THE UNIVERSITY OF MANITOBA

FACULTY OF GRADUATE STUDIES

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Lignan Synthesis from 2,3-Dibenzylidenesuccinates

BY

Timothy S. Hooper

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

Of

MASTER OF SCIENCE

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Master of Science

Department of Chemistry

University of Manitoba

Winnipeg, Manitoba, Canada

Acknowledgements

There are many people and agencies that are responsible for the completion of this thesis. I would like to firstly thank the members of my examining committee, Dr. Schweizer, Dr. Court and Dr. Charlton for their time and effort during the examination process. I would like to further thank Dr. Charlton for his support and tireless work as supervisor throughout the time required to complete the research and to write this thesis. In addition, I thank Dr. Charlton, the University of Manitoba and the Natural Science and Engineering Research Council of Canada for kindly providing funding and financial support while I was working on this thesis

I would also like to thank current and former research colleagues who provided invaluable assistance throughout my time here. These people are: Brigette Yvon, Chi Yau, Dr. Probal Data and Dr. Tokoure Assoumatine. In addition, I would like to thank Terry Woliwiec, Wayne Buchanan and Dr. Kirk Marat for all their assistance in performing both NMR spectroscopy and mass spectrometry for this thesis.

Finally, I would like to thank my family and especially my parents, William and Heather Hooper for their guidance and support throughout my academic career and the many trying times throughout the research and writing process for this thesis.

Table of Contents

Abbreviations

[O]	Oxidation
$[\alpha]_D$	Optical Rotation
Ac_2O	Acetic Anhydride
Ar	Aryl
c	Concentration
COD	Cyclooctadiene
d	Doublet (spectral)
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHN	Dihydronaphthalene
DIBAH	Diisobutylaluminum hydride
DIEA	Diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
EI-MS	Electron-impact mass spectrometry
EOE	Ethoxyethyl
EtOAc	Ethyl Acetate
EtOH	Ethanol
HIV	Human immunodeficiency virus
HMBC	Heteronuclear Multiple-Bond Correlation Spectroscopy
HMPA	Hexamethylphosphoramide
HOAc	Acetic Acid
HPLC	High Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
hν	Light
iPrOH	2-propanol
J	Coupling Constant (in NMR)
LDA	Lithium diisopropylamide
m	Multiplet (spectral)
m/z	Mass to charge ratio (mass spectrometry)
Me	Methyl
MeOH	Methanol
(4S,5S)-MOD-DIOP	(4S,5S)-[(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]-bis[bis(4-methoxy-3,5-dimethyl)phenyl]phosphine
MsCl	Mesyl Chloride
NMR	Nuclear Magnetic Resonance
OAc	Acetate
OEt	Ethoxide
OMe	Methoxide
o-QDM	*ortho*-quinodimethane
Ot.Bu	*tert*-Butoxide
ppm	Parts per million (NMR)

PPTS	Pyridinium *p*-toluenesulfonate
q	Quartet (Spectral)
R	Generic alkyl group
s	Singlet (spectral)
t	Triplet (spectral)
t.BuOH	*tert*-butanol
TBAF	Tetrabutylammonium fluoride
TBTU	Benzotriazol-1-yl-1,1,3,3-tetramethyl uronium tetrafluoroborate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMSCl	Trimethylsilylchloride
TsOH	*p*-toluenesulfonic acid
UV-Vis	Ultraviolet-visible
Δ	Heat
μ	Micro

Abstract

In this thesis, the photochemical reactions of *E,E*-dibenzylidenesuccinates were studied and exploited for synthetic purposes. It was determined that a variety of symmetrical *E,E*-dibenzylidenesuccinate derivatives undergo photochemical cyclisation reactions to form both *cis*-1,2-dihydronaphthalenes and *trans*-1,2-dihydronaphthalenes. It was also determined that these reactions show a decided preference for the formation of *cis*-dihydronaphthalenes over *trans*-dihydronaphthalene products.

In order to extend the photochemical work for use in asymmetric synthesis, a chiral auxiliary was introduced into to the dibenzylidenesuccinate moiety in order to influence the population of the two atropisomeric forms of the dibenzylidenesuccinate. The (+)-ephedrine cyclic amide ester of the bis(3,4,5-trimethoxybenzylidene)succinic acid was successfully prepared after considerable work to optimize the reaction conditions. As predicted the amide ester proved to adopt a single atropisomeric form, and its subsequent photochemical cyclisation resulted in a single photochemical product being isolated with a *trans*-1*S*,2*R*-dihydronaphthalene configuration.

The absolute configuration of the photoproduct was confirmed by using it for the asymmetric synthesis of (+)-dimethyllyoniresinol. The synthesis was relatively straightforward, although some complications arose during the final functional group manipulations. The desired natural product was determined to have the correct absolute stereochemistry by comparing the sign of the synthetic material against that reported for an authentic sample. This confirmed that the chiral auxiliary-mediated photochemical reaction performed had yielded a *trans*-1*S*,2*R*-dihydronaphthalene configuration as predicted from molecular modelling.

Chapter 1

Introduction

Lignans are natural product that are derived from plant sources and are noted for having a diversity of structure and function. R. D. Haworth first used the term lignan in 1936 to describe natural products isolated from plants that consisted of a n-phenylpropanoid dimer linked at the beta carbons[1]. It has been noted that there are wide variations in the general structure of lignans, which make them of great interest and of great challenge to synthetic chemists. The mixed and varied stereochemistry of lignan natural products adds further complexity to this synthetic challenge. One further point of interest about lignans is that some classes exhibit atropisomerism, which is the hindered rotation about carbon-carbon single bonds. This property can provide lignans with a type of helical chirality, which is thought to be exploitable for the asymmetric synthesis of even more complex lignans.

The drive to develop methods for preparing lignans is largely fuelled by the intriguing biologic activity shown by many groups of lignans. A wide variety of lignan natural products, across many lignan classes, show biologic activity ranging from anti-tumour and anti-mitotic properties to antiviral and antifungal activity. As a result, there is currently a drive to develop lignan-based pharmaceuticals either by completely synthetic or semi-synthetic methods. This thesis in general will look at a series of methods used for the synthesis of lignans, ultimately ending in a method for the preparation of the lignan natural product (+)-dimethyllyoniresinol. The introduction will provide a brief overview of the structure and definition of lignans, as well as a look into

the biologic properties of lignans and the various synthetic methods that have been developed previously.

1.1 A Definition for Lignans

R. D. Haworth defined lignans in 1936 as follows: "Lignans form a group of plant phenols whose structure is determined by the union of two cinnamic acid residues or their biogenetic equivalents."[1] In more general terms, lignans are essentially two substituted

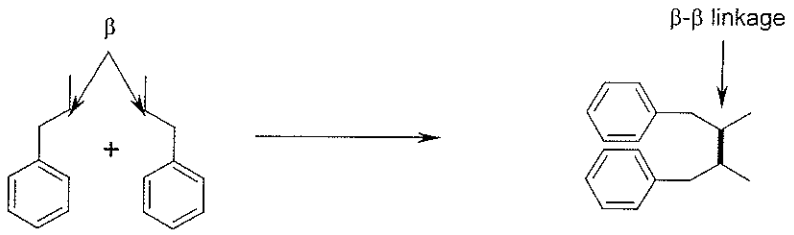


Figure 1

phenylpropane units that have been dimerized through a C_8-$C_{8'}$ linkage (also known as a β-β linkage) to form the basic lignan skeleton[2] (Figure 1). Compounds of this type are classical lignans and belong to the lignan class of dibenzylbutane lignans.

1.2 Lignan Structural Classifications

There are 13 general classes into which lignans fall. These classes generally encompass and distinguish between lignans that differ from each other through one of three basic changes to the classical lignan skeleton. The first of these differences is in the substitution patterns on the two phenyl rings in the molecule. At present, there are no naturally occurring lignans in which there is an unsubstituted phenyl ring present in the molecule; and there are very few lignans that have only a single substituent[3]. The nature of the phenyl substitution can be diversified through the location of the substituents on the phenyl ring (usually the 2-, 3-, 4- or 5-positions), by the number of substituents on the

ring (typically 2 or 3 substituents) and by the type of substituents (hydroxyl, 3,4,5-trimethoxy, 2,4,5-trimethoxy, 3,4-dimethoxy and 3,4-methylenedioxy are the most common)[3]. Current reviews[4-9] indicate that there are up to 15 differently substituted aryl groups that are found naturally in lignans, a remarkable testament to the incredible structural diversity of lignans. In addition, there are the possibilities of additional carbon-carbon or carbon oxygen linkages in the molecule that results in additional rings. The most common linkages include C_6-C_7, and C_6-C_6, linkages. These lead generally to the aryltetralin, arylnaphthalene and dibenzocyclooctadiene families of lignans. The final main structural variant is the level of oxidation in parts of the molecule. In the case of the aryltetralins, two-electron oxidation results in the aryldihydronaphthalene lignans, while further oxidation produces the arylnaphthalene family. In addition, further structural diversity occurs via a variety of possible side chains in the lignan, which range from alcohols to aldehydes and carboxylic acids and derivatives. In all, over 200 naturally occurring lignans have been catalogued belonging to the 13 main classes[10] (Figure 2). The most common classes are the dibenzylbutanes (**1**), dibenzylfurans (**2**), dibenzylbutyrolactones (**3**), aryltetralins (**4**), aryldihydronaphthalenes (**5**), arylnaphthalenes (**6**) and dibenzocyclooctadienes (**7**). Most of the other classes (**8-13**) contribute only a small number to the impressive diversity of natural lignans.

Somewhat related to lignans is the neolignan family. These are generally described as being phenylpropanoid dimers, but lack the β-β linkage of "true" lignans[11]. As a result of this structural difference, it is thought that there is a fundamental chemical difference between the two groups of compounds. Whether this is in fact true or not is still a matter of some dispute. However, it is known that the neolignans have much more diversity in

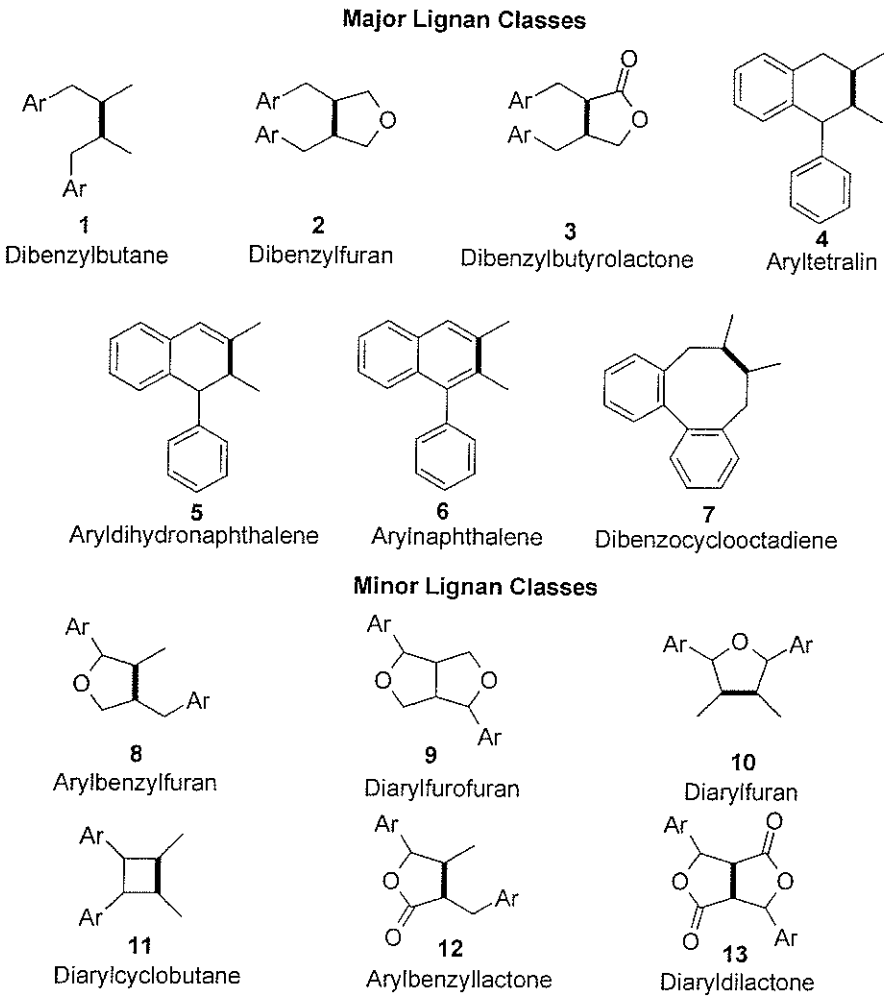
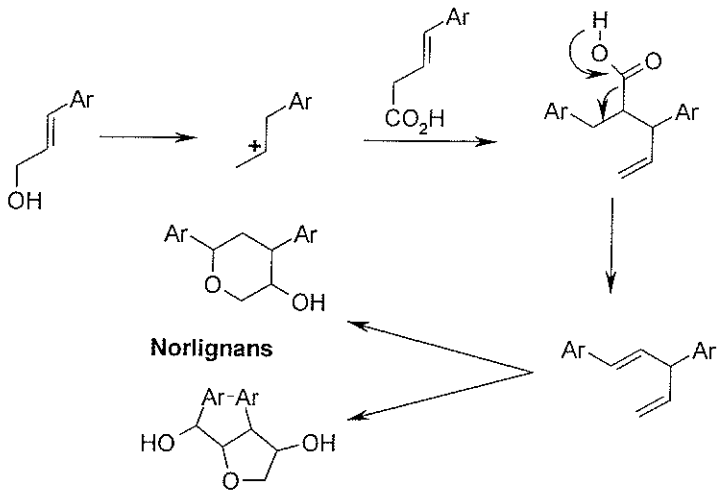


Figure 2

structure, due to the large number of ways that the two phenylpropane units can be linked up (either directly or through side chains). It should also be pointed out however, that neolignans are far less common in nature than are classical lignans and for the most part have only been isolated from two families of plants, namely the *Magnoliales* and *Piperales* families.

Also related are norlignans, which are noted for only having 17 carbons as opposed to classical lignans, which are C_{18}. Norlignans are lignans that are biosynthesized in a manner that is analogous to that of classical lignans, except that they undergo decarboxylation during the formation of the phenylpropanoid dimer[7,12] (Scheme 1). This

class of lignans has only really come to light in the past ten to fifteen years and not much is known about their general properties and uses.



Scheme 1

In all classes of lignans, neolignans and norlignans, a common system of nomenclature has proven to be elusive. Currently an IUPAC committee is studying ways to standardize the naming of these compounds, although nothing is officially in place. Trivial names are very widespread in the field, and many names are conventionally derived from the originating plant species. Where appropriate, this convention will be followed throughout this introduction and thesis.

1.3 Lignans From Natural Sources

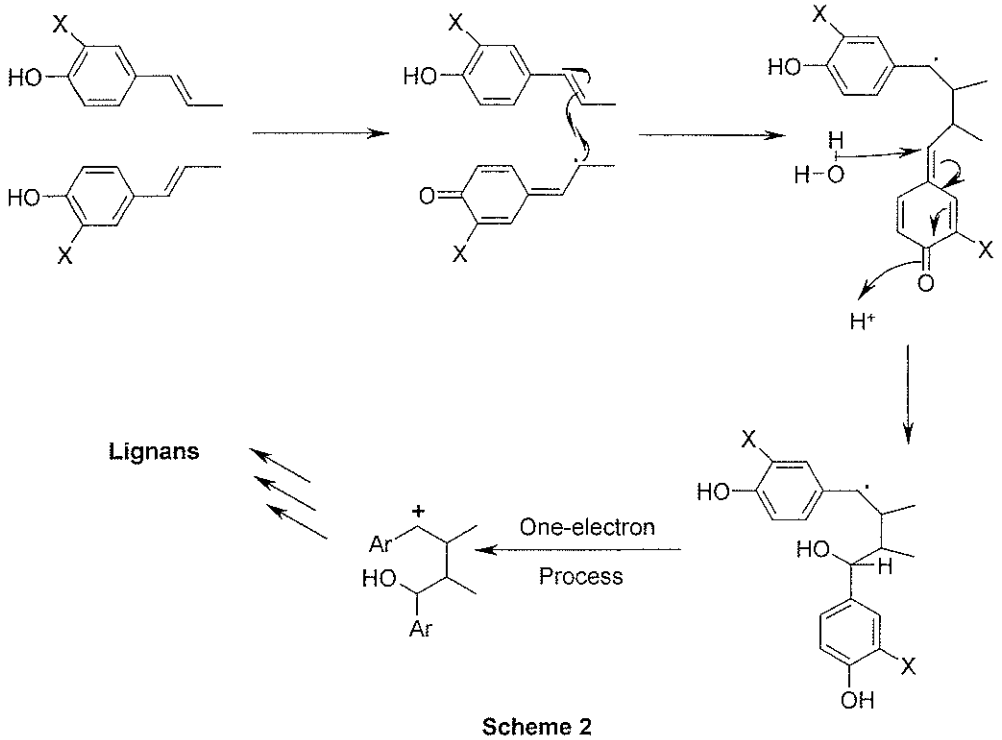
Lignans are primarily considered to be natural products that are derived from plant sources. There are however some lignans that have been only isolated from certain specific species of mammals. These lignans therefore have been termed as "mammalian lignans"[2]. Little is known about their importance in mammalian biochemistry. Current theories of this will be examined. The general origins and biosynthesis of many lignan classes are still largely unknown, and subject to much conjecture and controversy. Much work has been done and is proposed in the future to investigate this area. The location of

lignans in plants and their sources will be described, as will some of the best modern theories about lignan biosynthesis.

1.3.1 Lignans Derived From Plants

In general, lignans are derived as plant natural products. Lignans have been extracted from most parts of plants and trees, but the most common point of origin for lignans includes the wood and bark of trees and shrubs, as well as the roots, resin, leaves, flowers and seeds of all types of plants, trees and shrubs[10].

The general biosynthetic pathway of lignan natural products is still only partially understood. The mostly widely held theory is that the basic lignan structure is formed through a proposed phenolic oxidative coupling of two phenylpropanoid dimers (C_6-C_3 units). These processes are typically represented as being free-radical mediated, or involving some other two-electron process. These processes are shown in Scheme 2, and are generally thought of as being somewhat analogous to those present in lignin biosynthesis. The only problem with the theory presented above is that it is expected that any free-radical process would produce racemic products, as is seen in lignin synthesis; while lignans are typically biosynthesized as pure stereoisomers. It is now thought that lignan biosynthesis is achieved through an enzyme-mediated free-radical process[13], similar to that shown in Scheme 2.



Scheme 2

One major hurdle in the understanding of the biosynthesis of lignans is how the various phenyl substituents are built up in the molecule. The most widely held theory was that the substituent pattern was built up on the phenylpropanoid monomer prior to the oxidative coupling[13]. After a study by Jackson and Dewick however, it is now thought that the coupling reaction occurs first, followed by the build-up of the phenyl substituents[13,14]. In their experiment, Jackson and Dewick attempted to synthesise podophyllotoxin (**14**) from extant plant roots from the *podophyllum* family using carbon-14 (β-position) labelled substrates. The substrates used were cinnamic acid (**15a**), ferulic acid (**15b**), 3,4-methylenedioxycinnamic acid (**15c**), sinapic acid (**15d**) and 3,4,5-trimethoxycinnamic acid (**15e**) (Figure 3). As the podophyllotoxin structure contains both the 3,4-methylenedioxy and 3,4,5-substituted phenyl moieties, it was expected that the most predominant substrates to be found in the biosynthesized podophyllotoxin would be 3,4-methylenedioxycinnamic acid and either sinapic acid or 3,4,5-

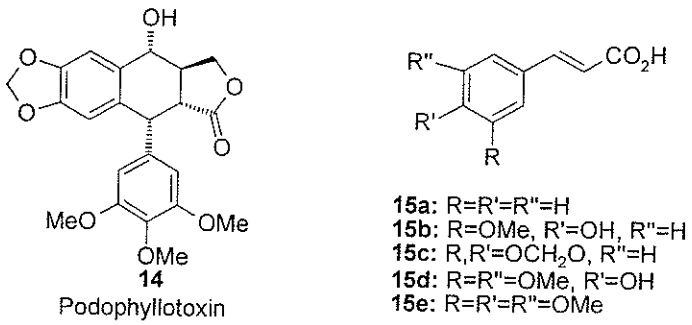


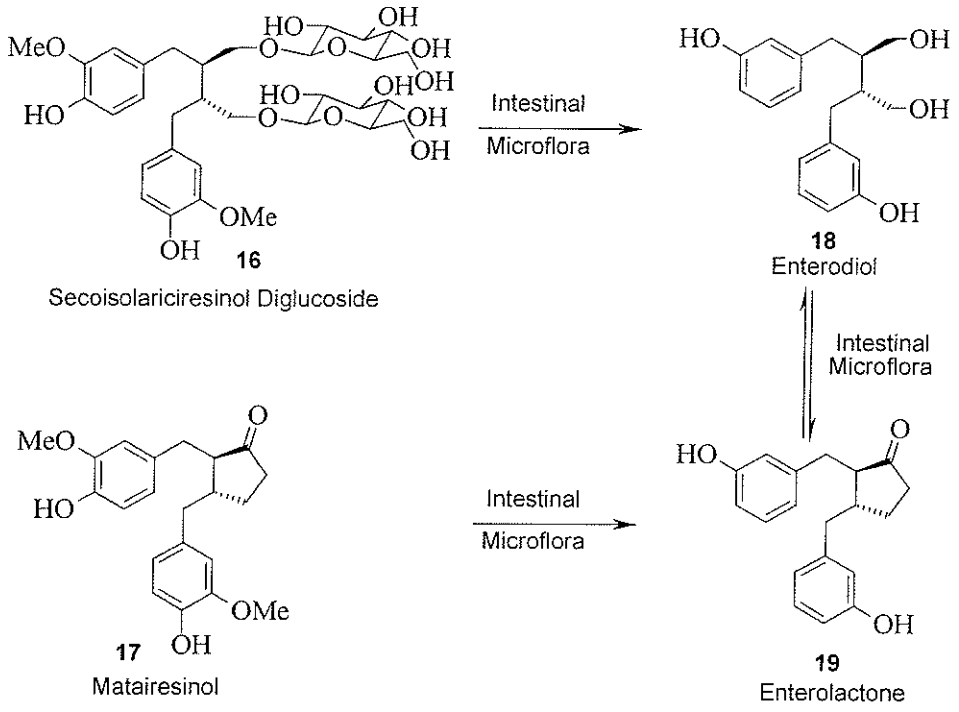
Figure 3

trimethoxycinnamic acid as they had the correct substituent patterns for assembling podophyllotoxin. It was thus somewhat surprising when their analysis showed that only cinnamic acid, ferulic acid and 3,4-methylenedioxycinnamic acid were incorporated into the molecule. The lack of incorporation of the 3,4,5-substituted acids would seem to imply that the pendant aryl group is built up after the couplings forms the basic podophyllotoxin skeleton. It also appears that podophyllotoxin is synthesized in nature from ferulic acid-type substrates and then modified to yield the correct overall structure. It is also assumed that this is a general process for the biosynthesis of most complex lignans and serves to underscore how poorly understood the field of lignan biosynthesis really is.

1.3.2 Mammalian Lignans

In recent years, analysis of urine, blood and bile samples from a number of mammals (namely humans, baboons, vervet monkeys and rats) have resulted in the discovery of two lignans[15-17]. These two lignans are enterolactone (**19**) and enterodiol (**18**) and are notable for the presence of a 3-position hydroxyl substituent on both phenyl rings, a substitution pattern found in no natural plant lignan. As a result, these lignans have been termed "mammalian lignans" as they have not been detected in any plant source.

Studies on these two lignans have shown that they probably originate from secoisolariciresinol diglucoside (**16**) and matairesinol (**17**) (Scheme 3). These two precursors are known to be found in a variety of fibre sources and it is thought that they are converted into the mammalian lignans through the metabolic activity of intestinal microflora[2]. These bacterial enzymes have been studied and been identified as being from the Clostridia group of digestive microorganisms.



Scheme 3

Recent advances in blood and urine analysis have allowed for a more detailed study of these lignans. GC-MS analysis has determined that the levels of enterolactone in human and baboon urine approach the level of steroid metabolites, and are near 800 times the level of total urinary estrogens[18]. That these amounts are close to that shown for steroid metabolites is seen as good confirmation that mammalian lignans are formed from digestive action on plant-based sources of dietary fibre. Further confirmation was achieved when it was determined that vegetarians and those on high-fibre diets had

mammalian lignan concentrations that were substantially higher than those in humans with omnivorous eating habits.

Mammalian lignans have been of some interest recently as a result of a study that showed that female urine analysis showed cyclical variations in the amounts of lignan present during the menstrual cycle. It was shown that peak amounts were detected during the luteal phase of the cycle and throughout the nine-month pregnancy period. Although it is thought that mammalian lignans have no impact on human biochemistry due to their presence as a metabolic by-product, this study would seem to imply that mammalian lignans may in fact have some sort of impact on the level of certain hormones in the body. Indeed, Axelson *et al.* have demonstrated that there is an enterohepatic route of circulation of the mammalian lignans in the body and that enterolactone and enterodiol interconvert through enzyme oxidation-reduction processes in the body[17]. It is now thought that there may be possible biochemical roles for the mammalian lignans in humans. It is obvious that further study is required in this area.

1.4 Medicinal and Biologic Properties of Lignans

Perhaps the most interesting and intriguing aspect of lignans and their role in biochemistry is the wide and varied biologic properties that lignans exhibit. Studies into various plants used in traditional folk remedies have resulted in the detection of many lignans as major constituents of the plant source and as the active ingredient in the remedy. As a result, interest in lignans for their biologic properties developed and has continued to grow to modern times. There are numerous literature reviews[3,10,19,20] available that outline the various biological activities of lignans. The main biologic activities of lignans cover the areas of anti-tumour, anti-mitotic and anti-viral properties,

which will be covered below. Other interesting properties include anti-fungal and anti-bacterial activity, which has led to lignans being used extensively as preservatives in industry and foodstuffs and as a stabilizing agent for adhesives, lubricants and plastics. In addition, some classes of lignans have been discovered to have substantial inhibitory effects on a variety of cellular enzymes and possibly on nucleic acid transport mechanisms, some of which will be discussed as part of this section.

1.4.1 Lignans in Folk Medicine

The use of lignans for medicinal purposes dates back almost 2000 years to East Asian culture, with accounts being found in both Chinese and Japanese records[21]. The first Western account dates to *circa.* 1000 in England where a salve consisting of 4-deoxypodophyllotoxin was used to treat certain cancers[22].

Independent of these uses was the use of podophyllotoxin extracts from *Podophyllum peltatum* in Native American culture for the treatment of poisonous snakebites and as a poison for arrows in times of war[23]. Colonial Americans used extracts of *P. peltatum* as a purgative[23,24]. Even in modern times, the lignan derived from the extract (Podophyllotoxin) was present in the U.S. Pharmacopeia until 1942 when it was removed due to its severe gastrointestinal toxicity.

Although not scientifically tested, the extracts of several plant products have been used, and continue to be used, in a variety of Asian cultures; especially in rural and more traditional areas where modern medicine has not yet become commonplace. An extract of *Kadsura coccinea* has been in use for much of the past century as a folk remedy in Japan for the treatment of gastric ulcers and rheumatoid arthritis[25]. Similarly, both the Chinese and Japanese have used an extract of *Fraxinus japonica* as a diuretic, analgesic

and as an antirheumatic agent[26]. It has been through an analysis of these traditional folk remedies that the modern interest in lignans as medicinal agents has been derived.

1.4.2 Anti-tumour Properties of Lignans

As a result of the discovery of a link between lignans after their discovery in 1936, and the active agents in folk remedies, there has been much interest in uncovering more detailed medicinal properties for lignans. A study performed shortly after the introduction of the lignan class of compounds showed that alcoholic extracts from two *Podophyllum* species resulted in the isolation of a class of aryltetralin lignans with the same basic structure[23] (Figure 4). This class is generally known as the podophyllotoxin

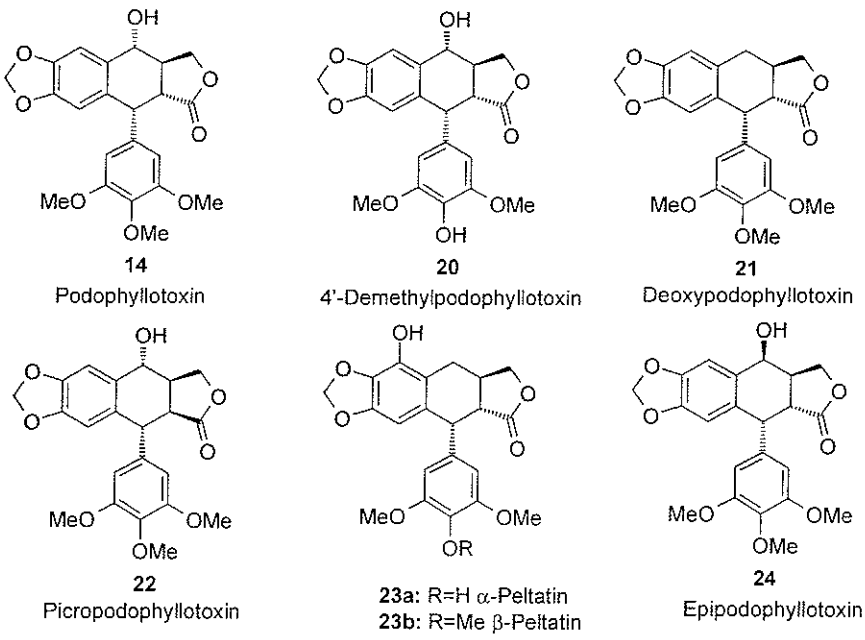


Figure 4

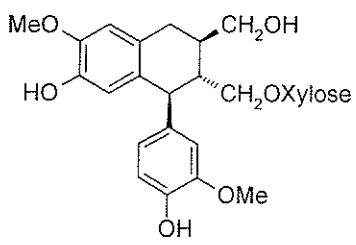
family and is named for the best known of the group, which is podophyllotoxin (**14**). When studies where done on this class of compounds, it was discovered that they were very effective against cancer cell aggregates in both humans and in animals[23].

When it was discovered that the podophyllotoxin group of lignans were effective against cancer cells, many studies were done to determine the structure-activity

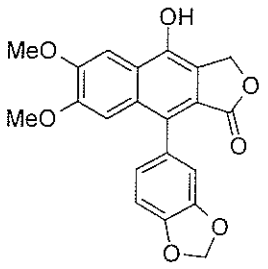
relationship for these compounds in order to maximize their effectiveness[27]. It was hoped that a coherent set of structure rules could be determined that would enable the development of synthetic or semi-synthetic derivatives of podophyllotoxin for use in cancer treatment. Unfortunately, none of these studies resulted in the exact determination of an overall optimum molecular structure[27]. Three main features were however determined. The first of these is that the configuration of the C-4 position is of paramount importance. The only difference between podophyllotoxin (**14**) and epipodophyllotoxin (**24**) is the C-4 configuration ("down" versus "up" respectively), but epipodophyllotoxin is less effective by a full order of magnitude that podophyllotoxin. The second major discovery was that the C-4 hydroxyl is rather redundant in how it effects the activity of the molecule towards cancer cells. Deoxypodophyllotoxin (**21**), which lacks the C-4 hydroxyl, is surprisingly almost as effective as podophyllotoxin in terms of anti-tumour activity. Moving the hydroxyl group to the 3,4-methylenedioxyphenyl ring at the 5-position as in β-peltatin (**23b**) results in a compound that is even more effective than podophyllotoxin. The third main structural theme was the formation of a derivative of the hydroxyl group. When the hydroxyl in β-peltatin was converted to a methoxy group, the effectiveness of the compound as an anti-tumour agent was greatly reduced. The addition of glucopyranoside to podophyllotoxin to form podophyllotoxin β-D-glucopyranoside resulted in a very drastic reduction in the effectiveness of podophyllotoxin against cancer cell aggregates. A possible fourth factor identified was the configuration at the C-2 position, but no real conclusions were drawn due to the lack of a large survey of compounds. Picropodophyllotoxin (**22**) differs from

podophyllotoxin at this position and was found to be much less effective than podophyllotoxin.

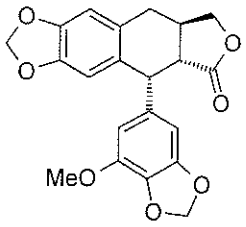
Although the aryltetralin class of lignans is the one that is most often identified with the anti-tumour activity of lignans, they are not the only class that shows this activity. In addition to the podophyllotoxin family, there are some 35 other natural lignans that have been shown to exhibit anti-tumour properties, although to a much lesser extent than the podophyllotoxins[28-33]. Some of these compounds are shown in Figure 5. Looking at these compounds (**25-30**), one is tempted to look for an underlying structural similarity. A common feature of many of these compounds and the podophyllotoxins is the presence of the 3,4-methylenedioxy group, but looking at (+)-dimethylisolariciresinol-2α-xyloside (**25**) shows that this is obviously not a major requirement. The presence of lignans from the arylnaphthalene and dibenzocyclooctadiene classes in the diagram, plus knowledge that aryldihydronaphthalenes and benzylbutyrolactones are also effective shows that there is nothing special about the aryltetralin class when it comes to lignan activity as anti-tumour agents. The sheer diversity of structure would seem to imply that there is no unifying structural feature and that there may be a variety of active sites and modes of action through which lignans can exercise their anti-tumour activity.



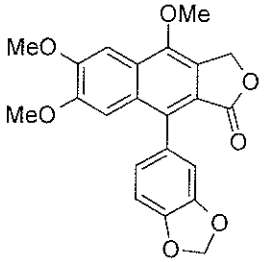
25
(+)-Dimethylisolariciresinol-2α-xyloside



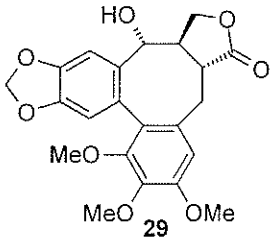
26
Diphyllin



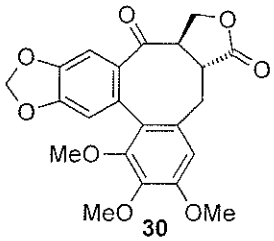
27
Austrobeilignan-1



28
Diphyllinin



29
Steganol



30
Steganone

Figure 5

Further complicating matters is the possible effects of mammalian lignans on cancer cell growths[34,35]. In some studies, the two mammalian lignans, enterolactone and enterodiol have been implicated as possibly having an anti-tumour effect. Studies have shown that women currently suffering from breast cancer have mammalian lignan levels that are significantly lower than those in women with no prior history of breast cancer. The implications of this result are likely twofold. Firstly, it would appear that there is a likely anti-tumour application of the mammalian lignans in the case of breast cancer and secondly, that women who eat a diet rich in plant-based fibre should have a lower incidence of breast cancer. Further work has now also implicated mammalian lignans as

having an anti-tumour activity towards prostate cancer in men. More study into this area is currently underway to determine a more exact link between these two types of cancer and the levels of mammalian lignans in the body.

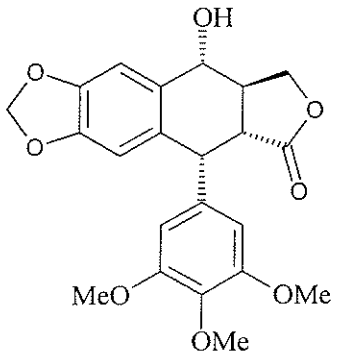
1.4.3 Lignans and the Inhibition of Tubulin Polymerization

Another major biologic effect of some lignans is their ability to inhibit the formation of microtubules in cells. Microtubules are cell components that give structural rigidity to the cell and are also very important during cell replication. They can be thought of as forming from polymerization of the proteins α- and β-tubulin and tubulin and microtubules coexist in a carefully controlled equilibrium in the cellular cytoplasm.

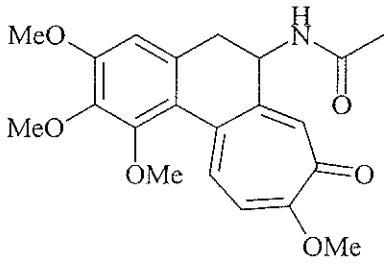
It has been shown that, *in vitro,* podophyllotoxin inhibits the polymerization of tubulin into microtubules in a concentration-dependent manner[27]. This discovery was soon followed by the further discovery that podophyllotoxin also exerts influence on microtubule assembly *in vivo*. *In vivo*, podophyllotoxin greatly disrupts the equilibrium between microtubules and tubulin monomers. This results in the gradual disassembly of the extant microtubules into tubulin and the disintegration of the cytoplasmic cytoskeletal framework and in the spindle fibres, resulting in cellular death. Moreover, by attacking the spindle fibres, podophyllotoxin prevents the separation of the cell's duplicated chromosomes during cell division. As a result, the cell cycle is stopped at the mitotic stage and cell death invariably ensues.

Another well-known tubulin inhibitor is colchicine (**31**), whose structure is given in Figure 6. It has been shown that podophyllotoxin-type lignans compete for the colchicines-binding site on tubulin[10,36]. Indeed, podophyllotoxin is almost twice as effective as an anti-mitotic agent as colchicine is. Due to the similarity in structure with

the 3,4,5-trimethoxyphenyl moiety, it was originally thought that both colchicine and podophyllotoxin competed for the same binding site. Consideration of kinetic studies showed that the binding of podophyllotoxin and colchicine differed somewhat from each other. Podophyllotoxin shows rapid and reversible binding to tubulin and is not affected much by temperature. By comparison, colchicine binds slowly and irreversibly to tubulin and the binding is very temperature sensitive. This result has now led to speculation that podophyllotoxin and colchicine occupy closely overlapping binding sites[37]. It is thought that there are three points of contact on tubulin; one specific for podophyllotoxin, one specific for colchicine and one that accepts the 3,4,5-trimethoxyphenyl moiety of either compound[10].



14
Podophyllotoxin



31
Colchicine

Figure 6

As in the case of lignan anti-tumour activity, structure-activity relationships were done to determine the most effective lignan anti-mitotic agents[36,38,39]. There were many findings, some of which will be summarised here. Introducing a glucose-derivative on the 4-position hydroxyl greatly reduced the anti-mitotic activity, a factor that will be elaborated in the next section. In general, the study showed that there are certain similarities between anti-tumour and anti-mitotic activities of these compounds, which would imply similar modes of action. The main structure-activity relationship elucidated

was that the lactone ring was absolutely critical to the activity of the molecule. Replacing the lactone moiety with a furan ring resulted in the activity falling off several-fold. Changing to a carbon (i.e. a cyclopentyl group) resulted in a ten-fold loss of activity. Changing to a sulfur atom decreased activity twenty-fold, while a sulfone moiety showed absolutely no anti-mitotic activity[10].

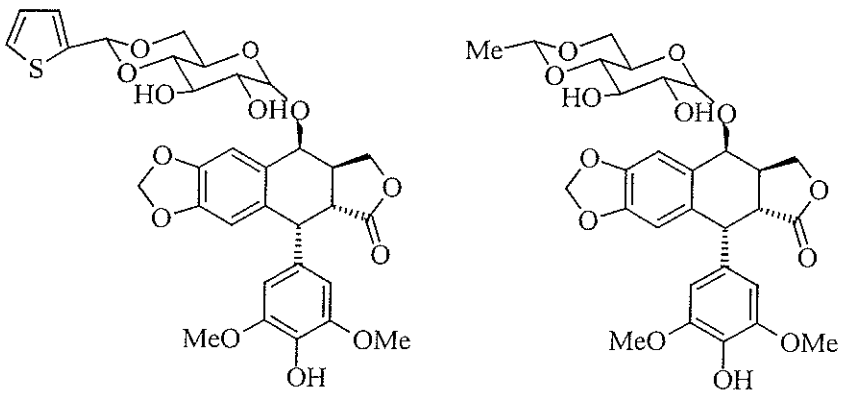
1.4.4 Teniposide and Etoposide – Lignan-Based Pharmaceuticals

One of the main drawbacks of using podophyllotoxin as an anti-tumour or anti-mitotic agent is that it is not very selective in its mode of action. As a result, it is observed that the podophyllotoxin-type lignans kill both healthy and cancerous cells indiscriminately. As was noted in the previous two sections, glycosylation of the 4-position hydroxyl group results in much lower activity for the resulting compound for both anti-tumour and anti-mitotic purposes[38]. This has been further extended in the case of two pharmaceuticals that have been derived from podophyllotoxin, namely teniposide (**32**) and etoposide (**33**) (Figure 7). These two compounds are semi-synthetic derivatives of epipodophyllotoxin that have strong anti-tumour activity despite the glucopyranosyl-groups at the 4-position hydroxyl group. However the anti-tumour activity is not due to tubulin binding as the carbohydrate moiety prevents teniposide and etoposide from accessing the tubulin active site.

It is now known that teniposide and etoposide act through their interference in cellular DNA replication. This effect is largely exerted through the inhibition of the key topoisomerase II enzyme[40-42]. It is also known that both teniposide and etoposide induce breaks in both single and double-stranded DNA under both *in vitro* and *in vivo* conditions. The topoisomerase II enzyme has a number of important cellular roles,

including DNA replication, DNA transcription, the resolution of DNA strands in newly replicated molecules and the segregation of chromosomal material at the conclusion of replication. This role is performed by cutting DNA at the 5'-ends with a 4 base stagger. Topoisomerase then becomes linked covalently to the DNA strands and replication ensues naturally. When the replication is complete, the enzyme releases the strands and allows them to recombine to form regular double-stranded DNA.

Teniposide and etoposide work by interfering with this process. In general, they both help to stabilize the topoisomerase II-DNA complex and trap it in that state. This



32 Teniposide **33** Etoposide

Figure 7

prevents proper replication of the DNA strands and completely prevents the strands from rejoining to form the expected double-stranded DNA. Essentially, this prevents the process of cellular replication and basically leads to massive cell death in the affected area.

These compounds are substantially less cytotoxic than podophyllotoxin-analogues, yet work much more effectively as anti-tumour agents. The prime reason for this selectivity is that they act primarily on the topoisomerase II enzyme and not through any other mechanism to any great extent. In addition, tumour cells often experience rapid

cellular division and replication. As a consequence, they contain substantially more topoisomerase II enzyme and as such are preferentially selected by teniposide and etoposide for action. This is the essential basis for the observed selectivity for teniposide and etoposide towards tumour cells in preference to healthy cells[10].

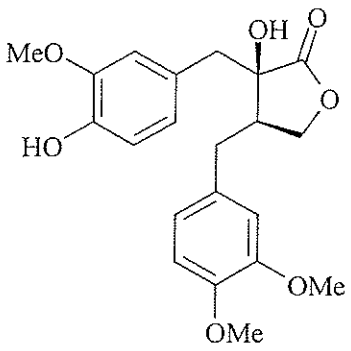
As a result of the selectivity and effectiveness of these drugs, more structure-activity studies have been performed[40-43]. The essential points noted were that demethylating the 4'-position improved the effectiveness of the pharmaceutical. In addition, epimerisation of the 4-position to the "up" position also resulted in increased selectivity and overall activity. The main factor was that the 4-position must be subjected to 4-D-glycosylation in order to maximize the effect and that the glucose moiety should have a 6-O-substituent[10].

1.4.5 Lignans as Anti-Viral Agents

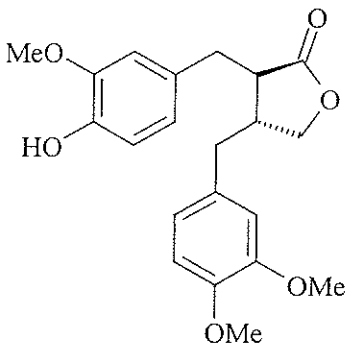
In addition to all of the biological effects previously noted for the podophyllotoxin family, it has also been noted that several of the compounds in the family also show antiviral effects. Perhaps the first of these to be discovered was that of podophyllotoxin itself. Podophyllotoxin has been shown to be effective, along with the analogues deoxypodophyllotoxin, picropodophyllotoxin and α-peltatin, in the treatment of herpes simplex virus I and in the treatment of venereal warts (podophyllotoxin only)[44]. These two viral infections are considered to be a major public health concern as they have been implicated in the onset of cervical cancer in women. In addition, extracts of *Podophyllum peltatum* have been shown to be useful against influenza A, herpes simplex virus II, vaccinia virus and measles[45].

Unfortunately, not a lot is really known about how podophyllotoxin analogues perform their anti-viral activity. The most likely hypothesis is that they act through microtubule inhibition as described previously[10]. This has been largely confirmed as a result of structure-activity studies that showed roughly the same trends and results for anti-viral activity as are shown for anti-mitotic activity of these lignans. In some cases, the structure-activity studies for the two effects were shown to be different, which implies that there could well be more than one mode of action for the anti-viral activity observed.

An example of this is shown by the benzylbutyrolactone lignans (-)-trachelogenin (**34**) and (-)-arctigenin (**35**) (Figure 8), which are both isolated from *Ipomoea cairica*. These are examples of non-aryltetralin lignans that show roughly the same anti-viral activity as podophyllotoxin analogues. These two compounds are effective in preventing the *in vitro* replication of HIV-1 and are thought to operate through the same topoisomerase II inhibition by which teniposide and etoposide work[9]. As shown, there is still much work to be done to fully understand the details of this and other lignan biological activities.



34
(-)-Trachelogenin



35
(-)-Arctigenin

Figure 8

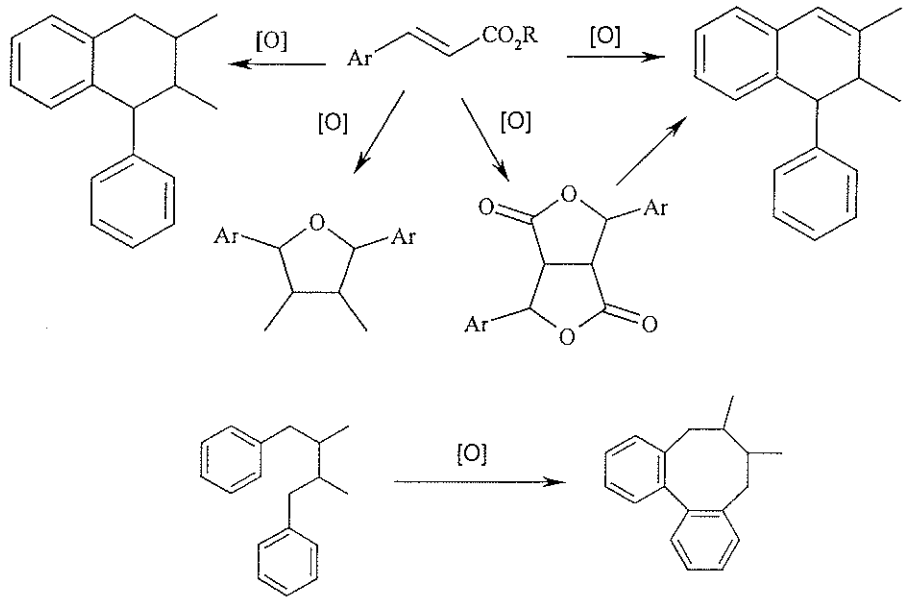
1.5 Methods of Lignan Synthesis

As has been noted previously, there is an enormous degree of structural diversity present in lignan natural products, to say nothing of purely synthetic lignan analogues. As a result, there are many approaches possible for performing lignan synthesis. Many reviews[3-9,46-49] have been published in the modern chemical literature that presents some of the techniques that have been used. As mentioned under lignan biosynthesis, the exact stereochemistry of lignans and the enormous impact that that feature can have on biological effectiveness makes them even more synthetically challenging. Modern lignan synthesis is primarily focused on the dual problems of preparing biologically interesting lignans and in the asymmetric synthesis of a variety of lignan natural products.

The general lignan skeleton is very similar, regardless of which class of lignan is being considered. As a result, the number of reactions and reaction-types that are used to build up the basic C_{18} skeleton is somewhat limited and are generally of a very fundamental nature. As mentioned previously, the major cause of the diversity between lignans is due to the variety of side chain substitution that is possible. These side chains are created primarily through a small group of reactions that are also quite fundamental and can generally be considered to be simple functional group interconversions.

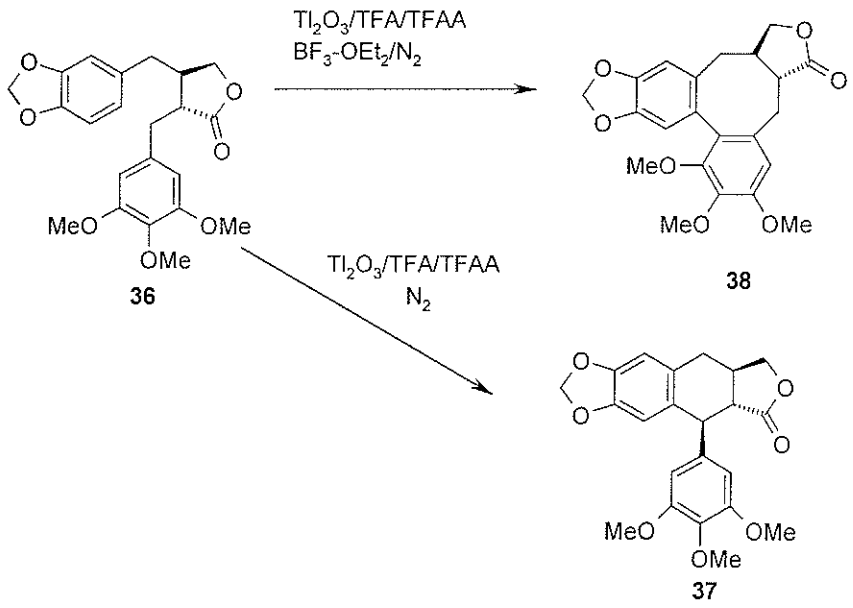
1.5.1 Lignans From Oxidative Coupling Reactions

One of the main interests in using oxidative coupling reactions is that they are excellent techniques for building the entire lignan skeleton. This is hardly surprising, considering that lignan biosynthesis is widely considered to be accomplished through the phenolic oxidative coupling of cinnamic acid residues. In general, many classes of lignans can be formed directly from phenylpropanoid units by oxidative coupling reactions (Scheme 4). However, these classes are relatively minor in their overall importance to lignans and their activities as a whole. As a result, the focus of this section will be on the formation of the more important classes of aryltetralins, arylnaphthalenes and dibenzocyclooctadienes through a variety of oxidative coupling methods.



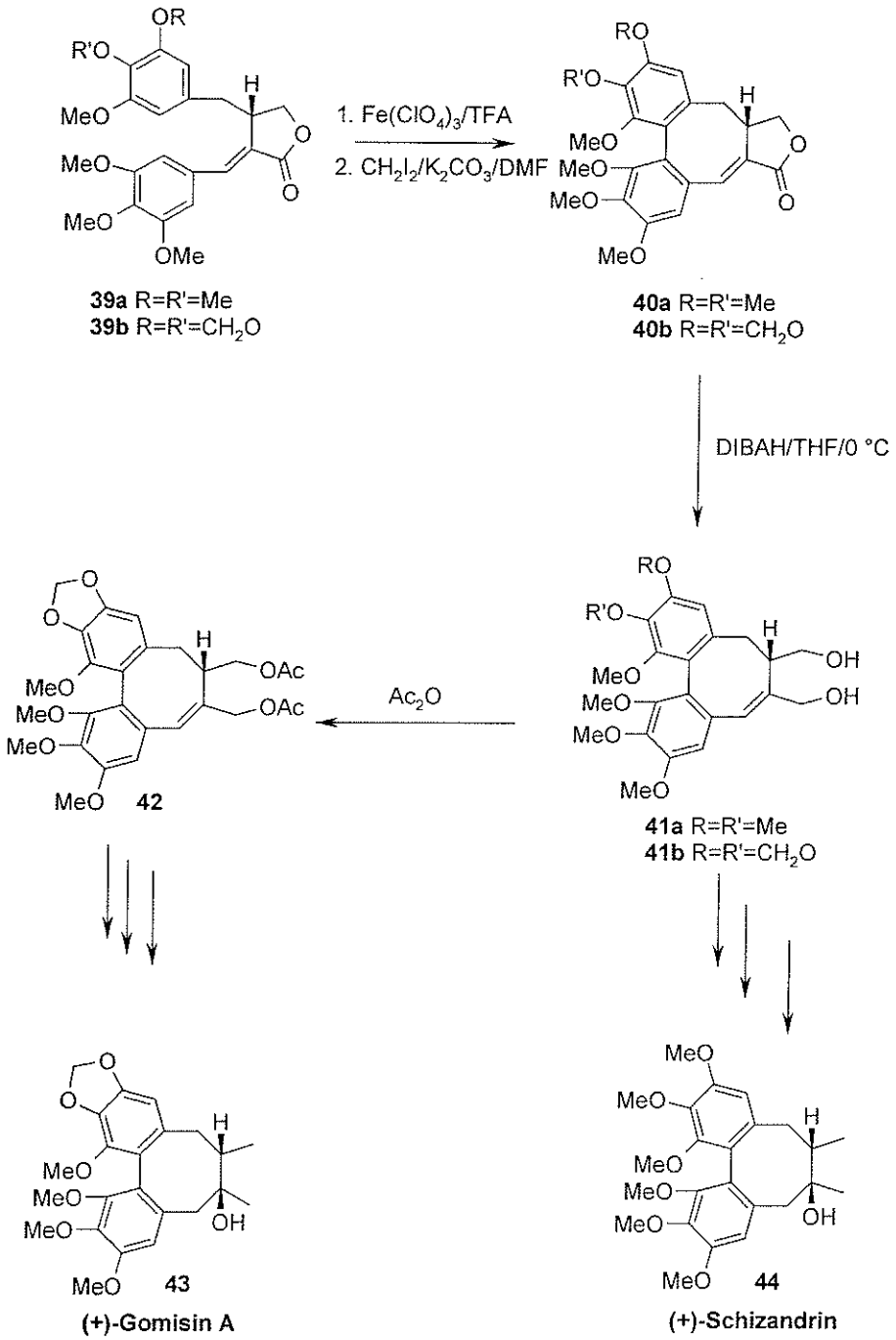
Scheme 4

The literature shows that the most common synthetic use of the oxidative coupling reaction is to form either aryltetralin lignans or to form dibenzocyclooctadiene lignans. These reactions have been performed using a wide variety of oxidizing agents. Robin *et al.* demonstrated that a series of metal oxidants could be used to perform the transformation of dibenzylbutyrolactones (**36**) into either aryltetralins (**37**) or into benzylcyclooctadienes (**38**)[50]. It was discovered in this case that changing the auxiliary reagents had a large effect on the stereochemical path of the coupling. The oxidations were performed with any of $Fe(OH)(OAc)_2$, Tl_2O_3, $Mn(OAc)_3$ or $Ce(OH)_4$ in the presence of either TFA or pentafluoropropanoic acid and TFAA. Depending on the required final structure, boron trifluoride etherate was also added. It was discovered that not adding the BF_3 complex resulted in the formation of aryltetralin products, while including BF_3 in the reaction mixture resulted in the formation of dibenzocyclooctadiene products (Scheme 5).



Scheme 5

Wakamatsu et al. used techniques similar to those of Robin *et al.* in their synthesis of optically pure (+)-gomisin A (**43**) and (+)-schizandrin (**44**)[51]. In this case, they used a different iron(III) oxidant, $Fe(ClO_4)_3$. It was discovered that using only iron (III) perchlorate resulted in no control over the regiochemistry of the coupling, (46% and 8%



Scheme 6

of the two isomers), and that a two-step process was required in order to control the regiochemistry. The first step involved the addition of iron (III) perchlorate and TFA in dichloromethane, followed by CH_2I_2, K_2CO_3 and DMF. Subsequent reactions converted the intermediates to (+)-gomisin and (+)-schizandrin in optically pure forms (Scheme 6).

Another oxidizing agent that has found wide acceptance for performing phenolic oxidative coupling is ruthenium (IV) oxide dihydrate. Robin *et al.* performed a series of investigations on a variety of dibenzocyclooctadiene precursors (**45**) to determine the optimum reaction conditions[52]. The acknowledged standard conditions for these coupling reactions are to conduct them in aprotic solvents using fluoro acids, (typically a mixture of TFA and TFAA) and boron trifluoride etherate. In this study, it was discovered that using the reagent pair of triflic acid and triflic anhydride worked in roughly the same yield but in only one-sixth the time required for the TFA/TFAA reaction (Scheme 7). It was also observed that coupling invariably occurs on the phenyl position *para* to an oxy-substituent. It is thought that the coupling reaction occurs through a phenoxy radical and calculations show that the greatest electron density is on

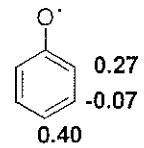
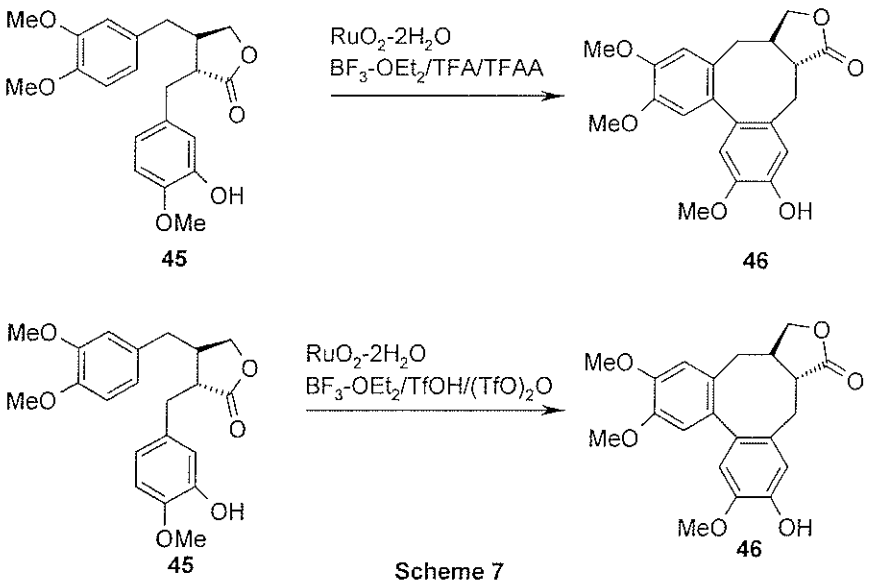


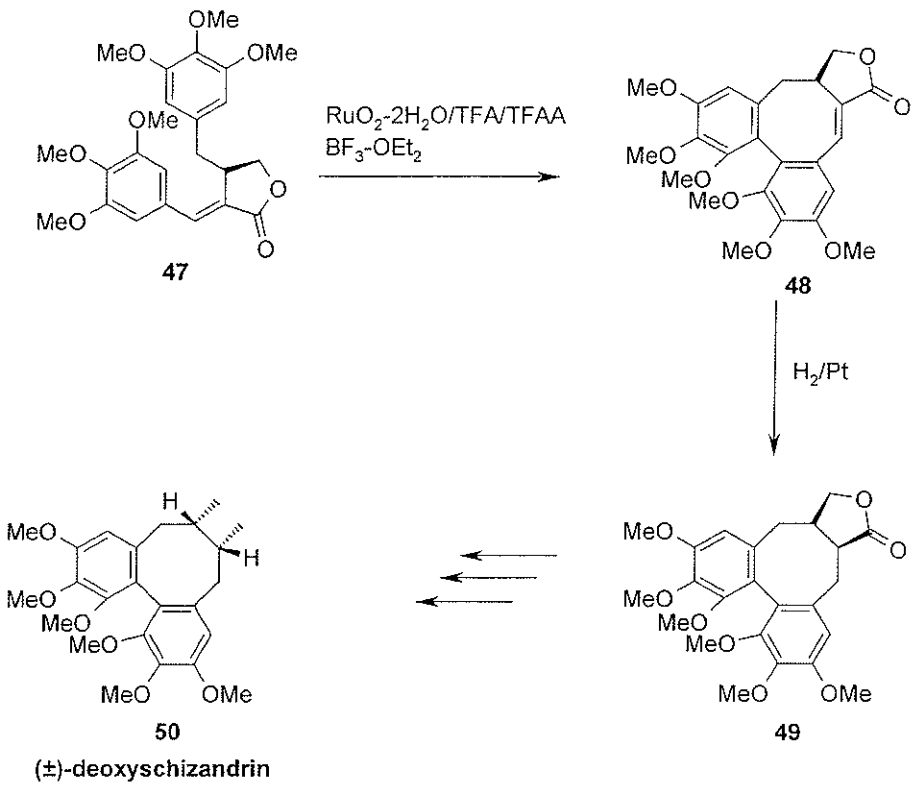
Figure 9



Scheme 7

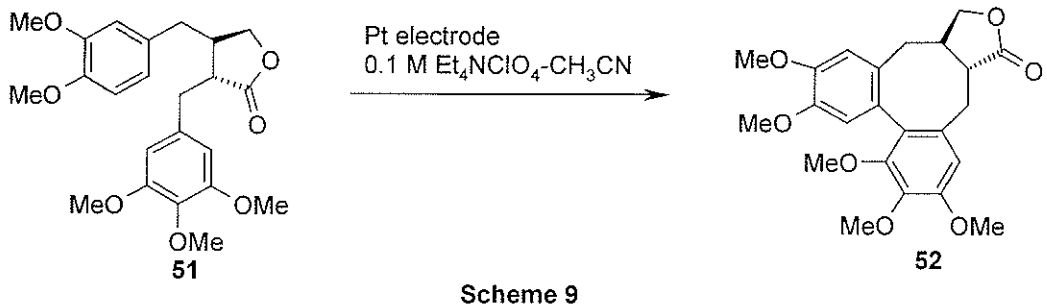
the *para*-position for the phenoxy radical (Figure 9).

Robin's group has also shown that these techniques can be equally well applied to non-phenolic coupling, although the reaction mechanism is still subject to some dispute. The method was used for the synthesis of racemic deoxyschizandrin (**50**) (Scheme 8)[53].



Scheme 8

Perhaps the most interesting method for oxidative coupling was devised by Fernandez *et al.* who report the conversion of benzylbutyrolactones (**51**) to dibenzocyclooctadienes (**53**) by anodic oxidation (Scheme 9)[54]. The conversion was performed in a three-compartment cell with two pieces of platinum foil serving as the working and auxiliary electrodes. The solution consisted of 0.1 M Et_4NClO_4-CH_3CN and 10.4 mM of the lignan precursor. In these examples, the yields after chromatography were in the range of 80-84%, which are quite good in comparison to chemical oxidative techniques.



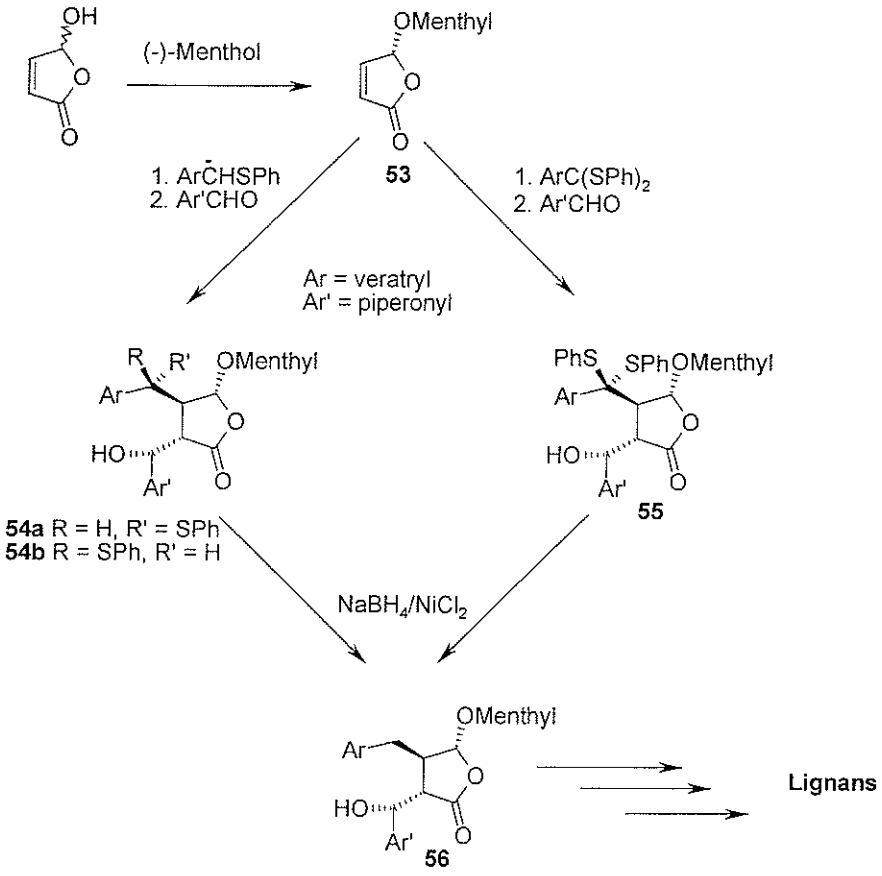
51 52

Scheme 9

1.5.2 Conjugate Addition Methods

The use of conjugate addition techniques has become very common in lignan synthesis. The technique has been used to synthesise many benzylbutyrolactone and dibenzylbutane lignans, and precursors to many other lignan classes. Typically, these reactions proceed through the use of sulphur-stabilized carbanions. In most cases these reactions also proceed as tandem conjugate addition reactions, with the substrate reacting first with the carbanion, then with an equivalent of various benzaldehydes or derivatives.

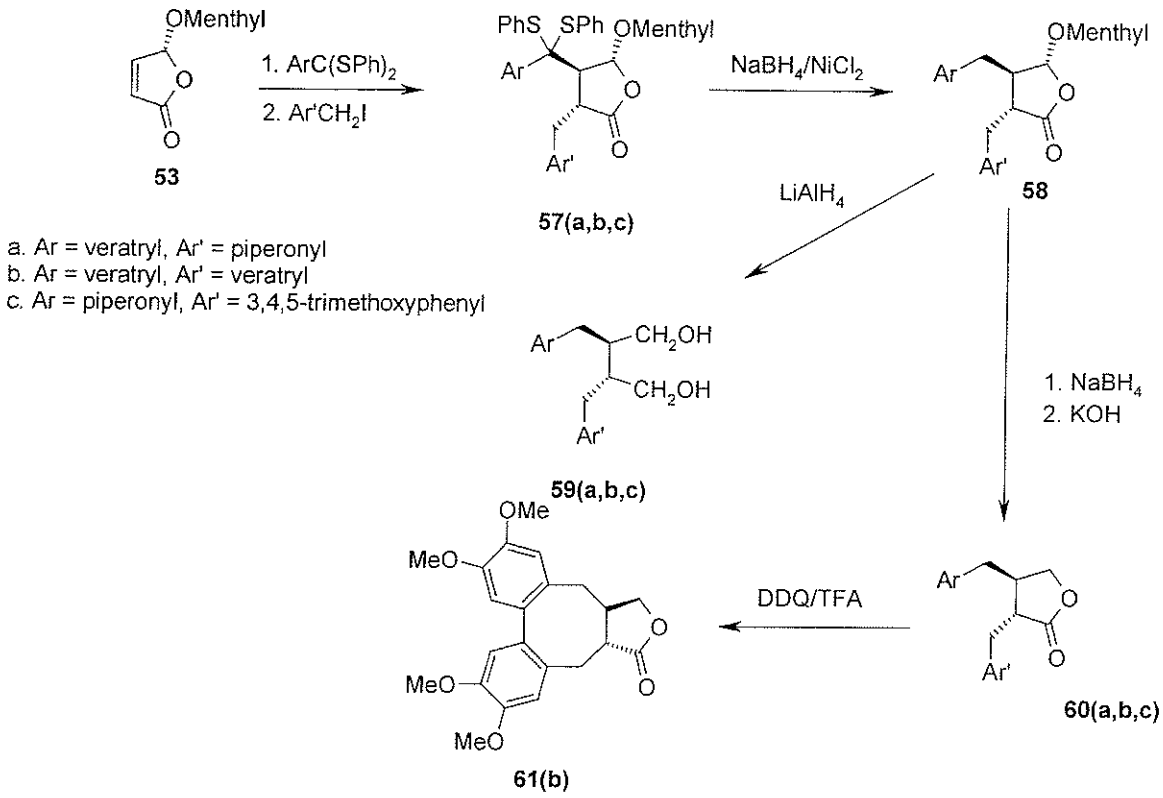
The first example of the use of this technique was published by Ward *et al.* who devised a method of tandem conjugate addition that was used for the enantioselective synthesis of justicidin P and derivatives, which was later discovered to be a general synthetic method for preparing aryltetralin lignans[55]. In their procedure, they formed a menthyl-protected butenolide (**53**), and then performed the tandem conjugate addition. The sulphur groups were then removed to form the hydroxylated product (**56**) (Scheme 10).



Scheme 10

A minor innovation on this technique was soon developed by Ward *et al.* that involved using an equivalent of benzylbromide or benzyliodide[56]. This modification avoids the formation of a hydroxyl group on completion of the second conjugate addition. This can greatly simplify the pathway to the formation of aryltetralin lignans. This technique was used to synthesise (-)-kusunokinin (**60a**), (-)-di-O-methylmatairesinol (**60b**), (-)-gatein (**60c**), (-)-dimethylsecoisolariciresinol (**59b**) and (-)-dihydroclusin (**59c**). Oxidation of one of the conjugate addition products with DDQ resulted in the formation of (+)-5-detigloyloxy-steganolide C (**61b**) (Scheme 11).

Feringa and Jansen adapted Ward's method to the synthesis of diarylfurofurans, in particular the enantioselective synthesis of (-)-eudesmin (**66**) (Scheme 12)[57]. As shown, the opening steps in the synthesis are identical to those of Ward's two papers. The γ-



53

57(a,b,c)

58

a. Ar = veratryl, Ar' = piperonyl
b. Ar = veratryl, Ar' = veratryl
c. Ar = piperonyl, Ar' = 3,4,5-trimethoxyphenyl

59(a,b,c)

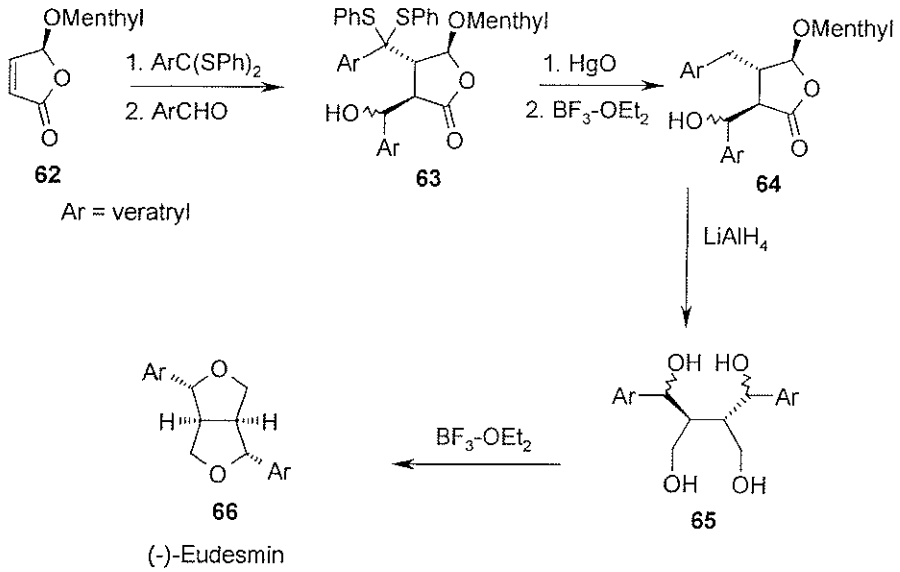
60(a,b,c)

61(b)

Scheme 11

lactone (**64**) is reduced by lithium aluminium hydride to form the tetra-hydroxylated product (**65**). This is then reacted with boron trifluoride etherate to perform the double ring closure that forms the diarylfurofuran, (-)-eudesmin.

Closely related to Ward's technique is another developed by Moritani *et al.* that



62

Ar = veratryl

63

64

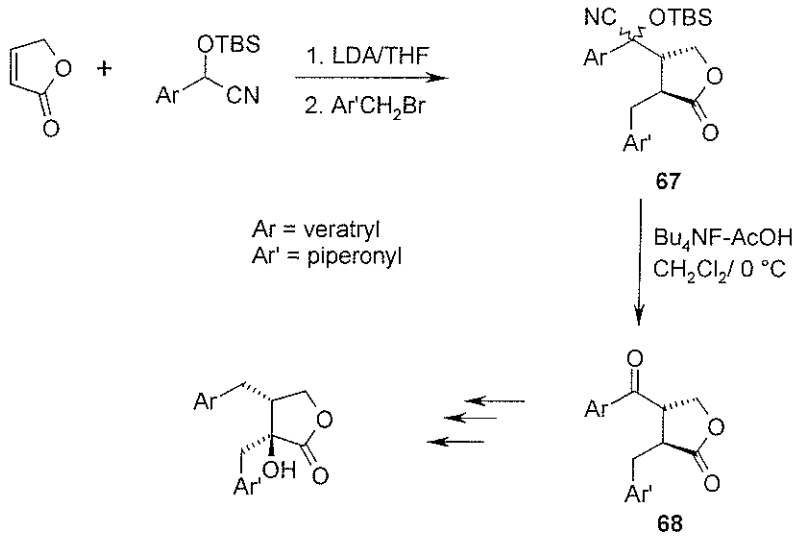
65

66

(-)-Eudesmin

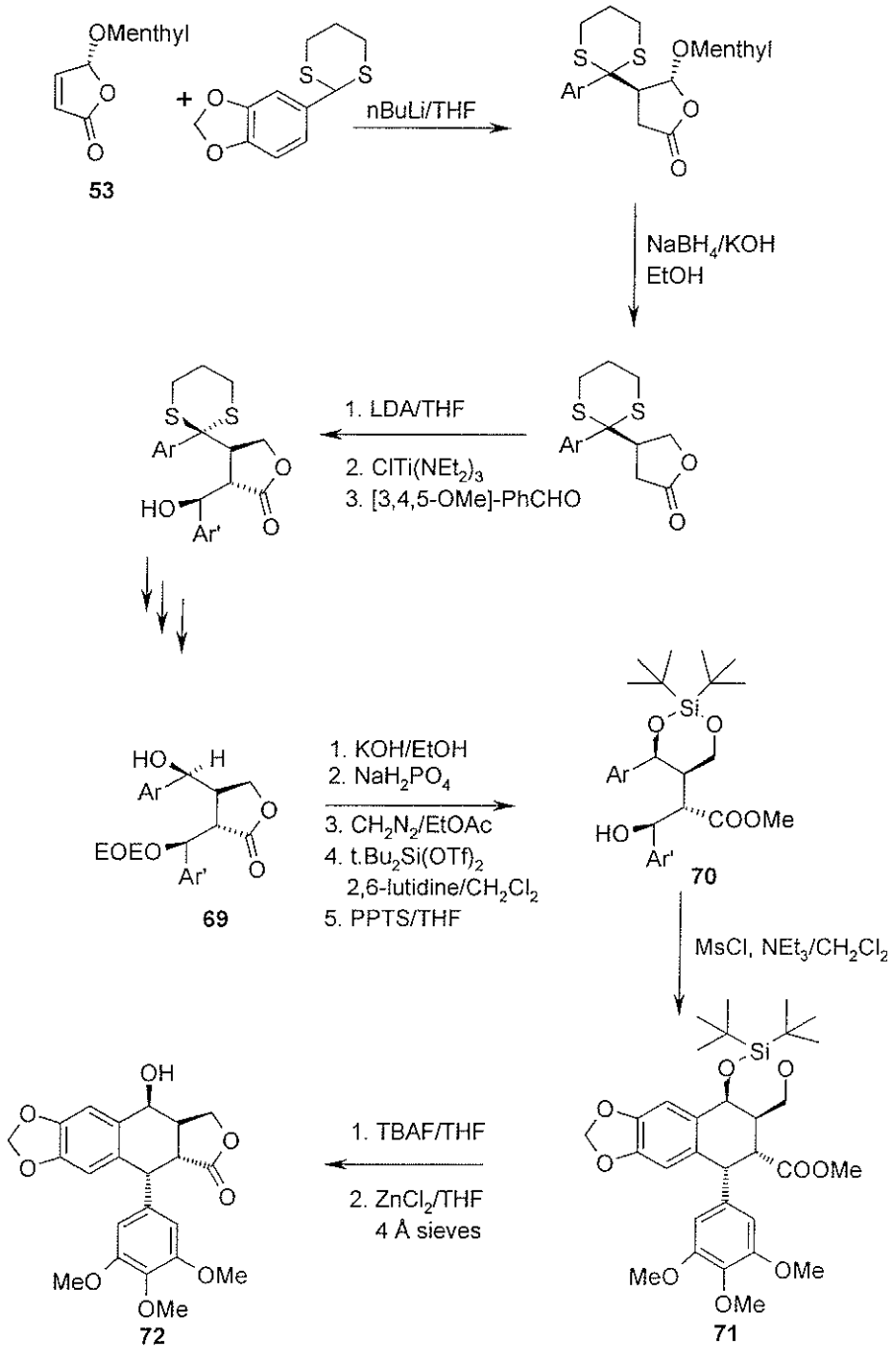
Scheme 12

makes use of a O-silylcyanohydrin (**67**) (Scheme 13)[58]. This method has been shown to be a general method for the stereoselective synthesis of α-substituted-*cis*-α,β-dibenzyl-γ-butyrolactones. Lignans such as guayadequiol and epitrachelogenin have been formed. It is thought that this technique can be used to synthesise many more lignan natural products.



Scheme 13

One problem of early conjugate addition techniques in lignan synthesis was that the resulting ring closure produced an all-trans geometry. In the case of podophyllotoxin synthesis, this leads to the uninteresting isopodophyllotoxin series, which does not have any medicinal effects. A modified conjugate addition technique was devised by van Speybroeck *et al.* resulting in the formation of the 1,2-*cis*; 2,3-*trans* geometry of the podophyllotoxin series of lignans (Scheme 14)[59]. In this specific example, the siladioxane (**70**) is used to induce the correct stereochemistry on ring closure. The silyl group is added after the second condensation, as it had a negative effect on stereochemical outcome if added earlier.



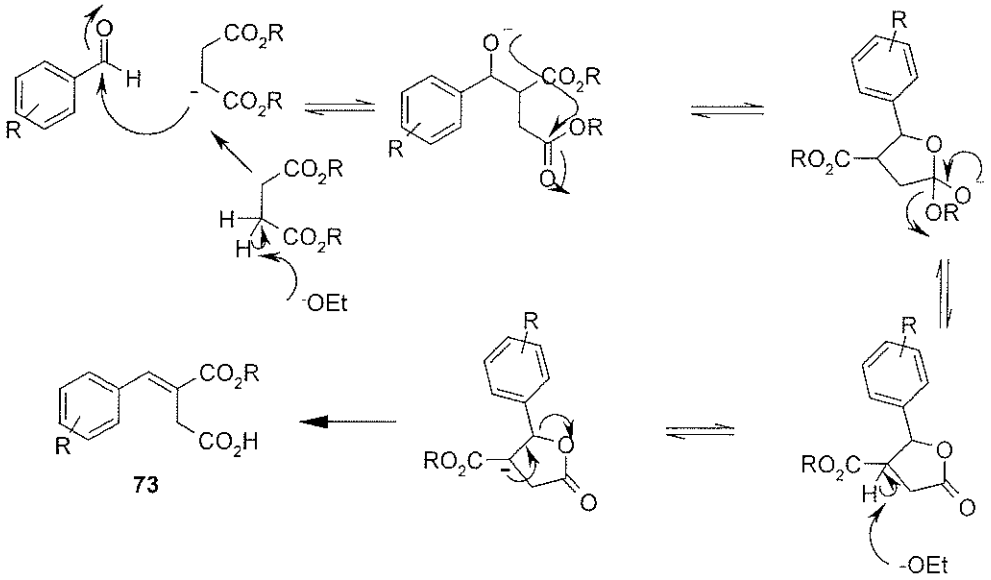
Scheme 14

1.5.3 The Stobbe Condensation

The Stobbe condensation is an extremely useful named reaction that can be used advantageously towards the synthesis of a large variety of lignans. The reaction, first reported by Stobbe in 1911, is likely one of the most important fundamental reactions in

lignan synthesis. In testament to this importance is the number of reviews and syntheses reported utilizing the Stobbe condensation[60-64].

In its most basic form, the Stobbe condensation is simply the condensation in basic solution of an aromatic aldehyde and a succinate diester, typically either diethyl or dimethyl succinate. The product from the Stobbe condensation is a benzylidenesuccinate half acid/ester as shown by the mechanism in Scheme 15. This benzylidenesuccinate acid/ester (**73**) is almost always in the preferred *E*-geometry about the newly formed carbon-carbon double bond[65,66a]. This geometry has been confirmed through a combination of both X-ray crystallography and proton NMR studies. In the case of NMR, it has been shown that the vinyl proton resonates in the region of 7.5-8.0 ppm due to the deshielding effects of the adjacent carbonyl moiety of the ester functional group. In the case of *Z*-geometry, this vinyl proton is not deshielded and resonates more upfield in the 5.0-6.0 ppm region of the spectrum.



Scheme 15

The Stobbe condensation can be repeated on the first formed product to form 2,3-dibenzylidenesuccinates. Typically the Stobbe acid/ester is re-esterified to form the

Stobbe diester, then a second equivalent of aromatic aldehyde is reacted to form the 2,3-dibenzylidenesuccinate as a mixed acid/ester. Just like the single-Stobbe product, the expected geometry is the *E,E*-dibenzylidenesuccinate, which has been confirmed many times by X-ray and NMR studies[66a,d-h].

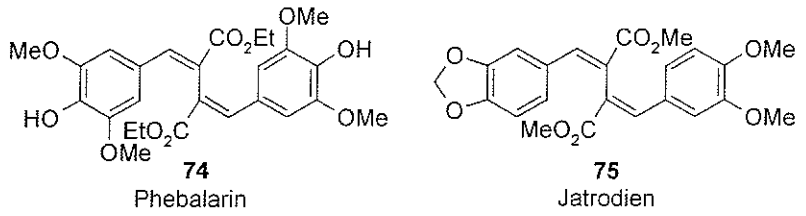
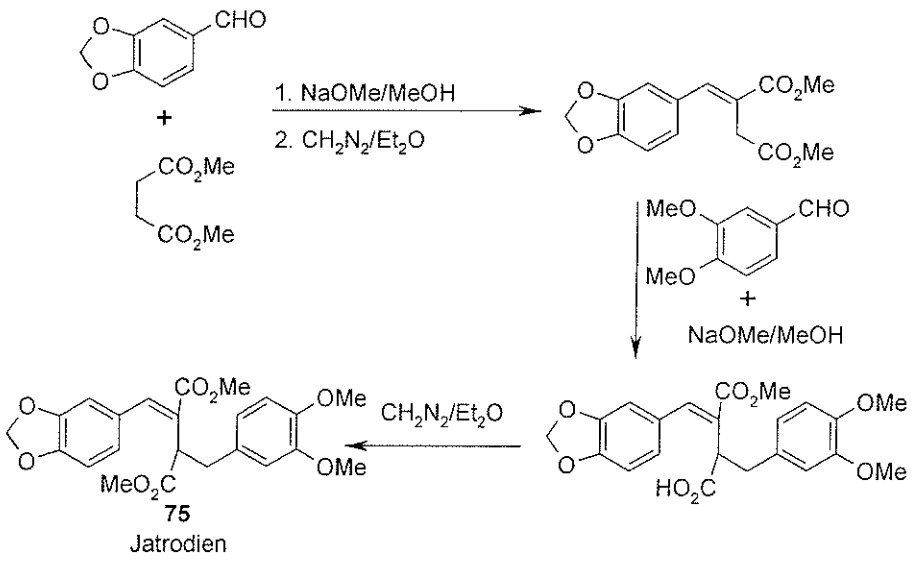


Figure 9

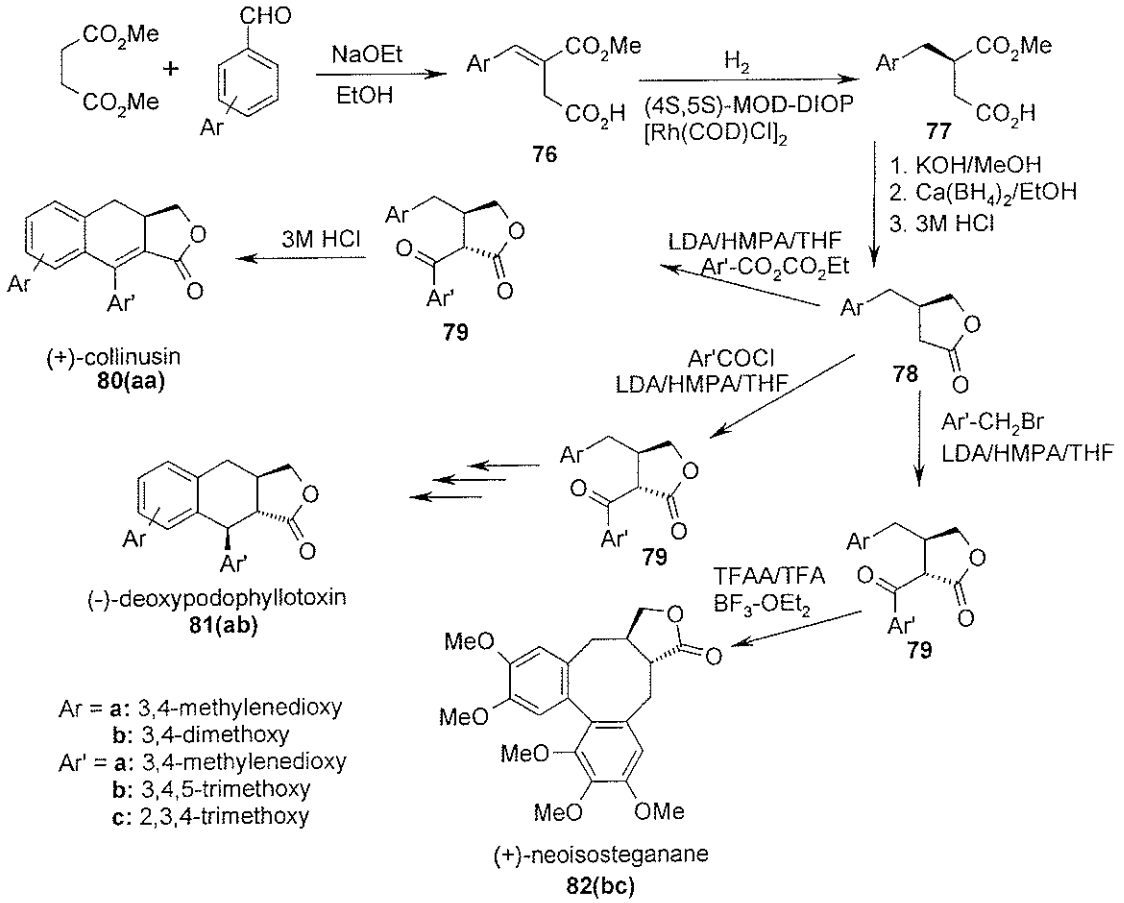
The usefulness of the double Stobbe condensation reaction lies in the fact that the final product has the basic structural features of a heavily modified dibenzylbutane lignan. From this basic Stobbe product, many classes of lignans can be synthesised directly in very few steps. As well, two natural lignans have the basic structure of Stobbe 2,3-dibenzylidenesuccinates, namely phebalarin[66b] (**74**) and jatrodien[66c] (**75**) (Figure 9). The synthesis of jatrodien is shown in Scheme 16 and illustrates exactly how the Stobbe



Scheme 16

condensation is utilized to form dibenzylidenesuccinates[66c].

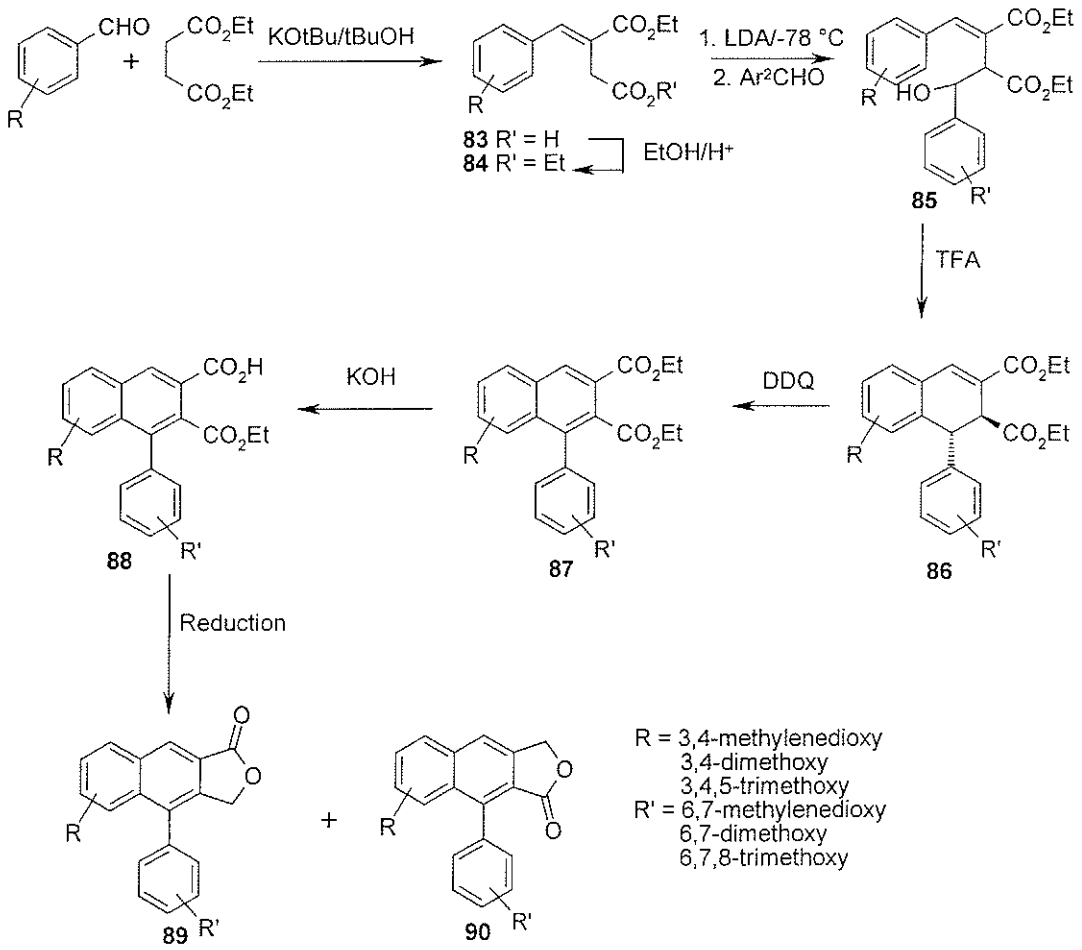
Morimoto *et al.* used the Stobbe condensation as the key first step in building the basic lignan skeleton in their synthesis of (+)-collinusin (**80aa**), (-)-deoxypodophyllotoxin (**81ab**) and (+)-neoisosteganane (**82bc**)[67] (Scheme 17). In their work, they used dimethyl succinate as their succinate source to perform the Stobbe condensation, which was followed by the selective hydrogenation of the resulting double bond. The Stobbe ester/acid was lactonized and then the various syntheses diverged from this intermediate. In the synthesis of (+)-neoisosteganane, the final step was the addition of the second aryl group followed by oxidative coupling using Robin's technique with TFAA to form the dibenzocyclooctadiene. (+)-Collinusin was formed by the addition of



Scheme 17

the second aryl group and followed by acid-catalyzed cyclization to form the desired aryldihydronaphthalene. The synthesis of (-)-deoxypodophyllotoxin followed a similar course, although it required further conversion to build up the complete general structure of the podophyllotoxin family.

Charlton *et al.* discovered that when performing the Stobbe condensation, they could prevent elimination from occurring after the second condensation if they quenched the reaction with LDA at low temperatures[68]. This served to prevent both the elimination and the lactonization of the alcohol (**85**) that normally occurs. This product could be cyclised with TFA to form aryldihydronaphthalene products (**86**). Further conversion



Scheme 18

resulted in arylnaphthalenes (**87**), which were subsequently lactonized (**89/90**) (Scheme 18). This technique could also presumably be used to form aryltetralins as the original aryldihydronaphthalenes could be hydrogenated to give the aryltetralin structure.

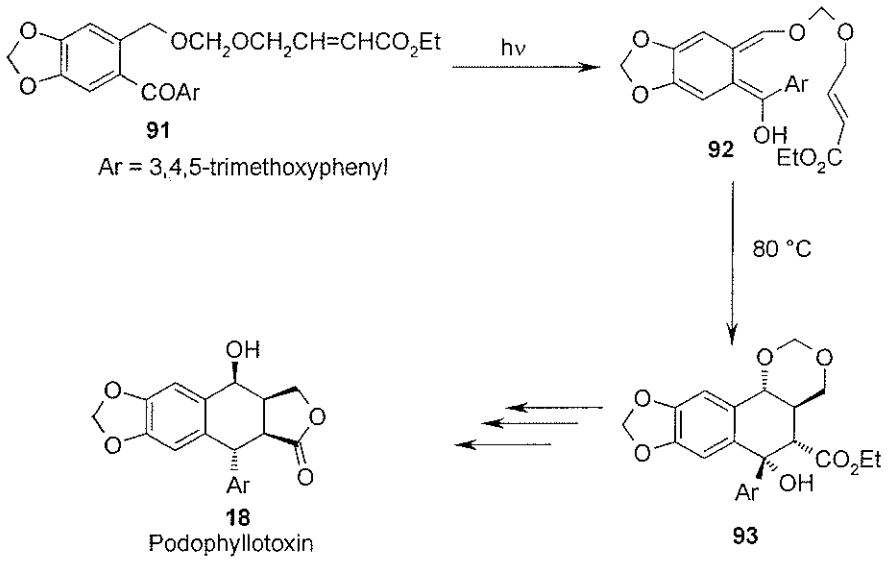
1.5.4 Pericyclic Reactions in Lignan Synthesis

Pericyclic reactions have many uses in organic synthesis and have proven to be particularly useful for the synthesis of lignan natural products. Pericyclic reactions follow sets of general rules that allows for predictable stereoselectivity in these reactions, which is very important for the asymmetric synthesis of lignans. In this section we will look at several types of pericyclic reactions, namely the Diels-Alder cycloaddition reaction, and a variety of electrocyclic and sigmatropic photochemical processes.

1.5.4.1 The Diels-Alder Reaction

The Diels-Alder reaction can be best classified simply as being a [4+2] cycloaddition reaction that requires both a diene and a dieneophile (usually an alkene or alkyne with strongly electron-withdrawing groups on it). The reaction results in the formation of two new carbon-carbon bonds between the terminal carbons of the diene and dieneophile. If the reaction substrates are chosen appropriately, the Diels-Alder reaction can lead to the direct formation of aryltetralin and aryldihydronaphthalene structures, an important feature for lignan synthesis[69-71].

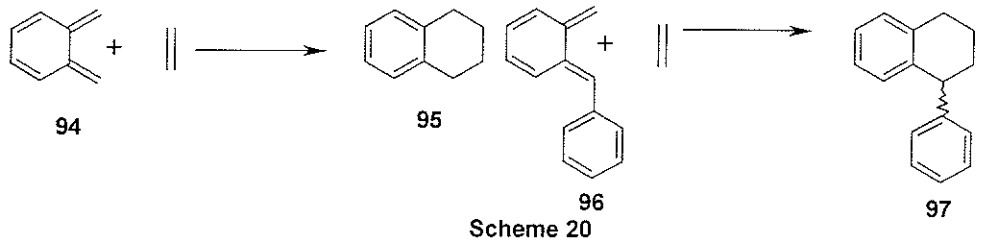
One very important consideration for Diels-Alder reactions is that they can proceed both intermolecularly and intramolecularly[72-78]. Kraus *et al.* showed how an intramolecular Diels-Alder reaction could be effectively used towards the synthesis of racemic podophyllotoxin (**18**)[79]. The key step of this process was the photochemical conversion of the starting material (**91**) into a pseudo-*ortho*-quinodimethane (**92**), which immediately reacted in an intramolecular Diels-Alder reaction. Further reactions led to the formation of racemic podophyllotoxin (Scheme 19).



Scheme 19

Over the past 15-20 years others have developed the use of Diels Alder reactions of *ortho*-quinodimethanes (*o*-QDMs) to achieve the synthesis of optically pure lignans[80-84]. *o*-QDMs are quite unstable, often with lifetimes of less than one second in solution and it is assumed that the reestablishment of aromaticity in the six-membered ring is the main driving force behind the short-lived nature of these compounds[85]. This feature also makes them very reactive towards dienophiles and makes them attractive reagents for Diels-Alder reactions. A simple Diels-Alder reaction between an *o*-QDM (**94**) and a

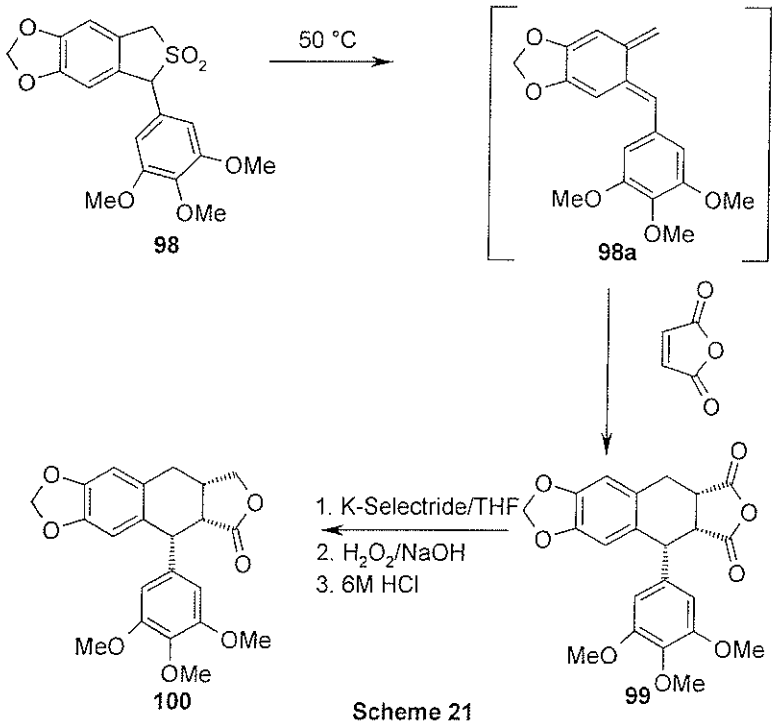
substituted ethene unit would result in the basic tetralin structure (**95**), while an aryl-substituted *o*-QDM (**96**) would result in an aryltetralin (**97**) (Scheme 20).



Scheme 20

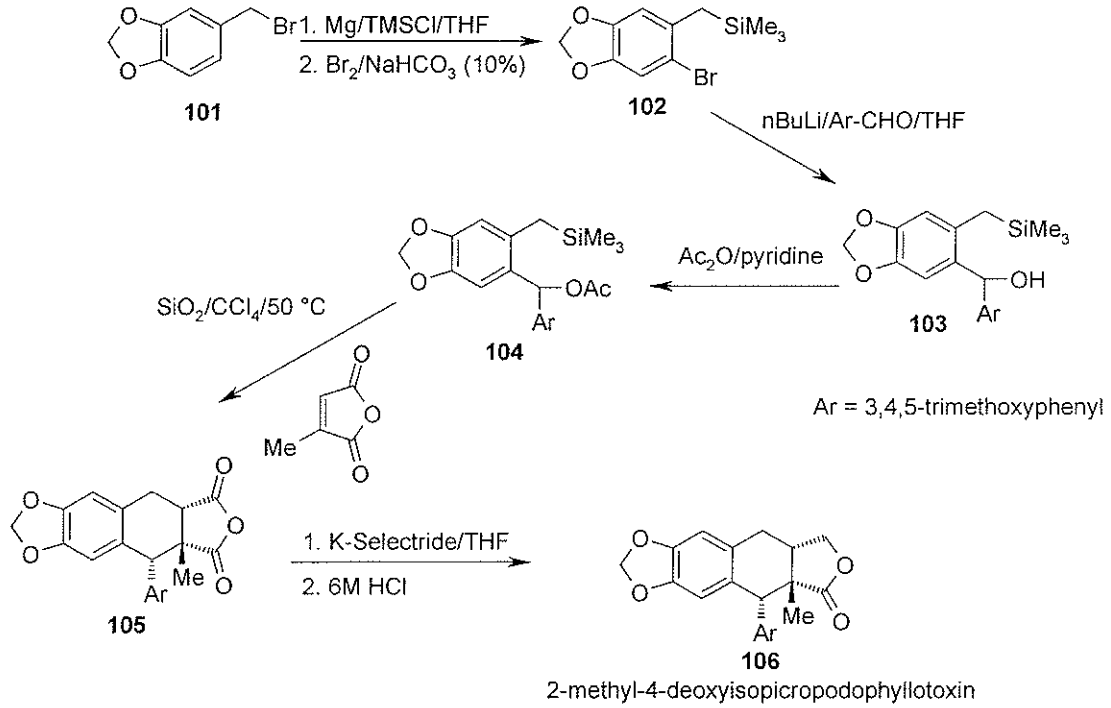
Mann *et al.* used an *o*-QDM in their synthesis of 4-deoxyisopicropodophyllotoxin (**100**)[86]. In this case, they formed the *o*-QDM through the chelotropic loss of sulfur dioxide. The very transient *o*-QDM intermediate (**98a**) was reacted *in situ* with maleic anhydride to form the aryltetralin structure (**99**) shown. Selective reduction of the anhydride to form the proper lactone was achieved with 4:1 selectivity by using K-Selectride to yield the desired 4-deoxyisopicropodophyllotoxin (**100**) (Scheme 21).

Beard *et al.* used a similar method to form the closely related 2-methyl-4-



Scheme 21

deoxyisopicropodophyllotoxin (**106**)[87]. In their synthesis, the key step was the use of a silyl-substituted compound (**104**) to serve as the *o*-QDM precursor. This was followed by a Diels-Alder reaction with 2-methylmaleic anhydride. Selective reduction with K-Selectride resulted in the formation of 2-methyl-4-deoxyisopicropodophyllotoxin (**106**) with good selectivity (Scheme 22). The silyl group was used because it was determined that the reaction was less selective and less efficient without it.



Scheme 22

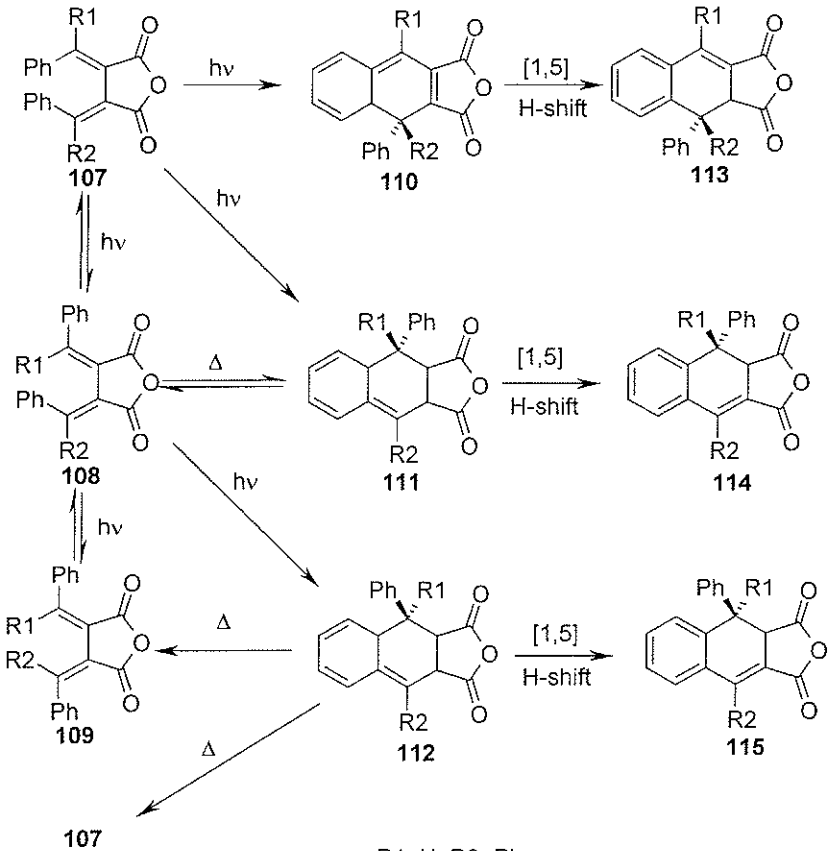
1.5.4.2 Electrocyclic and Sigmatropic Processes

Heller *et al.* has extensively studied the diverse intramolecular thermal and photochemical processes that a variety of dibenzylidenesuccinate derivatives undergo[66c,88-92]. Their prime interests have been in the reactions of the dibenzylidenesuccinic anhydrides (diarylfulgides) and the dibenzylidenesuccinimides (diaryl fulgimides), with the diarylfulgides being discussed at length in this section.

Some limited studies have been made of dibenzylidenebutyrolactones, which will be briefly discussed later in this section. In general, it was observed that these electrocyclic reactions (Scheme 23) proceed to give aryldihydronaphthalene products, which can obviously be further modified to give aryltetralin and arylnaphthalene products.

Heller discovered that the kind of photochemical and/or thermal pericyclic reaction exhibited by diarylfulgides was dependent on the substitution patterns of the double bonds and on the overall degree of steric crowding that was observed in the molecule. Fulgide (**107a**) was converted photochemically into both the 1,2-dihydronaphthalene (1,2-DHN) (**114a**) and the diarylfulgide (**108a**) (Scheme 23). It was assumed that the starting fulgide underwent conrotatory ring closure to produce the 1,8-dihydronaphthalene (1,8-DHN) intermediate (**111a**). This 1,8-DHN intermediate was then subject to two competing thermal processes; either a disrotatory ring opening to produce the isomerized fulgide (**108a**), or a supposed [1,5]-sigmatropic hydrogen shift to produce the 1,2-DHN product (**114a**). By studying product distributions under a variety of solvents and temperatures Heller *et al.* showed that the overall activation barrier for the [1,5]-sigmatropic shift was somewhat lower than the barrier for the disrotatory ring opening. In addition, it was also determined that the cyclization occurred exclusively onto the phenyl ring that had the greatest degree of substitution. This is of great predictive use in these types of reactions and could possibly be of some synthetic utility. Considering the structural similarities, it was not surprising to see that fulgide (**108a**) was also successfully converted into both 1,2-DHN (**115a**) and fulgide (**107a**), again presumably through the 1,8-DHN intermediate (**112a**). This process is considered to be exactly analogous to that described for the fulgide (**107a**)

In the case of the modified (**107b**), it was observed that quantitative conversion to a mixture of 1,2-DHN (**114b**) and (**115b**) was observed. This was explained as occurring from the expected photochemical conrotatory ring closure to produce the 1,8-DHN intermediate (**111b**), which either forms the expected 1,2-DHN (**114b**), or thermally opens to produce the fulgide (**108b**). If this second fulgide (**108b**) absorbs light, it is converted to 1,2-DNH (**115b**), via 1,8-DHN (**112b**). This cycle can continue indefinitely until total conversion to (**114b**) and (**115b**) is achieved.



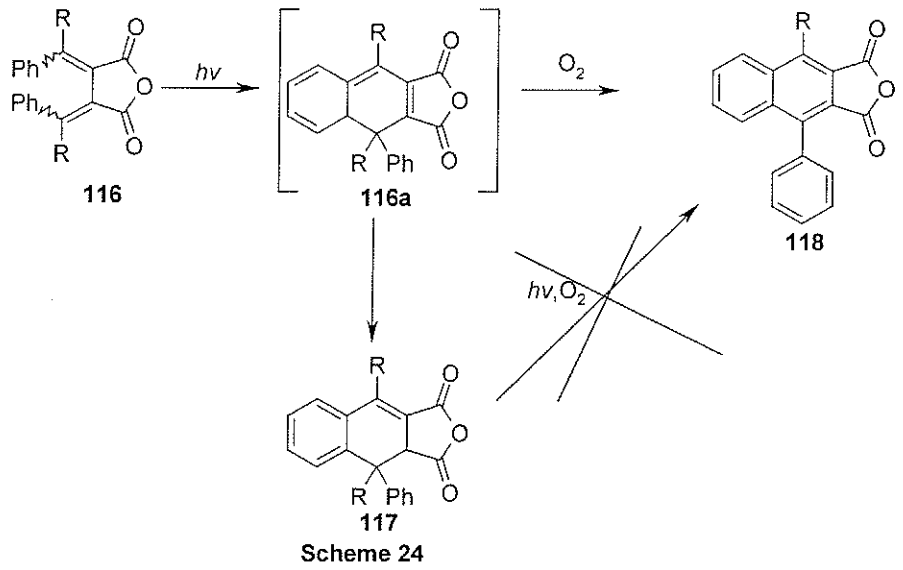
Scheme 23

As would be expected from its geometry, fulgide (**108c**) did not photocyclise to give the 1,8-DHN (**112c**), as was determined by a complete absence of 1,2-DHN (**115c**) in the product mixture. This was expected because the phenyl group on the more

substituted double bond was in the wrong orientation and could not interact with the π-system of the other benzylidene moiety. It has already been noted that these cyclizations preferentially occur to the phenyl group on the more-substituted double bond. In this case, that phenyl group is oriented in such a way that it can not interact with the other benzylidene group. When Heller *et al.* analysed the resultant product mixture, they discovered that the predominant product was the *cis-trans* isomerization product (**107b**). Indeed, more careful analysis showed that all three possible photoisomerization products were observed (i.e. the *E,E*-, *Z,E*- and *Z,Z*-geometry were all detected).

One unusual result was the discovery that both fulgides (**107a**) and (**108a**) were observed to form the 1,2-DHN product (**114a**) when subjected to lengthy periods of intense heating. It is expected that the fulgide (**108a**) would form 1,2-DHN (**114a**) through this mechanism, as it can access the 1,8-DHN intermediate (**111a**) through a thermal disrotatory ring closure, followed by the expected sigmatropic interconversion to the 1,2-DHN (**114a**). The situation is much less obvious for the fulgide (**107a**). It is thought that the intense steric crowding that occurs in (**107a**) between the two phenyl groups results in the molecule thermally isomerizing to form fulgide (**108a**), which has a much lessened steric interaction between a phenyl group and a hydrogen atom, resulting in greater stability. This then allows the thermal cyclization to form 1,2-DHN (**114a** through the mechanism outlined above. Consequently, it can be concluded that all thermal cyclizations occur through the *Z,E*-fulgide (**108a**).

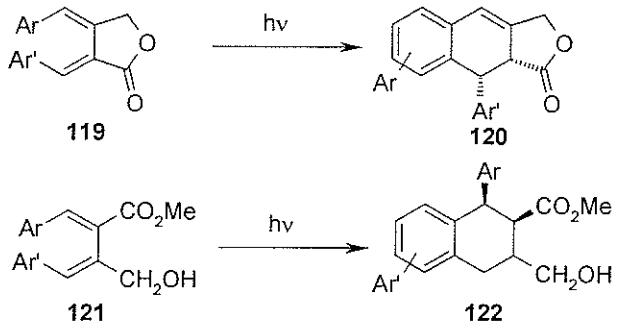
In all of the above reactions, it must be noted that oxygen was carefully excluded from the reaction solvent and headspace. Reactions done on these substrates (**116**) in the presence of oxygen resulted in the direct formation of arylnaphthalenes (**118**). It is



Scheme 24

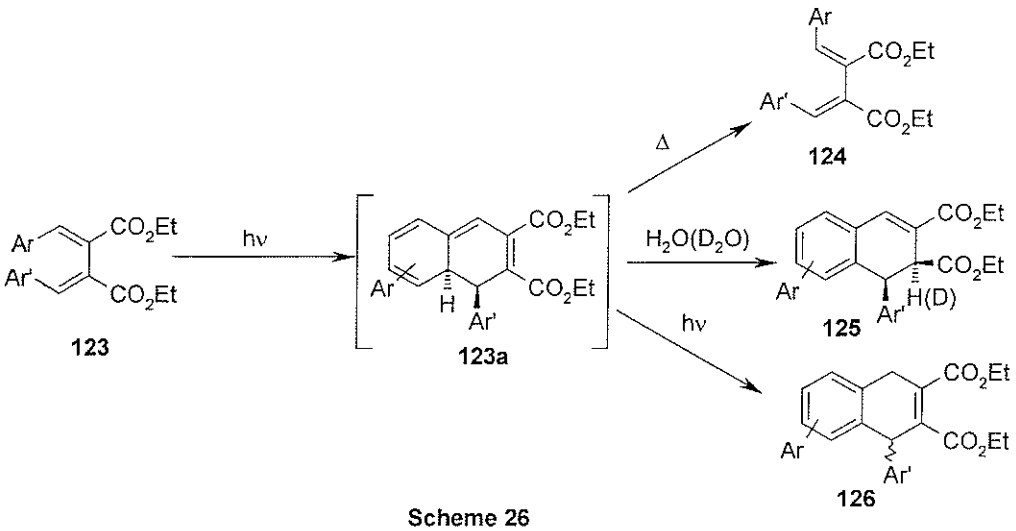
presumed that air oxidation of the 1,8-DHN intermediates (**116a**) occurs to form the observed arylnaphthalene compound. This assumption has been made based on the observation that the 1,2-DHN (**117**) does not form arylnaphthalenes, even in the presence of oxygen and even when irradiated for extended periods (Scheme 24).

Heller *et al.* have, as previously mentioned, also studied dibenzylidenebutyrolactones (**119**). It was noted by Heller that these compounds also react photochemically to produce the expected 1,2-DHN products (**120**), presumably through the corresponding 1,8-DHN intermediates. On thing of importance though was the observation that the cyclization appeared to occur exclusively onto the aryl group that was not in direct conjugation with the carbonyl group of the lactone moiety. A second study by Heller *et al.* with a modified dibenzylidenesuccinate (alcohol/methyl ester) (**121**) also showed that the cyclization occurred only onto the phenyl ring not conjugated to the carbonyl of the lactone moiety (**122**) (Scheme 25). This observation may also prove to be of some synthetic use for future photochemical studies of these fascinating compounds.



Scheme 25

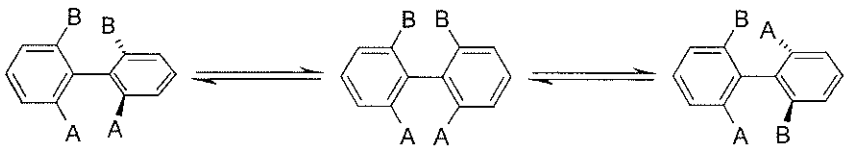
It was mentioned previously that the photochemically formed 1,8-DHN converts to the expected 1,2-DHN product through a [1,5]-sigmatropic hydrogen shift, which is in accordance with the original theory of Heller *et al.* A seminal 1979 report by Heller[88], followed by an update by Charlton and Assoumatine[93], has now corrected this incorrect assumption. Heller noted upon more careful study that the conversion of the 1,8-DHN to the 1,2-DHN was in fact the result of an acid-catalysed [1,5] hydrogen shift as opposed to the anticipated pericyclic sigmatropic shift. This also explains why the predominant product is a *cis*-1,2-DHN when the expected geometry for a sigmatropic [1,5]-shift would, in some cases, be the *trans*-1,2-DHN. Heller also observed that prolonged irradiation of the 1,8-DHN intermediate (**123a**) could result in the formation of a 1,4-dihydronaphthalene (1,4-DHN) product (**126**). Current work by Charlton and Assoumatine has now confirmed this observation for the 1,4-DHN product (**126**), which is thought to form via a photochemically allowed [1,3]-sigmatropic hydrogen shift (Scheme 26). In addition, performing the photochemical reactions in CD_3OD has resulted in the incorporation of deuterium atoms into the final 1,2-DHN products (**125**). This would imply that the conversion of 1,8-DHN to 1,2-DHN does in fact go through an acid-catalysed hydrogen shift.



Scheme 26

1.6 The Atropisomerism of Lignans

One interesting and useful property of lignans is that some of them exhibit the property of atropisomerism. Compounds that exhibit atropisomerism were first discovered in 1922 by Christie and Kenner who were successfully able to resolve 6,6'-dinitro-2,2'-diphenic acid (**127**) into their respective atropisomers[94]. The term itself was not introduced until Kuhn used it in a 1933 paper[95]. The term atropisomer is derived from the Greek *atropos* (a = not, tropos = turning). The literal translation accurately describes what atropisomerism is, molecular chirality due to hindered rotation about a carbon-carbon single bond (Scheme 27). As a result, two rotational isomers (rotamers) exist and if there are no other stereogenic centres in the molecule, the rotamers will be enantiomerically related; if other stereogenic centres are present, they will be diastereomerically related. The term atropisomer is used either to refer to the individual enantiomers or the individual diastereomers of an atropisomeric pair.



127: A = CO_2H, B = NO_2

Scheme 27

Due to the confusion regarding the resolvability of atropisomers, it was necessary to devise some sort of technical definition for atropisomers. Oki in 1983 arbitrarily defined atropisomerism to be a condition where the rotamers can be resolved and have a half-life of at least 1000 seconds (about 17 minutes) at 300 K (27 °C)[96]. This corresponds to a free energy barrier to rotation of approximately 22.3 kcal/mol at 300 K. Atropisomers that are stable at room temperature can be separated by conventional chromatographic techniques and stored for long periods of time, although this depends on the magnitude of the barrier to rotation. The barrier to rotation is caused by a variety of factors, but is primarily steric in nature. It is thought that coulombic and other electronic effects may play a role, but the steric effects are responsible for the existence of the majority of observed atropisomerism.

1.6.1 Biphenyls

Biphenyls were the class of molecule in which atropisomerism was first detected and characterized. For biphenyls, it is essentially the substituents on the *ortho*-positions of the two phenyl rings that determine the magnitude of the barrier to rotation. Bulky substituents tend to result in larger barriers to rotation than smaller substituents. It is thought that the Van der Waals radii of the substituents are the best predictive factor for the resulting barrier magnitude. It was also proposed that the use of A-values for cyclohexane substituents could be an effective predictive tool, but this has been somewhat disproven by experimentation. In cyclohexanes, the A-values are effective

because they pertain to synaxial interactions, while in biphenyls, the substituents in the *ortho*-positions are actually pointing at each other. As a result, the Van der Waals radii are thought to be a better predictive tool. Experimentation has shown this to be the case.

The *meta*-position in biphenyls is also thought to have some effect on the barrier to rotation. It is thought that *meta*-substituents, especially bulky ones, serve to prevent the *ortho*-substituents from avoiding each other while interconverting from one atropomeric form to the other. This served to increase the size of the barrier to rotation.

As atropisomers have a chiral nature, it is thought that they may have a useful role to play in organic synthesis, and especially in asymmetric synthesis. There are some biphenyl and binaphthenyl compounds that have been used as chiral auxiliaries in asymmetric synthesis, but overall these compounds have seen limited use.

1.6.2 Arylnaphthalenes

Considering the structural similarities between biphenyls and arylnaphthalenes, it is not surprising to note that arylnaphthalenes also exhibit atropisomerism. As the bridging carbon-carbon bond between the naphthalene moiety and the pendant aryl ring is analogous to the bridging bond in biphenyls, the two compounds can be considered to be identical for this purpose.

Similar to the biphenyl situation, it is observed that the *ortho*-positions are the most critical for determining the magnitude of the barrier to rotation (Figure 11). In addition, the 8-position on the naphthalene moiety can be thought of as being analogous an *ortho*-position and also plays a role in creating a barrier to rotation. Based on the "*meta*-effect" described for biphenyls, one would also expect the 2- and 7-positions on the naphthalene system to also exert some influence on the size of the barrier to rotation.

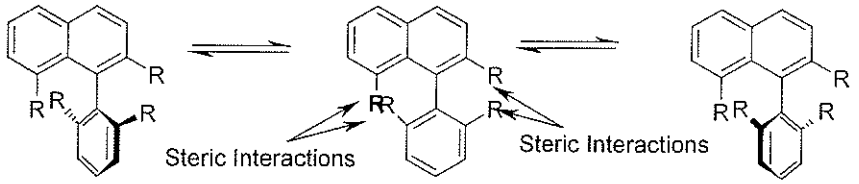
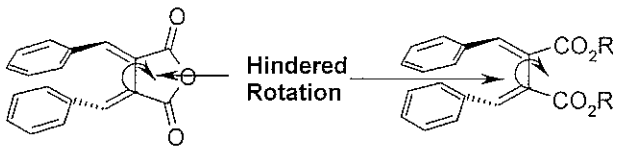


Figure 11

Arylnaphthalenes as a class have a number of members that exhibit atropisomerism and have barriers to rotation that are large enough that they can be measured and the isomers separated at low temperatures.

1.6.3 Diarylbutadienes

Compounds in this class that have been observed to show atropisomerism are restricted mainly to the dibenzylidenesuccinic anhydrides and the dibenzylidenesuccinates. The dibenzylidenesuccinic anhydrides (**128**) do not have true free rotation about the C_2-C_3 single bond (Figure 12). However, there is sufficient rotational freedom that the substituent aryl groups can pass by each other, but only with extreme difficulty. This results in the existence of two atropisomeric forms that can be easily detected by NMR spectroscopy, although only if the molecule contains diastereotopic protons (such as from a methylenedioxy group). The dibenzylidenesuccinate diesters (**129**) have atropisomerism similar to that described for



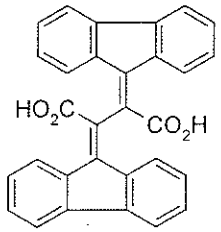
128 129

Figure 12

biphenyls and phenyl naphthalenes (Figure 12). As a result of the steric interaction of the aryl groups with each other and with the carboxyethyl groups these compounds behave more like two isolated cinnamic acid residues[66d,f]. This makes a difference to the

fundamental chemistry of these molecules, making them more labile and much more reactive than if they could lie in a single plane and be fully conjugated.

One of the first examples of dibenzylidenesuccinates exhibiting atropisomerism was that of fulgenic acid (**130**) (Figure 13), which was resolved by Goldschmidt in 1957[97]. Even in this situation, the resolved atropisomers were observed to racemize in only 20 minutes at 25 °C. This serves to underscore the difficulty in preventing less-rigidly held atropisomers (like dibenzylidenesuccinates) from quickly interconverting.

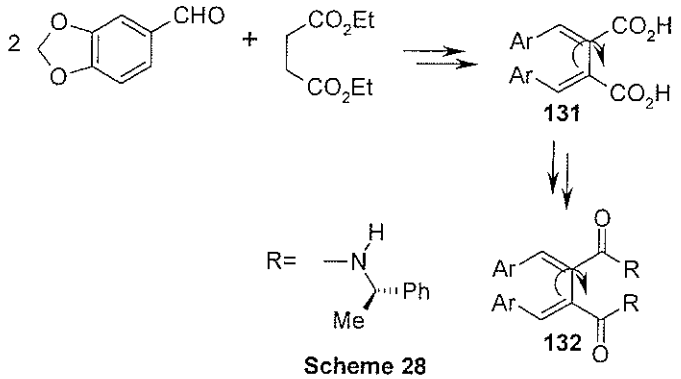


130
Fulgenic Acid

Figure 13

In our group, two different sets of experiments have been done to examine the barriers to rotation in dibenzylidenesuccinates. The first study by Hiebert, was performed on *E,E*-dibenzylidenesuccinates prepared by the Stobbe condensation[98]. He observed that the proton NMR spectra of the bis(3,4-methylenedioxy)benzylidenesuccinate (**131**) showed an unexpected separation of the CH_2 peak for the methylenedioxy group. These two protons are nominally equivalent, and are expected to be enantiotopic. The fact that they appeared as two separate peaks indicated that they were in fact diastereotopic and that there was some other chiral element present in the molecule. In this case, it was concluded that atropisomerism about the C_2-C_3 bond must be causing the doubling of the methylenedioxy peak in the proton NMR spectra. Hiebert noticed that when the compound was reacted with a chiral amine to form the bis(3,4-methylenedioxy)benzylidenesuccinamide (**132**) (Scheme 28), the entire spectra was

doubled. This led to the conclusion that the molecule did in fact exhibit atropisomerism. By studying the temperature dependence of the NMR spectra the barrier to rotation in the molecule was determined be roughly 17 kcal/mol.



Scheme 28

In later work, Yvon concluded that the bulk of the ester or amide group in dibenzylidene succinates had an impact on the size of the barrier to rotation. In her study, she investigated bis(3,4,5-trimethoxy)benzylidenesuccinates, which she reacted with one equivalent of racemic methyl mandelate[99]. This formed a mixed acid/ester, which was then studied to determine the barrier to rotation. As in the Hiebert study, dynamic NMR was used to roughly determine the magnitude of the barrier to rotation. Yvon determined that even with a bulky methyl mandelate ester, the barrier to rotation was only 20 kcal/mol. This was still too low for the atropisomers to be resolvable at room temperature.

At present, there are no known examples of *E,E*-dibenzylidenesuccinates that have barriers to rotation measured to be greater than the 22.3 kcal/mol required for them to be separable at room temperature. It is anticipated that more work will be done in this area in order to find possible stable atropisomers for these classes of compounds, largely due to their potential synthetic and biologic uses outlined previously in this section.

Chapter 2

Thesis Objectives

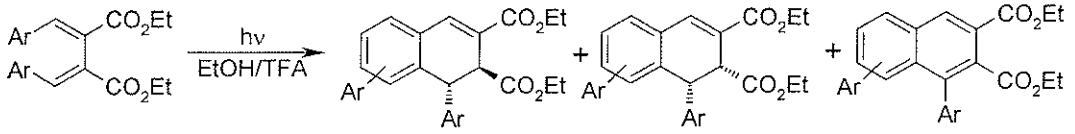
The final objective of the research to be described in this thesis is the development of a new method for the asymmetric synthesis of aryltetralin lignans, which could be adapted for the synthesis of 1-aryl-1,2-dihydronaphthalene lignans. It is hoped that by exploiting the inherent helical atropisomerism of dibenzylidenesuccinates, likely by using a chiral auxiliary, that stereocontrol over photochemical cyclisation to chiral 1,2-dihydronaphthalenes can be achieved. Work towards this goal can be broken down into three main parts. The first part involves a survey of the photochemical properties of a number of mixed and symmetric dibenzylidenesuccinates to determine product ratios and yields. The second part of this thesis will deal with the effect that a chiral auxiliary has on the photochemical reactions observed in the first part of the thesis. Finally, the asymmetric synthesis of a lignan natural product will be attempted with the important step being the photochemical cyclisation of a dibenzylidenesuccinate bearing a chiral auxiliary.

1. Survey of the Photochemistry of Dibenzylidenesuccinates

Dibenzylidenesuccinates have been shown to undergo photochemical ring closures analogous to those exhibited by diarylfulgides, diarylfulgimides and dibenzylidenebutyrolactones. Very little about these reactions is known and a detailed survey of this area is needed to determine the scope and synthetic utility of these reactions.

Previous work in our research group with the symmetric dibenzylidenesuccinate (**133aa**) derived from 3,4,5-trimethoxybenzaldehyde indicated that irradiation produced a

mixture of three products[99]. These products were later determined to be an arylnaphthalene (**136aa**), and both the *cis*-1-aryl-1,2-dihydronaphthalene (**135aa**) and the *trans*-1-aryl-1,2-dihydronaphthalene (**134aa**) (Scheme 29). The prime attraction of this reaction was that it allowed for the simple synthesis of *cis*-1-aryl-1,2-dihydronaphthalenes, a process that is typically quite difficult by conventional means. In addition, the products were separable by regular chromatographic techniques.

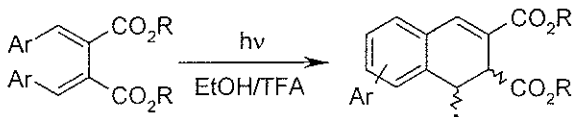


133 **134** **135** **136**

Ar = 3,4,5-trimethoxyphenyl

Scheme 29

It would be interesting to see if this photochemical cyclisation is a general procedure and could be applied to other dibenzylidenesuccinate compounds. To that end, a survey will be undertaken of a variety of symmetric and mixed dibenzylidenesuccinates and their derivatives to determine the overall utility of this reaction and if it can be used as the basis for the asymmetric synthesis of 1-aryl-1,2-dihydronaphthalenes (**134-136,138-140**) (Scheme 30) and hence the synthesis of aryltetralin lignans.



133: R=Et
137: R=H

134-136: R=Et
138-140: R=H

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

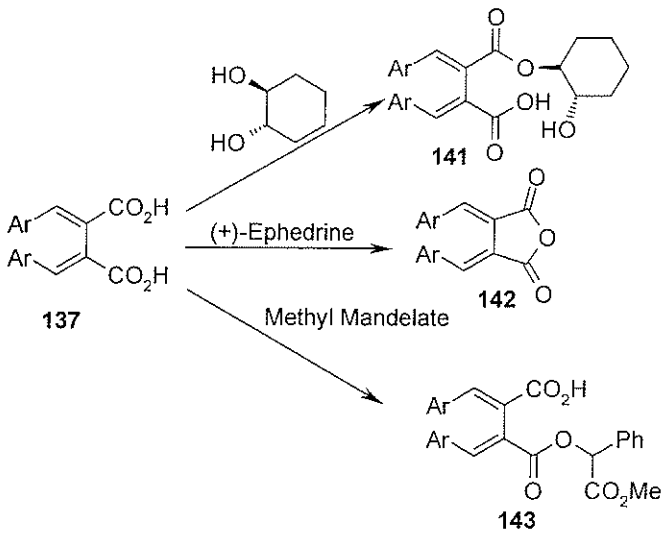
Scheme 30

2. Photochemistry of a Dibenzylidenesuccinate-Chiral Auxiliary Complex

It is thought that the addition of a chiral auxiliary to the starting dibenzylidenesuccinate may prejudice the molecule to prefer one atropisomeric configuration to all other possible configurations[98]. This may imply that if one helical

configuration is preferred that it may drive the photochemical cyclisation to preferentially form, or exclusively form, one of the two possible absolute configurations on ring closure.

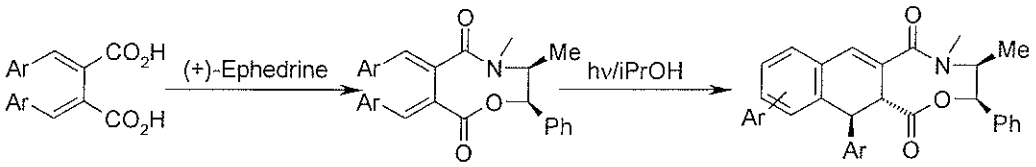
Previous work in our group had been directed towards the use of chiral auxiliaries in prejudicing the dibenzylidenesuccinate into adopting only one atropisomeric form[99,100]. Previous auxiliaries included methyl mandelate (**143**), *trans*-1,2-cyclohexandiol (**141**) and (+)-ephedrine (**142**) (Scheme 31). In each case, the coupling of the chiral auxiliary proved to be unsuccessful, or didn't result in the exclusive preference of one atropisomeric form; and no further work had been done in our group. When (+)-ephedrine was attempted, there was no observed formation of a dibenzylidenesuccinate-ephedrine adduct, but rather the formation of a diarylfulgide (**142**). A proposal to use γ-hydroxybutyrolactones was made, but never followed up.



Scheme 31

With these previous efforts in mind, it was decided to use (+)-ephedrine as the chiral auxiliary for this study, despite the previous failure in linking the ephedrine moiety to the dibenzylidenesuccinate. The flexible nature of (+)-ephedrine makes it ideal for our purposes and we proposed to try various other techniques to successfully form an

ephedrine adduct. As the bis(3,4,5-trimethoxy)benzylidenesuccinate system produced the best photochemical results, it was determined that this would be the benzylidenesuccinate to use for this investigation. The use of ephedrine brought about two main challenges. Firstly, an appropriate method of linking the ephedrine moiety to the bis(3,4,5-trimethoxy)benzylidenesuccinic acid (**137aa**) had to be devised. Then appropriate reaction conditions had to be developed for the attempted photochemical cyclisations of the dibenzylidenesuccinate-ephedrine adduct (**144aa**) (Scheme 32).



137aa **144aa** **145aa**

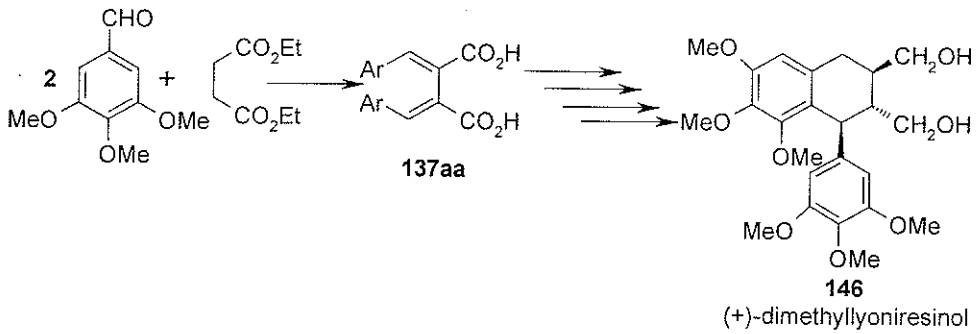
Ar = 3,4,5-trimethoxyphenyl

Scheme 32

3. Synthesis of (+)-dimethyllyoniresinol

The most challenging aspect of modern organic chemistry is the asymmetric and stereoselective synthesis of chiral compounds and natural products. Stereoselectivity has to be achieved using many techniques such as using optically active starting materials or reagents to influence the stereochemistry of the final product. In this project, chirality already existed in the molecule by way of the inherent atropisomerism of the dibenzylidenesuccinate moiety, and the molecule was induced to take up a single chiral form by the use of (+)-ephedrine as a chiral auxiliary.

The target compound (+)-dimethyllyoniresinol (**146**) was chosen for synthesis based on the results of the second section of this research. The substitution pattern on the two aryl groups in (+)-dimethyllyoniresinol matches those in our test compound for the chiral auxiliary photochemistry, making the synthesis relatively simple to complete (Scheme 33). Also, since the absolute configuration and rotation of dimethyllyoniresinol



Scheme 33

is known, it will be possible to compare its rotation to that of the synthetic material and thereby ultimately determine which atropisomeric form had been favoured by the ephedrine chiral auxiliary prior to the photochemical cyclization.

Chapter 3

Results and Discussion

The research presented in this thesis can be divided into three general sections. In the first of these sections, a study of the photochemical behaviour of a series of symmetric dibenzylidenesuccinates and mixed dibenzylidenesuccinates is presented. In each case the product distribution of each reaction was carefully studied, and in some cases the major products were characterized when separation was possible. Furthermore, the utility of this method for the asymmetric synthesis of 1,2-dihydronaphthalenes or aryltetralin lignans was evaluated.

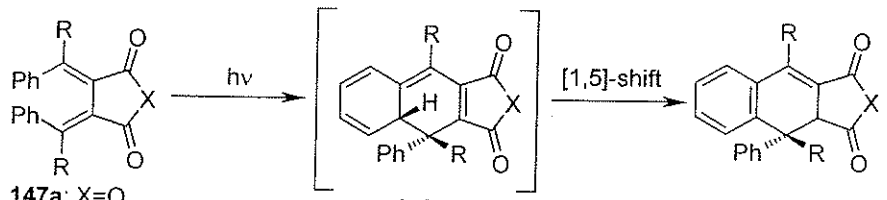
The second section involves an investigation into the ability of (+)-ephedrine to act as a chiral auxiliary to influence the atropisomer population of bis(3,4,5-trimethoxy)benzylidenesuccinic acid and a study of the stereochemistry of the following photochemical cyclisation reaction. Again, the potential synthetic uses of these results were evaluated.

Finally, the third section deals with the first asymmetric synthesis of the lignan (+)-dimethyllyoniresinol, with particular stress placed on the key photochemical reaction that produces the *trans*-1,2 stereochemistry of the ring closed product, a geometry that is required to create the correct stereochemistry for the natural product.

3.1 Survey of the Photochemistry of Dibenzylidenesuccinates

As noted previously, the main motivation for this survey was the ease with which the photochemical reactions of dibenzylidenesuccinates produce *cis*-1,2-dihydronaphthalenes. This appeared to be a promising technique for the asymmetric and nonasymmetric synthesis of both aryltetralin and aryldihydronaphthalene lignans.

The majority of the research in this section was inspired by the results of Heller *et al.* who found that diarylfulgides (**147a**), diarylfulgimides (**147b**) and dibenzylidenebutyrolactones all undergo photochemical and thermal electrocyclic ring closures, followed by an assumed 1,5-sigmatropic shift to yield 1,2-dihydronaphthalene compounds (**149**) (Scheme 34)[88-92]. These compounds are thought to be reached through a 1,8-dihydronaphthalene intermediate (**148**), which undergoes a 1,5-sigmatropic hydrogen shift. As mentioned in Chapter 1, new research by Charlton and Assoumatine has now shown that the formation of the 1,2-dihydronaphthalene goes via a protonation-deprotonation mechanism involving the reaction solvent[93]. In the case of the diarylfulgides, the product distributions from irradiation were found to be quite sensitive to the local geometry about the double bonds in the butadiene system, as well as to the nature of the substituents present and the resulting degree of steric crowding.



147a: X=O
147b: X=NR
R = Ph, Me, H

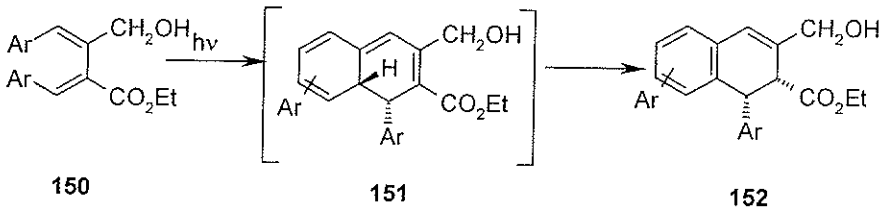
148 **149**

Scheme 34

The geometry of the 1,8-dihydronaphthalene intermediates are determined by the direction of the ring closure, conrotatory for photochemical cyclisations and disrotatory for thermal processes; as well as by the original configuration about the double bonds in the butadiene system. It should be noted that in the presence of oxygen that arylnaphthalenes were observed, which was attributed to the oxidation of the 1,8-dihydronaphthalene intermediates by oxygen. This suspicion was later strengthened by the discovery that 1,2-dihydronaphthalenes do not undergo further photochemical

reaction to produce arylnaphthalenes, even in the presence of oxygen. A more detailed description of these processes has already been presented in Chapter 1 of this thesis.

One investigation by Heller *et al.* on an acyclic diarylbutadiene derivative (**150**) showed that acyclic substrates reacted similarly to diarylfulgides and diarylfulgimides[90]. Irradiation of the alcohol/ester (**150**) resulted in the formation of a 1,2-dihydronaphthalene (**152**), presumably through a 1,8-dihydronaphthalene intermediate (**151**) (Scheme 35). It was noted that the ring closure occurred exclusively onto the group that was not conjugated to the carbonyl of the ester group.

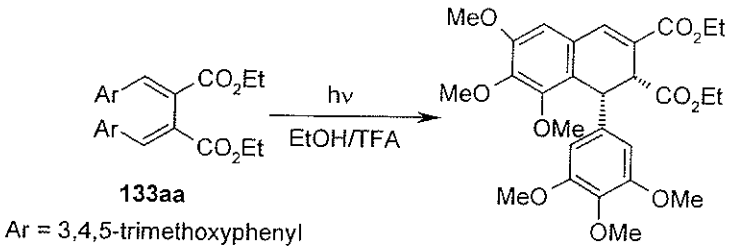


150 **151** **152**

Scheme 35

As a result of Heller's experiment with the acyclic diarylbutadiene, our group became interested in studying these reactions in other acyclic systems. One worry at the time was that the diarylfulgides only underwent electrocyclic ring closure due to the steric crowding around the pi-system in the molecule. The anhydride moiety in diarylfulgides provides a rigid backbone for the molecule and prevents free rotation about the carbon-carbon single bond in the butadiene system. As described in Chapter 1, these diarylfulgide systems are quite reactive due to the bending of the butadiene system and the resulting loss of conjugation. It is thought that this would force the diarylbutadiene segment to lie in a geometry that would be ideal for an electrocyclic reaction to occur. In open-chained diarylbutadiene systems like dibenzylidenesuccinate diesters, it was feared that the lack of conformational rigidity would make electrocyclic ring closure less likely.

A test study by Yvon on ethyl bis(3,4,5-trimethoxy)benzylidene succinate (**133aa**), showed that a photochemically-induced electrocyclic reaction worked well and produced a 1,2-dihydronaphthalene (**135aa**) with the *cis*-1,2 configuration about the two new stereogenic centres (Scheme 36)[99]. This was an important result, as it indicated that other easily available dibenzylidenesuccinate diesters might be used to prepare other *cis*-1,2-dihydronaphthalenes from which other lignans can be derived. The formation of *cis*-1,2-dihydronaphthalenes by this method is made even more important by the great difficulty normally observed for the preparation of aryltetralins or dihydronaphthalenes having the *cis*-1,2-configuration using conventional synthetic means. The fact that most lignans of medicinal interest have the *cis*-1,2 configuration, such as podophyllotoxin, only serves to underscore the importance of this result.



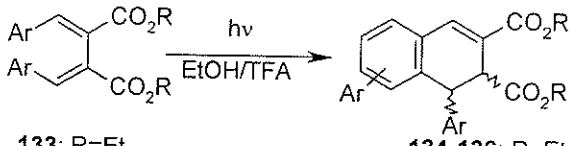
133aa

Ar = 3,4,5-trimethoxyphenyl

135aa

Scheme 36

Whereas Yvon's study was only done on ethyl bis(3,4,5-trimethoxy)benzylidene succinate (**133aa**), it was our intention to extend this to include other symmetric dibenzylidenesuccinates; for example bis-(3,4-dimethoxybenzylidene) (**133bb**) and bis-(3,4-methylenedioxybenzylidene) (**133cc**). As well, we proposed to investigate both the diacids (**137aa, 137cc**) as well as the diethyl diesters (Scheme 37). Some mixed dibenzylidenesuccinates were also investigated (**137ac**).



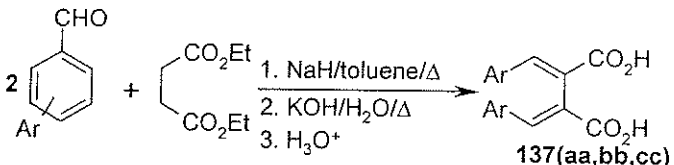
133: R=Et
137: R=H

134-136: R=Et
138-140: R=H

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

Scheme 37

The synthesis of the test compounds for this study was achieved by relatively straightforward chemistry. It was determined that the quickest route to the formation of symmetrical succinic diacids and diesters was to perform double Stobbe condensations of the appropriate benzaldehydes with diethyl succinate, followed by esterification, if required, to form the Stobbe diethyl esters. The synthesis of the diacids from the aldehyde and diethyl succinate was achieved by using sodium hydride as a base in refluxing toluene (Scheme 38). This method has been reported previously as being generally successful for the synthesis of many symmetrical dibenzylidenesuccinic acids[101]. The reaction proved to be quite successful and produced the desired diacids **(137aa, 137bb, 137cc)** in good yield (48-60%). The diacids were purified by recrystalization from methylene chloride/hexanes for photochemical studies, or were converted directly to the diesters if required.



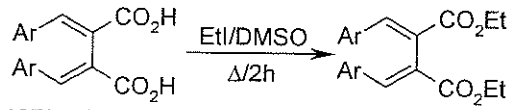
137(aa,bb,cc)

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

Scheme 38

Conversion of the diacids to the ethyl diesters was not straightforward. This was not surprising, considering the difficulties reported by Yvon in her study of the 3,4,5-trimethoxybenzylidene system[99]. The first attempts at forming the diesters followed

Yvon's procedure and involved refluxing with ethyl iodide and anhydrous potassium carbonate in ethyl alcohol solution. Even after 18 hours at reflux, the conversion was never more than 20%, as measured by chromatographic and NMR techniques. When the reaction was performed in DMSO at 70 °C, with ethyl iodide and anhydrous potassium carbonate, it went to completion, as monitored by TLC, within 2 hours (Scheme 39) and after chromatography (3:1 hexanes-ethyl acetate) the esters (**133aa, 133bb, 133cc**) were formed in good yield (65-75%).



137(aa,bb,cc) **133(aa,bb,cc)**

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

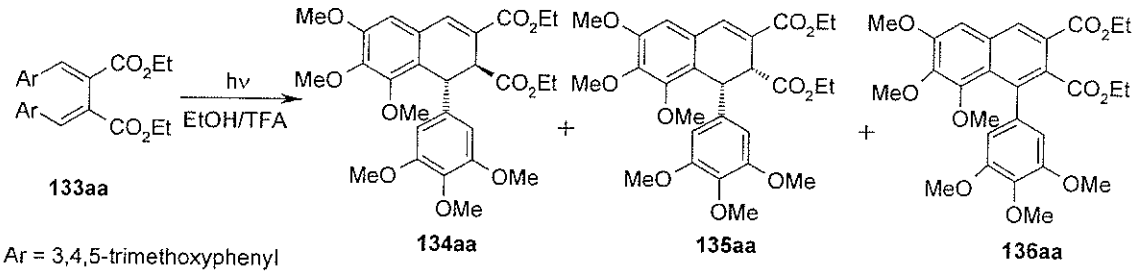
Scheme 39

The photochemical reactions of these compounds were quite varied with both reaction times and product distributions shown to be dependent on the substrate under investigation. Some investigation of the best solvent systems to use had already been undertaken by Yvon, so the correct solvent system was discovered quite quickly. The first compound that was investigated in the current survey was the same ethyl bis(3,4,5-trimethoxy)benzylidene succinate that Yvon studied as her test compound[99]. Further work on all of the various dibenzylidenesuccinates and succinic acids showed that the various systems all behaved in a like manner. As a result, detailed analysis will only be given for the ethyl bis(3,4,5-trimethoxy)benzylidene succinate compound as it is the one that our group has studied the most.

In her study, Yvon noticed that irradiating the diester in ethyl acetate resulted in the formation of a complex product mixture of at least 4 products that were not definitively identified[99]. Our reaction in ethyl acetate of the same compound resulted in no

appreciable accumulations of the expected *cis*- or *trans*-1,2-dihydronaphthalenes, although at least three products in addition to unreacted starting material were observed by HPLC analysis. An investigation of the resulting mixture by NMR failed to turn up any insight into the possible identity of these products. All attempts at resolving the product mixture into separate compounds by chromatographic or recrystalization techniques failed to produce any pure compounds.

Yvon noticed little difference between the results for the photochemical reaction in methanol and in a solution of 1% trifluoroacetic acid in anhydrous ethanol. In both cases she observed that the product distributions favoured the formation of the *cis*-1,2-dihydronaphthalene (**135aa**) over the *trans*-1,2-dihydronaphthalene (**134aa**) and the fully aromatic arylnaphthalene (**136aa**) (Scheme 40)[99]. The current study indicated that there



Scheme 40

was a substantial lessening of the amount of fully aromatic arylnaphthalene when the reaction was performed in acidic anhydrous ethanol. NMR analysis of the mixture seemed to indicate roughly a 24:2:1 ratio between the *cis*-1,2-dihydronaphthalene (**135aa**), the *trans*-1,2-dihydronaphthalene (**134aa**) and the arylnaphthalene (**136aa**) products. HPLC on the other hand seemed to indicate a substantially lesser of the *cis*-1,2-dihydronaphthalene product, (roughly an 83:17 product ratio between *cis-trans* respectively). This is being attributed, (as was done by Yvon), to a difference in the

absorption coefficients of the three compounds at the wavelength used for analysis of the HPLC eluant[99]. It was determined that the *trans*-dihydronaphthalene eluted first, followed by the *cis*-dihydronaphthalene and finally the arylnaphthalene.

Comparison of the NMR spectra of the products produced some interesting differences. The *cis*-compound gave rise to a doublet with a relatively large coupling constant at roughly 4.8 ppm (J = 9.1 Hz), which was assigned to the benzylic proton, while the *trans*-compound exhibited a signal for the same proton as a broad singlet at lower field near 5.0 ppm. These protons are of course coupled to the neighbouring allylic proton that gives rise to a signal at roughly 4.0 ppm. By applying the Karplus correlation[102], one can rationalize the observations and assign the stereochemistry of the two compounds. In the *trans*-dihydronaphthalene, the dihedral angle between the allylic and benzylic protons is very close to 90°, resulting in a small coupling constant. Alternatively, the *cis*-compound has a dihedral angle of about 20°, which results in a much larger coupling constant (Figure 14). One other interesting feature is the four-bond coupling observed between the allylic proton and the vinyllic proton, (which resonates at roughly 7.5 ppm). The *cis*-compound exhibits this four-bond coupling, while this long-range coupling is entirely absent in the case of the *trans*-compound. A rationale for this observation is that the C-H bond of the allylic proton in the *cis*-compound is essentially lined up with the pi-orbitals of the double bond, which allows for it to better integrate itself into that spin system. In the case of the *trans*-compound, the same C-H bond lies perpendicular to the pi-system and the same spin-spin interactions are impossible (Figure 14). This detailed analysis of the NMR spectra allowed us to definitively identify each compound and to compare their relative proportions from comparing the integrals of the

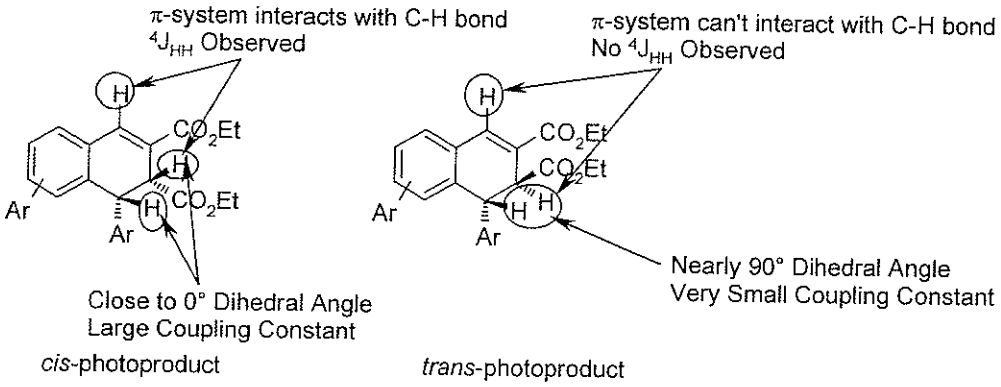


Figure 14

allylic and benzylic protons of both the *cis*- and *trans*-dihydronaphthalenes. This study also allowed us to make structural assignments in all of the other reactions in our survey as the same spectral features carried over to the corresponding products from irradiation of other dibenzylidenesuccinate diesters. In each case, the *cis*-dihydronaphthalene photoproduct was found to feature a doublet with a larger coupling constant and it also usually exhibited the four-bond coupling between the vinyl proton and the allylic proton; while the *trans*-compound invariably showed a doublet with a smaller coupling constant (or it appeared as a broad singlet) and no long-range coupling to the vinyl proton from the allylic proton.

The study done on the ethyl bis(3,4,5-trimethoxy)benzylidene succinate also provided guidance on about the optimum solution concentration of starting material for these photochemical reactions. It was discovered that maximum efficiency (maximum absolute amount of product formed in a given time with the same light intensity) was reached if the reaction was performed at a substrate concentration of about 1mg/mL of acidic anhydrous ethanol solution. When reactions were performed at this concentration, the reaction was essentially complete in 75 minutes, as opposed to the 2 hours that Yvon reported in her study of the same reaction[99]. When the reaction was performed using

concentrations greater than 1 mg/mL, the reaction was sluggish and typically did not go to completion (only 50-65% complete, even after irradiating for 3-5 hours). All future photochemical studies where thus performed at a concentration near 1 mg/mL.

More detailed study was then performed on the photochemical reactions of the remaining dibenzylidenesuccinate derivatives: bis(3,4,5-trimethoxy)benzylidenesuccinic acid (**137aa**), bis(3,4-methylenedioxy)benzylidenesuccinic acid (**137cc**), bis(3,4-dimethoxy)benzylidenesuccinic acid (**133bb**) and ethyl bis(3,4-methylenedioxy)benzylidenesuccinate (**133cc**). In each case, the product distributions were carefully studied. In cases where compounds were easily separable, more detailed structure elucidations and compound characterizations were undertaken.

We were originally somewhat apprehensive about pursuing this investigation after the preliminary results of Yvon in her attempted synthesis of magnoshinin[99]. The basic structure of magnoshinin includes two 2,4,5-trimethoxy-substituents. It was thought that this would be similar enough to 3,4,5-trimethoxy-substituted dibenzylidenesuccinates for a successful photochemical cyclisation reaction, but it was discovered that even prolonged irradiation of these compounds gave either only *cis-trans* isomerisation of the double bonds in the butadiene system, or in the formation of the fully aromatic arylnaphthalene product, (as evidenced by a new NMR peak at roughly 8.9 ppm for the naphthalenic proton α to the ester group). There was at least the possibility that the successful photocyclization of bis(3,4,5-trimethoxybenzylidene)succinate diethyl ester was unique to that compound and would fail for other derivatives.

When the other derivatives were studied, we were gratified to see that the procedure was in fact a general technique for the synthesis of *cis*-1,2-dihydronaphthalenes for most

dibenzylidenesuccinates. The number of compounds formed from the photochemical irradiation in acidic anhydrous ethanol varied from 4 to 7 depending on the substrate examined, but in each case the two major products formed appeared to be the *cis*- and *trans*-1,2-dihydronaphthalenes. Unfortunately, in each case the only reasonable way to separate the compound was to use an analytical HPLC column and collect fractions from multiple injections. This proved to be quite tedious and time-consuming, but also necessary as the retention times in each case proved to be too close to each other for any other method of chromatographic separation to be successful. It was anticipated that the compounds observed by HPLC would correspond to recovered starting material, the *cis*-dihydronaphthalene, the *trans*-dihydronaphthalene, the arylnaphthalene and the two other possible double bond isomers of the starting material (E,Z and Z,Z), depending on the nature of the substrate subjected to the irradiation.

As shown in Table 1, the various photoreactions showed a general preference to produce the *cis*-relative configuration over the *trans*-configuration. It was noted that the photochemical reactions involving the dibenzylidenesuccinic acids showed a lessened preference for formation of the *cis*-dihydronaphthalene than did the ethyl dibenzylidenesuccinates. Another interesting point is that the reaction with the 3,4-methylenedioxyphenyl aryl groups seemed to be much less selective than its counterparts with the other aryl groups. In addition, it is noted that the HPLC ratios don't match exactly with the NMR ratios given in the table. This has been previously explained by considering the differences in the absorption coefficients of the various products at the HPLC wavelength of detection (230 nm). NMR product ratios were determined by comparing the relative integration of both the vinylic and benzylic protons of the two

main photoproducts (*cis* and *trans*-products). Both the ethyl bis(3,4-dimethoxy)benzylidenesuccinate (**133bb**) and the bis(3,4-methylenedioxy)benzylidenesuccinic acid (**137cc**) analyses were complicated by the sheer number of products observed in the HPLC trace, or by overlapping peaks in the HPLC chromatogram. In some of these cases, the amount of product separated by HPLC for analysis was very low. Two of the *cis*-dihydronaphthalenes, **133aa** and **133cc** were fully characterised by ^{1}H NMR, ^{13}C NMR, mass spectrometry and exact-mass mass spectrometry. The remaining *cis*-dihdynaphthalenes were partially characterised by ^{1}H NMR, mass spectrometry and exact-mass mass spectrometry, due to the inability to purify sufficient quantities of product. We were unable to purify enough of the *trans*-dihydronaphthalenes to perform the ^{13}C NMRs required for full characterisation, but we were able to get full ^{1}H NMR, mass spectrometry and exact-mass mass spectrometry performed on these compounds, with the exception of the reaction of **137cc** for which the *trans*-photoproduct was not identified in the HPLC trace, nor to any appreciable extent in the crude or purified NMR spectra.

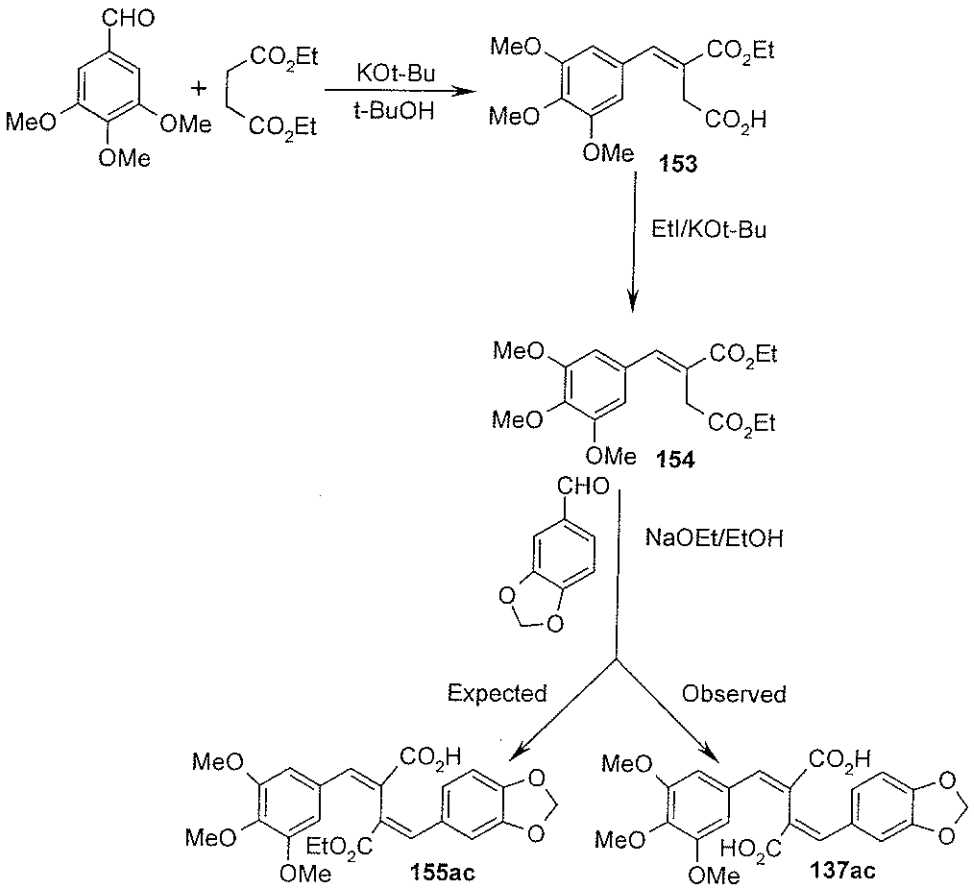
Table 1: Analysis of Photochemical Survey Reactions

Reaction Substrate	Relative *cis-trans* Product Ratio		Number of Products
	HPLC	^{1}H NMR	
133aa	83:17	12:1	4
133bb	77:23	15:1	4
133cc	52:48	4:1	4
137aa	73:27	4:1	5
137cc	*Trans*-product not identified		7

One reaction was attempted with a dibenzylidenesuccinic acid having dissimilar benzylidene groups. The aryl groups in this case were the 3,4,5-trimethoxy group and the 3,4-methylenedioxy group (as in compound **137ac**). The synthesis of this starting

material presented its own challenge. Whereas the symmetric compounds could be synthesised directly by a double Stobbe condensation with sodium hydride in toluene, mixed dibenzylidenesuccinates have to be synthesised via sequential Stobbe condensations. Thus, 3,4,5-trimethoxybenzaldehyde was reacted with an excess of diethyl succinate in a solution of potassium *t*-butoxide in *t*-butanol. This reaction produced the expected Stobbe ester-acid (**153ac**), which was immediately re-esterified by the addition of ethyl iodide to the basic *t*-butoxide solution. The Stobbe diester (**154ac**) was then purified by short-path vacuum distillation in reasonable yield (70%). A portion of the Stobbe diester was reacted with an equivalent of piperonal (3,4-methylenedioxybenzaldehyde) in a sodium ethoxide/ethanol solution to form the anticipated mixed acid/ester (**155ac**).

When the reaction product was analysed by NMR spectroscopy, it was determined that the product was in fact the mixed 3,4,5-trimethoxy/3,4-methylenedioxy Stobbe diacid (**137ac**) instead of the expected monoethyl ester (Scheme 41). It is known that the basic Stobbe condensation can produce small amounts of diacid products, thought to occur through an unstable dilactone[65]. Typically this reaction occurs at relatively low temperatures, and is unexpected in the case of a sequential Stobbe condensation. A possible explanation for the observed result is that the reaction did in fact form the anticipated Stobbe monoester product, but that this product was then hydrolysed by traces of hydroxide ion formed from traces of adventitious water. In any event it was possible to isolate the diacid in 38% yield.



Scheme 41

Not surprisingly, the photochemistry of this mixed dibenzylidenesuccinic acid proved to be very complicated with at least 10 products visible by HPLC. These products presumably corresponded to the starting material, 3 possible *cis-trans* isomerisation products (*E,Z*; *Z,E* and *Z,Z*), the three possible products from photocyclisation onto one aryl group (*cis*-dihydronaphthalene, *trans*-dihydronaphthalene and arylnaphthalene), and the three possible products from the photocyclisation onto the other aryl ring. Only six of the peaks were present to any great extend (greater than 4% relative intensity from the HPLC trace). Some of these peaks were not totally resolved by HPLC trace and would have been very difficult to separate. NMR provided very little information as to the identity or the relative amounts of individual compounds. As a result, no further investigation into the photochemistry of mixed dibenzylidenesuccinates was undertaken

The utility of these photochemical techniques for the synthesis of *cis*-1,2-dihydronaphthalenes and aryltetralin lignans was now evaluated. The survey reactions presented above indicated that the technique could produce reasonable yields of 1-aryl-1,2-dihydronaphthalenes with an excess of the *cis*-compound over the *trans*-compound. Opposed to this is the fact that most of the products from the reaction are very difficult to separate by any technique other than HPLC, making it unlikely that large-scale synthesis would be feasible by these methods. Another major drawback of the technique is that the synthesis of any aryldihydronaphthalene or aryltetralin lignan with mixed aryl groups by this technique would be extremely difficult, if not impossible, due to the lack of any control over the regiochemistry of the photocyclisation reaction. It might have been possible to get more control over the reaction if one were to use a mixed succinic acid derivative, such as the alcohol/ester compound that Heller investigated (see above). In that case Heller observed better regioselectivity in the photocyclization reaction although it is not known whether that would hold true for other derivatives. Further investigation into this area is still needed to answer some of these questions and to determine if there are any larger-scale synthetic uses for these intriguing photochemical reactions.

3.2 Photochemistry of a Dibenzylidenesuccinate-Chiral Auxiliary Adduct

As noted in the previous section, the photochemistry of dibenzylidenesuccinates is quite varied, but unfortunately is lacking in selectivity. The result observed in the case of the unsymmetrical dibenzylidenesuccinate showed that there was no control at all over the regiochemistry of the cyclisation, as products were observed as having arisen from cyclisation onto both aryl groups. In the case of the symmetric dibenzylidenesuccinates, a lack of control over the relative configurations of the products was observed as both the 1,2-*cis* and 1,2-*trans* products were formed in appreciable amounts.

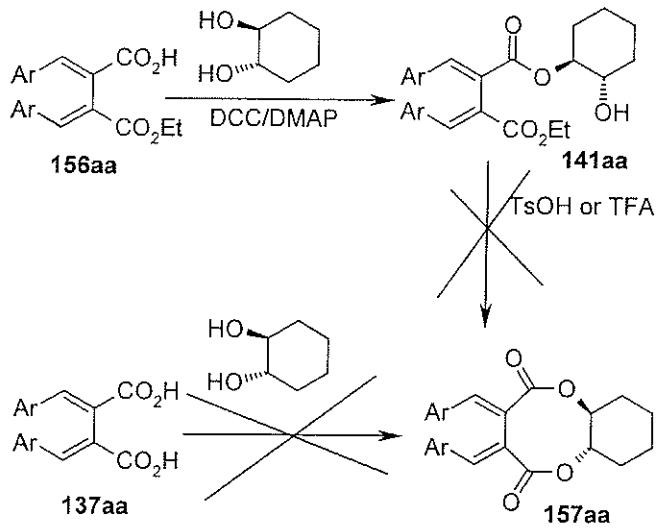
It should also be noted that the dibenzylidenesuccinates that were investigated in the previous section exhibit atropisomerism in a manner similar to what was described in Chapter 1 of this thesis. As there are no chiral elements in the molecule, other than the helical chirality provided by the atropisomerism, the two rotamers of the dibenzylidenesuccinate can be considered to be enantiomers of one another. As the barrier to rotation in the open-chained dibenzylidenesuccinates is much less than 23 kcal/mol, it is expected that the dibenzylidenesuccinates studied in the previous section existed as a racemic mixture of the two rotamers. Thusly, we would expect to find no control over the absolute configuration of the photoproducts and would expect them to be racemic in nature. The 1,2-*cis* product would be a racemic mixture of the 1*R*,2*R* and 1*S*,2*S* configurations, while the 1,2-*trans* product would be expected to be found as a racemic mixture of both the 1*R*,2*S* and 1*S*,2*R* configurations. If we wanted to perform an asymmetric synthesis of any lignan natural product using this method, we would be unable to form the target in anything other than a racemic mixture due to this lack of control over the absolute stereochemistry of the molecule.

This problem could be solved however if we were to consider attaching a chiral auxiliary to the dibenzylidenesuccinate. The attachment of a chiral auxiliary might allow one to gain some measure of control over the final absolute configuration of the reaction product. The addition of a chiral auxiliary would make the atropisomers of the dibenzylidenesuccinate diastereomeric in form instead of enantiomeric. These diastereomeric rotamers would then have differing ground-state energies and could be distinguished by spectroscopic techniques. If the difference in energy between the rotamers was great enough, it is possible that one of them might be formed in preference to the other rotamer. This in turn might give the photochemical reaction some preference for one particular absolute stereochemistry in the products of the photochemical cyclization. With this considered, we decided to explore the potential uses of a chiral auxiliary in the photochemistry of dibenzylidenesuccinates.

Some work had been performed previously by two colleagues in this area, and after some initial negative results some progress had been made. Yvon explored the use of a methyl mandelate group as a chiral auxiliary to help exploit the inherent atropisomerism of the dibenzylidenesuccinate (**137aa**)[99]. She had hoped that the auxiliary would prejudice the molecule to adopt one of the atropisomeric forms preferentially. As noted previously, the atropisomers (**143aa**) in the presence of another chiral element in the molecule become diastereomeric, and the diastereomers have different physical properties, including ground-state energy and NMR spectra. Yvon's study of the NMR spectra showed that the two rotamers were still present in roughly equal amounts. The addition of the methyl mandelate group also allowed for a determination of the effect of increasing the steric bulk of the succinate derivative on the magnitude of the barrier to

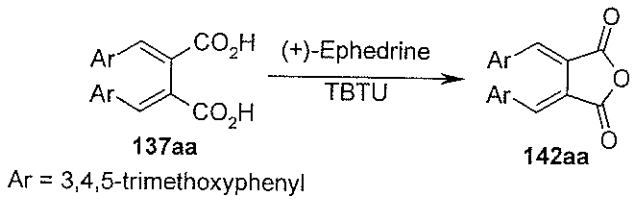
rotation. She had hoped that the steric bulk of the methyl mandelate group would increase the barrier to rotation to more than 23 kcal/mol, which would allow for the isolation of the atropisomeric forms. As noted in the introduction, she measured the barrier by dynamic NMR and found it to be slightly less than 20 kcal/mol. This is too low for the atropisomers to be separated at room temperature.

Yvon also tried using *trans*-1,2-cyclohexandiol to form a rigid 8-membered dilactone (**157aa**) in the hopes that it could help force the molecule to adopt only one atropisomeric conformation/configuration. Addition of the diol to the bis(3,4,5-trimethoxy)benzylidene ester/acid (**156aa**) was accomplished using DCC and DMAP to form the mixed ethyl/cyclohexyl diester (**141aa**) (Scheme 42)[99]. Several of the proton NMR peaks were observed to be doubled, indicating that there were two diastereomeric forms of the compound. Performing the trans-esterification reaction to form the desired dilactone proved to be impossible, either in acidic media (TsOH or TFA) and the direct reaction of bis(3,4,5-trimethoxy)benzylidenesuccinic acid (**137aa**) with *trans*-1,2-cyclohexandiol also failed. This failure was explained as being due to the difficulty of forming the 8-membered dilactone ring system. It is anticipated that the torsional strain of the system, which is similar to that found in all medium-sized rings is intolerable in the context of this system.



Scheme 42

Yau attempted to partially solve this problem by using a more flexible chiral auxiliary, (+)-ephedrine[100]. It was anticipated that this auxiliary would be more useful as it lacked the rigid cyclic backbone of the *trans*-1,2-cyclohexandiol and would have less torsional strain if it were to form a cyclic amide ester with the dibenzylidenesuccinic acid. When he attempted to form the cyclic 8-membered ester/amide structure using benzotriazol-1-yl-1,1,3,3-tetramethyl uronium tetrafluoroborate (TBTU) as a coupling agent, he discovered that he did not get the desired product. He observed that the reaction mixture went from the yellow of the succinic acid to a dark green colour, which was attributed to the presence of the diarylfulgide (**142aa**) (Scheme 43). He was not able to observe any coupling to the ephedrine to form the desired cyclic ester/amide.



137aa

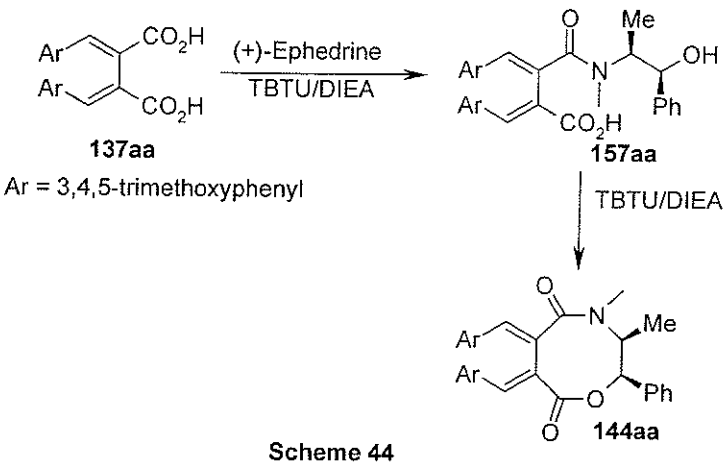
Ar = 3,4,5-trimethoxyphenyl

142aa

Scheme 43

Despite this setback, we were still interested in pursuing the use of ephedrine as a chiral auxiliary for our work. A postdoctoral colleague, Dr. P. Datta, initiated new work on this project. He decided to explore the coupling and photochemistry of the bis(3,4,5-trimethoxy)benzylidenesuccinate system as it was the photochemical reaction that was best understood in our group. He discovered that by performing the coupling reaction using a fourfold excess of Hunig's base (N,N-diisopropylethylamine or DIEA), and one equivalent of ephedrine and TBTU, resulted in the formation of a compound that had both amide and acid functionality (**157aa**) (Scheme 44). Analysis of the proton NMR indicated that the reaction product had the ephedrine coupled to one of the carboxylic acid groups, but not to the other. When reacted a second time with one equivalent of TBTU and four equivalents of DIEA, it was anticipated that the intermediate would couple to form the cyclic ester/amide (**144aa**) in good yield. Unfortunately, when the reaction was worked up and purified by chromatography (3:2 ethyl acetate-hexanes), it was determined that the desired product was only formed in 19% yield.

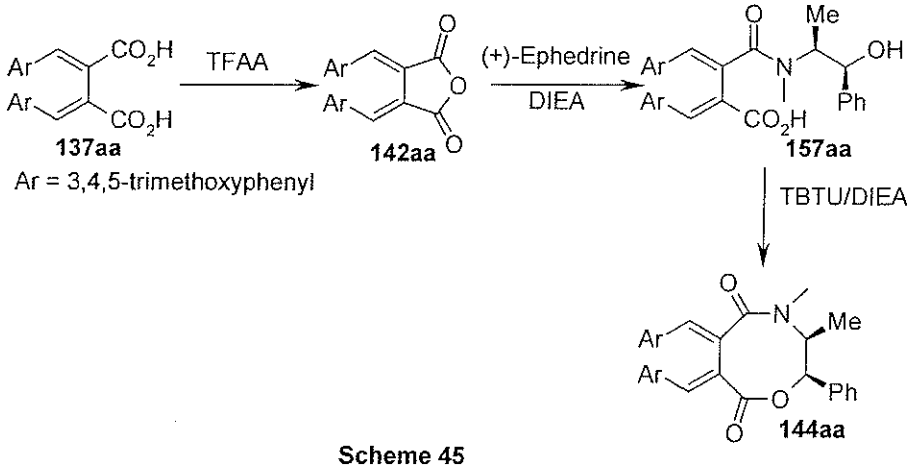
One of the observations from this process was that the first reaction proceeded through a greenish intermediate that was assumed to be the same diarylfulgide that Yau had observed in his attempted work on the ephedrine coupling[100]. At this point, a collaborative study with another postdoctoral colleague, Dr. T. Assoumatine, was performed on the merits of forming the fulgide directly. We decided to form the fulgide directly by adding five equivalents of trifluoroacetic anhydride (TFAA) directly to the



Scheme 44

diacid at 0 °C. Once the TFAA had been added, the solution was warmed to room temperature and monitored by TLC for the complete formation of the fulgide (**142aa**). Once the reaction reached completion, the solvent and excess TFAA was evaporated and fresh solvent was added along with one equivalent of ephedrine and three equivalents of DIEA (Scheme 45). It was hoped that the crude fulgide would react to form the desired ester/amide (**144aa**). Even after stirring for 4 days, no appreciable amount of the desired ester/amide was observed to form. After work-up, the crude product was analysed by NMR spectroscopy and was discovered to be almost entirely unreacted starting material. After several unsuccessful attempts, this approach was abandoned.

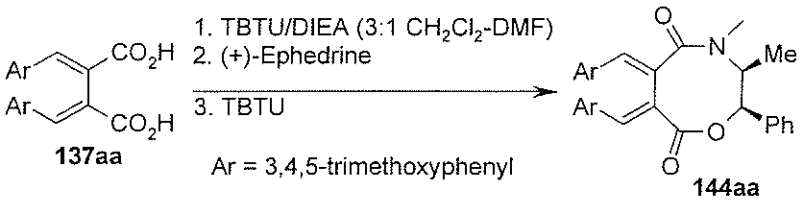
The coupling reaction with ephedrine, using TBTU and DIEA, was subsequently



Scheme 45

reattempted several times on the fulgide, again in collaboration with Dr. Assoumatine. In these trials, the resulting amide/acid was subsequently reacted with another equivalent of TBTU and excess DIEA (Scheme 45). The result of these reactions was the formation of a small amount of the desired cyclic ester/amide (**144aa**) (yields varied from 7-19% overall). This was not a great improvement over the original process, so further refinement of the procedure proved to be necessary.

Ultimately, an optimum procedure was developed by Dr. Assoumatine, which involved the addition of one equivalent of TBTU and four equivalents of DIEA to a methylene chloride/DMF solution of the bis(3,4,5-trimethoxy)benzylidenesuccinic acid (**137aa**). This was performed at 0° with stirring for 30 minutes. Then, a solution of one equivalent of ephedrine in methylene chloride/DMF was added and the reaction was allowed to warm to room temperature and stand overnight. The following day, another equivalent TBTU was added and the reaction was allowed to proceed overnight again (Scheme 46). After work-up, the desired ester/amide (**144aa**) was purified by chromatography (3:2 ethyl acetate-hexanes) in relatively good yield (yields ranged from 35-52%).



Scheme 46

Analysis of the NMR of this cyclic amide/ester showed an interesting detail. The NMR spectrum appeared to be that of a single atropisomeric form. This was obvious from the lack of double signals for the various hydrogen atoms in the molecule that we would expect if the spectra were that of a mix of atropisomers. This also stands in stark

contrast to Yvon's study of the methyl mandelate adduct in which she observed a mixture of two atropisomers in the NMR spectra of the reaction product. One could conclude that the ephedrine, while flexible enough to allow the cyclic 8-membered amide/ester to form, is able, because of the bulky groups on the its chiral centres, to force the dibenzylidenesuccinate to adopt a single preferred atropisomeric form.

In order to determine the actual structure of the ephedrine adduct, Spartan[103] molecular mechanics calculations were performed in order to determine what the lowest energy conformation of the molecule was. It was determined that the energy gap between the possible atropisomers resulted in essentially 100% of the molecules to exist in a single atropisomeric form. This structure (Figure 15) suggests that the aryl group that is adjacent to the ester moiety is being held above the plane of the molecule, while the aryl group next to the amide moiety is being held below the plane of the molecule. As will be discussed later, this structure was of some predictive use for determining the absolute stereochemistry of the ensuing photochemical reaction.

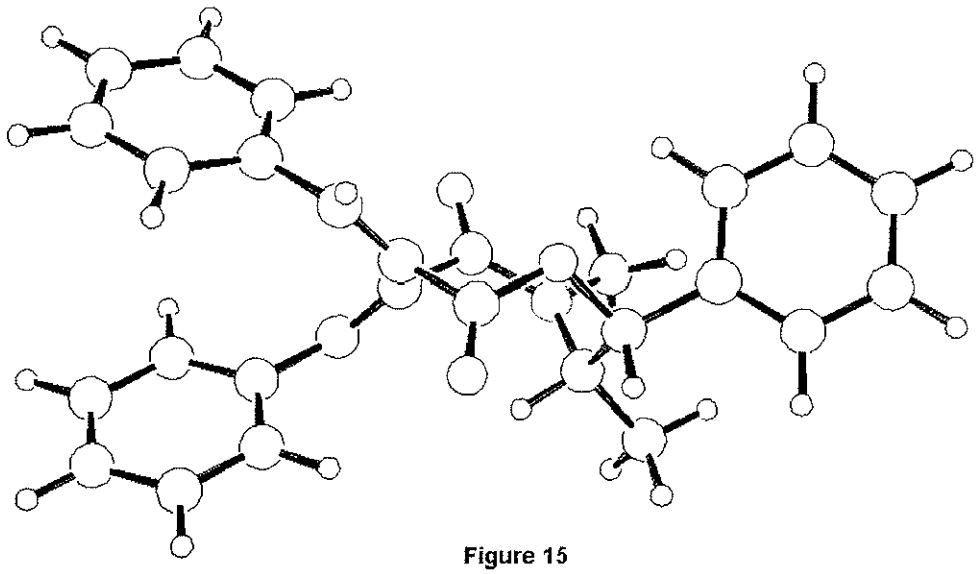
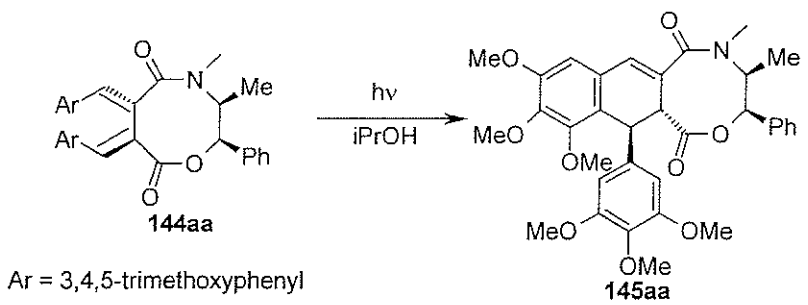


Figure 15

With the ephedrine adduct in hand, it was time to study how the chiral auxiliary influenced the photochemical properties of the dibenzylidenesuccinate moiety. It was determined through some collaborative work with Dr. Assoumatine that irradiation in 2-propanol was optimal (Scheme 47). When performed at concentrations between 0.5 and 1.0 mg/mL, the reaction yields were optimized to between 50-65% conversion to the major product (**145aa**). The major product could be isolated by crystallization from a small volume (roughly 1-2 mL) of a 1:1 solution of methylene chloride-ethanol as colourless crystals. HPLC analysis was performed on both the crystalline material and on the mother liquor. The crystals proved to be a pure compound as expected, while the mother liquor gave rise to three peaks in the HPLC trace. One of these peaks corresponded to a small amount of the major product, which presumably didn't completely crystallize. The other peaks corresponded to unreacted starting material and an unknown compound that was not characterized. It should be noted that a Dr. Datta had isolated and characterized a compound having a 1,4-dihydronaphthalene structure when he performed this same reaction in anhydrous ethanol. It is presumed that the unknown product may correspond to traces of 1,4-dihydronaphthalene in the mother liquor.



144aa → **145aa**

Ar = 3,4,5-trimethoxyphenyl

Scheme 47

One major drawback of this reaction is that it can only be performed efficiently on small scale. Performing the reaction on more than about 30 mg of reagent was observed to result in reduced yields, irrespective of how much solvent was used or the size and surface area of the irradiation vessel. This result has proven to be quite difficult to explain fully and a full explanation is still unknown. It might be possible that once a certain concentration of product is formed that it can absorb incident light and prevent any remaining starting material from being irradiated and reacting. It may also be that the 1,8-dihydronaphthalene intermediate absorbs more light and is photochemically converted to a 1,4-dihydronaphthalene product in a manner analogous to that recently described by Charlton and Assoumatine[93]. This could also possibly explain why a compound with a 1,4-dihydronaphthalene structure was observed in Dr. Datta's work, and could explain the extra peak found in the HPLC analysis. This phenomenon remains unanswered and more work is obviously required to explain this.

The proton NMR spectrum of the major photochemical product showed a small coupling constant between the allylic proton at roughly 4.2 ppm and the benzylic proton at roughly 4.8 ppm. In analogy to our work on dibenzylidenesuccinates described previously, the dihydronaphthalene photoproduct was determined to have a 1,2-*trans* relative configuration (either 1*R*,2*S* or 1*S*,2*R*).

A more pressing issue was the regiochemistry of the cyclisation reaction. It was impossible to determine from standard NMR techniques whether the ring closure had occurred on the aryl group that was next to the amide functionality or or on the aryl group next to the ester moiety. Two-dimensional NMR work was performed, with a heteronuclear multiple-bond correlation (HMBC) spectroscopy technique providing the

best indicator as to the actual structure of the final product. Analysis of this spectra resulted, in addition to the information provided by the one-dimensional proton and carbon NMR spectra, in the conclusion that the cyclisation occurred onto the aryl group next to the amide moiety.

Once we had isolated the main photoproduct, an optical rotation measurement was taken to ensure that the compound was in fact optically active, which would at least indicate that the compound formed was not a racemic mixture. The compound was observed to have a very large optical rotation of +475.7°, which indicated that one of the two possible enantiomers was formed in excess. Consideration of the Spartan[103] molecular mechanics structure presented earlier gave some ideas as to the absolute configuration of the photoproduct. The Spartan structure corresponds to the acyclic dibenzylidenesuccinate, and not the 1,8-dihydronaphthalene intermediate from which the *trans*-1,2-dihydronaphthalene was formed, but the calculated structure could be used to predict the structure of the 1,8-dihydronaphthalene intermediate. It was predicted that conrotatory ring closure onto the lower aryl group (the one adjacent to the amide group), would result in a 1,8-dihydronaphthalene intermediate that placed the pendant aryl group in an "up" position (S configuration). This configuration would then be carried through to the 1,2-dihydronaphthalene product. If NMR analysis showed that the relative stereochemistry was 1,2-*trans*, then the ester moiety from the ephedrine group would be placed in the "down" position (R configuration). This would predict that the absolute configuration of the *trans*-1,2-dihydronaphthalene would be 1*S*,2*R*. Conformation of this predicted absolute configuration is the subject of the next section, where this reaction will be used towards the asymmetric synthesis of a lignan natural product.

From the above result, it was now possible to utilise this reaction in an asymmetric synthetic pathway to form aryltetralin or aryldihydronaphthalene lignans with the 1,2-trans relative configuration, which results from the photochemistry. The ease with which the photoreaction proceeds makes this reaction very attractive for the synthesis of lignan natural products of these types. Further work in this area could be done to see if the effect of using ephedrine as a chiral auxiliary is general to all similar dibenzylidenesuccinate, or if it is specific to this one compound.

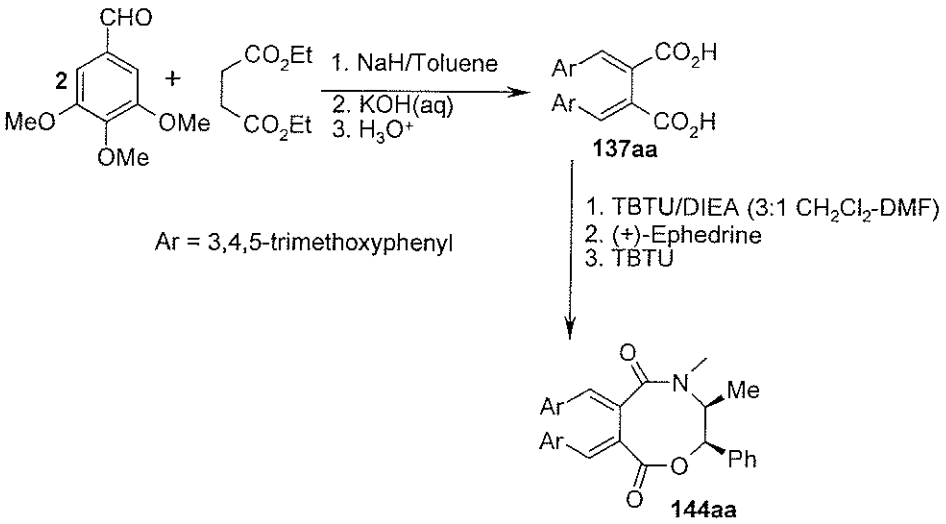
3.3 Asymmetric Synthesis of (+)-dimethyllyoniresinol

Once it was known that the dibenzylidenesuccinate/ephedrine adduct would produce a photoproduct that was observed to be optically active, a decision was made to exploit this result in the asymmetric synthesis of a lignan natural product. The chosen target molecule was (+)-dimethyllyoniresinol, which had a number of features that made it an appropriate choice for synthesis. Firstly, it is notable for being one of the few natural lignans that has been isolated having a 3,4,5-trimethoxy-substitution pattern on both aryl groups. Secondly, it has a 1,2-*trans* relative configuration that could easily be formed from the photochemistry of the bis(3,4,5-trimethoxy)benzylidenesuccinate/ephedrine adduct. Finally, it has a trans-1*S*,2*R* absolute configuration at those same stereogenic centres. This was the same as the absolute configuration that was predicted in the previous section as being the likely absolute configuration formed on the photochemical cyclisation of the dibenzylidenesuccinate/ephedrine adduct.

Another attractive aspect of this target lignan was that it had been partially characterized upon its isolation from natural sources, a characterization that included a

published optical rotation of +49.4°[104]. Previous syntheses of this compound showed a range of observed optical rotations that included +21.5°[105a], +26.0°[105b] and +30.0°[105b]. This would allow us to confirm our predicted absolute configuration for the product of the photochemical cyclisation. If our final synthetic (+)-dimethyllyoniresinol was found to have an optical rotation of roughly the same magnitude as that of the authentic sample, with the correct sign, then we would be quite confident that the synthesis had formed only one stereoisomer with the predicted absolute stereochemistry. However, if the direction of the rotation were reversed (i.e. roughly –21.5° to -49.4°) then it would indicate that a single isomer had been formed but with the opposite absolute configuration to that of (+)-dimethyllyoniresinol. At any rate, this result would allow us to unequivocally determine the absolute stereochemistry of key photocyclisation step to form the *trans*-1,2-dihydronaphthalene as described previously. This would be possible as the stereochemistry at those two stereogenic centres would remain unchanged throughout the remainder of the synthesis. From this, we would then be able to either prove or disprove our predicted absolute configuration for the photoproduct previously investigated.

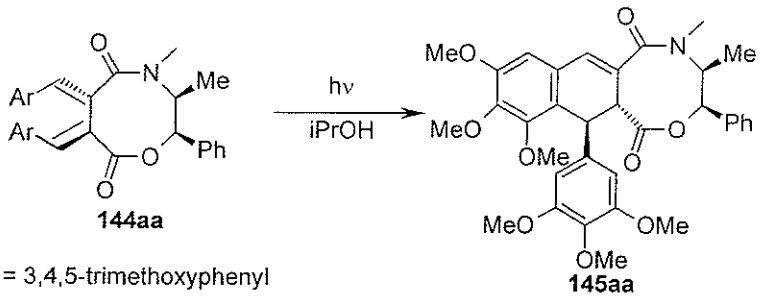
The early stages of the synthesis were very similar to work that has already been presented. In the first step, a double Stobbe condensation was performed using diethyl succinate and two equivalent of 3,4,5-trimethoxybenzaldehyde in a sodium hydride/toluene solution. This was refluxed overnight and worked up to produce the crude bis(3,4,5-trimethoxy)benzylidenesuccinic acid (**137aa**) (Scheme 48). Recrystalization from methylene chloride/hexanes afforded pure diacid in a reasonable yield (51%).



Scheme 48

The next step in the reaction sequence was to couple (+)-ephedrine to the diacid. The general procedure described in the previous section of sequential additions of one equivalent TBTU and four equivalents DIEA, followed by one equivalent of ephedrine and reaction for 18 hours, then a second equivalent of TBTU and further reaction for another 18 hours, was followed (Scheme 48). Sequential acid washings for the work-up and purification by chromatography (3:2 ethyl acetate-hexanes) yielded the pure cyclic ester/amide (**144aa**) (49%).

As noted in the previous section, the photoreaction seemed to only proceed to an optimum yield when the reaction was done on a small scale (typically 20-30 mg). A few larger scale reactions (40-60 mg) were attempted, but typically produced lower yields (in both mass and percentage terms) than the smaller scale reaction, even when the amount of solvent was scaled accordingly. As a result, our pure ester/amide was divided up into several small samples that were reacted separately (Scheme 49). The individual photoproducts (**145aa**) were purified by recrystalization from a small volume of 1:1 ethanol-methylene chloride and combined together for the next stage of the reaction sequence.



144aa

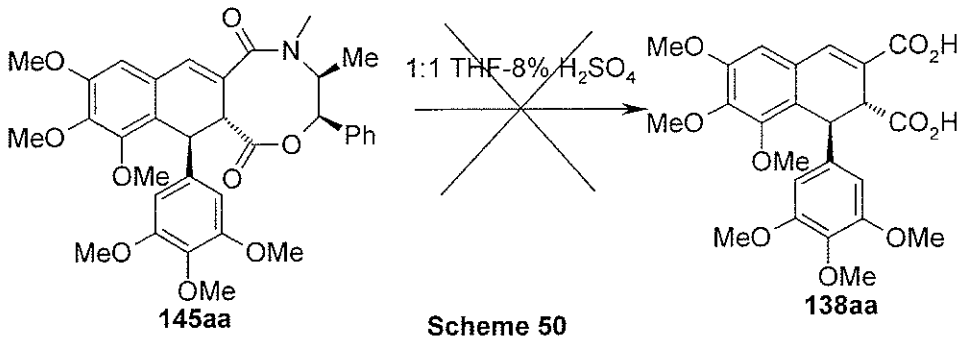
Ar = 3,4,5-trimethoxyphenyl

145aa

Scheme 49

Once the molecule had been induced to react photochemically to produce the desired product, it was time to remove the ephedrine group. This apparently simple reaction proved to be most difficult to perform and required several attempts before it was successful. Some medium-scale (8-12 mg) test reactions were performed under a variety of conditions, both acidic and basic to no effect.

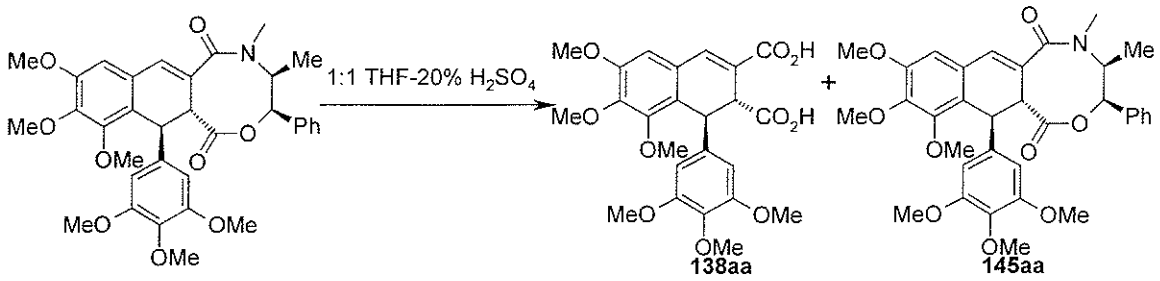
In the first trial, the ephedrine photoproduct (**145aa**) was reacted with a 1:1 solution of THF-8% sulphuric acid. THF was chosen as the solvent as it was one of the few solvents in which the photoproduct was soluble to any great extent. The reaction was performed at room temperature and was kept open to the atmosphere. The reaction was monitored both by TLC and HPLC over a period of 65 hours and hydrolysis did not appear to be occurring to any appreciable extent. When the reaction was worked up and analysed, it was determined that virtually no hydrolysis had occurred and that a considerable amount of air oxidation to the fully aromatic arylnaphthalene had occurred. As a result, the reaction was tried again on a smaller scale (3 mg) and under more carefully controlled conditions. In this experiment, the reaction was purged with nitrogen for 15 minutes, then conducted under a slight positive pressure of nitrogen gas at room temperature. The reaction was also monitored periodically by HPLC. It was observed that the reaction did not really proceed to any great extent when conducted at room temperature, even under nitrogen and even after 36 hours (Scheme 50).



145aa **138aa**

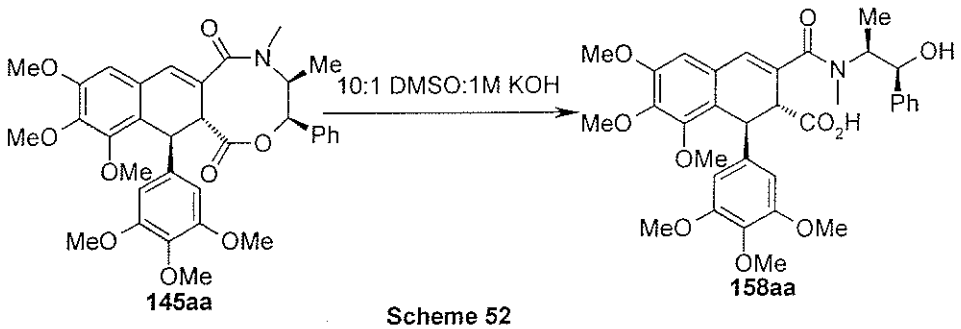
Scheme 50

With these failed experiments noted, a decision was made to reflux the mixture and increase the concentration of the sulphuric acid. A systematic HPLC study was conducted on a small sample of the ephedrine photoproduct (3.4 mg) in a small amount of 1:1 THF-20% sulphuric acid, which was purged with nitrogen, then heated at reflux. HPLC samples were taken every 30 minutes and analysed to determine the rate of product formation. It was determined that almost immediate hydrolysis occurs of the ephedrine ester to form an acid/amide (**158aa**). After about 30 minutes a second peak appeared in the HPLC trace that was eventually shown to be the diacid (**138aa**). At 30 minutes the ratio between the two compounds was observed to be 3:10 diacid-acid/amide (based on HPLC measurements), with significant amounts of unreacted ephedrine photoproduct remaining unreacted. After refluxing for one hour, the ratio switched to 13:5 in favour of the desired diacid, while after reacting for 90 minutes the ratio was on the order of 50:1 in favour of the diacid, but still with large amounts of unreacted starting material observed. Unfortunately, even after 2 hours of heating at reflux, the dominant component of the reaction mixture remained unreacted ephedrine photoproduct (**145aa**), which was almost double the intensity of the desired diacid product (**138aa**) based on the relative HPLC intensities (Scheme 51). As a result, this method was dropped from consideration as a reasonable approach to our problem of hydrolysing the ephedrine group.



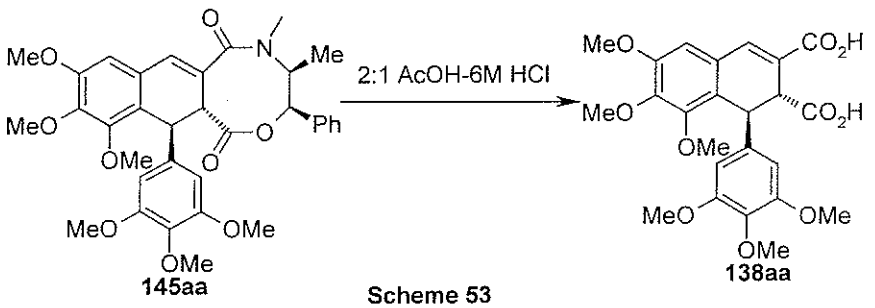
Scheme 51

It was then decided to try a base-hydrolysis to remove the ephedrine group from the molecule. Another small scale HPLC study was undertaken (1.1 mg) reaction. The reaction was carried out at room temperature in 10:1 DMSO-1M KOH, with periodic HPLC monitoring. The interesting thing about this reaction was the almost immediate disappearance of the HPLC peak corresponding to the ephedrine adduct (**145aa**) and the appearance of a large peak assumed to correspond to the acid/amide (**158aa**), based on our HPLC study of the ephedrine addition reaction previously described. However, after even 24 hours of reacting, there was no significant accumulation of the desired diacid, (estimated ratio of 1:60 between diacid and acid/amide). A second trial was attempted by heating a fresh sample at 70° for 24 hours and again monitoring by HPLC. Even at elevated temperatures, it was observed that no significant amount of the desired diacid was formed and that the reaction seemed to stop at the acid/amide intermediate, based on the analysis of the HPLC traces that were conducted (Scheme 52).



Scheme 52

Dr. Assoumatine then made a fortuitous discovery that a complex mixture of methylene chloride/acetic acid and 6M hydrochloric acid would cleave the ephedrine group completely. The basic procedure was to dissolve the ephedrine adduct in methylene chloride, then add one volume of acetic acid. At this point the methylene chloride was evaporated and if a large enough volume of acetic acid was added, the compound would stay in solution. The solution was then purged with nitrogen and while



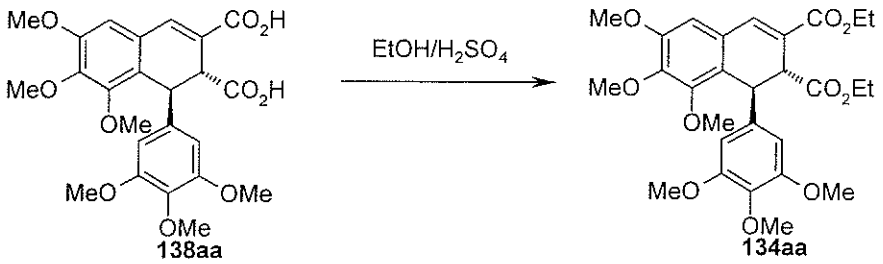
145aa **138aa**

Scheme 53

purging, two volumes of 6M HCl were added to the solution. When the nitrogen purge was complete, the solution was heated to reflux under nitrogen atmosphere for 3 hours, then worked up to produce a yellowish oil (Scheme 53). The NMR of the crude product was somewhat complex and showed evidence of other side products besides the desired diacid (**138aa**), but was also notable for the complete exclusion of any ephedrine containing compounds from the product mixture.

It was also noted that this reaction was very concentration dependent and worked much better on small scales. When the reaction was scaled up to greater than 40-50 mg, it was observed that much larger volumes of acetic acid and 6M HCl were required to keep the material in solution prior to refluxing the solution and that the overall reaction time tended to be longer. It was also observed that the overall yield was typically significantly worse for the hydrolysis reaction than it would be for doing the reaction in two smaller batches.

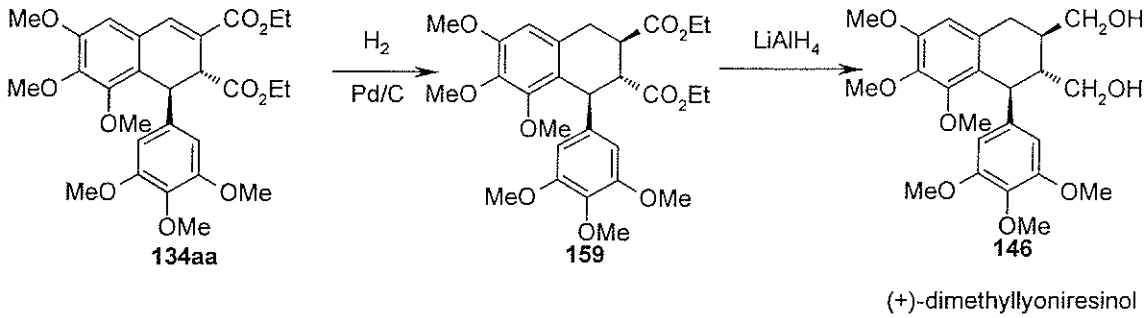
The resulting diacid (**138aa**) was re-esterified to the ethyl diester (**134aa**). In comparison to the previous hydrolysis reaction, this reaction was quite straightforward as



Scheme 54

it was performed in refluxing ethanol with a catalytic amount of concentrated sulphuric acid (Scheme 54). The reaction was allowed to proceed for 3 hours at which time HPLC analysis showed the disappearance of all diacid starting material. The product was worked up to a crude brownish oil that was purified by chromatography (3:1 hexanes-ethyl acetate) to yield a pale yellow oil (31% for the hydrolysis-esterification sequence). The NMR spectra of the resulting diester was compared to that reported in a previous study done in our group, and to the *trans*-1,2-dihydronaphthalene reported in the first section of this discussion. This product was found to have spectral characteristics that were identical to those previously reported[69].

Once the compound had been re-esterified, it was a simple matter to hydrogenate the double bond and then reduce the ester groups to form (+)-dimethyllyoniresinol (**146**) (Scheme 55). The hydrogenation was performed over Pd/C in methanol, which was allowed to react overnight. This reaction did cause some problems, as the reaction took the better part of three days to go to completion, when it was expected that it should only take several hours. One possible explanation is that a bad sample of palladium catalyst was used, which could greatly slow the reaction. This reaction and the surprising nature



Scheme 55

of the length of reaction may require further study and analysis before a detailed understanding becomes available.

The main issue of the hydrogenation reaction was the ultimate stereochemistry at the new chiral centre. It was expected that the bulky aryl group on the benzylic carbon, being positioned above the ring plane would block the access of hydrogen and catalyst from the top face of the double bond. As a result, we were predicting that the hydrogenation would occur on the bottom face of the double bond to give the all-*trans* geometry (**159**) that was desired. In addition, a former colleague had performed a series of hydrogenation reactions on a variety of similar 1,2-dihydronaphthalenes and found that the all-*trans* product was observed almost exclusively[100]. On analysis of the NMR spectrum, we were able to observe coupling between the protons on two of the three chiral centres that seemed to be most consistent with that expected of an all-*trans* (1*R*,2*S*,3*R*) arrangement. The H-1 to H-2 coupling was observed to be about 7.5 Hz, which is consistent with a 1,2-*trans* di-axial geometry. Close examination of the H-2 signal resulted in the appearance of a large coupling constant to H-3, which was estimated to be about 9 Hz, (although the overlapping signals for H-2, H-3 and H-4a/b made this little more than guesswork) Due to the overlapping nature of many of the key proton signals, a definitive analysis was not completely possible, but the proton coupling

that we could clearly observe were consistent with our predicted stereochemistry. It was also observed that there was an observable amount of a minor hydrogenation product, (about a 6:1 ratio by integration of the ^{1}H NMR signals). This was surprising considering how the hydrogenation reactions reported by Yau gave almost entirely the single all-*trans* product[100]. This result was in accordance with what was observed by a postdoctoral colleague, when he performed this reaction with the racemic 1,2-dihydronaphthalene.

The reduction of the ester groups was performed with lithium aluminium hydride in THF (Scheme 55). The reaction was quite quick and was over in less than 90 minutes. After work-up by Feiser's method[106], the crude product was purified by chromatography (4:1 ethyl acetate-hexanes) to give (+)-dimethyllyoniresinol (**146**) in 35% yield (hydrogenation/reduction steps) which was identified by comparison of its NMR spectrum to the published spectrum. The yield was somewhat disappointing as it was anticipated that the final two steps should proceed quantitatively. It is possible that some compound was lost during the work-up for the hydrogenation reaction, and also likely that some compound was lost during chromatography and work-up of the hydride reduction. The optical rotation for the synthesised (+)-dimethyllyoniresinol (**146**) (+24.8°) was less than that first reported in the literature for the compound (+49.4°)[104]. It is possible that some contaminants may have been present in our final product, likely due to the hydrogenation not being as selective as we would have liked it to be, or due to epimerisation of one of the stereogenic centres during the vigorous reaction conditions required for the ephedrine hydrolysis/re-esterification reaction sequence. Either of these could have led to the formation of small amounts of contaminants that had optical properties that were different from optically pure (+)-dimethyllyoniresinol (**146**). As

well, these contaminants would be extremely difficult to remove from the product by conventional chromatographic techniques as, being isomers, they would have retention times that were very close, if not identical, to that of the desired product. It should be noted however that this value falls in the middle of a range of values observed from other syntheses of (+)-dimethyllyoniresinol. Previous reports give +21.5°[105a], +26.0°[105b] and +30.0°[105b] as the observed optical rotation. A determination of the absolute optical purity of the final synthesized (+)-dimethyllyoniresinol is still elusive and further study is obviously required to determine the actual optical rotation of the pure compound.

As noted in the introduction of this section, one of the goals for this total synthesis was to use the result to confirm the absolute stereochemistry of the photoproduct formed when the bis(3,4,5-trimethoxy)benzylidenesuccinate/ephedrine adduct was irradiated. As the synthesised (+)-dimethyllyoniresinol had a measured optical rotation of +24.8°, which is in the same direction as the authentic compound, we can assume with some confidence that our photoreaction produced the *trans*-1*R*,2*S*-dihydronaphthalene with the absolute configuration that we had earlier predicted, and which matched that of the authentic sample of (+)-dimethyllyoniresinol.

One area for future work would be to determine if the reaction process described above, in particular the chiral induction provided by the ephedrine in the photochemical cyclisation, could be applied more generally to other dibenzylidenesuccinate systems. If it were possible, many more lignans could potentially be prepared asymmetrically as there are many more natural lignans with 3,4-dimethoxy and 3,4-methylenedioxy aryl groups than there are with 3,4,5-trimethoxy groups. Studies would have to be done to determine the preferred conformation of the most stable atropisomer when the ephedrine

group is added. It would be interesting to see if the chiral auxiliary influences the atropisomer population sufficiently to promote a different relative and absolute configuration than the trans-1*R*,2*S* configuration observed in this situation. However, once that is determined and the resulting photochemistry is studied, a whole host of natural lignans should be available to be asymmetrically synthesised and studied.

Another advantage of the chiral auxiliary method is that it provides a possible way to control the regiochemistry of ring closure for mixed-aryl dibenzylidenesuccinates. Presumably the ephedrine adduct for the mixed dibenzylidenesuccinate would also be locked into exclusively one atropisomeric form, from which only one photocyclisation reaction would be possible. It should be noted that two possible regioisomers would be possible for the formation of the ephedrine adduct in that case (amide group adjacent to one aryl group or the other), although it might be possible to separate them by chromatography and then carry each product through to a different lignan. If this potential problem could be overcome, it would be possible to utilise the techniques described in this thesis to effectively perform the asymmetric synthesis of numerous lignan natural products.

Chapter 4

Conclusions

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

The first part of the thesis involved a study of a series of photochemical reactions of dibenzylidenesuccinic acid derivatives. The compounds studied in this section differed both in the nature of the succinic acid derivative (either diacids or diethyl esters) and in the nature of the aryl substituents (3,4-methylenedioxy, 3,4-dimethoxy or 3,4,5-trimethoxy). The prime focus of these studies was on the reactivity of the symmetric dibenzylidenesuccinic acid derivatives, although one mixed diacid (3,4,5-trimethoxy/3,4-methylenedioxy) was also studied. The syntheses of the required acyclic precursors were successfully executed, and were then subjected to photochemical study. It was determined that a variety of photoreactions occurred while the samples were being irradiated, with the most common reactions being *cis-trans* isomerisation of the benzylidene groups and the conrotatory electrocyclic ring closure to form 1,8-dihydronaphthalenes, which then underwent further reaction to form 1,2-dihydronaphthalenes. For each of the symmetric dibenzylidenesuccinates, a variety of products were observed, with the *cis*-1,2-dihydronaphthalene typically being the major product and the *trans*-1,2-dihydronaphthalene being the next most common product, although usually to a much lesser extent than the *cis*-dihydronaphthalene. The study of the mixed 3,4,5-trimethoxy/3,4-methylenedioxy dibenzylidenesuccinic acid resulted in a very complex mixture of inseparable products and further work on mixed dibenzylidenesuccinates was abandoned. It was hoped that reactions of this sort would

prove to be of a general nature and of synthetic utility. Unfortunately, even though the reactions have been shown to be of a general nature for the dibenzylidenesuccinates studied, the difficulty in separating larger quantities of the reaction products would relegate these reactions to being more of an academic curiosity rather than of great synthetic use.

The second section of this thesis dealt with attempts to link a chiral auxiliary, namely (+)-ephedrine, to the symmetric dibenzylidenesuccinic acid formed from 3,4,5-trimethoxybenzaldehyde and diethyl succinate, and the subsequent photochemistry of the dibenzylidenesuccinate-ephedrine adduct. It was hoped that the addition of the chiral auxiliary would provide more control over subsequent photochemical reactions and make them more useful synthetically. Linkage of the ephedrine to the diacid proved to be difficult, but was eventually successful. We were gratified to see that the chiral auxiliary forced the molecule to adopt one atropisomeric form exclusively, as there was no evidence of any diasteromeric forms in the NMR spectra. This was supported by molecular mechanics calculations that showed that the dominant atropisomer was low enough in energy to be the conformation for essentially all of the molecules in solution. The photochemistry of the dibenzylidenesuccinate-ephedrine adducts proved to be challenging, but we were pleased to observe that the predominant photoproduct preferentially crystallised out of solution. This product proved to be the *trans*-1,2-dihydronaphthalene, which was the opposite to what was observed previously in the photochemical survey reaction where there was no rigid cyclic amide/ester group constraining the molecule. Due to the presence of the chiral auxiliary, we were also expecting that there would be a significant enrichment of one of the two possible relative

trans-1,2-configurations. The very large optical rotation indicated that the newly created chiral centres had been created asymmetrically as the chiral auxiliary, although optically pure, was not expected to give the compound such a high rotation. This result would imply that our single atropisomeric form of the dibenzylidenesuccinate photocyclised to a single diastereomeric form of the 1,8-dihydronaphthalene intermediate, which then formed a single diastereomeric *trans*-1,2-dihydronaphthalene. The determination of the absolute configuration of the *trans*-1,2-dihydronaphthalene had to wait for the completion of the synthesis of a lignan natural product of known absolute configuration and rotation.

The final section of this thesis dealt with the application of our knowledge of the photochemistry of the dibenzylidenesuccinate-ephedrine adducts to the asymmetric synthesis of a lignan natural product. In this case, the synthetic target was the natural lignan (+)-dimethyllyoniresinol. The target molecule was chosen largely for its pair of 3,4,5-trimethoxy aryl groups and the *trans*-1,2-geometry in the final product that could be created through the photocyclisation reactions described in the previous section. In addition, it had a known absolute *trans*-1,2-geometry from which we could determine the absolute geometry formed from the photochemical cyclisation reaction described in the preceding section. The synthesis of the acyclic dibenzylidenesuccinate-ephedrine adduct was easily achieved through experimental protocols that had been previously elucidated by earlier work described previously in this thesis. Once the adduct had been formed, the selective photocyclisation was performed as a series of small-scale reactions to form a pool of the desired *trans*-1,2-dihydronaphthalene. From the *trans*-1,2-dihydronaphthalene, four simple steps (ephedrine hydrolysis, re-esterification,

hydrogenation and ester reduction) were required to produce the desired (+)-dimethyllyoniresinol. We were pleased to note that the direction of the optical rotation of our synthesised (+)-dimethyllyoniresinol matched that of the authentic sample, although the magnitude was somewhat less. Therefore, we have concluded that the final product was impure as the magnitude of the optical rotation did not match that of the isolated natural product. It is possible that one of the more vigorous reactions later in the synthesis epimerized one of the stereogenic centres; or that the hydrogenation wasn't as selective as desired. As the sign of the optical rotations were the same, we were able to conclude that the authentic and synthesised samples of (+)-dimethyllyoniresinol had the same absolute configuration. By extension, we were also able to conclude that the photochemical cyclisation, which produced those stereogenic centres, also resulted in the same *trans*-1*S*,2*R*-configuration as in the natural product. It is thought that this chiral auxiliary technique may prove to be useful in the asymmetric synthesis of other lignan natural products.

Chapter 5

Experimental Section

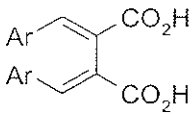
^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AM-300 FT instrument in deuterochloroform, unless otherwise noted. Chemical shifts reported are referenced in relation to TMS for both ^{1}H and ^{13}C-NMR spectroscopy. HRMS and mass spectra were obtained from a VG Analytical 7070E-HF instrument. All optical rotation measurements were recorded on a Rudolf Research Corporation Autopol III instrument. High-pressure liquid chromatography was performed on a C-18 reverse phase column utilising a Varian 9010 Solvent Delivery System and a Varian 9050 Variable Wavelength UV-Vis Detector. The mobile phase employed in the separation of compounds was a 50:50 solution of water-methanol for 10 minutes, followed by an increase to 20:80 water-methanol over 5 minutes and holding at 20:80 water-methanol for the final 5 minutes. Photochemical survey reactions were performed using a 450 watt Hanovia medium pressure mercury lamp (1 mm Pyrex filter) equipped with a cooling jacket. Photochemical reactions of the dibenzylidenesuccinate-ephedrine adduct were performed on an Ultraviolet Products Inc. mercury lamp (254 nm).

All chemicals were used as received commercially (Aldrich). Solvents were used as received (typically as analytic or HPLC grade), except for THF, CH_2Cl_2, DMF and toluene, which were purified by standard procedures[107]. Chromatography refers to the flash procedure using Sili-Cycle 230-400 mesh silica gel.

General Procedure for Preparation of Symmetric Dibenzylidenesuccinic Acids

The dibenzylidenesuccinic acids were prepared using a modified literature procedure[99,102]. A solution of diethyl succinate (10 mmol) and substituted-benzaldehyde (26 mmol) in toluene (60 mL), was added dropwise with stirring under N_2 to a slurry of sodium hydride (26 mmol) in toluene (40 mL). Once addition was complete, the solution was heated at reflux under N_2 for 18 hours. Upon cooling, water (35 mL) was added and the toluene was removed by rotary evaporation. To the aqueous residue was added an approximately 0.1 M solution of KOH (30 mL). The resulting mixture was refluxed for 2 hours. After cooling, the mixture was transferred to a separatory funnel and extracted with ethyl acetate (2 x 100 mL) to remove organic by-products. The aqueous phase was acidified with 0.1 M HCl (200 mL) and then extracted with more ethyl acetate (3 x 125 mL). The combined organic layers from the acidic extraction were dried over magnesium sulfate, filtered and evaporated to afford a reddish-brown oil. The oil was recrystallized from hexanes-methylene chloride to yield yellowish crystals of the desired product.

Bis(3,4,5-trimethoxy)benzylidenesuccinic acid (137aa)



137aa

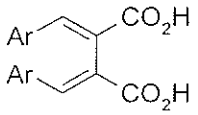
Ar = 3,4,5-trimethoxyphenyl

A solution of diethyl succinate (1.70 mL, 10.2 mmol) and 3,4,5-trimethoxybenzaldehyde (5.1020 g, 26.0 mmol) in toluene (60 mL) was added dropwise with stirring under N_2 to a slurry of sodium hydride (0.627 g, 26.0 mmol) in toluene (30 mL). The solution was heated at reflux for 19 hours with stirring under N_2. Upon cooling, water (35 mL) was added and the toluene was removed by rotary evaporation. A

solution of 0.1 M KOH (30 mL) was added to the residue and the mixture was heated at reflux for a further 2 hours. The mixture was extracted with ethyl acetate (2 x 125 mL), then the aqueous layer was acidified with 0.1 M HCl (200 mL). The mixture was then extracted with fresh ethyl acetate (3 x 125 mL). The combined organic layers from the acidic extraction were dried over magnesium sulfate, filtered and evaporated to produce a reddish-brown oil. The oil was recrystallized from hot methylene chloride-hexanes as yellowish crystals (1.97 g, 4.2 mmol) in 42% yield.

For **137aa:** ^{1}H NMR ($CDCl_3$): δ 3.73, s, 12H; 3.83, s, 6H; 6.81, s, 4H; 7.97, s, 2H. ^{13}C NMR ($CDCl_3$): δ 56.01, 60.90, 107.70, 124.68, 129.05, 140.26, 146.27, 153.14, 172.48. EI-MS m/z (relative intensity): 456 (M^+-18, 53), 454 (59), 392 (18), 289 (21), 181 (42), 168 (100). HRMS: For $C_{24}H_{24}O_9$ calculated 456.1420, found 456.1422.

Bis(3,4-dimethoxy)benzylidenesuccinic acid (137 bb)



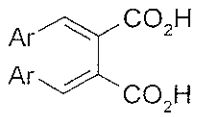
137bb

Ar = 3,4-dimethoxyphenyl

A solution of diethyl succinate (1.70 mL, 10.2 mmol) and 3,4-dimethoxybenzaldehyde (4.3207 g, 26.0 mmol) in toluene (60 mL) was added dropwise with stirring under N_2 to a slurry of sodium hydride (0.627 g, 26.0 mmol) in toluene (30 mL). The solution was heated at reflux for 19 hours with stirring under N_2. Upon cooling, water (35 mL) was added and the toluene was removed by rotary evaporation. A solution of 0.1 M KOH (30 mL) was added to the residue and the mixture was heated at reflux for a further 2 hours. The mixture was extracted with ethyl acetate (2 x 125 mL),

then the aqueous layer was acidified with 0.1 M HCl (200 mL). The mixture was then extracted with fresh ethyl acetate (3 x 125 mL). The combined organic layers from the acidic extraction were dried over magnesium sulfate, filtered and evaporated to produce a reddish-brown oil. The oil was immediately used in a further reaction without purification or characterisation.

Bis(3,4-methylenedioxy)benzylidenesuccinic acid (137cc)



137cc

Ar = 3,4-methylenedioxyphenyl

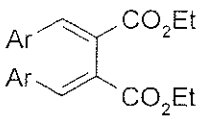
A solution of diethyl succinate (2.16 mL, 13.0 mmol) and 3,4-methylenedioxybenzaldehyde (4.44 g, 28.0 mmol) in toluene (60 mL) was added dropwise with stirring under N_2 to a slurry of sodium hydride (0.683 g, 28.0 mmol) in toluene (30 mL). The solution was heated at reflux for 19 hours with stirring under N_2. Upon cooling, water (35 mL) was added and the toluene was removed by rotary evaporation. A solution of 0.1 M KOH (30 mL) was added to the residue and the mixture was heated at reflux for a further 2 hours. When complete, the mixture was extracted with ethyl acetate (2 x 125 mL), then the aqueous layer was acidified with 0.1 M HCl (200 mL). The mixture was then extracted with fresh ethyl acetate (3 x 125 mL). The combined organic layers from the acidic extractions were dried over magnesium sulfate, filtered and evaporated to produce a reddish-brown oil. The oil was recrystallized from hot methylene chloride-hexanes as reddish crystals (2.08 g, 5.4 mmol) in 42% yield, that appeared to be tainted by at least one other product. The spectroscopic data was consistent with the formation of the expected dibenzylidenesuccinic acid product, which was used without further repurification.

For **137cc:** ^{1}H NMR ($CDCl_3$): δ 5.95, s, 4H; 6.75, m, 2H; 7.06, m, 4H; 7.91, s, 2H. ^{13}C NMR (acetone-d_6): δ 102.2, 108.4, 109.0, 124.7, 125.9, 129.8, 141.6, 149.0, 152.3, 172.4. EI-MS m/z (relative intensity): 382 (M^+ 2) 364 (25), 362 (32), 336 (16), 149 (52), 57 (100). HRMS: For $C_{20}H_{14}O_8$ calculated 382.0689, found 382.0692.

General Procedure for Preparation of Symmetric Diethyl Dibenzylidenesuccinates

Dibenzylidenesuccinic acid (1 mmol) was dissolved in DMSO (15 mL). To this was added anhydrous potassium carbonate (10 mmol) and ethyl iodide (50 mmol). The reaction proceeded with stirring at 70°C for 90 minutes. The crude reaction mixture was dissolved in ethyl acetate (50 mL), poured into a separatory funnel and washed with water (3 x 30 mL). The wash water was then re-extracted with two more separatory funnels containing fresh ethyl acetate (40 mL). The collected organic layers were dried with magnesium sulfate, filtered and evaporated to a black oil. The crude product was purified by chromatography using 3:1 hexanes-ethyl acetate as solvent.

Ethyl Bis(3,4,5-trimethoxy)benzylidenesuccinate (133aa)



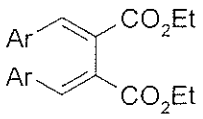
133aa

Ar = 3,4,5-trimethoxyphenyl

Diacid **137aa** (1.24 g, 2.61 mmol) was dissolved in DMSO (30 mL). To this was added potassium carbonate (3.15 g, 22.8 mmol) and ethyl iodide (9.5 mL, 119 mmol). The reaction was heated with stirring to 70 °C and allowed to react for 90 minutes. When TLC indicated completion, the reaction mixture was dissolved in ethyl acetate (60 mL) and poured into a separatory funnel. Two other funnels were also set up with fresh ethyl acetate (40 mL). Through each funnel, water was added sequentially (3 x 40 mL) to wash the crude product. The collected organic layers were dried over magnesium sulfate, filtered and evaporated to produce a black oil. Purification was achieved by chromatography with 3:1 hexanes-ethyl acetate to produce a clear, colourless oil (1.10 g, 2.12 mmol) in 81% yield.

For **133aa:** ^{1}H NMR ($CDCl_3$): δ 1.09, t, 6H, J = 7.1 Hz; 3.76, s, 12H; 3.82, s, 6H; 4.14, m, 4H; 6.76, s, 4H; 7.81, s, 2H. ^{13}C NMR ($CDCl_3$): δ 14.08, 55.99, 60.87, 61.16, 107.09, 126.78, 130.24, 139.46, 142.13, 153.06, 166.82. EI-MS m/z (relative intensity): 530 (M^+ 11), 528 (13), 484 (13), 456 (11), 411 (15), 317 (22), 289 (19), 181 (100). HRMS: For $C_{28}H_{34}O_{10}$ calculated 530.2152, found 530.2134.

Ethyl Bis(3,4-dimethoxy)benzylidenesuccinate (133bb)



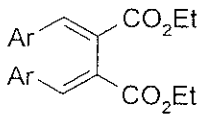
133bb

Ar = 3,4-dimethoxyphenyl

Diacid **137bb** (1.60 g, 3.86 mmol) was dissolved in DMSO (30 mL). To this was added potassium carbonate (4.80 g, 34.7 mmol) and ethyl iodide (12 mL, 150 mmol). The reaction was heated with stirring to 70 °C and allowed to react for 90 minutes. When TLC indicated completion, the reaction mixture was dissolved in ethyl acetate (60 mL) and poured into a separatory funnel. Two other funnels were also set up with fresh ethyl acetate (40 mL). Through each funnel, water was added sequentially (3 x 40 mL) to wash the crude product. The collected organic layers were dried over magnesium sulfate, filtered and evaporated to produce a black oil. Purification was achieved by chromatography with 3:1 hexanes-ethyl acetate to produce a clear, colourless oil (1.03 g, 2.17 mmol) in 56% yield.

For **133bb:** ^{1}H NMR ($CDCl_3$): δ 1.12, t, 3H, J = 7.1 Hz; 1.19, t, 3H, J = 7.1 Hz; 3.72, s, 6H; 3.74, s, 6H; 4.04, q, 2H, J = 7.1 Hz; 4.12, q, 2H, J = 7.1 Hz; 6.72-6.82, m, 3H; 7.69, s, 1H. ^{13}C NMR ($CDCl_3$): δ 14.06, 14.11, 55.66, 55.71, 60.73, 60.82, 111.02, 112.15, 122.49, 124.37, 127.62, 141.45, 148.76, 149.69, 167.31, 171.13. EI-MS m/z (relative intensity): 470 (M^+ 15), 468 (11) 424 (22), 396 (82), 351 (100), 332 (67), 259 (36), 165 (64), 69 (37). HRMS: For $C_{26}H_{30}O_8$ calculated 470.1941, found 470.1968.

Ethyl Bis(3,4-methylenedioxy)benzylidenesuccinate (133cc)



133cc

Ar = 3,4-methylenedioxyphenyl

Diacid **137cc** (1.01 g, 2.6 mmol) was dissolved in DMSO (30 mL). To this was added potassium carbonate (4.21 g, 30.4 mmol) and ethyl iodide (9.0 mL, 107 mmol). The reaction was heated with stirring to 70 °C and allowed to react for 90 minutes. When TLC indicated completion, the reaction mixture was dissolved in ethyl acetate (60 mL) and poured into a separatory funnel. Two other funnels were also set up with fresh ethyl acetate (40 mL). Through each funnel, water was added sequentially (3 x 40 mL) to wash the crude product. The collected organic layers were dried over magnesium sulfate, filtered and evaporated to produce a black oil. Purification was achieved by chromatography with 3:1 hexanes-ethyl acetate to produce a clear, colourless oil (0.78 g, 1.78 mmol) in 68% yield.

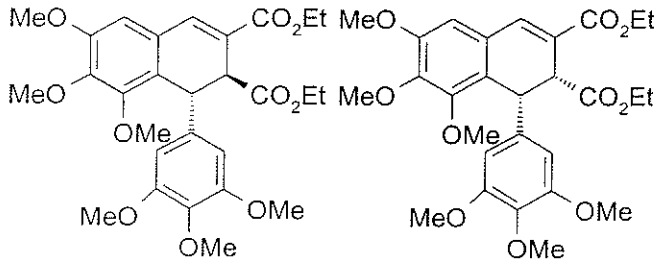
For **133cc:** ^{1}H NMR ($CDCl_3$): δ 1.15, t, 6H, J = 7.1 Hz; 4.17, q, 4H, J = 7.1 Hz; 5.93, s, 4H; 6.72, m, 2H; 6.99, m, 4H; 7.78, s, 2H. ^{13}C NMR ($CDCl_3$): δ 14.13, 61.02, 101.35, 108.38, 108.79, 124.98, 125.89, 129.07, 142.09, 147.89, 148.83, 166.96. EI-MS m/z (relative intensity): 438 (M^+ 23), 364 (16), 319 (21), 292 (21), 243 (17), 135 (100). HRMS: For $C_{24}H_{22}O_8$ calculated 438.1315, found 438.1307.

General Procedure for Photochemical Survey Reactions

Acyclic dibenzylidenesuccinate (40 mg) was dissolved in a solution of 1% trifluoroacetic acid in anhydrous ethanol (45 mL). The solution was poured into a large test-tube and purged with nitrogen for 15 minutes. After purging the solution and headspace, the tube was sealed and irradiated for a period of time ranging from 90-210

minutes (depending on the nature of the substrate). Upon completion of the irradiation, the solvent was removed from the crude product by rotary evaporation and dried by vacuum. Purification of the photoproduct was achieved by performing multiple HPLC runs utilising the elution method described previously. The various HPLC runs were combined and evaporated to afford the photoproducts as clear, colourless oils.

Photoreaction of Ethyl Bis(3,4,5-trimethoxy)benzylidenesuccinate (134aa/135aa)



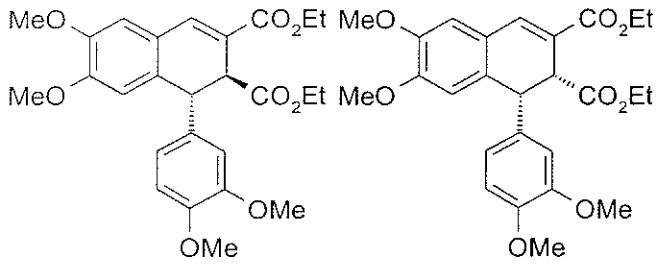
134aa **135aa**

Ethyl bis(3,4,5-trimethoxy)benzylidenesuccinate **133aa** (58.8 mg, 0.11 mmol) was dissolved in a solution of 1% trifluoroacetic acid in anhydrous ethanol (55 mL). The solution was poured into a large test-tube and purged with nitrogen for 15 minutes. After purging the solution and headspace, the tube was sealed and irradiated for 90 minutes. Upon completion of the irradiation, the solvent was removed from the crude product by rotary evaporation and dried by vacuum. The crude product was recovered as a yellowish oil (58.7 mg, 99.8%). Purification of the photoproduct was achieved by performing multiple HPLC runs utilising the elution method described previously. The various HPLC runs were combined and evaporated to afford the photoproducts (*trans*-dihydronaphthalene **134aa** and *cis*-dihydronaphthalene **135aa**) as clear, colourless oils. For **134aa:** ^{1}H NMR ($CDCl_3$): δ 1.19, t, 3H, J = 7.1 Hz; 1.31, t, 3H, J = 7.1 Hz; 3.67, s, 3H; 3.73, s, 6H; 3.77, s, 3H; 3.88, s, 3H; 3.89, s, 3H; 4.05, br s, 1H; 4.12, q, 2H, J = 7.1 Hz; 4.23, q, 2H, J = 7.1 Hz; 4.98, br s, 1H; 6.27, s, 2H; 6.72, s, 1H; 7.62, s, 1H. EI-MS

m/z (relative intensity): 530 (M^+ 63), 456 (100), 411 (77), 380 (27), 181 (17), 85 (13), 57 (11). HRMS: For $C_{28}H_{34}O_{10}$ calculated 530.2152, found 530.2123.

For **135aa:** ^{1}H NMR ($CDCl_3$): δ 0.91, t, 3H, J = 7.1 Hz; 1.26, t, 3H, J = 7.1 Hz; 3.48, s, 3H; 3.73, s, 6H; 3.74, s, 3H; 3.84, s, 3H; 3.88, s, 3H; 4.10, dd, 1H, J = 9.1 Hz, 2.7 Hz; 4.18, q, 2H, J = 7.1 Hz; 4.19, q, 2H, J = 7.1 Hz; 4.78, d, 1H, J = 9.1 Hz; 6.34, s, 2H; 6.64, s, 1H; 7.38, d, 1H, J=2.7 Hz. ^{13}C NMR ($CDCl_3$): δ 13.7, 14.2, 40.4, 48.0, 56.1, 60.4, 60.5, 60.6, 60.7, 60.8, 106.3, 107.9, 123.7, 126.2, 127.1, 135.3, 136.3, 137.1, 144.2, 151.0, 152.6, 152.8, 167.3, 171.5. EI-MS m/z (relative intensity): 530 (M^+ 100), 484 (44), 456 (62), 411 (65), 384 (33), 358 (69). HRMS: For $C_{28}H_{34}O_{10}$ calculated 530.2152, found 530.2139.

Photoreaction of Ethyl Bis(3,4-dimethoxy)benzylidenesuccinate (134bb/135bb)



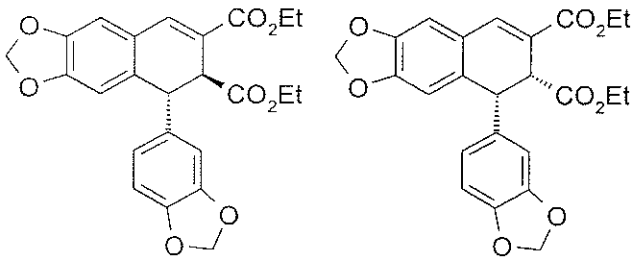
134bb **135bb**

Ethyl bis(3,4-dimethoxy)benzylidenesuccinate (44.3 mg, 0.094 mmol) was dissolved in a solution of 1% trifluoroacetic acid in anhydrous ethanol (50 mL). The solution was poured into a large test-tube and purged with nitrogen for 15 minutes. After purging the solution and headspace, the tube was sealed and irradiated for 210 minutes. Upon completion of the irradiation, the solvent was removed from the crude product by rotary evaporation and dried by vacuum. The crude product was recovered as a clear, colourless oil (44.1 mg, 99.5%). Purification of the photoproduct was achieved by performing multiple HPLC runs utilising the elution method described previously. The

various HPLC runs were combined and evaporated to afford the photoproducts (*trans*-dihydronaphthalene **134bb** and *cis*-dihydronaphthalene **135bb**) as clear, colourless oils. For **134bb:** ^{1}H NMR ($CDCl_3$): δ 1.27, t, 3H, J = 7.1 Hz; 1.35, t, 3H, J = 7.1 Hz; 3.77, s, 3H; 3.81, s, 3H; 3.84, s, 3H; 3.89, s, 3H; 4.05, d, 1H, J = 1.2 Hz; 4.21, q, 2H, J = 7.1 Hz; 4.29, q, 2H, J = 7.1 Hz; 5.08, d, 1H, J = 0.5 Hz; 6.35-7.10, m, 5H; 7.67, d, 1H, J = 1.9 Hz. EI-MS m/z (relative intensity): 470 (M^+, 12), 468 (9), 395 (100), 351 (50), 324 (29), 57 (8). HRMS: For $C_{26}H_{30}O_8$ calculated 470.1941, found 470.1927.

For **135bb:** ^{1}H NMR ($CDCl_3$): δ 0.93, t, 3H, J = 7.1 Hz; 1.27, t, 3H, J = 7.1 Hz; 3.42, s, 3H; 3.77, s, 6H; 3.84, s, 3H; 4.11, dd, 1H, J = 8.9 Hz, 2.7 Hz; 4.18, q, 2H, J = 7.1 Hz; 4.19, q, 2H, J = 7.1 Hz; 4.91, d, 1H, J = 8.9 Hz; 6.65, m, 2H; 6.70, m, 1H; 6.81, d, 1H, J = 8.5 Hz; 7.06, d, 1H, J = 8.4 Hz; 7.45, d, 1H, J = 2.7 Hz. EI-MS m/z (relative intensity): 470 (M^+, 39), 468 (96), 396 (59), 351 (37), 294 (55), 217 (100), 165 (63), 98 (44), 57 (73). HRMS: For $C_{26}H_{30}O_8$ calculated 470.1941, found 470.1944.

Photoreaction of Ethyl Bis(3,4-methylenedioxy)benzylidenesuccinate (134cc/135cc)



134cc **135cc**

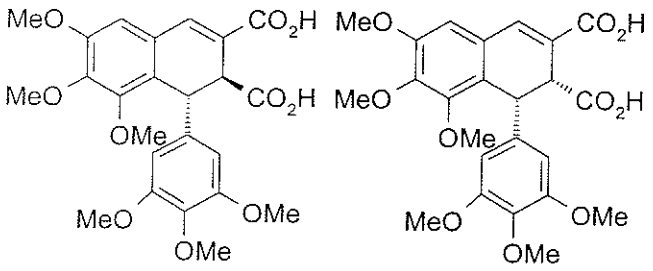
Ethyl bis(3,4-methylenedioxy)benzylidenesuccinate **133cc** (47.1 mg, 0.11 mmol) was dissolved in a solution of 1% trifluoroacetic acid in anhydrous ethanol (45 mL). The solution was poured into a large test-tube and purged with nitrogen for 15 minutes. After purging the solution and headspace, the tube was sealed and irradiated for a period of 195 minutes. Upon completion of the irradiation, the solvent was removed from the crude

product by rotary evaporation and dried by vacuum. The crude product was recovered as a yellowish oil (45.9 mg, 97.6%). Purification of the photoproduct was achieved by performing multiple HPLC runs utilising the elution method described previously. The various HPLC runs were combined and evaporated to afford the photoproducts (*trans*-dihydronaphthalene **134cc** and *cis*-dihydronaphthalene **135cc**) as clear, colourless oils.

For **134cc:** ^{1}H NMR (acetone-d_6): δ 1.15, t, 3H, J = 7.1 Hz; 1.25, t, 3H, J = 7.1 Hz; 3.98, d, 1H, J = 1.3 Hz; 4.05, q, 2H, J = 7.1 Hz; 4.17, q, 2H, J = 7.1 Hz; 4.81, br s, 1H; 5.92, br s, 2H; 6.02, br s, 2H; 6.60, m, 2H; 6.80, m, 1H; 6.84, d, 1H, J = 7.9 Hz; 7.07, d, 1H, J = 7.9 Hz; 7.68, s, 1H. EI-MS m/z (relative intensity): 438 (M^+, 12), 364 (100), 319 (50), 292 (50), 242 (22), 176 (15), 69 (11). HRMS: For $C_{24}H_{22}O_8$ calculated 438.1315, found 438.1301.

For **135cc:** ^{1}H NMR (acetone-d_6): δ 0.98, t, 3H, J = 7.2 Hz; 1.23, t, 3H, J = 7.1 Hz; 3.76, q, 2H, J = 7.1 Hz; 4.10, dd, 1H, J = 8.8 Hz, 2.4 Hz; 4.13, q, 2H, J = 7.2 Hz; 4.59, d, 1H, J = 8.8 Hz; 5.90, dd, 2H, J = 3.3 Hz, 1.0 Hz; 5.95, dd, 2H, J = 6.8 Hz, 0.8 Hz; 6.60, m, 1H; 6.65, m, 2H; 6.79, d, 1H, J = 7.9 Hz; 7.01, d, 1H, J = 7.9 Hz; 7.47, d, 1H, J = 2.4 Hz. ^{13}C NMR (acetone-d_6): δ 13.9, 14.2, 41.1, 47.7, 60.5, 60.6, 101.6, 102.4, 107.6, 108.0, 109.5, 119.0, 122.7, 124.4, 125.8, 126.1, 134.0, 136.1, 145.5, 147.4, 147.9, 150.4, 167.3, 171.0. EI-MS m/z (relative intensity): 438 (M^+, 79), 436 (76), 392 (31), 364 (100), 319 (43), 292 (88), 149 (40), 57 (66). HRMS: For $C_{24}H_{22}O_8$ calculated 438.1315, found 438.1299.

Photoreaction of Bis(3,4,5-trimethoxy)benzylidenesuccinic Acid (138aa/139aa)



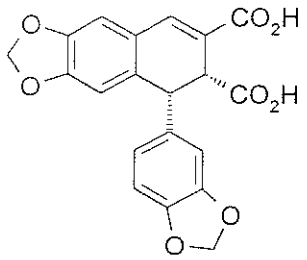
138aa **139aa**

Bis(3,4,5-trimethoxy)benzylidenesuccinic acid **137aa** (53.0 mg, 0.11 mmol) was dissolved in a solution of 1% trifluoroacetic acid in anhydrous ethanol (50 mL). The solution was poured into a large test-tube and purged with nitrogen for 15 minutes. After purging the solution and headspace, the tube was sealed and irradiated for 180 minutes. Upon completion of the irradiation, the solvent was removed from the crude product by rotary evaporation and dried by vacuum. The crude product was recovered as a yellowish oil (51.9 mg, 97.9%). Purification of the photoproduct was achieved by performing multiple HPLC runs utilising the elution method described previously. The various HPLC runs were combined and evaporated to afford the desired photoproducts (*trans*-dihydronaphthalene **138aa** and *cis*-dihydronaphthalene **139aa**) as clear, colourless oils. For **138aa:** ^{1}H NMR ($CDCl_3$): δ 3.64, s, 3H; 3.72, s, 6H; 3.77, s, 3H; 3.88, s, 3H; 3.89, s, 3H; 4.04, br s, 1H; 5.03, br s, 1H; 6.20, s, 2H; 6.73, s, 1H; 7.75, br s, 1H. EI-MS m/z (relative intensity): 456 (M^+-18, 7), 428 (100), 396 (33), 351 (20), 181 (17), 57 (51). HRMS: For $C_{24}H_{24}O_9$ calculated 456.1420, found 456.1415.

For **139aa:** ^{1}H NMR ($CDCl_3$): δ 3.47, s, 3H; 3.66, s, 6H; 3.69, s, 3H; 3.85, s, 3H; 3.89, s, 3H; 4.05, dd, 1H, J = 9.1 Hz, 2.4 Hz; 4.81, d, 1H, J = 9.1 Hz; 6.31, s, 2H; 6.67, s, 1H; 7.51, d, 1H, J = 2.4 Hz. EI-MS m/z (relative intensity): 456 (M^+-18, 99), 454 (100) 428

(22), 391 (27), 365 (16), 289 (16), 181 (26), 168 (64), 153 (25), 57 (15). HRMS: For $C_{24}H_{24}O_9$ calculated 456.1420, found 456.1439.

Photoreaction of Bis(3,4-methylenedioxy)benzylidenesuccinic acid (139cc)

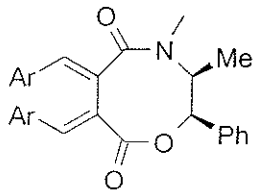


139cc

Bis(3,4-methylenedioxy)benzylidenesuccinic acid **137cc** (53.4 mg, 0.14 mmol) was dissolved in a solution of 1% trifluoroacetic acid in anhydrous ethanol (50 mL). The solution was poured into a large test-tube and was purged with nitrogen for 15 minutes. After purging the solution and headspace, the tube was sealed and irradiated for a period of 240 minutes. Upon completion of the irradiation, the solvent was removed from the crude product by rotary evaporation and dried by vacuum. The crude product was recovered as a yellowish oil (53.3 mg, 99.8%). Purification of the photoproduct was achieved by performing multiple HPLC runs utilising the elution method described previously. The various HPLC runs were combined and evaporated to afford the *cis*-dihydronaphthalene **139cc** as a clear, colourless oil.

For **139cc:** ^{1}H NMR (acetone-d_6): δ 4.10, br s, 1H; 4.59, br s, 1H; 5.84, br s, 2H; 5.91, br s, 2H; 6.56-6.91, m, 5H; 7.52, br s, 1H. EI-MS m/z (relative intensity): 364 (M^+-18, 83), 362 (23), 292 (39), 243 (51), 232 (100), 176 (45), 160 (90), 122 (72). HRMS: For $C_{20}H_{12}O_7$ calculated 364.0583, found 364.0581.

Bis(3,4,5-trimethoxy)benzylidenesuccinic Acid-Ephedrine Adduct (144aa)



144aa

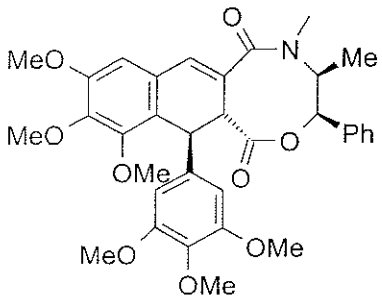
Ar = 3,4,5-trimethoxyphenyl

To a solution of bis(3,4,5-trimethoxy)benzylidenesuccinic acid (203.2 mg, 0.416 mmol) in 3:1 methylene chloride-DMF (8 mL) was added TBTU (126.7 mg, 0.414 mmol). The solution was cooled to 0 °C, then DIEA (300 μL, 1.65 mmol) was added. The solution was allowed to stir under nitrogen for 30 minutes. While the solution stirred, a second solution of (+)-ephedrine (69.7 mg, 0.411 mmol) in 3:1 methylene chloride-DMF (2 mL) was created. The ephedrine solution was then carefully added to the diacid/TBTU/DIEA solution and the resulting mixture was allowed to gradually warm to room temperature. The reaction proceeded with stirring under nitrogen for 24 hours, then a further equivalent of TBTU (127.1 mg, 0.416 mmol) was added and the headspace was purged with nitrogen. The reaction then proceeded for a further 18 hours with stirring under nitrogen. The reaction was worked up by preparing three separatory funnels with 30 mL of methylene chloride. The reaction mixture was poured into one of the separatory funnels and was sequentially washed with 0.1 M HCl (3 x 25 mL). The organic layers were then combined and washed with water (1 x 40 mL) and brine (1 x 40), dried over magnesium sulfate, filtered and evaporated to a greenish oil. The crude product was purified by chromatography (55:45 hexanes-ethyl acetate) to afford a pale yellow oil (144 mg, 0.24 mmol) in 57% yield.

For **144aa:** $[\alpha]_D$ = -342.9° (c = 2.05 mg/mL, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.34, d, 3H, J = 7.1 Hz; 2.89, s, 3H; 3.79, s, 3H; 3.81, s, 6H; 3.85, s, 3H; 3.86, m, 1H; 3.90, s, 6H; 6.28,

br s, 1H; 6.79, s, 2H; 7.07, s, 2H; 7.30-7.40, m, 6H; 7.62, s, 1H. ^{13}C NMR ($CDCl_3$): δ 11.8, 35.8, 56.1 (2), 56.4 (2), 60.81, 60.84, 64.6, 81.2, 107.3 (2), 108.4 (2), 125.7 (2), 126.1, 128.4, 128.67, 128.74, 129.0, 129.5, 139.4, 139.7, 139.9, 146.3, 145.4, 153.1 (2), 153.2 (2), 168.0, 169.9. MS-EI m/z (relative intensity): 603 (M^+ 20), 557 (25), 500 (12), 454 (33), 411 (20), 392 (16), 289 (11), 245 (8), 181 (32), 168 (54), 146 (24), 56 (100). HRMS: For $C_{34}H_{37}NO_9$ calculated: 603.2458, found: 603.2468.

Photoreaction of 144aa (145aa)



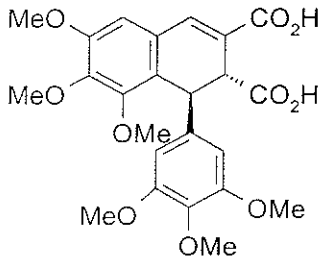
145aa

Ephedrine adduct **144aa** (20.5 mg, 0.034 mmol) was dissolved in isopropanol (45 mL). The solution was poured into a quartz vessel and purged with nitrogen for 15 minutes. While still bubbling nitrogen through the solution, the solution was irradiated for 30 minutes using the low pressure (254 nm) mercury lamp. Upon completion of the reaction, the solution was poured into a round-bottomed flask and evaporated to dryness. The crude residue was re-dissolved in a 1:1 solution of isopropanol-methylene chloride (10 mL) and was then evaporated to roughly 1 mL in volume. The solution was then stoppered and refrigerated to allow for crystallisation. The product was recovered as pure white crystals (10.5 mg, 0.018 mmol) in 52% yield.

For **145aa:** $[\alpha]_D$ = +475.7° (c = 2.32 mg/mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.22, d, 3H, J = 7.0 Hz; 2.49, s, 3H; 3.76, s, 3H; 3.79, s, 3H; 3.83, s, 6H; 3.85, s, 3H; 3.87, s, 3H; 4.21, br s, 1H; 4.43, dq, 1H, J = 7.0 Hz, 3.9 Hz; 4.84, br s, 1H; 5.36, d, 1H, J = 3.9 Hz; 6.48, m,

2H; 6.68, br s, 2H; 7.27-7.36, m, 6H. ^{13}C NMR ($CDCl_3$): δ 14.4, 29.4, 36.8, 52.3, 55.7, 56.0, 56.2 (2C), 60.74, 60.77, 60.81, 78.8, 104.3 (2C), 107.4, 121.5, 124.8, 127.5 (2C), 127.6, 128.2 (2C), 128.7, 128.8, 133.6, 136.9, 146.1, 143.5, 151.4, 152.5, 153.2 (2C), 172.5, 172.7. MS-EI m/z (relative intensity): 603 (M^+ 35), 557 (14), 502 (12), 454 (13), 441 (11), 412 (28), 369 (14), 245 (11), 181 (15), 168 (16), 105 (27), 56 (100). HRMS: For $C_{34}H_{37}NO_9$ calculated 603.2468, found 603.2475.

Hydrolysis of Ephedrine Photoproduct 145aa (138aa)

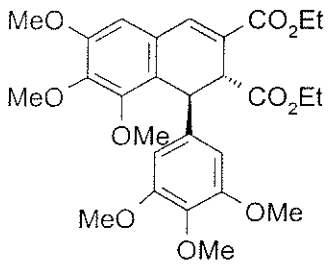


138aa

Photoproduct **145aa** (39.4 mg, 0.065 mmol) was dissolved in methylene chloride (8 mL). To this was added glacial acetic acid (10 mL). The methylene chloride was then evaporated and 6M HCl (20 mL) was added to the solution. The solution and headspace were then purged with nitrogen for 15 minutes, then the solution heated to reflux with stirring under nitrogen. After 3 hours, the mixture was cooled, diluted with water (20 mL) and extracted with methylene chloride (5 x 50 mL). The combined organic fractions were then dried over magnesium sulfate, filtered and evaporated to afford a yellowish oil (19.5 mg, 0.039 mmol, 60%) that was used in the next reaction without purification. Analysis of the crude ^{1}H-NMR was identical to that previously reported above.

For **138aa:** ^{1}H NMR ($CDCl_3$): δ 3.62, s, 3H; 3.70, s, 6H; 3.76, s, 3H; 3.87, s, 3H; 3.89, s, 3H; 4.00, br s, 1H; 5.02, br s, 1H; 6.23, s, 2H; 6.73, s, 1H; 7.73, br s, 1H

Esterification of *trans*-dihydronaphthalene diacid 138aa (134aa)



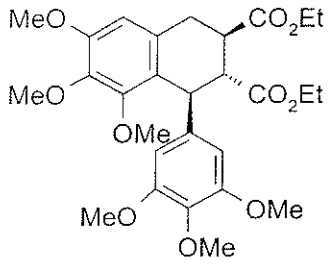
134aa

Crude *trans*-dihydronaphthalene diacid **138aa** (19.5 mg, 0.039 mmol) was dissolved in anhydrous ethanol (25 mL). To this was added concentrated sulfuric acid (1 mL). The solution and headspace were purged with nitrogen for 15 minutes, then the solution heated to reflux with stirring under a nitrogen atmosphere. After 3 hours, the reaction was complete (TLC) and the solution was diluted with water (15 mL). The reaction mixture was poured into a separatory funnel and was extracted with methylene chloride (5 x 25 mL). The collected organic fractions were dried with magnesium sulfate, filtered and evaporated to a brownish oil (17.5 mg). The crude product was purified by chromatography (3:2 hexanes-ethyl acetate) to afford a clear, colourless oil (9.8 mg, 0.018 mmol) in 47.4% yield.

For **138aa:** $[\alpha]_D$ = +107.8° (c = 2.01 mg/mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.19, t, 3H, J = 7.1 Hz; 1.30, t, 3H, J = 7.1 Hz; 3.67, s, 3H; 3.72, s, 6H; 3.77, s, 3H; 3.87, s, 3H; 3.89, s, 3H; 4.05, d, 1H, J = 1.2 Hz; 4.10, q, 2H, J = 7.1 Hz; 4.23, q, 2H, J = 7.1 Hz; 4.98, br s, 1H; 6.27, s, 2H; 6.72, s, 1H; 7.62, s, 1H. ^{13}C NMR ($CDCl_3$): δ 14.1, 14.3, 39.4, 46.3, 56.0 (2C), 60.75, 60.80, 60.9 (2C), 61.0, 61.2, 104.6 (2C), 108.3, 123.2, 125.0, 127.1, 136.8 (2C), 138.4, 144.3, 151.4, 152.7, 153.0, 166.5, 171.8, one quaternary signal unobserved. EI-MS m/z (relative intensity): 530 (M^+ 56), 456 (100), 411 (71), 384 (32),

380 (27). HRMS: For $C_{28}H_{34}O_{10}$ calculated 530.2152, found 530.2126. This product was spectroscopically identical to that previous reported[69].

Hydrogenation to Aryltetralin (160aa)

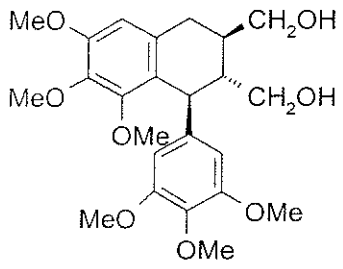


160aa

Pure diester **134aa** (15.6 mg, 0.029 mmol) was dissolved in methanol (15 mL). To this was added palladium catalyst on carbon black (9.0 mg, 5% Pd). The flask was purged twice with nitrogen, followed by purging three times with hydrogen. The reaction was allowed to proceed under a hydrogen atmosphere with vigorous stirring for 24 hours. The reaction mixture was filtered through celite and cotton wool to remove the catalyst and evaporated to a yellowish oil (15.2 mg, 0.029 mmol, 95%). The crude product **160aa** was used in the next step without purification.

For **160aa:** ^{1}H NMR ($CDCl_3$): δ 1.15, t, 3H, J = 7.1 Hz; 1.16, t, 3H, J = 7.1 Hz; 2.95-3.16, m, 4H; 3.29, s, 3H; 3.75, s, 6H; 3.77, s, 3H; 3.79, s, 3H; 3.86, s, 3H; 4.06, q, 2H, J = 7.1 Hz; 4.07, q, 2H, J = 7.1 Hz; 4.51, d, 1H, J = 7.5 Hz; 6.26, s, 2H; 6.48, s, 1H.

(+)-dimethyllyoniresinol (146)



146aa

Crude **160aa** (15.2 mg, 0.029 mmol) was dissolved in dry THF (15 mL). The solution was cooled to 0 °C, then lithium aluminium hydride (5.0 mg, 0.132 mmol) was added to the flask. The reaction was allowed to warm gradually to room temperature and stirred under nitrogen for 60 minutes. The reaction was quenched by Fieser's method[106] and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated to an orange oil (9.7 mg). The product was purified by chromatography (2:1 ethyl acetate-hexanes) to afford a clear, colourless oil (4.8 mg, 0.010 mmol) in 35% yield (based on diester **134aa**)

For **146:** $[\alpha]_D$ = +24.8° (c = 2.40 mg/mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.77-1.93, m, 2H; 2.59-2.80, m, 2H; 3.23, s, 3H; 3.60-3.74, m, 4H; 3.76, s, 3H; 3.77, s, 6H; 3.80, s, 3H; 3.86, s, 3H; 3.99, d, 1H, J = 8.0 Hz; 6.33, s, 2H; 6.47, s, 1H. ^{13}C NMR ($CDCl_3$): δ 34.0, 40.2, 43.7, 49.4, 55.8, 56.2, 59.6, 60.5, 60.9, 63.7, 66.6, 105.8, 106.7, 125.0, 133.1, 136.2, 140.7, 143.3, 152.0, 152.1, 152.9. EI-MS m/z (relative intensity): 448 (M^+ 38), 430 (100), 399 (28), 219 (45), 181 (93), 69 (63). HRMS: For $C_{24}H_{32}O_8$ calculated 448.2097, found 448.2079. The compound was observed to be spectroscopically identical to that previously reported[105a-d]. The optical rotation was observed to be within a range of values previously reported for the synthetic product. (+21.5[105a], +26.0[105b], +30.0[105b]), although outside of the rotation measured for the isolated natural product (+49.4°)[104].

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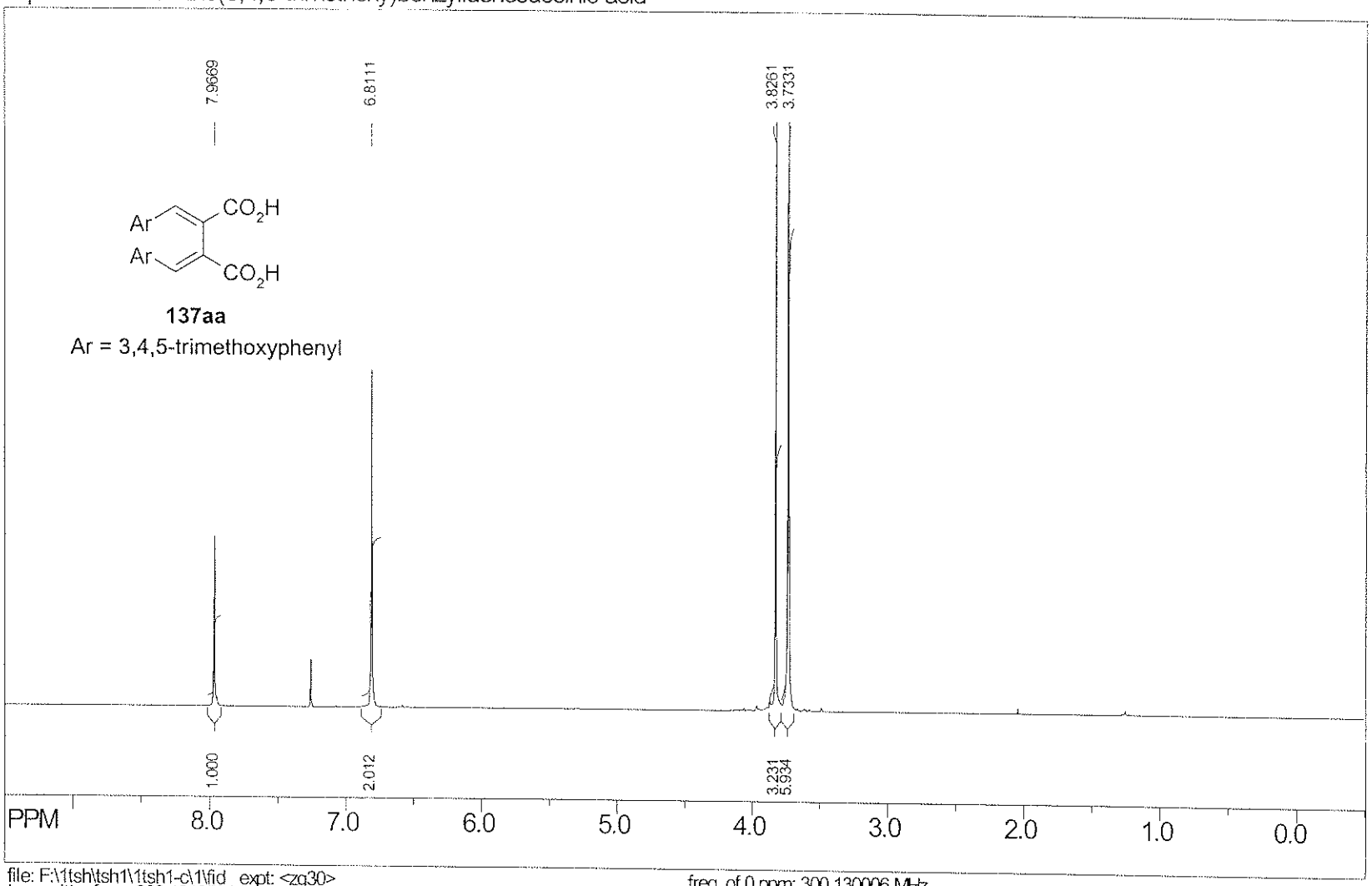
Appendix

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

SpinWorks 2.0: Bis(3,4,5-trimethoxy)benzylidenesuccinic acid



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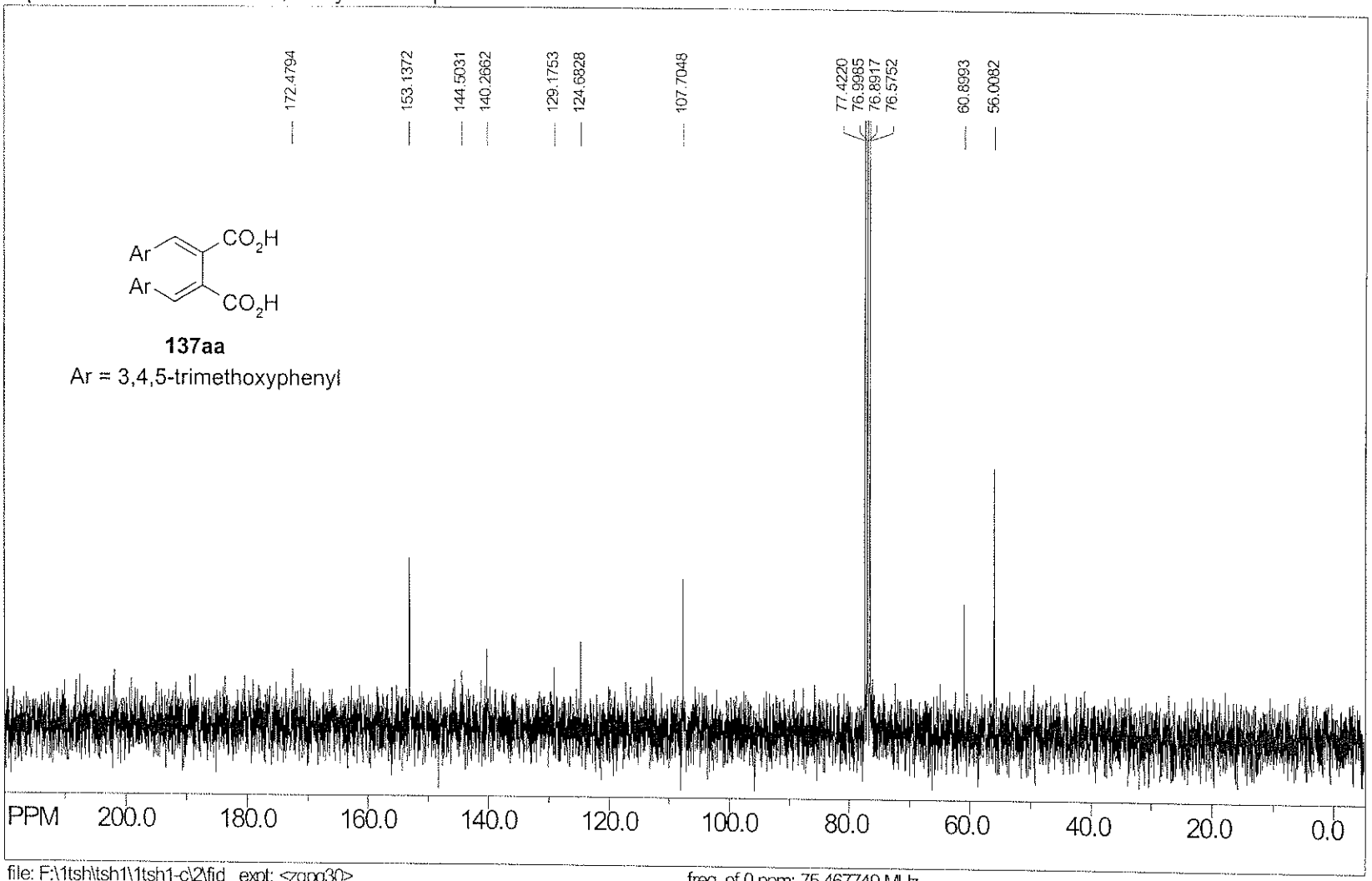
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 16

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

SpinWorks 2.0: 1TSH1-C, recrystallized product



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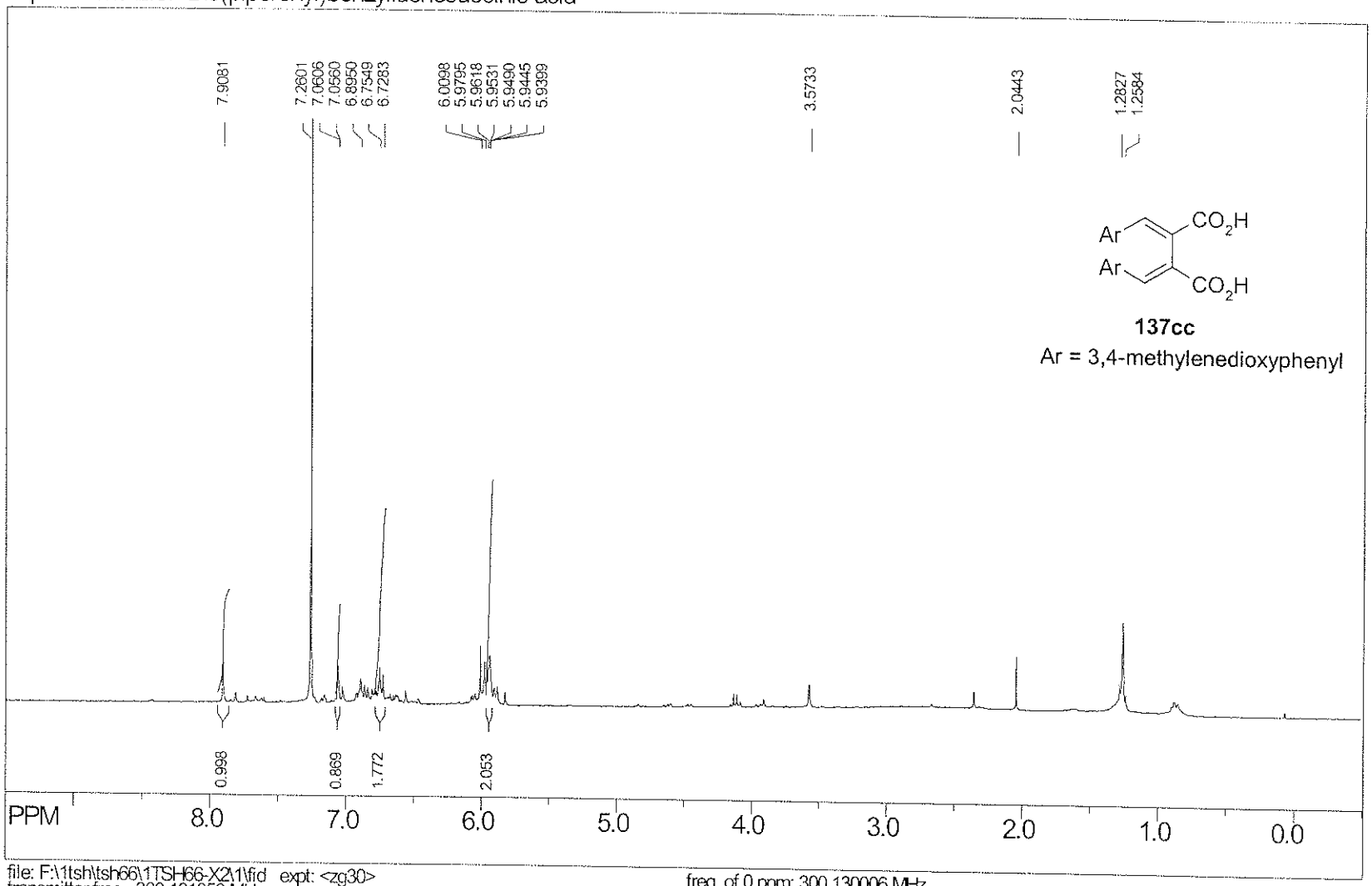
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 80

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

SpinWorks 2.0: Bis(piperonyl)benzylidenesuccinic acid



137cc

Ar = 3,4-methylenedioxyphenyl

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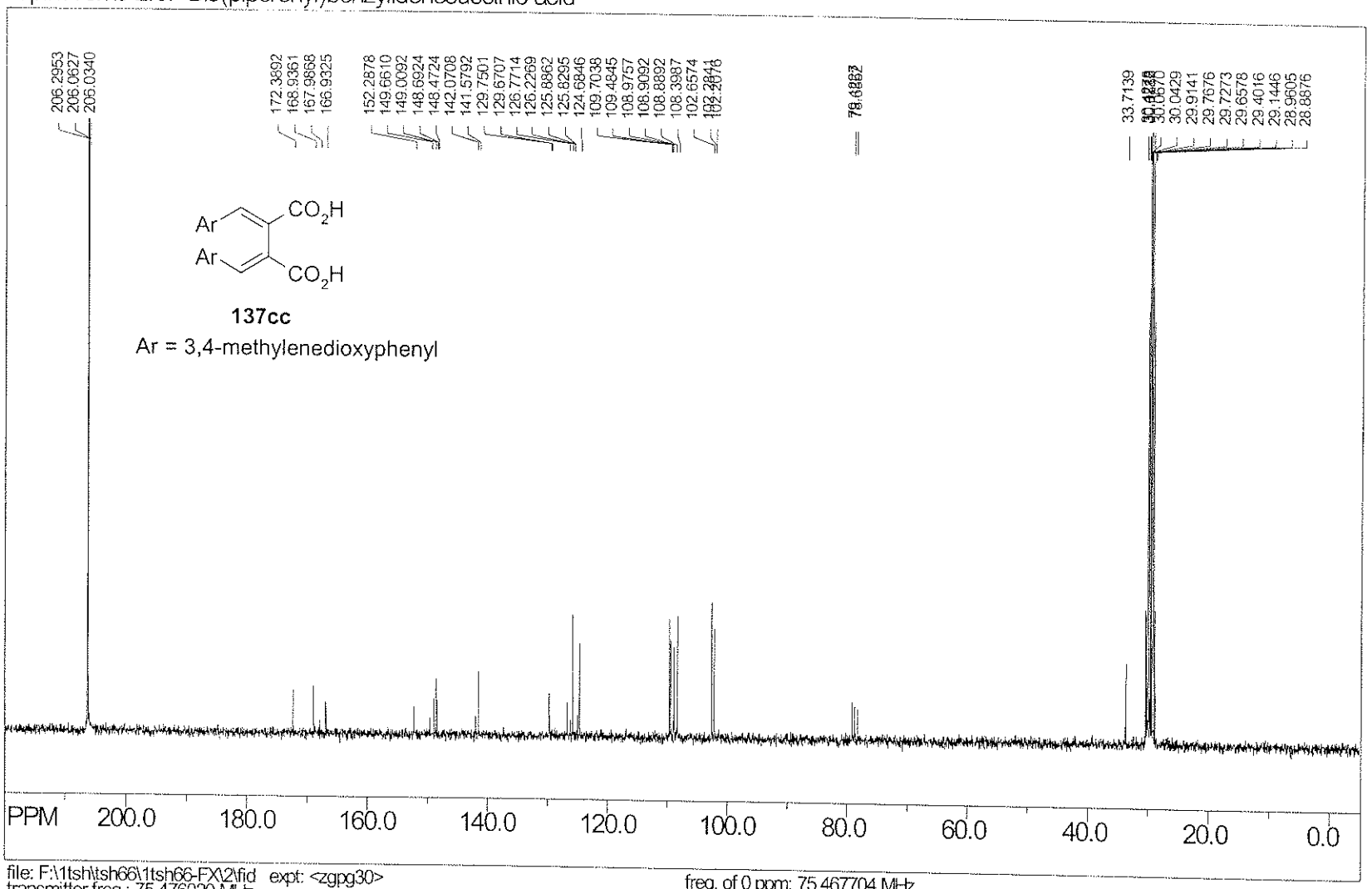
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 96

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

SpinWorks 2.0: Bis(piperonyl)benzylidenesuccinic acid



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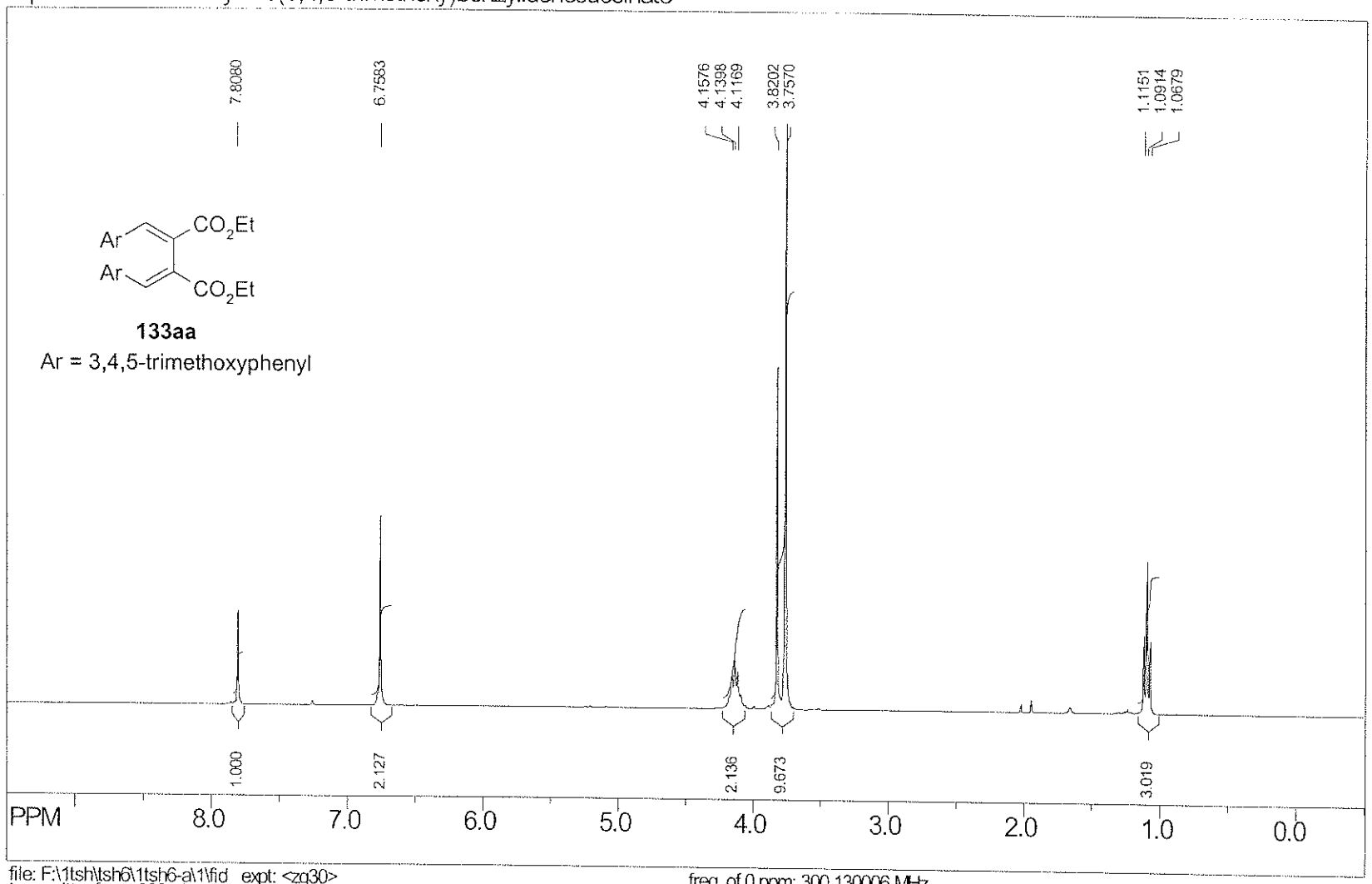
time domain size: 65536 points
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 256

freq. of 0 ppm: 75.467704 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000

SpinWorks 2.0: Ethyl Bis(3,4,5-trimethoxy)benzylidenesuccinate



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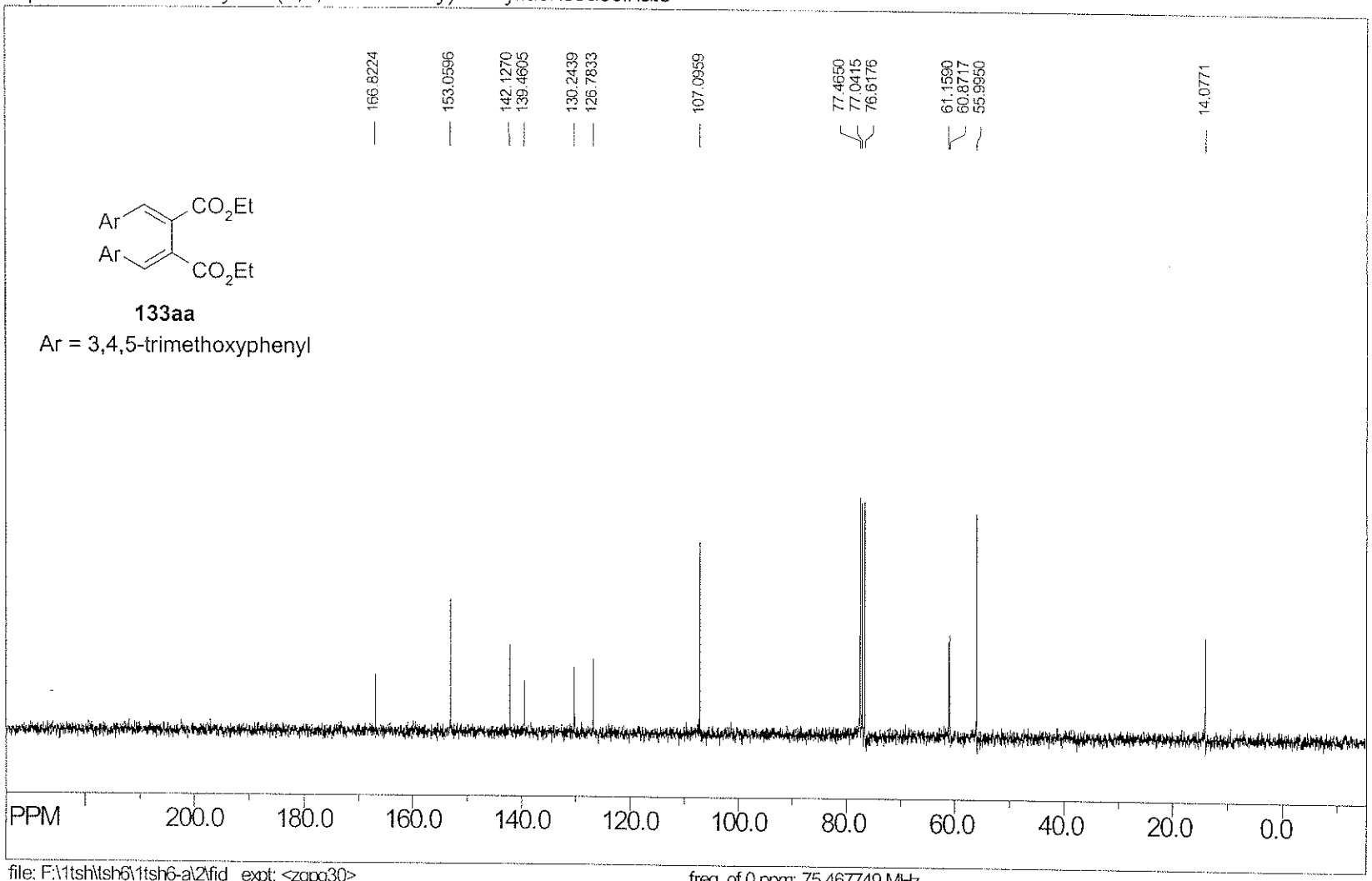
number of scans: 16

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

SpinWorks 2.0: Ethyl Bis(3,4,5-trimethoxy)benzylidenesuccinate



133aa

Ar = 3,4,5-trimethoxyphenyl

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time domain size: 65536 points
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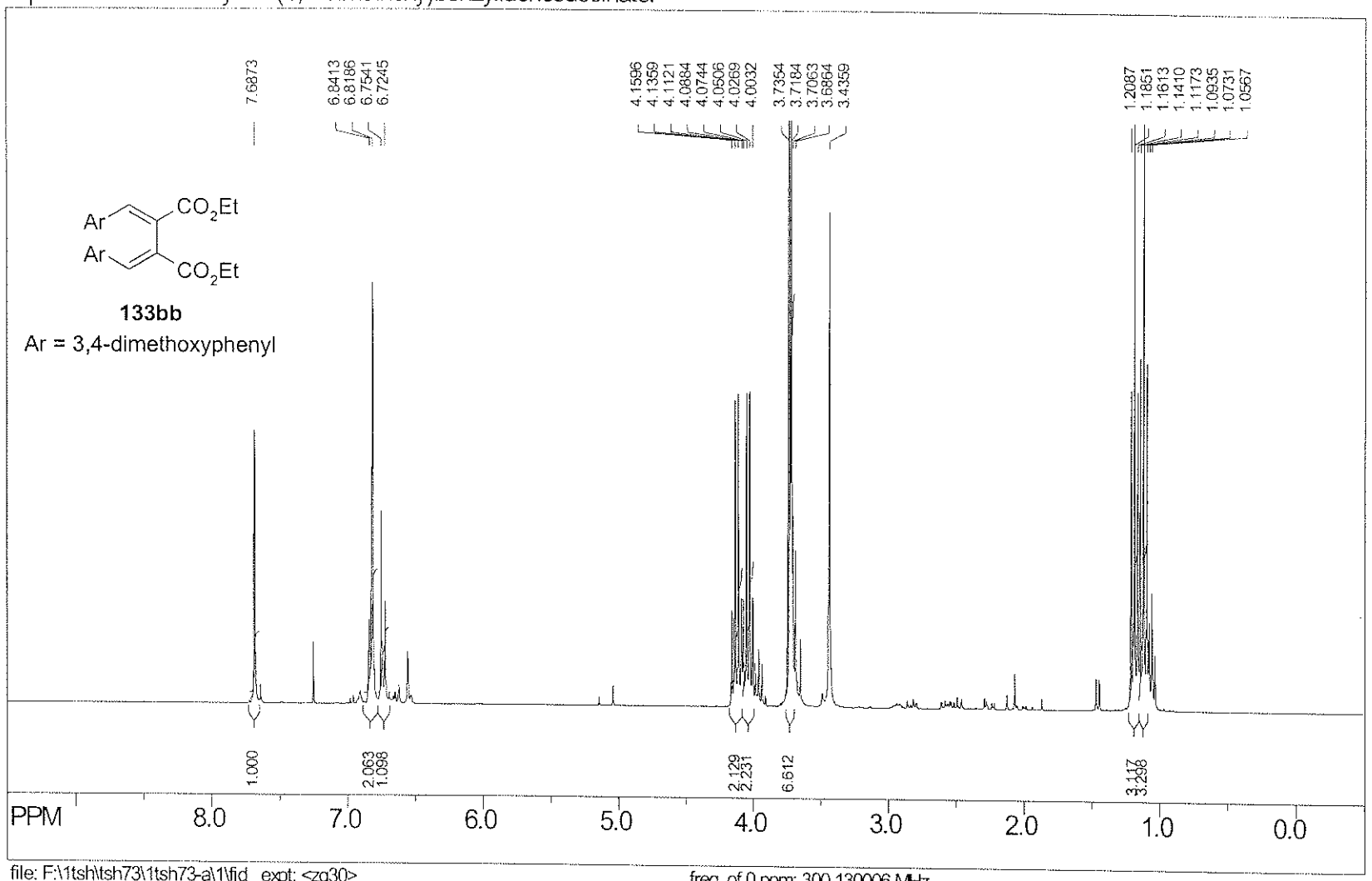
number of scans: 64

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

SpinWorks 2.0: Ethyl Bis(3,4-dimethoxy)benzylidenesuccinate.



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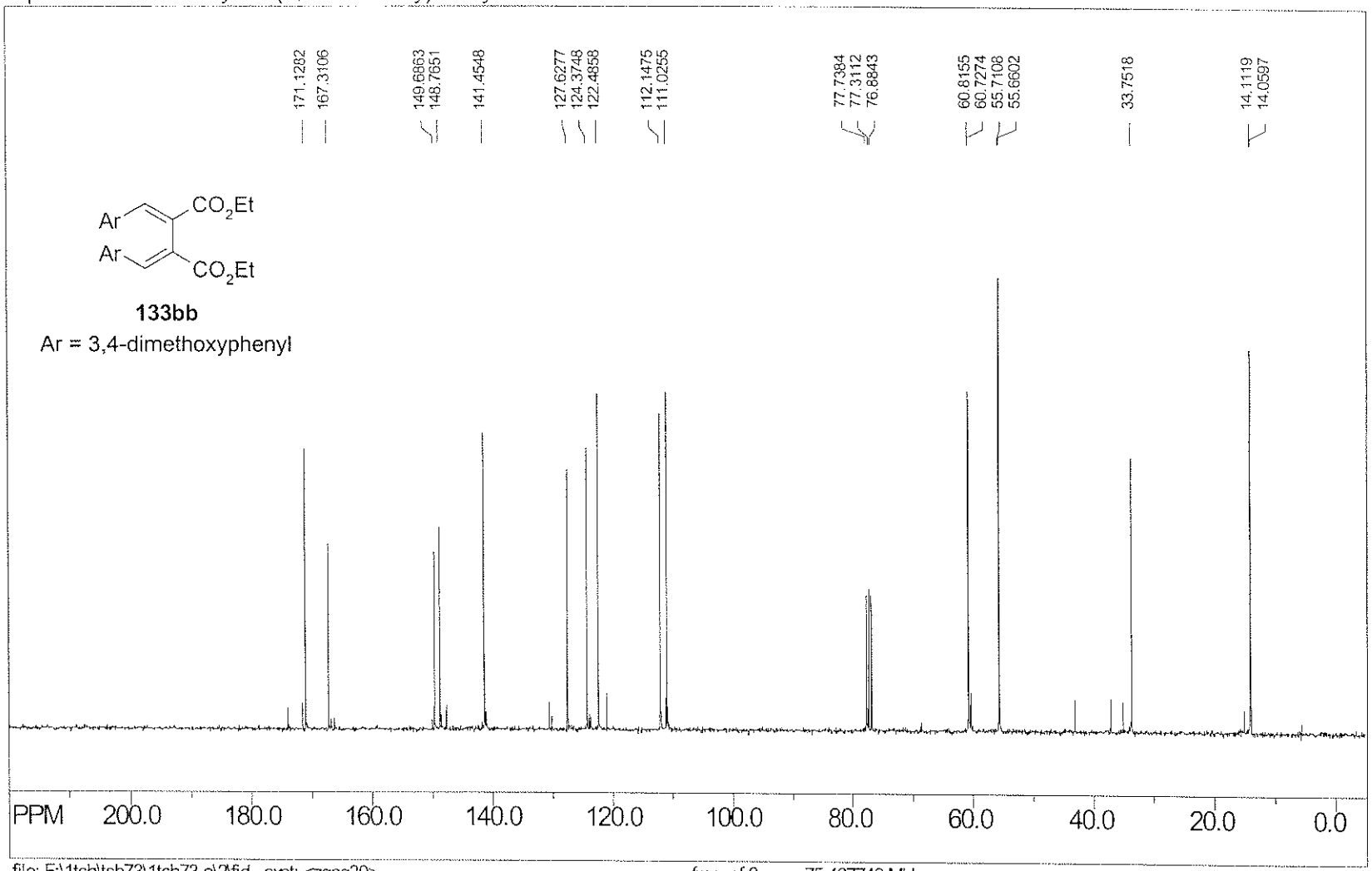
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 32

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

SpinWorks 2.0: Ethyl Bis(3,4-dimethoxy)benzylidenesuccinate



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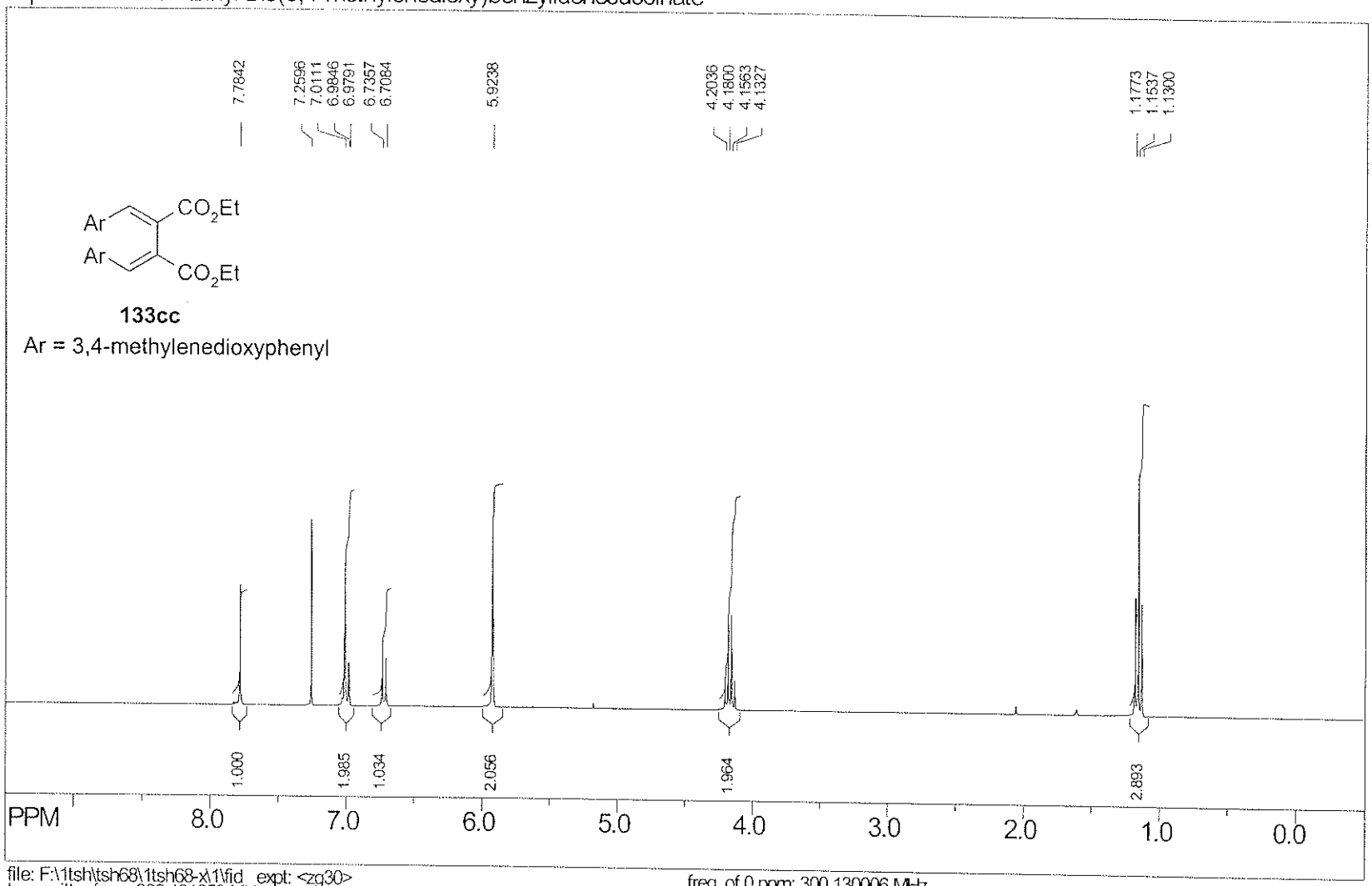
time domain size: 65536 points
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 128

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

SpinWorks 2.0: Ethyl Bis(3,4-methylenedioxy)benzylidenesuccinate



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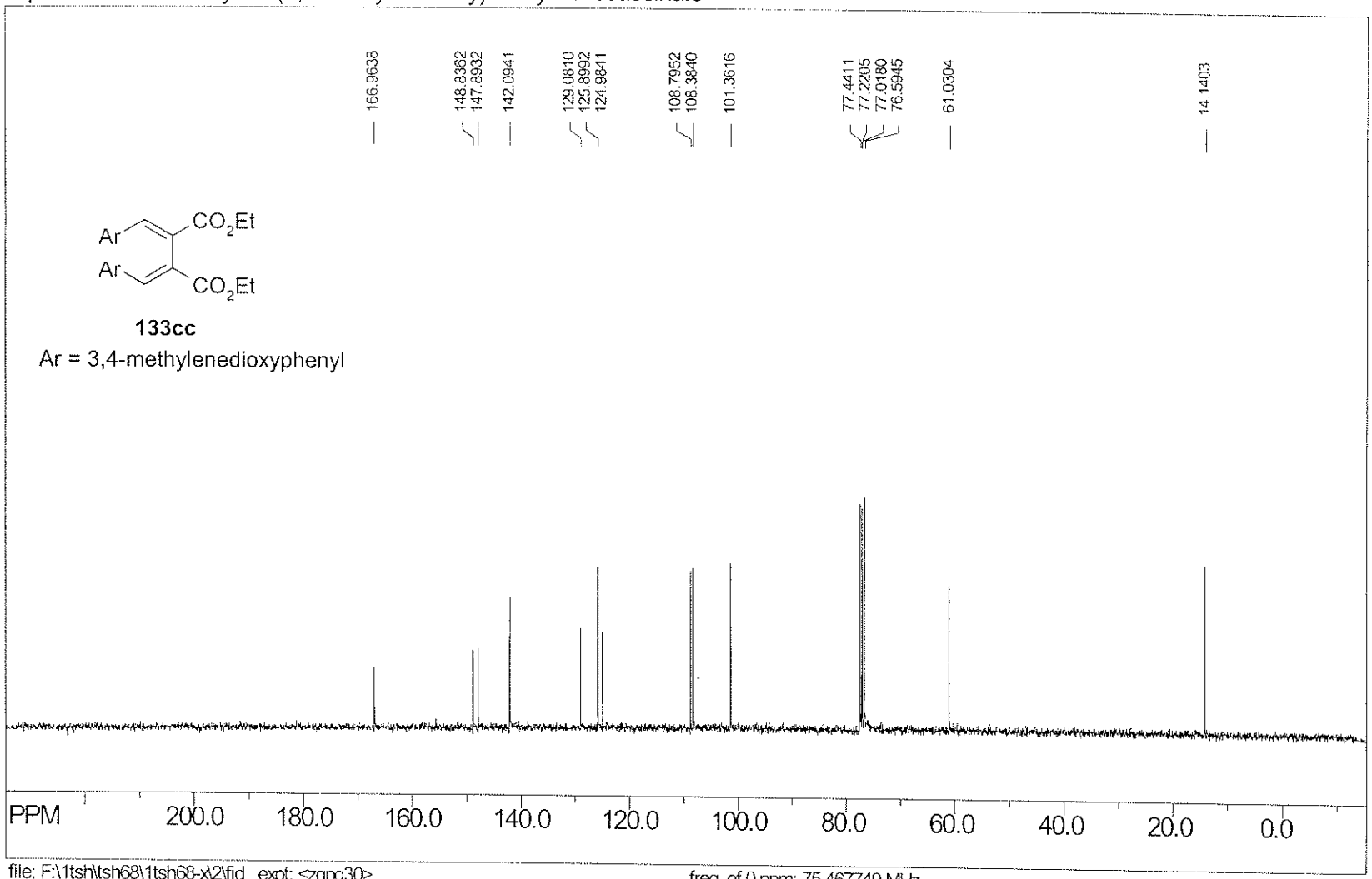
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 32

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

SpinWorks 2.0: Ethyl Bis(3,4-methylenedioxy)benzylidenesuccinate



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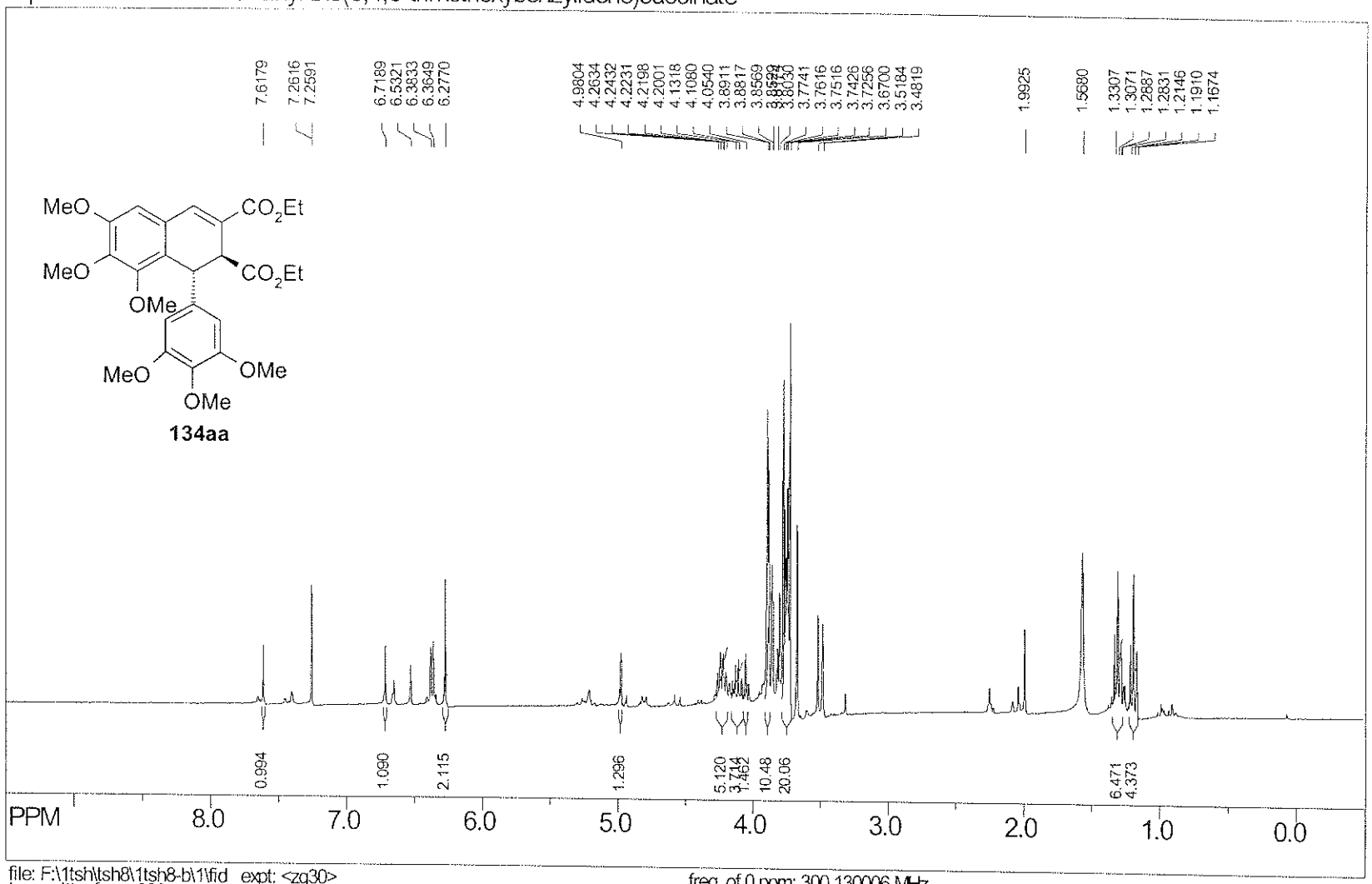
number of scans: 256

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

SpinWorks 2.0: Trans Ethyl Bis(3,4,5-trimethoxybenzylidene)succinate



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number of scans: 32

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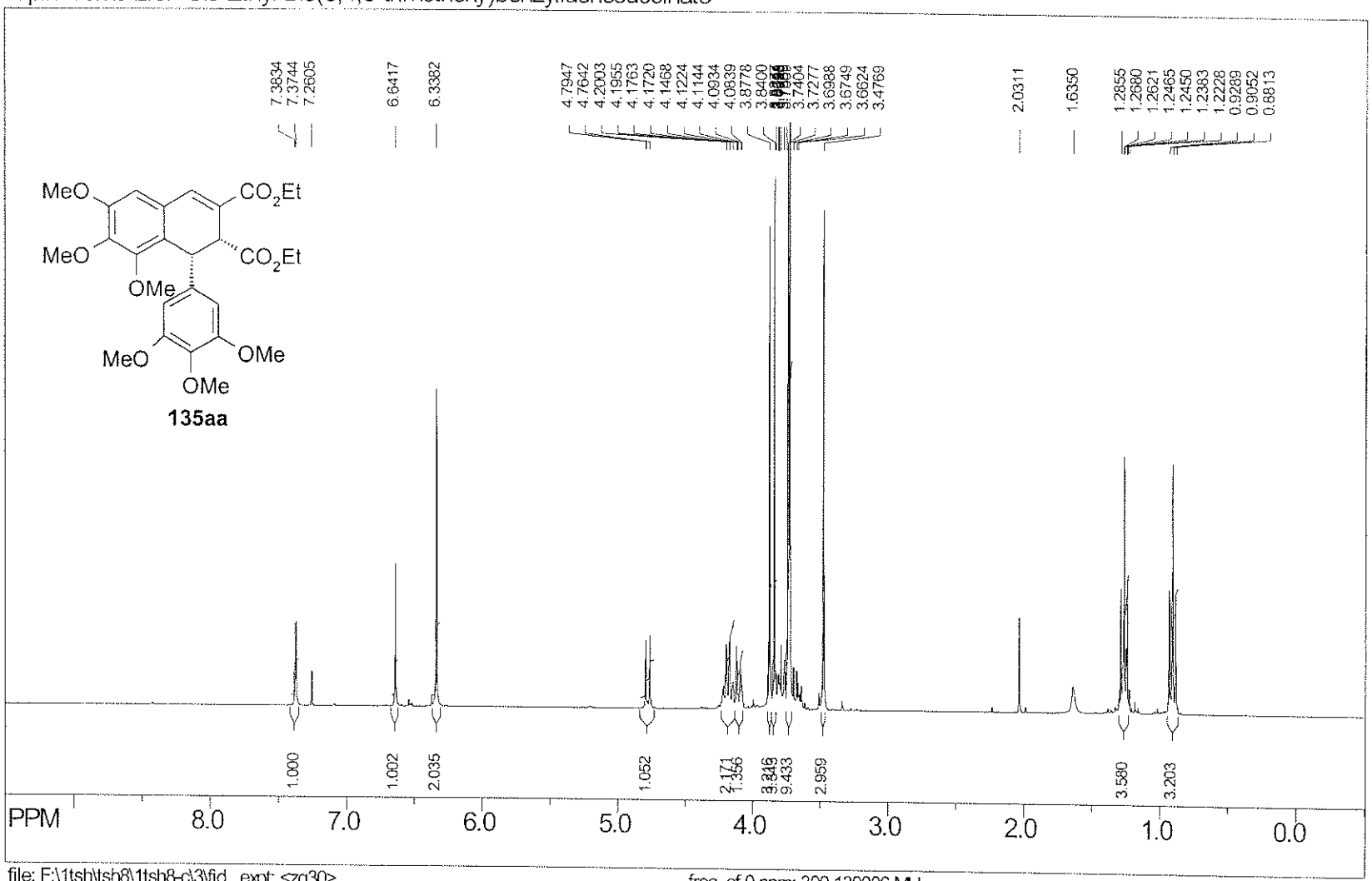
processed size: 32768 complex points
LB: 0.300 GB: 0.0000

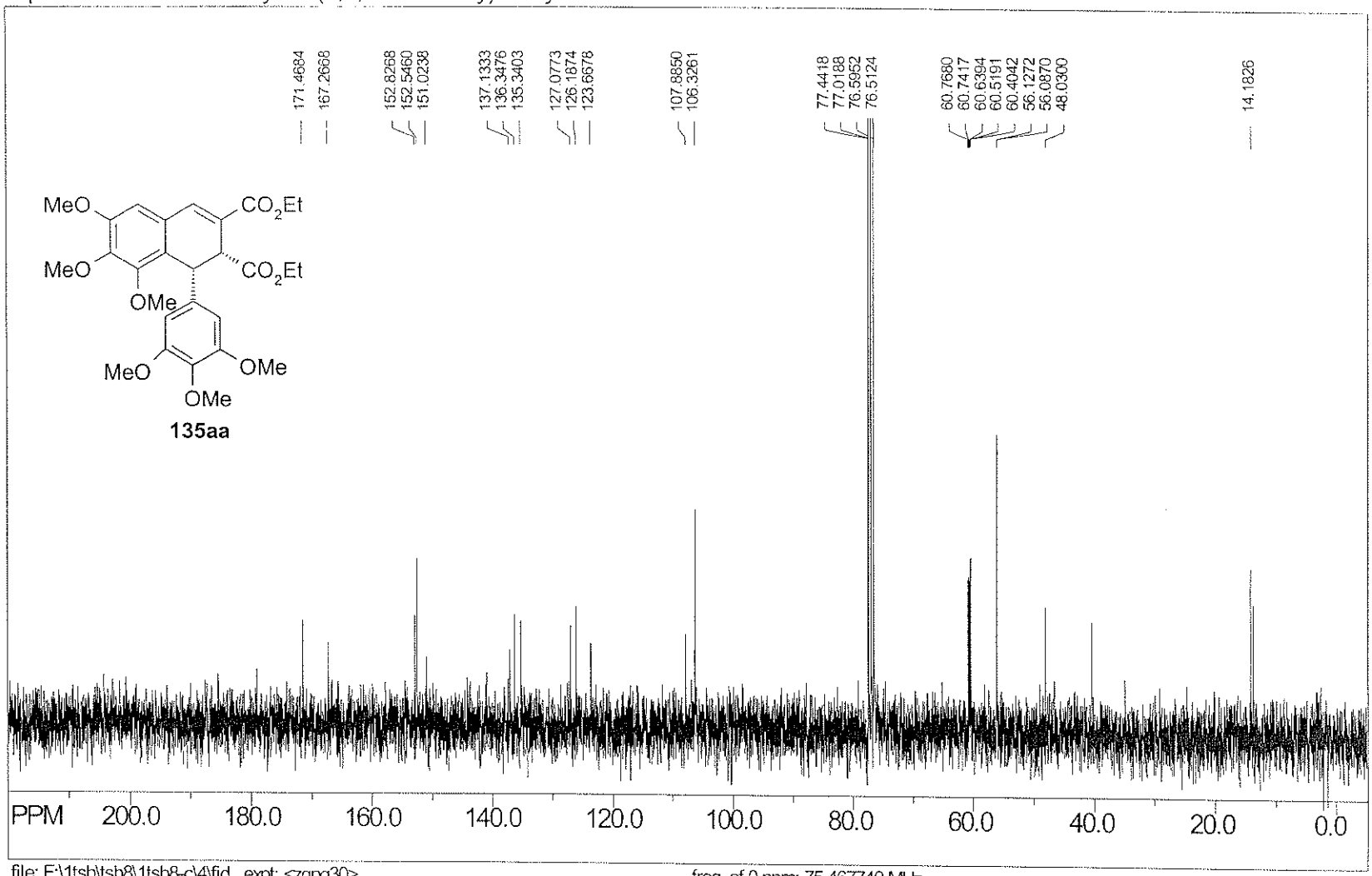
SpinWorks 2.0: Cis Ethyl Bis(3,4,5-trimethoxy)benzylidenesuccinate



file: F:\1tsh\tsh8\1tsh8-c\3\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 32

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

SpinWorks 2.0: Cis Ethyl Bis(3,4,5-trimethoxy)benzylidenesuccinate

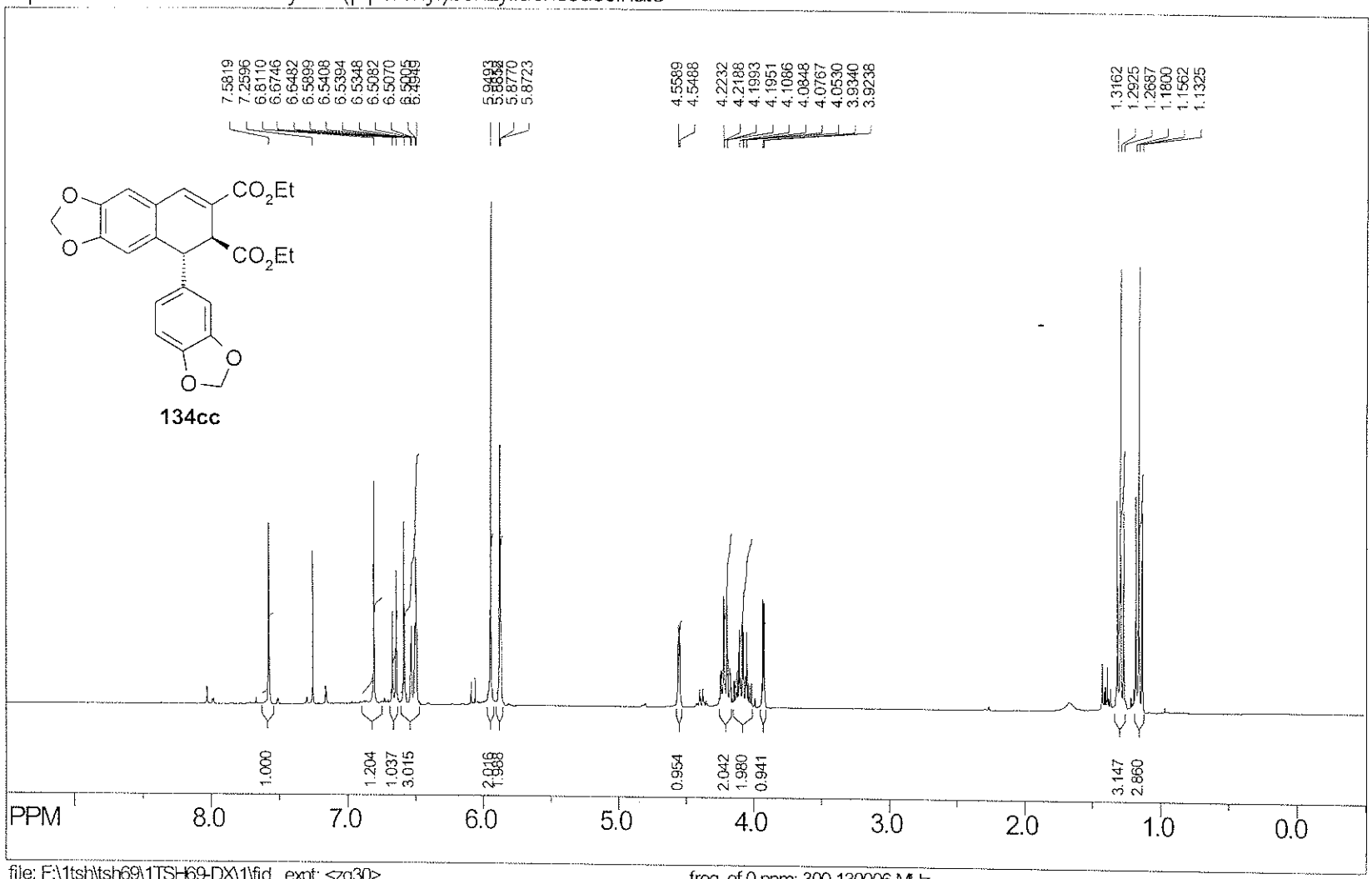


135aa

file: F:\1tsh\tsh8\1tsh8-c\4\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 64

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

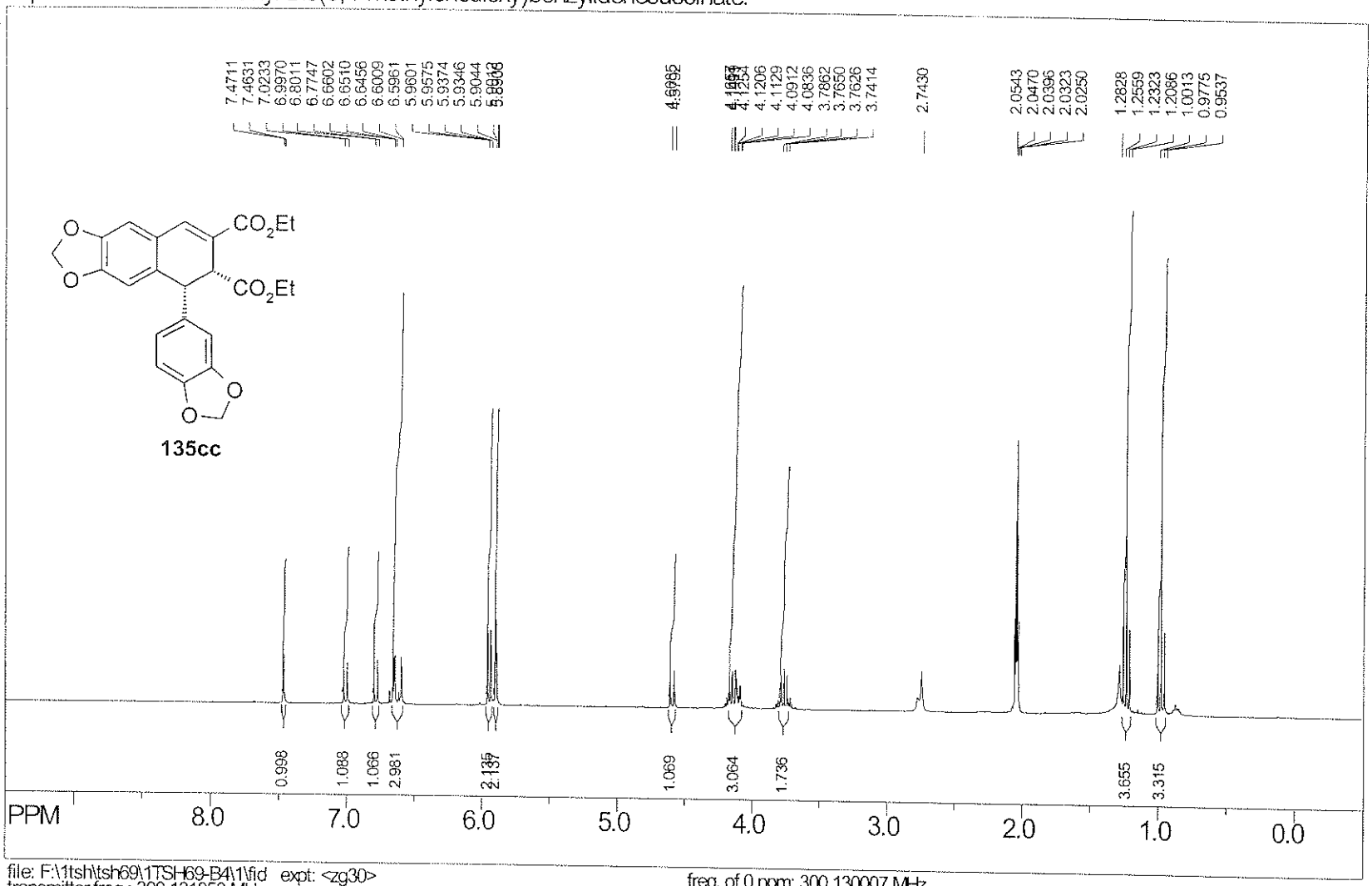
SpinWorks 2.0: Trans Ethyl Bis(piperonyl)benzylidenesuccinate



file: F:\1tsh\tsh69\1TSH69-DX\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 48

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

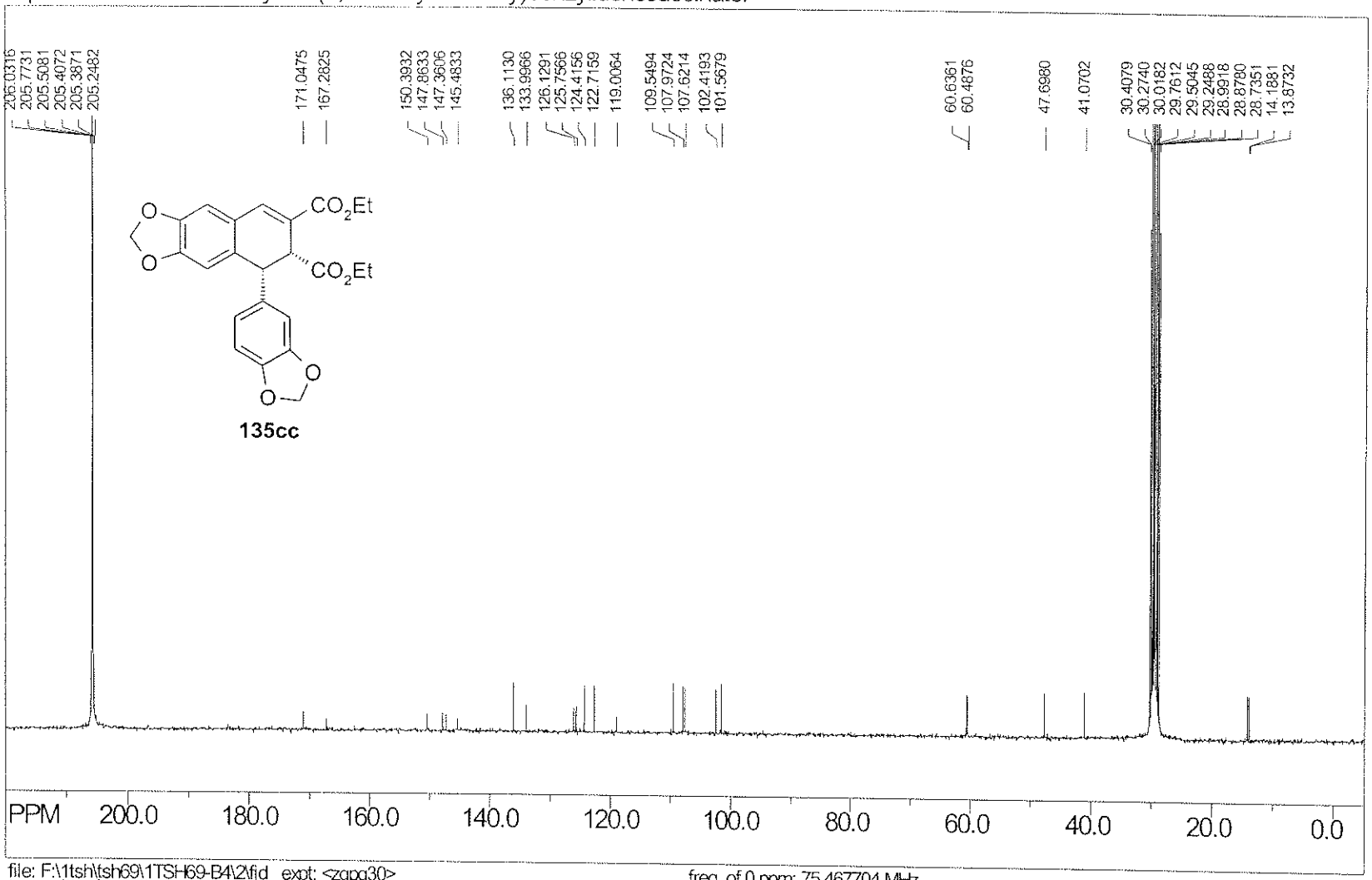
SpinWorks 2.0: Cis Ethyl Bis(3,4-methylenedioxy)benzylidenesuccinate.



file: F:\1tsh\tsh69\1TSH69-B4\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 256

freq. of 0 ppm: 300.130007 MHz
processed size: 32768 complex points
LB: 0.300 GB: 0.0000

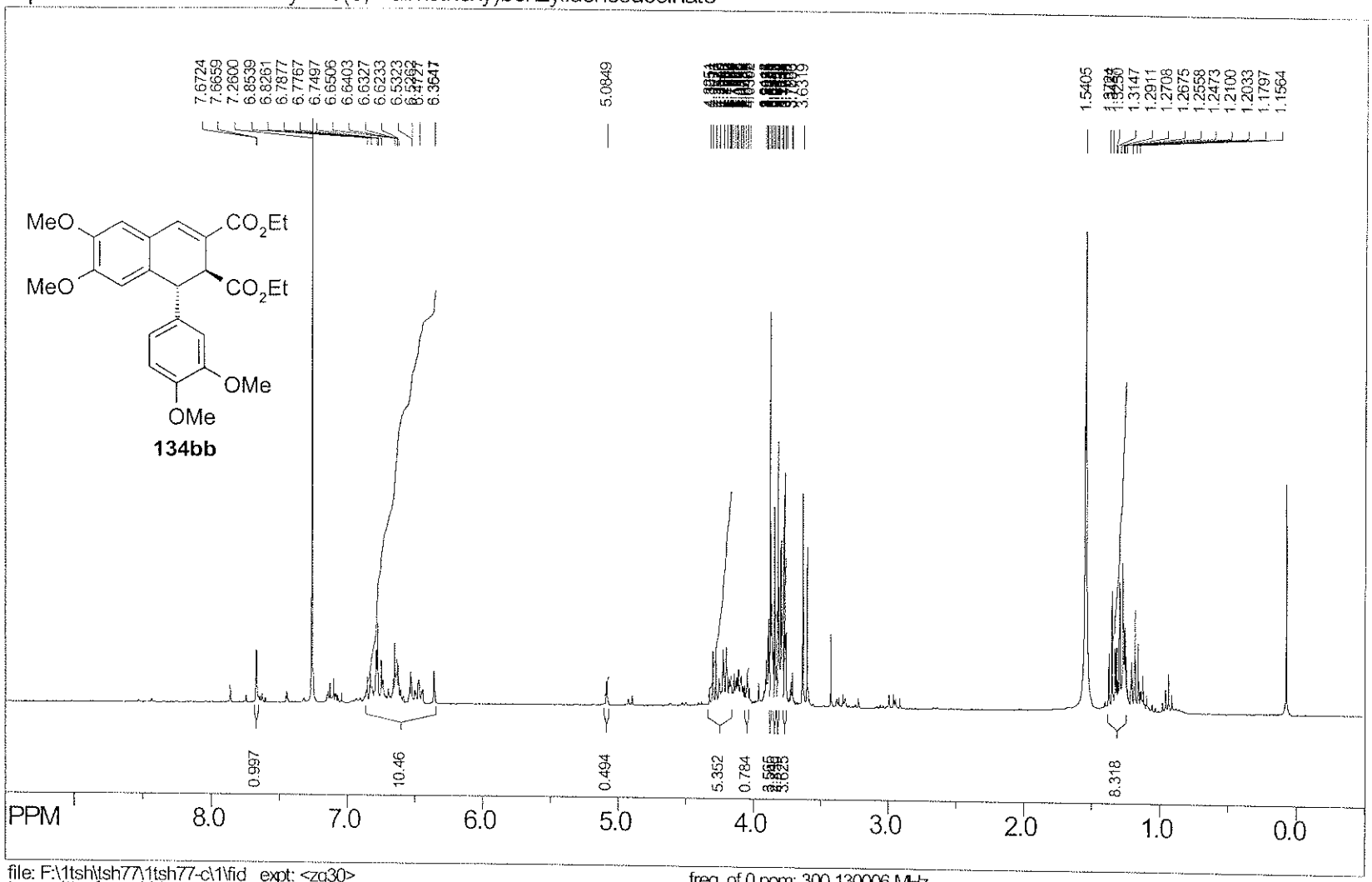
SpinWorks 2.0: Cis Ethyl Bis(3,4-methylenedioxy)benzylidenesuccinate.



file: F:\1tsh\tsh69\1TSH69-B4\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 12288

freq. of 0 ppm: 75.467704 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000

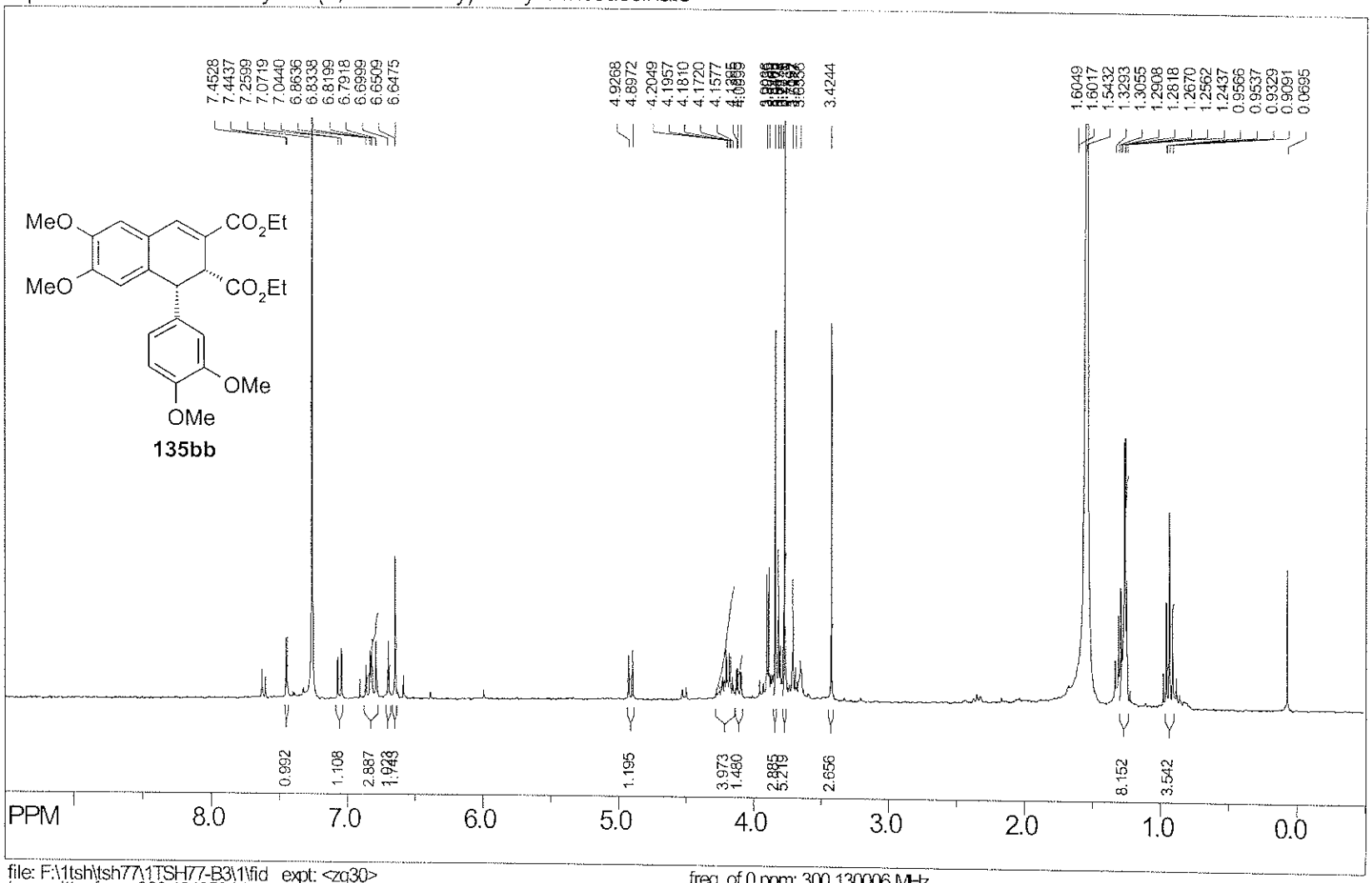
SpinWorks 2.0: Trans Ethyl Bis(3,4-dimethoxy)benzylidenesuccinate



file: F:\1tsh\tsh77\1tsh77-c\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 256

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

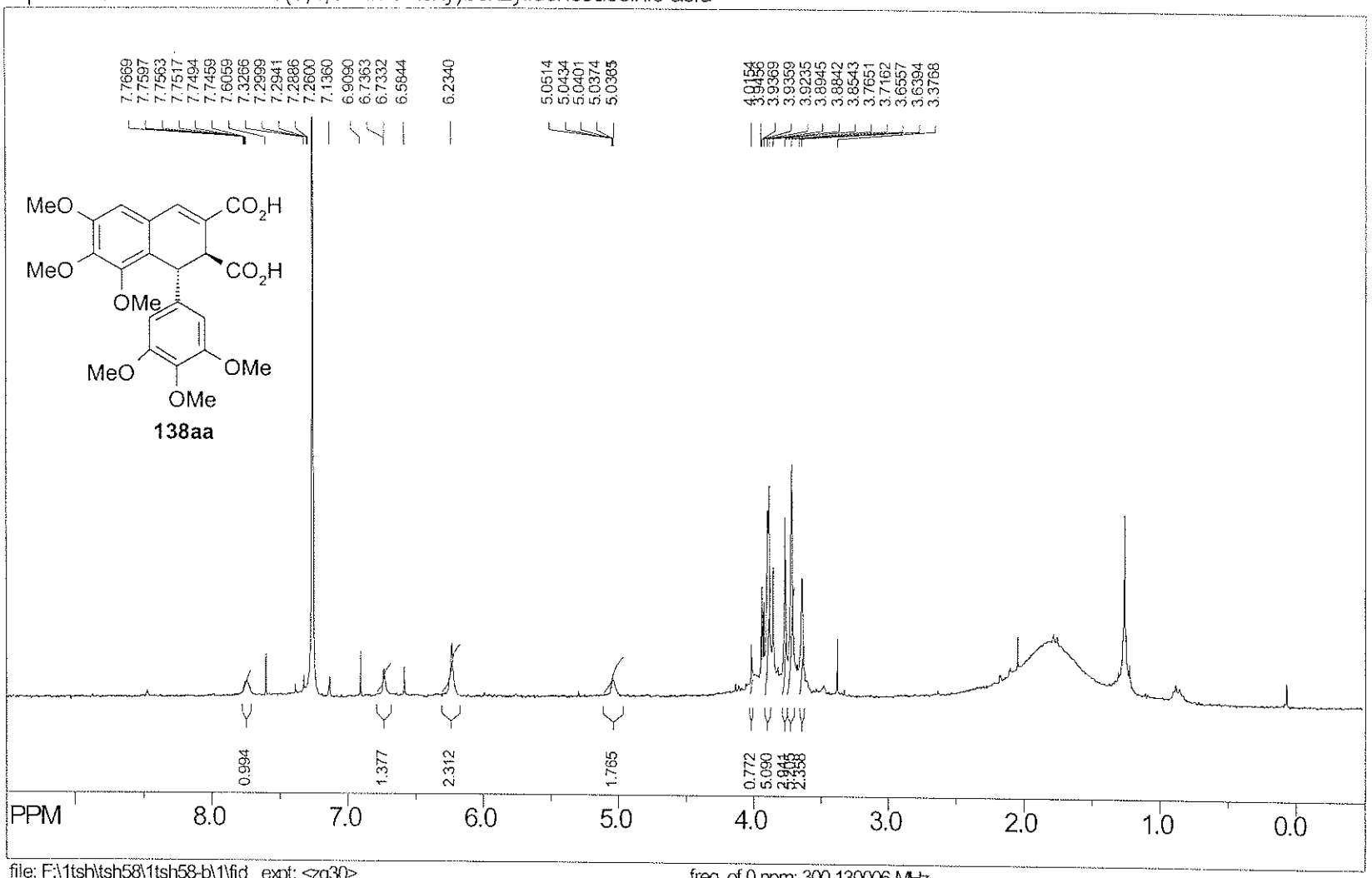
SpinWorks 2.0: Cis Ethyl Bis(3,4-dimethoxy)benzylidenesuccinate



file: F:\1tsh\tsh77\1TSH77-B3\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 256

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

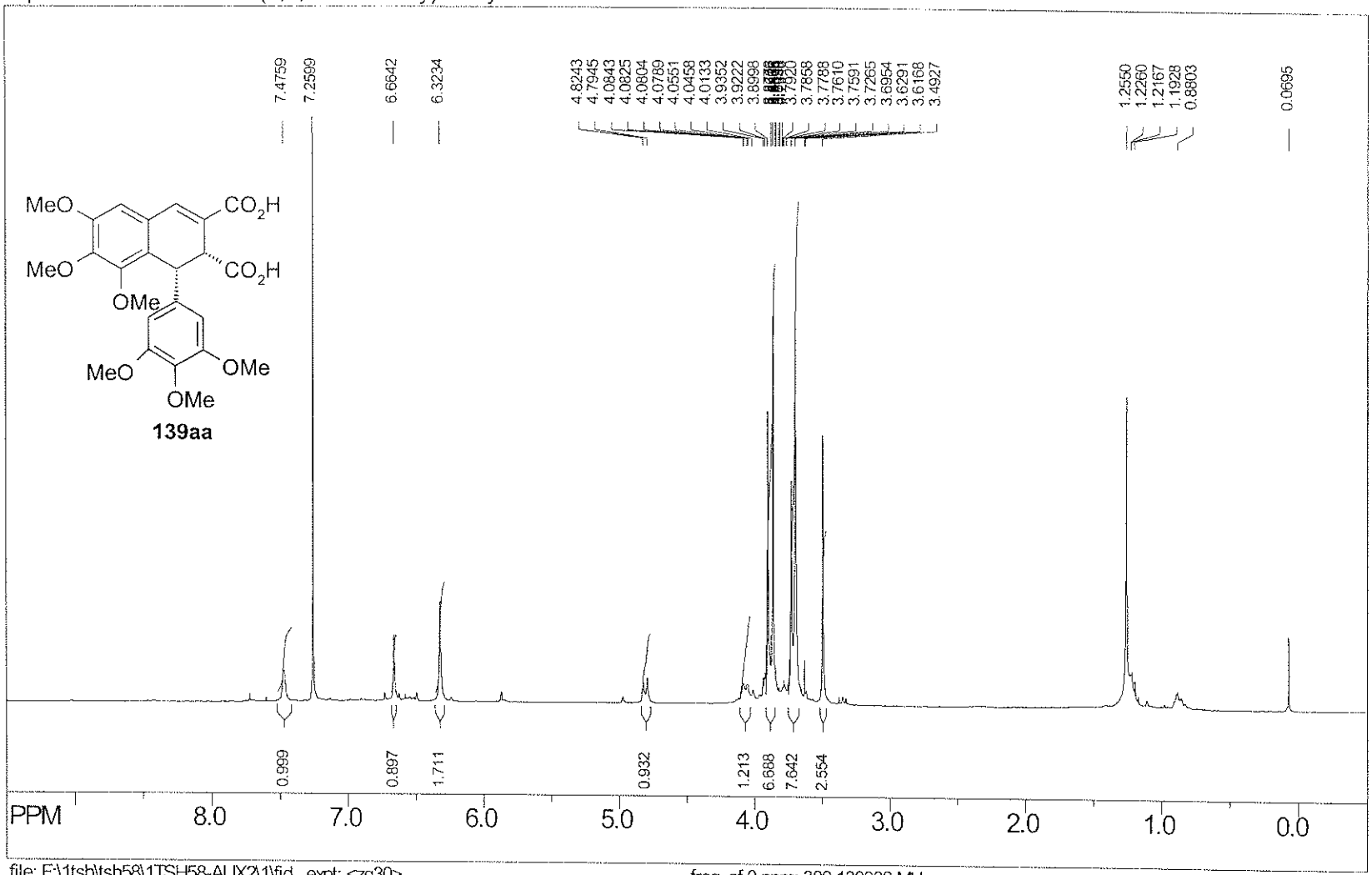
SpinWorks 2.0: Trans Bis(3,4,5-trimethoxy)benzylidenesuccinic acid



file: F:\1tsh\tsh58\1tsh58-b\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 153

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

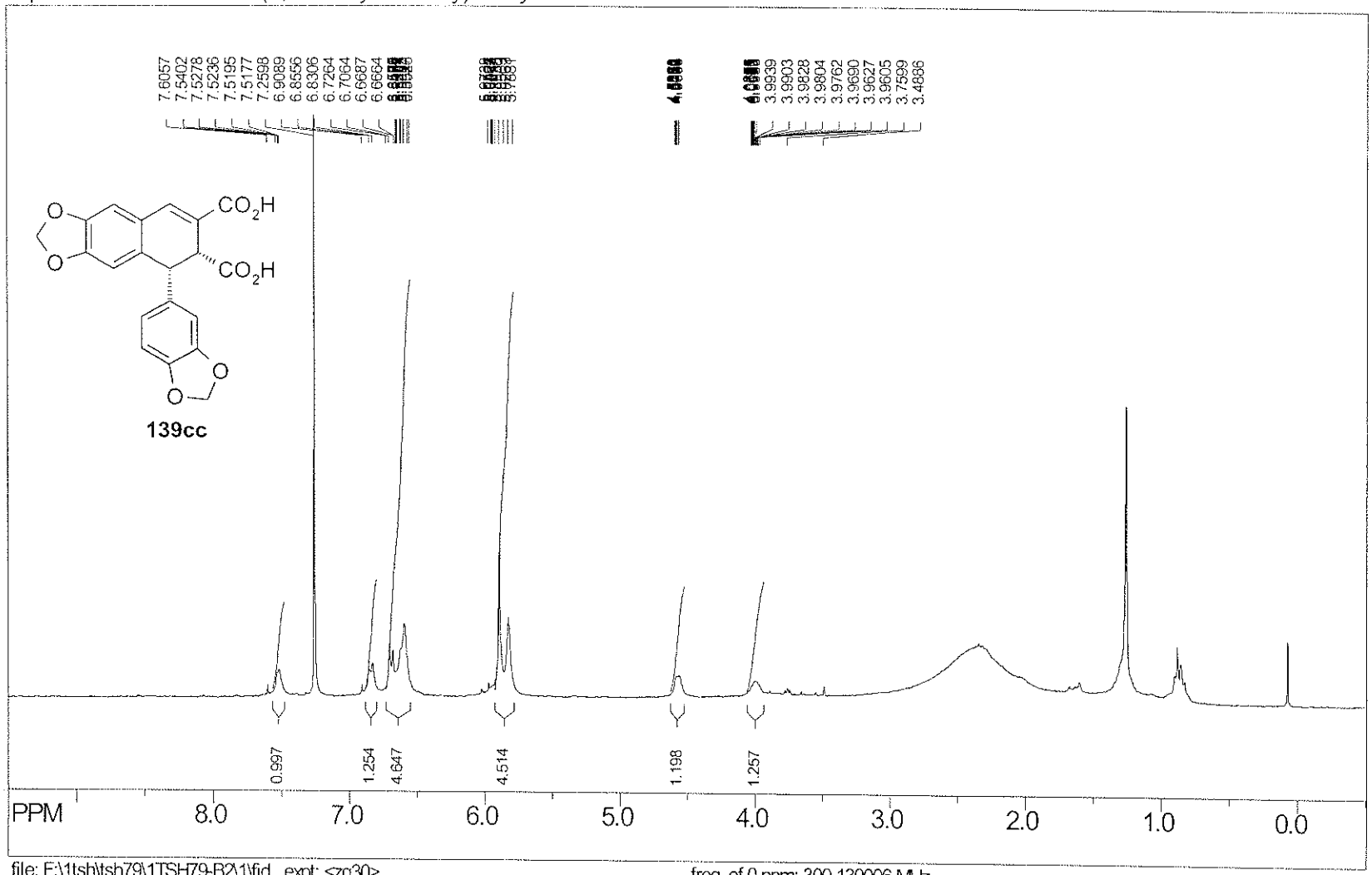
SpinWorks 2.0: Cis Bis(3,4,5-trimethoxy)benzylidenesuccinic acid



file: F:\1tsh\tsh58\1TSH58-AUX2\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 256

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

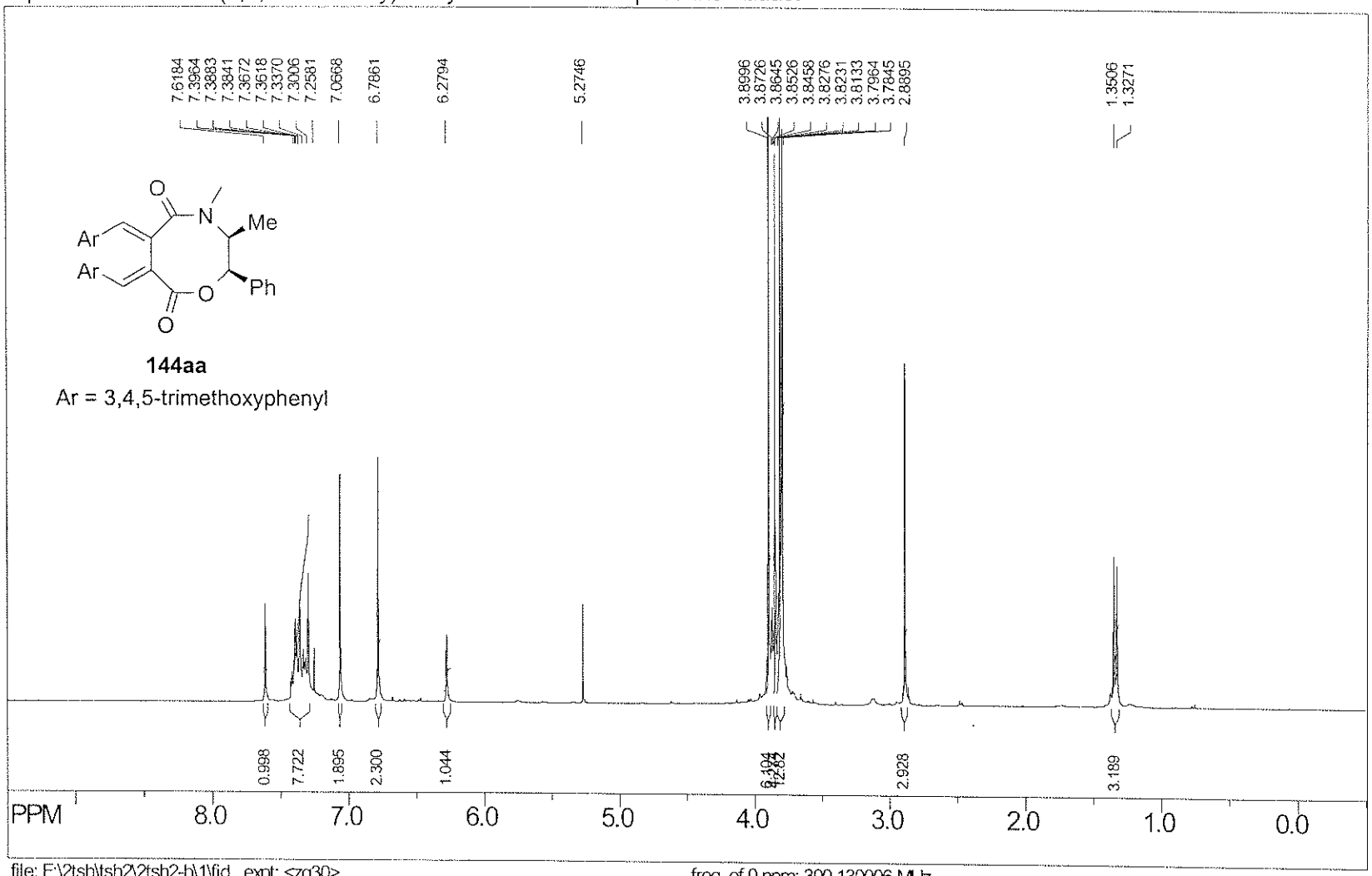
SpinWorks 2.0: Cis Bis(3,4-methylenedioxy)benzylidenesuccinic acid



file: F:\1tsh\tsh79\1TSH79-B2\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 256

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

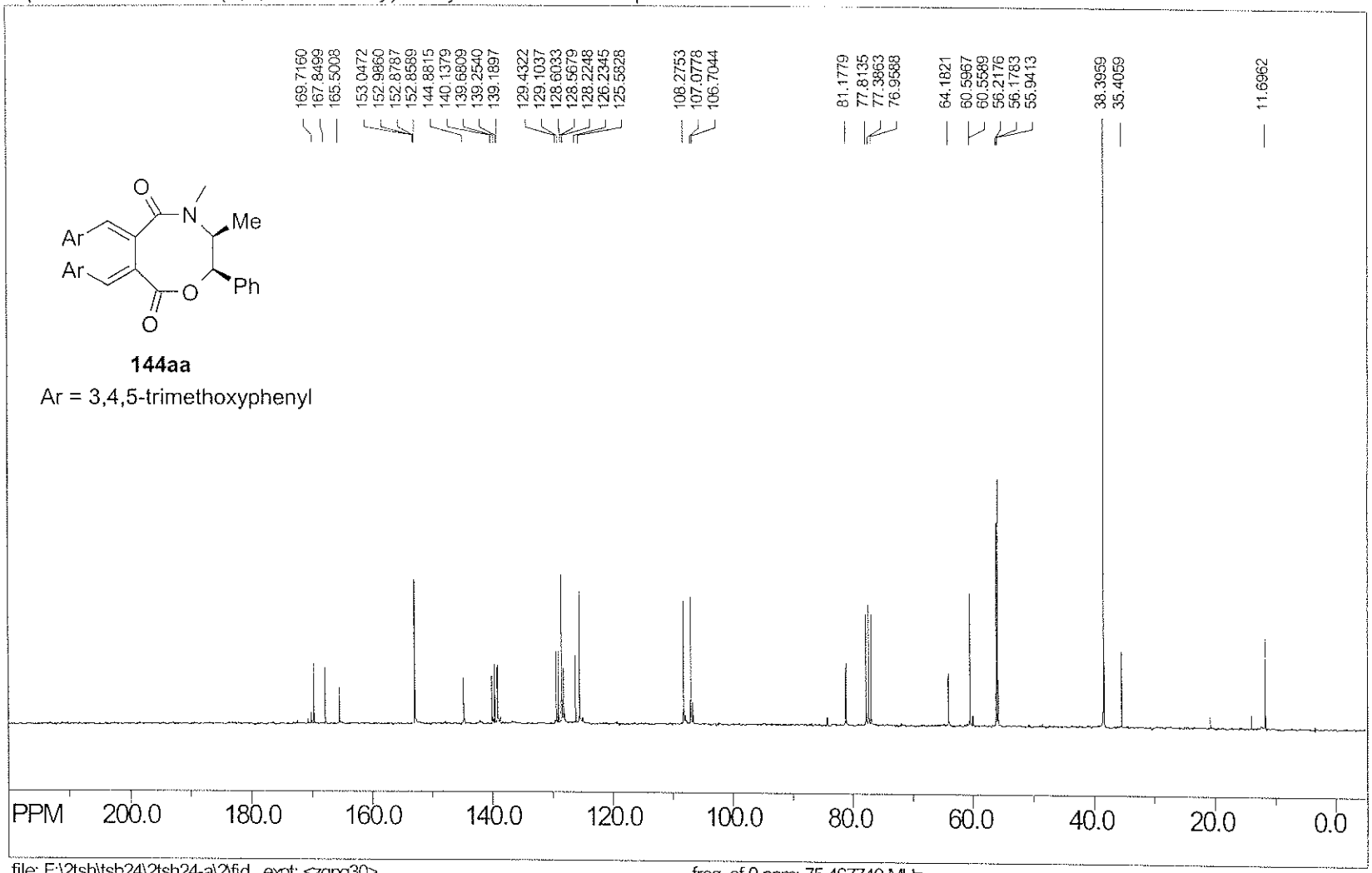
SpinWorks 2.0: Bis(3,4,5-trimethoxy)benzylidenesuccinate/Ephedrine Adduct



file: F:\2tsh\tsh2\2tsh2-b\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 32

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

SpinWorks 2.0: Bis(3,4,5-trimethoxy)benzylidenesuccinate/Ephedrine Adduct



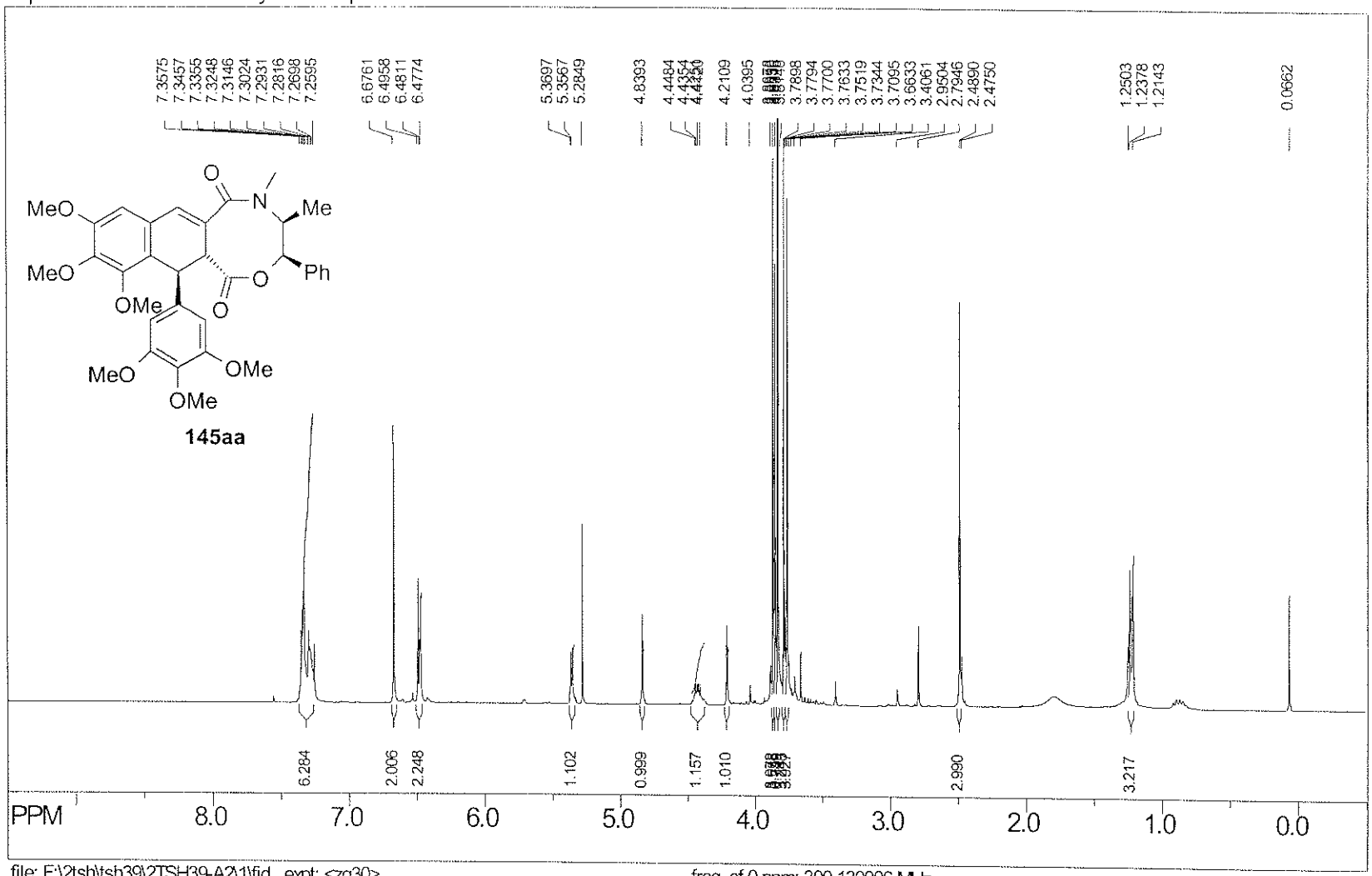
144aa

Ar = 3,4,5-trimethoxyphenyl

file: F:\2tsh\tsh24\2tsh24-a\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 384

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

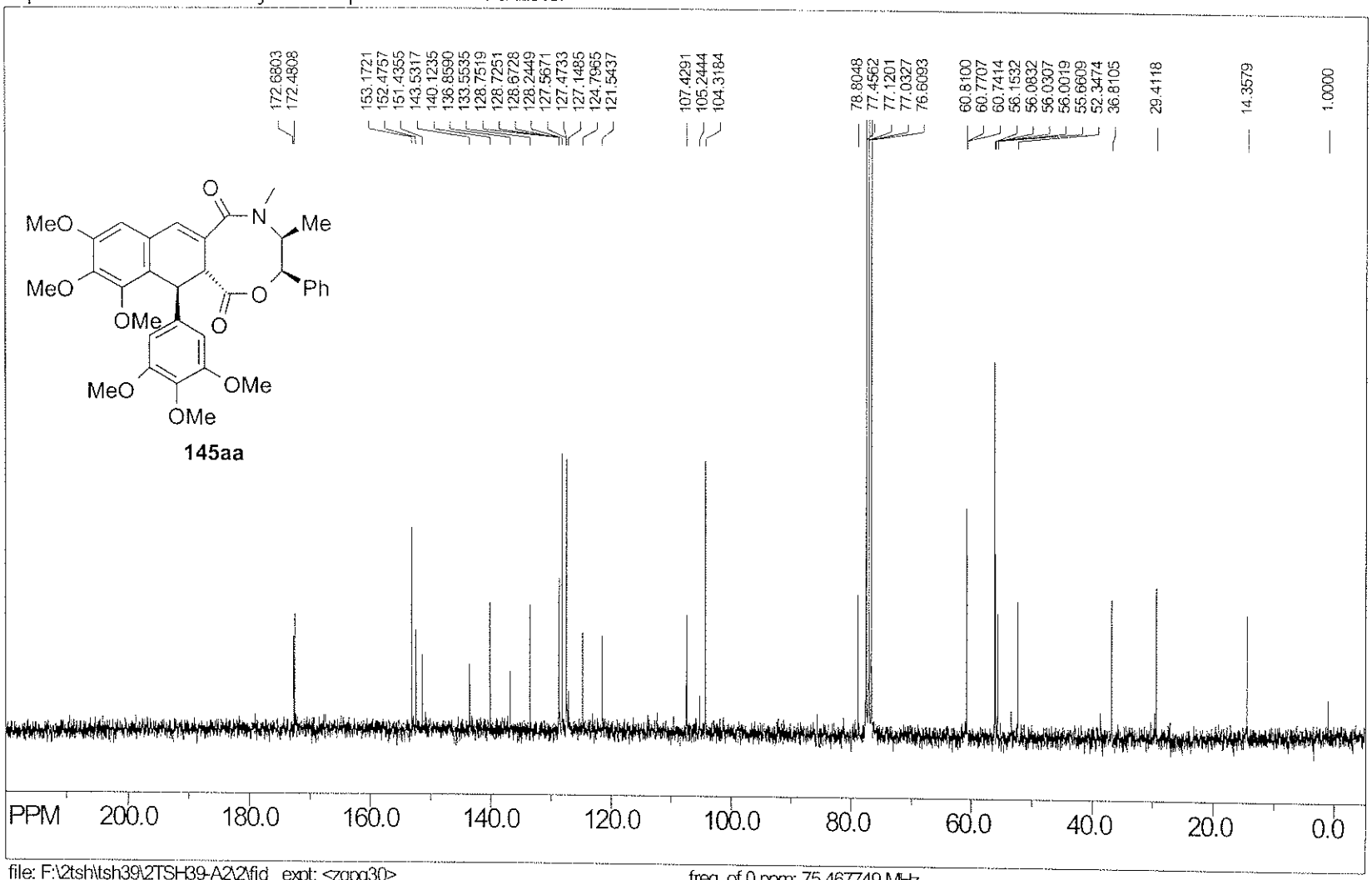
SpinWorks 2.0: Photocyclized Ephedrine Amide-Ester



file: F:\2tsh\tsh39\2TSH39-A2\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 64

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

SpinWorks 2.0: Photocyclized Ephedrine Amide/Ester

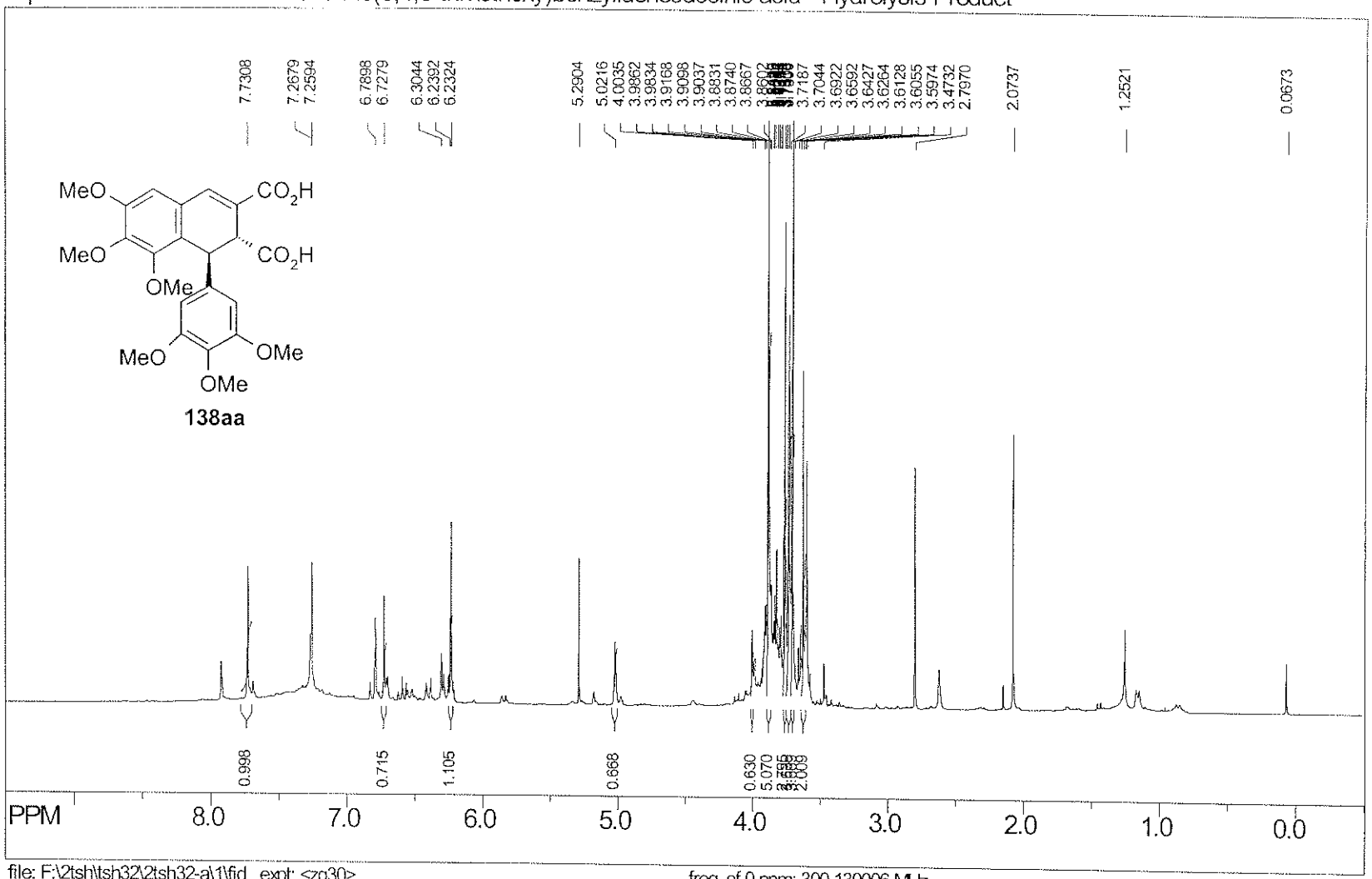


145aa

file: F:\2tsh\tsh39\2TSH39-A2\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 640

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

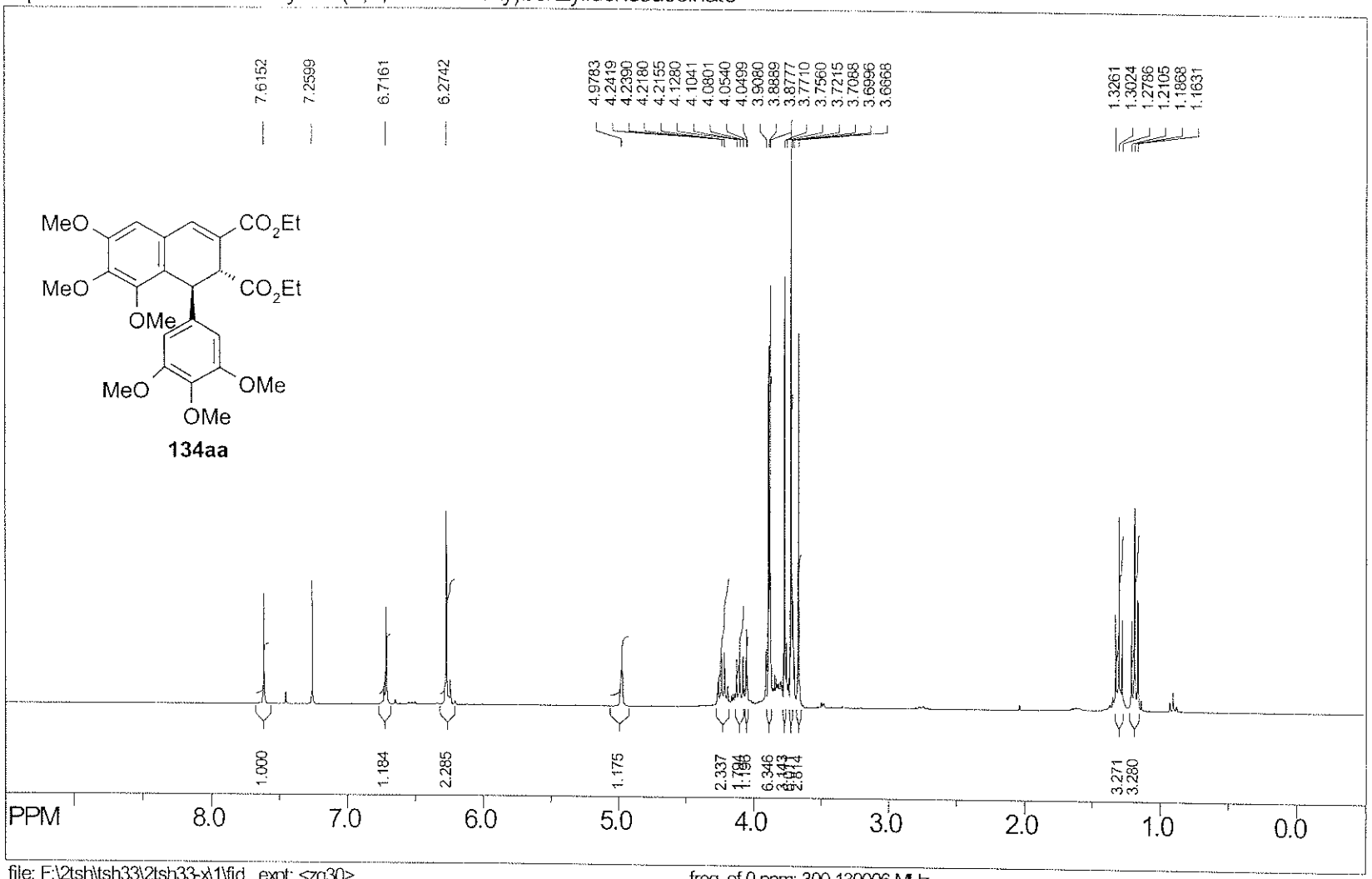
SpinWorks 2.0: CRUDE Trans Bis(3,4,5-trimethoxy)benzylidenesuccinic acid - Hydrolysis Product



file: F:\2tsh\tsh32\2tsh32-a\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 96

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

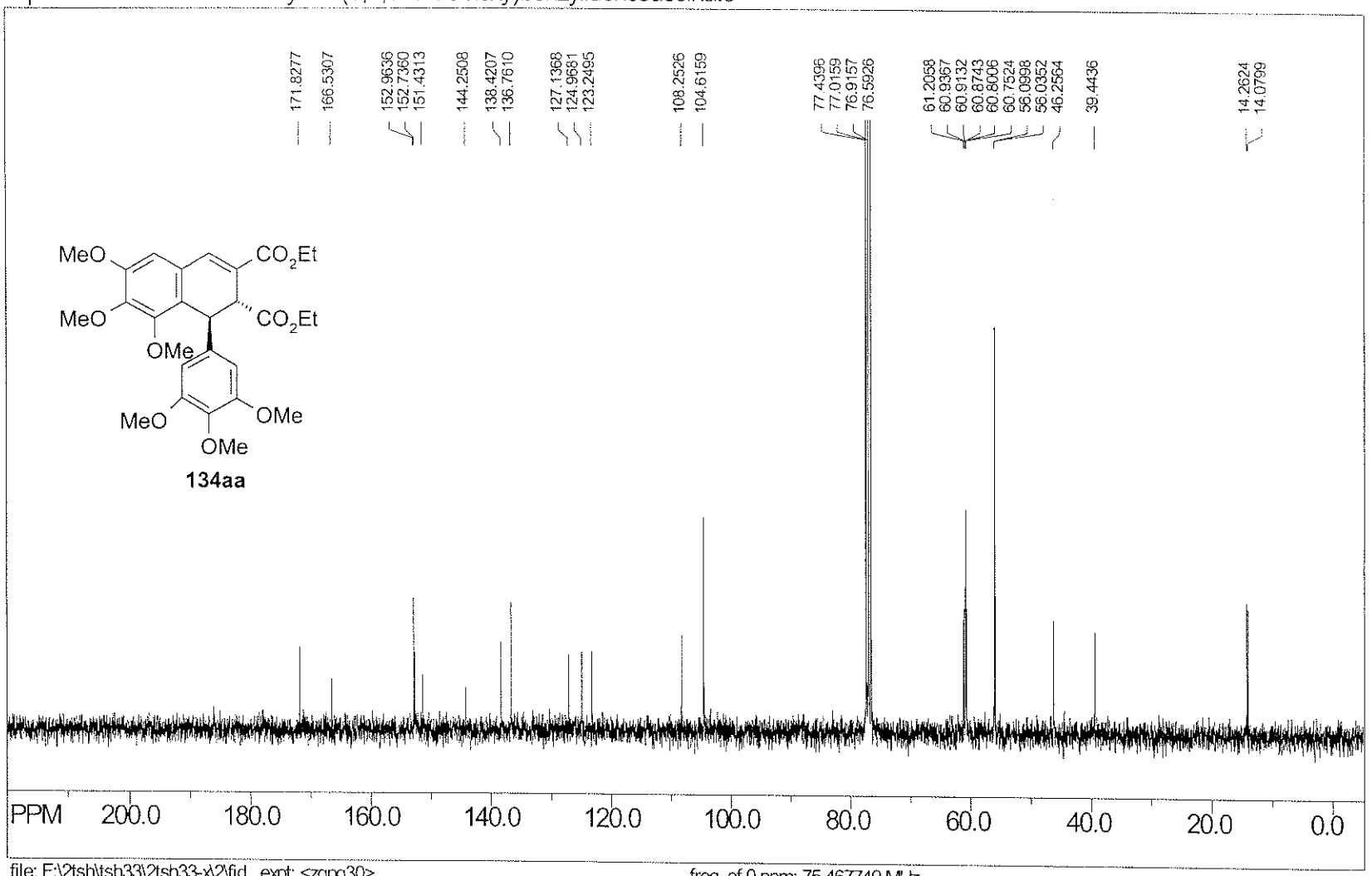
SpinWorks 2.0: Trans Ethyl Bis(3,4,5-trimethoxy)benzylidenesuccinate



file: F:\2tsh\tsh33\2tsh33-x\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 64

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

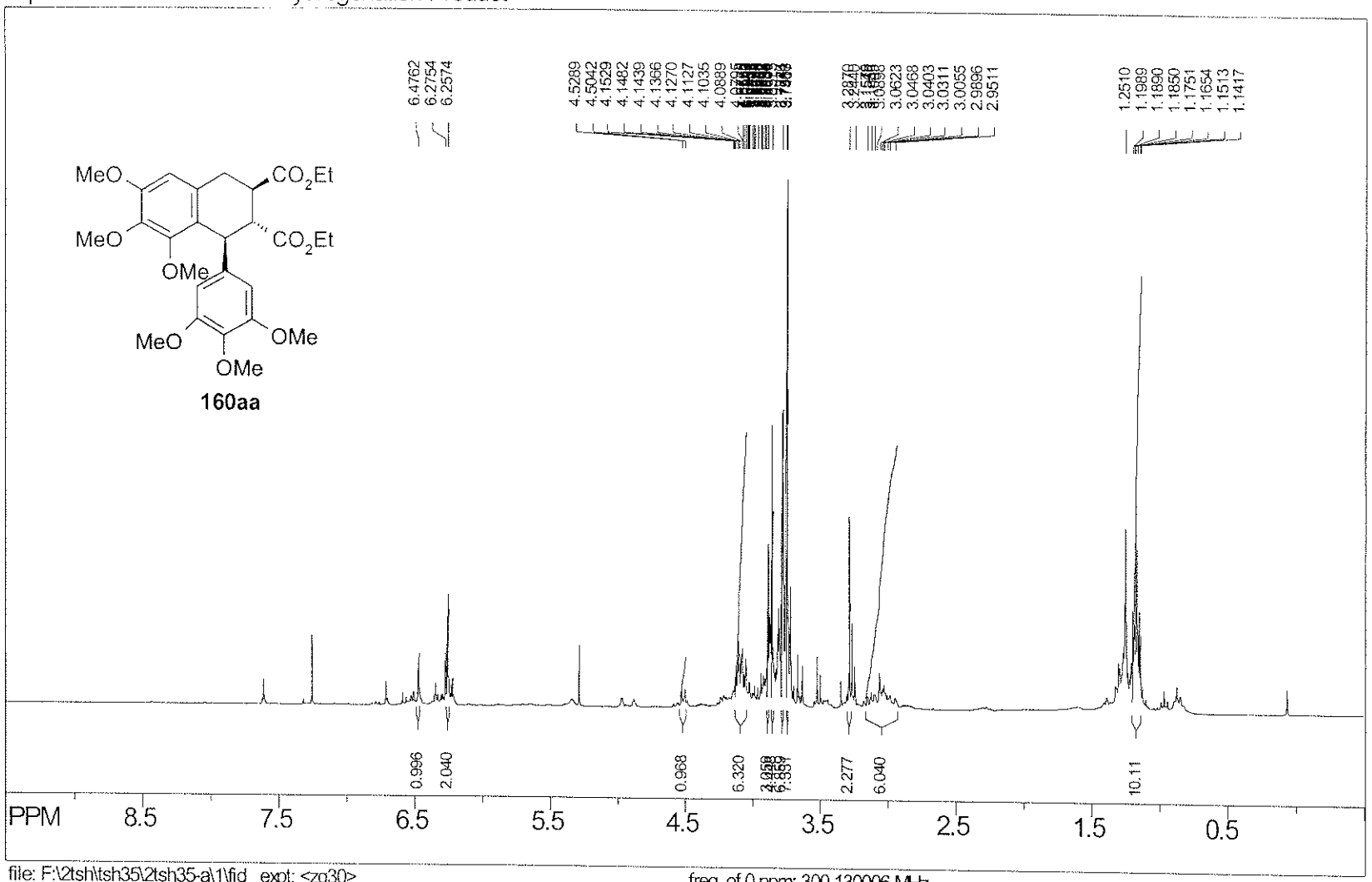
SpinWorks 2.0: Trans Ethyl Bis(3,4,5-trimethoxy)benzylidenesuccinate



file: F:\2tsh\tsh33\2tsh33-x\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 384

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

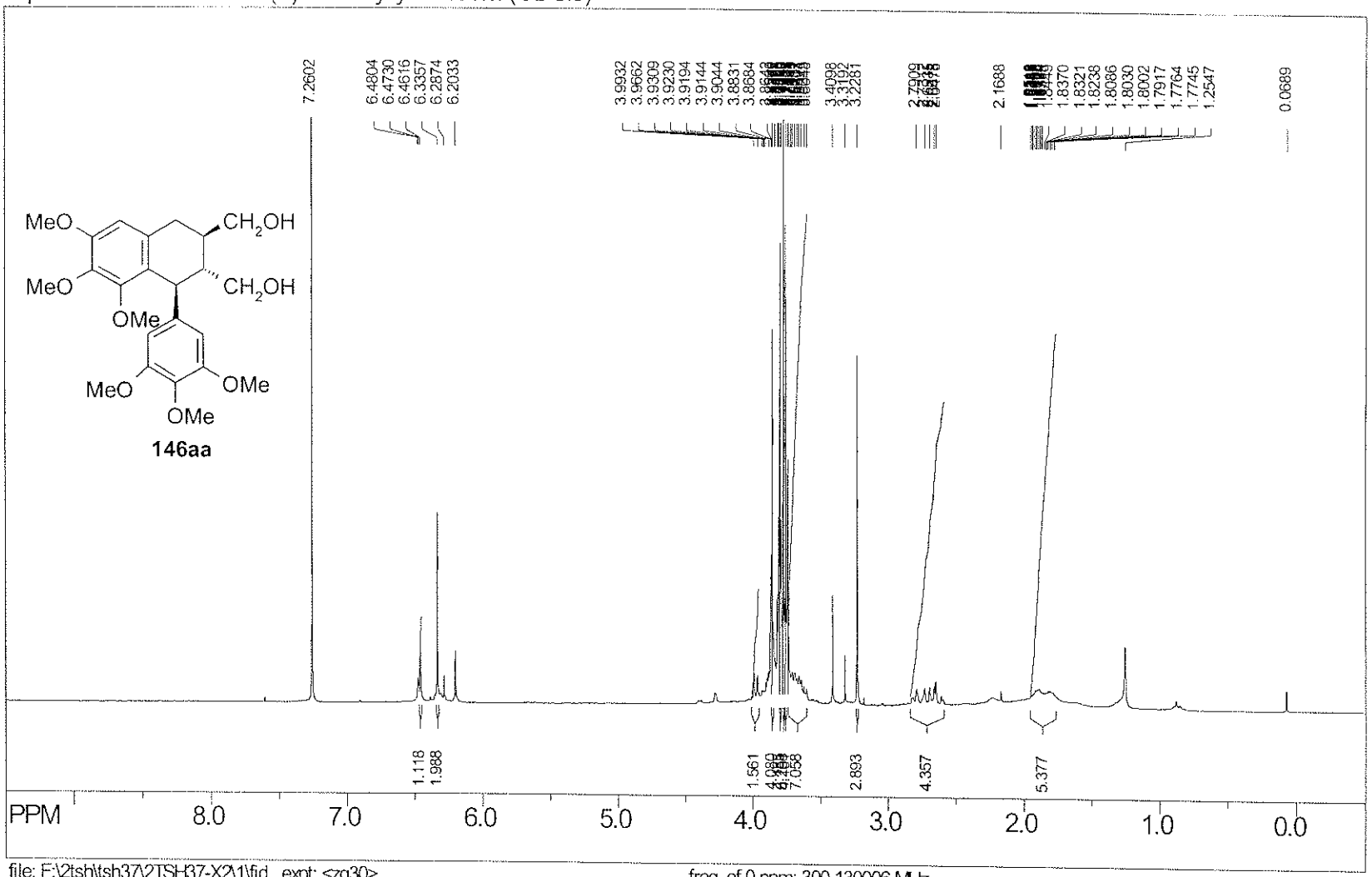
SpinWorks 2.0: CRUDE Hydrogenation Product



file: F:\2tsh\tsh35\2tsh35-a\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 128

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

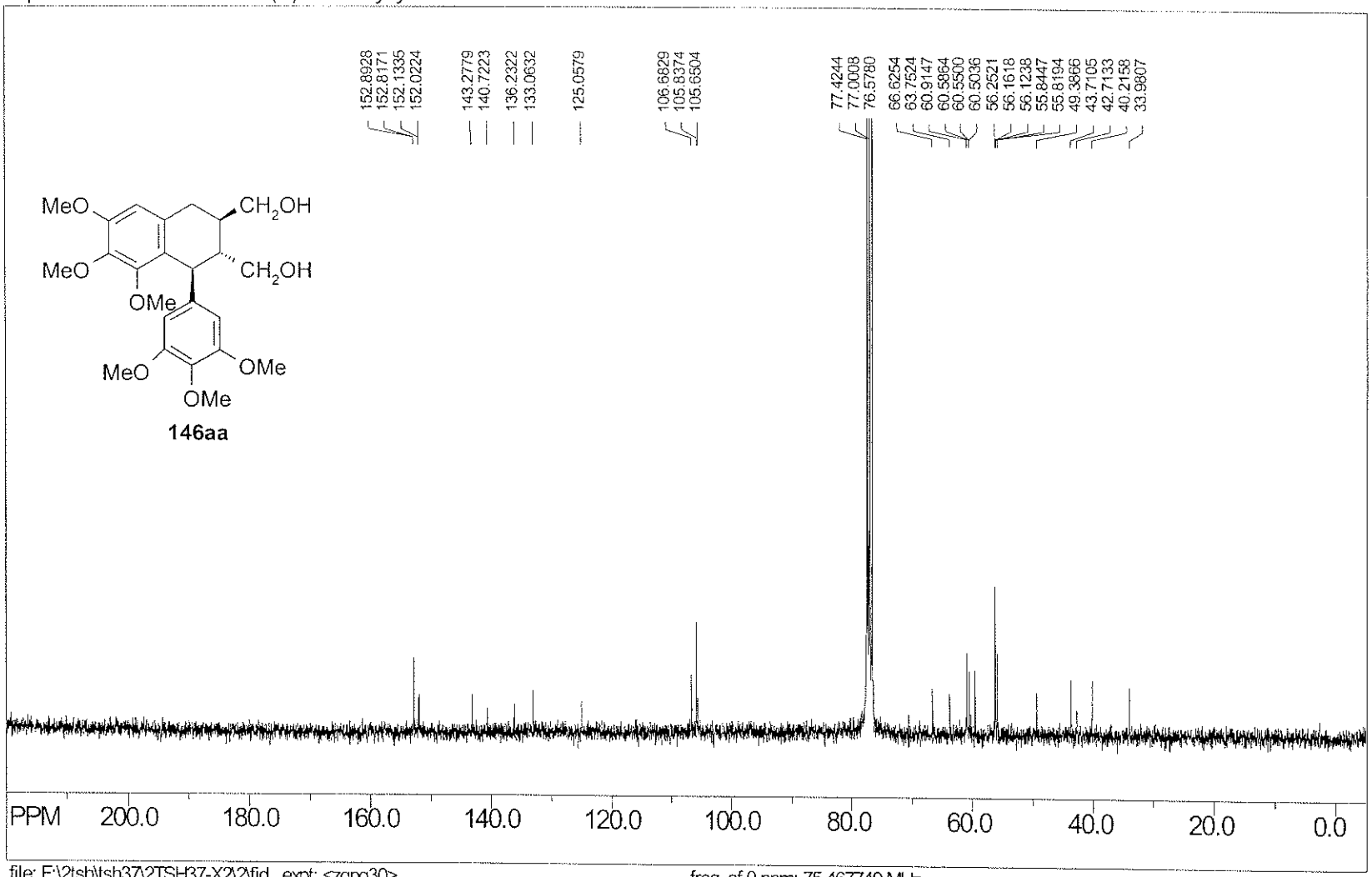
SpinWorks 2.0: Purified (+)-dimethyllyoniresinol (CDCl3)



file: F:\2tsh\tsh37\2TSH37-X2\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 256

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

SpinWorks 2.0: Purified (+)-dimethyllyoniresinol



146aa

file: F:\2tsh\tsh37\2TSH37-X2\2\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 13824

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