The Asymmetric Synthesis of Aryltetralin Lignans

by

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THE ASYMMETRIC SYNTHESIS OF ARYLTETRALIN LIGNANS

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

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This thesis is dedicated to the memory of
Margaret E. Hohenstein

TABLE OF CONTENTS

Abstract

In a recent synthesis of (-)-deoxypodophyllotoxin, a synthetic strategy was developed which gave the desired compound in 6% isolated yield. The strategy involved, as a key reaction, a [4 + 2] cycloaddition between the fumarate of methyl (*S*)-mandelate and an appropriately substituted α-hydroxy-α-aryl-*ortho*-quinodimethane. In an attempt to broaden the scope of the synthetic strategy in question, and consequently develop a more generalized method for the synthesis of aryltetralin lignans, the total asymmetric synthesis of (-)-isolariciresinol dimethyl ether and (-)-deoxysikkimotoxin was carried out. The synthesis of each compound was achieved by making selective modifications to the strategy used in the synthesis of (-)-deoxypodophyllotoxin. Optically pure (-)-isolariciresinol dimethyl ether was obtained in 9% overall yield, and optically pure (-)-deoxysikkimotoxin was obtained in 11% overall yield.

For the synthesis of (-)-deoxysikkimotoxin, the 6,7-dimethoxy analogue of (-)-deoxypodophyllotoxin, a substantial improvement in the synthesis was achieved. The improvement resulted from the development of a one-pot regioselective reduction/lactonization procedure for the final step of the synthesis, giving (-)-deoxysikkimotoxin in 93% isolated yield in that step. The reduction in question was completely regioselective. The analogous conversion in the synthesis of (-)-deoxypodophyllotoxin required four separate steps, and gave only 35% overall yield.

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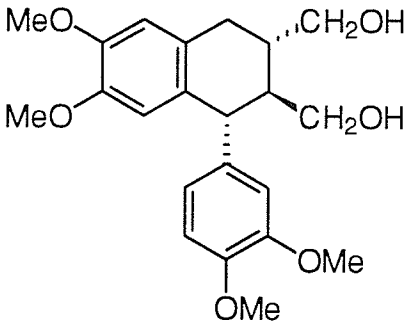
This thesis would not have been possible without the guidance of Dr. J. L. Charlton. I extend my sincere gratitude to him for allowing me the opportunity to pursue graduate research under his supervision, and to benefit from his knowledge of chemistry. To Jennifer Longman, my family, and my friends, I also express my deep appreciation for their support during my graduate career. I would like to thank the members of the Department of Chemistry at the University of Manitoba, particularly the academic, technical, and administrative staff, for their support. Finally, I would like to extend my appreciation to all those who participated in funding the research on which this thesis is based.

List of Schemes

1.0 Introduction

The research on which this thesis is based has dealt with the asymmetric synthesis of two members of a particular class of compounds which are referred to as aryltetralin lignans, namely (-)-isolariciresinol dimethyl ether (**1**) and (-)-deoxysikkimotoxin (**2**) (scheme 1.0). Asymmetric synthesis is a stereochemical

Scheme 1.0



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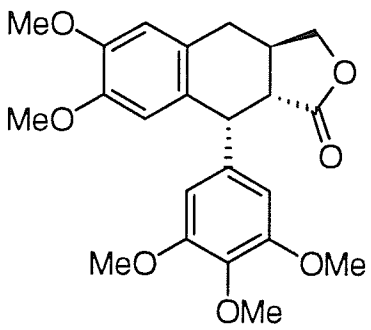


2

term, which is used to describe the selective formation of a compound possessing a particular chirality. In order to achieve the stereoselective formation of compounds **1** and **2** here, an asymmetric Diels-Alder reaction between an appropriately substituted *ortho*-quinodimethane and a chiral dienophile was employed. Hence, the introduction that follows begins with a brief discussion of stereochemistry, chirality and methods for obtaining chiral molecules. This is followed by a section in which a general overview of lignans is presented, as a prelude to a more detailed discussion of (-)-isolariciresinol dimethyl ether and (-)-deoxysikkimotoxin. The Diels-Alder reaction and its

stereochemical consequences comprise the penultimate portion of the introduction, which is followed by a very brief discussion of *ortho*-quinodimethanes.

1.1 Stereochemistry and Chiral Molecules

A) Introduction

Stereochemistry is the description of chemistry in three dimensions. Since most molecules are three dimensional, stereochemistry is inherent in virtually all of chemistry. It is important to realize, however, that stereochemistry is not so much a branch of chemistry, as it is a perspective which can be utilized to describe it. Whether or not one chooses the perspective of stereochemistry when discussing a particular problem, merely depends on the nature of the problem with which one is faced, and the tools which one has at hand.[1]

B) History

It has only been within relatively recent times that the concept of stereochemistry has entered in to chemical thought in a significant way. Despite this, the origins of stereochemistry can be traced back nearly two centuries to the discovery of plane polarized light by French physicist E. L. Malus.[2] This discovery was followed soon after by J. B. Biot's realization that certain quartz

crystals were capable of rotating plane polarized light to the left, whereas others caused it to rotate to the right.[3] Biot was able to extend his observations to organic compounds when he discovered the rotation of plane polarized light by liquids, such as turpentine, and solutions of solids, such as sucrose, camphor, and tartaric acid.[4]

Biot recognized the difference between the rotation of plane polarized light produced by crystals and that produced by organic substances. Rotation of plane polarized light by a crystal, he proposed, was a property of the crystal and, thus, was observed only in the solid state, and depended on the direction in which the crystal was viewed. On the other hand, rotation by an organic compound was a property of the individual molecules which made up the compound, and it could be observed in either the solid, liquid, or gaseous state.

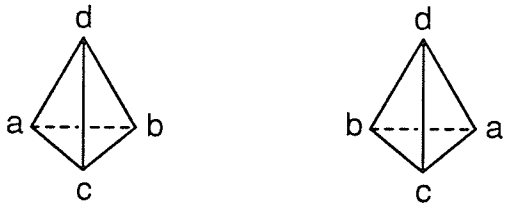
The term hemihedrism is used to describe the phenomenon whereby certain facets of a crystal are positioned such that they produce nonsuperimposible species. That is, two crystals which are mirror images of one another. Such mirror image species are said to be enantiomorphous. Sir John Herschel was the first to suggest the correlation between hemihedrism of crystals and the rotation of plane polarized light.[5] He was able to establish that, for a given pair of enantiomorphous crystals, one of the enantiomorphs would rotate plane polarized light to the left by a certain amount, whereas the other enantiomorph would cause it to rotate to the right by an equal amount. In other words, with respect to plane polarized light, the enantiomorphs had equal, but opposite rotation.

The correlation which Herschel had described for crystals regarding the rotation of plane polarized light, was extended to molecules in 1822 by L. Pasteur.[6] Pasteur obtained a crystalline, racemic mixture (i.e., a mixture containing equal amounts of each representative of an enantiomorphous pair) of sodium ammonium hydrogen tartrate, and was able, with the use of a microscope and tweezers, to separate the two hemihedric crystalline forms. Pasteur then made solutions of each of the two crystalline forms, and found that one solution rotated plane polarized light to the left, whereas the other rotated it to the right.

Pasteur soon recognized that in both crystals and in molecules, the ability to rotate plane polarized light had its source in dissymmetry, that is, the nonidentity of the crystal or molecule with its mirror image. Pasture then suggested that the two forms of tartaric acid which he had observed were related as an object to its mirror image. Thus, the two tartaric acid forms were enantiomorphous at the molecular level, or enantiomers. The term enantiomer is used to refer to each of the mirror image forms, when describing dissymmetry at the molecular level.

Pasteur's argument for enantiomerism was explained in sound geometric terms in 1874 when J. H. van't Hoff[7] and J. A. Le Bel[8] independently proposed the case for enantiomerism in a substance of the type Cabcd. In this case, the four substituents (i.e., a, b, c and d) can be arranged around the central carbon atom in a tetrahedral fashion to form two mirror image structures (scheme 1.1).

Scheme 1.1



A **B**

C) Chirality

The term chiral means to have the characteristic of handedness. The model corresponding to a given enantiomer (e.g., A in scheme 1.1) and the molecule which it represents are said to be chiral because, as is the case with hands, the molecules are not superimposable on their mirror image. Another way of defining chirality is to say that in order for a model to be chiral, it must possess no element of symmetry except at most an axis of rotation.[9]

It is important to recognize the difference between the chirality of a molecule and the chirality of a substance or sample. In order to say that a molecule is chiral, it must exist as either the left handed form or the right handed form. However, if a substance or sample is said to be chiral, then this simply means that it is made up of chiral molecules; it does not necessarily imply that all of the constituents of the sample have the same chirality.[1] A sample can be referred to as being either homochiral, in which case all of the molecules that make up the sample have the same sense of chirality, or it can be referred to as being heterochiral, in which case at least two of its constituent molecules have an opposite sense of chirality. An important case of a heterochiral mixture is one

which possess an equal number of molecules of opposite chirality. Such a mixture is said to be racemic.

D) Classification of Chiral Molecules

There are three commonly used systems of nomenclature whereby a particular enantiomer of a chiral molecule can be classified:[10]

i) An Operational Classification

Molecules can be classified according to the direction in which they rotate plane polarized light. If a given compound causes the plane of light to rotate counterclockwise, from the point of view of the observer, then it is referred to as levorotatory. If rotation of the plane of light is clockwise from the point of view of the observer, then the molecule causing that rotation is classified as dextrorotatory. The prefixes (-) and (+) or, *l* and *d* are used to designate compounds as either levorotatory or dextrorotatory, respectively. The direction of rotation of plane polarized light by a given compound is determined using an instrument called a polarimeter.

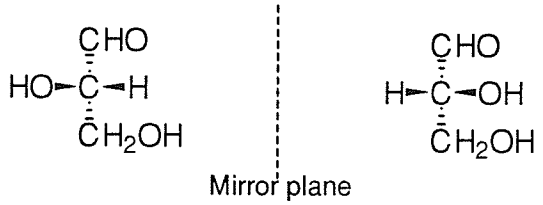
ii) The Fischer Convention

Using the Fischer convention, the configuration of groups about an asymmetric center, also referred to as a chiral center or stereogenic center, can be related to that of glyceraldehyde. Emil Fischer introduced the convention in 1891 in which the (-) and (+) stereoisomers of glyceraldehyde were designated L-glyceraldehyde and D-glyceraldehyde, respectively. The configuration

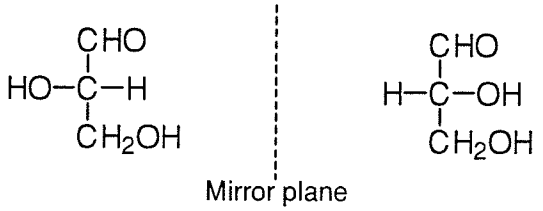
corresponding to these molecules is depicted in scheme 1.2. The Fischer projection is a shorthand method used to represent these molecules. In this type of a projection, the horizontal bonds are interpreted as extending above the plane of the paper, and the vertical bonds as extending below the plane of the paper.

Scheme 1.2

Geometric formulas



Fischer projections



L-Glyceraldehyde **D-Glyceraldehyde**

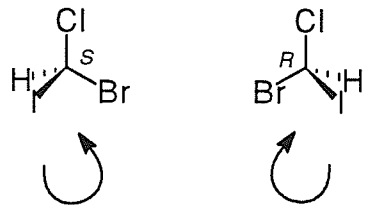
The configuration of groups about a chiral center in other molecules, particularly sugars and amino acids, could be related to that of glyceraldehyde by comparison of their three dimensional structures to glyceraldehyde. The Fischer convention has been largely abandonned in favor of other classification systems.

iii) The Cahn-Ingold-Prelog System

In this system, priority is assigned to the four groups surrounding a chiral center. The priority of a given group is established based on its atomic number,

relative to the atomic numbers of the other three groups about the chiral center; atoms of higher atomic number are given priority over atoms of lower atomic number. For example, the oxygen atom of a methoxy substituent would have priority over the carbon atom of a methyl substituent. If any of the first substituent atoms around a chiral center are of the same element, the priority of the groups to which those atoms belong is established from the atomic numbers of the second, third, etc., atoms outward from the asymmetric center.

Scheme 1.3



Priority:
H = 4
Cl = 3
Br = 2
I = 1

Once priority of the groups is established, the configuration of the chiral center is determined by viewing the molecule along the bond from the chiral center to the group of lowest priority. The direction of decreasing priority of the remaining three substituents is then determined; it will be either clockwise or counter clockwise. If the direction of decreasing priority is clockwise, then the chiral center is referred to as *R*. If the direction of decreasing priority is counterclockwise, the chiral center is referred to as *S* (scheme 1.3). The curved arrows in scheme 1.3 indicate the direction of decreasing priority of the halogen

substituents, as viewed along the carbon hydrogen bond from the asymmetric center.

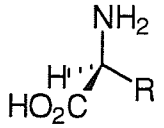
E) Methods for Obtaining Chiral Molecules

Four primary methods exist for obtaining chiral molecules in their optically active form.

i) Isolation of Chiral Molecules from Natural Sources

One of the most striking characteristics about life is its production of optically active molecules. Almost invariably, the biosynthesis of a substance possessing asymmetric centers occurs such that a pure stereoisomer is produced. The chemist can take advantage of this phenomenon by extracting a pure stereoisomer from its natural plant or animal source. Collectively, all of the optically active molecules obtained in this way, and those molecules which have the potential to be obtained in this way, are referred to as the chiral pool. All naturally occurring α-amino acids, for example, exist exclusively in the L form. All amino acids possesses the same arrangement of groups about the chiral α-carbon, and they differ only in the side chain substituent (scheme 1.4).

Scheme 1.4

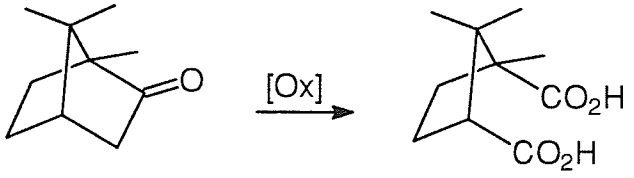


R = sidechain

ii) Chiral Pool Synthesis

Optically pure chiral molecules can also be obtained from what is referred to as a chiral pool synthesis. In a chiral pool synthesis, an optically pure molecule that is available from the chiral pool is transformed into a different compound, such that the chirality of the starting compound is retained. An example of this is seen in the oxidation of (-)-camphor to (+)-camphoric acid (scheme 1.5).

Scheme 1.5



(-)-camphor **(+)-camphoric acid**

iii) Resolution

A third method of obtaining optically pure chiral molecules is *via* a process called resolution. A resolution is the separation of a racemate into its enantiomeric constituents. The primary shortcoming of obtaining optically pure compounds in this way is that the yield can, at most, be 50%. Resolution methods fall into one of two categories: (a) those based on physical processes or (b) those based on chemical reactions. Some examples of each of these methods follow.

a) Physical Resolution Processes

A substance is said to be spontaneously resolved when crystallization of a racemate leads to the formation of a conglomerate. A conglomerate is a solid,

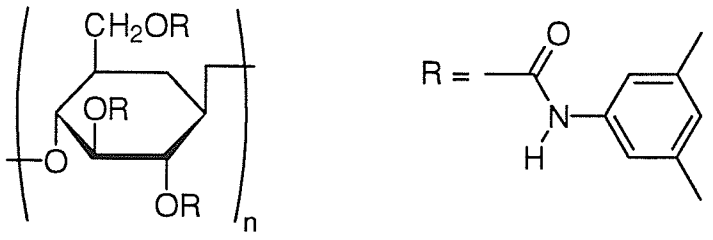
equimolar mixture of the two enantiomorphs of an enantiomorphous crystal. Once a conglomerate has formed, the crystals of which it is composed can be manually separated into two fractions, whose solutions are levorotatory and dextrorotatory. Such a process is referred to as triage, but for most purposes is not of practical value.

Preferential crystallization is another example of a physical resolution process which can be employed in the separation of the two enantiomers of a racemate. This procedure is initiated by inoculation, or seeding, of a saturated or supersaturated solution of the racemate with a crystal of one of the two enantiomers. A nonequilibrium crystallization process then begins, whereby only the seeded enantiomer precipitates from solution.

b) Chemical Reaction Based Processes

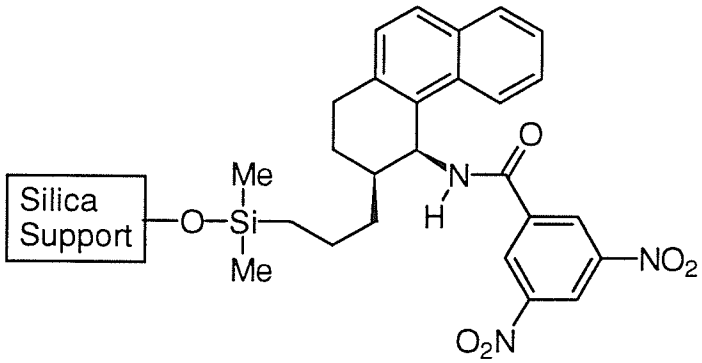
Various methods for the resolution of racemates *via* chemical means exist. One such method is to simply carry out solid/liquid chromatography using a homochiral stationary phase. The theory behind this technique is based on the assumption that each of the enantiomers of the racemate will exhibit a different affinity for the stationary phase because it is chiral. Hence, each enantiomer will be retained on the column to a different extent and separation will be possible. There are two basic types of chiral stationary phases that exist; the stationary phase can either be a chiral polymer, or it can be an achiral substrate to which chiral selector molecules are bound. Chiralcel OD, an example of a polymeric stationary phase, and the (*S,S*) Whelk O1 Pirkle chiral selector molecule, are shown in scheme 1.6 and scheme 1.7 respectively.[11]

Scheme 1.6



Chiralcel OD

Scheme 1.7



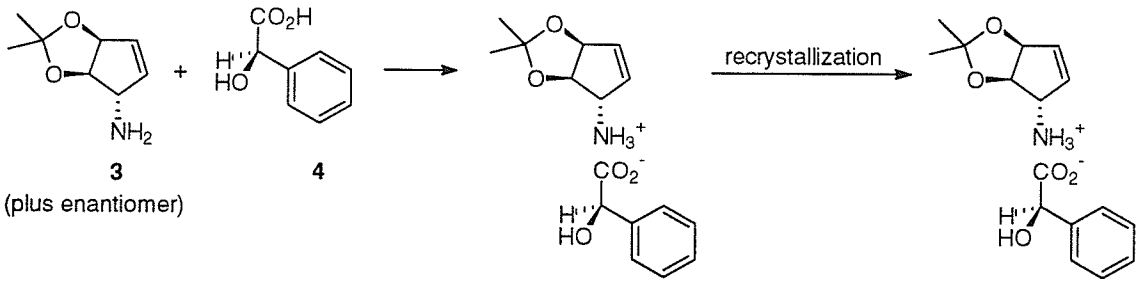
(*S*,*S*) Whelk O1

A second chemically based process for the resolution of a racemic compound is the conversion of the enantiomers of which the racemate is comprised, to diastereomers. Since diastereomers differ from each other in their physical and chemical properties, the resulting compounds can typically be separated according to relatively straight forward techniques, such as chromatography on an achiral substrate, or recrystallization. In order to generate a given pair of diastereomers from the corresponding enantiomers, the compound to be resolved is treated with one enantiomer of a chiral reactant. Such a compound is referred to as a resolving agent. The resulting

diastereomeric pairs may be ionic (i.e., diastereomeric salts), covalent, charge transfer complexes, or inclusion compounds.[1] Once separation of the diastereomers is achieved, the portion of each diastereomer that corresponds to the resolving agent can be removed, yielding the pure enantiomers.

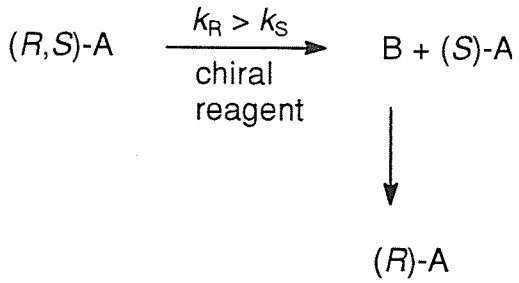
The racemic from of cyclopentenylamine acetonide (**3**), for instance, was resolved by reacting it with (*R*)-mandelic acid (**4**) in order to generate the corresponding diastereomeric salt (**5**). The diastereomeric mixture of crystals which resulted was then subjected to appropriate recrystallization conditions, causing the exclusive precipitation of the dextrorotatory salt (**6**) (scheme 1.8).[12]

Scheme 1.8



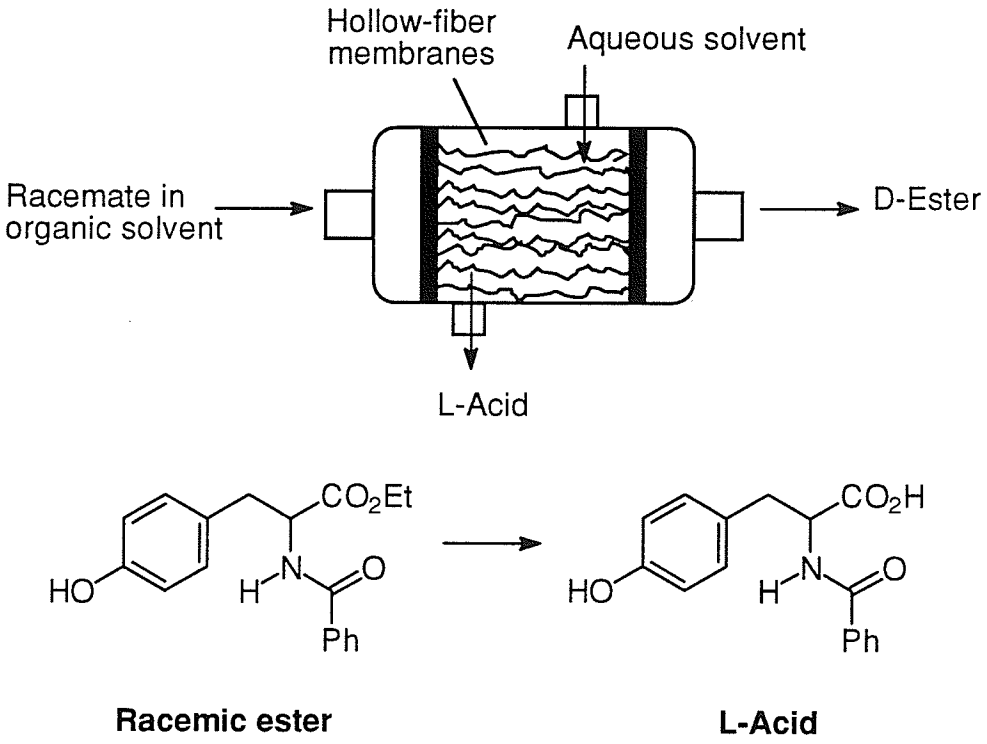
Kinetic resolution is the third and final resolution technique based on chemical processes that will be discussed here. A kinetic resolution is a chemical reaction of a racemate in which one of the enantiomers forms a product at a faster rate than the other. Resolution is achieved on recovery of the unreacted enantiomer from the product mixture. In order to regenerate the enantiomer which underwent reaction with the chiral reagent, the original enantioselective reaction is reversed in a nonselective manner (scheme 1.9).

Scheme 1.9



One such system for separating enantiomers, which is based on a kinetic resolution process similar to that shown in scheme 1.9, is the hollow-fiber

Scheme 1.10



Racemic ester **L-Acid**

membrane system employed in the separation of the racemic ethyl ester of *N*-benzoyltyrosine. Here, the racemic form of the compound enters the system dissolved in a relatively nonpolar solvent, and flows through a hollow fiber bundle

which contains enzymes immobilized within the fiber resin. The enzymes enantioselectively hydrolyze the racemic ester to the L-acid, and an aqueous solvent, which passes over the outside of the hollow fibers, carries the polar acidic product away. The original D-ester is carried out of the opposite end of the hollow fibers (scheme 1.10).[13]

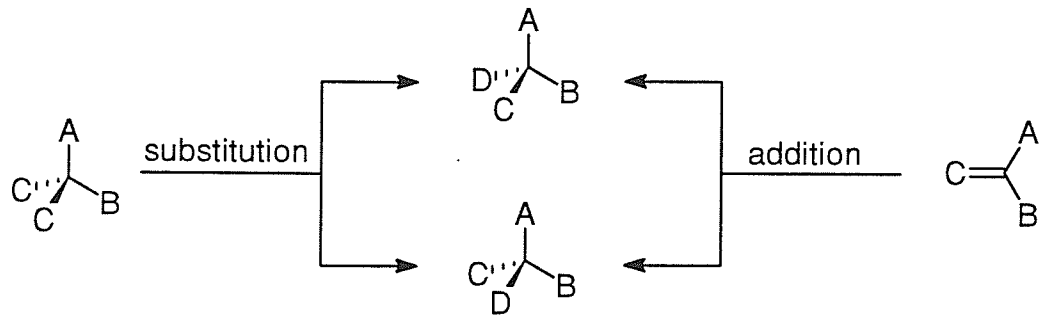
iv) Asymmetric Synthesis

An achiral, prochiral molecule, or unit within a molecule, can often be induced to undergo reaction in such a way that, of the two possible chiral forms which could result, one is formed to a greater extent than the other. Such a process, referred to as an asymmetric reaction, can be used as a means to generate chiral molecules. It should be noted here that some ambiguity exists regarding the term asymmetric synthesis. The definition given above includes both enantioselective and diastereoselective processes. However, the term asymmetric synthesis is sometimes used to refer to enantioselective processes exclusively. Henceforth, the former definition will be used in preference to the latter.

The introduction of new stereogenic centers into an achiral molecule is generally achieved using either one or the other of two different processes. The first of these two processes involves selective addition to one of the enantiotopic or diastereotopic faces of a double bond, and the second entails selective modification or substitution of one of the enantiotopic or diastereotopic ligands in a molecule (scheme 1.11).[1] A vast array of reactions exist whereby the processes just described can be achieved. Each of these reactions can,

however, be classified as belonging to one of relatively few generalized processes, some of which will be described here.

Scheme 1.11

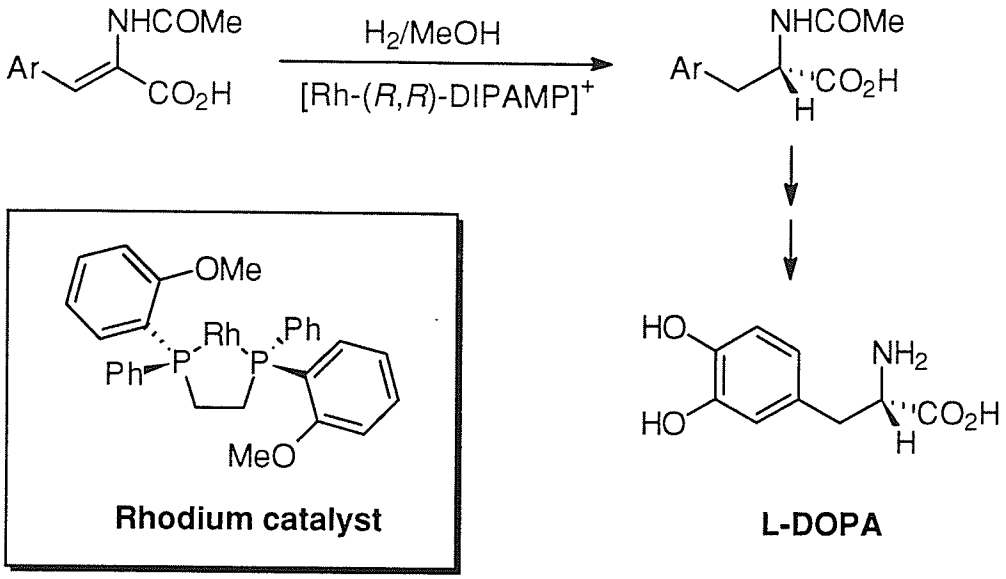


a) Asymmetric Synthesis with Chiral Catalysts

Asymmetric reactions involving chiral catalysts are among the most popular methods for introducing new stereogenic centers into molecules. These reactions can be further classified as those in which catalysis is achieved by chiral transition metal complexes, or by chiral bases, or by chiral Lewis acids.

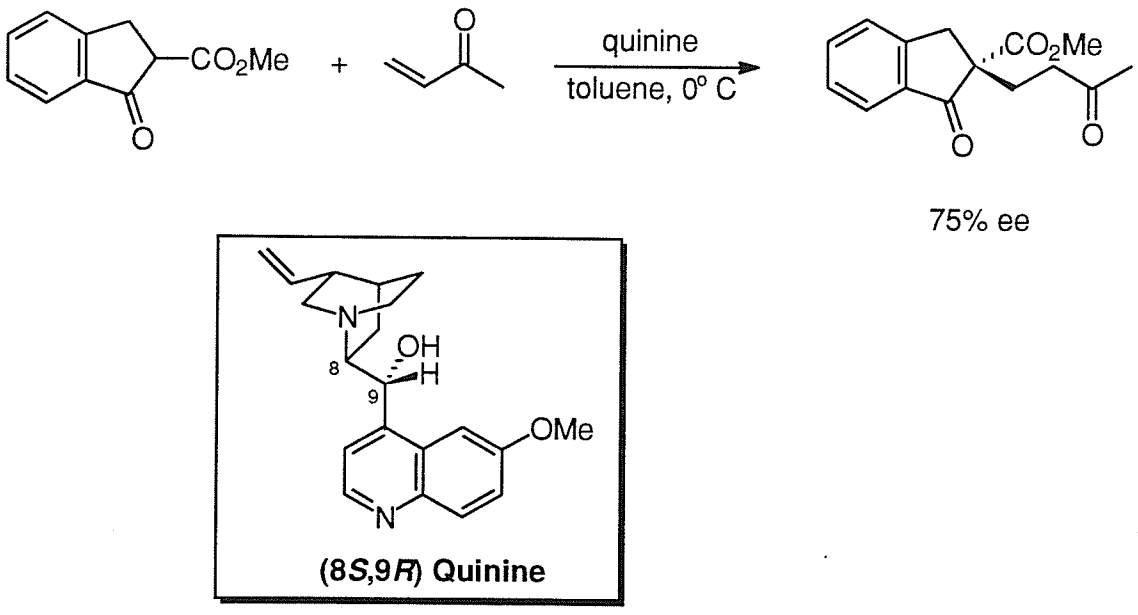
Enantioselective hydrogenations are one example of the way in which chiral transition metal complexes can be utilized for the asymmetric synthesis of molecules. Various soluble chiral rhodium and ruthenium complexes have, for example, been examined in the search for effective asymmetric synthetic routes to amino acids.[14] The synthesis of L-DOPA was achieved with 82% enantiomeric excess using the chiral rhodium based catalyst DIPAMP (scheme 1.12).[15] Asymmetric induction has also been achieved using chiral transition metal complexes in the epoxidation of alkenes and in cyclopropanations, among other reactions.[1]

Scheme 1.12



Chiral bases have long been used for the preparation of enantiomerically pure or enriched compounds. For instance, *Cinchona* alkaloids have been employed to carry out alkylation reactions of α,β-unsaturated enones in an

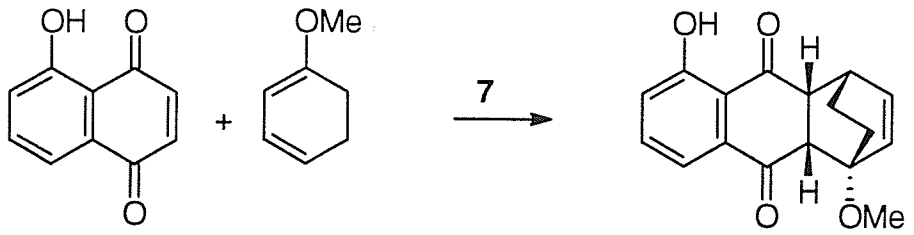
Scheme 1.13



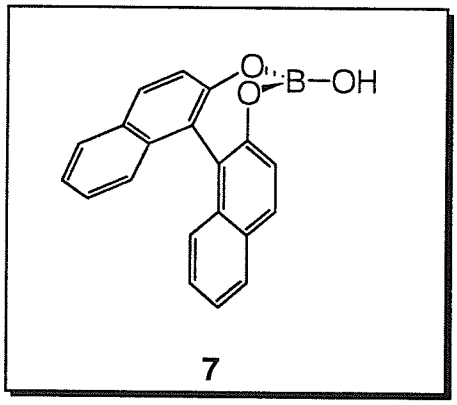
asymmetric fashion. An example of this type of reaction is given in scheme 1.13, where the *Cinchona* alkaloid quinine is used.[16]

Chiral Lewis acid catalysts have been utilized successfully to induce asymmetry in [4 + 2] cycloadditions, as well as in other reactions. The binaphthyl boronate **7**, for example, was found to direct the formation of compound **8** with 98% enantiomeric excess from diene **9** and dienophile **10** (scheme 1.14).[17]

Scheme 1.14



10 **9** **8**



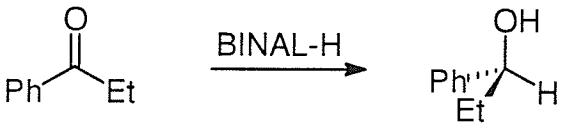
7

b) Chiral Nonracemic Reagents in Asymmetric Synthesis

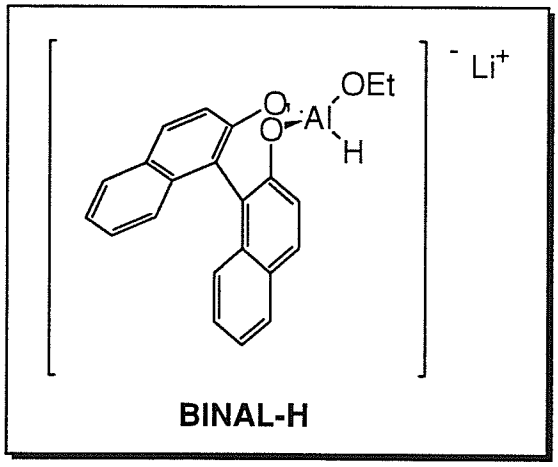
A wide range of chiral reagents are available for carrying out asymmetric reactions. Within this category of reactions, one finds reductions with chiral complex hydrides. A significant amount of work has been invested in obtaining chiral hydride reagents which afford good levels of enantioselection in the

reduction of ketones, and the like. Modification of lithium aluminum hydride by attachment of chiral ligands has been the focus of much of this work.[18,19] Enantiomeric excesses of 95-100% have been reported for the reduction of various ketones using the binaphthyl derivative BINAL-H (scheme 1.15). Hydride reductions, using chiral boranes for example, has also received a considerable amount of attention. Diisopinocampheylchloroborane has been established as the reagent of choice, in so far as this type of compound is concerned, for the reduction of a wide range of ketones.[20]

Scheme 1.15



98% ee

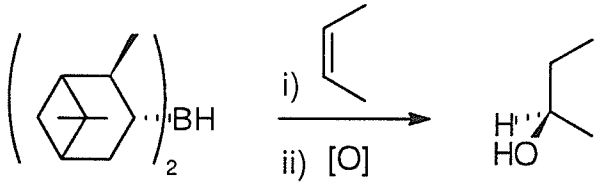


BINAL-H

Chiral boranes have also been used in the formation of alcohols from alkenes, such that an enantiomeric preference for one product over the other is established. Such a process, which relies on an oxidative work up procedure, is referred to as a hydroboration-oxidation reaction. The reaction of *cis* alkenes

with optically active diisopinocampheylborane (**11**) has been shown to lead, after oxidation with alkaline hydrogen peroxide, to optically active secondary alcohols.[21] Indeed, the hydroboration of *cis*-2-butene in diglyme with (-)-diisopinocampheylborane provided (*R*)-2-butanol in 87% enantiomeric excess (scheme 1.16).[22] Many other chiral boranes have been employed in a similar manner.

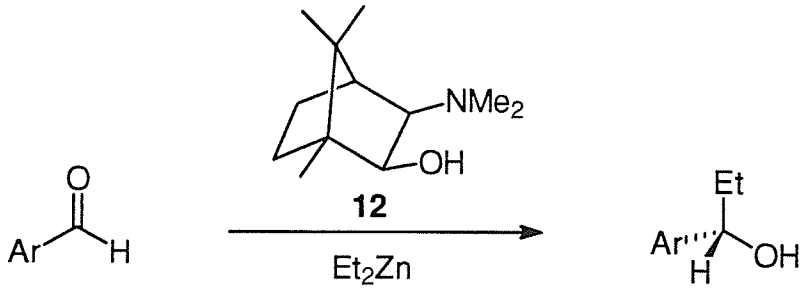
Scheme 1.16



11

Chiral reagents that undergo nucleophilic addition reactions can be used to form new carbon-carbon bonds asymmetrically. For example, the reaction of aromatic aldehydes with the chiral organometallic complex formed between 3-*exo*-dimethylaminoisoborneol (**12**) and either triethyl zinc or trimethyl zinc, proceeds enantioselectively to give the corresponding secondary alcohol in a carbon-carbon bond forming reaction (scheme 1.17).[23]

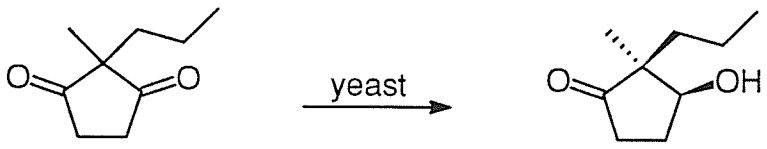
Scheme 1.17



c) Enzymes in Asymmetric Synthesis

Enantioselective syntheses can also be achieved by the use of naturally occurring enzymes. Various classes of enzymes exist, each of which is responsible for a different type of reaction. For example, bakers' yeast, which contains a *Saccharomyces* species possessing an oxidoreductase enzyme, has been used in the enantioselective reduction of the β-diketo compound **13** to the β-hydroxy ketone **14** (scheme 1.18).[24]

Scheme 1.18



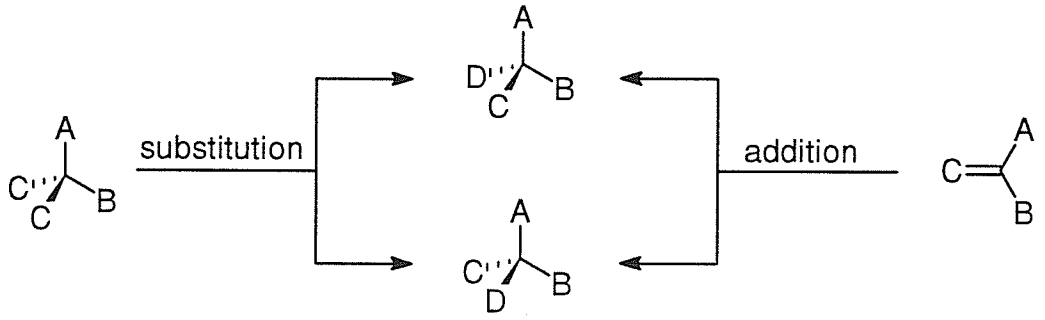
13 **14**

d) Chiral Auxiliaries in Asymmetric Synthesis

The final method for achieving the asymmetric synthesis of a given compound which will be discussed here, is a method which relies on a diastereoselective reaction to induce the desired asymmetry. Scheme 1.19 exemplifies a diastereoselective reaction when the substrates undergoing reaction are chiral. In order to carry out this type of reaction, a chiral auxiliary is temporarily attached to an achiral substrate, thereby creating a chiral environment. When allowed to react under appropriate conditions, the substrate acquires new stereogenic centers and, if more than one isomeric product is formed, the products will, as a matter of consequence, bear a diastereomeric relationship to one another. Once the appropriate diastereomer is acquired in

pure form, the chiral auxiliary is cleaved generating the desired chiral molecule. This type of synthesis is particularly convenient in that, for a synthesis which is not 100% diastereoselective, the diastereomers which result from the reaction can usually be separated by relatively straight forward purification techniques, given the inherent chemical and physical differences between the diastereomers.

Scheme 1.19

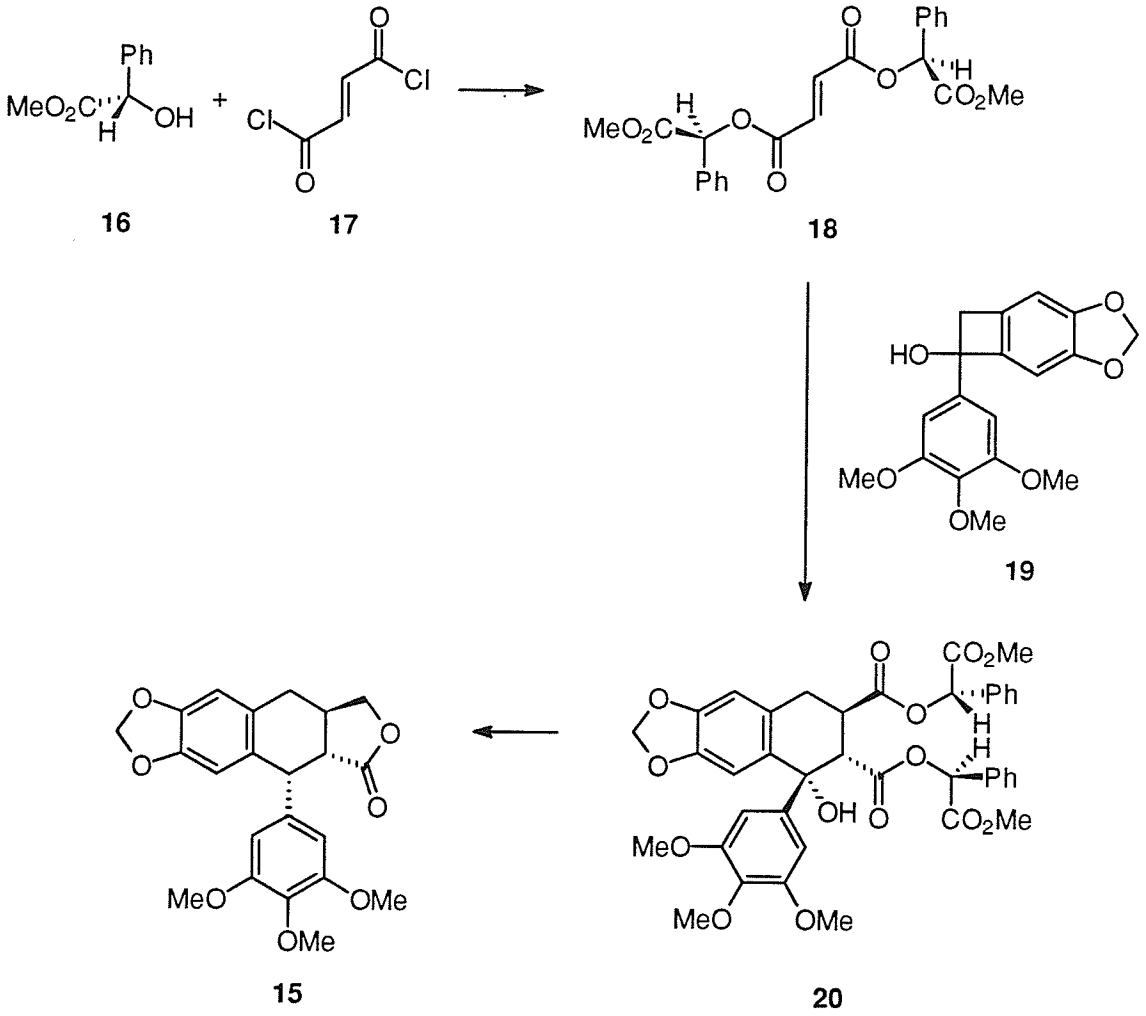


In a recent synthesis of (-)-deoxypodophyllotoxin (**15**),[25] the (*S*)-methyl mandelate group (**16**) was used as a chiral auxiliary to control the stereochemical outcome of a particular Diels-Alder reaction. The mandelate group was attached to fumaryl chloride (**17**) and the product of that reaction, the fumarate of methyl (*S*)-mandalate (**18**), was reacted with the α-hydroxy-α-aryl-*ortho*-quinodimethane **19**, giving the *endo* polyester cycloadduct **20** diastereoselectively. This compound was subsequently carried through a series of reactions yielding, ultimately, (-)-deoxypodophyllotoxin (**15**) (scheme 1.20).

It is hoped that, based on what has been presented thus far, some indication as to the vastness of the topic of stereochemistry has been made. In fact, the information that has been discussed in this section represents only a very small portion of what can be said about stereochemistry. Rather than

elaborate on stereochemistry to any further extent, the focus of this thesis introduction will now shift to a discussion of lignans, during which some of what has been presented up until now may be useful.

Scheme 1.20

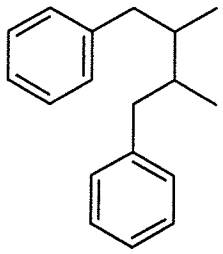


1.2 Lignans

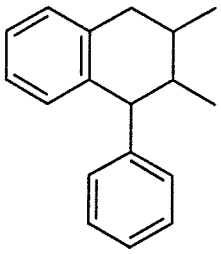
A) Introduction

The term lignan was advanced in 1936 by R. D. Haworth in order to describe a class of optically active plant products possessing a 2,3-dibenzylbutane carbon skeleton (**21**).[26] The aryltetralin lignans comprise a

Scheme 1.21



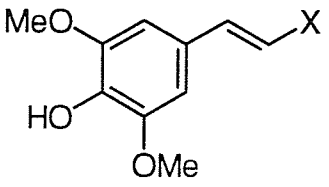
21



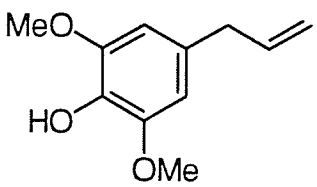
22

particular sub-class of lignans whose members possess the fused ring system shown for compound **22** (scheme 1.21). In nature, lignans are formed by the oxidative dimerization of various C_3 substituted phenols of which compounds **23**

Scheme 1.22



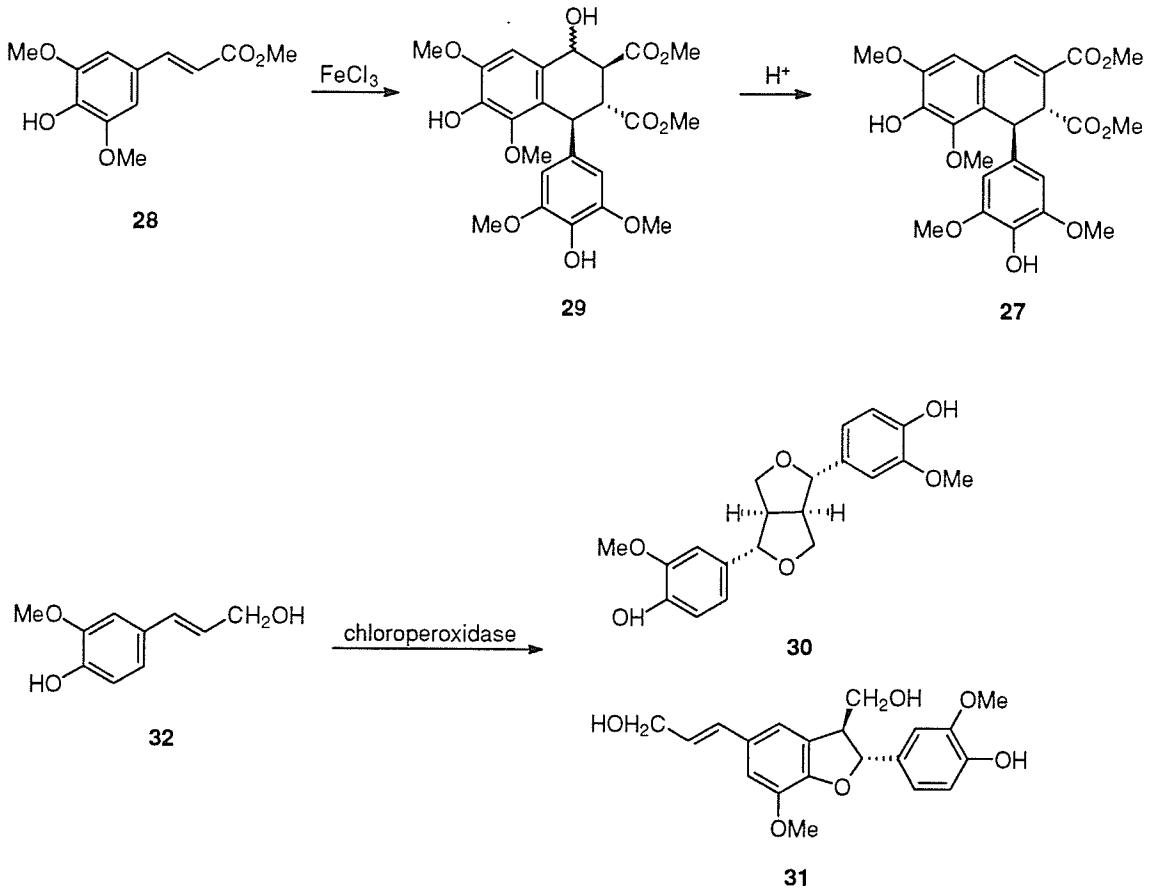
23 X = CH_2OH
24 X = CO_2Me
25 X = Me



26

to **26** are representative (scheme 1.22).[27] In fact, this oxidative dimerization process has been applied to the laboratory synthesis of certain lignan compounds, such as thomasidioic acid dimethyl ester (**27**) from methyl sinapate[28] (**28**) *via* compound **29**. Pinoresinol[29] (**30**) and dehydrodiconiferyl

Scheme 1.23



alcohol[30] (**31**) have also been prepared from coniferyl alcohol (**32**) *via* an oxidative dimerization procedure (scheme 1.23). The various structures which lignans possess can be accounted for by the many different ways in which the

phenolic radical generated by the oxidation of the C_3 substituted phenols can couple.

The occurrence of lignans in nature is widespread and they have been shown to posses considerable diversity in their biological activity. As such, there is a substantial interest in these compounds and their synthesis. Certain lignans are, for example, known to exhibit anti-tumor activity,[31,32] whereas others are known for their activity as anti-fungal agents.[33] A slightly more recent suggestion, stemming from the isolation of particular lignans from animals, is that they exhibit hormonal activity, acting to control cell growth.[34,35]

B) Deoxysikkimotoxin

i) Background

Podophyllum is a term which is reserved for the description of the dried roots and rhizomes obtained from plants belonging to species of *Podophyllum*, a member of the Berberidaceae family. When the podophyllum is extracted with alcohol, the resinous material obtained is referred to as podophyllin, a preparation that has long been included in the pharmacopoeia of the United States and several European countries.[36]

Certain species of *Podophyllum* have been known to possess medicinal value, since times dating back to the early 1600s.[37] The North American Indians and the native people of the Himalayas, for example, used these plants extensively for the treatment of warts.[38] Those species of *Podophyllum*

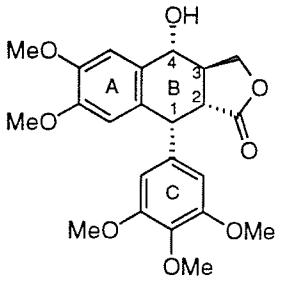
indigenous to North America were later used by early North American colonists as a cathartic, anthelmintic, emetic and mortal poison.

Three species of *Podophyllum* have been extensively studied in an attempt to characterize the podophyllin isolated from each. *Podophyllum peltatum*, more commonly known as the American mandrake or May apple, was first described in a general sense and given its modern botanical name by Linnaeus in 1753.[39] The plant is indigenous to North America, growing along the eastern coast from Quebec to Florida and westward to Minnesota and Texas. The first extensive chemical study of *Podophyllum peltatum* was pursued in 1880 by Podowyssotzki.[40] *Podophyllum emodi* is a plant which resembles *Podophyllum peltatum*, but grows in the interior regions of the Himalayan Mountains from Sikkim to Hazara. It was first described by Wallich in 1824[41] and first underwent chemical investigation by Umney in 1892.[42] More recently, the species *Podophyllum sikkimensis*, was described by Chatterjee and Mukerjee.[43] *Podophyllum sikkimensis* is native to the Himalayan region and, since the 1950s, has been the subject of thorough chemical investigation.

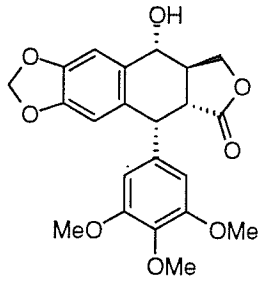
Many research groups have pursued chemical and pharmacological investigations of podophyllum, as reviewed in detail by Hartwell and Schrecker.[37] By 1955, a total of 16 compounds, four of which were pigments, had been isolated from the podophyllin obtained from various species of *Podophyllum*. All of the compounds isolated, excluding the pigments, are shown in scheme 1.24. It was clearly established by this time that, although the physiological properties

of podophyllins from different sources appeared essentially the same, the chemical composition differed significantly.

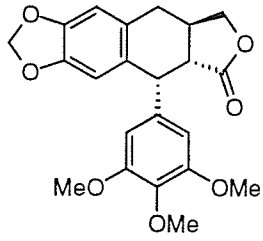
Scheme 1.24



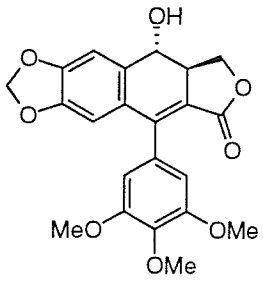
sikkimotoxin



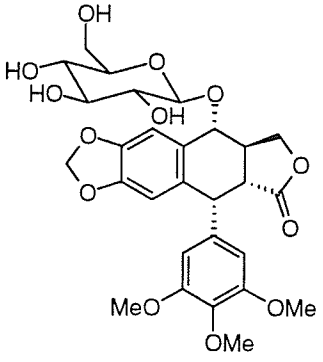
podophyllotoxin



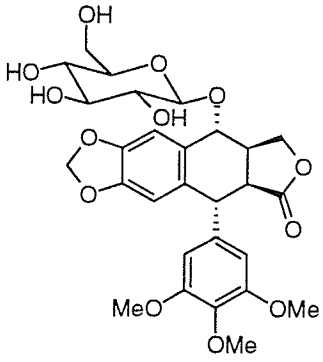
deoxypodophyllotoxin



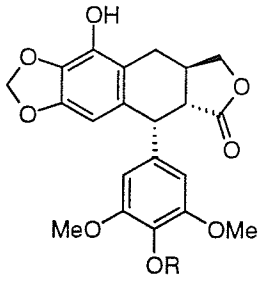
dehydropodophyllotoxin



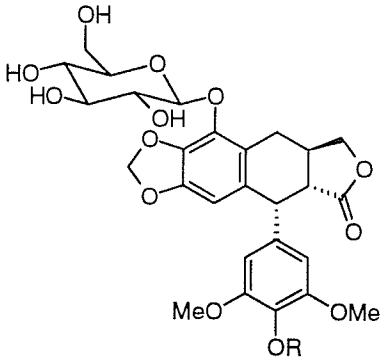
podophyllotoxin glucoside



picropodophyllotoxin glucoside



α-peltatin (R = H)
β-peltatin (R = Me)



α-peltatin glucoside (R = H)
β-peltatin glucoside (R = Me)

Certain common characteristics can be described which pertain to all of the compounds isolated from podophyllin to date: 1) Ring C in each of the compounds is a fully or partially methylated pyrogallol nucleus. 2) Ring A in

each of the compounds is a catechol derivative. 3) With the exception of the C2 epimerized picropodophyllotoxin derivatives, and the dehydropodophyllotoxin derivatives, all of the compounds possess a 1,2-*cis*-2,3-*trans* stereochemistry. 4) All of the compounds possess the same absolute stereochemistry at the C3 carbon.

ii) Isolation, Characterization and Biological Activity

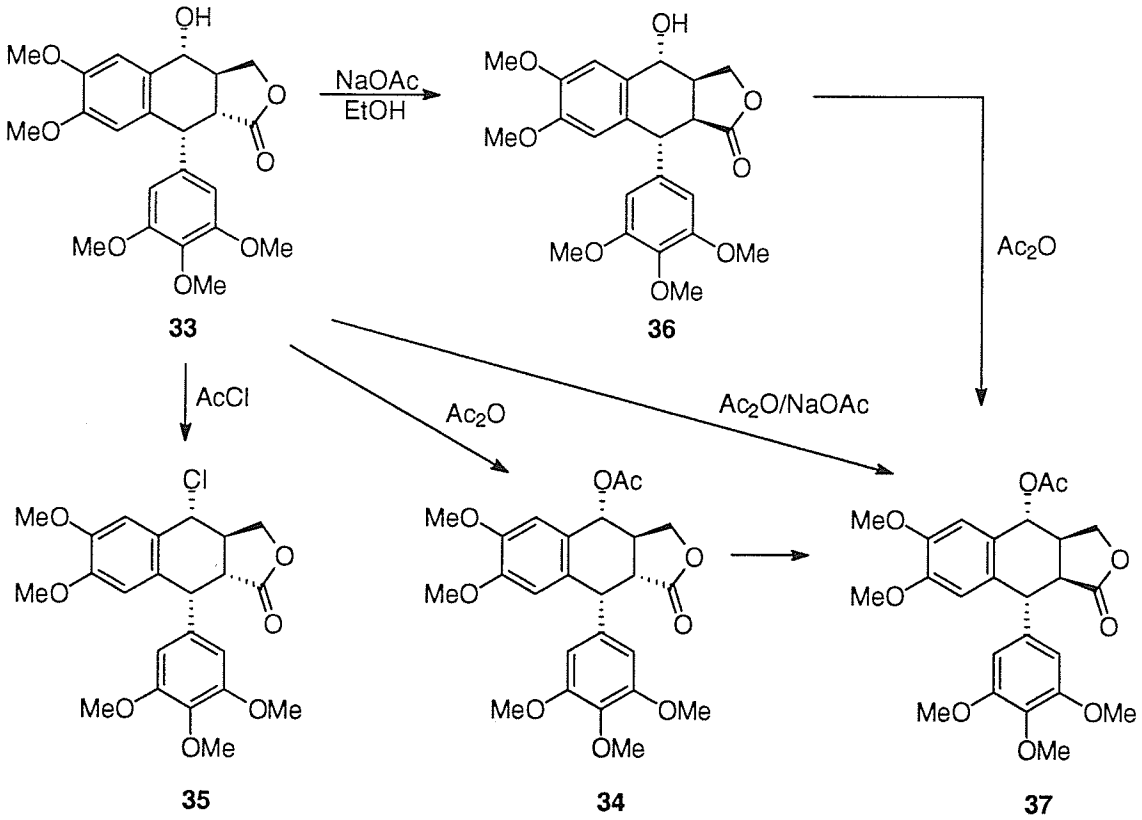
Sikkimotoxin (**33**) was first isolated in 1950 by Chaterjee and Datta from the roots and rhizomes of *Podophyllum sikkimensis*.[44] These parts of the plant were subjected to ethanol extraction *via* slow percolation of the alcohol through them. Precipitation with dilute hydrochloric acid, followed by chloroform extraction and crystallization from ethanol/benzene, gave a solid with a melting point of 120 °C. The solid obtained was then dried under vacuum at 90 °C, and was found to possess the empirical formula $C_{23}H_{26}O_8$, with five of the oxygens in the form of methoxy substituents.

The structure of sikkimotoxin was originally deduced based on work carried out by Chatterjee and Chakravarti.[45] The presence of a lactone ring was revealed from the saponification equivalent, and that of an alcoholic hydroxyl group from the formation of a monoacetyl derivative, acetyl-sikkimotoxin (**34**), and the failure of the compound to react with diazomethane. The hydroxyl group at C4 in sikkimotoxin was replaced with chlorine using acetyl chloride to give sikkimotoxin chloride (**35**). The strongly levorotatory sikkimotoxin was found to undergo base catalyzed epimerization to give the weakly dextrorotatory

picrosikkimotoxin (**36**). Acetyl-picrosikkimotoxin (**37**) was obtained by direct acetylation of picrosikkimotoxin, by treatment of sikkimotoxin with acetic anhydride and sodium acetate, and by direct epimerization of acetyl-sikkimotoxin (scheme 1.25).

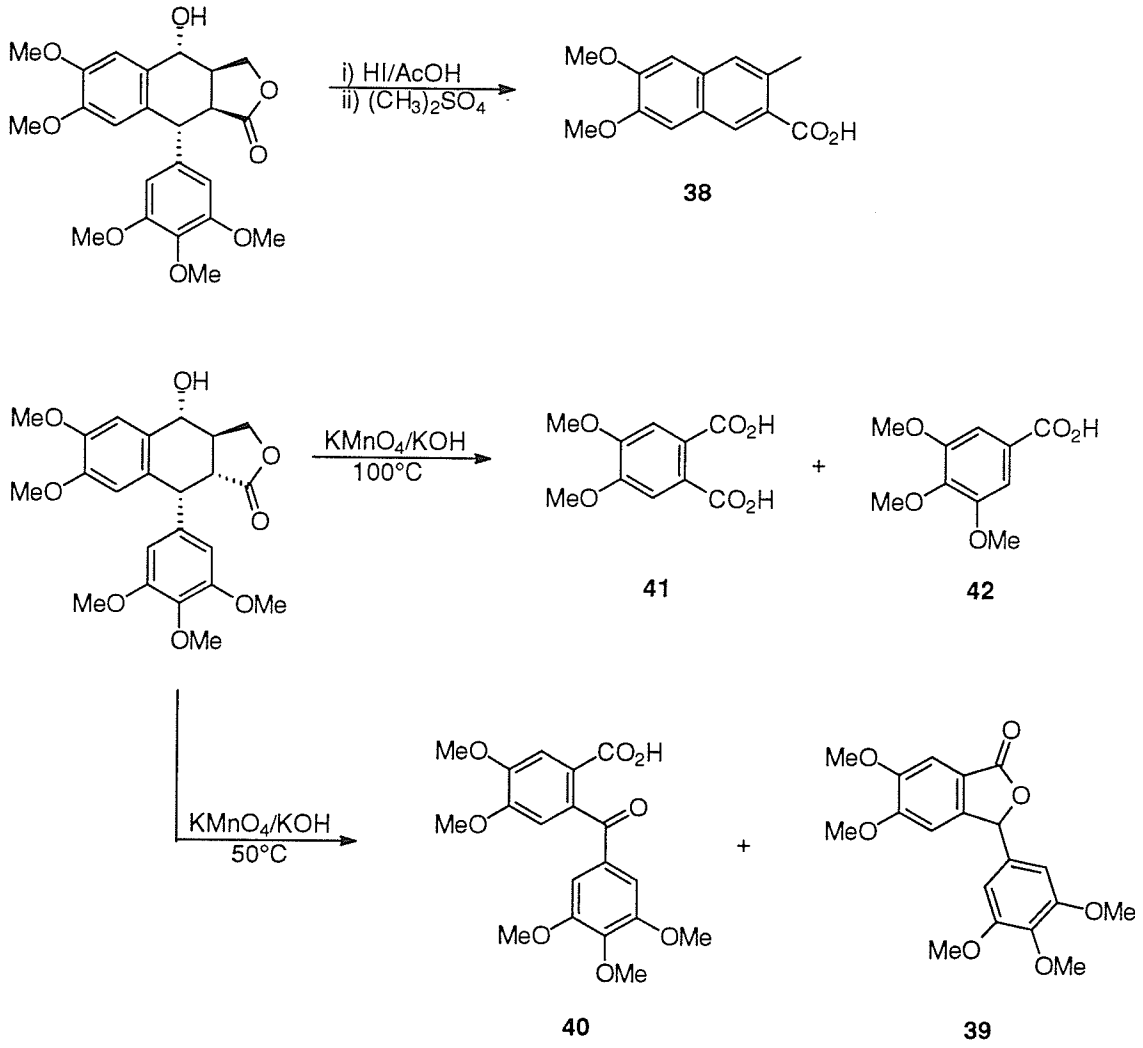
Based on the similarity of these results to results obtained earlier from work which had been carried out for the purpose of determining the structure of podophyllotoxin, it was hypothesized that sikkimotoxin was derived from podophyllotoxin, by the replacement of the methylenedioxy group with two methoxy residues. The correctness of this hypothesis was demonstrated by Chatterjee and Chakravarti through the isolation of several degradation

Scheme 1.25



products, which were analogous to those obtained from podophyllotoxin and picropodophyllotoxin (the C2 epimerized from of podophyllotoxin), by a similar degradation procedure.[46,47,48,49,50] Thus, hydroiodic acid degradation of

Scheme 1.26



sikkimotoxin, followed by methylation, gave phyllomeronic acid dimethyl ether (**38**). Sikkimotoxin was oxidized by alkaline permanganate to 5,6-dimethoxy-3-(3,4,5-trimethoxyphenyl)-phthalide (**39**) and 4,5-dimethoxy-2-(3,4,5-

trimethoxybenzoyl)-benzoic acid (**40**). At higher temperatures, the same oxidation process gave *meta*-hemipinic acid (**41**) and 3,4,5-trimethoxybenzoic acid (**42**) (scheme 1.26).

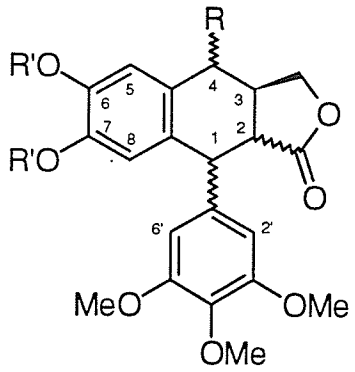
Further corroboration for the structure which had been proposed for sikkimotoxin came when picropodophyllin was converted to picrosikkimotoxin by cleavage of the methylenedioxy group, followed by methylation.[37]

The biological activity of sikkimotoxin was first investigated in 1954 by Kelly and Hartwell,[51] where a resinous fraction of the compound was found to be damaging to mouse sarcoma 37. As well, several derivatives of sikkimotoxin have been obtained from synthetic methods, and their biological activities have been assayed.

Sikkimotoxin obtained from synthetic means was found to inhibit the proliferation of P-815 mastocytoma cells *in vitro* with an ID-50 of 0.1 μg/mL. ID-50 refers to the concentration of a given compound that is required in order to inhibit the growth of mouse tumor cells by 50%. In fibroblast cultures, sikkimotoxin shows activity of the spindle poison type, as do all of its derivatives. That is, it causes the inhibition of cell spindle formation by binding to tublin and preventing it from polymerizing into the microtubles which form the spindle fibers. The net result of poisoning of this type is the cessation of cell division during metaphase and chromosomal clumping.[52] The stereoisomers of sikkimotoxin that have been tested are, for the most part, inactive in the mastocytoma test at a concentration of 10 μg/mL (compounds **43**, **45** and **46** in scheme 1.27).

Episikkimotoxin (**44**) is the only stereoisomer of sikkimotoxin possessing the ability to reduce the proliferation of mastocytoma cells, with an ID-50 of 6 μg/mL.

Scheme 1.27



Cytostatic potency of sikkimotoxin and derivatives

Com-pound	R	R'	H_{c1}-H_{c2}	H_{c2}-H_{c3}	H_{c3}-H_{c4}	Name	ID-50 P815 μg/mL
43	OH	Me	*trans*	*cis*	*trans*	picrosikkimotoxin	>10
44	OH	Me	*cis*	*trans*	*cis*	episikkimotoxin	6
45	OH	Me	*cis*	*cis*	*trans*	epipicrosikkimotoxin	>10
46	OH	Me	*trans*	*trans*	*trans*	epiisosikkimotoxin	>10
2	H	Me	*cis*	*trans*	-	deoxysikkimotoxin	0.2
47	H	Me	*trans*	*cis*	-	deoxypicrosikkimotoxin	>10
48	H	H	*cis*	*trans*	-	6,7-O-demethylde-oxysikkimotoxin	0.3

Deoxypodophyllotoxin was subjected to conditions for the selective cleavage of its methylenedioxy group, which gave 6,7-O-demethyldeoxysikkimotoxin (**48**). Compound **48** was then methylated to give deoxysikkimotoxin. Epimerization of deoxysikkimotoxin yielded the picro compound **47**. The cytostatic potency of each of these compounds is given in scheme 1.27. The most biologically active among these compounds were

assayed *in vivo* for suppression of mouse leukemia L-1210, but none of them increased the survival time of the disease-bearing animals.

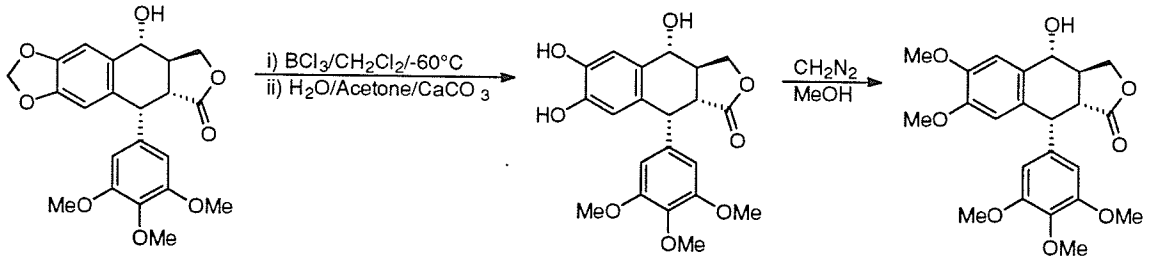
iii) Synthesis

Synthetic efforts directed towards deoxysikkimotoxin and sikkimotoxin are virtually nonexistent in the scientific literature. In fact, an exhaustive search of the literature has revealed only one total synthesis of deoxysikkimotoxin,[53] and one synthesis of sikkimotoxin.[54] It is important to note that, from a synthetic point of view, any synthesis of deoxysikkimotoxin may be considered a synthesis of sikkimotoxin. This is due to the fact that the C4 hydroxyl group of sikkimotoxin may be introduced directly from deoxysikkimotoxin, according to a procedure developed by Yamaguchi and co-workers.[55] As well, any synthesis of sikkimotoxin may be considered a synthesis of deoxysikkimotoxin, due to the fact that the C4 carbon-oxygen bond readily undergoes hydrogenolysis leaving a methylene group, in a reaction analogous to that which is used to convert podophyllotoxin to deoxypodophyllotoxin.[56,57] Thus, it is convenient to discuss the synthetic efforts directed at sikkimotoxin and deoxysikkimotoxin collectively.

The one synthesis of optically pure sikkimotoxin which appears in the literature was carried out in 1964 by Schreier. His chiral pool synthesis is, however, only a partial synthesis given that it uses as a starting compound, optically active podophyllotoxin isolated from natural sources. In his synthesis, (-)-podophyllotoxin was treated with boron trichloride in dichloromethane in order to selectively cleave the methylenedioxy group, giving compound (**49**).

Treatment of this diphenolic compound with diazomethane then gave optically active (-)-sikkimotoxin (**33**) directly (scheme 1.28).

Scheme 1.28



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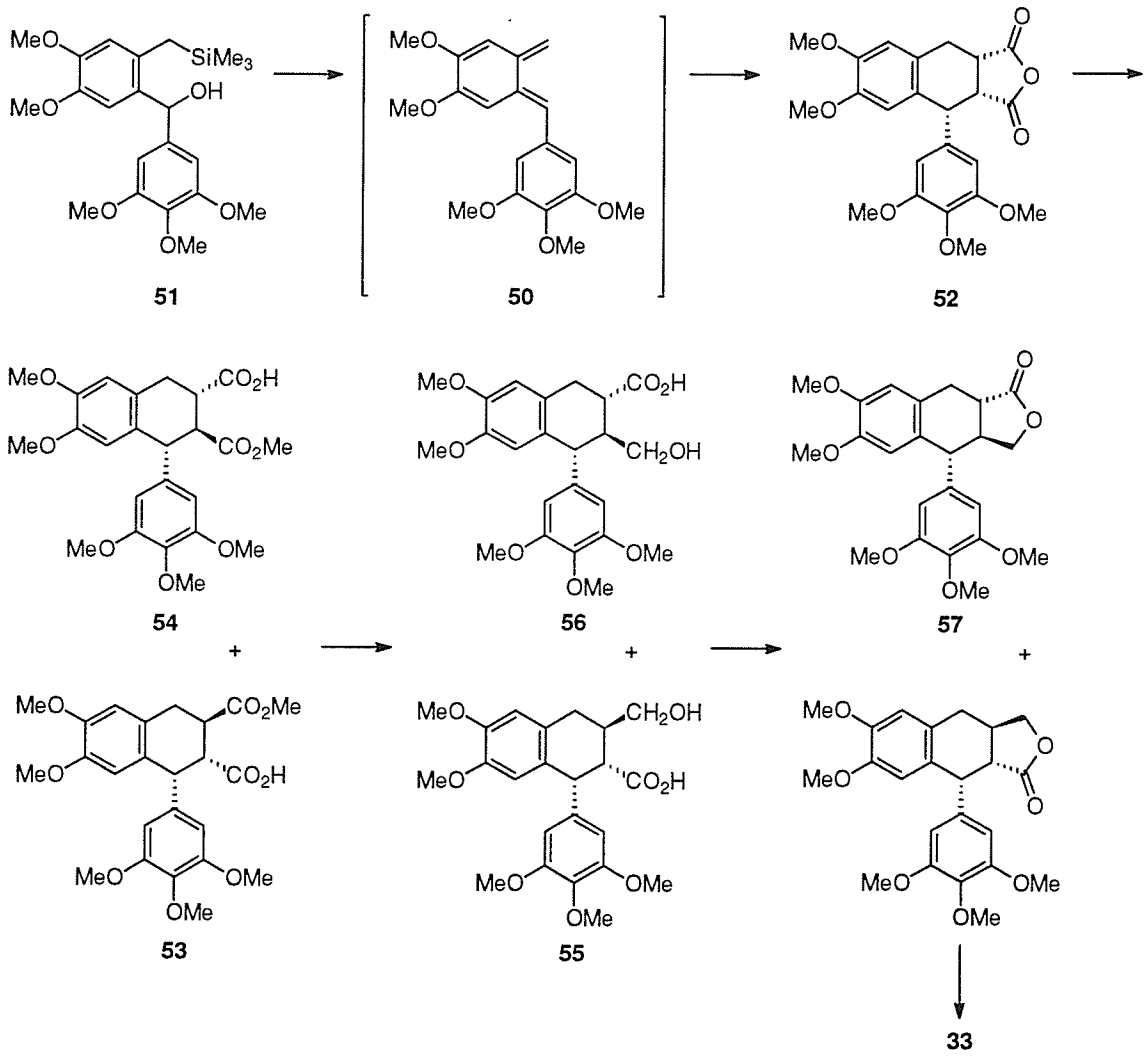
The only synthesis of deoxysikkimotoxin which appears in the literature is, in fact, part of a total synthesis of sikkimotoxin. The synthesis, carried out by Takano *et al.*, was not an asymmetric synthesis and, thus, gave racemic deoxysikkimotoxin and, ultimately, racemic sikkimotoxin. The method used was based on the Benzo-Peterson reaction,[58] a reaction used to generate an *ortho*-quinodimethane, followed by a Diels-Alder reaction. The *ortho*-quinodimethane in question (**50**) was obtained from the benzhydrol **51**, and underwent a Diels-Alder reaction with maleic anhydride while under reflux in toluene, to generate the all *cis endo* cycloadduct **52**. Although the cycloadduct obtained possessed the desired 1,2-*cis* stereochemistry of sikkimotoxin, it had the undesired 2,3-*cis* stereochemistry as well. Thus, in an attempt to correct this shortcoming, compound **52** was refluxed in methanolic sodium methoxide in hopes of achieving compound **53** selectively. This instead gave a mixture of the half esters **53** and **54**. The unpurified mixture of compounds **53** and **54** was treated with lithium triethylborohydride, which gave a mixture of the hydroxy acids **55**

and **56**. This mixture was reacted to give deoxysikkimotoxin and lactone **57** respectively. Chromatography at that point gave pure, racemic deoxysikkimotoxin which was subsequently converted to racemic sikkimotoxin (**33**) with an approximately 8% overall yield from compound **51** (scheme 1.29).

Scheme 1.29

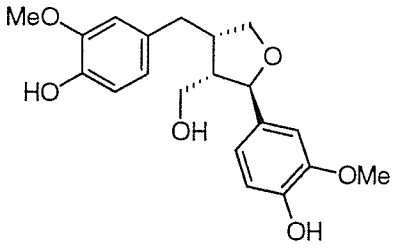


C) Isolariciresinol Dimethyl Ether

i) Background

To date, a considerable number of resins have been isolated from various plant sources and determination of the exact chemical composition of these resins has posed a significant challenge. Most resins isolated from plant sources posses some form of biological activity, with many of those exhibiting medicinal value. Lariciresinol (**58**), isolariciresinol (**59**) and phyltetralin (**60**) are each examples of compounds which have been isolated from the resinous extract of plants (scheme 1.30). These compounds are of particular significance here, as they are all compounds which are potential sources of isolariciresinol dimethyl ether. In fact, the latter two possess the same relative stereochemistry at carbons 1, 2 and 3 as isolariciresinol dimethyl ether.

Scheme 1.30



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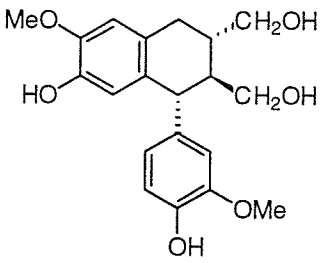

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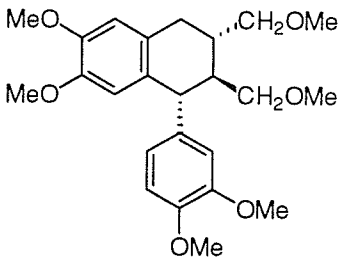


60

Lariciresinol is the primary constituent that is exuded from the bark of *Larix decidua*, more commonly known as the European larch, on injury.[59] *Larix decidua* is a deciduous conifer whose growth is wide spread in European countries of mild lowland climate. Isolariciresinol is among the compounds

isolated from *Reseda suffruticosa*, an endemic plant of Spain, present throughout the Iberian Peninsula on calcareous soil.[60] The leaves of *Phayllanthus niruri*, a member of the Euphorbiaceae family, is the source of phyltetralin, which is isolated along with four other lignans possessing a similar carbon skeleton.[61] It is a bitter plant, which has often been used in the treatment of jaundice, asthma and bronchial infections.[62]

ii) Isolation and Characterization

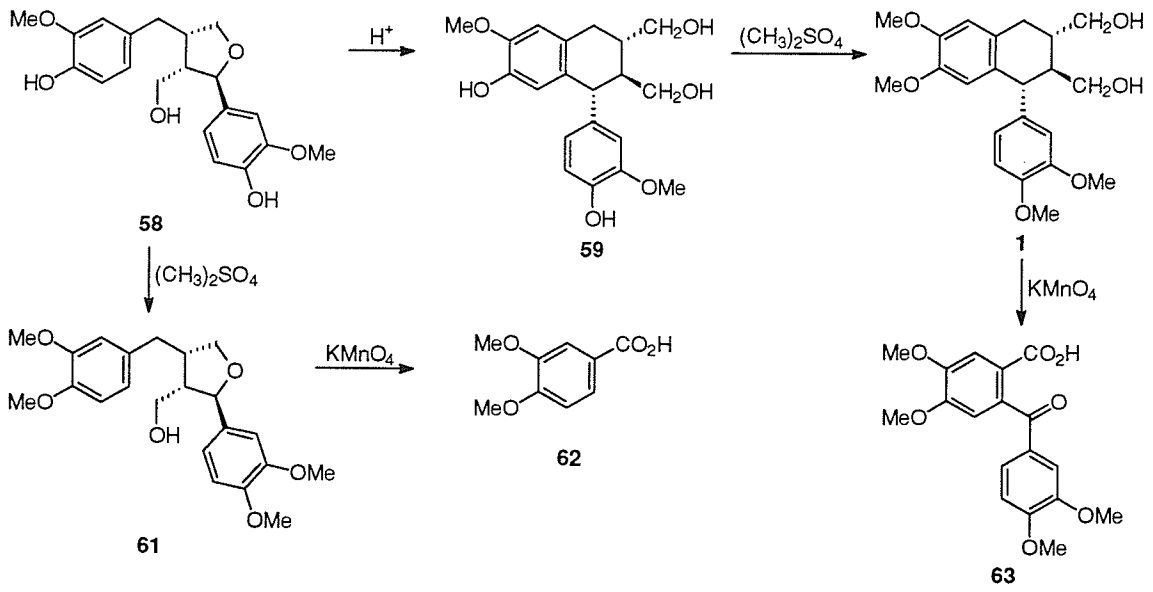
Isolariciresinol dimethyl ether was first obtained during the characterization of lariciresinol and, as a consequence, much of the work carried out towards its structural elucidation is in conjunction with the structural determination of lariciresinol.[59]

The resin of injured *Larix decidua* was collected from recently felled trees in a viscous, cream colored form. It was boiled in alcohol and the extract filtered and concentrated under vacuum to give a brown, viscous residue. An alcoholic solution of this residue was combined with aqueous potassium hydroxide, causing the precipitation of the potassium salt of lariciresinol. The salt was filtered and acidified with aqueous acid. Extraction and crystallization afforded pure lariciresinol. The vacuum dried product was found to possess the empirical formula $C_{20}H_{24}O_6$, with two of the oxygens in the from of methoxy substituents, and three as hydroxyls, two of which were phenolic.

That lariciresinol was converted to isolariciresinol by boiling it with dilute formic acid, was evidenced by the disappearance of the etheral oxygen and the

appearance of a second, primary hydroxyl group (scheme 1.31). Alkaline dimethyl sulfate treatment of isolariciresinol was found to give isolariciresinol dimethyl ether directly. The potassium permanganate mediated oxidative degradation of lariciresinol dimethyl ether (**61**), obtained from the methylation of larisiresinol, gave 3,4-dimethoxybenzoic acid (**62**). The same procedure gave, in the case of isolariciresinol dimethyl ether, 2-veratroylveratric acid (**63**). Based on the results obtained from these experiments and others of a similar nature, the structure shown for compound **1** was proposed by Haworth and Kelly for isolariciresinol dimethyl ether. Their justification for the relative stereochemistry

Scheme 1.31



shown, was based on the assumption that the conversion of lariciresinol to isolariciresinol proceeded *via* a carbonium ion mechanism. Hence, the more stable 1,2-*trans*-2,3-*trans* stereoisomer was expected to prevail. This hypothesis was proven correct in 1954 by Schrecker and Hartwell[63] by the synthesis of

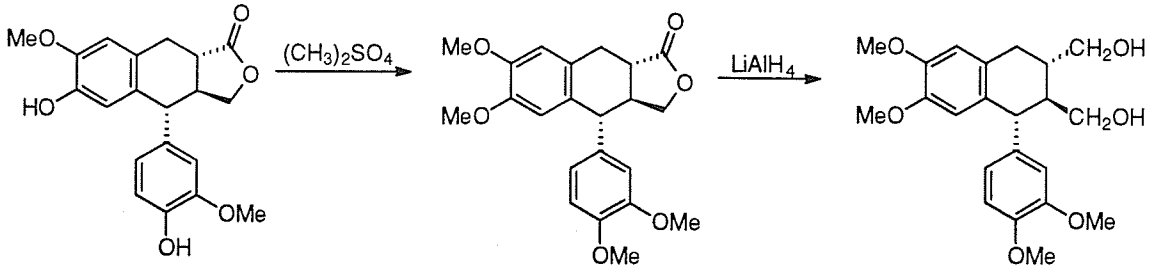
isolariciresinol dimethyl ether from optically active α-conidendrin (**64**), a compound whose structure was well established.

iii) Synthesis

A comprehensive examination of the chemical literature has revealed a total of three syntheses directed toward isolariciresinol dimethyl ether. Of these synthetic methods, however, only one, that achieved by Charlton and Alauddin, was carried out as a total synthesis in an asymmetric fashion.[64] Isolariciresinol dimethyl ether was synthesized in an optically pure state prior to the synthesis by Charlton and Alauddin, but this was only a partial synthesis beginning with optically pure α-conidendrin.[63] A racemic synthesis of isolariciresinol dimethyl ether was reported by Mann *et al.* in 1984.[65]

The α-conidendrin based chiral pool synthesis of isolariciresinol dimethyl ether was carried out by Schrecker and Hartwell in 1954. α-Conidendrin, obtained from natural sources, was methylated by reacting it with alkaline dimethylsulfate, giving optically pure α-conidendrin dimethyl ether (**65**). This

Scheme 1.32

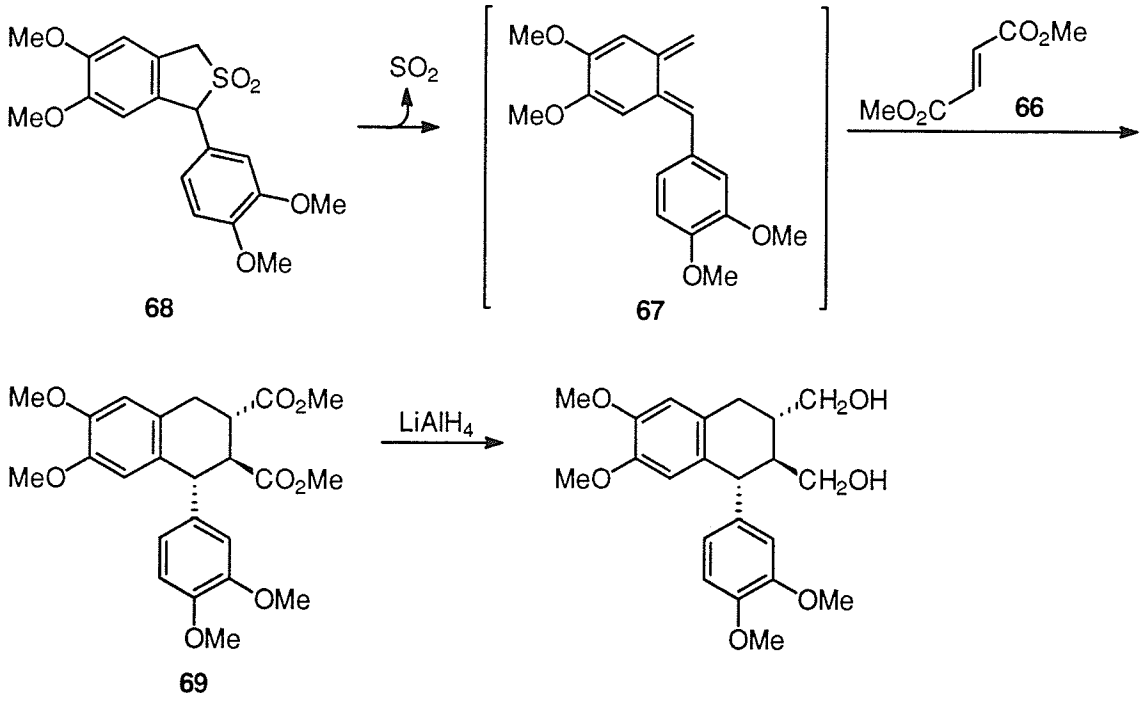


64 **65**

compound was then reduced, forming the diol isolariciresinol dimethyl ether (scheme 1.32).

The racemic synthesis carried out by Mann *et al.* was based on a Diels-Alder reaction between dimethyl fumarate (**66**) and *ortho*-quinodimethane **67**, which was generated by the thermal chelotropic elimination of sulfur dioxide from the 1-aryl-1,3-dihydrobenzo[*c*]thiophene-2,2-dioxide **68** (see section 1.4). The product of this reaction was the diester **69** which, when treated with lithium aluminum hydride, gave racemic isolariciresinol dimethyl ether (scheme 1.33).

Scheme 1.33



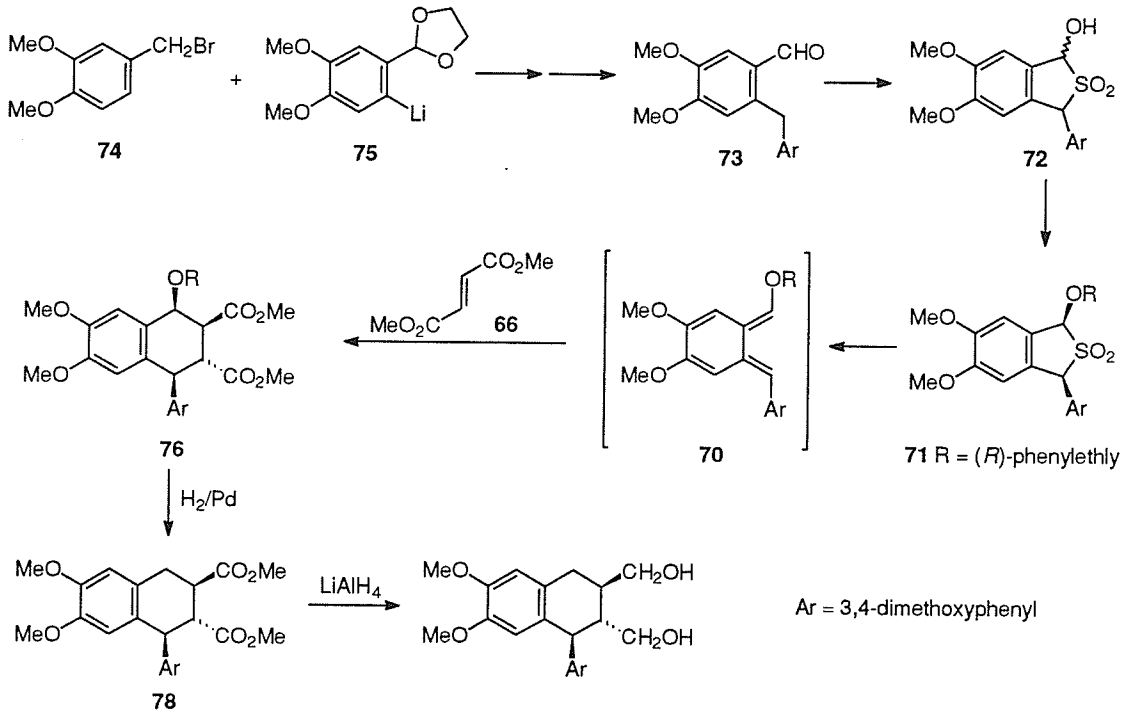
As in the synthesis of racemic isolariciresinol dimethyl ether by Mann *et al.*, the asymmetric synthesis of the same compound by Charlton and Alauddin relied on a Diels-Alder reaction occurring between dimethylfumarate and an appropriate *ortho*-quinodimethane, compound **70** in this case (scheme 1.34).

The *ortho*-quinodimethane in question was obtained from 3-(*R*)-phenylethoxy-1-aryl-1,3-dihydrobenzo[*c*]thiophene-2,2-dioxide (**71**), by the thermal extrusion of sulfur dioxide. Compound **71** was generated from the corresponding 3-hydroxy-1-aryl-1,3-dihydrobenzo[*c*]thiophene-2,2-dioxide **72**, by refluxing **72** in the presence of (*R*)-1-phenylethanol, and a catalytic amount of *para*-toluenesulfonic acid. In turn, compound **72** was generated by the chelotropic trapping of sulfur dioxide on irradiation of the *ortho*-benzylbenzaldehyde **73**, a compound obtained from the coupling of 3,4-dimethoxybenzylbromide (**74**) and the *ortho*-lithiumbenzylacetal **75**, followed by hydrolysis.

Although the product of the cycloadditon reaction possessed four chiral centers, thus allowing for the formation of up to eight diastereomers, only one major product was formed. The major cycloadduct which formed was shown, by analysis of the proton NMR spectrum, to have a 1,2-*trans*-2,3-*trans*-3,4-*cis* relative stereochemistry about the newly formed cyclohexene ring and, consequently, was assigned structure **76**. Compound **76** was obtained, along with its diastereomer **77**, as a 70/30 mixture, in favor of compound **76**. The significance of introducing the chiral phenylethyl substituent into compound **72**, giving compound **71**, towards obtaining isolariciresinol dimethyl ether in asymmetric form, was revealed at this point in the synthetic strategy. Given that compounds **76** and **77** bear a diastereomeric relationship to each other, chromatographic separation of them on silica gel was possible. Once separated from its diastereomer, **76** was subjected to conditions of catalytic reduction, giving crystalline dimethylester **78**. This compound was subsequently reduced

to optically active (+)-isolariciresinol dimethyl ether by treatment with lithium aluminum hydride (scheme 1.34).

Scheme 1.34



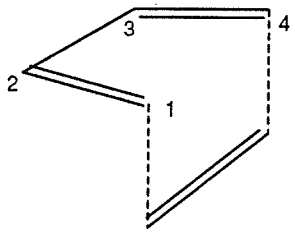
1.3 Diels-Alder Reaction

A) Introduction

A useful method for forming substituted cyclohexenes is the cycloaddition of alkenes and conjugated dienes, a reaction referred to as the Diels-Alder reaction. When discussing a process of this type, the alkene undergoing reaction is typically called a dienophile. In the terminology of orbital symmetry

classification, the Diels-Alder reaction is a $[_{\pi}4_{s} + {}_{\pi}2_{s}]$ cycloaddition, an allowed process. These reactions occur *via* a concerted mechanism, and the corresponding transition state requires that the diene adopt a *s-cis* conformation. Once this is achieved, the two reactive species approach each other on approximately parallel planes, and a stabilizing interaction occurs between C1 and C4 of the diene, and the two carbons of the dienophile (scheme 1.35).[66]

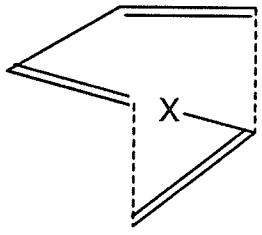
Scheme 1.35



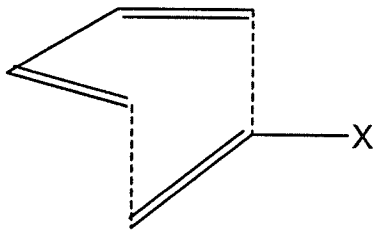
B) Stereochemistry and Stereoselectivity

There are two possible stereochemical orientations with respect to the diene, in the case of an unsymmetrical dienophile. In the first of these orientations, the *endo* orientation, the reference substituent (X in scheme 1.36) on the dienophile is oriented toward the π orbitals of the diene. In the other, the

Scheme 1.36



endo
transition state

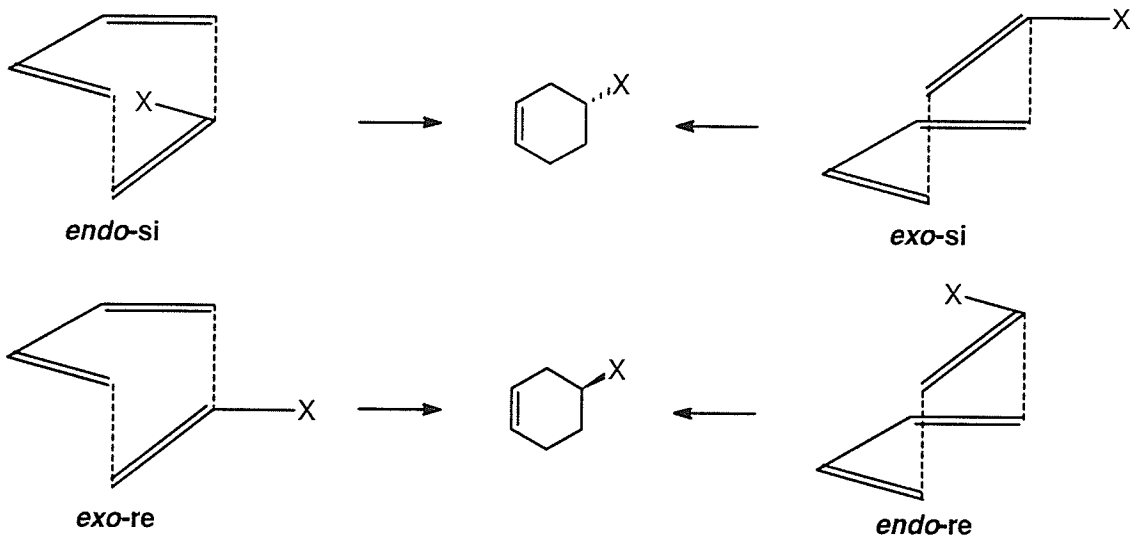


exo
transition state

exo orientation, the reference substituent is pointed away from the π orbitals (scheme 1.36).

From a geometric point of view, there are actually four different transition states which are attainable for a reaction of this type (scheme 1.37). These four transition states result from *endo* addition and *exo* addition to both the re face and the si face of the dienophile. Which one of the transition states is the most favorable depends on several factors, including steric and electronic factors, and, although some generalizations can be made, will differ from case to case.

Scheme 1.37



The stereochemical relationship between the products of the Diels-Alder reaction depicted in scheme 1.37 is that of enantiomers, assuming that X is achiral as in, for example methyl acrylate (**79**), where X = CO_2Me. Each enantiomer will be formed to the same extent during the reaction. That this is so, becomes obvious when we consider the possible transition states leading to the products. For both the *endo* and *exo* transition states, butadiene can add to

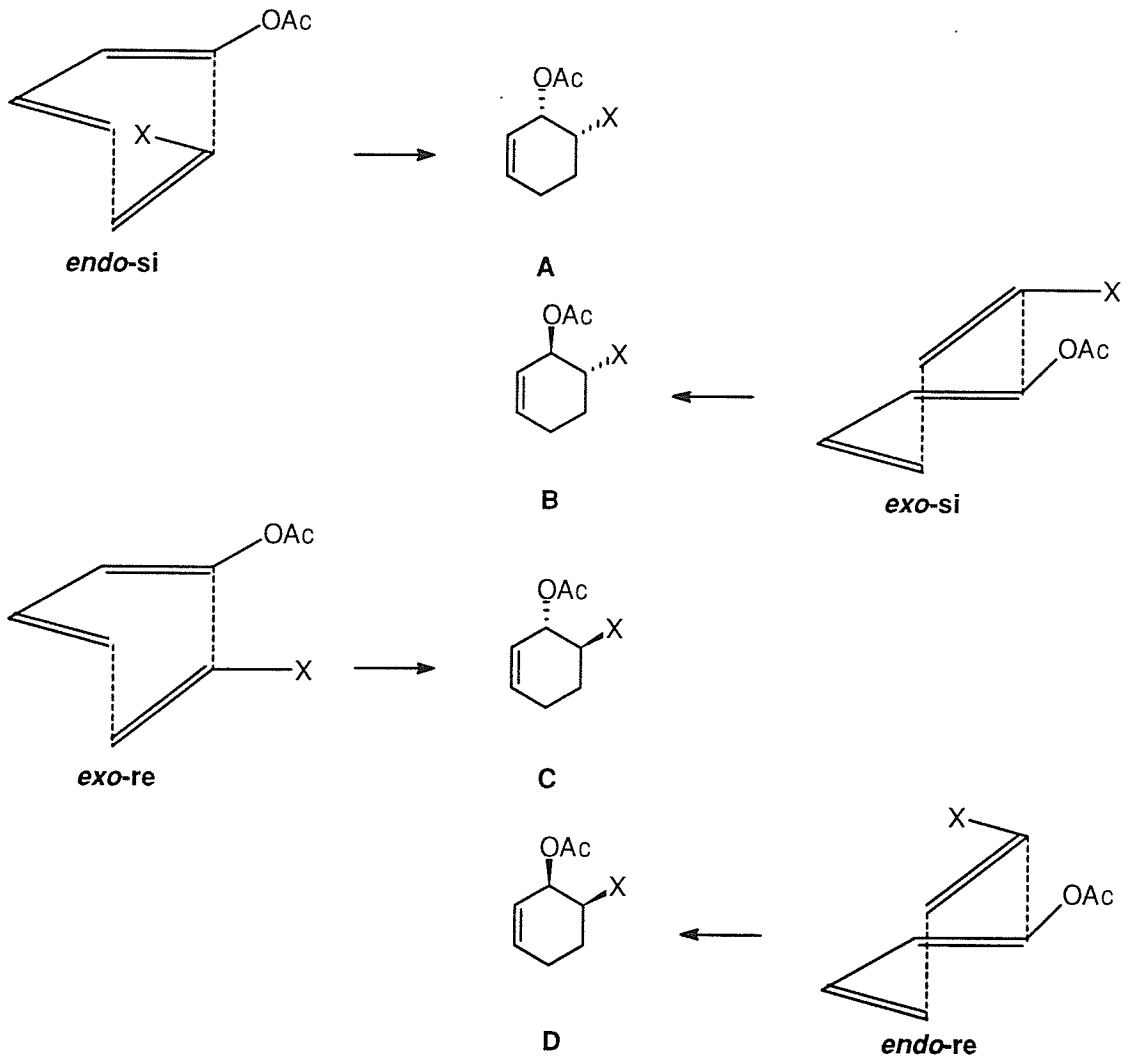
either face of the dienophile with equal probability. Both faces of butadiene are equivalent and, although the two faces of methyl acrylate are enantiotopic, the transition state energy for addition to each of its faces is identical for each of the *endo* and the *exo* transition states. In other words, both *endo* transition states will have the same energy and both *exo* transition states will have the same energy, even though the energy between the *endo* and *exo* transition states may differ. As it turns out, the *endo* transition state is of lower energy than the *exo* transition state in this particular case.

If a substituent is added to the terminal position of a diene and it undergoes a Diels-Alder reaction with an unsymmetrical dienophile, then the formation of diastereomeric products becomes important. The cycloaddition of methyl acrylate and 1-acetoxy butadiene (**80**) serves to exemplify this point (scheme 1.38). The reaction cannot be enantioselective for the reasons described above and, consequently, both enantiomers of each respective pair A/D and B/C will be produced to the same extent. However, the *endo* and *exo* transition states leading to the diastereomeric pair AD and BC respectively are different in energy; the *endo* transition state is lower in energy than the *exo* transition state. Thus, the reaction is diastereoselective with the AD enantiomeric pair being produced preferentially over its diastereomeric BC enantiomeric pair.

If both the diene and the dienophile are unsymmetrical, then the matter of regiochemistry also arises. For an unsymmetrical diene bearing a substituent in the 1 position, the two possible regioisomers that can form have the 1,2 (*ortho*)

and 1,3 (*meta*) orientation. When the substituent is in the 2 position of the diene, the regioisomers have the 1,3 (*meta*) and the 1,4 (*para*) orientation. Typically, the *ortho* or *para* regioisomer is preferred over the *meta* regioisomer.

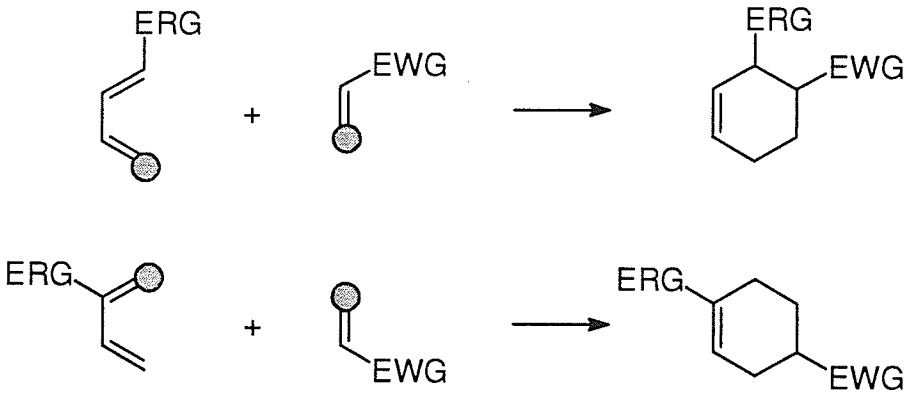
Scheme 1.38



This preference can be rationalized in terms of the frontier molecular orbital theory.[66,67] If we examine the most common case, referred to as the

normal electron demand Diels-Alder reaction, in which the diene bears an electron releasing substituent and the dienophile an electron withdrawing one, the strongest interaction is between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile. The reactants will orient so that the carbons which possess the highest coefficients in the two frontier orbitals can interact. For a dienophile with an electron withdrawing substituent, the carbon with the highest LUMO coefficient is C2. A diene substituted with an electron releasing group at C1 will have the highest HOMO coefficient at C4, and one which is substituted at C2 will have the highest HOMO coefficient at C1. The resulting interactions, and the products derived from these interactions, are depicted in scheme 1.39.

Scheme 1.39



● - indicates carbon of highest coefficient

A Diels-Alder reaction can result in the formation of one or more chiral centers in the product. For the situation depicted in scheme 1.37, where the diene is unsubstituted and the dienophile is monosubstituted, the product will

possess one chiral center. Scheme 1.38 shows an example of monosubstitution in both the diene and the dienophile, which results in the formation of two chiral centers. In so far as the number of stereogenic centers introduced into the cyclohexene product of a Diels-Alder reaction is concerned, the presence or absence of substituents at carbon one and at carbon four of the diene is important. Likewise, whether a dienophile bears zero, one or two substituents is significant. Depending on the substitution pattern of the diene and of the dienophile, the cyclohexene product of a Diels-Alder reaction may have zero, one, two, three, or four chiral centers.

If we consider the extreme case of dissymmetry in the Diels-Alder reaction, that in which both the diene and the dienophile are disubstituted and asymmetrical, then, given that four chiral centers will form in the product, a total of 16 stereoisomers are possible. Eight of these stereoisomers would possess a diastereomeric relationship with one another, and each of these eight diastereomers would have a corresponding enantiomer. Thus, from a synthetic point of view, it would be extremely beneficial to be able to control the stereochemical outcome of a Diels-Alder reaction of this type. As it turns out, under certain circumstances this is possible.

In order to carry out a Diels-Alder reaction asymmetrically, some means of discriminating between the two reactive faces of either the diene or the dienophile must exist. Such discrimination can only be achieved by the introduction of asymmetry at some point in the reaction process. The result of facial discrimination of this type will be a reaction which is either

diastereoselective or enantioselective. As mentioned, the reaction described by scheme 1.37 is nonasymmetric if X is achiral and, thus, both enantiomers are produced to the same extent. As well, although the reaction depicted by scheme 1.38 is a diastereoselective process, because each of the substituents (OAc and CO_2Me) is achiral, both enantiomers of the preferred diastereomeric product will be produced to the same extent. In theory, however, each of these reactions could have been induced to proceed asymmetrically if either a chiral catalyst were used, or if one or more of the substituents of the diene and/or dienophile possessed some form of asymmetry. In fact, these two approaches are those which are typically employed in carrying out Diels-Alder reactions asymmetrically.

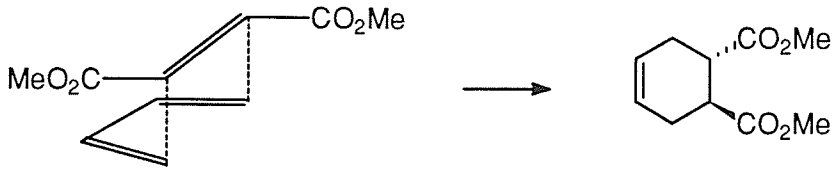
Diastereoselectivity in the Diels-Alder reaction is often achieved by the introduction of a chiral auxiliary into either the diene or the dienophile. Consider the example of the cycloaddition of dimethyl fumarate and butadiene (reaction A in scheme 1.40), as compared to the cycloaddition of (-)-dimenthyl fumarate (**81**) and butadiene[68] (reaction B in scheme 1.40). In both cases the reaction proceeds with butadiene in the *s-cis* conformation and the fumarate in the *s-trans* conformation. The situation results in the formation of two possible stereoisomers for each reaction (**82**/**83** for reaction A and **84**/**85** for reaction B), from addition to either the si or the re face of the dienophile. Note that in this particular case, because the dienophile is in the E (*trans*) configuration, the terms *endo* and *exo* addition are meaningless. Butadiene is C_2 symmetric and achiral, as is dimethyl fumarate. Thus, approach of the diene to either face of

the dienophile is equivalent, resulting in the formation of both enantiomers to the same extent. Although (-)-dimenthyl fumarate is C_2 symmetric, it is chiral and, as such, its si and re faces appear quite different from the point of view of an approaching diene. Thus, the transition state energy leading to the formation of one diastereomer will be lower than the transition state energy leading to the other diastereomer (**84** versus **85**). As a result, one diastereomer will be produced preferentially over the other. If the transition states shown in scheme 1.40 are assumed to be accurate then, based on steric factors, compound **84** should dominate the reaction mixture of the butadiene/(-)-dimenthyl fumarate system. It should be noted that, although this reaction proceeds in a diastereoselective manner, removal of the chiral menthyl groups would result in a net enantioselective process.

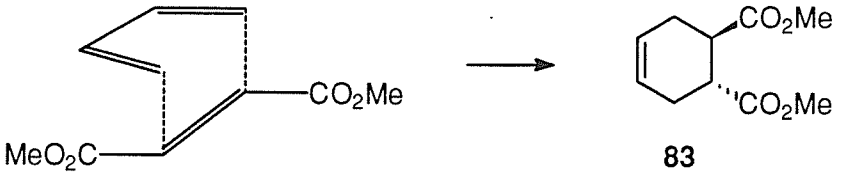
In order to achieve a truly enantioselective Diels-Alder reaction, a chiral catalyst of some sort would have to be employed. In this case, one could imagine the catalyst interacting with either the diene or the dienophile, both of which would have to be achiral, creating a temporary chiral complex which could then undergo cycloaddition. For example, If a chiral catalyst were to interact in some way with the dienophile of reaction A in scheme 1.40, a situation analogous to that in reaction B of the same scheme would arise. Thus, the transition state energies leading to the two possible enantiomers would be expected to differ, resulting in the unequal formation of the two enantiomers and, hence, an enantioselective reaction.

Scheme 1.40

Reaction A:

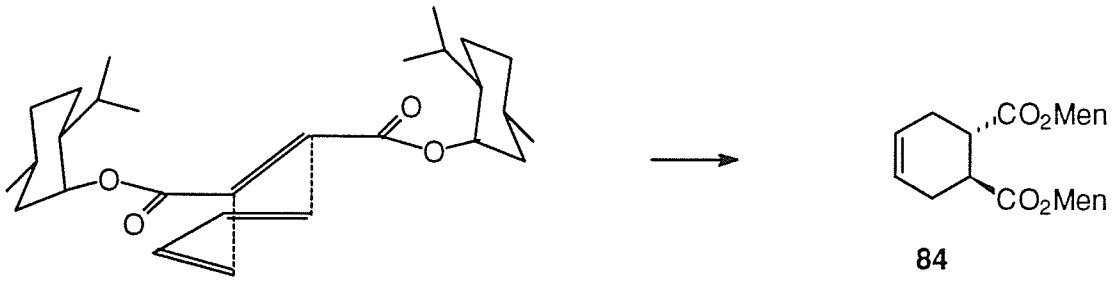


82

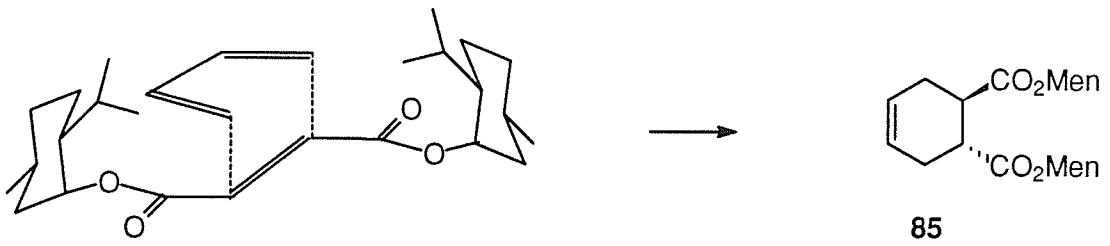


83

Reaction B:



84



85

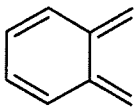
Men = (-)-menthyl

1.4 *ortho*-Quinodimethanes

A) Introduction

An *ortho*-quinodimethane is a compound which possess the general structure shown for compound **86** (scheme 1.41). These compounds, also

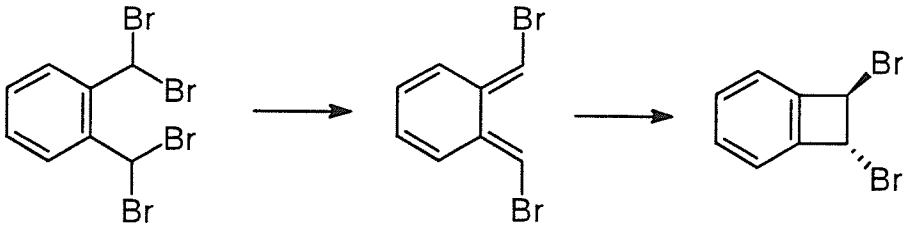
Scheme 1.41



86

known as *ortho*-xylylenes and *ortho*-quinodimethides, have been used extensively as intermediates in organic synthesis. The first suggestion that these compounds participated as reaction intermediates came in 1957.[69] The existence of *ortho*-quinodimethane **87** was suggested in an attempt to rationalize the conversion of α,α,α',α'-tetrabromo-*o*-xylene (**88**) to *trans*-α,α'-dibromobenzocyclobutene (**89**) (scheme 1.42). Later, the unsubstituted *ortho*-

Scheme 1.42



88 **87** **89**

quinodimethane **86** was observed *via* UV, fluorescence, and excitation spectroscopy, in a glassy matrix at -196 °C.[70]

B) Generation of *ortho*-Quinodimethanes

A variety of methods have been employed for the generation of *ortho*-quinodimethanes. Among these methods are 1,4-elimination processes as in, for example, the Benzo-Peterson reaction (scheme 1.29), and the thermal chelotropic extrusion of sulfur dioxide from dihydrobenzothiophene-2,2-dioxides (scheme 1.33 and scheme 1.34). These methods, as well as many others, have been reviewed by Charlton and Alauddin[71] and, with the exception of the generation of *ortho*-quinodimethanes by the thermolysis of benzocyclobutenes, a strategy important to this thesis, will not be discussed here.

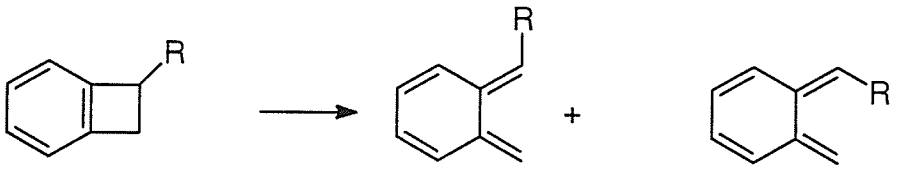
The thermal ring opening of benzocyclobutenes (**90**) is a frequently used method for the generation *ortho*-quinodimethanes (scheme 1.43). The transformation proceeds by way of a thermally allowed *con*-rotatory electrocyclic ring opening.[72,73] If a benzocyclobutene carries a substituent on the four-membered ring, then the substituent may open either outward or inward. Ring opening in the outward direction produces the the less sterically hindered (E)-*ortho*-quinodimethane (**91**), whereas ring opening in the inward direction gives the more sterically hindered (Z) geometry (**92**). As it turns out, it is not sufficient to describe the ring opening of benzocyclobutenes on the basis of steric arguments alone. Ring opening of these compounds has been shown to

proceed in a manner in keeping with the rules of torquoselectivity.[74] For example, α-aryl-α-hydroxy-*ortho*-quinodimethanes like compound **93** are known to ring open such that the hydroxyl group is in the (E) geometry (**94**), in preference to the (Z) geometry (**95**) (scheme 1.44). This fact is in contradiction to what would be expected on the basis of steric arguments alone, but is what would be expected on the basis of torquoselectivity rules.[74]

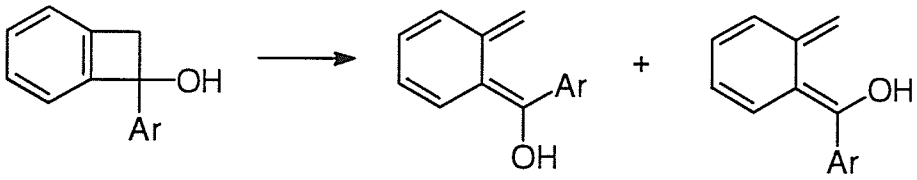
Scheme 1.43

90

Scheme 1.44



91 **92**



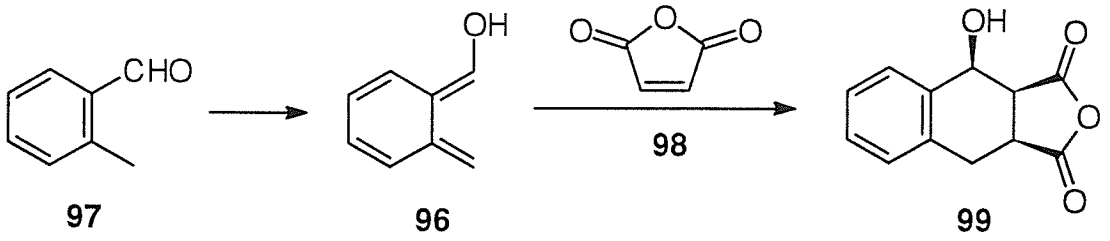
93 **94** **95**

C) *ortho*-Quinodimethanes as Dienes in Diels-Alder Reactions

ortho-Quinodimethanes have been used extensively as dienes in Diels-Alder reactions. The stereochemical outcome of the reaction of *ortho*-

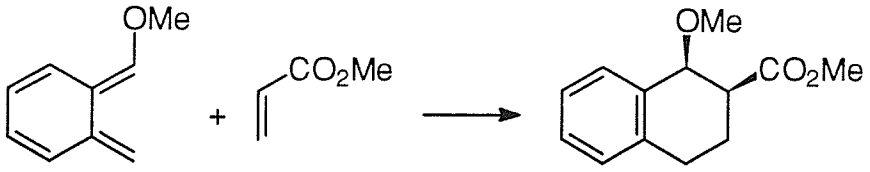
quinodimethanes with dienophiles depends significantly of the substitution and the geometry of both the *ortho*-quinodimethane and the dienophile. For example, reaction of α-hydroxy-*ortho*-quinodimethane **96**, generated by photolysis of *ortho*-methylbenzaldehyde (**97**), with maleic anhydride (**98**), results in the stereoselective formation of the all *cis* diastereomer (**99**) *via* an *endo* transition state[75] (scheme 1.45). Reaction of α-methoxy-*ortho*-quinodimethane (**100**) with methyl acrylate results in both the diastereoselective and regioselective formation of the all *cis* cycloadduct **101**, again *via* an *endo* transition state (scheme 1.46).

Scheme 1.45



97 **96** **99**

Scheme 1.46

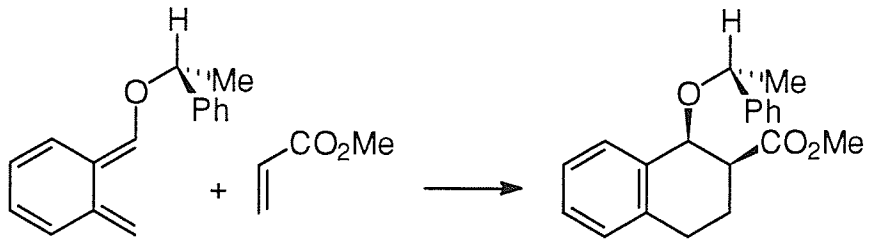


100 **101**

ortho-Quinodimethanes have also played roles as dienes in asymmetric Diels-Alder reactions. Typically, the asymmetric result is achieved by introduction of a chiral auxiliary into either the *ortho*-quinodimethane or the dienophile. For example, the chiral *ortho*-quinodimethane, α-(*R*)-1-

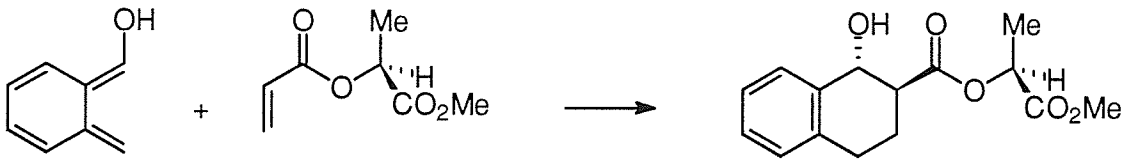
phenylethoxy-*ortho*-quinodimethane (**102**) has been shown to undergo reaction with methyl acrylate in a stereoselective manner to give the (1'*R*, 1*S*, 2*S*)-cycloadduct **103**, *via endo* addition to the si face of **102**[76] (scheme 1.47). As well, reaction of the acrylate of *S*-methyl lactate (**104**), a chiral dienophile, with α-hydroxy-*ortho*-quinodimethane, yields the *trans* cycloadduct **105** stereoselectively, *via exo* addition to re face of the dienophile[77] (scheme 1.48).

Scheme 1.47



102 **103**

Scheme 1.48



104 **105**

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2.0 Thesis Objectives

The research to which this thesis pertains was developed on the basis of three primary objectives:

1) To achieve the total asymmetric synthesis of the aryltetralin lignans (-)-isolariciresinol dimethyl ether and (-)-deoxysikkimotoxin.

The aryltetralin lignans are an important class of compounds which exhibit biologically activity of various types. For example, it was mentioned in section 1.2 A that these compounds act as anti-tumor agents, as anti-fungal agents and also play a role in the regulation of cell growth. An aryltetralin lignan may possess up to four chiral centers in its basic carbon skeleton alone. It has been established that the biological activity of these compounds is profoundly affected by the absolute and relative stereochemistry at these centers. Hence, the asymmetric synthesis of aryltetralin lignans has proven very important, and it presents to the organic chemist the significant challenge of controlling the absolute and relative stereochemistry of the product lignan. Thus, in an attempt to contribute to the understanding which exists regarding the synthesis of these compounds, the total asymmetric synthesis of the aryltetralin lignans (-)-isolariciresinol dimethyl ether and (-)-deoxysikkimotoxin was carried out.

2) To arrive at the total synthesis of the aforementioned compounds using, in part, a synthetic strategy recently developed by Charlton and Bogucki, in an attempt to broaden the scope of the strategy.

In order to synthesize (-)-deoxypodophyllotoxin, Charlton and Bogucki employed a synthetic strategy which relied on an asymmetric Diels-Alder reaction occurring between an α-aryl-α-hydroxy-*ortho*-quinodimethane, and a chiral dienophile. The *ortho*-quinodimethane used was obtained following thermolysis of an appropriately substituted benzocyclobutenol. On analyzing the method developed by Charlton and Bogucki, it seemed reasonable that it could be extended to benzocyclobutenols with other substitution patterns. These compounds could potentially undergo Diels-Alder reactions, ultimately giving rise to aryltetralin lignans exhibiting other substitution patterns. As well, it was thought that the relative and absolute stereochemistry of the product lignans might be manipulated as a route to other lignans. If the assumptions regarding manipulation of substitution patterns and stereochemistry proved true, then a somewhat generalized means of obtaining aryltetralin lignans would have been achieved. Hence, variations of the synthetic strategy described were used in order to synthesize (-)-isolariciresinol dimethyl ether and (-)-deoxysikkimotoxin, as a means of broadening the scope of the strategy.

3) To improve upon the synthesis of (-)-deoxypodophyllotoxin, by synthesizing its 6,7-dimethoxy analogue, (-)-deoxysikkimotoxin, *via* a shorter synthetic route.

The synthesis of (-)-deoxypodophyllotoxin described above, although effective, left some room for improvement in its final steps. Specifically, once the initial product of the Diels-Alder reaction was obtained, several steps, with an overall yield of only approximately 30%, were required in order to convert it to (-)-deoxypodophyllotoxin. It was hoped that the final stages of the synthetic strategy could be improved upon during the synthesis of (-)-deoxysikkimotoxin, the 6,7-dimethoxy analogue of (-)-deoxypodophyllotoxin, which could potentially result in an increase in the efficiency of the synthesis of (-)-podophyllotoxin.

2.1 Results and Discussion

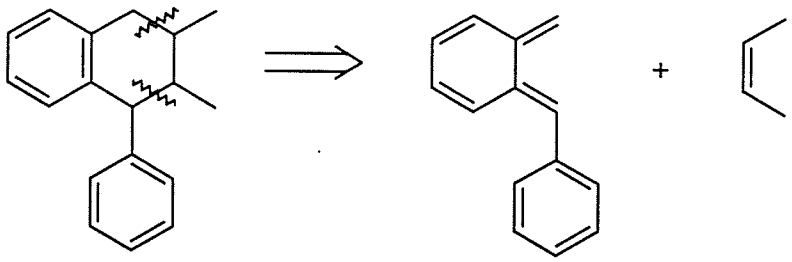
Taken collectively, the data obtained during the synthesis of (-)-isolariciresinol dimethyl ether and of (-)-deoxysikkimotoxin, fulfill the objectives of this thesis. In order to present this as clearly as possible, the results and discussion section contained herein is subdivided into three sections. The first of these sections contains background information which is intended to offer justification of the approach chosen for the synthesis of the aforementioned compounds. This section is followed by one which is devoted to the discussion of the results obtained during the synthesis of (-)-isolariciresinol dimethyl ether, and then by one discussing the results obtained during the synthesis of (-)-deoxysikkimotoxin.

A) Background

As mentioned in section 1.3, a Diels-Alder reaction can generate up to four chiral centers in the cyclohexene product. Although this type of reaction does present the formidable challenge of controlling the relative and absolute stereochemistry of the possible products, if the correct diene and dienophile are chosen, it is an excellent means of arriving at the carbon skeleton of many aryltetralin lignans. Retrosynthetic analysis of the carbon skeleton of an aryltetralin lignan suggests that the skeleton may by arrived at in a very elegant

way by employing a Diels-Alder reaction between an α-aryl-*ortho*-quinodimethane and an appropriately substituted dienophile (scheme 2.1).

Scheme 2.1

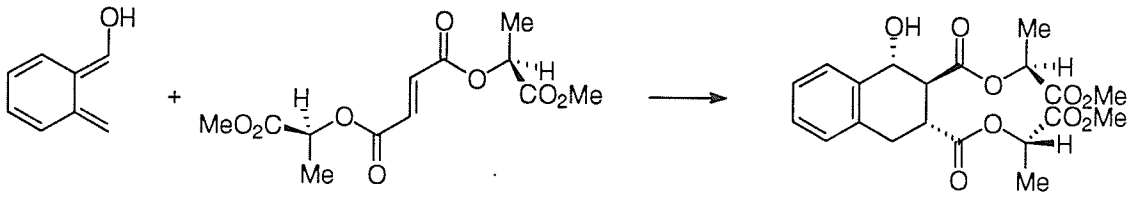


As is evident from section 1.2, the absolute and relative stereochemistries of aryltetralin lignans varies considerably. It therefore seems apparent that, in order to arrive stereoselectively at the diverse array of structures that exist, several distinct stereoselective synthetic methods would have to be employed. Many such methods do exist, with each resulting in a particular stereochemical outcome. Each of these methods typically relies on a certain key reaction in order to generate the desired stereochemistry. Clearly, it would be of considerable convenience if a single generalized synthetic strategy existed, whereby the synthesis of many different aryltetralin lignans possessing various stereochemistries and functionalities, could be achieved.

Towards the goal of obtaining a generalized synthetic strategy, Charlton *et al.* have carried out extensive research on the asymmetric synthesis of aryltetralin lignans. Included among the many discoveries in this work, was the fact that the fumarate and the acrylate of methyl (*S*)-lactate (compounds **106** and **104** respectively) each underwent a Diels-Alder reaction with α-hydroxy-*ortho*-

quinodimethane in a highly diastereoselective manner, giving cycloadducts **107** and **105** respectively (scheme 2.2 and 1.48 respectively).[1] In both cases,

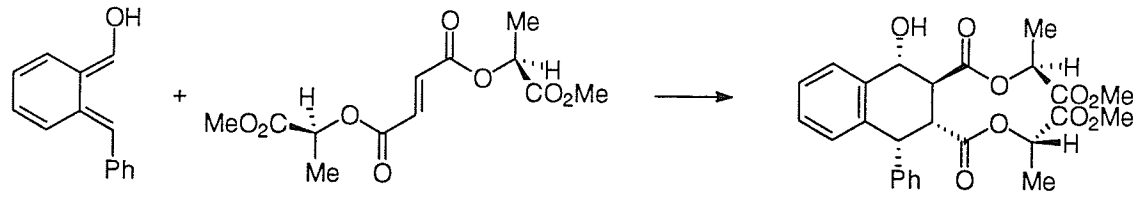
Scheme 2.2



106 **107**

addition occurred between the re face of the dienophile and the re face of the *ortho*-quinodimethane, through an *exo* transition state. Later, it was determined that the maleate of methyl (*S*)-lactate also added to α-hydroxy-*ortho*-quinodimethane diastereoselectively *via* a similar transition state, although the selectivity was not as great.[2] Replacement of the lactate group of lactyl acrylate with the mandelate group was shown to give similar results.[3] The fumarate of methyl (*S*)-lactate was also reacted with α-hydroxy-α'-phenyl-*ortho*-

Scheme 2.3

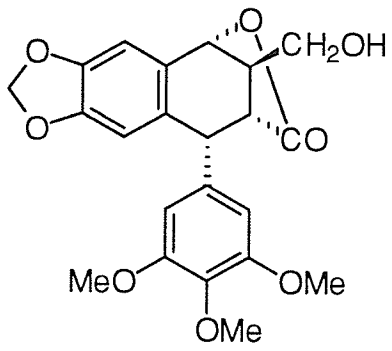


108 **109**

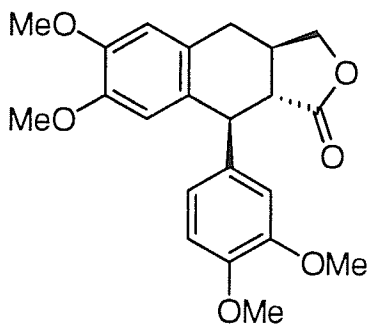
quinodimethane (**108**) and found to give an *exo* cycloadduct (**109**) possessing the same absolute stereochemistry as podophyllotoxin (scheme 2.3).[4] This discovery was exploited in the synthesis of (-)-neopodophyllotoxin[5] (**110** in scheme 2.4) and certain podophyllotoxin analogues.[3] In a similar reaction, the

fumarate of methyl (*R*)-mandelate gave an *exo* cycloadduct selectively, which was elaborated to (-)-α-dimethylretrodendrin (**111** in scheme 2.4) and three of its diastereomers.[6]

Scheme 2.4



110

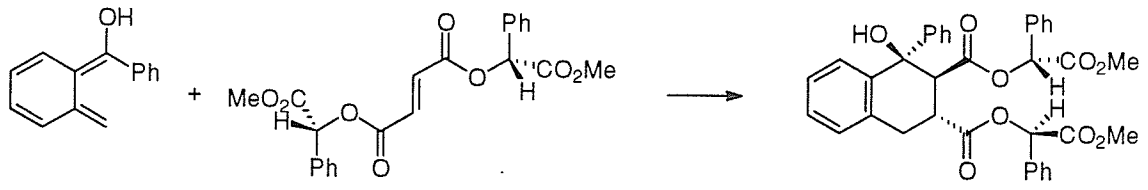


111

In all of the work by Charlton *et al.* cited thus far, the *exo* addition product has dominated. However, it was recently discovered that the cycloaddition between the fumarate of methyl (*R*)-mandelate and α-phenyl-α-hydroxy-*ortho*-quinodimethane (**112**) gave an unexpected *endo* addition product (**113**) with high diastereoselectivity[7] (scheme 2.5). This fact was recently exploited in the total asymmetric synthesis of (-)-deoxypodophyllotoxin (**15**), using the α-hydroxy-α-aryl-*ortho*-quinodimethane obtained by the thermal ring opening of the α-hydroxy-α-arylbenzocyclobutenol **19**, and the fumarate of methyl (*S*)-mandelate (**18**)[8] (scheme 2.6). The overall synthetic strategy developed in the latter case can be conveniently discussed in terms of three major parts. The first part deals with the synthesis of the appropriate benzocyclobutenol, the second with the

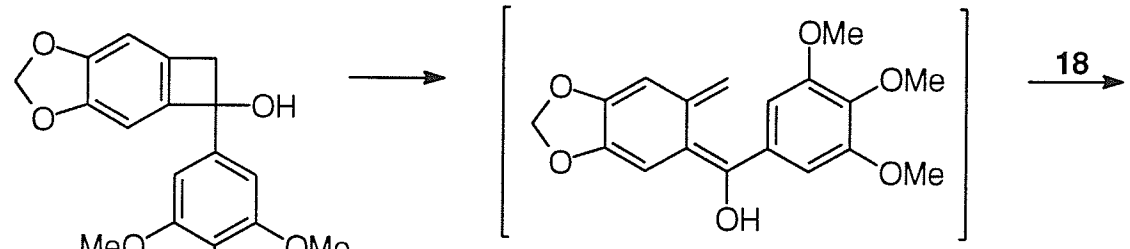
asymmetric Diels-Alder reaction, and the third with the elaboration of the cycloadduct to the final product.

Scheme 2.5

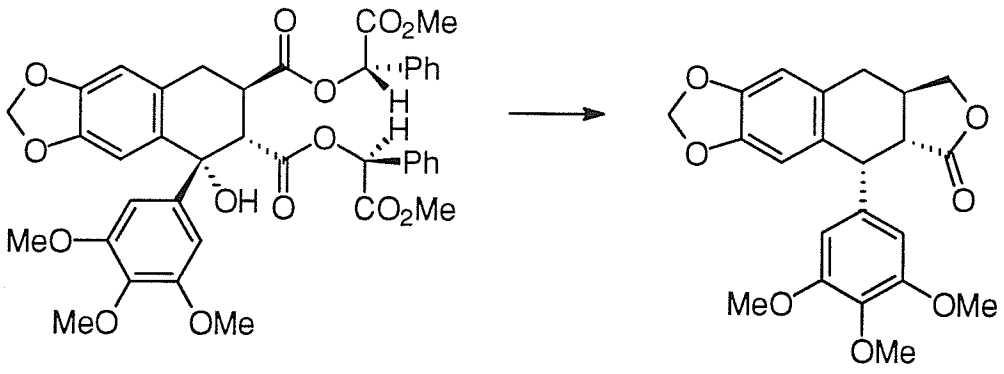


112 **113**

Scheme 2.6



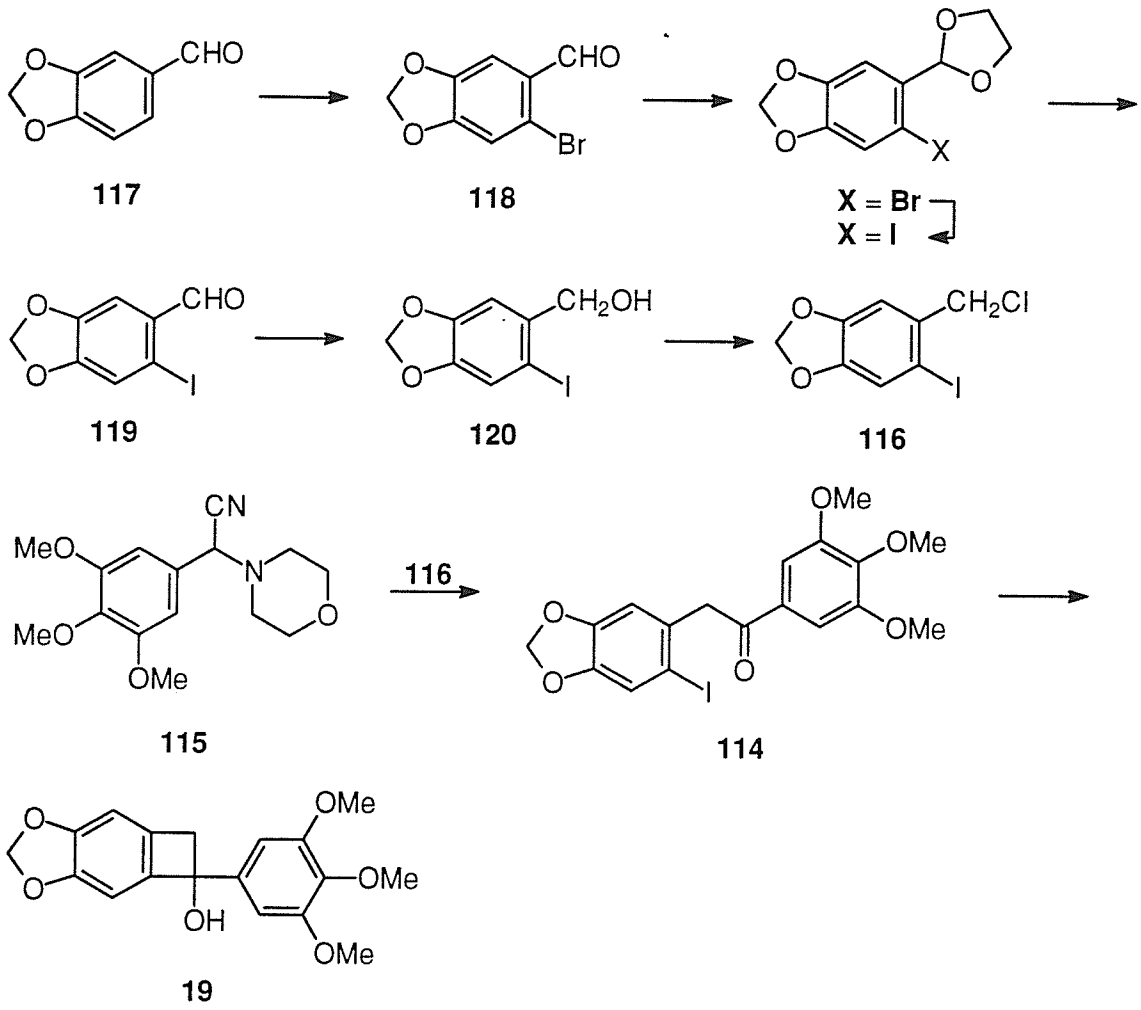
19



15

The benzocyclobutenol in question was obtained in good yield by cyclization of ketone **114** in the presence of *n*-butyllithium. The ketone, in turn, was generated by coupling α-aminonitrile **115** with the benzyl chloride **116**, in the

Scheme 2.7

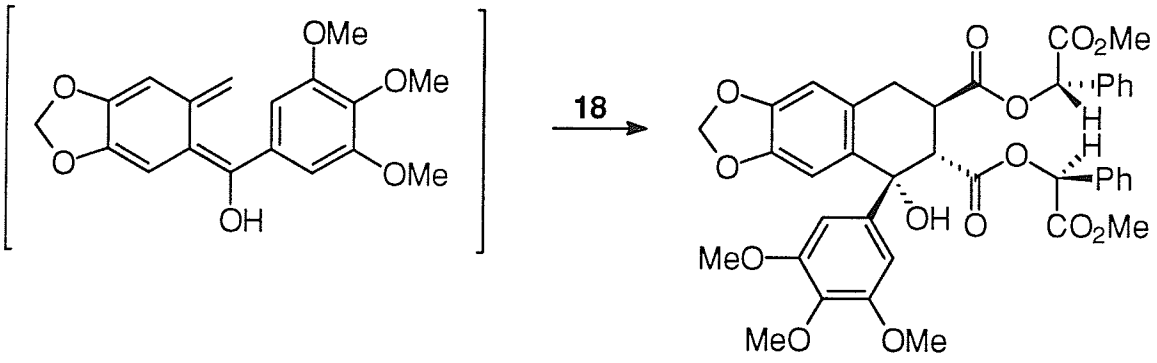


presence of sodium hydride, followed by hydrolysis. α-Aminonitrile **115** was obtained in 92% yield by the treatment of 3,4,5-trimethoxybenzaldehyde with aqueous potassium cyanide, hydrochloric acid and morpholine. The synthetic route to the benzyl chloride **116** began with the bromination of piperonal (**117**), using liquid bromine and glacial acetic acid, which gave 6-bromopiperonal (**118**) in high yield. This compound was subsequently converted to its corresponding iodo derivative (**119**), *via* the *ortho*-aryllithium derivative of the ethylene glycol

acetal. Sodium borohydride reduction of 6-iodopiperonal afforded the benzyl alcohol **120**, which was efficiently converted to the benzyl chloride **116** under conditions of 50/50 (v/v) glacial acetic acid/dichloromethane, and hydrogen chloride gas (scheme 2.7).

The Diels-Alder reaction leading to cycloadduct **20** was initiated by refluxing benzocyclobutenol **19** in toluene. This led to thermolysis of the cyclobutene ring (section 1.4 B), giving *ortho*-quinodimethane **121**, which was trapped *in situ* with the fumarate of methyl (*S*)-mandelate (scheme 2.8). The cycloadduct was obtained in 58% isolated yield following chromatography.

Scheme 2.8

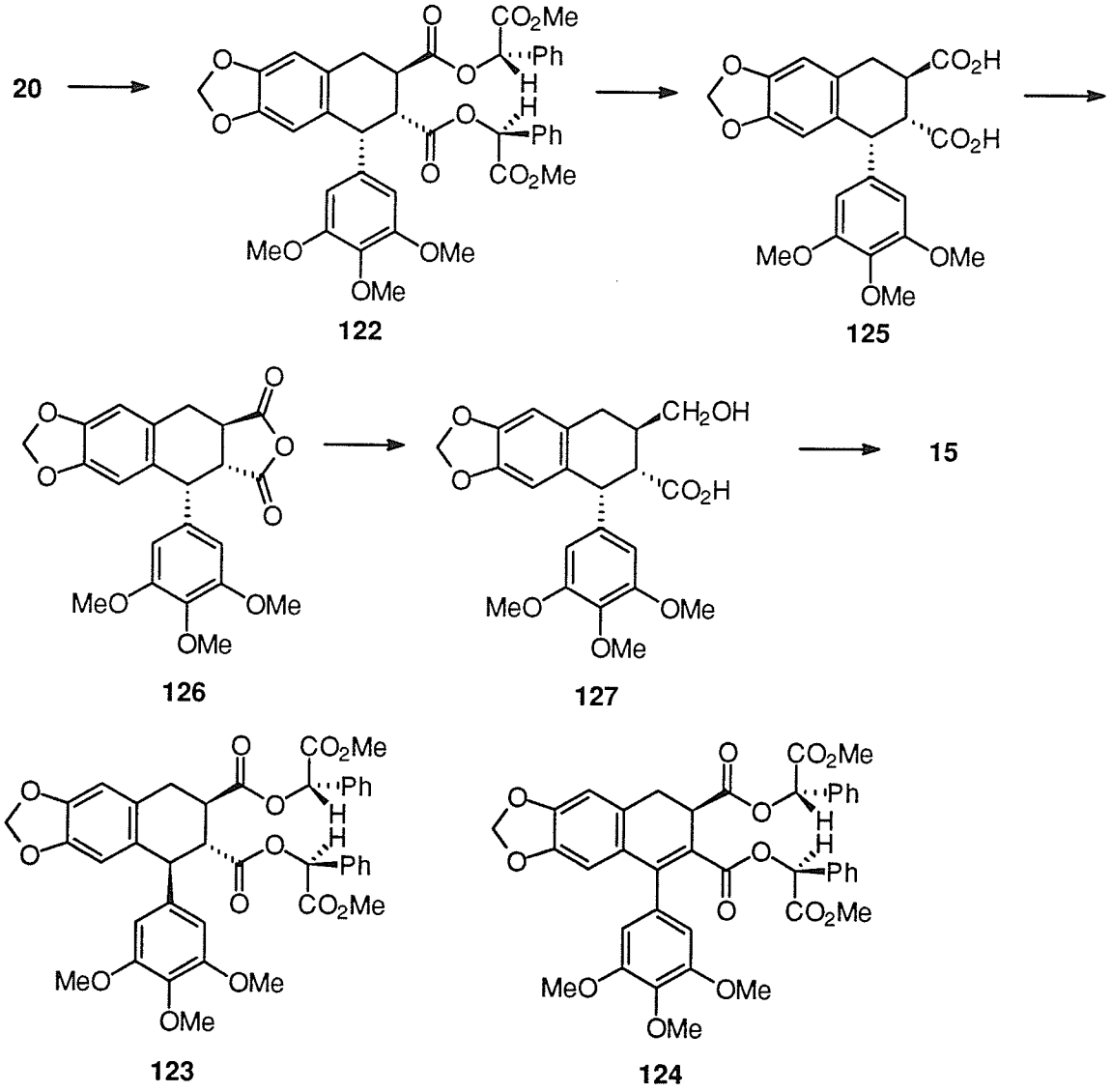


121 **20**

The remaining steps for the transformation of cycloadduct **20** to (-)-deoxypodophyllotoxin began with the selective reduction of compound **20** to give the 1,2-*cis*-2,3-*trans* compound **122**. The reduction, achieved by the use of boron trifluoride etherate and lithium aluminum hydride at low temperature, actually gave a mixture of the desired inversion compound **122**, its noninverted diastereomer **123**, and the elimination product **124**, in a 15:2:1 ratio. Catalytic hydrogenolysis of **122** removed the mandelate groups, leaving the diacid **125**.

The crude diacid was then refluxed in trifluoroacetic anhydride giving a compound presumed to be the anhydride **126**. Sodium borohydride was then used to regioselectively reduce anhydride **126** to the γ-hydroxy acid **127**, which readily lactonized to (-)-deoxypodophyllotoxin (**15**) (scheme 2.9).

Scheme 2.9



What is particularly intriguing about the synthetic strategy developed by Charlton and Bogucki, is that it seems to have the potential for a reasonable

amount of variation in each of its three parts. If this is true, then this synthetic strategy does indeed represent a potential means of arriving at variously substituted aryltetralin lignans, possessing an array of absolute and relative stereochemistries. For instance, the substitution pattern of the aromatic ring A is determined by which benzyl chloride is chosen to undergo coupling with the α-aminonitrile, and that of ring C is determined by the choice of α-aminonitrile. The pattern of substitution present in each of these two compounds is, of course, transferred to the product aryltetralin lignan through the corresponding benzocyclobutenol. Since both the benzyl chloride and the α-aminonitrile are benzaldehyde derivatives, it seems reasonable to assume that an array of aryltetralin lignans could be arrived at, based on commercially available benzaldehydes alone. It is also apparent that controlling the substitution of the benzocyclobutenol at the α'-position would control the substitution at C4 in the product aryltetralin lignan, allowing even more synthetic possibilities.

The question of absolute and relative stereochemistry could be easily dealt with using this synthetic method. For example, use of the fumarate of methyl (*S*)-mandelate gave cycloadduct **20**, which was ultimately elaborated to (-)-deoxypodophyllotoxin. Logically then, use of the fumarate of methyl (*R*)-mandelate would have ultimately given rise to (+)-deoxypodophyllotoxin. In each of the cases just described, the resulting cycloadduct possessed the 2,3-*trans* relative stereochemistry. However, one could easily envision the synthesis of an aryltetralin lignan possessing a 2,3-*cis* relative stereochemistry. Theoretically,

this could be obtained by the use of the maleate of methyl mandelate as a dienophile, thereby allowing a route to even more aryltetralin lignans.

The final elaborative stages of this synthetic strategy also hold the potential for a considerable amount of variation. For instance, epimerization reactions have been used quite frequently in aryltetralin lignan syntheses in the past and, potentially these types of reactions could be employed here to alter relative stereochemistries. As well, choice of reaction conditions could ultimately lead to a plethora of functionalities at carbons one to four, or at other carbon atoms in the aryltetralin lignan.

It is hoped that, from what has been expressed above, the importance of a generally useful reaction sequence for obtaining aryltetralin lignans is clear. The potential of the synthetic strategy developed by Charlton and Bogucki to accommodate variation, has been a primary focus of the research on which this thesis is based. Several of the variations described above were employed, allowing the inherent diversity of this synthetic strategy to be revealed. The results of this examination will now be expressed, through a description of the synthesis of (-)-isolariciresinol dimethyl ether and of (-)-deoxysikkimotoxin.

B) The Synthesis of (-)-Isolariciresinol Dimethyl Ether

By carrying out the synthesis of (-)-isolariciresinol dimethyl ether, the possibility of exploiting the aforementioned synthetic strategy, with respect to both substitution and relative stereochemistry, was explored. (-)-Isolariciresinol

dimethyl ether bears a methoxy substituent at each of carbons six and seven in the aromatic ring A. Consequently, the benzyl chloride chosen for this particular reaction sequence was 2-iodo-4,5-dimethoxybenzyl chloride (**128**). Synthesis of this particular compound began with methylation of the phenolic compound vanillin (**129**), according to an established literature procedure.[9] In keeping with the protocol, vanillin was subjected to conditions of alkaline dimethyl sulfate and, following work up and recrystallization, gave pure veratraldehyde (**130**) in 97% yield (mp 42-44 °C) (scheme 2.10). Elaboration of veratraldehyde to 6-bromoveratraldehyde (**131**) was readily achieved by first dissolving it in glacial acetic acid and then adding two equivalents of bromine. The bromination reaction was complete after four hours of stirring at room temperature, as determined by TLC. Work up consisted of dilution with a volume of ice-water equal to that of glacial acetic acid used, followed by crystallization induced by overnight cooling at 5 °C. The solid obtained after vacuum filtration, once washed, recrystallized from 80/20 (v/v) methanol/water, and oven dried, afforded pure 6-bromoveratraldehyde in 86% yield (mp 148-150 °C). The product of the reaction was exclusively the monobrominated product. This result seemed to be unaffected by longer reaction times, as evidenced by the exposure of veratraldehyde to identical conditions for a duration of 60 hours, which gave the same result.

The plan for the conversion of 6-bromoveratraldehyde to its corresponding iodo derivative (**132**) began with the formation of the bromoacetal **133**, the protected form of the aldehyde. This compound could then be

subjected to conditions of halogen exchange, followed by hydrolysis of the resulting iodoacetal (**134**) in order to remove the protecting group. Despite the apparent directness of the methodology chosen, an extreme sensitivity of the reaction to moisture, presumably due to the intermediacy of the acetal, made matters more complex. Once recognized, however, difficulties were readily overcome by altering the initial reaction conditions somewhat. Hence, 6-bromoveratraldehyde was dissolved in benzene, combined with two equivalents of ethylene glycol, and a catalytic amount of *para*-toluenesulfonic acid hydrate. The mixture was refluxed under nitrogen while attached to a Dean-Stark trap, in order to remove any water present. It was absolutely essential that the Dean-Stark trap be drained several times during reflux, so that all of the water would be removed and, thus, acetal formation would occur completely. That acetal formation was complete, was determined by removing a small aliquot of the reaction mixture and combining it with dry carbon tetrachloride in an NMR tube under nitrogen. Absence of the NMR signal corresponding to the aldehydic proton of 6-bromoveratraldehyde was taken to mean acetal formation was complete. Typically, it took approximately five hours of refluxing for this to occur. Once the acetal had been formed, it was quite stable and could be stored under nitrogen in the refrigerator for extended periods. In order to isolate the acetal, however, the reaction mixture had to be filtered through oven dried silica gel using 50/50 (v/v) ethyl acetate/hexanes.

The next stage of the reaction involved addition of 1.1 equivalents of *n*-butyllithium to the acetal, which was dissolved in freshly distilled tetrahydrofuran,

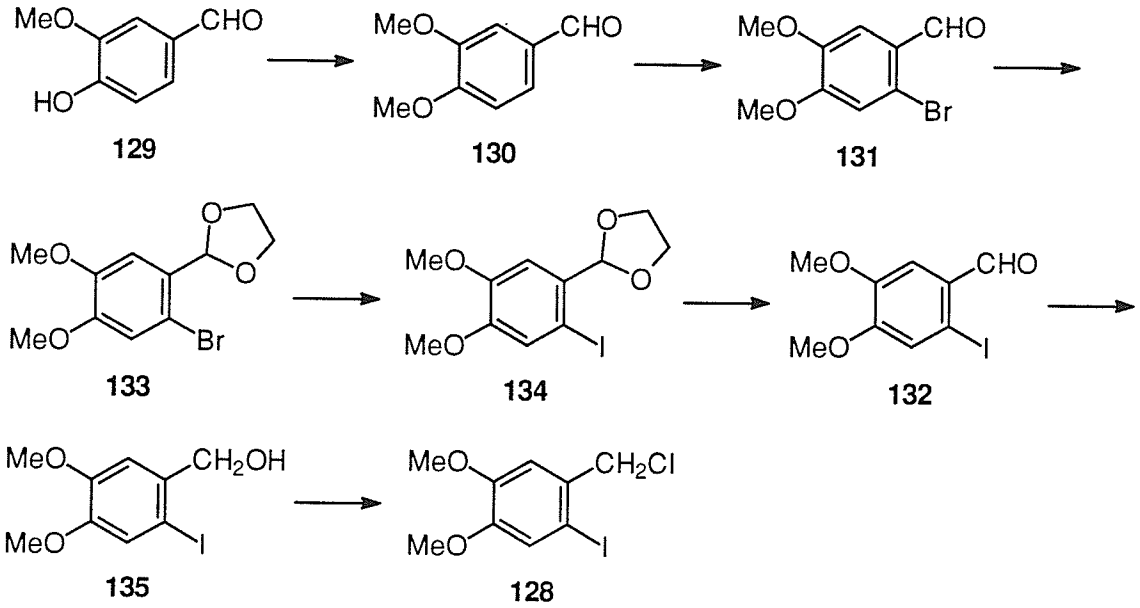
maintained at -78 °C, under a nitrogen atmosphere. This was followed by the addition of 1.1 equivalents of iodine, dissolved in tetrahydrofuran. It was necessary to allow the reaction mixture to warm to room temperature and to stir for approximately one hour, before reaction was complete. Excess iodine was destroyed by addition of saturated aqueous sodium bisulfite. Extraction of the resulting mixture gave an oily residue on evaporation, which was treated with dilute aqueous acid to hydrolyze the acetal. Once extracted from the aqueous components, the organic components were filtered using coarse silica gel and 50/50 (v/v) ethyl acetate/hexanes, thereby removing any ethylene glycol present after hydrolysis. Evaporation of the filtrate yielded pure colorless crystals of 6-iodoveratraldehyde in 94% yield (mp 134-136 °C).

Reduction of 6-iodoveratraldehyde to 2-iodo-4,5-dimethoxybenzyl alcohol (**135**) was carried efficiently and smoothly as follows. To a solution of isopropyl alcohol and 6-iodoveratraldehyde was added 1.1 equivalents of sodium borohydride. After 12 hours of refluxing, the mixture was made just acid and then evaporated to a minimum volume under vacuum at room temperature. A dichloromethane/water extraction gave an organic portion which, after drying and evaporation, yielded in 96% almost colorless crystals whose spectral data corresponded to that of 2-iodo-4,5-dimethoxybenzyl alcohol (mp 94-96 °C).

The final step leading to the benzyl chloride **128**, involved dissolving 2-iodo-4,5-dimethoxybenzyl alcohol in a 50/50 (v/v) mixture of glacial acetic acid and dichloromethane. Hydrogen chloride gas, generated by dripping concentrated sulfuric acid onto ammonium chloride which had been moistened

with concentrated hydrochloric acid, was bubbled through the resulting solution at a rate of approximately one bubble per second for 30 minutes. Following an alkaline work up procedure, almost colorless crystals of 2-iodo-4,5-dimethoxybenzyl chloride (mp 83-85 °C) were obtained in 98% yield.

Scheme 2.10



In order to arrive at the correct substitution pattern of the pendant aromatic ring of isolariciresinol dimethyl ether, the α-aminonitrile required for coupling with benzyl chloride **128** had to be derived from veratraldehyde. The procedure chosen initially was analogous to that used by Charlton and Bogucki in their synthesis of 3,4,5-trimethoxybenzyl-α-aminonitrile **115**. Their procedure, a variation of the Strecker synthesis, involved treating 3,4,5-trimethoxybenzaldehyde dissolved in methanol, with potassium cyanide and morpholine under acidic conditions.

When the reaction using 3,4,5-trimethoxybenzaldehyde was carried out, a precipitate began to form which was eventually isolated by filtration, washed with water, and shown to be compound **115**. However, when the same reaction was carried out with veratraldehyde, the only precipitate that formed after four days of stirring at room temperature was of an inorganic nature, as determined by combustion analysis and proton NMR in D_2O. In an attempt to isolate the organic components present, a portion of the reaction mixture was extracted with ethyl acetate, and then dried and evaporated to give an oily residue. NMR analysis of the oil revealed a mixture of what appeared to be two components. One of the compounds was the desired α-aminonitrile (**136**), but the identity of the other compound could not be clearly established. Repetition of the entire reaction procedure gave an identical result.

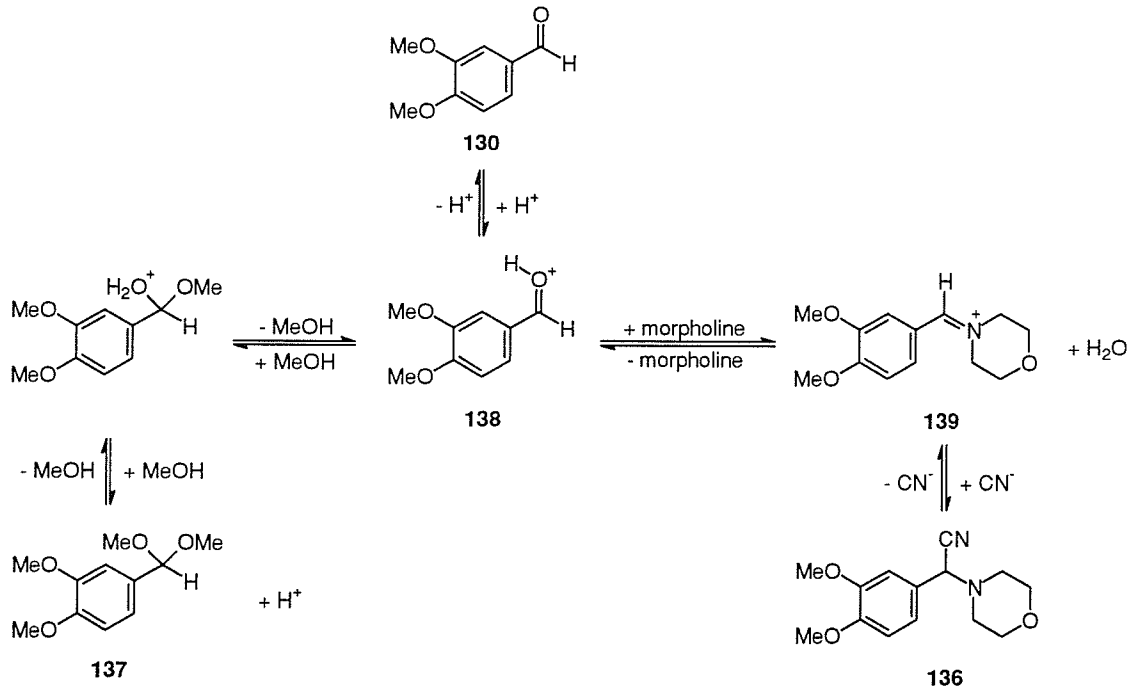
In an attempt to determine the identity of the second compound, the mixture of products was chromatographed on a silica gel column. The second compound was obtained in pure form using this procedure, as determined by TLC. However, when a proton NMR spectrum of the pure unknown compound was obtained, it revealed a mixture of the unknown compound and veratraldehyde. There was no indication of the presence of veratraldehyde from the TLC analysis carried out prior to NMR analysis. Apparently the compound in question was a veratraldehyde derivative, which was converted back to veratraldehyde following its isolation. Subtraction of the NMR signals corresponding to veratraldehyde from the spectrum obtained for the substance isolated following chromatography, revealed a series of peaks consistent with

the dimethyl acetal of veratraldehyde (**137**). In particular, the proton NMR spectrum possessed a six hydrogen singlet at 3.32 ppm, which would be expected to arise from the two identical methoxy groups of the acetal. It also exhibited a three hydrogen singlet at 3.87 ppm and one at 3.88 ppm which corresponded to the methoxy substituents of the aromatic ring. Also present was a one hydrogen singlet at 5.32 ppm, which was presumed to result from the acetal proton, and three sets of peaks in the 6.84 ppm to 7.00 ppm range, that showed a coupling pattern typical of a 1,3,4 tri-substituted benzene derivative. In fact, the six hydrogen singlet at 3.32 ppm and the one hydrogen singlet at 5.32 ppm, correlated extremely well to signals in the NMR spectrum of benzaldehyde dimethyl acetal.

It is well known that secondary amine salts react with aldehydes to give salts of the ternary iminium type and water,[10] and that these salts are susceptible to attack by nucleophiles such as the cyanide ion.[11] In fact, a mechanism based on these facts is what is generally accepted for the Strecker synthesis. As a result, the mechanism depicted in scheme 2.11 was proposed in order to account for the results obtained. According to this mechanism, the protonated from of veratraldehyde (**138**) undergoes a condensation reaction with morpholine to give the 3,4-dimethoxybenzylidenemorpholinium ion (**139**). This compound is then attacked by the cyanide ion, generating the α-aminonitrile (**136**). Under these conditions, one would also expect the protonated form of veratraldehyde to undergo reaction with methanol, ultimately giving rise to acetal **137**. Thus, the α-aminonitrile and acetal exist in equilibrium with one another. In

the case of the synthesis of compound **115** by Charlton and Bogucki, however, no acetal was detected. This observation is easily rationalized based on the mechanism depicted in scheme 2.11, due to the fact that, once formed, the α-aminonitrile **115** precipitated from solution. Therefore, the equilibrium in question would have been shifted in favor of the formation of the α-aminonitrile, thereby consuming any acetal which may have formed.

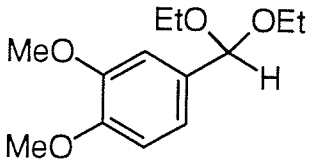
Scheme 2.11



Based on integration of the NMR signals resulting from the α-proton of α-aminonitrile **136** and the acetal proton of compound **137**, it was determined that the ratio of the two compounds was 1.0:2.4 in favor of the acetal. In an attempt to determine if the yield of α-aminonitrile could be increased, a similar reaction was carried out using ethanol as the solvent. After four days of stirring, the organic portion of the reaction mixture was isolated in a manner identical to that

used previously. Proton NMR analysis of the crude mixture obtained in this case, revealed the existence of the desired α-aminonitrile (**136**), and a second compound which had a structure consistent with that of veratraldehyde diethyl ether **140** (scheme 2.12). The spectrum exhibited a triplet at 1.19 ppm with a coupling constant of 7.0 Hz, and a quartet at 3.52 ppm with a coupling constant of 7.0 Hz. These signals were consistent with those expected from the methyl and methylene protons respectively of compound **140**. As well, a singlet appeared at 5.41 ppm, as did aromatic peaks corresponding to a substitution pattern like that of compound **140**. The ratio of α-aminonitrile to acetal in this case was 2.0:1.1, which showed a marked increase in the relative yield of the desired compound.

Scheme 2.12



140

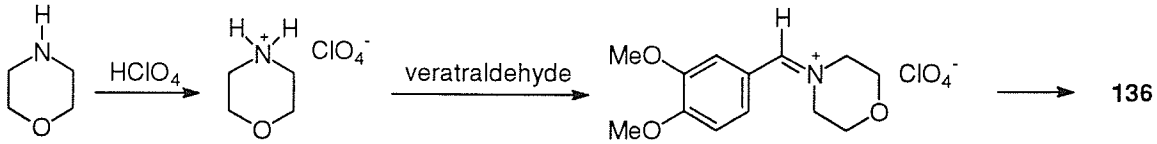
A reaction of the same type was again carried out, but this time 2-propanol was used as the solvent. Proton NMR analysis of the organic components of the reaction mixture obtained after four days of stirring, indicated the presence of the desired compound and veratraldehyde in a ratio of 12.6 to 1. There was no indication of the presence of benzaldehyde iso-propyl acetal in the spectrum. This fact was not surprising, given that the formation of acetals from sterically hindered alcohols, such as iso-propyl alcohol, is an unfavorable

process.[12] In fact, formation of acetals of this type, *via* acid catalyzed addition of alcohols to aldehydes, usually requires the azeotropic removal of water in order to drive the equilibrium in favor of acetal formation. Acetals resulting from sterically hindered alcohols are difficult to form, due to steric crowding in the transition states leading to their formation. The reaction proceeds *via* either S_N2 displacement of the protonated hydroxyl group of the hemiacetal, or by S_N1 attack of the carbocation resulting from elimination of the protonated hydroxyl group from the hemiacetal. The rate of reaction corresponding to either mechanism is diminished as the steric crowding of the respective transition state increases.[13] Presumably, the mixture of reaction products detected in the last reaction, namely α-aminonitrile **136** and veratraldehyde, resulted from incomplete conversion of the starting material to the desired product, *via* compound **138**, without the side reaction leading to acetal formation occurring. In fact, it was later determined that a longer reaction time of seven days led to almost exclusive formation of the desired compound with only a very slight trace (less than 2%) of veratraldehyde.

α-Aminonitrile **136** was also obtained directly from a compound presumed to be the morpholine perchlorate salt of veratraldehyde (**141**), in a manner which precluded the possibility of acetal formation. The procedure was initiated by combining morpholine, which was dissolved in diethyl ether, with 70% perchloric acid. This resulted in the formation of crystals possessing a melting point of 180-182 °C, which were presumed to be morpholine perchlorate. These crystals were combined in a one to one ratio with veratraldehyde in benzene, and

allowed to reflux while attached to a Dean-Stark trap for 21 hours. The precipitate of this reaction was removed by filtration and then rinsed with ice-cold ethanol to give crystals of what were thought to be 3,4-dimethoxybenzylidenemorpholinium perchlorate (**141**, mp 160-163 °C). These crystals were combined in a separatory funnel with a two phase solution consisting of diethyl ether and aqueous potassium cyanide. The molar ratio of potassium cyanide to compound **141** was 3:1. Following a period of shaking, the dichloromethane layer was removed from the separatory funnel, and then dried and evaporated to give off white crystals whose spectroscopic data corresponded to that of pure α-aminonitrile **136**. The overall yield from veratraldehyde to α-aminonitrile **136** was 83% (scheme 2.13).

Scheme 2.13



141

The coupling of benzyl chloride **128** and α-aminonitrile **136** to generate the aryliodoketone **142** (scheme 2.14), was initiated by the dropwise addition of the α-aminonitrile, dissolved in *N,N*-dimethyl formamide, to a room temperature suspension of sodium hydride in the same solvent, under nitrogen. This resulted in deprotonation at the α-carbon, causing the formation of the corresponding resonance stabilized carbanion. Dropwise addition of the benzyl chloride at this point allowed a substitution reaction to occur, whereby the anion of α-

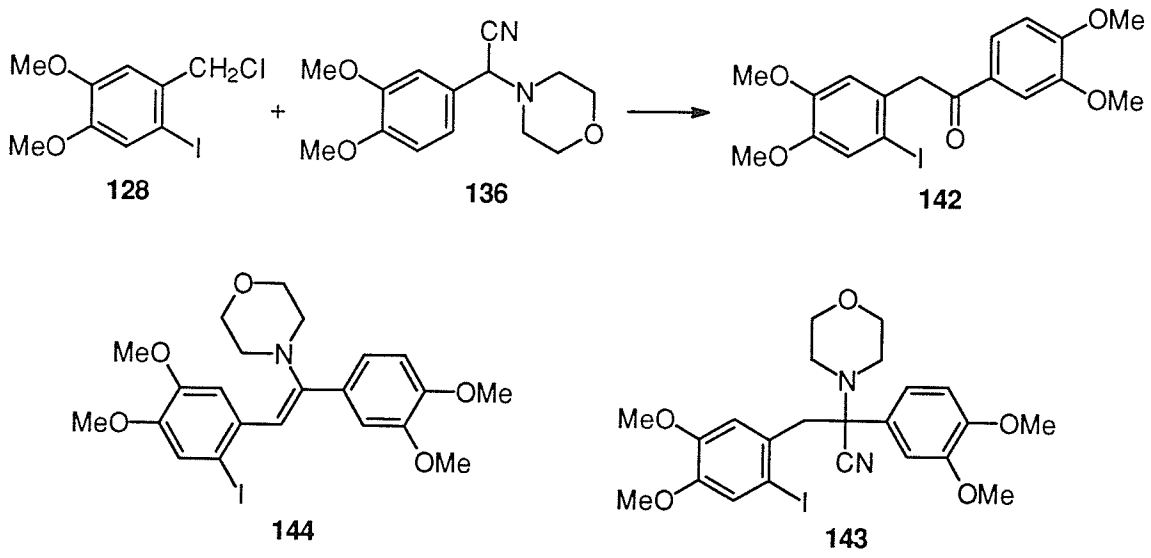
aminonitrile **136** caused displacement of the chloride ion of benzyl chloride **128**, yielding what was presumed to be the α-aminonitrile **143** exclusively, as determined by TLC. This compound was not isolated, but was instead subjected to acid catalyzed hydrolysis at room temperature, in an attempt to generate the desired ketone directly. Proton NMR analysis of the crude material obtained after work up indicated a mixture of two compounds. One of these compounds appeared to be the desired aryliodoketone, but the other could not be identified from the spectrum.

In an attempt to characterize the unknown compound, the mixture was separated on a silica gel column using ethyl acetate/hexanes as the eluting solvent. Despite the acquisition of both NMR and mass spectral data, no definite structure could be assigned to the unknown compound. Based on earlier work carried out by Charlton and Bogucki, however, it was thought that the unknown compound might be the enamine **144** from incomplete hydrolysis of the α-aminonitrile **143**. However, the spectroscopic data obtained did not support this hypothesis.

Given that TLC analysis of the reaction mixture before hydrolysis indicated the presence of only one compound, it seemed reasonable to assume that, whatever the identity of the unknown compound, it likely resulted from either incomplete or excessive hydrolysis. In an attempt to determine if the unknown compound was the result of incomplete hydrolysis, the reaction was carried out a second time using the same procedure as previously, except that the hydrolysis reaction was carried out at 65 °C for 16 hours. This resulted in

the formation of a white precipitate which dissolved in dichloromethane during extraction, and reformed on evaporation. NMR analysis of this solid indicated that it consisted of the desired aryliodoketone in a pure form. Thus, the unknown compound was indeed an artifact brought about by incomplete hydrolysis of the α-aminonitrile **143**. No further attempt was made to characterize it. The procedure for the isolation of the aryliodoketone was later optimized by simply isolating the precipitate from hydrolysis and then washing it with cold methanol. This gave compound **142** as pure colorless crystals in 94% isolated yield (mp 170-172 °C).

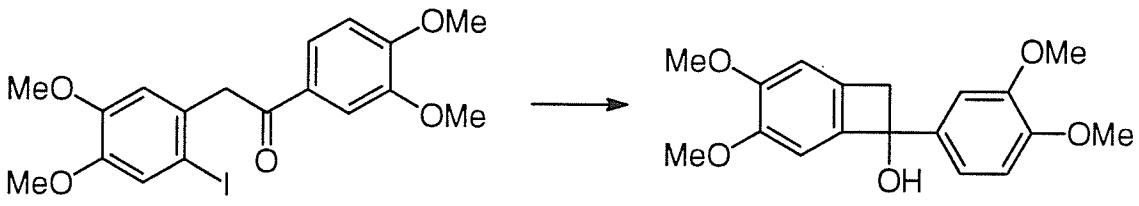
Scheme 2.14



Once the aryliodoketone had been obtained, formation of the desired benzocyclobutenol was achieved as follows. To effect cyclization, the aryliodoketone, in freshly distilled tetrahydrofuran under a nitrogen atmosphere,

was exposed to *n*-butyllithium at -78 °C. After reacting for 30 minutes cyclicization was complete and, consequently, the reaction was quenched with a 10% aqueous solution of ammonium chloride. Following extraction and chromatography on silica gel, benzocyclobutenol **145** was obtained in 74% yield (scheme 2.15).

Scheme 2.15

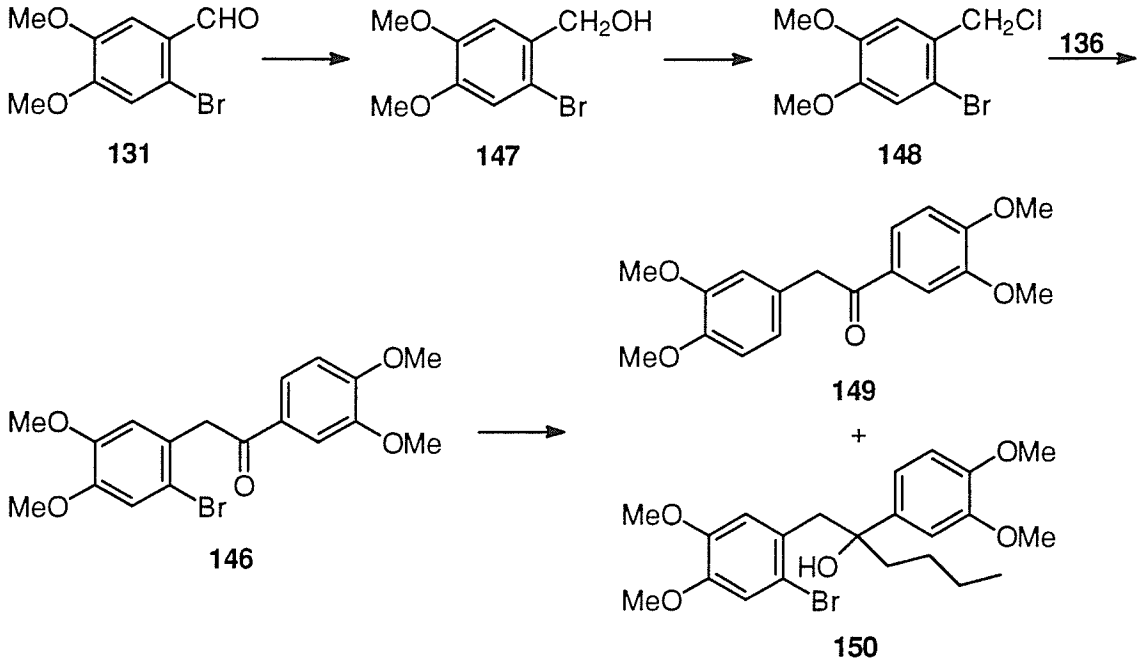


142 **145**

In an attempt to determine if the synthetic route to benzocyclobutenol **145** could be shortened, arylbromoketone **146** was obtained, and its cyclicization was attempted. Although Narasimhan *et al.* had reported little success with the cyclicization of similar compounds,[14] no data appeared for the specific case at hand and, thus, an investigation seemed worthwhile. The route to compound **146** began with the reduction of 6-bromoveratraldehyde, in a manner analogous to that for the reduction of 6-iodoveratraldehyde, which gave 2-bromo-4,5-dimethoxybenzyl alcohol (**147**). Elaboration to the corresponding benzyl chloride **148**, and then to the arylbromoketone **146** was, likewise, achieved according to a procedure analogous to that for the iodo compounds **128** and **142**, respectively. When cyclicization of compound **146** was attempted, an oily residue resulted which, when analyzed by proton NMR spectroscopy, revealed that no benzocyclobutenol had formed. Although the proton NMR spectrum of the crude

mixture could not be clearly interpreted, based on the work by Narasimhan *et al.*, the mixture was assumed to consist of the reduction product **149** and the product from attack of the butyl anion on the carbonyl group (**150**) (scheme 2.16). Clearly, this procedure was much less efficient than the procedure using the analogous iodo compounds and, as such, was not investigated further.

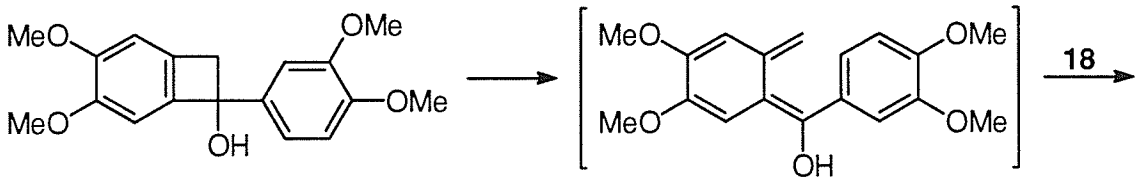
Scheme 2.16



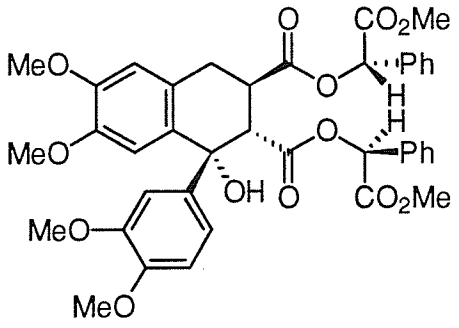
The next major step in the synthesis of (-)-isolariciresinol dimethyl ether involved the formation of cycloadduct **151** *via* the Diels-Alder reaction between the *ortho*-quinodimethane formed from benzocyclobutenol **145,** and the fumarate of methyl (*S*)-mandelate. The assumption that cycloadduct **151** would form as the major product of this reaction, was based on the results obtained by Charlton and Bogucki in their synthesis of (-)-deoxypodophyllotoxin, as discussed in

section 2.1 A. In order to achieve this reaction, the benzocyclobutenol was thermolyzed by refluxing it in toluene, giving *ortho*-quinodimethane **152**, which was trapped *in situ* with the fumarate of methyl (*S*)-mandelate. The proton NMR spectrum of the crude product showed signals consistent with the structure of compound **151**, with no indication of the formation of any other cycloadducts. Indeed, flash chromatography of the crude material using silica gel and ethyl acetate/hexanes, gave a single compound in 51% isolated yield whose structure was consistent with that of cycloadduct **151** (scheme 2.17). The relative stereochemistry of the cycloadduct had been established previously based on its similarity to compound **153**[15] (scheme 2.18), and the absolute stereochemistry was assumed based on analogy to the reaction by Charlton and Bogucki shown in scheme 2.8.

Scheme 2.17

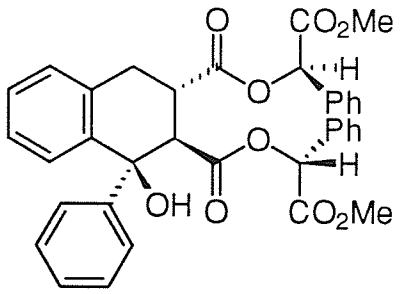


145 **152**



151

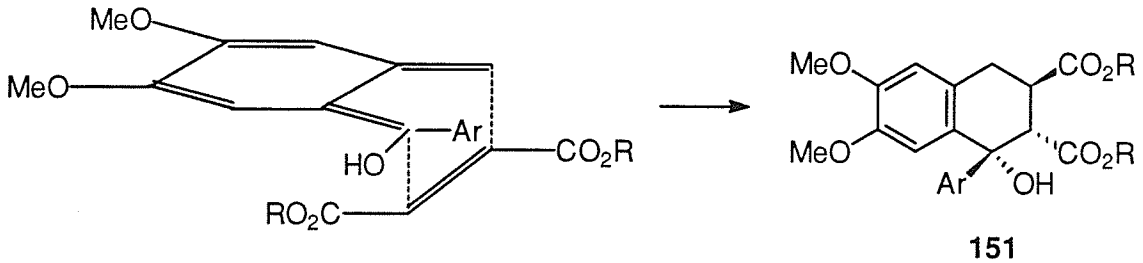
Scheme 2.18



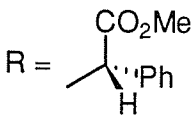
153

In order to arrive at the relative and absolute stereochemistry shown for compound **151**, the reaction must have proceeded through the transition state depicted in scheme 2.19. The assumption is made that the *ortho*-quinodimethane adopts a configuration in which the hydroxyl group is in the (E) geometry. This assumption is based on past experience as well as the torquoselectivity rules outlined by Houk *et al.*[16] Hence, the fumarate of methyl (*S*)-mandelate adds to the diene in an *endo* fashion, with addition occurring between the re face of the dienophile and the si face of the diene.

Scheme 2.19



151



Ar = 3,4-dimethoxyphenyl

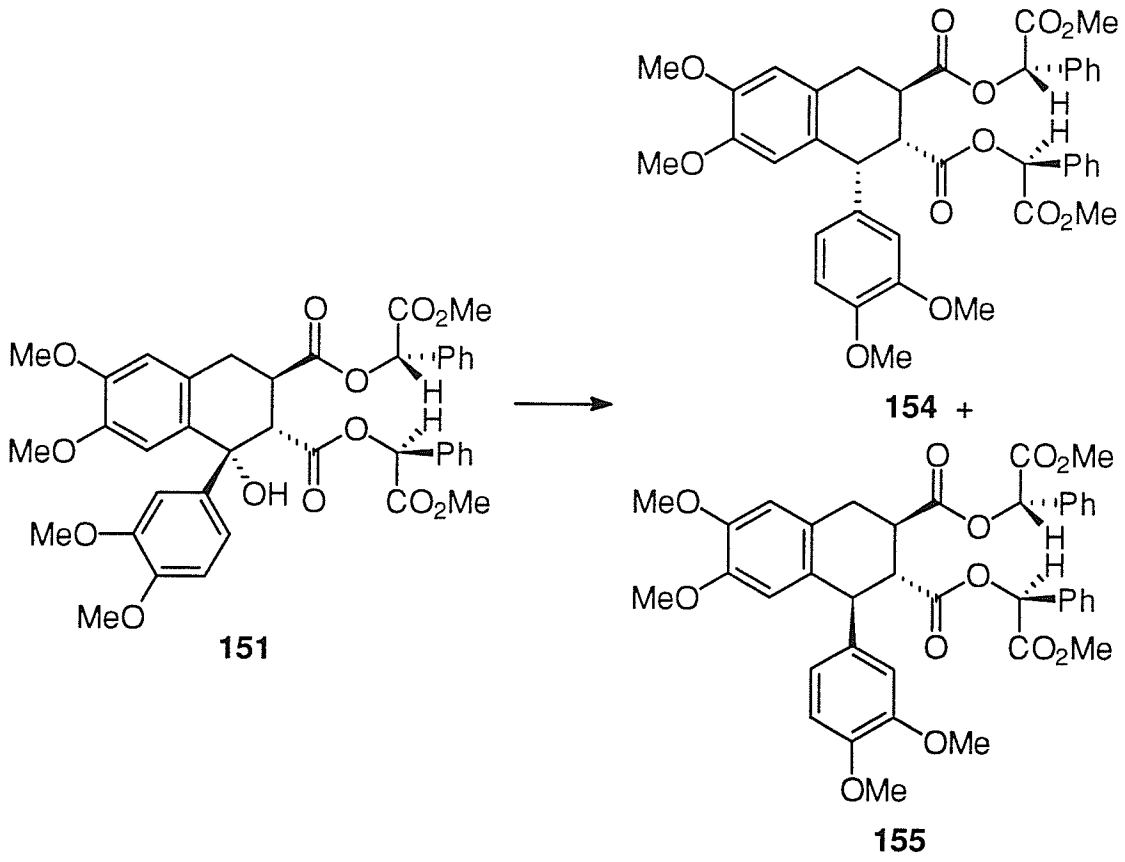
The first step in the elaboration of cycloadduct **151** to (-)-isolariciresinol dimethyl ether, involved the reductive removal of the C1 hydroxyl substituent. This conversion was carried out by exposing cycloadduct **151** to boron trifluoride etherate at low temperature. A dark blue solution, indicative of the formation of the benzyllic cation was produced, which was discolored on treatment with an ethereal solution of lithium aluminum hydride. Acidic work up, followed by extraction, and then drying and evaporation of the organic portion, gave an amorphous solid. Proton NMR analysis of this crude material revealed a mixture of products.

The assumption was made that the mixture of products consisted of two compounds, specifically, the inverted reduction product **154**, which was the major product, and the noninverted reduction product **155** (scheme 2.20). This assumption was based primarily on the existence of two doublets in the proton NMR spectrum, one at 4.56 ppm, with a coupling constant of 5.5 Hz, and the other at 4.23 ppm, with a coupling constant of 9.8 Hz. The doublets were presumed to arise from the C1 proton of compounds **154** and **155** respectively. The coupling constant of 5.5 Hz was consistent with coupling between H1 and H2 of compound **154**, given that these protons are oriented *cis* to one another. The H1 and H2 protons of compound **155** are in a *trans* orientation to one another and, hence, the coupling constant of 9.8 Hz is appropriate.

The crude reaction product was chromatographed, which gave 42% yield of a compound, whose spectral data corresponded to that of compound **154**. No material could be obtained from the chromatography column which

corresponded to compound **155**. The presence of compound **155** in the crude reaction product was confirmed, however, by comparison of the proton NMR spectrum obtained for compound **154** to the original spectrum. Once the signals corresponding to compound **154** were subtracted from the crude spectrum, signals consistent with a literature NMR spectrum of pure compound **155** remained. The ratio of compound **154** to compound **155** was determined to be approximately 8:1, based on integration of the H1 doublets.

Scheme 2.20

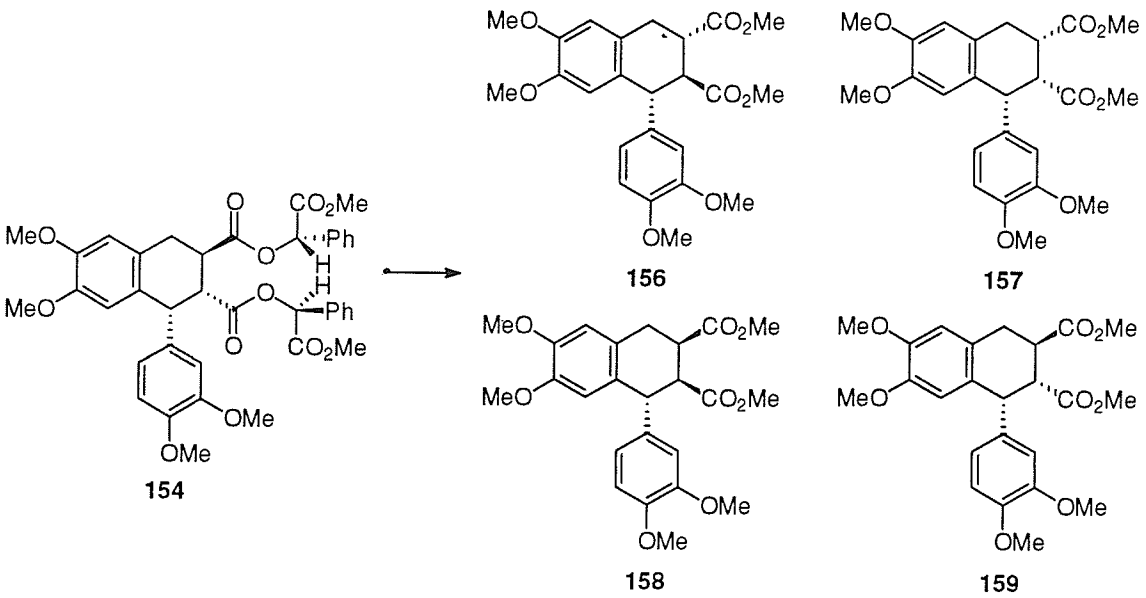


Although the 1,2-*cis*-2,3-*trans* relative stereochemistry of the polyester **122** from reduction of the cycloadduct **20** was desired in the case of the synthesis of (-)-deoxypodophyllotoxin, this same relative stereochemistry in

compound **154** was unsuitable for the synthesis of (-)-isolariciresinol dimethyl ether. This is due to the fact that (-)-isolariciresinol dimethyl ether possesses a 1,2-*trans*-2,3-*trans* relative stereochemistry. Thus, experiments were conducted to determine if the stereochemistry at carbons two and three of compound **154** could be altered, without disturbing the stereochemistry at carbon one.

It was assumed that the C2 and C3 centers of compound **154** could be efficiently epimerized to give the thermodynamically stable all *trans* relative configuration by treatment with methoxide ion. It was also thought that this might provide the added advantage of removing the mandelyl chiral auxiliary groups in the same step, giving compound **156** directly. Hence, 14 equivalents of a 0.1 M solution of sodium methoxide, was combined with the 1,2-*cis*-2,3-*trans* ester **154**, and the resulting solution was allowed to reflux for two hours. Analysis of the proton NMR spectrum of the crude product obtained after work up indicated the presence of the desired all *trans* compound, but also indicated that other compounds were present. The desired compound exhibited a distinct doublet at 4.17 ppm, with a $J_{1,2}$ coupling constant of 10.9 Hz, as was expected for coupling between protons possessing a *trans* relation to one another. It was thought that the other compounds which were present might be the other diastereomers of compound **156,** which could result from compound **154** *via* ester exchange, and epimerization in various ways at C2 and C3, that is compounds **157**, **158** and **159**. This assumption was based on the presence of three other signals in the crude spectrum, which appeared to be doublets, at 4.53 ppm, 4.64 ppm, and 4.67 ppm (scheme 2.21).

Scheme 2.21



The crude reaction mixture was chromatographed, but separation of the various components proved extremely difficult given the similarity of their retention factors. Among the fractions collected, was one corresponding to the pure all *trans* compound and one which contained the all *trans* isomer and, what appeared to be its 1,2-*cis*-2,3-*trans* diastereomer **159**, in approximately equal amounts. The second compound was assumed to be the 1,2-*cis*-2,3-*trans* isomer based on the small $J_{1,2}$ coupling of 2.3 Hz for the doublet at 4.67 ppm, and peaks at approximately 3.44 ppm, and 2.93 ppm, similar to the starting material. If this compound was, in fact, dimethyl ester **159**, then it must have resulted from ester exchange occurring without epimerization at either C2 or C3. No attempt was made to fully characterize any of the compounds other than **156** at this point. This was due to the fact that, towards obtaining (-)-isolariciresinol dimethyl ether, it seemed much more important to find an efficient means for the

selective epimerization and the ester exchange of compound **154** to the dimethyl ester **156**.

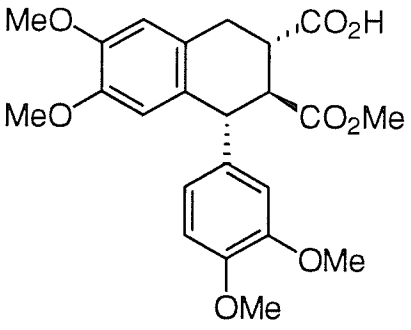
In another attempt to obtain compound **156** in a more efficient way from compound **154**, the 1,2-*cis*-2,3-*trans* isomer **154** was subjected to conditions of epimerization and ester exchange, using 140 equivalents of 0.1 M methoxide ion, and a reflux time of 22 hours. When compared to the results obtained for the previous epimerization experiment, it could be seen that all four doublets of what were presumed to be the four epimerization products were still present. It was noted, however, that the relative intensity of each of the doublets had changed, an observation which offered support for the notion that these signals did, indeed, arise from the compounds suggested. Most importantly, however, was the fact that the desired compound was present to a greater extent than before. Based on this observation, it was thought that even longer epimerization times, or harsher epimerization conditions, might lead to an even more exclusive formation of the desired compound.

Compound **154** was, thus, subjected to epimerization and ester exchange conditions using 1.04 M sodium methoxide for a period of 23 hours at reflux temperature. The proton NMR spectrum of the crude product of this reaction seemed to indicate the presence of only one compound, but it was not the desired all *trans* dimethyl ester **156**. The product corresponding to the NMR spectrum obtained appeared to posses only five methoxy peaks, but seemed to be similar in most other respects to the desired compound. Hence, it was thought that this compound might be either the half ester **160** or **161** (scheme

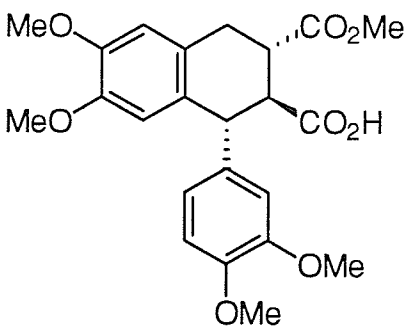
2.22). In order to determine if this was in fact the case, the crude material was subjected to methylation conditions of 3% hydrochloric acid in methanol for 15 hours. The proton NMR spectrum of the crude material of this reaction indicated what appeared to be exclusively the desired all *trans* dimethyl ester. This was established following purification of the crude material on silica gel which gave, in 83% isolated yield, a compound whose spectroscopic data corresponded to that of the all *trans* dimethyl ester **156**. Apparently then, the hypothesis regarding the intermediacy of one of the half esters **160** or **161** was correct.

Elaboration of the all *trans* dimethyl ester to (-)-isolariciresinol dimethyl ether was achieved efficiently, *via* an established literature procedure. In accordance with this procedure, the dimethyl ester was dissolved in tetrahydrofuran and then exposed to 1.1 equivalents of lithium aluminum

Scheme 2.22



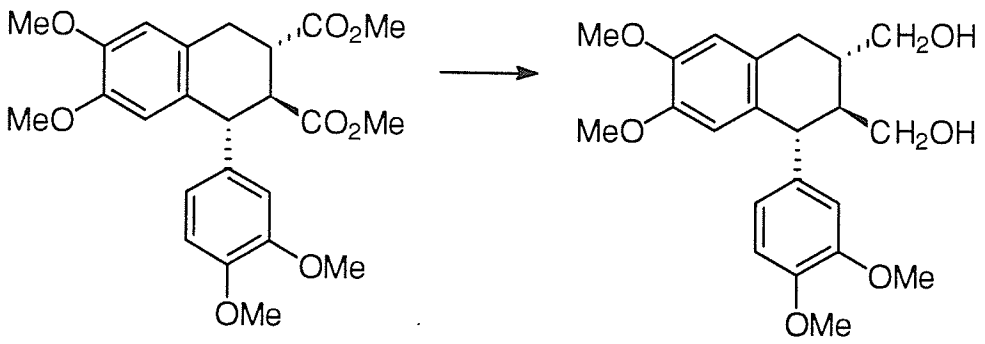
160



161

hydride, while under a nitrogen atmosphere. The sole product of this reaction following work up was isolariciresinol dimethyl ether (**1**), obtained in 96% isolated yield (scheme 2.23).

Scheme 2.23



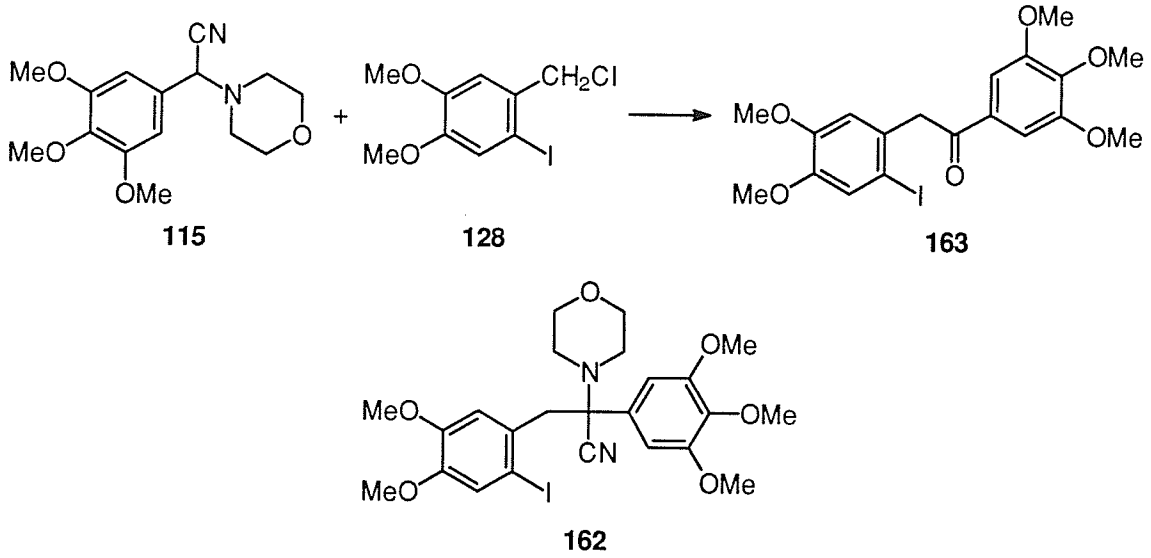
156 **1**

C) The Synthesis of (-)-Deoxysikkimotoxin

As in the case of (-)-isolariciresinol dimethyl ether, the aromatic ring A of (-)-deoxysikkimotoxin possesses methoxy substituents at carbons six and seven. Hence, the choice of the benzyl chloride for the α-aminonitrile coupling reaction of the (-)-deoxysikkimotoxin synthesis, was the same as that for the synthesis of (-)-isolariciresinol dimethyl ether, namely compound **128**. The pendant aromatic ring C, however, bears a 3,4,5-trimethoxy substitution pattern and, therefore, the α-aminonitrile chosen in this case was compound **115**. The synthesis of α-aminonitrile **115** was carried out according to the method outlined earlier (section 2.1 A), and depicted in scheme 2.7. Thus, 3,4,5-trimethoxybenzaldehyde was reacted with concentrated hydrochloric acid, potassium cyanide, and morpholine, which gave a colorless precipitate in 94% yield (mp 136-138 °C), whose spectroscopic data matched that of compound **115**.

Compound **115** was treated with sodium hydride, thereby generating its resonance stabilized carbanion, which was then allowed to react with the benzyl chloride **128**. The resulting α-aminonitrile **162** was not isolated, but was instead subjected to conditions of hydrolysis in a manner analogous to that of compound **143**. The precipitate which resulted from hydrolysis was isolated and then washed with cold methanol to give colorless crystals (mp 147-150 °C). Spectroscopic analysis of the crystals indicated that they were comprised of the desired aryliodoketone **163** (scheme 2.24). The overall yield of the reaction was 91%.

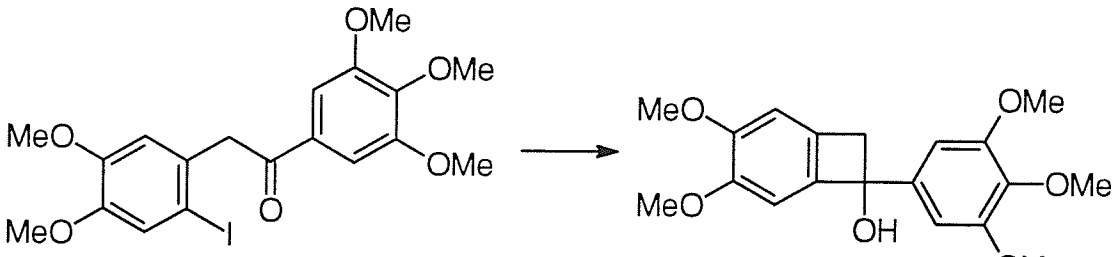
Scheme 2.24



It is interesting to note that for the synthesis of both aryliodoketone **142** and **163**, the product after hydrolysis precipitated from solution allowing for a very convenient means of isolating each of the compounds in a pure form. For

the synthesis of aryliodoketone **114** by Charlton and Bogucki, however, the product after hydrolysis was an amorphous, brown solid, obtained following extraction and then evaporation and drying of the resulting organic portion. In order to obtain compound **114** in a pure state, it was necessary to recrystallize the amorphous brown solid, which greatly affected the overall yield. Thus, it appears that the solubility of the aryliodoketones in *N,N*-dimethyl formamide is profoundly affected by the substituents on the aromatic ring which is derived from the benzyl chloride. The solubility is clearly decreased in going from the methylenedioxy substituent to the methoxy substituents.

Scheme 2.25



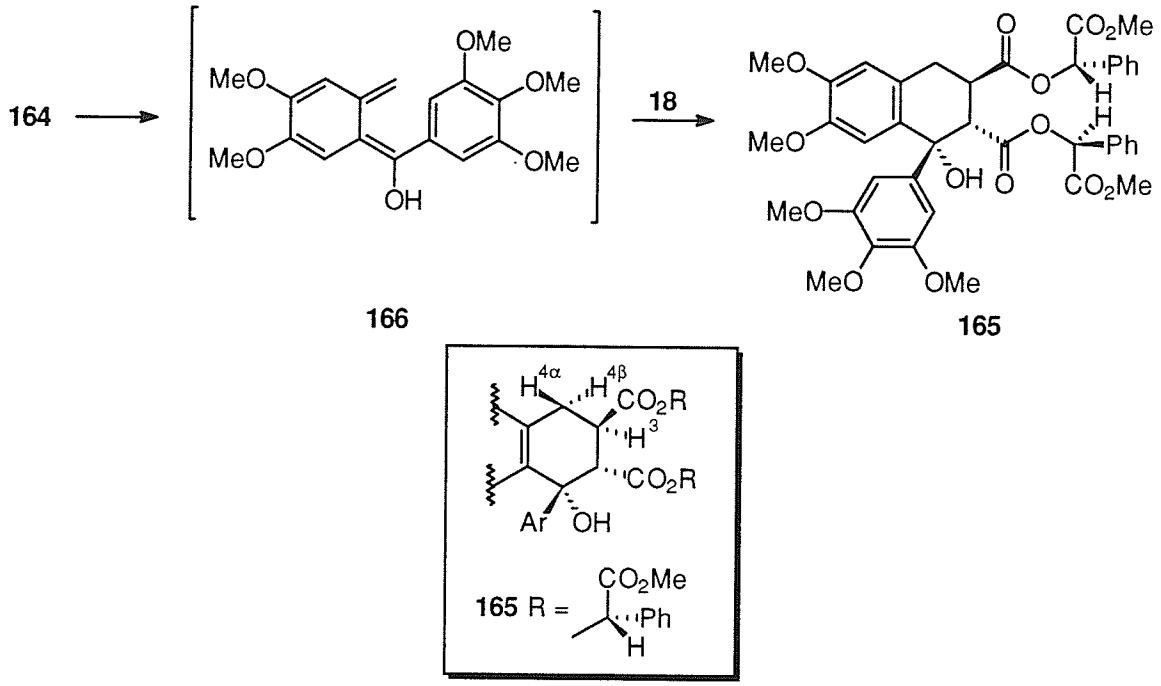
163 **164**

The next step of the reaction sequence leading to (-)-deoxysikkimotoxin was the cyclicization of aryliodoketone **163** to give benzocyclobutenol **164**. This reaction was carried out relatively uneventfully by treating compound **163**, which was dissolved in tetrahydrofuran and under a nitrogen atmosphere at -78 °C, with *n*-butyllithium. Following work up and chromatography on silica gel, benzocyclobutenol **164** was obtained in 72% yield (scheme 2.25).

Based on the results obtained for the cycloaddition reaction of benzocyclobutenol **19** and benzocyclobutenol **145** with the fumarate of methyl (*S*)-mandelate, it was assumed with considerable confidence that the major cycloadduct of the reaction between benzocyclobutenol **164** and the same dienophile would be compound **165**. The formation of compound **165** would occur *via* a transition state similar to that shown in scheme 2.19, where Ar = 3,4,5-trimethoxyphenyl. Hence, the benzocyclobutenol was refluxed in freshly distilled toluene, allowing thermolysis to occur such that *ortho*-quinodimethane **166** could form, which was trapped *in situ* with the fumarate of methyl (*S*)-mandelate. The proton NMR spectrum of the crude reaction product showed signals consistent with those expected for cycloadduct **165**, and did not indicate the presence of any other cycloadducts. In particular, a pair of double doublets appeared, one at 3.17 ppm and the other at 3.45 ppm. Each of the double doublets shared a coupling constant of 16.4 Hz, with one possessing a coupling constant of 11.4 Hz, and other a coupling constant of 4.3 Hz. By analogy to cycloadducts **20**, **151** and **153**, these signals were assumed to arise from $H4_{\alpha}$ and $H4_{\beta}$ of the *endo* cycloadduct. The large coupling constant of 16.4 Hz is consistent with geminal coupling between $H4_{\alpha}$ and $H4_{\beta}$. The coupling constant of 11.4 Hz is consistent with coupling between $H4_{\alpha}$ and H3, which are oriented *trans* to each other, and the coupling constant of 4.3 Hz is consistent with coupling between $H4_{\beta}$ and H3, which are oriented *cis* to each other. The

cycloadduct was obtained as a solid in 57% overall yield after chromatography (mp 82-85 °C) (scheme 2.26).

Scheme 2.26

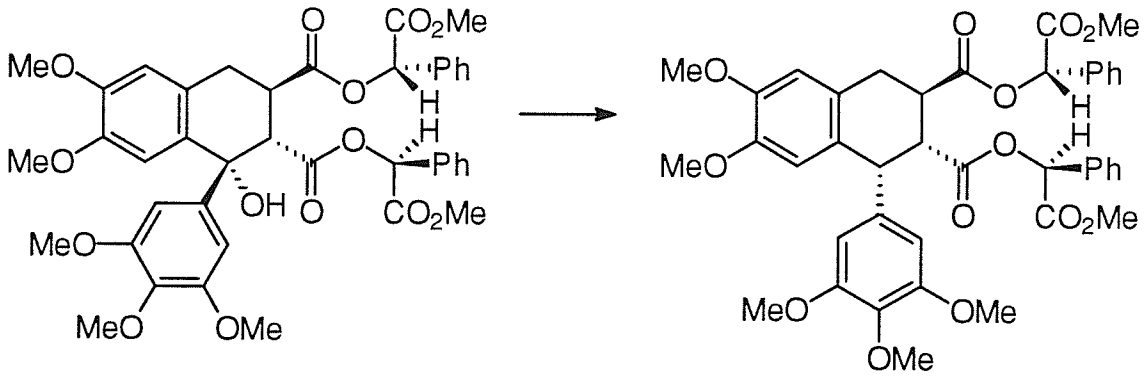


The next step of the synthesis of (-)-deoxysikkimotoxin involved the reduction of cycloadduct **165**, in order to remove the C1 hydroxyl substituent. The procedure that was chosen for this transformation was essentially the same as that chosen for the reduction of cycloadducts **20** and **151**. By analogy to the reduction of compound **20** and compound **151**, it was assumed that the major product of the reduction would be the 1,2-*cis*-2,3-*trans* polyester **167** (scheme 2.27). For the case at hand this was particularly convenient, given that (-)-deoxysikkimotoxin possesses the same relative stereochemistry at carbons one to three as the expected reduction product. Therefore, provided that the reduction compound could be elaborated to (-)-deoxysikkimotoxin in a way that

would not effect the absolute stereochemistry at carbons one, two or three, the primary stereochemical concerns of this synthesis would have been addressed at this point.

Cycloadduct **165** was dissolved in dichloromethane and exposed to boron trifluoride etherate at a temperature of -20 °C. This caused the solution to turn deep blue, which was assumed to mean that the corresponding benzyl cation had formed. The temperature of the solution was then lowered to -55 °C, at which point an ethereal solution of lithium aluminum hydride was added until the blue color disappeared. The resulting solution was allowed to stir for 20 minutes and was then warmed to room temperature. Work up consisted of acidification of the solution to destroy any excess reducing agent, followed by extraction into dichloromethane, and then drying and evaporation of the organic extract.

Scheme 2.27



165 **167**

Proton NMR analysis of the crude product indicated the presence of what appeared to be the desired compound, as well as an impurity. The presence of

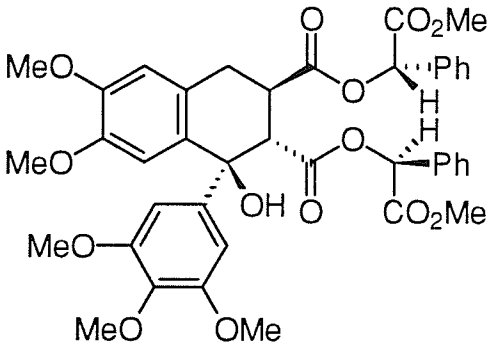
compound **167** was assumed based on the appearance of a doublet at 4.57 ppm with a coupling constant of 5.5 Hz, a situation very similar to that seen for compounds **122** and **154**. The identity of the impurity was thought to be unreacted starting material, that is cycloadduct **165**, by comparison of the NMR spectrum of the crude product to that of a known sample of **165**. This assumption was confirmed following chromatography of the crude reaction product, by the isolation of two compounds. The first of these compounds possessed spectral data identical to that of compound **165**, and the second compound was the desired reduction product, as revealed by the spectroscopic data obtained for it. Based on the integration of the singlets corresponding to the protons of the mandelyl chiral auxiliaries, the ratio of compound **167** to compound **165** was determined to be 3.75:1.

The reduction of compound **20** by a similar procedure to that employed here gave a total of three products. They were the inversion product **122**, the noninverted product **123**, and the elimination product **124**. The reduction of compound **151** by the same procedure also produced more than one product, namely the inverted product **154** and the noninverted product **155**. It is interesting to note that neither the noninversion product nor the elimination product was detected for the reduction of cycloadduct **165**.

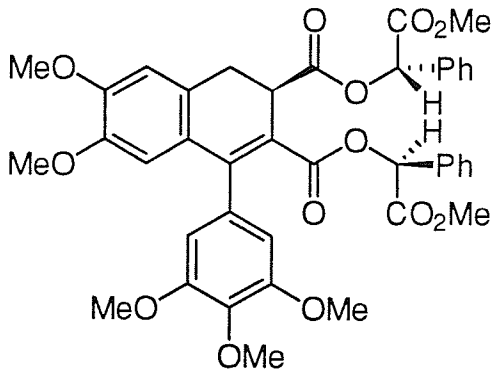
The mechanism of the reduction carried out here is presumed to involve the formation of a benzyl cation *via* Lewis acid mediated abstraction of the hydroxyl group at C1. It is thought that this produces a closely associated ion pair, since the diaryl cation has been observed to be quite stable. This is

evidenced by the fact that the blue color of the solution has been observed for long time periods at temperatures of up to -5 °C. If the assumptions regarding this mechanism are true, then the only reasonable explanation for the existence of the starting material in the crude product mixture is that formation of the diarylcation was incomplete, prior to the addition of reducing agent. Another less probable explanation that could account for the existence of the starting material in the crude product, is that the diarylcation did form to completion, but there was not enough reducing agent present to react with it. If this were the case, then presumably the cation could have reacted with the water added during the work up procedure, regenerating the hydroxyl substituent at C1. However, if this did occur, then there is no reason to assume that the compound possessing the opposite configuration at C1 (**168**) would not form as well. Also, in the absence

Scheme 2.28



168



169

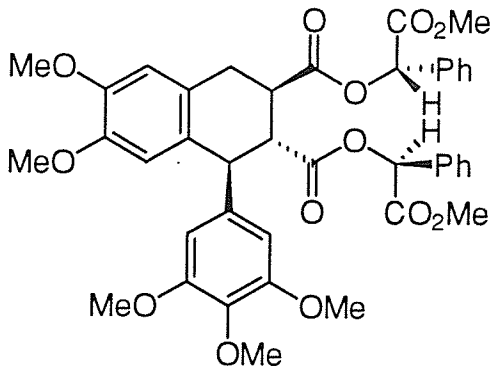
of enough reducing agent to react with the benzyl cation, one would almost surely expect the proton at C2 to eliminate, giving rise to compound **169**. Thus, since there were no signals present in the proton NMR spectrum of the crude

product consistent with either compounds **168** or **169**, the latter explanation was discounted in favor of the former (scheme 2.28).

In an attempt to show that the hypothesis regarding incomplete formation of the benzyl cation was true, a similar reaction was carried out, but the conditions leading to the formation of the diarylcation were altered somewhat. Specifically, the initial temperature of the reaction, that is the temperature at which the boron trifluoride etherate was added, was increased to -12 °C. It was thought that these conditions would be more conducive to the formation of the diarylcation. The temperature of the reaction was then lowered to -55 °C, and the same procedure as before was followed. Proton NMR analysis of the crude product of this reaction indicated the presence of the desired 1,2-*cis*-2,3-*trans* reduction product, as well as a compound presumed to be the 1,2-*trans*-2,3-*trans* reduction product (**170**) (scheme 2.29). The presence of the second compound was assumed based on the appearance of a doublet in the NMR spectrum at 4.25 ppm possessing a coupling constant of 9.8 Hz, a situation which was very similar to that for compounds **155** and **123**. The 1,2-*trans*-2,3-*trans* reduction product was present in only a trace amount, however, and in fact, the product ratio of compound **167** to compound **170** was shown to be approximately 12:1, as determined by integration of the doublets appearing in the proton NMR spectrum. Thus, based on the data obtained from this reaction, it seems that the diaryl cation did form to completion and then reacted completely with the reducing agent. However, in this case, reduction must have

occurred from both faces of the cation, giving both the inverted product and the noninverted product.

Scheme 2.29



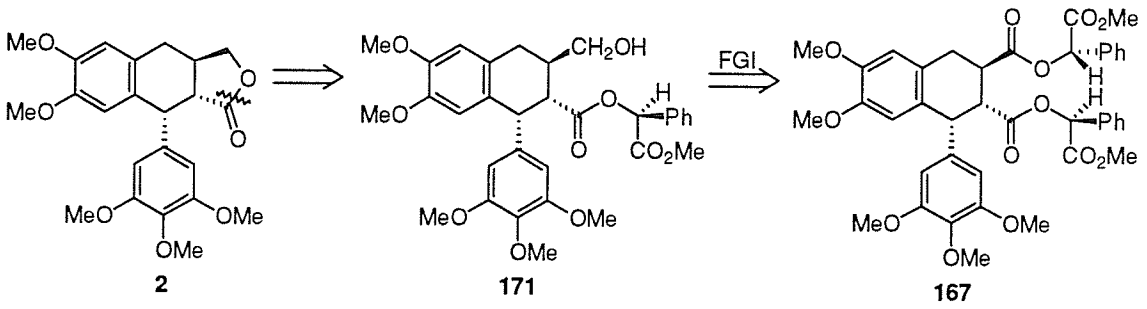
170

At this point in the synthesis, the correct absolute stereochemistry required for (-)-deoxysikkimotoxin had been established within the carbon skeleton. Two primary objectives remained; the chiral auxiliary groups had to be removed from the substituents at C2 and C3, and the requisite lactone had to be formed. During their synthesis of (-)-deoxypodophyllotoxin, Charlton and Bogucki had achieved these two objectives with compound **122** in a rather complicated way. To reiterate, compound **122** was converted to the diacid **125**, from which the anhydride **126** was obtained. Selective reduction of the anhydride afforded the γ-hydroxy acid **127**, which was subsequently lactonized to (-)-deoxypodophyllotoxin (**15**). Although this was an effective means of arriving at compound **15** from compound **122**, several steps were involved and the overall yield of approximately 35% from compound **122** to (-)-deoxypodophyllotoxin, left some room for improvement. It was hoped that this

method could be improved upon somewhat for the synthesis at hand, and could also potentially result in a corresponding increase in the efficiency of the synthesis of (-)-deoxypodophyllotoxin.

In order to achieve a more efficient synthetic route from the reduction product **167** to the target molecule, it was decided that the ideal situation would be one in which a single reaction achieved both of the remaining objectives. Initially, this seemed a rather optimistic suggestion. However, after analyzing the problem at hand from a retrosynthetic point of view (scheme 2.30), it was realized that a selective reduction of the ester substituent at C3 to give the γ-hydroxy ester **171** could potentially be followed by lactonization, whereby the remaining ester substituent would be displaced during lactone formation, yielding (-)-deoxysikkimotoxin directly. The real question then, was whether or not regioselective reduction of the ester functionality at carbon three could be achieved in preference to the ester group at carbon two. Based on data obtained during the synthesis of (-)-isolariciresinol dimethyl ether, it seemed reasonable to assume that this was so.

Scheme 2.30

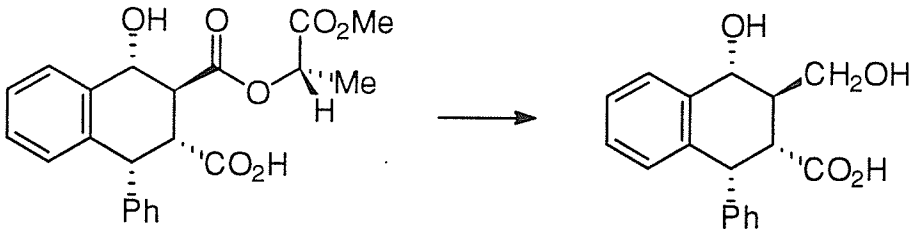


During the final stages of experimentation towards optimizing the epimerization and ester exchange of compound **154** to give compound **156**, it was noticed that the reaction proceeded to give either the half ester **160** or **161**. From the point of view of achieving the synthesis of (-)-isolariciresinol dimethyl ether, it was unnecessary to investigate this problem in any depth. That is, it was not necessary to determine which half ester had formed because the final result, namely compound **156**, would have been the same in each case. However, with respect to the present situation, this observation was now noteworthy in that it suggested that the two ester substituents were chemically distinct enough from one another to allow one to react preferentially over the other. On the basis of this information, it seemed reasonable to pursue a regioselective reduction.

Certain limitations were inherent in the reduction process. For example, the starting material for the reduction possessed four ester substituents, and any one of those four ester groups could have been the first to undergo reduction, profoundly effecting the overall outcome of the reaction. A second limitation was that only reducing agents capable of converting an ester to an alcohol could be used. It was known, however, that lithium triethylborohydride was effective in the reduction of ester substituents to hydroxyl substituents. As well, Charlton and Plourde had previously reported the use of lithium triethylborohydride for the reduction of compound **172** to **173**, thereby suggesting that reduction of the innermost ester substituents was possible, but not necessarily exclusive

(scheme 2.31). Thus, lithium triethylborohydride seemed a reasonable reagent from which to start the investigation.

Scheme 2.31



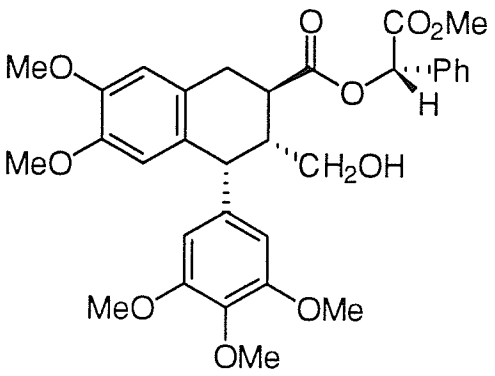
172 **173**

The conditions chosen initially for the reduction/lactonization of compound **167** were as follows. Compound **167** was dissolved in tetrahydrofuran at room temperature, under a nitrogen atmosphere. Three equivalents of a 1.0 M solution of lithium triethylborohydride were then added and the solution was allowed to stir for ten minutes. At that point, aqueous 10% hydrochloric acid was added to quench the reaction, and the resulting solution was allowed to stir for an additional 15 hours. Dilution of the solution with water, followed by extraction and evaporation of the organic extract afforded pale violet crystals. The proton NMR spectrum of the crude mixture displayed signals consistent with both (-)-deoxysikkimotoxin and the starting polyester **167** in a ratio of approximately 1:1, but also showed some other very minor signals. Thus, it appeared at this point that the hypothesis regarding the regioselective reduction and subsequent lactonization of compound **167** held some promise.

In an attempt to determine the exact composition of the crude mixture, it was subjected to chromatography which resulted in the isolation of a total of

three compounds. Two of the compounds were indeed compound **167** and (-)-deoxysikkimotoxin, as determined by proton NMR. The other compound, present to a much less extent, possessed proton NMR spectral data which seemed consistent with either the γ-hydroxy ester **171** or **174** (scheme 2.30 and scheme 2.32 respectively).

Scheme 2.32



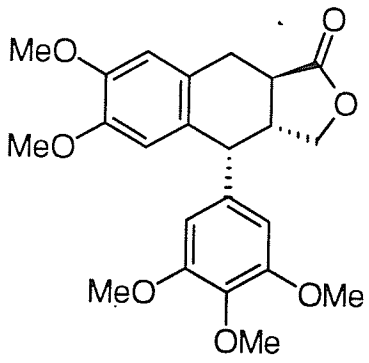
174

The spectrum of the unknown compound showed a singlet at 6.69 ppm, one at 6.62 ppm, and one at 6.31 ppm in a ratio of 1:1:2. This pattern is consistent with the signals arising from the aromatic protons at C5, C8, C2', and C6'. Each of the singlets at 6.69 ppm and 6.62 ppm could result from either the protons at C5 or at C8. The larger singlet at 6.31 ppm is consistent with the signal which would arise from the two equivalent C2' and C6' protons. Slightly upfield from these signals was one that was assumed to arise from the lone proton on the mandelyl substituent. It came at a chemical shift of 6.15 ppm, and showed an integration value approximately the same as that for the C5 and C8 protons. Signals consistent with those expected for the protons of the mandelyl

phenyl group were also present. The next significant observation regarding the NMR spectrum of the compound in question was that there were a total of five signals of the methoxy type. Each of these signals integrated for three protons, with the exception of one which integrated to twice the value of the others, as would be expected for the two equivalent C3' and C5' methoxy substituents. One of the methoxy substituents was displaced slightly downfield from the others at a chemical shift of 3.89 ppm and, in fact, corresponded almost exactly to a methoxy substituent in the starting compound, which had a chemical shift of 3.87 ppm.

It could not be determined from the spectrum acquired whether the compound in question was the γ-hydroxy ester **171** or **174**, but it seemed quite likely that it was indeed one of these two compounds. Intuitively, however, it seemed reasonable that, if the unknown compound were either the γ-hydroxy ester **171** or **174**, then it should be compound **174**. The reasoning for this is as follows. It was clearly established that (-)-deoxysikkimotoxin had formed, a result which depended on the lactonization of the intermediate γ-hydroxy ester **171** during the acidic work up. It does not seem reasonable that only a portion of compound **171** would lactonize under the conditions employed here, which would have been the case if the unknown compound were the γ-hydroxy ester **171**. It seems more likely that the unknown compound was compound **174**, which was simply unable to lactonize under the conditions used. In fact, the pericarbonyl lactone **175** (scheme 2.33), the expected product from lactonization of compound **174**, was not observed.

Scheme 2.33



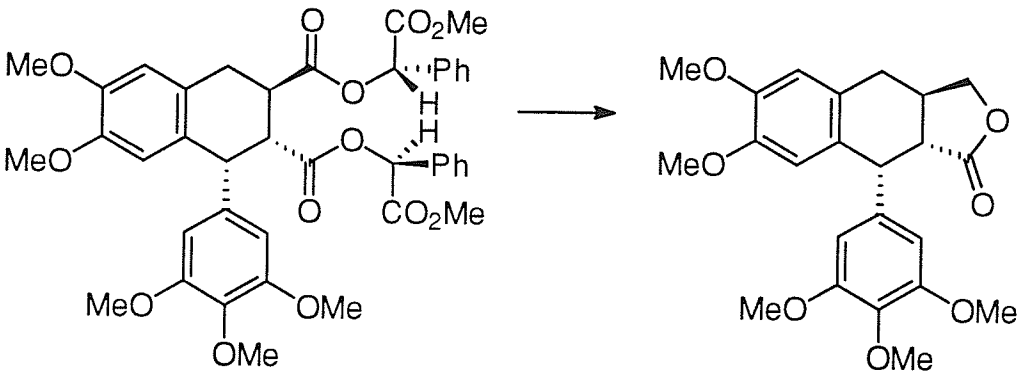
175

A first attempt at optimizing the reaction conditions for the conversion of compound **167** to (-)-deoxysikkimotoxin (scheme 2.34) involved increasing the number of equivalents of reducing agent used, with all other factors remaining the same. The amount of lithium triethylborohydride was thus doubled from three to six equivalents. NMR analysis of the crude reaction product in this case revealed that all of the starting material had been consumed, but indicated the presence of both (-)-deoxysikkimotoxin and the presumed compound **174**. As well, the spectrum revealed an increase in the amount of the presumed compound **174**, relative to that of (-)-deoxysikkimotoxin.

With the observations of the preceding reaction in mind, the reduction conditions were altered somewhat, in a manner that was expected to be more conducive to an increase in regioselectivity. Hence, a total of six equivalents of lithium triethylborohydride were used, an amount known to allow for complete reaction of the starting material, at a temperature of 0 °C, with all other conditions remaining the same. Proton NMR analysis of the crude reaction

product in this case indicated that all of the starting material had been consumed. As well, the only product that could be detected which was of the aryltetralin lignan type, was (-)-deoxysikkimotoxin. Thus, it appeared that regioselective reduction/lactonization of compound **167** could be readily achieved. Chromatography of the crude product did, in fact, yield (-)-deoxysikkimotoxin (**2**) in 93% isolated yield.

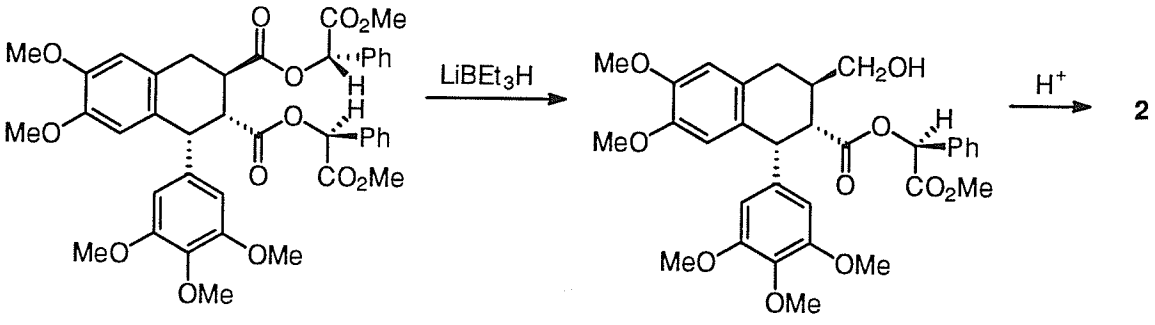
Scheme 2.34



167 **2**

The regioselective reduction observed here appears to be unprecedented. The mechanism of the reaction likely occurs as follows.

Scheme 2.35



167 **171**

Regioselective reduction of the ester functionality at C3 initiates the process. The product of this reaction, the γ-hydroxy ester **171** then undergoes lactonization displacing the remaining mandelyl chiral auxiliary, presumably following addition of acid during the work up procedure, in order to generate the desired lactone, (-)-deoxysikkimotoxin (**2**) (scheme 2.35).

2.2 Conclusion

At the outset of section two of this thesis, the research objectives on which this thesis is based were described. Each of these objectives has been fully achieved, as is evidenced by the data presented in the results and discussion section contained herein.

(-)-Isolariciresinol dimethyl ether and (-)-deoxysikkimotoxin were each synthesized in an asymmetric fashion with reasonable overall yields. The overall yield of (-)-isolariciresinol dimethyl ether was 9% from veratraldehyde, and it exhibited an specific rotation of -15.31. The specific rotation obtained agreed very well with that reported previously for the conversion of optically active α-conidendrin, which had been isolated from natural sources, to optically active isolariciresinol dimethyl ether. This is the first total asymmetric synthesis of (-)-isolariciresinol dimethyl ether which has been reported. In the case of (-)-deoxysikkimotoxin, the overall yield was 11% from veratraldehyde. The specific rotation obtained for (-)-deoxysikkimotoxin according to this procedure was -85.76. (-)-Deoxysikkimotoxin's specific rotation has not been reported previously. As well, this is the first total asymmetric synthesis of deoxysikkimotoxin which has been reported.

Through achieving the synthesis of (-)-isolariciresinol dimethyl ether and (-)-deoxysikkimotoxin, the second objective of this thesis was fulfilled. The scope of the synthetic strategy developed by Charlton and Bogucki has been broadened to account for different substitution patterns on each of the aromatic

rings of the aryltetralin lignan. In particular, it has been demonstrated that the methylenedioxy substituent of aromatic ring A can be replaced without negatively affecting the reaction sequence. It has also been shown that removal of the 5' methoxy substituent of aromatic ring C, does not impede the synthetic strategy in any way. As well, it was established that the functionality at carbons two and three of the aryltetralin lignan could be altered, through variation of the final steps of the strategy. The question of manipulating the relative stereochemistry was also addressed. Specifically, it was shown that the 1,2-*trans*-2,3-*trans* relative stereochemistry could be achieved, in addition to the 1,2-*cis*-2,3-*trans* relative stereochemistry.

The conversion of the reduction product **167** to (-)-deoxysikkimotoxin was achieved in one step with an overall yield of 93%, thereby satisfying the final objective of this thesis. For the analogous conversion carried out by Charlton and Bogucki, that is the conversion of compound **122** to (-)-deoxypodophyllotoxin, the overall yield was approximately 35%, and it involved a total of four steps. Clearly, the strategy developed here during the course of the research directed at the synthesis of (-)-deoxysikkimotoxin, was far superior to that used for the synthesis of (-)-deoxypodophyllotoxin. Given the similarity of these compounds to one another, it seems reasonable to conclude that a corresponding increase in the efficiency of the synthesis of (-)-deoxypodophyllotoxin could also be achieved.

2.3 References

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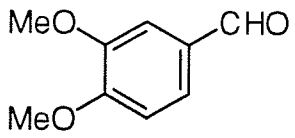
3.0 Experimental

^{1}H NMR and ^{13}C NMR spectra were obtained by using a Bruker AM-300 spectrometer, and tetramethylsilane as an internal reference. IR spectra were recorded on a Perkin Elmer 881 spectrometer. The HRMS and MS data were obtained using an Analytical VG 7070E-HF instrument. Melting points were measured on a hot stage instrument and were uncorrected. Optical rotations were acquired using a Rudolf Research Autopol III polarimeter.

3,4-Dimethoxybenzaldehyde (veratraldehyde) **130**

3,4-Dimethoxybenzaldehyde was preapred according to an established literature procedure.[1] Vanillin (152.52 g, 1.00 mol) was placed in a one liter, three necked flask equipped with a reflux condenser, a mechanical stirrer and two separatory funnels, one of which was supported on top of the reflux condenser. The vanillin was melted by heating it in a silicone oil bath with vigorous stirring. One of the separatory funnels was charged with KOH (82.05 g, 1.46 mol) dissolved in water (120 mL), and the other with dimethyl sulfate (120 mL, 160 g, 1.27 mol). The KOH solution was introduced into the three necked flask at a rate of two drops per second and, 20 seconds after that process was initiated, the dimethyl sulfate was added to the three necked flask at the same rate. As soon as all the reagents had entered the reaction vessel, the yellow mixture which had formed was poured into a porcelain mortar and allowed to

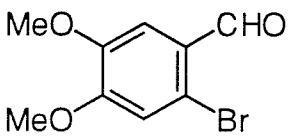
cool without disturbance for 16 hours. The hard crystalline mass which resulted was filtered and then ground with a pestle in a mortar, in the presence of ice-cold water (300 mL). The suspension was filtered and the solid was allowed to dry in a vacuum desiccator, yielding off white crystals (160.56 g, 0.97 mol, 97%); mp 42-44 °C; IR (CH_2Cl_2) 1681 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (s, 3H), 3.97 (s, 3H), 6.98 (d, 1H, J = 8.2), 7.41 (d, 1H, J = 1.9), 7.46 (dd, 1H, J = 1.9, 8.2), 9.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.0 (CH_3), 56.2 (CH_3), 109.0 (CH), 110.4 (CH), 126.8 (CH), 130.1 (C), 149.6 (C), 154.5 (C), 190.8 (CO); MS m/e (relative %) 166 (M^+, 100), 165 (54), 151 (17), 95 (19), 77 (19); HRMS for $C_9H_{10}O_3$ calculated = 166.0630, found = 166.0625.



2-Bromo-3,4-dimethoxybenzaldehyde (6-Bromoveratraldehyde) **131**

To a round bottom flask, equipped with a mechanical stirring apparatus, was added veratraldehyde (20.09 g, 120.9 mmol), and glacial acetic acid (145 mL). The resulting suspension was stirred at room temperature and, once all of the veratraldehyde had dissolved, bromine (2 equivalents, 12.5 mL, 242.6 mmol) was added and stirring was continued for an additional four hours. At that point, the mixture was diluted with ice-cold water (145 mL) and allowed to stand in a refrigerator at -5 °C over night. The mixture was then filtered and the resulting

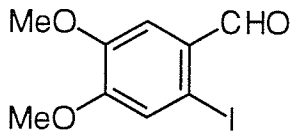
solid washed with ice-cold water (100 mL), and then re-filtered. The solid was then recrystallized from 80/20 (v/v) methanol/water and dried in an oven overnight at 50 °C. The process yielded a light beige crystalline compound (25.56 g, 104.3 mmol, 86%); mp 148-150 °C; IR (CH_2Cl_2) 1682 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3H), 3.96 (s, 3H), 7.05 (s, 1H), 7.40 (s, 1H), 10.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.1 (CH_3), 56.4 (CH_3), 110.4 (CH), 115.4 (CH), 120.3 (C), 126.5 (C), 148.8 (C), 154.4 (C), 190.6 (CO); MS m/e (relative %) 246 (100), 245 (58), 244 (M^+, 99), 243 (53), 231 (17), 229 (16), 94 (45); HRMS for $C_9H_9{}^{79}BrO_3$ calculated = 243.9735, found = 243.9800. Compound **131** had spectroscopic properties identical to those previously reported.[2]



2-Iodo-3,4-dimethoxybenzaldehyde (6-Iodoveratraldehyde) **132**

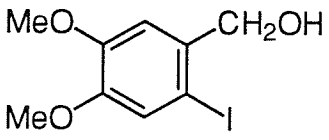
To a round bottom flask was added 6-bromoveratraldehyde (20.16 g, 82.26 mmol), benzene (300 mL), ethylene glycol (9.5 mL, 170.4 mmol) and *p*-toluenesulfonic acid hydrate (0.1002 g, 0.53 mmol). The flask was attached to a Dean-Stark trap and refluxed for 5 hours. The benzene was then evaporated to give a light yellow viscous liquid, which was filtered through silica gel (10 cm) with 50/50 (v/v) ethyl acetate/hexanes. The filtrate was evaporated to give a colorless crystalline compound. The crystals were dissolved in THF (150 mL) in

a round bottom flask which was sealed with a rubber septum, flushed with nitrogen, and placed in a dry ice/acetone bath. At that point, *n*-butyllithium (44 mL of a 2.03 M solution in hexanes, 89.32 mmol) was added and the resulting solution was stirred for 15 minutes. Iodine (25.00 g, 98.5 mmol), dissolved in THF (80 mL), was then added and the mixture was stirred for 15 minutes, removed from the dry ice/acetone bath, and stirred for an additional 60 minutes. Saturated aqueous sodium bisulphite (10 mL) was added to dissipate the dark color caused by the iodine, leaving the solution light yellow. The THF portion was removed and the aqueous portion was extracted three times with ethyl acetate. The organic portions were combined and evaporated to give an oily residue. The residue was dissolved in methanol (50 mL) and to this was added 10% $HCl_{(aq)}$ (10 mL). The resulting solution was allowed to stir for 20 hours at room temperature, by which time a white precipitate had formed. The product was extracted into dichloromethane and then evaporated to give a light colored oil. The oil was taken up in 50/50 (v/v) ethyl acetate/hexanes and filtered through silica gel (10 cm). Evaporation of the solvent gave colorless crystals (22.48 g, 76.97 mmol, 94%); mp 134-136 °C; IR (CH_2Cl_2) 1695 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3H), 3.96 (s, 3H), 7.31 (s, 1H), 7.41 (s, 1H), 9.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.1 (CH_3), 56.5 (CH_3), 92.7 (C), 111.1 (CH), 121.8 (CH), 128.4 (C), 149.7 (C), 154.4 (C), 194.8 (CO); MS m/e (relative %) 292 (M^+, 100), 291 (31), 277 (5), 164 (10), 136 (10); HRMS for $C_9H_9IO_3$ calculated = 291.9596, found = 291.9629.



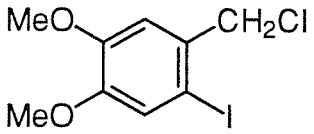
2-Iodo-4,5-dimethoxybenzyl alcohol **135**

6-Iodoveratraldehyde (1.52 g, 5.20 mmol) was dissolved in 2-propanol (40 mL). $NaBH_4$ (0.2320 g, 6.14 mmol) was then added and the mixture was refluxed for 12 hours. The resulting solution was made just acidic by the addition of 10% $HCl_{(aq)}$ and then evaporated to a minimum volume. It was then taken up in dichloromethane and washed with water. The aqueous portion was saturated with NaCl and extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give off-white crystals (1.47 g, 5.00 mmol, 96%); mp 94-96 °C; IR (CH_2Cl_2) 3605 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (bs, 1H), 3.84 (s, 6H), 4.56 (s, 2H), 6.98 (s, 1H), 7.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.8 (CH_3), 56.1 (CH_3), 68.7 (CH_2), 85.1 (C), 111.3 (CH), 121.3 (CH), 135.1 (C), 148.6 (C), 149.2 (C); MS m/e (relative %) 294 (M^+, 33), 166 (28), 71 (28), 69 (100), 57 (59); HRMS for $C_9H_{11}IO_3$ calculated = 293.9753, found = 293.9757.



2-Iodo-4,5-dimethoxybenzyl chloride **128**

2-Iodo-4,5-dimethoxybenzyl alcohol (0.7639 g, 2.60 mmol) was dissolved in dichloromethane (20 mL) and to that mixture was added glacial acetic acid (20 mL). HCl gas was passed through the resulting solution at a rate of approximately one bubble per second for 30 minutes. At that point, water (40 mL) was added to the solution and the organic portion was removed *via* a separatory funnel. The aqueous portion was then extracted twice with dichloromethane. The organic portions were combined and then washed with 10% $NaHCO_{3(aq)}$. The organic phase was removed, dried with $MgSO_4$, and evaporated to give off white crystals (0.793 g, 2.55 mmol, 98%); mp 83-85 °C; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 3.86 (s, 3H), 4.63 (s, 2H), 6.96 (s, 1H), 7.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 51.2 (CH_2), 55.8 (CH_3), 56.1 (CH_3), 87.8 (C), 112.6 (CH), 121.5 (CH), 132.0 (C), 149.3 (C), 149.4 (C); MS m/e (relative %) 314 (M^+, 13) 312 (M^+, 36), 278 (23), 277 (100), 151 (151), 107 (18); HRMS for $C_9H_{10}{}^{35}ClIO_2$ calculated = 311.9414, found = 311.9426.



1-(3,4-Dimethoxyphenyl)-1-*N*-morpholinoacetonitrile **136**

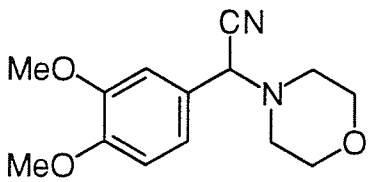
Procedure A:

Veratraldehyde (9.99 g, 60.1 mmol) was dissolved in 2-propanol (100 mL), in a round bottom flask. In a separate flask KCN (3.93 g, 60.3 mmol) was dissolved in water (5 mL) and then morpholine (5.27 mL, 5.26 g, 60.4 mmol) was added with stirring, and the resulting mixture was cooled in an ice bath. At that point, concentrated HCl (4.96 mL, approximately 5.24 g, approximately 60 mmol) was added dropwise with stirring. The resulting suspension was then added all at once to the veratraldehyde solution, and the final mixture was allowed to stir at room temperature for seven days. The suspension which formed was filtered off and the filtrate was evaporated to a minimum volume, giving a viscous oil. The oil was taken up in ethyl acetate and washed with water, and the aqueous portion was subsequently extracted with ethyl acetate. The organic portions were combined, dried with $MgSO_4$, and evaporated to give a colorless crystalline compound (13.2 g, 50.3 mmol, 84%) mp 64-66 °C.

Procedure B:

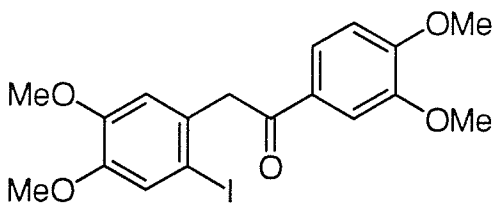
Morpholine (5 mL, 4.98 g, 57.1 mmol) was dissolved in diethyl ether (30 mL) and cooled in an ice bath. Perchloric acid (70%, 1:1 in ethanol) was then added until the solution was just acidic, which caused the formation of a white precipitate. The solvent was evaporated, leaving a soft solid which was

recrystallized from 2-propanol giving colorless crystals (mp 180-182 °C). The crystals (1.13 g, 6.03 mmol) were combined with veratraldehyde (1.00 g, 6.04 mmol) in benzene (30 mL), and the resulting solution was allowed to reflux for 21 hours while attached to a Dean-Stark trap. The reaction mixture was then cooled and the precipitate which had formed was filtered and rinsed with ice-cold ethanol leaving colorless crystals (1.83 g, 5.44 mmol, 90%, mp 160-163 °C). These crystals (0.507 g, 1.51 mmol) were added to a separatory funnel containing KCN (0.299 g, 4.59 mmol) dissolved in water (6 mL). To this solution was added diethyl ether (10 mL). Following a period of shaking, the diethyl ether layer was removed. Diethyl ether (10 mL) was again added and the process was repeated, and then repeated again. The organic portions were combined, dried with $MgSO_4$, and evaporated to give colorless crystals of α-aminonitrile **136** (0.364 g, 1.39 mmol, 92%); mp 64-66 °C; IR (CH_2Cl_2) 2305 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.57 (m, 4H), 3.72 (m, 4H), 3.89 (s, 3H), 3.91 (s, 3H), 4.76 (s, 1H), 6.87 (d, 1H, J = 8.3), 7.01 (d, 1H, J = 2.0), 7.10 (dd, 1H, J = 2.0, 8.3); ^{13}C NMR ($CDCl_3$) δ 49.9 (CH_2), 56.0$_0$ (CH_3), 56.0$_2$ (CH_3), 62.1 (CH), 66.6 (CH_2), 110.8 (CH), 110.9 (CH), 115.3 (C), 120.4 (CH), 124.8 (C), 149. 2 (C), 149.6 (C); MS m/e (relative %) 262 (M^+, 9), 177 (23), 176 (100), 151 (27), 111 (18), 97 (34), 83 (44), 69 (73), 57 (95); HRMS for $C_{14}H_{18}N_2O_3$ calculated = 262.1317, found = 262.1361.



Aryliodoketone **142**

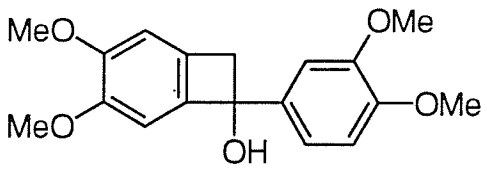
An NaH/oil mixture (50/50, w/w, 0.457 g, 9.53 mmol with respect to NaH) was combined with DMF (10 mL) in a round bottom flask, which was subsequently sealed with a rubber septum and flushed with nitrogen. The α-aminonitrile **136** (1.66 g, 6.33 mmol), dissolved in DMF (15 mL), was then added dropwise to the suspension over a period of five minutes. Once addition was complete, the benzyl chloride **128** (1.98 g, 6.33 mmol), dissolved in DMF (15 mL), was added dropwise to the suspension over a period of five minutes, and the resulting mixture was allowed to stir at room temperature for one hour. At that point, 10% $HCl_{(aq)}$ (10 mL) was added to the suspension and the mixture was allowed to stir for 16 hours at 65 °C, causing the formation of a precipitate. The precipitate was isolated from the solution and washed with cold methanol, leaving a colorless crystalline compound (2.64 g, 5.96 mmol, 94%); mp 170-172 °C; IR (CH_2Cl_2) 1682 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.86 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 4.35 (s, 2H), 6.76 (s, 1H), 6.91 (d, 1H, J = 8.4), 7.26 (s, 1H), 7.57 (d, 1H, J = 2.0), 7.72 (dd, 1H, J = 2.0, 8.4); ^{13}C NMR ($CDCl_3$) δ 49.6 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 56.1_0 (CH_3), 56.1_5 (CH_3), 89.1 (C), 110.1 (CH), 110.6 (CH), 113.2 (CH), 121.6 (CH), 123.1 (CH), 129.8 (C), 131.0 (C), 148.5 (C), 149.0 (C), 149.4 (C), 153.4 (C), 195.4 (CO); MS m/e (relative %) 442 (M^+, 1), 315 (26), 165 (100); HRMS for $C_{18}H_{19}O_5$ (M - I) calculated = 315.1232, found = 315.1255.



α-Hydroxy-α-aryl-benzocyclobutenol **145**

The aryliodoketone (1.64 g, 3.71 mmol) was dissolved in THF (40 mL) under a nitrogen atmosphere, and cooled in a dry ice/acetone bath. *n*-BuLi (2.5 M in hexanes, 3.0 mL, 7.5 mmol) was then added and the mixture was allowed to stir at low temperature for 30 minutes. At that point, 10% $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was allowed to stir while warming to room temperature. The THF portion was removed and the aqueous portion was extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give a yellow semisolid which, when chromatographed on silica gel using 60/40 (v/v) ethyl acetate/hexanes, gave a colorless crystalline compound (0.869 g, 2.75 mmol, 74%); mp 136-138 °C; IR (CH_2Cl_2) 3583 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (bs, 1H), 3.44 (d, 1H, J = 13.4), 3.49 (d, 1H, J = 13.4), 3.84 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.78 (d, 1H, J = 8.3), 6.79 (s, 1H), 6.81 (s, 1H), 6.90 (dd, 1H, J = 2.0, 8.3), 7.06 (d, 1H, J = 2.0); ^{13}C NMR ($CDCl_3$) δ 49.8 (CH_2), 55.9$_0$ (CH_3), 55.9$_1$ (CH_3), 56.2$_0$ (CH_3), 56.2$_4$ (CH_3), 80.5 (C), 105.3 (CH), 107.8 (CH), 109.1 (CH), 110.7 (CH), 117.8 (CH), 133.5 (C), 136.7 (C), 140.3 (C), 148.2 (C), 148.8 (C), 150.0 (C),

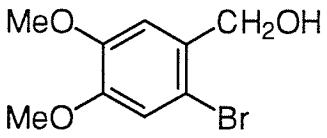
151.4 (C); MS m/e (relative %) 316 (M^+, 35), 315 (41), 301 (19), 286 (19), 285 (100), 179 (19), 165 (64), 69 (63), 55 (79); HRMS for $C_{18}H_{20}O_5$ calculated = 316.1311, found = 316.1283. Compound **145** had spectroscopic properties identical to those previously reported.[3]



2-Bromo-4,5-dimethoxybenzyl alcohol **147**

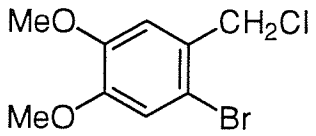
6-Bromoveratraldehyde (1.01 g, 4.13 mmol) was dissolved in 2-propanol (20 mL). $NaBH_4$ (0.1593 g, 4.21 mmol) was then added and the mixture was refluxed for 12 hours. The resulting solution was made just acidic by the addition of 10% $HCl_{(aq)}$ and then evaporated to a minimum volume. It was then taken up in dichloromethane and washed with water. The aqueous portion was saturated with NaCl and extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give almost colorless crystals (0.939 g, 3.80 mmol, 92%); mp 91-93 °C; IR (CH_2Cl_2) 6304 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (t, 1H, J = 5.9), 3.86 (s, 3H), 3.87 (s, 3H), 4.66 (d, 2H, J = 5.9), 4.67 (s, 1H), 7.00 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 56.4 (CH_3), 56.6 (CH_3), 65.2 (CH_2), 112.2 (CH), 112.8 (C), 115.8 (CH), 132.2 (C), 148.9 (C), 149.3 (C); MS m/e (relative %) 248 (M^+, 85), 246 (M^+, 92), 231 (27), 167 (32), 139 (100), 138

(54), 124 (38), 96 (54), 69 (73); HRMS for $C_9H_{11}{}^{79}BrO_3$ calculated = 245.9892, found = 245.9878.



2-Bromo-4,5-dimethoxybenzyl chloride **148**

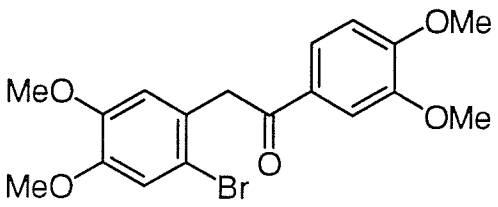
2-Bromo-4,5-dimethoxybenzyl alcohol (1.66 g, 6.72 mmol) was dissolved in dichloromethane (20 mL) and to that mixture was added glacial acetic acid (20 mL). HCl gas was passed through the resulting solution at a rate of approximately one bubble per second for 30 minutes. At that point, water (40 mL) was added to the solution and the organic portion was removed *via* a separatory funnel. The aqueous portion was then extracted twice with dichloromethane. The organic portions were combined and then washed with 10% $NaHCO_{3(aq)}$. The organic phase was removed, dried with $MgSO_4$, and evaporated to give almost colorless crystals (1.71 g, 6.45 mmol, 96%); mp 80-82 °C; ^{1}H NMR ($CDCl_3$) δ 3.83 (bs, 6H), 4.63 (s, 2H), 6.91 (s, 1H), 7.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.3 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 113.1 (CH), 114.3 (C), 115.4 (CH), 128.4 (C), 148.4 (C), 149.6 (C); MS m/e (relative %) 266 (M^+, 26), 264 (20), 231 (100), 229 (98), 185 (12), 107 (15), 63 (19); HRMS for $C_9H_{10}{}^{35}Cl^{79}BrO_2$ calculated = 263.9553, found = 263.9554.



Arylbromoketone **146**

An NaH/oil mixture (50/50, w/w, 0.705 g, 14.70 mmol with respect to NaH) was combined with DMF (10 mL) in a round bottom flask, which was subsequently sealed with a rubber septum and flushed with nitrogen. The α-aminonitrile **136** (1.79 g, 6.84 mmol), dissolved in DMF (15 mL), was then added dropwise to the suspension over a period of five minutes. Once addition was complete, the benzyl chloride **148** (1.77 g, 6.65 mmol), dissolved in DMF (15 mL), was added dropwise to the suspension over a period of five minutes, and the resulting mixture was allowed to stir at room temperature for one hour. At that point, 10% $HCl_{(aq)}$ (10 mL) was added to the suspension and the mixture was allowed to stir for 16 hours at 65 °C, causing the formation of a precipitate. The precipitate was isolated from the solution and washed with cold methanol, leaving a colorless crystalline compound (2.16 g, 5.46 mmol, 82%); mp 169-171 °C; IR (CH_2Cl_2) 1682 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 4.34 (s, 2H), 6.77 (s, 1H), 6.91 (d, 1H, J = 8.4), 7.05 (s, 1H), 7.57 (d, 1H, J = 2.0), 7.71 (dd, 1H, J = 2.0, 8.4); ^{13}C NMR ($CDCl_3$) δ 44.8 (CH_2), 56.0_0 (2 x CH_3), 56.0_5 (CH_3), 56.1 (CH_3), 110.1 (CH), 110.5 (CH), 113.8 (CH), 114.7 (C), 115.5 (CH), 123.1 (CH), 127.0 (C), 129.6 (C), 148.4 (C), 148.6

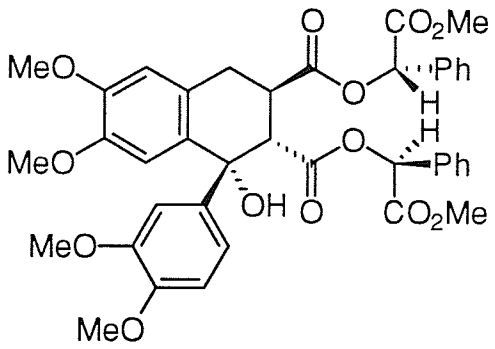
(C), 149.0 (C), 153.4 (C), 195.4 (CO); MS m/e (relative %) 315 (M^+ - Br, 12), 165 (100); HRMS for $C_{18}H_{19}O_5$ (M - Br) calculated = 315.1232, found = 315.1174.



Cycloadduct **151**

The fumarate of methyl (*S*)-mandelate (0.453 g, 1.10 mmol) was dissolved in toluene (5 mL) and heated in an oil bath to 98 °C. The benzocyclobutenol **145** (0.140 g, 0.44 mmol), dissolved in dichloromethane (4 mL), was then added and the mixture was allowed to boil, open to the atmosphere, until the dichloromethane had evaporated. At that point, a condenser was attached to the reaction flask and the mixture was refluxed for 48 hours. The contents of the flask were then evaporated under reduced pressure leaving a reddish-brown oil. Chromatography of the oil on silica gel with 40/60 (v/v) ethyl acetate/hexanes gave a colorless solid (0.164 g, 0.22 mmol, 51%); $[\alpha]_D^{20}$ 127.4 (c 0.31 g/100 mL in $CHCl_3$); IR (CH_2Cl_2) 3443 (OH), 1751 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.17 (dd, 1H, J = 11.7, 16.5), 3.44 (dd, 1H, J = 4.6, 16.5), 3.61 (s, 3H), 3.63 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), (H2 and H3 under the methoxyl signals), 5.74 (s, 1H), 5.90 (s, 1H), 6.45 (s, 1H, H8), 6.66 (s, 1H, H5), 6.87 (m, 2H), 6.99 (dd, 1H, J = 2.1, 8.4), 7.12 (d, 1H, J = 2.1),

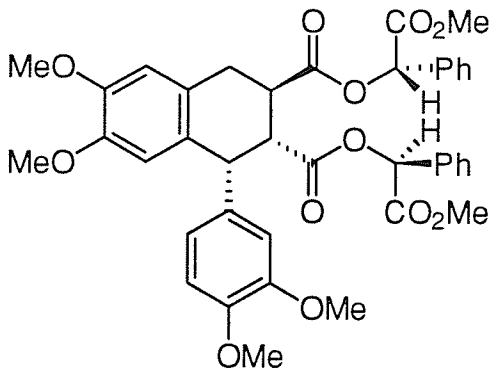
7.17-7.27 (m, 3H), 7.36-7.42 (m, 3H), 7.44-7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 32.4 (CH_2), 39.7 (CH), 52.6 (CH_3), 52.8 (CH_3), 54.9 (CH), 55.7 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 74.7 (CH), 74.9 (CH), 76.1 (C), 110.1 (2 x CH), 110.7 (CH), 112.1 (CH), 118.9 (CH), 125.7 (C), 127.1 (2 x CH), 127.6 (2 x CH), 128.4 (2 x CH), 128.7 (2 x CH), 129.0 (CH), 129.2 (CH), 132.4 (C), 132.8 (C), 133.2 (C), 139.2 (C), 147.9$_0$ (C), 147.9$_3$ (C), 148.5 (C), 148.7 (C), 169.3 (CO), 169.6 (CO), 171.5 (CO), 174.2 (CO); MS m/e (relative %) 710 (M^+ - H_2O, 29), 351 (64), 324 (40), 165 (21), 149 (64), 121 (100); HRMS for $C_{40}H_{38}O_{12}$ (M - H_2O) calculated = 710.2363, found = 710.2347. Compound **151** had spectroscopic properties identical to those previously reported.[3]



1,2-*cis*-2,3-*trans* reduction product **154**

The 1,2-*trans*-2,3-*trans* cycloadduct **151** (0.0869 g, 0.12 mmol) was dissolved in dichloromethane (20 mL) under nitrogen, and cooled to - 20 °C. boron tirfluoride etherate (0.10 mL, 0.80 mmol) was then added, causing the solution to turn dark blue. The mixture was cooled to - 55 °C and $LiAlH_4$ (0.37 M in diethyl ether, approximately 1.0 mL, approximately 0.37 mmol) was added

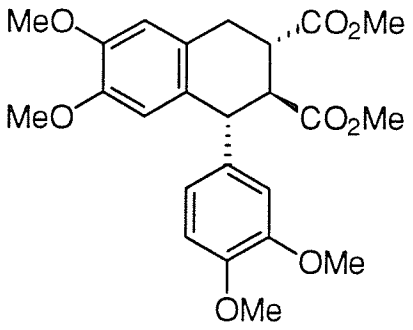
dropwise until all of the blue color had dissipated, followed by the addition of 50/50 (v/v) methanol/water (10 mL) dropwise. The resulting solution was stirred for 20 minutes at - 55 °C and was then allowed to warm to room temperature. At that point, 10% $HCl_{(aq)}$ (1 mL) was added and the organic portion was separated from the aqueous portion. The aqueous portion was extracted three times with dichloromethane and the original organic portion was washed with 10% $HCl_{(aq)}$. The organic portions were combined, dried with $MgSO_4$, and evaporated to give an amorphous solid which was chromatographed on silica gel with 30/70 (v/v) ethyl acetate/hexanes to give a colorless solid (0.0356 g, 0.05 mmol, 42%); $[\alpha]_D^{20}$ -54.3 (c 0.28 g/100 mL in $CHCl_3$); IR (CH_2Cl_2) 1746 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.04 (m, 1H), 3.38 (m, 2H), 3.52 (m, 1H), 3.64 (s, 3H), 3.68 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 3.87 (s, 3H), 4.56 (d, 1H, J = 5.5, H1), 5.67 (s, 1H), 6.07 (s, 1H), 6.32 (dd, 1H, J = 1.9, 8.3), 6.39 (s, 1H), 6.43 (d, 1H, J = 8.3), 6.50 (d, 1H, J = 1.9), 6.69 (s, 1H), 6.99 (d, 2H, J = 7.3), 7.08 (t, 2H, J = 7.6), 7.16-7.36 (m, 4H), 7.44-7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 31.8 (CH_2), 37.1 (CH), 45.7 (CH), 48.2 (CH), 52.4 (CH_3), 52.5 (CH_3), 55.4 (CH_3), 55.8 (3 x CH_3), 73.9 (CH), 74.6 (CH), 110.4 (2 x CH), 112.2 (CH), 112.8 (CH), 121.8 (CH), 125.6 (C), 127.0 (2 x CH), 127.9 (2 x CH), 128.2 (2 x CH), 128.6 (C), 128.7 (2 x CH), 129.2 (CH), 133.4 (C), 133.6 (C), 133.9 (C), 147.8 (C), 147.9 (C), 148.0 (C), 148.1 (C), 168.8 (CO), 169.5 (CO), 171.1 (CO), 174.2 (CO) ; MS m/e (relative %) 712 (M^+, 20), 563 (6), 518 (10), 485 (7), 398 (22), 397 (36), 351 (47), 325 (55), 149 (63), 121 (100); HRMS for $C_{40}H_{40}O_{12}$ calculated = 712.2520, found = 712.2502. Compound **154** had spectroscopic properties identical to those previously reported.[3]



1,2-*Trans*-2,3-*trans*-dimethylester **156**

The 1,2-*cis*-2,3-*trans*-dimethylmandelylester **154** (0.050 g, 7.02 x 10^{-2} mmol) was dissolved in dry methanol (10 mL) and sodium metal (0.2400 g, 10.44 mmol) was added under nitrogen. The solution was stirred at reflux for 23 hours. The mixture was acidified with 10% $HCl_{(aq)}$ and extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give a soft crystalline compound. The compound was dissolved in 3% HCl/methanol (10 mL) and stirred for 12 hours. The resulting solution was extracted three times with dichloromethane and the organic portions were combined, dried with $MgSO_4$, and evaporated to give a soft crystalline compound. The compound was subsequently chromatographed on silica gel using 30/70 (v/v) ethyl acetate/hexanes to give a colorless solid (0.026 g, 5.85 x 10^{-2} mmol, 83%); mp 126-127 °C; $[\alpha]_D^{20}$ -23.2 (c 0.21 g/100 mL in $CHCl_3$); IR (CH_2Cl_2) 1738 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.99-3.26 (m, 4H), 3.47 (s, 3H), 3.59 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.17 (d, 1H, J = 10.9), 6.23 (s, 1H), 6.58 (d, 1H, J = 1.9), 6.60 (s, 1H), 6.68 (dd, 1H, J = 1.9,

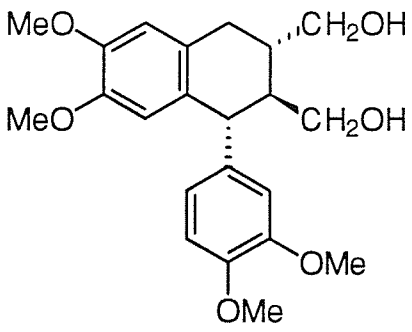
8.20), 6.79 (d, 1H, J = 8.2); ^{13}C NMR ($CDCl_3$) δ 31.8 (CH_2), 43.3 (CH), 48.8 (CH), 51.6$_7$ (CH), 51.6$_9$ (CH_3), 52.1 (CH_3), 55.8 (CH_3), 55.9$_0$ (2 x CH_3), 55.9$_2$ (CH_3), 110.7 (CH), 110.9 (CH), 111.7 (CH), 112.1 (CH), 121.5 (CH), 126.0 (C), 129.6 (C), 135.4 (C), 147.6 (C), 147.7 (C), 148.0 (C), 148.9 (C), 174.1 (CO), 174.5 (CO); MS m/e (relative %) 444 (M^+, 83), 384 (48), 325 (100), 269 (50), 222 (34); HRMS for $C_{24}H_{28}O_8$ calculated = 444.1784, found = 444.1816. Compound **156** had spectroscopic properties identical to those previously reported.[2]



Isolariciresinol Dimethyl Ether **1**

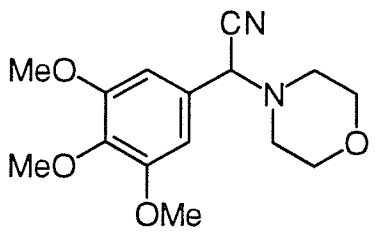
Isolariciresinol dimethyl ether was synthesized according to a literature procedure.[2] The dimethylester **156** (0.0118 g, 0.027 mmol) was dissolved in dry THF (5 mL) under nitrogen and added dropwise to a suspension of $LiAlH_4$ (0.0012 g, 0.032 mmol) in THF (5 mL) under nitrogen. The mixture was allowed to reflux for two hours. At that point, water (2 drops) and 10% $HCl_{(aq)}$ (0.5 mL) were added and then the mixture was dried with $MgSO_4$, and evaporated to give a solid. The solid was recrystallized from ethyl acetate/hexanes to give colorless crystals (0.0102 g, 0.026 mmol, 96%); mp 150-152 °C; $[\alpha]_D^{20}$ -15.3 (c 0.49 g/100

mL in $CHCl_3$); IR (CH_2Cl_2) 3616 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79-1.88 (m, 1H, H_2), 1.99-2.11(m, 1H, H_3), 2.34-2.56 (br s, 2H, OH), 2.73 (dd, 1H, H_4 cis to H_3, J = 5.2, 15.8), 2.83 (dd, 1H, H_4 trans to H_3, J = 11.3, 15.8), 3.52 (dd, 1H, one of the CH_2 protons vicinal to C_2, J = 5.2, 11.2), 3.57 (s, 3H), 3.74 (dd, 1H, one of the CH_2 protons vicinal to C_2, J = 6.5, 11.2), 3.77-3.91 (m, 3H, H_1, both CH_2 protons vicinal to C_3), 3.81 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.20 (s, 1H), 6.59 (s, 1H), 6.60 (d, 1H, J = 1.9), 6.73 (dd, 1H, J = 1.9, 8.2), 6.81 (d, 1H, J = 8.2); ^{13}C NMR ($CDCl_3$), δ 33.2 (CH_2), 39.9 (CH), 48.0 (CH), 48.2 (CH), 53.4 (CH_3), 55.8 (2 x CH_3), 56.0 (CH_3), 62.8 (CH_2), 66.5 (CH_2), 110.8 (CH), 111.1 (CH), 112.0 (CH), 113.0 (CH), 121.9 (CH), 128.2 (C), 131.8 (C), 137.7 (C), 147.1 (2 x C), 147.6 (C), 149.1 (C); MS m/e (relative %) 388 (M^+, 49), 370 (36), 340 (17), 339 (60), 269 (47), 189 (34), 151 (57); HRMS for $C_{22}H_{28}O_6$ calculated = 388.1886, found = 388.1875. Compound **1** had spectroscopic properties identical to those previously reported.[2]



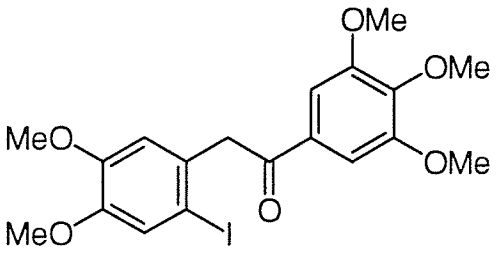
1-(3,4,5-Trimethoxyphenyl)-1-*N*-morpholinoacetonitrile **115**

3,4,5-Trimethoxybenzaldehyde (13.8 g, 70.3 mmol) was dissolved in methanol (200 mL), in a round bottom flask. In a separate flask KCN (5.16 g, 79.3 mmol) was dissolved in water (14 mL) and then morpholine (6.70 mL, 6.67 g, 76.6 mmol) was added with stirring, and the resulting mixture was cooled in an ice bath. At that point, concentrated HCl (6.5 mL, approximately 78 mmol) was added dropwise with stirring. The resulting suspension was then added all at once to the aldehyde solution, and the final mixture was allowed to stir at room temperature for seven days. The precipitate which had formed was filtered, dissolved in dichloromethane, re-filtered to remove the insoluble salts, dried with $MgSO_4$, and evaporated to give a colorless crystalline compound (19.3 g, 66.1 mmol, 94 %); mp 136-138 °C; IR (CH_2Cl_2) 2231 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (m, 4H), 3.74 (m, 4H), 3.85 (s, 3H), 3.89 (s, 6H), 4.75 (s, 2H), 6.76 (s, 1H), 6.77 (s, 1H) ;^{13}C NMR ($CDCl_3$) δ 50.0 (CH_2), 56.3 (CH_3), 60.8 (CH_3), 62.5 (CH), 66.7 (CH_2), 105.0 (CH), 115.2 (C), 127.9 (C), 138.4 (C), 153.5 (C); MS m/e (relative %) 292 (M^+, 1), 265 (15), 206 (8), 196 (21), 181 (100), 69 (35); HRMS for $C_{15}H_{20}N_2O_4$ calculated = 292.1423, found = 292.1394. Compound **115** had spectroscopic properties identical to those previously reported.[4]



Aryliodoketone **163**

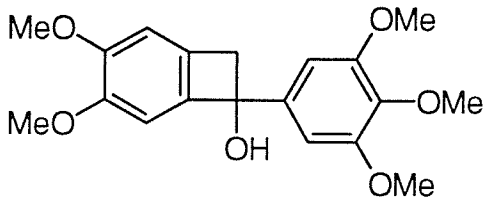
An NaH/oil mixture (50/50, w/w, 0.367 g, 7.65 mmol with respect to NaH) was combined with DMF (10 mL) in a round bottom flask, which was subsequently sealed with a rubber septum and flushed with nitrogen. The α-aminonitrile **115** (1.043 g, 3.57 mmol), dissolved in DMF (15 mL), was then added dropwise to the suspension over a period of five minutes. Once addition was complete, the benzyl chloride **128** (1.128 g, 3.61 mmol), dissolved in DMF (15 mL), was added dropwise to the suspension over a period of five minutes, and the resulting mixture was allowed to stir at room temperature for one hour. At that point, 10% $HCl_{(aq)}$ (10 mL) and water (10 mL) were added to the suspension and the mixture was allowed to stir for 16 hours at 65 °C, causing the formation of a precipitate. The precipitate was isolated from the solution and washed with cold methanol, leaving a colorless crystalline compound (1.53 g, 3.25 mmol, 91%); mp 147-150 °C; IR (CH_2Cl_2) 1684 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 3.93 (s, 6H), 4.35 (s, 2H), 6.76 (s, 1H), 7.26 (s, 1H), 7.29 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 49.8 (CH_2), 55.8 (CH_3), 56.1 (CH_3), 56.3 (CH_3), 60.8 (CH_3), 89.0 (C), 106.0 (CH), 112.8 (CH), 121.5 (CH), 130.7 (C), 131.5 (C), 142.6 (C), 148.5 (C), 149.4 (C), 152.9 (C), 195.6 (CO); MS m/e (relative %) 472 (M^+, 1), 344 (73), 329 (64), 195 (100); HRMS for $C_{19}H_{21}IO_6$ calculated = 472.0383, found = 472.0366.



α-Hydroxy-α-aryl-benzocyclobutenol **164**

The aryliodoketone **163** (2.006 g, 4.25 mmol) was dissolved in THF (40 mL) under nitrogen, and cooled in a dry ice/acetone bath. *n*BuLi (2.5 M in hexanes, 3.6 mL, 9.00 mmol) was then added and the mixture was allowed to stir at low temperature for 30 minutes. At that point, 10% $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was allowed to stir while warming to room temperature. The THF portion was removed and the aqueous portion was extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give a yellow semisolid which, when chromatographed on silica gel using 50/50 (v/v) ethyl acetate/hexanes, gave a colorless crystalline compound (1.056 g, 3.05 mmol, 72%); mp 121-123 °C; IR (CH_2Cl_2) 3588 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.66 (s, 1H), 3.45 (d, 1H, J = 13.4), 3.52 (d, 1H, J = 13.4), 3.81 (s, 6H), 3.83 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 6.67 (s, 2H), 6.81 (s, 1H), 6.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 50.0 (CH_2), 56.1 (CH_3), 56.2 (CH_3), 56.3 (CH_3), 60.8 (CH_3), 80.8 (C), 102.8 (CH), 105.1 (CH), 107.8 (CH), 133.7 (C), 137.2 (C), 139.6 (C), 140.0 (C), 150.1 (C), 151.6 (C), 153.0 (C); MS

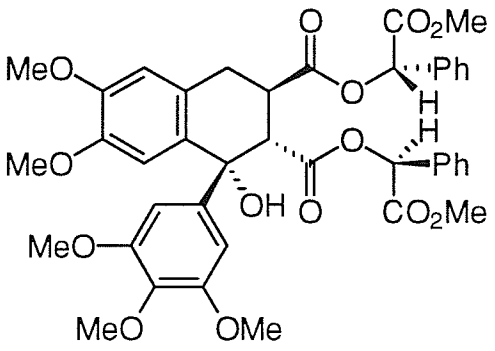
m/e (relative %) 346 (M^+, 5), 315 (7), 195 (3), 88 (10), 86 (64), 84 (100); HRMS for $C_{19}H_{22}O_6$ calculated = 346.1416, found = 346.1431.



Cycloadduct **165**

The fumarate of methyl (*S*)-mandelate (1.94 g, 4.70 mmol) was dissolved in toluene (10 mL) and heated in an oil bath to 98 °C. The benzocyclobutenol **164** (0.623 g, 1.80 mmol), dissolved in dichloromethane (4 mL), was then added and the mixture was allowed to boil, open to the atmosphere, until the dichloromethane had evaporated. At that point, a condenser was attached to the reaction flask and the mixture was refluxed for 48 hours. The contents of the flask were then evaporated under reduced pressure leaving a reddish-brown oil. Chromatography of the oil on silica gel with 40/60 (v/v) ethyl acetate/hexanes gave a colorless, crystalline compound (0.779 g, 1.03 mmol, 57%), mp 82-85 °C; $[\alpha]_D^{20}$ 136.3 (c 0.30 g/100 mL in $CHCl_3$); IR (CH_2Cl_2) 3475 (OH), 1741 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.17 (dd, 1H, J = 11.4, 16.4), 3.45 (dd, 1H, J = 4.3, 16.4), 3.59-3.92 (m, 2H), 3.63 (s, 6H), 3.73 (s, 3H), 3.79 (s, 6H), 3.87 (s, 3H), 3.90 (s, 3H), 5.75 (s, 1H), 5.90 (s, 1H), 6.46 (s, 1H), 6.66 (s, 1H), 6.73 (s, 2H), 6.95 (m, 2H), 7.20-7.28 (m, 2H), 7.36-7.40 (m, 4H), 7.44-7.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ

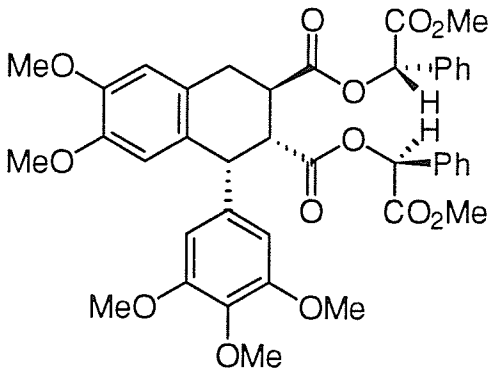
32.3 (CH_2), 39.8 (CH), 52.6 (CH_3), 52.8 (CH_3), 54.8 (CH), 55.8 (2 x CH_3; methoxy substituents on the 1,2,4,5 substituted aromatic ring), 56.2 (2 x CH_3), 60.9 (CH_3), 74.7 (CH), 75.0 (CH), 76.3 (C), 104.1 (2 x CH), 110.1 (CH), 112.1 (CH), 125.7 (C), 127.1 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 129.1 (CH), 129.3 (CH), 132.1 (C), 132.8 (C), 133.2 (C), 137.0 (C), 142.1 (C), 148.0 (C), 148.8 (C), 152.8 (C), 169.3 (CO), 169.5 (CO), 171.7 (CO), 174.1 (CO); MS m/e (relative %) 758 (M^+, 8), 740 (39), 548 (36), 381 (66), 355 (72), 107 (100); HRMS for $C_{41}H_{40}O_{13}$ (M - H_2O) calculated = 740.2469, found = 740.2457.



1,2-*cis*-2,3-*trans* reduction product **167**

The 1,2-*trans*-2,3-*trans* cycloadduct **165** (0.0767 g, 0.10 mmol) was dissolved in dichloromethane (20 mL) under nitrogen, and cooled to - 12 °C. boron trifluoride etherate (0.10 mL, 0.81 mmol) was then added, causing the solution to turn dark blue. The mixture was cooled to - 55 °C and $LiAlH_4$ (0.37 M in diethylether, approximately 1.5 mL, approximately 0.56 mmol) was added dropwise until all of the blue had dissipated, followed by the addition of 50/50

(v/v) methanol/water (10 mL) dropwise. The resulting solution was stirred for 20 minutes at -55 °C and was then allowed to warm to room temperature. At that point, 10% $HCl_{(aq)}$ (1 mL) was added and the organic portion was separated from the aqueous portion. The aqueous portion was extracted three times with dichloromethane and the original organic portion was washed with 10% $HCl_{(aq)}$. The organic portions were combined, dried with $MgSO_4$, and evaporated to give an off white crystalline mass. Chromatography using silica gel and 30/70 (v/v) ethyl acetate/hexanes gave pure **167** (0.0312 g, 0.043 mmol, 40%). $[\alpha]_D^{20}$ -43.0 (c 0.40 g/100 mL in $CHCl_3$); IR (CH_2Cl_2) 1744 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.05 (m, 1H), 3.39 (5 line m, 2H), 3.52 (6 line m, 2H), 3.58 (s, 3H), 3.63 (s, 6H), 3.69 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 3.87 (s, 3H), 4.57 (d, 1H, J = 5.5), 5.70 (s, 1H), 6.04 (s, 1H), 6.12 (s, 2H), 6.42 (s, 1H), 6.70 (s, 1H), 7.10-7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 31.8 (CH_2), 37.3 (CH), 46.2 (CH), 48.1 (CH), 52.5$_0$ (CH_3), 52.5$_4$ (CH_3), 55.8 (CH_3), 55.9 (CH_3), 56.2 (CH_3), 60.6 (CH_3), 74.1 (CH), 74.7 (CH), 107.2 (CH), 110.4 (CH), 112.2 (CH), 125.6 (C), 126.8, (CH), 127.9 (CH), 128.3 (C), 128.4 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 133.3 (C), 133.5 (C), 136.9 (C), 137.2 (C), 147.9 (C), 148.2 (C), 152.6 (C), 168.8 (CO), 169.4 (CO), 171.2 (CO), 174.1 (CO); MS m/e (relative %) 742 (M^+, 21), 578 (7), 548 (7), 515 (8), 427 (27), 381 (22), 355 (41), 149 (74), 121 (97), 107 (93), 91 (61), 77 (100); HRMS for $C_{41}H_{42}O_{13}$ calculated = 742.2625, found = 742.2575.

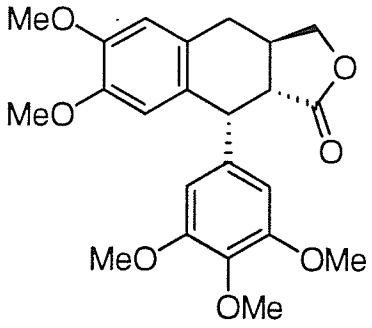


Deoxysikkimotoxin **2**

The 1,2-*cis*-2,3-*trans* polyester **167** (0.0236 g, 3.17 x 10^{-5} mol) was dissolved in THF (5 mL), under nitrogen. Lithium triethylborohydride (191 μL of a 1 M solution in THF, 1.91 x 10^{-4} mol, 6 equivalents) was then added at 0 °C, and the mixture was allowed to stir for two hours. 10% $HCl_{(aq)}$ (5 mL) was then added and the resulting solution was stirred overnight. The mixture was diluted with water and extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give a colorless, amorphous solid which was chromatographed on silica gel using 40/60 (v/v) ethyl acetate/hexanes to give pure (-)-deoxysikkimotoxin (0.0122 g, 2.94 x 10^{-5} mol, 93%); $[\alpha]_D^{20}$ -85.8 (c 3.3 g/100 mL in $CHCl_3$); IR (CH_2Cl_2) 1778 (CO) cm^{-1}; ^1H NMR ($CHCl_3$) δ 2.77 (m, 3H), 3.09 (m, 1H), 3.73 (s, 6H), 3.78 (s, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 3.92 (m, 1H), 4.47 (m, 1H), 4.65 (bd, 1H, J = 3.4), 6.35 (s, 2H), 6.54 (s, 1H), 6.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.8_0 (CH_2), 32.8_4 (CH), 43.4 (CH), 47.7 (CH), 55.9 (CH_3), 56.0 (CH_3), 56.2 (CH_3), 60.8 (CH_3), 72.1 (CH_2), 77.2 (C),

108.3 (CH), 111.4 (CH), 113.3 (CH), 127.1 (C), 129.4 (C), 136.4 (C), 148.0 (C), 148.2 (C), 152.5 (C), 175.0 (CO); MS m/e (relative %) 414 (M^+, 100), 246 (13), 181 (30); HRMS for $C_{23}H_{26}O_7$ calculated = 414.1679, found = 414.1649.

Compound **1** had spectroscopic properties identical to those previously reported.[5]



3.1 ^{1}H and ^{13}C NMR Spectra

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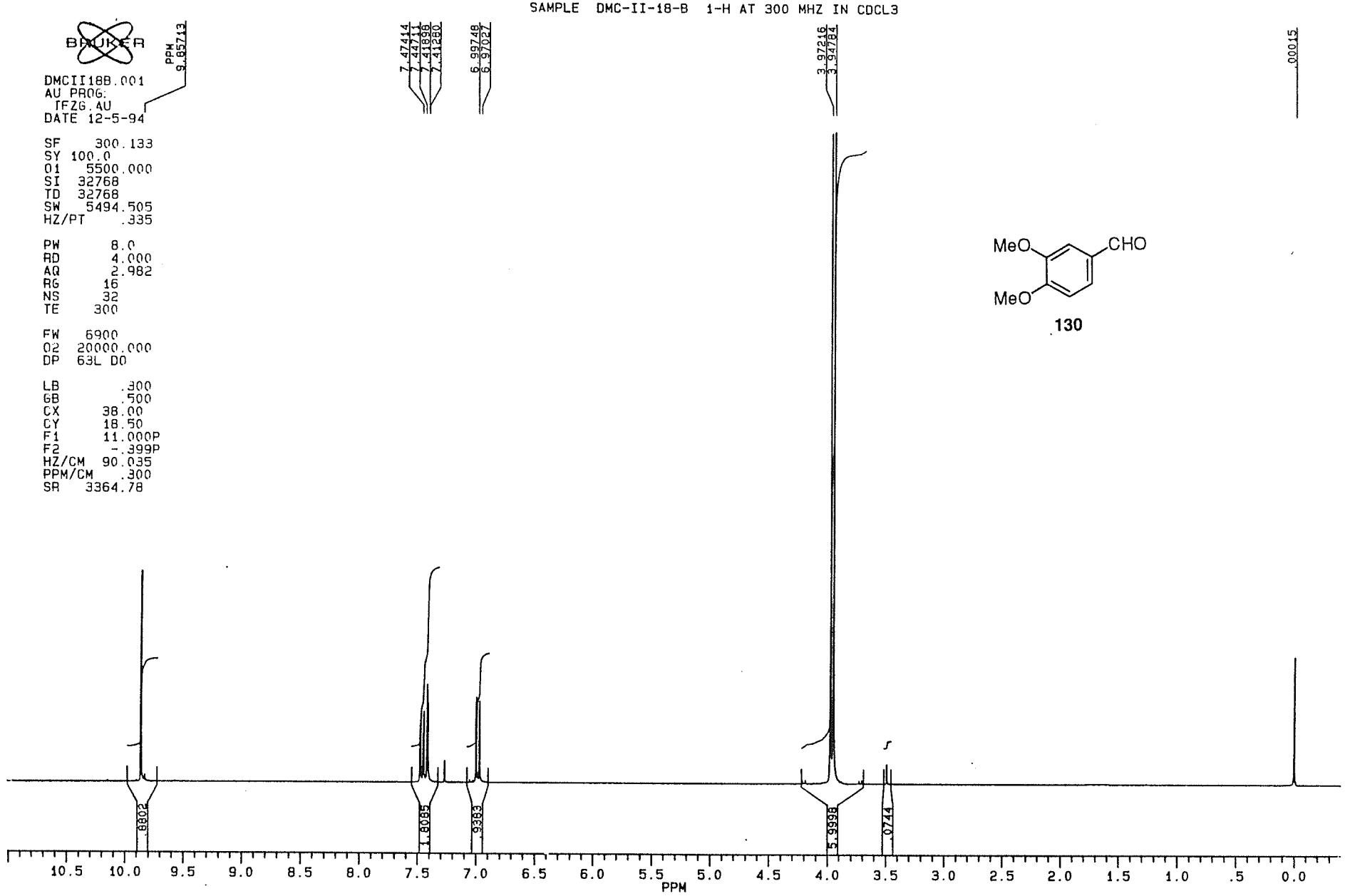
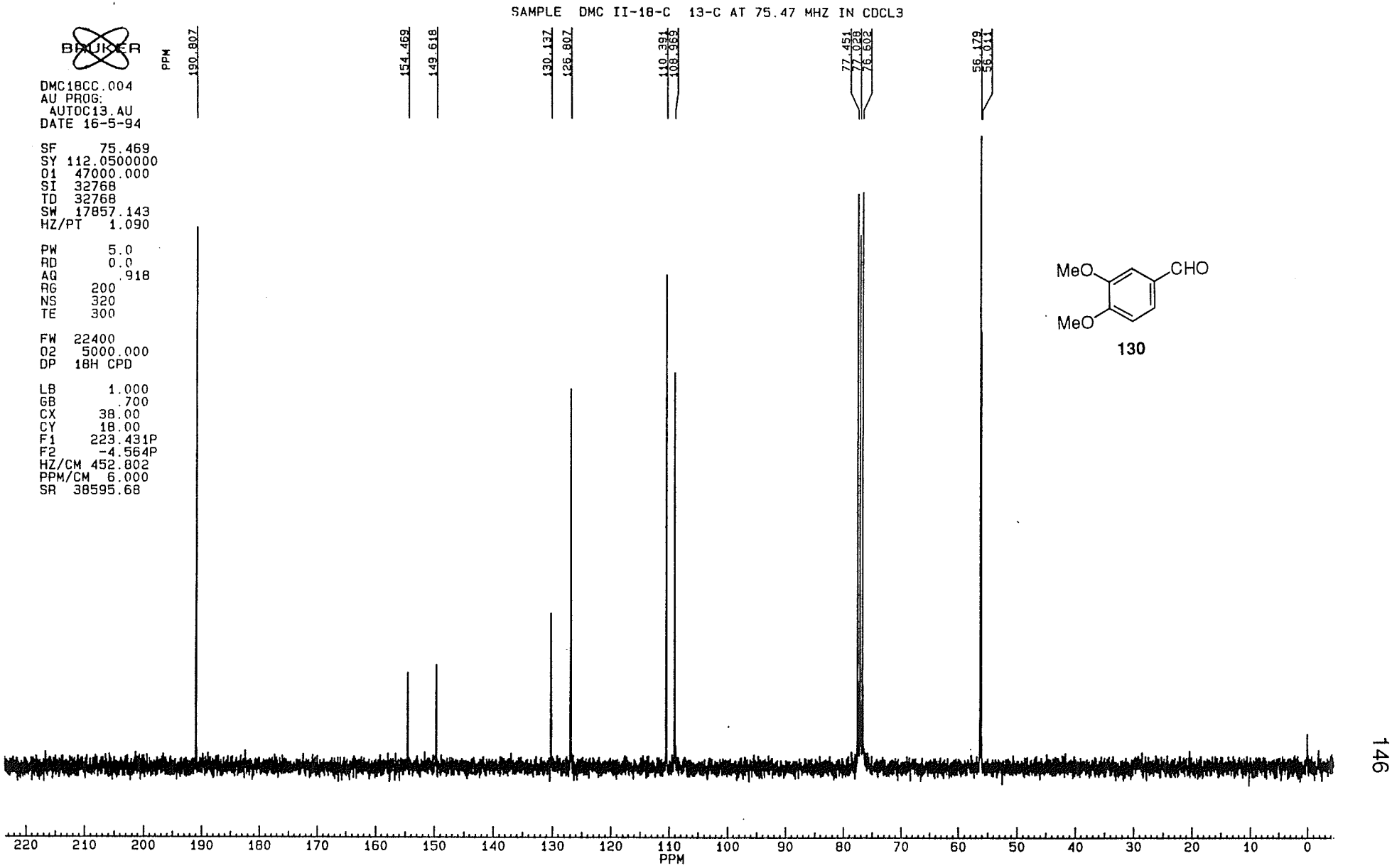


130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CY 18.00
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PPM

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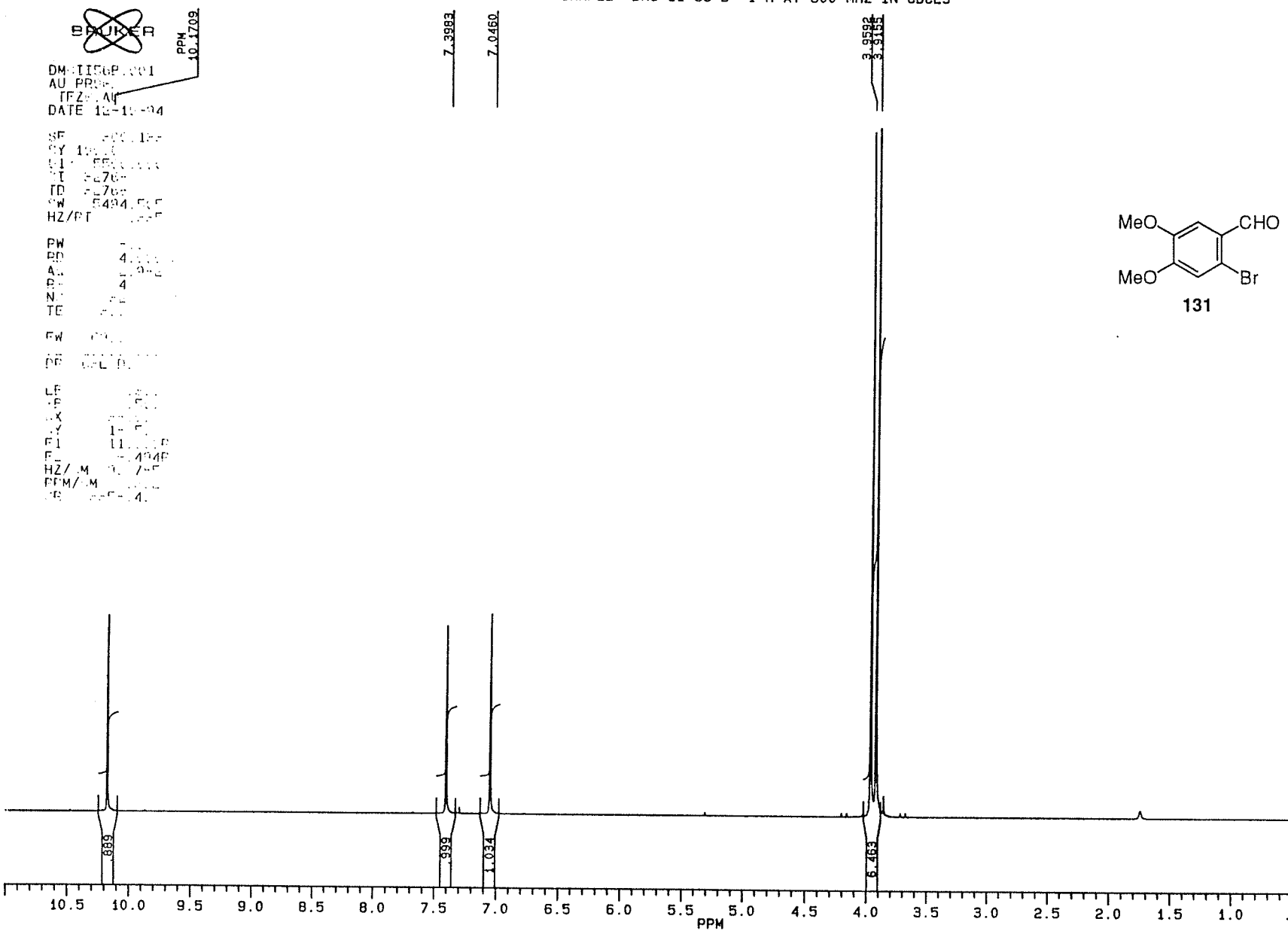
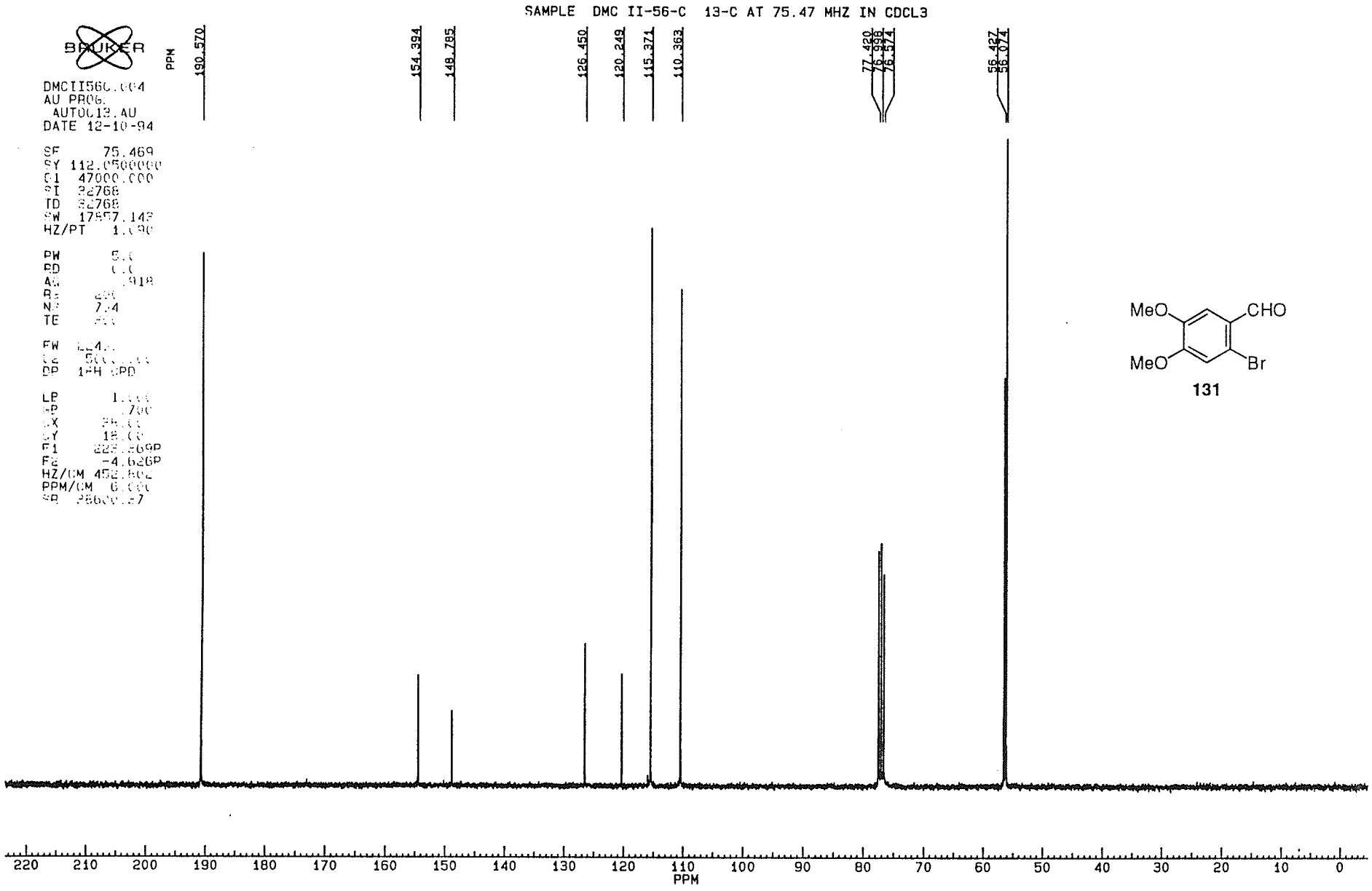


131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131
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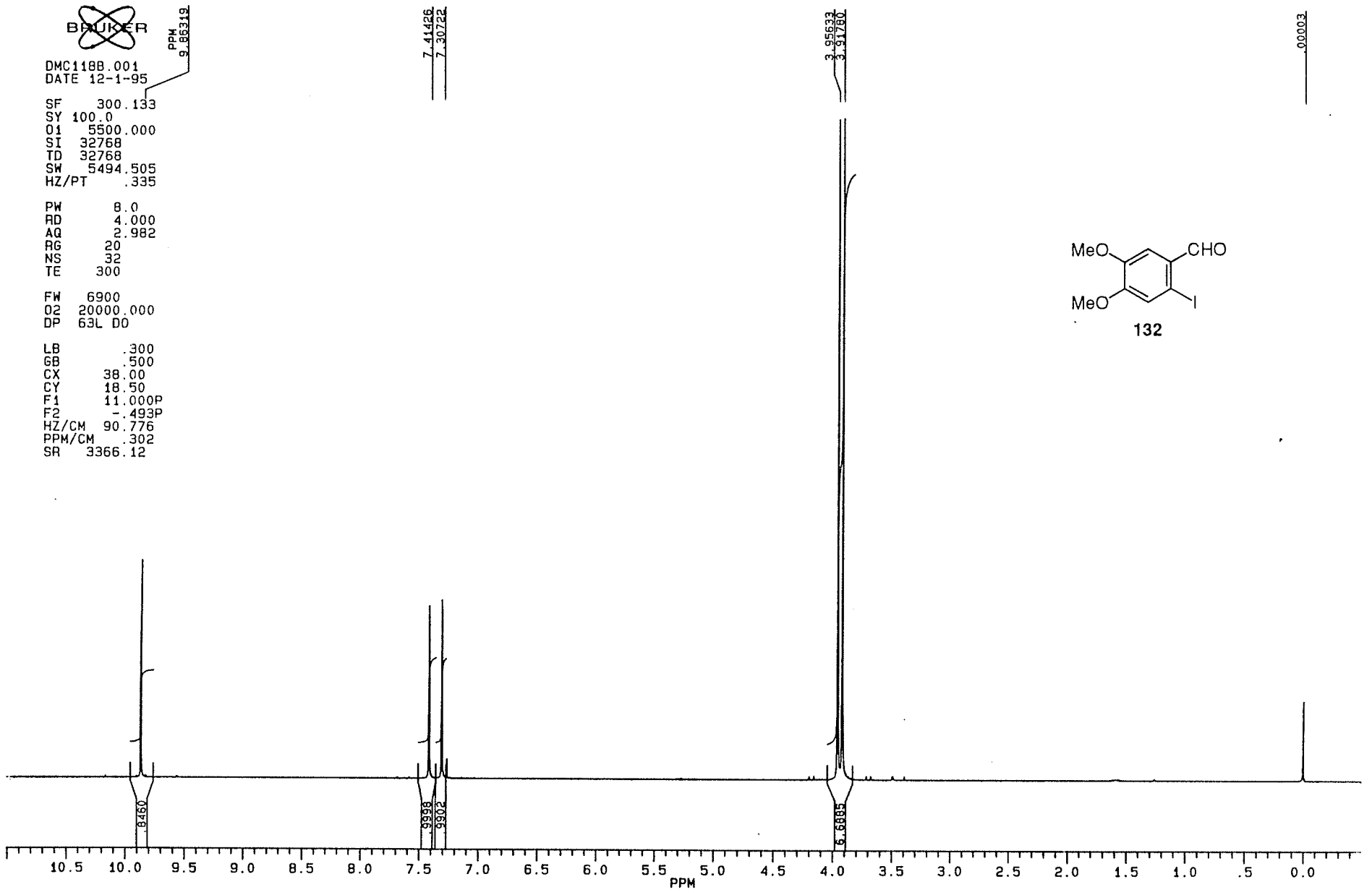

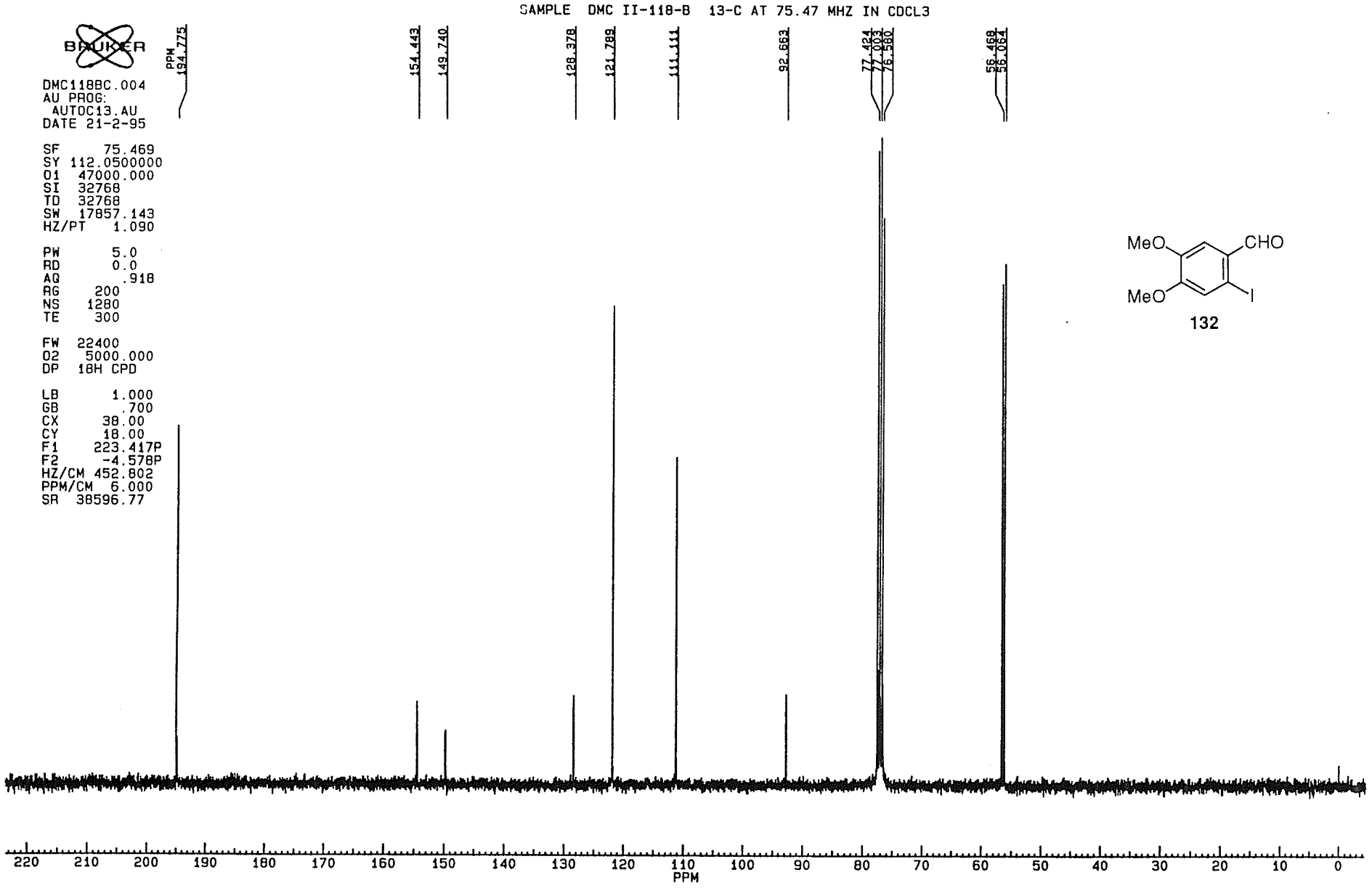
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CY 18.00
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F2 -4.578P
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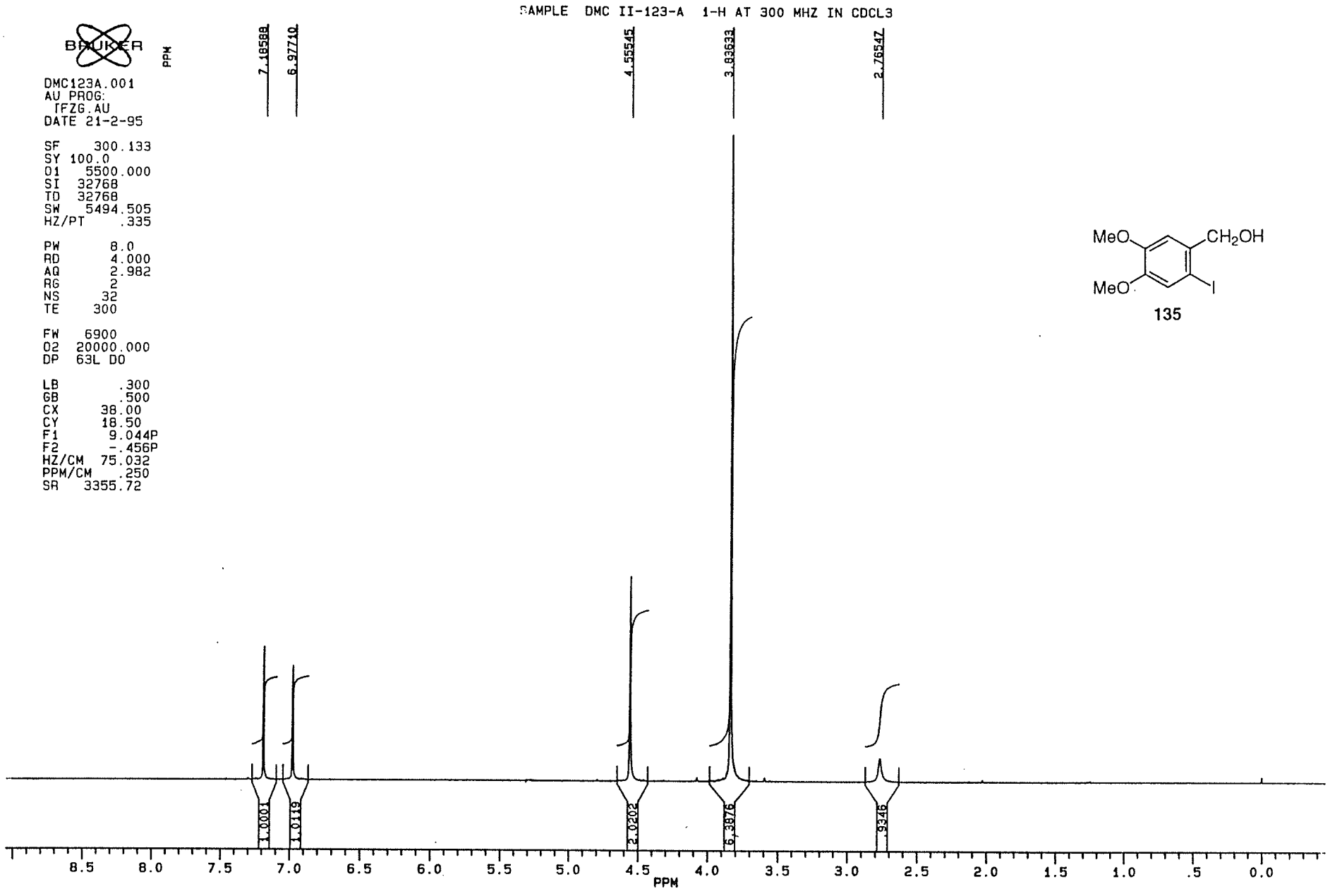
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HZ/CM 75.032
PPM/CM .250
SR 3355.72
1.0001
1.0119
2.0202
6.3876
.9346
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

MeO
CH2OH
MeO
I

135

SAMPLE DMC II-123-A 13-C AT 75.47 MHZ IN CDCL3

149.210
148.553
135.090
121.246
111.327
85.056
77.427
77.001
76.574
68.713
56.054
55.780

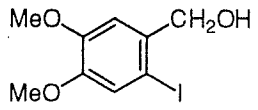
DMC123AC.004
AU PROG:
AUTOC13.AU
DATE 22-2-95

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 320
TE 300

FW 22400
O2 5000.000
DP 18H CPD

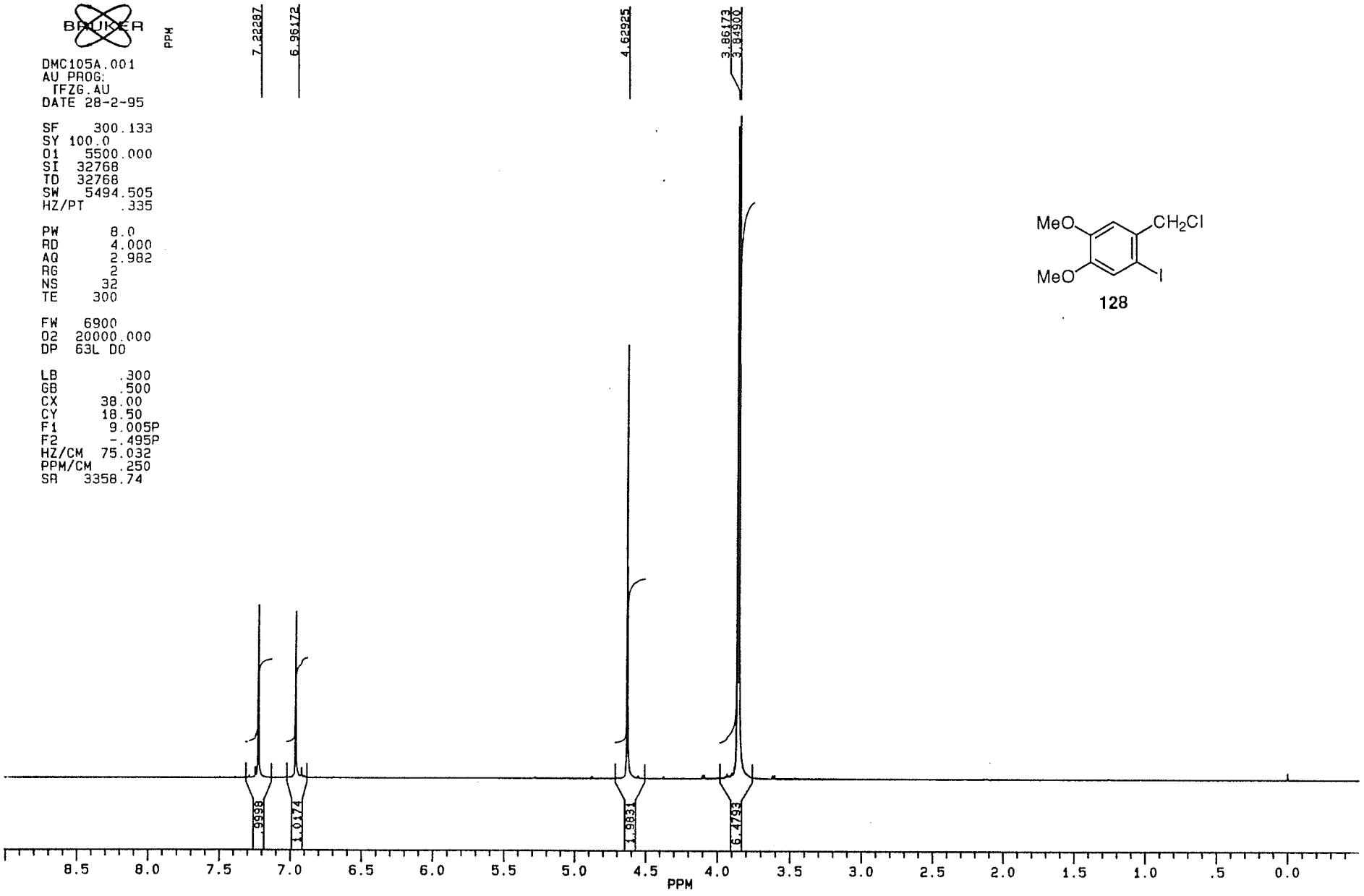
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.254P
F2 -4.741P
HZ/CM 452.802
PPM/CM 6.000
SR 38609.09



135

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 DMC II-105-A 1-H AT 300 MHZ IN CDCL3



128

SAMPLE DMC II-105-A 13-C AT 75.47 MHZ IN CDCL3

149.359
149.312
132.010
121.519
112.614
87.809
77.418
76.995
76.568
69.938
56.045
55.842
51.183

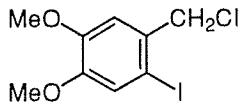
DMC105AC.004
AU PROG:
AUTOC13.AU
DATE 1-3-95

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 320
TE 300

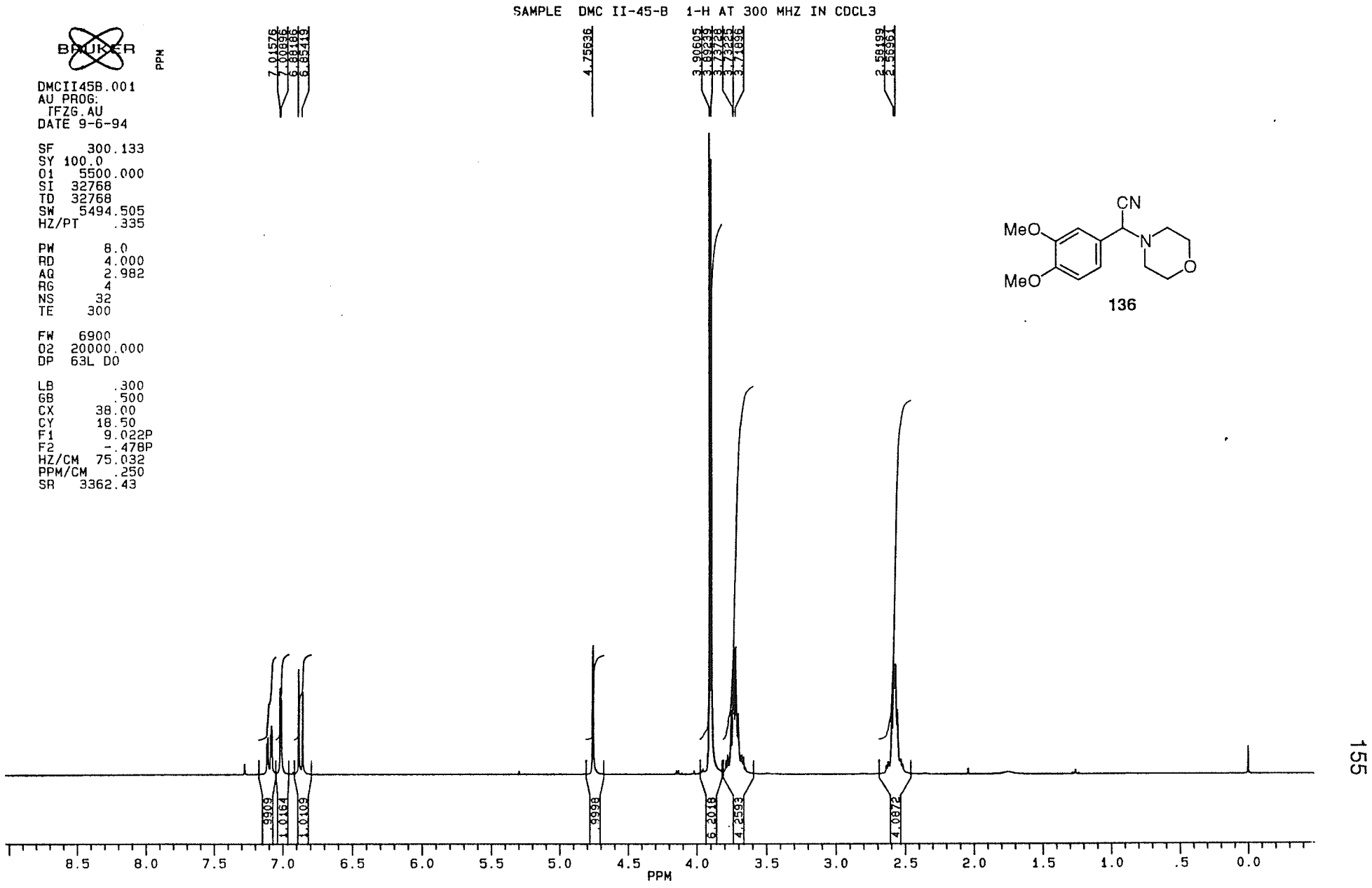
FW 22400
O2 5000.000
DP 18H CPD

LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.225P
F2 -4.770P
HZ/CM 452.802
PPM/CM 6.000
SR 38611.27

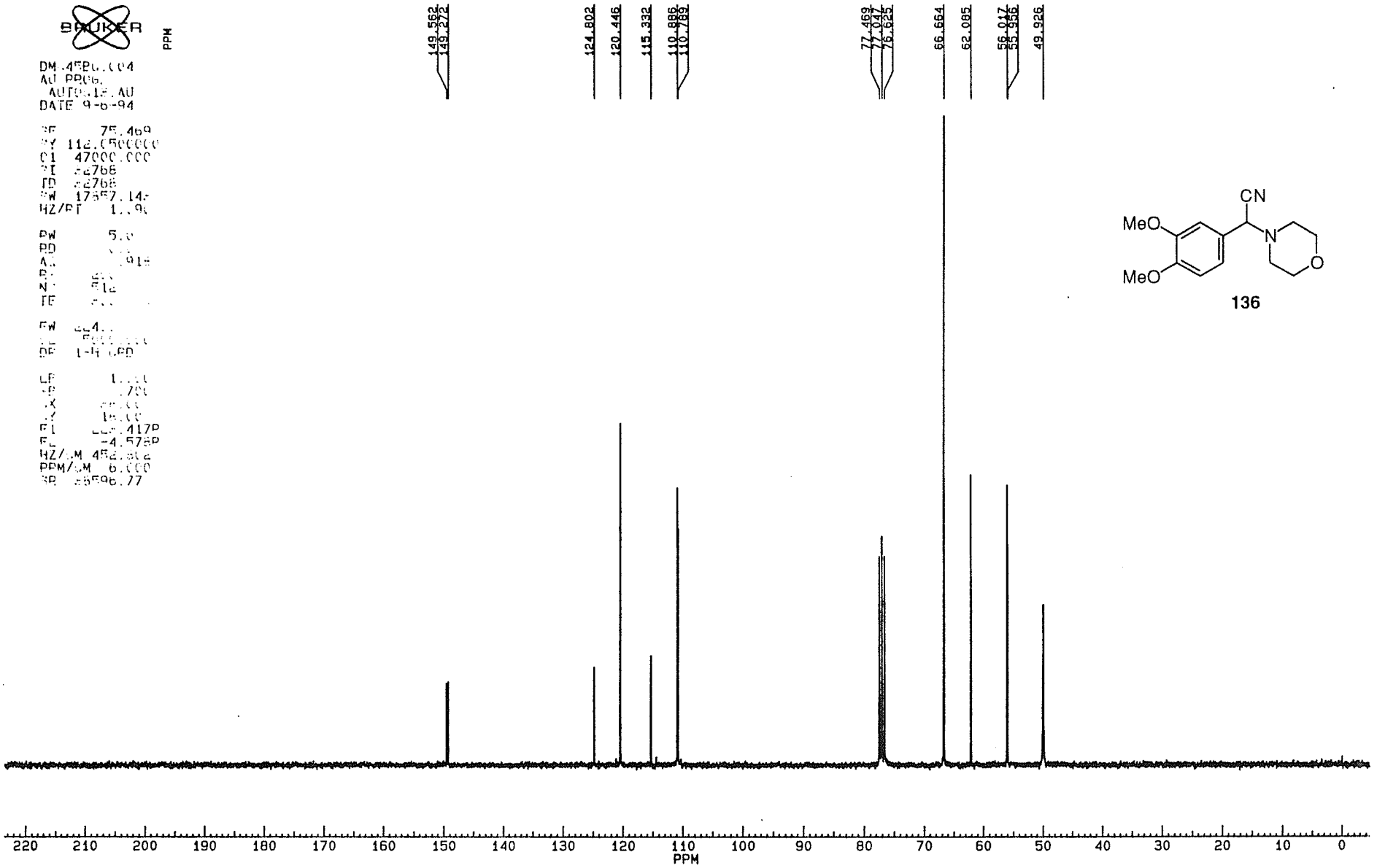


128

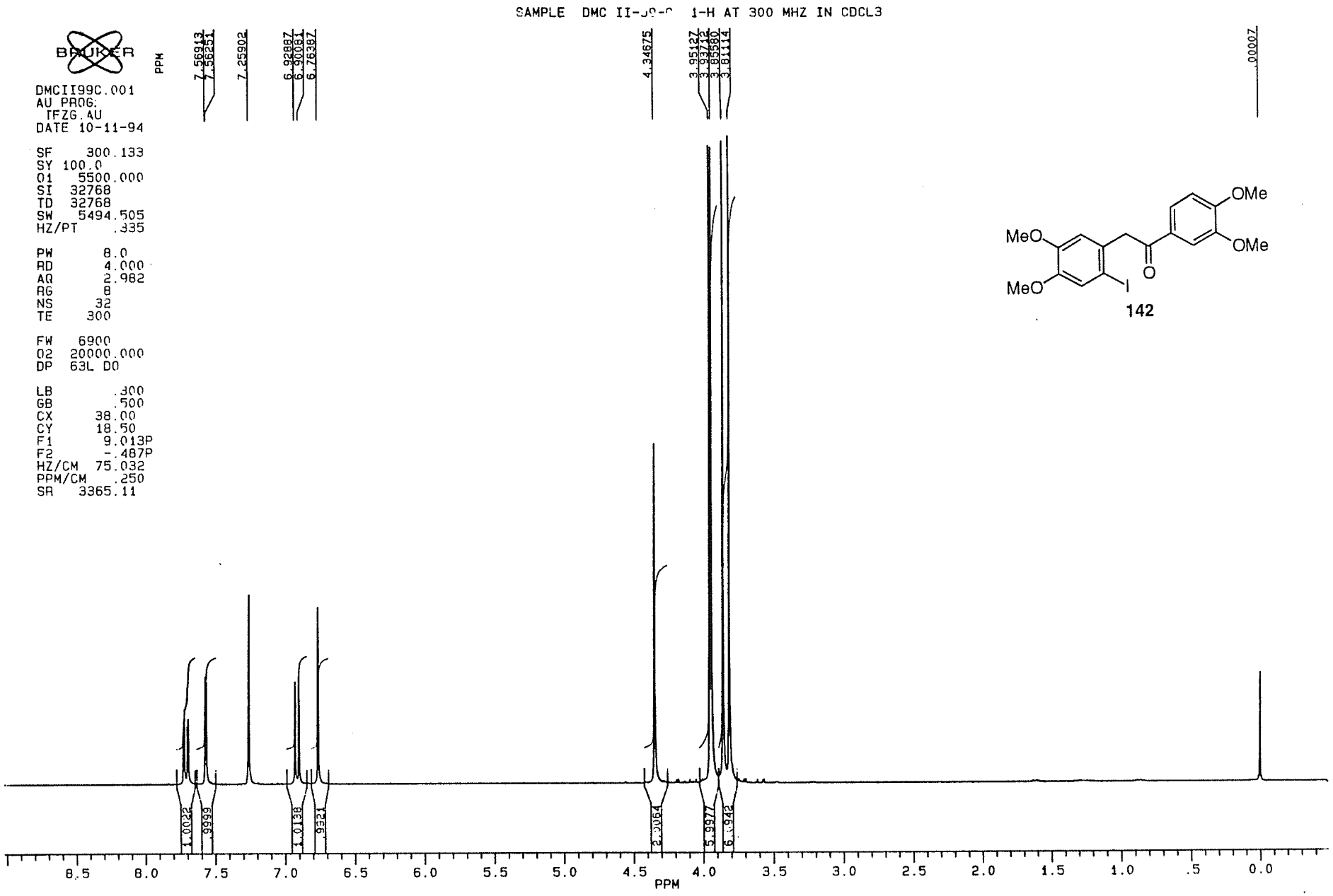
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

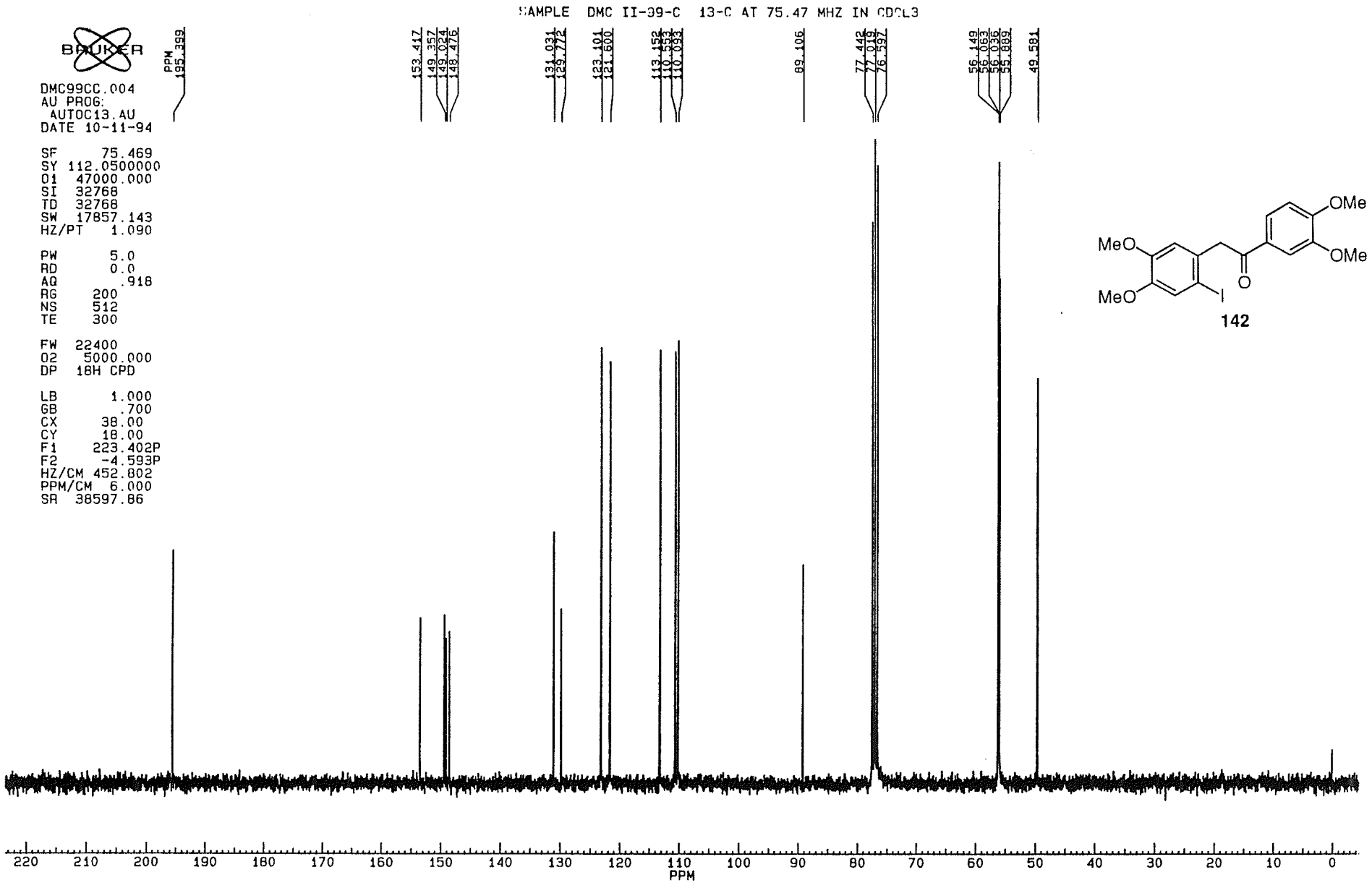

SAMPLE DMC II-45-B 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
DMCII45B.001
AU PROG:
TFZG.AU
DATE 9-6-94
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 4
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.022P
F2 -.478P
HZ/CM 75.032
PPM/CM .250
SR 3362.43
7.01576
7.00996
6.88186
6.85419
4.75636
3.90605
3.87433
3.73768
3.73225
3.71896
2.58199
2.56361
.9909
1.0164
1.0109
.9998
6.2018
4.2593
4.0872
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
CN
MeO
MeO
N
O
136

SAMPLE DMC II-45-B 13-C AT 75.47 MHZ IN CDCL3

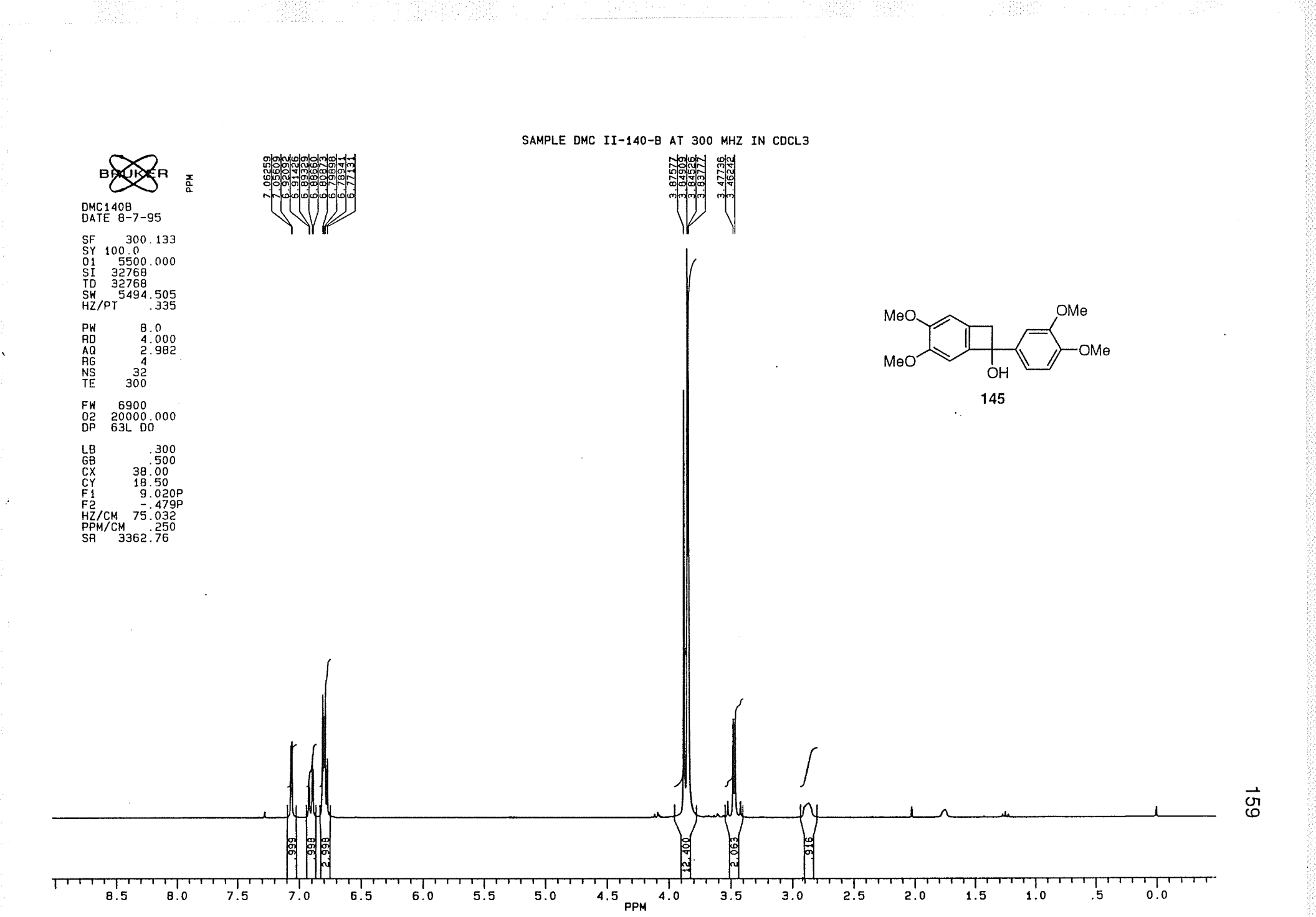


136

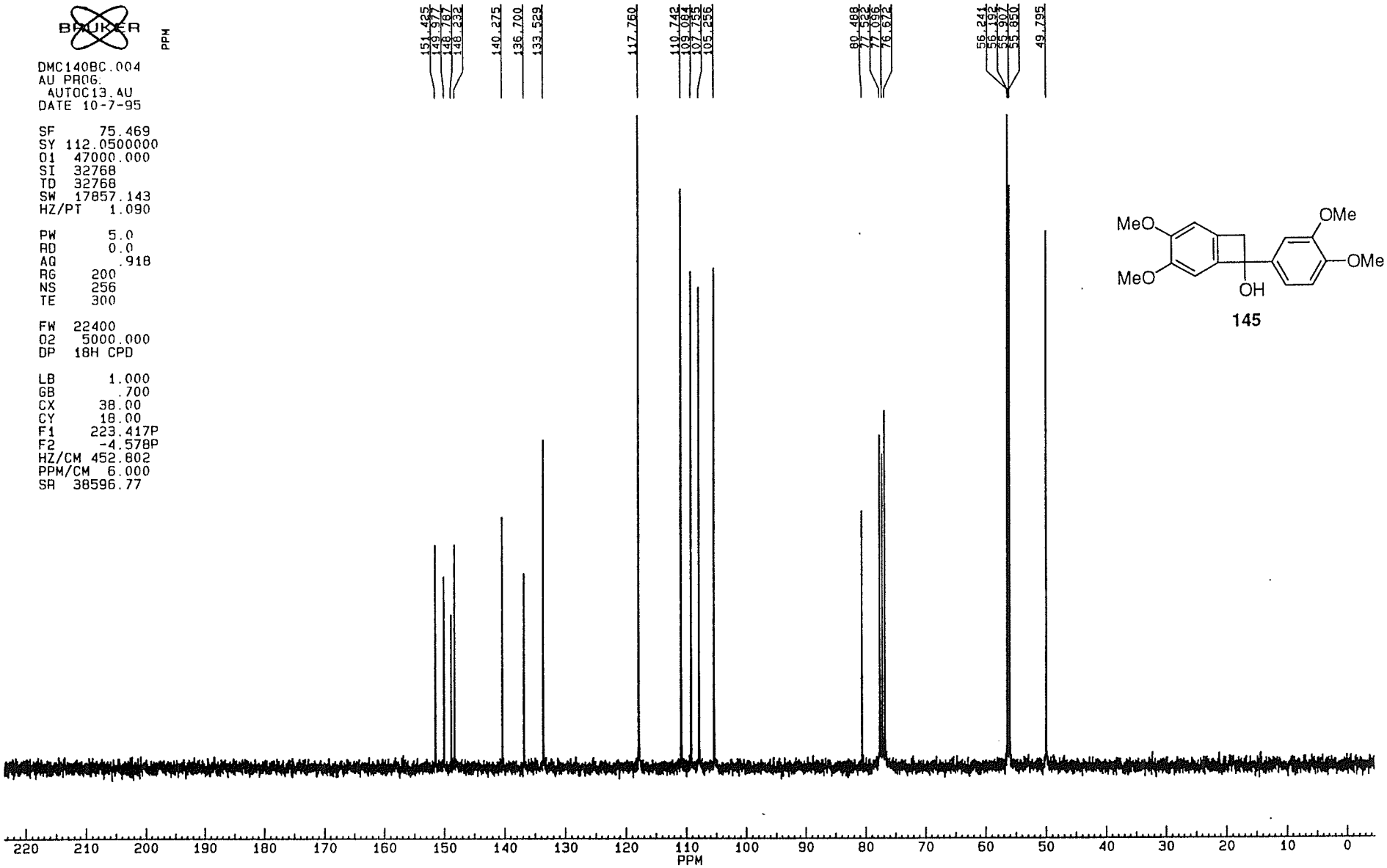

SAMPLE DMC II-
1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
7.56913
7.56251
7.25902
6.92887
6.90081
6.76387
4.34675
3.95127
3.93771
3.85560
3.81114
.0000
DMCII99C.001
AU PROG:
TFZG.AU
DATE 10-11-94
SF 300.133
SY 100.0
01 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 8
NS 32
TE 300
FW 6900
02 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.013P
F2 -.487P
HZ/CM 75.032
PPM/CM .250
SR 3365.11
1.0022
.9999
1.0138
.9321
2.0064
5.9977
6.0948
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
OMe
OMe
MeO
MeO
O
I
142


SAMPLE DMC II-99-C 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
195.399
153.417
149.357
149.024
148.476
131.031
129.772
123.101
121.600
113.152
110.553
110.093
89.106
77.442
77.018
76.597
56.149
56.063
56.036
55.889
49.581
DMC99CC.004
AU PROG:
AUTOC13.AU
DATE 10-11-94
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 512
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
MeO
OMe
MeO
OMe
O
I
142
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 DMC II-140-B AT 300 MHZ IN CDCL3



SAMPLE DMC-II-140-B 13-C AT 75.47 MHZ IN CDCL3



DMC140BC.004
AU PROG.
AUTOC13.AU
DATE 10-7-95

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 256
TE 300

FW 22400
O2 5000.000
DP 18H CPD

LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77

145

SAMPLE DMC-II-161-C 1-H AT 300 MHZ IN CDCL3

PPM

DMC161C.001
AU PROG:
ZFZG.AU
DATE 10-7-95

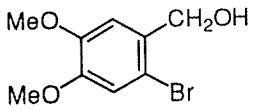
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335

PW 8.0
RD 4.000
AQ 2.982
RG 4
NS 32
TE 300

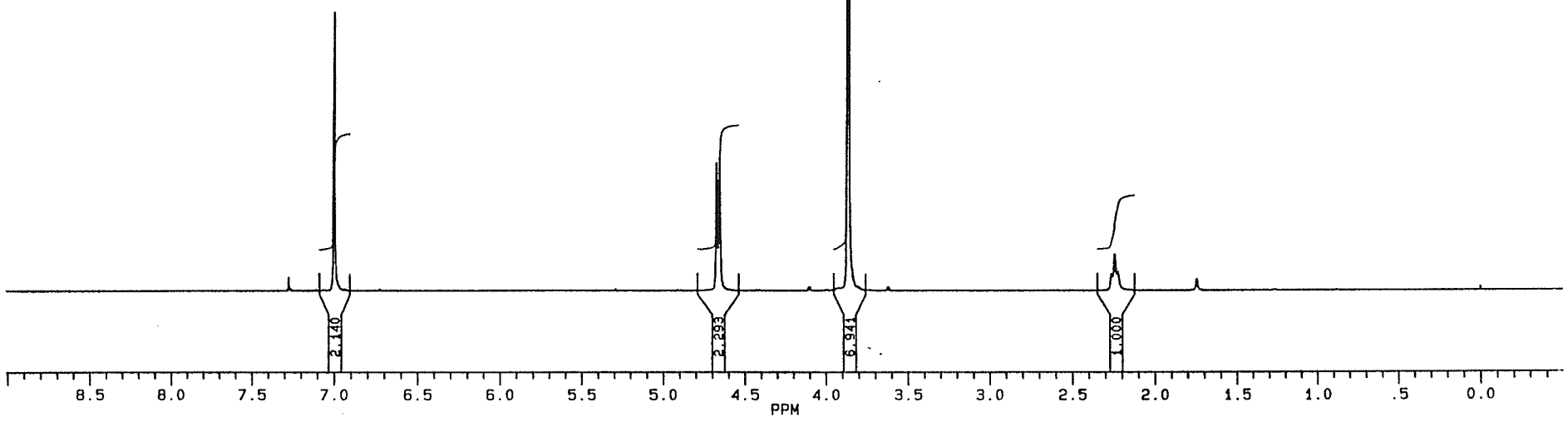
FW 6900
O2 20000.000
DP 63L D0

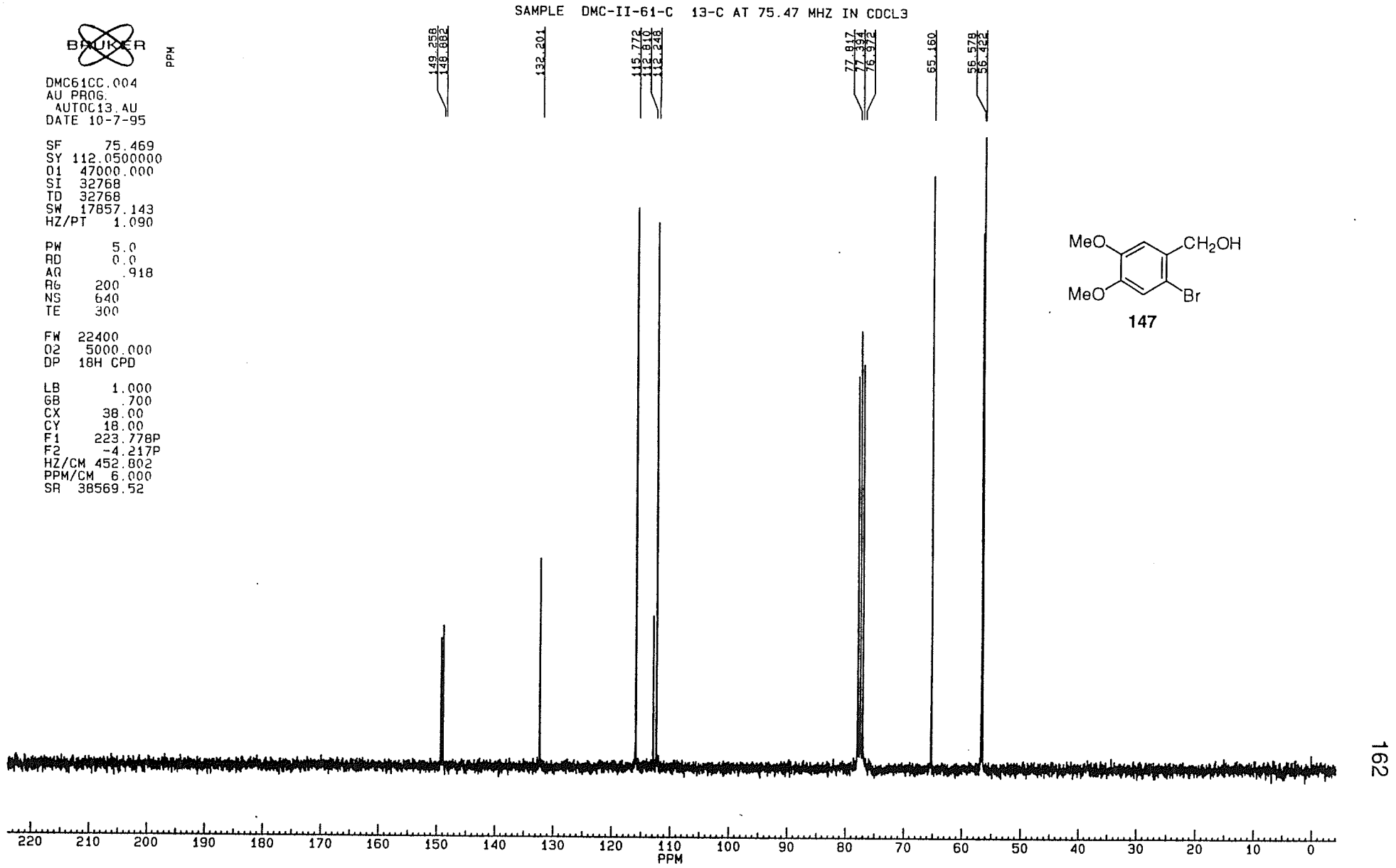
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3363.77

6.99763
4.67147
4.65172
3.86746
3.85750
2.26117
2.24201
2.22268

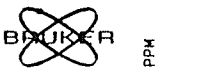


147




SAMPLE DMC-II-61-C 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
DMC61CC.004
AU PROG.
AUTOC13.AU
DATE 10-7-95
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 640
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.778P
F2 -4.217P
HZ/CM 452.802
PPM/CM 6.000
SR 38569.52
149.258
148.882
132.201
115.772
113.810
113.248
77.817
77.394
76.972
65.160
56.578
56.422
MeO
CH2OH
MeO
Br
147
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

DMC-II-78-C 1-H AT 300 MHZ IN CDCL3



PPM

6.98691
6.91349
4.62537
3.83153

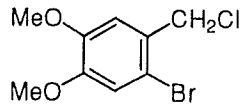
DMCII78.001
AU PROG:
AUTOH1
DATE 20-7-95

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

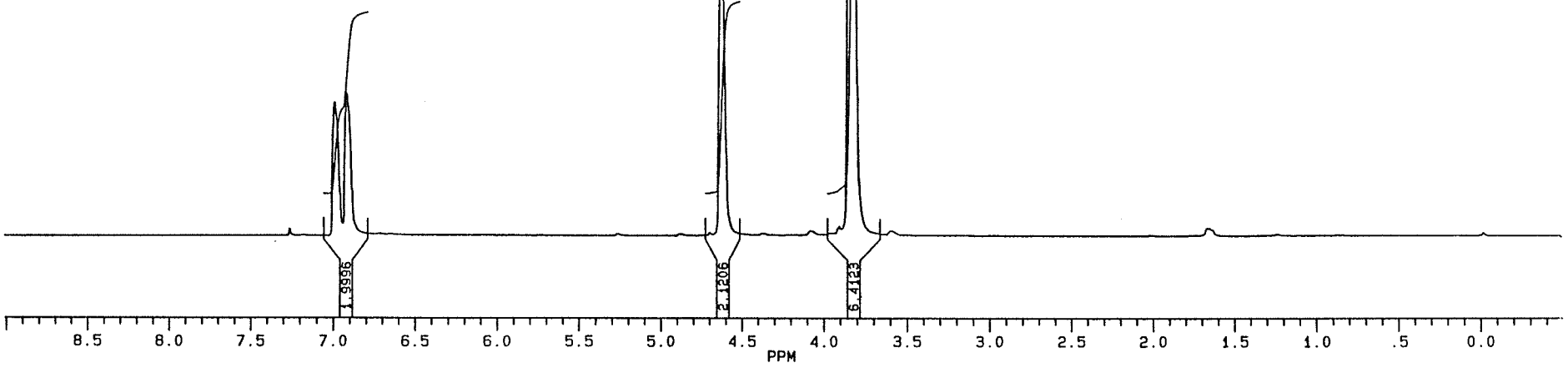
PW 8.0
RD 4.000
AQ 2.982
RG 2
NS 32
TE 300

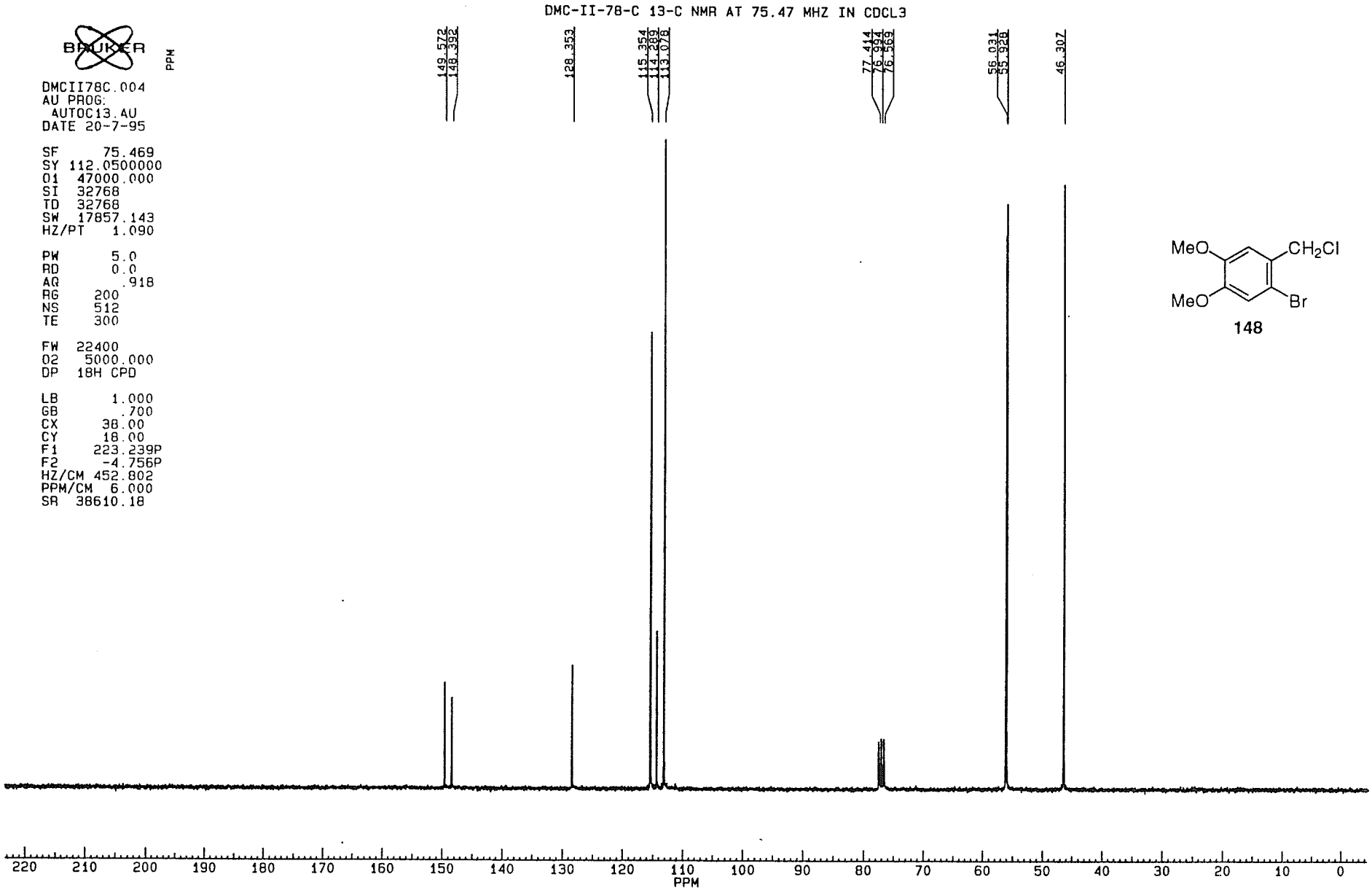
FW 6900
O2 20000.000
DP 63L DO

LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3367.42

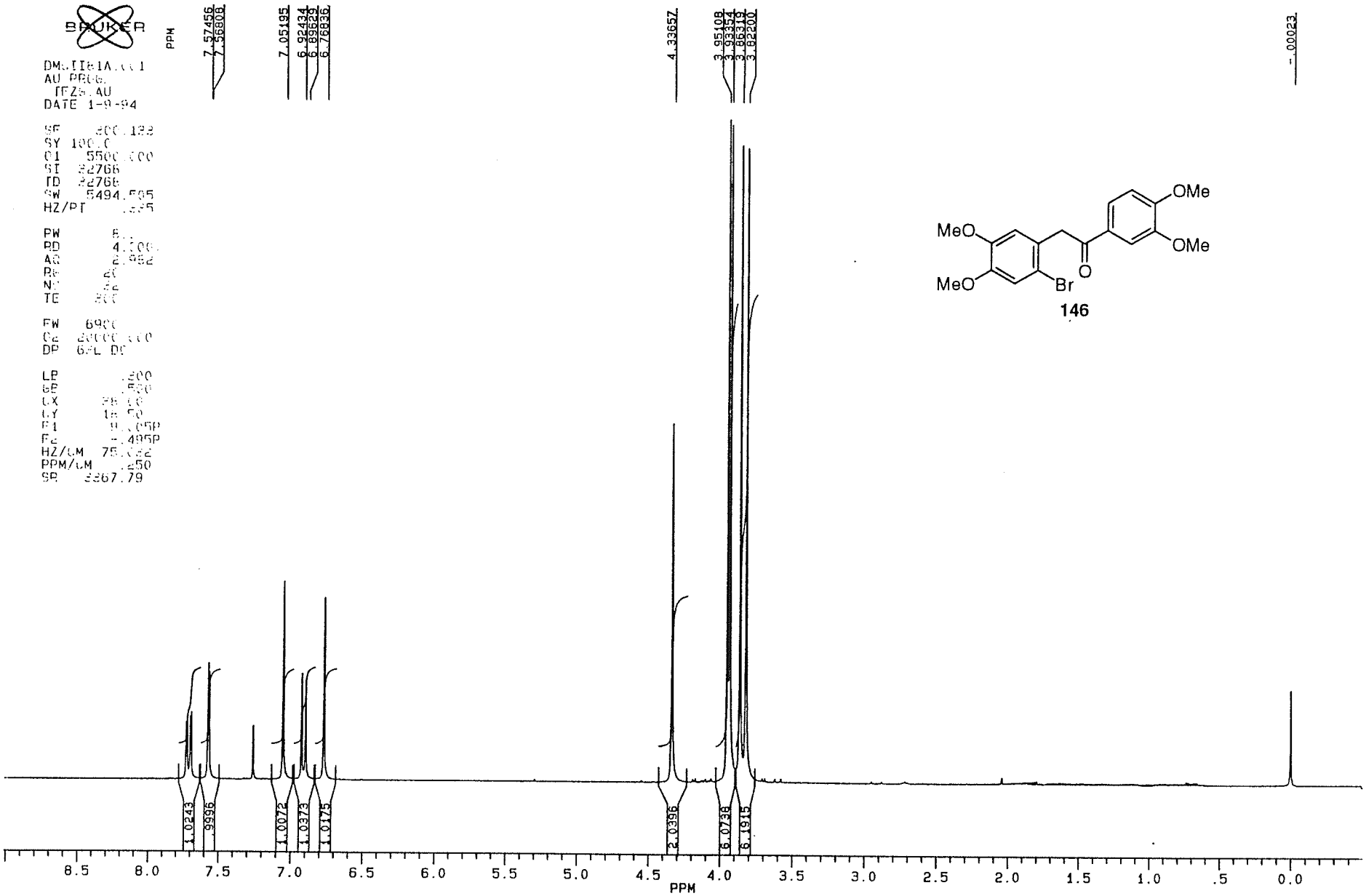


148

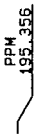



DMC-II-78-C 13-C NMR AT 75.47 MHZ IN CDCL3
BRUKER
PPM
DMCII78C.004
AU PROG:
AUTOC13.AU
DATE 20-7-95
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 512
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.239P
F2 -4.756P
HZ/CM 452.802
PPM/CM 6.000
SR 38610.18
149.572
148.392
128.353
115.354
114.289
113.078
77.414
76.994
76.569
56.031
55.928
46.307
MeO
CH2Cl
MeO
Br
148
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 DMC II-81-A 1-H AT 300 MHZ IN CDCL3



SAMPLE DMC-II-81-B 13-C AT 75.47 MHZ IN CDCL3



PPM
195.356

153.404
148.997
148.604
148.419
129.644
126.963
123.060
115.450
114.738
113.761
110.524
110.104
77.528
77.105
76.682
56.136
55.947
55.840
44.845

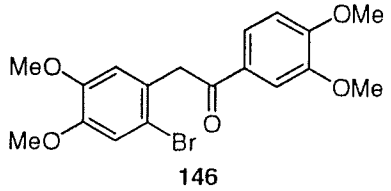
DMC81BC.004
AU PROG:
AUTOC13.AU
DATE 10-7-95

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 320
TE 300

FW 22400
O2 5000.000
DP 18H CPD

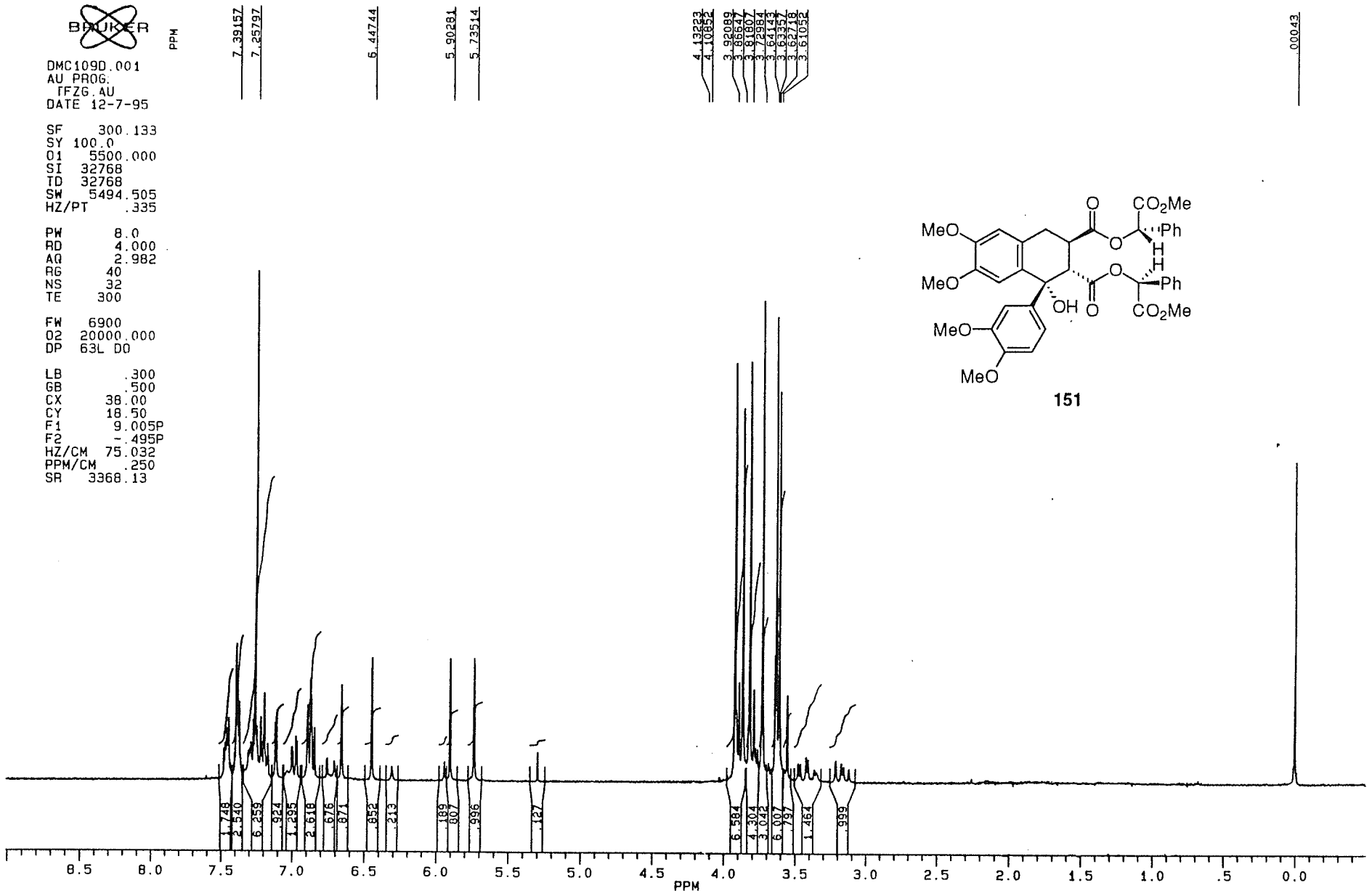
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77



146

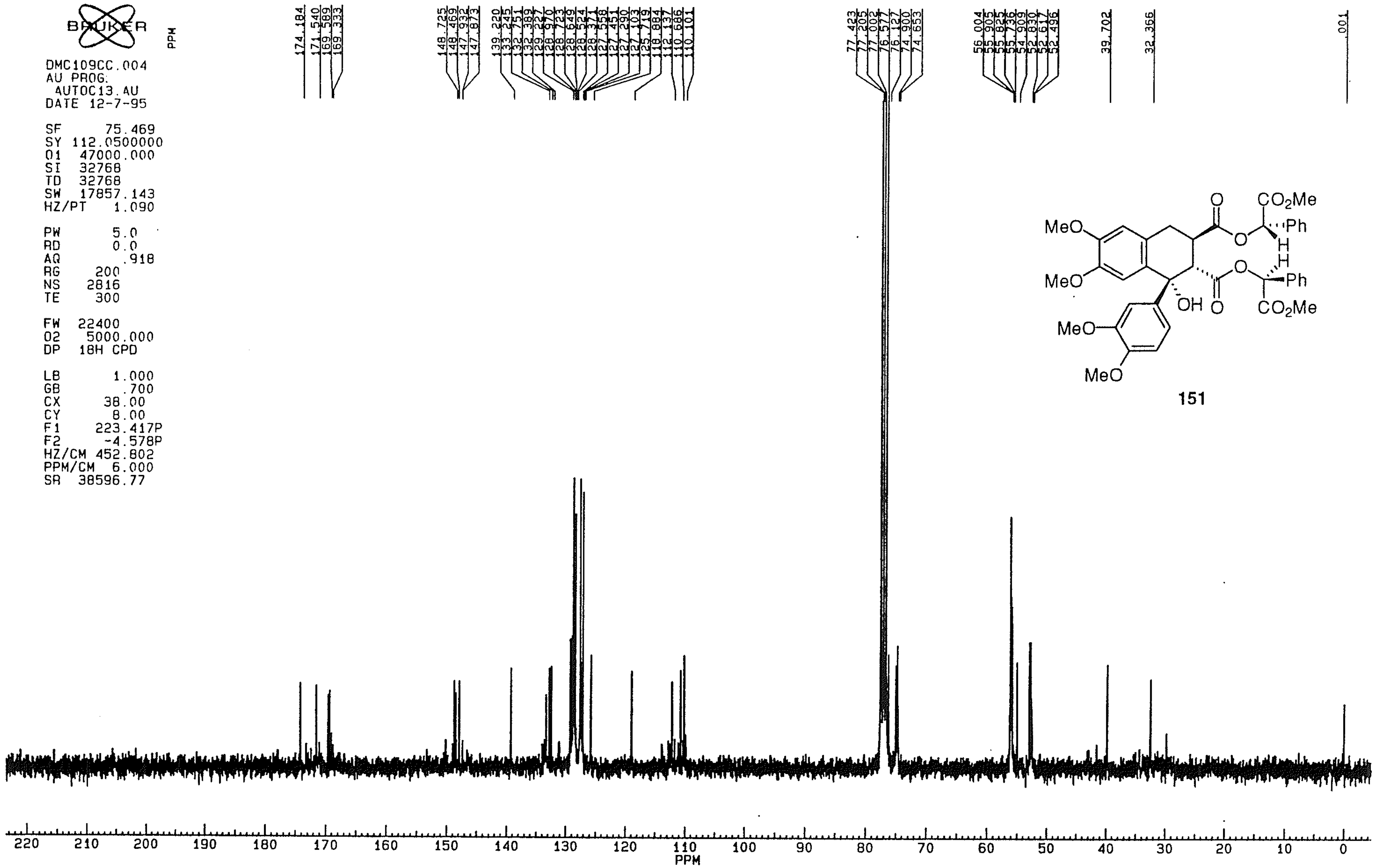
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

SAMPLE DMC-II-109-D 1-H AT 300 MHZ IN CDCL3



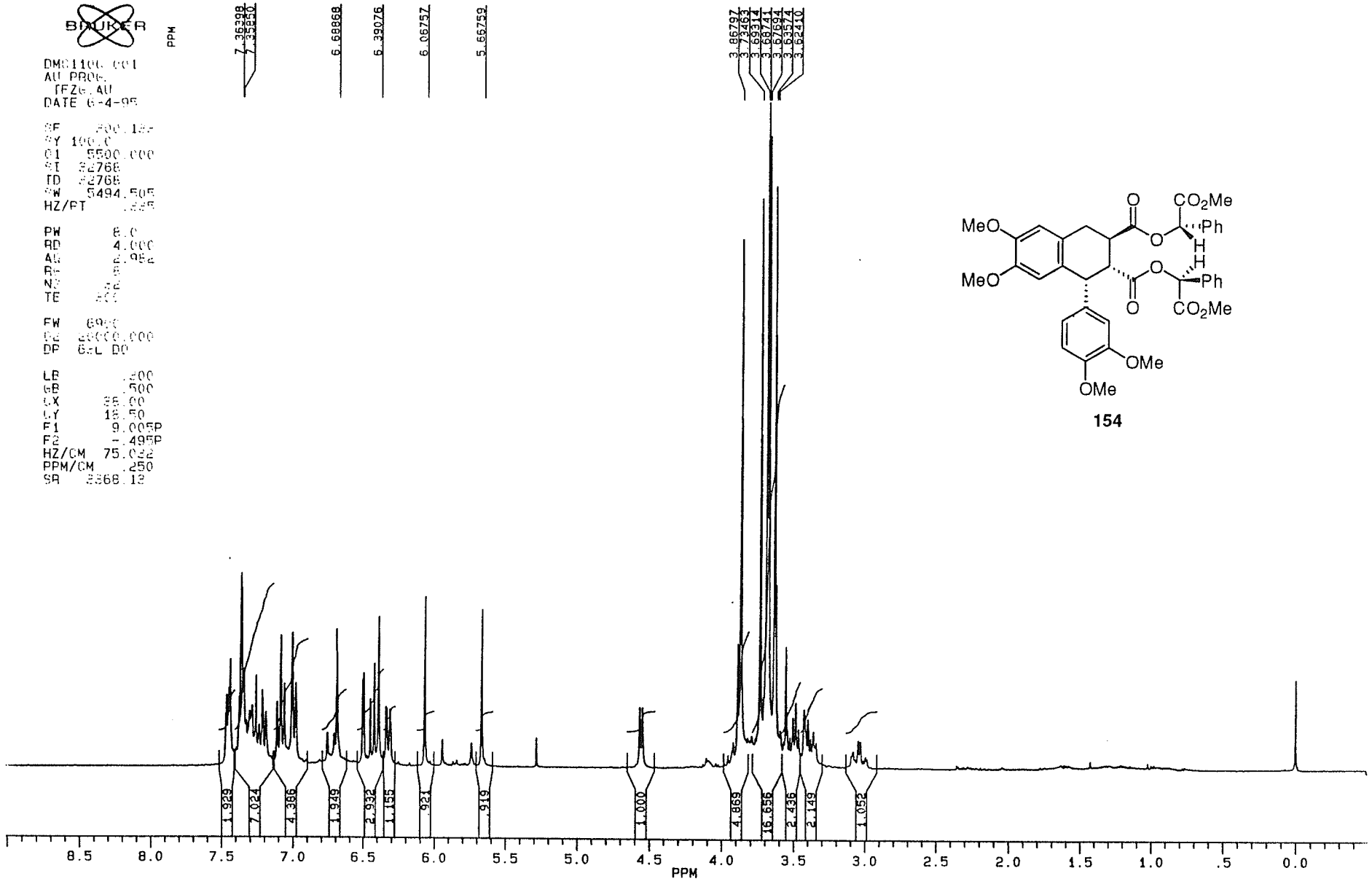
151

SAMPLE DMC-II-109-C 13-C AT 75.47 MHZ IN CDCL3

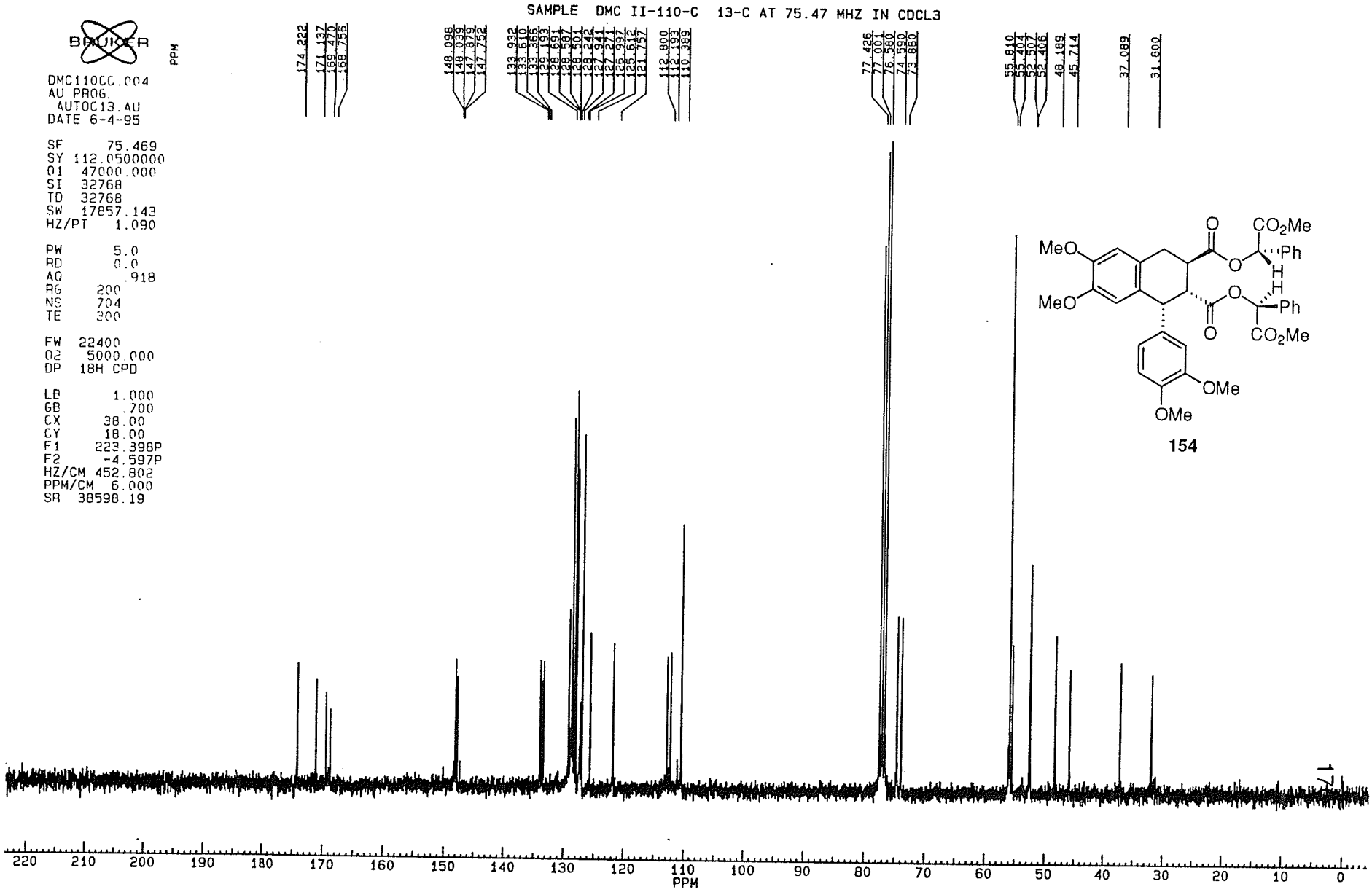


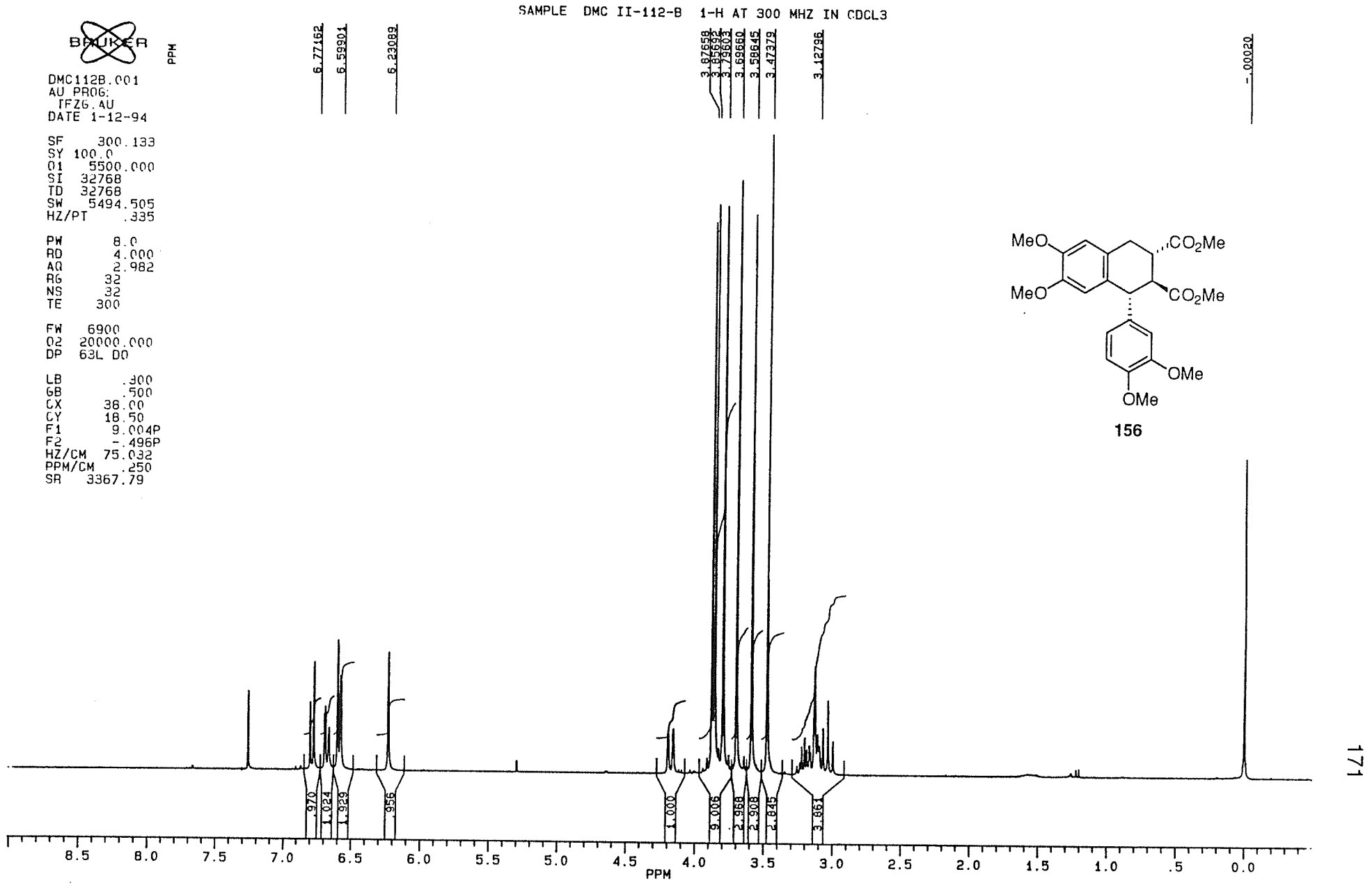
151

SAMPLE DMC II-110-C 1-H AT 300 MHZ IN CDCL3



154


SAMPLE DMC II-110-C 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
DMC110CC.004
AU PROG.
AUTOC13.AU
DATE 6-4-95
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 704
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
174.222
171.137
169.470
168.756
148.098
148.039
147.879
147.752
133.932
133.610
133.366
129.193
128.691
128.567
128.302
128.242
127.941
127.274
126.997
125.612
121.757
112.800
112.193
110.389
77.426
77.001
76.580
74.590
73.880
55.810
55.404
52.507
52.406
48.189
45.714
37.089
31.800
MeO
MeO
O
CO2Me
Ph
H
H
Ph
CO2Me
OMe
OMe
154
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 DMC II-112-B 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
DMC112B.001
AU PROG:
TFZG.AU
DATE 1-12-94
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 32
NS 32
TE 300
FW 6900
02 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
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F2 -.496P
HZ/CM 75.032
PPM/CM .250
SR 3367.79
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6.59901
6.23089
3.87658
3.73602
3.69660
3.58645
3.47379
3.12796
-.00020
.970
1.024
1.929
.956
1.000
9.006
2.968
2.908
2.845
3.861
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
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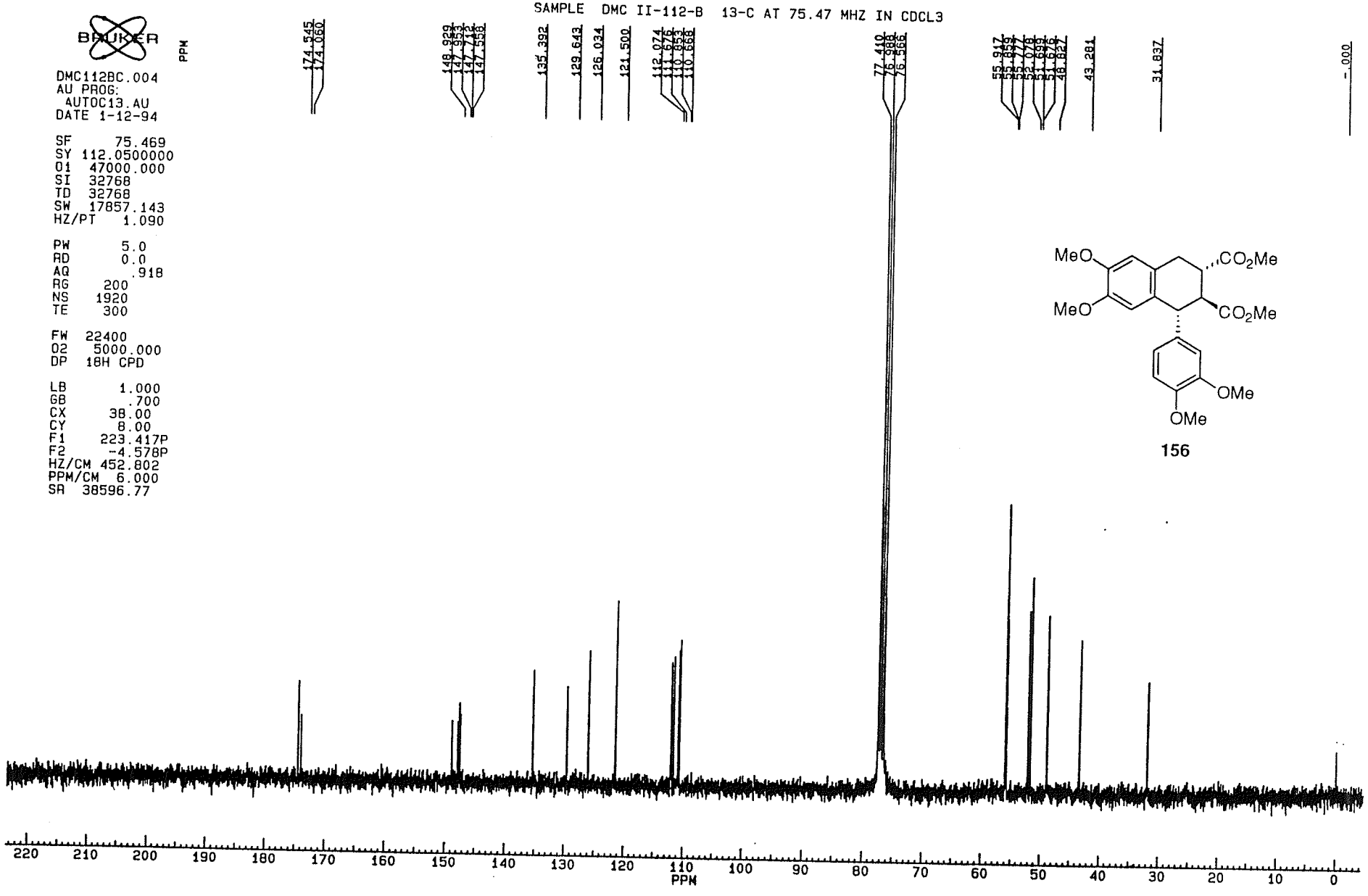
0.0
PPM

MeO
MeO
CO2Me
CO2Me
OMe
OMe

156


SAMPLE DMC II-112-B 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
DMC112BC.004
AU PROG:
AUTOC13.AU
DATE 1-12-94
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 1920
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 8.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77
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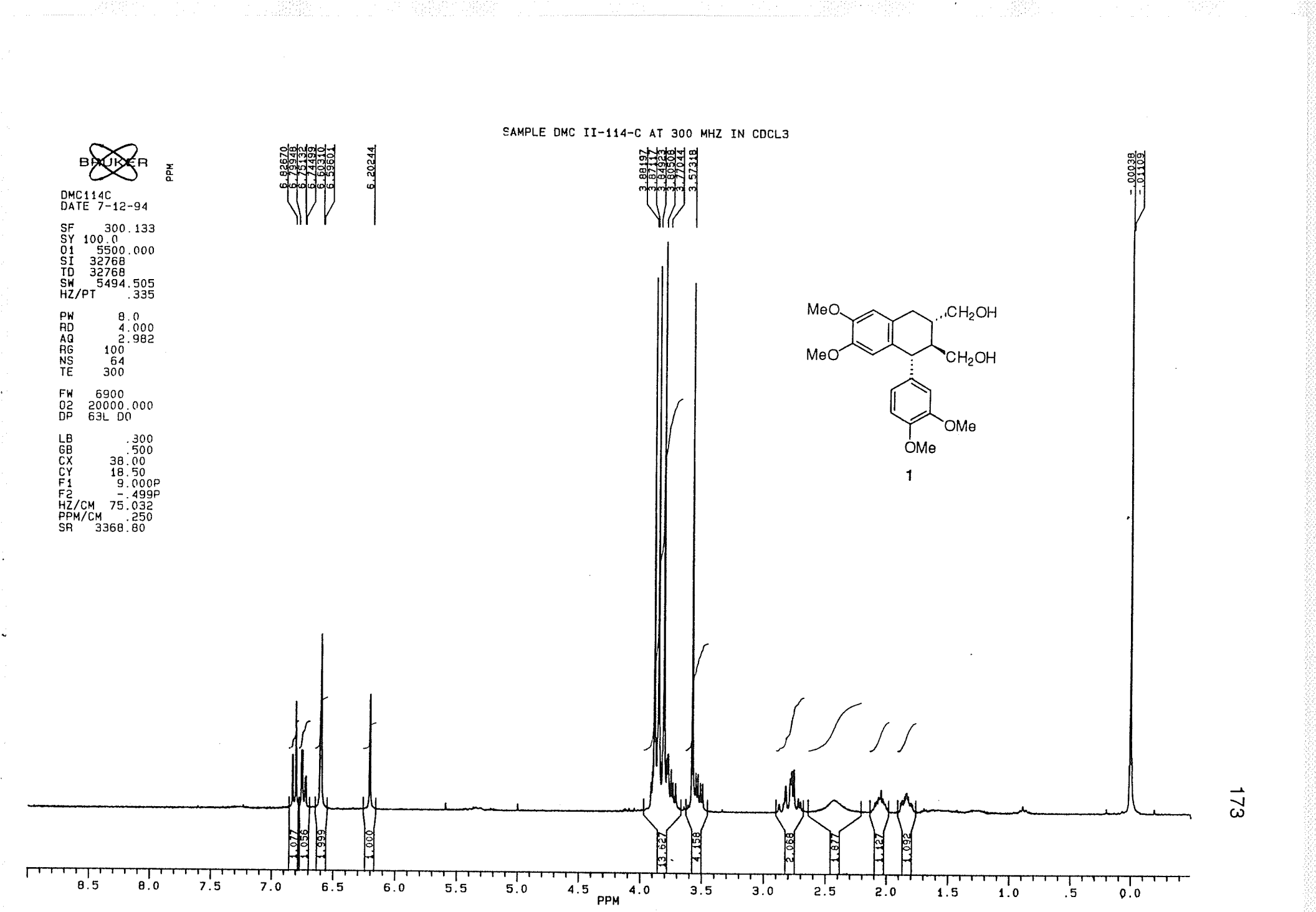
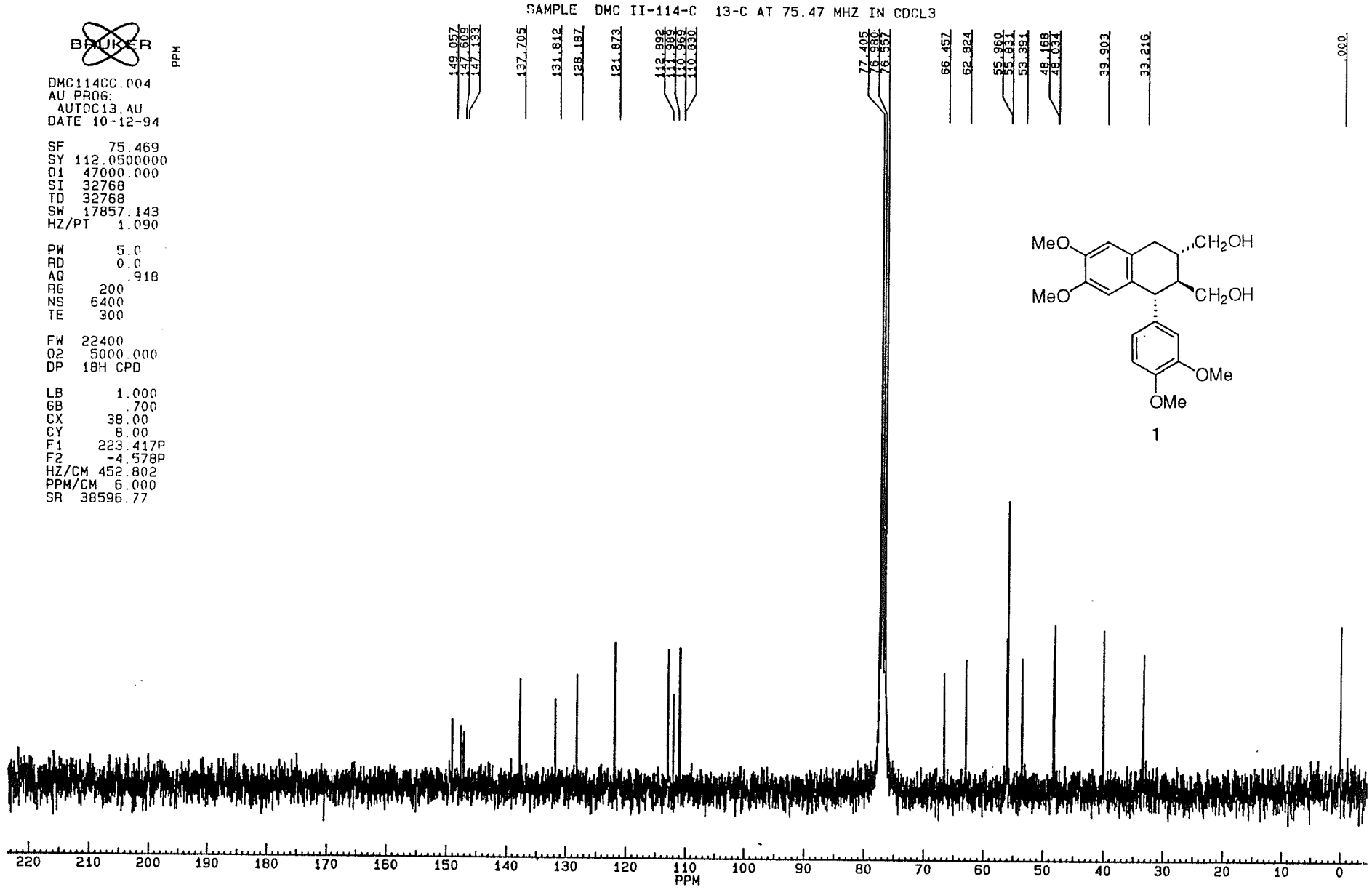
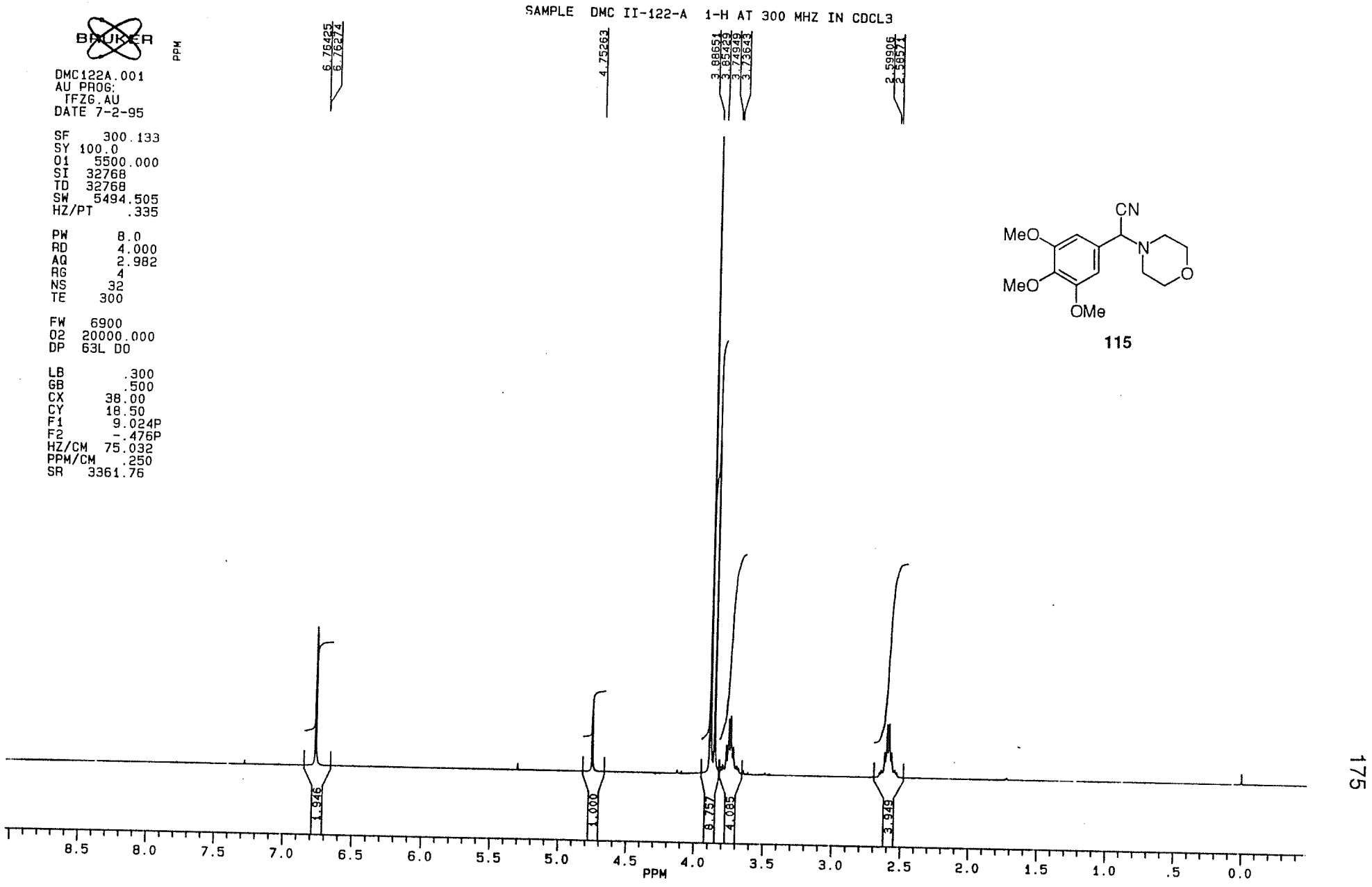
174.060
148.929
147.953
147.713
147.558
135.392
129.643
126.034
121.500
112.074
111.676
110.933
110.688
77.410
76.988
76.565
55.917
55.859
55.777
52.078
51.699
51.675
48.827
43.281
31.837
-.000
MeO
MeO
CO2Me
CO2Me
OMe
OMe
156
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

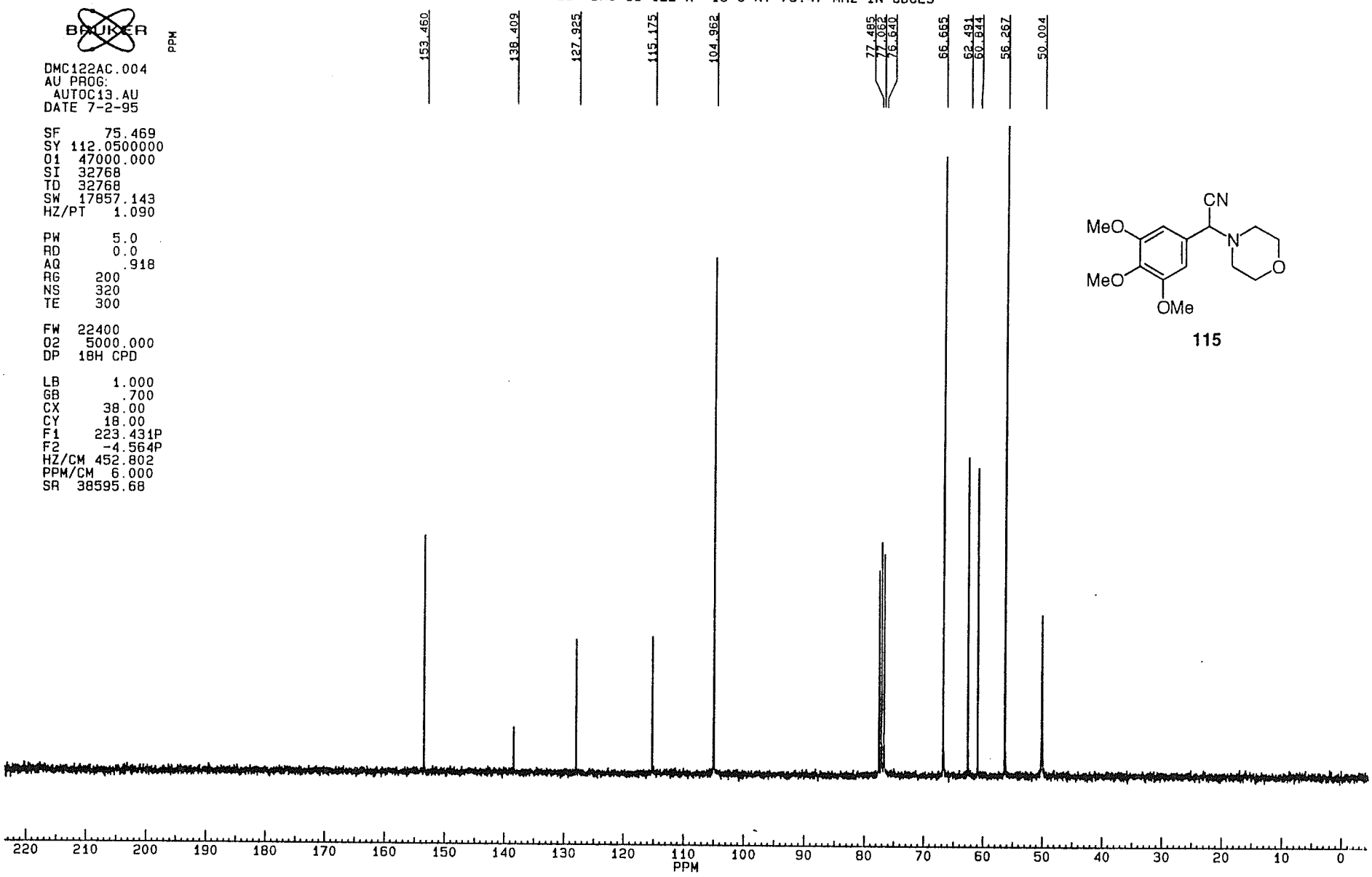
SAMPLE DMC II-114-C AT 300 MHZ IN CDCL3




SAMPLE DMC II-114-C 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
DMC114CC.004
AU PROG:
AUTOC13.AU
DATE 10-12-94
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 6400
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 8.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77
149.057
147.609
147.133
137.705
131.812
128.187
121.873
112.892
111.969
111.969
110.969
110.830
77.405
76.980
76.557
66.457
62.824
55.960
55.831
55.831
53.391
48.168
48.034
39.903
33.216
.000
MeO
MeO
CH2OH
CH2OH
OMe
OMe
1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

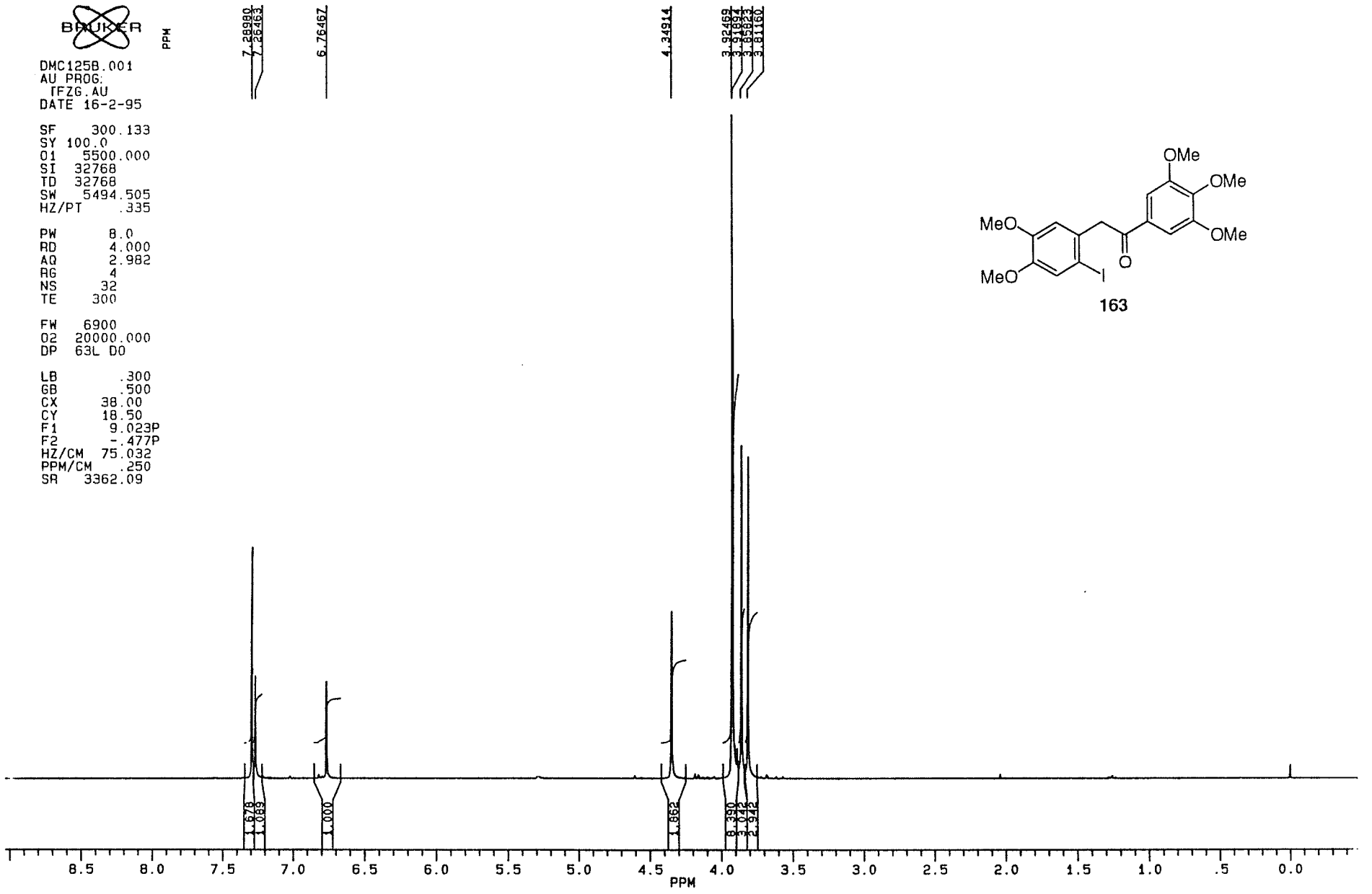

SAMPLE DMC II-122-A 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
DMC122A.001
AU PROG:
TFZG.AU
DATE 7-2-95
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 4
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.024P
F2 -.476P
HZ/CM 75.032
PPM/CM .250
SR 3361.76
6.76425
6.76274
4.75263
3.88651
3.85429
3.74949
3.73643
2.59906
2.58571
1.946
1.000
8.757
4.065
3.949
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
CN
MeO
MeO
OMe
N
O
115

SAMPLE DMC II-122-A 13-C AT 75.47 MHZ IN CDCL3



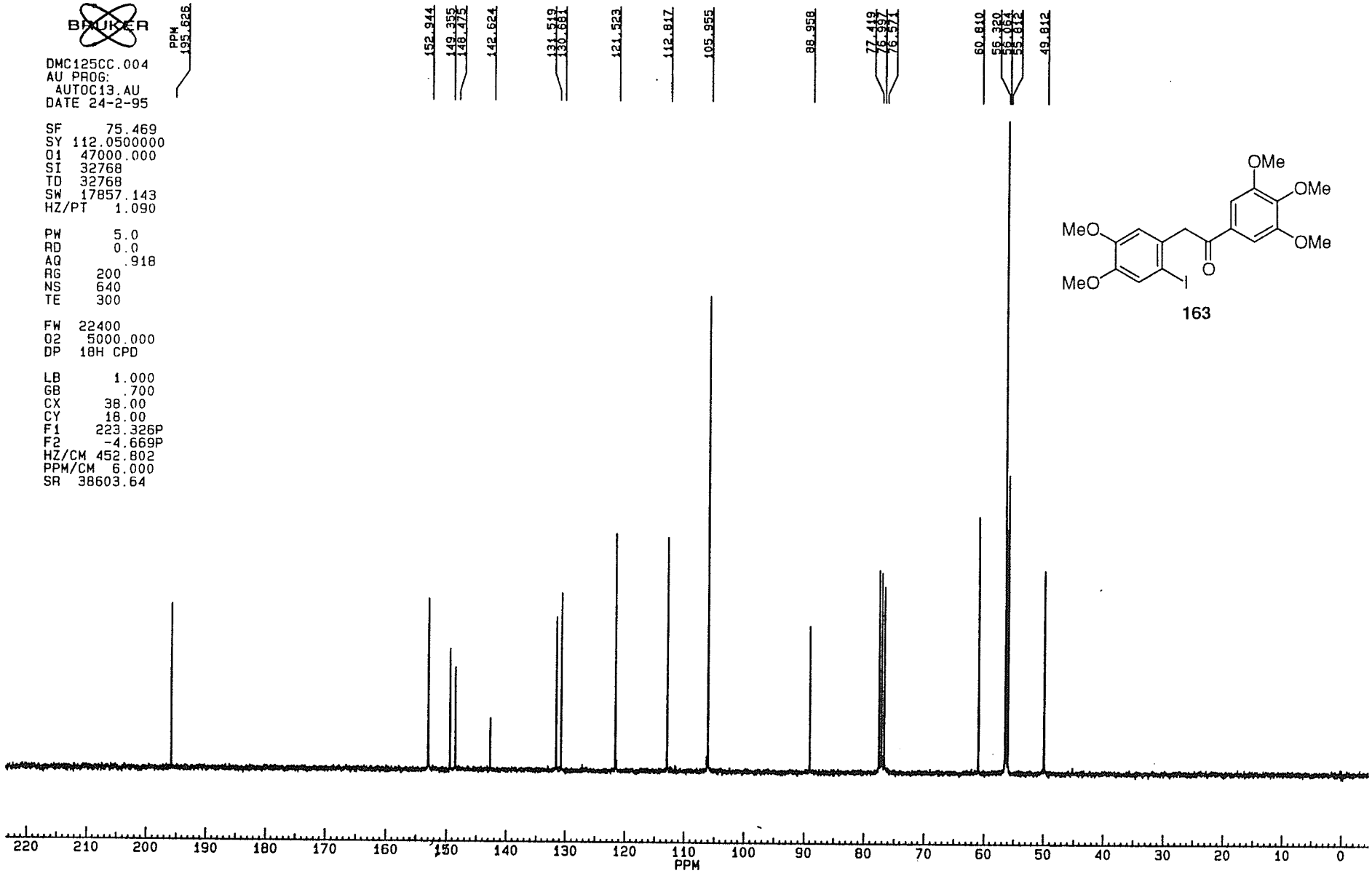
115

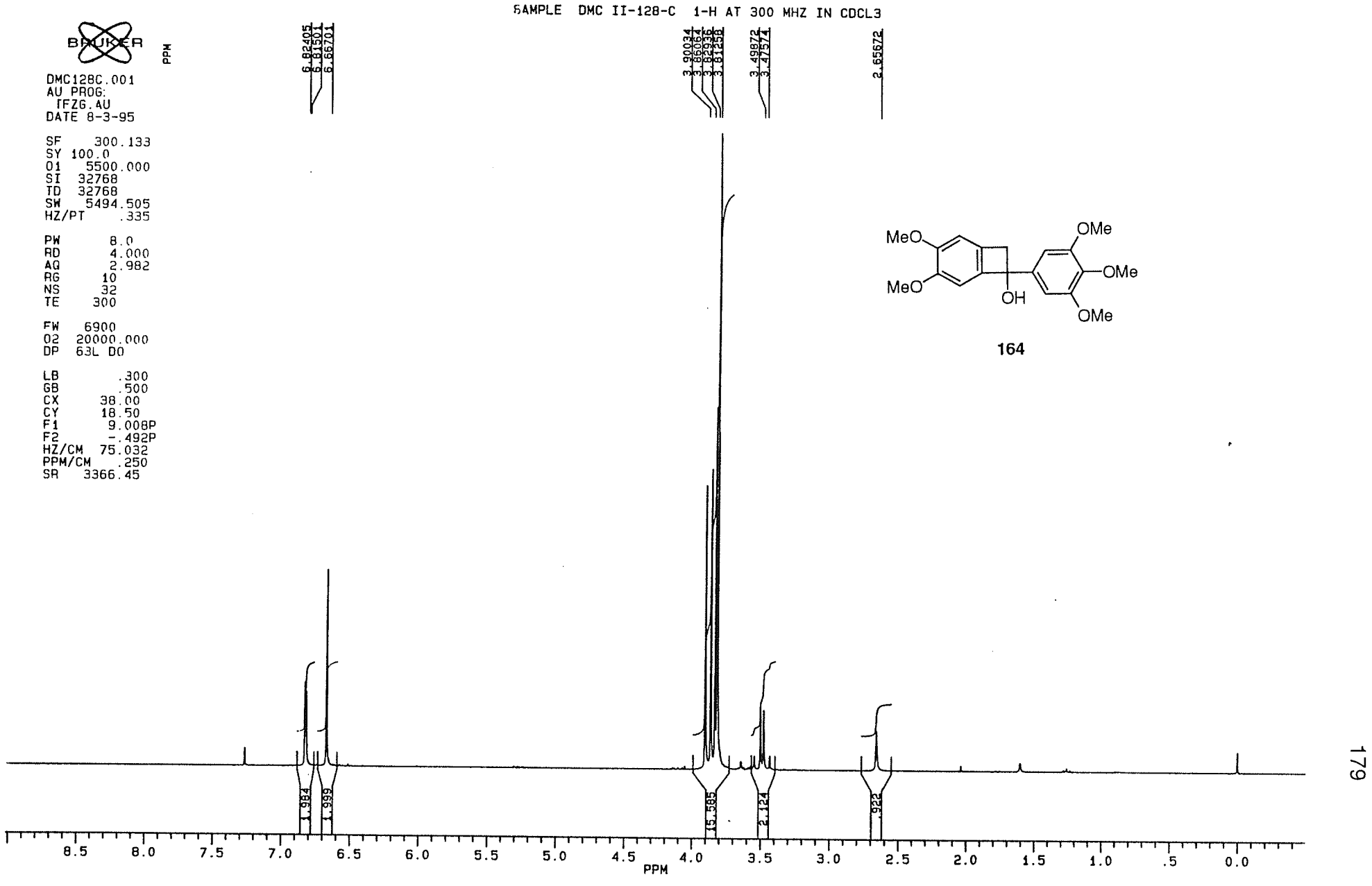
SAMPLE DMC II-125-B 1-H AT 300 MHZ IN CDCL3



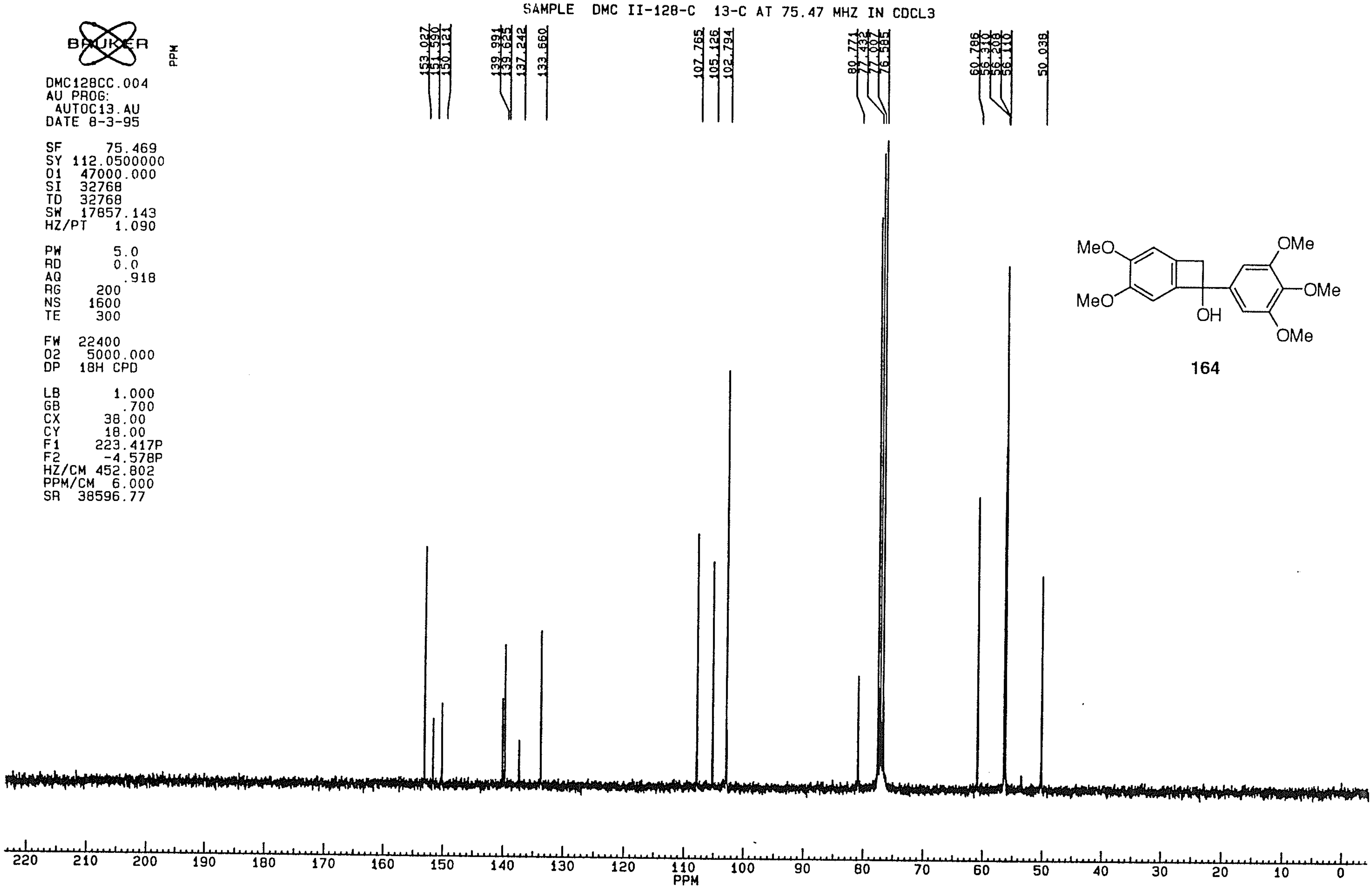
163

SAMPLE DMC II-125-C 13-C AT 75.47 MHZ IN CDCL3



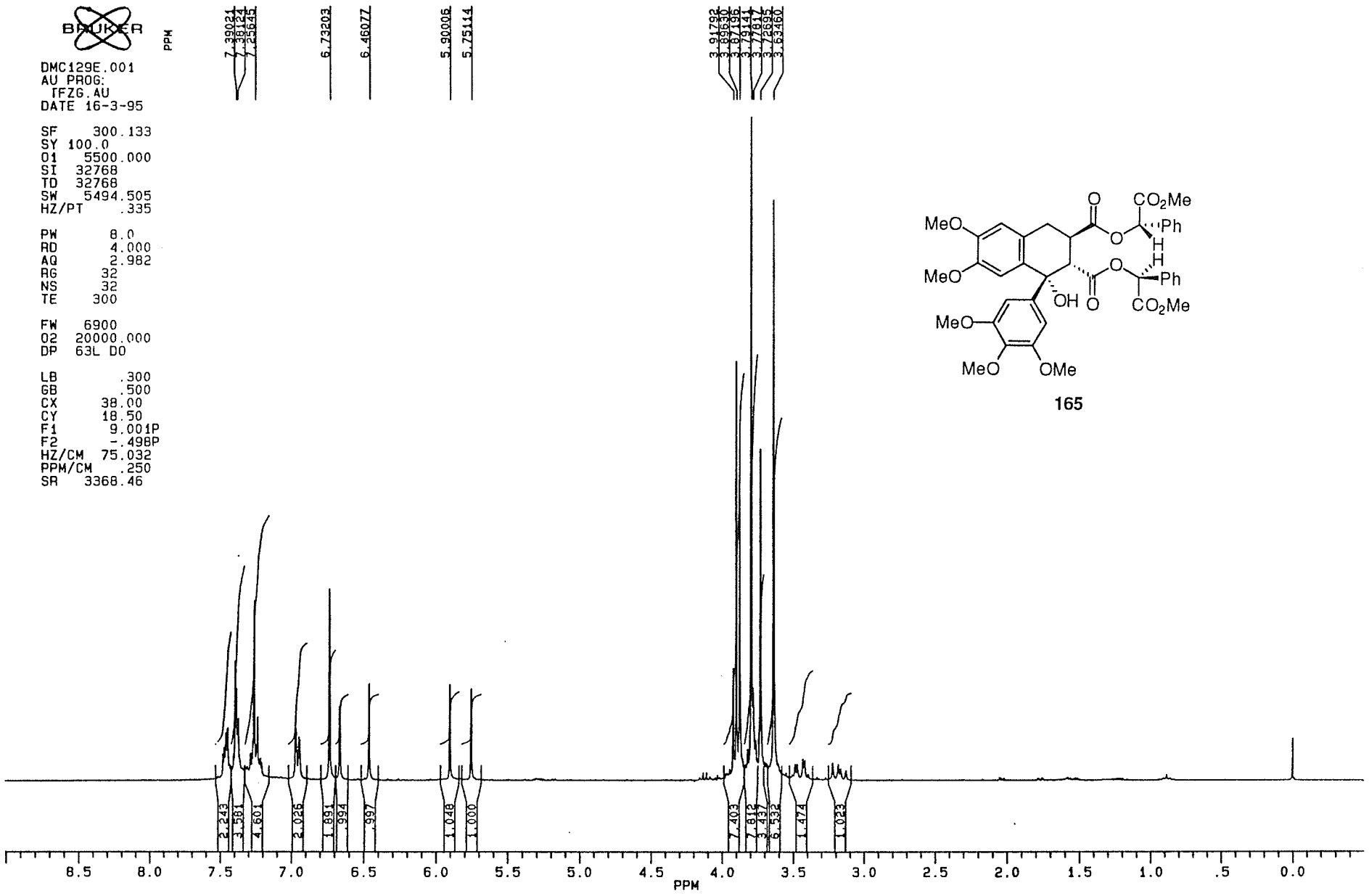

SAMPLE DMC II-128-C 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
DMC128C.001
AU PROG:
TFZG.AU
DATE 8-3-95
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 10
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.008P
F2 -.492P
HZ/CM 75.032
PPM/CM .250
SR 3366.45
6.82405
6.81501
6.66701
3.90034
3.86061
3.85032
3.84336
3.81258
3.49872
3.47574
2.65672
1.984
1.999
15.585
2.124
.922
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
MeO
MeO
OMe
OMe
OMe
OH

164


SAMPLE DMC II-128-C 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
DMC128CC.004
AU PROG:
AUTOC13.AU
DATE 8-3-95
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 1600
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77
153.027
151.590
150.121
139.991
139.625
137.242
133.660
107.765
105.126
102.794
80.771
77.432
77.007
76.585
60.786
56.310
56.208
56.110
50.038
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM
MeO
MeO
OH
OMe
OMe
OMe

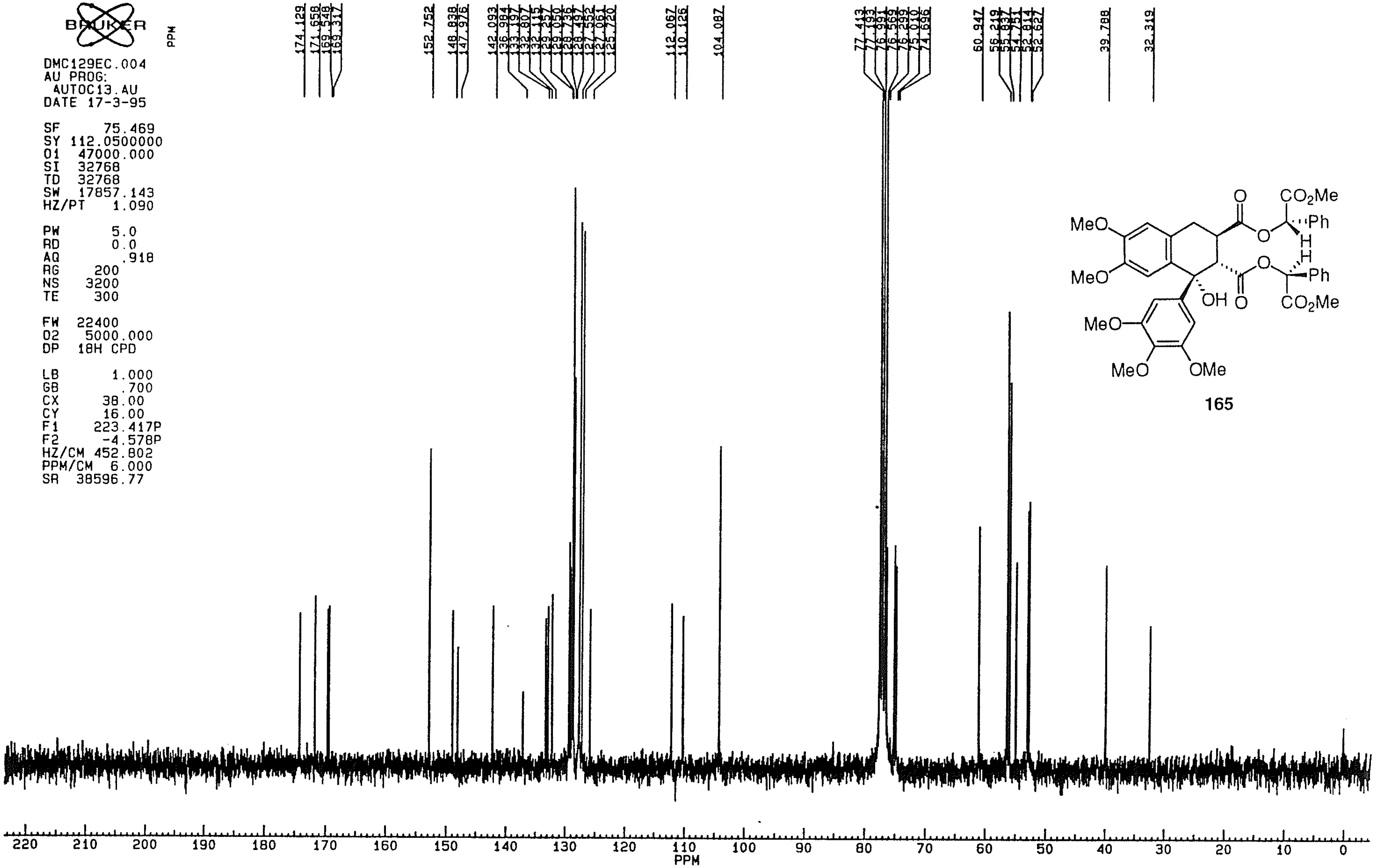
164

SAMPLE DMC II-129-E 1-H AT 300 MHZ IN CDCL3

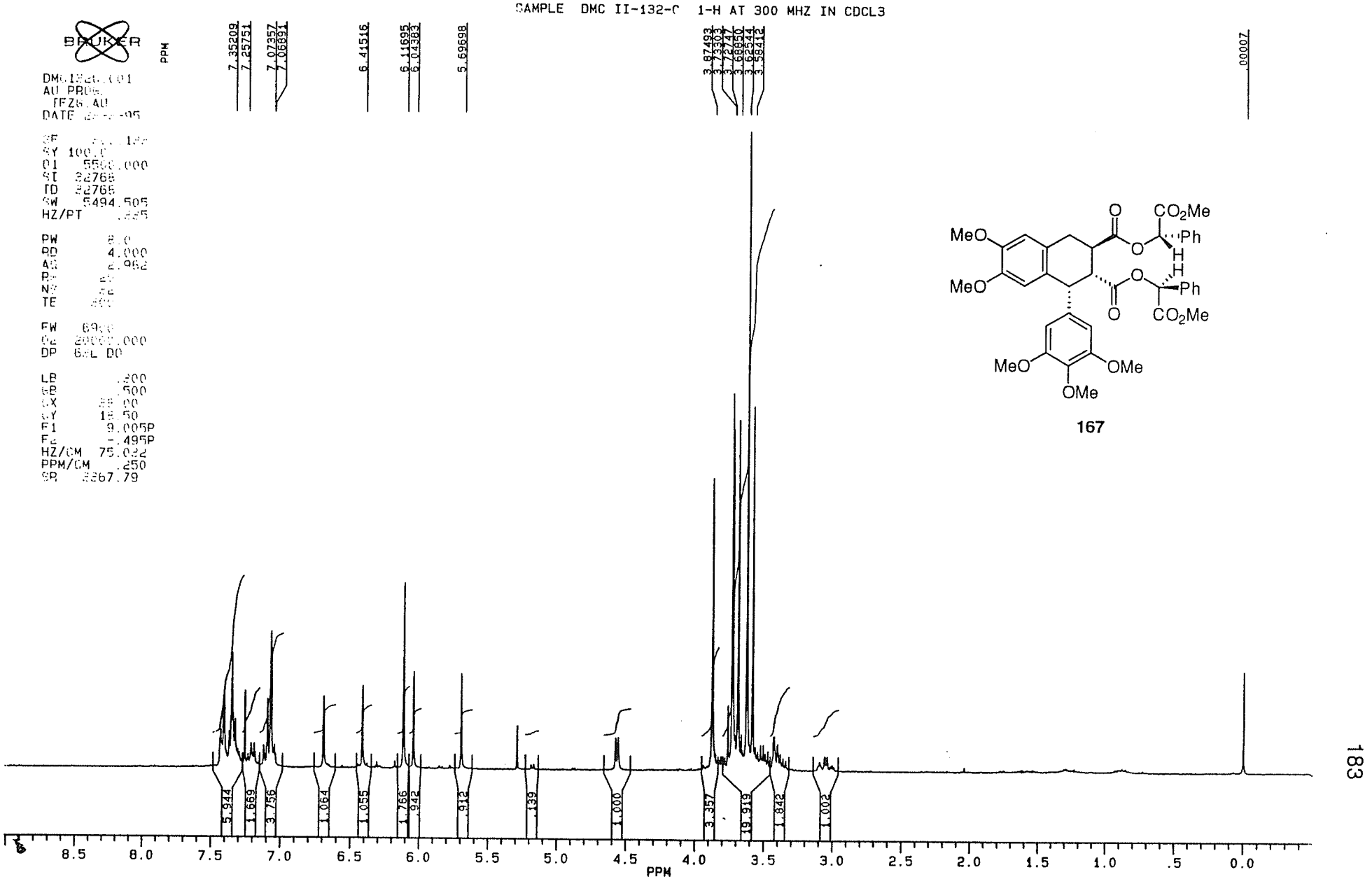


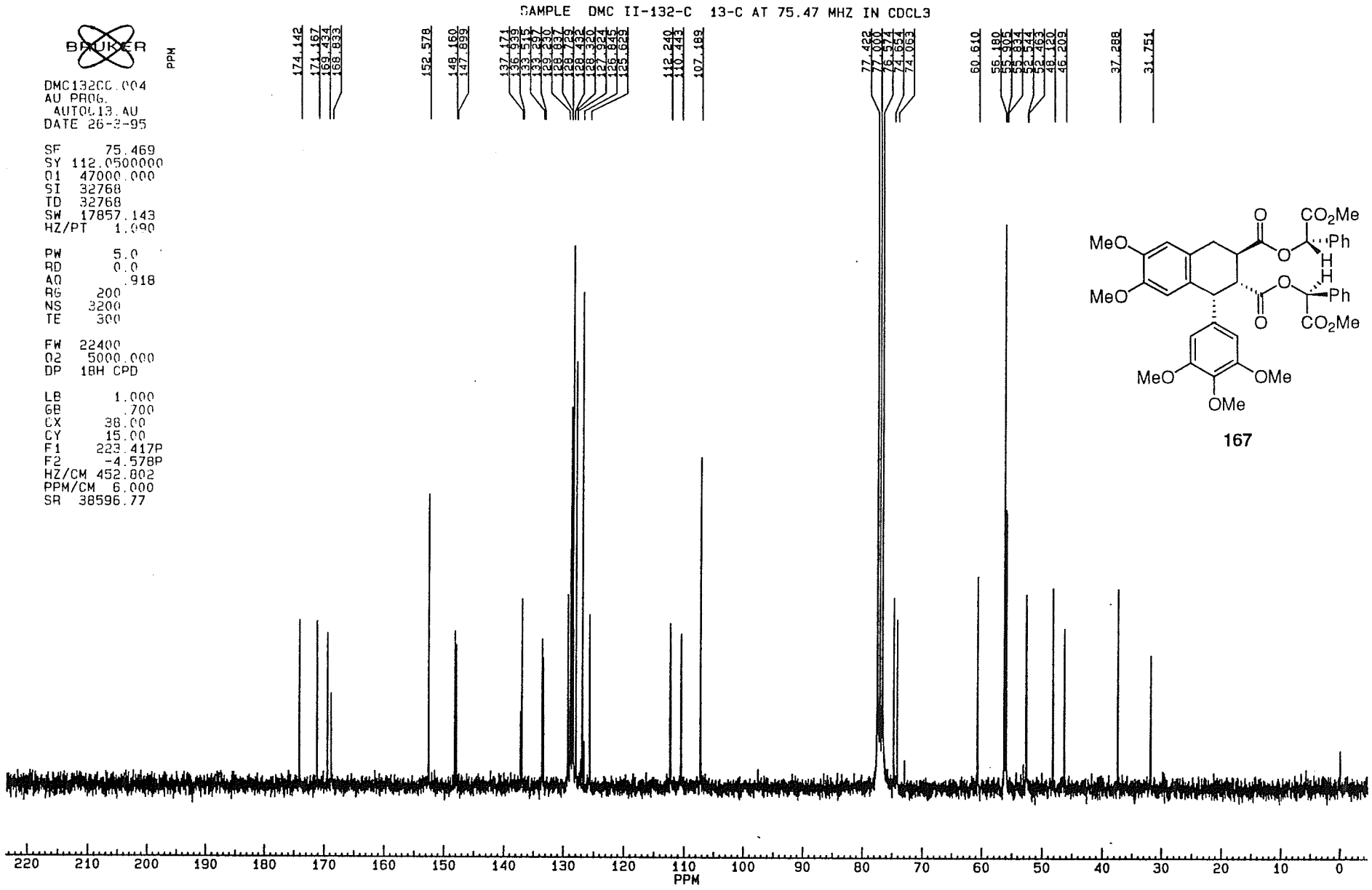
165

SAMPLE DMC II-129-E 13-C AT 75.47 MHZ IN CDCL3



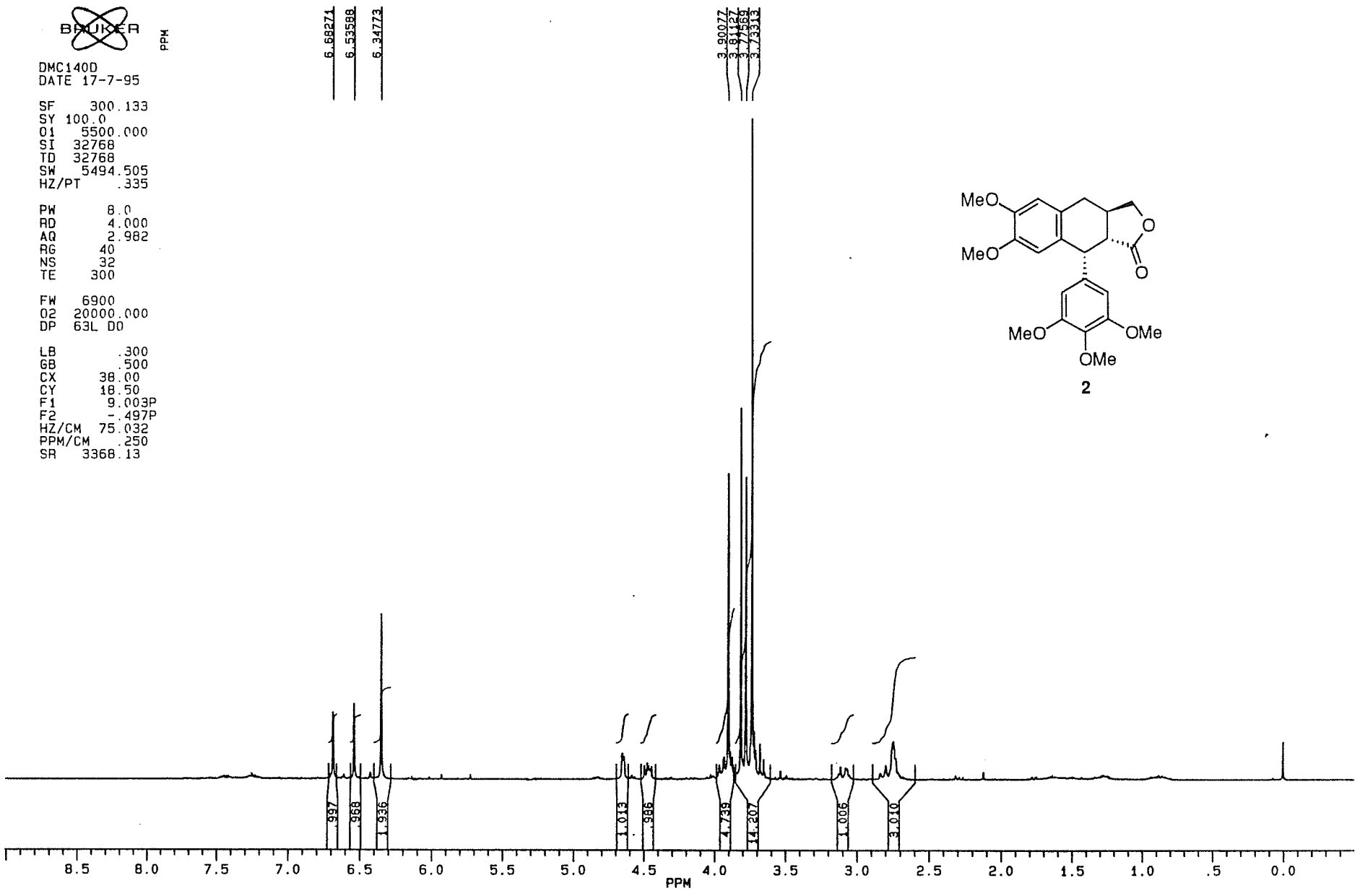
165

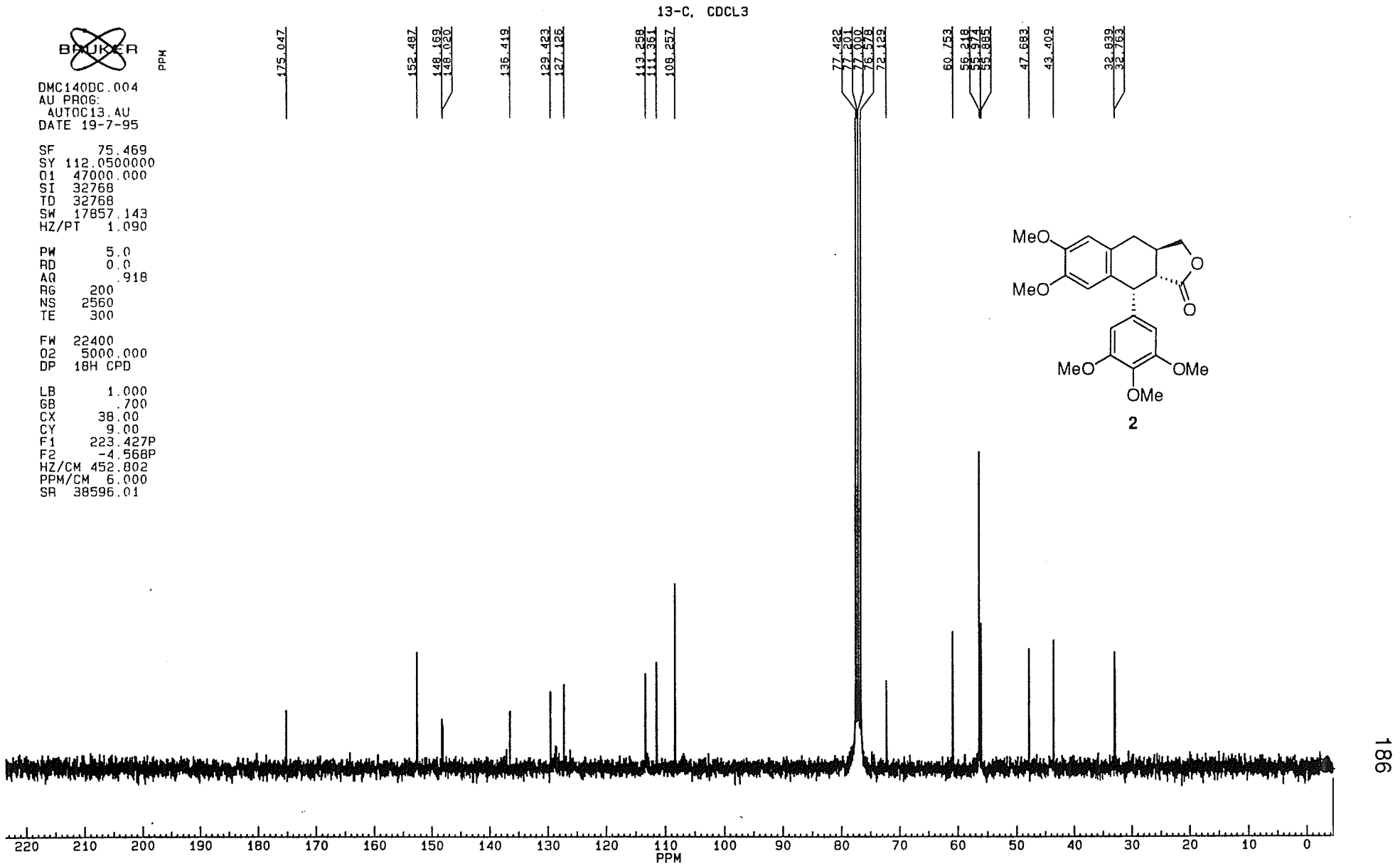

SAMPLE DMC II-132-C 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
7.35209
7.25751
7.07357
7.06891
6.41516
6.11695
6.04383
5.69698
3.87493
3.73303
3.72747
3.66850
3.62544
3.58412
.00007
MeO
MeO
CO2Me
Ph
H
H
Ph
CO2Me
MeO
OMe
OMe
167
5.944
1.669
3.756
1.064
1.055
1.766
.942
.913
.139
1.000
3.357
19.919
1.842
1.002
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 DMC II-132-C 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
DMC132CC.004
AU PR06.
AUTOL13.AU
DATE 26-3-95
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 18H CPD
LB 1.000
GB .700
CX 38.00
CY 15.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77
174.142
171.167
169.434
168.833
152.578
148.160
147.899
137.171
136.939
133.515
133.287
129.230
128.837
128.729
128.433
128.336
127.924
127.845
125.629
118.240
110.443
107.189
77.422
77.000
76.574
74.514
74.063
60.610
56.180
55.905
55.334
53.244
52.763
48.120
46.209
37.288
31.751
MeO
MeO
CO2Me
Ph
Ph
CO2Me
MeO
OMe
OMe
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

167

SAMPLE DMC II-140-D IN CDCL3 AT 300 MHZ




13-C, CDCL3
BRUKER
PPM
DMC140DC.004
AU PROG:
AUTOC13.AU
DATE 19-7-95
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 2560
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 9.00
F1 223.427P
F2 -4.568P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.01
175.047
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148.169
148.020
136.419
129.423
127.126
113.258
111.361
109.257
77.422
77.201
77.000
76.578
72.129
60.753
56.218
55.974
55.885
47.683
43.409
32.939
32.763
MeO
MeO
O
O
MeO
OMe
OMe
2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

3.2 References

1. Vogel, A. *Textbook of Pratical Organic Chemistry*, Longman, New York, **1978**.
2. Charlton, J. L. and Alauddin, M. M. *J. Org. Chem.* **1986**, *51*, 3490.
3. Maddaford, S. P. *ortho-Quinodimethanes in Asymmetric Synthesis of Lignans* **1993**, Ph. D. thesis submitted to the Faculty of Graduate Studies at the University of Manitoba, Winnipeg, Manitoba, Canada.
4. Bogucki, D. E. and Charlton, J. L. *J. Org. Chem.* **1995**, *60*, 588.
5. Takano, S., Sato, N., Otaki, S. and Ogasawara, K. *Heterocycles* **1987**, *25*, 69.