Atropisomerism and The Synthesis of Lignans

by

Chi Yau

a thesis

submitted to the Faculty of Graduate Studies

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THE UNIVERSITY OF MANITOBA

FACULTY OF GRADUATE STUDIES

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ATROPISOMERISM AND THE SYNTHESIS OF LIGNANS

BY

CHI YAU

A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirement of the degree

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MASTER OF SCIENCE

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Table of Contents

Abbreviations

AcOH	acetic acid
Ar	aryl
t-Bu	*tert*-butyl
calcd.	calculated
d	doublet (spectral)
DCC	dicyclohexylcarbodiimide
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethyformamide
DMSO	dimethylsulfoxide
Et	ethyl
EtI	ethyliodide
EtOAc	ethyl acetate
EtOH	ethanol
FCC	flash column chromatography
hν	light
HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
J	coupling constant (in NMR)
k	kilo
LAH	lithium aluminum hydride
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
Bs	benzenesulfonate
o-QDM	*ortho*-quinodimethane
PFC	pyridiniumfluorochromate
ppm	parts per million
q	quartet
rt	room temperature
s	singlet (spectral)
S_N2	bimolecular nucleophilic substitution
t	triplet (spectral)
TBTU	Benzotriazol-1-y-1,1,3,3-tetramethyl uronium tetrafluoroborate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	triflic acid
THF	tetrahydrofuran

TLC	thin layer chromatography
TsOH	p-toluenesulfonic acid
UV	ultraviolet
vis	visible

Abstract

A new synthetic methodology was developed to synthesize two chosen lignans, galbulin and cagayanin, with the intent of applying this synthetic scheme for the synthesis of structurally similar lignans. The Stobbe condensation was ideally suited for generating the starting materials for constructing the aryltetralin skeleton. Two successive Stobbe condensations were executed to generate the starting dibenzylidenesuccinates. It was discovered that triflic acid-catalyzed cyclization of these dibenzylidenesuccinates produced the desired aryltetralin lignan structures in good yields. From these aryltetralin skeletons, functional interconversions were performed ultimately to generate the two target natural lignans, galbulin and cagayanin.

The dibenzylidenesuccinates, upon treatment with acid, demonstrated some intriguing chemistry. In an attempt to further understand this cyclization step, several other dibenzylidenesuccinates with different substituent patterns were synthesized. These reactions were studied in detail to investigate the effect of the substituent patterns on the outcome of the reaction. Two plausible explanations and detailed mechanisms were postulated to account for the formation of the aryltetralins with literature evidence to support these theories.

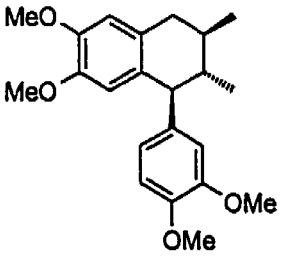
It was also preferable that the new methodology could be utilized for the synthesis of enantiomerically pure natural lignans. This might be achieved by separating the dibenzylidenesuccinates into their corresponding atropisomers. These conformational isomers, or rotamers, arise from hindered rotation about the carbon-carbon single bond. Conventional separation proved to be difficult, as the barrier to rotation about this single bond was too small. However, methods for coercing the dibenzylidenesuccinate to adopt

one atropisomer over the other were studied and the preliminary results are presented. The intent was to force the molecule to adopt one conformation by introducing a chiral auxiliary. From this point the new synthetic methodology could be applied to the preparation of enantiomerically enriched dibenzylidenesuccinates and eventually enantiomerically enriched natural lignans.

Chapter 1

Introduction

This thesis is focused on research into the development of a new synthetic methodology for generating lignans, natural products isolated from plants. This project was undertaken in an attempt to broaden the synthetic scope of laboratory methods leading to lignans of interest. Lignans have been challenging targets for synthetic organic chemists due to their varied structures. Their synthesis is also interesting since they are prime candidates for human therapeutics possessing antifungal, antibacterial, antiviral, and anticancer activities.[1-4,6a] The introduction will give a brief review of lignans, lignan biological activity and lignan synthesis, followed by a discussion of the proposed new synthetic methodology planned for the two natural lignans, galbulin (1) and cagayanin (2). The previous syntheses of these compounds will also be reviewed.



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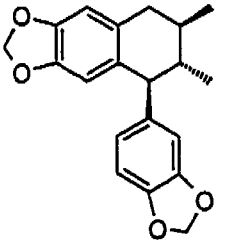


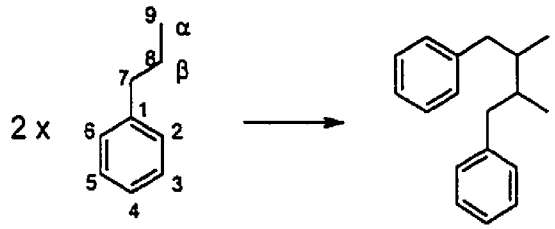
2

Scheme 1

1.1 Lignans

Lignans have been used for medicinal purposes dating back to 1000 A.D. Natives of China, Japan and America used lignan-rich plants to treat cancer, arthritis, ulcers and pain. Haworth introduced the term 'lignan' in 1936 to describe a group of optically active extracts isolated from plant material.[5] These extracts contained dimeric

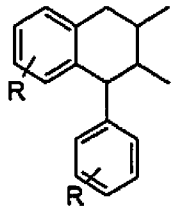
compounds consisting of two phenylpropanoid units linked β-β` (8-8`) through the central carbons of their propane sidechains as represented in Scheme 2.[5]



Scheme 2

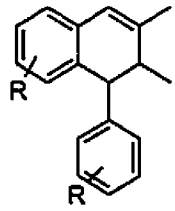
Gottlieb extended the lignan family to include 'neolignans'[7-9], compounds created from the coupling of phenylpropanoid units via oxidative formation of a carbon oxygen bond. Normal lignans are formed from the β-β` (8-8`) oxidative coupling of cinnamyl phenols and their related compounds. The lignan family consists of 6 subclasses, compared to 15 subclasses in the neolignan family. The neolignan family is a diverse group that will not be discussed here. This thesis will instead concentrate on the lignan family.

Different subclasses of lignans were described to coincide with the discovery and characterization of new lignans that were isolated. The lignan subclasses that relate to this thesis are the aryltetralins **3**, aryldihydronaphthalenes **4**, and arylnaphthalenes **5**. Other common subclasses include dibenzylbutyrolactones **6**, dibenzylbutanes **7** and dibenzocyclooctadienes **8** (Scheme 3).



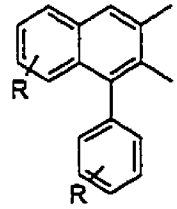
Aryltetralin

3



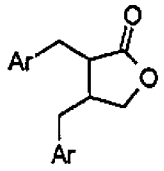
Aryldihydronaphthalene

4



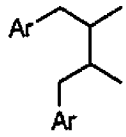
Arylnaphthalene

5



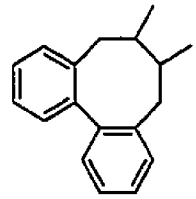
Dibenzylbutyrolactone

6



Dibenzylbutane

7



Dibenzocyclooctadiene

8

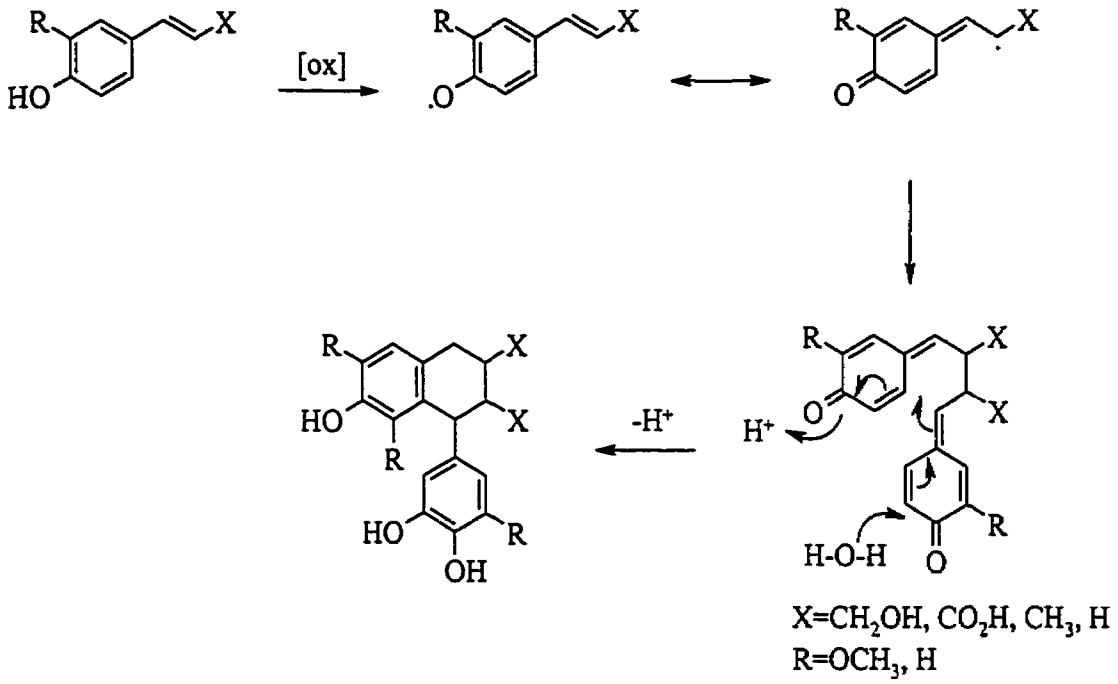
Scheme 3

The distinguishing features of the first three subclasses **3-5** above are the cyclic skeleton, varying degrees of saturation, and complex terminal groups with different oxidation levels. The substitution on the aromatic rings varies from one lignan to the next, however, no naturally occurring lignan has ever been found with an unsubstituted aryl group.[6a]

1.1.1 Plant Lignans

Lignans are found in a wide variety of plants worldwide. The bark, root, flower and seed components of plants have all yielded lignans. Biosynthetically, lignans are synthesized in plants, in part, via the shikimate pathway. This is a major metabolic pathway for the construction of many aromatic compounds.[6b] The biosynthesis of lignans in plants is hypothesized to occur by a peroxidase enzyme-catalyzed free radical

dimerization of phenylpropanoids.[4] A representative example of the oxidative couplings of two cinnamic residues is shown below (Scheme 4).[5]

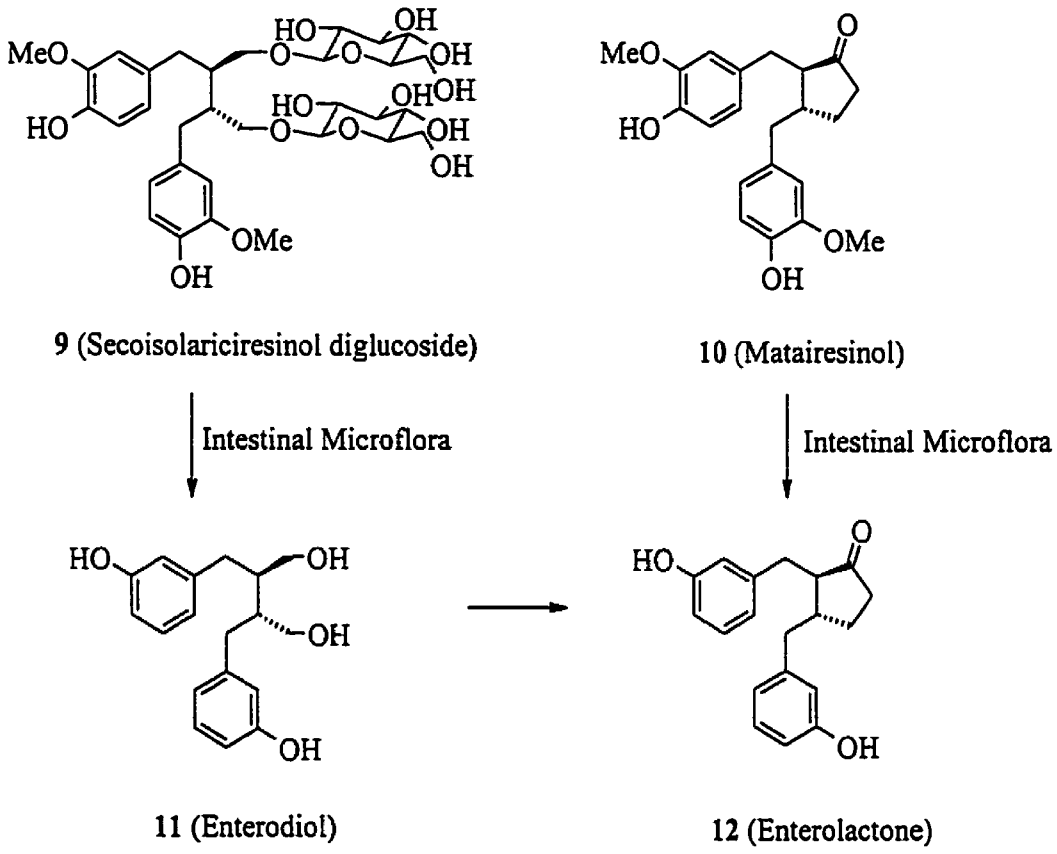


Scheme 4

1.1.2 Mammalian Lignans

It is interesting to note that the literature makes use of the term 'mammalian lignans'.[6a] All lignans are plant compounds. It is a misnomer to use the term 'mammalian lignans' as there is no evidence to support a mammalian synthesis of these compounds. Enterodiol **11** and enterolactone **12** are two lignans that have been isolated from humans and other animals.[6c] However, it is believed that these lignans are the by-products of the intestinal microflora since the mammalian body lacks the molecular machinery to synthesize such compounds. The dietary precursors to enterodiol and enterolactone are believed to be seco-isolariciresinol **9** and matairesinol **10**, respectively (Scheme 5). These two compounds have been implicated as anticancer agents. It was

found that people consuming a high vegetarian diet rich in soybean and flaxseed had lower incidences of hormone-dependent cancers such as breast and prostate cancer.[21]



9 (Secoisolariciresinol diglucoside)

10 (Matairesinol)

11 (Enterodiol)

12 (Enterolactone)

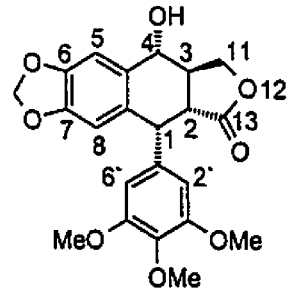
Scheme 5

1.2 Biological Activities of Lignans

The discovery that lignans possess a variety of biological activities stimulated pharmaceutical and academic research in the field of lignan studies and syntheses. The diversity of lignan biological activity has intrigued chemists for the past 60 years. Although the mechanisms of action of many classes of lignans are not yet well understood, there is a consensus on the mechanisms of action of the *podophyllum* lignans and their derivatives. The effects that these lignans have on the human body will be discussed in detail, as it is illustrative of the importance that lignans can have in treating

human diseases. It also makes apparent the value of new synthetic methods for the synthesis of lignans, such as the proposed new methodology described in this thesis. Galbulin **1** and cagayanin **2**, the synthetic targets for this thesis, have structures very similar to podophyllotoxin **13**.

1.2.1 *Podophyllum* Lignans as Antineoplastics



13

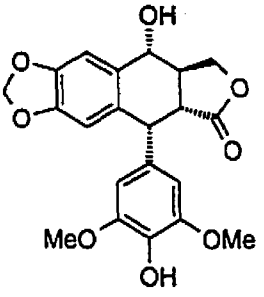
Scheme 6

The discovery that lignans possessed numerous biological activities urged several research groups to study *Podophyllum* lignans and their anticancer properties.[2,3] The alcoholic extracts of the roots and rhizomes of *Podophyllum* were used in folk medicine by American Indians to topically treat venomous snakebites. It is known today that the active ingredient in that extract was podophyllotoxin. Podophyllotoxin (**13**) was first isolated from the May apple or American mandrake (*Podophyllum peltatum*), a member of the *Berberidaceae* family.[6a] Podophyllin was the alcoholic extract of the roots and rhizomes. It was used in America between 1820 and 1942 as a cathartic and cholagogue agent, a result of its severe gastrointestinal toxicity.

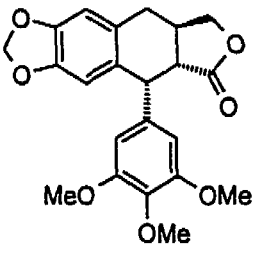
The mechanism of action of podophyllotoxin has been well documented.[2,3,6a] It disrupts the equilibrium between assembled and disassembled microtubules, a cellular

microstructure that forms the foundation of the cellular cytoskeleton. Microtubules are tubular polymers, chains constructed from repeating protomers. A single protomer is a heterodimer of α- and β-tubulin. Podophyllotoxin binds to tubulin effectively disrupting the equilibrium between microtubules and tubulin. The result is destruction of the cytoskeleton and the required spindle needed for cell division, or mitosis. Therefore, the cell is arrested at the last stages of mitosis and is unable to divide its cell wall. Eventually the destruction of the cytoskeleton leads to cell death.

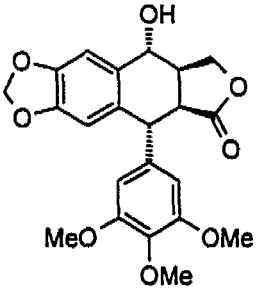
Many other podophyllotoxin analogues were synthesized and structure-activity relationships studied on the binding to tubulin.[2] It was found that some analogues possessed comparable activities whereas others did not possess the activity of podophyllotoxin.



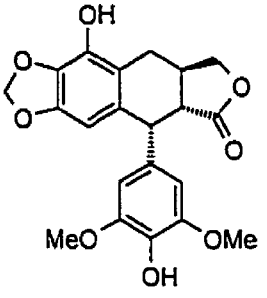
14 (4'-Demethylpodophyllotoxin)



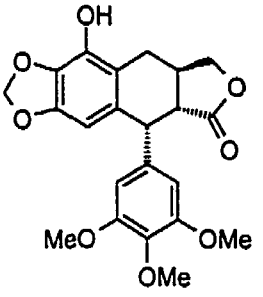
15 (Deoxypodophyllotoxin)



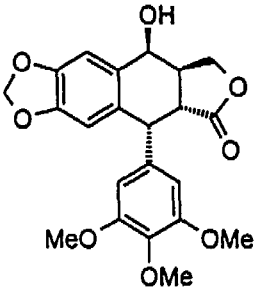
16 (Picropodophyllotoxin)



17 (α-Peltatin)



18 (β-Peltatin)



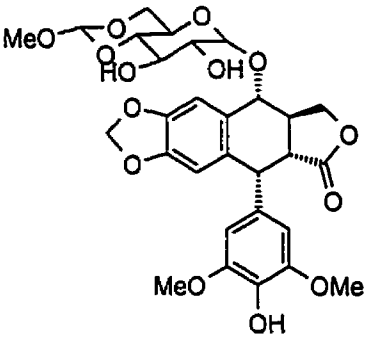
19 (Epipodophyllotoxin)

Scheme 7

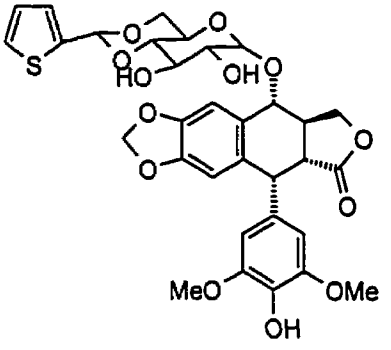
All the podophyllotoxin derivatives depicted in Scheme 7 above have demonstrated antitumour activity. The podophyllotoxin analogues have structural differences that either enhanced or reduced their activities compared to that of podophyllotoxin. A diastereomer of podophyllotoxin, epipodophyllotoxin **19** has the opposite stereochemistry at the C-4 hydroxyl group, and this feature reduces its potency as an antitumour agent by an order of magnitude. However, if this C-4 hydroxyl group is removed as in deoxypodophyllotoxin **15**, the potency of this compound is restored to an activity comparable to podophyllotoxin. Further studies on positioning the hydroxyl group at C-5 as in β-peltatin **18** increased potency to four times more than that of podophyllotoxin. It may be possible that the binding site in tubulin is flexible enough to

accommodate either a C-5 or C-4 hydroxyl group yet this interaction is not required for binding. If the 4`-methoxy group on the pendant ring of β-peltatin is replaced with a phenolic group as in α-peltatin then the activity is restored to podophyllotoxin levels. This result provided some insight on the effects of replacing substituents on the aryl rings.

1.2.2 Etoposide and Teniposide



20 (Etoposide (VM-26))



21 (Teniposide (VP-16-213))

Scheme 8

Etoposide **20** and Teniposide **21** are semi-synthetic derivatives of podophyllotoxin that were developed by Sandoz in an attempt to maintain the cytotoxic and anticancer activities of podophyllotoxin and eliminate the unwanted gastrointestinal toxicity.[6a] These two compounds are effective antineoplastics for the treatment of small-cell lung cancer, testicular cancer, lymphoma, and acute lymphocytic leukemia. Their mechanism of action differs dramatically from that of their podophyllotoxin precursor. Instead of acting as an anti-mitotic agent, etoposide and teniposide induce single- and double-stranded DNA breaks through interaction with topoisomerase II, an essential

enzyme needed for unravelling of the DNA double helix during DNA replication. These two compounds are selectively toxic towards rapidly proliferating cancer cells.

1.3 Stereochemistry and Chiral Molecules

Stereochemistry is the concept of viewing and describing chemistry in three dimensions.[10] The three-dimensional structure of a molecule is important for understanding the pharmaceutical action of a molecule and how it interacts with its intended biological binding site. One three-dimensional form of a molecule may be biologically active whereas the other form may be inactive against the target. Therefore stereochemistry is vital in the design and synthesis of biologically active compounds. Organic chemists refer to the synthesis of organic compounds in specific three-dimensional forms as asymmetric syntheses. One of the objectives of this project was to determine if it was possible to accomplish an asymmetric synthesis of the two chosen natural products. A brief history of the origins of stereochemistry will be presented along with definitions of some stereochemical terms.

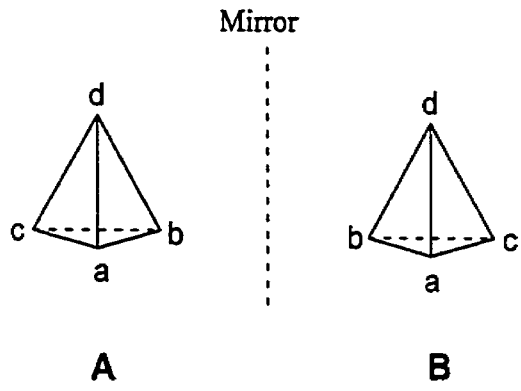
1.3.1 Stereochemistry

The study of stereochemistry dates back to 1809 when plane-polarized light was first discovered by the French physicist Malus.[10] Biot used this observation to study quartz crystals and found that they could rotate plane-polarized light either to the left or to the right.[10] Later he examined organic molecules and found similar results for liquid turpentine and dissolved solutions of sucrose, camphor, and tartaric acid. From these results Biot realized that the rotation of polarized light was a property of the crystal in the solid state, dependent on the angle at which it was viewed. However, organic substances

rotated light based on a property of individual molecules and therefore could be observed in all three physical states of the molecule.

In 1848, Pasteur was able to separate the sodium salt of tartaric acid into its two enantiomers, (+)-tartaric acid and (-)-tartaric acid.[10] He was able to crystallize the sodium salt of tartaric acid, separate the enantiomers, dissolve them in solution and study their effects on plane-polarized light. (+)-Tartaric acid or dextro-tartaric acid was widely available at that time and known to rotate polarized light to the right. However, for (-)-tartaric acid, this was the first time that it had been isolated and it rotated polarized light in the opposite direction, to the left. From these observations Pasteur was able to make the correlation that crystals and molecules exhibit dissymmetry. The two forms of tartaric acid were enantiomeric or non-superimposable mirror images of each other. Enantiomers were related as a right hand is related to a left hand and were able to rotate the plane of plane-polarized light in opposite directions.

Van't Hoff extended the concept of enantiomerism to describe the three dimensional structure of a tetravalent carbon atom.[10] Four different substituents bonded to carbon are spatially arranged to point towards the corners of a tetrahedron. Two possible arrangements are shown in Scheme 9. There are two non-superimposible arrangements that produce two tetrahedrons.

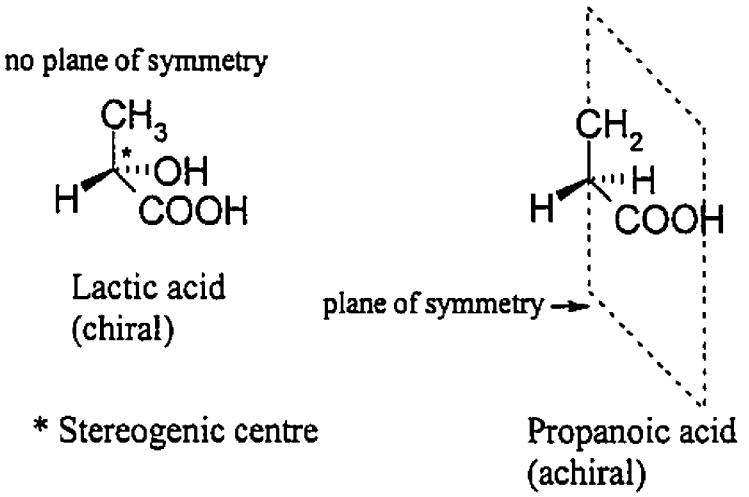


Scheme 9

1.3.2 Chirality

The term chirality, the property of being chiral, is defined as being not superposable with a mirror image. Sometimes chirality is equated to handedness, with the two mirror images being called the left and right hand forms. When applied to molecules, the two non-superimposable forms are referred to as enantiomers.[10,11] When a sample is referred to as being chiral or consisting of chiral molecules it does not necessarily mean that all the molecules making up the sample have the same chirality, left-handedness or right-handedness. Homochiral, or enantiomerically pure, would be a better term to use to describe molecules in a sample that all have the same chirality. Racemic, is the term used to describe a sample made up of equal numbers of molecules of opposite sense of chirality.[10] The term chiral will be used in this thesis only to describe molecules and not to describe chiral syntheses in which chiral molecules are produced.

The determining characteristic of chiral molecules is the absence of elements of symmetry (plane or centre) as seen in lactic acid (Scheme 10).[11] If a plane of symmetry is present, then the molecule is termed achiral, as exemplified in propanoic acid. The most common element that a molecule has, that causes chirality, is the presence of chiral centres or stereogenic centres. In lactic acid the central carbon is a stereogenic centre because it is bonded to four different substituents.

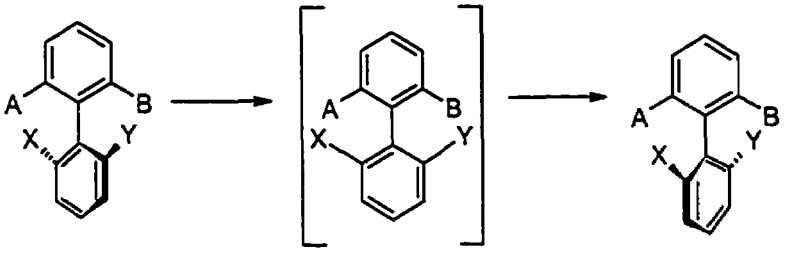


Scheme 10

1.4 Atropisomerism: Chiral Molecules Devoid of Chiral Centres

Atropisomerism is a central theme in this thesis as it is possible that it can be used to expand the proposed new methodology to the realm of asymmetric syntheses (the synthesis of the separate enantiomers) of lignan natural products. Therefore, it is important to fully discuss this property exhibited by crowded molecules and the role it can play in asymmetric synthesis. An example of a natural product synthesis that exploits atropisomerism will be presented to facilitate the later discussion of how such methods might be applied to asymmetric syntheses of lignans.

Atropisomerism is another type of enantiomerism, however it is chirality in molecules that are devoid of stereogenic centres. Atropisomerism was a term introduced by Kuhn to describe molecules with a chiral axis maintained by hindered rotation about single bonds.[12] The steric hindrance about this single bond was generated by bulky groups or substituents, generally on aromatic rings. Atropisomerism can be attributed to a type of conformational or rotational isomerism in which the atropisomers can be separated if the barrier to rotation is large enough. The term was originally used for optical isomers of biphenyls many of which have been investigated (Scheme 11).[10,13,69]



Scheme 11

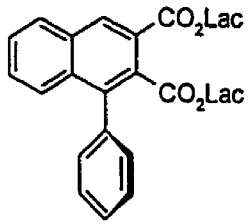
The biphenyl structure is joined by a carbon-carbon single bond (C1-C1') and it is the rotation about this bond that is affected by steric interactions. This is clearly evident in the *ortho*-substituted biphenyls in Scheme 11 where the two nonplanar rotamers are enantiomers (non-superimposable mirror images) of each other. As the bulkiness of the *ortho*-groups increases the barrier to interconversion also increases.[70] The transition between the two enantiomers will produce a state in which the aryl rings are coplanar. There is an energetic penalty associated with this interaction. Therefore the molecule

avoids this by adopting a perpendicular arrangement yielding two atropisomeric populations.

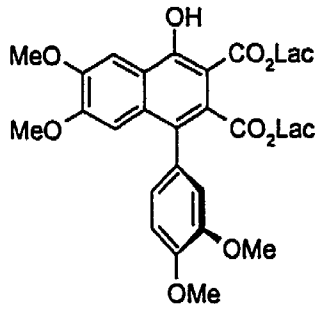
When the barrier to rotation between the interconverting atropisomers becomes too high, the interconversion is hindered to the point where separation of the atropisomers is possible. The calculated energy barrier where atropisomers can be isolated at room temperature is approximately 22 kcal/mol.[12] NMR and other spectroscopic methods are the only means of monitoring molecules with barriers to rotation less than this value. Molecules with barriers to rotation greater than this value can be separated by conventional chromatographic techniques.

1.4.1 Atropisomerism in Arylnaphthalene Lignans

Closely related to the biphenyls are the arylnaphthalenes, compounds with a more extended ring structure. Many arylnaphthalenes have the potential to display atropisomerism.[13,14] The chirality displayed in these compounds, devoid of chiral centres, is brought on by hindered rotation about the aryl-naphthalene bond. Charlton *et al.* have studied this phenomenon by synthesizing the natural products justicidin A, justicidin B, retro-justicidin B and helioxanthin as well as four other arylnaphthalene lignan analogues (Scheme 12).[13]



22



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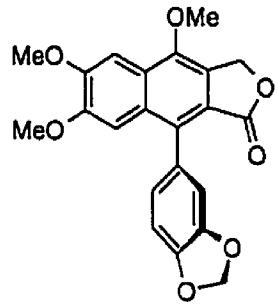
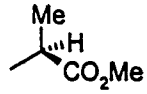
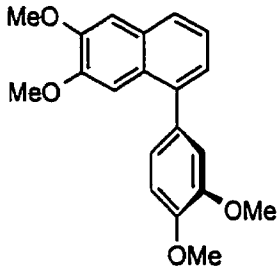


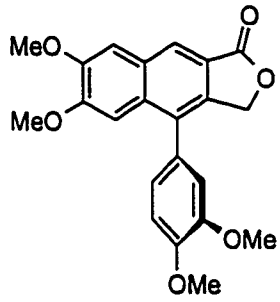
24 (Justicidin A)

Lac =

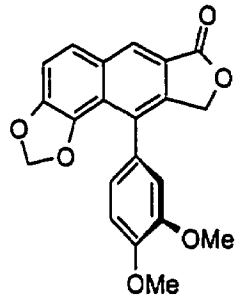




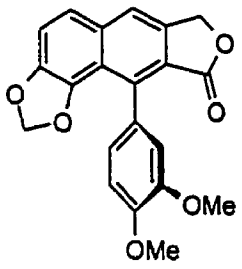
25 (Justicidin B)



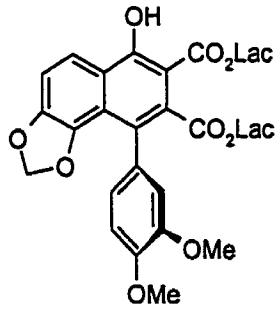
26 (Retro-Justicidin B)



27 (Helioxanthin)



28 (Retro-Helioxanthin)



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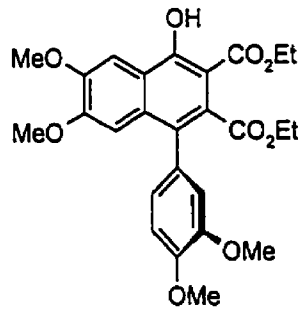


30

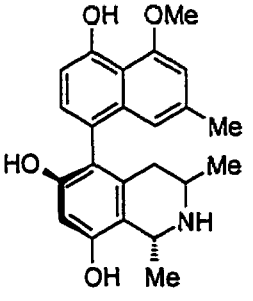
Scheme 12

These compounds were studied by dynamic NMR and HPLC to determine the barriers to rotation and the corresponding half-lives of the individual atropisomers. It was found

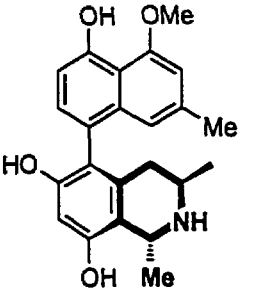
that the lactate ester at C-2 (as in **23** and **29**) presented a higher barrier to rotation than the 2,3-lactones of either orientation (as in **24**, **26**, **27**, or **28**). The 7,8-methylenedioxy ring (as in **28** and **29**) decreased the barrier to rotation relative to hydrogens at positions 7 and 8. It was concluded from this study that the barrier to rotation, while high enough to allow for detection of atropisomers by NMR spectroscopy, was too small for individual atropisomers to be isolated at room temperature. However, this provided unequivocal evidence of the existence of atropisomeric populations in arylnaphthalenes.

1.4.2 Atropisomerism and the Synthesis of Korupensamines A and B

Bringmann and co-workers described a synthesis of the antimalarials, korupensamines A **31** and B **32** using atropisomerism as the key aspect of the synthesis (Scheme 13).[15]



31 (Korupensamine A)

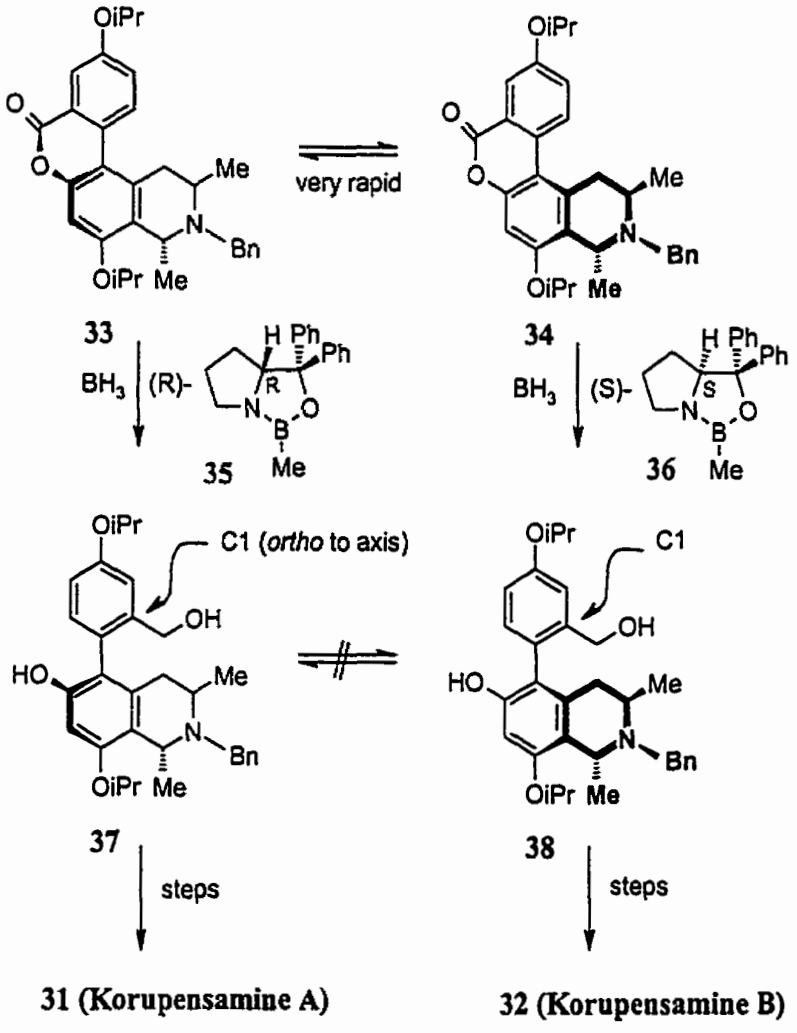


32 (Korupensamine B)

Scheme 13

These intriguing naphthylisoquinolone alkaloids, isolated from the Cameroon liana *Ancistrocladus korupensis* (Ancistrocladaceae) exhibited good antimalarial activities. Korupensamine A differed from korupensamine B only in the rotation about its chiral axis. The synthesis utilized the "lactone methodology" developed by the same

group.[16] This method had several advantages such as high coupling yields, good asymmetric induction and the recycling of undesired atropisomers of late precursors back to the lactones (**33, 34**) (Scheme 14).



Scheme 14

This method required a C-1 substituent *ortho* to the axis in order to generate the ester/lactone bridge (see labelled **37** and **38**). This C-1 functionality was apparently lacking in the natural products. However upon closer inspection this group was not really

missing but existed in a hidden (cryptic) form as part of the naphthalene ring in the natural products (**31** and **32**). Bringmann's group circumvented this problem by starting with the axially chiral phenylisoquinolines instead of the naphthylisoquinolines. The phenylisoquinolines were built with a C-1 subunit next to the axis that served a dual purpose; it provided the required *ortho*-subunit and the scaffold for generation of the naphthylisoquinoline.

The phenylisoquinoline lactone (**33** and **34**) interconverts rapidly between its two atropisomeric forms and consequently it lacks a stable chiral axis. The designation M- or P- was used in the paper as a means of conferring a helical label to the chirality of the molecule, i.e. left- or right-handedness. For this designation, only the ligands of highest priority in front and in the back of the framework are considered. If one were to view these molecules along their chiral axis from front to back the configuration is P if the two highest priority groups are arranged in a counterclockwise direction. The configuration is designated M if the arrangement is in a clockwise direction.[10] The axial chirality was fixed by the reductive ring cleavage, to afford either the P-configured diol (**37**) or the M-configured diol (**38**) dependent on the chiral oxazaborolidine-borane used. The (R)-oxazaborolidine (**35**) afforded the P-configured diol whereas the (S)-oxazaborolidine (**36**) gave the M-configured diol. These compounds were stable entities that were not observed to interconvert. Eventually after several synthetic steps the P-diol and the M-diol were converted to korupensamine A and B, respectively. The synthetic strategy was well rewarded with an overall yield of 10% for korupensamine B and 7% for korupensamine A.

The observed atropisomeric properties of korupensamine A and B are interesting from the aspect that the precursors are also atropisomers that are converted to the natural products. It is known that the synthetic precursors, the dibenzylidenesuccinates, of lignans displays atropisomerism. It might be quite possible to exploit that property to make separate enantiomeric forms of the final target lignans (an asymmetric synthesis). In fact, this reverse strategy of the example given above for the syntheses of Korupensamine A and B might be realized if one atropisomeric form of dibenzylidenesuccinates could be used as the precursor molecule to the chiral aryltetralin lignans, such as galbulin **1** and cagayanin **2** (see section 3.3). The dibenzylidenesuccinates will be discussed in depth separately in a later section after a review of classical lignan syntheses. It would be difficult to review all the literature on the synthesis of lignans in this thesis. Therefore, only a select few methods, related to the synthesis of molecules similar to galbulin **1** and cagayanin **2**, will be discussed. These examples will illustrate the syntheses of aryltetralins **3**, aryldihydronaphthalenes **4**, and arylnaphthalenes **5**, compounds all related within the scope of this thesis. Furthermore all the previous syntheses of galbulin and cagayanin will be reviewed. More information can be obtained from several excellent reviews that have been published over the years to cover all of the isolation and syntheses of lignans.[17-24]

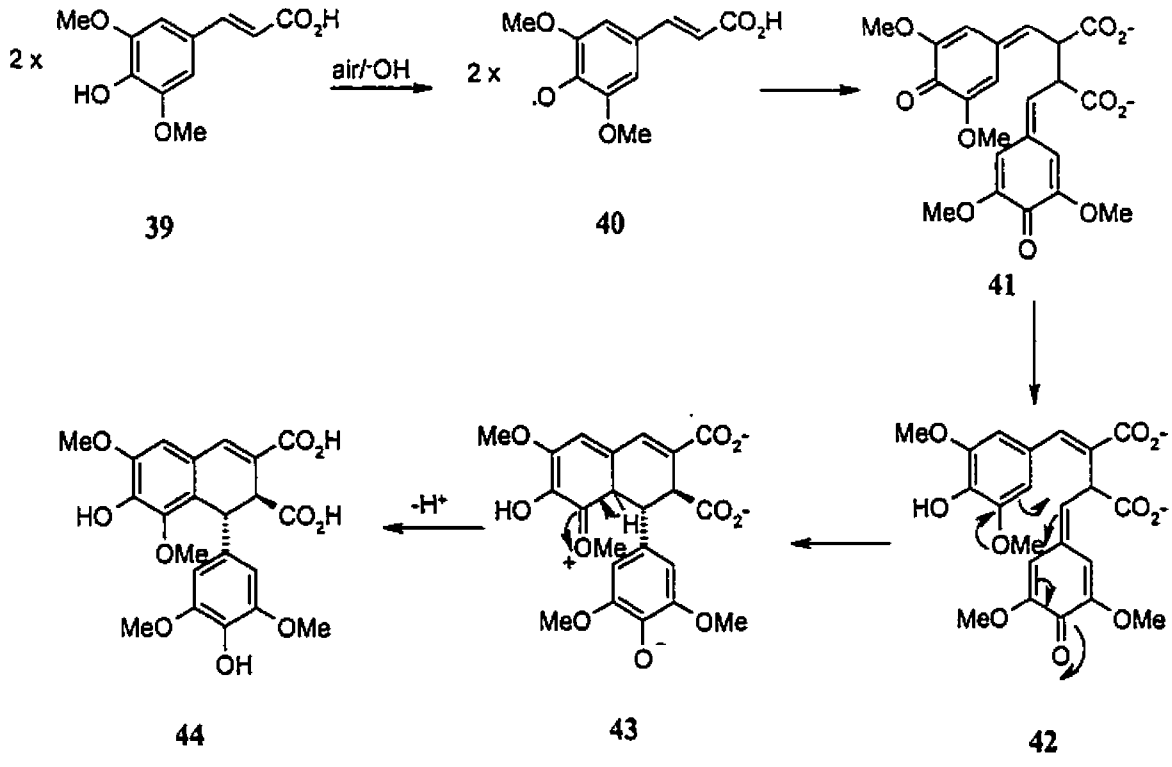
1.5 Synthesis of Lignans

Lignans have been prepared by many different general methods. Examples from some of the major methods are reviewed in this section.

1.5.1 Oxidative Coupling

The biosynthesis of lignans in plants is believed to occur by a phenolic oxidative dimerization event. The phenylpropanoids are joined via free radicals at the β-carbons of their propane sidechains. In a synthesis of thomasidioic acid 44, Charlton and Lee[25] proposed a biomimetic synthesis by this free radical phenolic oxidation mechanism (Scheme 15).

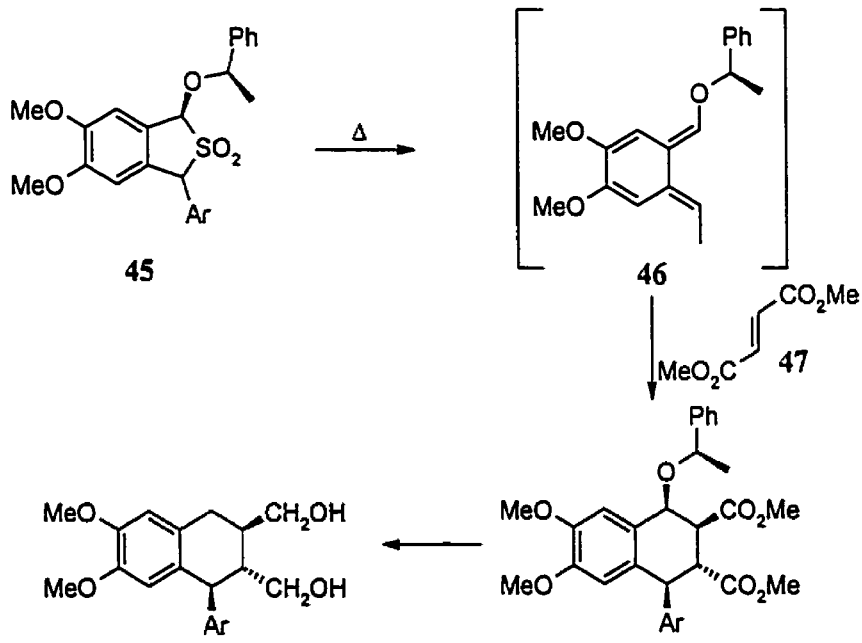
Thomasidioic acid 44 was prepared by air oxidation of sinapic acid 39 in an alkaline aqueous solution. The results of the study did not provide conclusive evidence that the oxidative coupling occurred by a free radical mechanism although it seems a reasonable conclusion given the prior literature in this area.[26]



Scheme 15

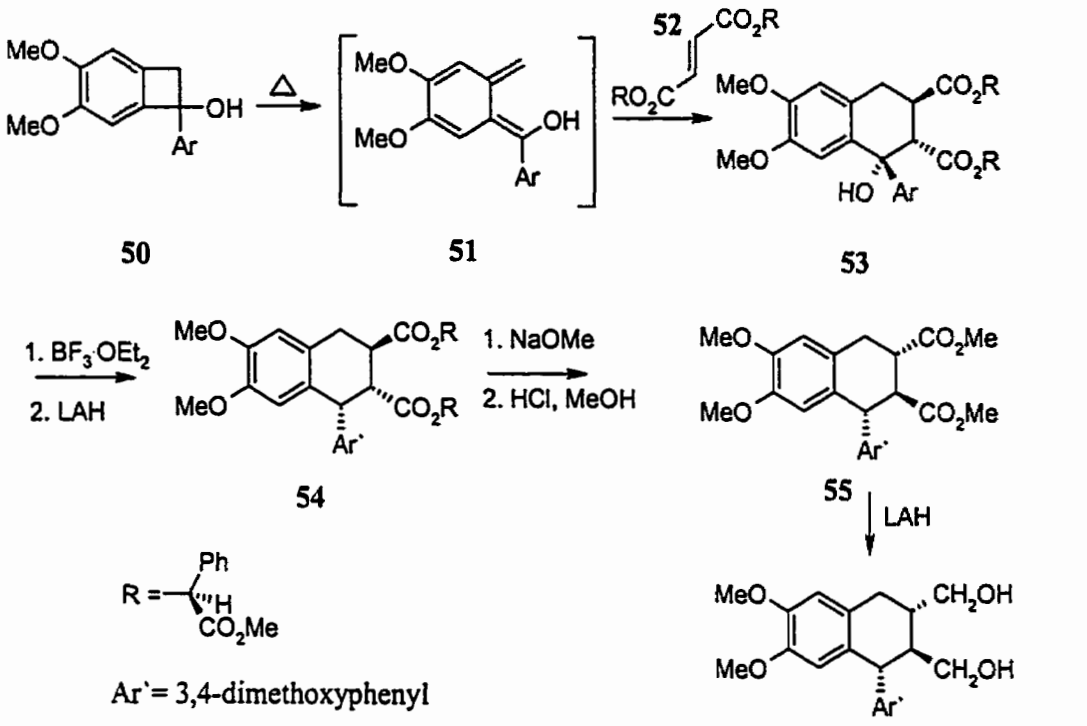
1.5.2 Diels Alder Cyclisations

Charlton and Alauddin have synthesised (+)-isolariciresinol dimethyl ether **49a** using a cycloaddition reaction.[27,31] The key synthetic step was the pericyclic extrusion of sulfur dioxide to yield the *ortho*-quinone-methide **46**. This compound underwent a Diels-Alder cycloaddition with diethyl fumarate **47** to afford a 70% yield of the major adduct **48**. The major diastereomer was separated and carried forward to the product (Scheme 16).



Scheme 16

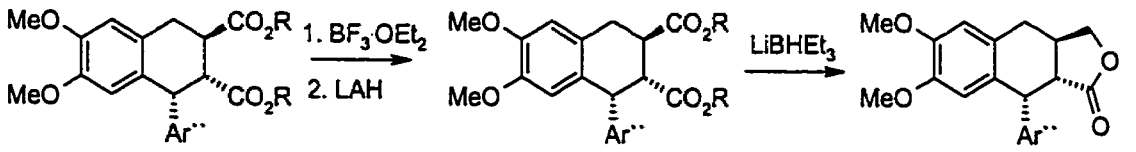
The *ortho*-quinone dimethide Diels-Alder cycloaddition was also utilised to synthesize (-)-isolariciresinol dimethyl ether **49b** (Scheme 17a) and (-)-deoxysikkimotoxin **58** (Scheme 17b).[28,31]



49b ((-)-Isolariciresinol dimethyl ether)

Scheme 17a

The key steps of this synthetic route were the attachment of the second aryl ring using a modified Strecker synthesis where an aromatic aldehyde is converted to an α-aminonitrile, followed by the generation of a benzocyclobutenol **50** from *ortho*-lithiation, and thirdly conversion of the benzocyclobutenol to the *ortho*-quinone-dimethide. The *ortho*-quinone dimethide was subjected to Diels-Alder reaction conditions with the fumarate of methyl (S)-mandelate **52** to afford the aryltetralin product **53**. Subsequent functional interconversions generated **49b**. Functional interconversion of the aryltetralin **56** afforded (-)-deoxysikkimotoxin **58** (Scheme 17b).



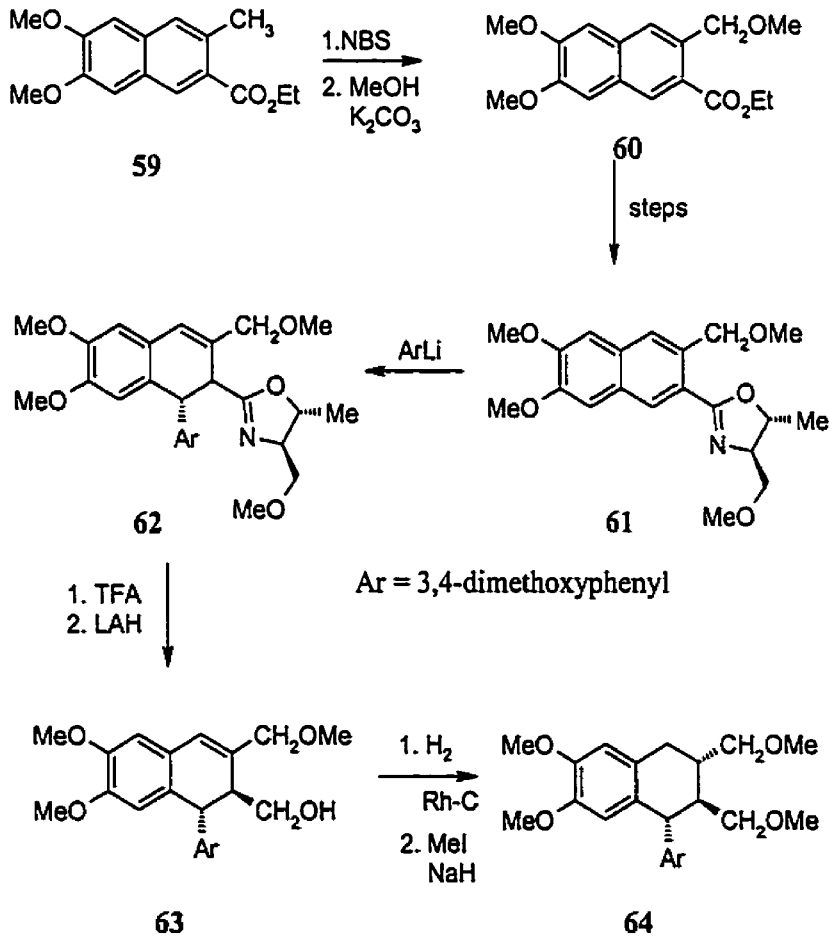
56 57 **58 ((-)-Deoxysikkimotoxin)**

Ar'' = 3,4,5-trimethoxyphenyl

Scheme 17b

1.5.3 The Use of Chiral Auxiliaries

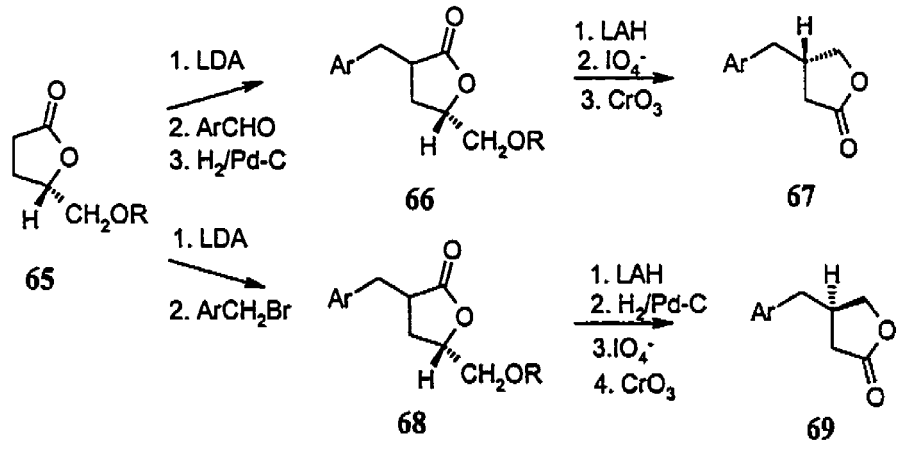
The use of chiral oxazolines was employed by Meyers to synthesise (+)-phyltetralin **64** and (-)-podophyllotoxin **13**.[30,31] This involved an asymmetric tandem addition of aryllithium reagents to non-racemic naphthalene compounds (Scheme 18).



Scheme 18

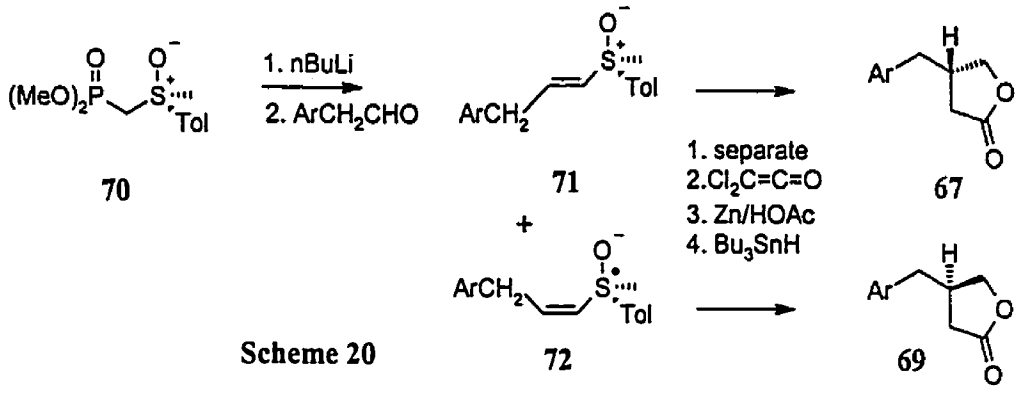
This synthetic sequence favoured the synthesis of (+)-phyltetralin **64** as it possessed the *trans*-stereochemistry at C-1 and C-2 of the tetralin ring. However, for compounds with the *cis*-stereochemistry, as in (-)-podophyllotoxin **13** (synthesis not shown), the synthetic method was less attractive because of the numerous steps it took to set up the correct relative stereochemistry at C-2, C-3, and C-4.

The diastereoselective alkylation of chiral butyrolactones has been used as another strategy for generating chiral lignans (shown in Scheme 22). Different approaches to synthesize the required precursor chiral butyrolactones **67** and **69** were taken by Koga, Kosugi, and Brown. Koga prepared the desired butyrolactone by alkylating the benzyl or trityl ethers of 4-hydroxymethyl butyrolactone followed by carbonyl transposition to afford the butyrolactone (Scheme 19).[32,31]



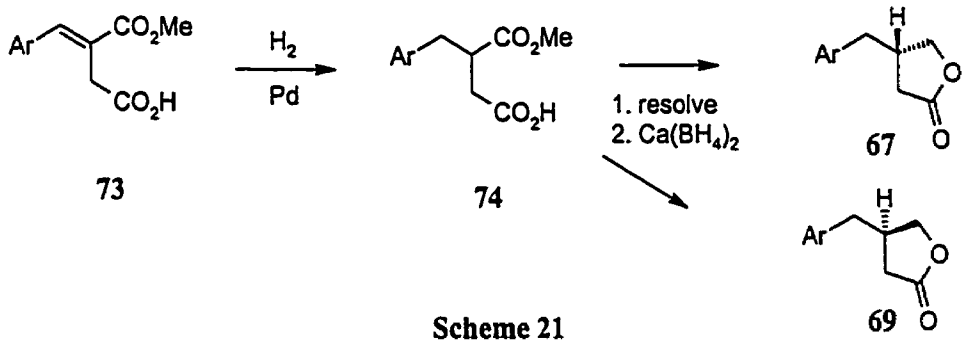
Scheme 19

Kosugi, on the other hand, generated the butyrolactones in high enantiomeric excess (94% and 96%) by stereoselective cyclization of alkenyl sulphoxides with dichloroketene (Scheme 20).[33,31]



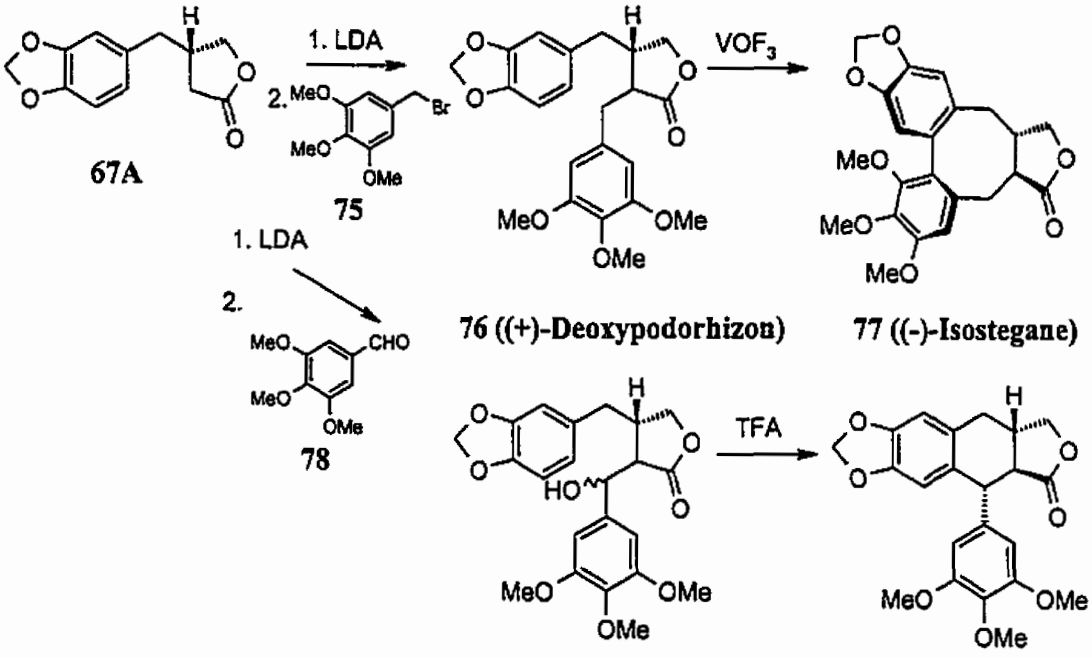
Scheme 20

The method developed by Brown required the hydrogenation of Stobbe condensation products followed by resolution to afford both enantiomers of the chiral butyrolactones (Scheme 21).[34,31]



Scheme 21

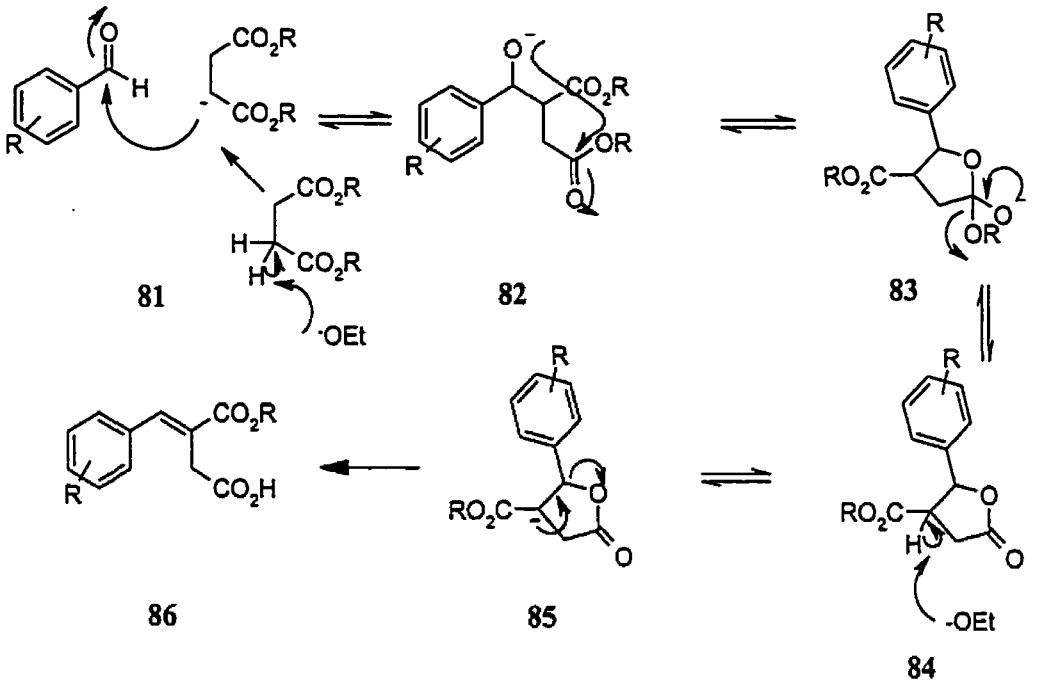
Chiral butyrolactones have been used in the synthesis of many lignans. As an example, the chiral butyrolactone **67A** was functionally converted by alkylation to (+)-deoxypodorhizon **76**. Subsequent intramolecular oxidative coupling afforded (-)-isostegane **77**. Alternatively compound **67A** underwent a Stobbe condensation to afford (+)-epipodorhizol **79** and ensuing treatment with TFA generated (+)-deoxyisopodophyllotoxin **80**.



Scheme 22

1.5.4 The Stobbe Condensation

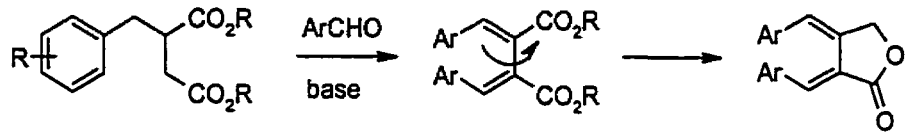
The Stobbe condensation[35,36] is ideally suited for construction of the aryltetralin lignan skeleton. The reaction between an aromatic aldehyde and a succinate ester generates an aromatic succinic acid **86**. This compound is formed from an aldol type reaction between the carbonyl group of the ketone and an α-methylene of the succinic ester. The high reactivity of the α-methylene groups of succinic esters is not the sole contributor to the success of this reaction. What drives this reaction is the formation of a five-membered ring **84** followed by the irreversible ring cleavage to generate the Stobbe monoacid-ester **86** (Scheme 23).[36]



Scheme 23

1.5.4.1 Diarylfulgides and Dibenzylidenesuccinates

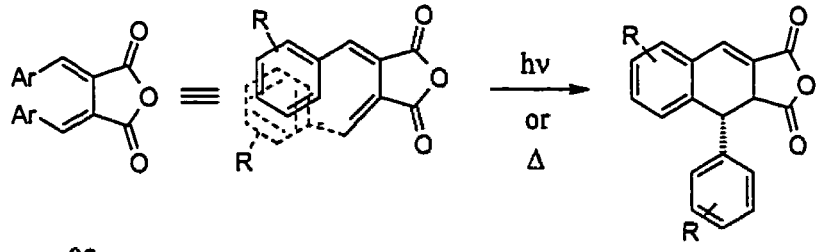
A second successive Stobbe condensation generates the dibenzylidenesuccinates **87** or the diarylfulgides **89**, compounds that demonstrate hindered rotation about the butadiene single bond (atropisomerism) (Scheme 24). These compounds have demonstrated both photochemical and thermal electrocyclic reactions and sigmatropic rearrangements to give various dihydronaphthalene derivatives **90** that can be modified to aryltetralins or arylnaphthalenes.



89A **90** **91 (Taiwanin A)**

Ar = 3,4-methylenedioxyphenyl or 3,4-dimethoxy

Ar = 3,4-methylenedioxyphenyl



92

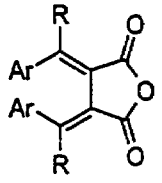
E,E-Dibenzylidene Succinic Anhydride

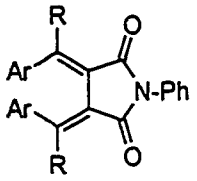
93

Scheme 24

These types of compounds were first synthesized and studied in their succinic anhydride or fulgide form **89** by Stobbe.[35] The compounds obtained by the Stobbe condensation almost always have a *trans,trans* (*E,E*)-arrangement of aryl and carbonyl groups (**87** and Taiwanin A **88**).[37a,b] The diarylfulgides are typically isolated as highly crystalline compounds having both thermochromic and photochromic properties. If these compounds are subjected to either irradiation or strong heating, cyclization and dehydrogenation affords the 1-arylnaphthalene-2,3-dicarboxylic anhydrides **93** (Scheme 24).

Heller *et al.* have studied the dibenzylidenefulgide **91** [37a,b,39-45] and the dibenzylidenefulgimide **92** [38a,b,39,42,] systems extensively (Scheme 25).



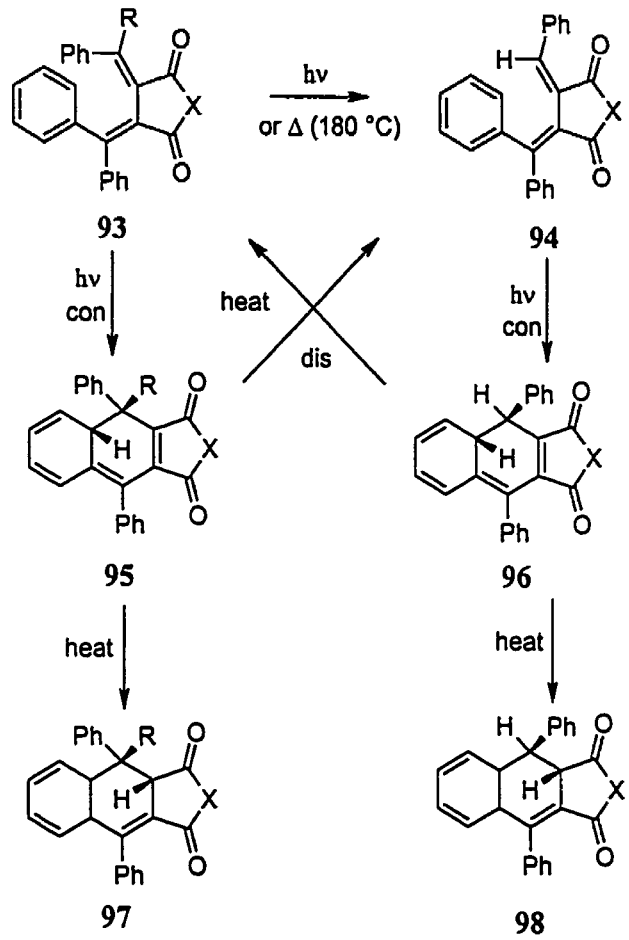


91 (Dibenzylidenefulgides) **92** (Dibenzylidenefulgimides)

R=Alkyl, H

Scheme 25

They have proposed a photorearrangement of the *E,E*-diarylfulgides **93a** and **93c** or *E,E*-diarylfulgimides **93b** and **93d** by a conrotatory ring closure to give the *E*-1,8-dihydronaphthalene intermediates **95a-d**, respectively (Scheme 26). This intermediate could undergo two competing thermal reactions: disrotatory ring opening to give the *E,Z*-isomer of the diarylfulgide **94a,c** or diarylfulgimide **94b,d**, or a suprafacial 1,5-sigmatropic hydrogen shift to give the 1,2-dihydronaphthalene **97a-d**.[38a]



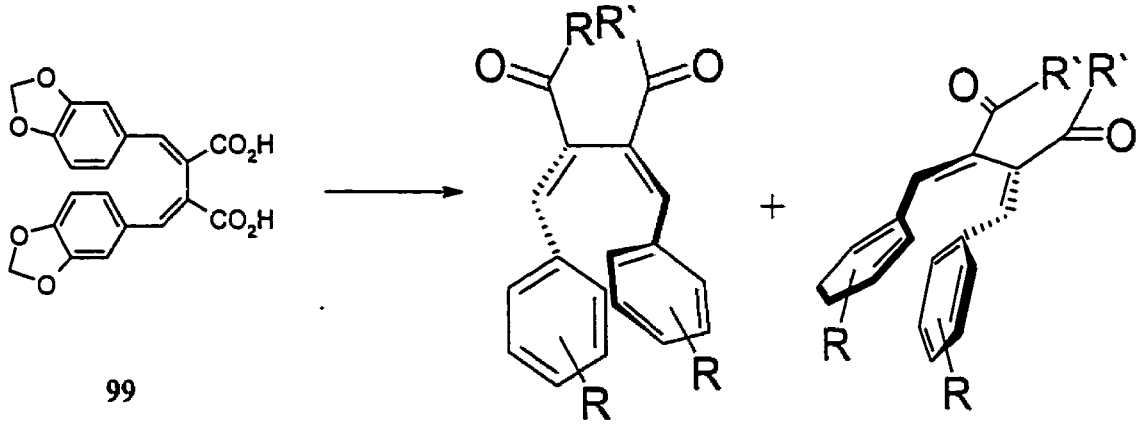
a) X= O,R=H
b) X= NPh, R=H
c) X= O, R=Ph
d) X= NPh, R=Ph

Scheme 26

However, under thermal conditions (180 °C) compounds **93a** and **93b** isomerize to the thermodynamically more stable *E,Z*-isomers **94a** and **94b**. At this temperature these two compounds undergo disrotatory ring closure followed by a 1,5-sigmatropic hydrogen shift to give predominantly **97a** and **97b**. Therefore, photochemical ring closure goes by conrotation whereas thermal ring closure goes by disrotation. It was determined from the temperature studies of other substituted diarylfulgides that the

activation energy for the 1,5-hydrogen shift is lower than for the disrotatory ring opening process.[33]

Charlton and Hiebert have noted that the *E,E* isomer of bis-3,4-methylenedioxybenzylidene succinic acid **99** demonstrated atropisomeric behaviour (Scheme 27).[53] The ^{1}H NMR spectrum showed that the methylenedioxy protons were diastereotopic with splitting due to mutual coupling. Since the molecule lacked tetrahedral carbon stereogenic centres the only possible explanation for this chirality was hindered rotation about the butadiene single bond generating atropisomers. In subsequent experiments the carboxylic acid groups were converted to the chiral diamide **100** and **101** and a dynamic NMR study was performed to determine the barrier to rotation. The calculated barrier to rotation was found to be 16.7 kcal/mol, well below the 22 kcal/mol required to allow separation of atropisomers at room temperature.



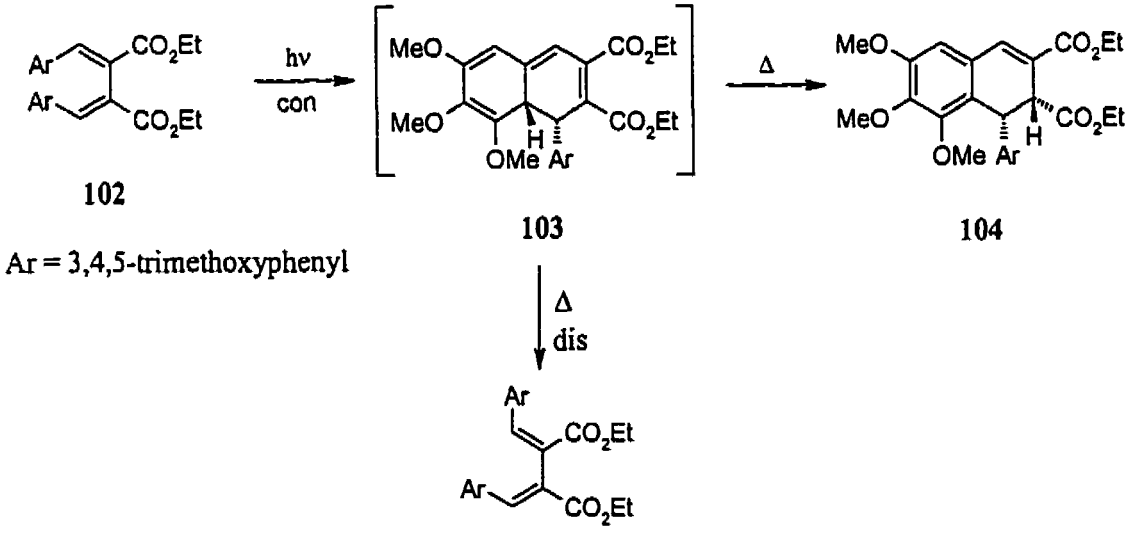
99 **100** **101**

R` = NH-CH(CH$_3$)-Ph

R =3,4-methylenedioxy

Scheme 27

Recently, Yvon discovered that the *E,E*-bis-3,4,5-trimethoxybenzylidene succinate **102** also demonstrates atropisomerism.[54] This compound undergoes photochemical electrocyclization followed by a 1,5-sigmatropic shift to give a 1,2-dihydronaphthalene that has the *cis* geometry at C-1 and C-2, similar to podophyllotoxin **13** (in Scheme 6). This is a unique development as this *cis* geometry is difficult to accomplish in one step by classical synthetic routes (see Scheme 18). The 1,8-dihydronaphthalene **103** could either undergo the 1,5-sigmatropic shift to give **104** or it could ring open by disrotation to give **105**. Fortunately, the reaction gave predominantly the 1,2-dihydronaphthalene **104**. The above result demonstrated that the open diethyl ester form of dibenzylidenesuccinates undergoes photocyclization in good agreement with Heilers' studies of the more conformationally restricted fulgides or fulgimides.



102

Ar = 3,4,5-trimethoxyphenyl

103

104

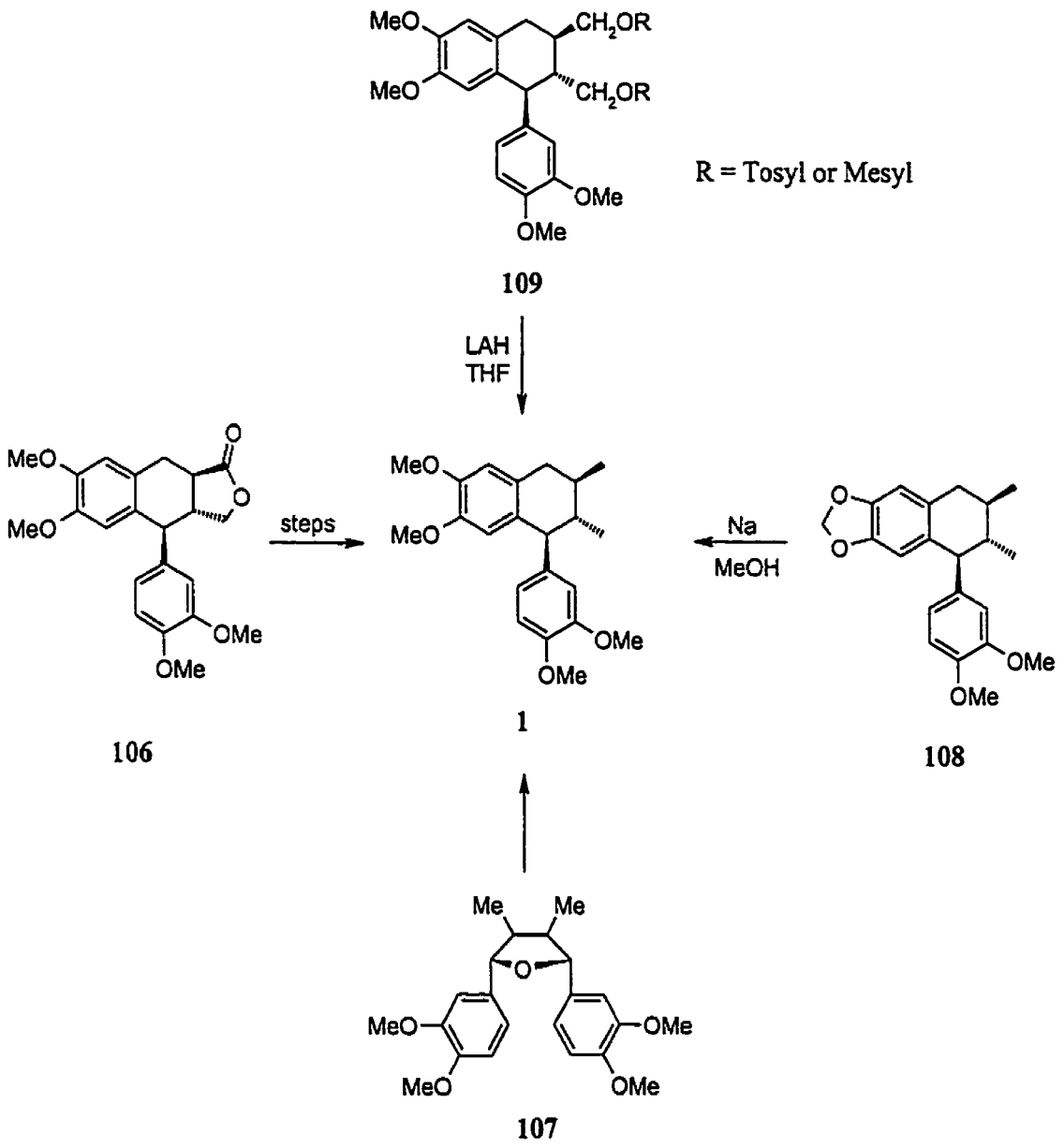
105

Scheme 28

The first part of this research is a continuation of work done (Scheme 27 and 28) by two previous students. The dibenzylidenesuccinates and their atropisomeric properties are of particular interest as they are the focus for a synthesis of galbulin and cagayanin. A review of past syntheses of these two compounds is given below.

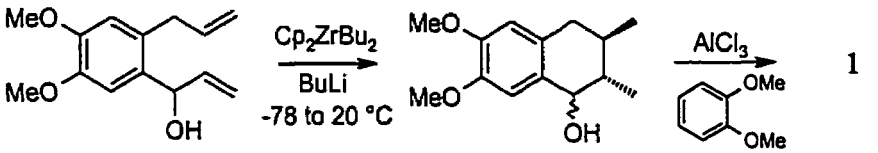
1.6 Galbulin

Galbulin was first isolated from *Himantandra baccata* by Hughes & Ritchie.[55] A full characterization can be found in two papers.[66,67] Several reported syntheses of galbulin involved the interconversion of other known lignans to galbulin. Conversions from α-conidendrin[56] **106**, veraguensin[57] **107**, (-)-galcatin[58] **108**, and the ditosyl- or dimesyl- (+)-isolariciresinol dimethyl ether[59] **109** to galbulin were successful (Scheme 29).



Scheme 29

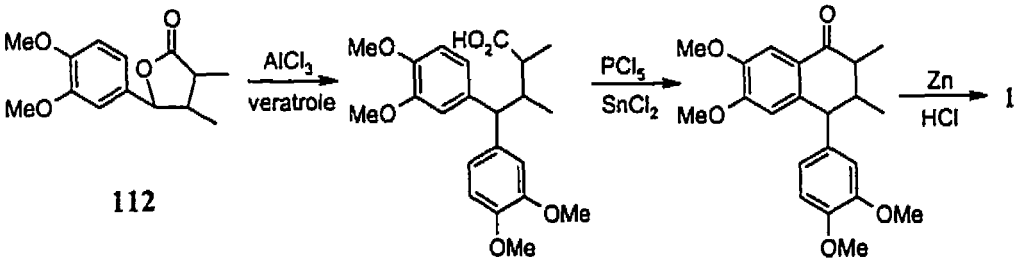
The most recent and more novel synthesis involved the use of zirconium chemistry.[60] The key synthetic step was the use of zirconium to promote the cyclization of 1,7-dienes **110** (Scheme 30).



110 111

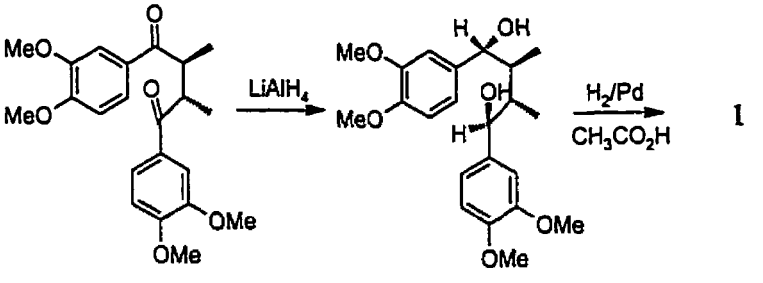
Scheme 30

Other novel syntheses include the cationic cyclization of 4,4-diveratryl-2,3-dimethylbutanoic acid[61] **113** (Scheme 31) and the oxidative coupling of 1,4-diveratryl-2,3-dimethylbutane[62] **115** (Scheme 32).



112 113 114

Scheme 31

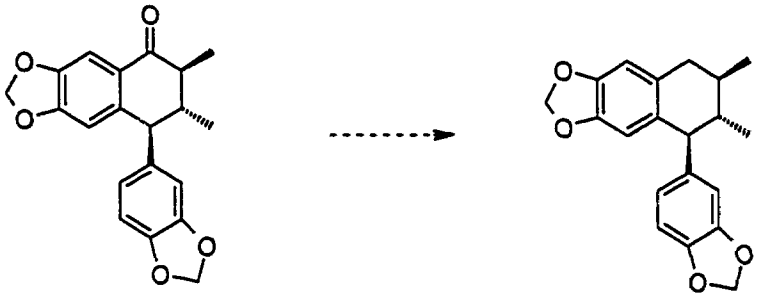


115 116

Scheme 32

1.7 Cagayanin

Cagayanin was first isolated from the nutmegs of *Myristica cagayanesis* by Kuo's group.[63] Cagayanin was converted to galbulin and compared to an authentic sample of galbulin. The results verified that indeed cagayanin was isolated. A subsequent paper gave a full characterization of cagayanin.[64] Presently there are no reported syntheses of cagayanin. There is, however, a reported synthesis of a structurally similar compound called cagayanone 117.[65,64] Presumably this compound could be converted to cagayanin if the carbonyl function at C-4 could be selectively removed (Scheme 33).



117 (Cagayanone) **2**

Scheme 33

Chapter 2

Thesis Objectives and Outline

The objective of this research project was to develop a new methodology for the synthesis of natural lignans with the expectation of applying this methodology to the synthesis of a wide-range of lignans. In addition it would be preferable if the methods were applicable to the synthesis of enantiomerically enriched lignans. The cyclization of dibenzylidenesuccinates to aryltetralins was proposed as part of the new synthetic methodology. Galbulin and cagayanin were chosen as ultimate synthetic targets.

The research can be divided into three parts. The first part explored substituent effects on acid-catalyzed cyclization of dibenzylidenesuccinates. The purpose was to establish the feasibility of acid-catalyzed cyclization and the effects on rates of cyclization. In the second part, a new functional interconversion strategy was established for the conversion of 1,2-dihydronaphthalenes to galbulin and cagayanin. The third part examined the possibility of syntheses of enantiomerically pure lignans (Galbulin and Cagayanin) and lignan analogues using atropisomerism exhibited in the dibenzylidenesuccinates to achieve this.

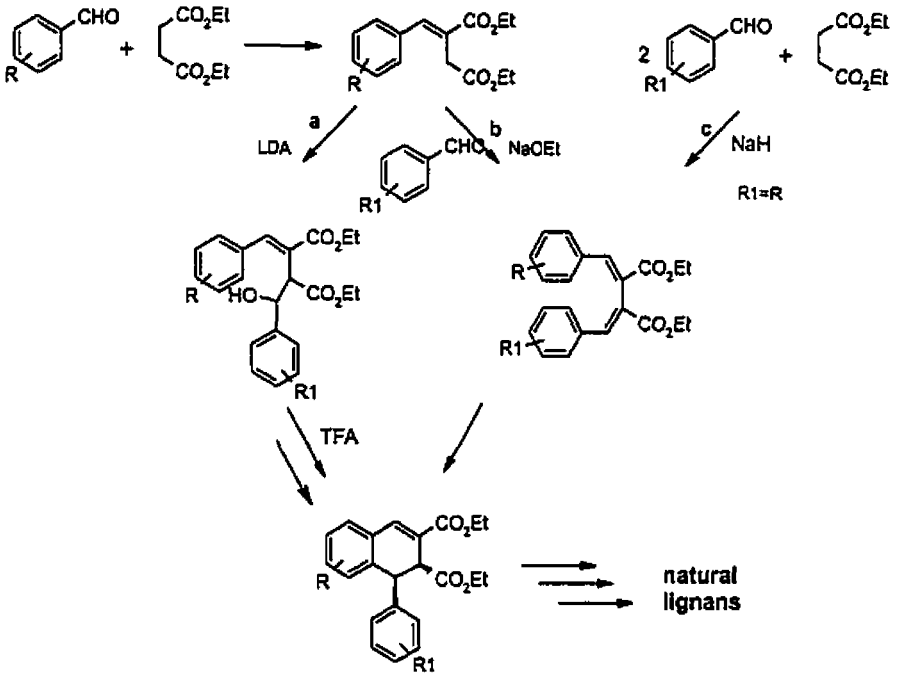
1) Substituent Effects on the Rate of Cyclization and Product Formation

Preliminary work on the acid-catalyzed ring closure demonstrated that certain symmetrical dibenzylidenesuccinates with methoxy groups in the 2 and 2` positions generated the desired 1,2-dihydronaphthalenes requiring less reaction time than dibenzylidenesuccinates lacking methoxy groups in these positions. Therefore, it was plausible to assume that different substituent patterns on the aryl rings could affect the rate of cyclization. Symmetrical dibenzylidenesuccinates (Scheme 34c) with similarly

substituted aryl rings as well as unsymmetrical dibenzylidenesuccinates (Scheme 34b) with differently substituted aryl groups were synthesized and studied. Some of the results were expected while others were not. Plausible explanations and mechanisms were postulated to rationalize these developments.

2) Development of the New Methodology

The Stobbe condensation was ideally suited for the construction of the framework leading to galbulin and cagayanin. In fact, two successive Stobbe condensations provided the starting dibenzylidenesuccinates needed for the study (Scheme 34b). The key step in this synthesis was the acid-catalyzed cyclization leading to the aryltetralin lignan structure. Previous work by Cow *et al.* on the synthesis of Taiwanin C, Chinensin, Justicindin B and E[68] as well as the work by Yvon *et al.* on Magnoshinin and Cyclogalgravin[54,71] demonstrated that the second aryl condensation could be achieved utilizing LDA (Scheme 34a), followed immediately, after work up, by treatment with trifluoroacetic acid (TFA) to afford the 1,2-dihydronaphthalenes. A discovery by a post-doctoral fellow, P. K. Datta provided some insight into acid-catalyzed ring closure of the dibenzylidenesuccinates. Although the use of either sulfuric acid or TFA as a catalyst for cyclizing dibenzylidenesuccinates did not yield a substantial amount of the desired product, the research deserved continued investigation. The conventional synthetic route required five steps for generating symmetrical dibenzylidenesuccinates whereas this new route could be done in two steps (Scheme 34c). This possibility of synthesizing the basic aryltetralin skeleton through a shorter route was very appealing.



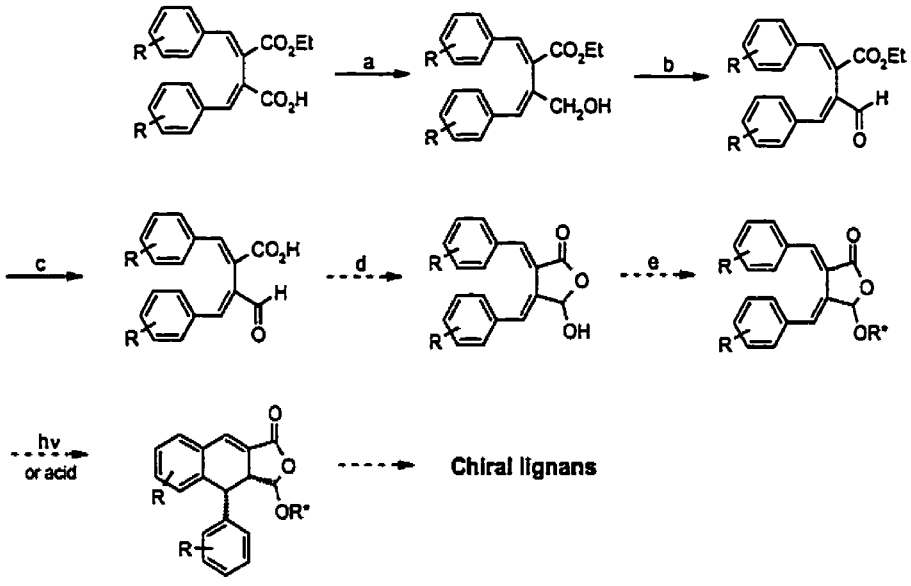
Scheme 34

3) Strategy for Enantiomerically Enriched Syntheses of Galbulin and Cagayanin

The most challenging aspect of synthetic organic chemistry is the stereoselective synthesis of chiral compounds. There are many techniques that can be used to achieve this, such as the use of chiral starting materials and chiral reagents, or the use of chiral auxiliaries to influence the outcome of the stereochemistry in the final product. However, for this project chirality already existed in the form of atropisomers found in the dibenzylidenesuccinates. Atropisomers are molecules that exist in two enantiomeric forms brought on by hindered rotation about a single bond. If it were possible to coerce the dibenzylidenesuccinate to adopt one atropisomer in favour of the other by using a chiral auxiliary, then the possibility of generating enantiomerically pure, or at least

enriched, photoproducts would present itself. As demonstrated by Yvon, attaching a chiral auxiliary to the *E,E*-bis-(3,4,5-trimethoxydibenzylidene) succinate monoacid-ester **125d** did not force this dibenzylidenesuccinate to adopt one atropisomeric form.[54] Furthermore, the barrier to rotation in this compound was not high enough to allow for separation by any conventional chromatographic technique. However, using a more rigid chiral auxiliary, such as the γ-hydroxybutyrolactone shown in Scheme 35, might limit the conformational flexibility to the point where one atropisomer might be favoured over the other. If the γ-hydroxybutyrolactone could be generated then the possibility of attaching a second chiral auxiliary onto the hydroxyl group would be available.

The first few steps of the reaction sequence were attempted as time constraints prevented continuation of this project. These preliminary results were included and discussed. Further investigation was warranted before any results could be presented.



Scheme 35

a) BH_3SMe_2, THF, rt, 5h; b)MnO_2, toluene, 18 h; c) K_2CO_3, EtOH, 48 h;
d) TsOH, benzene; e) chiral R*

Chapter 3

Results and Discussion

The research presented in this chapter on the synthesis of natural lignans is divided into three sections. The first section describes experiments carried out to determine the effect of substituents on the photochemical and acid-catalyzed cyclization of dibenzylidenesuccinates. The rate of cyclization of dibenzylidenesuccinates with symmetrically and unsymmetrically substituted aryl rings provided some insight on the mechanism of cyclization. This cyclization later provided the key step in the synthetic scheme used to prepare natural lignans. The intent of the studies on substituent effects was to determine if certain substitutions could enhance the reactivity of dibenzylidenesuccinates to generate aryldehydrotetralins. If this were the case then the scope of the reaction could be expanded to produce a wide array of natural lignans.

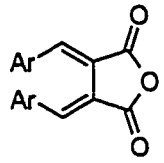
The second section outlines a parallel synthetic route leading to galbulin 1 and cagayanin 2. The synthetic series began with two successive Stobbe condensations to generate the appropriate dibenzylidenesuccinates. The next synthetic reaction involved treatment of the dibenzylidenesuccinate with triflic acid to catalyze the ring cyclization to generate an aryldehydrotetralin. The resulting aryldehydrotetralin structure was manipulated through functional interconversions to generate the desired natural lignans.

Finally, in the third section, the possibility of producing enantiomerically pure natural lignans by exploiting the atropisomeric properties of dibenzylidenesuccinates was examined. The introduction of a rigid chiral auxiliary was attempted with the goal of preventing free rotation about the carbon-carbon single bond. This would presumably restrict the interconversion between the atropisomers. It was also anticipated that the

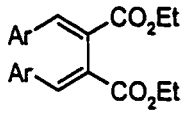
chiral influence would coerce the molecule to adopt one conformation. The enantiomerically enriched dibenzylidenesuccinates might then be carried through the proposed synthetic methodology to generate enantiomerically enriched lignan natural products.

3.1 Aryl Substitution on Dibenzylidenesuccinates

As stated in the introduction the dibenzylidenesuccinates are an interesting class of compounds that have phototropic and thermotropic properties. These compounds have been studied extensively in their succinic anhydride (fulgide) form **89** (Scheme 36).



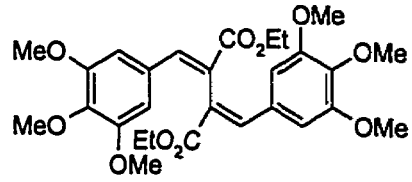
89



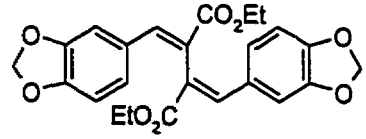
102 Ar = 3,4,5-trimethoxyphenyl

Scheme 36

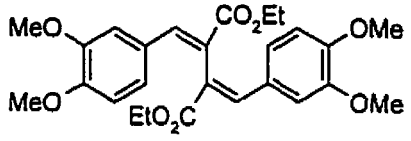
The fulgides have fewer degrees of freedom, as the anhydride restricts conformational flexibility. However, the dibenzylidenesuccinate diesters (**102** for example) have more conformational freedom, as there is no bond between the two ester groups. They rotate and interconvert between their rotamers more freely. The work described in the first part of this section is continuation of the work by a previous student who was able to photocyclize the symmetrical *E,E*-bis-3,4,5-trimethoxybenzylidene succinate **102**. It was assumed that this result could be extended to other symmetrical dibenzylidenesuccinates such as the *E,E*-bis-3,4-methylenedioxybenzylidene succinate **118** the *E,E*-bis-3,4-dimethoxybenzylidene succinate **119**, and the *E,E*-bis-2,4,5-trimethoxybenzylidene succinate **120**.



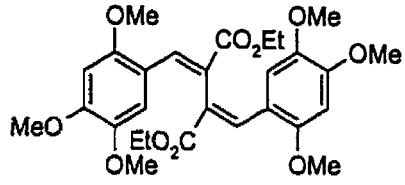
102



118



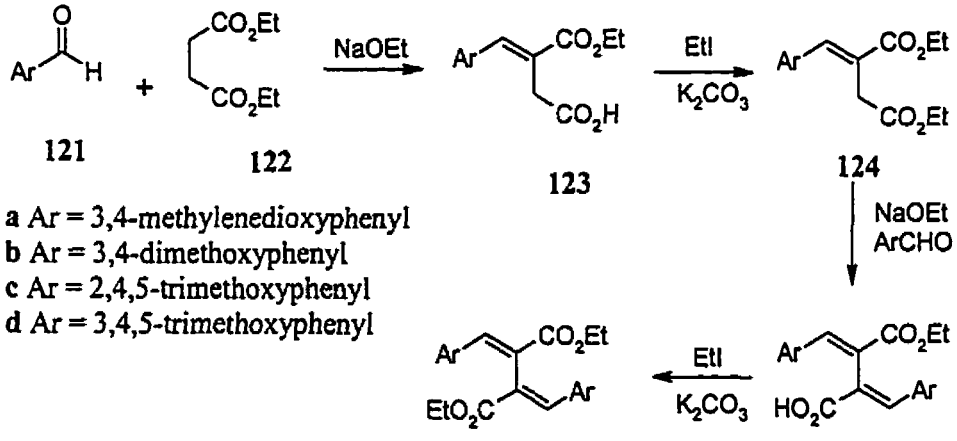
119



120

Scheme 37

In preparation for testing the above hypothesis, compounds **102, 118, 119, 120** were synthesised by two successive Stobbe condensations (Scheme 38). The Stobbe condensation is a versatile reaction whose mechanism was discussed in Chapter 1.



121 122 123 124 125

a Ar = 3,4-methylenedioxyphenyl
b Ar = 3,4-dimethoxyphenyl
c Ar = 2,4,5-trimethoxyphenyl
d Ar = 3,4,5-trimethoxyphenyl

118 Ar = 3,4-methylenedioxyphenyl (88%)
119 Ar = 3,4-dimethoxyphenyl (37%)
120 Ar = 2,4,5-trimethoxyphenyl (45%)
102 Ar = 3,4,5-trimethoxyphenyl (88%)

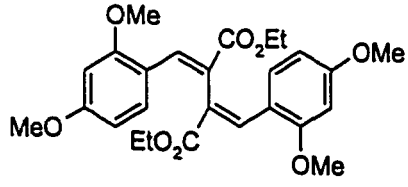
Scheme 38

In the Stobbe condensations piperonal **121a** (3,4-methylenedioxybenzaldehyde), veratraldehyde (3,4-dimethoxybenzaldehyde) **121b**, 2,4,5-trimethoxybenzaldehyde **121c**, or 3,4,5-trimethoxybenzaldehyde **121d** were condensed with diethyl succinate **122** using sodium ethoxide as the base. After work up, the Stobbe half-esters **123a-d** were esterified using EtI and K_2CO_3 in acetone at reflux temperature. The Stobbe diesters **124a-d** were purified by distillation to give yellow oils (ca. 50-60%). A second Stobbe condensation was employed to condense **124a-d** with another equivalent of the appropriate benzaldehyde. Sodium ethoxide was used again as the base. This reaction afforded the diaryl half-esters **125a-d**. For the synthesis of compound **118** and **102** the reaction was worked up and compounds **125a** and **125d** were isolated by column-chromatography (EtOAc-hexanes/AcOH) followed by esterification in acetone using EtI and K_2CO_3 to give **118** and **102** respectively. This procedure was not used for the synthesis of compounds **119** and **120**. Since the diaryl half-esters **125b** and **125c** already existed as their sodium salts in solution after refluxing overnight, a direct conversion to their diesters without workup was attempted by adding EtI directly to the reaction mixture. This proved to be successful and the diesters **119** and **120** were isolated after column chromatography (EtOAc-hexanes) as yellow oils (37% and 87%, respectively).

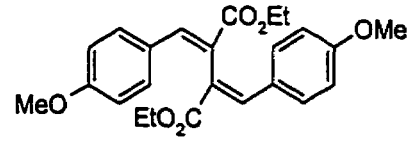
This simplified procedure could not be used for preparation of diester **118** as purification problems were encountered. After *in situ* esterification of **125a**, the diester was very difficult to isolate by column chromatography as some unreacted piperonal would remain and contaminate the product. Piperonal and diester **118** had similar elution times and therefore separation by column chromatography was difficult, producing many mixed fractions. The only way to circumvent this problem was to purify **125a** before

esterification. After esterification, no further purification was necessary, and the diester was isolated in quantitative yield.

A second method was also used to synthesize symmetrical dibenzylidenesuccinates such as the *E,E*-bis-2,4-dimethoxybenzylidene succinate **126** and the *E,E*-bis-4-methoxybenzylidene succinate **127** (Scheme 39).



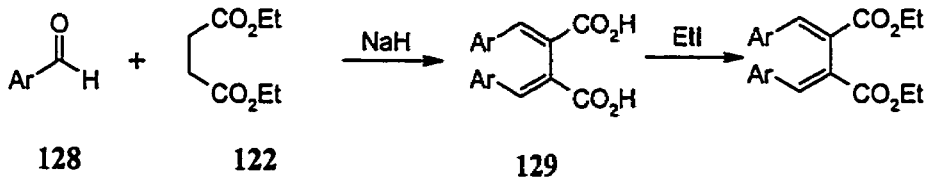
126



127

Scheme 39

Diester **126** was synthesised with the help of a coworker.[73] The experimental procedure (developed by the coworker) was repeated and the characterization data for **126** are included in the experimental section of this thesis. This second method used a modified Stobbe condensation[72,54], where NaH was used as the base, to successively condense two equivalents of either 2,4-dimethoxybenzaldehyde or 4-methoxybenzaldehyde with diethyl succinate in a one-pot reaction (Scheme 40). This reaction was carried out in DMF to afford the diaryl diacids **129a** + **129b** after work up. Compound **129a** was isolated and esterified by refluxing with excess EtI in DMSO to give **126** (59%). Diacid **129b** was esterified *in situ* by adding excess EtI to the initial reaction mixture. After purification diester **127** was isolated (54%).



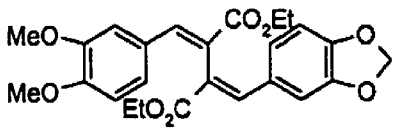
128 122 129

a Ar = 2,4-dimethoxyphenyl
b Ar = 4-methoxyphenyl

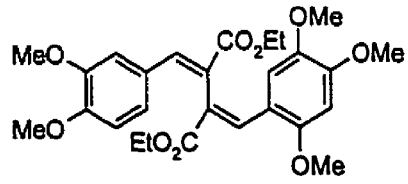
126 Ar = 2,4-dimethoxyphenyl (59%)
127 Ar = 4-methoxyphenyl (54%)

Scheme 40

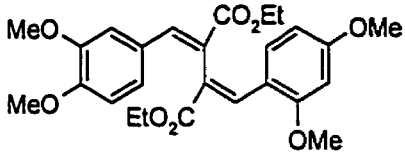
The only method suitable for the syntheses of unsymmetrical dibenzylidenesuccinates was to perform two successive Stobbe condensations. All of the desired unsymmetrical dibenzylidenesuccinates were synthesized by condensing the Stobbe diesters **124a-d** (Scheme 38) with the appropriate benzaldehyde following the procedure described above. Esterification, after the second aryl condensation, was done by adding EtI directly to the reaction mixture. In all, four unsymmetrical diarylbutadienes, shown in Scheme 41, were prepared (**130** (23%), **131** (46%), **132** (36%), **133** (29%)).



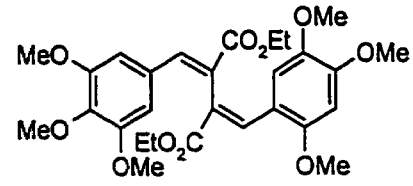
130



131



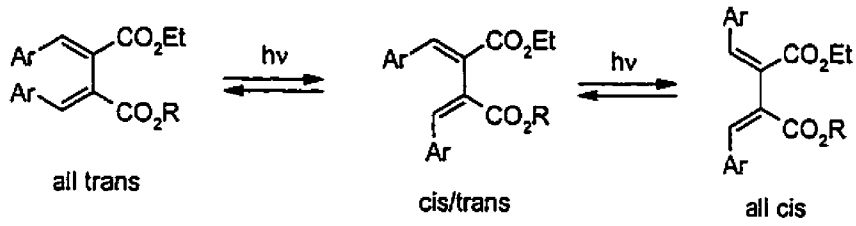
132



133

Scheme 41

Irradiation experiments were carried out to determine if the monoacid-ester **125a** and diester **119** would photocyclize to the 1,2-dihydronaphthalenes. The compounds were dissolved in EtOAc and irradiated with a medium pressure mercury lamp through Pyrex glass (3 mm) for 2 h. The progress of the reaction was monitored by HPLC. The reactions were halted after 2 h. The solvent was evaporated and a ^{1}H NMR spectrum was taken of the crude mixture. The conclusion drawn from the NMR spectra of the crude mixtures was that cis/trans isomerization of the dibenzylidenesuccinates was probably occurring (Scheme 42). This was evident in the ^{1}H NMR spectrum for irradiated **119**, as there was no appearance of peaks typical of the cyclized aryldehydrotetralin, however the appearance of extra vinyl proton and ester group proton peaks would be reasonable to deduce the occurrence of cis/trans isomerization. This meant that at least three compounds were present in the crude mixture. The HPLC trace confirmed the presence of three compounds, 50% all trans starting material, 40% of a compound tentatively assigned the cis/trans structure, and 10% of what is probably the all cis compound (Scheme 42).



all trans cis/trans all cis

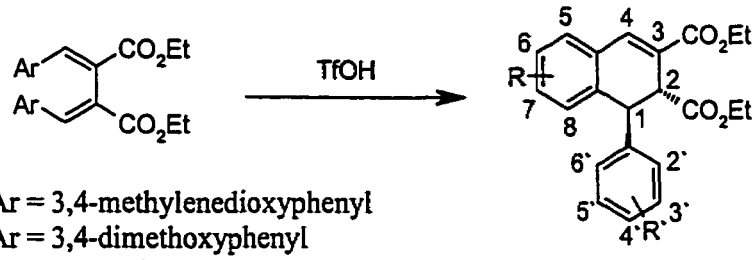
125a Ar = 3,4-methylenedioxyphenyl, R = H
118 Ar = 3,4-methylenedioxyphenyl, R = Et
119 Ar = 3,4-dimethoxyphenyl, R = Et

Scheme 42

For irradiated **125a**, the ^{1}H NMR spectrum showed the presence of only two compounds, 65% all trans starting material and 35% of a compound thought to be the cis/trans isomer of the starting material. The photochemical cyclization of dibenzylidenesuccinates was abandoned, as there was no evidence to confirm the easy formation of the 1,2-dihydronaphthalenes similar to that Yvon had successfully synthesized from diester **102** via this method.[54] Apparently the efficiency of the photocyclization reactions is highly dependent on the exact substituents present.

The photochemical cyclization of dibenzylidenesuccinates could not be applied to other symmetrical dibenzylidenesuccinates. Therefore a search for another general method for cyclizing dibenzylidenesuccinates was undertaken. A coworker eventually discovered that acid could catalyze the cyclization of dibenzylidenesuccinates to aryldehydrotetralins. The preliminary reactions involved treating diester **102** with either dilute sulfuric acid or trifluoroacetic acid (TFA). After work up and isolation, mostly starting material was recovered but a minor fluorescent compound could be detected by TLC in the TFA-catalyzed reaction. It was presumed that this compound was quite possibly the 1,2-dihydronaphthalene **137** (Scheme 43). Two observations were made

from this reaction. Either the dibenzylidenesuccinate was not reactive enough or the acid chosen was not strong enough to catalyze this reaction. Therefore, the more reactive trifluoromethane sulfonic acid (TfOH) was chosen to further probe this possibility. The reaction was done, using the same substrate **102**, in neat TfOH and analysis of the reaction by TLC showed many compounds were produced. It seemed that the right acid had been chosen but that the concentration of TfOH relative to the substrate was too high. In a subsequent reaction, a lower concentration of TfOH (1 eq.) was used, with substrate (1 eq.) dissolved in methylene chloride. The starting material disappeared slowly with little of the fluorescent product being formed. It was postulated that this substrate was not reactive enough for this chosen concentration. Therefore a different substrate was chosen to test its reactivity. Compound **120** was treated with TfOH (1 eq.) and gratifyingly generated the 1,2-dihydronaphthalene **136**. This compound was indeed much more reactive than **102** and later trials using even catalytic amounts of TfOH afforded the corresponding 1,2-dihydronaphthalene in quantitative yields. With this discovery in hand it was decided that a full exploration of acid-catalyzed cyclizations of different dibenzylidenesuccinates should be undertaken to test the generality of this reaction. As part of this thesis work the preliminary work of the coworker was repeated and investigations of other symmetrical dibenzylidenesuccinates were pursued. The results are summarized in Scheme 43.



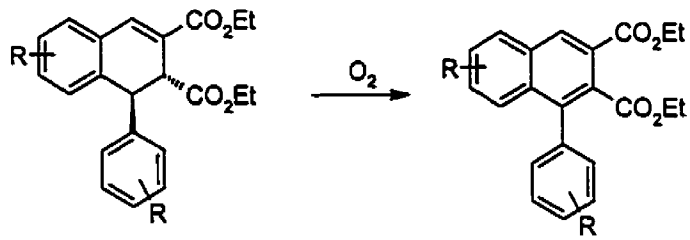
118 Ar = 3,4-methylenedioxyphenyl
119 Ar = 3,4-dimethoxyphenyl
120 Ar = 2,4,5-trimethoxyphenyl
102 Ar = 3,4,5-trimethoxyphenyl
126 Ar = 2,4-dimethoxyphenyl
127 Ar = 4-methoxyphenyl

134 R = 6,7-methylenedioxy, R` = 3`,4`-methylendioxy (36%)
135 R = 6,7-dimethoxy, R` = 3`,4`-dimethoxy (42%)
136 R = 5,7,8-trimethoxy, R` = 2`,4`,5`-trimethoxy (97%)
137 R = 6,7,8-trimethoxy, R` = 3`,4`,5`-trimethoxy (-)
138 R = 5,7-dimethoxy, R` = 2`,4`-dimethoxy (26%)
139 R = 7-methoxy, R` = 4`-methoxy (36%)

Scheme 43

The acid-catalyzed reactions were first done on the symmetrical dibenzylidenesuccinates shown in scheme 43. Although it was observed that the bis-2,4,5-trimethoxybenzylidene succinate **120** reacted readily with one equivalent of TfOH it was decided to determine the optimum concentration needed to catalyze the cyclization. As mentioned, the coworker was successful in converting **120** to **136** using a catalytic amount of TfOH. The experiment was repeated to confirm this result and indeed only a catalytic amount of TfOH was necessary for full conversion to the 1,2-dihydronaphthalene **136**. This was the first indication that substrates with a methoxy group in the 2 and 2` (*ortho*) positions of the aryl rings were more reactive than compounds such as **102** bearing 3- and 3` (*meta*) -methoxy groups. It was assumed that the bis-3,4-dimethoxybenzylidenesuccinate **119** and bis-3,4-methylenedioxybenzylidenesuccinate **118** would not be as reactive as **120** since they lacked the 2- and 2`-methoxy groups. Therefore one equivalent of TfOH was used initially with these two compounds. Diester **119** produced dihydronaphthalene **135** after

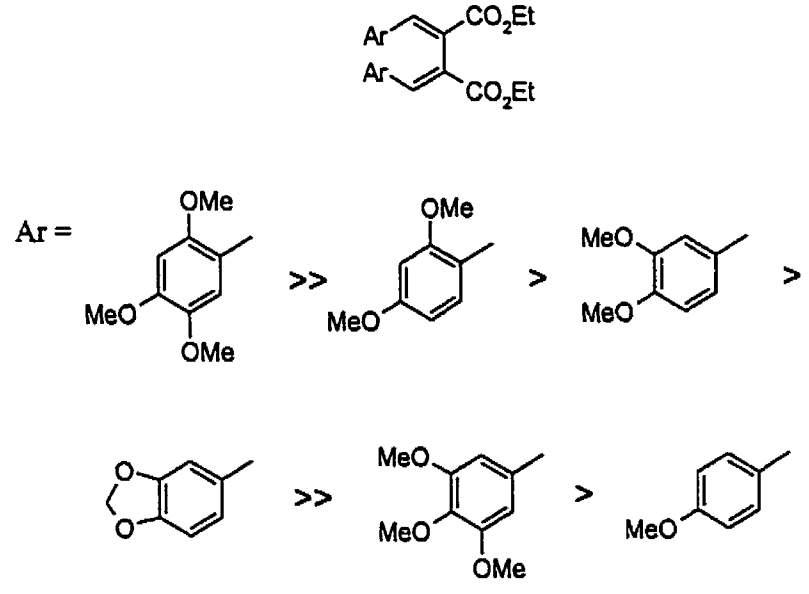
a 5 h reaction time, however the cyclization of **118** to dihydronaphthalene **134** did not go to completion in that time. The yield for the latter reaction was low and the amount of recovered starting material **118** was substantial. As expected, the reactivities for compounds **119** and **118** were lower than that of compound **120**. The acid-catalyzed cyclization was attempted again for **118** using 1.5 equivalents of TfOH and stirring for 8.5 h. The reaction was monitored by TLC and after an 8.5 h reaction time, TLC showed approximately 90% completion (90% product, 10% starting material). The purpose of stopping the reaction at 90% completion was to eliminate unwanted side reactions that occurred over prolonged periods of stirring. These side reactions will be discussed later in the section on cyclization of unsymmetrical dibenzylidenesuccinates. The cyclization of diester **102** was also attempted using 3 equivalents of TfOH and maintaining the reaction temperature at 45 °C for 18 h. The reaction produced a mixture of compounds that were not characterized. One possible compound might have been the fully aromatized arylnaphthalene **102a**. It was known from the coworker's results that some of this compound would form in the presence of oxygen (Scheme 43a). Even though this reaction was performed in a sealed tube, some oxygen might have leaked in during mixing of the reagents. This might have accounted for one the products formed.



102 R = 3,4,5-trimethoxy **102a**

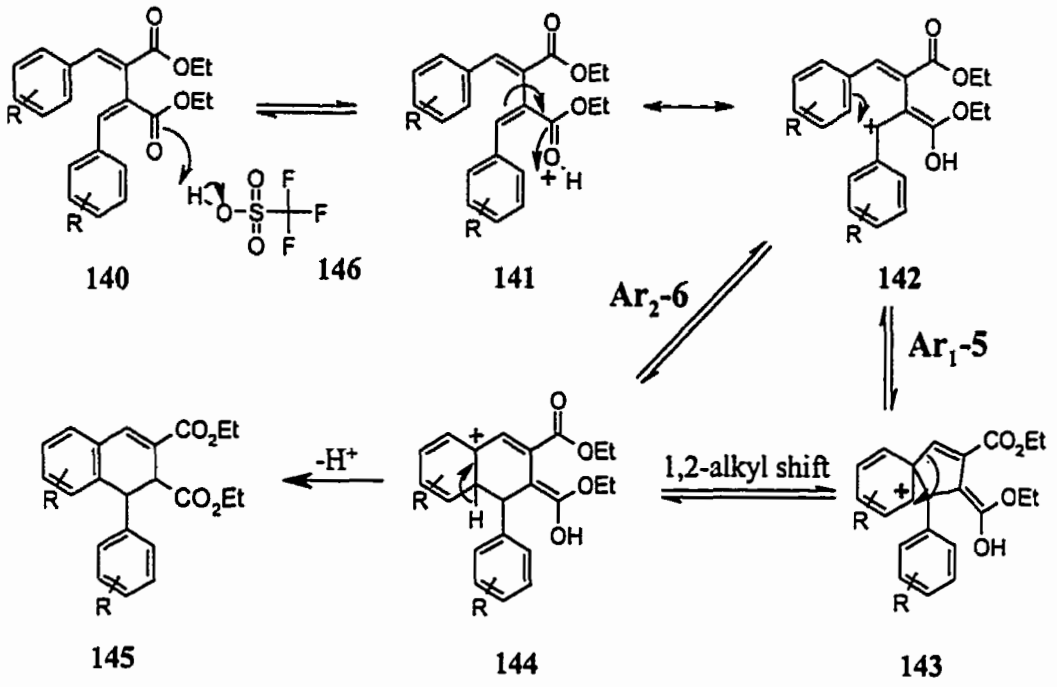
Scheme 43a

The results of the first four reactions depicted an emerging pattern for the effects of aryl substitution, and the position of those substituents, on the rate of cyclization. Further investigation involved the cyclization of bis-2,4-dimethoxybenzylidenesuccinate **126** and the bis-4-methoxybenzylidenesuccinate **127**. The result for the cyclization of **126** reinforced the notion that a 2- and 2`-methoxy substituent aided in cyclization. Diester **126** required 1 equivalent of TfOH and stirring for 4 h to achieve substantial reaction. Compound **127** required 5 equivalents of TfOH and a reaction time of 72 h, by far the longest reaction time for all of the compounds tested. From these results an order of reactivity could be established (Scheme 44). It must be noted that the order of reactivity depicted in Scheme 44 is a rough estimate of the reaction rate as the substrates tested were not done under identical reaction conditions.



Scheme 44

The results indicated that methoxy groups in the *ortho* (2 and 2`) and *para* (4 and 4`) positions accelerated the reaction, presumably by lowering the energy barrier to cyclization. Two proposed mechanisms (Ar_1-5 and Ar_2-6) are outlined in Scheme 45. Substituents in the *meta* (3 and 3`) positions did not appear to accelerate the reaction. A direct electrophilic substitution at the C-2 position to produce intermediate **144** (Scheme 45) would presumably be enhanced by methoxy groups at the *meta* positions. On the contrary, as pointed out above, this type of substitution did not enhance the rate of reaction. Therefore a different mechanism for formation of the product was sought. Winstein and Heck, in a study of 4-aryl-*n*-butyl-*p*-bromobenzenesulfonates made similar observations of substituent effects on cyclization rates.[81] They proposed an alternate cyclization mechanism to explain the substituent effects (see below). Applying their model leads to the proposition that cationic intermediate **143** precedes the formation of intermediate **144** (Scheme 45).

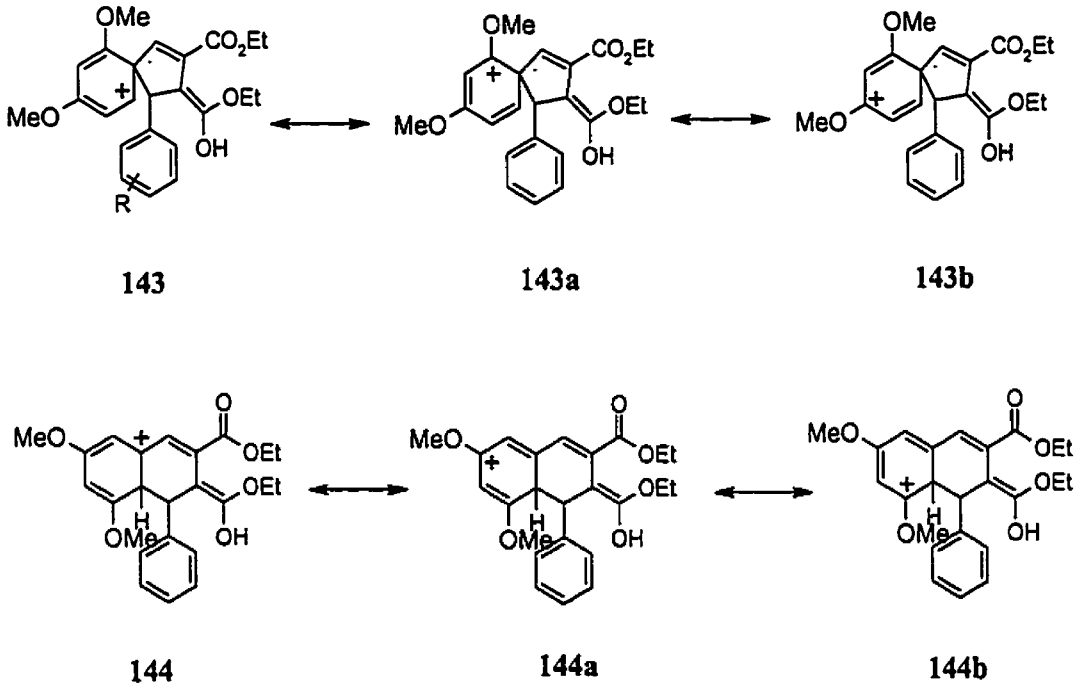


Scheme 45

A protonated ester carbonyl group could be generated by transfer from TfOH. The resulting cation can be drawn in two resonance forms, **141** and **142**. Intermediate **142** could follow two possible cyclization routes. The first route would involve a direct one-step cyclization to produce the cationic intermediate **144**. Intermediate **144** would presumably be a high-energy species since the aromaticity of the aryl ring is lost in this intermediate. Alternatively compound **142** could undergo a two step cyclization forming the spiro-carbocation **143** first, followed by a 1,2-alkyl migration to then afford the intermediate **144**. The result from both pathways would be the eventual formation of the high-energy intermediate **144**.

In the rate limiting step between intermediates **142** and **144** the direct Ar_2-6 mechanism presumably has a higher activation energy barrier compared to the indirect two-step Ar_1-5 mechanism. If this were true, then methoxy groups *ortho* and *para* to the

ipso centre (C-1 of aryl ring) in **143**, which could stabilize the positive charge at C-2 adjacent to the ipso centre, would presumably increase its rate of formation. This in turn would accelerate the overall reaction, as observed. The resonance contributors to intermediate **143** can better illustrate how the substituents stabilize **143** (Scheme 45a).



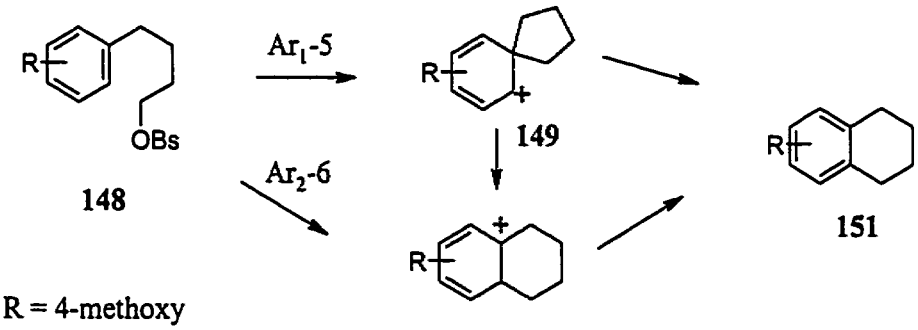
Scheme 45a

It is evident that the resonance contributors **143a** and **143b** are both positively charged at the methoxy group carbon centres. The electron donating effects of methoxy groups would stabilize the positive charge in both resonance structures. The result would be an overall lowering in energy of species **143** and subsequently the barrier leading to it. In the case of the Ar_2-6 mechanism the resonance contributors **144a** and **144b,** with methoxy groups in the *meta* positions, could also contribute to stabilizing species **144**.

Since it was observed that *ortho* and *para* substituted substrates cyclized more readily, one is led to believe that the Ar_1-5 pathway is more important in this reaction.

The proposal of the two possible intermediates (**143** and **144**) leading to the aryltetralin structure is supported by the studies of Winstein and Heck on the 4-phenyl-1-butyl systems.[74-76] Their experiments delved into the participation of aryl groups on the solvolysis of 4-aryl-1-butyl *p*-bromobenzenesulfonates **148**. Furthermore the substituent effects of methoxy groups on the aryl ring were also studied in detail.

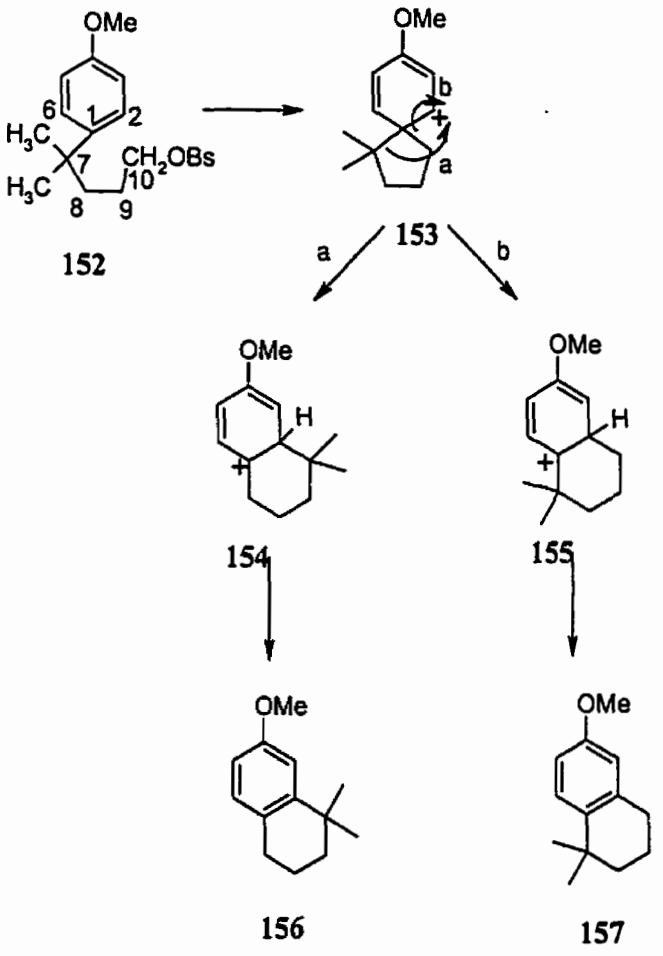
The general notation Ar_a-*n* was used to denote the possible mechanisms, where *a* represented the position of the participating aryl group involved in creating the ring in the intermediate and *n* indicated the size of the ring being formed.[74] Depending on the substitution on the aryl rings the reaction went either via the Ar_1-5 **149** or the Ar_2-6 **150** mechanism (Scheme 46). It was proposed that the 4-methoxybenzenesulfonate **148a** and the 2,4-dimethoxybenzenesulfonate **148b** cyclized through only the Ar_1-5 mechanism and the cyclization of 3-methoxybenzenesulfonate **148c** and 3,5-dimethoxybenzenesulfonate **148d** went exclusively through the Ar_2-6 transition state. The reasons postulated for the enhanced reactivity through the Ar_1-5 mechanism are similar to the argument made for cyclization of dibenzylidenesuccinates in Scheme 45. Methoxy groups in the *ortho* and *para* positions to the C-1 ipso centre will have a greater rate accelerating effect if the reaction is proceeding through an Ar_1-5 that an Ar_2-6 mechanism. Similarly methoxy groups in the *meta* positions would be more rate accelerating if the reaction were proceeding through an Ar_2-6 mechanism. The fact that 2,4-dimethoxybenzenesulfonate reacts faster than 3,5-dimethoxybenzenesulfonate illustrates the importance of the Ar_1-5 route.[81]



a R = 4-methoxy
b R = 2,4-dimethoxy
c R = 3-methoxy
d R = 3,5-dimethoxy
e R = 3,4-dimethoxy

Scheme 46

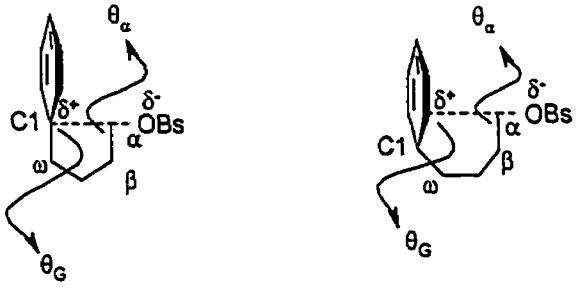
Further experimental evidence was gathered to support the formation of the spiro-carbocation **149**. This experiment involved eliminating the plane of symmetry of the proposed intermediate **149** by adding a reporter group onto the alkyl chain in 4-methoxybenzenesulfonate **152**. The purpose of this experiment was to test the migratory preference of the 1,2-alkyl shift (Scheme 47), if this intermediate formed at all. If the 1,2-alkyl shift were to occur, as in pathway 'a' then the reporter group would end up on C-10 as in **156**. On the other hand if pathway 'b' were to occur then the reporter group would remain on C-7 as in **157**. In general, the predicted migratory aptitude descends the order from most substituted alkyl group (tertiary) to the least substituted alkyl group (primary).[81] Since pathway 'a' has the tertiary carbon centre, migration of this group would be preferred over migration of the primary carbon centre in pathway 'b'. This was observed as solvolysis produced entirely tetralin **156**. This provided unequivocal evidence for the formation of the spiro-carbocation **153**. The only mechanism for formation of tetralin **156** would have to involve rearrangement of the spiro-carbocation **153** via pathway 'a'.[81-83]



Scheme 47

As mentioned before, substituents on the aryl ring played an important role in activating and deactivating the reaction through the proposed mechanisms during cyclization. For *ortho* and/or *para* methoxy substituted compounds, the Ar_1-5 mechanism predominated whereas *meta* methoxy substitution enhanced the Ar_2-6 mechanism. Benzenesulfonate **148e** was prepared by Winstein and Heck to test the effects of having simultaneous substitution at the *meta* and *para* positions. If the Ar_1-5 and Ar_2-6 mechanisms were independent of one another then it was assumed that there

would be competition between the two. Furthermore the rate of the reaction for the disubstituted molecule should be approximately equal to the sum of the rates of the reaction for the *meta* and *para* monosubstituted benzenesulfonates (**148c** and **148a**). In fact, the rate of cyclization of benzenesulfonate **148e** exceeded the sum of the rates of **148c** and **148a**. This seemed to implicate the rate-enhancing effects of the *meta* methoxy group. However, the authors did not believe that the Ar_1-5 and Ar_2-6 participation reactions were so electron-demanding to elicit this increased rate. They believed that this methoxy group actually retarded this cyclization since the more electron-demanding Ar_1-3 participation studies, done previously, had a *meta* methoxy group that hindered the reaction. It is plausible that the Ar_1-5 and Ar_2-6 mechanism are not completely distinct or independent of one another in this case. An explanation was provided to rationalize all the observations described above (Scheme 48).[75]



Ar_1-5 transition state

Ar_2-6 transition state

Scheme 48

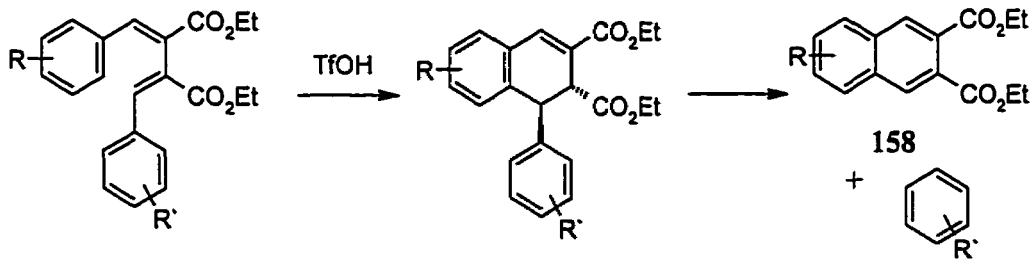
For both Ar_1-5 and Ar_2-6 the approach of C_α towards the aryl C-1 or C-2, respectively would be 180°, the normal hybridization of an internal substitution reaction. This approach would also be perpendicular to the plane of the benzene ring. For the Ar_1-5 mechanism this approach forms the relatively strainless five-membered ring.

Expanding to the relatively strain-free six-membered ring can also occur, as in the Ar_2-6 mechanism. Furthermore formation of he five-membered ring is inherently faster than formation of the six-membered ring.

Weinstein and Heck's work is in good agreement with the dibenzylidenesuccinate results.

Jackman and Hadon have extended Winstein and Heck's work and demonstrated through deuterium labelling of 4-aryl-1-butyl *p*-bromobenzenesulfonates that cyclization does not go exclusively through the Ar_1-5 or Ar_2-6 mechanisms.[77] In fact they were able to calculate a percentage for each mechanism that contributes to the overall product formation. They used the hydrogen-deuterium kinetic isotope effects to study the *p*-methoxy substituted systems and found that it cyclized 74.2% Ar_1-5 and 25.8% Ar_2-6. This situation was reversed when the methoxy group was replaced with a methyl group. The cyclization was 69.4% Ar_2-6 and 30.6% Ar_1-5. This was also the case for positioning the methoxy group at the *meta* position. It was predicted that the mechanism for this cyclization proceeded exclusively through the Ar_2-6 mode.

The high reactivity of dibenzylidenesuccinates with aryl rings bearing the 2 and 2`- (*ortho*) methoxy substituent proved to be a disadvantage for acid-catalyzed cyclization of unsymmetrical dibenzylidenesuccinates. The more reactive aryl ring would cyclize onto the less reactive aryl ring. This would seem to be an excellent outcome since that would constitute a stereoselective reaction. However, due to the high reactivity of the aryl ring bearing the *ortho*-methoxy it undergoes dearylation (Scheme 49).



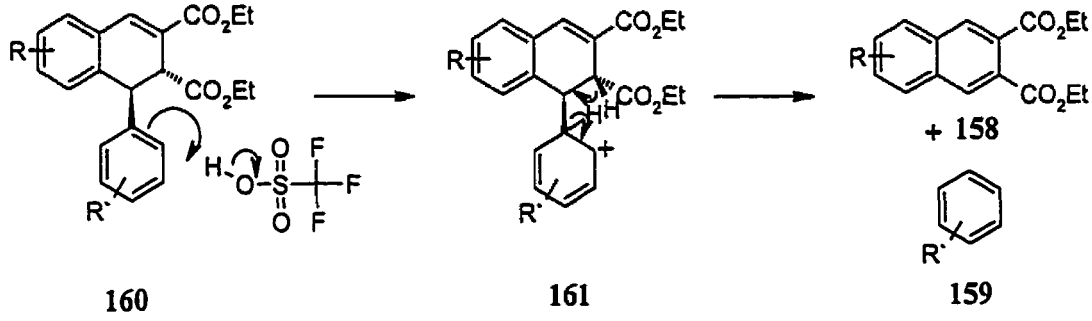
130 R = 3,4-dimethoxy, R` = 3,4-methylenedioxy
131 R = 3,4-dimethoxy, R` = 2,4,5-trimethoxy
132 R = 3,4-dimethoxy, R` = 2,4-dimethoxy
133 R = 3,4,5-trimethoxy, R` = 2,4,5-trimethoxy

158a R = 3,4-dimethoxy
158b R = 3,4,5-trimethoxy

159a R` = 2,4,5-trimethoxy
159b R` = 2,4-dimethoxy

Scheme 49

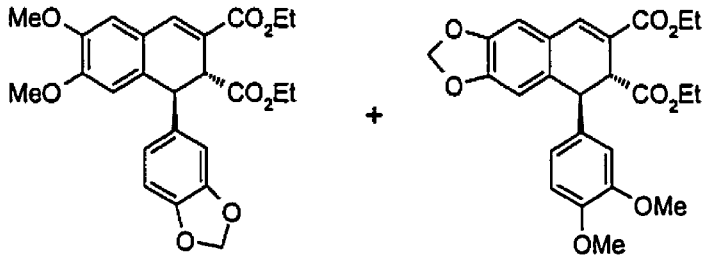
The mechanism for this dearylation probably involved protonation of the pendant aryl ring (**160**) followed by aromatization of the tetralin ring (**161**) with the pendant ring **159** acting as a leaving group (Scheme 50).



160 **161** **159**

Scheme 50

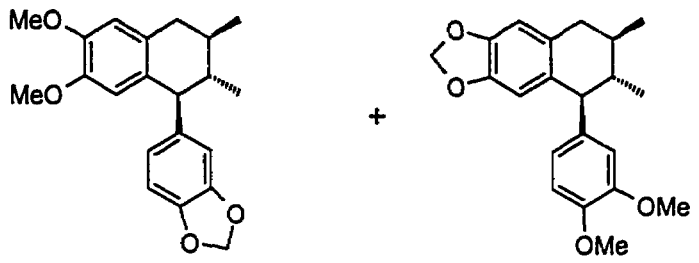
The driving force for this reaction is most likely the aromatization of the tetralin ring to give the naphthalene ring **158a,b**. For unsymmetrical diester **130**, that bore the less reactive 3,4-methylenedioxyaryl group and the 3,4-dimethoxyaryl group, dearylation did not occur in this case. Instead cyclization afforded a mixture of the two possible 1,2-dihydronaphthalenes **162** and **163**.



162 **163**

Scheme 51

Unfortunately it was difficult to drive this reaction to completion as evidenced by the ^1H NMR spectrum of the isolated material. Integration of the vinyl peaks showed a ratio of 2:1 unreacted dibenzylidenesuccinate **130** and a mixture of the 1,2-dihydronaphthalenes **162** and **163**. The mixture of products consisted of 75% of dihydronaphthalene **162** and 25% of dihydronaphthalene **163**. Separation of the two isomers by column chromatography was difficult as they had virtually identical elution times. It was unfortunate that the product selectivity was not closer to 100% as that would have generated one pure isomer. Either isomer could presumably have been converted to the respective natural lignans, Isogalcatin **164** and Galcatin **165** (Scheme 52).



164 165

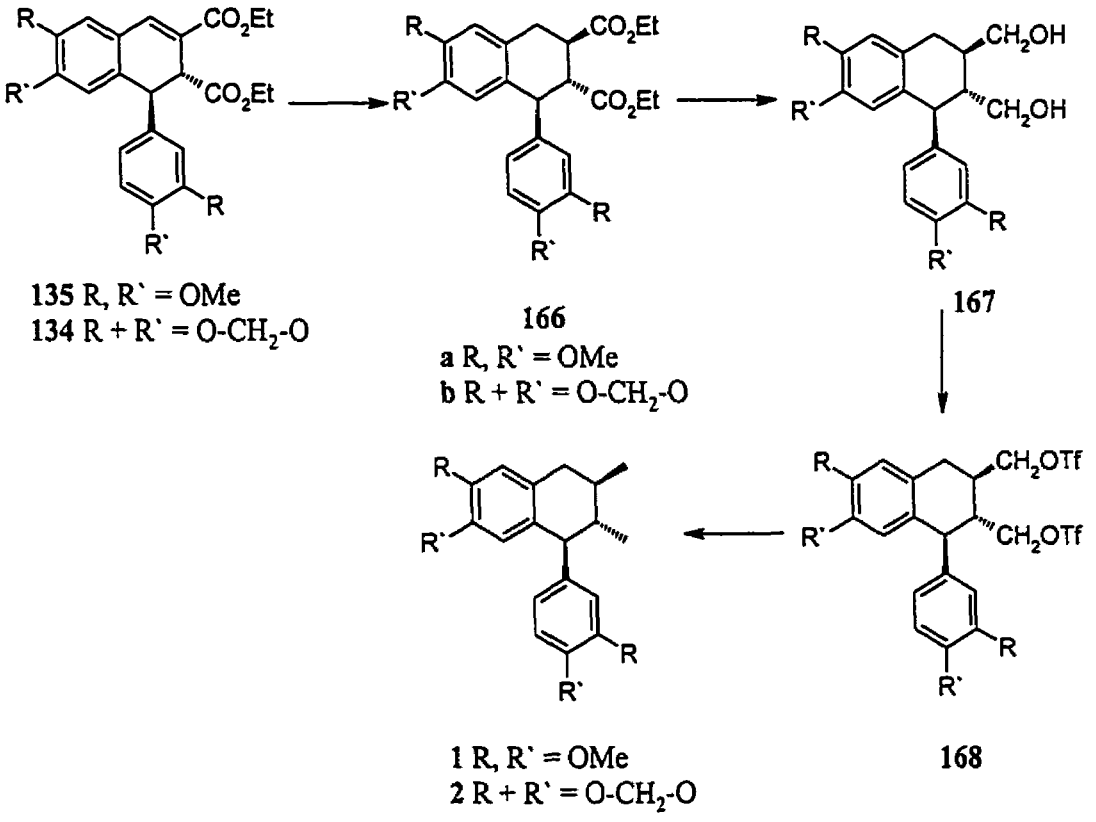
Scheme 52

This would have been most beneficial towards expanding the scope of this thesis for the preparation of other natural lignans using the proposed new synthetic methodology.

3.2 Synthesis of Galbulin and Cagayanin: The New Synthetic Methodology

The acid-catalyzed cyclization of dibenzylidenesuccinates was studied in depth in the last section with two plausible mechanisms proposed to explain the results. These results were consistent with those reported in the literature for 4-aryl-1-butyl-bromobenzenesulfonates (Scheme 46 and 47). The successful synthesis of the 1,2-dihydronaphthalenes paved the way for the use of this reaction in lignan synthesis.

Galbulin and cagayanin were chosen as synthetic targets as they both have similarly substituted aryl groups and it could be imagined that they could be derived from symmetrically substituted dibenzylidenesuccinates. Galbulin bears the bis 3,4-dimethoxy substituents and cagayanin bears the bis 3,4-methylenedioxy substituents. The core structures of the lignans correspond exactly to two of the 1,2-dihydronaphthalenes produced in the earlier work (**135** and **134**). To obtain these natural lignans, all that was required was functional group conversion of the ethyl ester groups to methyl groups and the reduction of the vinylic functional group. The synthetic protocol is outlined in Scheme 53.



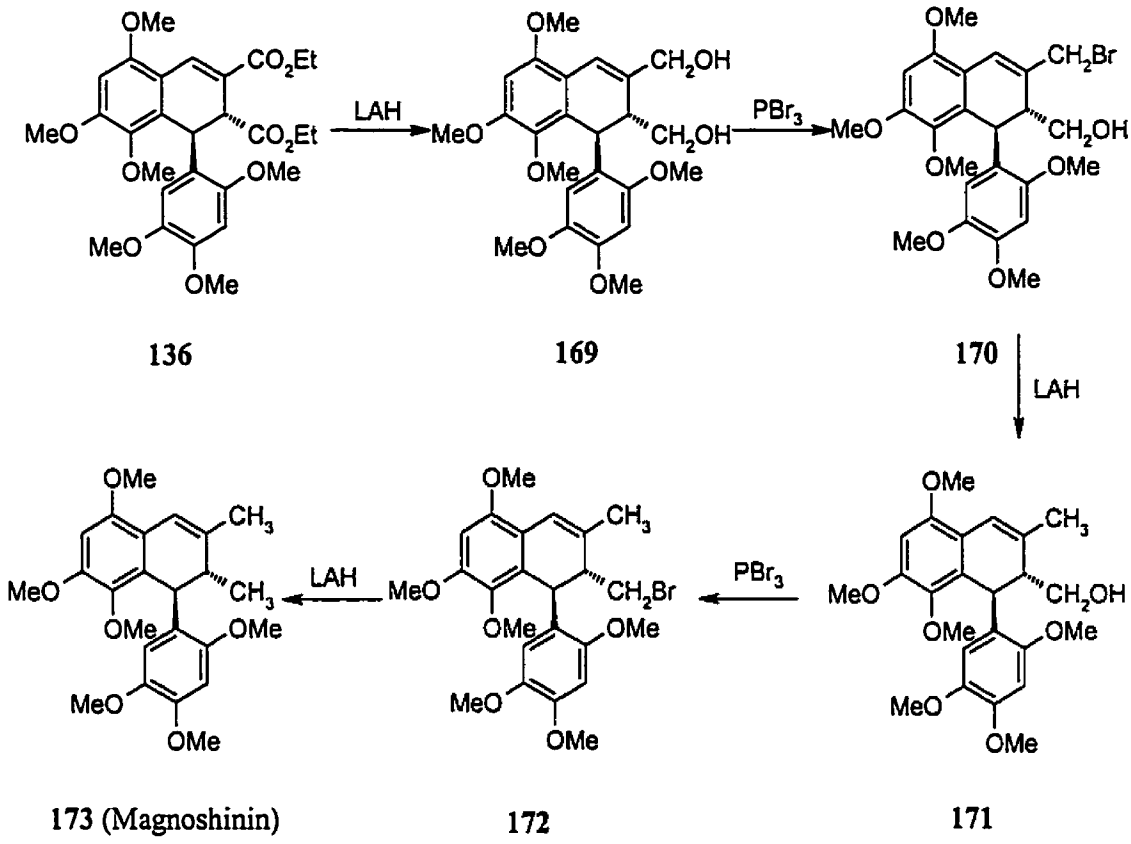
Scheme 53

Starting from the 1,2-dihydronaphthalene **135**, the first synthetic step involved reducing the double bond. This was achieved by hydrogenation using H_2 over a palladium on activated carbon catalyst, in ethanol. The palladium catalyst was removed and the saturated diester **166a** was isolated in nearly quantitative yield. The ^1H NMR verified the structure as evident from the disappearance of the vinyl proton at 7.6 ppm and the appearance of a multiplet at 3.9 ppm corresponding to the new C-4 methylene group.

The ester groups were reduced to produce the diol **167a**. This was achieved using LAH in THF, stirring at room temperature under N_2. After 30 minutes the reaction was complete as determined by TLC. Fieser workup gave the resulting diol **160a** that was

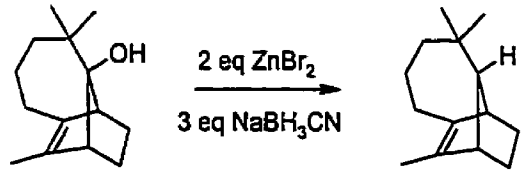
stable enough at room temperature to obtain a ^{1}H NMR spectrum. The ^{1}H NMR spectrum validated the authenticity of this compound through the disappearance of proton peaks corresponding to the two ester functionalities. A pair of triplets at 0.96 and 1.24 ppm and a pair of multiplets at *ca.* 4.1 ppm were replaced by a pair of broad multiplets at 1.8 and 2.0 ppm. The pair of triplets and multiplets corresponded to the two diethyl esters and the two broad multiplets confirmed the generation of two methylene groups.

Difficulties arose in deoxygenating the diol **167a** to produce the dimethyl functionality as found in galbulin and cagayanin. It was at first thought that the diol could be deoxygenated in a two step process by conversion to the dibromide followed by reduction to the hydrocarbon. However, attempts at conversion of the diol to the dibromide using PBr_3 proved to be unsuccessful. This was surprising as this was the method employed by Yvon in her synthesis of Magnoshinin 173 (Scheme 54).[54] The only structural difference, other than the aryl rings, between magnoshinin **173** and galbulin **1**, was the unsaturated double bond.



Scheme 54

An example of deoxygenating alcohols to alkyl groups was given in Smith[79] with reference to a paper by Volkmann *et al* on the synthesis of longifolene.[80] In one synthetic step, zinc bromide and sodium cyanoborohydride were used to reduce a bridgehead alcohol to an alkyl group (Scheme 55).

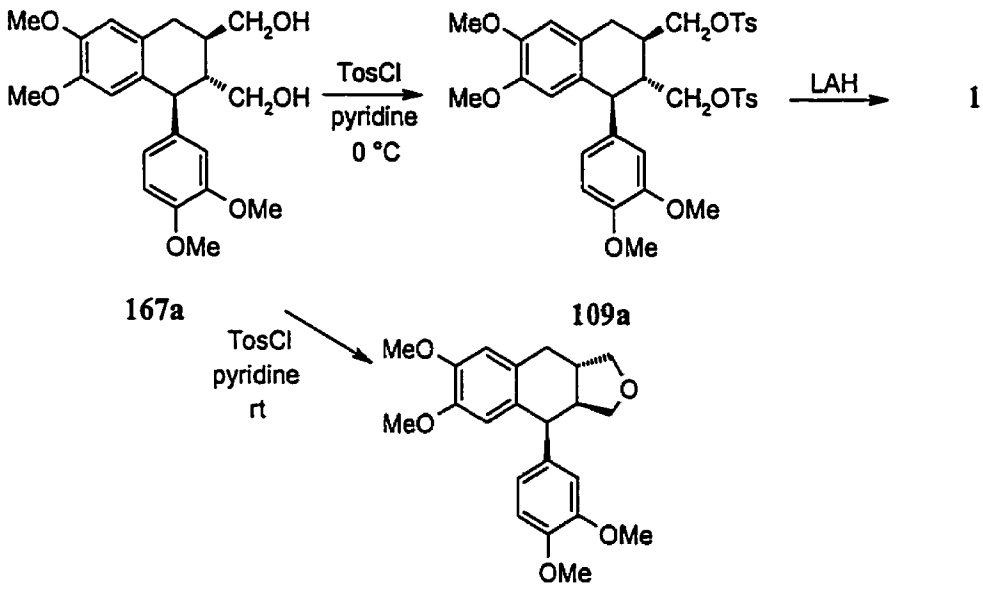


Scheme 55

This one step reaction was attempted for diol **167a**, however it did not give the desired product. In hindsight the chances for success of this reaction was probably low because the reaction mechanism presumably goes through a carbocation. The tertiary carbocation formed at the bridgehead, although strained, would be more stable than the primary carbocation formed in diol **167a**.

The two step procedure for reduction of the diol **167a** via conversion to a bis sulfonate, followed by reduction was next considered. Sulfonation was attempted using *p*-toluenesulfonyl (tosyl) chloride (TsCl) and diisopropylethylamine (DIPEA). The reaction was stirred for 4 h at room temperature and after workup the ditosylate **109a** (Scheme 56) could not be detected in the ^{1}H NMR spectrum of the crude product. A second attempt was carried out, bypassing the characterization of the ditosylate. Instead the presumed ditosylate, was immediately reduced using LAH. Again, this proved to be unsuccessful as the ^{1}H NMR spectrum did not show proton peaks of galbulin.

While writing this thesis it was discovered in a literature paper that the conversion to the ditosylate and its subsequent reduction to galbulin had already been achieved. This was accomplished with tosyl chloride and pyridine under cold conditions (Scheme 56).[59]



174

Scheme 56

Furthermore the authors reported that performing this reaction at room temperature severely reduced the yield of galbulin and increased the yield of a side reaction, the formation of the corresponding tetrahydrofuran **174**. This would account for the unsuccessful attempt at conversion of **167a** to galbulin using tosyl chloride and DIPEA. Since the reaction was done at room temperature the possibility of tetrahydrofuran formation was conceivable. Subsequent reduction of the tetrahydrofuran using LAH would have been difficult. A third attempt following the literature procedure might be successful in generating galbulin. Unfortunately at the time of the study this literature procedure had not been discovered and therefore a different synthetic conversion was attempted.

A coworker suggested that conversion of the diol to the ditriflate **168a** followed by reduction with LAH might afford galbulin. The triflate group is a highly reactive

species that often features in studies of substitution reactions since they are such excellent leaving groups. Preparation of the ditriflate was attempted using triflic anhydride and DIPEA in methylene chloride at –10 °C. Triflic anhydride was added dropwise to the cooled diol solution and after 15 minutes, the reaction quenched with water. To prevent the formation of the tetrahydrofuran **174**, no attempt was made to isolate or characterize the ditriflate **168a**. After work up, the solvent was removed and the residual compound immediately reduced using LAH in THF that had been cooled to –10 °C. After 20 minutes had elapsed the reaction was subjected to Fieser workup and the resulting residue was chromatographed (EtOAc-hexanes). The major product isolated after chromatography was galbulin **1** (43%). The synthesis of cagayanin **2** (77%) was achieved by performing a parallel synthesis using the same synthetic protocol, as shown in Scheme 53. The evidence to support the synthesis of galbulin is in the comparison of the ^{1}H NMR spectra of the isolated product with data found in the literature on galbulin.[28,29] Although a synthesis of cagayanin has never been published previously, a full characterization was made when it was first isolated. The ^{1}H NMR spectrum of the synthetic cagayanin, from above, and that reported of natural cagayanin were identical. The most characteristic peaks that verify the structures of both galbulin and cagayanin are two doublets at *ca.* 1.0 ppm. These are assigned to the two methyl groups at C-2 and C-3.

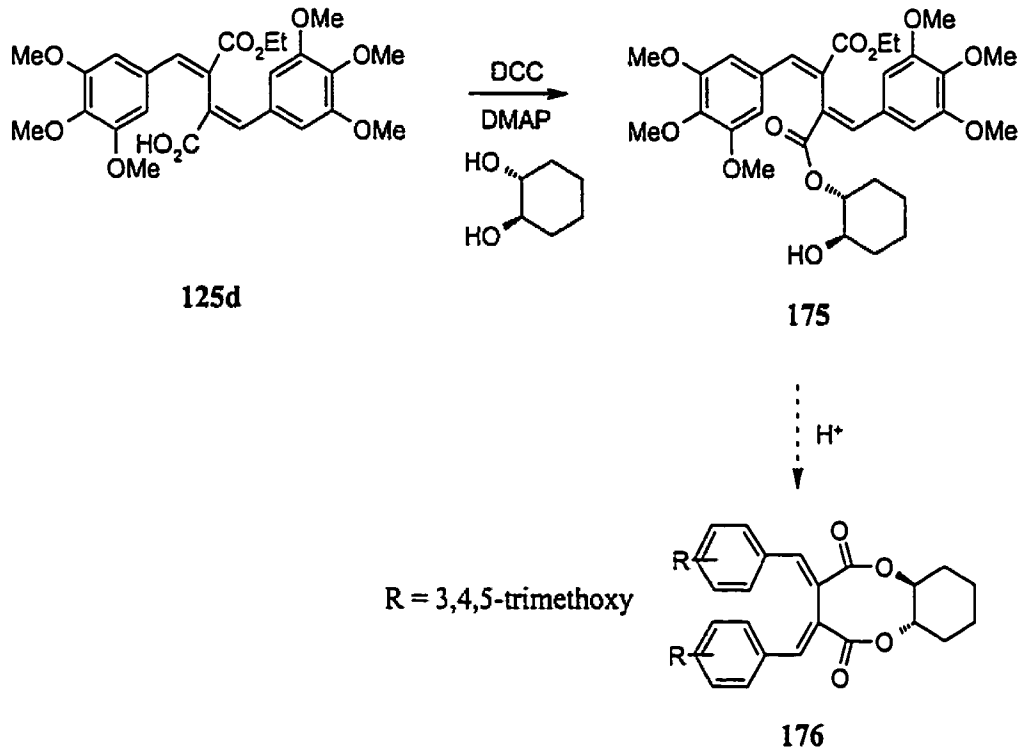
3.3 Atropisomerism and Asymmetric Syntheses of Lignans

The intent of the third part of this thesis work was to extend the project started by the two previous colleagues mentioned in section 1.5.4.1 of the introduction. Hiebert studied the *E,E*-bis-3,4-methylenedioxybenzylidene succinic acid (**99** in Scheme 27) and

found that attaching chiral α-methylbenzylamide groups led to the formation of atropisomeric diasteromers (**100** and **101**) as detected by NMR spectroscopy. Unfortunately, the diastereomers were not stable enough to allow for separation. Yvon discovered that the *E,E*-bis-3,4,5-trimethoxybenzylidenesuccinate **102** also demonstrated atropisomeric diastereomerism after the addition of a single methyl mandelyl group (see Scheme 59).[54] Unfortunately this also did not provide the required steric bulk for slowing of interconversion to allow for separation of the rotamers. As with the amides prepared by Hiebert, only detection of the atropisomeric populations by NMR spectroscopy was possible.

Further attempts by Yvon at introducing a chiral auxiliary that would more successfully hinder interconversion of the diastereomers proved to be unsuccessful although she did manage to make some partial progress towards this end (Scheme 57). The objective was to condense *trans*-1,2-cyclohexanediol to the dibenzylidenesuccinate to form the rigid cyclic ester **176**. Using dicyclohexylcarbodiimide (DCC) and DMAP she was able to condense the monoacid **125d** to one of the alcohol groups. The ^{1}H NMR of the isolated cyclohexyl ester **175** provided the evidence for the formation of this compound. Several of the proton peaks were doubled indicating the existence of two diastereomers. These two diasteromers were confirmed by analysis of the ^{13}C NMR that also showed evidence of the two atropisomeric diastereomers of **175**. Several attempts at trans-esterification of the ethyl ester with the other alcohol group of cyclohexanediol in **175** to **176**, all failed. The treatment of cyclohexyl ester **175** with either TsOH or TFA did not produce the desired dilactone **176**. A subsequent attempt at tandem coupling of the *E,E*-bis-(3,4,5-trimethoxybenzylidene) succinic acid **177** to *trans*-1,2-cyclohexanediol

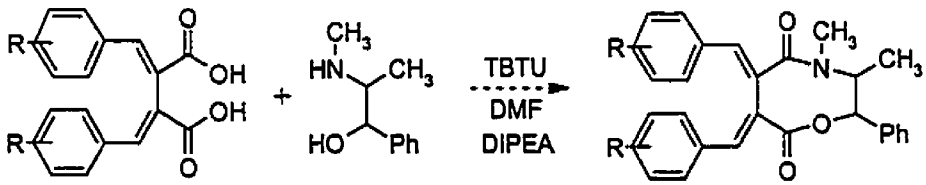
also did not produce the dilactone. The failure of these reactions was attributed to the difficulty of forming eight-membered rings. The torsional strain produced in medium sized rings could not be tolerated in this system.



Scheme 57

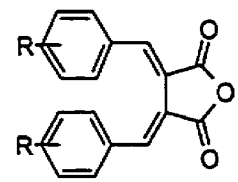
A further attempt to prepare isolable atropisomeric diastereomers of dibenzylidenesuccinates was made in this thesis. Instead of using a ring system, such as cyclohexanediol, as the chiral auxiliary, a more flexible chiral auxiliary, ephedrine 178 was chosen. Ephedrine contains a secondary amine and an alcohol group in a 1,2 relationship and could conceivably be used to form a cyclic ester-amide as shown in scheme 58. The flexibility of ephedrine would presumably allow the system to relieve the torsional strain generated in the eight-membered ring.

The coupling was attempted between *E,E*-bis-(3,4,5-trimethoxybenzylidene) succinic acid **177** and ephedrine **178** using benzotriazol-1-y-1,1,3,3-tetramethyl uronium tetrafluoroborate (TBTU) as the coupling reagent (Scheme 58). The colour of the reaction changed from yellow to green as the reaction progressed and formation of the succinic anhydride (fulgide) was suspected. Several attempts produced the same result. It was speculated that formation of the fulgide was much faster and energetically and entropically more favourable than coupling to ephedrine. Yvon also encountered this problem in her attempt to couple the diacid **177** to cyclohexanediol using DCC.[54] At first, it appeared that the eight-membered ring of the dilactone had formed so therefore she irradiated the compound but the product formed was consistent with the aryltetralin anhydride formed from the fulgide. It was determined that the peaks in the ^{1}H NMR corresponding to the cyclohexyl group arose from the cyclohexyl urea byproduct of DCC and not from the expected dilactone cyclohexyl group.



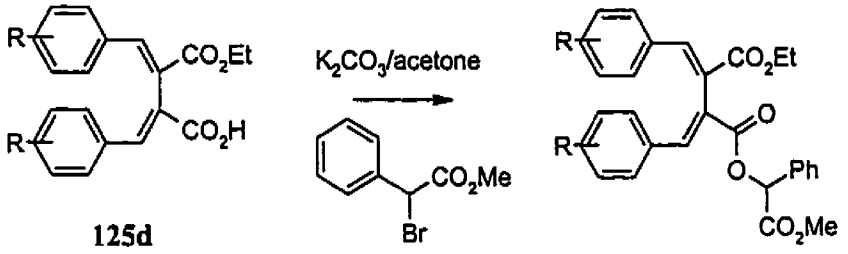
177 **178** **179**

R = 3,4,5-trimethoxy



Scheme 58 **180**

Yvon was able to successfully synthesise the *E,E*-dibenzylidenesuccinate methylmandelylethyl ester **182** by coupling of the monoacid-ester **125d** with methyl α-bromophenylacetate **181** (Scheme 59).[54]



125d

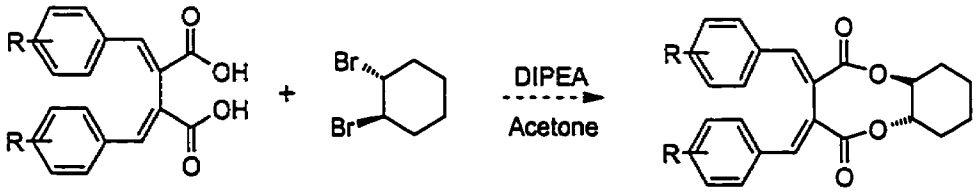
R = 3,4,5-trimethoxy

181

182

Scheme 59

The methylmandelyl ester **182** was used in the dynamic NMR studies to probe the atropisomerism demonstrated in this sterically congested molecule. The use of a brominated alkylating agent to esterify the carboxylic acid group was successful therefore the use of a bromine species to form the dilactone eight-membered ring was contemplated.



177

183

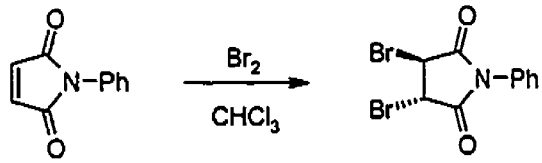
184

R = 3,4,5-trimethoxy

Scheme 60

In a first attempt at a dialkylation reaction *E,E*-bis-(3,4,5-trimethoxybenzylidene) succinic acid **177** was reacted with *trans* 1,2-dibromocyclohexane **183** (Scheme 60).

This reaction was unsuccessful, as the ^{1}H NMR spectrum showed no cyclohexyl proton peaks in the aliphatic region. Only the recovered diacid **177** was detected. It was surmised that dibromocyclohexane **183** was not reactive enough for the substitution reaction. An activated dibromide species would be more susceptible to S_N2 substitution. *N*-phenylmaleimide **185** was chosen as a starting reagent as it contained an unsaturated double bond that could be halogenated. Furthermore it contained two electron-withdrawing carbonyl groups that could promote the substitution to the diacid **177**. *N*-phenylmaleimide **185** was commercially available and the phenyl protection of the imide group was necessary to prevent unwanted side reactions at this centre. Bromination of the double bond was achieved using bromine in chloroform following a literature procedure (Scheme 61).[84]

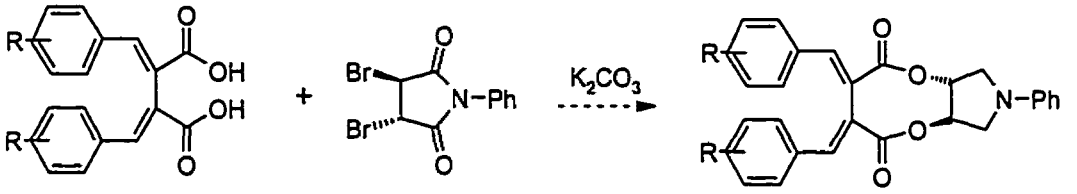


185 **186**

Scheme 61

The vicinal dibromide **186** precipitated out of chloroform as a white solid. A ^{1}H NMR of **186** was compared to the ^{1}H NMR of the starting *N*-phenylmaleimide. The dibromide structure was confirmed by the disappearance of the succinimide peaks at 6.8 ppm corresponding to the two vinyl protons and the appearance of a two proton singlet at 4.9 ppm corresponding to the two vicinal protons attached to the bromine centres. Several attempts at substituting the diacid **177** with the more reactive dibromosuccinimide **186**

proved to be difficult, as it produced only a mixture of unidentifiable products (Scheme 62).

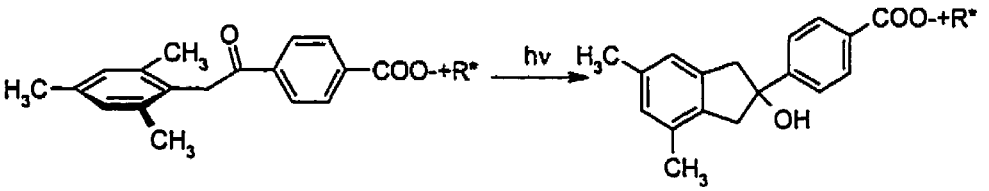


177 186 187

R = 3,4,5-trimethoxy

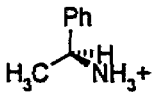
Scheme 62

An idea for achieving enantioselective photocyclization of dibenzylidenesuccinates emerged from Scheffer's research on photochemistry of molecules in the solid state.[85-89] Scheffer's group studied the effects of ionic chiral auxiliaries on the cyclization of many compounds that contained a carboxylic acid functionality. The principle behind the chemistry was to crystallize the compounds as chiral amine salts. Upon crystallisation, molecules can pack into a crystal lattice of one enantiomeric form. An example of a chiral crystalline salt is shown for an α-mesitylacetophenone derivative **188** in scheme 63 below.

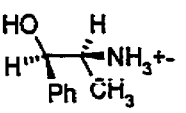


188 189

a R* = (S)-(-)-α-methylbenzylamine

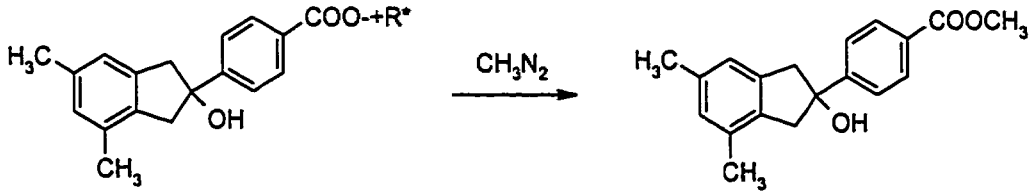


b R* = (1S,2R)-(+)-norephedrine



Scheme 63

The photochemistry of the carboxylic acid forms of these compounds had previously been studied.[88] (ref. 2) Irradiation of these keto-acids in solution generated a racemate of the indanols **189**. If these compounds could be induced to undergo the same photochemical reaction in a nonracemic chiral environment, like that found in a chiral crystalline phase, it might be possible to prepare enantiomerically enriched photoproducts. The chiral salts **188a** and **188b** were easily prepared by dissolving the carboxylic acid in an appropriate solvent followed by the addition of the enantiomerically pure amine, (S)-(-)-α-methylbenzylamine or (1S,2R)-(+)-norephedrine. The chiral salt precipitated out of solution and was collected by suction filtration. The crystals were subjected to irradiation under N_2 by squeezing a thin layer of the crystals between two Pyrex plates. Chiral salt **188a** and **188b** were irradiated to give products **189a** and **189b**, respectively, and upon workup with diazomethane they generated the indanol methyl ester **190**, enriched in one enantiomeric form (Scheme 64).



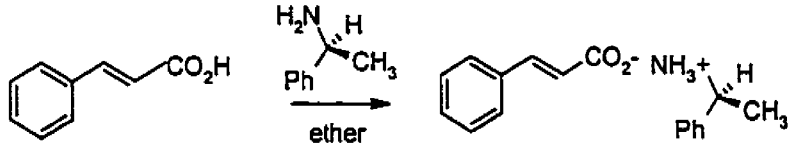
189 **190**

Scheme 64

The ionic chiral auxiliary method was proven to be synthetically viable, giving high enantiomeric excesses and moderate to good yields. For chiral salt **188a**, irradiation at room temperature resulted in only 16% conversion but achieved 94% enantiomeric excess (enantiomeric excess (ee) = (% major enantiomer - % minor enantiomer)). In a

second attempt using a longer irradiation time the yield was increased to 69% but there was also a decrease of the enantiomeric excess to 69%. This decrease of stereoselectivity with percent conversion increase has been observed previously by the authors and they postulated that it results from the loss of topochemical control that occurs as the ordered crystal lattice breaks down during conversion of the starting chiral salt to the photoproduct.[88] For the norephedrine salt **188b**, 12% conversion at room temperature produced an enantiomeric excess of 90% on the first attempt. A second attempt, with longer irradiation times, increased the yield to 80% but reduced the ee to 80% as well. As can be seen this method does have its limitations when it comes to yield and enantiomeric excess.

The previous synthetic method was explored as a possible solution for synthesizing enantiomerically enriched lignans. The strategy was to test if the dibenzylidene succinic acids could be precipitated as chiral salts in one atropisomeric form. If this could be achieved, then irradiation of these crystals should afford enantimerically enriched aryldehydrotetralins. However, a model compound was first chosen to establish the technique for the formation of amine salts.



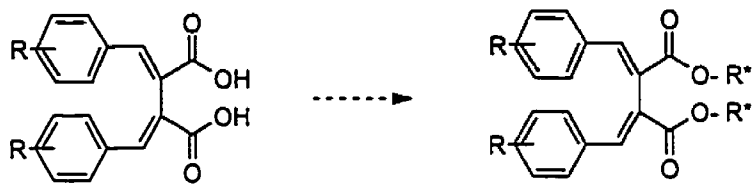
191 **192**

Scheme 65

Cinnamic acid 191 was dissolved in ether and pure α-methylbenzylamine (1 eq.) was added neat to the solution. Upon addition of the amine, a white precipitate was

immediately formed and after 1 h of stirring, collected by suction filtration. After drying overnight a ^{1}H NMR spectrum was taken of the white solid. The spectrum verified the formation of the chiral salt **192** as evident from the appearance of a doublet at 1.5 ppm corresponding to the protons on the α-methyl group and a quartet at 4.3 ppm corresponding to the α-proton.

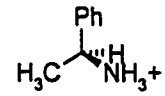
Using the *E,E*-bis-(3,4,5-trimethoxybenzylidene) succinic acid **177**, several attempts at precipitating the chiral amine salts were made (Scheme 66).



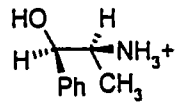
177 **193**

R = 3,4,5-trimethoxy

a R* = (S)-(-)-α-methylbenzylamine



b R* = (1S,2R)-(+)-norephedrine

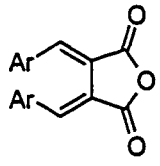


Scheme 66

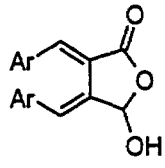
The first attempt used α-methylbenzylamine to form the chiral salt. Unfortunately a solid did not form upon addition of neat α-methylbenzylamine. The solution turned cloudy after stirring for several hours, however, evaporation of the solvent gave only an oily product. In a second attempt, norephedrine was used as the amine. A similar result ensued after the addition of the amine. No precipitate was produced and only an oily substance was obtained. It was concluded that either the atropisomers were reluctant to crystallize, or the steric congestion of the aryl rings made lattice packing unfavourable.

Although it was evident from the result using cinnamic acid that salt formation was feasible and practical this method was not successful for the dibenzylidenesuccinic acid tested. A new approach was conceived.

It has been well documented that the diarylfulgides photocyclize to aryldehydrotetralin compounds (see Introduction). The succinic anhydride form presumably restricts the conformational freedom of this molecule. As it contains a plane of symmetry, cyclization of the fulgide atropisomers would produce racemic aryldehydrotetralin. A γ-hydroxybutyrolactone structure such as **197** also has a five-membered ring system similar to the fulgide **180** but lacks the plane of symmetry, and contains a chiral centre.



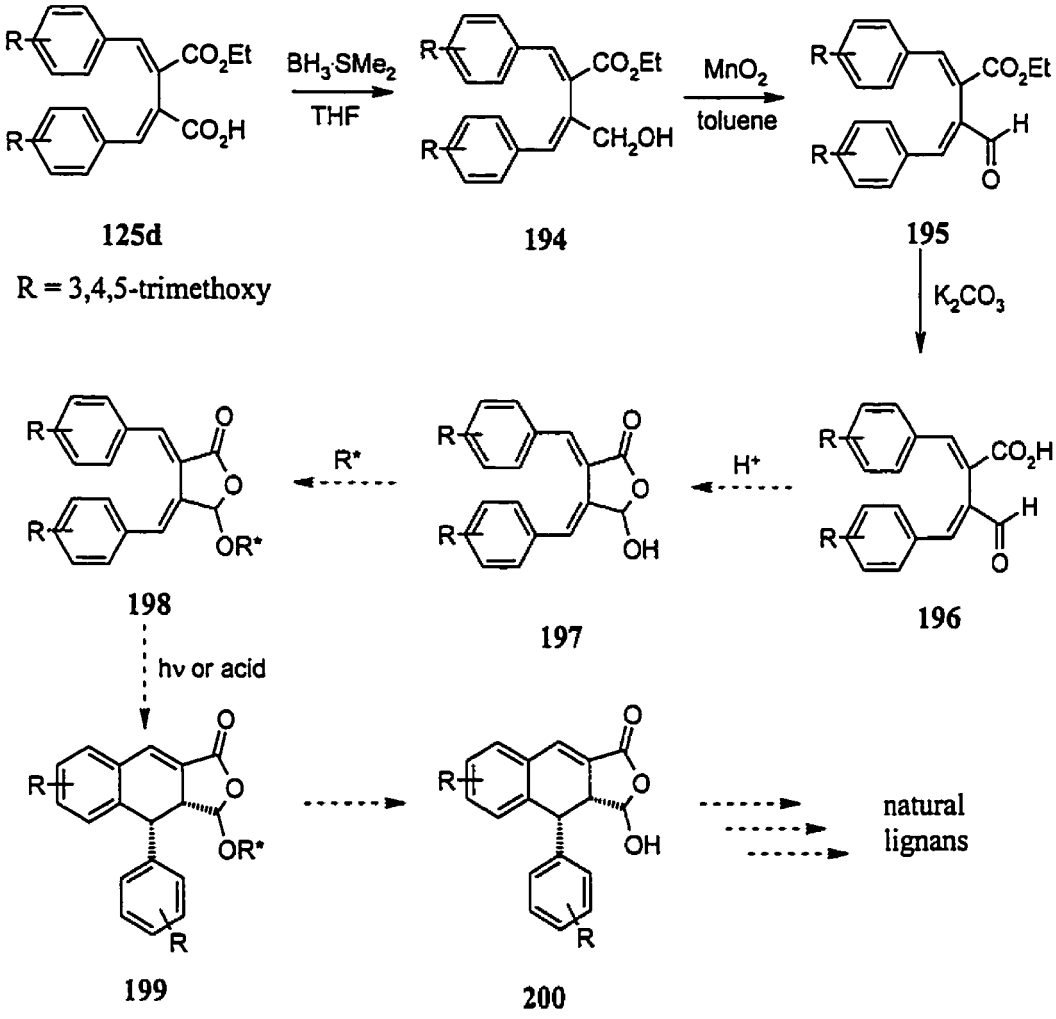
180



197

Scheme 67

Furthermore the free hydroxyl group could be used to attach chiral auxiliaries. This would introduce an additional chiral influence closer to the atropisomeric centre that would presumably exert a better effect in coercing the molecule to adopt one atropisomeric form. If the molecule were to adopt one atropisomeric form then it could be subjected to irradiation or acid treatment to afford enantiomerically enriched aryldehydrotetralins. The removal of the chiral auxiliary and functional interconversions to the desired functionalities could generate enantiomerically pure natural lignans. The synthetic scheme is outlined in Scheme 68 shown below.



Scheme 68

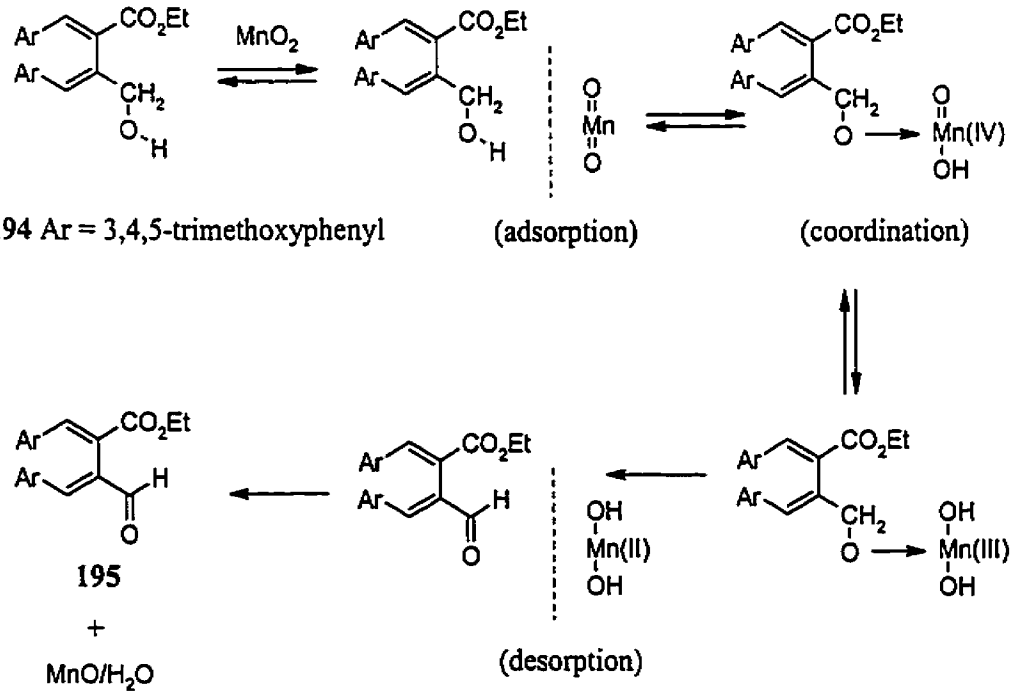
The first three steps of the sequence have been successfully accomplished. Starting from the monoacid-ester **125d**, the carboxylic acid group was reduced to the monoalcohol **194** using borane-dimethylsulfide in tetrahydrofuran following a literature procedure.[68] The monoacid-ester **125d** was treated with 10 equivalents of $BH_3{\cdot}SMe_2$ complex at room temperature for 5 h. The crude monoalcohol **194** was washed several times with ethanol and isolated as a yellow oil. The structure of the monoalcohol **194** was confirmed by its ^1H NMR spectrum. The proton peaks corresponding to the

methoxy groups on the aryl rings were doubled indicating the different chemical nature of the two aryl rings. Several attempts at oxidation of the monoalcohol **194** to the monoaldehyde **195** were made. The first attempt used the Jones Reagent, a 5% CrO_3 in 5% H_2SO_4 solution, to oxidize the alcohol to the aldehyde. The monoalcohol **194** was treated with 10 equivalents of the Jones reagent at 0 °C for 3 h. The first attempt produced a brown substance that was, according to TLC analysis, a mixture of several compounds. It was presumed that the oxidation was allowed to occur for too long. In a second attempt, a shortened reaction time of 2 h was used. Analysis by TLC determined that the aldehyde and another compound were present. The appearance of an aldehyde proton peak at 9.6 ppm in the ^{1}H NMR spectrum was a good indication of product formation. This other compound also had a signal in the aldehyde proton region and was presumed to be the carboxylic acid. It is known that the Jones reagent can oxidize primary alcohols to the carboxylic acid.

In another attempt, a less reactive oxidizing agent was used in order to stop the oxidation at the aldehyde stage. Pyridiniumfluorochromate (PFC) was chosen as the oxidizing agent. One equivalent of PFC was used to react with one equivalent of the monoalcohol. The first attempt using this reagent produced the desired aldehyde but only with 50% conversion in a ½ h. A longer reaction time was necessary for full conversion into the aldehyde. A second attempt involved treating one equivalent of monoalcohol with one equivalent of PFC for 2½ h. After the first 1 ½ h a second equivalent of PFC was added. After workup, a ^{1}H NMR spectrum was taken of the product isolated. It showed almost complete conversion to the aldehyde **195**, however the presence of the carboxylic acid was again detected as a contaminant. The problem encountered was that

PFC was oxidizing the monoalcohol to the monoaldehyde but it was also slowly oxidizing the monoaldehyde to the carboxylic acid.

Manganese dioxide (MnO_2) was used in another attempt to form aldehyde **195**. This reagent is known to work well for oxidizing allylic alcohols. After a reaction time of 72 h, the aldehyde was isolated in quantitative yield and required no further purification. Furthermore, no evidence of carboxylic acid formation was detected. Steric congestion of the aryl rings and the ester group may have caused the reaction to progress slowly. The mechanism of this reaction is believed to occur through a free radical (Scheme 69).[79]



194 Ar = 3,4,5-trimethoxyphenyl (adsorption) (coordination) (desorption)

Scheme 69

The monoalcohol adsorbs onto the Mn surface and coordinates to form a complex. This complex promotes electron transfer to the allylic position of the alcohol accompanied by reduction of Mn(IV) to Mn(III). The formation of this free radical is

stabilized at the allylic position by conjugative effects. A second electron transfer generates the aldehyde adsorbed on $Mn(OH)_2$. Finally the aldehyde is desorbed, with loss of water, to complete the oxidation.

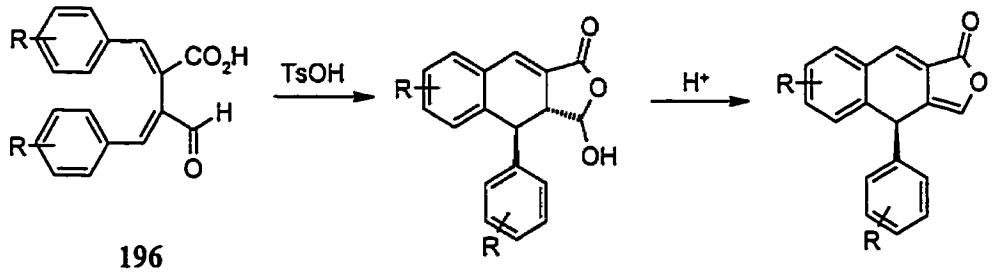
After obtaining the aldehyde it was assumed that this compound could be cyclized directly to generate the γ-hydroxybutyrolactone **197**. Unfortunately this was not the case, as several repeated attempts using potassium carbonate to hydrolyze the ester followed by acidification to form the lactol did not lead to the desired product. It was presumed that the base would hydrolyze the ester and *in situ* the carboxylic acid would attack the carbonyl of the aldehyde. The equilibrium for formation of the lactol presumably lies well on the side of the reactant, or uncyclized form. If the equilibrium could be shifted towards formation of the product then lactol formation would be enhanced. It was conceived that trapping the γ-hydroxy group on the butyrolactone via an alkyl group might prevent the reversible reaction from occurring. Furthermore the equilibrium would shift towards the right as more product was formed. To maintain the equilibrium, more starting material would be converted to product eventually converting all of the starting material to product.

The key step in the whole synthetic scheme was formation of the aryl γ-hydroxybutyrolactone. The first attempt at cyclizing the monoacid-aldehyde **196** to the lactol ether was performed in a NMR tube so that the reaction could be monitored by NMR spectroscopy. Deuterated methanol was used as the solvent and *p*-toluenesulfonic acid (TsOH) was used to catalyze the reaction. The reagents were added to a NMR tube and a ^1H NMR spectrum was taken immediately. The spectrum could not be interpreted as TsOH masked the peaks corresponding to the product. The reaction was worked up

and the compound passed through silica gel to remove the TsOH. The spectrum of the purified product could not be correctly assigned due to the interference from other unidentifiable signals.

The next attempt used normal methanol with TsOH catalyzing the reaction. Once again this generated extra proton signals that could not be assigned. It was postulated that TsOH might be too strong an acid. A weaker acid was chosen for the next attempt. The acid-aldehyde was dissolved in methanol and a catalytic amount of acetic acid was dispensed into the reaction mixture. The product was isolated after 3 h and a ^{1}H NMR spectrum taken. There was no spectral evidence to support the formation of the butyrolactol ether as the spectrum lacked the γ-proton signal geminal to the alkoxyl group.

In a last attempt to form the lactol **197** the monoacid-aldehyde **196** was treated with 0.7 equivalents of TsOH in benzene for 21 h at room temperature. After workup and purification a pure compound was obtained. The ^{1}H NMR spectrum appeared very promising and at first, it was thought that butyrolactone **197** had been formed. There were two vinyl proton peaks at 7.98 and 8.35 ppm and a peak at 6.5 ppm that could have been the γ-proton. However, upon closer inspection it was determined that the monoacid-aldehyde had cyclized to the aryldehydrotetralin **201** in scheme 70 below.



196

201

202

R = 3,4,5-trimethoxy

Scheme 70

The proton peaks of the aryl rings proved that it was this compound. Instead of two two-proton singlets that would be expected of the aryl protons, 2:1 proton singlets were observed. That would be more consistent with the one-proton signal from the aryltetralin aryl proton and the two-proton signal from the pendant aryl protons. Furthermore the two vinyl peaks could be explained by the formation of compound **202**. The formation of the compound **202** would be reasonable since under acidic conditions the hydroxyl group would be lost to generate the unsaturated double bond. The formation of compound **202** proved that the butyrolactone does form but one question that remains unanswered is in what order does the formation and cyclization occur?

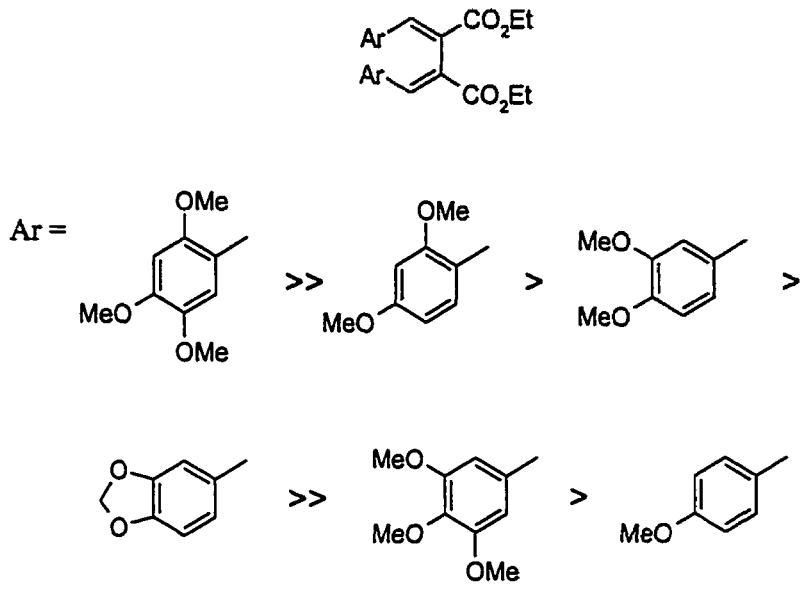
Unfortunately time had run out for continued investigation of this question. Completion of the third part of this thesis was halted after this reaction. Further probing with the use of different acids would be the next logical exploration. Weaker acids might prevent the elimination of the hydroxyl group. As mentioned above trapping experiments should be attempted if γ-hydroxybutyrolactone **197** formation precedes the cyclization.

Chapter 4

Conclusions

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

1) The first part of the thesis involved the study of using acid to catalyze the ring cyclizations of symmetrical and unsymmetrical dibenzylidenesuccinates. Acid treatment of symmetrical dibenzylidenesuccinates afforded the corresponding aryldehydrotetralins in fair to excellent yields. Several different types of symmetrical dibenzylidenesuccinates were synthesized. It was interesting to note that the substitution on the aryl groups had a dramatic effect on the rate of cyclization. It was found that methoxy groups in the *ortho* (2 and 2`) and *para* (4 and 4`) positions of the aryl rings enhanced the cyclization whereas methoxy groups in the *meta* (3 and 3`) positions hindered ring formation. Two mechanisms were proposed to account for aryl group participation during ring cyclization. It was proposed that dibenzylidenesuccinates with 2 and 2`-alkoxy substituted aryl rings undergoes ring cyclization with formation of the intermediate spirocarbocation, known as an Ar_1-5 mechanism whereas for dibenzylidenesuccinates with 3 and 3`-substitution the cyclization goes through a six-membered ring carbocation or $Ar_2$-6 mechanism. Methoxy groups in the 2 and 2` positions stabilize the intermediate spirocarbocation whereas methoxy groups in the 3 and 3` positions stabilize the six-membered carbocation intermediate. Furthermore it was postulated that reactions proceeding by the Ar_1-5 mechanism were faster than those proceeding by the Ar_2-6 mechanism. From these results a crude order of reactivity was deduced.

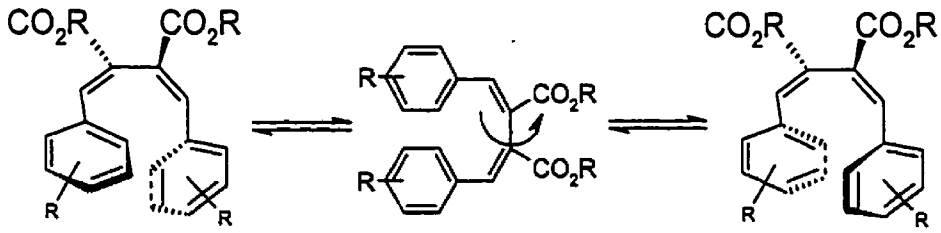


Attempts at cyclization of unsymmetrical dibenzylidenesuccinates proved to be less useful. The aryldehydrotetralins were formed but under acidic conditions they would undergo dearylation of the more reactive pendant ring. A mechanism was proposed to rationalize this result.

2) The second part of this thesis carried forward two results obtained from the first part. The *E,E*-bis-3,4-dimethoxybenzylidene succinate and the *E,E*-bis-3,4-methylenedioxybenzylidene succinate were successfully converted by triflic acid to their corresponding 1,2-dihydronaphthalenes. A search of the literature revealed that two natural lignans contained the same aryl ring substitution. Galbulin had the 3,4-dimethoxy substituted aryl rings and Cagayanin had the 3,4-methylenedioxy substituted aryl groups. Therefore it was presumed that these two natural products could be derived from their respective dihydronaphthalenes. This was successfully executed in four steps from the dihydronaphthalenes. This new synthetic methodology was developed with the intent of expanding the scope of lignan synthesis. This was demonstrated for the unsymmetrical

dibenzylidenesuccinate that contained a 3,4-dimethoxy aryl ring and a 3,4-methylenedioxy aryl ring. This compound did not undergo dearylation owing to the fact that it contained a less reactive substituted aryl group. It was treated with triflic acid and found to form a 3:1 mixture of isomeric dihydronaphthalenes with the major isomer having a 3,4-methylenedioxy pendant aryl ring. If the major and minor isomer could be successfully resolved then both could be carried through to their respective lignan natural products, Isogalcatin and Galcatin.

3) The third part of this thesis explored several possible routes to achieving asymmetric syntheses of natural lignans starting from dibenzylidenesuccinates. Dibenzylidenesuccinates are interesting from an asymmetric synthesis standpoint because they demonstrate atropisomerism, chirality in a molecule that arises from hindered rotation about a single bond.



The intent of this part of the research was to coerce the molecule to adopt one atropisomeric form. This was attempted using several approaches. The first approach involved introducing a rigid chiral auxiliary in the form of an eight-membered ring linking the ester groups. This proved to be very difficult, as the eight-membered ring was reluctant to form, possibly due to ring strain. In a second approach attempts were made to crystallize the dibenzylidene succinic acids as chiral amine salts. The idea was that upon crystallization the molecule might adopt only one conformationally favoured

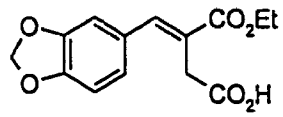
atropisomeric form. If this was the case then the crystals could be subjected to solid state photochemistry to induce cyclization in the severely restricted chiral space group. Unfortunately the compounds were difficult to crystallize into solids with the chiral amines chosen. This reluctance to crystallize from solution may be a result of the inherent nature of dibenzylidenesuccinate diacids. The final approach that was attempted was to form the five-membered γ-hydroxybutyrolactone ring from the dibenzylidenesuccinate monoacid-ester. It was previously shown that the anhydrides cyclized readily to form the dihydronaphthalenes. It was presumed that formation of a butyrolactone would also lend itself to cyclization. Furthermore with the presence of a free hydroxyl group, attaching a chiral auxiliary was possible. This chiral influence would aid in prejudicing which atropisomeric form would predominate. The enantiomerically enriched dibenzylidenesuccinate could then be subjected to the proposed synthetic methodology to generate enantiomerically pure lignans. The first three steps of this synthetic scheme were successfully completed, however, preliminary experiments in forming the butyrolactone have not yielded this compound. This step is probably the most difficult as it may be sterically too demanding for the aryl groups to adopt the crowded conformation expected in the butyrolactone. Further experiments to form the butyrolactones are necessary before the synthetic scheme can progress.

Chapter 5

Experimental

^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 300 FT instrument using Xwinnmr software. Residual $CHCl_3$ in the $CDCl_3$ was used as the chemical shift standard for ^{1}H spectra (7.26 ppm) and the carbon resonance of the solvent was used as the standard for the ^{13}C spectra (77.2 ppm). Flash column chromatography (FCC) was performed using Silicycle 230-400 mesh silica gel. High resolution and electron impact mass spectra were obtained on a VG Analytical 7070E-HF instrument. High-pressure liquid chromatography was performed on a C-18 reverse phase column using a Varian 9010 Solvent Delivery instrument and a Varian 9050 Variable Wavelength UV-Vis detector. HPLC samples were eluted with either an increasing (0-100%) acetonitrile in water gradient over 25 minutes or an increasing (65-70%) methanol in water gradient over 15 minutes then increasing (0-100%) acetonitrile in water gradient for 5 minutes. THF was freshly distilled from sodium and benzophenone under nitrogen and CH_2Cl_2 was freshly distilled from CaH_2 under nitrogen. All other solvents used were commercial grade purchased from Fisher. A 450 watt Hanovia medium pressure mercury lamp (3 mm Pyrex filter) equipped with a cooling jacket was used in irradiation experiments. Room temperature (rt) indicates ambient temperature between 21-25 °C.

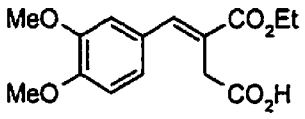
3,4-Methylenedioxybenzylidenesuccinate monoacid-ester



123a

Potassium metal (4.7 g, 120 mmol) was added to *tert*-butyl alcohol (130 mL) in a flame dried 300-mL three-neck flask. The mixture was heated to 70 °C with stirring until the potassium had dissolved (ca. 1½ h). A solution of diethyl succinate (33 mL, 200 mmol) and piperonal (3,4-methylenedioxybenzaldehyde, 15 g, 100 mmol) in t-butyl alcohol (100 mL) was prepared by heating to dissolve the benzaldehyde. This solution was added to the potassium t-butoxide solution via a dropping funnel over 20 min, with stirring. The dropping funnel was rinsed with t-butyl alcohol (20 mL) and the reaction was left to stir for 3 h at reflux temperature, during which time a yellow precipitate formed. The t-butyl alcohol was evaporated and saturated aqueous $NaHCO_3$ (100 mL) and EtOAc (75 mL) were added. The mixture was poured into a separatory funnel, the organic layer was removed and the aqueous layer was extracted with EtOAc (2 x 75 mL). The residual aqueous fraction was acidified with 10% HCl solution, and extracted with fresh EtOAc (3 x 75 mL). This second organic extract was washed with water (100 mL), dried ($MgSO_4$), filtered, and evaporated to give crude product that was reacted in the next step without further purification. This compound had ^1H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[68]

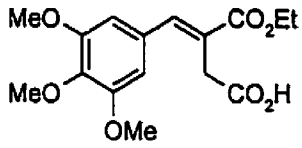
3,4-Dimethoxybenzylidenesuccinate monoacid-ester



123b

Anhydrous ethanol (50 mL) and sodium metal (0.51 g, 22.1 mmol) were added to a flame dried 100-mL three-neck flask, heated to 70 °C with stirring until all the sodium had dissolved (ca. ½ h). A solution of diethyl succinate (3.2 mL, 18.9 mmol), veratraldehyde (3,4-dimethoxybenzaldehyde, 2.62 g, 15.8 mmol), and ethanol (20 mL) was prepared with gentle heating to dissolve the benzaldehyde. This solution was added to the sodium ethoxide solution via a dropping funnel over 20 min. The dropping funnel was rinsed with ethanol (10 mL) and the reaction was left to stir for 20 h at reflux temperature, during which time a yellow precipitate formed. The ethanol was evaporated and saturated aqueous $NaHCO_3$ (50 mL) and EtOAc (25 mL) were added. The mixture was transferred to a separatory funnel, the organic fraction was removed and the aqueous fraction was extracted with EtOAc (2 x 25 mL). The basic aqueous solution was acidified with 10% HCl solution, and extracted with fresh EtOAc (3 x 25 mL). This second organic extract was washed with water (50 mL), dried ($MgSO_4$), filtered, and evaporated to give crude product that was reacted in the next step without further purification. This compound had ^1H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[68]

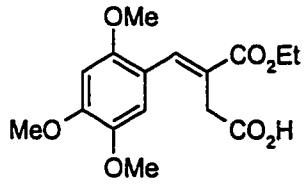
3,4,5-Trimethoxybenzylidenesuccinate monoacid-ester



123d

Anhydrous ethanol (100 mL) and sodium metal (1.65 g, 72.0 mmol) were charged to a flame dried 250-mL three-neck flask, heated to 70 °C with stirring until all the sodium had reacted (ca. ½ h). A solution of diethyl succinate (12.0 mL, 18.9 mmol), 3,4,5-trimethoxybenzaldehyde (11.77 g, 60.0 mmol), and ethanol (80 mL) was prepared with gentle heating to dissolve the benzaldehyde. This solution was poured into a dropping funnel and added slowly over 20 min to the sodium ethoxide solution. The dropping funnel was rinsed with ethanol (20 mL) and after stirring for 20 h at reflux temperature a yellow precipitate formed. The ethanol was evaporated and saturated aqueous $NaHCO_3$ (75 mL) and EtOAc (75 mL) were added. The mixture was transferred to a separatory funnel, the organic fraction was drained and the aqueous fraction was extracted with EtOAc (2 x 75 mL). The basic aqueous solution was acidified with 10% HCl solution, and extracted with fresh EtOAc (3 x 75 mL). This second organic extract was washed with water (75 mL), dried ($MgSO_4$), filtered, and evaporated to give crude product that was reacted in the next step without further purification. This compound had ^1H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[68]

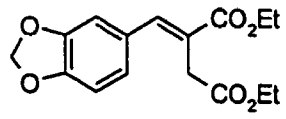
2,4,5-Trimethoxybenzylidenesuccinate monoacid-ester



123c

Anhydrous ethanol (60 mL) and sodium metal (0.64 g, 20.0 mmol) were added to an oven dried 100-mL three-neck flask and heated to dissolve the sodium (ca. ½ h). A solution composed of diethyl succinate (4.0 mL, 24.0 mmol), 2,4,5-trimethoxybenzaldehyde (3.92 g, 20.0 mmol), and ethanol (30 mL) was prepared with gentle heating to dissolve the benzaldehyde. A dropping funnel was used to slowly dispense this solution over 20 minutes. A small amount of ethanol (10 mL) was used to rinse the funnel. The reaction was left to stir for 20 h at reflux temperature, during which time the formation of a yellow precipitate was observed. The ethanol was evaporated and saturated aqueous $NaHCO_3$ (50 mL) and EtOAc (25 mL) were added. The mixture was poured into a separatory funnel, the organic fraction was removed and the aqueous fraction was extracted with EtOAc (2 x 25 mL). 10% HCl solution was used to acidify the residual aqueous solution followed by extraction with fresh EtOAc (3 x 25 mL). These organic extracts were pooled, washed with water (50 mL), dried ($MgSO_4$), filtered, and evaporated to give crude product that was reacted in the next step without further purification. This compound had ^1H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[54]

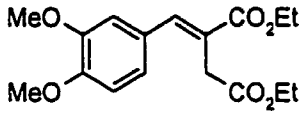
Diethyl 3,4-Methylenedioxybenzylidene succinate



124a

The crude 3,4-methylenedioxybenzylidenesuccinate monoacid-ester **123a** (2.78 g, 10.0 mmol) was dissolved in acetone (100 mL, ca. 0.1-0.2 M). K_2CO_3 (6.92 g, 50.0 mmol) and EtI (1.6 mL, 20.0 mmol) were added and the mixture was heated at reflux for 20 h. The excess K_2CO_3 was removed by filtration and the acetone was evaporated. The residue was taken up in EtOAc (100 mL), dried ($MgSO_4$), filtered, and evaporated to give yellow-brown oil. The crude product was purified by short-path, high vacuum (0.01 mm Hg, 150-180 °C) distillation to give a yellow oil (1.62 g, 53%). This compound had ^1H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[68]

Diethyl 3,4-Dimethoxybenzylidene succinate

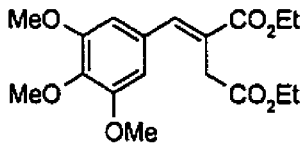


124b

The crude 3,4-dimethoxybenzylidenesuccinate monoacid-ester **123b** (4.27 g, 14.5 mmol) was dissolved in acetone (100 mL, ca. 0.1-0.2 M). K_2CO_3 (10.0 g, 72.5 mmol) and EtI (2.3 mL, 29.0 mmol) were added and the mixture was heated at reflux for 20 h. The excess K_2CO_3 was filtered and the acetone was evaporated. The residue was diluted with EtOAc (100 mL), dried ($MgSO_4$), filtered, and stripped of solvent to give a yellow-brown oil. The crude product was purified by short-path, high vacuum (0.01 mm Hg,

150-180 °C) distillation to give a yellow oil (2.67 g, 57%). This compound had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[68]

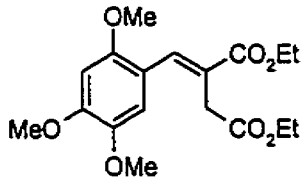
Diethyl 3,4,5-Trimethoxybenzylidene succinate



124d

The crude 3,4,5-trimethoxybenzylidenesuccinate monoacid-ester **123d** (4.82 g, 14.9 mmol) was dissolved in acetone (100 mL, ca. 0.1-0.2 M) and transferred to a dry flask. K_2CO_3 (10.3 g, 74.3 mmol) and EtI (3.0 mL, 37.1 mmol) were added and the mixture was heated at reflux for 20 h. The undissolved K_2CO_3 was removed by filtration and the acetone was evaporated. The remaining material was taken up in EtOAc (100 mL), dried ($MgSO_4$), filtered, and evaporated to give yellow-brown oil. The crude product was subjected to short-path, high vacuum (0.01 mm Hg, 150.180 °C) distillation to give a pure yellow oil (2.67 g, 57%). This compound had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[68]

Diethyl 2,4,5-Trimethoxybenzylidene succinate

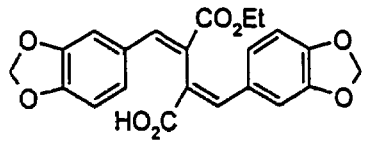


124c

The crude 2,4,5-trimethoxybenzylidenesuccinate monoacid-ester **123c** (5.19 g, 16.0 mmol) was dissolved in acetone (100 mL, ca. 0.1-0.2 M). K_2CO_3 (11.06, 80.0

mmol) and EtI (2.6 mL, 32.0 mmol) were added and the mixture was heated at reflux for 20 h. The remaining K_2CO_3 was removed by filtration and the acetone was eliminated on the rotatory evaporator. The resulting tar-like substance was taken up in EtOAc (100 mL), dried with anhydrous $MgSO_4$, filtered, and evaporated to give a yellow-brown oil. The crude product was purified by short-path, high vacuum (0.01 mm Hg, 150-180 °C) distillation. A yellow oil (3.80 g, 67%) was obtained in high purity. This compound had ^1H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[54]

***E,E*-bis-(3,4-methylenedioxybenzylidene) monoacid-monoester**

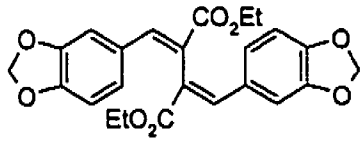


125a

Absolute ethanol (30 mL) was added to a 100-mL, flame dried three-neck flask. Sodium metal (0.14 g, 6.1 mmol) was added and the flask was immersed in a 90 °C oil bath. The sodium metal completely reacted after stirring for ½ h. Diethyl 3,4-methylenedioxy succinate (**124a**) (1.56 g, 5.1 mmol) and piperonal (0.92 g, 6.1 mmol) were separately dissolved in ethanol (10 mL each). These two solutions were added successively, via dropping funnel, to the reaction flask. The dropping funnel was rinsed with ethanol (10 mL) and the reaction mixture was stirred at reflux for 20 h, during which time a yellow-orange precipitate formed. The mixture was poured into a separatory funnel and saturated aqueous $NaHCO_3$ (50 ml) added. This solution was extracted with EtOAc (2 x 50 mL). The residual aqueous fraction was acidified with 10% HCl. This solution was extracted with fresh aliquots of EtOAc (2 x 50 mL). The organic extracts

were pooled and washed with water (25 mL), dried ($MgSO_4$), filtered and concentrated to give crude product (1.60 g, 78%). The product was isolated by FCC using 30% EtOAc-hexanes and 2% AcOH to give a yellow oil (0.82 g, 39%). ^1H NMR ($CDCl_3$) δ 1.17 (t, 3H, J = 7.1), 4.19 (m, 2H), 5.89 (m (AB), 2H), 5.91 (m (AB), 2H), 6.70 (d, 1H, J = 4.7), 6.73 (d, 1H, J = 4.7), 6.99 (m, 2H), 7.04 (m, 2H), 7.83 (s, 1H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 61.2 (CH_2), 101.4 (CH_2), 101.5 (CH_2), 108.5 (2 x CH), 108.8 (CH), 108.9 (CH), 123.9 (C), 124.2 (C), 126.2 (CH), 126.6 (CH), 128.7 (C), 128.8 (C), 142.6 (CH), 144.2 (CH), 147.9 (C), 148.0 (C), 149.0 (C), 149.4 (C), 166.8 (C), 172.3 (C); mass spectrum *m/z* (relative intensity) 410 (M^+, 26), 364 (57), 292 (30), 243 (30), 176 (48), 149 (28), 135 (68), 122 (54), 86 (100), 63 (22); HRMS calcd. for $C_{22}H_{18}O_8$ 410.1001, found 410.0992.

Diethyl *E,E*-bis-(3,4-methylenedioxybenzylidene) succinate

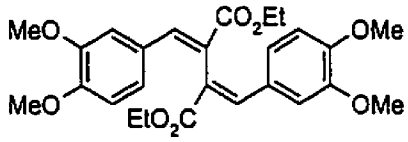


118

E,E-bis-(3,4-methylenedioxybenzylidene) monoacid-ester **125a** (0.77 g, 1.9 mmol) was dissolved with acetone (25 mL). K_2CO_3 (0.78 g, 5.6 mmol) and EtI (0.30 mL, 3.7 mmol) were added and the mixture was stirred at reflux for 20 h. Excess K_2CO_3 was removed by filtration and the acetone was evaporated. The residue was taken up in EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), washed with water (50 mL), dried ($MgSO_4$), filtered, and concentrated to give product (0.75 g, 88%) that required no further purification. ^1H NMR ($CDCl_3$) δ 1.14 (t, 6H, J = 7.1), 4.15 (m, 4H),

5.91 (s, 2H), 6.71 (d, 2H, J = 8.0), 6.97 (d, 1H, J = 1.7), 7.00 (s, 2H), 7.78 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1 (2 x CH_3), 61.0 (2 x CH_2), 101.4 (2 x CH_2), 108.4 (2 x CH), 108.8 (2 x CH), 125.0 (2 x C), 125.9 (2 x CH), 129.0 (2 x C), 142.1 (2 x CH), 147.9 (2 x C), 148.8 (2 x C), 167.0 (2 x C); mass spectrum *m/z* (relative intensity) HRMS calcd. for $C_{24}H_{22}O_8$ 438.1314 found 438.1339.

Diethyl *E,E*-bis-(3,4-dimethoxybenzylidene) succinate

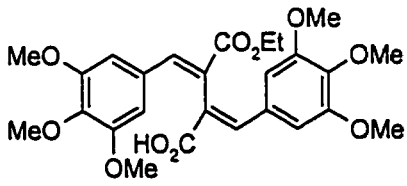


119

Anhydrous ethanol (30 mL) and sodium metal (0.10 g, 4.6 mmol) were added to a flame dried 100-mL three-neck flask. The flask was immersed in a 90 °C oil bath and the solution was stirred for ½ h to dissolve the sodium. Diethyl 3,4-dimethoxybenzylidene succinate (**124b**) (1.05 g, 3.3 mmol) and veratraldehyde (0.65 g, 3.9 mmol) were separately dissolved in ethanol (10 mL each). The first solution was transferred slowly in a dropping funnel to the sodium ethoxide solution. After ½ h of stirring the veratraldehyde was added to the reaction flask. The dropping funnel was rinsed with ethanol (10 mL) and the reaction mixture was stirred at reflux for 20 h, during which time a yellow-orange precipitate formed. EtI (0.62 mL, 7.8 mmol) was added directly to the reaction mixture and stirred for an additional 20 h. The mixture was poured into a separatory funnel and EtOAc (75 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added. Saturated salt solution (25 mL) was added to separate the aqueous layer from the organic layer. The organic fraction was removed and the aqueous fraction was extracted with EtOAc (75 mL). The organic extracts were combined, washed with water (75 mL),

dried ($MgSO_4$), filtered and evaporated to give crude product (1.10 g, 72%). The product was isolated by FCC using 30% EtOAc-hexanes as the eluant to give a yellow oil (0.41 g, 37%). ^1H NMR ($CDCl_3$) δ 1.12 (t, 6H, J = 7.1), 3.75 (s, 6H), 3.86 (s, 6H), 4.15 (m, 4H), 6.79 (d, 2H, J = 8.4), 7.10 (dd, 2H, J = 2.0, 8.4), 7.14 (d, 2H, J = 2.0), 7.86 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1 (2 x CH_3), 55.7 (2 x CH_3), 55.8 (2 x CH_3), 61.0 (2 x CH_2), 110.8 (2 x CH), 111.8 (2 x CH), 124.4 (2 x CH), 125.1 (2 x C), 127.8 (2 x CH), 142.0 (2 x CH), 148.7 (2 x C), 150.4 (2 x C), 167.2 (2 x C); mass spectrum *m/z* (relative intensity) 470 (M^+, 26), 396 (17), 351 (39), 324 (24), 287 (14), 259 (19), 195 (10), 165 (29), 151 (100), 139 (15); HRMS calcd. for $C_{26}H_{30}O_8$ 470.1940 found 470.1935.

***E,E*-bis-(3,4,5-trimethoxybenzylidene) succinate monoacid-ester**

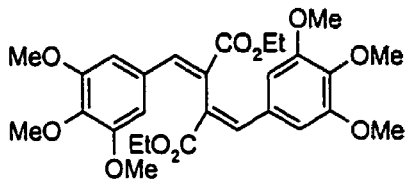


125d

Absolute ethanol (30 mL) was added to a 100-mL, flame dried three-neck flask. Sodium metal (0.083 g, 3.6 mmol) was added and the flask was immersed in a 90 °C oil bath. The sodium metal completely reacted after stirring for ½ h. Diethyl 3,4,5-trimethoxybenzylidene succinate (**124d**) (1.06 g, 3.0 mmol) and 3,4,5-trimethoxybenzaldehyde (0.59 g, 3.0 mmol) were separately dissolved in ethanol (10 mL each). The first solution was added slowly through a dropping funnel. The reaction was stirred for ½ h followed by the addition of the benzaldehyde solution. The dropping funnel was cleansed with ethanol (10 mL) and the reaction mixture stirred at reflux for 20 h. Over this period of time a yellow-orange precipitate formed. The mixture was

transferred to a separatory funnel and made basic with saturated aqueous $NaHCO_3$ (50 ml). This solution was extracted with EtOAc (2 x 50 mL) and the resulting aqueous fraction was acidified with 10% HCl. This acidified solution was extracted with fresh aliquots of EtOAc (2 x 50 mL). The EtOAc extracts were pooled, washed with water (25 mL), dried using $MgSO_4$, filtered and concentrated to give crude product (1.29 g, 85%). The product was isolated by FCC using 40% EtOAc-hexanes and 2% AcOH to give a yellow oil (0.27 g, 18%). This compound had ^1H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[54]

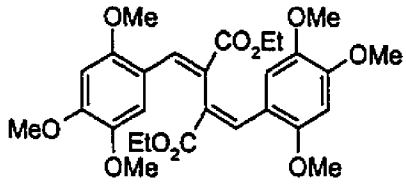
Diethyl *E,E*-bis-(3,4,5-trimethoxybenzylidene) succinate



102

E,E-bis-(3,4,5-trimethoxybenzylidene) monoacid-ester **125d** (0.92 g, 1.8 mmol) and K_2CO_3 (0.76 g, 5.5 mmol) were dissolved in acetone (25 mL). EtI (0.29 mL, 3.7 mmol) was added and the mixture was stirred at reflux for 20 h. The crystalline K_2CO_3 was removed by filtration and the acetone was evaporated. The residue was taken up in EtOAc (25 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), washed with water (50 mL), dried with $MgSO_4$, filtered, and concentrated to give product (0.84 g, 88%) that required no further purification. This compound had ^1H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[54]

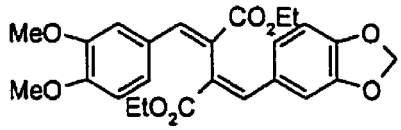
Diethyl *E,E*-bis-(2,4,5-trimethoxybenzylidene) succinate



120

Absolute ethanol (5 mL) and sodium metal (0.0066 g, 0.3 mmol) were added to a flame dried 50-mL flask. The flask was immersed in a 90 °C oil bath and the solution was stirred for ½ h to dissolve the sodium. Diethyl 2,4,5-trimethoxybenzylidene succinate (**124c**) (0.066 g, 0.2 mmol) and 2,4,5-trimethoxybenzaldehyde (0.044 g, 0.2 mmol) were separately dissolved in ethanol (5 mL each). These two solutions were added successively to the reaction flask. A yellow-orange precipitate formed over 20 hours stirring at reflux. EtI (0.02 mL, 0.2 mmol) was added directly to the reaction mixture and stirred for an additional 20 h. The mixture was poured into a separatory funnel. EtOAc (25 mL) and saturated aqueous $NaHCO_3$ (25 mL) were added. Saturated salt solution (10 mL) was added to separate the organic layer from the aqueous layer. The organic fraction was drained and the aqueous fraction was extracted again with EtOAc (25 mL). The two organic extracts were combined, washed with water (50 mL), dried ($MgSO_4$), filtered and evaporated to give crude product (0.087 g, 87%). The compound was purified by FCC using 30% EtOAc-hexanes as the mobile phase to give a yellow oil (0.045 g, 45%). This compound had ^1H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[54]

Diethyl *E,E*-2(3,4-dimethoxybenzylidene)-3(3,4-methylenedioxybenzylidene) succinate

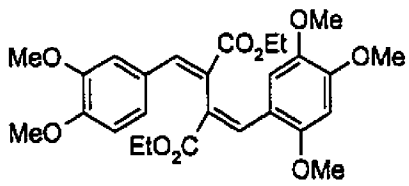


130

Sodium metal (0.13 g, 5.8 mmol) and absolute ethanol (30 mL) were added to a flame dried 100-mL three-neck flask. The flask was immersed in a 90 °C oil bath and the solution stirred for ½ h to dissolve the sodium. Diethyl 3,4-dimethoxybenzylidene succinate (**124b**) (1.33 g, 4.1 mmol) and piperonal (0.74 g, 4.9 mmol) were separately dissolved in ethanol (10 mL each). The first solution was dispensed in a dropping funnel to the reaction flask. After a ½ h interval, piperonal was slowly added. The dropping funnel was rinsed with ethanol (10 mL) and the reaction mixture refluxed for 20 h, during which time a yellow-orange precipitate formed. EtI (0.66 mL, 8.2 mmol) was added directly to the reaction mixture and stirred for an additional 20 h. The mixture was poured into a separatory funnel and EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added. Saturated salt solution (25 mL) was added to separate the organic layer from the aqueous layer. The organic fraction was removed and the aqueous fraction was extracted with EtOAc (50 mL). The organic extracts were combined, washed with water (75 mL), dried over anhydrous $MgSO_4$, filtered and evaporated to give crude product (1.62 g, 87%), which was purified by FCC using 30% EtOAc-hexanes as the eluant to give a yellow oil (0.42 g, 23%). ^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3H, J = 7.1), 1.15 (t, 3H, J = 7.1), 3.76 (s, 3H), 3.86 (s, 3H), 4.16 (2 x m, 4H), 5.93 (m (AB), 2H), 6.73 (d, 1H, J = 8.2), 6.78 (d, 1H, J = 8.3), 7.00 (dd, 1H, J = 1.8, 8.3), 7.04 (d, 1H, J = 1.8), 7.10 (dd, 1H, J = 1.9, 8.3), 7.12 (d, 1H, J = 1.9), 7.82 (s, 1H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1

(2 x CH_3), 55.7 (CH_3), 55.8 (CH_3), 61.0 (CH_2), 61.0 (CH_2), 101.3 (CH_2), 108.4 (CH), 108.8 (CH), 110.8 (CH), 111.9 (CH), 124.4 (CH), 124.6 (C), 125.5 (C), 125.9 (CH), 127.8 (C), 129.1 (C), 141.8 (CH), 142.3 (CH), 147.9 (C), 148.7 (C), 148.9 (C), 150.3 (C), 167.0 (C), 167.2 (C); HRMS calcd. for $C_{25}H_{26}O_8$ 454.1628 found 454.1619.

Diethyl *E,E*-2(3,4-dimethoxybenzylidene)-3(2,4,5-trimethoxybenzylidene) succinate

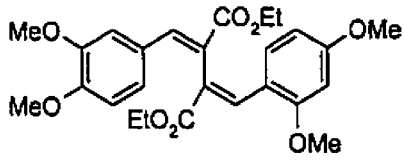


131

Anhydrous ethanol (30 mL) and sodium metal (0.08 g, 3.7 mmol) were added to a flame dried 100-mL three-neck flask. The flask was immersed in a 90 °C oil bath and the solution stirred for ½ h to dissolve the sodium. Diethyl 2,4,5-trimethoxybenzylidene succinate (**124c**) (0.92 g, 2.6 mmol) and veratraldehyde (0.52 g, 3.1 mmol) were separately dissolved in ethanol (10 mL each). A dropping funnel was used to slowly dispense the first solution. After a ½ h interval veratraldehyde was added similarly. The dropping funnel was rinsed with ethanol (10 mL) and the mixture stirred at reflux for 20 h, during which time a yellow-orange precipitate formed. EtI (2.09 mL, 26.2 mmol) was added directly to the reaction mixture and stirred for an additional 20 h. The mixture was transferred to a separatory funnel and combined with EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The addition of saturated salt solution (25 mL) aided in the separation of the organic layer from the aqueous layer. The organic fraction was drained and the aqueous fraction was extracted again with EtOAc (50 mL). The organic extracts were combined, washed with water (75 mL), dried using $MgSO_4$, filtered and evaporated

to give a crude oil (1.20 g, 92%). The crude product was purified by FCC using 30% EtOAc-hexanes as the eluant to give a yellow oil (0.60 g, 46%). ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.1), 1.15 (t, 3H, J = 7.1), 3.63 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.16 (m, 2H), 4.17 (m, 2H), 6.41 (s, 1H), 6.76 (d, 1H, J = 8.3), 7.03 (dd, 1H, J = 2.0, 8.3), 7.11 (s, 1H), 7.40 (d, 1H, J = 2.0), 7.78 (s, 1H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2 (2 x CH_3), 55.6 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 56.4 (CH_3), 60.8 (CH_2), 60.9 (CH_2), 96.5 (CH), 110.7 (CH), 111.6 (CH), 111.7 (CH), 115.5 (C), 124.5 (CH), 124.6 (C), 125.7 (C), 127.9 (C), 136.6 (CH), 141.4 (CH), 142.7 (C), 148.6 (C), 150.2 (C), 151.3 (C), 153.5 (C), 167.4 (C), 167.4 (C); mass spectrum *m/z* (relative intensity) 500 (M^+, 54), 426 (52), 381 (49), 366 (22), 351 (20), 195 (25), 181 (52), 168 (100), 151 (23); HRMS calcd. for $C_{27}H_{32}O_9$ 500.2046 found 500.2061.

Diethyl *E,E*-2(3,4-dimethoxybenzylidene)-3(2,4-dimethoxybenzylidene) succinate

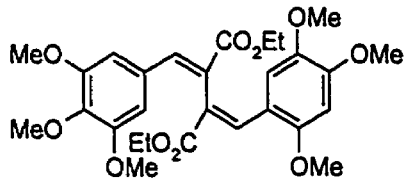


132

Absolute ethanol (30 mL) and sodium metal (0.13 g, 5.8 mmol) were added to a flame dried 100-mL three-neck flask. The flask was heated to 90 °C in a hot oil bath and the solution stirred for ½ h to dissolve the sodium. Diethyl 3,4-dimethoxybenzylidene succinate (**124b**) (1.32 g, 4.1 mmol) and 2,4-dimethoxybenzaldehyde (0.82 g, 4.9 mmol) were separately dissolved in ethanol (10 mL each). The first solution was added to the sodium ethoxide solution in a dropping funnel. After a ½ h the benzaldehyde solution was dispensed via the dropping funnel. The dropping funnel was rinsed with ethanol (10

mL) and the reaction mixture stirred at reflux for 20 h. During the reflux period a yellow-orange precipitate formed. EtI (3.28 mL, 41.1 mmol) was added directly to the reaction mixture and stirred for an additional 20 h. The mixture was combined with EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) in a separatory funnel. Saturated salt solution (25 mL) was added to separate the homogeneous solution into the organic and aqueous layers. The organic fraction was removed and the aqueous fraction was extracted a second time with EtOAc (50 mL). The organic extracts were pooled, washed with water (75 mL), dried with $MgSO_4$, filtered and evaporated to give crude product, which was purified by FCC using 30% EtOAc-hexanes as the eluant to give a yellow oil (0.70 g, 36%). ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.1), 1.14 (t, 3H, J = 7.1), 3.75 (s, 1H), 3.76 (s, 1H), 3.78 (s, 3H), 3.85 (s, 3H), 4.14 (m, 2H), 4.15 (m, 2H), 6.32 (dd, 2H, J = 2.1, 8.2), 6.75 (d, 1H, J = 8.3), 7.01 (dd, 1H, J = 2.0, 8.3), 7.12 (d, 1H, J = 2.0), 7.39 (d, 1H, J = 8.2), 7.73 (s, 1H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 14.2 (CH_3), 55.3 (CH_3), 55.4 (CH_3), 55.5 (CH_3), 55.8 (CH_3), 60.8 (CH_2), 60.8 (CH_2), 98.0 (CH), 104.7 (CH), 110.7 (CH), 111.5 (CH), 117.1 (C), 124.4 (CH), 125.0 (C), 125.5 (C), 128.0 (C), 129.9 (CH), 137.1 (CH), 141.6 (CH), 148.6 (C), 150.0 (C), 159.3 (C), 162.1 (C), 167.4 (C), 167.5 (C); mass spectrum *m/z* (relative intensity) 470 (M^+, 18), 424 (20), 396 (86), 351 (100), 332 (68), 287 (16), 259 (30), 195 (15), 165 (42), 151 (49), 138 (25); HRMS calcd. for $C_{26}H_{30}O_8$ 470.1940 found 470.1978.

Diethyl *E,E*-2(3,4,5-trimethoxybenzylidene)-3(2,4,5-trimethoxybenzylidene) succinate

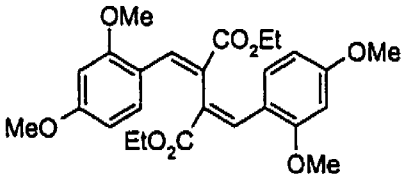


133

A flame-dried 100-mL three-neck flask containing absolute ethanol (30 mL) and sodium metal (0.29 g, 12.8 mmol) was immersed in a 90 °C oil bath. The solution was stirred for ½ h to dissolve the sodium. Diethyl 3,4,5-trimethoxybenzylidene succinate (**124d**) (2.26 g, 2.0 mmol) and 2,4,5-trimethoxybenzaldehyde (1.51 g, 7.7 mmol) were separately dissolved in ethanol (20 mL each). The first solution was dispensed from a dropping funnel to the sodium ethoxide solution. After 30 min the dissolved benzaldehyde was similarly dispensed. The dropping funnel was rinsed with ethanol (10 mL) and the reaction mixture refluxed for 20 h, during which time a yellow-orange precipitate formed. The reaction mixture was stirred for another 20 h after the addition of EtI (1.0 mL, 2.0 mmol). The mixture was transferred to a separatory funnel and EtOAc (75 mL) and saturated aqueous $NaHCO_3$ (100 mL) were added. Saturated salt solution (50 mL) was added to separate the organic layer from the aqueous layer. The organic fraction was drained and the aqueous fraction was extracted with a second aliquot of EtOAc (75 mL). The organic extracts were combined, washed with water (100 mL), dried with $MgSO_4$, filtered and evaporated to give crude product (2.07 g, 61%). The compound was isolated by FCC using 30%-50% EtOAc-hexanes as the eluant to give a yellow-orange oil (0.98 g, 29%). ^1H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.1), 1.15 (t, 3H, J = 7.1), 3.65 (s, 3H), 3.75 (s, 6H), 3.79 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 4.15 (m, 2H),

4.17 (m, 2H), 6.39 (s, 1H), 6.71 (s, 2H), 7.06 (s, 1H), 7.72 (s, 1H), 8.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 14.2 (CH_3), 55.9 (CH_3), 55.9 (CH_3), 56.1 (CH_3), 56.3 (CH_3), 60.8 (CH_3), 60.9 (CH_2), 61.0 (CH_2), 96.4 (CH), 107.0 (2 x CH), 111.7 (CH), 115.4 (C), 124.7 (C), 127.4 (C), 130.3 (C), 136.9 (CH), 139.1 (C), 141.4 (CH), 142.7 (C), 151.4 (C), 152.9 (2 x C), 153.5 (C), 167.2 (C), 167.3 (C); mass spectrum *m/z* (relative intensity) 530 (M^+, 16), 484(13), 456 (26), 411 (20), 362 (18), 317 (12), 289 (15), 195 (14), 181 (51), 168 (100), 149 (30), 57 (18); HRMS calcd for $C_{28}H_{34}O_{10}$ 530.2151 found 530.2147.

Diethyl *E,E*-bis-(2,4-dimethoxybenzylidene) succinate

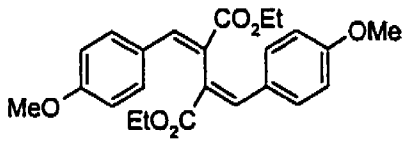


126

A slurry of NaH (57% suspension in oil, 1.00 g, 23.8 mmol) and DMF (20 mL) was prepared in a flame dried 100-mL three-neck flask. The flask was immersed in a 100 °C oil bath. A solution of 2,4-dimethoxybenzaldehyde (2.08 g, 12.5 mmol), diethyl succinate (0.9 mL, 5.5 mmol) and DMF (20 mL) was prepared with gentle heating. This solution was transferred to a dropping funnel and slowly added to the NaH-DMF slurry. The addition was completed in 30 min while stirring. The dropping funnel was rinsed with DMF (5 mL) and the reaction mixture stirred at reflux for 8 h. An aqueous 1.0 M KOH solution (25 mL) was added and refluxed for an additional 4 h. The solution was cooled to rt, combined with water (100 mL) and transferred to a separatory funnel. The mixture was extracted with EtOAc (2 x 50 mL). The basic aqueous layer was acidified with 10% HCl, extracted with fresh EtOAc (3 x 60 mL), washed with water (2 x 100

mL), dried ($MgSO_4$), and concentrated to give crude product (2.27 g, 99%). The crude product was taken up in DMSO (20 mL). K_2CO_3 (7.64 g, 55 mmol) and EtI (17.6 mL, 220 mmol) were added and the mixture heated at 80 °C for 5 h then cooled to rt. The reaction mixture was transferred to a separatory funnel and water (100 mL) added. This solution was extracted with EtOAc (3 x 50 mL). The aqueous fraction was drained and discarded. The three organic extracts were combined, washed with water (2 x 100 mL), dried with $MgSO_4$, filtered, and concentrated. The compound was isolated by FCC using 25% EtOAc-hexanes as the eluant to give a yellow oil (1.53 g, 59%). This compound was prepared with the aid of a fellow collaborator.[73] ^{1}NMR ($CDCl_3$) δ 1.13 (t, 6H, J = 7.1), 3.73 (s, 6H), 3.76 (s, 6H), 4.13 (q, 4H, J = 7.1), 6.32 (dd, 4H, J = 2.4, 7.7), 7.36 (d, 2H, J = 8.8), 8.01 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1 (2 x CH_3), 55.3 (4 x CH_3), 60.7 (2 x CH_2), 97.9 (2 x CH), 104.5 (2 x CH), 117.5 (2 x C), 125.6 (2 x C), 130.0 (2 x CH), 137.0 (2 x CH), 159.1 (2 x C), 161.8 (2 x C), 167.7 (2 x C); mass spectrum *m/z* (relative intensity) 470 (M^+, 17), 395 (43), 351 (45), 332 (23), 259 (10), 165 (100), 151 (24); HRMS calcd. for $C_{26}H_{30}O_8$ 470.1940 found 470.1968.

Diethyl *E,E*-bis-(4-methoxybenzylidene) succinate

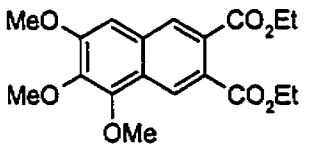


127

A slurry of NaH (57% suspension in oil, 2.53 g, 60.0 mmol) and DMF (75 mL) was charged to a flame dried 300-mL three-neck flask and immersed in a 100 °C oil bath. A solution of p-anisaldehyde (4-methoxybenzaldehyde, 6.81 g, 50.0 mmol), diethyl

succinate (3.0 mL, 18.0 mmol) and DMF (50 mL) was prepared with gentle heating. A dropping funnel was used to slowly dispense this solution to the NaH-DMF slurry. The addition was completed in 30 min while stirring. The dropping funnel was rinsed with DMF (25 mL) and the solution stirred at reflux for 6 h. EtI (16.0 mL, 200.0 mmol) was added directly to the reaction mixture and stirred for an additional 18 h. The reaction was quenched with water (150 mL) and extracted with EtOAc (3 x 150 mL). The organic fractions were pooled, washed with $NaHCO_3$ (200 mL) and water (200 mL), dried with $MgSO_4$, filtered, and concentrated to give a brown oil (9.0 g, 88%). A portion of the crude product (0.20 g) was purified by FCC using 30% EtOAc-hexanes to give a yellow-orange oil (0.11 g, 54%). ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 6H, J = 7.1), 3.75 (s, 6H), 4.14 (q, 4H, J = 7.1), 6.77 (d, 2H, J = 1.9), 6.79 (d, 2H, J = 1.9), 7.44 (d, 2H, J = 1.9), 7.47 (d, 2H, J = 1.9), 7.85 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1 (2 x CH_3), 55.2 (2 x CH_3), 60.9 (2 x CH_2), 114.0 (4 x CH), 124.7 (2 x C), 127.7 (2 x C), 131.6 (4 x CH), 142.1 (2 x CH), 160.6 (2 x C), 167.3 (2 x C); mass spectrum *m/z* (relative intensity) 410 (M^+, 34), 337 (52), 291 (45), 264 (60), 249 (20), 229 (13), 165 (28), 135 (100), 121 (60); HRMS calcd. for $C_{24}H_{26}O_6$ 410.1729 found 410.1740.

3,4,5-Trimethoxynaphthalene diester

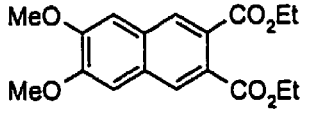


158b

Diethyl *E,E*-2(3,4,5-trimethoxybenzylidene)-3(2,4,5-trimethoxybenzylidene) succinate (**133**) (0.078 g, 0.15 mmol) was dissolved in CH_2Cl_2 (5 mL) and purged with

N_2 for 10 min. TfOH (100 μL) was diluted with CH_2Cl_2 (1 mL) and an aliquot (130 μL, 0.15 mmol) was added to the reaction. The reaction was quenched with water (15 mL) after stirring at rt for 2h. The solution was poured into a separatory funnel and CH_2Cl_2 (10 mL) added. The aqueous layer was removed and the organic layer was washed with water (15 mL), dried ($MgSO_4$), filtered, and concentrated to give a blue-green oil (0.076 g, 98%). This crude product was purified by FCC using 30% EtOAc-hexanes as the eluant to give a yellow oil (0.036 g, 46%). ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, J = 7.1), 1.39 (t, 3H, J = 7.1), 3.98 (s, 6H), 4.06 (s, 3H), 4.38 (q, 2H, J = 7.1), 4.40 (q, 2H, J = 7.1), 6.99 (s, 1H), 8.04 (s, 1H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 14.2 (CH_3), 56.0 (CH_3), 61.2 (CH_3), 61.4 (CH_3), 61.5 (CH_2), 61.6 (CH_2), 102.8 (CH), 124.2 (CH), 124.5 (C), 126.6 (C), 128.2 (C), 129.0 (CH), 131.0 (C), 142.5 (C), 148,4 (C), 155.2 (C), 167.9 (C), 168.0 (C); mass spectrum *m/z* (relative intensity) 362 (M^+, 100), 347 (32), 319 (16), 289 (37), 245 (9), 231 (12), 202 (9); HRMS calcd. for $C_{19}H_{22}O_7$ 362.1365 found 362.1347.

3,4-Dimethoxynaphthalene diester

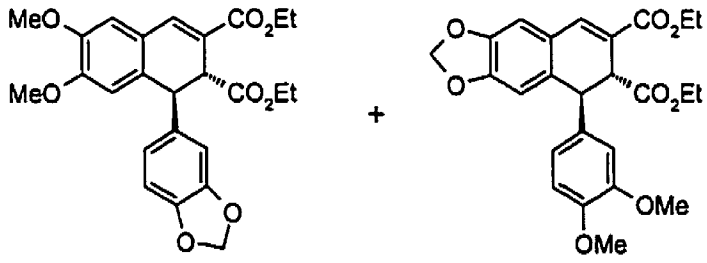


158a

Diethyl *E,E*-2(3,4-dimethoxybenzylidene)-3(2,4-dimethoxybenzylidene) succinate (**132**) (0.043 g, 0.091 mmol) was dissolved in CH_2Cl_2 (3 mL) and purged with N_2 for 10 min. TfOH (30 μL, 0.34 mmol) was added and the reaction stirred for 18 h at rt. The reaction was quenched with water (10 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer was extracted with another portion

of CH_2Cl_2 (10 mL). The CH_2Cl_2 fractions were combined, dried with $MgSO_4$, filtered and evaporated to give a dark yellow-brown oil (0.031 g, 71%). The compound was isolated by FCC using 30% EtOAc-hexanes as the solvent system to give a yellow oil (0.023, 54%). ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 6H, *J* = *7.1*), 3.99 (s, 6H), 4.39 (q, 4H, *J* = *7.1*), 7.15 (s, 2H), 8.07 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2 (2 x CH_3), 56.0 (2 x CH_3), 61.5 (2 x CH_2), 106.7 (2 x CH), 127.3 (2 x C), 128.2 (2 x CH), 129.5 (2 x C), 151.4 (2 x C), 168.0 (2 x C); mass spectrum m/z (relative intensity) 332 (M^+, 43), 287 (17), 259 (100), 214 (17), 186 (22), 115 (9); HRMS calcd. for $C_{18}H_{20}O_6$ 332.1259 found 332.1261.

Dihydronaphthalene diesters

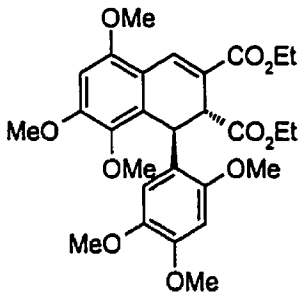


162 **163**

Diethyl *E,E*-2(3,4-dimethoxybenzylidene)-3(3,4-methylenedioxybenzylidene) succinate (**130**) (0.88 g, 1.9 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and added to a flame-dried pyrex tube, 17 cm long and 1cm in diametre. TfOH (170 mL, 1.9 mmol) was diluted with CH_2Cl_2 (1 mL) and added to the reaction tube. The sample was degassed by several freeze-pump-thaw cycles and sealed under vacuum. The reaction tube was submerged in a 40 °C water bath for 4 h. The sealed tube was broken and the contents poured into a separatory funnel. The reaction was quenched with water (5 mL), diluted with CH_2Cl_2 (5 mL), and the aqueous layer discarded. The organic layer was washed

with water (2 x 10 mL), dried with $MgSO_4$, filtered, and solvent removed to give a dark brown oil. The compound was isolated by FCC (30% EtOAc-hexanes) to give a mixture of two products (0.58 g, 66%). It was determined that the major product (75%) was **162** and the minor product (25%) was **163** by comparison with previous characterisation (^{1}H NMR, ^{13}C NMR and mass spectroscopy) data.[68]

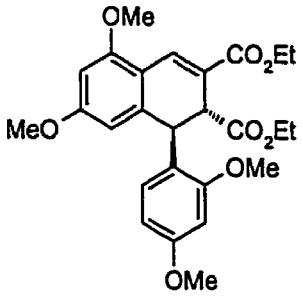
Bis 2,4,5-trimethoxydihydronaphthalene diester



136

Diethyl *E,E*-bis-(2,4,5-trimethoxybenzylidene) succinate (**120**) (0.045 g, 0.09 mmol) was dissolved in dry CH_2Cl_2 (2 ml) and added to pyrex tube, 10 cm long and 0.5 cm in diameter, that was flame-dried under high vacuum. TfOH (10 μL, 0.1 mmol) was diluted with CH_2Cl_2 (1 mL) and an aliquot (100 μL) was added to the reaction tube. The sample was degassed by several freeze-pump-thaw cycles and sealed under vacuum. The reaction tube was submerged in a 35 °C water bath for 4 h. The sealed tube was cracked and the solution poured into a separatory funnel. The mixture was quenched with water (5 mL), diluted with CH_2Cl_2 (5 ml), and the aqueous layer discarded. The organic layer was washed with NaS_2O_3 (2 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to give a brown oil that required no further purification (0.044 g, 97 %). This compound had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.

Bis 2,4-dimethoxydihyronaphthalene diester

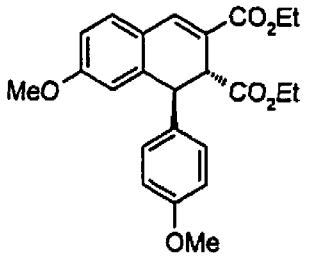


138

Diethyl *E,E*-bis-(2,4-dimethoxybenzylidene) succinate (**126**) (0.12 g, 0.3 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and placed in a small flame dried flask. The flask was purged with N_2 and TfOH (22 μL) was added dropwise. The reaction was stirred at rt for 4 h and quenched with water (5 mL). The solution was diluted with CH_2Cl_2 and the water layer was removed. The organic fraction was washed with water (2 x 15 ml), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by FCC using 30% EtOAc-hexanes as the eluant to give a yellow oil (0.031 g, 26%). ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H, J = 7.1), 1.28 (t, 3H, J = 7.1), 3.73 (s, 6H), 3.87 (s, 3H), 3.89 (s, 3H), 3.98 (d, 1H, J = 2.7), 4.06 (m, 2H, J = 7.1), 4.18 (m, 2H, J = 7.1), 5.00 (d, 1H, J = 2.7), 6.20 (dd, 1H, J = 2.4, 8.4), 6.25 (d, 1H, J = 2.3), 6.32 (d, 1H, J = 2.3), 6.40 (d, 1H, J = 8.4), 6.45 (d, 1H, J = 2.4), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 14.3 (CH_3), 39.7 (CH), 44.6 (CH), 55.2 (CH_3), 55.3 (CH_3), 55.5 (2 x CH_3), 60.3 (CH_2), 60.7 (CH_2), 97.0 (CH), 98.5 (CH), 103.8 (CH), 105.5 (CH), 115.1 (C), 121.7 (C), 122.2 (C), 129.3 (CH), 131.3 (CH), 140.6 (C), 157.4 (C), 157.9 (C), 159.6 (C), 162.5 (C), 167.1 (C), 172.7 (C); mass spectrum *m/z* (relative intensity) 470 (M^+, 15), 396 (56), 351 (100), 332 (25), 287 (19),

236 (35), 177 (61), 165 (74), 151 (69), 135 (18), 121 (35), 84 (58), 71 (48), 57 (50); HRMS calcd for $C_{26}H_{30}O_8$ 470.1940 found 470.1926.

Bis 4-methoxydihydronaphthalene diester

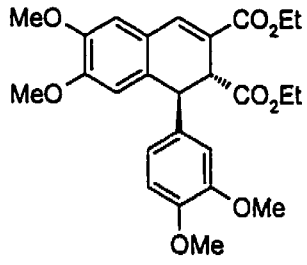


139

Bis-4-methoxybenzylidenesuccinate diester (**127**) (0.11 g, 0.3 mmol) was dissolved in CH_2Cl_2 (9 mL) and charged to a flame-dried flask. The solution was purged with N_2 for 10 min, TfOH (0.12 mL, 1.3 mmol) added and the reaction stirred at rt for 72 h. The reaction was quenched with water (15 mL) and CH_2Cl_2 (20 mL) added. The aqueous fraction was removed and the organic layer was washed with water (2 x 25mL), dried with $MgSO_4$, filtered and evaporated to give a crude yellow-brown oil (0.080 g, 74%). The compound was isolated by FCC using 30% EtOAc-hexanes as the eluant to give a yellow oil (0.040 g, 36%). ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.1), 1.29 (t, 3H, J = 7.1), 3.74 (s, 3H), 3.76 (s, 3H), 3.98 (d, 1H, J = 3.4), 4.07 (m, 2H,), 4.20 (m, 2H), 4.61 (d, 1H, J = 3.4), 6.64 (d, 1H, J = 2.5), 6.74 (d, 1H, J = 2.0), 6.77 (d, 1H, J = 2.0), 6.79 (dd, 1H, J = 2.5, 8.3), 6.96 (d, 1H, J = 2.0), 6.99 (d, 1H, J = 2.0), 7.28 (d, 1H, J = 8.4), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 14.2 (CH_3), 46.0 (CH), 47.3 (CH), 55.2 (CH_3), 55.3 (CH_3), 60.6 (CH_2). 61.0 (CH_2), 112.8 (CH), 113.9 (2 x CH), 114.8 (CH), 122.8 (C), 124.7 (C), 128.7 (2 x CH), 130.6 (CH), 134.4 (C), 137.1 (CH), 139.3 (C), 158.4 (C), 161.4 (C), 166.7 (C), 172.5 (C); mass spectrum *m/z* (relative intensity) 410

(M^+, 9), 336 (100), 308 (10), 291 (49), 264 (63), 250 (14), 227 (19), 189 (11), 149 (19), 135 (26), 121 (22); HRMS calcd. for 410.1729 $C_{24}H_{26}O_6$ found 410.1741.

Bis 3,4-dimethoxydihydronaphthalene diester

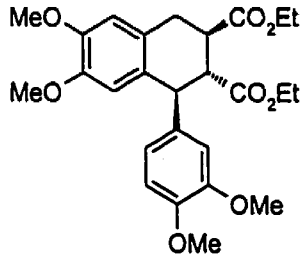


135

Diethyl *E,E*-bis-(3,4-dimethoxybenzylidene) succinate (119) (0.49 g, 1.0 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and added to a pyrex tube, 17 cm long and 1 cm in diameter, that was flame-dried under high vacuum. TfOH (82 μL, 0.9 mmol) in CH_2Cl_2 (1 mL) was dispensed into the reaction tube. The sample was degassed by several freeze-pump-thaw cycles and sealed under vacuum. The reaction tube was submerged in a 40 °C water bath for 5 h then cooled to rt. The sealed tube was cracked, water (10 mL) and CH_2Cl_2 (10 mL) were added. The aqueous layer was discarded and the organic layer was washed with NaS_2O_3 (2 x 10 mL), washed with water (10 mL), dried with $MgSO_4$, filtered, and evaporated to give a brown oil (0.40 g, 81%). The crude product was purified by FCC using 40% EtOAc-hexanes as the eluant to give a yellow oil (0.20 g, 42%). ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H, J = 7.1), 1.22 (t, 3H, J = 7.1), 3.73 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 3.84 (s, 3H), 3.94 (d, 1H, J = 3.1), 4.04 (m, 2H), 4.14 (m, 2H), 4.56 (d, 1H, J = 3.1), 6.42 (dd, 1H, J = 2.0, 8.3), 6.60 (d, 2H, J = 2.1), 6.63 (d, 1H, J = 8.3), 7.60 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 14.2 (CH_3), 45.7 (CH), 47.4 (CH), 55.8 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 55.9 (CH_3), 60.5 (CH_2), 61.0 (CH_2), 111.0 (CH), 111.1

(CH), 111.7 (CH), 112.0 (CH), 119.8 (CH), 123.2 (C), 124.3 (C), 130.3 (C), 135.0 (C), 137.0 (CH), 147.9 (C), 148.1 (C), 148.8 (C), 150 .7 (C), 166.5 (C), 172.4 (C); mass spectrum *m/z* (relative intensity) 470 (M+, 14), 396 (100), 351 (57), 324 (34), 310 (8), 151 (10); HRMS calcd for $C_{26}H_{30}O_8$ 470.1940 found 470.1930. This compound had ^1H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[68]

Bis 3,4-dimethoxyaryltetralin diester

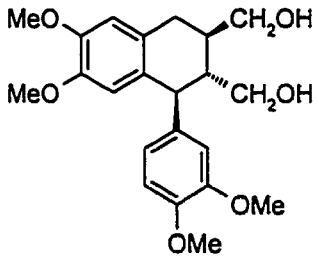


166a

Bis 3,4-dimethoxydihydronaphthalene diester **135** (0.15 g, 0.3 mmol) was dissolved in anhydrous EtOH (10 mL) and Pd/C (0.023 g, 0.2 mmol) was added. The flask was flushed with N_2 to evacuate the O_2. The flask was flushed and evacuated with H_2 several times followed by stirring at rt for 18 h under H_2 at 1 atmosphere of pressure. The reaction mixture was filtered through celite and concentrated to give a clear, colourless oil (0.14 g, 92 %). The product required no further purification for the next step. ^1H NMR ($CDCl_3$) δ 0.96 (t, 3H, J = 7.1), 1.24 (t, 3H, J = 7.1), 3.00 (t, 1H of C2, J = 10.8), 3.06-3.24 (m, 3H(H of C,3,4), 3.57 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 3.92 (m, 2H), 4.12 (m, 2H), 4.14 (d, 1H of C1, J = 10.7), 6.22 (s, 1H), 6.59 (d, 2H, J = 2.2), 6.68 (dd, 1H, J = 2.1, 8.2), 6.78 (d, 1H, J = 8.2); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 14.1 (CH_3), 31.9 (CH_2), 43.4 (CH), 49.0 (CH), 51.5 (CH), 55.8 (2 x CH_3), 55.9 (2x CH_3), 60.3 (CH_3), 60.9 (CH_3), 110.7 (CH), 110.9 (CH), 111.9 (CH), 112.1 (CH), 121.7 (CH),

126.2 (C), 129.9 (C), 135.4 (C), 147.5 (C), 147.7 (C), 148.0 (C), 149.0 (C), 173.7 (C), 174.1 (C); mass spectrum *m/z* (relative intensity) 472 (M^+, 50), 398 (42), 325 (100), 269 (22), 236 (20), 151 (29); HRMS calcd. for $C_{26}H_{32}O_8$ 472.2097 found 472.2086.

(+/-)-Isolariciresinol dimethyl ether

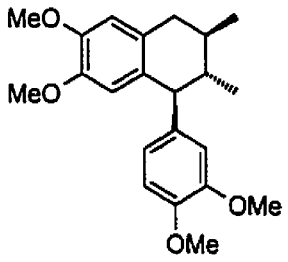


49/167a

Bis 3,4-dimethoxyaryltetralin diester **166a** (0.14 g, 0.3 mmol) was dissolved in dry THF (8 mL) and added to a slurry of $LiAlH_4$ (0.066 g, 1.7 mmol) and dry THF (2 mL) at rt. The reaction was stirred under N_2 for ½ h at rt and worked up using Fieser's method. In succession 0.09 mL water, 0.09 mL 15% aqueous NaOH, and 0.27 mL water were added to quench the reaction. The solution was diluted with EtOAc (15 mL), dried with $MgSO_4$, filtered through Celite, and evaporated to give a white amorphous solid (0.10 g, 92%); mp 146-149 °C. ^1H NMR ($CDCl_3$) δ 1.75-1.85 (m, 1H, H_2), 1.97-2.08 (m, 1H, H_3), 2.70 (dd, 1H, H_4 cis to H_3, J = 5.3, 16.0), 2.72 (dd, 1H, H_4 trans to H_3, J = 11.6, 16.0), 2.94 (br s, 2H of OH), 3.47 (dd, 1H, J = 5.3, 11.3), 3.56 (s, 3H), 3.70 (m, 2H), 3.78 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.80-3.85 (m, 2H), 6.19 (s, 1H), 6.58 (d, 1H, J = 3.0), 6.72 (dd, 1H, J = 2.0, 8.2), 6.79 (d, 1H, J = 8.2); ^{13}C NMR ($CDCl_3$) δ 33.2 (CH_2), 39.9 (CH), 48.0 (CH), 48.3 (CH), 55.8 (2 x CH_3), 55.9 (2 x CH_3), 62.7 (CH_2), 66.4 (CH_2), 110.9 (CH), 111.0 (CH), 112.1 (CH), 112.9 (CH), 121.9 (CH), 128.2 (C), 131.9 (C), 137.8 (C), 147.1 (C), 147.2 (C), 147.6 (C), 149.1 (C); HRMS calcd. for $C_{22}H_{28}O_6$

388.1885 found 388.1896. This compound had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[27,28,59]

(+/-)-Galbulin

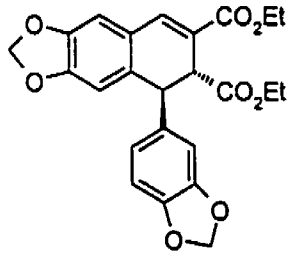


1

(+/-)-Isolariciresinol dimethyl ether **167a** (0.027 g, 0.07 mmol) was dissolved in dry CH_2Cl_2 (3 mL) and diisopropylethylamine (0.027 g, 0.2 mmol) was added. The flask was purged with N_2 and cooled to –10 °C in a salt-ice water bath. Triflic anhydride (0.059 g, 0.2 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to the cooled reaction mixture. The reaction was stirred for 15 min then quenched with water (3 mL) and diluted with CH_2Cl_2 (5 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (6 mL), dried with $MgSO_4$, filtered, and stripped of solvent. This crude product was immediately taken up in THF (2 mL) and added to a slurry of $LiAlH_4$ (0.016 g, 0.4 mmol) and THF (1 mL) at –10 °C. After 20 min of stirring, the reaction was worked up by Fieser's method (20 μL water, 20 μL 15% aq. NaOH, 60 μL water) followed by the addition of EtOAc (5 mL). The solution was dried with $MgSO_4$, filtered through Celite and concentrated to give a light brown crude oil. This crude product was purified by FCC using 30% EtOAc-hexanes as the eluant to give a light yellow oil (0.011 g, 43%). ^{1}NMR ($CDCl_3$) δ 0.87 (d, 3H, J = 6.3), 1.08 (d, 3H, J = 6.3), 1.59 (m, 2H), 2.62 (dd, 1H,

J = 11.2, 16.2), 2.77 (dd, 1H, J = 4.6, 16.2), 3.42 (d, 1H, J = 10.2), 3.56 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 6.16 (s, 1H), 6.57 (dd, 2H, J = 2.2, 4.3), 6.70 (dd, 1H, J = 1.7, 8.2), 6.80 (d, 1H, J = 8.0); ^{13}C NMR ($CDCl_3$) δ 17.2 (CH_3), 20.0 (CH_3), 35.6 (CH), 39.0 (CH_2), 43.8 (CH), 54.3 (CH), 55.3 (CH_3), 55.8 (2 x CH_3), 55.9 (CH_3), 110.7 (CH), 110.7 (CH), 112.1 (CH), 112.9 (CH), 121.9 (CH), 129.1 (C), 132.5 (C), 139.0 (C), 146.9 (C), 147.1 (C), 147.3 (C), 148.9 (C); HRMS calcd. for $C_{22}H_{28}O_4$ 356.1987 found 356.1991. This compound had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[55,66,67]

Bis 3,4-methylenedioxydihydronapthalene diester

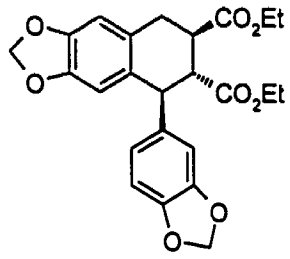


134

Diethyl *E,E*-bis-(3,4-methylenedioxybenzylidene) succinate (**118**) (0.32 g, 0.7 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and added to a flame dried flask. TfOH (0.096 mL, 1.1 mmol) in CH_2Cl_2 (1 mL) was added. The reaction was stirred under N_2 for 8½ h and quenched with $NaHCO_3$ (5 mL). The mixture was diluted with CH_2Cl_2 (15 mL), the organic fraction separated, washed with water (15 mL), dried with $MgSO_4$, filtered and concentrated to give a dark yellow oil (0.24 g, 77%). The product was isolated by FCC using 30% EtOAc-hexanes as the eluting solvent system to give a yellow oil (0.12 g, 36%). ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, J = 7.1), 1.30 (t, 3H, J = 7.1), 3.93 (d, 1H, J = 3.1), 4.08 (m, 2H), 4.21 (m, 2 H), 4.55 (d, 1H, J =3.1), 5.88 (m (AB), 2H), 5.96

(s, 2H), 6.52 (m, 2H), 6.59 (s, 1H), 6.66 (d, 1H, J = 7.8), 6.81 (s, 1H), 7.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 14.2 (CH_3), 46.1 (CH), 47.3 (CH), 60.7 (CH_2), 61.1 (CH_2), 100 9 (CH_2), 101.4 (CH_2), 108.1 (CH), 108.2 (CH), 108.8 (CH), 109.7 (CH), 120.8 (CH), 123.2 (C), 125.5 (C), 132.0 (C), 136.3 (C), 137.0 (CH), 146.4 (C), 147.0 (C), 147.7 (C), 149.3 (C), 166.5 (C), 172.1 (C); mass spectrum *m/z* (relative intensity) 438 (M^+, 11), 364 (100), 319 (48), 263 (17), 233 (13), 176 (19); HRMS calcd. for $C_{24}H_{22}O_8$ 438.1314 found 438.1324. This compound had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[68]

Bis 3,4-methylenedioxyaryltetralin diester

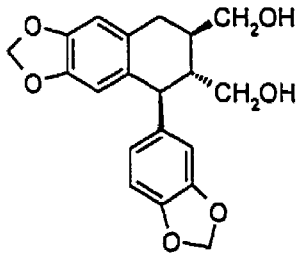


166b

Bis 3,4-methylenedioxydihydronaphthalene diester **134** (0.032 g, 0.07 mmol) was dissolved in anhydrous EtOH (15 mL) and Pd/C (0.015 g, 0.1 mmol) added. The flask was flushed with N_2 to evacuate the O_2. The reaction flask was flushed and evacuated with H_2 several times and stirred at rt for 27 h under H_2 at 1 atmosphere of pressure. The reaction mixture was filtered through Celite and concentrated to give a light yellow oil (0.020 g, 64%). The product required no further purification for the next step. ^{1}H NMR ($CDCl_3$) δ 1.01 (t, 3H, J = 7.1), 1.25 (t, 3H, J = 7.1), 2.97 (t, 1H, H_2 J = 10.8), 3.06 (m, 2H, H_4), 3.13 (m, 1H, H_3), 3.96 (m, 2H), 4.08 (m, 1H, H_1, J = 11.0), 4.14 (m, 2H), 5.85 (m (AB), 2H), 5.92 (s, 2H), 6.22 (s, 1H), 6.54 (d, 1H, J = 1.6), 6.56 (s, 1H), 6.60 (dd, 1H,

J = 1.7, 7.8), 6.71 (d, 1H, J = 7.8); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 14.1 (CH_3), 32.4 (CH_2), 43.4 (CH), 49.2 (CH), 51.5 (CH), 60.4 (CH_2), 60.9 (CH_2), 100.8 (CH_2), 100.9 (CH_2), 107.7 (CH), 107.9 (CH), 109.0 (CH), 109.1 (CH), 122.6 (CH), 127.2 (C), 131.0 (C), 136.8 (C), 146.2 (C), 146.3 (C), 146.6 (C), 147.9 (C), 173.5 (C), 173.9 (C); mass spectrum *m/z* (relative intensity) 440 (M^+, 32), 366 (47), 263 (26), 235 (21), 220 (12), 135 (22); HRMS calcd. for $C_{24}H_{24}O_8$ 440.1471 found 440.1473.

Bis 3,4-methylenedioxyaryltetralin diol

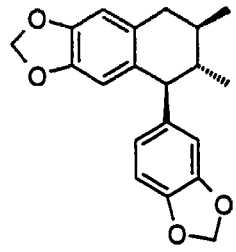


167b

Bis 3,4-methylenedioxyaryltetralin diester **166b** (0.020 g, 0.05 mmol) was dissolved in THF (3 mL) and added to a slurry of $LiAlH_4$ (0.024 g, 0.6 mmol) and dry THF (2 mL) at rt. The reaction was stirred under N_2 for ½ h at rt followed by work up using Fieser's method. In succession 0.06 mL water, 0.06 mL 15% aqueous NaOH, and 0.18 mL water were added to quench the reaction. The solution was diluted with EtOAc (15 mL), dried with $MgSO_4$, filtered through Celite, and evaporated to give a white milky oil (0.016 g, 100%). ^{1}H NMR ($CDCl_3$) δ 1.71-1.83 (m, 1H, H_2), 1.93-2.03 (m, 1H, H_3), 2.55 (br s, 2H, OH) 2.68 (m, 2H, H_4), 3.48 (dd, 1H, H_1, J = 5.2, 11.3), 3.72 (m, 2H,), 3.78 (m, 2H), 5.83 (m (AB), 2H), 5.92 (s, 2H), 6.20 (s, 1H), 6.54 (d, 1H, J = 1.8), 6.55 (s, 1H), 6.64 (dd, 1H, J = 1.7, 7.8), 6.74 (d, 1H, J = 7.8); ^{13}C NMR ($CDCl_3$) δ 33.6 (CH_2),

39.8 (CH), 48.2 (CH), 48.3 (CH), 62.7 (CH_2), 66.3 (CH_2), 100.6 (CH_2), 100.9 (CH_2), 107.8 (CH), 108.0 (CH), 109.1 (CH), 109.6 (CH), 122.8 (CH), 129.2 (C), 132.8 (C), 139.1 (C), 145.7 (C), 145.8 (C), 146.2 (C), 148.0 (C); mass spectrum *m/z* (relative intensity) 356 (M^+, 100), 338 (32), 307 (73), 280 (54), 267 (50), 238 (52), 210 (27), 185 (26), 173 (50), 152 (41), 135 (89), 115 (29), 76 (19); HRMS calcd. for $C_{20}H_{20}O_6$ 356.1259 found 356.1262.

(+/-)-Cagayanin

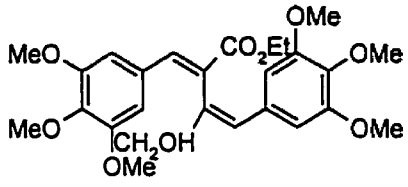


2

Bis 3,4-methylenedioxyaryltetralin diol **167b** (0.016 g, 0.05 mmol) was taken up in dry CH_2Cl_2 (4 mL) and diisopropylethylamine (0.018 g, 0.1 mmol) was added. The flask was purged with N_2 and cooled to –10 °C in a salt-ice water bath. Triflic anhydride (0.039 g, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to the cooled reaction mixture. The reaction was stirred under N_2 for 1 h 30 min after which water (3 mL) was added to quench the reaction. The solution was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 10 mL). The organic fraction was recovered, dried with $MgSO_4$, filtered, and stripped of solvent. The crude product was dissolved in THF (2 mL) and added to a slurry of $LiAlH_4$ (0.018 g, 0.5 mmol) and THF (2 mL) at –10 °C. The reaction was stirred under N_2 at rt for 45 min and worked up by Fieser's method (60

μL water, 60 μL 15% aq. NaOH, 180 μL water) followed by the addition of EtOAc (20 mL). The solution was dried with $MgSO_4$, filtered through Celite and concentrated to give a white oil. This crude product was purified by FCC using 20% EtOAc-hexanes as the eluant to give a clear, colourless oil (0.011 g, 77%). ^{1}NMR ($CDCl_3$) δ 0.87 (d, 3H, J = 6.3), 1.05 (d, 3H, J = 6.3), 1.48 (m, 1H, H_2), 1.60 (m, 1H, H_3), 2.56 (dd, 1H, H_4, J = 11.2, 16.1), 2.71 (dd, 1H, H_4, J = 4.5, 16.1), 3.38 (d, 1H, H_1, J = 10.4), 5.81 (s, 2H), 5.92 (s, 2H), 6.17 (s, 1H, H_8), 6.52 (s, 2H), 6.62 (dd, 1H, J = 1.6, 8.0), 6.74 (d, 1H, J = 7.9); ^{13}C NMR ($CDCl_3$) δ 17.1 (CH_3), 19,9 (CH_3), 35.4 (CH), 39.4 (CH_2), 43.8 (CH), 54.6 (CH), 100.5 (CH_2), 100.8 (CH_2), 107.6 (CH), 107.7 (CH), 109.1 (CH), 109.6 (CH), 122.8 (CH), 130.1 (C), 133.4 (C), 140.5 (C), 145.4 (C), 145.6 (C), 145.9 (C), 147.8 (C); mass spectrum *m/z* (relative intensity) 324 (M^+, 100), 267 (57), 238 (77), 210 (25), 187 (13), 152 (26), 135 (17), 76 (23), 57 (16); HRMS calcd. for $C_{20}H_{20}O_4$ 324.1361 found 324.1355. This compound had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[63,64]

***E,E*-bis-(3,4,5-trimethoxybenzylidene) succinate monoalcohol-ester**

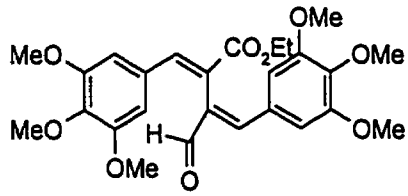


194

E,E-bis-(3,4,5-trimethoxybenzylidene) succinate monoacid-ester **125d** (0.56 g, 1.1 mmol) was dissolved in THF (20 mL) and added to a dry 50-mL flask. A 2.0 M solution of BH_3·SMe_2 in THF (5.6 mL, 11.1 mmol) was added to the reaction flask. The reaction was stirred at rt under N_2 for 4½ h and quenched with EtOH (25 mL). The

solvent was evaporated and a second aliquot of EtOH (25 mL) was added and evaporated. This procedure was repeated twice more. The residue was taken up in $CHCl_3$ (40 mL), washed with $NaHCO_3$ (2 x 25 mL), dried with $MgSO_4$, filtered and stripped of solvent to give a light yellow oil that required no further purification (0.47 g, 86%). ^1H NMR ($CDCl_3$) δ 1.19 (t, 3H, J = 7.1), 3.74 (s, 6H), 3,76 (s, 6H), 3.80 (s, 3H), 3.85 (s, 3H), 4.20 (m, 2H,), 4.27 (m, 2H), 6.64 (s, 2H), 6.79 (d, 1H, J = 3.7), 6.90 (s, 2H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 55.9 (2 x CH_3), 56.1 (2 x CH_3), 60.8 (CH_3), 60.9 (CH_3), 61.4 (CH_2), 66.7 (CH_2), 105.4 (2 x CH), 107.1 (2 x CH), 129.2 (CH), 129.7 (C), 129.8 (C), 131.9 (C), 135.7 (C), 137.6 (C), 139.5 (C), 140.6 (CH), 153.0 (2 x C), 153.1 (2 x C), 167.5 (C); mass spectrum *m/z* (relative intensity) 488 (M^+, 14), 470 (14), 442 (8), 397 (18), 366 (9), 274 (10), 181 (100), 168 (27), 153 (9), 84 (75); HRMS calcd. for $C_{26}H_{32}O_9$ 488.2046 found 488.2022.

***E,E*-bis-(3,4,5-trimethoxybenzylidene) succinate monoaldehyde-ester**

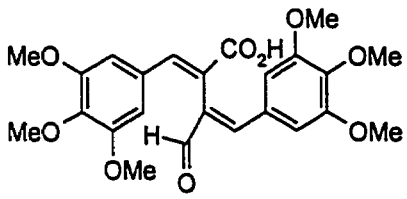


195

E,E-bis-(3,4,5-trimethoxybenzylidene) succinate monoalcohol-ester **194** (0.47 g, 1.0 mmol) was dissolved in toluene (20 mL) and MnO_2 (0.84 g, 9.6 mmol) added. The reaction was stirred at rt under N_2 for 24 h after which MnO_2 was removed by filtration. Fresh MnO_2 (0.84 g, 9.6 mmol) was added and the solution was stirred for an additional 48 h under N_2. The mixture was filtered through Celite to give a yellow oil that required no further purification (0.47 g, 72%). ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, J = 7.2), 3.72 (s,

6H), 3.78 (s, 6H), 3.82 (s, 3H), 3.86 (s, 3H), 4.14 (m, 2H, J = 7.2), 6.68 (s, 2H), 6.88 (s, 2H), 7.50 (s, 1H), 7.96 (s, 1H), 9.60 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 56.0 (2 x CH_3), 56.1 (2 x CH_3), 60.9 (CH_3), 61.0 (CH_3), 61.3 (CH_2), 107.5 (2 x CH), 107.6 (2 x CH), 124.7 (C), 129.6 (C), 129.7 (C), 136.3 (C), 139.7 (C), 140.6 (C), 143.2 (CH), 150.4 (CH), 153.1 (2 x C), 153.3 (2 x C), 166.2 (C), 191.9 (CH); mass spectrum *m/z* (relative intensity) 486 (M^+, 12), 412 (12), 318 (8), 273 (13), 181 (100), 168 (16); HRMS calcd. for $C_{26}H_{30}O_9$ 486.1889 found 486.1882.

_E,E_-bis-(3,4,5-trimethoxybenzylidene) succinate monoaldehyde-acid

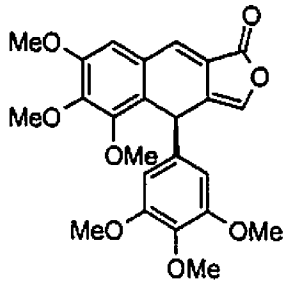


196

E,E-bis-(3,4,5-trimethoxybenzylidene) succinate monoaldehyde-ester **195** (0.34 g, 0.7 mmol) in anhydrous EtOH (20 mL) was charged to a dry flask. A solution of K_2CO_3 (1.91 g, 13.8 mmol) in water (15 mL) was prepared, added to the reaction flask and stirred at rt under N_2 for 19½ h. The solution was acidified with 10% HCl (50 mL) and extracted with $CHCl_3$ (2 x 25 mL). The $CHCl_3$ layers were combined, dried with $MgSO_4$, filtered and evaporated to give a yellow oil (0.29 g, 91%). The product was carried on to the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 6H), 3.77 (s, 6H), 3.82 (s, 3H), 3.87 (s, 3H), 6.70 (s, 2H), 6.89 (s, 2H), 7.52 (s, 1H), 8.05 (s, 1H), 9.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.0 (2 x CH_3), 56.1 (2 x CH_3), 60.9 (CH_3), 61.0 (CH_3), 107.4 (2 x CH), 107.7 (2 x CH), 123.4 (C), 129.2 (C), 129.3 (CH), 135.7 (CH), 140.2 (C), 140.8 (C), 145.3 (C), 151.2 (C), 153.1 (2 x C), 153.3 (2 x C), 170.8 (C), 192.0 (CH); mass

spectrum *m/z* (relative intensity) 458 (M^+, 25), 440 (37), 412 (12), 273 (16), 195 (14), 181 (100), 168 (38), 153 (17), 84 (10), 77 (10); HRMS calcd. for $C_{24}H_{26}O_9$ 458.1576 found 458.1569.

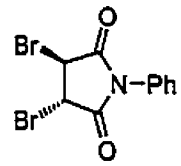
4-(3,4,5-Trimethoxyphenyl)-4*H*-3,4,5-trimethoxynaptho[2,3,*c*]furan-1-one



202

E,E-bis-(3,4,5-trimethoxybenzylidene) succinate monoaldehyde-acid (0.026 g, 0.06 mmol) was dissolved in benzene (5 mL). *Para*-toluenesulfonic acid (0.008 g, 0.03 mmol) was added to the reaction mixture and the solution was stirred for 20 h at rt. The solvent was removed and the compound was isolated by FCC using 40% EtOAc-hexanes as the eluting solvent. The compound was obtained as a white oil (0.007 g, 26%). ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 6H), 3.85 (s, 3H), 4.00 (s, 3H), 4.03 (s, 6H), 6.46 (s, 1H), 6.54 (s, 2H), 7.12 (s, 1H), 7.98 (s, 1H), 8.35 (s, 1H).

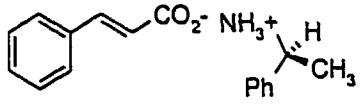
***N*-phenyl-3,4-dibromosuccinimide**



186

N-phenylmaleimide (1.00 g, 5.8 mmol) was dissolved in chloroform (7 mL) with gentle heating. Bromine (1.02 g, 6.4 mmol) was added dropwise to give a dark brown solution. As the brown colour faded formation of a white precipitate was observed. The reaction was stirred at rt for 4 h and the white precipitate (1.52 g, 79%) was collected by suction filtration. ^{1}H NMR ($CDCl_3$) δ 4.87 (s, 2H), 7.35 (m, 2H), 7.50 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 41.9 (2 x CH), 126.0 (CH), 129.4 (2 x CH), 129.5 (2 x CH), 169.5 (2 x C); mass spectrum *m/z* (relative intensity) 333 (M^+,13), 251 (49), 173 (100), 133 (25), 119 (26), 103, (16), 91 (23), 82 (53), 64 (23); HRMS calcd. for $C_{10}H_7O_2N^{81}Br_2$ 334.8802 found 334.8817.

α–(S)-Methylbenzylammonium salt of cinnamic acid



192

Cinnamic acid (0.016 g, 0.1 mmol) was dissolved in ether (1 mL) with gentle heating. Neat α–(S)-methylbenzylamine (0.014 mL, 0.1 mmol) was added dropwise to this stirred solution and a white precipitate was immediately formed. The precipitate was collected by filtration and washed with ether (0.021 g, 74%). ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 2H, J = 6.7), 4.27 (q, 1H, J = 6.7), 6.29 (d, 2H, J = 15.9), 7.30 (m, 5H).

References

1. MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207-1220.
2. Kelleher, J. K. *Cancer Treatment Rep.* **1978**, *62*, 1443-1447.
3. Kelly, M. G.; Hartwell, J. L. *J. Nat. Canc. Inst.* **1954**, 967-971.
4. Markkanen, T.; Makinen, M. L.; Maunuksela, E.; Himanen, P. *Drugs Exptl. Clin. Res.* **1981**, *7*, 711-718.
5. Haworth, R. D. *Ann. Rep. Prog. Chem.* **1936**, *33*, 266-279.
6. a) Aryes, D. C.; Loike, J. D. In *Lignans: Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, **1990**, pp 1-137; b) Kaufman, P. B.; Cseke, L. J.; Warber, S.; Duke, J. A.; Brielmann, H. L. In *Natural Products from Plants*; CRC Press: New York, 1999, pp 51-55; c) Axelson, M.; Sjovall, J.; Gustafsson, B. E.; Setchell, K. D. R. *Nature* **1982**, *290*, 659-665.
7. Gottlieb, O. R. *Phytochemistry* **1972**, *11*, 1537-70.
8. Gottlieb, O. R. *Rev. Latinoamer. Quin.* **1974**, *5*, 1-11.
9. Gottlieb, O.R. *Neolignans Fortschr. Org. Chem. Naturst.* **1978**, *35*, 1-72.
10. Eliel, E. L.; Wilen, S. H. In *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc.: New York, **1994**, pp 1-6, 1119-1155.
11. McMurry, J. Organic Chemistry 3rd Ed.; Brooks/Cole Publishing Co.: Belmont, 1992, pp 284-289.
12. Kuhn, R. Molekulare Asymmetrie. In *Stereochemie*, Freudenberg, H. Ed., Franz Deutzie: Leipzig-Wein, **1933**, pp 803-824.
13. Charlton, J. L.; Oleschuk, C. J.; Chee G. L. *J. Org. Chem.* **1996**, *61*, 3452-3457.
14. Charlton, J. L.; Datta, P. K.; unpublished work.

15. Bringmann, G.; Ochse, M.; Gotz, R. *J. Org. Chem.* **2000**, *65*, 2069-2077.

16. Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* 1999, 525-530.

17. Ward, R. S. *Chem. Soc. Rev.* **1982**, 75-125.

18. Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191-211.

19. Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499-525.

20. Whiting, D. A. *Nat. Prod. Rep.* **1990**,*7*, 349-364.

21. Ward, R. S. *Nat. Prod. Rep.* **1993**, *10*, 1-28.

22. Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183-204.

23. Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43-74.

24. Wallis, A. F. A. *Amer. Chem. Soc.* **1998**, 323-333.

25. Charlton, J. L.; Lee, K. A. *Tetrahedron Lett.* **1997**, *38*, 7311-7312.

26. Lee, K. A. In *Oxidative Coupling of Sinapic Acid*; University of Manitoba, **1999**, and references cited therein.

27. Charlton, J. L.; Alauddin, M. M. *J. Org. Chem.* **1986**, *51*, 3490-3493.

28. Coltart, D. M.; Charlton, J. L. *Can. J. Chem.* **1996**, *74*, 88-94.

29. Charlton, J. L.; Bogucki, D.; Guo, P. *Can. J. Chem.* **1995**, *73*, 1463-1467.

30. Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446-5452.

31. Ward, R. S. *Tetrahedron* **1990**, *46*, 5029-5041.

32. Tomioka, K.; Mizuguchi, H.; Koga, K. *Tetrahedron Lett.* **1978**, *19*, 4687-4690.

33. Kosugi, H.;Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, *25*, 2627-2630.

34. Brown, E.; Daugan, A. *Tetrahedron Lett.* **1985**, *26*, 3997-3998.

35. Stobbe, H. *Annalen* **1911**, *380*, 1-129.

36. Johnson, W. S.; Daub, G. H. In *Organic Reactions*; John Wiley & Sons, Inc.: New York, *6*, 1-73.

37. a) Heller, H. G.; Swinney, B. *J. Chem. Soc. (C)* **1967**, 2452-2456; b) Heller, H. G.; Strydom, P. J. *J. Chem. Soc. Chem. Comm.* **1976**, 50-51.

38. a) Hart, R. J.; Heller, H. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1321-1324; b) Hart, R. J.;Heller, H. G.; Salisbury, K. *Chem. Comm.* **1968**, 1627-1628.

39. Heller, H. G.; Megit, R. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 923-927.

40. Heller, H. G.; Szewczyk, M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1483-1487.

41. Heller, H. G.; Szewczyk, M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1487-1492.

42. Hart, R. J.; Heller, H. G.; Megit, R. M.; Szewczyk, M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2227-2232.

43. Darcy, P. J.; Hart, R. J.; Heller, H. G. *J. Chem. Soc. (C)* **1978**, 571-576.

44. Crescente, O.; Heller, H. G.; Oliver, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 150-153.

45. Heller, H. G.; Oliver, S.; Shawe, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 154-157.

46. Momose, T.; Kanai, K. -I.; Nakamur, T.; Kuni, Y. *Chem. Pharm. Bull.*, **1977**, *25*, 2755-2760.

47. Cohen, M. D.; Kaufman, H. W.; Sinnreich, D.; Schmidt, G. M. J. *J. Chem Soc. (B)* **1970**, 1035-1039.

48. Ayres, D. C.; Carpenter, B. G.; Denney, R. C. *J. Chem. Soc.* **1965**, 3578-3582.

49. Davidse, P. A.; Dillen, J. L. M.; Heyns, A. M.; Modro, T. A.; van Rooyen, P. H. *Can. J. Chem.* **1990**, *68*, 741-746.

50. Boeyens, J. C. A.; Denner, L.; Perold, G. W. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1749-1758.

51. Boeyens, J. C. A.; Denner, L.; Perold, G. W. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1999-2005.

52. Anjaneyulu, A. S. R.; Raghu, P.; Ramakrishna Rao, K. V. *Indian J. Chem.* **1979**, *18B*, 535-537.

53. Charlton, J. L.; Hiebert, S. In *Synthesis of a Precursor to Cyclolignan Formation and Hindered Rotation Study of an (E,E)-2,3-Dipiperonylidenesuccinimide*; University of Manitoba, **1997**, 1-22.

54. Yvon, B. L. In *The Synthesis of Lignans and Lignans Analogs*; University of Manitoba, **2000**, and references cited therein.

55. Hughes, G. K.; Ritchie, E. *Aust. J. Chem.* **1954**, *7*, 104-113.

56. Carnmalm, B. *Acta. Chem. Scand.* **1954**, *8*, 1827-1829.

57. Crossley, N. S.; Djerassi, C. *J. Chem. Soc.* **1962**, 1459-1462.

58. Birch, A. J.; Milligan, B.; Smith, E.; Speake, R. N. *J. Chem. Soc.* **1958**, 4471-4476.

59. Schrecker, A. W.; Hartwell, J. L. *J. Am. Chem. Soc.* **1955**, *77*, 432-437.

60. Kasatkin, A. N.; Checksfield, G.; Whitby, R. J. *J. Org. Chem.* **2000**, *65*, 3236-3238.

61. Muller, A.; Vajda, M. *J. Org. Chem.* **1952**, *17*, 800-806.

62. Biftu, T.; Hazra, B. G.; Stevenson, R.; Williams, J. R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1147-1150.

63. Kuo, Y. -H.; Wu, R. -E. *J. Chin. Chem. Soc.* **1985**, *32*, 177-178.

64. Kuo, Y. -H.; Lin, S. -T.; Wu, R. -E. *Chem. Pharm. Bull.* **1989**, *37*, 2310-2312.

65. Kuo, Y. -H.; Lin, S. -T. *Chem. Pharm. Bull.* **1993**, *41*, 1507-1512.

66. McAlpine, J. B.; Riggs, N. V. *Aust. J. Chem.* **1975**, *28*, 831-847.

67. Fonseca, S. F.; Nielsen, L. T.; Ruveda, E. A. *Phytochemistry* **1979**, *18*, 1703-1708.

68. Cow, C.; Leung, C.; Charlton, J. L. *Can. J Chem.* **2000**, *78*, 553-561.

69. Hayashi, T.; Nizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101-9102.

70. Chee, G.-L. In *The Study of the Asymmetric Synthesis of Lignans*; University of Manitoba, 1997, and references cited therein.

71. Yvon, B. L.; Datta, P. K.; Le, T. N.; Charlton, J. L. *Synthesis*, in press.

72. Andersson, J. *Acta. Chem. Scand. B* **1997**, 31-36.

73. The *E,E*-bis-2,4-dimethoxybenzylidene succinate was provided by Probal K. Datta.

74. Heck, R. H.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 3105-3113.

75. Heck, R. H.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 3114-3118.

76. Heck, R. H.; Winstein, S. *J. Org. Chem.* **1972**, *37*, 825-836.

77. Jackman, L. M.; Haddon, V. R. *J. Am. Chem. Soc.* **1974**, *96*, 5130-5138.

78. Gates, M.; Frank, D. L.; von Felten, W. C. *J. Am. Chem. Soc.* **1974**, *96*, 5138-5143.

79. Smith, M. B. In *Organic Synthesis*; McGraw-Hill, Inc.: New York: 1994, 382-384, 245-249.

80. Volkmann, R. A.; Andrews, G. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 4777-4779.

81. Winstein, S.; Heck, R.; Lapporte, S.; Baird, R. *Experientia* **1956**, *12*, 138-141.

82. Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 756-757.

83. Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1962**, *84*, 788-792.

84. Mestdagh, H.; Puechbery, A. *J. Chem. Ed.* **1991**, *68*, 515-516.

85. Leibovitch, M.; Olovsson, G.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1998**, *120*, 12755-12769.

86. Janz, K. M.; Scheffer, J. R. *Tetrahedron Lett.* **1999**, *40*, 8725-8728.

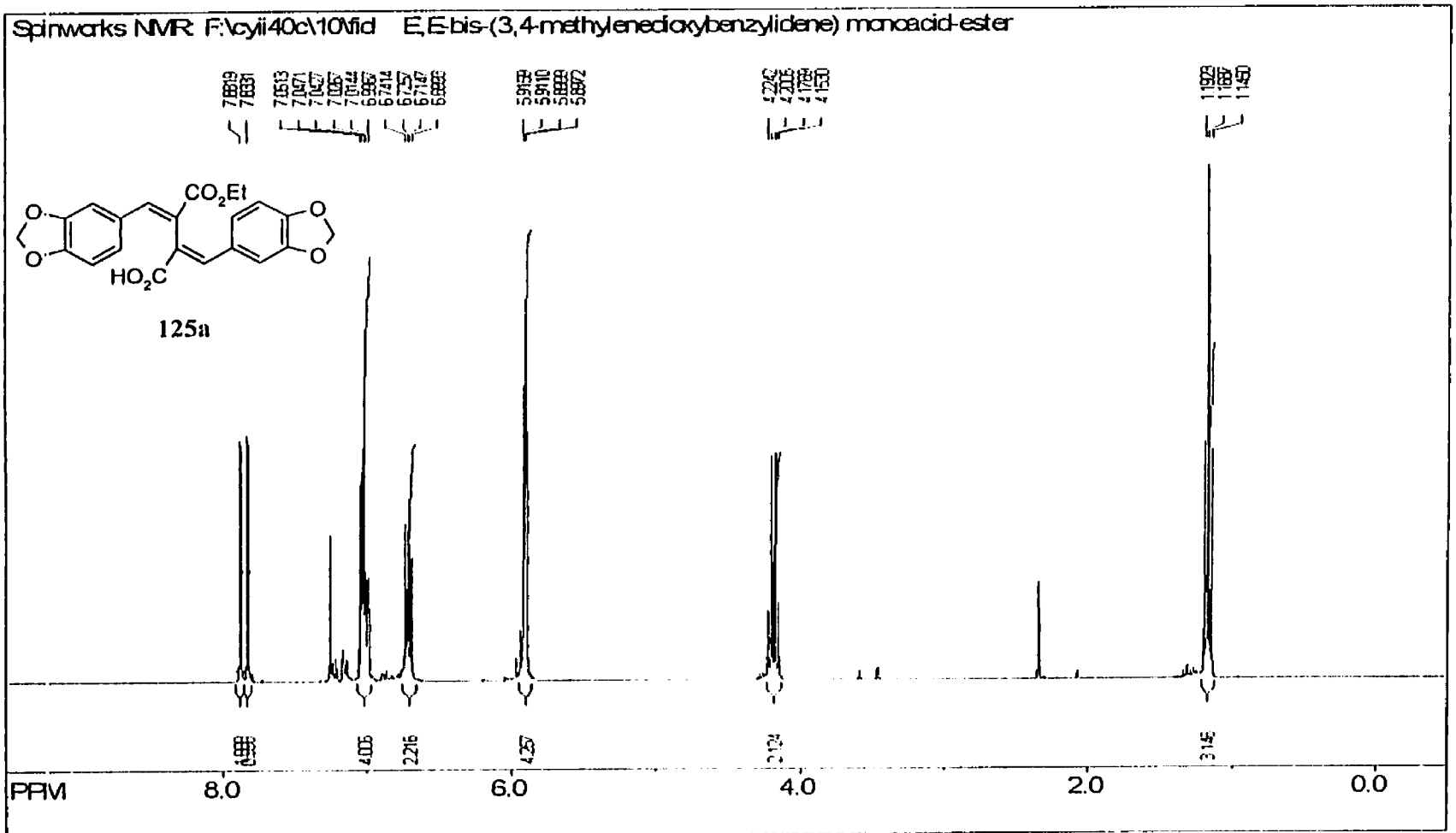
87. Cheung, E.; Kang, T.; Raymond, J. R.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1999**, *40*, 8729-8732.

88. Cheung, E.; Rademacher, K.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1999**, *40*, 8733-8736.

89. Cheung, E.; Netherton, M. R.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1999**, *40*, 8737-8740.

Appendix:

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



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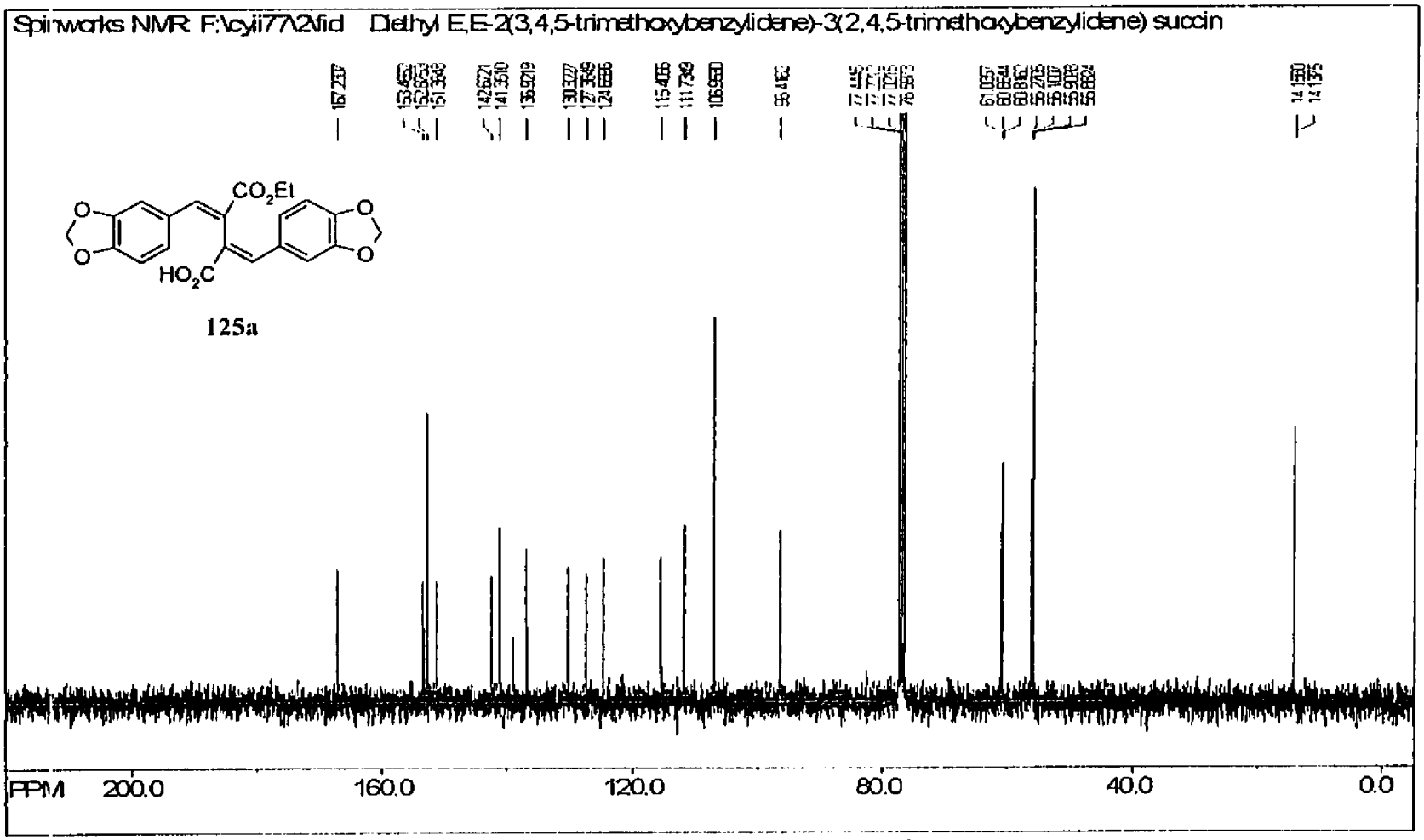
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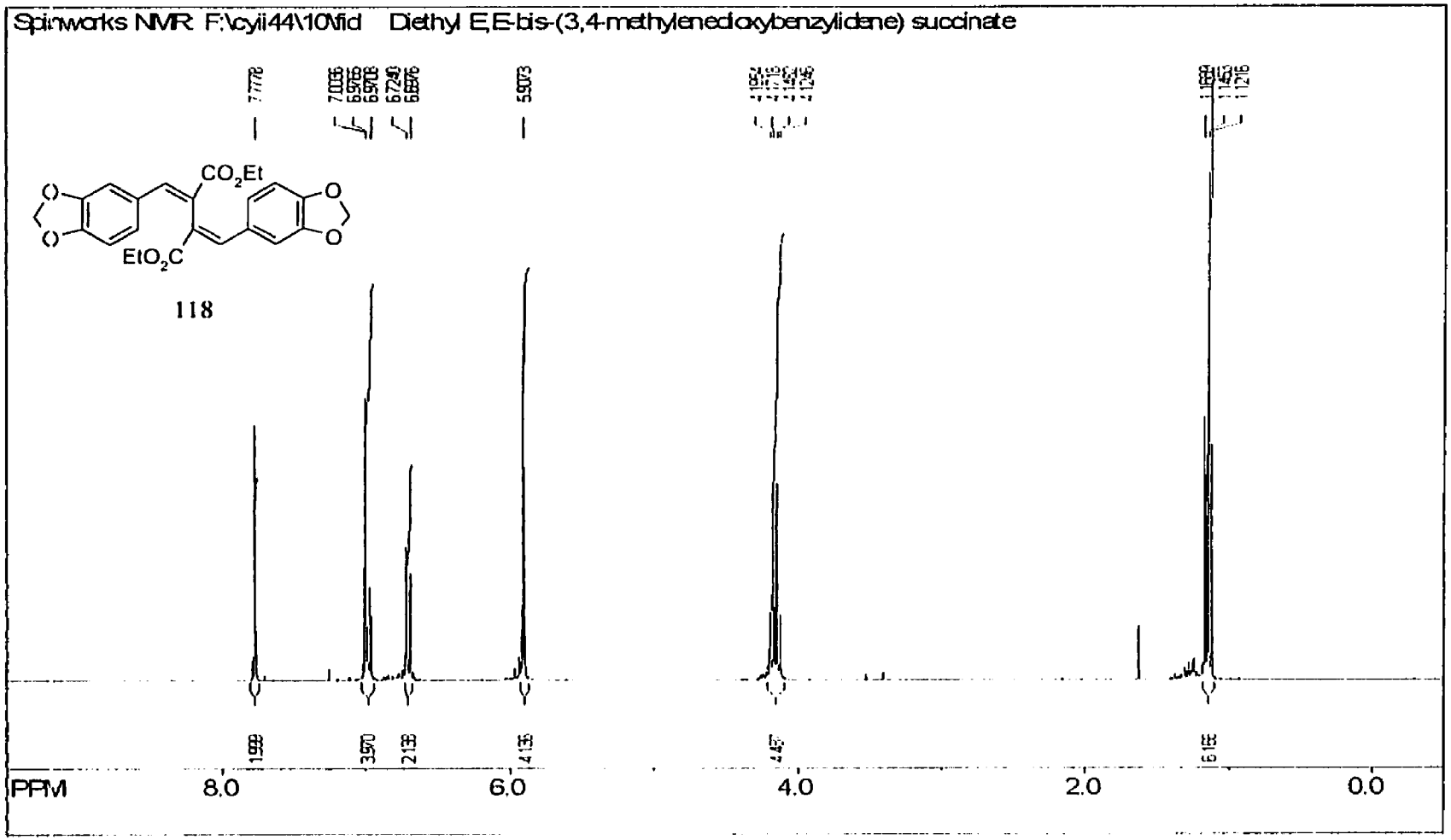
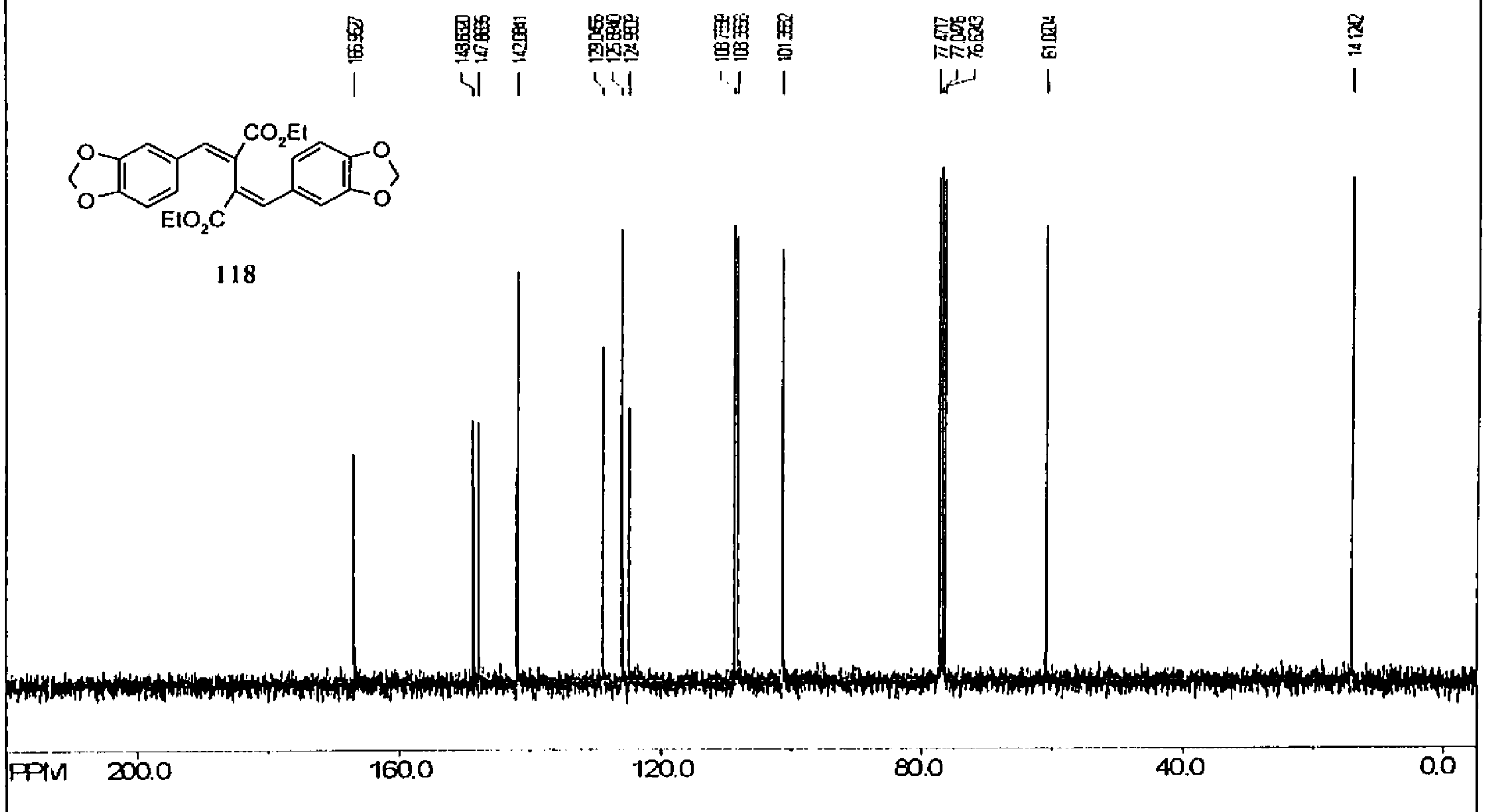
O
O
O
O
125a
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file: F:\cyji77\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 256
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 real points
LB: 1.00 GB: 0.000



file F:\cyil44\10\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

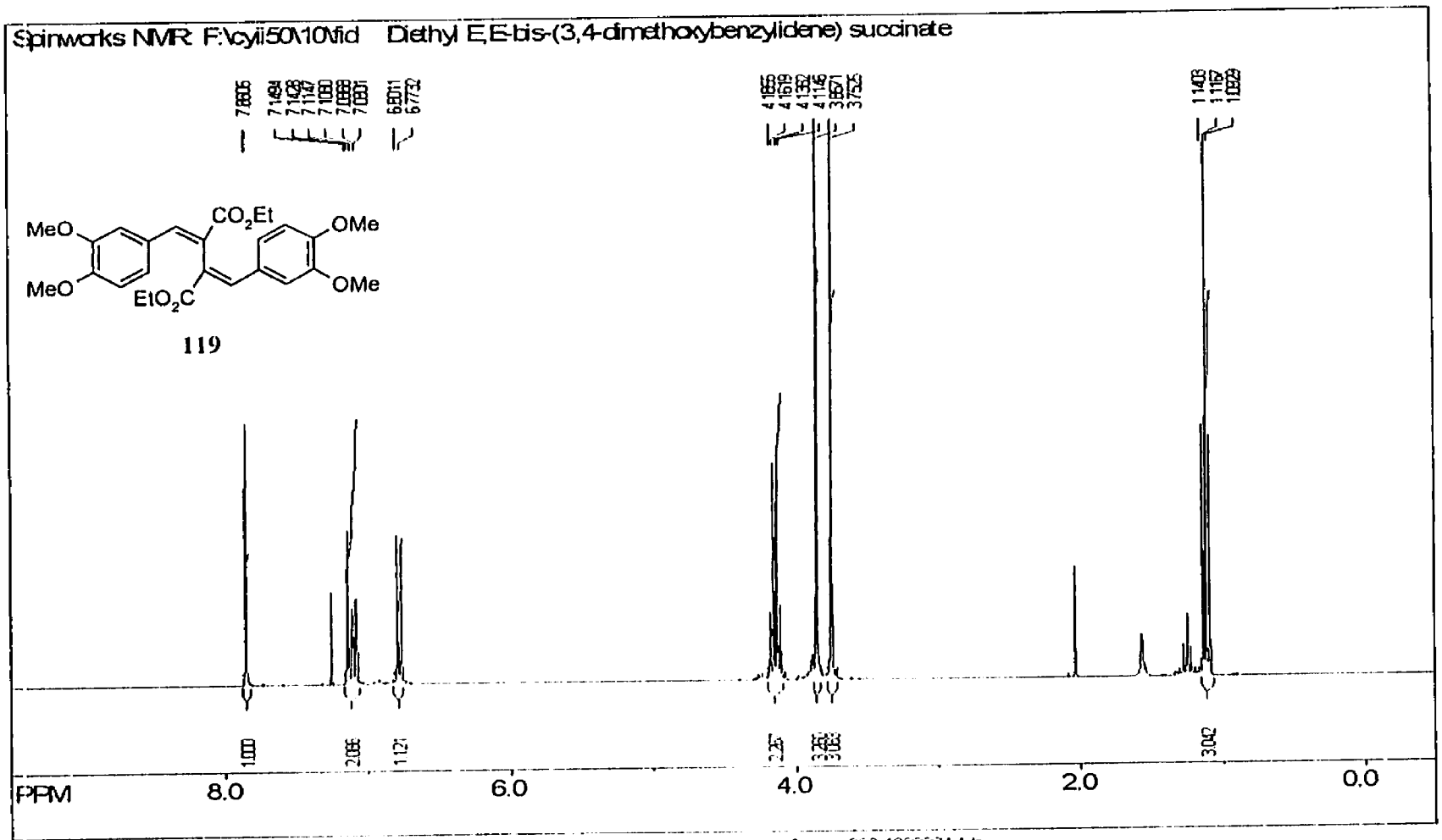
freq. of 0 ppm: 300.130005 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000

Spinworks NMR F:\cyii44\11\fid Diethyl E,E-bis-(3,4-methylenedioxybenzylidene) succinate



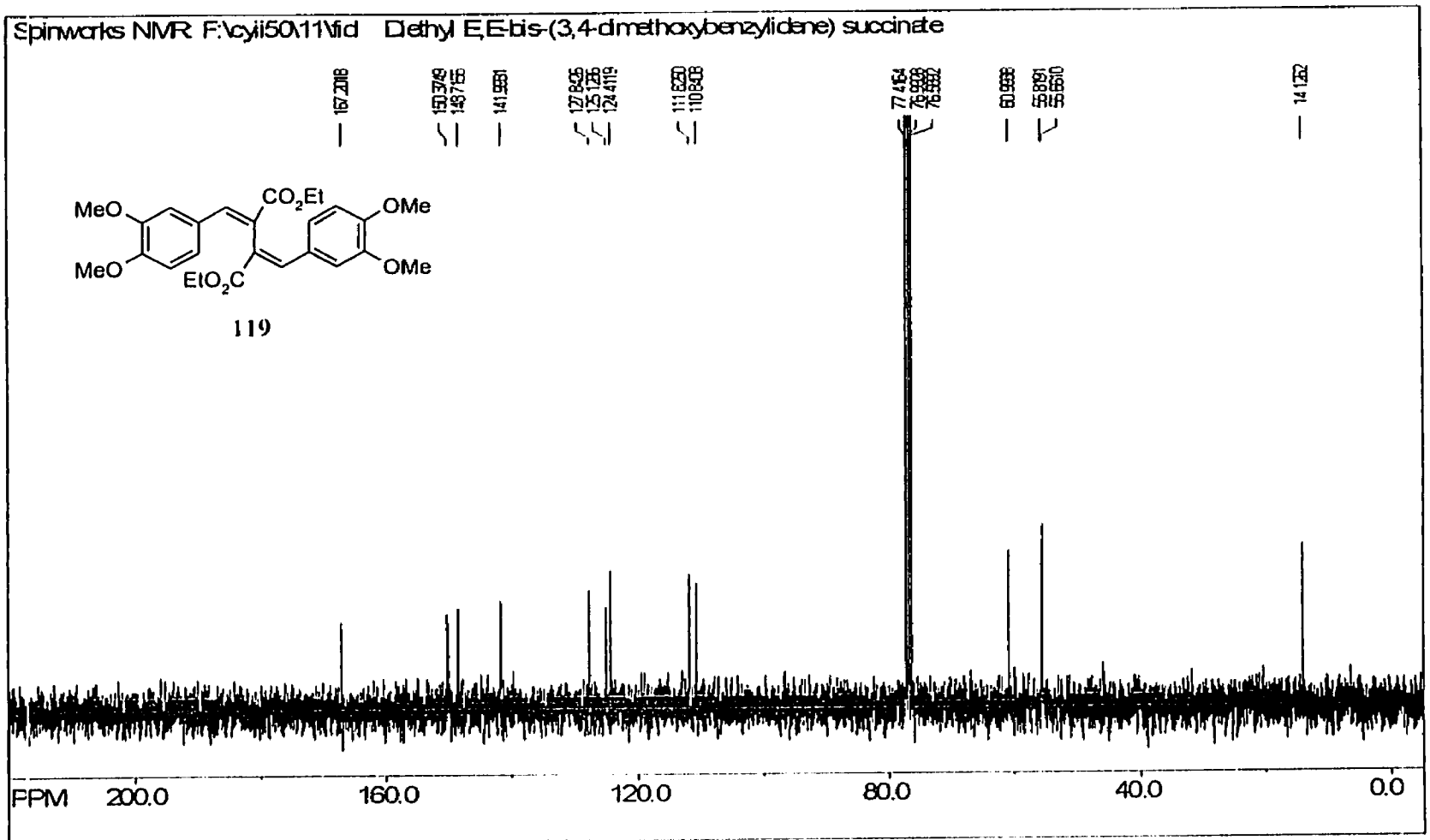
file F:\cyii44\11\fid expt <zgpg30>
transmitter freq 75.478020 MHz
time domain size 65536 points
width 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans 128

freq of 0 ppm 75.467749 MHz
processed size 32768 real points
LB 1.000 GB 0.0000



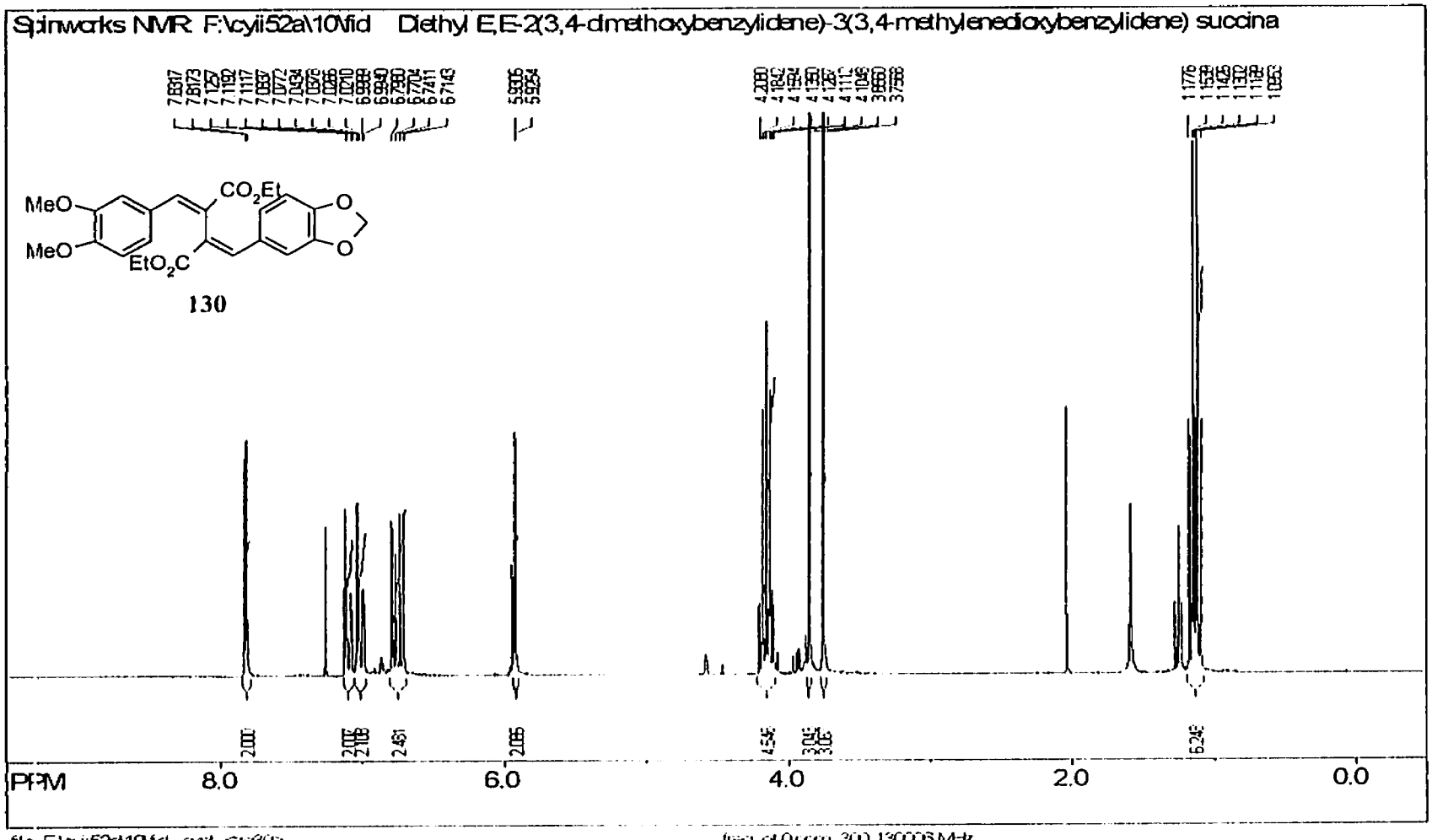
file: F:\cyil50\10\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

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



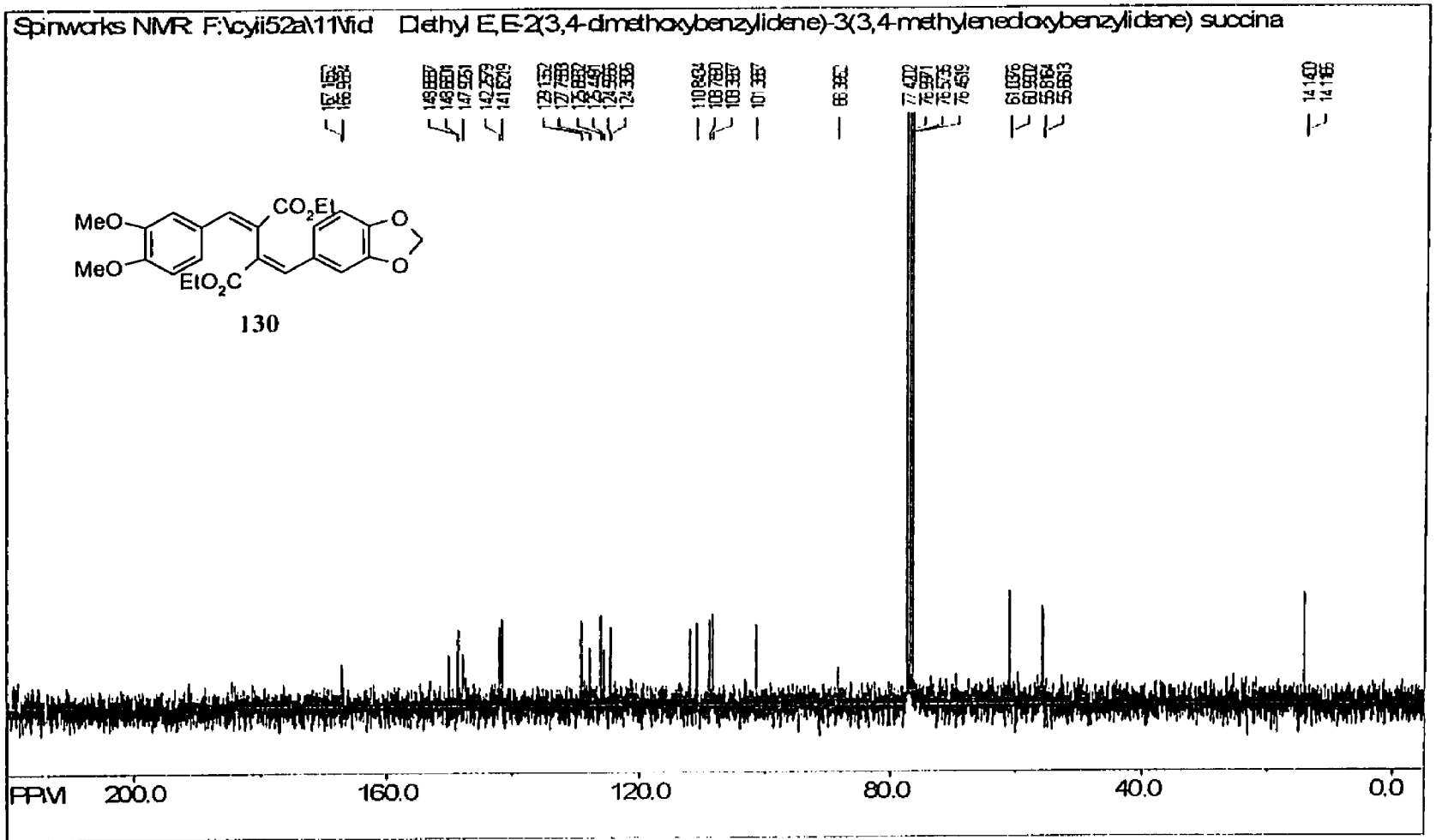
file F:\cyil50\11\fid expt <zgpg30>
transmitter freq 75.478020 MHz
time domain size 65536 points
width 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans 128

freq. of 0 ppm 75.467749 MHz
processed size 32768 real points
LB 1.000 GB 0.0000



file F:\cyil52a\10\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

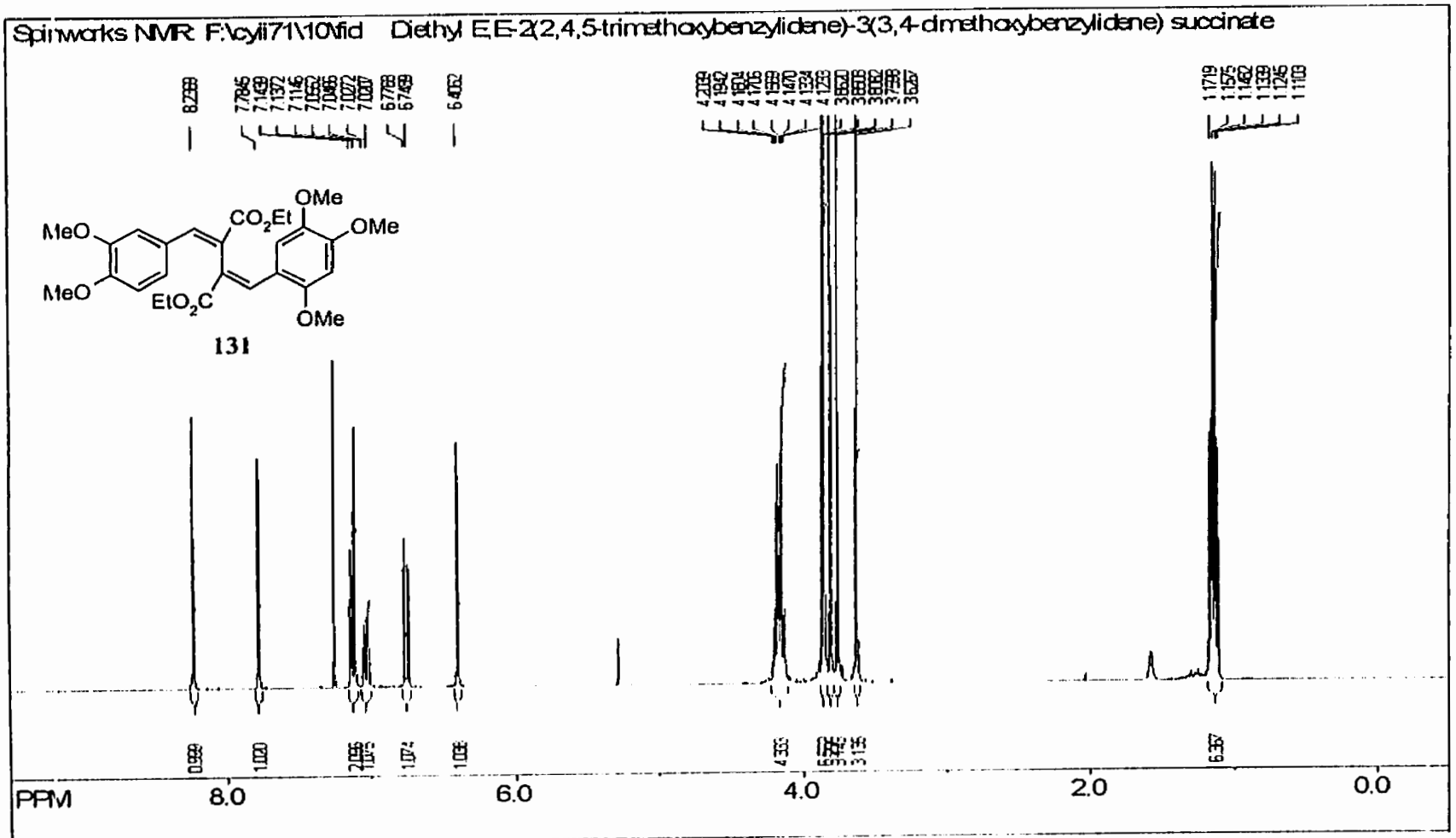
freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



130

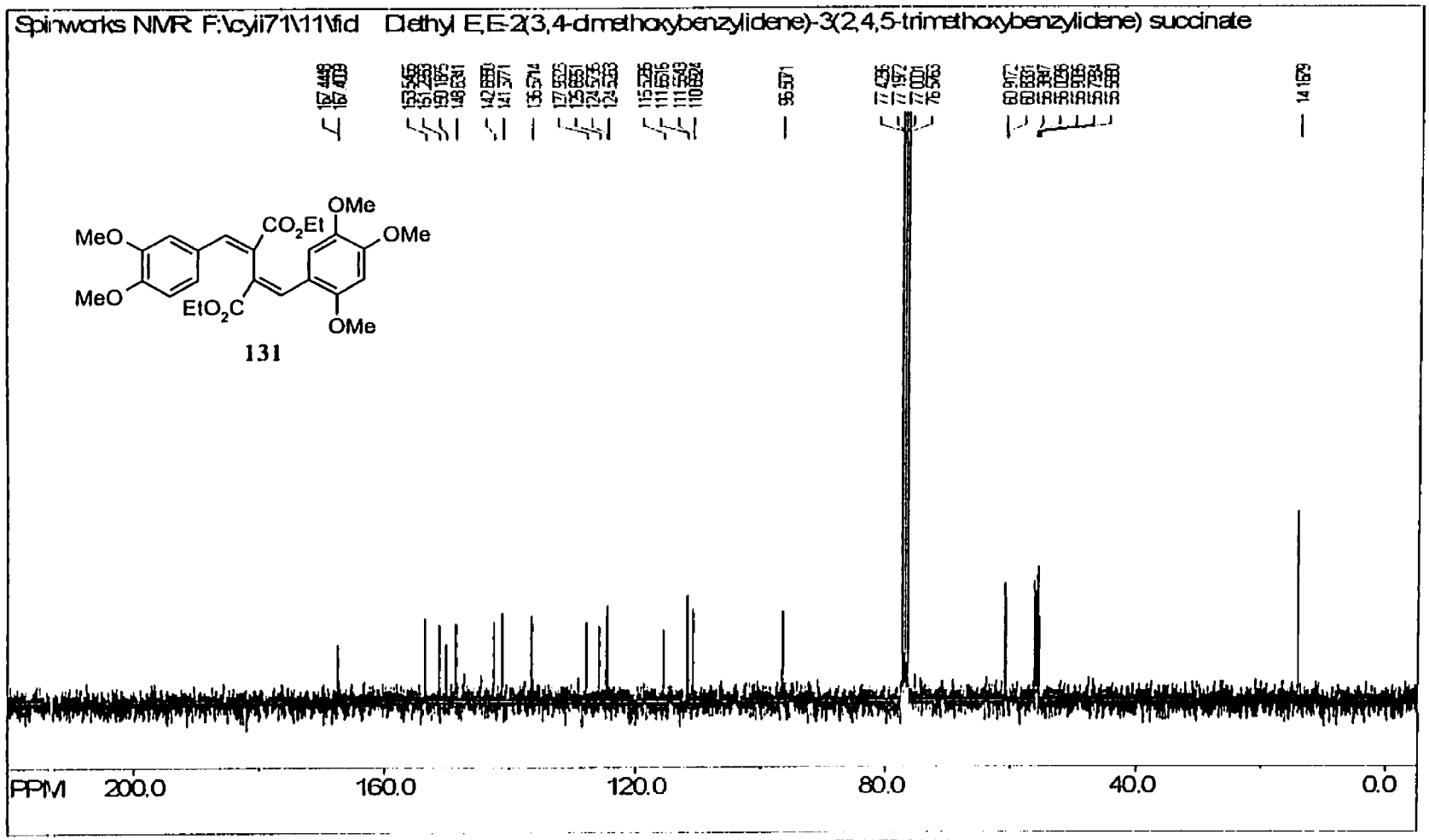
file: F:\cyli52a\11\fid exp: <zgpg30>
transmitter freq: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 192

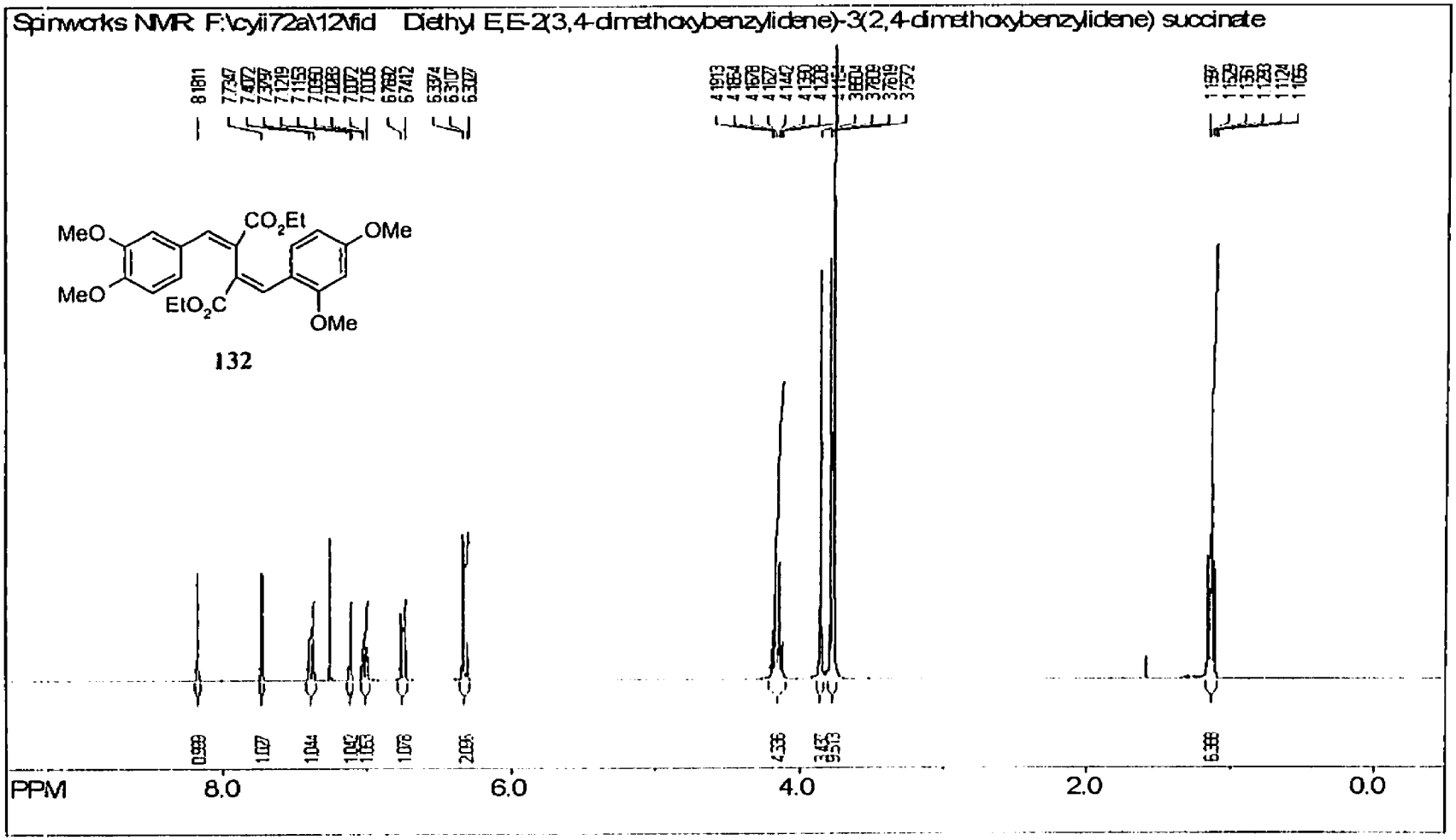
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 real points
D3: 1.00 GB: 0.0000

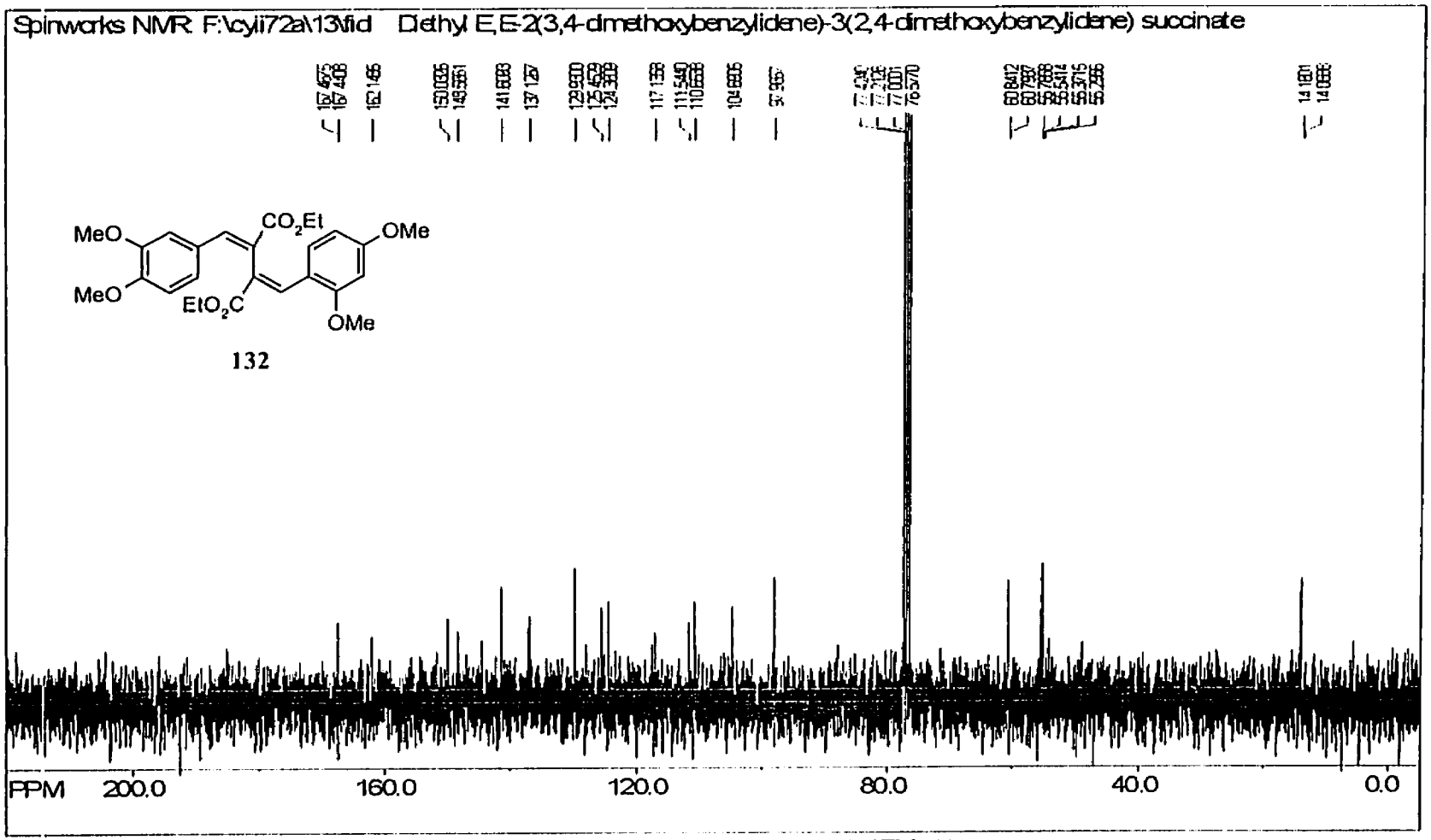


file: F:\cyli71\10\fid exp1 <zg30>
transmitter freq: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094180 Hz/pt
number of scans: 16

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


Spinworks NMR F:\cyil71\11\fid Diethyl E,E-2(3,4-dimethoxybenzylidene)-3(2,4,5-trimethoxybenzylidene) succinate
MeO
MeO
CO2Et
EtO2C
OMe
OMe
OMe
131
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file F:\cyil71\11\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 256
freq of 0 ppm 75.467749 MHz
processed size 32768 real points
LB 1.000 GB 0.000

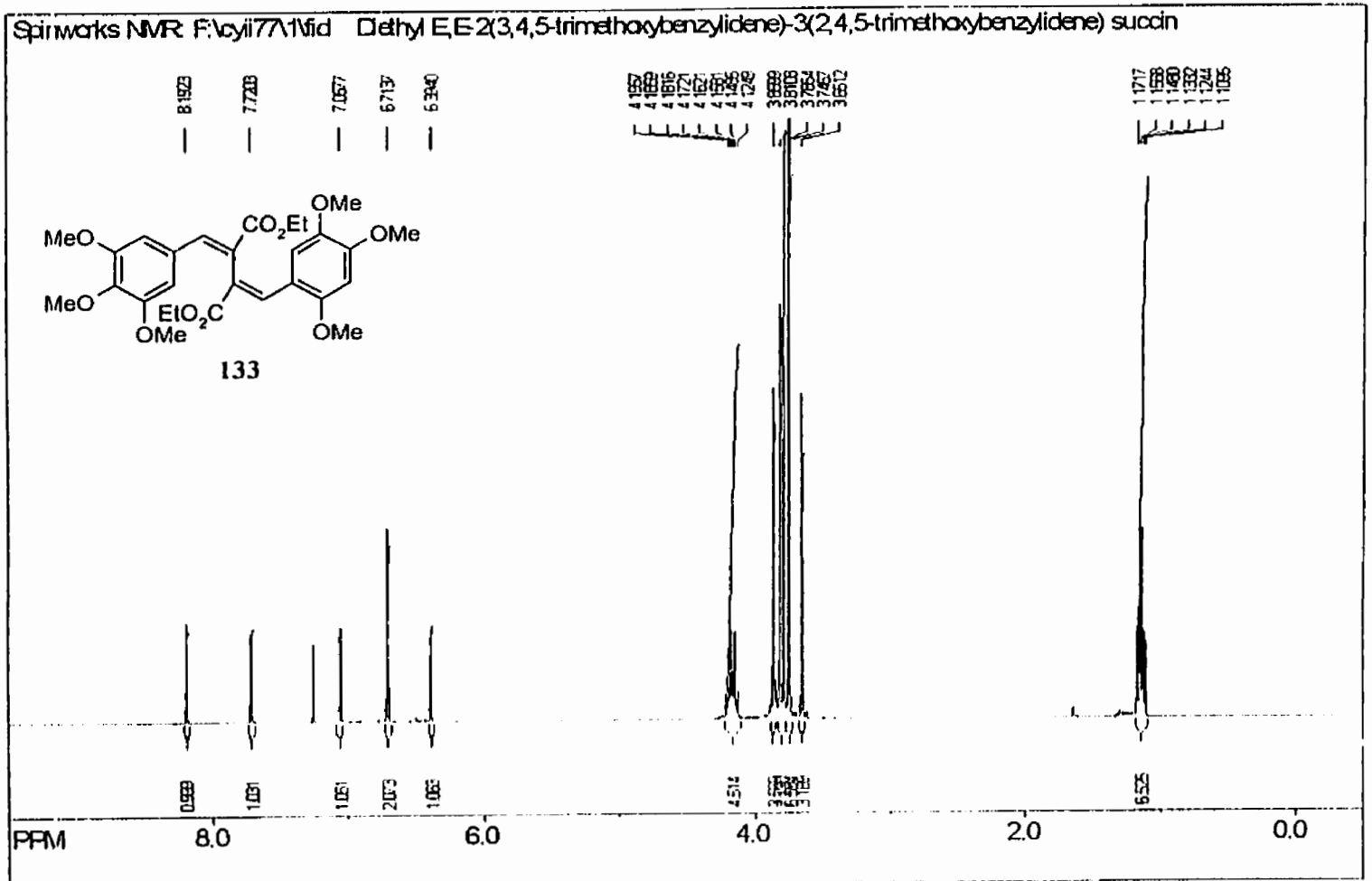

Spinworks NMR F:\cyil72a\12fid Diethyl E,E-2(3,4-dimethoxybenzylidene)-3(2,4-dimethoxybenzylidene) succinate
MeO
MeO
CO2Et
EtO2C
OMe
OMe
132
PPM
8.0
6.0
4.0
2.0
0.0
file = \cyil72a\12fid expt <zg30>
transmitter freq 300.131853 MHz
time domain size 65536 points
width 6172.80 Hz = 20.567092 ppm = 0.094169 Hz/pt
number of scans 16
freq of 0 ppm 300.130005 MHz
processed size 32768 real points
LB 0.300 GB 0.0000



132

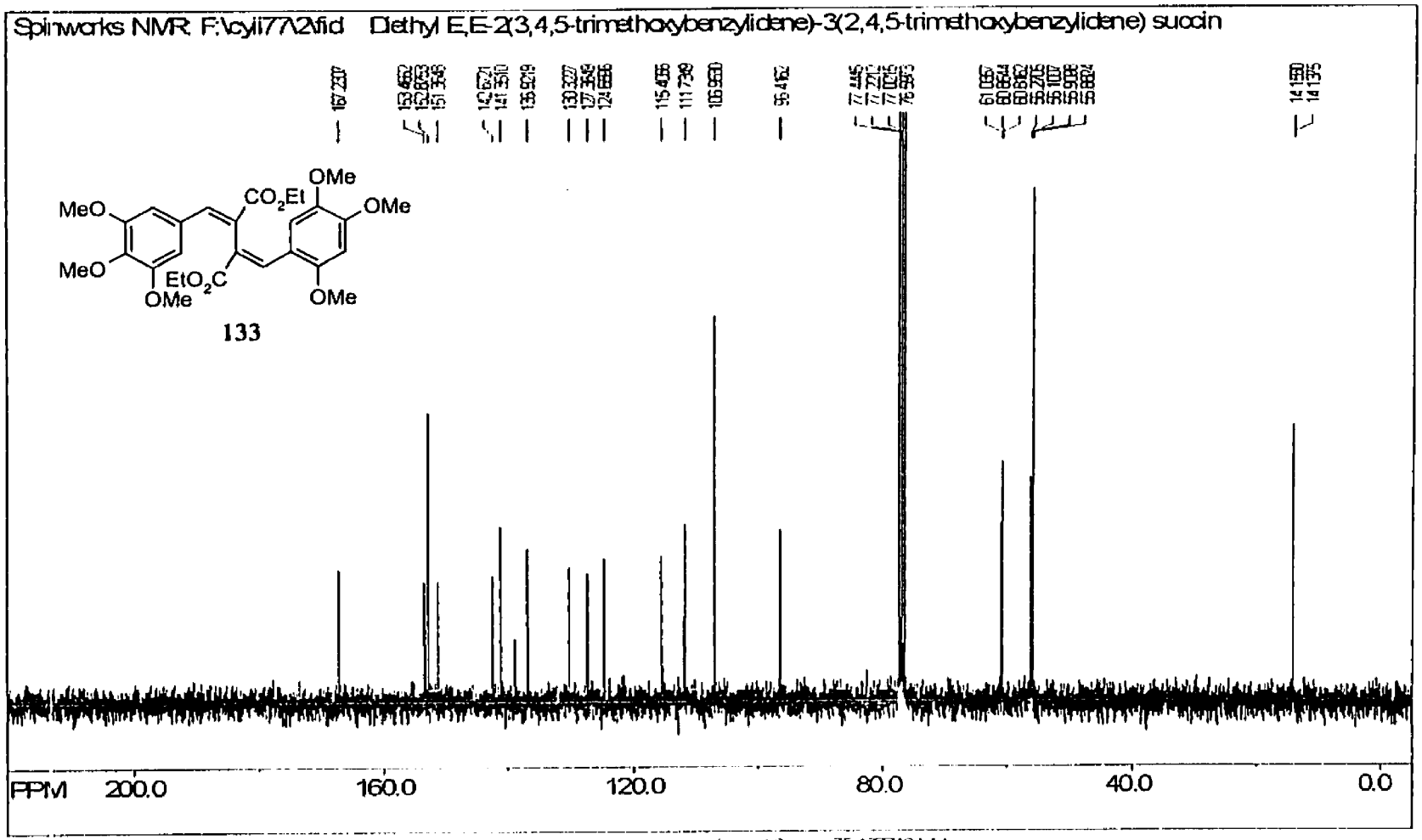
file: F:\cyli72a\13\fid exp1 <zgpg30>
transmitter freq: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 32

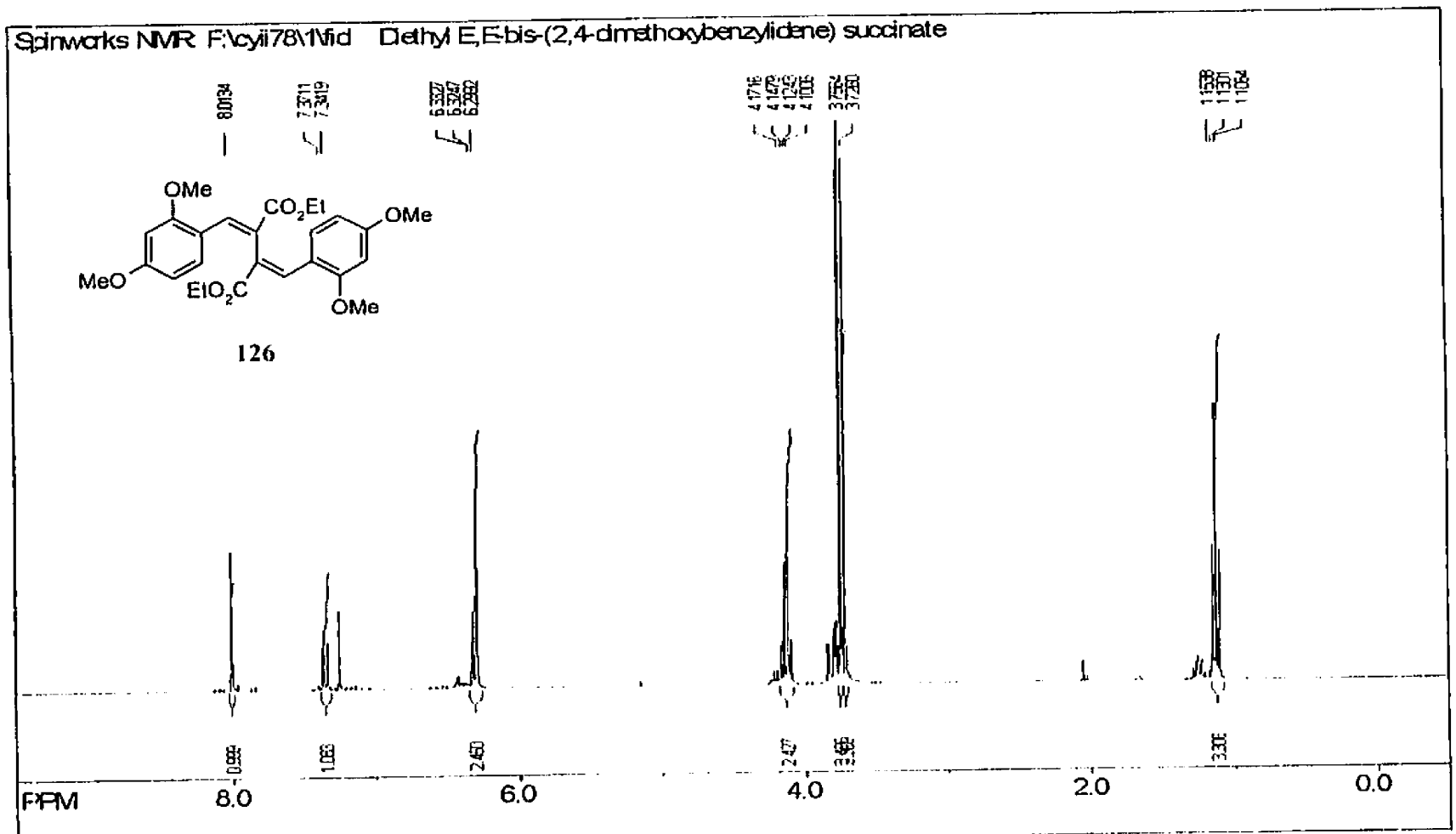
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 real points
LB: 1.00 GB: 0.0000

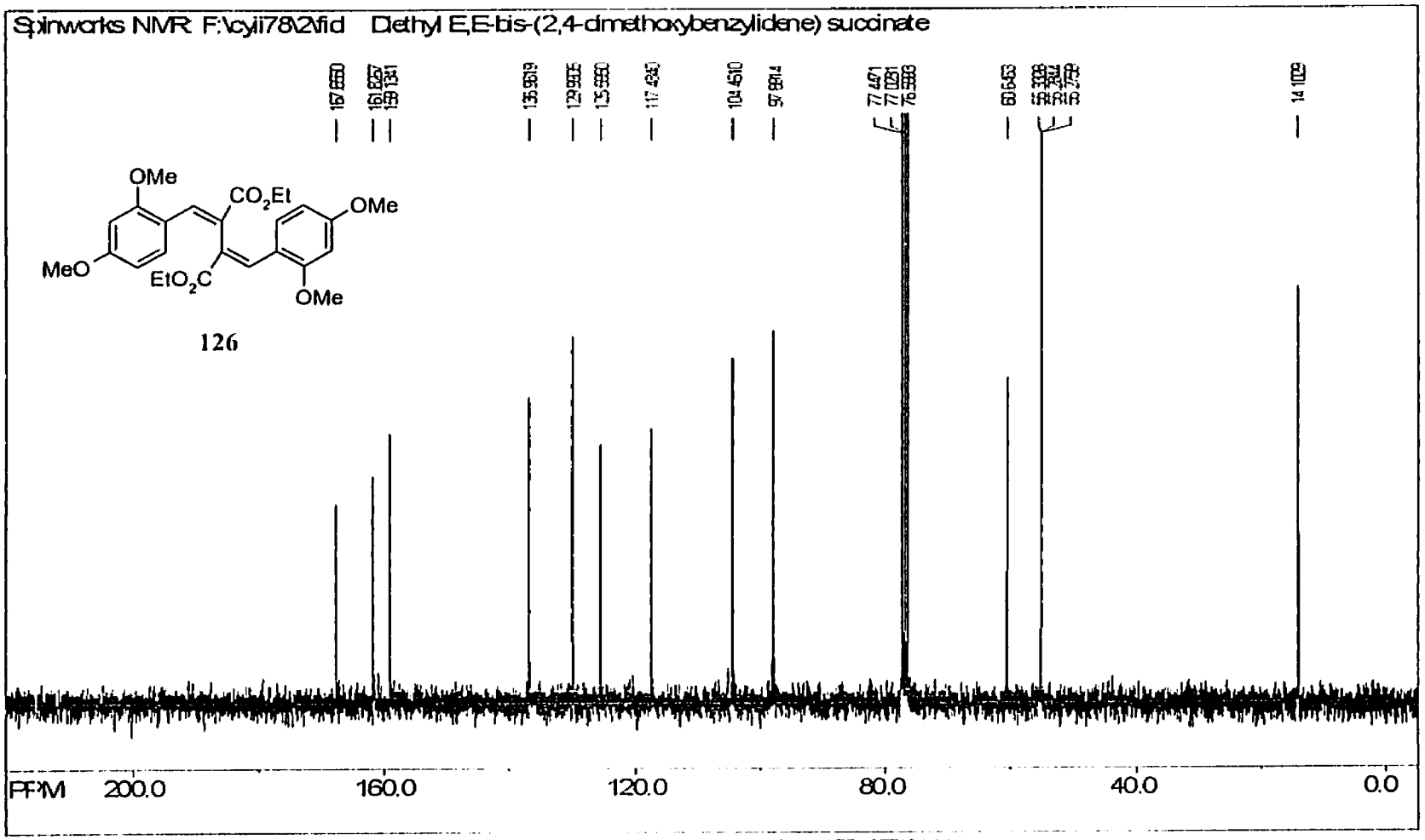


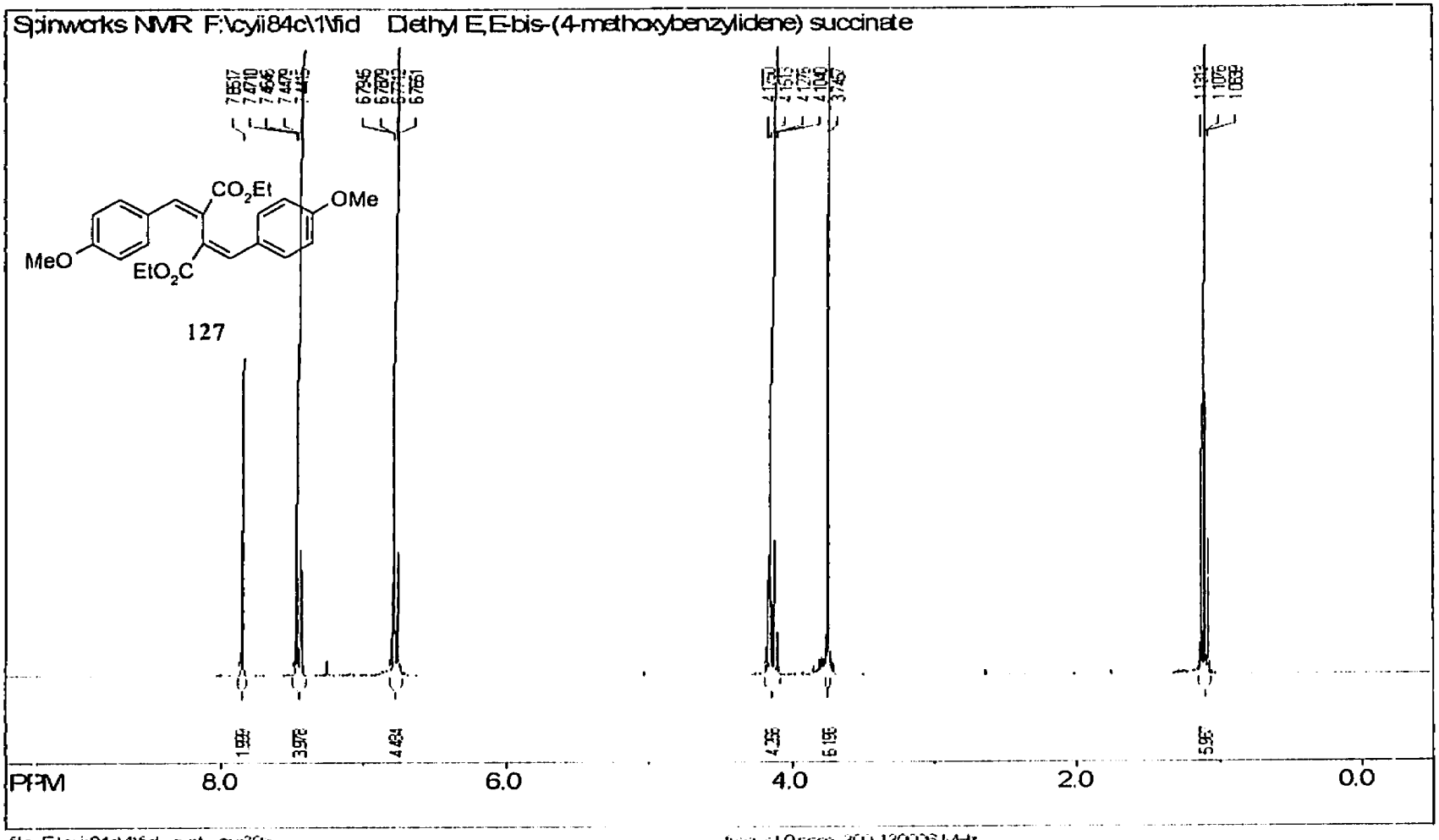
file F:\cyil77\1\fid expt: <zg30>
transmitter freq: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567032 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.30 GB: 0.0000


Spinworks NMR: F:\cyli77\2\fid Diethyl E,E-2(3,4,5-trimethoxybenzylidene)-3(2,4,5-trimethoxybenzylidene) succin
MeO
MeO
CO2Et
OMe
OMe
EtO2C
OMe
OMe
133
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file F:\cyli77\2\fid expt: <zgpg30>
transmitter freq: 75.476020 MHz
time domain size: 65536 points
width: 16830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 256
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000

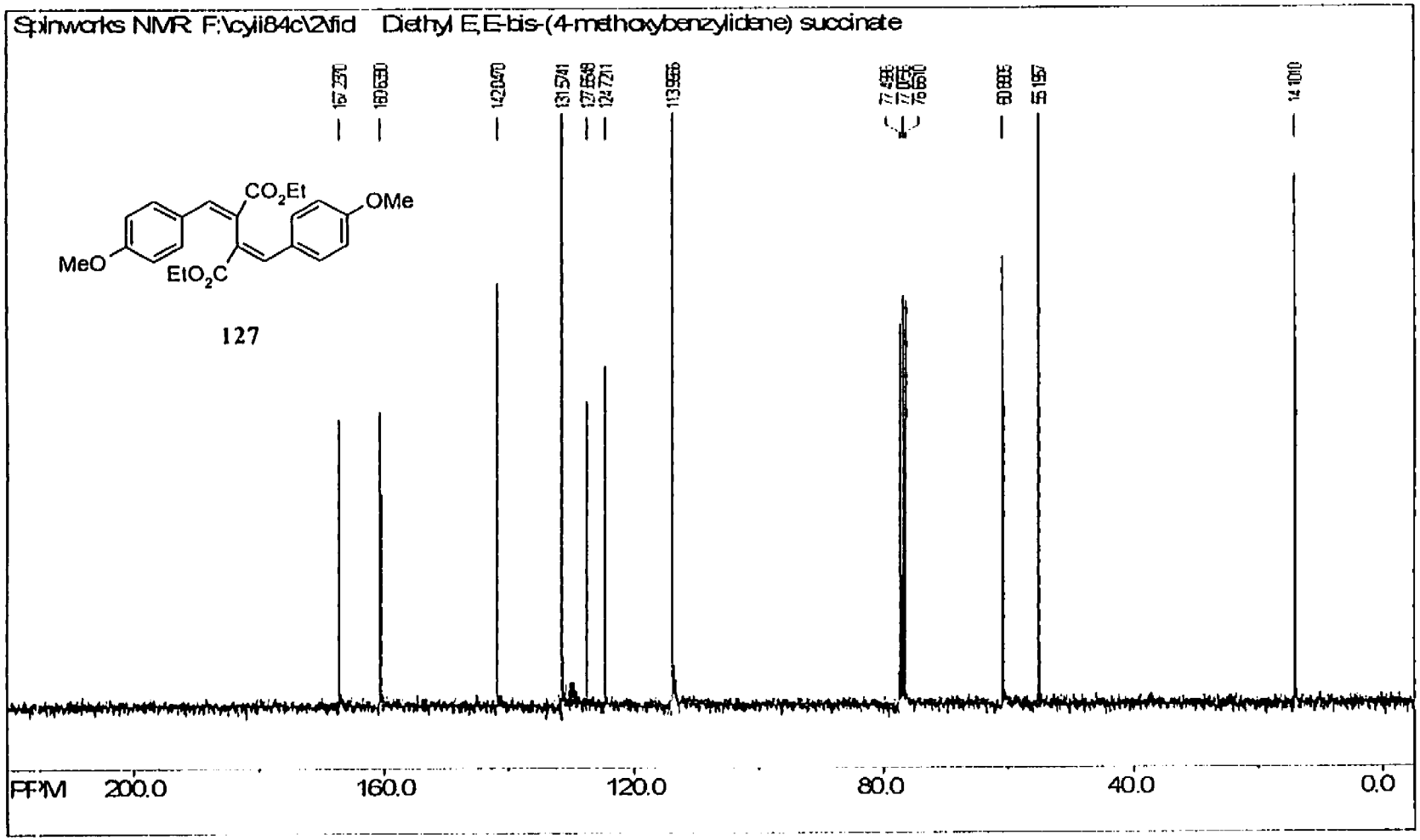

Spinworks NMR F:\cyil78\1\fid Diethyl E,E-bis-(2,4-dimethoxybenzylidene) succinate
OMe
CO2Et
OMe
MeO
EtO2C
OMe
126
PPM
8.0
6.0
4.0
2.0
0.0
file F:\cyil78\1\fid exp1 <zg30>
transmitter freq 300.131853 MHz
time domain size 65536 points
width 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans 16
freq of 0 ppm 300.130006 MHz
processed size 32768 real points
LB 0.300 GB 0.0000

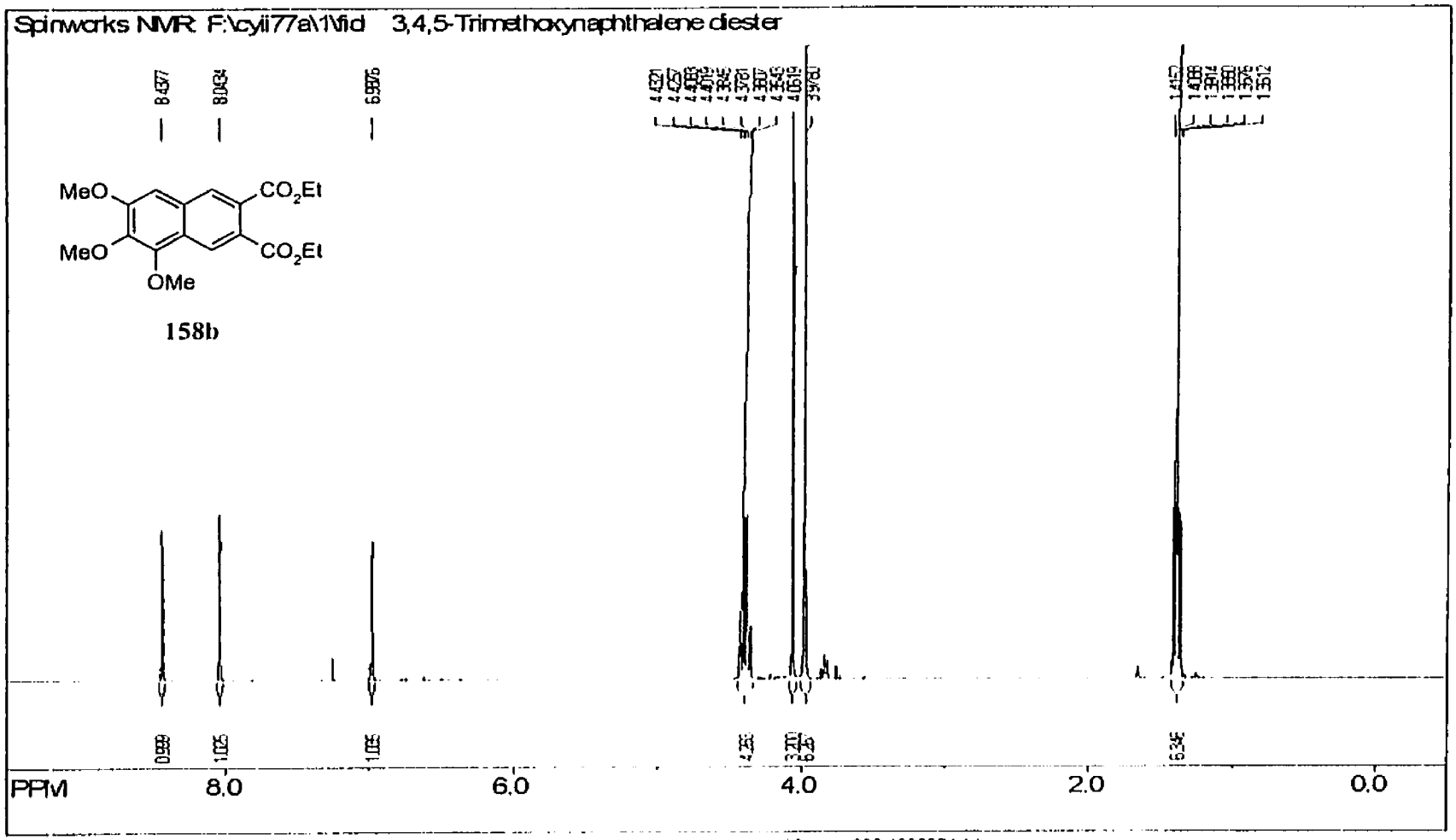

Spinworks NMR: F:\cyli78\2\fid Diethyl E,E-bis-(2,4-dimethoxybenzylidene) succinate
OMe
CO2Et
OMe
MeO
EtO2C
OMe
126
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file: F:\cyli78\2\fid expt: <zgpg30>
transmitter freq: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 256
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 real points
LB: 1.00 GB: 0.0000



file F:\cyil84c\1\fid expt: <zg30>
transmitter freq: 300.1318631 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 32

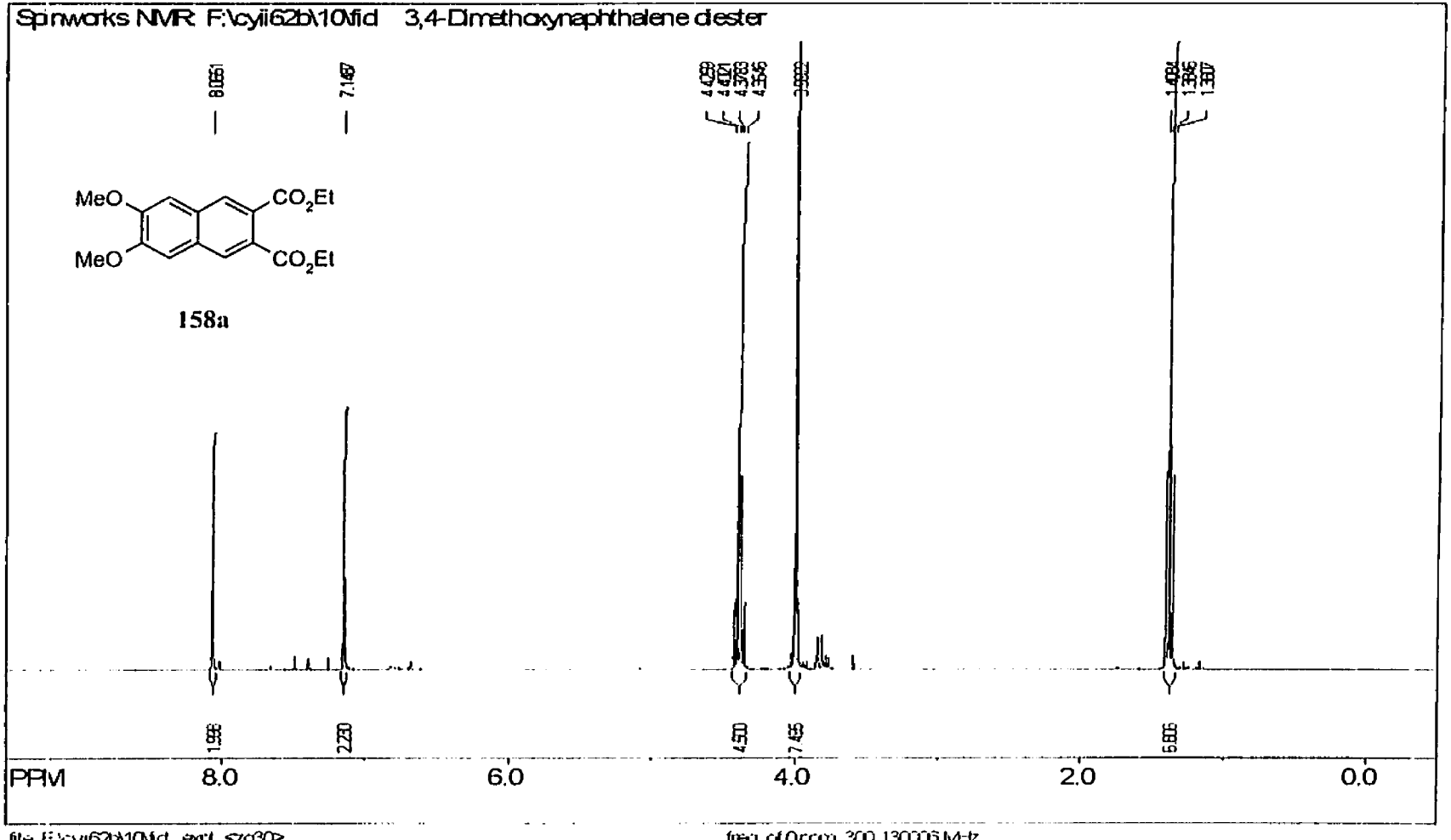
freq. of 0 ppm: 300.1300036 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000


Spinworks NMR F:\cyli84c\2\fid Diethyl E,E-bis-(4-methoxybenzylidene) succinate
167.2510
160.6530
142.0470
131.5741
127.8568
124.7211
113.9556
77.4886
77.0755
76.6610
60.8835
55.1957
14.1010
CO2Et
OMe
MeO
EtO2C
127
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file F:\cyli84c\2\fid exp1 <sp-cp30>
transmitter freq: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 256
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000



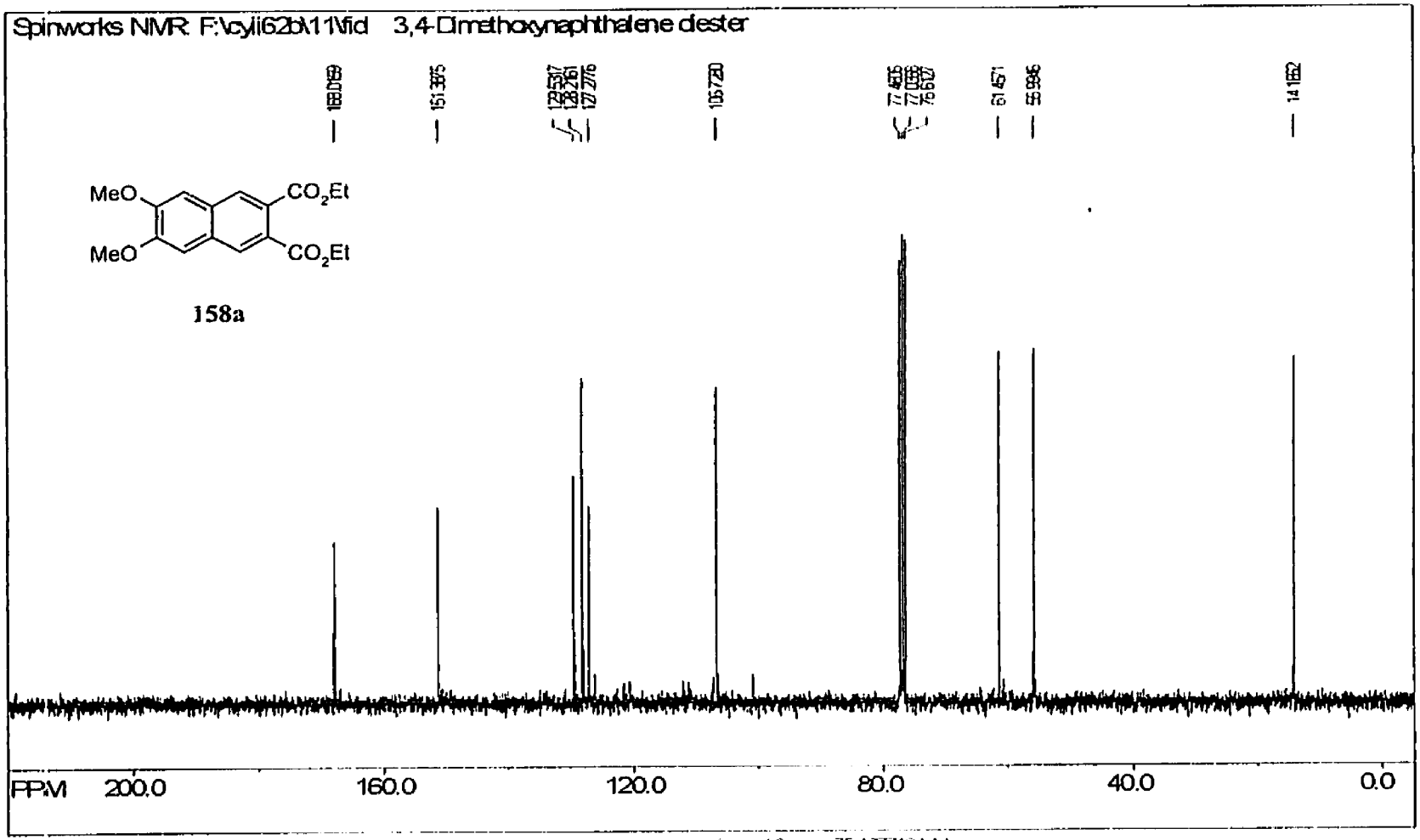
file F:\cyli77a\1\fid expt <zg30>
transmitter freq 300.131853 MHz
time domain size 65536 points
width 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans 16

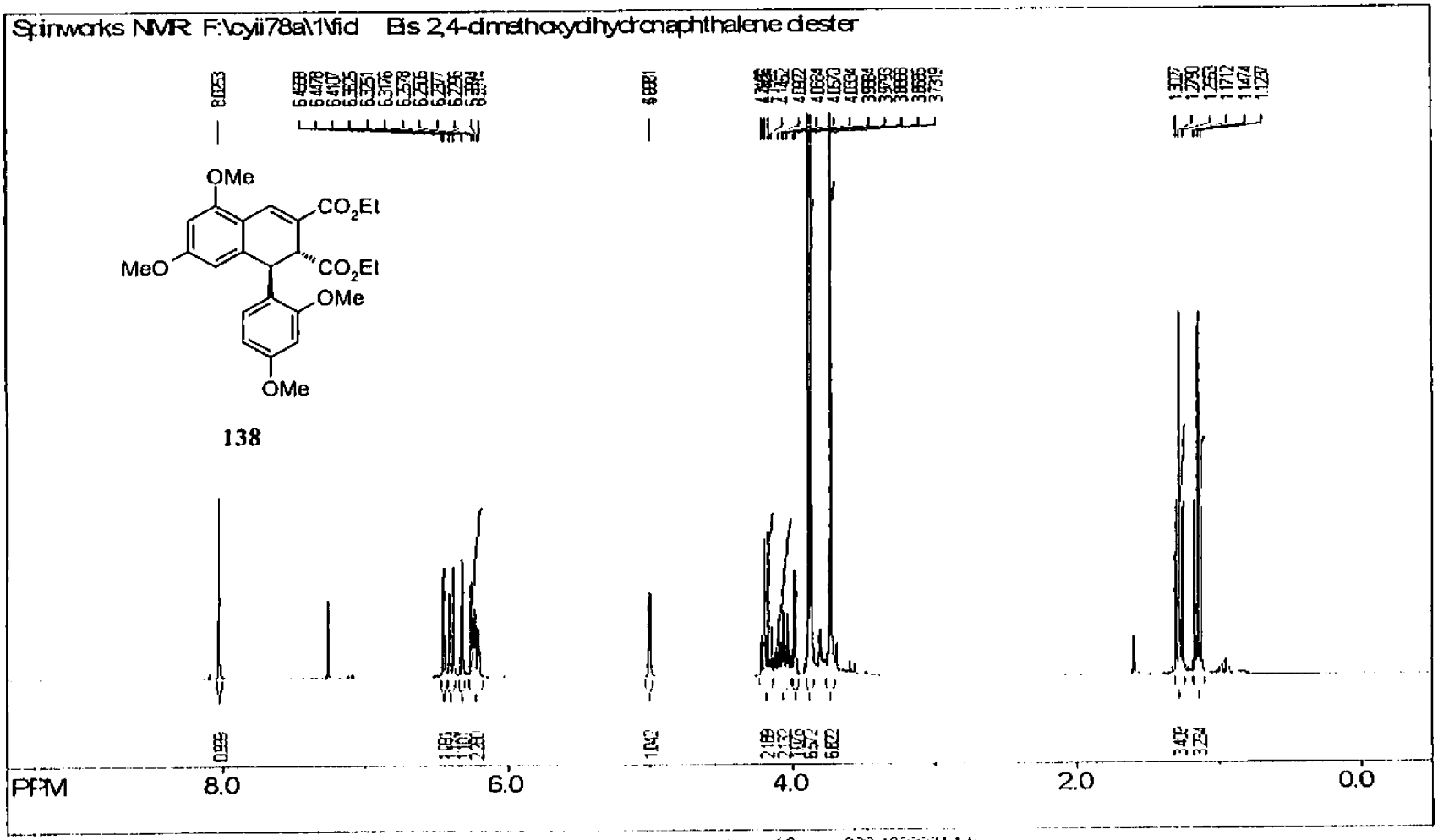
freq. of 0 ppm 300.130006 MHz
processed size 32768 real points
LB 0.300 GB 0.0000

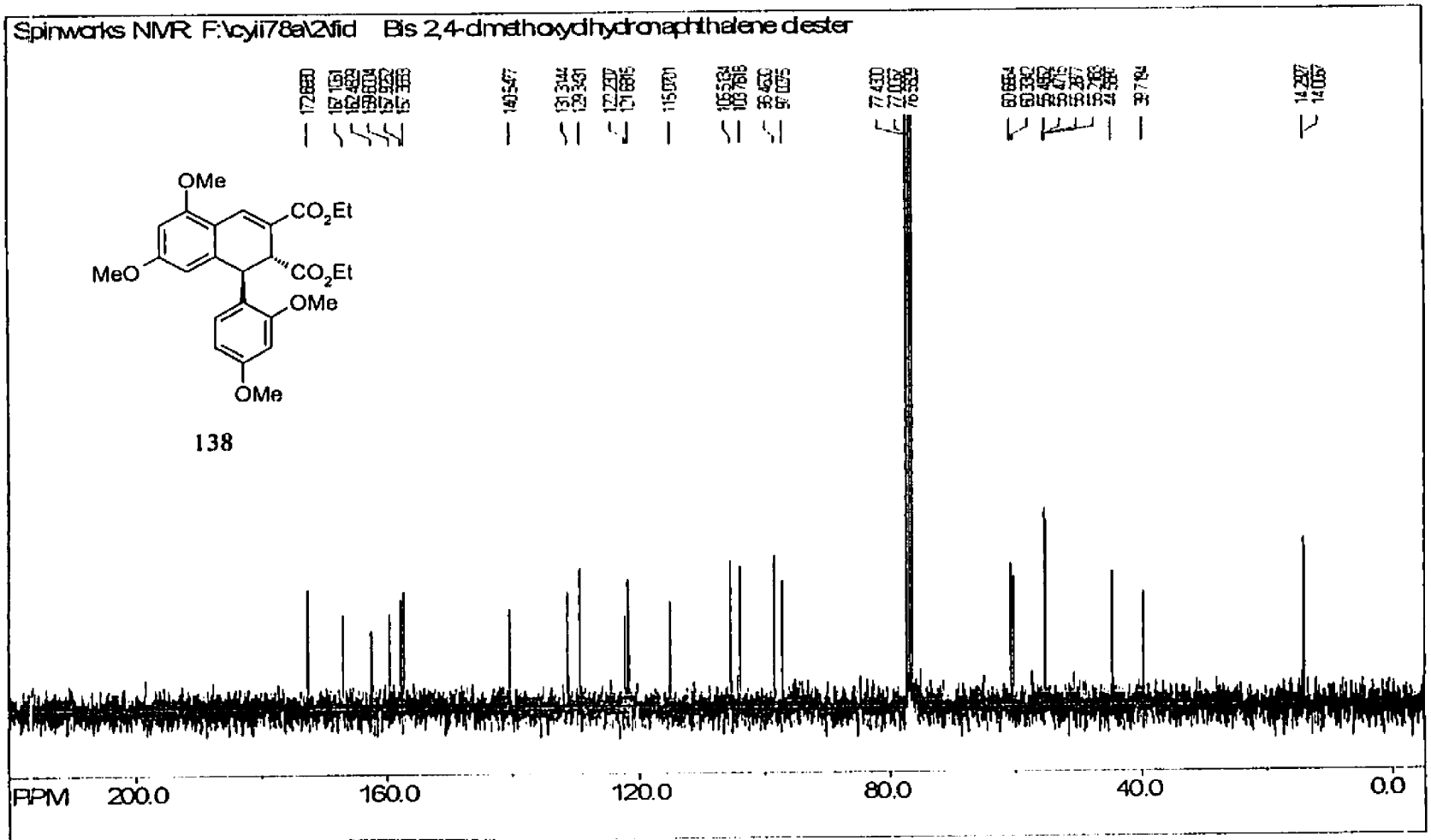


file: F:\cyli62b\10\fid exp: <zg30>
transmitter freq: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

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


Spinworks NMR: F:\cyli62b\11\fid 3,4-Dimethoxynaphthalene diester
MeO
CO2Et
MeO
CO2Et
158a
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file F:\cyli62b\11\fid expt <zgpg30>
transmitter freq. 75476020 MHz
time domain size 65536 points
width 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans 192
freq. of 0 ppm 75467749 MHz
processed size 32768 real points
LB 1.000 GB 0.000

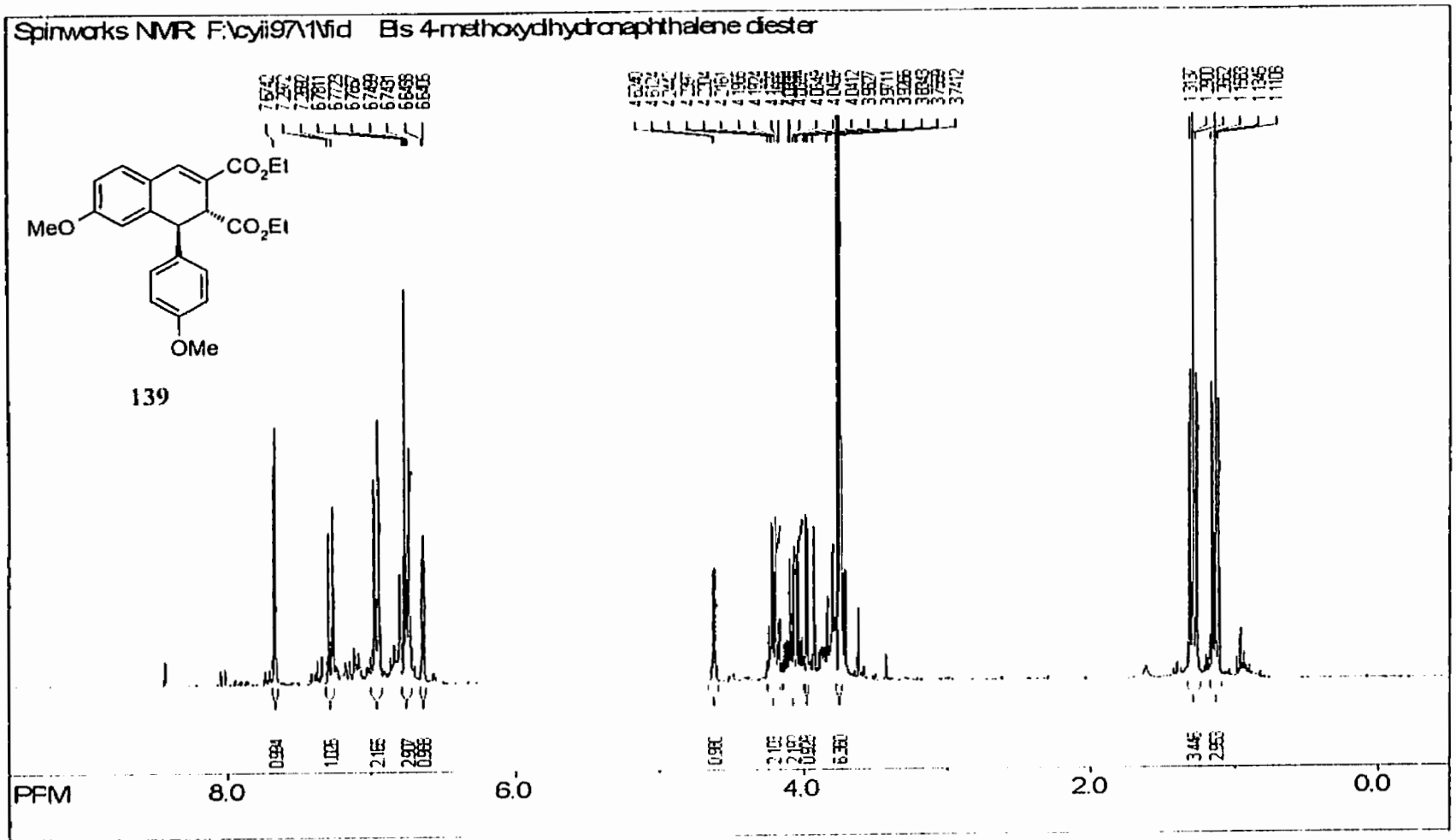

Spinworks NMR F:\cyli78a\1\fid Bis 2,4-dimethoxydihydronaphthalene diester
OMe
CO2Et
MeO
CO2Et
OMe
OMe
138
PPM
8.0
6.0
4.0
2.0
0.0
file F:\cyli78a\1\fid expt <zg30>
transmitter freq 300.131853 MHz
time domain size 65536 points
width 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans 16
freq. of 0 ppm 300.130006 MHz
processed size 32768 real points
LB 0.300 GB 0.0000

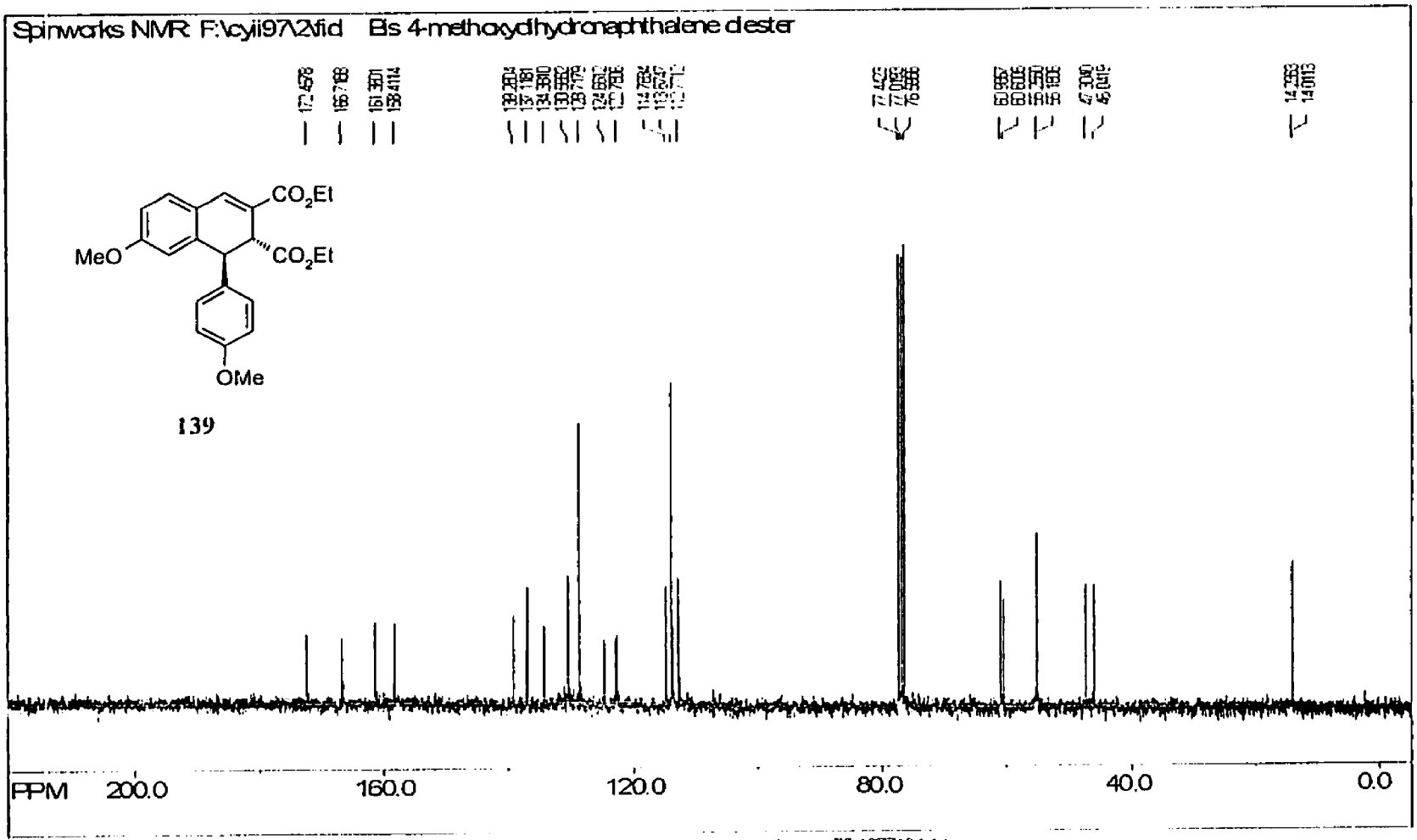


138

file F:\cyi78a\2fid 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 160

freq. of 0 ppm 75.467749 MHz
processed size 32768 real points
LB 1.00 GB 0.0000

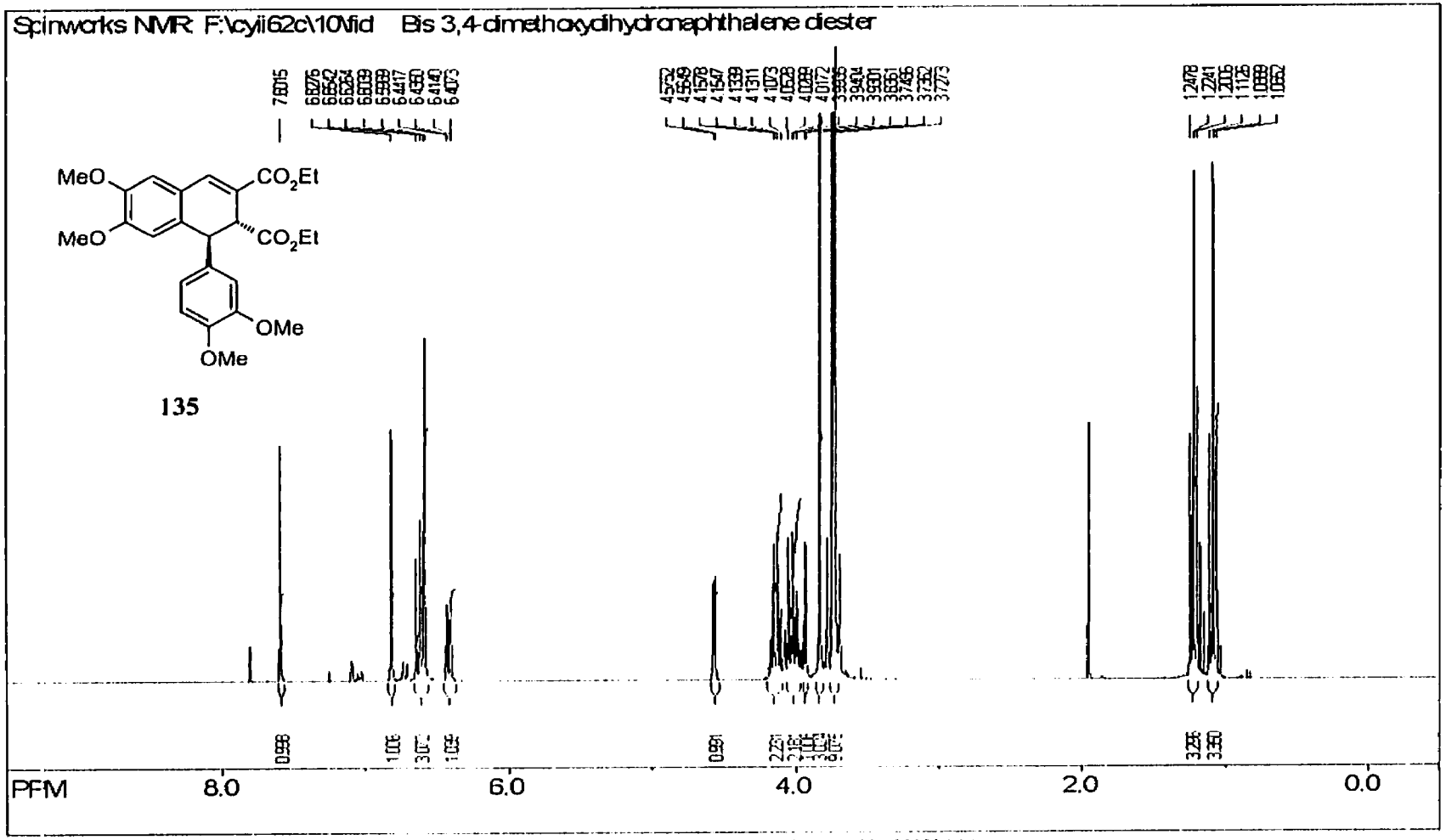

Spinworks NMR F:\cyji97\1\fid Bis 4-methoxydihydronaphthalene diester
CO2Et
MeO
CO2Et
OMe
139
PPM
8.0
6.0
4.0
2.0
0.0
file F:\cyji97\1\fid expt <zg30>
transmitter freq 300.131853 MHz
time domain size 65536 points
width 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans 16
freq of 0 ppm 300.130005 MHz
processed size 32768 real points
LB 0.300 GB 0.0000



139

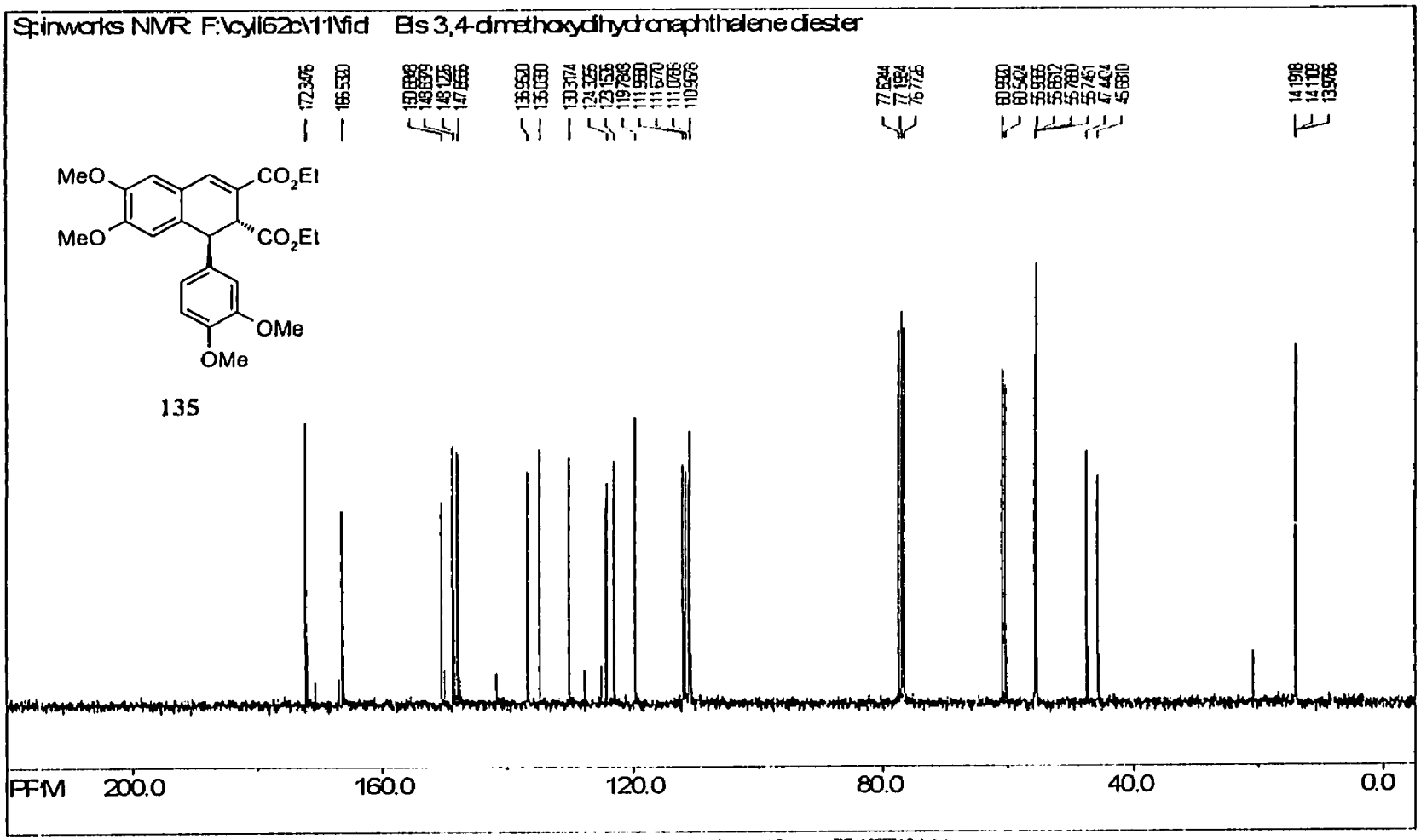
file F:\cyli97\2\fid expt <zgpg30>
transmitter freq 75478020 MHz
time domain size 65536 points
width 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans 256

freq. of 0 ppm 75467749 MHz
processed size 32768 real points
LB 1.00 GB 0.0000



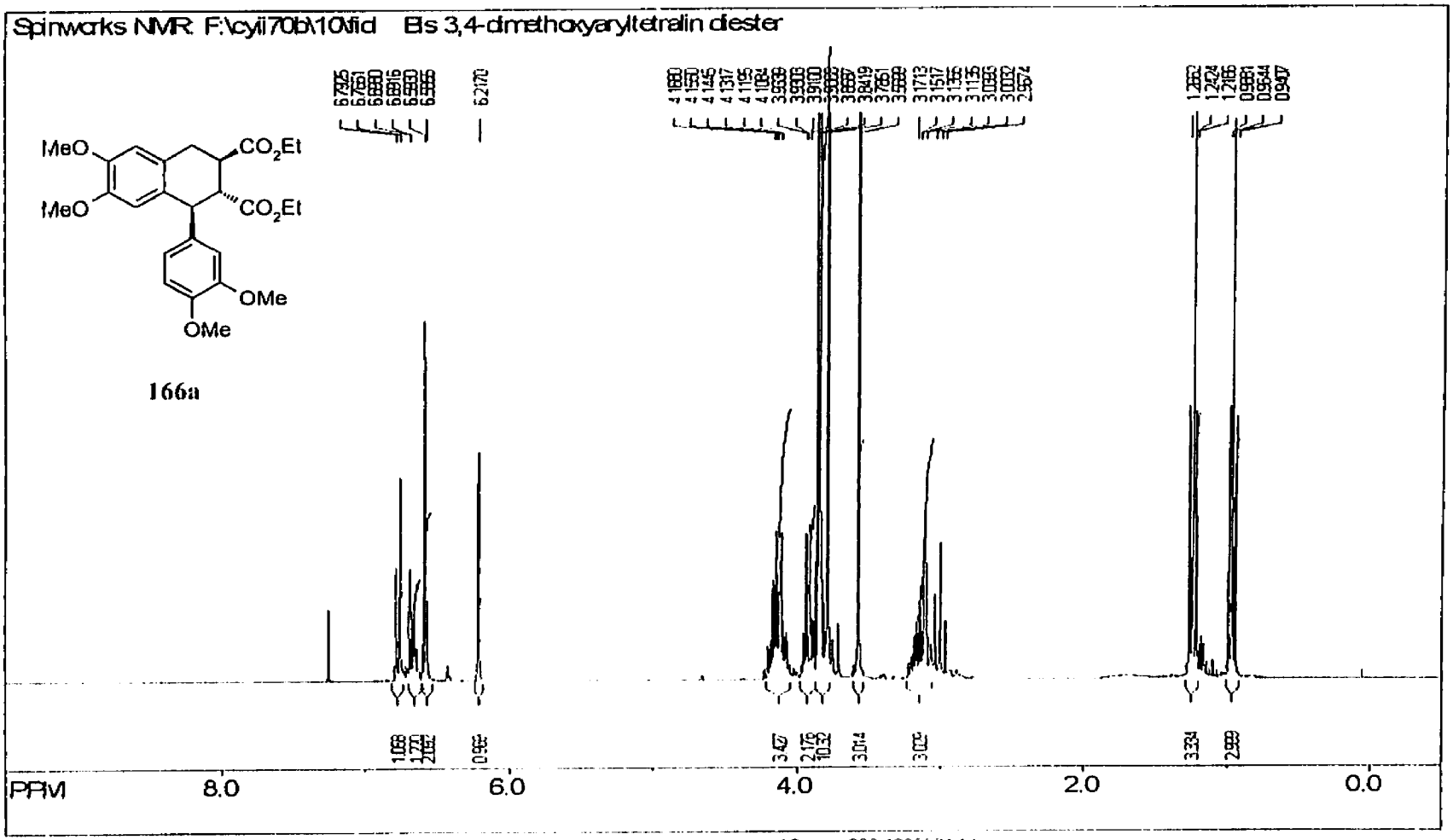
file: F:\cyli62c\10fid expt: <zg30>
transmitter freq: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130005 MHz
processed size: 32768 real points
LB: 0.30 GB: 0.0000



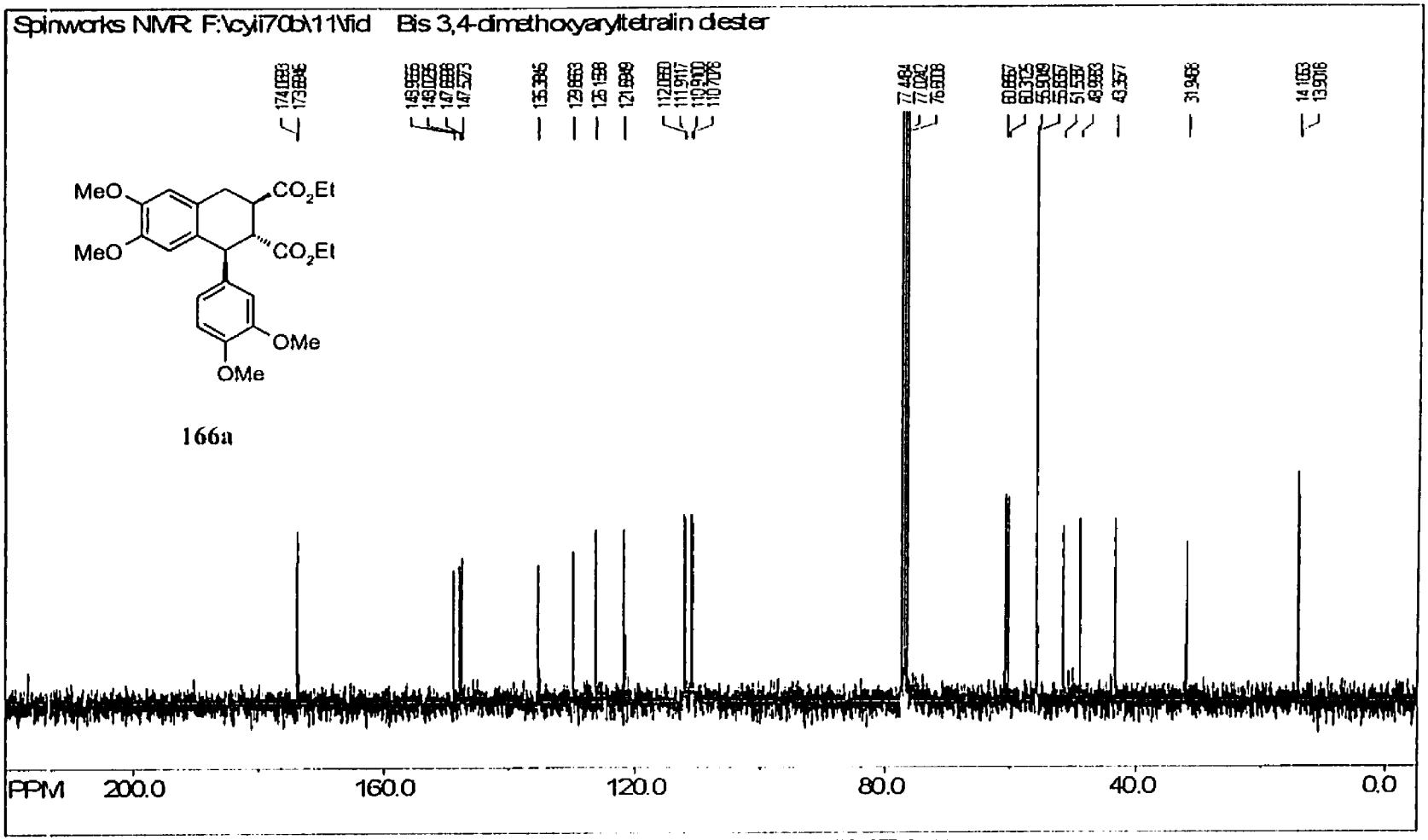
file: F:\cyli62c\11\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 256

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.0000

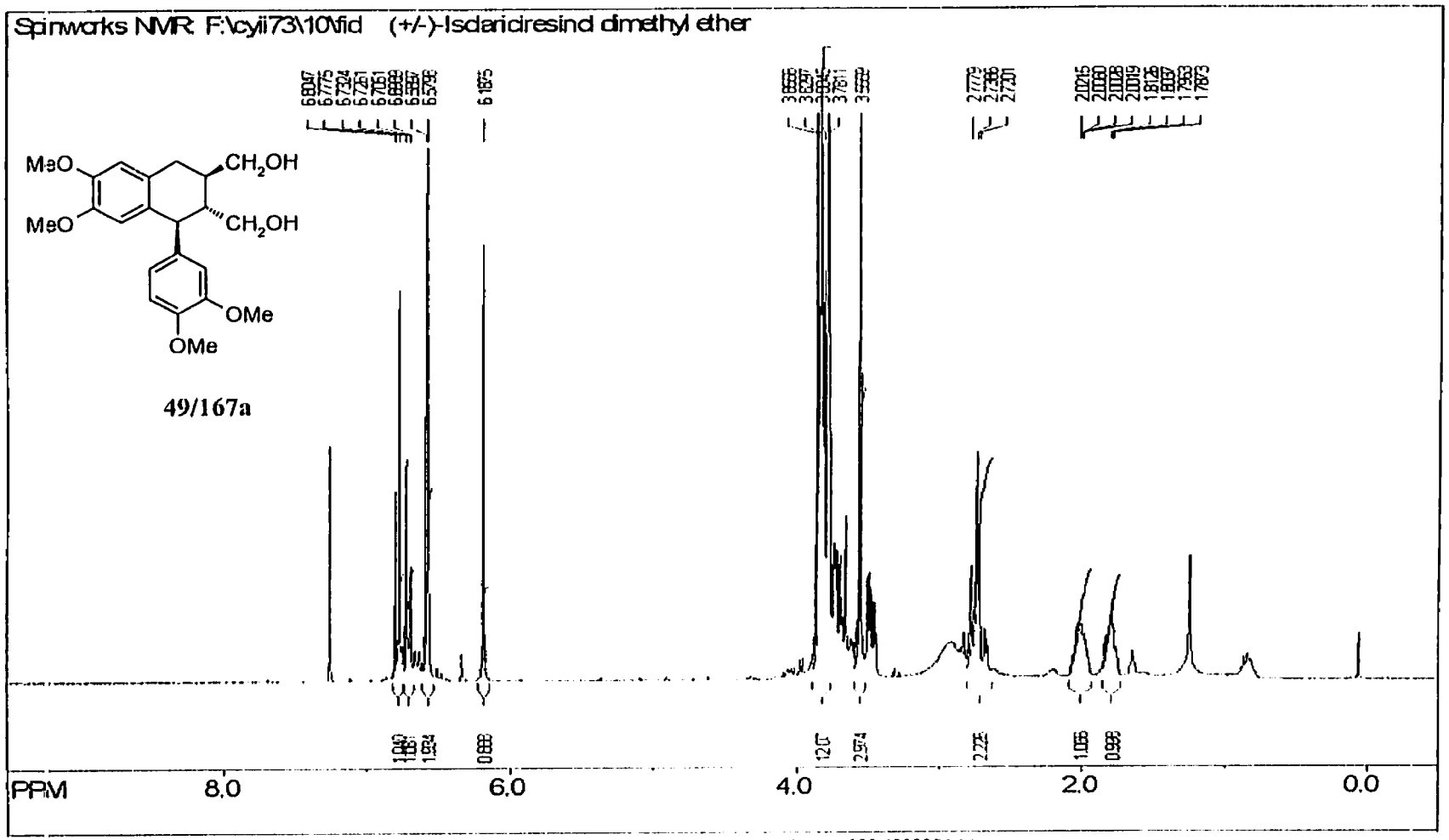


file F:\cyil70b\10\fid expt <zg30>
transmitter freq 300.131853 MHz
time domain size 65536 points
width 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans 16

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

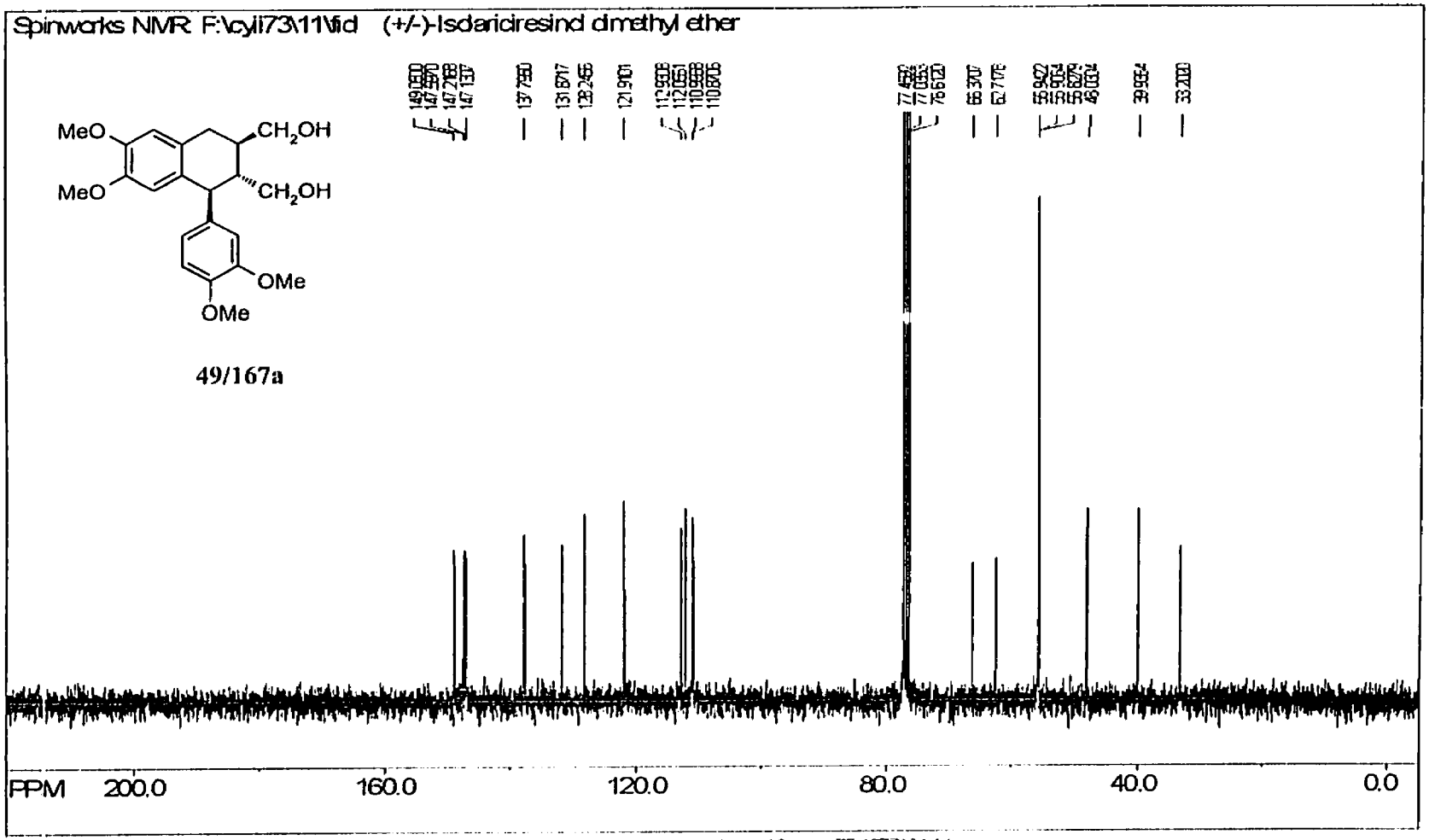

Spinworks NMR F:\cyli70b\11\fid Bis 3,4-dimethoxyaryltetralin diester
MeO
MeO
CO2Et
CO2Et
OMe
OMe
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file F:\cyli70b\11\fid expt <zg30>
transmitter freq 75.478020 MHz
time domain size 65536 points
width 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans 256
freq of 0 ppm 75.467749 MHz
processed size 32768 real points
LB 1.000 GB 0.0000

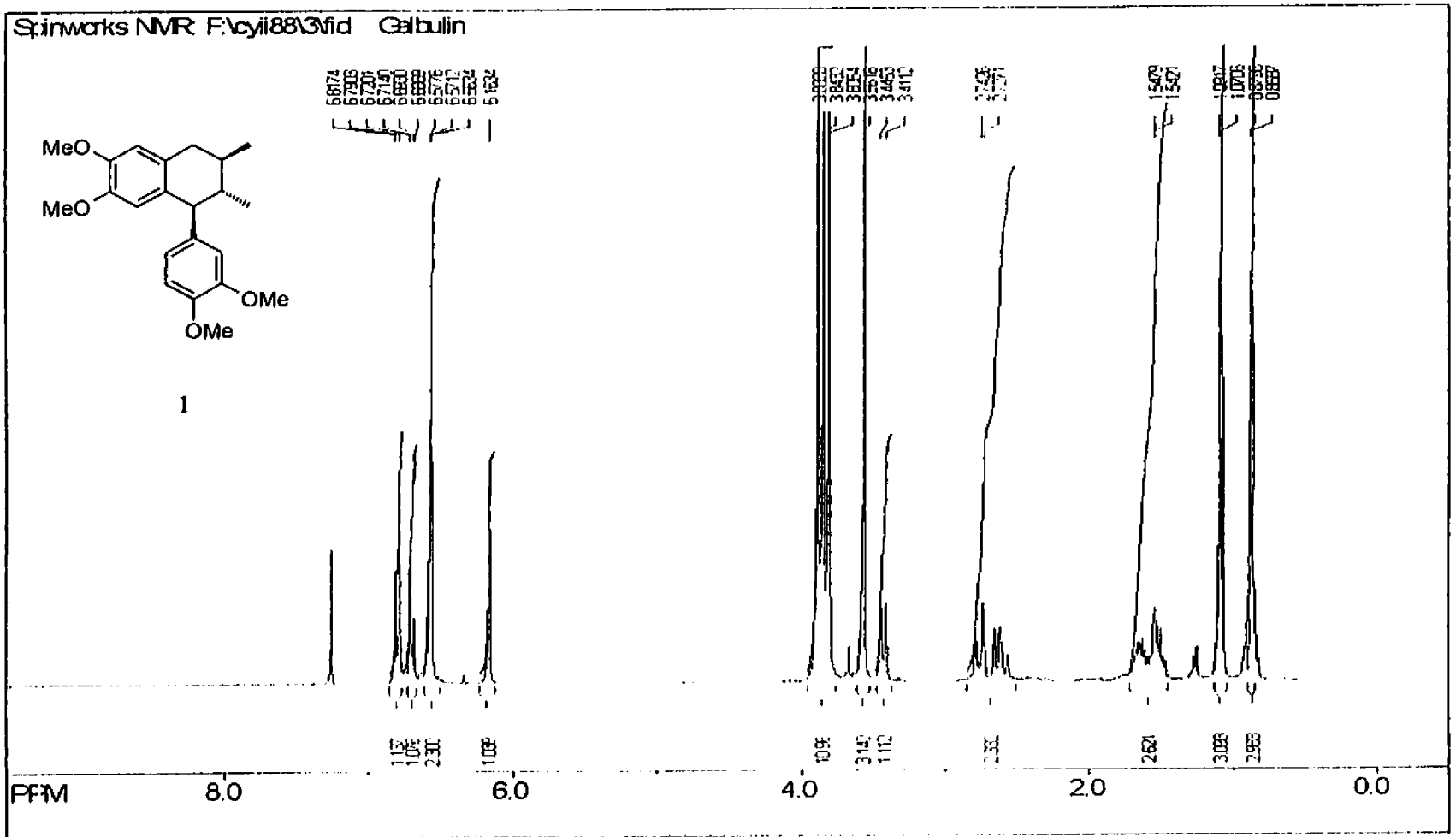
166a

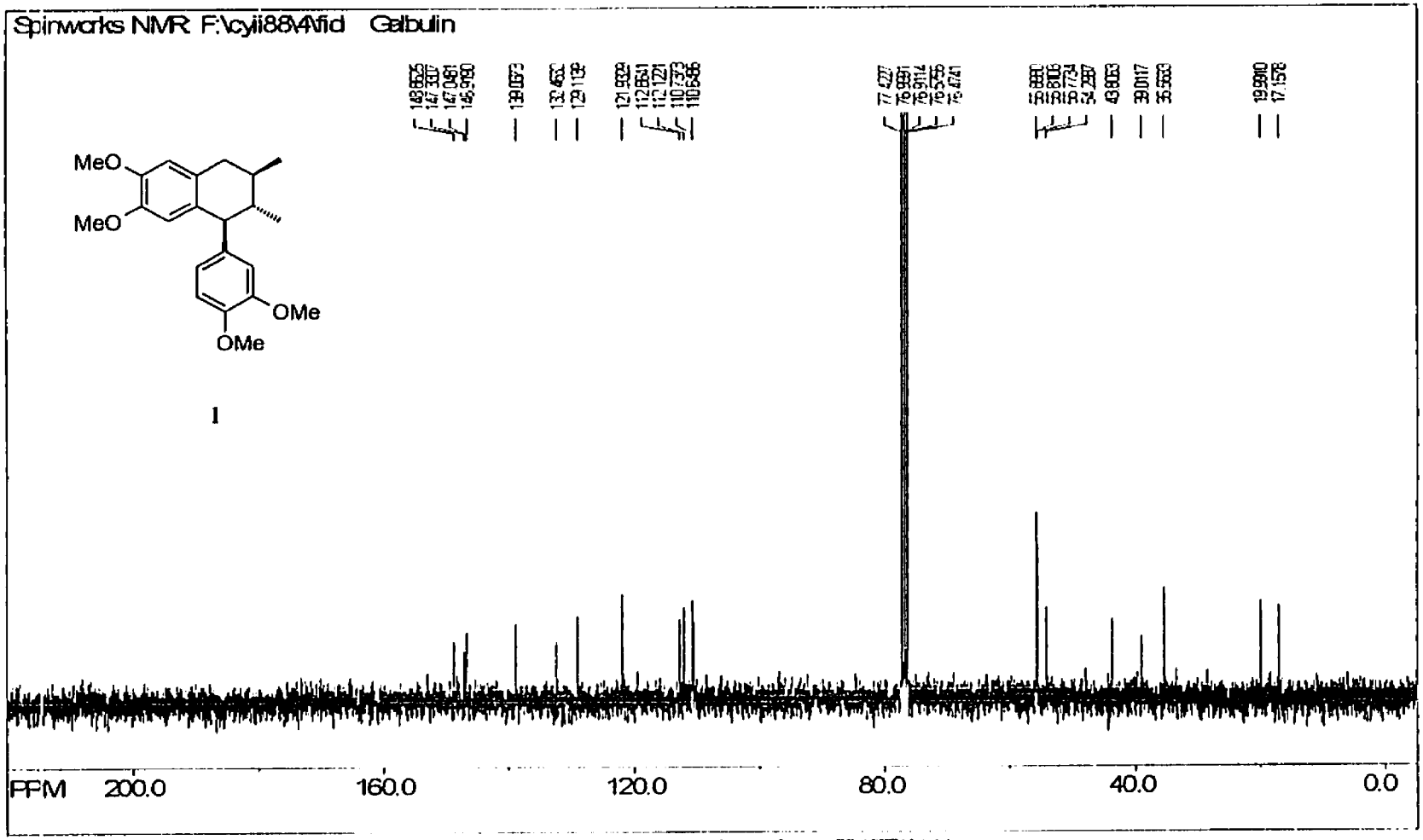


file: F:\cyli73\10\fid expt: <zg30>
transmitter freq: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

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


Spinworks NMR: F:\cyll73\11\fid (+/-)-Isdaridiresinol dimethyl ether
MeO
MeO
CH2OH
CH2OH
OMe
OMe
49/167a
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file = \cyll73\11\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 256
freq of 0 ppm 75.467749 MHz
processed size 32768 real points
LB 1.000 GB 0.000.0

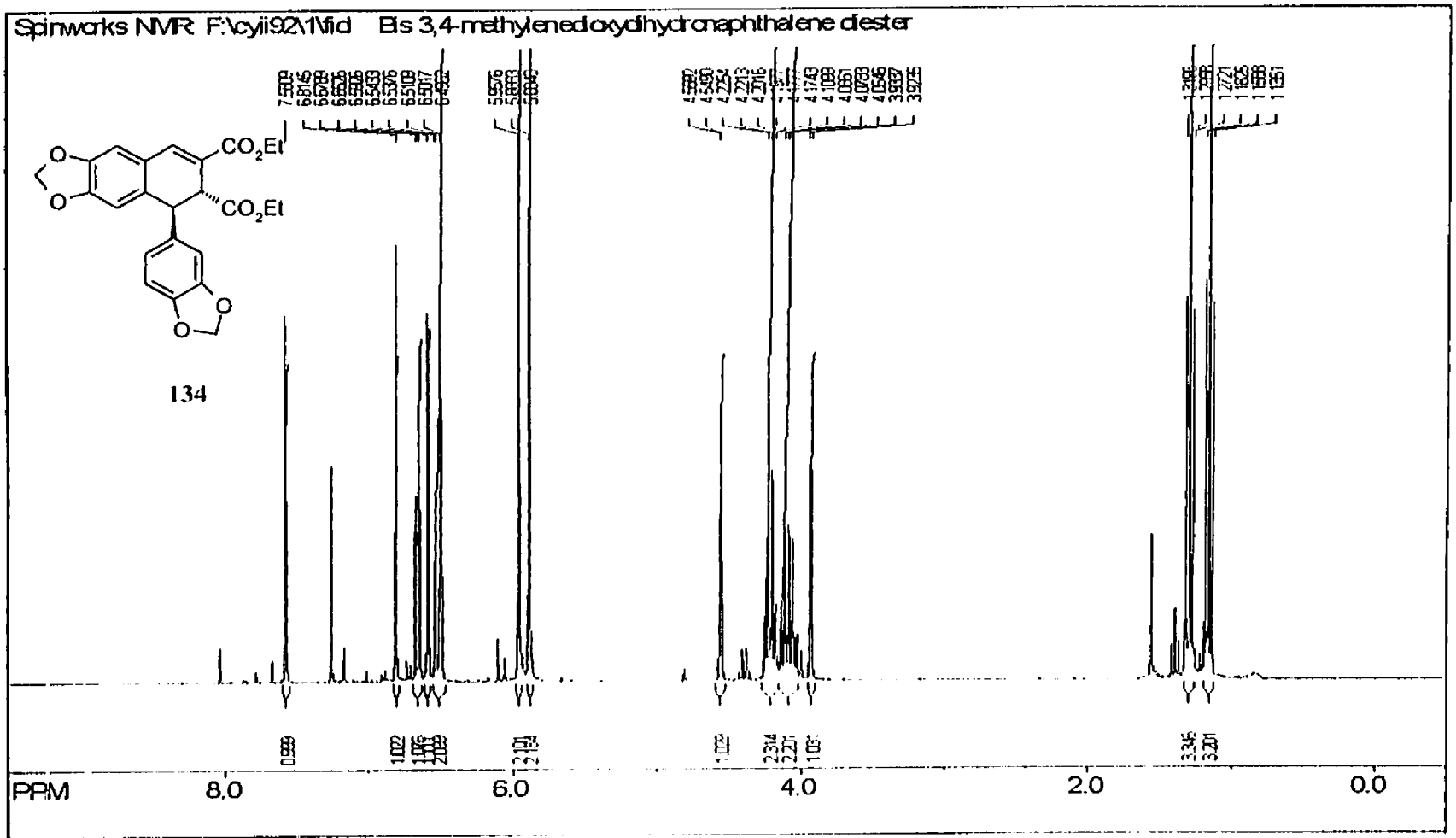

Spinworks NMR F:\cyli88\3\fid Galbulin
MeO
MeO
OMe
OMe
1
PPM
8.0
6.0
4.0
2.0
0.0
file F:\cyli88\3\fid expt <zg30>
transmitter freq. 300.131853 MHz
time domain size 65536 points
width 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans 48
freq. of 0 ppm 300.130006 MHz
processed size 32768 real points
LB 0.300 GB 0.0000



1

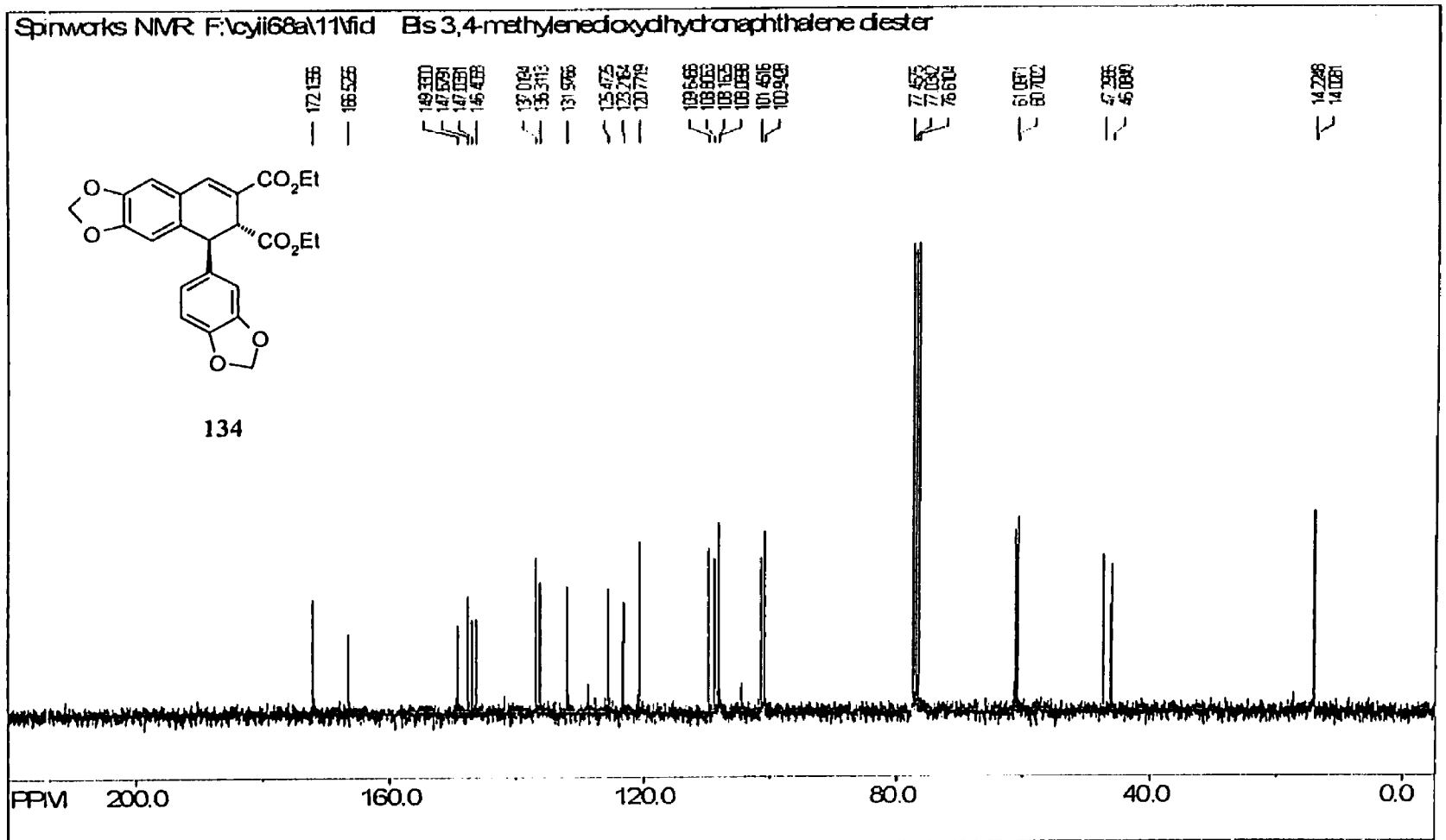
file: F:\cyli884\fid exp: <zgpg30>
transmitter freq: 75.476020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 256

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 real points
LB: 1.00 GB: 0.0000



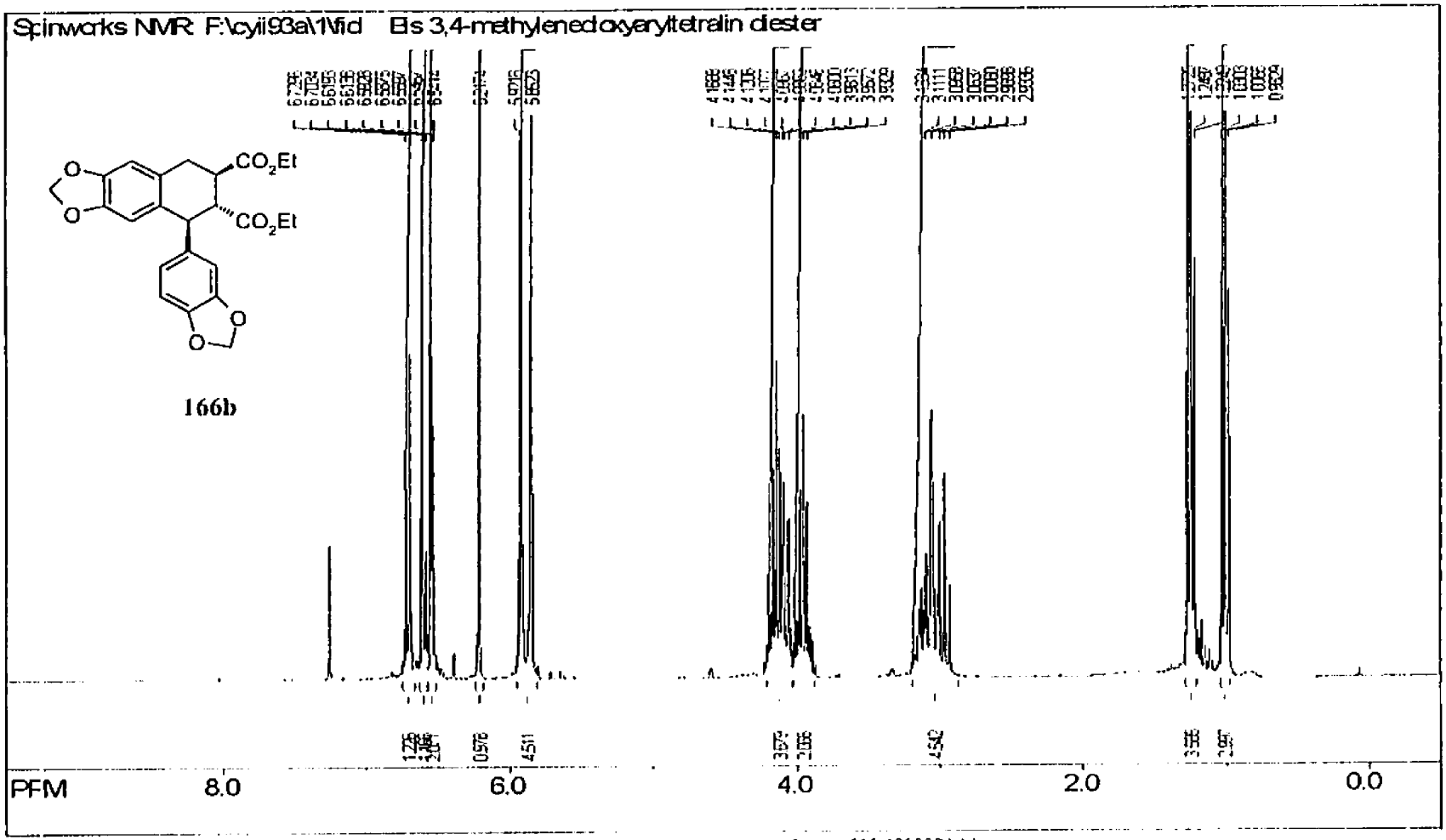
file: F:\cyli92\1\fid expt: <zg30>
transmitter freq: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 64

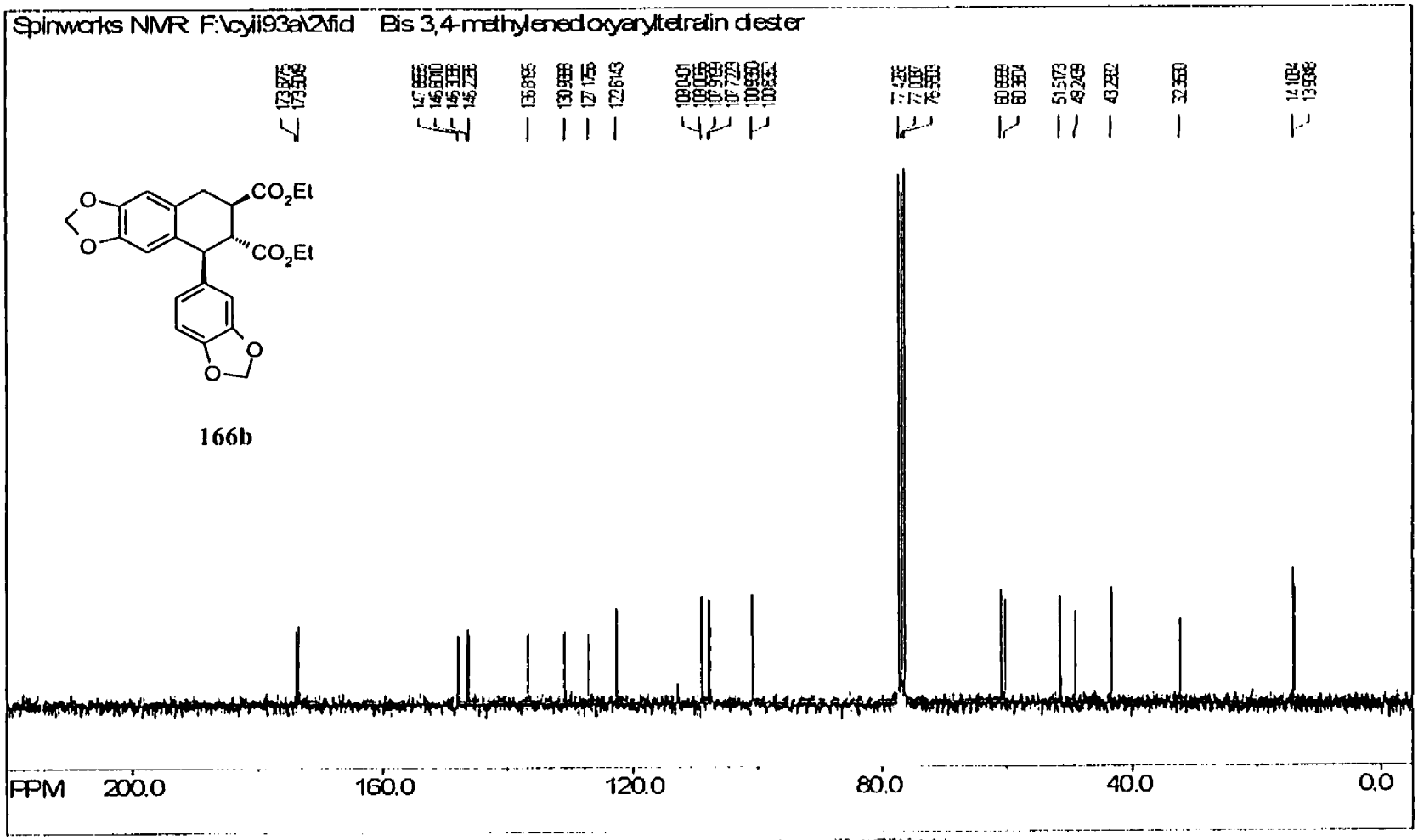
freq. of 0 ppm: 300.130003 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000



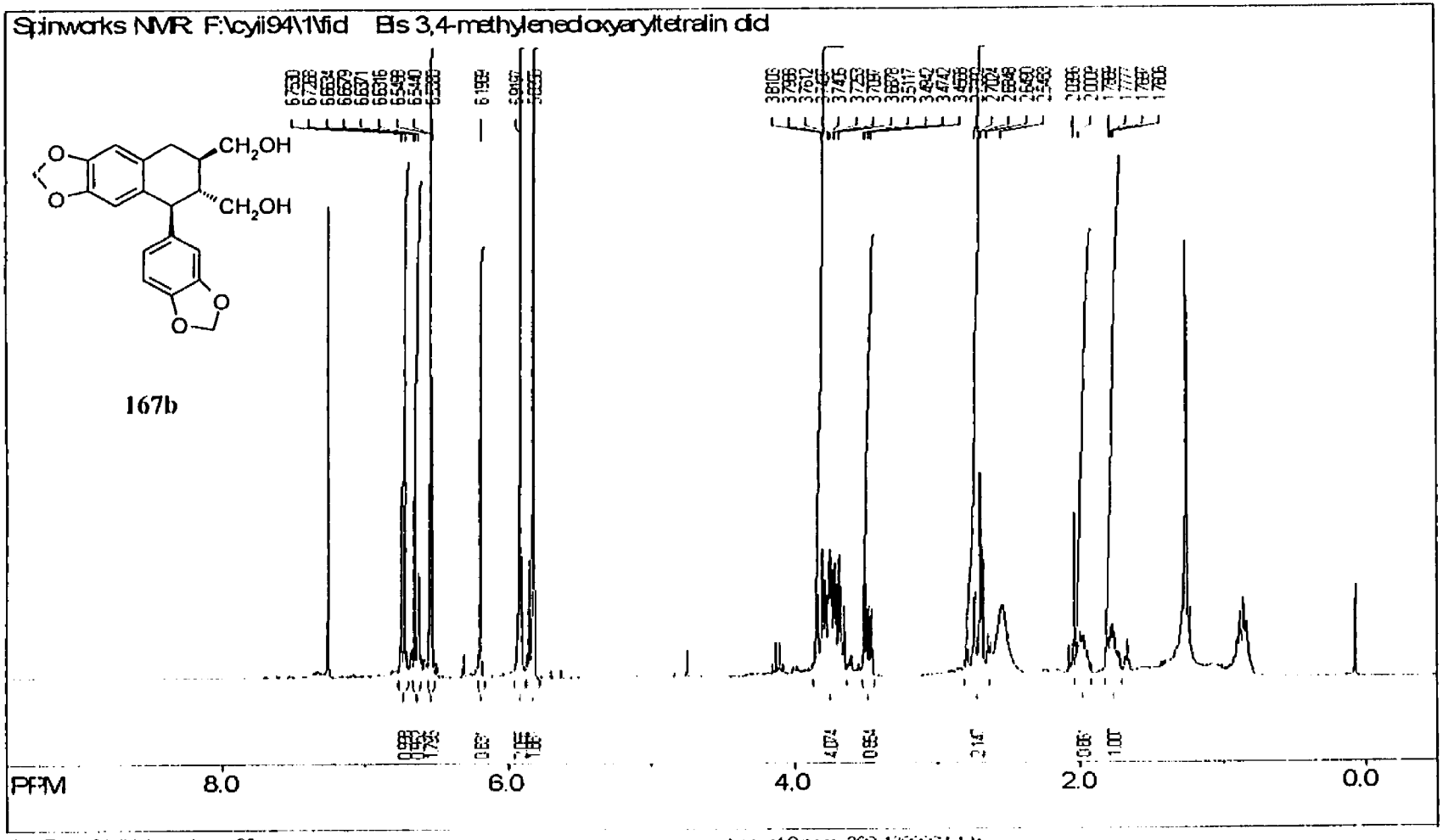
file F:\cyii68a\11\fid expt <zgpg30>
transmitter freq 75476020 MHz
time domain size 65536 points
width 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans 192

freq of 0 ppm 75467749 MHz
processed size 32768 real points
LB 1.000 GB 0.000


Spinworks NMR: F:\cyil93a\1\fid Bis 3,4-methylenedioxyaryltetralin diester
CO2Et
CO2Et
O
O
O
O
166b
PPM
8.0
6.0
4.0
2.0
0.0
1.225
1.366
2.000
0.576
4.511
3.575
2.000
4.542
3.338
2.000
file: F:\cyil93a\1\fid expt: <2g30>
transmitter freq: 300.131653 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 128
freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000

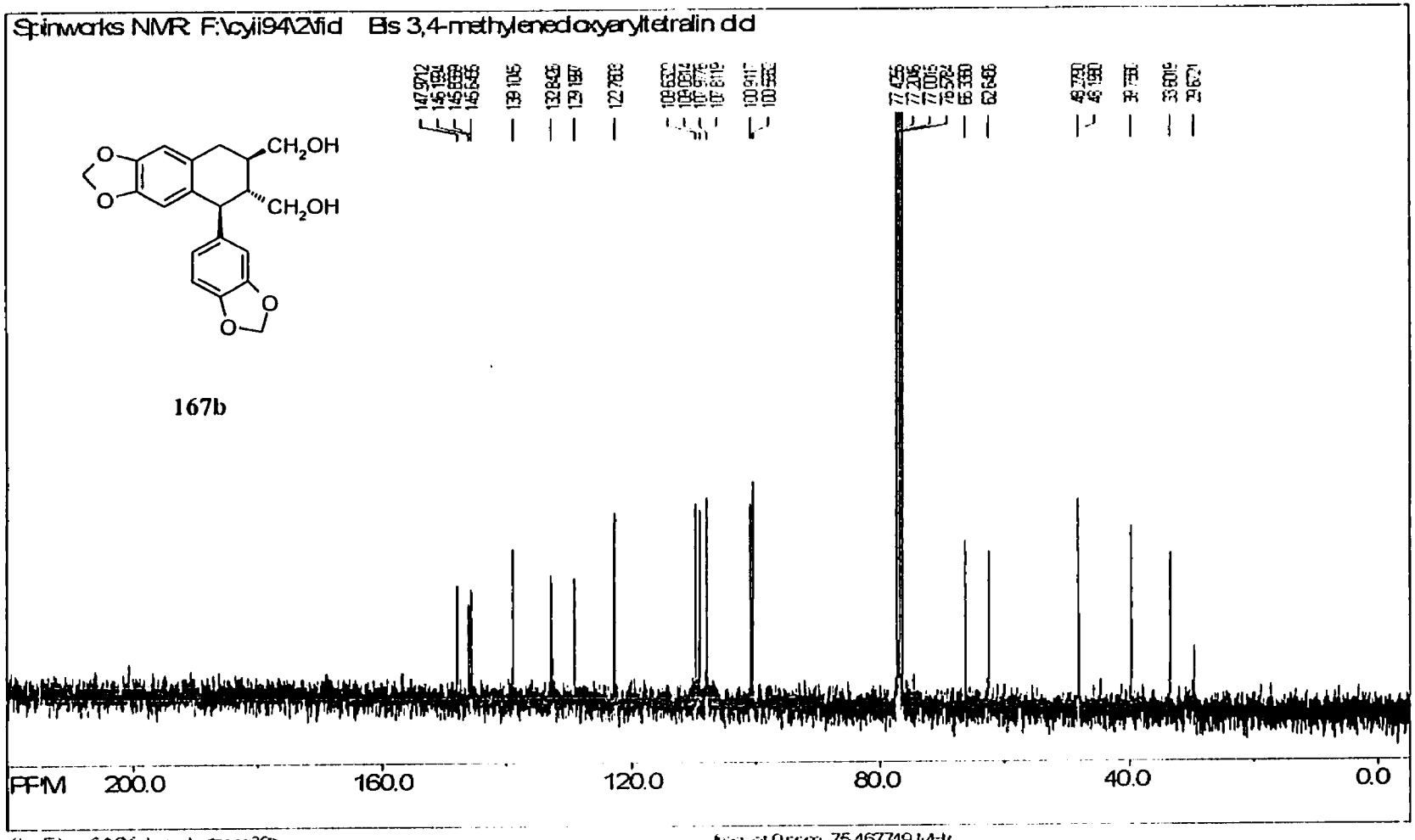

Spinworks NMR: F:\cyil93a\2\fid Bis 3,4-methylenedioxyaryltetralin diester
CO2Et
CO2Et
O
O
O
O
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file: F:\cyil93a\2\fid expt: <zgpg30>
transmitter freq.: 75.476000 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 320
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 real points
LB: 1.00 GB: 0.0000

166b



file F:\cyil94\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 96

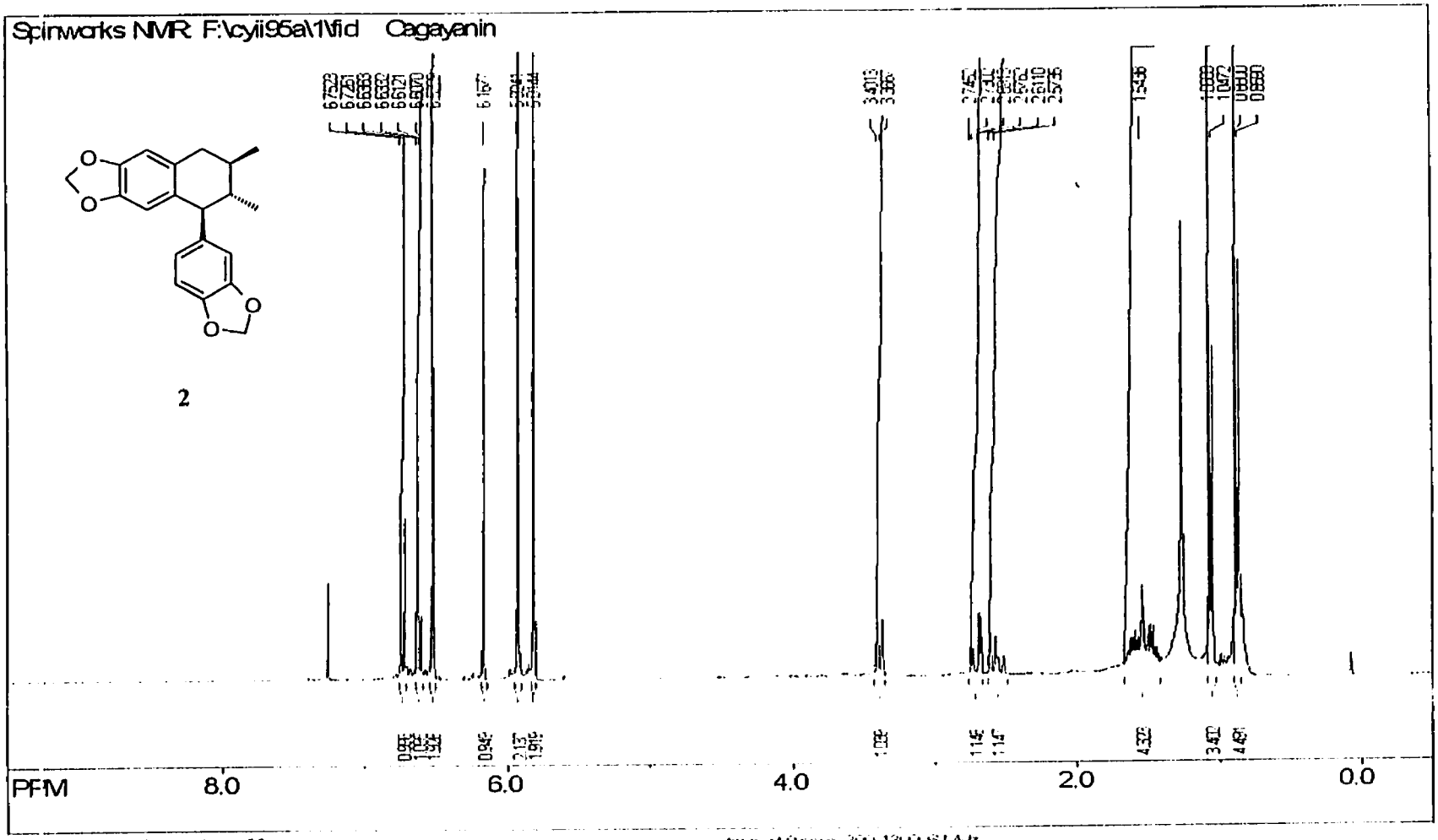
freq of 0 ppm 300.130003 MHz
processed size 32768 real points
LB 0.300 GB 0.0000

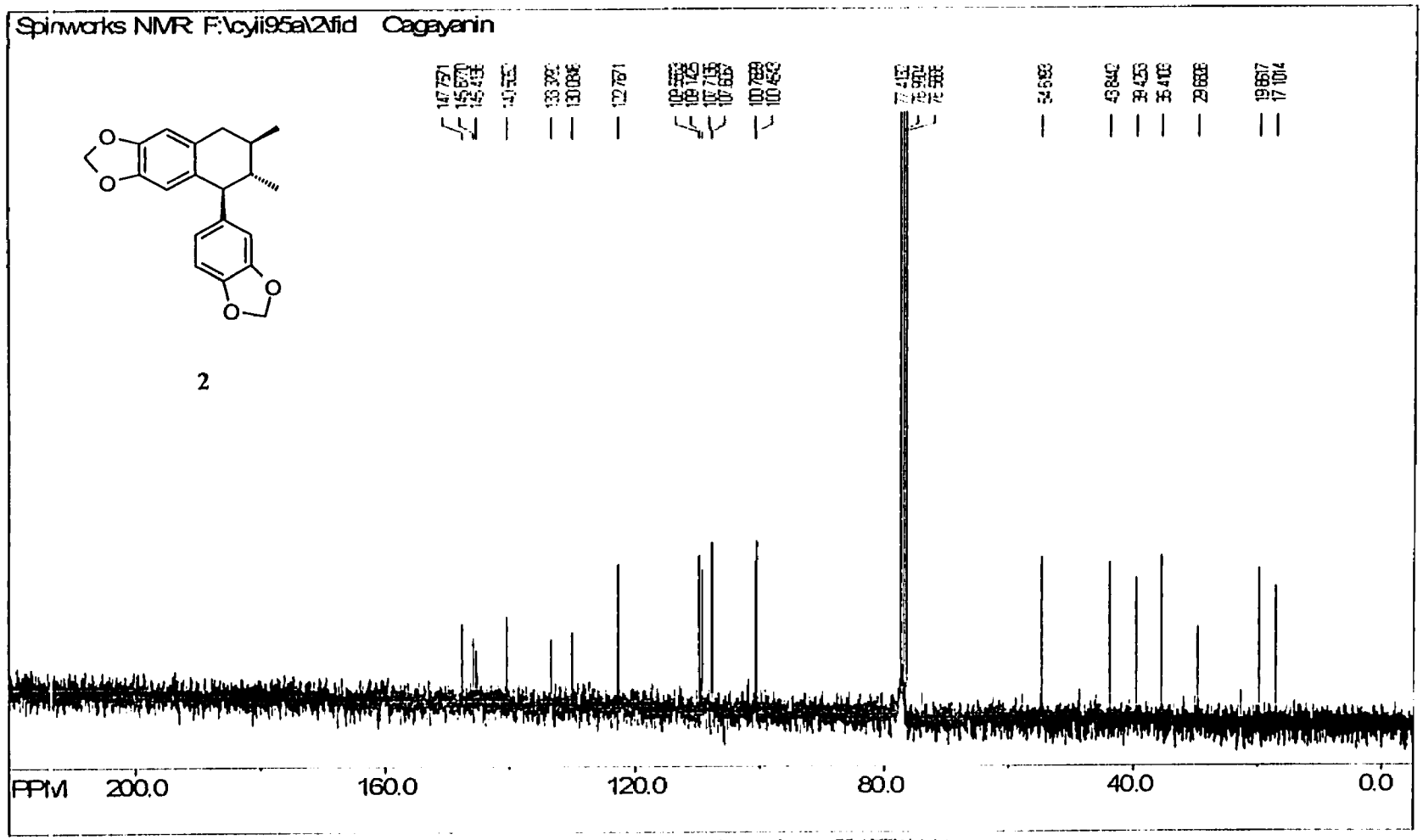


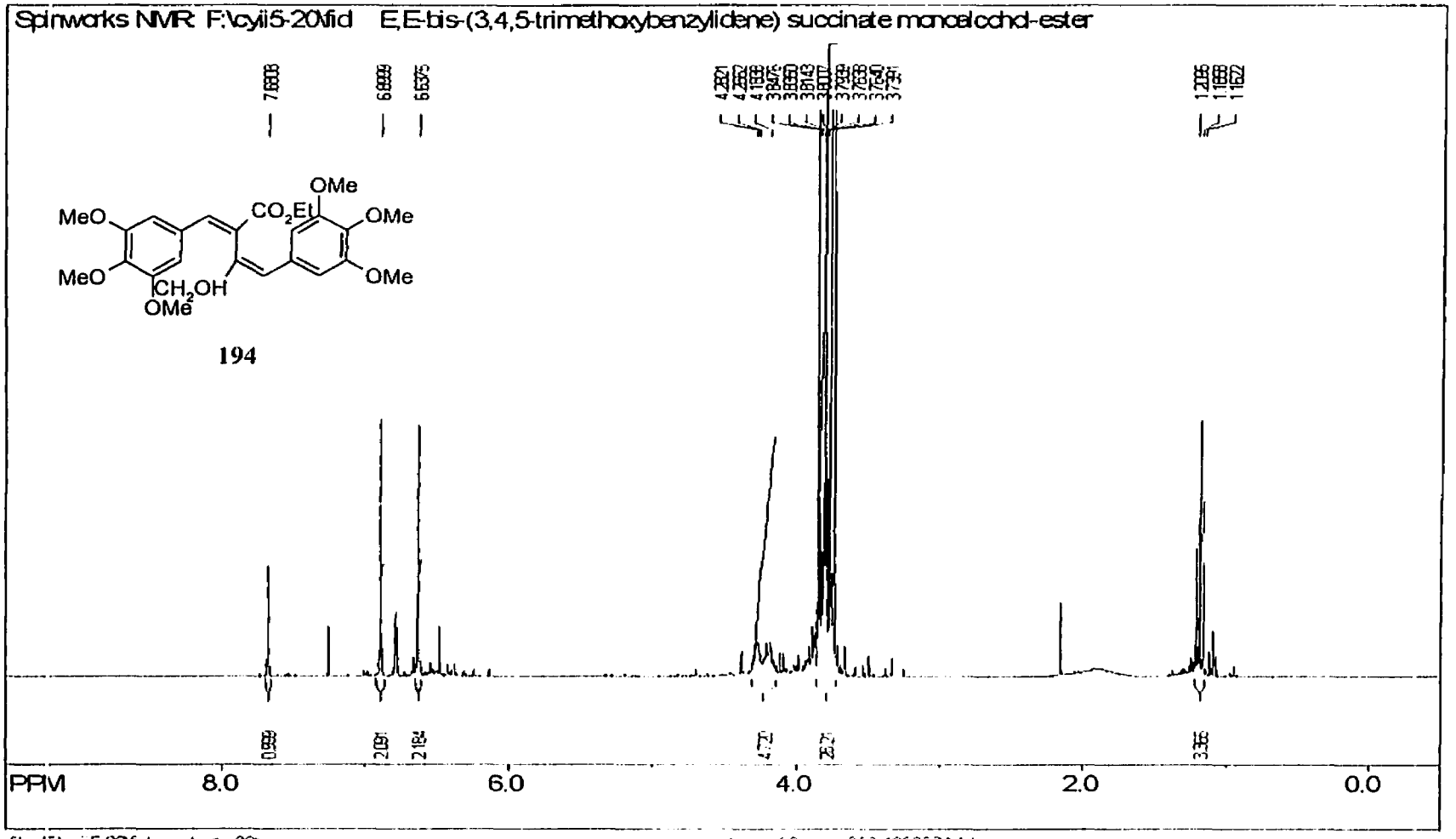
167b

file F:\cyli94\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 256

freq. of 0 ppm 75.467749 MHz
processed size 32768 real points
LB 1.000 GB 0.0000


Spinworks NMR: F:\cyli95a\1\fid Cagayanin
2
PPM
8.0
6.0
4.0
2.0
0.0
file: F:\cyli95a\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: 128
freq. of 0 ppm: 300.130005 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000

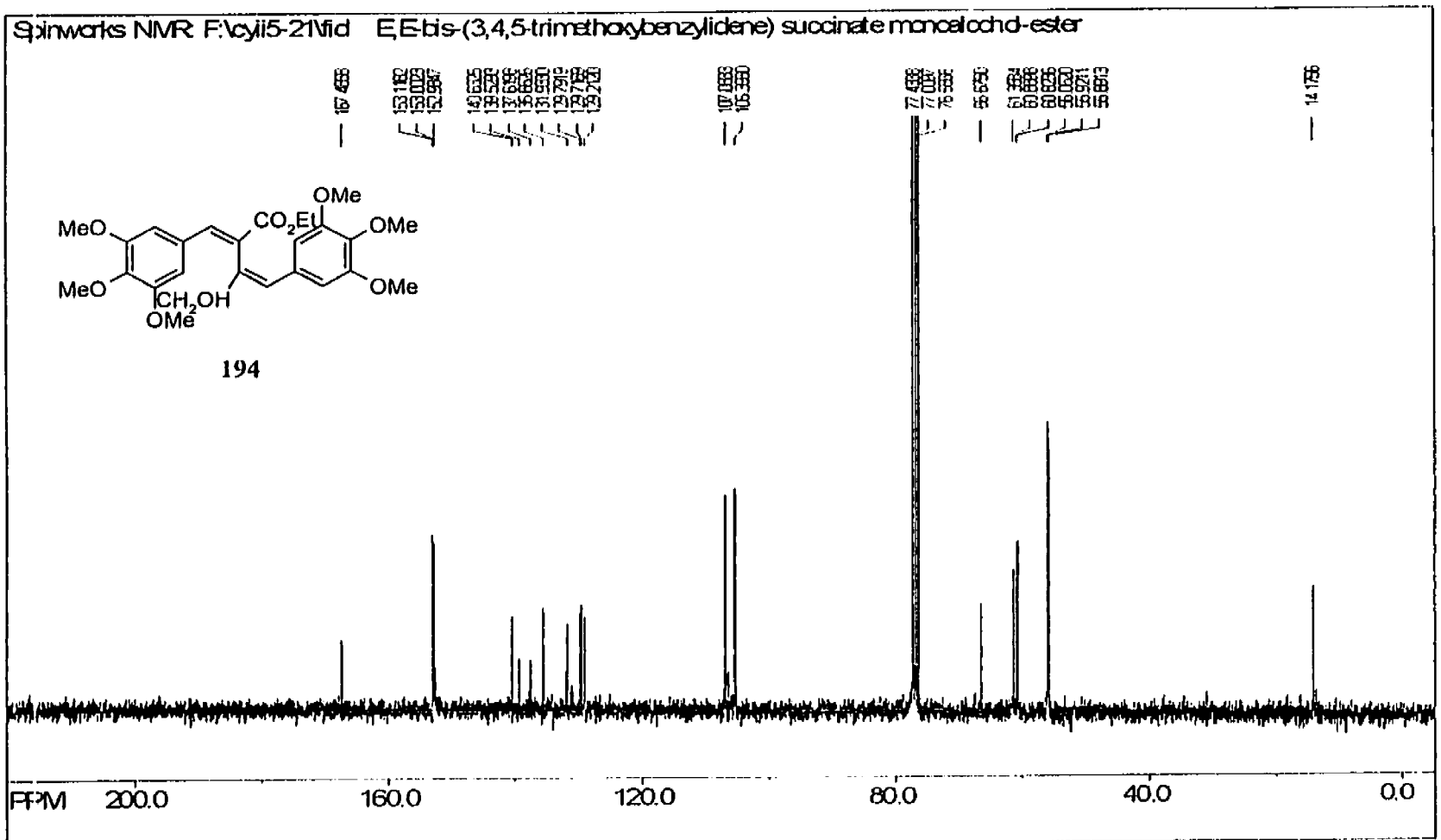

Spinworks NMR: F:\cyli95a\2\fid Cagayanin
2
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file: F:\cyli95a\2\fid exp: <zgpg30>
transmitter freq: 75.478020 MHz
time domain size: 65536 points
width: 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans: 256
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 real points
LB: 1.000 GB: 0.000



194

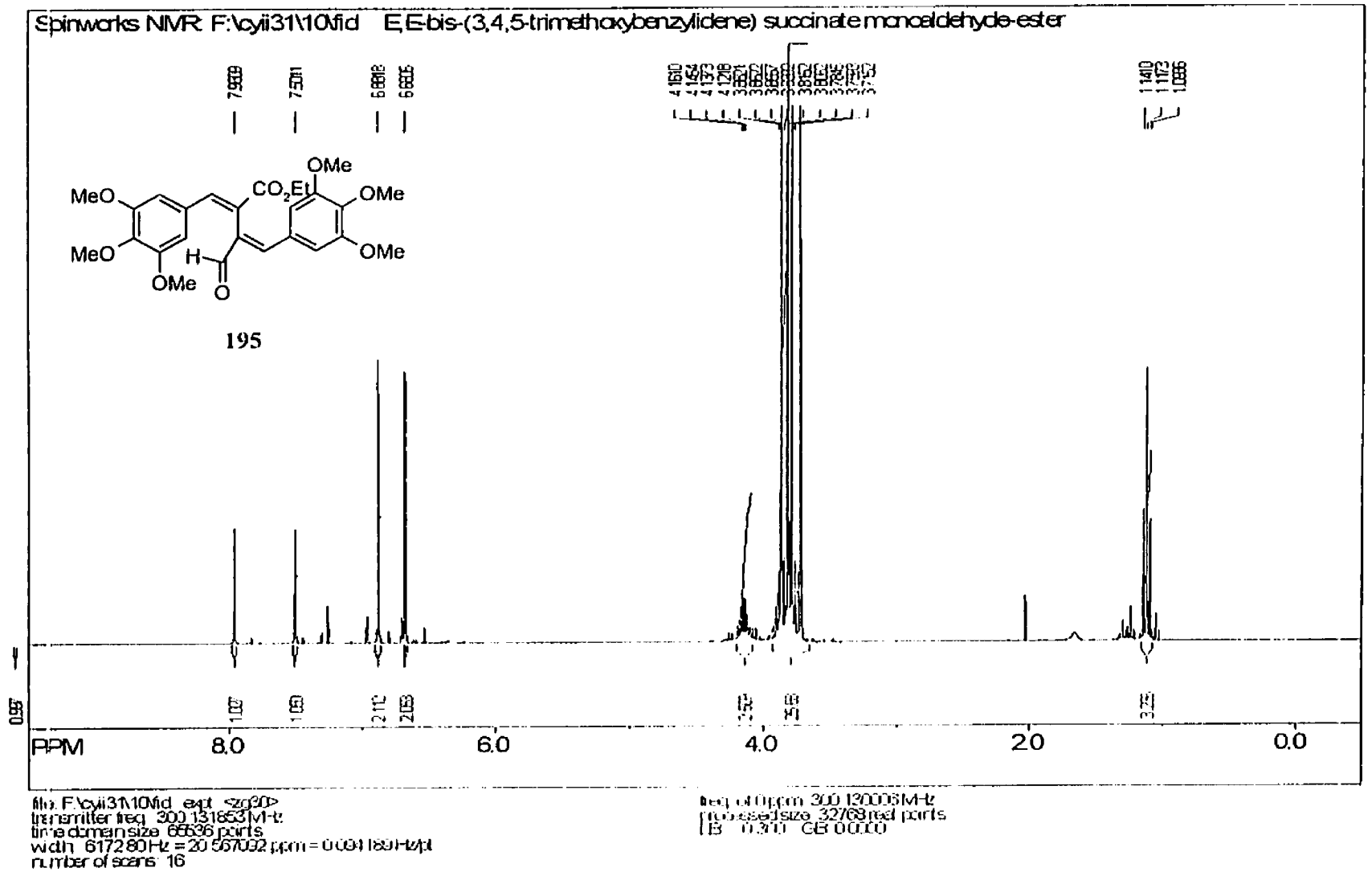
file: F:\cyil5-20\fid expt: <zg30>
transmitter freq: 300.1318653 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 16

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.200 GB: 0.0000



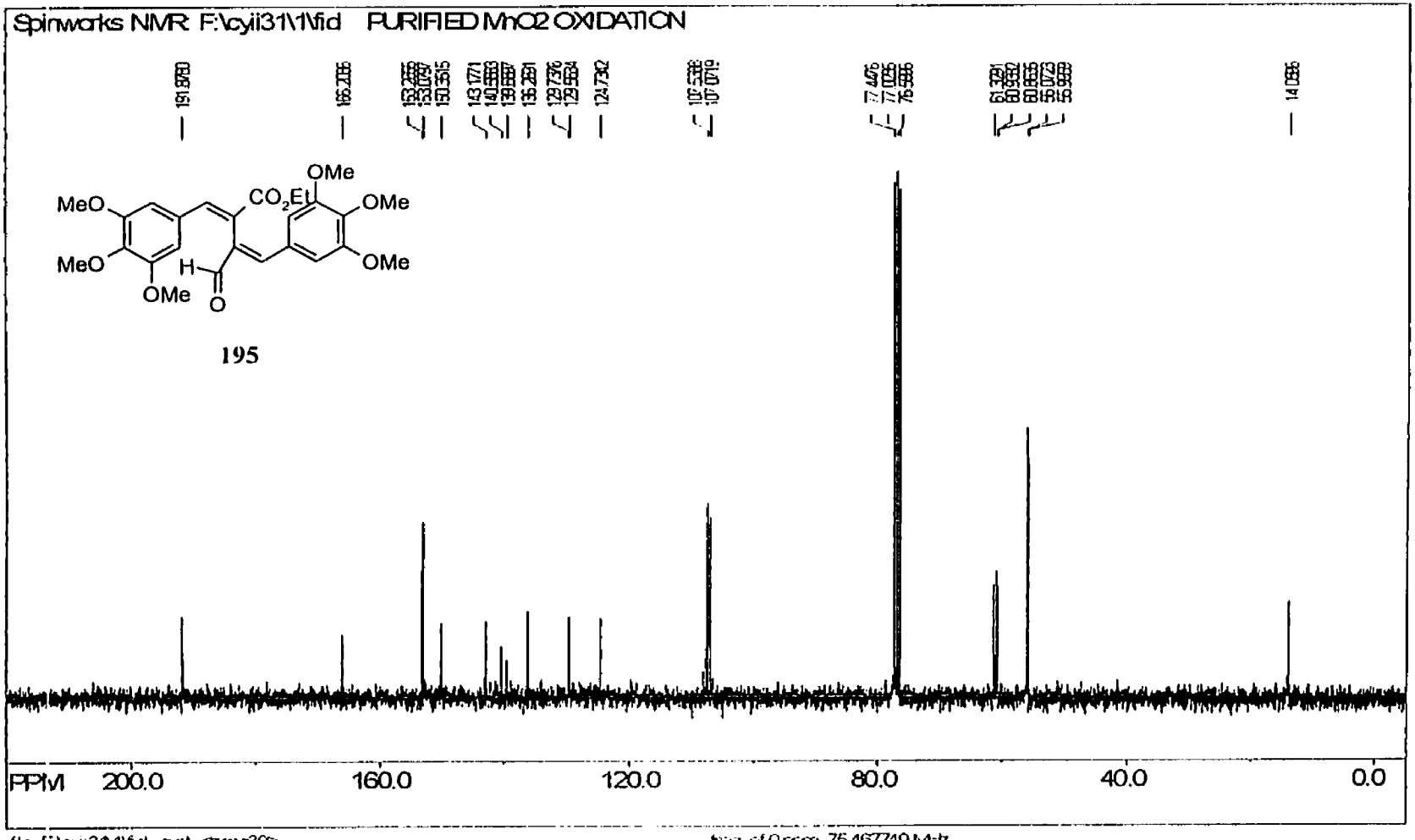
file F:\cyli5-21\fid expt <zgpg30>
transmitter freq 75.476020 MHz
time domain size 65536 points
width 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans 1024

freq of 0 ppm 75.467749 MHz
processed size 32768 real points
LB 1.000 GB 0.0000



file: F:\cyii31\10fid 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

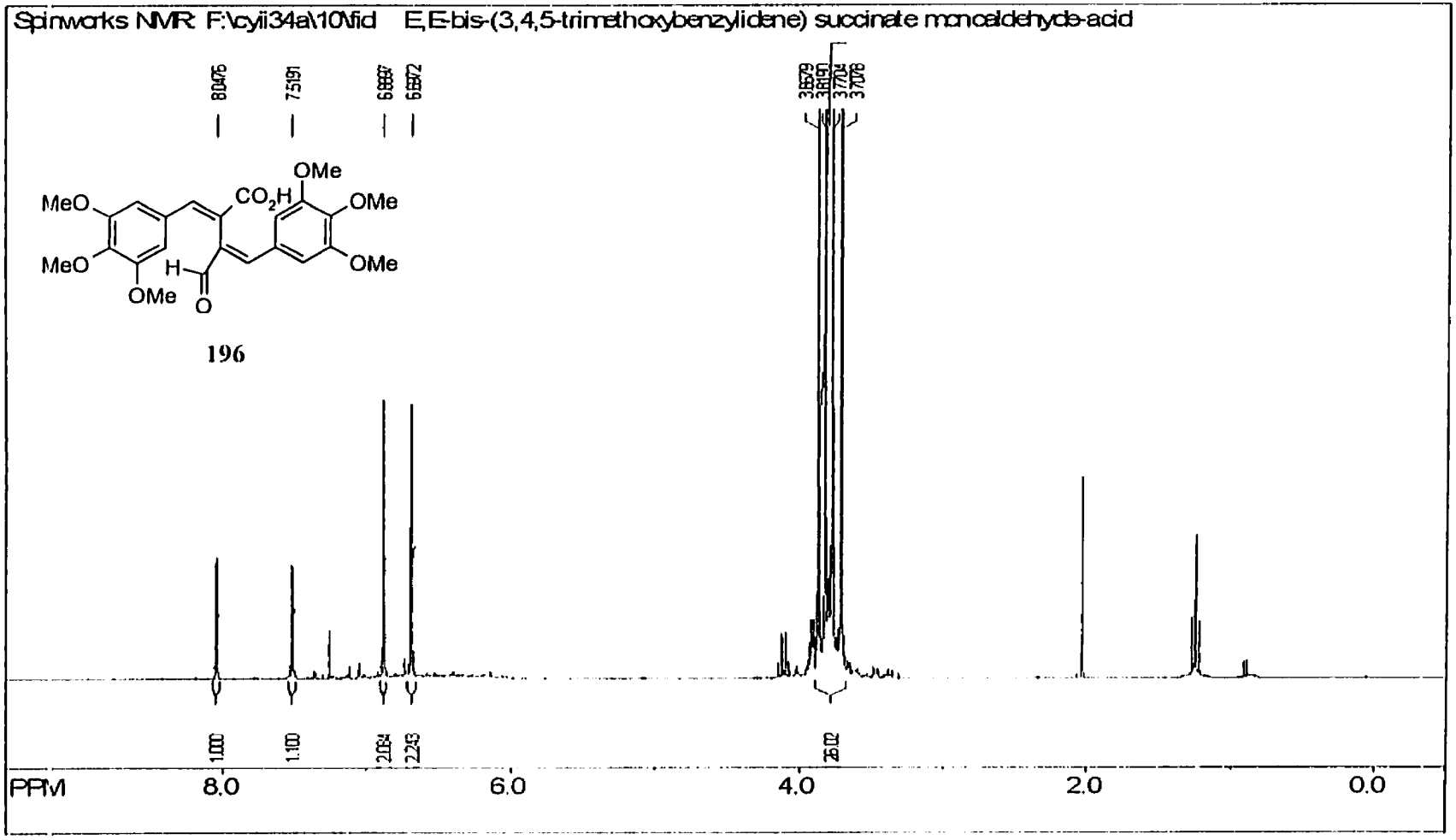
freq. of 0 ppm: 300.130005 MHz
processed size: 32768 real points
LB: 0.300 GB: 0.0000

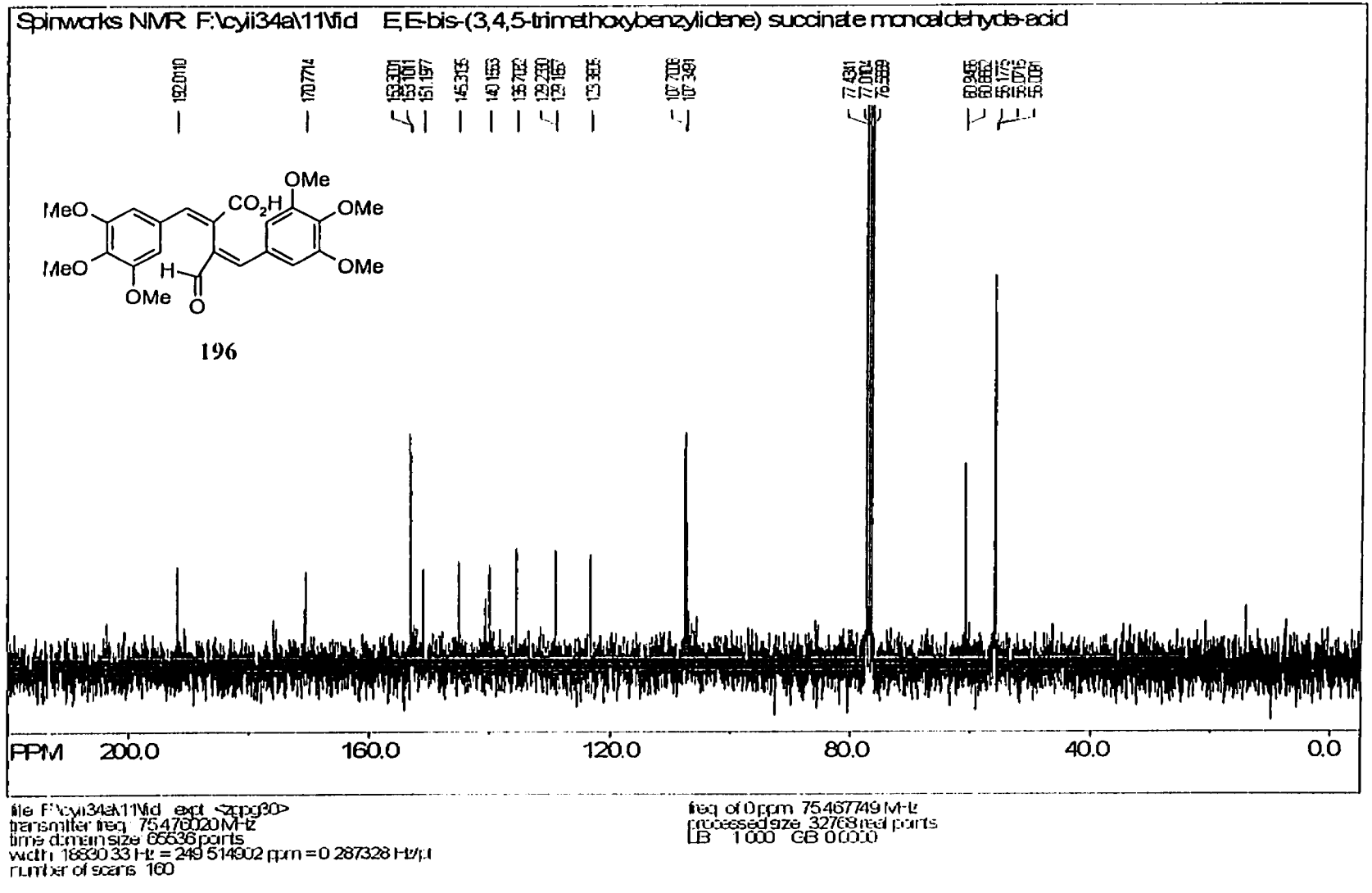


195

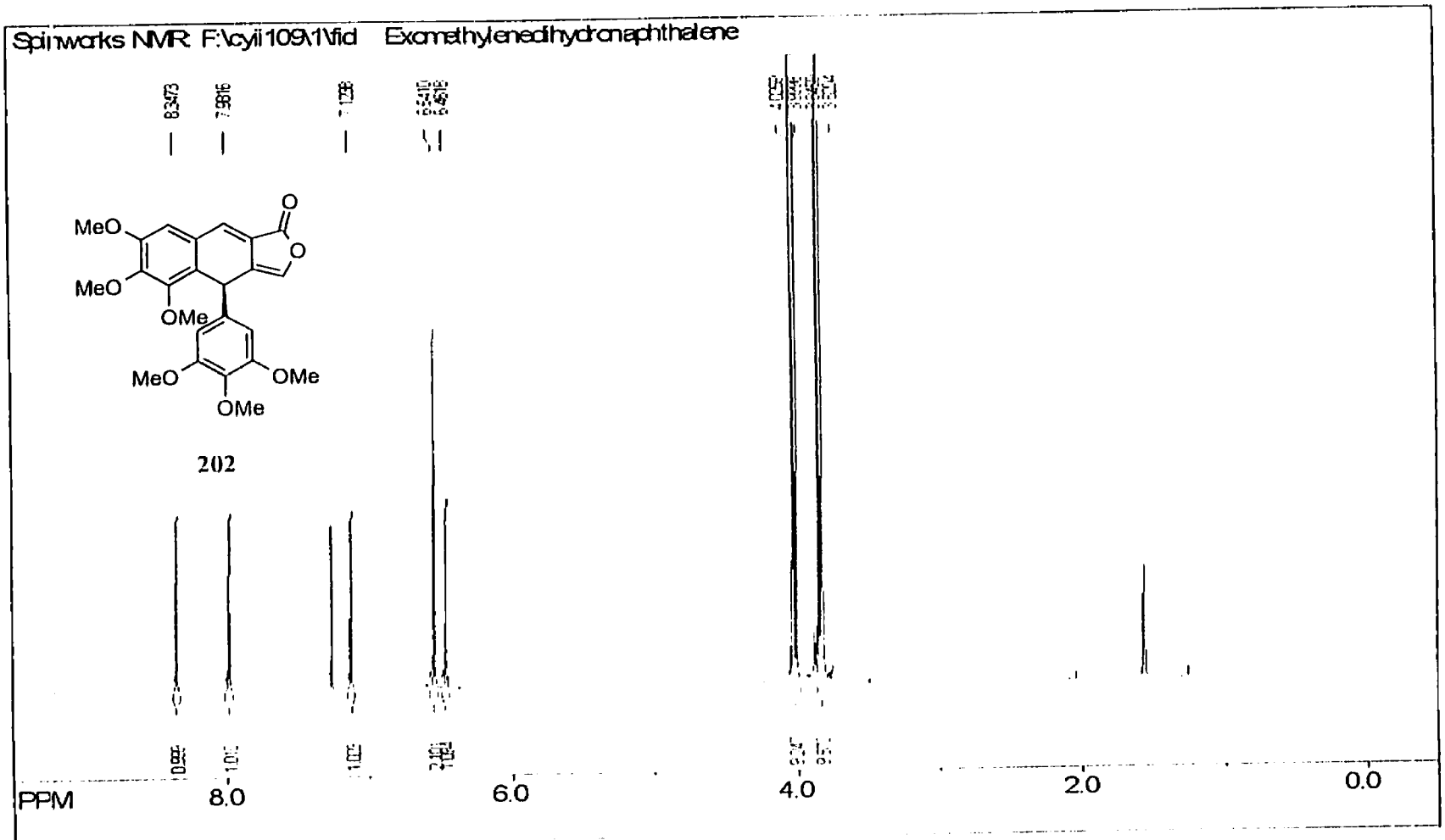
file F:\cyil31\1\fid expt <zgpg30>
transmitter freq 75.476020 MHz
time domain size 65536 points
width 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans 184

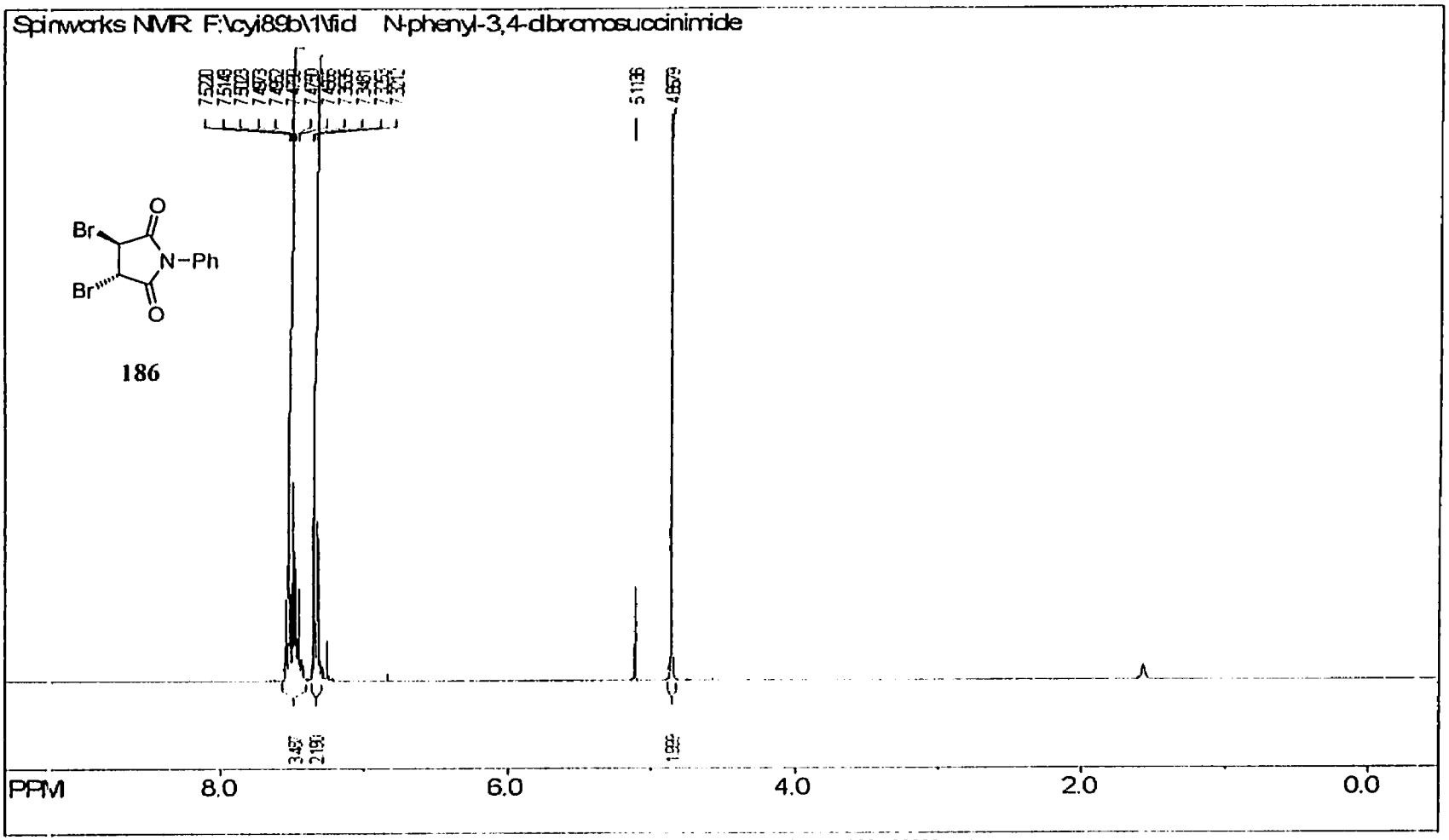
freq. of 0 ppm 75.467749 MHz
processed size 32768 real points
LB 1.000 GB 0.0000


Spinworks NMR: F:\cyji34a\10\fid E,E-bis-(3,4,5-trimethoxybenzylidene) succinate monoaldehyde-acid
8.0476
7.5191
6.8897
6.8572
3.8579
3.8191
3.7704
3.7076
OMe
MeO
CO2H
OMe
MeO
H
OMe
OMe
O
196
1.000
1.100
2.084
2.243
26.012
PPM
8.0
6.0
4.0
2.0
0.0
file F:\cyji34a\10\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 F:\cyji34a\11\fid E,E-bis-(3,4,5-trimethoxybenzylidene) succinate monoaldehyde-acid
MeO
MeO
OMe
CO2H
OMe
OMe
H
O
OMe
PPM 200.0 160.0 120.0 80.0 40.0 0.0
file F:\cyji34a\11\fid expt <zgpg30>
transmitter freq 75476020 MHz
time domain size 65536 points
width 18830.33 Hz = 249.514902 ppm = 0.287328 Hz/pt
number of scans 160
freq of 0 ppm 75467749 MHz
processed size 32768 real points
LB 1.000 GB 0.0000

196

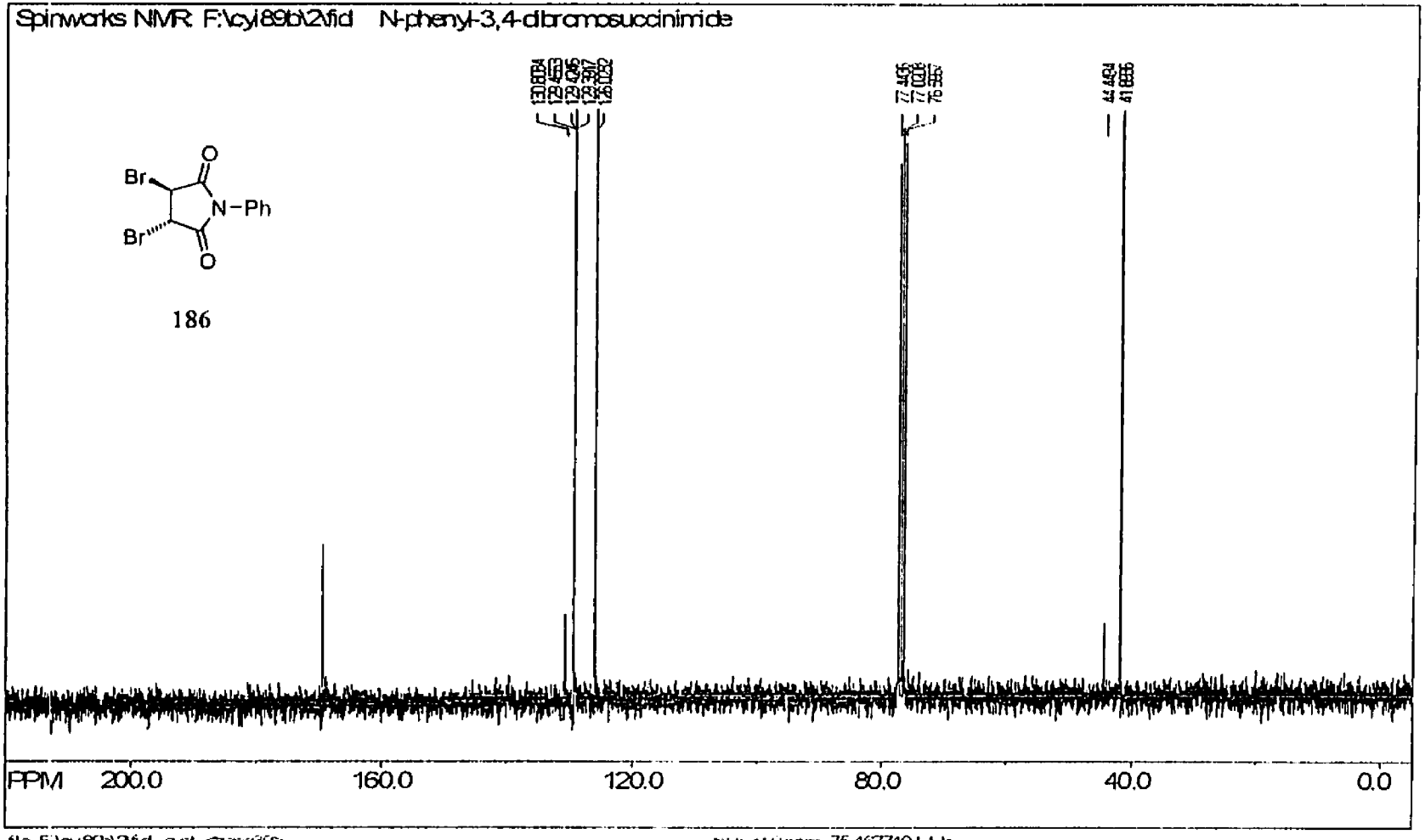

Spinworks NMR: F:\cyil109\1\fid Exomethylenedihydronaphthalene
8.3473
7.3816
7.1238
6.5410
6.4518
MeO
MeO
OMe
MeO
OMe
OMe
O
O
202
PPM
8.0
6.0
4.0
2.0
0.0
file: F:\cyil109\1\fid expt: <2d1d>
transmitter freq: 300.131653 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567092 ppm = 0.094189 Hz/pt
number of scans: 64
freq. of 0 ppm: 300.130006 MHz
processed size: 32768 real points
LB: 0.30 GB: 0.0000



186

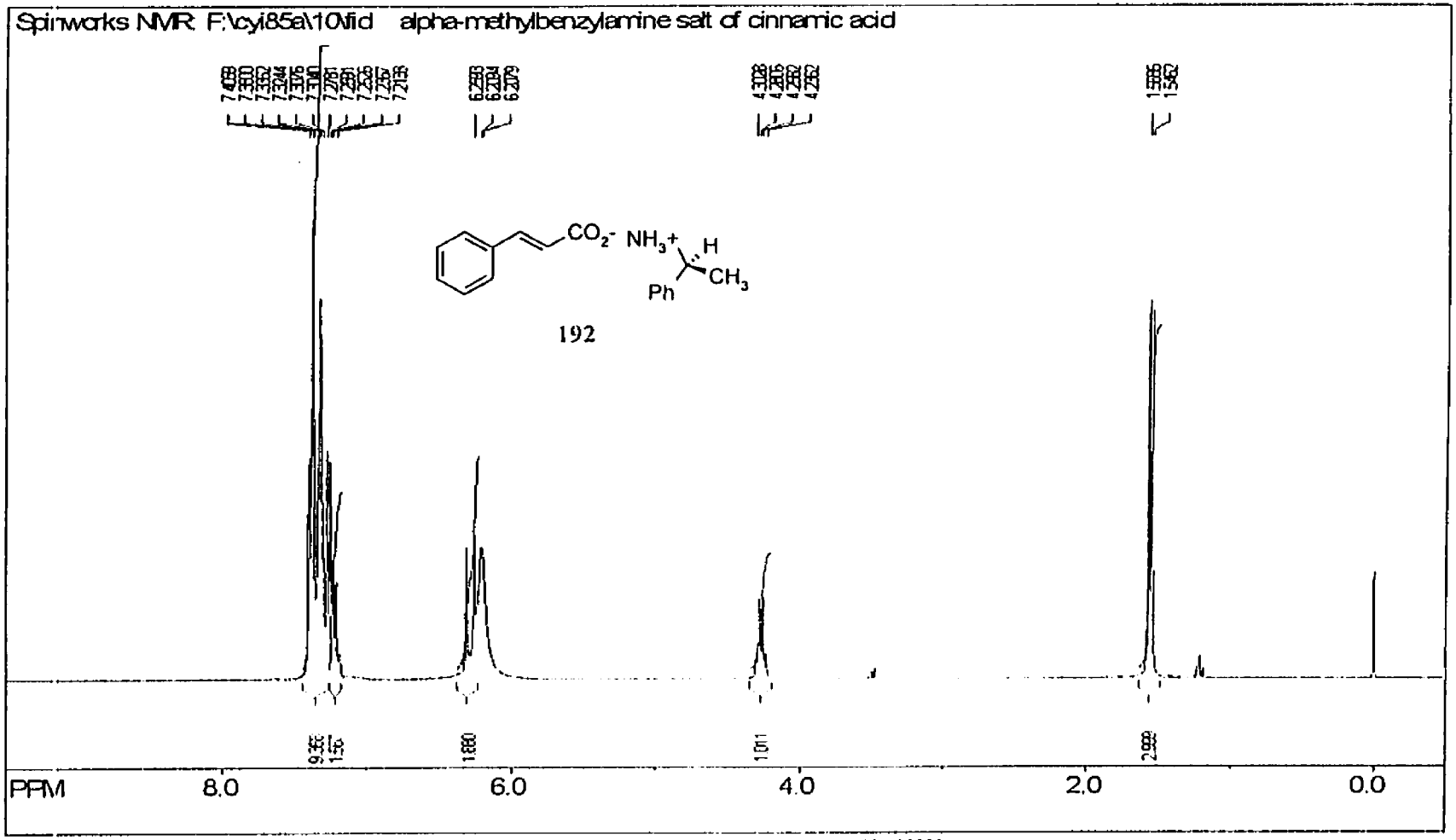
file: F:\cyi89b\1\fid expt: <zg30>
transmitter freq: 300.131853 MHz
time domain size: 65536 points
width: 6172.80 Hz = 20.567002 ppm = 0.094189 Hz/pt
number of scans: 16

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



file F:\cyl89b\2\fid exp: <zgpg30>
transmitter freq: 75.478020 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: 75.467749 MHz
processed size: 32768 real points
LB: 1.00 GB: 0.0000


Spinworks NMR: F:\cyi85a\10\fid alpha-methylbenzylamine salt of cinnamic acid
CO2- NH3+ H
CH3
Ph
192
9.355
1.560
1.880
1.011
2.989
PPM
8.0
6.0
4.0
2.0
0.0
file F:\cyi85a\10\fid exgt <zg30>
transmitter freq 300.131653 MHz
time domain size 65536 points
width 6172.80 Hz = 20.567082 ppm = 0.094164 Hz/pt
number of scans 16
freq. of 0 ppm 300.130006 MHz
processed size 32768 real points
LB 0.30 GB 0.0000