THE STUDY OF

THE ASYMMETRIC SYNTHESIS OF LIGNANS

by

GAIK-LEAN CHEE

a thesis
submitted to the Faculty of Graduate Studies
of the University of Manitoba in partial fulfillment
of the requirements for the Degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry
University of Manitoba
Winnipeg, Manitoba, Canada

THE UNIVERSITY OF MANITOBA

FACULTY OF GRADUATE STUDIES

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ACKNOWLEDGMENTS

I wish to take this opportunity to thank Professor J. Charlton for his patience and invaluable supervision provided during the course of this work. I have learned chemistry from him and gained from his experience. Professor Charlton has always been very supportive and helpful to his students and I will always owe him my greatest respect and gratitude!

I would also like to express my appreciation to Professors T. Scheafer, N. Hunter, F. Hruska, and K. Sadana for their concern, support, and many interesting discussions during the course of this work.

I am especially grateful to Professors D. McKinnon, A. Secco and S. Arntfield for being the members of my advisory committee. Their encouragement, understanding, and advice have led me through many hard decisions and difficult times.

Special thanks also go to the skillful and friendly technicians, Mr. T Foniok, W. Buchannon, and Dr. K. Marat.

I am sincerely thankful to the University of Manitoba for financial assistance provided in the form of a Graduate Fellowship.

My brother and sisters have always been extremely caring and supportive to me. I thank them with all my heart!

This thesis is dedicated to the most important people in my life: my husband, and my late parents. Without their devotion and encouragement, I would not have achieved the present success.

ABBREVIATIONS

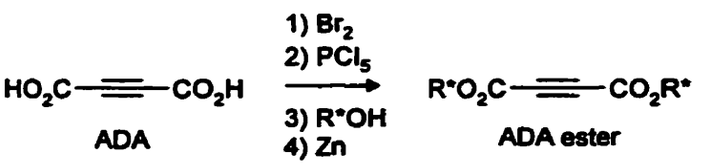
Ac	acetyl
Ac_2O	acetic anhydride
AcCl	acetyl chloride
AcOH	acetic acid
ADA	acetylenedicarboxylic acid
AIBN	azadiisobutyronitrile
Anal.	elemental analysis
Ar	aryl
Bu	butyl
calcd.	calculated
CE	capillary electrophoresis
de	diastereomeric excess
dabco	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo-[5,4,0]-undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBALH	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
Et	ethyl
EtOAc	ethyl acetate
GC	gas chromatography
HMPA	hexamethylphosphorotriamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infra-red spectroscopy
LDA	lithium diisopropylamide
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
mp	melting point
NaHMDS	N-sodiohexamethyldisilazane
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
o-QDM	*ortho*-quinodimethane
PIFA	phenyliodonium bis-trifluoroacetate
p-TsOH	*para*-toluenesulfonic acid
rt	room temperature
SFC	supercritical fluid chromatography
TBDMS	*t*-butyldimethylsilyl

TBDMSTf	*t*-butyldimethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	toluenesulfonyl

ABSTRACT

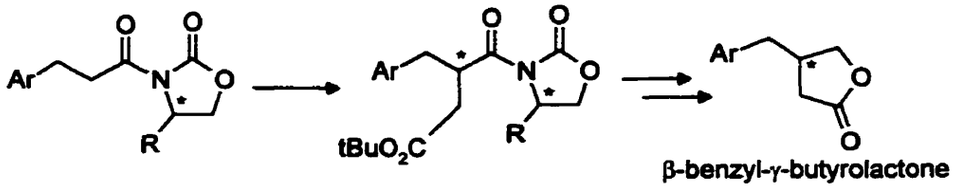
Many lignan natural products possess a diverse spectrum of biological properties. Developing synthetic methods for this large class of phenylpropanoid dimers, especially the ones with multiple chiral centers, is a challenge to synthetic chemists. The work in this thesis focuses on the asymmetric synthesis of lignans by approaches such as Diels-Alder reactions, asymmetric alkylation reactions, and intramolecular oxidative coupling reactions. In addition to developing asymmetric synthetic methodologies for chiral lignans, an investigation of chirality in arylnaphthalene lignans which lack stereogenic centers has also been carried out.

In the first project, a bis-(methyl (*S*)-lactyl) ester of acetylenedicarboxylic acid (ADA) was used in asymmetric Diels-Alder reactions with dienes such as *ortho*-quinodimethanes (*o*-QDMs) and isobenzofurans to produce aryltetralin lignans. As part of this study, a general and versatile method was developed for the preparation of ADA esters and applied to the synthesis of both chiral and achiral esters.



Moderate asymmetric induction was observed in Diels-Alder reactions of the bis-(methyl (*S*)-lactyl) ester of ADA with α-hydroxy-*o*-QDMs. In one case, an unusual solvent-induced reversal of asymmetric induction was observed.

An approach to the synthesis of optically active lignans via asymmetric alkylation of a chiral benzylbutyrolactone was undertaken. The key intermediate was synthesized by employing a highly diastereoselective alkylation of a chiral imide enolate of a dihydrocinnamic acid.

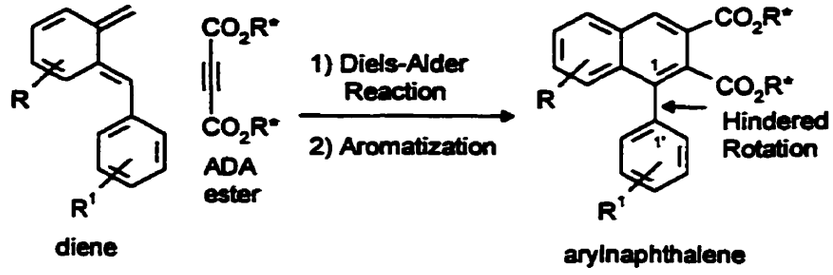


Ar = 3,4-(methylenedioxy)phenyl

The resulting enantiomerically pure β-benzyl-γ-butyrolactone was subsequently transformed into the benzylidenebenzylbutyrolactone lignans gossypifan and savinin via aldol condensation/dehydration reactions, and to the dibenzylbutyrolactone lignan 4'-demethylyatein through alkylation.

A study of intramolecular oxidative coupling reactions of phenylpropanoid dimers and a monophenolic dibenzylbutyrolactone lignan was also undertaken. Oxidations of sinapic acid ester dimers were attempted using metal and nonmetal oxidants. Unfortunately, the oxidation reactions of these dimers were unsuccessful. The focus on oxidative coupling reactions of diol disinapates was redirected to oxidative cyclization of 4'-demethylyatein, a biologically important precursor to cyclolignans. The oxidation reactions of this compound were carried out using DDQ as oxidant. Aryltetralin lignan 4'-demethylisodeoxypodophyllotoxin was formed, as well as *cis*- and *trans*-benzylidenebenzylbutyrolactones, in good to excellent yield.

1-Arylnaphthalenes, prepared by aromatization of the Diels-Alder products from *o*-QDM and acetylenedicarboxylates, were found to exhibit hindered rotation about the phenyl-naphthalene (C1-C1') bond.



To test if hindered rotation in naturally occurring arylnaphthalene lignans might give rise to isolable enantiomeric rotamers, eleven arylnaphthalene lignans and analogs were synthesized and the barriers to rotation about the phenyl-naphthalene bonds were measured using dynamic NMR and low temperature HPLC techniques. The barriers to rotation ranged from 16.9 to 21.5 kcal/mol, which translated to half-lives for individual rotamers of less than 15 min at room temperature. The experimental rotational barriers of these compounds were compared to those obtained from molecular orbital calculations.

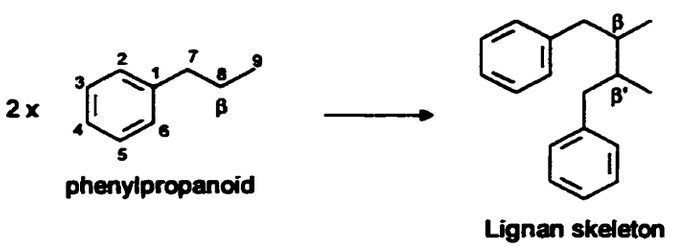
CHAPTER 1

INTRODUCTION TO LIGNANS

Lignans are widespread natural metabolites whose occurrence is mainly restricted to vascular plants.[1] A few lignans have also been isolated from mammals which have consumed a vegetarian diet.[2] The term "lignan" was introduced by Haworth[3] in 1941 to categorize a group of phenylpropanoid dimers whose classification and structures will be discussed in Section 1.1. Lignans have attracted extensive attention mainly due to their interesting biological and pharmacological properties. The biological activity of lignans will be briefly reviewed in Section 1.2. From the synthetic point of view, lignans present a challenge for both non-asymmetric and asymmetric synthesis due to their varied structures and multiple chiral centers. The synthesis of achiral and chiral lignans will be reviewed in Sections 1.3 and 1.4, respectively. Since oxidative coupling reactions play an important role in both the biosynthesis and some chemical synthesis of lignans, this topic will also be briefly discussed in this chapter (see Section 1.5).

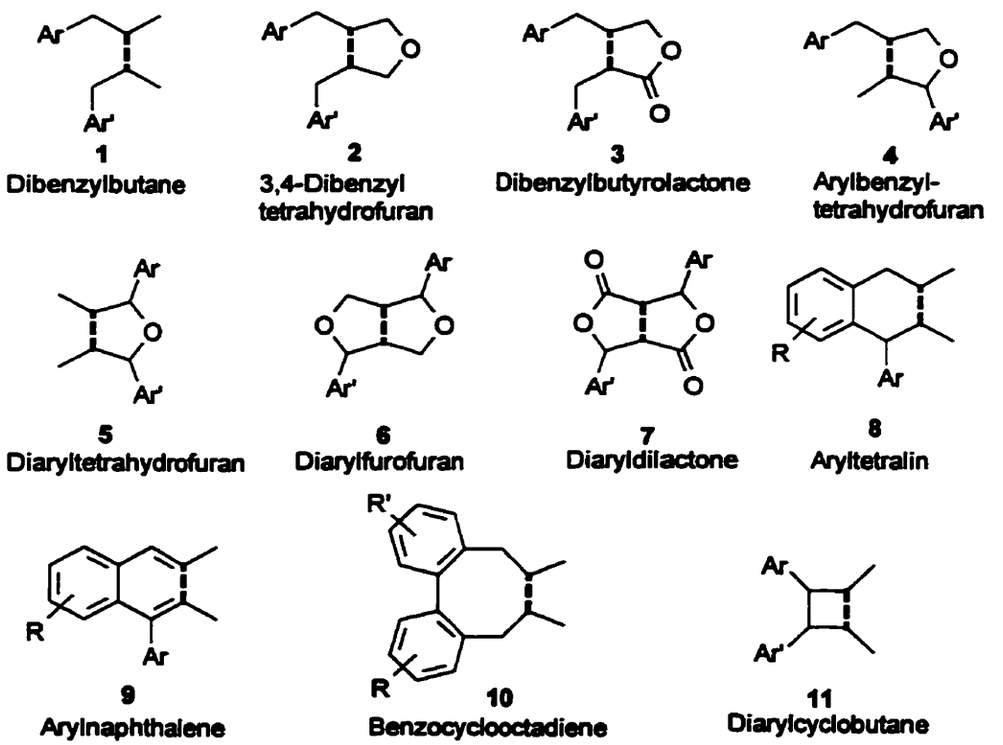
1.1 DEFINITIONS AND CLASSIFICATION OF LIGNANS

Lignans were defined by Haworth[3] as dimers of phenylpropanoid metabolites linked via β-β' (or C8-C8') bonds as shown below:



Scheme 1.1

Lignans are divided into several subgroups with the general structures exemplified in Scheme 1.2. The β-β' bonds in the structures are highlighted. Diarylbutanes **1** are the group having phenylpropanoid dimers linked ***only*** by β-β' bonds, while the other subgroups (**2-11**) have additional linkages besides β-β' bonds. Phenylpropanoid dimers that are linked by other than β-β' bonds are known as neolignans.



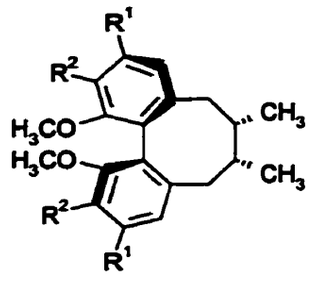
Scheme 1. 2

The numbering and nomenclature of lignans has not yet been standardized. Therefore, when numbering is used, it is important that it is always provided in a given structure. The common nomenclature of lignans, which is usually based on the name of the plant species, will be retained in the following discussion.

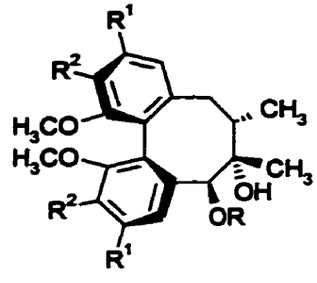
1.2 BIOLOGICAL ACTIVITIES OF LIGNANS

Plants containing lignans have been used as folk medicines by many cultures for over 2000 years. Lignan natural products possess a wide range of biological activities, of which the most important are anticancer, antiviral, and insecticidal activities. The biological activities of lignans have been extensively[4-12] and partly[13-17] reviewed by many authors. Only a few examples of these activities will be discussed here.

The fruits, dried roots and stems of the plants which belong to the genus *Schisandra* have been used in traditional Chinese medicine for over 2000 years as a tonic and sedative.[13] These traditional medicines were also found to exhibit antihepatotoxic property.[13] Recently, a series of dibenzocyclooctadiene lignans (at least twenty) were isolated from these plants and were elucidated as the active principles through animal studies. Two examples of these compounds, the schisandrins and schisantherins, are given in Scheme 1.3.



Schisandrins 12

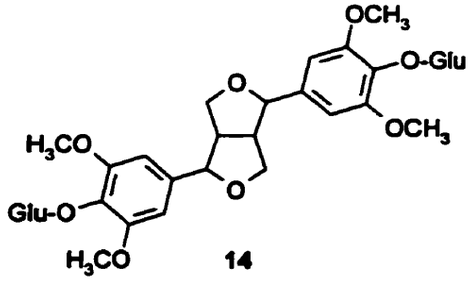


Schisantherins 13

Scheme 1.3

Oral administration of certain types of schisandrins and schisantherins gave protection against CCl_4-induced liver damage in mice. The antihepatotoxic action of these compounds has led to studies of their use for treatment of viral hepatitis in humans.[18]

Siberian ginseng (*Eleutherococcus senticosus*), which is a native plant of Siberia and northern China, has been used traditionally to increase the body's capacity for mental and physical stress.[19] Extract of this plant are still widely taken by modern Russian athletes to improve their performance in sports.[19c] One of the chemical components found responsible for the plant's interesting biological property is the diarylfurofuran lignan eleutheroside E (see Scheme 1.4). The mechanism of action of this compound has not yet been elucidated.

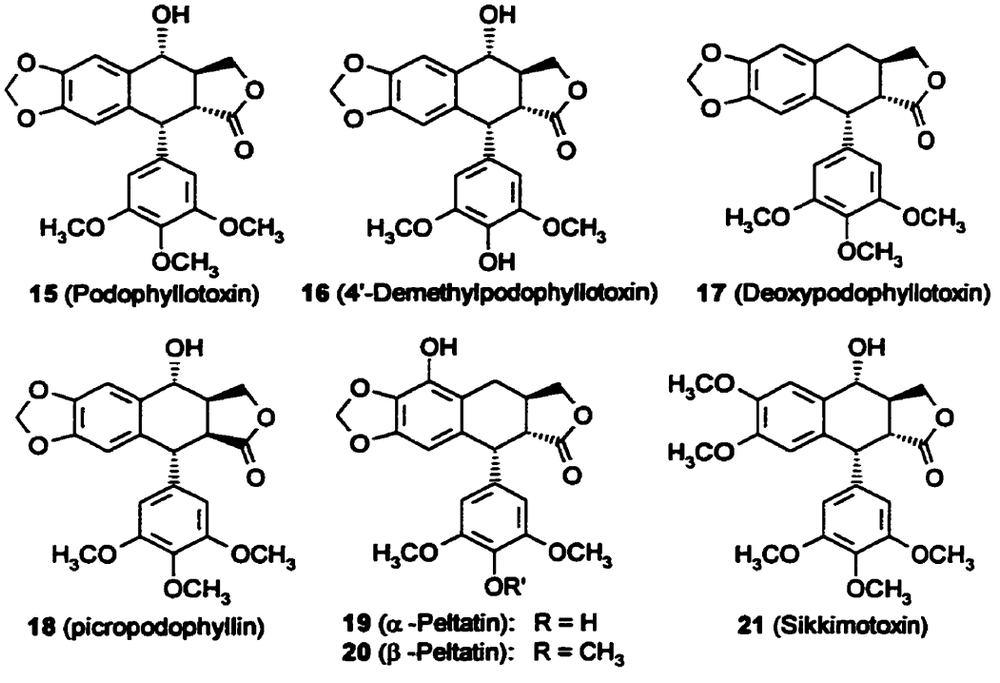


14

(Eleutheroside E)

Scheme 1.4

The scientific search for lignan natural products as potential anticancer agents was begun by Hartwell *et al.* in the 1940's.[15,16,20] They found that the lignan constituents in the alcoholic extract of the dried root and rhizome of two plant species called *Podophyllum peltatum* and *emodi* exhibited a destructive effect on animal cancer cells. The group of lignans in these plants have an aryltetralin general structure and some examples are given in Scheme 1.5.

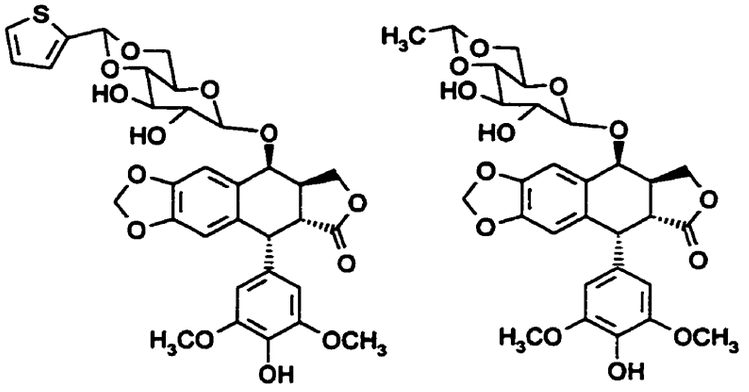


Scheme 1.5

Podophyllotoxin, which is the main constituent of the *Podophyllum* extract (up to 20%), was the most potent among the isolated aryltetralin lignans in inhibiting cancerous cell-growth.[10,14,17] The mode of action by which podophyllotoxin kills cells is the inhibition of the assembly of the protein tubulins into microtubules, an important process in cell division. The inhibition disrupts the dynamic equilibrium between microtubules and tubulins, thereby inducing the disassembly of microtubules into tubulins. The net result

is the destruction of the cytoskeletal framework in the cytoplasm and the spindle fibres that are needed for pulling apart the duplicated chromosomes during cell division. The nonselective attack on normal and cancerous cells by podophyllotoxin has limited its use as a cancer chemotherapeutic agent.

Based on the findings by Hartwell and others on podophyllotoxin, two clinically useful drugs, teniposide and etoposide, were developed and used for treating germinal testicular cancer, small cell lung cancer, and certain forms of leukemia. Teniposide (**22**, also called VM-26) and etoposide (**23**, VP-16-213) (see Scheme 1.6) are semi-synthetic derivatives of podophyllotoxin developed by Sandoz Ltd. in Switzerland.[14,17]



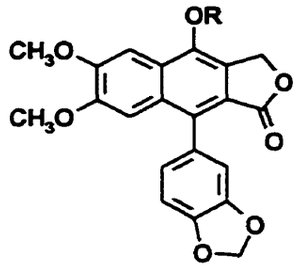
22 (Teniposide) **23** (Etoposide)

Scheme 1.6

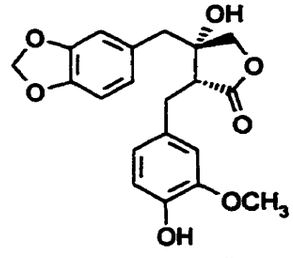
Unlike podophyllotoxin, the mechanism of action of teniposide and etoposide in cell killing is the inhibition of topoisomerase II, a critical enzyme in DNA replication. Topoisomerase II promotes breakage of supercoiled DNA and allows another section of unbroken DNA helix to pass through the break point before the break is resealed by the enzyme. By doing that, the enzyme allows the supercoiled DNA to relax to a circular DNA so that the replication of DNA can occur. Teniposide and etoposide stabilize the

topoisomerase II-DNA complex, thereby resulting in increased DNA scission and failure to rejoin the broken DNA. This leads to chromosomal aberrations, increased chromosome number, and eventually cell killing. Teniposide and etoposide attack cancer cells selectively presumably due to their interference in the intense activity of topoisomerase II found in rapidly proliferating cancer cells.

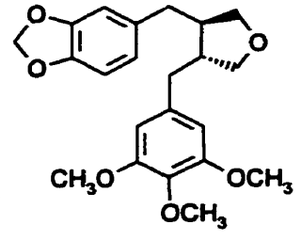
Many lignans other than podophyllotoxin derivatives have shown antitumor activity although their potency is not comparable to that of the podophyllotoxin derivatives. Some examples of other antitumor lignans are given in Scheme 1.7.[8,11] Arylnaphthalene lignans diphyllin (**24**) and justicidin A (**25**),[21] dibenzylbutyrolactone lignan wikstromol (**26**),[22] furan lignan burseran (**27**),[23] dibenzylbutane lignan nordihydroguaiaretic acid (**28**),[24] and dibenzocyclooctadiene lignan, (-)-steganacin (**29**),[25] have all exhibited activity against *in vitro* cancerous cell growth. Podophyllotoxin derivatives **15-23** and lignans **24-29** are structurally so varied that identifying a common structural characteristic to explain their antitumor activity seems impossible. The diverse structural features of these compounds may in fact be indicative of their different mechanism of antitumor action.



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

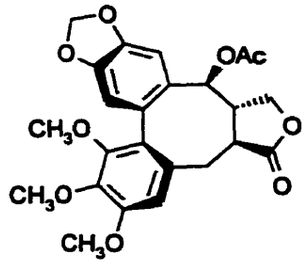


26 (Wikstromol)



27 (Burseran)

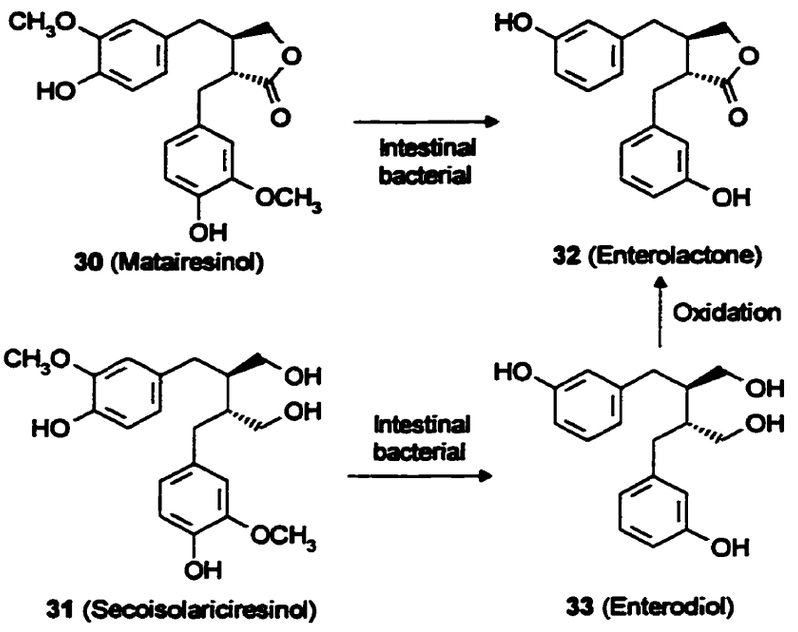
28 (Nordihydro guaiaretic acid)



29 ((-)-Steganacin)

Scheme 1.7

Some mammalian lignans have recently been suggested to be cancer-protective agents, although they do not exhibit direct antitumor activity on cancer cells.[2] Two major mammalian lignans isolated from body fluids are enterolactone (**32**) and enterodiol (**33**). They are formed from dietary plant precursors matairesinol (**30**) and secoisolariciresinol (**31**), respectively, by the action of intestinal bacteria (see Scheme 1.8).[26] Enterolactone and enterodiol are excreted in large amounts in urine by persons having a rich diet of berries, seeds (especially soybean and flaxseed), and grain, the vegetarian diet which has long been known to reduce hormone-related cancer risk. Enterolactone and enterodiol are thought to be the responsible factor whose mode of action in reducing such cancer risks seems to be the modulation of the synthesis of sex hormones.[2]

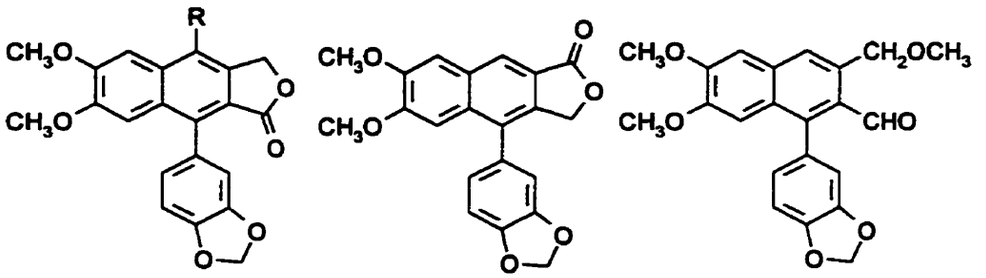


Scheme 1.8

In addition to an inhibitory effect on cancer cells, podophyllotoxin[10] has also been used for the clinical treatment of venereal warts (condyloma acuminatum, a sexually transmitted desease caused by the human papilloma virus),[27] and psoriasis vulgaris (a chronic hereditary skin lesion).[28] Other than the papilloma virus, in some preliminary trials, podophyllotoxin as well as its derivatives (**16-21**) were found effective against other viruses[29] such as measles, cytomegalovirus, and herpes simplex type I. Although the mechanism of podophyllotoxin's antitumor activity has been well elucidated, the compound's antiviral mechanism still remains unknown.

Other lignans found exhibiting antiviral activity are exemplified in Scheme 1.9.[29] Two arylnaphthalene lignans diphyllin (**24**) and justicidin B (**34**), isolated from the Formosan plant, *Justicia procumbens*, were effective in inhibiting the growth of Sindbis virus, with up to 100% inhibition at drug concentration of 1.0 μg/ml. Other

arylnaphthalene lignans, retrojusticidin B (**35**) and phyllamycin B (**36**) isolated from Chinese herbs *Phyllanthus myrtifolius*, have recently shown strong inhibitory effect on human immunodeficiency virus-1 reverse transcriptase activity.[30] The enzyme catalyses the synthesis of a complementary DNA strand using a viral RNA strand as a template. The same compounds, on the other hand, have little effect on human DNA-polymerase-α activity, making them candidates as anti-HIV drugs.



24 (Diphyllin): R = OH
34 (Justicidin B): R = H

35 (Retrojusticidin B)

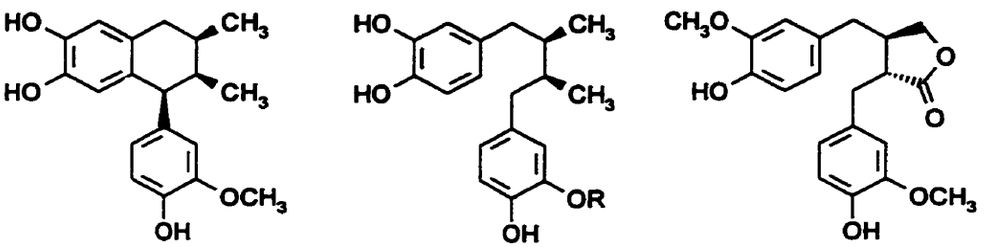
36 (Phyllamycin B)

Scheme 1.9

As well as being medicinally important, lignans also have use or potential use in food industries and agriculture. The phenolic lignan, nordihydroguaiaretic acid (**28**, see Scheme 1.7), a main constituent of the creosote bush (*Larrea tridentata*) grown in south-western USA and Mexico, has been used in the food industry as an antioxidant since 1943.[31] This compound is very effective in inhibiting the lipoxidase- and hematin-catalyzed autoxidation of unsaturated fatty acids in vegetable and animal oils, respectively, during the oil processing stage. The autoxidation of unsaturated fatty acids causes chain cleavage and results in the formation of volatile components which are responsible for oil rancidity. Nordihydroguaiaretic acid is also useful in non-food industrial applications as a stabilizer for polymers, lubricants, rubber, as well as

pharmaceutical preparations. In addition to these industrial applications, this compound was also once used as a phytotoxin on train right-of-ways to prevent weed growth.

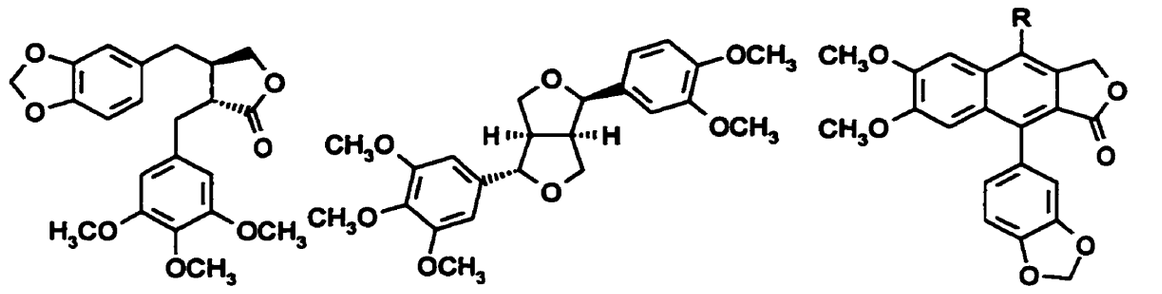
The potential use of lignans in agriculture is due to the important role they play in plant defense against bacterial and fungal infection, and against insect attack. Antimicrobial and antifungal properties have been reported for lignans such as norisoguaiacin (**37**) and dihydroguaiaretic acid (**38**), as well as matairesinol (**30**) and nordihydroguaiaretic acid (**28**) described above (Scheme 1.10).[32]



37 (Norisoguaiacin) **38** (Dihydroguaiaretic acid): R = CH_3 **30** (Matairesinol)
28 (Nordihydroguaiaretic acid): R = H

Scheme 1.10

Some examples of lignans as insect antifeedants and piscicides are yatein (**39**) from *Libocedrus yateensis*,[33] epimagnolin A (**40**) from the flower buds of *Magnolia fargesii*,[34] and the previously described arylnaphthalene lignans diphyllin (**24**), justicidin A (**25**) and justicidin B (**34**) (Scheme 1.11).[33,35] The piscicidal activity of the arylnaphthalene lignans are comparable to that of rotenone, a potent commercially used piscicide.[35]



39 (Yatein) **40** (Epimagnolin A)

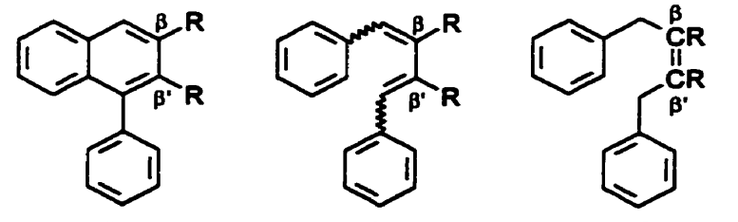
24 (Diphyllin): R = OH
25 (Justicidin A): R = OCH_3
34 (Justicidin B): R = H

Scheme 1.11

The exceedingly numerous biological activities displayed by lignans have made further study of this class of natural products a priority. The development of synthetic methods for lignans is necessary for more in depth evaluation of these interesting compounds.

1.3 SYNTHESIS OF NOMINALLY ACHIRAL LIGNANS

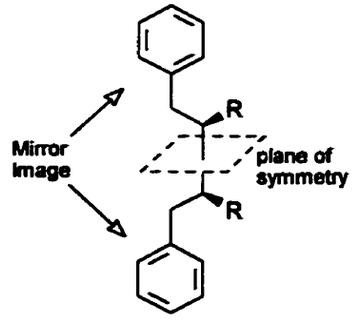
A molecule is achiral if it is superimposable on its mirror image. Most achiral lignans belong to the arylnaphthalene subgroup **9**, although a few also belong to the dibenzylidene and dibenzylbutene subgroups **41** and **42** (see Scheme 1.12).



9 Arylnaphthalene **41** Dibenzylidene **42** Dibenzylbutene

Scheme 1.12

These subgroups possess general structures which lack stereogenic centers (stereogenic tetravalent atoms). Despite their lack of stereogenic centers, arylnaphthalene and dibenzylidene lignans may nevertheless exist as separable enantiomers if there is hindered rotation about certain carbon-carbon single bonds present in the molecules (see Chapter 2 for detail). As part of the project on hindered rotation in lignans (see section 4.4), several arylnaphthalene lignans were prepared. A review of the existing literature on the synthesis of achiral lignans (not including *meso* structures such as **43** in Scheme 1.13) will be presented here.

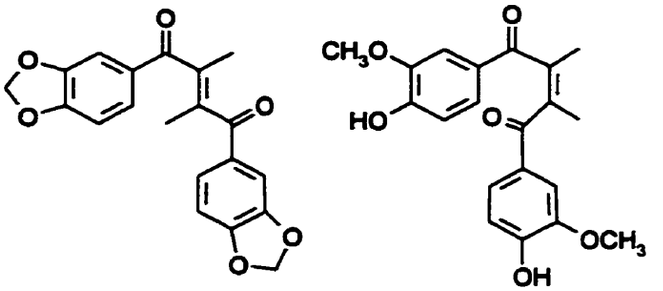


meso lignan **43**

Scheme 1.13

1.3.1 Dibenzylbutene and Dibenzylidene Lignans

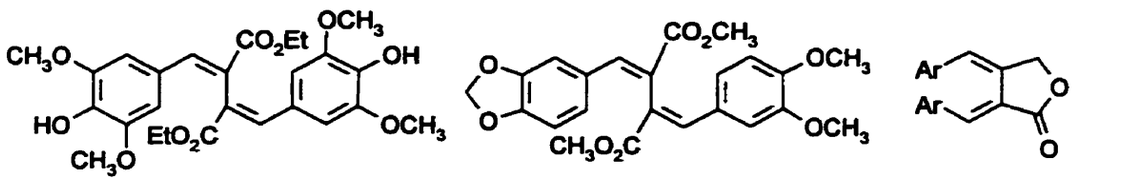
There are only two known natural dibenzylbutene lignan, zuihonin D (**44**) isolated from *Machilus zuihoensis*[36] and furoguaiaoxidin (**45**) isolated from *Guaiacum officinale*[37] (structures in Scheme 1.14). The synthesis of **44**, **45**, and other dibenzylbutene lignan analogs have not been reported.



44 (Zuihonin D) **45** (Furoguaiaoxidin)

Scheme 1.14

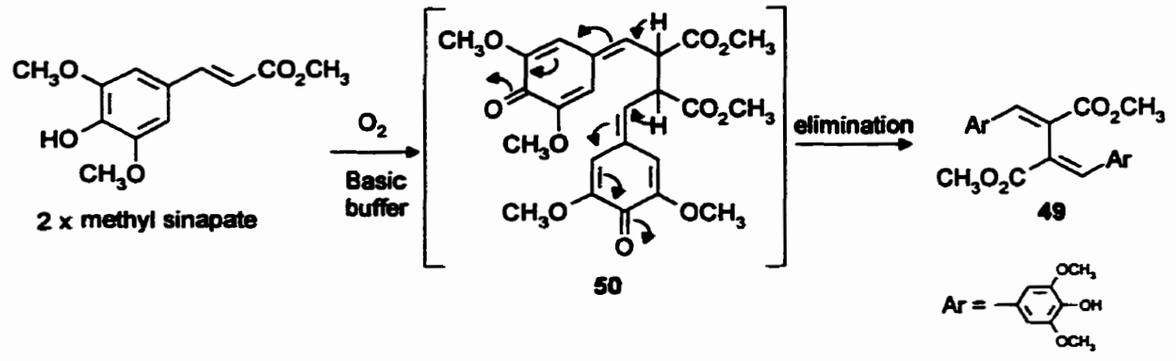
A literature search for naturally occurring dibenzylidene lignans reveals only three such compounds, phebalarin (**46**),[38] jatrodien (**47**),[39] and taiwanin A (**48**),[40] isolated from *Phebalium nudum*, *Jatropha gossypifolia*, and *Taiwania crypptomeriodes*, respectively (Scheme 1.15).



46 (Phebalarin) **47** (Jatrodien) **48** (Taiwanin A): Ar = 3,4-(methylene-dioxy)phenyl

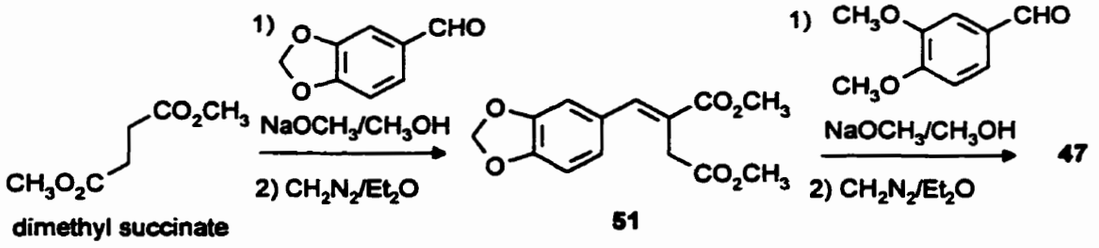
Scheme 1.15

Although the synthesis of phebalarin has not been reported, preparation of its derivative, the dimethyl ester **49** (Scheme 1.16) has been accomplished.[41] Oxidative coupling of methyl sinapate under oxygenated basic buffer condition afforded dibenzylidine **49**. It was proposed that elimination of a bis-(quinone methide) intermediate (**50**) was involved, as depicted in Scheme 1.16.



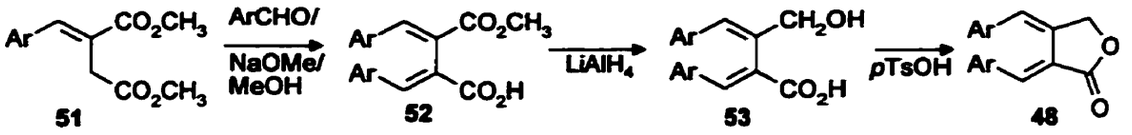
Scheme 1.16

Dibenzylidene compounds are more often synthesized by Stobbe condensation of a succinic acid ester and a benzaldehyde. Synthesis of jatrodien (**47**) was achieved using a two-stage Stobbe condensation approach illustrated in Scheme 1.17.[39] Dimethyl succinate was condensed with piperonal in refluxing $NaOCH_3$/methanol, followed by methylation of the resulting carboxylic acid to afford **51**. Condensation of **51** with veratraldehyde and methylation of the resulting half ester gave jatrodien (**47**).



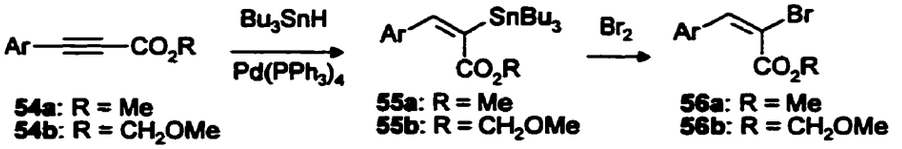
Scheme 1.17

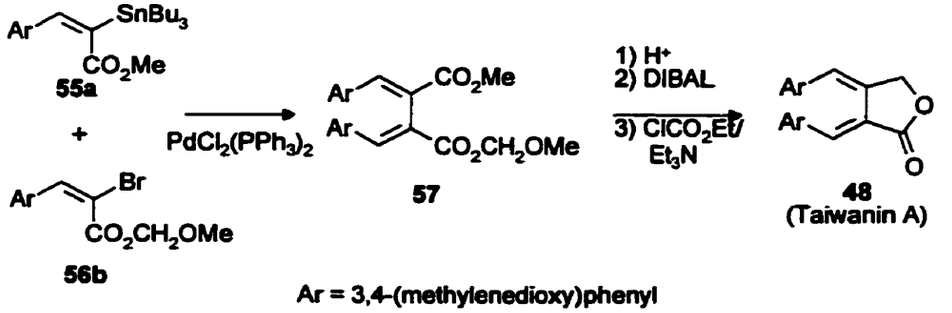
The Stobbe condensation approach was also applied to the preparation of taiwanin A (**48**) (Scheme 1.18).[42] Treatment of **51** with piperonal afforded half-ester **52**, which was then reduced to hydroxy acid **53** with $LiAlH_4$. Subsequent cyclization of **53** with *p*-TsOH completed the synthesis of taiwanin A.



Scheme 1.18

Taiwanin A (**48**) has also been synthesized by palladium-catalyzed cross-coupling of vinylstannane **55a** and vinyl bromide **56b** as illustrated in Scheme 1.19.[43] These vinyl derivatives were prepared from propiolates **54**. Cross-coupling of **55a** and **56b** gave butadiene **57**, which was then transformed into taiwanin A by acid hydrolysis of methoxymethyl ester, reduction of methyl ester, and lactonization. Other dibenzylidene lactones were also prepared using the cross-coupling method.

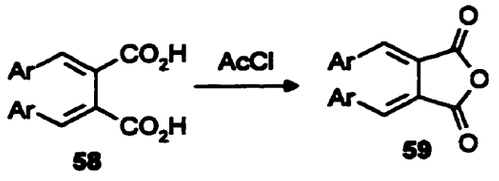




Scheme 1.19

Dibenzylidene lignan analogs are frequently employed as intermediates for the synthesis of arylnaphthalene lignans. The dibenzylidene lignan analogs used usually possess a general structure of fulgenic anhydride **59**. Anhydride **59** can be prepared from

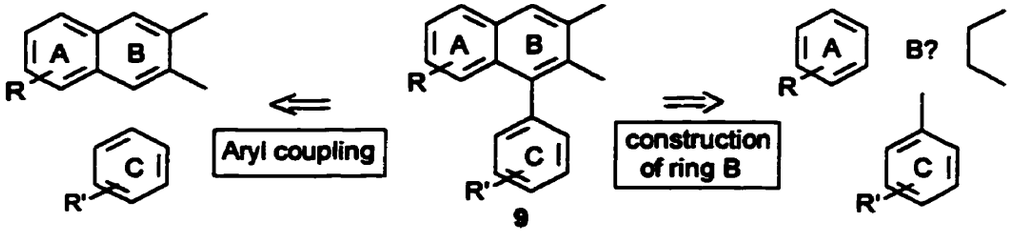
fulgide **58** (Scheme 1.20), which in turn can be prepared by Stobbe condensations.[44] The cyclization of fulgenic anhydrides to arylnaphthalene lignans will be discussed in the following section.



Scheme 1.20

1.3.2 Arylnaphthalene Lignans

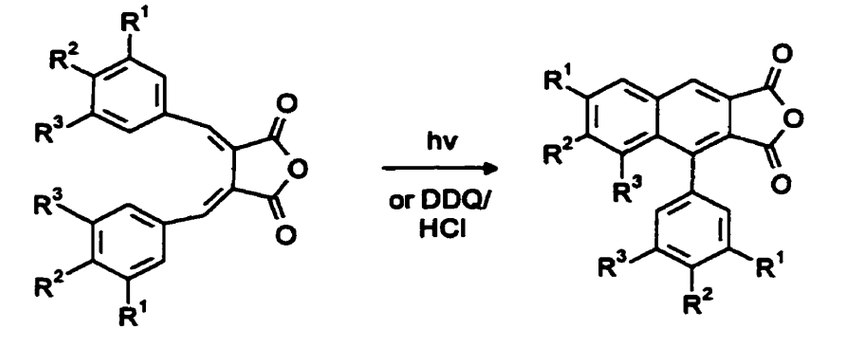
A wide variety of methods have been developed for the synthesis of arylnaphthalene lignans (**9**). These methods can generally be classified into two groups as illustrated in Scheme 1.21. The first group involves the assembly of ring B via methods such as (i) Stobbe condensation and tandem conjugate addition, followed by intramolecular cyclization, (ii) pericyclic reaction of bis-(arylpropiolyl) derivatives, and (iii) the Diels-Alder reaction. The second group of methods involves the intermolecular cross-coupling of a naphthyl molecule with an aryl molecule.



Scheme 1.21

The Stobbe condensation approach to arylnapthalene lignans usually involves intramolecular cyclization of intermediate fulgides having general structure **59** by either UV-irradiation, heat, or oxidants. The fulgides are generally prepared by the methods described in the previous section (see Scheme 1.20).

Cyclization of symmetrical fulgenic anhydride (general structure **59**) usually affords predominantly a single arylnaphthalene product in good yield and thus is regarded as a useful approach for the preparation of certain arylnaphthalene lignans. For instance, irradiation of anhydride **59a**,[45] and treatment of anhydride **59b**[46] with DDQ/HCl afforded arylnaphthalene anhydrides **60a** and **60b**, respectively, as the sole product in each case (Scheme 1.22).



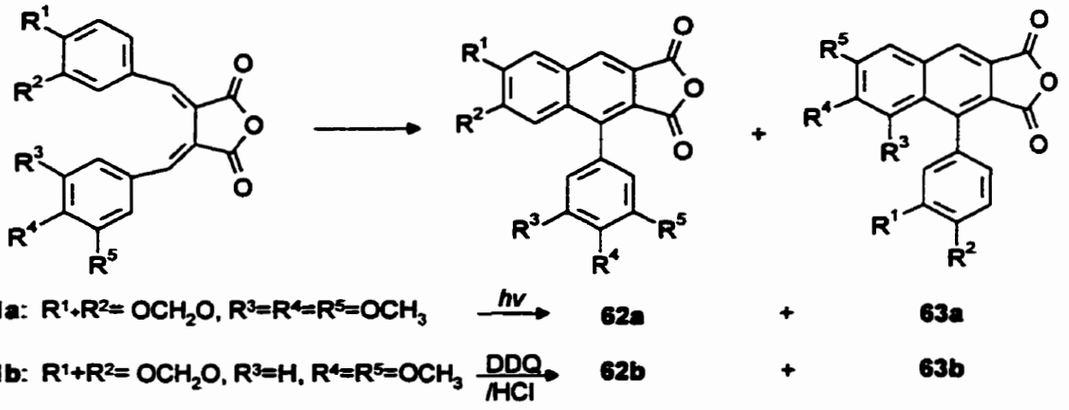
59a: $R^1=R^2=R^3=OCH_3$
59b: $R^1=H$, $R^2=R^3=OCH_3$

60a: $R^1=R^2=R^3=OCH_3$
60b: $R^1=H$, $R^2=R^3=OCH_3$

Scheme 1.22

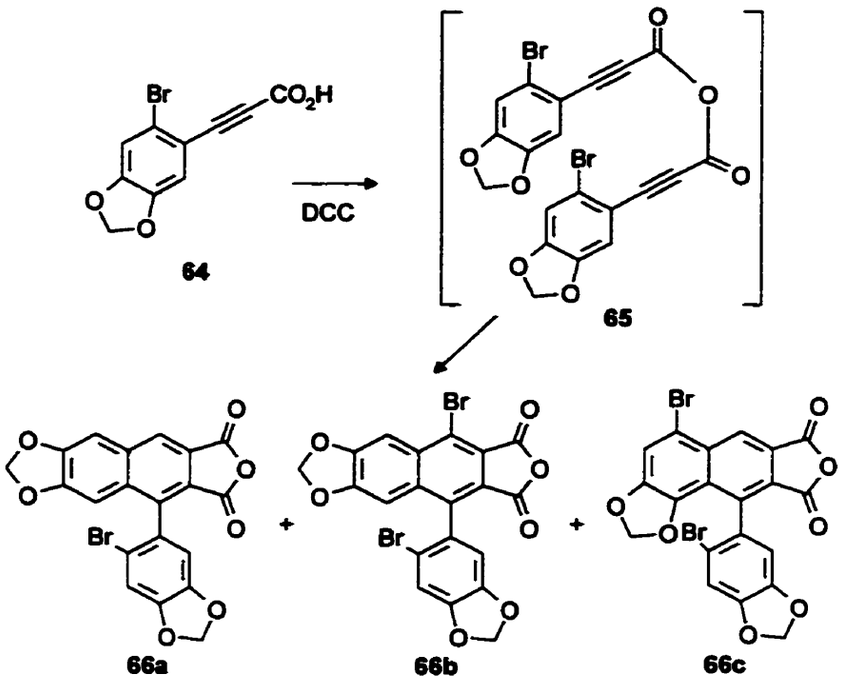
Cyclization of unsymmetrical fulgenic anhydrides has not been as efficient as the cyclization of the symmetrical ones described above because it usually produces a mixture of regioisomeric products. UV irradiation of unsymmetrical anhydride **61a** gave rise to a mixture of two arylnaphthalene anhydrides, **62a** and **63a** (Scheme 1.23).[45]

Similarly, treating **61b** with DDQ/HCl afforded a mixture of arylnaphthalene anhydrides **62b** and **63b**.[46]



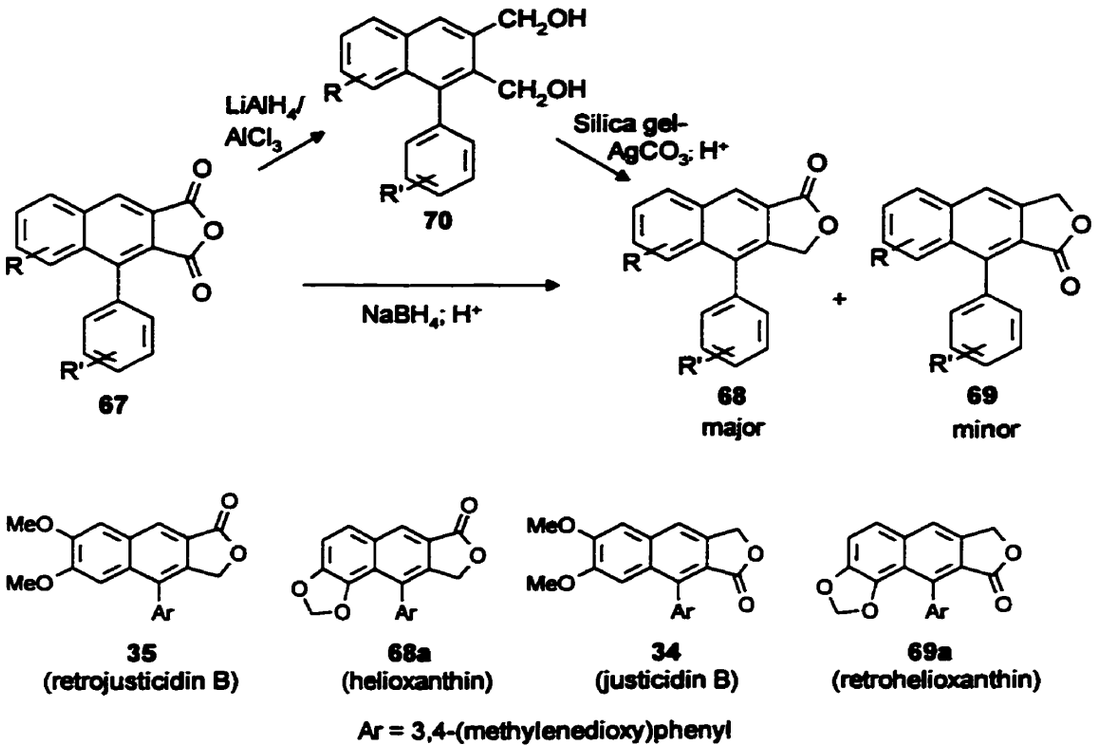
Scheme 1.23

Holmes *et al.* have used the pericyclic cyclization of arylpropiolyl anhydrides to prepare arylnapthalenes (Scheme 1.24).[47] Treatment of **64** with DCC at low temperature resulted in anhydride (**65**) formation and simultaneous ring closure to afford a mixture of the three arylnaphthalene anhydrides **66a**, **66b**, and **66c**. The general applicability of this procedure for other arylpropiolic acids has been developed, but the formation of a mixture of products is usually inevitable.



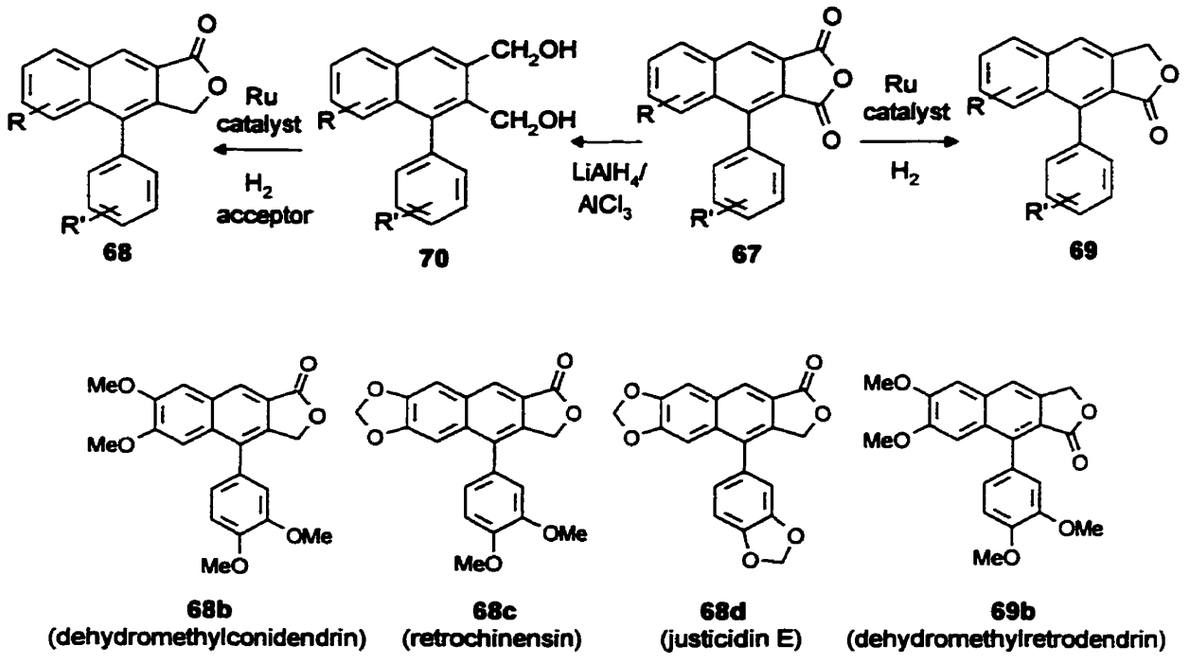
Scheme 1.24

Arylnaphthalene anhydrides prepared by the above described procedures have been transformed into naturally occurring arylnaphthalene lactone lignans. The transformation of anhydrides having the general structure **67** into lactones of general structures **68** and **69** was achieved by three approaches. The first involved the reduction of anhydride **67** with $LiAlH_4/AlCl_3$ to afford diol **70**. Oxidation of **70** with Fetizon's reagent (silver carbonate on silica gel) gave a mixture of arylnaphthalenelactone lignans **68** (major) and **69** (minor) (see Scheme 1.25). Arylnaphthalene lignans justicidin B (**34**), retrojusticidin B (**35**), helioxanthin (**68a**) and retrohelioxanthin (**69a**) have been prepared using this procedure.[46,47]



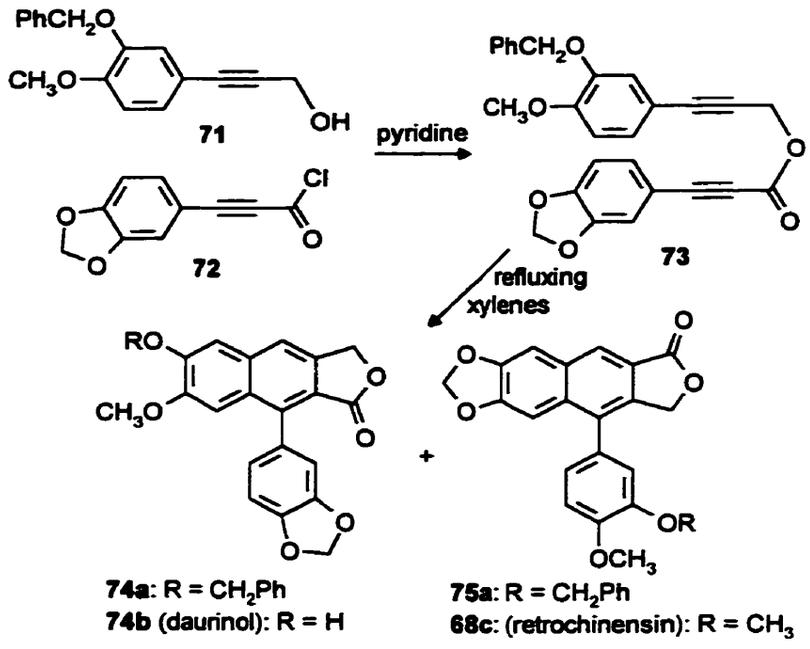
Scheme 1.25

The second approach involves the direct reduction of anhydride **69** by $NaBH_4$ followed by acid catalyzed lactonization to **68** and **69**.[48] The regioselectivity was similar to that achieved with the Fetizon's oxidation reaction (see Scheme 1.25). The third approach for conversion of anhydrides such as **67** to the lactones **68** and **69** has been described by Ishii *et al.* (see Scheme 1.26).[49] They were able to regioselectively reduce anhydride **67** by a ruthenium catalyst/H_2 to afford predominantly lactone **69** in 88% yield. On the other hand, regioselective ruthenium catalyzed dehydrogenation of diol **70** afforded lactone **68** in >88% yield. The natural lignans dehydrodimethylretrodendrin (**69b**), dehydromethylconidendrin (**68b**), retrochinensin (**68c**), and justicidin E (**68d**) were synthesized using these methods.



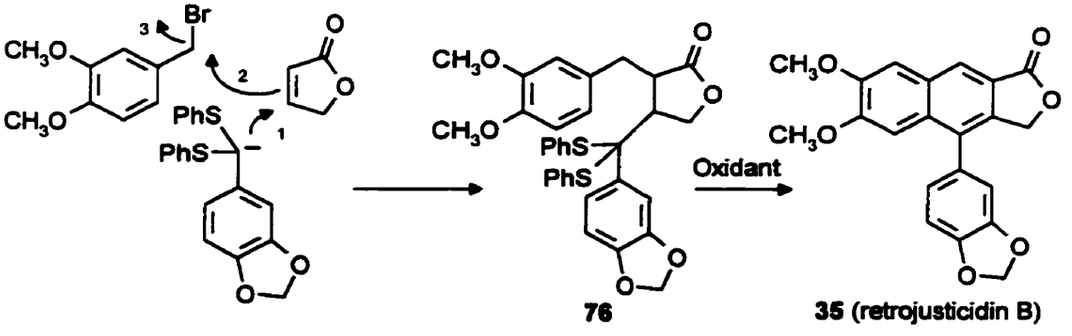
Scheme 1.26

Instead of using arylpropiolyl anhydrides as intermediates (**65** in Scheme 1.24), arylnaphthalene lactones can be prepared directly from bis-(arylpropiolyl) esters through intramolecular cyclization.[50] An example of this method is depicted in Scheme 1.27.[50a] Bis-(arylpropiolyl) ester **73**, prepared by esterification of propargyl alcohol **71** with acid chloride **72**, was heated in xylenes at reflux to afford a mixture of arylnaphthalene lactones **74a** and **75a** in 1:1 ratio. Deprotection of **74a** by catalytic hydrogenation afforded the natural lignan daurinol (**74b**), whereas deprotection of **75a** followed by methylation gave the natural lignan retrochinensin (**68c**).



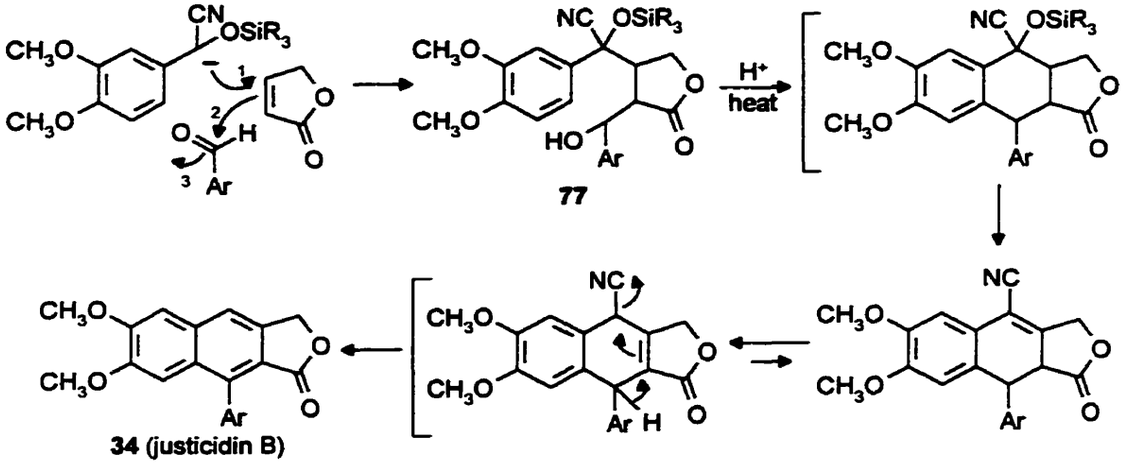
Scheme 1.27

Tandem conjugate addition followed by cyclization and aromatization of the resulting dibenzylbutyrolactone has represented an alternative approach for the preparation of arylnaphthalene lignans.[51] For instance, dibenzylbutyrolactone **76** was prepared via the tandem conjugate addition reaction shown in Scheme 1.28. Treatment of **76** with heavy metal oxidants such as $HgCl_2$ afforded retrojusticidin B (**35**) in 50% yield.[51a]



Scheme 1.28

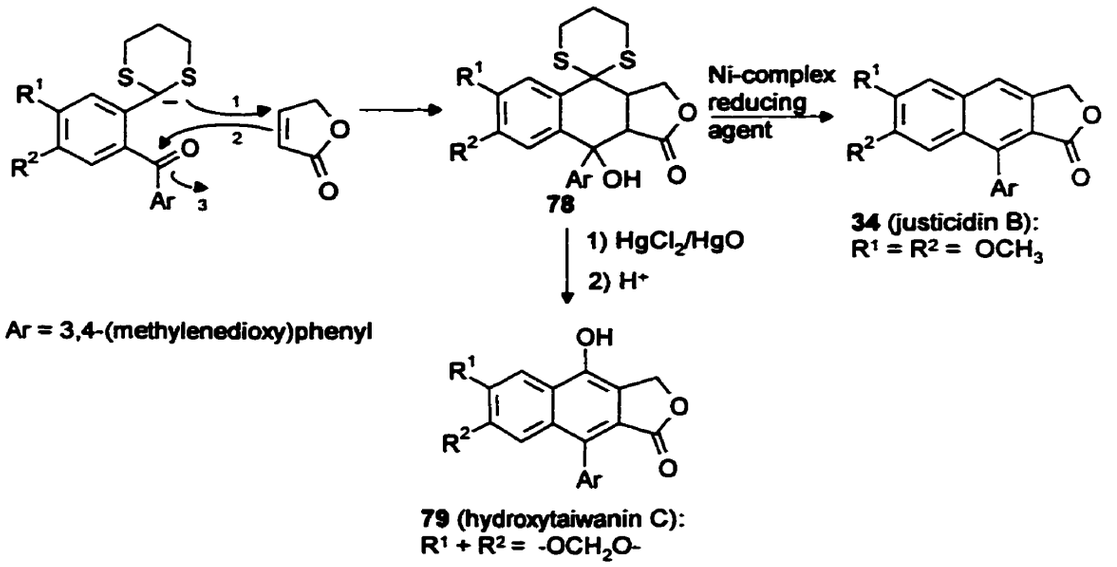
Ogiku *et al.* have also reported a similar procedure for the preparation of justicidin B (**34**) (see Scheme 1.29), a reaction in which the cyclization of the tandem conjugate adduct (**77**) was initiated by an acid instead of an oxidant.[51b] The mechanism of aromatization is as proposed in Scheme 1.29.



34 (justicidin B)

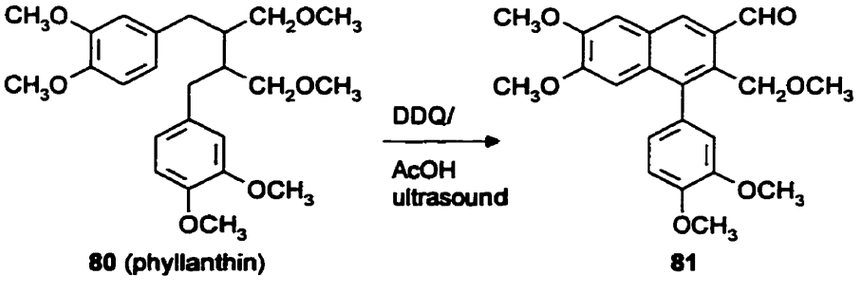
Scheme 1.29

A modification of the above approach where tandem conjugate addition yielded directly a cyclized product (**78**) has been employed by Harrowven in the synthesis of the arylnaphthalene lignan hydroxytaiwanin C (**79**) (Scheme 1.30).[51c] Kamal *et al.* have repeated the procedure but treated cyclized product **78** with a nickel-complex reducing agent instead to afford justicidin B (**34**) (Scheme 1.30).[51d]



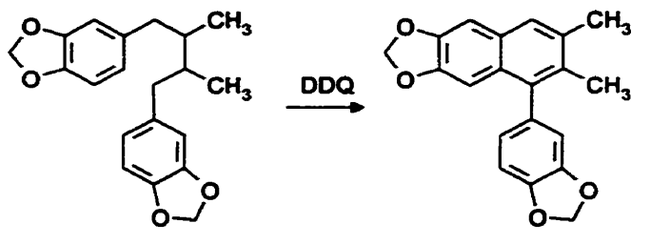
Scheme 1.30

Arynaphthalene lignans can also be prepared directly from naturally occurring dibenzylbutane lignans.[52] DDQ oxidation of phyllanthin (**80**) in the presence of AcOH with ultrasonic agitation gave arylnaphthalene lignan analog **81** in 70% yield (Scheme 1.31).[52a]



Scheme 1.31

Heating (-)-austrobailignan-5 (**82**) and DDQ in refluxing dioxane resulted in the formation of arylnaphthalene lignan analog **83** in 60% yield (Scheme 1.32).[52b]

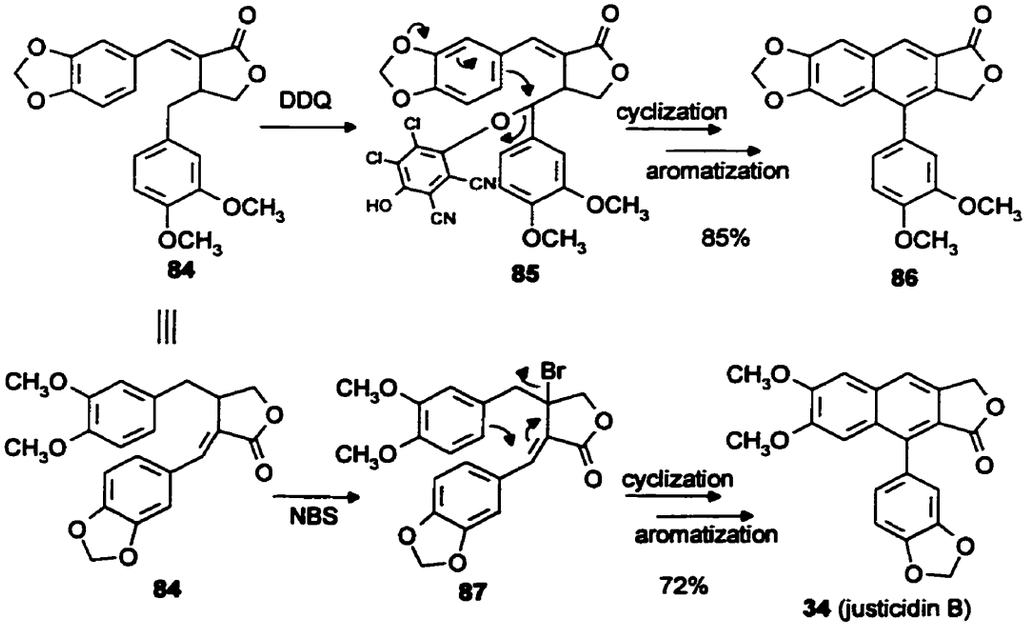


82
((-)-austrobailignan-5)

83

Scheme 1.32

By analogy to dibenzylbutane lignans, benzylidenebenzylbutyrolactone **84** can also undergo oxidative cyclization to afford arylnaphthalene lactones. An interesting example of this is illustrated in Scheme 1.33.[53] Upon treatment with DDQ, benzylidenebenzylbutyrolactone **84** underwent cyclization and aromatization to afford arylnaphthalene lignan analog **86** in 85% yield via reactive intermediate **85**. On the other hand, treating **84** with NBS resulted in the formation of justicidin B (**34**), presumably via allylic brominated intermediate (**87**).

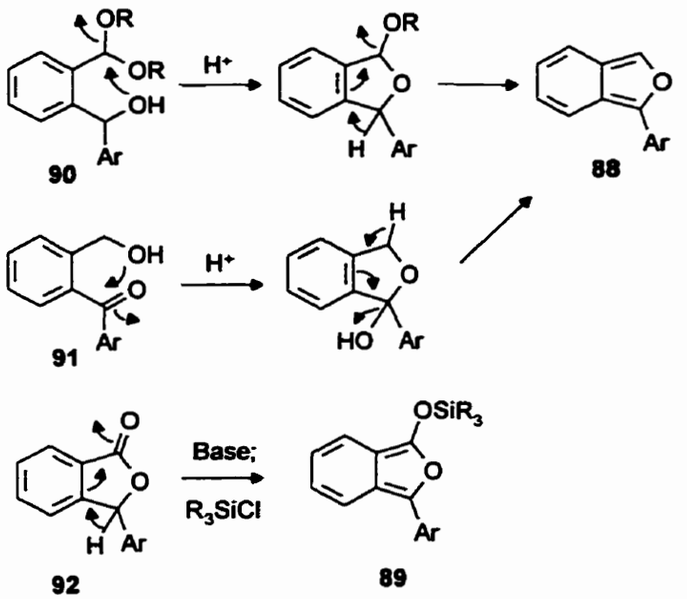


84 **85** **86**

84 **87** **34** (justicidin B)

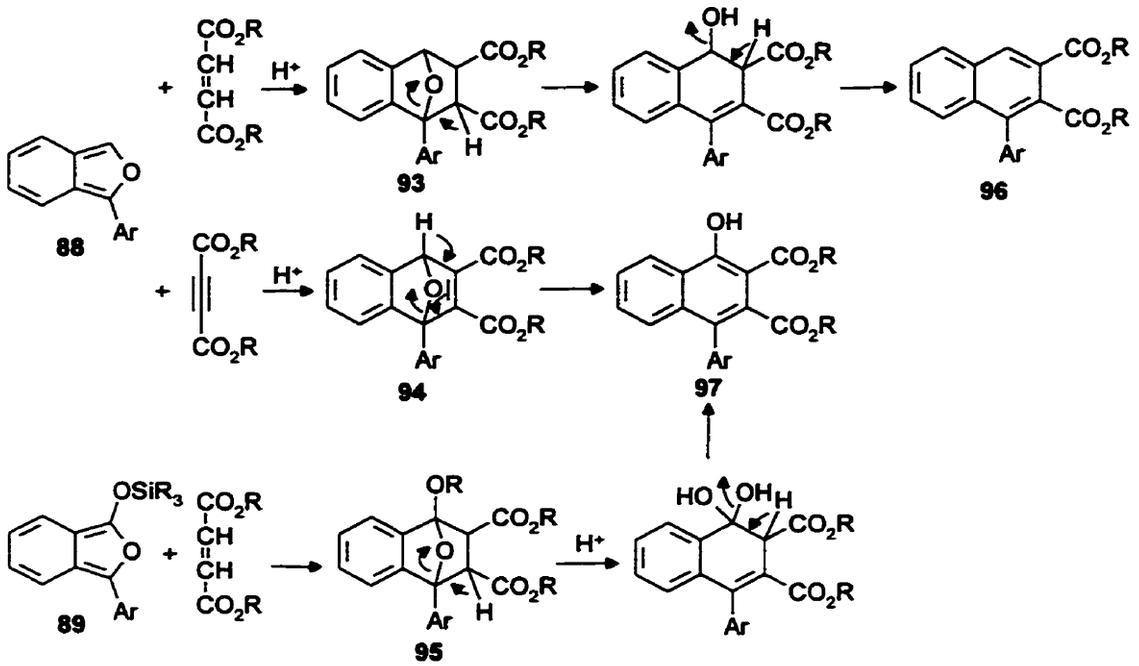
Scheme 1.33

The Diels-Alder reactions of isobenzofuran dienes[54] are the most popular of all the many methods developed for the synthesis of both phenolic and non-phenolic arylnaphthalene lignans. In the general method, reactive isobenzofurans **88** or **89** are generated from hydroxyacetal **90**/hydroxyketone **91** or phthalide **92**, respectively. The reaction mechanisms and the intermediates involved are illustrated in Scheme 1.34.



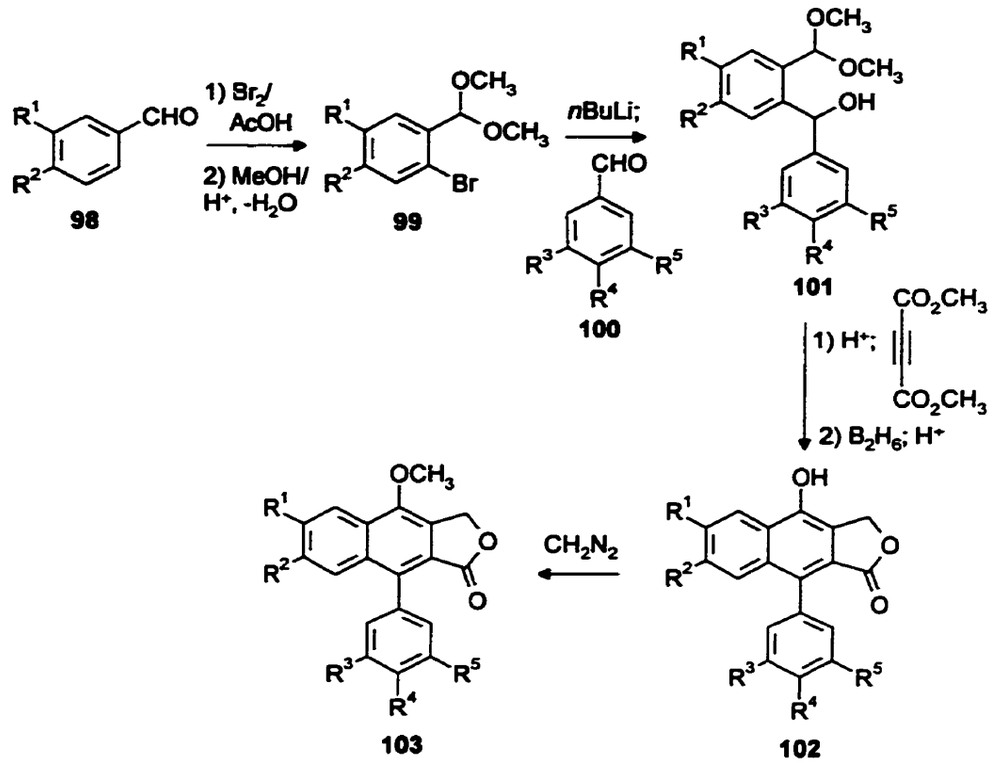
Scheme 1.34

Diels-Alder reactions of isobenzofuran **88** with fumarate/maleate, and acetylenedicarboxylate dienophiles give rise to the formation of cycloadducts **93** and **94**, respectively. Aromatization of cycloadducts **93** and **94** affords, respectively, arylnaphthalene **96** and phenolic arylnaphthalene **97**. On the other hand, reacting isobenzofuran **89** with fumarate/maleate affords cycloadduct **95** where desilylation and aromatization leads to the formation of phenolic arylnaphthalene **97** as well. The reaction mechanism is depicted in Scheme 1.35.



Scheme 1.35

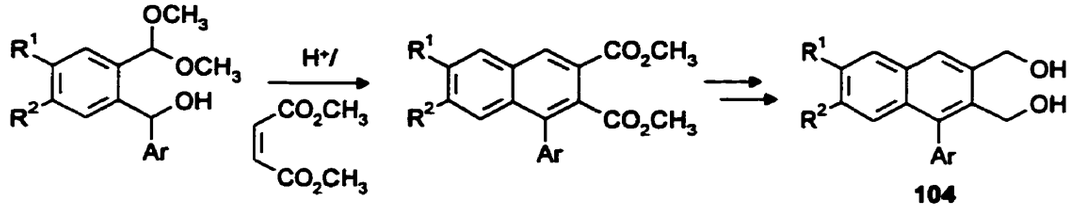
The use of hydroxyacetals as isobenzofuran precursors in the preparation of arylnaphthalene lignans was initially described by Rodrigo *et al.* (Scheme 1.36).[55] Acetal **99** which was prepared from benzaldehyde **98** by bromination and acetylation, was treated successively with *n*-BuLi and benzaldehyde **100** to afford hydroxyacetal **101**. Treatment of hydroxyacetal **101** with acid and dimethyl acetylenedicarboxylate afforded cycloadducts that reacted further to give a phenolic arylnaphthalene diester. Regioselective reduction of the ester adjacent to the phenol followed by lactonization gave natural lignans such as taiwanin E (**102a**), chinensinaphthol (**102b**), and dehydropodophyllotoxin (**102c**). Methylation of taiwanin E and chinensinaphthol gave the natural lignans taiwanin E methyl ether (**103a**) and chinensinaphthol methyl ether (**103b**), respectively.



R¹	R²	R³	R⁴	R⁵	
OCH_2O		OCH_2O		H	**102a** (Taiwanin E): **103a** (Taiwanin E methylether)
OCH_2O		OCH_3	OCH_3	H	**102b** (Chinensinaphthol) **103b** (Chinensinaphthol methylether)
OCH_2O		OCH_3	OCH_3	OCH_3	**102c** (Dehydropodophyllotoxin)

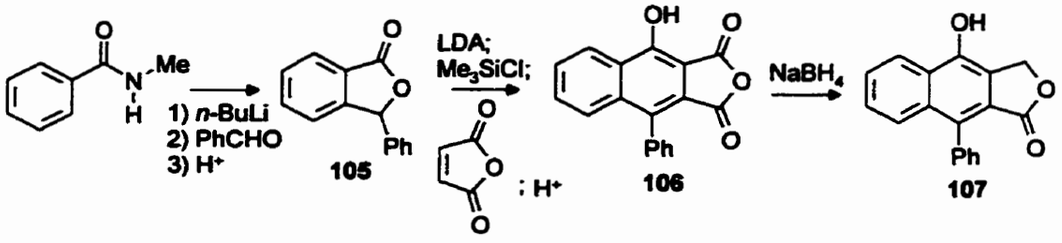
Scheme 1.36

Rodrigo's method has been adopted by others for the preparation of a series of nonphenolic lignans **104** as well, as shown in Scheme 1.37.[56]



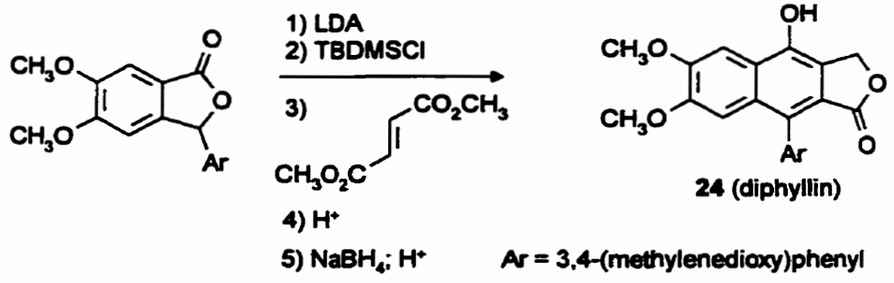
Scheme 1.37

Narasimhan *et al.*[57] have prepared a phenolic arylnaphthalene anhydride by treating phthalide **105** with LDA and Me_3SiCl, followed by Diels-Alder reaction of the resulting isobenzofuran with maleic anhydride. Regioselective reduction of phenolic anhydride **106** by $NaBH_4$ afforded lactone **107** (see Scheme 1.38).



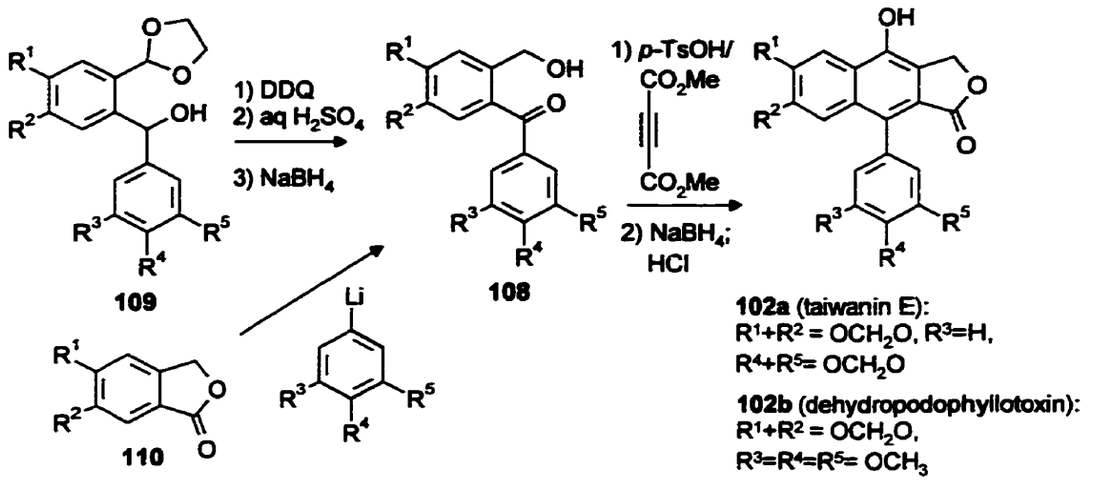
Scheme 1.38

Iwao *et al.* extended this approach to the synthesis of diphyllin (**24**) (Scheme 1.39).[58]



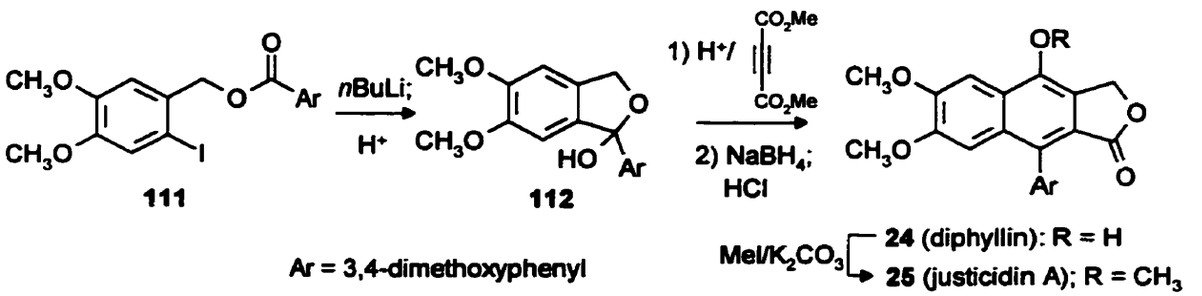
Scheme 1.39

In addition to phthalide **105** (structure in Scheme 1.38), Narasimhan *et al.* have also shown that hydroxyketone **108** can be used as isobenzofuran precursor (Scheme 1.40).[57] Treatment of hydroxyketone **108** with dimethyl acetylenedicarboxylate in the presence of acid, followed by reduction with $NaBH_4$ afforded phenolic arylnaphthalene lignans taiwanin E (**102a**) and dehydropodophyllotoxin (**102c**). Hydroxyketone **108** was in turn prepared from hydroxyacetal **109** or lactone **110** as shown in Scheme 1.40.



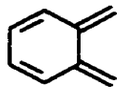
Scheme 1.40

Rodrigo has introduced a new approach to the generation of isobenzofurans using iodoester **111** as starting material (Scheme 1.41).[59] Treatment of iodoester **111** with *n*-BuLi followed by neutralization with acid gave the immediate precursor for the isobenzofuran, the hydroxyphthalan **112**. Subsequent treatment of hydroxyphthalan **112** with acid and dimethyl acetylenedicarboxylate followed by reduction and lactonization resulted in the formation of diphyllin (**24**), the methylation of which gave justicidin A (**25**).



Scheme 1.41

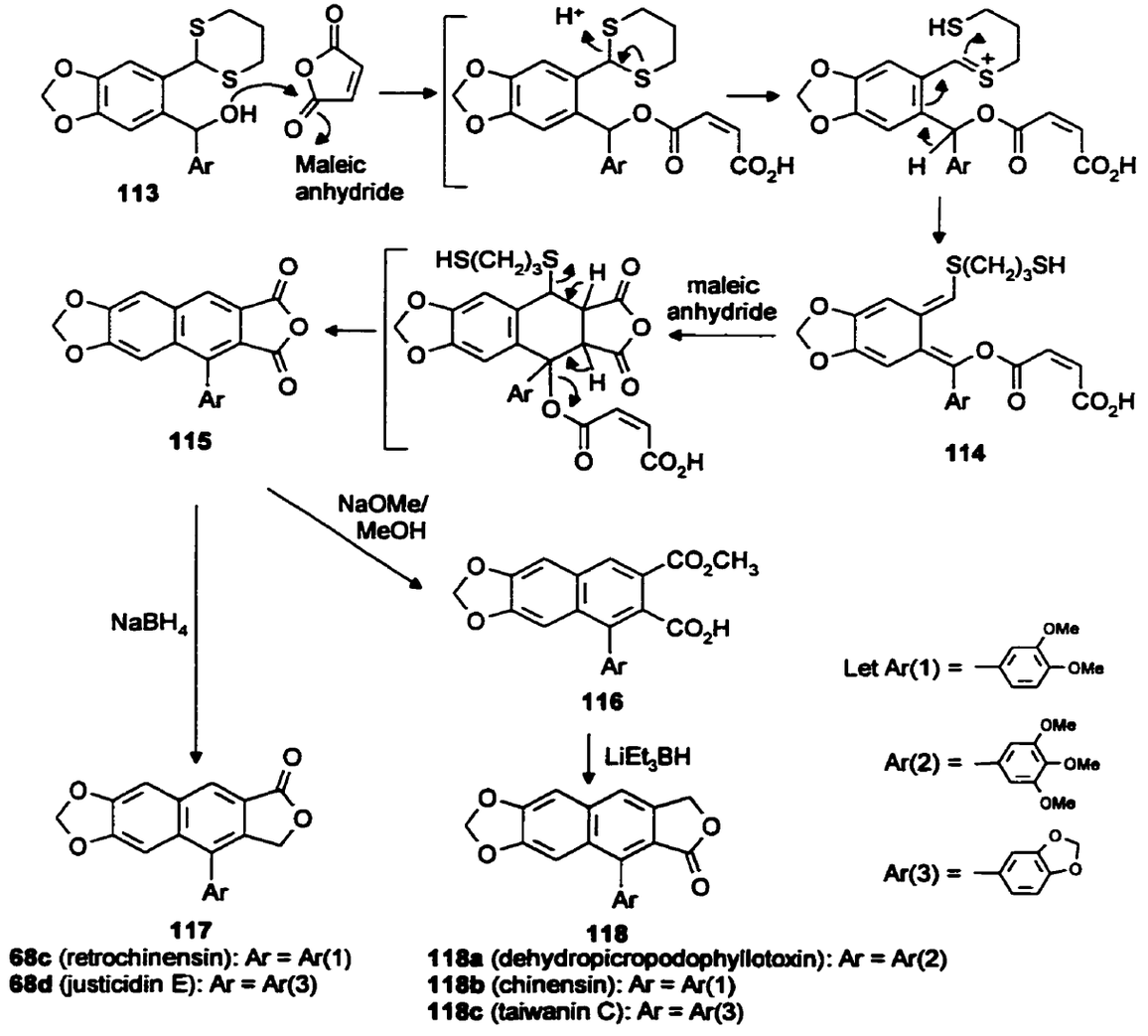
In addition to isobenzofurans, *o*-QDMs (Scheme 1.42) have also been used in Diels-Alder reaction for the preparation of arylnaphthalene lignans.



o-QDM

Scheme 1.42

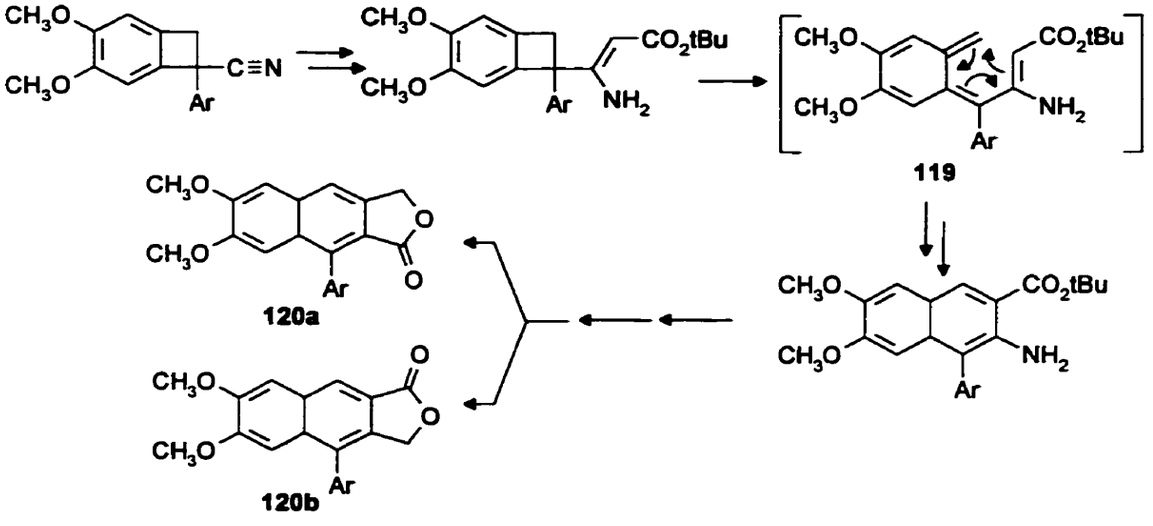
Takano *et al.*[48a] have prepared arylnapthalene lignans by treating dithioacetals **113** with a large excess of maleic anhydride in refluxing toluene. They proposed that an *o*-QDM intermediate, **114**, was generated as shown in Scheme 1.43.



Scheme 1.43

Reduction and lactonization of the resulting aromatized product arylnapthalene anhydride **115** afforded a mixture of products **117** and **118**, with lactone **117** being predominant. On the other hand, treatment of anhydride **115** with NaOMe/MeOH followed by reduction afforded only arylnaphthalene lignan **118**. The lignans having general structure **117**, retrochinensin (**68c**) and justicidin E (**68d**), and the lignans having general structure **118**, dehydroanhydropicropodophyllin (**118a**), chinensin (**118b**), and taiwanin C (**118c**), were prepared using this approach.

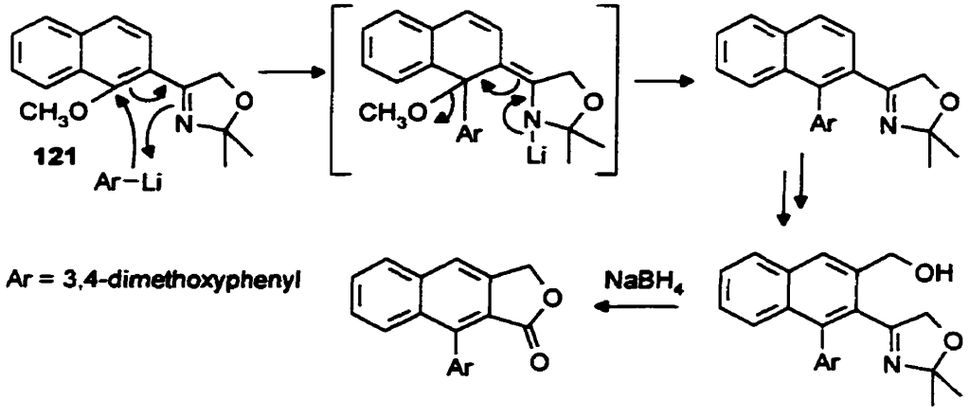
An intramolecular pericyclic reaction of an *o*-QDM (**119**) was reported by Kobayashi *et al.* for the synthesis of nonphenolic arylnapthalene lignans **120** (Scheme 1.44).[60] This procedure is not recommended due to the large number of steps involved.



Scheme 1.44

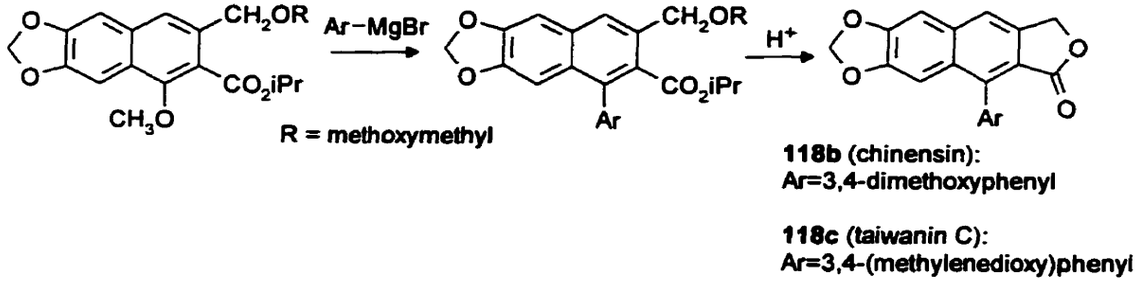
A more direct route to the synthesis of arylnapthalene lignans is the joining of an aryl ring and a naphthyl ring by a biaryl cross-coupling reaction. Meyers and Avila have synthesized an arylnaphthalene lignan analog by oxazoline-mediated nucleophilic

aromatic substitution of naphthalene **121** with an aryllithium reagent.[61] The method is illustrated in Scheme 1.45. Although the approach appears direct, a large number of steps were involved in the preparation of the naphthalene starting material and the functional group transformations of the coupled naphthyl-aryl product.



Scheme 1.45

The biaryl cross-coupling approach to arylnaphthalene lignans received no further attention until very recently. Hattori *et al.* have replaced the Meyer's oxazoline group with an ester functionality and slightly shortened the number of steps employed (Scheme 1.46).[62] The method has been extended to the preparation of chinensin (**118b**) and taiwanin C (**118c**).

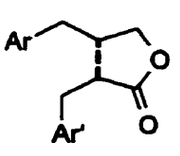


Scheme 1.46

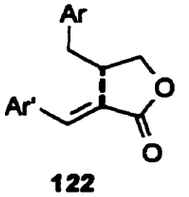
1.4 ASYMMETRIC SYNTHESIS OF LIGNANS

Asymmetric synthesis was defined by Morrison and Mosher as a reaction where an achiral unit within a substrate is converted into a chiral unit in such a manner that the stereoisomeric products are formed in unequal amount.[63] Due to the fact that many biologically active natural products exist in the form of a single enantiomer and possess different biological activity from their enantiomeric counterparts, selective preparation of a single active enantiomer is desirable. A highly stereoselective asymmetric synthesis is the method of choice because it accomplishes this task economically, as well as reducing the contamination by the other enantiomer. Asymmetric synthesis of drugs also provides compounds of higher specific activity.

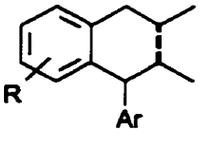
The asymmetric synthesis of lignans has been extensively[64,65] and partly[4-6,10,66-68] reviewed by many authors. Because the asymmetric synthesis of dibenzylbutyrolactones **3**, benzylidenebenzylbutyrolactones **122**, and aryltetralin lignans **8** (Scheme 1.47) are the subject of this thesis work, a literature review of the asymmetric synthesis of these three lignan subgroups will be provided here. Before the literature methods are reviewed, general approaches to the synthesis of these lignan subgroups will be briefly introduced.



3
(dibenzylbutyrolactone)



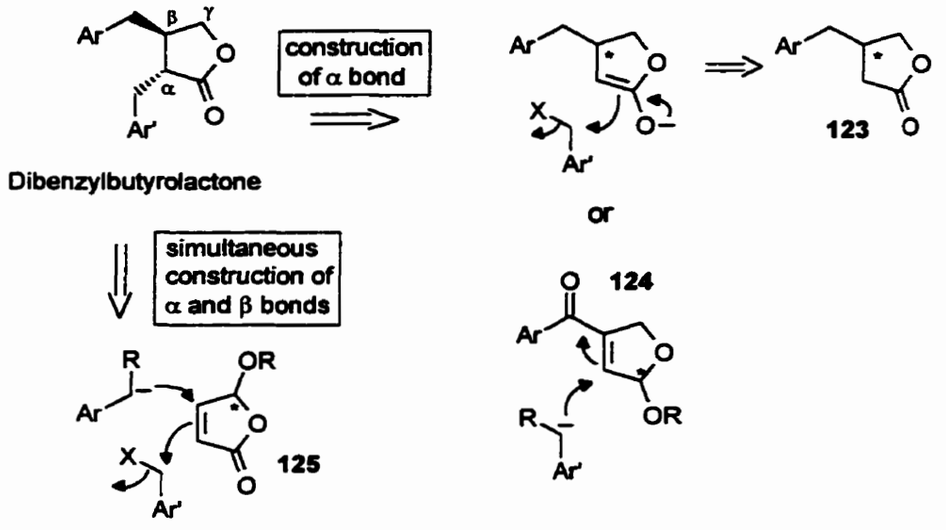
122
(benzylidenebenzylbutyrolactone)



8
(aryltetralin)

Scheme 1.47

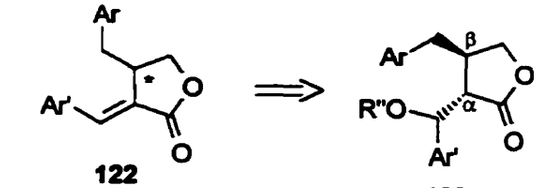
The asymmetric syntheses of dibenzylbutyrolactone lignans are numerous but the methods can generally be categorized into two groups: (i) the attachment of a benzylic group to the α position of a pre-formed β-benzyl-γ-butyrolactone (**123**) or dihydrofuran **124**, and (ii) simultaneous attachment of both α and β benzyl groups, as depicted in Scheme 1.48.



Scheme 1.48

The attachment of benzyl group to the α position of benzylbutyrolactones **123** has been achieved by reacting enolates of optically active **123** with benzyl alkylating agents. Conjugate addition of benzyl carbanions to optically active benzoyldihydrofurans **124** has also been used to accomplish this reaction although the former approach has so far gained more popularity than the latter one. The simultaneous attachment of both the α and β benzylic groups has been accomplished by tandem conjugate addition-alkylation of optically active butenolide such as **125**.

The asymmetric syntheses of benzylidenebenzylbutyrolactone lignans often involve dibenzylbutyrolactone lignan analogs **126** as intermediates (Scheme 1.49). Butyrolactones **126** are in turn prepared by reaction of benzaldehydes with benzylbutyrolactones **123**. As such, the synthesis of dibenzylbutyrolactone and benzylidenebenzylbutyrolactone lignans share some common features.

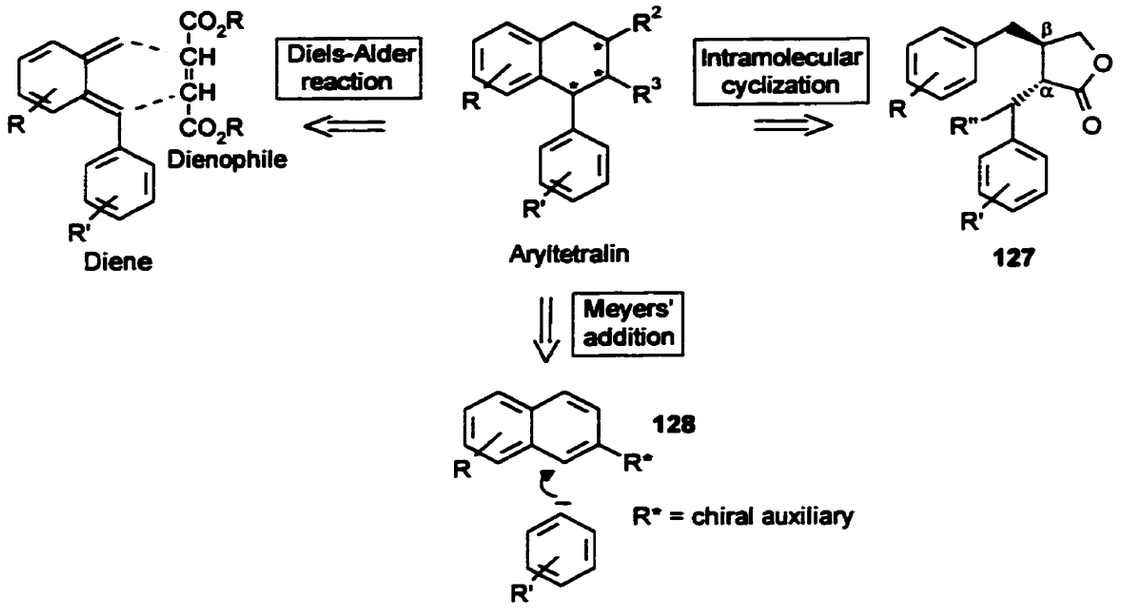


122
Benzylidene-benzylbutyrolactone

126

Scheme 1.49

Although there have been many asymmetric synthetic methods developed for the synthesis of aryltetralin lignans, in general only three asymmetric approaches have been employed (see Scheme 1.50). The first approach is the intramolecular cyclization of enantiomerically pure dibenzylbutyrolactone intermediates **127** which are in turn prepared via the approach depicted in Scheme 1.48. The second approach is the asymmetric Diels-Alder reactions where the diene or the dienophile bears a chiral auxiliary. The third approach, which was introduced by Meyers,[69] involves the asymmetric addition of an aryllithium to an enantiomerically pure chiral naphthalene **128**.

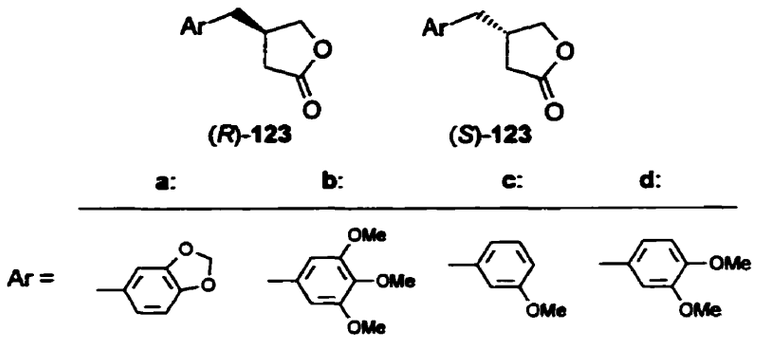


Scheme 1.50

Since the asymmetric synthesis of dibenzylbutyrolactones, benzylidenebenzylbutyrolactones, and aryltetralin lignans share common intermediates and approaches, the following discussion of lignan asymmetric synthesis is organized according to the type of approach, rather than on the classification of lignan itself.

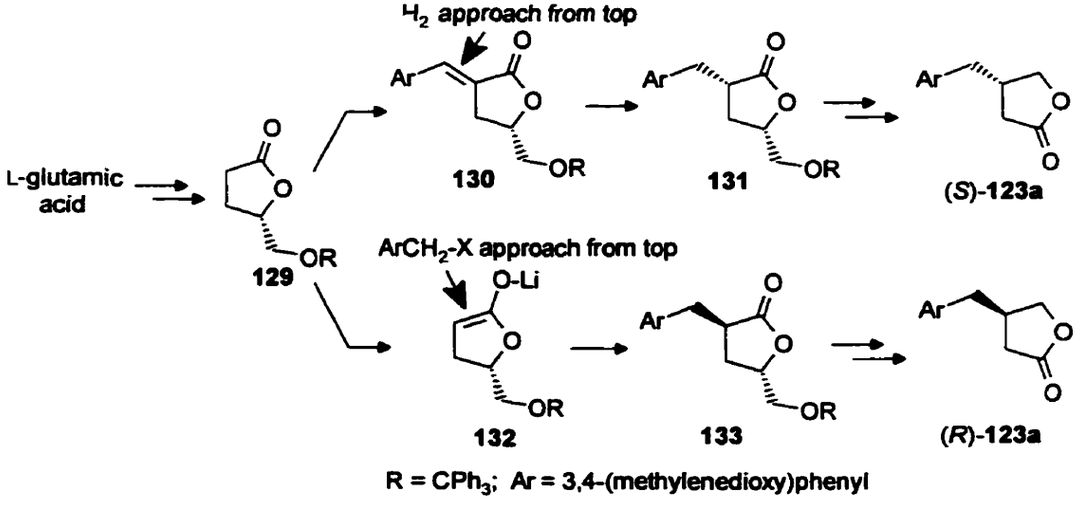
1.4.1. Asymmetric Synthesis of Lignans via β-Benzyl-γ-butyrolactones

Optically active β-benzyl-γ-butyrolactones of general structure **123** (Scheme 1.51) are the most versatile intermediates used in asymmetric synthesis of many lignan subgroups. A large number of asymmetric synthetic approaches have been developed for the preparation of optically active butyrolactones **123** and these methods will be thoroughly reviewed in this section.



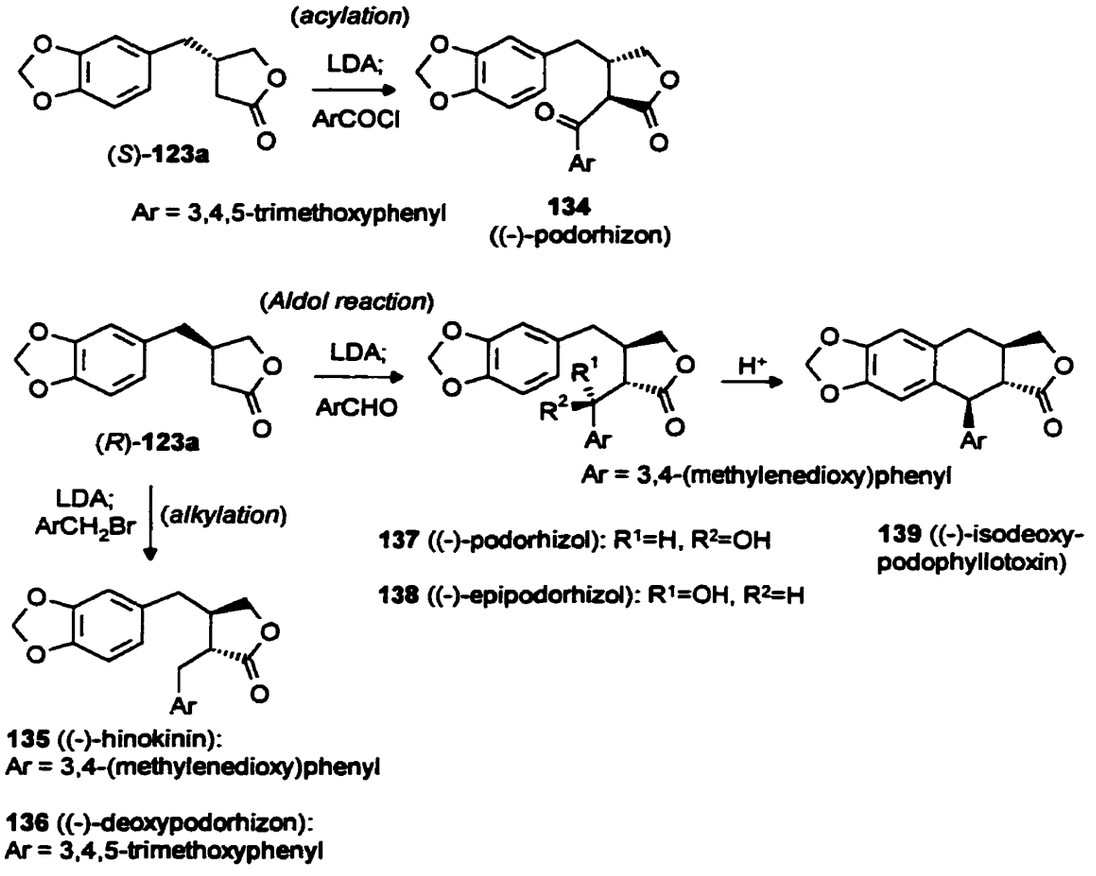
Scheme 1.51

The first asymmetric synthesis of a β-benzyl-γ-butyrolactone (**123**) was reported by Tomioka and Koga,[70] as illustrated in Scheme 1.52. Optically active benzylbutyrolactones **123a** were synthesized from lactone **129** which was in turn prepared in a multistep sequence from L-glutamic acid. Alkene **130** was hydrogenated selectively from the least sterically hindered face to afford **131**, which was then converted to (*S*)-**123a**.[70a] On the other hand, alkylation of **129** where the benzylbromide also approached from the least hindered face gave **133**. Subsequent reactions of **133** resulted in the formation of (*R*)-**123a**.[70b]



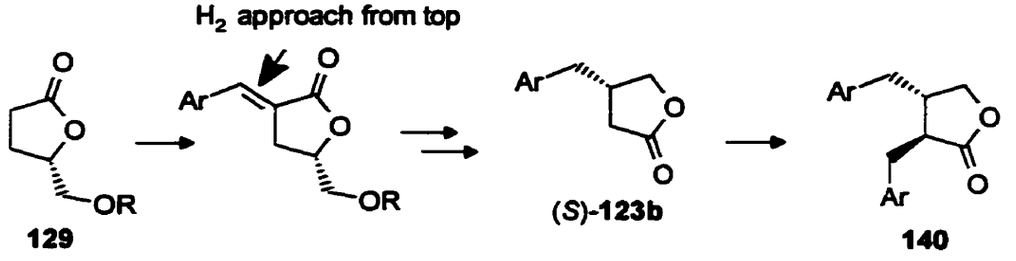
Scheme 1.52

The conversion of benzylbutyrolactones (*R*)- and (*S*)-**123a** to lignans is illustrated in Scheme 1.53. Butyrolactone (*S*)-**123a** was converted to (-)-podorhizon (**134**) by acylation. Butyrolactone (*R*)-**123a** was converted to (-)-hinokinin (**135**) and (-)-deoxypodorhizon (**136**) by alkylation, and to (-)-podorhizol (**137**) and (-)-epipodorhizol (**138**) by aldol reaction. In these reactions, the benzylic electrophiles approached the benzylbutyrolactone enolates from the least hindered side to afford *trans*-products. Acid-catalyzed intramolecular cyclization of the aldol products **137** and **138** gave (-)-isodeoxypodophyllotoxin (**139**).



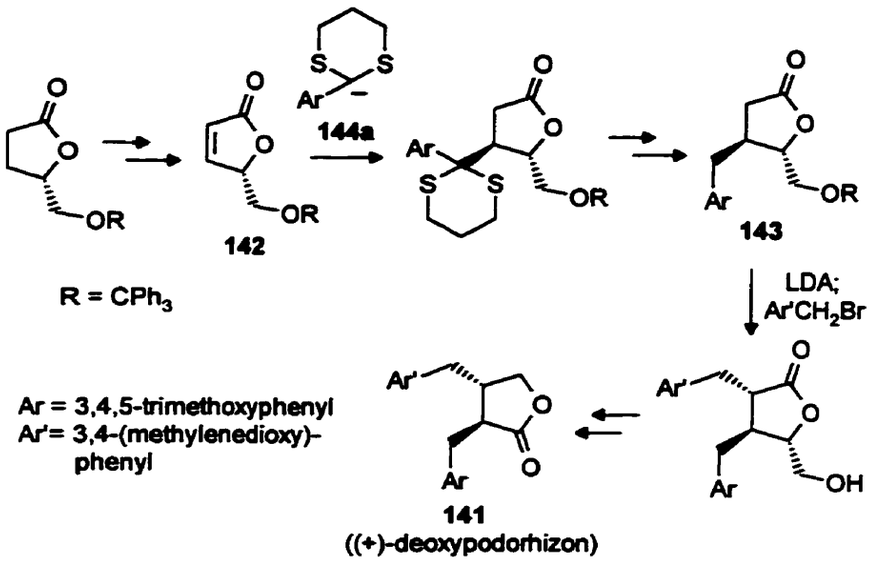
Scheme 1.53

The procedure used by Tomioka and Koga for the preparation of butyrolactone (*S*)-**1a** (see Scheme 1.52) was also used by Shibuya *et al.*[71] who extended it to the preparation of dibenzylbutyrolactone lignan analog **140** through (*S*)-**123b** as illustrated in Scheme 1.54.



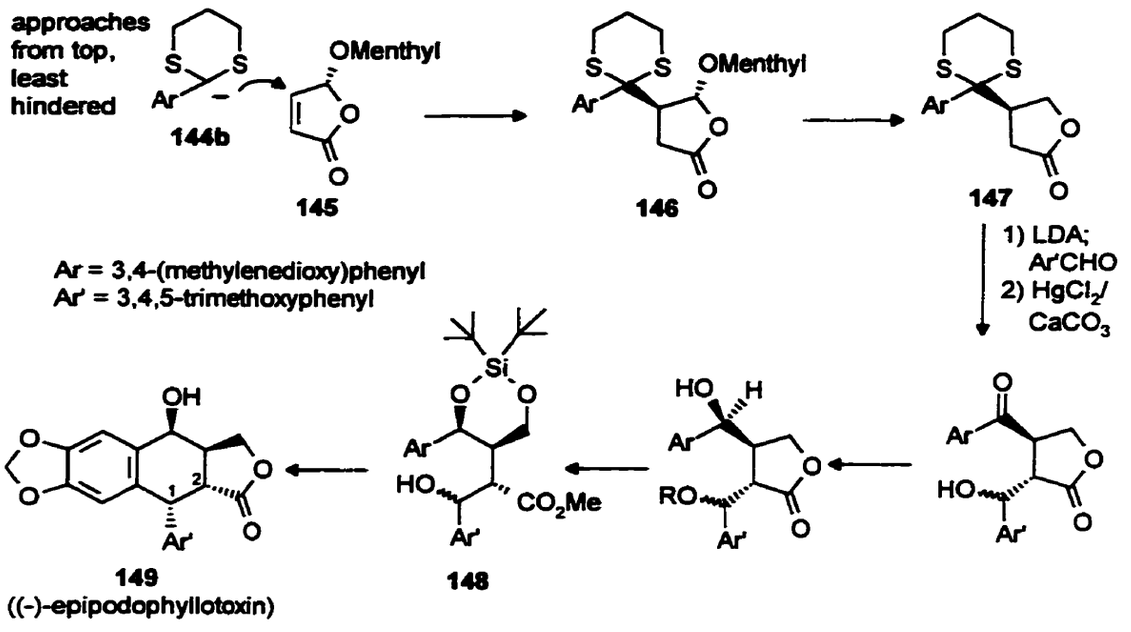
Scheme 1.54

Tomioka and Koga[72] have also accomplished the synthesis of (+)-deoxypodorhizon (**141**) using a modification of their previous approach shown in Scheme 1.52. In this modified procedure (Scheme 1.55), conjugate addition on a chiral butenolide, **142**, was used to prepare the γ-substituted β-benzyl-γ-butyrolactone **143**. This approach (Scheme 1.55) was inferior to the previous one (Scheme 1.52) since more steps were required.



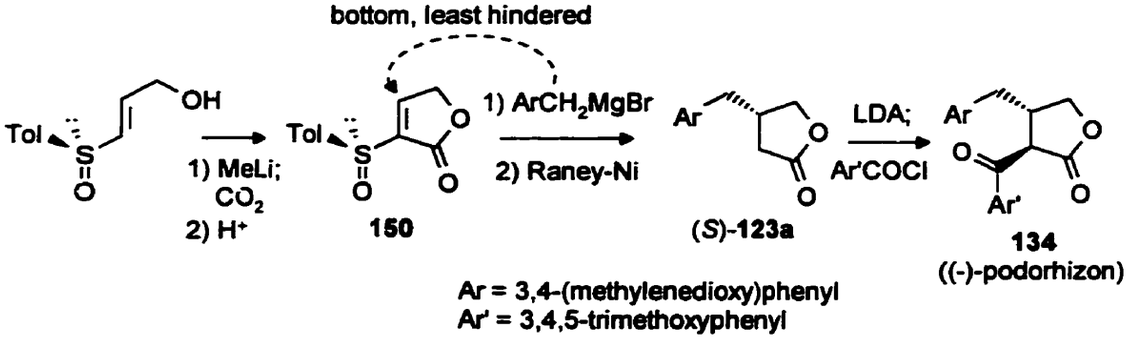
Scheme 1.55

Conjugate addition to a chiral butenolide has also been employed by Vandewalle *et al.* to prepare dithioketal butyrolactone **147** which was subsequently converted to (-)-epipodophyllotoxin (**149**) (Scheme 1.56).[73] Stabilized carbanion **144b** added to (5*R*)-(*l*)-menthyl butenolide **145** diastereoselectively (also see Section 1.4.3 for more detail) to afford butyrolactone **146**, which was then transformed to **148** using a multistep sequence. The siladioxane ring controlled the stereoselective ring closure of **148** in such a way that only a C1/C2 *cis*-product was produced.



Scheme 1.56

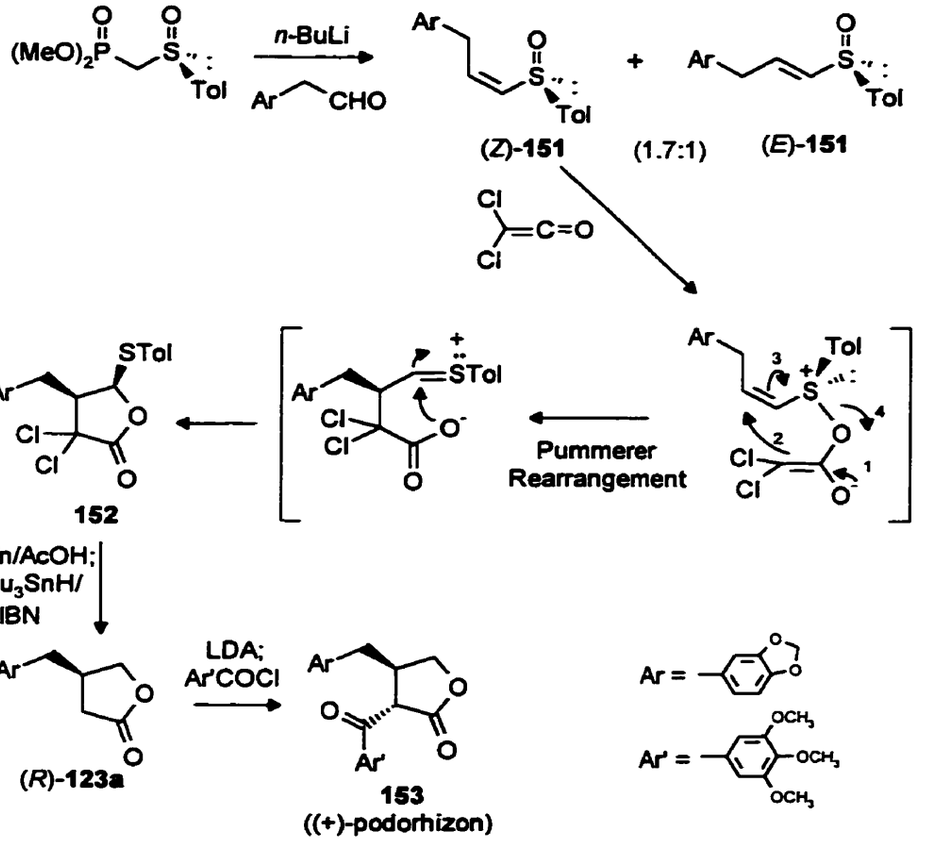
An alternative asymmetric synthesis of chiral benzylbutyrolactone (*S*)-**123a** was achieved by diastereoselective conjugate addition to an enantiomerically pure α-sulfinyl-γ-butenolide, **150**, as illustrated in Scheme 1.57.[74] Butyrolactone (*S*)-**123a** was then acylated as described before by Tomioka and Koga to afford (-)-podorhizon (**134**).



Scheme 1.57

Another optically active vinyl sulfoxide used as chiral synthon for the synthesis of benzylbutyrolactones **123** is illustrated in Scheme 1.58.[75] The use of this approach is

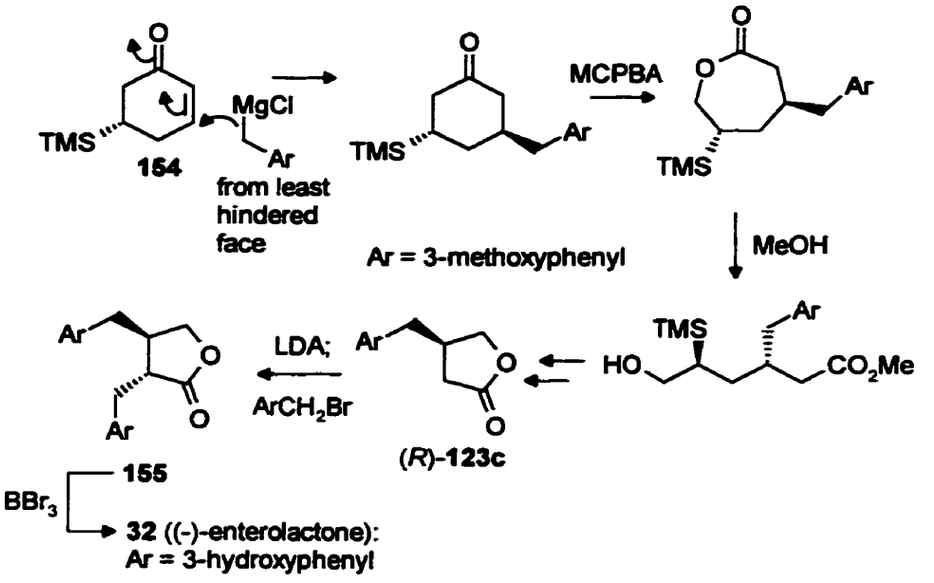
disadvantageous in that the preparation of chiral synthon is inefficient, leading to both the formation of (*Z*)-vinyl sulfoxide **151** (the desirable product), as well as the (*E*)-isomer. Nevertheless, (*Z*)-**151** reacted with dichloroketene with high diastereoselectivity to afford butyrolactone **152** as sole product. The removal of the sulfur and chlorine substituents by Zn/AcOH and Bu_3SnH/AIBN afforded (*R*)-**123a** which was later converted into (+)-podorhizon (**153**) by acylation.



Scheme 1.58

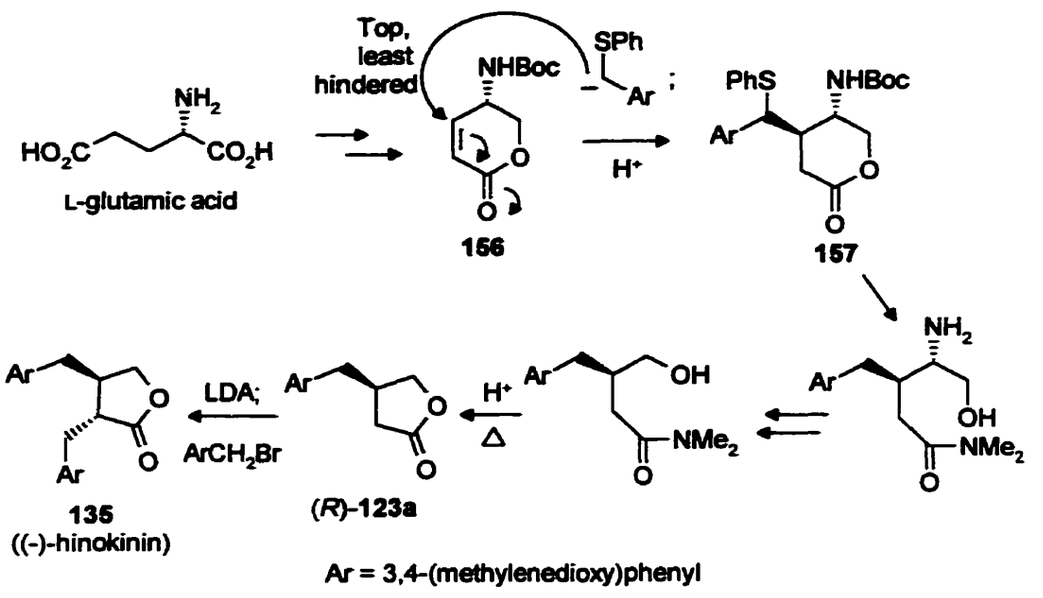
Asaoka *et al.*[76] have introduced an asymmetric synthetic method for the mammalian lignan (-)-enterolactone (**32**) through the use of 5-trimethylsilyl-2-cyclohexenone (**154**) as chiral synthon (Scheme 1.59). Benzylbutyrolactone (*R*)-**123c**

was prepared using a laborious multistep sequence which involved diastereoselective alkylation of optically active cyclohexenone **154** in the key step. Alkylation of benzylbutyrolactone (*R*)-**123c** followed by demethylation of dibenzylbutyrolactone **155** with BBr_3 completed the synthesis of (-)-enterolactone.



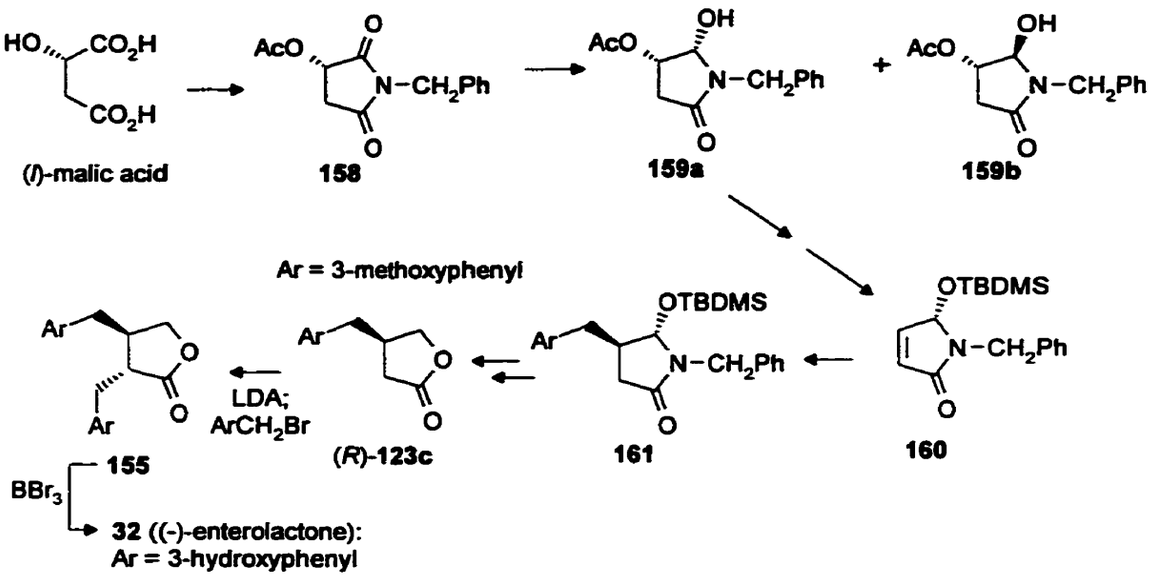
Scheme 1.59

Diastereoselective conjugate addition to a chiral unsaturated 6-membered ring lactone (**156**) was employed by Yoda *et al.*[77] to prepare benzylbutyrolactone (*R*)-**123a** (Scheme 1.60). A large number of steps were involved in the preparation of optically active unsaturated lactone **156** from L-glutamic acid. The conjugate addition product **157** was formed in 70% with *de* >99%. However, the subsequent conversion of **157** to (*R*)-**123a** was relatively lengthy. Alkylation of (*R*)-**123a** as described before afforded the dibenzylbutyrolactone lignan (-)-hinokinin (**135**).



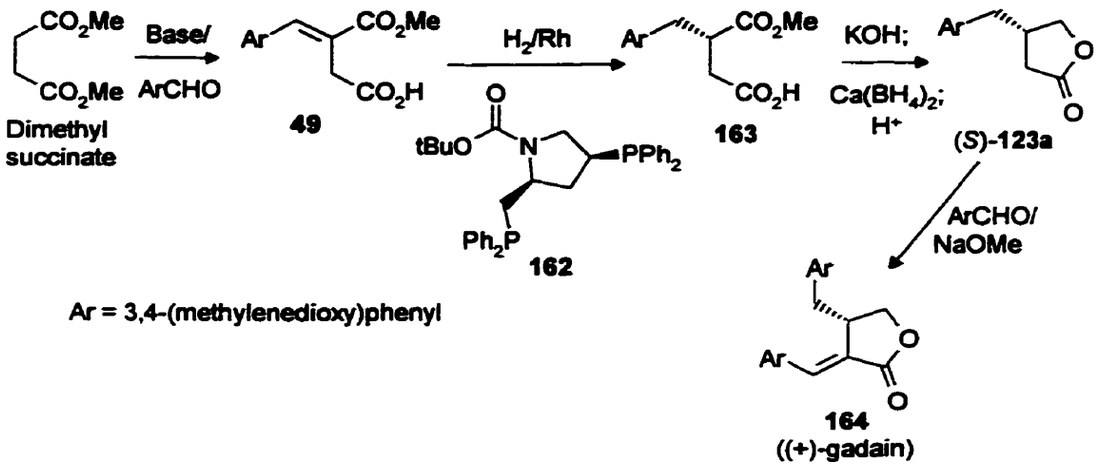
Scheme 1.60

Later, Yoda *et al.* carried out a conjugate addition reaction on a chiral unsaturated lactam **160** in the preparation of mammalian lignan (-)-enterolactone (**32**) via butyrolactone (*R*)-**123c** (Scheme 1.61).[78] The number of steps required for the preparation of chiral synthon **160** from L-malic acid was relatively few. Yet, the method involved a rather unsatisfactory stereoselective reduction step, where imide **158** was reduced with only moderate selectivity to afford a mixture of diastereomers **159a** and **159b** in a 78:22 ratio, respectively. In spite of the difficulty in the preparation of chiral synthon **160**, the key reaction for the preparation of benzylbutyrolactone (*R*)-**123c**, *i.e.* conjugate addition to **160**, proceeded with high diastereoselectivity to afford diastereomer **161** as sole product.



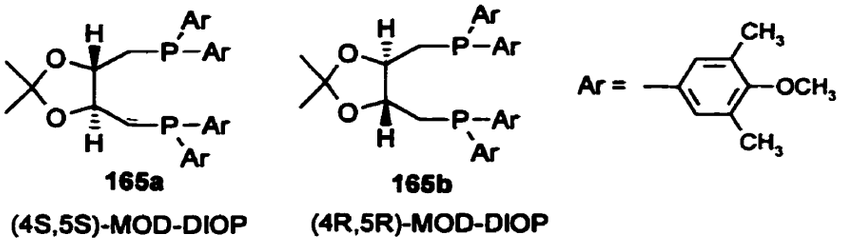
Scheme 1.61

An elegant catalytic asymmetric hydrogenation of itaconates was pioneered by Achiwa in 1979 for the preparation of a β-benzyl-γ-butyrolactones (Scheme 1.62).[79] Itaconate **49**, prepared by Stobbe condensation of methyl succinate and 3,4-(methylenedioxy)benzaldehyde, was hydrogenated in high enantioselectivity using a chiral pyrrolidinephosphine-rhodium chelating agent (**162**) as catalyst. The resulting enantiomer **163** was reduced and lactonized to give (*S*)-**123a** which was then converted to benzylidenebenzylbutyrolactone lignan (+)-gadain (**164**) by a condensation reaction.



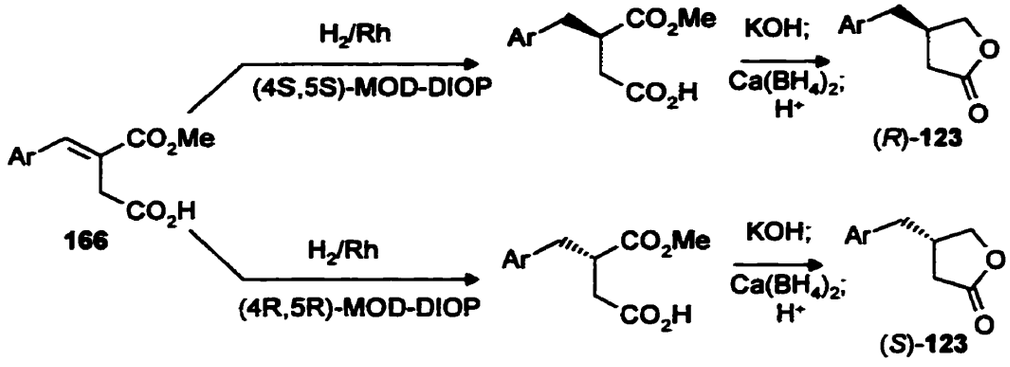
Scheme 1.62

Later, Achiwa *et al.*[64] used a more efficiently prepared chiral rhodium chelating agent MOD-DIOP **165** (see Scheme 1.63) in place of chiral chelating agent **162** in a reaction similar to that described above.



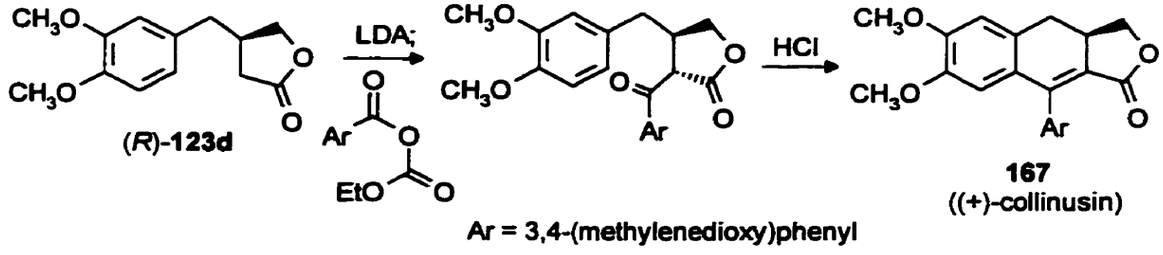
Scheme 1.63

In general, hydrogenation of itaconates of general structure **166** in the presence of (4*S*,5*S*)-MOD-DIOP-rhodium(I) (**165a**) complex followed by reduction and lactonization results in the formation of (*R*)-enantiomers of benzylbutyrolactones **123**. On the contrary, use of the (4*R*,5*R*)-MOD-DIOP-rhodium(I) complex (**165b**) affords (*S*)-**123** (Scheme 1.64).



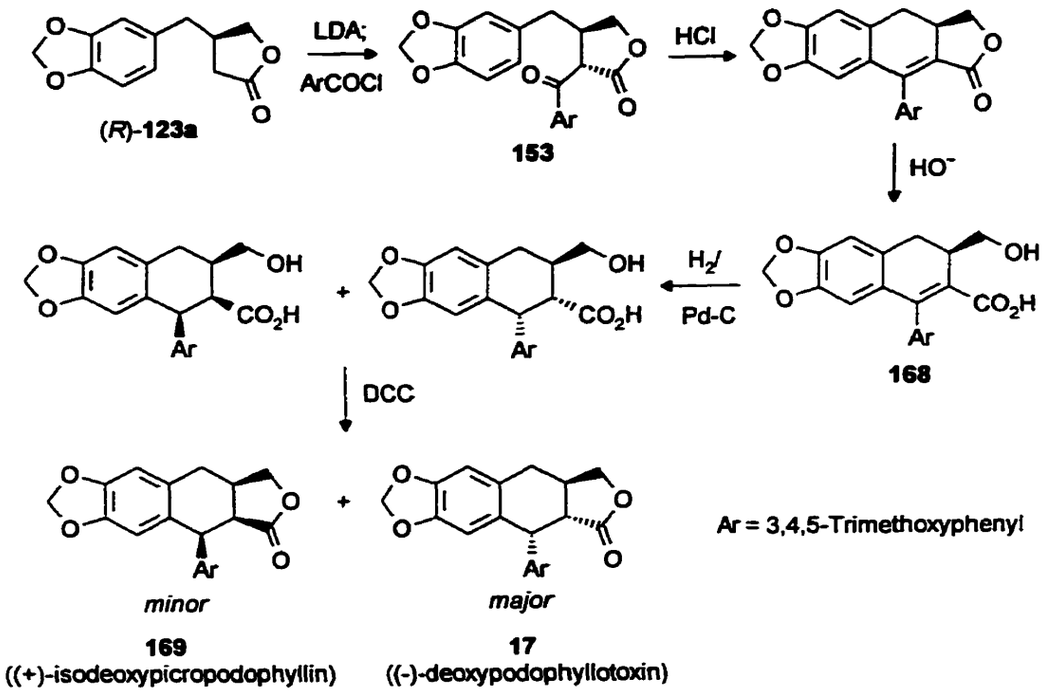
Scheme 1.64

The β-benzyl-γ-butyrolactones synthesized using this new method have been employed to prepare a wide variety of lignans and analogs. For instance, dehydroaryltetralin lignan (+)-collinusin (**167**) was prepared by acylation of benzylbutyrolactone (*R*)-**123d** followed by cyclization and elimination (Scheme 1.65).[80]



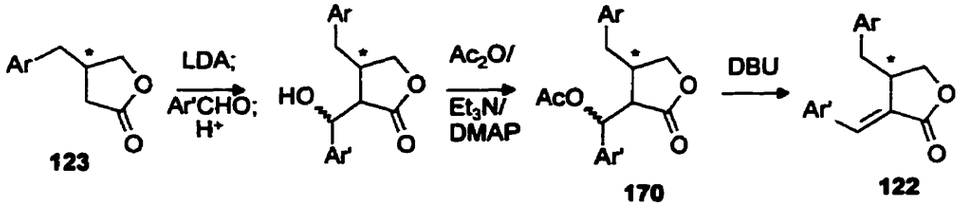
Scheme 1.65

Similar treatment of benzylbutyrolactone (*R*)-**123a** followed by hydrolysis gave dehydroaryltetralin **168**, hydrogenation of which proceeded with moderate selectivity giving a mixture of aryltetralin lignans (-)-deoxypodophyllotoxin (**17**) and (+)-isodeoxypicropodophyllin (**169**) after lactonization (Scheme 1.66).[81]



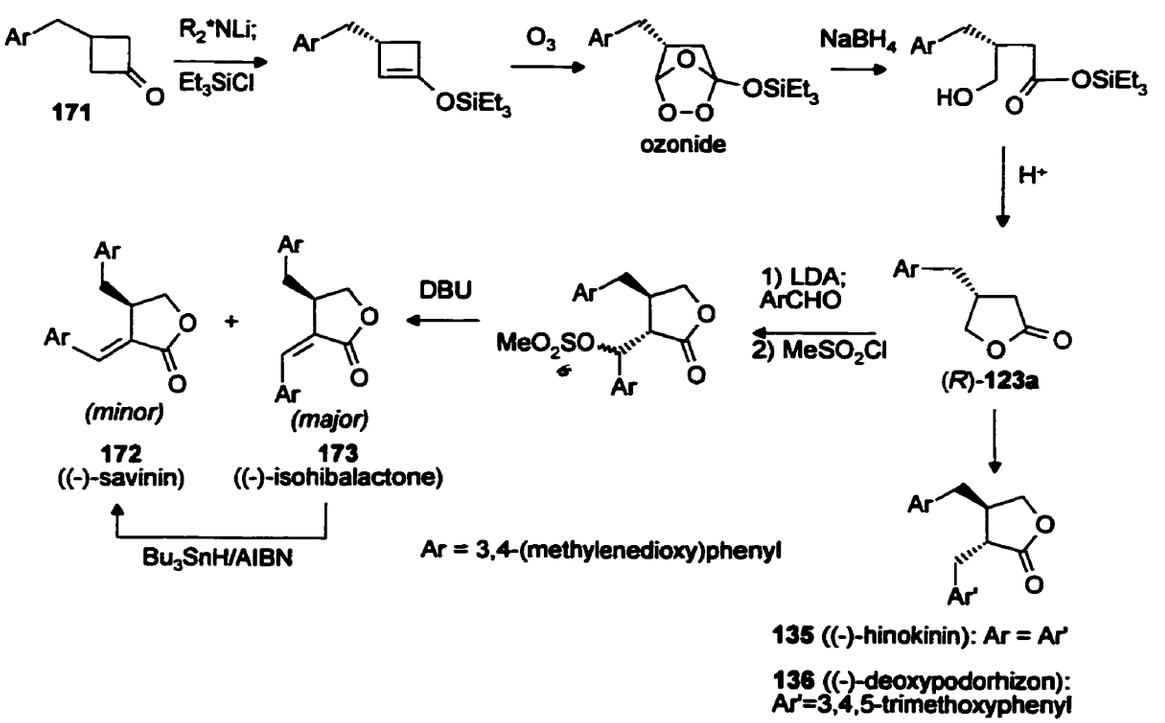
Scheme 1.66

Tanaka *et al.*[82] have prepared a series of benzylidenebenzylbutyrolactone lignan analogs **122** from benzylbutyrolactones **123** which were in turn synthesized using Achiwa's asymmetric hydrogenation method described above. The condensation of **123** was achieved in excellent yield by DBU elimination of acetylated aldol products **170** as illustrated in Scheme 1.67. The benzylidenebenzylbutyrolactone lignan analogs were used as intermediates for the preparation of dibenzocyclooctadiene lignans (**10**, see Scheme 1.2).



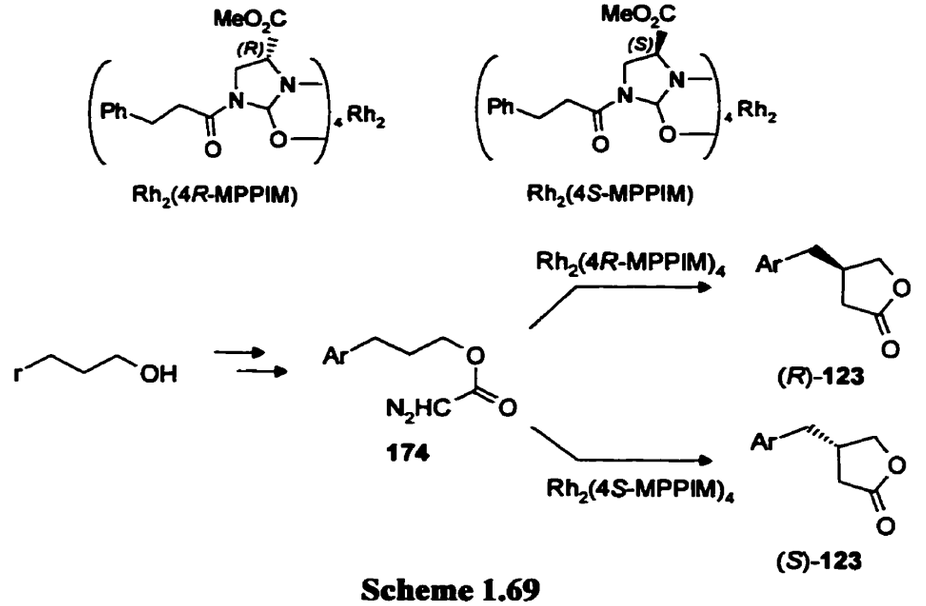
Scheme 1.67

More recently, Honda *et al.* have employed enantioselective deprotonation of a 3-benzylcyclobutanone **171** as a key step in the synthesis of benzylbutyrolactone (*R*)-**123a** (Scheme 1.68).[83] Although only a few steps were involved in the synthesis, the enantioselectivity of the key reaction, *i.e.* deprotonation of benzylcyclobutanone **171** by lithium (*S,S'*)-αα'-dimethyldibenzylamide, was only moderate. Nevertheless, the resulting benzylbutyrolactone (*R*)-**123a** which had low optical purity was subsequently alkylated to afford (-)-hinokinin (**135**) and (-)-deoxypodorhizon (**136**). Butyrolactone (*R*)-**123a** also underwent aldol reaction, mesylation, and elimination to afford a mixture of benzylidenebenzylbutyrolactone lignan (-)-savinin (**172**) and non-natural lignan (-)-isohibalactone (**173**), where the latter product was later isomerized to the former using Bu_3SnH/AIBN.



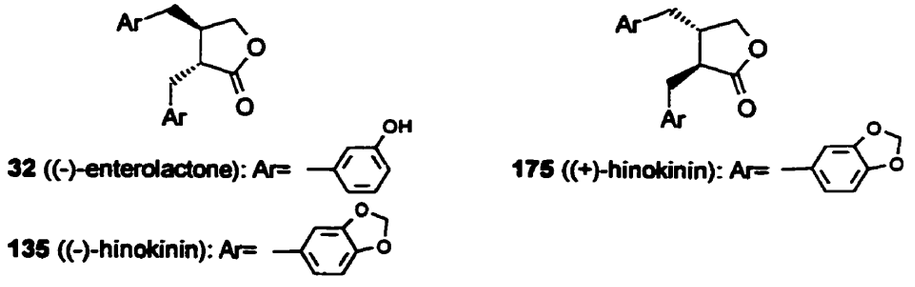
Scheme 1.68

Doyle *et al.* reported a novel and efficient synthesis of β-benzyl-γ-butyrolactones via an enantioselective intramolecular C-H insertion reaction of an alkyl diazoacetate **174** (Scheme 1.69).[84] Chiral oxoimidazolidene carboxylate dirhodium catalysts, Rh_2(MPPIM) enantiomers, were applied in the key reaction to afford a chiral benzylbutyrolactone **123** in up to 94% ee.



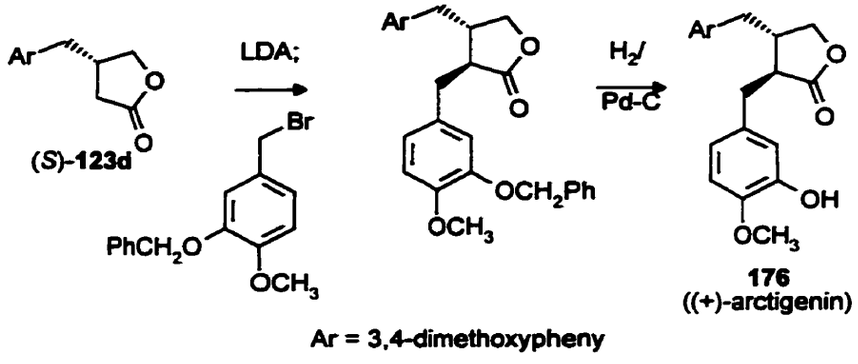
Scheme 1.69

They have used these benzylbutyrolactones to prepare a series of natural lignans (see Scheme 1.70). (+)-Enterolactone (**32**) and hinokinin enantiomers (**135** and **175**) were prepared as described in the previous examples from the corresponding optically active benzylbutyrolactones by alkylation.[84a]



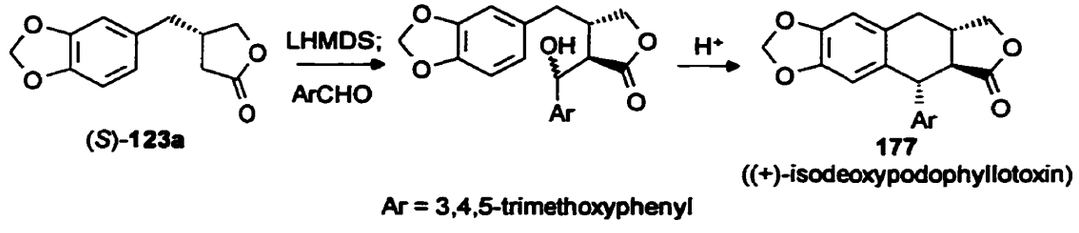
Scheme 1.70

(+)-Arctigenin (**176**) was also prepared by alkylation of benzylbutyrolactone (*S*)-**123d** followed by deprotection of the phenolic group by hydrogenation (Scheme 1.71).[84b]



Scheme 1.71

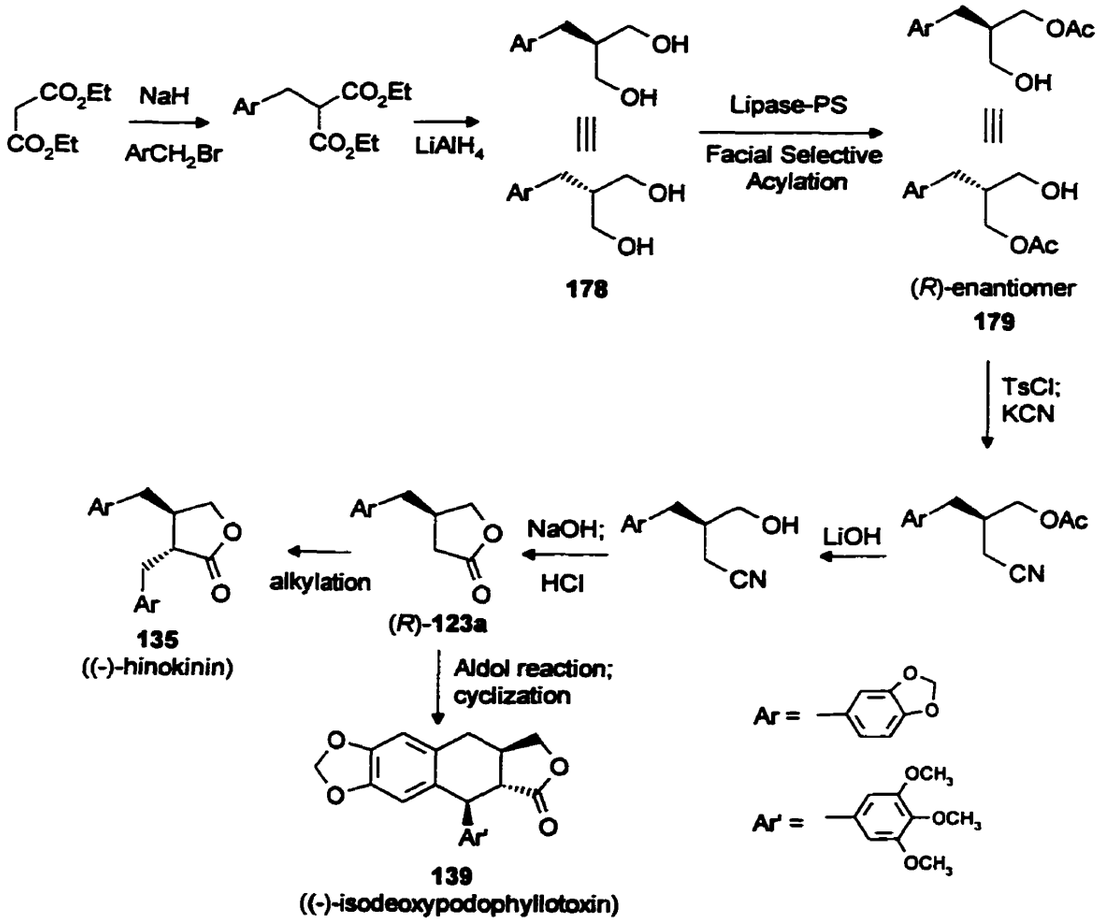
In addition, aldol reaction of benzylbutyrolactone (*S*)-**123a** with a benzaldehyde followed by acid treatment gave the all *trans*-aryltetralin lignan (+)-isodeoxypodophyllotoxin (**177**), as shown below.[84b]



Scheme 1.72

Asymmetric enzymatic transesterification of a prochiral diol has been employed by Itoh *et al.* to synthesize optically active β-benzyl-γ-butyrolactones.[85] The reaction sequence is depicted in Scheme 1.73. Prochiral diol **178** was acylated selectively by lipase-PS (from *Pseudomonas fluorescens*) to afford only (*R*)-enantiomer of monoacetate **179** in >98% *ee*. Although the process was highly enantioselective, relatively large amounts of the enzyme were needed. Using a four-step procedure which included

tosylation, nitrile formation, hydrolysis, and lactonization, monoacetate **179** was transformed into optically active benzylbutyrolactone (*R*)-**123a**. Alkylation and aldol reaction followed by acid-catalyzed cyclization of lactone (*R*)-**123a**, as described in the previous examples, afforded (-)-hinokinin (**135**) and (-)-isodeoxypodophyllotoxin (**139**), respectively. The enantioselective enzymatic approach was repeated by Yang *et al.*[86] and extended to the preparation of (-)-arctigenin and derivatives, using the procedure reported previously (see Scheme 1.71).

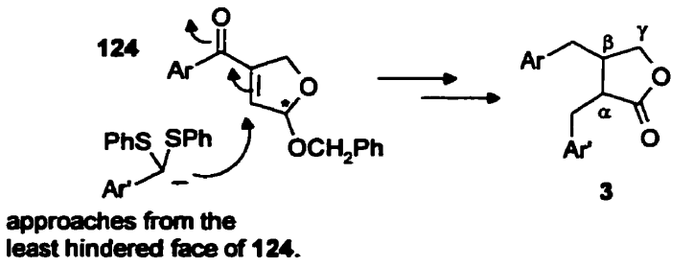


Scheme 1.73

Although the above reported methods have provided elegant routes to the preparation of optically active β-benzyl-γ-butyrolactones, many problems still exist. These include laborious methods, poor overall yields, unsatisfactory enantiomeric purity, and/or the use of expensive reagents. A simple and efficient approach for the asymmetric synthesis of β-benzyl-γ-butyrolactones is still required. In section 4.3, a new, simple, six-step procedure for the asymmetric synthesis of β-benzyl-γ-butyrolactone enantiomers using a highly diastereoselective alkylation of a N-acyloxazolidinone enolate as key step will be described.

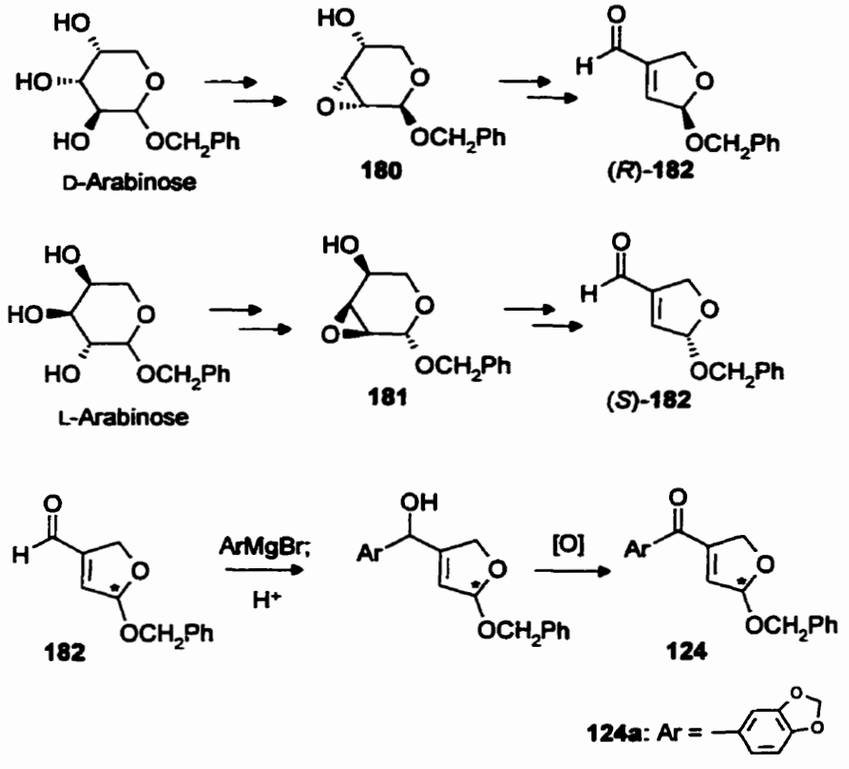
1.4.2. Asymmetric Synthesis of Lignans via Benzoyldihydrofurans

Conjugate addition of a benzyl carbanion to optically active benzoyldihydrofurans **124** as illustrated in Scheme 1.74 has represented an alternative method for the introduction of the α benzyl group of dibenzylbutyrolactone lignans (also see Scheme 1.48). Nevertheless, unlike the approach which utilizes β-benzyl-γ-butyrolactones (**123**) as intermediates (discussed in Section 1.4.1), this method, developed by Rehnberg and Magnusson,[87] has not gained much popularity.



Scheme 1.74

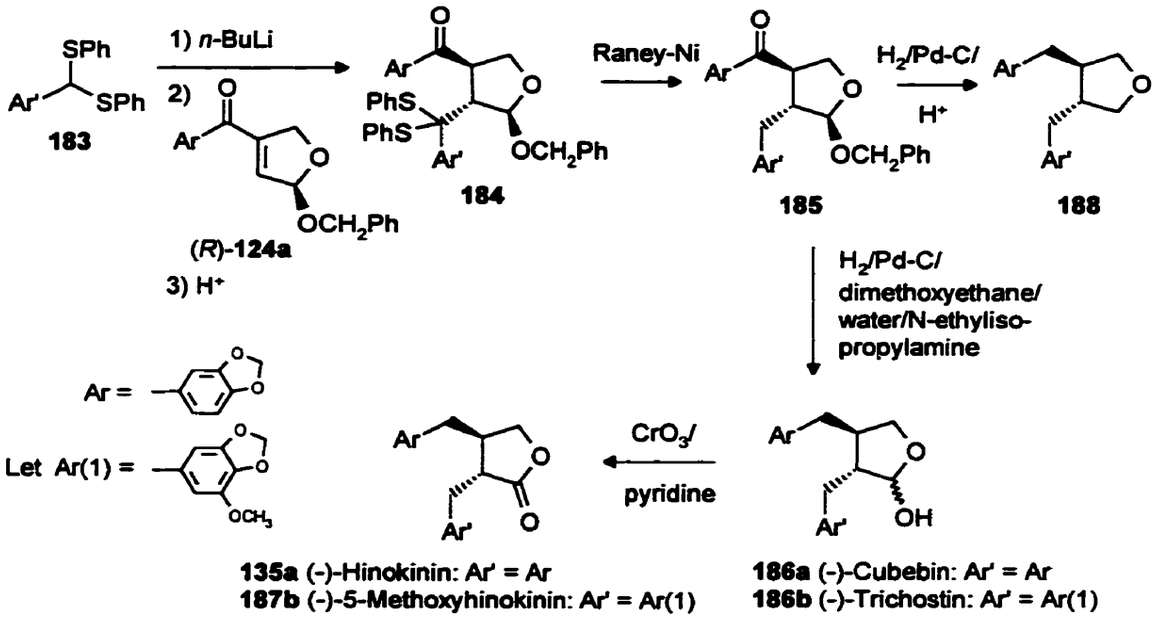
Magnusson *et al.*[87,88] have prepared several optically active benzoyldihydrofurans **124** from arabinose enantiomers, as illustrated in Scheme 1.75. D-Arabinose was converted to (*R*)-**124** via the riboside oxirane **180** and (*R*)-**182**, using a multistep sequence. Similarly, L-arabinose was transformed into (*S*)-**124** via riboside oxirane **181** and (*S*)-**182**.



Scheme 1.75

Conjugate addition of benzylic anion of diphenylthioacetal **183** to enantiomerically pure benzoyldihydrofuran (*R*)-**124a** afforded **184** in >99% *ee*, as shown in Scheme 1.76. Desulfurization of the conjugate addition product **184** with Raney-Ni followed by hydrogenolysis over Pd-C gave oxygenated the tetrahydrofuran lignans (-)-cubebin (**186a**) and (-)-trichostin (**186b**), oxidation of which resulted in the formation of

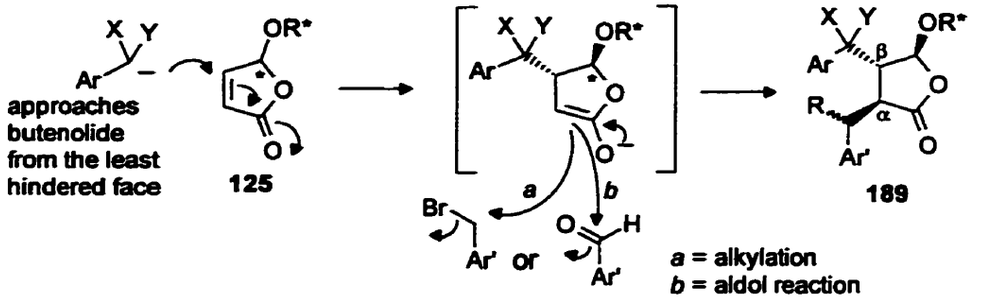
dibenzylbutyrolactone lignans (-)-hinokinin (**135**) and (-)-5-methoxyhinokinin (**187**), respectively. Several optically active tetrahydrofuran lignans of general structure **188** were also prepared in good yield by hydrogenolysis of addition products of the general structure **185**.



Scheme 1.76

1.4.3 Asymmetric Synthesis of Lignans via Tandem Conjugate Addition to Butenolides

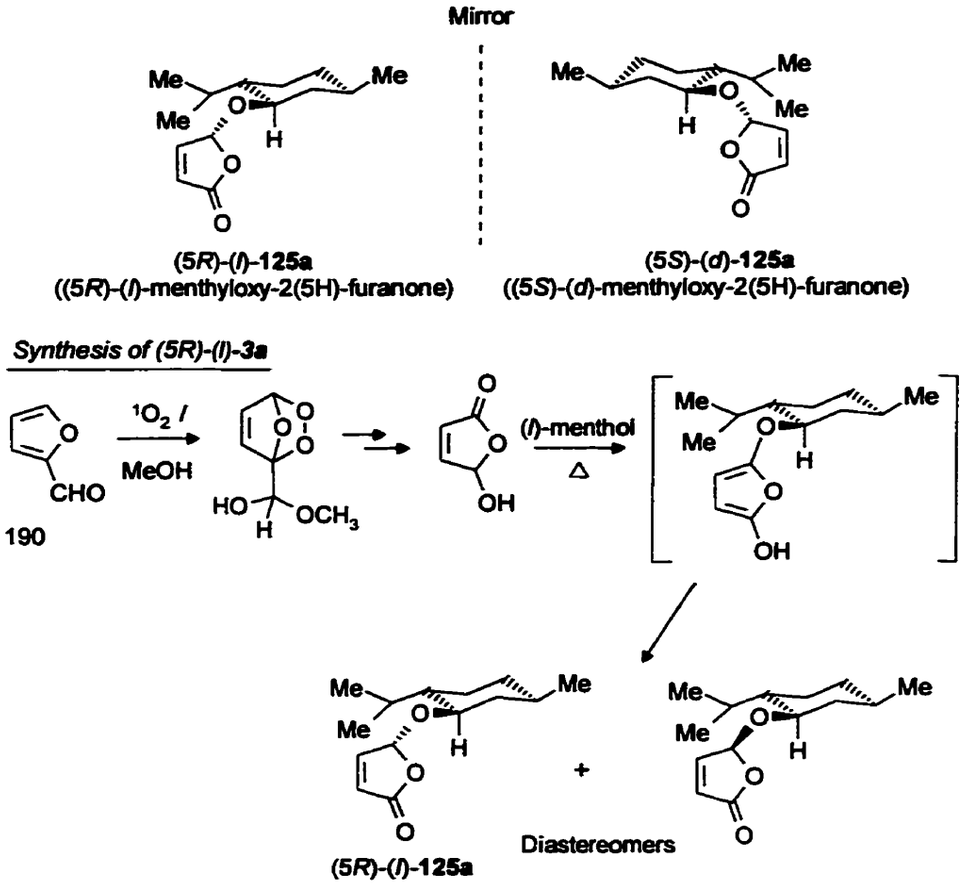
Tandem conjugate addition-alkylation/aldol reaction of optically active butenolide **125**, pioneered by Ward *et al.*,[89] demonstrates an efficient method of simultaneously introducing both α and β benzylic groups of the dibenzylbutyrolactone derivatives **189**. The general approach is illustrated in Scheme 1.77 (also see Scheme 1.48).



Scheme 1.77

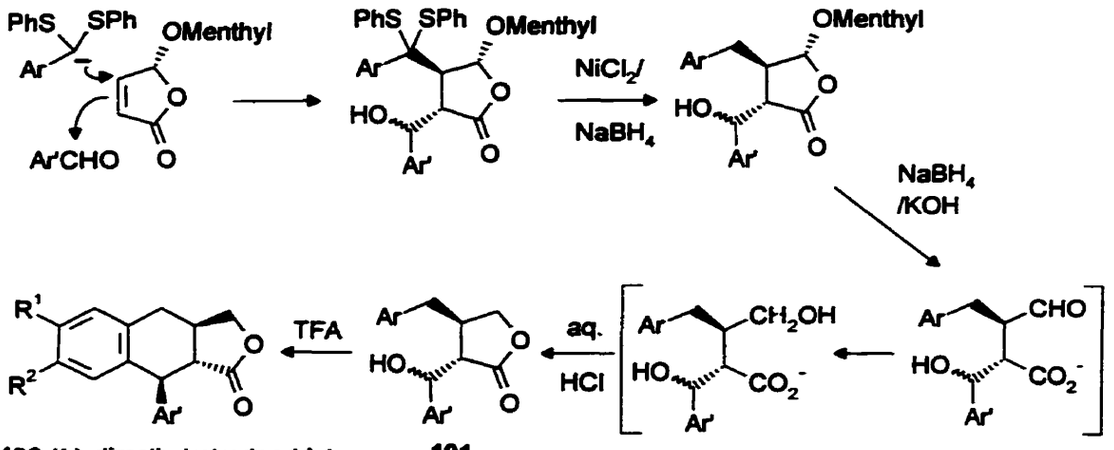
Conjugate addition of a stabilized benzylic anion to the chiral butenolide **125** usually proceeds with high diastereoselectivity, approaching the electrophilic carbon center via the least hindered face of **125** (Scheme 1.77). Subsequent alkylation or aldol reaction of the resulting enolate results in the formation of the all *trans*-butyrolactone derivative **189**, which can be converted into various lignan subgroups such as dibenzylbutyrolactones (**3**), furofurans (**6**), aryltetralins (**8**), and dibenzocyclooctadienes (**10**) (structures in Scheme 1.2).

The chiral butenolides, menthyloxy-2(5H)-furanone enantiomers (5*R*)-(*l*)- and (5*S*)-(*d*)-**125a** shown in Scheme 1.78, are usually used in the above reaction (Scheme 1.77). An example for the preparation of (5*R*)-(*l*)-**125a** is given in Scheme 1.78, where it is prepared by photooxidation of furfural **190** followed by treatment with (*l*)-menthol and fractional crystallization of the resulting diastereomeric mixture.[90]



Scheme 1.78

Asymmetric syntheses of lignans by tandem conjugate addition-alkylation/aldol reaction are frequently reported. This new approach was first developed by Ward *et al.* for the synthesis of aryltetralin lignans (-)-α-dimethylretrodendrin (**192**) and (-)-isodeoxypodophyllotoxin (**139**) as shown in Scheme 1.79.[89c] The tandem conjugate addition/aldol reaction proceeded as shown in Scheme 1.77. Desulfurization and removal of the chiral auxiliary were achieved using $NiCl_2/NaBH_4$ and $KOH/NaBH_4$, respectively, to eventually afford hydroxy-dibenzylbutyrolactone **191**. Acid-mediated cyclization of this intermediate gave aryltetralin lignans with the all *trans*-geometry.



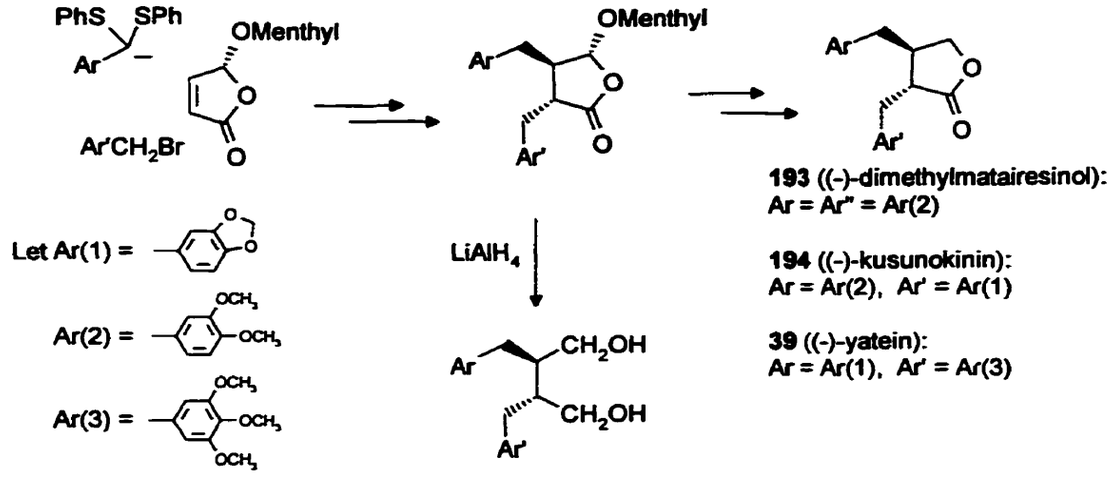
192 ((-)-dimethylretrodendrin):
R^1=R^2= OMe,
Ar'=3,4-dimethoxyphenyl

191

139 ((-)-deoxyisopodophyllotoxin):
R^1+R^2= OCH_2O,
Ar'=3,4,5-trimethoxyphenyl

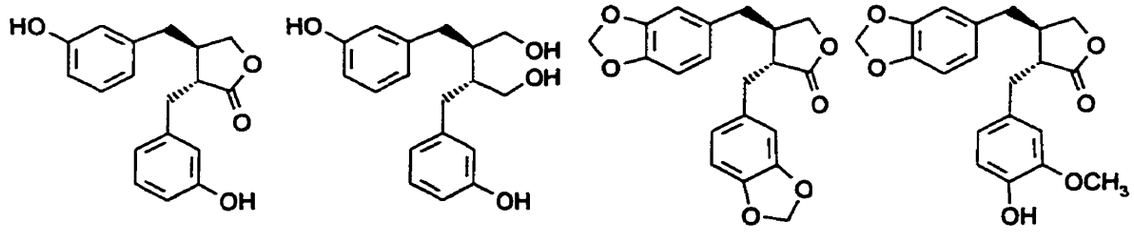
Scheme 1.79

Ward *et al.* have further extended the tandem conjugate addition approach to the preparation of optically active dibenzylbutyrolactone lignans (-)-dimethylmatairesinol (**193**), (-)-kusunokinin (**194**), and (-)-yatein (**39**), as well as dibenzylbutanediol lignans (-)-dimethylsecoisolariciresinol (**195**) and (-)-dihydroclusin (**196**), as illustrated in Scheme 1.80.[89d]



Scheme 1.80

Using the Ward's method, Feringa *et al.*[91] prepared several (-)-dibenzylbutyrolactone lignans, enterolactone (**32**), enterodiol (**33**), pluviatolide (**197**), and hinokinin (**135**) (structures in Scheme 1.81) for biological study.[91a]

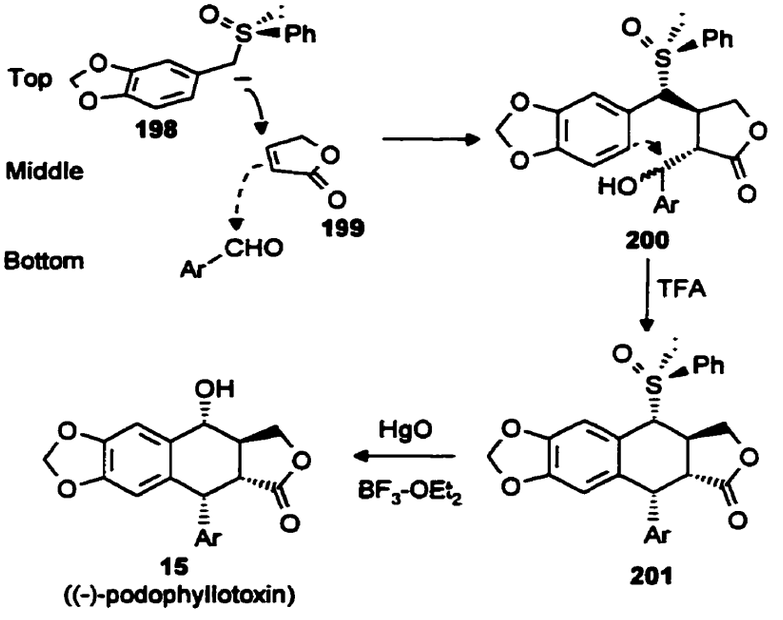


32 (enterolactone) **33** (enterodiol) **135** (hinokinin) **197** (pluviatolide)

Scheme 1.81

An alternative elegant asymmetric tandem conjugate addition was reported by Bhat *et al.* recently for the synthesis of (-)-podophyllotoxin (**15**).[92] Conjugate addition of (*S*)-(-)-piperonyl phenyl sulfoxide anion (**198**) to an achiral butenolide (**199**) followed by aldol reaction of the resulting enolate with trimethoxybenzaldehyde afforded chiral

alcohol **200** in 60% yield. A rationalization of the asymmetric induction in this tandem conjugate addition/aldol reaction was not given in the report. However, it is presumed here that the anion **198** approached butenolide **199** with the orientation shown in Scheme 1.82. Ring closure of alcohol **200** proceeded stereoselectively to give cycloadduct **201** which possessed a *cis*- geometry at C1 and C2. The factor which produced this stereoselectivity is unknown. Finally, Pummerer type elimination of the sulfoxide chiral auxiliary yielded (-)-podophyllotoxin (**15**).

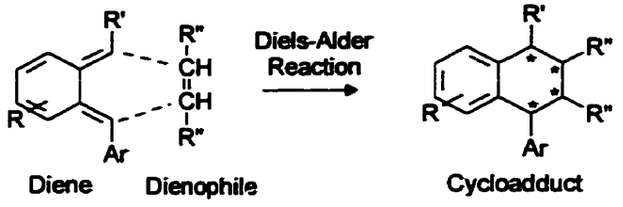


Scheme 1.82

1.4.4 Asymmetric Synthesis of Lignans via Diels-Alder Reactions

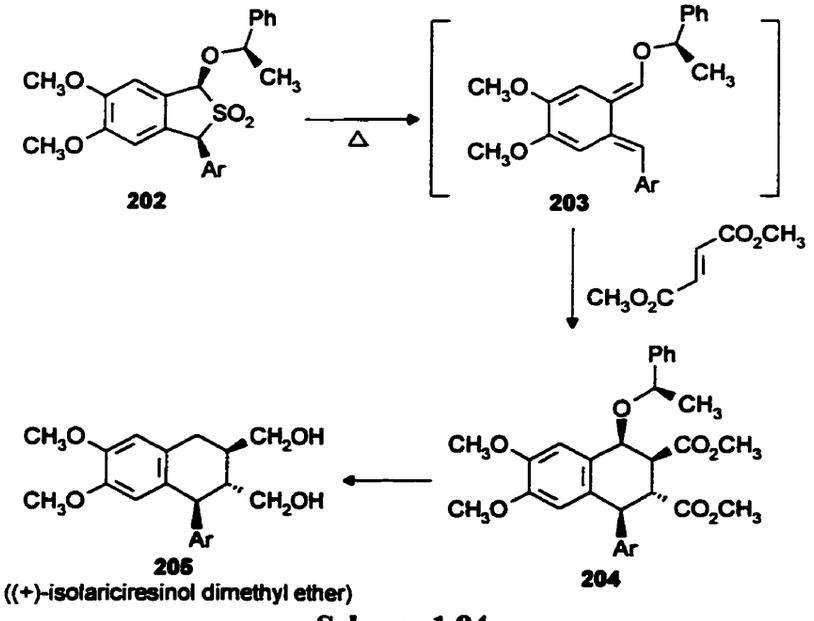
Asymmetric Diels-Alder reactions represent one of the most efficient approaches to the construction of aryltetralin units. In this method, up to four new chiral centers can

be generated simultaneously as shown in Scheme 1.83. The dienes employed in this asymmetric approach are typically *o*-QDMs and *o*-quinonoid pyrones, whereas the commonly used dienophiles are the fumarates, maleates, and butenolides.



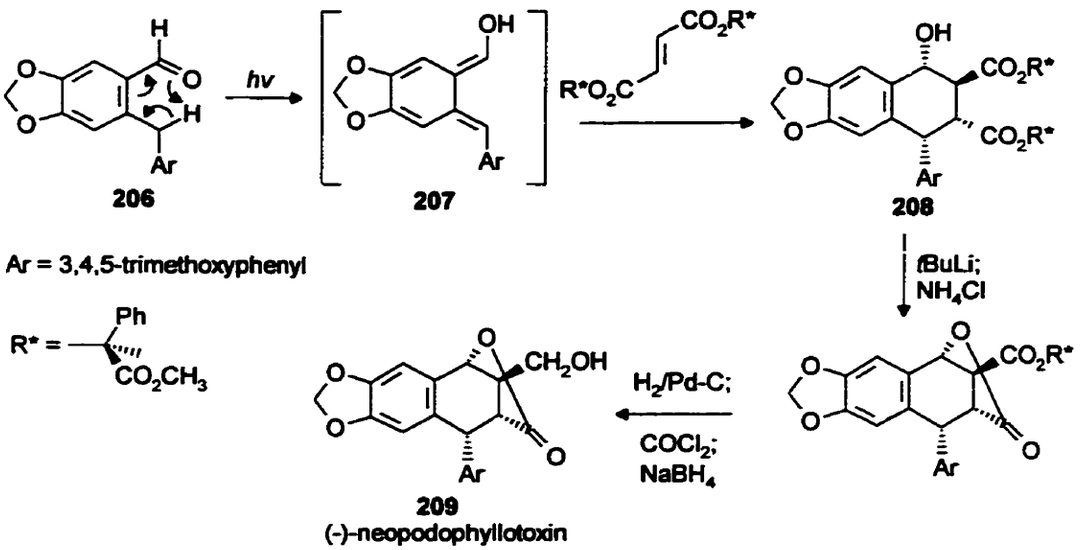
Scheme 1.83

Asymmetric Diels-Alder reactions in the synthesis of aryltertralin lignans have been extensively studied by Charlton *et al.*.[93] At the outset of their study,[93a] a homochiral *o*-QDM **203** generated from sulfone **202** in refluxing benzene was found to react with dimethyl fumarate to give a mixture of two diastereomers, with **204** given in Scheme 1.84 being predominant. The removal of the chiral auxiliary by hydrogenolysis followed by ester reduction with $LiAlH_4$ afforded (+)-isolariciresinol dimethyl ether (**205**).



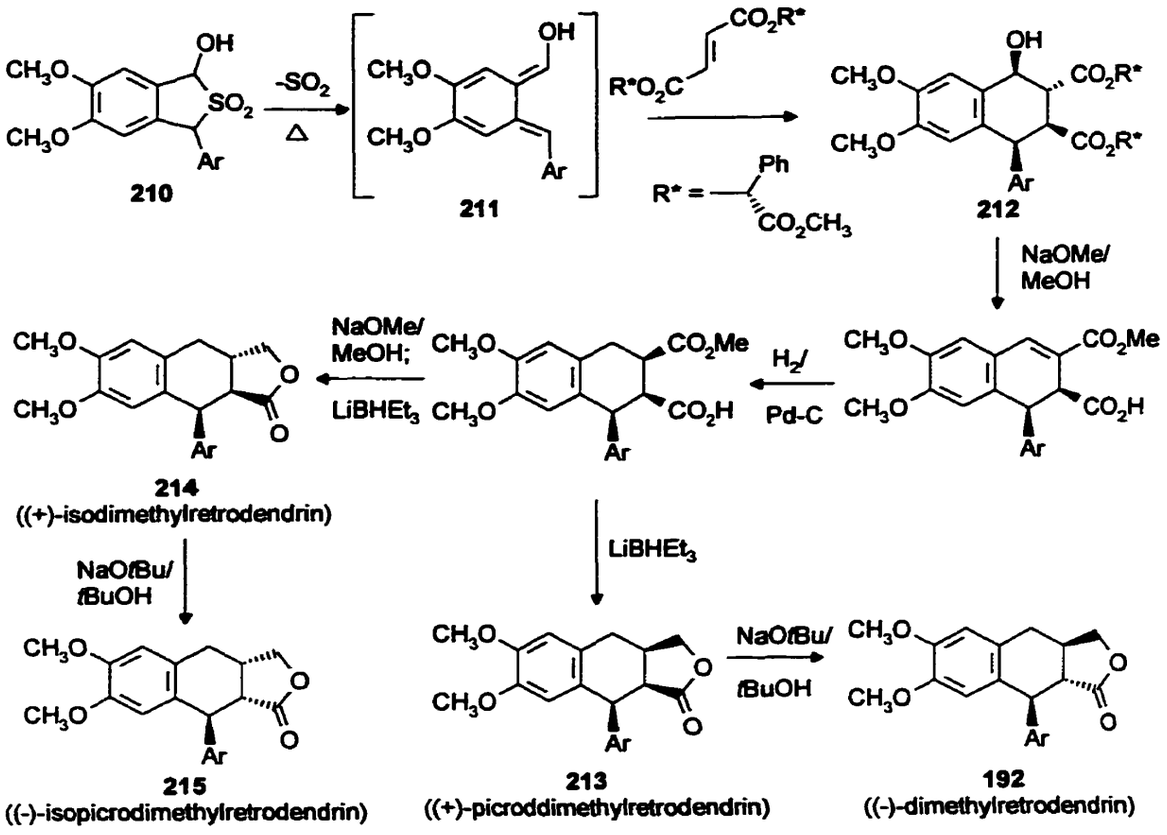
Scheme 1.84

Later, a chiral dienophile instead of a chiral diene was used by the Charlton's group to affect asymmetric induction during Diels-Alder reactions.[93b] *o*-QDM **207** generated photochemically from aldehyde **206** reacted with the fumarate of methyl (*S*)-mandelate to afford a mixture of two diastereomers, of which **208** shown in Scheme 1.85 was predominant. Subsequent transformations afforded (-)-neopodophyllotoxin (**209**) in 97% optical purity.



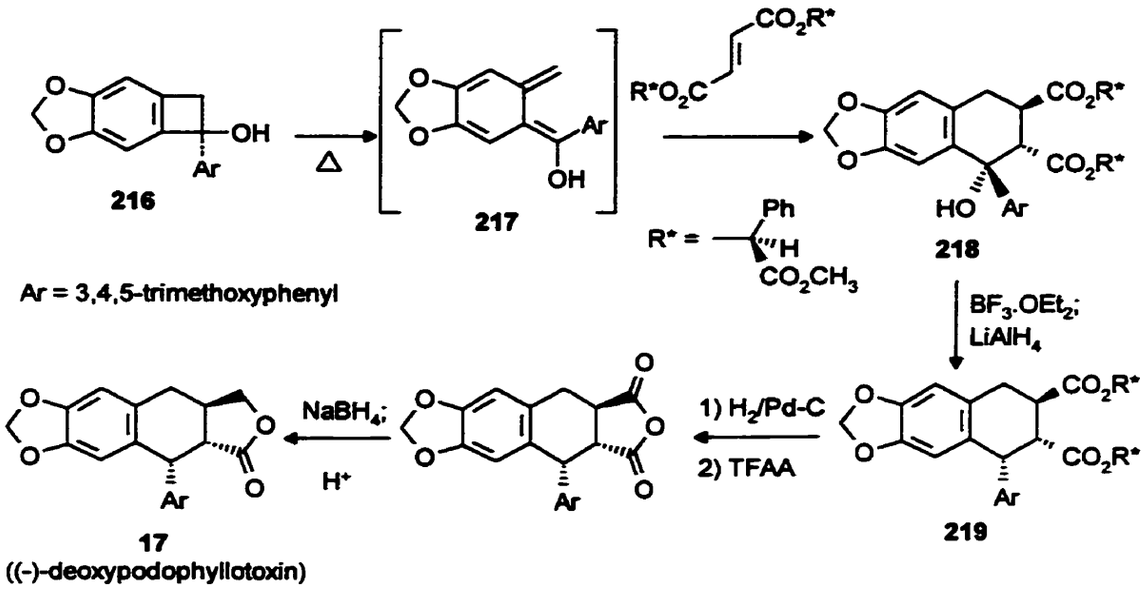
Scheme 1.85

The isomerization of fumarate to maleate during the photolysis of aldehyde **206** limited the yield of cycloadduct **208**. In order to avoid isomerization of fumarate to maleate, thermal generation of the *o*-QDM was attempted.[93c] *o*-QDM **211**, generated by thermolysis of sulfone **210** in refluxing toluene, was trapped with the fumarate of methyl (*R*)-mandelate to afford predominantly cycloadduct **212**. Using the reaction sequence depicted in Scheme 1.86, including some interesting epimerization reactions, (-)-dimethylretrodendrin (**192**) and three of its derivatives, **213-215**, were prepared.



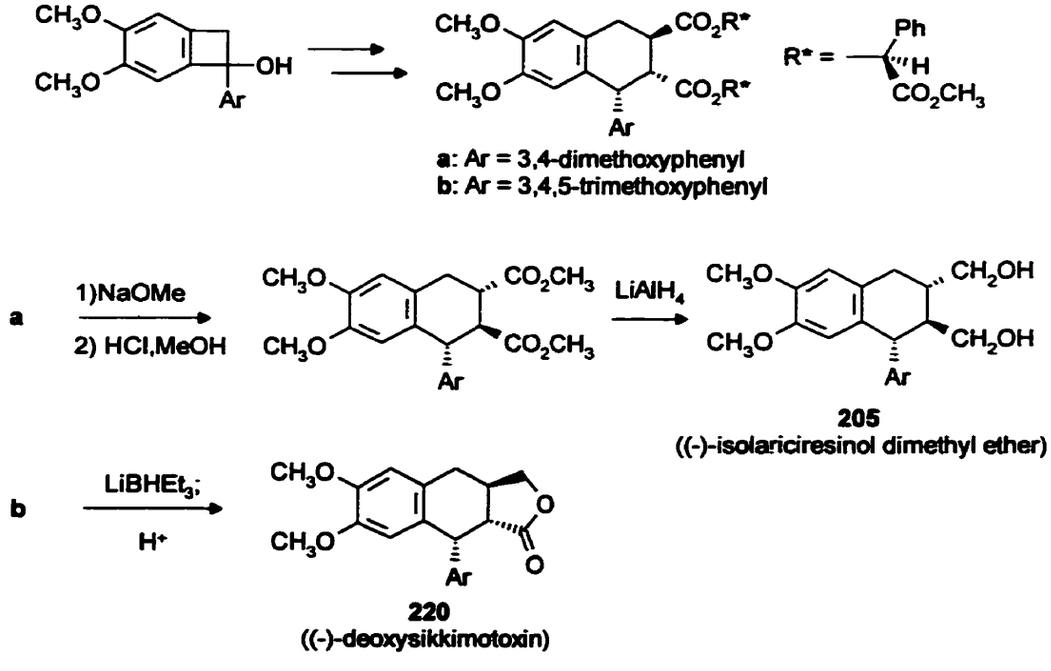
Scheme 1.86

The asymmetric Diels-Alder reaction approach was recently extended to the preparation of (-)-deoxypodophyllotoxin (**17**).[93d] *o*-QDM **217** was generated by thermally inducing ring opening of benzocyclobutenol **216**, and then trapped with the fumarate of methyl (*R*)-mandelate to give **218** as a major cycloadduct (Scheme 1.87). An interesting dehydroxylation of **218** was achieved with inversion of stereochemistry at the dibenzylic center, affording **219** as the major diastereomer. Subsequent hydrogenolysis, anhydride formation, reduction, and lactonization gave (-)-deoxypodophyllotoxin (**17**) in 30% yield from cycloadduct **218**.



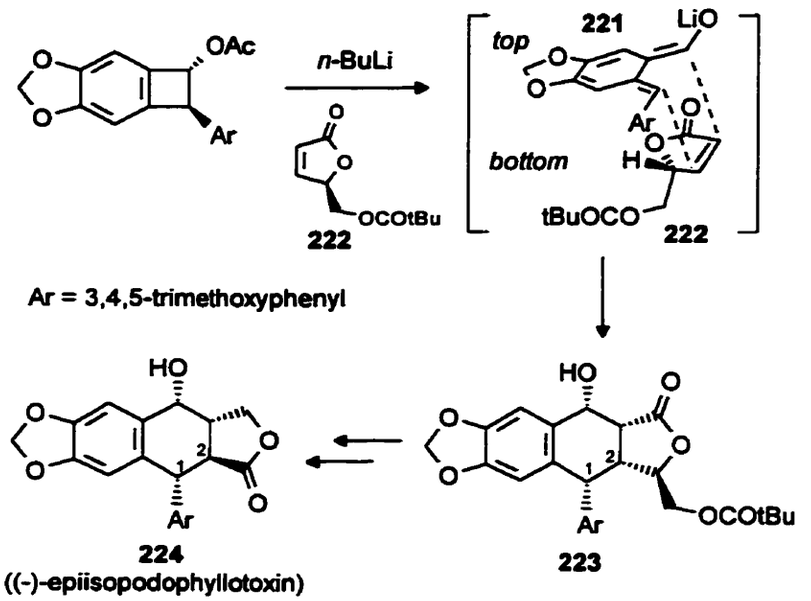
Scheme 1.87

This cycloaddition reaction was later applied to the synthesis of (-)-isolariciresinol dimethyl ether (**205**) and (-)-deoxysikkimotoxin (**220**) as shown in Scheme 1.88.[93e]



Scheme 1.88

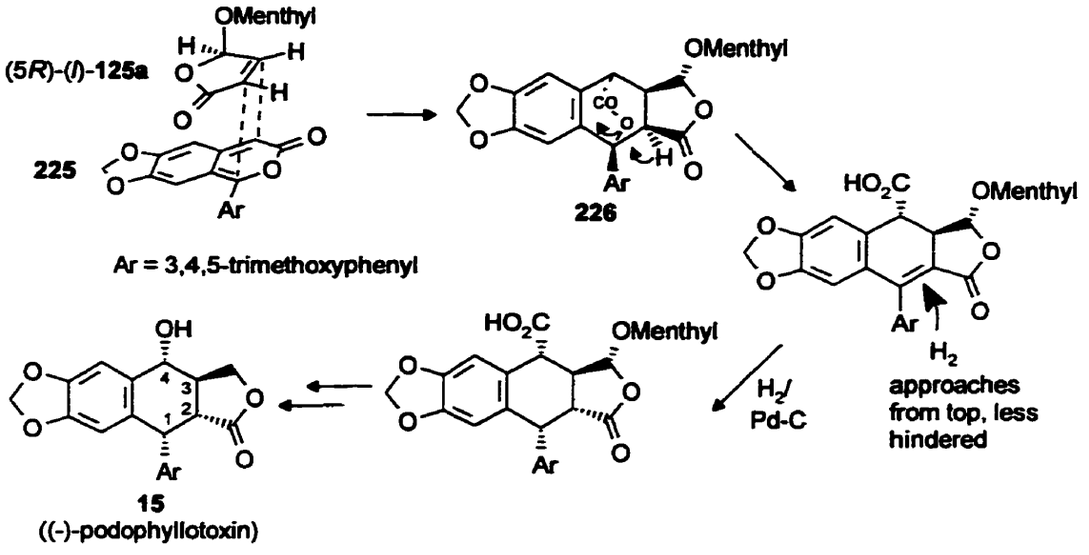
In addition to Charlton's group, Choy *et al.*[94] have also utilized the versatile cycloaddition approach to construct the aryltetralin skeleton, as illustrated in Scheme 1.89. Anionic Diels-Alder reaction of *o*-QDM **221** and optically active butenolide **222** proceeded with high diastereoselectivity through *endo* addition, giving the cycloadduct **223** with all *cis*-geometry. Subsequent reactions, including removal of chiral auxiliary and epimerization at C2, led to the formation of (-)-epiisopodophyllotoxin (**224**).



Scheme 1.89

Analogous to *o*-QDMs, *o*-quinonoid pyrones has also been applied as dienes in asymmetric Diels-Alder reactions with homochiral butenolides.[95] The orientation of the diene **225** and dienophile (5*R*)-(*l*)-**125a** is as proposed in Scheme 1.90. An all *cis*-cycloadduct (**226**) was formed predominantly. Elimination followed by hydrogenation gave the correct stereogenic centers for (-)-podophyllotoxin at C1 and C2. Subsequent

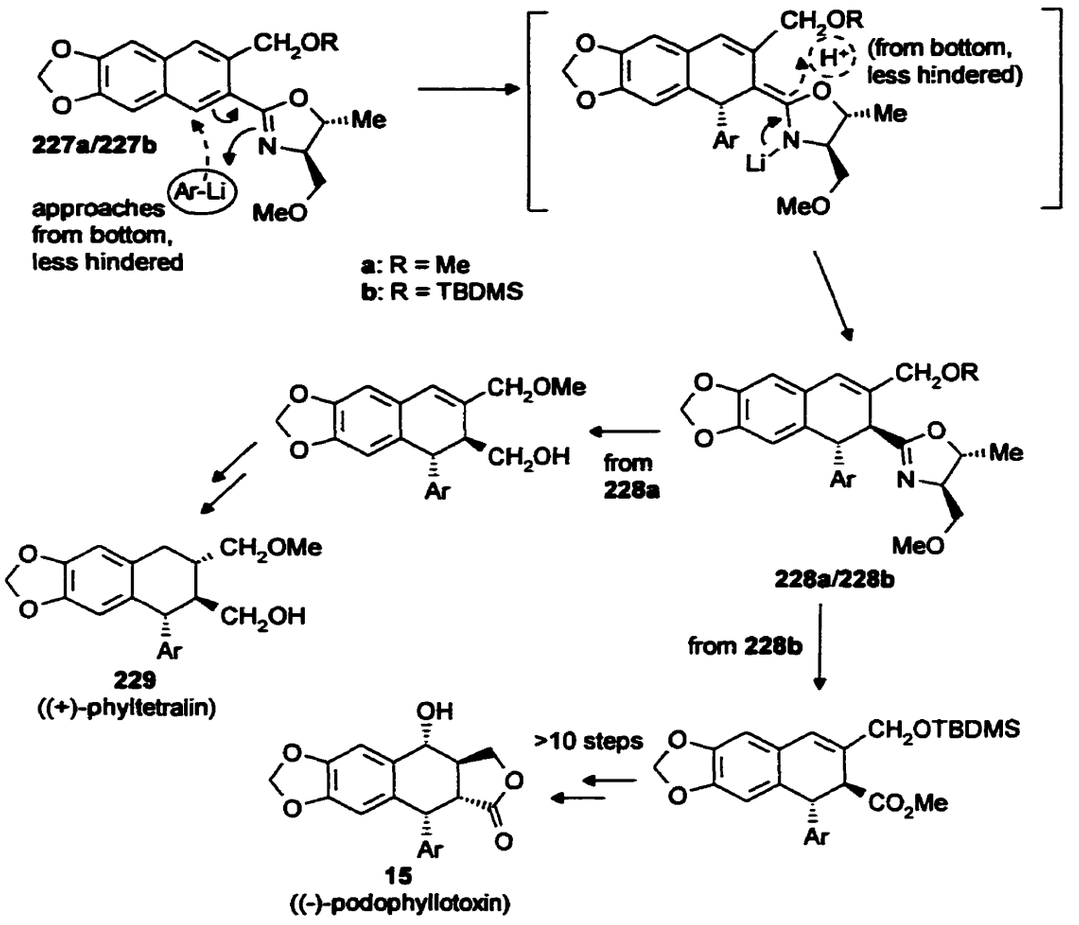
reactions including removal of chiral auxiliary and oxidation at C4 gave (-)-podophyllotoxin (**15**).



Scheme 1.90

1.4.5 Asymmetric Synthesis of Lignans via Other Approaches

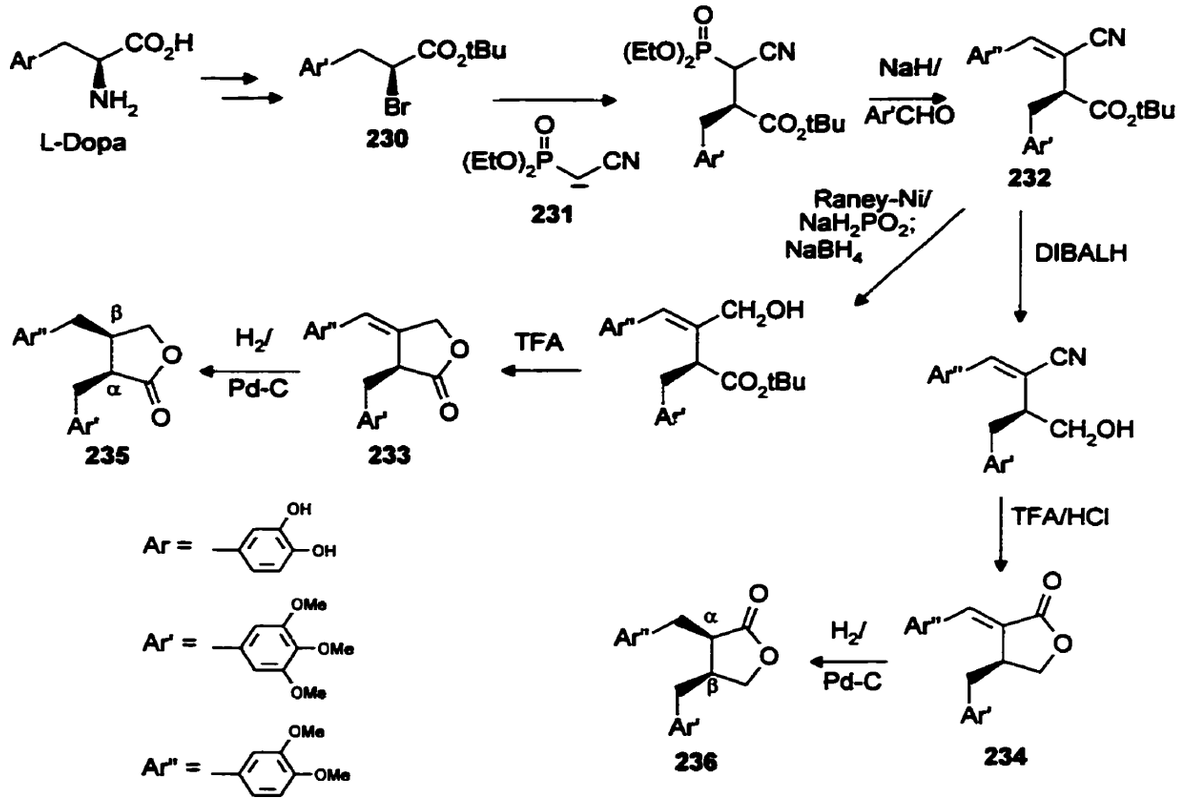
Asymmetric synthesis of lignans through approaches other than the use of benzylbutyrolactones as intermediates, tandem conjugate addition reactions, or Diels-Alder reactions will be included here. The first example is an approach described by Meyers *et al.* in which oxazolines were used as chiral auxiliaries (see Scheme 1.91).[69] The addition of an aryl anion to the chiral naphthalenic oxazoline **227a/227b** and subsequent protonation occurred with high diastereoselectivity to afford diastereomer **228a/228b**. Further reactions of cycloadducts **228a** and **228b** gave (+)-phyltetralin (**229**) and (-)-podophyllotoxin (**15**), respectively. The procedure was exceedingly lengthy and the overall yield was low.



Scheme 1.91

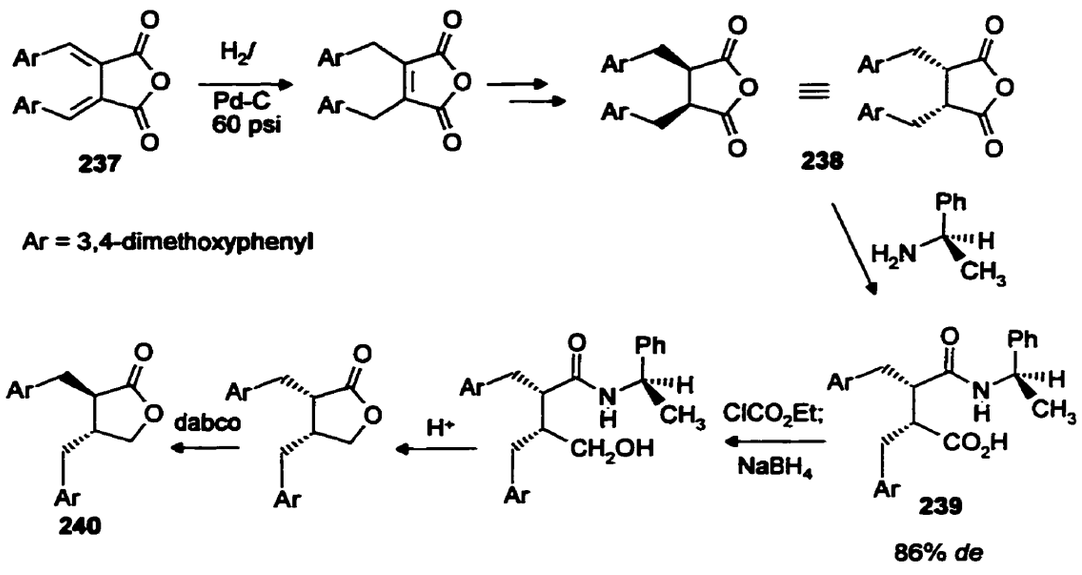
Dibenzylbutyrolactone lignans, synthesized using the asymmetric synthetic approaches described previously in this introduction, often possess the *trans*-geometry at C_α and C_β. Suarez *et al.* have made use of an amino acid, L-dopa, as a chiral starting material to prepare dibenzylbutyrolactone lignans which possess a *cis*-geometry at C_α and C_β instead.[96] The method is outlined in Scheme 1.92. Alkylation of bromo ester **230** with a phosphonate carbanion **231** followed by condensation with a benzaldehyde afforded the key intermediate **232**. Subsequent selective reduction of the nitrile group or the *t*-butyl ester in **232** accompanied by lactonization gave two positionally isomeric

lactones **233** and **234**. Catalytic hydrogenation of these resulted in the formation of dibenzylbutyrolactone lignans (**235** and **236**) possessing a *cis*-geometry at C_α and C_β.



Scheme 1.92

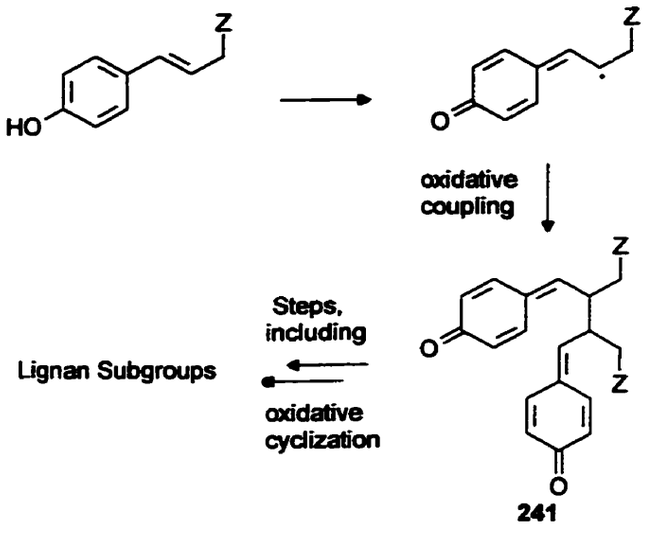
The final example of the asymmetric synthesis of a lignan is the approach recently reported by Ward *et al.* in which a *meso* anhydride was used as a key intermediate (Scheme 1.93).[97] A symmetrical Stobbe condensation product **237** was transformed into a *meso* anhydride **238** which was then reacted with (+)-α-methylbenzylamine diastereoselectively to give acid amide **239** in 86% *de*. Reduction of the carboxylic group, lactonization, and epimerization afforded enantiomerically enriched lignan lactone **240**.



Scheme 1.93

1.5 INTRAMOLECULAR OXIDATIVE CYCLIZATION REACTIONS IN THE SYNTHESIS OF LIGNANS

Biosynthesis of lignans have been recognized to occur through the oxidative coupling of phenolic phenylpropanoids as shown in Scheme 1.94.[9-11] The resulting phenylpropanoid bis-(quinone methides) **241** are believed to undergo further reactions including intramolecular oxidative cyclization, giving rise to cyclolignans such as aryltetralins (**8**), furofurans (**6**), and dibenzocyclooctadienes (**10**).



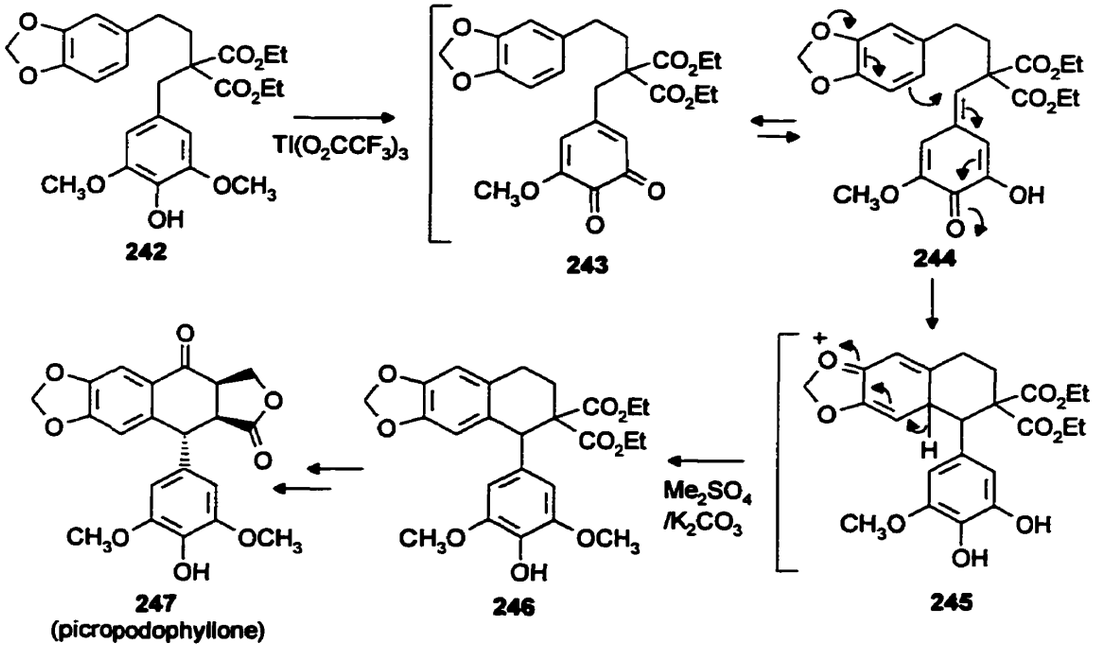
Scheme 1.94

The recognition of this fact has stimulated a considerable amount of work directed toward the biomimetic syntheses of lignans.

The use of dibenzylbutane derivatives as biosynthetic precursor to cyclolignans is of particular interest here due to related work that will be described later in this thesis. The literature reports on the biomimetic synthesis of cyclolignans based on the intramolecular oxidative cyclization of dibenzylbutane derivatives will be briefly discussed in this section.

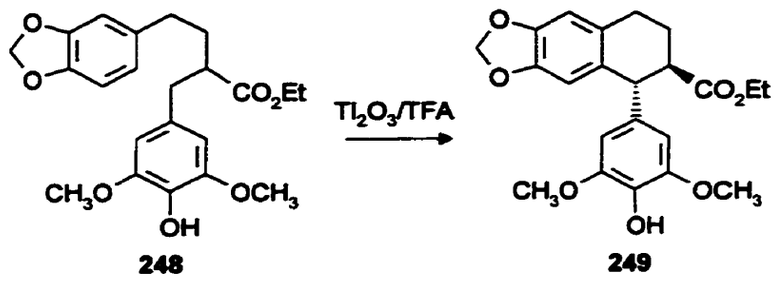
Dibenzylbutane derivatives used in oxidative cyclization reactions can be generally categorized into two groups, the phenolics and the non-phenolics (*i.e.* the phenol-ethers). The oxidative cyclization of the former group has always been reported to be less successful than the latter, as the formation of intractable product mixtures is often encountered. Only a few examples of the successful cyclization of members of the former group were available.

Kende *et al.* have carried out a biomimetic synthesis of an aryltetralin lignan by oxidatively cyclizing a phenolic diarylbutane.[98] The reaction and the proposed mechanism are depicted in Scheme 1.95. Diarylbutane **242** when treated with thallium(III) trifluoroacetate followed by methylation with $MeSO_4/K_2CO_3$ afforded cyclization product **246** in 55% yield. It was proposed that diarylbutane **242** underwent oxidative demethylation to uncyclized *o*-quinone **243** which was in equilibrium with the quinone methide **244**. Subsequent cyclization of the quinone methide intermediate **244** gave **245**, and methylation of which afforded **246**. Further transformation of **246** over several steps gave (±)-picropodophyllone (**247**).



Scheme 1.95

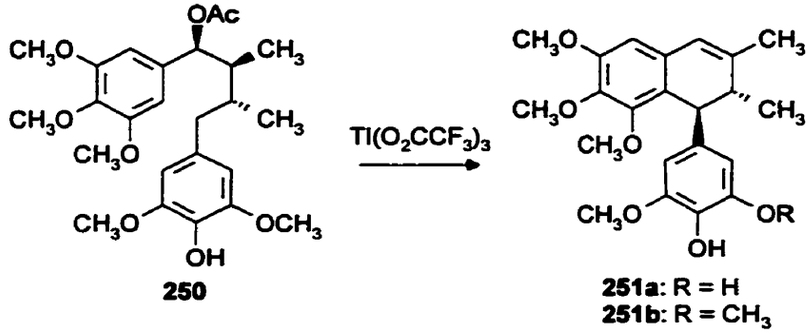
The next similar example is reported by Burden *et al.*,[99] who cyclized diarylbutane **248** to **249** (65% yield) in the presence of thallium(III) oxide/TFA (Scheme 1.96).



248 **249**

Scheme 1.96

The third example is the cyclization of dibenzylbutane **250** to dehydroaryltetralins **251a** (minor) and **251b** (major) using thallium(III) trifluoroacetate as oxidant (Scheme 1.97).[100] This oxidative cyclization mechanism is similar to that reported by Kende (see above).

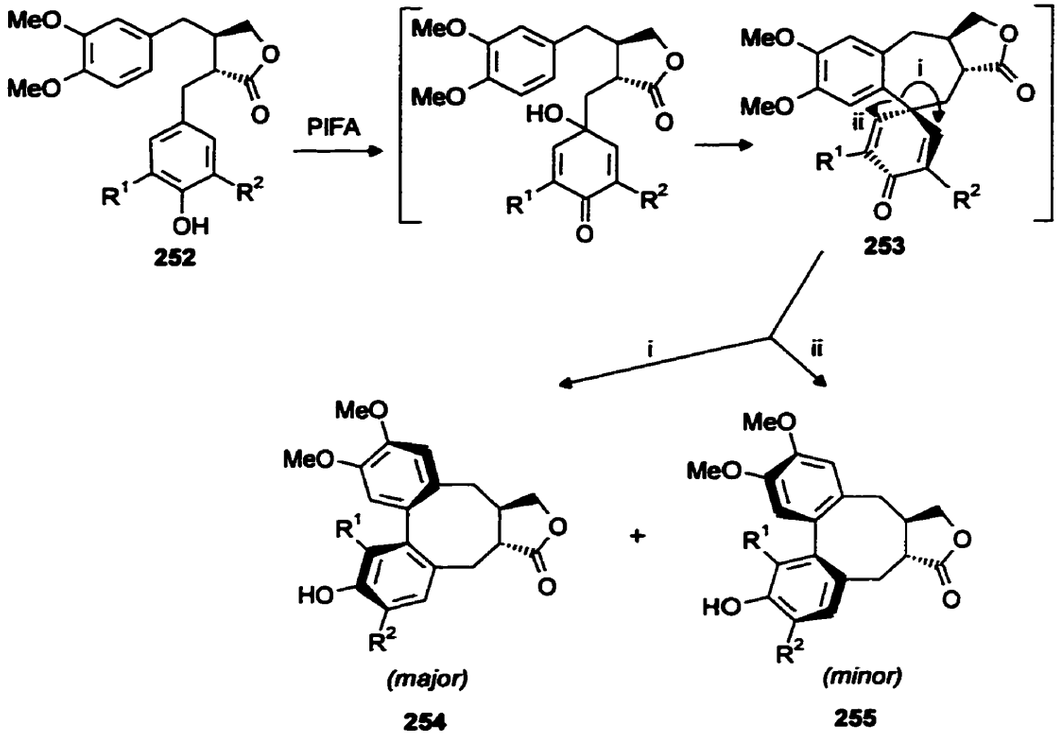


250

251a: R = H
251b: R = CH_3

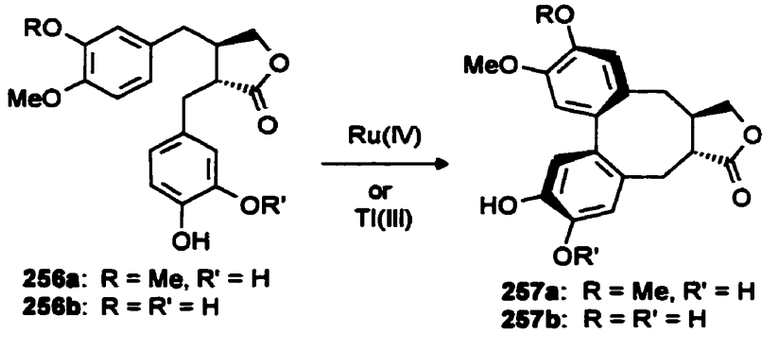
Scheme 1.97

Some phenolic dibenzylbutane derivatives undergo oxidative cyclization to dibenzocyclooctadienes instead of aryltetralins. Pelter *et al.*[101] have reported a successful oxidative cyclization of a monophenolic dibenzylbutyrolactone (**252**) using phenyliodonium bis(trifluoroacetate) (PIFA) as oxidant (Scheme 1.98). The procedure afforded a mixture of dibenzocyclooctadiene diastereomers **254** (major) and **255** (minor) in good yield. It was proposed that the aryl group of spirodienone intermediate **253** preferentially migrated to the top of the cyclohexadienone ring to yield **254** as major product.



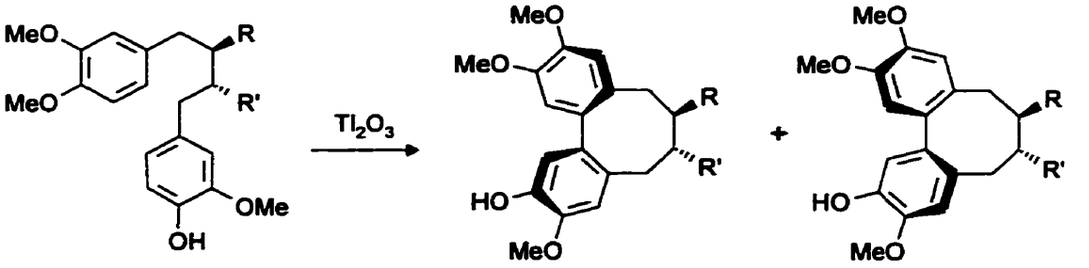
Scheme 1.98

In addition to Pelter's work, Robin *et al.* have also successfully cyclized monophenolic (**256a**) and diphenolic dibenzylbutyrolactones (**256b**) to the corresponding benzocyclooctadienes, **257a** and **257b**, respectively (Scheme 1.99).[102] Interestingly, only one diastereomer was obtained, unlike the result reported by Pelter *et al.*.



Scheme 1.99

Burden *et al.*[99] have also reported a similar reaction of dibenzylfuran **258a** and dibenzylbutane diacetate **258b** using thallium(III) oxide as oxidant. Both compounds were oxidized to mixtures of two diastereomers **259** and **260** (Scheme 1.100), as in the examples provided by Pelter *et al.*.



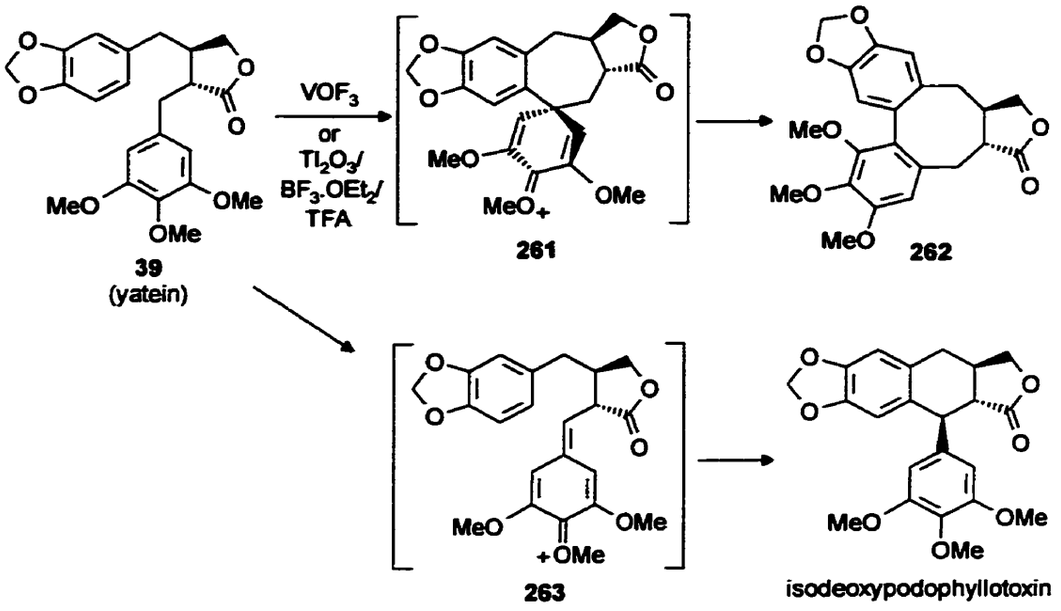
258a: R+R' = -CH_2OCH_2-
258b: R = R' = CH_2OAc

259a: R+R' = -CH_2OCH_2-
259b: R = R' = CH_2OAc

260a: R+R' = -CH_2OCH_2-
260b: R = R' = CH_2OAc

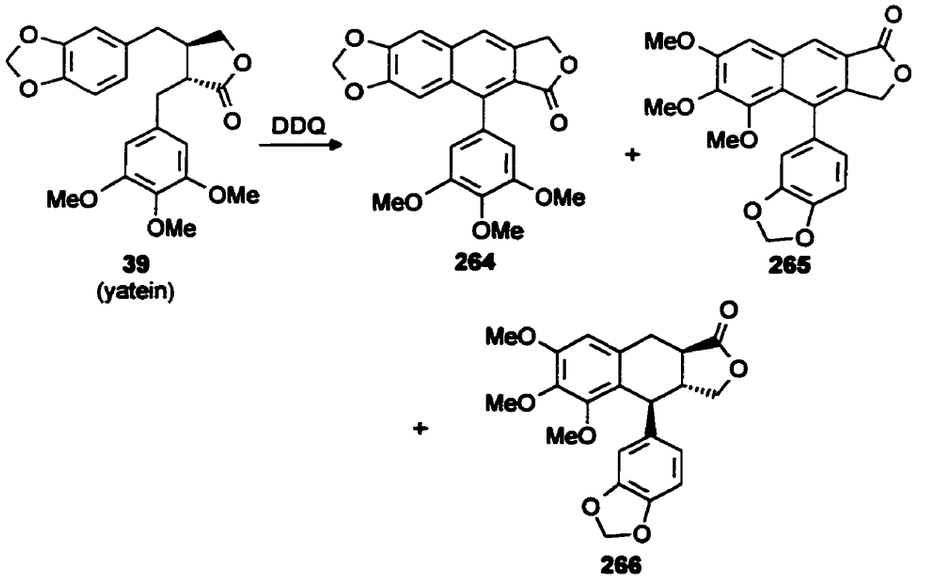
Scheme 1.100

Oxidative cyclization of non-phenolic dibenzylbutane derivatives are very frequently reported and often give good yields of cyclized products. The literature reports on the cyclization of this group of compounds will not be detailed here. However, a particularly interesting example, dibenzylbutyrolactone lignan yatein, will be discussed due to the relevance to the work to be described later (*i.e.* 4'-demethylyatein, see the end of this discussion). Schlessinger *et al.*[103] and Cambie *et al.*[104] have separately shown that (±)-yatein reacted smoothly with vanadium oxytrifluoride or $Tl_2O_3/BF_3{\cdot}OEt_2$/TFA to give dibenzocyclooctadiene diastereomers **262**, presumably via the spirodienone intermediate **261** (Scheme 1.101) (also see **253** in Scheme 1.98, example by Pelter *et al.* described above). Cambie *et al.*[104] have also shown that treating (±)-yatein with Tl_2O_3/ /TFA in the absence of $BF_3{\cdot}OEt_2$ resulted in the formation of an aryltetralin lignan, (±)-isodeoxypodophyllotoxin, via quinone methide **263** (Scheme 1.101).



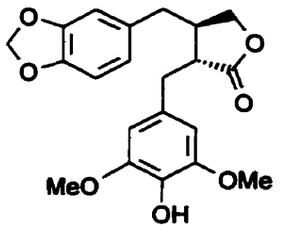
Scheme 1.101

In addition to using inorganic oxidants, organic oxidants such as DDQ have also been able to affect cyclization of yatein.[105] However, this reaction appeared nonselective, leading to a mixture of three products, arylnaphthalenes **264** and **265**, and aryltetralin **266** (Scheme 1.102).



Scheme 1.102

Despite these precedents, attempts to cyclize monophenolic form of yatein, *i.e.* 4'-demethylyatein (structure see Scheme 1.103) under conditions where inorganic oxidants were employed were totally unsuccessful, leading to only intractable products.[99] A reexamination of the oxidation of this compound using DDQ as oxidant was undertaken and will be discussed in detailed in Section 4.3.2.



4'-demethylyatein

Scheme 1.103

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CHAPTER 2

HINDERED ROTATION AND ATROPISOMERISM

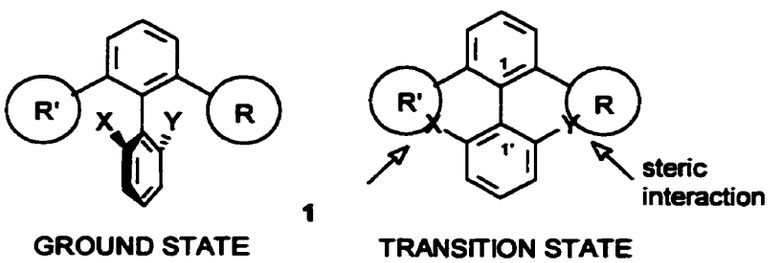
2.1 ATROPISOMERISM

The term atropisomerism was introduced by Kuhn in 1933 to describe molecules that are chiral solely due to hindered rotation about a carbon-carbon single bond in the molecule.[1] These molecules can exist in two enantiomeric forms, that are actually conformational rotamers. In order to differentiate atropisomers from classical conformational isomers, the term atropisomerism has been restricted to those cases in which individual isomers can be isolated. However, the definition of atropisomerism remained ambiguous because the isolation temperature of the conformers was not clearly defined. More recently, Oki has arbitrarily defined the condition for the existence of atropisomerism as one in which the conformers are isolable at room temperature and have a half-life of at least 1000 seconds.[2] Nevertheless, many authors still accept the term atropisomer for conformers isolable at any technically achievable temperature.

If a molecule exhibiting atropisomerism also bears other classical stereogenic centers (stereogenic tetravalent atoms), then the two rotamers will be diastereomers, rather than enantiomers. Although Kuhn's original definition did not explicitly include such cases, the term atropisomerism is currently used for cases in which the chiral rotamers are either enantiomeric or diastereomeric.

The magnitude of the rotational hindrance about a carbon-carbon single bond in a molecule is determined by a combination of steric, coulombic, and stereoelectronic

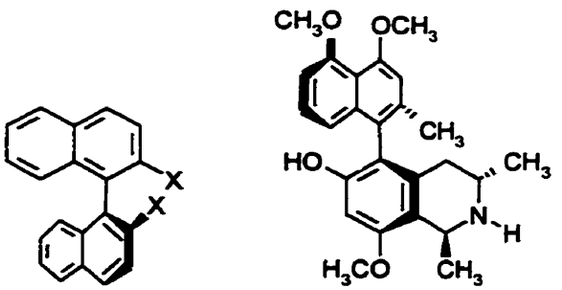
effects. In some cases, steric effects play the only role in determining the barrier to rotation. This is especially true for chiral biphenyl derivatives **1**, a class of compounds for which the term atropisomerism was originally coined (see Scheme 2.1).[1] In these compounds, increasing the bulkiness of an *ortho*-substituent, R or R', does not increase the steric interaction in the ground state of the biphenyls because the planes of the two benzene rings are almost mutually orthogonal in the ground state. However, increasing the bulkiness of the substituents greatly increases the steric interactions in the planar conformation of the molecule. This conformation corresponds to the transition state for rotation from one chiral form to the other, and sterically bulky *ortho*-substituents raises the barrier to the interconversion of the rotamers.



Scheme 2.1

Isolation of atropisomers at room temperature requires that the molecules possess a relatively high barrier to rotation, *i.e.* a minimum of *ca.* 22 kcal/mol, or a half-life of at least 16 min at room temperature.[3] Compounds with barriers to rotation greater than *ca.* 22 kcal/mol could be easily separated chromatographically or by co-crystallization with a chiral reagent. These stable atropisomers constitute attractive synthetic goals because they could be used as chiral reagents in asymmetric organic synthesis. Common examples of these stable atropisomers are the binaphthyl derivatives **2** (see Scheme 2.2),

which are widely employed as chiral ligands in metal-catalyzed asymmetric organic reactions.[4] From the biological point of view, stable atropisomers might exhibit different pharmacological properties. A known example of this is ancistrocladine (**3**) (see Scheme 2.2), where only the (-)-enantiomer is naturally occurring and possesses biological activity (more examples will be given in Section 2.4).[5]



2 **3**
((-)-Ancistrocladine)

Scheme 2.2

Separation of atropisomers with rotational energy barriers lower than 22.3 kcal/mol can be carried out only at temperatures below room temperature. Since these atropisomers are conformationally unstable at room temperature, their isolation is of interest only for the study of their stereodynamic properties.

It is obvious that before the separation of atropisomers can be carried out, the rotational energy barrier of the compound in question must be determined or estimated so that one would know the required temperature for the separation. The rotational energy barrier between atropisomers are usually measured using NMR techniques, or estimated from molecular orbital calculations. The measured rotational energy barrier of some atropisomers can also be reconfirmed using dynamic chromatographic techniques. The measurement of rotational energy barriers will be discussed in the following section.

2.2 MEASUREMENT OF ROTATIONAL ENERGY BARRIERS

The type of technique used in the investigation of rotation about a single bond depends on the rate of the rotation.[2] For small molecules which possess rapid internal rotations (energy barrier < 5 kcal/mol), high frequency spectroscopies such as vibrational, microwave, and far-infrared spectroscopies are used for the investigation. For atropisomers (*i.e.* isolable conformers possessing slow internal rotation), the methods of choice for investigating internal rotation is NMR spectroscopy because the time scale of the NMR technique is large enough to detect the slow internal rotation in atropisomers (energy barriers between 5 - 25 kcal/mol). However, barriers to rotation in more stable atropisomers such as the binaphthyl derivatives (energy barrier > 25 kcal/mol) cannot be determined using NMR techniques because NMR spectroscopy is able to detect only higher rotational frequencies (typically between 10^{-1} to 10^{5} Hz).[3] These frequencies are much higher than the rate of internal rotation of stable atropisomers ($k < 10^{-5}$ Hz). The details of the NMR technique employed in the determination of rotational energy barrier will be disclosed in Section 2.2.1.

Hindered rotation in stable atropisomers is, at present, best studied using dynamic chromatographic techniques.[3] Dynamic chromatographic techniques can also be used to study atropisomers that are unstable at room temperature as long as the separation temperatures are kept low. A detailed discussion of dynamic chromatography in determination of rotational energy barriers will be presented in Section 2.2.2.

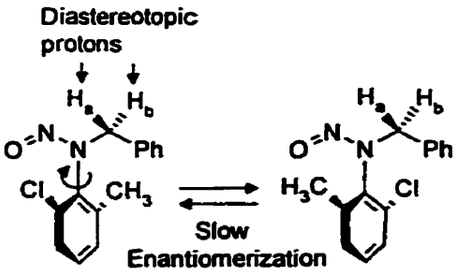
2.2.1 Dynamic Nuclear Magnetic Resonance Spectroscopy

Dynamic nuclear magnetic resonance (dynamic NMR) deals with changes in NMR spectra that are associated with chemical exchange processes.[6] Exchange processes can be studied as a function of external variables such as temperature (mostly used), pH, and magnetic fields. There are two types of chemical exchange processes amenable to a dynamic NMR investigation. The first of these includes the intramolecular exchange processes that include conformational interconversions such as rotational isomerizations, atomic inversions, ring reversals and valence isomerizations. The second includes intermolecular exchange processes such as protons, ligands and ions migrating between molecules of the same or different kinds. The changes in NMR spectra caused by the chemical exchange processes are due to the fact that the nuclei being observed by NMR are rapidly alternating between two (or more) environments or sites where the chemical shifts of the nuclei, or the coupling constants to the nuclei, are different. By studying these changes in the dynamic NMR spectra, quantitative data about rate constants (in the range of 10^{-1} to 10^{5} or 10^{6} s^{-1}) of dynamic processes such as conformational interconversions can be obtained.[6a] In addition, dynamic NMR studies also provide direct information about the parts of the molecule affected by the exchange processes.

In order to detect if a compound exists as a mixture of atropisomers at a given temperature, its NMR spectrum is acquired at that temperature and examined. Doubling or broadening of peaks is often a sign of a slow dynamic exchange process. If one observes anomalies in an NMR spectrum at a given temperature, then the operating temperature of the spectrometer should be gradually raised in order to observe the effect

of temperature change on the anomaly. Further peak broadening, peak merging or peak coalescence is often observed. In contrast, if one does not observe any anomaly in the NMR spectrum obtained at a given temperature, then the NMR operating temperature can be decreased below that temperature until anomalies such as unusual peak splitting and/or resolution (decoalescence) is observed. Ordinary NMR spectrometers are designed for operation between -100 and +200 °C.[3] Compounds which do not show any change in their NMR spectra beyond these temperature limits cannot be studied by dynamic NMR. The types of anomaly that one observes in NMR spectra of compounds undergoing slow internal rotation will be given below. Following that will be a discussion of how one studies the changes in NMR spectra to extract thermodynamic data about an exchange process.

There are three situations in which it is possible to detect interconversion of atropisomers by using NMR spectroscopy. The first case is for compounds that lack a stereogenic center (other than the one generated by the hindered internal rotation), but carry a pair of nuclei that are diastereotopic due to the chirality generated by the slow internal rotation. If the diastereotopic nature of such nuclei is maintained on the NMR time scale, the nuclei are detected as distinct entities. Let us look at a simple example, N-benzyl-2-chloro-6-methyl-N-nitrosoaniline (**4**), shown in Scheme 2.3.[6b]



4

Scheme 2.3

This compound becomes a mixture of enantiomers if rotation about the N-C_{Ar} bond is slow. As a result, the prochiral methylene protons (H_a and H_b) in the benzyl groups are ***diastereotopic*** to each other at slow rotation, and appear as two signals (an AB pattern) in the ^{1}H-NMR spectrum. These two signals broaden as the experimental temperature is raised, and eventually coalesce into one broad signal which sharpens at still higher temperatures. An example of the coalescence of an AB pattern is illustrated in Figure 2.1.

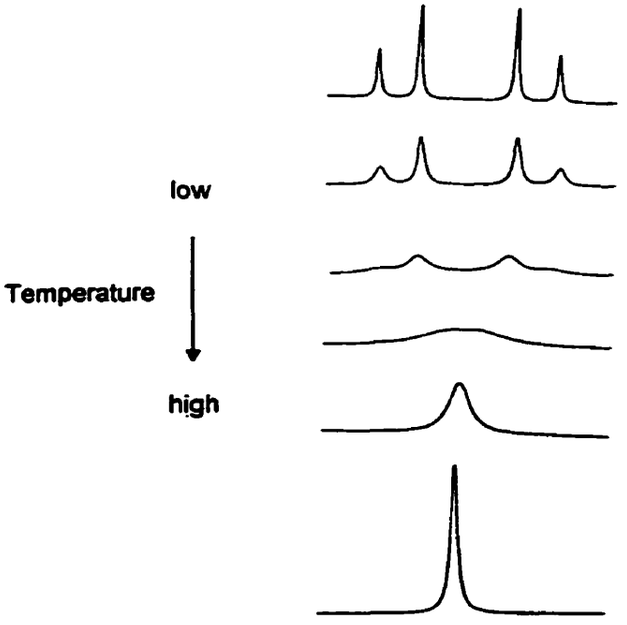
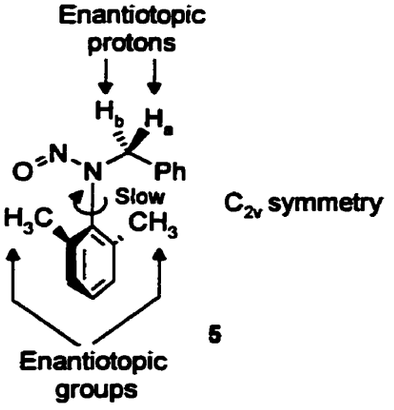


Figure 2.1. Coalescence of AB signal as temperature increases (figure taken from reference 6).

The occurrence of peak broadening and coalescence as temperature increases is due to the increase in the rate of rotation about the N-C_{Ar} bond, which averages the environment of the two methylene protons and thereby causes the eventual loss of their diastereotopic nature. In other words, at fast rotation, the methylene protons become ***enantiotopic*** and indistinguishable by NMR spectroscopy.

The second case in which the detection of atropisomerism using NMR spectroscopy is possible is for compounds that lack other stereogenic centers and ***do not*** carry diastereotopic protons. In this case the study of the atropisomerization processes requires the use of a ***chiral*** solvating agent so that the ***enantiotopic*** protons in the molecule will become ***diastereotopic*** in the newly created chiral environment.[3] A good example of this would be N-benzyl-2,6-dimethyl-N-nitrosoaniline (**5**) (see Scheme 2.4).

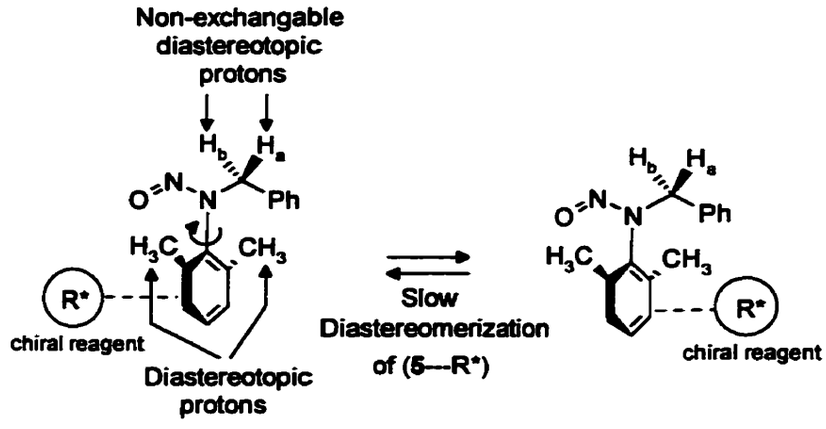


5

Scheme 2.4

The molecule maintains C_{2v} symmetry even when rotation about the N-C_{Ar} bond is slow. Consequently, the methylene protons in the benzyl group, as well as the methyl protons in the phenyl group, are enantiotopic (therefore, undetectable by NMR). One should also be aware that the enantiotopic methylene protons in aniline **5** are not interconverted by

the rotation about the N-C_{Ar} bond and thus cannot be used to monitor the exchange process even in a chiral environment. On the other hand, the enantiotopic methyl groups on the aromatic ring are exchanged by the rotation about the N-C_{Ar} bond. As a result, upon addition of a chiral solvating agent, the 2,6-dimethyl groups (which are now diastereotopic) can be used to study the exchange process (Scheme 2.5). The 2,6-dimethyl's protons will appear as two distinct singlets and coalescence of these two entities into one singlet will be expected at a higher temperature.



Scheme 2.5

The third case detectable by NMR is for compounds that already have one or more stereogenic centers. Slow rotation in this class of compounds will give rise to a mixture of two diastereomers, each with its own unique NMR spectrum. As temperature increases, these sets of signals coalesce into only one set which is a statistically weighted average of the signals from the two diastereomers.

The NMR spectra of atropisomers acquired over the temperature range in which peak broadening and coalescence occur are generally analyzed using complete bandshape analysis techniques.[6] The most widely used program for accomplishing complete

bandshape analysis, called DNMR3, was written by Binsch.[6c] This program allows simulation of simple and complex experimental bandshapes by means of formulae that include the rate constant of exchange. The analysis is performed on a high-speed computer, by taking into consideration a set of input parameters that includes a set of experimental constants directly extracted from the NMR spectra, and variables that change with temperature. The experimental constants are spectral frequency and width, type of exchange, coupling constants of exchanging signals, the populations of the exchanging species, and transverse relaxation times. Temperature sensitive variables are the chemical shifts which are extrapolated from experimental data, and rate constants. These two variables are manually adjusted until the outcomes of the bandshape analysis, *i.e.* the simulated spectra, visually match the experimental spectra. The theoretical calculations pertinent to the bandshape theories will not be discussed here. Interested readers are referred to dynamic NMR textbooks by Sandstrom,[6a] and Oki,[6b] or articles by Binsch.[6c,6d]

The complete bandshape analysis utilizes all the information contained in the bandshape and is therefore quite insensitive to measurement and systematic errors. As a consequence, the rate constants derived from a correctly performed analysis have relatively high accuracy, although the errors in k are normally higher at the extreme ends of the temperature range.

The rate constants at various temperatures obtained from the above simulations can be used to calculate the thermodynamic parameters, such as the free energy of activation ($\Delta G^{\ddagger}$), enthalpy of activation ($\Delta H^{\ddagger}$), and entropy of activation ($\Delta S^{\ddagger}$) for the

exchange process. The methods for the evaluation of activation parameters and the half-life of exchanging species will be presented in Section 2.3.

More stable atropisomers, with rotational energy barriers greater than 25 kcal/mol, will not show peak broadening or coalescence in the NMR spectra even at high temperatures. This is because the rate constant for exchange of the atropisomers is too low, even at high temperature, to cause peak broadening or coalescence on the NMR time scale. The determination of rotational energy barriers for slowly exchanging atropisomers requires the use of dynamic chromatographic techniques.

2.2.2 Dynamic Chromatographic Techniques

Dynamic chromatography is a technique by which slow chemical exchange processes can be detected due to the effects that these processes have on chromatographic elution profiles.[3,7] The changes in chromatograms (or elution profiles) are mainly due to competition between separation and interconversion of compounds on the chromatographic column. Normally, only processes which involve equilibration (exchange) between molecules having distinct chemical properties (structural isomers or diastereomers) can be studied. However, when the separation is performed on a chiral phase, processes which cause exchange between enantiomeric forms can also be examined.

The types of dynamic chromatographic techniques that can be employed in the study of hindered rotation and atropisomerism in organic molecules include dynamic high-performance liquid chromatography (dynamic HPLC), dynamic supercritical fluid

chromatography (dynamic SFC), dynamic gas chromatography (dynamic GC), and dynamic capillary electrophoresis (dynamic CE). The high speed of analysis and the broad range of operating temperatures (-90 to 250 °C) that these powerful techniques afford make the study of dynamic phenomena an easy task.[3]

Detection of atropisomers by dynamic chromatography is not as complicated as detection by dynamic NMR. If atropisomers have half-lives exceeding approximately 16 min at a particular temperature, then they are likely separable on a chromatographic column at that temperature. A chromatogram which shows well resolved peaks indicates that the chromatographic separation of atropisomers is faster than interconversion. At higher temperature where time for interconversion of the exchanging species is on the same order of magnitude as their average retention times in the chromatographic column, a chromatographic profile with an intermediate plateau between the resolved peaks will be observed. It follows that at a much higher temperature where atropisomerization is much more rapid than resolution, a single peak due to complete coalescence will be observed. A temperature-dependent elution profile is illustrated in Figure 2.2.[3]

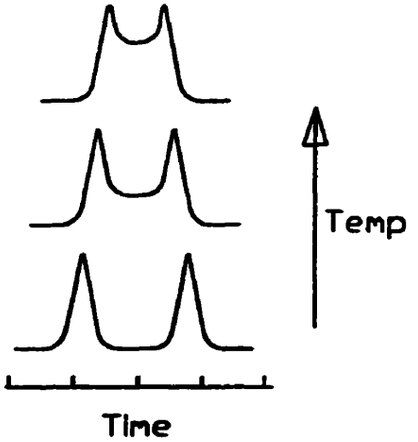


Figure 2.2. Temperature-dependent chromatographic elution profile.

The elution profiles of atropisomers acquired at variable temperatures are generally analyzed using a discontinuous plate mathematical model,[8] computed using the program "SIMUL", introduced by Jung,[9] on a high-speed computer. The input data are retention times, dead time, number of theoretical plates, and the rate constant as a variable parameter. The output of the analysis is a simulated chromatogram which can be matched to the experimental elution profile. The rate constants obtained from the dynamic chromatographic techniques are treated in the same way as those derived from dynamic NMR studies. They are used to derive $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the exchange processes (see Section 2.3 for evaluation of activation parameters). Peak form analysis in dynamic chromatography has produced values for energy barriers very close to those determined by the well-established dynamic NMR technique.

The attractive features of dynamic chromatography are numerous. They include the low amount of sample required, and the broad working temperature range (-80 to 120 °C for HPLC, SFC and CE, up to 200 °C for GC) which enables the study of exchange processes with barrier in the range of 17-30 kcal/mol for HPLC, SFC and CE, and 22-36 kcal/mol for GC. Accordingly, dynamic chromatography allows analysis of both stereolabile and stable atropisomers. In addition, this technique can also provide nearly pure atropisomers for further nonchromatographic investigations.

2.3 EVALUATION OF ACTIVATION PARAMETERS

The interconversion of atropisomers can be treated as an elementary reaction as shown below:

Scheme 2.6

If one can assume that the starting state is in equilibrium with the transition state then rate constants for the overall process can be calculated using ***transition-state theory***.[10] According to this theory, molecules in the transition state, which are at the point of maximum energy on a reaction path, "fall downhill" to products or back to the starting materials at the same rate (*i.e.* $k_{-1} = k_2$). The rate of the reaction then depends only on the equilibrium between the starting materials and the transition state. The Eyring equation, was derived to correlate the rate constant of the reaction shown in Scheme 2.6 with the free energy of activation at a given temperature:

$$k = \kappa \frac{k_B T}{h} e^{-\Delta G^{\ddagger}/RT} \tag{2.1}$$

(where k is rate constant (s^{-1}), κ is the transmission coefficient commonly assumed to be unity, k_B is the Boltzmann constant (3.29986×10^{-27} kcal K^{-1}), h is the Planck's constant (1.58369×10^{-37} kcal s), R is the universal gas constant (1.98719×10^{-3} kcal mol^{-1} K^{-1}), $\Delta G^{\ddagger}$ is the free energy of activation (in kcal mol^{-1}), and T is the temperature (in K)).

When only a single rate constant value at a particular temperature for an exchange process can be obtained, equation (2.2) which is derived from equation (2.1) is used to calculate $\Delta G^{\ddagger}$ at that temperature.

$$\Delta G^{\ddagger}_{\text{at } T} = RT\,[23.760 + \ln T - \ln k)] \tag{2.2}$$

It is somewhat difficult to assess the reliability of $\Delta G^{\ddagger}$ determined in this way because the measurement of the rate constant is performed at a single point, and no meaningful

standard deviation can be attached to the value. The usefulness of the $\Delta G^{\ddagger}$ value is also limited by the fact that its temperature dependence is not known.

If a set of rate constants can be obtained at different temperatures then one can extrapolate to find k and $\Delta G^{\ddagger}$ at ***any*** temperature using $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ determined from either equations (2.3) or (2.4). Substitution of (2.3) into (2.1) gives (2.4) from which both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can be determined by iterative non-linear least-squares fitting of the exponential curve.

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \tag{2.3}$$

$$k = \frac{k_B T}{h} e^{-\Delta H^{\ddagger}/RT} e^{\Delta S^{\ddagger}/R} \tag{2.4}$$

However, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can also be determined from the linear form of equation (2.4) (see equation (2.5)) by plotting $\ln(k/T)$ against $1/T$.

$$\ln (k/T) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R + \ln(k_B/h) \tag{2.5}$$

The enthalpy ($\Delta H^{\ddagger}$) and entropy of activation ($\Delta S^{\ddagger}$) are extracted from the slope and intercept of the straight line using equations (2.6) and (2.7), respectively.

$$\Delta H^{\ddagger} = \text{-slope x } R \tag{2.6}$$

$$\Delta S^{\ddagger} = R[\text{intercept - } \ln(k_B/h)] \tag{2.7}$$

These values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can be used to calculate $\Delta G^{\ddagger}$ at ***any*** temperature using equation (2.3). A careful examination of the Eyring equation shows that $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (especially the latter) are very sensitive to errors in rate constants, especially those at the extreme ends of the temperature range. Unfortunately, the errors in rate constants at both temperature extremes obtained via dynamic NMR or dynamic chromatographic

techniques are usually, and quite unavoidably, higher than around the coalescence point. As a result, it is not surprising that one might sometimes encounter large errors in $\Delta H^{\ddagger}$ and, especially $\Delta S^{\ddagger}$. One should therefore bear in mind that the values of these activation parameters should always be interpreted cautiously. In spite of the relatively large errors associated with $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, they balance out, and values of $\Delta G^{\ddagger}$ calculated from $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are quite a bit more reliable.

Unlike $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, the direct determination of $\Delta G^{\ddagger}$ using equation (2.2) demands only modest accuracy in the rate constant. This is because the rate constant, k, enters (2.2) logarithmatically. From this equation, one can see that errors of 10, 25, and 100% in rate constant produce errors in $\Delta G^{\ddagger}$ of only 0.06, 0.1, and 0.4 kcal/mol, respectively, at 300 K. From this equation, we see that even a temperature error of 3 K can be readily tolerated, with the typical precision in $\Delta G^{\ddagger}$ of ±0.2 kcal/mol remaining valid.

The half life (τ) for a dynamic exchange process is defined as the reciprocal of the rate constant k (see equation (2.8)).

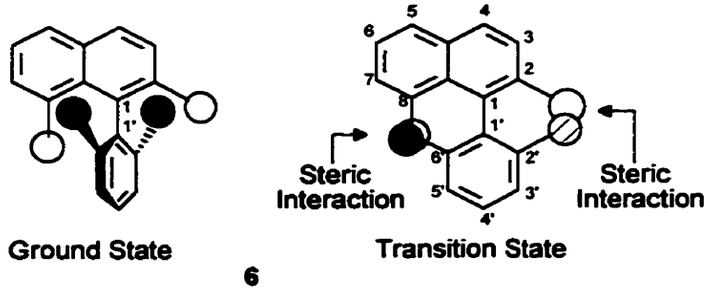
$$\tau = \frac{1}{k} \qquad (2.8).$$

The theories, derivation of mathematical formulae, and their use in calculations of free energy, enthalpy and entropy of activation ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$, respectively), and the half-life can all be found in most physical organic chemistry textbooks.[10]

2.4 HINDERED ROTATION IN 1-ARYLNAPHTHALENES

The subject of atropisomerism has been well reviewed by Oki.[2] A brief review of atropisomerism can also be found in stereochemistry textbooks by Dodziuk,[11] and Eliel *et al.*[12] In this section, the subject of atropisomerism in 1-arylnaphthalene derivatives, including 1-arylnaphthalene lignans, will be presented.

Atropisomerism in 1-arylnaphthalenes **6** is due to the restricted rotation about the C1-C1' bond, which is mainly caused by the steric interactions between the substituents at positions 2 and 8 with the *ortho*-substituents (*i.e.* at positions 2' and 6') on the pendent phenyl ring, as shown in Scheme 2.7.



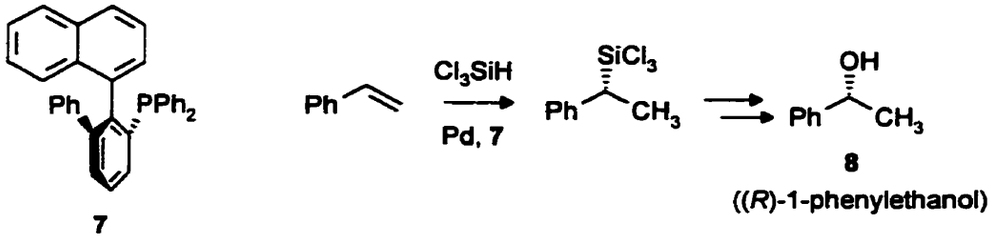
6

Scheme 2.7

It is obvious that the bulkier these substituents are, the higher the rotational energy barrier will be. As such, factors that affect the magnitude of the steric interactions of these substituents determine the energy barrier to rotation about the C1-C1' bond. For instance, some substituents at position 3, 7, 3', or 5' may also contribute to an increase in the rotational barrier by reducing the flexibility of the substituents at positions 2, 8, 2', or 6', respectively, thereby augmenting the steric interaction described above. It is also reasonable to anticipate some electronic effects exerted by 4, or 4'-substituents on the

barrier to rotation in some systems. For instance, electron donating 4, and 4'-substituents may increase the electron density on carbon atoms 1 and 1', and thus facilitate the out-of-plane bending in the transition state. This might reduce the steric interactions to the *ortho*- substituents and the barrier to rotation. All of these factors have not been carefully examined in the arylnaphthalene systems, unlike the well-studied biphenyl and binaphthyl systems.

Since the study of atropisomerism in arylnaphthalenes has not gained as much attention as the biphenyls and the binaphthyls, atropisomeric arylnaphthalenes still have not found much use as chiral reagents in asymmetric organic synthesis. A few systems have been studied and one example is the chiral arylnaphthalene phosphine ligand **7**. This atropisomer is very stable and it does not undergo enantiomerization even after 36 h in refluxing toluene.[13]



7

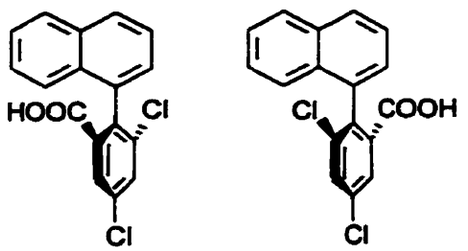
8

((*R*)-1-phenylethanol)

Scheme 2.8

This chiral ligand was found to be effective for the palladium-catalyzed asymmetric hydrosilylation of styrene with trichlorosilane to give (*R*)-1-phenylethanol (**8**) of 91% ee (see Scheme 2.8).

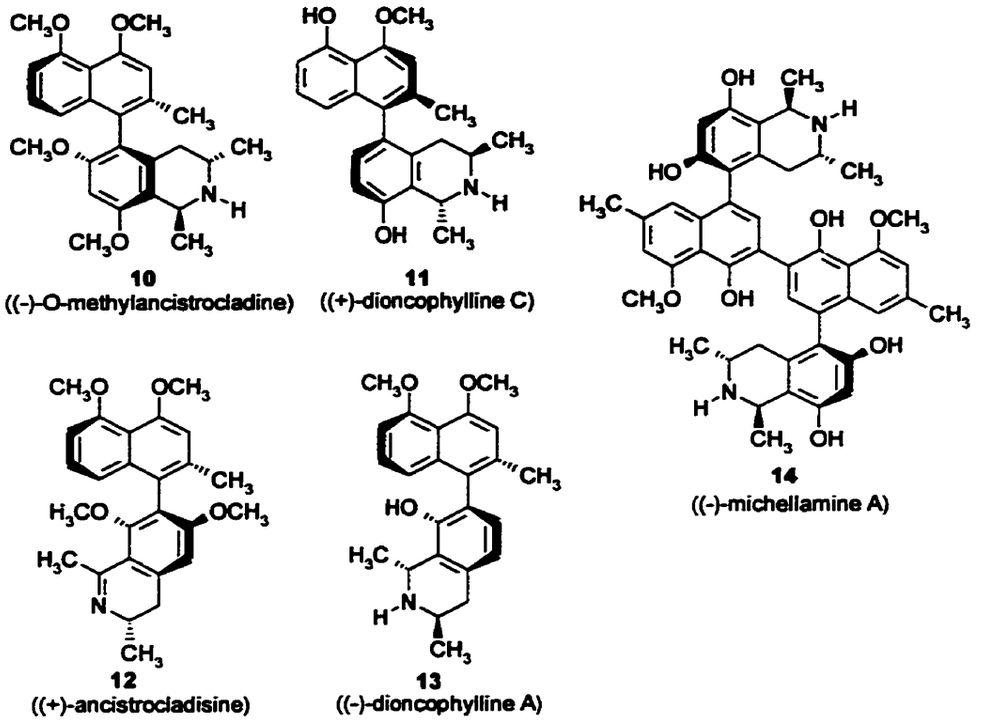
Enantiomers of arylnaphthalene **9** (Scheme 2.9) have found use as a chiral agent, not in asymmetric synthesis, but in NMR spectroscopy, to determine the absolute configuration of secondary alcohols.[14]



9

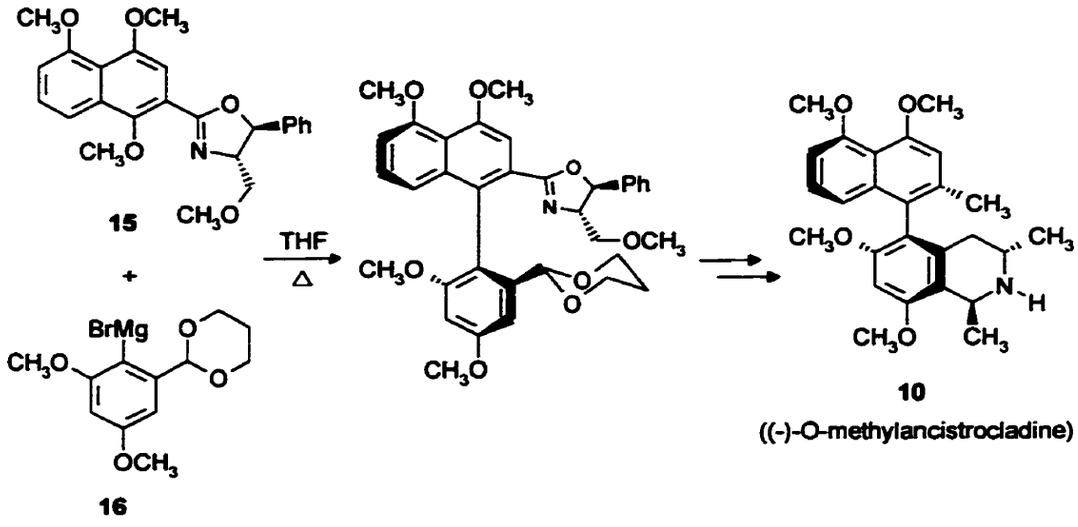
Scheme 2.9

A few stable atropisomeric arylnaphthalenes have shown interesting pharmacological activity which depends on the atropisomeric form. The naphthylisoquinoline alkaloids, extracted from the plant families Dioncophyllaceae and Ancistracladaceae, are well known examples of pharmacologically active atropisomers.[15] Extracts of these plants were used in traditional medicine to treat malaria and dysentery. These atropisomers are configurationally stable up to *ca.* 200 °C.[16,17] Some examples are (-)-O-methylancistrocladine (**10**), (+)-dioncophylline C (**11**), (+)-ancistrocladisine (**12**), (-)-dioncophylline A (**13**), and the dimeric alkaloid (-)-michellamine A (**14**), which has also been found to inhibit the cytopathic effects of AIDS virus (see scheme 2.10).[16]



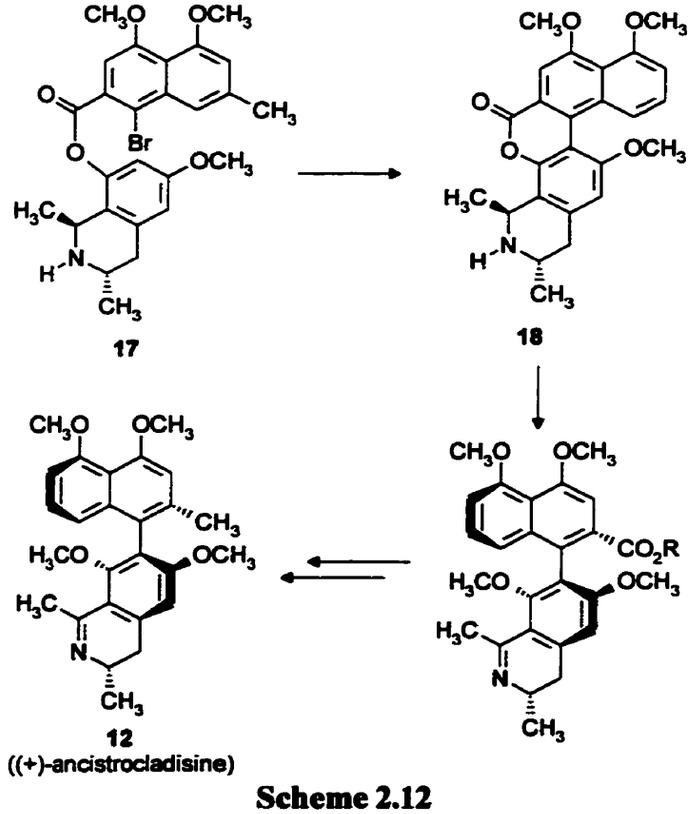
Scheme 2.10

All of the above stable atropisomers have been synthesized by others either via asymmetric biaryl coupling reactions, or by coupling of bridged biaryls followed by asymmetric ring opening.[18] For example, (-)-O-methylancistrocladine (**10**) was synthesized through asymmetric coupling of the oxazoline **15** with Grignard reagent **16**, as illustrated in Scheme 2.11.[16]



Scheme 2.11

An example of the second approach is the synthesis of (+)-ancistrocladisine (**12**) via intramolecular coupling of the bridged biaryl **17** followed by atropdiastereoselective ring opening of the axial-prostereogenic lactone **18**, as shown in Scheme 2.12.[17]



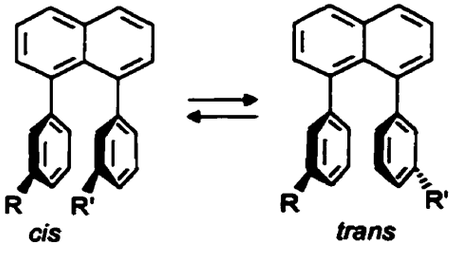
Scheme 2.12

Asymmetric biaryl coupling reactions have been reviewed by Bringmann *et al.*,[18] and Salvadori *et al.*,[4a] and will not be further discussed here.

It is noteworthy that all of the above stable atropisomers possess bulky substituents at the 2' and/or 6' positions. We know little about the effect of other substituents on the height of the rotational barrier. The absence of careful studies about these has hindered the prediction about, and design of, stable atropisomeric arylnaphthalenes.

It is quite possible that some arylnaphthalenes will exhibit unusual spectral or physical properties even though the barrier to rotation is quite low. Such stereolabile atropisomers of arylnaphthalenes may not be useful in asymmetric organic synthesis, but a study of their rotational characteristics might provide a better understanding of their structure and properties.

There are only a few studies of the conformationally less stable arylnaphthalenes to date. Hindered rotation in the 1,8-diarylnaphthalenes **19** shown in Scheme 2.13 have been studied by dynamic NMR and the rotational barriers in these compounds were found to be 15-17 kcal/mol.[19] These rotational barriers are too small to permit the resolution of the atropisomers at room temperature.



19a: R = H, R' = $C(CH_3)_2OH$
19b: R = R' = Cl
19c: R = R' = CO_2CH_3

Scheme 2.13

The NMR spectra of diarylnaphthalene **19a** (Scheme 2.13) acquired by House *et al.* at increasing temperatures are given in Figure 2.3.[19] The signals monitored were the diastereotopic methyl groups. Each of the methyl groups appeared as two overlapping singlets which eventually coalesced into one singlet at high temperature.

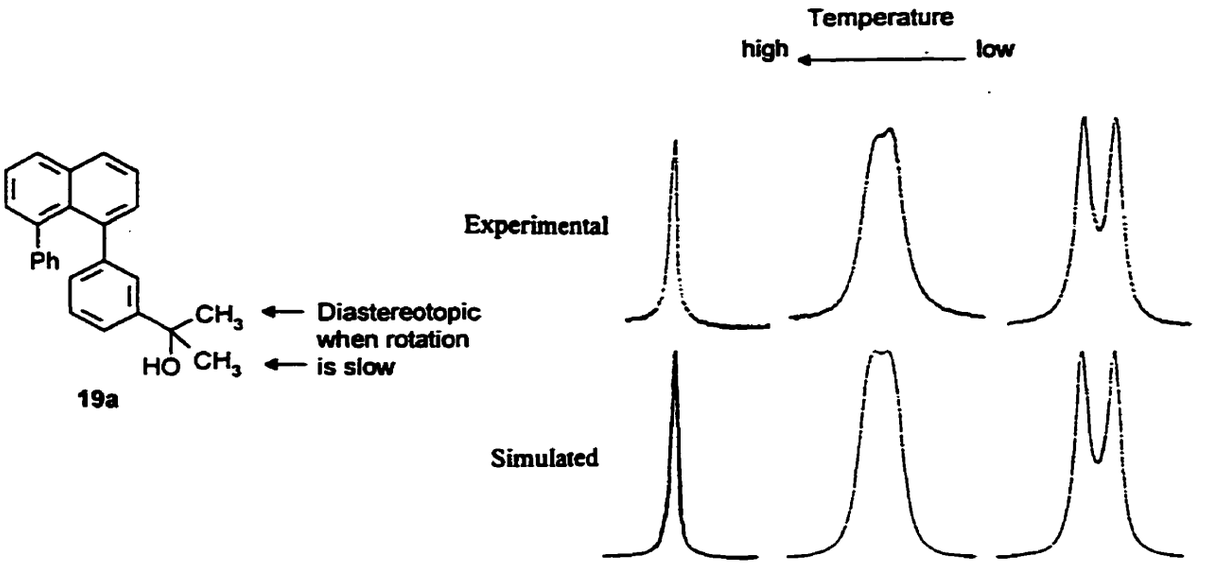
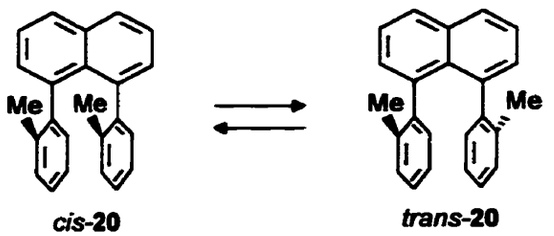


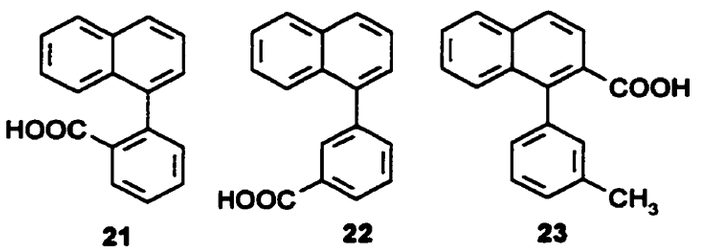
Figure 2.3. Dynamic NMR spectra of the diastereotopic methyl groups in **19a**.

If the pendent phenyl groups of a 1,8-diarylnaphthalene bears *ortho*-substituents, the resulting increase in the rotational barrier is expected to be substantial. 1,8-Bis(*o*-tolyl)naphthalene (**20**) (Scheme 2.14) was found to exhibit a 24.1 kcal/mol barrier to rotation,[19a] compared to *ca.* 16 kcal/mol obtained for diarylnaphthalenes **19**. This high energy barrier permits the isolation of **20** as *cis*- and *trans*-diastereomers at room temperature.



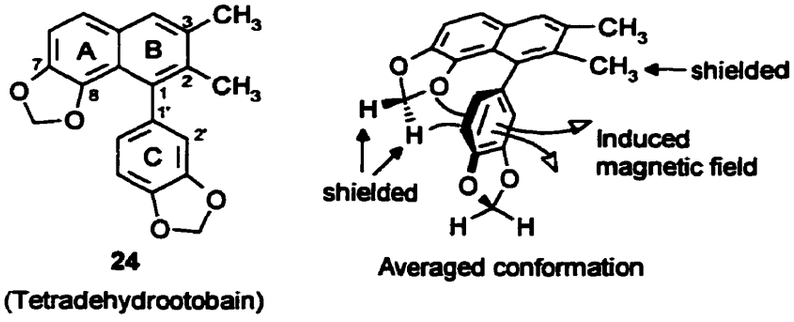
Scheme 2.14

In an earlier work, hindered rotation in several 1-phenylnaphthalene carboxylic acids (see Scheme 2.15) was studied by examining the optical stability of pure atropisomeric enantiomers.[21] 1-phenylnaphthalene-2'-carboxylic acid (**21**) has been resolved into optically active (+)-**21** using a chiral base such as brucine. The optical activity of (+)-**21** dissipated slowly on standing due to racemization of the molecule. Its half-life was found to be 2 min at 20 °C in $CHCl_3$. Unlike phenylnaphthalene **21**, the authors have not been able to resolve the enantiomeric forms of either phenylnaphthalene **22** or **23** due to the rapid racemization in these compounds. The result implied higher rotational barrier in phenylnaphthalenes **21** than in **22** and **23**, presumably because an *ortho*-substituent on the pendent phenyl ring is a more effective impediment to rotation about C1-C1' bond.



Scheme 2.15

Gilchrist *et al.* reported the presence of hindered rotation in an arylnaphthalene lignan, tetradehydrootabain, based on the observation of shielding effects in its ^{1}H-NMR spectrum.[22] Based on a molecular model for an averaged molecular conformation of tetradehydrootobain (**24**) (Scheme 2.16), they suggested that placing a methylenedioxy group at position 7 and 8 must restrict the rotation of ring C, and that ring C lies at right angle to the plane of the naphthalene ring. In this conformation, the methylene protons on ring A and the 2-methyl protons are shielded and appear at a higher applied field than the methylene protons on ring C, and the 3-methyl protons, respectively. The observed spectrum of tetradehydrootobain substantiated the averaged conformations mentioned above, although there was no other evidence provided to support the above hypothesis.



24
(Tetradehydrootobain)

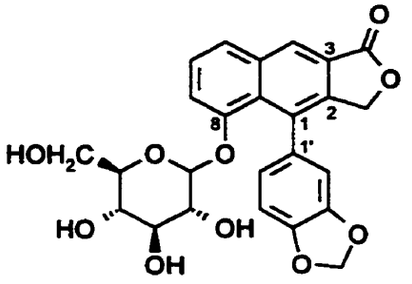
Averaged conformation

Scheme 2.16

Many arylnaphthalene lignans contain a methylenedioxy group as illustrated in Scheme 2.16 (see the structure of tetradehydrootobain). The methylene protons of the methylenedioxy group will be diastereotopic, and thus detectable by NMR as an AB signal, if rotation about the C1-C1' bond is slow on the NMR time scale. In fact, this type of anomaly has been observed in many arylnaphthalene lignans possessing

methylenedioxy group(s) although no correlation to hindered rotation has ever been made.[23]

Trujillo *et al.* recently observed an interesting doubling of proton signals in the NMR spectrum of glycoside arylnaphthalene **25** (Scheme 2.17).[24]



25

Scheme 2.17

Since arylnaphthalene **25** contains a chiral glucose substituent, restricted rotation about the C1-C1' bond would give rise to a mixture of diastereomers. As mentioned in Section 2.2.1, diastereomers are detectable as distinct entities by NMR spectroscopy, and each contributes its own unique spectrum. Therefore, the doubling of most of the proton signals in arylnaphthalene **25** was a good indication of slow internal rotation about the C1-C1' bond. Nevertheless, the barrier to rotation in this compound was not measured and the contribution that the bulky 8-substituent makes to the magnitude of barrier cannot be compared to others mentioned above.

The hindered rotation in arylnaphthalenes awaits further study in order that the factors that govern the height of the rotational barrier in these compounds can be elucidated. We have conducted a careful study of hindered rotation in some arylnaphthalene lignans using both dynamic NMR and molecular orbital calculations.

The results have shed some light on steric effects on the rotational barriers in arylnaphthalene lignans. Detailed discussion of the study is given in Section 4.4.

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CHAPTER 3

THESIS OBJECTIVES

The objectives of this thesis research were to establish efficient approaches to the asymmetric synthesis of various types of lignans. During the studies, four primary approaches were undertaken:

I. Use of Chiral Esters of Acetylenedicarboxylic Acid in Diels-Alder Reactions for the Asymmetric Synthesis of Aryltetralin Lignans.

Asymmetric induction in Diels-Alder reactions of the fumarate or acrylate of methyl lactate has been the subject of numerous studies. These dienophiles were found to react with α-hydroxy-*o*-QDMs with excellent diastereoselectivity, affording cycloadducts that were successfully transformed into podophyllotoxin derivatives (see Chapter 1 for a review). It was felt that a study of the acetylenedicarboxylate of methyl lactate might be as worthwhile as that of the fumarate and acrylate. In addition, the preparation of complex acetylenedicarboxylic acid (ADA) esters was known to be difficult and literature reports of chiral esters of ADA, other than the dimenthyl esters, were infrequent. Developing a method for the preparation of a complex chiral ester of ADA and a study of its Diels-Alder reactions would be useful, not only for the asymmetric synthesis of lignans, but also for the synthesis of other types of natural products. The synthesis of the bis-(methyl (*S*)-lactyl) ester of ADA and its Diels-Alder reactions with dienes such as phenylbutadiene, *o*-QDMs, isobenzofuran, and hexadienol were undertaken.

II. Asymmetric Synthesis of Benzylidenebenzylbutyrolactone and Dibenzylbutyrolactone Lignans Using Oxazolidinones as Chiral Auxiliaries.

Many of the methods for the asymmetric synthesis of chiral lignans have involved the intermediacy of enantiomerically pure β-benzyl-γ-butyrolactones because they offer more flexibility in eventual structural variability that can be achieved otherwise (see Chapter 1). There are many elegant asymmetric synthetic approaches to the preparation of optically active β-benzyl-γ-butyrolactones. However, problems such as laborious methods, poor overall yields, unsatisfactory enantiomeric purity, and/or expensive reagents still exist in the reported approaches.

Substituted oxazolidinones are effective chiral auxiliaries giving excellent asymmetric induction in alkylation reactions. Enolates derived from N-acyloxazolidinones can be alkylated with α-bromoacetate to afford diastereomerically pure succinate derivatives. These succinates can then be transformed into β-substituted γ-butyrolactones in high optical purity. This approach is simpler than the other reported methods used in the preparation of β-substituted γ-butyrolactones. The synthesis and subsequent transformations of these intermediates into dibenzylbutyrolactone and benzylidenebenzylbutyrolactone lignans would provide an alternative to the currently available methods.

III. The Study of Intramolecular Oxidative Coupling Reactions

Phenolic phenylpropanoids are basic units of many plant products such as lignans, neolignans, and lignin. In lignan biosynthesis, these basic units undergo oxidative

coupling reactions catalyzed by enzymes to form dimers linked at the β carbons (see Chapter 1). Among the many phenolic phenylpropanoids that undergo intermolecular oxidative coupling, sinapic acid was found to undergo the reaction most efficiently to afford a single product under most conditions. For instance, treating sinapic acid in basic buffer with oxygen resulted solely in the formation of the 3,4-dihydroarylnaphthalene lignan thormasidioic acid. On the other hand, a fused dilactone of dihydrosinapic acid was formed from oxidation of sinapic acid by metal oxidants such as $FeCl_3$. In view of these interesting oxidative coupling results, two questions were posed. Could the same success be obtained for the intramolecular oxidative coupling of two sinapic acid molecules joined by an ester linkage? If yes, could a chiral linking agent impose any asymmetric induction on the reaction? This novel study of an intramolecular oxidative coupling reaction was thereby proposed.

Intramolecular oxidative cyclization reactions of dibenzylbutyrolactone lignans have been widely studied in order to gain a better understanding of lignan biosynthesis and also to provide alternative routes for the chemical synthesis of lignans (see Chapter 1). The oxidation reactions of monophenolic dibenzylbutyrolactones have not been as successful as their nonphenolic counterparts. If project *III* described above makes available a monophenolic dibenzylbutyrolactone lignan, then it could be used for the study of intramolecular oxidative cyclization. In this way some light might be shed on the process of lignan biosynthesis.

IV. The Study of Hindered Rotation in Arylnaphthalene Lignans

Atropisomerism is a word used to describe molecules that exist in enantiomeric forms solely due to hindered rotation about carbon-carbon single bonds (see Chapter 2). Some 1-substituted naphthalenes have been found to suffer hindered rotation and some have even been isolated as stable enantiomers (atropisomers) that exhibit different biological activities. Some of these stable atropisomers, such as (-)-O-methylancistrocladine, were synthesized via asymmetric biaryl coupling reactions.

Arylnaphthalene lignans are abundant in plants but their atropisomeric properties have not been carefully studied. The question of the possible existence of these products as stable atropisomers was raised. Therefore a study of hindered rotation in several lignans and lignan analogs using dynamic NMR and low temperature HPLC was proposed.

CHAPTER 4

RESULTS AND DISCUSSION

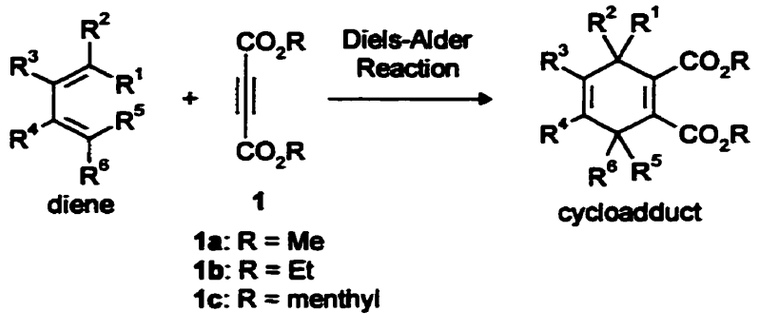
The work on the asymmetric synthesis of lignans using Diels-Alder reactions, asymmetric alkylation reactions, and intramolecular oxidative coupling reactions will be discussed in detail in Sections 4.1, 4.2, and 4.3, respectively. This chapter will also disclose the details of the work on hindered rotation in arylnaphthalene lignans (see Section 4.4)

4.1 SYNTHESIS OF ACETYLENEDICARBOXYLIC ACID ESTERS AND ASYMMETRIC DIELS-ALDER REACTIONS OF THE BIS-(METHYL (*S*)-LACTYL) ESTER

This section is divided into two parts. In the first part, a general method for the synthesis of various types of acetylenedicarboxylic acid (ADA) esters, including the bis-(methyl (*S*)-lactyl) ester is presented. In the second part, the asymmetric Diels-Alder reactions of the acetylenedicarboxylate of methyl (*S*)-lactate with dienes such as phenylbutadiene, *o*-QDMs, isobenzofuran, and hexadienol are described.

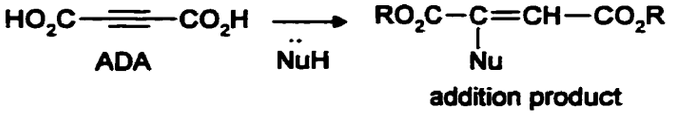
4.1.1 Synthesis of Acetylenedicarboxylic Acid Esters

The simple esters of ADA such as the dimethyl (**1a**), diethyl (**1b**) and dimenthyl (**1c**) esters have been useful in organic synthesis, particularly as dienophiles in cycloaddition reactions.[1] They react efficiently in Diels-Alder reactions with dienes such as butadienes, isobenzofurans, and *o*-QDMs, as illustrated in Scheme 4.1.



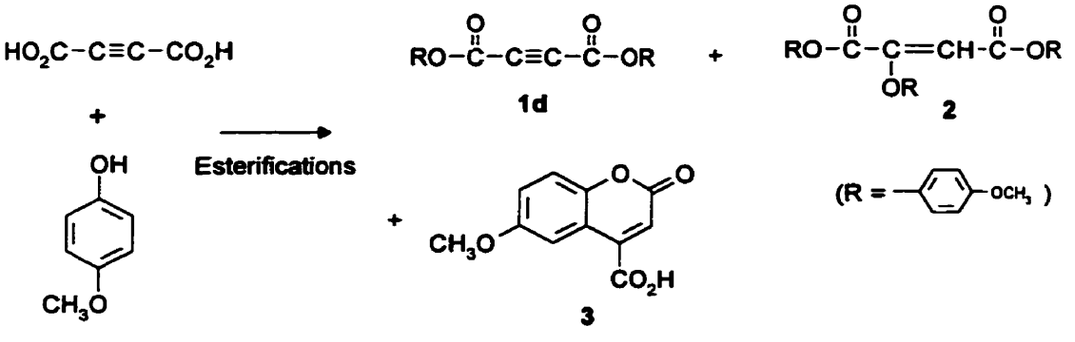
Scheme 4.1

The preparation of some of the simpler dialkyl acetylenedicarboxylates can be achieved by conventional esterification of the acid in satisfactory yield. However, in some cases, direct esterification of ADA is complicated by the addition of the alcohol to the reactive triple bond polarized by the carboxylate groups (Scheme 4.2).[2]



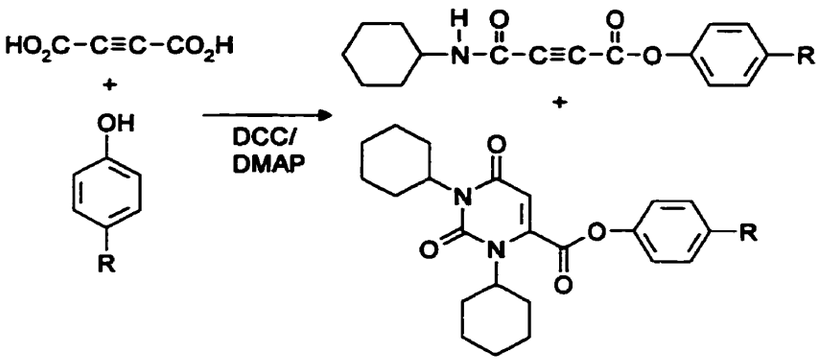
Scheme 4.2

For instance, esterification of ADA with phenols catalyzed by *p*-TsOH resulted in only 14-15% of the desired ADA esters (**1d**), while addition products **2** and **3** were predominant (see Scheme 4.3).[3]



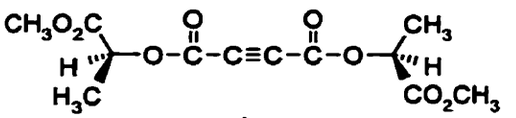
Scheme 4.3

On the other hand, Verbit *et al.* have claimed that they were able to prepare aryl diesters in satisfactory yield by reacting ADA with an excess of the phenol in the presence of sulfuric acid.[4] The use of DCC as a condensing agent with DMAP as a catalyst in the esterification of ADA with phenols has been shown to be ineffective, with none of the desired ADA ester being formed (see Scheme 4.4).[3]



Scheme 4.4

An attempt was made to apply the conventional esterification methods described above to the preparation of the methyl (*S*)-lactyl ester of ADA (**1e**).

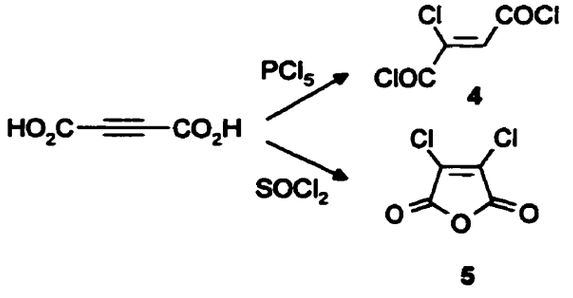


1e

Scheme 4.5

Esterifications catalyzed by H_2SO_4, HCl, and *p*-TsOH, and condensations using DCC/DMAP were totally unsuccessful. The possible reason for this failure, besides nucleophilic addition to the triple bond of ADA, is the susceptibility of methyl (*S*)-lactate itself to side reactions such as transesterification.

The synthesis of ADA esters via the acid chloride of ADA is an impractical route because addition to the triple bond appears to be an unavoidable major reaction.[3] Besides, the preparation of the acid chloride itself is another difficult task to be overcome. Jung *et al.* claimed that acid chloride of ADA could be prepared by treating ADA with PCl_5 but the authors were unable to isolate or purify the acid chloride due to its high reactivity.[5] In contrast, previous authors[6] have described their inability to prepare the acid chloride via direct chlorination of ADA using PCl_5 or $SOCl_2$. The products chlorofumaryl chloride **4** or dichloromaleic anhydride **5**, respectively, were instead isolated (see Scheme 4.6).[6a]



Scheme 4.6

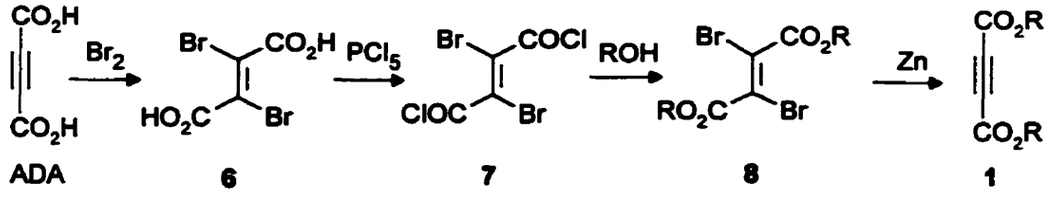
We were also unable to repeat the work described by Jung *et al.*[5] for the preparation of the ADA acid chloride.

Diels has described a method for the preparation of the acid chloride of ADA in moderate yield via thermal decomposition of anthracene-9,10-endoacetylenedicarboxylyl dichloride in the presence of maleic anhydride.[6c] We did not attempt to repeat this method due to its complexity. Attempts by Ruggli[6b] to prepare the acid chloride from $BrMgC{\equiv}CMgBr$ and $COCl_2$ gave only tar.

Herkes and Simmons reported that some esters of ADA could be obtained in relatively good yields via the use of the less reactive acid fluoride.[7] However, the use of highly corrosive SF_4 needed to prepare the acid fluoride constitutes an important limitation to the procedure. Moreover, addition to the triple bond was observed as an important side reaction during the preparation of a diaryl ester.

From the information obtained from the literature, and from our own preliminary experiments, it appeared that it was impractical to prepare complex ADA esters from ADA itself. The difficulty in preparing complex ADA esters is consistent with the infrequent report of these esters as dienophiles in cycloaddition reactions. In order to study asymmetric cycloaddition reactions using complex chiral ADA esters, their preparation by an approach that avoids nucleophilic addition to the reactive triple bond must be accomplished.

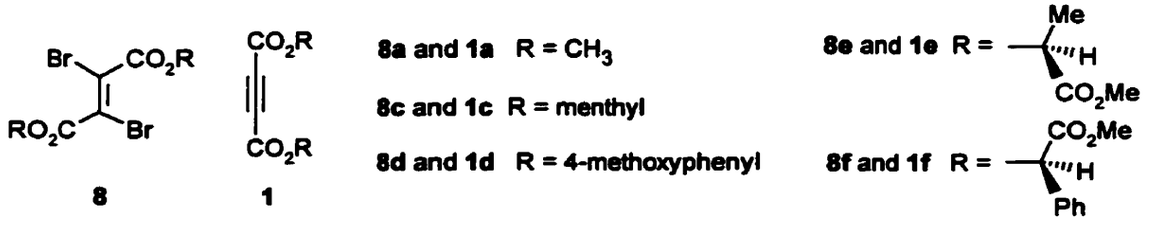
Esterification of dibromofumaryl chloride followed by dehalogenation provides an alternative method for the synthesis of ADA esters (Scheme 4.7). Dibromofumaryl chloride **7** can be prepared by bromination of ADA followed by treatment of the resulting product **6** with PCl_5. Treating the acid chloride with two equivalents of an alcohol affords the corresponding dibromofumaric acid ester **8**, which can then be debrominated with zinc to yield the ADA ester **1**.



Scheme 4.7

This approach was investigated in the late 1800s[8] and the early 1900s,[9] but since that time it has been largely ignored except for a preparation of acetylenediamides, published in 1970.[10] We have reinvestigated the approach and found it extremely versatile. Prior bromination of ADA allows the subsequent reactions such as acid chloride formation and esterification to proceed without the formation of addition products which were frequently observed in the direct reactions of ADA with $SOCl_2$, PCl_5, alcohols and other nucleophilic agents. The vicinal dibromide, which can then be converted to the acetylene by reductive elimination, acts as a masked triple bond. This general procedure allows the preparation of many esters in excellent yield and is superior to direct esterification or transesterification methods as an excess of alcohol is not required.

We have synthesized two new chiral ADA esters, the bis-(methyl (*S*)-lactyl) (**1e**) and bis-(methyl (*R*)-mandelyl) (**1f**) esters, in order to study their asymmetric Diels-Alder reactions. The preparations of dimethyl (**1a**),[11] dimenthyl acetylenedicarboxylates (**1c**),[12] and bis-4-methoxyphenyl (**1d**)[3,4] have been previously reported, and were prepared again by our procedure for comparison purposes (all structures are given in Scheme 4.8). The esters were synthesized according to the general procedure shown in Scheme 4.7 in excellent yield. Other than the bromination of ADA (80%), every step afforded a yield of > 90%.



Scheme 4.8

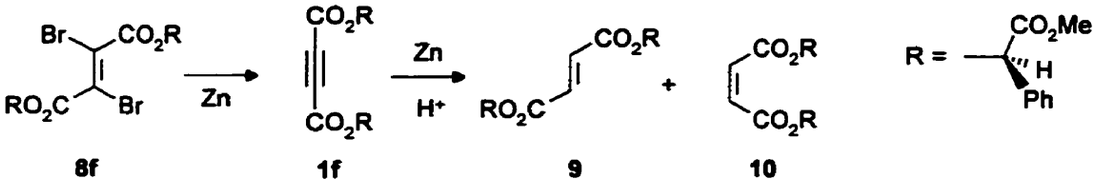
Although each step in the general approach illustrated in Scheme 4.7 has been previously described in the literature, we found that some of the procedures could be improved. Bromination of ADA as described by Ott[9] was both laborious and time consuming and therefore, the method used by Eichelberger[13] for the iodination of ADA was adopted with some slight modifications. Treatment of the dipotassium salt of ADA with bromine in NaBr solution afforded dibromofumaric acid (**6**) in 80% yield after recrystallization from THF/hexane. PCl_5 rather than thionyl chloride was used for the preparation of dibromofumaryl chloride since the latter caused the liberation of bromine which led to formation of unidentified by-products. The esterification of the crude acid chloride proceeded smoothly in carbon tetrachloride using a pyridine catalyst with ice cooling. Of all the steps leading to the acetylenic esters, zinc promoted debromination of the dibromofumarates was the most troublesome. Each of the dibromofumarate esters required different reaction conditions in order to achieve debromination in high yield (see Table 4.1).

Table 4.1. ADA Esters 1 from Debromination of Dibromofumarates 8.[a]

Product[b]	Reduction metal/ catalyst	Temp./time	Yield[c] (%)	mp (°C)
1a	granular Zn	reflux/2 h	92	-
1c	Hg-Zn dust	25°C/16 h	90	131-133
1d	granular Zn/I_2	reflux/6 h	90	145-147
1e	granular Zn	reflux/4 h	95	78-81
1f	Hg-Zn dust	reflux/1 h	85	-

[a]Dibromofumarates were used without prior purification.
[b]All new compounds were fully characterized by their spectroscopic (IR, ^1H and ^{13}C NMR, MS) and elemental analysis data.
[c]Crude Yield.

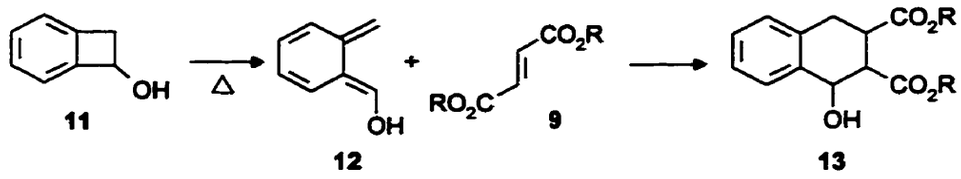
The difficulties were especially obvious during the debromination of the bis-(methyl (*S*)-lactyl) and bis-(methyl (*R*)-mandelyl) esters of dibromofumaric acid (**8e** and **8f**, respectively). The former could be reduced with granular zinc in refluxing THF in 4 h, while the latter required the much more reactive amalgamated zinc. In addition, the preparation of the mandelyl ADA ester **1f** from the dibromofumarate **8f** using amalgamated zinc dust in refluxing THF (1 h) gave rise to the fumarate and maleate of the corresponding ester (**9** and **10**, respectively) as by-products (3-4% each) (Scheme 4.9).



Scheme 4.9

Under the same conditions, these types of products, which result from the reduction of the acetylenic triple bond, were not observed during the preparation of lactyl ADA ester **1e**. The reason for this is not known. It was found that the mandelyl ADA ester **1f** and its fumarate (**9**) were inseparable by chromatography. However, we discovered that α-hydroxy-*o*-QDM **12**, which is a short lived intermediate that can be prepared thermally from benzocyclobutenol (**11**),[14] reacted with the fumarate at a much faster rate than with the acetylenic ester. Therefore, treating a mixture of mandelyl ADA ester **1f** and its fumarate (**9**) with a trace amount of benzocyclobutenol (**11**) in refluxing toluene allowed almost complete removal of the 4% fumarate as a cycloadduct (**13**) after chromatography

(Scheme 4.10). The removal of the fumarate can be monitored by the disappearance of the olefinic protons at 7.06 ppm.



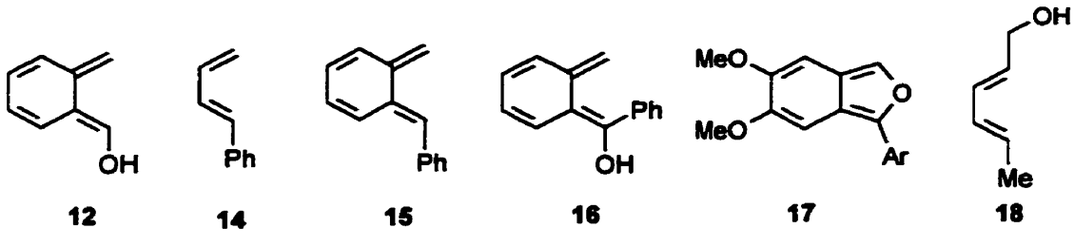
11 12 9 13

Scheme 4.10

Although the approach in Scheme 4.7 does not offer any superiority to direct esterification methods for simple dialkyl esters of ADA (**1a** and **1c**), it does provide a method for the synthesis of complex ADA esters (**1d**, **1e**, and **1f**). The previously reported bis-(4-methoxyphenyl) ester of ADA (**1d**), which could be prepared only in 14-15% by direct esterification of ADA or acetylenedicarbonyl chloride,[3] could now be prepared using the approach in Scheme 4.7 in an overall yield of > 70%.

4.1.2 Diels-Alder Reactions of the Bis-(methyl (S)-lactyl) ester of ADA (1e)

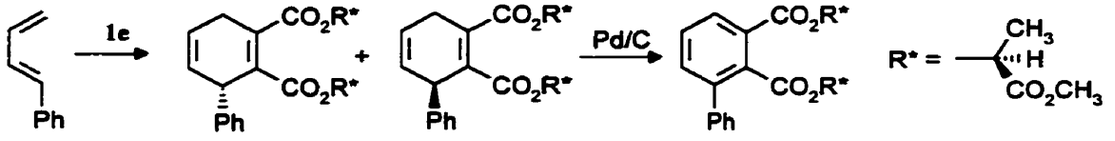
The approach in Scheme 4.7 makes possible the preparation of the lactyl ADA ester **1e**. As a result, the Diels-Alder reactions of lactyl ADA ester **1e** with various types of dienes were investigated. The dienes chosen for study were (*E*)-1-phenyl-1,3-butadiene (**14**), various *o*-QDMs (α-phenyl **15**, α-hydroxy **12**, and α-hydroxy-α-phenyl **16**), an aryl isobenzofuran **17**, and 2,4-hexadien-1-ol (**18**) (Scheme 4.11). These dienes have been used extensively in organic synthesis for the construction of biaryl, aryltetralin, naphthalene, and cyclohexadiene compounds.



12 14 15 16 17 18

Scheme 4.11

(*E*)-1-Phenyl-1,3-butadiene (**14**)[15] was reacted with lactyl ADA ester **1e** in refluxing xylenes to give a mixture of two diastereomeric cycloadducts (**19/20**) in a 1:1.3 ratio,[16] as determined by integration of the four methoxy singlets between 3.5 and 3.8 ppm in the NMR spectrum. Carrying out the reaction in CH_2Cl_2 at room temperature using $MeAlCl_2$ as catalyst gave only a slightly improved 1:2 mixture of the two diastereomers. The diastereomers were not separated but, in order to confirm their structures, they were further dehydrogenated to the biaryl **21** using Pd/C in refluxing xylenes (Scheme 4.12).

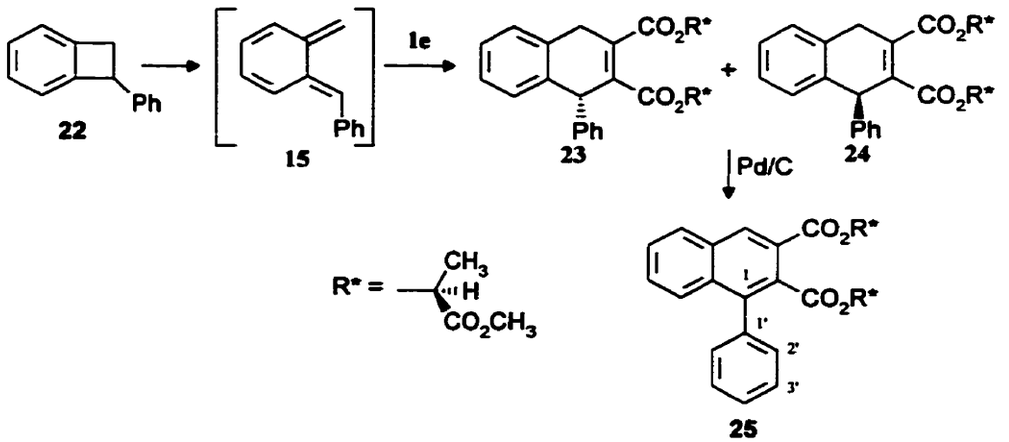


14 19 20 21

Scheme 4.12

α-Phenyl-*o*-QDM **15**, prepared thermally from α-phenylbenzocyclobutene (**22**) in refluxing toluene, also reacted nonselectively with ADA ester **1e** to give a mixture of two diastereomers (**23** and **24**) in a 1:1.4 ratio[16] (see Scheme 4.13). In view of the poor diastereoselectivity, no attempt was made to separate the two diastereomers. The structures were confirmed by aromatization using Pd/C in refluxing xylenes to afford the phenylnaphthalene **25**. This aromatized product showed an interesting ^{13}C NMR feature

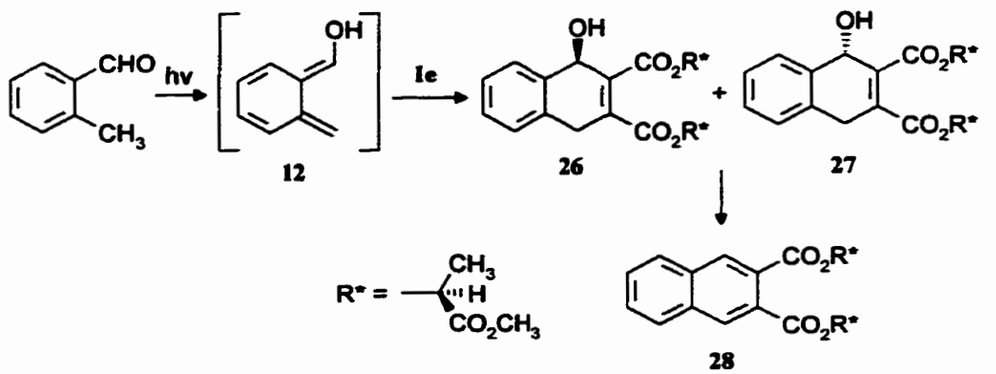
in that ten instead of eight aromatic CH peaks were observed. This indicates that the C-2' and C-3' on the pendent phenyl group were not identical to C-6' and C-5', respectively, on the NMR time scale at room temperature. This is attributed to the restricted rotation about the C1-C1' bond of the molecule. Restricted rotation in arylnaphthalene derivatives giving rise to atropisomers has been studied elsewhere,[18] but to the best of our knowledge, the observed ^{13}C NMR properties of these compounds have not been reported. The study of hindered rotation in phenylnaphthalene **25** will be discussed in detail in Section 4.4.



Scheme 4.13

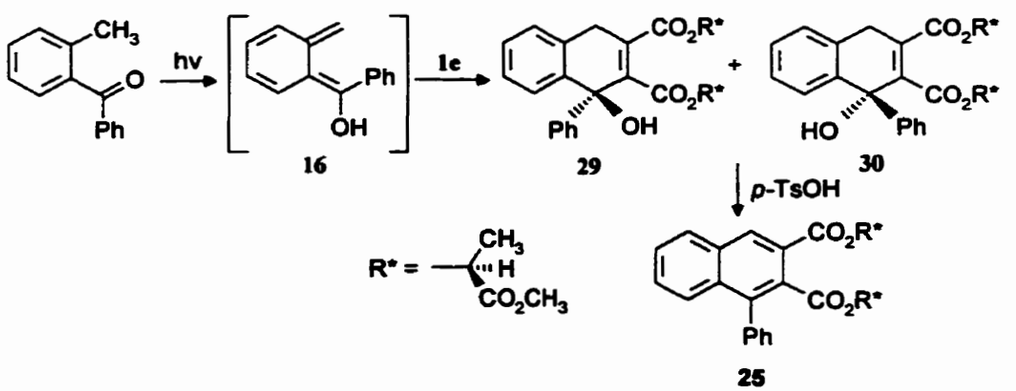
2-Methylbenzaldehyde, a precursor that can be photochemically converted to α-hydroxy-*o*-QDM **12**, was prepared by oxidation of readily available 2-methylbenzyl alcohol using chromic acid. The aldehyde is quite volatile and prone to oxidation. It was immediately irradiated with lactyl ADA ester **1e** in benzene solution. The addition of the α-hydroxy-*o*-QDM **12** to the chiral acetylenedicarboxylate was modestly diastereoselective, generating a mixture of two fairly unstable diastereomers **26** and **27** (1:5 ratio).[16] These dehydrated slowly to give naphthalene **28** upon standing at room

temperature (Scheme 4.14). When the α-hydroxy-*o*-QDM **12** was generated thermally from benzocyclobutenol (**11**)[14] and treated with the acetylenedicarboxylate in refluxing benzene, only naphthalene **28** was isolated.



Scheme 4.14

α-Hydroxy-α-phenyl-*o*-QDM **16**, generated by irradiation of 2-methylbenzophenone, was reacted with lactyl ADA ester **1e** to give a mixture of two diastereomers **29** and **30** (1:2.1 ratio)[16] which were characterized by NMR spectroscopy. The structures of the diastereomers were confirmed by dehydration using *p*-TsOH in refluxing benzene to afford the phenylnaphthalene **25**. The reaction is depicted in Scheme 4.15.



Scheme 4.15

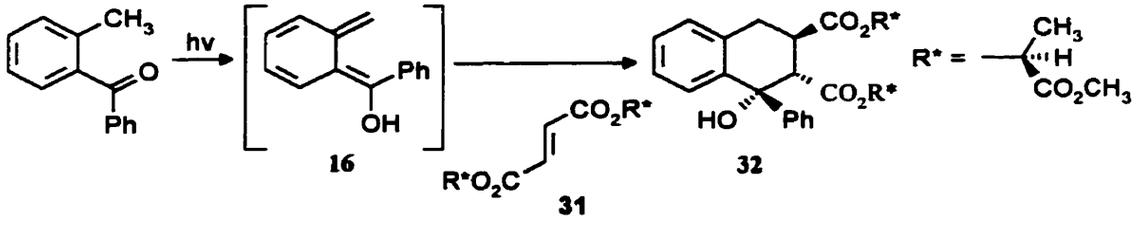
Although the diastereoselectivity of the reaction was unsatisfactory, an interesting phenomenon was observed during the search for other solvents that might improve diastereoselectivity. When polar solvents such ethyl acetate, acetone, acetonitrile, or methanol were used, the ratio of the two diastereomers was reversed, as shown in Table 4.2.

Table 4.2. Solvent effects on the diastereofacial selectivity in the Diels-Alder reaction of α-hydroxy-α-phenyl-*o*-QDM 16 with bis-(methyl (*S*)-lactyl) ester of ADA (1e).

Solvent	Ratio of Isomers[a] A : B
Hexane/benzene	1 : 2
Benzene	1 : 2.1
Ethyl acetate	2.2 : 1
Acetone	2.4 : 1
Acetonitrile	2 : 1
Methanol	2 : 1

[a] Measured using the integration ratios of two methyl doublets between 1.2 and 1.4 ppm in the ^{1}H NMR ($CDCl_3$) spectra (see Experimental).

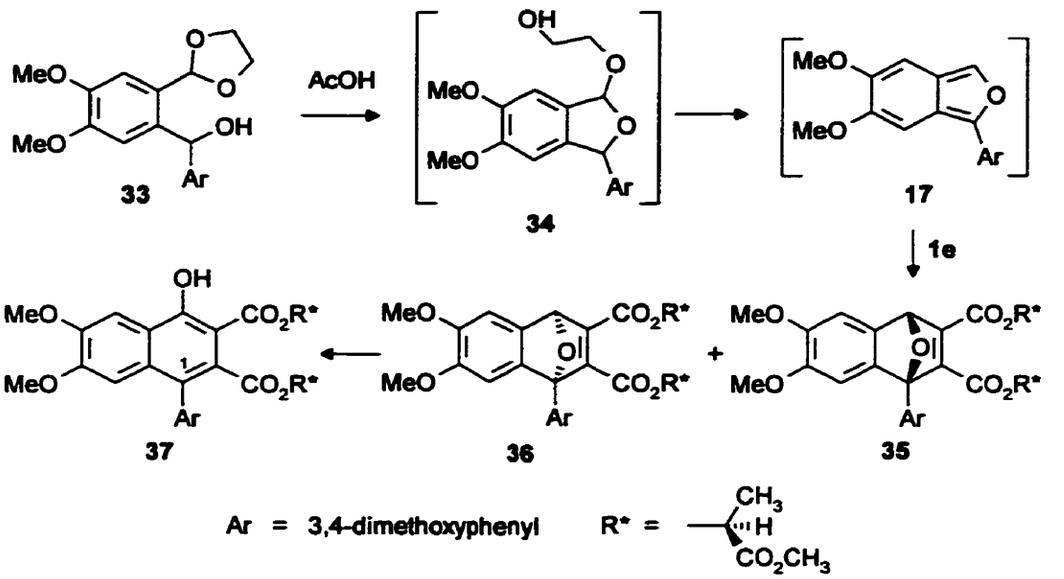
To examine if a similar solvent effect exists on the reaction of other dienophiles carrying the same chiral auxiliary, a cycloaddition experiment was carried out between fumarate of methyl (*S*)-lactyl (**31**) and α-hydroxy-α-phenyl-*o*-QDM **16**.



Scheme 4.16

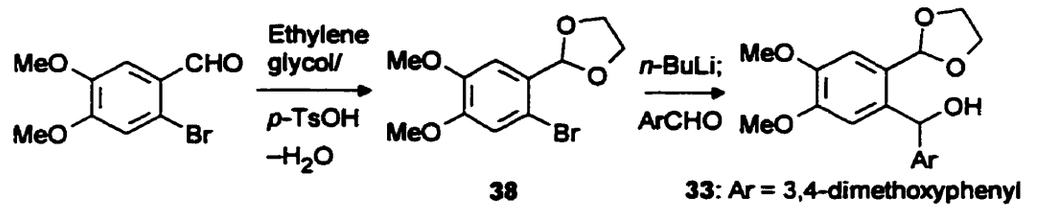
In solvents such as benzene, acetone, and ethyl acetate, the reaction afforded predominantly diastereomer **32** (> 90% de) as given in Scheme 4.16.[19] In methanol, the diastereoselectivity of the reaction was reduced, but not reversed, affording the two diastereomers in a 1:1.4 ratio. Solvent effects on Diels-Alder reactions are well known and can result in notable improvement in reaction rates, *endo/exo* diastereoselectivity, and diastereofacial selectivity.[20] The selectivities have been explained by solvophobicity and electrostatic interactions of the solute and solvent.[21] While changes in stereoselectivity with change of solvent is expected, the unusual solvent induced reversal of asymmetric induction in Diels-Alder reactions is very seldom reported. Recently, Jorgenson *et al.* has observed the reversal of stereoselectivity with changes of solvent polarity in a hetero Diels-Alder reaction.[22a] Other than changes in solvent polarity, Lewis acids have also been found to cause reversal of stereoselectivity in Diels-Alder reactions. $TiCl_4$-catalyzed Diels-Alder reaction of the fumarate of methyl lactate with cyclopentadiene yields a product of opposite configuration to that of the uncatalyzed reaction.[22b] In addition to Diels-Alder reactions, a solvent induced reversal of asymmetric induction has been observed in the photodeconjugation of an α,β-unsaturated lactyl ester.[23] A complete understanding of the effect of solvents on the asymmetric control of the Diels-Alder reaction of ADA ester **1e** and *o*-QDM **16** will require further study.

The Diels-Alder reaction of isobenzofuran **17** and the ADA ester **1e** was also studied. Isobenzofuran **17** was generated using a modified literature procedure, via phthalan **34**, by the acid catalyzed elimination reaction of hydroxyacetal **33** (Scheme 4.17) (literature review of isobenzofurans is given in Section 1.3.2).[24]



Scheme 4.17

Precursor **33**[25] was prepared via transmetallation of bromoacetal **38**[26] with *n*-BuLi, followed by addition to 3,4-dimethoxybenzaldehyde (Scheme 4.18).



Scheme 4.18

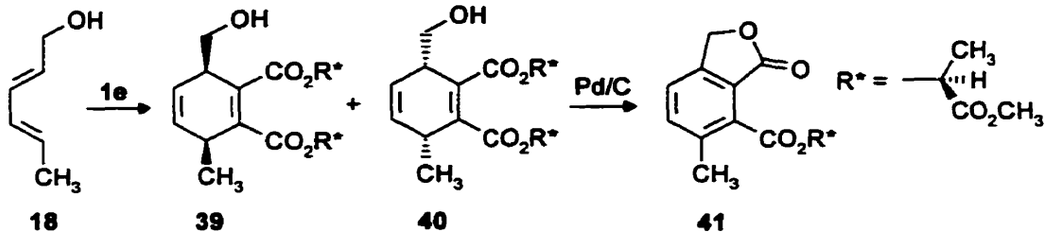
Due to its instability, precursor **33** was not fully purified, but was reacted immediately with ADA ester **1e** in the presence of a catalytic amount of glacial AcOH at 95 °C for 20 min. The reaction afforded the aromatized cycloadduct naphthol **37** as a major product (80 ± 5%), and two bridged cycloadducts (**35** and **36**) (see Scheme 4.17) as minor products (20 ± 5%) in a 1:1.2 ratio,[16] as determined by the integration of two pairs of lactyl doublets between 1.0-1.6 ppm. The use of $MeAlCl_2$ or Et_2AlCl in place of glacial

AcOH as a catalyst for the formation of isobenzofuran **17** and for the Diels-Alder reaction, at either room temperature or at 70 °C, failed to afford any cycloadduct from hydroxyacetal **33** and ester **1e**.

Since the formation of **35** and **36** showed no diastereoselectivity, no attempt was made to isolate the bridged cycloadducts. The crude product was reacted further in the presence of AcOH to convert both minor products to the naphthol **37** which was isolated in 80% yield after chromatography. Its ^{1}H NMR spectrum showed an interesting feature in that most of the characteristic peaks of naphthol **37** were split into doublets. As for phenylnaphthalene **25**, the phenomenon is attributed to the restricted rotation about the C1-C1' bond, which causes naphthol **37** to exist in two diastereomeric forms as observable in the NMR spectrum. The investigation of the hindered rotation in arylnaphthalene lignans will be discussed in Section 4.4.

From the above it appears that good diastereoselectivity is not attainable in the Diels-Alder reactions of **1e** with dienes lacking α-hydroxy groups, such as the phenylbutadiene **14**, α-phenyl-*o*-QDM **15**, and isobenzofuran **17**. The acetylenedicarboxylate of methyl (*S*)-lactate (**1e**) is a straight long rod-shaped molecule with two chiral lactyl groups attached to both ends. As such, the lactate groups are apparently too far from the reaction center to exert a significant effect. However, the dienes with α-hydroxyl groups reacted with **1e** with relatively good diastereoselectivity. This could be due to hydrogen bonding between the α-hydroxyl group of the *o*-QDM and the carbonyl group of the chiral auxiliary, an association that would bring the chiral auxiliary closer to the reaction center. The use of a diene with a more flexible and

extended hydroxyl group, such as 2,4-hexadien-1-ol (**18**), might compensate for the stiffness of the ADA ester and afford an even easier interaction with the carbonyl group of the chiral auxiliary. To test this hypothesis, ester **1e** was reacted with 2,4-hexadiene-1-ol (**18**) in refluxing xylenes for 15 h (see Scheme 4.19). A mixture of two diastereomers (**39** and **40**) was obtained in a 1:1.3 ratio,[16] as determined by ^{1}H NMR spectroscopy. The diastereomers were aromatized to **41** for full characterization. The use of Lewis acids such as $BF_3{\cdot}OEt_2$ or $MeAlCl_2$ to catalyze the reaction failed completely, leading to a mixture of unidentified products.



Scheme 4.19

The overall results for the Diels-Alder reactions of ADA ester **1e** with various types of diene are summarized in Table 4.3. In summary, the dienes without α-hydroxy groups afforded stable cycloadducts, but disappointingly, gave poor diastereoselectivity. This was only marginally increased in the presence of the Lewis acid $MeAlCl_2$. In reactions with *o*-QDMs, diastereofacial selectivity was poorer than when using the fumarate of methyl (*S*)-lactate (**31**), which is known to give *de*'s of >95%.[19,27] Even though reasonable diastereoselectivity was observed in reactions with α-hydroxy-*o*-QDMs, the cycloadducts tended to be fairly unstable due to their ease of dehydration. The reaction of isobenzofuran **17** with ADA ester **1e** was nonselective, and was not

suitable for use in the preparation of diastereomerically pure aryltetralins. The use of the Lewis acids Et_2AlCl or $MeAlCl_2$ to catalyze this reaction stopped cycloadduct formation entirely. Diels-Alder reaction of **1e** and a diene with a more flexible hydroxyl group (**18**) did not give any better stereoselectivity.

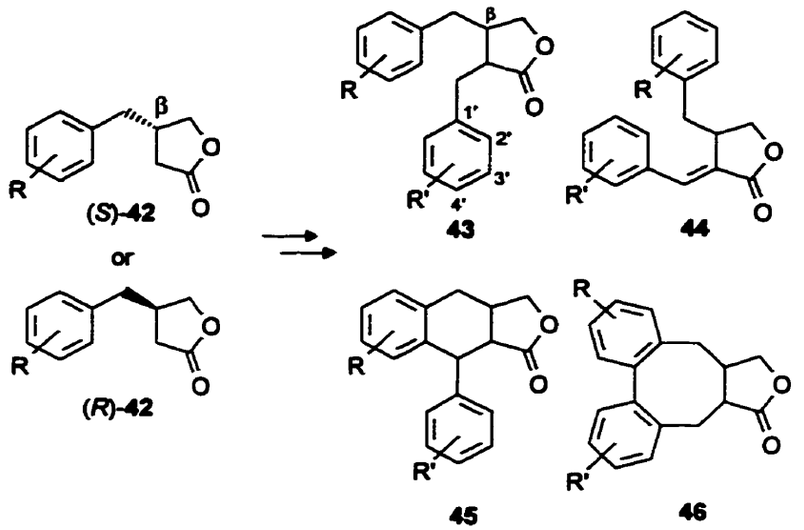
Table 4.3. Yields and diastereomer ratios of the Diels-Alder reactions of bis-(methyl (*S*)-lactyl) ester of ADA (1e) with various dienes.

Type of Diene	Cycloadducts (% yield)[a]	Ratio of two Diastereomers[b]	Aromatization Product (% Yield)[c]
Phenylbutadiene **14**	82 75[d]	1 : 1.3 1 : 2[d]	92
o-QDM **15**	62	1 : 1.3	90
o-QDM **12**	46	1 : 5	39
o-QDM **16**	82	1 : 2	80
Isobenzofuran **17**	20	1 : 1.2	80
2,4-hexadiene-1-ol (**19**)	86	1 : 1.3	90

[a] After chromatography
[b] Measured using the integration ratios of their ^{1}H-NMR ($CDCl_3$) spectra.
[c] Either isolated from the cycloaddition reactions, or after specific treatments of the cycloadducts for structural confirmation (see Experimental).
[d] $MeAlCl_2$ catalyzed (see Experimental).

4.2 Asymmetric Synthesis of Benzylidenebenzylbutyrolactone and Dibenzylbutyrolactone Lignans Using Oxazolidinones as Chiral Auxiliaries

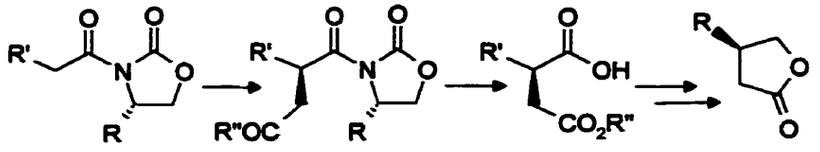
Many of the methods for the asymmetric synthesis of chiral lignans have involved the intermediacy of enantiomerically pure β-benzyl-γ-butyrolactones, (*S*)- and (*R*)-**42** (see Section 1.4.1 for more discussion). These have been used in the synthesis of dibenzylbutyrolactones **43**, benzylidenebenzylbutyrolactones **44**, aryltetralins **45**, and dibenzocyclooctadienes **46**, as illustrated in Scheme 4.20.



Scheme 4.20

In comparison to other general methods for lignan synthesis, the use of butyrolactones **42** as intermediates offers more flexibility in structural variability that can be achieved otherwise. Therefore, a method for the asymmetric synthesis of lignans via chiral β-benzyl-γ-butyrolactones was considered.

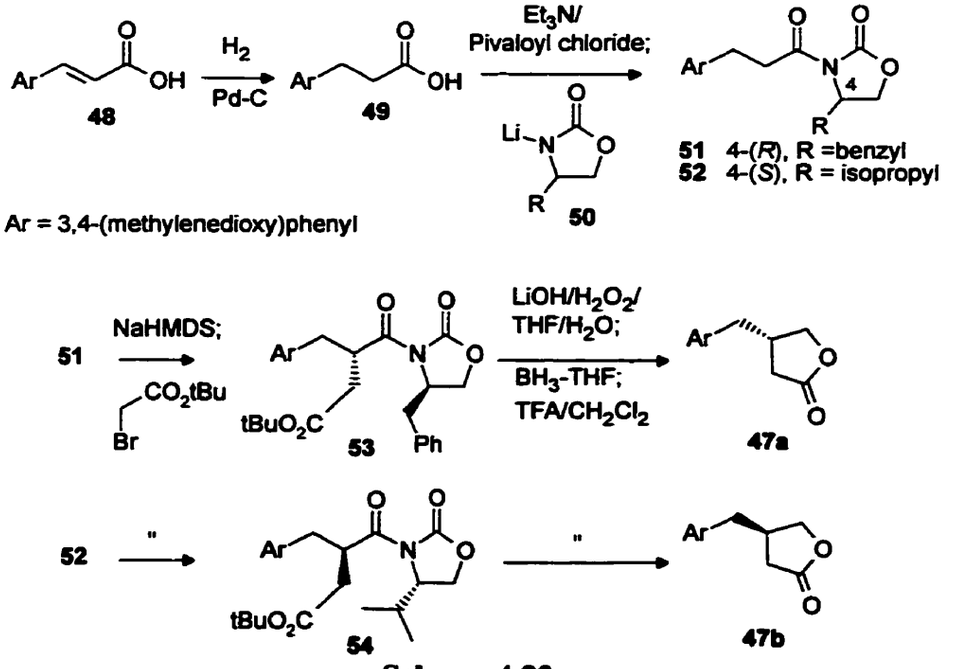
After examining several possible asymmetric routes to chiral benzylbutyrolactones **42** (see Section 1.4.1 for literature review), a route based on the use of oxazolidinone chiral auxiliaries was adopted. Substituted oxazolidinone heterocycles[28] are effective chiral auxiliaries giving excellent asymmetric induction in reactions such as alkylations, hydrogenations, and Diels-Alder reactions. Enolates derived from N-acyloxazolidinones can be alkylated with α-bromoacetate to afford diastereomerically pure substituted succinate derivatives.[29] After the removal of the oxazolidinone chiral auxiliary, the chiral half ester can be reduced and lactonized to afford the β-substituted butyrolactones in high optical purity (Scheme 4.21).[29a]



Scheme 4.21

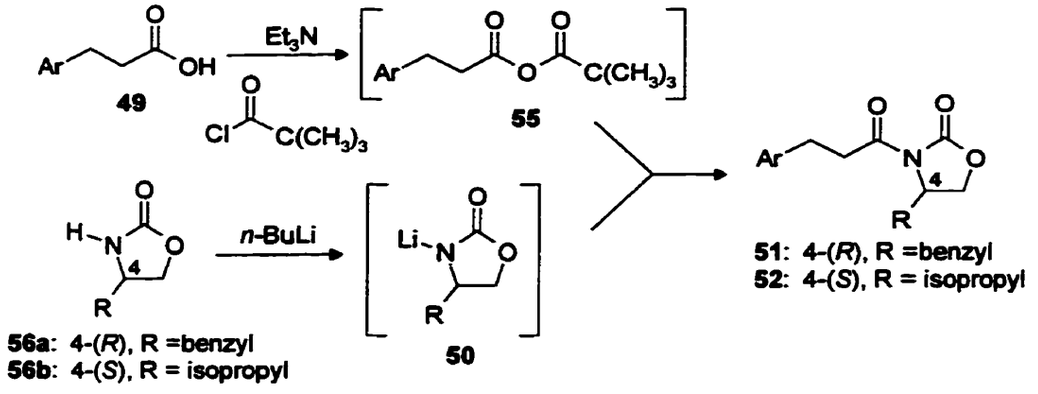
We have used this simple and versatile method for the asymmetric synthesis of β-benzyl-γ-butyrolactones, **47a** and **47b** (see Scheme 4.22 later). These were subsequently transformed into the benzylidenebenzylbutyrolactone lignans gossypifan and savinin via aldol condensation/dehydration reactions, and into the dibenzylbutyrolactone lignan 4'-demethylyatein, through alkylation (see discussion later).

The enantiomerically pure (*S*)- and (*R*)-β-3,4-(methylenedioxy)benzyl-γ-butyrolactones (**47a** and **47b**, respectively) were efficiently synthesized in six steps from 3,4-(methylenedioxy)cinnamic acid (**48**), as shown in Scheme 4.22, in an overall yield of >45%.



Scheme 4.22

3,4-(Methylenedioxy)cinnamic acid (**48**) is commercially available, but was synthesized here by heating 3,4-(methylenedioxy)benzaldehyde and malonic acid in pyridine/piperidine. Hydrogenation of cinnamic acid **48** using Pd/C in DMF under H_2 at atmospheric pressure afforded dihydrocinnamic acid **49** in excellent yield. Using a modified literature procedure,[29] commercially available (4*R*)-benzyl (**56a**) and (4*S*)-isopropyl-2 oxazolidinone (**56b**) were each N-acylated with dihydrocinnamic acid **49** to give N-acyloxazolidinones **51** and **52** in 88% and 84% yield, respectively, as detailed in Scheme 4.23. The N-acylation was achieved by treating dihydrocinnamic acid **49** with pivaloyl chloride and triethylamine to give an ahydride intermediate **55**, which was then reacted with the oxazolidinone anions **50** to afford the N-acylated products (**51** and **52**).



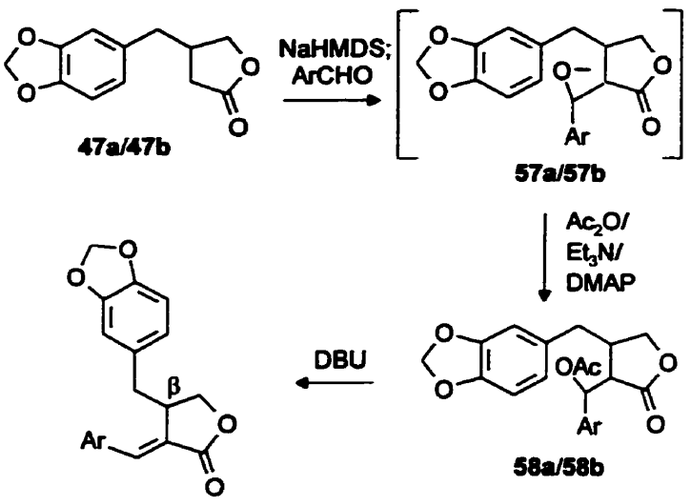
Scheme 4.23

The N-acyloxazolidinones **51** and **52** were treated with NaHMDS and the resultant enolates were alkylated with *t*-butyl bromoacetate diastereoselectively to afford one major diastereomer in each case (**53** and **54**, respectively *ca.* 80% yield), having >95% diastereomeric excess as shown by ^{1}H NMR spectroscopy. Although the absolute

configuration could not be determined at this stage it was expected to be that shown in Scheme 4.22. The oxazolidinone chiral auxiliaries of **53** and **54** were removed with $LiOH/H_2O_2$ without affecting the *t*-butyl ester. The resulting crude acids were reduced to alcohols using BH_3·THF, then lactonized with TFA to afford the benzylbutyrolactones **47a** and **47b** in about 70% yield from the N-acyloxazolidinones **53** and **54**, respectively. The benzylbutyrolactones **47a** and **47b** have optical activities and other spectroscopic characteristics consistent with previously reported values.[30] Based on their optical activity, the enantiomeric excesses of these lactones were >95%. The chiral auxiliaries, (4*R*)-benzyl- (**56a**) and (4*S*)-isopropyl-2-oxazolidinone (**56b**), were readily recovered from the lactonized product by chromatography. Compared to previously reported methods (see Section 1.4.1), the present approach to the synthesis of β-benzyl-γ-butyrolactones (general structure **42**) is more efficient. It is simple, gives high asymmetric induction, and uses commercially available reagents.

Having obtained the enantiomerically pure butyrolactones **47a** and **47b**, their conversion to optically pure lignans was undertaken. The benzylidenebenzylbutyrolactone lignans gossypifan (**59a**) and savinin (**59b**) were synthesized from **47a** and **47b** following a modified literature procedure[31] as illustrated in Scheme 4.24. The benzylbutyrolactones **47a** and **47b** were each deprotonated with NaHMDS, and then treated with 3,4-dimethoxybenzaldehyde (for **47a**) and 3,4-(methylenedioxy)benzaldehyde (for **47b**) to afford aldol products **57a** and **57b** which were acetylated in situ by adding a mixture of Ac_2O/DMAP/Et_3N to the reaction mixtures. The crude acetylated products **58a** and **58b** were then treated with DBU in

refluxing toluene to produce the *trans*-benzylidene lignans gossypifan (**59a**) and savinin (**59b**), respectively, in >90% overall yield (from benzylbutyrolactones **47**).

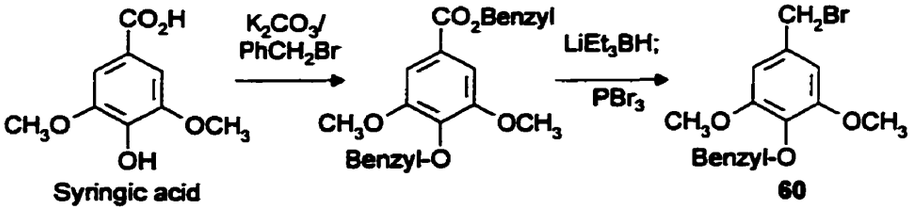


Scheme 4.24

Gossypifan (**59a**) is a naturally occurring lignan recently isolated from a plant (*Jatropha gossypifolia*) and possesses medicinal and pesticidal properties.[32] The synthetic material, **59a**, had both rotation and other spectroscopic properties consistent with those reported for the natural product.[32] This is the first reported synthesis of this compound. Similarly, savinin (**59b**), which is an insecticide synergist,[33] also had properties consistent with those previously reported.[34]

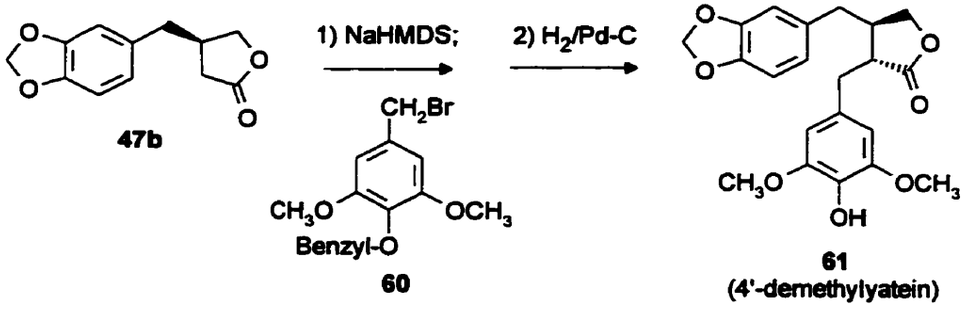
In addition to savinin (**59b**), butyrolactone **47b** was also converted to 4'-demethylyatein (**61**, see Scheme 4.26 later), a naturally occurring dibenzylbutyrolactone lignan which has been regarded as a biosynthetic precursor to 4'-demethylpodophyllotoxin derivatives (see Section 4.3.2 for more detail).[35] Benzylbromide **60**, which was used in the alkylation reaction of butyrolactone **47b**, was

prepared from syringic acid by dibenzylation using benzylbromide, reduction using $LiEt_3BH$, and bromination using PBr_3[36], as shown in Scheme 4.25.



Scheme 4.25

The butyrolactone **47b** was treated with NaHMDS and reacted with benzylbromide **60**. Careful control of the reaction temperature during benzylation of **47b** was necessary in order to prevent formation of the dibenzylated product. HMPA, often used for this type of benzylation, was not required for this reaction. The resulting crude 4'-benzylated yatein was hydrogenated to afford 4'-demethylyatein (**61**) in an overall yield of 62% from **47b** (see Scheme 4.26). The synthetic 4'-demethylyatein (**61**) had spectroscopic properties identical to those reported previously.[37]



Scheme 4.26

In conclusion, a versatile asymmetric synthesis of β-benzyl-γ-butyrolactones (general structure **42**), key intermediates in the synthesis of lignans, was achieved using a six step procedure, in an overall yield of >45% from 3,4-(methylenedioxy)cinnamic acid.

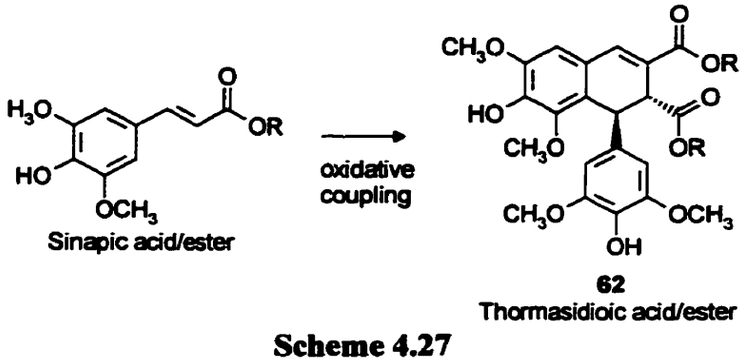
The method afforded the β-benzyl-γ-butyrolactones in >95% optical purity. These intermediates were used in the synthesis of the benzylidene lignans gossypifan and savinin, and the dibenzylbutyrolactone lignan 4'-demethylyatein, in good to excellent yield.

4.3 THE STUDY OF INTRAMOLECULAR OXIDATIVE COUPLING REACTIONS

This section is separated into two parts. The first part deals with the synthesis and the study of oxidation reactions of disinapic acid esters and anhydride. The second part of this section details the oxidation study of a naturally occurring dibenzylbutyrolactone lignan, 4'-demethylyatein.

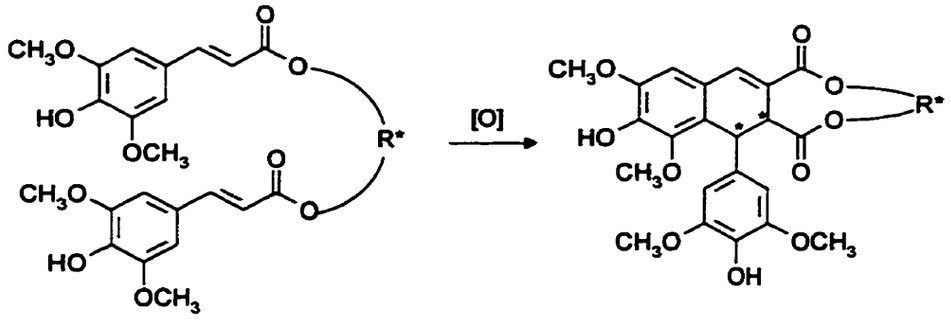
4.3.1 The synthesis and the Study of Oxidation Reactions of Disinapic Acid Esters and Anhydride

Sinapic acid and esters in basic buffer solution have been found to effectively undergo intermolecular oxidative coupling reactions in the presence of oxygen to afford the dihydroarylnaphthalene lignan ester **62** (Scheme 4.27),[38] the free acid of which is a naturally occurring lignan.[39]



Scheme 4.27

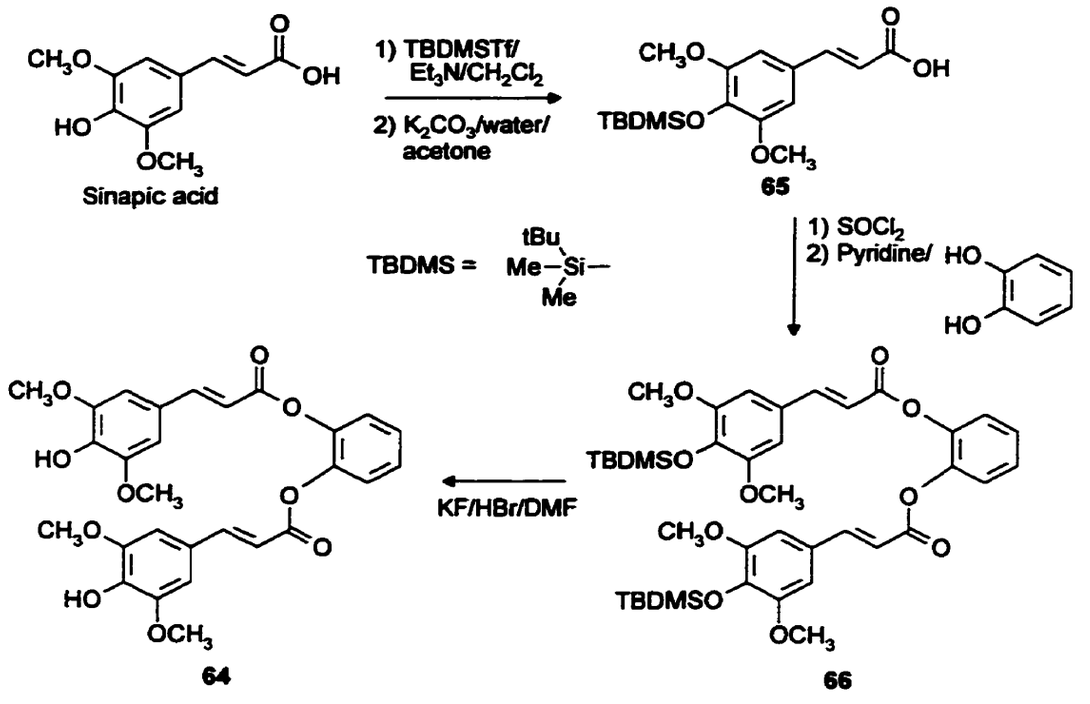
In view of this interesting oxidation results, a study of intramolecular oxidative coupling of diol disinapates **63** was undertaken, in the hope that the absolute and relative stereochemistry of the adduct could be controlled using either a chiral diol R*, or a chiral oxidant (see Scheme 4.28).



63

Scheme 4.28

At the outset of this project, catechol disinapate **64** was prepared, as illustrated in Scheme 4.29. Sinapic acid was treated with 2 equivalents of TBDMSTf, followed by hydrolysis of the TBDMS ester to afford the protected acid **65** in 85% yield. The acid **65** was then treated with thionyl chloride in CCl_4 and the resulting acid chloride was esterified with 0.5 equivalent of catechol to afford the diprotected diester **66** in 68% yield. Deprotection of the phenolic groups was achieved in DMF with KF and a catalytic amount of 50% aqueous HBr, affording diester **64** in 95% yield.



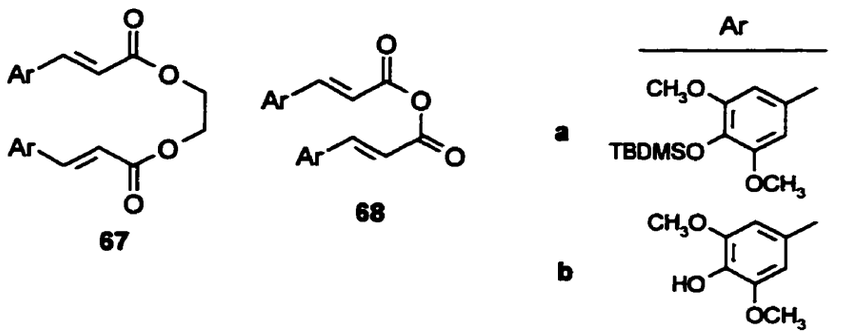
Scheme 4.29

The oxidation of diester **64** were conducted using various oxidants such as O_2, DDQ, $FeCl_3$, $Fe(ClO_4)_3$, $Ce(NH_4)_2(NO_3)_6$, and Tl_2O_3. The diester was first dissolved in solvent or a solvent mixture, and then the oxidant in solvent added dropwise (except for the oxidant O_2, which was supplied in air bubbling through the solution). The reactions were run for about 15 min at various temperatures. Unfortunately, despite repeated attempts to affect the intramolecular coupling of diester **64** with the above described oxidants, only unidentifiable products were produced

The inability to induce intramolecular coupling in the catechol diester **64** may have been due to a stiffness in the diester linkage that sterically hindered the coupling process. It was suspected that intermolecular coupling and eventual polymerization was a more favorable process, leading to the formation of intractable mixtures of products.

However, even conducting the oxidation reactions at lower substrate concentrations did not have any effect on the outcome of the reactions.

Two other disinapic acid substrates were also prepared in order to study intramolecular oxidative coupling. These were the ethylene glycol diester **67b**, and disinapic acid anhydride **68b** (Scheme 4.30). The TBDMS-protected diester **67a** and the deprotected diester **67b** were prepared as described for **66** and **64**, whereas anhydride **68b** was prepared by treating the 4-protected sinapic acid **65** with TFAA at ice temperature, followed by deprotection of the 4-hydroxyl group of **68a** as described for **64**.



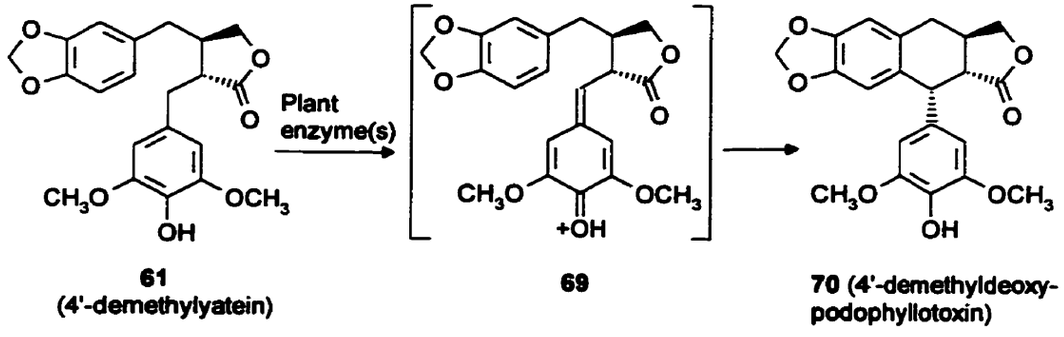
Scheme 4.30

Purified diester **67b** and anhydride **68b** were characterized only by ^{1}H NMR spectroscopy before being used in the following oxidation reactions. Attempts were made to induce intramolecular oxidative coupling in these two substrates using the same oxidants and conditions described above for the catechol diester **64**. Similar to the catechol diester **64**, the results from the attempted coupling reactions of both diester **67** and anhydride **68** were very disappointing. Both substrates gave only mixtures of unidentifiable products. These results discouraged any further study of the intramolecular oxidative coupling of disinapic acid derivatives. The procedure for the preparation of ester **64** and its full

characterization is provided in the Experimental section. The partially characterized ester **67** and anhydride **68** (characterized by ^{1}H NMR only) were not further characterized due to the complete failure of their subsequent oxidation reactions. However, their preparation procedures and ^{1}H NMR data are provided in the Experimental section for reference purposes.

4.3.2 Oxidation Reactions of 4'-Demethylyatein Using DDQ

The study of intramolecular oxidative coupling reactions of a naturally occurring dibenzylbutyrolactone lignan, 4'-demethylyatein (**61**), was proposed due to its availability from the previous project (see Section 4.2) and the possibility that this compound is an intermediate in the biosynthesis of certain cyclolignans.[35] 4'-Demethylyatein is considered to be a biosynthetic precursor to aryltetralin lignans having the podophyllotoxin pattern of substitution (see Scheme 4.31).[35] It has been proposed that oxidation to a quinone methide **69** is followed by cyclization to 4'-demethyldeoxypodophyllotoxin (**70**) as depicted in Scheme 4.31.



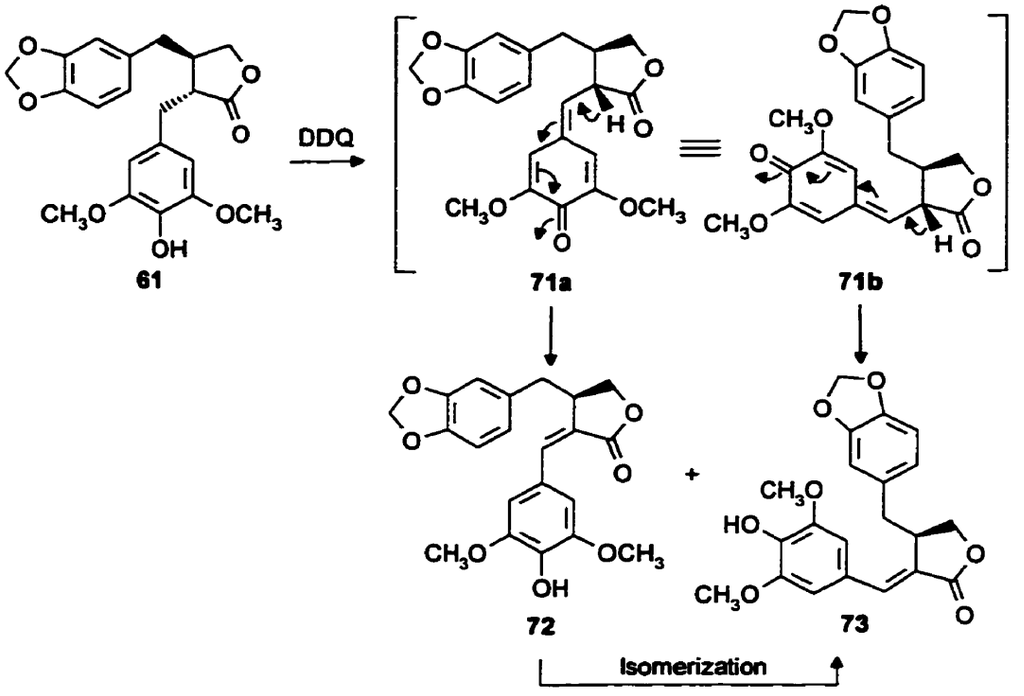
61 (4'-demethylyatein) **69** **70** (4'-demethyldeoxy-podophyllotoxin)

Scheme 4.31

As described in Section 1.5, Kende *et al.* was able to mimic the biosynthetic pathway and oxidatively cyclize a similar diarylbutane.[40] In addition, Pelter *et al.* have reported a successful oxidative cyclization of a monophenolic dibenzylbutyrolactone using PIFA as oxidant, a procedure that afforded a mixture of dibenzocyclooctadiene diastereomers in good yield.[41] Despite these precedents, attempts to cyclize 4'-demethylyatein itself by others were unsuccessful.[42] A reexamination of the oxidation of this biologically important precursor, using DDQ as oxidant, was undertaken.

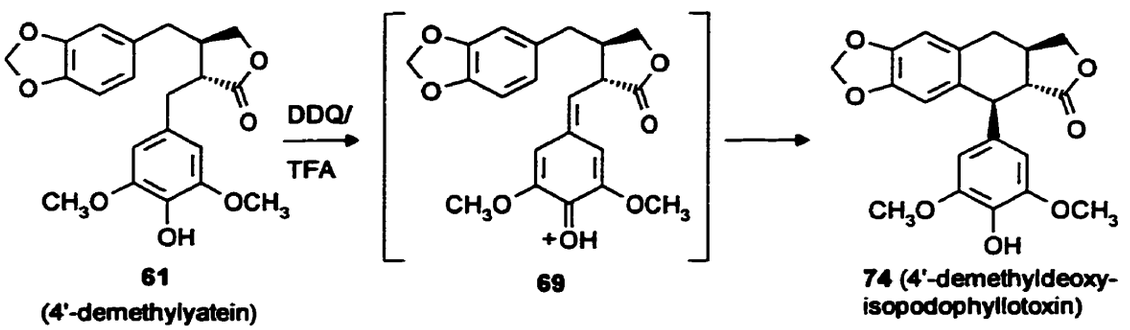
The oxidation reactions of 4'-demethylyatein using DDQ were very successful. Oxidation of this substrate with DDQ in THF at room temperature resulted in the formation of a mixture of two compounds, *cis*- and *trans*-benzylidenelactones, **72** and **73**, in 95% total yield. The ratio of the *cis*- to *trans*-isomer was about 1.3:1, as determined by ^{1}H NMR spectroscopy. The proposed mechanism is shown in Scheme 4.32. Similar to the proposed biosynthetic mechanism illustrated in Scheme 4.31, quinone methide **71** is considered to be the reactive intermediate. Elimination of a proton from **71** (from conformations **71a** or **71b**) could lead to **72** or **73**. The oxidation result obtained for 4'-demethylyatein appears to confirm the possibility that benzylidene lignans such as **72** and **73** (general structure **44** in Scheme 4.20) are formed biosynthetically via oxidation of dibenzylbutyrolactones **43** (Scheme 4.20).[35a] After standing exposed to the air at room temperature for two weeks, *cis*-benzylidenelactone **72** isomerized to the *trans*-isomer **73**, leaving only **73**. The isomerization process could also be achieved in 2 h by irradiating a refluxing solution of the *cis*- and *trans*-isomeric mixture with iodine in benzene. The

isomerization process indicates the instability of the *cis*-isomer **72** and may explain the lack of reports of isolation of *cis*-benzylidenebenzylbutyrolactone lignans from plants.



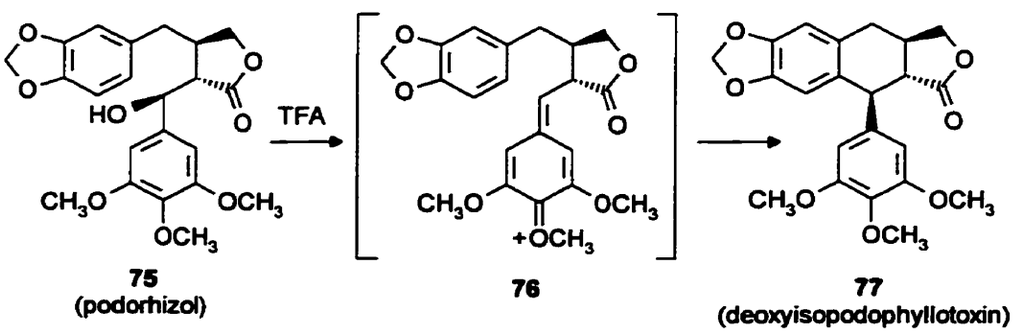
Scheme 4.32

If quinone methide **71** is formed during oxidation of **61**, addition of acid might divert it from the elimination reaction and into an alternative reaction pathway. Treating 4'-demethylyatein with DDQ in the presence of TFA resulted in the formation of 4'-demethylisodeoxypodophyllotoxin (**74**), a naturally occurring all *trans*-aryltetralin lignan (Scheme 4.33), in about 65% yield after recrystallization and preparative TLC. The concentration and the ratio of substrate to reagent were found to be very critical to the cyclization process.



Scheme 4.33

Protonated quinone methide **69** is proposed as the intermediate in the cyclization reaction. Friedel-Crafts substitution on the other aryl group would lead to compound **74**. Notably, **74** has an all *trans*-geometry in contrast to the podophyllotoxin type of stereochemistry often found in aryltetralin lignans formed biosynthetically (see **70** in Scheme 4.31). An all *trans*-stereochemistry (see **77** in Scheme 4.34) is also found in the product obtained from the acid-catalyzed cyclization of podorhizol (**75**) and structural analogs.[35a] These reactions presumably involve an intermediate delocalized benzylic cation similar to **69** (see **76** in Scheme below).



Scheme 4.34

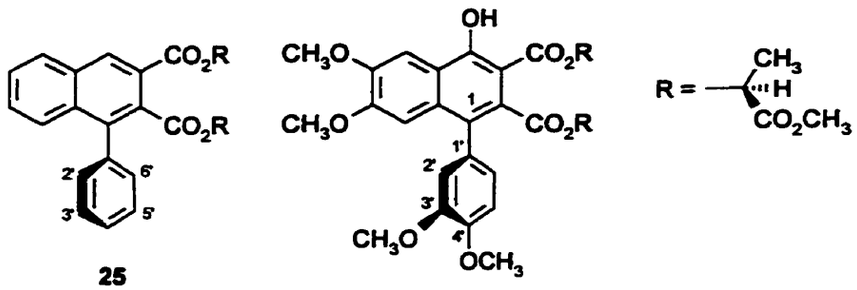
To the best of our knowledge, the oxidative conversion of a monophenolic dibenzylbutyrolactone lignan to either an aryltetralin lignan or

benzylidenebenzylbutyrolactone is unprecedented. Despite the fact that these reactions have been proposed biosynthetically they have not previously been demonstrated in the laboratory. Combining our current results with the earlier observations of Pelter *et al.*,[41] it now seems reasonable to conclude that benzylidenebenzylbutyrolactone, aryltetralin, and dibenzocyclooctadiene lignans with 4'-hydroxyl groups (**44**, **45**, and **46** in Scheme 4.20) could all arise biosynthetically from a common 4'-hydroxydibenzylbutyrolactone precursor. The successful cyclization reaction of 4'-demethylyatein with DDQ/TFA has also provided a new method for the synthesis of aryltetralin lignans.

4.4 HINDERED ROTATION IN ARYLNAPHTHALENE LIGNANS

Although hindered rotation and atropisomerism have been studied in some 1-substituted naphthalenes (sulfoxides, amines, ketones and imines) there are relatively few studies of atropisomerism in 1-phenylnaphthalenes (more discussion in Chapter 2). To our knowledge there have been no dynamic NMR studies of such compounds and few reports of stable atropisomers.

In the work discussed in Section 4.1.2, we noted that arylnaphthalenes **25** and **37** (structures are given in Scheme 4.35) showed a doubling of peaks for some NMR transitions.

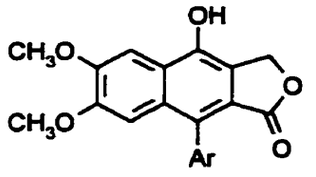


Scheme 4.35

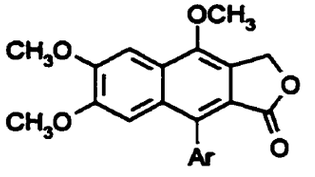
For instance, in compound **25** the 2' and 3' carbons appeared at a different chemical shift than the 6' and 5' carbons in the ^{13}C NMR spectrum. This meant that the rotation of the phenyl group was slow enough on the NMR time scale to make C-2' (C-3') diastereotopic with respect to C-6' (C-5'). Similarly in compound **37**, a doubling of many lines was observed. In this case the hindered rotation of the unsymmetrical phenyl group gave rise to a new element of asymmetry and the existence of two different diastereomers whose lifetimes were long enough that the individual isomers could be observed in the NMR spectrum.

A relatively high barrier to rotation may give rise to separable rotational enantiomers (atropisomers) which might have quite different pharmacological properties. In order to investigate this possibility we have synthesized the natural products diphyllin (**78**), justicidin A (**79**), justicidin B (**80**), retrojusticidin B (**81**), helioxanthin (**82**), and retrohelioxanthin (**83**), as well as seven other arylnaphthalene lignan analogs **25**, **37**, and **84-88** (see Schemes 4.35 and 4.36). The synthetic methods are described in the first part of this section.

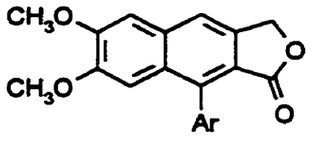
Lignan Natural Products



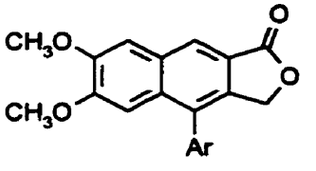
78 (diphyllin)



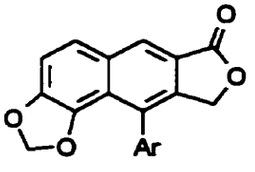
79 (justicidin A)



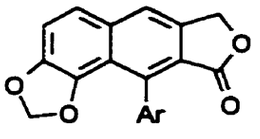
80 (justicidin B)



81 (retrojusticidin B)



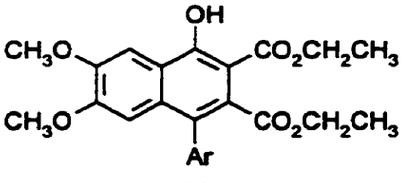
82 (helioxanthin)



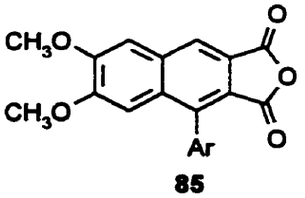
83 (retrohelioxanthin)

Ar = 3,4-(methylenedioxy)phenyl

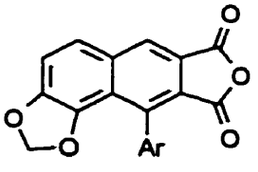
Lignan Analogs



84

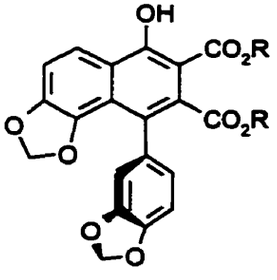


85

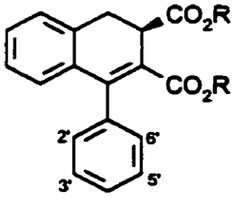


86

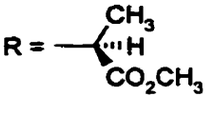
Ar = 3,4-(methylenedioxy)phenyl



87



88



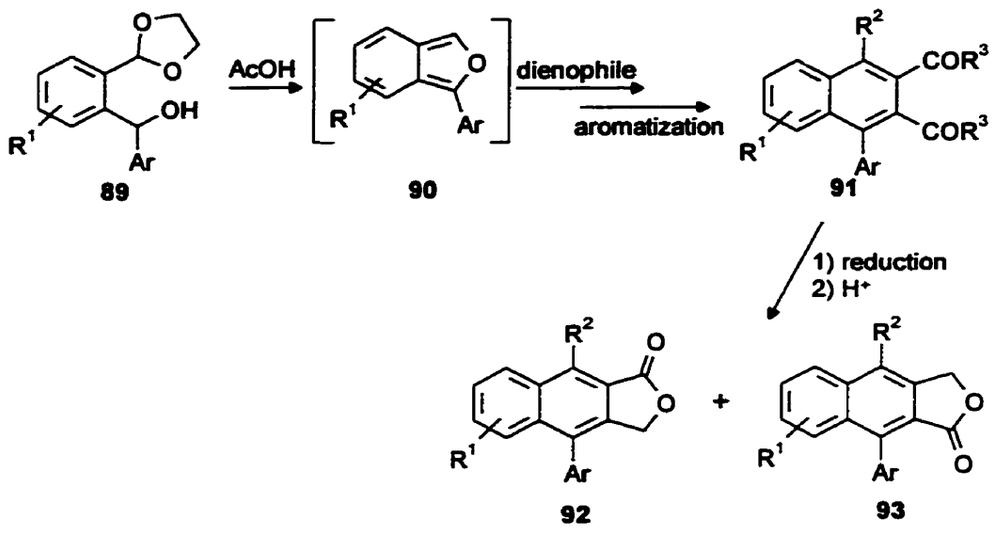
Scheme 4.36

The aryl-naphthalene rotational barrier in these compounds (except for **85** and **86**) was studied by dynamic NMR and low temperature HPLC and the experimentally found

barriers were compared to those obtained from molecular orbital calculations. These details are discussed in the second part of this section.

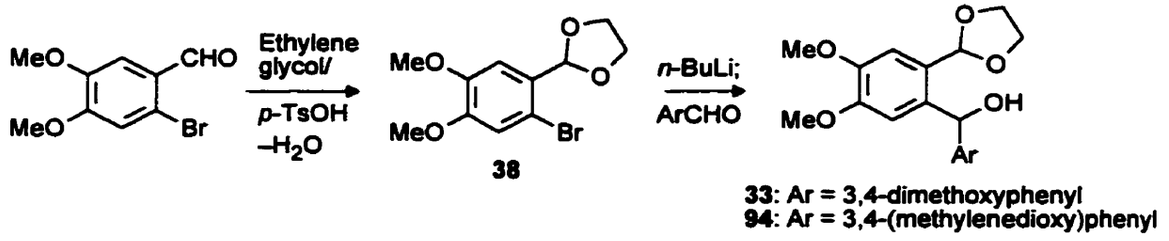
4.4.1 Synthesis of Arylnaphthalene Lignans

The synthesis of arylnaphthalene lignans has been reviewed in Section 1.3.2. One of the literature methods for the synthesis of arylnaphthalene lignans, which employed the Diels-Alder reactions of isobenzofurans as key step, was found to be very useful during our study of the Diels-Alder reactions of bis-(methyl (*S*)-lactyl) ester of ADA (**1e**) (see Section 4.1.2). In the study, although **1e** reacted non-diastereoselectively with an isobenzofuran, the resulting unstable diastereomeric cycloadducts further aromatized *in situ* to afford arylnaphthalene analog **37** in excellent yield. Therefore, the Diels-Alder reaction of isobenzofuran was incorporated as key step in the approach designed for the preparation of other arylnaphthalene lignans and analogs listed in Scheme 4.36. The general synthetic approach is summarized in Scheme 4.37. The transient isobenzofurans **90** generated from hydroxyacetals **89** by acid catalysis will be trapped with dienophiles such as acetylenedicarboxylates and maleic anhydride. The resulted acid-sensitive Diels-Alder cylcoadducts will further undergo aromatization to afford arylnaphthalene lignan analogs with general structure **91**. The reduction of **91** should afford arylnaphthalene lactones **92** and/or **93**, the general structures found in most of the natural arylnaphthalene lignans.



Scheme 4.37

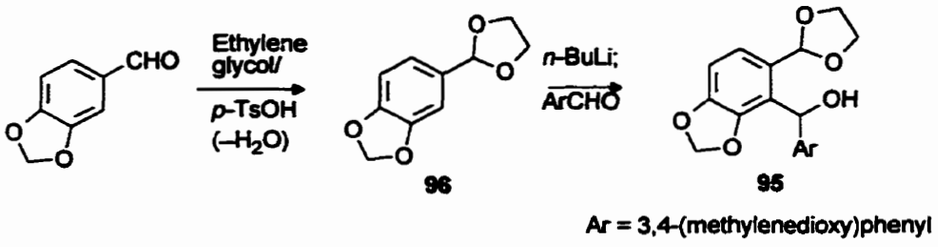
Hydroxyacetals **33** and **94** illustrated in Scheme 4.38 were the isobenzofuran precursors used for the preparation of arylnaphthalenes **37**, and **84** and **85**, respectively (see Scheme 4.35 and 4.36 for structures). The procedure for the preparation of **33** has already been described in Section 4.1.2 and the same procedure was also used for the preparation of hydroxyacetal **94**. The synthesis of hydroxyacetals **33** and **94** via acetal **38** is summarized in Scheme 4.38.



Scheme 4.38

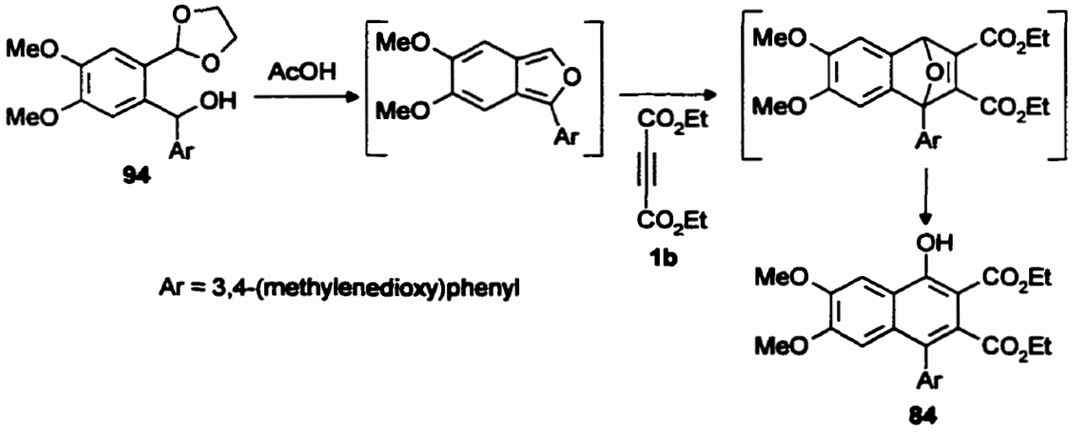
Hydroxyacetal **95**, the isobenzofuran precursor used for the preparation of arylnaphthalenes **86** and **87** (see Schemes 4.36 for structures), was prepared using a

modified literature procedure by direct *ortho*-lithiation of acetal **96** using *n*-BuLi, followed by addition to piperonal (Scheme 4.39).[24]



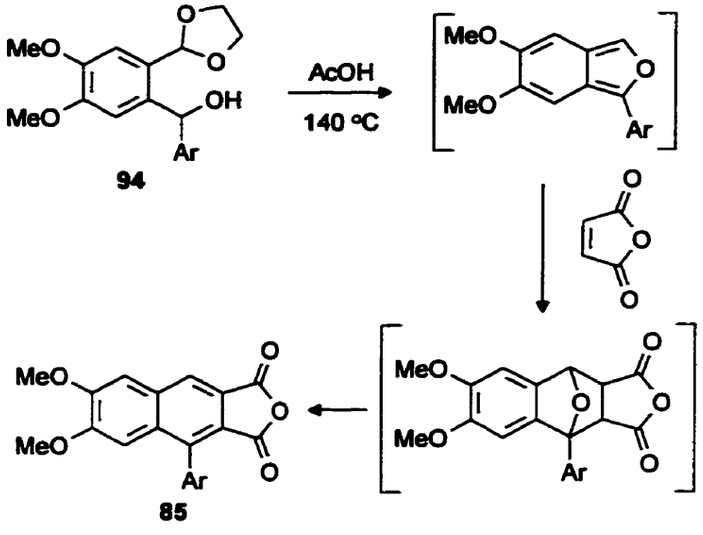
Scheme 4.39

Because hydroxyacetals **33**, **94** and **95** were unstable intermediates which decomposed on standing, they were not isolated, but were converted directly to the transient isobenzofurans by heating in the presence of AcOH. The synthesis of arylnaphthalene **37** from hydroxyacetal **33** and ADA ester **1e** has already been described in section 4.1.2 (see Scheme 4.17). Following the procedure described for **33**, hydroxyacetal **94** was converted to an isobenzofuran and reacted with diethyl acetylenedicarboxylate (**1b**) to afford arylnaphthalene **84** in 80% yield after recrystallization from CH_2Cl_2/hexanes (Scheme 4.40).



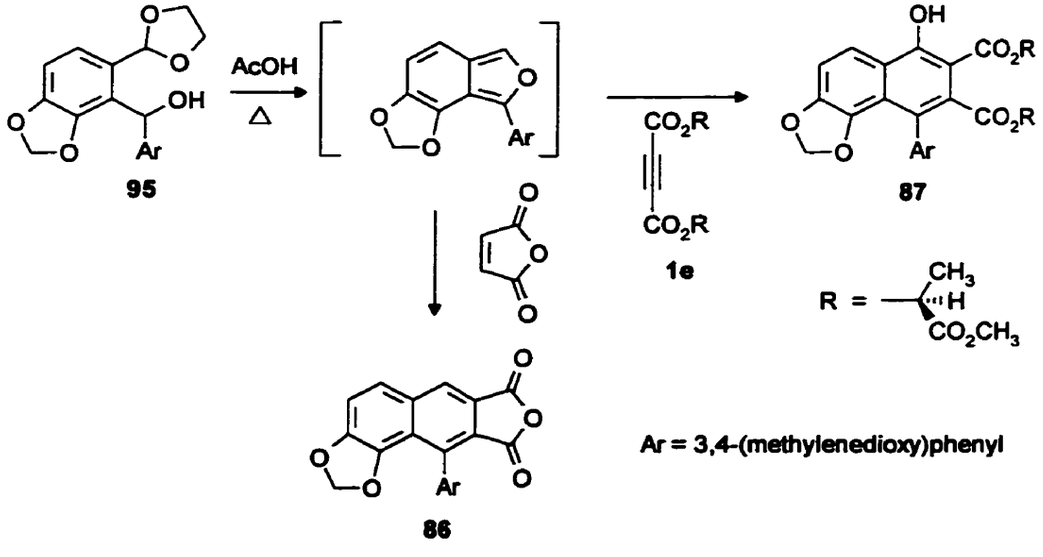
Scheme 4.40

The isobenzofuran generated from hydroxyacetal **94** was also trapped with maleic anhydride in Ac_2O at 140 °C to afford arylnaphthalene **85** in good yield (Scheme 4.41).



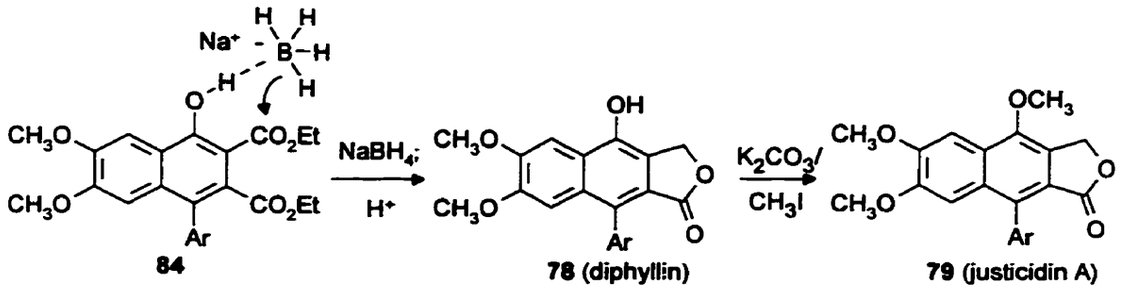
Scheme 4.41

Hydroxyacetal **95** was similarly heated with maleic anhydride and **1e** in glacial $AcOH/CH_2Cl_2$ to give arylnaphthalenes **86** and **87**, respectively (see Scheme 4.42).



Scheme 4.42

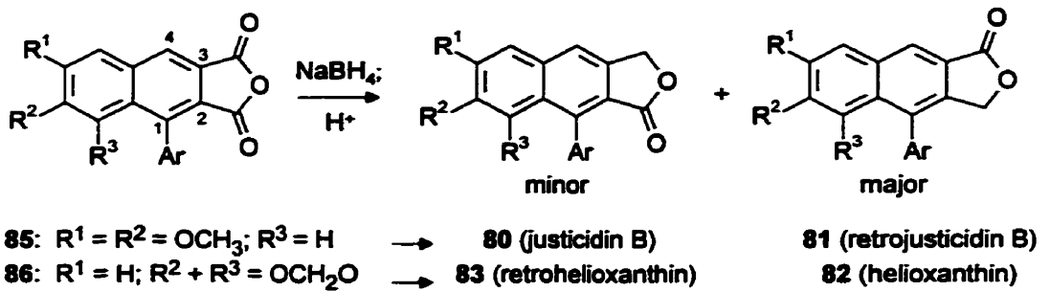
Arylnaphthalene **84**, the product from Diels-Alder reaction of hydroxyacetal **94** and diethyl acetylenedicarboxylate (**1b**) (see Scheme 4.40), was reduced regioselectively by $NaBH_4$, and lactonized with dilute aqueous HCl to give diphyllin (**78**) as the only product. The phenolic group of **84** is believed to guide reduction at the adjacent ester group, leading to selective formation of one of the two possible lactones. Methylation of diphyllin's phenolic group with methyl iodide/K_2CO_3 in refluxing acetone afforded justicidin A (**79**) in 95% yield. The reduction of **84** and methylation of diphyllin (**78**) are illustrated in Scheme 4.43.



Ar = 3,4-(methylenedioxy)phenyl

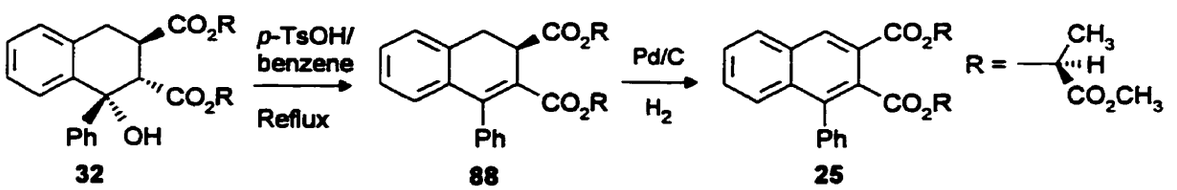
Scheme 4.43

The anhydrides **85** and **86** (see Schemes 4.41 and 4.42 for the preparation) which were only characterized by ^1H NMR were converted to mixtures of lactones **80** and **81**, and, **82** and **83**, respectively, by reducing with $NaBH_4$ followed by treatment with acid (Scheme 4.44). In the absence of a 4-phenolic group to direct the attack of $NaBH_4$, the reduction of **85** and **86** occurred preferably at the more hindered carbonyl carbon (*i.e.* the ester group at the 2-position) to afford, respectively, lactones **81** and **82** as major products. Although similar preferential attack of $NaBH_4$ at more hindered carbonyls has been reported by others,[43] the reason for this is not known.



Scheme 4.44

Phenylnaphthalene **25** was synthesized by aromatization of dihydronaphthalene **88** using Pd/C in refluxing xylenes (Scheme 4.45). Compound **88** was in turn prepared from the known cycloadduct **32** (preparation of **32** has already been described in Section 4.1.2) through dehydration catalyzed by *p*-TsOH (see Scheme 4.45 below). Although phenylnaphthalene **25** was also prepared as described in Section 4.1.2, the present approach was used here so that the hindered rotation in intermediate **88** could also be examined.



Scheme 4.45

4.4.2 The Study of Hindered Rotation in Arylnaphthalene Lignans

As stated previously, the main goal in studying hindered rotation in arylnaphthalenes is to determine if the hindered rotation can give rise to atropisomers (stable rotamers) that are isolable at room temperature. If so, it would be reasonable to

prepare and test the pharmacological activity of individual isomers. In order to accurately assess the stability of individual atropisomers at any temperature it is necessary to know the activation barrier for the rotation that interconverts the two isomers. A discussion of hindered rotation and atropisomerism, including the use of dynamic NMR and dynamic chromatography for the measurement of rotational energy barriers in organic molecules was presented in Chapter 2.

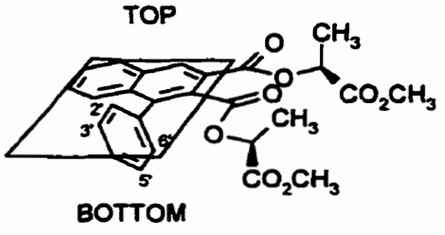
The possibility that there is hindered rotation in the arylnaphthalenes and dihydroarylnaphthalene lignans listed in Schemes 4.35 and 4.36 was first investigated by examining their ^{1}H NMR spectra obtained at room temperature. The NMR spectra of compounds **25, 37, 78-84,** and **87** at room temperature indicated that there was hindered rotation about aryl-naphthalene bond, whereas this property was absent in dihydronaphthalene **88** (for details see discussion below). Compounds **25, 37, 78-84,** and **87** were further studied by analyzing their NMR spectra at various temperatures above 300 K. Diphyllin (**78**) could not be analyzed at higher temperatures because of the lack of a high boiling solvent that was suitable for the NMR study. For solvents in which diphyllin was soluble (DMSO and cyclohexanol), there was insufficient separation of the diastereotopic protons to allow analysis of the spectra. Table 4.4 indicates the preliminary examination results, the conditions for the variable temperature NMR study, and the exchanging signals monitored.

Table 4.4. Solvent, temperature range and peaks analyzed for dynamic NMR study.

Compd	Solvent	Temp (°K)	Exchanging Signals
25	DMSO-d_6	300-383	129.82 (CH),130.16 (CH) C2' and C6'
37	DMSO-d_6	300-353	no broadening or coalescence
78	-	-	could not find suitable solvent
79	Toluene-d_8	300-363	5.27 (d, 1H, J = 1.48), 5.42 (d, 1H, J = 1.48) -OCH_2O-
80	Toluene-d_8	300-363	5.26 (d, 1H, J = 1.49), 5.40 (d, 1H, J = 1.49) -OCH_2O-
81	DMSO-d_6	300-353	5.26 (d, 1H, J = 14.8), 5.36 (d, 1H, J = 14.8) lactone CH_2
82	DMSO-d_6	300-358	6.06 (s, 1H, J =0.49), 6.11 (s, 1H, J = 0.49) phenyl -OCH_2O-
83	DMSO-d_6	300-338	5.91 (s, 1H), 5.93 (s, 1H) naphthyl -OCH_2O-
84	DMSO-d_6	300-353	no broadening or coalescence
87	DMSO-d_6	300-378	1.06 (d, 3H, J = 6.81), 1.01 (d, 3H, J = 6.81) lactyl C-CH_3
88	$CDCl_3$ or DMSO-d_6	300	no hindered rotation

Slow rotation about the aryl-naphthalene bond in compounds **25**, **37**, **78-84**, and **87** at the lowest temperature (300 K) gave rise to signals from individual diastereotopic protons/carbons (or from individual diastereomers for compounds **37** and **87**). As mentioned previously (see the beginning of Section 4.4), at the slow rotation limit, the 2'

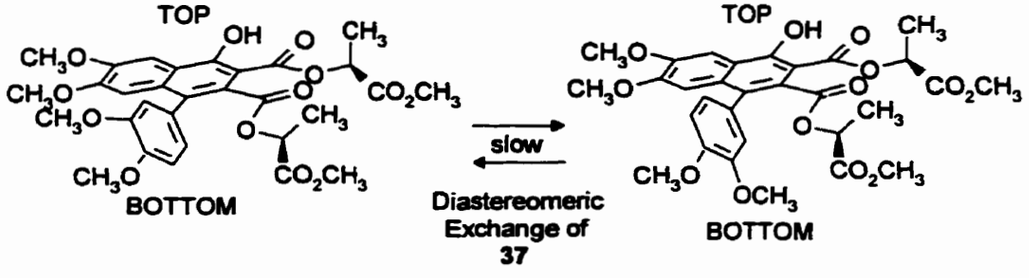
and 3' carbons in compound **25** are diastereotopic to the 6' and 5' carbons and appear at a different chemical shift in the ^{13}C NMR spectrum (Scheme 4.46).



25

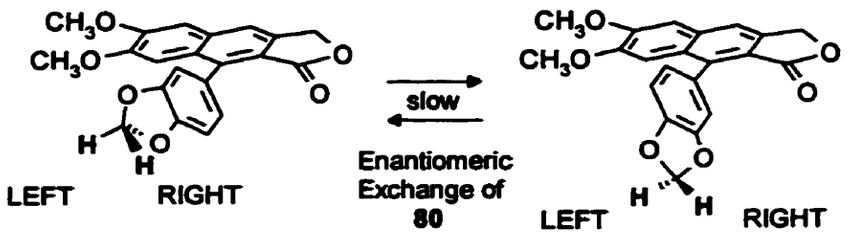
Scheme 4.46

Compounds **37** and **87** show a doubling of signals for all protons since slow rotation in these compounds gives rise to two diastereomers (Scheme 4.47), each with their own spectrum.



Scheme 4.47

In compounds **78-83**, all of the methylene groups (on both the methylenedioxy and lactone groups) give rise to AB patterns, rather than singlets, since the two protons are diastereotopic when rotation is slow (Scheme 4.48). Similar AB patterns are observed for the methylenedioxy protons in compound **84**.



Scheme 4.48

As the temperature increases, the rate of rotation of the pendent aryl ring increases, thereby speeding up the exchange of the diastereotopic protons (or the diastereomeric protons for compounds **37** and **87**). If the rotation is rapid enough the signals broaden and begin to coalesce. Peak broadening and coalescence were observed in compounds **25**, **79-83**, and **87**, but not in **37** and **84** even at 80 °C. Therefore, dynamic NMR analysis for the determination of the rate of, and barrier to, rotation was applicable only to compounds **25**, **79-83**, and **87** (see Section 2.2.1 for a discussion of dynamic NMR). For compound **37**, low temperature HPLC analysis on an achiral reverse phase column was used to estimate the barrier to rotation at a particular temperature (see discussion below). In the case of diphyllin (**78**) and compound **84**, the rotational barriers were instead determined by using dynamic subcritical fluid chromatography (dynamic SubFC) in collaboration with Wolf *et al.*[44] (see Section 2.2.2 for the introduction of dynamic chromatography, and discussion below for the work by Wolf *et al.*).

The experimental ^{1}H NMR spectra of the compounds which showed peak broadening and coalescence (*i.e.* **25**, **79-83**, and **87**) were simulated using the computer program DNMR3[45] (see Section 2.2.1). Required input parameters for this program were the chemical shifts (δ) of the signals being simulated, coupling constants among the

nuclei (J), the transverse relaxation time (T_2), the populations of the exchanging species, and the rate constant for exchange (k). The input parameters were manually adjusted until the simulated spectra visually matched the experimental spectra. As an example, the observed and simulated spectra for compound **87** are given in Figure 4.1, and the input parameters for DNMR3 program are given in Table 4.5 (dynamic NMR spectra and DNMR3 input parameters of other compounds are given in Appendix 1). In compound **87**, slow rotation of the pendent aryl ring gives rise to diastereomeric atropisomers. At low temperature the NMR spectrum of **87** exhibits four separate doublets for the lactyl methyls, and as the temperature increases, these four doublets slowly collapse and ultimately form two doublets (although this limit was not reached in the present study).

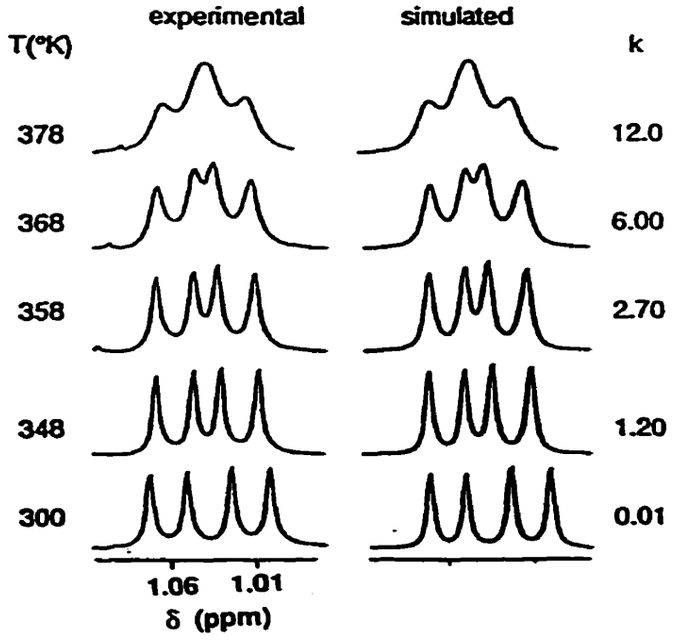


Figure 4.1. ^{1}H dynamic NMR spectra of lignan analog **87** (lactyl methyl region).

Table 4.5. Exchange Rate Constants (k), Free Energies of Activation for Exchange ($\Delta G^{\ddagger}$), Chemical Shifts of Exchange Signals (δ), Coupling Constants (J), and Transverse Relaxation Time T_2, as a Function of Temperature for Compound 87.

Temp, °K	k, s^{-1}	$\Delta G^{\ddagger}$,[a] kcal/mol	δ,[b] ppm	J,[c] Hz	T_2,[d] s
300	0.01	20.31	1.06, 1.01	6.81	0.20
348	1.20	20.35	1.11, 1.09	6.81	0.23
358	2.70	20.37	1.12, 1.09	6.81	0.24
368	6.00	20.38	1.13, 1.10	6.81	0.24
378	12.00	20.43	1.14, 1.11	6.81	0.24

[a] Calculated from $\Delta G^{\ddagger} = RT[23.760 + \ln(T/k)]$, where $R = 1.983 \times 10^{-3}$ kcal/mol/K.
[b] Chemical shifts for the exchanging lactyl methyl groups.
[c] Coupling constants to the neighboring methine hydrogen were constant for both signals.
[d] Transverse relaxation times measured from a reference signal.

Having determined the rate constants for rotamer interconversion at various temperatures, the enthalpies and entropies of activation ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively) for the rotational processes were calculated using the Eyring equation (see Section 2.3 for the discussion of the evaluation of activation parameters). For comparison purposes, the energy barrier to rotation ($\Delta G^{\ddagger}$), rate constants and thereby half-lives of the individual rotamers at 23 °C were recalculated using the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ obtained for each interconversion process (see the following for details). The half-lives of the rotamers at 23 °C will indicate if the individual rotamers can be isolated at room temperature.

The enthalpies and entropies of activation ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, see Table 4.6) for the rotational barrier in compounds **25**, and **79-83**, and **87** were determined based on equation (4.1):

$$k = \frac{k_B T}{h} e^{-\Delta H^{\ddagger}/RT} e^{\Delta S^{\ddagger}/R} \qquad (4.1)$$

by iterative non-linear least-square adaptation of the exponential plot of k versus T. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ obtained were then substituted into (4.1) to obtain a set of best curve-fit k values at various temperatures. Both sets of experimental and curve-fit k's were plotted as a function of temperature (T) using the linearized Eyring equation:

$$\ln (k/T) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R + \ln(k_B/h) \qquad (4.2)$$

to show how much the experimental k's deviate from the curve-fit k's. The Eyring plot of the experimental exchange rate constants for compound **87** is given in Figure 4.2.

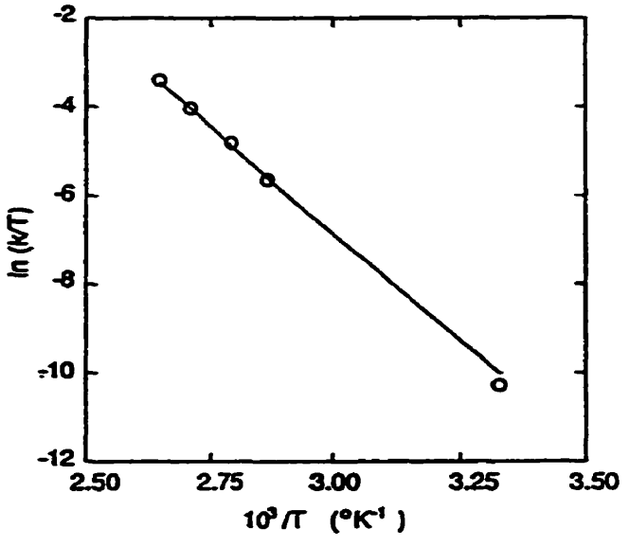


Figure 4.2. Eyring plot of rate constants (k) obtained from the analysis of the dynamic NMR spectra of **87**. The circles are data points for experimental k's and the straight line is for curve-fit k's.

The free energy of activation $\Delta G^{\ddagger}$, and half-life τ for exchange were calculated for each molecule at 23°C from equations (4.3) and (4.4), respectively:

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \qquad (4.3)$$

$$\text{and } \tau = 1/k \qquad (4.4)$$

where k was calculated from the fundamental Eyring equation:

$$k = \frac{k_B T}{h} e^{-\Delta G^{\ddagger}/RT} \tag{4.5}$$

All of the thermodynamic and rate parameters are given in Table 4.6.[46]

Table 4.6. Rate and thermodynamic parameters for hindered rotation in arylnaphthalenes.

compd	$\Delta H^{\ddagger}$,[a] kcal/mol	$\Delta S^{\ddagger}$,[a] cal/mol/K	$\Delta G^{\ddagger}_{23°}$,[b] kcal/mol	$\Delta H^{\ddagger}_{calcd,}$ [c] kcal/mol	$\tau_{23°}$ sec
25	18.7 (0.7)	-3.6 (1.9)	19.8	-	42.5
37	-	-	21.4	14.6	894.0
78	-	-	18.5 (-21 °C) [e]	13.2	-
79	18.3 (0.4)	-0.6 (1.1)	18.5	13.4 (17.6)[d]	4.8
80	19.3 (1.0)	2.8 (2.8)	18.5	13.6	4.8
81	17.0 (0.5)	0.1 (2.8)	16.9	11.9	0.3
82	16.9 (0.4)	-3.7 (1.2)	18.0	11.9	2.1
83	18.8 (0.4)	4.4 (1.1)	17.5	13.3	0.9
84	-	-	21.8 (28 °C) [e]	15.2	1067 (28 °C) [e]
87	19.0 (0.3)	-3.8 (0.7)	20.1	14.5	70.2
88	-	-	-	6.1	-

[a] From Eyring plots of exchange rate constants.
[b] Calculated using $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.
[c] From AM1 calculations.
[d] Value obtained from *ab initio* STO-3G calculation for justicidin A only.
[e] Value obtained from dynamic SFC analysis.[44]

The NMR spectra of compounds **37** and **84** were invariant with temperature, indicating that the rate of rotation of the pendent aryl group was too slow in these compounds to measure by dynamic NMR effects. Since compound **37** would exist as a mixture of ***diastereomers*** if rotation were slow, an attempt was made to determine the ratio of the two diastereomers by separating them by HPLC using an achiral reverse

phase column. Analysis at room temperature gave two poorly resolved peaks but lowering the temperature of the column to 4°C allowed for almost baseline separation. The experimental setup for the low temperature HPLC separation is illustrated in Figure 4.3. The temperature of the column was maintained at 4 ± 2 °C by blowing a steady stream of cold air through the insulator jacket containing the HPLC column and a thermometer.

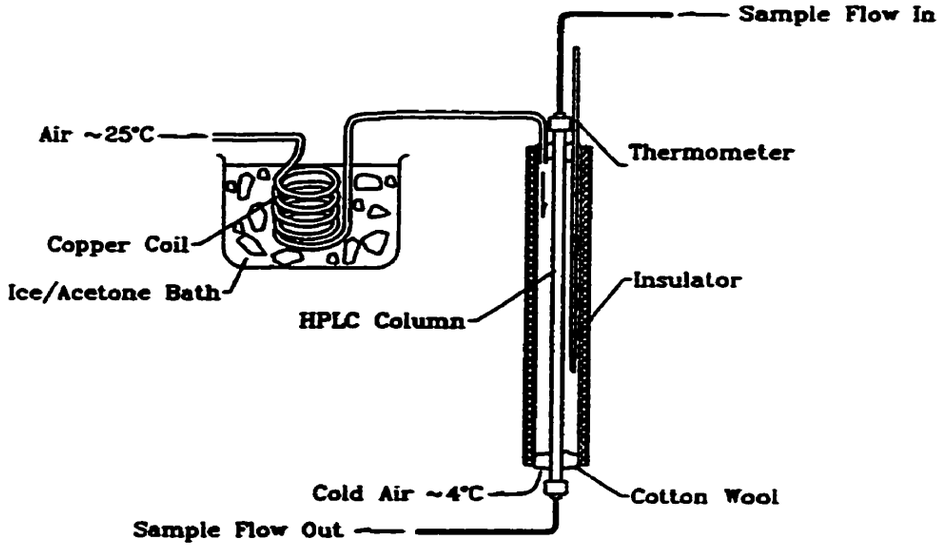


Figure 4.3. Experimental setup for low temperature HPLC analysis of lignan analog **37**.

The slower running component was collected and after storing at 23 °C for various times ranging from 0 to 86 minutes, was reinjected (see Figure 4.4). In this way a very crude estimate of the rate constant for return to the original equilibrium mixture at 23 °C could be calculated.

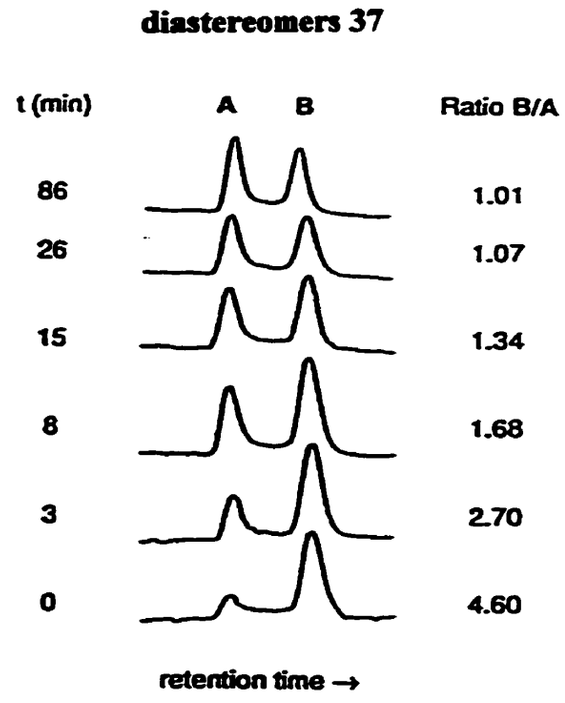
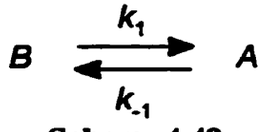


Figure 4.4. HPLC analysis of the atropisomeric equilibration of lignan analog **37** at 23 °C.

The derivation of the equation used for the calculation of the rate constant for a reaction which approaches an equilibrium is shown as follows.[47] Assuming in the following equations that B refers to the diastereomer which was collected using low temperature HPLC and allowed to return to the original equilibrium mixture which contained B itself and the other diastereomer A (see Scheme 4.49).



Scheme 4.49

The assumptions on the concentrations of diastereomers A and B in the above reaction are given in Table 4.7.

Table 4.7. The concentrations of diastereomers A and B at the begining, at time *t*, and at equilirium of the reaction shown in Scheme 4.49.

Diastereomer	Initially	at time, *t*	at equilibrium
B	$B_O = 1$	$B_t = B_O - A_t$	$B_e = B_O - A_e$
A	$A_O = 0$	$A_t = B_O - B_t$	$A_e = B_O - B_e$

The kinetic equation for the above conversion is

$$-\frac{dB_t}{dt} = \frac{dA_t}{dt} = k_1(B_o - A_t) - k_{-1}(A_t) \tag{4.6}$$

At equilibrium $$0 = k_1(B_o - A_e) - k_{-1}(A_e)$$

therefore $$k_{-1} = \frac{k_1(B_o - A_e)}{A_e} \tag{4.7}$$

Substitute (4.7) into (4.6) gives

$$-\frac{dB_t}{dt} = \frac{dA_t}{dt} = k_1(B_o - A_t) - \frac{k_1(B_o - A_e)}{A_e}(A_t)$$

$$\frac{dA_t}{dt} = k_1 B_o \frac{(A_e - A_t)}{A_e}$$

Integration gives $$\int_0^{A_t} \frac{dA_t}{(A_e - A_t)} = \frac{k_1 B_o}{A_e} \int_0^t dt$$

$$\ln\left(\frac{A_e}{A_e - A_t}\right) = \frac{k_1 B_o}{A_e} t$$

$$\ln\left(\frac{A_e}{A_e - A_t}\right) = (k_1 + k_{-1})t \tag{4.8}$$

Recall that $A_t = B_o - B_t$ and $A_e = B_o - B_e$. Substitute these into (4.8) gives

$$\ln\frac{(B_o - B_e)}{(B_t - B_e)} = (k_1 + k_{-1})t \tag{4.9}$$

If $B + A = 1$ and let $\frac{B}{A} = x$, then $A = \frac{1}{x+1}$ and $B = \frac{x}{1+x}$

As a result, $B_o = 1$, $B_e = \frac{x_e}{x_e+1}$, $B_t = \frac{x_t}{x_t+1}$

and $A_o = 0$, $A_e = \frac{1}{x_e+1}$, $A_t = \frac{1}{x_t+1}$,

and $x_e = \frac{B_e}{A_e}$, $x_t = \frac{B_t}{A_t}$

Finally, substitution of these in (4.9) gives

$$\ln\frac{(x_t+1)}{(x_t-x_e)} = (k_1 + k_{-1})t \qquad (4.10)$$

A plot of $\ln\frac{(x_t+1)}{(x_t-x_e)}$ vs t before the system reaches equilibrium (Figure 4.5) should give a straight line with a slope = $(k_1 + k_{-1})$.

From equation (4.7), one obtains,

$$k_1 = \frac{A_e}{B_o}(k_1 + k_{-1})$$

$$= \frac{1}{(x_e+1)}(k_1 + k_{-1})$$

Since $x_e \approx 1$, then $k_1 = \frac{1}{2}(k_1 + k_{-1})$ (4.11)

or $k_1 = \frac{1}{2}(slope)$

The rate constant k_1, which is half the slope of the best-fit line shown in Figure 4.5, was found to be 0.0671 ± 0.0053 min^{-1}. This rate constant (k_1) at 23 °C was then used as k to calculate the free energy of activation, $\Delta G^{\ddagger}_{23°}$, using equation (4.12):

$$\Delta G^{\ddagger}_{23°} = RT\,[23.760 + \ln(T/k)] \qquad (4.12)$$

(where R = 1.983 x 10^{-3} kcal/mol/K, and T = 296 K). Equation (4.12) is in turn derived from the fundamental Eyring equation:

$$k = \frac{k_B T}{h} e^{-\Delta G^{\ddagger}/RT} \tag{4.5}$$

The half-life of diastereomer B was calculated using equation (4.4), $\tau = 1/k$. The free energy of activation ($\Delta G^{\ddagger}_{23°}$) for the rotation of the pendent aryl group and the half-life of lignan analog **37** at 23°C are also given in Table 4.6.

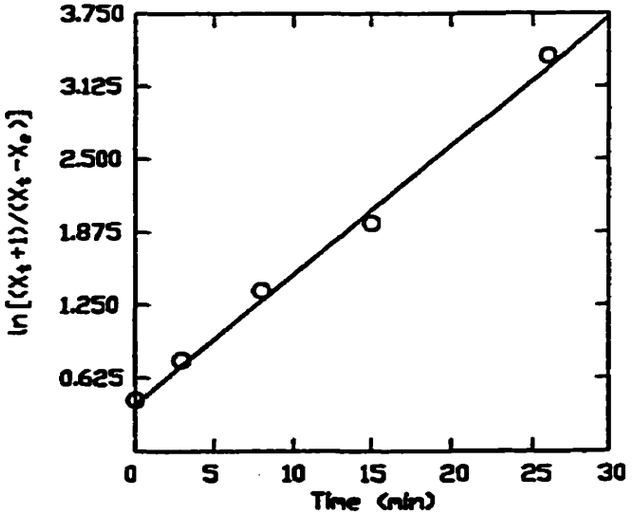


Figure 4.5. Plot of equation (4.10), $\ln[(x_t + 1)/(x_t - x_e)]$ vs t, in order to evaluate the rate constant for the atropisomeric equalibration of lignan analog **37** at 23 °C.

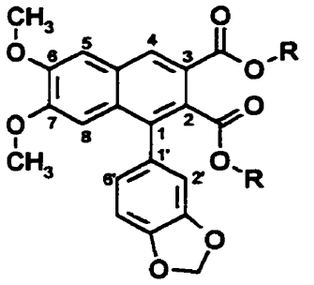
Unlike compound **37**, diphyllin (**78**) and ester **84** would exist as a mixture of ***enantiomers*** instead of diastereomers if rotation about the aryl-naphthalene bond were slow. Since the barrier to rotation of diphyllin (**78**) and ester **84** cannot be obtained using the dynamic NMR technique, samples of these compounds were instead sent to Dr. S. Maddaford at the University of Calgary for HPLC analysis. His attempts to separate these enantiomers by HPLC on a chiral column at room temperature were unsuccessful.

The poor resolution of these enantiomers by HPLC could either be due to the low efficiency of the chiral column to arylnaphthalene compounds, or the still rapid enantiomerization of these compounds at room temperature.

Samples of diphyllin (**78**) and ester **84** were also sent to Wolf *et al.* at the University of Illinois for analysis.[44] They successfully determined the energy barrier to rotation in diphyllin and ester **84** by dynamic SFC on a chiral polyWhelk-O stationary phase (see Section 2.2.2 for discussion of dynamic chromatographic techniques). They acquired the elution profiles for diphyllin and ester **84** at temperatures ranging from -30 to -10 °C, and from 0 to 50 °C, respectively. The elution profiles were then simulated using a computer program package "Mimesis" using the discontinuous plate model for the determination of the rate constants for the exchange. The procedure for computer simulation and determination of rate constants has been described in Section 2.2.2. The rotational energy barriers for diphyllin and ester **84** found using the dynamic SFC technique are also given in Table 4.6.

An attempt was made to use molecular orbital methods to determine if calculations could provide a reliable indication of the relative barriers to rotation in arylnaphthalenes. The computer program Spartan[48] was used at the AM1 level with geometry optimization to determine the energy difference between the relaxed molecule and the molecule with the dihedral angle 2-1-1'-2' (for numbering see scheme 4.50) fixed at 0°. All calculations were performed starting with the arylnaphthalene carbon skeleton in one plane and substituents oriented as shown in Scheme 4.50, coplanar with the

aromatic ring. The computed rotational energy barriers for **37**, **78-84**, **87** and **88** are given in Table 4.6 as $\Delta H^{\ddagger}_{calcd}$.

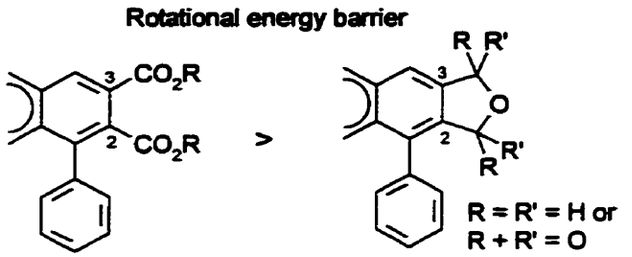


Scheme 4.50

The major conclusion to be drawn from the dynamic NMR, HPLC, and dynamic SFC measurements is that all of the arylnaphthalene lignans and analogs studied have a rotational barrier too small for individual atropisomers to be isolated at room temperature. The highest barrier was found in compounds **37** and **84** (*ca.* 21.8 kcal/mol), both of which have an ester group at position 2 and a hydrogen at position 8. The average half-lives of the individual rotamers of these compounds was *ca.* 16 min (at 23-28 °C). A γ-lactone at carbons 2 and 3 in either orientation seems to present a smaller barrier than an ester group at position 2, as evidenced by the lower values of $\Delta G^{\ddagger}_{23^{\circ}}$ (16.9 to 18.5 kcal/mol) obtained for diphyllin (**78**), justicidin A (**79**), justicidin B (**80**), retrojusticidin B (**81**), helioxanthin (**82**), and retrohelioxanthin (**83**).

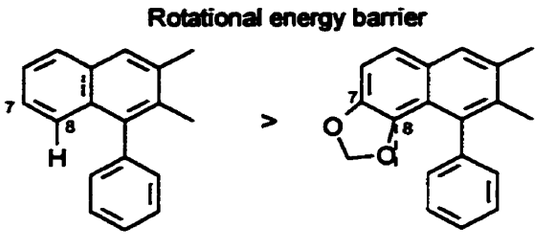
The AM1 computations are ***relatively*** consistent with the experimental values from the aspect that arylnaphthalenes with an ester at carbon 2 present higher barriers than those with a γ-lactone at carbons 2 and 3 (Scheme 4.51). For instance, the $\Delta G^{\ddagger}_{23^{\circ}}$(experimental) and $\Delta H^{\ddagger}_{calcd}$(AM1) (see Table 4.6) for compounds carrying 2-ester

groups (**37**, **84**, and **87**) are higher than for those carrying a γ-lactone at carbons 2 and 3 (**78-83**).



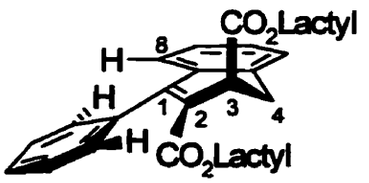
Scheme 4.51

The computer modeling also indicates that there is a smaller rotational barrier when a methylenedioxy ring is attached at positions 7 and 8 than when a hydrogen is present at position 8 (Scheme 4.52). For instance one can compare compound **87** to **37**, **83** to **80**, and **82** to **81**. The compounds in each pair have very similar structures except that the first compound in a pair has a methylenedioxy substituent at carbons 7 and 8, whereas the second compound in that pair has a hydrogen at carbon 8. As shown in Table 4.6, $\Delta H^{\ddagger}_{calcd}$(AM1) for **87** and **83** are slightly less than that for **37** and **80**, respectively, whereas that of **82** and **81** are equal. The experimentally derived barriers also reflect this trend: $\Delta G^{\ddagger}_{23^{\circ}}$(experimental) for **87** and **83** are slightly less than that of **37** and **80**, respectively, whereas $\Delta G^{\ddagger}_{23^{\circ}}$(experimental) for **82** is unexpectedly greater than that of **81**. From a consideration of the computational model, it appears that the smaller rotational barrier in arylnaphthalene lignans carrying a methylenedioxy ring at positions 7 and 8 is the result of ring distortion caused by the methylenedioxy ring pulling the 8 substituent away from the pendent phenyl ring (Scheme 4.52).



Scheme 4.52

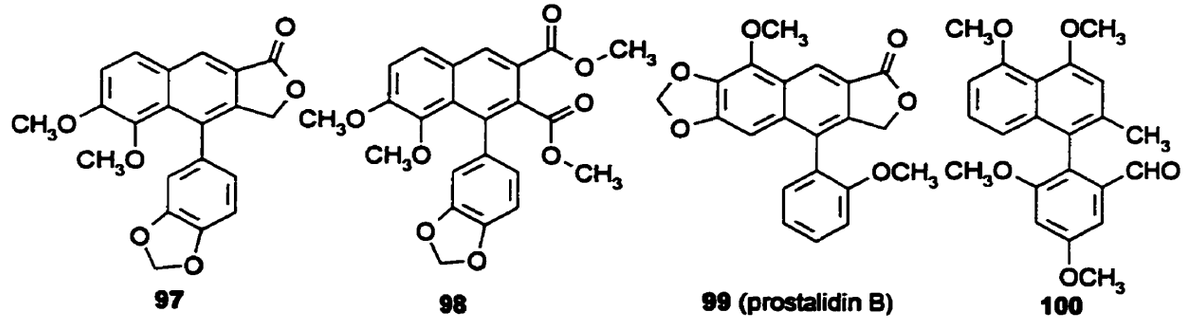
Finally, dihydronaphthalene **88** showed no effects from hindered rotation at all in its NMR spectrum at room temperature, in contrast to the fully aromatized compound **25**. Notably, the calculated barrier to rotation, $\Delta H^{\ddagger}_{calcd}$(AM1), was 6.1 kcal/mol for **88**, the lowest value among the compounds studied, which is in agreement with the ^{1}H NMR spectrum of this compound. It seems reasonable to conclude that hindered rotation will not be observed in natural lignans having a 3,4-dihydronaphthalene structure. This is because the single bond at carbons 3 and 4 in the dihydronaphthalene ring allows more flexibility and ring distortion (Scheme 4.53). This reduces steric interactions between the 2 and 8 substituents on the dihydronaphthalene ring and the *ortho*-H's of the pendent phenyl ring during rotation.



Scheme 4.53

Molecular orbital calculations at the AM1 level are relatively unsophisticated and it was not surprising that the calculated barriers to rotation, although in the correct relative order, were far removed from the absolute values measured experimentally.

Molecular orbital calculations at the *ab initio* level would have been preferred but the computational time required was excessive at that level. For comparison to the AM1 calculations, an *ab initio* computation at the STO 3G level was performed on justicidin A (**79**). A $\Delta H^{\ddagger}_{calcd}$(STO 3G) of 17.6 kcal/mol was found to be closer to the experimentally measured barrier of 18.5 kcal/mol than the value of 13.4 kcal/mol obtained from an AM1 calculation (see Table 4.6). However, the total computational time required was about three days! Despite the fact that AM1 calculations are less exact, the calculations do show that AM1 computations can predict ***relative*** barriers to rotation. They should be useful for calculating relative barriers to rotation in related compounds. In this respect, we have calculated the barriers in lignan analogs **97** and **98**, prostalidin B (**99**, natural lignan, a depressant), and compound **100** (a known stable atropisomer) in order to assess the effect of a methoxy group at the 8 position, as well as substituents at the 2' and 6' positions (Scheme 4.54).



Scheme 4.54

Comparing the calculated 11.9 kcal/mol barrier for **97** with retrojusticidin B (**81**) and helioxanthin (**82**) in Table 4.6 would indicate that the 8-methoxy substituent alone is

insufficient to give rise to stable atropisomers. However, the simultaneous presence of an 8-methoxy substituent and a 2-ester group, as illustrated in compound **98**, raises the barrier to 15.7 kcal/mol, indicating the significant effect of the 2-ester group. The calculated barrier for prostalidin B (**99**) is higher than any of the calculated barriers listed in Table 4.6 and may indicate the possibility that it will exist as stable atropisomers at room temperature. The 29.1 kcal/mol barrier for **100** is consistent with the fact that it is known to form stable atropisomers. Apparently, a substituent at 2', 6', or both positions increases the barrier to rotation more drastically than substitution at any other positions in the arylnaphthalene ring. The significant effect of substituents at these critical positions on the barrier height was also observed in previous studies (see Section 2.4).

In conclusion, the rotational barriers in arylnaphthalene lignans diphyllin (**78**), justicidin A (**79**), justicidin B (**80**), retrojusticidin B (**81**), helioxanthin (**82**), and retro-helioxanthin (**83**), as well as the lignan analogs **25**, **37**, **84**, **87** and **88** were found to be too small for these compounds to exist as isolable atropisomers at room temperature. The study clearly demonstrated what structural features would be necessary before separable rotamers of arylnaphthalene lignans could be isolated.

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46. The standard deviations in the calculated enthalpies and entropies of activation shown in Table 4.6, produced by non-linear least-square adaptation of the exponential plot of k versus T, should be interpreted cautiously. This is because the number of data points in each plot was small and the temperature range over which data was collected was also relatively small.

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CHAPTER 5

CONCLUSIONS

The research work discussed in this thesis can be summarized as follows:

(i) A general method has been developed for the preparation of acetylenedicarboxylic acid esters and applied to the synthesis of both chiral and achiral esters. The bis-(methyl (*S*)-lactyl), bis-(methyl (*R*)-mandelyl), and dimenthyl esters, as well as achiral diaryl and dialky esters, were prepared in overall yields of >65%, using a four step procedure. Asymmetric Diels-Alder reactions of the bis(methyl (*S*)-lactyl) ester with dienes such as phenylbutadiene, *o*-QDMs, isobenzofuran, and hexadienol, were investigated. The reactions of bis-(methyl (*S*)-lactyl) ester with dienes without an α-hydroxyl group afforded stable cycloadducts but, with poor diastereoselectivity. Reasonable diastereoselectivity was observed in reactions with α-hydroxy-*o*-QDMs. Nevertheless, the cycloadducts tended to be fairly unstable due to their ease of dehydration. The use of Lewis acids such as Et_2AlCl, $MeAlCl_2$, or $BF_3{\cdot}OEt_2$ in one case marginally increased the diastereoselectivity, while in other cases entirely stopped cycloadduct formation. The study has shown that the acetylenedicarboxylate of methyl (*S*)-lactate is not a suitable dienophile for asymmetric synthesis of aryltetralin lignans via Diels-Alder reactions.

(ii) A versatile asymmetric synthesis of β-benzyl-γ-butyrolactones, key intermediates in the synthesis of lignans, has been achieved using a six-step procedure, in an overall yield

of >45% from 3,4-(methylenedioxy)cinnamic acid. The key asymmetric step in this sequence was a highly diastereoselective alkylation of an N-acyloxazolidinone enolate. This simple procedure afforded the β-benzyl-γ-butyrolactones in >95% optical purity. These intermediates were used in the synthesis of the benzylidene lignans gossypifan and savinin, and the dibenzylbutyrolactone lignan 4'-demethylyatein, in good to excellent yield.

(iii) In view of the successful intermolecular oxidative coupling reactions observed in sinapic acid and esters, a study of intramolecular oxidative coupling reactions of disinapic acid esters was undertaken. Unfortunately, the study has shown that two sinapic acids linked via ester or anhydride linkage did not readily undergo intramolecular oxidative coupling. The oxidation reactions of a naturally occurring dibenzylbutyrolactone lignan, 4'-demethylyatein, was studied. 4'-Demethylyatein reacted smoothly with DDQ, affording *trans*-benzylidenebenzylbutyrolactone and its unstable *cis*-counterpart, which, on standing exposed to air, isomerized to the trans-isomer. DDQ oxidation of 4'-demethylyatein in the presence of TFA gave an aryltetralin lignan 4'-demethylisodeoxypodophyllotoxin. The latter procedure provides an alternative route for the preparation of aryltetralin lignans. In addition, the study has contributed to a better understanding of the biosynthesis of lignans.

(iv) To test the hypothesis that hindered rotation may give rise to isolable rotational enantiomers, eleven natural and non-natural arylnaphthalene and dihydroarylnaphthalene

lignans were synthesized. The hindered rotation about the aryl-naphthalene bond in these compounds was studied by dynamic NMR and low temperature HPLC, and barriers to rotation were found ranging from 16.9 to 21.4 kcal/mol. This translated to half-lives for individual atropisomers of less than 15 min at room temperature. Ester groups at the 2 position presented a higher barrier than the 2,3-lactones of either orientation. A 7,8-methylenedioxy ring substituent decreased the aryl-naphthalene rotational energy barrier relative to a hydrogen at the 8 position. It was also found that AM1 computations with geometry optimization provided correct *relative* barriers to rotation for the above arylnaphthalene lignans and should be useful for calculating relative barriers to rotation in structurally related compounds. The study clearly shows the structural features required in arylnaphthalene lignans for existence of stable atropisomers.

CHAPTER 6

EXPERIMENTAL

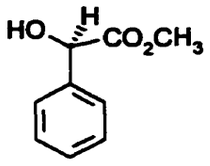
Compound numbers in the Experimental section correspond to those used in the Results and Discussion section, Chapter 4.

^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AM-300 FT instrument using tetramethylsilane as internal standard, unless otherwise specified. IR spectra were recorded on a Perkin Elmer 881 spectrometer. HRMS/mass spectra were obtained on an Analytical VG 7070E-HF instrument. Optical rotations were recorded on a Rudolf Research Corporation Autopol III instrument. Elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario, Canada. Melting points were measured on a hot stage instrument and are uncorrected. Aldrich 28,859-4 silica gel was used for all chromatography. Preparative thin layer chromatography was carried out on glass plates precoated with Macherey Nagel-silica gel P/UV_{254} 81638 (2 mm thickness). THF was distilled from sodium/benzophenone under N_2. A 450 watt Hanovia medium pressure mercury lamp (1 mm Pyrex filter) equipped with a cooling jacket was used in irradiation experiments.

The NMR spectrometer used to perform the dynamic NMR studies was the same as described above. Temperature was calculated by making reference to the known temperature dependent spectra of methanol (at low temperature) and ethylene glycol (at high temperature) and was accurate to ±1 °C. Simulation of the experimental dynamic NMR spectra were performed using a computer program (Marat, K. *XSIM*, copyright

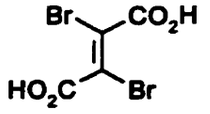
1995) incorporating DNMR3 by Kleiser, D. A.; Binsch, G. *DNMR3-A computer program for the calculation of complex exchange-broaden NMR spectra*, QCPE program 165, 1970.

Methyl (*R*)-mandelate



A mixture of (*R*)-mandelic acid (2.40 g, 15.7 mmol) and conc. H_2SO_4 (1.0 mL) in MeOH (25 mL) was heated at reflux for 3 h. The reaction mixture was cooled, concentrated under vacuum to remove most of the MeOH, and diluted with CH_2Cl_2 (30 mL). The mixture was washed with water (2 x 20 mL), 5% aqueous $NaHCO_3$ (3 x 20 mL), and water (1 x 20 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum to afford a colorless oil which solidified on standing (2.35 g, 90%): mp 54-55 °C; ^{1}H NMR ($CDCl_3$) δ 3.42 (br s, 1H), 3.76 (s, 3H), 5.17 (d, 1H, J = 5.4), 7.34-7.42 (m, 5H), data consistent with those reported previously.[1]

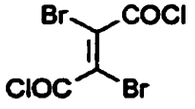
Dibromofumaric acid (6)



A modification of a literature procedure was used.[2] An aqueous solution of KOH (2 M, *ca.* 20 mL) was added to the monopotassium salt of ADA (5.51 g, 36.3 mmol) with

stirring until the resulting solution became neutral. Bromine (6.33 g, 39.6 mmol) was added to sodium bromide (18.7 g, 0.18 mol) in water (80 mL), and this solution was then added to the neutral solution of ADA. Water was added to the mixture to give a total volume of 150 mL. The brown color of the solution discharged after 2 h in the dark at room temperature. It was left standing for a further day. The colorless solution was acidified with concentrated HCl to pH 1-2, and extracted with EtOAc (4 x 20 mL). The organic layer was washed with saturated sodium bisulfite (3 x 20 mL), dried ($MgSO_4$), and concentrated under vacuum to give a colorless solid (9.44 g). The product was recrystallized from THF/hexanes to give colorless needles (8.0 g, 80%): mp 237-238 °C, identical to that reported previously[3]; IR (CH_2Cl_2) 1697 (C=O) cm^{-1}; ^{13}C NMR (H_2O/D_2O) δ 113.1 (2 x C), 168.6 (2 x CO); mass spectrum *m/z* (relative intensity) 276 ($M^+(^{81}Br)$, 1), 274 ($M^+(^{79}Br)$, 2), 272 (1), 186 (4), 184 (6), 182 (3), 151 (16), 149 (17), 106 (95), 104 (100).

Dibromofumaryl chloride (7)



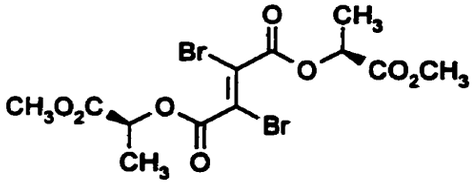
The compound was prepared according to Ott's procedure.[3] Dibromofumaric acid (**6**, 4.69 g, 17.1 mmol), petroleum ether (30 mL), and phosphorus pentachloride (7.17 g, 34.4 mmol) were stirred together at room temperature until the precipitate dissolved (*ca.* 5 h). The solution was poured onto crushed ice and stirred for 15 min. The organic layer was separated, dried ($MgSO_4$), and concentrated under vacuum to give a pale yellow

liquid (4.87 g, 92%): IR (CH_2CL_2) 1779 (C=O) cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 114.6 (2 x C), 162.0 (2 x CO); mass spectrum *m/z* (relative intensity) 312 ($M^+(^{81}Br)$, 4), 310 ($M^+(^{79}Br)$, 5), 277 (24), 275 (36), 257 (10), 256 (14), 249 (25), 247 (35), 213 (18), 211 (11), 184 (17), 133 (98), 131 (100). HRMS calcd. for $C_4Br(79)Br(81)Cl(35)_2O_2$ 309.7621, found 309.7578.

General procedure for the preparation of dibromofumarates 8 (except for the dimethyl ester)

To the alcohol (3.18 mmol) and pyridine (0.255g, 3.22 mmol) in CCl_4 (20 mL) at 0 °C under N_2, was added dibromofumaryl chloride (7, 0.497 g, 1.60 mmol) in CCl_4 (10 mL), dropwise, over a period of 10 min. The mixture was stirred for 20 min and then at room temperature for another 40 min. It was washed with water (2 x 20 mL), 5% sodium bicarbonate (4 x 20 mL), and water (2 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum.

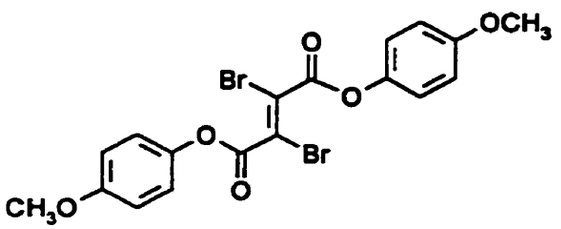
Dibromofumarate of methyl (*S*)-lactate (8e)



Methyl (*S*)-lactate (0.33 g, 3.18 mmol) was reacted with dibromofumaryl chloride (7) as described in the above general procedure to afford a yellow liquid (0.66 g, 93%): [α]$^{20}_D$ -22.4° (c 0.923, $CHCl_3$); IR (CH_2Cl_2) 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (d, 6H, *J* = 7.1), 3.79 (s, 6H), 5.27 (q, 2H, *J* = 7.1); ^{13}C NMR ($CDCl_3$) δ 16.7 (2 x CH_3), 52.6 (2 x

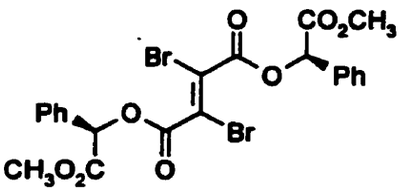
CH_3), 70.8 (2 x CH), 112.7 (2 x C), 161.2 (2 x CO), 169. 6 (2 x CO); mass spectrum *m/z* (relative intensity) 367 (15), 365 (15.1), 345 (7), 343 (15), 341 (8), 293 (15), 291 (15), 183 (37), 155 (14), 86 (100). Anal. calcd. for $C_{12}H_{14}Br_2O_8$: C, 32.31, H, 3.16; found: C, 32.43, H, 3.21.

Bis-(4-methoxyphenyl) dibromofumarate (8d)



4-Methoxyphenol (0.39 g, 3.18 mmol) was reacted with dibromofumaryl chloride (7) as described in the above general procedure to afford a pale yellow solid (0.75 g, 96%): mp 146-148 °C; IR (CH_2Cl_2) 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (s, 6H), 6.93 (d, 4H, $J = 9.1$), 7.15 (d, 4H, $J = 9.1$); ^{13}C NMR ($CDCl_3$) δ 55.6 (2 x CH_3), 113.3 (2 x C), 114.6 (4 x CH), 121.8 (4 x CH), 143.4 (2 x C), 157.9 (2 x C), 160.8 (2 x CO); mass spectrum *m/z* (relative intensity) 486 (M^+, 2), 365 (3), 363 (6), 361 (4), 326 (8), 284 (4), 282 (5), 124 (100), 123 (48), 109 (95). Anal. calcd. for $C_{18}H_{14}Br_2O_6$: C, 44.47, H, 2.90; found: C, 44.47, H, 2.86.

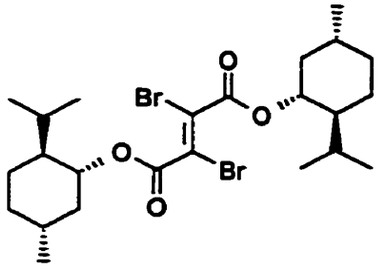
Dibromofumarate of methyl (*R*)-mandelate (8f)



Methyl (*R*)-mandelate (0.53 g, 3.18 mmol) was reacted with dibromofumaryl chloride (7) as described in the above general procedure to afford a colorless liquid which

crystallized upon standing (0.85 g, 93%): mp 61-63 °C; $[\alpha]^{20}_{D}$ -103.3° (c 1.462, $CHCl_3$); IR (CH_2Cl_2) 1749, 1751 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 6H), 6.07 (s, 2H), 7.39-7.41 (m, 6H), 7.48-7.51 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 52.9 (2 x CH_3), 76.4 (2 x CH), 113.1 (2 x C), 127.6 (4 x CH), 128.9 (4 x CH), 129.6 (2 x CH), 132.5 (2 x C), 161.2 (2 x CO), 167.9 (2 x CO); mass spectrum *m/z* (relative intensity) 407 (2), 405 (4), 403 (2), 189 (14), 150 (31), 149 (100.0) 121 (36), 118 (22), 105 (45). Anal. calcd. for $C_{22}H_{18}Br_2O_8$: C, 46.34, H, 3.18; found: C, 46.58, H, 3.18.

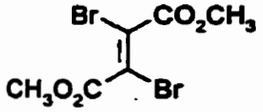
Dimenthyl dibromofumarate (8c)



(1R,2S,5R)-Menthol (0.50 g, 3.18 mmol) was reacted with dibromofumaryl chloride (7) as described in the above general procedure to afford a colorless oil which crystallized upon standing (0.88 g, 100%): mp 82-85 °C; $[\alpha]^{20}_{D}$ -55 (c 0.418, $CHCl_3$); IR (CH_2Cl_2) 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (d, 6H, J = 6.9), 0.84-0.93 (m, 2H), 0.92 (d, 6H, J = 7.1), 0.94 (d, 6H, J = 6.7), 1.11 (m, 4H), 1.50 (m, 4H), 1.71 (m, 4H), 2.02 (dp, 2H, J = 2.7, 7.0), 2.06 (m, 2H), 4.84 (dt, 2H, J = 4.4, 10.9); ^{13}C NMR ($CDCl_3$) δ 16.0 (2 x CH_3), 20.7 (2 x CH_3), 22.0 (2 x CH_3), 23.2 (2 x CH_2), 26.0 (2 x CH), 31.4 (2 x CH), 34.1 (2 x CH_2), 40.2 (2 x CH_2), 46.9 (2 x CH), 77.8 (2 x CH), 112.0 (2 x C), 161.8 (2 x CO); mass spectrum *m/z* (relative intensity) 395 (0.5), 273 (2), 271 (4), 269 (2), 149 (17),

139 (22), 138 (50), 123 (31), 95 (94), 81 (85). Anal. calcd. for $C_{24}H_{38}Br_2O_4$: C, 52.38, H, 6.96; found: C, 52.54, H, 7.04.

Dimethyl dibromofumarate (8a)



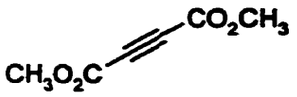
A mixture of dibromofumaryl chloride (7, 0.425 g, 1.38 mmol) and MeOH (4 mL) was refluxed under N_2 for 2 h. The solvent was evaporated and the precipitate was dissolved in CH_2Cl_2 (5 mL), washed with 5% aqueous $NaHCO_3$ (3 x 10 mL) and water (2 x 10 mL). The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated under vacuum to give a colorless solid (0.393 g, 94%): mp 36-37 °C; IR (CH_2Cl_2) 1744 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 53.7 (2 x OCH_3), 112.7 (2 x C), 162.6 (2 x C); mass spectrum *m/z* (relative intensity) 304 (14), 302 (28), 300 (15), 273 (48), 271 (97), 269 (51), 223 (30), 221 (30), 195 (15), 193 (17), 149 (20), 147 (20), 133 (35), 131 (35); HRMS calcd. for $C_6H_6Br_2O_4$ 301.8612, found 301.8606.

General procedure for the preparation of acetylenedicarboxylates 1 (not including the bis-(methyl (*R*)-mandelyl) and dimenthyl esters)

Dibromofumarate **8** (1 mmol), dry THF (10 mL) and granular zinc (0.4 g, 6 mmol) were refluxed under N_2 for 2-5 h depending on the type of ester (Note: the bis-(4-methoxyphenyl) ester required a catalytic amount of I_2). The granular zinc was filtered off and THF evaporated. The brown residue was dissolved in CH_2Cl_2 (5 mL), and

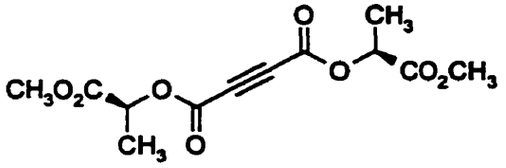
washed with water (4 x 10 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum.

Dimethyl acetylenedicarboxylate (1a)



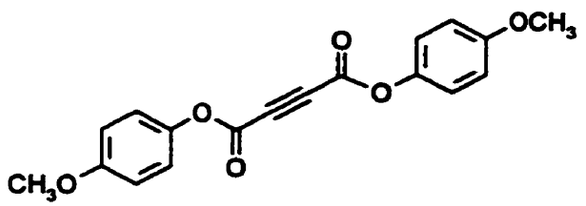
The reaction was complete after 2 h reflux with granular zinc. A colorless liquid was obtained (93%): ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 53.4 (2 x CH_3), 74.6 (C≡C), 152.1 (2 x CO), identical to that reported previously.[4]

Bis-(methyl (*S*)-lactyl) ester of ADA (1e)



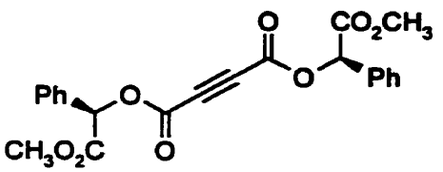
The reaction was complete after 4 h reflux with granular zinc. A yellow oil which crystallized upon standing was obtained (95%). The solid was recrystallized from EtOAc/hexane: mp 78-81 °C; $[\alpha]^{20}_D$ +8.0° (c 0.365, $CHCl_3$); IR (CH_2Cl_2) 1732, 1760 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57 (d, 6H, J = 7.1), 3.78 (s, 6H), 5.23 (q, 2H, J = 7.1); ^{13}C NMR ($CDCl_3$) δ 16.7 (2 x CH_3), 52.7 (2 x CH_3), 70.7 (2 x CH), 75.0 (C≡C), 150.8 (2 x C), 169.5 (2 x C); mass spectrum *m/z* (relative intensity) 255 (2), 227 (13), 183 (100), 155 (49), 111 (46), 87 (31), 83 (51), 80 (39). Anal. calcd. for $C_{12}H_{14}O_8$: C, 50.35, H, 4.93; found: C, 50.10, H, 4.95.

Bis-(4-methoxyphenyl) acetylenedicarboxylate (1d)



This reaction required a 5 h reflux with granular zinc and I_2 (20 mg). A colorless oil which crystallized upon standing was obtained (93%): mp 146-147 °C; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 6H), 6.91 (br d, 4H, J = 9.1), 7.09 (br d, 4H, J = 9.2), identical to that previously reported;[5] ^{13}C NMR ($CDCl_3$) δ 55.6 (2 x CH_3), 76.0 (C≡C), 114.7 (4 x CH), 121.8 (4 x CH), 143.0 (2 x C), 150.3 (2 x C), 158.0 (2 x CO).

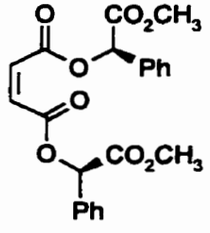
Bis-(methyl (*R*)-mandelyl) ester of ADA (1f)



Bis-(methyl (*R*)-mandelyl) dibromofumarate (**8f**, 71 mg, 0.12 mmol), dry THF (3 mL), and amalgamated zinc dust (47 mg, 0.72 mmol) were refluxed under N_2 for 1 h. The solution was worked up as in the general procedure above to give a pale yellow liquid (47 mg, 95%). The ^{1}H NMR spectrum of the crude product showed the presence of two by-products (3-4% each). One was identified as the fumarate of methyl (*R*)-mandelate (**9**) by comparison to an authentic sample,[1] while the other appeared to be the maleate ester (see below). The fumarate was inseparable from mandelyl ester **1f** by chromatography. This by-product could be removed by reacting the crude product (40

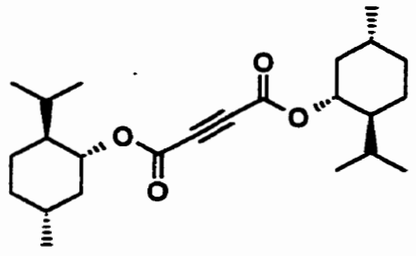
mg) with a small amount of benzocyclobutenol[6,10] (**11**, 6 mg) in refluxing toluene (2 mL) for 30 min, followed by chromatography with 10% EtOAc/hexanes which afforded the pure mandelyl ester **2** (38 mg, 85%): $[\alpha]^{20}_{D}$ -45.6° (c 0.485, $CHCl_3$); IR (CH_2Cl_2) 1761 ,1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 6H), 6.03 (s, 2H), 7.39-7.48 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 53.0 (2 x CH_3), 75.1 (C≡C), 76.2 (2 x CH), 127.7 (4 x CH), 128.9 (4 x CH), 129.8 (2 x CH), 132.2 (2 x C), 150.6 (2 x CO), 167.6 (2 x CO); mass spectrum *m/z* (relative intensity) 351 (M-CO_2CH_3, 1), 189 (6), 159 (10), 150 (31), 149 (24), 118 (66), 105 (80), 91 (100), 77 (71); Anal. calcd. for $C_{22}H_{18}O_8$: C, 64.39, H, 4.42; found: C, 65.38, H, 4.42.[7]

Bis-(methyl (*R*)-mandelyl) maleate (10)



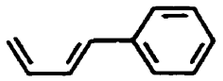
mp 73-74 °C; $[\alpha]^{20}_{D}$ -172.7° (c 0.15, $CHCl_3$); IR (CH_2Cl_2) 1755, 1763 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (s, 6H), 5.90 (s, 2H), 6.43 (s, 2H), 7.35 (br s, 10H); ^{13}C NMR ($CDCl_3$) δ 52.6 (2 x CH_3), 75.1 (2 x CH), 127.6 (4 x CH), 128.7 (4 x CH), 129.2 (2 x CH), 129.8 (2 x CH), 133.2 (2 x C), 163.8 (2 x CO), 168.6 (2 x CO); mass spectrum *m/z* (relative intensity) 255 (6), 248 (2), 165 (3), 150 (50), 149 (100), 121 (42), 105 (31), 91 (22), 77 (30). Anal. calcd. for $C_{22}H_{20}O_8$·EtOAc: C, 62.39, H, 5.64; found: C, 62.71, H, 5.16.

Dimenthyl acetylenedicarboxylate (1c)



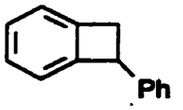
Dimenthyl dibromofumarate (**8c**, 75 mg, 0.13 mmol), dry THF (3 mL), and amalgamated zinc dust (84 mg, 1.28 mmol) were stirred under N_2 at room temperature for 16 h. The solution was worked up as in the general procedure described above, to give a colorless solid (46 mg, 92%): mp 131-133 °C; $[\alpha]^{20}_D$ -79.1° (c 0.139, $CHCl_3$); IR (CH_2Cl_2) 1726 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (d, 6H, J = 6.9), 0.91 (d, 6H, J = 7.0), 0.92 (d, 6H, J = 6.5), 0.85-0.93 (m, 2H), 1.06 (m, 4H), 1.44 (m, 4H), 1.70 (m, 4H), 1.89 (dp, 2H, J = 2.6, 6.9), 2.03 (m, 2H), 4.84 (dt, 2H, J = 4.4, 10.9); ^{13}C NMR ($CDCl_3$) δ 16.1 (2 x CH_3), 20.7 (2 x CH_3), 21.9 (2 x CH_3), 23.3 (2 x CH_2), 26.1 (2 x CH), 31.5 (2 x CH), 34.0 (2 x CH_2), 40.4 (2 x CH_2), 46.8 (2 x CH), 74.9 (C≡C), 77.7 (2 x CH), 151.6 (2 x C); mass spectrum *m/z* (relative intensity) 139 (24), 138 (49), 129 (16), 123 (30), 95 (100), 83 (90), 81 (82). Anal. calcd. for $C_{24}H_{38}O_4$·1.5 EtOAc: C, 68.93, H, 9.64; found: C,68.95, H, 9.62.

(*E*)-1-Phenyl-1,3-butadiene (14)



A modified literature procedure was used.[8] *n*-BuLi (2.0 M, 5.6 mL, 11.2 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (3.95 g, 11.0 mmol) in ether (30 mL) under N_2 in an ice bath. The precipitate dissolved and the solution was stirred for 30 min and then cooled to -78 °C, followed by dropwise addition of *trans*-cinnamaldehyde (1.39 g, 10.5 mmol) in ether (10 mL). The mixture was gradually warmed to room temperature and stirred for another 2 h. The colorless precipitate was filtered off with the aid of Celite, and the filtrate was concentrated under vacuum. The residue was redissolved in petroleum ether (10 mL) and eluted through a short silica gel column, washed with petroleum ether (*ca.* 20 mL) and the collected solution concentrated under vacuum to leave a pale yellow liquid (0.75 g, 55%), which was used in the next reaction without purification: ^{1}H NMR ($CDCl_3$) δ 5.17 (dd, 1H, J = 1.5, 10.1), 5.33 (dd, 1H, J = 1.5, 16.2), 6.50 (ddd, 1H, J = 10.1, 10.4, 16.2), 6.55 (d, 1H, J = 15.8), 6.78 (dd, 1H, J = 10.4, 15.8), 7.18-7.42 (m, 5H).

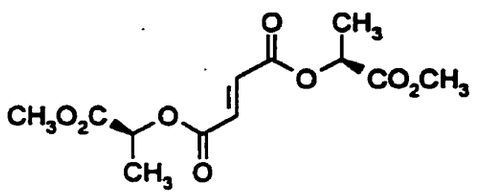
α-Phenylbenzocyclobutene (22)



A modified literature procedure was used.[9] Benzocyclobutenol[10] (0.105 g, 0.88 mmol) in benzene (10 mL) was concentrated to half of the original volume to

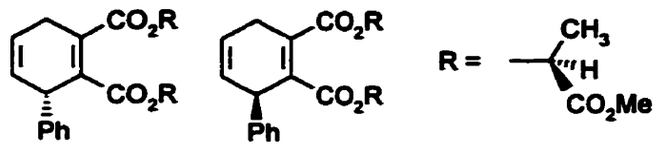
azeotropically remove traces of water present in the benzene. $BF_3 \cdot OEt_2$ was then added to the above solution under N_2. After refluxing for 30 min, the reaction mixture was concentrated under vacuum, diluted with CH_2Cl_2 (10 mL), and washed with 5% aqueous $NaHCO_3$ (3 x 10 mL), water (10 mL) and brine (10 mL). The organic phase was then dried ($MgSO_4$) and concentrated under vacuum to give a yellow oil (0.142 g, 89%): ^{1}H NMR ($CDCl_3$) δ 3.08 (dd, 1H, J = 2.7, 13.9), 3.69 (dd, 1H, J = 5.6, 13.9), 4.69 (dd, 1H, J = 2.7, 5.6), 7.13-7.29 (m, 9H), consistent with that previously reported.[9]

Fumarate of methyl (*S*)-lactate (31)



A literature procedure was used.[11] A mixture of fumaryl chloride (**7**, 2.43 g, 15.9 mmol) and methyl (*S*)-lactate (3.23 g, 31.0 mmol) was heated at 110 °C for 17 h. The mixture was diluted with EtOAc (25 mL) and washed with 5% aqueous $NaHCO_3$ (3 x 20 mL), water (1 x 20 mL), and brine (1 x 20 mL). The organic phase was dried ($MgSO_4$) and concentrated to afford a yellow oil (7.59 g, 85%) which was used in the next reactions without further purification: ^{1}H NMR ($CDCl_3$) δ 1.56 (d, 3H, J = 7.1), 3.77 (s, 6H), 5.21 (q, 2H, J = 7.1), 6.97 (s, 2H), identical to that reported previously.[11]

Cycloadducts 19 and 20



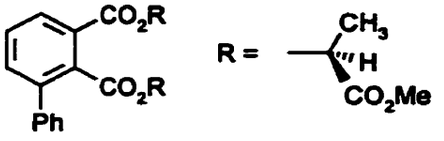
A mixture of (*E*)-1-phenyl-1,3-butadiene (**14**, 0.177 g, 1.36 mmol), **1e** (0.118 g, 0.41 mmol), and hydroquinone (2 mg) in xylenes (4 mL) was refluxed under N_2 for 6 h. The resulting solution was run through a short silica gel column and rinsed with hexanes to remove xylenes. The product was then eluted with EtOAc and concentrated under vacuum to give a pale yellow liquid (0.17 g), containing mainly two diastereomers in a 1:1.3 ratio, as determined by ^{1}H NMR spectroscopy.[12] The product was chromatographed using 25% EtOAc/hexanes to give an oil (0.14 g, 82%): IR (CH_2Cl_2) 1745 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, a mixture of two diastereomers) δ 1.23 (d, 3H, J = 7.0), 1.25 (d, 4H, J = 7.0), 1.50 (d, 3H, J = 7.0), 1.53 (d, 4H, J = 7.0), 3.12 (m, 2.3H), 3.30 (m, 2.3H), 3.59 (s, 3H), 3.60 (s, 4H), 3.74 (s, 3H), 3.76 (s, 4H), 4.44 (m, 2.3H), 4.95 (q, 1H, J = 7.0), 5.09 (q, 1.3H, J = 7.0), 5.20 (q, 1H, J = 7.0), 5.23 (q, 1.3H, J = 7.0), 5.80 (m, 4.6H), 7.15-7.30 (m, 11.7H); mass spectrum *m/z* (relative intensity) 414 (M-2H, 2), 312 (34), 225 (78), 181 (100), 153 (33), 149 (31). HRMS (CIMS, NH_4^+) calcd. for $C_{22}H_{24}O_8 \cdot NH_4$ 434.1815, found 434.1780.

Lewis acid-catalyzed Diels-Alder reaction of 1e and phenylbutadiene 14

A mixture of phenylbutadiene **14** (55 mg, 0.43 mmol), **1e** (15.5 mg, 0.054 mmol), and $MeAlCl_2$ (1.0 M in hexanes, 0.22 mL, 0.21 mmol) in CH_2Cl_2 (2 mL) was stirred

under N_2 at room temperature for 20 h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with water (3 x 10 mL), dried ($MgSO_4$), and concentrated to afford a brown residue (60 mg). ^1H NMR spectrum of the crude product showed the presence of two diastereomers in a 1:2 ratio, with the chemical shifts identical to that of cycloadducts **19** and **20**. The product was chromatographed using 25% EtOAc/hexanes to give an oil (17 mg, 75%).

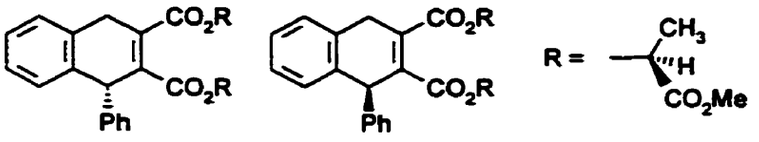
Biaryl 21



A mixture of diastereomers **19** and **20** (70 mg, 0.17 mmol) was refluxed with Pd/C (0.3 g) in xylenes (4 mL) for 10 h. The mixture was filtered through a short column of silica gel, and rinsed with hexanes to remove xylenes. The product was eluted with EtOAc and concentrated to leave a pale yellow oil (65 mg, 92%): $[\alpha]^{20}_D$ -21.76° (c 0.625, $CHCl_3$); IR (CH_2Cl_2) 1743 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 7.0), 1.61 (d, 3H, J = 7.0), 3.62 (s, 3H), 3.76 (s, 3H), 5.25 (q, 1H, J = 7.0), 5.33 (q, 1H, J = 7.0), 7.37-7.41 (m, 5H), 7.55 (m, 2H), 8.06 (dd, 1H, J = 4.8, 7.9); ^{13}C NMR ($CDCl_3$) δ 16.7 (CH_3), 16.9 (CH_3), 52.1 (CH_3), 52.3 (CH_3), 69.5 (2 x CH), 127.8 (CH), 128.0 (CH), 128.1 (2 x CH), 128.9 (2 x CH), 129.0 (CH), 129.3 (CH), 133.8 (C), 134.5 (CH), 138.9 (C), 141.1 (C), 164.8 (C), 167.2 (C), 170.6 (C), 170.7 (C); mass spectrum *m/z* (relative

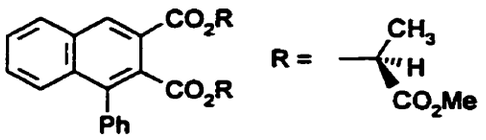
intensity) 414 (M^+, 10), 311 (47), 225 (85), 152 (19), 84 (100). HRMS calcd. for $C_{22}H_{22}O_8$ 414.1314, found 414.1293.

Cycloadducts 23 and 24



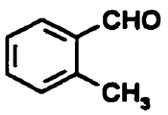
A mixture of **1e** (0.10 g, 0.35 mmol) and α-phenylbenzocyclobutene (**22**) (95 mg, 0.52 mmol) in toluene (5 mL) was refluxed for 5 h. The solution was concentrated under vacuum to give an oily residue which was chromatographed using 25% EtOAc/hexanes to afford a mixture of two diastereomers (**23** and **24**, 0.10 g, 62%) in a 1:1.3 ratio, as determined by ^{1}H NMR spectroscopy:[12] IR (CH_2Cl_2) 1750 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, a mixture of two diastereomers) δ 1.35 (d, 4H, J = 7.0), 1.36 (d, 3H, J = 7.0), 1.52 (d, 4H, J = 7.0), 1.57 (d, 3H, J = 7.0), 3.64 (s, 4H), 3.67 (s, 3H), 3.77 (s, 3H), 3.78 (s, 4H), 3.84 (dd, 1.3H, J = 3.4, 22.2), 3.85 (dd, 1H, J = 3.4, 22.2), 4.02 (dd, 1H, J = 4.4, 22.2), 4.06 (dd, 1.3H, J = 4.4, 22.2), 5.06 (q, 1.3H, J = 7.0), 5.18 (m, 2.3H), 5.26 (m due to overlap of two quartets, 2.3H), 7.13-7.25 (m, 21H); mass spectrum m/z (relative intensity) 464 (M-H_2, 6), 362 (19), 275 (30), 231 (54), 202 (32), 119 (66) 116 (63). HRMS (CIMS, NH_4^+) calcd. for $C_{26}H_{26}O_8 \cdot NH_4$ 484.1971, found 484.1937.

Phenylnaphthalene 25



A mixture of diastereomers **23** and **24** (50 mg, 0.11 mmol), and Pd/C (0.30 g) in xylenes (5 mL) was refluxed for 20 h. The work-up procedure for biaryl **21** was used to give a yellow oil (45 mg, 90%): $[\alpha]^{20}_{D}$ +13.7° (c 0.54, $CHCl_3$); IR (CH_2Cl_2) 1744 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, 3H, J = 7.0), 1.66 (d, 3H, J = 7.0), 3.63 (s, 3H), 3.77 (s, 3H), 5.18 (q, 1H, J = 7.0), 5.39 (q, 1H, J = 7.0), 7.13-7.53 (m, 8H), 8.01 (br d, 1H, J = 8.0), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.7 (CH_3), 17.1 (CH_3), 52.1 (CH_3), 52.4 (CH_3), 69.4 (CH), 69.5 (CH), 124.1 (C), 127.0 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 128.0_4 (CH), 129.1 (CH), 129.3 (CH), 129.9 (C), 130.4 (CH), 130.5 (CH), 131.7 (CH), 132.4 (C), 134.3 (C), 136.3 (C), 139.2 (C), 164.9 (C), 167.2 (C), 170.7 (C), 170.9 (C); mass spectrum *m/z* (relative intensity) 464 (M^+, 37), 361 (41), 275 (100), 231 (20), 202 (62); HMRS calcd. for $C_{26}H_{24}O_8$ 464.1471, found 464.1499.

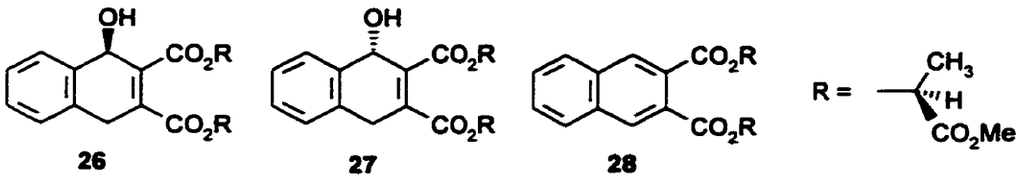
2-Methylbenzaldehyde



To a solution of 2-methylbenzyl alcohol (0.335 g, 2.74 mmol) in ether (6 mL) at 0 °C was added, in one portion, a solution of 5% CrO_3 in 10% H_2SO_4 (4 mL). The resulting dark brown solution was stirred vigorously at 0 °C for 15 min, and then diluted with ether (10 mL) and water (10 mL). The aqueous layer was discarded. The organic

layer was washed with water (3 x 20 mL), dried ($MgSO_4$), and concentrated to give a volatile yellow liquid with a vanilla odour (0.21 g, 65%). The unstable crude product was immediately used in the next reaction without further purification: ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.64 (s, 3H), 7.23 (d, 1H, J = 7.6), 7.33 (m, 1H), 7.44 (m, 1H), 7.75 (d, 1H, J = 7.6), 10.24 (s, 1H), consistent with that previously reported.[11]

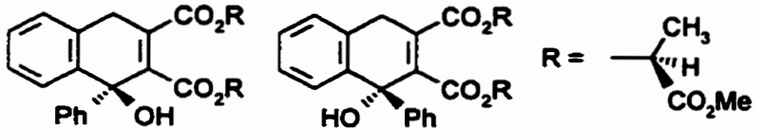
Cycloadducts 26 and 27, and naphthalene 28



A solution of **1e** (0.145 g, 0.51 mmol) and 2-methylbenzaldehyde (0.303 g, 2.5 mmol) in benzene (10 mL) in a pyrex test tube was degassed by nitrogen bubbling for 20 min. The degassed mixture was irradiated for 2.5 h using a 450 watt Hanovia medium pressure mercury lamp (1 mm Pyrex filter) equipped with a pyrex cooling jacket. The solution was concentrated under vacuum, and the resulting crude yellow product was chromatographed using 25% EtOAc/hexanes to afford two fairly unstable diastereomers (**26** and **27**, 96 mg, 46%) in a 1:5 ratio, as determined by ^{1}H NMR spectroscopy:[12] IR (CH_2Cl_2) 3489 (OH), 1742 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, major diastereomer) δ 1.57 (d, 3H, J = 7.1), 1.60 (d, 3H, J = 7.1), 3.69 (dd, 1H, J = 4.6, 23.0), 3.99 (dd, 1H, J = 3.8, 23.0), 3.78 (s, 3H), 3.81 (s, 3H), 5.29 (q, 1H, J = 7.1), 5.45 (q, 1H, J = 7.1), 5.72 (t, 1H, J = 4.4), 7.20-7.38 (m, 3H), 7.79 (dd, 1H, J = 1.9, 6.9); A by-product (81 mg, 39%) which was determined to be naphthalene **28** by ^{1}H and ^{13}C NMR was also isolated from the

chromatography of the crude diastereomers: $[\alpha]^{20}_{D}$ +24.57° (c 0.46, $CHCl_3$); IR (CH_2Cl_2) 1746 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (d, 6H, J = 7.1), 3.73 (s, 6H), 5.33 (q, 2H, J = 7.1), 7.57 (dd, 2H, J = 3.19, 3.24), 7.88 (dd, 2H, J = 3.24, 3.3), 8.30 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 17.0 (2 x CH_3), 52.4 (2 x CH_3), 69.6 (2 x CH), 127.7 (2 x C), 128.8 (4 x CH), 130.7 (2 x CH), 133.5 (2 x C), 166.5 (2 x C), 171.1 (2 x C); mass spectrum *m/z* (relative intensity) 388 (M^+, 16), 285 (54), 199 (100), 171 (14), 149 (15); HRMS calcd. for $C_{20}H_{20}O_8$ 388.1158, found 388.1150.

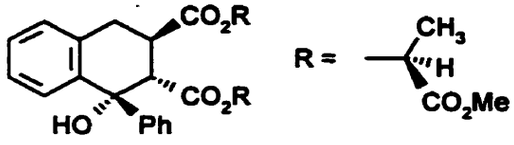
Cycloadducts 29 and 30



1e (69 mg, 0.24 mmol) and 2-methylbenzophenone (78 mg, 0.40 mmol) were irradiated in benzene for 2 h as described for cycloadducts **26** and **27**. The reaction mixture was concentrated under vacuum and chromatographed (EtOAc/hexanes) to give a mixture of two diastereomers (**29** and **30**, 95 mg, 82 %) in a 1:2.1 ratio, as shown in the ^1H NMR spectrum:[12] IR (CH_2Cl_2) 3458 (OH), 1741 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, mixture of two diastereomers) δ 1.24 (d, 3H, J = 7.0), 1.34 (d, 6.3H, J = 7.0), 1.56 (d, 3H, J = 7.0), 1.57 (d, 6.3H, J = 7.0), 3.68 (s, 3H), 3.74 (s, 6.3H), 3.76 (s, 6.3H), 3.79 (s, 3H), 3.85 (d, 3.1H, J = 22.6), 4.02 (d, 2.1H, J = 22.6), 4.03 (d, 1H, J = 22.6), 4.43 (s, 2.1H), 4.69 (s, 1H), 5.15 (m due to overlap of four quartets, 6.2H), 7.16-7.59 (m, 27.9H); mass spectrum *m/z* (relative intensity) 464 (M-H_2O, 32), 361 (34), 301 (26), 275 (100), 202 (53); HRMS calcd. for $C_{26}H_{26}O_9$-H_2O 464.1470, found 464.1442. A mixture of

diastereomers **29** and **30** (20 mg, 0.04 mmol) was refluxed with *p*-TsOH (6 mg) in benzene for 1 h. The solution was filtered through a short silica gel column, and concentrated under vacuum to give an oily residue (16 mg, 80%), which had an NMR spectrum identical to that of phenylnaphthalene **25** (see above).

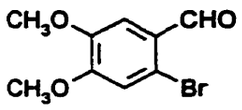
Cycloadduct 32



The fumarate of methyl (*S*)-lactate (140 mg, 0.48 mmol) and 2-methylbenzophenone (93 mg, 0.47 mmol) were irradiated in benzene for 20 h as described for cycloadducts **26** and **27**, and then concentrated under vacuum. The ^{1}H NMR spectrum of the crude product showed the presence of predominantly one diastereomer (> 90% *de*), and a by-product (*ca.* 20%) which was identified as the maleate of methyl (*S*)-lactate by comparison to an authentic sample.[11] The cycloadduct and the maleate were inseparable by chromatography. The latter could be removed by reacting the crude product (0.233 g) with an excess of benzocyclobutenol[10] (0.15 g) in refluxing toluene for 5 h, followed by chromatography with 15-25% EtOAc/hexanes which afforded the pure cycloadduct **32**[13] (0.10 g, 44%): $[\alpha]^{20}_D$ +48.6° (c 0.500, $CHCl_3$); IR (CH_2Cl_2) 3436 (OH), 1744 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3H, *J* = 7.0), 1.54 (d, 3H, *J* = 7.0), 3.15 (dd, 1H, *J* = 12.0, 16.3), 3.43 (dd, 1H, *J* = 4.3, 16.3), 3.57-3.82 (m, 2H), 3.68 (s, 3H), 3.77 (s, 3H), 4.20 (s, 1H, OH), 4.90 (q, 1H, *J* = 7.0), 5.12 (q, 1H, *J* = 7.0), 6.91 (d, 1H, *J* = 7.1), 7.02-7.42 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 16.3 (CH_3), 16.8

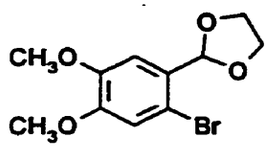
(CH_3), 32.8 (CH_2), 39.3 (CH), 52.3 (CH_3), 52.6 (CH_3), 55.0 (CH), 68.8 (CH), 68.9 (CH), 76.3 (C), 126.2 (2 x CH), 126.6 (CH), 127.0 (CH), 127.6 (2 x CH), 127.7 (CH), 128.1 (CH), 130.2 (CH), 133.3 (C), 140.4 (C), 146.6 (C), 171.2 (CO), 171.5 (CO), 171.6 (CO), 174.2 (CO); mass spectrum *m/z* (relative intensity) 466 (M-H_2O, 0.3), 334 (10), 274 (16), 231 (45.3), 205 (100), 202 (57); HRMS calcd. for $C_{26}H_{28}O_9$-H_2O 466.1628, found 466.1657.

2-Bromo-4,5-dimethoxybenzaldehyde



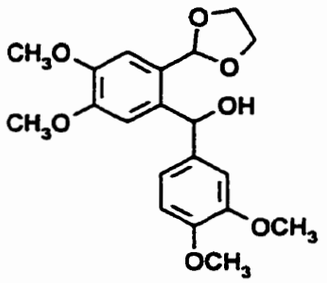
A slightly modified literature procedure was employed.[14] To a constantly stirred solution of 3,4-dimethoxybenzaldehyde (10 g, 0.06 mol) in glacial AcOH (50 mL) in an Erlenmeyer flask was added Br_2 (6.2 mL, 0.12 mol). A precipitate formed immediately. After stirring for 20 min, the resulting mixture was diluted with water (50 mL), filtered, and the solid washed with ice cold water to remove all of the AcOH/Br_2. The precipitate was dissolved in a boiling 3:1 MeOH/H_2O mixture. The bromide crystallized as colorless flakes from the cooled solution and was filtered and dried under vacuum at 40 °C (13.2 g, 93%): mp 148-150 °C (lit.,[15] mp 148-150); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 3.96 (s, 3H), 7.05 (s, 1H), 7.42 (s, 1H), 10.19 (s, 1H).

Ethylene glycol acetal of 2-bromo-4,5-dimethoxybenzaldehyde (38)



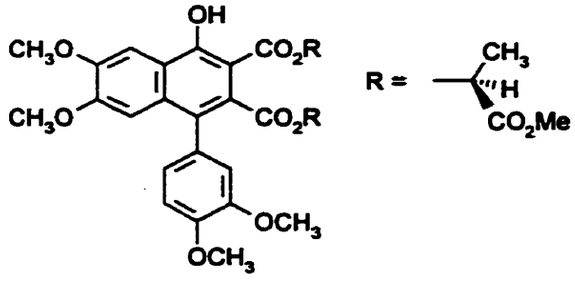
A slightly modified literature procedure was used.[15] A mixture of 2-bromo-4,5-dimethoxybenzaldehyde (1.32 g, 5.40 mmol), ethylene glycol (0.503 g, 8.1 mmol), and *p*-TsOH·H_2O (81 mg) in benzene (60 mL) was refluxed under N_2, using a Dean-Stark trap to occasionally remove benzene distillate containing water. A clear benzene distillate was an indication that the reaction was complete. When *ca.* 15 mL of benzene solution were left in the reaction flask (total of about 3 h reflux), the mixture was cooled to rt and filtered through a short column of dry silica gel using 50% EtOAc/hexanes as eluant. The solvent was concentrated under vacuum to afford a light yellow solid which contained only the acetal, as shown by the ^{1}H NMR spectrum (CCl_4). The acetal was very susceptible to hydrolysis and decomposed in a few hours on being left open to the air. It was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 6H), 4.00-4.28 (m, 4H), 6.00 (s, 1H), 7.01 (s, 1H), 7.14 (s, 1H), identical to that reported previously.[15]

Hydroxyacetal 33



Crude ethylene glycol acetal of 2-bromo-4,5-dimethoxybenzaldehyde (1.56 g) in dry THF (40 mL) under N_2 was cooled to -78° C, and *n*-BuLi (2.45 M in hexanes, 2.30 mL, 5.6 mmol) added dropwise over 5 min. The mixture was stirred for another 15 min, followed by the dropwise addition of 3,4-dimethoxybenzaldehyde (0.85 g, 5.11 mmol) in THF (10 mL). After stirring for 30 min, the solution was gradually warmed to room temperature and was stirred for another 2.5 h, followed by the addition of H_2O (30 mL). The resulting mixture was extracted with Et_2O (3 x 30 mL), dried ($MgSO_4$), and concentrated to give a colorless solid (1.90 g, 100%) which turned dark green upon standing at room temperature. The unstable product was not further purified, but was used immediately in the following Diels-Alder reactions: ^{1}H NMR ($CDCl_3$) δ 3.21 (d, 1H, OH, J = 3.9), 3.75 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 4.00-4.05 (m, 2H), 4.10-4.18 (m, 2H), 5.91 (s, 1H), 6.13 (d, 1H, J = 3.9), 6.77 (s, 1H), 6.83 (d, 1H, J = 8.3), 6.89 (dd, 1H, J = 8.3, 1.7), 6.99 (d, 1H, J = 1.7), 7.14 (s, 1H), identical to that previously reported.[16]

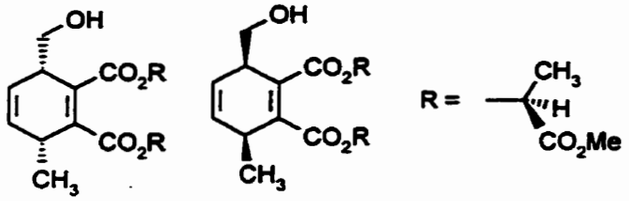
Arylnaphthol 37



A modified literature procedure was used.[17] **1e** (0.10 g, 0.35 mmol) and hydroxyacetal **33** (0.16 g, 0.41 mmol) were dissolved in a minimum amount of CH_2Cl_2(*ca.* 0.5 mL), and then maintained at 95 °C in the presence of glacial AcOH (0.2 mL) for 20 min. The NMR spectrum of the crude product (1 mg in $CDCl_3$) showed the presence of naphthol **29** (80 ± 5%), and two diastereomers (**26** and **27**, 20 ± 5%). The remainder of the crude mixture was reacted for another 20 min, and then chromatographed using 25-35% EtOAc/hexanes to give a colorless solid (0.17 g, 80%): mp 69-72 °C; $[\alpha]^{20}_D$ +27° (c 1.05, $CHCl_3$); IR (CH_2Cl_2) 3350 (OH), 1739 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3H, *J* = 6.9), 1.07 (d, 3H, *J* = 6.9), 1.57 (d, 3H, *J* = 7.0), 1.58 (d, 3H, *J* = 7.0), 3.65 (d, 6H, *J* = 4.1), 3.73 (d, 6H, *J* = 2.0), 3.78 (s, 6H), 3.86 (d, 6H, *J* = 4.1), 3.94 (d, 6H, *J* = 0.9), 4.05 (s, 6H), 5.16 (dq, 2H, *J* = 4.8, 6.9), 5.40 (dq, 2H, *J* = 2.5, 7.0), 6.73 (d, 2H, *J* = 5.8), 6.88-6.97 (m, 6H), 7.74 (s, 2H), 12.00 (d, 2H, *J* = 3.5); ^{13}C NMR ($CDCl_3$) δ 16.2 (CH_3), 16.3 (CH_3), 16.7 (CH_3), 16.7 (CH_3), 51.9 (2 x OCH_3), 52.3 (2 x OCH_3), 55.6 (2 x OCH_3), 55.8 (2 x OCH_3), 55.8 (2 x OCH_3), 55.9 (2 x OCH_3), 69.2 (OCH), 69.2 (OCH), 70.0 (2 x OCH), 100.5 (2 x C), 102.7 (2 x CH), 105.7 (2 x CH), 110.5 (CH), 110.6 (CH), 114.2 (CH), 114.2_5 (CH), 119.8 (2 x C), 123.3 (CH), 123.4 (CH), 127.4 (2 x C), 128.3 (C), 128.4 (C), 129.0 (C), 129.0_2 (C), 132.3 (2 x C), 148.2 (C),

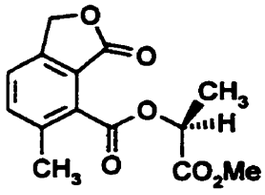
148.2 (C), 148.4 (C), 148.5 (C), 149.7 (2 x C), 152.4 (2 x C), 159.4 (C), 159.5 (C), 167.2 (CO), 167.3 (CO), 168.8 (CO), 168.9 (CO), 170.0 (2 x CO), 170.3 (2 x CO); mass spectrum *m/z* (relative intensity) 600 (M^+, 11), 496 (17), 410 (100), 84 (14); HRMS calcd. for $C_{30}H_{32}O_{13}$ 600.1842, found 600.1847.

Cycloadducts 39 and 40



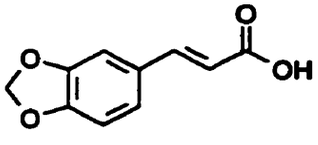
A mixture of **1e** (70 mg, 0.24 mmol), 2,4-hexadiene-1-ol (**18**, 0.118 g, 1.2 mmol), and hydroquinone (5 mg, 0.04 mmol) in xylenes (5 mL) was heated at reflux for 15 h. The mixture was absorbed onto a short column of silica gel and rinsed with hexanes to remove xylenes. The product was eluted with EtOAc, concentrated under vacuum, and chromatographed (1:2 EtOAc/hexanes) to afford a mixture of two diastereomers (**39** and **40**, 79 mg, 86%) in a 1:1.3 ratio, as determined by ^{1}H NMR spectroscopy:[12] IR (CH_2Cl_2) 1749, 1755 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, 2.3H, J = 7.0), 1.32 (d, 3H, J = 7.0), 1.51 (d, 2.3H, J = 7.0), 1.52 (d, 3H, J = 7.0), 1.53 (d, 5.3H, J = 7.0), 1.77 (br s, 1H), 2.37 (br s, 0.8H), 3.21-3.47 (m, 1.8H), 3.47-3.44 (m, 1.8H), 3.64 -3.77 (m, 2H), 3.75_3 (s, 3H), 3.75_5 (s, 3H), 3.76_0 (s, 2.3H), 3.76_5 (s, 2.3H), 3.83-3.90 (m, 1.5H), 5.16-5.33 (m due to overlap of four quartets, 3.5H), 5.65-5.74 (m, 1.8H), 5.88 (br dd, 1.8H, J = 4.2, 9.8); mass spectrum *m/z* (relative intensity) 353 (M-OCH_3, 0.3), 339 (3), 281 (7), 250 (16), 235 (81), 177 (56), 163 (26); HRMS calcd. for $C_{17}H_{21}O_8$ (M-OCH_3) 353.1236, found 353.1226.

Aromatized product 41



A mixture of diastereomers **39** and **40** (40 mg, 0.1 mmol) and Pd/C (10 mg) in xylenes (2 mL) was heated at reflux for 20 h. The reaction mixture was worked up as described for cycloadducts **39** and **40** to afford a light yellow solid (26 mg, 90%) after chromatography (15-33% EtOAc/hexanes): mp 93-96 °C; IR (CH_2Cl_2) 1756, 1775, 1783 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (d, 3H, J = 7.1), 2.53 (s, 3H), 3.81 (s, 3H), 5.28 (s, 2H), 5.50 (q, 1H, J = 7.1), 7.44 (d, 1H, J = 7.9), 7.55 (d, 1H, J = 7.9); ^{13}C NMR ($CDCl_3$) δ 16.8 (CH_3), 18.5 (CH_3), 52.4 (CH_3), 69.2 (CH_2), 69.8 (CH), 122.9 (C), 123.1 (CH), 130.7 (C), 136.2 (CH), 137.0 (C), 144.2 (C), 165.8 (C), 168.7 (C), 171.0 (C); mass spectrum *m/z* (relative intensity) 278 (M^+, 2), 219 (1), 191 (1), 175 (100), 129 (14); HRMS calcd. for $C_{14}H_{14}O_6$ 278.0790, found 278.0781.

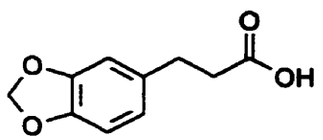
3,4-(Methylenedioxy)cinnamic acid (48)



A literature procedure was employed.[18] A mixture of piperonal (2.51 g, 16.7 mmol), malonic acid (3.77 g, 36.2 mmol), piperidine (0.5 mL), and pyridine (15 mL) was heated at 100 °C for an hour, then at vigorous reflux for 20 min. It was cooled to room temperature and poured onto ice containing 5% aqueous HCl (15 mL). The resulting

colorless precipitate was filtered, washed with water (3 x 50mL), and dried under vacuum for about 5 h. It was recrystallized from AcOH to give a colorless solid (2.52 g, 78%): mp 242-243 °C; ^{1}H NMR (DMSO-d_6) δ 6.07 (s, 2H), 6.38 (d, 1H, J = 15.9), 6.94 (d, 1H, J = 8.0), 7.15 (dd, 1H, J = 8.0, 1.6), 7.36 (d, 1H, J = 1.6), 7.50 (d, 1H, J = 15.9). All data are identical to those previously reported.[4]

3,4-(Methylenedioxy)dihydrocinnamic acid (49)

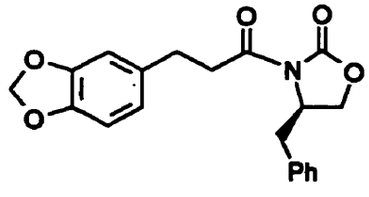


3,4-(Methylenedioxy)cinnamic acid (**48**, 1.86 g, 9.69 mmol) was dissolved in DMF (*ca.* 25 mL) and stirred with Pd/C (0.2 g) under H_2 (1 atm) for 24 h. The suspension was filtered through Celite, rinsing with water and EtOAc. The organic solution was separated, and the aqueous solution extracted with EtOAc (3 x 15 mL). The organic solutions were combined, washed with water (5 x 20 mL) to remove residual DMF, dried ($MgSO_4$), and concentrated under vacuum to afford a colorless crystalline solid (1.88 g, 100%): mp 82-84 °C; IR (CH_2Cl_2) 3085 (COOH), 1711 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.64 (t, 2H, J = 7.5), 2.88 (t, 2H, J = 7.5), 5.92 (s, 2H), 6.63-6.74 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 30.3 (CH_2), 35.9 (CH_2), 100.8 (CH_2), 108.3 (CH), 108.7 (CH), 121.1 (CH), 133.9 (C), 146.0 (C), 147.6 (C), 179.1 (C); mass spectrum *m/z* (relative intensity) 194 (M^+, 32), 176 (3), 149 (7), 135 (100); HRMS calcd. for $C_{10}H_{10}O_4$ 194.0579, found 194.0570.

General procedure for the preparation of N-acyloxazolidinones 51 and 52

A modified literature procedure was used.[19] To a solution of 3,4-(methylenedioxy)dihydrocinnamic acid (**49**, 0.50 g, 2.53 mmol) in THF (6 mL) under N_2 at -70 °C was added successively dropwise Et_3N (0.41 mL, 2.9 mmol) and pivaloyl chloride (0.32 mL, 2.6 mmol). The mixture was gradually warmed to 0 °C, stirred for an hour, and then recooled to -70 °C. *n*-BuLi (1.1 mL, 2.45 M in hexane, 2.6 mmol) was added dropwise to a solution of the (4*R*)-benzyl (**56a**) or (4*S*)-isopropyl-2-oxazolidinone (**56b**) (2.53 mmol) in THF (15 mL) under N_2 at -70 °C. The resulting lithium salt was added dropwise to the above dihydrocinnamic acid mixture via a double-tipped needle at -70 °C over a period of 15 min. The resulting mixture was stirred for an hour, and then warmed gradually to 0 °C. After stirring at 0 °C for 35 min, saturated aqueous NH_4Cl (2 mL) was added. The solution was concentrated under vacuum to remove most of the THF. Water (10 mL) was added and the solution was extracted with EtOAc (4 x 10 mL), dried ($MgSO_4$), and evaporated.

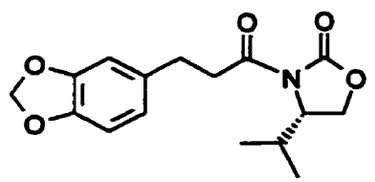
N-acyloxazolidinone 51



Reacting dihydrocinnamic acid **49** and (4*R*)-benzyl-2-oxazolidinone (**56a**) as described above gave an oil (0.89 g) which slowly crystallized. Recrystallization from EtOAc/hexanes gave colorless crystals (0.78 g, 88%): mp 68-70 °C; $[\alpha]^{20}_D$ -48.3° (c 0.30, $CHCl_3$); IR (CH_2Cl_2) 1783 and 1702 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76 (dd, 1H,

J = 9.5, 13.4), 2.91-2.96 (m, 2H), 3.13-3.32 (m, 3H), 4.15-4.19 (m, 2H), 4.66 (m, 1H), 5.91 (s, 2H), 6.71-6.76 (m, 3H), 7.17 (dd, 2H, J = 8.0, 1.7), 7.25-7.32 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 30.0 (CH_2), 37.4 (CH_2), 37.8 (CH_2), 55.1 (CH), 66.2 (CH_2), 100.8 (CH_2), 108.2 (CH), 109.0 (CH), 121.3 (CH), 127.3 (CH), 128.9 (2 x CH), 129.4 (2 x CH), 134.2 (C), 135.2 (C), 145.9 (C), 147.6 (C), 153.4 (C), 172.3 (C); mass spectrum *m/z* (relative intensity) 353 (M^+, 40.5), 309 (4), 219 (5), 176 (34), 148 (82), 135 (100); HRMS calcd. for $C_{20}H_{19}O_5N$ 353.1263, found 353.1263.

N-acyloxazolidinone 52

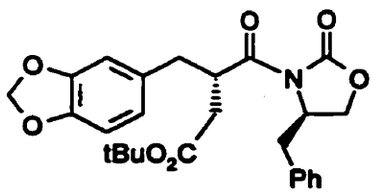


Reacting dihydrocinnamic acid **49** and (4*S*)-isopropyl-2-oxazolidinone (**56b**) as described above gave an oil. This was chromatographed with 20% EtOAc/hexanes to afford a light yellow oil (0.65 g, 84%): $[\alpha]^{20}_D$ +60.6° (c 0.98, $CHCl_3$); IR (CH_2Cl_2) 1786 and 1708 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, J = 7.0), 0.90 (d, 3H, J = 7.0), 2.35 (dseptet, 1H, J = 3.9, 7.0), 2.90 (m, 2H), 3.10-3.33 (m, 2H), 4.22 (m, 2H), 4.42 (m, 1H), 5.91 (s, 2H), 6.68-6.74 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.6 (CH_3), 17.9 (CH_3), 28.4 (CH), 30.2 (CH_2), 37.4 (CH_2), 58.4 (CH), 63.4 (CH_2), 100.8 (CH_2), 108.2 (CH), 109.0 (CH), 121.3 (CH), 134.2 (C), 145.9 (C), 147.6 (C), 154.0 (C), 172.3 (C); mass spectrum *m/z* (relative intensity) 305 (M^+, 9), 180 (13), 179 (25), 178 (17), 176 (13), 149 (13), 148 (29), 135 (27); HRMS calcd. for $C_{16}H_{19}O_5N$ 305.1263, found 305.1269.

General procedure for alkylation of N-acyloxazolidinones 51 and 52 with *t*-butyl bromoacetate

A modification of a literature procedure was employed.[19] NaHMDS (2.10 mL, 1.0 M in THF, 2.10 mmol) was added dropwise to a solution of the N-acyloxazolidinone (2.0 mmol) in THF (15 mL) under N_2 at -73 °C, over a period of 10 min. After stirring at -73 °C for an hour, *t*-butyl bromoacetate (0.92 mL, 6.30 mmol) was added dropwise. The mixture was stirred for 2 h before being quenched with saturated aqueous NH_4Cl (4 mL). It was concentrated under vacuum to remove most of the THF, and then diluted with EtOAc (15 mL) and water (10 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3x10 mL). The organic solutions were combined, washed with saturated aqueous NH_4Cl (15 mL), 5% aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated to afford a liquid which crystallized when triturated with hexane. The hexane washings were concentrated and chromatographed using hexanes/2-propanol (15:1) to give more product. The colorless solid was combined and recrystallized (see below).

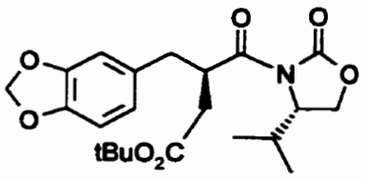
Alkylated product 53



N-acyloxazolidinone **51** (0.706 g, 2.0 mmol) was alkylated as above to give a colorless solid which was further recrystallized from MeOH (0.72 g, 77%): mp 138-139 °C; $[\alpha]^{20}_D$ -98.5° (c 0.135, $CHCl_3$); IR (CH_2Cl_2) 1782, 1722, 1700 (C=O) cm^{-1}; ^1H NMR

($CDCl_3$) δ 1.40 (s, 9H), 2.36 (dd, 1H, J = 4.1, 16.9), 2.51 (dd, 1H, J = 9.3, 13.2), 2.75 (dd, 1H, J = 9.9, 13.4), 2.80 (dd, 1H, J = 10.9, 17.0), 2.97 (dd, 1H, J = 5.7, 13.2), 3.32 (dd, 1H, J = 3.2, 13.6), 4.03-4.15 (m, 2H), 4.39 (m, 1H), 4.60 (m, 1H), 5.91 (s, 2H), 6.67-6.79 (m, 3H), 7.25-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.1 (3 x CH_3), 36.5 (CH_2), 37.6 (CH_2), 37.8 (CH_2), 41.6 (CH), 55.5 (CH), 66.0 (CH_2), 80.8 (C), 100.9 (CH_2), 108.1 (CH), 109.6 (CH), 122.2 (CH), 127.2 (CH), 128.9 (2 x CH), 129.5 (2 x CH), 131.7 (C), 135.6 (C), 146.3 (C), 147.6 (C), 153.0 (C), 171.2 (C), 175.2 (C); mass spectrum *m/z* (relative intensity) 467 (M^+, 1), 411 (5), 234 (25), 192 (16), 135 (100), 92 (90); HRMS calcd. for $C_{26}H_{29}O_7N$ 467.1944, found 467.1924.

Alkylated product 54



N-acyloxazolidinone **52** (0.610 g, 2.0 mmol) was alkylated as above to give a colorless solid which was further recrystallized from EtOAc/hexanes (0.67 g, 80%): mp 123-124 °C; $[\alpha]^{20}_D$ +92.4° (c 0.37, $CHCl_3$); IR (CH_2Cl_2) 1779 and 1723 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, 3H, J = 6.8), 0.93 (d, 3H, J = 6.8), 1.39 (s, 9H), 2.32 (dd, 1H, J = 4.3, 16.8), 2.34 (m, 1H), 2.47 (dd, 1H, J = 9.3, 13.2), 2.74 (dd, 1H, J = 10.5, 16.8), 2.94 (dd, 1H, J = 5.8, 13.2), 4.15 (m, 2H), 4.36 (m, 2H), 5.96 (s, 2H), 6.67 (dd, 1H, J = 1.5, 7.9), 6.72 (d, 1H, J = 7.9), 6.78 (d, 1H, J = 1.5); ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 18.0 (CH_3), 28.0 (3 x CH_3), 28.3 (CH), 36.6 (CH_2), 37.6 (CH_2), 41.5 (CH), 58.8 (CH), 63.2 (CH_2), 80.6 (C), 100.8 (CH_2), 108.1 (CH), 109.6 (CH), 122.2 (CH), 131.9 (C), 146.2

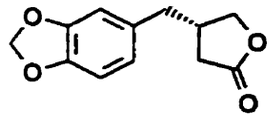
(C), 147.6 (C), 153.5 (C), 171.1 (C), 175.1 (C); mass spectrum *m/z* (relative intensity) 419 (M^+, 3), 363 (36), 346 (9), 304 (8), 303 (6), 234 (17), 206 (19), 175 (20), 149 (14), 135 (100); HRMS calcd. for $C_{22}H_{29}O_7N$ 419.1944, found 419.1951.

General procedure for the preparation of β-benzyl-γ-butyrolactones 47

A modification of a literature procedure was used.[20] The alkylated product (**53** or **54**, 1.40 mmol) was dissolved in THF (20 mL), and water added (7.0 mL). The solution was cooled to ice temperature, followed by addition of H_2O_2 (0.66 mL, 30% in H_2O, 5.8 mmol) and $LiOH{\cdot}H_2O$ powder (0.12 g, 2.8 mmol). The resulting mixture was stirred at 0-5 °C for 1.5 h, then at rt for 3 h. After recooling to 0 °C, saturated aqueous $NaHSO_3$ (2 mL), cold water (50 mL), and 2% aqueous HCl (2 mL) were added. The solution was carefully kept at 0 °C during the additions to prevent hydrolysis of the *t*-butyl ester. The resulting mixture was extracted with EtOAc (4 x 25 mL). The organic solutions were combined, washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated to give a liquid which was used in the following reaction without further purification. The crude liquid was redissolved in THF (25 mL) and cooled to 0 °C. $BH_3{\cdot}THF$ (1.68 mL, 1.0M in THF, 1.68 mmol) was added dropwise to the acid solution over a period of 10 min. The resulting mixture was stirred at 0 °C for 1 h, then at rt for 4 h. It was recooled to 0 °C, MeOH (0.5 mL) added dropwise to destroy excess $BH_3{\cdot}THF$, followed by cold water (10 mL) and 2% aqueous HCl (5 mL). The mixture was concentrated under vacuum to remove most of the THF. The remaining solution was extracted with EtOAc (3 x 15 mL). The combined EtOAc solution was washed with

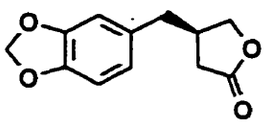
water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford a light brown liquid. The crude product was redissolved in CH_2Cl_2 (4 mL), cooled to 0 °C, and TFA (4 mL) added dropwise. The mixture was stirred for 1 h at ice temperature, 3 h at rt followed by concentration under vacuum with several coevaporations with benzene to remove all of the TFA. The resulting brown liquid was chromatographed with 20-33% EtOAc/hexanes.

Benzylbutyrolactone 47a



Alkylated product **53** (0.65 g, 1.4 mmol) was hydrolyzed, reduced, and lactonized as described in the above general procedure to give, after chromatography, a light yellow liquid (0.215 g, 70% from **53**): $[\alpha]^{20}_D$ -4.8° (c 0.50, $CHCl_3$) (lit.,[21] $[\alpha]^{20}_D$ -4.78° (c 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.28 (dd, 1H, J = 6.9, 17.4), 2.60 (dd, 1H, J = 8.0, 17.4), 2.66-2.71 (m, 2H), 2.78 (m, 1H), 4.02 (dd, 1H, J = 6.1, 9.2), 4.32 (dd, 1H, J = 6.9, 9.2), 5.94 (s, 2H), 6.59 (dd, 1H, J = 1.6, 7.8), 6.63 (d, 1H, J = 1.6), 6.75 (d, 1H, J = 7.8); HRMS calcd. for $C_{12}H_{12}O_4$ 220.0736, found 220.0738. Spectral data were consistent with those published previously.[21]

Benzylbutyrolactone 47b



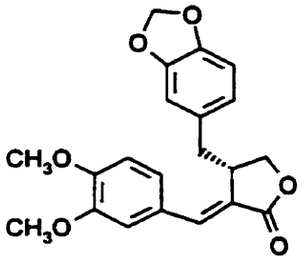
Alkylated product **54** (0.586 g, 1.4 mmol) was treated as above to afford a light yellow liquid (0.202 g, 66% from **54**): $[\alpha]^{20}_D$ +4.8° (c 0.665, $CHCl_3$) (lit.,[21] $[\alpha]^{20}_D$ +4.87° (c 0.87, $CHCl_3$); spectroscopic data were identical to that obtained from **47a**.

General procedure for preparation of benzylidenebenzylbutyrolactones 59a and 59b

A modified literature procedure was employed.[22] To a solution of benzylbutyrolactone **47a** or **47b** (61 mg, 0.28 mmol) in THF (1 mL) under N_2 at -70 °C was added NaHMDS (0.33 mL, 1.0 M in THF, 0.33 mmol) over a period of 5 min. The solution was stirred at -70 °C for 15 min, then at -20 °C (CCl_4/dry ice) for 15 min to ensure complete deprotonation. The color of the solution changed from light yellow to intense bright yellow. The mixture was recooled to -70 °C and a solution of a benzaldehyde (3,4-dimethoxybenzaldehyde for **59a**; 3,4-(methylenedioxy)benzaldehyde for **59b**) (0.28 mmol) in THF (1 mL) was added dropwise. After stirring at -70 °C for 1.3 h, a mixture of Ac_2O (78 μL, 0.83 mmol), Et_3N (0.16 mL, 1.14 mmol), and DMAP (6 mg, 0.049 mmol) in THF (1 mL) was added dropwise to the reaction mixture. The resulting thick mixture was warmed to rt and stirred for 1.5 h before water (1 mL) was added. The solution was concentrated to remove most of the THF, diluted with water (5 mL) and 2% aqueous HCl (2 mL), and then extracted with CH_2Cl_2 (3 x 10 mL). The combined CH_2Cl_2 phases were washed with 2% aqueous HCl (3 x 5 mL), 5% aqueous

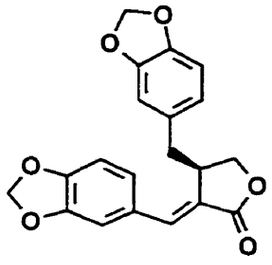
$NaHCO_3$ (2 x 5 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under vacuum to give a foamy residue. The crude product was redissolved in toluene (3 mL), DBU (90 μL, 0.61 mmol) added, and the solution heated to 80 °C. After 1.5 h the mixture was diluted with EtOAc (10 mL), washed successively with 2% aqueous HCl (2 x 5 mL), water (2 x 10 mL) and brine (15 mL), dried ($MgSO_4$), and evaporated to afford a yellow residue which crystallized on standing under vacuum.

Gossypifan (59a)



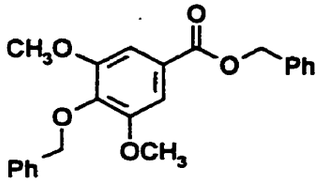
Benzylbutyrolactone **47a** (0.61 g, 0.28 mmol) was acylated with 3,4-dimethoxybenzaldehyde (46 mg, 0.28 mmol), acetylated and treated with DBU as described above. The crude product was chromatographed with EtOAc/Hexanes (1:2) to afford a light yellow solid (95 mg, 92%): mp 143-146 °C (lit.,[23] 145-146 °C); $[\alpha]^{20}_D$ 79.1° (c 0.110, $CHCl_3$) (lit.,[23] $[\alpha]^{20}_D$ 82.4° (c 0.875, $CHCl_3$)); ^1H NMR ($CDCl_3$) δ 2.61 (dd, 1H, J = 10.2, 14.4), 3.04 (dd, 1H, J = 4.3, 14.4), 3.82 (m, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 4.26 (m, 2H), 5.93 (AB, 2H, Δδ = 1.93, J = 1.4), 6.62 (dd, 1H, J = 1.7, 7.8), 6.65 (d, 1H, J = 1.7), 6.73 (d, 1H, J = 7.8), 6.94 (d, 1H, J = 8.4), 7.05 (d, 1H, J = 2.0), 7.23 (dd, 1H, J = 2.0, 8.4), 7.53 (d, 1H, J = 1.8); HRMS calcd. for $C_{21}H_{20}O_6$ 368.1260, found 368.1237. Spectral data were consistent with those published previously.[23]

Savinin (59b)



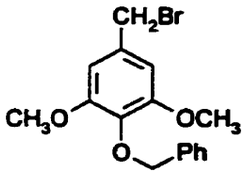
Benzylbutyrolactone **47b** (0.61 g, 0.28 mmol) was acylated with 3,4-(methylenedioxy)benzaldehyde (42 mg, 0.28 mmol), acetylated and treated with DBU as described above. The yellow residue crystallized upon standing under vacuum and was recrystallized from EtOH/$CHCl_3$ to afford colorless crystals (89 mg, 90%): mp 139-142 °C; $[\alpha]^{20}_D$ -82.9° (c 0.135, $CHCl_3$) (lit.,[24a] $[\alpha]^{20}_D$ -82° (C 2.5, $CHCl_3$); lit.,[24b] $[\alpha]^{20}_D$ -88° (c 1.0, $CHCl_3$)); ^1H NMR ($CDCl_3$) δ 2.58 (dd, 1H, J = 10.0, 14.2), 2.98 (dd, 1H, J = 4.5, 14.0), 3.73 (m, 1H), 4.24 (AB, 1H, Δδ = 11.8, J = 9.3), 4.26 (s, 1H), 5.93 (AB, 2H, Δδ = 2.7, J = 0.2), 6.04 (s, 2H), 6.63 (dd, 1H, J = 1.6, 7.8), 6.66 (d, 1H, J = 1.6), 6.73 (d, 1H, J = 7.8), 6.88 (d, 1H, J = 8.1), 7.04 (d, 1H, J = 1.6), 7.07 (dd, 1H, J = 1.6, 8.1), 7.50 (d, 1H, J = 1.8); HRMS calcd. for $C_{20}H_{16}O_6$ 352.0947, found 352.0937. Spectral data were consistent with those published previously.[25]

Benzyl ester of 4-O-(benzyl)syringic acid



A mixture of syringic acid (3.12 g, 15.7 mmol), benzyl bromide (5.6 mL, 47 mmol), and dry K_2CO_3 (11 g, 78 mmol) in acetone (80 mL) was refluxed under N_2 for 24 h. The resulting suspension was cooled to rt, concentrated under vacuum, diluted with water (100 mL), and extracted with CH_2Cl_2 (4 x 20 mL). The organic solution was dried ($MgSO_4$), concentrated, and chromatographed with hexanes and 6% EtOAc/hexanes to remove benzyl bromide. The product was eluted with EtOAc and concentrated to leave a colorless solid (5.70 g, 95%): mp 64-65 °C; IR (CH_2Cl_2) 1714 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 6H), 5.08 (s, 2H), 5.35 (s, 2H), 7.27-7.48 (m1, 2H); ^{13}C NMR ($CDCl_3$) δ 56.2 (2 x CH_3), 66.8 (CH_2), 74.9 (CH_2), 107.0 (2 x CH), 125.2 (C), 127.9 (CH), 128.1_3 (2 x CH), 128.1_6 (2 x CH), 128.2 (CH), 128.4 (2 x CH), 128.6 (2 x CH) 136.1 (C), 137.3 (C), 141.1 (C), 153.2 (2 x C), 166.1 (C); mass spectrum *m/z* (relative intensity) 378 (M^+, 4), 287 (6), 181 (6), 149 (7), 105 (11), 91 (100); HRMS calcd. for $C_{23}H_{22}O_5$ 378.1467, found 378.1463.

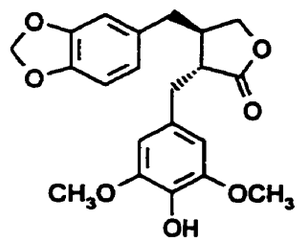
4-O-(Benzyl)syringyl bromide (60)



To a solution of the benzyl ester of 4-O-(benzyl)syringic acid (0.919 g, 2.43 mmol) in THF (10 mL) under N_2 at ice temperature was carefully added $LiEt_3BH$ (7.0 mL, 0.8 M in THF, mmol). The resulting mixture was stirred for 2 h and then 10% aqueous HCl (15 mL) was slowly added. The solution was concentrated under vacuum, diluted with water (10 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was washed successively with 5% aqueous HCl (3 x 20 mL), 5% aqueous $NaHCO_3$ (2 x 20 mL), and brine (20 mL). It was then dried ($MgSO_4$) and concentrated to afford an oil. The crude product (0.893 g) was redissolved in anhydrous ether (10 mL), followed by addition of pyridine (0.6 mL) and PBr_3 (0.55 mL, 5.79 mmol). The resulting colorless suspension was stirred for 2.5 h before filtering through Celite. The filtrate was diluted with CH_2Cl_2 (10 mL), washed with 3% aqueous HCl (3 x 20 mL), water (2 x 20 mL) and brine (25 mL), dried ($MgSO_4$), concentrated, and chromatographed (6-15% EtOAc/hexanes) to give a colorless liquid (0.53 g, 65%) which slowly solidified on standing: mp 53-55 °C (lit.,[26] 40-42 °C); IR (CH_2Cl_2) 1593, 1503, 1461, 1336, 1130 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s, 6H), 4.45 (s, 2H), 4.99 (s, 2H), 6.60 (s, 2H), 7.25-7.35 (m, 3H), 7.48 (dd, 2H, J = 8.1, 1.7); ^{13}C NMR ($CDCl_3$) 34.3 (CH_2), 56.1 (2 x CH_3), 75.0 (CH_2), 106.2 (2 x CH), 127.8 (CH), 128.1 (2 x CH), 128.4 (2 x CH), 133.2 (C), 137.1 (C), 137.7 (C), 153.5 (2 x C); mass spectrum *m/z* (relative intensity) 338 ($M^+(^{81}Br)$, 0.1), 336

($M^+(^{79}Br)$, 0.1), 148 (22), 136 (12), 91 (100); HRMS calcd. for $C_{16}H_{17}O_3Br(79)$ 336.0361, found 336.0333.

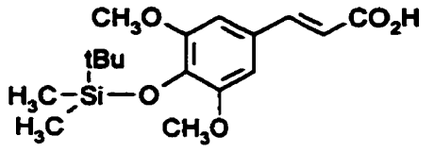
4'-Demethylyatein (61)



Benzylbutyrolactone **47b** (86 mg, 0.39 mmol) in THF (1.5 mL) under N_2 was cooled to -72 °C. NaHMDS (0.45 mL, 1.0 M in THF, 0.45 mmol) was then added dropwise over a period of 10 min. The mixture was stirred at that temperature for 15 min, then at -20 °C (CCl_4/dry ice) for 25 min. It was recooled to -72 °C and a solution of syringyl bromide **60** (0.135 g, 0.40 mmol) in THF (2 mL) was added. After stirring at -72 °C for 5 h, the reaction mixture was quenched with 5% aqueous NH_4Cl (1 mL). The mixture was concentrated, diluted with 2% aqueous HCl (10 mL), and extracted with CH_2Cl_2 (3 x 7 mL). The organic fractions were combined, washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to afford an oil (0.20 g). The crude product was redissolved in EtOAc and stirred with Pd/C (40 mg) under H_2 overnight. The suspension was filtered through Celite and the filtrate was concentrated and chromatographed (50% EtOAc/hexanes) to afford an oil (93 mg, 62%): $[\alpha]^{20}_D$ -25.8° (c 0.225, CH_2Cl_2) (lit.,[27] $[\alpha]^{20}_D$ -25° (c 0.32, CH_2Cl_2)); ^1H NMR ($CDCl_3$) δ 2.43-2.64 (m, 4H), 2.90 (dd, 2H, J = 1.4, 5.6), 3.86 (s, 6H), 3.87 (m, 1H), 4.15 (dd, 1H, J = 7.0, 9.2),

5.43 (br s, 1H), 5.93 (AB, 2H, $\Delta\delta = 2.7$, $J = 1.3$), 6.36 (s, 2H), 6.46 (m, 2H), 6.69 (dd, 1H, $J = 1.6, 6.8$); HRMS calcd. for $C_{21}H_{22}O_7$ 386.1366, found 386.1372. Spectral data were consistent with those published previously.[27]

4-O-(TBDMS)sinapic acid 65



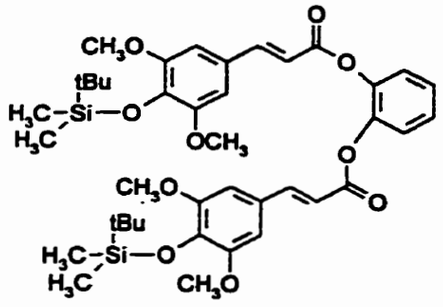
Et_3N (0.17 mL, 1.2 mmol) was added to a suspension of sinapic acid (0.107 g, 0.48 mmol) in CH_2Cl_2 (20 mL), under N_2 at 0 °C. The precipitate dissolved. TBDMSTf (0.25 mL, 1.08 mmol) was then added dropwise over a period of 10 min. The color of the reaction mixture changed from green to red to brown on complete addition of TBDMSTf. After stirring for 15 min, water (10 mL) was added. The organic phase was separated and the aqueous phase washed with CH_2Cl_2 (2 x 10 mL). The organic solutions were combined, dried ($MgSO_4$), and concentrated under vacuum to afford a brown solid which was redissolved in acetone (20 mL), and aqueous K_2CO_3 (10 mL, 0.2 M, 2 mmol) added. The resulting mixture was stirred for an hour, cooled to ice temperature, acidified to *ca.* pH 2, followed by extraction with EtOAc (4 x 20 mL). The combined organic solutions were dried ($MgSO_4$) and concentrated under vacuum to give a brown liquid which solidified on standing. It was recrystallized from hexanes to afford colorless needles (0.138 g, 85%): mp 136-138 °C; IR (CH_2Cl_2)1689 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, 6H), 1.01 (s, 9H), 3.83 (s, 6H), 6.31 (d, 1H, $J = 15.8$), 6.75 (s, 2H), 7.69 (d, 1H, $J =$

15.8); ^{13}C NMR ($CDCl_3$) δ -4.6 (2 x CH_3), 18.8 (C), 25.7 (3 x CH_3), 55.8 (2 x CH_3), 105.7 (2 x CH), 114.9 (CH), 126.6 (C), 137.4 (C), 147.5 (CH), 151.8 (2 x C), 172.2 (C); mass spectrum *m/z* (relative intensity) 338 (M^+, 0.1), 323 (3), 308 (2), 281 (64), 266 (100); HRMS calcd. for $C_{17}H_{26}O_5Si$ 338.1550, found 338.1538.

General procedure for the preparation of TBDMS-protected diol disinapates 66 and 67a

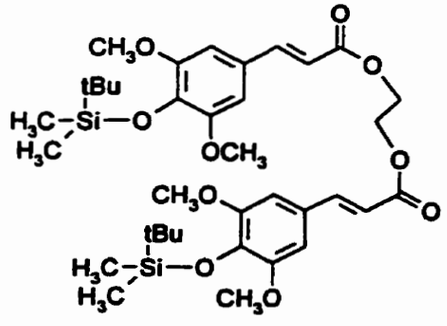
A mixture of acid **65** (0.201 g, 0.59 mmol) and thionyl chloride (0.26 mL, 3.54 mmol) in CCl_4 (10 mL) was heated at reflux under N_2 for 4 h. The mixture was concentration under vacuum with several coevaporations of CCl_4 to remove all of the thionyl chloride. The resulting solid was redissolved in CCl_4, cooled to ice temperature, and a mixture of the diol (0.29 mmol) and dry pyridine (0.19 mL, 2.36 mmol) in CCl_4 (15 mL) was added dropwise over a period of 30 min. After stirring for 2 h, the resulting white suspension was filtered through Celite, rinsing with CCl_4. The filtrate was washed with 5% aqueous $CuSO_4$ (3 x 10 mL), dried ($MgSO_4$), and concentrated under vacuum to give a brown solid.

TBDMS-protected catachol disinapate 66



Catechol (32 mg, 0.29 mmol) was reacted with acid **65** (0.201 g, 0.59 mmol) as described above. Recrystallization from EtOAc/MeOH gave colorless needles (0.30 g, 68%): mp 155-156 °C; IR (CH_2Cl_2) 1739 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 12H), 1.00 (s, 18H), 3.76 (s, 12H), 6.45 (d, 2H, J = 15.8), 6.72 (s, 4H), 7.29 (s, 4H), 7.75 (d, 2H, J = 15.8); ^{13}C NMR ($CDCl_3$) δ -4.6 (4 x CH_3), 18.6 (2 x C), 25.7 (6 x CH_3), 55.7 (4 x CH_3), 105.6 (4 x CH), 114.3 (2 x CH), 123.5 (2 x CH), 126.5_3 (2 x CH), 126.5_7 (2 x C), 137.4 (2 x C), 142.6 (2 x C), 147.5 (2 x CH), 151.8 (4 x C), 164.6 (2 x C); mass spectrum *m/z* (relative intensity) 693 (M-*t*Bu, 4), 373 (7), 321 (100), 281 (14), 266 (210, 249 (32); HRMS calcd. for $C_{36}H_{45}O_{10}Si_2$ (M-*t*Bu) 693.2551, found 693.2541.

TBDMS-protected ethylene glycol disinapate 67a



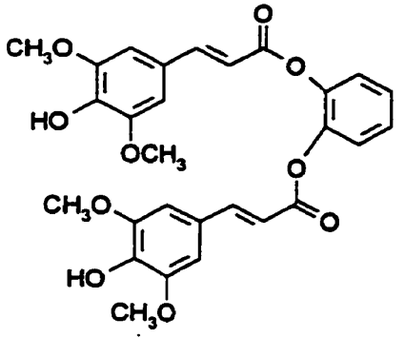
Ethylene glycol (17.9 mg, 0.29 mmol) was reacted with acid **65** (0.201 g, 0.59 mmol) as described above. Chromatography of the crude product using 25% EtOAc/hexanes

afforded a colorless solid (0.21 g, 51%): ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 12H), 1.00 (s, 18H), 3.81 (s, 12H), 4.48 (s, 4H), 6.34 (d, 2H, J = 15.9), 6.73 (s, 4H), 7.63 (d, 2H, J = 15.9). This compound was not fully characterized. See Results and Discussion section.

General procedure for the preparation of diol disinapates 64 and 67b

48% Aqueous HBr (20 μL) was added to a mixture of the TBDMS-protected diol disinapate (0.17 mmol) and potassium fluoride (0.197 g, 3.4 mmol) in DMF (2.2 mL) at 0 °C. After stirring for 8 h, crushed ice and 5% aqueous HCl (5 mL) were added, followed by extraction with EtOAc (3 x 10 mL). The organic solutions were combined, washed with water (3 x 10 mL), dried ($MgSO_4$), and concentrated under vacuum.

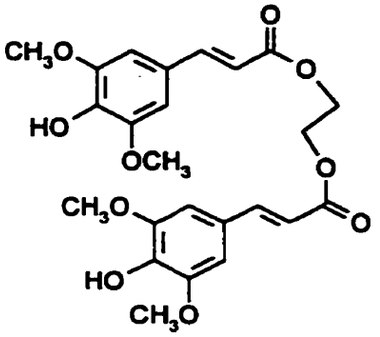
Catechol disinapate 64



66 (0.130 g, 0.17 mmol) was treated as described in the general procedure to afford a light yellow oil which solidified on standing. Recrystallization from CH_2Cl_2/hexanes gave a colorless solid (84 mg, 95%): mp 175-177 °C; IR (CH_2Cl_2) 3524 (OH), 1729 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 12H), 5.77 (br s, 2H), 6.45 (d, 2H, J = 15.8), 6.74 (s, 4H), 7.30 (s, 4H), 7.74 (d, 2H, J = 15.8); ^{13}C NMR ($CDCl_3$) δ 56.3 (4 x CH_3), 105.3 (4 x CH), 114.2 (2 x CH), 123.5 (2 x CH), 125.5 (2 x C), 126.6 (2 x CH), 137.6 (2

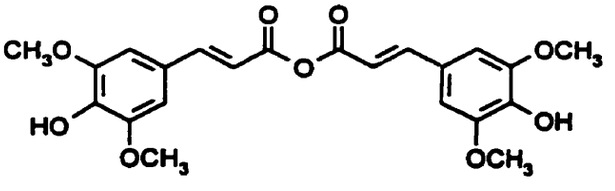
x C), 142.6 (2 x C), 147.2 (2 x CH), 147.3 (4 x C), 164.6 (2 x C); mass spectrum *m/z* (relative intensity) 522 (M^+, 0.1), 221 (20), 207 (100), 175 (45); HRMS calcd. for $C_{28}H_{26}O_{10}$ 522.1526, found 522.1554.

Ethylene glycol disinapate 67b



67a (0.119 g, 0.17 mmol) was treated as described in the general procedure to afford a light brown solid. Chromatography (50% EtOAc/hexanes) of the crude product gave a colorless solid (75 mg, 93%): ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 12H), 4.49 (s, 4H), 4.70-5.10 (br s, 2H, 2 x OH) 6.34 (d, 2H, J = 15.9), 6.78 (s, 4H), 7.63 (d, 2H, J = 15.9). This compound was not fully characterized. See Results and Discussion section.

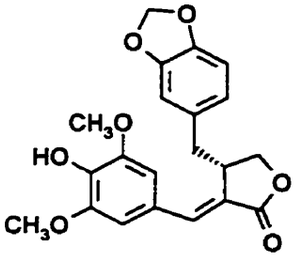
Disinapic acid anhydride 68



Acid **65** (63 mg, 0.20 mmol) was stirred in TFAA (0.4 mL) at ice temperature for 10 h. The mixture was concentrated under vacuum and chromatographed (6-15% EtOAc/hexanes) to afford the desired product (32 mg, 49%) in the first eluted fraction,

whereas the unreacted acid **65** (26 mg, 41%) was recovered from the third fraction. The product (32 mg, 0.049 mmol) was then redissolved in DMF (1 mL), cooled to 0 °C, and KF (58 mg, 1.0 mmol) and 48% aqueous HBr (6 μL) added. After stirring at 0 °C for 3 h, crushed ice and 5% aqueous HCl (1 mL) were added, followed by extraction with EtOAc (3 x 5 mL). The organic solutions were combined, washed with water (3 x 5 mL), dried ($MgSO_4$), and concentrated under vacuum to afford a yelow solid (21 mg, 49% from acid **65**). ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 12H), 6.82 (s, 2H, 2 x OH), 6.39 (d, 2H, J = 15.8), 6.82 (s, 4H), 7.76 (d, 2H, J = 15.8). This compound was not fully characterized. See Results and Discussion section.

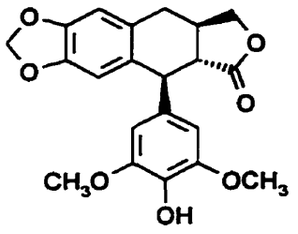
***Trans*-benzylidene 73**



To 4'-demethylyatein (**61**, 20 mg, 0.052 mmol) in THF (1 mL) was added dropwise a solution of DDQ (14 mg, 0.062 mmol) in THF under N_2. A temporary blue color appeared after each addition of the DDQ solution. The resulting mixture was stirred for 12 h and worked up by adding saturated aqueous $NaHSO_3$ (1 mL) and 2% aqueous HCl (2 mL), and extracting with EtOAc (3 x 5 mL). The organic solutions were combined, washed with 5% aqueous $NaHCO_3$ (5 x 5 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to afford a light yellow oil (22 mg). The crude

product contained two compounds, the *cis*- and *trans*-benzylidenes **72** and **73** respectively, in a 1.3:1 ratio as determined by ^{1}H NMR spectroscopy. After standing exposed to the air at rt for about two weeks, the crude product was found to contain only the *trans*-isomer **73**, as indicated by the ^{1}H NMR spectrum. This product resisted crystallization. It was purified by chromatography (EtOAc/hexanes 1:2 ratio) to afford an oil which slowly solidified (18 mg, total 95% from 4'-demethylyatein). The isomerization process observed above was also achieved by refluxing a crude product mixture of **72** and **73** (2 mg) in benzene (1.5 mL) in the presence of I_2 (1 mg), for 1.5 h, with UV irradiation for the first 10 min of reflux. The light pink solution was worked up by adding saturated aqueous $NaHSO_3$ (0.5 mL) and extracting with EtOAc (3 x 5 mL). The extract was dried ($MgSO_4$) and evaporated to give a lightly yellow residue (1.7 mg, 85%) which contained only *trans*-isomer **73**, as shown by the ^{1}H NMR spectrum: mp 130-132 °C; $[\alpha]^{20}_D$ -54° (c 0.31, $CHCl_3$); IR (CH_2Cl_2) 3529 (OH), 1748 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.65 (dd, 1H, J = 10.0, 14.5), 3.04 (dd, 1H, J = 4.6, 14.5), 3.84 (m, 1H), 3.92 (s, 6H), 4.23-4.32 (m, 2H), 5.92 (AB, 2H, Δδ = 2.4, J = 1.4), 6.61 (m, 2H), 6.71 (d, 1H, J = 7.9), 6.81 (s, 2H), 7.50 (d, 1H, J = 1.8); ^{13}C NMR ($CDCl_3$) δ 37.6 (CH_2), 39.6 (CH), 56.4 (2 x CH_3), 69.6 (CH_2), 101.1 (CH_2), 107.2 (2 x CH), 108.4 (CH), 109.0 (CH), 121.8 (CH), 125.4 (C), 125.5 (C), 131.3 (C), 136.9 (C), 137.9 (CH), 146.6 (C), 147.2 (2 x C), 148.0 (C), 172.5 (C); mass spectrum *m/z* (relative intensity) 384 (M^+, 11), 249 (90), 189 (14), 135 (100); HRMS calcd. for $C_{21}H_{20}O_7$ 384.1209, found 384.1222.

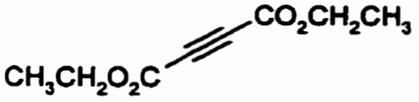
4'-Demethylisodeoxypodophyllotoxin (74)



To 4'-demethylyatein (**61**, 35 mg, 0.091 mmol) in THF (3 mL) at 4 °C was added TFA (24 μL, 0.31 mmol), followed by a solution of DDQ (42 mg, 0.185 mmol) in THF (1 mL). The solution turned green. It was stirred at ice temperature for 1.5 h, a further 16 h at rt. At this time, the color of the solution had become deep red. The reaction mixture was diluted with saturated aqueous $NaHSO_3$ (1 mL), concentrated to remove most of the THF, and diluted again with 5% aqueous $NaHCO_3$ (5 mL). The resulting bright yellow solution was extracted with CH_2Cl_2 (4 x 5 mL). The combined CH_2Cl_2 extracts were washed with 5% aqueous $NaHCO_3$ (5 x 5 mL) and water (10 mL), dried ($MgSO_4$), and concentrated to afford a light yellow solid (35 mg) which was sparingly soluble in EtOAc, Et_2O, and MeOH, but more soluble in CH_2Cl_2 and $CHCl_3$. Recrystallization of the crude solid from CH_2Cl_2 gave fine colorless needles (25 mg, 71%). The recrystallized product, analyzed by ^1H NMR, was shown to be contaminated by an unknown component (*ca.* 5%) which could not be eliminated even after multiple recrystallizations from CH_2Cl_2. This by-product was removed by preparative TLC using a solvent mixture of $CHCl_3$/MeOH/AcOH (25:1:1) to yield a colorless solid (22 mg, 65% from 4'-demethylyatein): mp 282-285 °C (lit.,[21a] 285-287 °C); $[\alpha]^{20}_D$ -76.9° (c 0.26, $CHCl_3$) (lit.,[21a] $[\alpha]^{20}_D$ -81°); ^1H NMR ($CDCl_3$) δ 2.50 (dd, 1H, J = 10.9, 13.4), 2.60 (m, 1H), 2.91

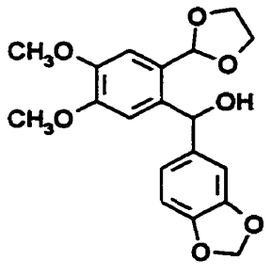
(br dd, 1H, J = 15.4, 14.9), 2.97 (br dd, 1H, J = 5.1, 14.9), 3.85 (s, 6H), 3.98 (dd, 1H, J = 8.6, 10.3), 4.03 (br d, 1H, J = 10.9) 4.51 (dd, 1H, J = 6.4, 8.6), 5.43 (br s, 1H), 5.88 (AB, 2H, $\Delta\delta$ = 4.4, J = 1.3), 6.34 (s, 1H), 6.42 (s, 2H), 6.59 (s, 1H); HRMS calcd. for $C_{21}H_{20}O_7$ 384.1209, found 384.1215. Spectral data were consistent with those published previously.[21a]

Diethyl acetylenedicarboxylate (1b)



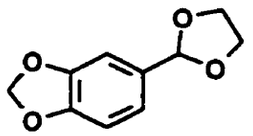
ADA (2.52 g, 22.1 mmol) and H_2SO_4 (1 mL) were refluxed in EtOH (30 mL) for 5 h. The solution was neutralized with 5% aqueous $NaHCO_3$, concentrated under vacuum to remove most of the EtOH, diluted with water (30 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried ($MgSO_4$) and evaporated to leave a pale yellow oil which was then distilled under high vacuum (11 mm Hg) to give a colorless liquid (bp 106-109 °C/11 mm , 3.08 g, 82%): ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 3.8), 4.22 (q, 2H, J = 3.8), identical to that previously reported.[4]

Hydroxyacetals 94.



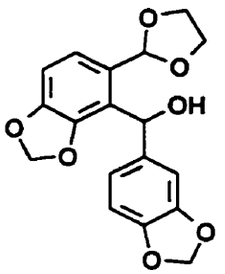
The procedure was similar to that reported for the preparation of hydroxyacetal **33**. The crude ethylene glycol acetal of 2-bromo-4,5-dimethoxybenzaldehyde was dissolved in dry THF (40 mL) under N_2, cooled to -78° C, and *n*-BuLi (2.45 M in hexanes, 2.30 mL, 5.6 mmol) added dropwise over 5 min. The mixture was stirred for another 15 min, followed by the dropwise addition of 3,4-(methylenedioxy)benzaldehyde (0.77 g, 5.11 mmol) in THF (10 mL). After stirring for 30 min, the solution was gradually warmed to room temperature and was stirred for another 2.5 h, followed by the addition of H_2O (30 mL). The resulting mixture was extracted with Et_2O (3 x 30 mL), dried ($MgSO_4$), and concentrated to give a light green solid (1.80 g, 98%) which turned dark green upon standing at room temperature. The unstable product was not further purified, but was used immediately in the following Diels-Alder reactions. ^1H NMR spectrum of Hydroxyacetal **94** was not obtained as it turned dark green immediately on dissolving in $CDCl_3$.

Ethylene glycol acetal of 3,4-(methylenedioxy)benzaldehyde (96).



3,4-(methylenedioxy)benzaldehyde (2.50 g, 16.6 mmol) and ethylene glycol (1.44 g, 23.2 mmol) were treated as described for the preparation of acetal **38** to afford an unstable yellow oil (2.96 g, 92%) which was used in next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 3.98-4.04 (m, 2H), 4.08-4.14 (m, 2H), 5.71 (s, 1H), 5.95 (s, 2H), 6.79 (dd, 1H, J = 0.7, 7.5), 6.93-6.96 (m, 2H).

Hydroxyacetal 95



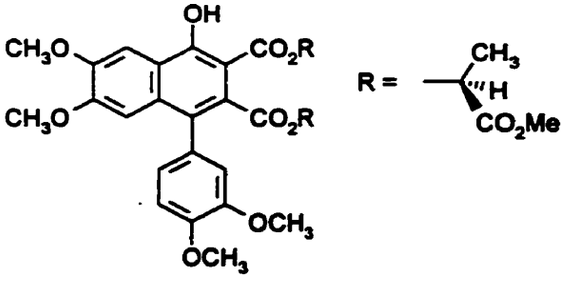
The general procedure for preparation of this compound has been published by Rodrigo.[17] The unstable crude acetal **96** was dissolved in dry THF (40 mL), followed by dropwise addition of *n*-BuLi (2.45 M in hexanes, 2.30 mL, 5.6 mmol) under N_2. The mixture was stirred for 15 min, then at ice temperature for 20 min. The mixture was again cooled to -78°C, followed by dropwise addition of 3,4-(methylenedioxy)benzaldehyde (0.77 g, 5.11 mmol) in THF (10 mL). The resulting orange solution was stirred at that temperature for 20 min, then at room temperature for

1.5 h. The work-up procedure was similar to that described for the preparation of hydroxyacetals **33** and **94**, and the brown-green residue (1.75 g, 94%) isolated was also used in the following reactions without further purification: ^{1}H NMR ($CDCl_3$) δ 3.79 (d, 1H, OH, J = 9.4), 3.89-4.10 (m, 4H), 5.67 (s, 1H), 5.93 (AB, 2H, Δδ = 2.5, J = 1.5), 5.97 (AB, 2H, Δδ = 14.0 , J = 1.4), 6.14 (br d, 1H, J = 9.4), 6.74 (d, 1H, J = 8.2), 6.76 (d, 1H, J = 8.3), 6.81-6.86 (m, 1H), 6.89 (br s, 1H), 7.11 (d, 1H, J = 8.2).

General procedure for the synthesis of arylnaphthalenes

Glacial AcOH was added to a mixture of hydroxyacetal **33**, **94** or **95** and dienophile in a minimum amount of solvent and the temperature of the mixture quickly brought up to 140 °C. The mixture was heated for 1-20 h, depending on the type of dienophile used. The cooled mixture was diluted with CH_2Cl_2 (10 mL), washed with 5% sodium bicarbonate solution (3 x 10 mL), dried ($MgSO_4$), and concentrated under vacuum.

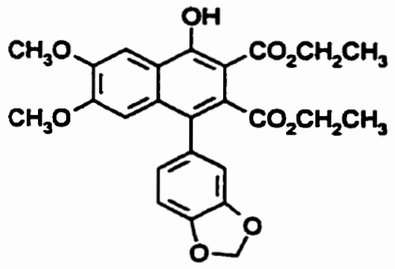
Arylnaphthol 37



This compound has been prepared in the project (Diels-Alder reactions of **1e**) described above, but was prepared again using the improved general procedure. Hydroxyacetal **33** (0.16 g, 0.41 mmol), **1e** (0.10 g, 0.35 mmol), CH_2Cl_2 (0.3 mL), and

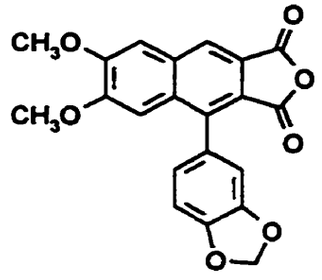
AcOH (0.2 mL) were heated at 140 °C for 1 h and worked up as above. Chromatography of the crude product using 25-35% EtOAc/hexanes afforded a colorless solid (0.18 g, 85%): mp 69-72 °C, identical to that reported above.

Lignan analog 84



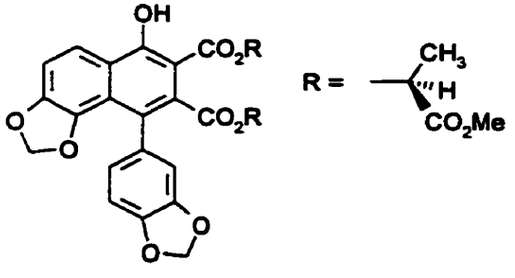
Hydroxyacetal **94** (0.247 g, 0.69 mmol), **1b** (0.119 g, 0.70 mmol), CH_2Cl_2 (0.3 mL), and AcOH (0.2 mL) were heated at 140 °C for 1 h. After work-up as above, the crude product was recrystallized from CH_2Cl_2/hexanes to afford a colorless solid (0.28 g, 80%): mp 152-153 °C; IR (CH_2Cl_2) 3303 (OH), 1730, 1658 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.95 (t, 3H, J = 7.1), 1.26 (t, 3H, J = 7.1), 3.65 (s, 3H), 3.93 (s, 3H), 3.95 (q, 2H, J = 7.1), 4.34 (q, 2H, J = 7.1), 6.09 (AB, 2H, Δδ = 10.1, J = 0), 6.68 (dd, 1H, J = 7.9, 1.6), 6.72 (s, 1H), 6.78 (d, 1H, J = 1.5), 7.00 (d, 1H, J = 7.9), 7.64 (s, 1H), 11.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 13.9 (CH_3), 55.8 (CH_3) 56.1 (CH_3), 60.8 (CH_2), 61.9 (CH_2), 101.0 (CH_2), 101.1 (C), 102.8 (CH), 105.7 (CH), 107.9 (CH), 111.4 (CH), 119.8 (C), 124.3 (CH), 127.4 (C), 129.0 (C), 130.6 (C), 132.2 (C), 147.0 (C), 147.2 (C), 149.6 (C), 152.3 (C), 159.6 (C), 168.7 (CO), 170.2 (CO); mass spectrum *m/z* (relative intensity) 468 (M^+, 23), 422 (19), 394 (88), 149 (75); HRMS calcd. for $C_{25}H_{24}O_9$ 468.1420, found 468.1409.

Anhydride 85



Hydroxyacetal **94** (0.30 g, 0.83 mmol), maleic anhydride (83 mg, 0.85 mmol), Ac_2O (0.3 mL), CH_2Cl_2 (0.3 mL), and glacial AcOH (0.2 mL) were heated at 140 °C for 20 h and worked up as above to give a yellow oily solid (0.35 g) which was used directly in the next reduction reaction without purification: ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 4.09 (s, 3H), 6.10 (AB, 2H, $\Delta\delta$ = 10.69, J = 1.4), 6.86 (m, 1H), 6.88 (s, 1H), 7.00 (dd, 1H, J = 7.7, 0.6), 7.21 (s, 1H), 7.36 (s, 1H), 8.33 (s, 1H).

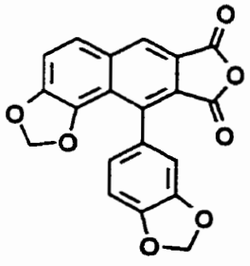
Lignan analog 87



Hydroxyacetal **95** (0.500 g, 1.45 mmol), **1e** (0.411 g, 1.44 mmol), CH_2Cl_2 (0.5 mL) and AcOH (0.6 mL) were heated at 140 °C for 1.5 h. The foamy brown solid obtained after workup was recrystallized from MeOH to afford light yellow crystals (0.72 g, 88%): mp 150-151 °C; $[\alpha]^{20}_D$ +34.1° (c 0.47, $CHCl_3$); IR (CH_2Cl_2) 3370 (OH), 1746 and 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.01 (d, 3H, J = 7.0), 1.06 (d, 3H, J = 7.0), 1.45

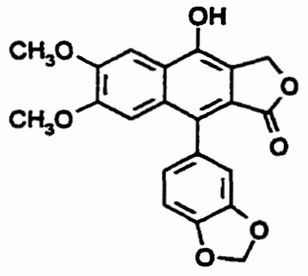
(d, 3H, J = 7.0), 1.46 (d, 3H, J = 7.0), 3.59 (s, 6H), 3.69 (s, 3H), 3.70 (s, 3H), 4.99 (q, 2H, J = 7.0), 5.35 (q, 1H, J = 7.0), 5.37 (q, 1H, J = 7.0), 5.91-6.07 (m, 8H), 6.62-6.89 (m, 6H), 7.46 (d, 2H, J = 8.8), 8.08 (d, 2H, J = 8.8), 11.78 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 16.4 (CH_3), 16.5 (CH_3), 16.8 (CH_3), 17.1 (CH_3), 52.2 (2 x CH_3), 52.5 (2 x CH_3), 69.5 (CH), 69.6 (CH), 70.2 (2 x CH), 99.6 (C), 99.7 (C), 100.9 (2 x CH_2), 101.6 (2 x CH_2), 107.0 (2 x CH), 110.7 (3 x CH), 111.6 (CH), 111.8 (CH), 119.8 (CH), 120.9 (2 x C), 121.6_7 (C), 121.7_4 (C), 124.3 (CH), 124.5 (CH), 125.0 (C), 125.1 (C), 129.8_8 (C), 129.9_0 (C), 130.8 (2 x C), 130.9 (2 x C), 142.5_6 (C), 142.6_0 (C), 146.4 (2 x C), 147.0 (2 x C), 148.8 (2 x C), 161.9 (CO), 162.0 (CO), 166.7_8 (CO), 166.8_0 (CO), 168.8_3 (CO), 168.9 (CO), 170.2 (CO), 170.4 (CO); mass spectrum *m/z* (relative intensity) 568 (M^+, 10), 464 (10), 378 (91), 306 (17); HRMS calcd. for $C_{28}H_{24}O_{13}$ 568.1216, found 568.1241.

Anhydride 86



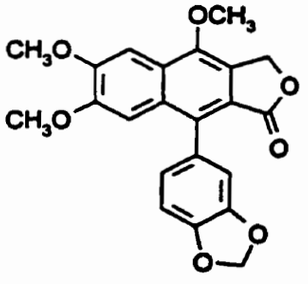
Hydroxyacetal **95** (0.50 g, 1.45 mmol), maleic anhydride (0.142 g, 1.45 mmol), Ac_2O (0.5 mL), CH_2Cl_2 (0.5 mL), and AcOH (0.2 mL) were heated at 140 °C for 24 h. A yellow solid (0.44 g, 85%) was obtained after work-up and was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 6.00 (AB, 2H, Δδ = 6.3, J = 1.2), 6.07 (AB, 2H, Δδ = 10.6, J = 1.4), 6.82 (m, 1H), 6.84 (s, 1H), 6.89 (dd, 1H, J = 7.5, 0.9), 7.44 (d, 1H, J = 8.6), 7.75 (d, 1H, J = 8.6), 8.43 (s, 1H).

Diphyllin (78)



Diphyllin (**78**) was prepared using a modification of a procedure published by Sammes *et. al.*[28] Analog **84** (0.10 g, 0.20 mmol), $NaBH_4$ (38 mg, 1 mmol), and *i*-PrOH (20 mL) were refluxed under N_2 for 24 h. 10% aqueous HCl (*ca.* 6 mL) was added cautiously and the mixture was stirred for 1 h, followed by extraction with ether. The solution was concentrated to give a yellow solid which was then recrystallized from EtOH to afford pure diphyllin (46 mg, 60%): mp 284-286 °C (lit.,[29] 284-287 °C); ^{1}H NMR (acetone-d_6) δ 3.72 (s, 3H), 4.00 (s, 3H), 5.37 (s, 2H), 6.08 (AB, 2H, Δδ = 3.6, J = 1.0), 6.80 (dd, 1H, J = 7.8, 1.6), 6.84 (d, 1H, J = 1.6), 6.96 (d, 1H, J = 7.8), 7.09 (s, 1H), 7.70 (s, 1H), identical to that previously reported.[29]

Justicidin A (79)



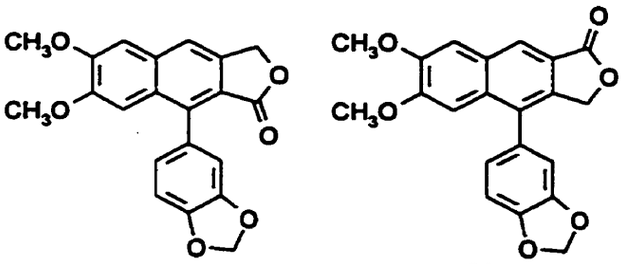
Diphyllin (**78**, 17 mg, 0.04 mmol), DMSO (10 mL), MeI (0.1 mL, 1.6 mmol), and anhydrous K_2CO_3 (0.1 g, 1.4 mmol) were refluxed for 20 min. The mixture was acidified

to pH 1-2 with 10% aqueous HCl (*ca.* 4 mL), extracted with benzene (3 x 10 mL), concentrated, and chromatographed (20-50% EtOAc/hexanes) to give a light yellow solid collected in the first eluted fraction (15 mg, 95%): mp 262-263 °C (lit.,[29] 261-263 °C); ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.07 (s, 3H), 4.13 (s, 3H), 5.54 (s, 2H), 6.07 (AB, 2H, Δ δ = 13.4, J = 1.4), 6.79 (dd, 1H, J = 7.8, 1.6), 6.82 (d, 1H, J = 1.6), 6.95 (d, 1H, J = 7.8), 7.06 (s, 1H), 7.54 (s, 1H), consistent with that reported previously.[29]

General procedure for the preparation of justicidin B (80), retrojusticidin B (81), helioxanthin (82), and retrohelioxanthin (83)

A modified literature procedure was used.[30] The appropriate anhydride **85** or **86**, $NaBH_4$, and THF were stirred at room temperature for 40 min. The mixture was worked up as in the procedure described for the preparation of diphyllin (**78**). The crude product was chromatographed with 33% EtOAc/hexanes to give the first (major) and the second (minor) fractions which contained the lactones resulting from the reduction at the more and the less hindered carbonyl atoms, respectively.

Justicidin B (80) and retrojusticidin B (81)

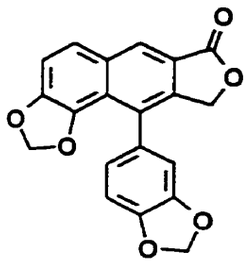


80 (justicidin B) **81** (retrojusticidin B)

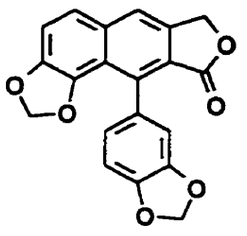
Anhydride **85** (72 mg, 0.18 mmol), $NaBH_4$ (20 mg, 0.53 mmol), and THF (10 mL) were treated as above. The ^1H NMR spectrum of the crude product indicated a ratio of 3:2 of retrojusticidin B to justicidin B. The first eluted fraction contained retrojusticidin B (**81**) as a colorless solid (35 mg, 51%): mp 214-216 °C (lit.,[31] 218-220 ° C); ^1H NMR (DMSO-d_6) δ 3.74 (s, 3H), 3.93 (s, 3H), 5.33 (AB, 2H, Δδ = 30.3, J = 14.8), 6.14 (AB, 2H, Δδ = 9.7), 6.97 (dd, 1H, J = 8.0, 1.6), 7.11 (m, 3H), 7.68 (s, 1H), 8.38 (s, 1H).

The second eluted fraction contained justicidin B (**80**), which was isolated as a colorless solid (18 mg, 26%): mp 234-237 °C (lit.,[29] 235-238 °C); ^1H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.05 (s, 3H), 5.37 (AB, 2H, Δδ = 0.9, $J \approx 14$), 6.07 (AB, 2H, Δδ = 12.5, J = 1.5), 6.79 (dd, 1H, J = 7.8, 1.5), 6.85 (s, 1H), 6.96 (d, 1H, J = 7.8), 7.10 (s, 1H), 7.18 (s, 1H), 7.69 (s, 1H), identical to that previously reported.[29]

Helioxanthin (82) and retrohelioxanthin (83)



82
(helioxanthin)

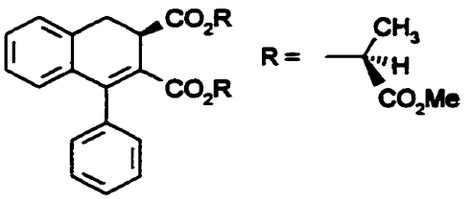


83
(retrohelioxanthin)

Anhydride **86** (60 mg, 1.6 mmol), $NaBH_4$ (20 mg, 0.53 mmol), and THF (10 mL) were treated as described in the general procedure. The ^1H NMR spectrum showed the presence of helioxanthin and retro-helioxanthin in a ratio of 10:1. The first collected chromatography fraction was helioxanthin (**82**), obtained as a light yellow solid (43 mg, 77%): mp 239-242°C (lit.,[32] 243-244 °C); ^1H NMR (DMSO-d_6) δ 5.29 (s, 2H), 6.00 (AB, 2H, Δδ = 5.8, J = 0.7), 6.09 (AB, 2H, Δδ = 14.5, J = 0.5), 6.89 (dd, 1H, J = 7.9, 1.6), 6.97 (d, 1H, J = 7.9), 7.01 (d, 1H, J = 1.6), 7.50 (d, 1H, J = 8.7), 7.94 (d, 1H, J = 8.7), 8.28 (s, 1H).

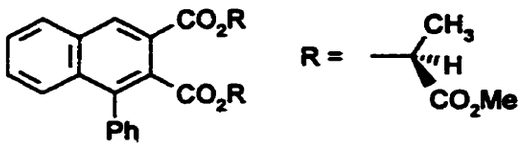
The second eluted fraction afforded a bright orange residue (4.8 mg, 8%) which was identified as retro-helioxanthin (**83**); mp 262-266 °C (lit.[32] 264-268 °C); ^1H NMR (DMSO-d_6) δ 5.43 (s, 2H), 5.92 (AB, 2H, Δδ = 4.3), 6.08 (AB, 2H, Δδ = 4.8), 6.74 (dd, 1H, J = 7.9, 1.6), 6.88 (d, 1H, J = 1.6), 6.90 (d, 1H, J = 7.9), 7.53 (d, 1H, J = 8.7), 7.72 (d, 1H, J = 8.7), 8.08 (s, 1H).[32]

Dihydrophenylnaphthalene 88



Cycloadduct **32** (0.201 g, 0.43 mmol), which was formed from α-phenylbenzocyclobutene (**22**) and the fumarate of methyl (*S*)-lactate, was refluxed with *p*-TsOH (30 mg) in benzene (10 mL) for 2 h. The reaction mixture was concentrated under vacuum and chromatographed (EtOAc/hexanes) on silica gel to give a yellow material (0.15 g, 79%): $[\alpha]^{20}_{D}$ +42.2 (c 0.018, $CHCl_3$); IR ($CHCl_3$) 1671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3H, J = 7.0), 1.44 (d, 3H, J = 7.0), 3.39 (m, 2H), 3.61 (s, 3H), 3.66 (s, 3H), 4.00 (dd, 1H, J = 4.6, 6.6), 4.81 (q, 1H, J = 7.0), 5.08 (q, 1H, J = 7.0), 6.75 (d, 1H, J = 7.7), 7.08 (m, 1H), 7.24 (m, 4H), 7.37 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 16.2 (CH_3), 16.9 (CH_3), 31.3 (CH_2), 41.0 (CH), 52.0$_9$ (CH_3), 52.1 (CH_3), 68.6 (CH), 68.8 (CH), 123.3 (C), 126.8 (CH), 127.4 (CH), 127.8$_0$ (CH), 127.8$_4$ (3 x CH), 128.8 (2 x CH), 129.5 (CH), 134.4 (C), 134.6 (C), 138.9 (C), 149.3 (C), 167.2 (CO), 170.9$_0$ (CO), 170.9$_5$ (CO), 171.9 (CO); mass spectrum *m/z* (relative intensity) 466 (M^+, 0.4), 334 (10), 274 (15), 231 (39); HRMS calcd. for $C_{26}H_{26}O_8$ 466.1628, found 466.1657.

Phenylnaphthalene 25



A mixture of the dihydrophenylnaphthalene **88** (0.12 g, 0.25 mmol) and Pd/C (0.30 g) in xylenes (10 mL) was refluxed vigorously for 40 h. The mixture was filtered through a short column of silica gel washing with hexanes. The product was then eluted with EtOAc and concentrated to give a pale yellow oil (0.100 g, 90%) with properties identical to that reported above.

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APPENDIX 1

DYNAMIC NMR MATERIALS

Dynamic NMR simulation input parameters, and experimental and simulated NMR spectra for arylnaphthalene lignans **25, 79-83** (*i.e.* compounds which showed peak broadening or coalescence) are included here.

Dynamic NMR Simulation Input Parameters as a Function of Temperature:

k = Exchange rate constants (s^{-1})

δ = Chemical shifts for the exchanging signals (Hz)

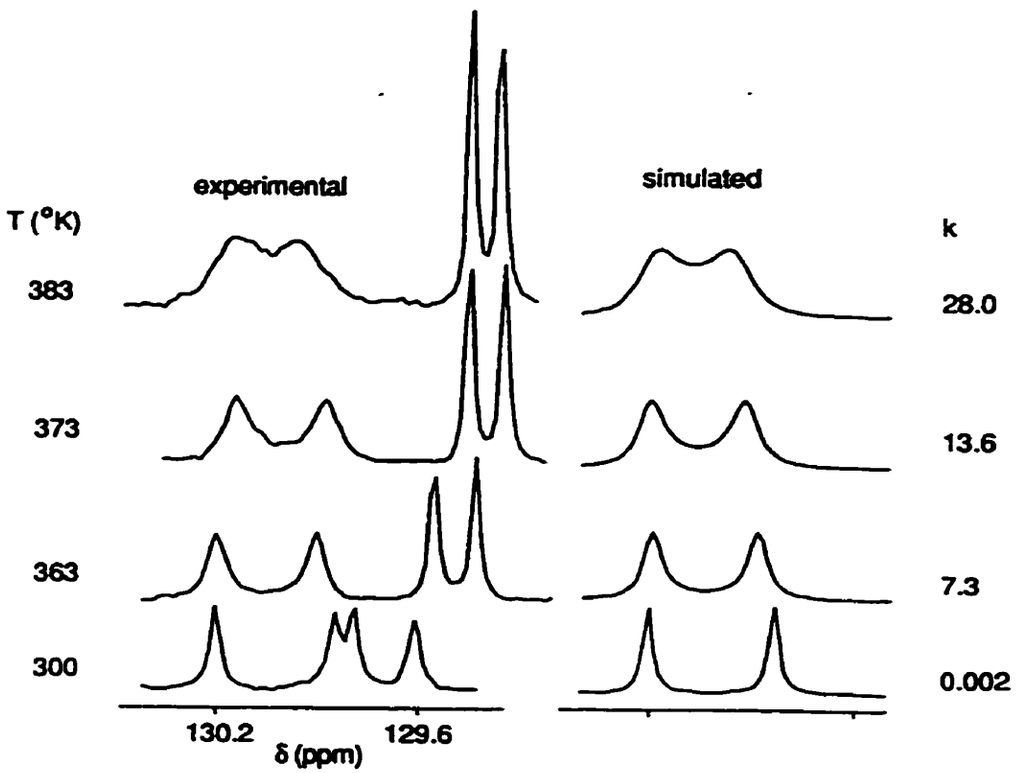
J = Coupling constants of the exchanging signals to the neighboring hydrogen (Hz)

T_2 = Transverse relaxation times (s) measured from a reference signal, using equation:

T_2 = (width at half-height of a single peak not broadened by exchange)$^{-1}$

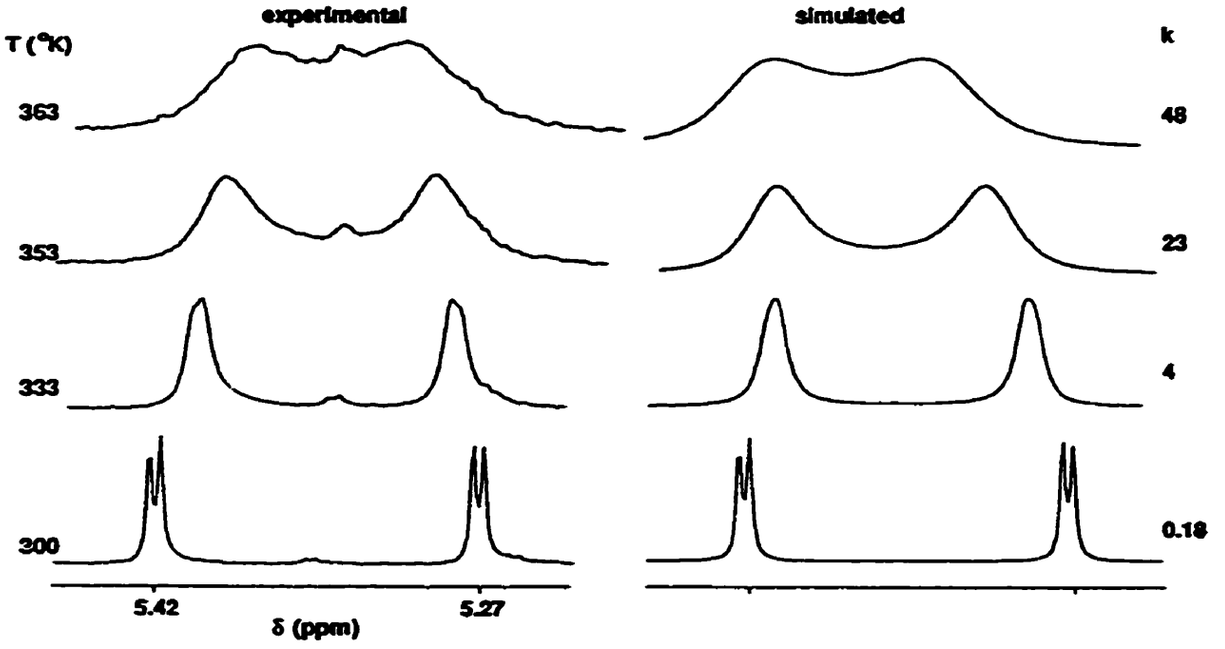
Phenylnaphthalene 25 (^{13}C NMR, DMSO-d_6)

Temp, °K	k, s^{-1}	δ, Hz	J, Hz	T_2, s
300	0.002	9823, 9796	0	0.13
363	7.3	9823, 9800	0	0.13
373	13.6	9823, 9802	0	0.13
383	28.0	9823, 9803	0	0.14



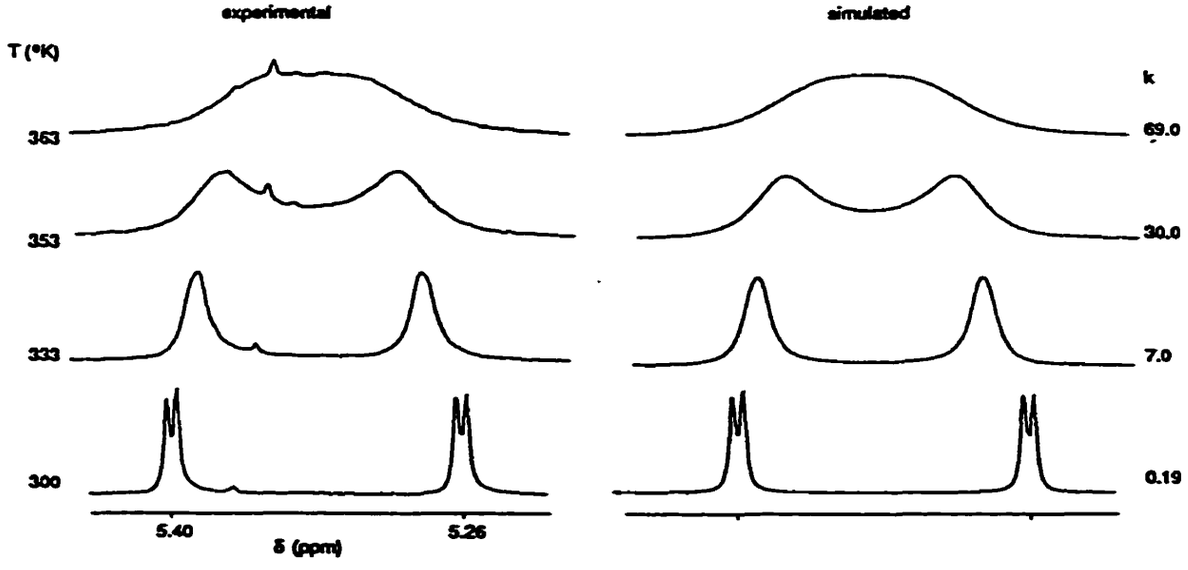
Justicidin A (79) (^{1}H NMR, Toluene-d_8)

Temp, °K	k, s^{-1}	δ, Hz	J, Hz	T_2, s
300	0.18	1627, 1582	1.48	0.29
333	4.0	1635, 1601	1.48	0.20
353	23.0	1644, 1614	1.48	0.20
363	48.0	1646, 1617	1.48	0.20



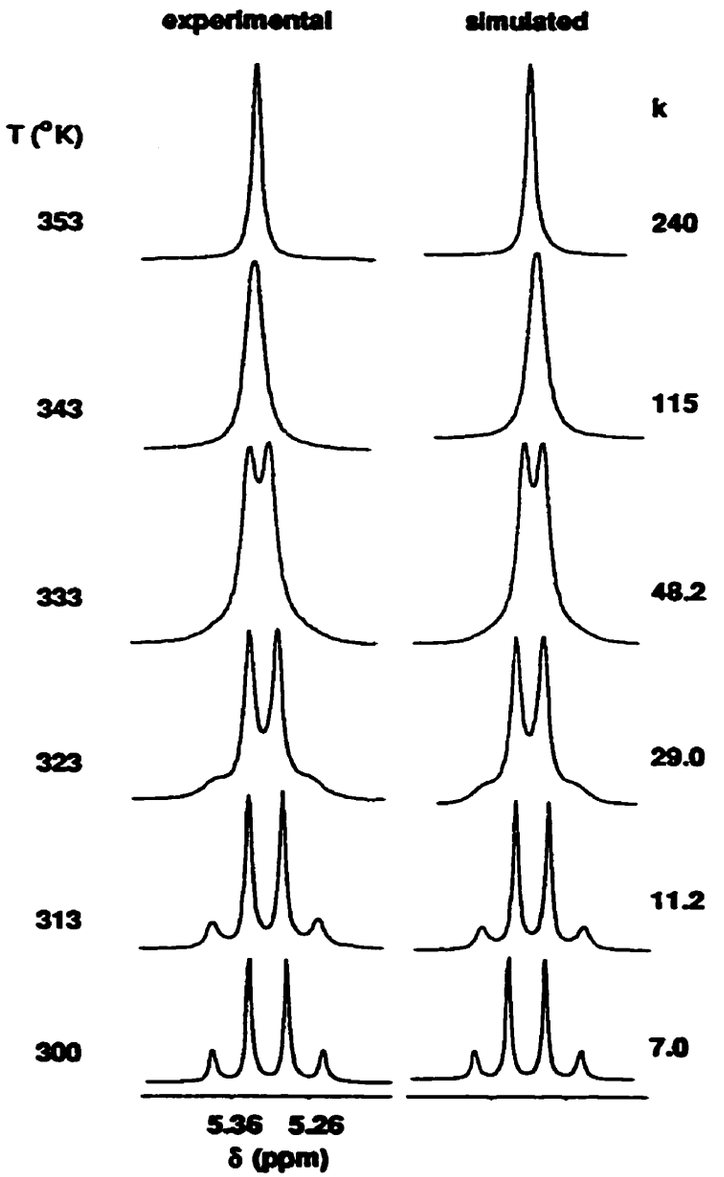
Justicidin B (80) (^{1}H NMR, Toluene-d_8)

Temp, °K	k, s^{-1}	δ, Hz	J, Hz	T_2, s
300	0.19	1621, 1579	1.49	0.35
333	7.0	1635, 1601	1.49	0.28
353	30.0	1640, 1611	1.49	0.30
363	69.0	1632, 1602	1.49	0.30



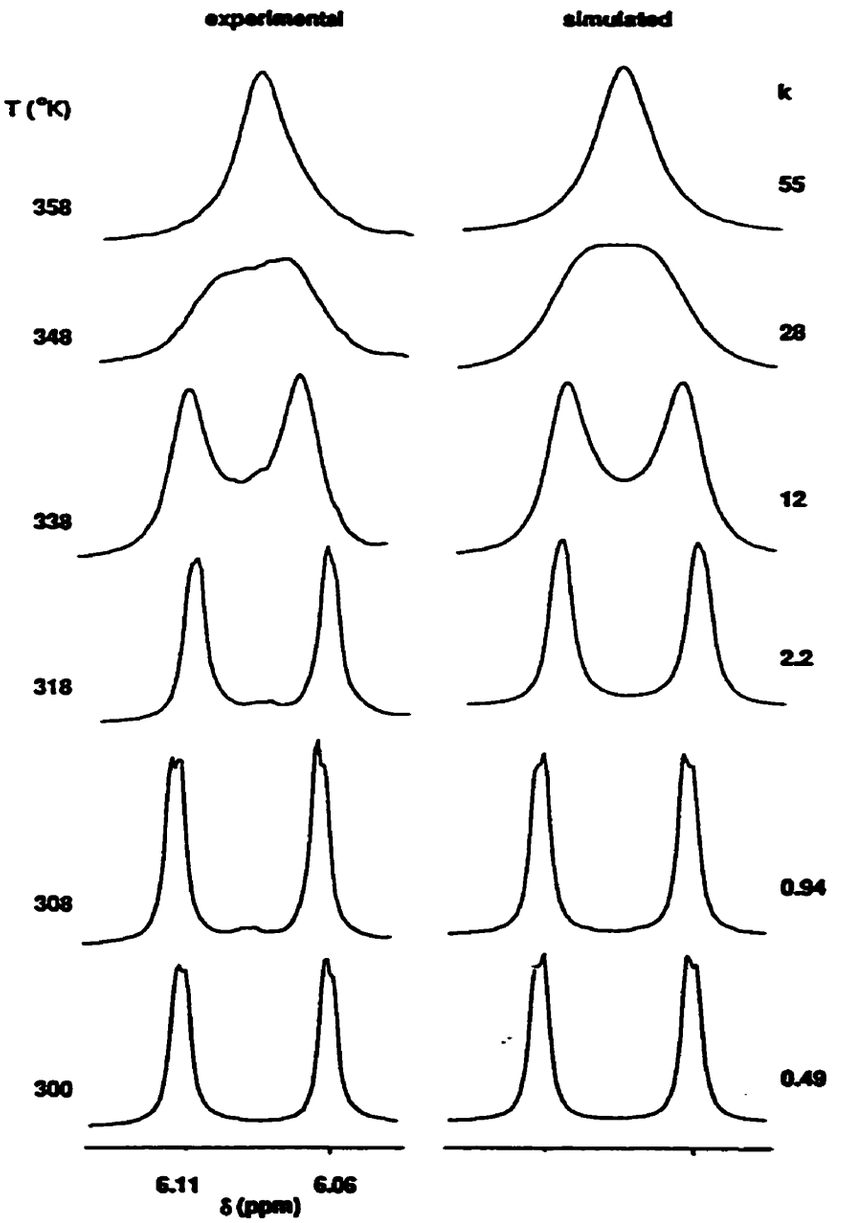
Retrojusticidin B (**81**) (^{1}H NMR, DMSO-d_6)

Temp, °K	k, s^{-1}	δ, Hz	J, Hz	T_2, s
300	7.0	1608, 1578	14.8	0.30
313	11.2	1603, 1578	14.8	0.30
323	29.0	1601, 1577	14.8	0.30
333	48.2	1598, 1577	14.8	0.30
343	115.0	1597, 1575	14.8	0.30
353	240.0	1595, 1574	14.8	0.30



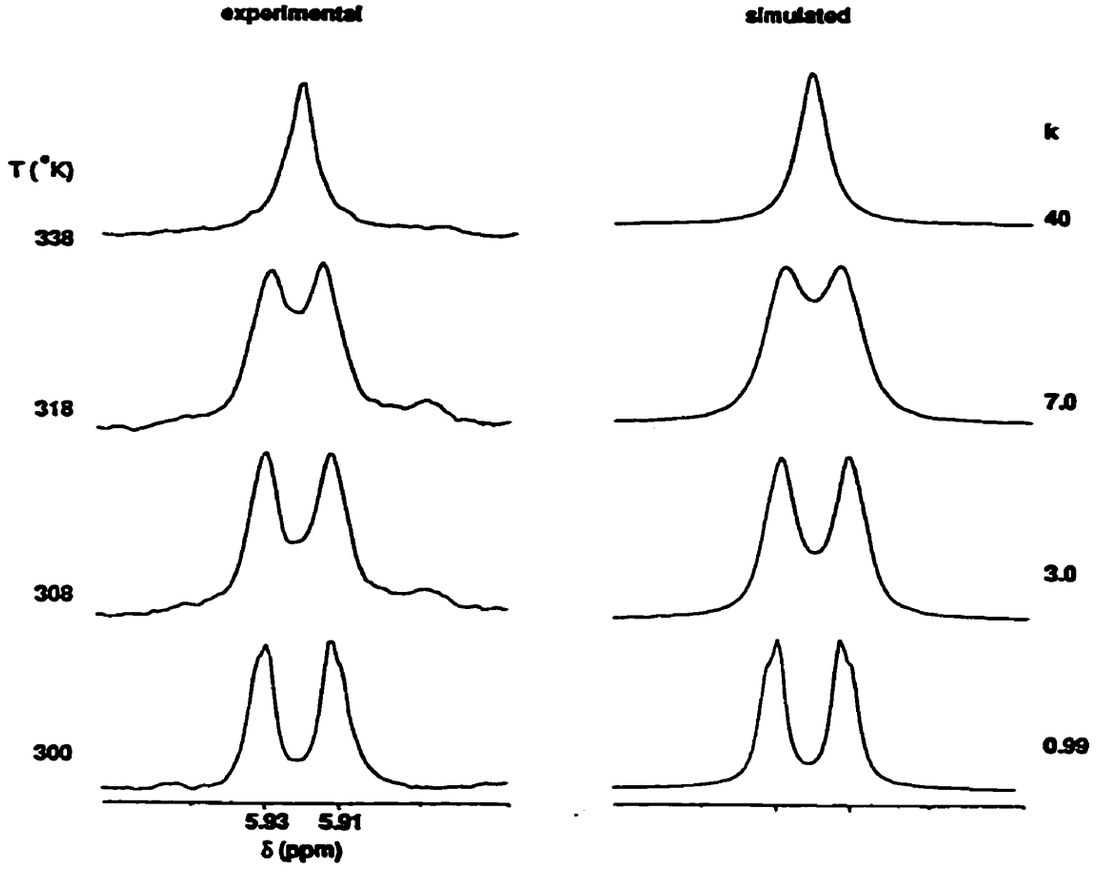
Helioxanthin (82) (^{1}H NMR, DMSO-d_6)

Temp, °K	k, s^{-1}	δ, Hz	J, Hz	T_2, s
300	0.49	1833, 1818	0.49	0.28
308	0.94	1833, 1818	0.49	0.30
318	2.2	1833, 1819	0.49	0.29
338	12.0	1833, 1819	0.49	0.30
348	28.0	1833, 1820	0.49	0.30
358	55.0	1833, 1820	0.49	0.30



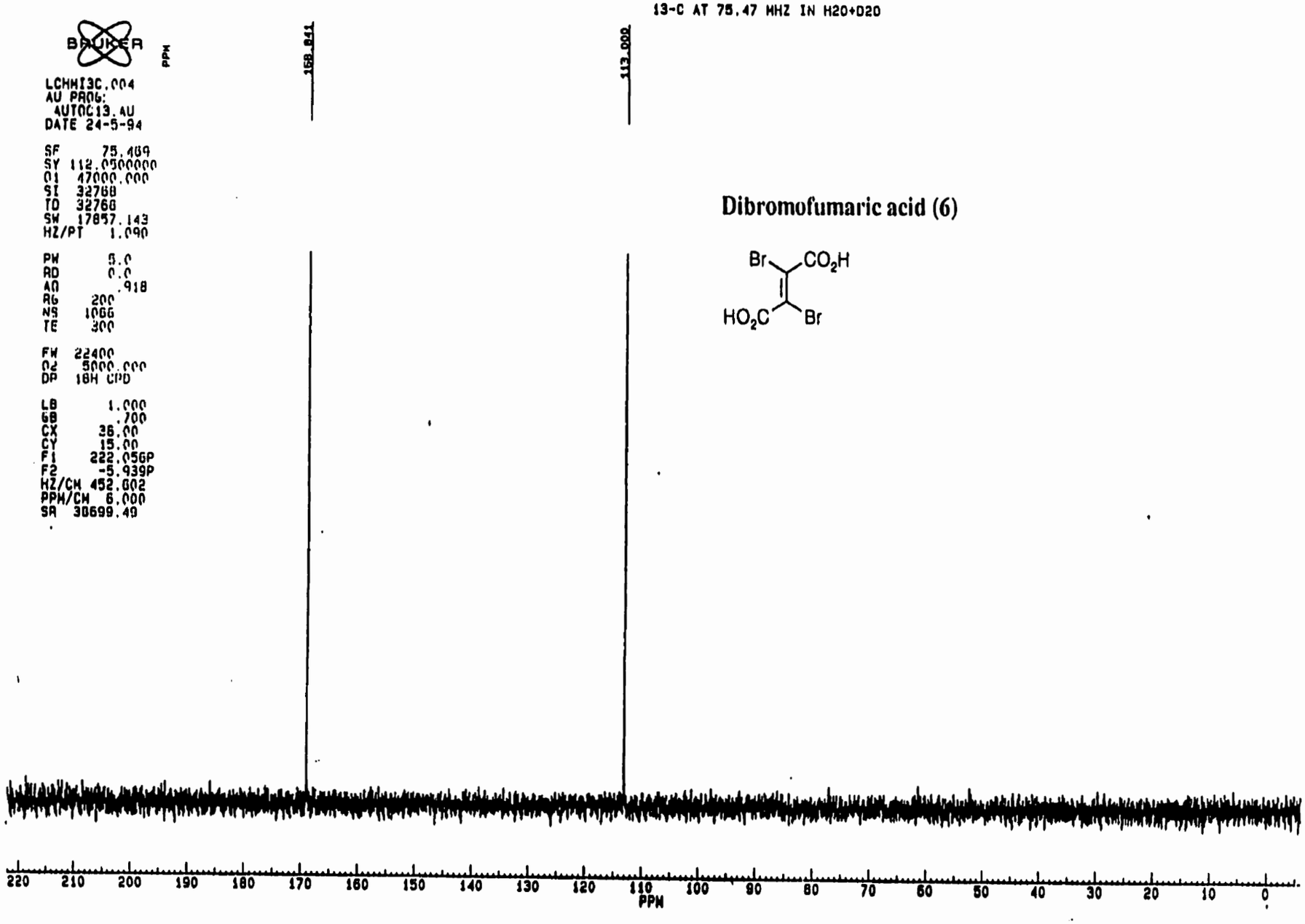
Retrohelioxanthin (83) (^{1}H NMR, DMSO-d_6)

Temp, °K	k, s^{-1}	δ, Hz	J, Hz	T_2, s
300	0.99	1781, 1777	0	0.27
308	3.0	1781, 1777	0	0.25
318	7.0	1780, 1776	0	0.25
338	40.0	1779, 1777	0	0.25

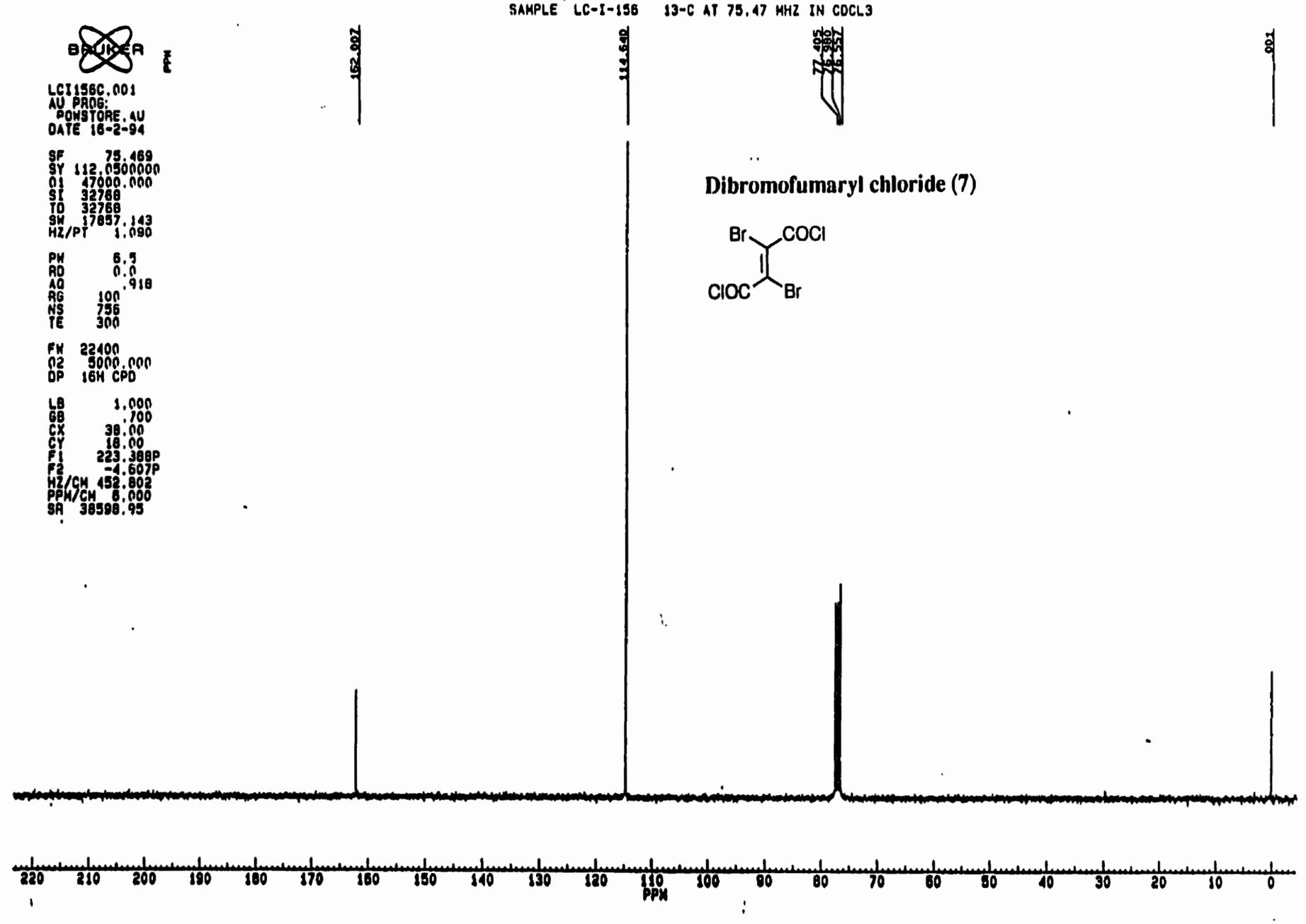


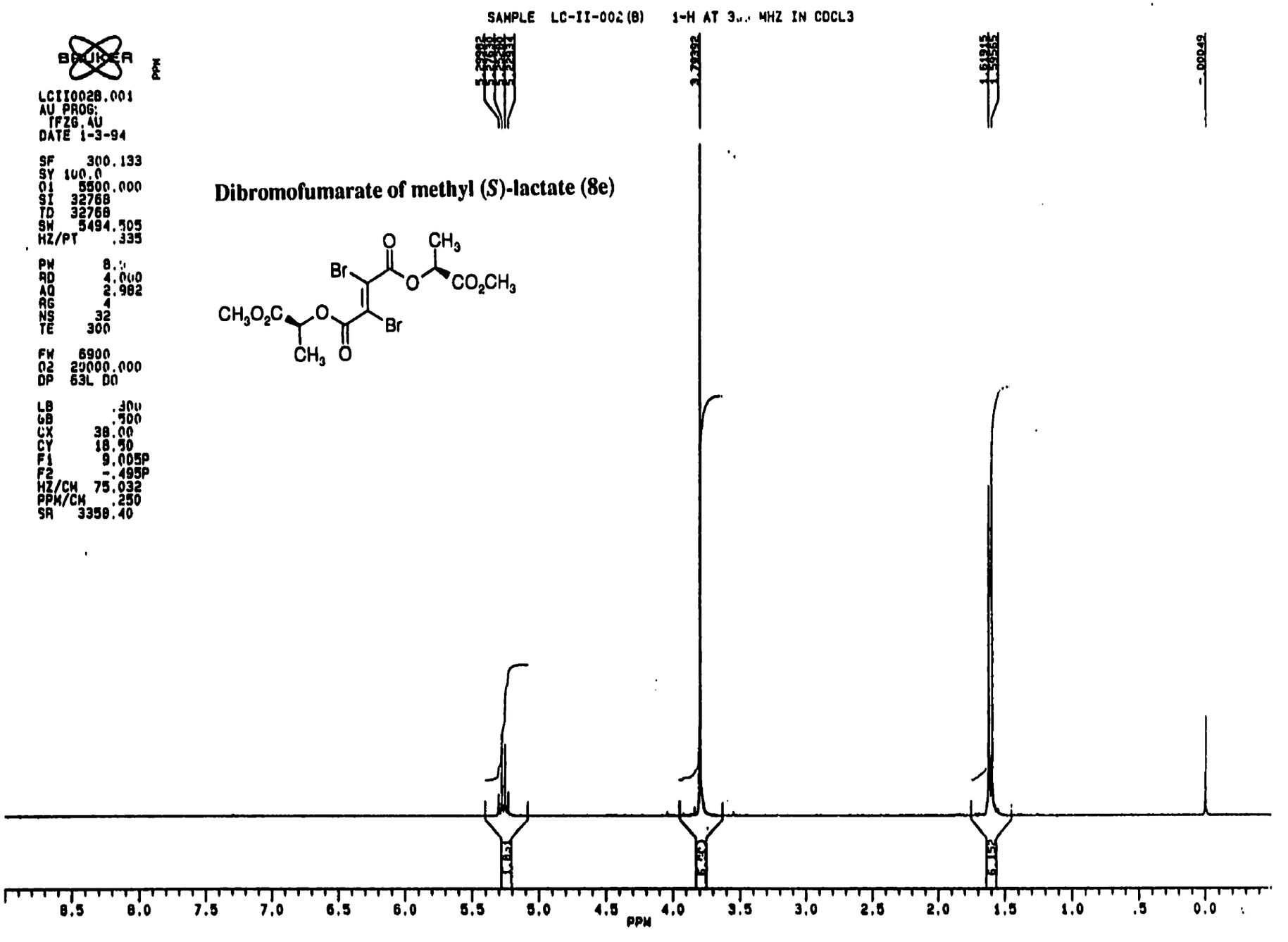
APPENDIX 2

^{1}H AND ^{13}C NMR SPECTRA



Dibromofumaric acid (6)


SAMPLE LC-I-156 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
162.002
114.649
77.405
76.986
76.557
1.00
LCI156C.001
AU PROG:
POWSTORE.AU
DATE 16-2-94
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 6.5
RD 0.0
AQ .918
RG 100
NS 756
TE 300
FW 22400
O2 5000.000
DP 16W CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.388P
F2 -4.607P
HZ/CM 452.802
PPM/CM 6.000
SR 38598.95
Dibromofumaryl chloride (7)
Br
COCl
ClOC
Br
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


SAMPLE LC-II-002(8) 1-H AT 3.. MHZ IN CDCL3
BRUKER
PPM
LCII0028.001
AU PROG:
TFZG.AU
DATE 1-3-94
SF 300.133
SY 100.0
OI 6500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.
RD 4.000
AQ 2.982
RG 4
NS 32
TE 300
FW 6900
O2 29000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.90
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3359.40
Dibromofumarate of methyl (S)-lactate (8e)
Br
O
CH3
CO2CH3
CH3O2C
Br
CH3
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

SAMPLE LC-II-103-C 13-C AT 75.47 MHZ IN CDCL3

LCII103C.001
AU PROG:
POWSTORE.AU
DATE 22-9-94

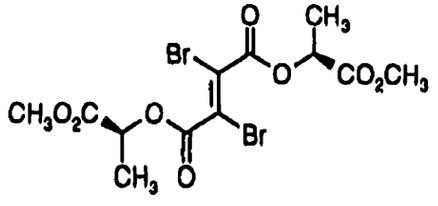
SF 75.469
SY 112.0500000
O1 47000.000
SI 32760
TD 32768
SW 17857.143
HZ/PT 1.090

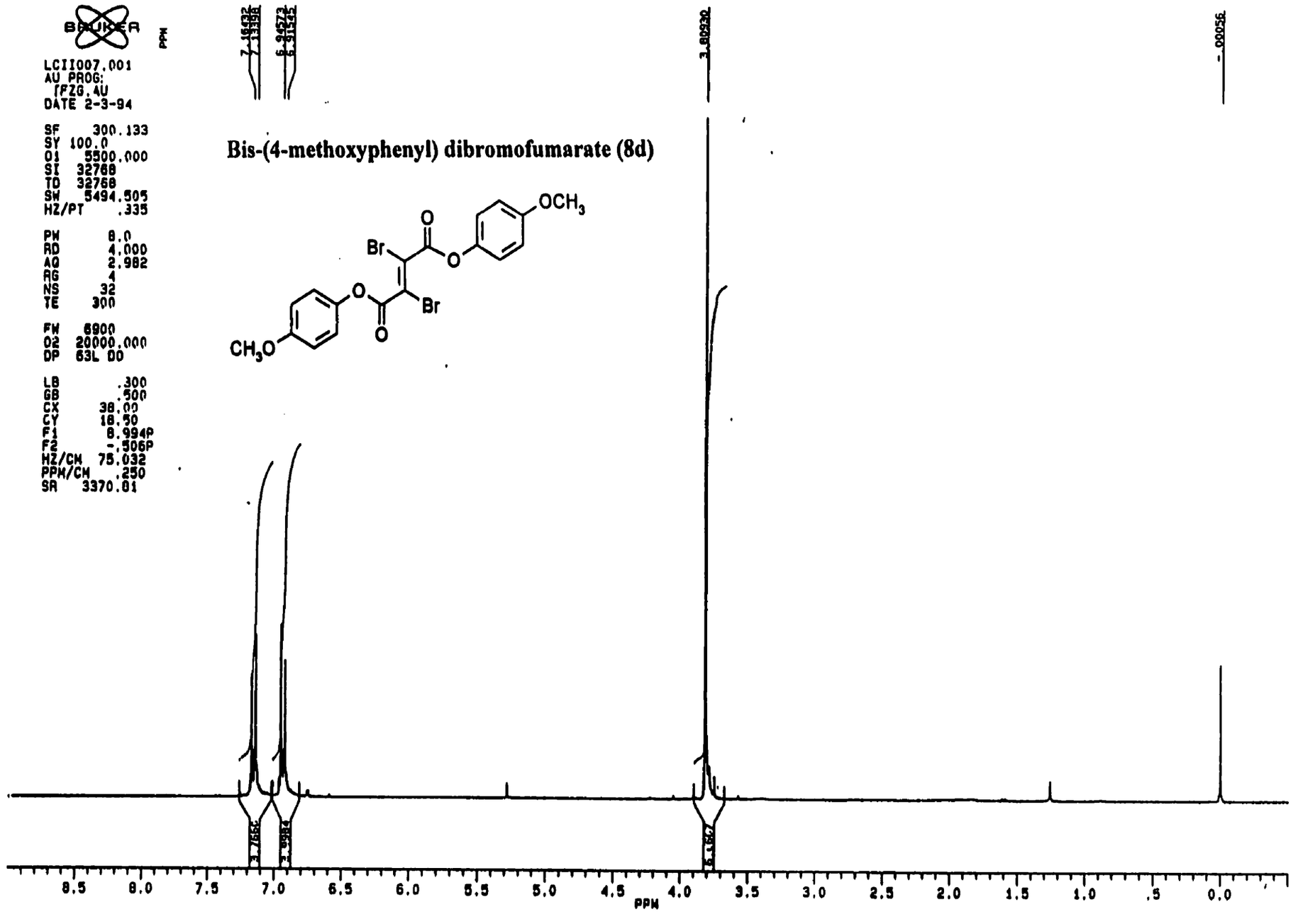
PW 6.5
RD 0.0
AQ .918
RG 100
NS 768
TE 300

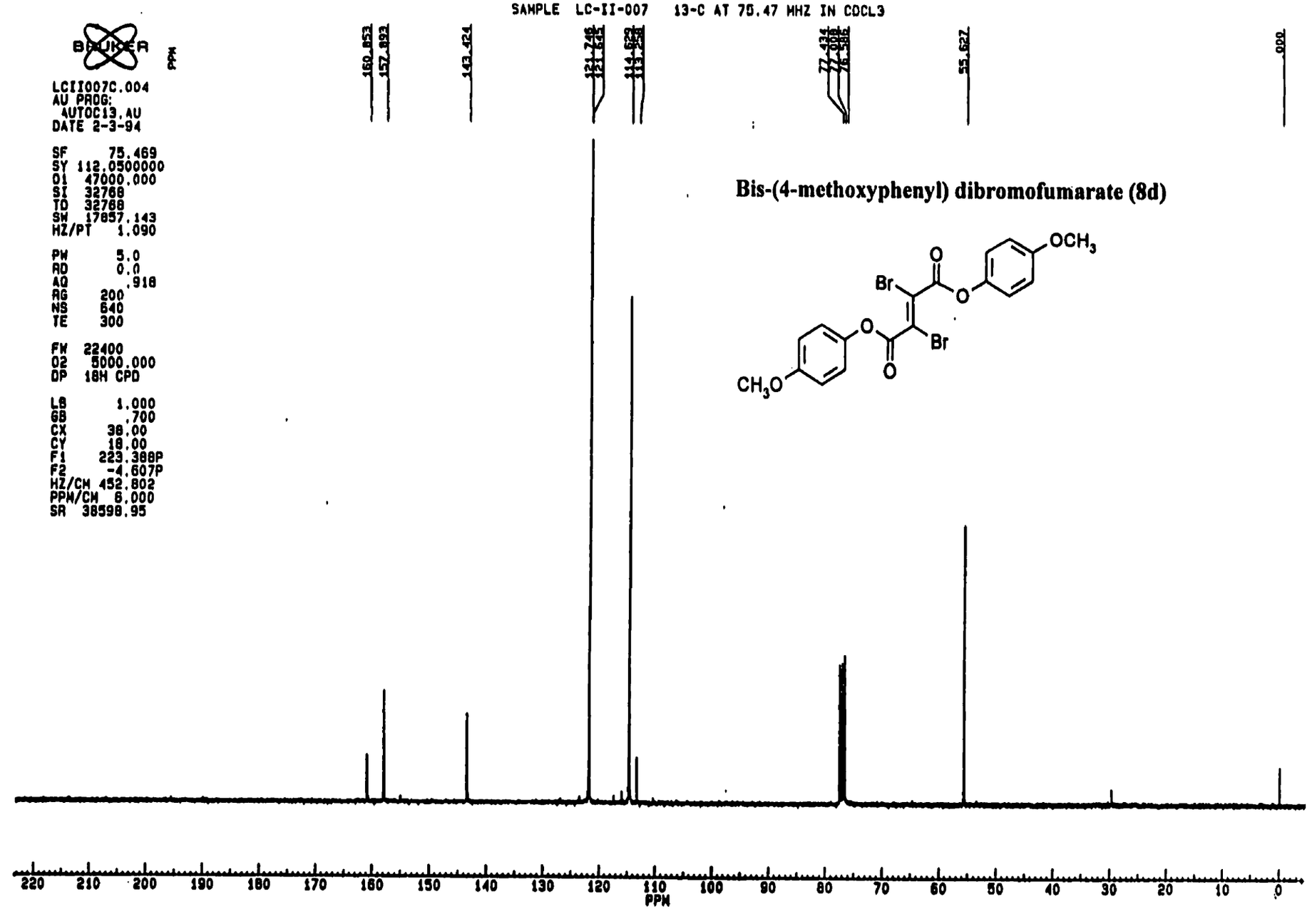
FW 22400
O2 5000.000
DP 18H CPD

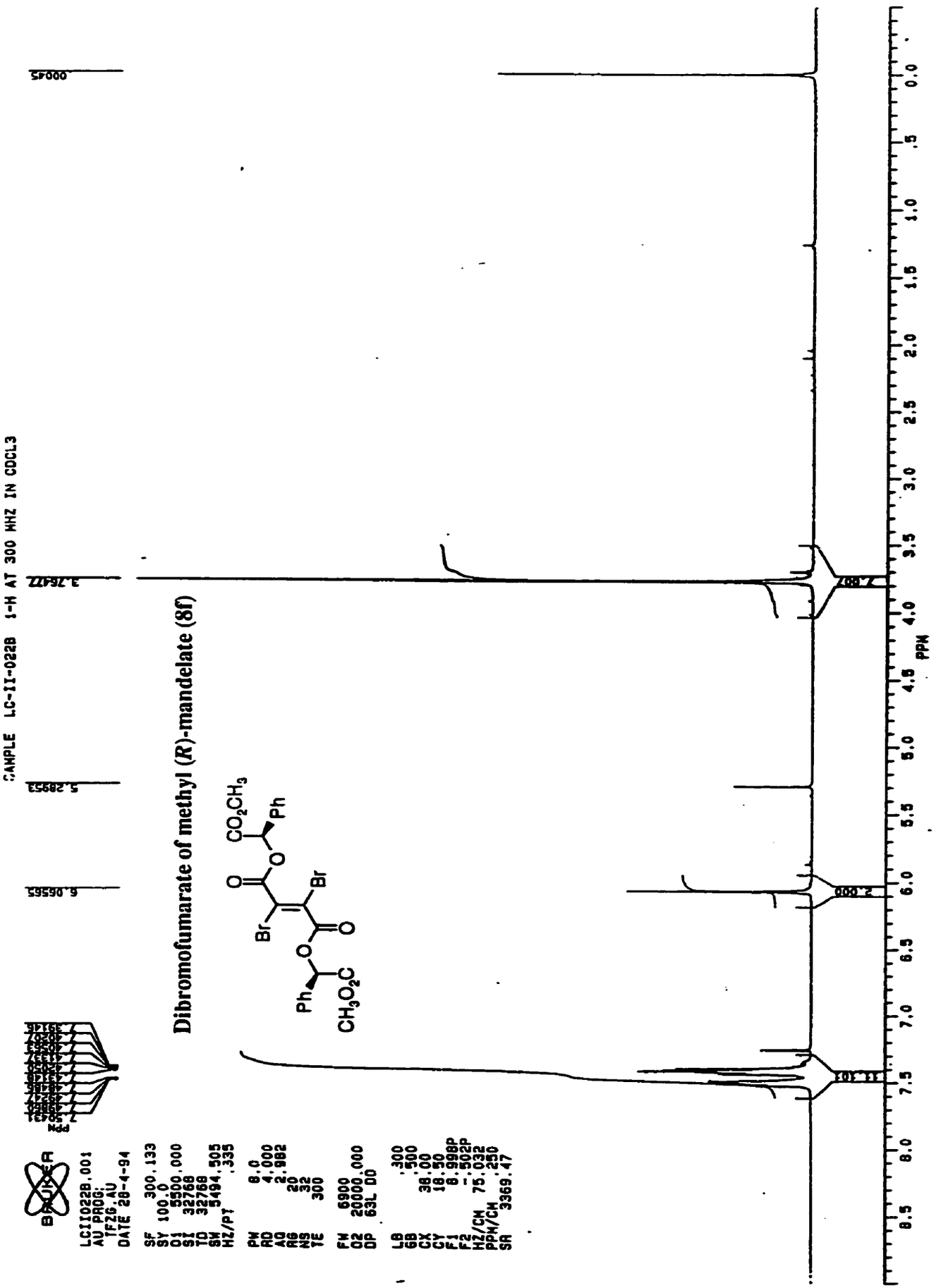
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.547P
F2 -4.448P
HZ/CM 452.802
PPM/CM 6.000
SR 38586.96

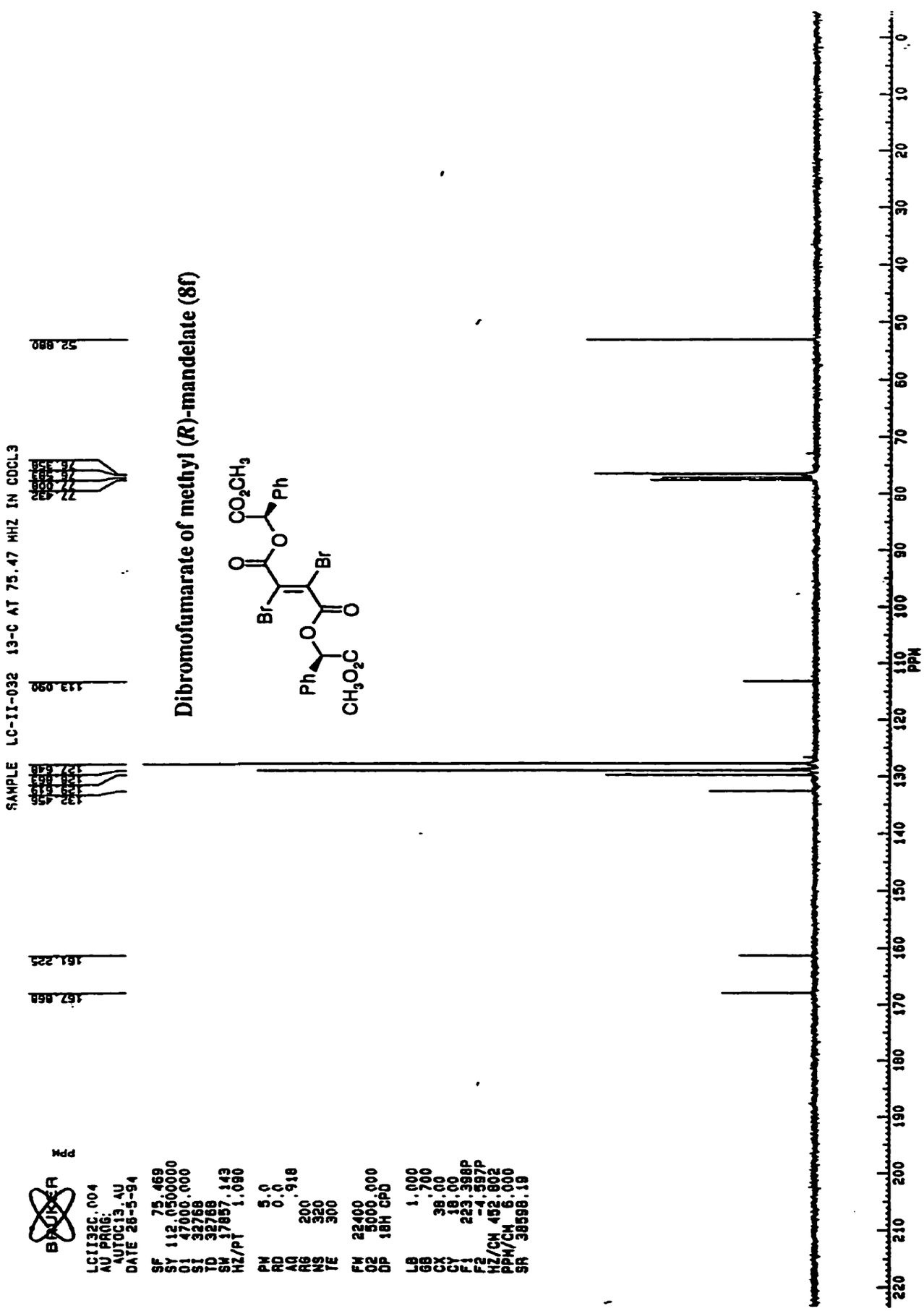
Dibromofumarate of methyl (*S*)-lactate (8e)

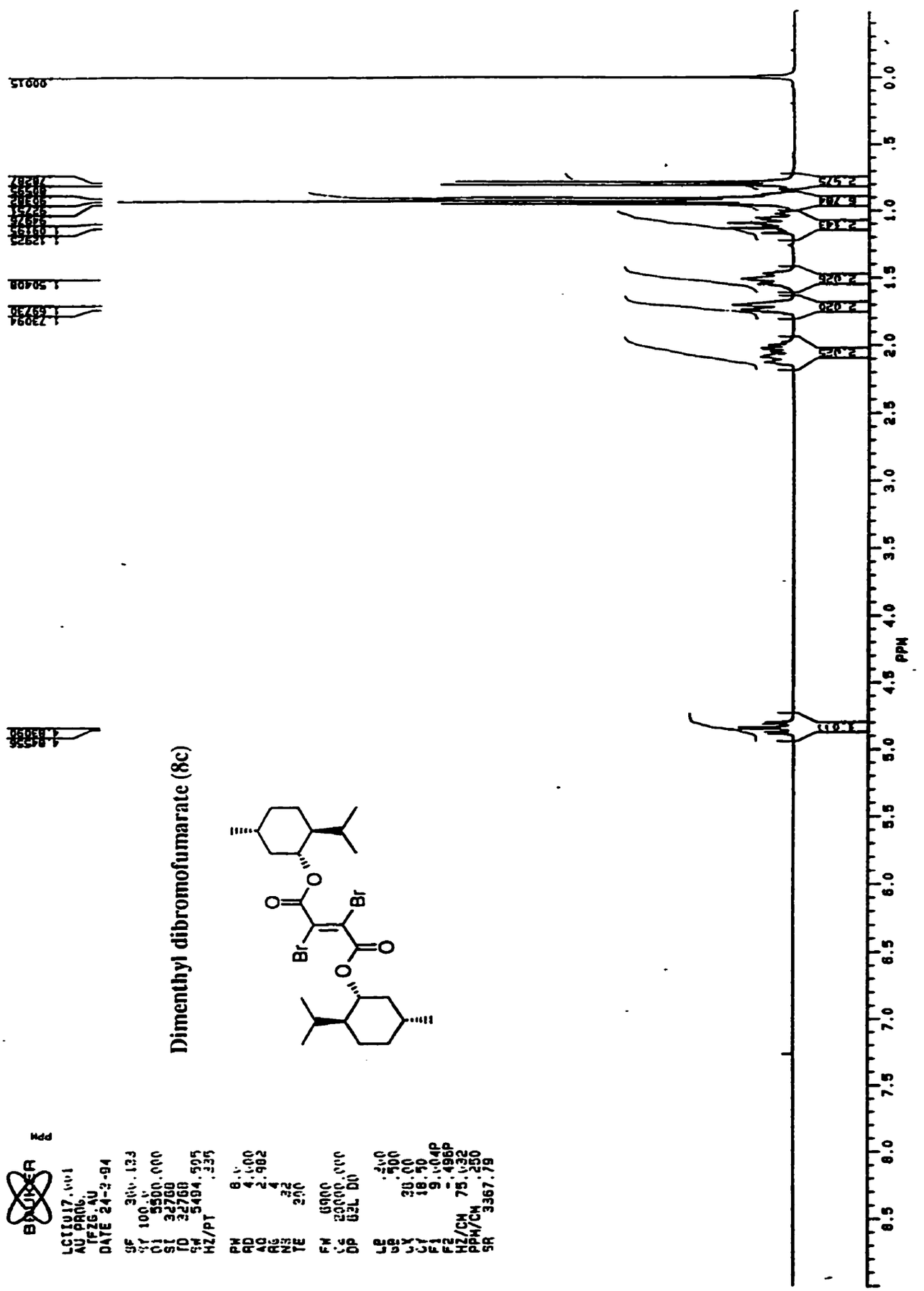



SAMPLE LC-II-007 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
LCII007.001
AU PROG:
ZFZG.AU
DATE 2-3-94
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 4
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.994P
F2 -.506P
HZ/CM 75.032
PPM/CM .250
SR 3370.01
7.16432
7.13398
6.34273
6.31545
3.80230
-.00056
Bis-(4-methoxyphenyl) dibromofumarate (8d)
OCH3
Br
O
O
Br
O
CH3O
3.7656
2.9984
6.1567
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

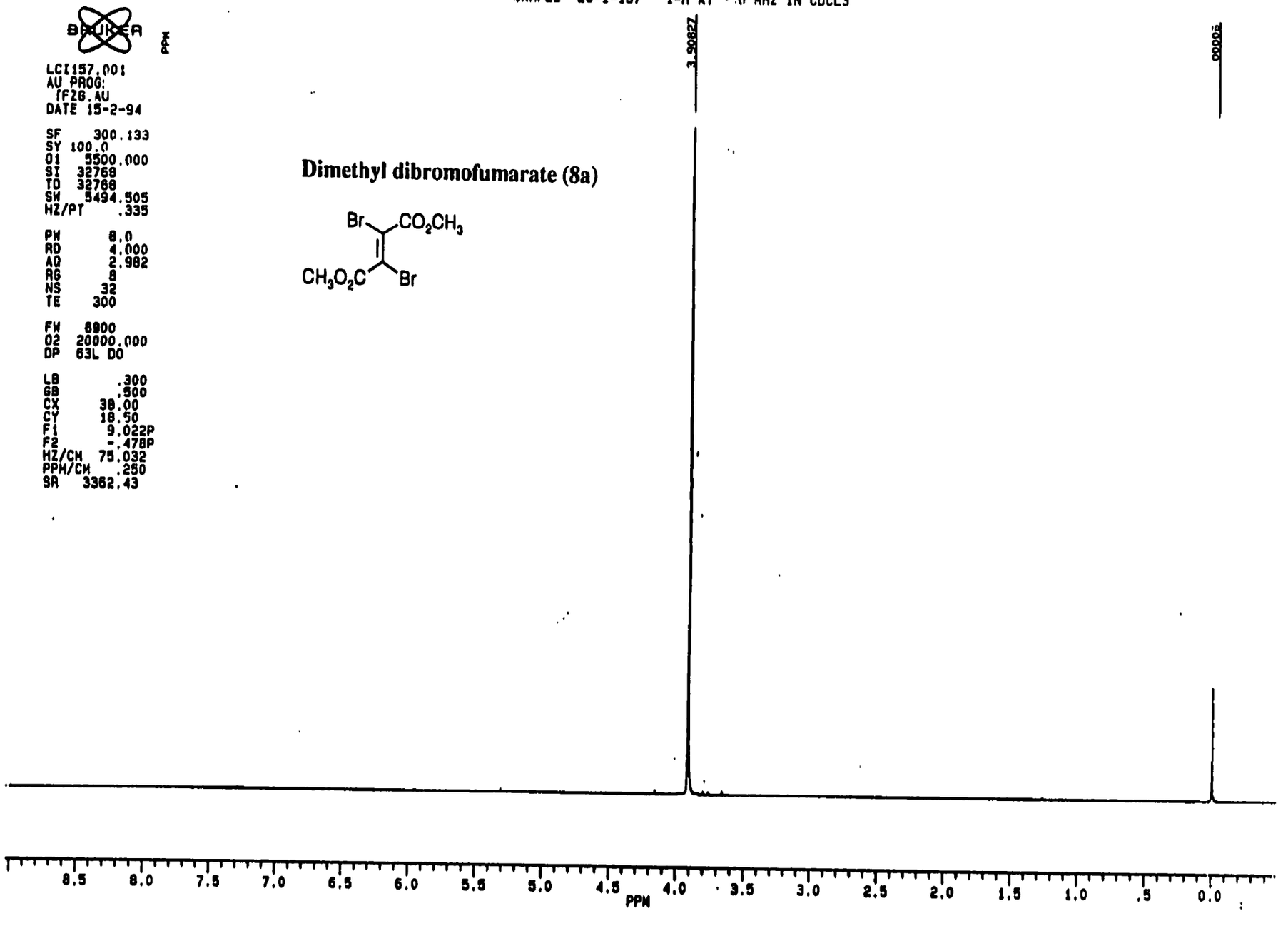

SAMPLE LC-II-007 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
160.853
157.893
143.424
131.746
121.643
114.623
113.238
77.434
77.000
76.566
55.627
.000
LCII007C.004
AU PROG:
AUTOC13.AU
DATE 2-3-94
SF 75.469
SY 112.0500000
D1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 640
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.388P
F2 -4.607P
HZ/CM 452.802
PPM/CM 6.000
SR 38598.95
Bis-(4-methoxyphenyl) dibromofumarate (8d)
OCH3
O
Br
O
O
Br
O
CH3O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


SAMPLE LC-II-022B 1-H AT 300 MHZ IN CDCL3
Dibromofumarate of methyl (R)-mandelate (8f)
PPM


Dibromofumarate of methyl (R)-mandelate (8f)
SAMPLE LC-II-032 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
LC1132C.004
AU PROG:
AUTOC13.AU
DATE 26-5-94
SF 75.469
SY 112.0500000
01 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 320
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.398P
F2 -4.597P
HZ/CH 452.802
PPM/CH 6.000
SR 38598.19
PPM


SAMPLE LC-II-117 1-H AT 300 MHZ IN CDCL3
Dimenthyl dibromofumarate (8c)
Br
Br
O
O
O
O
PPM

SAMPLE LC-II-017 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
LCU17C.004
AU PROG:
AUTOC13.AU
DATE 25-3-94
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1280
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.402P
F2 -4.593P
HZ/CM 452.802
PPM/CM 6.000
SR 38597.86
161.839
112.012
96.083
77.782
77.305
76.828
76.541
46.836
40.194
34.058
31.454
23.953
23.204
21.947
20.725
16.017
-.002
Dimenthyl dibromofumarate (8c)
Br
O
O
O
Br
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM


SAMPLE LC-I-157 1-H AT 3.0 MHZ IN CDCL3
BRUKER
PPM
LCI157.001
AU PROG:
IFZG.AU
DATE 15-2-94
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 8
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.022P
F2 -.478P
HZ/CM 75.032
PPM/CM .250
SR 3362.43
3.90827
Dimethyl dibromofumarate (8a)
Br
CO2CH3
CH3O2C
Br
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

SAMPLE LC-I-157 13-C AT 75.47 MHZ IN CDCL3

LCI157C.001
AU PROG:
POWSTORE.AU
DATE 16-2-94

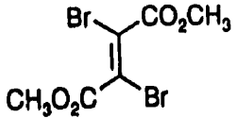
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090

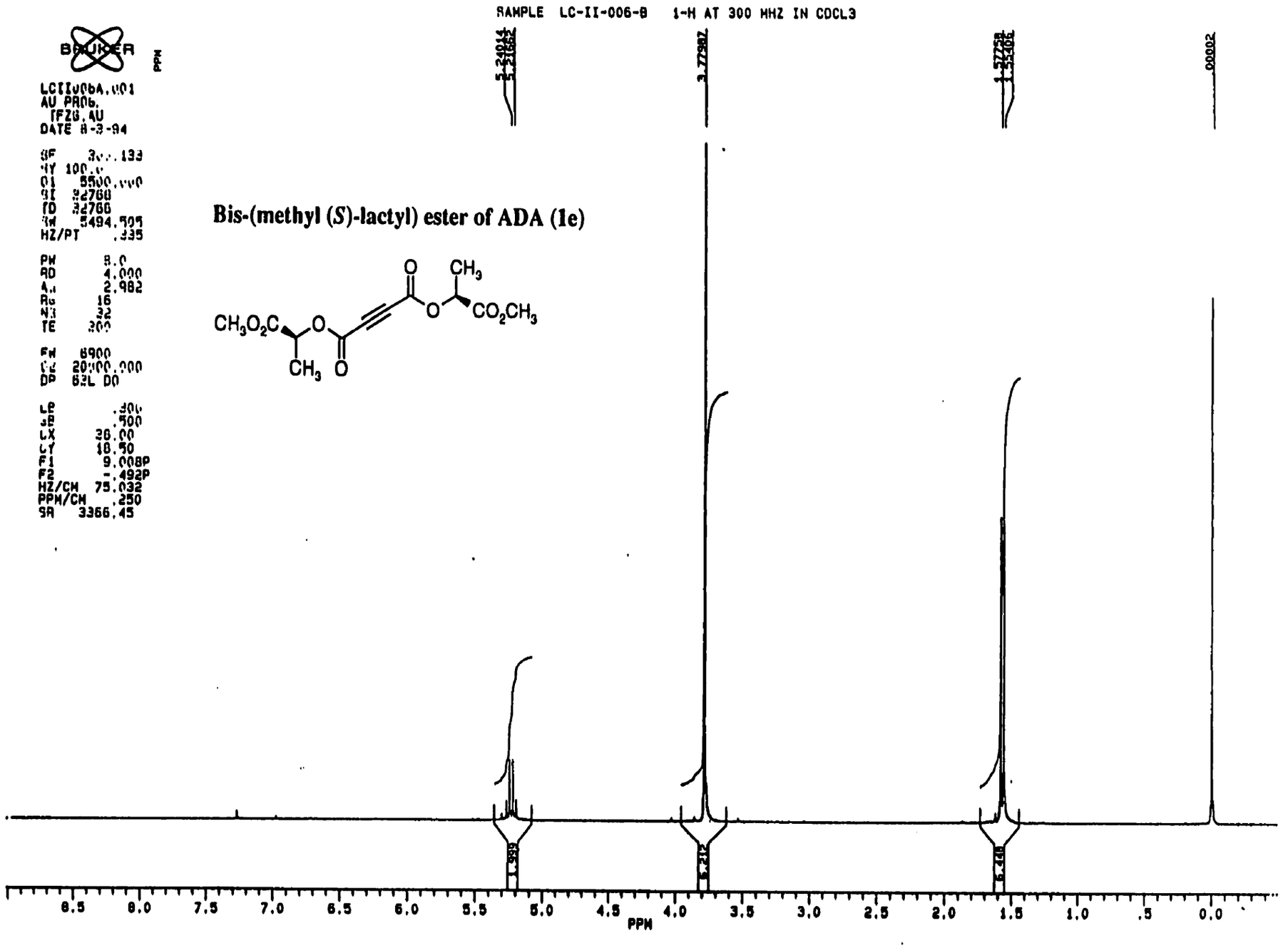
PW 6.5
RD 0.0
AQ .918
RG 100
NS 561
TE 300

FW 22400
O2 5000.000
DP 16H CPD

LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.431P
F2 -4.564P
HZ/CM 452.802
PPH/CM 6.000
SR 38595.68

Dimethyl dibromofumarate (8a)




SAMPLE LC-II-006-B 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
LCIIu06A.001
AU PR06.
TFZG.AU
DATE 8-3-94
Bis-(methyl (S)-lactyl) ester of ADA (1e)
CH3O2C
CO2CH3
CH3
CH3
O
O
O
O
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

SAMPLE LC-II-006-B 13-C AT 75.47 MHZ IN CDCL3

BRUKER

PPM

169.474
150.764
77.423
77.000
76.576
74.381
70.722
52.764
16.741
0.00

LCII6BC.004
AU PROG:
AUTOC13.AU
DATE 10-3-94

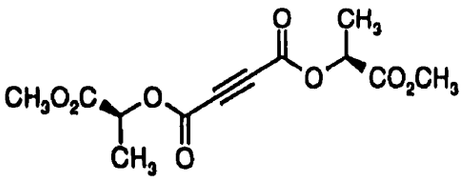
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090

PW 5.0
RD 0.0
AQ .918
RG 200
NS 384
TE 300

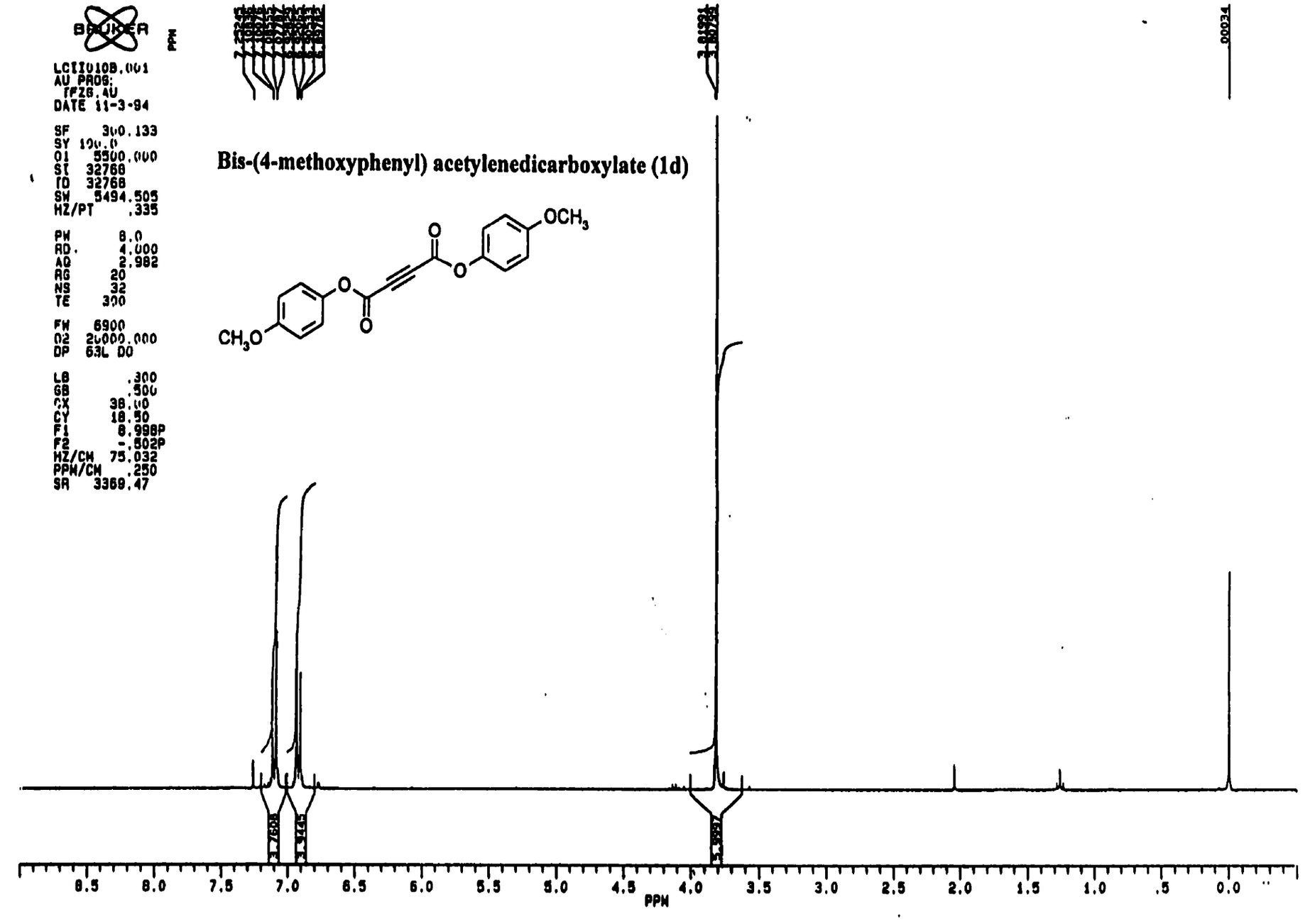
FW 22400
O2 5000.000
OP 18H CPD

LB 1.000
GB .700
CX 38.00
CY 16.00
F1 223.431P
F2 -4.564P
HZ/CM 452.802
PPM/CM 6.000
SR 38595.66

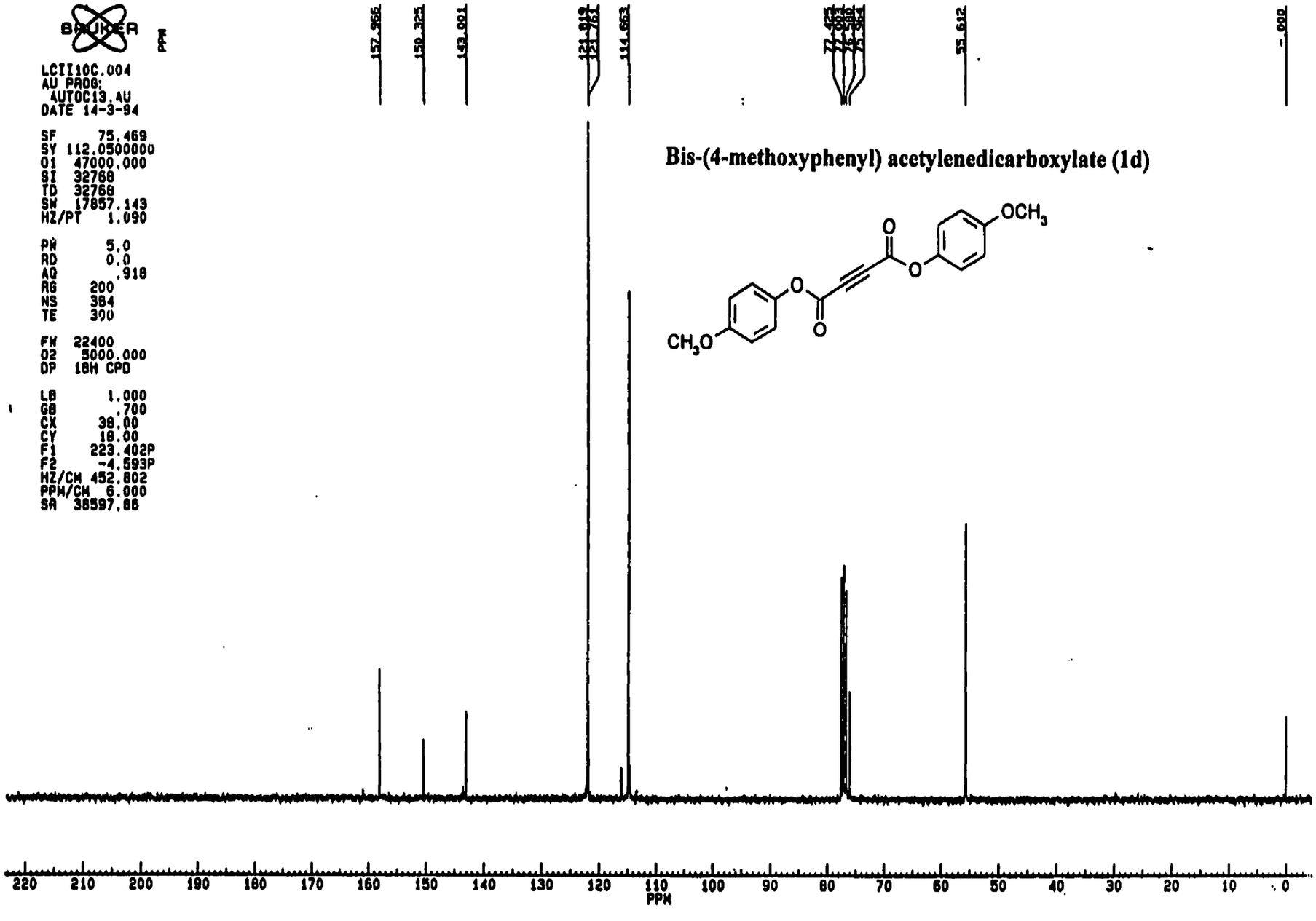
Bis-(methyl (*S*)-lactyl) ester of ADA (1e)

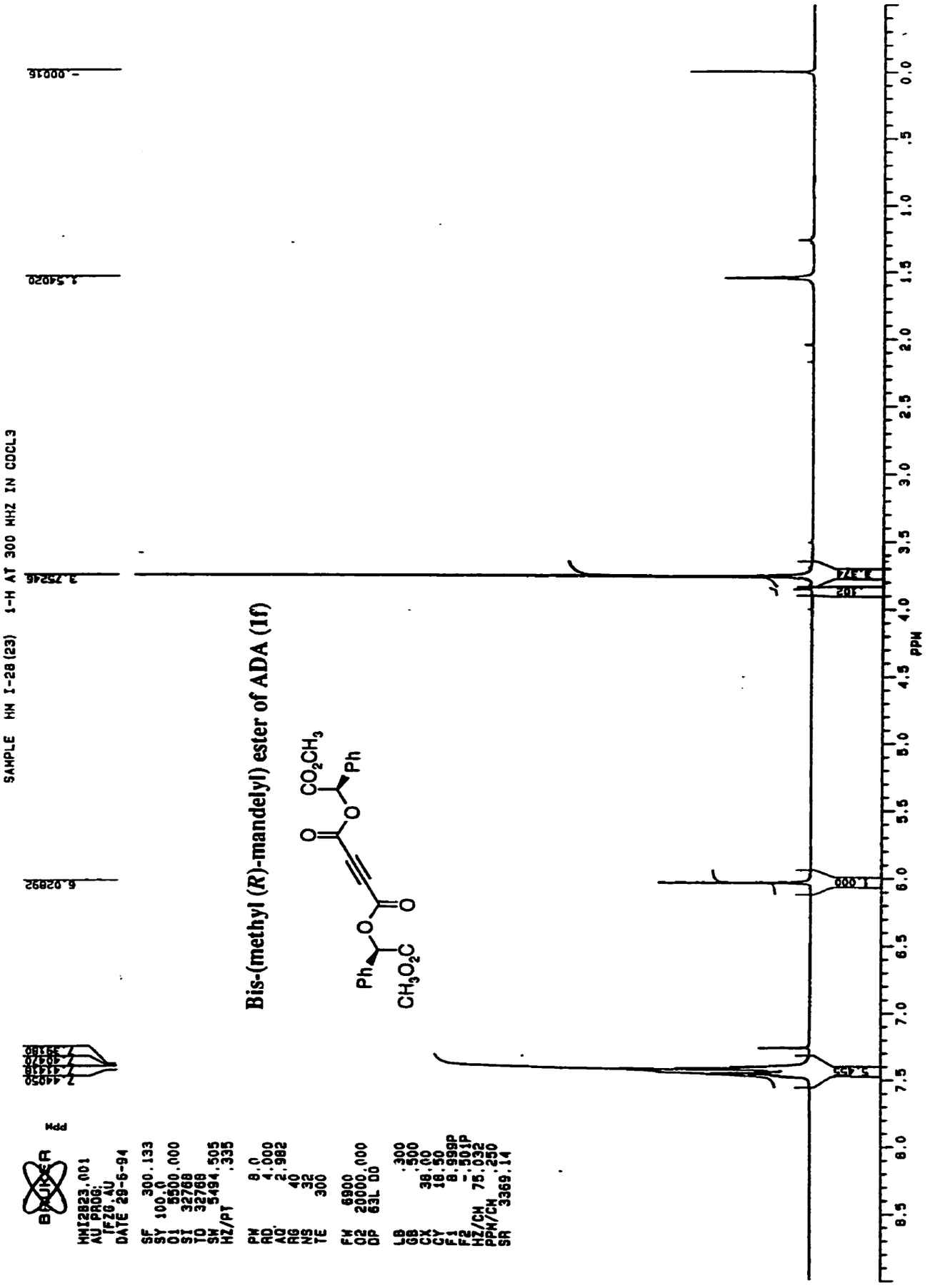


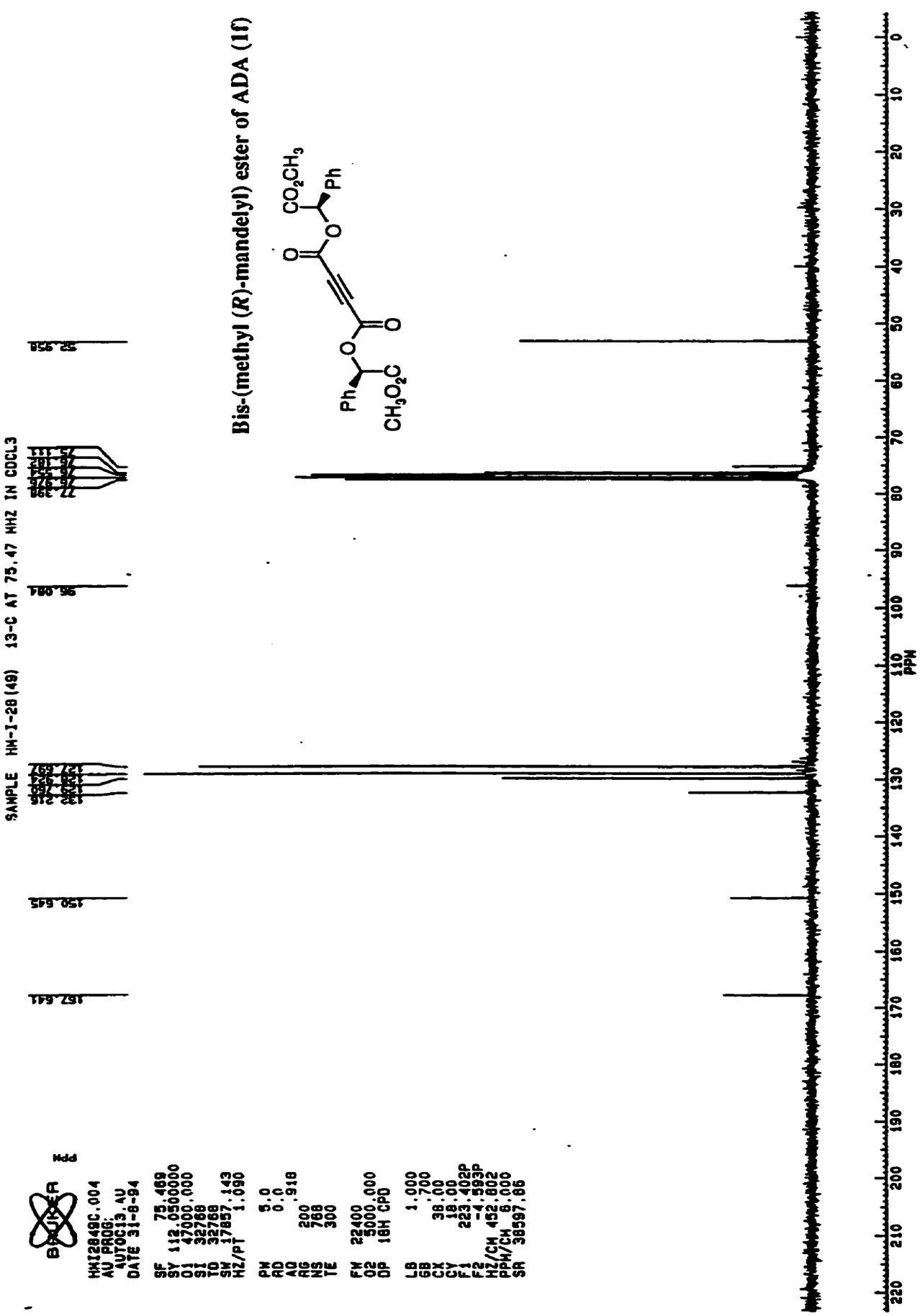
SAMPLE LC-II-010-B 1-H AT 300 MHZ IN CDCL3

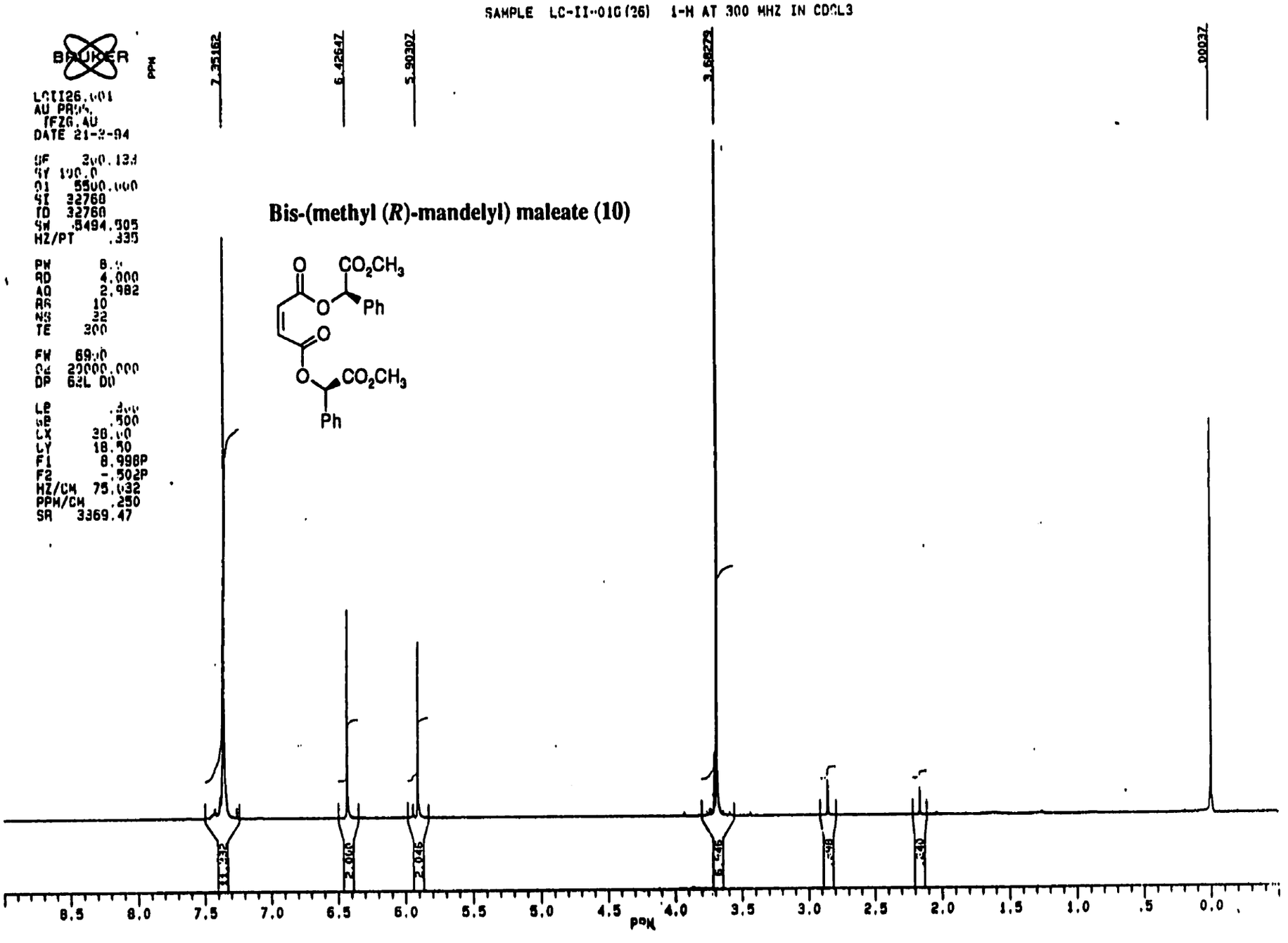


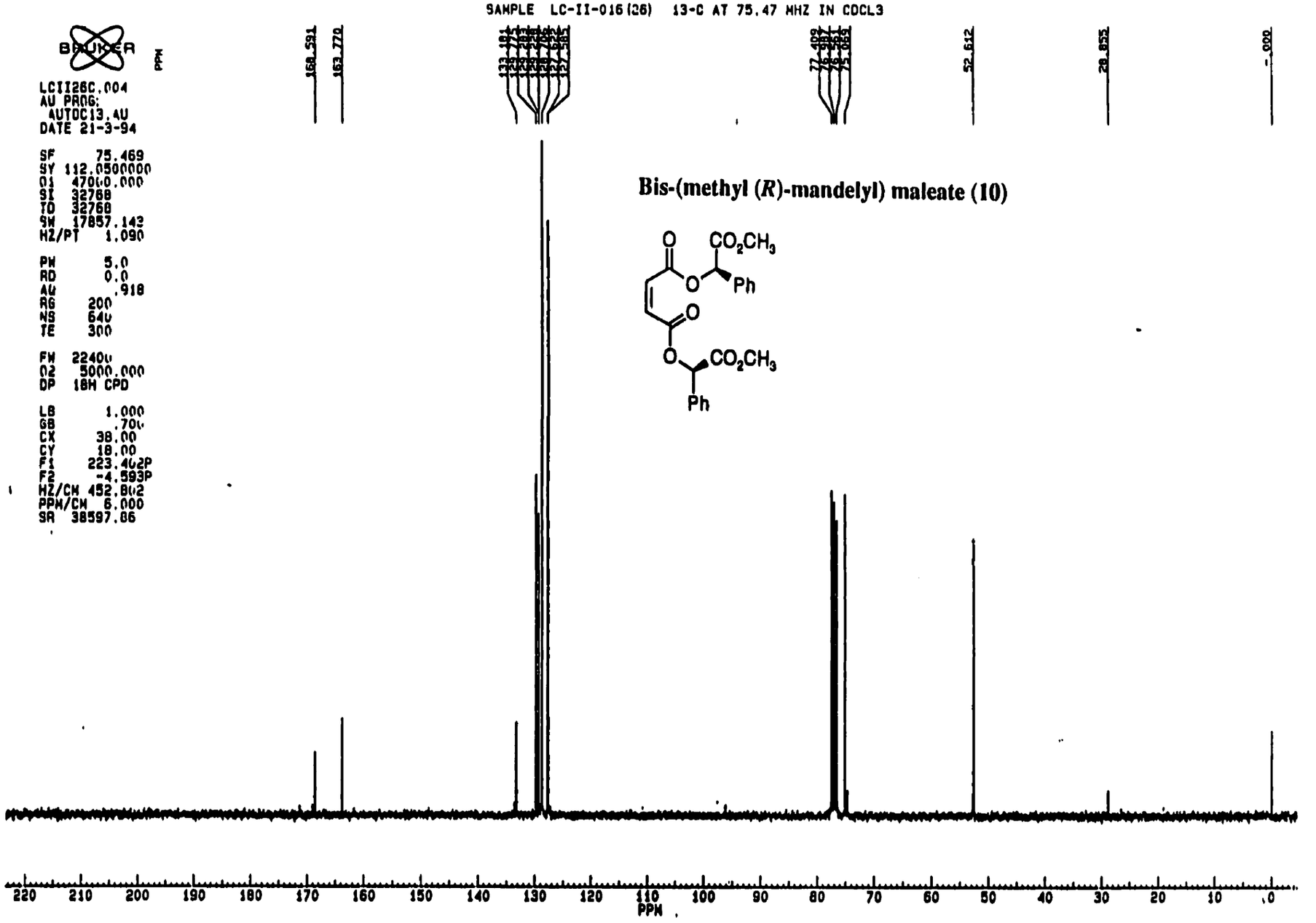
SAMPLE LC-II-010 13-C AT 75.47 MHZ IN COCL3

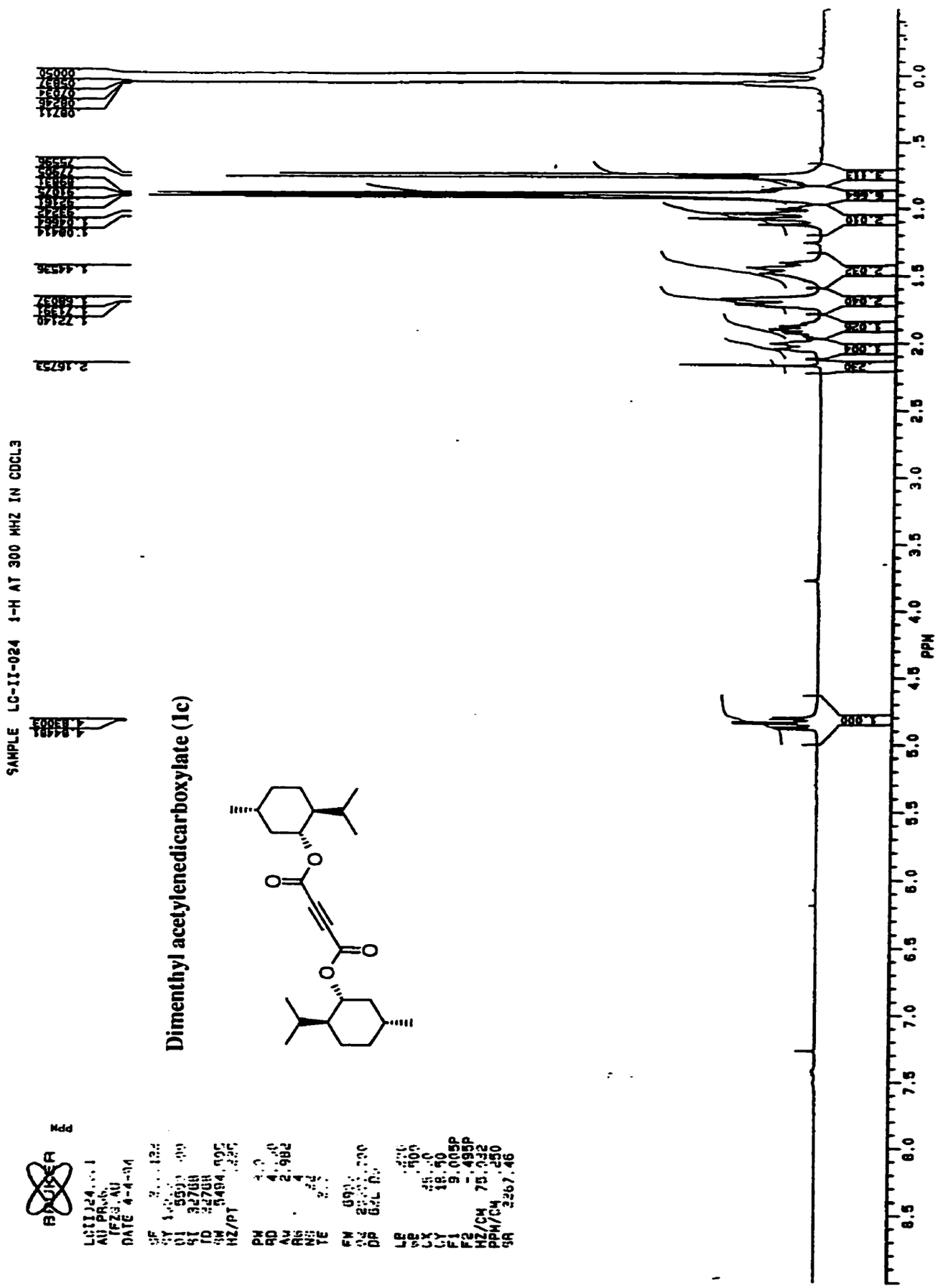


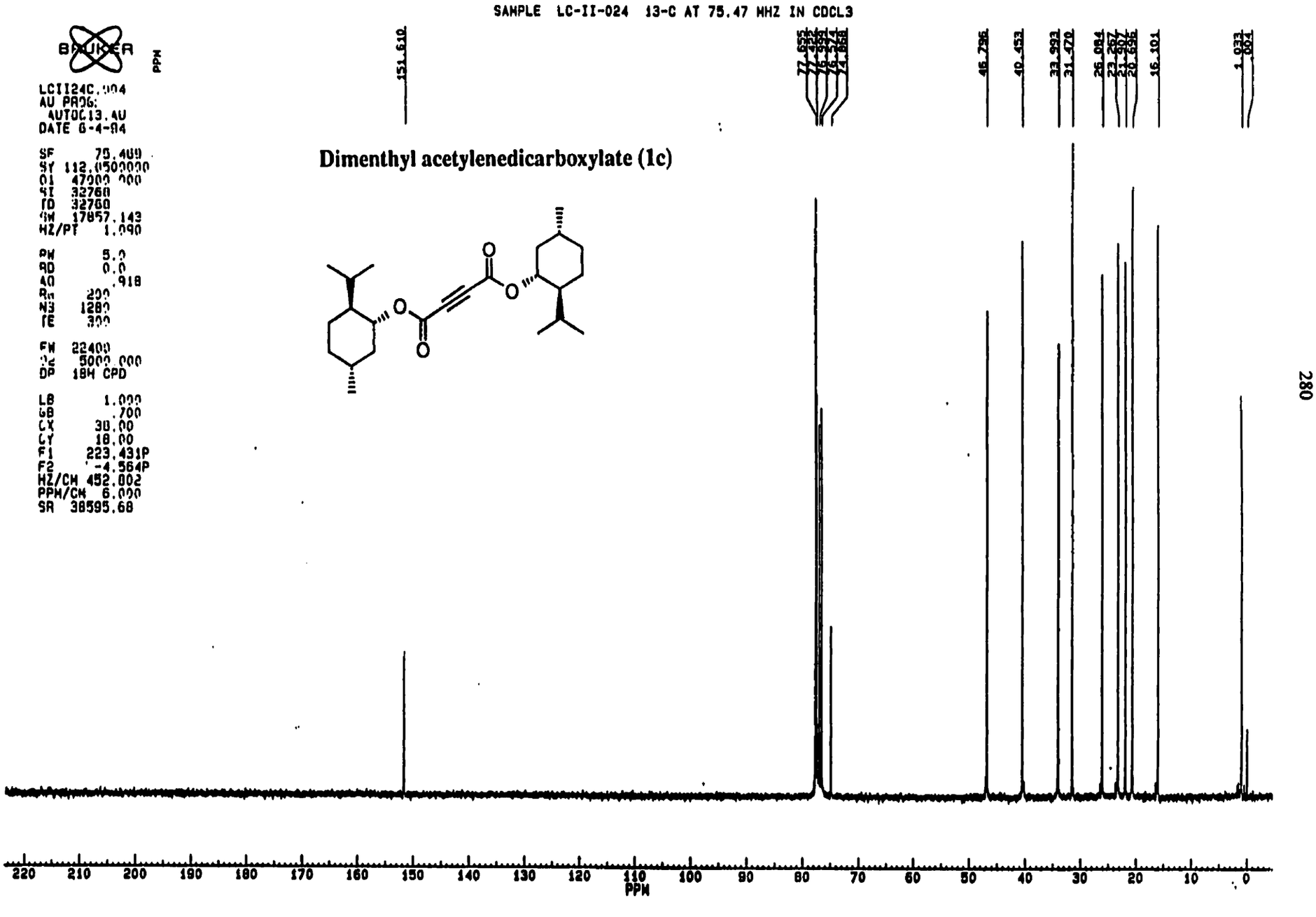

SAMPLE HN I-28(23) 1-H AT 300 MHZ IN CDCL3
Bis-(methyl (R)-mandelyl) ester of ADA (1f)
CO2CH3
Ph
O
O
O
O
O
Ph
CH3O2C
PPM

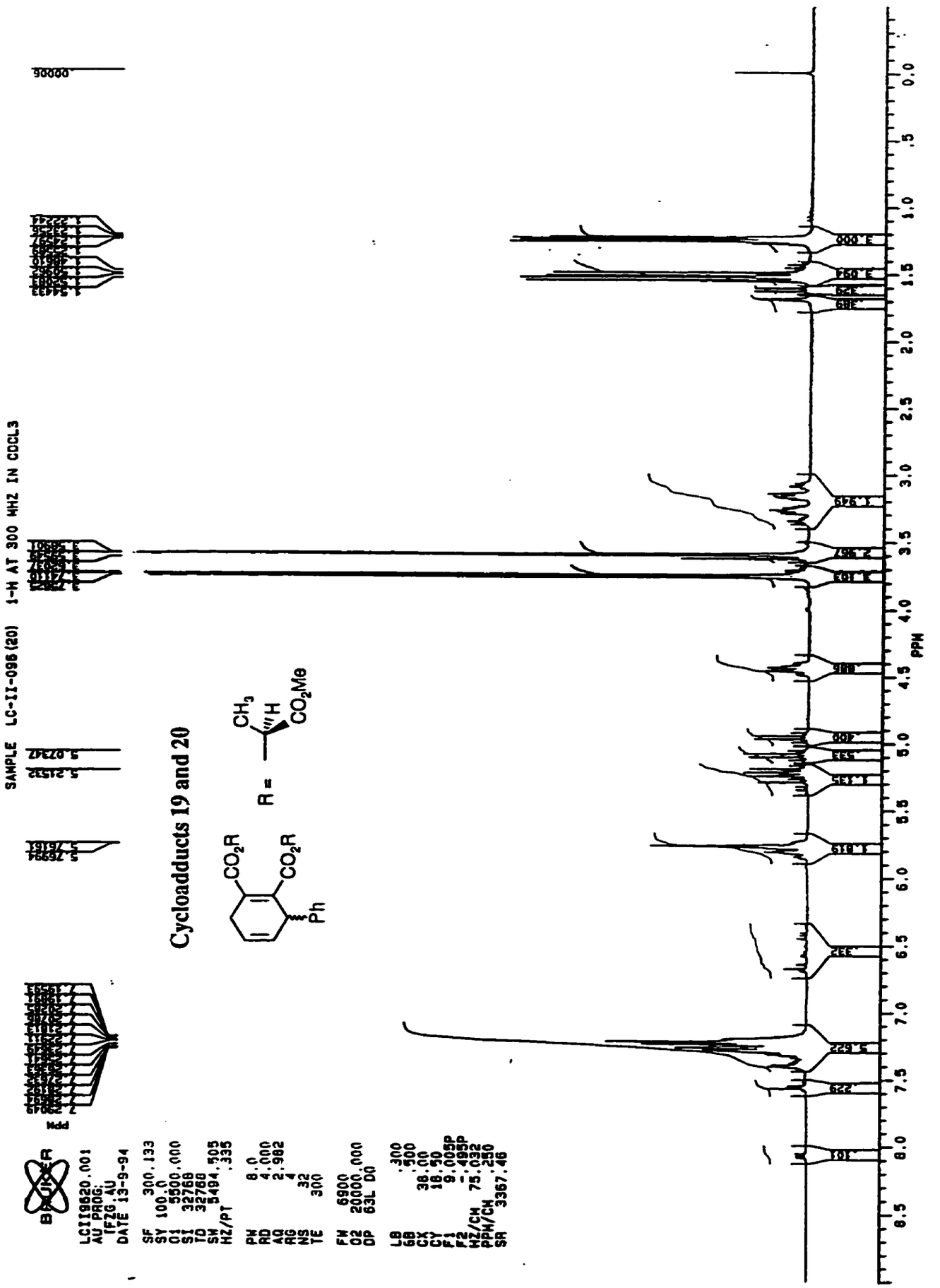

Bis-(methyl (R)-mandelyl) ester of ADA (1f)
SAMPLE HW-1-28(49) 13-C AT 75.47 MHZ IN CDCL3
PPM

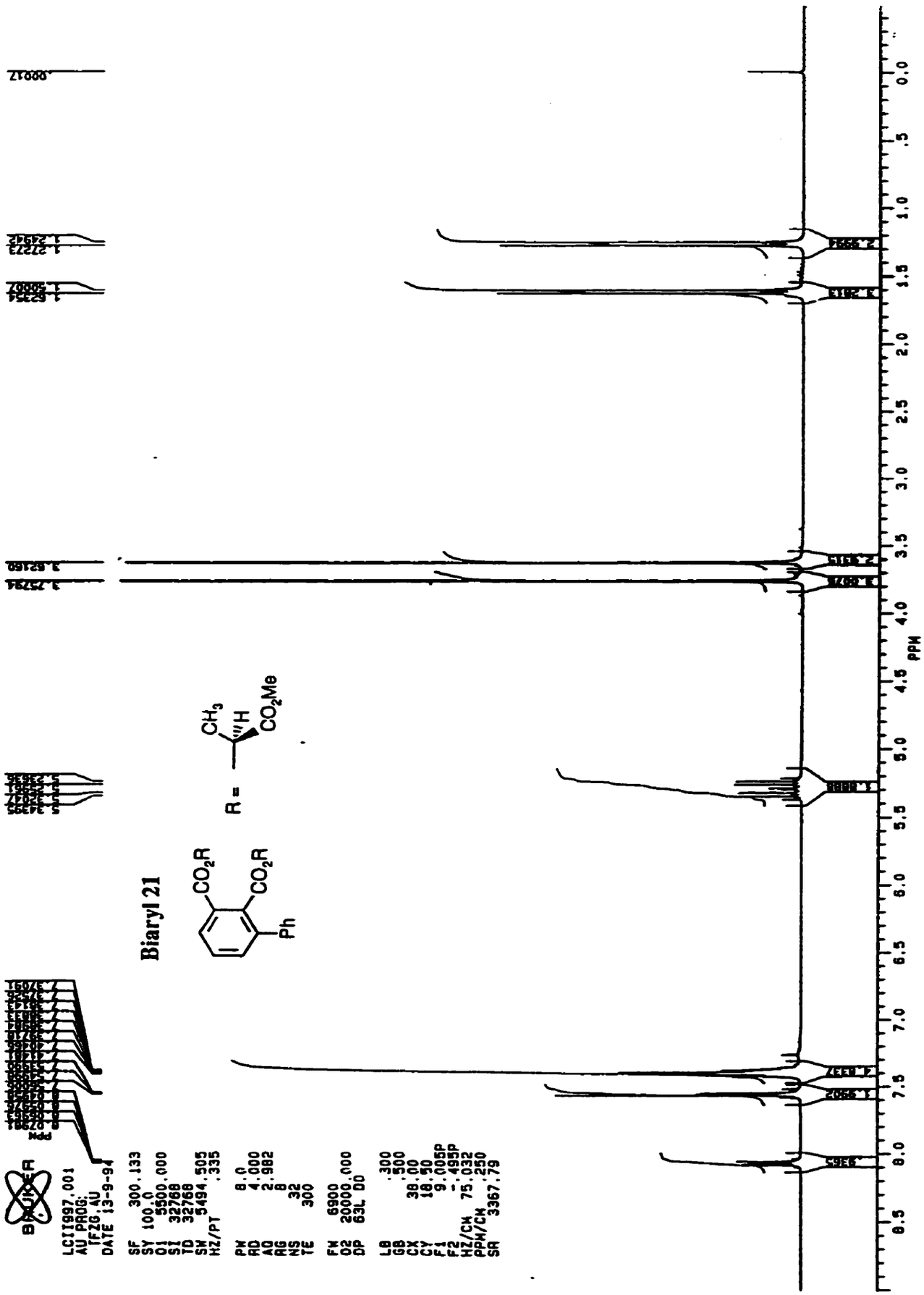

SAMPLE LC-II-010(26) 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
7.35162
6.42647
5.90302
3.68228
.00037
Bis-(methyl (R)-mandelyl) maleate (10)
O
CO2CH3
Ph
O
O
O
CO2CH3
Ph
11.232
2.000
2.045
6.245
.598
.640
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

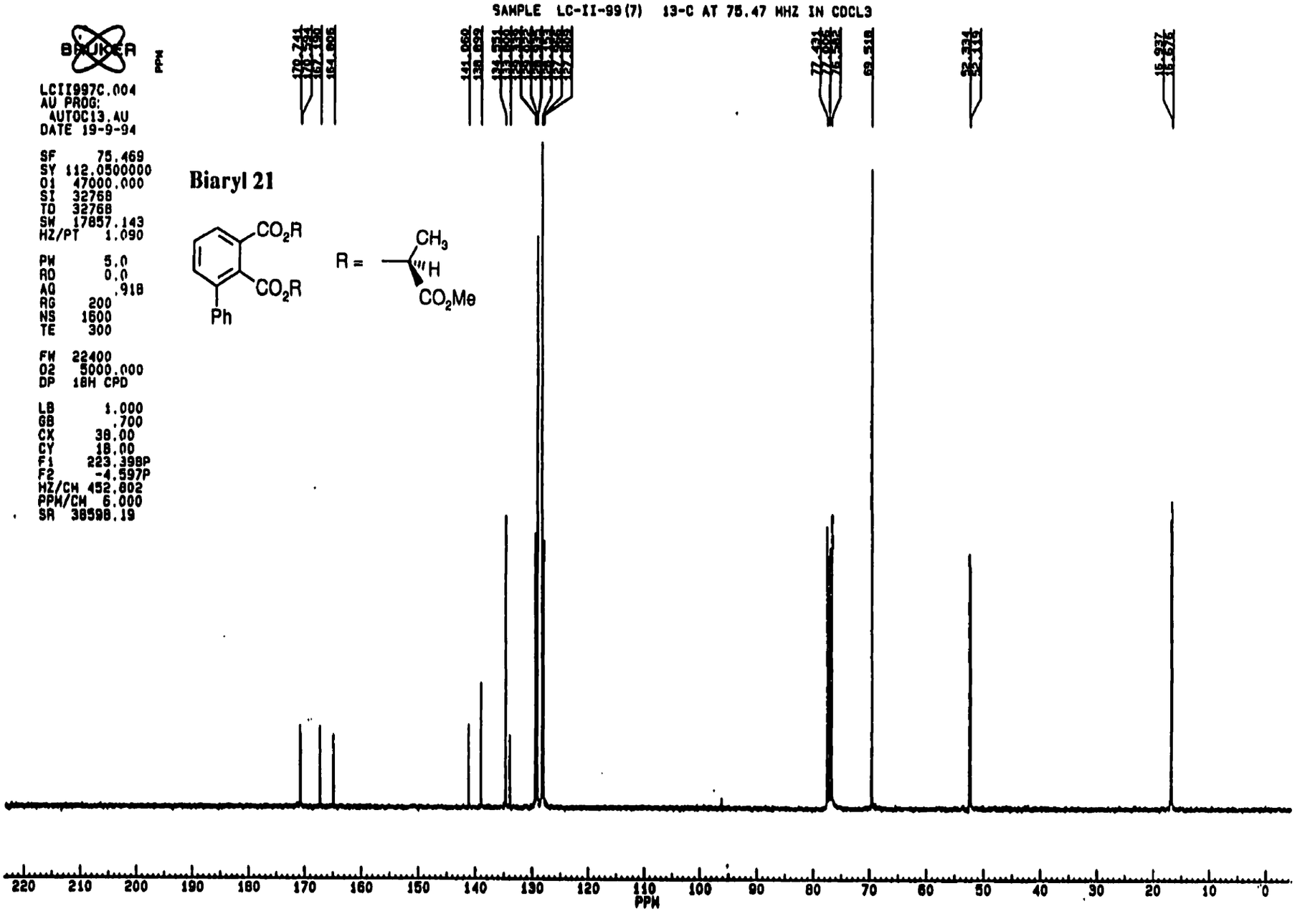

SAMPLE LC-II-016(26) 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
168.591
163.770
52.612
28.855
0.000
LCII26C.004
AU PROG:
AUTOC13.AU
DATE 21-3-94
SF 75.469
SY 112.0500000
O1 4700.000
SI 32768
TD 32768
SW 17857.142
HZ/PT 1.090
PW 5.0
RD 0.0
AU .918
RG 200
NS 640
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.402P
F2 -4.593P
HZ/CM 452.802
PPM/CM 6.000
SR 38597.86
Bis-(methyl (R)-mandelyl) maleate (10)
O
CO2CH3
O
Ph
O
O
CO2CH3
Ph
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

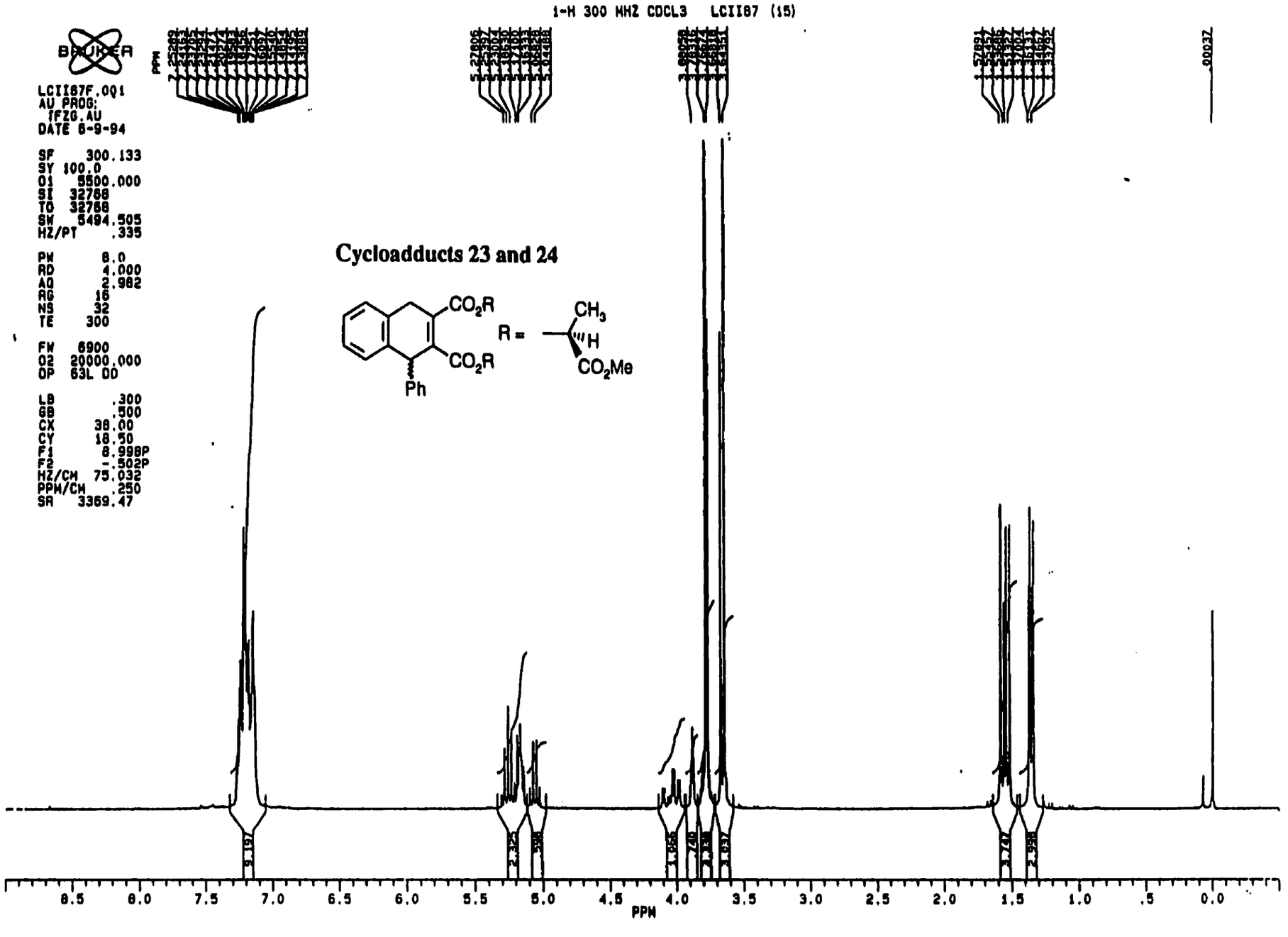

SAMPLE LC-II-024 1-H AT 300 MHZ IN CDCL3
Dimenthyl acetylenedicarboxylate (1c)
PPM

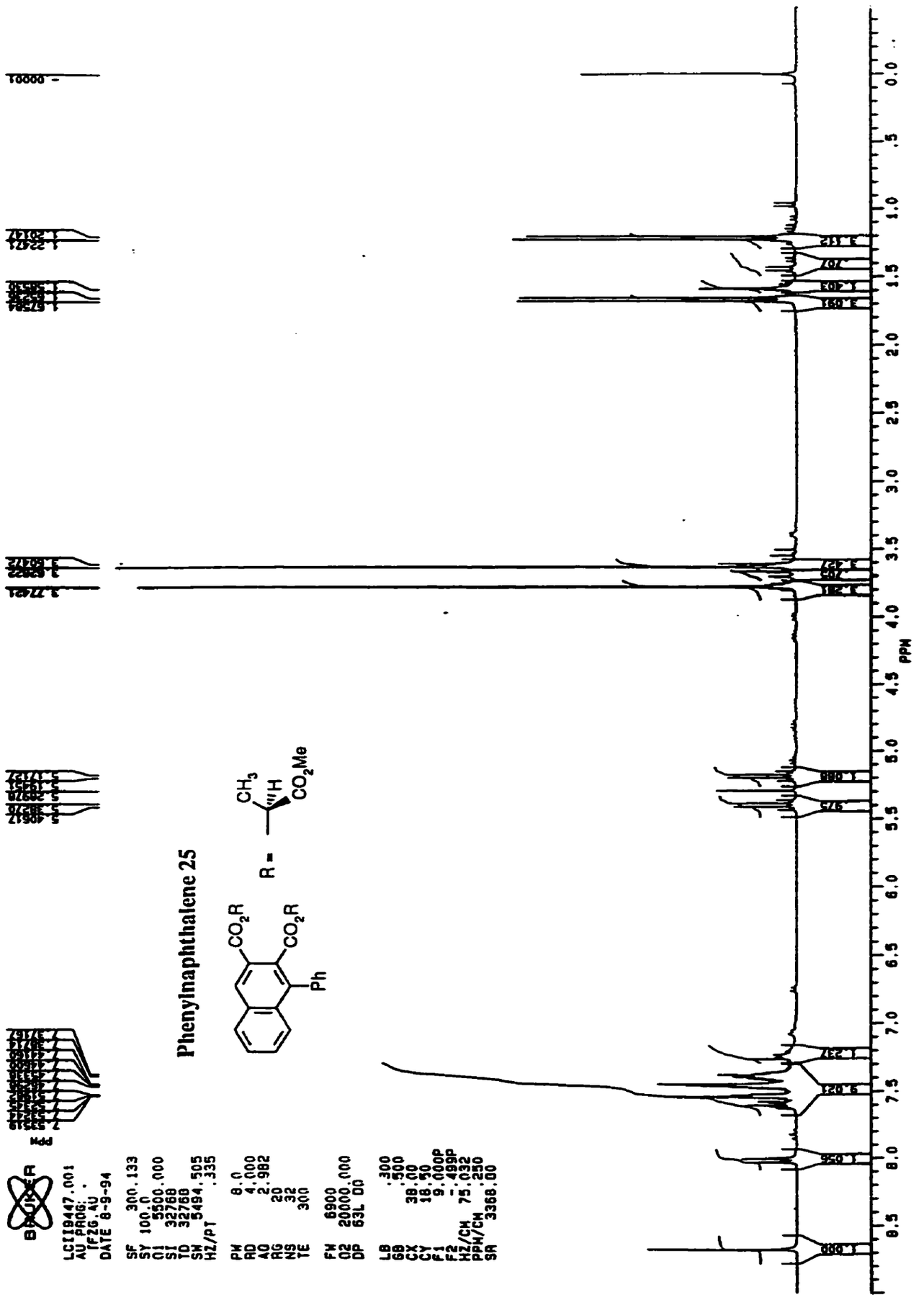

SAMPLE LC-II-024 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
LCII24C.004
AU PROG:
AUTOC13.AU
DATE 6-4-94
SF 75.409
SY 112.0500000
01 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1280
TE 300
FW 22400
DE 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 30.00
CY 18.00
F1 223.431P
F2 -4.564P
HZ/CM 452.002
PPM/CM 6.000
SR 38595.68
151.610
77.633
77.422
77.211
76.999
76.374
74.868
46.796
40.453
33.993
31.470
26.084
23.267
21.907
20.696
16.101
1.933
1.001
Dimenthyl acetylenedicarboxylate (1c)
O
O
O
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

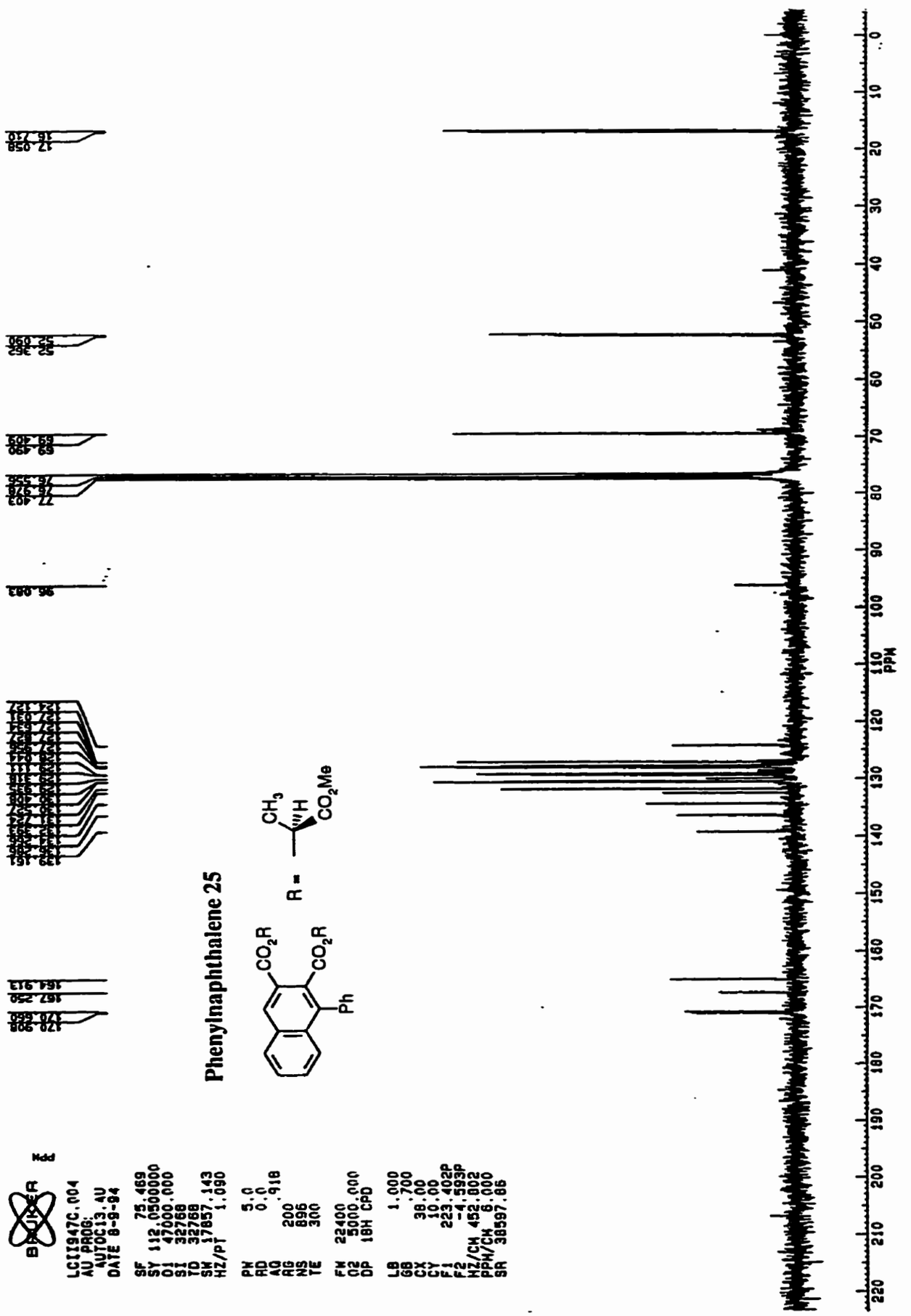

SAMPLE LC-II-098(20) 1-H AT 300 MHZ IN CDCL3
Cycloadducts 19 and 20
R =
CO2Me
CH3
CO2R
CO2R
Ph
PPM

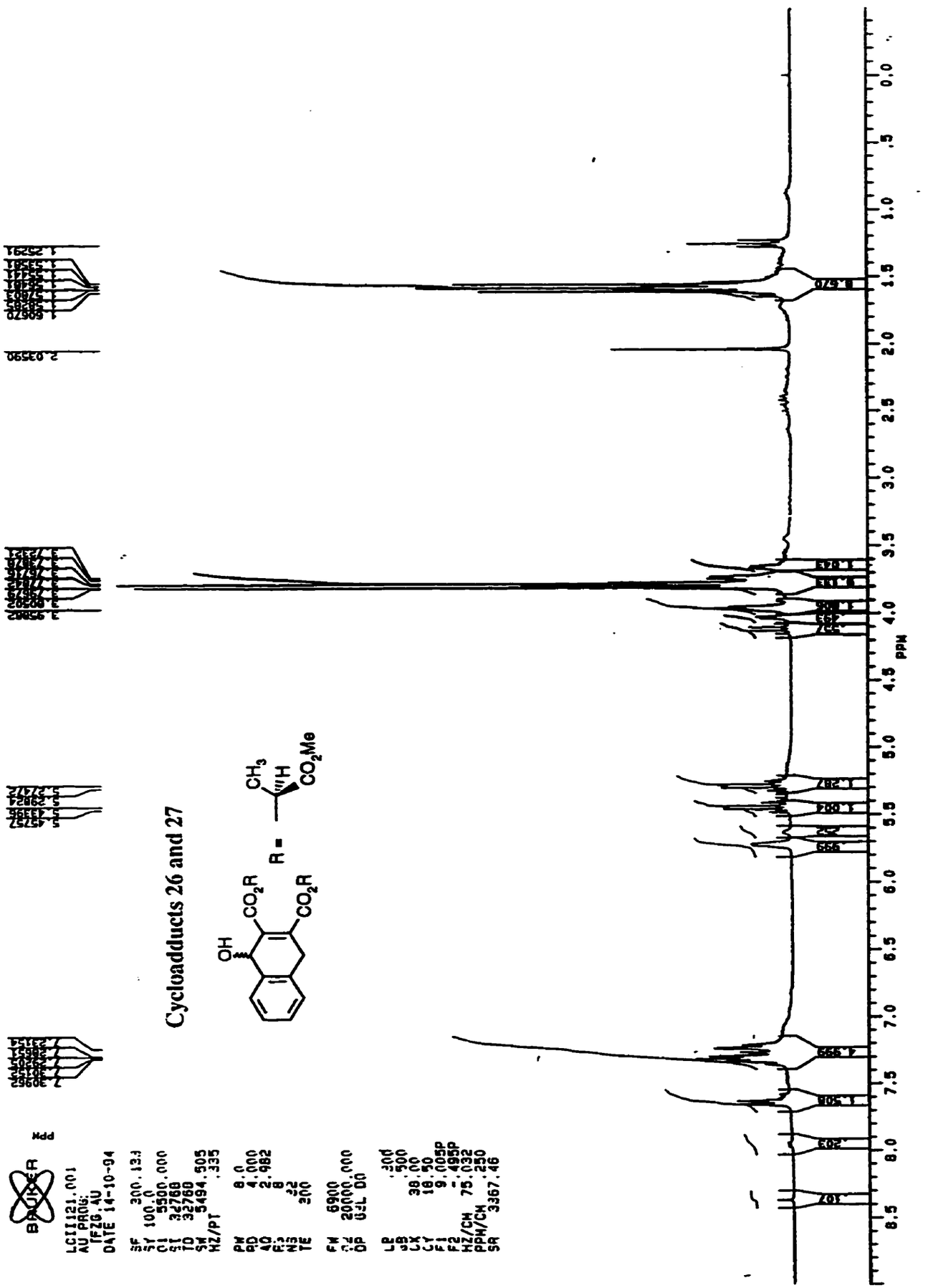

SAMPLE LC-II-099(7) 1-H AT 300 MHZ IN CDCL3
Biaryl 21
R =
CO2Me
CH3
H
CO2R
CO2R
Ph
PPM

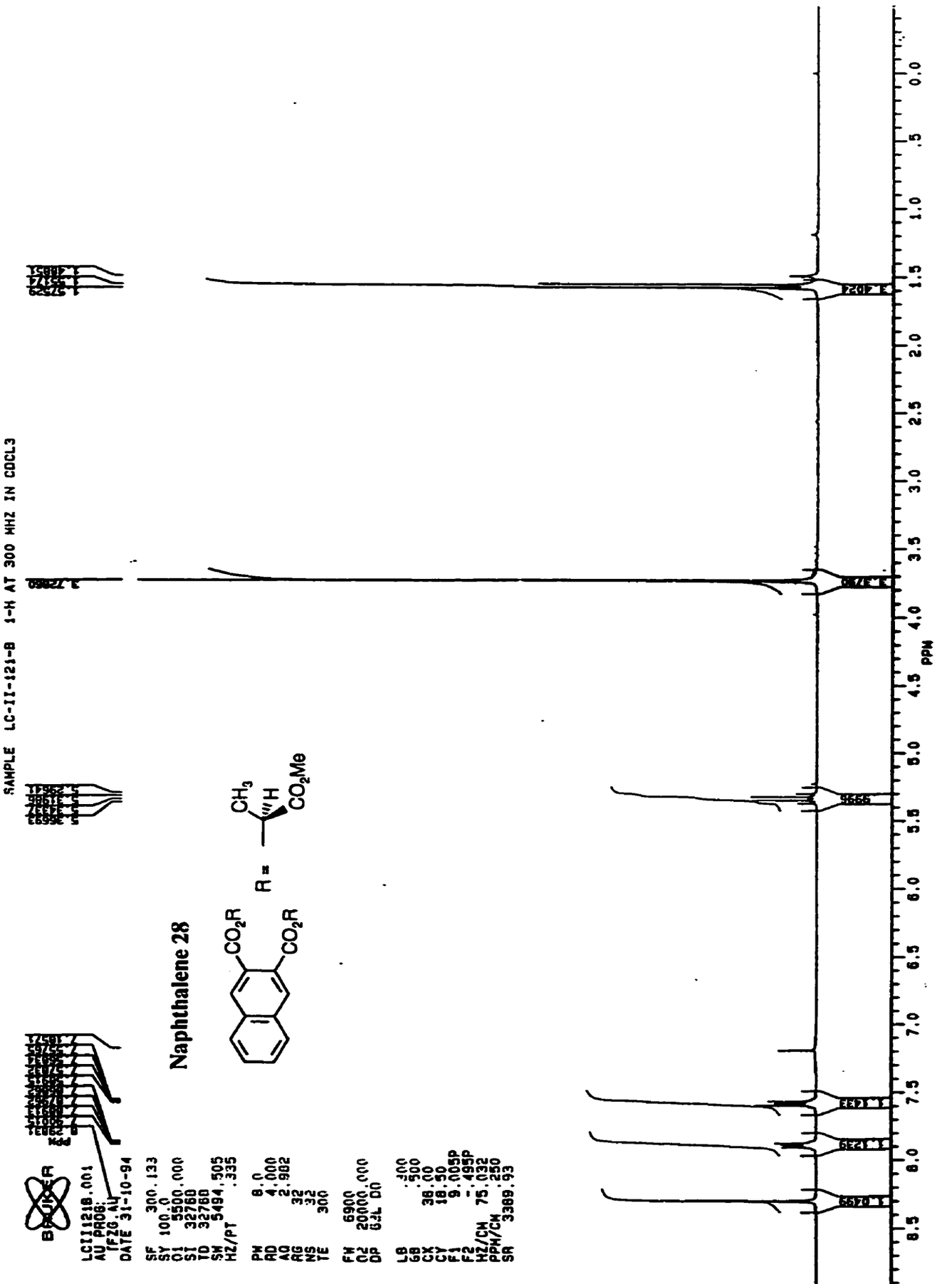

SAMPLE LC-II-99(7) 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
LCII997C.004
AU PROG:
AUTOC13.AU
DATE 19-9-94
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TO 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1600
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.398P
F2 -4.597P
HZ/CM 452.802
PPM/CM 6.000
SR 38598.19
Biaryl 21
CO2R
CO2R
Ph
R =
CH3
H
CO2Me
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

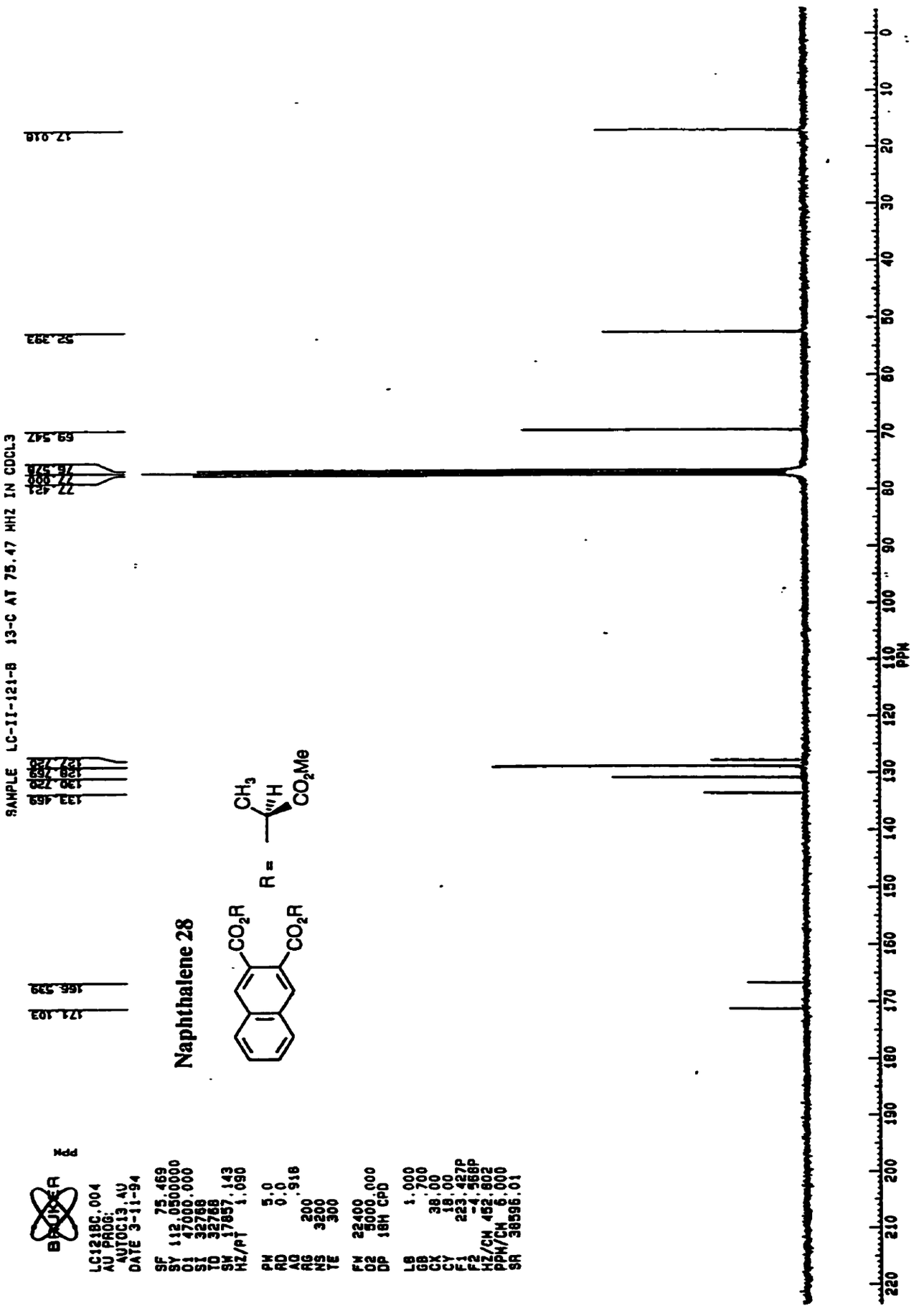

1-H 300 MHZ CDCL3 LCII87 (15)
BRUKER
LCII87F.001
AU PROG:
1FZG.AU
DATE 6-9-94
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 16
NS 32
TE 300
FW 6900
O2 20000.000
OP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.998P
F2 -.502P
HZ/CM 75.032
PPM/CM .250
SR 3369.47
Cycloadducts 23 and 24
CO2R
CO2R
Ph
R =
CH3
H
CO2Me
PPM

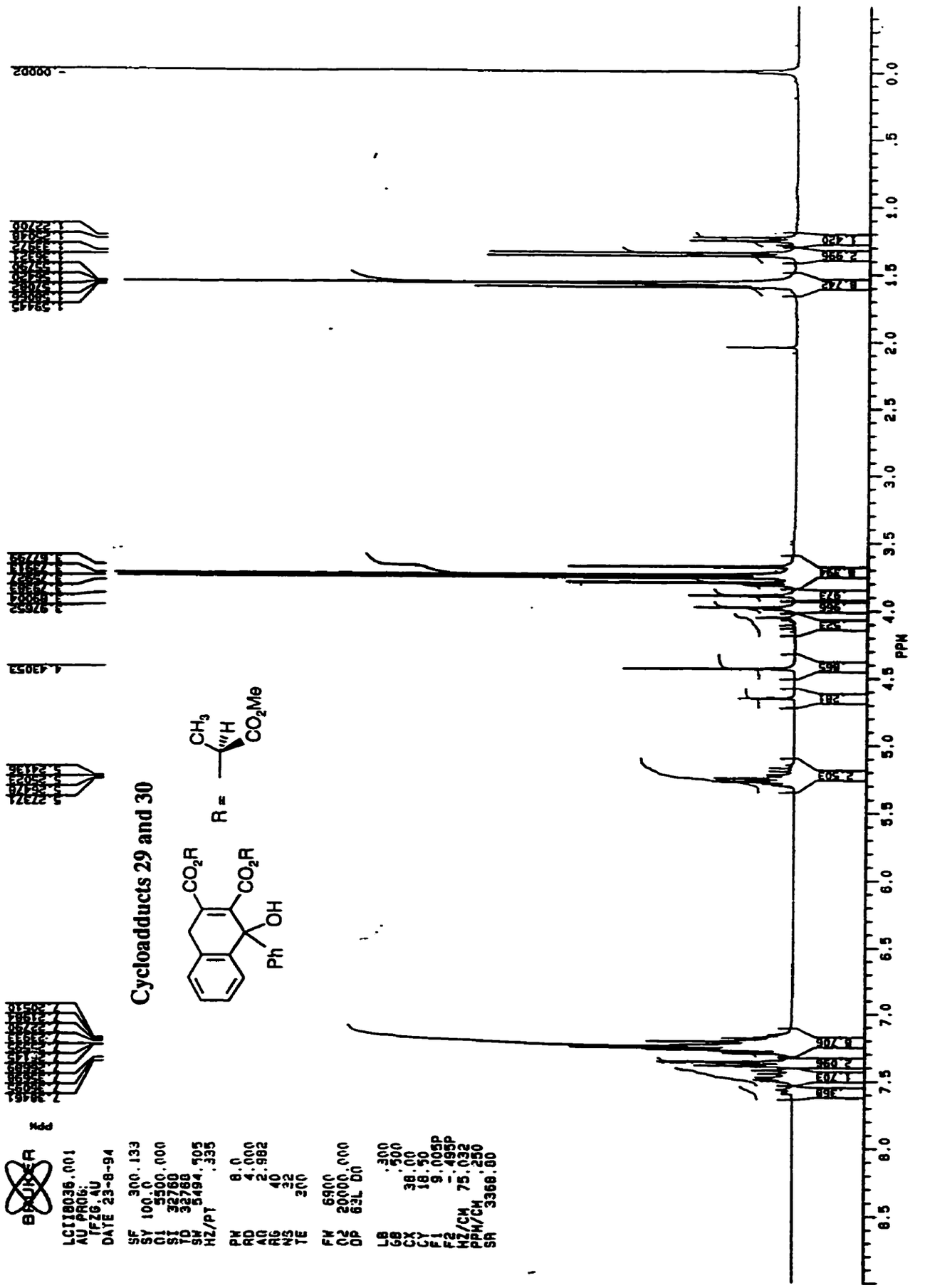

SAMPLE LC-II-94(47) 1-H AT 300 MHZ IN CDCL3
Phenylnaphthalene 25
R =
CO2R
CO2R
Ph
CH3
H
CO2Me
PPM

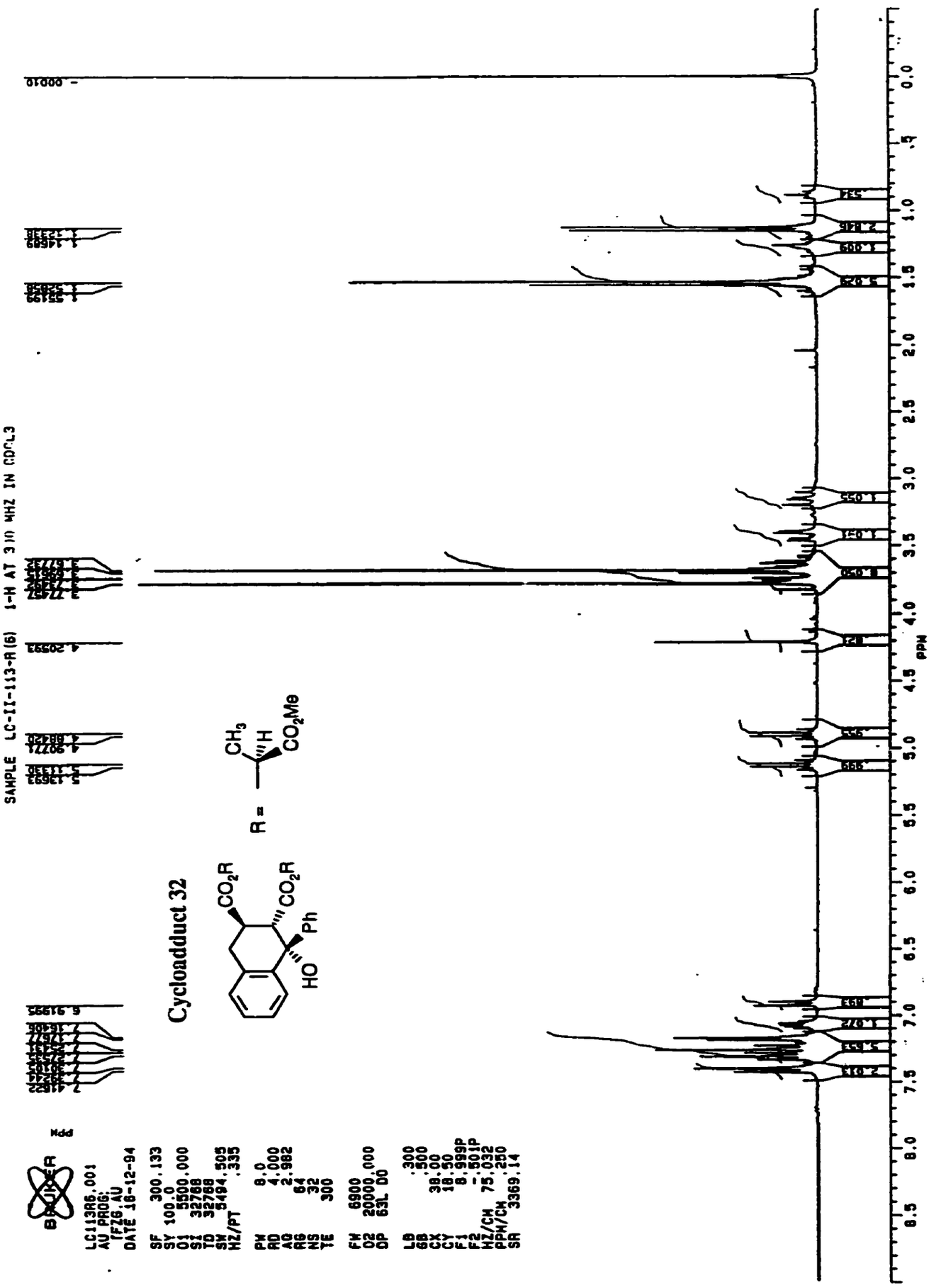

SAMPLE LC-II-94(47) 13-C AT 75.47 MHZ IN CDCL3
Phenylnaphthalene 25
R =
CO2R
CO2R
Ph
CH3
H
CO2Me
PPM

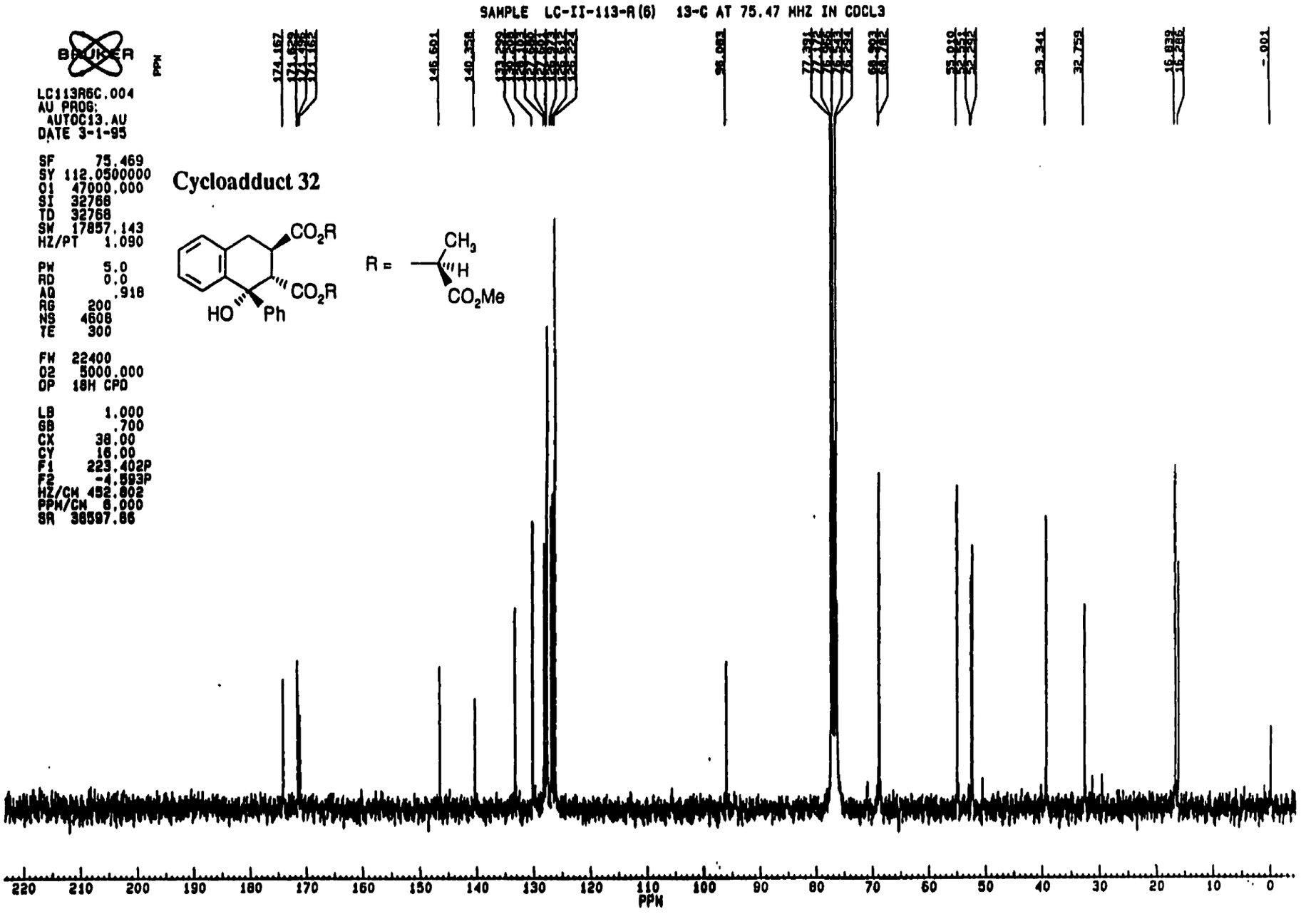

SAMPLE LC-II-121 1-H AT 300 MHZ IN CDCL3
Cycloadducts 26 and 27
R =
OH
CO2R
CO2R
CH3
H
CO2Me
PPM

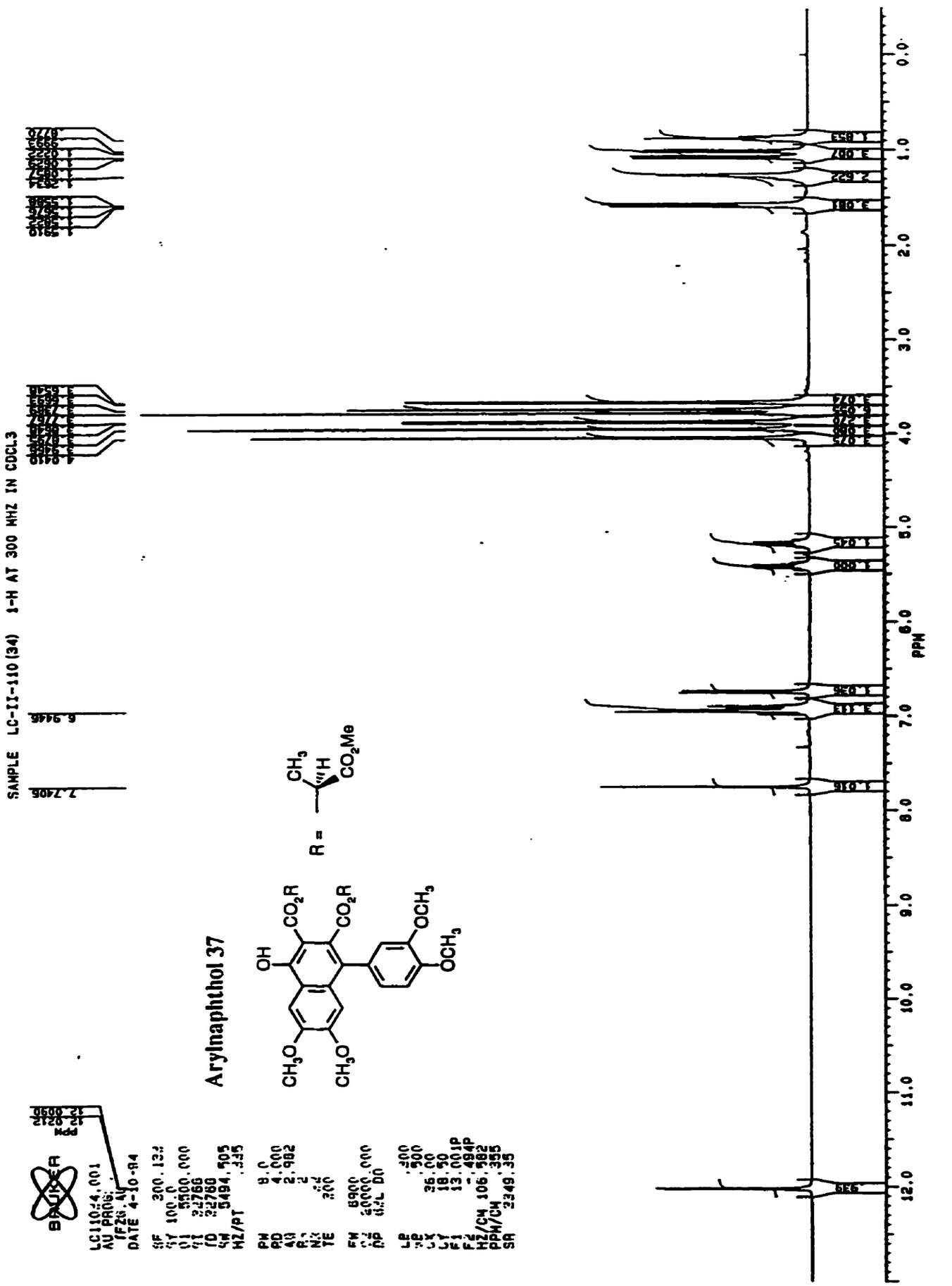

SAMPLE LC-II-121-B 1-H AT 300 MHZ IN CDCL3
Naphthalene 28
R =
PPM

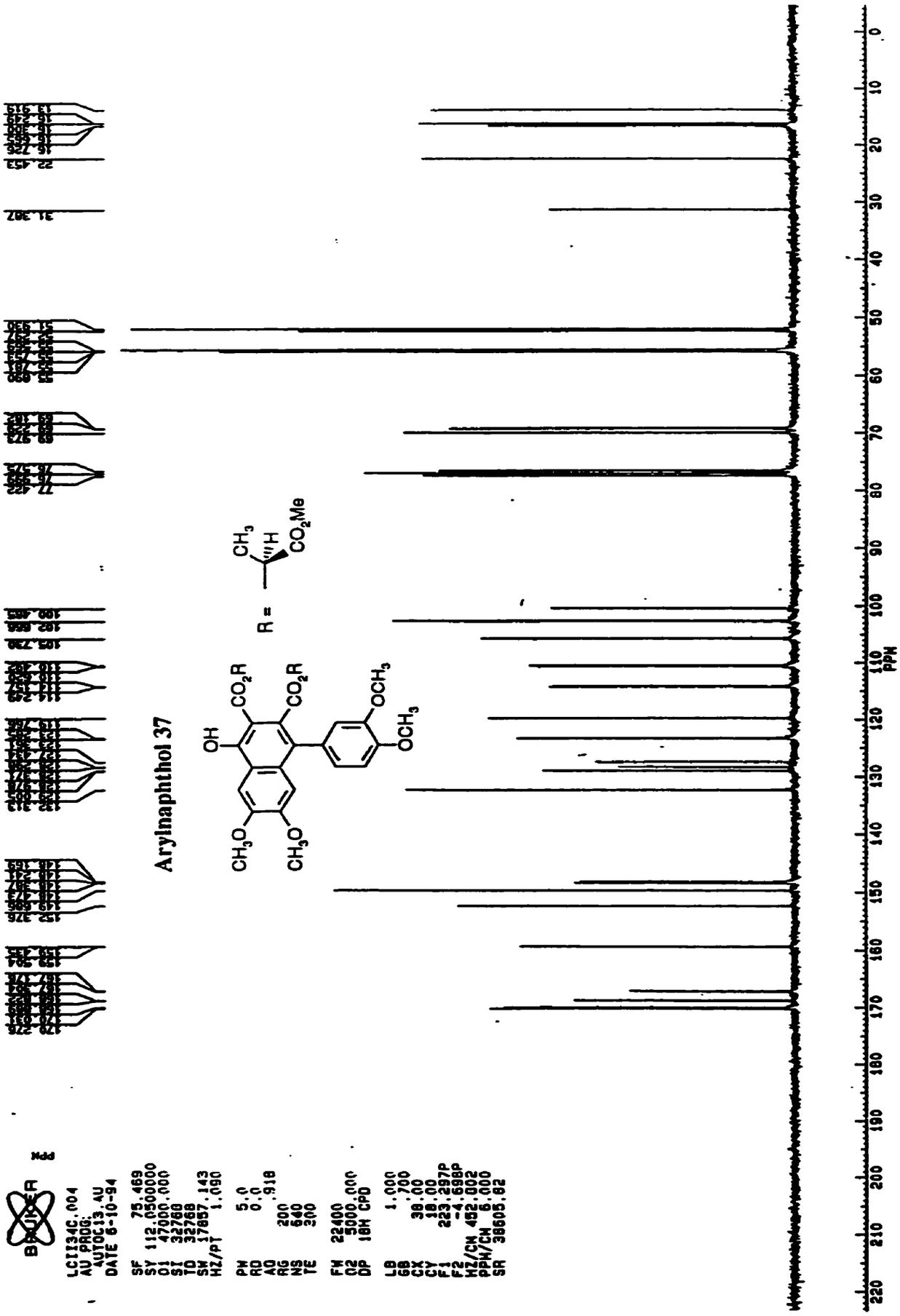

SAMPLE LC-II-121-B 13-C AT 75.47 MHZ IN CDCL3
Naphthalene 28
R =
CO2R
CO2R
CH3
H
CO2Me
LC121BC.004
AU PROG:
AUTOC13.AU
DATE 3-11-94
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 3200
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.427P
F2 -4.568P
HZ/CM 452.602
PPM/CM 6.000
SR 38596.01
PPM
PPM

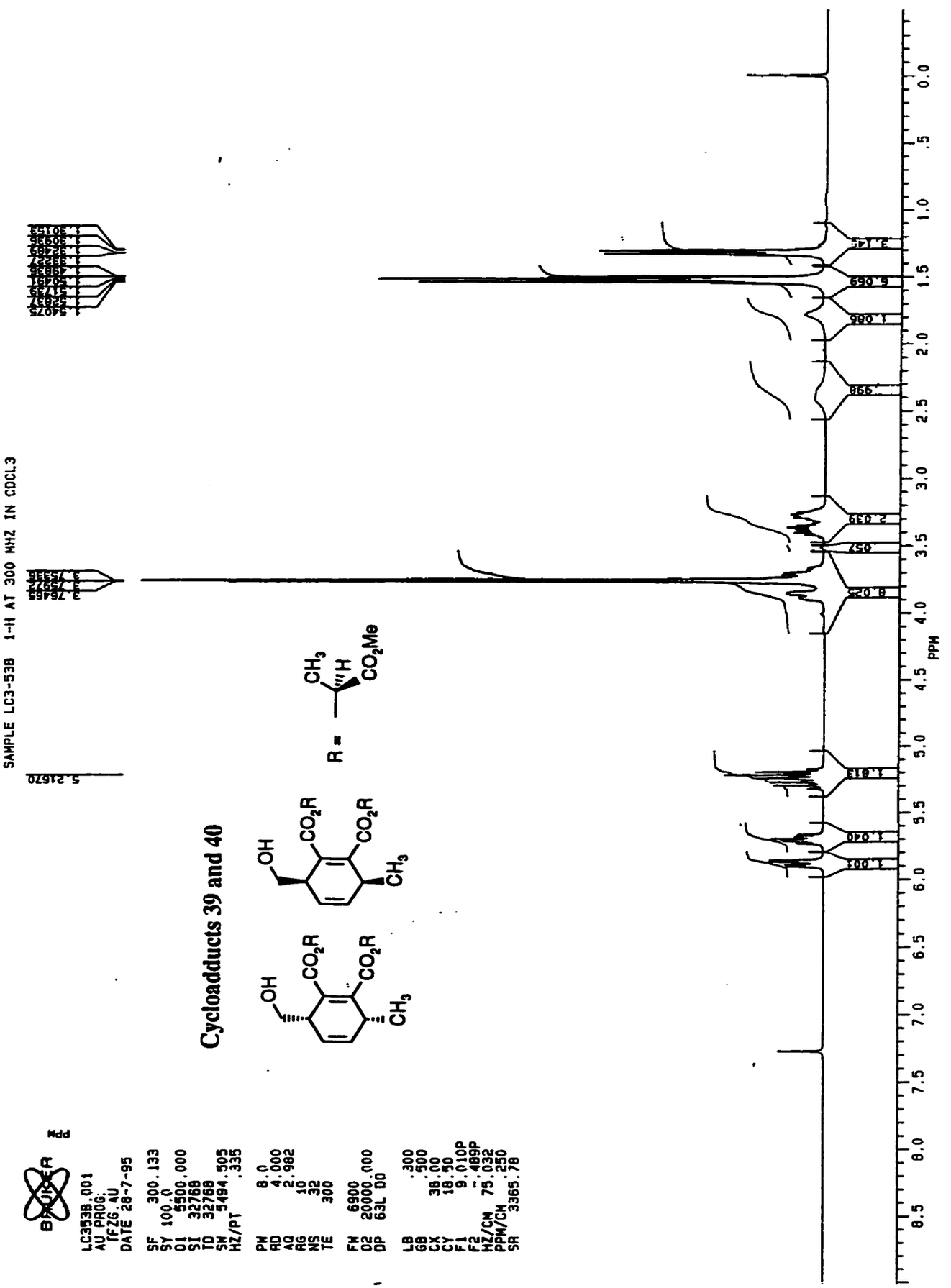

SAMPLE LC-II-080(36) 1-H AT 300 MHZ IN CDCL3
Cycloadducts 29 and 30
R =
CH3
H
CO2Me
CO2R
CO2R
OH
Ph
PPM
LCII8036.001
AU PROG:
IFIG.AU
DATE 23-8-94
SF 300.133
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
NS 40
DS 32
TE 300
FW 6900
DP 63L DD
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3368.60

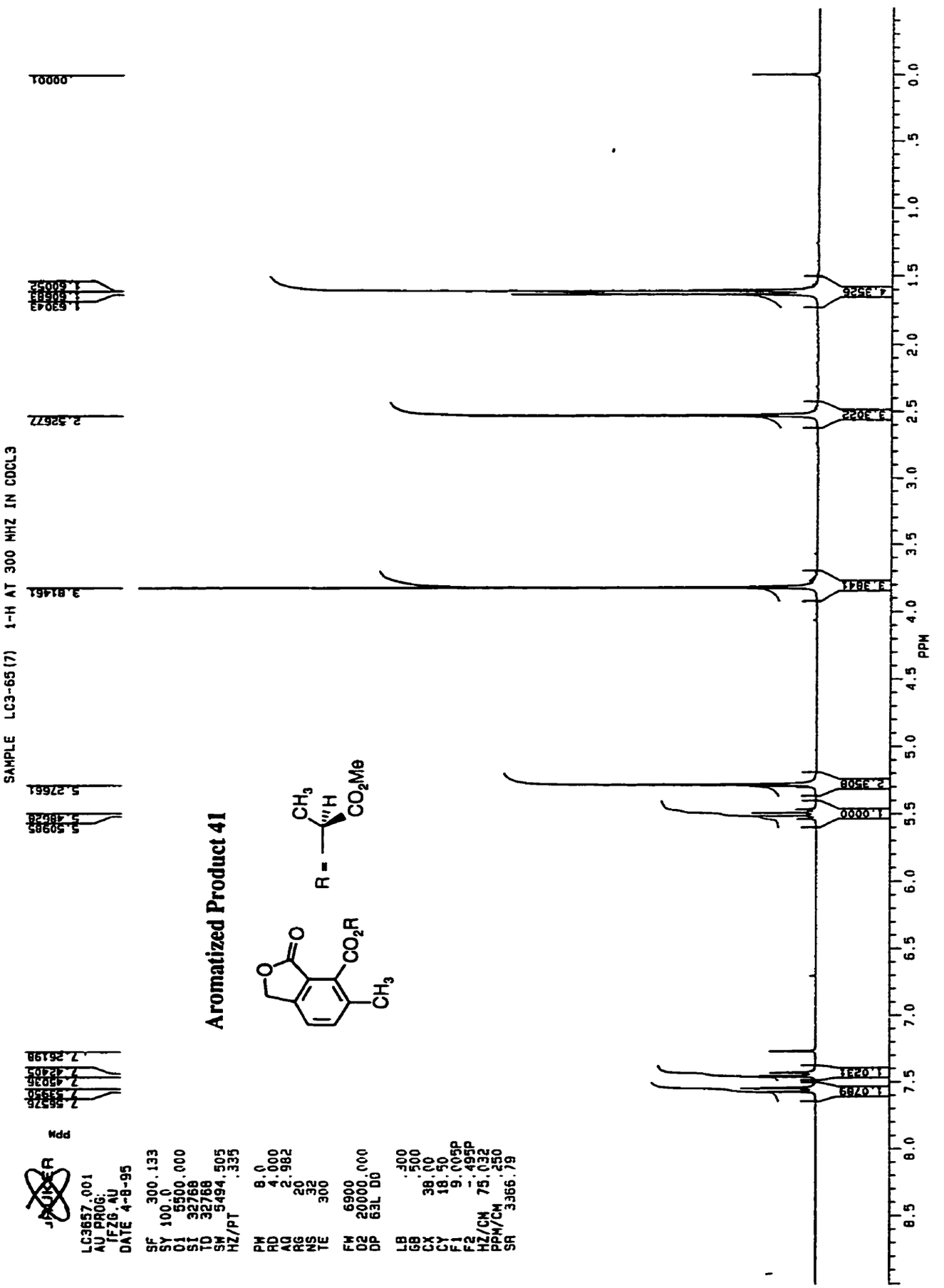

Cycloadduct 32
R =
CH3
H
CO2Me
CO2R
CO2R
Ph
HO
SAMPLE LC-II-113-R(6) 1-H AT 300 MHZ IN CDCL3
LC113R6.001
AU PROG:
(FZ6.AU
DATE 16-12-94
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 64
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.999P
F2 -.501P
HZ/CM 75.032
PPM/CM .250
SR 3369.14
PPM

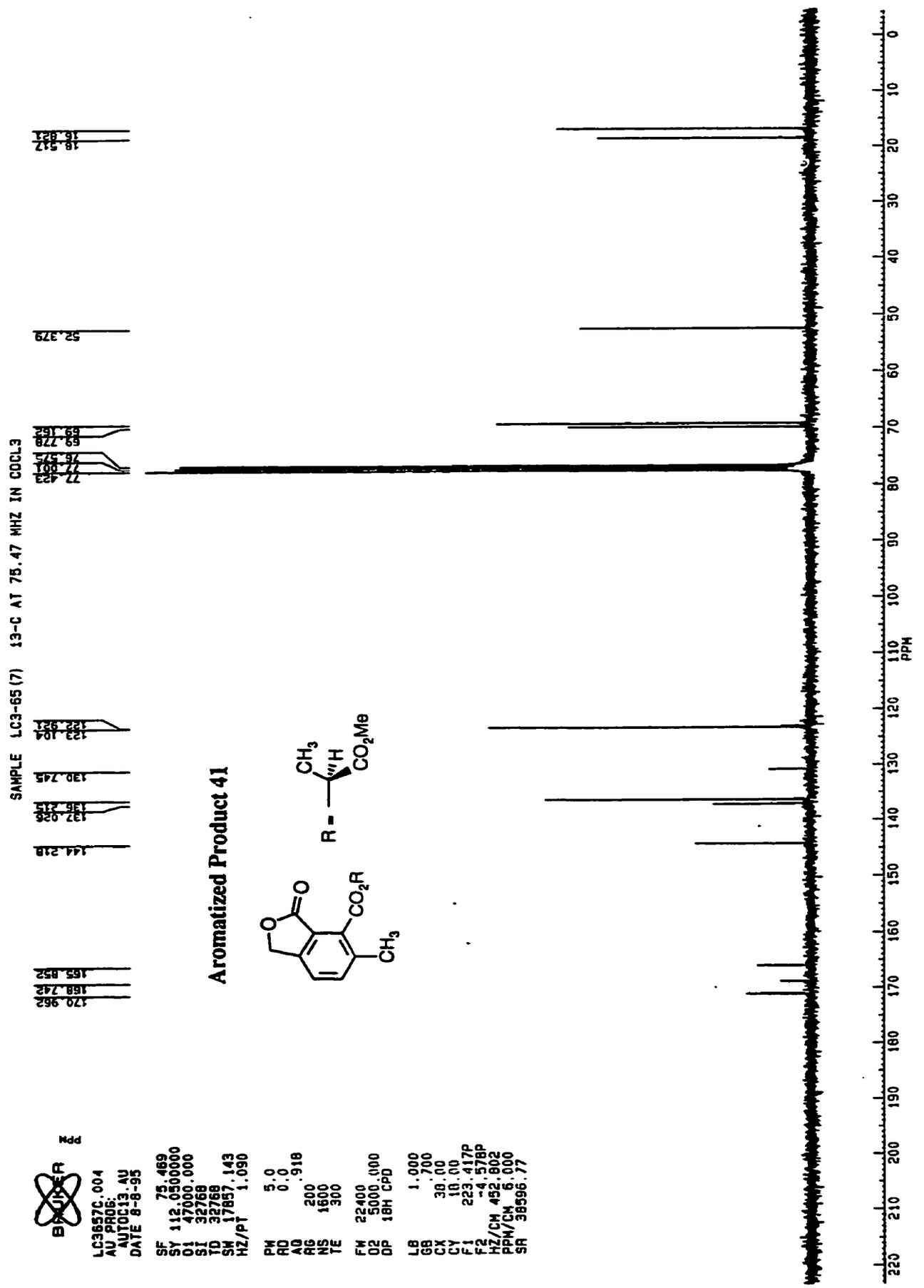

SAMPLE LC-II-113-R(6) 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
LC113R6C.004
AU PROG:
AUTOC13.AU
DATE 3-1-95
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 4608
TE 300
FW 22400
O2 5000.000
OP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 16.00
F1 223.402P
F2 -4.593P
HZ/CM 452.602
PPM/CM 6.000
SR 38597.86
Cycloadduct 32
CO2R
CO2R
HO
Ph
R =
CH3
H
CO2Me
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


SAMPLE LC-II-110(34) 1-H AT 300 MHZ IN CDCL3
Arylnaphthol 37
R =
PPM

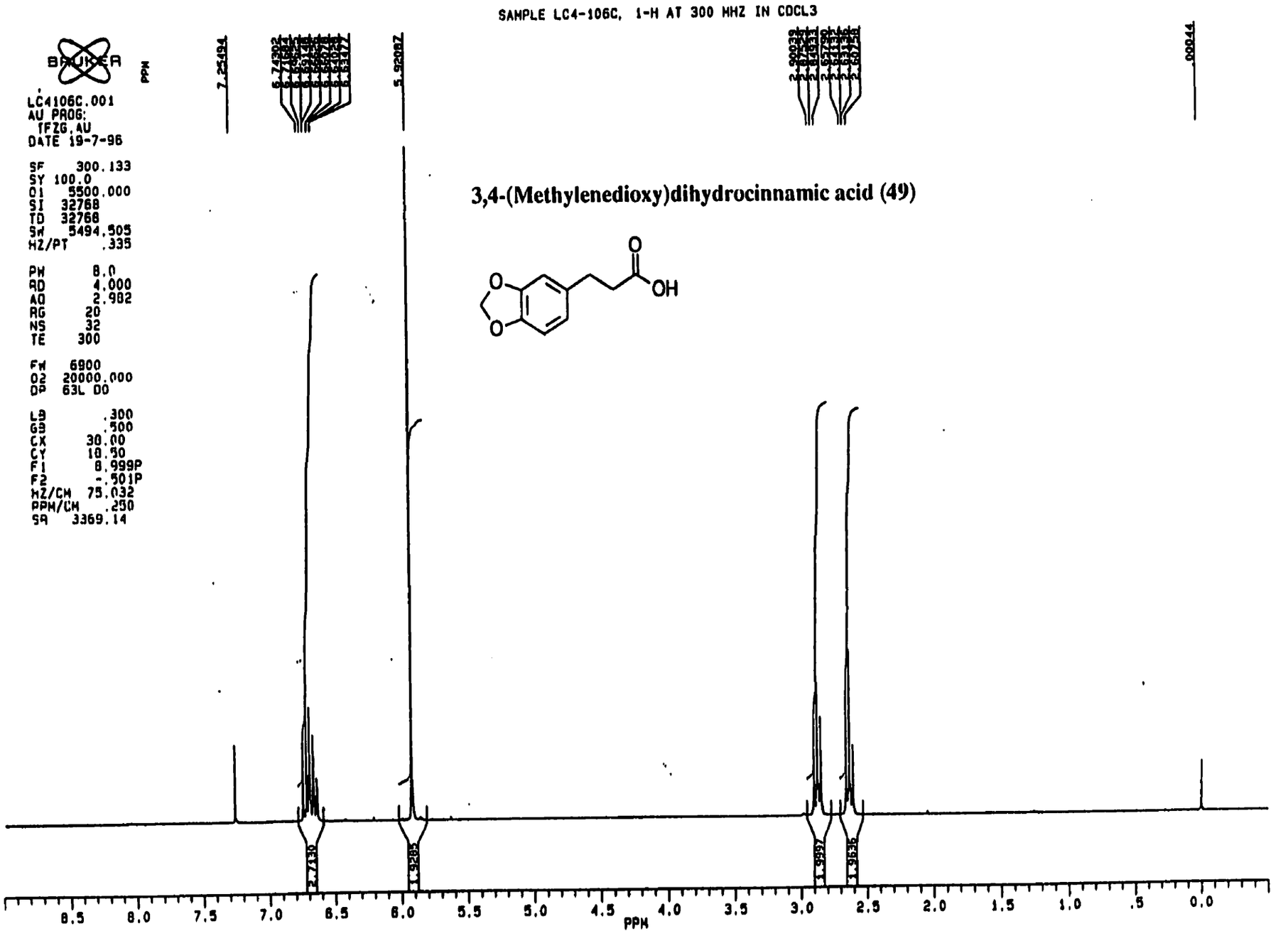

SAMPLE LC-II-110(34) 13-C AT 75.47 MHZ IN CDCL3
Arylnaphthol 37
OH
CO2R
CO2R
OCH3
OCH3
CH3O
CH3O
R =
CH3
H
CO2Me
PPM


SAMPLE LC3-53B 1-H AT 300 MHZ IN CDCL3
Cycloadducts 39 and 40
R =
CO2Me
CH3
H
OH
CO2R
CH3
PPM

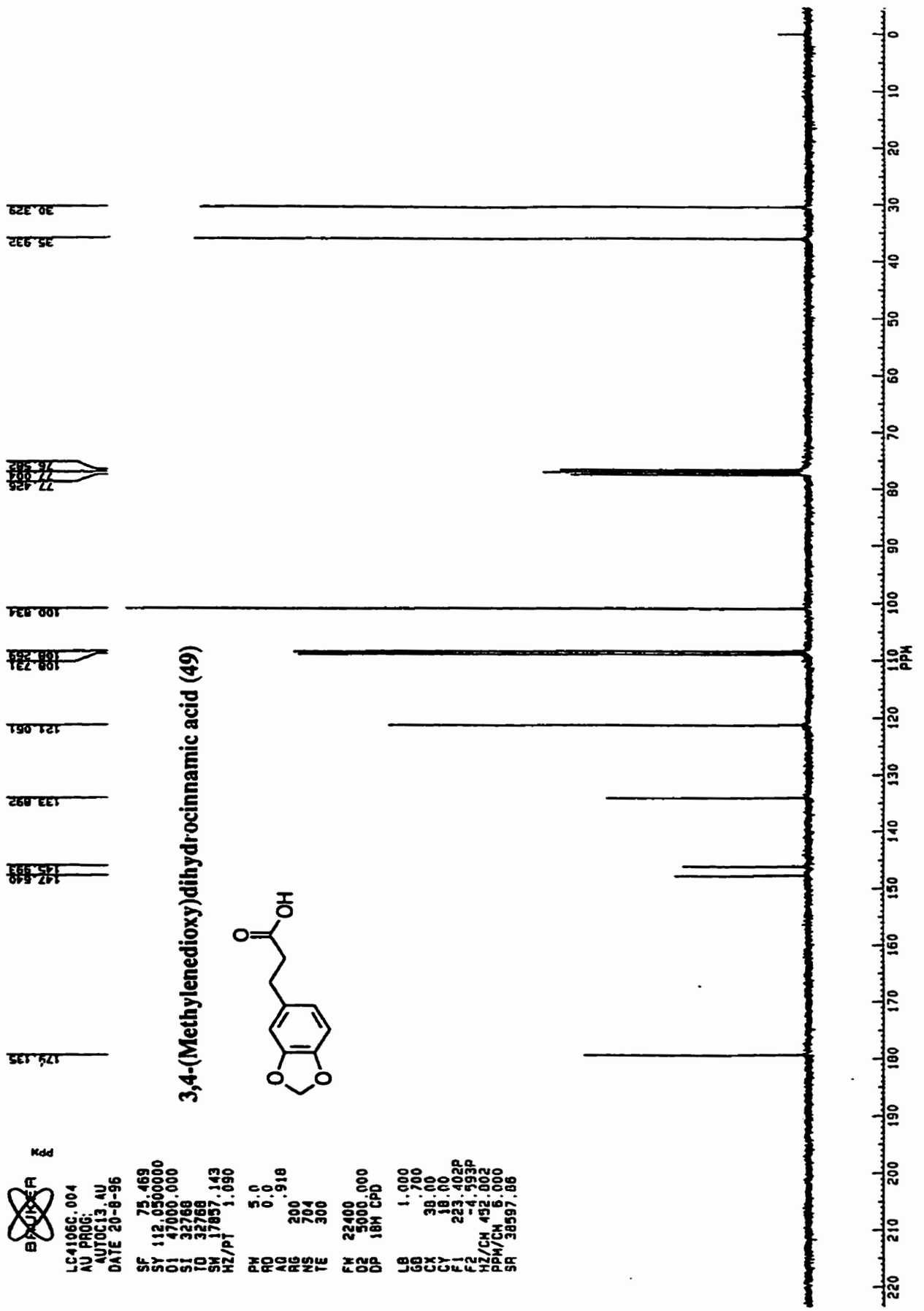

SAMPLE LC3-65(7) 1-H AT 300 MHZ IN CDCL3
Aromatized Product 41
R =
CH3
H
CO2Me
O
CO2R
CH3
PPM
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
4.3526
3.3022
3.3841
2.3508
1.0000
1.0234
1.0769
LC3657.001
AU PROG:
IFZG.AU
DATE 4-8-95
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DD
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3366.79

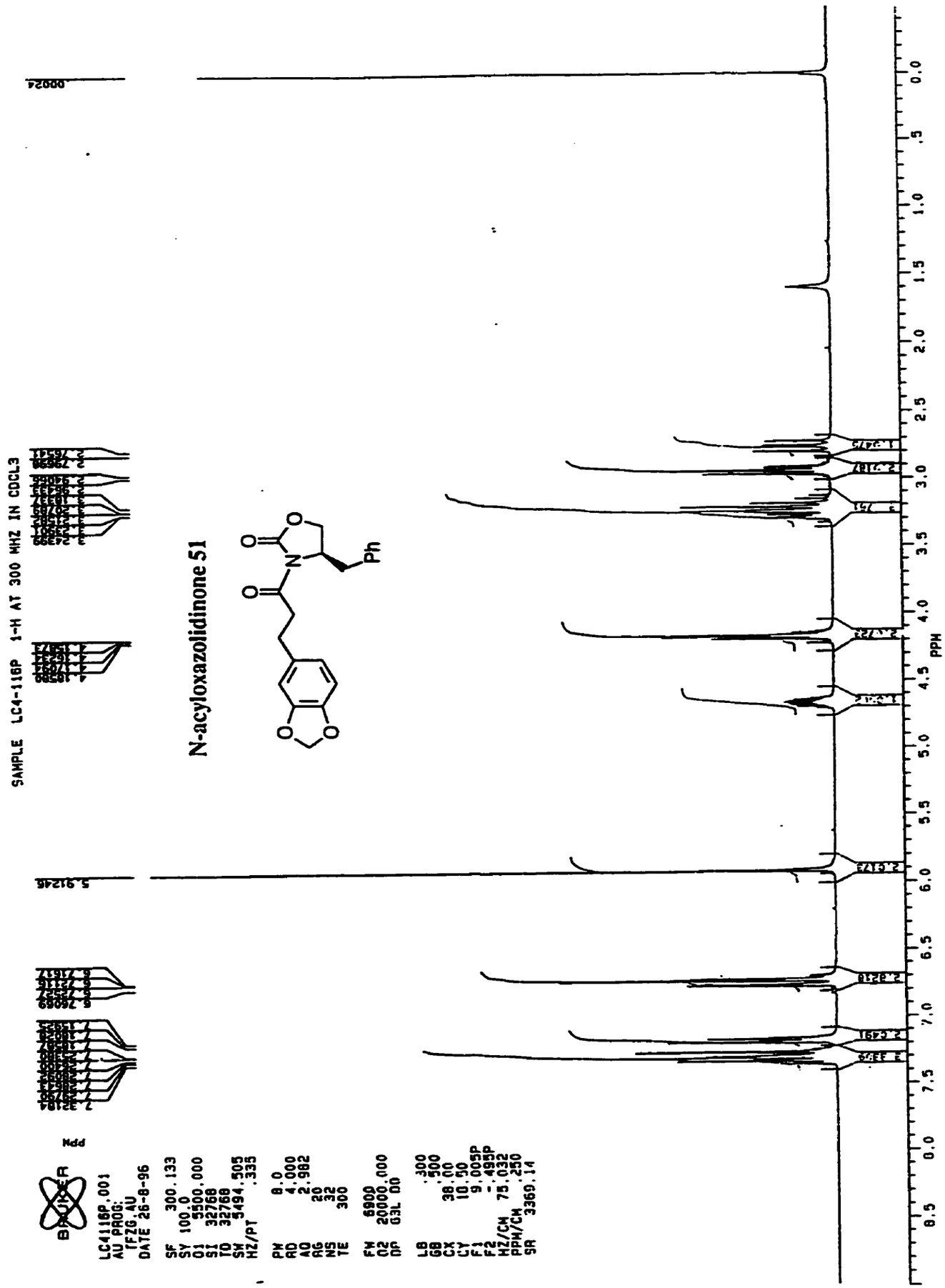

SAMPLE LC3-65(7) 13-C AT 75.47 MHZ IN COCL3
Aromatized Product 41
R =
CH3
H
CO2Me
O
O
CO2R
CH3
PPM

SAMPLE LC4-106C, 1-H AT 300 MHZ IN CDCL3

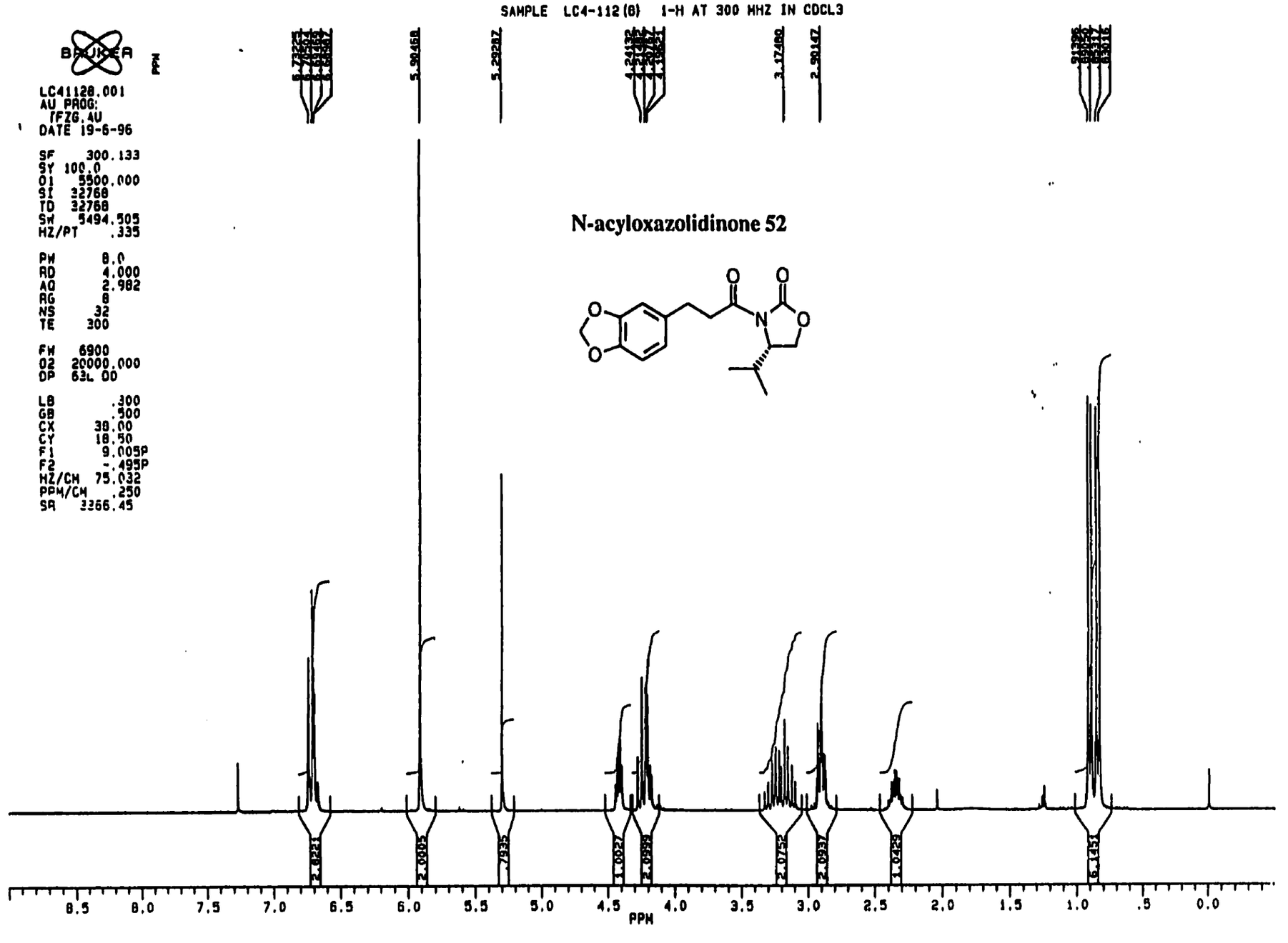


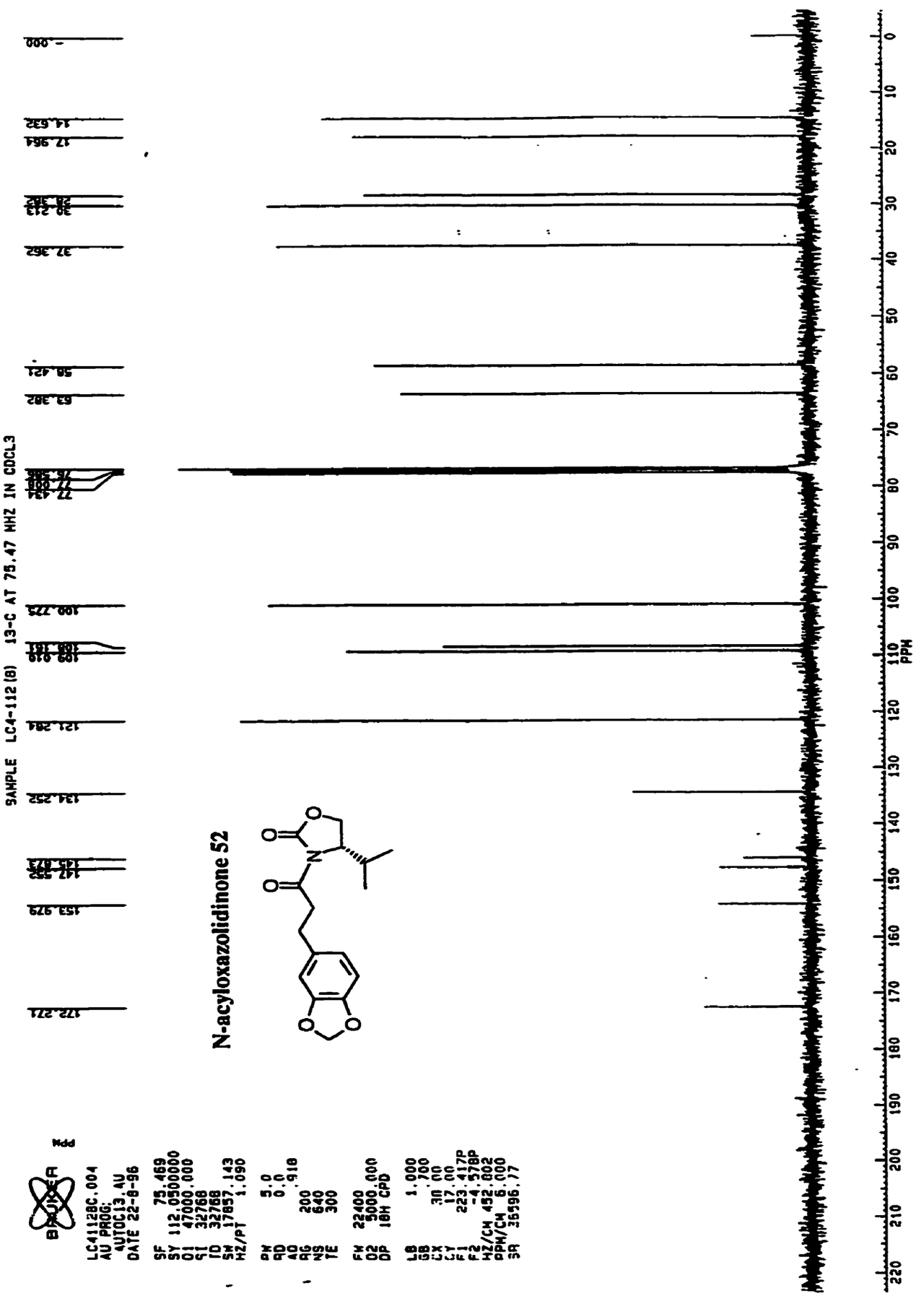
3,4-(Methylenedioxy)dihydrocinnamic acid (49)

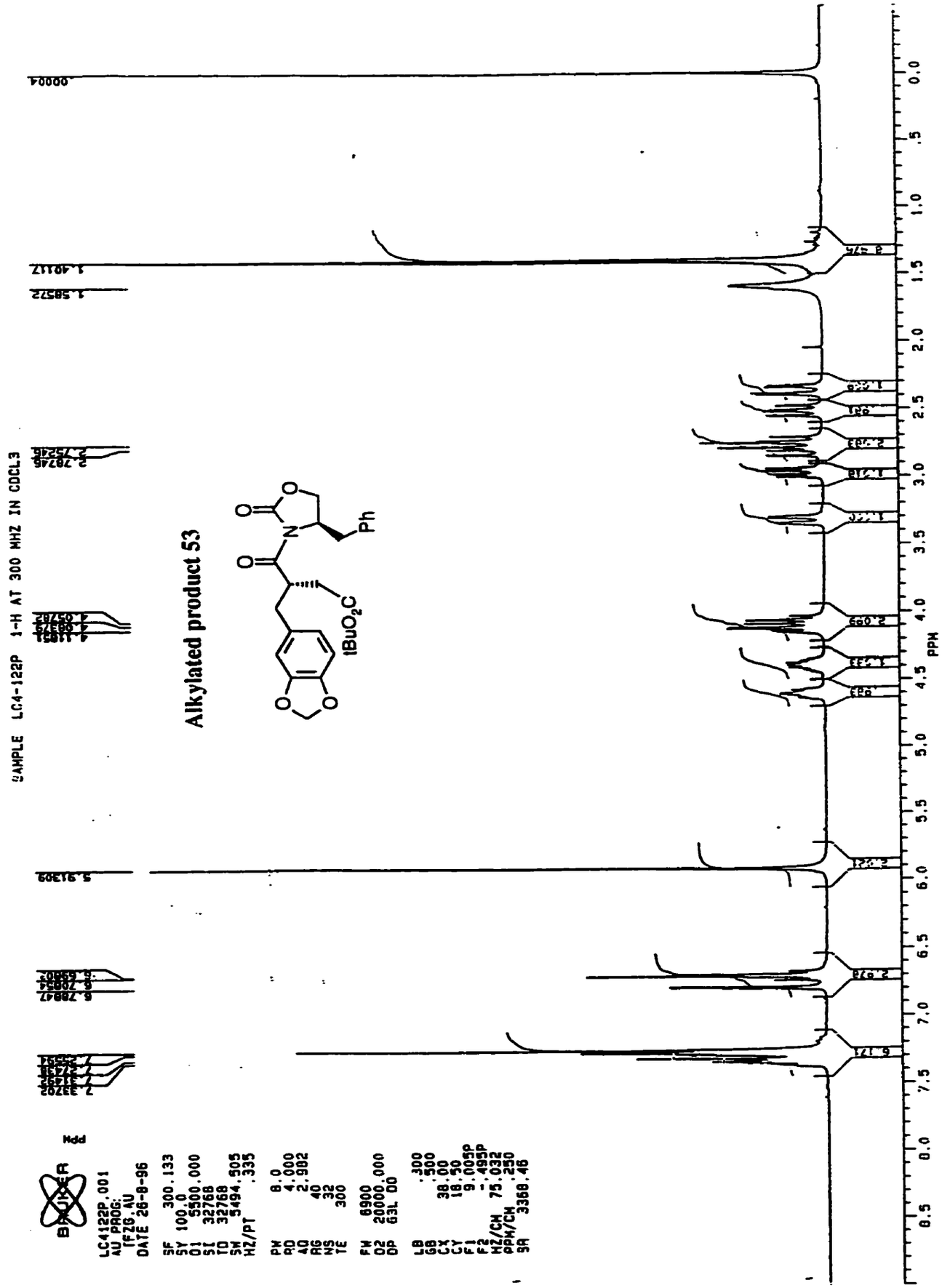

SAMPLE LC4-106 13-C AT 75.47 MHZ IN CDCL3
3,4-(Methylenedioxy)dihydrocinnamic acid (49)
OH
O
O
O
LC4106C.004
AU PROG:
AUTOC13.AU
DATE 20-8-96
SF 75.469
SY 112.0500000
OI 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ 0.918
RG 200
NS 704
TE 300
FW 22400
O2 5000.000
DP 18M CPD
LB 1.000
GB .700
CX 30.00
CY 18.00
F1 223.402P
F2 -4.593P
HZ/CM 492.002
PPM/CM 6.000
SR 38597.86
PPM

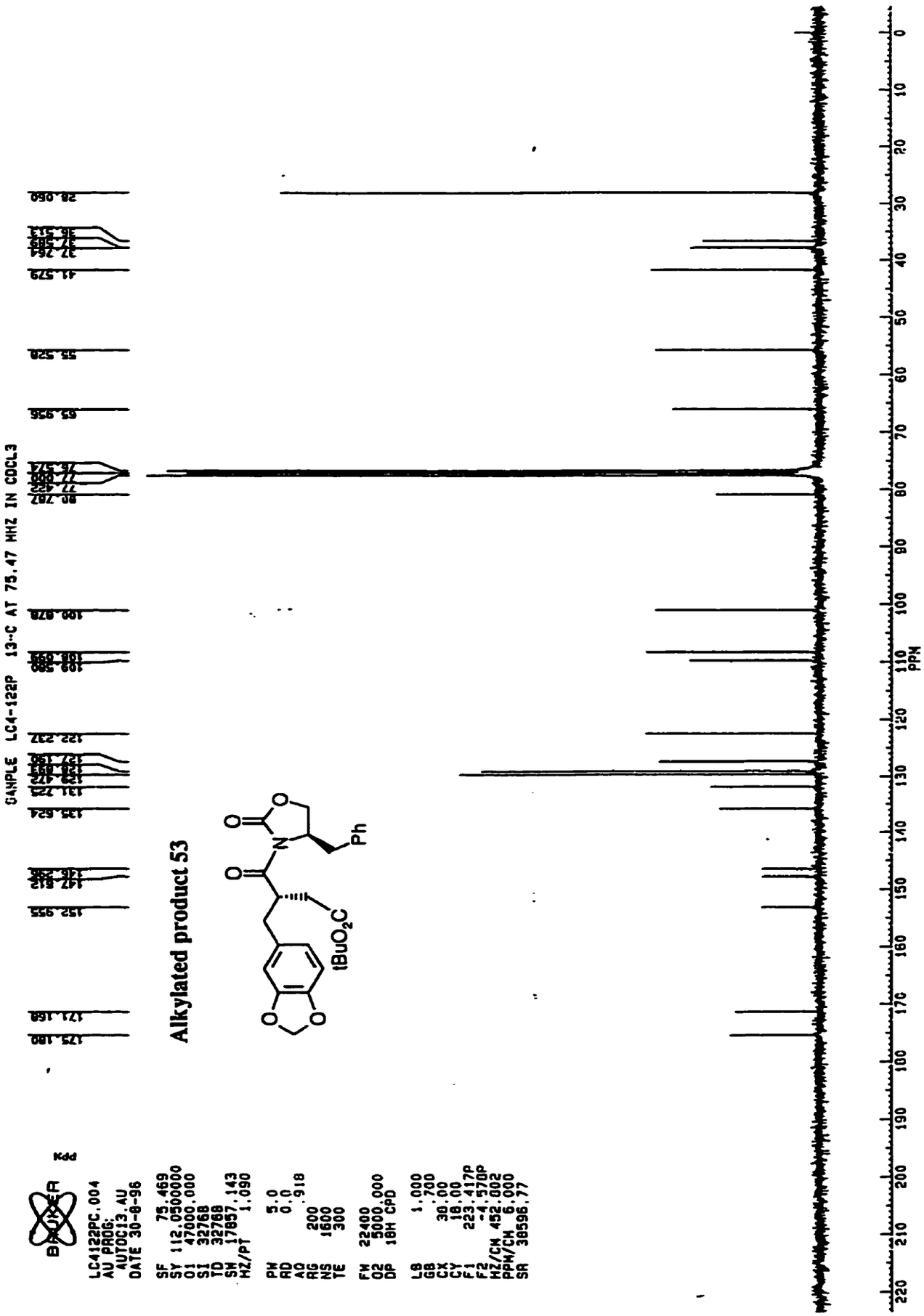

N-acyloxazolidinone 51
Ph
SAMPLE LC4-116P 1-H AT 300 MHZ IN CDCL3
LC4116P.001
AU PROG:
[FZG.AU
DATE 26-8-96
SF 300.133
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
AG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP D3L D0
LB .300
GB .500
CX 38.00
CY 10.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3369.14
PPM

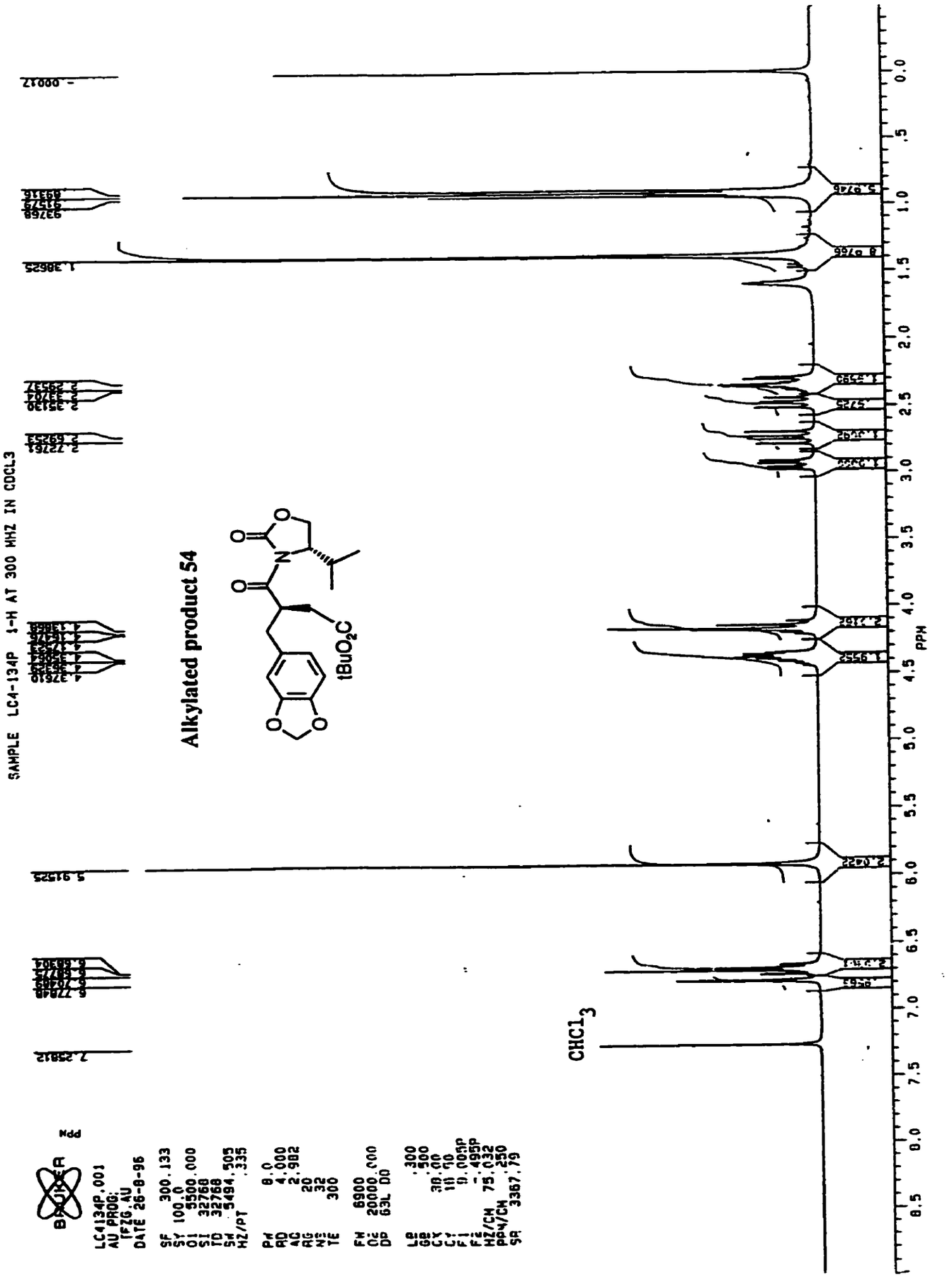

SAMPLE LC4-116P 13-C AT 75.47 MHZ IN CDCL3
N-acyloxazolidinone 51
Ph
O
N
O
O
O
O
LC4116PC.004
AU PROG:
AUTOC13.AU
DATE 29-8-96
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1600
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.402P
F2 -4.593P
HZ/CM 452.802
PPM/CM 6.000
SR 38597.06
PPM
PPM

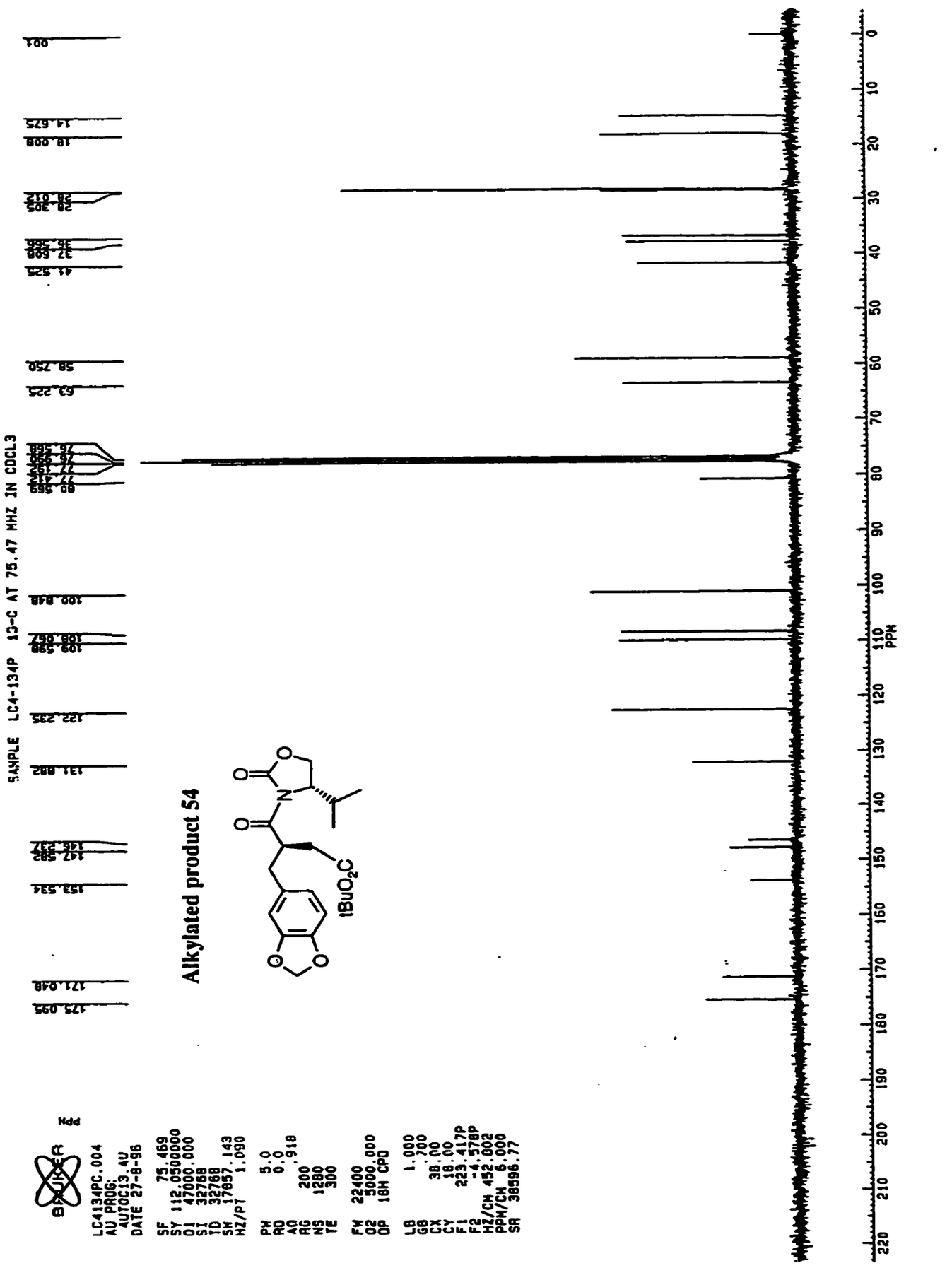

SAMPLE LC4-112(8) 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
LC41128.001
AU PROG:
ZFZG.AU
DATE 19-6-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 8
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3366.45
N-acyloxazolidinone 52
PPM

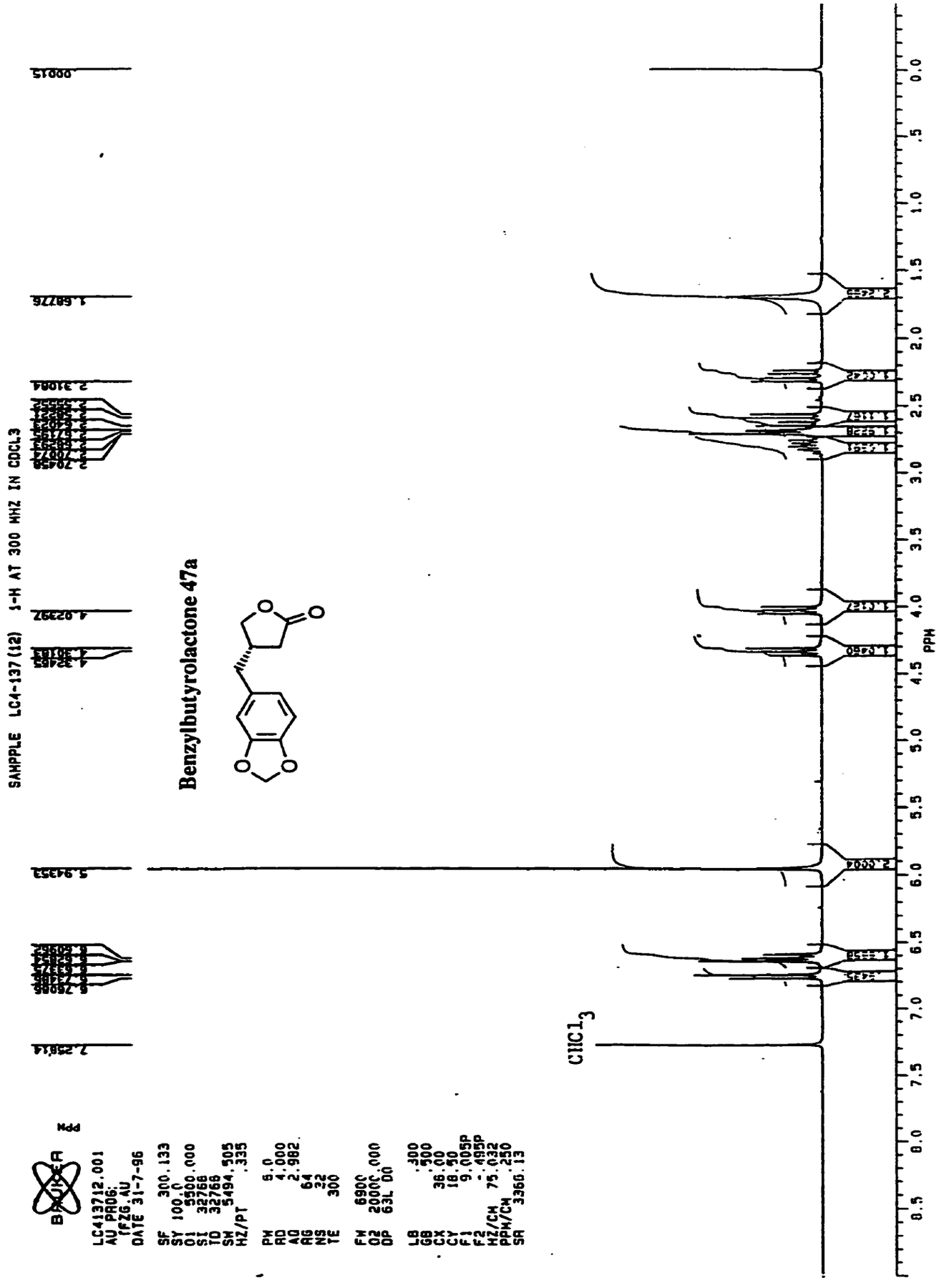

SAMPLE LC4-112(8) 13-C AT 75.47 MHZ IN CDCL3
N-acyloxazolidinone 52
BRUKER
LC41128C.004
AU PROG:
AUTOC13.AU
DATE 22-8-96
SF 75.469
SY 112.0500000
OI 47000.000
SI 32768
ID 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 640
TE 300
FW 22400
O2 5000.000
DP 10H CPD
LB 1.000
GB .700
GX 30.00
GY 17.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 35196.77
PPM
PPM

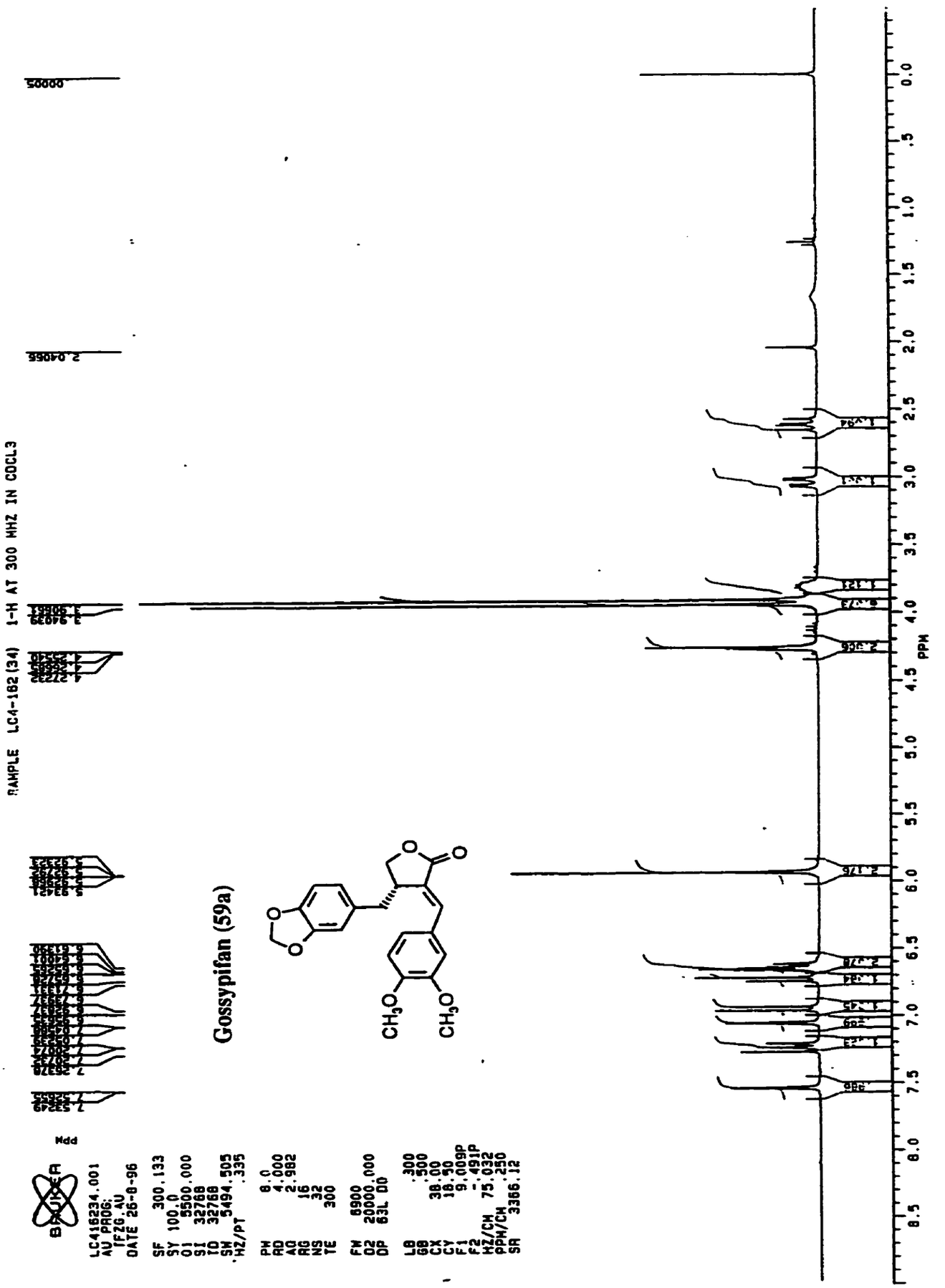

SAMPLE LC4-122P 1-H AT 300 MHZ IN CDCL3
Alkylated product 53
Ph
tBuO2C
PPM
LC4122P.001
AU PROG:
[FZG.AU
DATE 28-8-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
PD 4.000
AQ 2.982
RG 40
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.0059P
F2 -.495P
HZ/CM 75.0332
PPM/CM .250
9R 3368.46

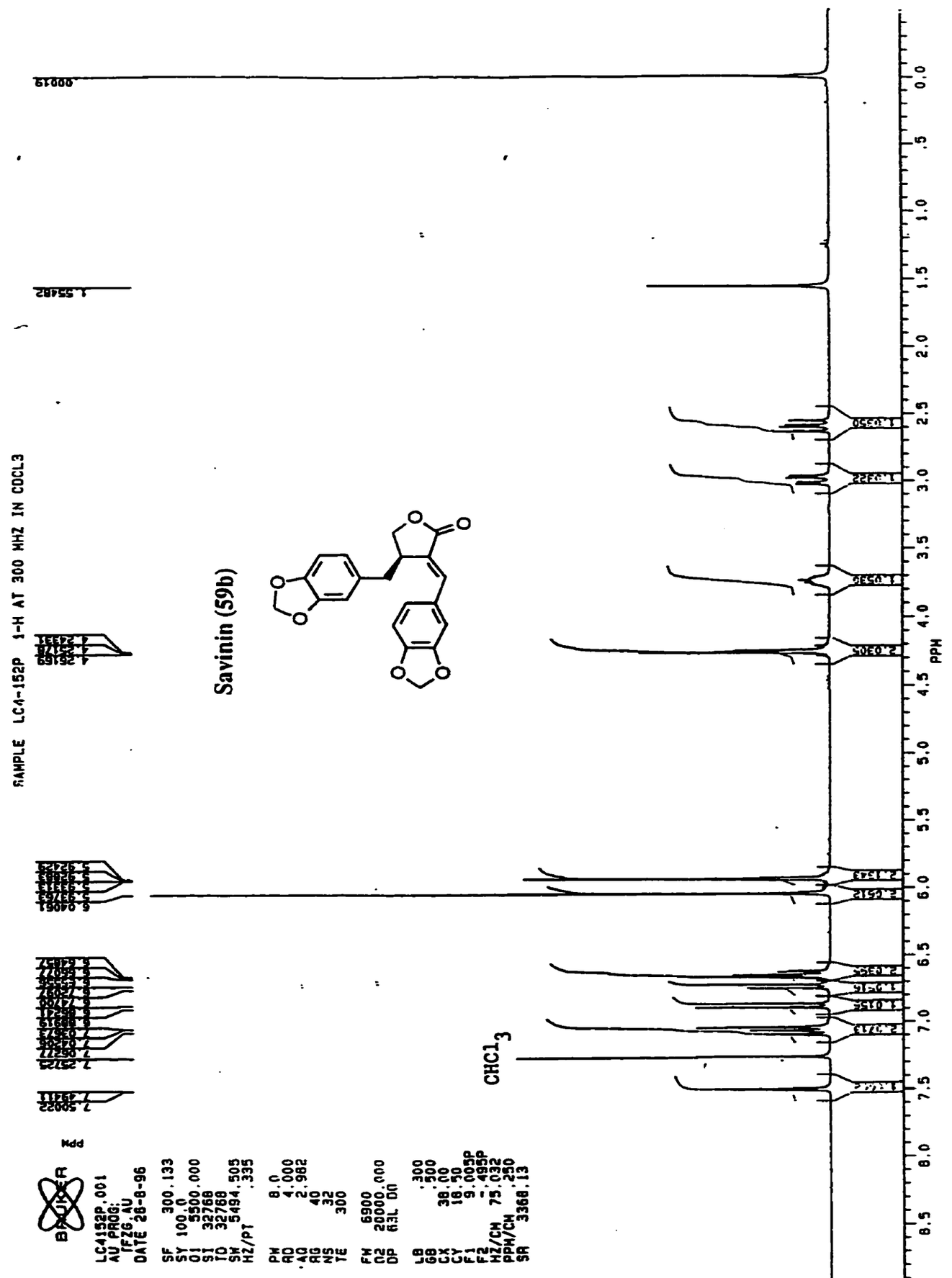

Alkylated product 53
SAMPLE LC4-122P 13-C AT 75.47 MHZ IN CDCL3
LC4122PC.004
AU PROG:
AUTOC13.AU
DATE 30-8-96
SF 75.469
SY 112.0500000
O1 47000.000
S1 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AO .918
RG 200
NS 1600
TE 300
FM 22400
O2 5000.000
DP 16H CPD
LB 1.000
GB .700
CX 30.00
CY 18.00
F1 223.417P
F2 -4.570P
HZ/CM 452.002
PPM/CM 6.000
SR 38596.77
PPM
tBuO2C
Ph

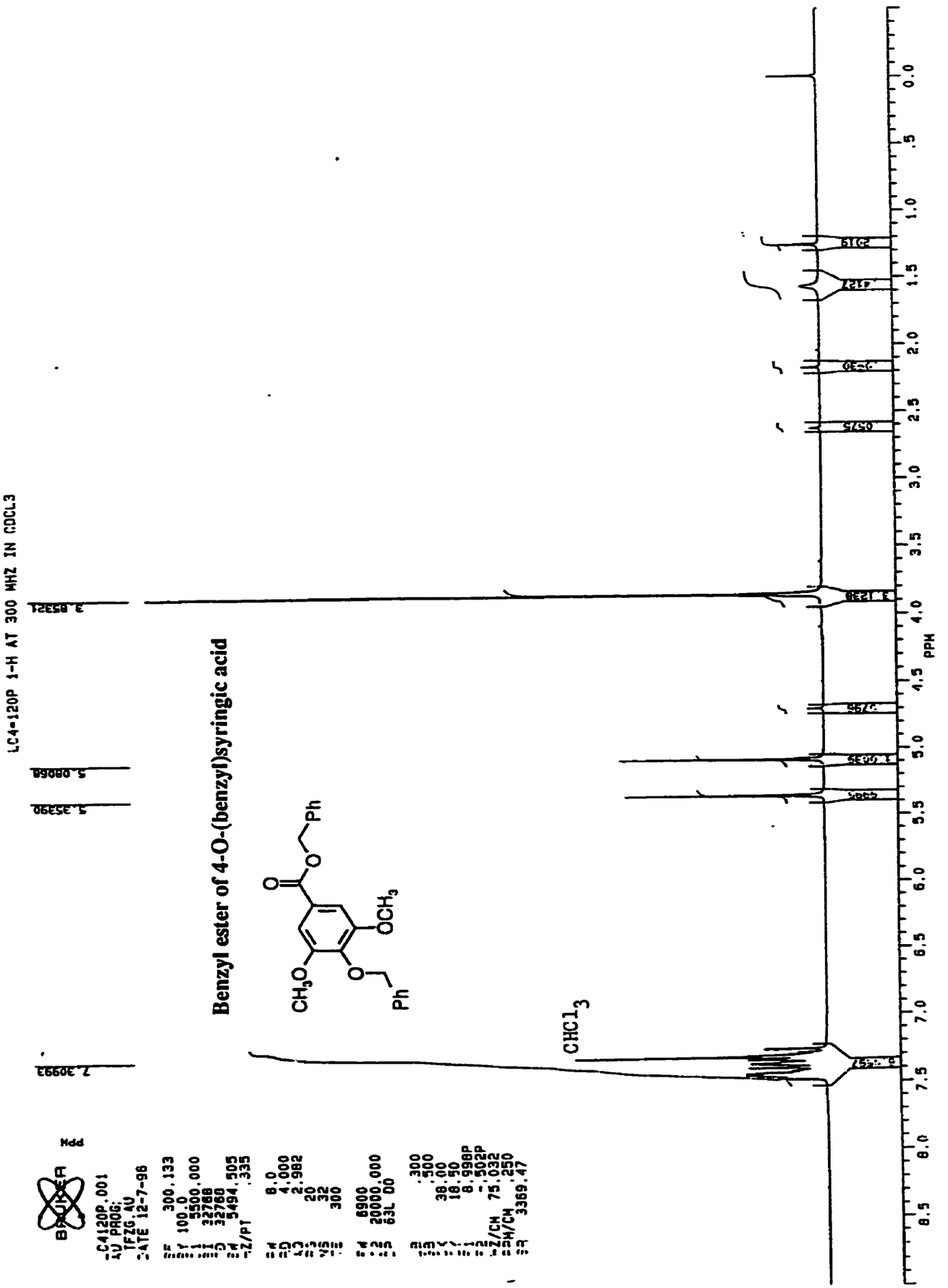

SAMPLE LC4-134P 1-H AT 300 MHZ IN CDCL3
Alkylated product 54
tBuO2C
CHCl3
PPM
LC4134P.001
DATE 26-8-96
SF 300.133
SW 5494.505
HZ/PT .335
PW 8.0
AQ 2.982
TE 300
FW 6900
DB 63L DD
HZ/CM 75.032
PPM/CM .250
SR 3367.79

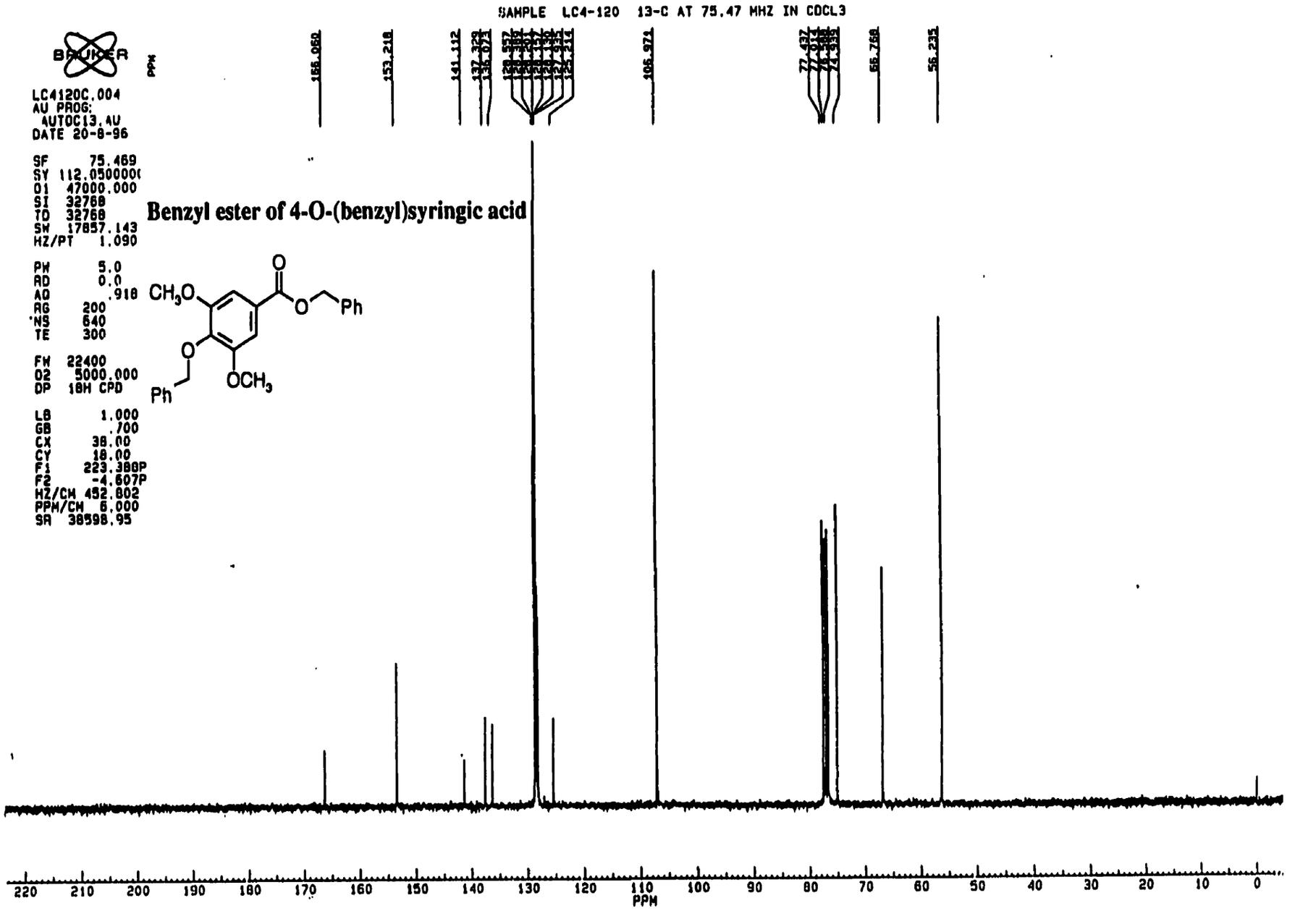

SAMPLE LC4-134P 13-C AT 75.47 MHZ IN CDCL3
Alkylated product 54
tBuO2C
BRUKER
LC4134PC.004
AU PROG:
AUTOC13.4U
DATE 27-8-96
SF 75.469
SY 112.0500000
DI 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1280
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.4117P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77
PPM

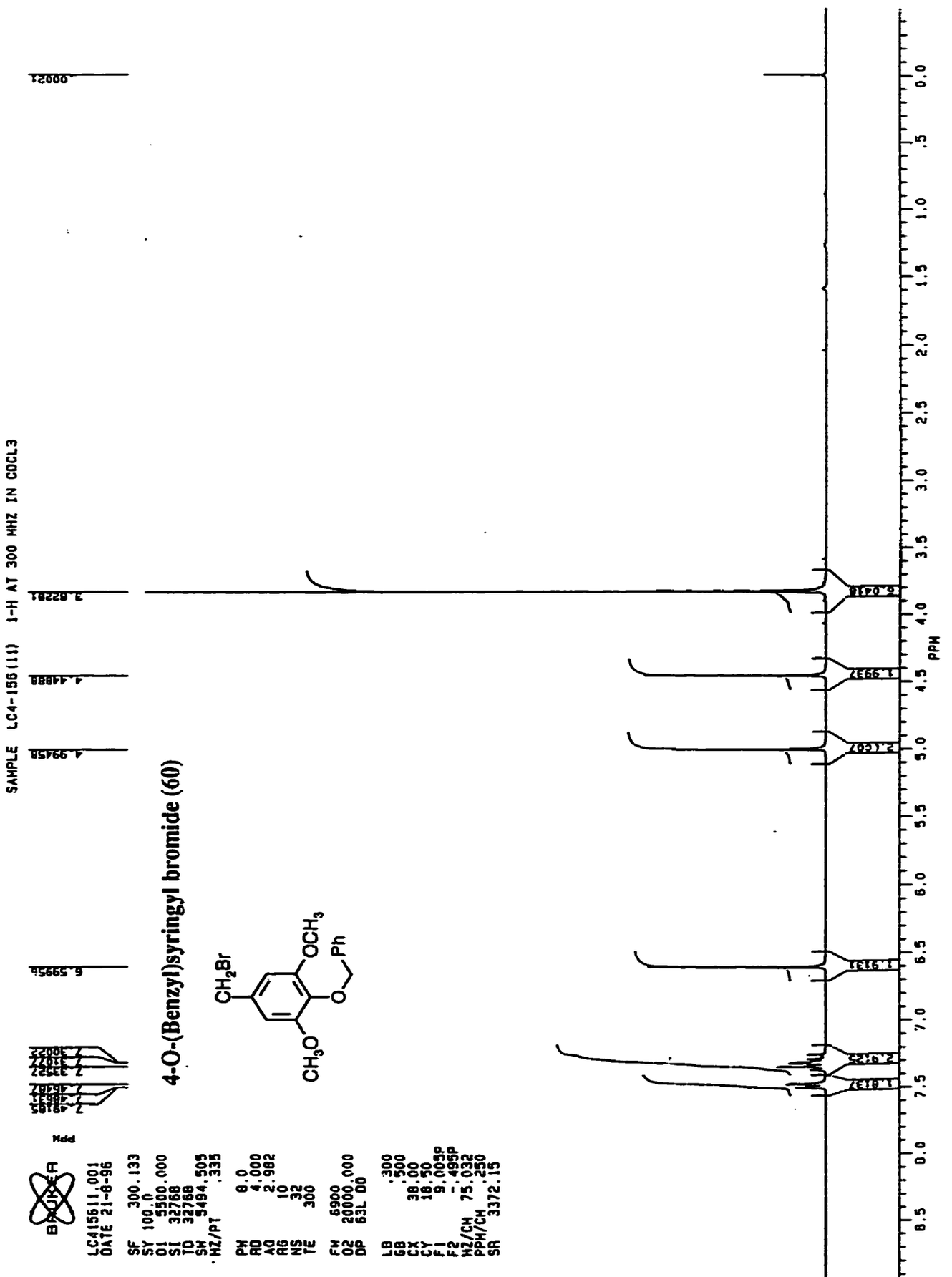

SAMPLE LC4-137(12) 1-H AT 300 MHZ IN CDCL3
Benzylbutyrolactone 47a
CHCl3
PPM

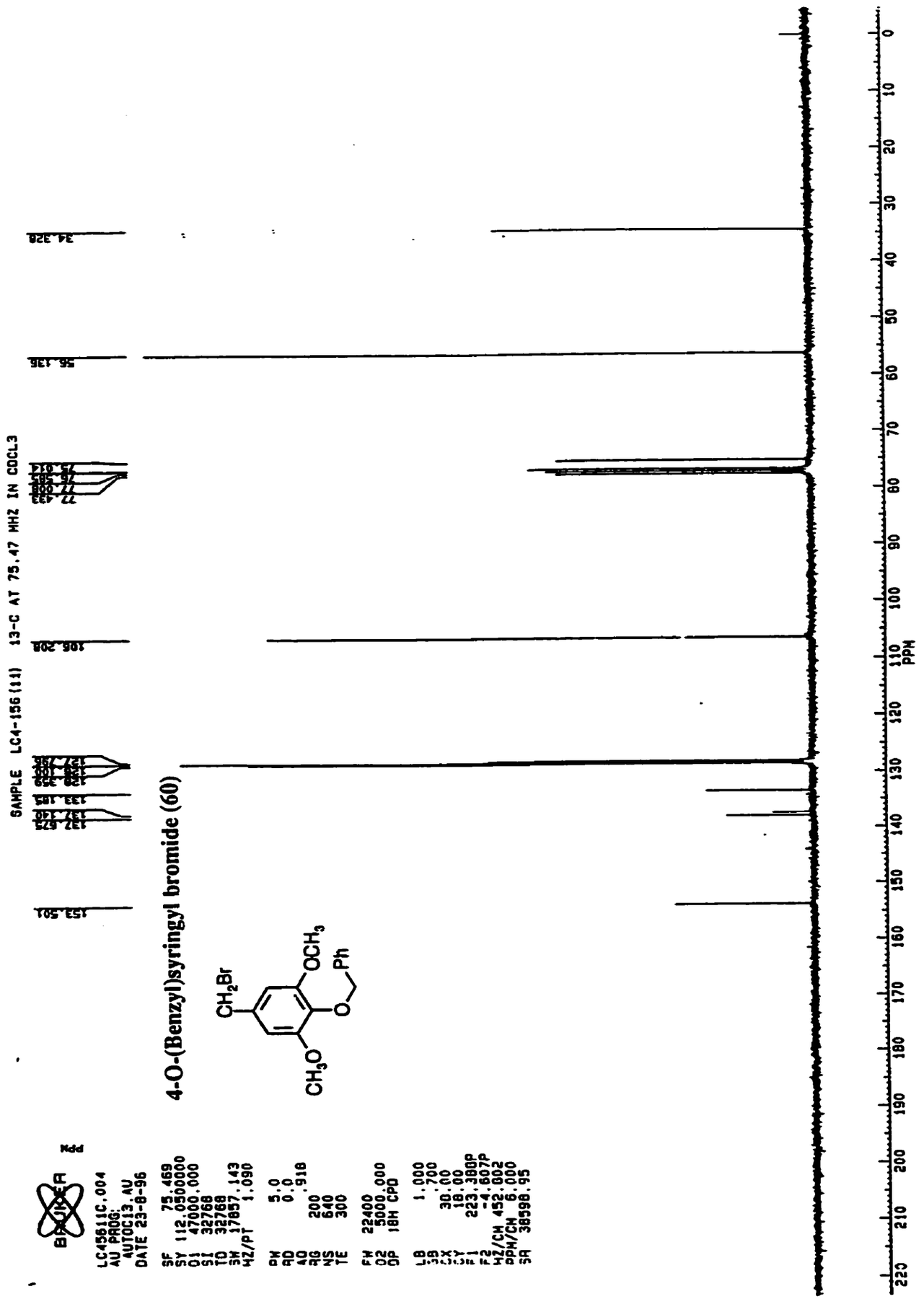

Gossypifan (59a)
SAMPLE LC4-162(34) 1-H AT 300 MHZ IN CDCL3
LC416234.001
AU PROG:
TFZG.AU
DATE 26-6-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AG 2.982
RG 16
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.009P
F2 .491P
HZ/CM 75.032
PPM/CM .250
SR 3366.12
PPM

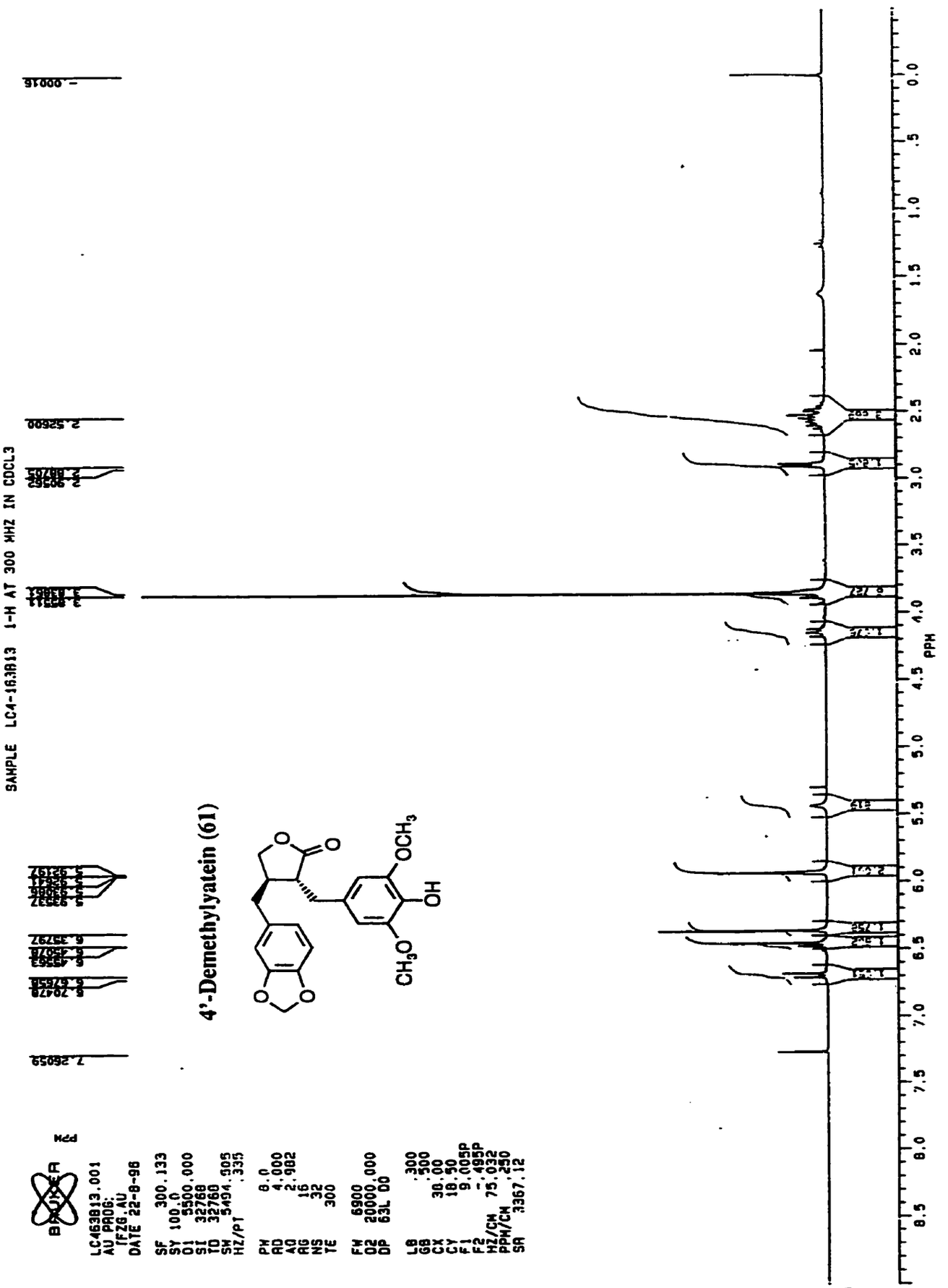

SAMPLE LC4-152P 1-H AT 300 MHZ IN CDCL3
Savinin (59b)
CHCl3
PPM

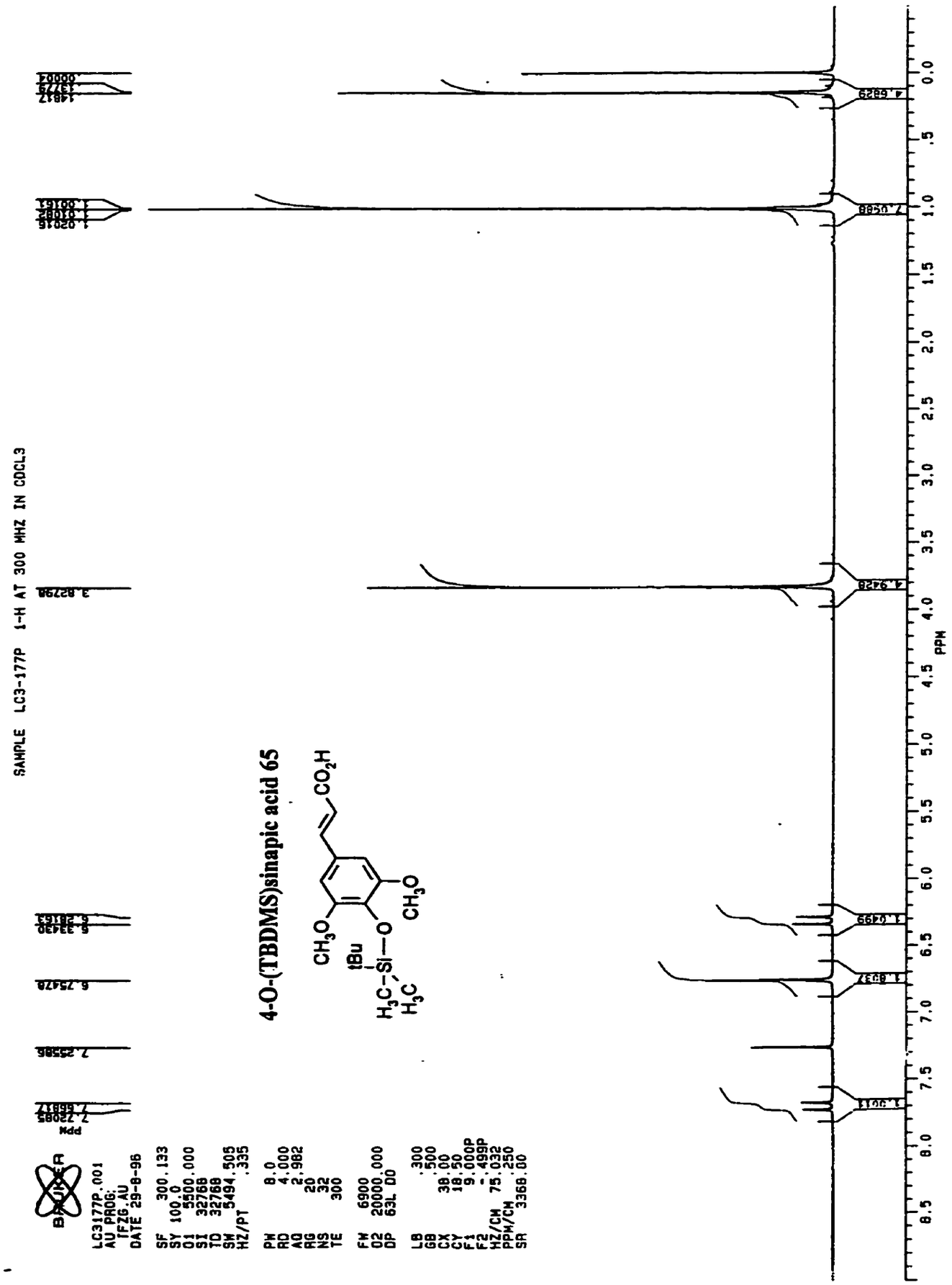

LC4-120P 1-H AT 300 MHZ IN CDCL3
Benzyl ester of 4-O-(benzyl)syringic acid
CHCl3
PPM

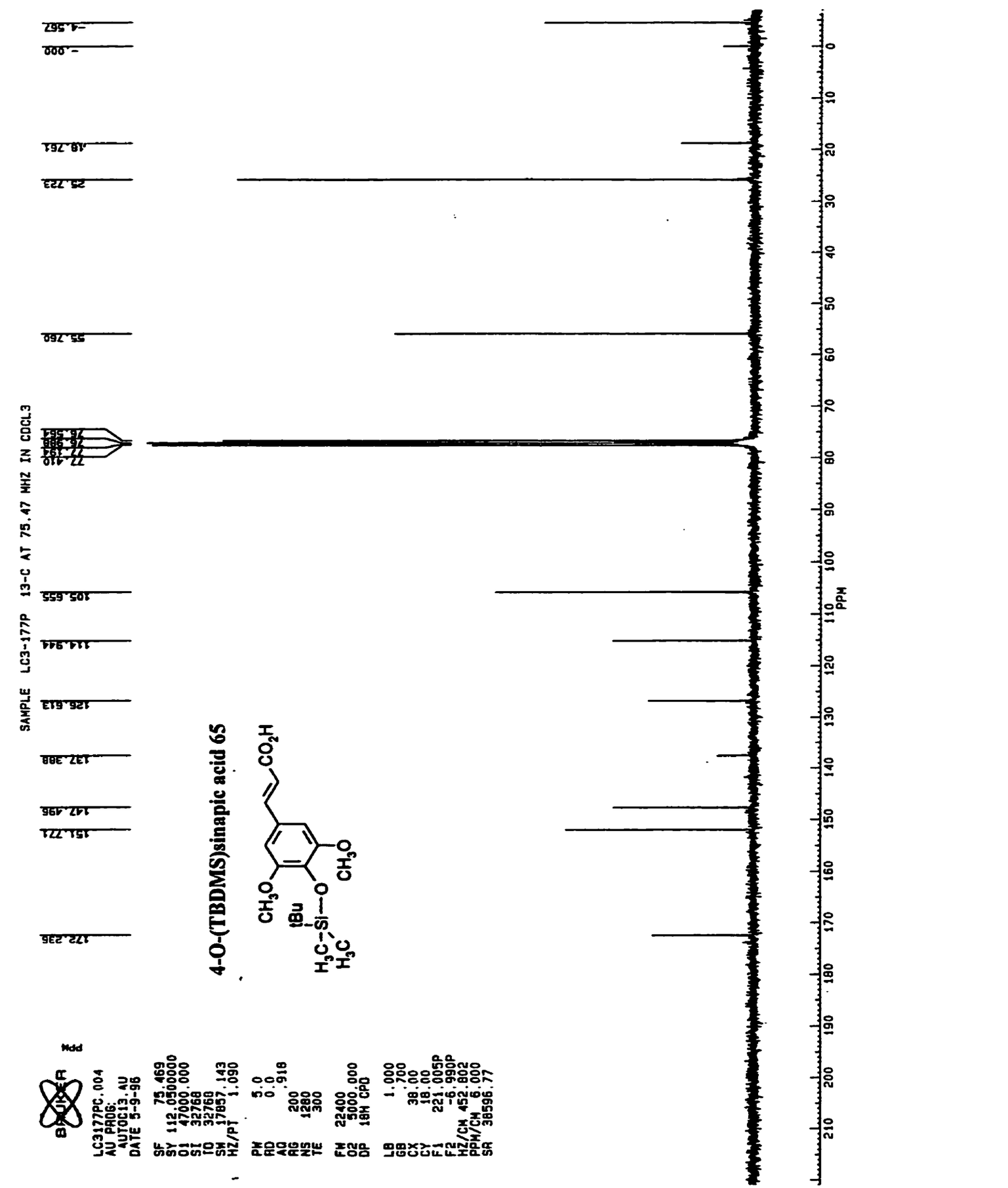

SAMPLE LC4-120 13-C AT 75.47 MHZ IN COCL3
BRUKER
PPM
166.060
153.218
141.112
137.329
136.872
106.971
77.437
66.768
56.235
LC4120C.004
AU PROG:
AUTOC13.AU
DATE 20-8-96
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 640
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.388P
F2 -4.607P
HZ/CM 452.802
PPM/CM 6.000
SR 38598.95
Benzyl ester of 4-O-(benzyl)syringic acid
CH3O
O
O
Ph
O
Ph
OCH3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

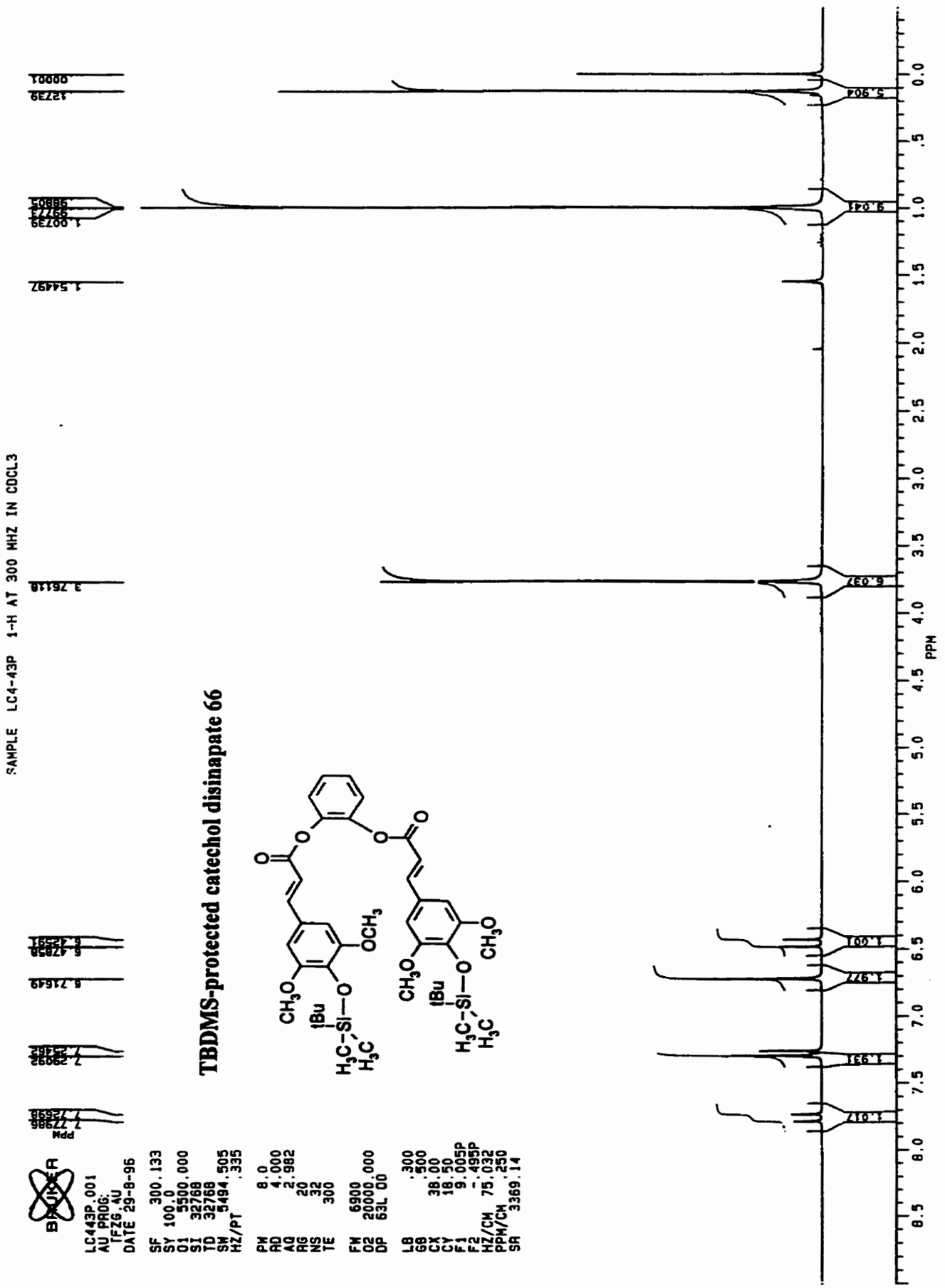

SAMPLE LC4-156(11) 1-H AT 300 MHZ IN CDCL3
4-O-(Benzyl)syringyl bromide (60)
CH_2Br
OCH_3
Ph
CH_3O
LC4156111.001
DATE 21-8-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 10
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CH 75.032
PPM/CH .250
SR 3372.15
PPM

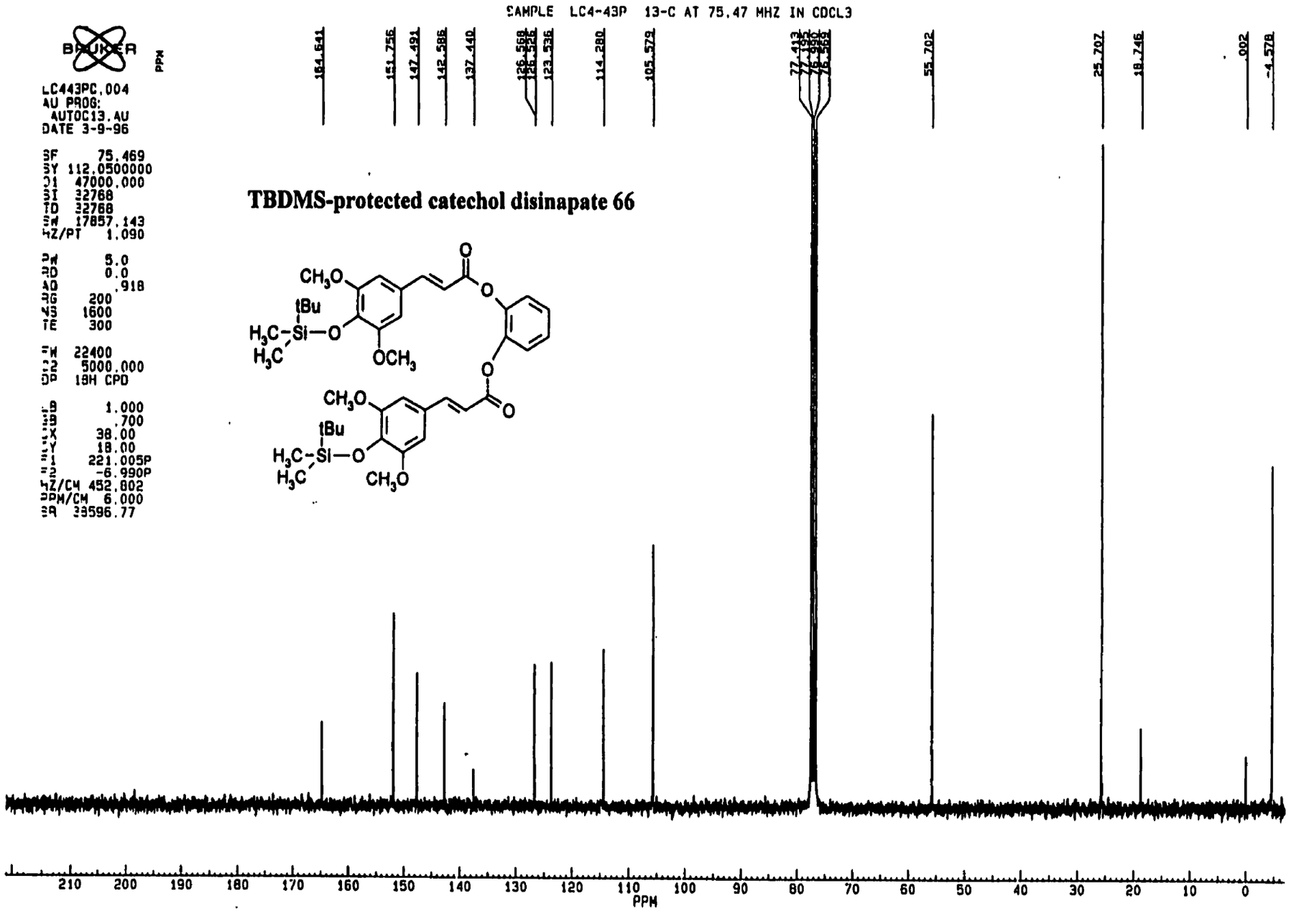

4-O-(Benzyl)syringyl bromide (60)
SAMPLE LC4-156(11) 13-C AT 75.47 MHZ IN CDCL3
LC45611C.004
AU PROG:
AUTOC13.AU
DATE 23-8-96
PPM
PPM

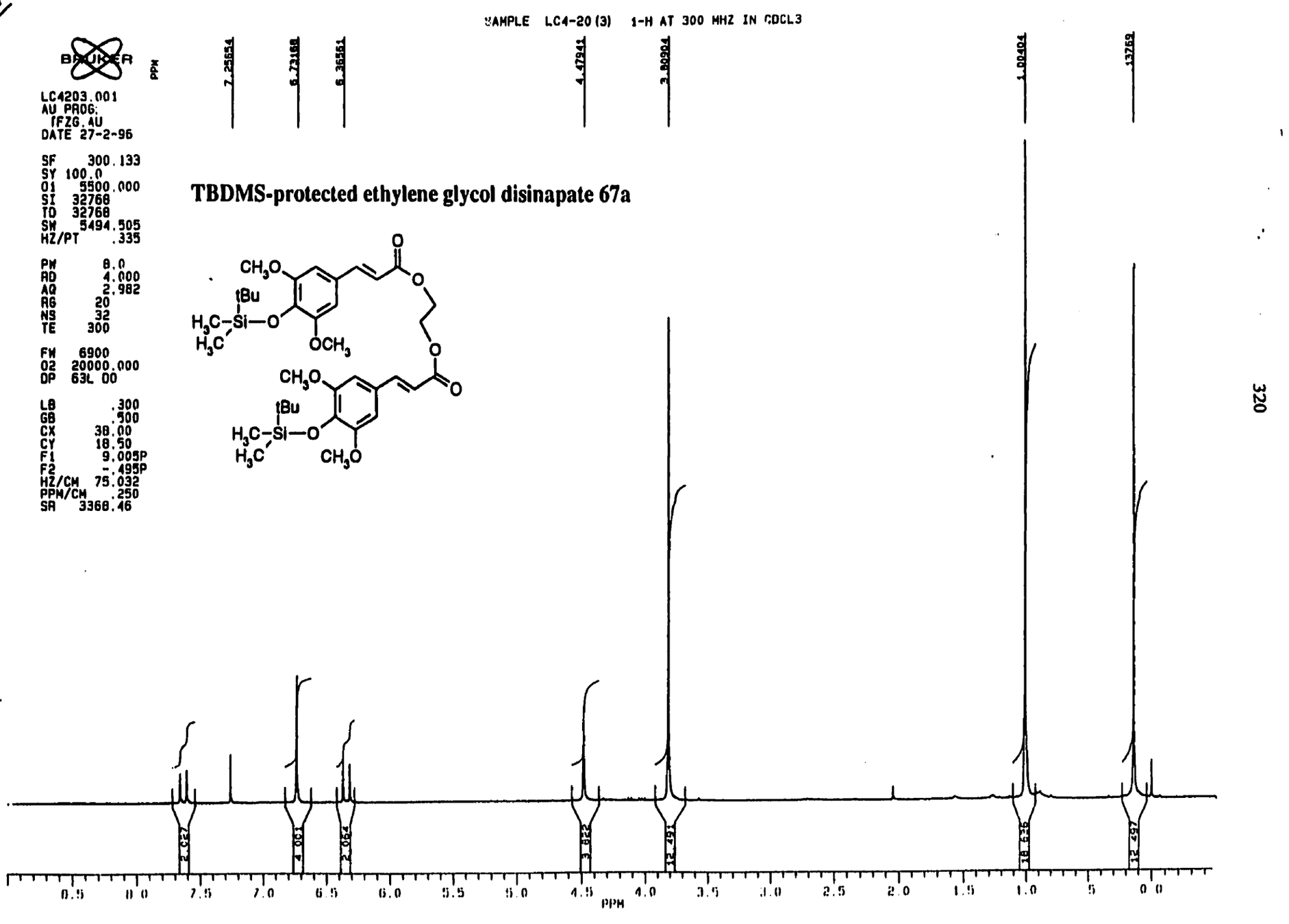

SAMPLE LC4-16.3B13 1-H AT 300 MHZ IN CDCL3
4'-Demethylyatcin (61)
OCH3
OH
CH3O
PPM


SAMPLE LC3-177P 1-H AT 300 MHZ IN CDCL3
4-O-(TBDMS)sinapic acid 65
LC3177P.001
AU PROG:
IFZG.AU
DATE 29-8-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.0000P
F2 -.499P
HZ/CM 75.032
PPM/CM .250
SR 3368.00
PPM
4.6829
7.0588
4.9428
1.0499
1.8037
1.9013

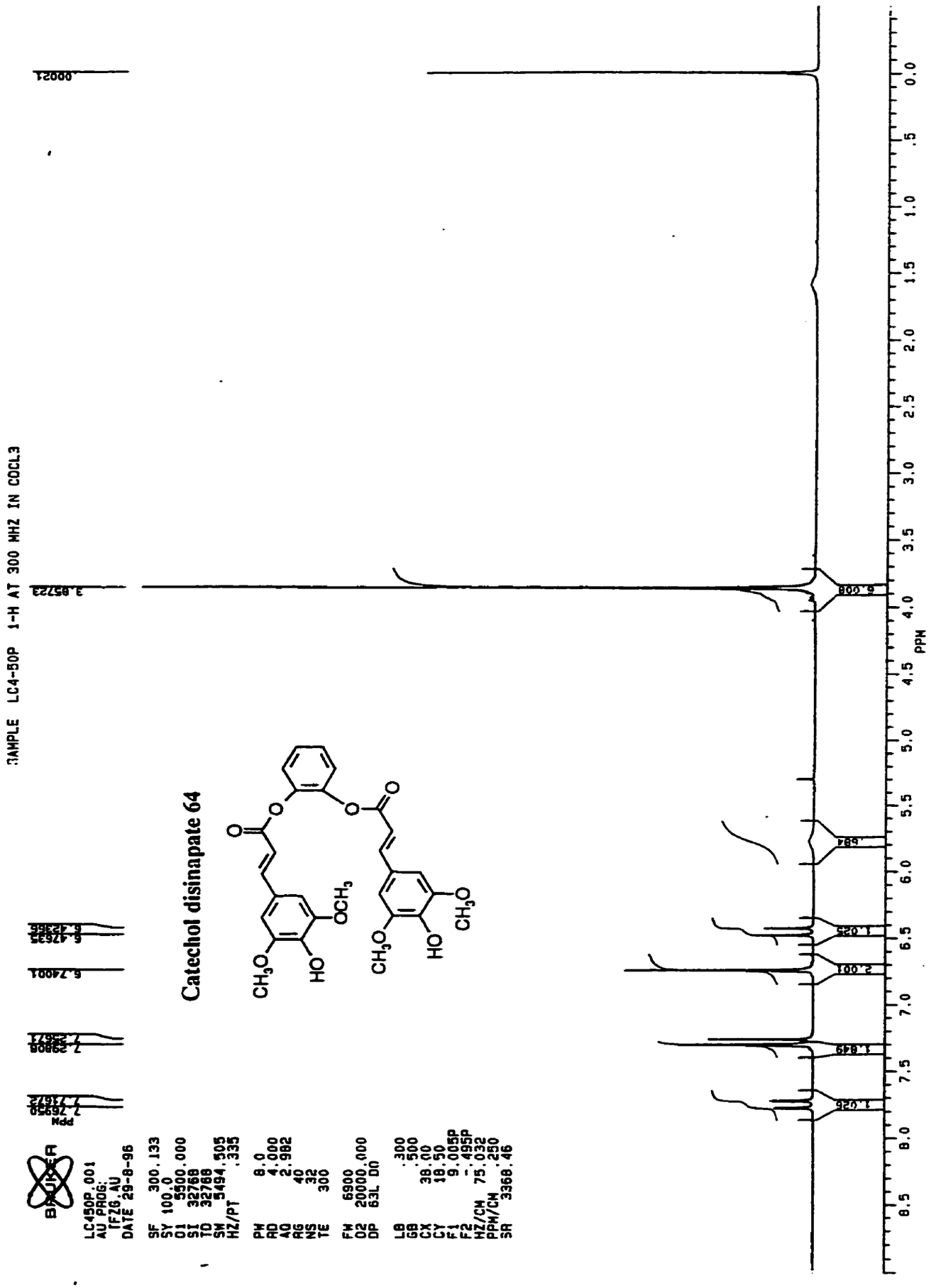

SAMPLE LC3-177P 13-C AT 75.47 MHZ IN CDCL3
4-O-(TBDMS)sinapic acid 65
CO2H
CH3O
CH3O
tBu
H3C-Si-O
H3C
LC3177PC.004
AU PROG:
AUTOC13.AU
DATE 5-9-96
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
IO 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1280
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 221.005P
F2 -6.990P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77
PPM

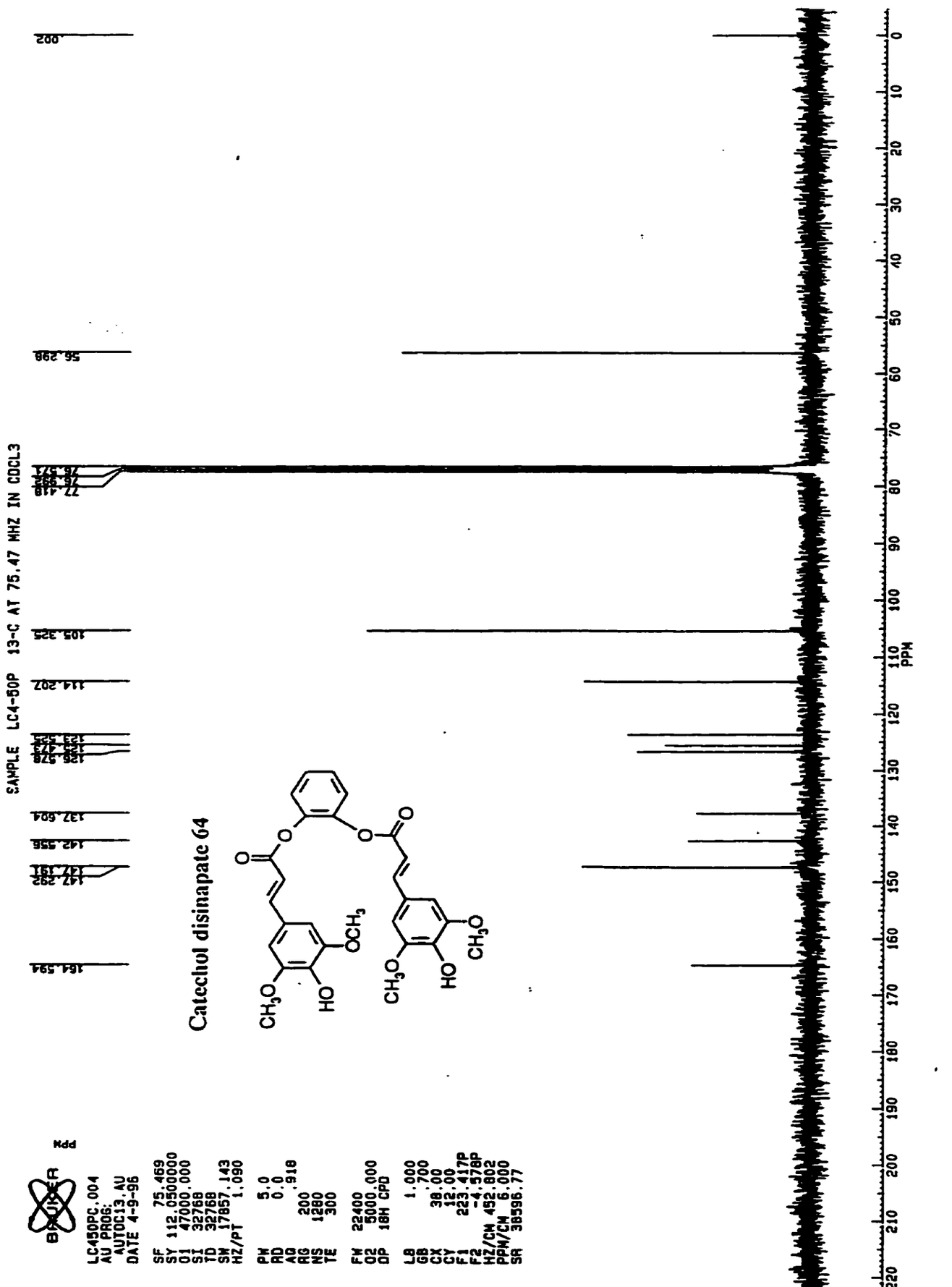

SAMPLE LC4-43P 1-H AT 300 MHZ IN CDCL3
BRUKER
LC443P.001
AU PROG:
[FZG.AU
DATE 29-8-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3369.14
TBDMS-protected catechol disinapate 66
PPM


SAMPLE LC4-43P 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
LC443PC.004
AU PROG:
AUTOC13.AU
DATE 3-9-96
SF 75.469
SY 112.0500000
D1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1600
TE 300
FW 22400
D2 5000.000
DP 18H CPD
PLW1 1.000
PLW2 .700
XXX 38.00
YYY 18.00
PH1 221.005P
PH2 -6.990P
HZ/CM 452.802
PPM/CM 6.000
SR 39596.77
184.641
151.756
147.491
142.586
137.440
136.568
126.526
123.536
114.280
105.579
77.413
77.192
76.966
76.268
55.702
25.707
18.746
.002
-4.578
TBDMS-protected catechol disinapate 66
CH3O
tBu
H3C-Si-O
H3C
OCH3
O
O
O
O
CH3O
tBu
H3C-Si-O
H3C
CH3O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


SAMPLE LC4-20(3) 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
7.25654
6.73168
6.36561
4.47941
3.80904
1.00494
13769
LC4203.001
AU PROG:
IFZG.AU
DATE 27-2-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3368.46
TBDMS-protected ethylene glycol disinapate 67a
2.027
4.001
2.064
3.822
12.491
18.636
12.297
PPM

320


SAMPLE LC4-50P 1-H AT 300 MHZ IN CDCL3
Catechol disinapate 64
BRUKER
LC450P.001
AU PROG:
TFZG.AU
DATE 29-8-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.10
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3368.46
PPM
3.85723
6.008
.884
1.025
2.001
1.849
1.926


SAMPLE LC4-50P 13-C AT 75.47 MHZ IN CDCL3
Catechol disinapate 64
LC450PC.004
AU PROG:
AUTOC13.AU
DATE 4-9-96
SF 75.469
SY 112.0500000
01 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1280
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 12.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77
PPM

SAMPLE LC4-22 1-H AT 300 MHZ IN CDCL3

BRUKER

LC422.001
AU PROG:
IFZG.AU
DATE 29-2-96

SF 300.133
SY 100.0
O1 6500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335

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

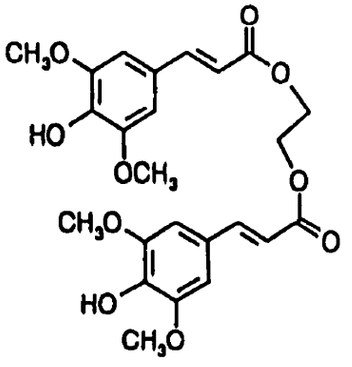
FW 6900
O2 20000.000
DP 63L DO

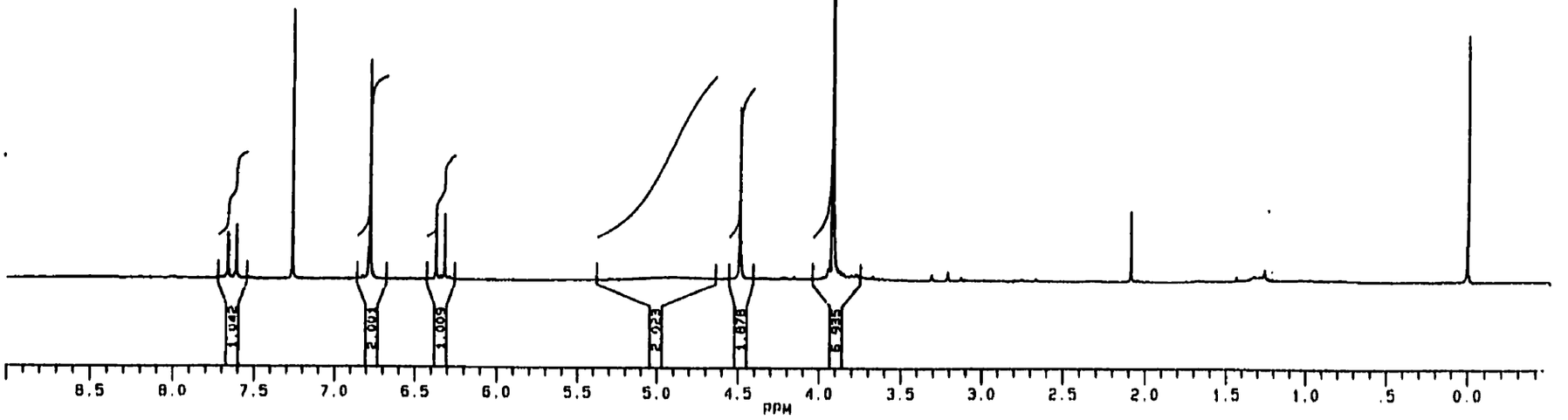
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPH/CM .250
SR 3366.79

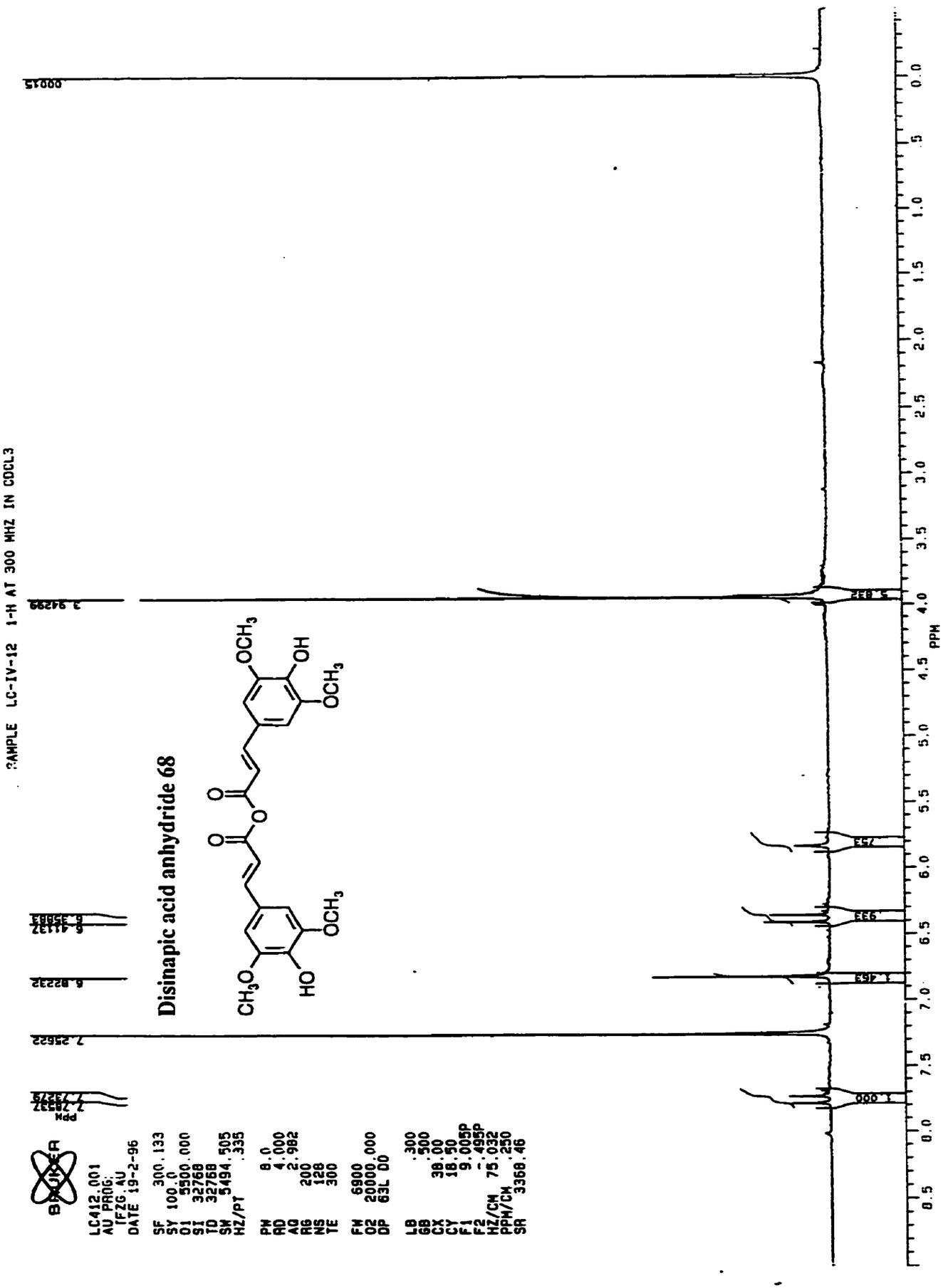
PPM

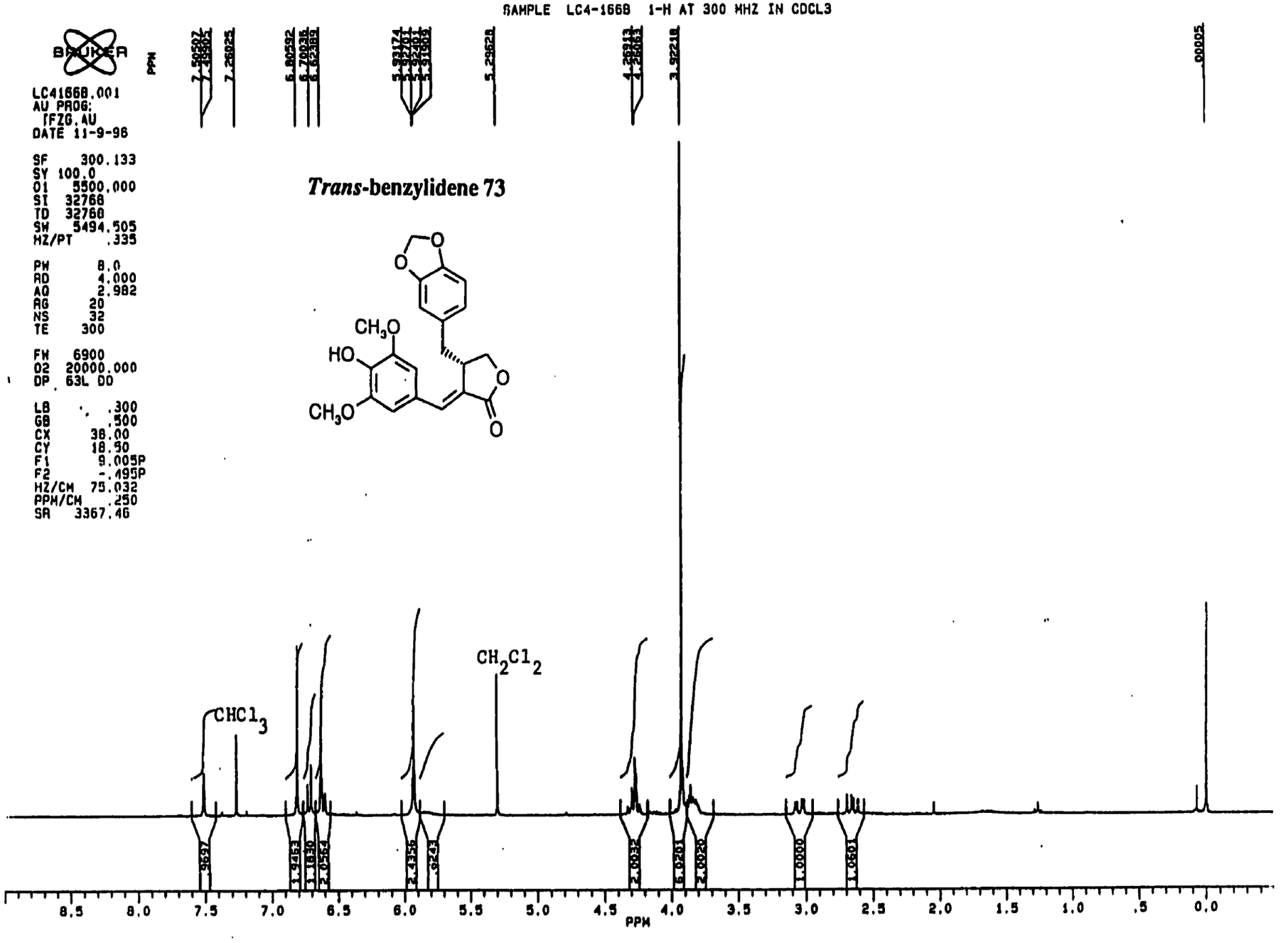
7.65111
7.60824
7.28195
6.77792
6.37050
6.31763
4.48654
3.91416
.00015

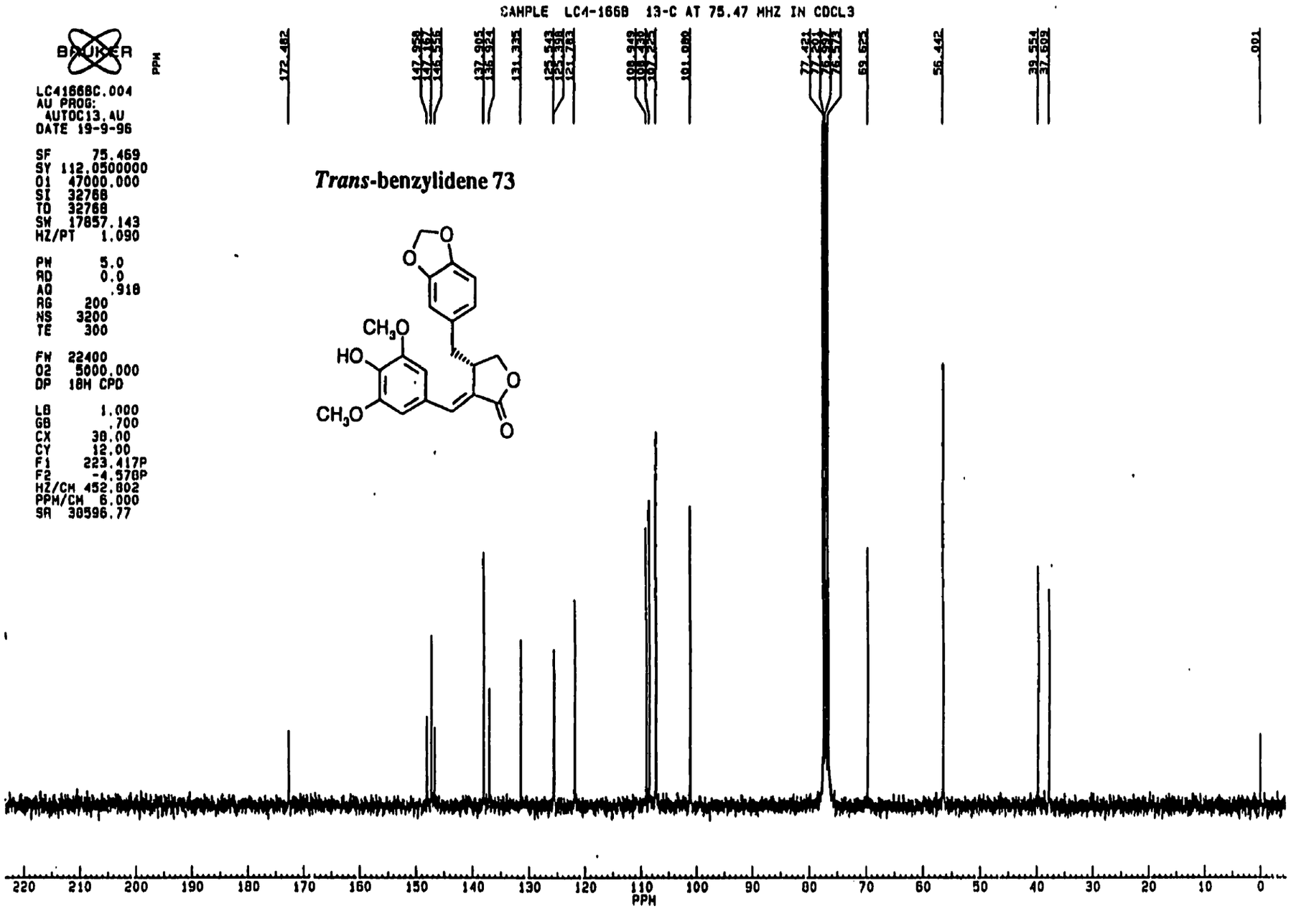
Ethylene glycol disinapate 67b

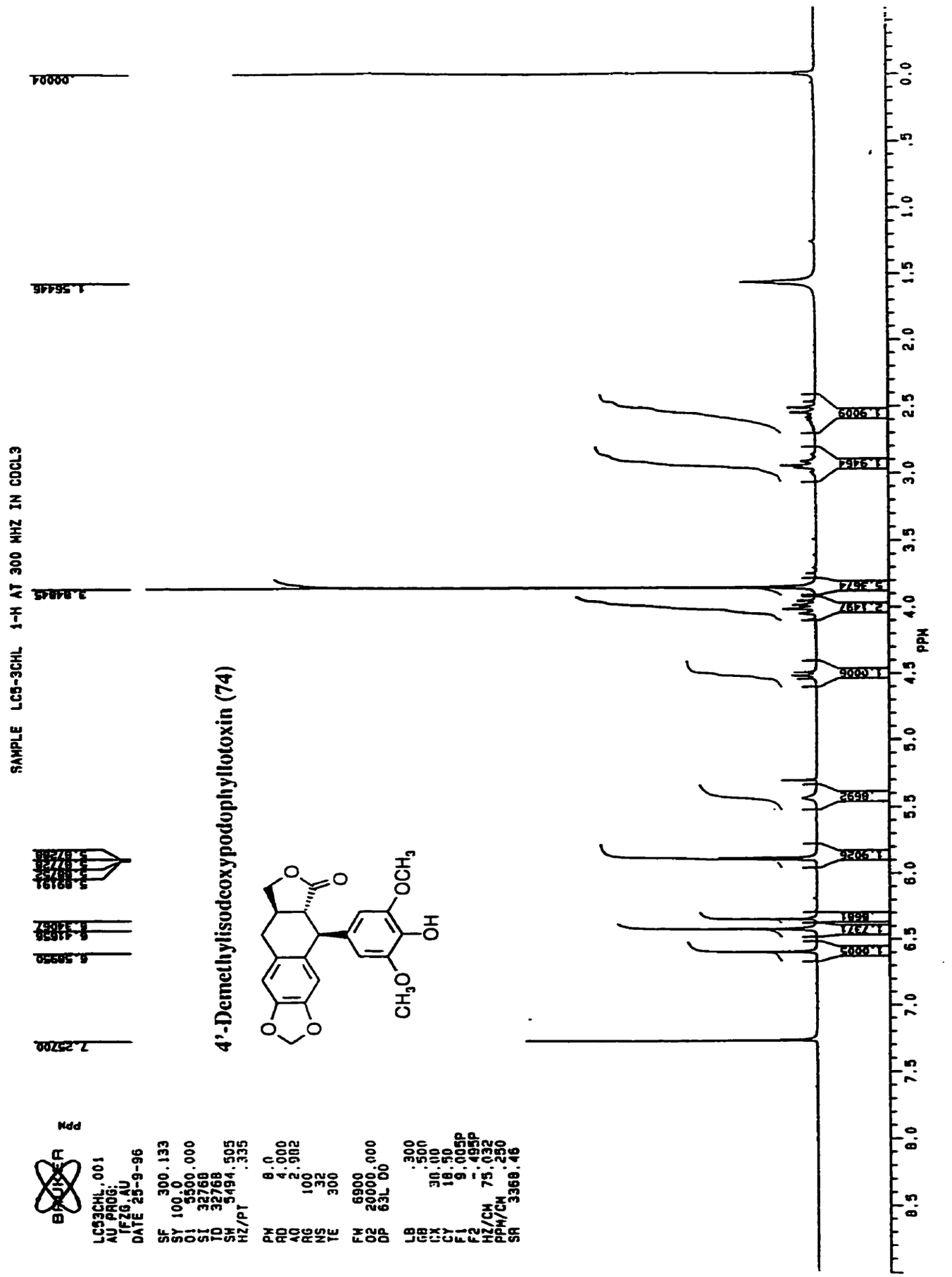


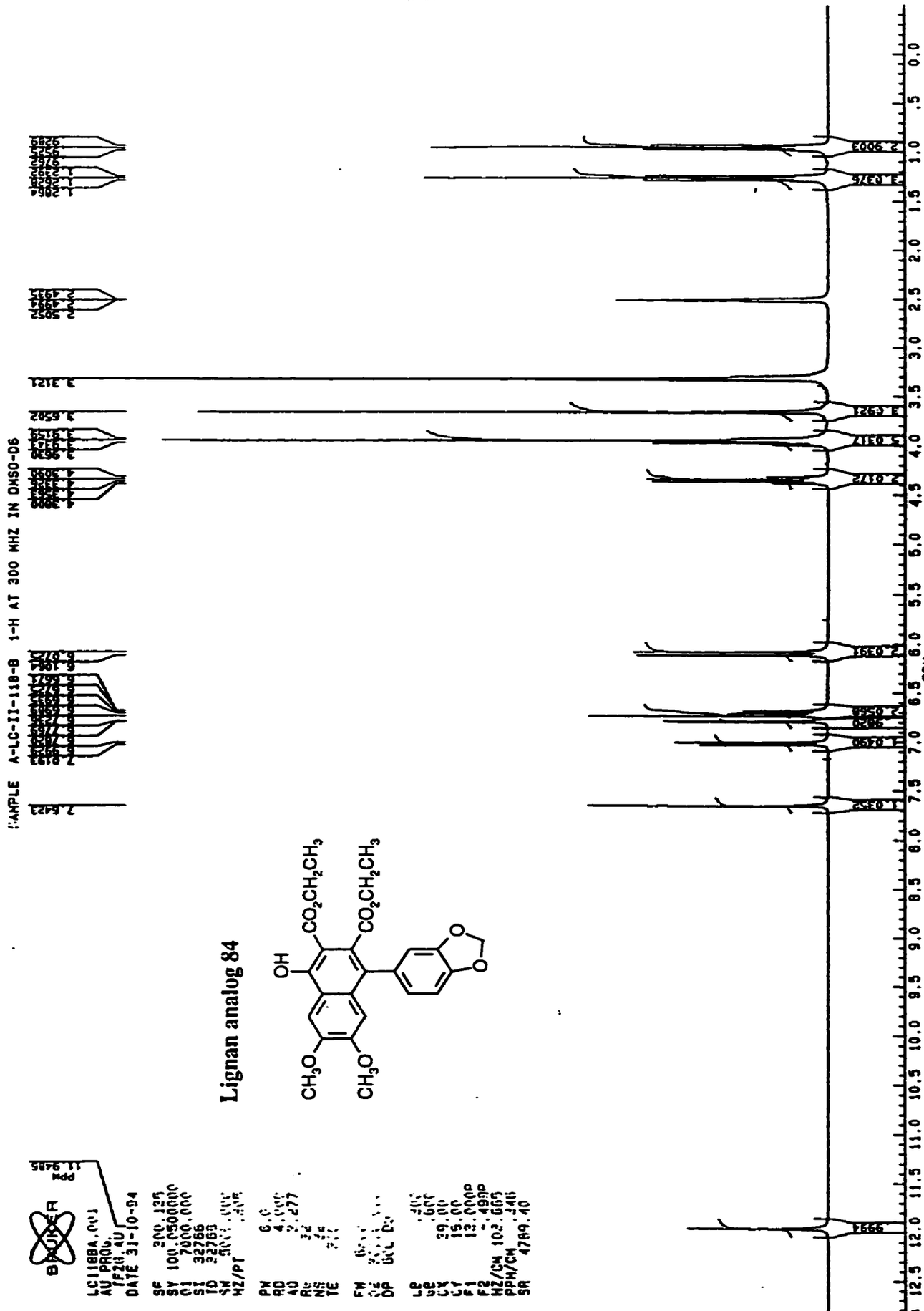


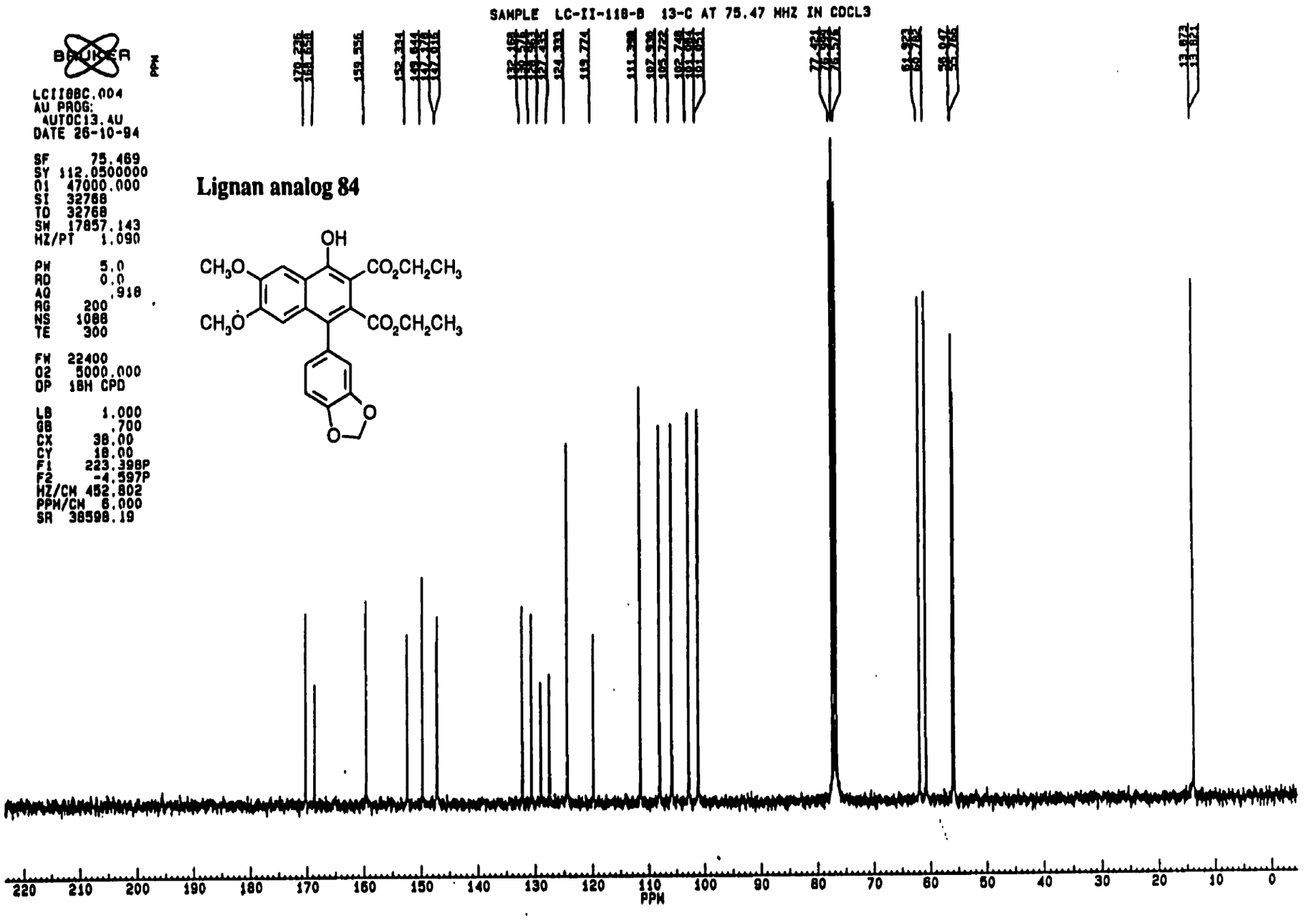

SAMPLE LC-IV-12 1-H AT 300 MHZ IN CDCL3
Disinapic acid anhydride 68
OCH3
OH
OCH3
O
O
O
OCH3
CH3O
HO
BRUKER
LC412.001
AU PROG.
TFZG.AU
DATE 19-2-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 200
NS 128
TE 300
FW 6900
O2 20000.000
DP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3368.46
PPM
0.5
0.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

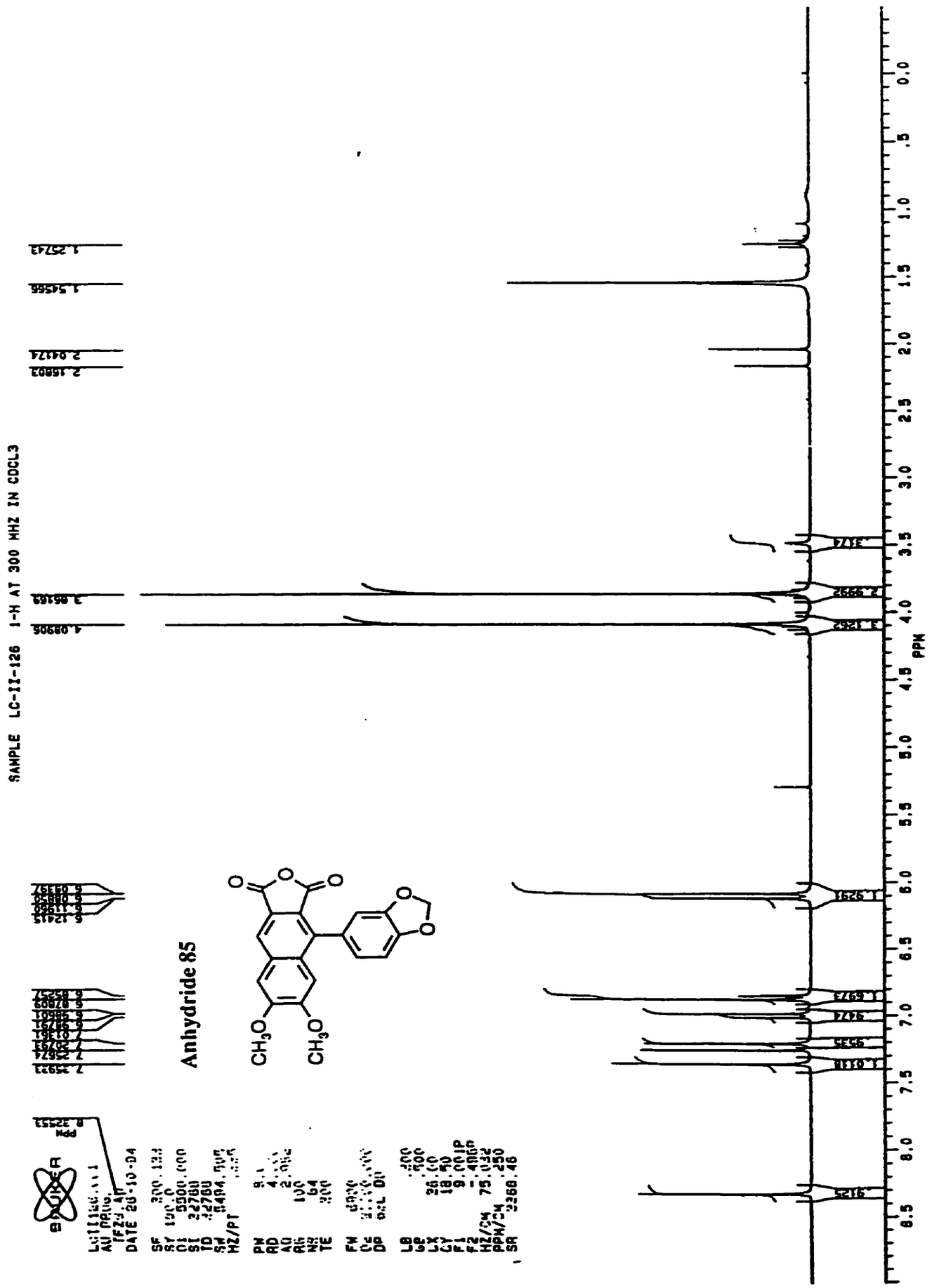

SAMPLE LC4-166B 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
LC41668.001
AU PROG:
IFZG.AU
DATE 11-9-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DD
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3367.46
Trans-benzylidene 73
CH3O
HO
CH3O
O
O
O
CHCl3
CH2Cl2
PPM


SAMPLE LC4-166B 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
172.482
147.959
147.167
146.556
137.905
136.921
131.335
123.543
123.398
121.781
108.948
108.433
107.922
101.080
77.431
77.204
76.997
76.571
69.625
56.442
39.554
37.602
.001
LC4166BC.004
AU PROG:
AUTOC13.AU
DATE 19-9-96
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 3200
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 12.00
F1 223.417P
F2 -4.570P
HZ/CM 452.802
PPM/CM 6.000
SR 30596.77
Trans-benzylidene 73
CH3O
HO
CH3O
O
O
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


SAMPLE LC5-3CHL 1-H AT 300 MHZ IN CDCL3
4'-Demethylisodeoxypodophyllotoxin (74)
OCH3
OH
CH3O
PPM


Lignan analog 84
OH
$CO_2CH_2CH_3$
$CO_2CH_2CH_3$
CH_3O
CH_3O
O
O
PPM


SAMPLE LC-II-118-B 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
LCII88C.004
AU PROG:
AUTOC13.AU
DATE 26-10-94
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1088
TE 300
FW 22400
O2 5000.000
OP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.398P
F2 -4.597P
HZ/CM 452.802
PPM/CM 6.000
SR 38598.19
Lignan analog 84
OH
CH3O
CO2CH2CH3
CH3O
CO2CH2CH3
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


SAMPLE LC-II-126 1-H AT 300 MHZ IN CDCL3
Anhydride 85
PPM

SAMPLE LC3-23P 1-H AT 300 MHZ IN DMSO-D6

BRUKER

PPM

LC3-23P.001
AU PROG.
TFZG.AU
DATE 5-4-95

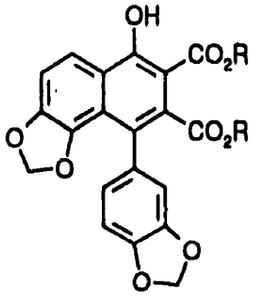
SF 300.135
SY 100.0500000
CI 7000.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

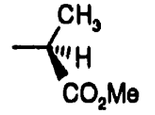
PW 6.0
RD 4.000
AQ 3.277
RG 40
NS 32
TE 300

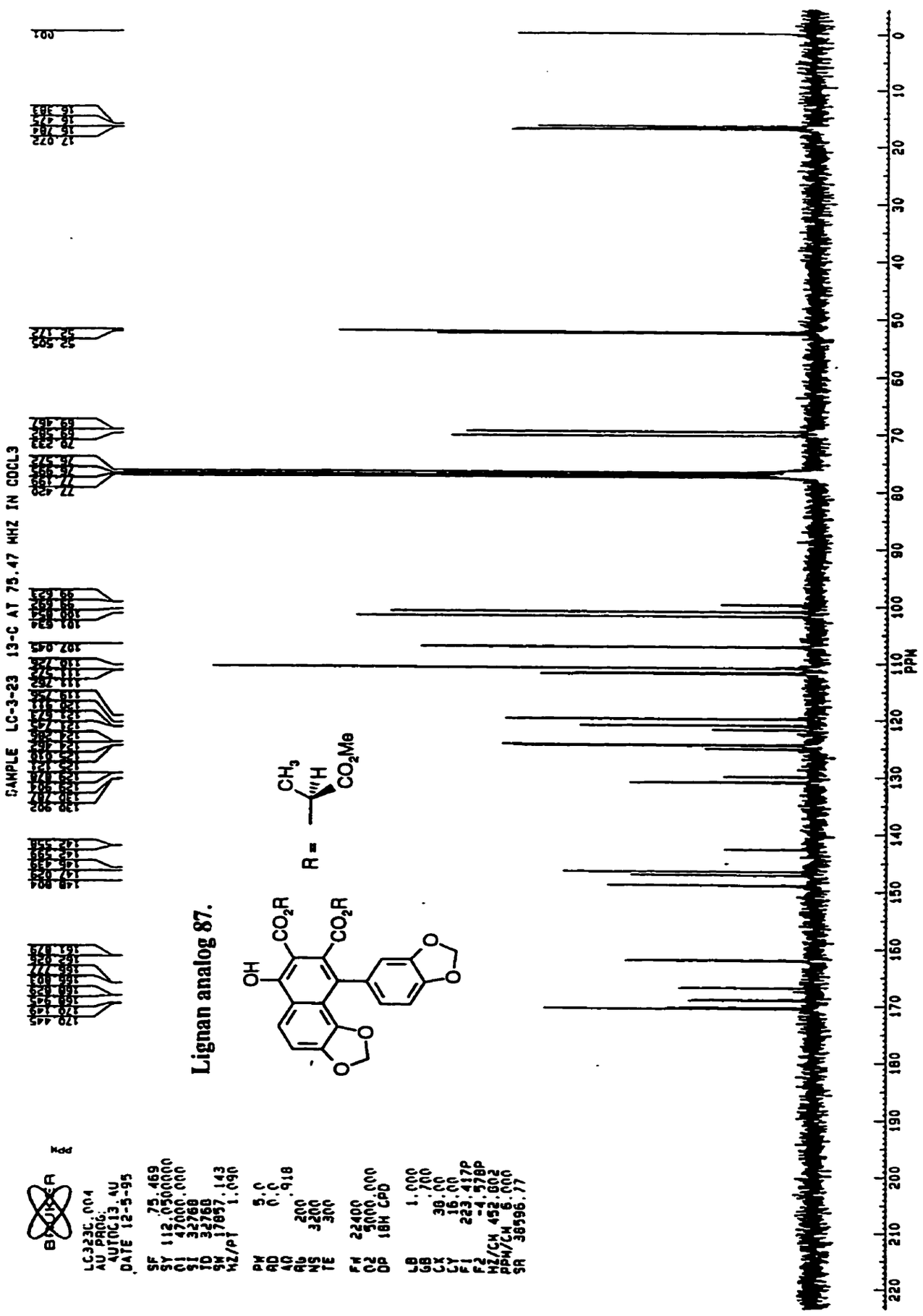
FW 6400
DE 30000.000
DP DEL DO

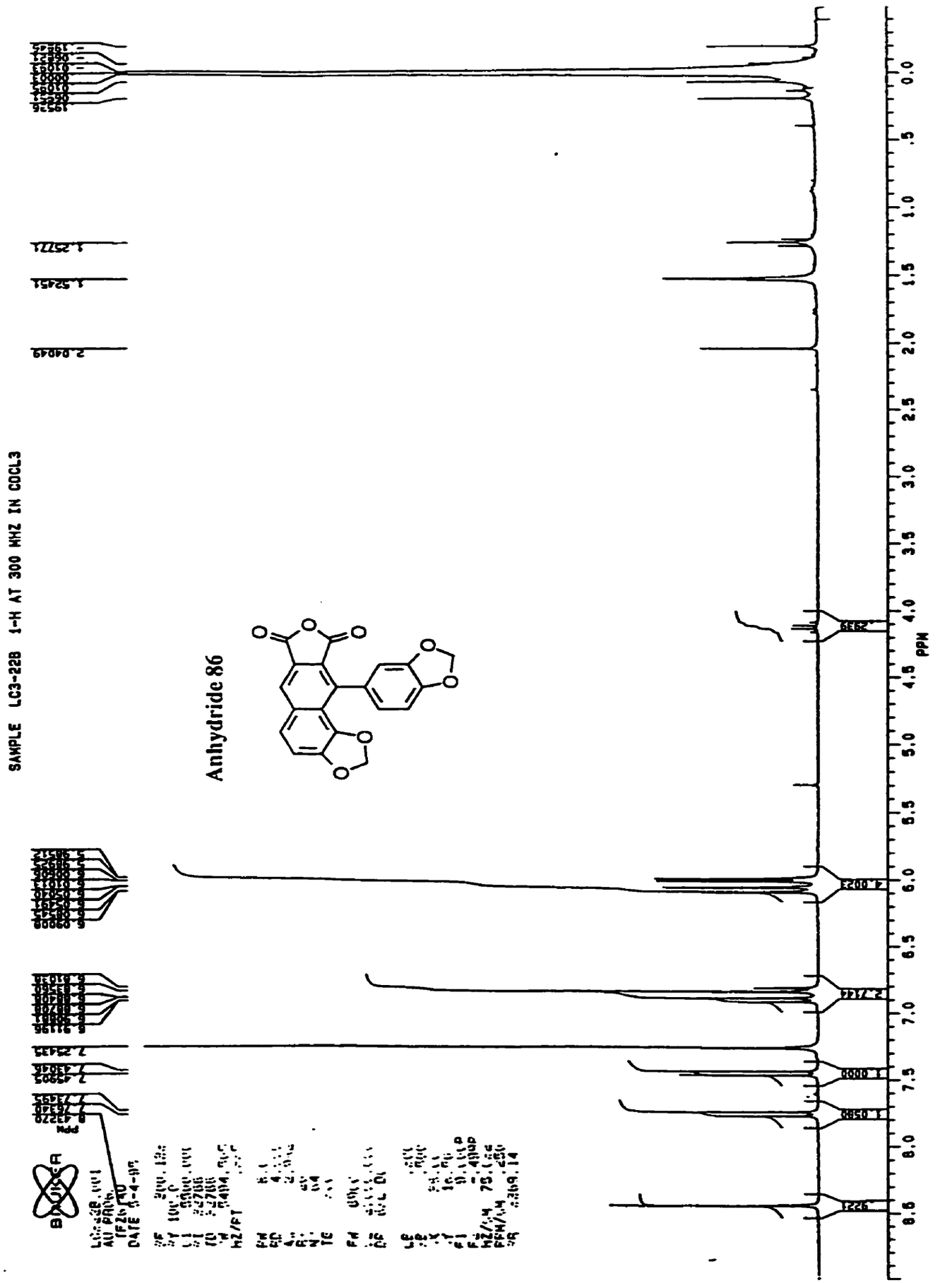
LB .300
GB .600
WX 39.00
CY 18.50
F1 13.0000P
F2 -.499P
HZ/CM 103.085
PPM/CM .346
SR 4769.09

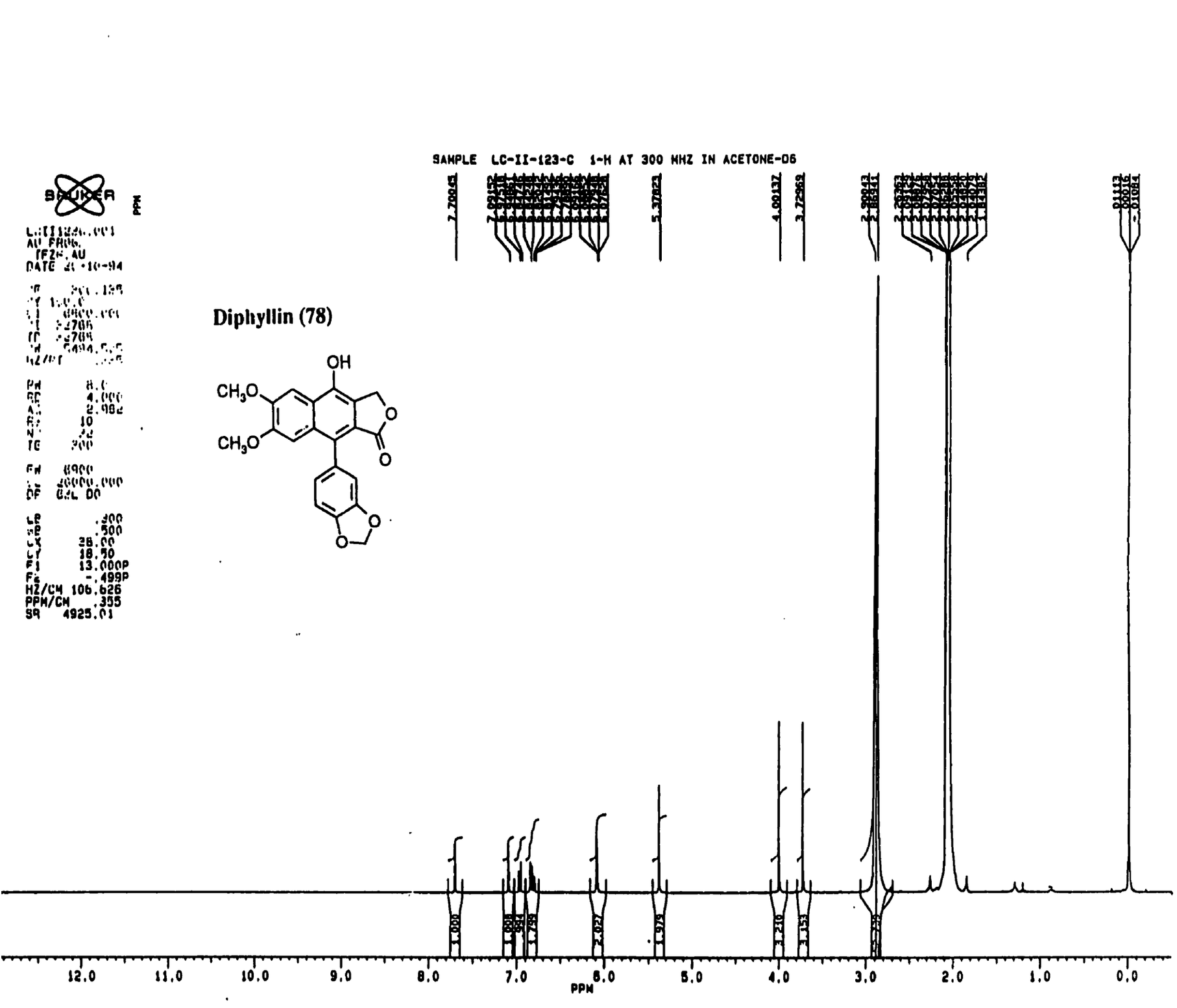
Lignan analog 87.



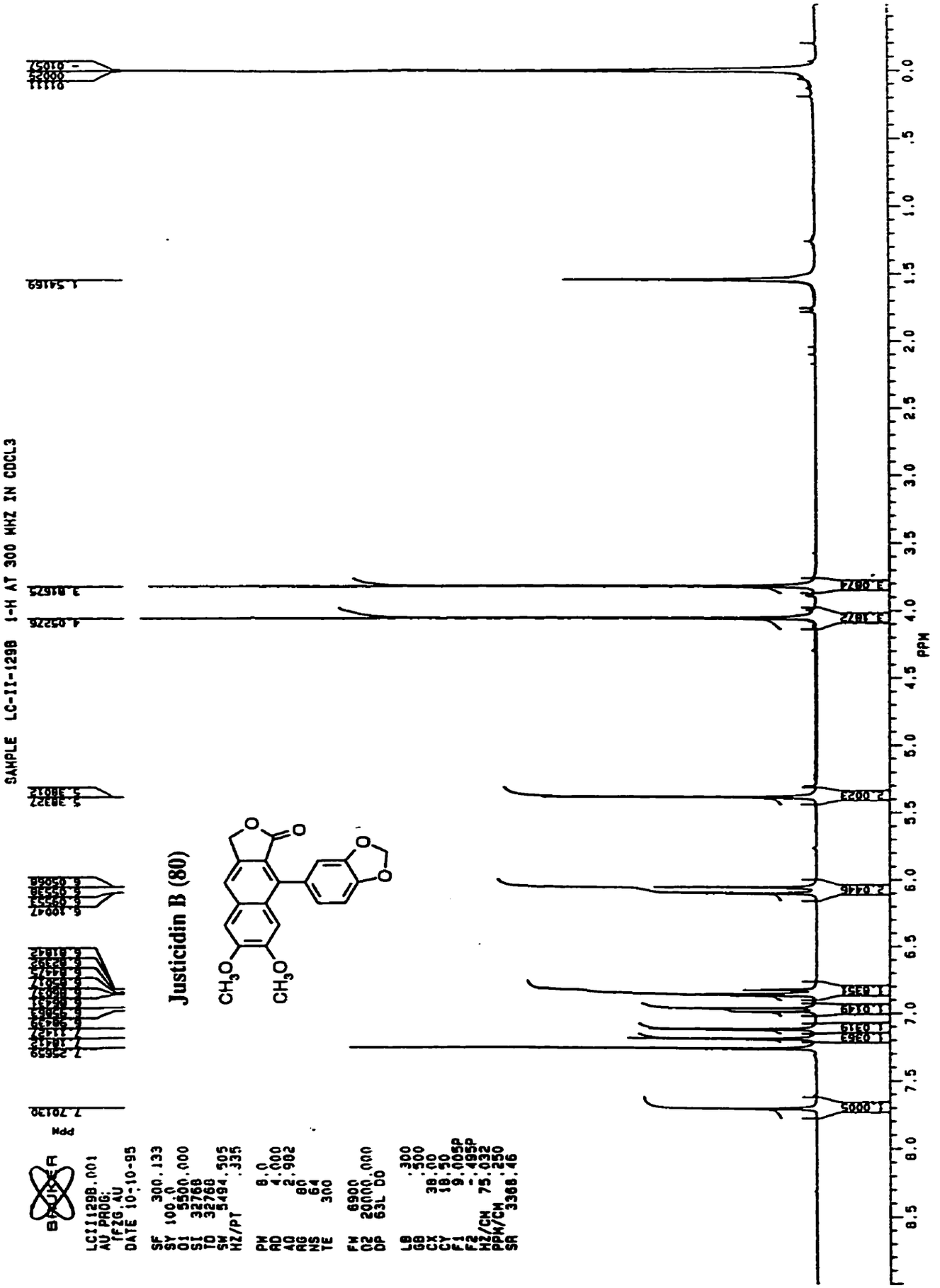
R = 

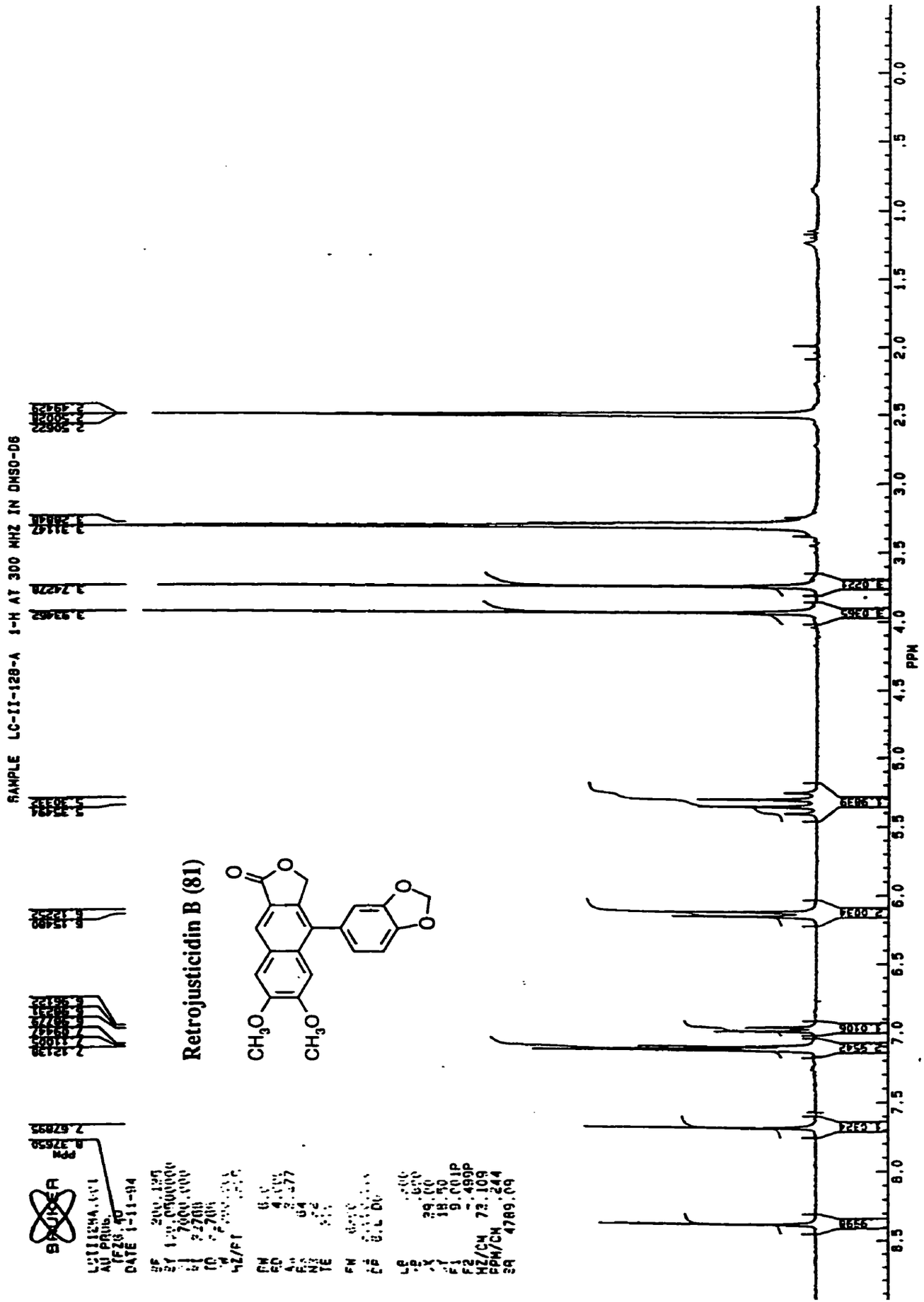

SAMPLE LC-3-23 13-C AT 75.47 MHZ IN CDCL3
Lignan analog 87.
R =
CH3
H
CO2Me
OH
CO2R
CO2R
O
O
O
O
O
PPM
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

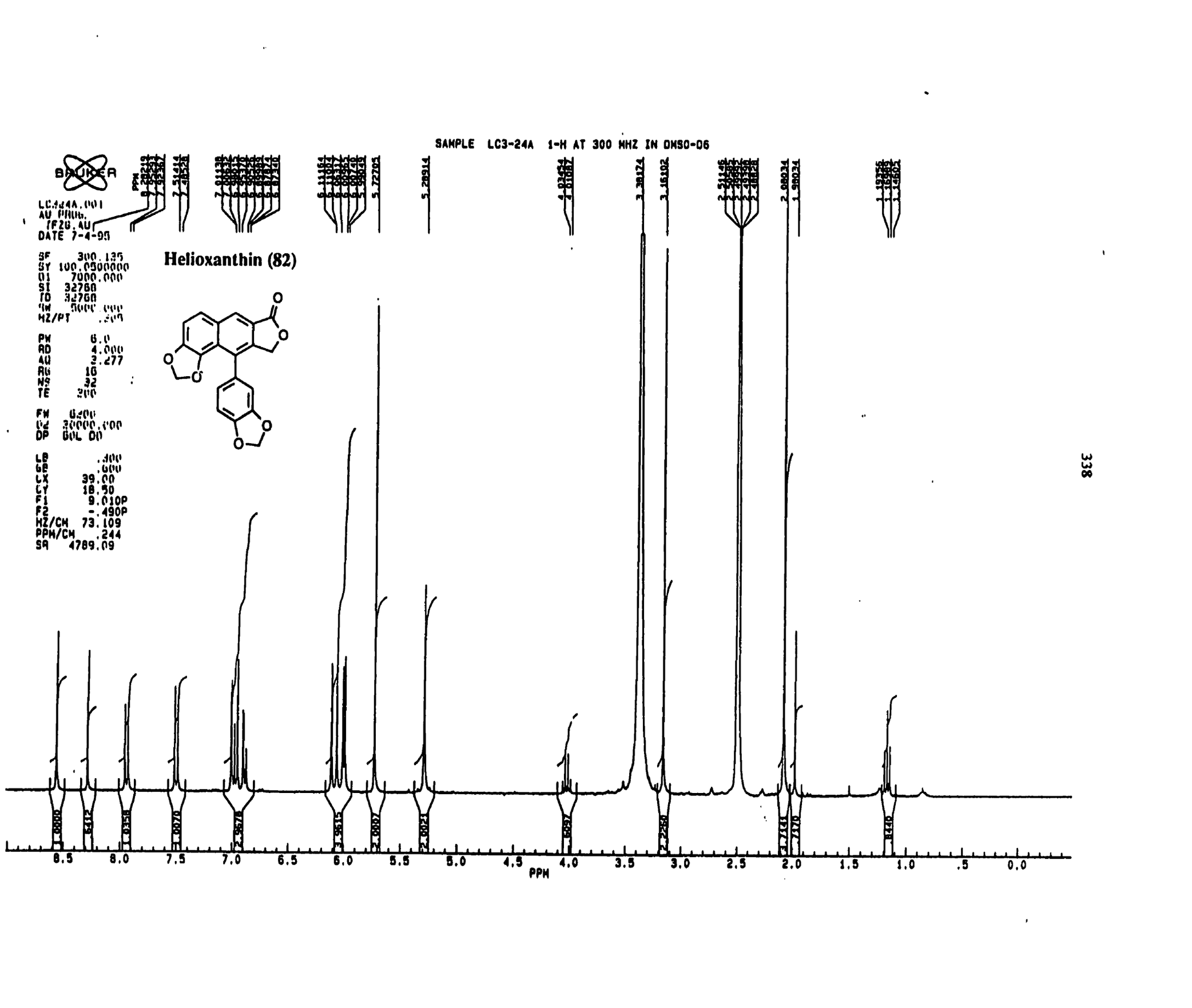

SAMPLE LC3-22B 1-H AT 300 MHZ IN CDCL3
Anhydride 86
PPM

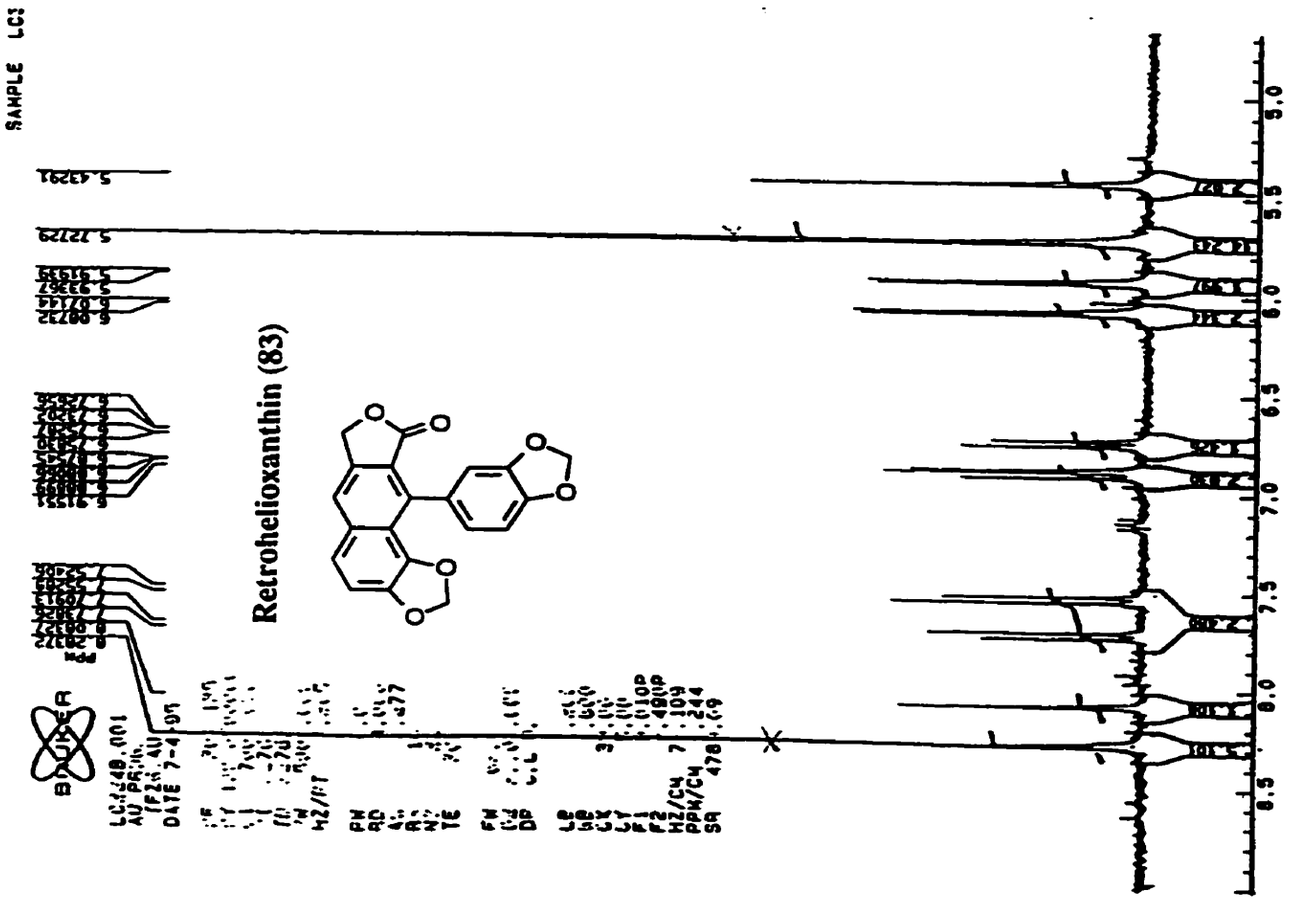

SAMPLE LC-II-123-C 1-H AT 300 MHZ IN ACETONE-D6
BRUKER
PPM
Diphyllin (78)
OH
CH3O
CH3O
O
O
O
O
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

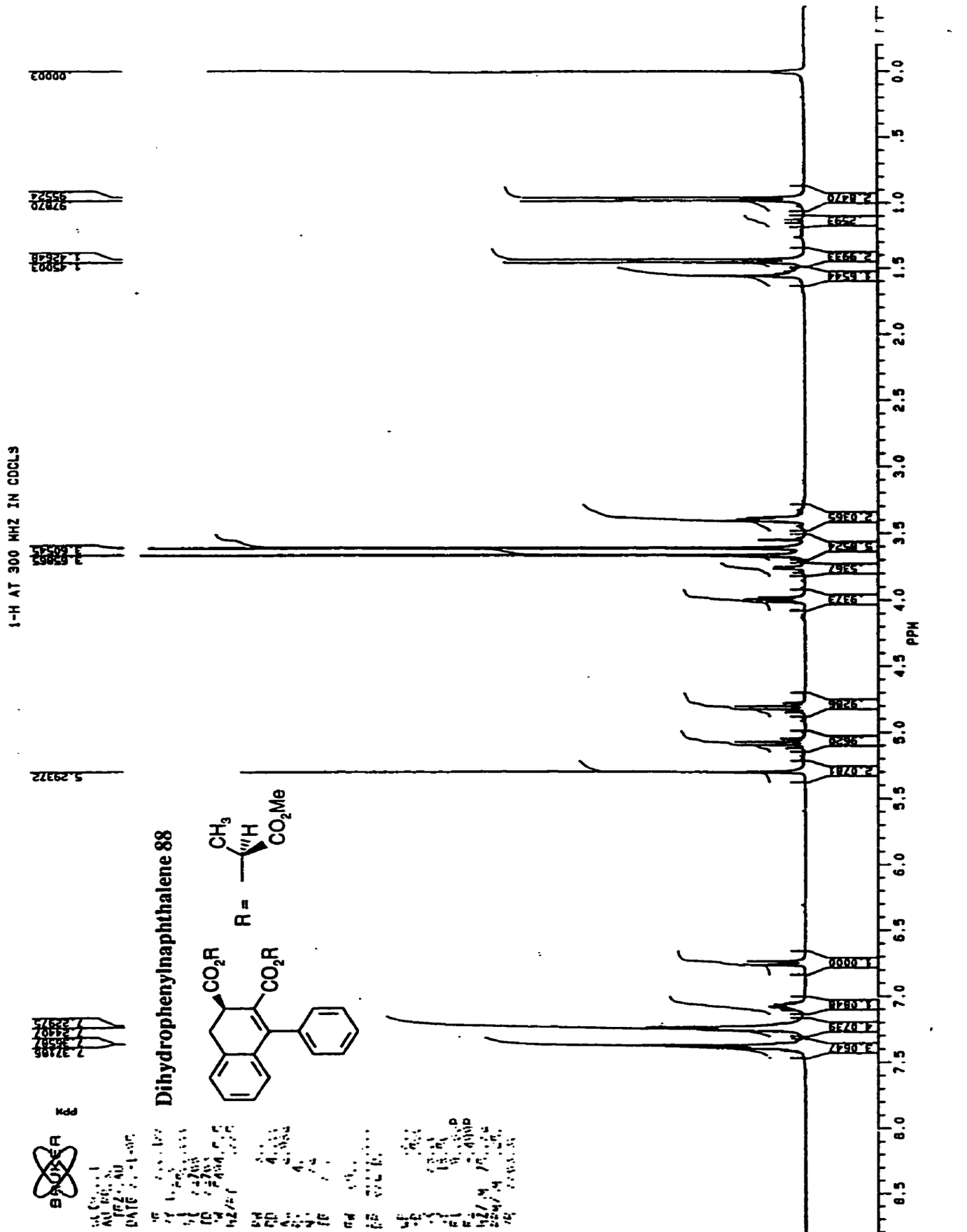

SAMPLE LC-II-131(7) 1-H AT 300 MHZ IN CDCL3
Justicidin A (79)
OCH3
CH3O
CH3O
PPM
BRUKER
LC111317.001
AU PROG:
IFZG.AU
DATE 30-11-94
SF 300.133
SY 100.0
01 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 100
NS 64
TE 300
FW 6900
O2 20000.000
DP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 11.0000P
F2 -.498P
HZ/CH 90.820
PPM/CH .303
SR 3360.80


SAMPLE LC-II-129B 1-H AT 300 MHZ IN CDCL3
Justicidin B (80)
CH_3O
CH_3O
LC111298.001
AU PROG:
(F2G.AU
DATE 10-10-95
SF 300.133
SY 100.0
OI 9500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.902
RG 80
NS 64
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3368.46
PPM
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0


SAMPLE LC-II-128-A 1-H AT 300 MHZ IN DMSO-D6
Retrojusticidin B (81)
PPM


SAMPLE LC3-24A 1-H AT 300 MHZ IN DMSO-D6
BRUKER
LC424A.001
AU PROG.
DATE 7-4-95
SF 300.135
SW 100.0500000
O1 7000.000
SI 32768
TD 32768
HZ/PT .305
PW 6.0
RD 4.000
AU 3.277
RG 16
NS 32
TE 300
FW 6200
DP DOL DD
LB .300
GB .000
CX 39.00
CY 18.90
F1 9.010P
F2 -.490P
HZ/CH 73.109
PPM/CH .244
SR 4789.09
Helioxanthin (82)
PPM


Retrohelioxanthin (83)


Dihydrophenylnaphthalene 88
R =
CH3
H
CO2Me
CO2R
CO2R
1-H AT 300 MHZ IN CDCL3
PPM

13-C AT 75.47 MHZ IN CDCL3

BRUKER

COI9C.004
AU PROG:
AUTOC13.AU
DATE 1-2-95

SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090

PW 5.0
RD 0.0
AQ .918
RG 200
NS 3200
TE 300

FW 22400
O2 5000.000
DP 16H CPD

LB 1.000
GB .700
CX 38.00
CY 16.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77

Dihydrophenylnaphthalene 88