CH_3), 56.8 (CH_3), 57.2 (CH_3), 60.5 (CH_2), 60.6 (CH_3), 60.8 (CH_2), 95.4 (CH), 98.1 (CH), 114.2 (CH), 114.6 (C), 121.9 (C), 122.1 (C), 131.5 (CH), 132.3 (C), 140.6 (C), 142.6 (C), 148.7 (C), 151.3 (C), 154.0 (C), 155.6 (C), 167.2 (C), 172.3 (C); mass spectrum *m/z* (relative intensity) 530 (M^+, 64), 456 (83), 412 (25), 410 (32), 381 (48); HRMS calcd. for $C_{28}H_{34}O_{10}$ 530.2151, found 530.2133.

The dihydronaphthalene monoester-acid was eluted in the last fraction as a yellow wax (0.028 g, 17%) with 100% EtOAc: ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3H, J = 7.0), 3.50 (s, 3H), 3.51 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.95 (s, 1H), 4.07 (m, 2H), 5.45 (s, 1H), 5.99 (s, 1H), 6.40 (s, 1H), 6.50 (s, 1H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 33.2 (CH), 44.1 (CH), 55.9 (CH_3), 56.1 (CH_3), 56.2 (CH_3), 56.8 (CH_3), 57.3 (CH_3), 60.7 (CH_3), 61.0 (CH_2), 95.4 (CH), 98.1 (CH), 114.3 (CH), 114.5 (C), 120.9 (C), 121.6 (C), 132.5 (CH), 134.0 (C), 140.6 (C), 142.7 (C), 148.9 (C), 151.3 (C), 154.4 (C), 156.1 (C), 171.8 (C), 172.2 (C); mass spectrum *m/z* (relative intensity) 502 (M^+, 26), 456 (55), 454 (100), 411 (33), 408 (64), 393 (34), 168 (78); HRMS calcd. for $C_{26}H_{30}O_{10}$ 502.1838, found 502.1806.

The crude product remaining (1.86 g), after a portion had been removed for chromatography, was dissolved in acetone (17 mL), and K_2CO_3 (2.15 g) and ethyl iodide (0.5 mL) added to the solution. The mixture was stirred at reflux for 3.5 hours then cooled to room temperature and filtered. The precipitate was rinsed several times with acetone. The filtrate was evaporated to give a yellow residue, which was dissolved in CH_2Cl_2, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to yield a brown amorphous solid (1.59 g). The crude mixture was purified by flash column chromatography over silica gel (100 mL) using 30% EtOAc/Hexanes (ca. 1250 mL) as the eluent. Once the aldehyde had been eluted, the solvent system was changed to 40% EtOAc/Hexanes (ca. 1000 mL) and finally 50% EtOAc/Hexanes (ca. 400 mL) to afford the dihydronaphthalene diester (0.798 g, 56%).

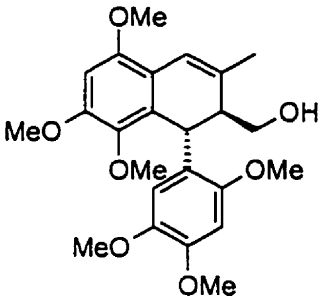
Dihydronaphthalene diol 173



Dihydronaphthalene diester **5** (0.128 g, 0.241 mmol) was dissolved in freshly distilled THF (4 mL) and added to a slurry of lithium aluminum hydride (0.587g, 1.55 mmol) in THF (1 mL). The reaction mixture was stirred at room temperature under nitrogen for 30 minutes and worked up by Fieser's method. In succession, water (0.06 mL), 15% aqueous NaOH (0.06 mL) and water (0.18 mL) were added to the reaction mixture followed by EtOAc. The solution was dried over anhydrous magnesium sulfate

and the solvent was removed under reduced pressure to afford a cloudy colorless oil (0.103 g, 96%). This compound was unstable and had to be reacted quickly in the next step. ^{1}H NMR ($CDCl_3$) δ 2.55 (dd, 1H, J = 6.0, 7.3), 3.30 (s, 3H), 3.47 (dd, 1H, J = 7.3, 12.6), 3.50 (s, 3H), 3.56 (dd, 1H, J = 6.0, 10.2), 3.78 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 3.85 (d, 1H, J = 10.2), 4.01 (d, 1H, J = 12.6), 4.76 (s, 1H), 6.10 (s, 1H), 6.36 (s, 1H), 6.46 (s, 1H), 6.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.3 (CH), 45.2 (CH), 55.8 (CH_3), 56.0 (2 x CH_3), 56.6 (CH_3), 56.9 (CH_3), 60.4 (CH_3), 65.6 (CH_2), 66.8 (CH_2), 95.8 (CH), 97.8 (CH), 114.0 (CH), 115.8 (CH), 118.7 (C), 123.1 (C), 130.6 (C), 136.1 (C), 140.7 (C), 142.4 (C), 148.0 (C), 150.7 (C), 151.8 (C), 152.8 (C); mass spectrum *m/z* (relative intensity) 444 (8), 428 (100), 398 (63), 397 (38), 383 (49), 352 (71), 337 (47); HRMS calcd. for (M+-18) $C_{24}H_{30}O_8$ 446.1940, found 446.1940.

Dihydronaphthalene alcohol 176



Dihydronaphthalene diol **6** (0.103 g, 0.231 mmol) was dissolved in freshly distilled THF (6 mL) in a flask flushed with N_2 (nitrogen atmosphere was maintained throughout the reaction) and cooled to –10°C. Phosphorus tribromide (0.23 mL, 2.4 mmol) was added to the solution, which was stirred at –10°C for 20 minutes. The reaction mixture was diluted with THF (10 mL) and added to a slurry of lithium aluminum hydride (0.321 g, 8.46 mmol) in THF (30 mL). The reaction mixture was

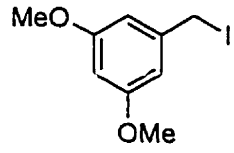
stirred at reflux for 2 hours and worked up by Fieser's method. In succession, water (0.35 mL), 15% aqueous NaOH (0.35 mL) and water (0.9 mL) were added to the reaction mixture followed by EtOAc. The solution was dried over anhydrous magnesium sulfate and stripped of solvent under reduced pressure to give an oil (0.094 g). The NMR spectrum and HPLC analysis indicated the presence of two compounds in the ratio of 10:7.

The mixture (0.094 g, 0.218 mmol) was dissolved in a 0.23 M solution of potassium t-butoxide in t-butanol (15 mL), stirred at room temperature for 18 hours and then refluxed for 1 hour. HPLC analysis during the reaction indicated that the minor component was slowly equilibrated to the major component.

The reaction was quenched with 20% aqueous HCl and extracted into EtOAc (3x 10 mL). The combined organic layers were washed with water (2 x 5 mL), dried over anhydrous magnesium sulfate and solvent was removed under reduced pressure. The reaction mixture was purified by column chromatography on silica gel (20 mL) using a concentration gradient of 30%-50% EtOAc in Hexanes as the eluent. The conjugated alcohol (0.030 g, 30%) was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.77 (d, 3H, J = 1.4), 2.37 (dd, 1H, J = 4.5, 8.6), 3.39 (s, 3H), 3.42 (dd, 1H, J = 8.6, 10.5), 3.56 (s, 3H), 3.64 (dd, 1H, J = 4.5, 10.5), 3.84 (s, 6H), 3.85 (s, 3H), 3.92 (s, 3H), 4.98 (s, 1H), 6.25 (s, 1H), 6.41 (s, 1H), 6.53 (s, 1H), 6.63 (d, 1H, J = 1.4); ^{13}C NMR ($CDCl_3$) δ 23.4 (CH_3), 31.7 (CH), 49.3 (CH), 56.1 (CH_3), 56.2 (CH_3), 56.3 (CH_3), 57.0 (CH_3), 57.1 (CH_3), 60.5 (CH_3), 64.1 (CH_2), 96.3 (CH), 98.2 (CH), 114.0 (CH), 117.0 (C), 117.3 (CH), 124.6 (C), 129.6 (C), 132.6 (C), 141.3 (C), 142.8 (C), 148.0 (C), 150.5 (C), 151.0 (C),

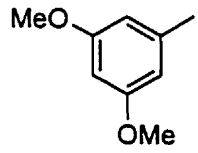
152.1 (C); mass spectrum *m/z* (relative intensity) 430 (M^+, 41), 412 (100), 399 (76), 397 (50), 384 (37), 352 (35); HRMS calcd. for $C_{24}H_{30}O_7$ 430.1991, found 430.1949.

3,5-Dimethoxybenzyl iodide 175a



In order, triphenylphosphine (0.234 g, 0.892 mmol), imidazole (0.061 g, 0.896 mmol) and iodine (0.227 g, 0.894 mmol) were added to dry dichloromethane. A solution of 3,5-dimethoxybenzyl alcohol (0.100 g, 0.595 mmol) was added and the reaction mixture was stirred at room temperature under N_2 for 30 minutes. The solution was concentrated under vacuum and the product was purified by column chromatography on silica gel using 30% EtOAc/Hexanes as the eluent to afford large, colorless crystals (0.064 g, 40%): ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 6H), 4.38 (s, 2H), 6.34 (t, 1H, J = 2.2), 6.52 (d, 2H, J = 2.2).

3,5-Dimethoxytoluene 175b



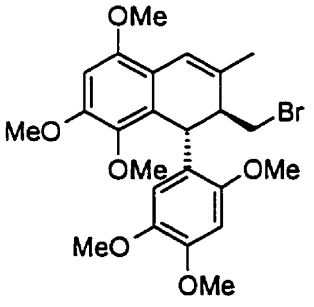
Method A: A solution of 3,5-dimethoxybenzyl iodide (0.064 g, 0.230 mmol) in dry THF (2.5 mL) was added to a slurry of lithium aluminum hydride (0.060 g, 1.58 mmol) in THF (2.5 mL). The reaction mixture was stirred at room temperature under N_2 for 1 hour then worked up by Fieser's method. In succession, water (0.06 mL), 15%

aqueous NaOH (0.06 mL) and water (0.18 mL) were added to the reaction followed by EtOAc. The ensuing solution was dried over anhydrous magnesium sulfate and concentrated under vacuum to afford a clear colorless liquid (0.019 g, 53%).

Method B: To a solution of 3,5-dimethoxybenzyl alcohol (0.049 g, 0.293 mmol) in freshly distilled THF (3 mL) was added phosphorus tribromide (0.03 mL, 0.316 mmol). The mixture was stirred at room temperature for 1 hour, diluted with THF (5 mL) and added to a slurry of lithium aluminum hydride (0.067 g, 1.76 mmol) in THF (5 mL). The reaction mixture was refluxed for 2 hours and worked up by Fieser's method. In order, water (0.07 mL), 15% aqueous NaOH (0.07 mL) and water (0.21 mL) were added to the reaction mixture followed by EtOAc. The solution was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to yield a clear and colorless liquid (0.027 g, 59%).

Both procedures gave essentially a single product, as indicated by NMR: ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.78 (s, 6H), 6.29 (s, 1H), 6.34 (s, 2H).

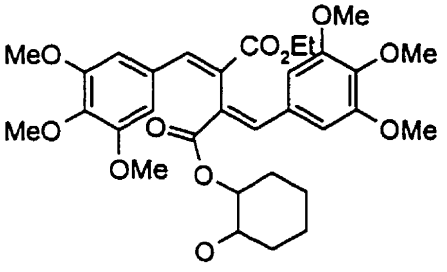
Dihydronaphthalene bromide 180



Phosphorus tribromide (0.03 mL, 0.316 mmol) was added to a solution of dihydronaphthalene alcohol **176** (0.030 g, 0.069 mmol) in dry CH_2Cl_2 (4 mL), which was then stirred at reflux for 3 hours. The reaction mixture was concentrated in vacuo and

purified by passing it through a column of silica gel (7 x 1 cm) using 30% EtOAc/Hexanes as the eluent. The fractions containing product were combined, dried over anhydrous magnesium sulfate and stripped of solvent under reduced pressure to give a clear, colorless oil (0.009 g, 26%): ^{1}H NMR ($CDCl_3$) δ 1.76 (d, 3H, J = 1.5), 2.57 (ddd, 1H, J = 1.0, 3.9, 10.6), 3.09 (dd, 1H, J = 10.2, 10.6), 3.47 (dd, 1H, J = 3.9, 10.2), 3.53 (s, 3H), 3.54 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 5.20 (d, 1H, J = 1.0), 6.18 (s, 1H), 6.42 (s, 1H), 6.52 (s, 1H), 6.62 (d, 1H, J = 1.5); ^{13}C NMR ($CDCl_3$) δ 23.0 (CH_3), 33.1 (CH), 35.3 (CH_2), 47.6 (CH), 56.1 (CH_3), 56.2 (CH_3), 56.3 (CH_3), 57.0 (CH_3), 57.2 (CH_3), 60.9 (CH_3), 96.3 (CH), 98.6 (CH), 114.1 (CH), 116.6 (C), 117.9 (CH), 123.2 (C), 129.1 (C), 133.2 (C), 141.7 (C), 142.8 (C), 148.3 (C), 151.2 (C), 151.3 (C), 152.6 (C); mass spectrum *m/z* (relative intensity) 494 (M^+, 33), 412 (100), 397 (52), 245 (92), 181 (69); HRMS cald. for $C_{24}H_{29}O_6{}^{81}Br$ 494.1127, found 494.1117.

3,4,5-Trimethoxybenzylidenesuccinate cyclohexyl ethyl ester 186



To a solution of bis(3,4,5-trimethoxybenzylidene)succinate monoacid-ester (0.653g, 1.30 mmol) in dry CH_2Cl_2 were added DMAP (0.032 g, 0.260 mmol) and trans-1,2-cyclohexanediol (0.302 g, 2.6 mmol) and the mixture was cooled to 0°C. DCC (1.32 g, 6.40 mmol) was added, and the solution stirred at 0°C for 5 minutes, and at room temperature for 3 hours. The reaction mixture was filtered, concentrated under vacuum

and the residue was dissolved in CH_2Cl_2 and filtered again. The filtrate was washed with 0.5 N aqueous HCl (2 x 20 mL) and 5% $NaHCO_3$ (2 x 20 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford a yellow oil (2.33 g) as the crude product. Purification by flash column chromatography on silica gel (100 mL) using 30% EtOAc/Hexanes as the solvent system to gave a cream colored amorphous solid (0.230 g, 12%): ^1H NMR ($CDCl_3$) (a mixture of two diastereomers) δ 1.08 – 1.41 (m, 8H) 1.12 (t, 3H, J = 7.1), 1.18 (t, 3H, J = 7.1), 1.55 – 2.05 (m, 8H), 3.47 (m, 2H), 3.78 (s, 24H), 3.64 (s, 12H), 4.18 (m, 4H), 4.61 (m, 2H), 6.47 (s, 2H), 6.76 (s, 2H), 6.78 (s, 2H), 6.79 (s, 2H), 7.77 (s, 1H), 7.83 (s, 1H), 7.84 (s, 1H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$) (a mixture of two diastereomers) δ 14.2 (CH_3), 23.7 (CH_2), 23.9 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 32.4 (2 x CH_2), 56.1 (CH_3), 56.2 (CH_3), 61.0 (CH_3), 61.3 (CH_3), 61.6 (CH_3), 72.3 (CH), 72.6 (CH), 79.2 (CH), 79.3 (CH), 107.0 (CH), 107.1 (CH), 107.3 (CH), 126.4 (C), 126.5 (C), 126.8 (C), 127.0 (C), 129.9 (C), 130.0 (C), 130.1 (C), 130.2 (C), 139.6 (C), 141.9 (CH), 142.2 (CH), 142.7 (CH), 142.9 (CH), 153.1 (C), 153.2 (C), 153.4 (C), 166.8 (C), 166.9 (C), 167.0 (C), 167.4 (C); mass spectrum *m/z* (relative intensity) 600 (M^+, 6), 456 (20), 289 (20), 181 (100), 168 (58), 98 (29); HRMS calcd. for$C_{32}H_{40}O_{11}$ 600.2570, found 600.2587.

References

1. Axelson, M.; Sjovall, J.; Gustafsson, B. E.; Setchell, K. D. R. *Nature* **1982**, *290*, 659.
2. Haworth, R. D. *Ann. Rep. Prog. Chem.* **1936**, *33*, 266.
3. Ayres, D. C.; Loike, J. D. in *Lignans: Chemical, Biological and Clinical Properties*; Cambridge University Press, Cambridge, **1990**, p. 1.
4. MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207.
5. Whiting D. A. *Nat. Prod. Rep.* **1985**, 191.
6. Ward, R. S. *Nat. Prod. Rep* **1995**, 183.
7. Whiting, D. A. *Nat. Prod. Rep.* **1990**, 349.
8. Whiting, D. A. *Nat. Prod. Rep.* **1987**, 499.
9. Ward, R. S. *Nat. Prod. Rep.* **1997**, 43.
10. Ward, R. S. *Nat. Prod. Rep.* **1993**, *1*.
11. Gottlieb, O. R. *Phytochemistry* **1972**, *11*, 1544.
12. Setchell, K. D. R; Lawson, A. M.; Mitchell, F. L. ; Aldercrentz, H.; Kirk, D. N.; Axelson, M. *Nature* **1980**, *287*, 740.
13. Stitch, S. R.; Toumba, J. K.; Groen, M. B.; Funke, C. W.; Leemhuis, J.; Vink, J; Woods, G. F. *Nature* **1980**, *287*, 738.
14. Setchell, K. D. R; Lawson, A. M.; Conway, E.; Taylor, N. F.; Kirk, D. N.; Cooley, G; Farrant, R. D.; Wynn, S; Axelson, M. *Biochem. J.* **1981**, *197*, 447.
15. Tang, W.; Eisenbrard, G. in *Chinese Drugs of Plant Origin*; Springer-Verlag, Berlin, Heidelberg, **1992**, pp. 903-917.
16. Pelter, A. *Recent Adv. Phytochem.* **1986**, *20*, 201.
17. Davin, L. B.; Lewis, N. G. *Recent Adv. Phytochem.* **1992**, *26*, 325.

18. Kelly, M. G.; Hartwell, J. L. *J. Nat.Canc. Inst.* **1954**, 967.

19. Kelleher, J. K. *Cancer Treatment Rep.* **1978**, *62*, 1443.

20. Cairnes, D. A.; Ekuyundayo, O.; Kingston, D. G. *J. Nat. Prod.* **1980**, *43*, 495.

21. Thompson, L. U.; Robb, P.; Serraino, M.; Cheung, F. *Nutr. Cancer*, **1991**, *16*, 43.

22. Cole, J. R.; Bianchi, E.; Trumbell, E. R. *J. Pharm. Sci.* **1969**, *58*, 175.

23. Burk, D.; Woods, M. *Radiat. Res. Suppl.* **1963**, *3*, 212.

24. Hartwell, J. L. *Cancer Treatment Rep.* **1976**, *60*, 1031.

25. McDoniel, P. B.; Cole, J. R. *J. Pharm. Sci.* **1972**, *61*, 1992.

26. Gonzalez, A. G.; Darias, V.; Alonso, G. *Planta Med.* **1979**, *36*, 200.

27. Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Gilmore, C. J.; Restivo, R. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 1334.

28. Brewer, C. F.; Loike, J. D.; Horowitz, S. B. *J. Med. Chem.* **1979**, *22*, 215.

29. Lehninger, A. L.; Nelson, D. L.; Cox, M. M. in *Principles of Biochemistry* Second Edition; Worth Publishers, New York, **1993**, p. 44.

30. Wolfe, S. L. in *Molecular and Cellular Biology*; Wadsworth Publishing Company, Belmont, California, **1993**, pp. 417-429.

31. Cortese, F.; Bhattacharyya, B; Wolff, J. *J. Biol. Chem.* **1977**, *252*, 1134.

32. Lee, K.- H. in *Plant Phenolic Compounds as Cytotoxic Antitumor Agents*; ACS Symp. Ser.: Washington, DC, **1992**, *507*, pp. 367-379.

33. May, G.; Willuhn, G. *Drug Res.* **1978**, *28*, 1.

34. Bedows, E.; Hatfield, G. M. *J. Nat. Prod.* **1982**, *45*, 725.

35. Momose, T.; Kanai, K. –I.; Nakamura, T.; Kuni, Y. *Chem. Pharm. Bull.* **1977**, *25*, 2755.

36. Ward, R. S. *Tetrahedron*. **1990**, *46*, 5029.

37. Chee, L. –G. in *The Study of the Asymmetric Synthesis of Lignans*; University of Manitoba, **1997**, and references cited therein.

38. Takei, Y.; Mori, K.; Matsui, M. *Agric. And Biol. Chem.* **1973**, *37*, 637.

39. Pelter, A.; Ward, R. S.; Watson, D. J.; Collins, P.; Kay, I. T. J. *Chem. Soc., Perkin Trans. 1*, **1982**, 175.

40. Kumada, Y.; Nagana, H.; Takeuchi, T.; Umezawa, H.; Yamashita, K.; Watanabe, K. *J. Antibiotics* **1978**, *31*, 105.

41. Ahmed, R.; Schreiber, F. G.; Stevenson, R.; Williams, J. R.; Yeo, H. M. *Tetrahedron* **1976**, *32*, 1339.

42. Wallis, A. F. A.; *Aust. J. Chem.* **1973**, *26*, 585.

43. Pelter, A.; Ward, R. S.; Satyanarayan, P. *Tetrahedron Lett.* **1981**, 1549.

44. Ziegler, F. E.; Schwartz, J. A. *J. Org. Chem.* **1978**, *43*, 985.

45. Damon, R. E.; Schlessinger, R. H.; Blount, J. P. *J. Org. Chem.* **1976**, *41*, 3772.

46. Tomioka, K.; Mizuguchi, H.; Koga, K. *Tetrahedron Lett.* **1978**, 4687.

47. Tomioka, K.; Koga, K. *Tetrahedron Lett.*, **1979**, 3315.

48. Brown, E.; Robin, J. –P. *Tetrahedron Lett.* **1978**, 3612.

49. Johnson, W. S.; Daub, G. H. in *Organic Reactions*; John Wiley and Sons, Inc., New York, **1951**, pp. 1-73.

50. Brown, E.; Dhal, R.; Robin, J. –P. *Tetrahedron Lett.* **1979**, 733.

51. Robin, J. –P.; Gringore, O.; Brown, E. *Tetrahedron Lett.* **1980**, 2709.

52. Ayres, D. C.; Carpenter, B. G.; Denney, J. *J. Chem. Soc.* **1965**, 3578.

53. Heller, H. G.; Strydon, P. J. *J. Chem. Soc., Chem. Commun.* **1976**, 50.

54. Hori, Z. –I.; Ohkawa, K.; Iwata, C. *Chem. Pharm. Bull.* **1972**, *20*, 624.

55. Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**,

56. De Silva, S. O.; St. Denis, C.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 995.

57. Johnson, W. S.; Daub, G. H. in *Organic Reactions Vol VI*; John Wiley and Sons, Inc., New York, **1951**, pp. 1-73.

58. (a) Heller, H. G.; Swinney, B. *J. Chem. Soc. (C)* **1967**, 2452; (b) Briggs, L. H.; Cambie, R. C. *Tetrahedron* **1958**, 2, 256; (c) Das, B.; Padwa, R. S.; Srinivas, K. V. N. S.; Das, R. *Phytochemistry* **1996**, *41*, 985; (d) Lin, Y. T.; Lo, T. B.; Shih, E. H.; J. *Chin. Chem. Soc.* **1955**, *2*, 87; (e) Cohen, M. D.; Kaufman, H. W.; Sinnreich, D.; Schmidt G. M. J. *J. Chem. Soc. (B)* **1970**, 1035; (f) Hart, R. J.; Heller, H. G. *J. Chem. Soc. Perkin Trans. I* **1972**, 1321; (g) Davidse, P. A.; Dillen, J. L. M.; Heyns, A. M.; Modro, T. A.; van Rooyen, P. H. *Can J. Chem.* **1990**, *68*, 741; (h) Boeyens, J. C. A.; Denner, L.; Perold, G. W. *J. Chem. Soc. Perkin Trans. II* 1988, 1749; (i) Boeyens, J. C. A.; Denner, L.; Perold, G. W. *J. Chem. Soc. Perkin Trans. II* **1988**, 1999

59. Ganeshpure, P. A.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1681.

60. Schneiders, G. E.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 999.

61. Cow, C; Leung, C; Charlton, J. L. *Can. J.Chem.* **2000**, *78*, 553.

62. Holmes, T. L.; Stevenson, J. R. *J. Org. Chem.* **1971**, *36*, 3450.

63. Brown, D.; Stevenson, R. *Tetrahedron Lett.* **1964**, 3213.

64. Brown, D.; Stevenson, R . *J. Org. Chem.* **1965**, *30*, 1759.

65. Satyanarayana, P.; Koteswara, R. P. *Indian J. Chem.* **1985**, *24B*, 151.

66. Klemm, L. H.; Gopinath, K. *Tetrahedron Lett.* **1963**, 1243.

67. Klemm, L. H.; Gopinath, K.; Hsu-Lee, D.; Kelly, F. W.; Trod, E.; McGuire, T, M. *Tetrahedron* **1966**, *22*, 1797.

68. Klemm, L. H.; Santhanam, P. S. *J. Org. Chem.* **1968**, *33*, 1268.

69. Klemm, L. H.; Olson, D. R.; White, D. V. *J. Org. Chem.* **1971**, *36*, 3740.

70. Joshi, B. S.; Viswanathan, N.; Balakrishnan, V.; Gawad, D. H.; Ravindranath, K. R. *Tetrahedron* **1979**, *35*, 1665.

71. Block, E.; Stevenson, R. Chem. *J. Org. Chem.* **1971**, *36*, 3453.

72. Kohen, F.; Maclean, I.; Stevenson, R. *J. Chem. Soc.* (C), **1966**, 1775.

73. Rodrigo, R. *Tetrahedron* **1988**, 2093.

74. Iwasaki, T.; Kondo, K.; Kuroda, T.; Moritani, Y.; Yamagata, S.; Suguira, M.; Kikkawa, H.; Kaminuma, O.; Ikezawa, K. *J. Med. Chem.* **1996**, *39*, 2696.

75. Narasmhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1987**, *138*, 63.

76. Iwao, M.; Inoue, H.; Kuraishi, T. *Chem. Lett.* **1984**, 1263.

77. Horne, S.; Rodrigo, R.; *J. Chem. Soc., Chem. Commun.* 1992, 164.

78. Charlton, J. L.; Alauddin, M. M.; *J. Org. Chem.* **1986**, *51*, 3490.

79. Charlton, J. L.; Koh, K. *J. Org. Chem.* **1992**, *57*, 1514.

80. Maddaford, S. P.; Charlton, J. L. *J. Org. Chem.* **1993**, *58*, 4132.

81. Bogucki, D. E.; Charlton, J. L. *J. Org. Chem.* **1995**, *60*, 588.

82. Coltart, D. M.; Charlton, J. L. *Can. J. Chem.* **1996**, *74*, 88.

83. Crescente, O.; Heller, H. G.; Oliver, S. *J. Chem. Soc. Perkin Trans. I* **1979**, 150.

84. Heller, H. G.; Oliver, S.; Shawe, M. *J. Chem. Soc. Perkin Trans. I* **1979**, 154.

85. Heller, H. G.; Strydom, P. J. *J. Chem. Soc. Chem. Comm.* **1976**, 50.

86. Heller, H. G.; Szewczyk, M. *J. Chem. Soc. Perkin Trans. I* **1974**, 1487.

87. Anjaneyulu, A. S. R.; Raghu, P.; Ramkrishna, R. *Indian J. Chem.* **1979**, *18B*, 535.

88. Kuhn, R. Molekulare Asymmtrie. In *Stereochimie*, Freudenberg, H. Ed., Franz Deutzie: Leipzig-Wein, **1933**, pp. 803-824.

89. Bringmann, G.; Jansen, J. R.; Hille, A.; Reuscher, H. Symposia "*6eme Colloque Internationale , consacre aux Plantes Medicinales et Substances d'Origine Naturelle*", Angers (France) **1988**, p. 181.

90. Charlton, J.L.; Oleschuk, C.J.; Chee, G. -L. *J. Org. Chem.* **1996**, *61*, 3452.

91. Hayashi, T.; Nizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101.

92. Stobbe, H. *Annalen* **1911**, *380*, 71.

93. Yokoyama, Y.; Uchida, S.; Yokoyama, Y.; Sugawara, Y.; Kurita, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3100.

94. Elbe, H. –L.; Kobrich, G. *Chem. Ber.* **1974**, *107*, 1654.

95. Hiebert, S. in *Synthesis of a Precursor to Cyclolignan Formation and Hindered Rotation Study of an (E, E)-2,3-Dipiperonylidenesuccinamide*; University of Manitoba, **1997**.

96. Moore, P. *New Scientist* **1998**, *158*, 40.

97. Rowe, P. M. *Lancet (North American ed.)* **1998**, *351*, 1496.

98. Milgrom, L.; MacRobert, S. *Chem. Br.* **1998**, *34*, 45.

99. Dougherty, T. J.; Gomer, C. J.; Henderson, B. W.; Jori, G.; Kessel, D.; Korbelik, M.; Moan, J.; Peng, Q. *J. Natl. Cancer Inst.* **1998**, *90*, 889.

100. Sternberg, E. D.; Dolphin, D.; Bruckner, C. *Tetrahedron* **1998**, *54*, 4151, and references cited therein.

101. Oki, M. in *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH Publishers, Inc.: Florida, **1985**.

102. Carey, F. A.; Sundberg, R. J. in *Advanced Organic Chemistry B*; Plenum Press: New York, **1990**.

103. Marat, K. Xsim. University of Manitoba, © 1995

104. Mahalanabis, K. K.; Mumtaz, M.; Snieckus, V. *Tetrahedron Lett.* **1982**, *23*, 3975.

105. Andersson, J. *Acta. Chem. Scand.* B **1977**, 31.

106. Lambert, J.; Shurvell, H. F.; Lightener, D.; Cooks, G. in *Introduction to Organic Spectroscopy*; Macmillan Publishing Company: New York, **1987**.

107. Lawetz, C.; Liuzzi, M. *Antiviral Res.* **1998**, *39*, 35.

108. Yoshida, S. –I.; Ogiku, T.; Ohmizu, H.; Iwasaki, T. *Synlett* **1994**, 895.

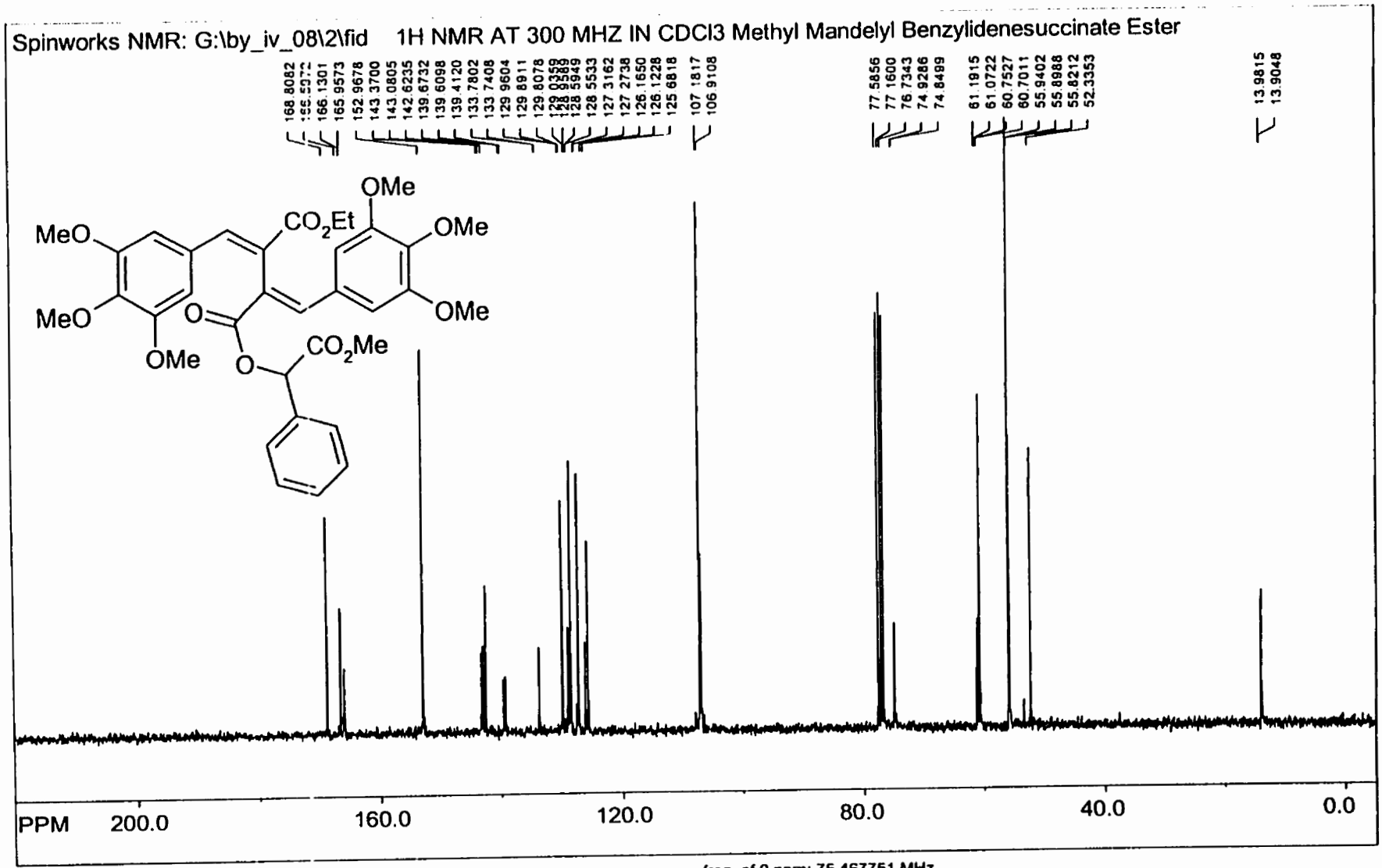
109. Kadota, S.; Tsubono, K.; Makino, T. *Tetrahedron Lett.* **1987**, *28*, 2857.

110. Lange, G.; Gottardo, C. *Synthetic Comm.* **1990**, *20*, 1473.

111. Ucciani, E.; Siouffi, A. –M.; Naudet, M. *Bull. Soc. Chim. Fr.* **1967**, 2018.

Appendix:

^{1}H and ^{13}C NMR Spectra



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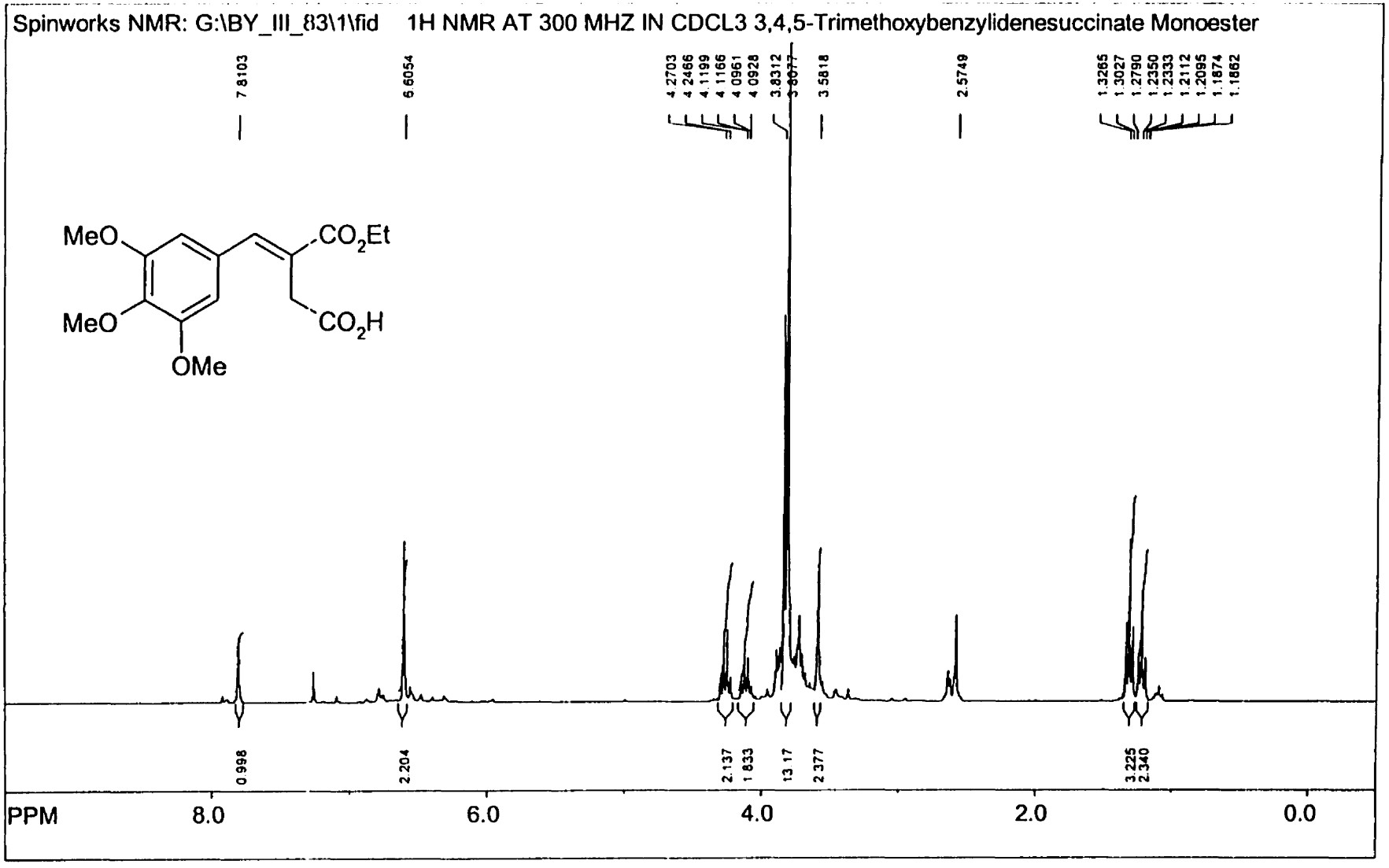

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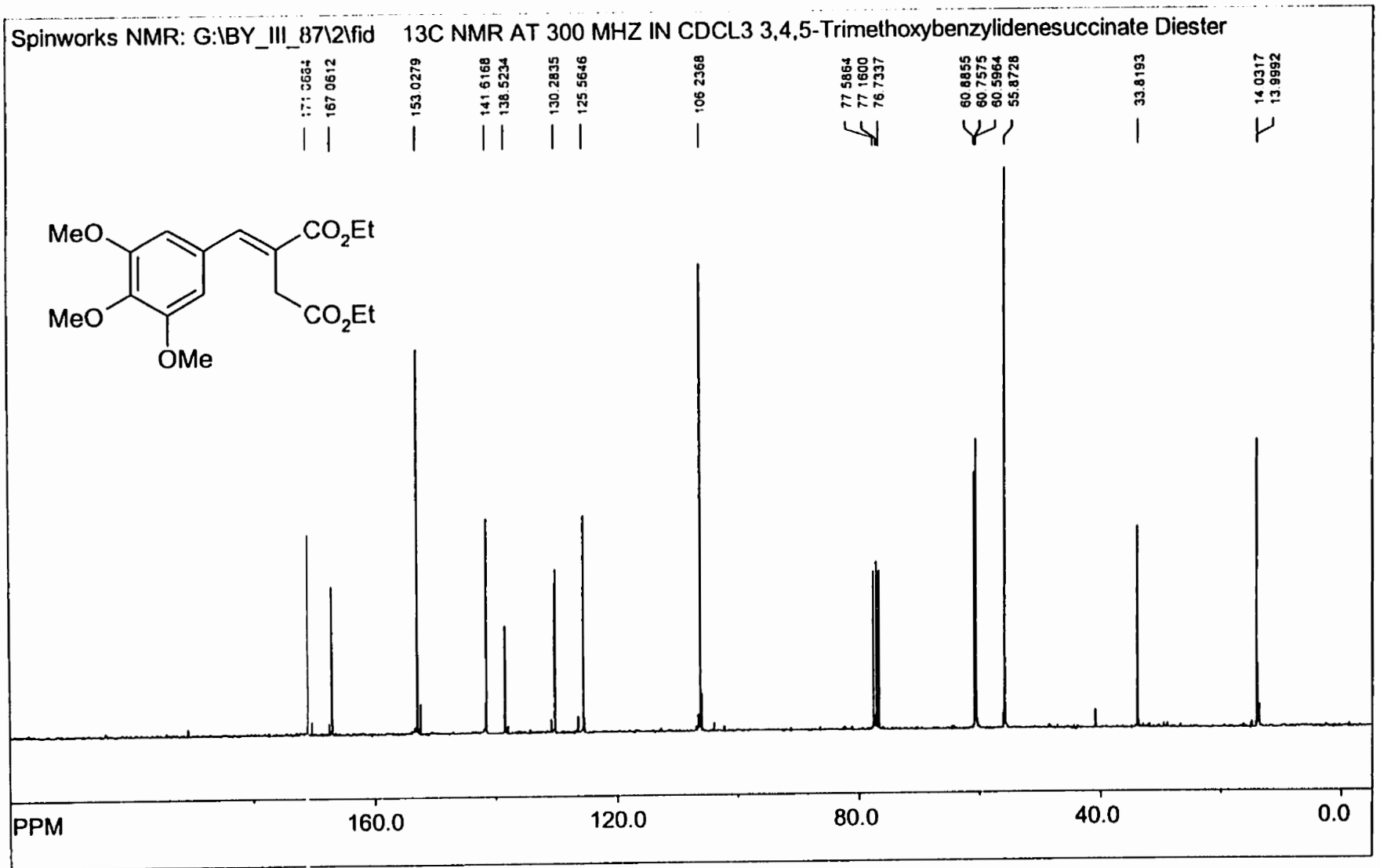

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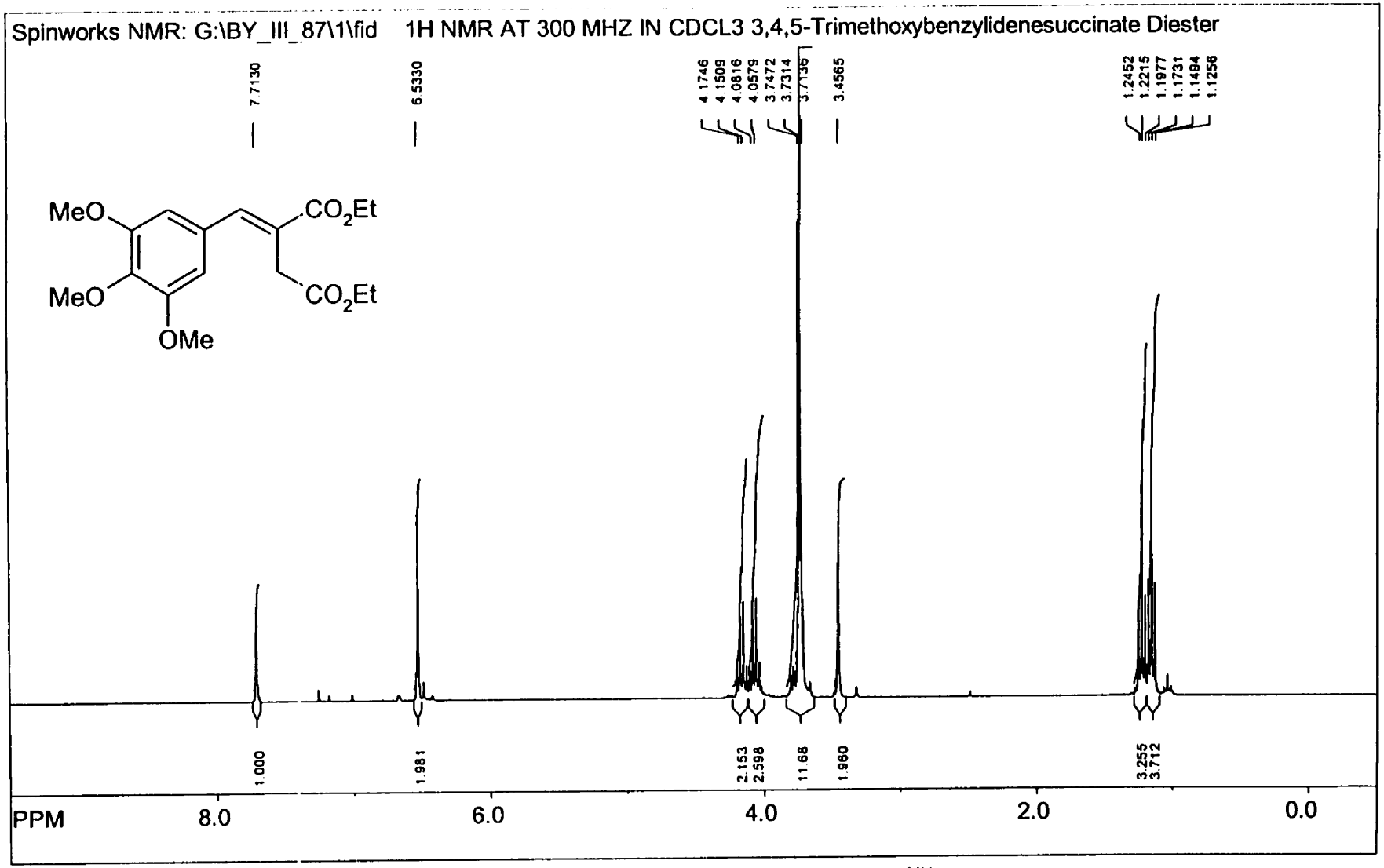

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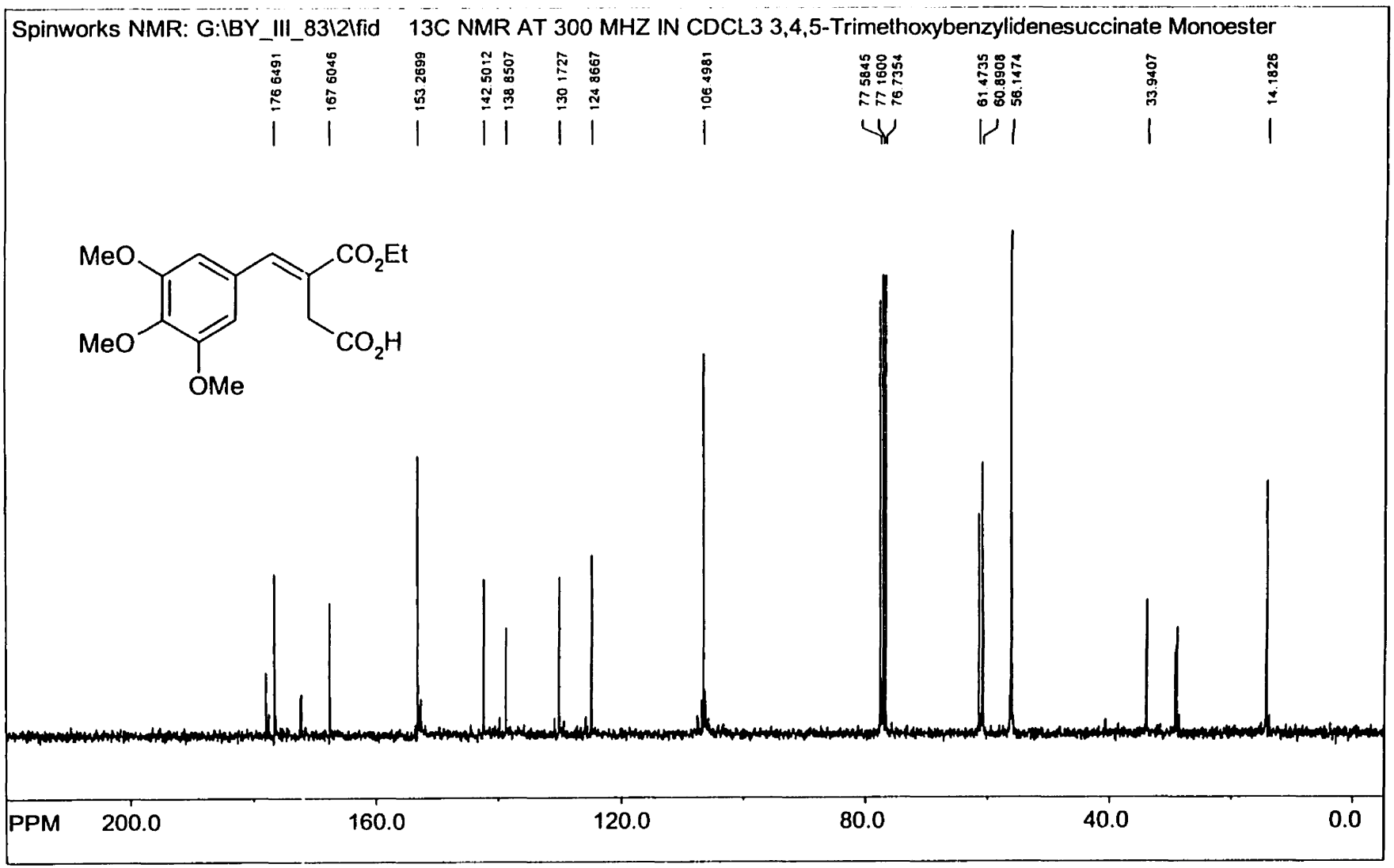
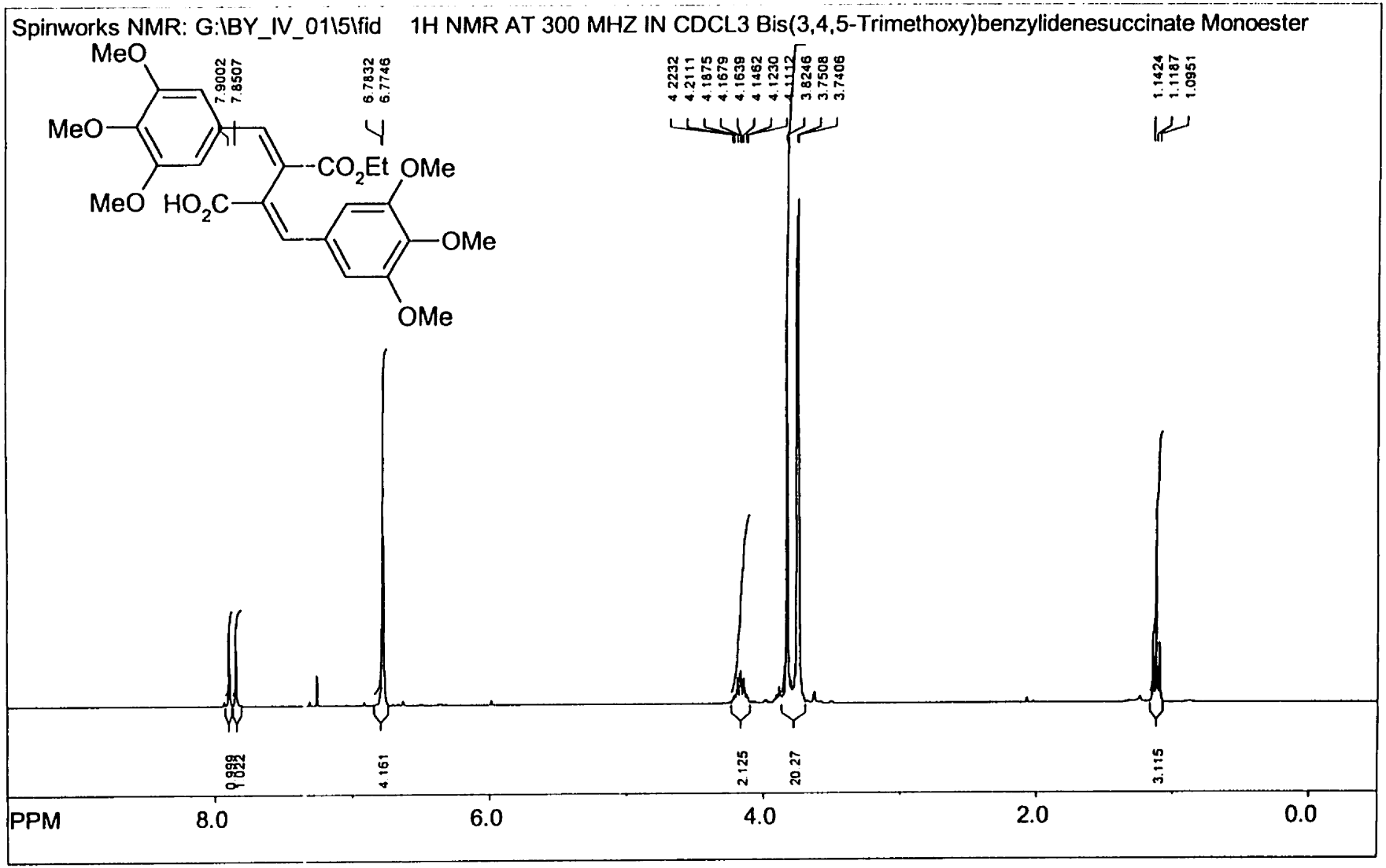
processed size: 32768 real points
LB: 0.300 GB: 0.0000



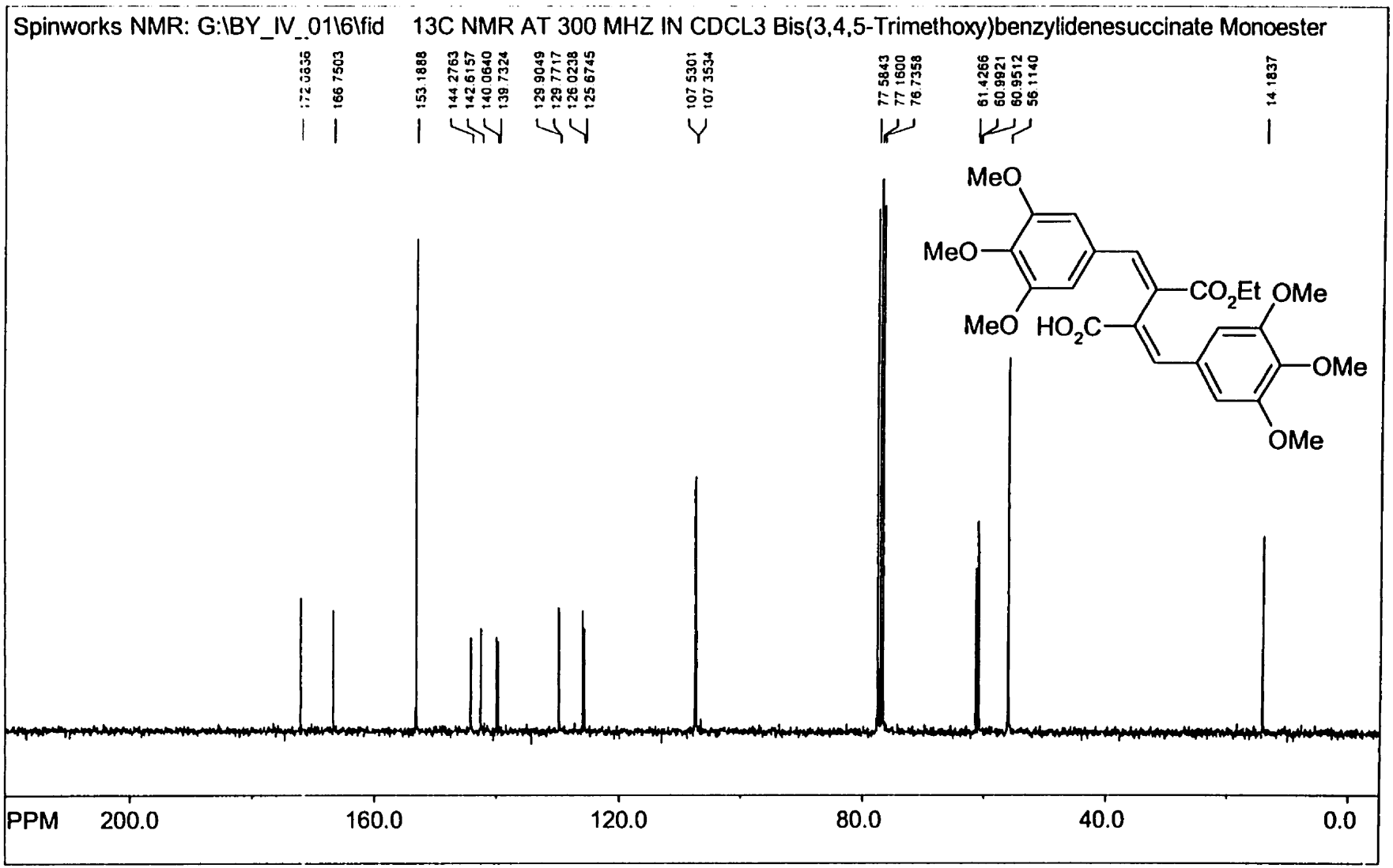
file: G:\BY_III_83\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 512

freq. of 0 ppm: 75.467745 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



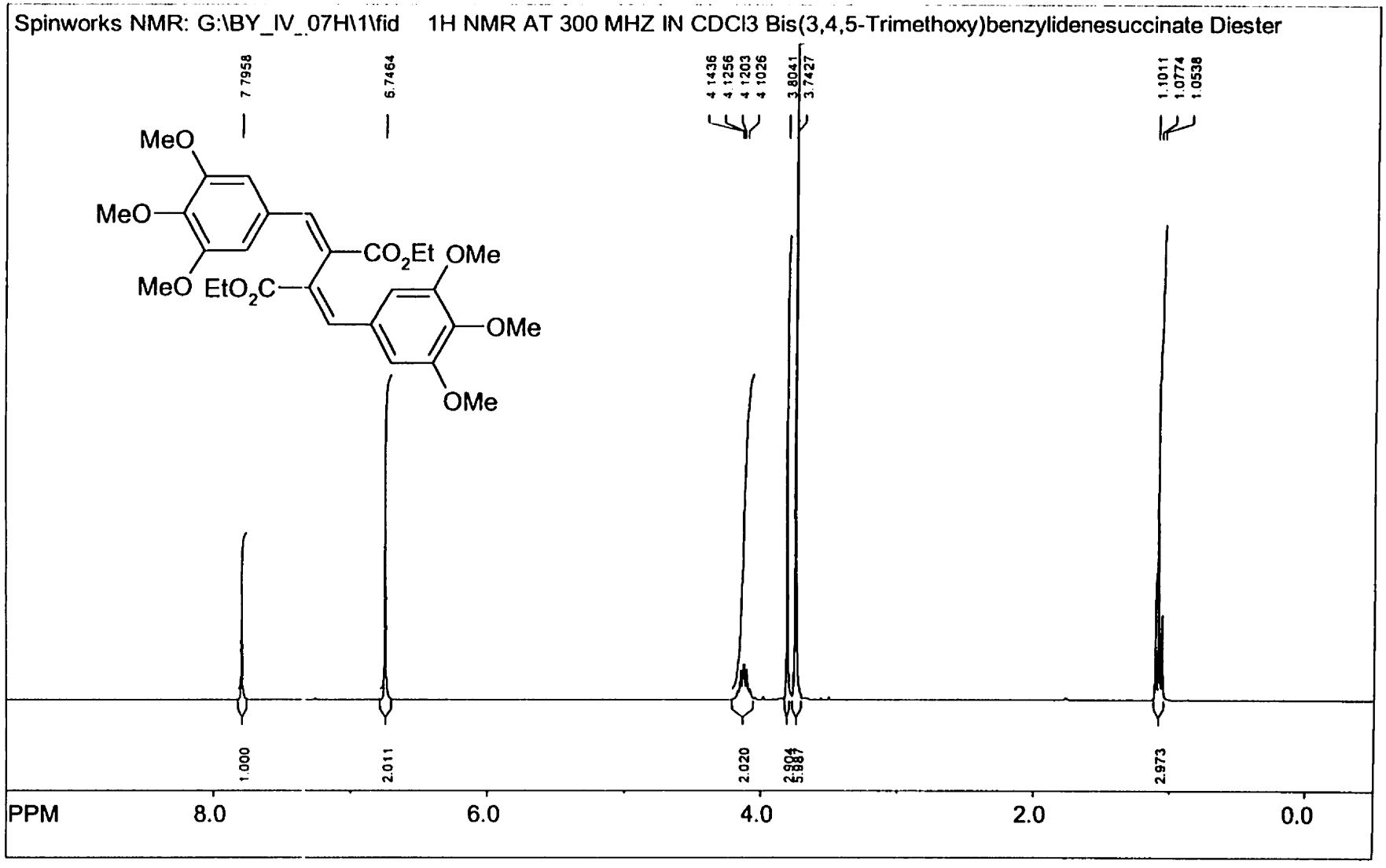
file: G:\BY_IV_01\5\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



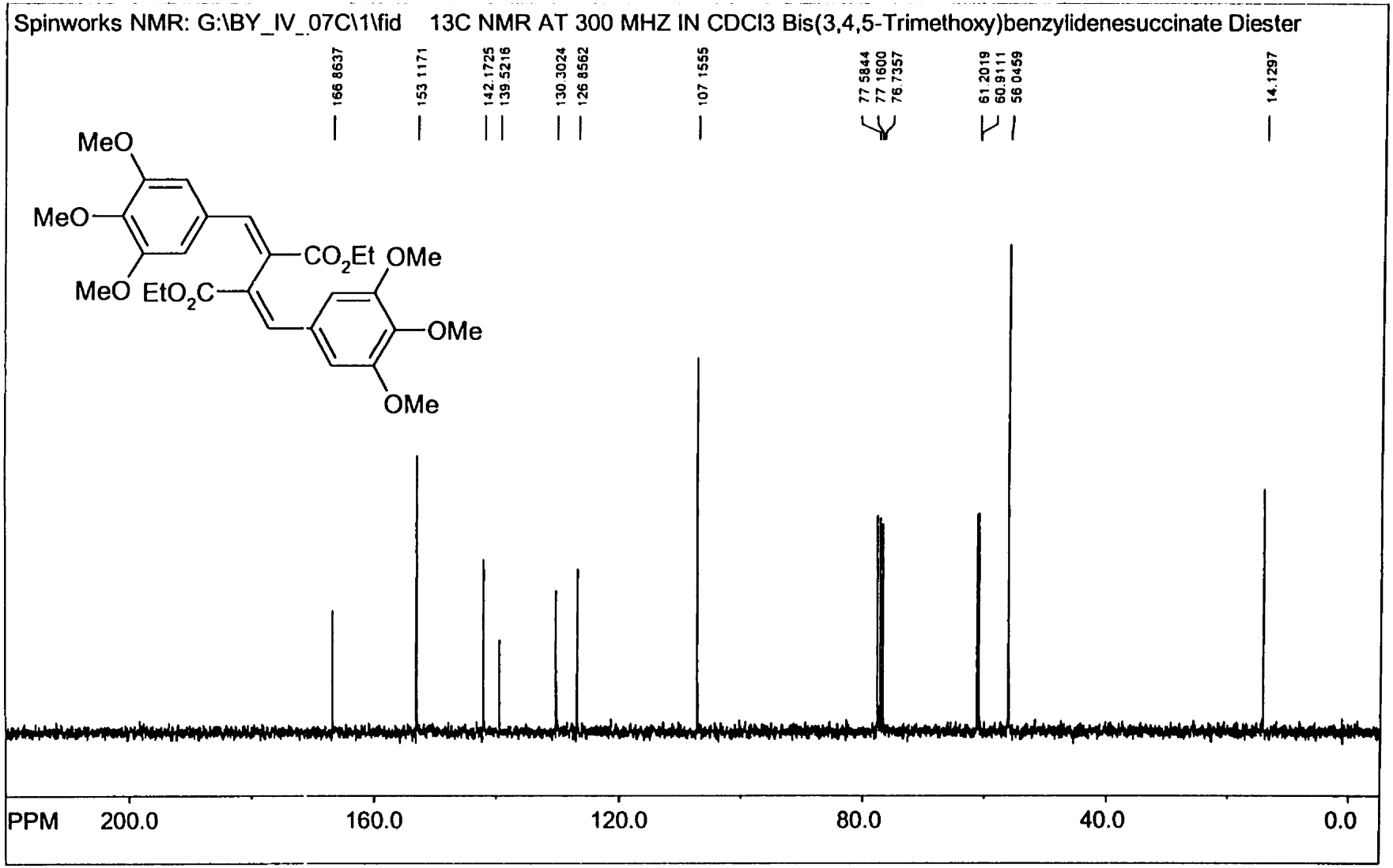
file: G:\BY_IV_01\6\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 1024

freq. of 0 ppm: 75.467740 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



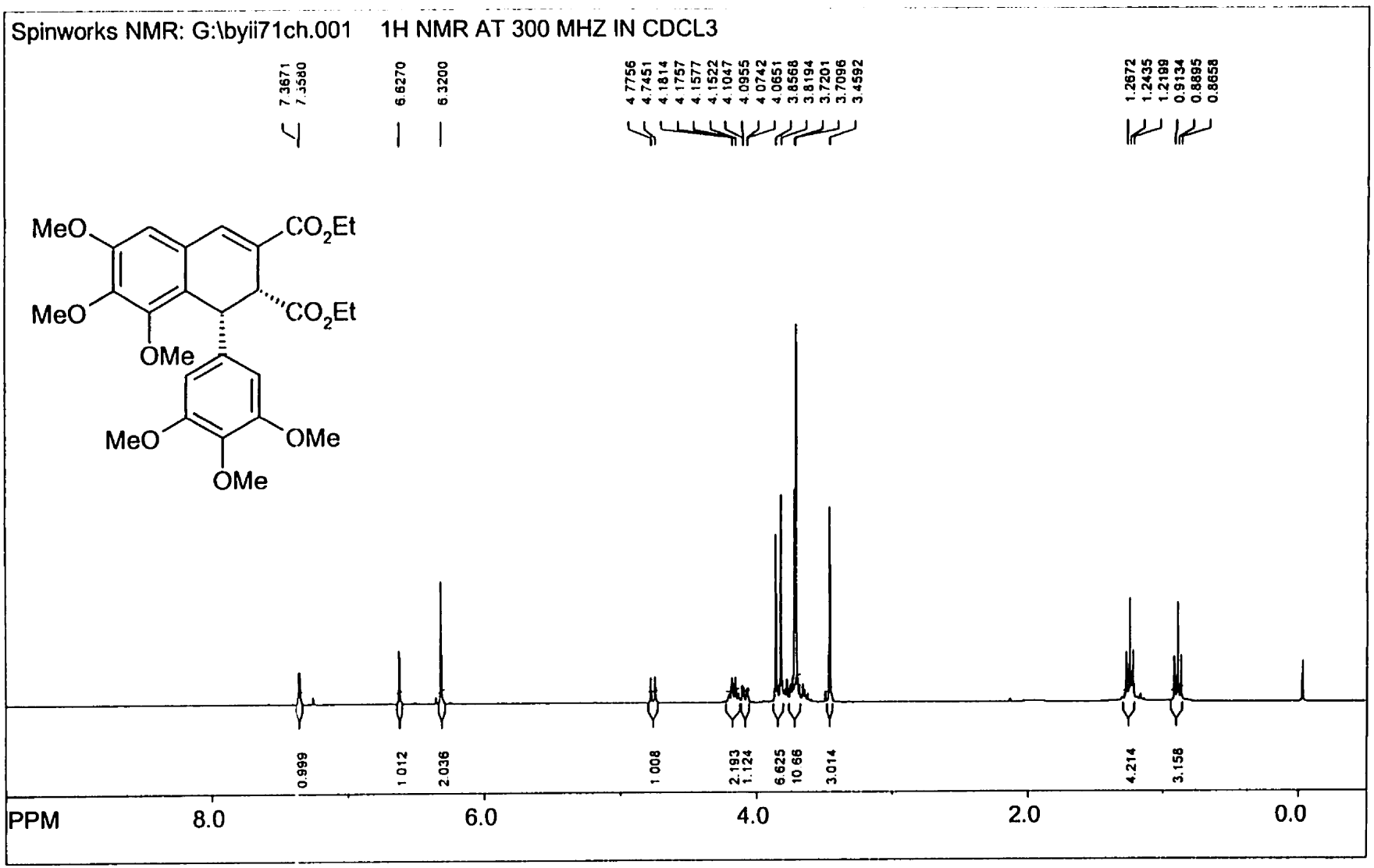
file: G:\BY_IV_07H\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130005 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



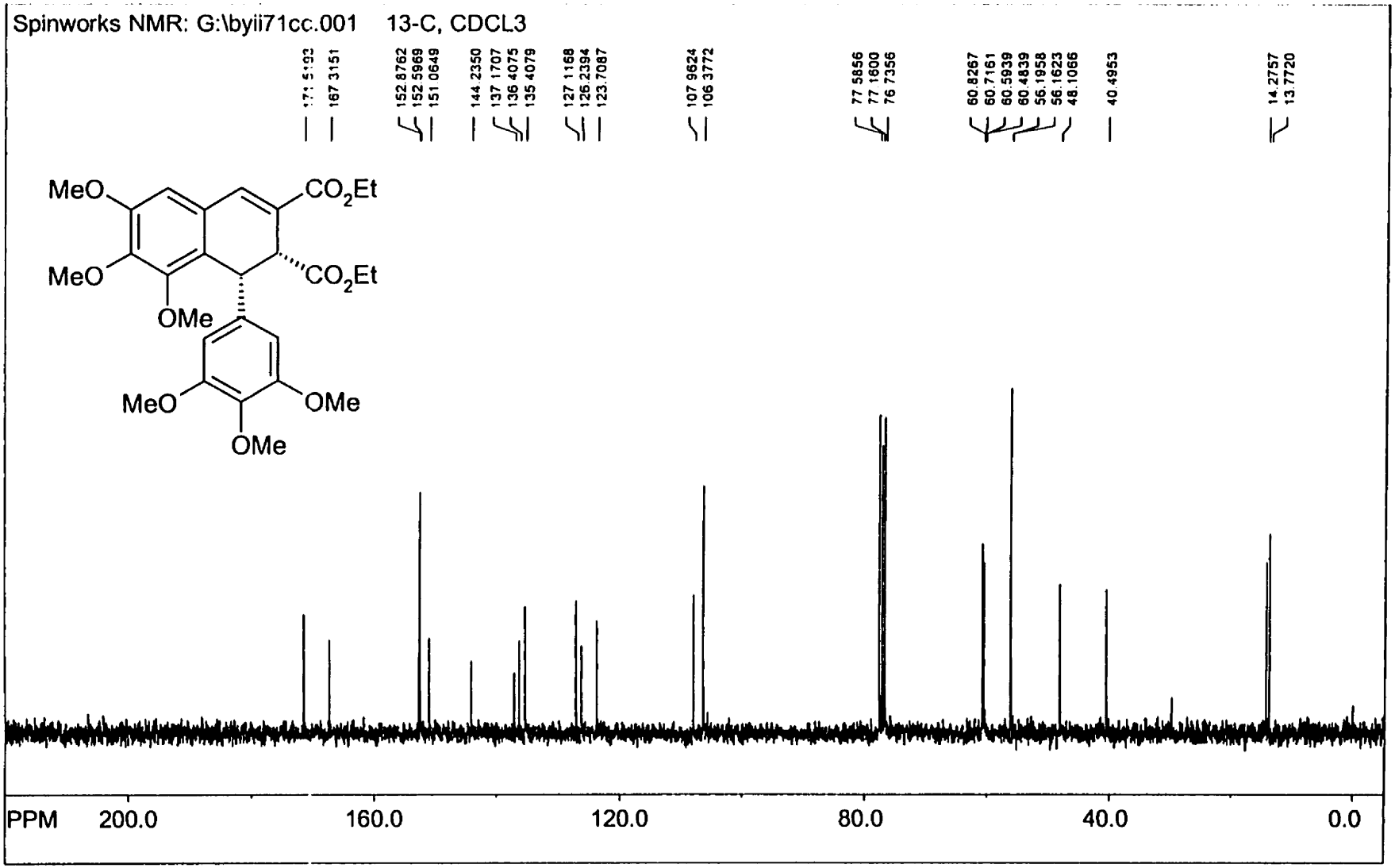
file: G:\BY_IV_07C\1\fid expt: <zgpg3(I>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 64

freq. of 0 ppm: 75.467742 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



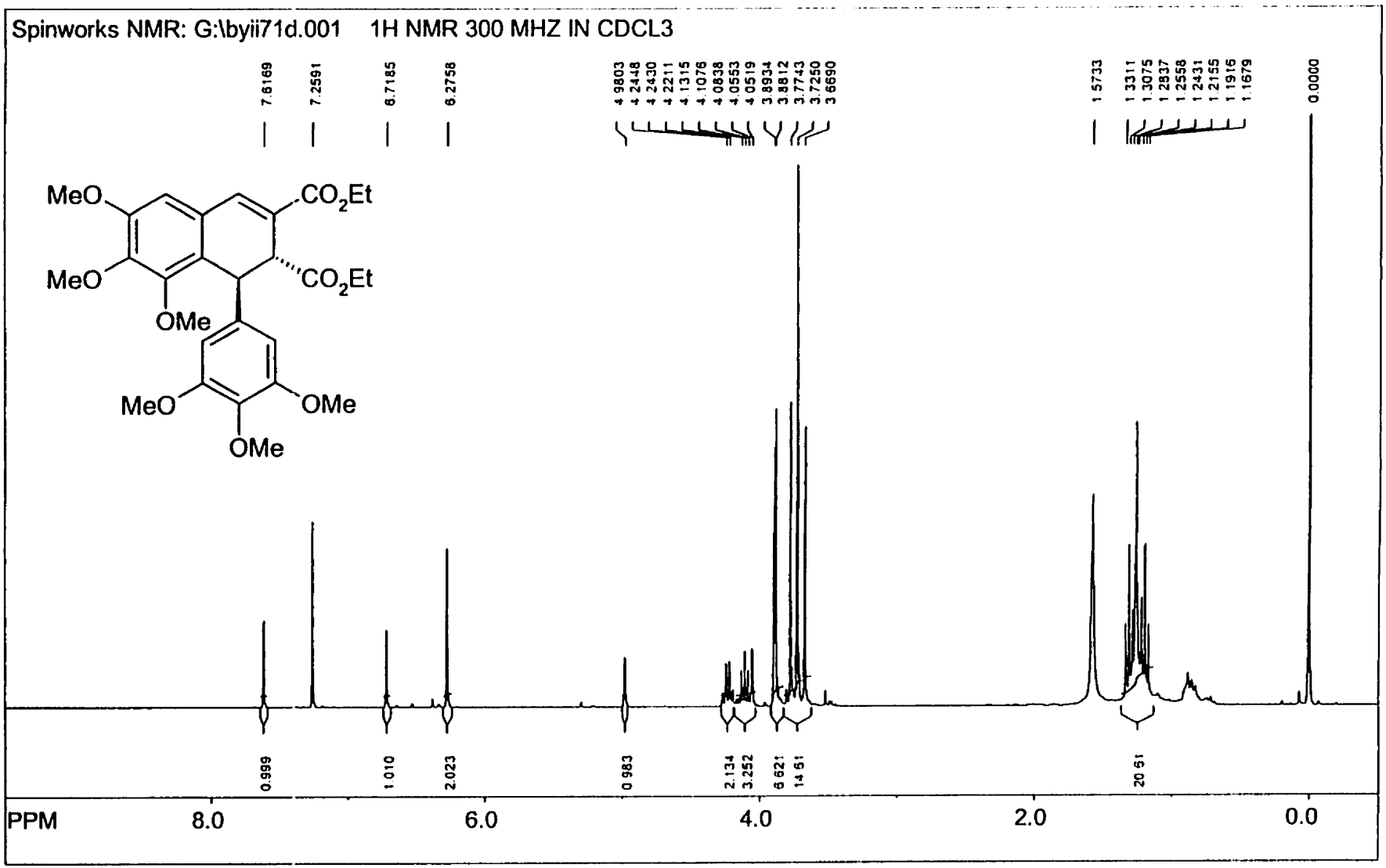
file: G:\byii71ch.001 expt: H1AUTO
transmitter freq.: 300.135500 MHz
time domain size: 32768 points
width: 5494.51 Hz = 18.306880 ppm = 0.167679 Hz/pt
number of scans: 32

freq. of 0 ppm: 300.133367 MHz
processed size: 16384 real points
LB: 0.335 GB: 0.0000



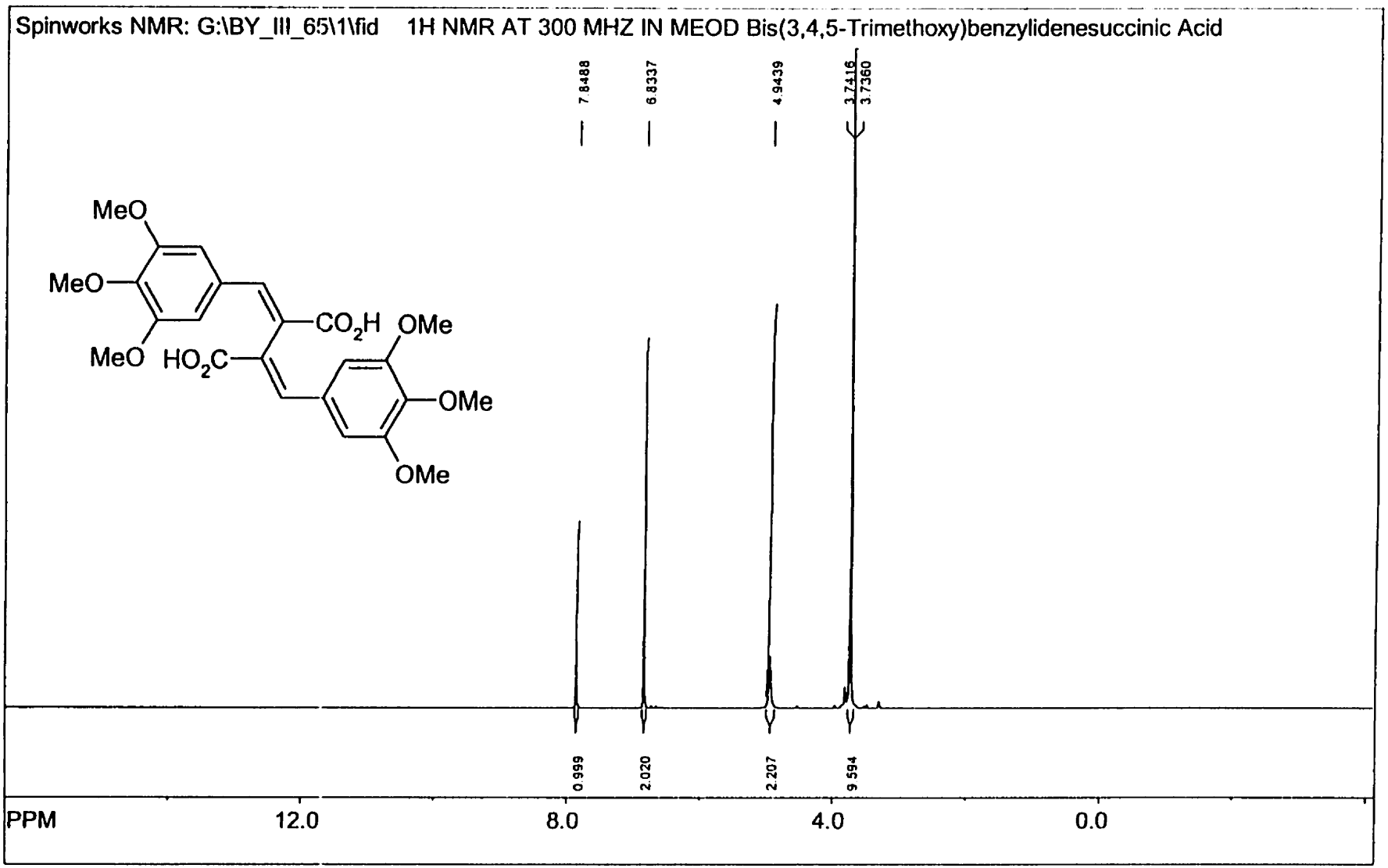
file: G:\byii71cc.001 expt: XAUTO
transmitter freq.: 75.477000 MHz
time domain size: 32768 points
width: 17857.14 Hz = 236.616880 ppm = 0.544957 Hz/pt
number of scans: 256

freq. of 0 ppm: 75.468588 MHz
processed size: 16384 real points
LB: 1.090 GB: 0.0000



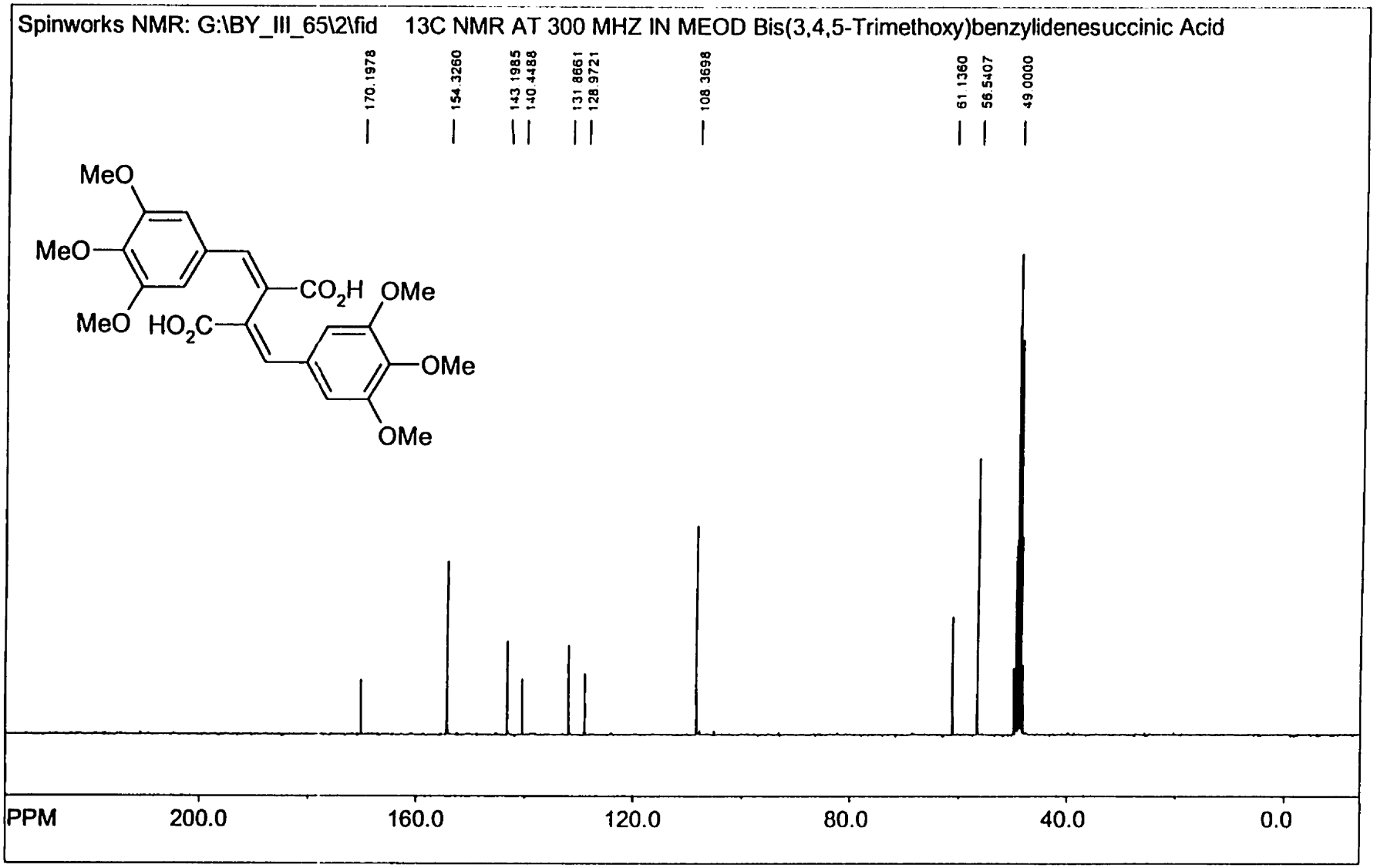
file: G:\byii71d.001 expt: H1AUTO
transmitter freq.: 300.135500 MHz
time domain size: 32768 points
width: 5494.51 Hz = 18.306880 ppm = 0.167679 Hz/pt
number of scans: 32

freq. of 0 ppm: 300.133368 MHz
processed size: 16384 real points
LB: 0.335 GB: 0.0000



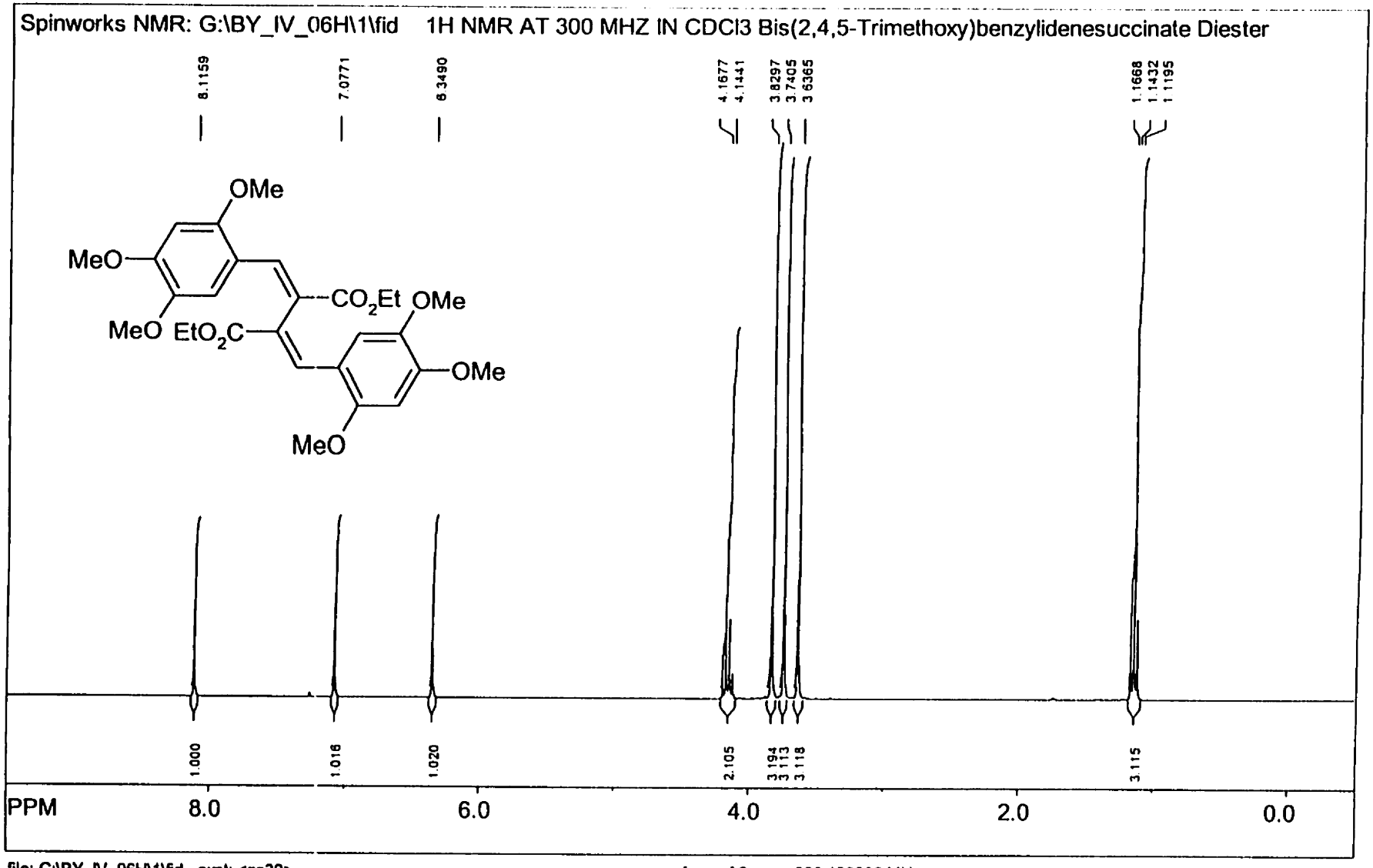
file: G:\BY_III_65\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130004 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



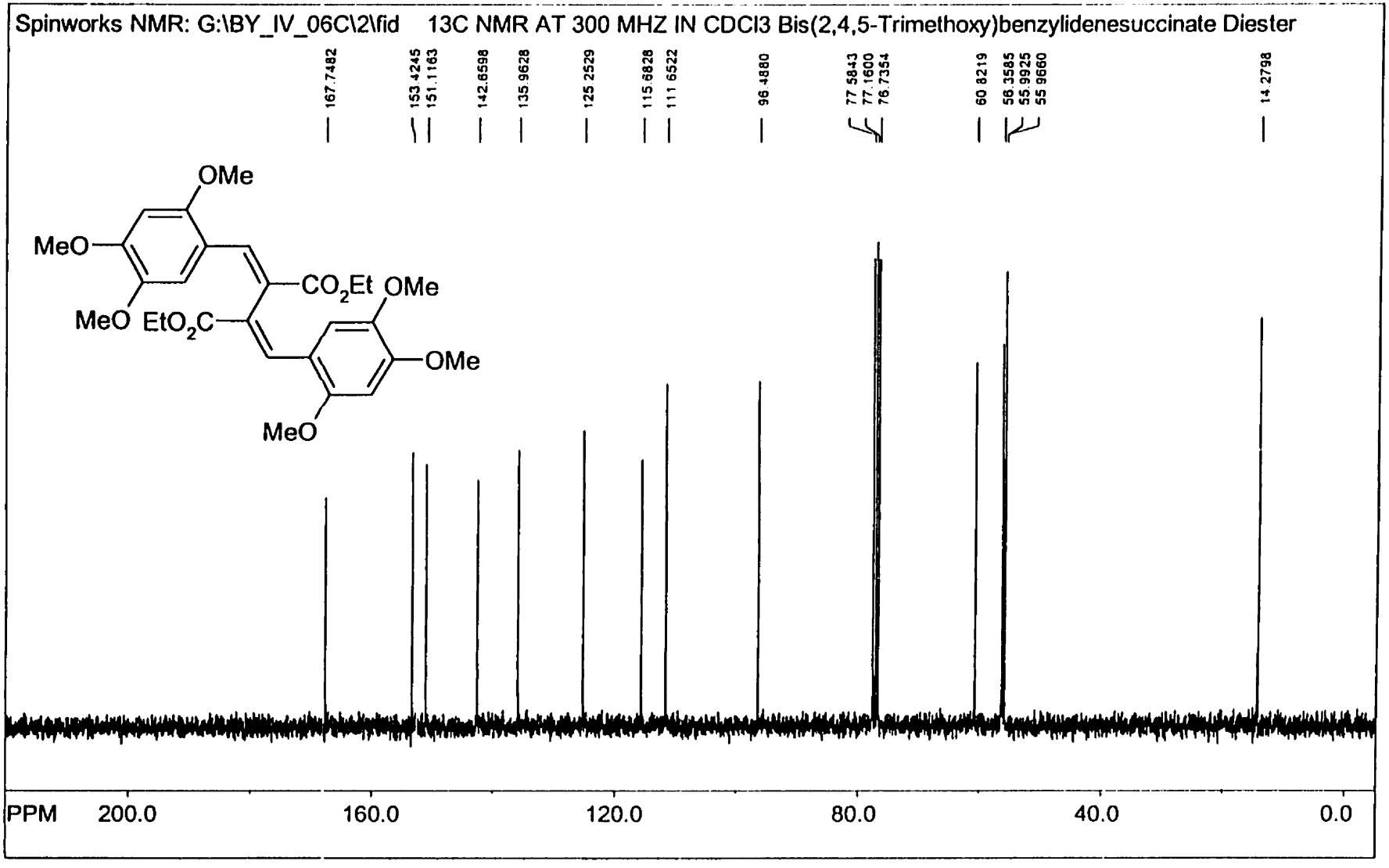
file: G:\BY_III_65\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.30 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 512

freq. of 0 ppm: 75.467645 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



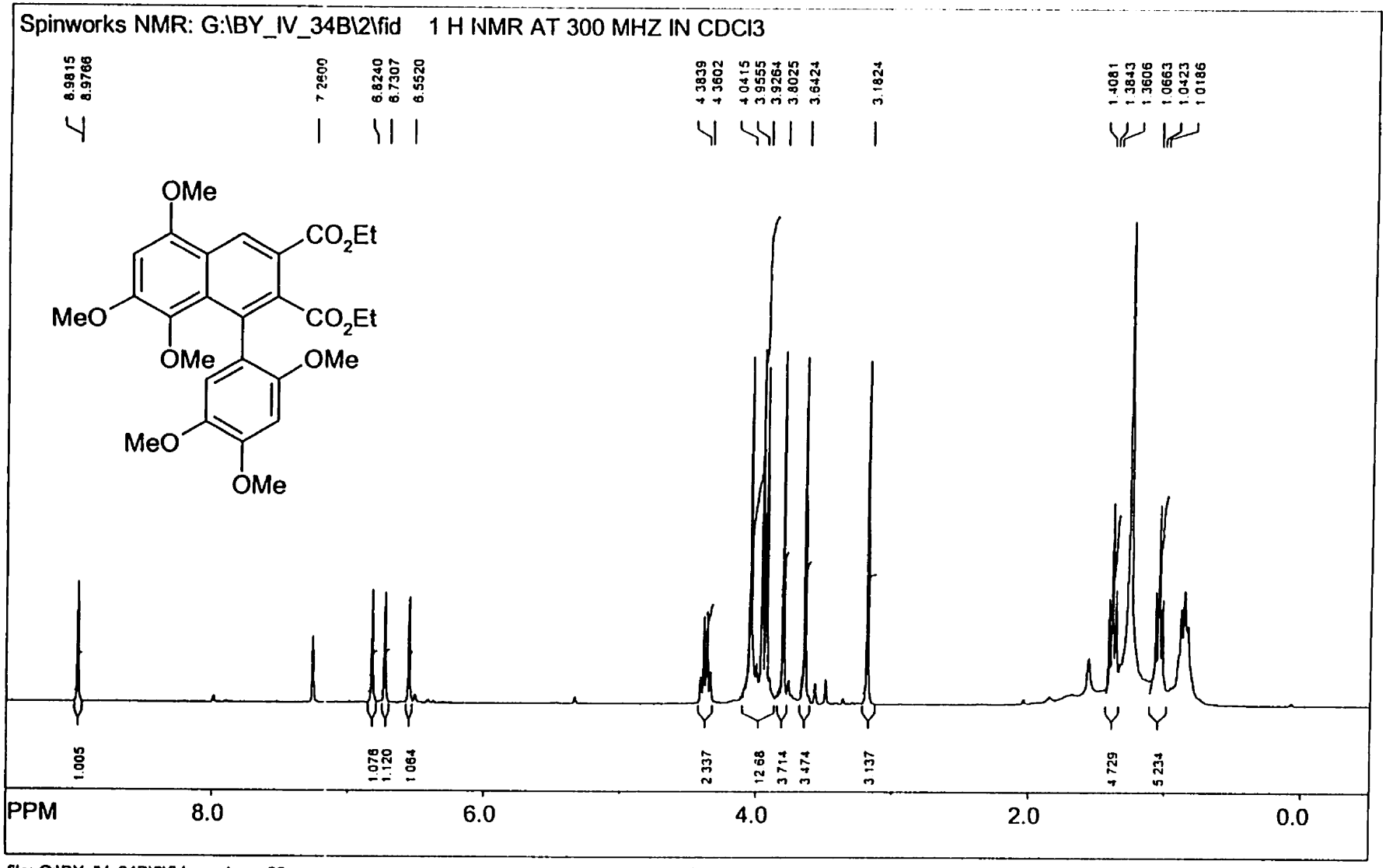
file: G:\BY_IV_06H\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



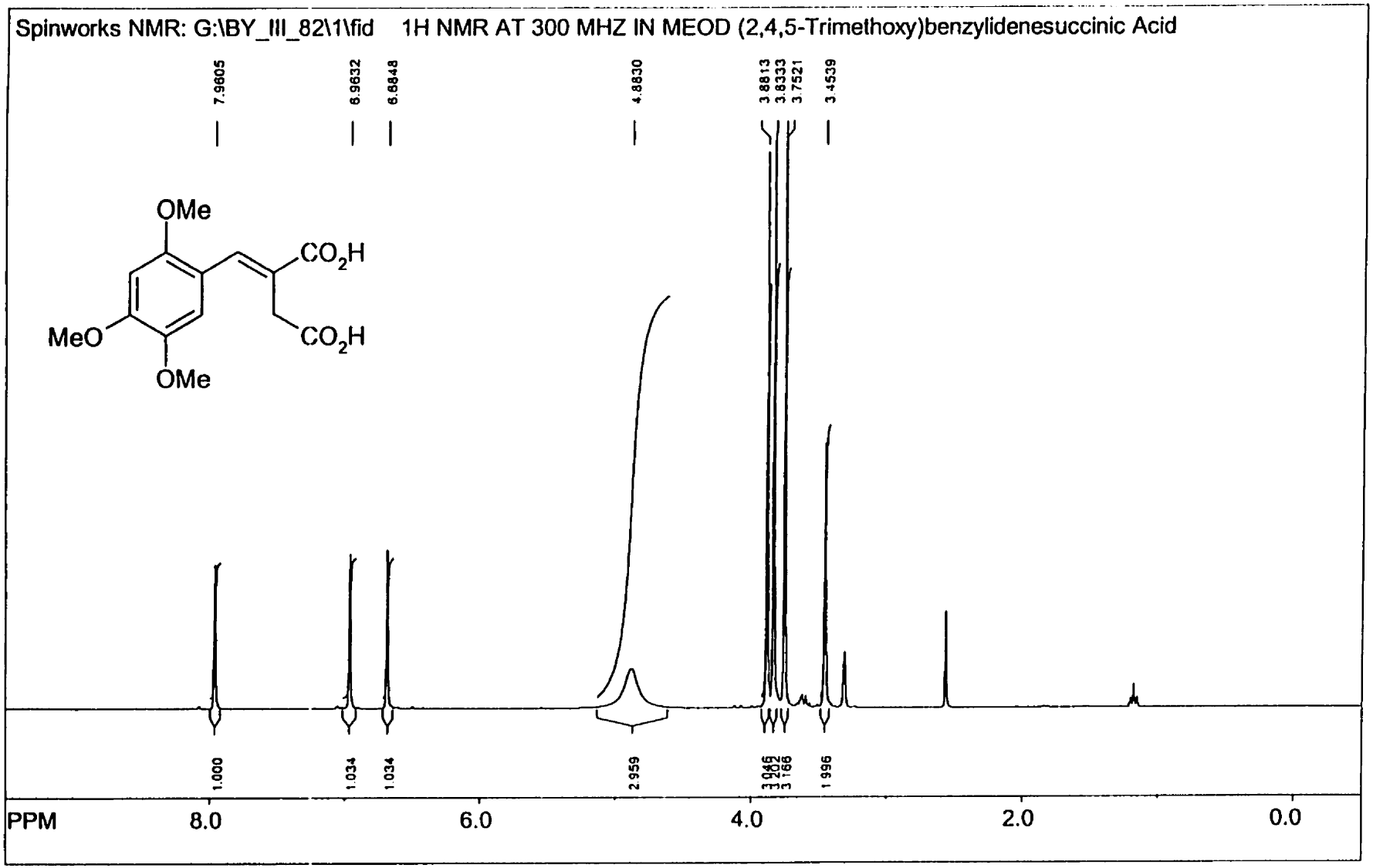
file: G:\BY_IV_06C\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 128

freq. of 0 ppm: 75.467742 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



file: G:\BY_IV_34B\2\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

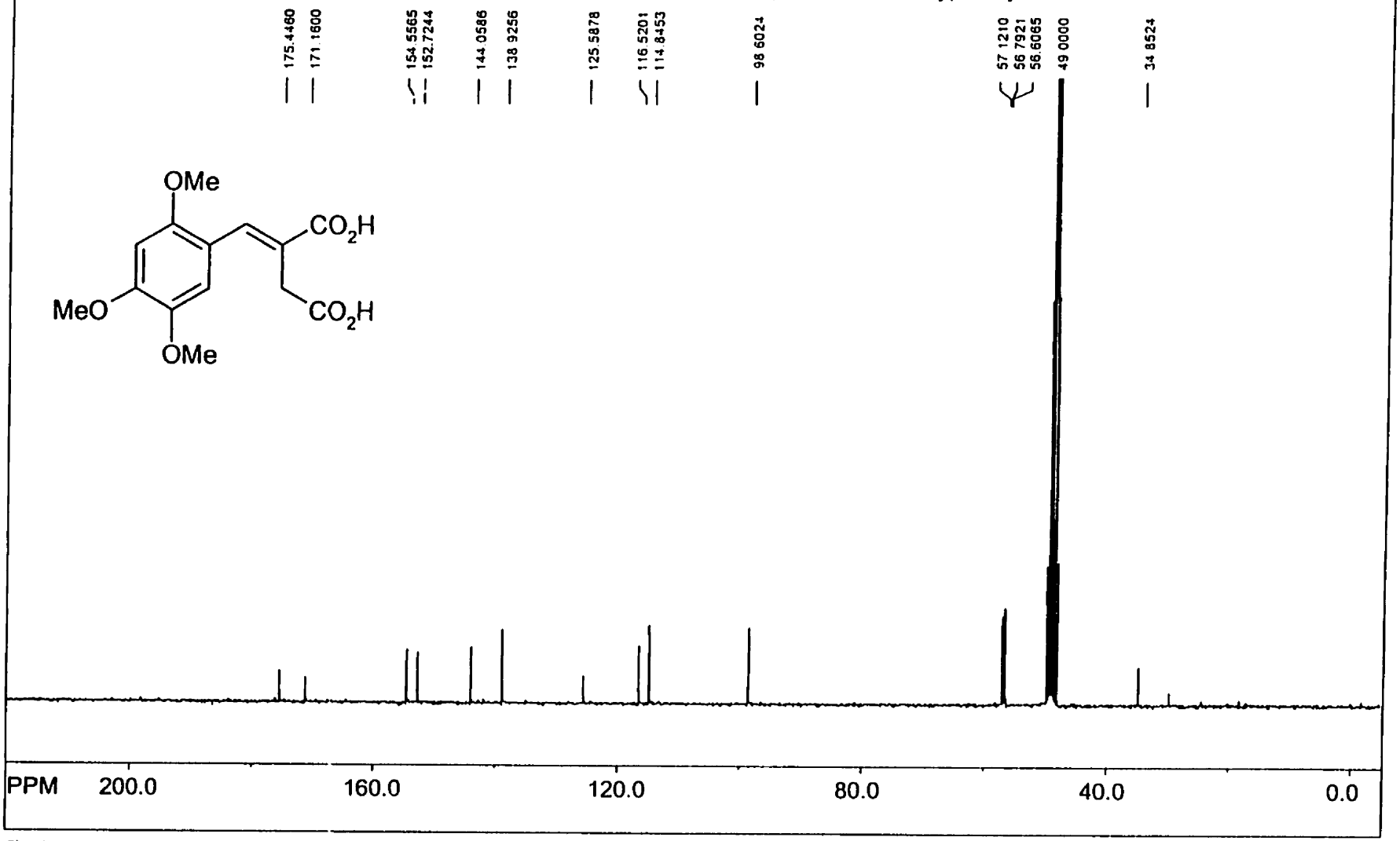
freq. of 0 ppm: 300.130005 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



file: G:\BY_III_82\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

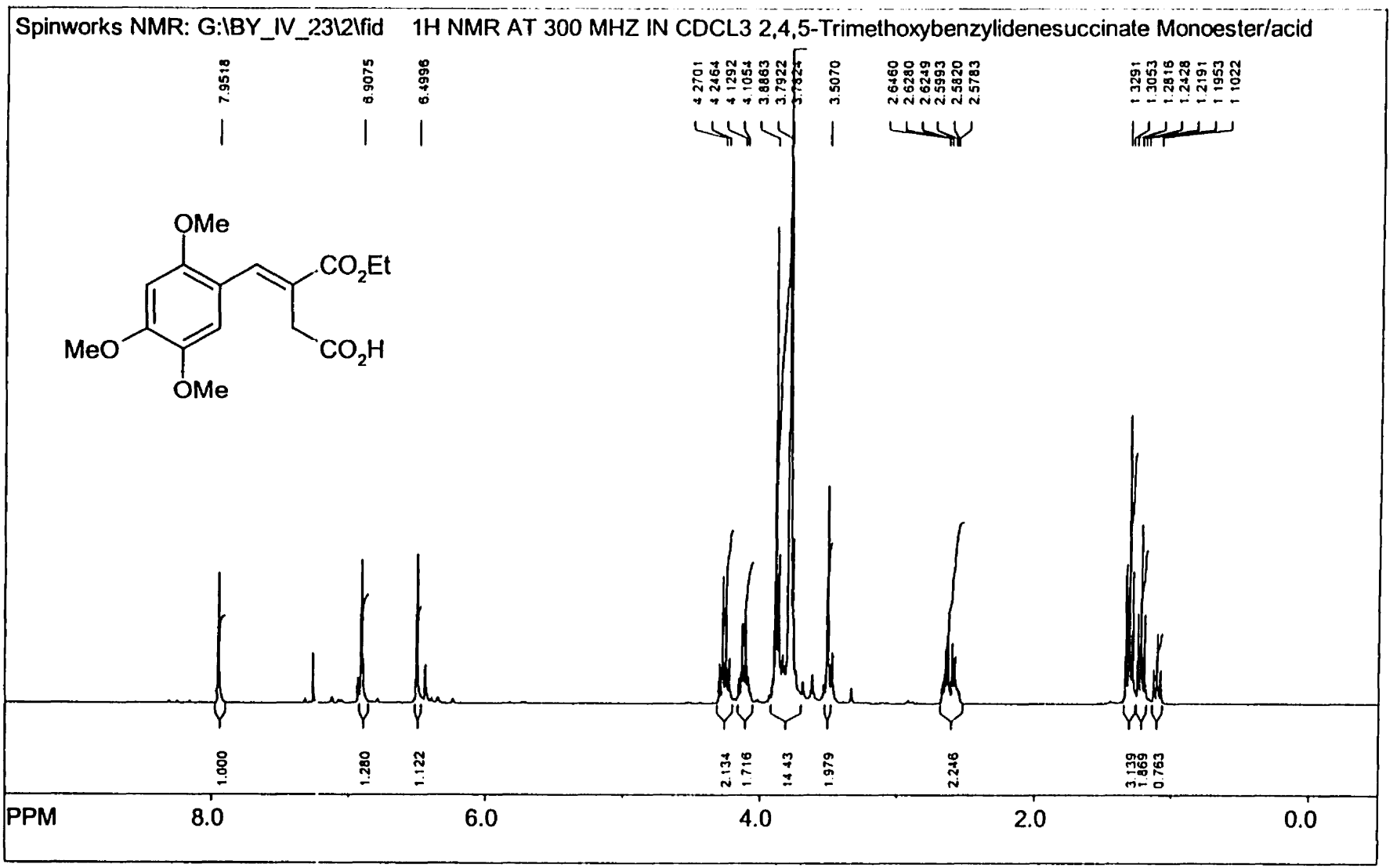
freq. of 0 ppm: 300.130004 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000

Spinworks NMR: G:\BY_III_82\2\fid 13C NMR AT 300 MHZ IN MEOD (2,4,5-Trimethoxy)benzylidenesuccinic Acid



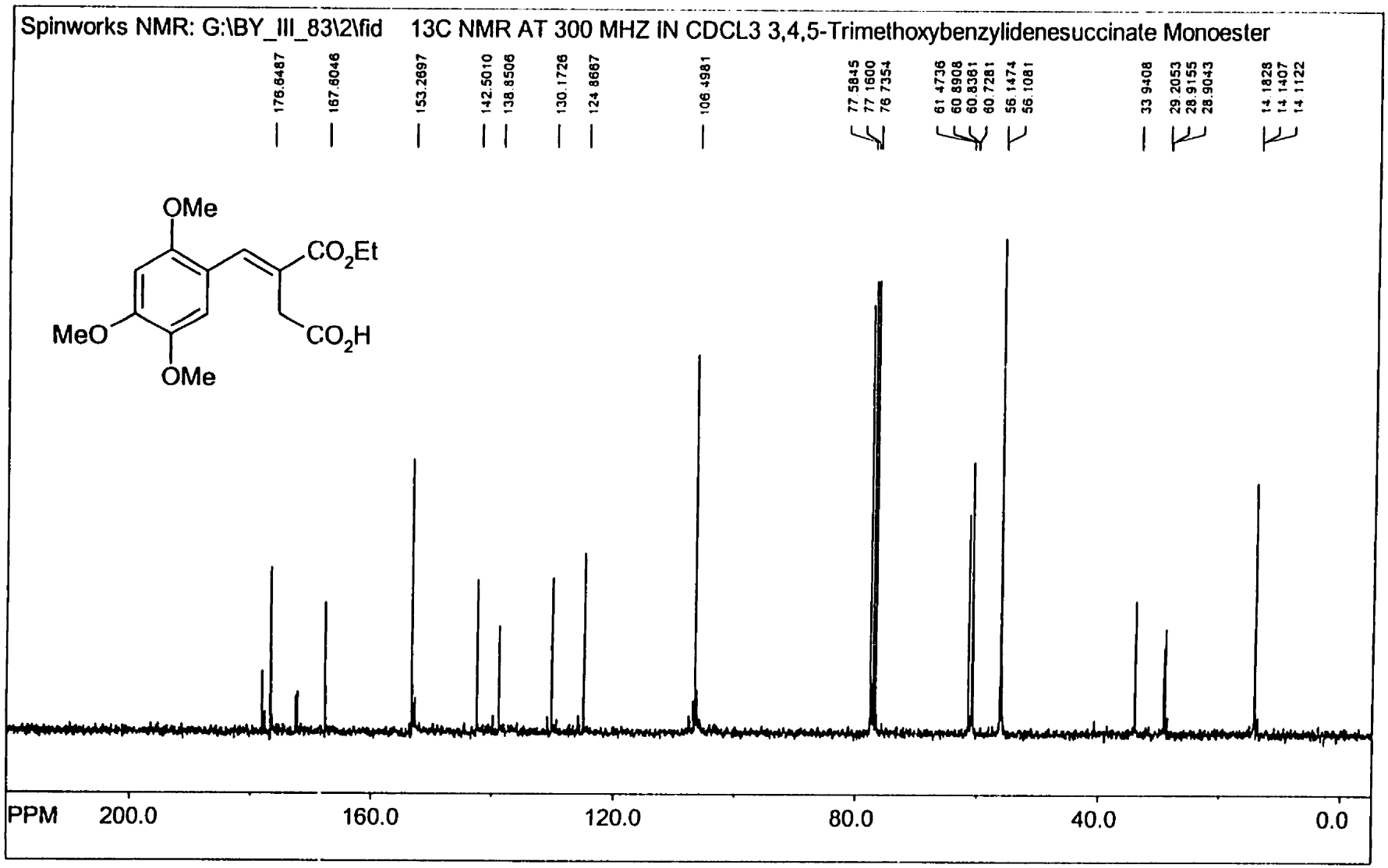
file: G:\BY_III_82\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.30 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 1024

freq. of 0 ppm: 75.467643 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



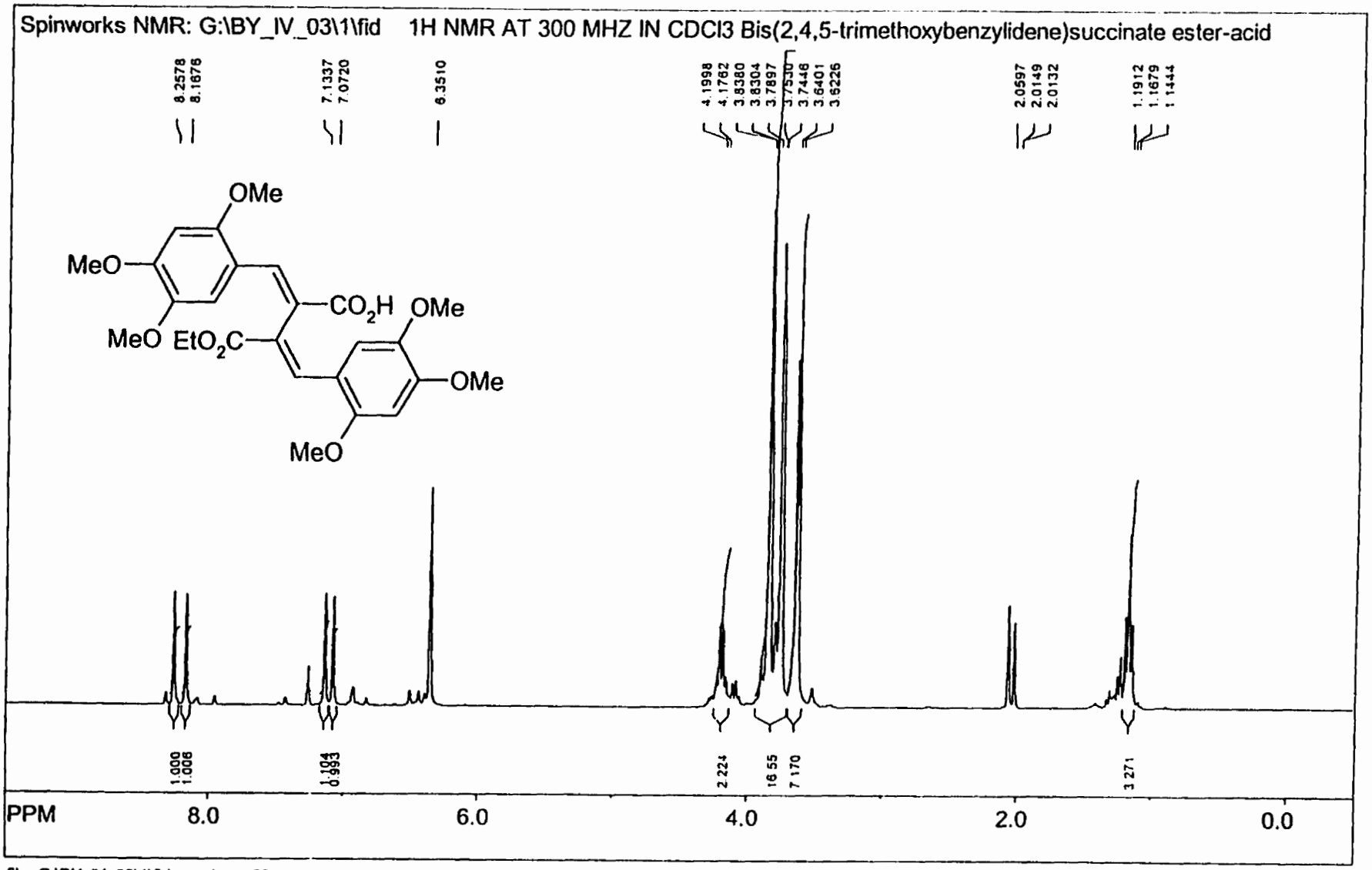
file: G:\BY_IV_23\2\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130005 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



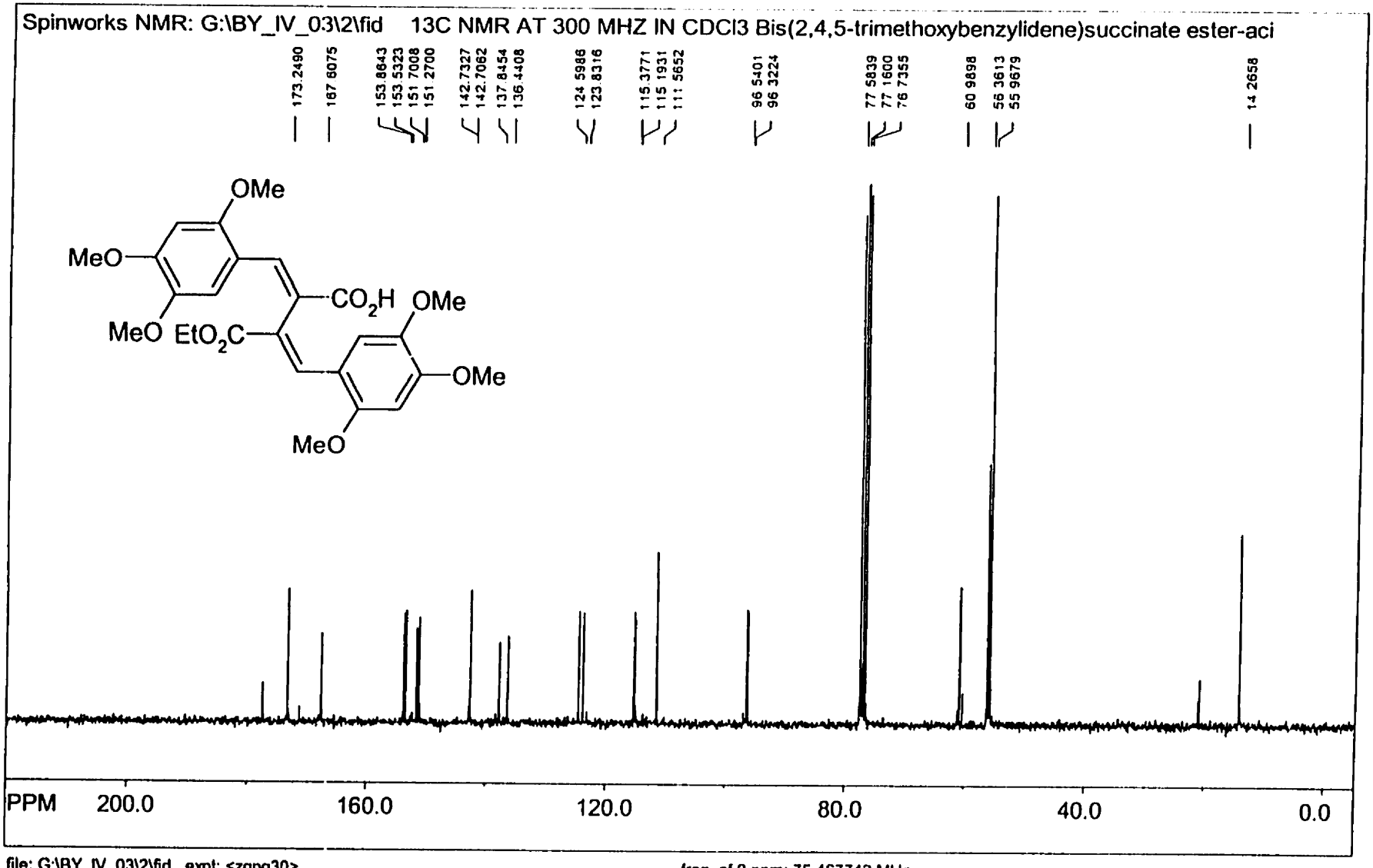
file: G:\BY_III_83\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 512

freq. of 0 ppm: 75.467745 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



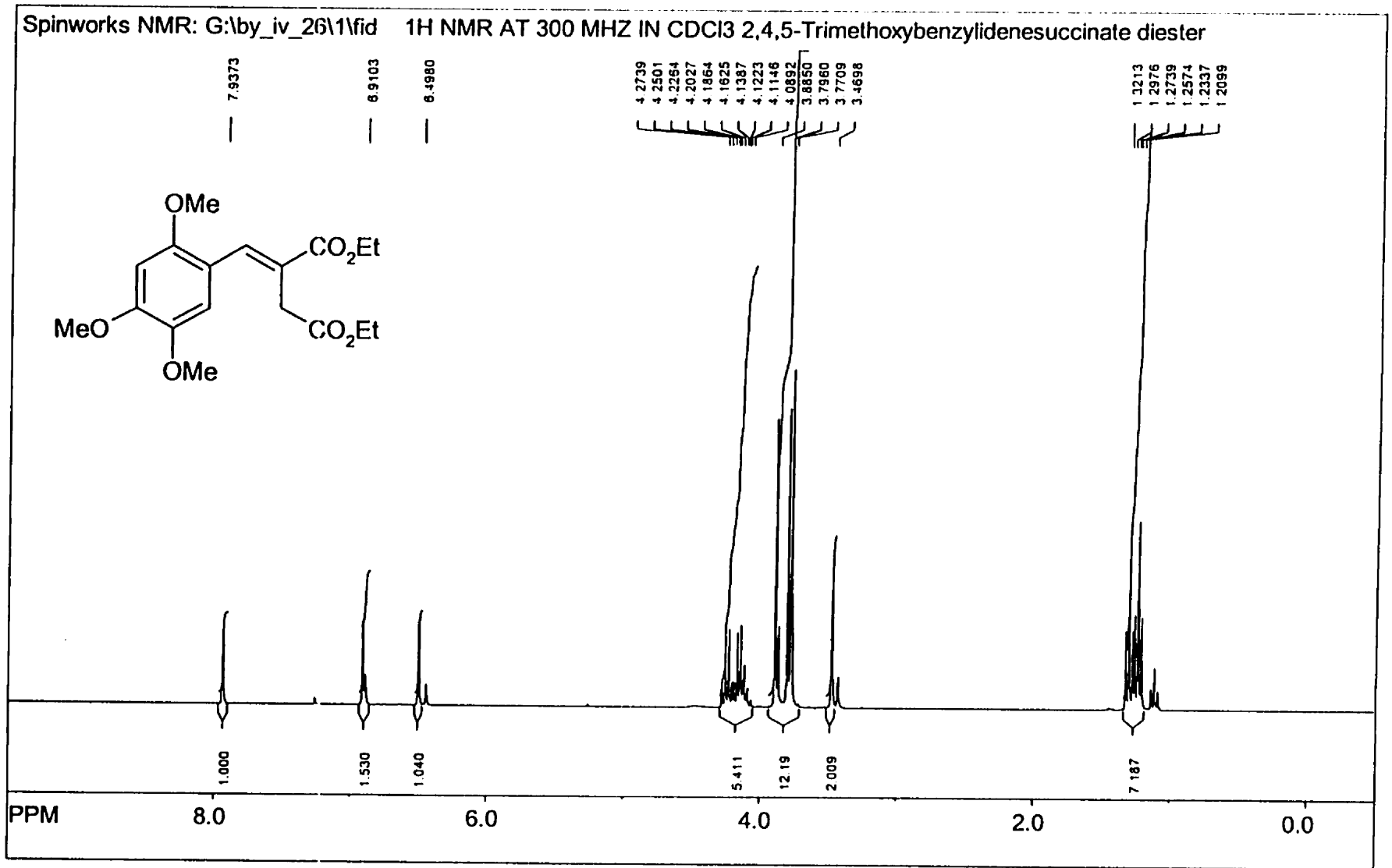
file: G:\BY_IV_03\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



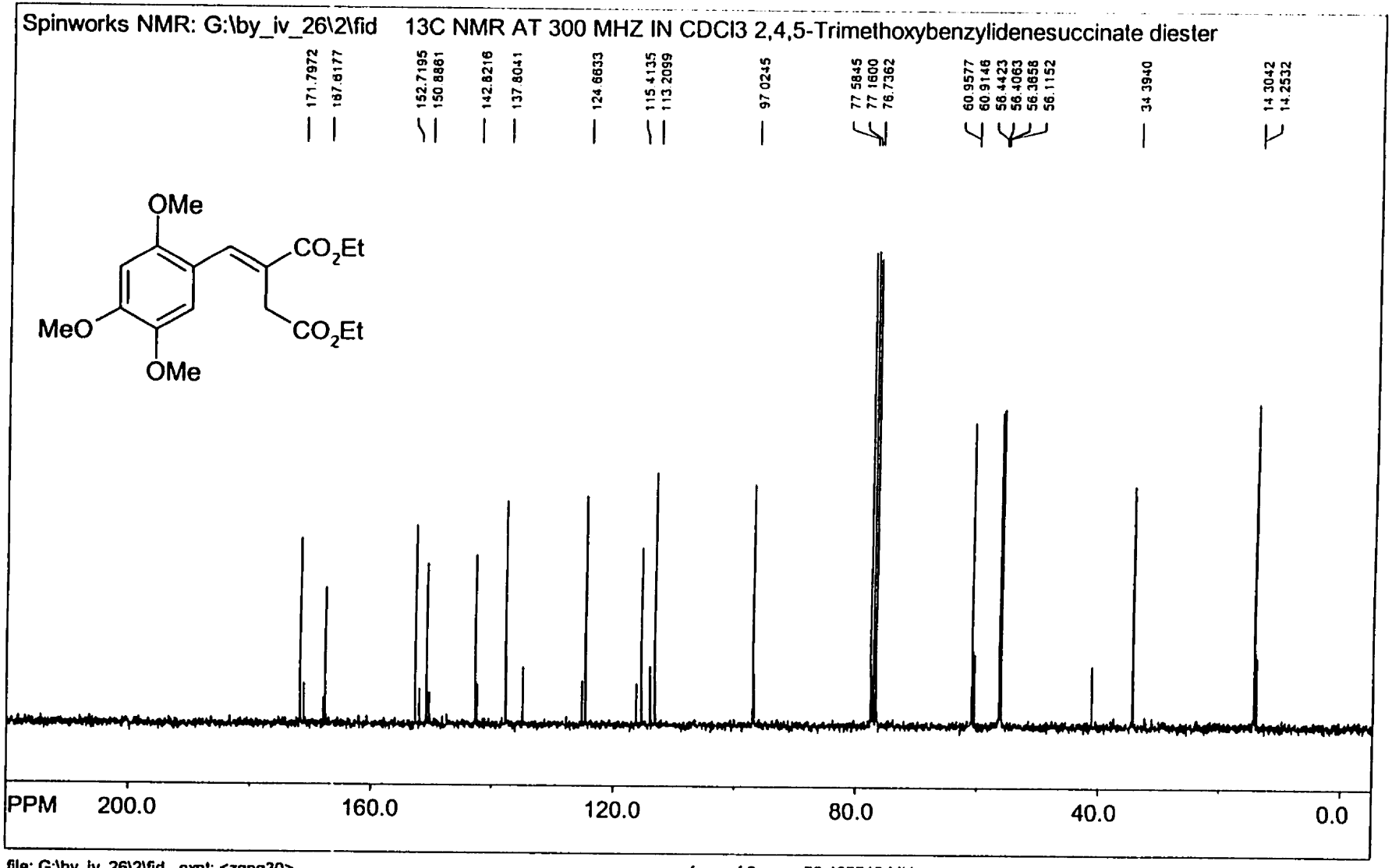
file: G:\BY_IV_03\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 1024

freq. of 0 ppm: 75.467742 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



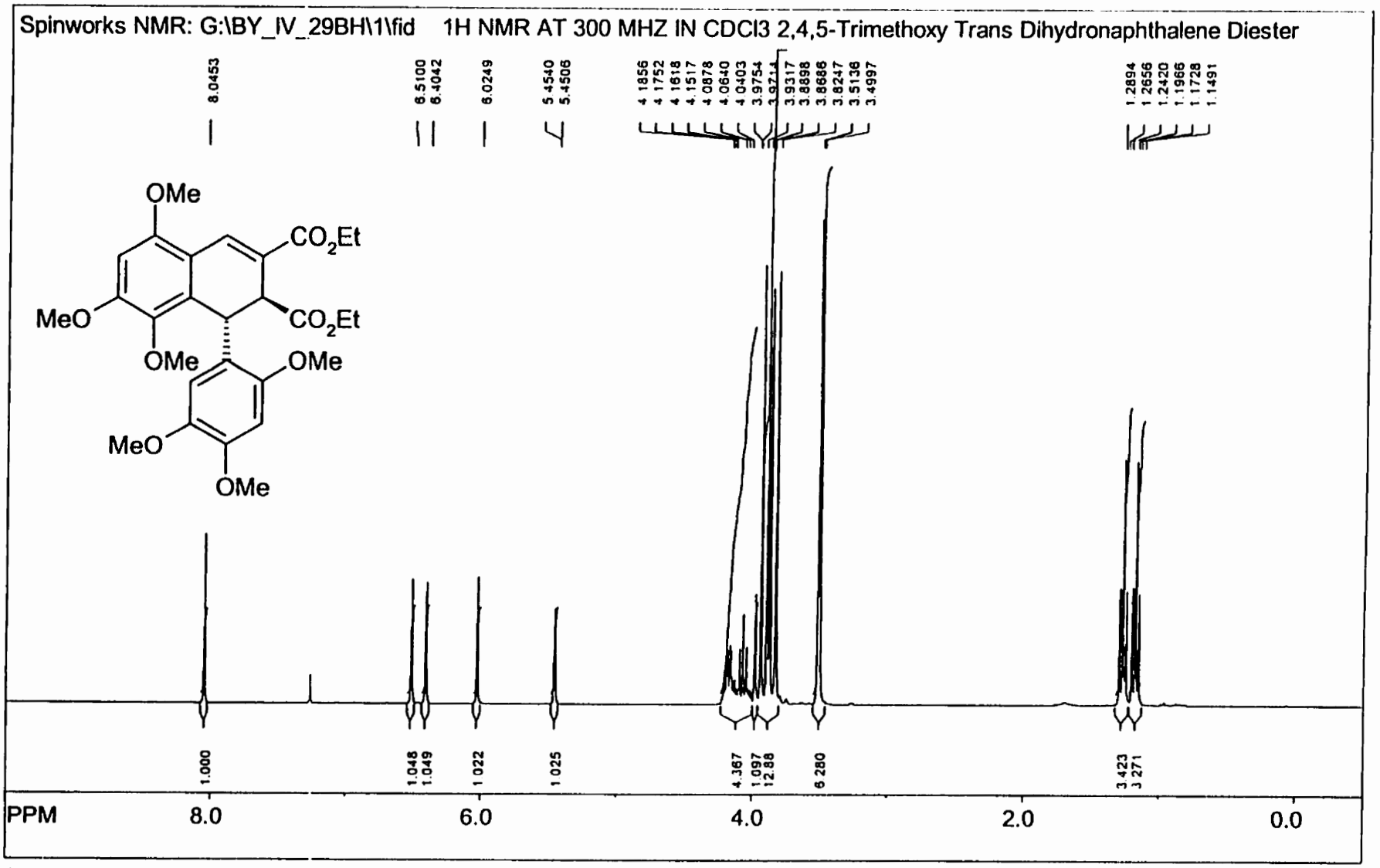
file: G:\by_iv_26\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0 094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130005 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



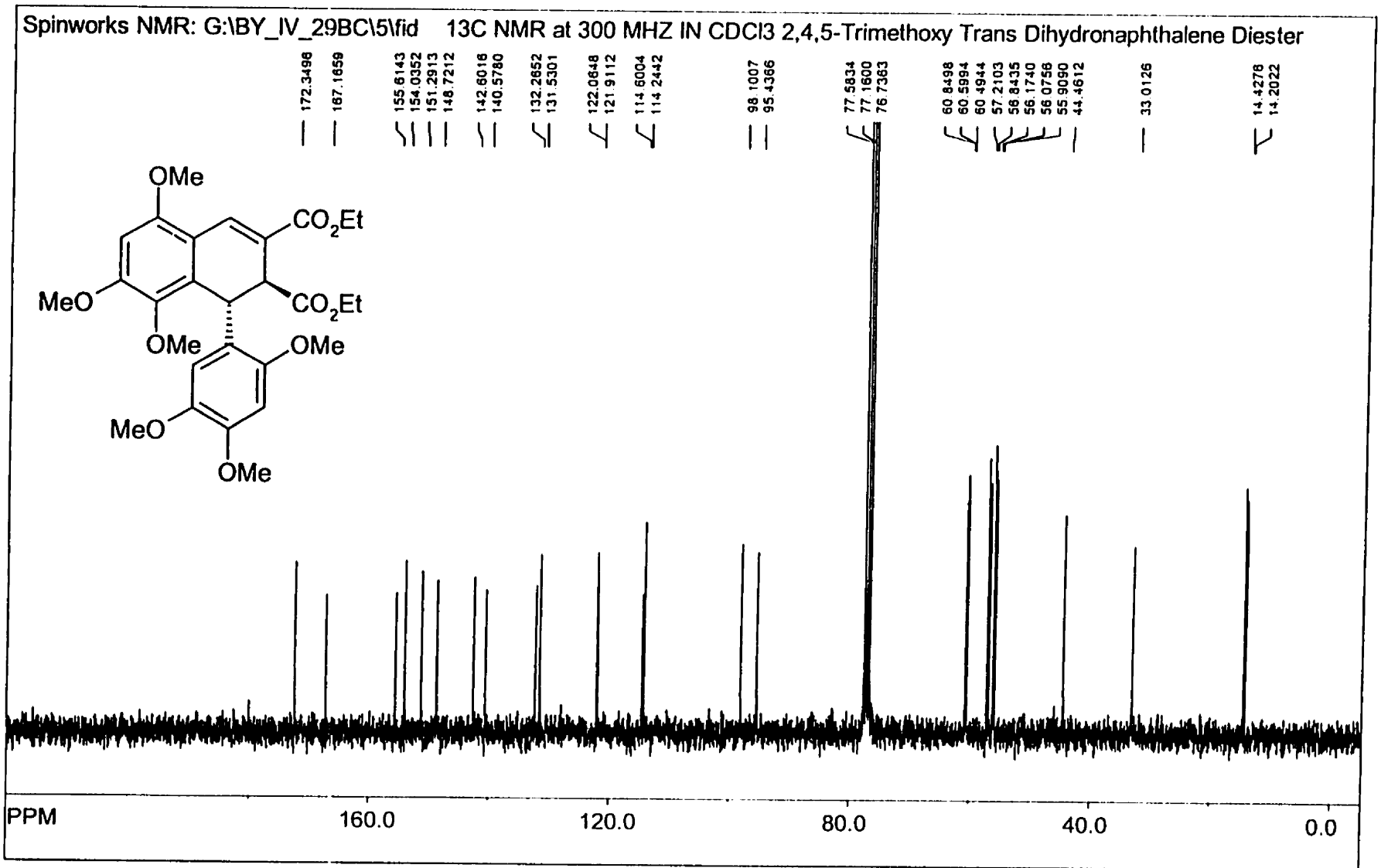
file: G:\by_iv_26\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 512

freq. of 0 ppm: 75.467742 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



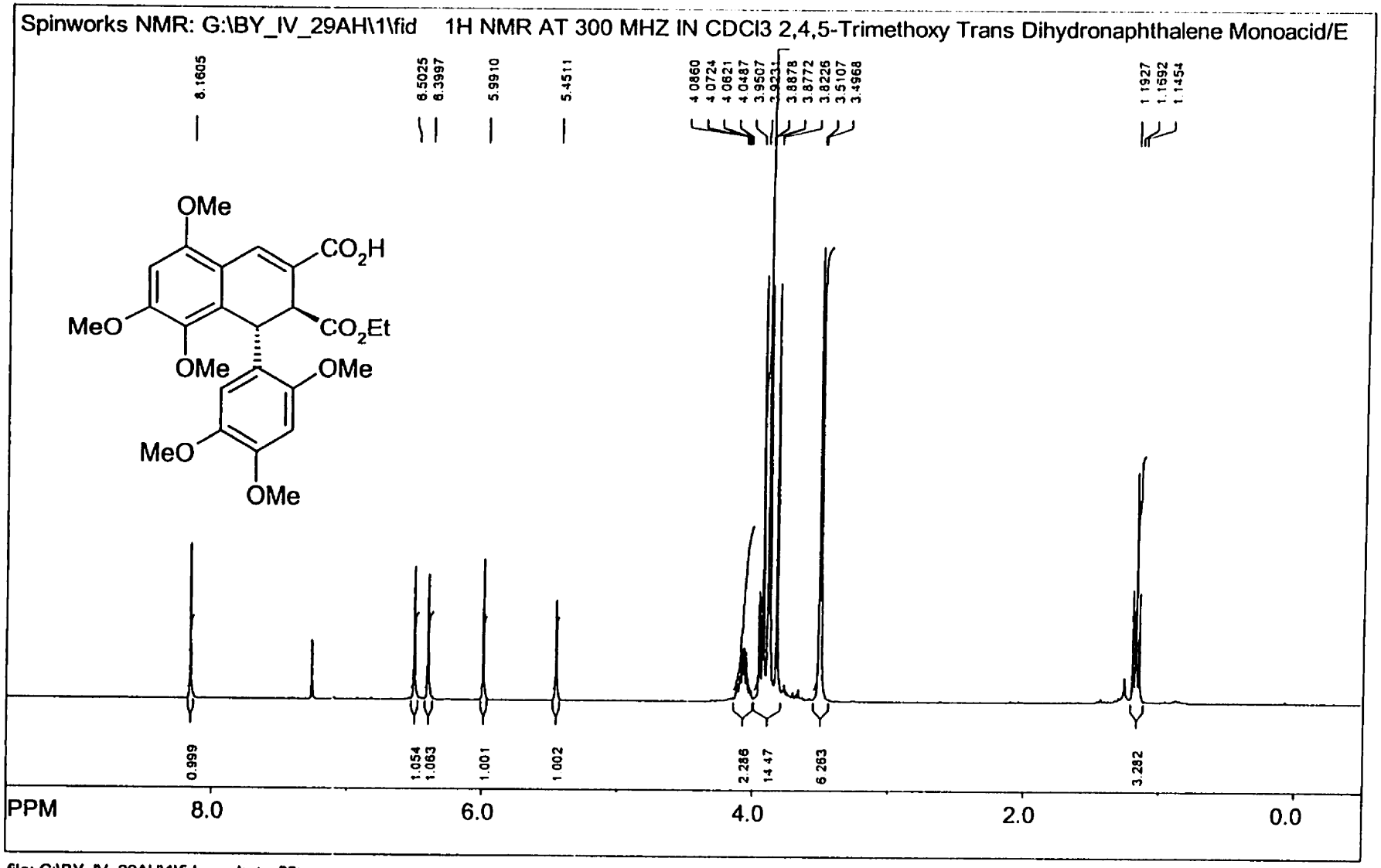
file: G:\BY_IV_29BH\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



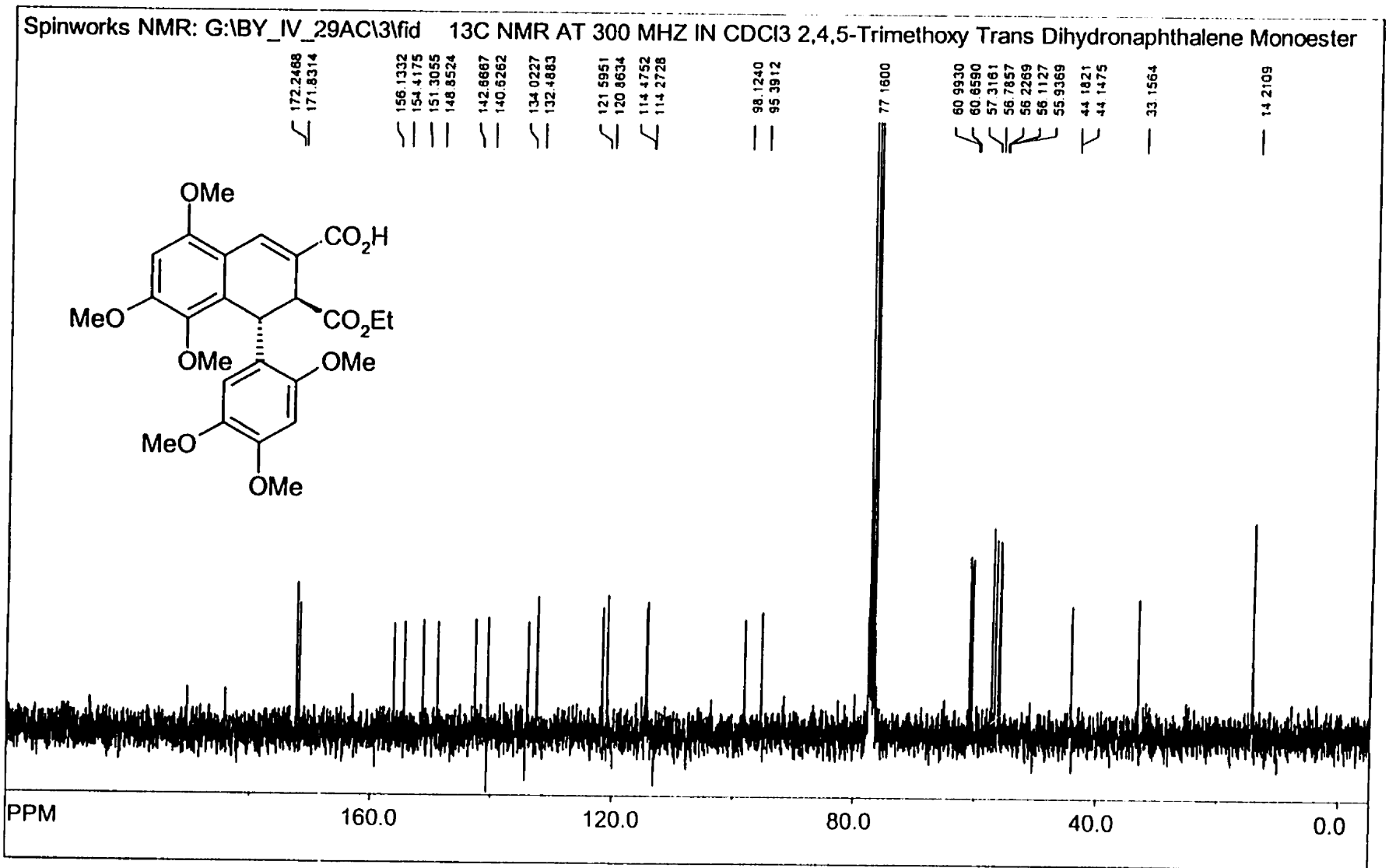
file: G:\BY_IV_29BC\5\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 512

freq. of 0 ppm: 75.467738 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



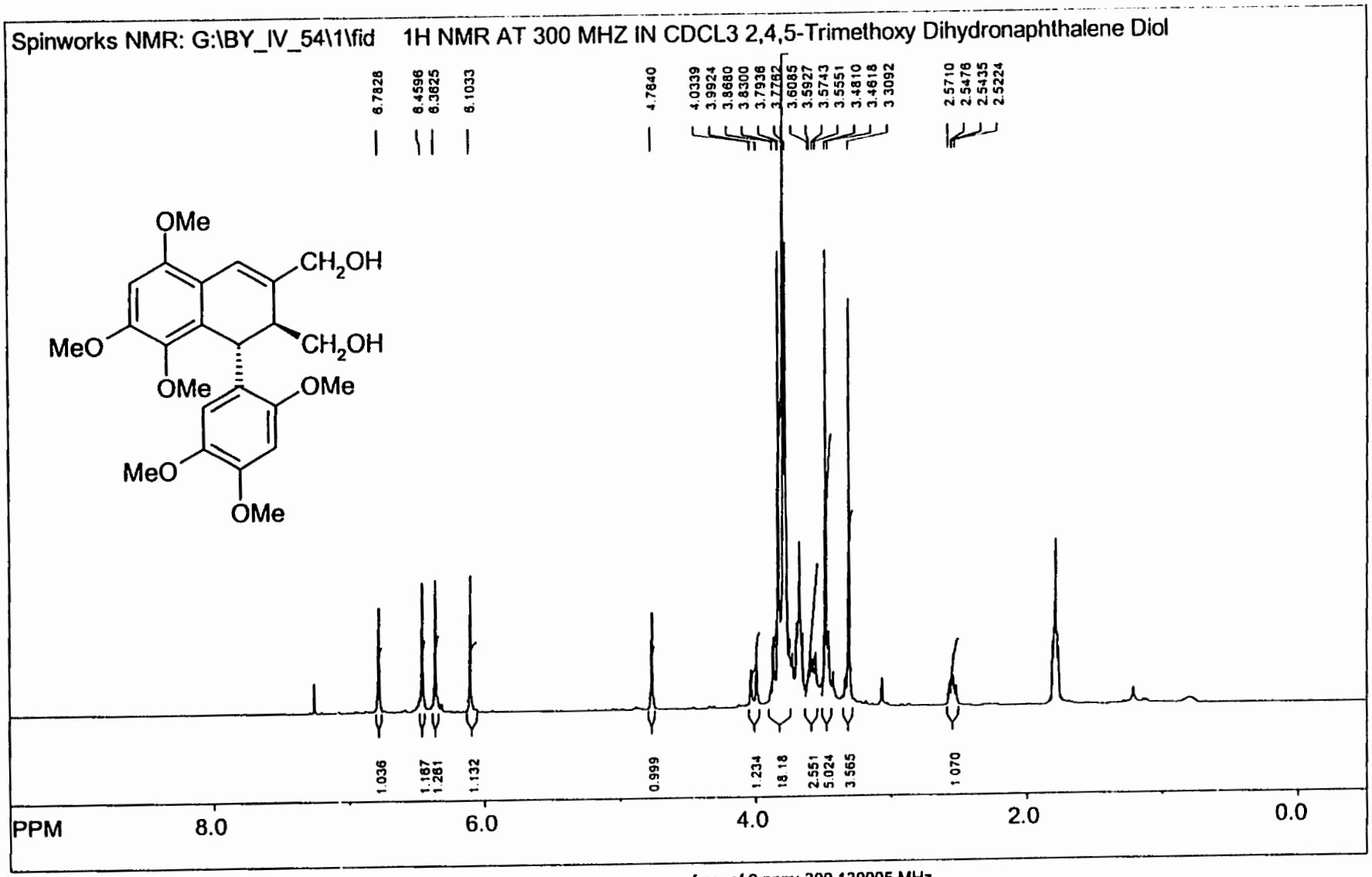
file: G:\BY_IV_29AH\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



file: G:\BY_IV_29AC\3\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.32 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 1024

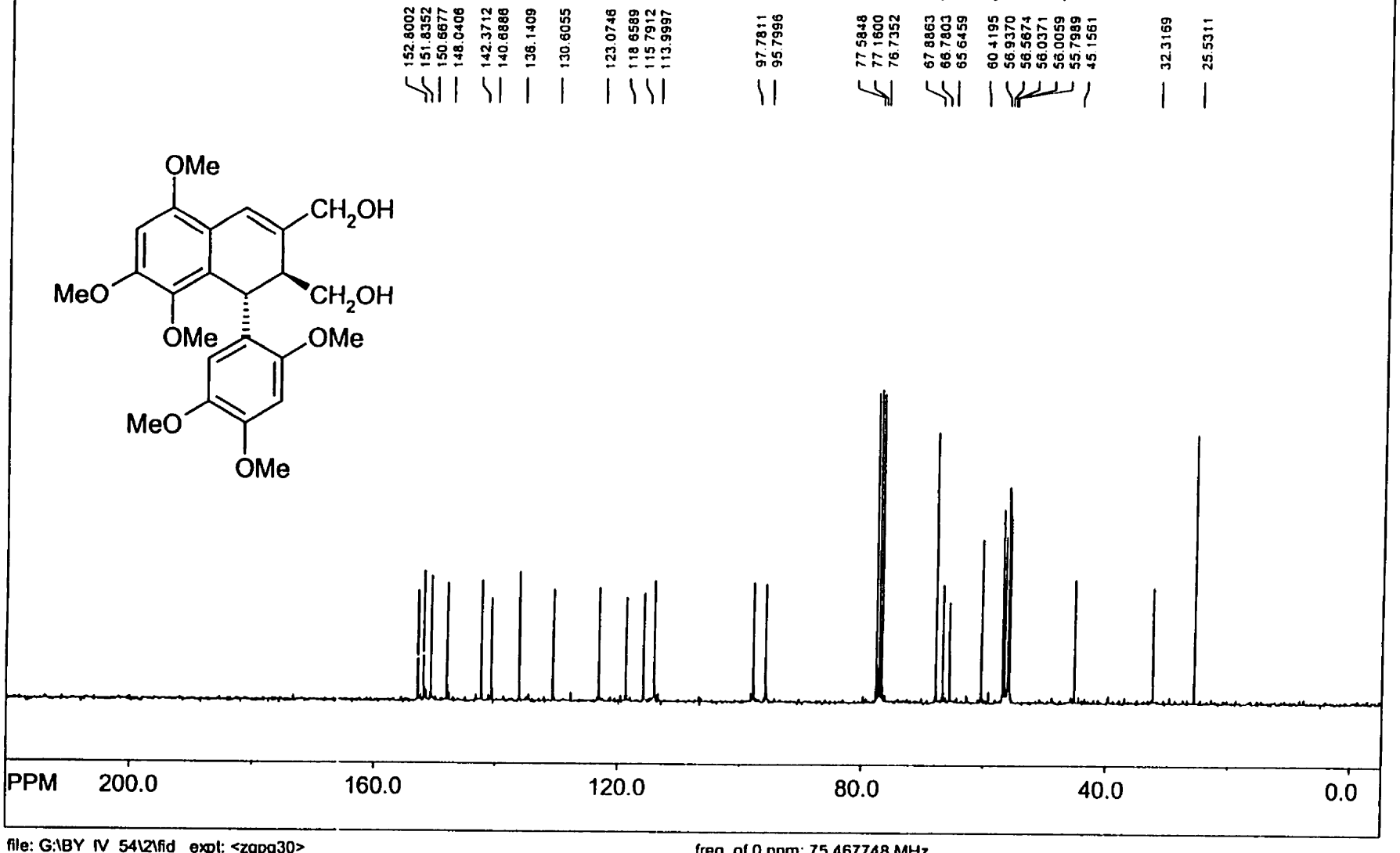
freq. of 0 ppm: 75.467736 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



file: G:\BY_IV_54\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

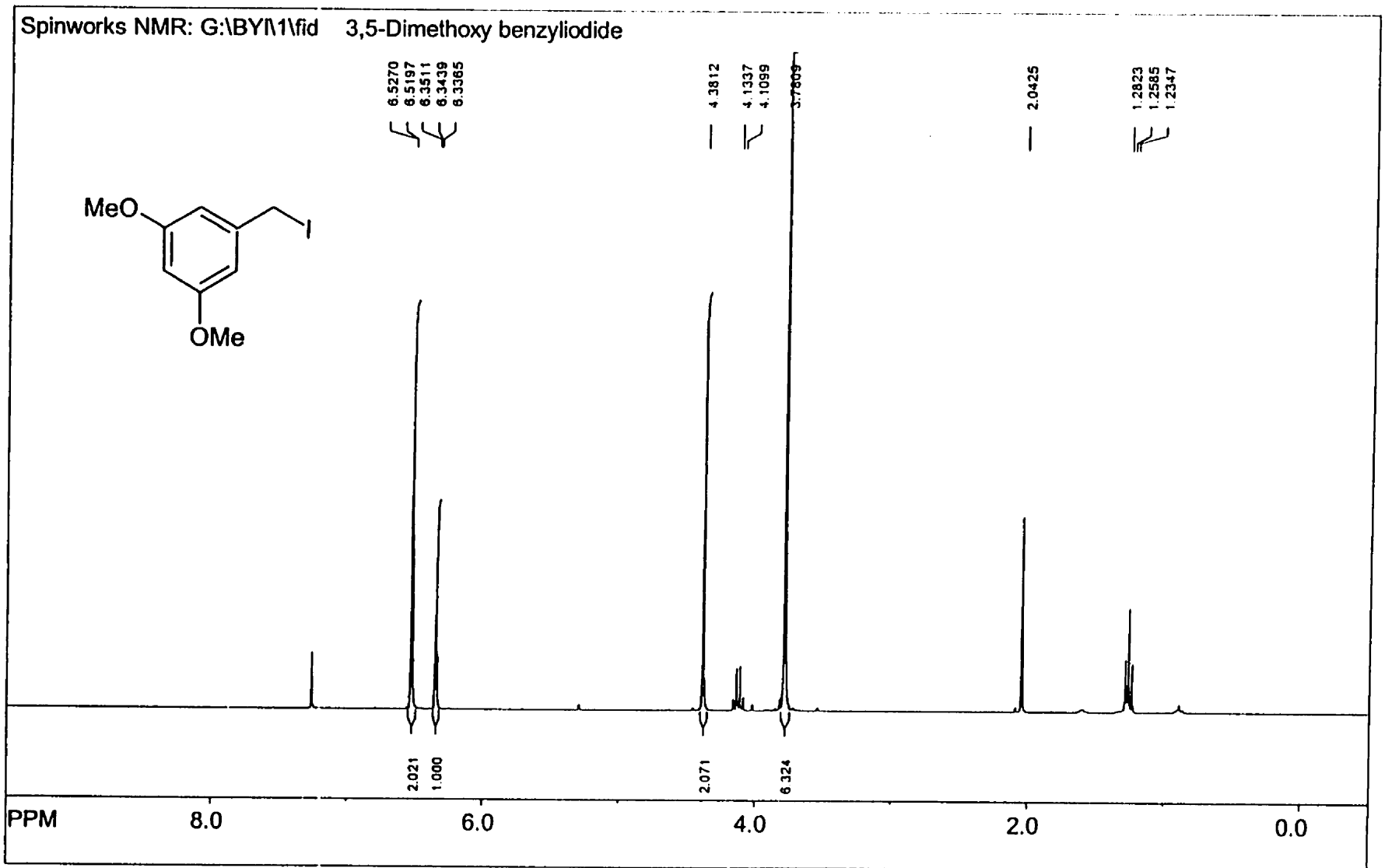
freq. of 0 ppm: 300.130005 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000

Spinworks NMR: G:\BY_IV_54\2\fid 13C NMR AT 300 MHZ IN CDCL3 2,4,5-Trimethoxy Dihydronaphthalene Diol



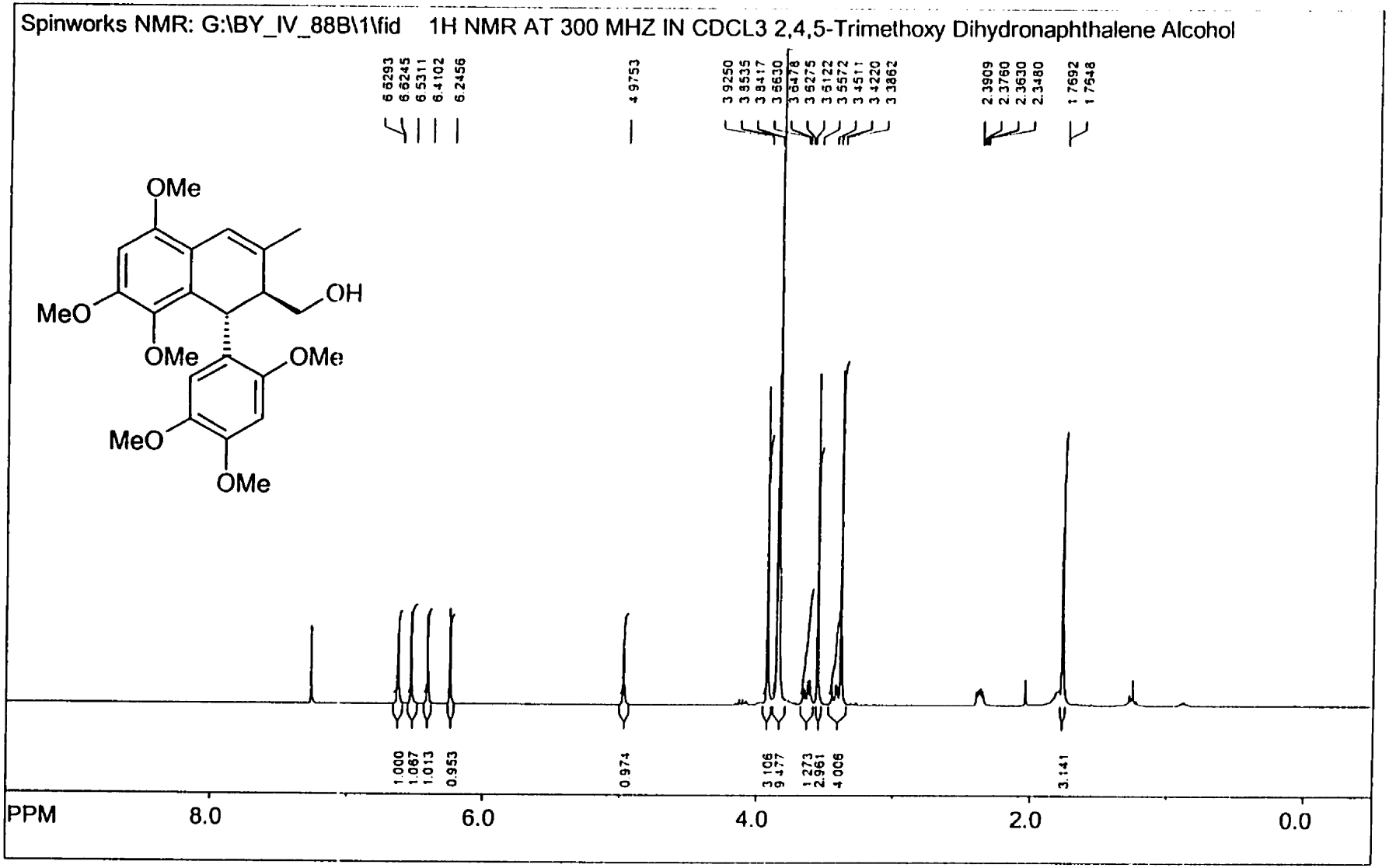
file: G:\BY_IV_54\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 1024

freq. of 0 ppm: 75.467748 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



file: G:\BYI\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

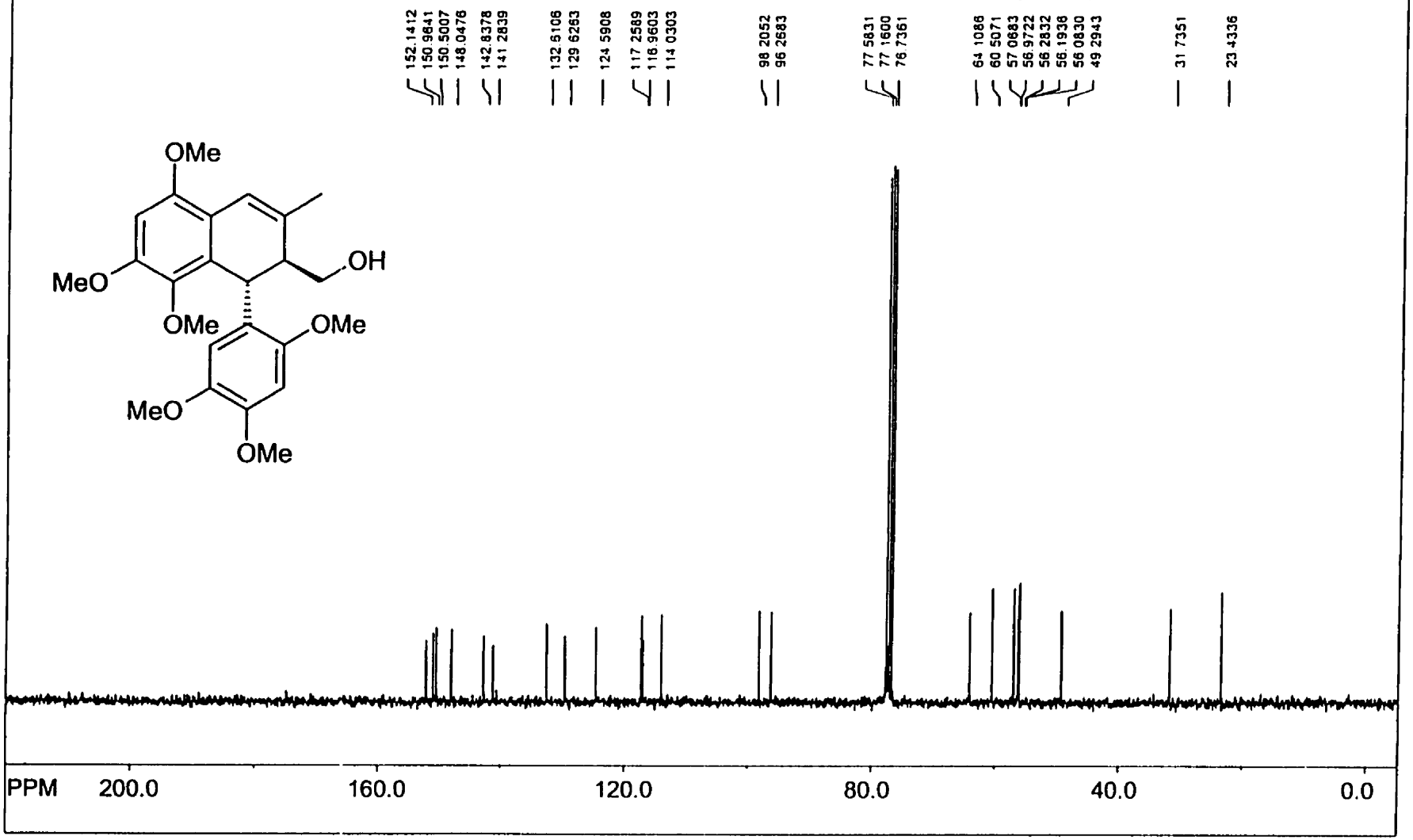
freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



file: G:\BY_IV_88B\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

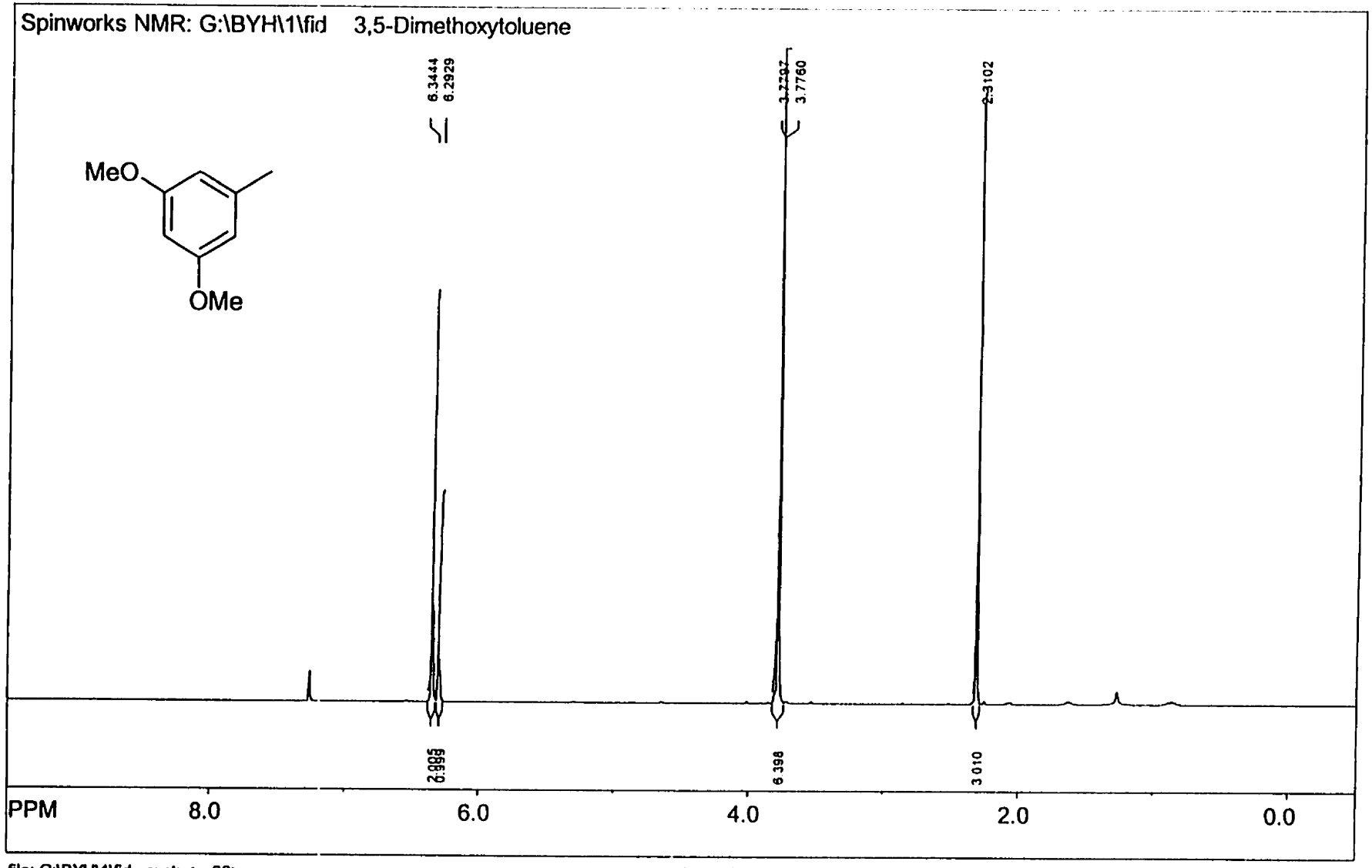
freq. of 0 ppm: 300.130005 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000

Spinworks NMR: G:\BY_IV_88B\2\fid 13C NMR AT 300 MHZ IN CDCL3 2,4,5-Trimethoxy Dihydronaphthalene Alcohol



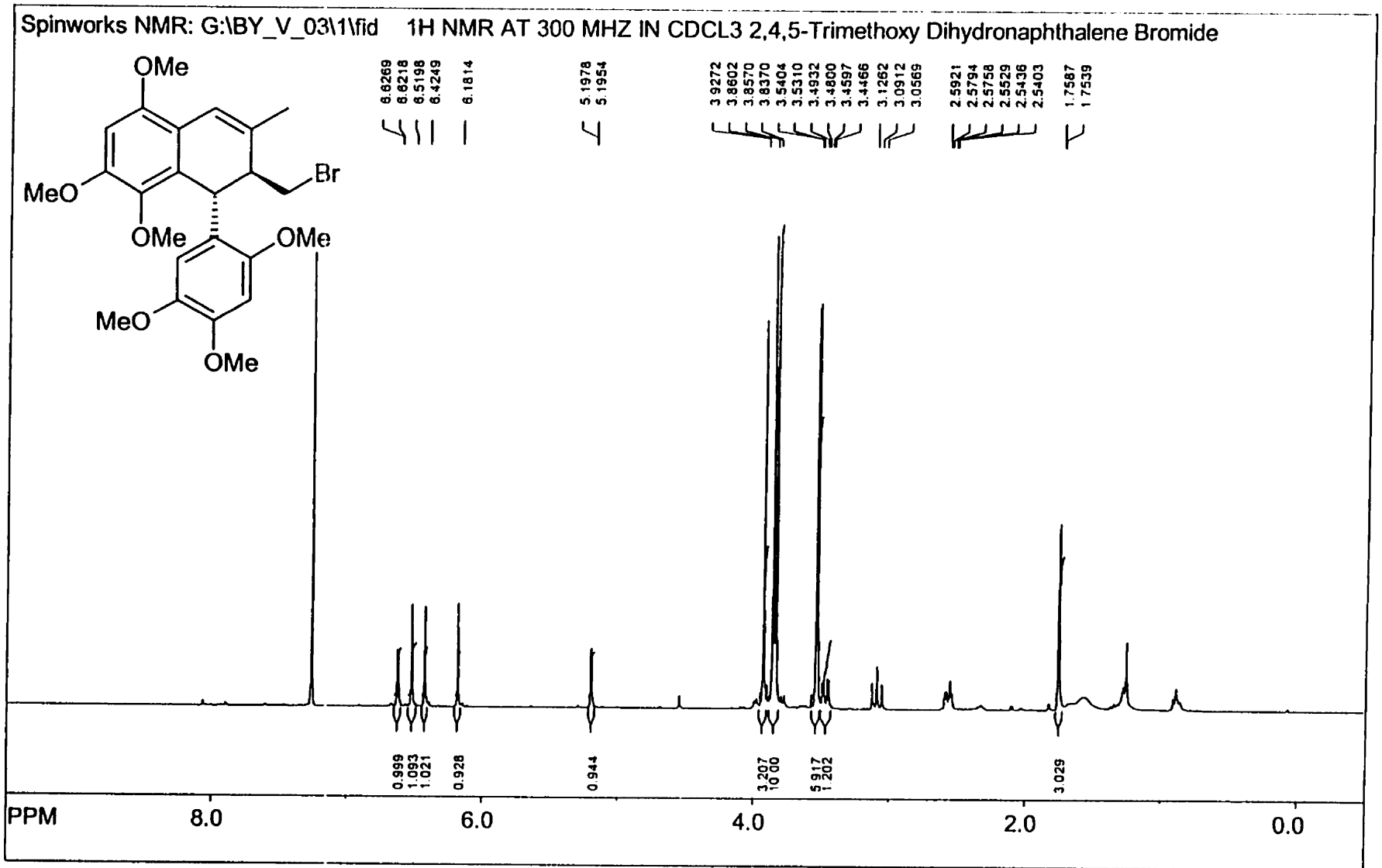
file: G:\BY_IV_88B\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 1024

freq. of 0 ppm: 75.467738 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



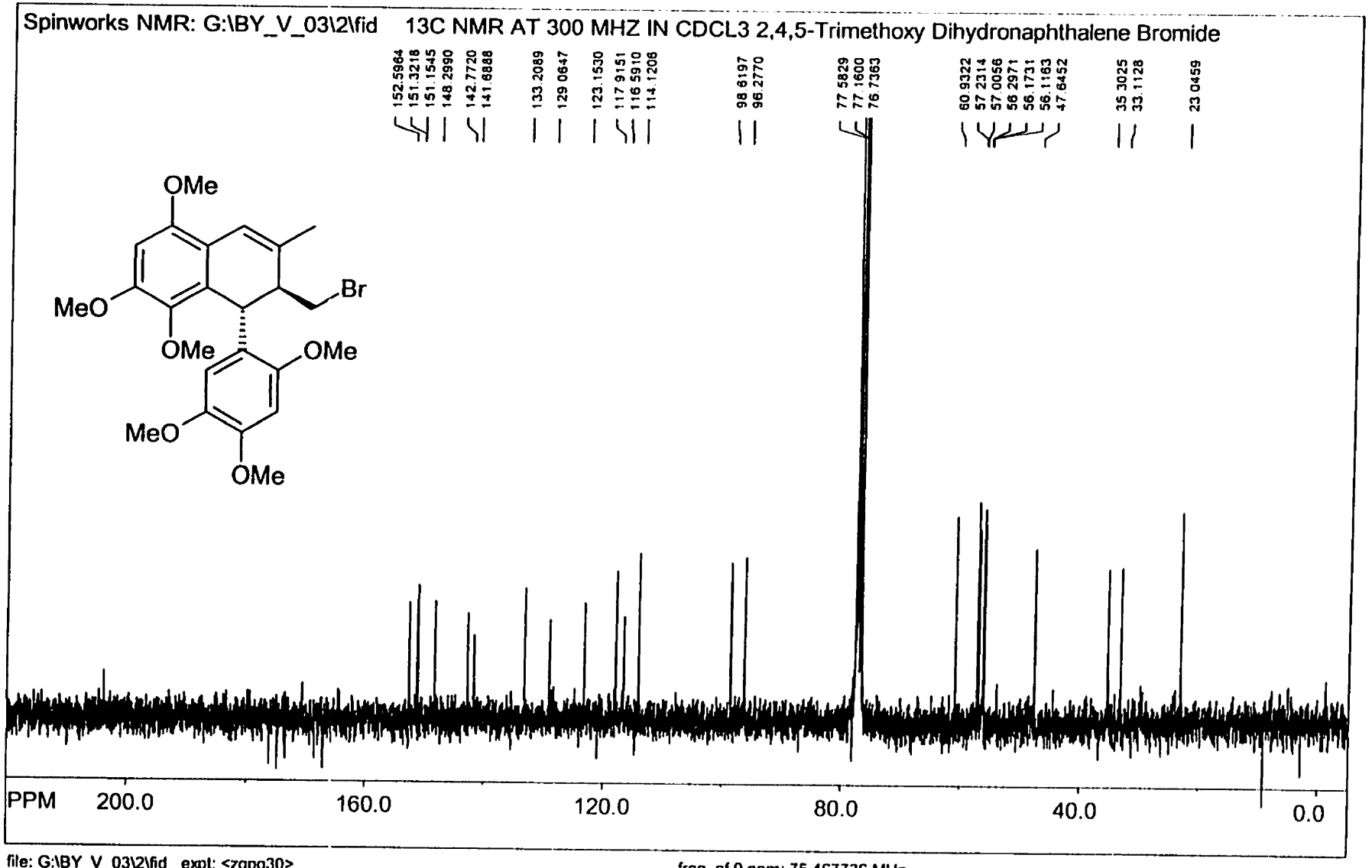
file: G:\BYH\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



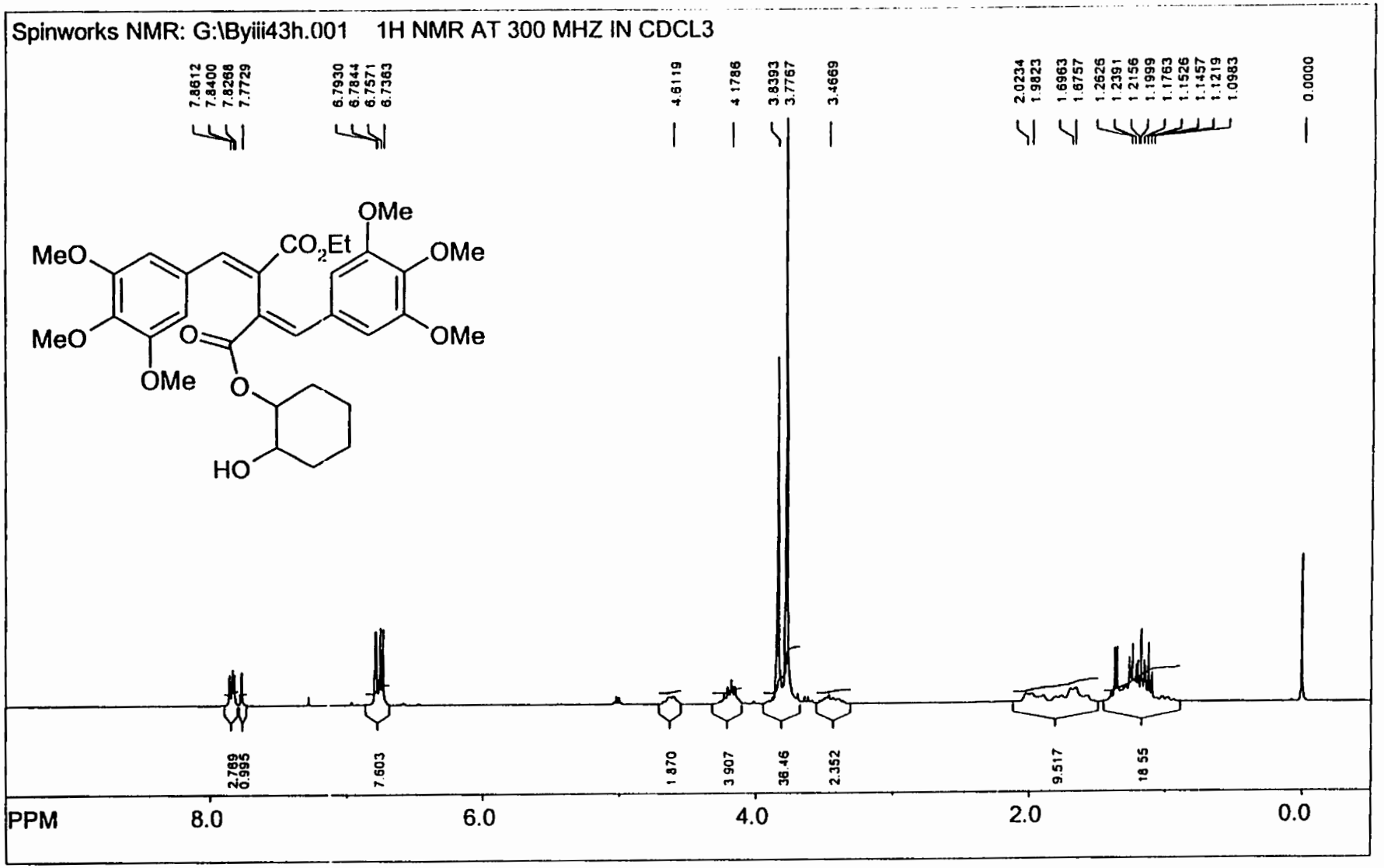
file: G:\BY_V_03\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



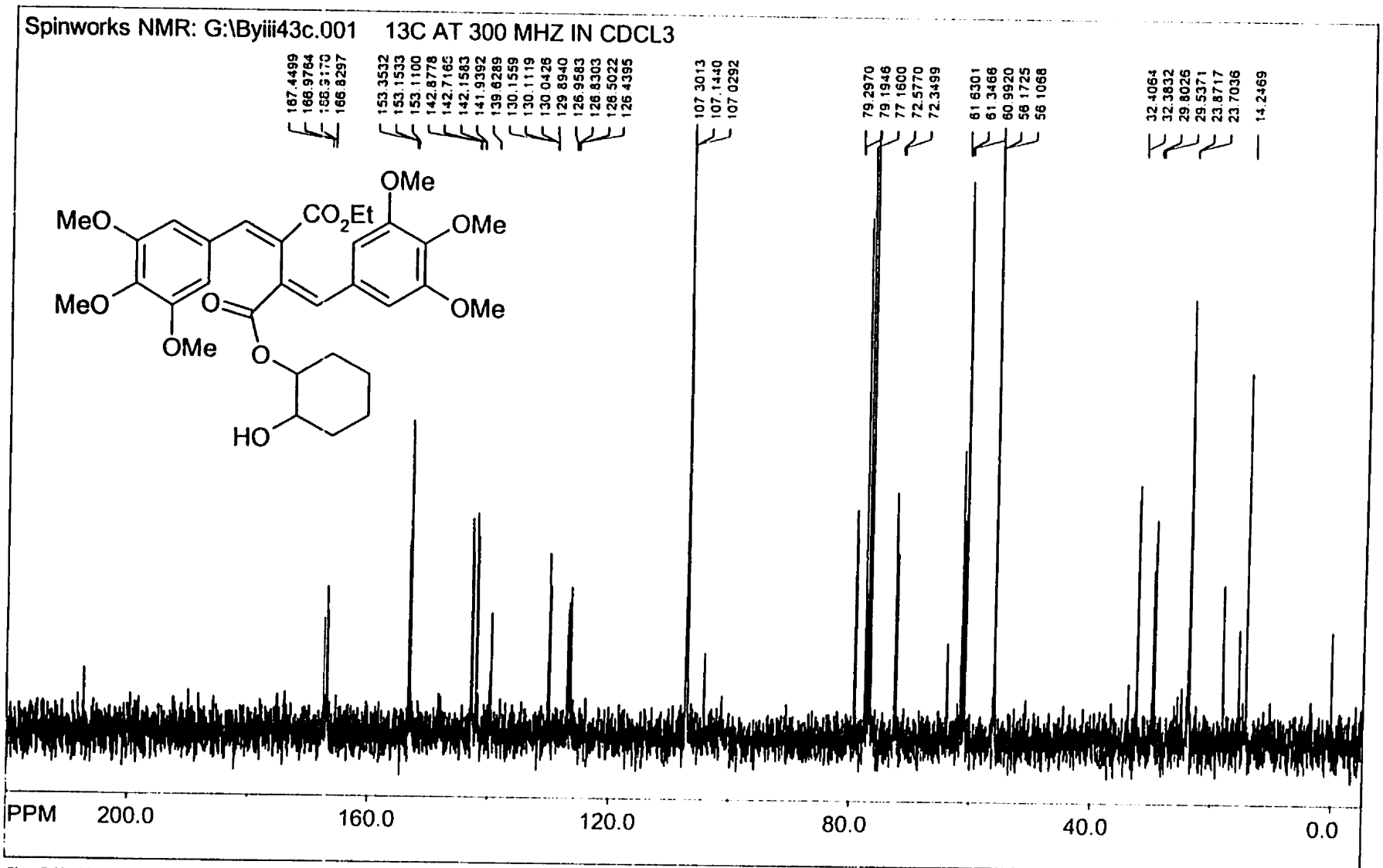
file: G:\BY_V_03\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.32 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 4096

freq. of 0 ppm: 75.467736 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



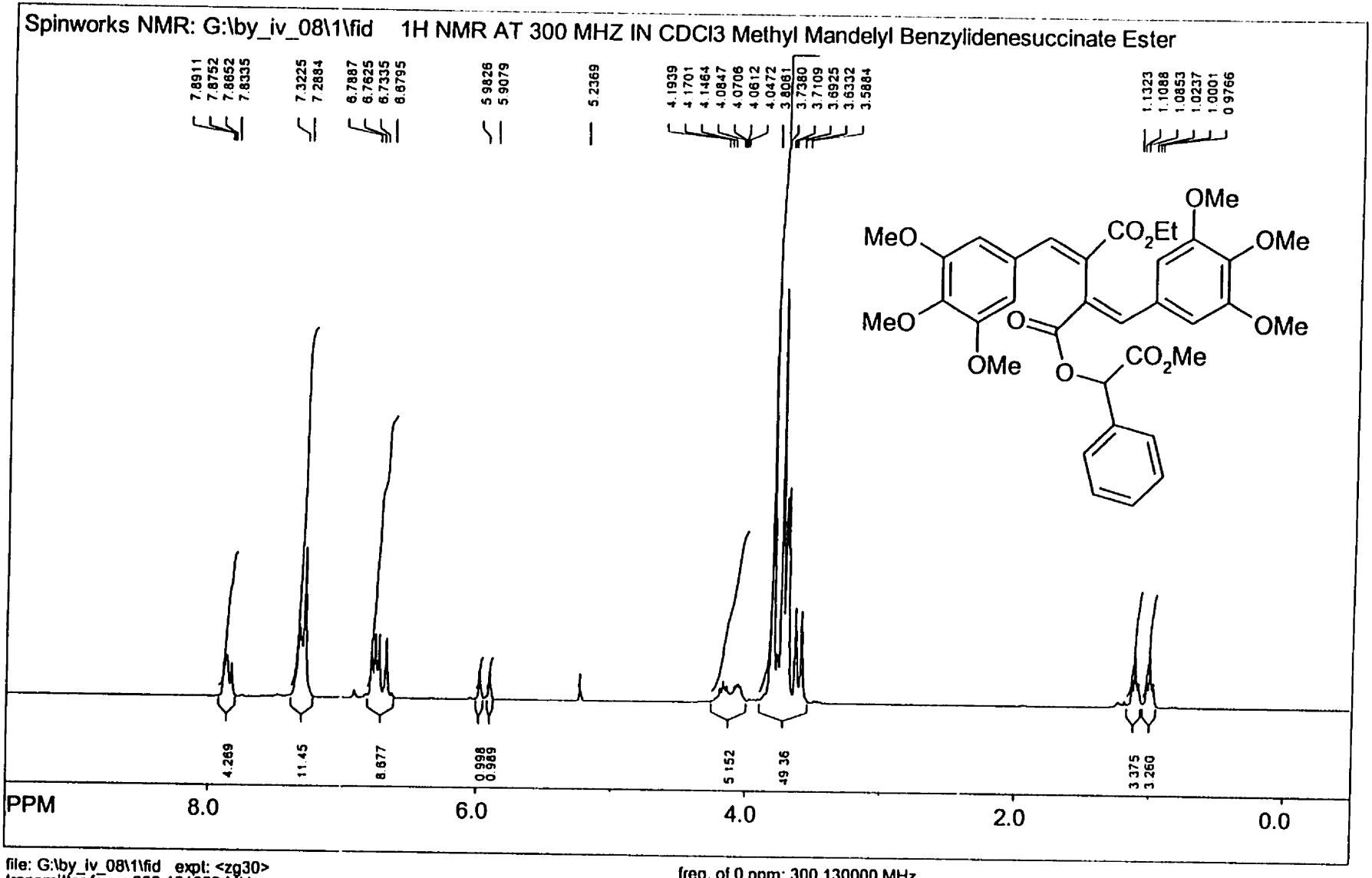
file: G:\Byiii43h.001 expt: H1AUTO
transmitter freq.: 300.135500 MHz
time domain size: 32768 points
width: 5494.51 Hz = 18.306880 ppm = 0.167679 Hz/pt
number of scans: 32

freq. of 0 ppm: 300.133362 MHz
processed size: 16384 real points
LB: 0.335 GB: 0.0000



file: G:\Byiii43c.001 expt: XAUTO
transmitter freq.: 75.477000 MHz
time domain size: 32768 points
width: 17857.14 Hz = 236.616880 ppm = 0.544957 Hz/pt
number of scans: 128

freq. of 0 ppm: 75.468586 MHz
processed size: 16384 real points
LB 1.090 GB: 0.0000



file: G:\by_iv_08\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130000 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000